TRANSITION-METAL-CATALYZED RADICAL REACTIONS: CARBON-CARBON BOND-FORMING REACTIONS UTILIZING ALKYL ELECTROPHILES

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

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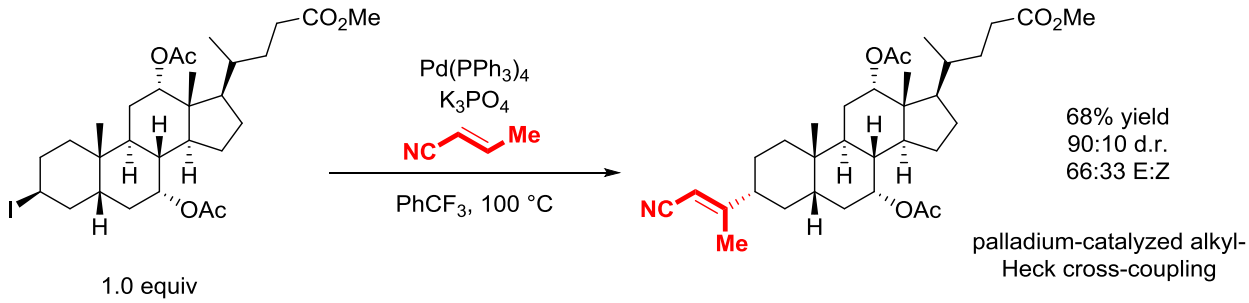
ABSTRACT

Caitlin M. McMahon: Transition-Metal-Catalyzed Radical Reactions: Carbon-Carbon Bond Forming Reactions Utilizing Alkyl Electrophiles
(Under the direction of Erik J. Alexanian)

I. Alkyl Electrophiles in Cross-Coupling

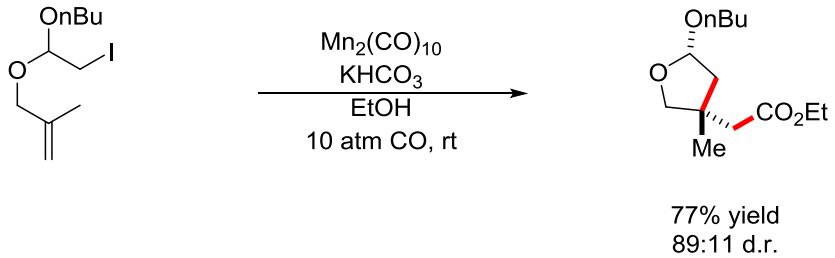
An overview of the importance and challenges of applying alkyl electrophiles to cross-coupling reactions is presented. The current state of alkyl cross-coupling is discussed, focusing on both reaction development and mechanistic investigation. Hybrid organometallic-radical reactivity is also described, along with relevant examples.

II. Palladium-Catalyzed Intermolecular Heck-Type Cross-Couplings of Unactivated Alkyl Iodides



A palladium-catalyzed, intermolecular Heck-type coupling of alkyl iodides and alkenes is described. This process is successful with a variety of primary and secondary unactivated alkyl iodides as reaction partners, including those with hydrogen atoms in the β position. The mild catalytic conditions enable intermolecular C-C bond formations with a diverse set of alkyl iodides and alkenes, including substrates containing base- or nucleophile-sensitive functionality.

III. Manganese-Catalyzed Carboacylation of Alkenes Using Alkyl Iodides



77% yield
89:11 d.r.

- Alkene difunctionalization
- 1st-row transition metal catalyst
- Low CO pressures

A manganese-catalyzed carboacylation of alkenes with alkyl halides and carbon monoxide is described. This reaction forms two C-C bonds in one step resulting in cyclized 5-, 6-, and 7-membered ring products. Primary and secondary unactivated iodides undergo reaction with a variety of alkene substitution patterns, including the formation of all-carbon quaternary centers. The reaction has promising applicability in organic synthesis due to the use of an inexpensive, earth-abundant catalyst and mild reaction conditions under low CO pressure.

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Finally, I would like to thank my parents and the rest of my family for always being there for me and believing in me. I wish that my dad were here to see me finish – but I know how proud he would be and I know how much he has influenced me to be where I am today. Thank you to my mom, who has always been my biggest fan, has always provided for me, and will always be my rock. Thank to my sister Molly, to my grandparents, and my aunts and uncles and cousins who all make trips home so enjoyable and who have made me who I am. And thank you, most of all, to God, to whom all credit is due and who has enabled me to be who I was meant to be. I hope that I can honor God with the many gifts that have been given to me, wherever the future may take me.

To my mom
for her unwavering love and support

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LIST OF ABBREVIATIONS AND SYMBOLS

˚C	degrees Celsius
µL	microliter
µm	micrometer
2D-NMR	two-dimensional nuclear magnetic resonance
9-BBN	9-borabicyclo(3.3.1)nonane
Å	angstrom
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
ATRP	atom transfer radical polymerization
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	tert-butyloxycarbonyl
br. s.	broad singlet
Bu	butyl
BuOH	n-butanol
C-C	carbon-carbon bond
C-H	carbon-hydrogen bond
cm	centimeter
CO	carbon monoxide
C-X	carbon-halogen bond
Cy_2NMe	dicyclohexylmethylamine
d	doublet

DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMA	N,N-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
dppe	diphenylphosphinoethane
dppf	diphenylphosphinoferrocene
dpph	diphenylphosphinohexane
dppp	diphenylphosphinopropane
dr	diastereomeric ratio
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
ESR	electron spin resonance
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
Et_3SiH	triethylsilane
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron-withdrawing group
g	gram
h	hours
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide

HMQC	heteronuclear multiple quantum correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
hv	light
iBuOH	isobutanol
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IPA	isopropanol
iPr	isopropyl
iPr_2NEt	diisopropylethyl amine
iPr_2NH	diisopropylamine
iPr_2O	diisopropylether
iPrOH	isopropanol
IR	infrared
KOtBu	potassium tert-butoxide
L	ligand
LDA	lithium diisopropylamide
LED	light-emitting diode
LR GC/MS	low resolution gas chromatography/mass spectrometry
LRMS	low resolution mass spectrometry
M	metal
m	multiplet
Me	methyl
Me_4NF	tetramethylammonium fluoride
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz

mL	milliliters
mmol	millimole
MS	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
nBu	n-butyl
nBuLi	n-butyl lithium
nDec	n-decyl
NHC	N-heterocyclic carbene
nHex	n-hexyl
NIS	N-iodosuccinimide
nm	nanometer
NMI	N-methylimidazole
NMP	N-methylpyrrolidinone
NMR	nuclear magnetic resonance
nOct	n-octyl
NOESY	nuclear Overhauser effect spectroscopy
Nuc	nucleophile
OTf	triflate
p-	para-
$P(tBu)_2Me$	di(tert-butyl)methylphosphine
PCy_3	tricyclohexylphosphine
$PCyp_3$	tricyclopentylphosphine
Ph	phenyl
$PhCF_3$	trifluorotoluene
PhH	benzene
PhMe	toluene
PMB	para-methoxybenzene
PMDETA	pentamethyldiethylenetriamine

PMP	pentamethylpiperidine
PPh_2tBu	diphenyltert-butylphosphine
PPh_3	triphenylphosphine
psi	pounds per square inch
q	quartet
qd	quartet of doublets
quin	quintet
R	generic carbon substitutent
rt	room temperature
s	singlet
salen	2,2'-ethylenebis(nitrilomethylidene)diphenol
SET	single electron transfer
SIMes	1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
S_N2	substitution nucleophilic bimolecular
$SnBu_3H$	tributyltin hydride
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
td	triplet of doublets
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy radical
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet
X	halogen
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Δ	reflux
π	pi
σ	sigma

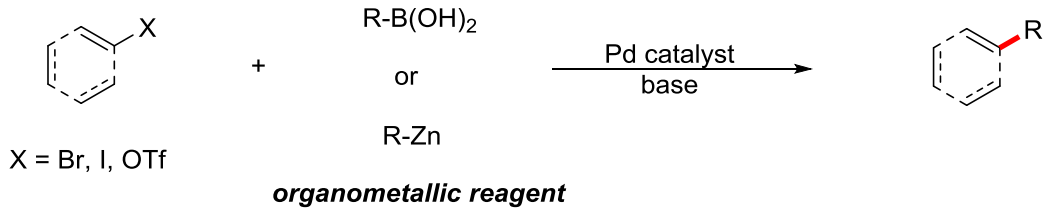
CHAPTER 1: Alkyl Electrophiles in Cross-Coupling

1.1 Introduction

The ability to efficiently form carbon-carbon bonds is crucial to the field of organic chemistry. Synthetic chemists use the available toolbox of developed organic reactions and transformations to build complex molecules, and reactions that form the central C-C bonds in organic molecules have a significant impact on the fields of biochemistry, medicinal and pharmaceutical chemistry, polymers and materials, agrochemistry, etc. Due to the diversity, complexity, and continued discovery of new molecules of interest in these areas of science, there is a constant need to improve and develop new C-C bond-forming reactions to facilitate more efficient syntheses.

Organometallic cross-coupling reactions have been recognized and proven as excellent methods to form C-C bonds. Heck, Negishi, and Suzuki were awarded the Nobel Prize in 2010 for their work in developing reactions that couple aryl or vinyl electrophiles with an organometallic reagent (or an alkene, in the case of Heck) using transition-metal catalysis (Figure 1-1).[1] Employing these reactions, chemists have been able to build molecules quickly and efficiently using easily synthesized organic fragments in sp^2-sp^2 couplings. In particular, the Heck reaction precludes the need for a prefunctionalized organometallic compound, enabling the use of simple alkene starting materials and making it an extremely valuable tool for complex synthesis.[2]

Organometallic cross-coupling reactions



Heck reaction

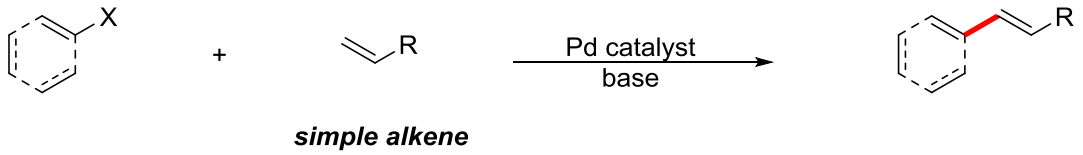


Figure 1-1. General cross-coupling reaction schemes.

A typical cross-coupling mechanism starts with oxidative addition of the transition metal catalyst into the organohalide or pseudohalide, resulting in an aryl- or vinyl-metal species with a net two-electron oxidation of the metal (Figure 1-2). Transmetalation with the organometallic reagent then occurs, followed by reductive elimination to form the coupled product and regenerate the catalyst. The Heck reaction undergoes alkene insertion, rather than transmetalation, and products are formed via β-hydride elimination.

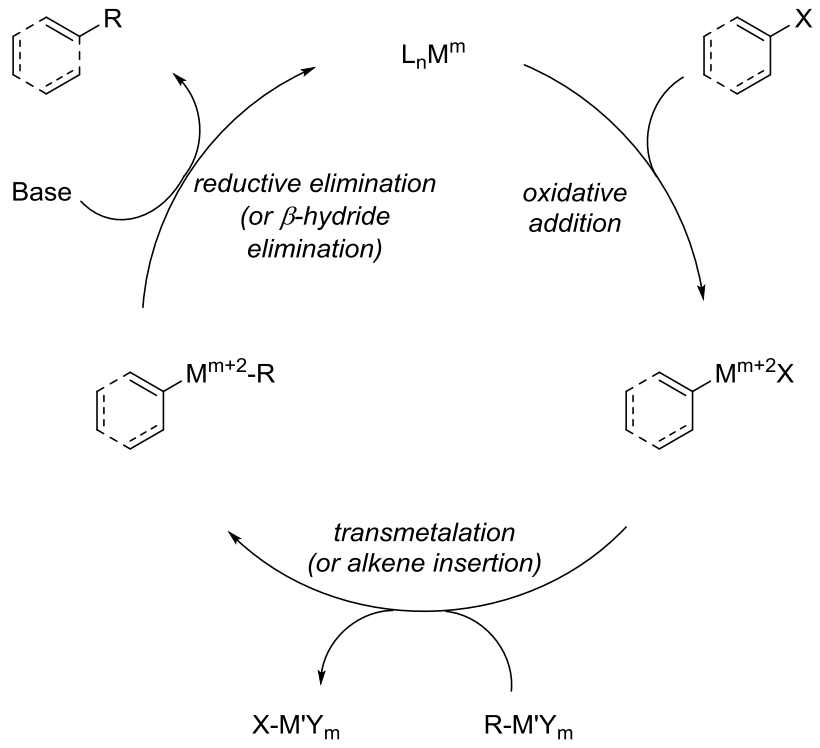


Figure 1-2. General cross-coupling mechanism.

Besides cross-coupling, carbonylation is one of the most important C-C bond forming reactions in organic synthesis. The carbonylation of alkyl halides in particular has great industrial significance, as evidenced by the Monsanto-Cativa production of acetic acid from methanol via generation and carbonylation of methyl iodide.[3] Furthermore, addition of carbon monoxide to traditional cross-coupling methods enables the synthesis of diverse aldehyde, ketone, ester, and amide products (Figure 1-3).[4]

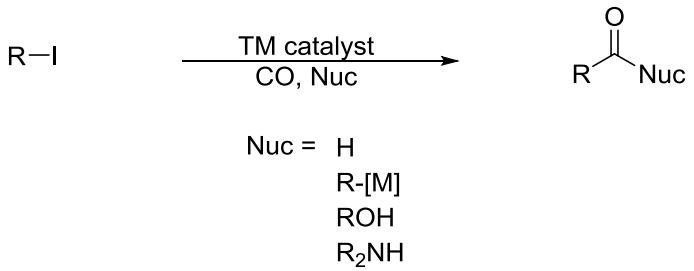


Figure 1-3. General carbonylation scheme.

1.2 Cross-Coupling with Alkyl Electrophiles

While the utility of cross-coupling has been demonstrated in the literature, it has been traditionally limited to the use of aryl and vinyl halides or sulfonates. In order to expand the use of cross-coupling and make facile C-C bond formation available with a wider variety of simple starting materials, it would be desirable to employ alkyl electrophiles in these reactions as well. The use of alkyl halides would enable the formation of sp^3-sp^2 C-C bonds and provide a new potential retrosynthetic disconnection for constructing molecules – formation of the σ bond rather than the π bond (Figure 1-4). Additionally, forming a bond with an sp^3-carbon offers new and expanded possibilities for stereoselective reactions.

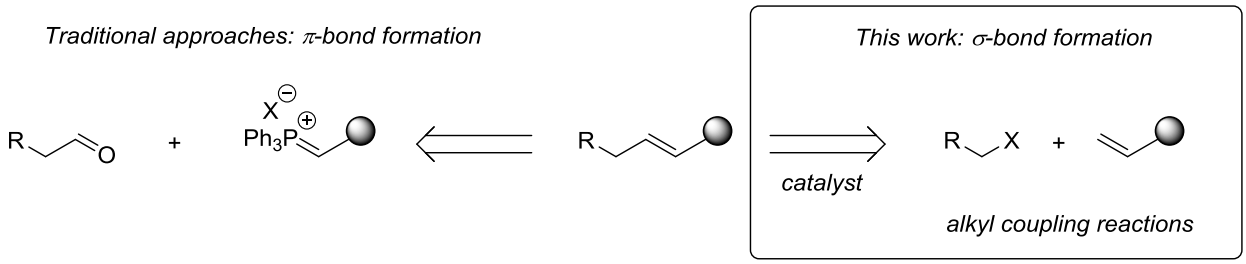


Figure 1-4. Standard synthetic approaches to alkene building blocks.

1.2.1 Utility and Activation of Alkyl Halides

Alkyl halides are extremely common and useful organic building blocks. Over 300 alkyl halides are available for purchase from Sigma Aldrich alone, making them widely commercially available as well as fairly inexpensive. Additionally, alkyl halides can be made easily in one step from even more common starting materials such as alcohols or alkenes. These features make alkyl halides attractive starting compounds for building organic molecules (Figure 1-5).

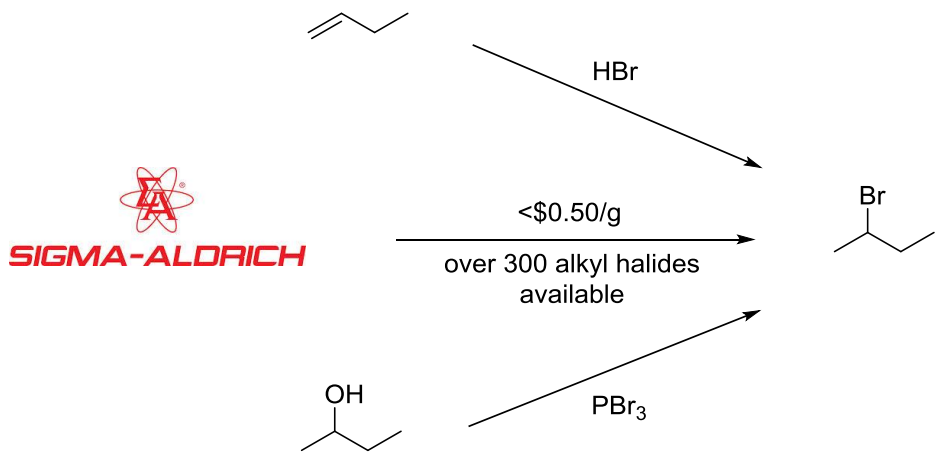


Figure 1-5. Commercial and synthetic availability of alkyl halides.

Traditional methods to activate alkyl halides for C-C bond formation include the use of either reducing metals or radical initiation (Figure 1-6). Reducing metals such as lithium or magnesium react with alkyl halides to form highly basic and nucleophilic organometallic species. The harsh conditions associated with this reactivity have significant drawbacks regarding functional group compatibility, limiting the potential substrate scope. Radical activation offers a more mild set of reaction conditions; however, the high reactivity of radical intermediates causes this method to suffer from selectivity issues. Free radical reactions allow the possibility of many unproductive side reactions, including hydrogen atom abstraction, radical-radical coupling, and polymerization. In order to avoid both harsh conditions and promiscuous radical activity, transition metal catalysts can be used to activate alkyl halides for C-C bond formation. Using transition-metal-catalyzed activation, alkyl halides could be employed as electrophiles in valuable reactions such as cross-coupling and carbonylation.[5]

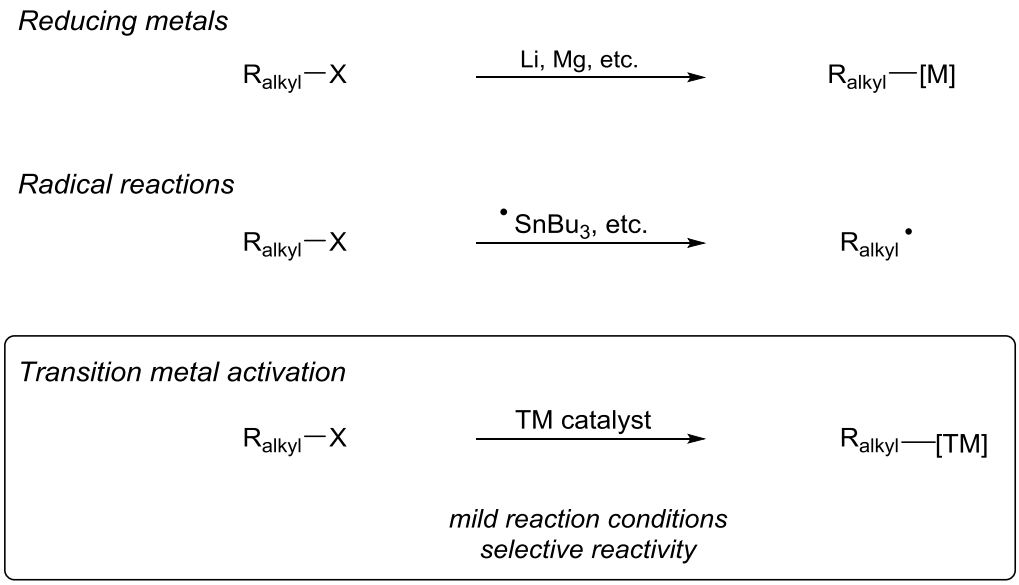


Figure 1-6. Methods for activating alkyl halides for C-C bond formation.

1.2.2 Challenges of Using Alkyl Electrophiles in Cross-Coupling

While utilization of alkyl electrophiles in cross-coupling reactions is desirable, there are several reasons why this application has taken much longer to develop (Figure 1-7).[6] The first challenge is the higher electron density of the sp^3-hybridized C-X bond which results in slower oxidative addition of the transition-metal catalyst. Subsequently, if oxidative addition does occur, the resulting alkyl-metal species has a high propensity to undergo fast β-hydride elimination before the desired coupling. Many of the same obstacles are applicable to carbonylative transformations as well. Avoiding these challenges altogether, examples of cross-coupling with activated alkyl halides such as α-halocarbonyls or benzylic halides have been reported as early as the 1980's (Figure 1-8).[7,8] The electron-withdrawing groups increase the rate of oxidative addition, and in many cases take the place of problematic β-hydrogens. Other examples of alkyl halides, unactivated by electron-withdrawing groups but without accessible β-hydrogens, were also shown to participate in transition-metal-catalyzed cross-coupling.[9]

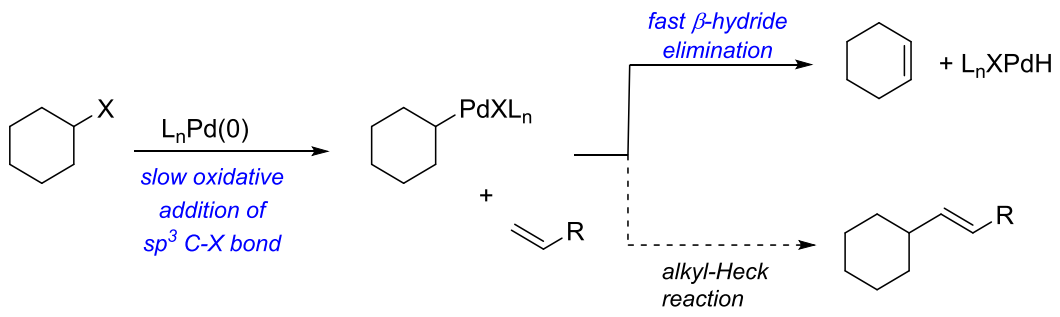


Figure 1-7. Challenges to transition-metal cross-coupling with alkyl halides.

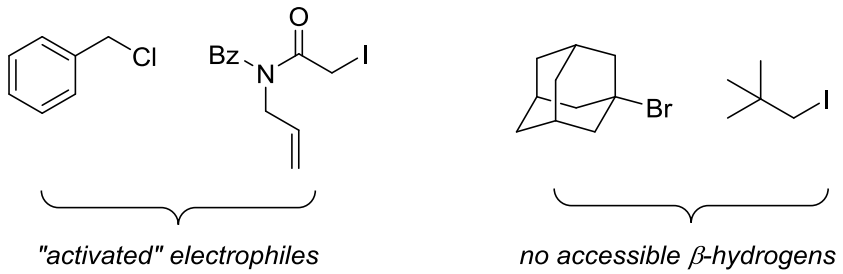


Figure 1-8. Privileged alkyl electrophiles used in cross-coupling.

1.2.3 Alkyl Cross-Coupling Reactions

Despite the significant challenges to adapting cross-coupling reactions to alkyl halides, over the past fifteen years the number of reported transformations using unactivated alkyl electrophiles with β-hydrogens has increased dramatically.[5,6,10–12] In the early 2000's, Fu disclosed examples of palladium-catalyzed Suzuki,[13] Stille,[14] and Negishi[15] reactions which coupled unactivated alkyl halides to organometallic reagents (organoboranes, -stannanes, -zincs, respectively) (Figure 1-9). Bulky, trialkylphosphine ligands allowed for more facile oxidative addition to unactivated substrates in these transformations by adding more electron density to the metal - even less reactive alkyl chlorides and tosylates were viable electrophiles in addition to bromides and iodides. These ligands also helped to minimize premature β-hydride elimination through steric encumbrance.

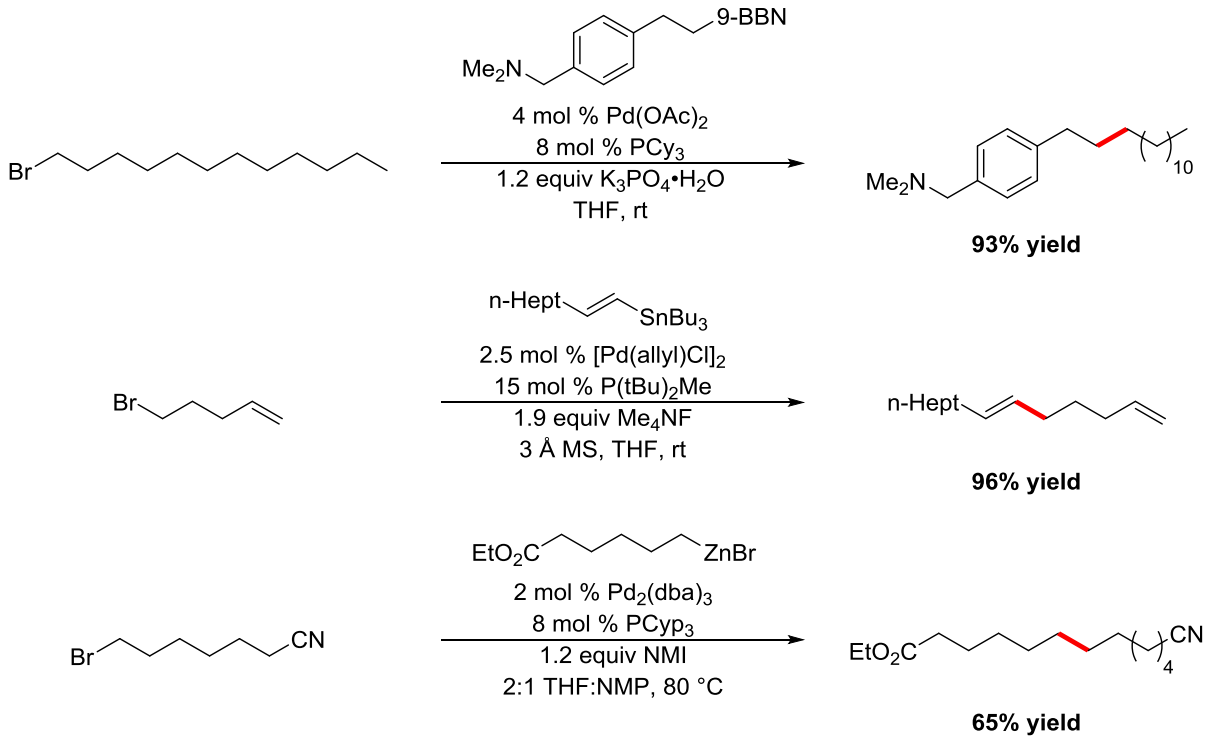


Figure 1-9. Early examples of alkyl cross-coupling reactions.

These reactions are proposed to go through conventional cross-coupling mechanisms of oxidative addition, transmetalation, and reductive elimination. Organopalladium species resulting from stoichiometric oxidative addition of palladium(0) with alkyl bromides have been isolated and characterized crystallographically in support of this mechanism.[16] Additionally, an invertive S_N2 oxidative addition is proposed based on studies with stereochemically defined deuterated alkyl tosylates (Figure 1-10).[17] Further studies that indicate an S_N2 pathway include a decreased activation barrier with more polar solvents and significantly lower levels of reactivity with sterically hindered branched substrates. Nickel-catalyzed variants of many of these reactions have since been developed, including enantioselective transformations of activated alkyl halides, and are proposed to proceed by radical mechanisms .[10,18,19]

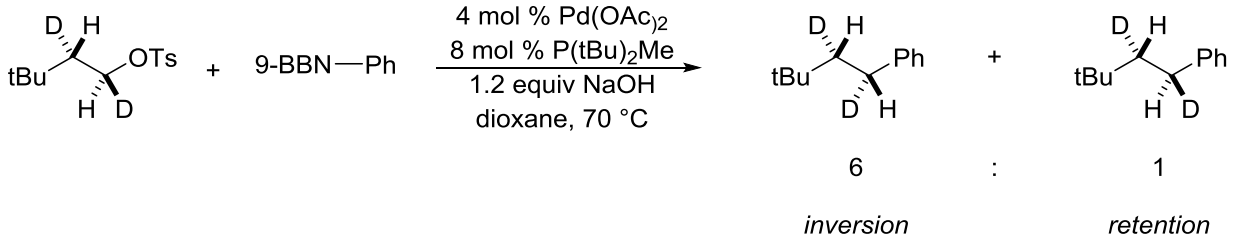


Figure 1-10. Mechanistic evidence for S_N2-type oxidative addition pathway.

While palladium is the traditional cross-coupling metal catalyst, researchers have since displayed alkyl cross-coupling using other first-row transition metals such as nickel, cobalt, and iron. For example, Cárdenas reported an alkyl-Kumada coupling using an iron catalyst and an N-heterocyclic carbene ligand (Figure 1-11).[20] NHCs as a ligand class have proven to be useful in many cross-coupling reactions, including Pd-catalyzed alkyl-Sonogashira, -Negishi, and -Suzuki reactions, due to their strong σ-donating properties.[11] Pybox and bipyridine ligands are also common, especially in Ni-catalyzed alkyl cross-couplings used for coupling secondary alkyl halides.[10]

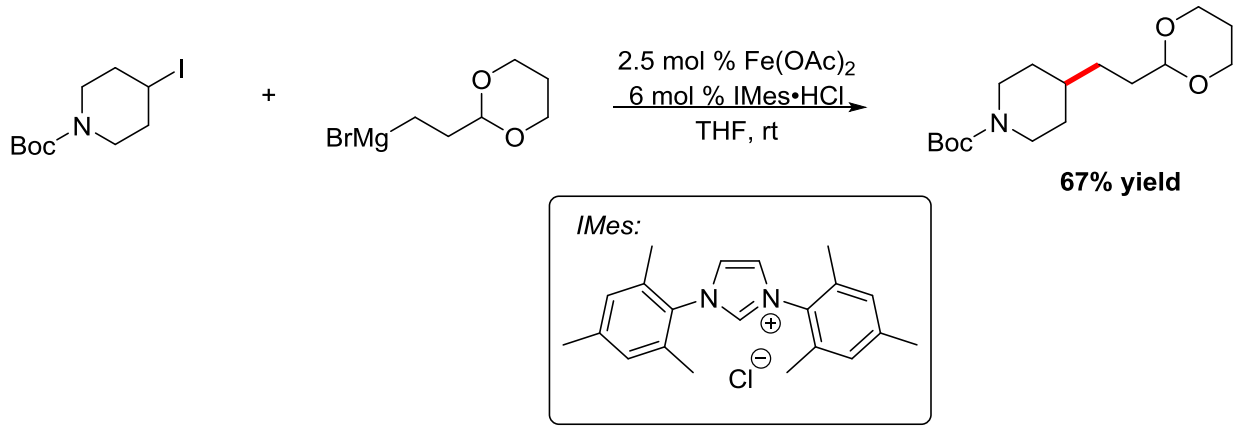


Figure 1-11. Iron-catalyzed alkyl-Kumada coupling.

While substantial developments have been made in the field of alkyl cross-coupling, application to the Heck reaction has lagged notably behind. The major difference in Heck coupling is the use of an alkene component rather than an organometallic nucleophile. This difference results in unique mechanistic features including precoordination of the alkene to the metal and β-hydride elimination to form the alkene product. In order for these processes to occur, an open coordination site is needed on

palladium or the transition metal of choice (Figure 1-12). For these reasons, applying the strategies used in other alkyl cross-coupling reactions has not been as successful for the Heck reaction. Bulky electron-rich ligands, which assist oxidative addition and prevent premature β-hydride elimination, block the coordination sites required for alkene coordination and product-forming β-hydride elimination, limiting productive Heck reactivity.

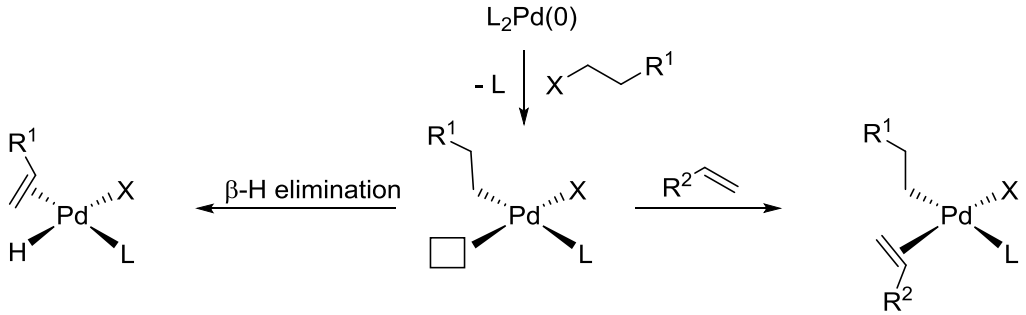
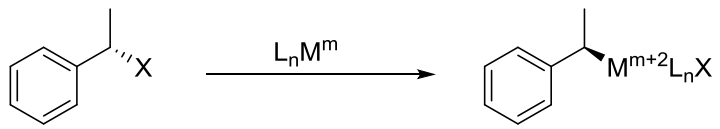


Figure 1-12. Open coordination site needed for Heck reaction promotes β-hydride elimination.

1.2.4 Single-Electron Activation of Alkyl Electrophiles

The challenges described are primarily associated with a typical two-electron oxidative addition of the metal with the alkyl halide. This type of activation is generally thought of as an S_N2-type process, proceeding through inversion of stereochemistry at the alkyl halide center and resulting in an alkyl-metal intermediate which can then undergo productive coupling or unproductive β-hydride elimination (Figure 1-13a). While two-electron oxidative addition is common, another type of activation is also possible. Many transition metals are known to participate in single-electron oxidative addition processes with alkyl halides.[21] This activation can occur by simple one-electron halogen atom abstraction by the metal, producing an alkyl radical, or by single-electron-transfer (SET) resulting in a radical anion which can then disproportionate to the alkyl radical and halide anion (Figure 1-13b). This type of process generally results in stereoablation due to the formation of the sp^2-hybridized radical intermediate.

a) *Two-electron oxidative addition:*



b) *Single-electron oxidative addition*

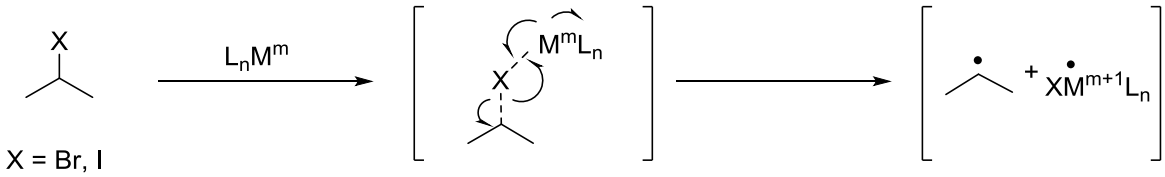


Figure 1-13. Possible pathways for oxidative addition of transition metals with alkyl electrophiles.

Hybrid organometallic-radical reactivity has proven quite useful in synthesis, as the high reactivity of radical species can lead to rate acceleration, while transition metals can help to tame the promiscuous activity that can lead to unselective side reactions.[21] An excellent example of this transition metal control over radical reactions is demonstrated in atom transfer radical polymerization (ATRP).[22] ATRP uses an alkyl halide initiator to polymerize an alkene monomer with the help of a transition metal catalyst, often copper (Figure 1-14). The catalyst plays an essential role in determining the rate and mechanism of the polymerization. The metal undergoes single electron oxidative addition with the dormant polymer chain, capped with an alkyl bromide, resulting in a one-electron oxidation of the metal and generating an alkyl radical, which is the active polymer chain. That radical can add into the next alkene monomer, propagating the polymerization. However, because the equilibrium established by the redox of the metal lies to the left, the radical quickly abstracts a bromide from the metal species and the concentrations of active radical polymer are kept low, minimizing chain terminating side reactions and allowing for continuous, uniform chain growth.

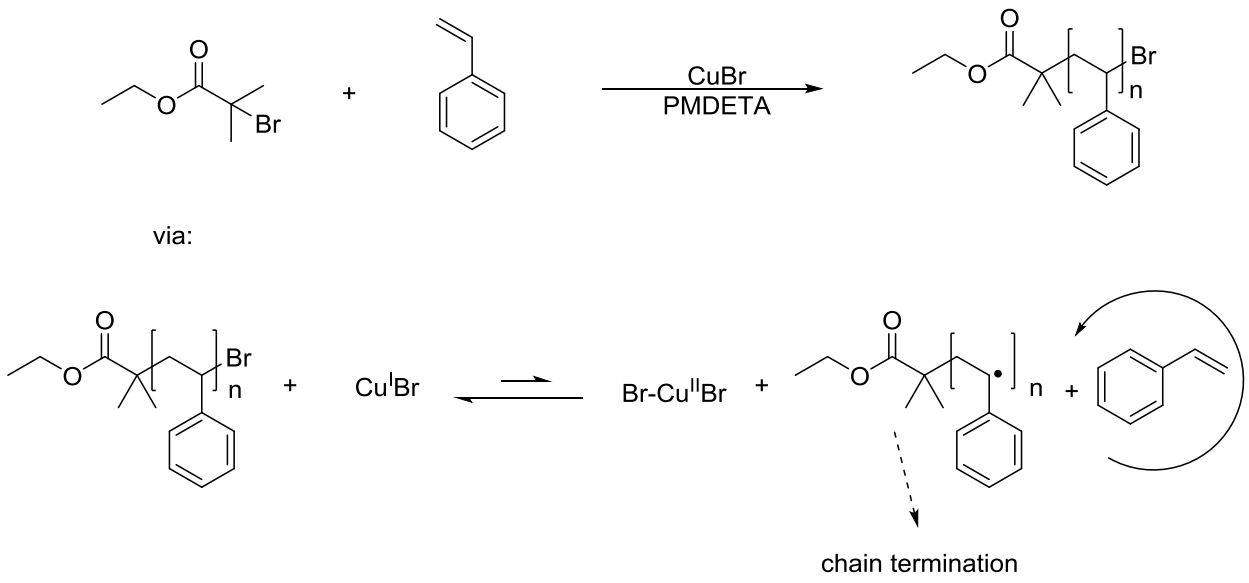


Figure 1-14. Mechanism of atom transfer radical polymerization.

While the pioneering palladium-catalyzed reactions of alkyl electrophiles shown above were determined to proceed via an S_N2-type oxidative addition, many other alkyl cross-couplings appear to be radical in nature. These hybrid organometallic radical pathways could contribute to successful reactivity, minimizing the presence of the potentially problematic alkyl-metal intermediates. Fu proposes radical mechanisms for many of his nickel-catalyzed processes, including an alkyl-Suzuki reaction. In this transformation, cyclization occurs in the presence of a pendant olefin, and the stereochemistry of the products obtained are practically identical to that observed with a $SnBu_3H$-mediated radical cyclization, indicating the likelihood of a radical intermediate (Figure 1-15a).[23] An example of single-electron cobalt-catalyzed cross-coupling can be seen in Oshima's alkyl Kumada reaction, where a cobalt(0) to cobalt(I) oxidation is proposed, participating in SET with an alkyl bromide, followed by recombination and reductive elimination (Figure 1-15b).[24] Many carbonylations also proceed via radical mechanisms, as illustrated by the successful carbonylation of alkyl halides by a variety of transition metal carbonyl complexes by Watanabe (Figure 1-15c).[25] They were able to detect the presence of radicals in these reactions by ESR spin radical trapping experiments.

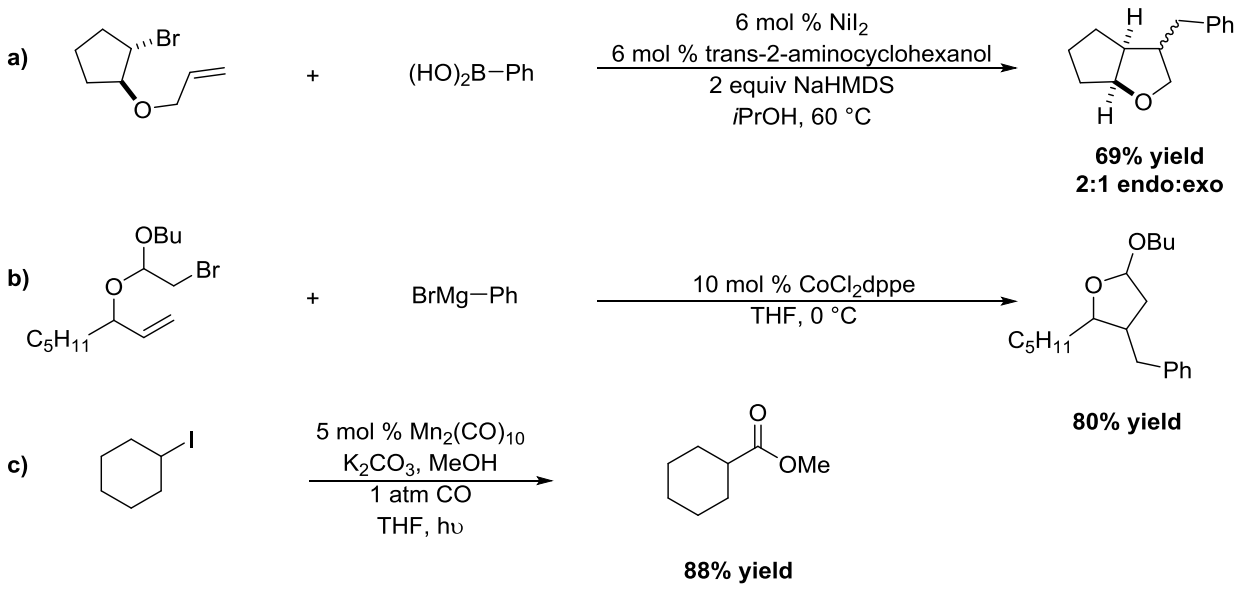


Figure 1-15. Alkyl C-C bond-forming reactions proposed to proceed via radical mechanisms.

Many examples of palladium-catalyzed C-C bond-forming processes with alkyl electrophiles (cross-coupling, carbonylation, halogen atom transfer, etc.) propose radical intermediates (Figure 1-16).[26] The mechanisms are generally proposed to go through palladium(I) species resulting from one-electron oxidation of palladium(0). In some cases, radical chain reactions are operative, while others participate in hybrid organometallic-radical pathways.

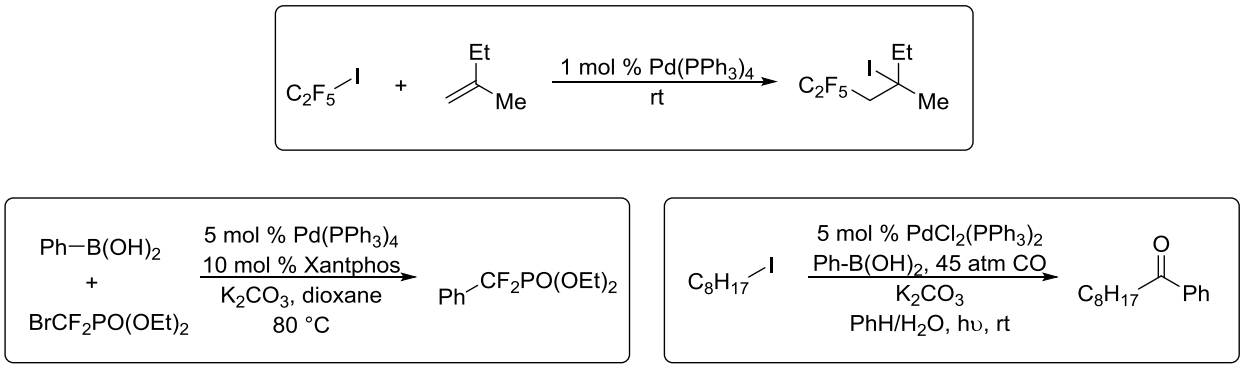


Figure 1-16. Examples of Pd-catalyzed processes proposed to involve radical intermediates.

1.3 Summary and Outlook

The success of organometallic-radical processes in cross-coupling provides a potential solution to the development of an alkyl-Heck reaction. In fact, several seminal examples have been reported using alkyl electrophiles in a Heck-type reaction, invoking single-electron pathways (see Chapter 2). However,

there remains a need for a general alkyl-Heck transformation that can couple a broad range of simple unactivated alkyl electrophiles with alkenes under mild conditions. Methodologies to accomplish this goal, as well as the development of other C-C bond-forming reactions with unactivated alkyl halides, are presented herein.

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CHAPTER 2: Palladium-Catalyzed Intermolecular Heck-Type Cross-Couplings of Unactivated Alkyl Iodides

2.1 Introduction

The development of efficient cross-coupling reactions over the past several decades has provided an invaluable tool for carbon-carbon bond formation in organic synthesis. Originally, these reactions were limited to the use of aryl or vinyl electrophiles, forming bonds between sp^2-hybridized carbon atoms (Figure 2-1). The adaptation of cross-coupling methods to sp^3-hybridized alkyl electrophiles has met many challenges, including slow oxidative addition and fast premature β-hydride elimination; however, significant advances have been made in this area. The Heck reaction, unique in its use of an alkene coupling partner rather than a prefunctionalized organometallic reagent, has faced an even higher level of difficulty in achieving this goal due to its need for an open coordination site on the metal catalyst (see Chapter 1).

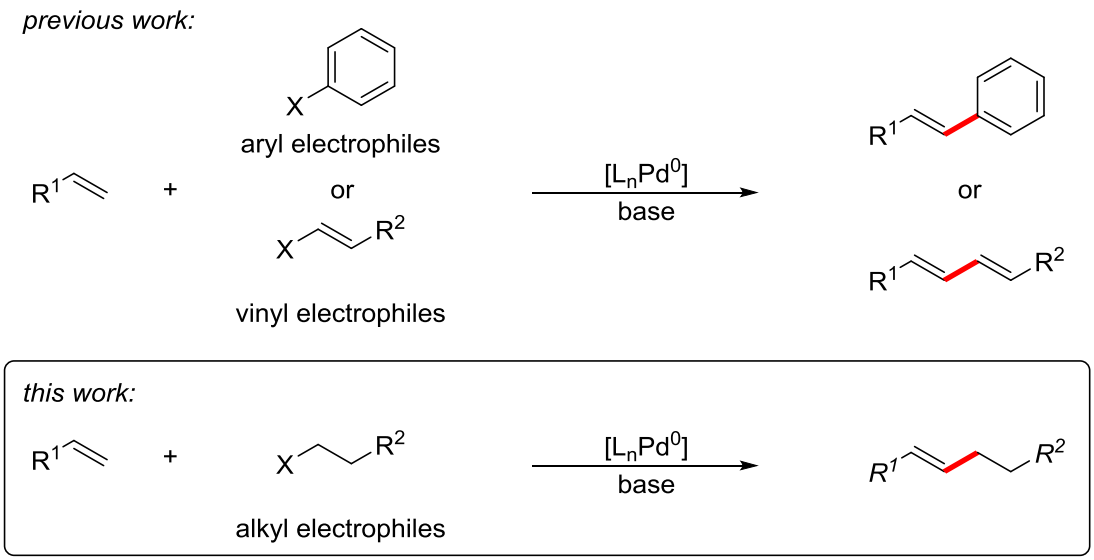


Figure 2-1. Palladium-catalyzed Heck cross-couplings.

There remains a need for a general, mild alkyl-Heck reaction that can efficiently couple unactivated alkyl electrophiles and alkenes. Developing this capability would unlock new synthetic C-C

bond disconnections and enable the synthesis of molecules ranging from natural products to pharmaceuticals to functional materials. With mild reaction conditions, an alkyl-Heck coupling could be applied to make simple small molecule building blocks, as well as in late-stage stapling or modification of larger molecules (Figure 2-2).[1,2]

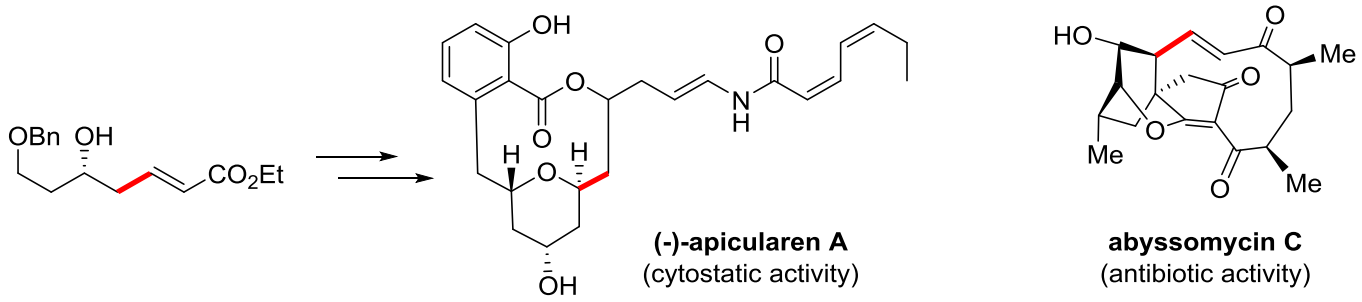


Figure 2-2. Potential applications for alkyl-Heck reactivity in complex synthesis.

2.2 Background

While many challenges have hindered the development of an alkyl-Heck reaction, especially in comparison to other cross-coupling methods, limited examples have been disclosed. Many of these capitalize on hybrid organometallic-radical chemistry to enable successful Heck-type transformations and avoid problematic intermediates (see Chapter 1).

2.2.1 Intramolecular Alkyl-Heck Reactions

In 2007, Fu reported an intramolecular Heck reaction catalyzed by palladium using an electron-rich NHC ligand.[3] The reaction was exclusive to the 5-exo cyclization of primary bromides and chlorides and terminal alkenes. A two-electron organometallic mechanism was suggested for this coupling, and evidence was provided by the reaction of a deuterium-labeled alkyl bromide, which resulted in a single diastereomer (Figure 2-3). The diastereomer obtained is that which would be expected from an S_N2 mechanism of oxidative addition involving inversion of stereochemistry.

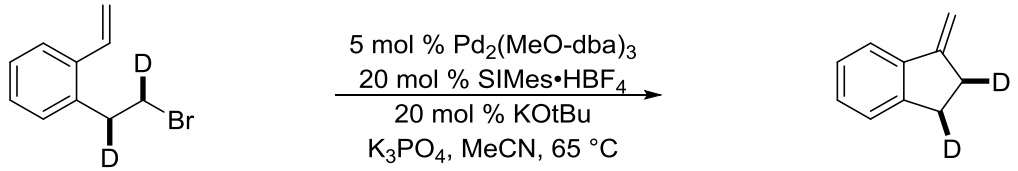


Figure 2-3. Evidence for two-electron oxidative addition in Pd-catalyzed intramolecular alkyl-Heck reaction.

Our laboratory aimed to develop a general, more broadly applicable alkyl-Heck cyclization, and was able to optimize a system that could accommodate both primary and secondary alkyl halides, as well as a variety of alkene substitution patterns (Figure 2-4).[4] Five- and six-membered rings could both be formed in good yields, including the formation of tetrahydrofuran and pyrrolidine rings and bicyclic systems. Contrary to Fu's transformation, the reaction was proposed to proceed via a single-electron mechanism. A plausible catalytic cycle begins with single-electron oxidative addition of palladium(0) with the alkyl iodide, resulting in an alkyl radical (Figure 2-5). Fast radical cyclization onto the alkene can then occur, followed by recombination with palladium and β-hydride elimination to form the alkene product. The addition of one equivalent of persistent radical TEMPO provided 24% of the TEMPO-trapped product, corroborating the presence of radical intermediates (Figure 2-6).

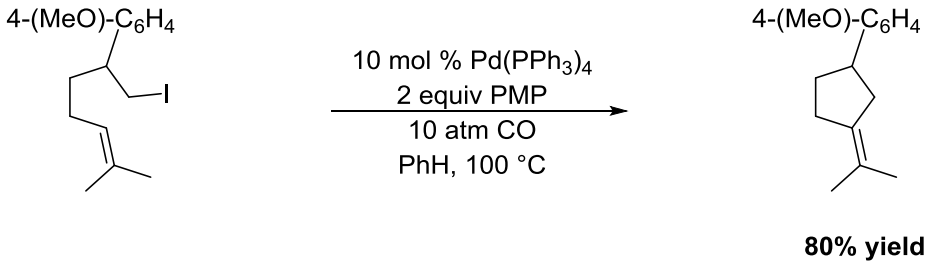


Figure 2-4. Pd-catalyzed alkyl-Heck cyclization.

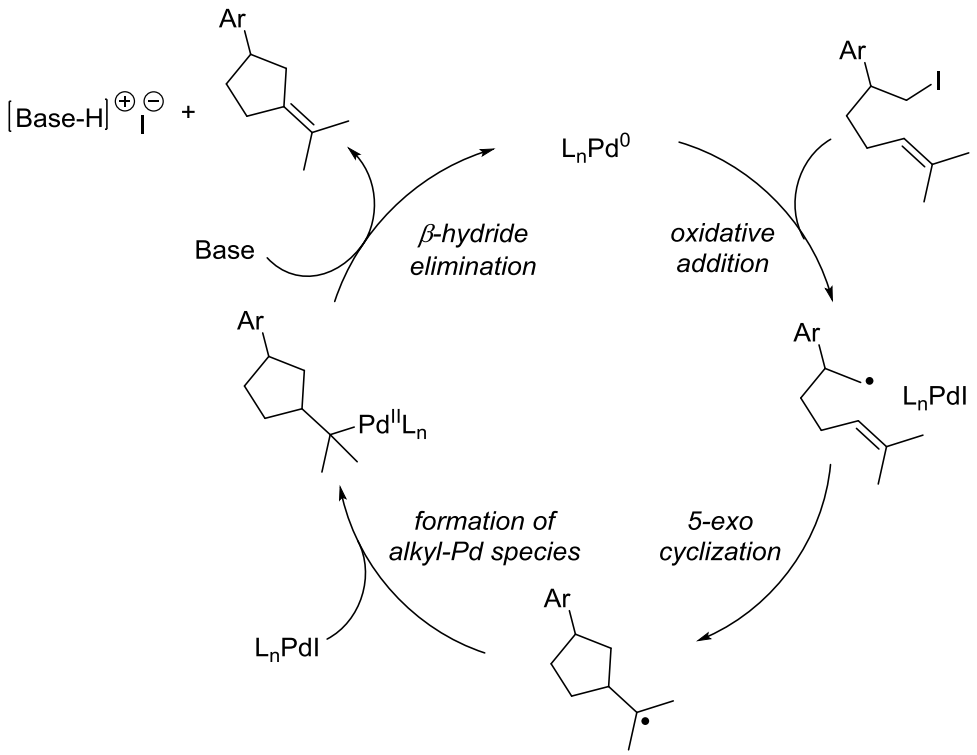


Figure 2-5. Proposed single-electron mechanism of Pd-catalyzed alkyl-Heck cyclization.

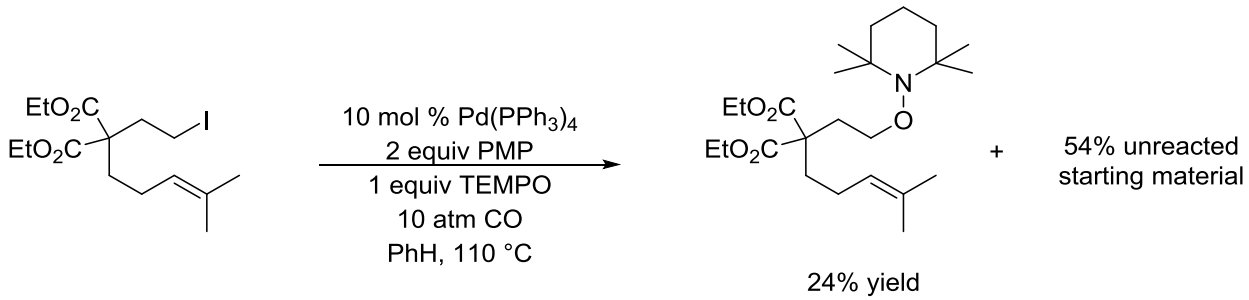


Figure 2-6. TEMPO-trapping experiment with alkyl-Heck cyclization.

Another example of an intramolecular alkyl-Heck transformation suggested to proceed through a radical mechanism was reported by Carreira.[5] This transformation is catalyzed by stannyl- or alkyl-cobaloxime species in the presence of base and blue LEDs, and is highlighted by mild reaction conditions and functional group compatibility (Figure 2-7). The proposed mechanism also involves a single-electron oxidative addition of the catalyst with the alkyl iodide, producing a carbon-centered radical.

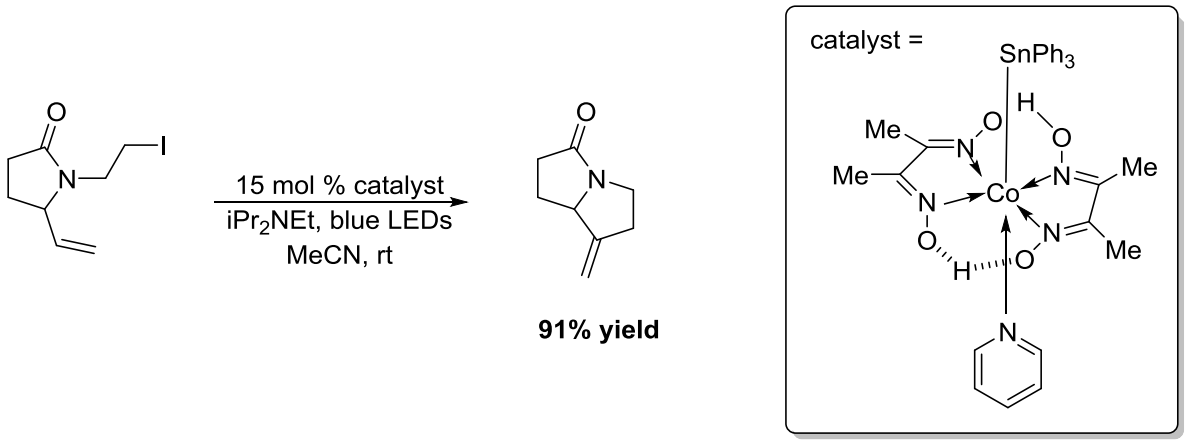


Figure 2-7. Cobaloxime catalyzed intramolecular alkyl-Heck reaction.

2.2.2 Intermolecular Alkyl-Heck Reactions

While intramolecular Heck-type cyclizations have numerous useful applications, the development of an intermolecular reaction would greatly increase versatility and enable coupling of simple organic building blocks. Intermolecular alkyl-Heck-type reactivity has also been demonstrated in the literature (Figure 2-8). In 1988, the first example was reported by Lebedev, wherein he showed the reaction of several simple alkyl bromides with styrene under nickel catalysis to provide Heck products.[6] The reaction requires stoichiometric zinc as a reductant for catalyst turnover and gave low to moderate yields of product. More recently, Lei disclosed another nickel-catalyzed Heck-type reaction with α-carbonyl alkyl bromides.[7] These substrates are primed for activation because of the electron-withdrawing carbonyl group.

Other metals have also been used for intermolecular alkyl-Heck reactions, including cobalt, similarly to the intramolecular example described above. Oshima reported that a variety of unactivated alkyl halides could be coupled to styrenes in good yields using a catalytic system consisting of $CoCl_2$ and diphenylphosphinohexane (dpph) and 2.5 equivalents of a Grignard reagent as a reductant.[8,9] A titanocene catalyst can also successfully couple alkyl bromides and chlorides to styrenes in the presence of a Grignard reagent.[10] Copper has also been shown to be an effective catalyst for the reaction of activated tertiary α-halocarbonyls and styrenes.[11] During the review process of our work, a palladium-catalyzed alkyl-Heck reaction was also reported by Zhou, but was again limited to styrene coupling partners.[12]

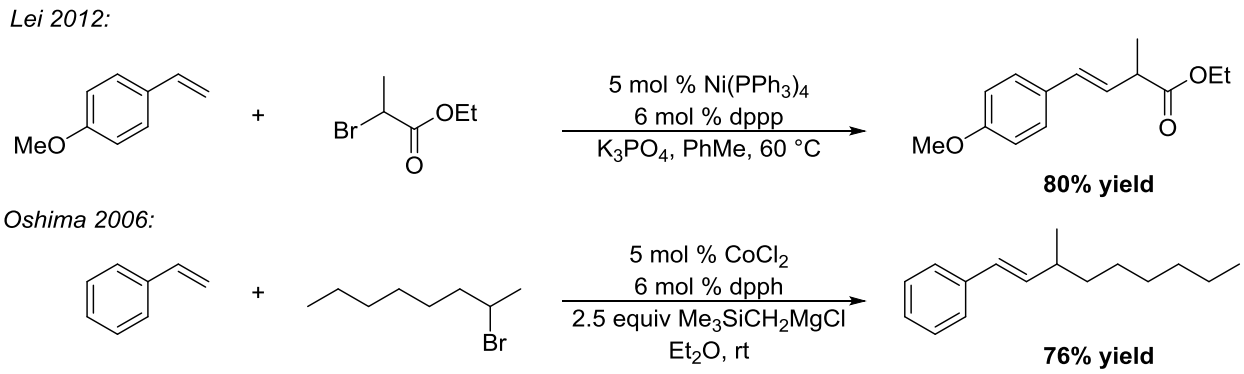


Figure 2-8. Selected examples of intermolecular alkyl-Heck-type reactions.

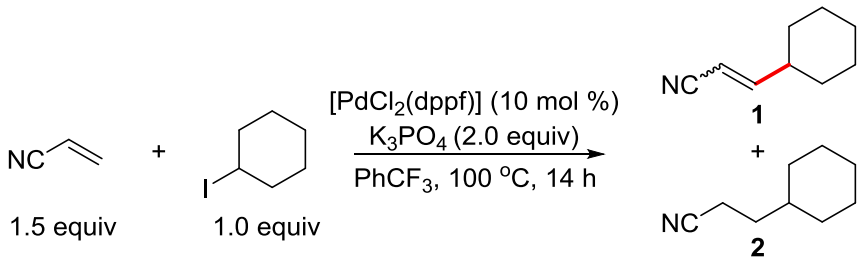
While intermolecular alkyl-Heck reactivity has been previously demonstrated, many examples use stoichiometric reductants, limiting the functional group compatibility. Additionally, styrenes are used exclusively as the alkene coupling partner, and many use privileged alkyl halide electrophiles,[13,14] activated by electron-withdrawing groups. There remains a need for a milder, more general catalytic system to efficiently couple simple unactivated alkyl halide and alkene starting materials, and described herein are the efforts in pursuit of that goal.[15]

2.3 Optimization of Catalytic System

We commenced our studies by investigating the intermolecular coupling between cyclohexyl iodide and acrylonitrile, with the goal of developing a useful system with mild reaction conditions and an expanded substrate scope (Table 2-1). Significant optimization of the catalytic system from our previously developed intramolecular alkyl-Heck-type reactions proved necessary to increase the yield to synthetically useful 72% (Table 2-1, entry 1). Through optimization, we found that the identity of the base was very important. The use of an organic amine base (Cy_2NMe) in the acrylonitrile coupling led to a substantial amount of undesired reductive byproduct **2** (entry 2). We proposed that this reductive byproduct could be forming via two different potential pathways. First, after addition to the acrylonitrile, a palladium enolate-type species could be forming and subsequently being protonated by the conjugate acid of the amine base in solution. The other possibility is, if proceeding through a single-electron mechanism, the carbon-centered radical resulting from addition to the alkene could be abstracting a hydrogen atom from a weak C-H bond present in the amine base, solvent, or substrate. These problems

were mitigated by using an inorganic base (K_3PO_4 worked best) (entries 1 and 3), and a solvent without abstractable hydrogen atoms ($PhCF_3$). Further study showed that 100 °C was the optimal reaction temperature, along with a slight excess of alkene (entries 4-5). The excess of alkene was needed to compensate for loss due to polymerization. [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride ([$PdCl_2$(dppf)]) proved to be the superior catalytic system compared to other palladium sources and phosphine ligands, although a mixture of $Pd(OAc)_2$ and diphenylphosphinoferrocene (dppf) did proceed identically to the premade catalyst (entries 6-9). While $Pd(PPh_3)_4$ provided a useful 55% yield of product, many other mono- and bidentate phosphine ligands were unsuccessful. A control reaction without palladium was performed and yielded no product (entry 10). The reaction did proceed in the absence of light (entry 11), however with a slower rate (24 h was required compared to 14 h). This result seems to indicate that light may play a slight activating role, perhaps helping to activate the alkyl iodide for oxidative addition.

Table 2-1. Optimization of alkyl-Heck-type cross-coupling of cyclohexyl iodide and acrylonitrile.



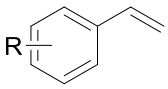
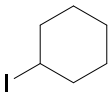
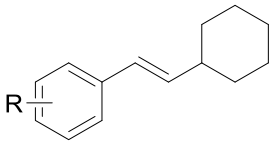
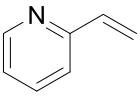
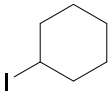
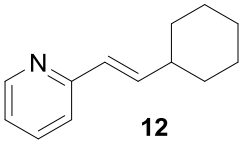
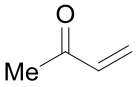
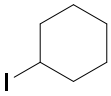
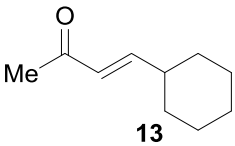
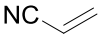
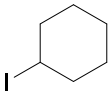
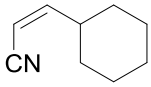
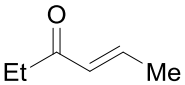
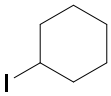
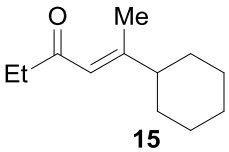
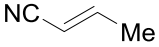
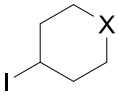
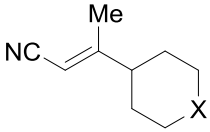
entry	deviation from conditions above	% yield **1** (% **2**)[a]
1	none	72
2	Cy_2NMe instead of K_3PO_4	18 (24)
3	Cs_2CO_3 instead of K_3PO_4	57
4	80 °C instead of 100 °C	24
5	1.0 equiv alkene, 2.0 equiv iodide	54
6	$[Pd(PPh_3)_4]$ (10 mol %) instead of [$PdCl_2$(dppf)] (10 mol %)	55 (5)
7	$Pd(OAc)_2$ (10 mol %) and BINAP (20 mol %) instead of [$PdCl_2$(dppf)]	17
8	$Pd(OAc)_2$ (10 mol %) and dppe (20 mol %) instead of [$PdCl_2$(dppf)]	<2
9	$Pd(OAc)_2$ (10 mol %) and dppf (20 mol %) instead of [$PdCl_2$(dppf)]	73
10	no [$PdCl_2$(dppf)]	<2
11	reaction in the dark, 24 h	69

[a] Calculated by ^{1}H NMR spectroscopy of the crude reaction mixtures using an internal standard.

2.4 Substrate Scope

After investigating and optimizing reaction conditions, we then looked to expand the substrate scope. Electronically diverse styrenes were all viable coupling partners in this reaction, including those with varying substitution patterns (ortho-, meta-, and para-substitution were all successful) (Table 2-2, entries 1-9). Base- and nucleophile-sensitive functionality was tolerated, highlighting the mild reaction conditions (entries 5, 7). We found that the amine base, Cy_2NMe, was optimal in styrene cross-couplings where the formation of the reductive byproduct was not problematic. With one of our major goals being to expand this reactivity beyond the limitations of styrenes, we were able to show that heterocyclic 2-vinylpyridine also participates in the reaction in modest yield (entry 10), as well as other electron poor alkenes such as acrylonitrile and methyl vinyl ketone (entries 11-12). The reaction with methyl vinyl ketone required the substitution of [{Pd(allyl)Cl}$_2$] (5 mol %) and PPh_2tBu (40 mol %) for [$PdCl_2$(dppf)]. We propose that the decreased yield, and need to change catalyst systems could be due to strong coordination of the alkene to palladium, limiting the catalyst's potential to undergo oxidative addition with the iodide. The use of a more electron-rich phosphine (PPh_2tBu) could be either helping to prevent coordination or adding additional electron density to the metal, facilitating oxidative addition. 1,2-disubstituted alkenes were also successful coupling partners, providing tri-substituted alkene products in good yields (entries 13-15). These reactions gave a mixture of E and Z isomers, similar to results from the standard Heck reaction using aryl electrophiles.[16] In these cases, $Pd(PPh_3)_4$ proved to be the optimal catalyst.

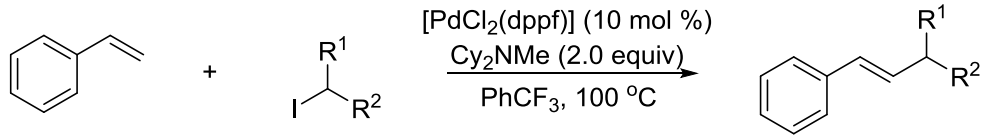
Table 2-2. Alkene scope of Pd-catalyzed alkyl-Heck cross coupling.

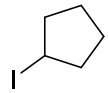
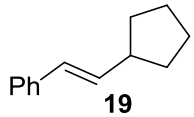
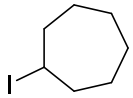
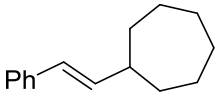
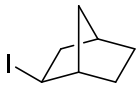
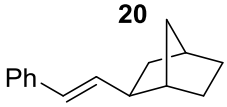
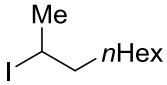
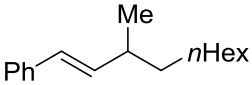
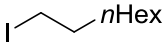
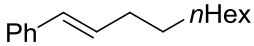
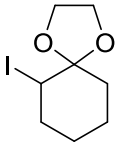
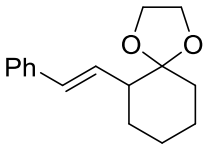
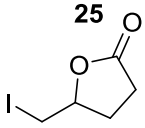
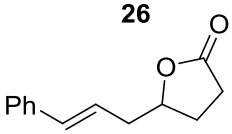
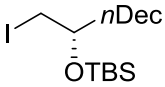
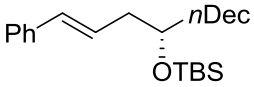
entry	alkene	alkyl iodide	product	% yield[b,c]
				
1	R = H		**3**	84
2	R = 4-OMe		**4**	66
3	R = 4-Me		**5**	64
4	R = 4-CF_3		**6**	82
5	R = 4-CH_2OH		**7**	64[d]
6	R = 4-F		**8**	76 (83:17 E:Z)
7	R = 4-C(O)Me		**9**	61[d] (80:20 E:Z)
8	R = 3-OMe		**10**	67
9	R = 2-Me		**11**	72 (50:50 E:Z)
10			 **12**	35
11			 **13**	35[e,f]
12			 **14**	70[e] 29:71 *E:Z*
13			 **15**	55[e,g,h] 66:33 *E:Z*
				
14		X = CH_2	**16**	80[e,g,i](66:33 *E:Z)*
15		X = NTs **17**	**18**	79[e,g,i](66:33 *E:Z)*

[a] Reactions run using 1.0 equiv alkyl iodide and 1.5 equiv alkene 0.5 M in $PhCF_3$ at 100 ˚C in the presence of 10 mol % $PdCl_2$(dppf) and 2.0 equiv Cy_2NMe for 14 h. [b] Yields of isolated product. E isomers were observed unless otherwise noted. [c] Product ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d] Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixture using internal standard. [e] 2.0 equiv K_3PO_4 used as base. [f] 5 mol % $[Pd(allyl)Cl]_2$ and 40 mol % PPh_2tBu used as catalyst, 5 h. [g] 10 mol % $Pd(PPh_3)_4$ used as catalyst. [h] 2.0 equiv alkyl iodide and 1.0 equiv enone used. [i] 3.0 equiv crotononitrile used.

Various alkyl halide electrophiles were also investigated for use in this reaction. Both cyclic and acyclic secondary iodides were efficient substrates (Table 2-3, entry 1-4). Primary iodides show moderate reactivity, as demonstrated by the reaction of 1-iodooctane (entry 5). Potentially due to a greater barrier to activation for primary iodides, a higher temperature (130 ˚C) was required, and yields decreased slightly. Alkyl iodides with α-oxygen functionality also participated in the cross-coupling (entries 6-8). Because there are many useful ways to make these substrates enantioselectively, subsequent alkyl-Heck cross-coupling could prove quite useful as a C-C bond-forming tool in the synthesis of highly functionalized, enantiopure, small molecules. The reaction with enantiopure TBS-protected alcohol highlights this feature, resulting in a complete retention of stereochemistry (entry 8). The stereochemical retention indicates that reversible β-hydride elimination of the halide is not occurring prior to coupling. Alkyl bromides did not undergo coupling under these catalytic conditions.

Table 2-3. Iodide scope of Pd-catalyzed alkyl-Heck cross-coupling.



entry	alkyl iodide	product	% yield[b,c]
1		 **19**	70 86:14 *E:Z*
2		 **20**	76
3		 **21**	80 88:12 *E:Z* >95:5 dr
4	 **22**	 **23**	74 88:12 *E:Z*
5		 **24**	46[d]
6	 **25**	 **26**	79
7		 **27**	42[d,e]
8	 >99:1 er **28**	 >99:1 er **29**	51[d] 80:20 *E:Z*

[a] Reactions run using 1.0 equiv alkyl iodide and 1.5 equiv alkene 0.5 M in $PhCF_3$ at 100 °C in the presence of 10 mol % $PdCl_2$(dppf) and 2.0 equiv Cy_2NMe for 14-15 h. [b] Yields of isolated product. E isomers were obtained unless otherwise noted. [c] Product ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d] Reaction run at 130 °C. [e] Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixture using internal standard.

Illustrating the mild catalytic conditions and breadth of available substrates, the cross-coupling was also performed on an alkyl iodide easily derived from a complex natural product, cholic acid.

Reaction with crotononitrile formed the alkene product diastereoselectively in 68% yield (Figure 2-9). In order to determine the diastereoselectivity of this cross-coupling, subsequent ruthenium-catalyzed oxidation of the alkene to the ketone was performed to convert the product into a known compound. This transformation also illustrates the versatility and synthetic utility of the products of the alkyl-Heck reaction.

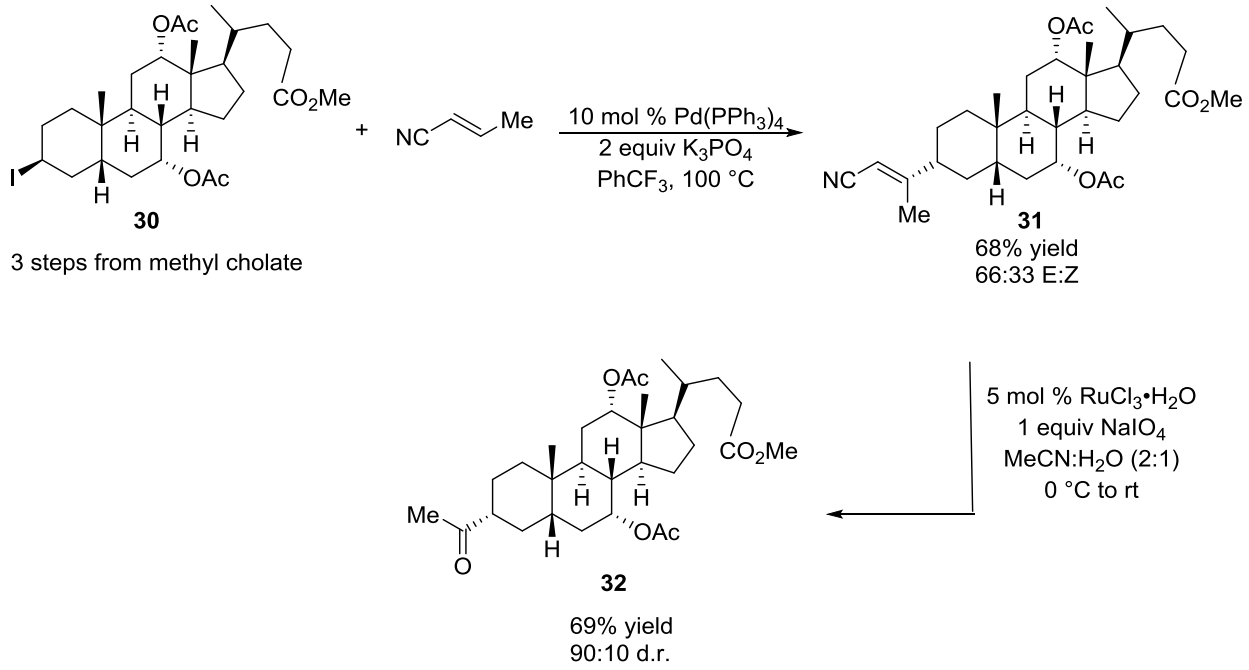


Figure 2-9. Intermolecular alkyl-Heck coupling of a complex iodide.

In the application of unactivated alkenes to the Heck reaction, regioselectivity is often a problem and this coupling has been considered more challenging in comparison to more polarized alkenes. While chelation has often been used as a strategy to direct regiochemistry in oxidative Heck transformations catalyzed by palladium(II),[17] catalyst-controlled reactions with aliphatic olefins selective for the terminal position[18] or the internal position are also known.[19] There are no known examples of the use of electronically-unbiased alkenes in combination with unactivated alkyl electrophiles. This type of reaction would be even more difficult, with less differentiation electronically between the electrophile and alkene, and no conjugation to funnel β-hydride elimination to one position. However, using a similar catalytic system to that developed for the electronically-matched alkyl-Heck reaction, we obtained preliminary results indicating the cross-coupling of a heterocyclic alkyl iodide with 1-octene in a 28% yield, albeit as a mixture of alkene isomers, resulting from chain-walking β-hydride elimination/reinsertion (Figure 2-10).

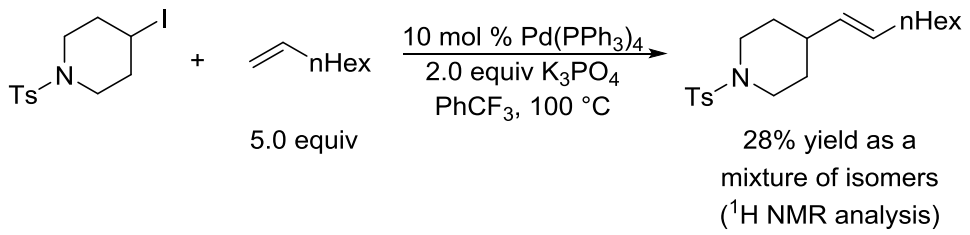


Figure 2-10. Intermolecular alkyl-Heck coupling with an unactivated olefin.

2.5 Mechanistic Studies

We hypothesize that this reaction proceeds through a hybrid-organometallic-radical pathway. In an effort to trap a proposed radical intermediate generated via single-electron oxidative addition of the alkyl iodide, the coupling of iodocyclohexane and crotononitrile was run with standard conditions with the addition of 1 equivalent of a TEMPO, a persistent radical trap. The presence of TEMPO resulted in no conversion to the alkene product, however no TEMPO-trapped radical adducts were observed (Figure 2-11). The ability of TEMPO to inhibit the reaction could be suggestive of a radical mechanism, however TEMPO has also been shown to interact with palladium catalysts.[20] Due to this possible behavior, the lack of alkyl-Heck reactivity in this case provided ambiguous results, as the radical trap could have simply been inhibiting palladium catalysis in general. Looking to other mechanistic probes, the reaction of acrylonitrile with a diastereomerically pure substrate was carried out, resulting in complete stereoablation (Figure 2-12a). This is consistent with a single-electron mechanism, as an sp^2-hybridized radical intermediate could add to the alkene from the top or bottom face, whereas a 2-electron oxidative addition would be stereospecific and result in inversion. Additionally, the reaction of styrene with a radical-clock substrate (6-iodo-1-hexene) provided the cyclic product in 38% yield, and no linear coupling product was observed (Figure 2-12b). Based on these experimental results, a proposed catalytic cycle is shown in Figure 2-13. Oxidative addition of palladium(0) to the alkyl iodide via single electron transfer (or halogen atom abstraction) creates an alkyl radical and a putative palladium(I) species. Addition of the carbon-centered radical to the alkene results in a new secondary alkyl radical, which can then recombine with palladium to form an alkyl-palladium(II) intermediate. Finally, β-hydride elimination delivers the cross-coupling alkene product.

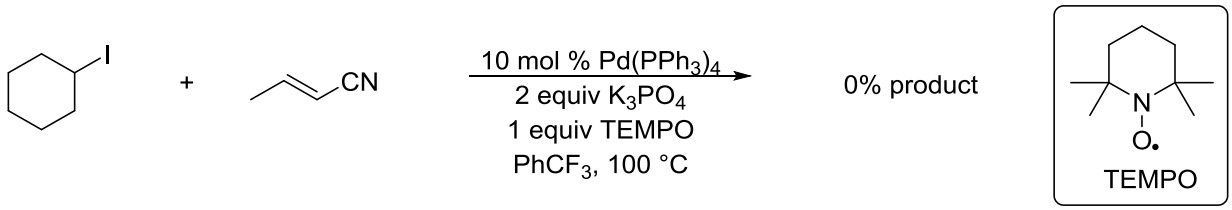


Figure 2-11. The effect of persistent radical trap TEMPO on Pd-catalyzed intermolecular alkyl-Heck reaction.

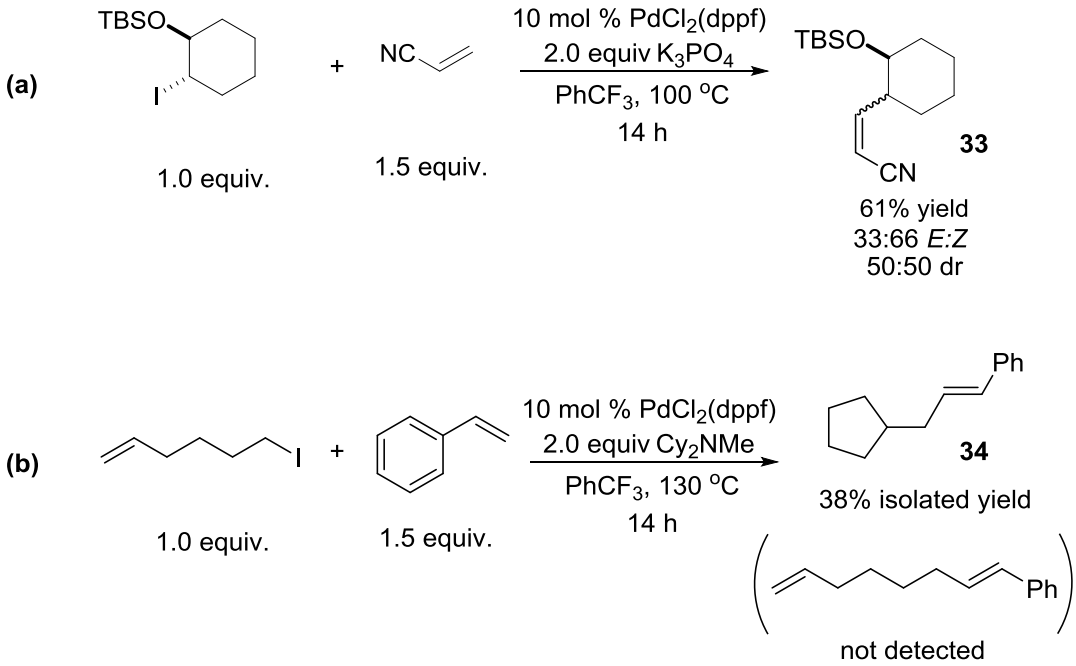


Figure 2-12. Mechanistic studies probing the presence of a radical intermediate.

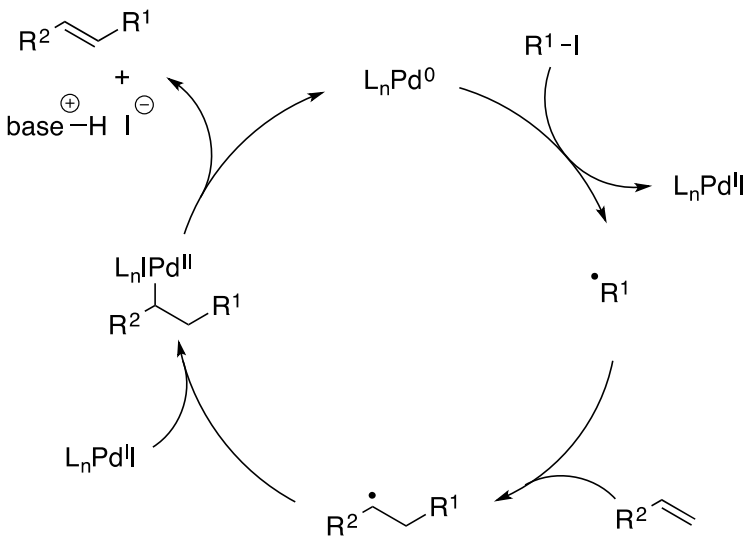


Figure 2-13. Proposed mechanism for Pd-catalyzed intermolecular alkyl-Heck cross-coupling.δ

2.6 Summary

In conclusion, we have developed a general intermolecular alkyl-Heck reaction, including the first use of non-styrenyl substrates, significantly expanding the scope of the Heck reaction and enabling the formation of useful alkene products under mild, palladium-catalyzed conditions. The reaction is applicable to a wide range of easily accessible alkenes and alkyl iodides and its utility has been demonstrated on sensitive and complex substrates. Experimental study suggests that the reaction occurs via a hybrid organometallic-radical mechanism. The generality and mild conditions provide a new attractive reaction for use in organic synthesis.

2.7 Experimental

2.7.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or a Bruker AVANCE III 600 CryoProbe (^{1}H NMR at 400 MHz or 600 MHz and ^{13}C NMR at 151 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling

constants (Hz), and integration. Mass spectra were obtained using a Micromass (now Waters Corporation, 34 Maple Street, Milford, MA 01757) Quattro-II, Triple Quadrupole Mass Spectrometer, with a Zspray nano-Electrospray source design, in combination with a NanoMate (Advion, 19 Brown Road, Ithaca, NY 14850) chip based electrospray sample introduction system and nozzle, or using an Agilent 6850 series gas chromatography system equipped with an Agilent 5973N mass selective detector. HPLC spectra were obtained using an Agilent 1200 series HPLC with detection at 210, 230, 280 and 254 nm using a Chiralpak IB column using a flow rate of 1mL per minute. The solvent system used for HPLC resolution of enantiomers was hexanes (A1) and isopropanol (B2). Thin layer chromatography (TLC) was performed on SiliaPlate 250µm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic p-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 µm) or SiliaFlash T60 silica gel (5-20 µm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, toluene, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Trifluorotoluene was sparged with argon before storage in the glovebox. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted. The sealed tubes used were purchased from Ace Glass.

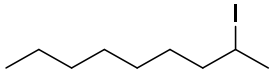
2.7.2 Substrate Preparation

Styrene, 4-methoxystyrene, 2-vinylpyridine, methyl vinyl ketone, and acrylonitrile were purchased from commercial sources, deoxygenated via multiple freeze-pump-thaw cycles, purified by vacuum transfer, and stored at -35 °C under an inert atmosphere prior to use. Crotononitrile and 4-hexen-3-one were purchased from commercial sources as mixtures of E and Z isomers. Iodocyclohexane, iodocyclopentane, and iodooctane were purchased from commercial sources, purified by distillation, and stored at -35 °C under an inert atmosphere prior to use.

4-methylstyrene, 4-trifluoromethylstyrene,[21,22] (4-vinylphenyl)methanol,[4] 4-fluorostyrene,[21,23] (4-vinylphenyl)ethanone,[4] 3-methoxystyrene,[24,25] and 2-methylstyrene[21,26] were prepared according to literature procedures. Iodocycloheptane,[27,28] trans-2-(tert-butyldimethylsilyl)-1-iodocyclohexane, [29,30,31,32] 2-iodonorbornane (as a 6:1 exo:endo mixture),[33,34] 5-(iodomethyl)dihydrofuran-2(3H)-one,[35,36] and 6-

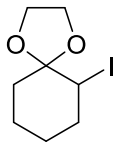
iodo-hex-1-ene[37] were prepared according to literature procedures. All physical and spectral data were in accordance with literature data.

Synthesis of 2-iodononane (22)[27]



To a 0 °C solution of PPh_3 (3.93 g, 15.0 mmol), imidazole (1.02 g, 15.0 mmol), and I_2 (3.81 g, 15.0 mmol) in CH_2Cl_2 (38 mL), 2-nonanol (1.74 mL, 10.0 mmol) was added dropwise as a solution in CH_2Cl_2 (25 mL). The reaction was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for 2 hours. It was then quenched with H_2O and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with sat. $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated in vacuo. Purified by trituration with pentane (x3) and filtered through a plug of silica to provide 1.9 g (74%) of **22** as a colorless oil. Analytical data for **22**: IR (thin film, cm^{-1}) 2956, 2925, 2855, 2360, 1459, 1376, 1196, 1135, 722; ^1H NMR (600 MHz, $CDCl_3$) δ = 4.21 (qd, *J* = 6.9, 13.4 Hz, 1 H), 1.94 (d, *J* = 6.6 Hz, 3 H), 1.86 (dtd, *J* = 4.8, 9.5, 14.1 Hz, 1 H), 1.63 (tdd, *J* = 5.1, 9.9, 14.7 Hz, 1 H), 1.49 (tdd, *J* = 4.5, 8.8, 13.3 Hz, 1 H), 1.43 - 1.24 (m, 9 H), 0.91 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 42.95, 31.80, 30.99, 29.75, 29.17, 28.96, 28.74, 22.66, 14.12; LR GC/MS calculated for $[C_9H_{19}I\text{-}I]^+$ = 127.15, found = 127.

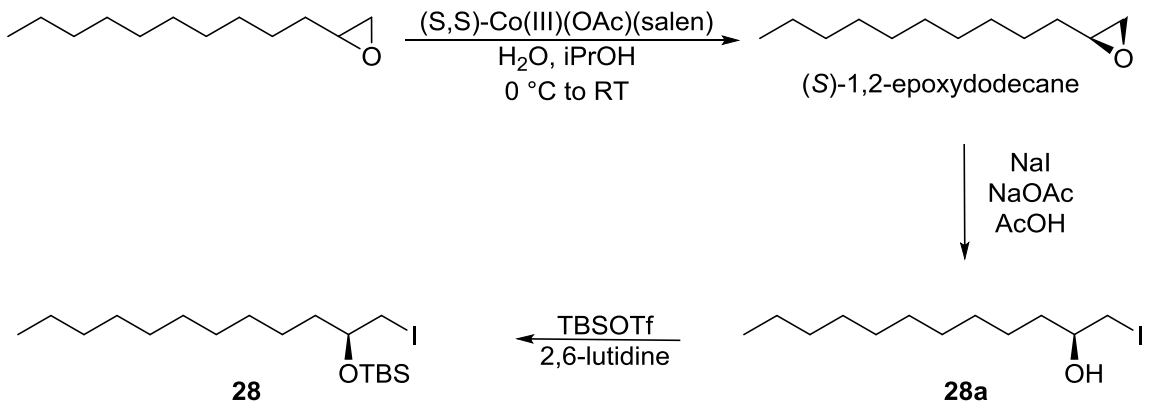
Synthesis of 6-iodo-1,4-dioxaspiro[4.5]decane (25)[38]



To a solution of cyclohexanone (1.0 mL, 10.0 mmol) and ethylene glycol (16.8 mL, 300 mmol) in acetonitrile (40 mL), I_2 (1.27 g, 5.0 mmol) and ceric ammonium nitrate (2.74 g, 5.0 mmol) were added. The reaction was heated to reflux and stirred 15 hours. The mixture was then poured into H_2O and extracted (x3) with Et_2O. The organic layers were combined and washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Purified by column chromatography (20:1 Hex:EtOAc) to provide 1.89 g (71%) of **25** as a yellow oil. Analytical data for **25**: IR (thin film, cm^{-1}) 2938, 2886, 2360, 1443, 1331, 1275, 1226, 1150, 1125, 1103, 1078, 1024, 949, 933, 882, 802, 688, 625, 520; ^1H NMR (400

MHz, $CDCl_3$) δ = 4.33 (dd, *J* = 4.5, 10.5 Hz, 1 H), 4.24 - 4.11 (m, 2 H), 4.06 - 3.95 (m, 2 H), 2.31 (dt, *J* = 4.1, 8.8 Hz, 1 H), 2.24 - 2.03 (m, 2 H), 1.78 - 1.52 (m, 4 H), 1.46 - 1.32 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 107.78, 65.49, 65.31, 38.63, 37.23, 33.67, 26.47, 23.35; LR GC/MS calculated for $[C_8H_{13}O_2I]^+$ = 267.99, found = 268.

Synthesis of (S)-tert-butyl((1-iodododecan-2-yl)oxy)dimethylsilane (28)



1) Kinetic Resolution:

The active Co(III) catalyst was prepared by dissolving (S,S)-Co(II)salen (121 mg, 0.2 mmol) in toluene (2 mL) and treating with acetic acid (23 µL, 0.4 mmol). The solution was allowed to stir at room temperature, open to air, for 1 hour, turning from red to brown. The solution was the concentrated in vacuo. The resulting black catalyst residue was dissolved in iPrOH (8.9 mL) and racemic 1,2-epoxydodecane (8.9 mL, 40.7 mmol) was added. The mixture was stirred under Ar and cooled to 0 °C. H_2O (0.4 mL) was added dropwise, and the reaction was warmed to room temperature and stirred for 24 hours. Triturating with hexanes and filtering (x2) removed the diol (white solid) to give a red oil after concentration. Purification by column chromatography (20:1 Hex:EtOAc) provided 3.19 g (43% yield) of (S)-1,2-epoxydodecane as a red oil.

2) Epoxide Opening:

To a solution of (S)-1,2-epoxydodecane (2.0 g, 10.85 mmol) and EtOAc (109 mL) under Ar were added NaI (2.1 g, 14.11 mmol), NaOAc (0.98 g, 11.94 mmol), and AcOH (0.7 mL, 11.94 mmol) sequentially. The reaction was stirred at room temperature for 24 hours and was then diluted with H_2O and brine. The

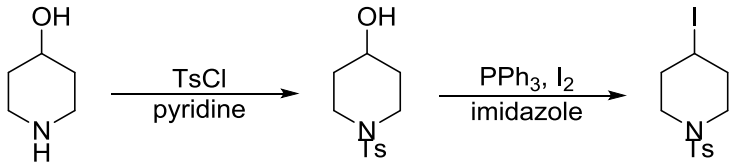
aqueous layer was separated and extracted with EtOAc (x2). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo to provide 3.31 g (98% yield) of crude **28a** as a brown oil.[39] Analytical data for **28a**: IR (thin film, cm^{-1}) 3364, 2924, 2853, 1462, 1182, 1079, 1013, 803, 721, 623; ^{1}H NMR (400 MHz , $CDCl_3$) δ = 3.58 - 3.49 (m, 1 H), 3.42 (dd, *J* = 3.4, 10.0 Hz, 1 H), 3.26 (dd, *J* = 6.8, 10.0 Hz, 1 H), 1.97 (br. s., 1 H), 1.61 - 1.52 (m, 2 H), 1.50 - 1.41 (m, 2 H), 1.39 - 1.21 (m, 14 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (151 MHz , $CDCl_3$) δ = 71.01, 36.63, 31.92, 29.61, 29.57, 29.52, 29.47, 29.34, 25.70, 22.70, 16.92, 14.15; LRMS (ESI) calculated for $[C_{12}H_{25}OI+Na]^+$ = 335.08, found = 335.37.

3) TBS Protection:

28a (3.12 g, 10.0 mmol) was added to a solution of 2,6-lutidine (3.5 mL, 30.0 mmol) in CH_2Cl_2 (60 mL) at -78 °C under Ar. To this mixture, TBSOTf was added (4.6 mL, 20.0 mmol) and the reaction was stirred for 1.5 hours. H_2O was added to quench and the solution was extracted with CH_2Cl_2 (x3). Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purified by column chromatography (hexanes) to provide 3.3 g (77%) of **28** as a colorless oil. Analytical data for **28** was in accordance with literature data.[40,41]

A racemic version of **28** was prepared in the same way starting with racemic 1,2-epoxydodecane, skipping step 1 (kinetic resolution) and proceeding with steps 2 and 3. Analytical data matched that of **28**.

Synthesis of 4-iodo-1-tosylpiperidine (17)



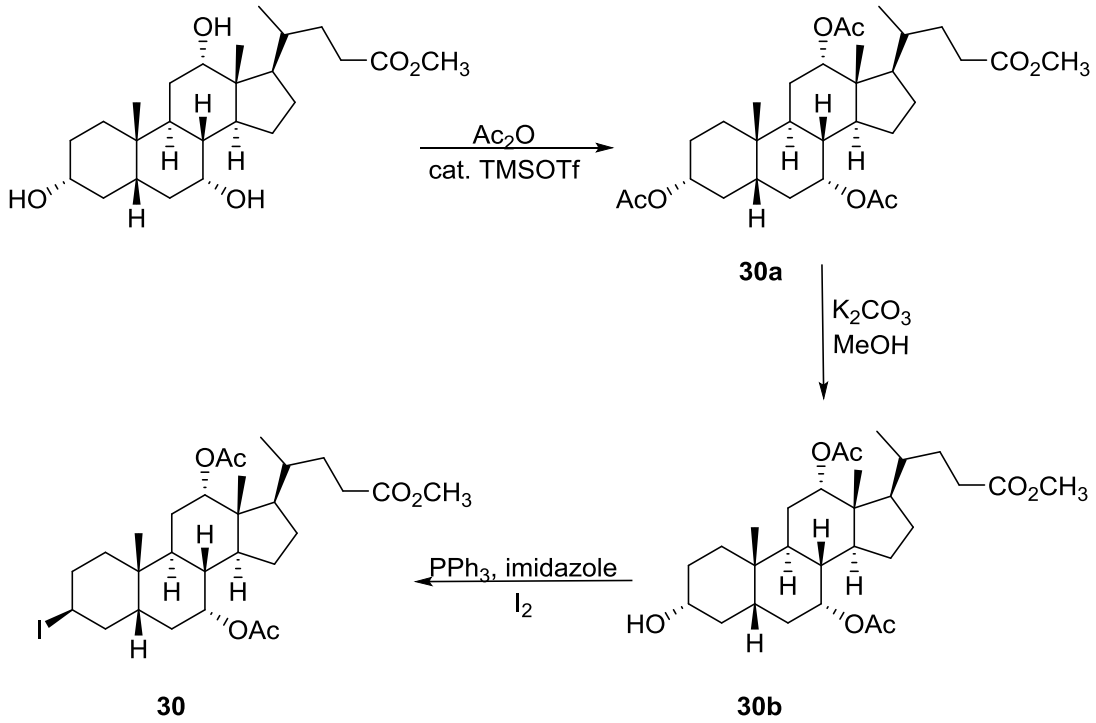
17a **17**

17 was prepared from 4-hydroxypiperidine via tosylation and iodination as described below.[42,27]

To a solution of 4-hydroxypiperidine (0.40 g, 5.0 mmol) in pyridine (25 mL) was added tosyl chloride (4.2 g, 22.5 mmol). The reaction was stirred at room temperature under argon for 36 hours, after which it was quenched with H_2O and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with 1N HCl and then 1N NaOH, dried over $MgSO_4$, and concentrated in vacuo. The crude product was then recrystallized from CH_2Cl_2/Et_2O, and further purified by column chromatography (2:1 EtOAc:Hex) providing 0.6 g (46%) of **17a** as a white solid. [43]

A solution of PPh_3 (0.46 g, 1.76 mmol), imidazole (0.12 g, 1.76 mmol), and I_2 (0.45 g, 1.76 mmol) in CH_2Cl_2 (4.4 mL) was stirred at 0 °C under Ar for 15 minutes. **17a** (0.3 g, 1.17 mmol) was added dropwise as a solution in CH_2Cl_2 (3 mL), and the reaction was stirred at 0 °C for 30 minutes. It was then warmed to room temperature and stirred for 4 hours. Water was added to quench and it was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution, dried over $MgSO_4$, and concentrated in vacuo. Purified by column chromatography (2:1 Hex:EtOAc) to provide 354 mg (82%) of **17** as a white solid.[44]

Synthesis of Methyl 7α,12α-diacetoxy-3β-iodo-5β-cholan-24-ate (30)



30 was prepared from methyl cholate via acetylation, selective deacetylation, and iodination as described below.[45,46]

To a solution of acetic anhydride (2.0 mL, 21.2 mmol) and TMSOTf (51 µL, 0.28 mmol) in CH_2Cl_2 (12 mL), was added methyl cholate (2.0 g, 4.7 mmol). The reaction was stirred 12 hours at room temperature, and then quenched with $NaHCO_3$. It was extracted with CH_2Cl_2 (x3), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purified by recrystallization from acetone/hexane to provide 2.25 g (87%) of **30a** as a white powder.

To a solution of **30a** (1.5 g, 2.73 mmol) in dry MeOH (23 mL) was added K_2CO_3 (0.68 g, 4.91 mmol) and stirred at room temperature for 36 hours. The reaction was then quenched with AcOH (1.5 mL) and concentrated in vacuo. The residue was redissolved in EtOAc, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. A portion of the resulting sticky white solid (500 mg) was purified by column chromatography (1:1 Hex:EtOAc) to provide 340 mg (68% recovery) of **30b** as a white solid.

To a solution of **30b** (0.3 g, 0.59 mmol) in a 4:1 benzene:acetonitrile mixture (10 mL), PPh_3 (0.84 g, 3.2 mmol) and imidazole (0.23 g, 3.4 mmol) were added. After 10 minutes, I_2 (0.75 g, 2.95 mmol) was added portionwise and then stirred for one hour. The reaction mixture was poured into H_2O with a few drops of 30% H_2O_2 and extracted with EtOAc. The organic layers were washed with sat. $Na_2S_2O_5$, dried over $MgSO_4$, and concentrated in vacuo. Purified by column chromatography (5:1 Hex:EtOAc) to provide 363 mg (73%) of **30** as a white solid.

2.7.3 General Procedure for Alkyl-Heck Reaction

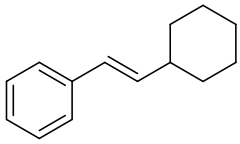
In a glovebox, the alkyl iodide (1.0 equiv), alkene (1.5 equiv), $PdCl_2$(dppf) (0.1 equiv), Cy_2NMe (2.0 equiv), and $PhCF_3$ (0.5 M) were combined in a sealed tube. After removing the tube from the glovebox it was heated in an oil bath at 100 °C for 14 hours (unless otherwise noted). The reaction mixture was diluted with dichloromethane or Et_2O and washed with 1 N HCl. The aqueous layer was then extracted with dichloromethane or Et_2O (x3). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The resulting alkene was purified by flash chromatography with the specified solvent system.

Table 2-1, entry 11, Ambient light control studies

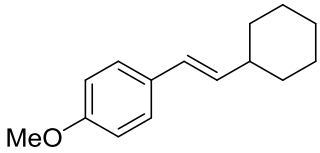
This reaction was performed using the general procedure, only the sealed tube was wrapped in aluminum foil and kept in the dark. When the reaction was stopped at 14 hours, a 45% ^{1}H NMR yield was obtained, and the reaction did not go to full conversion (a significant amount of iodocyclohexane remained). When the reaction was allowed to run for 24 hours, full conversion was obtained along with a 69% ^{1}H NMR yield, consistent with reactions run in exposure to background light without foil. This indicates a faster activation in the presence of light. However, the same rate decrease in the absence of light was not seen using styrene as the coupling partner.

2.7.4 Alkyl-Heck Product Characterization

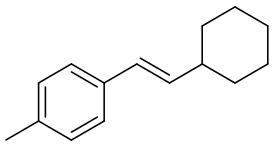
Table 2-2 – entries 1-16:



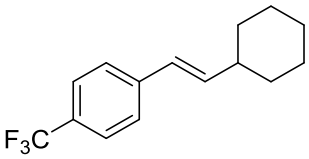
(*E*)-(2-cyclohexylvinyl)benzene (**3**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and styrene (151 µL, 1.31 mmol). The resulting alkene was purified by flash chromatography (hexanes) to afford **3** (137.1 mg, 0.74 mmol, 84% yield) as a colorless oil. All analytical data for **3** was in accordance with literature data.[47]



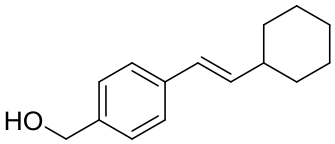
(E)-1-(2-cyclohexylvinyl)-4-methoxybenzene (**4**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and 4-methoxystyrene (176 mg, 1.31 mmol). The resulting alkene was purified by column chromatography (20:1 Hex:EtOAc). To remove phosphine, CuCl (12 mg) was added to the mixture in CH_2Cl_2,[48] and filtered through silica to afford **4** (123.9 mg, 0.57 mmol, 66% yield) as a colorless oil. All analytical data for **4** was in accordance with literature data.[49]



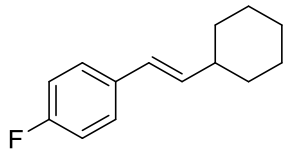
(E)-1-(2-cyclohexylvinyl)-4-methylbenzene (**5**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and 4-methylstyrene (155 mg, 1.31 mmol). The resulting alkene was purified by column chromatography (hexanes) to afford **5** (112.3 mg, 0.56 mmol, 64% yield) as a pale orange oil. All analytical data for **5** was in accordance with literature data.[8]



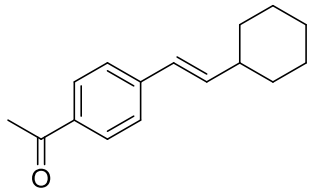
(E)-1-(2-cyclohexylvinyl)-4-(trifluoromethyl)-benzene (**6**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and 4-trifluoromethylstyrene (225.5 mg, 1.31 mmol). The resulting alkene was purified by flash chromatography (hexanes) to afford **6** (181.9 mg, 0.72 mmol, 82% yield) as white crystals. Analytical data for **6**: IR (thin film, cm^{-1}) 2927, 2853, 1615, 1449, 1413, 1325, 1164, 1124, 1067, 1015, 967, 856, 810, 596; ^{1}H NMR (400 MHz ,$CDCl_3$) δ = 7.61 (d, *J* = 8.3 Hz, 0.12 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.37 (d, *J* = 8.1 Hz, 0.12 H), 6.40 (d, *J* = 16.0 Hz, 1 H), 6.30 (dd, *J* = 6.6, 16.0 Hz, 1 H), 5.62 (t, *J* = 11.0 Hz, 0.06 H), 2.61 - 2.49 (m, 0.06 H), 2.25 - 2.11 (m, 1 H), 1.91 - 1.67 (m, 5 H), 1.44 - 1.15 (m, 5 H); ^{13}C NMR (151 MHz ,$CDCl_3$) d = 141.57, 139.61, 128.85-128.42 (q, $^{2}J_{CF}$ = 33 MHz), 126.12, 126.05, 125.44-125.36 (q, $^{3}J_{CF}$ = 5 MHz), 127.03-121.63 (q, $^{1}J_{CF}$ = 270 MHz), 41.22, 32.75, 26.10, 25.97; LR GC/MS calculated for $[C_{15}H_{17}F_3]^+$ = 254.13, found = 254.



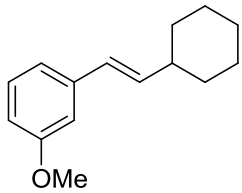
(E)-(4-(2-cyclohexylvinyl)phenyl)methanol (**7**) was synthesized according to the general procedure using iodocyclohexane (63.5 µL, 0.49 mmol) and (4-vinylphenyl)methanol (100 mg, 0.74 mmol) and run for 15 hours. The resulting alkene was purified by flash chromatography (4:1 Hex:EtOAc) to afford **7** as an inseparable mixture with remaining (4-vinylphenyl)methanol in 64% yield, determined by using the ^{1}H NMR internal standard 1,3,5-trimethoxybenzene. All analytical data for **7** was in accordance with literature data.[4]



1-(2-cyclohexylvinyl)-4-fluorobenzene (**8**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and 4-fluorostyrene (160 mg, 1.31 mmol) for 15 hours. The resulting alkene was purified by flash chromatography (hexanes) to afford **8** (135.7 mg, 0.66 mmol, 76% yield, 5:1 E:Z) as a colorless oil. All analytical data for **8** was in accordance with literature data.[50]

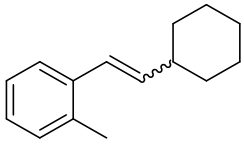


1-(4-(2-cyclohexylvinyl)phenyl)ethanone (**9**) was synthesized according to the general procedure using iodocyclohexane (78 µL, 0.60 mmol) and (4-vinylphenyl)ethanone (131.6 mg, 0.90 mmol). The resulting alkene was purified by flash chromatography (30:1 Hex:EtOAc) to afford **9** as an inseparable mixture with remaining (4-vinylphenyl)ethanone in 61% yield (4:1 E:Z), determined by using the ^{1}H NMR internal standard 1,3,5-trimethoxybenzene. All analytical data for **9** was in accordance with literature data.[4]

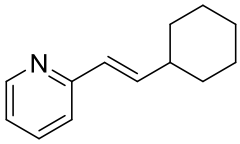


(E)-1-(2-cyclohexylvinyl)-3-methoxybenzene (**10**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and 3-methoxystyrene (176 mg, 1.31 mmol) for 16 hours. The resulting alkene was purified by flash chromatography (50:1 Hex:EtOAc) to afford **10** (126.5 mg, 0.58 mmol, 67% yield) as a pale yellow oil. Analytical data for **10**: IR (thin film, cm^{-1}) 2923, 2850, 1601, 1581, 1489, 1450, 1287, 1264, 1156, 1048, 966, 872, 773, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 (t, *J* = 7.9 Hz, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.93 - 6.90 (m, 1 H), 6.77 (dd, *J* = 2.4, 8.2 Hz, 2 H), 6.35 (d, *J* = 16.0 Hz, 1 H), 6.20 (dd, *J* = 6.8, 16.0 Hz, 1 H), 3.84 (s, 3 H), 2.21 - 2.09 (m, 1 H), 1.88 - 1.67 (m, 4 H), 1.43 -

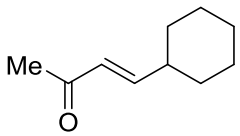
1.14 (m, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 159.78, 139.56, 137.23, 129.43, 127.11, 118.66, 112.42, 111.21, 55.20, 41.16, 32.94, 26.18, 26.06; LRMS (ESI) calculated for $[C_{15}H_{20}O+H]^+$ = 217.15, found = 217.13.



(E/Z)-1-(2-cyclohexylvinyl)-2-methylbenzene (**11**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and 2-methylstyrene (155 mg, 1.31 mmol) for 15 hours. The resulting alkene was purified by flash chromatography (hexanes) to afford **11** (126.3 mg, 0.63 mmol, 72% yield, 1:1 E:Z) as a colorless oil. All analytical data for **11** was in accordance with literature data.[51]

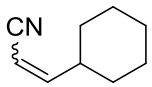


(E)-2-(2-cyclohexylvinyl)pyridine (**12**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and 2-vinylpyridine (141 µL, 1.31 mmol). The resulting alkene was purified by column chromatography (10:1 Hex:EtOAc) to afford **12** (56.6 mg, 0.30 mmol, 35% yield) as a pale yellow oil. Analytical data for **12**: IR (thin film, cm^{-1}) 3003, 2923, 2850, 1649, 1586, 1563, 1468, 1447, 1430, 1301, 1149, 970, 889, 841, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 4.6 Hz, 1 H), 7.61 (dt, *J* = 1.7, 7.7 Hz, 1 H), 7.26 (d, *J* = 7.8 Hz, 1 H), 7.12 - 7.07 (m, 1 H), 6.72 (dd, *J* = 7.0, 15.8 Hz, 1 H), 6.46 (dd, *J* = 1.1, 15.8 Hz, 1 H), 2.27 - 2.16 (m, 1 H), 1.90 - 1.65 (m, 5 H), 1.41 - 1.16 (m, 5 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.36, 149.41, 141.42, 136.38, 127.43, 121.49, 121.11, 40.99, 32.62, 26.14, 26.01; LRMS (ESI) calculated for $[C_{13}H_{17}N+H]^+$ = 188.14, found = 188.07.

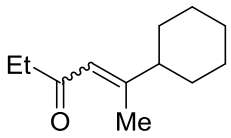


(E)-4-cyclohexylbut-3-en-2-one (**13**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and methyl vinyl ketone (106 µL, 1.31 mmol). $[Pd(allyl)Cl]_2$ (16.1

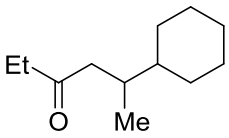
mg, 0.044 mmol) and PPh_2tBu (84.8 mg, 0.35 mmol) was used as catalyst and K_3PO_4 (369 mg, 1.74 mmol) was used as base and the reaction was run for 5 hours. The resulting alkene was purified by flash chromatography (20:1 Hex:EtOAc) to afford **13** (46.8 mg, 0.31 mmol, 35% yield) as a pale orange oil. All analytical data for **13** was in accordance with literature data.[52]



(E/Z)-3-cyclohexylacrylonitrile (**14**) was synthesized according to the general procedure using iodocyclohexane (55 µL, 0.42 mmol) and acrylonitrile (41 µL, 0.63 mmol). K_3PO_4 (178 mg, 0.84 mmol) was used as base. The resulting alkene was purified by column chromatography (10:1 Hex:EtOAc) to afford **14** (40.4 mg, 0.30 mmol, 70% yield) as a yellow oil (1:2.5 E:Z mixture, assigned based on coupling constants of vinyl protons). Analytical data for **14**: IR (thin film, cm^{-1}) 2928, 2854, 2220, 1627, 1558, 1449, 1340, 1237, 1133, 970, 889, 746; ^1H NMR (400 MHz, $CDCl_3$, E/Z signals) δ = 6.69 (dd, *J* = 6.7, 16.5 Hz, 0.4 H)/6.33 (t, *J* = 10.4 Hz, 1 H), 5.28 (d, *J* = 16.6 Hz, 0.4 H)/5.22 (d, *J* = 11.0 Hz, 1 H), 2.71 - 2.58 (m, 1 H), 2.16 (s, 0.4 H), 1.84 - 1.66 (m, 7 H), 1.47 - 1.07 (m, 7 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.89, 160.18, 117.96, 116.24, 97.52, 97.18, 41.47, 41.10, 31.76, 31.21, 25.70, 25.56, 25.47, 25.13; LRMS (ESI) calculated for $[C_9H_{13}N+H]^+$ = 136.11, found = 136.04.



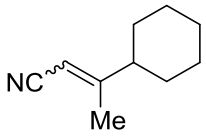
15



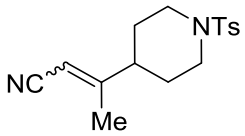
15a

(E/Z)-5-cyclohexylhex-4-en-3-one (**15**) was synthesized according to the general procedure using iodocyclohexane (2.0 equiv, 226 µL, 1.74 mmol) and 4-hexen-3-one (1.0 equiv, 99.5 µL, 0.87 mmol). K_3PO_4 (369 mg, 1.74 mmol) was used as base, and $Pd(PPh_3)_4$ (100.5 mg, 0.087 mmol) was used as catalyst. The resulting alkene was purified by flash chromatography (50:1 Hex:EtOAc) to afford a mixture of PPh_3 and **15**. To remove PPh_3, CuCl (5 mg) was added to the mixture in CH_2Cl_2,[48] and filtered through silica to provide **15** (85.75 mg, 0.48 mmol, 55% yield) as a pale orange oil (2:1 E:Z mixture), as an in

separable mixture with **15a** (4% yield). Analytical data for **15**: IR (thin film, cm^{-1}) 2927, 2853, 1686, 1014, 1448, 1375, 1121, 1025, 894, 849; ^1H NMR (400 MHz, $CDCl_3$, E/Z signals) δ = 6.06 (s, 1 H)/5.98 (s, 0.5 H), 3.65 - 3.54 (m, 0.5 H), 2.52 - 2.40 (m, 3 H), 2.13 (s, 3 H), 2.02 - 1.91 (m, 1 H), 1.81 (s, 1.5 H), 1.86 - 1.65 (m, 8 H), 1.48 - 1.13 (m, 9 H), 1.11 - 1.03 (m, 4.5 H), 0.84 (**15a**, d, *J* = 6.8 Hz, 0.3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 202.36, 201.32, 163.79, 163.14, 122.99, 121.15, 48.96, 40.40, 37.54, 37.50, 31.39, 30.92, 26.42, 26.23, 26.20 26.12, 21.07, 17.84, 8.21, 8.06; LRMS (ESI) calculated for $[C_{12}H_{20}O+H]^+$ = 181.16, found 181.0.



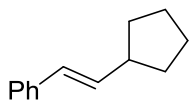
(E/Z)-3-cyclohexylbut-2-enenitrile (**16**) was synthesized according to the general procedure using iodocyclohexane (113 µL, 0.87 mmol) and crotononitrile (212 µL, 1.31 mmol, 3 equiv). K_3PO_4 (369 mg, 1.74 mmol) was used as base, and $Pd(PPh_3)_4$ (100.5 mg, 0.087 mmol) was used as catalyst. To remove PPh_3, CuCl (30 mg) was added to the mixture in CH_2Cl_2,[48] and filtered through silica. The resulting alkene was purified by column chromatography (100:1 Hex:EtOAc) to afford **16** (103.5 mg, 0.69 mmol, 80% yield) as a colorless oil (2:1 E:Z mixture, assigned based on 1D NOESY NMR data). Analytical data for **16**: IR (thin film, cm^{-1}) 2929, 2855, 2216, 1621, 1448, 1381, 1028, 890, 811, 533; ^1H NMR (400 MHz, $CDCl_3$, E/Z signals) δ = 5.10 (br. s, 1 H)/5.03 (br. s, 0.55 H), 2.82 - 2.73 (m, 0.55 H)/2.09 - 2.00 (m, 1 H), 2.05 (s, 3 H), 1.85 - 1.59 (m, 8 H), 1.72 (s, 1.65 H), 1.45 - 1.11 (m, 8 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.16, 170.07, 117.67, 116.92, 94.04, 93.61, 46.61, 44.63, 31.17, 30.62, 26.11, 25.87, 25.85, 25.74, 19.50; LRMS (ESI) calculated for $[C_{10}H_{15}N+H]^+$ = 150.13, found = 150.11.



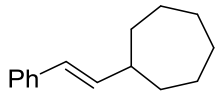
(E/Z)-3-(1-tosylpiperidin-4-yl)but-2-enenitrile (**18**) was synthesized according to the general procedure using **17** (105.9 mg, 0.29 mmol) and crotononitrile (70.8 µL, 0.87 mmol, 3 equiv). K_3PO_4 (123 mg, 0.58

mmol) was used as base and $Pd(PPh_3)_4$ (33.5 mg, 0.029 mmol) was used as catalyst. The resulting alkene was purified by flash chromatography (2:1 Hex:EtOAc) to afford **18** (69.6 mg, 0.23 mmol, 79% yield) as an orange solid (~2:1 E:Z mixture). Analytical data for **18**: IR (thin film, cm^{-1}) 3632, 3545, 3059, 2925, 2851, 2216, 1623, 1597, 1446, 1333, 1251, 1162, 1093, 1052, 931, 816, 726, 582, 548; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.36 (t, *J* = 7.8 Hz, 2 H), 5.14 - 5.09 (m, 1 H), 3.92 (br. s., 1 H), 3.89 (br. s., 1 H), 2.74 - 2.63 (m, 0.5 H), 2.47 (s, 1.5 H), 2.45 (s, 1.5 H), 2.27 (ddt, *J* = 2.3, 5.3, 12.0 Hz, 2 H), 2.02 (s, 1.5 H), 2.00 - 1.94 (m, 0.5 H), 1.85 (s, 1.5 H), 1.80 - 1.53 (m, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.09, 166.64, 143.90, 143.76, 132.88, 132.42, 129.79, 129.75, 129.73, 127.71, 116.88, 116.35, 95.94, 95.32, 46.09, 46.06, 43.75, 41.82, 29.48, 28.98, 21.56, 19.26; LRMS (ESI) calculated for $[C_{16}H_{20}N_2O_2S+H]^+$ = 305.13, found = 305.13.

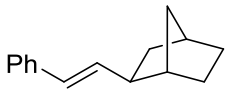
Table 2-3 – entries 1-8:



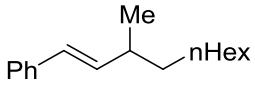
(2-cyclopentylvinyl)benzene (**19**) was synthesized according to the general procedure using iodocyclopentane (100.6 µL, 0.87 mmol) and styrene (151 µL, 1.31 mmol) for 15 hours. The resulting alkene was purified by column chromatography (hexanes) to afford **19** (105.8 mg, 0.61 mmol, 70% yield, 6:1 E:Z) as a colorless oil. All analytical data for **19** was in accordance with literature data.[50]



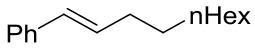
(E)-(2-cycloheptylvinyl)benzene (**20**) was synthesized according to the general procedure using iodocycloheptane (195 mg, 0.87 mmol) and styrene (151 µL, 1.31 mmol). The resulting alkene was purified by column chromatography (hexanes) to afford **20** (132.0 mg, 0.66 mmol, 76% yield) as a colorless oil. All analytical data for **20** was in accordance with literature data.[50]



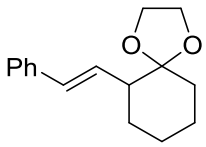
(exo)-2-(styryl)bicycle[2.2.1]heptane (**21**) was synthesized according to the general procedure using 2-iodonorbornane (193 mg, 0.87 mmol, 6:1 exo:endo) and styrene (151 µL, 1.31 mmol). The resulting alkene was purified by column chromatography (hexanes) to afford **21** (139.5 mg, 0.70 mmol, 80% yield, 7:1 E:Z) as a colorless oil. All analytical data for **21** was in accordance with literature data.[53]



(3-methyldec-1-en-1-yl)benzene (**23**) was synthesized according to the general procedure using 2-iodononane (**22**) (221 mg, 0.87 mmol) and styrene (151 µL, 1.31 mmol) for 15 hours. The resulting alkene was purified by column chromatography (hexanes) to afford **23** (148.9 mg, 0.65 mmol, 74% yield, 7:1 E:Z) as a colorless oil. All analytical data for **23** was in accordance with literature data.[54]

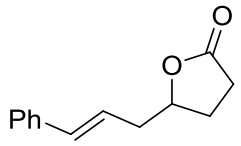


(E)-dec-1-en-1-ylbenzene (**24**) was synthesized according to the general procedure using iodooctane (157 µL, 0.87 mmol) and styrene (151 µL, 1.31 mmol), and heated to 130 °C. The resulting alkene was purified by column chromatography (hexanes) to afford **24** (85.8 mg, 0.40 mmol, 46% yield) as a pale yellow oil. All analytical data for **24** was in accordance with literature data.[55]

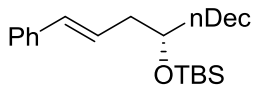


(E)-6-styryl-1,4-dioxaspiro[4.5]decane (**26**) was synthesized according to the general procedure using **25** (233 mg, 0.87 mmol) and styrene (151 µL, 1.31 mmol). The resulting alkene was purified by column chromatography (50:1 hexanes:EtOAc) to afford **26** (168.8 mg, 0.69 mmol, 79% yield) as a colorless oil.

Analytical data for **26**: IR (thin film, cm^{-1}) 3025, 2934, 2861, 2672, 1598, 1493, 1446, 1351, 1214, 1161, 1087, 967, 925, 871, 748, 695, 523; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 7.6 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 6.47 (d, *J* = 16.1 Hz, 1 H), 6.27 (dd, *J* = 7.9, 16.0 Hz, 1 H), 4.00 - 3.86 (m, 4 H), 2.48 (ddd, *J* = 4.2, 7.8, 11.5 Hz, 1 H), 1.86 - 1.45 (m, 7 H), 1.40 - 1.28 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.91, 130.96, 130.01, 128.48, 126.95, 126.11, 110.23, 65.31, 65.05, 49.26, 35.52, 30.50, 24.59, 23.95; LRMS (ESI) calculated for $[C_{16}H_{20}O_2+H]^+$ 245.15, found 245.08.



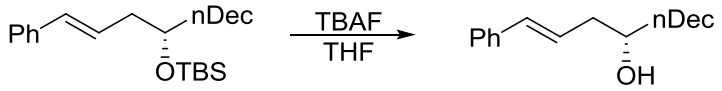
(E)-5-(3-phenylallyl)dihydrofuran-2(3H)-one (**27**) was synthesized according to the general procedure using 5-(iodomethyl)dihydrofuran-2(3H)-one (196.6 mg, 0.87 mmol) and styrene (151 µL, 1.31 mmol), heated to 130 °C, to afford **27** in 42% yield, determined by using the ^{1}H NMR internal standard 1,3,5-trimethoxybenzene (due to inability to separate from byproducts). The resulting alkene was purified by column chromatography (5:1 Hex:EtOAc) to afford **27** as a colorless oil. Analytical data for **27**: IR (thin film, cm^{-1}) 3025, 2922, 2360, 1770, 1452, 1354, 1260, 1176, 1022, 969, 916, 800, 745, 695, 533; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 - 7.30 (m, 4 H), 7.27 - 7.23 (m, 1 H), 6.54 (d, *J* = 15.9 Hz, 1 H), 6.21 (td, *J* = 7.2, 15.8 Hz, 1 H), 4.66 (quin, *J* = 6.8 Hz, 1 H), 2.73 - 2.51 (m, 4 H), 2.42 - 2.32 (m, 1 H), 2.01 (dtd, *J* = 7.6, 9.4, 12.7 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.09, 136.86, 133.96, 128.62, 127.60, 126.20, 123.34, 80.02, 38.73, 28.71, 27.15; LRMS (ESI) calculated for $[C_{13}H_{14}O_2+H]^+$ = 203.11, found = 203.06.



(S)-tert-butyldimethyl((1-phenyltetradec-1-en-4-yl)oxy)silane (**29**) was synthesized according to the general procedure using **28** (371 mg, 0.87 mmol) and styrene (151 µL, 1.31 mmol), and heated to 130 °C for 15 hours. The resulting alkene was purified by column chromatography (hexanes) to afford **29** (179.9 mg, 0.45 mmol, 51% yield, 4:1 E:Z) as a pale yellow oil. Analytical data for **29**: IR (thin film, cm^{-1}) 2927,

2855, 1465, 1363, 1253, 1092, 965, 835, 774, 741, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 7.8 Hz, 2 H), 7.32 (t, *J* = 7.8 Hz, 2 H), 7.22 (t, *J* = 7.1 Hz, 1 H), 6.41 (d, *J* = 16.1 Hz, 1 H), 6.25 (td, *J* = 7.1, 16.1 Hz, 1 H), 3.77 (quin, *J* = 5.7 Hz, 1 H), 2.38 (dd, *J* = 6.1, 12.2 Hz, 2 H), 1.53 - 1.44 (m, 2 H), 1.35 - 1.24 (m, 16 H), 0.95 - 0.87 (m, 12 H), 0.08 (s, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.79, 131.72, 128.48, 127.51, 126.87, 125.96, 72.35, 41.13, 37.15, 31.93, 29.79, 29.66, 29.63, 29.37, 25.93, 25.41, 22.71, 18.18, 14.15, 1.04, -4.34, -4.48; LRMS (ESI) calculated for $[C_{26}H_{46}OSi+H]^+$ = 403.34, found = 403.31.

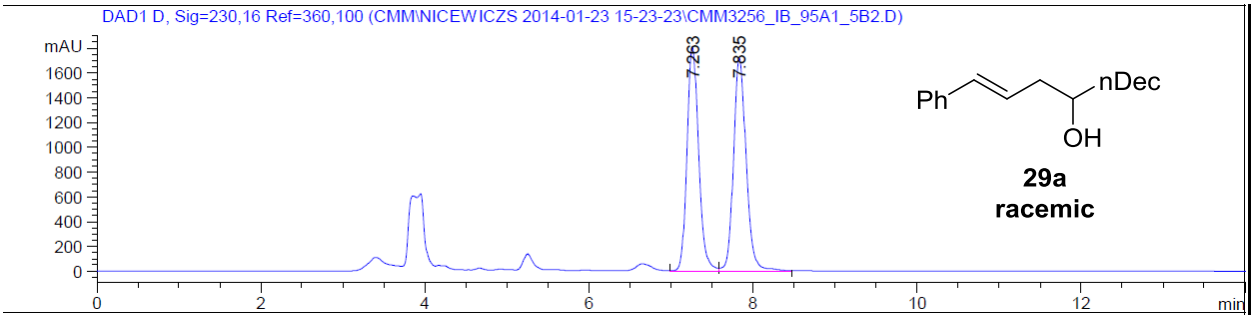
Enantiopurity was determined by first deprotecting **29** by the following procedure:



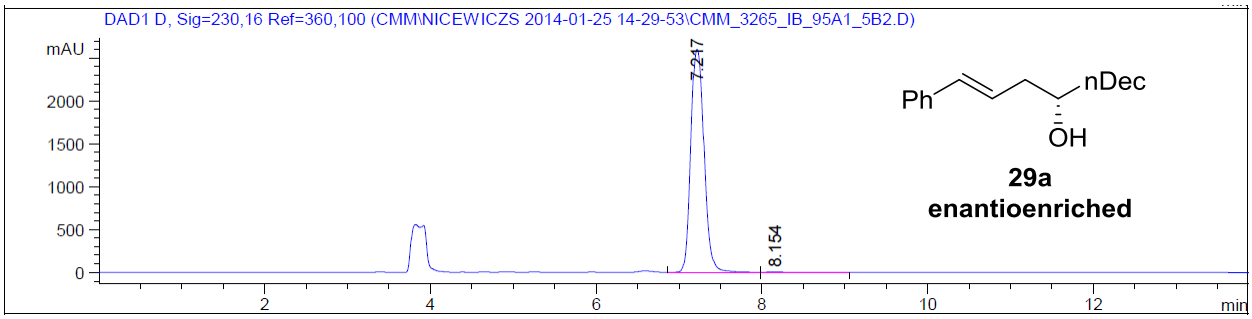
29a

A solution of **29** (50 mg, 0.13 mmol) was dissolved in THF (1.25 mL) and added to a stirred solution of tetrabutylammonium fluoride (0.25 mL, 0.25 mmol) in THF (0.25 mL) under Ar at room temperature. The reaction was allowed to stir overnight 15 hours and was then quenched with sat. NH_4Cl, extracted with EtOAc (x3) and dried over $MgSO_4$. Concentration in vacuo, followed by purification by column chromatography (10:1 Hex:EtOAc) provided **29a** (21.1 mg, 0.073 mmol, 58% yield) as a white solid. Analytical data for **29a**: IR (thin film, cm^{-1}) 3407, 2920, 2850, 2360, 1466, 1075, 965, 908, 735, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 7.2 Hz, 2 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.24 (t, *J* = 7.2 Hz, 1 H), 6.51 (d, *J* = 15.9 Hz, 1 H), 6.27 (td, *J* = 7.2, 16.0 Hz, 1 H), 3.80 - 3.71 (m, 1 H), 2.52 - 2.43 (m, 1 H), 2.38 - 2.28 (m, 1 H), 1.62 (m, 2 H), 1.58 - 1.42 (m, 2 H), 1.42 - 1.24 (m, 14 H), 0.91 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.27, 133.10, 128.55, 127.26, 126.42, 126.10, 71.20, 41.17, 36.96, 31.94, 29.69, 29.64, 29.36, 25.74, 22.71, 14.14; LRMS (ESI) calculated for $[C_{20}H_{32}O+H]^+$ = 289.25; found = 289.21; HPLC: Chiralpak IB, 95:5 Hexanes/IPA, er: 99.6:0.4.

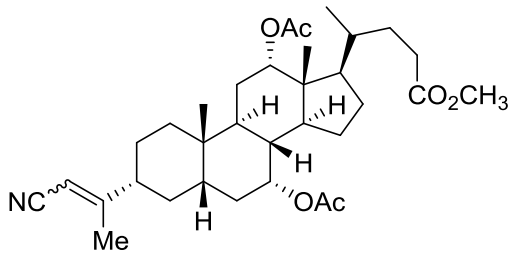
A racemic version of **29** was prepared in an analogous way, by reaction of the racemic version of **28** with styrene following the general procedure, and subsequent deprotection following the procedure above. All analytical data matched that of **29** and **29a**. HPLC: Chiralpak IB, 95:5 Hexanes/IPA, er: 51:49.



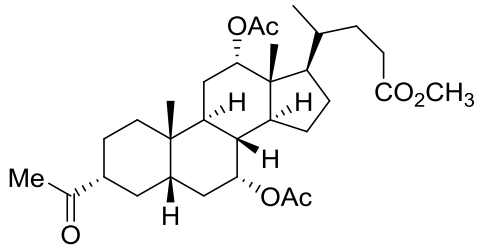
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.263	VV	0.1531	1.78710e4	1810.89307	49.0876
2	7.835	VV	0.1658	1.85354e4	1719.10120	50.9124



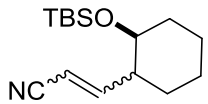
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.217	VV	0.1784	2.91023e4	2603.73315	99.6421
2	8.154	VB	0.2428	104.53123	6.19698	0.3579



Methyl-7α,12α-diacetoxy-3α-(1-cyanoprop-1-en-2-yl)-5β-cholan-24-ate (**31**) was synthesized according to the general procedure using **30** (185 mg, 0.30 mmol) and crotononitrile (73.2 µL, 0.90 mmol, 3 equiv). K_3PO_4 (127.4 mg, 0.60 mmol) was used as base and $Pd(PPh_3)_4$ (34.6 mg, 0.03 mmol) was used as catalyst and reaction was run for 17 hours. The resulting alkene was purified by flash chromatography (2:1 Hex:EtOAc) to afford **31** (113.5 mg, 0.20 mmol, 68% yield, ~2:1 E:Z, 10:1 d.r.) as an orange solid. Analytical data for **31**: IR (thin film, cm^{-1}) 2950, 2870, 2360, 2215, 1733, 1621, 1438, 1376, 1246, 1170, 1054, 825, 734, 701; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.13 - 5.06 (m, 2 H), 4.95 - 4.90 (m, 1 H), 3.67 (s, 3 H), 2.68 - 2.59 (m, 0.3 H), 2.40 - 2.31 (m, 1 H), 2.26 - 2.13 (m, 2 H), 2.12 - 2.10 (m, 3 H), 2.08 - 2.06 (m, 3 H), 2.05 - 2.03 (m, 2 H), 2.03 - 1.87 (m, 5 H), 1.85 (d, *J* = 1.5 Hz, 1 H), 1.83 - 1.02 (m, 17 H), 0.97 - 0.93 (m, 3 H), 0.83 (dd, *J* = 2.4, 6.4 Hz, 3 H), 0.77 - 0.71 (m, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.57, 174.55, 170.39, 170.18, 170.15, 169.30, 168.83, 117.50, 116.66, 94.59, 93.75, 75.46, 75.42, 70.93, 70.85, 51.57, 47.35, 45.45, 45.01, 44.99, 43.34, 43.32, 42.31, 41.90, 37.74, 37.70, 36.36, 36.12, 34.64, 34.61, 34.51, 34.32, 33.76, 32.89, 31.39, 31.30, 30.87, 30.76, 30.75, 28.88, 28.83, 27.20, 27.17, 25.68, 25.39, 25.32, 24.91, 22.95, 22.86, 22.81, 22.80, 21.61, 21.53, 21.31, 21.21, 20.09, 19.24, 17.51, 12.22, 12.21; LRMS (ESI) calculated for $[C_{33}H_{49}NO_6+H]^+$ = 556.36, found = 556.31. The stereochemical assignment of the product was made by performing an oxidative cleavage of **31** to form the ketone (**32**) and comparing to literature data.[38] The large coupling constants (12.2 Hz) of the proton alpha to the carbonyl in the major product is indicative of axial-axial interactions, placing the ketone (and by analogy, acrylonitrile) group in an equatorial position.

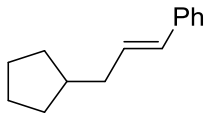


Methyl-7α,12α-diacetoxy-3α-acetyl-5β-cholan-24-ate (**32**). To a solution of SI-36 in a 2:1 CH_3CN:H_2O mixture (0.15 M), $NaIO_4$ (193 mg, 0.90 mmol) and $RuCl_3$ xH_2O (40% Ru, 1.3 mg, 0.005 mmol) were added at 0 °C. The reaction was then stirred at room temperature for 6 hours. The mixture was diluted with H_2O, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo.[39] Purified by column chromatography (2:1 Hex:EtOAc) to provide **32** (37 mg, 0.07 mmol, 69 % yield, 10:1 d.r.) as a white solid. Analytical data for **32**: IR (thin film, cm^{-1}) 2950, 2870, 1734, 1438, 1376, 1245, 1171, 1024, 938, 755, 606; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.07 (t, *J* = 2.8 Hz, 1 H), 4.90 - 4.87 (m, 1 H), 3.66 (s, 3 H), 2.58 - 2.54 (m, 0.1 H), 2.34 (ddd, *J* = 5.1, 10.2, 15.5 Hz, 1 H), 2.29 - 2.22 (m, *J* = 12.2, 3.1 Hz, 1 H), 2.22 - 2.17 (m, 1 H), 2.13 (s, 3 H), 2.12 (s, 3 H), 2.08 (s, 3 H), 2.05 - 1.94 (m, 0 H), 1.90 - 1.71 (m, 0 H), 1.69 - 1.58 (m, 0 H), 1.54 - 1.19 (m, 0 H), 0.93 (s, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 0.72 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 211.84, 174.53, 170.66, 170.61, 75.37, 70.79, 52.48, 51.51, 47.31, 45.03, 43.33, 42.14, 37.76, 36.23, 34.67, 34.59, 31.38, 31.12, 30.86, 30.75, 28.88, 28.13, 27.16, 25.51, 23.35, 23.01, 22.79, 21.63, 21.44, 17.48, 12.21. LRMS (ESI) calculated for $[C_{31}H_{48}O_7+Na]^+$ = 555.33, found = 555.31.



(E/Z)-3-(2-((tert-butyldimethylsilyl)oxy)cyclohexyl)acrylonitrile (**33**) was synthesized according to the general procedure using trans-2-(tert-butyldimethylsilyl)-1-iodocyclohexane (102.1 mg, 0.30 mmol) and acrylonitrile (30 µL, 0.45 mmol). K_3PO_4 (127 mg, 0.60 mmol) was used as base and the reaction was run for 15 hours. The resulting alkene was purified by column chromatography (50:1 Hex:EtOAc) to afford **33** (48.5 mg, 0.18 mmol, 61% yield) as a yellow oil (1:2 E:Z, 1:1 dr). Analytical data for **33**: IR (thin film, cm^{-1}) 2931, 2857, 2360, 2221, 1630, 1466, 1363, 1254, 1099, 1058, 1021, 875, 835, 775, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.79 (dd, *J* = 7.3, 16.6 Hz, 0.27 H), 6.69 (dd, *J* = 8.1, 16.4 Hz, 0.35 H), 6.59 (dd, *J* =

10.0, 11.0 Hz, 0.56 H), 6.30 (t, *J* = 10.8 Hz, 0.48 H), 5.36 - 5.28 (m, 1.49 H), 3.94-3.90 (m, 0.78 H) 3.44 - 3.30 (m, 0.91 H), 2.76 - 2.58 (m, 1.09 H), 1.97 - 1.89 (m, 1.06 H), 1.83 - 1.62 (m, 6 H), 1.53 - 1.18 (m, 6 H), 0.93 - 0.86 (m, 13 H), 0.11 - 0.01 (m, 9 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 159.03, 158.85, 158.57, 158.24, 117.87, 117.71, 116.36, 116.32, 99.63, 99.62, 99.15, 97.97, 73.94, 73.87, 69.62, 69.46, 50.20, 49.47, 46.57, 45.82, 35.68, 35.23, 33.18, 32.93, 30.45, 29.96, 29.72, 29.60, 26.20, 25.81, 25.77, 25.74, 25.18, 24.55, 24.50, 24.47, 24.42, 24.21, 19.77, 18.11, 18.08, 18.00, 17.95, -3.93, -4.09, -4.46, -4.47, -4.62, -4.65, -4.94, -5.03; LRMS (ESI) calculated for $[C_{15}H_{27}NOSi+H]^+$ = 266.19, found = 266.10.



(*E*)-(3-cyclopentylprop-1-en-1-yl)benzene (**34**) was synthesized according to the general procedure using 6-iodohex-1-ene (63 mg, 0.30 mmol) and styrene (52 µL, 0.45 mmol) at 130 °C. The resulting alkene was purified by flash chromatography (pentane) to afford **34** (21.3 mg, 0.11 mmol, 38% yield) as a colorless oil. All analytical data for **34** was in accordance with literature data.[40]

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CHAPTER 3: Manganese-Catalyzed Carboacylation of Alkenes Using Alkyl Iodides

3.1 Introduction

The importance of efficient C-C bond formation in the synthesis of biologically active or otherwise functional molecules is constantly driving the development of new transition-metal-catalyzed reactions. While many reactions, such as cross-coupling and carbonylation have been successfully developed for aryl and vinyl electrophiles, expanding these transformations to include alkyl halides would constitute a significant advancement in the scope. The utility of single-electron processes in catalysis using alkyl electrophiles has been demonstrated, allowing for both increased reactivity and selectivity (see Chapter 1).

Our lab has developed many reactions to activate alkyl halides for C-C bond formation, including a carbonylative alkyl Heck cyclization of alkenes.[1] Carbonylative transformations of alkyl electrophiles offer a method for using common and readily synthesized compounds to form C-C bonds and install a functional group for further manipulation. We hypothesized that by applying similar hybrid organometallic-radical pathways, we could perform an alkene difunctionalization and generate a new set of carboacylation products by trapping intermediates with CO, rather than terminating with elimination (Figure 3-1).

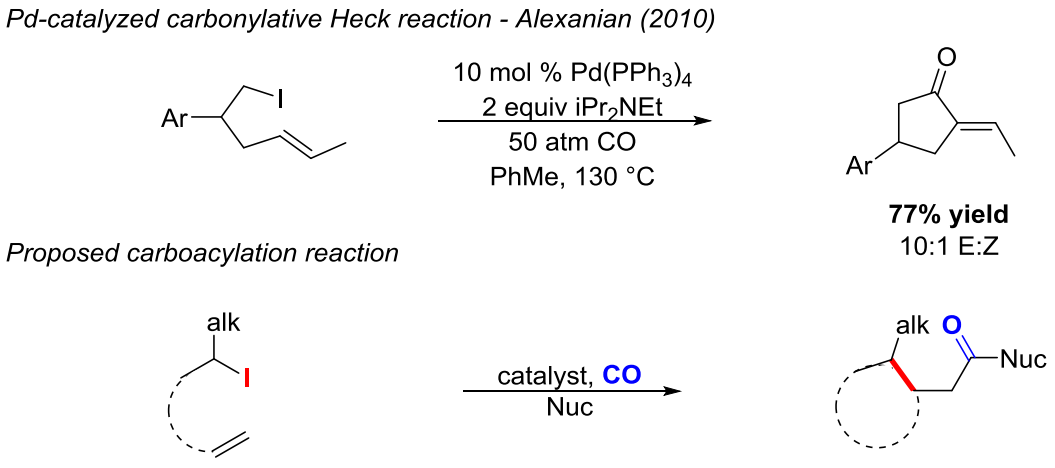


Figure 3-1. Carbonylative transformations of alkyl electrophiles.

3.2 Background

3.2.1 Alkene Difunctionalization

Catalytic alkene difunctionalization is an extremely valuable transformation for the efficient generation of complexity in small molecules. Vicinal heteroatom difunctionalizations, such as dioxygenation, aminooxidation, and diamination, have been well-developed, while C-C difunctionalization has remained much more limited. Several examples of cross-coupling cascade reactions to achieve this transformation have been reported, most of which involve an arylation or vinylation of the alkene, followed by trapping the intermediate with an organometallic reagent.[2–10] Variations of this include an enantioselective cyclization of aryl boronic esters onto alkenes, which terminates in cross-coupling with alkyl bromides, developed by Fu[11] and an aryl carbopalladation/carbonylation sequence from Somfai (Figure 3-2).[12] Widenhofer reported a similar arylation/carbonylation, initiated by a C-H activation.[13] Other instances of C-C difunctionalizations include intramolecular cyanoarylations and carboacylations initiated by C-C bond activation.[14–16]

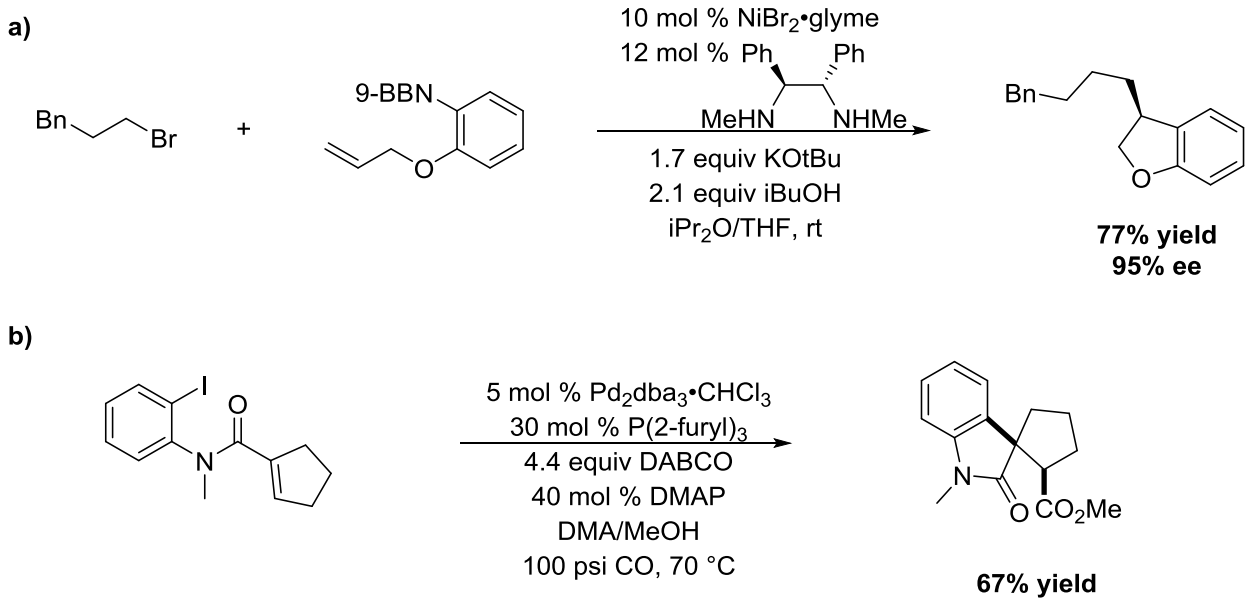


Figure 3-2. Cross-coupling cascade alkene difunctionalizations.

The addition of an sp^3-hybridized carbon to an alkene and resulting in a difunctionalization is much more rare. Ryu has reported an intermolecular palladium-catalyzed carboacylation which uses an alkyl halide addition to an alkene followed by carbonylation under high CO pressures, however it uses

activated electrophiles and terminal alkenes almost exclusively, with the exception of one intramolecular cyclization example with an unactivated halide (Figure 3-3a).[17] Another example of a three-component palladium-catalyzed carboacylation from the Miyaura group consists of iodoalkene cyclization, carbonylation and cross-coupling with 9-BBN reagents to form ketones (Figure 3-3b).[18] However, this transformation is limited in that an excess of the iodide component is required. We proposed that we could perform an efficient alkyl carboacylation using unactivated iodides, low CO pressures, and a first-row transition-metal catalyst.

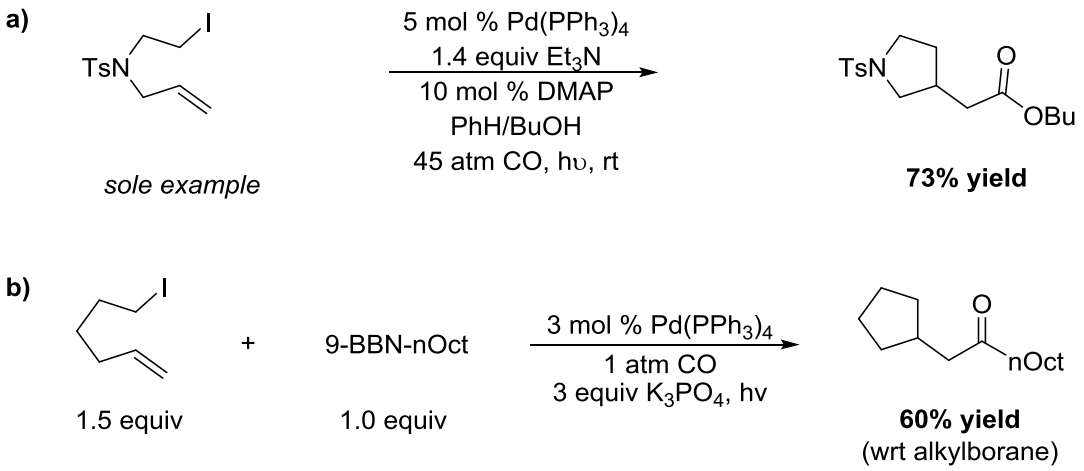


Figure 3-3. Precedent for carboacylation of alkenes with alkyl halides.

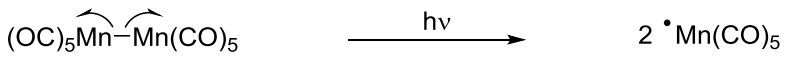
3.2.2 Manganese Catalysis

While palladium is the traditional catalyst of choice for cross-coupling and both of the alkyl carboacylations shown above, the use of a cheaper, more environmentally-friendly catalytic system would be desired. With this goal in mind, we explored the use of other catalysts for this transformation and settled on manganese. Manganese offers significant advantages compared to second- and third-row transition metals, in terms of both cost and abundance. Typical manganese catalysts are much less expensive than noble metals such as palladium. In addition, the annual production of manganese in 2015 was 18,000,000 metric tons, while that of palladium was only 208.[19]

Besides advantages in cost and sustainability, manganese is also well known for its single-electron chemistry, rendering it an excellent choice for an organometallic-radical reaction. First-row metals are generally better at performing SET than second- and third-row metals. While manganese(III) is

widely known for its single-electron oxidizing power, manganese(0) can serve as a single-electron reductant. A common dimer, manganese carbonyl ($Mn_2(CO)_{10}$), easily undergoes thermal or photolytic cleavage to produce two 17-electron manganese(0) radical species. This type of manganese catalyst is known to interact with alkyl halides either by halogen abstraction or single electron transfer followed by disproportionation to form carbon-centered radicals (Figure 3-4).

Thermal or photolytic cleavage of dimers produces 17 e⁻ Mn(0) radicals



Single electron transfer or direct halogen atom abstraction

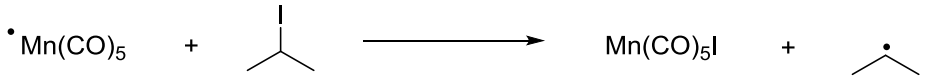


Figure 3-4. Cleavage of Mn dimers and single-electron activation of alkyl halides

This type of activation has been demonstrated in a variety of systems for further transformation. $Mn_2(CO)_{10}$ is able to accomplish Kharasch additions to alkenes using $BrCCl_3$ under photolytic conditions, and can activate more electron-rich aliphatic alkyl halides for reductive coupling with alkenes as well (Figure 3-5a).[20–22] Whittaker has reported atom transfer cyclizations, which use α-halo carbonyls to form unactivated alkyl halides (Figure 3-5b),[23] and radical addition to imino compounds is also known.[24] $Mn_2(CO)_{10}$ can also catalyze direct carbonylation of alkyl iodides to produce esters or amides, as demonstrated by Ryu with irradiation at high CO pressures (45-75 atm) (Figure 3-5c).[25,26]

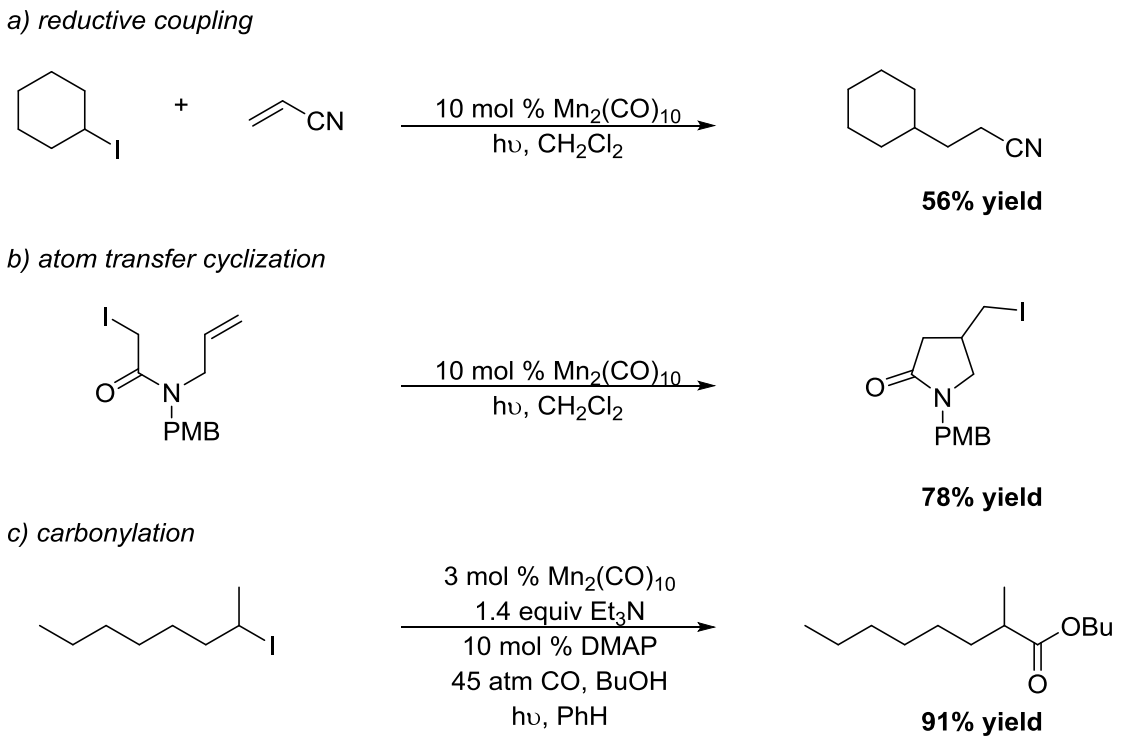


Figure 3-5. Single-electron Mn activation of alkyl halides.

In this work, we aimed to develop a general system for alkene difunctionalization through the activation and cyclization of alkyl iodides and low CO pressures. The intramolecular carboacylation we now report forms two C-C bonds across an alkene in one step, operates under mild conditions, and creates a variety of interesting cyclic molecular scaffolds with potential application for complex synthesis (Figure 3-6).

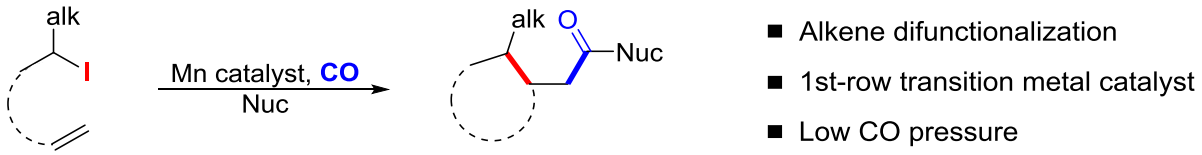


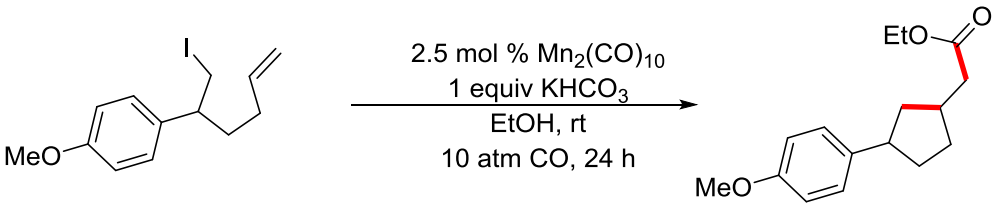
Figure 3-6. Mn-catalyzed carboacylation of alkenes with alkyl iodides.

3.3 Development of Catalytic System

We began our studies into the manganese-catalyzed carboacylation with 5-iodo-1-hexenyl substrate **35**. When stirred at room temperature under 10 atm CO in the presence of 2.5 mol % of commercially available $Mn_2(CO)_{10}$ and 1.0 equiv $KHCO_3$ in EtOH, 84% yield of desired cyclized

carbonylated ester product **36** was obtained (Table 3-1, entry 1). The bromide-substituted manganese(I) catalyst $Mn(CO)_5Br$ resulted in a significant decrease in yield to 14% (entry 2). Other metal catalysts, including $Pd(PPh_3)_4$ and carbonyl complexes such as $Co_2(CO)_8$ were not successful – no conversion was observed (entries 3-4). Interestingly, if K_3PO_4 was used as base with $Pd(PPh_3)_4$, matching Miyaura's conditions and more similar to our alkyl-Heck conditions, only dehydrohalogenation was observed. Amine bases such as *i*Pr_2NEt were slightly less effective than $KHCO_3$ (entry 5). Reducing the pressure to 1 atm CO gave no desired product (entry 6), however 5 atm CO provided product **36** in comparable yield (entry 7). Ambient visible light is necessary for this reaction to occur, as no reactivity was observed when run in the dark (entry 8). While it is unclear exactly what the role of light is, it is not simply an initiator, as running the reaction in the light for 2 hours, followed by continuation for the full 24 hours in the dark, led to no desired carboacylation product. Additionally no reaction occurred in the control reaction in the absence of manganese catalyst (entry 9).

Table 3-1. Optimization of Mn-catalyzed carboacylation.



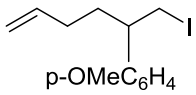
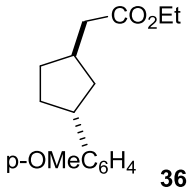
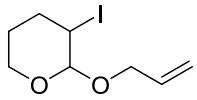
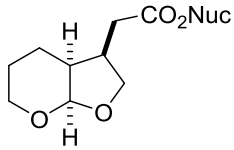
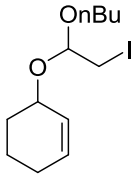
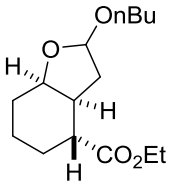
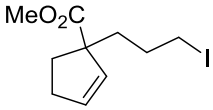
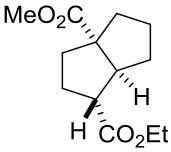
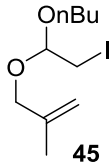
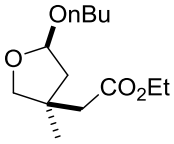
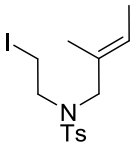
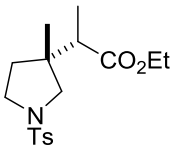
35 **36**

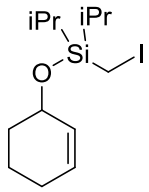
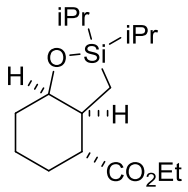
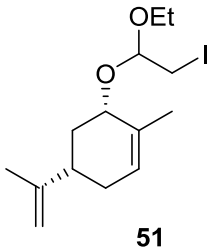
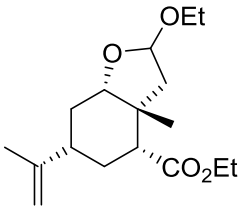
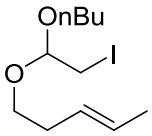
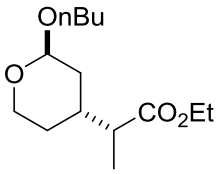
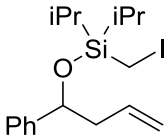
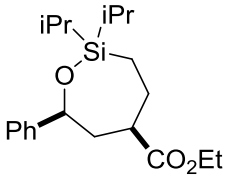
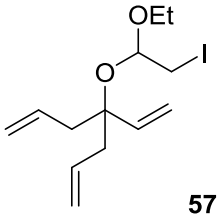
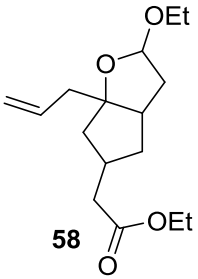
entry	deviation from standard conditions above	% yield
1	none	84
2	5 mol % $Mn(CO)_5Br$ instead of $Mn_2(CO)_{10}$	14
3	2.5 mol % $Co_2(CO)_8$ instead of $Mn_2(CO)_{10}$	0
4	5 mol % $Pd(PPh_3)_4$ instead of $Mn_2(CO)_{10}$	0
5	iPr_2NEt instead of $KHCO_3$	76
6	1 atm CO instead of 10 atm CO	0
7	5 atm CO instead of 10 atm CO	76
8	dark	0
9	no Mn catalyst	0

3.4 Substrate Scope

With a viable catalytic system in hand, we investigated the scope of the carboacylation reaction. Primary and secondary unactivated iodides were both successful (Table 3-2, entries 1-2). Amine nucleophiles also readily participated, forming amide products in good yields (entry 2b-c). Cyclic disubstituted alkenes were also successful, providing bicyclic products in excellent yields and good diastereoselectivities (entries 3-4). The use of 1,1-disubstituted and 1,1,2-trisubstituted alkenes also gave high yields of products and resulted in the formation of all-carbon quaternary centers (entries 5-6). Oxygen, nitrogen, all-carbon, and silyl-tethered substrates (entries 5-7) all underwent cyclization giving carbonylated products in good yields. A carvone-derived iodide participated in the reaction, resulting in a more complex bicyclic 5,6-ring system containing a quaternary center (entry 8). 6-exo cyclization was demonstrated, which is traditionally more difficult in radical mechanisms due to a slower rate of cyclization, providing a 6-membered ring product in moderate yield (entry 9). Using a silyl-tethered compound the formation of a 7-membered ring, resulting from a 7-endo radical cyclization, was also accomplished (entry 10). Tandem 5-exo cyclizations were observed when using a triene substrate, forming 3 C-C bonds and 2 rings in one step (entry 11). Alkyl bromides were not viable substrates in this reaction.

Table 3-2. Substrate scope of Mn-catalyzed alkene carboacylation.

entry	substrate	product	% yield[a]
1	 **35**	 **36**	83 (2:1)
2	 **37**	 a) Nuc = OEt **38** b) Nuc = NEt_2 **39** c) Nuc = NMePh **40**	77 (10:1) 67 (8:1)[b] 73 (10:1)[b]
3	 **41**	 **42**	90 (7:1)[c]
4	 **43**	 **44**	89 (7:1)
5	 **45**	 **46**	77 (8:1)[d]
6	 **47**	 **48**	79 (1:1)[d]

7	 **49**	 **50**	72 (9:1)
8	 **51**	 **52**	73 (3:1)[c][e]
9	 **53**	 **54**	64 (2.5:1)[c][d]
10	 **55**	 **56**	78 (3:1)
11	 **57**	 **58**	77[d]

See Table 3-1 for conditions. [a] Isolated yields. Diastereomeric ratios based on ^{1}H NMR spectroscopy of reaction mixture. [b] 2 equiv of amine and $KHCO_3$ used in EtOH. [c] Diastereomeric ratio of cyclization (see Section 3.7 for more details). [d] 5 mol % $Mn_2(CO)_{10}$ used. [e] 10 mol % $Mn_2(CO)_{10}$ used.

Diastereoselectivity was dictated by substrate control and was consistent with similar radical cyclizations. We were able to determine the diastereoselectivity of the cyclizations in some cases by performing further manipulations of the products, removing extraneous acetal stereocenters. Oxidations and reductions of the acetals were both viable post-reaction modifications, resulting in simplified lactone

or saturated oxygen heterocycles, respectively (Figure 3-7). These transformations also illustrate the versatility of the carboacylation products for chemical synthesis.

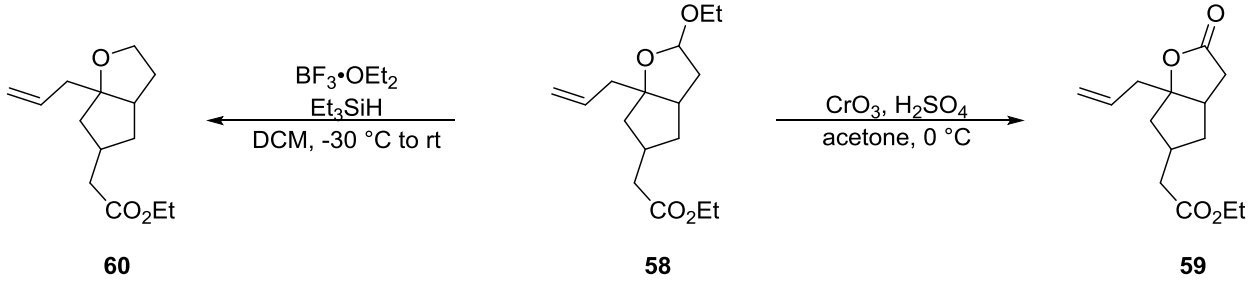
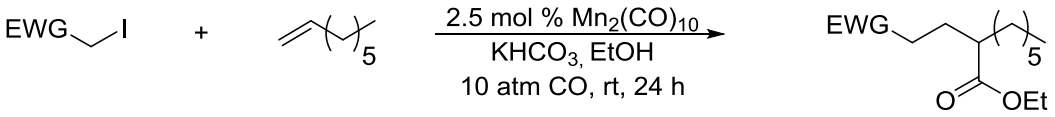


Figure 3-7. Post-reaction modifications of carboacylation products.

An intermolecular variant of this reaction was also demonstrated using activated alkyl iodides. Alpha-iodoethyl acetate and perfluorohexyl iodide both underwent addition to 1-octene, followed by carbonylation, providing ester products in good yields (Figure 3-8). This coupling could also be performed with α-iodoesters made easily from complex steroid-derived alcohols. Diosgenin and methyl cholate derivatives were both coupled to 1-octene via a carboacylation in 61% and 78% yield, respectively (Figure 3-9). This reaction could be applied to late-stage fragment coupling for synthesis or modification of complex molecules such as natural products or pharmaceuticals.



61 EWG = C_6F_{13} **65%**
62 EWG = COOEt **62%**

Figure 3-8. Intermolecular Mn-catalyzed carboacylation using activated alkyl halides.

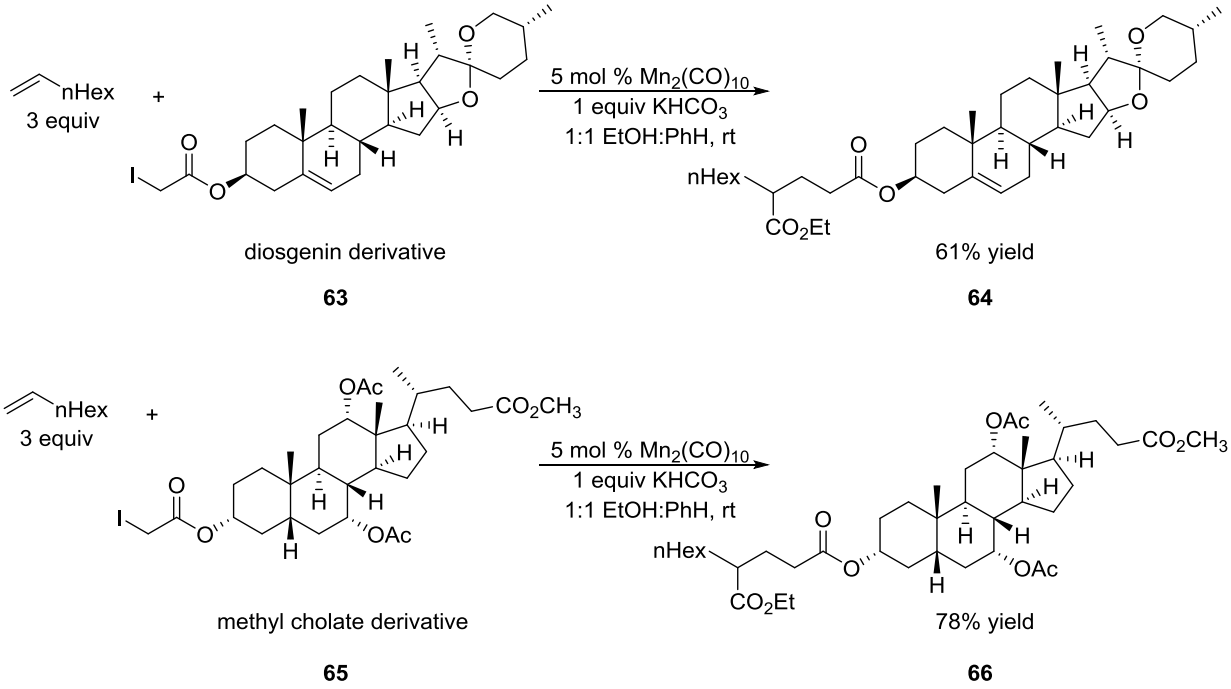


Figure 3-9. Intermolecular Mn-catalyzed carboacylation with complex alkyl halides.

In an effort to expand the intermolecular carboacylation to the use of unactivated alkyl halides, reactions with iodocyclohexane and iodooctane were attempted with both aliphatic alkenes and styrenes, with no reactivity observed. However, when a slightly activated iodolactone was used, 29% yield of the desired carboacylation coupling product was obtained with 1-octene (Figure 3-10).

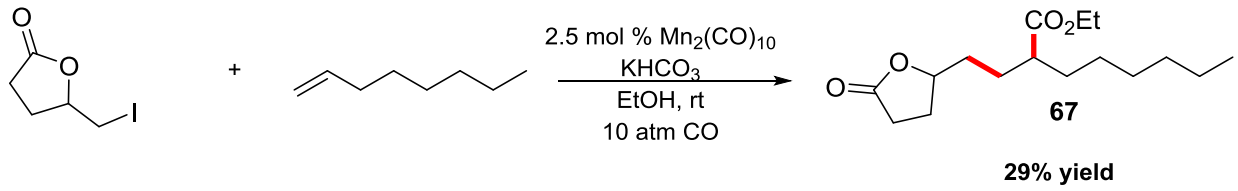


Figure 3-10. Preliminary result of intermolecular carboacylation with unactivated alkyl halide.

Interestingly, when 1,1,2-trisubstituted alkene **68** was used as a substrate under carboacylation conditions, 83% Heck-type product **69** was observed instead of carbonylation (Figure 3-11). This switch in reactivity could be attributed to steric factors hindering the tertiary radical from accessing manganese-bound CO, or rapid oxidation to form a tertiary carbocation followed by elimination. When the reaction was conducted without CO, a lower yield of the same Heck-type product was obtained. In this case,

pressure or amount of CO could be having an impact on the turnover or stability of the active catalyst. Using an acetal substrate with a similar alkene substitution pattern, a mixture of Heck-type alkene and tertiary carbonylation were obtained. These results indicate the potential for optimizing divergent catalytic systems for each of these pathways in the future (Figure 3-12).

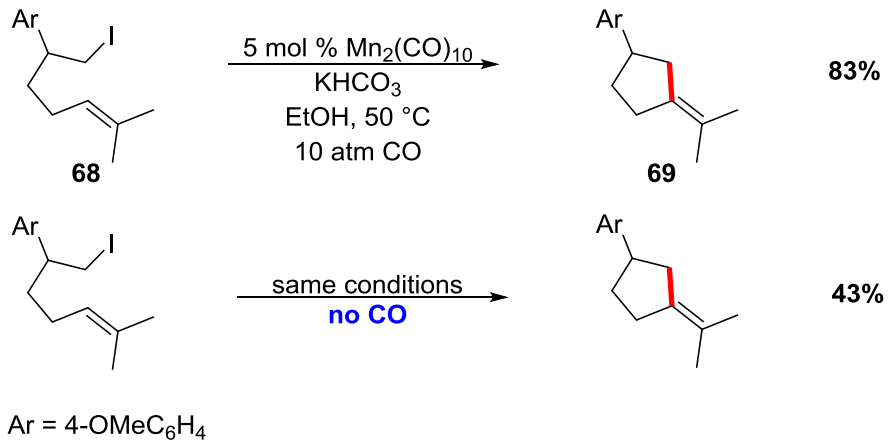


Figure 3-11. Preliminary Heck-type reactivity observed with 1,1,2-trisubstituted alkene substrate.

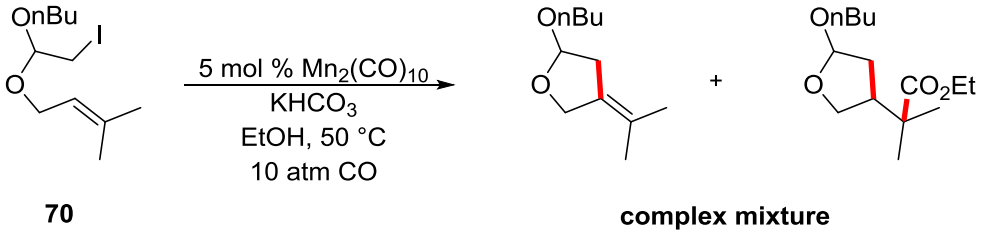


Figure 3-12. Mixture of products observed with trisubstituted alkene substrate.

3.5 Mechanistic Studies

We propose a mechanism for this manganese-catalyzed carboacylation according to Figure 3-13. We hypothesize that the reaction is initiated by a homolytic cleavage of the $Mn_2(CO)_{10}$ dimer to form the 17-electron manganese(0) radical. This radical can then abstract the iodine atom from the substrate to form a carbon-centered radical **II**, followed by a fast radical cyclization. The resulting radical **III** could then undergo carbonylation directly from CO in solution or from the metal via either an inner- or outer-sphere pathway, potentially forming acyl-manganese species **IV**. Substitution by the nucleophile yields product and turns over the catalyst.

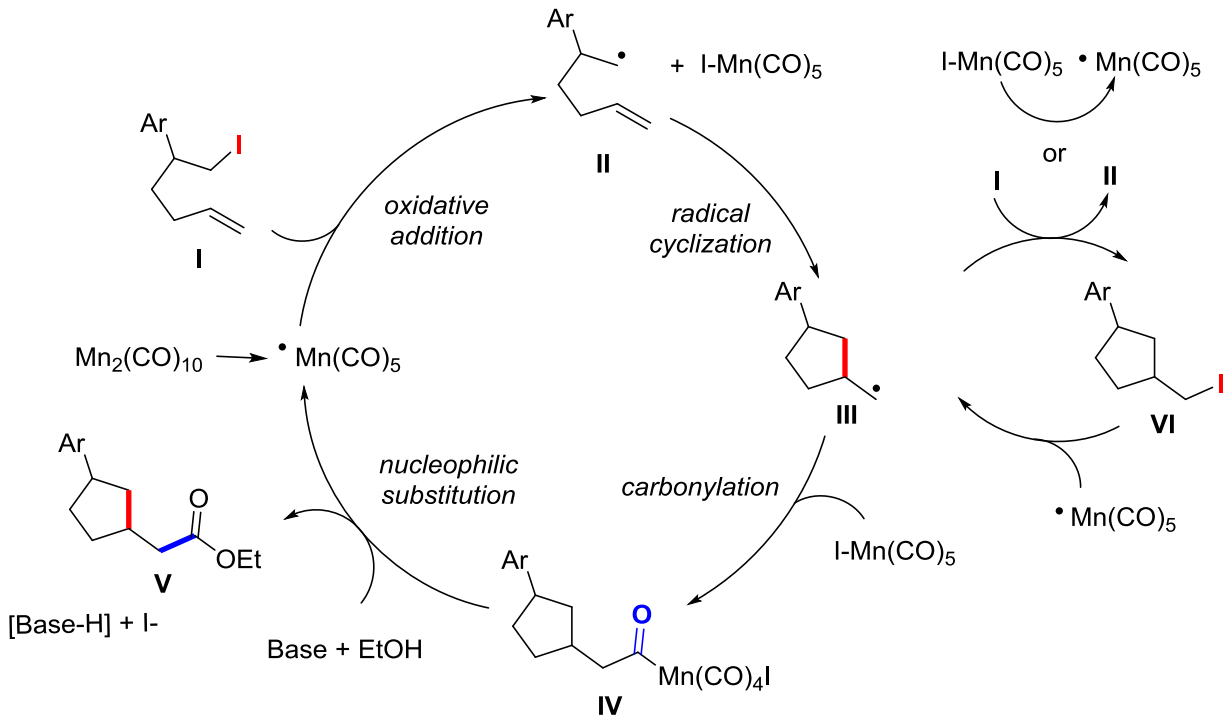
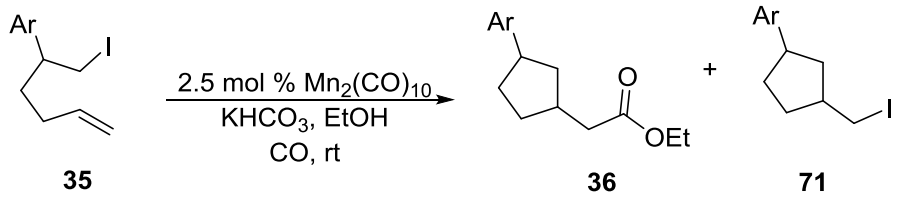


Figure 3-13. Proposed mechanism of Mn-catalyzed carboacylation.

An alternative pathway could also be occurring, in which the radical intermediate **III** participates in atom transfer and abstracts an iodine atom from either the manganese(I) species or from another molecule of starting material. If the latter occurs, the possibility for a chain reaction arises. If the iodine atom transfer product **VI** is formed, it could then undergo a single electron oxidative addition with the catalyst again, funneling back into the catalytic cycle via **III**. To determine whether **VI** is an intermediate along the pathway towards product, we hypothesized that lower amounts of CO may favor the iodine atom transfer pathway. We observed that decreasing the CO from 10 atm to 5 atm or 1 atm decreased the amount of carboacylation product and increased the amount of iodine atom transfer (Table 3-3). Significantly, when no CO or nucleophile was used, 60% yield of the iodine atom transfer product was observed.

Table 3-3. CO pressure screen of carboacylation.



CO pressure	% yield **36**	% yield **71**
10 atm	84%	0%
5 atm	76%	11%
1 atm	0%	7%
no CO, PhH	0%	60%

In order to further test whether the iodine atom transfer product was a possible intermediate towards product, we isolated the iodide **71** and resubjected it to the carboacylation conditions and saw 100% conversion to the ester (Figure 3-14). Additionally, by stopping the reaction after only 2 hours, a mixture of ester and iodide was obtained (Figure 3-15). These experiments suggest that the iodide is indeed a potential intermediate in the carboacylation, although it remains unclear whether it is the only operative pathway. In order to probe whether the extent of iodine atom transfer is dependent on the substrate, identical iodides differing only in their alkene substitution were reacted under standard carboacylation conditions, again stopping them before completion (Figure 3-16). At this point in the reaction, the substrate with the terminal alkene (and thus primary radical formed after cyclization) resulted in 31% carboacylation product and 10% iodine atom transfer. In contrast, in the reaction with the disubstituted alkene which would form a more stable secondary radical after cyclization, no substantial accumulation of iodine atom transfer product was observed. This suggests that a more stable radical is more likely to undergo direct carbonylation, whereas a less stable radical may be prone to quickly abstract an iodine atom before being converted to product.

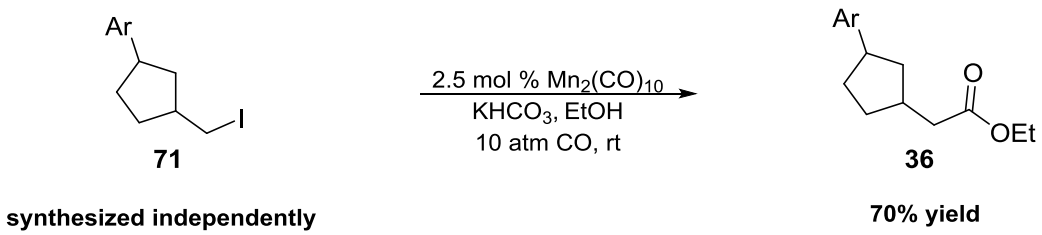


Figure 3-14. Resubjection of possible iodine atom transfer intermediate to reaction conditions.

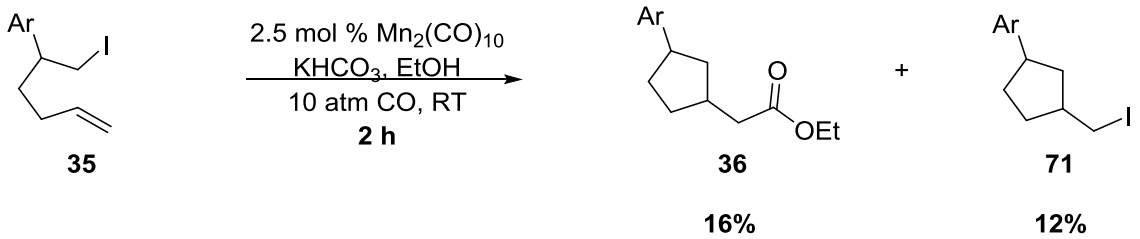


Figure 3-15. Study of reaction progress before completion.

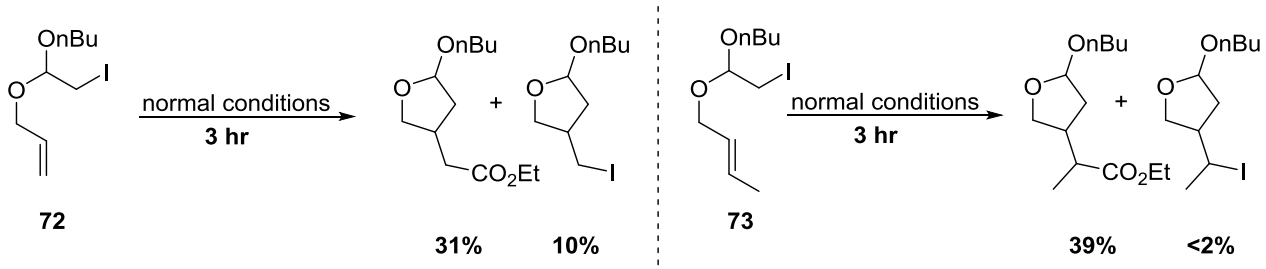


Figure 3-16. Difference in product outcomes based on substrate alkene substitution.

3.6 Summary

In conclusion, we have developed a manganese-catalyzed carboacylation of alkenes using alkyl iodides. Both primary and secondary electrophiles can be successfully activated by $Mn_2(CO)_{10}$, and react with alkenes of a variety of substitution patterns. Five-, six-, and seven-membered rings can all be formed via cyclization, and intermolecular reactivity is demonstrated using α-halocarbonyl substrates, including with natural-product derived iodides. Experimental studies indicate that iodides resulting from atom transfer are possible intermediates in the catalytic cycle. This transformation accomplishes a new C-C alkene difunctionalization that utilizes an inexpensive, first-row transition metal catalyst, mild conditions, and low CO pressures, with direct applications for complex synthesis and late-stage functionalization.

3.7 Experimental

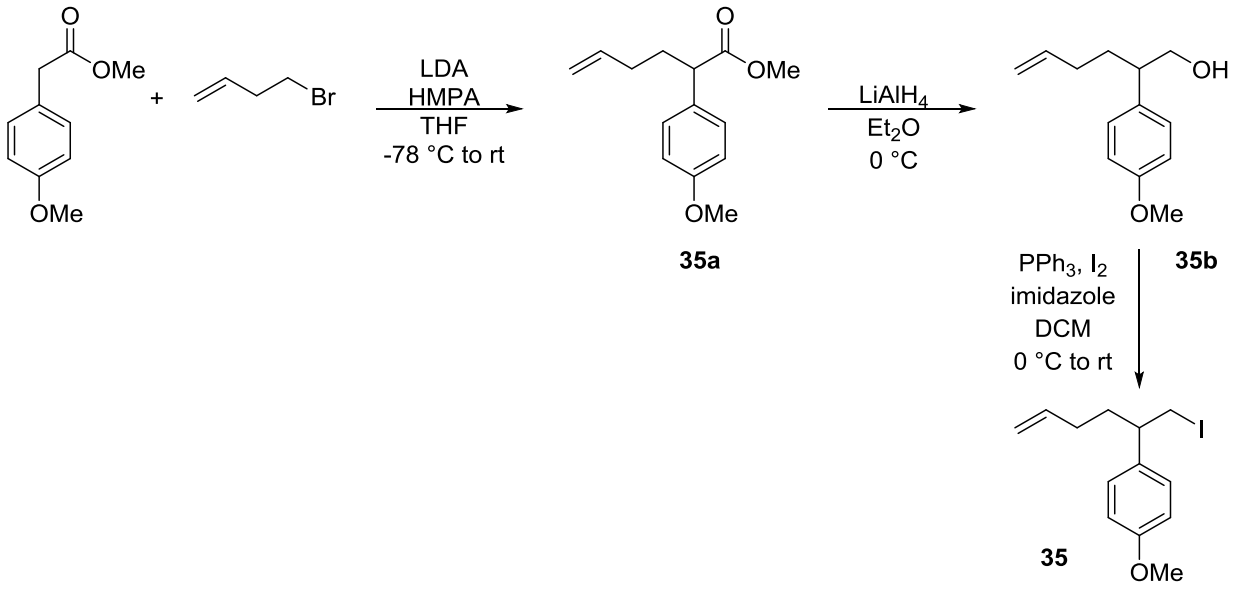
3.7.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or a Bruker AVANCE III 600 CryoProbe (^{1}H NMR at 400 MHz or 600 MHz and ^{13}C NMR at 151 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm or C_6D_6 at 7.16 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm or C_6D_6 at 128.06 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. High resolution mass spectra were obtained using a Thermo LTQ-FT-ICR-MS-7T mass spectrometer with positive ion electrospray ionization (ESI). Low resolution mas spectra were obtained using an Agilent 6850 series gas chromatography system equipped with an Agilent 5973N mass selective detector. Thin layer chromatography (TLC) was performed on SiliaPlate 250μm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Tetrahydrofuran, diethyl ether and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Acetone was dried over potassium carbonate. Ethanol and methanol were sparged with argon and dried over molecular sieves. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted. The sealed tubes used were purchased from Ace Glass. Pressure adapters were assembled from Swagelock parts (see Figure 3-17).

3.7.2 Substrate Preparation

Trans-2-(allyloxy)-3-iodotetrahydro-2H-pyran,[27] 3-(1-butoxy-2-iodoethoxy)cyclohex-1-ene,[28] (E)-N-(2-iodoethyl)-4-methyl-N-(2-methylbut-2-en-1-yl)benzenesulfonamide (**47**),[29] and (iodomethyl)diisopropyl((1-phenylbut-3-en-1-yl)oxy)silane[30] were prepared according to literature procedures. All physical and spectral data were in accordance with literature data.

Synthesis of 35



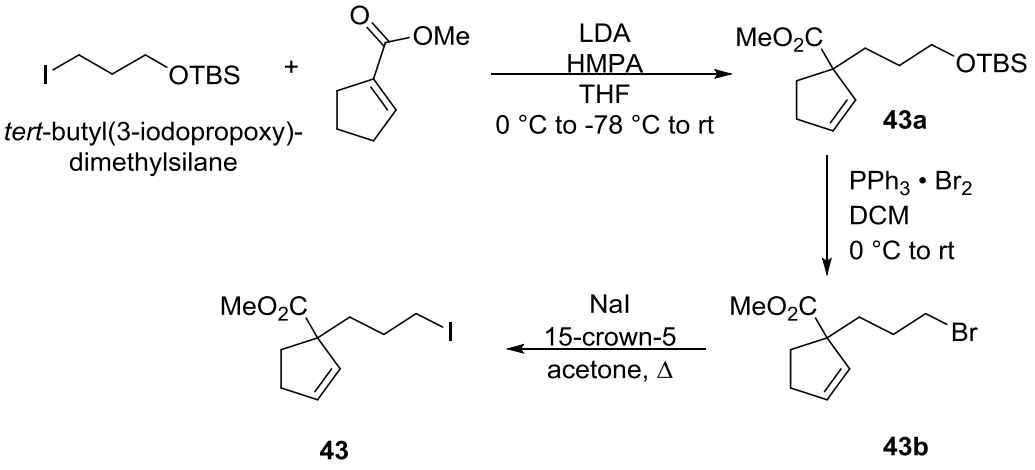
1) **35a** To a 0 °C solution of iPr_2NH (4.6 mL, 33 mmol) in THF (111 mL), n-BuLi (12.4 mL, 33 mmol, 2.66 M in hexanes) was added dropwise. The reaction was stirred at 0 °C for 10 minutes, then cooled to -78 ˚C. A solution of methyl 2-(4-methoxyphenyl)acetate (4.8 mL, 30 mmol) in THF (8 mL) was added dropwise and the reaction was stirred for 30 minutes. A solution of 4-bromobut-1-ene (3.7 mL, 36 mmol) in THF (8 mL) was added, followed by HMPA (3.13 mL, 18 mmol). The reaction was allowed to warm to room temperature and stirred overnight. It was then diluted with Et_2O and hexanes and washed with NH_4Cl and brine. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (20:1 Hex:EtOAc) to provide 4.98 g (71%) of **35a** as a colorless oil. Analytical data for **35a**: IR (thin film, cm^{-1}) 2950, 2837, 1734, 1641, 1611, 1511, 1438, 1302, 1249, 1160, 1035, 914, 831, 531; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.80 - 1.91 (m, 1 H) 2.00 (dt, *J*=7.83, 6.85 Hz, 2 H) 2.07 - 2.20 (m, 1 H) 3.53 (t, *J*=7.58 Hz, 1 H) 3.65 (s, 3 H) 3.79 (s, 3 H) 4.96 - 5.03 (m, 2 H) 5.77 (m,

J=16.99, 10.39, 6.60, 6.60 Hz, 1 H) 6.86 (dd, *J*=8.56, 4.65 Hz, 2 H) 7.22 (dd, *J*=8.80, 4.65 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.67, 158.72, 137.57, 130.90, 128.94, 115.34, 113.96, 55.20, 51.90, 49.78, 32.47, 31.42; HRMS (ESI) calculated for $[C_{14}H_{18}O_3+Na]^+$ = 257.11477, found = 257.114845.

2) **35b** $LiAlH_4$ (1.46 g, 38.4 mmol) was stirred as a suspension in Et_2O (38 mL) at 0 ˚C. **35a** (4.5 g, 19.2 mmol) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was then cooled to 0 ˚C and quenched with H_2O (1.5 mL), 10% NaOH (3.0 mL), and H_2O (4.5 mL) and stirred at room temperature for 20 minutes. The solids were filtered out and the filtrate was concentrated in vacuo. Purified by flash chromatography (2:1 Hex:EtOAc) to provide 3.48 g (88%) of **35b** as a white solid. Analytical data for **35b**: IR (thin film, cm^{-1}) 3371, 2930, 1640, 1611, 1511, 1460, 1300, 1247, 1179, 1035, 911, 830, 550; ^1H NMR (400MHz , $CDCl_3$) δ = 7.13 (dd, *J* = 4.6, 8.6 Hz, 2 H), 6.88 (dd, *J* = 4.9, 8.6 Hz, 2 H), 5.77 (m, *J* = 6.5, 10.4, 17.0 Hz, 1 H), 5.02 - 4.91 (m, 2 H), 3.80 (s, 3 H), 3.77 - 3.64 (m, 2 H), 2.91 - 2.71 (m, 1 H), 1.95 (m, *J* = 6.4, 7.6 Hz, 2 H), 1.84 - 1.71 (m, 1 H), 1.71 - 1.50 (m, 2 H), 1.31 (br. s., 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.38, 138.36, 133.75, 128.98, 114.71, 114.06, 67.54, 55.21, 47.07, 31.32, 31.21; HRMS (ESI) calculated for $[C_{13}H_{18}O_2+Na]^+$ = 229.119931, found = 229.119860.

3) **35** A solution of PPh_3 (6.7 g, 25.4 mmol), imidazole (1.7 g, 25.4 mmol), and I_2 (6.4 g, 25.4 mmol) was stirred at 0 ˚C in DCM (64 mL). A solution of **35b** (3.48 g, 16.9 mmol) in DCM (42 mL) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with H_2O and extracted with DCM (x3). The combined organic layers were washed with $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated in vacuo. Purified by column chromatography (10:1 Hex:EtOAc) to provide 4.87 g (92%) of **35** as a colorless oil. Analytical data for **35**: IR (thin film, cm-1) 3073, 2997, 2929, 2834, 1640, 1610, 1583, 1511, 1457, 1301, 1248, 1177, 1106, 1036, 998, 913, 829, 734, 709, 602, 553; ^1H NMR (400MHz, $CDCl_3$) δ = 7.07 (dd, *J* = 4.6, 8.8 Hz, 2 H), 6.87 (dd, *J* = 4.6, 8.6 Hz, 2 H), 5.81 - 5.68 (m, 1 H), 5.08 - 4.92 (m, 2 H), 3.81 (s, 3 H), 3.35 (m, *J* = 2.4, 7.3 Hz, 2 H), 2.82 (m, *J* = 2.9, 3.9 Hz, 1 H), 2.03 - 1.85 (m, 3 H), 1.78 - 1.62 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.47, 137.91, 134.71, 128.33, 115.02, 113.90, 55.19, 46.69, 34.77, 31.58, 14.42; LR GC/MS calculated for $[C_{13}H_{17}OI]^+$ = 316.0324, found = 316.

Synthesis of 43



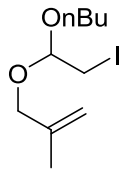
1) **43a** To a 0 °C solution of iPr_2NH (0.99 mL, 7 mmol) in THF (7 mL), n-BuLi (2.4 mL, 6.3 mmol, 2.66 M in hexanes) was added dropwise. The reaction was cooled to -78 ˚C and stirred for 5 minutes. HMPA (1.1 mL, 6.3 mmol) was added and the reaction was stirred for 30 minutes. Methyl cyclopent-1-ene-1-carboxylate (0.61 mL, 5 mmol) was added dropwise and the reaction was stirred for 10 minutes. tert-butyl(3-iodopropoxy)dimethylsilane[31] (2.25 g, 7.5 mmol) was added and the reaction was stirred for 3 hours warming to room temperature. It was then diluted with Et_2O, quenched with NH_4Cl, and extracted with Et_2O (x3). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (25:1 Hex:EtOAc) to provide 832 mg (56%) of **43a** as a yellow oil. Analytical data for **43a**: IR (thin film, cm^{-1}) 2951, 2857, 2360, 1733, 1462, 1387, 1361, 1317, 1253, 1196, 1099, 1030, 836, 776, 725, 662, 511; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.80 (dt, *J*=5.62, 2.20 Hz, 1 H), 5.69 (dt, *J*=5.75, 2.02 Hz, 1 H), 3.67 (s, 3 H), 3.57 (t, *J*=6.48 Hz, 2 H), 2.30 - 2.46 (m, 3 H), 1.76 (m, *J*=8.56 Hz, 2 H), 1.62 (m, *J*=12.96 Hz, 1 H), 1.37 - 1.52 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.92, 133.52, 132.27, 63.28, 59.83, 51.88, 34.84, 32.72, 31.75, 28.71, 25.96, 18.36, -5.26; HRMS (ESI) calculated for $[C_{16}H_{30}O_3Si+Na]^+$ = 321.185676, found = 321.185590.

2) **43b** To a 0 °C solution of **43a** (832 mg, 2.8 mmol) in DCM (28 mL), PPh_3•Br_2 (1.4 g, 3.4 mmol) was added. The reaction was stirred, warming to room temperature gradually. It was then concentrated in vacuo, redissolved in Et_2O, and filtered. The filtrate was concentrated in vacuo. Purified by flash

chromatography (20:1 Hex:EtOAc) to provide 424 mg (61%) of **43b** as a pale orange oil. Analytical data for **43b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.84 (dt, *J*=5.50, 2.26 Hz, 1 H), 5.67 (dt, *J*=5.62, 1.96 Hz, 1 H), 3.68 (s, 3 H), 3.37 (t, *J*=6.11 Hz, 2 H), 2.34 - 2.48 (m, 3 H), 1.72 - 1.88 (m, 5 H), 1.58 (s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.54, 132.99, 132.90, 59.53, 52.04, 37.04, 33.74, 32.80, 31.81, 28.76; LR GC/MS calculated for $[C_{10}H_{15}O_2Br – CO_2CH_3]^+$ = 187.01223, found = 187.

3) **43** To a solution of **43b** (424 mg, 1.7 mmol) in acetone (7 mL), NaI (764 mg, 5.1 mmol) was added. 15-crown-5 (165 µL, 0.85 mmol) was added. The reaction was heated to reflux and stirred overnight. It was then diluted with DCM, washed with $Na_2S_2O_3$, and extracted with DCM (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (20:1 Hex:EtOAc) to provide 428 mg (86%) of **43** as a pale yellow oil. Analytical data for **43**: IR (thin film, cm^{-1}) 2947, 1728, 1433, 1217, 1162, 727; ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.83 (dt, *J* = 2.3, 5.6 Hz, 1 H), 5.67 (dt, *J* = 2.1, 5.6 Hz, 1 H), 3.68 (s, 3 H), 3.14 (t, *J* = 6.2 Hz, 2 H), 2.47 - 2.34 (m, 3 H), 1.85 - 1.68 (m, 5 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.48, 132.99, 132.94, 59.40, 51.99, 39.26, 32.79, 31.75, 29.48; HRMS (ESI) calculated for $[C_{10}H_{15}O_2I+H]^+$ = 295.01950, found = 295.01877.

Synthesis of 45



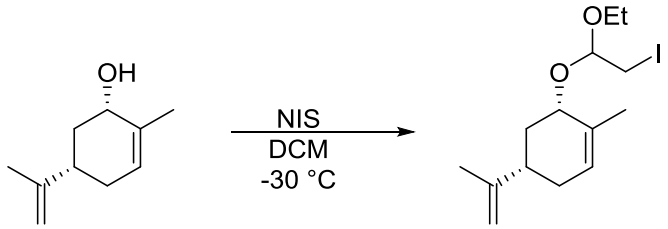
To a -30 °C solution of butyl vinyl ether (1.48 mL, 11.4 mmol) and 2-methyl-2-propen-1-ol (0.80 mL, 9.5 mmol) in DCM (9.5 mL), N-iodosuccinimide (2.14 g, 9.5 mmol) was added portionwise. The reaction was stirred at -30 °C for 4 hours. The reaction was allowed to warm to room temperature and stirred overnight. It was then diluted with DCM. It was washed with H_2O, $Na_2S_2O_3$, and brine. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (30:1 Hex:EtOAc) to provide 2.07 g (73%) of **45** as a colorless oil. Analytical data for **45**: IR (thin film, cm^{-1}) 2958, 2932, 2870, 1657, 1455, 1342, 1177, 1112, 1036, 901, 605; ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.00 (s, 1 H), 4.91 (s, 1 H), 4.64 (t, J=5.38 Hz, 1 H), 3.91 - 4.07 (m, 2 H), 3.55 - 3.70 (m, 1 H), 3.40 - 3.55 (m, 1 H), 3.24 (d,

J=5.62 Hz, 2 H), 1.78 (s, 3 H), 1.52 - 1.64 (m, 2 H), 1.40 (sxt, J=7.43 Hz, 2 H), 0.93 (t, J=7.34 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 141.52, 112.75, 101.12, 70.23, 66.26, 31.69, 19.70, 19.29, 13.83, 5.21; LR GC/MS calculated for $[C_{10}H_{19}O_2\text{-}I]^+$ = 171.1385, found = 171.

Synthesis of 49

To a 0 ˚C solution of chloro(iodomethyl)diisopropylsilane[30] (937 mg, 3 mmol) and DMAP (18.3 mg, 0.15 mmol) in DCM (10 mL), triethylamine (418 µL, 3 mmol) was added. A solution of cyclohex-2-en-1-ol (323 µL, 3.3 mmol) in DCM (5 mL) was added. The reaction was stirred at 0 °C. The reaction was allowed to warm to room temperature, quenched with NH_4Cl and then extracted with DCM (x3). It was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (hexanes) to provide 675 mg (64%) of **49** as a colorless oil. Analytical data for **49**: IR (thin film, cm^{-1}) 3025, 2939, 2864, 1462, 1388, 1085, 1023, 881, 834, 797, 726; ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.82 - 5.68 (m, 2 H), 4.38 (br. s., 1 H), 2.10 (s, 2 H), 2.06 - 1.97 (m, 1 H), 1.97 - 1.75 (m, 3 H), 1.69 - 1.43 (m, 2 H), 1.34 - 1.15 (m, 2 H), 1.09 (t, *J* = 6.8 Hz, 12 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 130.63, 129.53, 66.98, 32.57, 24.91, 19.38, 17.72, 17.70, 17.43, 12.45, 12.43; LR GC/MS calculated for $[C_{13}H_{25}OSiI]^+$ = 352.0719, found = 352.

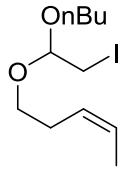
Synthesis of 51



To a -30 °C solution of ethyl vinyl ether (0.75 mL, 7.9 mmol) and (1S,5S)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ol)[32] (1.0 g, 6.6 mmol) in DCM (6.6 mL), N-iodosuccinimide (1.48 g, 6.6 mmol) was added portionwise. The reaction was stirred at -30 °C for 4 hours and allowed to warm to room

temperature overnight. It was then diluted with DCM. It was washed with H_2O, $Na_2S_2O_3$, and brine. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (25:1 Hex:EtOAc) to provide 2.02 g (87%) of **51** as a colorless oil. Analytical data for **51**: IR (thin film, cm^{-1}) 3078, 2972, 2918, 1644, 1450, 1373, 1323, 1179, 1103, 1029, 924, 889, 810, 609, 539; ^1H NMR (600 MHz, $CDCl_3$) δ ppm 1.24 (t, *J*=6.97 Hz, 3 H) 1.46 - 1.61 (m, 1 H) 1.68 - 1.83 (m, 6 H) 1.89 - 1.98 (m, 1 H) 2.00 - 2.07 (m, 1 H) 2.14 - 2.25 (m, 2 H) 3.19 - 3.29 (m, 2 H) 3.56 - 3.70 (m, 2 H) 4.06 - 4.27 (m, 1 H) 4.69 - 4.81 (m, 3 H) 5.53 (d, *J*=14.31 Hz, 1 H) 5.66 (d, *J*=19.44 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 148.80, 148.79, 134.73, 134.56, 125.11, 125.05, 109.21, 109.12, 102.78, 99.83, 78.15, 75.31, 60.99, 60.98, 40.68, 40.50, 35.94, 34.59, 30.82, 30.77, 20.39, 20.37, 19.89, 19.50, 15.20, 15.08, 6.28, 5.56; HRMS (ESI) calculated for $[C_{14}H_{23}O_2I+Na]$ = 373.06404, found = 373.06293.

Synthesis of 53

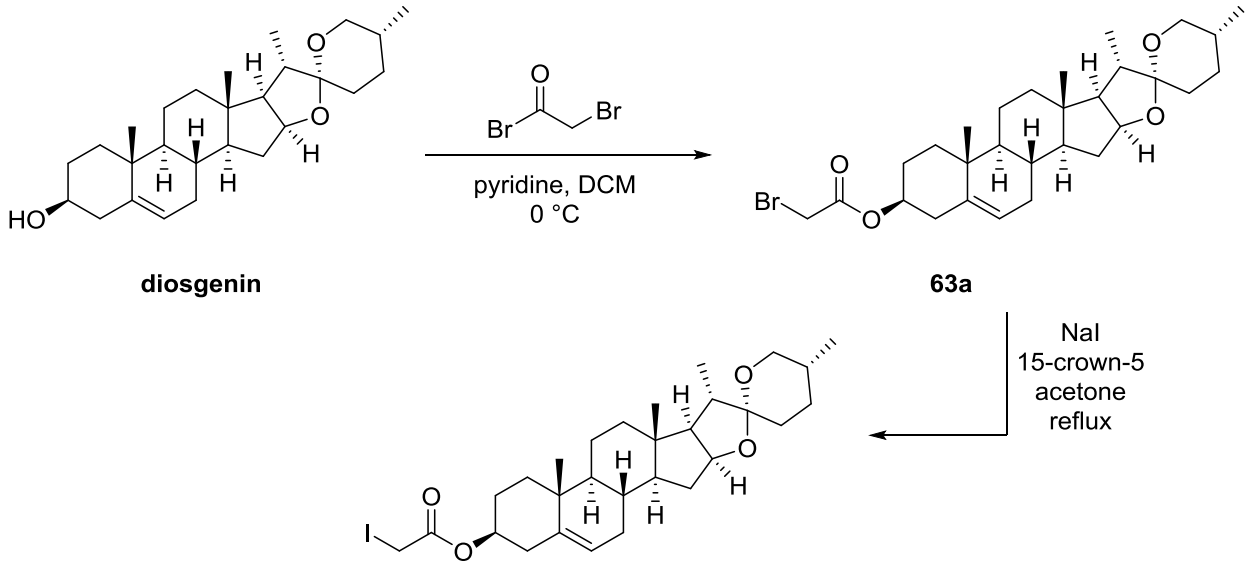


To a -30 °C solution of butyl vinyl ether (1.5 mL, 12 mmol) and cis-3-penten-1-ol (1.02 mL, 10 mmol) in DCM (10 mL), N-iodosuccinimide (2.25 g, 10 mmol) was added portionwise. The reaction was stirred at -30 °C for 4 hours. The reaction was allowed to warm to room temperature and then diluted with DCM. It was washed with H_2O, $Na_2S_2O_3$, and brine. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (20:1 Hex:EtOAc) to provide 2.98 g (96%) of **53** as a colorless oil. Analytical data for **53**: IR (thin film, cm^{-1}) 3747, 3016, 2958, 2870, 2360, 1650, 1459, 1344, 1176, 1111, 1045, 706; ^1H NMR (400MHz, $CDCl_3$) δ = 5.62 - 5.48 (m, *J* = 4.4, 6.8, 6.8, 6.8, 6.8 Hz, 1 H), 5.47 - 5.37 (m, 1 H), 4.62 (t, *J* = 5.5 Hz, 1 H), 3.62 (q, *J* = 7.6 Hz, 2 H), 3.55 - 3.42 (m, 2 H), 3.22 (d, *J* = 5.4 Hz, 2 H), 2.36 (q, *J* = 6.8 Hz, 2 H), 1.69 - 1.54 (m, 5 H), 1.49 - 1.28 (m, 2 H), 0.93 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 126.15, 126.07, 101.85, 66.40, 65.91, 31.68, 27.47, 19.29, 13.84, 12.90, 5.33.

Synthesis of 57

To a -30 °C solution of ethyl vinyl ether (0.82 mL, 8.68 mmol) and 4-vinylhepta-1,6-dien-4-ol[33] (1.0 g, 7.24 mmol) in DCM (7.1 mL), N-iodosuccinimide (1.63 g, 7.24 mmol) was added portionwise. The reaction was stirred at -30 °C for 4 hours. The reaction was allowed to warm to room temperature, stirred overnight, and then diluted with DCM. It was washed with H_2O, $Na_2S_2O_3$, and brine. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. Purified by flash chromatography (20:1 Hex:EtOAc) to provide 1.44 g (60%) of **57** as a colorless oil. Analytical data for **57**: IR (thin film, cm^{-1}) 3076, 2977, 2931, 1640, 1414, 1096, 1060, 1005, 916; ^1H NMR (400MHz, $CDCl_3$) δ = 5.78 - 5.94 (m, 3 H), 5.20 - 5.32 (m, 2 H), 5.03 - 5.11 (m, 4 H), 4.74 (t, J=5.38 Hz, 1 H), 3.53 (q, J=7.09 Hz, 2 H), 3.14 - 3.28 (m, 2 H), 2.36 - 2.51 (m, 4 H), 1.19 (t, J=6.97 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 140.63, 133.57, 133.33, 118.12, 117.96, 116.44, 96.61, 79.61, 60.20, 41.15, 40.54, 15.13, 7.10.

Synthesis of 63



1) **63a** To a solution of diosgenin (2.5 g, 6.0 mmol) in DCM (24 mL) at 0 ˚C, pyridine (0.97 mL, 12.0 mmol) was added slowly. Bromoacetyl bromide (1.05 mL, 12.0 mmol) was added slowly and the reaction was stirred at 0 ˚C and warmed to room temperature overnight. The reaction was then quenched with water, extracted with DCM (x3). The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated in vacuo. Purified by recrystallization (DCM & EtOAc) to provide 1.74 g (54%) of **63a** as a tan powder. Analytical data for **63a**: IR (thin film, cm^{-1}) 2939, 1747, 1377, 1285, 1174, 1076, 979, 893; ^1H NMR (600MHz, $CDCl_3$) δ = 5.39 (d, *J* = 4.4 Hz, 1 H), 4.70 - 4.64 (m, 1 H), 4.41 (q, *J* = 7.6 Hz, 1 H), 3.81 (s, 2 H), 3.49 - 3.45 (m, 1 H), 3.37 (t, *J* = 11.0 Hz, 1 H), 2.36 (d, *J* = 7.7 Hz, 2 H), 2.05 - 1.95 (m, 2 H), 1.92 - 1.83 (m, 3 H), 1.80 - 1.71 (m, 2 H), 1.68 - 1.41 (m, 10 H), 1.28 (dt, *J* = 6.2, 12.8 Hz, 1 H), 1.21 - 1.06 (m, 3 H), 1.04 (s, 3 H), 1.02 - 0.90 (m, 4 H), 0.85 - 0.76 (m, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.67, 139.19, 122.79, 109.27, 80.76, 76.01, 66.82, 61.99, 56.36, 49.83, 41.56, 40.21, 39.66, 37.71, 36.79, 36.67, 31.99, 31.80, 31.33, 30.26, 28.76, 27.43, 26.39, 20.77, 19.30, 17.13, 16.27, 14.52; HRMS (ESI) calculated for $[C_{29}H_{43}BrO_4+H]$ = 535.24229, found = 535.36096.

2) **63 -** 63a (1.0 g, 1.87 mmol) was dissolved in dry acetone (6.3 mL). Sodium iodide (0.84 g, 5.60 mmol) and 15-crown-5 (186 µL, 0.934 mmol) were added. The reaction was heated to reflux and stirred overnight. After cooling to room temperature, the mixture was diluted with DCM and stirred 15 minutes. The reaction was washed with $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purified by recrystallization (DCM & EtOAc) followed by flash chromatography (10:1 Hex:EtOAc) to provide 0.457 g (42%) of **63** as a white solid. Analytical data for **63**: IR (thin film, cm^{-1}) 2945, 2360, 1728, 1051, 751, 670, 513; ^1H NMR (400MHz, $CDCl_3$) δ = 5.41 (d, *J* = 4.0 Hz, 1 H), 4.68 - 4.62 (m, 1 H), 4.43 (q, *J* = 7.7 Hz, 1 H), 3.68 (s, 2 H), 3.50 - 3.48 (m, 1 H), 3.39 (t, *J* = 11.0 Hz, 1 H), 2.36 (d, *J* = 7.7 Hz, 2 H), 2.05 - 1.98 (m, 2 H), 1.91 - 1.87 (m, 3 H), 1.79 (dd, *J* = 7.0, 8.4 Hz, 1 H), 1.75 (td, *J* = 3.0, 12.3 Hz, 1 H), 1.70 - 1.43 (m, 10 H), 1.33 - 1.26 (m, 1 H), 1.23 - 1.10 (m, 3 H), 1.06 (s, 3 H), 1.02 - 0.96 (m, 4 H), 0.82 - 0.80 (m, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.29, 139.22, 122.71, 109.27, 80.77, 75.62, 66.82, 61.99, 56.36, 49.83, 41.56, 40.21, 39.66, 37.51, 36.76, 36.67, 31.99, 31.80, 31.33, 30.26, 28.76, 27.25, 20.78, 19.32, 17.13, 16.27, 14.52, -4.55; HRMS (ESI) calculated for $[C_{29}H_{43}O_4I+H]^+$ = 583.227884, found = 583.22774.

3.7.3 General Carboacylation Procedure

In a glovebox, the alkyl iodide (1.0 equiv), $KHCO_3$ (1.0 equiv), EtOH (0.2 M), and $Mn_2(CO)_{10}$ (2.5 mol %, unless otherwise noted) were combined in a sealed tube, the cap of which was fitted with a quick-connect adapter (see Figure 3-17). After removing the tube from the glovebox it was purged with 10 atm CO (x 3) and pressurized to 10 atm CO. The reaction was stirred at room temperature for 24 hours. After 24 hours, the tube was depressurized and 3-5 drops of DBU were added. The reaction was allowed to stir for 1 hour, after which it was diluted with EtOAc and washed with brine. The aqueous layer was then extracted with EtOAc (x3). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude mixture was then filtered through a silica plug with 10:1 hexanes:ethyl acetate. The resulting product was purified by flash chromatography with the specified solvent system.

3.7.4 Product Modification - Oxidation Procedure:

A solution of acetal product (30 mg, 0.12 mmol) in acetone (1.5 mL) was cooled to 0 ˚C. CrO_3 (60 mg, 0.60 mmol) was dissolved in 25% aqueous H_2SO_4 (375 µL) and that solution was added to acetone solution dropwise. The reaction was stirred at 0 ˚C for 2 hours. After completion, Et_2O was added, and the reaction was quenched with iPrOH and neutralized with saturated $NaHCO_3$. The mixture was extracted with Et_2O (x2) and the organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting product was purified by flash chromatography with the specified solvent system.

3.7.5 Description of reaction setup

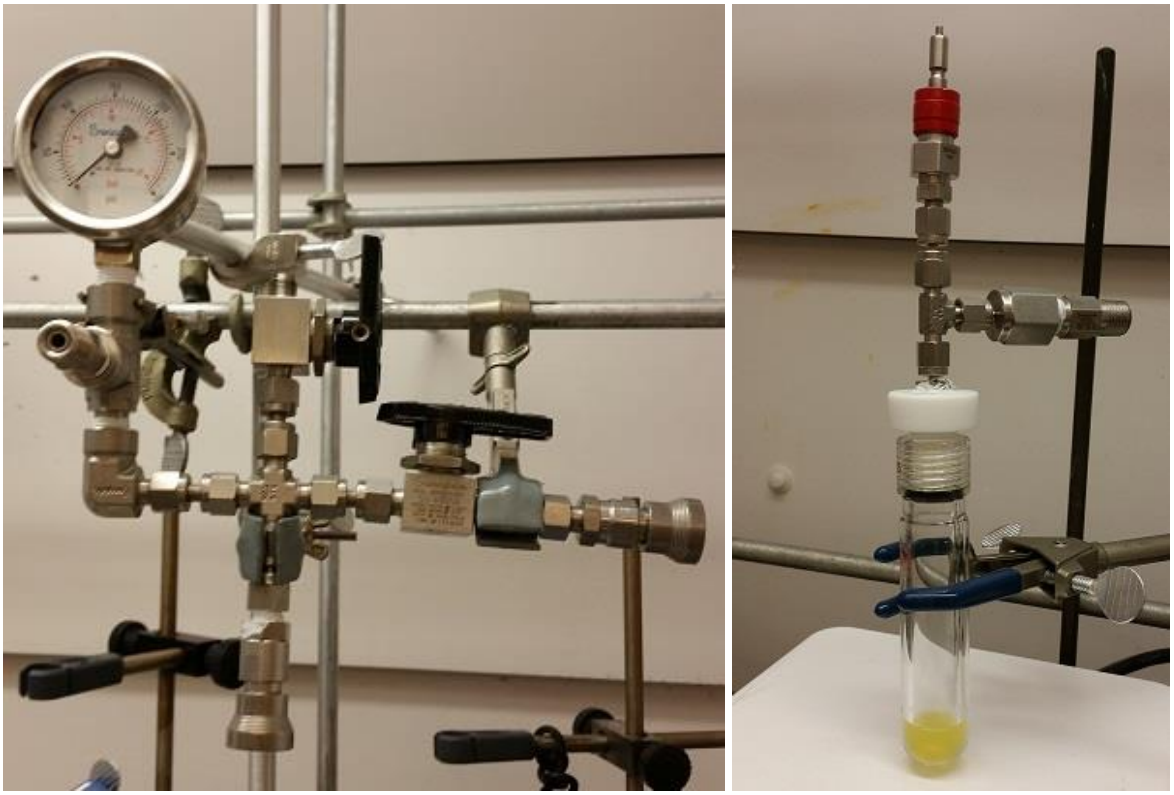
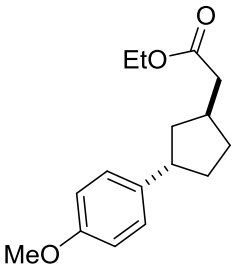


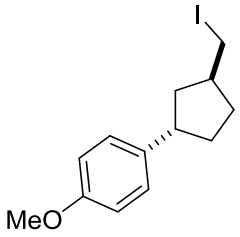
Figure 3-17. Photos of regulator used to pressurize CO reactions (left) and sealed tubes used to run CO reactions (right) – Each tube gets connected to the regulator via a quick-connect connection at the bottom connection on the regulator (left) and the red top connection on the tube adapter (right).

3.7.6 Manganese-Catalyzed Carboacylation Product Characterization

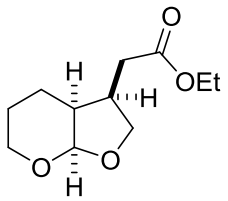
Table 3-2– entries 1-12:



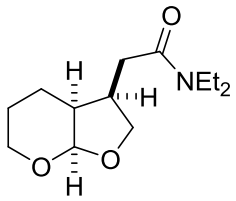
36 was synthesized according to the general procedure using **35** (94.9 mg, 0.30 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc) to afford **36** as a mixture of inseparable diastereomers (65.2 mg, 0.25 mmol, 83% yield, 2:1 d.r.) as a yellow oil. The major diastereomer was determined via 2D NMR analysis. Analytical data for **36**: IR (thin film, cm^{-1}) 2946, 2865, 2360, 1732, 1611, 1582, 1512, 1463, 1372, 1246, 1180, 1035, 828, 577, 539; ^{1}H NMR (600MHz, $CDCl_3$) δ = 7.17 - 7.09 (m, 2 H), 6.90 - 6.82 (m, 2 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 3.79 (s, 3 H), 3.12 - 3.00 (m, 1 H), 3.05 - 2.99 (m, 1 H), 2.56 (td, *J* = 7.5, 15.0 Hz, 0.8 H), 2.46 - 2.36 (m, 2 H), 2.27 - 2.21 (m, 0.4 H), 2.12 - 1.98 (m, 2 H), 1.88 (m, 0.8 H), 1.77 (m, 0.8 H), 1.70 - 1.57 (m, 1 H), 1.49 - 1.41 (m, 0.4 H), 1.36 - 1.28 (m, 0.8 H), 1.26 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.14, 157.66, 157.61, 138.25, 137.71, 127.76, 113.60, 60.12, 55.18, 44.80, 43.44, 41.83, 41.02, 40.67, 40.06, 36.30, 35.49, 35.05, 33.28, 32.94, 31.47, 14.23; HRMS (ESI) calculated for $[C_{16}H_{22}O_3+H]$ = 263.164171, found = 263.16400.



71 was synthesized according to the general procedure using **35** (189.7 mg, 0.60 mmol) and $KHCO_3$ (60 mg, 0.60 mmol), with no CO pressure and benzene (4.6 mL) instead of EtOH. The resulting ester was purified by flash chromatography (hexanes) to afford **71** as a mixture of inseparable diastereomers (173 mg, 0.55 mmol, 90% yield, 3:1 d.r.) as a pale yellow oil. The major diastereomer was determined in analogy to **36**. Analytical data for **71**: IR (thin film, cm^{-1}) 2947, 2859, 2360, 1611, 1511, 1460, 1245, 1178, 1036, 828, 585, 537; ^{1}H NMR (600MHz, $CDCl_3$) δ = 7.19 - 7.08 (m, 2 H), 6.90 - 6.84 (m, 2 H), 3.81 (s, 3 H), 3.35 - 3.25 (m, 2 H), 3.14 (d, *J* = 7.1 Hz, 1 H), 2.54 - 2.45 (m, 0.75 H), 2.39 - 2.28 (m, 0.5 H), 2.21 - 2.08 (m, 1.75 H), 1.93 - 1.84 (m, 1.5 H), 1.79 - 1.64 (m, 1 H), 1.60 - 1.51 (m, 0.5 H), 1.45 - 1.30 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 157.76, 157.70, 137.66, 137.18, 127.78, 127.74, 113.64, 55.22, 45.29, 43.72, 42.80, 42.21, 41.64, 40.99, 35.26, 34.05, 33.59, 32.36, 14.93, 14.22; LR GC/MS calculated for $[C_{13}H_{17}OI]^+$ = 316.0324, found = 316.

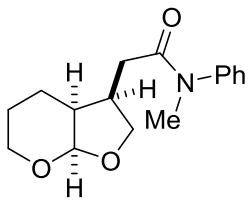


38 was synthesized according to the general procedure using **37** (80.4 mg, 0.30 mmol). The resulting ester was purified by flash chromatography (10:1 followed by 2:1 Hex:EtOAc) to afford **38** as a mixture of inseparable diastereomers (49.2 mg, 0.23 mmol, 77% yield, 10:1 d.r.) as a colorless oil. The major diastereomer was determined via 2D NMR analysis. Analytical data for **38**: IR (thin film, cm^{-1}) 2938, 1732, 1371, 1255, 1178, 1146, 1023, 950, 903; ^1H NMR (400MHz, $CDCl_3$) δ = 5.28 (d, *J* = 3.7 Hz, 0.9 H), 5.00 (d, *J* = 3.3 Hz, 0.1 H), 4.41 (t, J = 8.4 Hz, 0.1 H), 4.13 (q, *J* = 7.3 Hz, 2 H), 4.04 (t, *J* = 8.1 Hz, 0.9 H), 3.77 - 3.59 (m, 2.9 H), 3.42 (dt, *J* = 2.4, 11.6 Hz, 0.1 H), 2.80 - 2.72 (m, 1 H), 2.53 (dd, *J* = 4.8, 15.8 Hz, 0.1 H), 2.45 (dd, *J* = 7.3, 16.1 Hz, 0.9 H), 2.34 (dd, *J* = 8.1, 16.1 Hz, 0.9 H), 2.26 (dd, *J* = 9.7, 16.0 Hz, 0.1 H), 2.10 - 2.05 (m, 1 H), 1.71 - 1.53 (m, 3H), 1.43 - 1.36 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = Major: 172.17, 101.67, 69.63, 61.06, 60.55, 36.90, 36.41, 32.59, 22.87, 19.49, 14.13; Minor: 101.59, 73.58, 64.38, 43.61, 37.25, 34.40, 22.14, 20.46; HRMS (ESI) calculated for $[C_{11}H_{18}O_4+Na]$ = 237.109760, found = 237.10957.

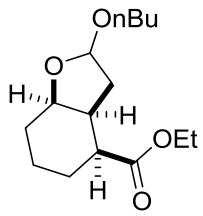


39 was synthesized according to the general procedure using **37** (80.4 mg, 0.30 mmol), 2 equiv $KHCO_3$ (60 mg, 0.60 mmol), 2 equiv Et_2NH (62 µL, 0.60 mmol). The resulting amide was purified by flash chromatography (1:1 Hex:EtOAc) to afford **39** (48.7 mg, 0.20 mmol, 67% yield, 8:1 d.r.) as a pale orange oil. The major diastereomer was determined in analogy to **38**. Analytical data for **39**: IR (thin film, cm^{-1}) 3492, 2934, 1638, 1434, 1379, 1251, 1221, 1142, 1100, 1021, 949, 902, 603; ^1H NMR (600MHz, $CDCl_3$) δ = 5.31 (d, *J* = 3.7 Hz, 0.85 H), 5.04 (d, *J* = 3.4 Hz, 0.15 H), 4.50 (t, *J* = 8.4 Hz, 0.15 H), 4.11 (t, *J* = 8.2 Hz, 0.85 H), 3.94 - 3.58 (m, 3 H), 3.48 - 3.27 (m, 4 H), 2.93 - 2.72 (m, 1 H), 2.60 (dd, *J* = 4.6, 15.9 Hz,

0.15 H), 2.51 - 2.43 (m, 0.85 H), 2.40 - 2.26 (m, 1 H), 2.19 (m, 1 H), 1.85 - 1.64 (m, 1 H), 1.63 - 1.56 (m, 2 H), 1.52 - 1.35 (m, 1 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H) ^{13}C NMR (151 MHz, $CDCl_3$) δ = Major: 170.17, 101.80, 70.15, 61.13, 41.84, 40.07, 37.02, 36.50, 31.09, 23.03, 19.75, 14.23, 13.00; Minor: 101.49, 74.21, 64.26, 43.58, 36.82, 34.87, 22.50, 20.63; HRMS (ESI) calculated for [$C_{13}H_{23}NO_3$+H] = 242.175070, found = 242.17486.

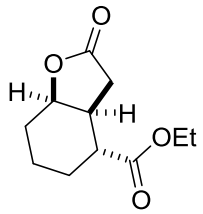


40 was synthesized according to the general procedure using **37** (80.4 mg, 0.30 mmol), 2 equiv $KHCO_3$ (60 mg, 0.60 mmol), 2 equiv N-methylaniline (65 µL, 0.60 mmol), and 5 mol % $Mn_2(CO)_{10}$ (5.8 mg, 0.015 mmol). The resulting amide was purified by flash chromatography (1:1 Hex:EtOAc) to afford **40** (60.1 mg, 0.22 mmol, 73% yield, 10:1 d.r.) as a white solid. The major diastereomer was determined in analogy to **38**. Analytical data for **40**: IR (thin film, cm^{-1}) 3503, 2938, 1655, 1594, 1495, 1421, 1390, 1293, 1251, 1205, 1144, 1020, 948, 903, 870, 776, 702, 649, 562, 523; ^{1}H NMR (600MHz ,$CDCl_3$) δ = 7.46 (t, *J* = 7.8 Hz, 2 H), 7.41 - 7.36 (m, 1 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 5.28 (d, *J* = 3.7 Hz, 0.9 H), 4.93 (d, *J* = 3.2 Hz, 0.1 H), 4.44 (t, *J* = 8.7 Hz, 0.1 H), 4.01 (t, *J* = 8.3 Hz, 0.9 H), 3.90 - 3.85 (m, 0.1 H), 3.75 - 3.53 (m, 2.9 H), 3.28 (s, 3 H), 2.92 - 2.65 (m, *J* = 8.8 Hz, 1 H), 2.27 - 2.00 (m, 3 H), 1.56 - 1.41 (m, 3 H), 1.30 - 1.16 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = Major: 171.20, 143.67, 129.85, 127.94, 127.09, 101.63, 69.70, 60.87, 37.21, 37.17, 36.18, 32.11, 22.86, 19.41; Minor: 171.47, 143.74, 127.24, 101.38, 73.93, 64.21, 43.32, 37.53, 36.26, 34.93, 29.60, 22.22, 20.49; HRMS (ESI) calculated for [$C_{16}H_{21}NO_3$+H] = 276.159420, found = 276.15927.



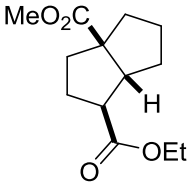
42 was synthesized according to the general procedure using **41** (97.3 mg, 0.30 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc) to afford **42** (73.2 mg, 0.27 mmol, 90% yield, 7:1 d.r. with respect to cyclization/carbonylation – determined by oxidation of acetal (see **42a**) as a pale orange oil. The major diastereomer was determined by comparison of **42a** to similar radical cyclizations.[27,34,35] Analytical data for **42**: IR (thin film, cm^{-1}) 2937, 2868, 1730, 1450, 1375, 1292, 1256, 1175, 1094, 1069, 1027, 909; ^{1}H NMR (400MHz, C_6D_6) δ = 5.19 - 5.03 (m, 1 H), 4.21 - 4.08 (m, 2.5 H), 4.08 - 4.03 (m, 0.5 H), 3.77 - 3.63 (m, 1 H), 3.43 - 3.31 (m, 1 H), 2.84 (m, 1 H), 2.30 - 2.21 (m, 1 H), 2.18 - 2.10 (m, 1 H), 2.08 - 1.82 (m, 3 H), 1.63 - 1.47 (m, 5 H), 1.42 - 1.29 (m, 3 H), 1.28 - 1.21 (m, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (151 MHz, C_6D_6) δ = Major: 176.01, 175.57, 103.71, 103.17, 77.56, 74.39, 67.94, 67.55, 60.31, 60.16, 45.06, 43.02, 39.67, 39.33, 38.85, 37.53, 31.73, 28.10, 27.99, 27.89, 26.80, 19.41, 19.39, 19.34, 19.28, 14.19, 14.17, 13.81, 13.79; Minor: 174.21, 173.89, 102.91, 77.94, 68.11, 66.98, 60.30, 60.24, 41.65, 39.28, 36.35, 32.16, 31.83, 31.68, 29.21, 29.08, 22.09, 21.92, 20.92, 19.29, 13.77; HRMS (ESI) calculated for [$C_{15}H_{26}O_4$+Na] = 293.172360, found = 293.17207.

Oxidized product:

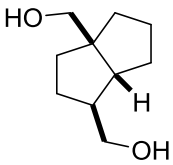


42a was synthesized according to the general oxidation procedure using **42** (30 mg, 0.11 mmol). The resulting lactone was purified by flash chromatography (2:1 Hex:EtOAc) to afford **42a** as a mixture of inseparable diastereomers (18 mg, 0.08 mmol, 77% yield, 7:1 d.r.) as a colorless oil. Analytical data for **42a**: IR (thin film, cm^{-1}) 2938, 1778, 1727, 1297, 1155, 559; ^{1}H NMR (400MHz, $CDCl_3$) δ = 4.59 (q, *J* = 3.5 Hz, 0.88 H), 4.57 - 4.53 (m, 0.12 H), 4.17 - 4.12 (m, 2 H), 3.11 - 3.03 (m, 0.12 H), 2.70 (dd, *J* = 6.8, 17.1

Hz, 0.88 H), 2.66 - 2.61 (m, 0.88 H), 2.52 - 2.45 (m, 0.12 H), 2.41 - 2.35 (m, 1 H), 2.26 - 2.19 (m, 1.76 H), 2.17 - 2.11 (m, 0.12 H), 2.00 - 1.95 (m, 0.88 H), 1.93 - 1.87 (m, 0.12 H), 1.87 - 1.80 (m, 0.12 H), 1.68 - 1.57 (m, 2 H), 1.54 - 1.47 (m, 1 H), 1.41 - 1.34 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = Major: 176.62, 174.18, 78.51, 60.89, 43.59, 37.37, 37.15, 26.90, 26.86, 18.81, 14.15; Minor: 176.09, 172.78, 42.08, 36.22, 28.69, 28.32, 21.93, 21.07; HRMS (ESI) calculated for [$C_{11}H_{16}O_4$+H] = 213.112135, found = 213.11200.

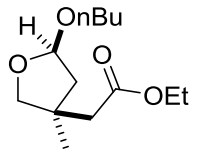


44 was synthesized according to the general procedure using **43** (88.2 mg, 0.30 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc) to afford **44** (64.2 mg, 0.27 mmol, 89% yield, 7:1 d.r.) as a colorless oil. The major diastereomer was determined via 2D NMR analysis of reduced product **44a**. Analytical data for **44**: ^{1}H NMR (600 MHz, C_6D_6) δ = 3.98 - 3.92 (m, 2 H), 3.32 - 3.29 (m, 3 H), 3.29 - 3.24 (m, 0.88 H), 3.14 - 3.08 (m, 0.12 H), 2.88 - 2.83 (m, 0.12 H), 2.50 (ddd, *J* = 3.5, 6.5, 12.7 Hz, 0.88 H), 2.37 - 2.31 (m, 0.12 H), 2.26 - 2.21 (m, 0.88 H), 2.10 - 1.94 (m, 2 H), 1.79 - 1.73 (m, 2 H), 1.55 - 1.44 (m, 2 H), 1.41 - 1.29 (m, 2 H), 1.19 - 1.14 (m, 1 H), 0.98 - 0.92 (m, 3 H); ^{13}C NMR (151 MHz, C_6D_6) δ = Major: 177.41, 173.99, 59.87, 59.82, 52.80, 51.67, 51.26, 38.24, 36.90, 33.01, 30.54, 25.50, 13.93; Minor: 177.33, 172.54, 59.58, 59.37, 51.22, 50.69, 48.26, 38.67, 36.03, 30.01, 26.97, 26.91, 14.02; HRMS (ESI) calculated for [$C_{13}H_{20}O_4$+Na]$^+$ = 263.125410; found = 263.12542.

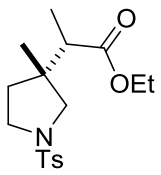


44a was made from **44** (12 mg, 0.05 mmol), added dropwise to a slurry of $LiAlH_4$ (5 mg, 0.13 mmol) in Et_2O (600 µL) at 0 ˚C. The reaction was warmed to room temperature and stirred overnight. It was quenched with water and 10% NaOH, extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo.

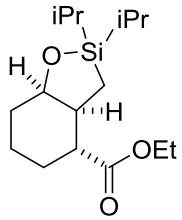
The resulting diol was purified by flash chromatography (1:2 Hex:EtOAc) to afford **44a** (0.05 mmol, quantitative yield) as a colorless oil. Analytical data for **44a**: IR (thin film, cm^{-1}) 3326, 2934, 2856, 1466, 1034, 527; ^{1}H NMR (600MHz, C_6D_6) δ = 3.44 - 3.36 (m, 2 H), 3.26 - 3.20 (m, 2 H), 1.84 - 1.78 (m, 1 H), 1.73 (dt, *J* = 3.1, 7.4 Hz, 1 H), 1.68 - 1.61 (m, 1 H), 1.61 - 1.56 (m, 1 H), 1.54 - 1.46 (m, 3 H), 1.41 - 1.26 (m, 5 H), 1.20 (ddd, *J* = 6.6, 9.8, 12.6 Hz, 2 H); ^{13}C NMR (151 MHz, C_6D_6) δ = 69.58, 65.87, 55.95, 50.33, 48.53, 37.05, 35.87, 33.44, 29.30, 25.51; HRMS (ESI) calculated for $[C_{10}H_{18}O_2+H]$ = 171.137956, found = 171.13783.



46 was synthesized according to the general procedure using **45** (89.5 mg, 0.30 mmol) and 5 mol % $Mn_2(CO)_{10}$ (5.8 mg, 0.015 mmol). The resulting ester was purified by flash chromatography (20:1 Hex:EtOAc) to afford **46** as a mixture of inseparable diastereomers (55.2 mg, 0.23 mmol, 77% yield, 8:1 d.r.) as a yellow oil. The major diastereomer was determined via 2D NMR analysis. Analytical data for **46**: IR (thin film, cm^{-1}) 2960, 2872, 1733, 1460, 1369, 1344, 1204, 1096, 1033, 931, 580; ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.13 (dd, *J* = 2.8, 5.7 Hz, 0.89 H), 5.12 - 5.10 (m, 0.11 H), 4.12 (q, *J* = 7.3 Hz, 2 H), 3.80 (d, *J* = 8.8 Hz, 1 H), 3.70 - 3.62 (m, 2 H), 3.36 (td, *J* = 6.6, 9.5 Hz, 1 H), 2.50 (s, 1.8 H), 2.36 - 2.33 (m, 0.2 H), 1.96 (dd, *J* = 5.5, 13.6 Hz, 1 H), 1.83 (dd, *J* = 2.9, 13.6 Hz, 1 H), 1.57 - 1.50 (m, 2 H), 1.39 - 1.31 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.14 (s, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = Major: 171.79, 104.34, 77. 11, 67.49, 60.22, 46.27, 44.43, 40.50, 31.76, 24.97, 19.32, 14.20, 13.84; Minor: 104.50, 76.66, 64.20, 63.13, 45.69, 44.44, 41.24, 30.59, 23.61, 19.15, 15.23, 13.66; HRMS (ESI) calculated for $[C_{13}H_{24}O_4+Na]$ = 267.156710, found = 267.15644.

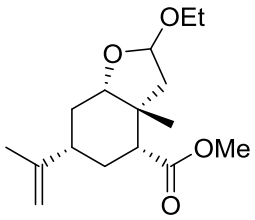


48 was synthesized according to the general procedure using **47** (118 mg, 0.30 mmol) and 5 mol % $Mn_2(CO)_{10}$ (5.8 mg, 0.015 mmol). The resulting ester was purified by flash chromatography (2:1 Hex:EtOAc) to afford **48** as a mixture of inseparable diastereomers (80.4 mg, 0.24 mmol, 79% yield, 1:1 d.r.) as a pale orange oil. Analytical data for **48**: IR (thin film, cm^{-1}) 2977, 2880, 1727, 1597, 1453, 1344, 1192, 1159, 1094, 1058, 860, 816, 731, 709, 663, 593, 548; ^1H NMR (400MHz, $CDCl_3$) δ = 7.70 (dd, *J* = 3.1, 8.3 Hz, 2 H), 7.32 (dd, *J* = 1.5, 8.4 Hz, 2 H), 4.14 - 4.05 (m, 2 H), 3.39 - 3.34 (m, 1 H), 3.27 - 3.21 (m, 1 H), 3.21 - 3.14 (m, 1 H), 3.04 (s, 1 H), 2.43 (s, 3 H), 2.35 - 2.31 (m, 1 H), 1.83 (td, *J* = 9.2, 12.8 Hz, 0.5 H), 1.64 - 1.55 (m, 1.5 H), 1.22 (dt, *J* = 7.1, 18.2 Hz, 3 H), 1.07 – 1.06 (d, *J* = 4.4 Hz, 3 H), 0.84 (s, 1.5 H), 0.78 (s, 1.5 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.18, 174.03, 143.37, 143.29, 133.72, 133.56, 129.56, 129.54, 127.36, 60.35, 60.26, 58.66, 58.02, 46.92, 46.55, 46.14, 43.78, 43.74, 36.68, 36.53, 21.46, 19.97, 19.46, 14.16, 14.14, 12.94, 12.56; HRMS (ESI) calculated for [$C_{17}H_{25}NO_4S$+H] = 340.157705, found = 340.15748.



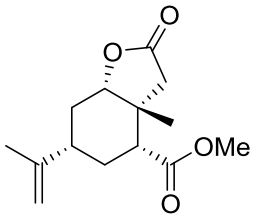
50 was synthesized according to the general procedure using **49** (105.7 mg, 0.30 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc) to afford **50** (64.7 mg, 0.22 mmol, 72% yield, 9:1 d.r.) as a colorless oil. The major diastereomer was determined by comparison to other similar radical cyclizations.[27,34,35] Analytical data for **50**: IR (thin film, cm^{-1}) 2938, 2864, 1732, 1463, 1372, 1288, 1243, 1164, 1141, 1068, 1035, 977, 906, 882, 832, 792, 714, 613; ^1H NMR (400MHz, $CDCl_3$) δ = 4.22 - 4.06 (m, 2 H), 4.06 - 3.97 (m, 0.9 H), 3.78 - 3.75 (m, 0.1 H), 2.72 - 2.65 (m, 0.1 H), 2.65 - 2.59 (m, 0.1 H), 2.36 - 2.25 (m, 1.8 H), 2.04 - 1.87 (m, 1 H), 1.85 - 1.70 (m, 1 H), 1.61 - 1.42 (m, 4 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.12 - 0.97 (m, 15 H), 0.95 - 0.88 (m, 1 H), 0.64 (dd, *J* = 1.8, 15.0 Hz, 0.9 H), 0.48 - 0.44 (m, 0.1 H);

^{13}C NMR (151 MHz, $CDCl_3$) δ = Major: 175.90, 75.88, 60.14, 45.49, 39.35, 30.63, 28.00, 19.13, 17.95, 17.84, 17.46, 17.32, 14.24, 13.02, 12.99, 11.68; Minor: 174.21, 77.49, 60.04, 44.80, 39.78, 30.90, 22.58, 21.20, 17.69, 17.45, 17.35, 14.29, 13.06, 12.77, 4.21; HRMS (ESI) calculated for [$C_{16}H_{30}O_3Si$+H] = 299.203702, found = 299.20349.



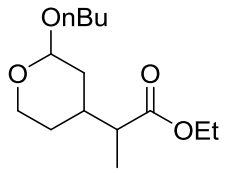
52 was synthesized according to the general procedure using **51** (105 mg, 0.30 mmol) and 10 mol% $Mn_2(CO)_{10}$ (11.7 mg, 0.03 mmol) in MeOH (2.3 mL) instead of EtOH. The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc) to afford **52** (56.6 mg, 0.20 mmol, 67% yield, 3:1 d.r. with respect to cyclization/carbonylation (see **52a**)) as colorless oil. The major diastereomer was determined via 2D NMR analysis of the oxidized product **52a**. Analytical data for **52**: ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.26 - 5.17 (m, 0.8 H), 5.10 (dd, *J* = 2.1, 5.7 Hz, 0.2 H), 4.77 - 4.71 (m, 2 H), 3.98 (dd, *J* = 6.2, 10.4 Hz, 0.2 H), 3.91 - 3.72 (m, 1.6 H), 3.72 - 3.65 (m, 3.2 H), 3.53 - 3.43 (m, 1 H), 2.97 (t, *J* = 5.1 Hz, 0.2 H), 2.65 - 2.45 (m, 1.2 H), 2.39 - 2.33 (m, 0.2 H), 2.21 (dd, *J* = 5.4, 13.7 Hz, 0.4 H), 2.00 - 1.84 (m, 2.4 H), 1.81 - 1.57 (m, 6.6 H), 1.29 - 1.16 (m, 5.4 H), 1.10 (s, 0.6 H); HRMS (ESI) calculated for [$C_{16}H_{26}O_4$+Na]$^+$ = 305.172360, found = 305.17249.

Oxidized product:



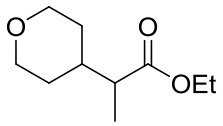
52a was synthesized according to the general oxidation procedure using **52** (30 mg, 0.106 mmol). The resulting lactone was purified by flash chromatography (2:1 Hex:EtOAc) to afford **52a** as a mixture of inseparable diastereomers (11.4 mg, 0.045 mmol, 43% yield, 3:1 d.r.) as a colorless oil. Analytical data

for **52a**: ^{1}H NMR (400MHz, C_6D_6) δ = 4.65 (t, *J* = 25.7 Hz, 1 H), 4.51 (s, 1 H), 4.10 (dd, *J* = 5.9, 9.5 Hz, 0.3 H), 3.44 (dd, *J* = 6.2, 11.0 Hz, 0.7 H), 3.20 (s, 2.1 H), 3.16 (s, 0.9 H), 2.58 (d, 0.7 H), 2.35 (t, *J* = 5.3 Hz, 0.3 H), 2.26 (d, *J* = 16.9 Hz, 0.3 H), 2.10 (d, *J* = 17.6 Hz, 0.7 H), 1.99 (dd, *J* = 3.9, 12.7 Hz, 0.7 H), 1.87 - 1.74 (m, 1 H), 1.63 (d, *J* = 17.2 Hz, 0.3 H), 1.56 - 1.48 (m, 1 H), 1.45 (s, 0.9 H), 1.39 (s, 2.1 H), 1.33 (ddd, *J* = 4.4, 9.5, 14.3 Hz, 0.7 H), 1.28 - 1.15 (m, 1 H), 1.13 - 1.06 (m, 0.3 H), 0.88 - 0.87 (m, 2.1 H), 0.87 - 0.83 (m, 0.9 H), 0.82 - 0.81 (m, 1 H)^{13}C NMR (151 MHz, C_6D_6) δ = Major: 174.80, 172.72, 147.05, 110.06, 83.78, 51.14, 49.41, 40.14, 39.87, 36.13, 35.11, 30.31, 26.24, 20.55; Minor: 174.20, 173.58, 109.91, 82.93, 51.04, 45.23, 39.92, 39.30, 35.94, 33.03, 27.92, 22.67, 21.04; HRMS (ESI) calculated for $[C_{14}H_{20}O_4+H]^+$ = 253.143436, found = 253.14369.

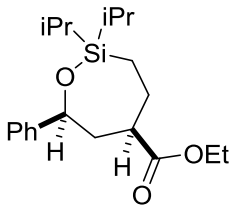


54 was synthesized according to the general procedure using **53** (93.7 mg, 0.30 mmol) and 5 mol % $Mn_2(CO)_{10}$ (5.8 mg, 0.015 mmol). The resulting ester was purified by flash chromatography (20:1 Hex:EtOAc) to afford **54** as a complex mixture of 4 diastereomers (49.3 mg, 0.19 mmol, 64% yield) as a colorless oil. Analytical data for **54**: IR (thin film, cm^{-1}) 2958, 2935, 2874, 2360, 1733, 1461, 1374, 1342, 1246, 1176, 1129, 1073, 985, 892, 851, 812; ^{1}H NMR (400MHz, $CDCl_3$) δ = 4.83 (dd, *J* = 2.9, 9.3 Hz, 0.75 H), 4.38 - 4.34 (m, 0.25 H), 4.20 - 4.11 (m, 2 H), 4.10 - 4.00 (m, 0.25 H), 3.90 - 3.75 (m, 1 H), 3.70 - 3.58 (m, 1.5 H), 3.50 - 3.41 (m, 0.5 H), 3.41 - 3.33 (m, 0.75 H), 2.34 - 2.26 (m, 0.25 H), 2.26 - 2.13 (m, 1.5 H), 1.92 - 1.86 (m, 0.25 H), 1.83 - 1.76 (m, 0.25 H), 1.69 - 1.49 (m, 4 H), 1.47 - 1.32 (m, 4 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.20 - 1.11 (m, 3 H), 0.98 - 0.90 (m, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.83, 175.80, 175.77, 175.68, 101.72, 101.63, 96.65, 68.74, 66.76, 66.73, 64.99, 64.78, 60.34, 60.31, 60.17, 59.31, 59.23, 45.22, 44.79, 44.74, 44.72, 37.25, 37.18, 36.23, 34.88, 34.85, 34.48, 33.97, 32.39, 32.16, 31.86, 31.85, 31.77, 31.61, 29.91, 29.88, 28.91, 28.42, 22.68, 19.49, 19.32, 19.29, 18. 91, 14.33, 14.31, 14.30, 14.27, 14.07, 14.04, 14.03, 13.96, 13.92, 13.44; HRMS (ESI) calculated for $[C_{14}H_{26}O_4+Na]$ = 281.172360, found = 281.17218.

Reduced product:

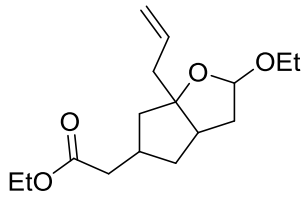


54a was synthesized by dissolving **54** (25 mg, 0.10 mmol) in DCM (2.5 mL) at -30 ˚C and adding Et_3SiH (16 µL, 0.10 mmol) and BF_3•OEt_2 (7.7 µL, 0.03 mmol). The reaction was warmed to -10 ˚C and stirred for 4 hours. An additional 16 µL of Et_3SiH was then added and the mixture stirred overnight at room temperature and then concentrated. The resulting tetrahydropyran was purified by flash chromatography (5:1 Hex:EtOAc) to afford **54a** (11.7 mg, 0.062 mmol, 64% yield) as a colorless oil. Analytical data for **54a**: IR (thin film, cm^{-1}) 2931, 1732, 1453, 1176, 1093; ^1H NMR (400MHz, $CDCl_3$) δ = 4.15 (q, *J* = 7.1 Hz, 2 H), 4.05 - 3.93 (m, 2 H), 3.48 - 3.33 (m, 2 H), 2.27 (quin, *J* = 7.3 Hz, 1 H), 1.85 - 1.73 (m, 1 H), 1.71 - 1.57 (m, 1 H), 1.57 - 1.48 (m, 1 H), 1.47 - 1.31 (m, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.15 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.88, 67.95, 67.85, 60.17, 45.09, 38.00, 30.95, 29.73, 14.26, 13.90; HRMS (ESI) calculated for $[C_{10}H_{18}O_3+H]$ = 187.132871, found = 187.13274.



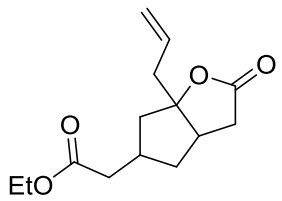
56 was synthesized according to the general procedure using **55**[30] (120.7 mg, 0.30 mmol) and 5 mol % $Mn_2(CO)_{10}$ (5.8 mg, 0.015 mmol). The resulting ester was purified by flash chromatography (hexanes, then 2:1 Hex:EtOAc) to afford **56** (81.4 mg, 0.23 mmol, 78% yield, 3:1 d.r.) as colorless oil. The major diastereomer was determined via 2D NMR analysis. Analytical data for **56**: IR (thin film, cm^{-1}) 2939, 2864, 2360, 1730, 1462, 1369, 1306, 1236, 1159, 1095, 1067, 1037, 884, 797, 737, 698; ^1H NMR (400MHz, $CDCl_3$) δ = 7.44 (d, *J* = 7.0 Hz, 0.5 H), 7.39 (d, *J* = 7.3 Hz, 1.5 H), 7.32 (t, *J* = 7.5 Hz, 2.25 H), 7.25 - 7.22 (m, 0.75 H), 5.25 (d, *J* = 7.3 Hz, 0.25 H), 4.85 (d, *J* = 9.9 Hz, 0.75 H), 4.20 - 4.16 (m, 0.5 H), 4.11 - 4.05 (m, 1.5 H), 2.76 - 2.71 (m, 0.25 H), 2.50 - 2.45 (m, 0.75 H), 2.35 - 2.16 (m, 2 H), 2.03 - 1.76 (m, 2 H), 1.29 (t, *J* = 7.2 Hz, 0.75 H), 1.22 (t, *J* = 7.2 Hz, 2.25 H), 1.12 - 1.00 (m, 8 H), 0.99 - 0.94 (m, 6.5 H), 0.91 - 0.79

(m, 1.5 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = Major: 176.02, 145.86, 128.07, 127.99, 126.84, 125.22, 125.14, 75.62, 60.40, 49.26, 45.05, 26.86, 17.88, 17.76, 17.64, 17.42, 13.49, 9.61; Minor: 175.54, 145.79, 128.20, 126.95, 126.49, 126.40, 125.19, 60.34, 60.24, 45.56, 42.49, 41.80, 24.71, 17.85, 17.67, 17.51, 14.32, 12.87, 7.17; HRMS (ESI) calculated for [$C_{20}H_{32}O_3Si$+Na] = 371.201326, found = 371.20094.

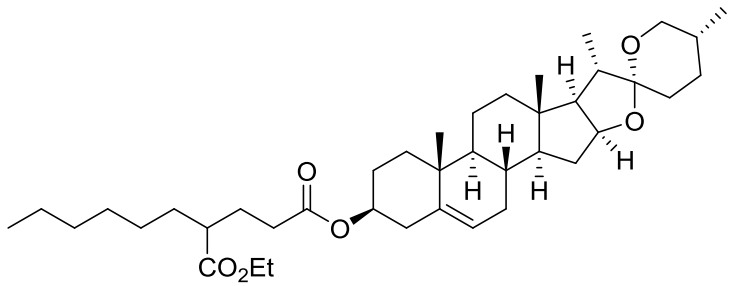


58 was synthesized according to the general procedure using **57** (100.9 mg, 0.30 mmol) and 5 mol % $Mn_2(CO)_{10}$ (5.8 mg, 0.015 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc) to afford **58** (65.4 mg, 0.23 mmol, 77% yield, 1.5:1 d.r. with respect to cyclization/carbonylation (see **59**)) as a pale yellow oil. Analytical data for **58**: IR (thin film, cm^{-1}) 3074, 2976, 2938, 1735, 1640, 1443, 1374, 1339, 1242, 1159, 1101, 1002, 916; ^{1}H NMR (400MHz ,$CDCl_3$) δ = 5.95 - 5.73 (m, 1 H), 5.22 - 5.03 (m, 3 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.83 - 3.65 (m, 1 H), 3.44 - 3.32 (m, 1 H), 2.63 - 2.48 (m, 1 H), 2.45 - 2.19 (m, 5 H), 2.17 - 2.02 (m, 2 H), 1.96 - 1.70 (m, 2 H), 1.68 - 1.57 (m, 1 H), 1.47 - 1.32 (m, 1 H), 1.27 - 1.14 (m, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.99, 172.97, 172.82, 172.79, 135.02, 134.71, 134.10, 117.82, 117.45, 117.39, 117.26, 106.20, 105.93, 104.63, 104.40, 96.19, 95.10, 94.95, 94.93, 62.77, 62.44, 62.05, 60.21, 60.19, 60.16, 60.06, 46.68, 46.24, 46.23, 45.35, 45.28, 45.26, 45.16, 45.07, 44.65, 44.27, 44.08, 43.69, 41.42, 41.07, 40.48, 40.23, 39.99, 39.91, 39.83, 39.80, 39.63, 39.49, 38.94, 38.40, 37.14, 36.78, 33.74, 33.63, 15.17, 15.08, 15.02, 14.21; HRMS (ESI) calculated for [$C_{16}H_{26}O_4$+Na] = 305.172360, found = 305.17200.

Oxidized product:



59 was synthesized according to the general oxidation procedure using **58** (30 mg, 0.11 mmol). The resulting lactone was purified by flash chromatography (2:1 Hex:EtOAc) to afford **59** as a mixture of inseparable diastereomers (25 mg, 0.10 mmol, 90% yield, 1.5:1 d.r.) as a colorless oil. Analytical data for **59**: IR (thin film, cm^{-1}) 3525, 2935, 1771, 1731, 1641, 1418, 1378, 1206, 1156, 1028, 979, 926; ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.81 - 5.73 (m, 1 H), 5.20 - 5.15 (m, 2 H), 4.11 (q, *J* = 7.0 Hz, 2 H), 2.87 - 2.81 (m, 0.65 H), 2.74 - 2.64 (m, 1 H), 2.56 - 2.45 (m, 2 H), 2.43 - 2.19 (m, 6 H), 1.77 (dd, *J* = 6.2, 13.2 Hz, 0.65 H), 1.71 - 1.55 (m, 1.35 H), 1.34 (dd, *J* = 12.1, 13.6 Hz, 0.65 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.20 - 1.12 (m, 0.35 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.02, 176.58, 172.34, 172.12, 131.87, 131.53, 120.20, 119.84, 96.56, 95.58, 60.46, 44.07, 44.00, 43.78, 43.21, 42.22, 40.76, 40.47, 39.98, 38.86, 38.65, 37.29, 35.56, 35.25, 33.85, 14.20; HRMS (ESI) calculated for $[C_{14}H_{20}O_4+H]$ = 253.143436, found = 253.14328.



64 was synthesized according to the general procedure using **63** (87.4 mg, 0.15 mmol), 1-octene (70.6 µL, 0.45 mmol), 1:1 EtOH:PhH (1.15 mL) and 5 mol % $Mn_2(CO)_{10}$ (2.9 mg, 0.0075 mmol), for 48 hours. The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc) to afford **64** (70.4 mg, 0.11 mmol, 73% yield) as a viscous colorless oil. Analytical data for **64**: IR (thin film, cm^{-1}) 2931, 1733, 1454, 1375, 1242, 1174, 1052, 982, 899; ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.37 (d, *J* = 4.4 Hz, 1 H), 4.77 - 4.53 (m, 1 H), 4.41 (td, *J* = 7.3, 8.6 Hz, 1 H), 4.14 (q, *J* = 7.3 Hz, 2 H), 3.70 - 3.43 (m, 1 H), 3.43 - 3.23 (m, 1 H), 2.39 - 2.14 (m, 5 H), 2.04 - 1.95 (m, 2 H), 1.90 - 1.70 (m, 7 H), 1.68 - 1.40 (m, 14 H), 1.32 - 1.23 (m,

11 H), 1.20 - 1.06 (m, 3 H), 1.03 (s, 3 H), 0.97 (d, *J* = 7.1 Hz, 3 H), 0.91 - 0.84 (m, 3 H), 0.79 (t, *J* = 3.1 Hz, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.73, 172.44, 139.59, 122.31, 109.22, 80.74, 73.80, 66.77, 61.95, 60.17, 56.34, 49.82, 44.74, 41.52, 40.17, 39.64, 38.01, 36.86, 36.65, 32.31, 32.28, 31.96, 31.76, 31.58, 31.30, 30.22, 29.09, 28.72, 27.66, 27.21, 27.13, 22.52, 21.40, 20.73, 19.30, 17.12, 16.26, 14.51, 14.31, 14.05; HRMS (ESI) calculated for $[C_{40}H_{64}O_6+H]$ = 641.477566, found = 641.47687.

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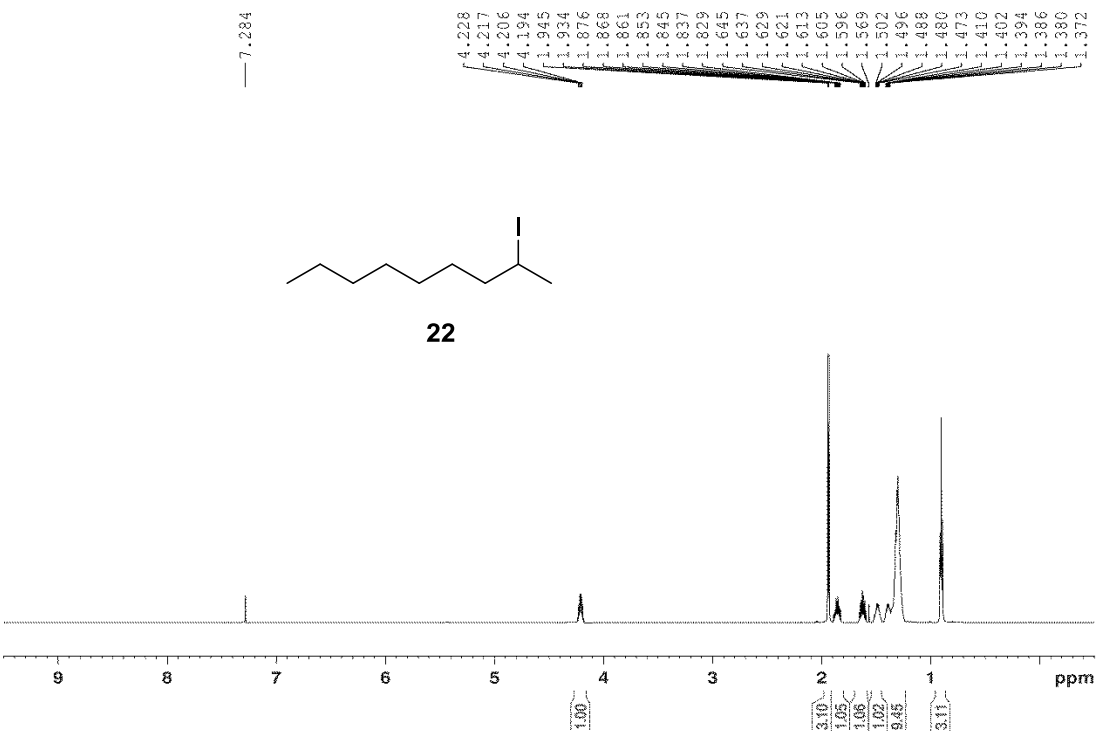
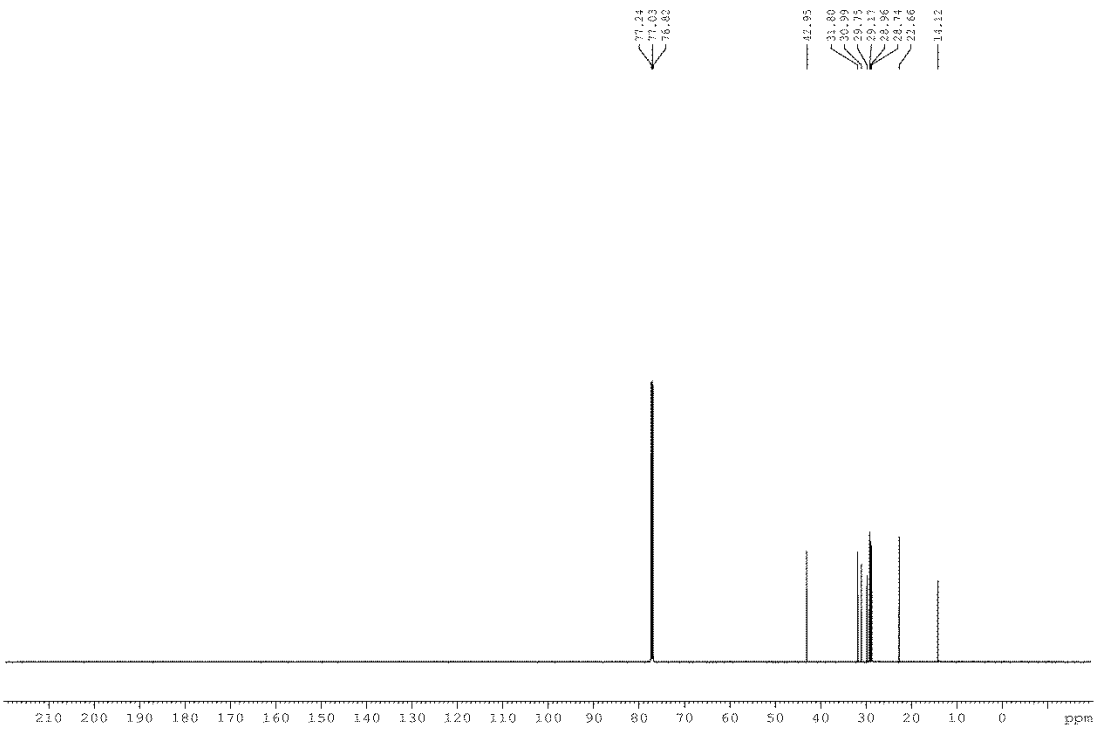
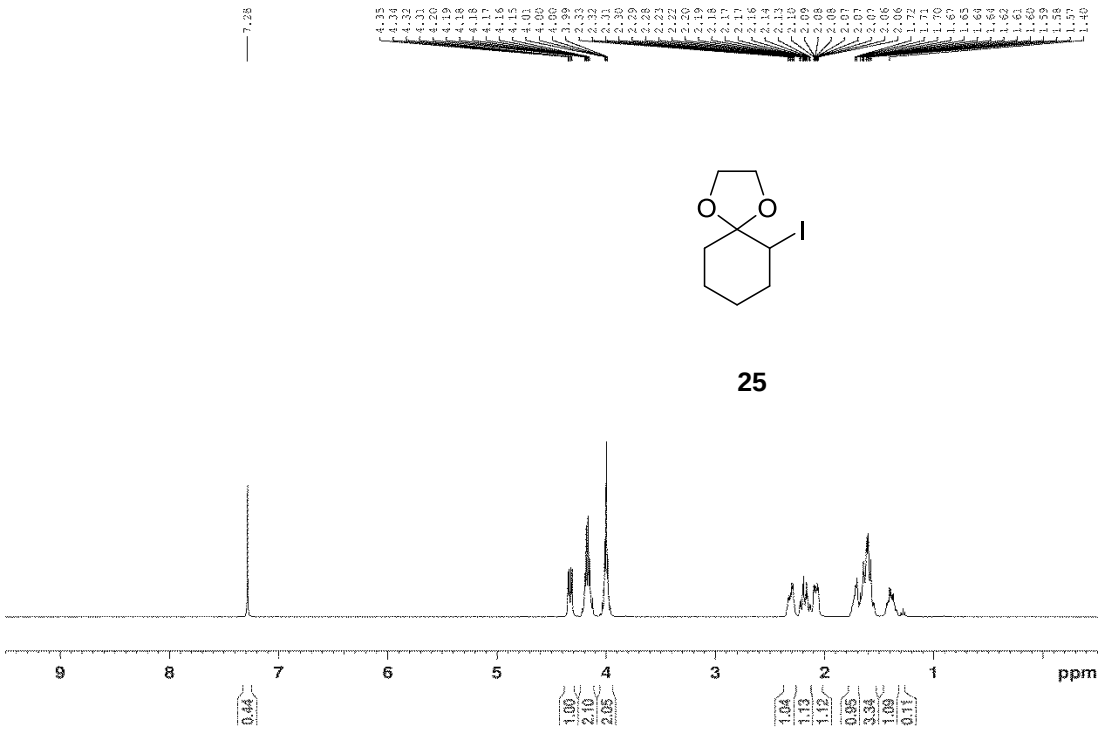
APPENDIX A: SPECTRAL DATA FOR CHAPTER 2



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O
O
I
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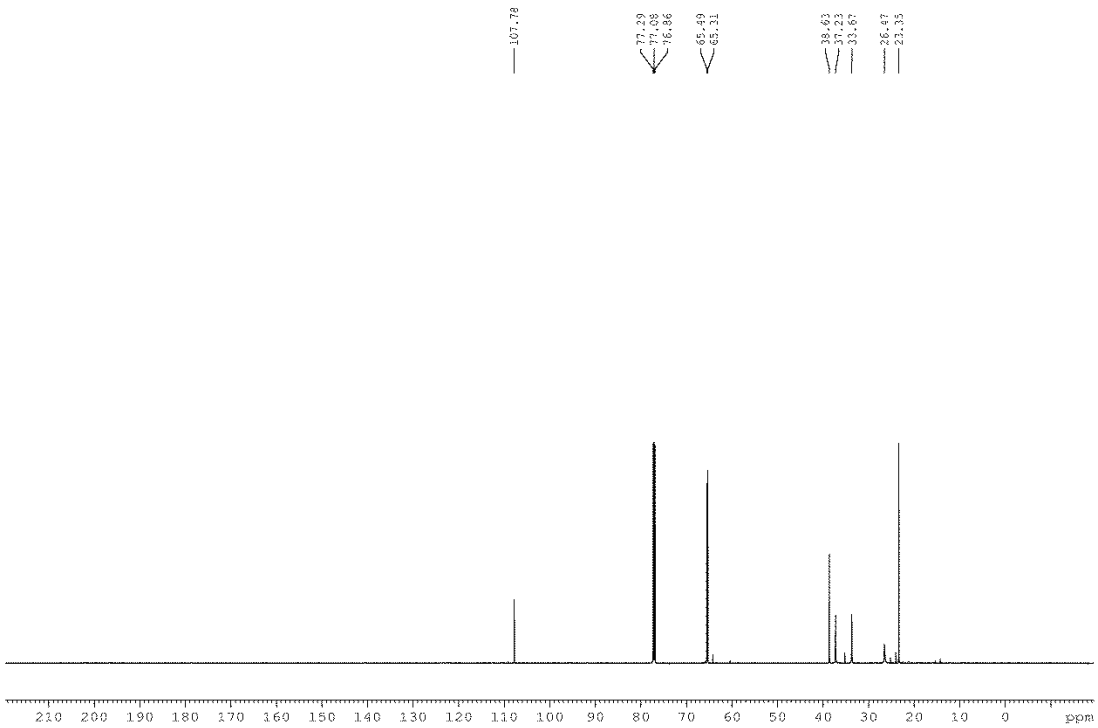
25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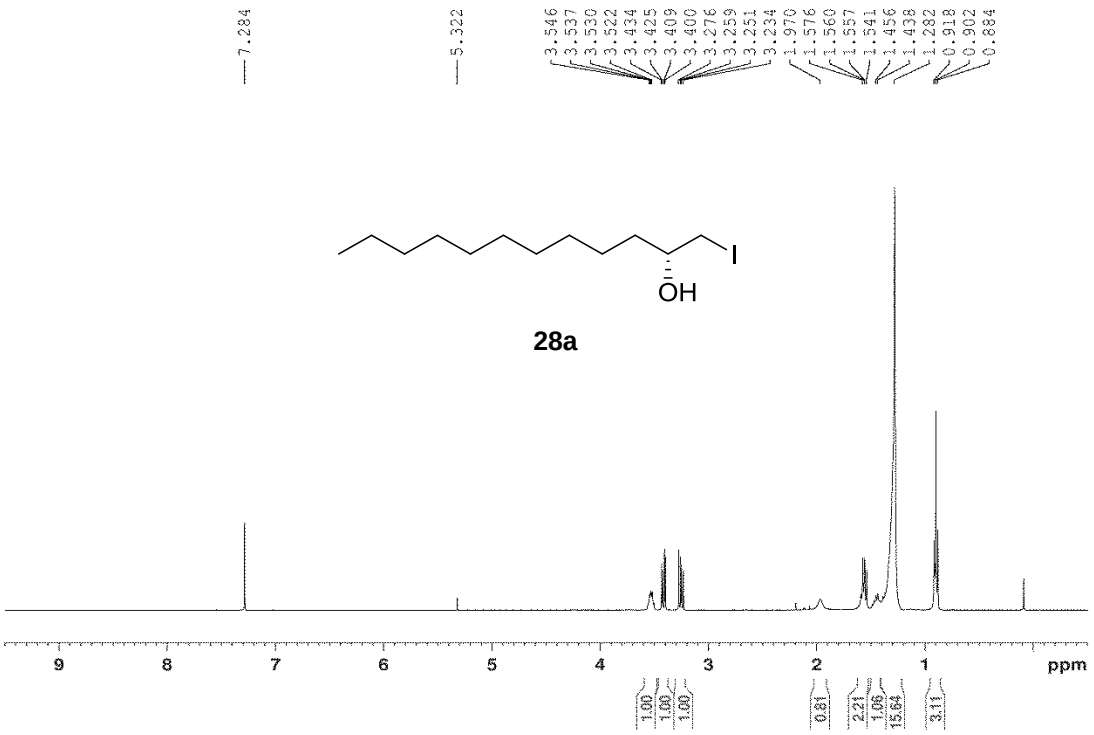
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3.234
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1.576
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1.557
1.541
1.456
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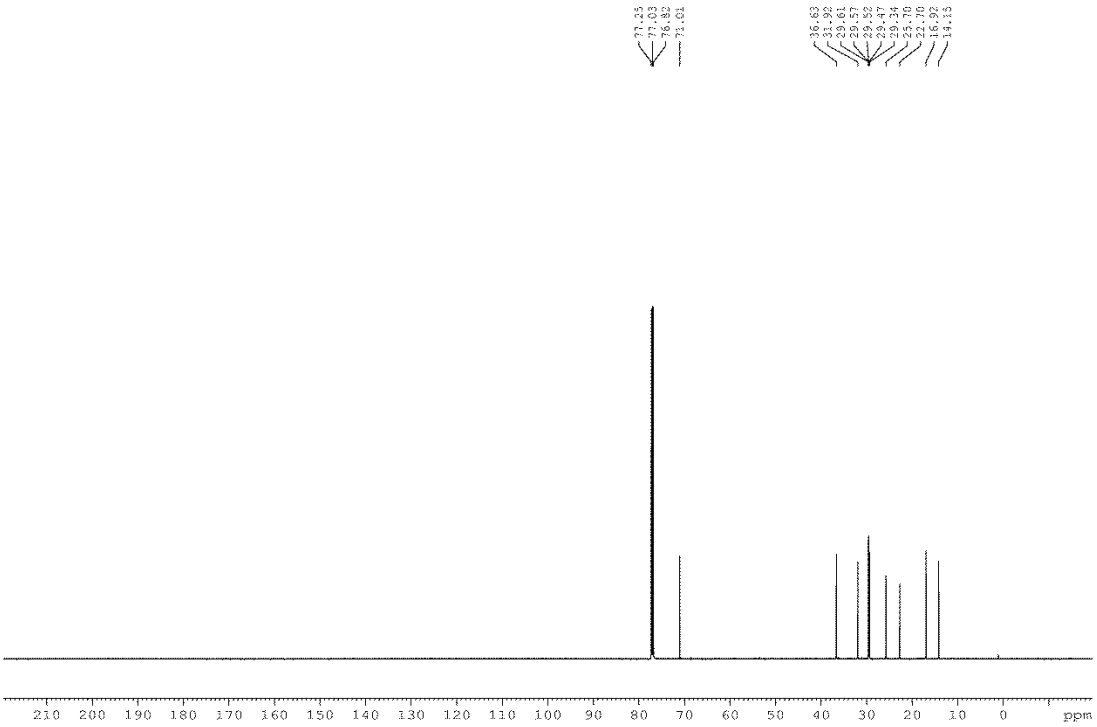
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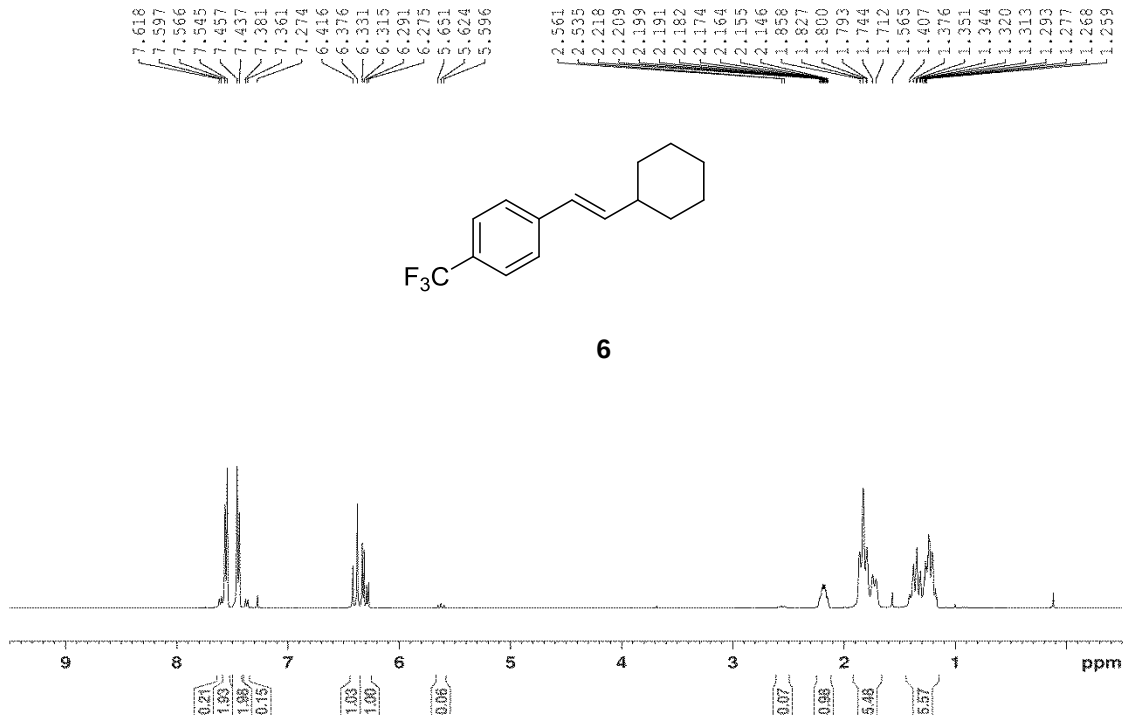
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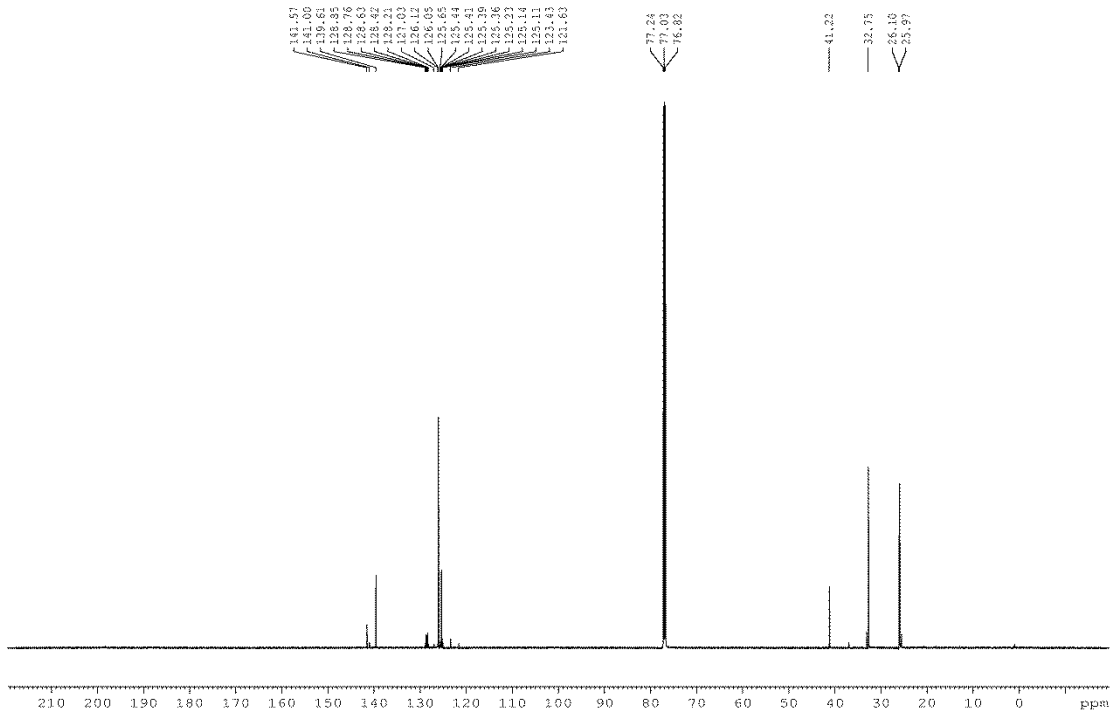
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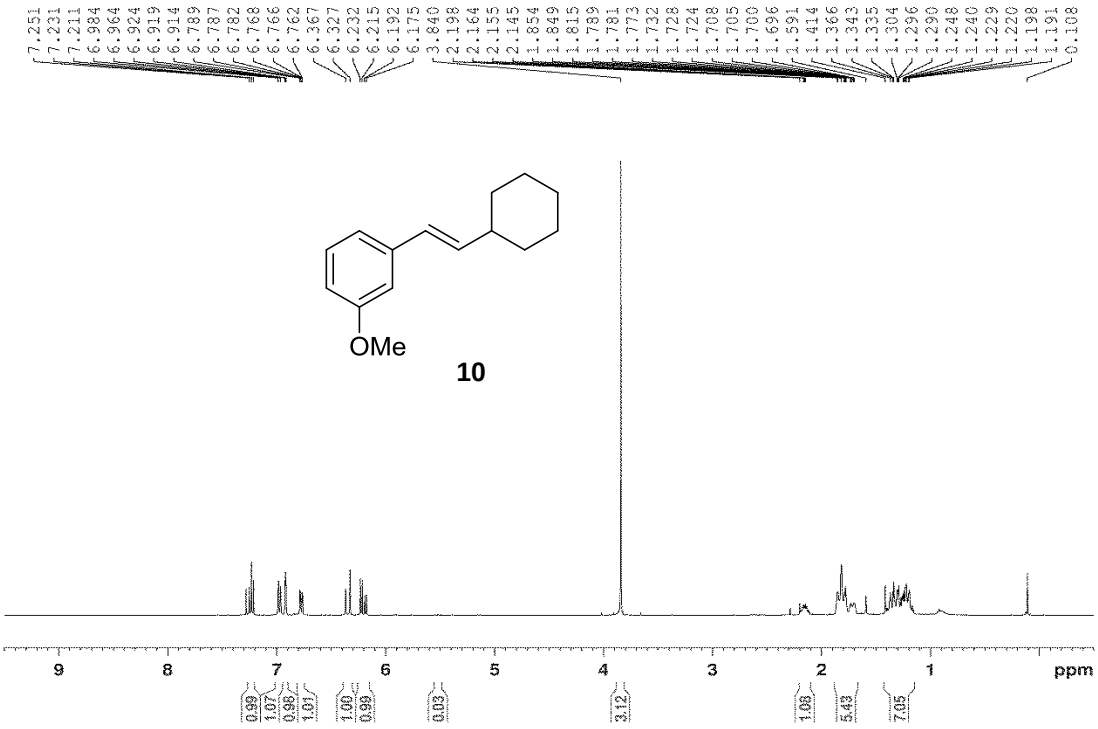
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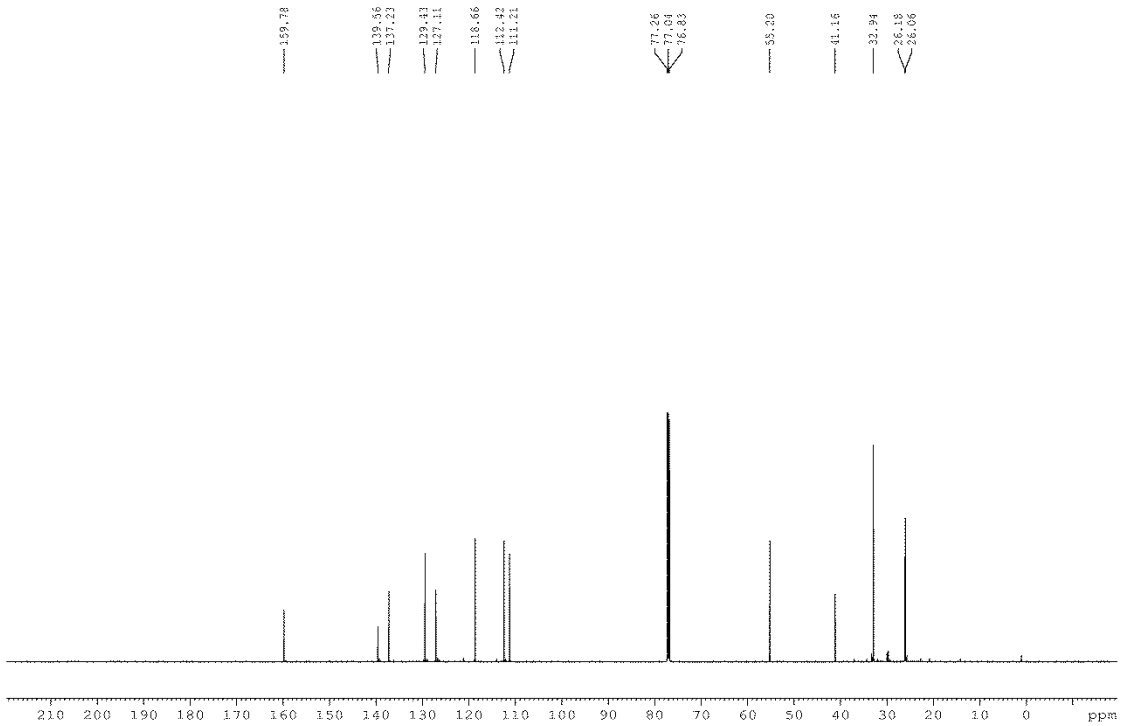
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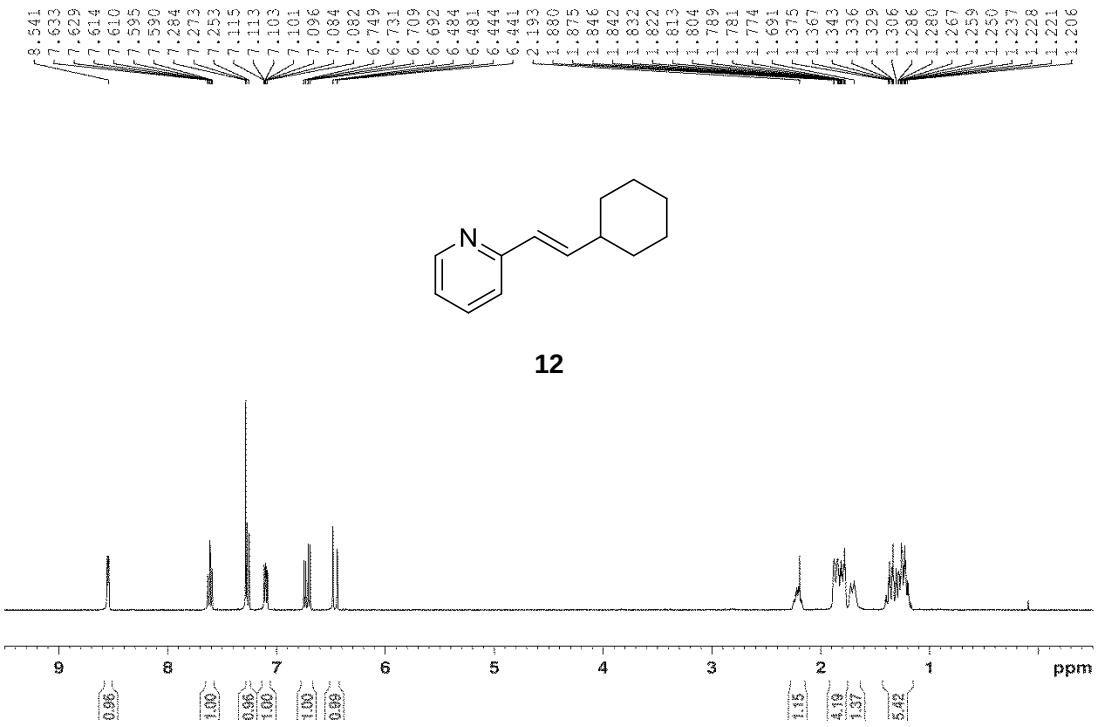
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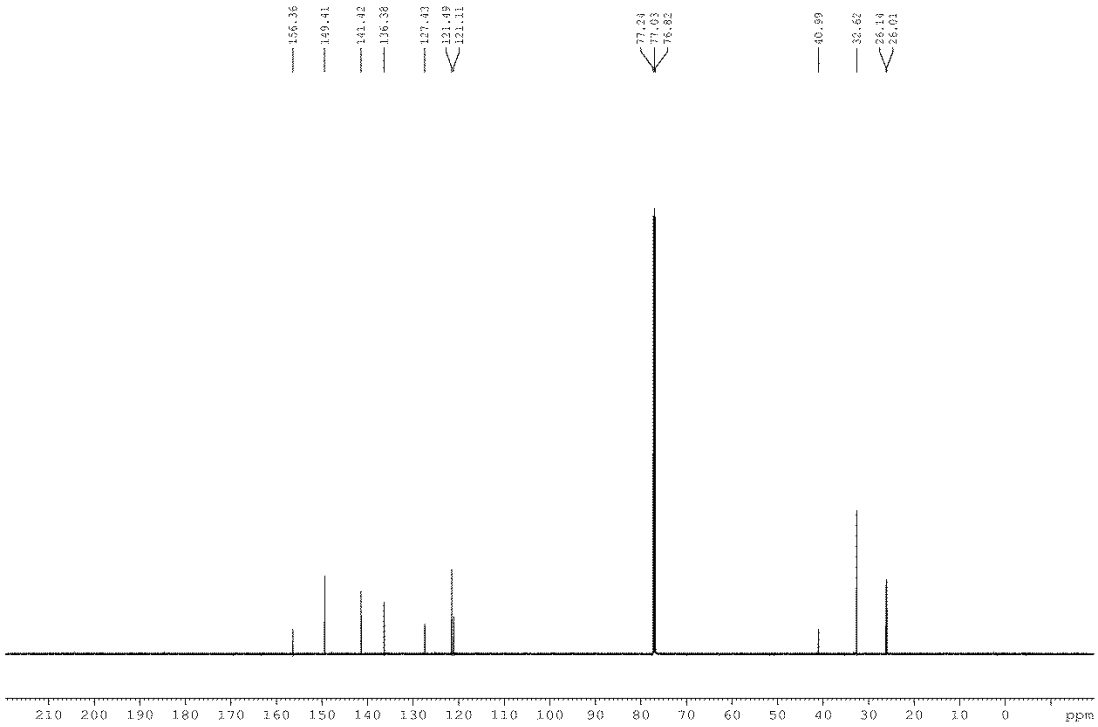
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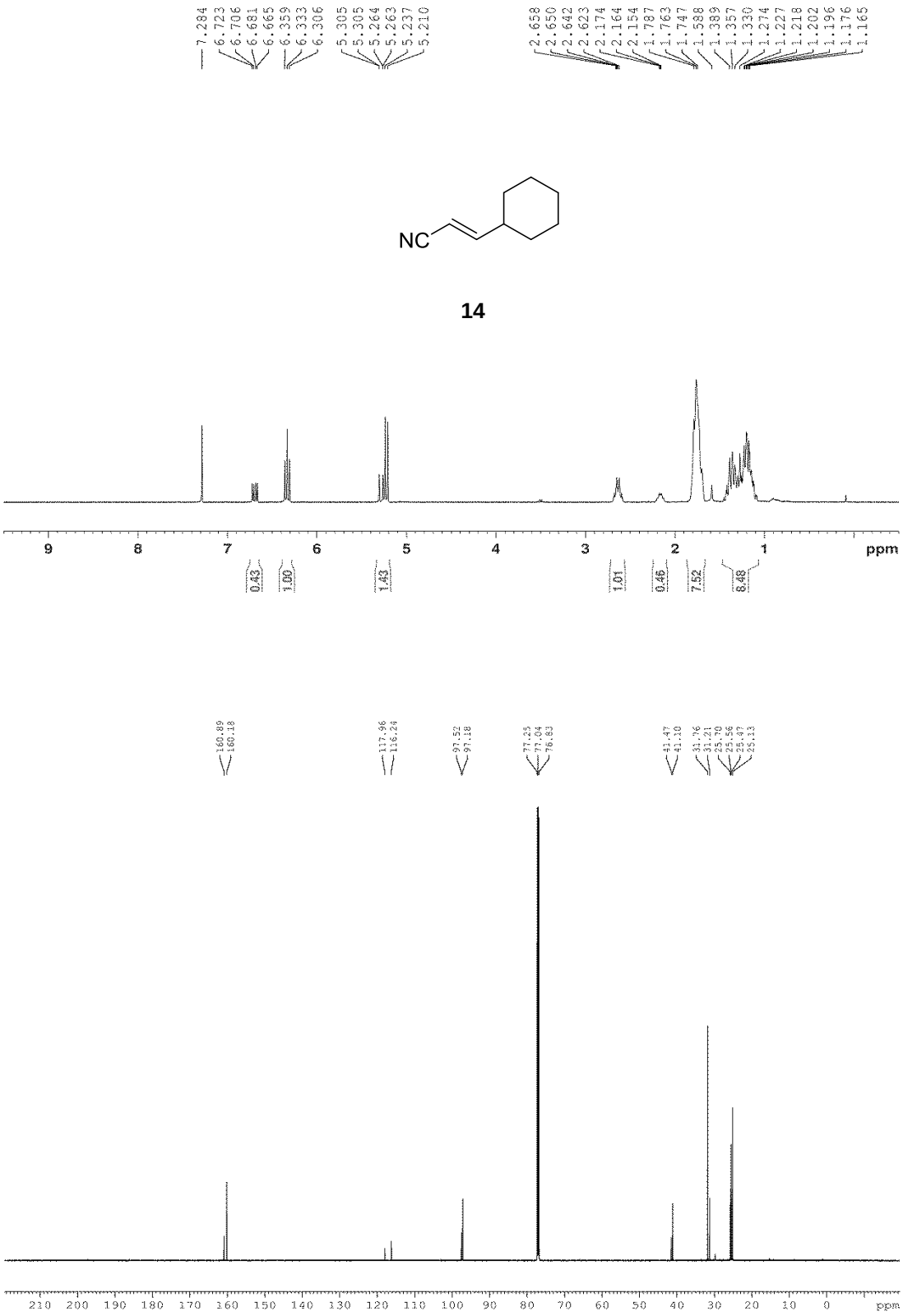
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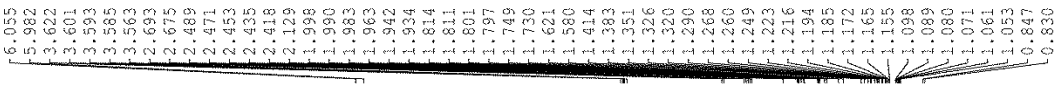
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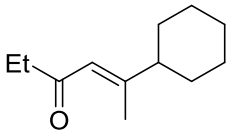
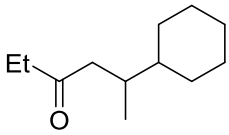
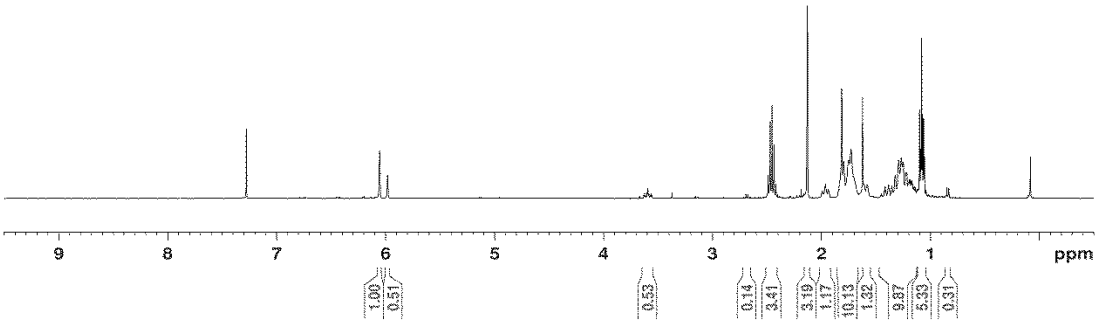
0.830

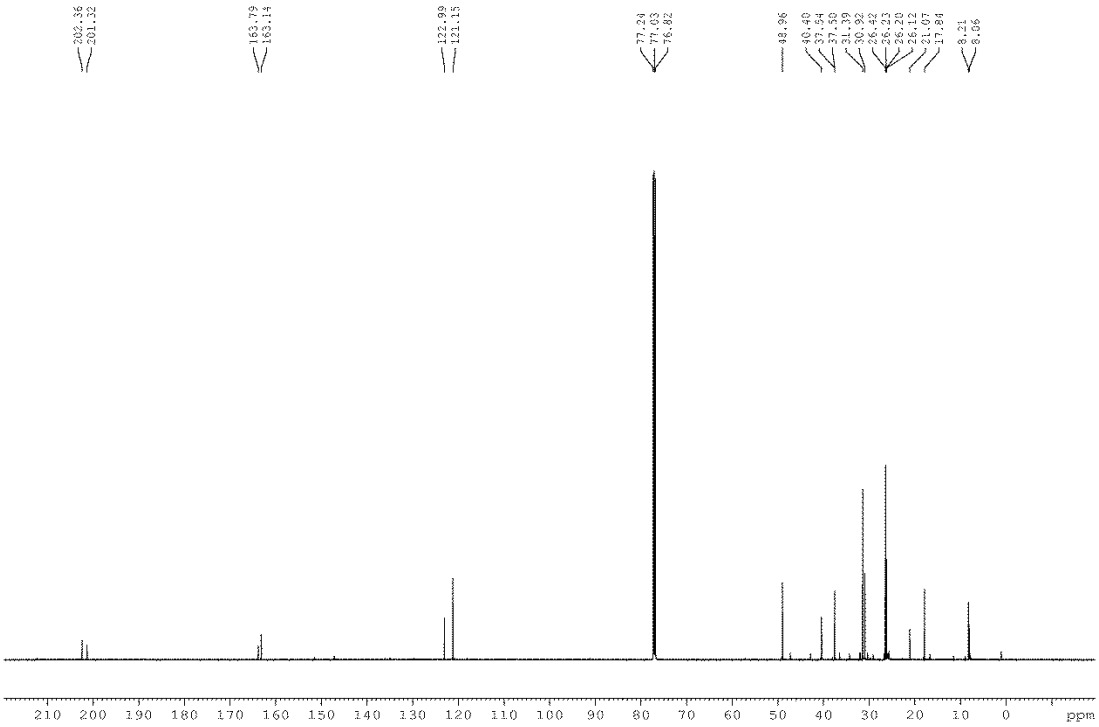

Et
O

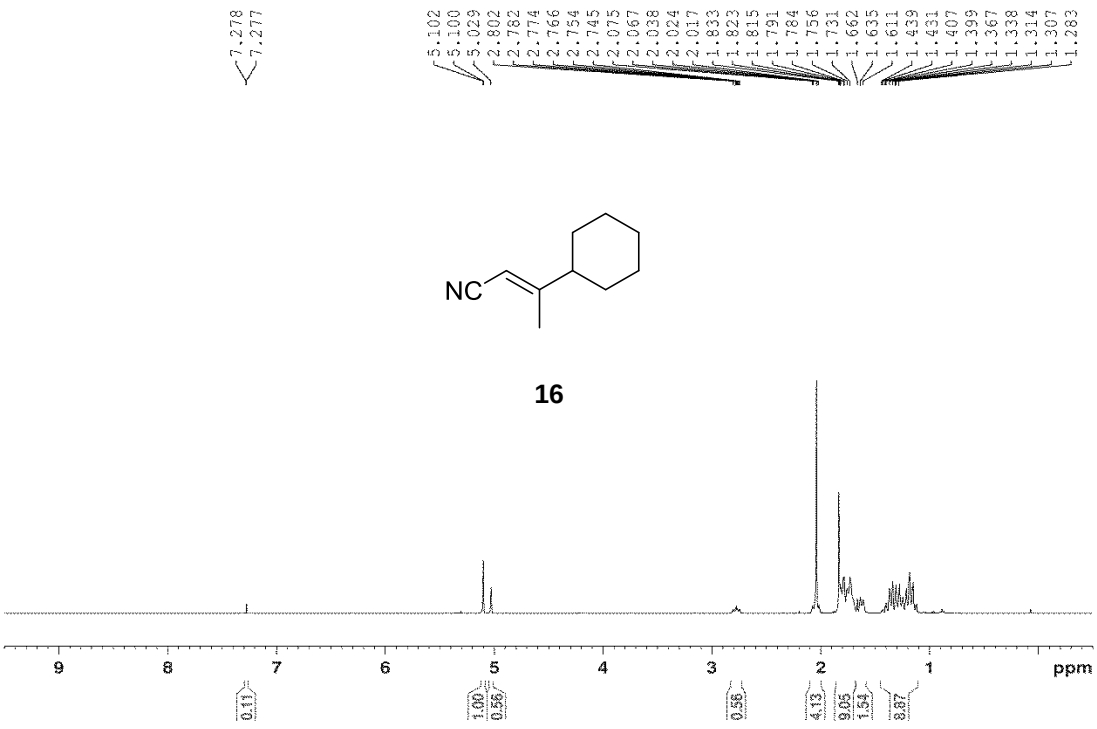
15

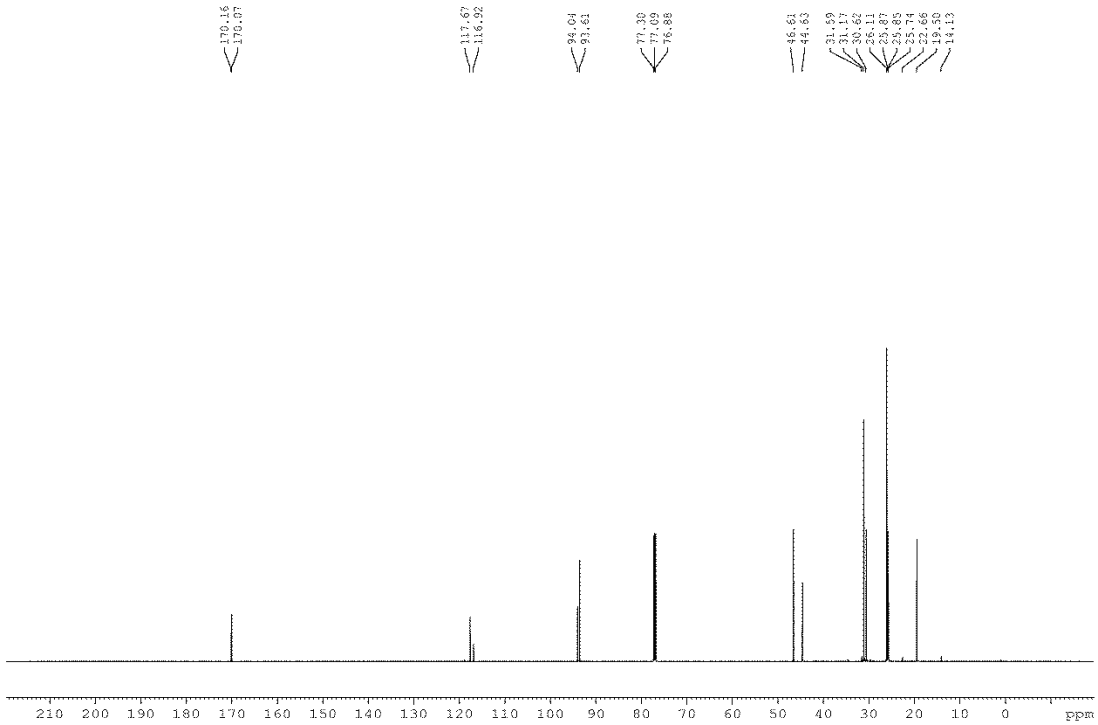

Et
O

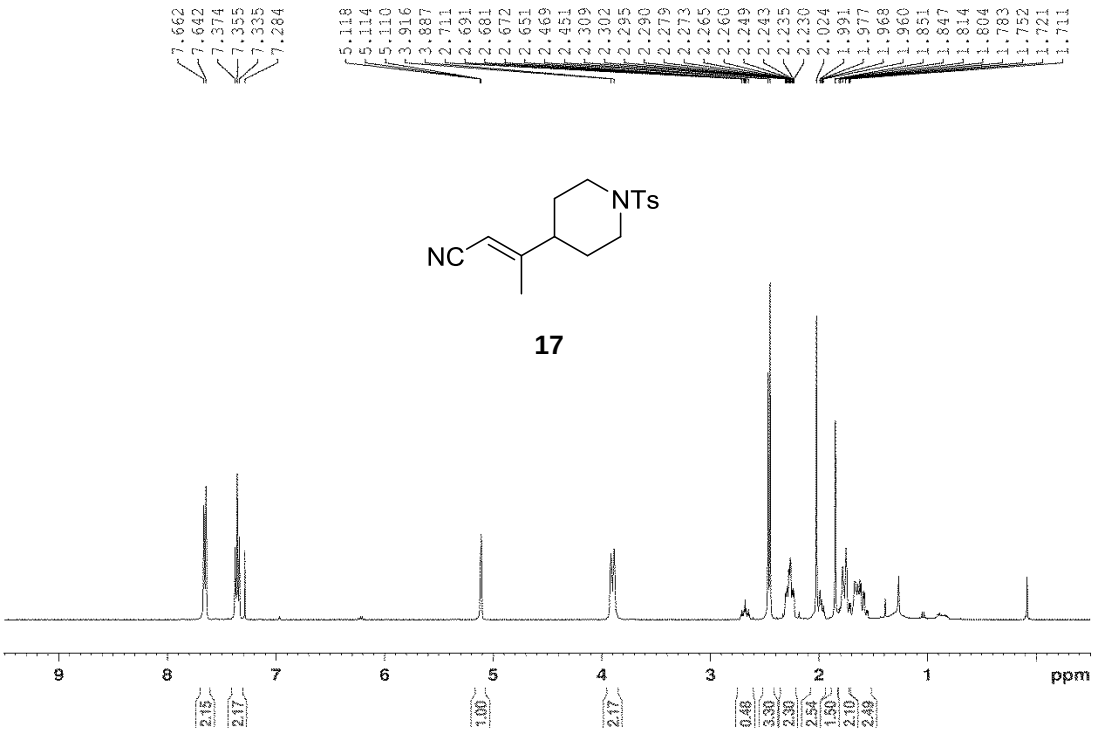
15a

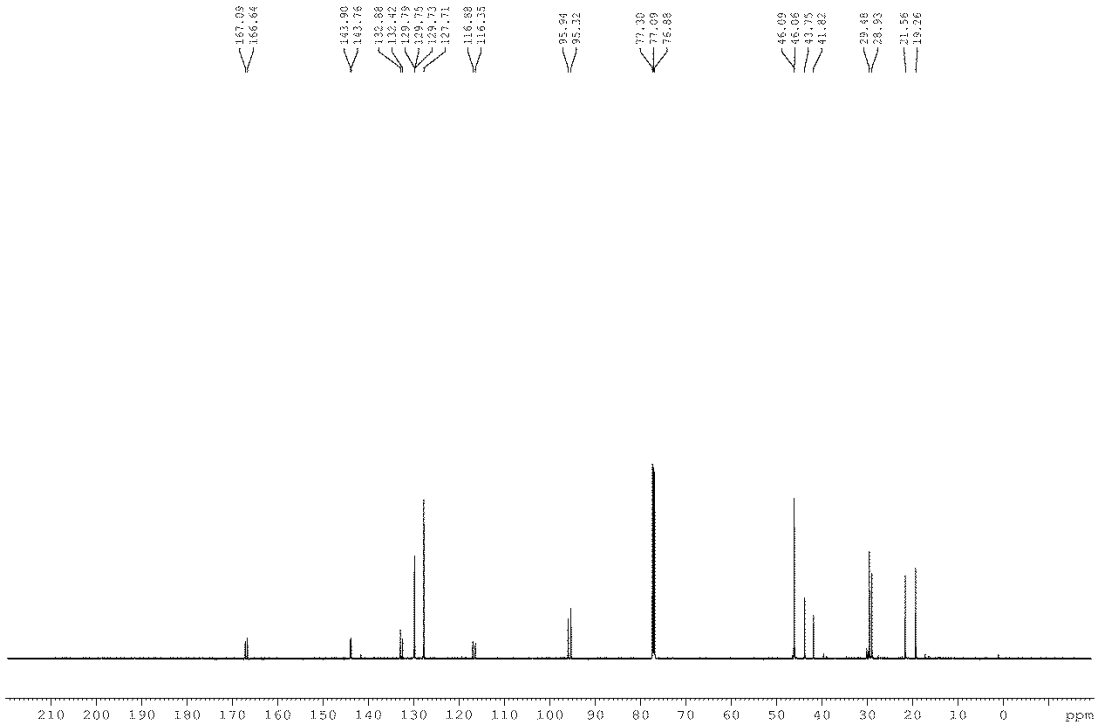

9
8
7
6
5
4
3
2
1
ppm
1.00
0.51
0.53
0.14
3.41
3.19
1.17
10.13
1.22
9.87
5.53
0.31

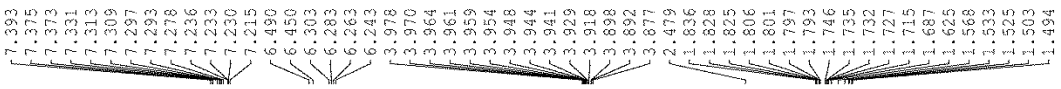

202.36
201.32
163.79
163.14
122.99
121.15
77.24
77.03
76.82
48.96
40.40
37.54
37.50
31.39
30.92
26.42
26.23
26.20
26.12
21.07
17.84
8.21
8.06
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

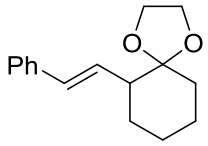

7.278
7.277
5.102
5.100
5.029
2.802
2.782
2.774
2.766
2.754
2.745
2.075
2.067
2.038
2.024
2.017
1.833
1.823
1.815
1.791
1.784
1.756
1.731
1.662
1.635
1.611
1.439
1.431
1.407
1.399
1.367
1.338
1.314
1.307
1.283
NC
16
9
8
7
6
5
4
3
2
1
ppm
0.11
1.00
0.56
0.58
4.13
9.05
1.54
8.87


170.16
170.07
117.67
116.92
94.04
93.61
77.30
77.09
76.88
46.61
44.63
31.59
31.17
30.62
26.11
25.87
25.85
25.74
22.66
19.50
14.13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

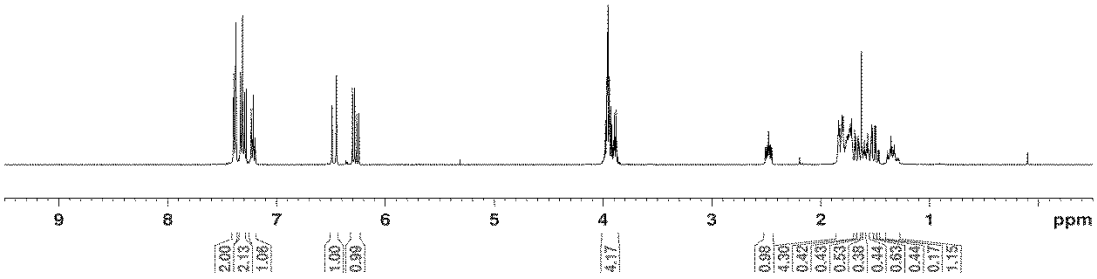

7.662
7.642
7.374
7.355
7.335
7.284
5.118
5.114
5.110
3.916
3.887
2.711
2.691
2.681
2.672
2.651
2.469
2.451
2.309
2.302
2.295
2.290
2.279
2.273
2.265
2.260
2.249
2.243
2.235
2.230
2.024
1.991
1.977
1.968
1.960
1.851
1.847
1.814
1.804
1.783
1.752
1.721
1.711
NTs
NC
17
9
8
7
6
5
4
3
2
1
ppm
2.15
2.17
1.00
2.17
0.48
3.30
2.30
2.54
1.50
2.10
2.49

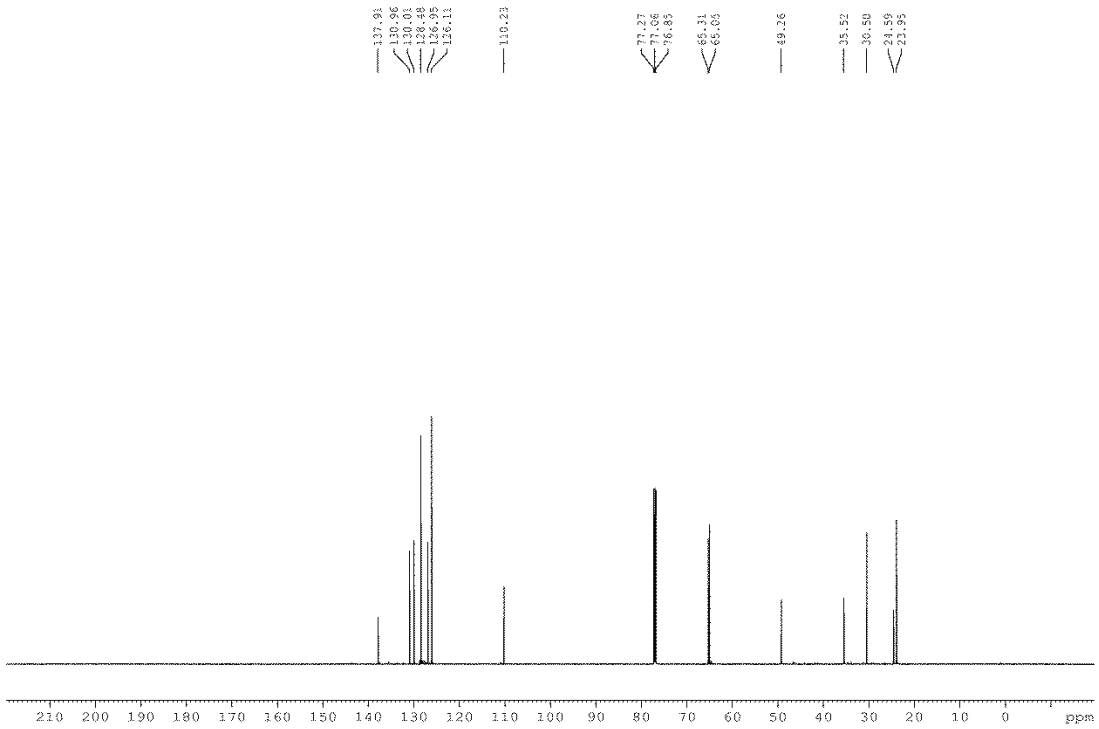

167.09
166.64
143.90
143.76
132.88
132.42
129.79
129.75
129.73
127.71
116.88
116.35
95.94
95.32
77.30
77.09
76.88
46.09
46.06
43.75
41.82
29.48
28.93
21.56
19.26
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

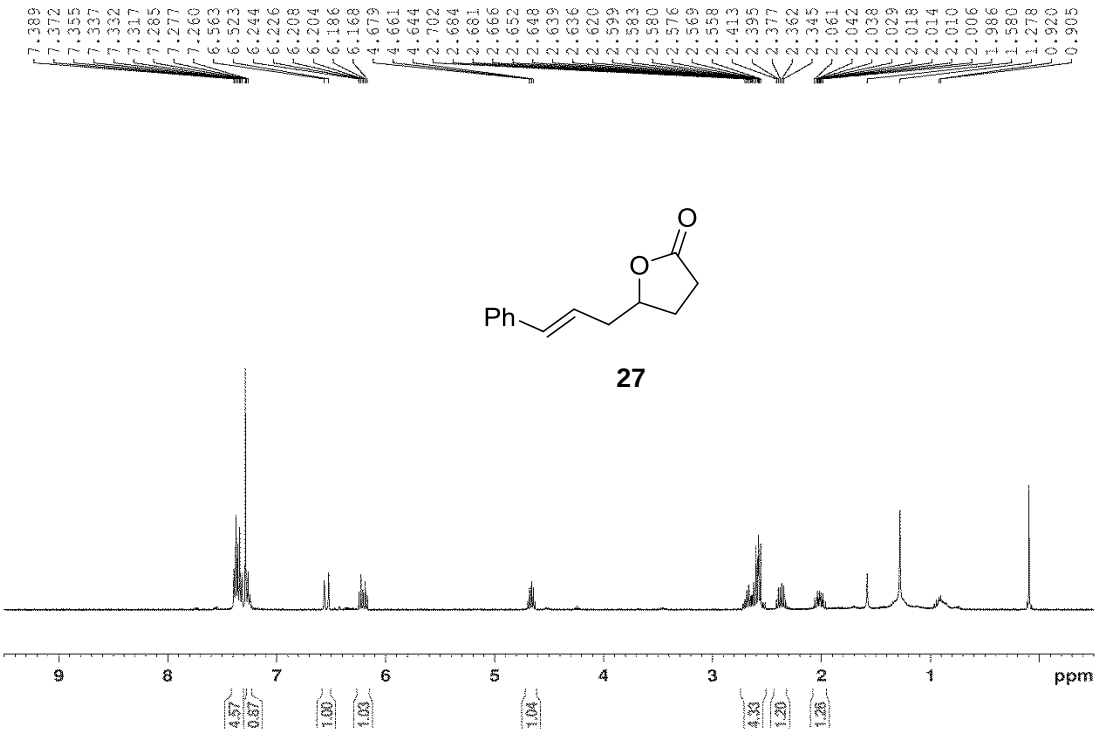

7.393
7.375
7.373
7.331
7.313
7.309
7.297
7.293
7.278
7.236
7.233
7.230
7.215
6.490
6.450
6.303
6.283
6.263
6.243
3.978
3.970
3.964
3.961
3.959
3.954
3.948
3.944
3.941
3.929
3.918
3.898
3.892
3.877
2.479
1.836
1.828
1.825
1.806
1.801
1.797
1.793
1.746
1.735
1.732
1.727
1.715
1.687
1.625
1.568
1.533
1.525
1.503
1.494


Ph
O
O

26


9
8
7
6
5
4
3
2
1
ppm
2.00
2.13
1.06
1.00
0.99
4.17
0.98
4.36
0.42
0.49
0.53
0.38
0.44
0.65
0.44
0.17
1.15


137.91
130.96
130.01
128.48
126.95
126.11
110.23
77.27
77.06
76.85
65.31
65.05
49.26
35.52
30.50
24.59
23.95
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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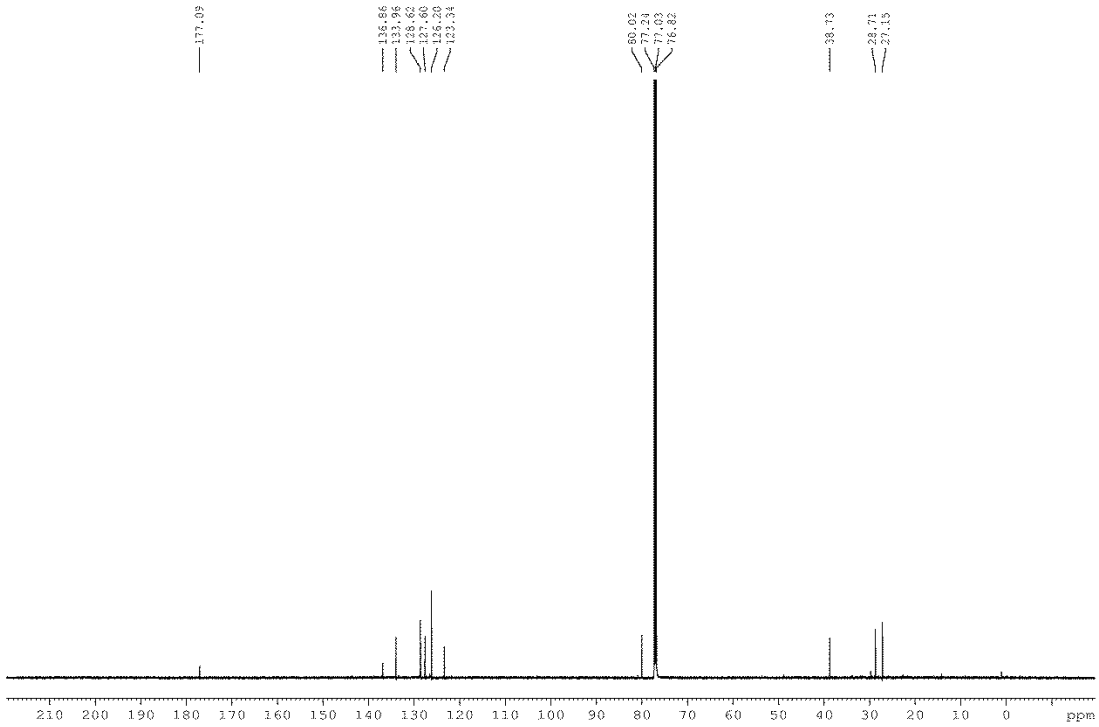
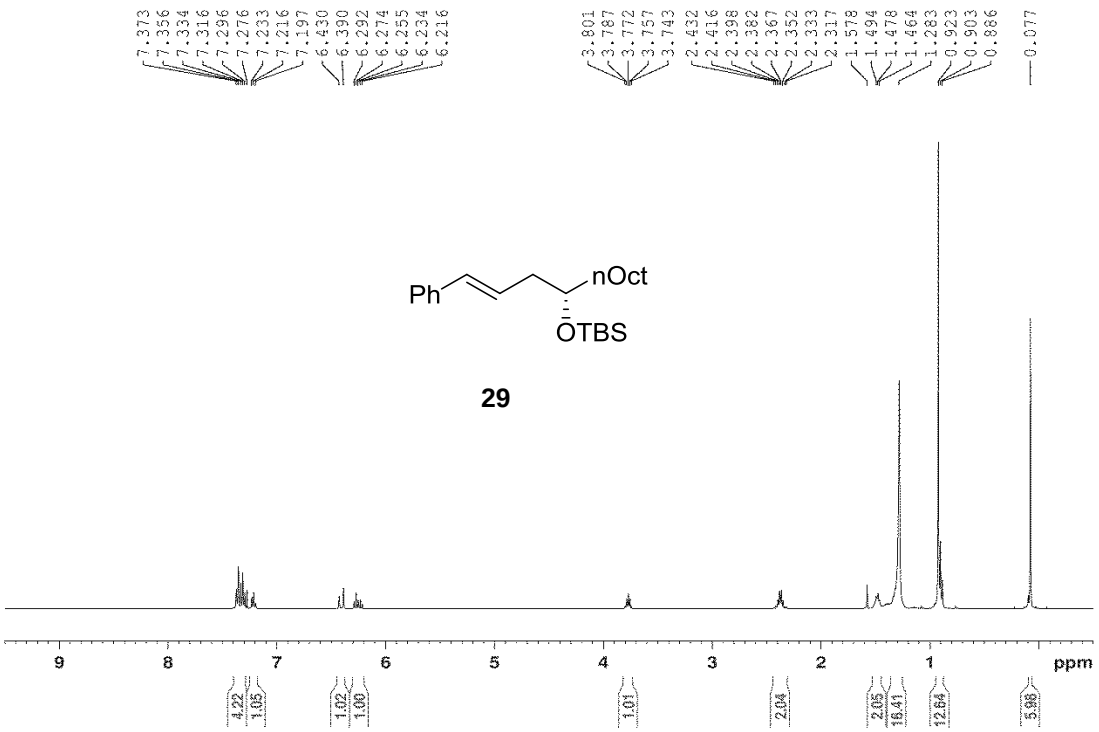
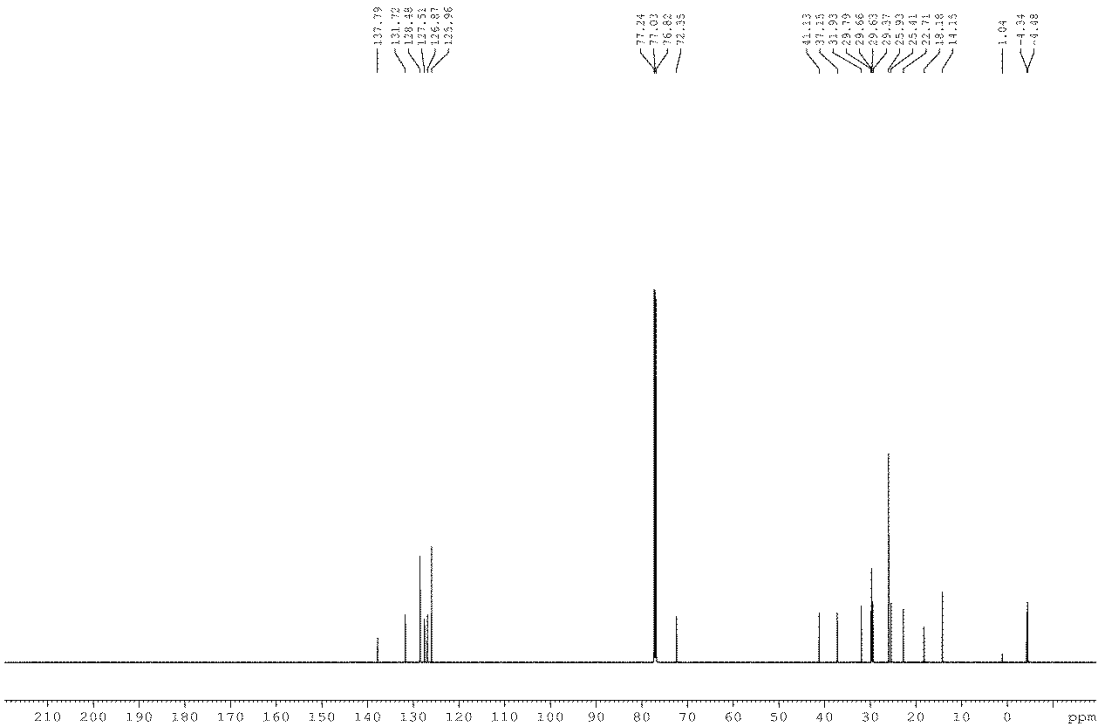
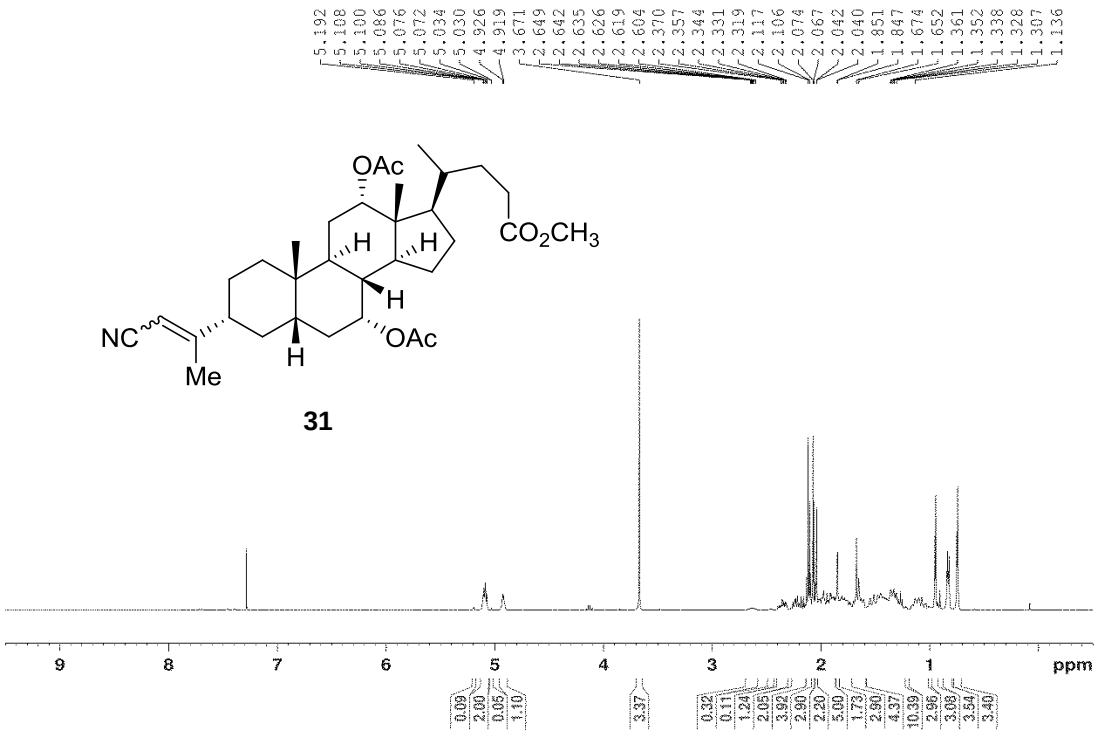
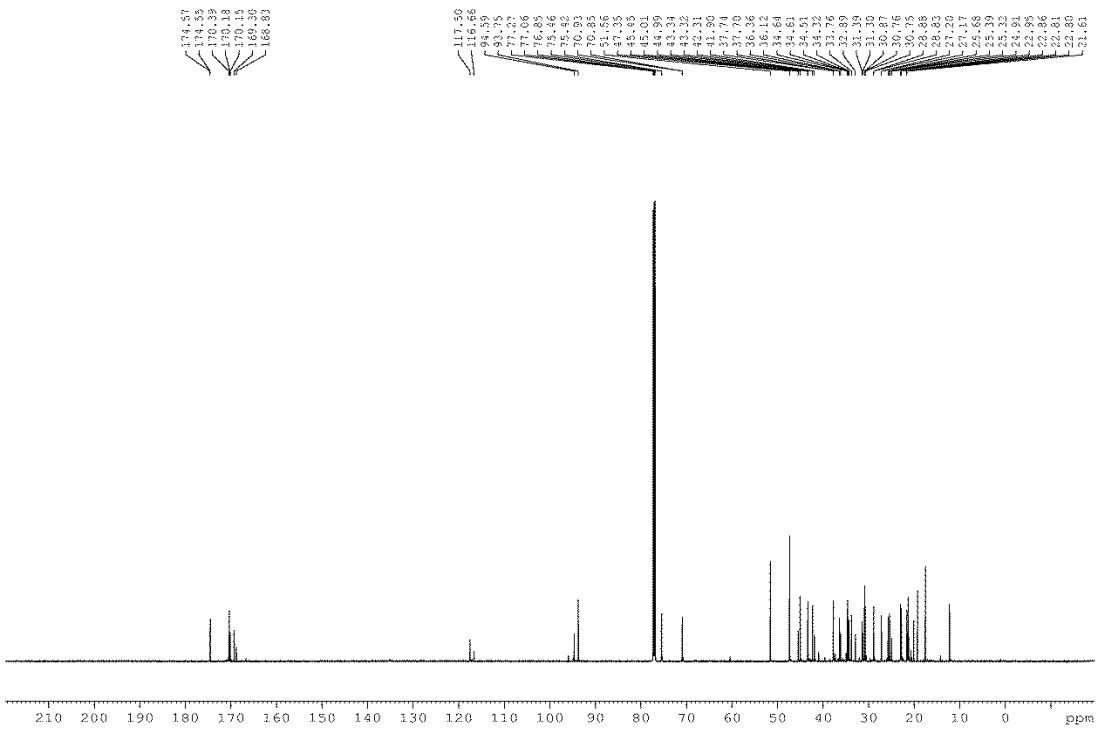
7.332
7.317
7.285
7.277
7.260
6.563
6.523
6.244
6.226
6.208
6.204
6.186
6.168
4.679
4.661
4.644
2.702
2.684
2.681
2.666
2.652
2.648
2.639
2.636
2.620
2.599
2.583
2.580
2.576
2.569
2.558
2.413
2.395
2.377
2.362
2.345
2.061
2.042
2.038
2.029
2.018
2.014
2.010
2.006
1.986
1.580
1.278
0.920
0.905
O
O
Ph
27
9
8
7
6
5
4
3
2
1
ppm
4.57
0.87
1.00
1.03
1.04
4.33
1.20
1.26

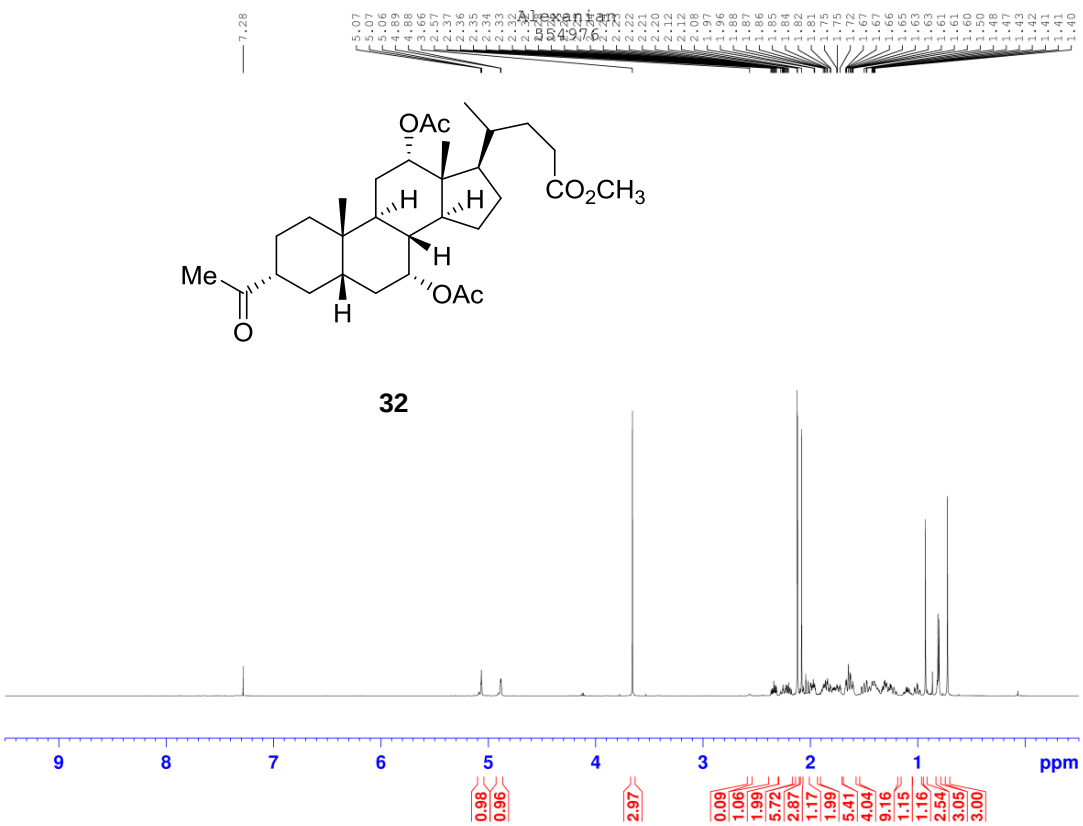

177.09
136.86
133.96
128.62
127.60
126.20
123.34
80.02
77.24
77.03
76.82
38.13
28.71
27.15
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

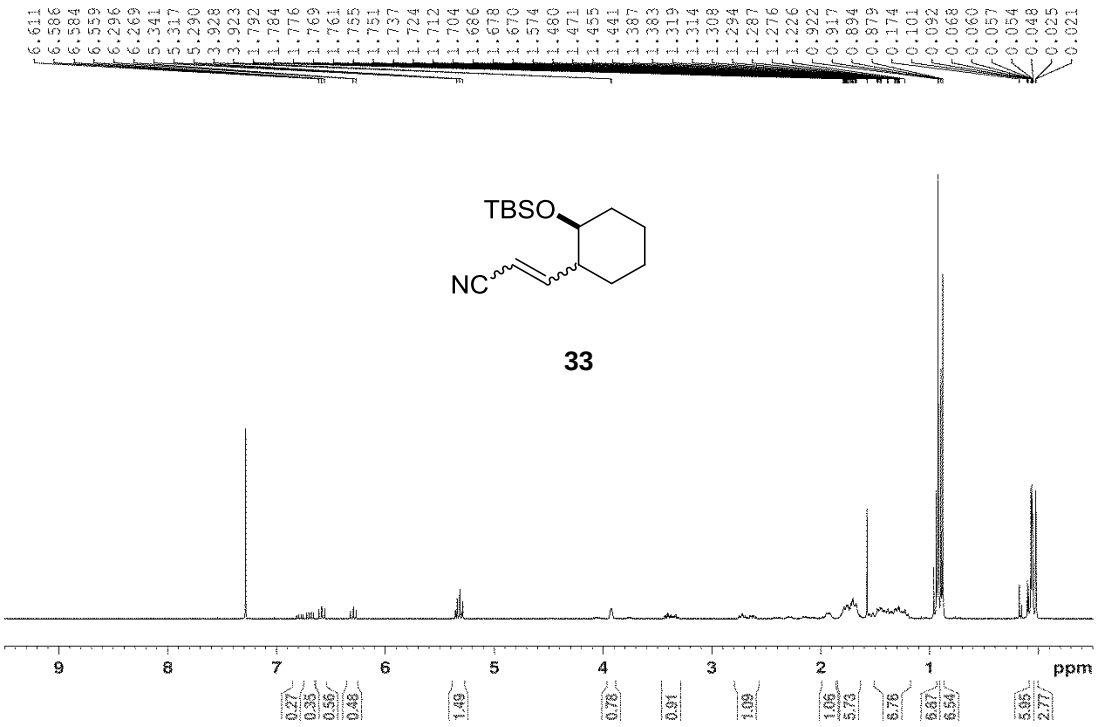

7.373
7.356
7.334
7.316
7.296
7.276
7.233
7.216
7.197
6.430
6.390
6.292
6.274
6.255
6.234
6.216
3.801
3.787
3.772
3.757
3.743
2.432
2.416
2.398
2.382
2.367
2.352
2.333
2.317
1.578
1.494
1.478
1.464
1.283
0.923
0.903
0.886
0.077
Ph
nOct
OTBS
29
9
8
7
6
5
4
3
2
1
ppm
4.22
1.05
1.02
1.00
1.01
2.04
2.05
16.41
12.64
5.98

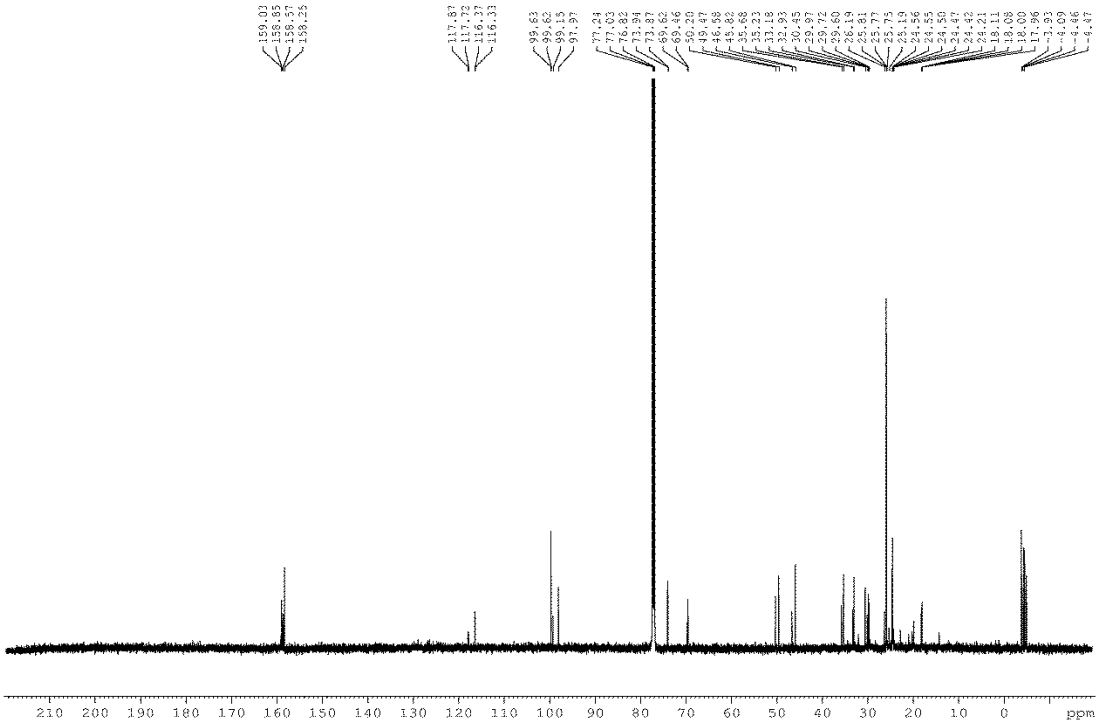

137.79
131.72
128.48
127.51
126.87
125.96
77.24
77.03
76.82
72.35
41.13
37.15
31.93
29.79
29.66
29.63
29.37
25.93
25.41
22.71
18.18
14.15
1.04
-4.34
-4.48
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OAc
CO2CH3
H
H
H
NC
OAc
H
Me
31
ppm

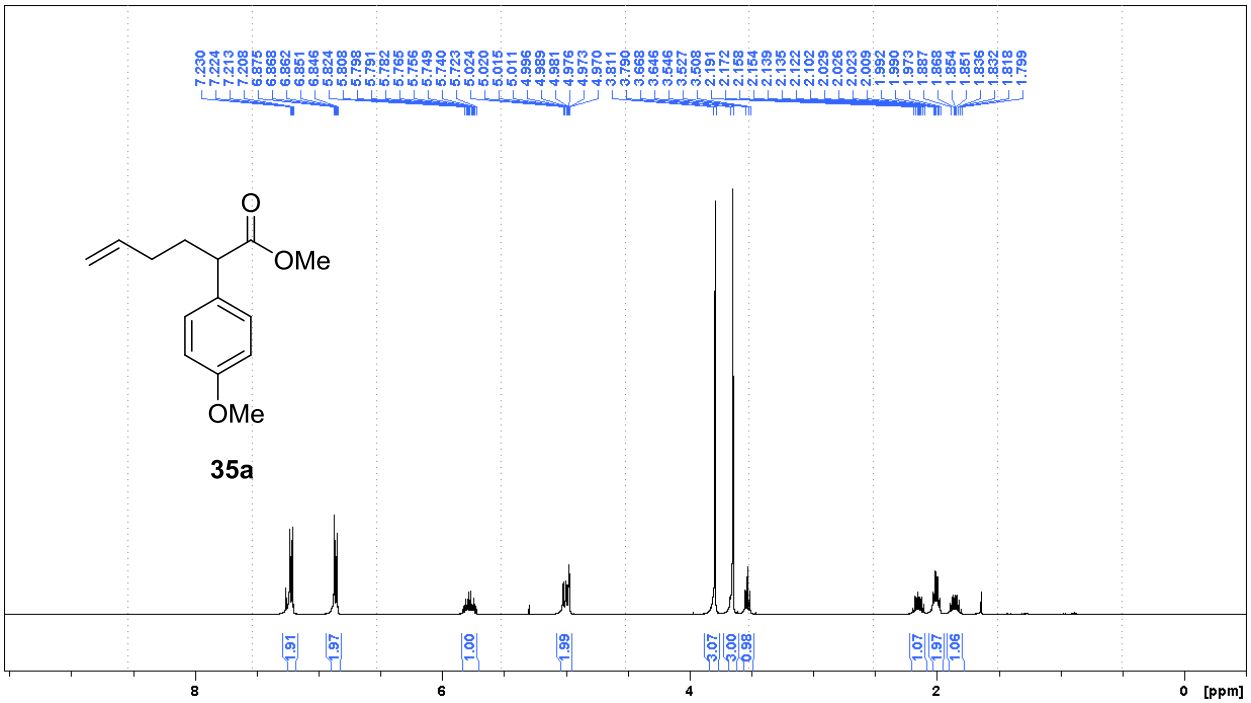

ppm

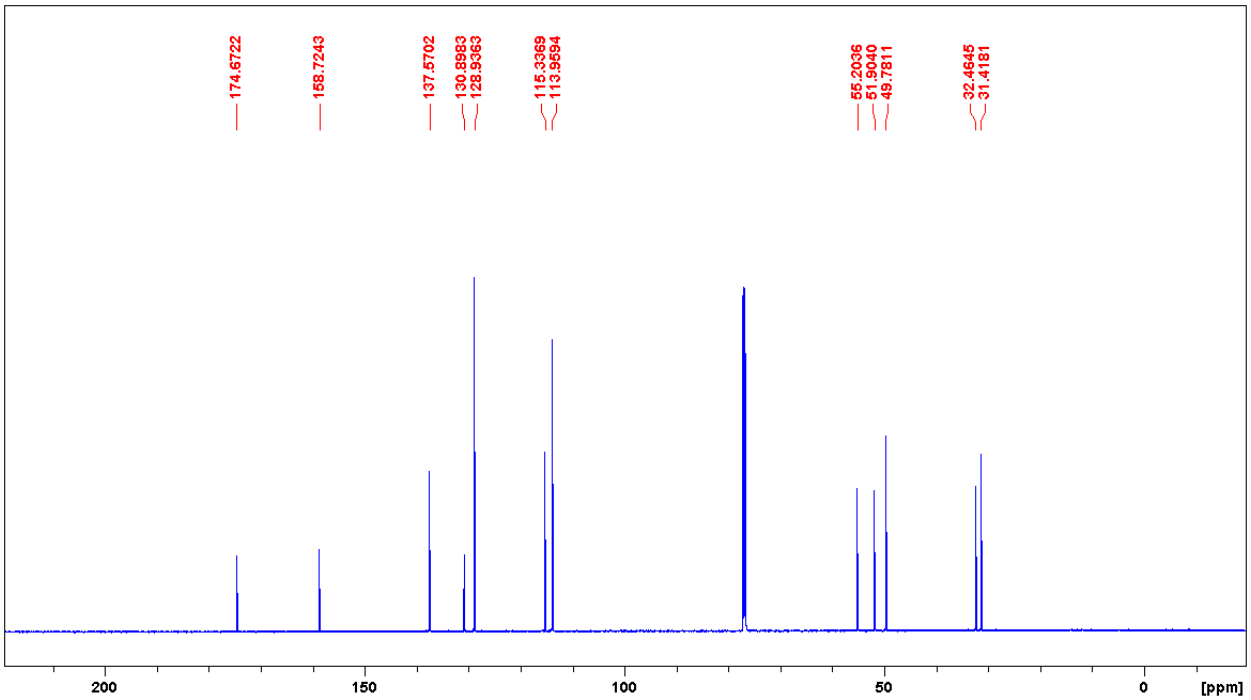

Alexanian
BS4976
OAc
CO2CH3
H
H
H
Me
O
H
OAc
32
9
8
7
6
5
4
3
2
1
ppm
0.98
0.96
2.97
0.09
1.06
1.99
5.72
2.87
1.17
1.99
5.41
4.04
9.16
1.15
1.16
2.54
3.05
3.00

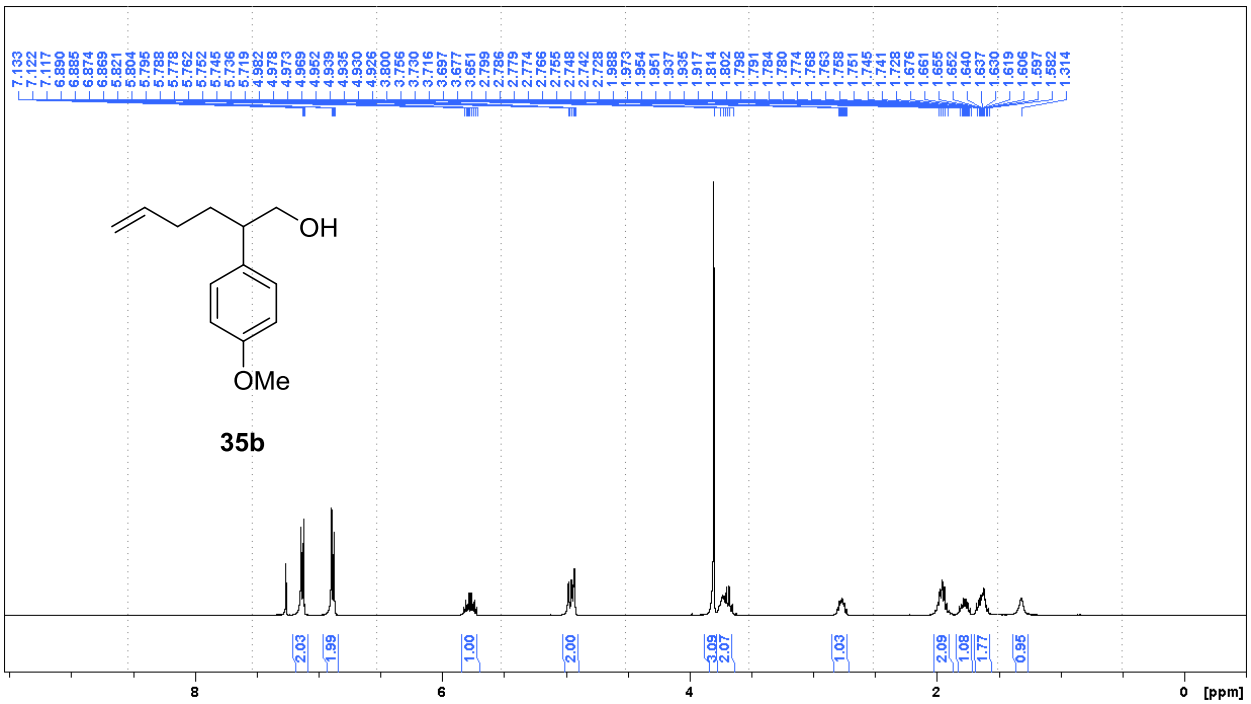

TBSO
NC
33
ppm

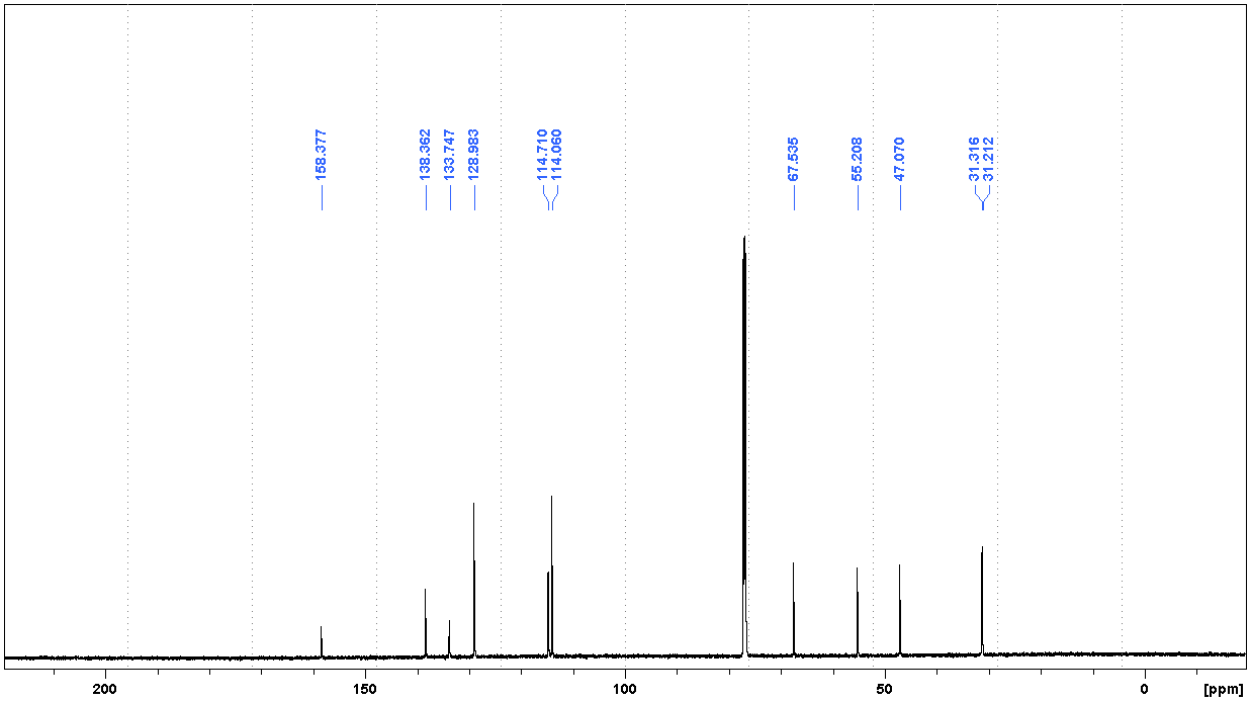

ppm

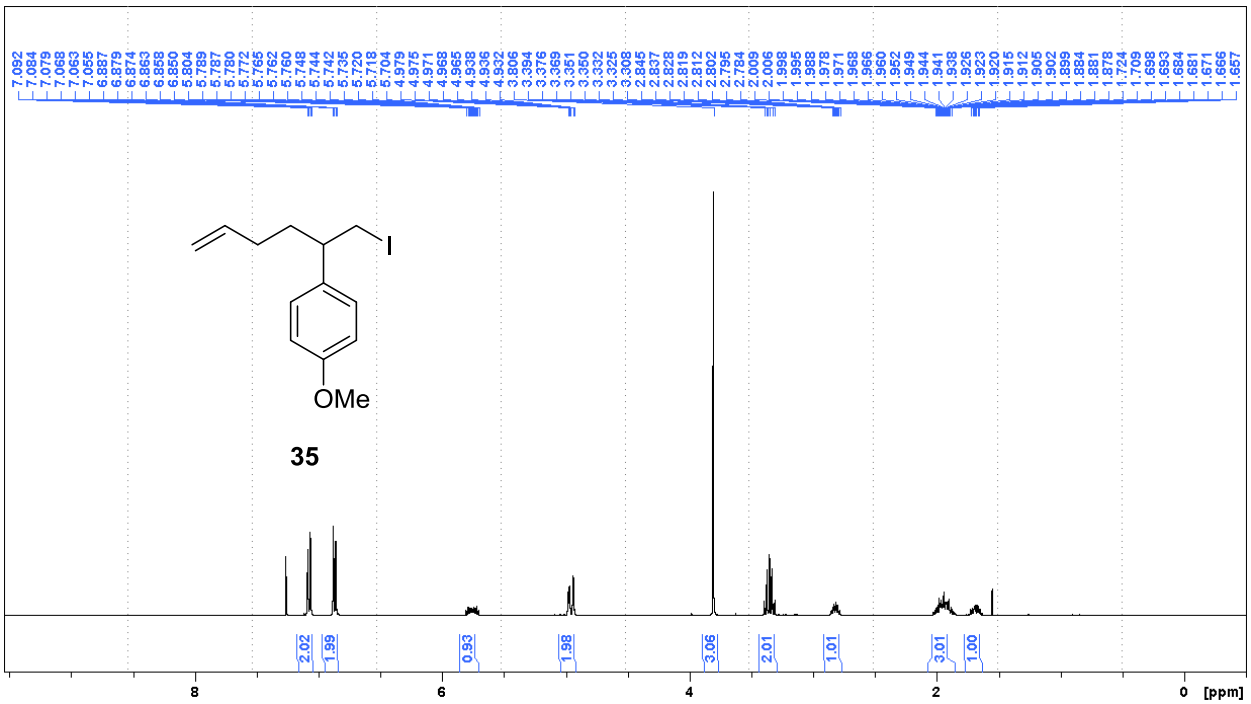
APPENDIX B: SPECTRAL DATA FOR CHAPTER 3

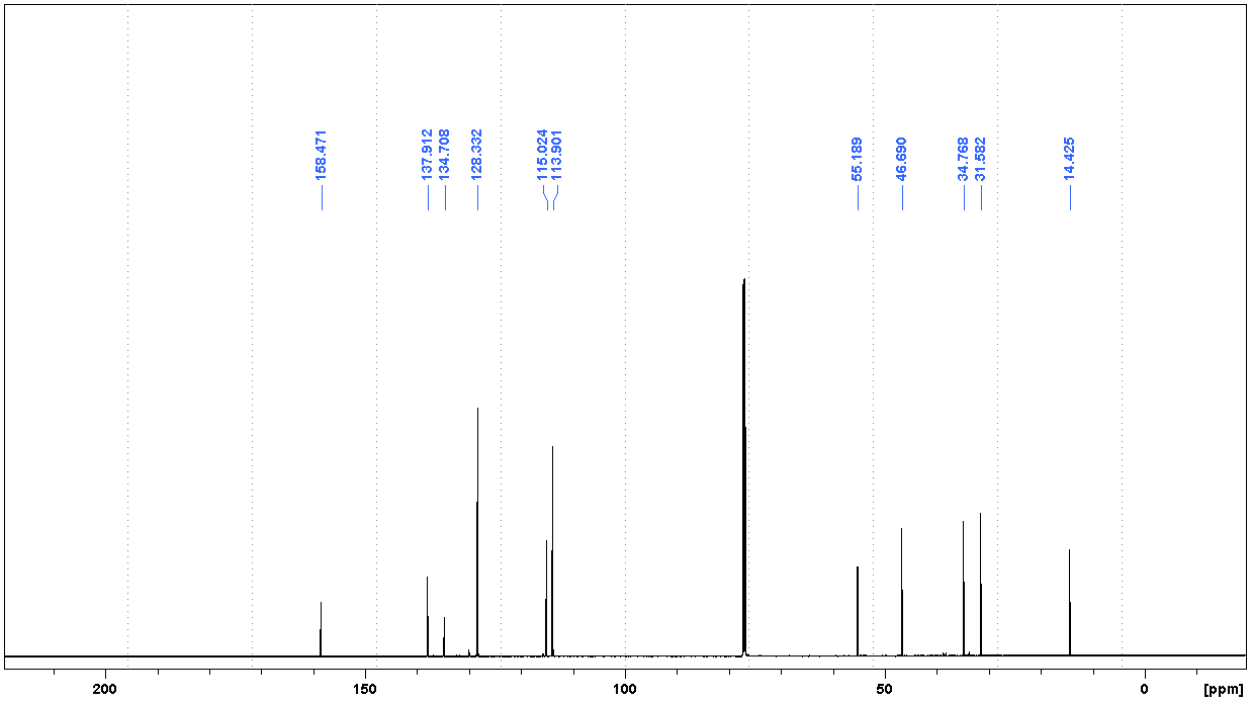


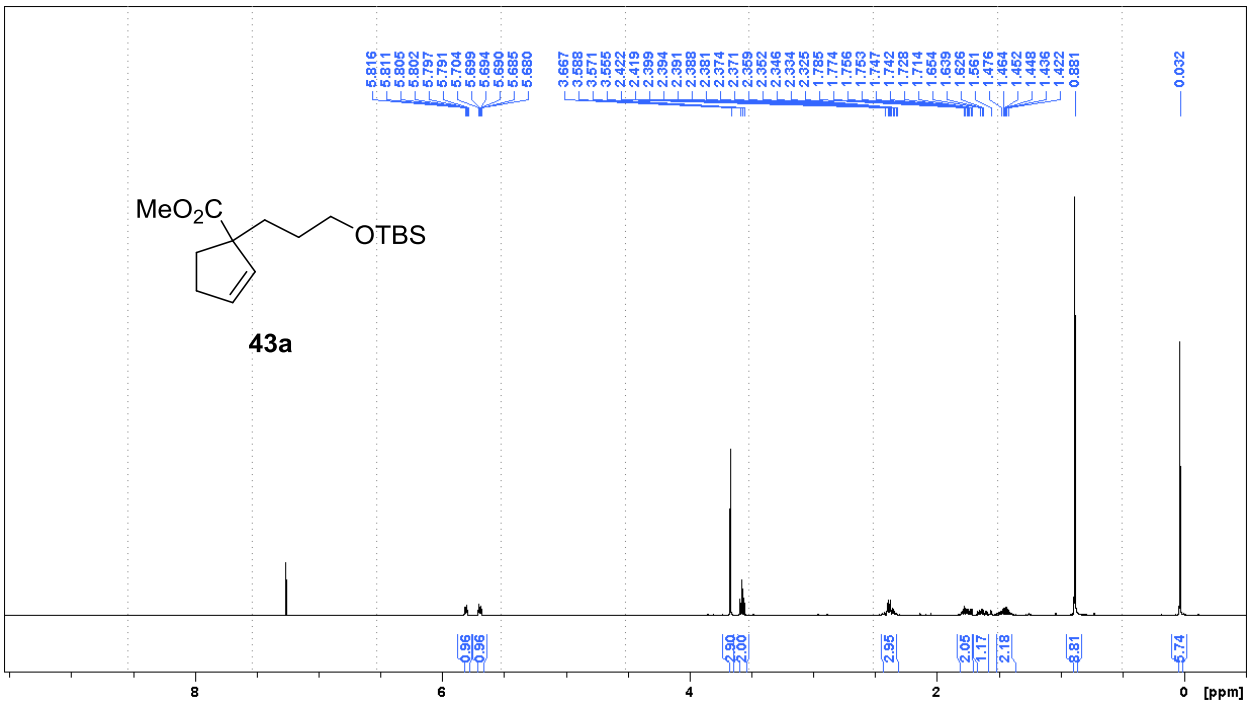


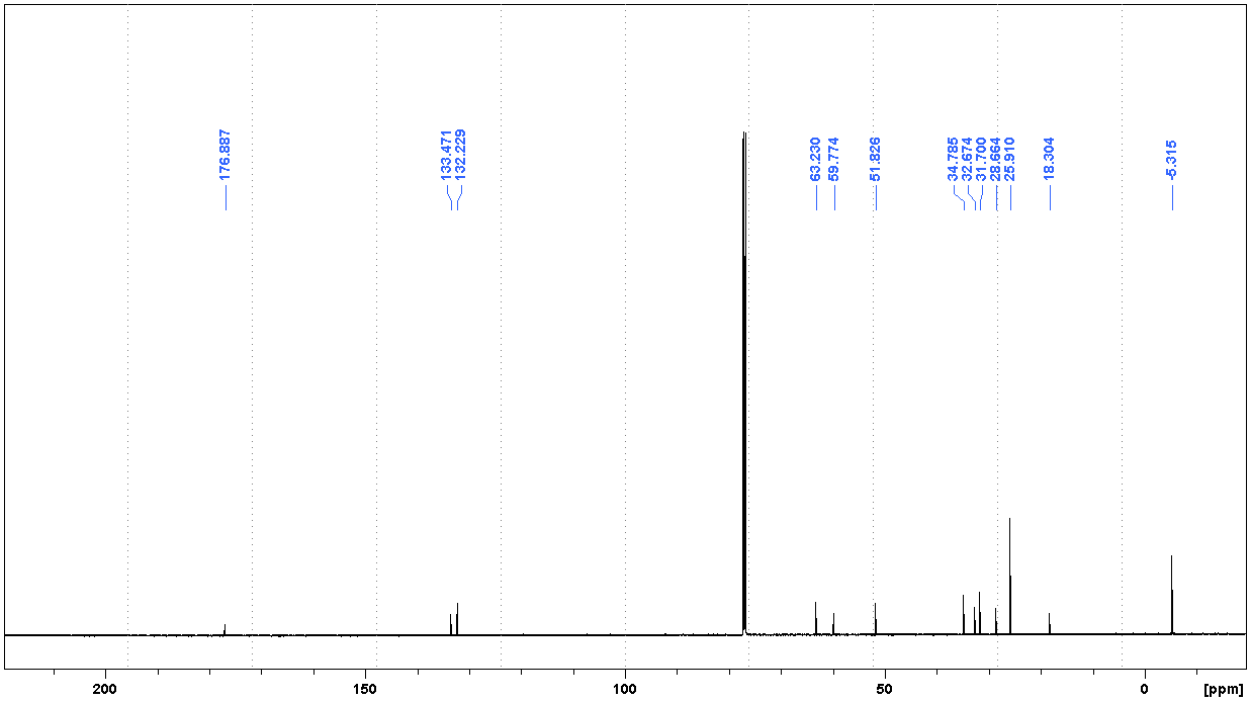

OH
OMe
35b
[ppm]

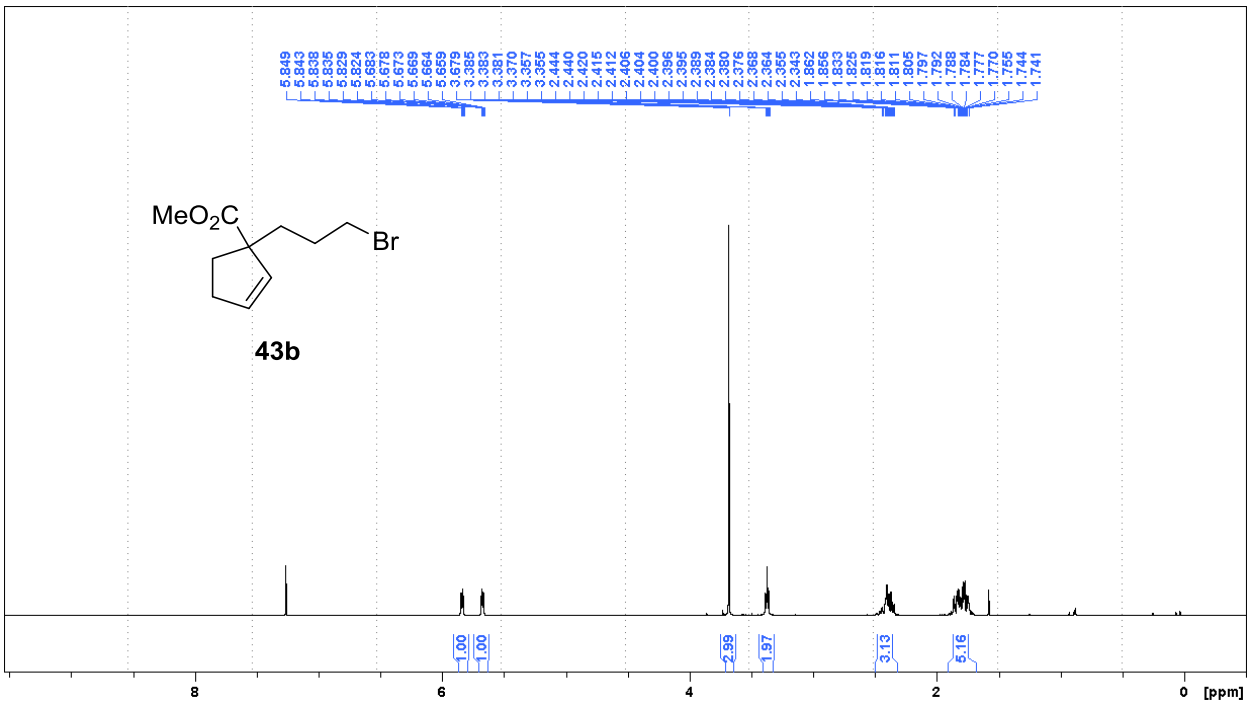

158.377
138.362
133.747
128.983
114.710
114.060
67.535
55.208
47.070
31.316
31.212
[ppm]

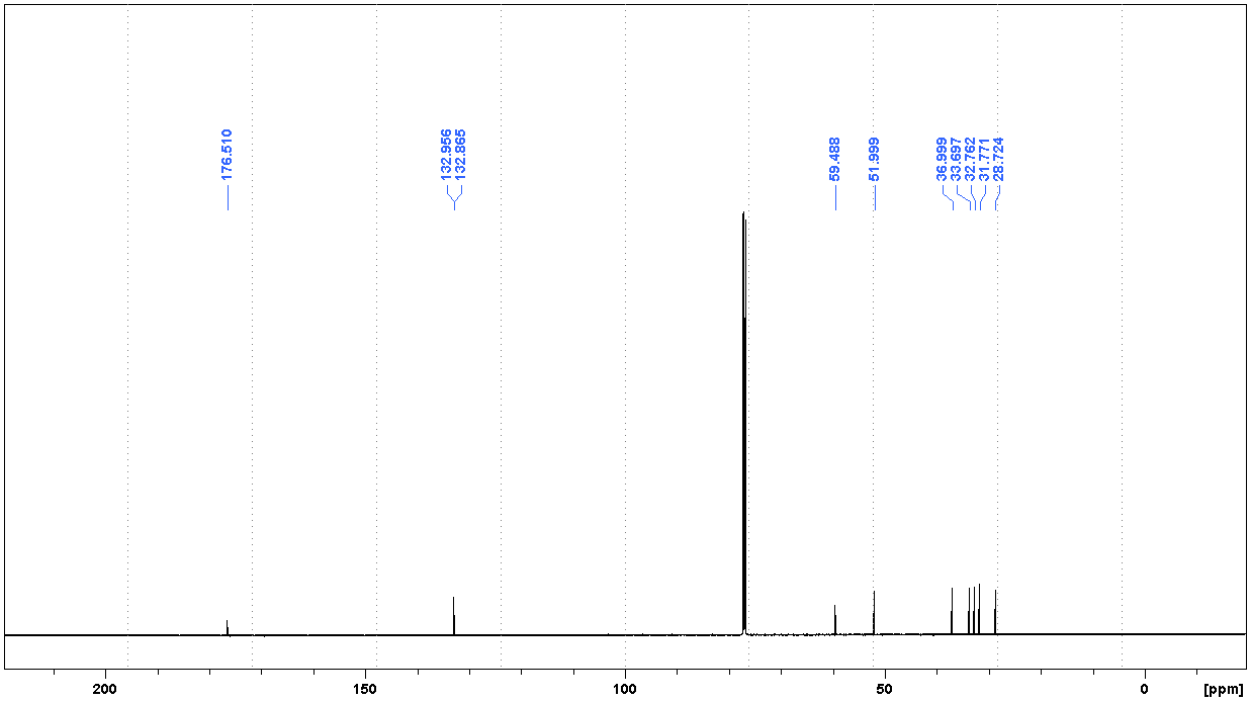

I
OMe
35
2.02
1.99
0.93
1.98
3.06
2.01
1.01
3.01
1.00
8
6
4
2
0
[ppm]

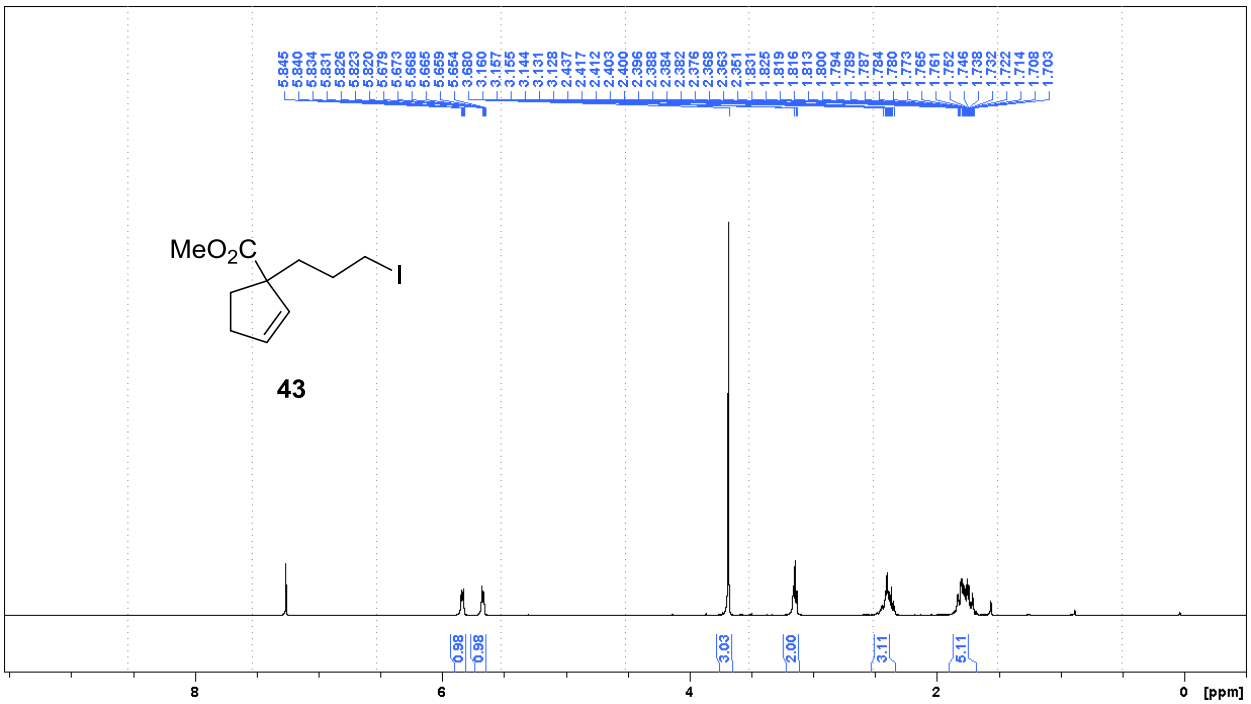

158.471
137.912
134.708
128.332
115.024
113.901
55.189
46.690
34.768
31.582
14.425
200
150
100
50
0
[ppm]


MeO2C
OTBS
43a
5.816
5.811
5.805
5.802
5.797
5.791
5.704
5.699
5.694
5.690
5.685
5.680
3.667
3.588
3.571
3.555
2.422
2.419
2.399
2.394
2.391
2.388
2.381
2.371
2.374
2.371
2.369
2.352
2.346
2.334
2.325
1.785
1.774
1.756
1.753
1.747
1.742
1.728
1.714
1.654
1.639
1.626
1.561
1.475
1.464
1.452
1.448
1.436
1.422
0.881
0.032
0.96
0.96
2.90
2.00
2.95
2.05
1.17
2.18
8.81
6.74
8
6
4
2
0
[ppm]


176.887
133.471
132.229
63.230
59.774
51.826
34.785
32.674
31.700
28.664
25.910
18.304
-5.315
200
150
100
50
0
[ppm]


5.849
5.843
5.838
5.835
5.829
5.824
5.683
5.678
5.673
5.669
5.664
5.659
3.679
3.385
3.383
3.381
3.370
3.357
3.355
2.444
2.440
2.420
2.415
2.412
2.406
2.404
2.400
2.396
2.395
2.389
2.384
2.380
2.376
2.368
2.364
2.355
2.343
1.862
1.856
1.833
1.825
1.819
1.816
1.811
1.805
1.797
1.792
1.788
1.784
1.777
1.770
1.755
1.744
1.741
MeO2C
Br
43b
1.00
1.00
2.99
1.97
3.13
5.16
8
6
4
2
0
[ppm]


176.510
132.956
132.865
59.488
51.999
36.999
33.697
32.762
31.771
28.724
200
150
100
50
0
[ppm]


5.845
5.840
5.834
5.831
5.826
5.823
5.820
5.679
5.673
5.668
5.665
5.659
5.654
3.160
3.157
3.155
3.144
3.131
3.123
2.437
2.417
2.412
2.403
2.400
2.396
2.388
2.384
2.382
2.376
2.368
2.363
2.351
1.831
1.825
1.819
1.816
1.813
1.800
1.794
1.789
1.787
1.784
1.780
1.773
1.765
1.761
1.752
1.746
1.738
1.732
1.722
1.714
1.708
1.703
MeO2C
I
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0.98
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2.00
3.11
5.11
8
6
4
2
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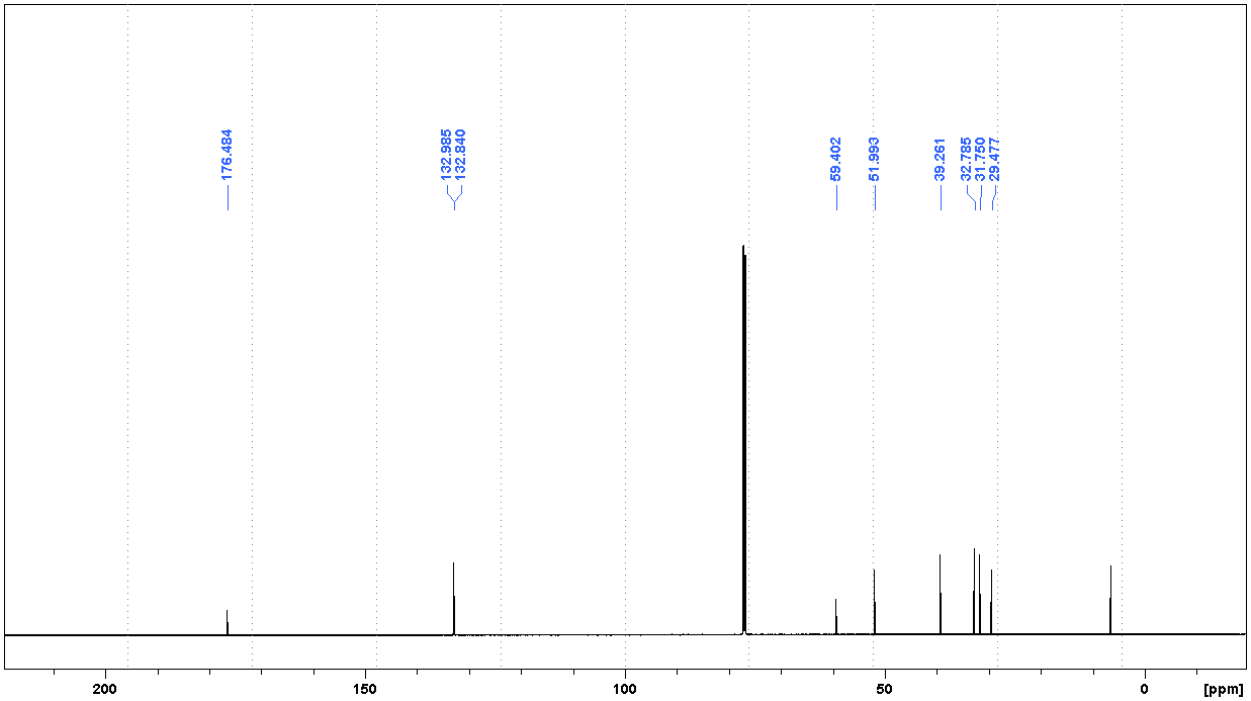
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32.785
31.750
29.477
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100
50
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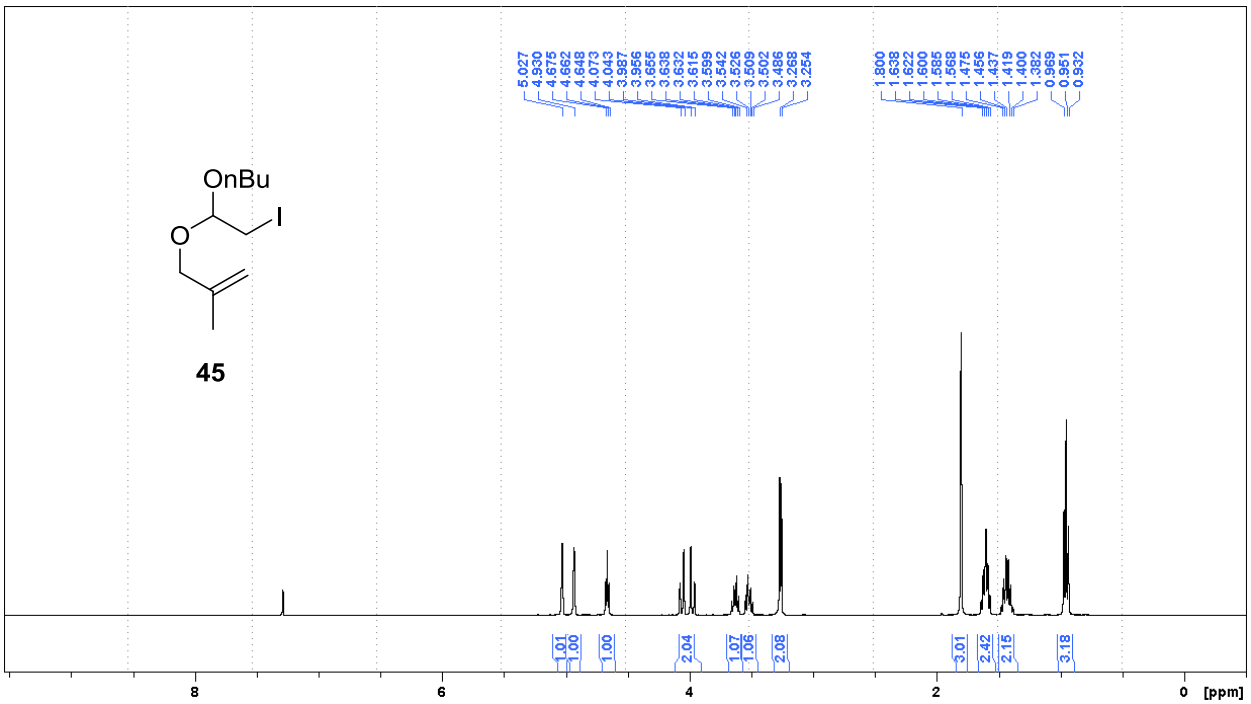
OnBu
O
I
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4.662
4.648
4.073
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3.987
3.956
3.655
3.638
3.632
3.615
3.599
3.542
3.526
3.509
3.502
3.486
3.288
3.254
1.800
1.638
1.622
1.600
1.585
1.568
1.475
1.456
1.437
1.419
1.400
1.382
0.969
0.951
0.932
1.01
1.00
1.00
2.04
1.07
1.06
2.08
3.01
2.42
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3.18
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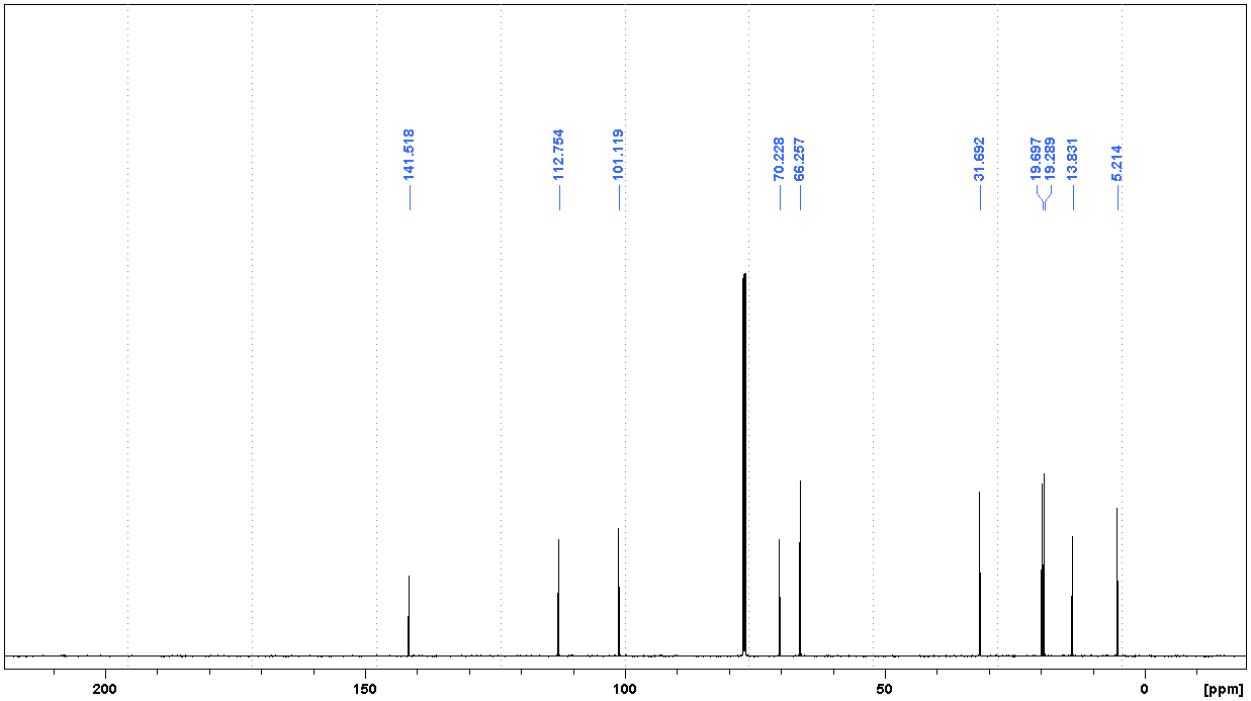
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112.754
101.119
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19.697
19.289
13.831
5.214
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100
50
0
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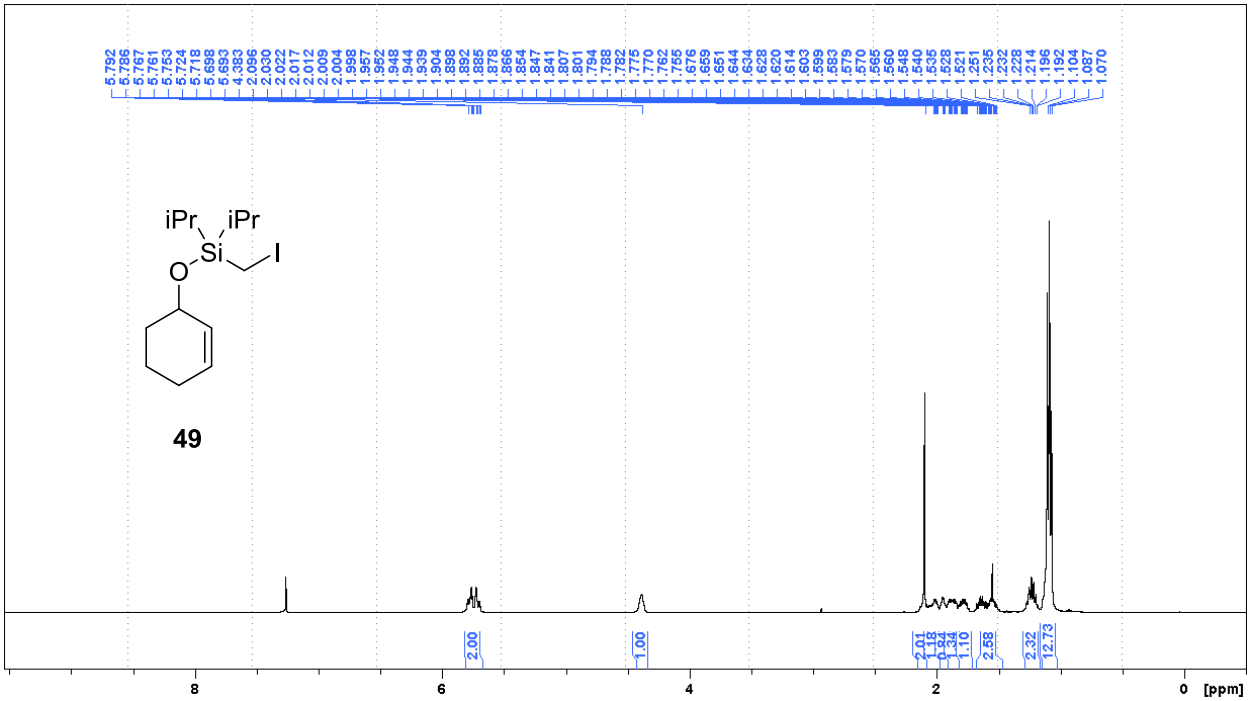
iPr
iPr
Si
O
I
49
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1.00
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1.18
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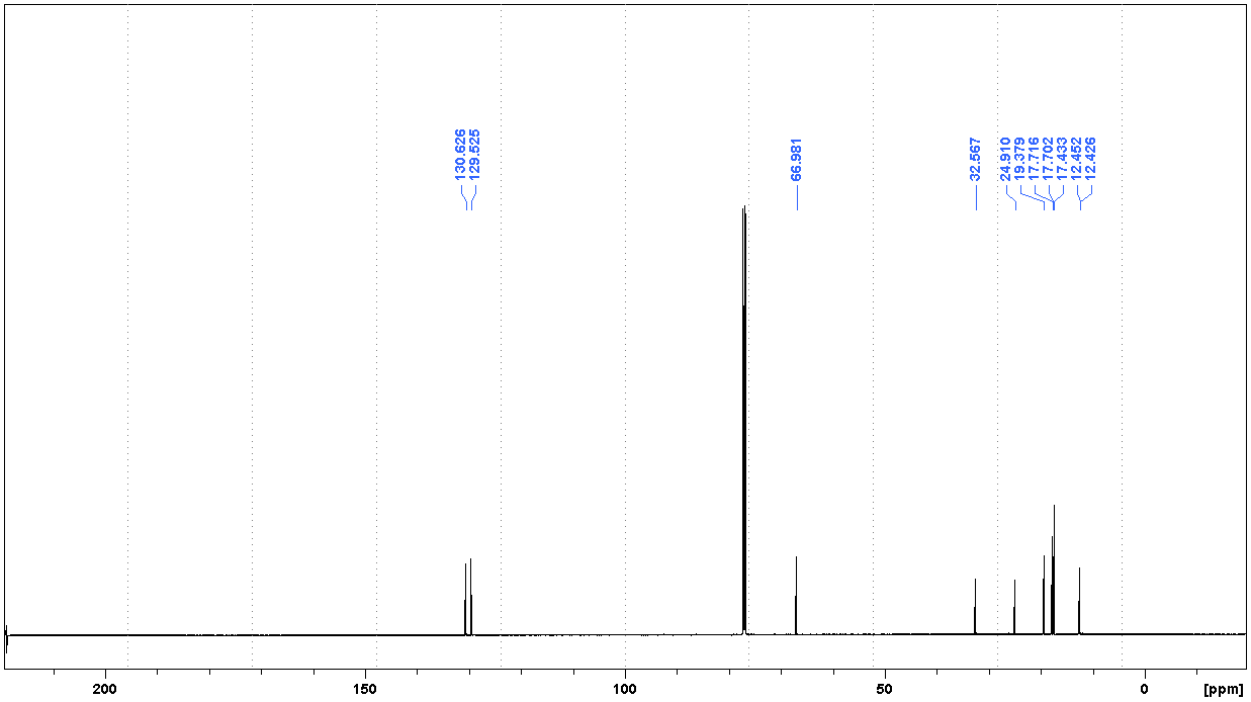
1.34
1.10
2.58
2.32
12.73
8
6
4
2
0
[ppm]


130.626
129.525
66.981
32.567
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19.379
17.716
17.702
17.433
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12.426
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100
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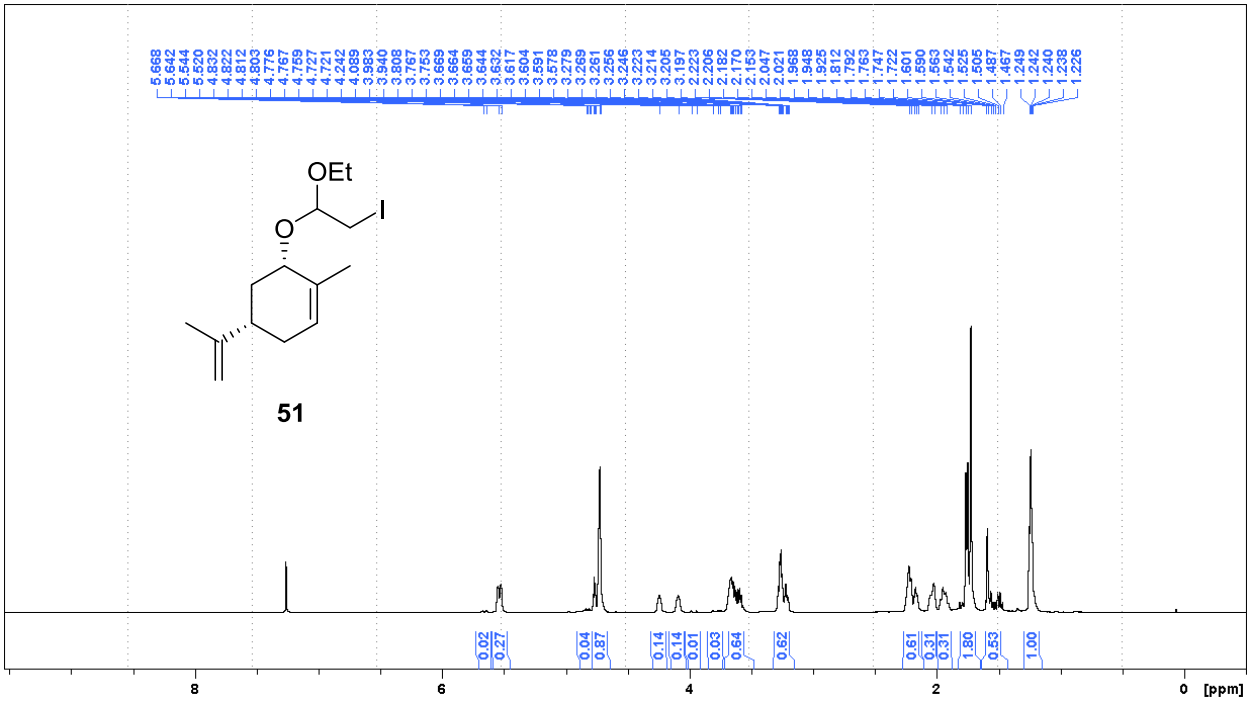
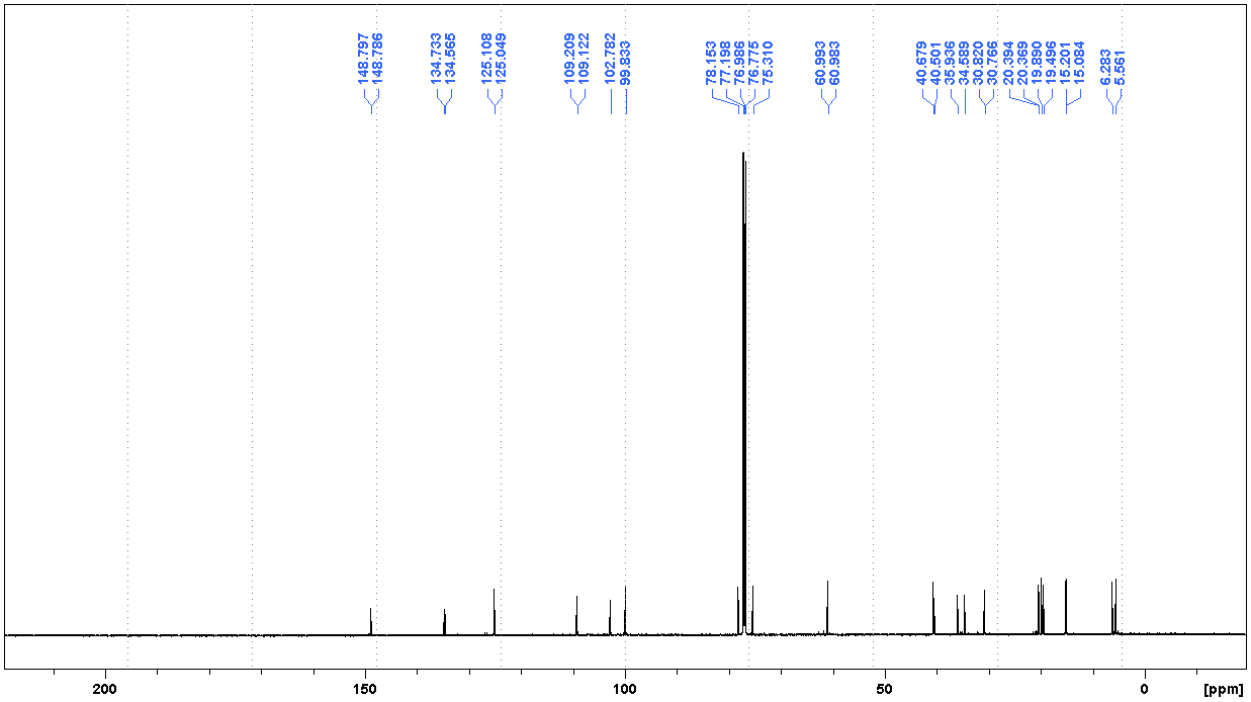

OEt
O
I
51
[ppm]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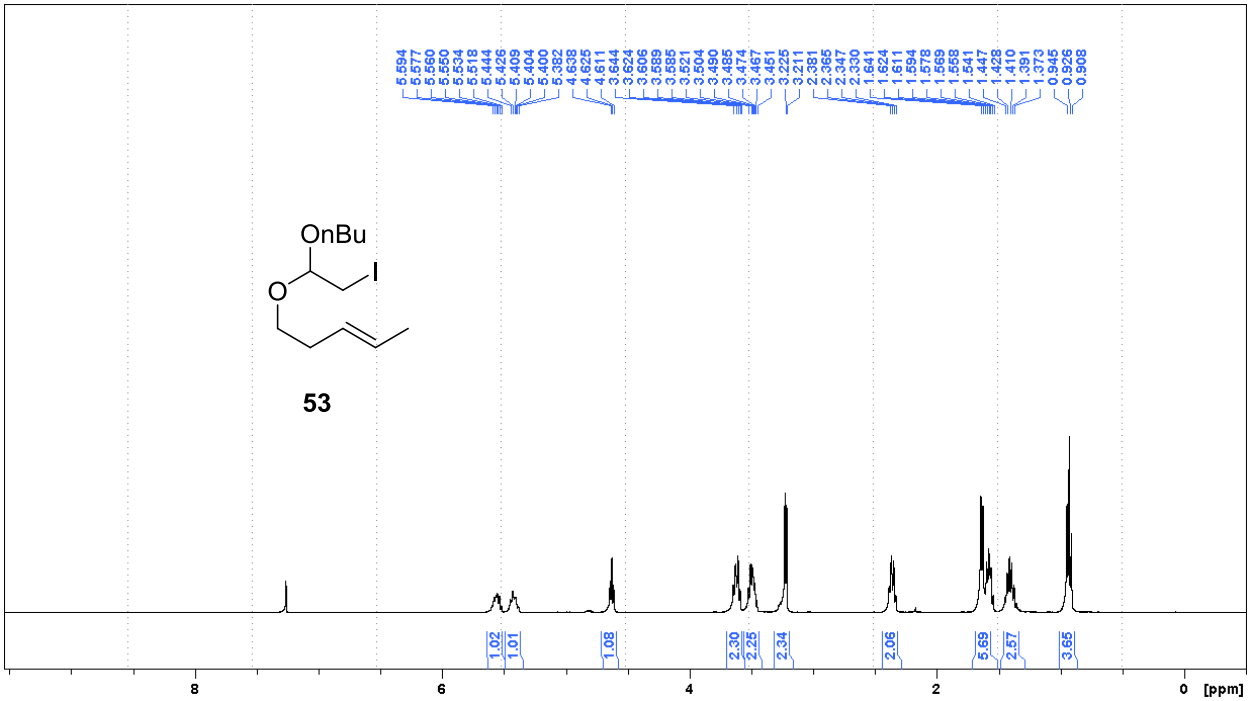
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5.560
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5.534
5.518
5.444
5.426
5.409
5.404
5.400
5.382
4.638
4.625
4.611
3.644
3.624
3.606
3.589
3.585
3.521
3.504
3.490
3.485
3.474
3.467
3.451
3.225
3.211
2.381
2.365
2.347
2.330
1.641
1.624
1.611
1.594
1.578
1.569
1.558
1.541
1.447
1.428
1.410
1.391
1.373
0.945
0.926
0.908
OnBu
O
I
53
1.02
1.01
1.08
2.30
2.25
2.34
2.06
5.69
2.57
3.65
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4
2
0
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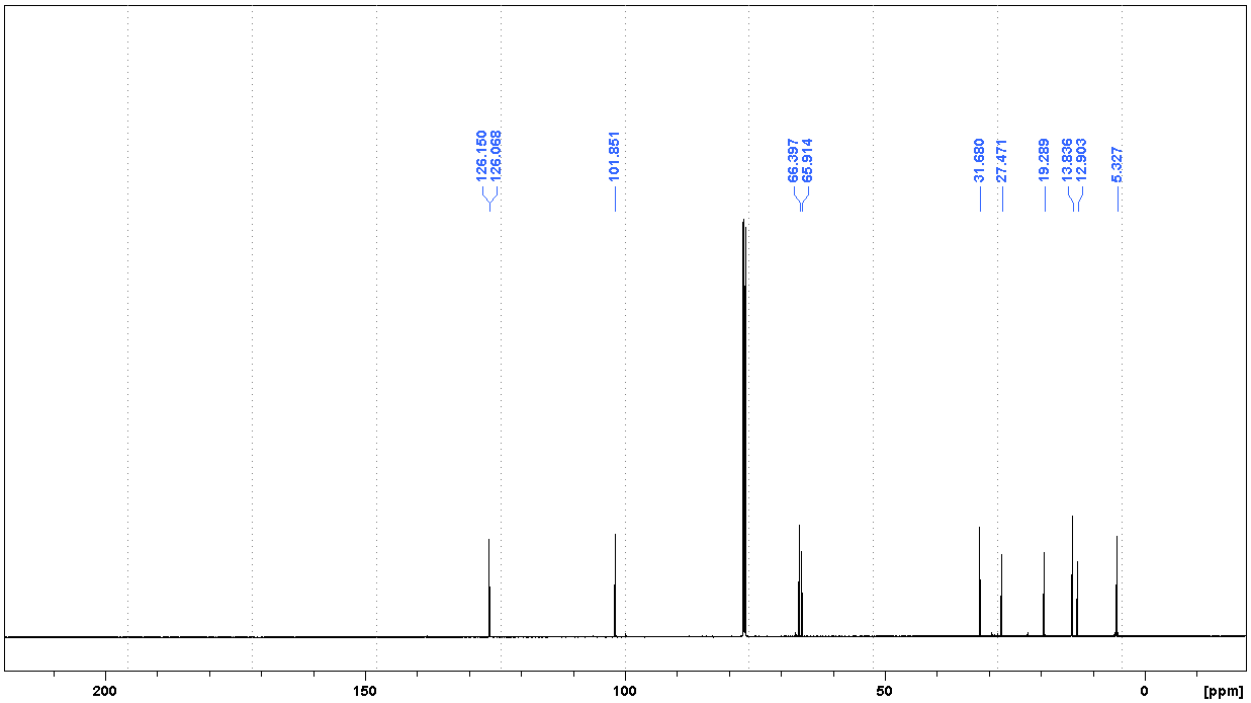
126.150
126.068
101.851
66.397
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31.680
27.471
19.289
13.836
12.903
5.327
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100
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0
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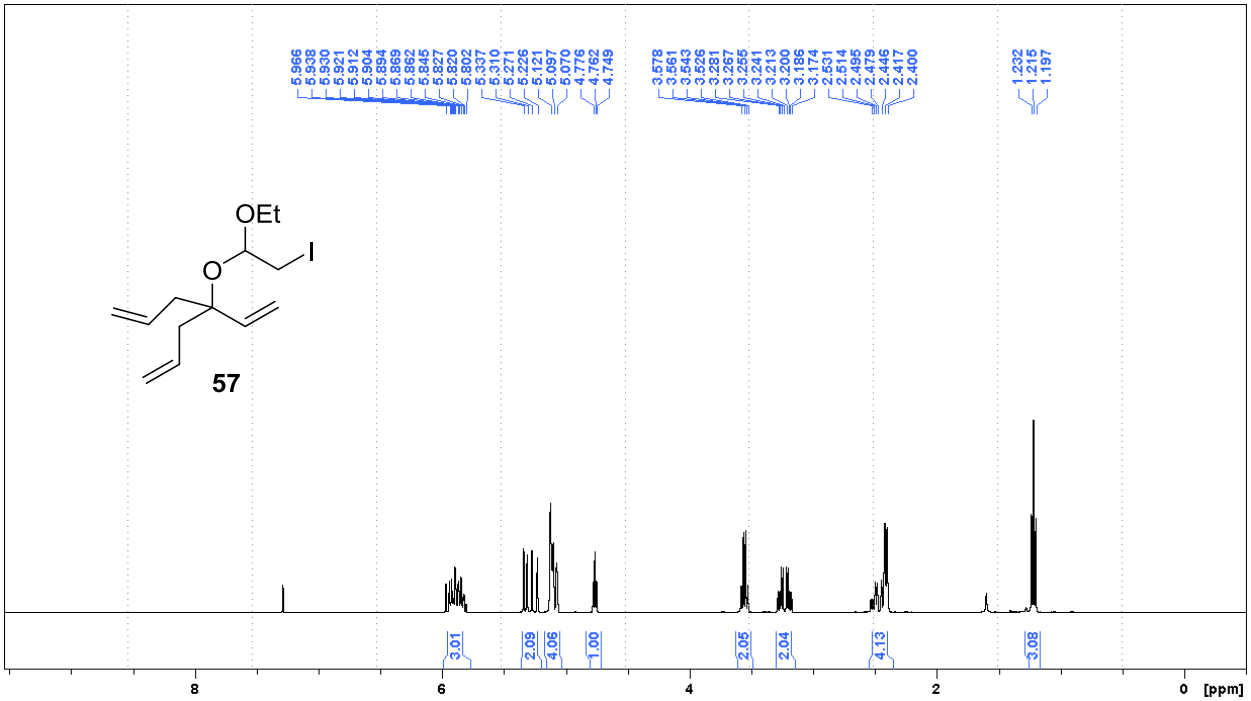
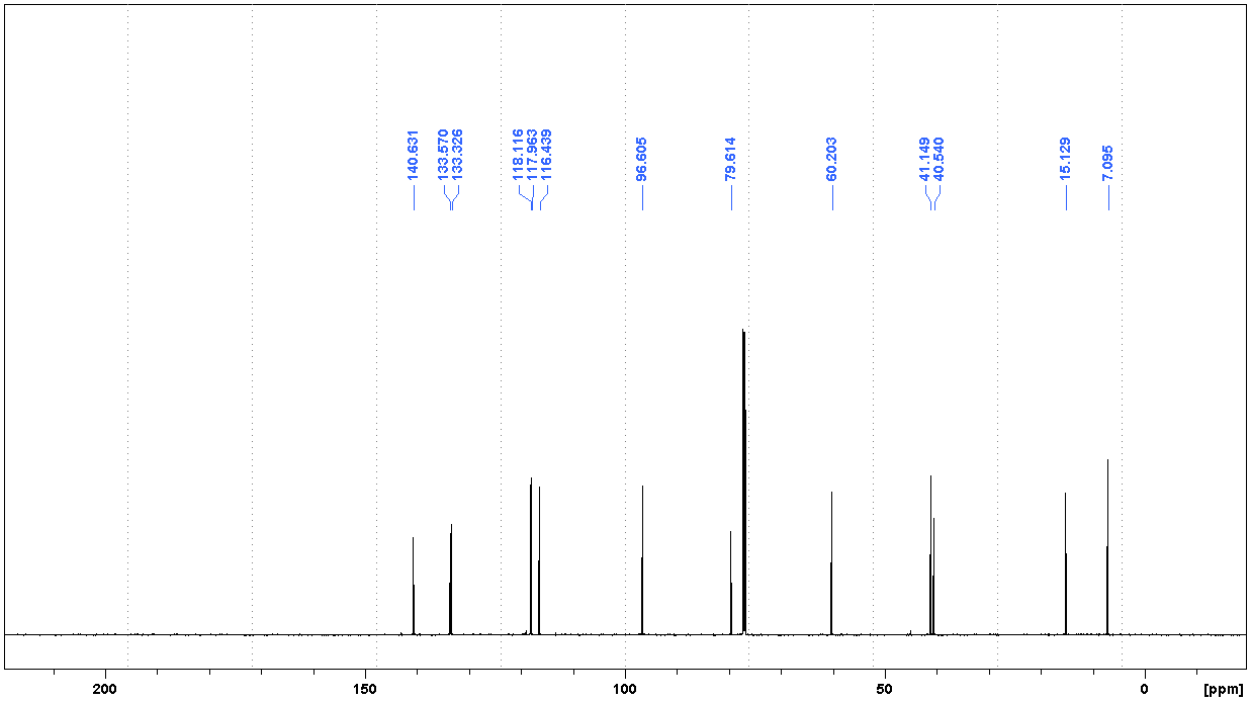
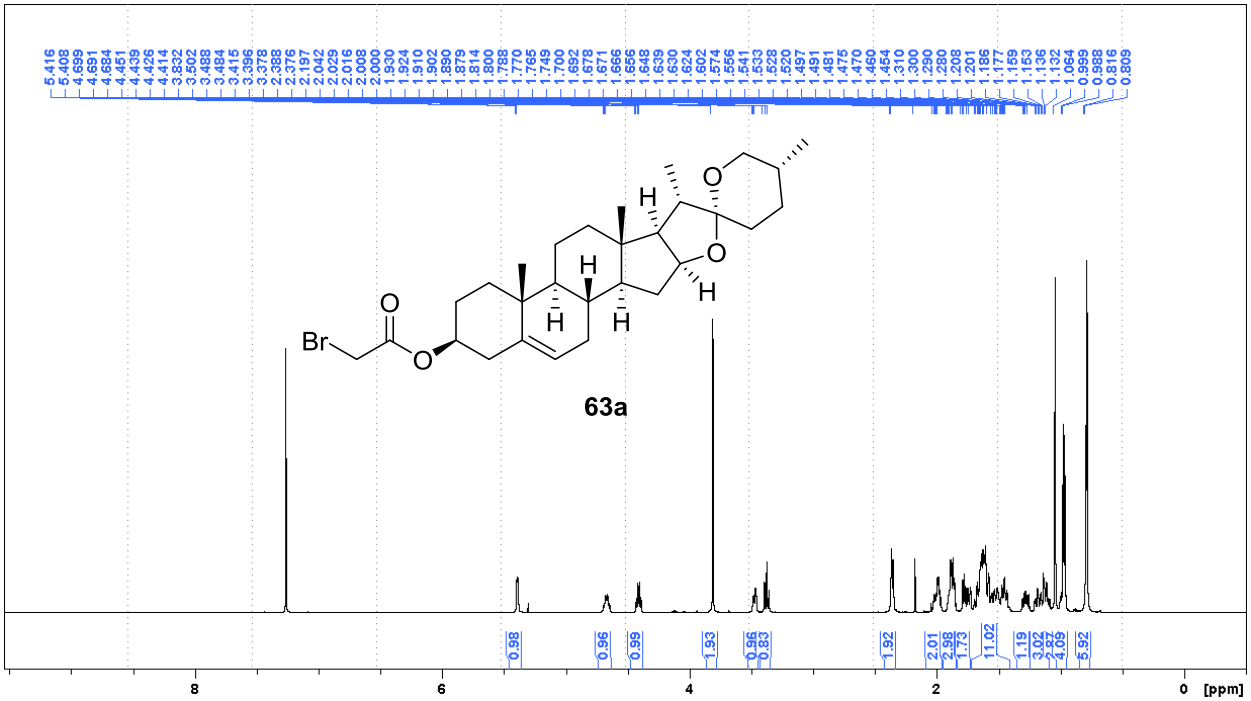

5.966
5.938
5.930
5.921
5.912
5.904
5.894
5.869
5.862
5.845
5.827
5.820
5.802
5.337
5.310
5.271
5.226
5.121
5.057
5.070
4.776
4.762
4.749
3.578
3.561
3.543
3.526
3.281
3.267
3.255
3.241
3.213
3.200
3.186
3.174
2.531
2.514
2.495
2.479
2.446
2.417
2.400
1.232
1.215
1.197
OEt
O
I
57
3.01
2.09
4.06
1.00
2.05
2.04
4.13
3.08
8
6
4
2
0
[ppm]


140.631
133.570
133.326
118.116
117.963
116.439
96.605
79.614
60.203
41.149
40.540
15.129
7.095
200
150
100
50
0
[ppm]


63a
Br
O
O
H
H
H
H
O
O
H
8
6
4
2
0
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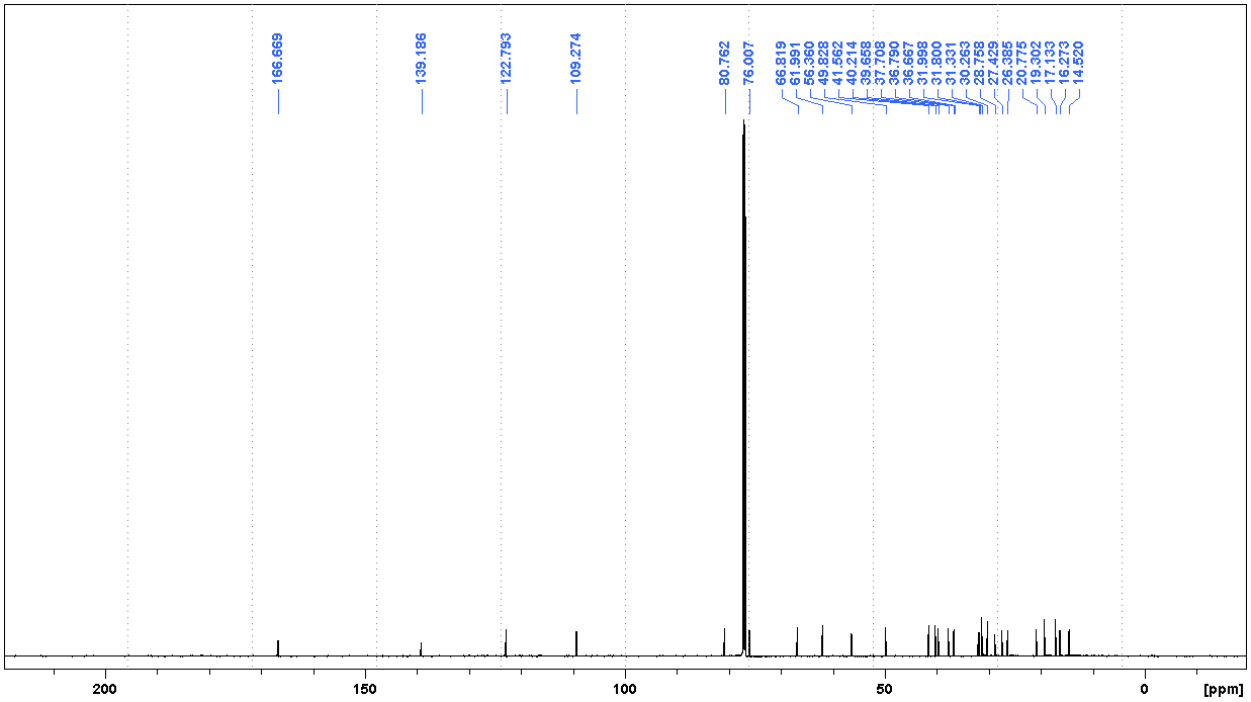
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139.186
122.793
109.274
80.762
76.007
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150
100
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0
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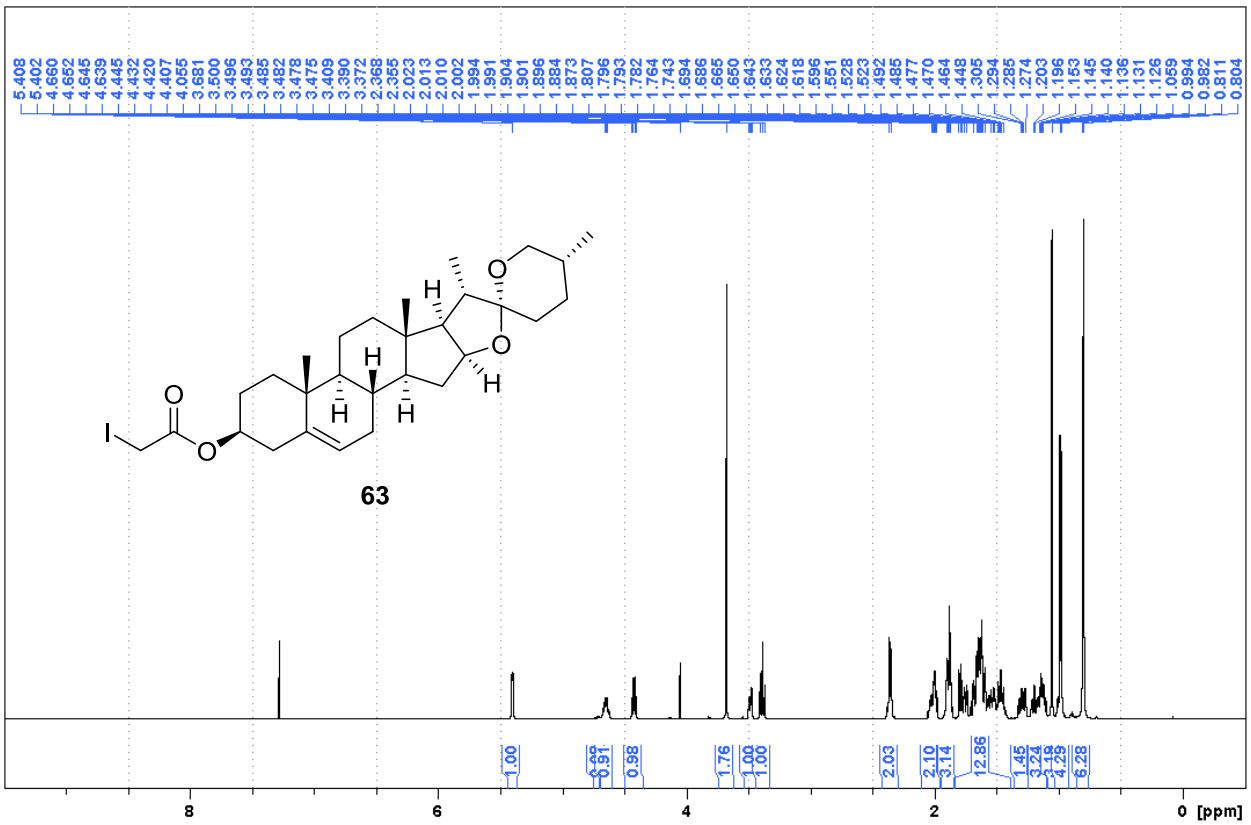
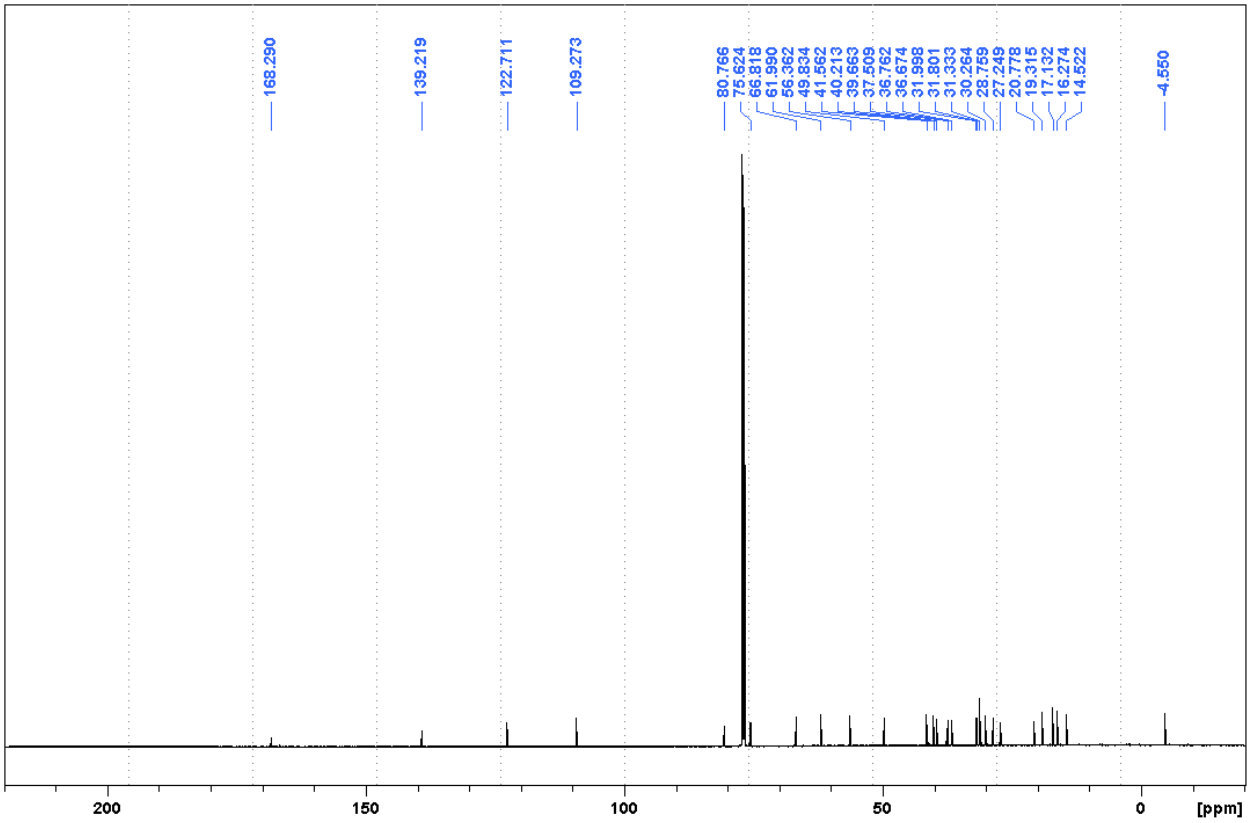

63
8
6
4
2
0 [ppm]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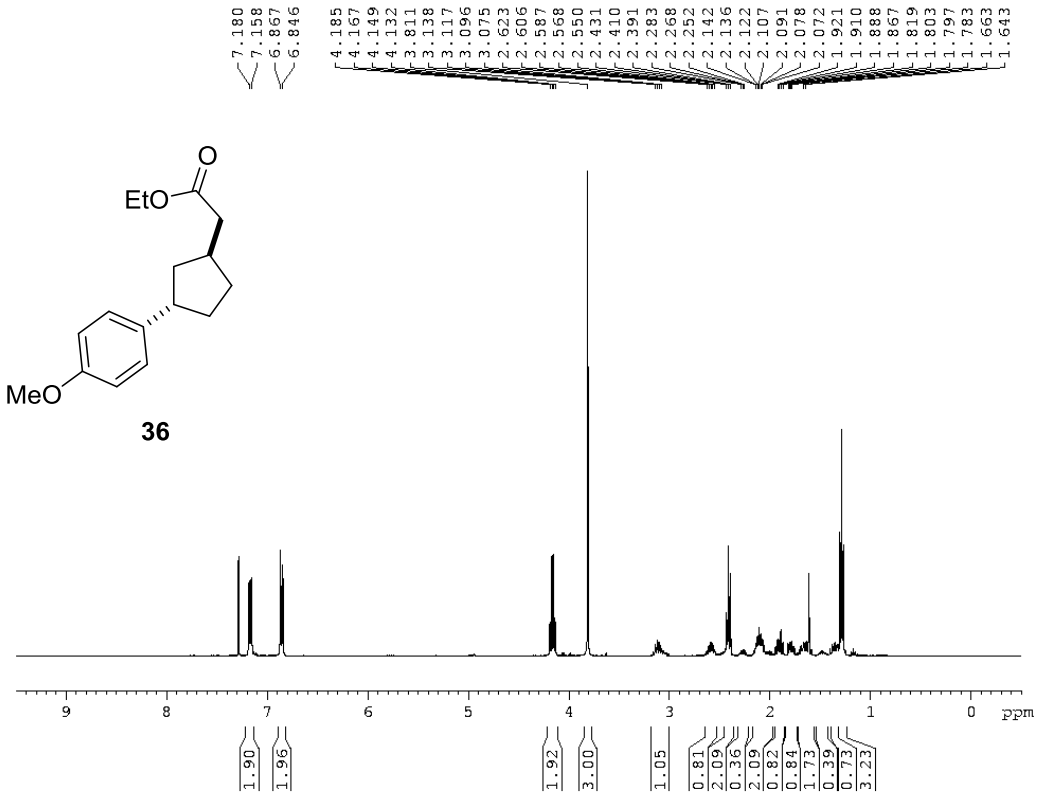
150
100
50
0 [ppm]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6.846
4.185
4.167
4.149
4.132
3.811
3.138
3.117
3.096
3.075
2.623
2.606
2.587
2.568
2.550
2.431
2.410
2.391
2.283
2.268
2.252
2.142
2.136
2.122
2.107
2.091
2.078
2.072
1.921
1.910
1.888
1.867
1.819
1.803
1.797
1.783
1.663
1.643
O
EtO
MeO
36
9
8
7
6
5
4
3
2
1
0
ppm
1.90
1.96
1.92
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1.05
0.81
2.09
0.36
2.09
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0.84
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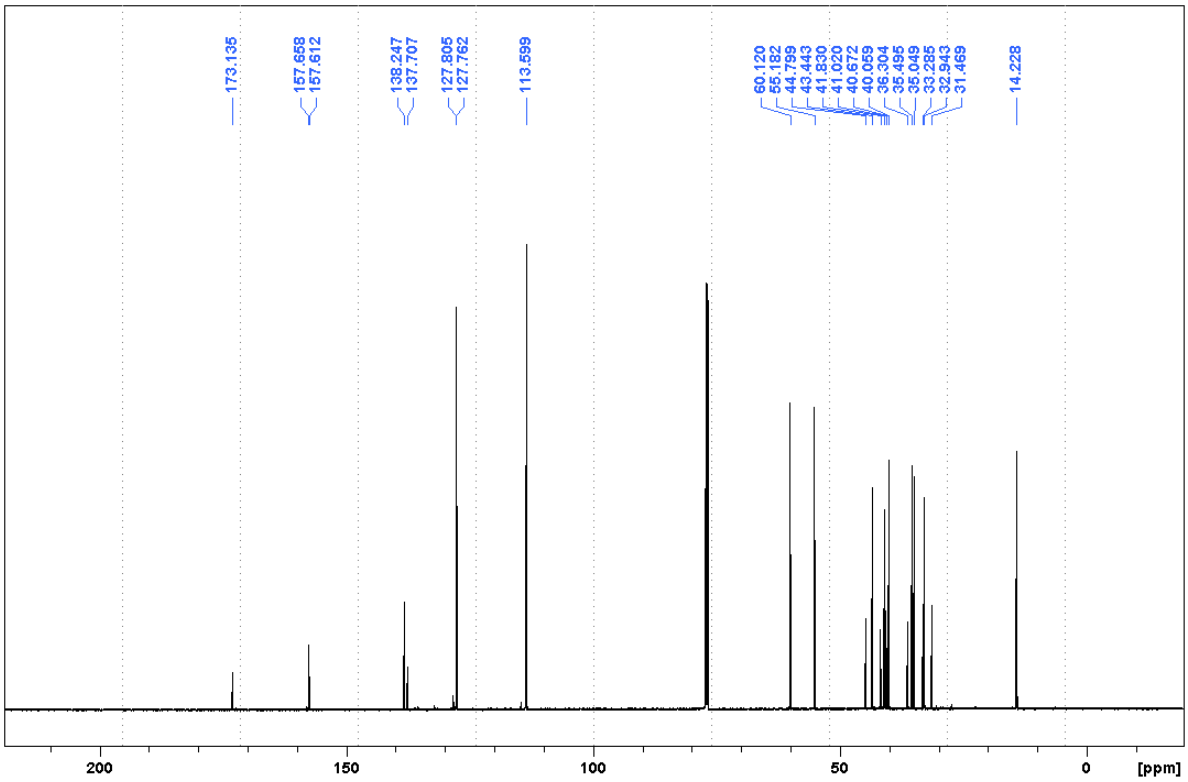
0.39
0.73
3.23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137.707
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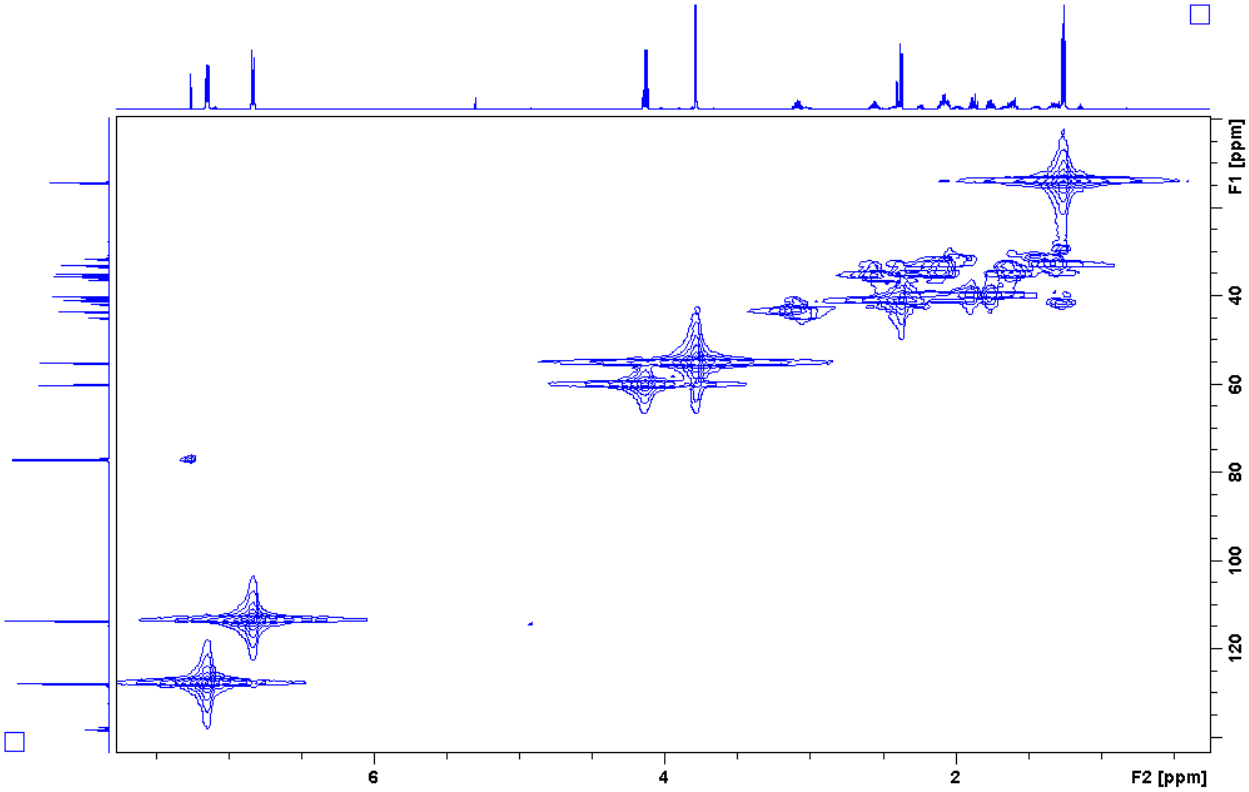
127.762
113.599
60.120
55.182
44.799
43.443
41.830
41.020
40.672
40.059
36.304
35.495
35.049
33.285
32.943
31.469
14.228
200
150
100
50
0
[ppm]


F1 [ppm]
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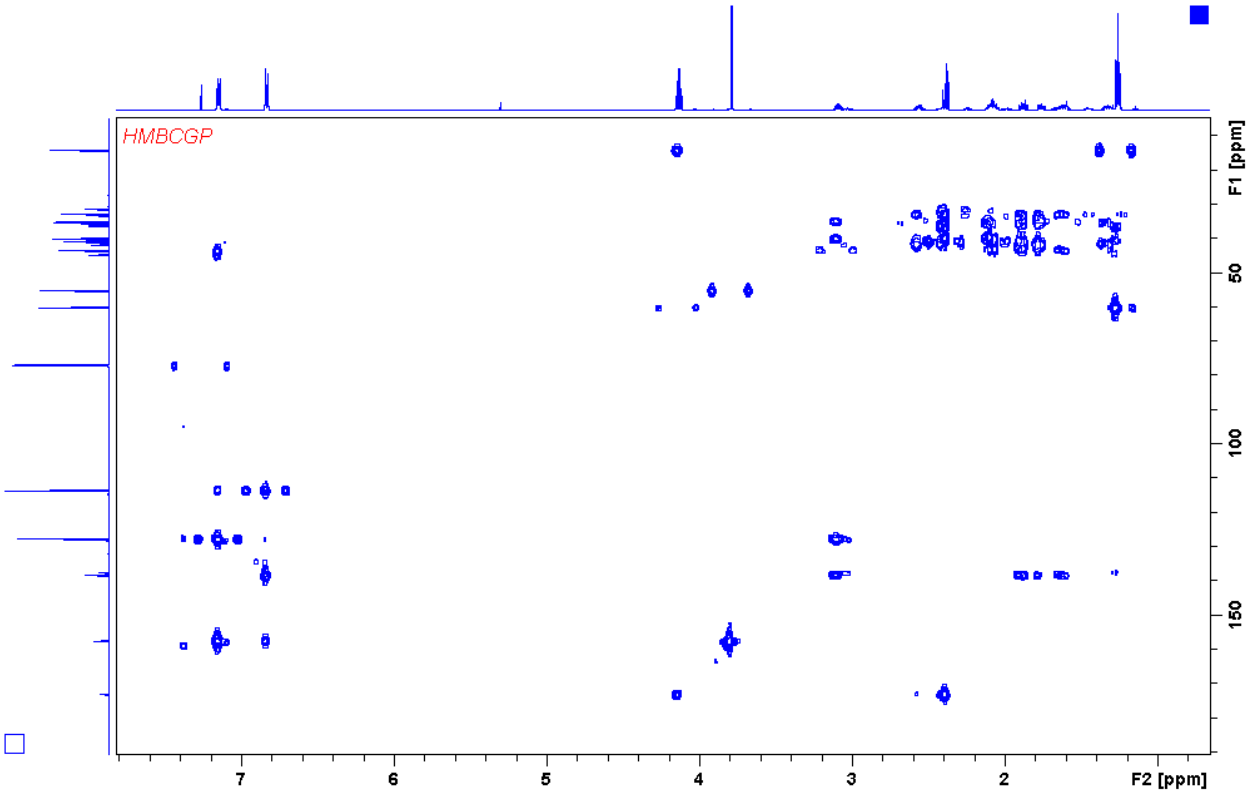
60
80
100
120
6
4
2
F2 [ppm]


HMBCGP
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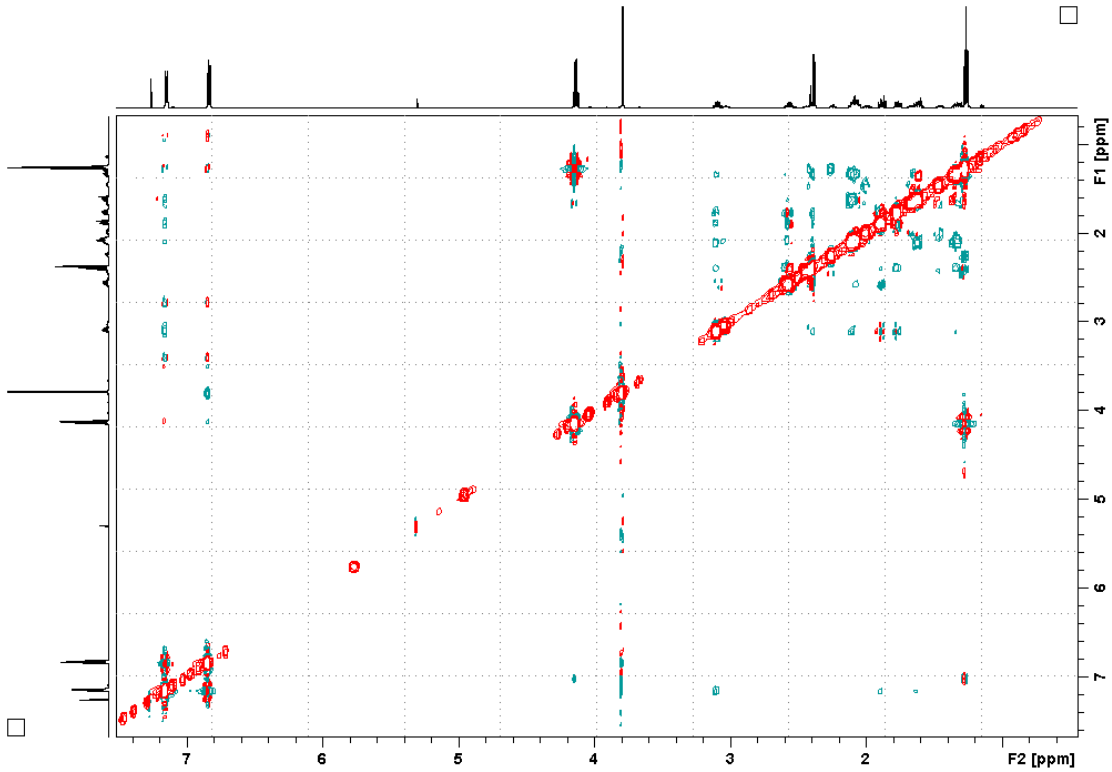
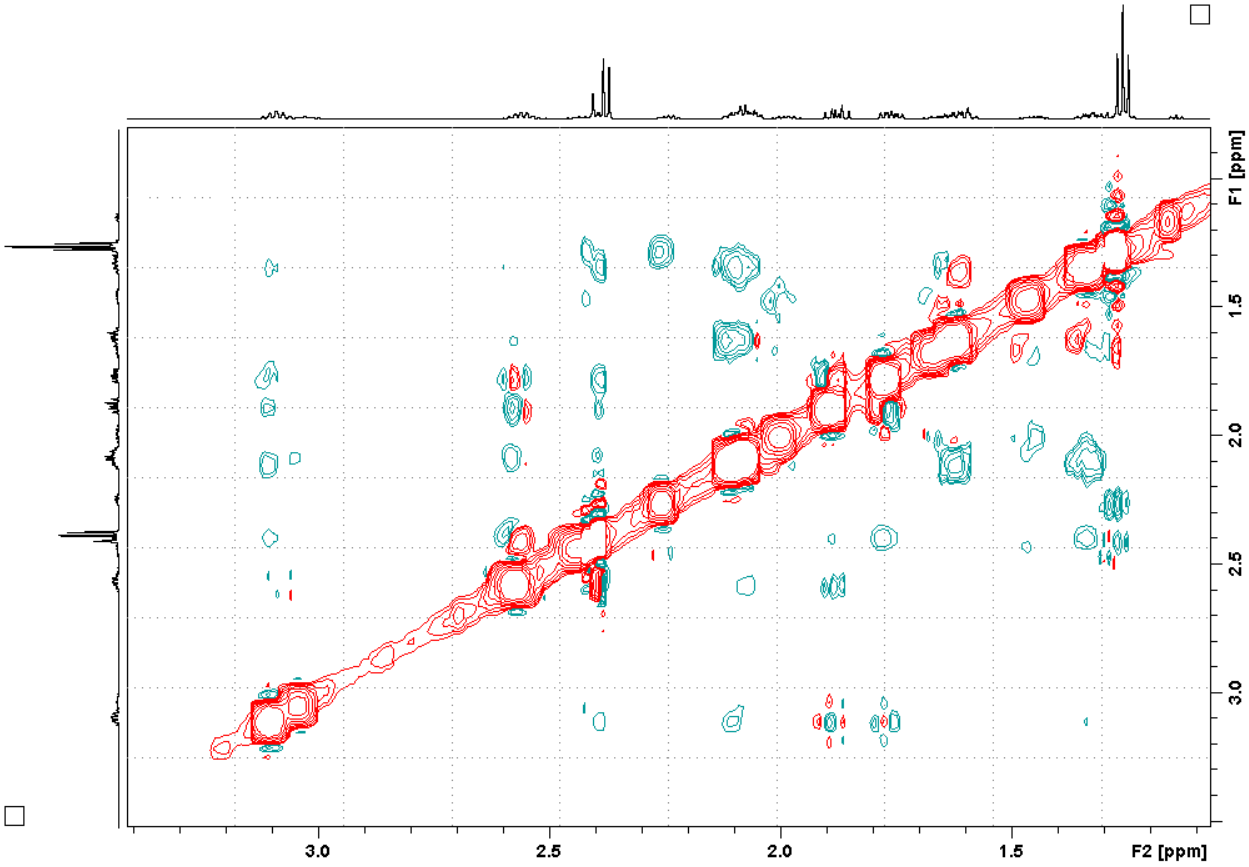
100
150
7
6
5
4
3
2
F2 [ppm]


F1 [ppm]
F2 [ppm]
7
6
5
4
3
2


F1 [ppm]
F2 [ppm]
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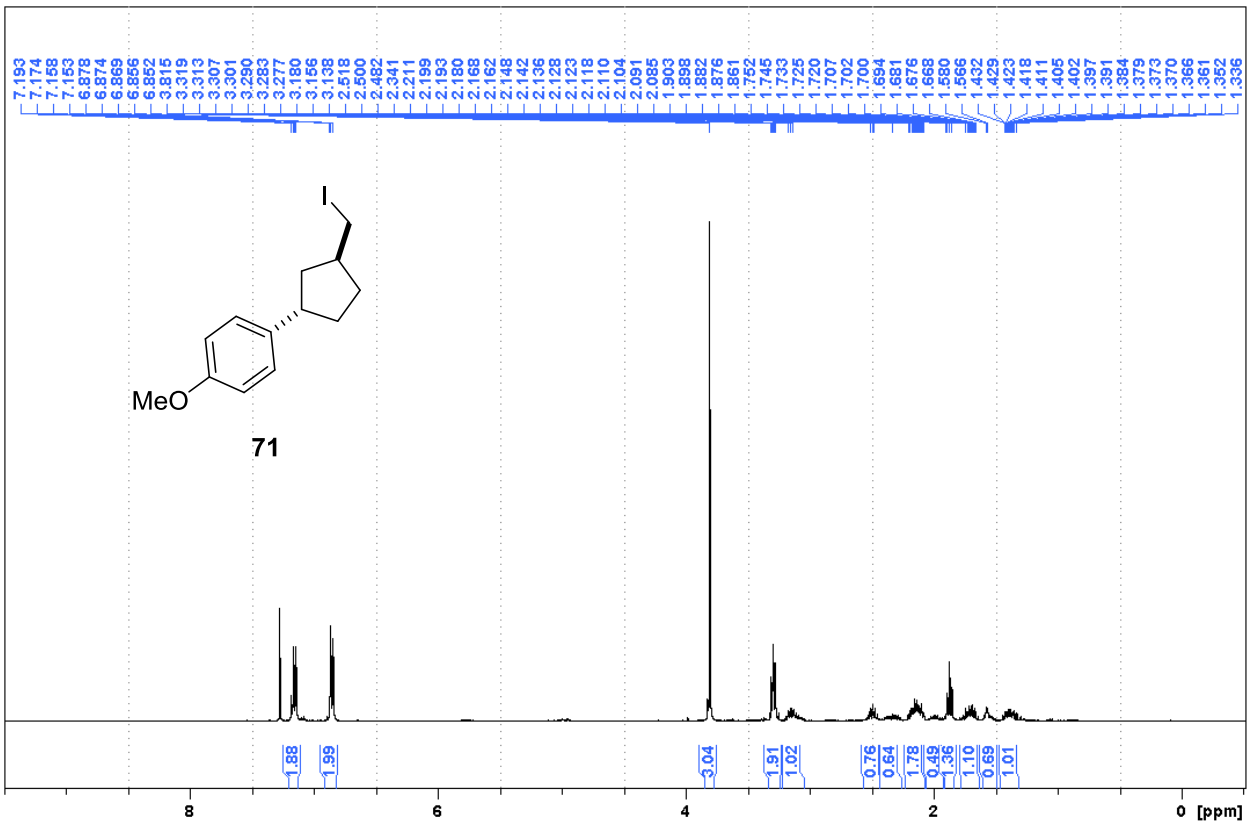
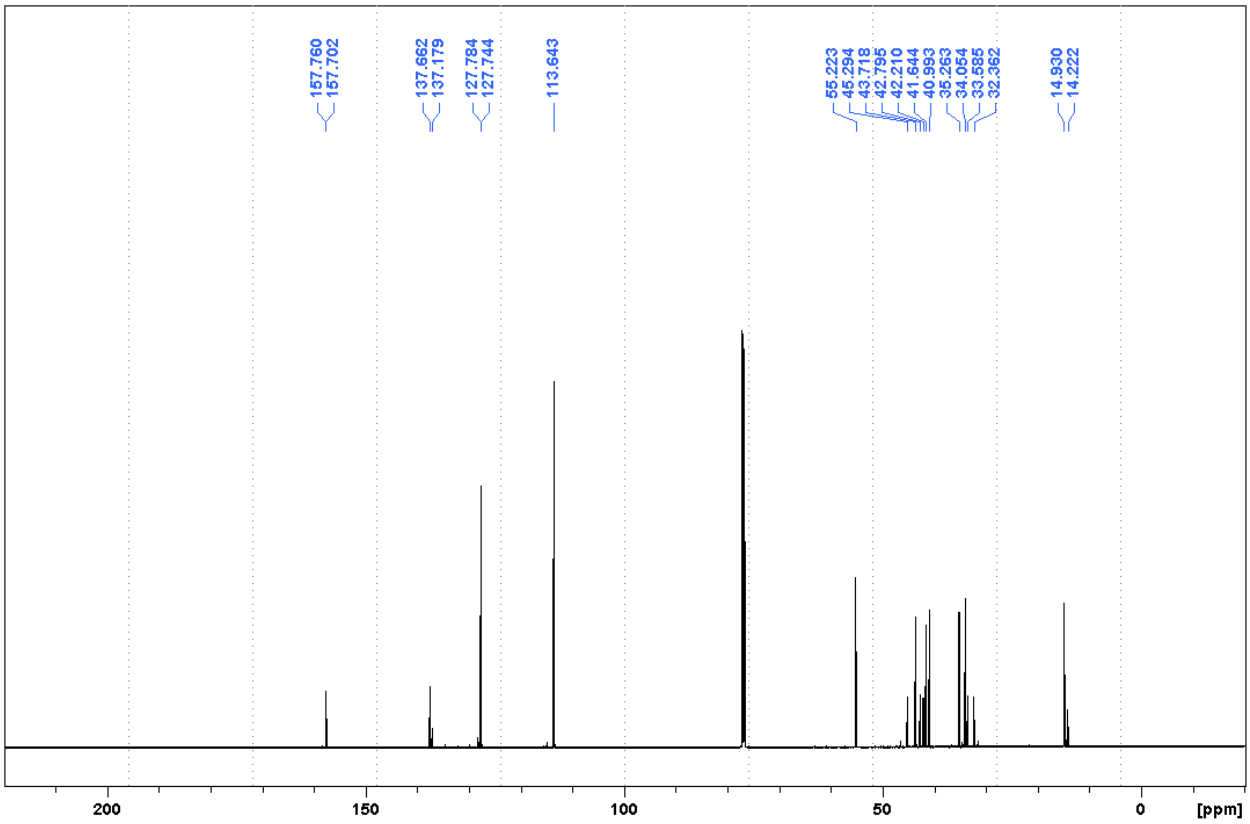
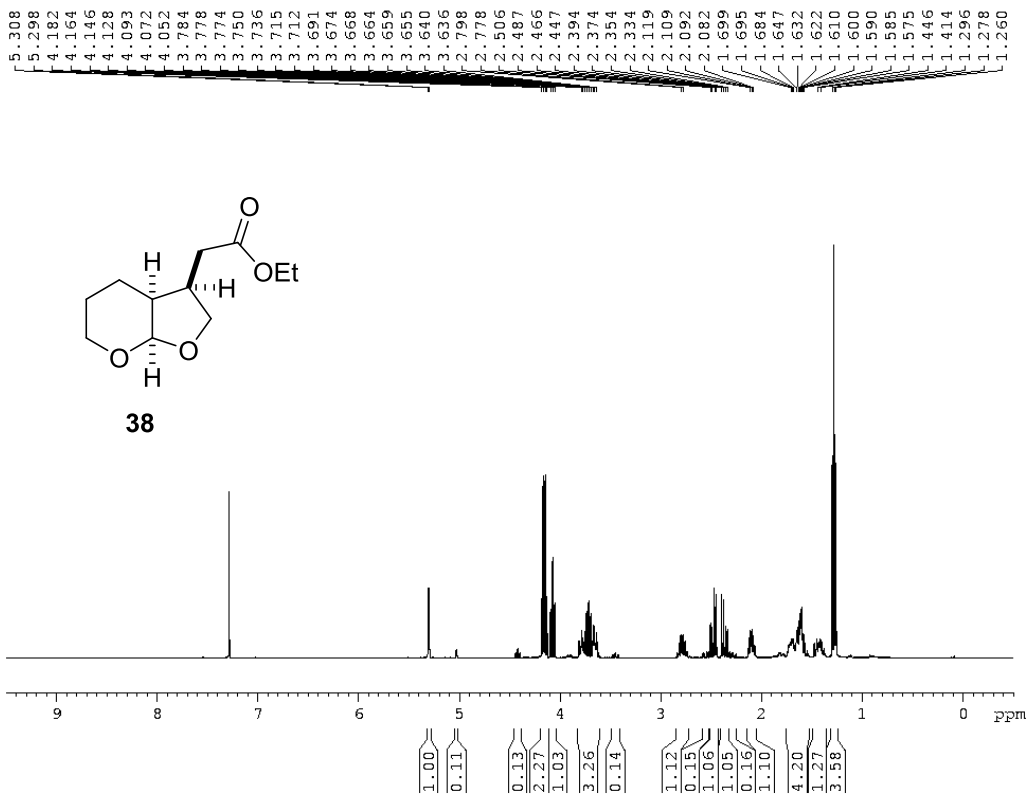
2.5
2.0
1.5


7.193 7.174 7.158 7.153 6.878 6.874 6.869 6.856 6.852 6.815 3.319 3.313 3.307 3.301 3.290 3.283 3.277 3.180 3.156 3.138 2.518 2.500 2.482 2.341 2.211 2.199 2.193 2.180 2.168 2.162 2.148 2.142 2.136 2.128 2.123 2.118 2.110 2.104 2.091 2.085 1.903 1.898 1.882 1.876 1.861 1.752 1.745 1.733 1.725 1.720 1.707 1.702 1.700 1.694 1.681 1.676 1.668 1.580 1.566 1.432 1.429 1.423 1.418 1.411 1.405 1.402 1.397 1.391 1.384 1.379 1.373 1.370 1.366 1.361 1.352 1.336
I
MeO
71
1.88 1.99 3.04 1.91 1.02 0.76 0.64 1.78 0.49 1.36 1.10 0.69 1.01
8 6 4 2 0 [ppm]


157.760 157.702
137.662 137.179
127.784 127.744
113.643
55.223 45.294 43.718 42.795 42.210 41.644 40.993 35.253 34.054 33.585 32.362
14.930 14.222
200 150 100 50 0 [ppm]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4.128
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4.072
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3.778
3.774
3.750
3.736
3.715
3.712
3.691
3.674
3.668
3.664
3.659
3.655
3.640
3.636
2.798
2.778
2.506
2.487
2.466
2.447
2.394
2.374
2.354
2.334
2.119
2.109
2.092
2.082
1.699
1.695
1.684
1.647
1.632
1.622
1.610
1.600
1.590
1.585
1.575
1.446
1.414
1.296
1.278
1.260
O
OEt
H
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5
4
3
2
1
0
ppm
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0.13
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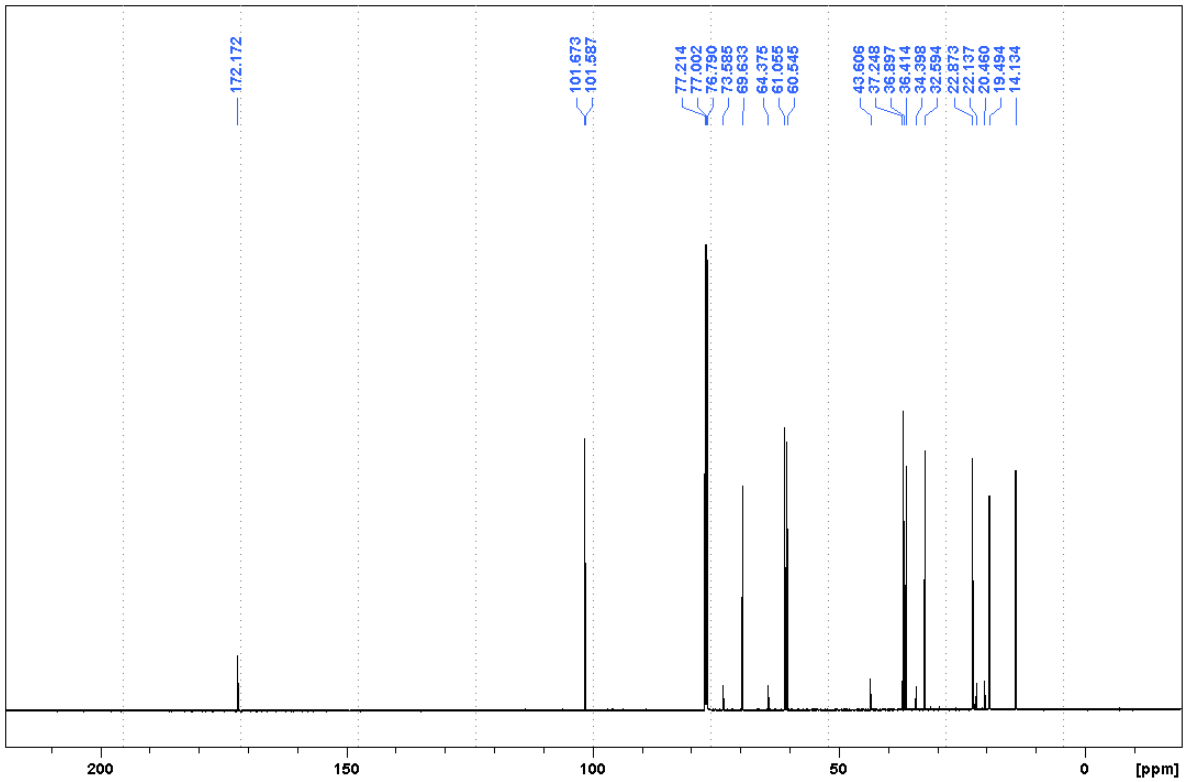
3.58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101.587
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76.790
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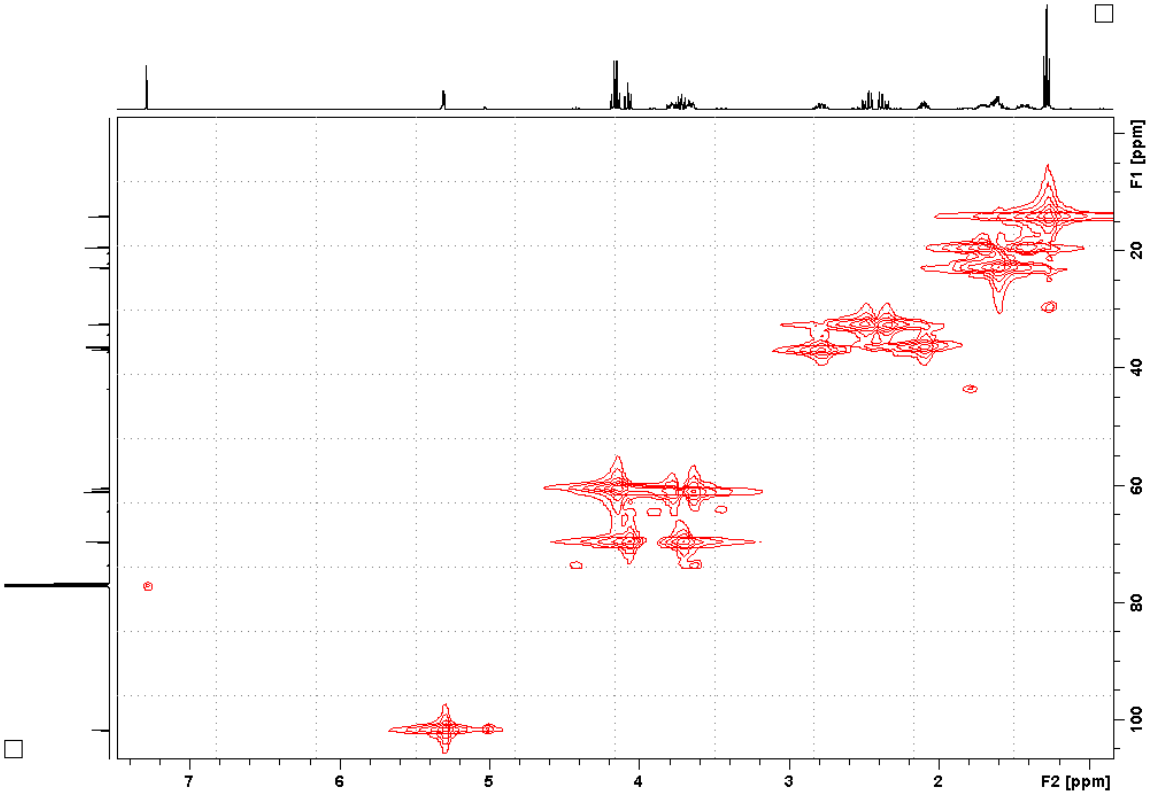
69.633
64.375
61.055
60.545
43.606
37.248
36.897
36.414
34.398
32.594
22.873
22.137
20.460
19.494
14.134
200
150
100
50
0
[ppm]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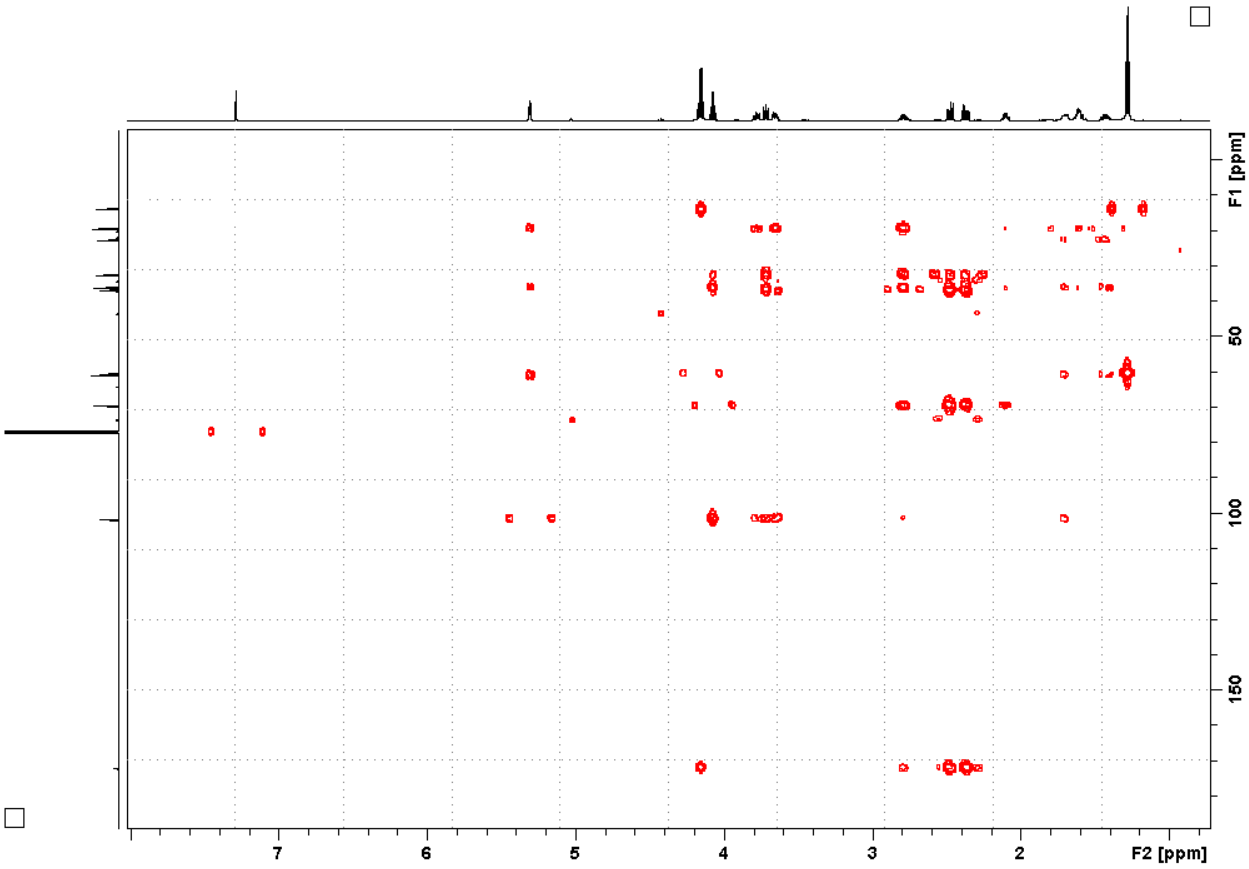
80
100
7
6
5
4
3
2
F2 [ppm]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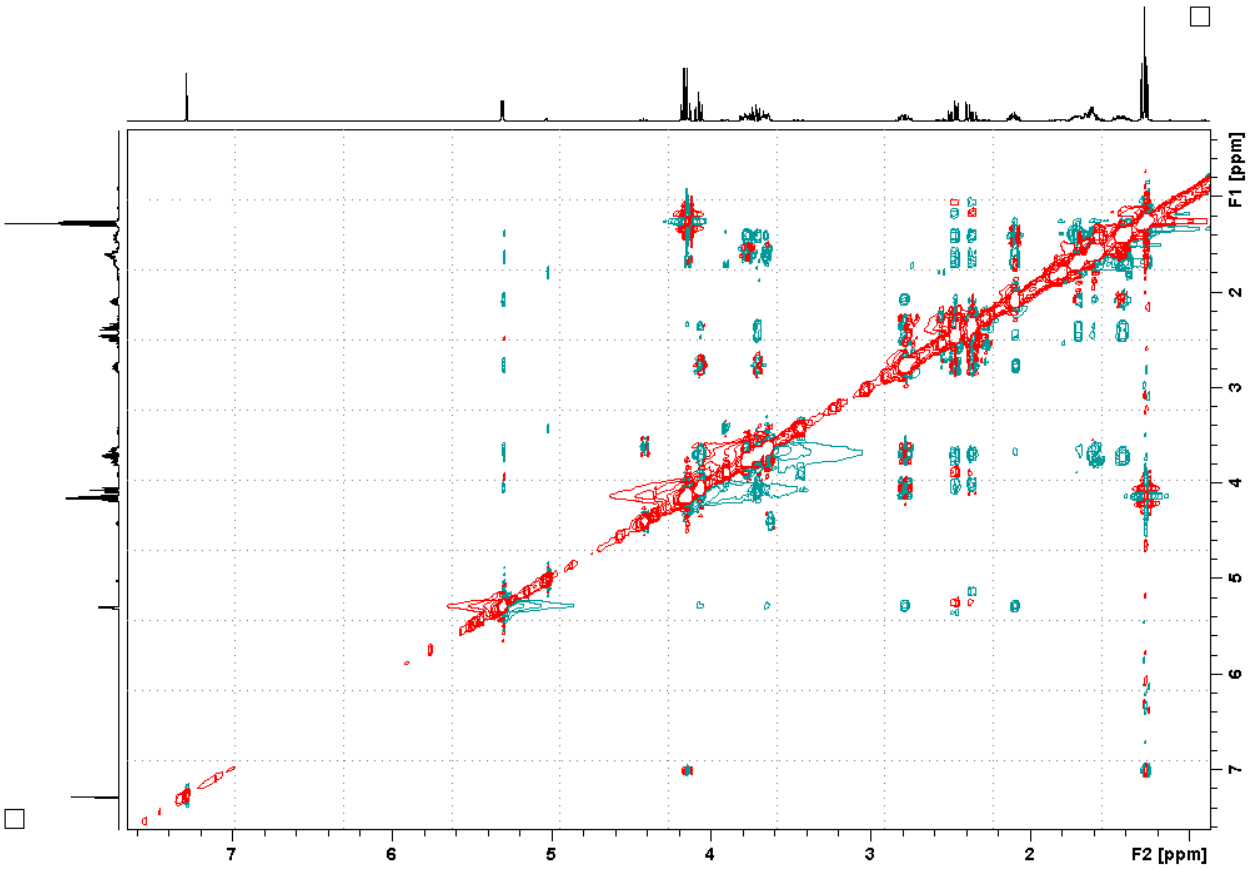
100
150
7
6
5
4
3
2
F2 [ppm]


F1 [ppm]
F2 [ppm]
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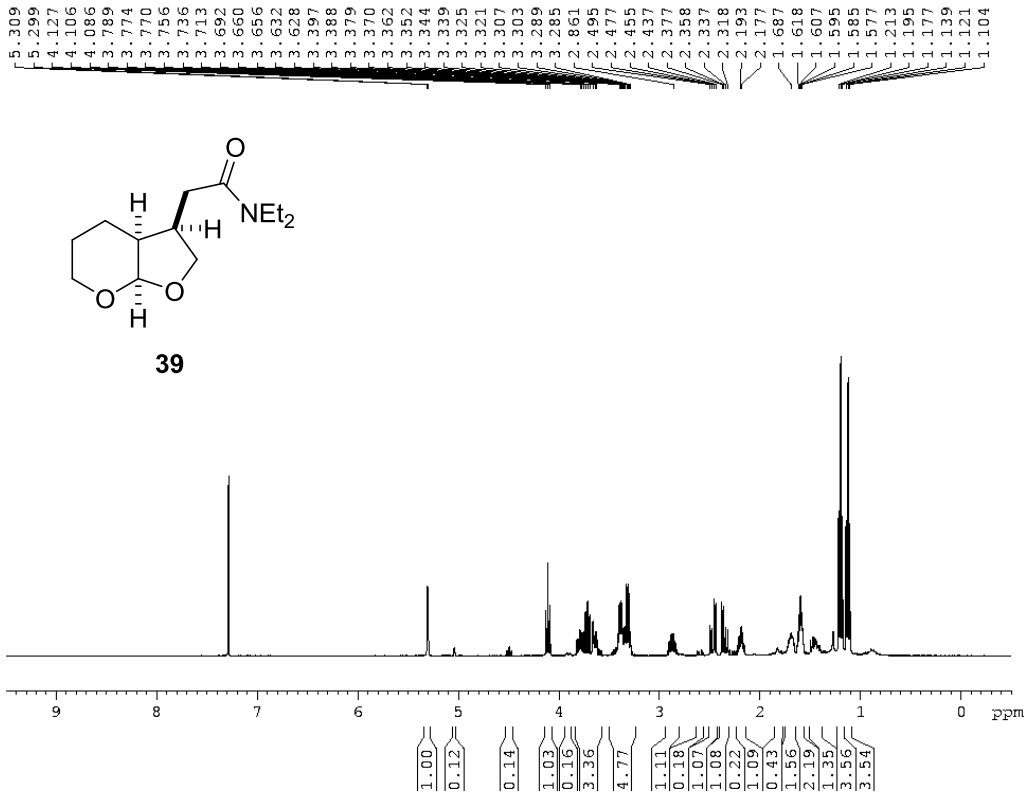
6
5
4
3
2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3.770
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3.713
3.692
3.660
3.656
3.632
3.628
3.397
3.388
3.379
3.370
3.362
3.352
3.344
3.339
3.325
3.321
3.307
3.303
3.289
3.285
2.861
2.495
2.477
2.455
2.437
2.377
2.358
2.337
2.318
2.193
2.177
1.687
1.618
1.607
1.595
1.585
1.577
1.213
1.195
1.177
1.139
1.121
1.104
O
NEt2
H
H
O
O
H
39
9
8
7
6
5
4
3
2
1
0
ppm
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0.12
0.14
1.03
0.16
3.36
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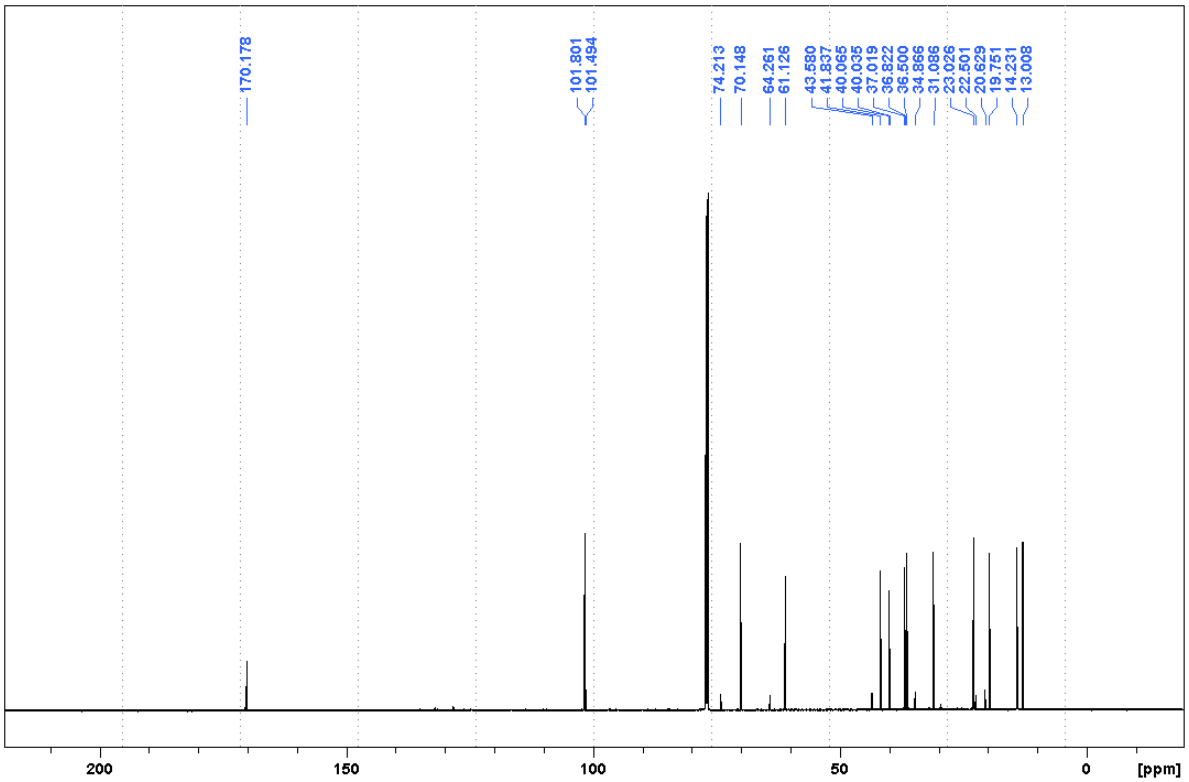
3.54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43.580
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40.065
40.035
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36.822
36.500
34.866
31.086
23.026
22.501
20.629
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13.008
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50
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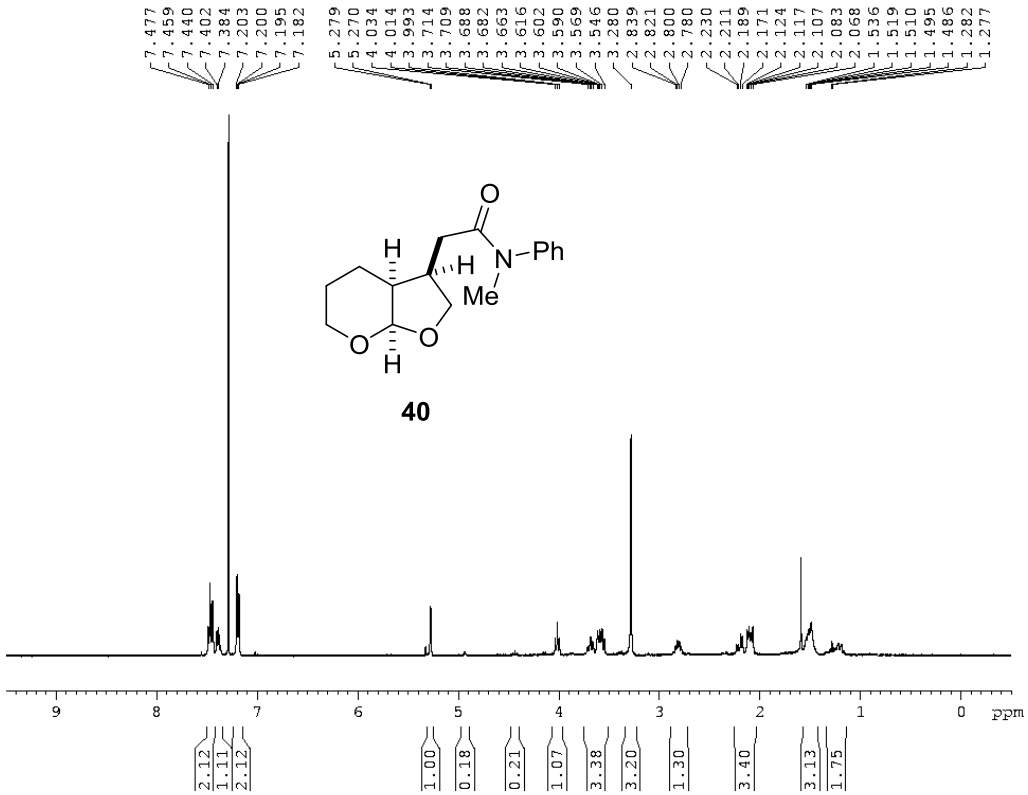
[ppm]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7.195
7.182
5.279
5.270
4.034
4.014
3.993
3.714
3.709
3.688
3.682
3.663
3.616
3.602
3.590
3.569
3.546
3.280
2.839
2.821
2.800
2.780
2.230
2.211
2.189
2.171
2.124
2.117
2.107
2.083
2.068
1.536
1.519
1.510
1.495
1.486
1.282
1.277
O
H
H
N–Ph
Me
O
O
H
40
9
8
7
6
5
4
3
2
1
0
ppm
2.12
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0.21
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3.38
3.20
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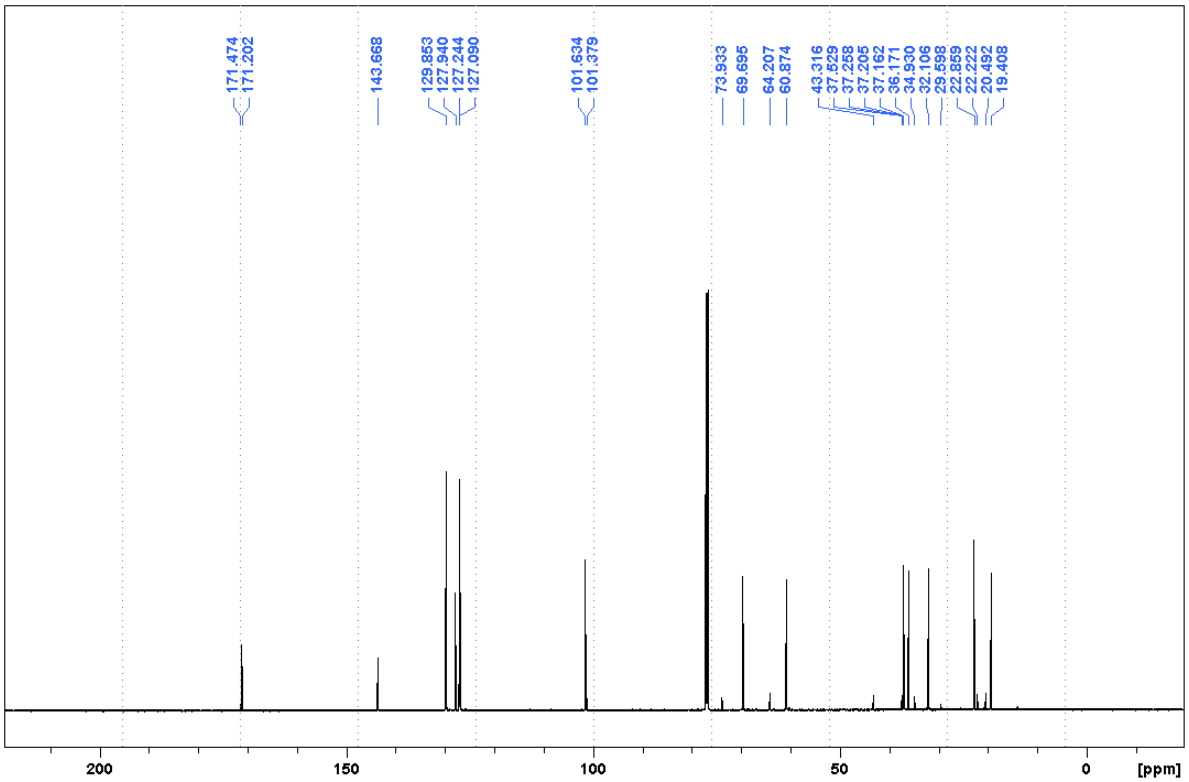
3.40
3.13
1.75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60.874
43.316
37.529
37.258
37.205
37.162
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22.222
20.492
19.408
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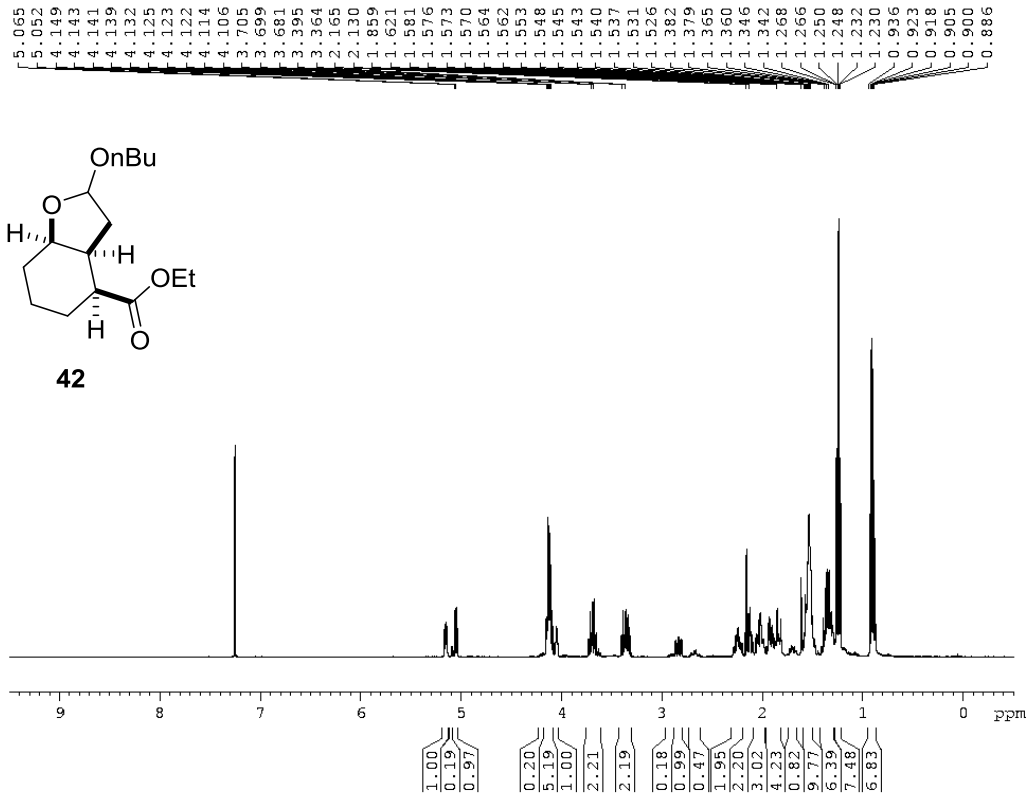
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4.141
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4.132
4.125
4.123
4.122
4.114
4.106
3.705
3.699
3.681
3.395
3.364
2.165
2.130
1.859
1.621
1.581
1.576
1.573
1.570
1.564
1.562
1.553
1.548
1.545
1.543
1.540
1.537
1.531
1.526
1.382
1.379
1.365
1.360
1.346
1.342
1.268
1.266
1.250
1.248
1.232
1.230
0.936
0.923
0.918
0.905
0.900
0.886
OnBu
O
H
H
OEt
H
O
42
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.19
0.97
0.20
5.19
1.00
2.21
2.19
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0.47
1.95
2.20
3.02
4.23
0.82
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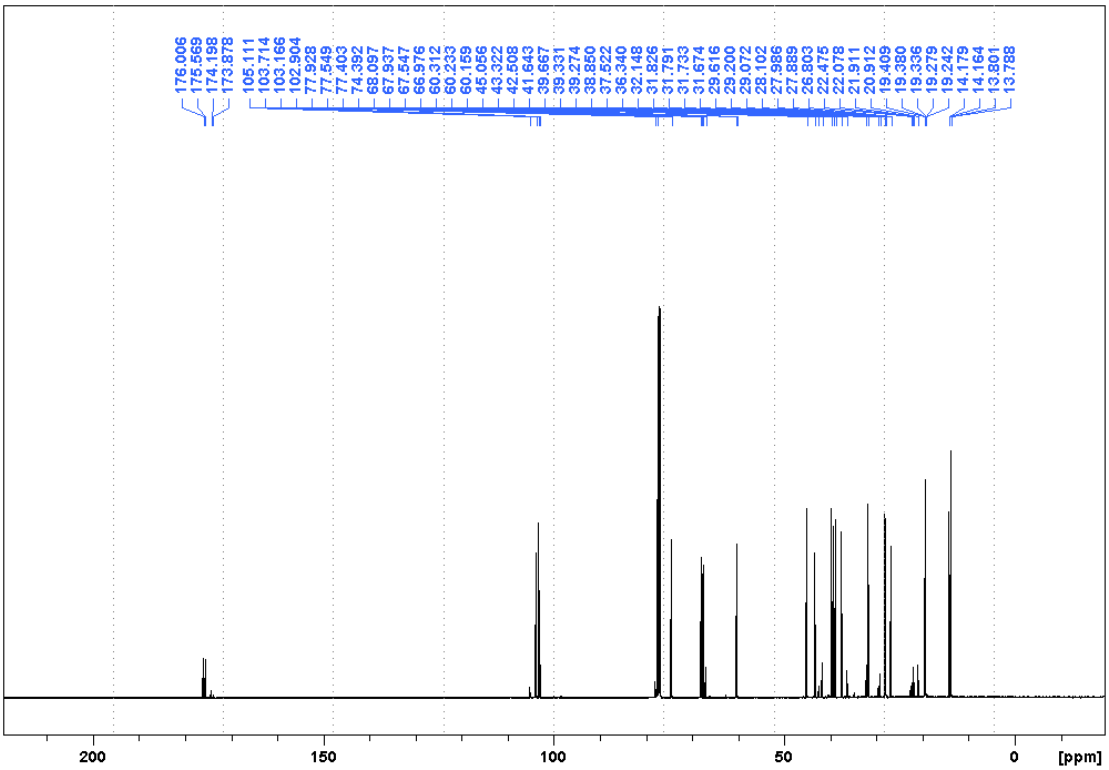
7.48
6.83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77.403
74.392
68.097
67.937
67.547
66.976
60.312
60.233
60.159
45.056
43.322
42.508
41.643
39.667
39.331
39.274
38.850
37.522
36.340
32.148
31.826
31.791
31.733
31.674
29.616
29.200
29.072
28.102
27.986
27.889
26.803
22.475
22.078
21.911
20.912
19.409
19.380
19.336
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19.242
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14.164
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100
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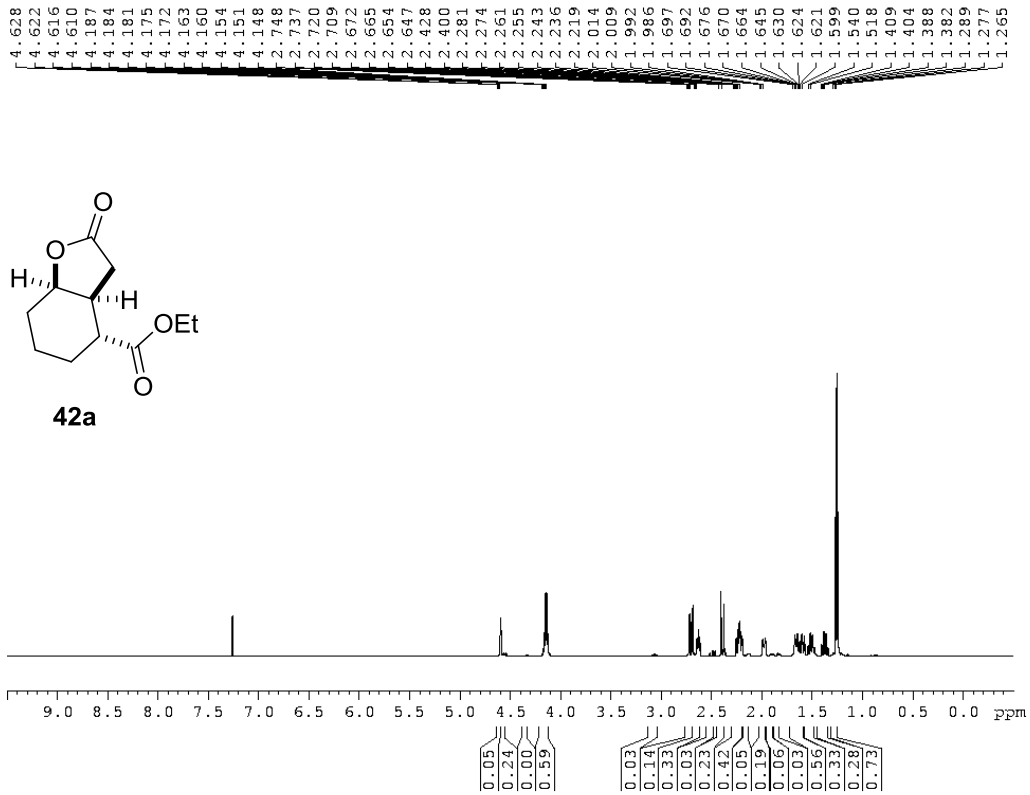
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4.622
4.616
4.610
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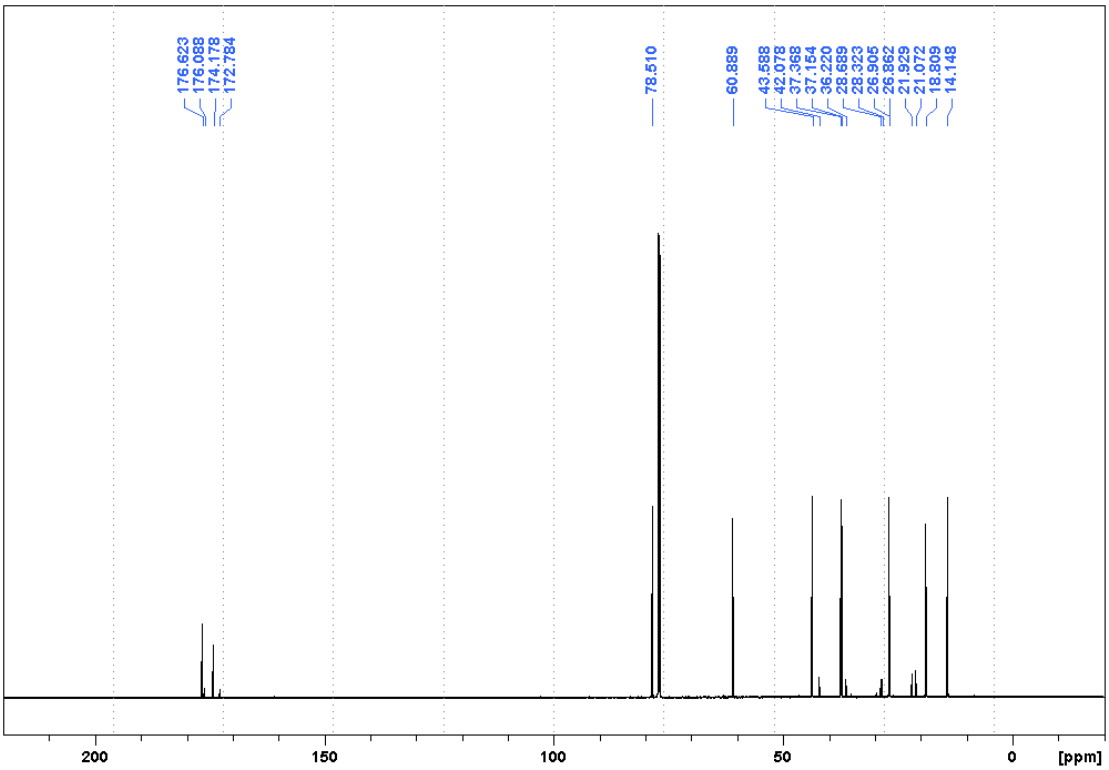
4.184
4.181
4.175
4.172
4.163
4.160
4.154
4.151
4.148
2.748
2.737
2.720
2.709
2.672
2.665
2.654
2.647
2.428
2.400
2.281
2.274
2.261
2.255
2.243
2.236
2.219
2.014
2.009
1.992
1.986
1.697
1.692
1.676
1.670
1.664
1.645
1.630
1.624
1.621
1.599
1.540
1.518
1.409
1.404
1.388
1.382
1.289
1.277
1.265
O
O
H
H
OEt
O
42a
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.05
0.24
0.00
0.59
0.03
0.14
0.33
0.03
0.23
0.42
0.05
0.19
0.06
0.03
0.56
0.33
0.28
0.73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60.889
43.588
42.078
37.368
37.154
36.220
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28.323
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26.862
21.929
21.072
18.809
14.148
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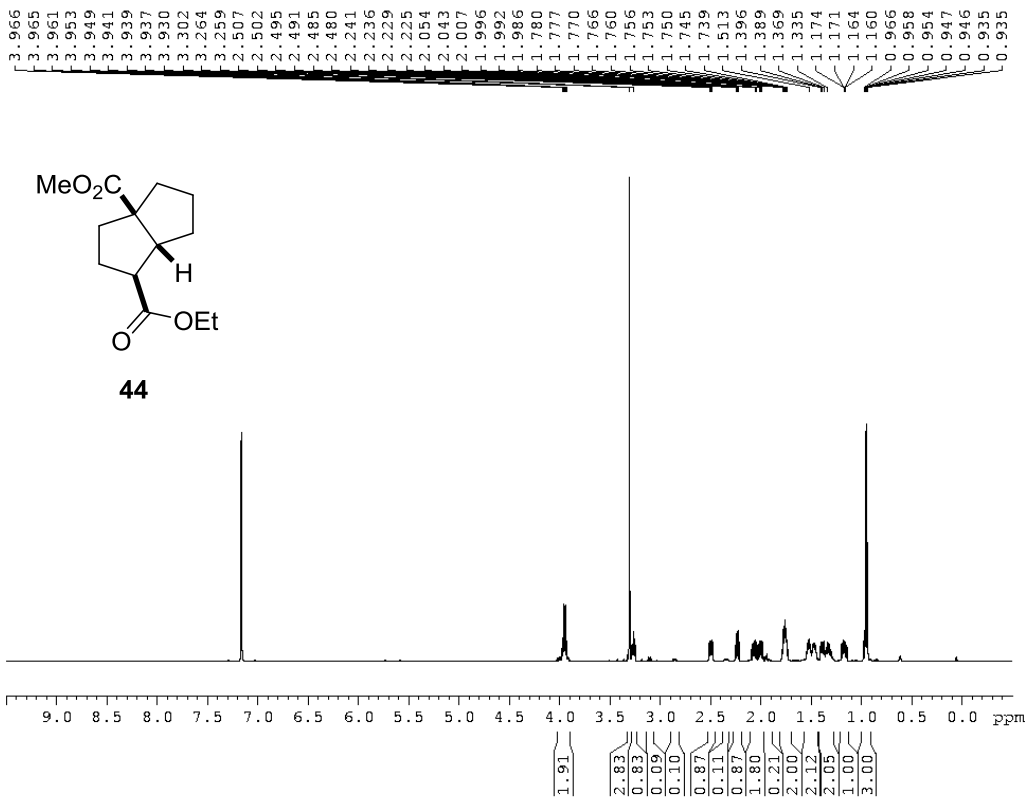
100
50
0
[ppm]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3.939
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3.930
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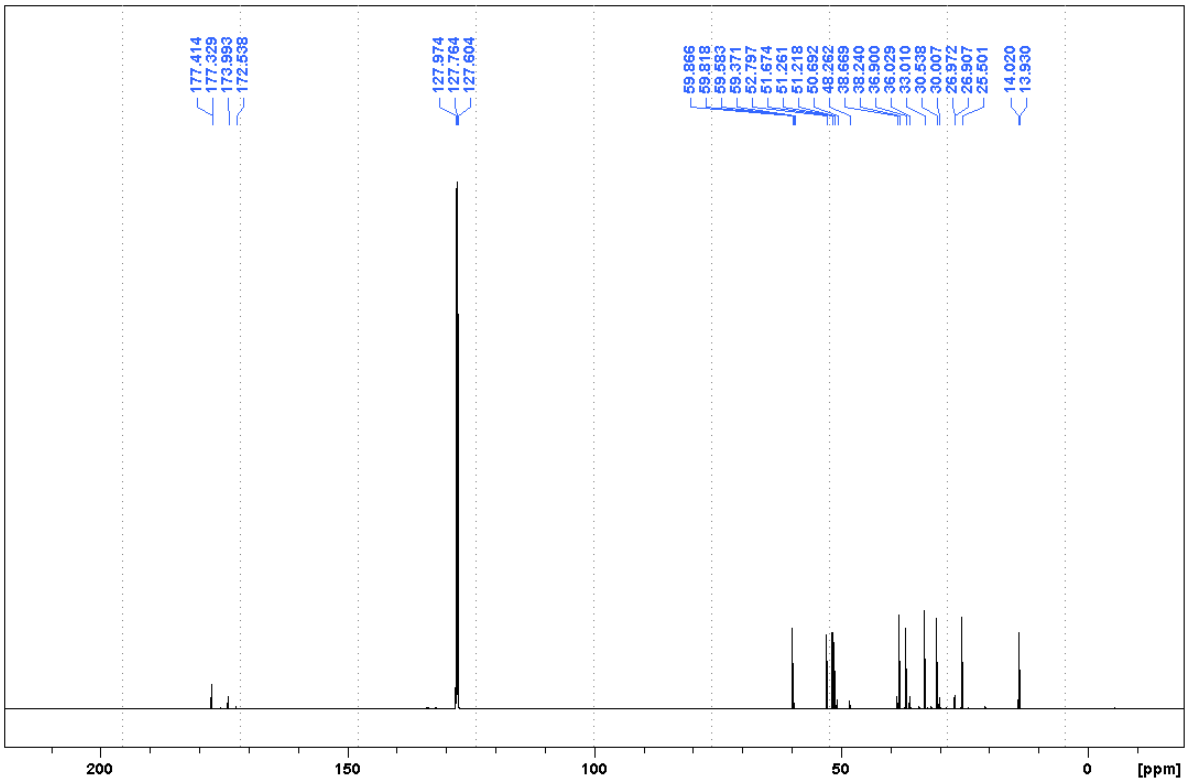
3.264
3.259
2.507
2.502
2.495
2.491
2.485
2.480
2.241
2.236
2.229
2.225
2.054
2.043
2.007
1.996
1.992
1.986
1.780
1.777
1.770
1.766
1.760
1.756
1.753
1.750
1.745
1.739
1.513
1.396
1.389
1.369
1.335
1.174
1.171
1.164
1.160
0.966
0.958
0.954
0.947
0.946
0.935
0.935
MeO2C
H
OEt
O
44
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.91
2.83
0.83
0.09
0.10
0.87
0.11
0.87
1.80
0.21
2.00
2.12
2.05
1.00
3.00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59.818
59.583
59.371
52.797
51.674
51.261
51.218
50.692
48.262
38.669
38.240
36.900
36.029
33.010
30.538
30.007
26.972
26.907
25.501
14.020
13.930
200
150
100
50
0
[ppm]


3.421
3.411
3.395
3.385
3.255
3.238
3.226
1.814
1.812
1.805
1.794
1.740
1.733
1.728
1.721
1.716
1.665
1.658
1.646
1.638
1.603
1.590
1.583
1.570
1.500
1.497
1.494
1.486
1.478
1.473
1.464
1.400
1.388
1.386
1.379
1.373
1.367
1.365
1.358
1.353
1.346
1.342
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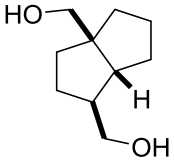
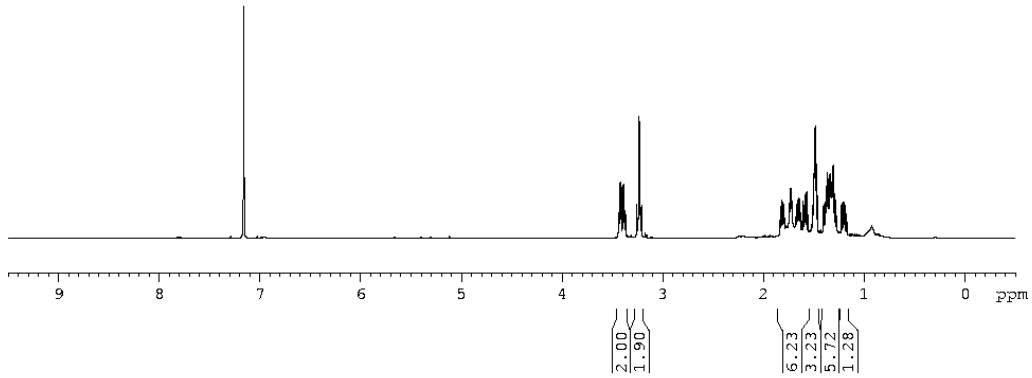
1.210
1.200


HO
H
OH

44a


9
8
7
6
5
4
3
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1
0
ppm
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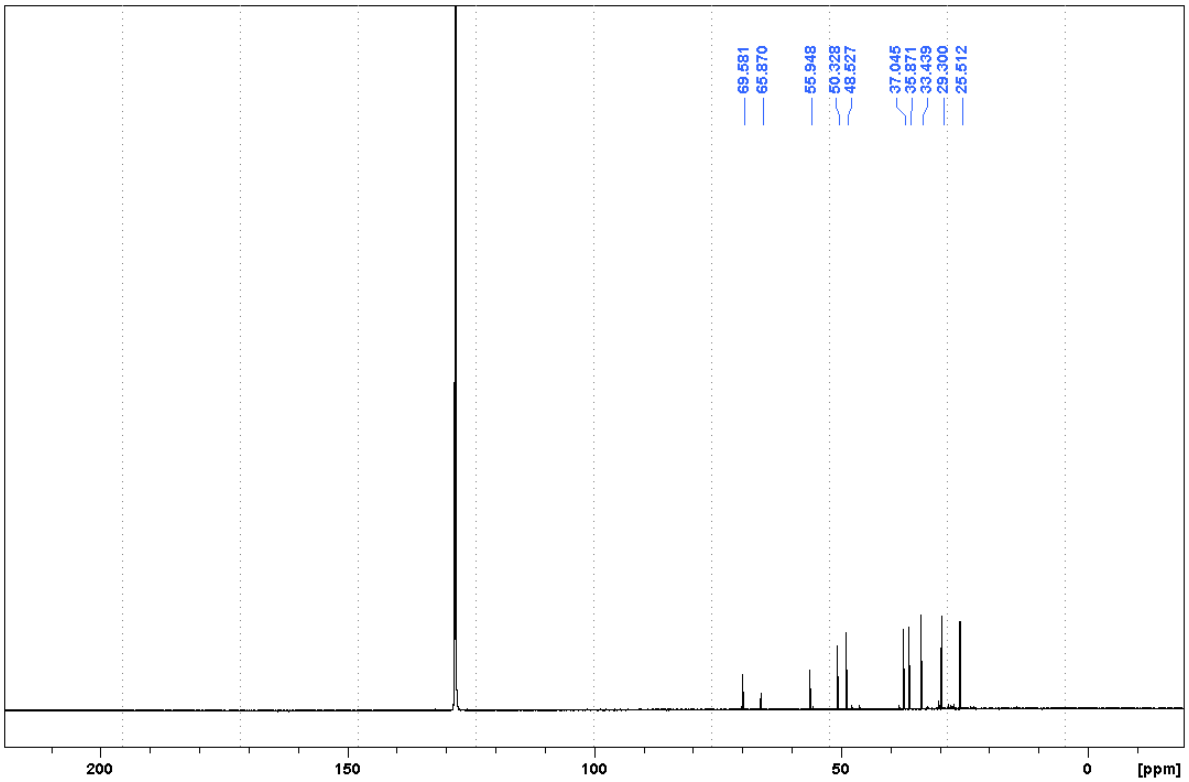
1.90
6.23
3.23
5.72
1.28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37.045
35.871
33.439
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25.512
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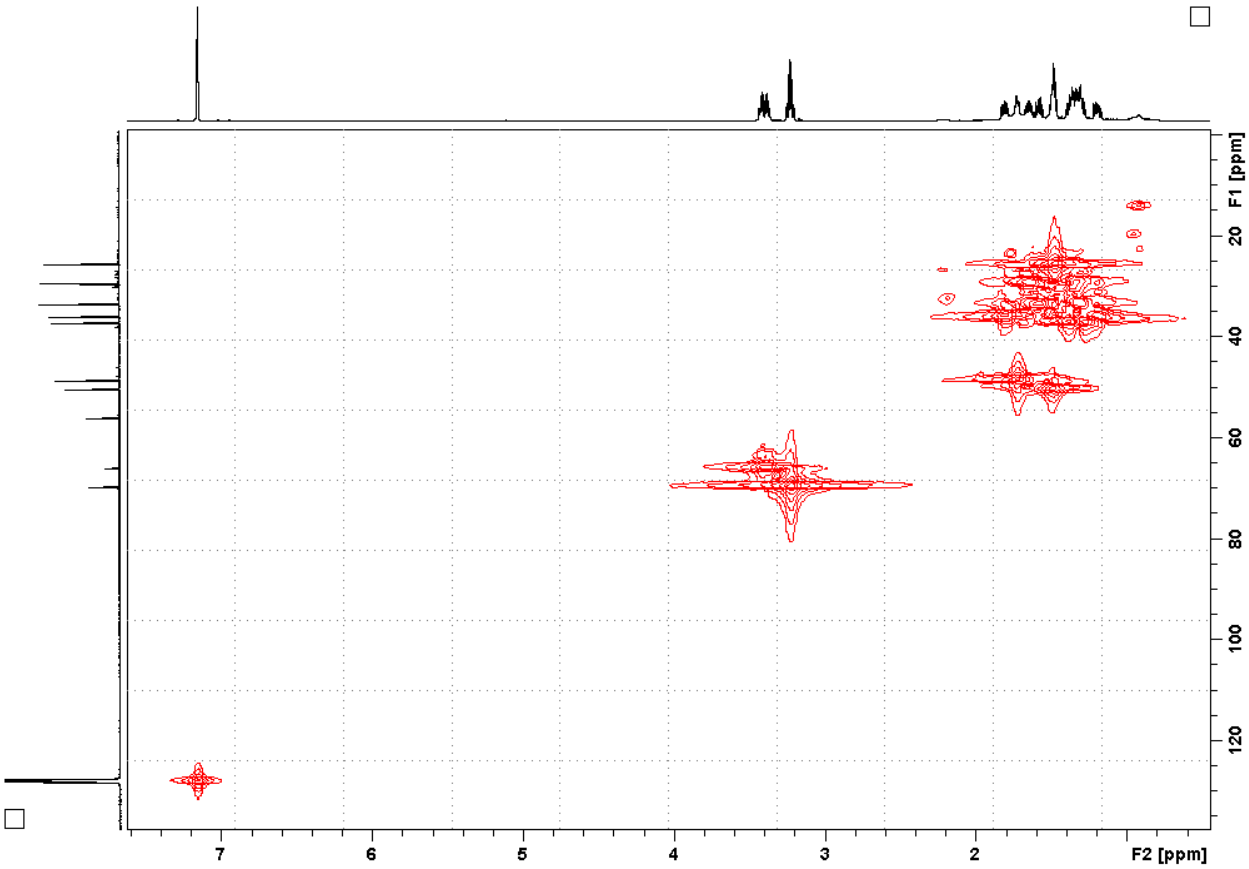
150
100
50
0
[ppm]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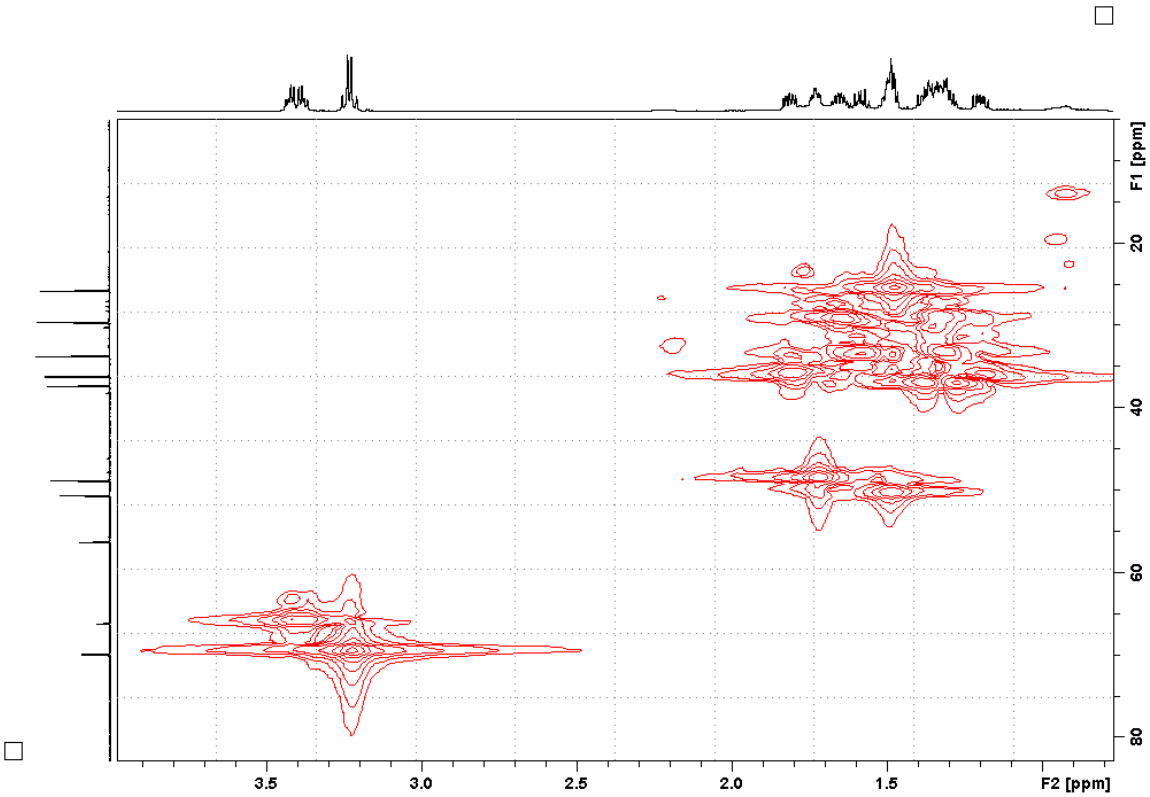
60
80
100
120
7
6
5
4
3
2
F2 [ppm]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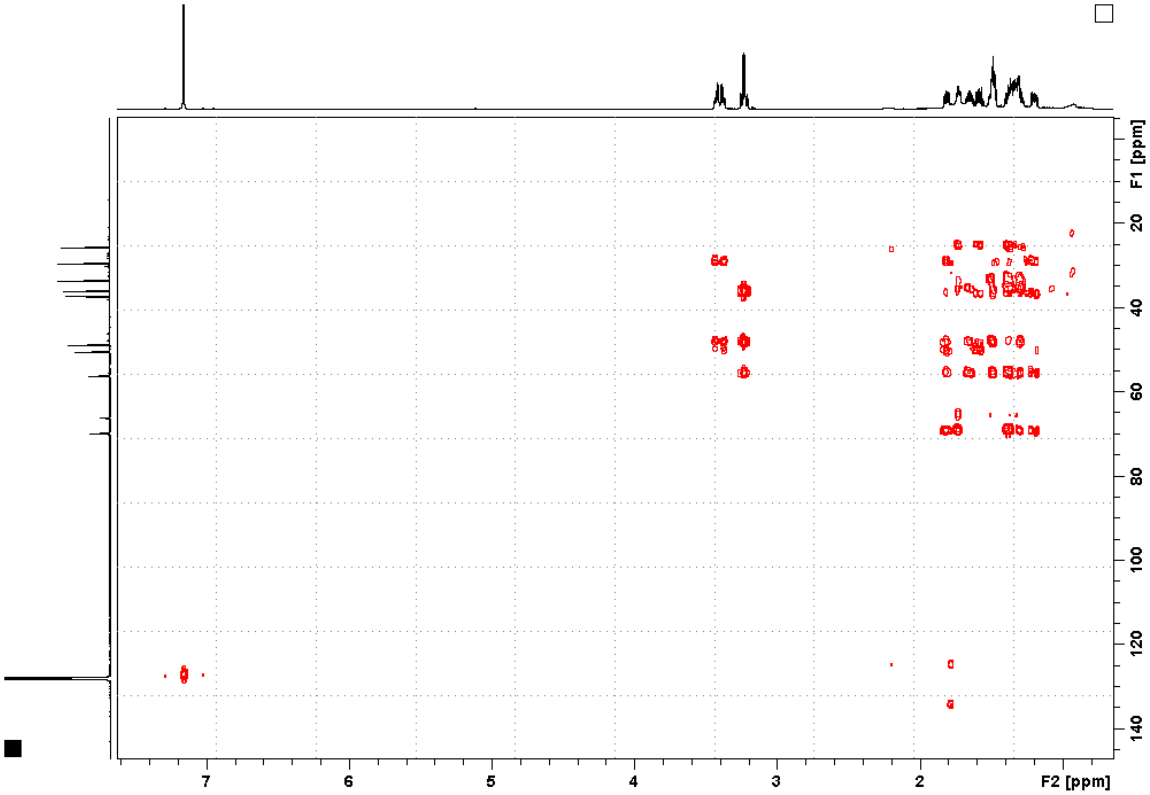
20
40
60
80
3.5
3.0
2.5
2.0
1.5
F2 [ppm]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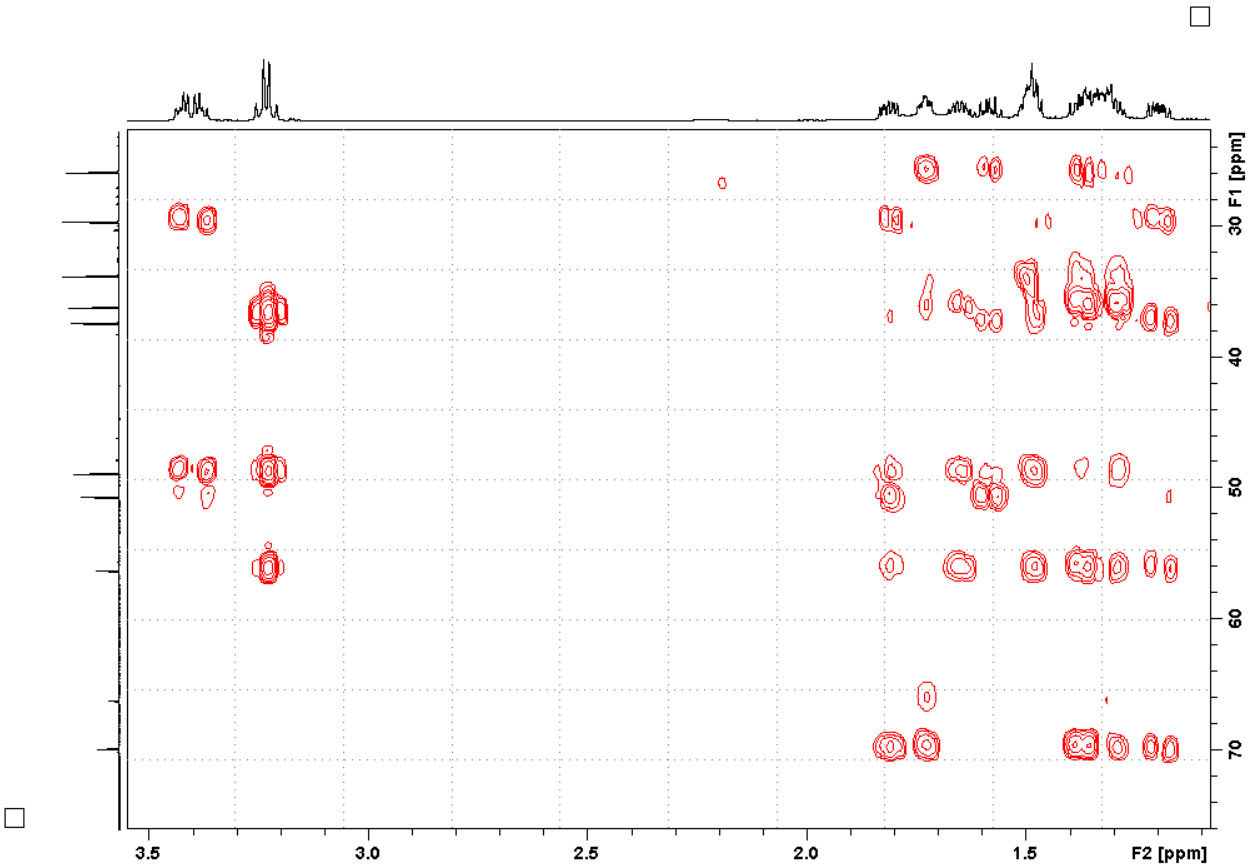
40
60
80
100
120
140
7
6
5
4
3
2
F2 [ppm]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50
60
70
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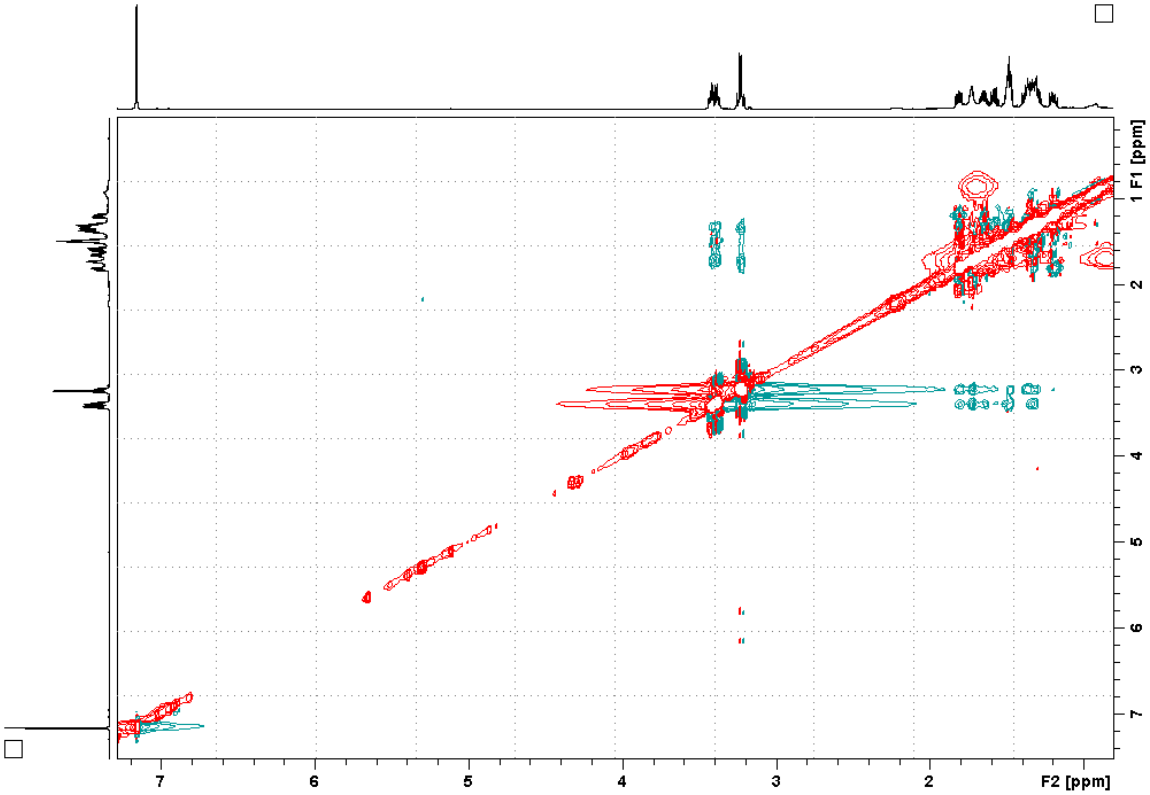
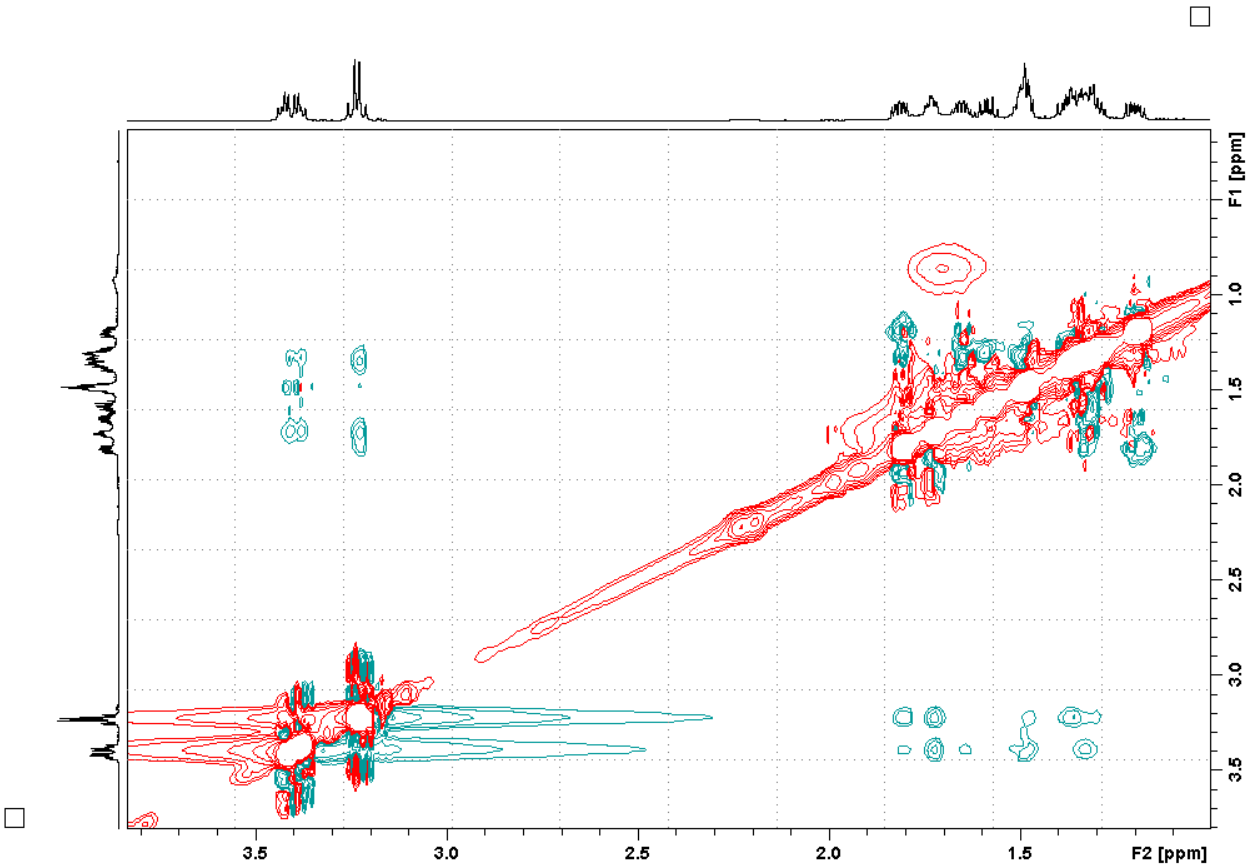
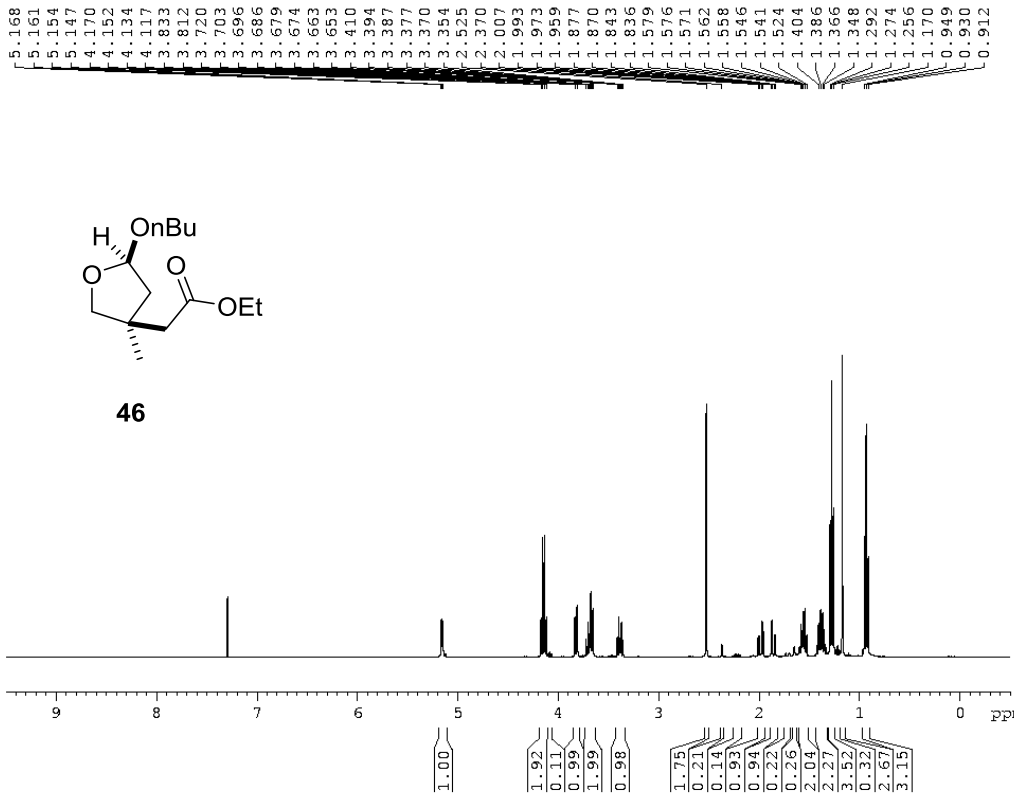
2.5
2.0
1.5
F2 [ppm]


F1 [ppm]
F2 [ppm]


F1 [ppm]
F2 [ppm]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5.147
4.170
4.152
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3.812
3.720
3.703
3.696
3.686
3.679
3.674
3.663
3.653
3.410
3.394
3.387
3.377
3.370
3.354
2.525
2.370
2.007
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1.973
1.959
1.877
1.870
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1.836
1.579
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1.571
1.562
1.558
1.546
1.541
1.524
1.404
1.386
1.366
1.348
1.292
1.274
1.256
1.170
0.949
0.930
0.912
H
OnBu
O
O
OEt
46
9
8
7
6
5
4
3
2
1
0
ppm
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0.99
1.99
0.98
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0.94
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2.27
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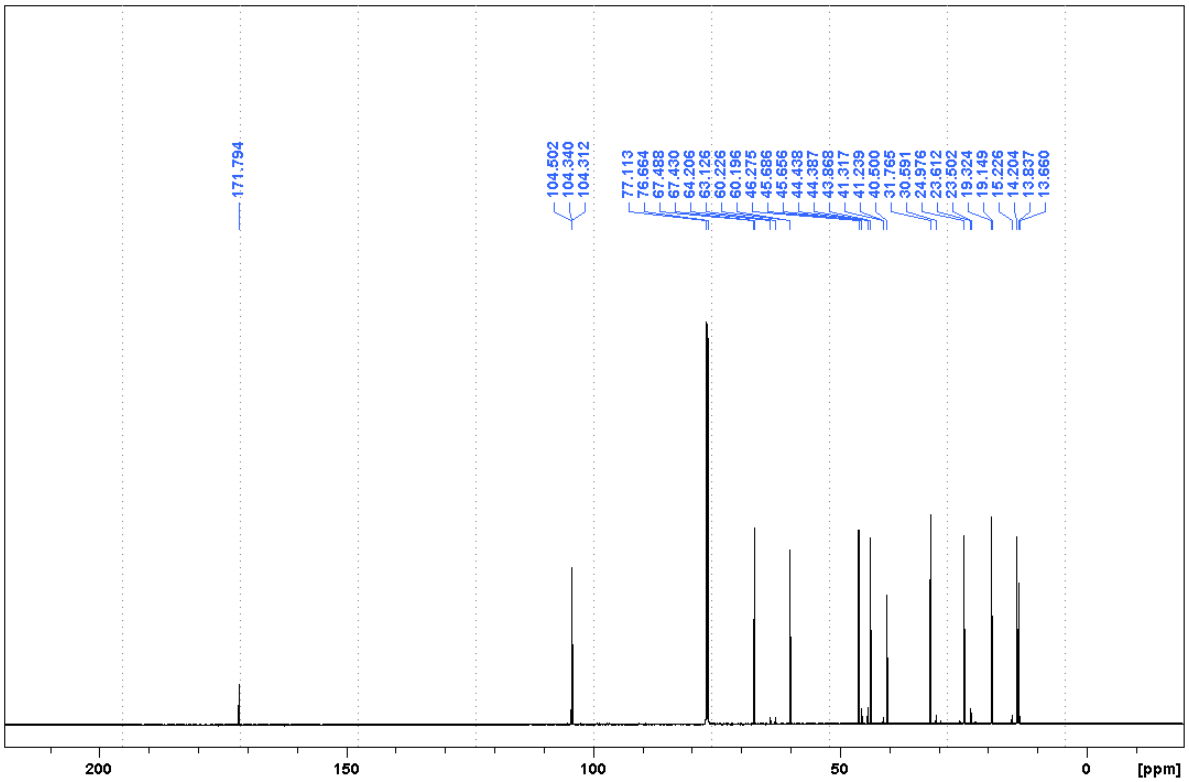
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104.312
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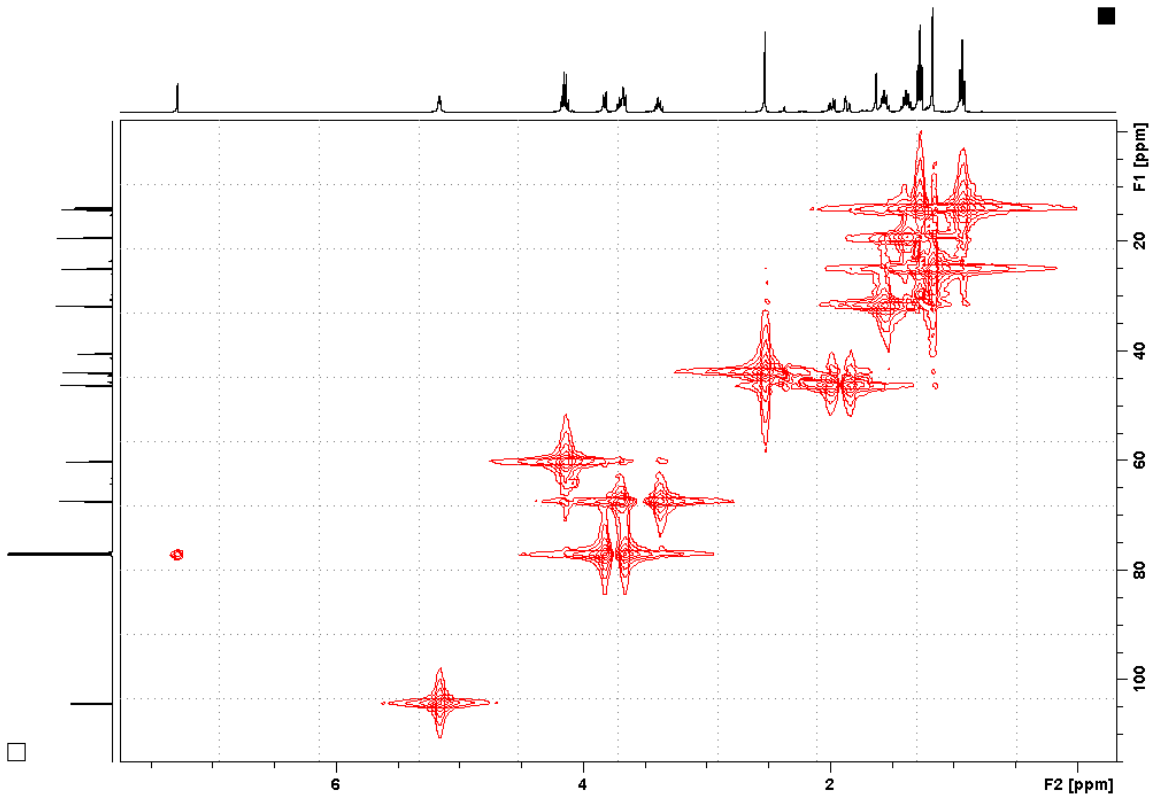
67.430
64.206
63.126
60.226
60.196
46.275
45.686
45.656
44.438
44.387
43.868
41.317
41.239
40.500
31.765
30.591
24.976
23.612
23.502
19.324
19.149
15.226
14.204
13.837
13.660
200
150
100
50
0
[ppm]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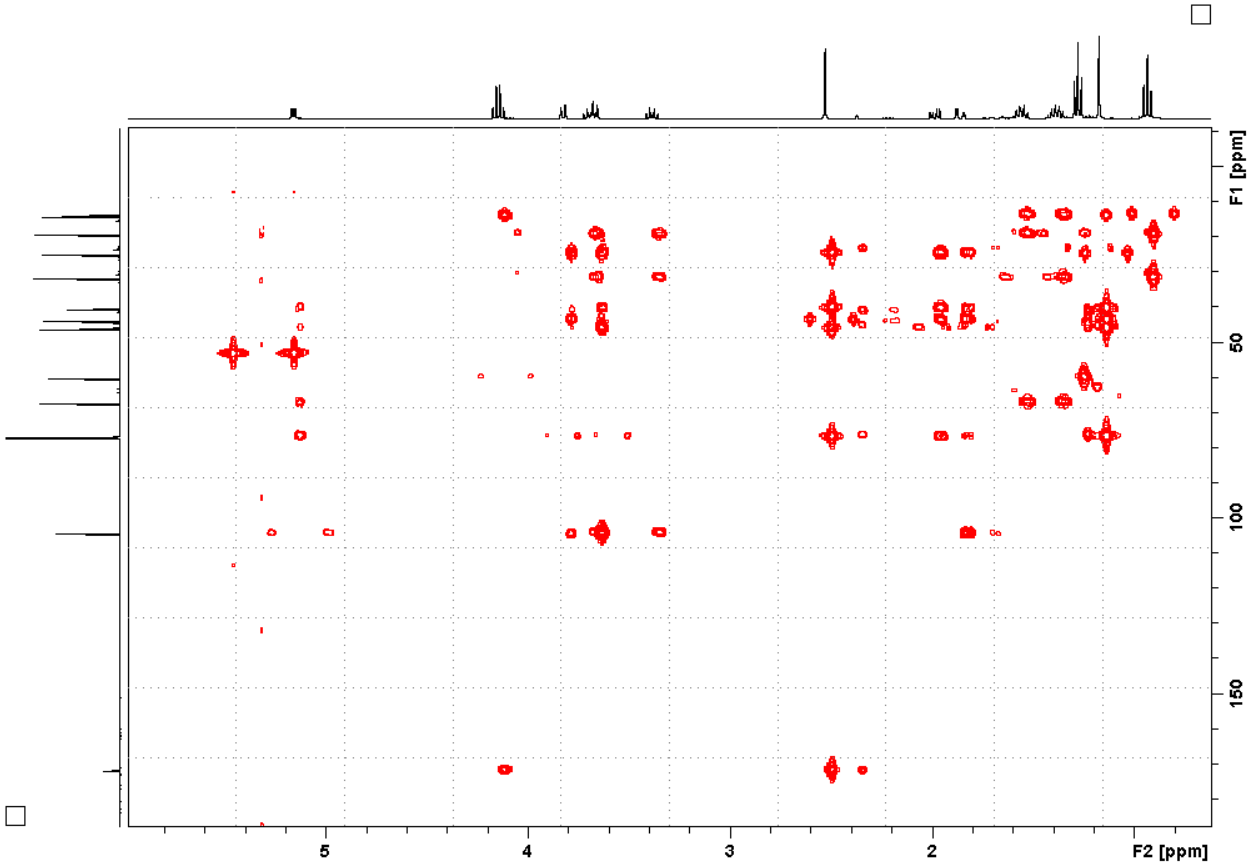
20
40
60
80
100
6
4
2
F2 [ppm]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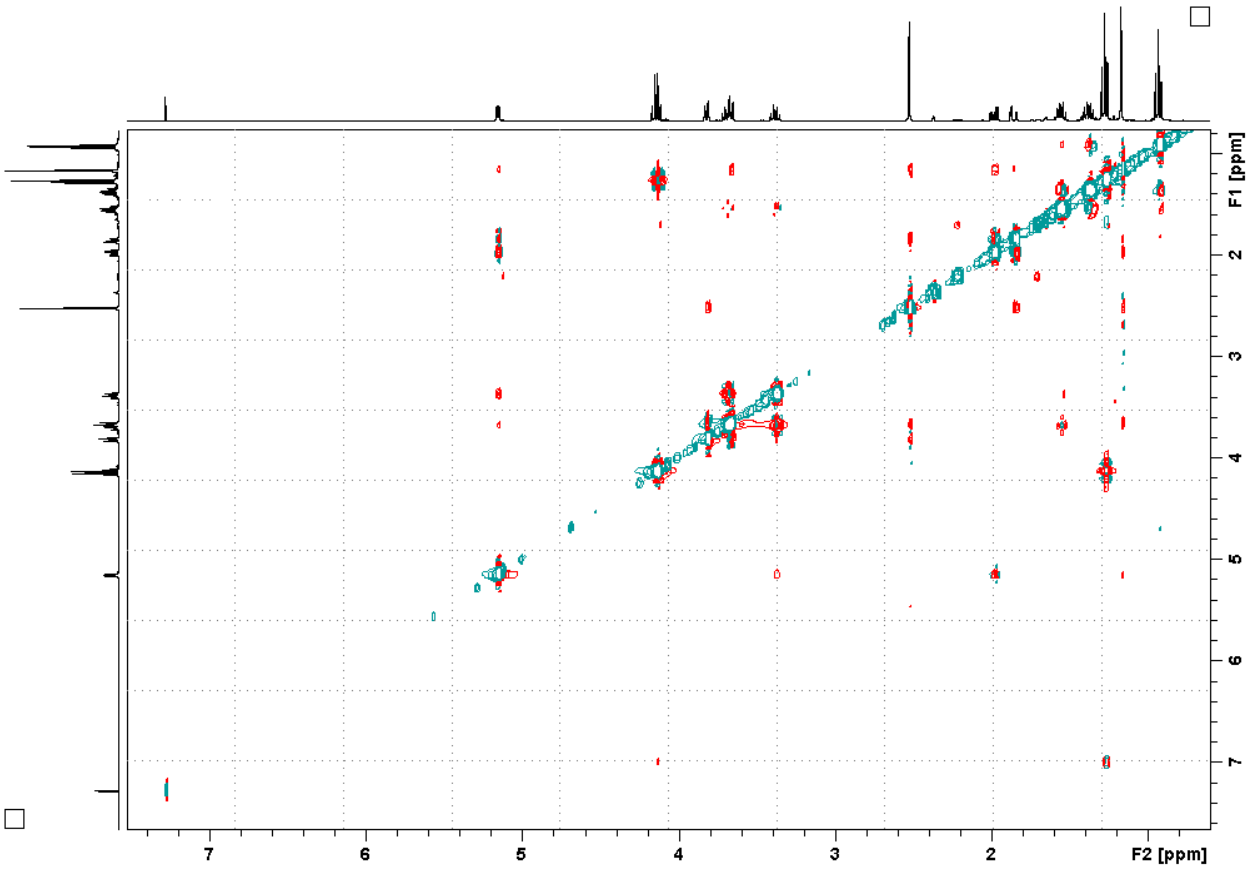
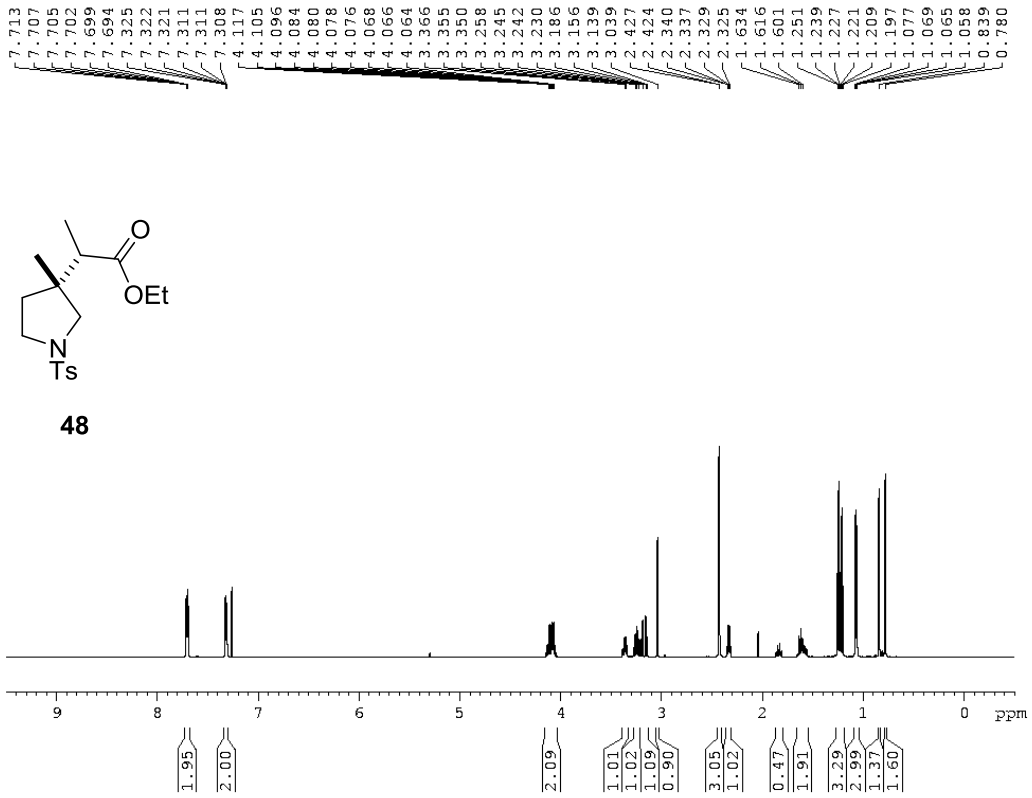
100
150
5
4
3
2
F2 [ppm]


F1 [ppm]
F2 [ppm]
7
6
5
4
3
2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7.705
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7.694
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7.322
7.321
7.311
7.311
7.308
4.117
4.105
4.096
4.084
4.080
4.078
4.076
4.068
4.066
4.064
3.366
3.355
3.350
3.258
3.245
3.242
3.230
3.186
3.156
3.139
3.039
2.427
2.424
2.340
2.337
2.329
2.325
1.634
1.616
1.601
1.251
1.239
1.227
1.221
1.209
1.197
1.077
1.069
1.065
1.058
0.839
0.780
O
OEt
N
Ts
48
9
8
7
6
5
4
3
2
1
0
ppm
1.95
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2.09
1.01
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1.09
0.90
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1.02
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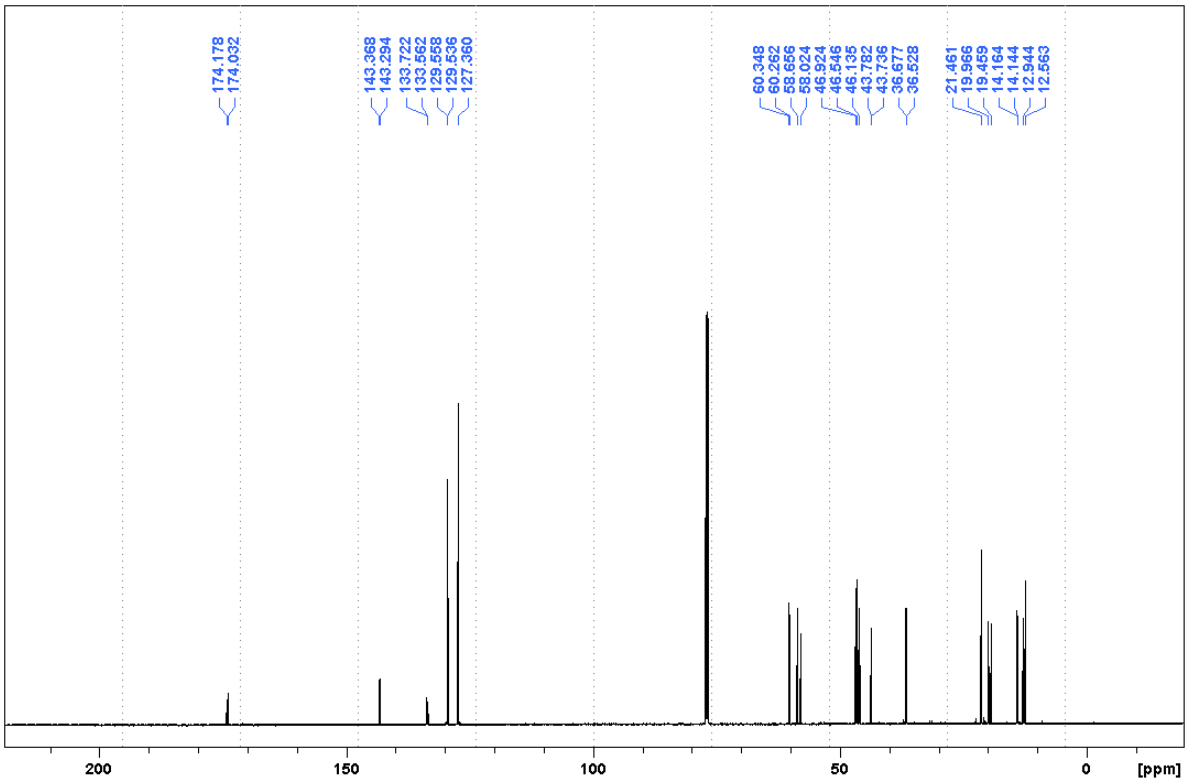
1.60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60.262
58.656
58.024
46.924
46.546
46.135
43.782
43.736
36.677
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12.563
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100
50
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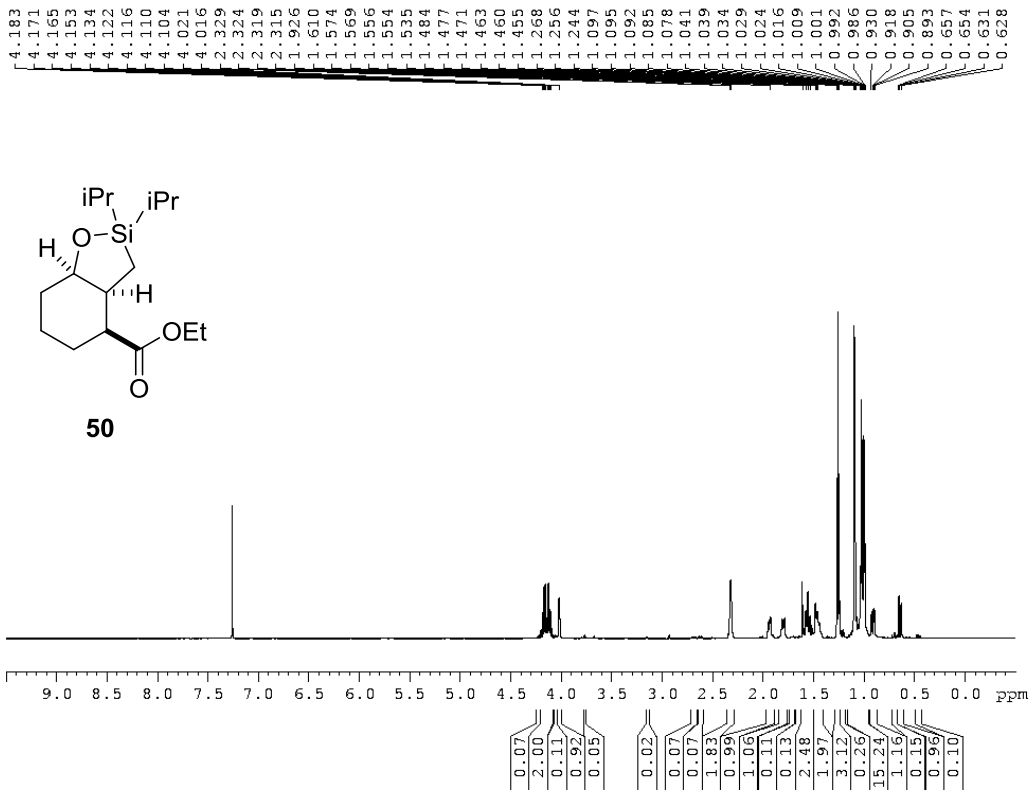
[ppm]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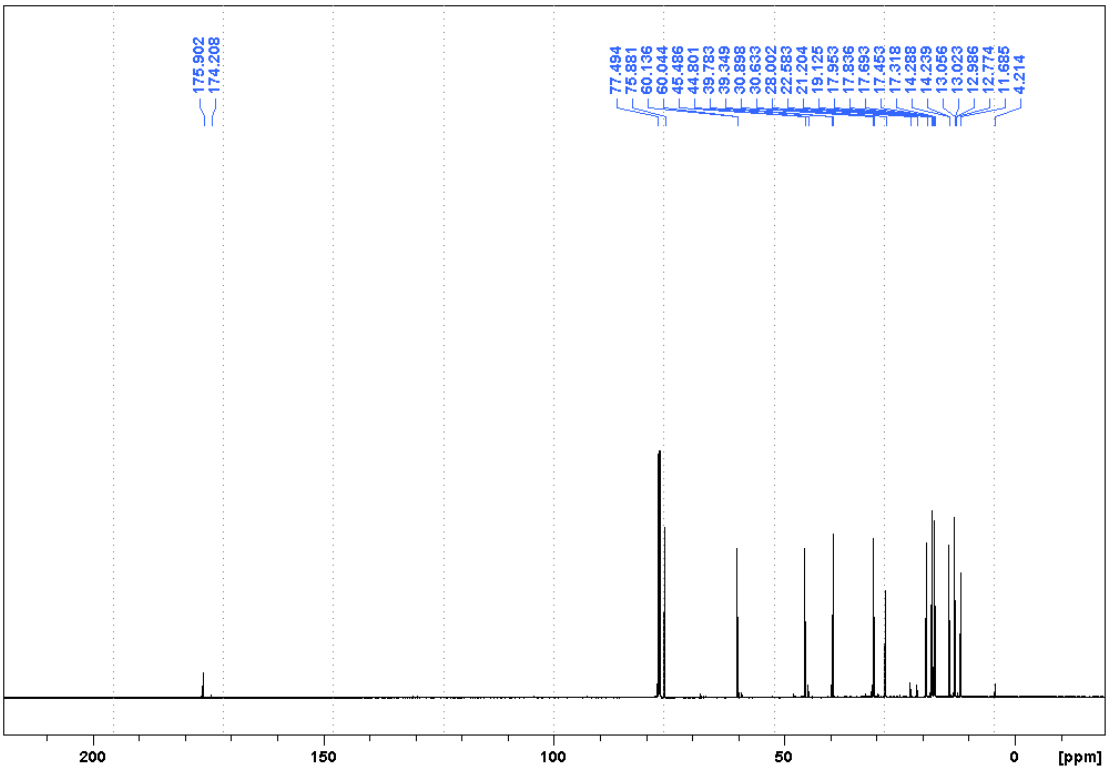
iPr
iPr
Si
O
H
H
OEt
O
50
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.07 2.00 0.11 0.92 0.05 0.02 0.07 0.07 1.83 0.99 1.06 0.11 0.13 2.48 1.97 3.12 0.26 15.24 1.16 0.15 0.96 0.10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45.486
44.801
39.783
39.349
30.898
30.633
28.002
22.583
21.204
19.125
17.953
17.836
17.693
17.453
17.318
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13.056
13.023
12.986
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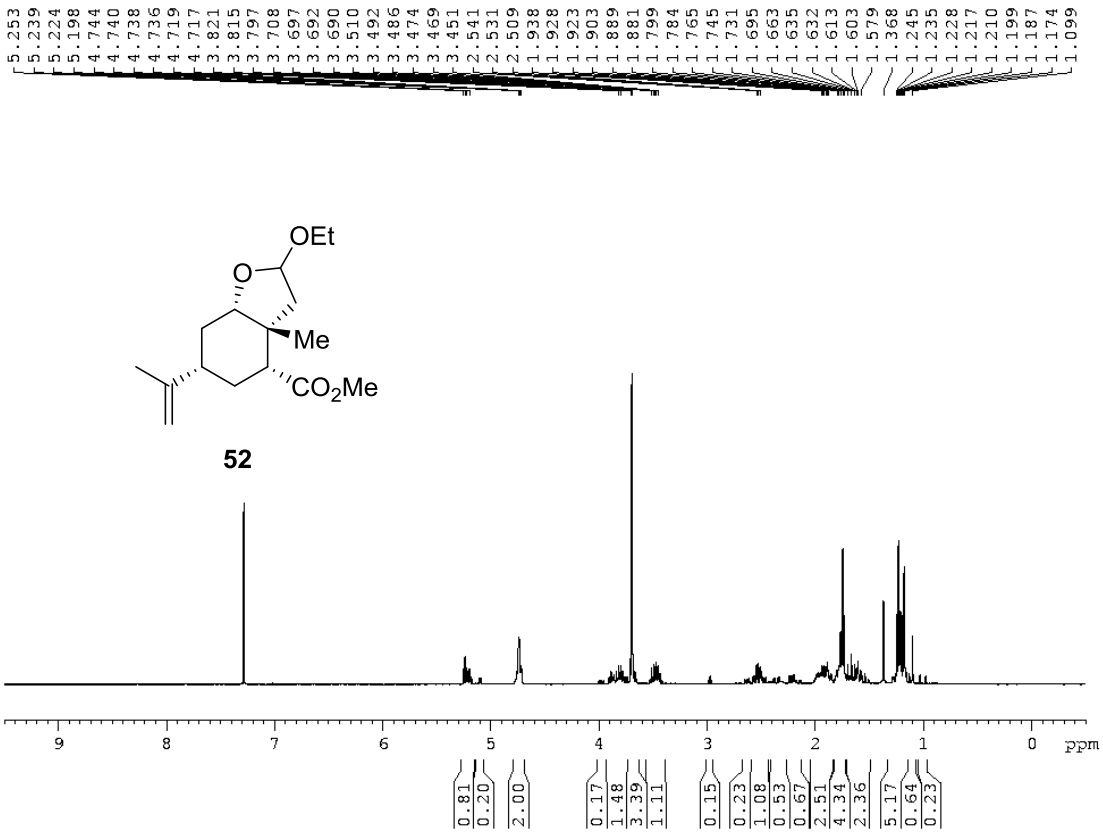
200
150
100
50
0
[ppm]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4.717
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3.797
3.708
3.697
3.692
3.690
3.510
3.492
3.486
3.474
3.469
3.451
2.541
2.531
2.509
1.938
1.928
1.923
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1.889
1.881
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1.632
1.613
1.603
1.579
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1.245
1.235
1.228
1.217
1.210
1.199
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1.174
1.099
OEt
O
Me
CO2Me
52
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8
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6
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4
3
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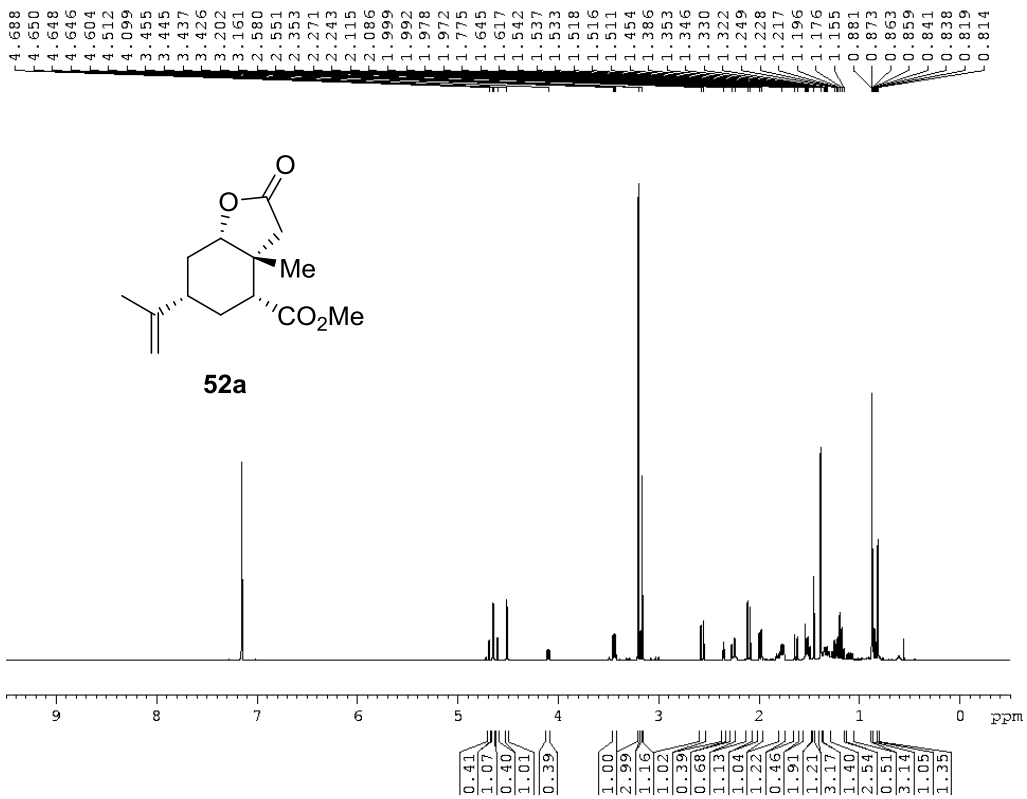
0.23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2.551
2.353
2.271
2.243
2.115
2.086
1.999
1.992
1.978
1.972
1.775
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1.617
1.542
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1.516
1.511
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1.322
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1.228
1.217
1.196
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0.859
0.841
0.838
0.819
0.814
O
O
Me
CO2Me
52a
9
8
7
6
5
4
3
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ppm
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0.68
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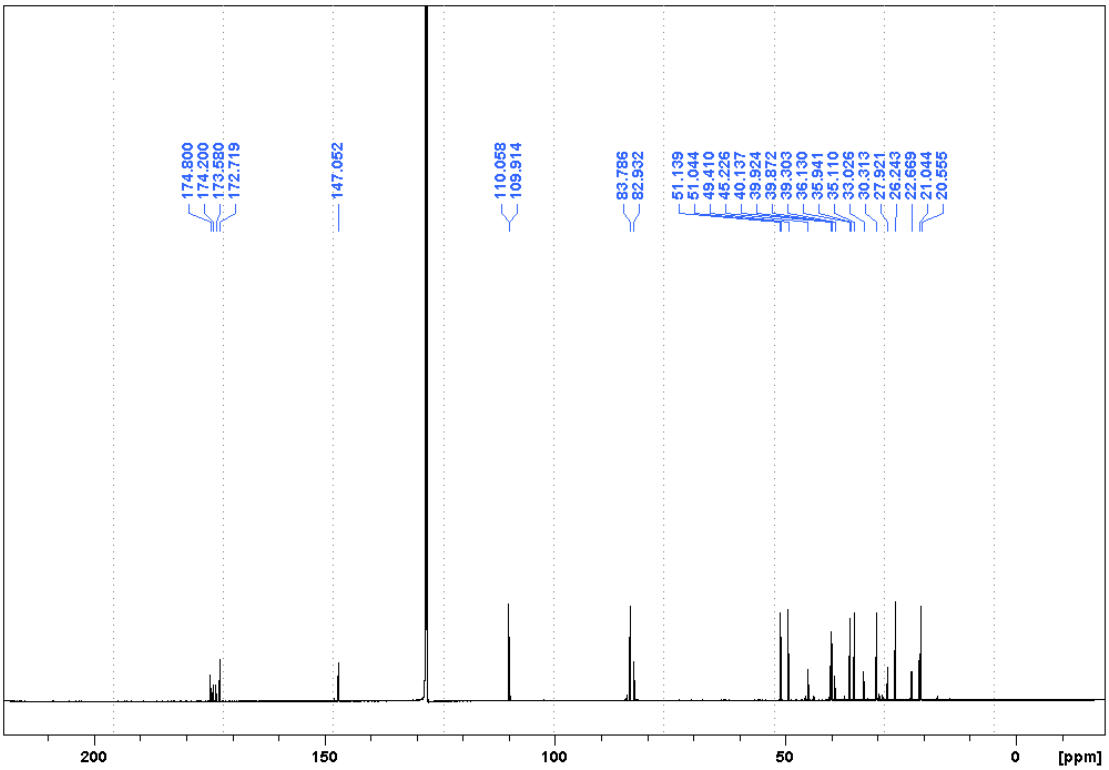
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49.410
45.226
40.137
39.924
39.872
39.303
36.130
35.941
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27.921
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22.669
21.044
20.555
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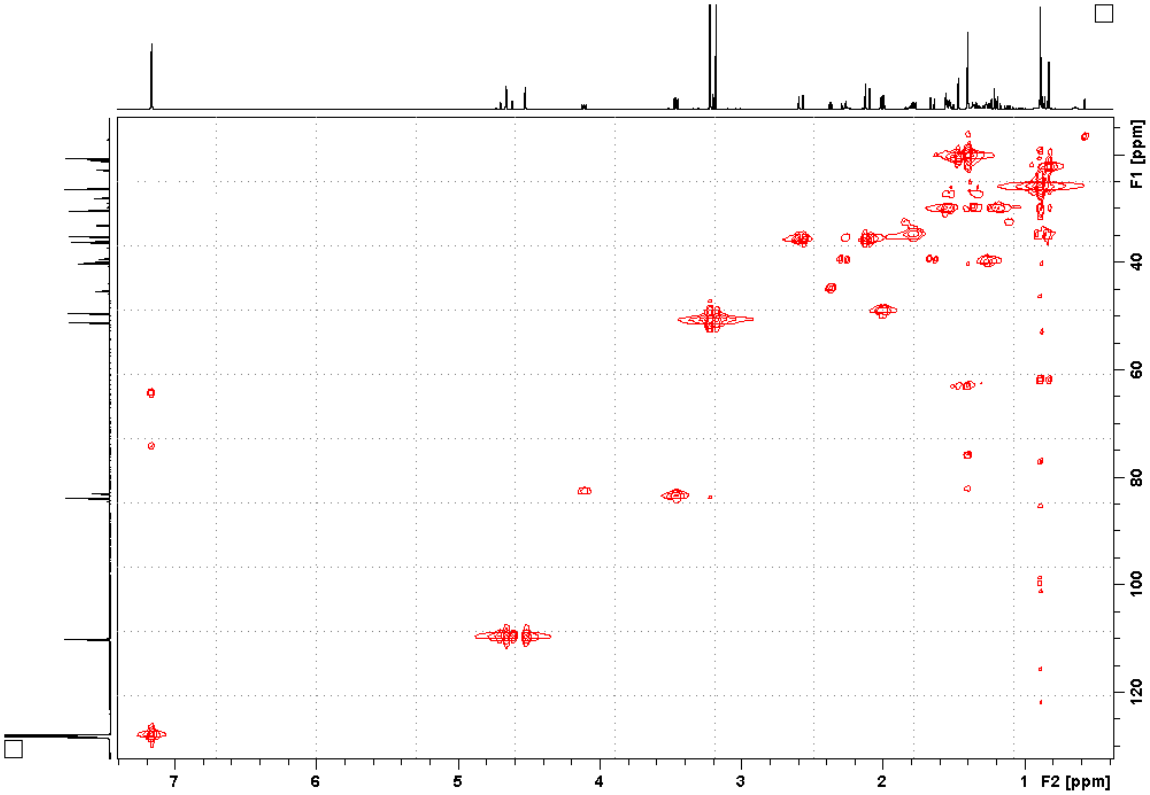
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6
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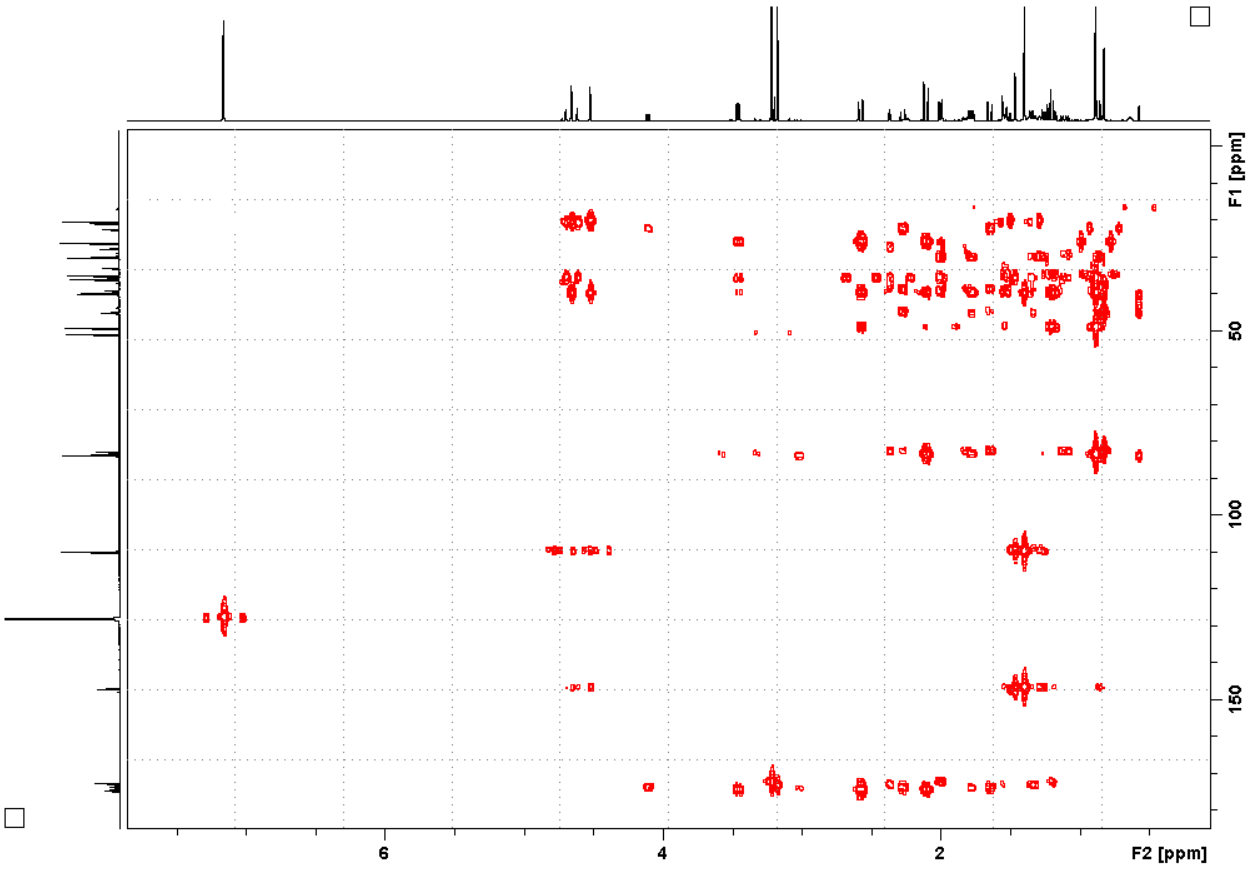
4
3
2
1
F2 [ppm]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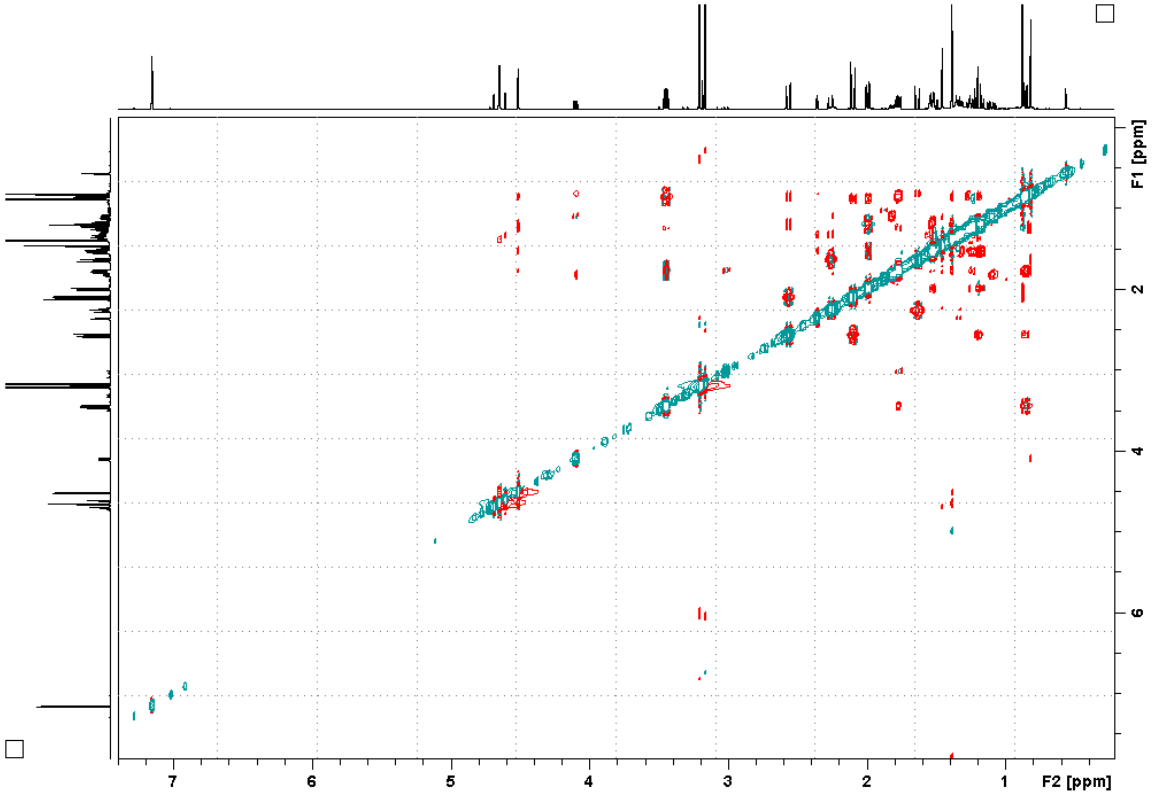
100
150
6
4
2
F2 [ppm]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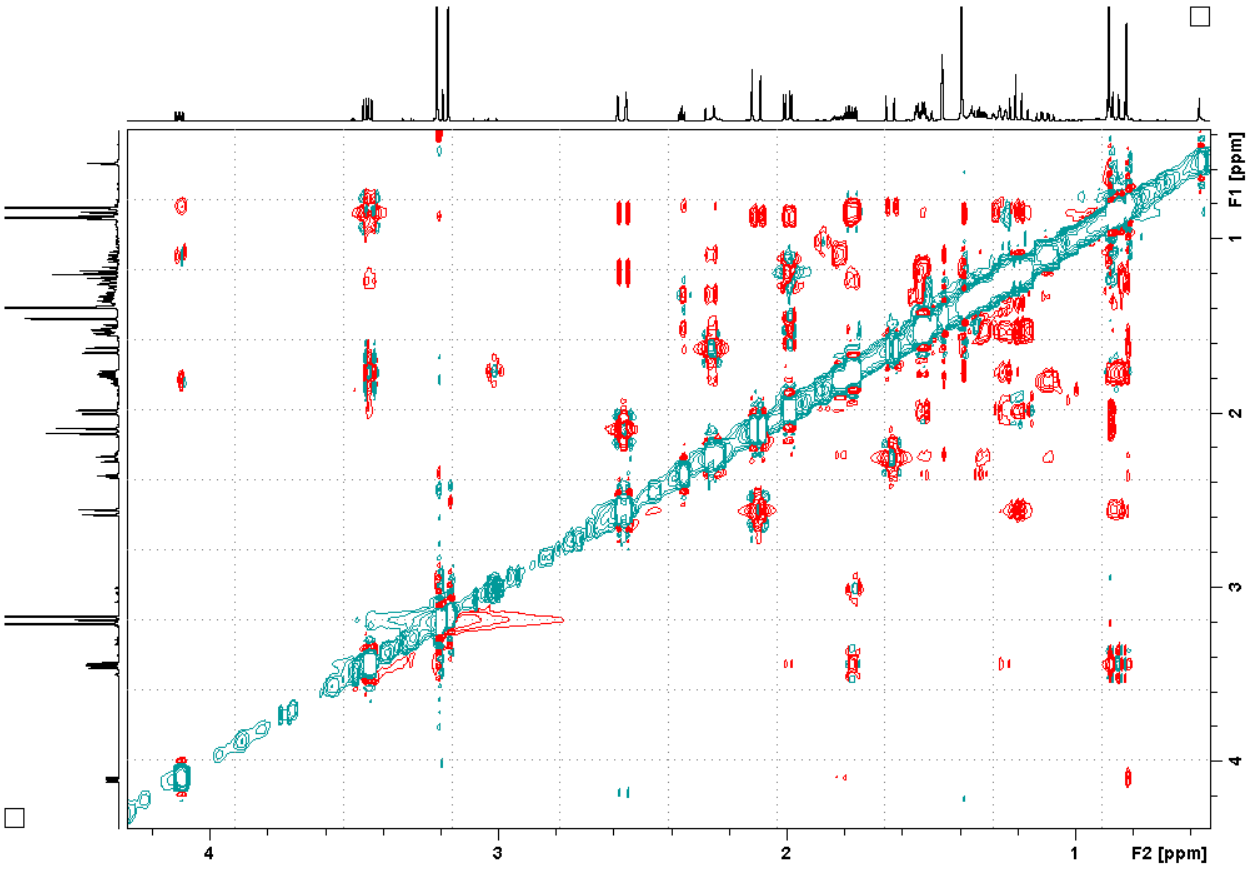
F2 [ppm]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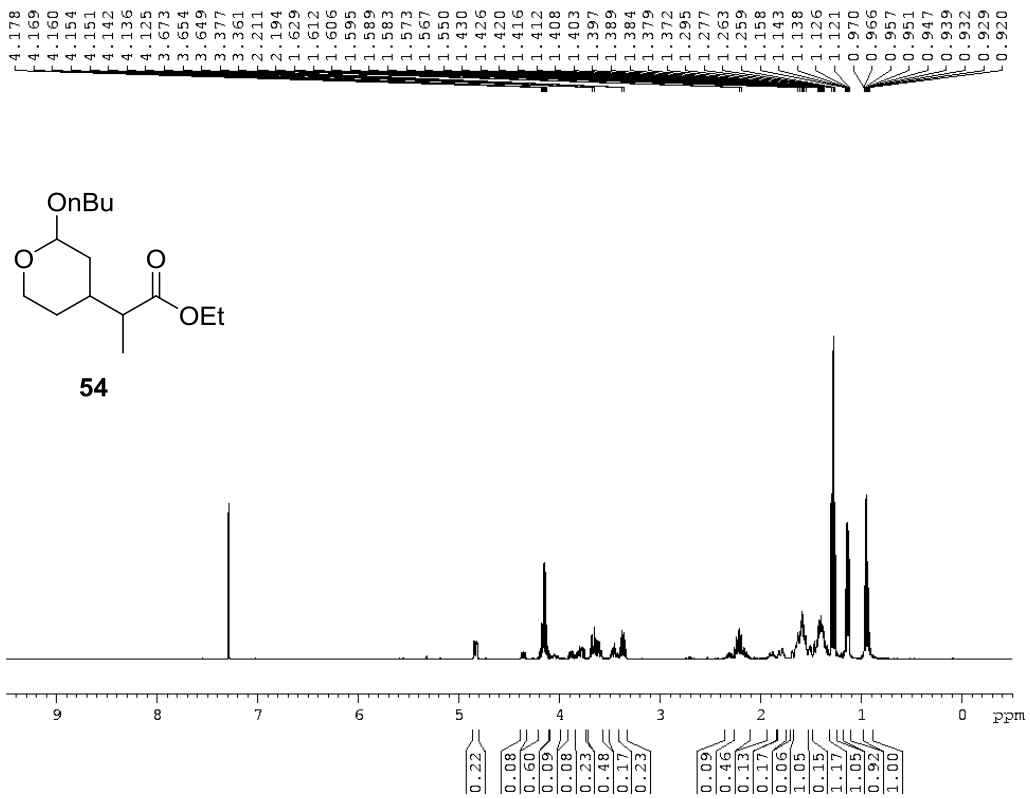
F2 [ppm]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3.377
3.361
2.211
2.194
1.629
1.612
1.606
1.595
1.589
1.583
1.573
1.567
1.550
1.430
1.426
1.420
1.416
1.412
1.408
1.403
1.397
1.389
1.384
1.379
1.372
1.295
1.277
1.263
1.259
1.158
1.143
1.138
1.126
1.121
0.970
0.966
0.957
0.951
0.947
0.939
0.932
0.929
0.920
OnBu
O
O
OEt
54
9
8
7
6
5
4
3
2
1
0
ppm
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0.08
0.60
0.09
0.08
0.23
0.48
0.17
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0.13
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0.06
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0.15
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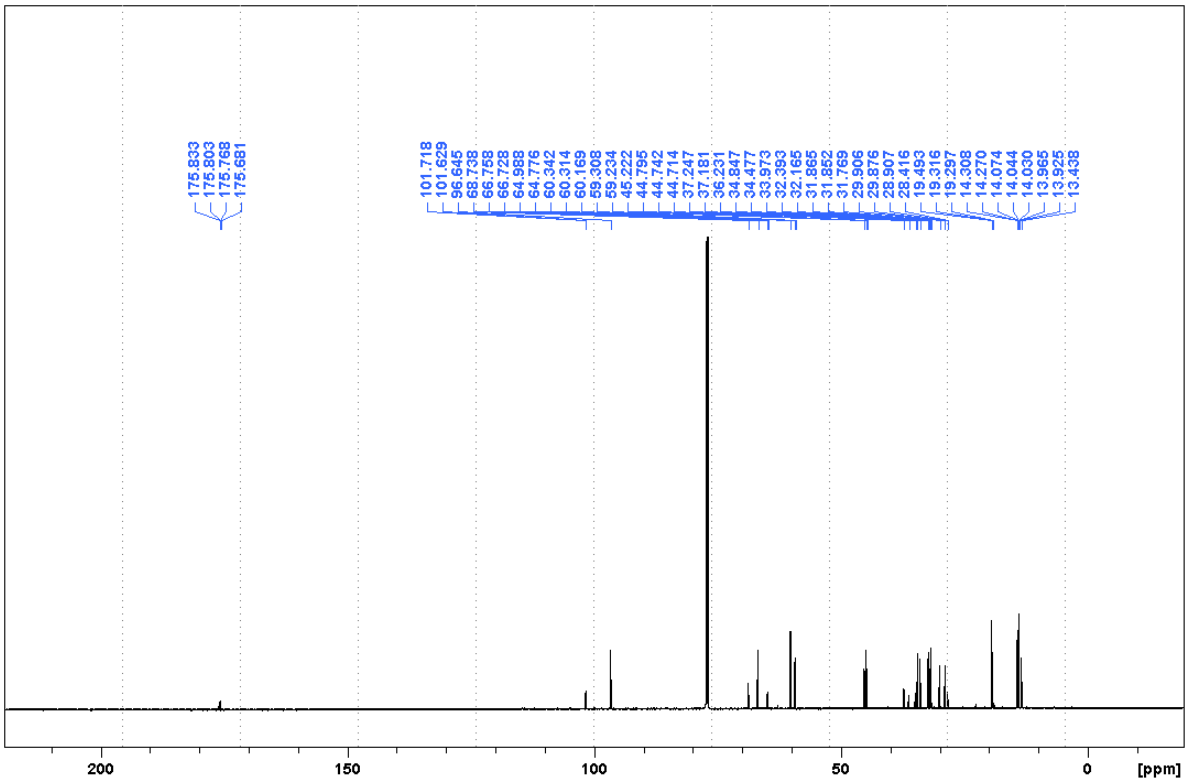
1.00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60.342
60.314
60.169
59.308
59.234
45.222
44.795
44.742
44.714
37.247
37.181
36.231
34.847
34.477
33.973
32.393
32.165
31.865
31.852
31.769
29.906
29.876
28.907
28.416
19.493
19.316
19.297
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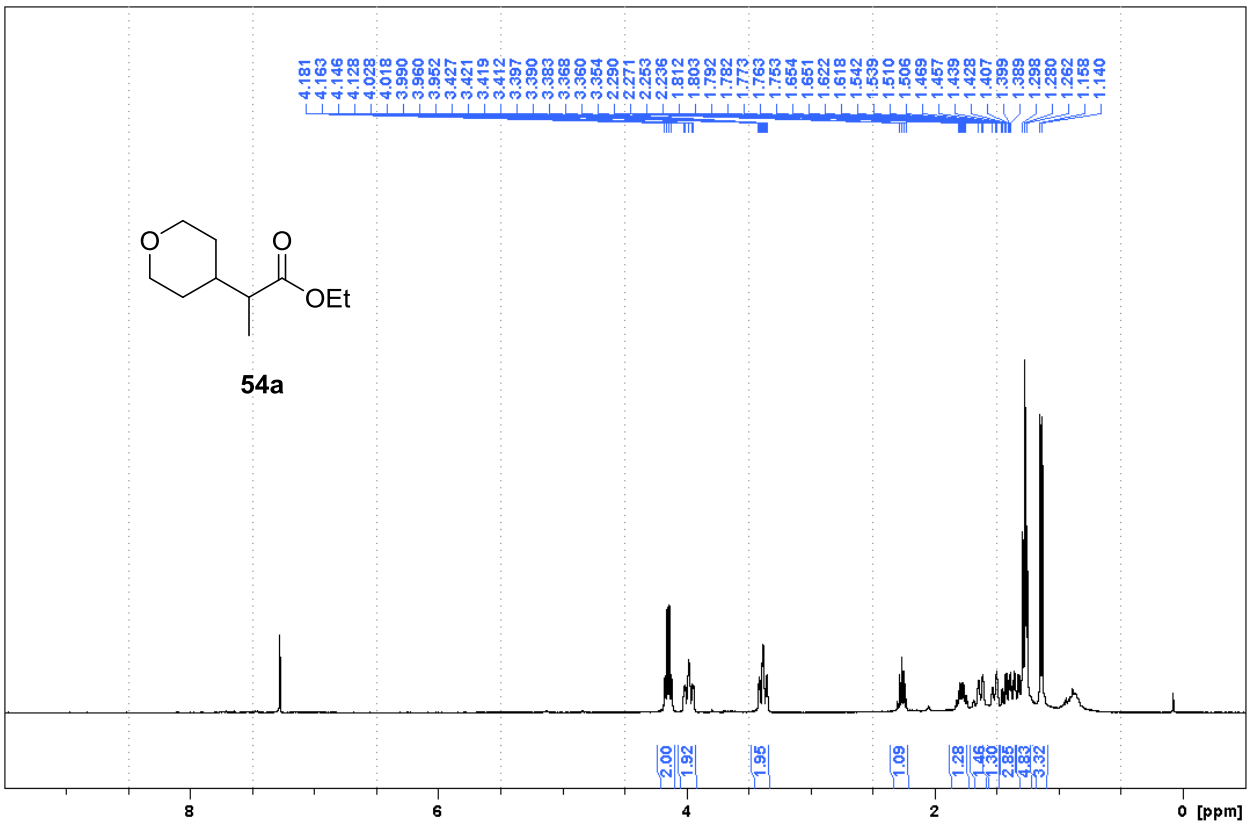
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4.018
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3.960
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3.427
3.421
3.419
3.412
3.397
3.390
3.383
3.368
3.360
3.354
2.290
2.271
2.253
2.236
1.812
1.803
1.792
1.782
1.773
1.763
1.753
1.654
1.651
1.622
1.618
1.542
1.539
1.510
1.506
1.469
1.457
1.439
1.428
1.407
1.399
1.389
1.298
1.280
1.262
1.158
1.140
O
O
OEt
54a
2.00
1.92
1.95
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1.28
1.46
1.30
2.85
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3.32
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6
4
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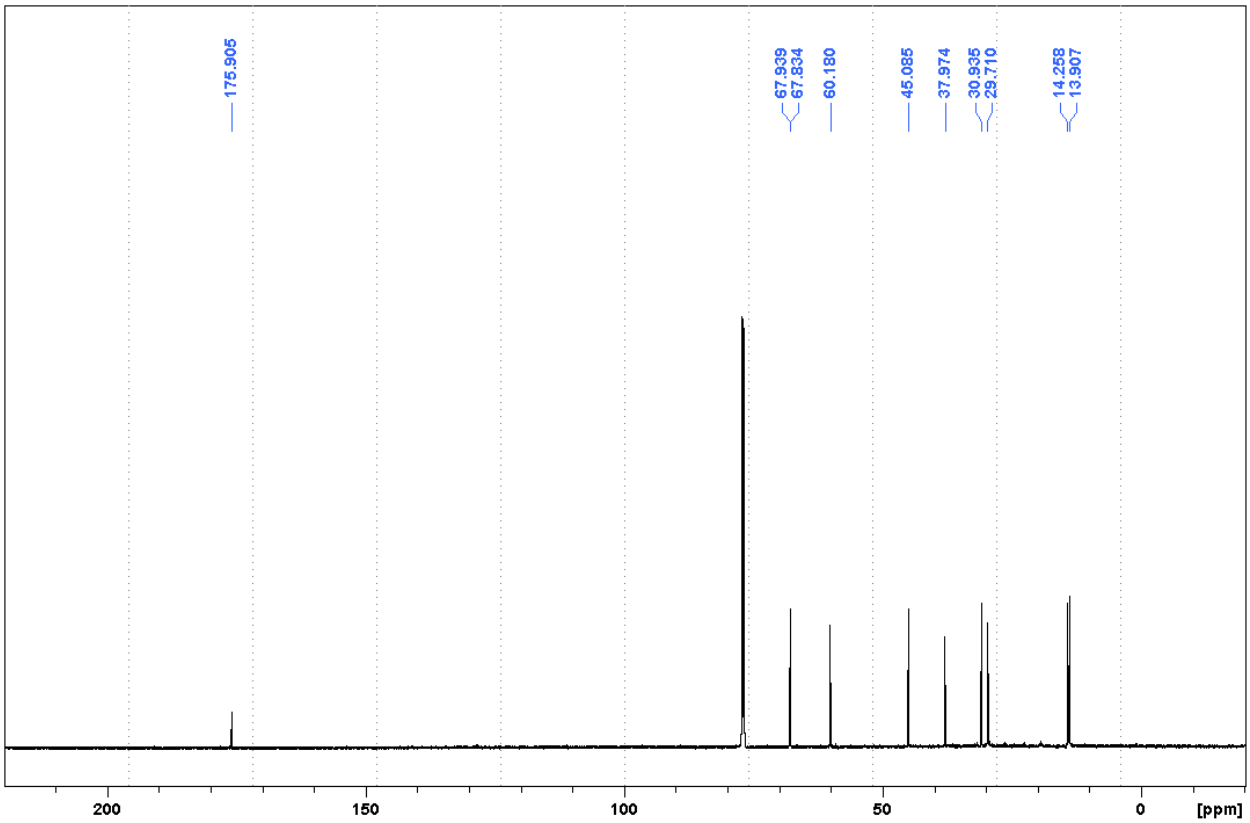
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100
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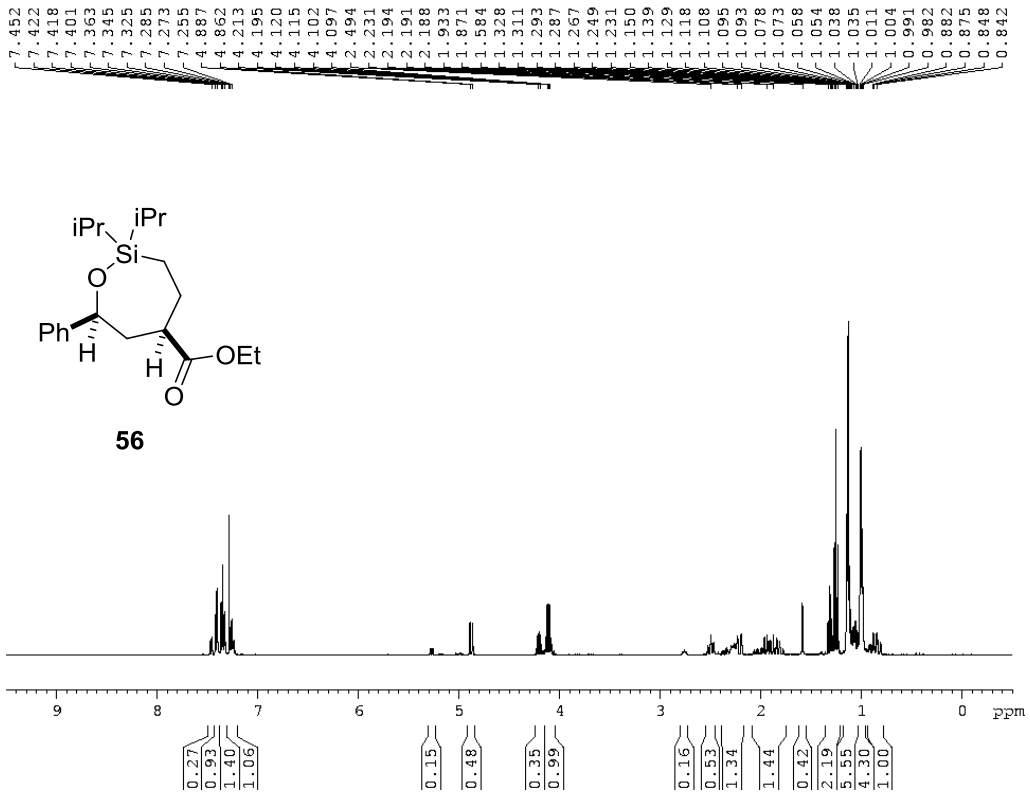
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4.862
4.213
4.195
4.120
4.115
4.102
4.097
2.494
2.231
2.194
2.191
2.188
1.933
1.871
1.584
1.328
1.311
1.293
1.287
1.267
1.249
1.231
1.150
1.139
1.129
1.118
1.108
1.095
1.093
1.078
1.073
1.058
1.054
1.038
1.035
1.011
1.004
0.991
0.982
0.882
0.875
0.848
0.842
iPr
iPr
Si
O
Ph
H
H
OEt
O
56
9
8
7
6
5
4
3
2
1
0
ppm
0.27
0.93
1.40
1.06
0.15
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0.16
0.53
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0.42
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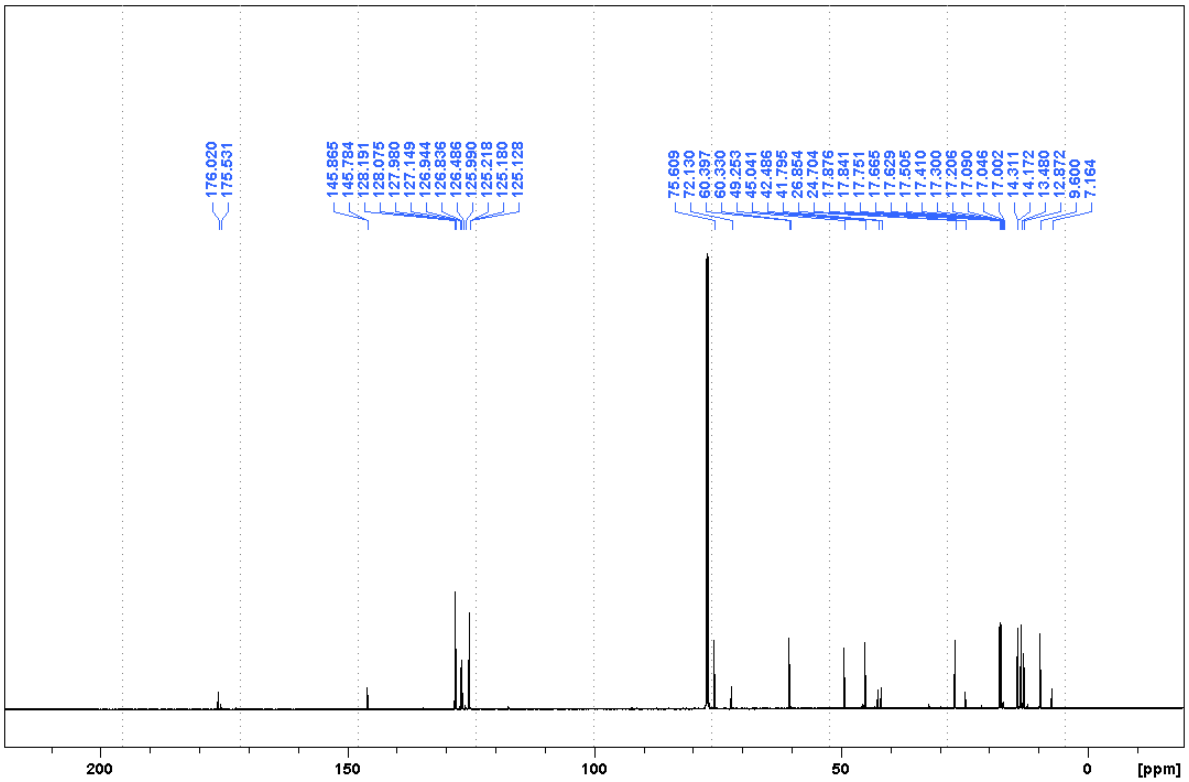
1.00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125.218
125.180
125.128
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26.854
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17.665
17.629
17.505
17.410
17.300
17.206
17.090
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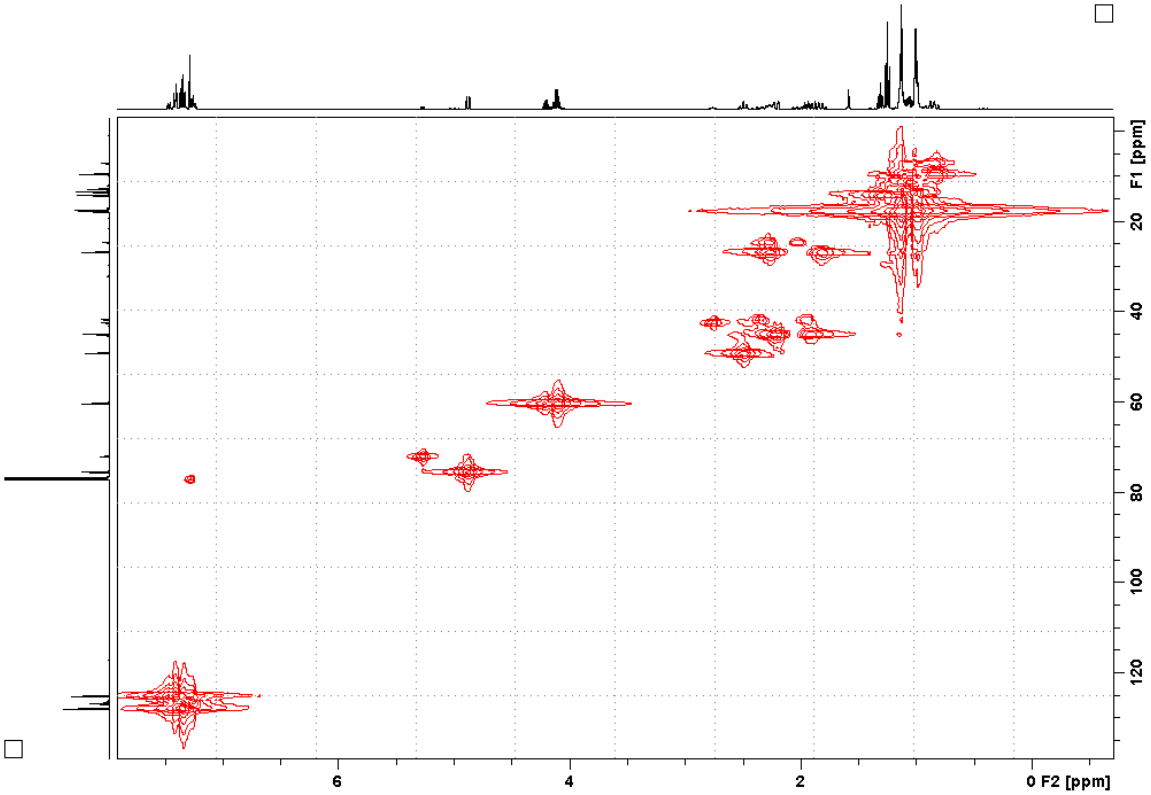
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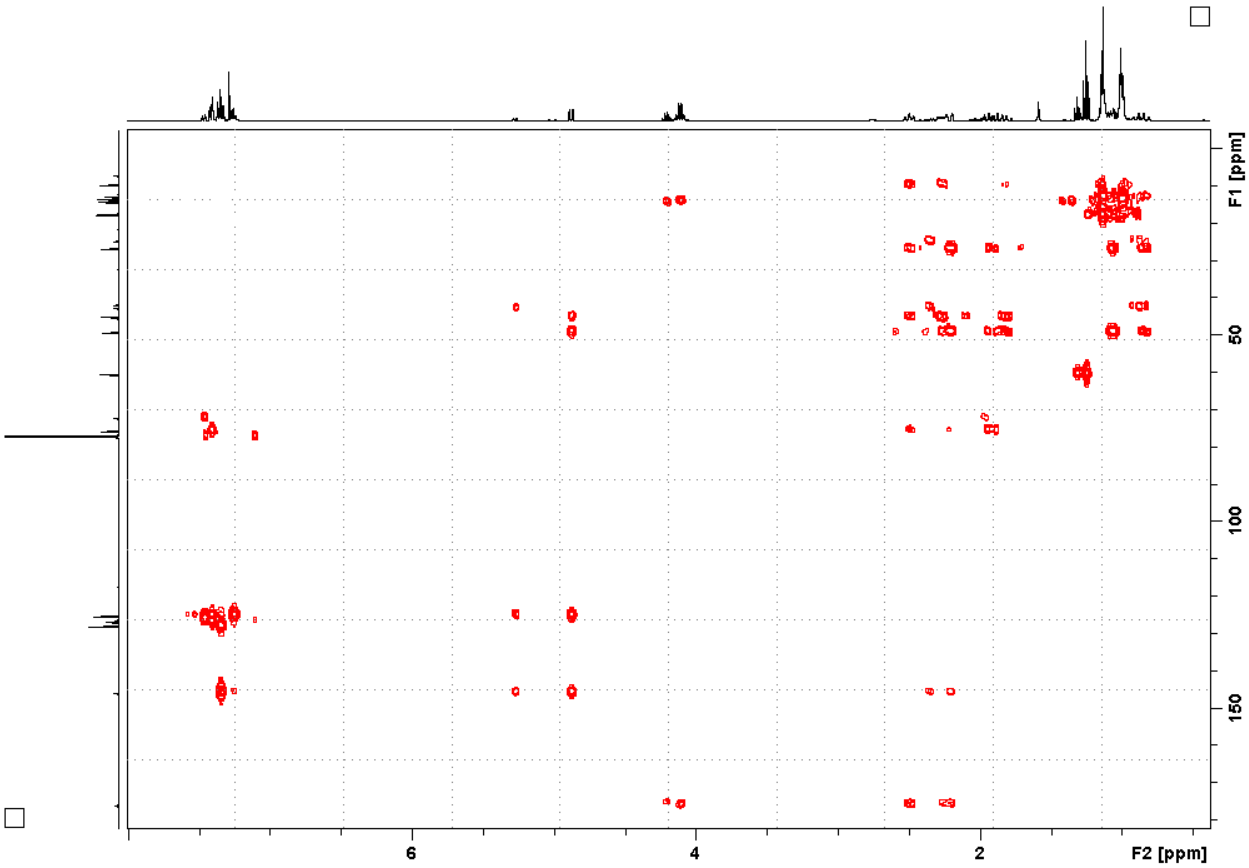
40
60
80
100
120
6
4
2
0 F2 [ppm]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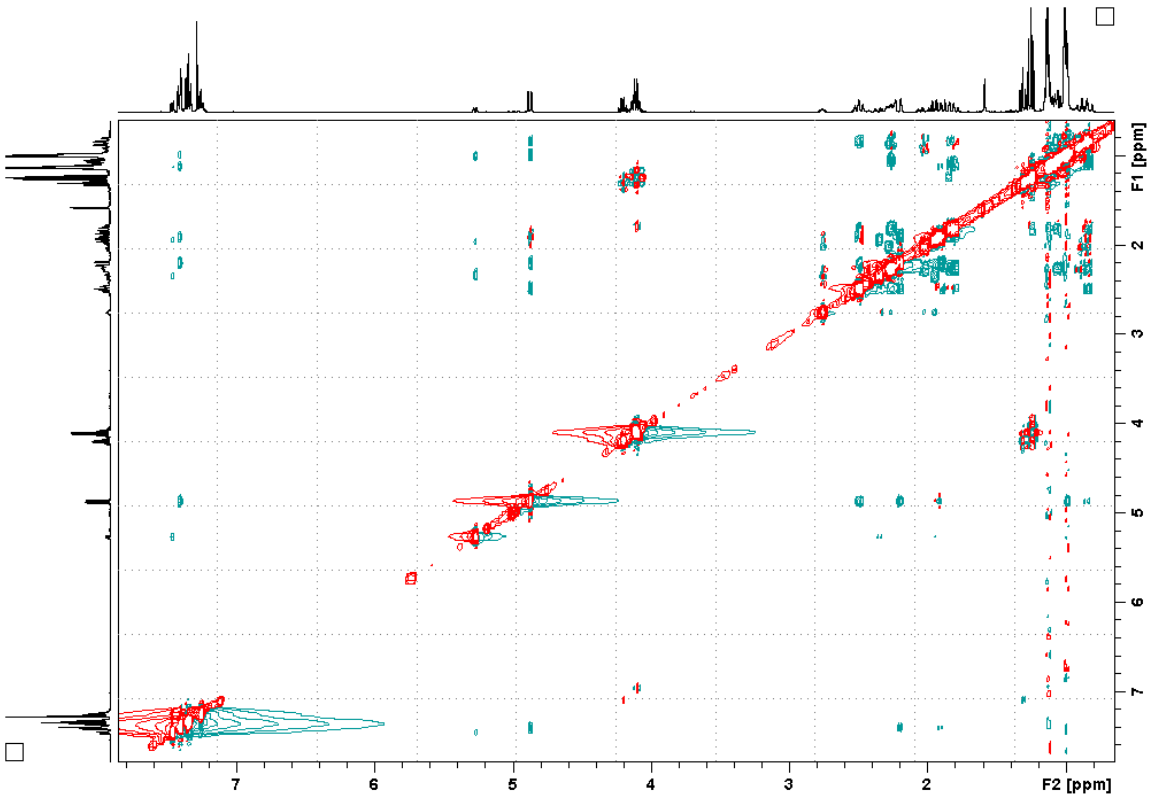
100
150
6
4
2
F2 [ppm]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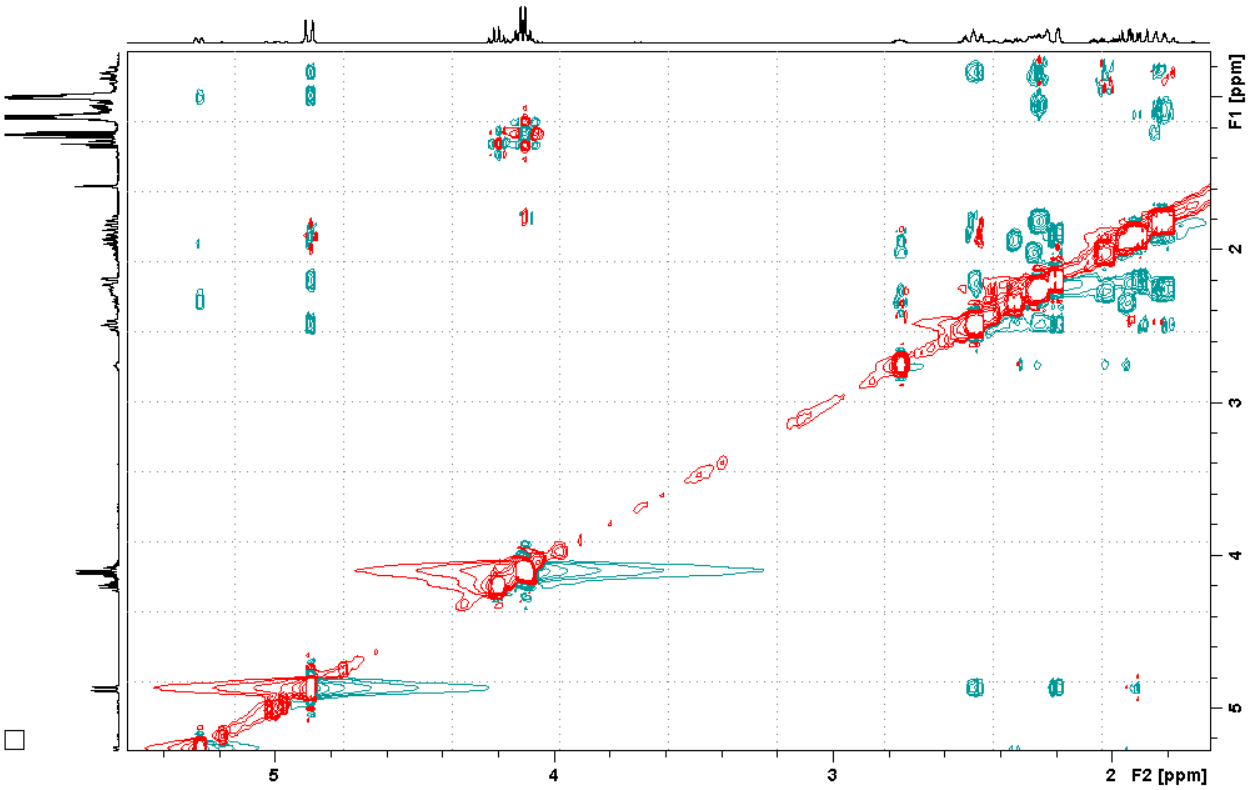
F2 [ppm]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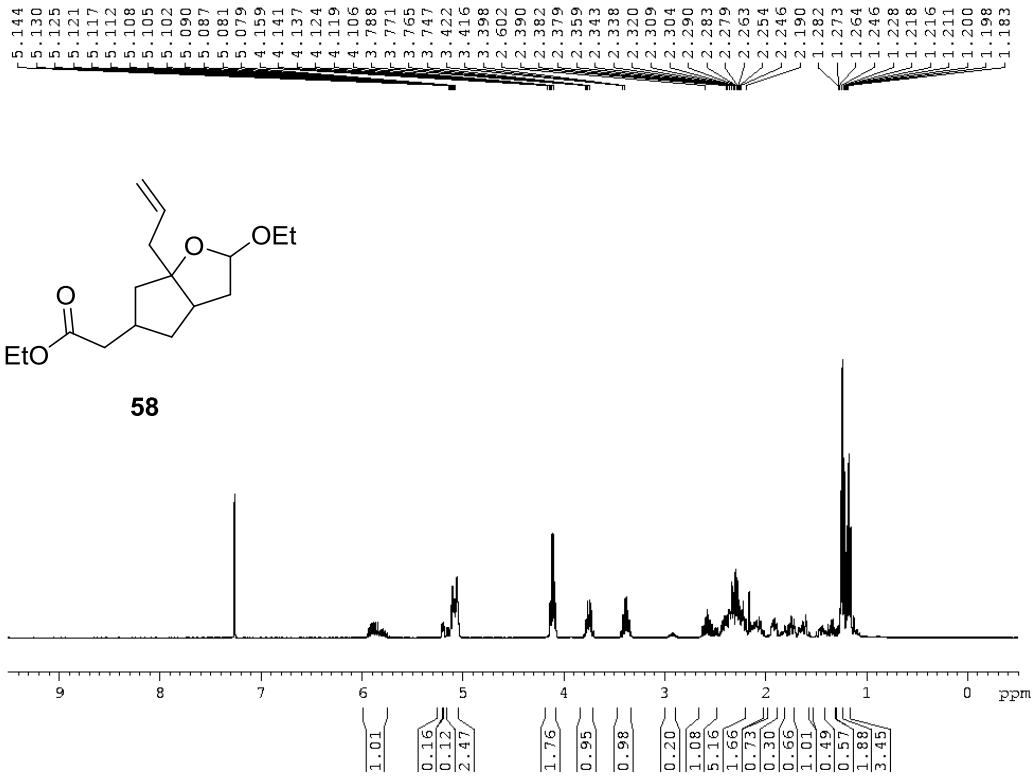
F2 [ppm]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4.141
4.137
4.124
4.119
4.106
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3.747
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3.416
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2.338
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2.279
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2.254
2.246
2.190
1.282
1.273
1.264
1.246
1.228
1.218
1.216
1.211
1.200
1.198
1.183
OEt
O
O
EtO
58
9
8
7
6
5
4
3
2
1
0
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0.12
2.47
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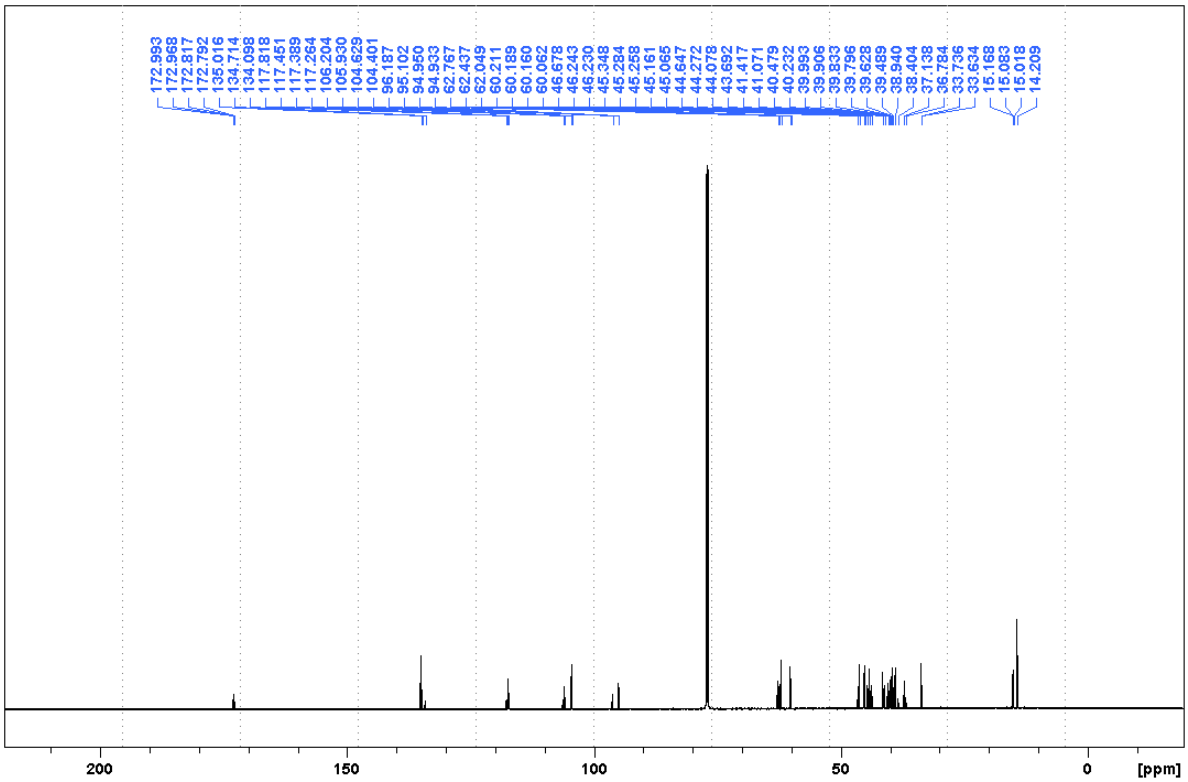
3.45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104.401
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95.102
94.950
94.933
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62.437
62.049
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60.160
60.062
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46.230
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45.284
45.258
45.161
45.065
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39.993
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39.833
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39.628
39.489
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38.404
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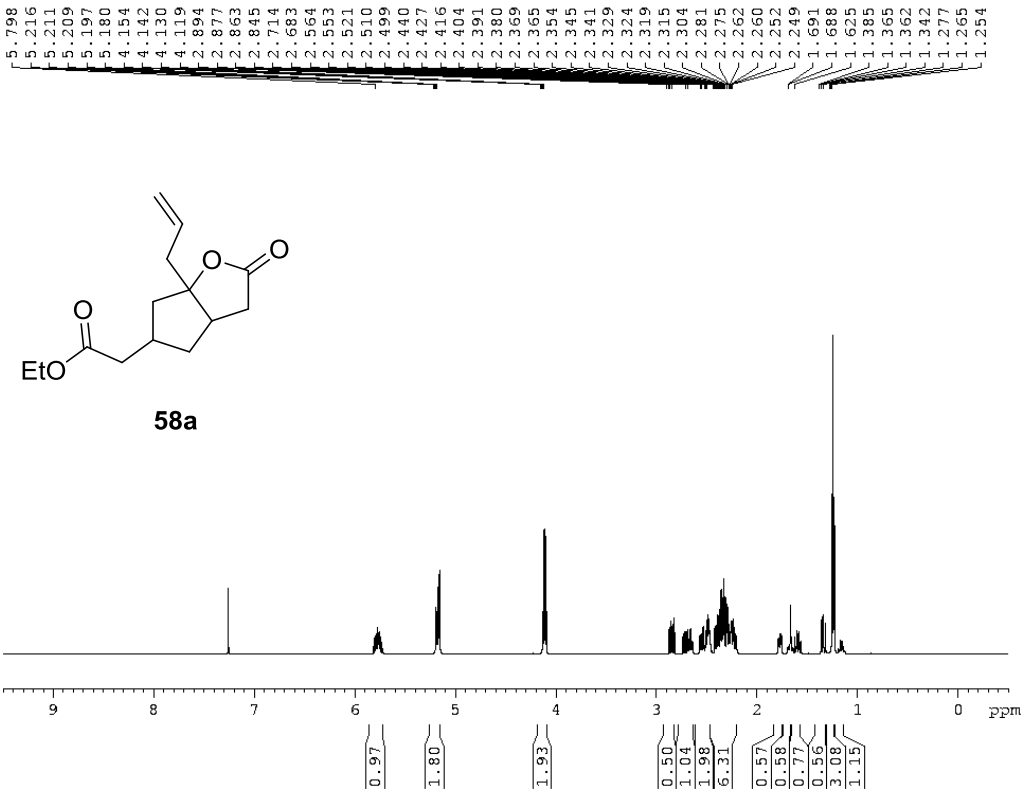
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2.845
2.714
2.683
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2.553
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2.440
2.427
2.416
2.404
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2.260
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2.249
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1.365
1.362
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O
O
EtO
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9
8
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5
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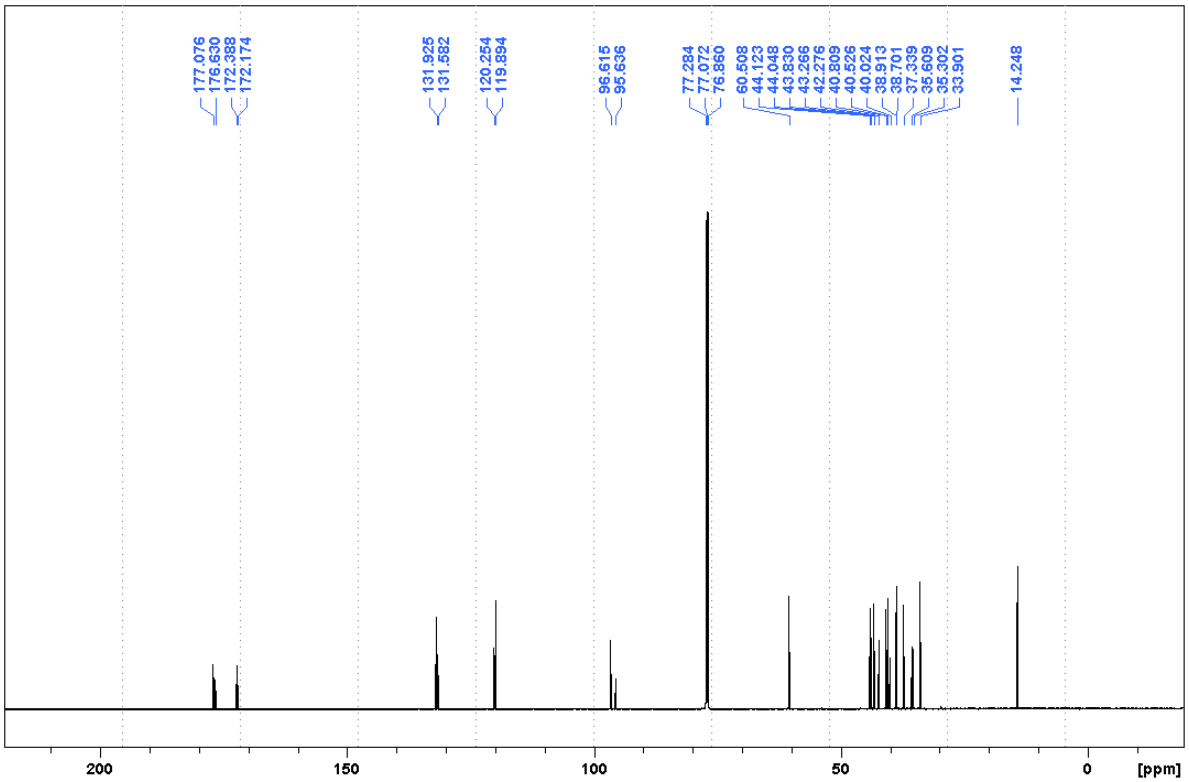
1.15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76.860
60.508
44.123
44.048
43.830
43.266
42.276
40.809
40.526
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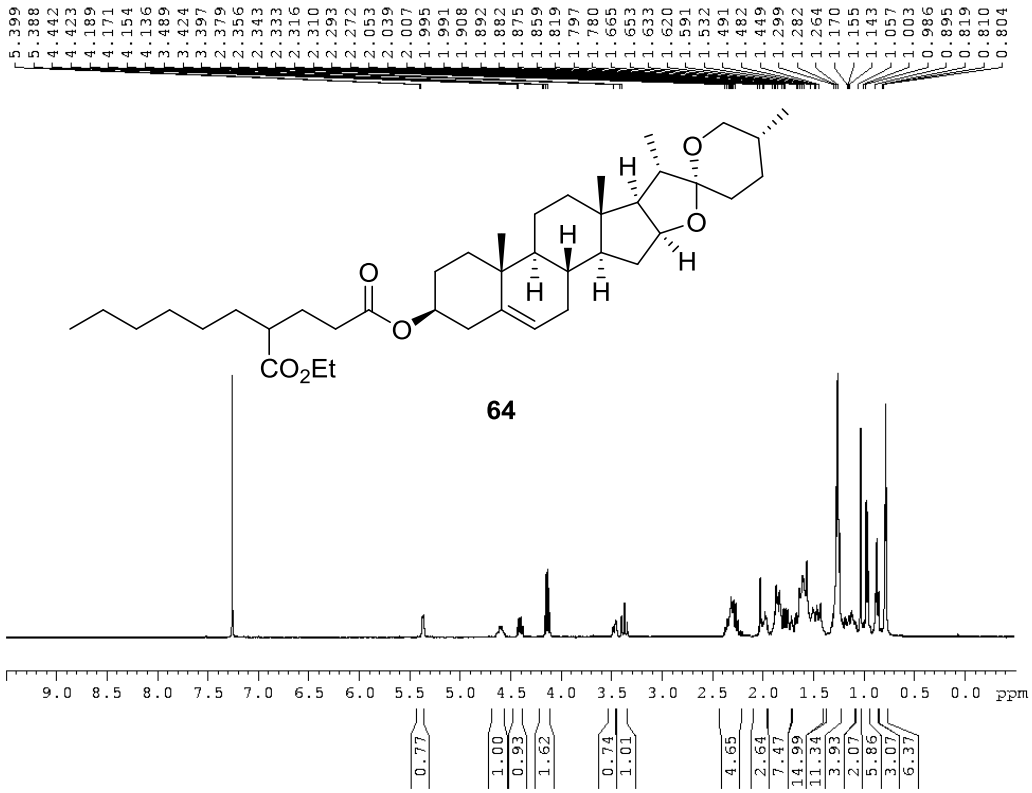
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2.343
2.333
2.316
2.310
2.293
2.272
2.053
2.039
2.007
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1.882
1.875
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1.155
1.143
1.057
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0.819
0.810
0.804
O
H
O
H
H
H
H
O
O
CO_2Et
64
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1.00
0.93
1.62
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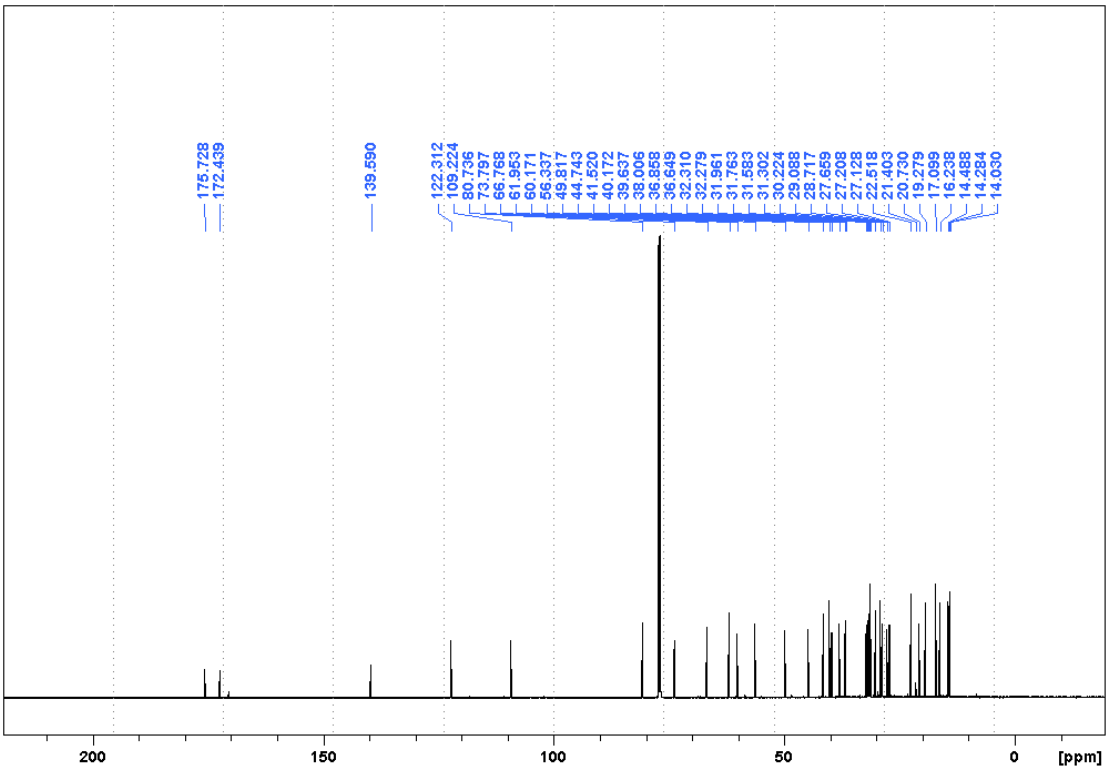
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41.520
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38.006
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36.649
32.310
32.279
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31.763
31.583
31.302
30.224
29.088
28.717
27.659
27.208
27.128
22.518
21.403
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