I) ENANTIOSELECTIVE CONJUGATE ADDITION OF ALKENYLBORONIC ACIDS TO INDOLE-APPENDED ENONES

II) SYNTHETIC DEVELOPMENTS TOWARD THE APLYKURODIN FAMILY

A Dissertation Presented to

the Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

Brian Jeffrey Lundy

May 2013

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II) SYNTHETIC DEVELOPMENTS TOWARD THE APLYKURODIN FAMILY

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Dedicated to my family

Jan, Andy, Mark, Kevin, and Matthew

for their undying love, encouragement, and support

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ABSTRACT

This dissertation presents two different projects, the first being the use of boronic acids in conjugate addition reactions on different substituted indoles, and the second discusses the strategies toward the synthesis of the natural product, aplykurodinone 1.

Conjugate addition reactions are very valuable reactions in forming carbon-carbon bonds and have been studied quite a bit over the years. However, the use of conjugate addition reactions have not been shown to be plausible with unprotected indoles enantioselectively. The previous methods used to do these types of reactions on indoles suffer from limited scope and also require protecting the indole nitrogen. What will be discussed is a very general reaction that tolerates different functional groups such as electron donating and electron withdrawing, as well as tolerating unprotected indoles making it a very useful and powerful method for organic synthesis.

The second project I will discuss is efforts toward the total synthesis of the natural product aplykurodinone 1. Aplykurodinone 1 is part of the aplykurodin family of natural products that was found to have potential cytotoxic activity against cancer cell lines. This potential biological activity combined with the interesting steroidal type structure of the natural product piqued our interest and desire to focus efforts to make it synthetically.

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ABBREVIATIONS AND ACRONYMS

AcO	acetate
app.	apparent
aq.	aqueous
9-BBN	9-borabicyclo (3.3.1) nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1′-Bi-2-naphthol
boc	di-*tert*-butyl dicarbonate
Bn	benzyl
Bs	benzenesulfonyl
Bu	*n*-butyl
ºC	degrees Celsius
calc'd	calculated
CBz	carboxybenzyl
d	doublet
DCE	dichloroethane

DCM	dichloromethane
de	diastereomeric excess
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	*N*,*N*-dimethyl sulfoxide
ED_{50}	50% effective dose
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
Et_3N	triethylamine
Et_2O	ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
H_2O	water
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry

HPLC	high performance liquid chromatography
Hz	hertz
IC_{50}	50% inhibitory concentration
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m	multiplet or milli
m/*z*	mass to charge ratio
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
mol	mole(s)
MOM	methoxymethyl

MS	molecular sieves
MTBE	methyl *tert*-butylether
NMR	nuclear magnetic resonance
O	ortho
*p*ABSA	4-Acetamidobenzenesulfonyl azide
PDC	pyridinium dichromate
Ph	phenyl
PhMe	toluene
ppm	parts per million
Pr	propyl
*i*Pr	isopropyl
q	quartet
rt	room temperature
R_F	retention factor
s	singlet
S.M.	starting material

t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet

Chapter One

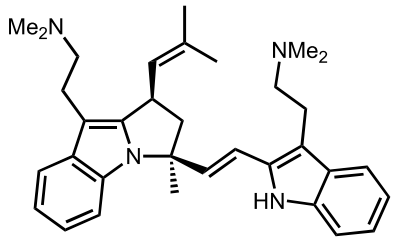
The Need For An Enantioselective Conjugate Addition to Indole-Appended Enones

1.1 Introduction

Asymmetric carbon-carbon bond-forming reactions are very useful transformations in preparing compounds enantioselectively.[1] In a natural product that interested our group, flinderole C, an advanced intermediate in a proposed synthesis required the use of one of the aforementioned asymmetric carbon-carbon bonds being formed. Extensive research was done to determine the most efficient and effective way to form this new bond in order to successfully synthesize the desired natural product, and this will be discussed in the following sections.

1.2 Flinderole C and the Inspiration for Reaction Development

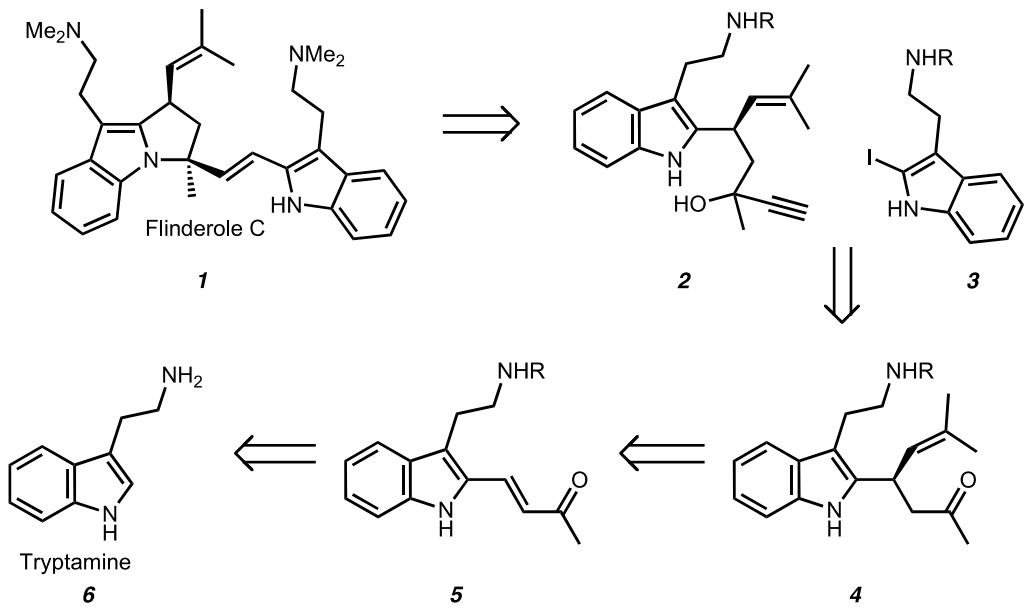
Flinderole C is a natural product that was extracted from the plant *Flindersia amboinensis.* It was identified as a possible antimalarial compound after being run through an initial screening program from a natural product library at the Eskitis Institute. Flinderole C was shown to inhibit parasite growth with an IC_{50} of 0.34 μ*M* against the chloroquine-resistant *Plasmodium falciparum.* It was this activity that made flinderole C an attractive natural product to synthesize.[2]



1

Figure 1.2 Structure of flinderole C, of the plant *Flindersia amboinensis*

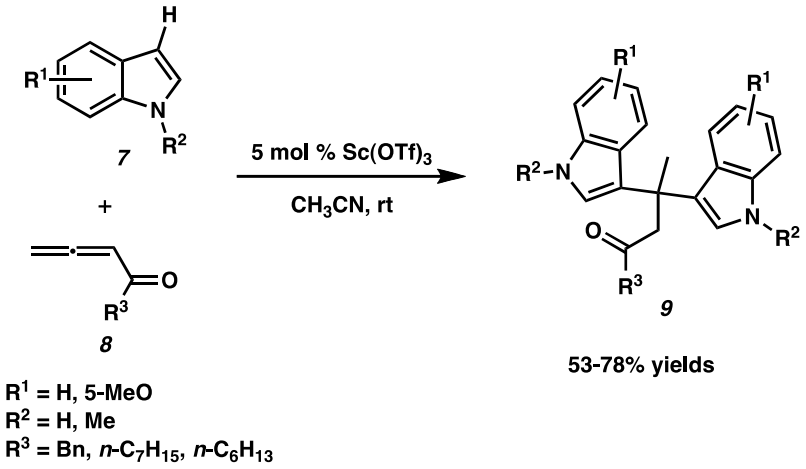
As shown in our proposed retrosynthesis (Scheme 1.2) we were looking for a way to effect a conjugate addition to an indole-appended enone in our synthetic strategy toward flinderole C (i.e., 5 to 4). Being able to perform this reaction without using protecting groups is important as it prevents the need for the additional steps of protection followed by deprotection. Only when attempting this reaction did we realize the lack of such a reaction in the literature. Initial attempts involved searching for conjugate additions to indoles containing α-β-unsaturated carbonyl functionalities. What was found in terms of indole-based reactions will be discussed in the next section.



Scheme 1.2 Retrosynthetic approach for the total synthesis of flinderole C

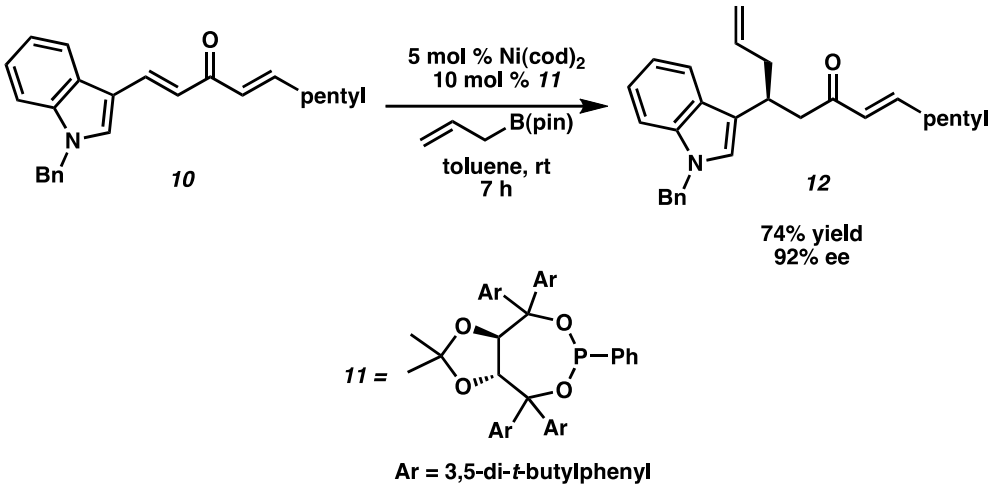
1.3 Conjugate Addition Reactions to Indole-Appended Enones

The precedent for enantioselective 1,4-additions to unprotected indoles was non-existent with only one example of a racemic reaction on an unprotected indole, and two other examples of enantioselective additions on protected indoles. In 2005, the Ma group formed β,β-bisindolyl ketones by way of 1,4-addition using scandium triflate as catalyst as shown in Scheme 1.3.1. In one pot starting with an unprotected indole and a 1,2-allenic ketone using scandium triflate, the allenic ketone reacts with indole, to form an α,β-unsaturated indole intermediate to which another equivalent of indole is added in a 1,4-fashion to form the desired bisindolyl compounds.[3] This reaction only satisfies half of what we would like for our reaction. It is compatible with unprotected indoles, however it does not have the ability to form stereoselective products which is what is needed for our reaction in the synthesis of flinderole C.



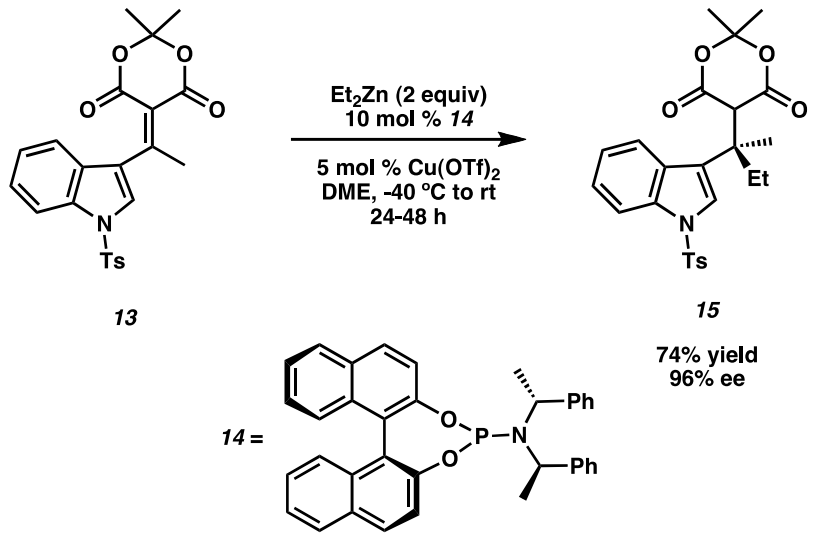
Scheme 1.3.1 Formation of bisindoles catalyzed by scandium triflate

An enantioselective example reported in the literature of 1,4-addition to indoles came with the work of James Morken in 2007. He showed that using nickel cyclooctadiene catalyst with an allylboronic acid pinacol ester 1,4-addition would occur on the indole side of a dialkylidene ketone as shown in Scheme 1.3.2. The limitation with this chemistry as shown in the scheme is that a protected indole is needed as well as the limited scope shown for indole substrates, with the only example shown. We wish to find a method in which the indole does not have to be protected, which as previously discussed allows for step reduction to make syntheses more efficient.[4]



Scheme 1.3.2 Allylation of dialkylidene ketone using a nickel catalyst with a phosphonite ligand

The final example in the literature of a precedent for conjugate addition to indole-appended enones enantioselectively came in 2009 in work done by Eric Fillion at the University of Waterloo. Using catalytic copper with a phosphoramidate ligand, they were able to alkylate an indolyl Meldrum's acid derivative using organozinc reagents, which is shown in Scheme 1.3.3. The limitations of this chemistry are the same that plague the previous methods described. While it is a stereoselective reaction, there is only one example of an indole substrate working and the indole is protected.[5]



Scheme 1.3.3 Enantioselective conjugate addition of a Meldrum's acid derived indole using organozinc, copper triflate, and phosphoramidate ligand

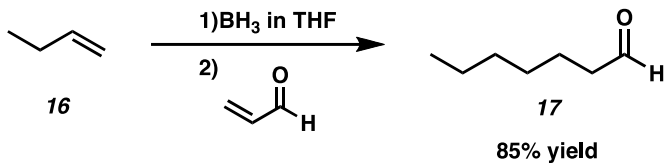
The methods described above were the only precedent we were able to find in the literature of conjugate additions to indolyl enones that used unprotected indoles or were enantioselective, and each method had its incompatibilities to the proposed synthesis of flinderole C. Therefore, other methods were to be explored for more promising results that would be highly enantioselective as well as mild enough to work with unprotected indoles.

When searching literature precedent we found how versatile and mild boron-based nucleophiles could potentially be. Boron-based reagents have become very valuable tools to help form carbon-carbon bonds with good efficiency and when applicable, enantioselectivity. Boron has been used in asymmetric reductions,[6] aldol reactions,[7] α-halo boronic ester chemistry,[8] and conjugate addition reactions.[9] Since the

work that will be presented herein focuses on using organoboranes in 1,4-conjugate addition reactions, that will be the focus on the discussion of organoboranes.

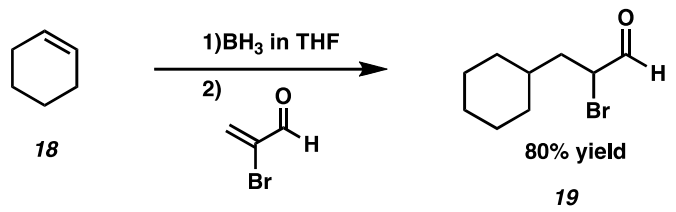
1.4 Pioneering Work By H.C. Brown

In 1967, Herbert C. Brown showed he was able to react organoboranes with acrolein in a 1,4-addition in order to form elongated aldehyde skeletons. The utilization of trialkyl boranes in Brown's reaction allow for an incredibly simple and general procedure toward the formation of new aldehydes. It was presumed at the time that the reaction intermediate produced is a boron-enolate upon which hydrolysis yields the desired product. This presumption led to the exciting realization that this chemistry could be done on a wide variety of α,β-unsaturated substrates.[10]



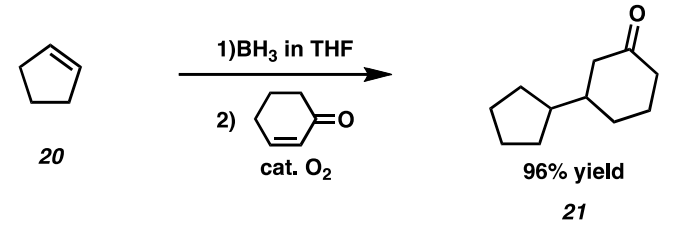
Scheme 1.4.1 Formation of aldehydes by 1,4-addition of trialkylboranes to acrolein

A year later he was able to get 2-bromoacrolein to undergo addition of organoboranes to form α-bromo aldehydes. In this work he is not only able to give an example of another 1,4-addition of boranes, but he was also able to show that these reactions are useful synthetically. At the time, it was difficult to form α-bromo aldehydes by methods such as the direct bromination of an aldehyde; however, utilizing his method the preparation of these bromo aldehydes could be done in one step and with ease.[11]



Scheme 1.4.2 One pot synthesis of α-bromo aldehydes using trialkylboranes

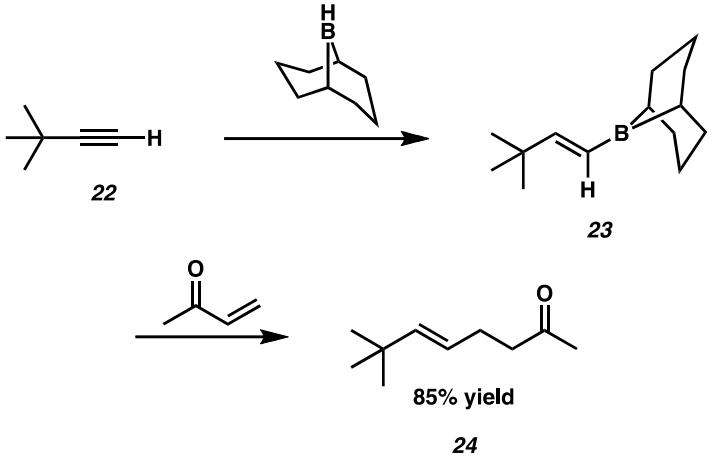
Following his work with acroleins, Brown was able to show the 1,4-addition of α,β-unsaturated carbonyls of typically inert enone systems by using trialkylboranes and catalytic O_2. While his previous methods of forming carbon-carbon bonds were typically pretty general, there were still some α,β-unsaturated compounds that proved to be unreactive under his reaction conditions, including cyclic enones. He was able to circumvent this problem by using a catalyst, in this case O_2, which changed the reaction mechanism to a radical reaction making it possible for the previously unreactive substrates to now react effectively.[12]



Scheme 1.4.3 Conjugate addition of previously unreactive enones using O_2 as a catalyst

The last example of work that will be discussed by H.C Brown came in 1976 with the reaction of alkenyl-9-BBN compounds to methyl vinyl ketone. In his work he was able to expand not only the substrate scope with which the 1,4-additions were effective,

but was also able to introduce a new type of product formed by his chemistry, γ,δ-unsaturated ketones. As previously mentioned the initial intermediate formed is the enol-boronate, which is then hydrolyzed. In the case of the reaction of alkenyl-9-BBN substrates with methyl vinyl ketones, after hydrolysis the desired γ,δ-unsaturated ketones were afforded.[13]



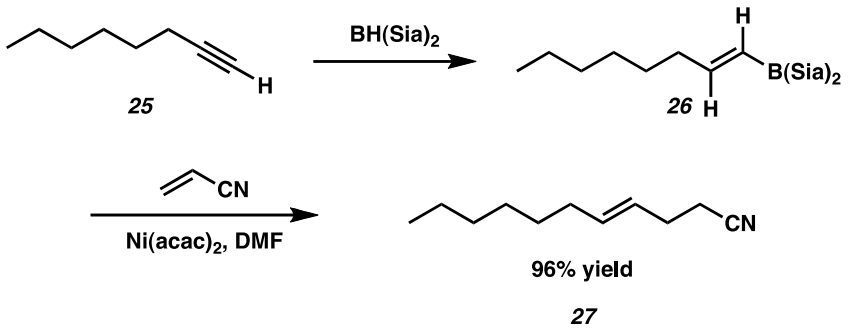
Scheme 1.4.4 Formation of γ,δ-unsaturated ketones using alkenyl-9-BBN nucleophiles

The work done by H.C. Brown set a very nice precedent for the expansion of these types of reactions, and led other scientists to expand on what had been done to include the use of new substrates, boron-derived nucleophiles, and catalysts. Some examples of this expansion will be discussed.

1.5 Akira Suzuki Work

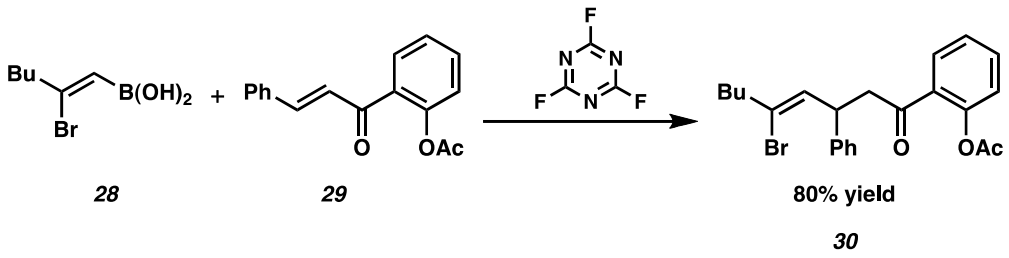
Following in H.C. Brown's footprint, Akira Suzuki was another very important figure in helping to develop the potential of using boron for 1,4-conjugate addition

reactions. In 1996, he showed that 1-alkenyl(disiamyl)boranes would undergo 1,4-additions to α,β-unsaturated ketones, esters, and nitriles catalyzed by nickel acetylacetonate.[14]



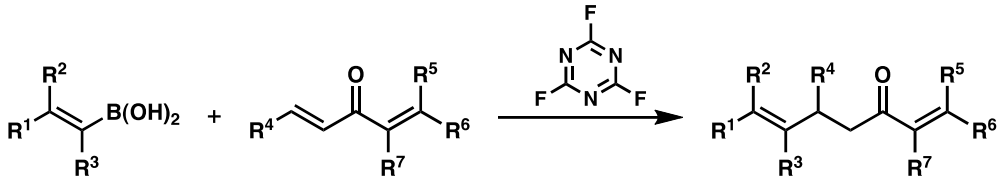
Scheme 1.5.1 Nickel catalyzed conjugate addition of 1-alkenyl(disiamyl)boranes to nitriles

Additionally in 1996, the Suzuki group showed the possibility of using alkenylboronic acids to undergo conjugate addition with α,β-unsaturated ketones using organocatalytic methods instead of organometallics, in this instance using cyanuric fluoride as the catalyst. The use of cyanuric fluoride allowed for an increase of functionality in the scope of the reaction that previously could not be accommodated with such methods as the use of organozinc or copper reagents.[15]



Scheme 1.5.2 Cyanuric fluoride catalyzed addition of alkenyl boronic acids to enones

The last example of Suzuki's work that will be discussed is the use of cyanuric fluoride on an advanced substrate scope to include doubly saturated ketones that showed the alkenylboronic acids will react at the position that is least sterically hindered. This is a useful method that allows for a regioselective reaction to direct the alkylation at the desired carbon by adjusting the substitution on the respective carbon electrophilic sites.[16]



31 *32* **58-93 % yields** *33*

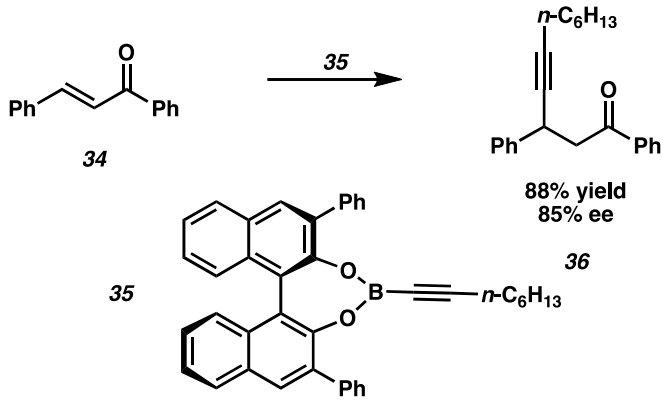
Scheme 1.5.3 Regioselective addition of alkenylboronic acids to doubly saturated enones catalyzed by cyanuric fluoride

The work that will be explained in the next section is that done by Michael Chong. His work is the most impactful and relevant in terms of what will be discussed in the development of the reaction by our lab shown in the following chapter.

1.6 Michael Chong's Work Using Binaphthyl Derived Additives

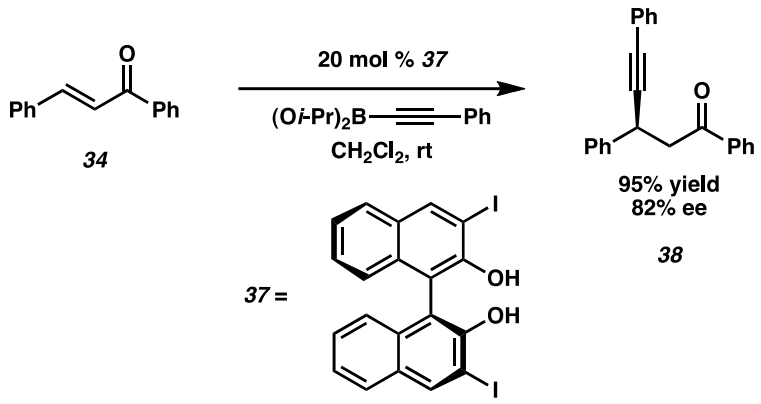
The work done by the Chong group involves the use of binaphthyl derived additives initially in stoichiometric amounts then later improved to be used catalytically, all of which will be discussed. Initially, in 2000 Chong and his group realized that while conjugate alkynyl group transfer using achiral reagents had been accomplished using alkynylboron and aluminum reagents it hadn't been done in an asymmetric version. At this point they surmised that alkynylboronates coupled with chiral diols could produce

such products with a desirable stereoselectivity. Using boronic esters and coupling them with binaphthol, then introducing them into a system with enones, they were able to obtain moderate to good reaction yields and enantioselectivities as shown in Scheme 1.6.1.[17]



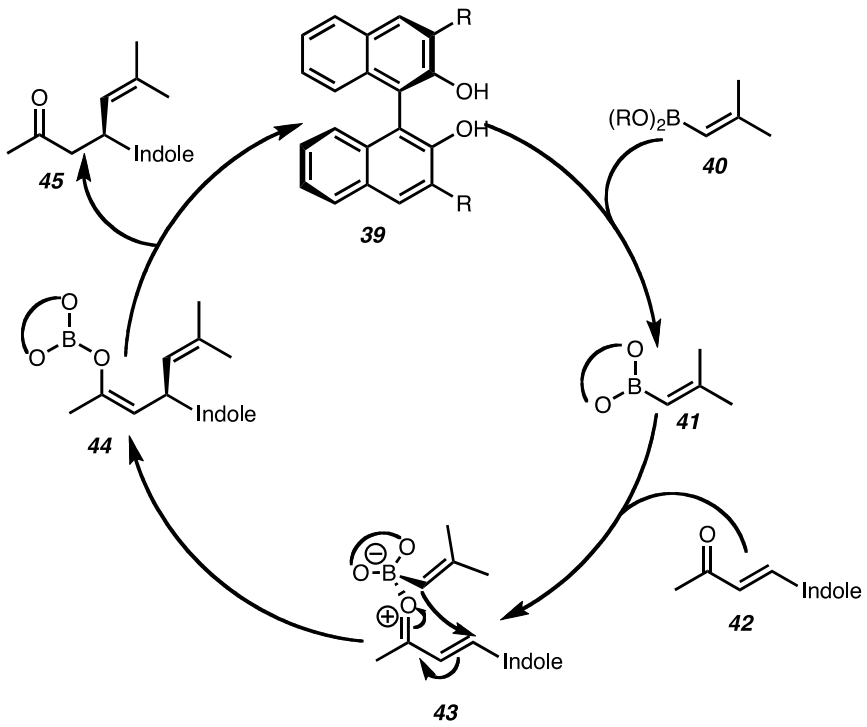
Scheme 1.6.1 Stoichiometric use of binaphthol complexes for nucleophilic addition to enones

While this reaction was novel in the use of chiral alkynylboronate derivatives generated in situ, it then led to the idea of introducing the chiral diol catalytically, instead of as a stoichiometric reagent. In 2005, Chong was able to successfully execute just that type of reaction. Using very similar chalcone-type substrates that were used in his previous work, he was able to induce a 1,4-conjugate addition of boronic ester nucleophiles in the presence of catalytic amounts of binaphthyl-derived catalysts seen in Scheme 1.6.2.[9]



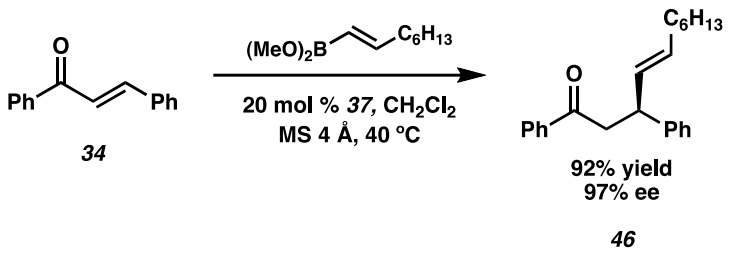
Scheme 1.6.2 Catalytic use of binaphthol derivatives (**37**) for 1,4-addition of boronic esters to enones

The proposed mechanism of this transformation begins with transesterification of the catalyst (**39**) with boronic acid (**40**). After generating this complex in situ resulting in a more Lewis acidic boron nucleophile, **41**, addition then takes place in the 4-position of an enone forming the "ate" complex (**43**) followed by the boron-enolate **44**. Disproportionation then occurs resulting in the regeneration of the catalyst followed by hydrolysis of the boron enolate to generate the desired product, **53**. The catalytic cycle is shown in Scheme 1.7.3.[1,9,18]



Scheme 1.6.3 Proposed catalytic cycle for Chong's work using catalytic amounts of binaphthol-derived compounds

These results showed the possibility of a very versatile and synthetically useful reaction that could allow for a wide range of α,β-unsaturated substrates under mild conditions. Following his catalytic work, Chong and his group were then able to introduce alkenylboronic esters, expanding the utility of the reaction from the alkynylboronic esters previously used. By using different substituted boronic esters, he was able to show the promise of his work.[19]



Scheme 1.6.4 Addition of alkenylboronic esters to enones

The proposed transition states for the stereoselectivity displayed by Chong's reaction are as shown in Figure 1.6. It can be rationalized by showing a six-membered chair-like transition state. The major enantiomer obtained in the reaction is the result of the β-substituent to the enone being in the pseudo-equatorial position as shown in transition state **47**. In the more favored chair-like transition state there is less steric interaction, whereas the disfavored transition state **(48)** is destabilized by the interaction with the substituents on the binaphthol complex.[19]

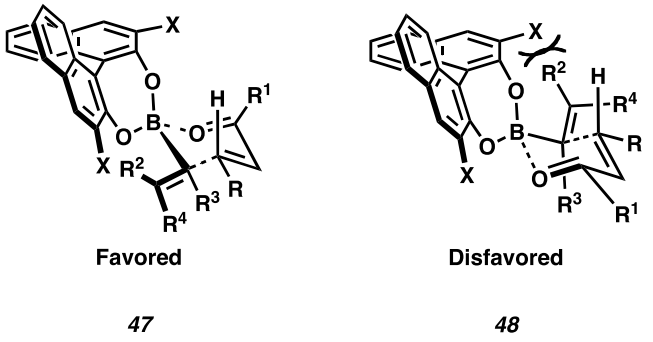
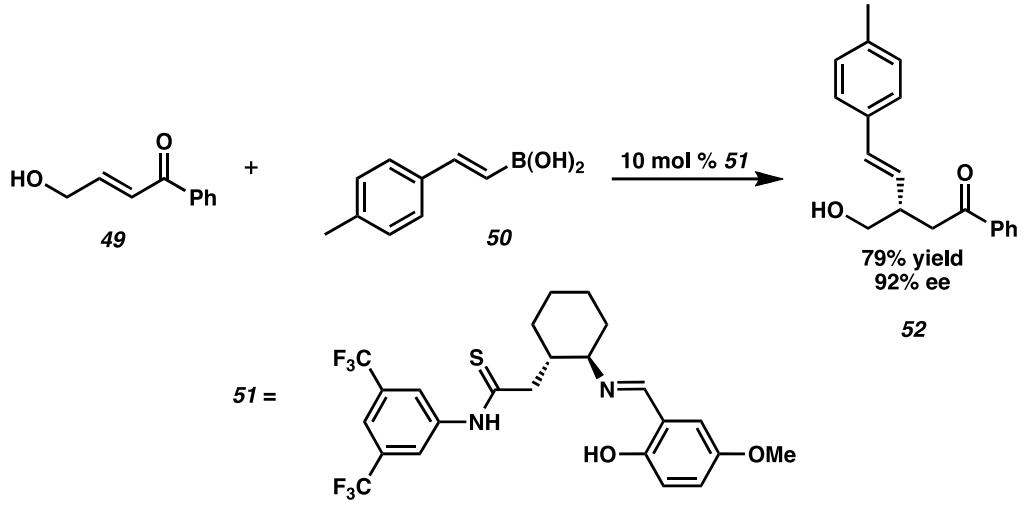


Figure 1.6 Proposed transition states to explain the stereoselectivity of the reaction catalyzed by binaphthol-derived compounds

1.7 Recent Organocatalytic Methods

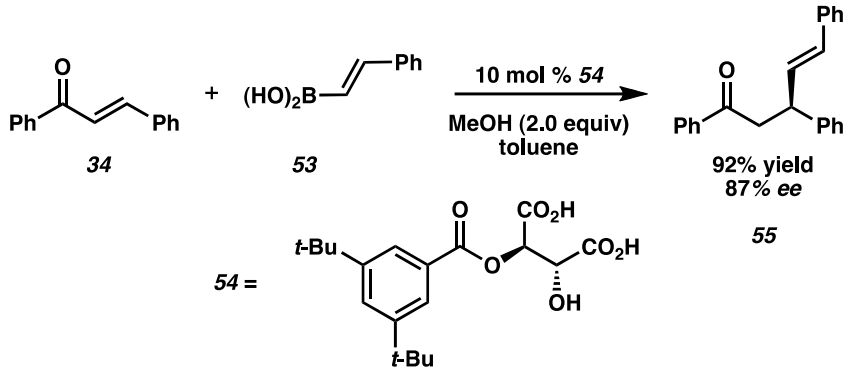
The work presented later in this thesis involves an organocatalytic, enantioselective method. It is important to understand a couple other methods available and their limitations, to show why a more general and synthetically useful method should be developed. In 2009, Takemoto used iminophenol-type thiourea catalysts to react boron nucleophiles with α,β-unsaturated ketones containing terminal hydroxyl functionality (Scheme 1.7.1). While this reaction had fair yields and enantioselectivities, the limitations lie in the required hydroxyl group. This group is needed to coordinate with the catalyst to enhance the reactivity of the substrate. It is not synthetically useful unless an enone with terminal oxidation is necessary.[20]



Scheme 1.7.1 Iminophenol-type thiourea catalysts utilized in 1,4-conjugate additions to hydroxyl-terminated enones

In 2010, Suguira used *O*-monoaryltartaric acid catalysts to undergo nucleophilic attack of boronic acids on α,β-unsaturated ketones as shown in Scheme 1.7.2. While it is

an attractive method in terms of using a mild organocatalyst, the substrate scope of this reaction is once again limited. The enones presented in the publication had a terminal phenyl group and with the exception of one ester and one methyl group, the other terminal position was also substituted with a phenyl derivative. With the exception of a very limited number of substrates, this reaction also suffers from less than desirable yields and enantioselectivities.[21]



Scheme 1.7.2 *O*-Monoaryltartaric acid catalyzed 1,4-conjugate addition of boronic acids to enones.

1.8 Conclusion

Based on the extensive research done on the different conjugate addition methods available, we decided to begin with the binaphthol organocatalyst used by Chong. This was decided based on the inherent mild-nature and general ability of the catalyst, as we plan to try the chemistry with different indoles. There was some proof that the reaction has the potential to be a very general and synthetically useful method, to which the extent of such had not been explored. In the next chapter it will be discussed the approach to the

new reaction developed, as well as the optimization, substrate scope, and details that the new reaction encompasses.

1.9 Notes and References

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Chapter Two

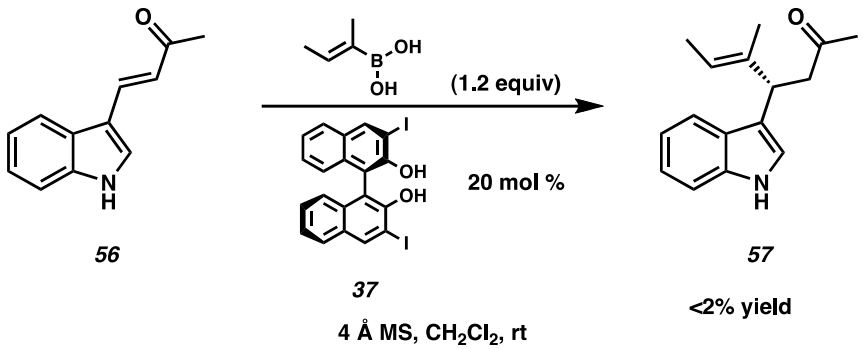
Enantioselective Conjugate Addition of Alkenylboronic Acids to Indole-appended Enones

2.1 Introduction

As mentioned in Chapter 1, the development of a carbon-carbon bond forming reaction under mild conditions to afford products in high yields and enantioselectivities is always an important topic to synthetic chemists. When these reactions encompass a wide range of substrates including heterocycles they become even more beneficial and synthetically useful. This chapter of the thesis will be dedicated to an in-depth explanation of a reaction that was developed for 1,4-conjugate addition to indole-appended enones that is both mild enough to work on unprotected indoles and efficient enough to afford high product yields and enantioselectivities.

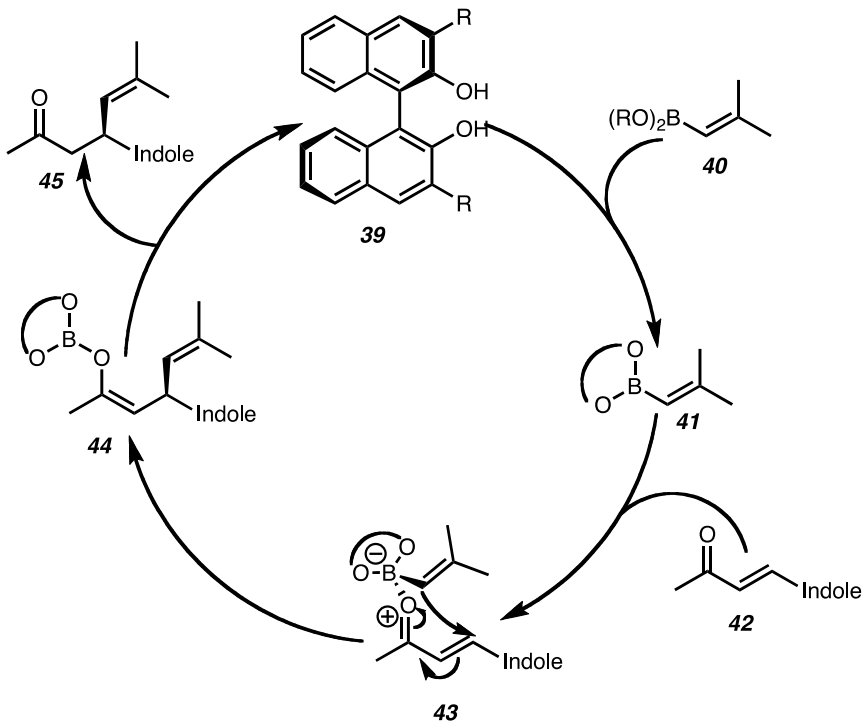
2.2 The Approach

The first attempt made to successfully perform conjugate additions enantioselectively on indoles used existing conditions,[1] which under the best circumstances yielded 2% of product with an unprotected indole as shown in Scheme 2.2.1.



Scheme 2.2.1 Initial attempt of 1,4-conjugate addition on unprotected indoles

Therefore, we examined the mechanism (Scheme 2.2.2) to try to find ways to improve the efficiency of the reaction. The first place we looked to improve the reaction was using boronic acids in the place of boronic esters. The use of low molecular weight boronic esters created difficulties in terms of affinity for water, volatility, and decomposition during handling and storage. Boronic acids, however, are readily available, easier to handle, and more stable. Additionally, vinyl organoboranes are easier to use compared to similar reagents consisting of zinc, copper, aluminum, or magnesium.



Scheme 2.2.2 Proposed catalytic cycle for Chong's work using catalytic amounts of binaphthol-derived compounds

Another way to improve the reaction focused on the catalyst used. It was known that relative to chalcones, less reactive, electron-rich indole substrates, would be problematic and require a more reactive catalyst. The literature showed that there was a relationship between the reactivity of the substrates and the electron-withdrawing proficiency of the groups at the 3 and 3′ positions of the BINOL catalyst.[1-3] It was proposed that a more electron-withdrawing group in those positions would increase the Lewis-acidity of the nucleophile, thus making it more reactive for the desired 1,4-addition reaction.[4] The next section of this chapter will talk about the optimization of this

reaction based on the changes proposed in this section. The optimizations described were performed on both a furanyl enone and an indolyl enone.

2.3 Reaction Optimization

As shown in Scheme 2.2 and explained in the previous section, the use of an existing conjugate addition method that had been developed for chalcones for substrates with unprotected indoles proved to be unsuccessful. Using the logic discussed in Section 2.2 however, we were able to optimize the reaction initially on a furanyl enone, then again show the optimization on an indole substrate.

The variables that were adjusted included reaction temperature, reaction solvent, the 3 and 3′ substitutions on the BINOL catalyst, as well as the possibility of additives to help the reaction proceed. In the following subsections the methods of optimization on the furanyl enone with be discussed.

2.3.1 Catalyst Optimization

There are multiple variables of the reaction that we were interested in testing in order to find the optimal conditions. One of the previously mentioned key factors of the reaction is the catalyst that is used. It has been shown that as you increase the electron-withdrawing ability of the substituents on the 3,3′-positions of the BINOL catalyst, it should in essence increase the reactivity of the catalyst. Shown below in Table 2.3.1 are the results of using a few different catalysts we had available at the time of the optimization process. The catalysts that will be shown are 3,3′-diiodobinhapthol (**37**),[5] 3,3′-dinitrophenyl binapthol (**60**),[6] and 3,3′-dipentafluorophenyl binapthol (**61**).[7]

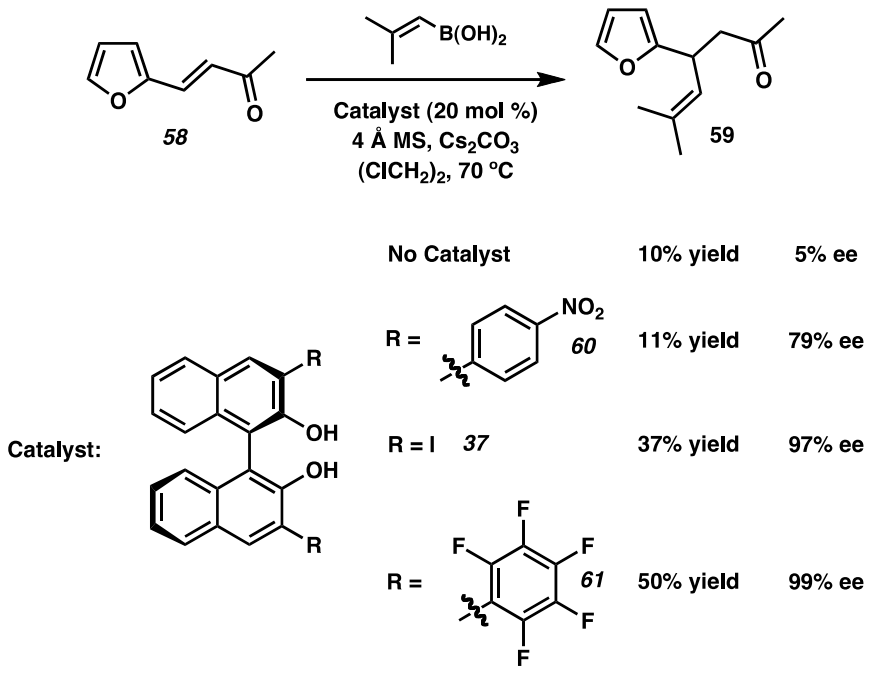


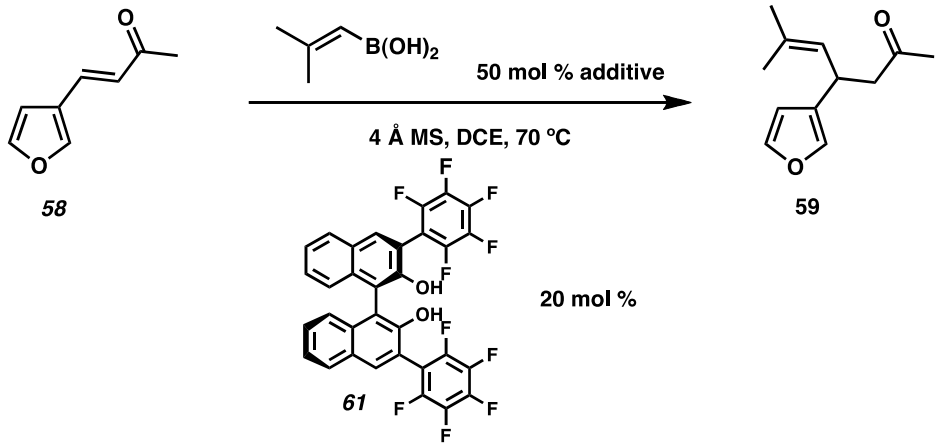
Table 2.3.1 Binaphthyl catalyst screen with furanyl enone substrate

As shown in Table 2.3.1, without the use of any catalyst the reaction does not work very well; however, a background reaction does provide for minor amounts of product formation. Therefore an effective catalyst must be reactive enough that the catalyzed reaction occurs significantly faster than the uncatalyzed reaction for the purposes of stereoselectivity. Using catalyst **60** with a nitro group in the para position did not have much of an affect on the reaction and also showed poor stereoselectivity. Having iodide in the 3 and 3′ positions of the catalyst (**37**) increased both the yield as well as the selectivity. The best result obtained was using a pentafluorophenyl group in the 3 and 3′ positions of BINOL (**61**). It gave product in 50% yield with a high enantioselectivity, meaning the catalyzed reaction was faster than the uncatalyzed reaction; however, it was unable to carry the reaction to completion. Therefore, in

subsequent experiments the pentafluorophenyl BINOL catalyst was used. The next component of the reaction that was optimized was the use of an additive to increase the efficiency of the reaction.

2.3.2 Additive Optimization

The possibility of an additive accelerating the reaction was found in the knowledge that additives often have positive effects on reactions. We therefore decided to test a wide variety of bases and acids in the reaction mixture to see if they had any effect and which would work best. Based on availability, the choice of substrate for optimization was a commercially available furanyl enone. As shown in Table 2.3.2.1, a wide range of additives were tested with this enone. These additives included titanium and aluminum Lewis acids, as well as cesium, sodium, magnesium, calcium, and amine bases.



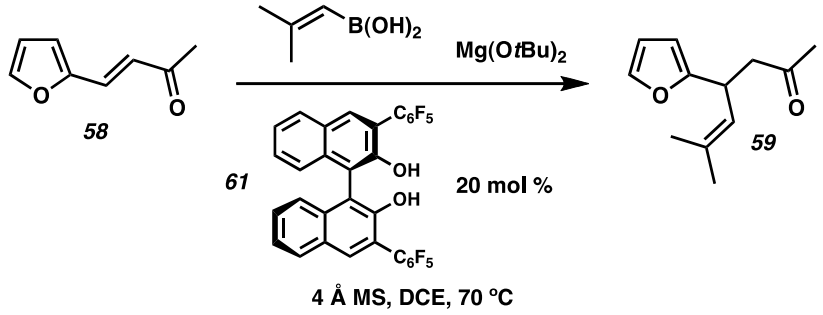
entry	additive	yield[a]	ee[b]
1	CsOAc	N.R.	N.A.
2	$Ti(OiPr)_4$	4%	99%
3	$Al(OtBu)_3$	4%	98%
4	Et_3N	20%	99%
5	Na_2HPO_4	28%	98%
6	$CaCO_3$	39%	98%
7	$CsOH·H_2O$	43%	98%
8	Cs_2CO_3	54%	99%
9	CsF	55%	98%
10	NaO*t*Bu	61%	97%
11	$Mg(OtBu)_2$	63%	97%

Table 2.3.2.1 Optimization of additives for the conjugate addition reaction. [a]NMR yield on crude reaction mixture. [b]Run on HPLC as crude reaction mixture.

In Table 2.3.2.1 are shown 11 different additives and their effects. As seen in entries 2 and 3, the use of Lewis acids did not prove to be effective. Among a variety of cesium bases (entries 1,7, 8, and 9) the carbonate base worked the best at 54% yield. It

turns out, however, that the *tert*-butoxide bases (entries 10 and 11) functioned the best, with magnesium proving to be a little bit more efficient than its sodium counterpart. When compared to Table 2.3.1, which had no additives, it is apparent that the use of $Mg(OtBu)_2$ increased the yield over 10%.

In addition to the identification of the nature of additive that had the most beneficial result, we also needed to find the optimal loading of the additive. We tested 10 mol %, 20 mol %, 50 mol %, 100 mol %, 200 mol %, and 500 mol % of the $Mg(OtBu)_2$. The results of this screen are shown in Table 2.3.2.2.



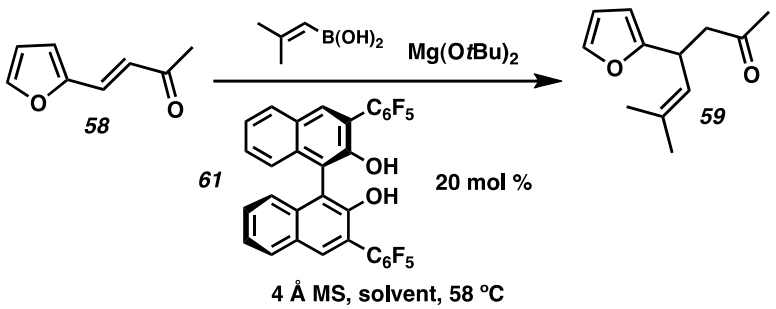
entry	additive loading	yield[a]
1	10 mol %	82%
2	20 mol %	65%
3	50 mol %	53%
4	100 mol %	82%
5	200 mol %	70%
6	500 mol %	23%

Table 2.3.2.2 Loading of $Mg(OtBu)_2$. [a]NMR yield performed on crude reaction mixture.

Based on the table above, we decided that the best loading to use would be 10 mol %, entry 1, based on the yield and economic advantages of only having to use a catalytic amount. While 100 mol %, entry 4, was also very efficient it was rejected based on the amount of additive required. The results of this table show an interesting trend in that the yield decreases as more base is added, before spiking again at 100 mol % only to drop off again with each successive entry in the table. At this point in our optimization we have looked at catalyst effects as well as additive effects and loading. The next section takes the optimization to the next step by examining the solvent effects.

2.3.3 Solvent Effects on the Conjugate Addition Reaction

The solvent that we originally worked with was dichloroethane. Previous work by the Chong used dichloromethane; however, we decided to use dichloroethane so the reaction could be heated to a higher temperature. However, as with almost every other aspect of the reaction, the use of different solvents needed to be examined to see if our initial inclination that dichloroethane was the best solvent was correct, or if there was a solvent that would work better. The results from a solvent screen can be seen in Table 2.3.3.



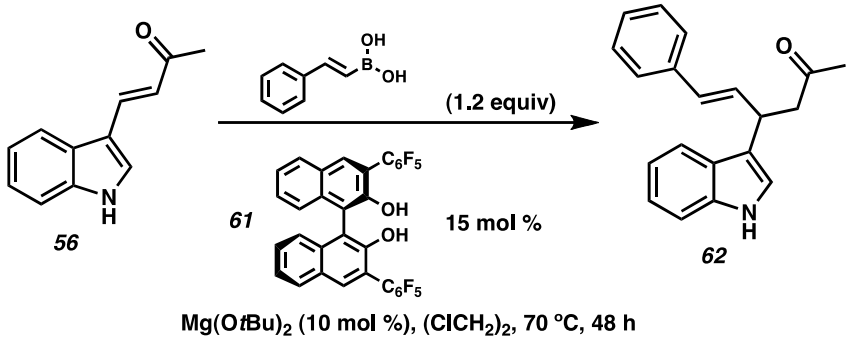
entry	solvent	yield[a]	ee[b]
1	DMF	N.R.	N.A.
2	EtOH	2%	99%
3	THF	7%	96%
4	PhMe	52%	98%
5	$CHCl_3$	59%	99%
6	DCE	63%	97%

Table 2.3.3 Solvent optimization screen for conjugate addition. [a]NMR yield performed on crude reaction mixture. [b]Run on HPLC as crude reaction mixture.

We tested solvents from each general solvent class including, polar aprotic (entry 1), polar protic (entry 2), ethereal (entry 3), aromatic (entry 4) and halogenated (entries 5 and 6). Polar solvents such as DMF and EtOH did not work very well at all. THF also worked very poorly, but then yields increase greatly with the use of toluene. The class that worked the best turned out to be halogenated solvents with dichloroethane performing better than chloroform. The reason for the use of dichloroethane over dichloromethane with become more clear in the next section that will show how temperature affects the reaction.

2.3.4 Temperature Effects on the Conjugate Addition Reaction

Most of the optimization conditions were run at 70 ºC based on initial results when the reaction was first successful. This is also the reason we decided to use the higher boiling dichloroethane over dichloromethane. We, however, wanted to make sure that 70 ºC was the best temperature at which to run the reaction. Therefore we ran the reaction under conditions that changed only in temperature as shown in Table 2.3.4 below.



entry	temperature	yield	er
1	23 °C	44%	99:1
2	50 °C	69%	98:2
3	70 °C	87%	98:2
4	85 °C	81%	96:4
5	100 °C[a]	79%	96:4

Table 2.3.4 Optimization of the reaction temperature. [a]Reaction run in a sealed tube.

As can be seen in Table 2.3.4 the reaction yields increase as the temperature increases up to 70 ºC, after which the reaction yields begin to decrease. This is due to decreased reaction rates at lower temperatures. When the temperature is increased too

much, then the products begin to breakdown and decompose more readily. Therefore, it was essential to find the temperature that allows for optimal reactivity without the loss of product due to decomposition. After optimal conditions were established, it was time to develop the substrate scope and see which indoles would be tolerated. In the next section the indole scope will be shown and discussed.

2.4 Indole Substrate Scope

After the optimization of the reaction conditions, we then wanted to determine the versatility of the reaction and found it to be very successful on different types of indoles. We treated indole-appended enones with *trans*-2-phenylvinylboronic acid and (*R*)-3,3′-bis(pentafluorophenyl)-BINOL. The results are shown in Scheme 2.4. The reaction proved to be compatible with a methyl (**62**), phenyl (**63**), isopropyl (**64**), or *tert*-butyl group (**65**) as the ketone substituent. When the group was a *tert*-butyl the reaction worked well, but proved to be a little sluggish. This methodology isn't limited to unprotected indoles, as we observed excellent reactivity with both Boc- (**66**) and methyl-protected (**67**) indoles. You can also use cyclic enones that provide an example of substitution in the α-position to the ketone (**68**). On the substrate we used we observed a 1.2:1 mixture of diastereomers, though both diastereomers were provided with high enantioselectivity. If the indole ring is substituted with an electron-withdrawing group (**69**) or an electron-donating group (**70**), the reactivity is not affected and still works very efficiently. In addition the reaction was not limited to enones on the 3-position of indole as we also got some reactivity with the enone on the 2-position (**71**). However, indoles with the enone on the 2-position were certainly less reactive than the 3-position.

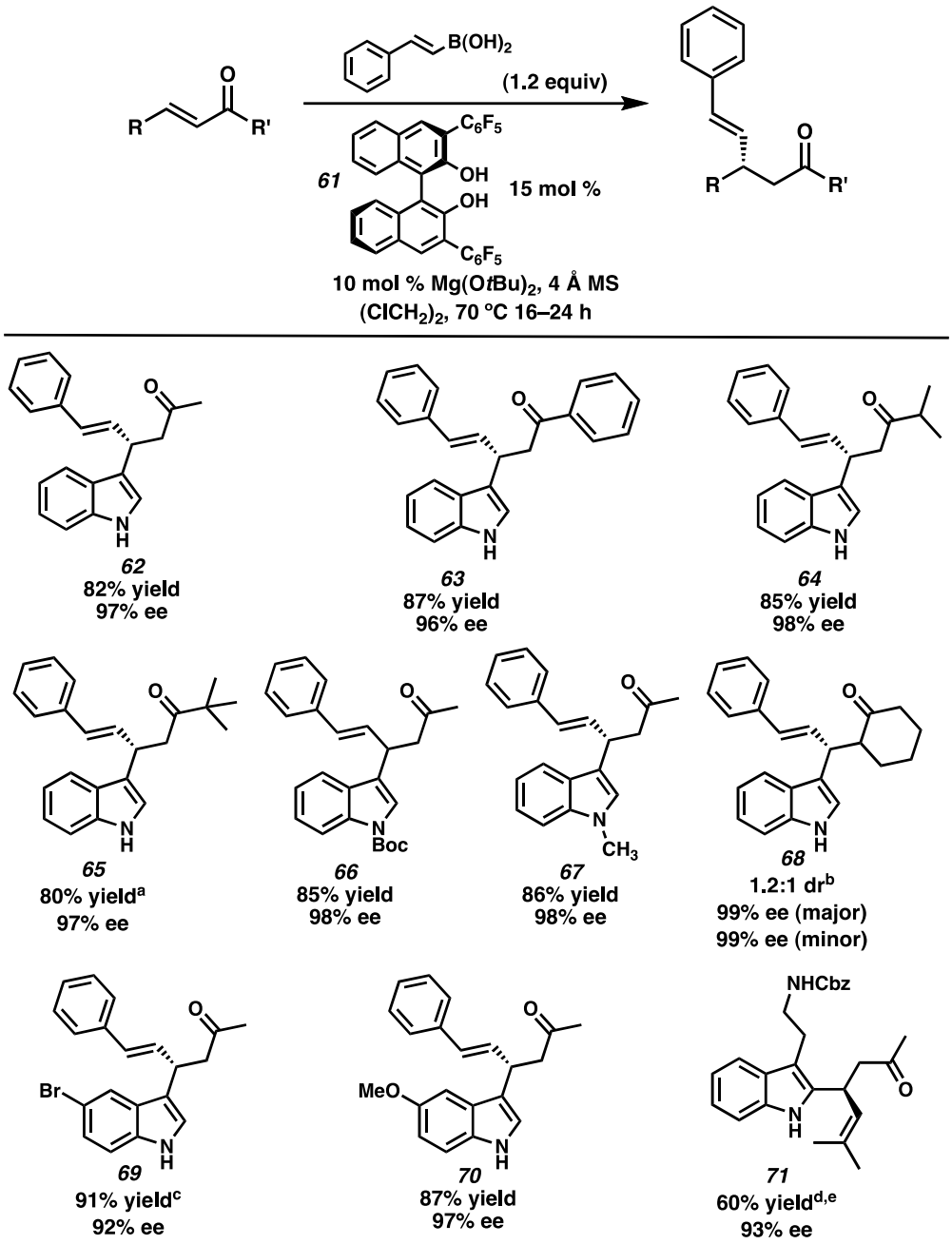


Table 2.4 Indole-appended enone 1,4-addition products. [a]Reaction time 48 h. [b]Determined through integration of NMR peaks for the crude reaction mixture. [c]Reaction time 36 h. [d] 20 mol% 3,3'-diiodobinaphthol catalyst used with 3 equiv of 2,2-dimethylvinylboronic acid. [e] Yield was based on recovered starting material.

2.5 2-Substitued Indoles vs. 3-Substituted Indoles[8]

One of the interesting indoles to take notice of is **71**. It is the only indole in Table 2.4 that has the enone in the 2-position of the indole, while all other examples have the enone in the 3-position of the indole. It is also worthy to note that it had the lowest yield of any of the indoles in the table. This observation was troublesome so a few experiments were run to try to figure out if the problem lies in the electronics of the indoles with the enone in the 2-position, or if it is a steric possibility as that is the only indole that also has substitution on the carbon adjacent to the enone position. Figure 2.5 shows our comparison in which conclusions will be discussed.

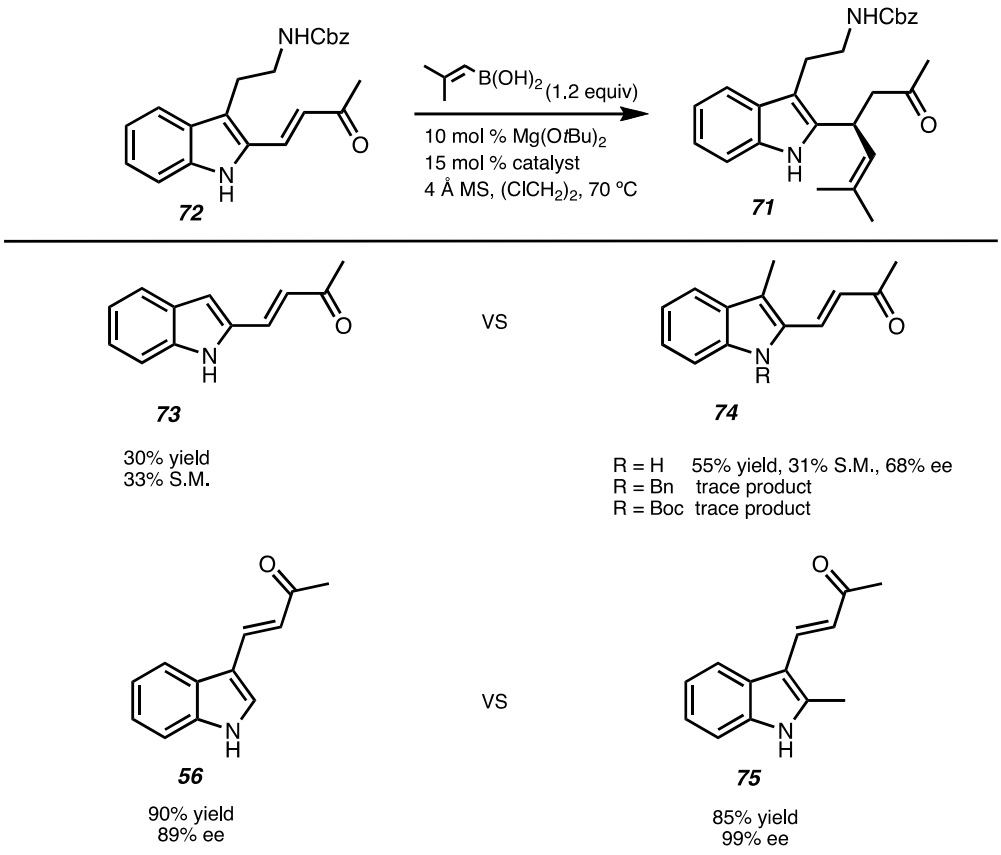


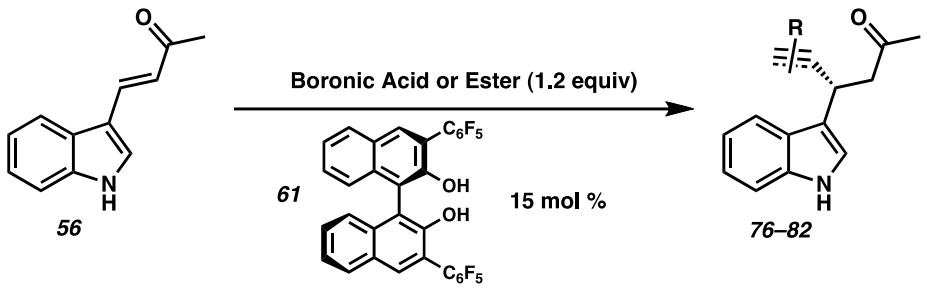
Figure 2.5 Exploration of steric and electronic effects on both indoles with the enone in 2-position versus indoles with the enone in the 3-position

Figure 2.5 shows the reaction yields of indoles that have double substitution patterns to test for the steric effects of the extra substitution adjacent to the enone position on the indole, as well as a couple of examples that do not have the substitution on the indole to examine if there is an electronic effect hindering the reactivity of indoles with the enone in the 2-position. It is shown in indole **73** versus indole **56** that when there is no extra substituent on the indole ring adjacent to the enone position, the indole with the enone on the 3-position greatly outperforms the indole with the enone on the 2-position. When looking at indole **74**, which has an extra substituent on the ring, the reactivity is not satisfactory. Even if the indole is protected with a Bn- or Boc-protecting group, it actually hurts the reactivity greatly. However, indole **75** has the same type of substitution pattern in reverse, and it reacts with good yield and excellent enantioselectivity. Therefore, it can be concluded that sterics don't seem to affect the reactivity of the substrates, however the position of the enone has a great affect on the reactivity. Several optimization attempts of indoles with the enone in the 2-position were attempted with very little success. However, some key observations made during the optimization attempts is that using $Mg(O\textit{t}Bu)_2$ causes rapid decomposition of the product formation. In addition, decomposition of the formed product tends to occur if the reaction is allowed to run longer, no matter what additive is included in the reaction.

2.6 Boronic Acid Versatility

After determining the scope of the indoles compatible with our reaction, enone **56** was treated with a variety of different boronic acids as shown in Scheme 2.6. Alkylvinylboronic acids with different substitution patterns such as dimethylvinyl (**76**),

1,2-dimethylbutene (**77**), as well as vinylcyclohexyl boronic acid (**78**) were all tolerated. In addition arylvinylboronic acids were also compatible such as styrenyl (**79**), para-fluorostyrenyl (**80**), as well as para-methoxystyrenyl (**81**). We also showed the possibility of using alkynylboronic esters (**82**) as nucleophiles. The reason for using the boronic ester in this case was due to the inability to handle the boronic acid due to stability issues. So overall, aliphatic boronic acids, cyclic and acyclic, as well as aromatic boronic acids were reactive. Electron-donating aromatics and electron-withdrawing aromatics in addition to alkynyl nucleophiles were also tolerated.



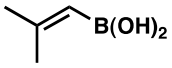
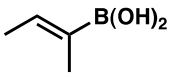
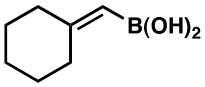
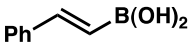
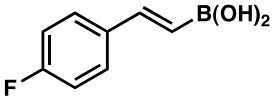
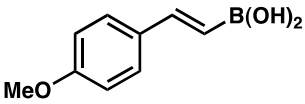
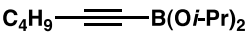
entry	boronic acid	product	yield[a]	ee
1		*76*	90%[b]	89%
2		*77*	82%[c]	96%
3		*78*	74%	87%
4		*79*	87%	96%
5		*80*	86%	96%
6		*81*	85%	94%
7		*82*	71%[b,d]	98%

Table 2.6 Alkenyl and alkynyl nucleophile scope. [a]All yields are isolated yields averaged over 2-3 reactions. [b]3 equiv of boronic acid or ester. [c]PhMe was used as solvent at 115 ºC in a sealed tube. [d]Mg(O*t*-Bu)$_2$ omitted.

2.7 Conclusion

Shown in this chapter was the method we developed in our lab for a highly efficient and stereoselective 1,4-conjugate addition on unprotected indoles. It was shown that the reaction is very versatile in not only the indoles that are compatible, but also the boron nucleophiles that are tolerated. This is the first example of the ability to undergo these conjugate additions in an enantioselective manner on unprotected indoles, which should prove to be a very powerful tool for synthetic chemists.

2.8 Experimental Section

2.8.1 General Considerations

All of the reactions were performed in flame- or oven-dried glassware. THF, Et_2O, toluene, MeCN, and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash column chromatography was performed on 60Å silica gel (Sorbent Technologies). Preparative plate chromatography was performed on EMD silica gel plates, 60Å, with UV-254 indicator. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using TMS or residual solvent peak as an internal standard. Hexafluorobenzene (δ = -164.9) was employed as an external standard in ^{19}F NMR spectra. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm.

2.8.2 Materials

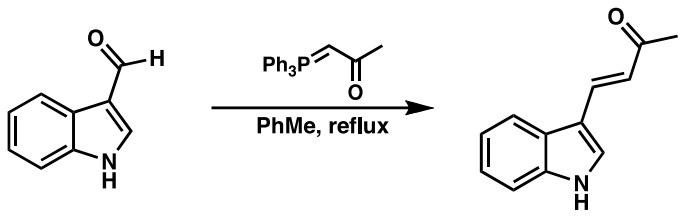
Commercially available compounds were purchased from Aldrich, Acros, or Alfa Aesar and were used without further purification.

2.8.3 General Reaction Procedure for Conjugate Addition Optimization

A 2-dram vial was charged with a magnetic stir bar and 4Å powdered molecular sieves and then was flame-dried under high vacuum. Indole enone (**56**) or furanyl enone (**58**), catalyst, additive, boronic acid, and solvent were added under argon atmosphere. The vial was sealed, and the reaction mixture was vigorously stirred at the indicated temperature. After cooling the reaction mixture to room temperature, MeOH was added. The reaction mixture was filtered through a plug of celite and washed with MeOH.

2.8.4 Procedures for Starting Material Synthesis

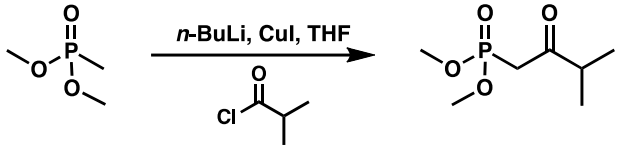
2.8.4.1 Synthesis of (*E*)-(1 *H*-indol-3-yl)but-3-en-2-one (56)



To a flask equipped with a stir bar and a condenser was added indole-3-carboxaldehyde (1.5 g, 10.33 mmol, 1.0 equiv), 1-(triphenylphosphoranylidene)-2-propanone (4.1 g, 12.92 mmol, 1.25 equiv), and toluene (14 mL). The reaction mixture was refluxed for 20 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via column chromatography with a

gradient of 10–40% ethyl acetate in hexanes as eluent on silica gel. (1.38 g, 7.45 mmol, 74% yield) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (bs, 1H), 7.87 (d, J = 7.4 Hz, 1H), 7.72 (d, J = 16.0 Hz, 1H), 7.48 (d, J = 2.8 Hz, 1H) 7.36 (d, J = 7.4 Hz, 1H), 7.24-7.18 (m, 2H), 6.74 (d, J = 16.0 Hz, 1H), 2.32 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 199.4, 138.0, 137.6, 130.0, 125.6, 123.8, 123.4, 122.0, 120.8, 113.8, 112.3, 27.7 ppm. IR (neat): 3139, 2932, 2887, 1659, 1555, 1497, 1446, 1364, 1270, 1247, 1225, 1132, 973, 768 cm^{-1}. Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56; O, 8.64. Found: C, 77.40; H, 6.02; N, 7.53; O, 9.05. R_F: 0.22 in 50% ethyl acetate in hexanes.

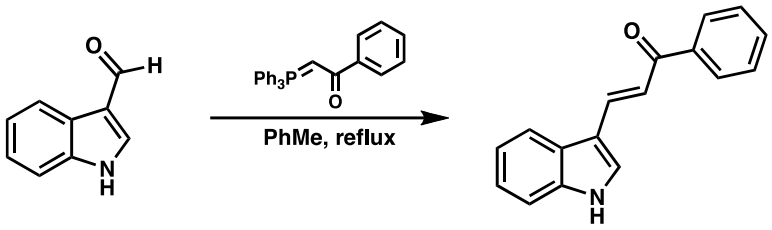
2.8.4.2 Synthesis of Dimethyl 3-methyl-2-oxobutylphosphonate



A slightly modified approach to that previously used.[9] To a flame-dried flask equipped with a stir bar was added THF (90 mL) and *n*-BuLi (2.5 *M* in hexane, 4.1 mL, 10.2 mmol, 1.1 equiv) and this was cooled to -78 ºC. Dimethyl methylphosphonate (1.0 ml, 9.2 mmol, 1.0 equiv) was then added to the flask dropwise. This solution was stirred for 15 minutes, and then CuI (1.93 g, 10.2 mmol, 1.1 equiv) was added in one portion. The stirred solution was slowly warmed to -30 ºC over 2.5 hours, then held there for 1 hour. The dark grey mixture was then cooled to -40 ºC and isobutyryl chloride (1.5 mL, 14.3 mmol, 1.5 equiv) was added dropwise. The reaction was allowed to slowly warm to room temperature and stirred for 20 hours. Water (40 mL) was added to quench the reaction with a concomitant color change from light yellow to yellow-orange, and then

chloroform (100 mL) was added. The resulting suspension was filtered through a cotton pad and rinsed with chloroform. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, and pure ketophosphonate was obtained via column chromatography with a gradient of 5–10% ethyl acetate in hexanes as eluent on silica gel. (1.70 g, 8.76 mmol, 95% yield). All spectral properties were identical to those reported in the literature.[9] (Work done by Dr. Jeremy May)

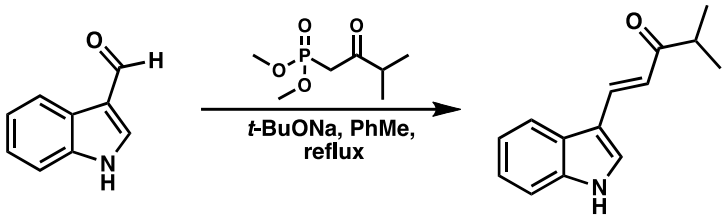
2.8.4.3 Synthesis of (*E*)-3-(1*H*-indol-3-yl)-1-phenylprop-2-en-1-one, precursor to 63



To a flask equipped with a stir bar and a condenser was added indole-3-carboxaldehyde (250 mg, 1.72 mmol, 1.0 equiv), 1-(triphenylphosphoranylidene)-2-propanone (820 mg, 2.15 mmol, 1.25 equiv) and toluene (2.2 mL). The reaction was allowed to reflux for 17 hours. After completion, the crude reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was then purified via column chromatography with 30% ethyl acetate in hexanes as eluent on silica gel. (355 mg, 1.43 mmol, 83% yield) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (bs, 1H), 8.04 (d, J = 15.4 Hz, 1H), 8.00-7.94 (m, 3H), 7.55-7.49 (m, 3H), 7.46-7.43 (m, 2H), 7.40-7.36 (m, 1H), 7.26-7.22 (m, 2H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 191.4, 139.4, 139.3, 137.6, 132.6, 130.7, 128.9, 128.7, 125.7, 123.9, 122.1, 121.1, 121.0, 118.2, 114.8, 112.3

ppm. IR (neat): 3147, 2927, 1640, 1591, 1553, 1521, 1368, 1278, 1208, 1033, 1018, 770, 745 cm^{-1}. Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66; O, 6.47. Found: C, 82.28; H, 5.16; N, 5.60; O, 6.96. R_F: 0.39 in 50% ethyl acetate in hexanes.

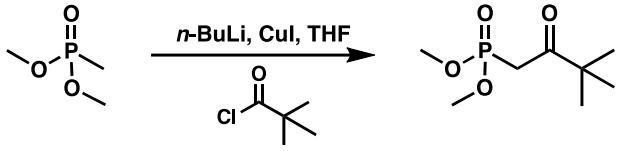
2.8.4.4 Synthesis of (*E*)-1-(1*H*-indol-3-yl)-4-methylpent-1-en-3-one, precursor to 64



To a flask charged with dimethyl 3,3-dimethyl-2-oxobutylphosphonate (418 mg, 2.15 mmol, 1.25 equiv) and equipped with a magnetic stir bar was added indole-3-carboxaldehyde (250 mg, 1.2 mmol, 1.0 equiv) and toluene (17 mL). *t*-BuONa (182 mg, 1.89 mmol, 1.1 equiv) was then added and the flask was equipped with a condenser. The reaction mixture was refluxed for 23 hours, and then allowed to cool to room temperature. Saturated aq. $NaHCO_3$ solution was added to the reaction, and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, and the organic phase was dried over $MgSO_4$. After the solvent was removed via rotary evaporation, the crude mixture was purified via column chromatography using a 20–30% gradient of ethyl acetate in hexanes as the eluent to afford product. (210.5 mg, 0.987 mmol, 57% yield) (Work done by Dr. Jeremy May) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (bs, 1H), 7.87 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.83 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.38-7.34 (m, 1H), 7.23-7.19 (m, 2H), 6.82 (d, *J* = 16.0 Hz, 1H), 2.89 (septet, *J* = 6.8 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 205.0,

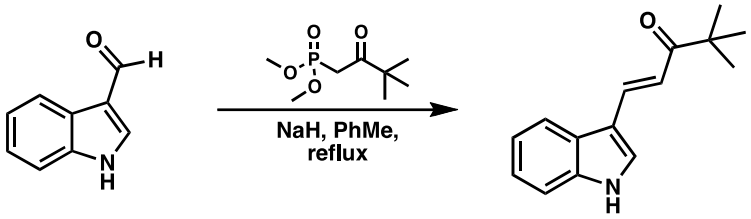
137.5, 136.9, 130.1, 125.7, 123.7, 121.9, 120.8, 120.6, 114.1, 112.3, 39.5, 19.2 ppm. IR (neat): 3187, 2966, 1669, 1582, 1564, 1433, 1266, 1249, 1132, 1115, 1060, 731 cm^{-1}. R_F: 0.45 in 50% ethyl acetate in hexanes.

2.8.4.5 Dimethyl 3,3-dimethyl-2-oxobutylphosphonate



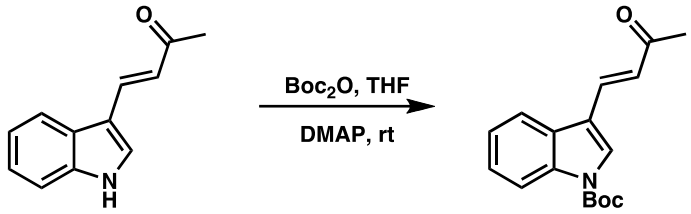
To a flame-dried flask equipped with a stir bar was added THF (90 mL) and *n*-BuLi (2.5 *M* in hexane, 4.1 mL, 10.15 mmol, 1.1 equiv), and this was cooled to -78 ºC. dimethyl methylphosphonate (1.0 mL, 9.23 mmol, 1.0 equiv) was then added to the flask dropwise. This solution was stirred for 15 minutes, and then CuI (1.93 g, 10.15 mmol, 1.1 equiv) was added in one portion. Then, the stirred solution was slowly warmed to -30 ºC over 2.5 hours and held there for 1 hour. The dark grey mixture was cooled to -40 ºC and pivaloyl chloride (1.14 mL, 9.25 mmol, 1.0 equiv) was added dropwise. The reaction was allowed to slowly warm to room temperature and stirred for 20 hours. Water (40 mL) was added to quench the reaction with a concomitant color change from light yellow to yellow-orange, and then chloroform (100 mL) was added. The resulting suspension was filtered through a cotton plug and rinsed with chloroform. The phases were separated and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, and pure ketophosphonate was obtained via column chromatography with a gradient of 5–10% ethyl acetate in hexanes as eluent on silica gel. All spectral properties were identical to those reported in the literature.[9] (Work done by Dr. Jeremy May)

2.8.4.6 Synthesis of (*E*)-1-(1*H*-indol-3-yl)-4,4-dimethylpent-1-en-3-one, precursor to 65



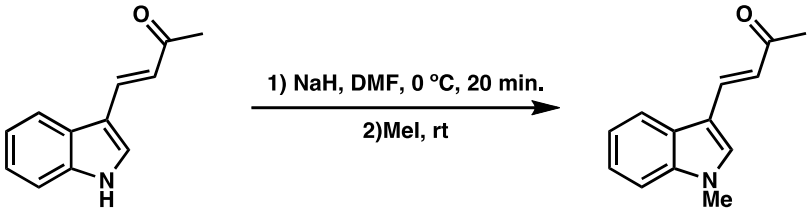
To a flask charged with NaH (69.0 mg, 1.72 mmol, 1.25 equiv) and equipped with a magnetic stir bar was added THF (15 mL), followed by dimethyl 3,3-dimethyl-2-oxobutylphosphonate (573.7 mg, 2.76 mmol, 2.0 equiv) added in a dropwise fashion. Indole-3-carboxaldehyde (200.0 mg, 1.38 mmol, 1.0 equiv) was then added and the flask was equipped with a condenser. The reaction mixture was refluxed for 16 hours, and then allowed to cool to room temperature. Saturated aq. $NaHCO_3$ solution was added to the reaction, and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, and the organic phase was dried over $MgSO_4$. After the solvent was removed via rotary evaporation, the crude mixture was purified via column chromatography using 20% ethyl acetate in hexanes as the eluent to afford the product. (219.2 mg, 0.964 mmol, 70% yield) (Work done by Dr. Jeremy May) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (bs, 1H), 7.90-7.84 (m, J = 2.8 Hz, 2H), 7.47 (d, J = 2.86 Hz, 1H), 7.38-7.34 (m, 1H), 7.23-7.19 (m, 2H), 7.12 (d, J = 15.4 Hz, 1H), 1.20 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 205.4, 137.5, 137.1, 130.0, 125.7, 123.7, 121.8, 120.9, 117.1, 114.6, 112.2, 43.3, 27.1 ppm. IR (neat): 3220, 2964, 1659, 1581, 1562, 1434, 1390, 1358, 1275, 1082, 1009, 974, 824, 735 cm^{-1}. R_F: 0.57 in 50% ethyl acetate in hexanes.

2.8.4.7 Synthesis of (*E*)-*tert*-butyl-3-(3-oxobut-1-enyl)-1*H*-indole-1-carboxylate, precursor to 66



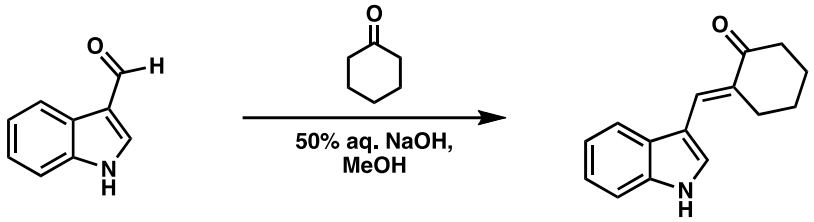
To a flask equipped with a stir bar was added 4-(1H-indol-3-yl)but-3-en-2-one (250 mg, 1.35 mmol, 1.0 equiv) and THF (16 mL). Di-*t*-butyl dicarbonate (442 mg, 2.02 mmol, 1.5 equiv) and 4-(dimethylamino)pyridine (16.5 mg, 0.13 mmol, 0.1 equiv) were then added and the reaction mixture was allowed to stir at room temperature for 20 minutes. After completion, water was added. The organic layer was then extracted with ethyl acetate. The reaction mixture was concentrated via rotary evaporation and purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel to afford product. (357 mg, 1.25 mmol, 93% yield) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18-8.06 (m, 1H), 7.82 (s, 1H), 7.80-7.75 (m, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.34-7.23 (m, 2H), 6.77 (d, *J* = 16.0 Hz, 1H), 2.32 (s, 3H), 1.61 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 198.7, 149.3, 136.6, 135.6, 129.4, 128.1, 126.8, 125.7, 124.0, 120.6, 117.0, 115.9, 85.1, 28.4, 27.8 ppm. IR (neat): 2981, 1737, 1605, 1452, 1366, 1309, 1232, 1151, 1096, 853, 743 cm^{-1}. Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91; O, 16.82. Found: C, 71.01; H, 6.57; N, 4.79; O, 17.63. R_F: 0.29 in 20% ethyl acetate in hexanes.

2.8.4.8 Synthesis of (*E*)-4-(1-methyl-1*H*-1-indol-3-yl)but-3-en-2-one, precursor to 67



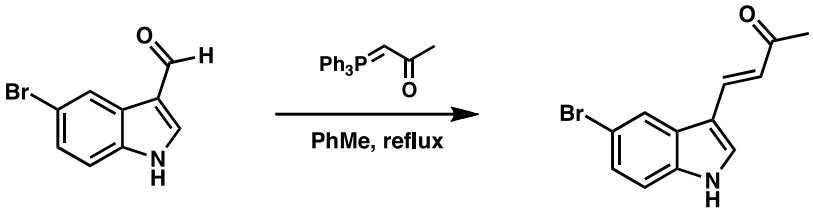
(*E*)-4-(1H-indol-3-yl0but-3-en-2-one (250 mg, 1.35 mmol, 1.0 equiv) was treated with NaH (40 mg, 1.62 mmol, 1.2 equiv) in DMF (3 mL) at room temperature for 20 minutes. Methyl iodide (253 μL, 4.86 mmol, 3.0 equiv) was then added to the reaction mixture at room temperature. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with water and brine solution. The organic layer was dried with Na_2SO_4 and filtered. The solvent was then removed via rotary evaporation. The crude product was then purified via column chromatography with 10–30% gradient of ethyl acetate in hexanes on silica gel. (170 mg, 0.853 mmol, 63% yield) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 16.0 Hz, 1H), 7.29-7.24 (m, 3H), 7.20-7.17 (m, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 3.72 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 198.9, 138.5, 137.4, 134.0, 126.3, 123.4, 122.7, 121.8, 120.9, 112.3, 110.4, 33.6, 27.7 ppm. IR (neat): 3100, 3043, 2935, 1671, 1581, 1563, 1532, 1376, 1280, 1194, 1180, 980, 736 cm^{-1}. R_F: 0.30 in 50% ethyl acetate in hexanes.

2.8.4.9 Synthesis of (*E*)-2-((1*H*-indol-3-yl)methylene)cyclohexanone, precursor to 68



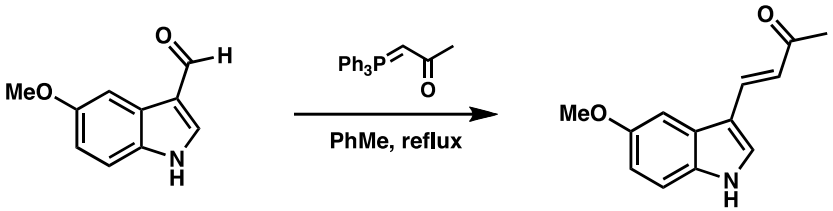
To a flask with indole-3-carboxaldehyde (500 mg, 3.444 mmol, 1.0 equiv) was added MeOH (2.5 mL) followed by cyclohexanone (535 μL, 5.167 mmol, 1.5 equiv). 50% aq. NaOH (2.5 mL) was added to the reaction mixture and the reaction was allowed to stir for 5 days at room temperature. After 5 days, 1 *M* HCl was added to the reaction mixture and the product precipitated from solution. The reaction mixture was filtered through a filter funnel and the collected precipitate was washed with MeOH to afford the desired product (305 mg, 1.354 mmol, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (bs, 1H), 8.00 (t, *J* = 2.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 2.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.23-7.15 (m, 2H), 2.71 (td, *J* = 6.3, 2.2 Hz, 2H), 2.47 (t, *J* = 6.3 Hz, 2H), 1.89-1.77 (m, 4H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 200.8, 135.8, 131.6, 128.5, 128.4, 126.5, 123.7, 121.4, 119.6, 113.8, 111.5, 40.2, 30.1, 23.9, 23.5 ppm. IR (neat): 3150, 2874, 1645, 1539, 1489, 1437, 1375, 1325, 1247, 1139, 742 cm^{-1}. R_F: 0.32 in 50% ethyl acetate in hexanes.

2.8.4.10 Synthesis of (*E*)-4-(5-bromo-1*H*-indol-3-yl)but-3-en-2-one, precursor to 69



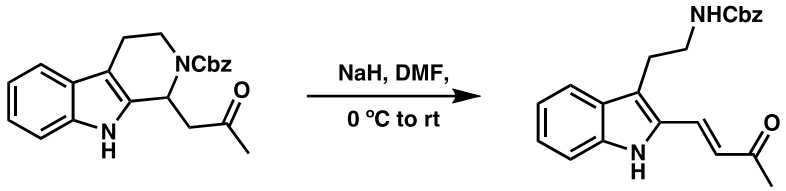
To a flask equipped with a stir bar and a condenser was added 5-bromoindole-3-carboxaldehyde (300 mg, 1.33 mmol, 1.0 equiv), 1-triphenylphorphoranyldene)-2-propanone (533 mg, 1.67 mmol, 1.25 equiv) and toluene (3 mL). The reaction mixture was allowed to reflux for 24 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was then purified via column chromatography with a 10-40% gradient of ethyl acetate in hexanes as eluent on silica gel. (250 mg, 0.947 mmol, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (bs, 1H), 7.99 (d, *J* = 1.7 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.32 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 2.32 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 198.9, 136.7, 136.0, 130.1, 127.3, 126.8, 124.1, 123.5, 115.4, 113.6, 13.5, 27.8 ppm. IR (neat): 3153, 3029, 2941, 2903, 1612, 1514, 1454, 1431, 1267, 1233, 1122, 955, 799 cm^{-1}. Anal. Calcd. for $C_{12}H_{10}BrNO$: C, 54.56; H, 3.82; N, 3.82; Br, 30.25; O, 6.06. Found: C, 55.05; H, 3.72; N, 5.31; Br, 29.52; O, 6.40. R_F: 0.21 in 50% ethyl acetate in hexanes.

2.8.4.11 Synthesis of (*E*)-4-(5-methoxy-1*H*-indol-3-yl)but-3-en-2-one, precursor to 70



To a flask equipped with a stir bar and a condenser was added 5-methoxyindole-3-carboxaldehyde (300 mg, 1.71. mmol, 1.0 equiv), 1-(triphenylphosphoranylidene)-2-propanone (681 mg, 2.14 mmol, 1.25 equiv) and toluene (3 mL). The reaction mixture was allowed to reflux for 24 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was purified via column chromatography with a 10-40% gradient of ethyl acetate in hexanes as eluent on silica gel. (225 mg, 1.05 mmol, 61% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (bs, 1H), 7.71 (d, *J* = 16.0 Hz, 1H), 7.45 (d, *J* = 2.8 Hz, 1H), 7.27-7.24 (m, 2H), 6.88 (dd, *J* = 9.1, 2.2 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 3.83 (s, 3H), 2.32 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 199.3, 155.9, 138.1, 132.4, 130.1, 126.3, 123.0, 113.8, 113.6, 112.9, 102.8, 56.3, 27.5 ppm. IR (neat): 3173, 3105, 3058, 2911, 1603, 1512, 1483, 1446, 1268, 1249, 1216, 1148, 1074, 791, 717 cm^{-1}. R_F: 0.16 in 50% ethyl acetate in hexanes.

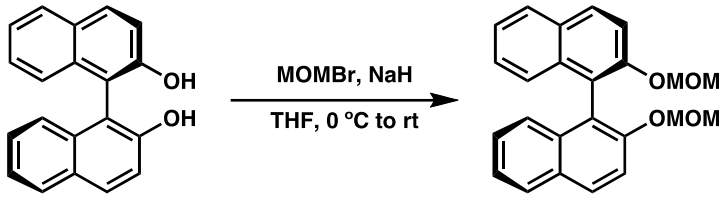
2.8.4.12 Synthesis of (*E*)-benzyl-2-(2-(3-oxobut-1-enyl)-1*H*-indol-3-yl)ethylcarbamate 72[10,11]



To a solution of starting material (3.39 g, 10.8 mmol, 1.0 equiv) in DMF (80 mL) was added NaH (60% dispersion in mineral oil, 0.65 g, 16.3 mmol, 1.5 equiv) at 0 ºC. The mixture was stirred at 0 ºC for 30 min then stirred at room temperature for 2 hours. After completion, the reaction was quenched with water and diluted with dichloromethane. The organic phase was then extracted with dichloromethane (30 mL x 3). The organic layer was washed with water and brine solution, dried with Na_2SO_4, filtered, and concentrated via rotary evaporation. The crude product was purified with 25% ethyl acetate in hexanes on silica gel. (3.54 g, 9.43 mmol, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (bs, 1H), 7.57-7.54 (m, 2H), 7.30-7.19 (m, 7H), 7.04 (t, J = 7.4 Hz, 1H), 6.42 (d, J = 16.6 Hz, 1H), 5.10-5.03 (m, 2H), 4.76 (bt, J = 6.3 Hz, 1H), 3.41 (dd, J = 13.1 Hz, 6.8 Hz, 2H), 3.07 (app. t, J = 6.8 Hz, 2H), 2.30 (s, 3H) ppm. ^{13}C NMR (125.77 Hz, $CDCl_3$): δ 198.4, 156.7, 138.0, 136.7, 131.0, 128.9, 128.6, 128.5, 128.4, 125.8, 124.1, 120.7, 120.1, 111.7, 67.0, 42.2, 27.5, 25.1 ppm. IR (neat): 3325, 1689, 1607, 1529, 1326, 1264, 1139, 1078, 1008, 741 cm^{-1}. R_F: 0.21 in 40% ethyl acetate in hexanes.

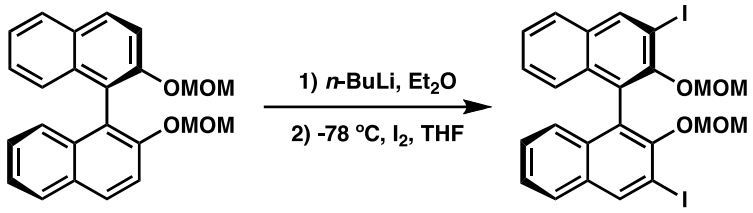
2.8.5 Procedures for Catalyst Synthesis

2.8.5.1 Synthesis of (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl



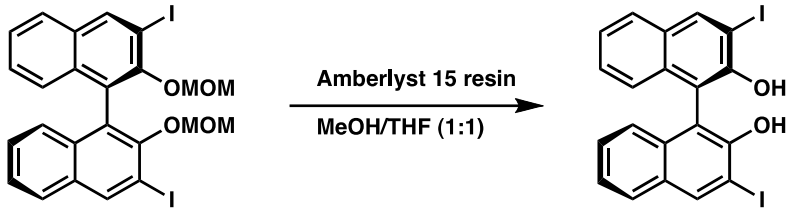
Compound was prepared as previously described in the literature.[5] To a flame-dried flask equipped with a stir bar and addition funnel was added NaH (60% dispersion in mineral oil, 1.23 g, 30.73 mmol, 2.2 equiv) and THF (50 mL) and was cooled to 0 ºC. *R*-(+)-BINOL (4.00 g, 13.97 mmol, 1.0 equiv) dissolved in THF (20 mL) was then added dropwise through the addition funnel. The reaction mixture was stirred at 0 ºC for 1 hour, then at room temperature for 30 min. The mixture was cooled back down to 0 ºC and MOM-Br (2.85 mL, 34.93 mmol, 2.5 equiv) was added dropwise. The reaction was allowed to stir at room temperature for 30 min. After completion, the reaction mixture was quenched with saturated aq. NH_4Cl, extracted with CH_2Cl_2, and washed with brine solution. The organic layer was dried with Na_2SO_4 and the solvent was removed via rotary evaporation. The crude product mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel. (1.39 g, 3.72 mmol, 77% yield).

2.8.5.2 Synthesis of (*R*)-3,3'-diido-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl



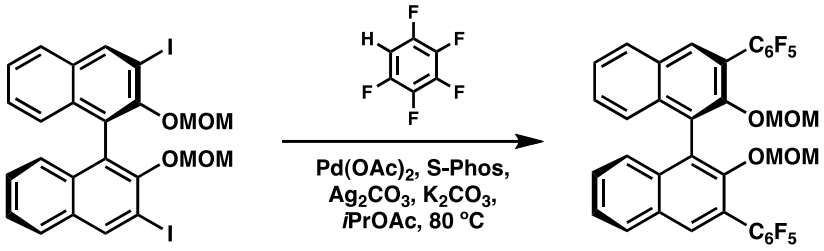
It was prepared as previously described in the literature.[5] To a flame-dried flask equipped with a stir bar was added MOM-protected binaphthyl. (3.68 g, 9.82 mmol, 1.0 equiv) and Et_2O (196 mL) 2.5 *M* *n*-BuLi (11.8 mL, 29.46 mmol, 3.0 equiv) was added to the reaction. The reaction mixture was allowed to stir for 4 hours at room temperature. THF (94 mL) was then added and the reaction stirred for 45 min. The reaction mixture was then cooled to 0 ºC and I_2 (7.48 g, 29.46 mmol, 3.0 equiv) was added as one portion. The reaction was allowed to slowly warm to rt and stir overnight. After completion, Et_2O was added and the organic layer was washed with 10% aq. $Na_2S_2O_3$ followed by brine solution. The organic layer was dried with Na_2SO_4 and the solvent was removed via rotary evaporation. The crude product mixture was then purified via column chromatography with 5% ethyl acetate in hexanes as eluent on silica gel. (3.77g, 6.02 mmol, 61% yield).

2.8.5.3 Synthesis of (*R*)-3,3'-diiodo-1,1'-binaphthyl-2,2'-diol (37)



Compound **37** was prepared as previously described in the literature.[5] To starting compound (2.25 g, 3.59 mmol) was added MeOH (35 mL) and THF (35 mL). Amberlyst 15 resin (2g) was then added and the reaction was allowed to reflux at 65 ºC overnight. After completion, the resin was filtered off and the organic layer concentrated to reduce solvent amount. The organic layer was then passed through a silica plug with 20% ethyl acetate in hexanes as eluent to afford the hydrolyzed product. (1.82 g, 3.38 mmol, 94% yield).

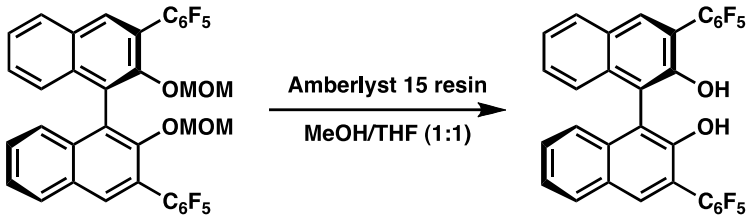
2.8.5.4 Synthesis of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(perfluorophenyl)-1,1'-binapththyl



To a flame-dried sealable flask equipped with a magnetic stir bar was added K_2CO_3 (830 mg, 6.00 mmol, 4.0 equiv), Ag_2CO_3 (414 mg, 1.50 mmol, 1.0 equiv), S-Phos (148 mg, 0.24 equiv), and $Pd(OAc)_2$ (40.4 mg, 0.12 equiv). To this mixture pentafluorobenzene (0.5 mL, 4.50 mmol, 3.0 equiv) and *i*-PrOAC (1.5 mL) were added. The reaction mixture was allowed to stir for 1 min at room temperature before the

addition of 3,3'-diido-2-2'-bis(methoxymethoxy)-1,1'-binaphthyl (940 mg, 1.50 mmol, 1.0 equiv). The reaction temperature was increased to 80 ºC and stirred at this temperature for 12 hours. The reaction mixture as then cooled to room temperature and passed through a plug of celite, washing with ethyl acetate. After removal of solvents via rotary evaporation, the reaction mixture was purified by column chromatography on silica gel using 5% ethyl acetate in hexanes as eluent. The product was obtained as a white solid (524 mg, 0.742 mmol, 50% yield) and the spectral data agreed with the reported data.[12] (Work done by Santa Jansone-Popova)

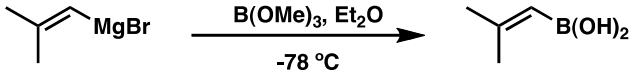
2.8.5.5 (*R*)-3,3'-bis(perfluorophenyl)-1,1'-binaphthyl-2,2'-diol (61)



To starting material (2.25 g, 3.59 mmol, 1.0 equiv) was added MeOH (8 mL) and THF (8 mL). Amberlyst 15 resin (0.08 g) was then added and the reaction was refluxed overnight. After completion, the resin was filtered off and the solvent removed via rotary evaporation. The reaction mixture was then purified by column chromatography on silica gel using 5% ethyl acetate in hexanes as eluent. The product was a white solid (542 mg, 0.742 mmol, 98% yield). All spectral properties were identical to those reported.[13]

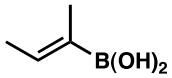
2.8.6 Procedures for Boronic Acid/Ester Synthesis

2.8.6.1 Synthesis of 2-methylprop-1-enylboronic[14]



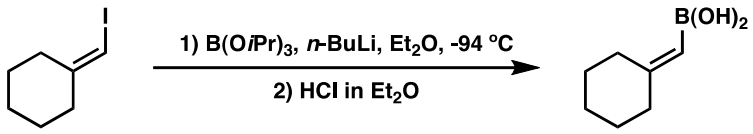
To a flame-dried flask fitted with an addition funnel was added trimethyl borate (3.92 mL, 34.5 mmol, 1.1 equiv), and Et_2O (73 mL). The solution was cooled to -78 ºC. 0.5 *M* 2-Methyl-2-propenyl magnesium bromide in THF (63 mL, 31.35 mmol, 1.0 equiv) was added slowly through the addition funnel. The reaction was allowed to slowly warm to room temperature and stir overnight. The next day it was quenched with 1 *M* HCl until the reaction mixture becomes clear and stirred for 1 hour. It was then extracted with Et_2O and washed with saturated aq. $NaHCO_3$ and brine solution. The organic layer was dried with Na_2SO_4 and then concentrated via rotary evaporation. The crude solid was recrystallized with hexanes in Et_2O. (1.28 g, 12.810 mmol, 41% yield).

2.8.6.2 Synthesis of (Z)-but-2-en-2-ylboronic acid



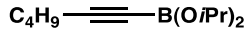
The procedure followed was that as previously reported in the literature.[15] (Work done by Santa Jansone-Popova)

2.8.6.3 Synthesis of Cyclohexylidenemethylboronic acid



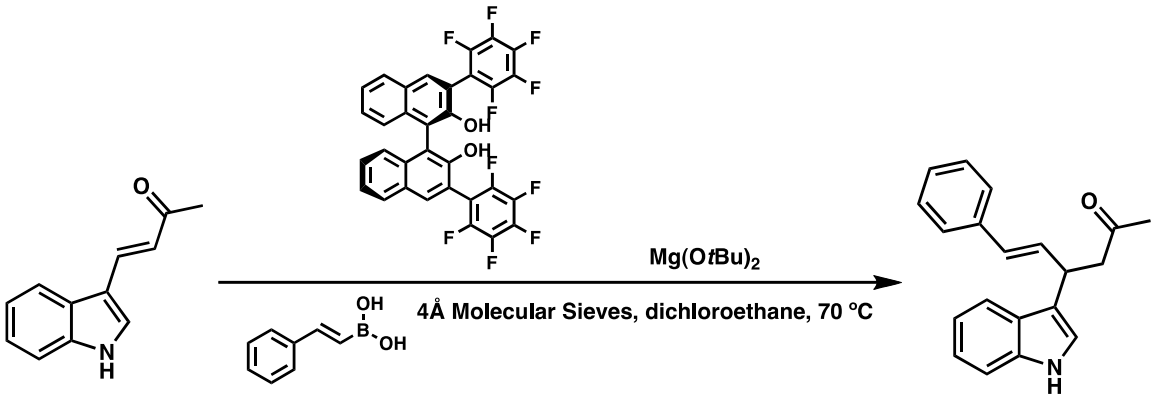
To a flame-dried flask equipped with a stir bar was added (Iodomethylene)cyclohexane) (prepared as reported previously in the literature[16]) (360 mg, 1.62 mmol, 1.0 equiv) and Et_2O (4 mL). The reaction mixture was cooled to -94 ºC (hexane/liquid N_2 bath) and *n*-BuLi (2.5 *M* in hexane, 0.65 mL, 1.62 mmol, 1.0 equiv) was added slowly. The reaction mixture was allowed to stir for 20 min. at -94 ºC. In a separate flame-dried flask equipped with a stir bar was added triisopropylborane (0.37 mL, 1.62 mmol, 1.0 equiv) and Et_2O (2.0 mL). The reaction mixture was cooled to -78 ºC. The vinyl lithium that was generated in the first flask was slowly added to the second flask via cannula. The reaction was allowed to stir at -78 ºC for 2 hours after which a 2.0 *M* HCl solution in Et_2O (0.83 mL, 1.62 mmol, 1.0 equiv) was added. The reaction mixture was allowed to warm to room temperature and then filtered through a celite plug washing with Et_2O. After removal of the solvents, 1 *M* aq. HCl solution (2.0 mL) was added to the reaction mixture. The formed precipitate was filtered off and washed with 10 mL of H_2O followed by 10 mL of pentane affording the product. (81 mg, 36% yield). All spectral properties were identical to those reported in the literature.[17] (Work done by Santa Jansone-Popova)

2.8.6.4 Synthesis of Diisopropyl hex-1-ynylboronate



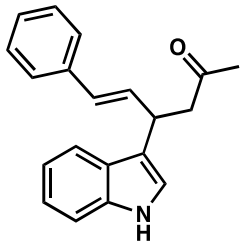
The procedure followed was the same as that previously reported in the literature.[18] (Work done by Santa Jansone-Popova).

2.8.7 General Procedure for 1,4-Conjugate Addition



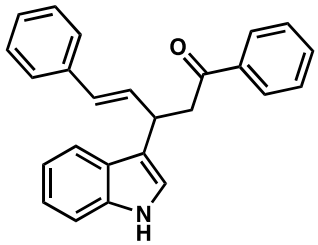
To a flask equipped with a stir bar and a condenser was added 4Å powdered molecular sieves (100 mg) and the flask was flamed-dried under high vacuum. The flask was then back filled with argon. Indole enone (0.22 mmol, 1.0 equiv), $Mg(OtBu)_2$ (3.8 mg, 0.022 mmol, 0.1 equiv), boronic acid (39 mg, 0.26 mmol, 1.2 equiv), and BINOL catalyst (20.4 mg, 0.033 mmol, 0.15 equiv) were then added. Freshly distilled dichloroethane (4.4 mL) was added and the reaction was heated to 70 ºC and allowed to stir at this temperature (see each product for specific reaction times). After completion, methanol was added and the reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was then dry-loaded onto silica gel and purified via column chromatography on silica gel with ethyl acetate in hexanes (see each product for eluent concentrations) as eluent.

2.8.7.1 Synthesis of (*E*)-4-(1*H*-indol-3-yl)6-phenylhex-5-en-2-one (62)



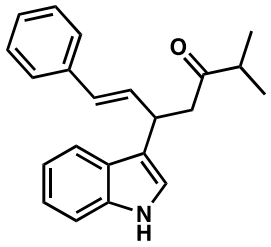
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 18 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 57.6 mg, 0.199 mmol, 90% yield, 98.1:1.9 er; Trial 2: 54.7 mg, 0.189 mmol, 86% yield, 98.6:1.4 er; 53.4 mg, 0.184 mmol, 84% yield, 97.7:2.3 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (bs, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.25 (app. d, *J* = 7.4 Hz, 2H), 7.20 (app. t, *J* = 7.4 Hz, 2H), 7.14-7.10 (m, 2H), 7.03 (app. t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.42-6.33 (m, 2H), 4.32 (dd, *J* = 14.3, 6.8 Hz, 1H), 3.03-2.92 (m, 2H), 2.06 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.0, 137.6, 136.9, 132.5, 130.1, 128.8, 127.5, 126.7, 126.6, 122.5, 121.5, 119.8, 117.8, 111.6, 49.4, 36.1, 30.9 ppm. IR (neat): 3385, 1703, 1337, 1104, 930, 772, 756, 699, 650 cm^{-1}. R_F: 0.55 in 50% ethyl acetate in hexanes.

2.8.7.2 Synthesis of (*E*)-3-(1*H*-indol-3-yl)-1,5-diphenylpent-4-en-1-one (63)



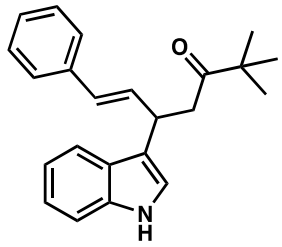
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 16 hours. The crude reaction mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 61.7 mg, 0.175 mmol, 80% yield, 99.0:1.0 er; Trial 2: 64.9 mg, 0.184 mmol, 84% yield, 99.0:1.0; Trial 3: 64.1 mg, 0.182 mmol, 83% yield, 98.0:2.0 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 7.88 (dd, *J* = 7.4, 1.1 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.5, 1.7 Hz, 2H), 7.18-7.16 (m, 2H), 7.14-7.07 (m, 2H), 7.05-7.01 (m, 2H), 6.47-6.39 (m, 2H), 4.54 (dd, *J* = 13.1, 6.3 Hz, 1H) 3.57-3.48 (m, 2H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 199.0, 137.7, 137.5, 136.9, 133.3, 132.7, 130.2, 128.9, 128.7, 128.4, 127.4, 126.8, 126.6, 122.5, 121.6, 119.9, 119.8, 118.3, 111.6, 44.4, 36.1 ppm. IR (neat): 3404, 3028, 1738, 1679, 1450, 1362, 1214, 967, 750, 738, 690 cm^{-1}. R_F: 0.58 in 50% ethyl acetate in hexanes.

2.8.7.3 Synthesis of (*E*)-5-(1*H*-indol-3-yl)-2-methyl-7-phenylhept-6-en-3-one (64)



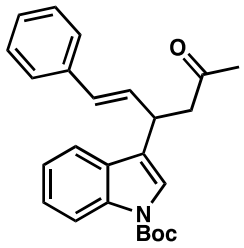
See the general procedure for the 1,4-conjugate addition reaction above. The reaction time for this substrate was 20 hours. The crude reaction mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 61.4 mg, 0.193 mmol, 88% yield, 98.1:1.9 er; Trial 2: 60.1 mg, 0.189 mmol, 86% yield, 98.4:1.6 er; Trial 3: 56.4 mg, 0.178 mmol, 81% yield, 98.1:1.9 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.24 (app. d, *J* = 8.0, 6.8 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.41-6.34 (m, 2H), 4.35 (q, *J* = 12.6, 6.8 Hz, 1H), 3.04-3.00 (m, 2H0, 2.52-2.44 (m, 1H), 0.97 (d, *J* = 7.4 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 213.5, 137.7, 136.9, 132.8, 130.0, 128.7, 127.7, 126.7, 126.5, 122.4, 121.5, 119.9, 119.8, 118.1, 111.6, 46.2, 41.7, 36.0, 18.3, 18.2 ppm. IR (neat): 3422, 2970, 1702, 1456, 1338, 1100, 963, 823, 693 cm^{-1}. R_F: 0.78 in 50% ethyl acetate in hexanes.

2.8.7.4 Synthesis of (*E*)-5-(1*H*-indol-3-yl)-2,2-dimethyl-7-phenylhept-6-en-3-one (65)



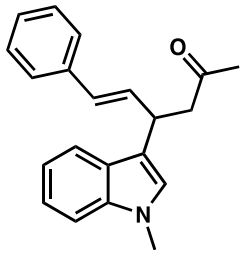
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 48 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 57.9 mg, 0.175 mmol, 79% yield, 98.3:1.7 er; Trial 2: 59.4 mg, 0.179 mmol, 81% yield, 98.6:1.6 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (bs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.24 (dd, J = 8.5, 1.2 Hz, 2H), 7.20-7.17 (m, 2H), 7.13-7.08 (m, 2H), 7.03 (dt, J = 8.0, 1.2 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.37 (app. d, J = 4.5 Hz, 2H), 4.43-4.38 (m, 1H), 3.09-3.03 (m, 2H), 1.00 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 214.2, 137.9, 136.9, 132.8, 130.0, 128.7, 127.3, 126.7, 126.5, 122.4, 121.5, 120.0, 119.7, 118.4, 111.5, 44.6, 42.5, 35.6, 26.4 ppm. IR (neat): 3404, 2966, 1698, 1456, 1336, 1103, 961, 817 cm^{-1}. R_F: 0.86 in 50% ethyl acetate in hexanes.

2.8.7.5 Synthesis of (*E*)-*tert*-butyl 3-(5-oxo-1-phenylhex-1-en-3-yl)-1*H*-indole-1-carboxylate (66)



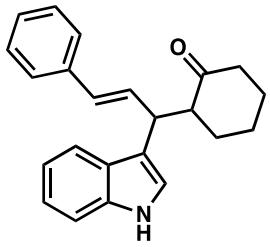
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 18 hours. The crude reaction mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 73.5 mg, 0.189 mmol, 86% yield, 99.0:1.0 er; 72.5 mg, 0.186 mmol, 84% yield, 99.0:1.0 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (bs, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.36 (bs, 1H), 7.24-7.11 (m, 7H), 6.39 (d, J = 16.0 Hz, 1H), 6.29 (dd, J = 16.0, 7.4 Hz, 1H), 4.26 (app. dd, J = 7.4, 6.8 Hz, 1H), 3.01-2.92 (m, 2H), 2.09 (s, 3H), 1.60 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 207.1, 150.2, 137.3, 131.3, 131.0, 129.9, 128.8, 127.7, 126.6, 124.8, 122.8, 122.6, 122.4, 120.0, 115.7, 84.0, 48.6, 35.4, 31.1, 28.6 ppm. IR (neat): 2979, 1724, 1452, 1370, 1256, 1156, 1090, 766, 745, 694 cm^{-1}. R_F: 0.39 in 20% ethyl acetate in hexanes.

2.8.7.6 Synthesis of (*E*)-4-(1-methyl-1*H*-indol-3-yl)-6-phenylhex-5-en-2-one (67)



See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 22 hours. The crude reaction mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes on silica gel. (Trial 1: 58.2 mg, 0.192 mmol, 87% yield, 98.2:1.8 er; Trial 2: 56.1 mg, 0.185 mmol, 84% yield, 98.6:1.4 er; Trial 3: 63.4 mg, 0.209 mmol, 94% yield, 98.7:1.3 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.26-7.09 (m, 5H), 7.01 (td, *J* = 8.0, 1.1 Hz, 1H), 6.83 (s, 3H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.34 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.30 (app. t, *J* = 6.8 Hz, 1H), 3.68 (s, 3H), 3.01-2.91 (m, 2H), 2.05 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.1, 137.6, 137.5, 132.7, 129.9, 128.7, 127.4, 127.1, 126.5, 126.3, 122.0, 119.8, 119.2, 116.1, 109.7, 49.5, 36.1, 33.0, 30.8 ppm. IR (neat): 2937, 1711, 1475, 1357, 1328, 1245, 1156, 966, 742, 695 cm^{-1}. R_F: 0.56 in 50% ethyl acetate in hexanes.

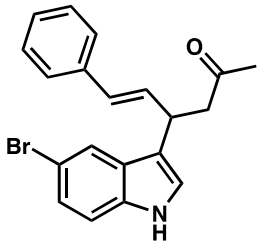
2.8.7.7 Synthesis of (*E*)-2-(1-(1*H*-indol-3-yl)-3-phenylallyl)cyclohexanone (68)



See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 17 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. The diastereomers were separated for characterization by preparatory TLC using 20% ethyl acetate in hexanes as eluent and running the plate 5 times. (Trial 1: 48.4 mg, 0.147 mmol, 67% yield, 1.2:1.0 dr, major diastereomer 99.7:0.3 er, minor diastereomer 99.6:0.4 er; Trial 2: 51.5 mg, 0.156 mmol, 71% yield, 1.1:1.0 dr, major diastereomer 99.5:0.5 er, minor diastereomer 99.2:0.8 er; Trial 3: 52.3 mg, 0.159 mmol, 72% yield, 1.2:1.0 dr, major diastereomer 99.3:0.7 er, minor diastereomer 99.0:1.0 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ major diastereomer: 7.97 (bs, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.18-7.01 (m, 6H), 6.53 (dd, *J* = 16.0 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 4.12 (t, *J* = 8.5 Hz, 1H), 2.98-2.93 (m, 1H), 2.41-2.36 (m, 1H), 2.34-2.28 (m, 1H), 1.91-1.88 (m, 1H), 1.81-1.67 (m, 3H), 1.57-1.41 (m, 2H) ppm; minor diastereomer: δ 7.94 (bs, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.27 (app. t, *J* = 6.8 Hz, 3H), 7.21-7.16 (m, 2H), 7.12-7.09 (m, 2H), 7.05-7.02 (m, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.35 (dd, *J* = 16.0, 8.5 Hz, 1H), 4.37 (t, *J* = 8.0 Hz, 1H), 2.90-2.86 (m, 1H), 2.37-2.33 (m, 1H), 2.21-2.15 (m, 1H), 2.11-2.06 (m, 1H), 1.91-1.84 (m, 2H), 1.73-1.68 (m, 2H), 1.61-1.57 (m, 1H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ major diastereomer: 213.5, 137.8,

136.7, 132.1, 130.1, 128.7, 127.3, 126.6, 122.9, 122.3, 119.9, 119.7, 116.4, 111.6, 55.8, 42.7, 40.4, 32.8, 28.8, 24.5 ppm; minor diastereomer: δ 212.6, 137.8, 136.5, 131.1, 128.8, 127.4, 127.2, 126.6, 122.4, 122.2, 119.7, 119.6, 117.4, 111.5, 55.6, 42.2, 39.4, 31.2, 28.4, 24.4 ppm. IR (neat): major diastereomer: 3415, 2939, 2868, 1701, 1456, 1338, 963, 908 cm^{-1}; minor diastereomer 3428, 2944, 1701, 1457, 1337, 966, 736, 693, 669, 653, 633, 617, 604 cm^{-1}. R_F: major diastereomer: 0.63 in 20% ethyl acetate in hexanes (5x); minor diastereomer: 0.59 in 20% ethyl acetate in hexanes (5x).

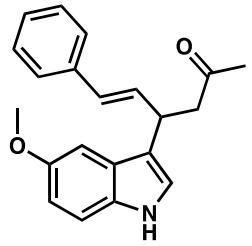
2.8.7.8 Synthesis of (*E*)-4-(5-bromo-1*H*-indol-3-yl)-6-phenylhex-5-en-2-one (69)



See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 36 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes on silica gel. (Trial 1: 68.5 mg, 0.186 mmol, 85% yield, 97.2:2.8 er, Trial 2: 73.9 mg, 0.201 mmol, 94% yield, 94.5:3.5 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99, (bs, 1H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.26-7.24 (m, 2H), 7.21-7.16 (m, 4H), 7.13-7.11 (m, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 3.68-6.29 (m, 2H), 4.26 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.95 (dd, *J* = 16.0, 7.4 Hz, 1H), 2.93 (dd, *J* = 16.0, 7.4 Hz, 1H), 2.06 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 207.7, 137.4, 135.4, 132.1, 130.3, 128.8, 128.4, 127.6, 126.6, 125.4, 122.9, 122.2, 117.5, 113.1, 49.3, 35.8, 30.9 ppm. IR (neat): 3367, 1705, 1458, 1162, 1108, 1053, 1032, 979, 884,

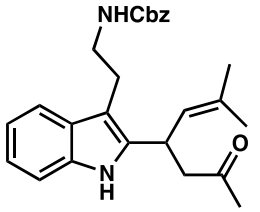
858, 798, 768, 740 cm^{-1}. Anal. Calcd. for $C_{20}H_{18}BrNO$: C, 65.23; H, 4.93; Br, 21.70; N, 3.80, O, 4.34. Found: C, 65.04; Br, 21.47, N, 3.63; O, 5.01. R_F: 0.60 in 50% ethyl acetate in hexanes.

2.8.7.9 Synthesis of (*E*)-4-(5-methoxy-1*H*-indol-3-yl)-6-phenylhex-5-en-2-one (70)



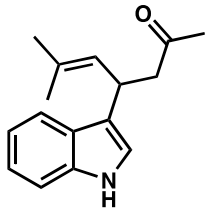
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 18 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes on silica gel. (Trial 1: 60.0 mg, 0.188 mmol, 85% yield, 99.2:0.8 er; Trial 2: 61.1 mg, 0.191 mmol, 87% yield, 97.0:3.0 er; Trial 3: 62.8 mg, 0.197 mmol, 89% yield, 99.1:0.9 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (bs, 1H), 7.24 (dd, *J* = 6.8, 1.7 Hz, 2H), 7.20-7.17 (m, 3H), 7.12-7.09 (m, 1H), 7.17 (d, *J* = 2.2 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.39 (d, *J* = 16 Hz, 1H), 6.33 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.27 (app. q, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 3.00-2.90 (m, 2H), 2.06 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.0, 154.2, 137.6, 132.5, 132.0, 130.1, 128.8, 127.5, 127.2, 126.5, 122.3, 117.5, 112.5, 101.7, 56.3, 49.3, 36.0, 30.7 ppm. IR (neat): 3426, 2945, 1716, 1485, 1452, 1297, 1210, 1174, 1033, 970, 802, 701 cm^{-1}. R_F: 0.59 in 50% ethyl acetate in hexanes.

2.8.7.10 Synthesis of benzyl 2-(2-(2-methyl-6-oxohept-2-en-4-yl)-1*H*-indol-3-yl)ethylcarbamate (71)



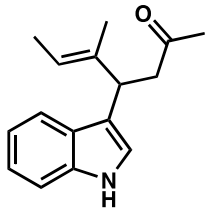
See the general procedure for 1,4-conjugate addition reaction above. 3 Equivalents of boronic acid and 20 mol % of 3,3'-I_2-BINOL catalyst were used in this reaction. The reaction time for this substrate was 48 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. This substrate was not dry-loaded. (Trial 1: 19.3 mg, 0.046 mmol, 61% yield (based on recovered starting material); 12.0 mg, 0.029 mmol, 30% starting material recovered, 97.1:2.9 er; Trial 2: 36.8 mg, 0.088 mmol, 57% yield (based on recovered starting material); 23.3 mg, 0.064 mmol, 29% starting material recovered; 96.6:3.4 er). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (bs, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.26-7.19 (m, 5H), 7.05 (td, *J* = 7.7, 0.9 Hz, 1H), 6.98 (td, *J* = 7.7, 0.9 Hz, 1H), 5.35 (d, *J* = 9.1 Hz, 1H), 5.05-4.98 (m, 2H), 4.81 (bt, *J* = 5.5 Hz, 1H), 4.20-4.15 (m, 1H), 3.44-3.34 (m, 2H), 2.91-2.81 (m, 3H), 2.71 (dd, *J* = 16.9, 5.5 Hz, 1H), 2.00 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.4, 156.7, 138.2, 135.7, 134.7, 128.8, 128.5, 128.4, 124.1, 121.8, 119.7, 118.6, 111.0, 107.6, 66.9, 49.7, 41.8, 31.9, 31.1, 26.0, 25.1, 18.3 ppm. IR (neat): 3357, 2920, 1699, 1517, 1460, 1247, 1138, 1032, 742 cm^{-1}. R_F: 0.10 in 40% ethyl acetate in hexanes.

2.8.7.11 Synthesis of 4-(1*H*-indol-3-yl)-6-methyhept-5-en-2-one (76)



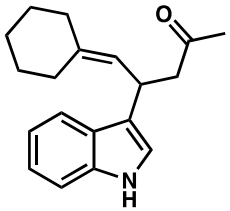
See the general procedure for 1,4-conjugate addition reaction above. 3 Equivalents of boronic acid were used in this reaction. The reaction time for this reaction substrate was 16 hours. The crude reaction mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 47.8 mg, 0.198 mmol, 90% yield, 94.5:5.5 er; Trial 2: 48.3 mg, 0.200 mmol, 91% yield, 94.5:5.5 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (bs, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.11 (td, *J* = 6.8, 1.1 Hz, 1H), 7.04 (td, *J* = 8.0, 1.1 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 5.25 (dt, *J* = 9.7, 1.1 Hz, 1H), 4.30 (td, *J* = 9.1, 6.3 Hz, 1H), 2.89 (dd, *J* = 15.4, 6.3 Hz, 1H), 2.70 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.03 (s, 3H), 1.71 (d, *J* = 1.1 Hz, 3H), 1.63 (d, *J* = 1.1 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.9, 136.8, 132.3, 127.3, 122.3, 120.9, 119.6, 119.5, 119.4, 50.4, 32.3, 30.9, 26.1, 18.4 ppm. IR (neat): 3419, 2970, 1705, 1456, 1353, 1261, 1098, 1011, 741 cm^{-1}. Anal. Calcd. for $C_{16}H_{19}NO$: C, 70.63; H, 7.94; N, 5.80; O, 6.63. Found: C, 79.44; H, 7.82; N, 5.74; O, 7.00. R_F: 0.58 in 50% ethyl acetate in hexanes.

2.8.7.12 Synthesis of (*E*)-4-(1*H*-indol-3-yl)-5-methylheptene-5-en-2-one (77)



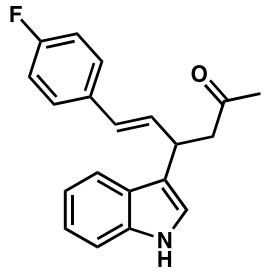
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate is 18 hours. This reaction ran with toluene as solvent in a sealed tube at reflux. The crude reaction mixture was purified via column chromatography with 20% ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 46.9 mg, 0.194 mmol, 88% yield, 98.7:1.3 er; Trial 2: 39.7 mg, 0.164 mmol, 75% yield, 97.5:2.5 er). (Santa Jansone-Popova ran this reaction). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 7.55 (d, *J* = 6.9 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.10 (ddd, *J* = 6.9, 1.2 Hz, 1H), 7.01 (ddd, *J* = 8.0, 1.2 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 5.52-5.45 (m, 1H), 4.09 (app. t, *J* = 8.0, 7.4 Hz, 1H), 2.87 (dd, *J* = 2.3, 1.7 Hz, 2H), 2.04 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H), 1.44 (d, *J* = 1.2 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.9, 137.0, 136.8, 127.2, 122.3, 121.7, 119.9, 119.8, 119.6, 117.8, 111.4, 47.9, 42.1, 30.3, 14.0, 13.8 ppm. IR (neat): 3314, 2923, 1689, 1457, 1361, 1267, 1106, 748, 647 cm^{-1}. R_F: 0.42 in 40% ethyl acetate in hexanes.

2.8.7.13 Synthesis of 5-cyclohexylidene-4-(1*H*-indol-3-yl)pentan-2-one (78)



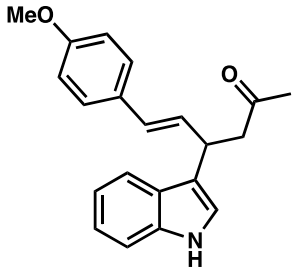
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 24 hours. The crude reaction mixture was purified via column chromatography with a 10–25% gradient of ethyl acetate in hexanes on silica gel. (Trial 1: 45.8 mg, 0.135 mmol, 74% yield, 93.2:6.8 er; Trial 2: 38.0 mg, 0.163 mmol, 61% yield, 93.7:6.3 er). (Santa Jansone-Popova ran this reaction). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (bs, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.14-7.00 (m, 2H), 6.88 (d, *J* = 1.8 Hz, 1H), 5.17 (d, *J* = 9.6 Hz, 1H), 4.40-4.30 (m, 1H), 2.89 (dd, *J* = 15.1, 6.0 Hz, 1H), 2.69 (dd, *J* = 15.1, 8.7 Hz, 1H), 2.36-2.13 (m, 2H), 2.04 (S, 3H), 2.02-1.96 (m, 2H), 1.54-1.37 (m, 6H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.8, 140.2, 136.8, 126.7, 124.0, 122.3, 120.8, 119.8, 119.6, 119.5, 111.6, 50.6, 37.5, 31.4, 31.0, 29.5, 28.9, 28.1, 27.1 ppm. IR (neat): 3343, 2926, 2859, 1700, 1459, 1444, 1340, 1260, 1107, 1015, 741 cm^{-1}. Anal. Calcd. for $C_{19}H_{23}O$: C, 81.10; H, 8.24; N, 4.98; O, 5.69. Found: C, 80.38; H, 8.38; N, 4.90; O, 5.89. R_F: 0.45 in 40% ethyl acetate in hexanes.

2.8.7.14 Synthesis of (*E*)-6-(4-fluorophenyl)-4-(1*H*-indol-3-yl)hex-5-en-2-one (80)



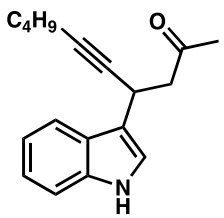
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 20 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 56.2 mg, 0.183 mmol, 83% yield, 97.6:2.4 er; Trial 2: 56.8 mg, 0.184 mmol, 84% yield, 98.0:2.0 er; Trial 3 60.8 mg, 0.197 mmol, 90% yield, 98.2:1.8 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (bs, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.20-7.18 (m, 2H), 7.12 (td, *J* = 6.8, 1.1 Hz, 1H), 7.02 (td, *J* = 6.8, 1.1 Hz, 1H), 6.96 (d, *J* = 2.8 Hz, 1H), 6.87 (app. t, *J* = 8.5 Hz, 2H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.30 (app. q, *J* = 7.4 Hz, 1H), 3.03-2.92 (m, 2H), 2.05 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 207.9, 163.4, 161.4, 136.9, 133.7, 132.3, 128.9, 128.0, 126.7, 122.6, 121.5, 119.9, 119.8, 117.7, 115.7, 115.5, 111.6, 49.3, 36.0, 30.9 ppm. IR (neat): 3411, 1707, 1507, 1457, 1356, 1226, 1158, 968, 822, 743 cm^{-1}. R_F: 0.55 in 50% ethyl acetate in hexanes.

2.8.7.15 Synthesis of (*E*)-4-(1*H*-indol-3-yl)-6-(4-methoxyphenyl)hex-5-en-2-one (81)



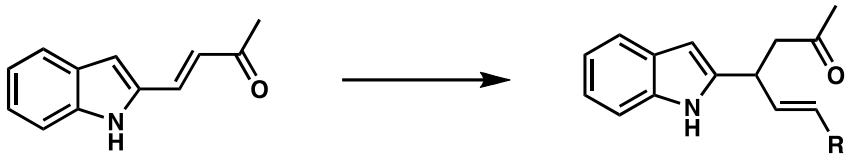
See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 18 hours. The crude reaction mixture was purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 58.5 mg, 0.183 mmol, 83% yield, 96.2:3.8 er; Trial 2: 60.3 mg, 0.188 mmol, 86% yield, 97.1:2.9 er; Trial 3: 60.8 mg, 0.190 mmol, 86% yield, 98.2:1.8 er). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (bs, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19-7.15 (m, 2H), 7.12 (td, *J* = 8.0, 1.2 Hz, 1H), 7.03 (app. t, *J* = 6.8 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 4.29 (q, *J* = 14.8, 7.4 Hz, 1H), 3.71 (s, 3H), 2.99 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.93 (dd, *J* = 16.0, 7.4 Hz, 1H), 2.05 (s, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 208.2, 159.2, 136.8, 130.4, 129.4, 127.7, 126.7, 122.4, 121.5, 119.8, 119.7, 117.9, 114.2, 111.6, 55.6, 49.5, 36.2, 30.9 ppm. IR (neat): 3310, 1703, 1607, 1513, 1249, 1176, 1039, 821, 747 cm^{-1}. Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39; O, 10.02. Found: C, 78.71; H, 6.61; N, 4.28; O, 10.40. R_F: 0.53 in 50% ethyl acetate in hexanes.

2.8.7.16 Synthesis of 4-(1*H*-indol-3-yl)dec-5-yn-2-one (82)



See the general procedure for 1,4-conjugate addition reaction above. The reaction time for this substrate was 24 hours. 3 Equivalents of boronic ester were used in this reaction. The crude reaction mixture was purified via column chromatography with a 10–25% gradient of ethyl acetate in hexanes as eluent on silica gel. (Trial 1: 43.0 mg, 0.161 mmol, 73% yield, 98.6:1.4 er; Trial 2: 40.2 mg, 0.150 mmol, 68% yield, 98.8:1.2 er). (Reaction run by Santa Jansone-Popova). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.15-7.10 (m, 1H), 7.09-7.03 (m, 2H), 4.37-4.36 (m, 1H), 2.92 (d, J = 7.4 Hz, 2H), 2.12 (td, J = 6.9, 2.3 Hz, 2H), 2.09 (s, 3H), 1.45-1.37 (m, 2H), 1.37-1.28 (m, 2H), 0.83 (app. t, J = 7.4, 6.9 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 207.3, 137.0, 125.9, 122.5, 122.1, 119.8, 119.6, 116.6, 111.6, 82.4, 81.1, 51.0, 31.4, 31.0, 25.2, 22.3, 18.8, 14.0 ppm. IR (neat): 3362, 2933, 1713, 1458, 1404, 1369, 1164, 1104, 741, 660, 613 cm^{-1}. Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24; O, 5.98. Found: C, 80.63; H, 7.92; N, 5.16; O, 6.29. R_F: 0.44 in 40% ethyl acetate in hexanes.

2.9 Attempts to Optimize on 2-Indoles



R-group	solvent	temp.	dessicant	additive	catalyst	yield
$C_6H_4F^a$	MeCN	65 °C	4Å M.S.	$Cs_2CO_3{}^b$	$H_2{}^c$	trace
$C_6H_4F^a$	THF	65 °C	4Å M.S.	$Cs_2CO_3{}^b$	$H_2{}^c$	trace
$C_6H_4F^a$	DMF	65 °C	4Å M.S.	$Cs_2CO_3{}^b$	$H_2{}^c$	trace
$C_6H_4F^a$	PhMe	65 °C	4Å M.S.	$Cs_2CO_3{}^b$	$H_2{}^c$	37%
$C_6H_4F^a$	PhMe	90 °C	4Å M.S.	$Cs_2CO_3{}^b$	$H_2{}^c$	48%
$C_6H_4F^a$	PhMe	90 °C	$MgSO_4$	$Cs_2CO_3{}^b$	$H_2{}^c$	trace
$C_6H_4F^a$	PhMe	90 °C	Na_2SO_4	$Cs_2CO_3{}^b$	$H_2{}^c$	trace
$C_6H_4F^a$	PhMe	90 °C	silica gel	$Cs_2CO_3{}^b$	$H_2{}^c$	23%
$C_6H_4F^a$	PhMe	90 °C	silica gel	$Cs_2CO_3{}^b$	$I_2{}^c$	10%
$C_6H_4F^a$	PhMe	90 °C	4Å M.S.	$Cs_2CO_3{}^b$	$I_2{}^c$	50%
$C_6H_4F^a$	PhMe	120 °C	4Å M.S.	$Cs_2CO_3{}^b$	$I_2{}^c$	55%
$C_6H_4F^a$	PhMe	120 °C	4Å M.S.	$Mg(OtBu)_2{}^d$	$I_2{}^c$	None
$C_6H_4F^a$	PhMe	120 °C	4Å M.S.	$Cs_2CO_3{}^b$	$C_6F_5{}^c$	50%
$C_6H_5{}^a$	PhMe	70 °C	4Å M.S.	$Mg(OtBu)_2{}^d$	$H_2{}^e$	None
$C_6H_5{}^a$	PhMe	70 °C	4Å M.S.	$Mg(OtBu)_2{}^d$	$I_2{}^e$	40%
$C_6H_5{}^a$	PhMe	70 °C	4Å M.S.	$Mg(OtBu)_2{}^d$	$C_6F_5{}^e$	23%
$C_6H_5{}^a$	PhMe	90 °C	4Å M.S.	$Cs_2CO_3{}^b$	$H_2{}^c$	31%
$C_6H_5{}^a$	PhMe	90 °C	4Å M.S.	$Cs_2CO_3{}^b$	$I_2{}^c$	38%
$C_3H_6{}^a$	DCE	70 °C	4Å M.S.	$Mg(OtBu)_2{}^d$	$I_2{}^c$	None
$C_3H_6{}^a$	PhMe	120 °C	4Å M.S.	$Mg(OtBu)_2{}^d$	$I_2{}^c$	23%
$C_3H_6{}^a$	PhMe	120 °C	4Å M.S.	$Cs_2CO_3{}^b$	$I_2{}^c$	36%

R-group	solvent	temp.	dessicant	additive	catalyst	yield
C_3H_6[a]	DCE	70 °C	4Å M.S.	Cs_2CO_3[b]	I_2[c]	31%
C_3H_6[a]	DCE	reflux	4Å M.S.	Cs_2CO_3[b]	I_2[c]	14%
C_3H_6[a]	DCE	100 °C	4Å M.S.	Cs_2CO_3[b]	I_2[c]	24%
C_3H_6[a]	DCE	70 °C	4Å M.S.	Cs_2CO_3[b]	C_6F_5[c]	13%
C_3H_6[a]	DCE	100 °C	4Å M.S.	Cs_2CO3[b]	C_6F_5[c]	8%
C_6H_5[a]	DCE	70 °C	4Å M.S.	Cs_2CO_3[b]	C_6F_5[c]	none
C_6H_5[a]	DCE	70 °C	4Å M.S.	$Mg(OtBu)_2$[d]	C_6F_5[c]	none
C_6H_5[a]	DCE	70 °C	4Å M.S.	$Mg(OtBu)_2$[b]	I_2[c]	38%

Table 2.9 Optimization attempts of 2-indole substrates. [a]3.0 equiv used. [b]1.0 equiv used. [c]0.2 equiv used. [d]0.1 equiv used. [e]0.15 equiv used.

2.10 Notes and References

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APPENDIX ONE

Spectra Relevant to Chapter 2:

Enantioselective Conjugate Addition of Alkenylboronic Acids to Indole-appended Enones

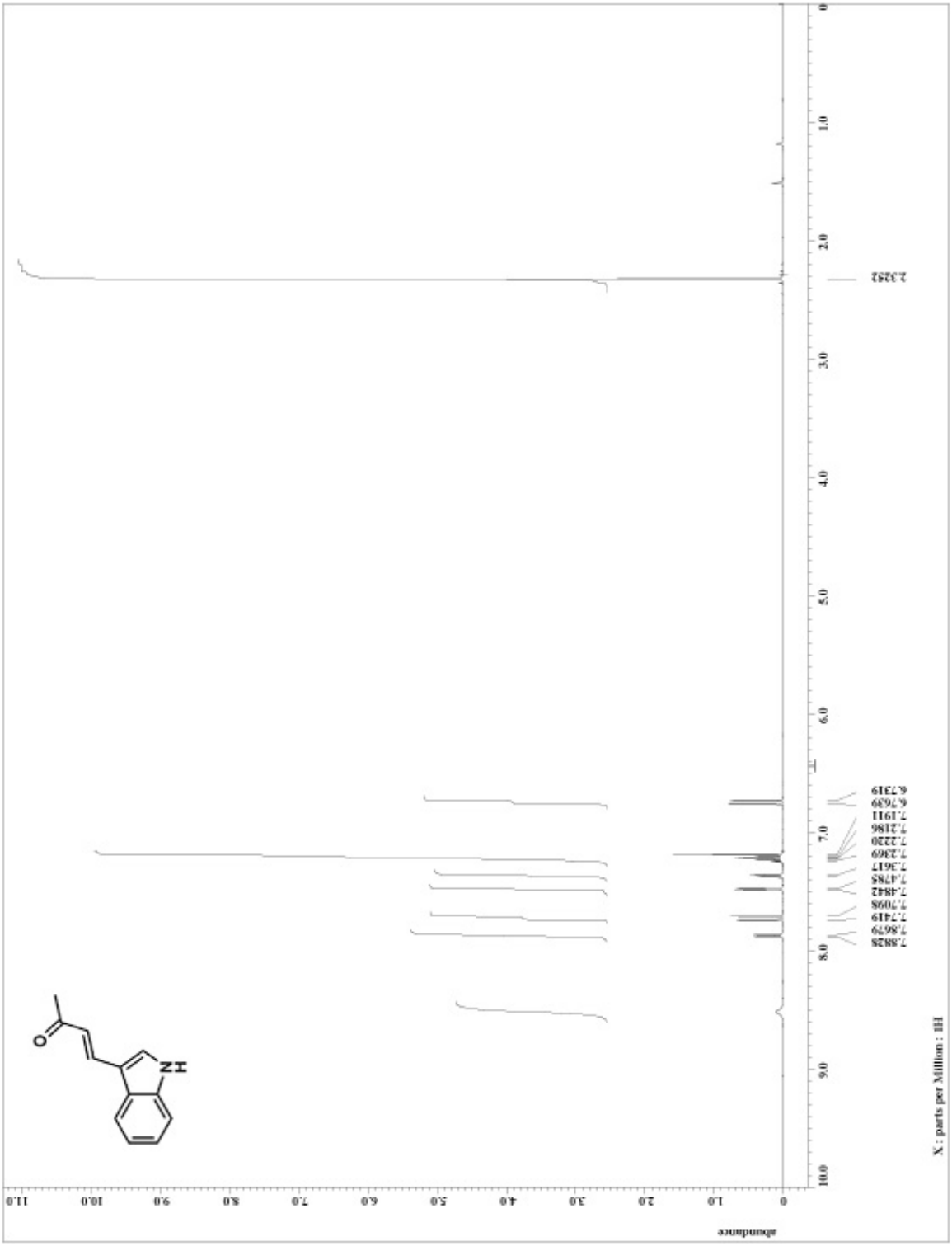


Figure A.1.1 ^{1}H NMR for compound **56**

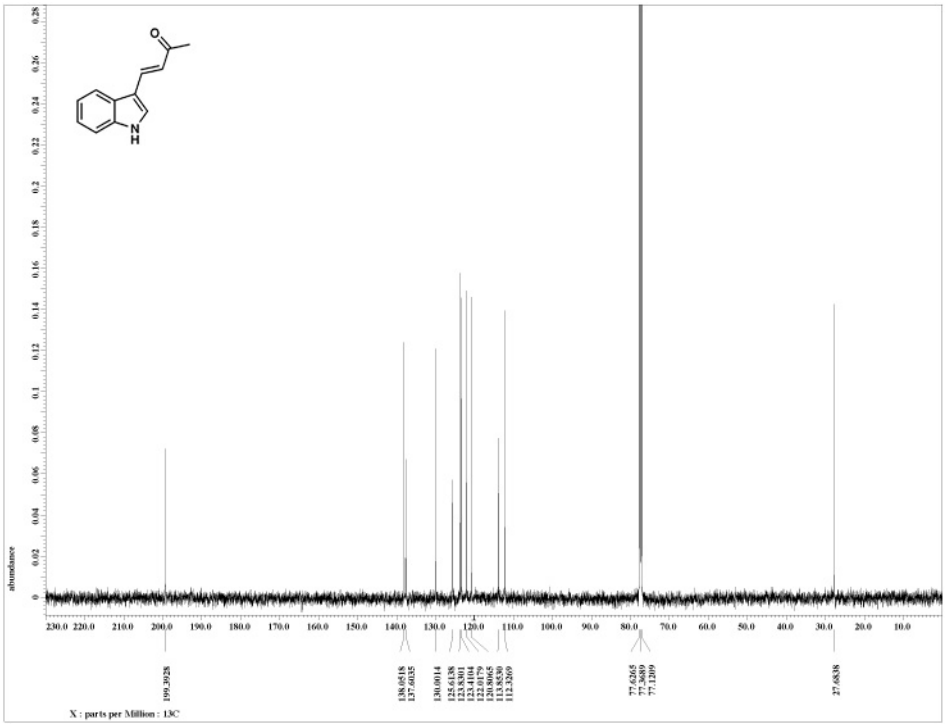


Figure A.1.2 ^{13}C NMR for compound **56**

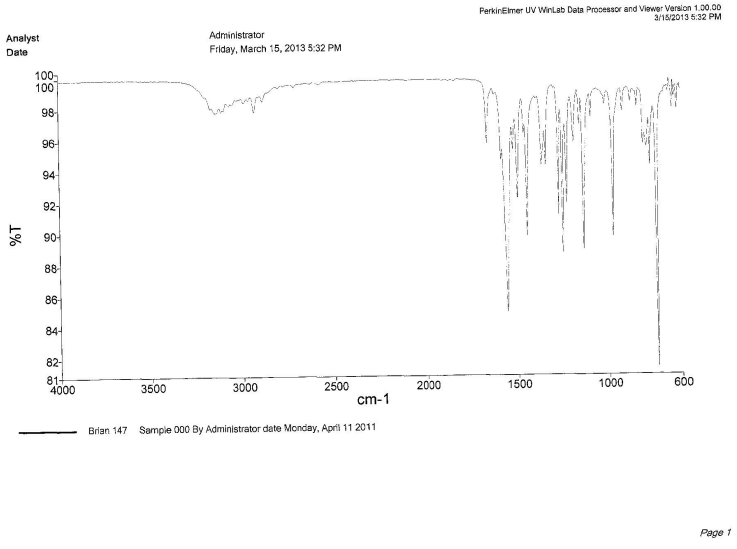


Figure A.1.3 IR spectra for compound **56**

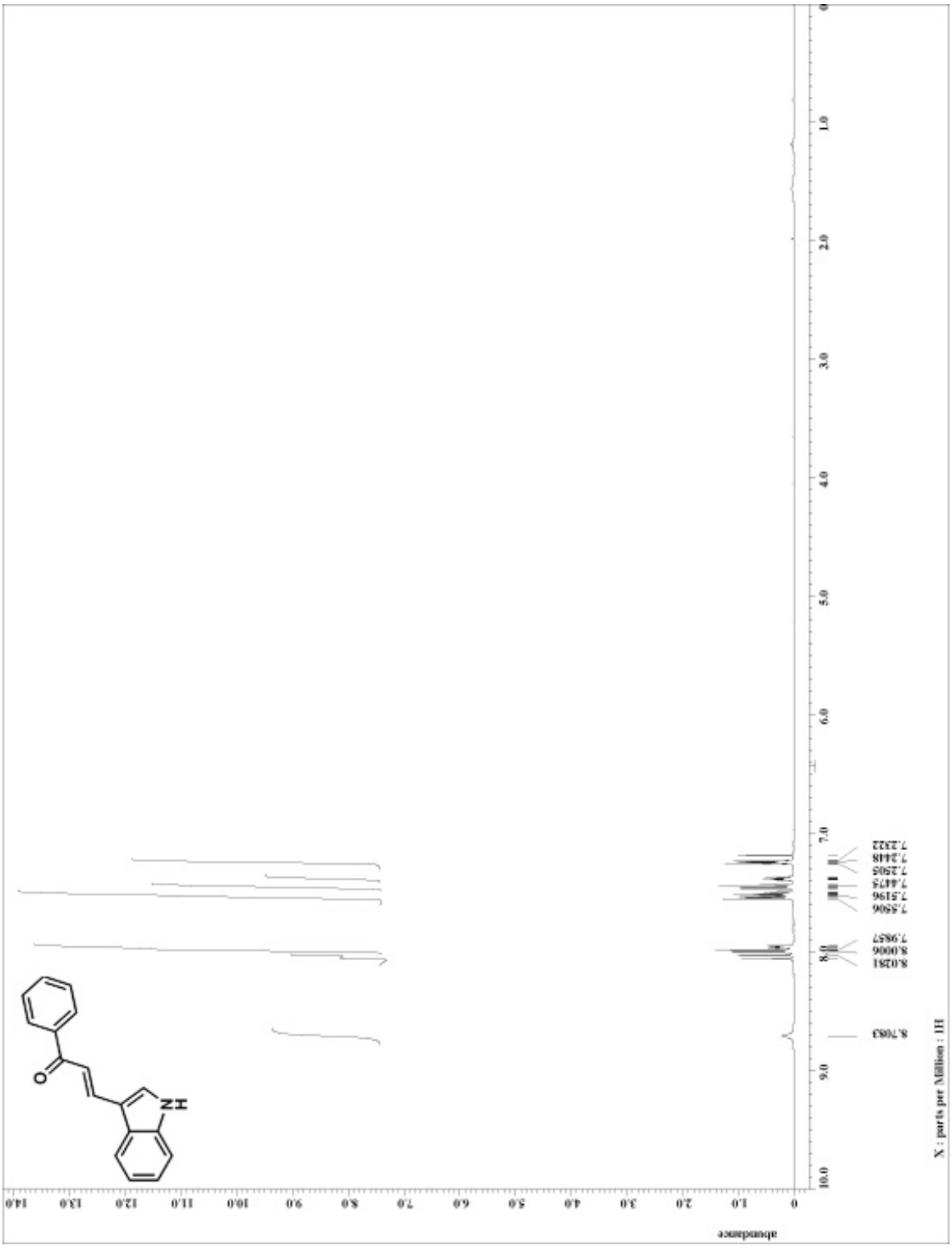


Figure A.1.4 ^{1}H NMR for precursor to compound **63**

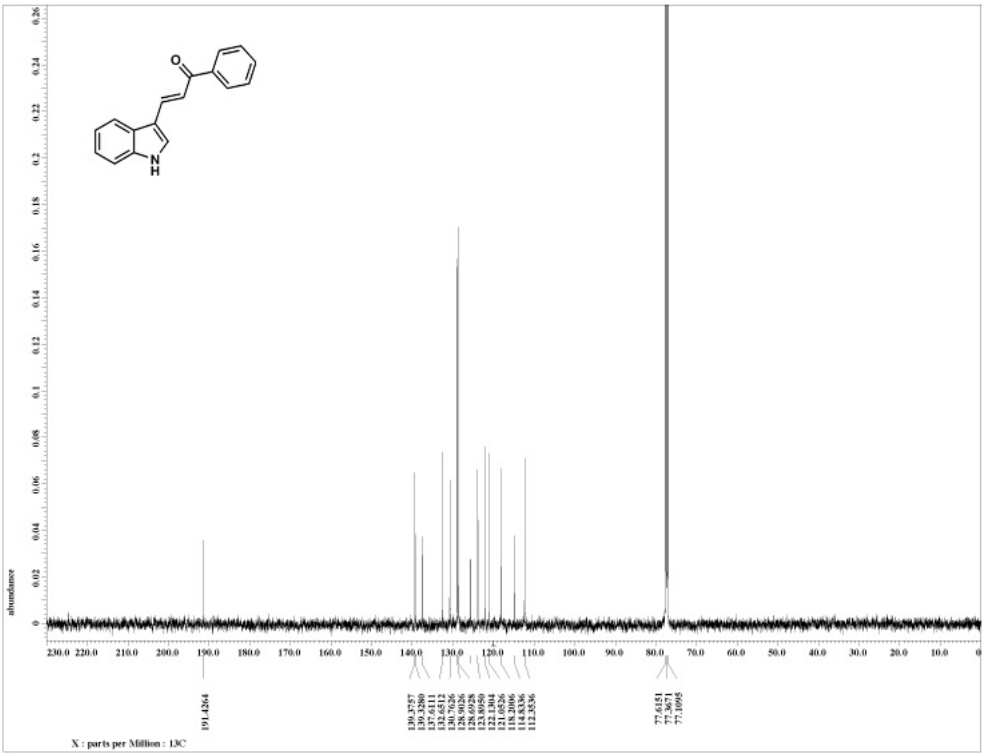


Figure A.1.5 ^{13}C NMR for precursor to compound **63**

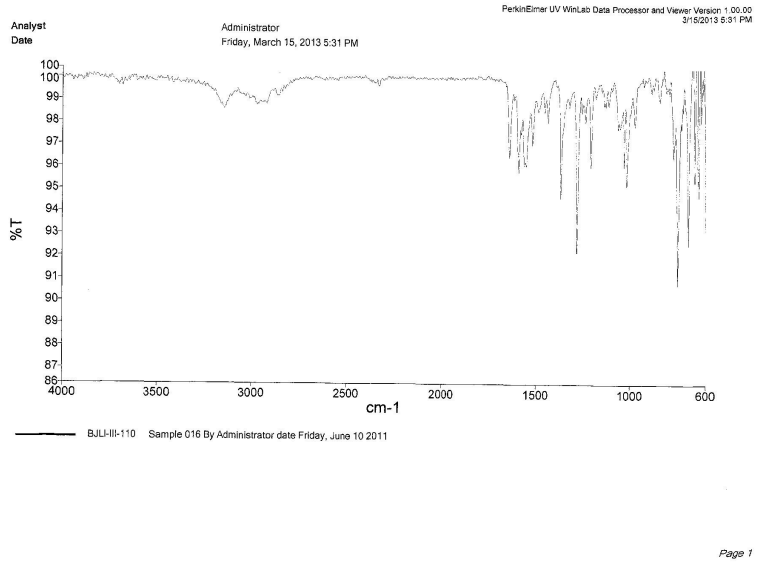


Figure A.1.6 IR spectra for precursor to compound **63**

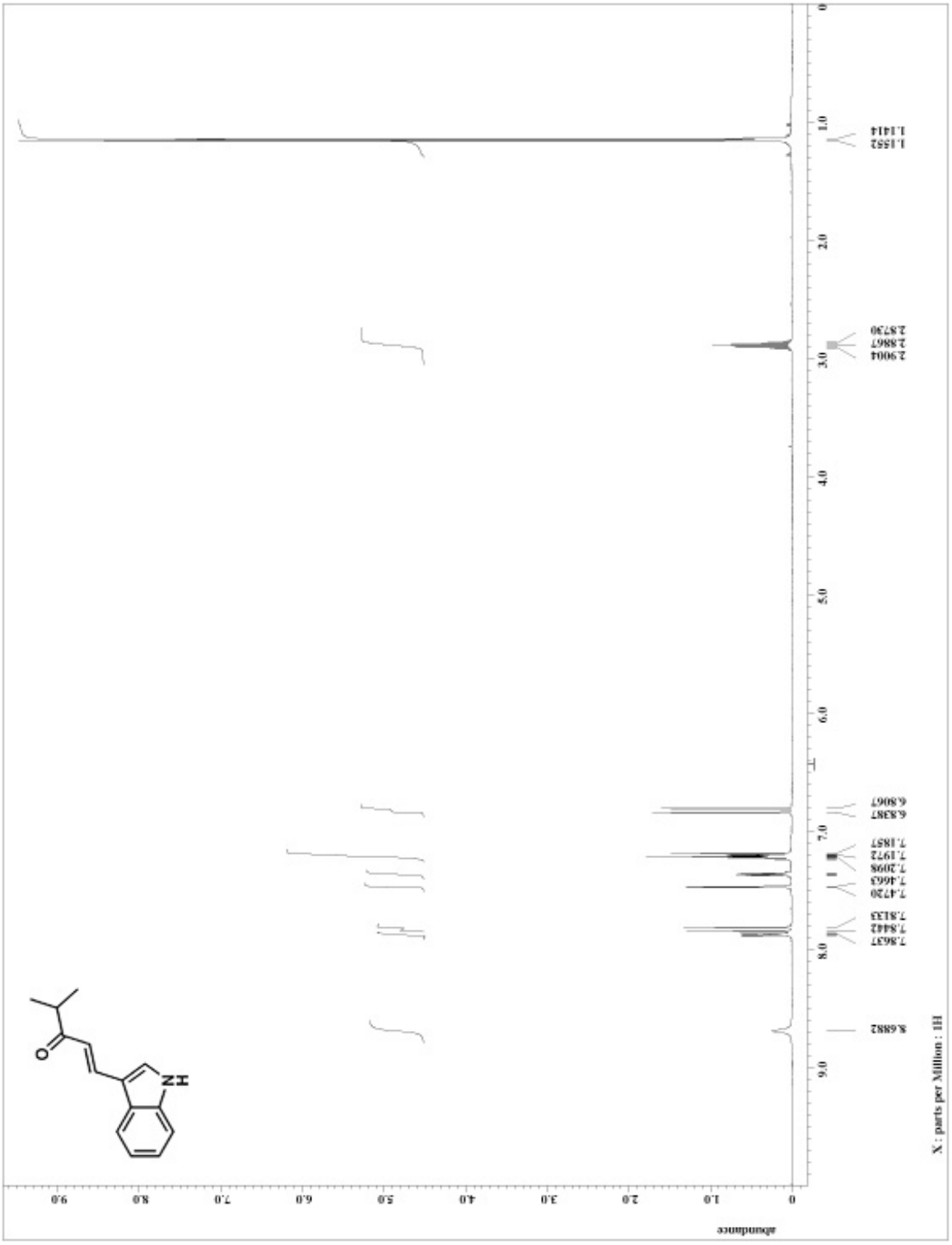


Figure A.1.7 ^{1}H NMR for precursor to compound **64**

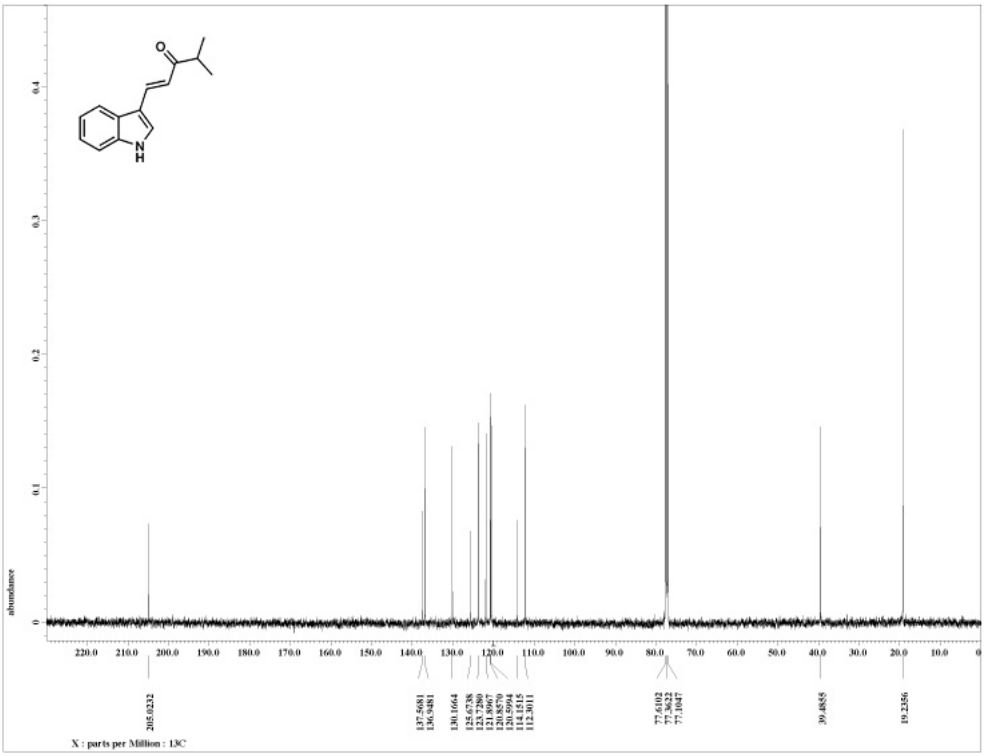


Figure A.1.8 ^{13}C NMR for precursor to compound **64**

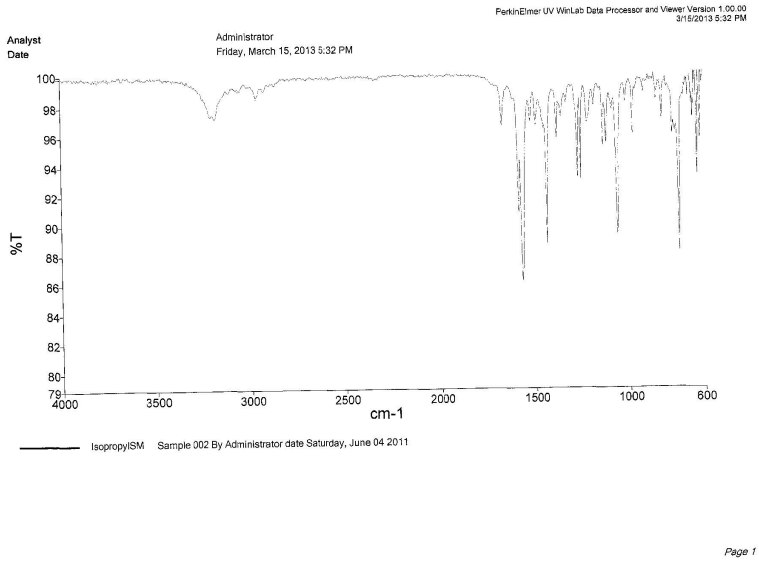


Figure A.1.9 IR spectra for precursor to compound **64**

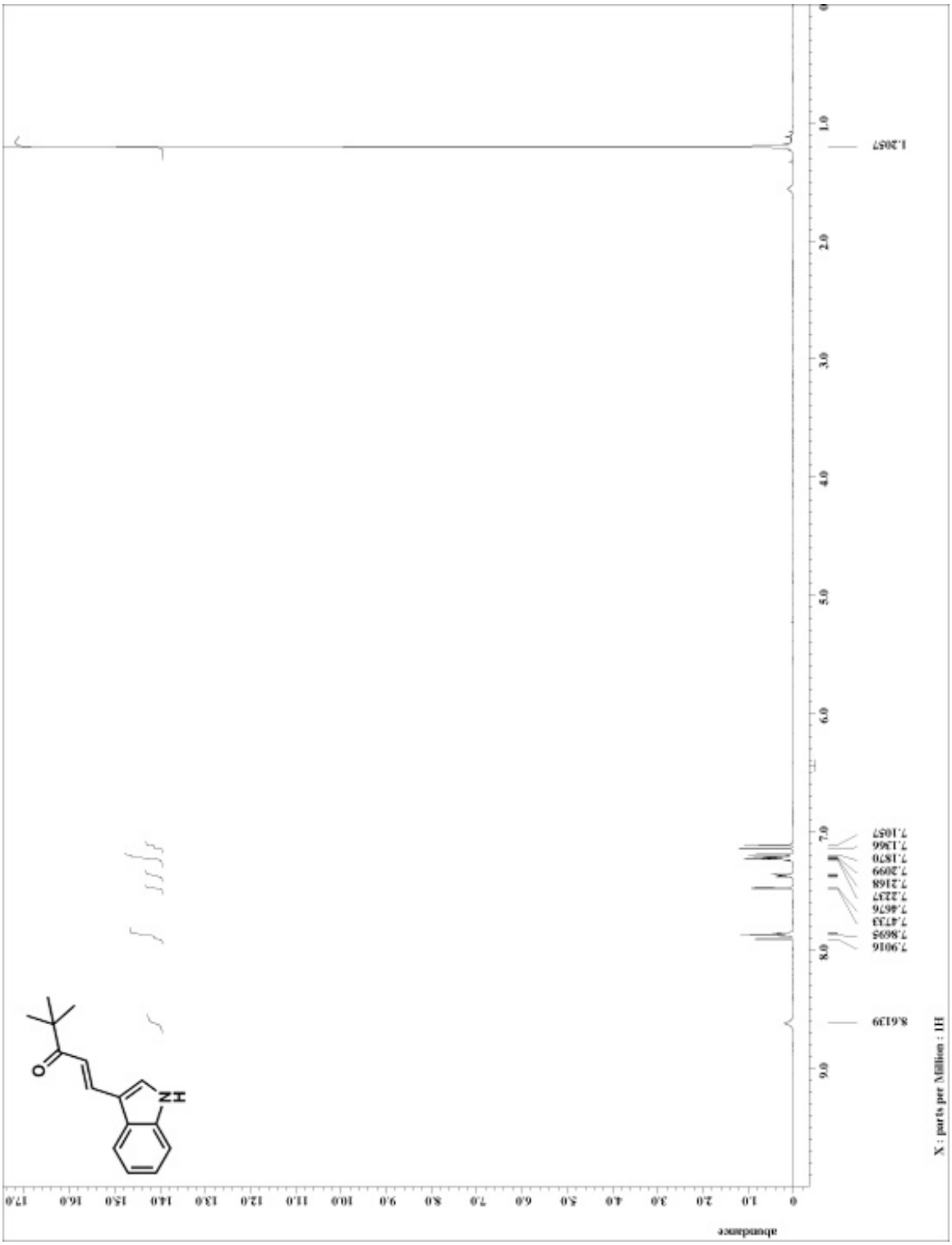


Figure A.1.10 ^{1}H NMR for precursor to compound **65**

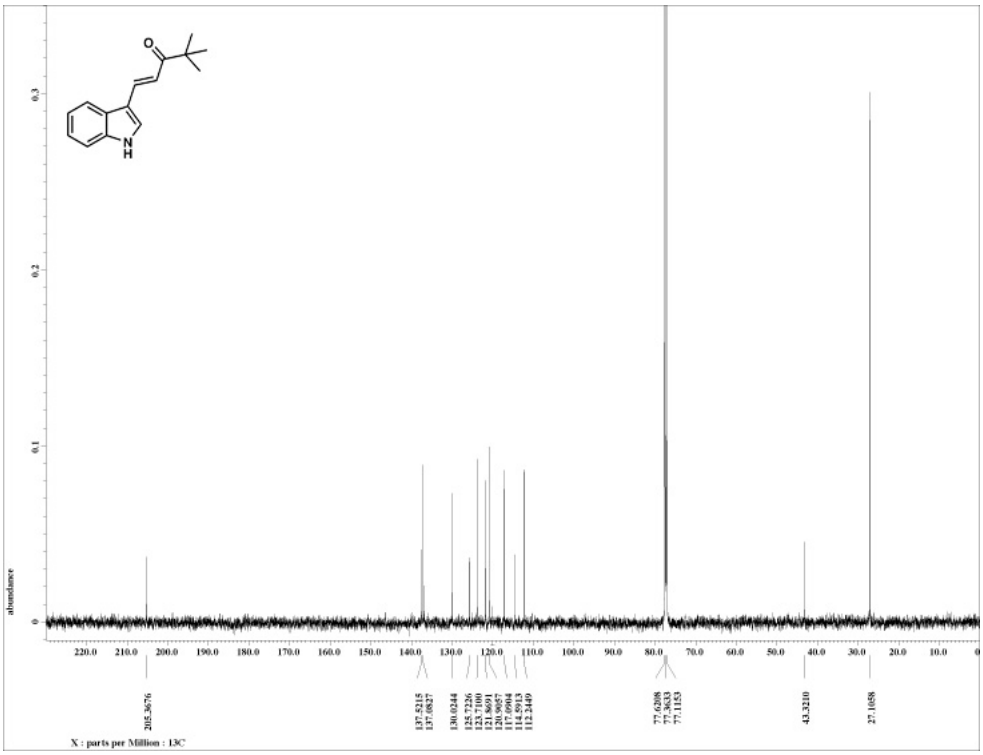


Figure A.1.11 ^{13}C NMR for precursor to compound **65**

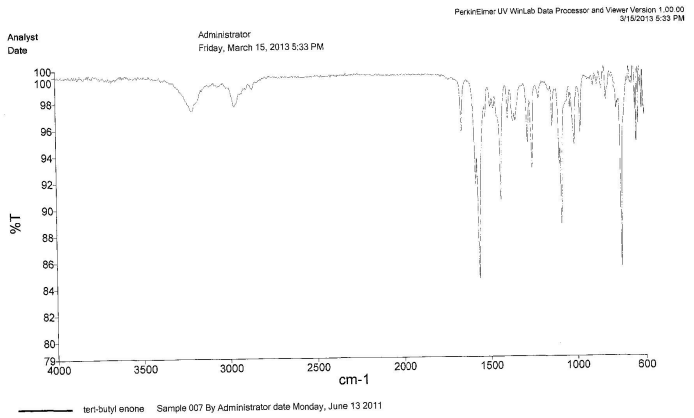


Figure A.1.12 IR Spectra for precursor to compound **65**

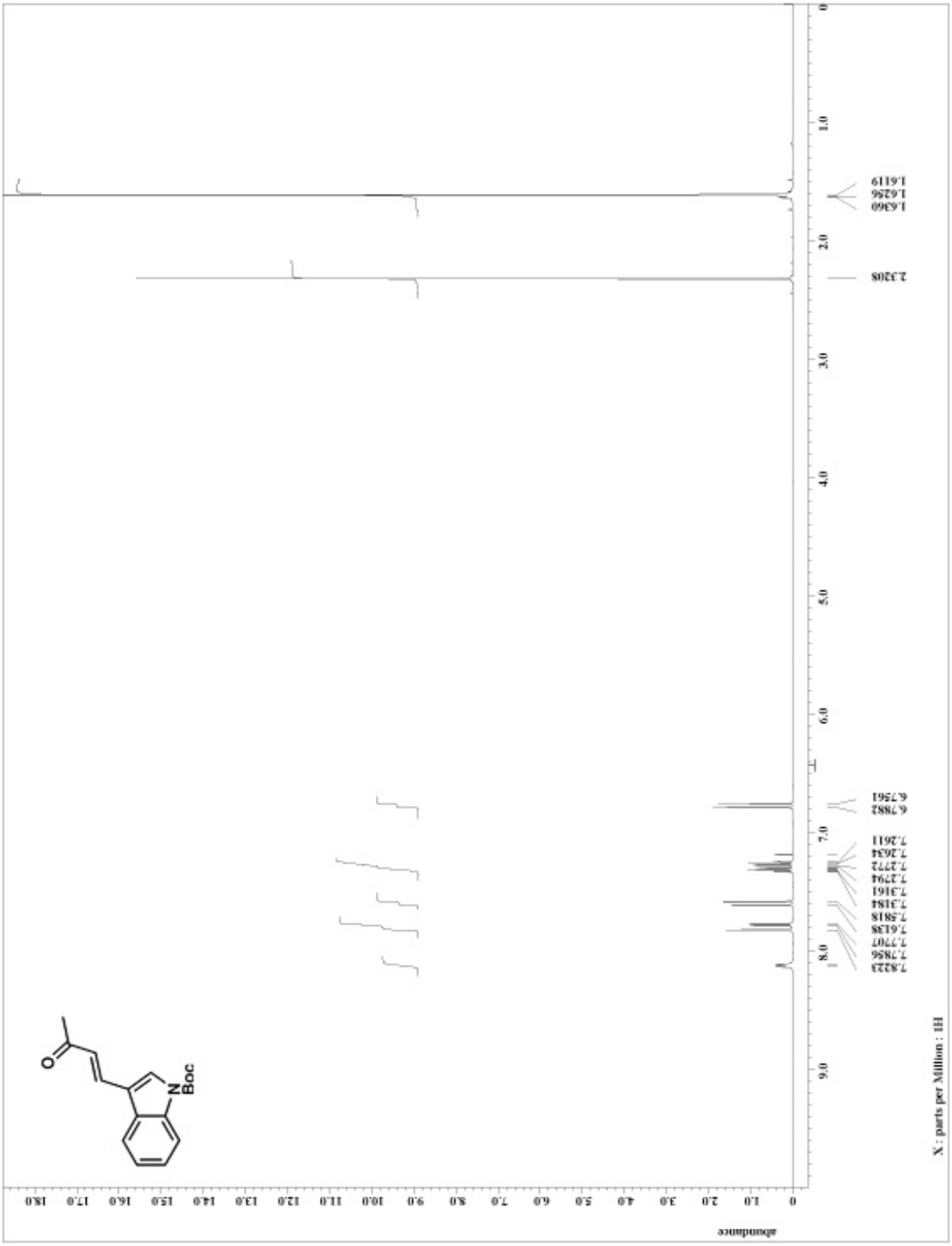


Figure A.1.13 ^{1}H NMR for precursor to compound **66**

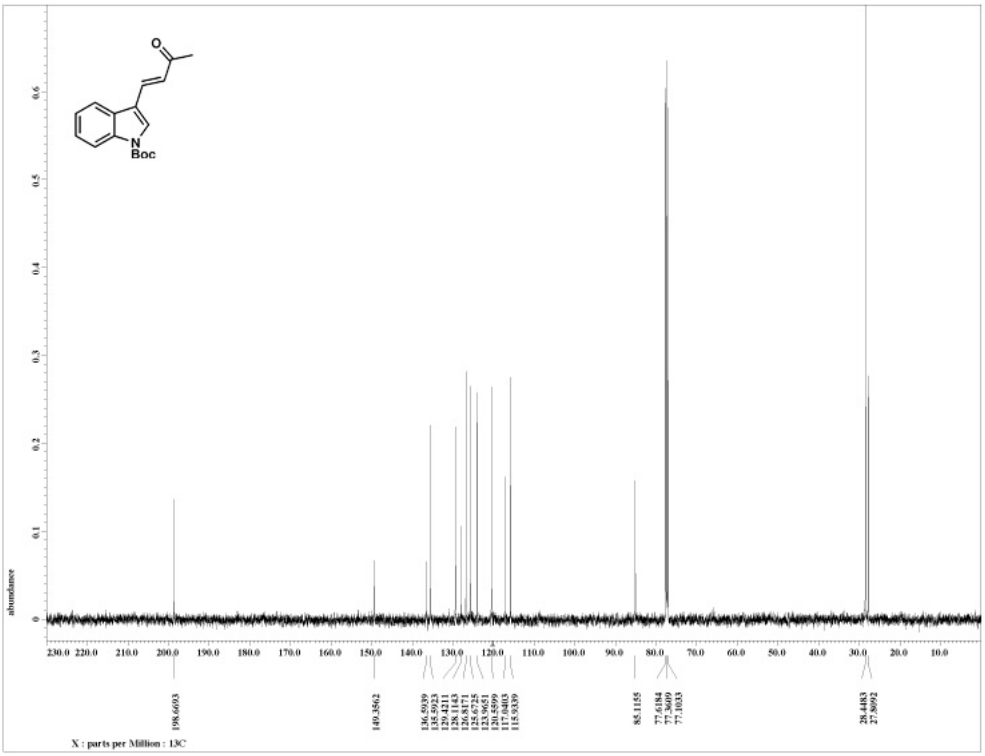


Figure A.1.14 ^{13}C NMR for precursor to compound **67**

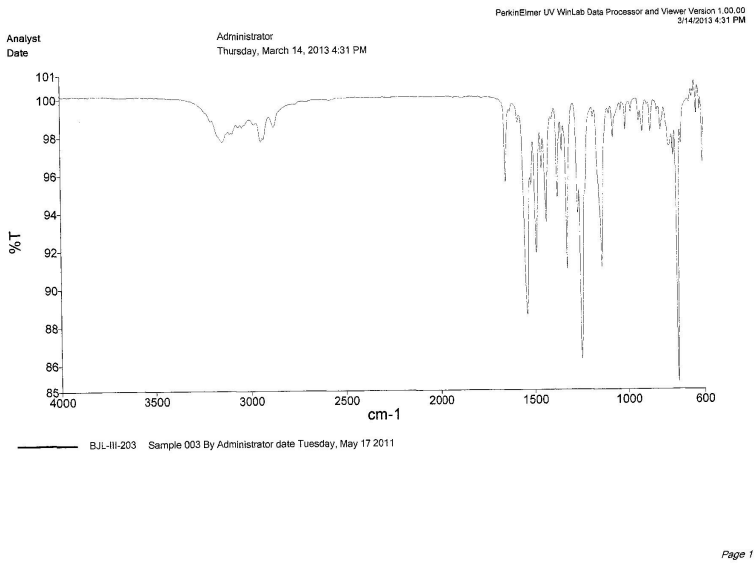


Figure A.1.15 IR spectra for precursor to compound **67**

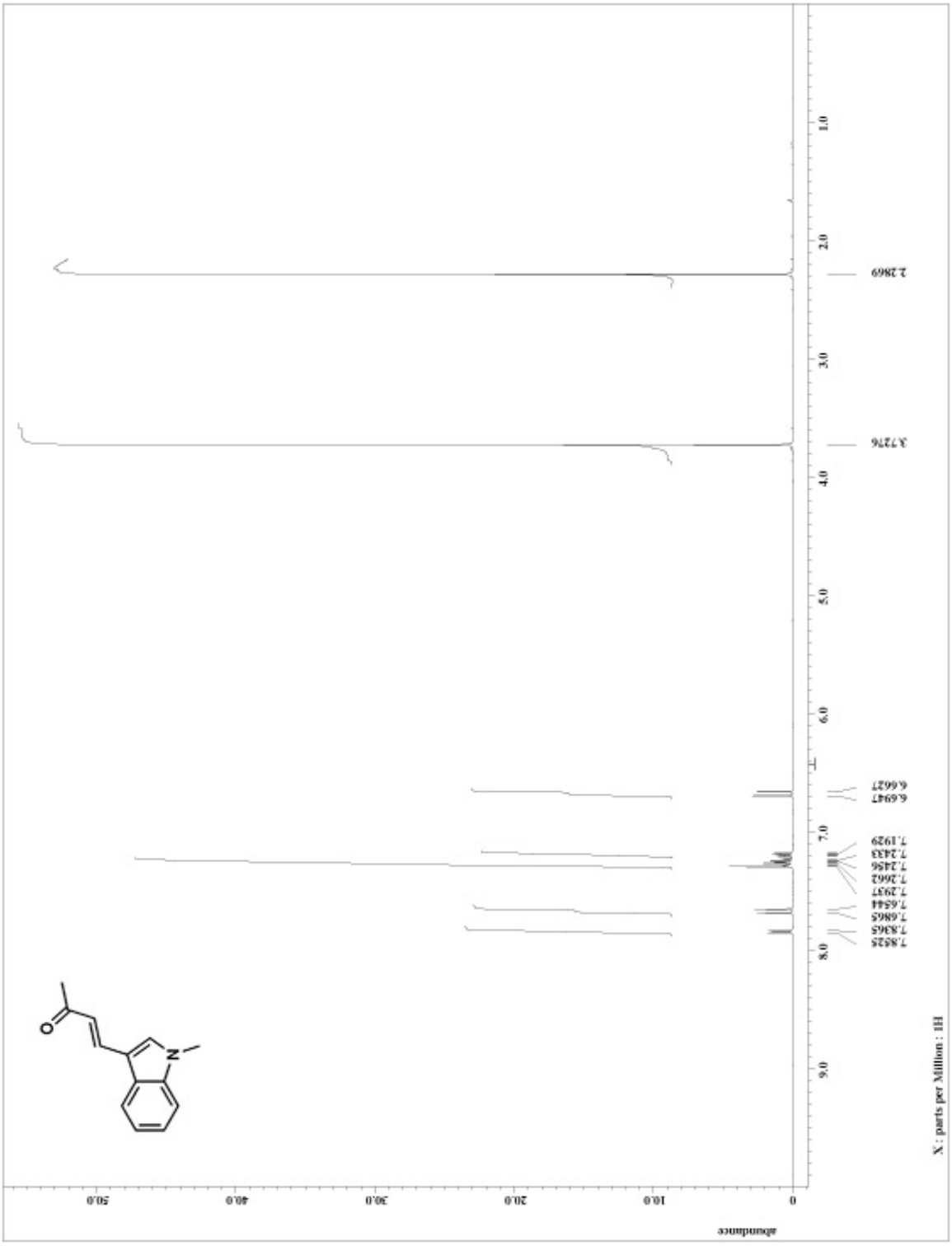


Figure A.1.16 [1]H NMR for precursor to compound **67**

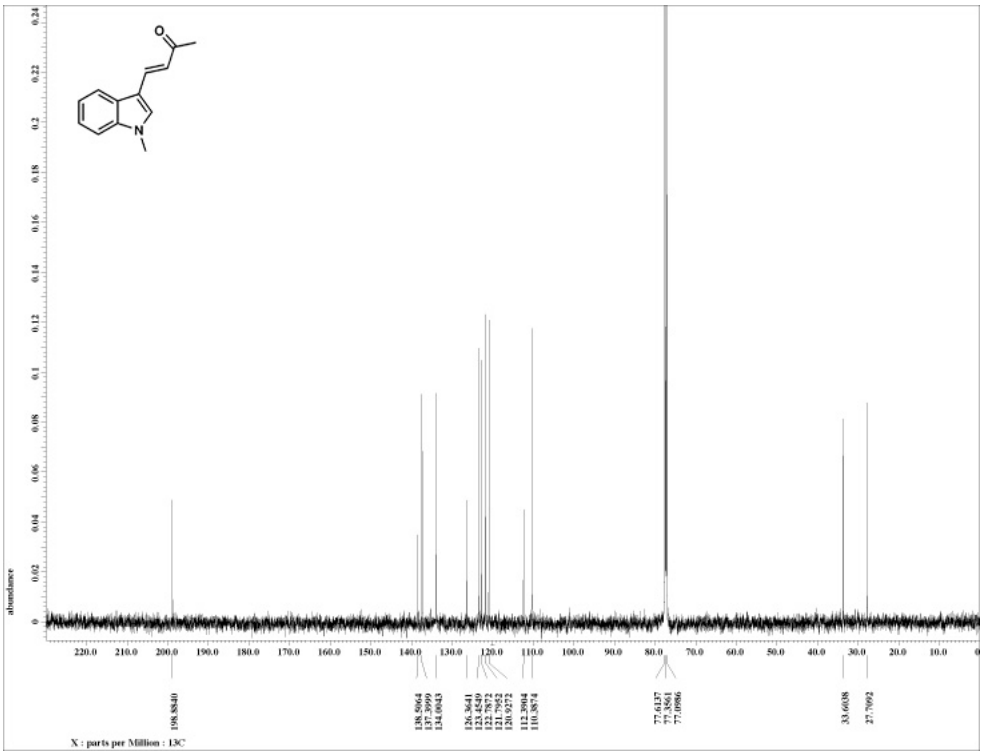


Figure A.1.17 ^{13}C NMR for precursor to compound **67**

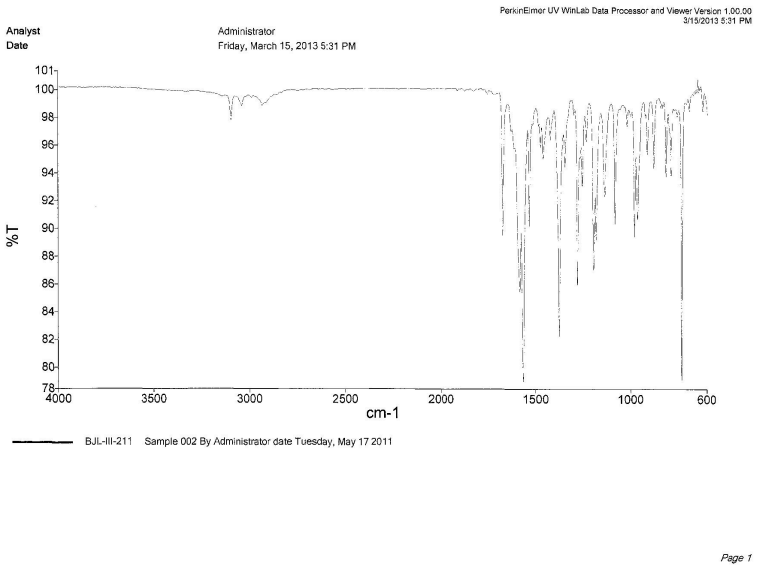


Figure A.1.18 IR spectra for precursor to compound **67**

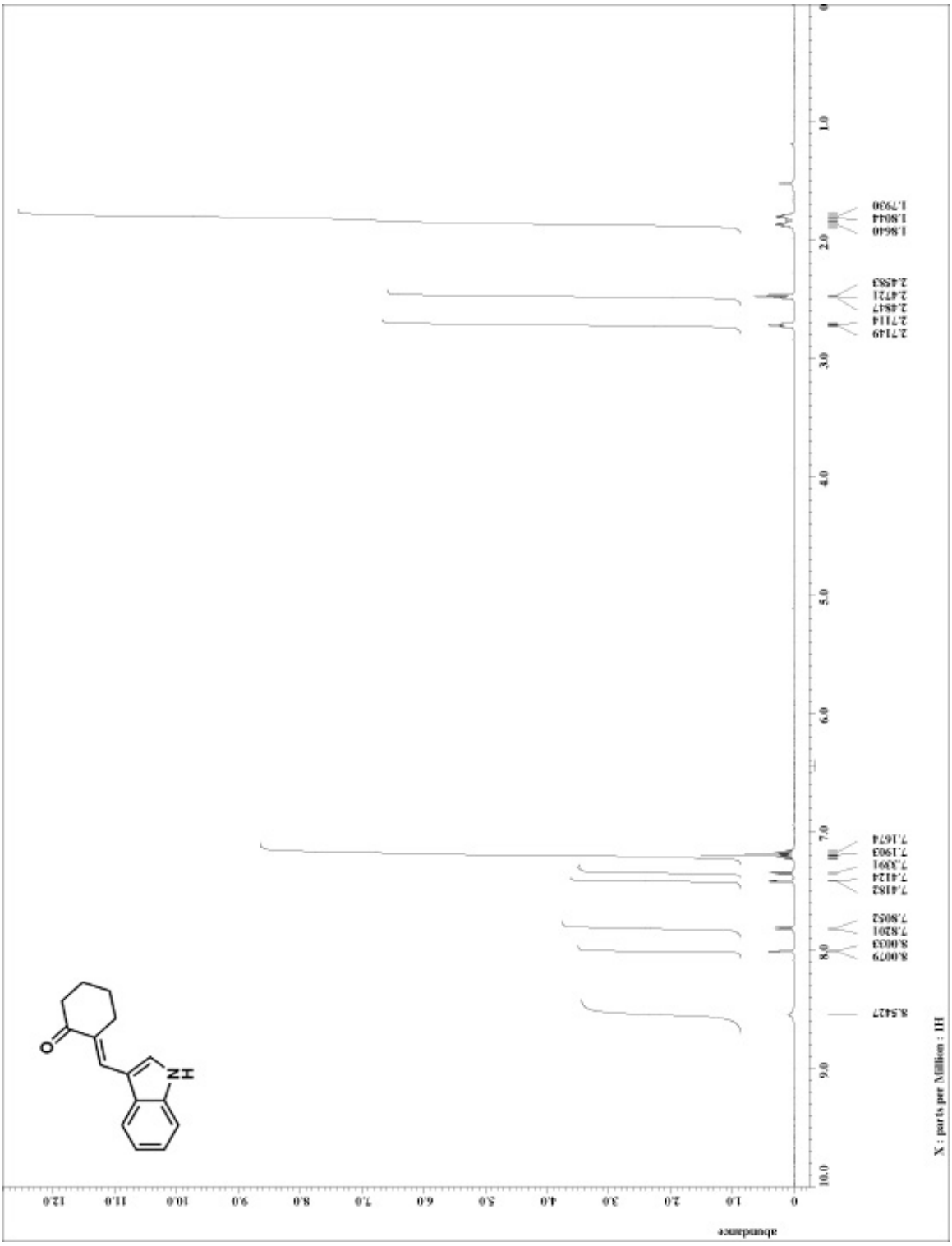


Figure A.1.19 ^{1}H NMR for precursor to compound **68**

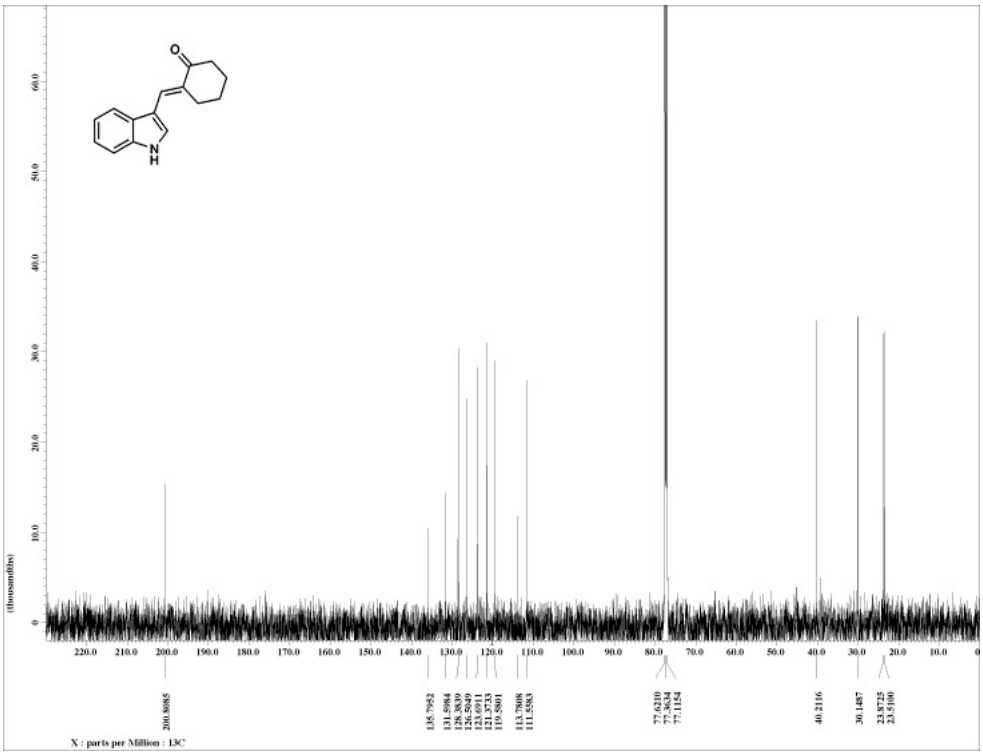


Figure A.1.20 ^{13}C NMR for precursor to compound **68**

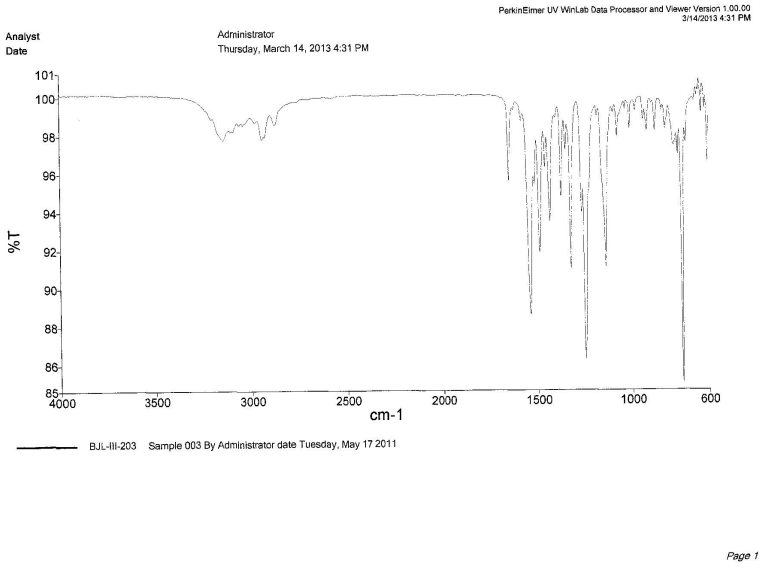


Figure A.1.21 IR spectra for precursor to compound **68**

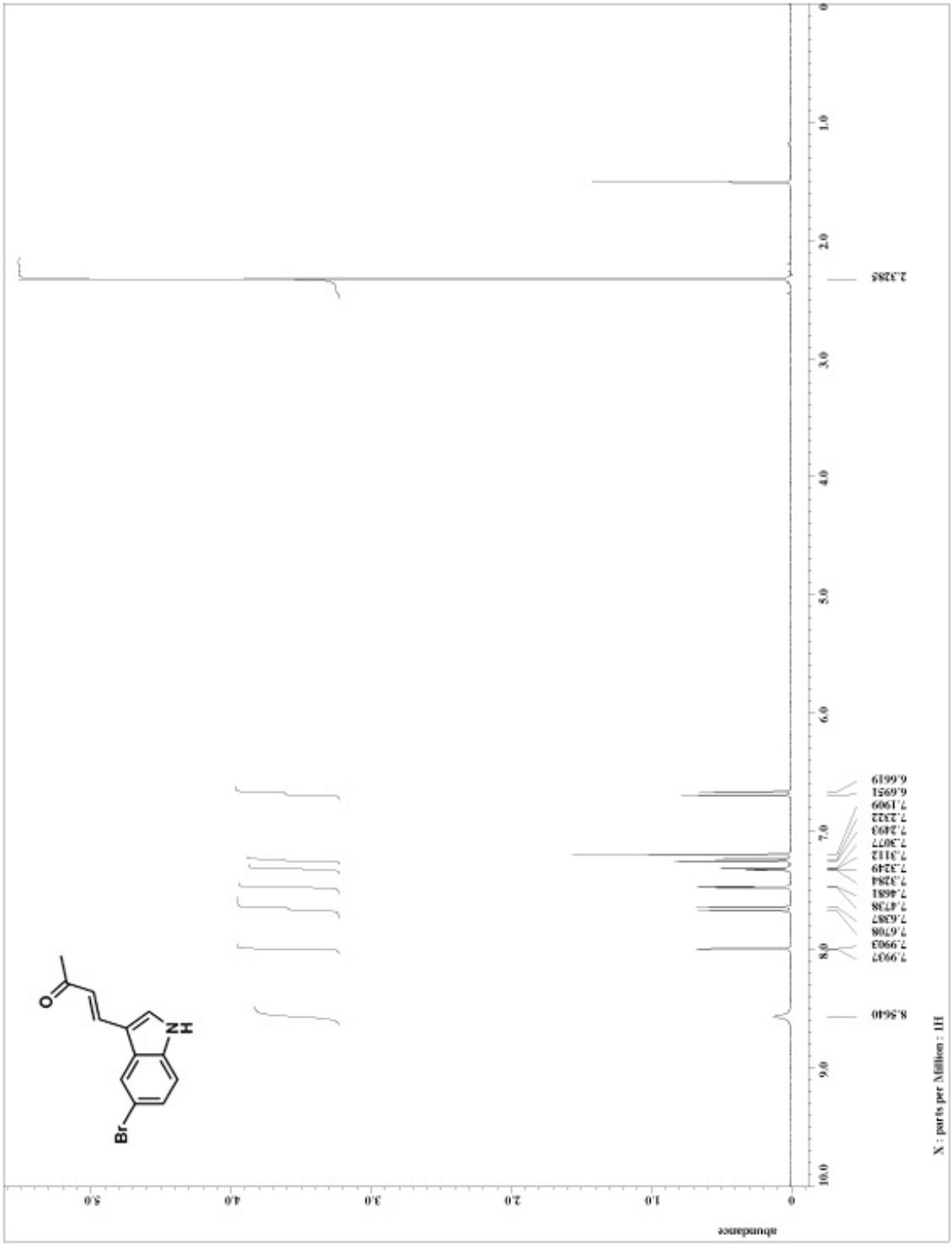


Figure A.1.22 ^{1}H NMR for precursor to compound **69**

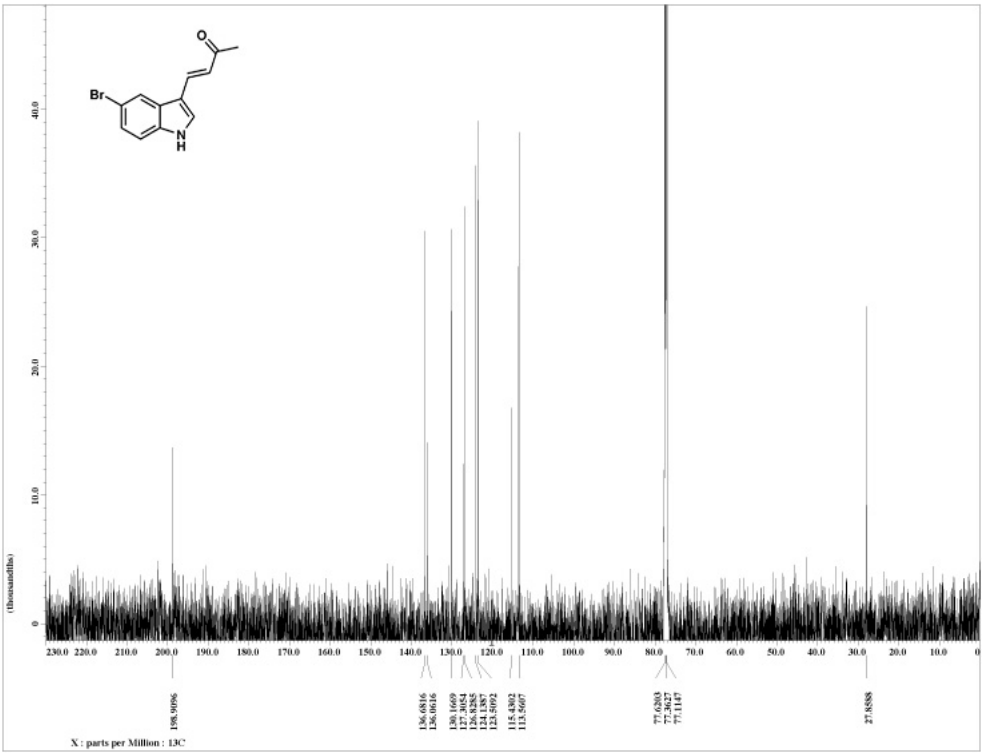


Figure A.1.23 ^{13}C NMR for precursor to compound **69**

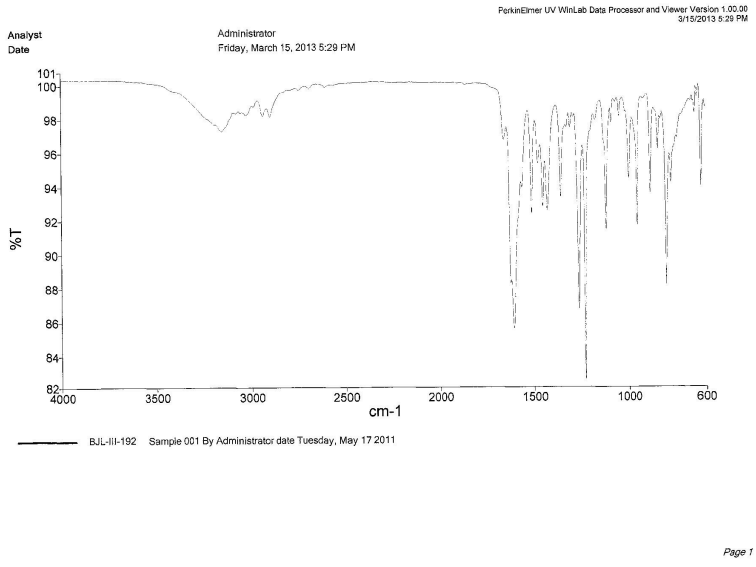


Figure A.1.24 IR spectra for precursor to compound **69**

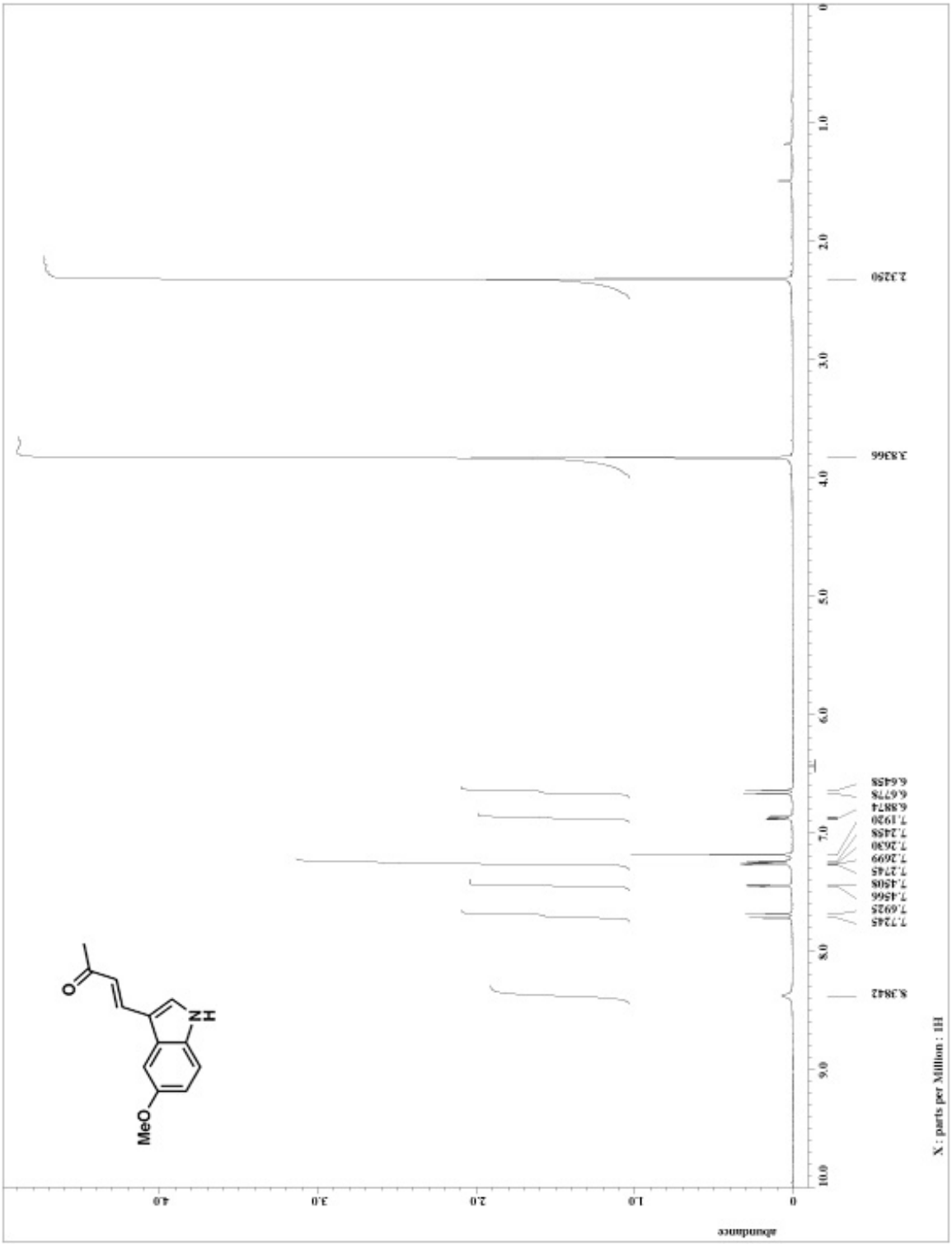


Figure A.1.25 ^{1}H NMR for precursor to compound **70**

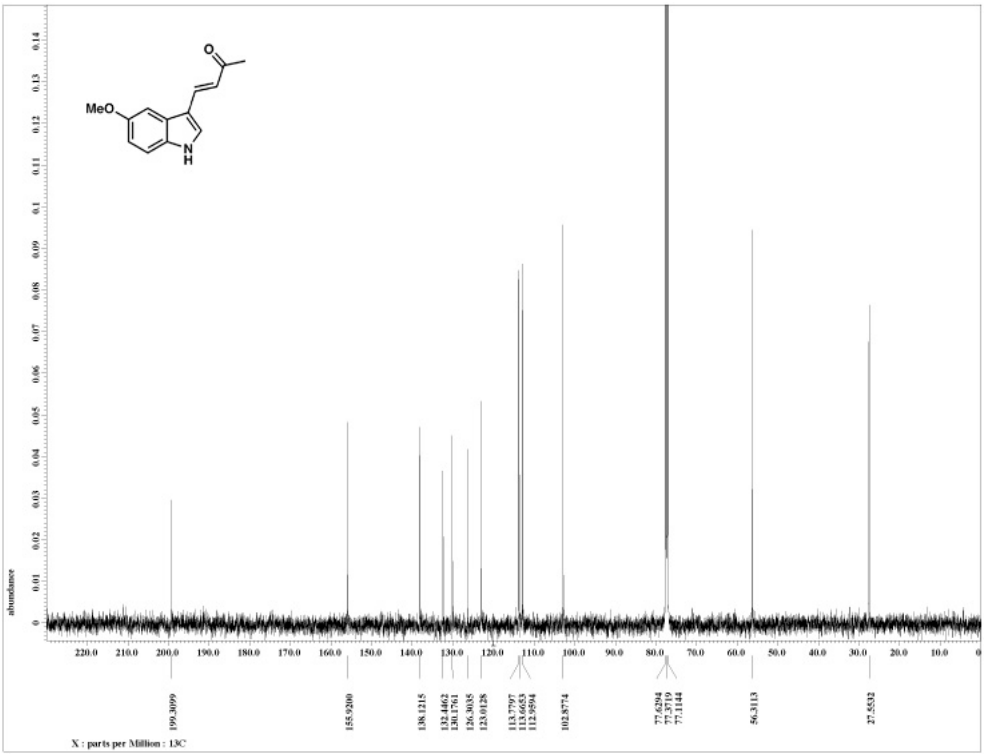


Figure A.1.26 ^{13}C NMR for precursor to compound **70**

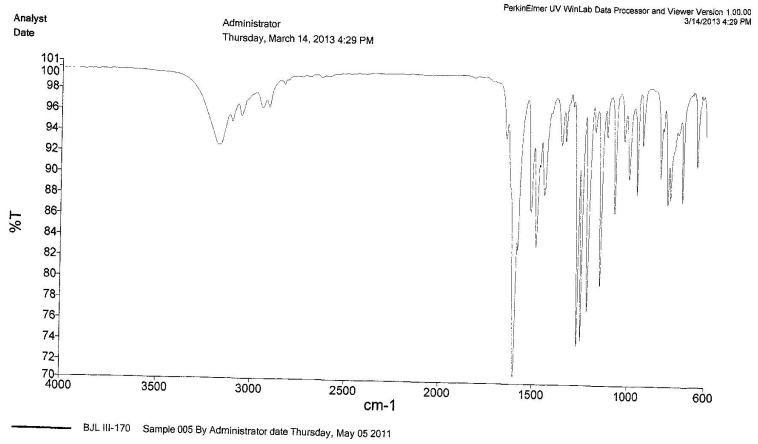


Figure A.1.27 IR spectra for precursor to compound **70**

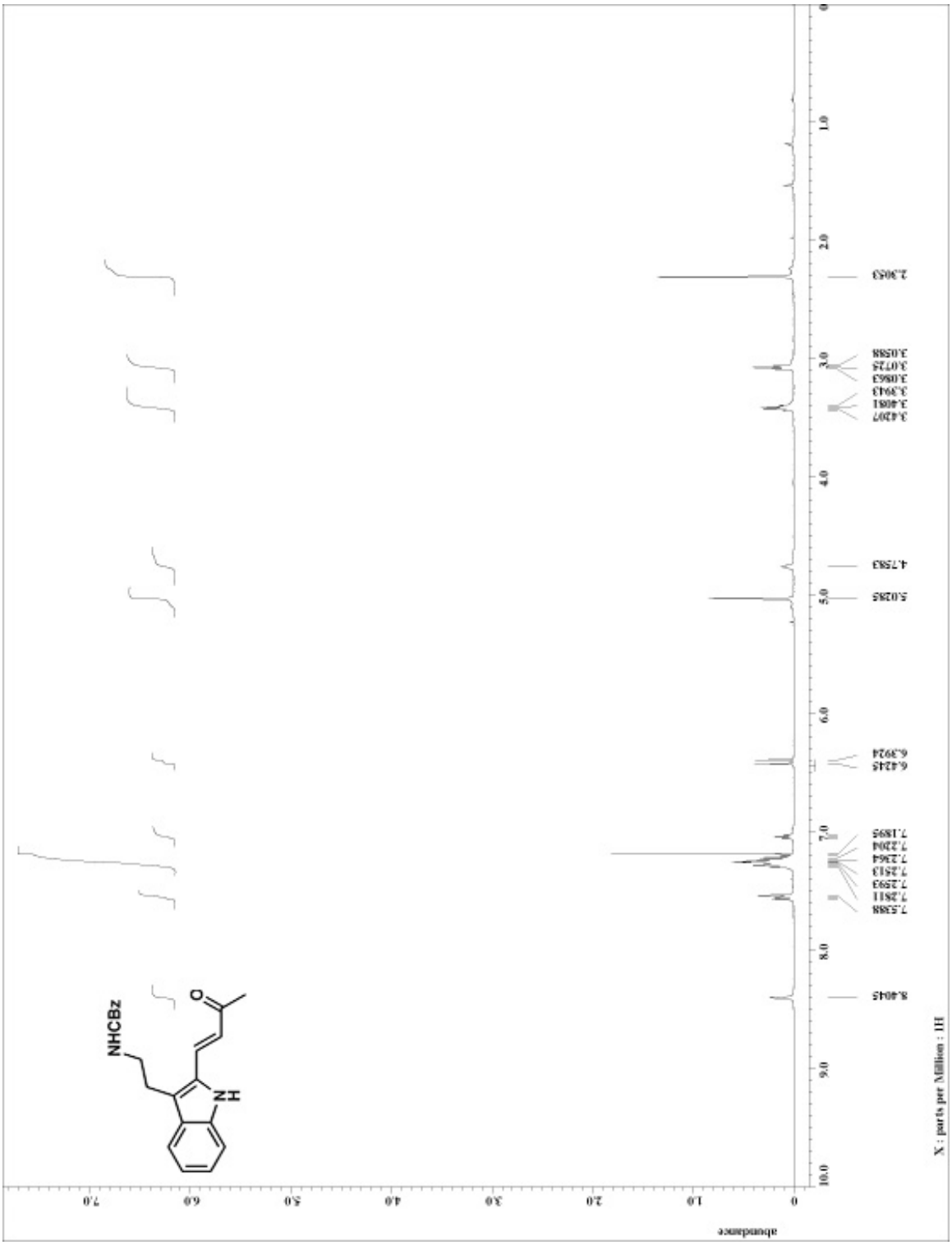


Figure A.1.28 ^{1}H NMR for compound **72**

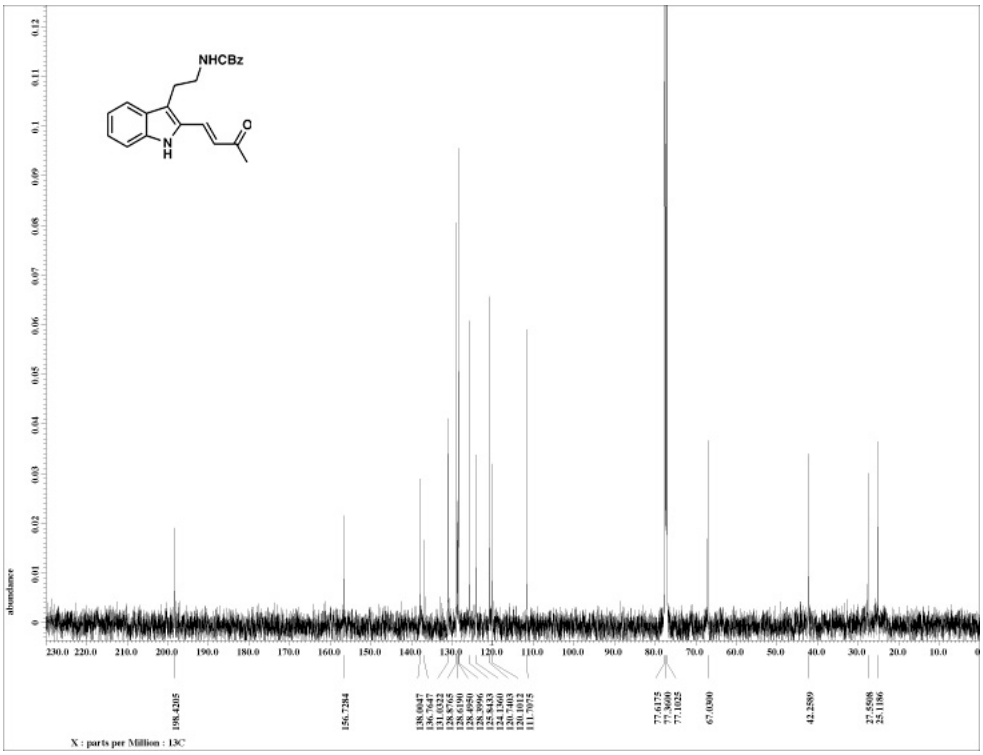


Figure A.1.29 ^{13}C NMR for compound **72**

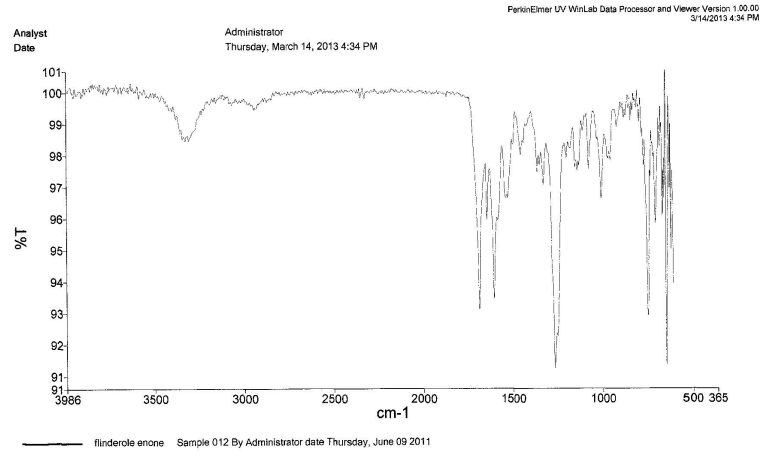


Figure A.1.30 IR spectra for compound **72**

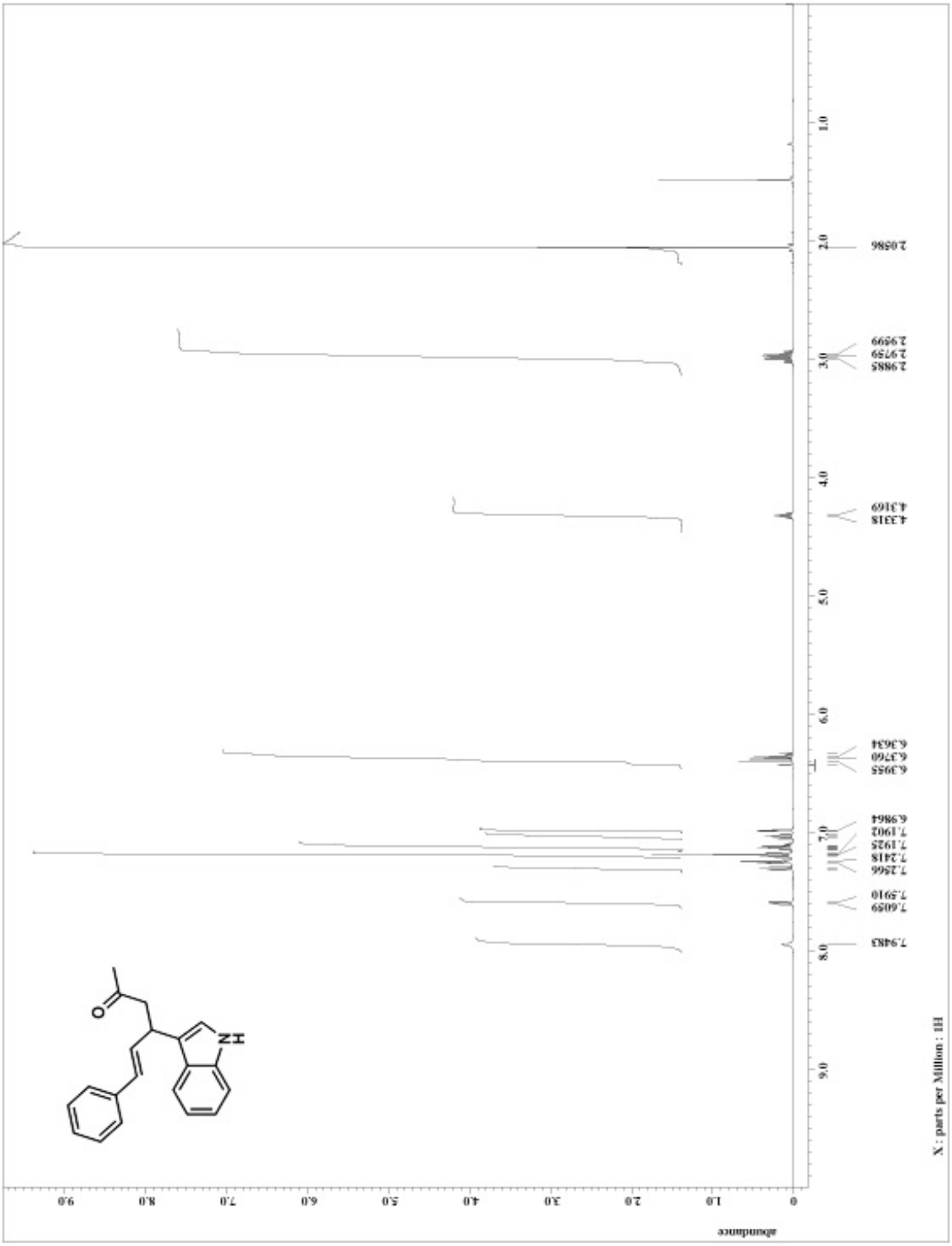


Figure A.1.31 ^{1}H NMR for compound **62**

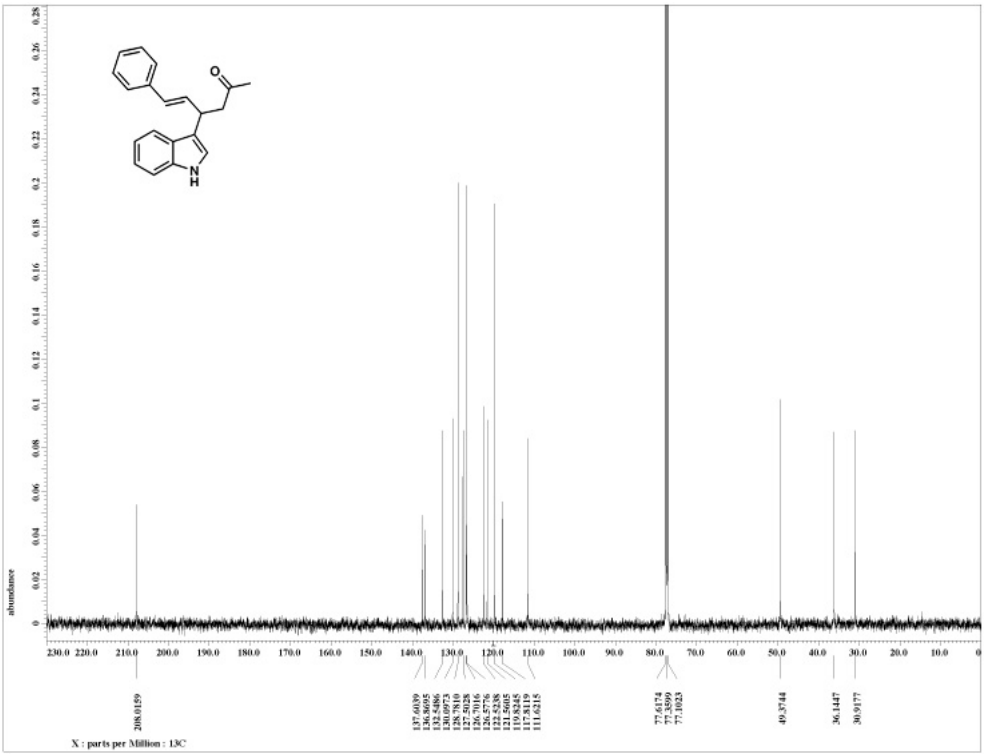


Figure A.1.32 ^{13}C NMR for compound **62**

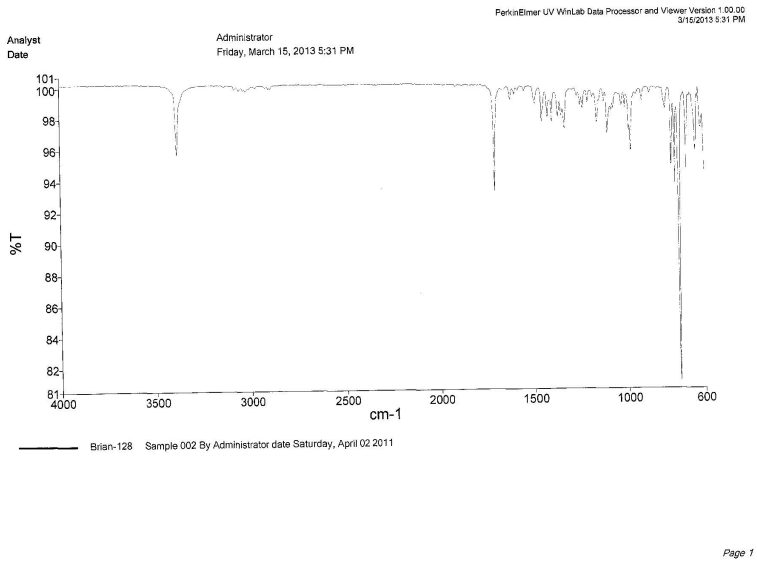
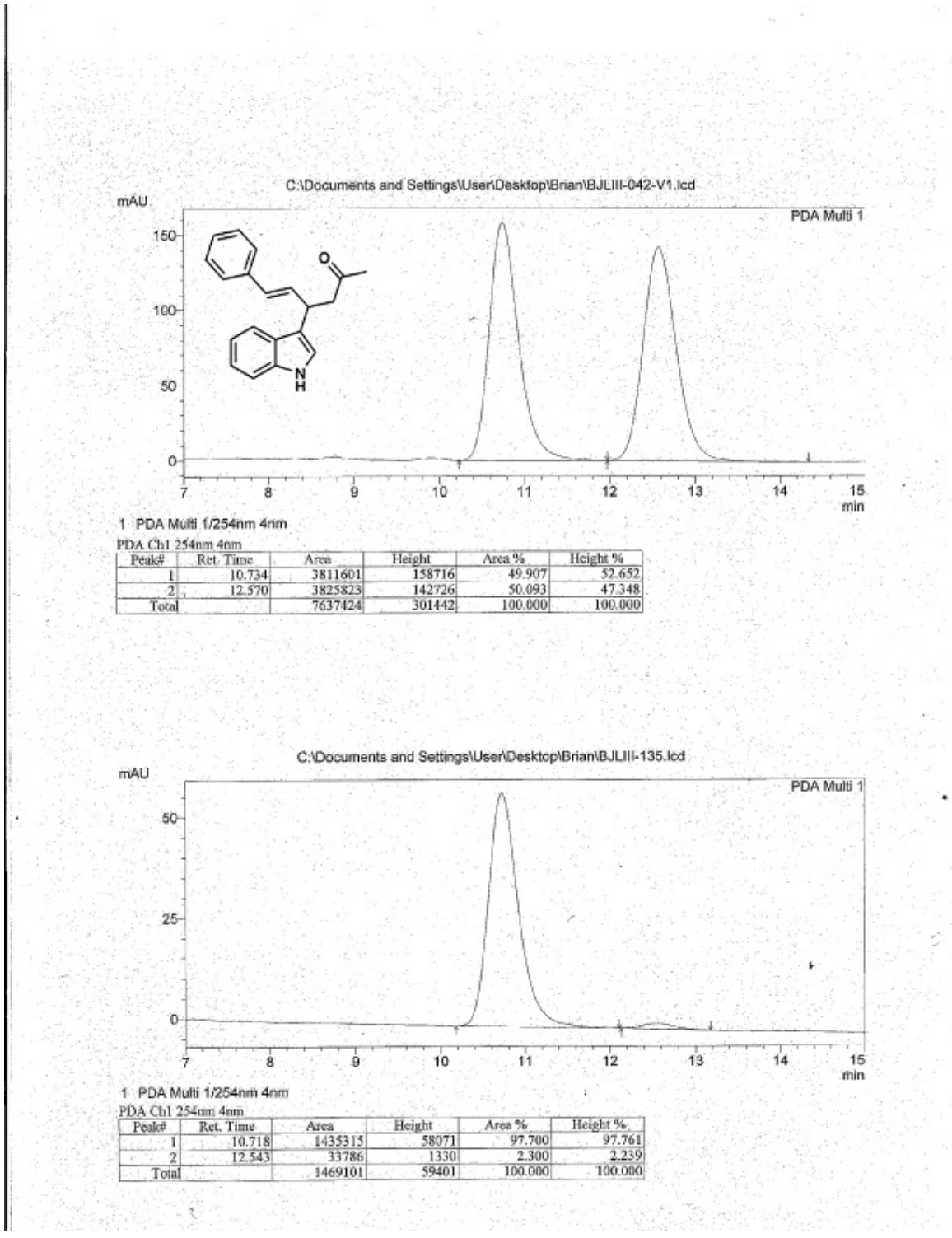


Figure A.1.33 IR spectra for compound **62**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.734	3811601	158716	49.907	52.652
2	12.570	3825823	142726	50.093	47.348
Total		7637424	301442	100.000	100.000

1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.718	1435315	58071	97.700	97.761
2	12.543	33786	1330	2.300	2.239
Total		1469101	59401	100.000	100.000

Figure A.1.34 HPLC trace for compound **62**

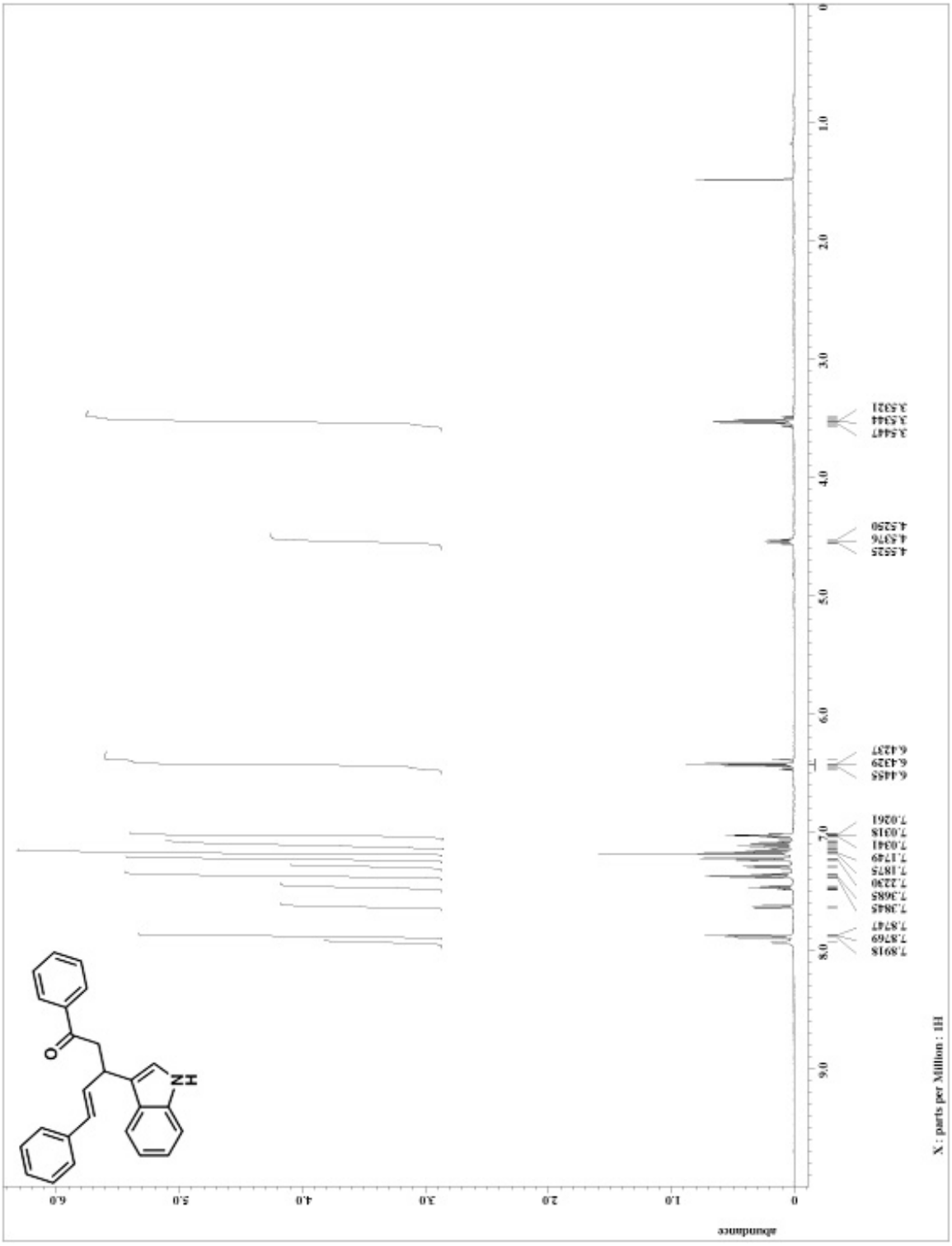


Figure A.1.35 ^{1}H NMR for compound **63**

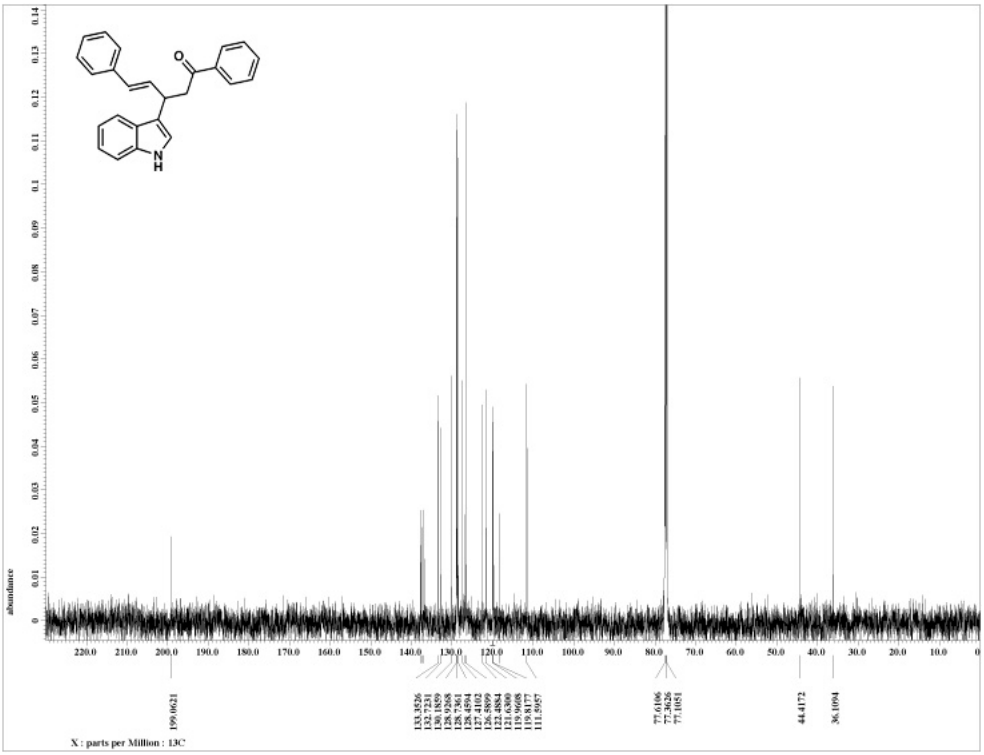


Figure A.1.36 ^{13}C NMR for compound **63**

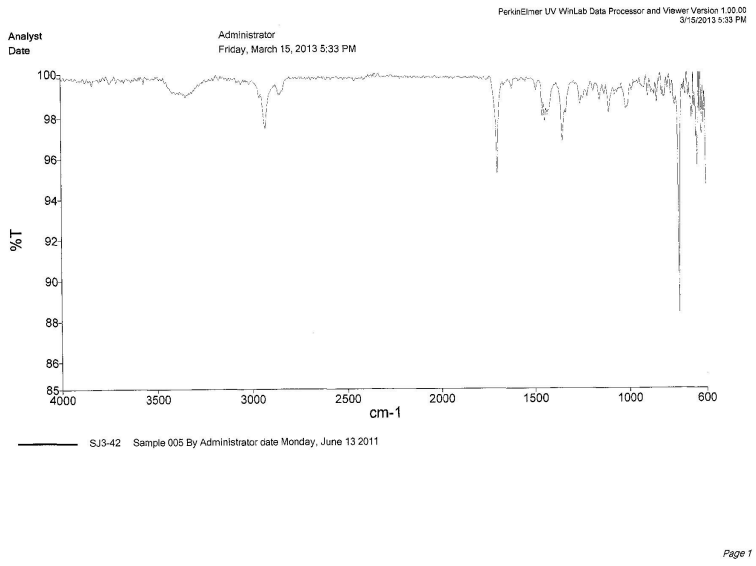
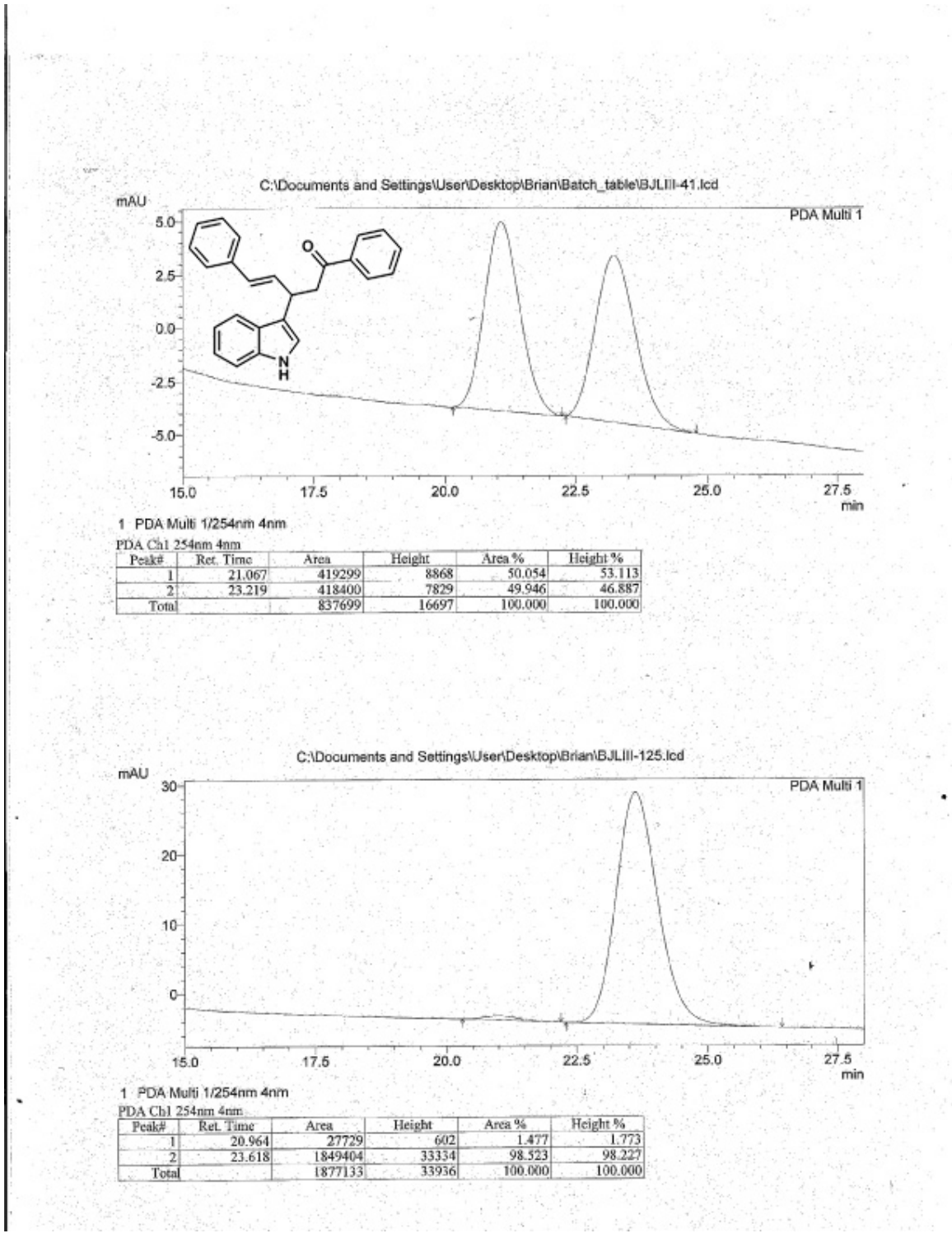


Figure A.1.37 IR spectra for compound **63**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.067	419299	8868	50.054	53.113
2	23.219	418400	7829	49.946	46.887
Total		837699	16697	100.000	100.000

1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.964	27729	602	1.477	1.773
2	23.618	1849404	33334	98.523	98.227
Total		1877133	33936	100.000	100.000

Figure A.1.38 HPLC trace for compound **63**

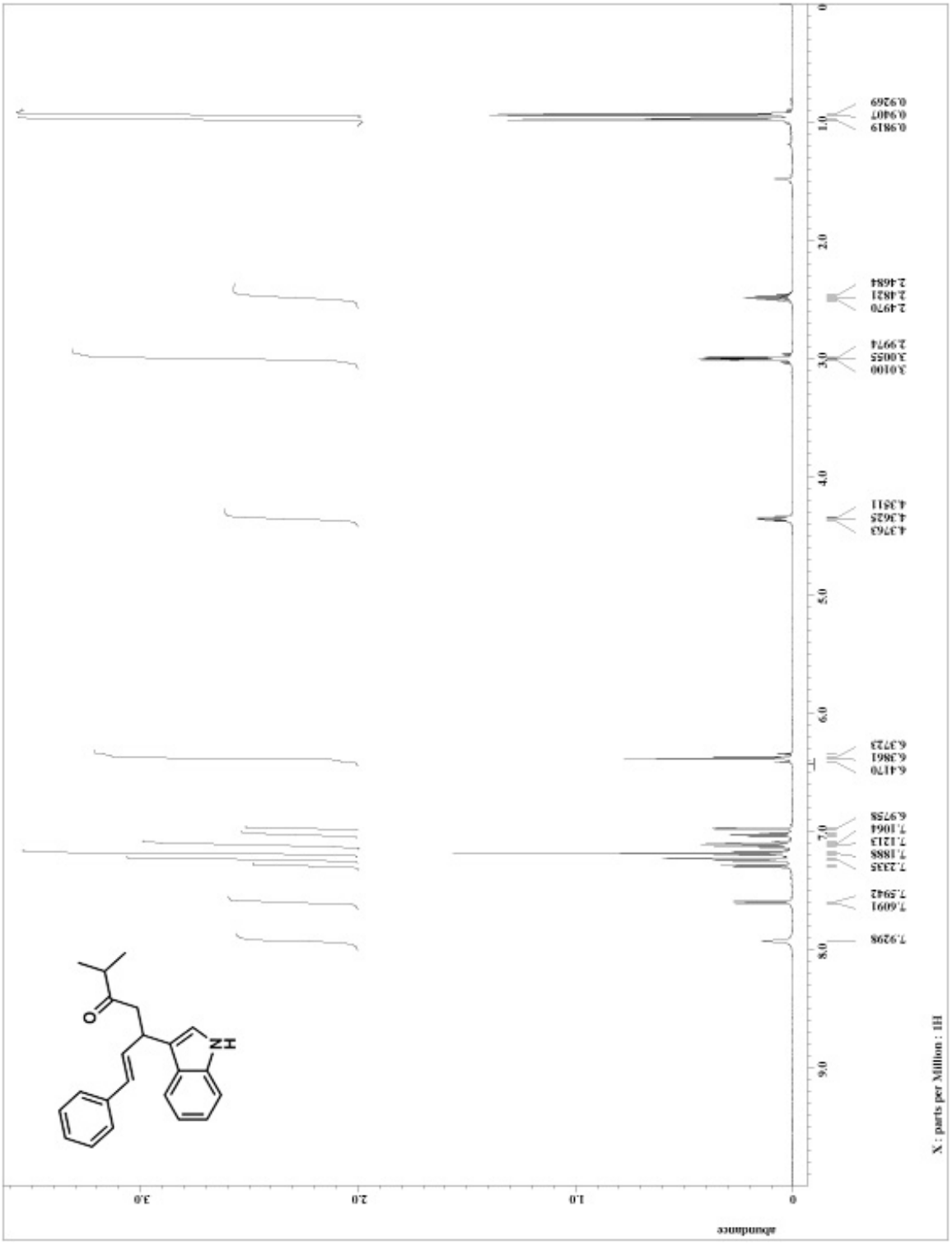


Figure A.1.39 ^{1}H NMR for compound **64**

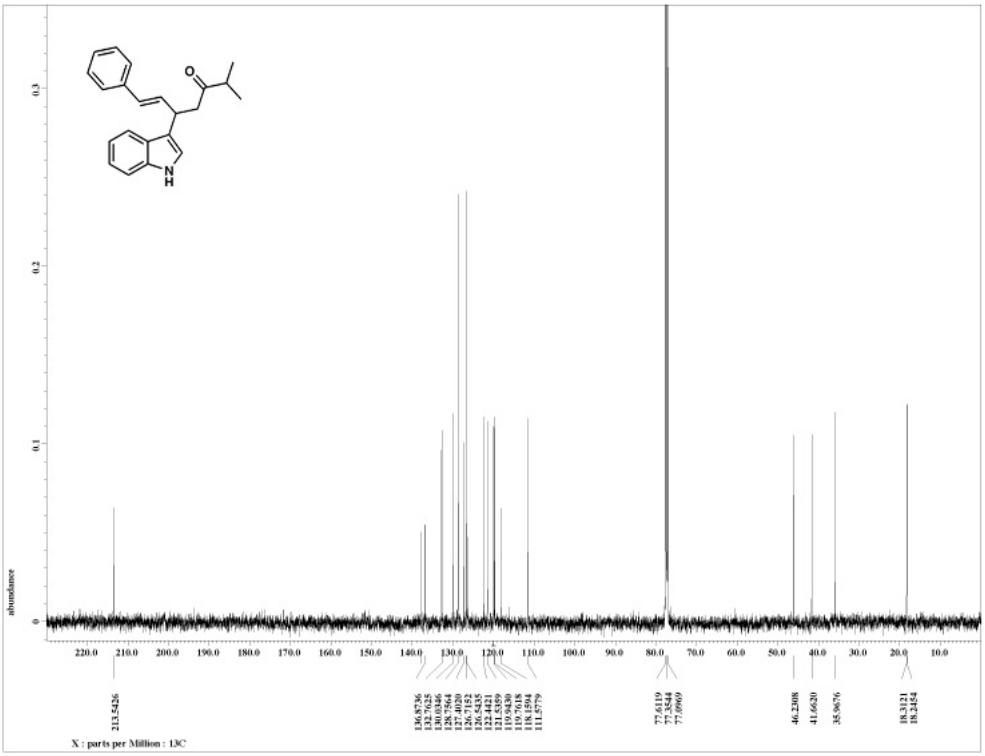


Figure A.1.40 ^{13}C NMR for compound **64**

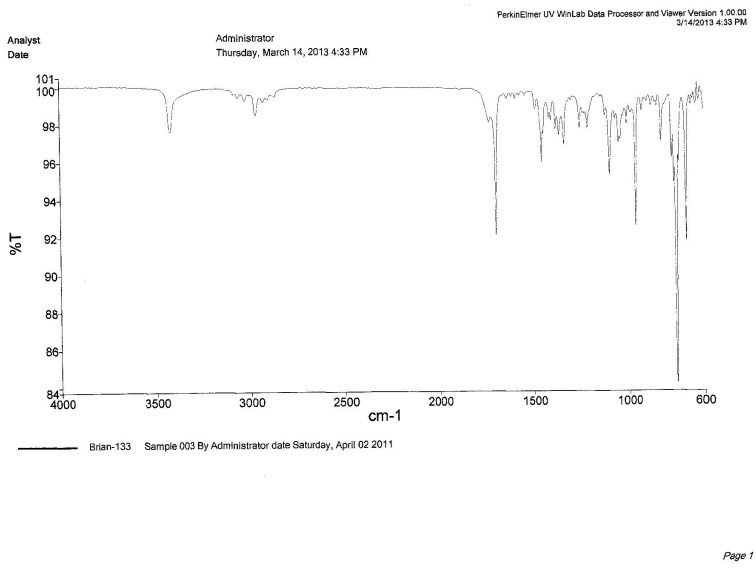
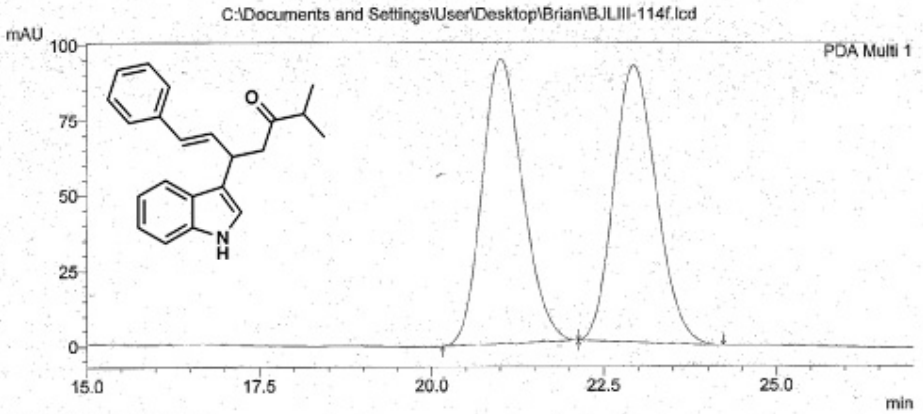


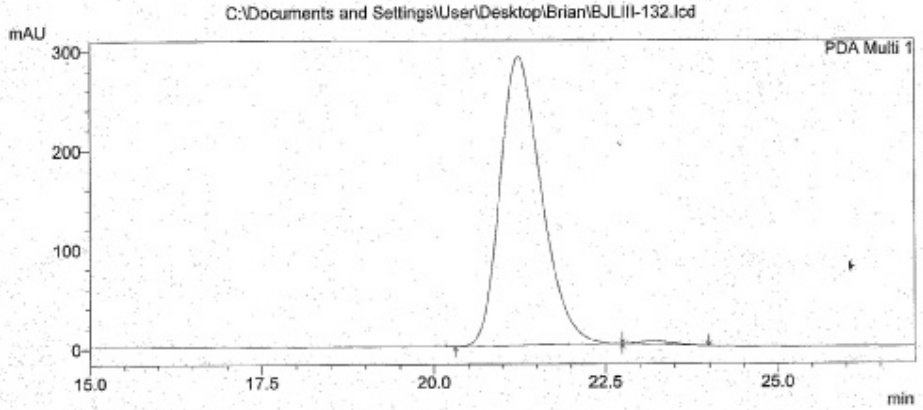
Figure A.1.41 IR spectra for compound **64**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.003	3928718	94713	49.903	50.678
2	22.934	3943998	92180	50.097	49.322
Total		7872716	186893	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.232	12225345	291078	99.120	98.980
2	23.178	108502	3000	0.880	1.020
Total		12333847	294078	100.000	100.000

Figure A.1.42 HPLC trace for compound **64**

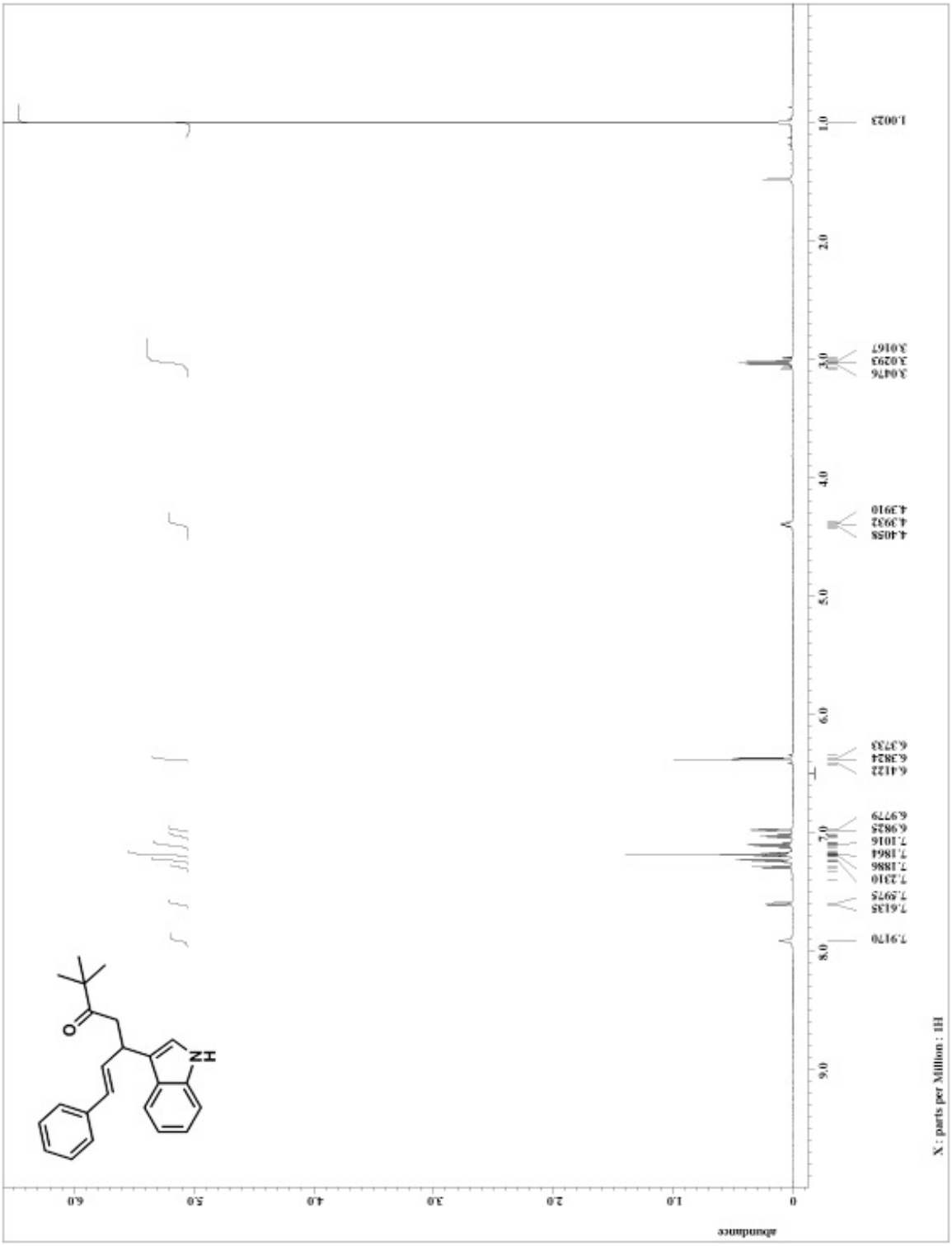


Figure A.1.43 ^{1}H NMR for compound **65**

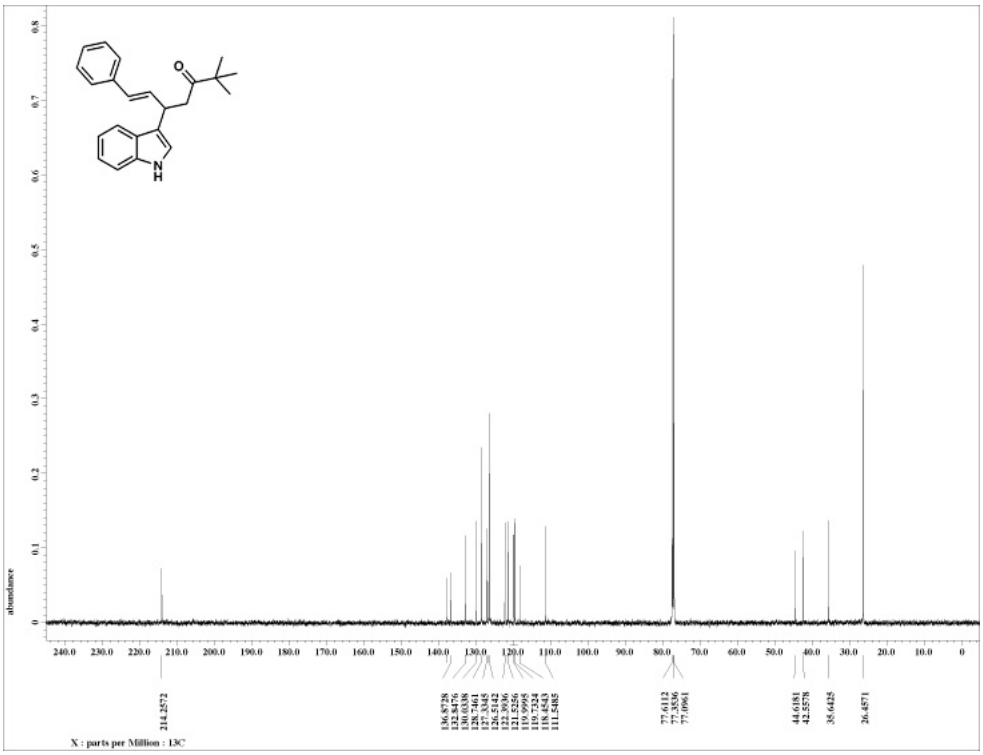


Figure A.1.44 ^{13}C NMR for compound **65**

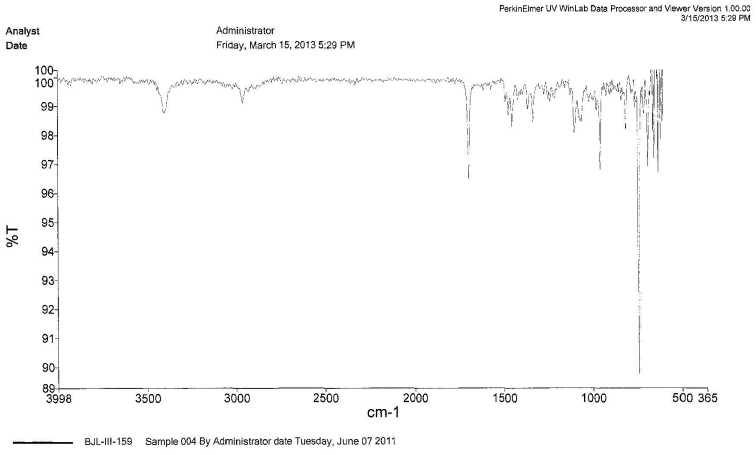
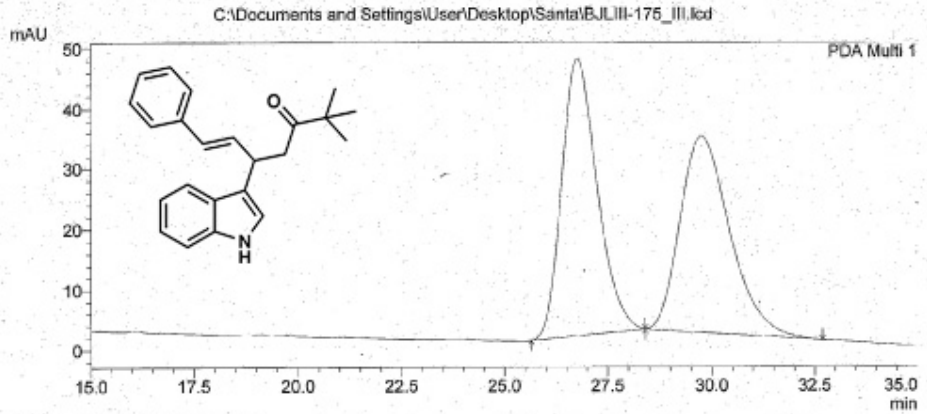


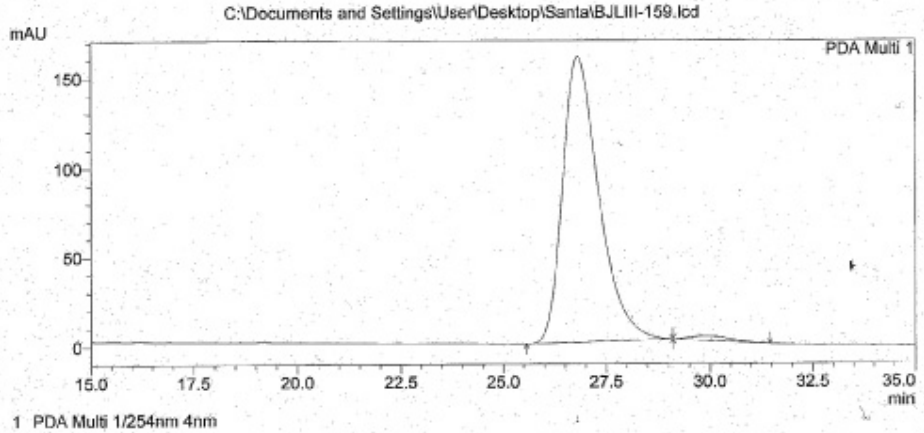
Figure A.1.45 IR spectra for compound **65**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.768	2744032	45967	50.330	58.541
2	29.748	2708103	32554	49.670	41.459
Total		5452135	78521	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.808	9764401	159702	98.320	98.470
2	29.901	166840	2481	1.680	1.530
Total		9931240	162184	100.000	100.000

Figure A.1.46 HPLC trace for compound **65**

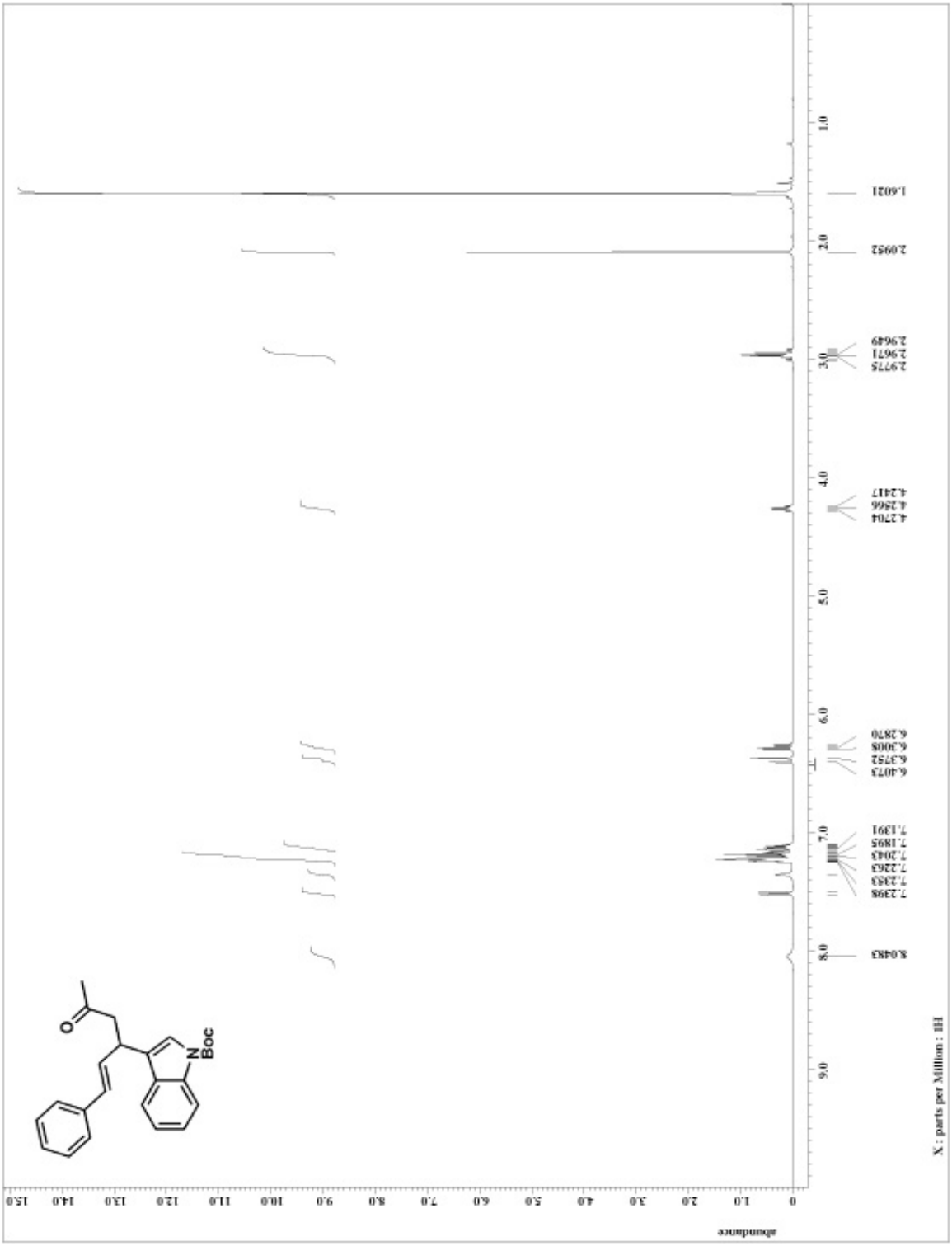


Figure A.1.47 ^{1}H NMR for compound **66**

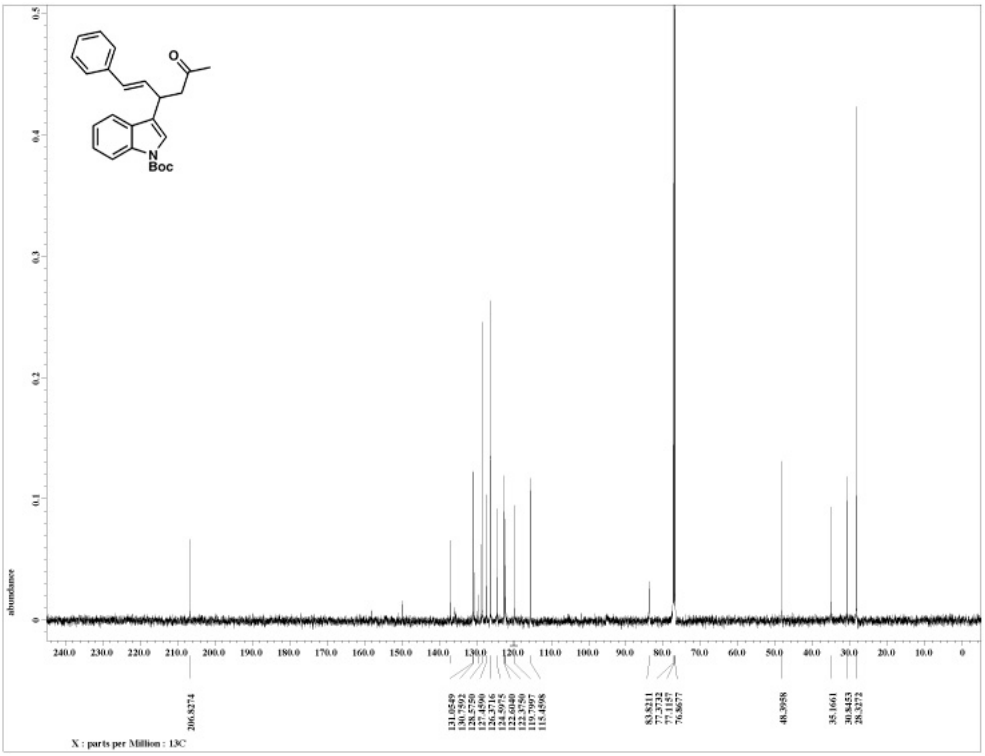


Figure A.1.48 ^{13}C NMR for compound **66**

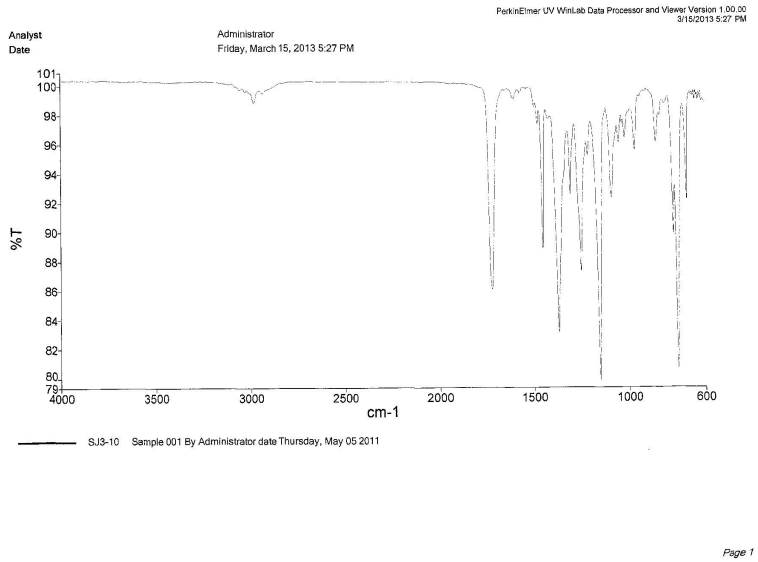
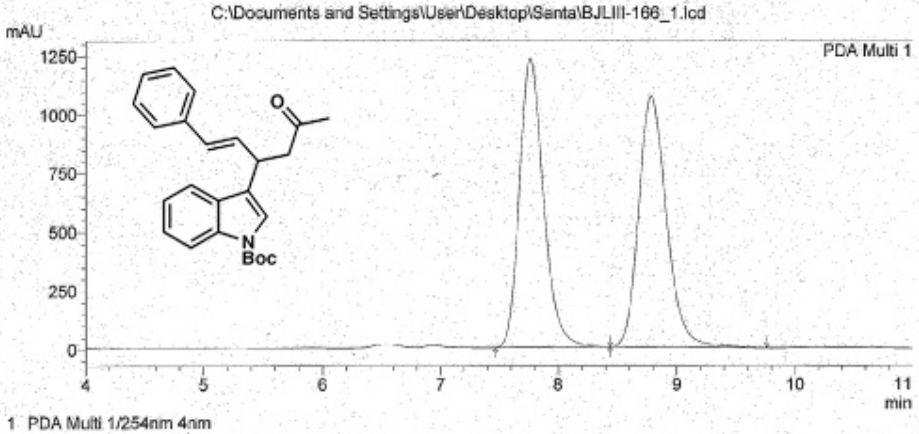


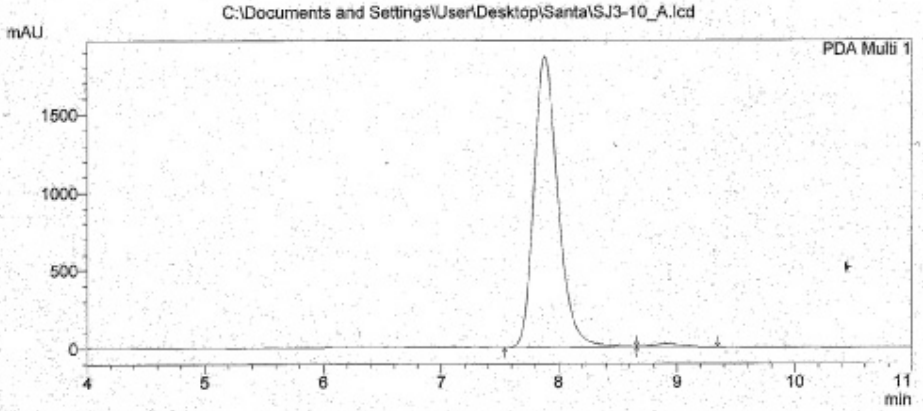
Figure A.1.49 IR spectra for compound **66**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.758	17484689	1234630	49.951	53.493
2	8.780	17518956	1073400	50.049	46.507
Total		35003645	2308031	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.879	26292075	1863651	98.950	99.040
2	8.911	279095	18059	1.050	0.960
Total		26571171	1881709	100.000	100.000

Figure A.1.50 HPLC trace for compound **66**

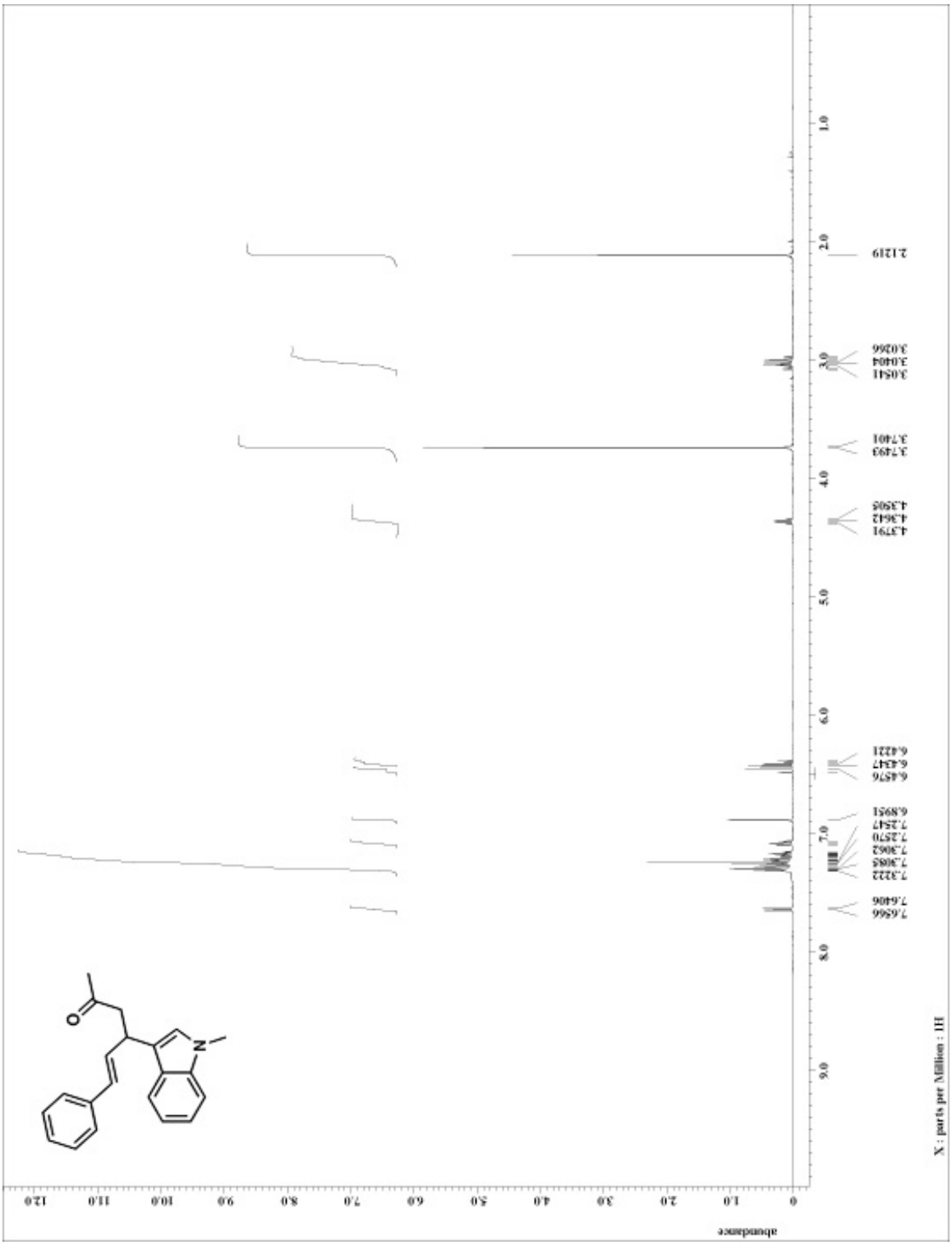


Figure A.1.51 ^{1}H NMR for compound **67**

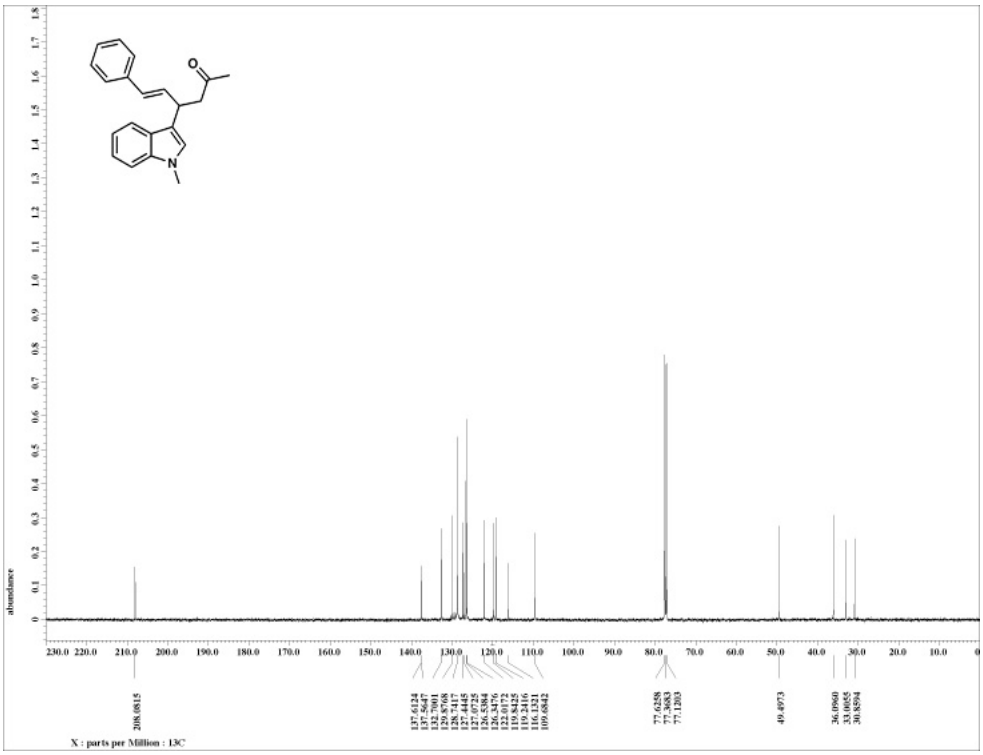


Figure A.1.52 ^{13}C NMR for compound **67**

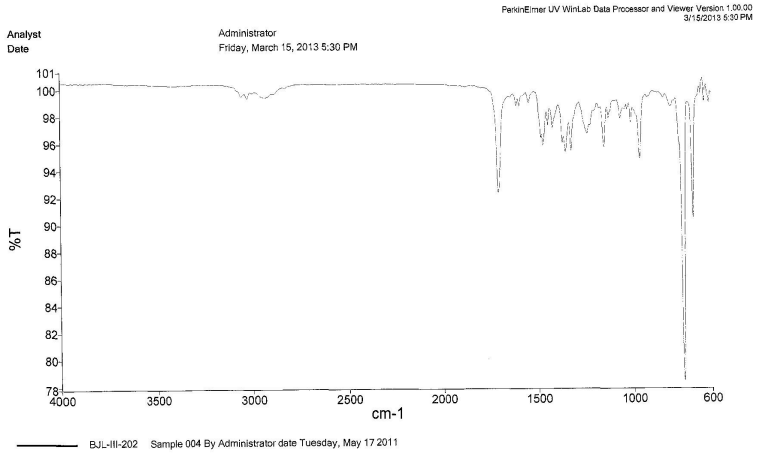
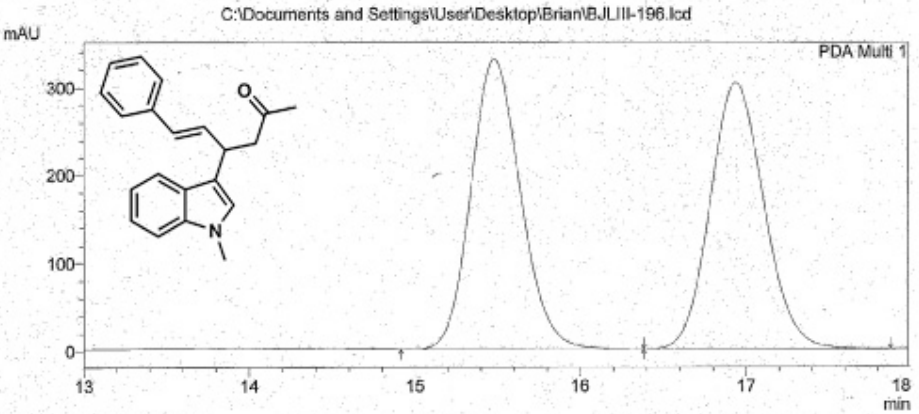


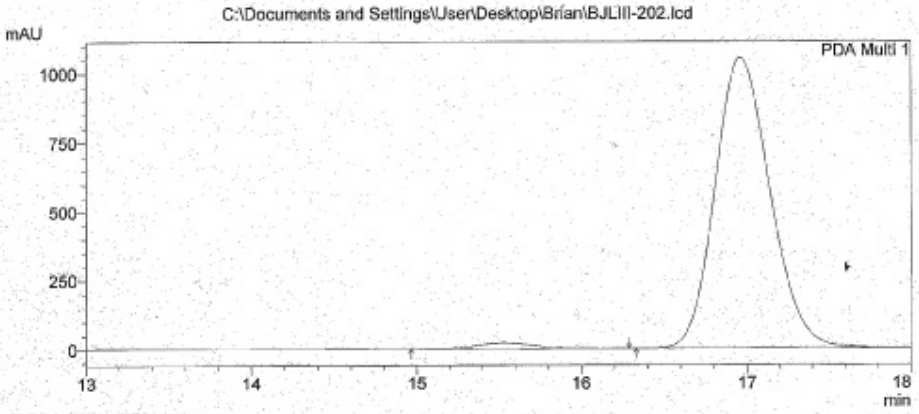
Figure A.1.53 IR spectra for compound **67**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.476	6923548	330443	50.225	52.091
2	16.932	6861610	303912	49.775	47.909
Total		13785158	634355	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.526	444943	20537	1.788	1.909
2	16.957	24438141	1054974	98.212	98.091
Total		24883085	1075510	100.000	100.000

Figure A.1.54 HPLC trace for compound **67**

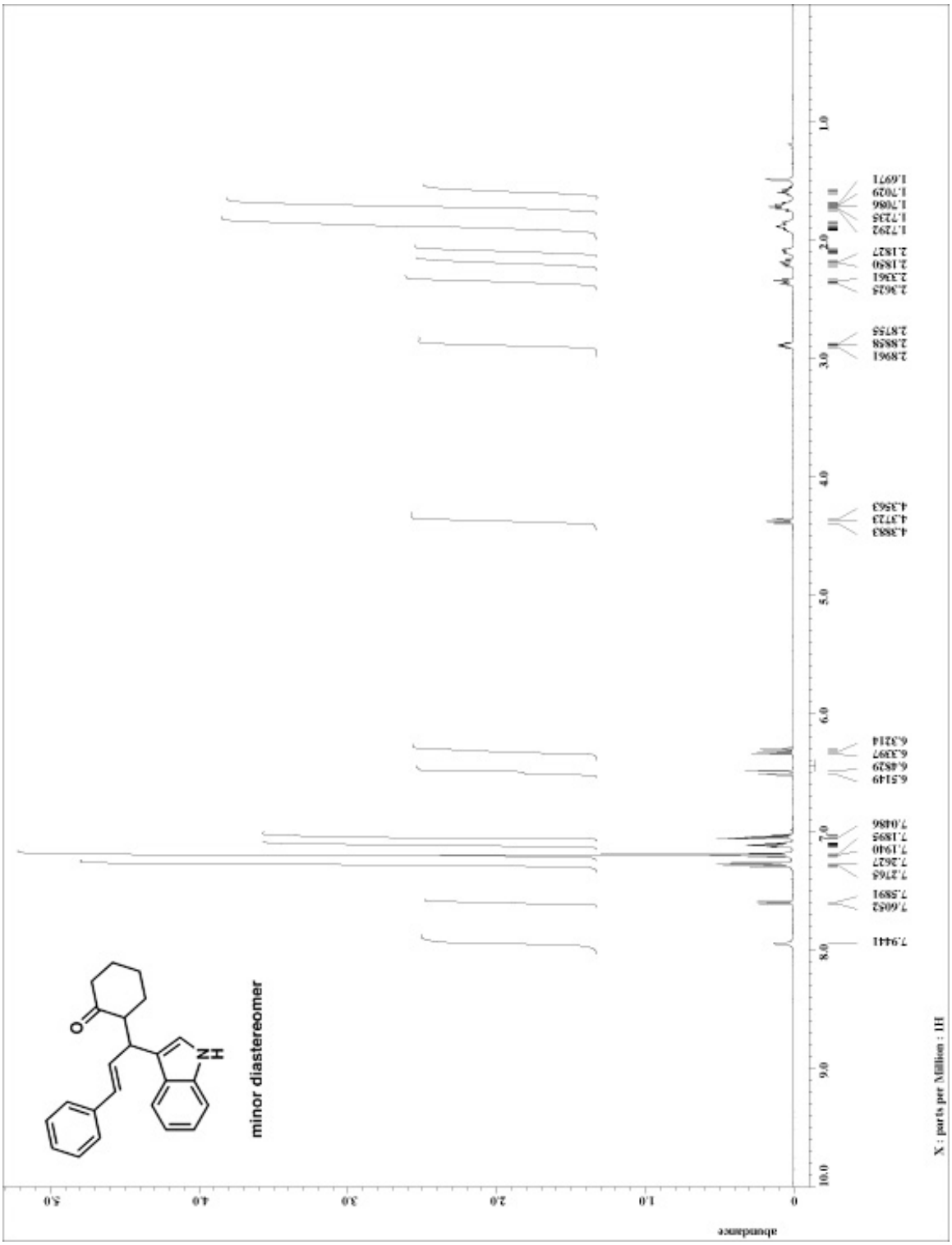


Figure A.1.55 ^{1}H NMR for compound **68**

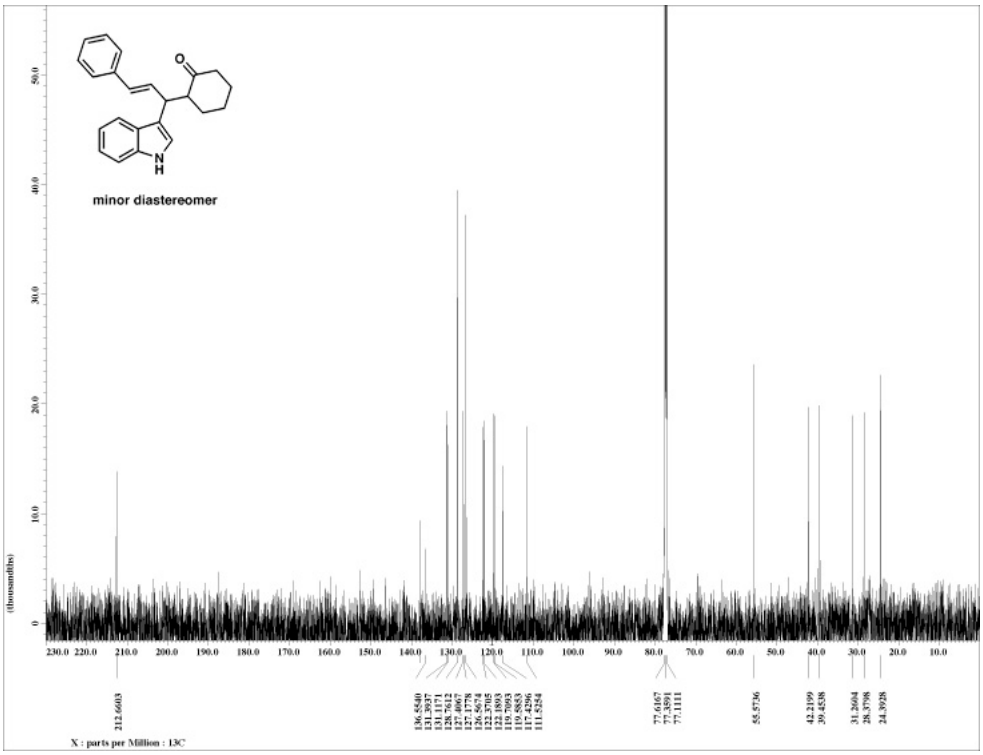


Figure A.1.56 ^{13}C NMR for compound **68**

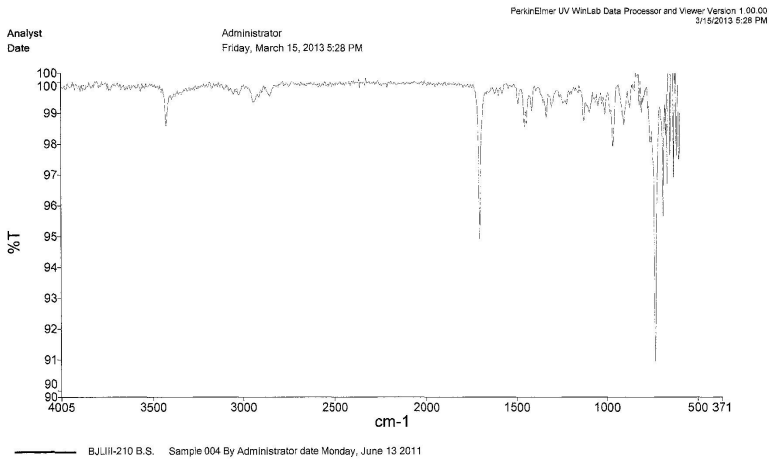
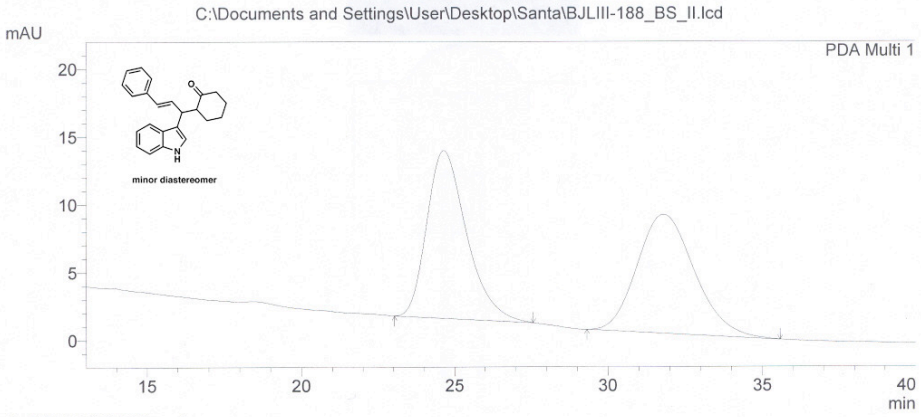


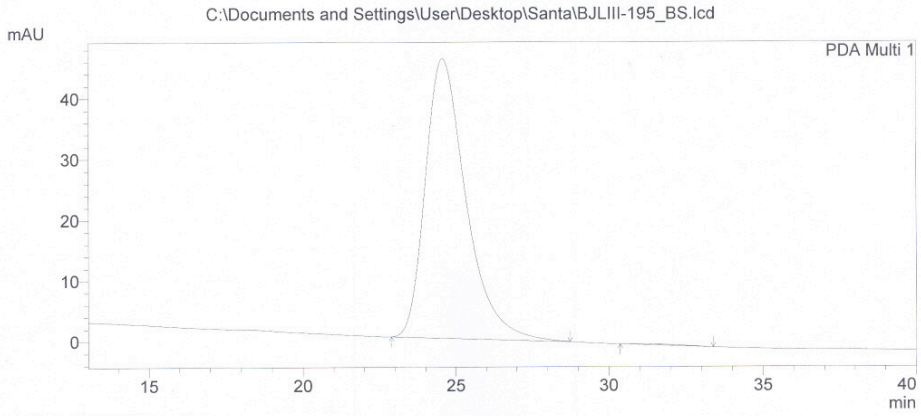
Figure A.1.57 IR spectra for compound **68**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.651	1121094	12376	49.826	58.478
2	31.823	1128924	8787	50.174	41.522
Total		2250018	21163	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.552	4294598	46035	99.622	99.962
2	30.440	16294	17	0.378	0.038
Total		4310892	46052	100.000	100.000

Figure A.1.58 HPLC trace for compound **68**

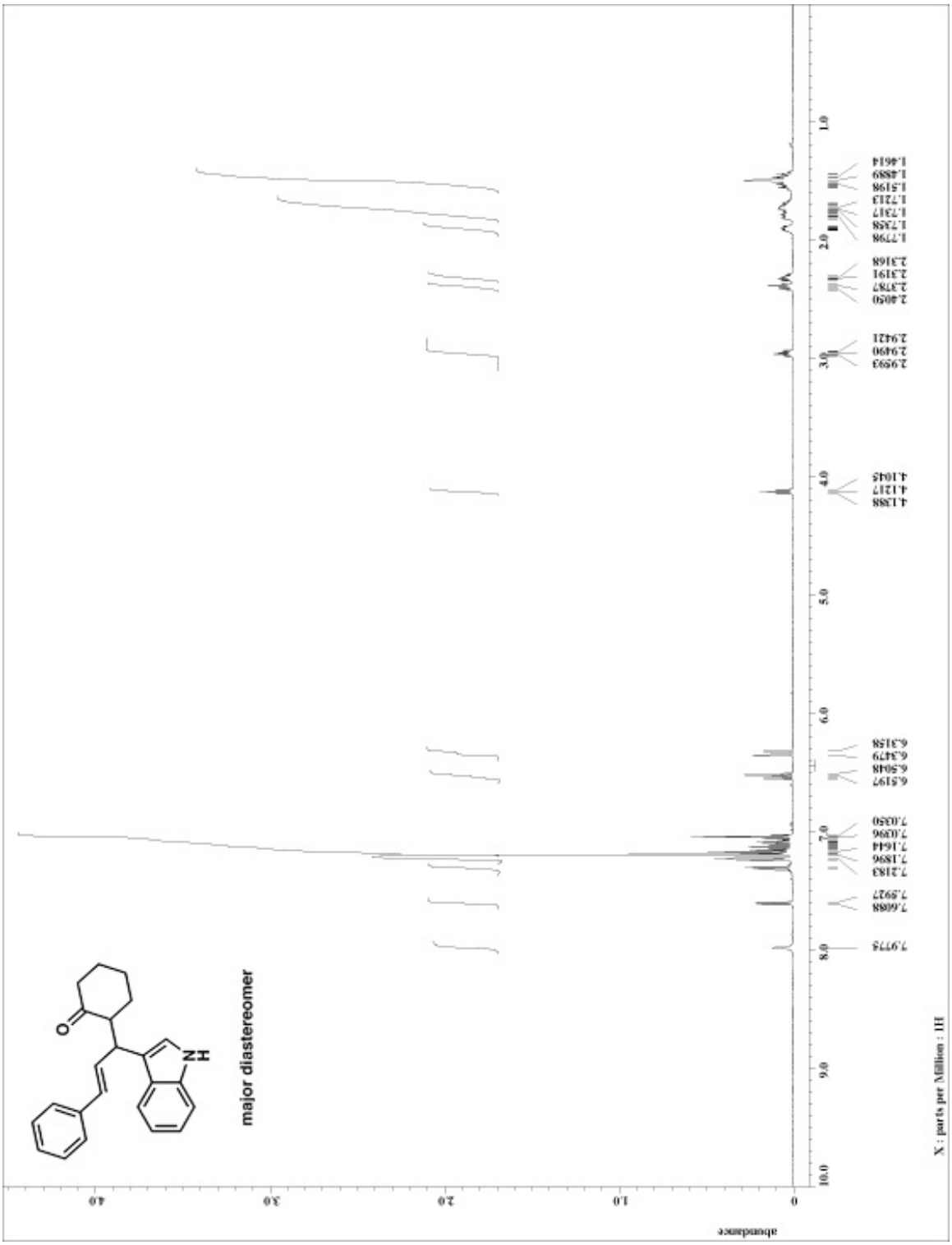


Figure A.1.59 ^{1}H NMR for compound **68**

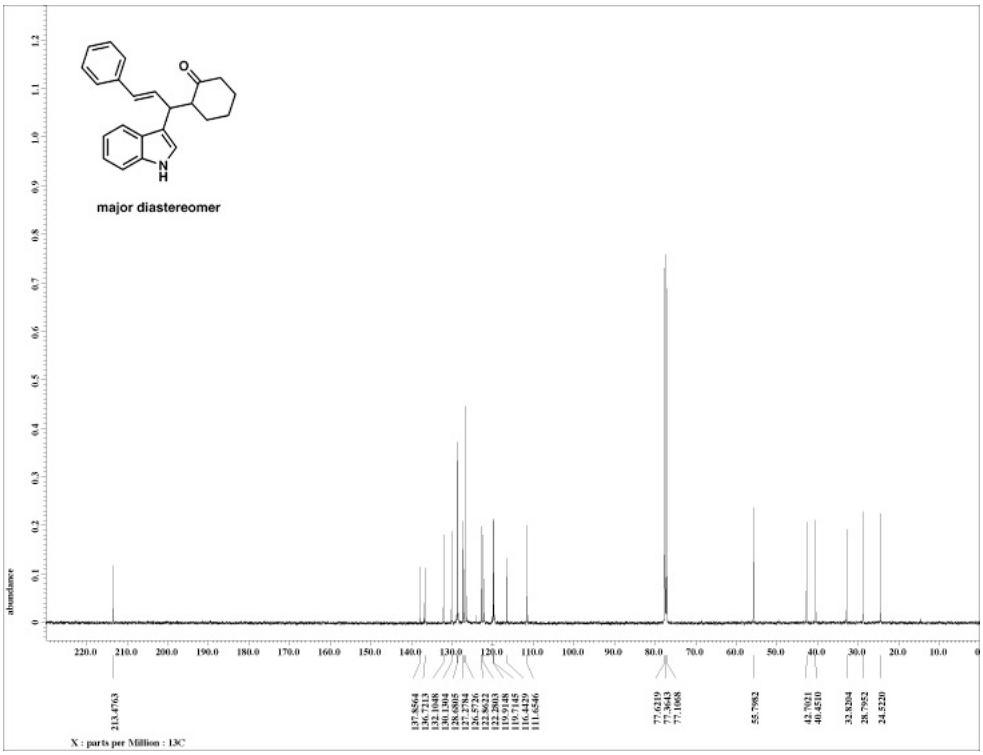


Figure A.1.60 ^{13}C NMR for compound **68**

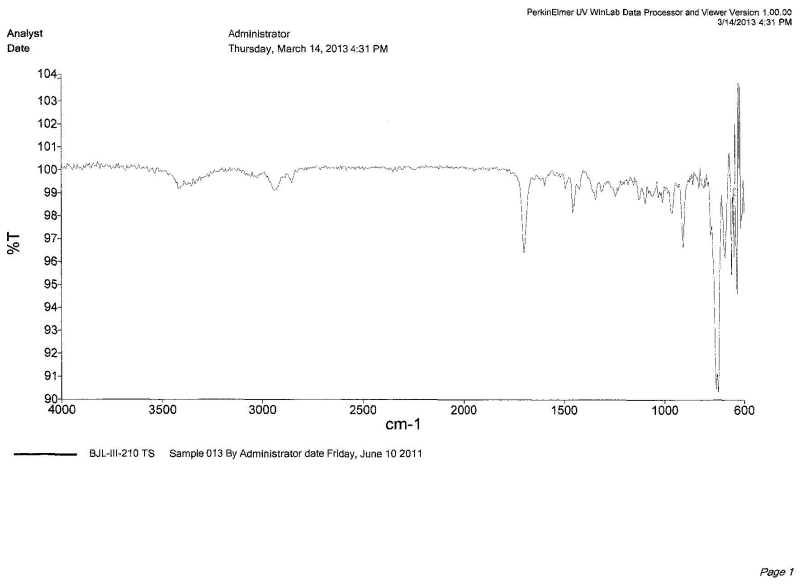
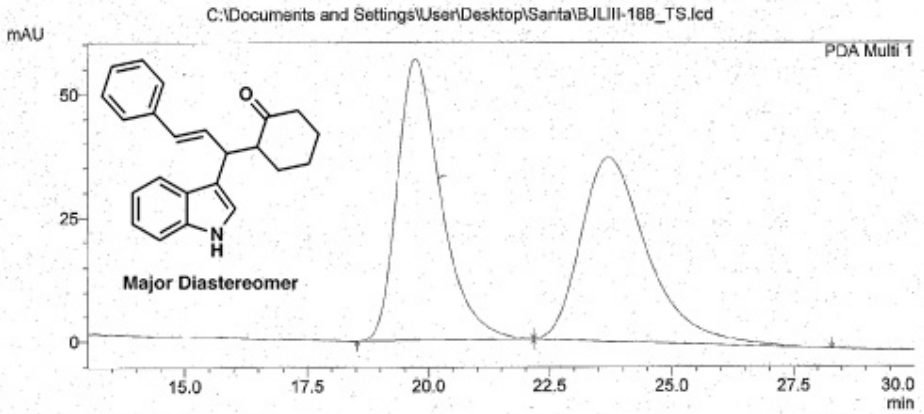


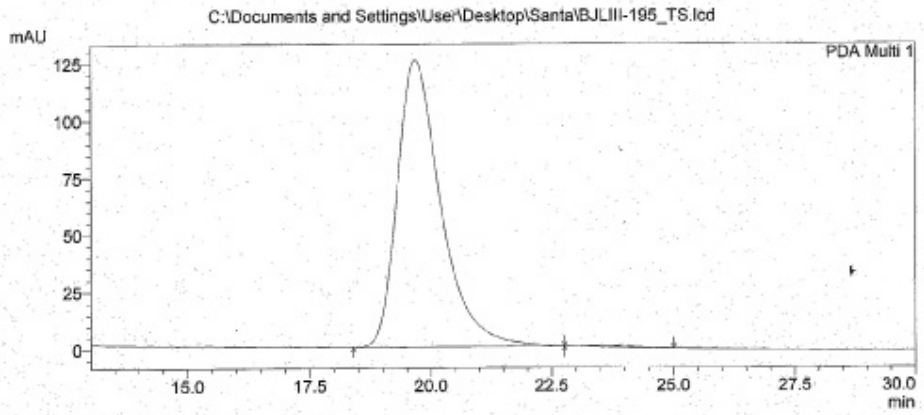
Figure A.1.61 IR spectra for compound **68**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.731	3578309	56869	50.282	60.475
2	23.708	3538205	37168	49.718	39.525
Total		7116514	94037	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.674	7863370	125430	99.665	99.992
2	22.778	26433	10	0.335	0.008
Total		7889803	125440	100.000	100.000

Figure A.1.62 HPLC trace for compound **68**

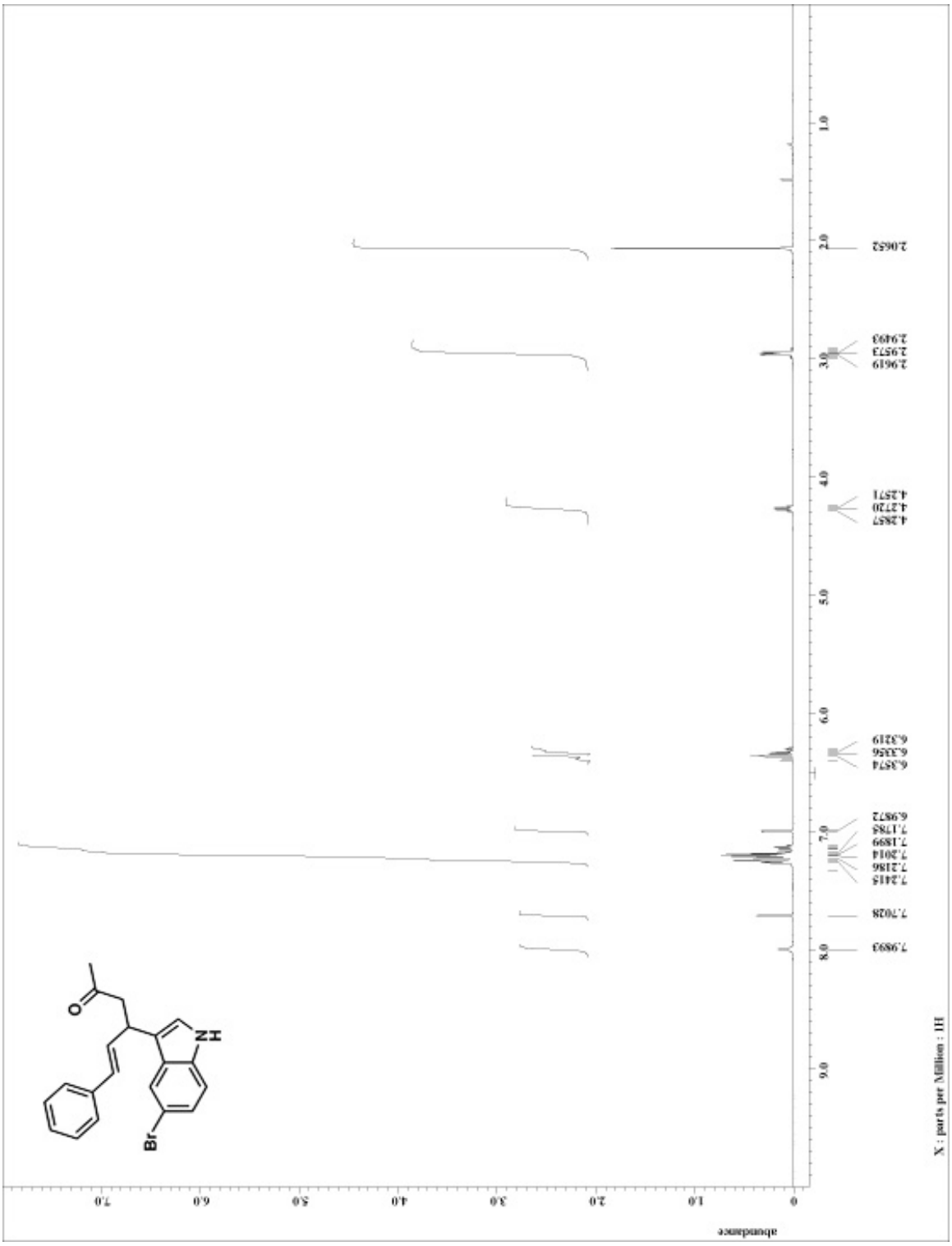


Figure A.1.63 ^{1}H NMR for compound **69**

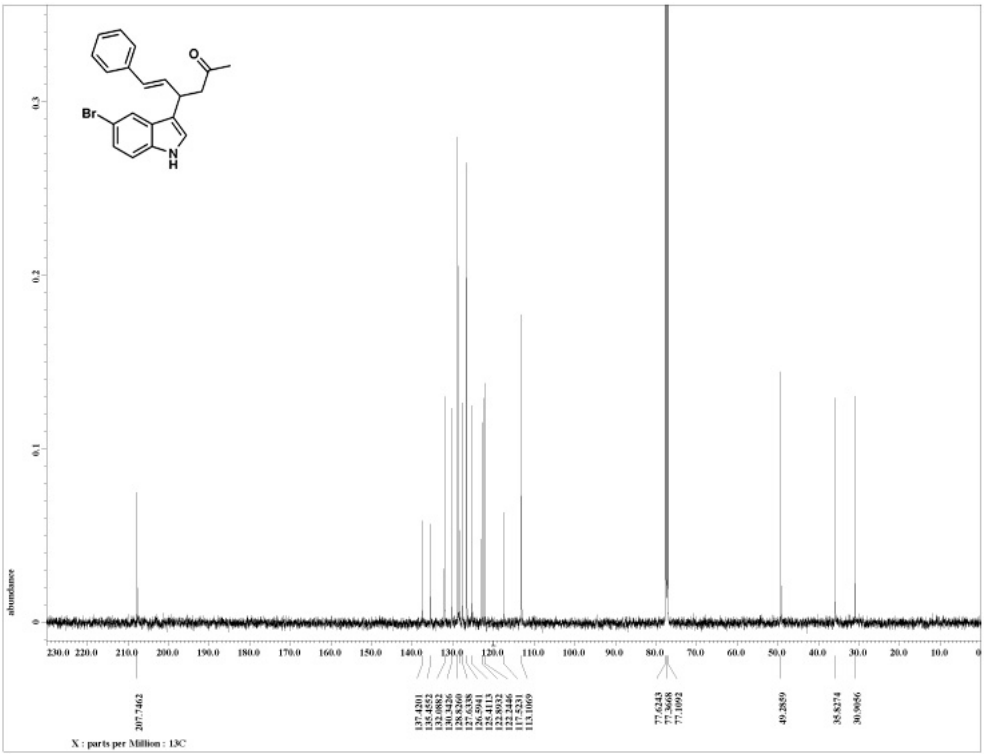


Figure A.1.64 ^{13}C NMR for compound **69**

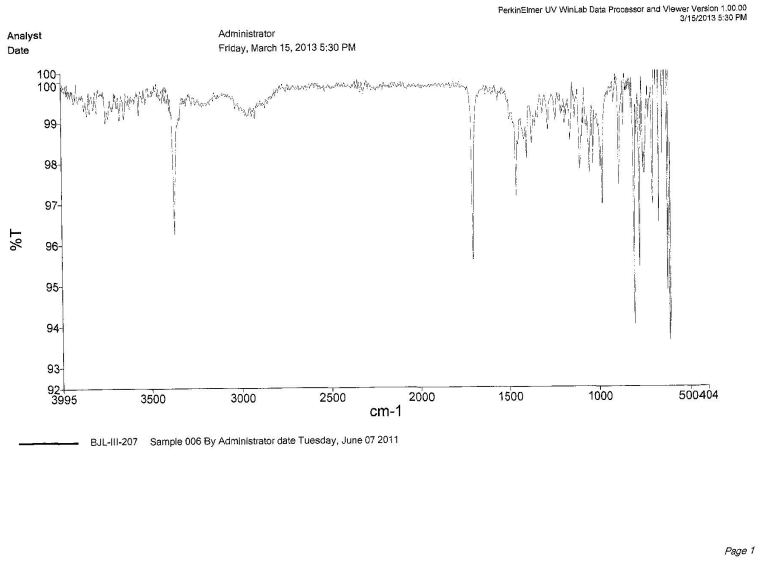
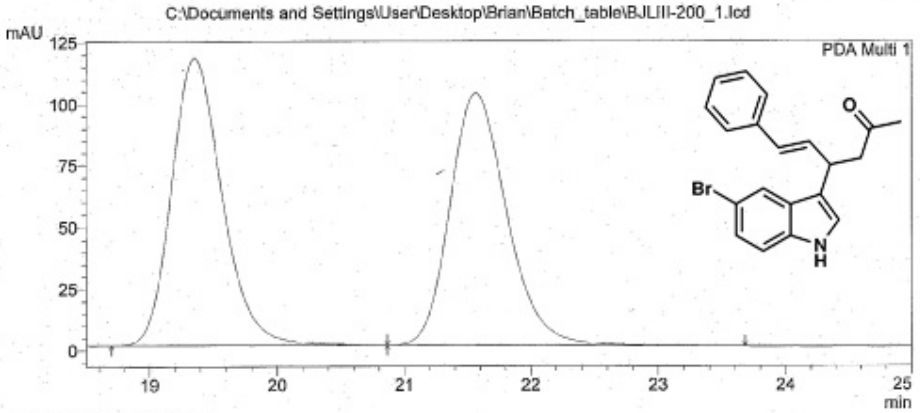


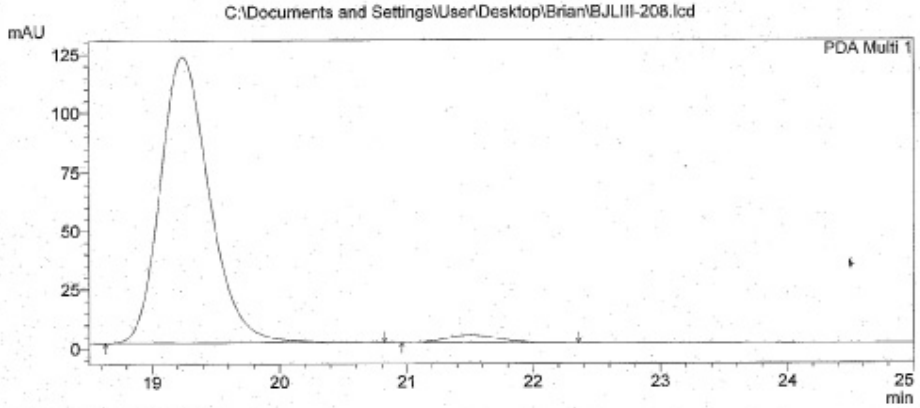
Figure A.1.65 IR spectra for compound **69**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.349	3209470	116652	49.916	53.209
2	21.559	3220314	102584	50.084	46.791
Total		6429784	219236	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.238	3253967	121523	97.261	97.578
2	21.497	91644	3016	2.739	2.422
Total		3345611	124539	100.000	100.000

Figure A.1.66 HPLC trace for compound **69**

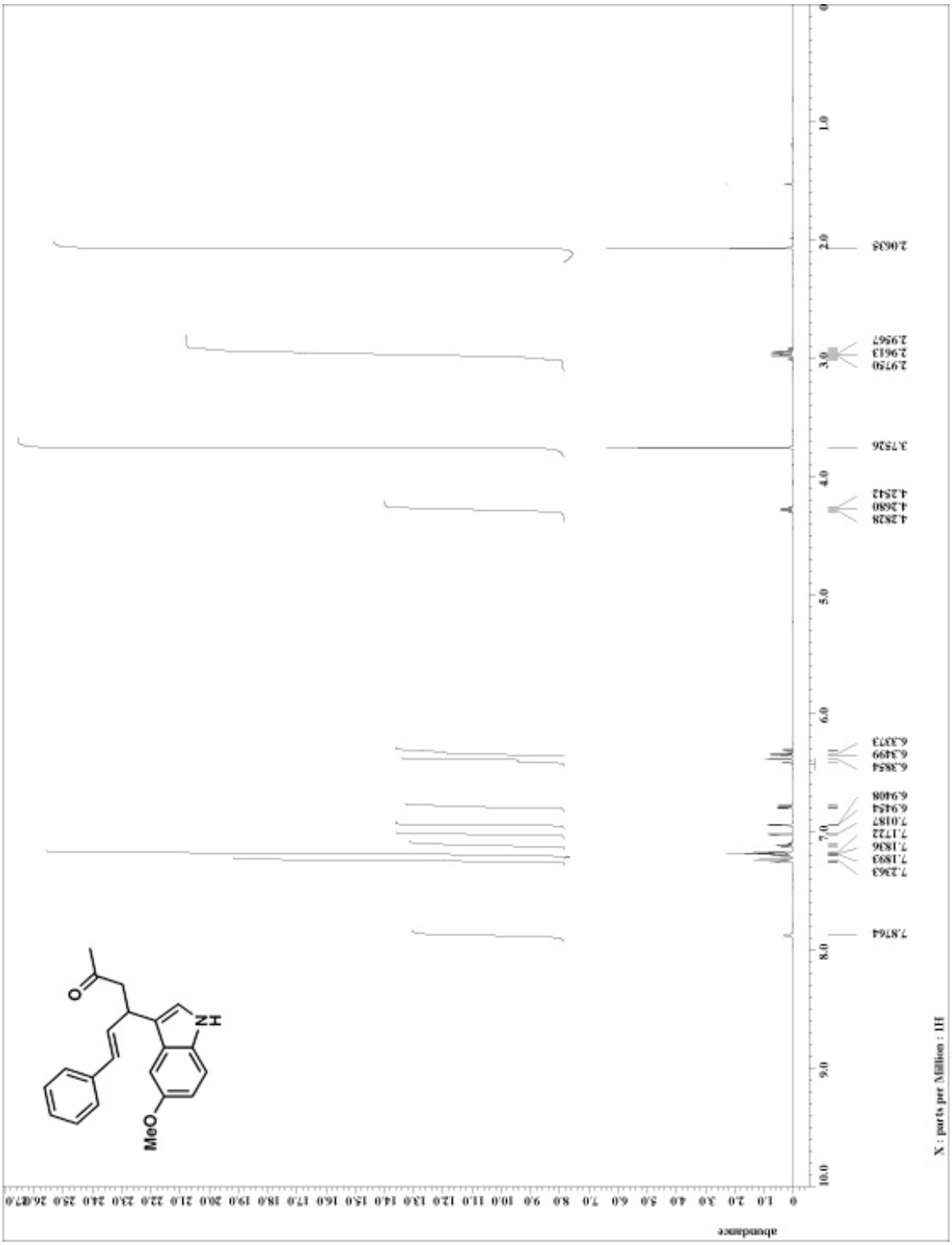


Figure A.1.67 ^{1}H NMR for compound **70**

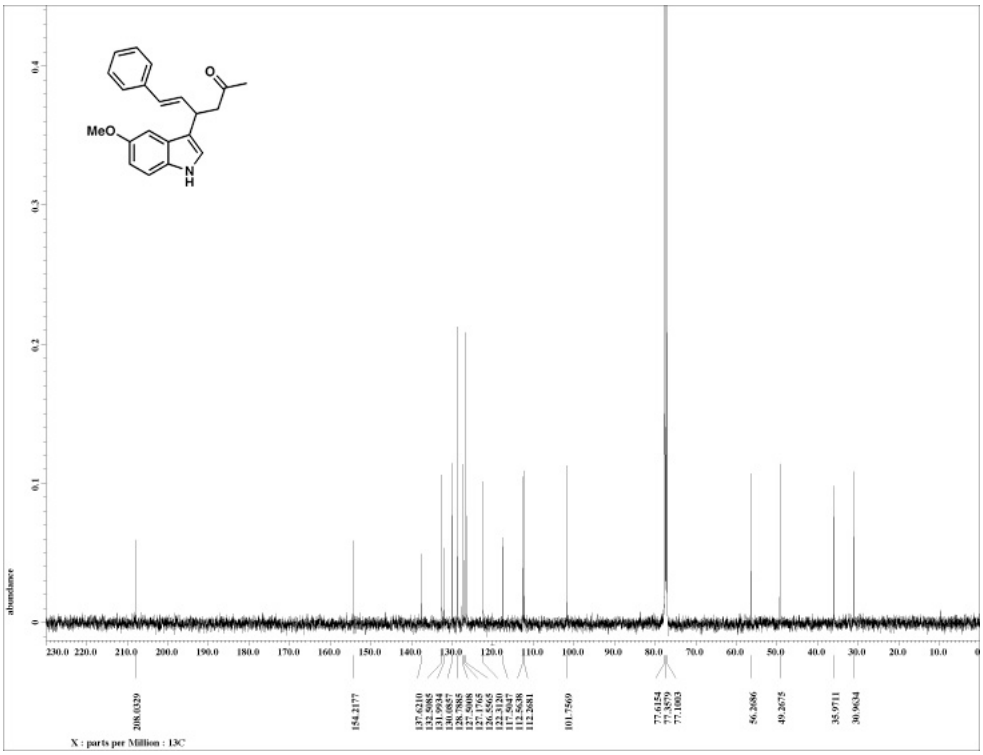


Figure A.1.68 ^{13}C NMR for compound **70**

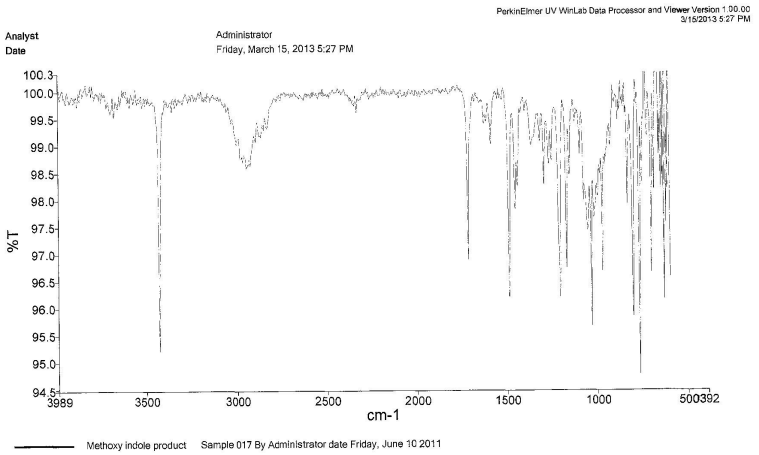
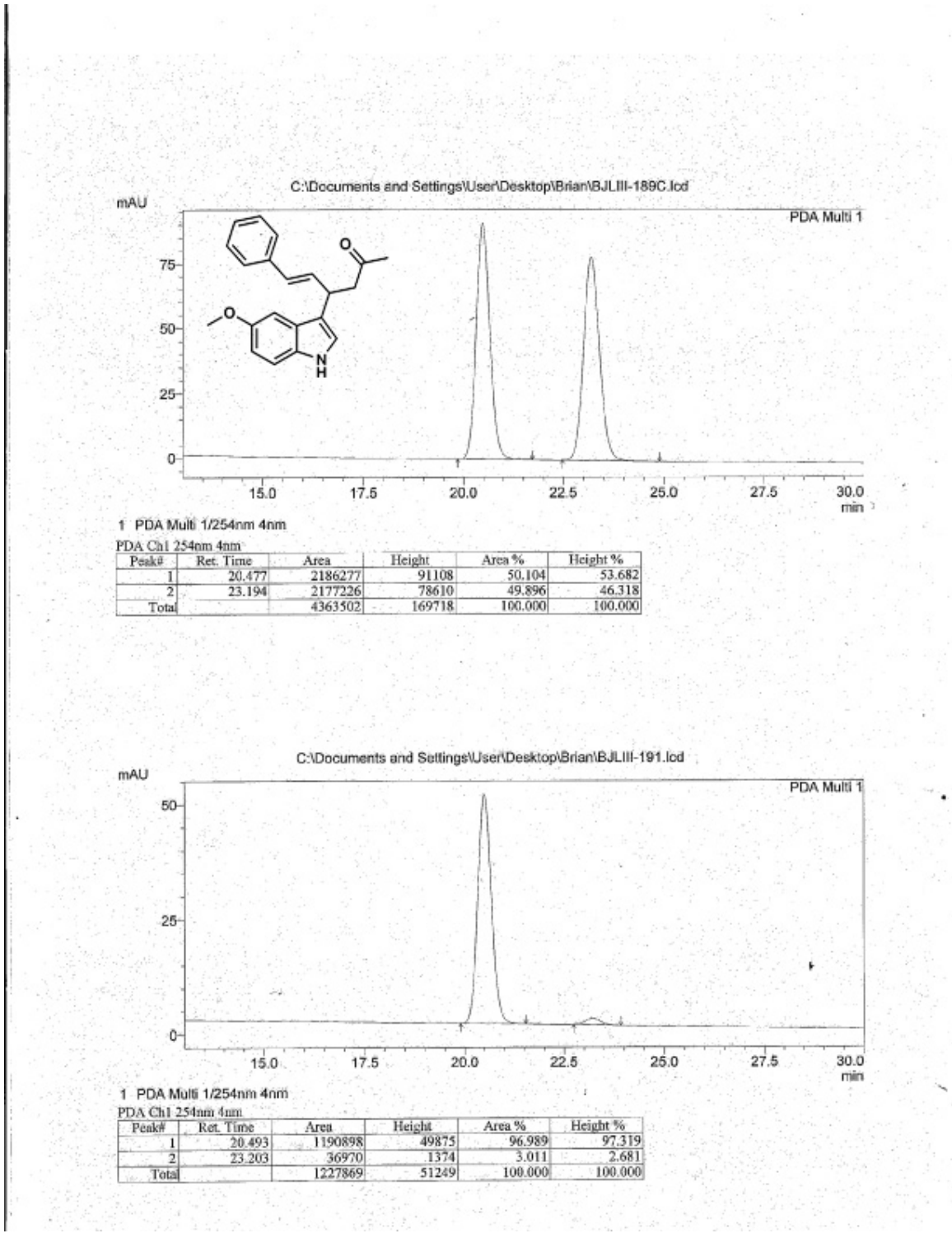


Figure A.1.69 IR spectra for compound **70**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.477	2186277	91108	50.104	53.682
2	23.194	2177226	78610	49.896	46.318
Total		4363502	169718	100.000	100.000

1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.493	1190898	49875	96.989	97.319
2	23.203	36970	1374	3.011	2.681
Total		1227869	51249	100.000	100.000

Figure A.1.70 HPLC trace for compound **70**

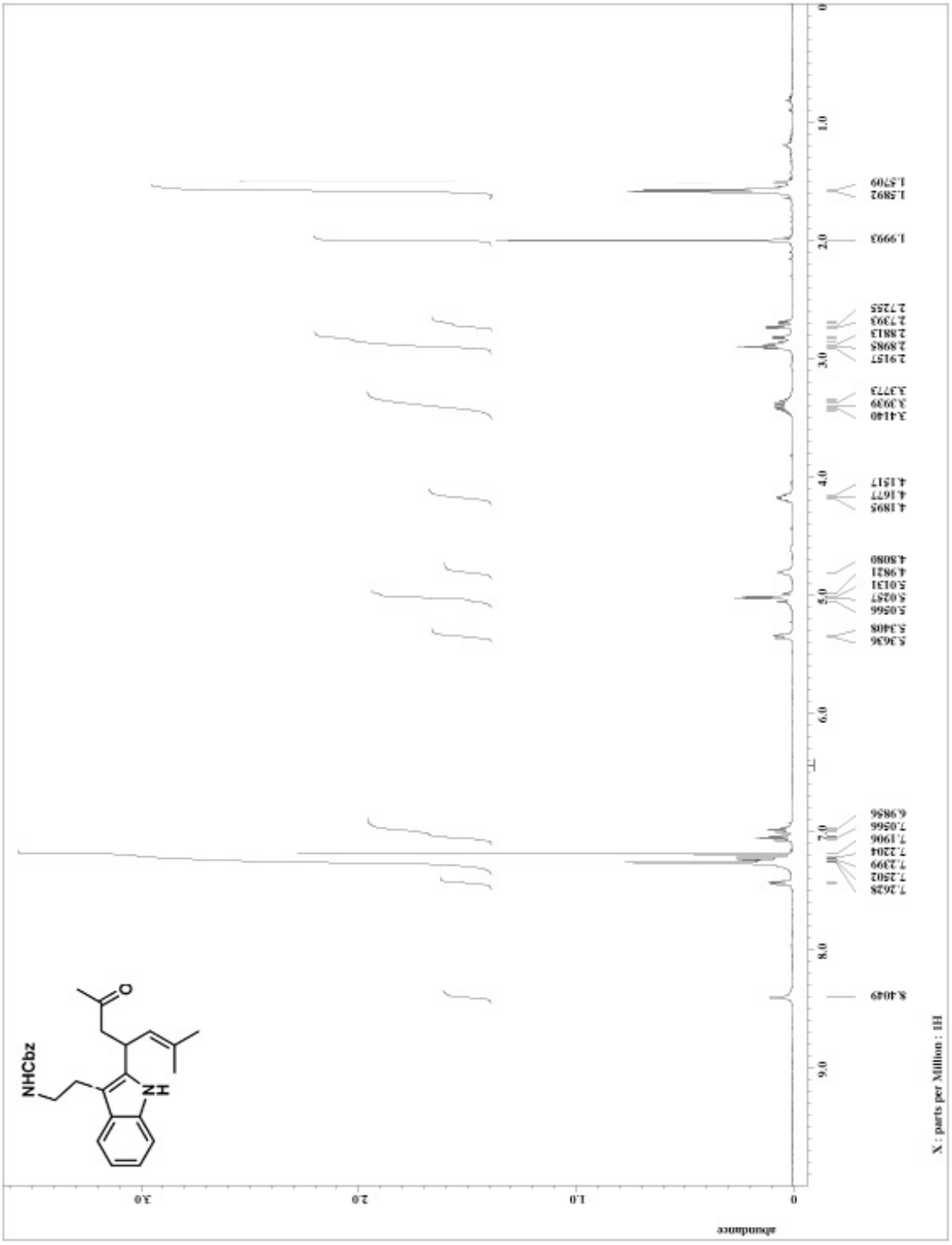


Figure A.1.71 ^{1}H NMR for compound **71**

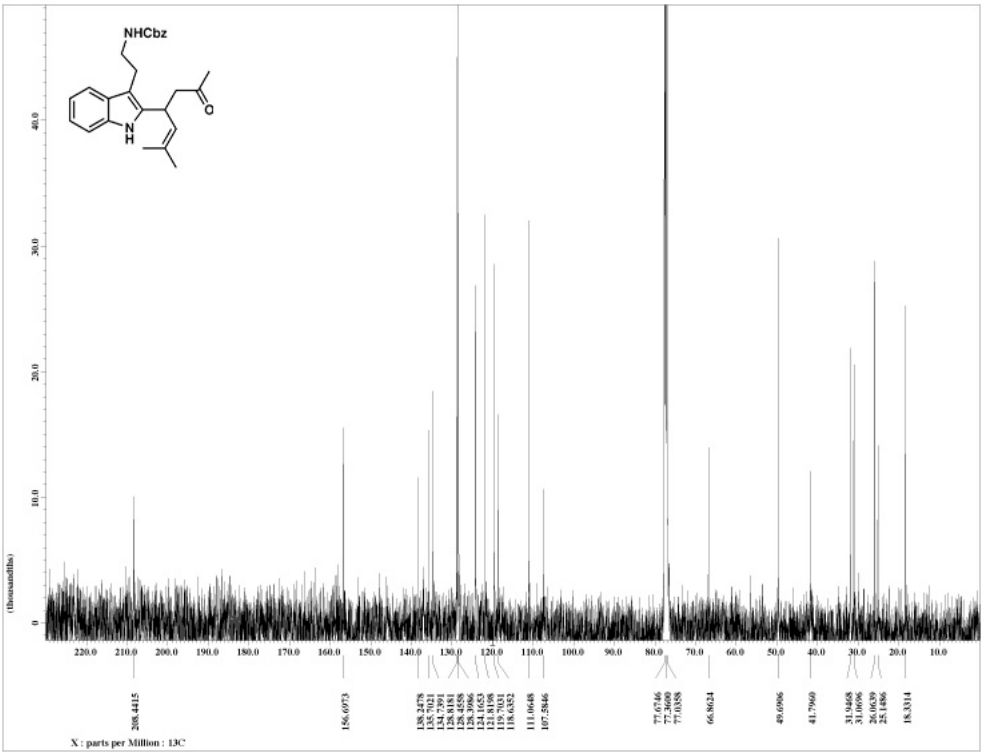


Figure A.1.72 ^{13}C NMR for compound **71**

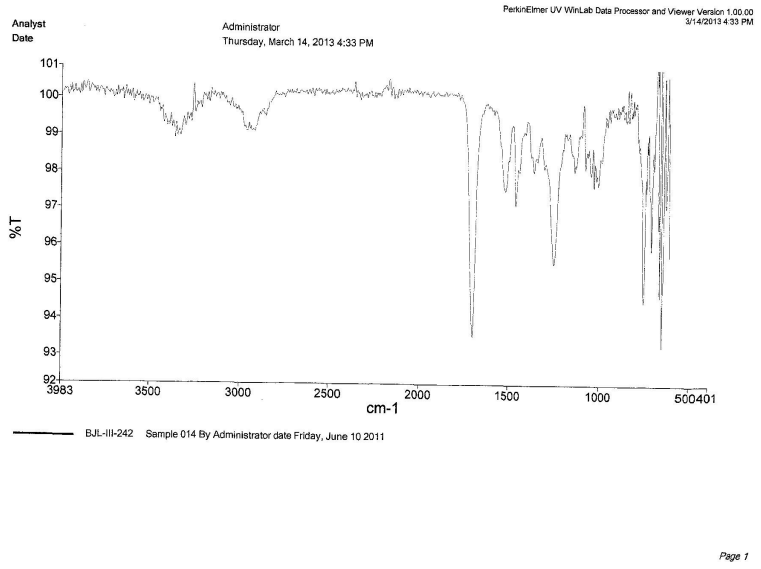
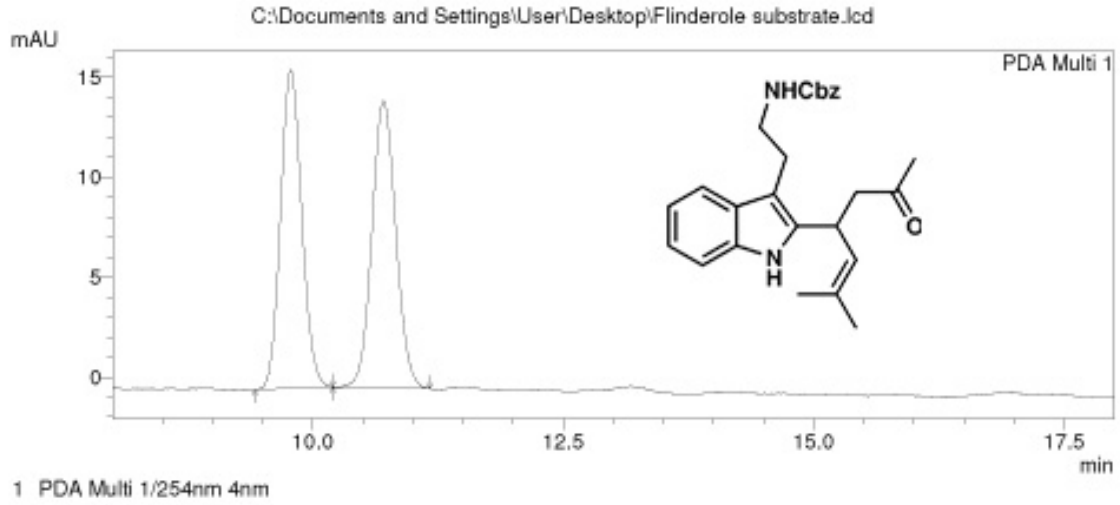


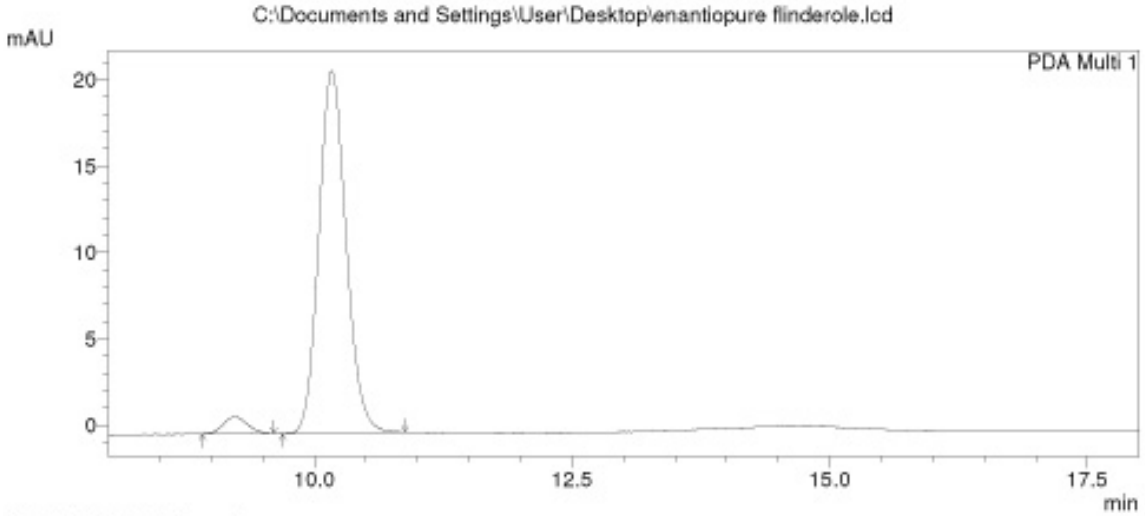
Figure A.1.73 IR spectra for compound **71**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.772	234359	15937	49.646	52.616
2	10.699	237704	14352	50.354	47.384
Total		472063	30289	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.219	15969	985	3.982	4.492
2	10.164	385107	20954	96.018	95.508
Total		401076	21940	100.000	100.000

Figure A.1.74 HPLC trace for compound **71**

Figure A.1.75 ^{1}H NMR for compound **76**

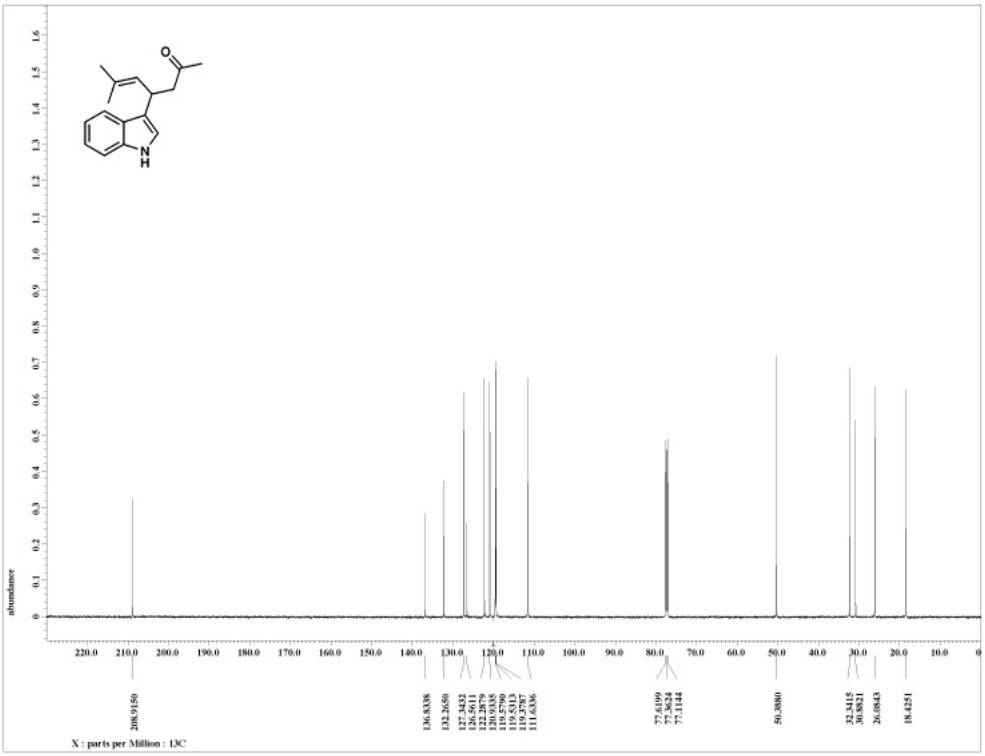


Figure A.1.76 ^{13}C NMR for compound **76**

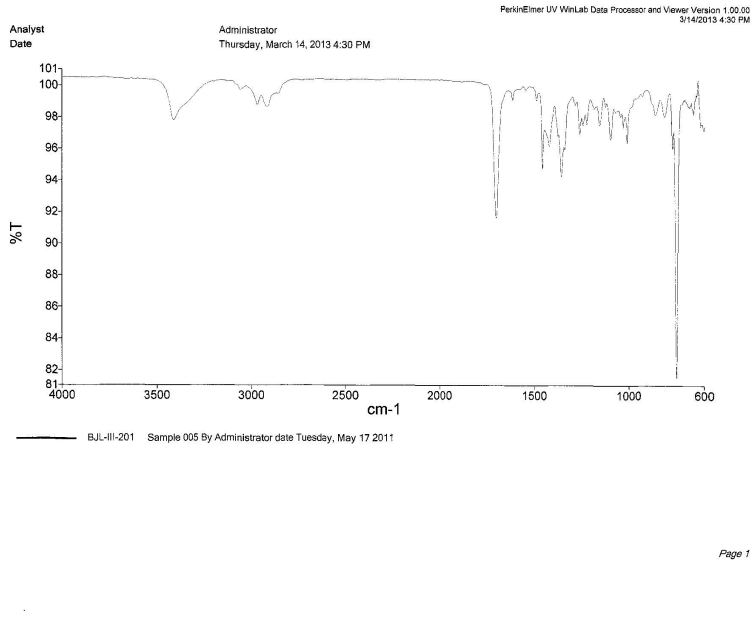
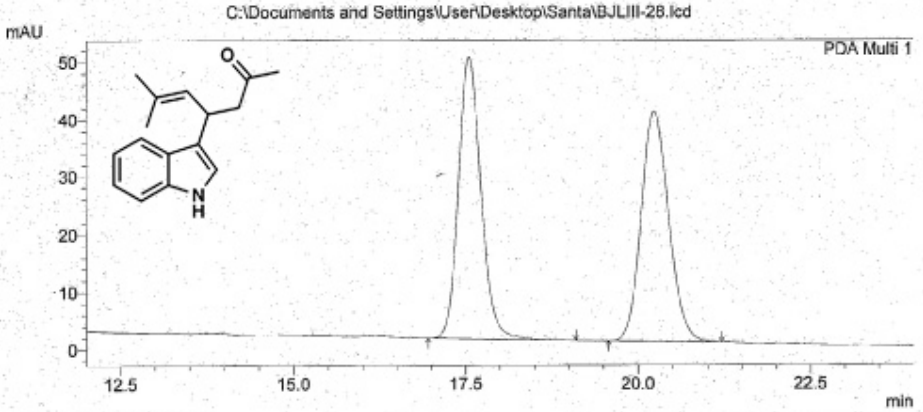


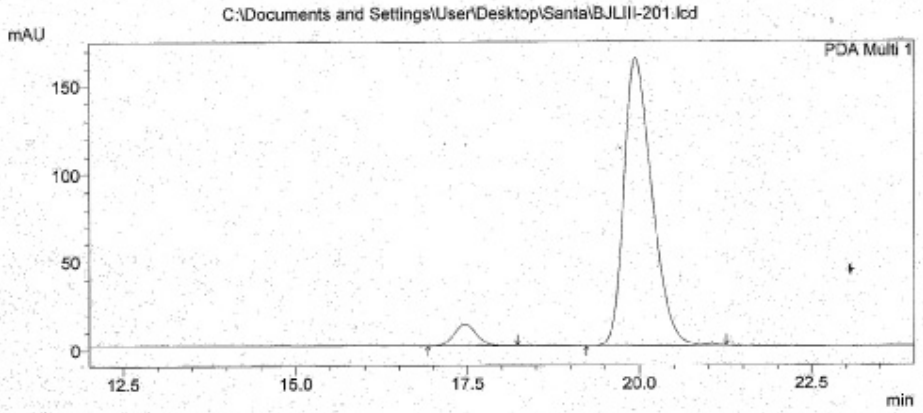
Figure A.1.77 IR spectra for compound **76**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.542	1124434	49052	50.380	55.006
2	20.228	1107455	40124	49.620	44.994
Total		2231889	89176	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.458	269425	12159	5.518	6.910
2	19.940	4613390	163814	94.482	93.090
Total		4882815	175973	100.000	100.000

Figure A.1.78 HPLC trace for compound **76**

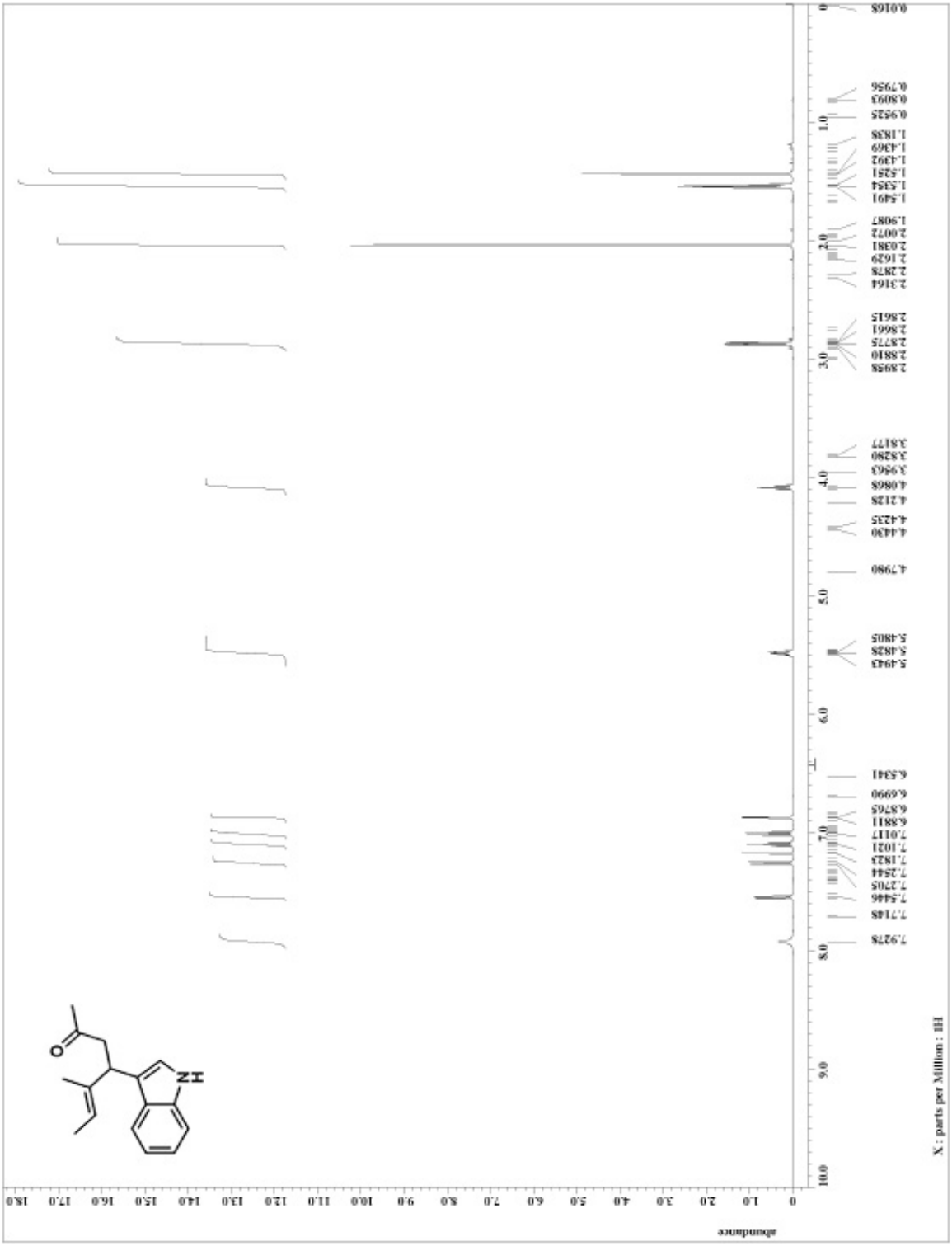


Figure A.1.79 ^{1}H NMR for compound **77**

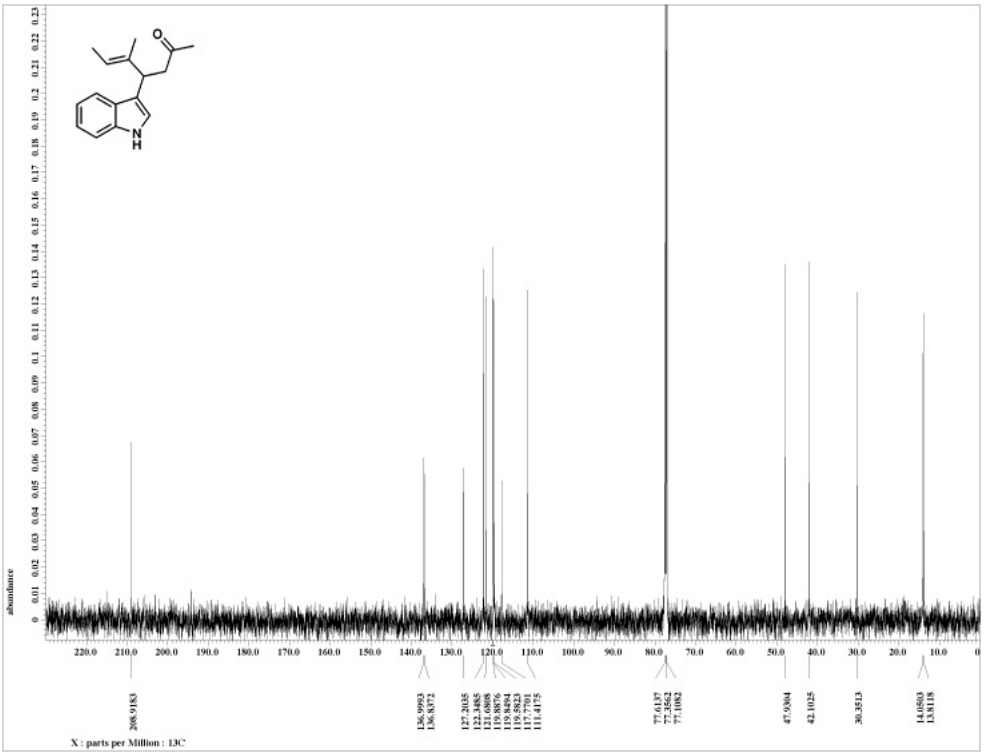


Figure A.1.80 ^{13}C NMR for compound **77**

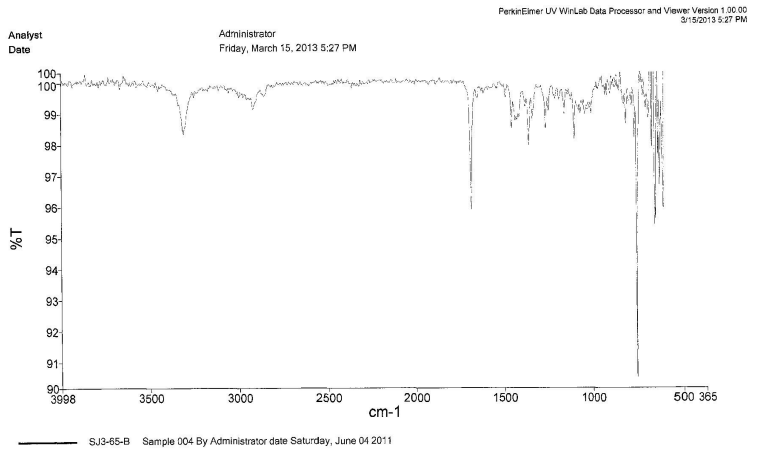
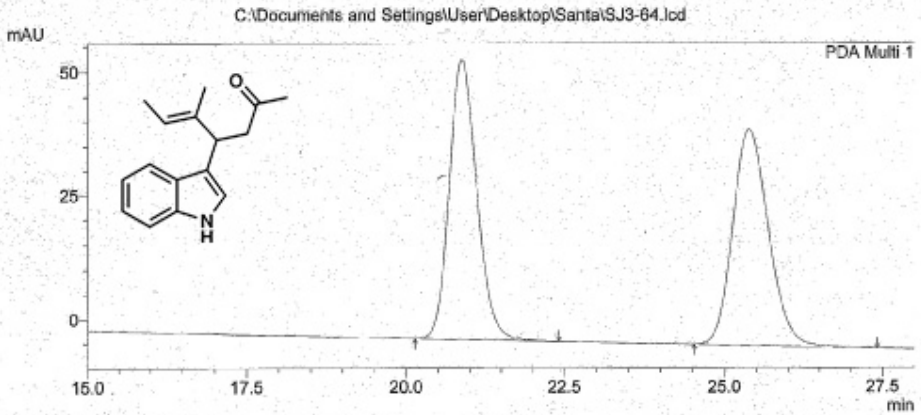


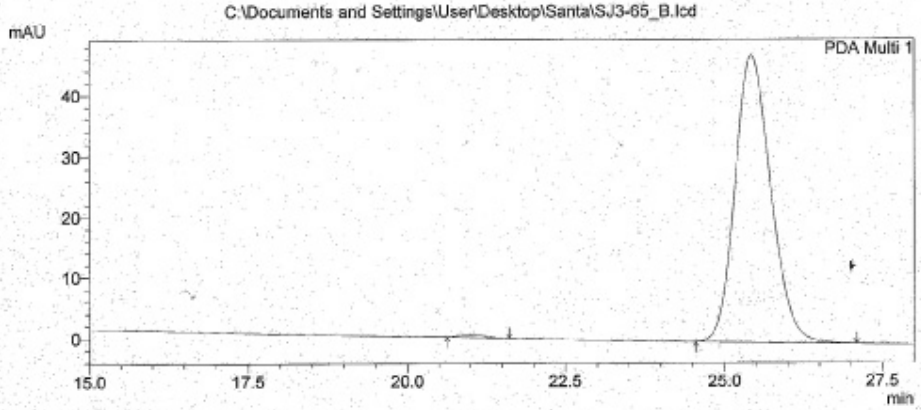
Figure A.1.81 IR Spectra for compound **77**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.873	1714121	56518	50.088	56.349
2	25.383	1708104	43782	49.912	43.651
Total		3422226	100300	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.977	13373	493	0.717	1.031
2	25.415	1851484	47281	99.283	98.969
Total		1864857	47774	100.000	100.000

Figure A.1.82 HPLC trace for compound **77**

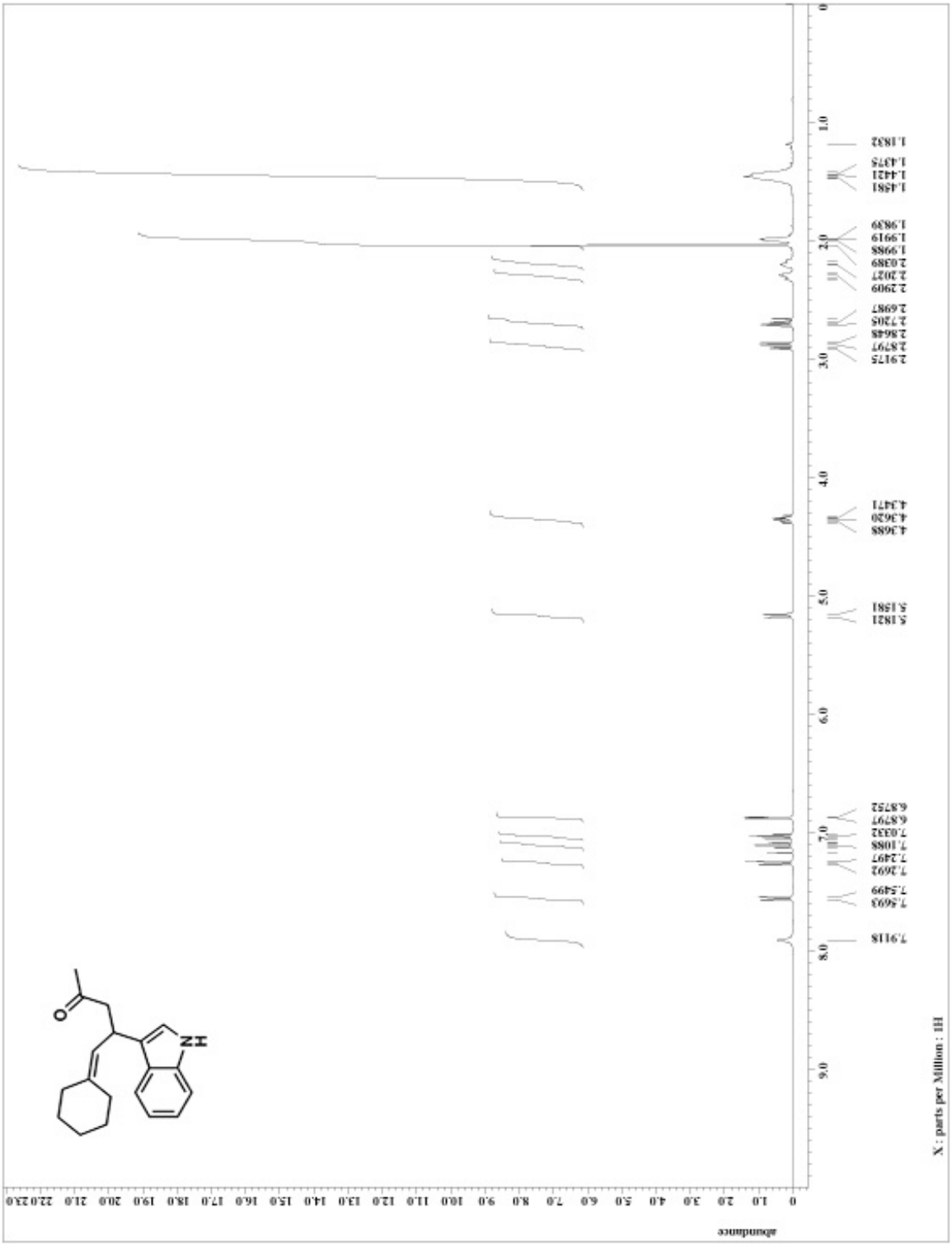


Figure A.1.82 ^{1}H NMR for compound **78**

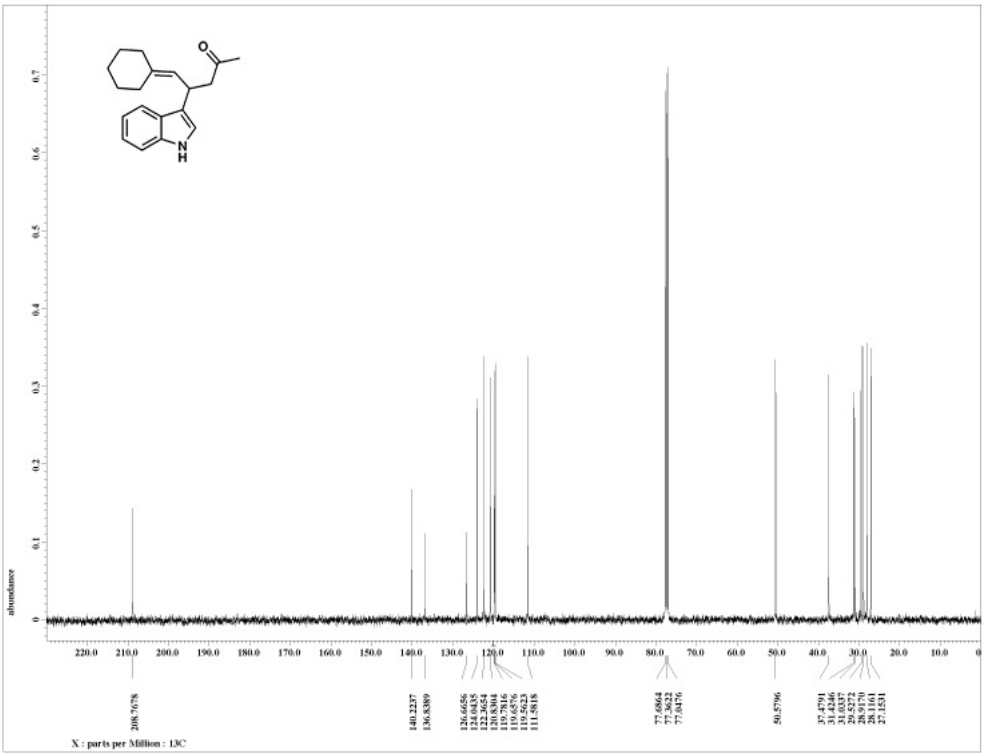


Figure A.1.84 ^{13}C NMR for compound **78**

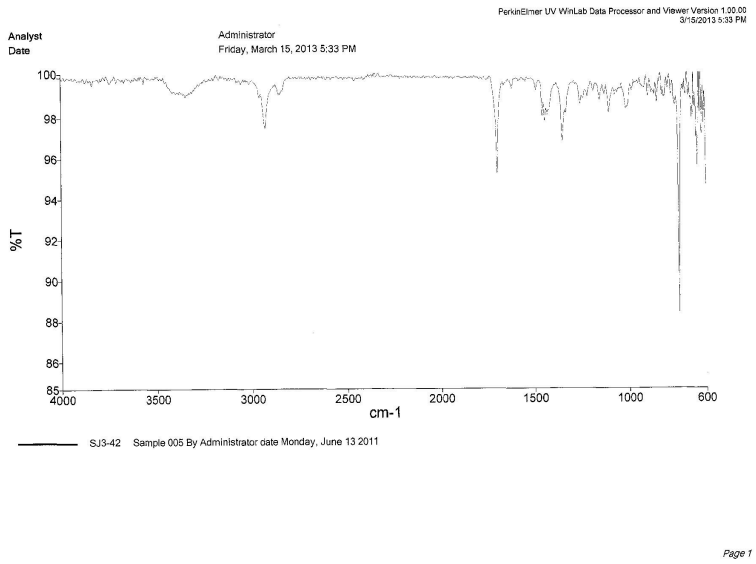
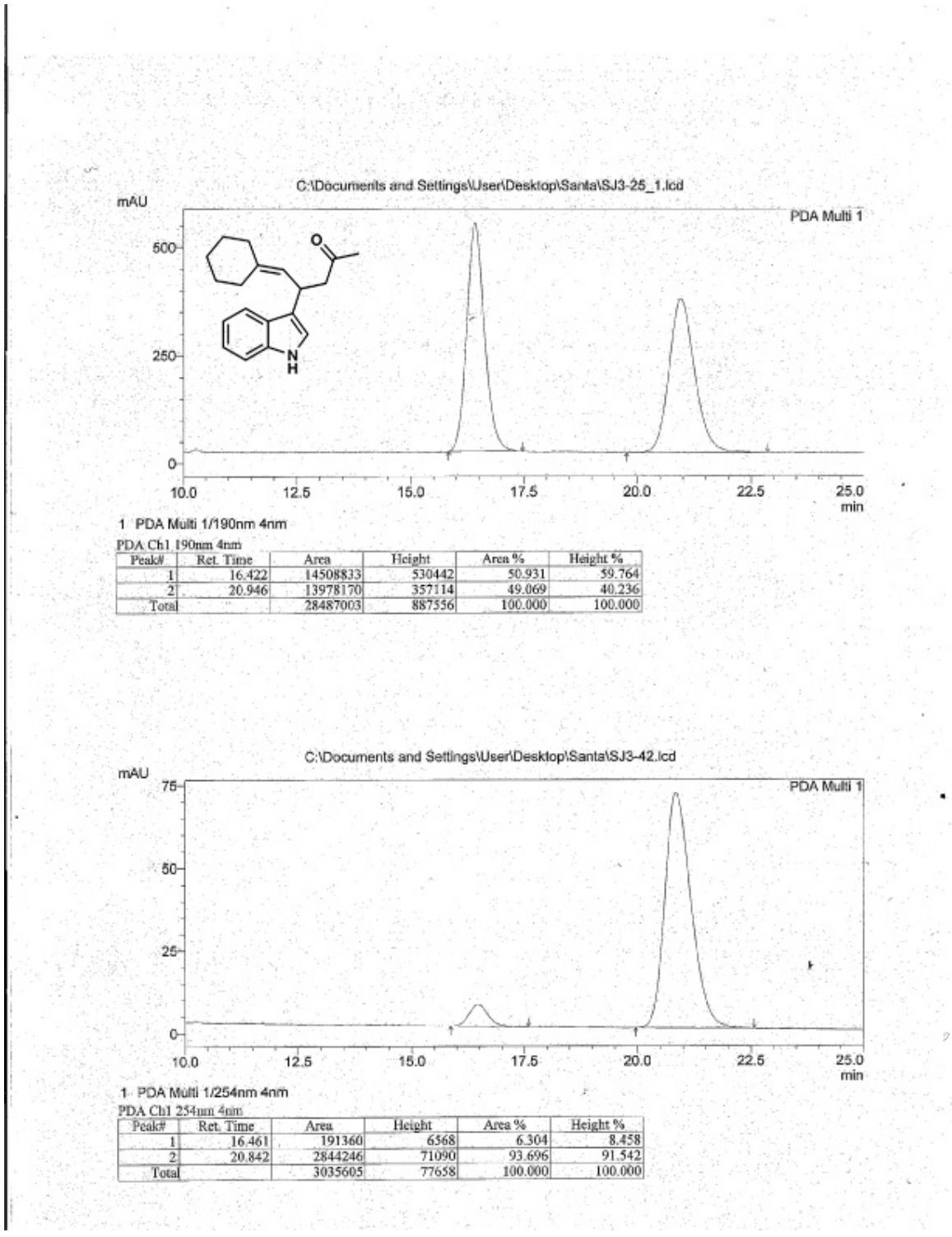


Figure A.1.85 IR Spectra for compound **78**



1 PDA Multi 1/190nm 4nm

PDA Ch1 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.422	14508833	530442	50.931	59.764
2	20.946	13978170	357114	49.069	40.236
Total		28487003	887556	100.000	100.000

1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.461	191360	6568	6.304	8.458
2	20.842	2844246	71090	93.696	91.542
Total		3035605	77658	100.000	100.000

Figure A.1.86 HPLC trace for compound **78**

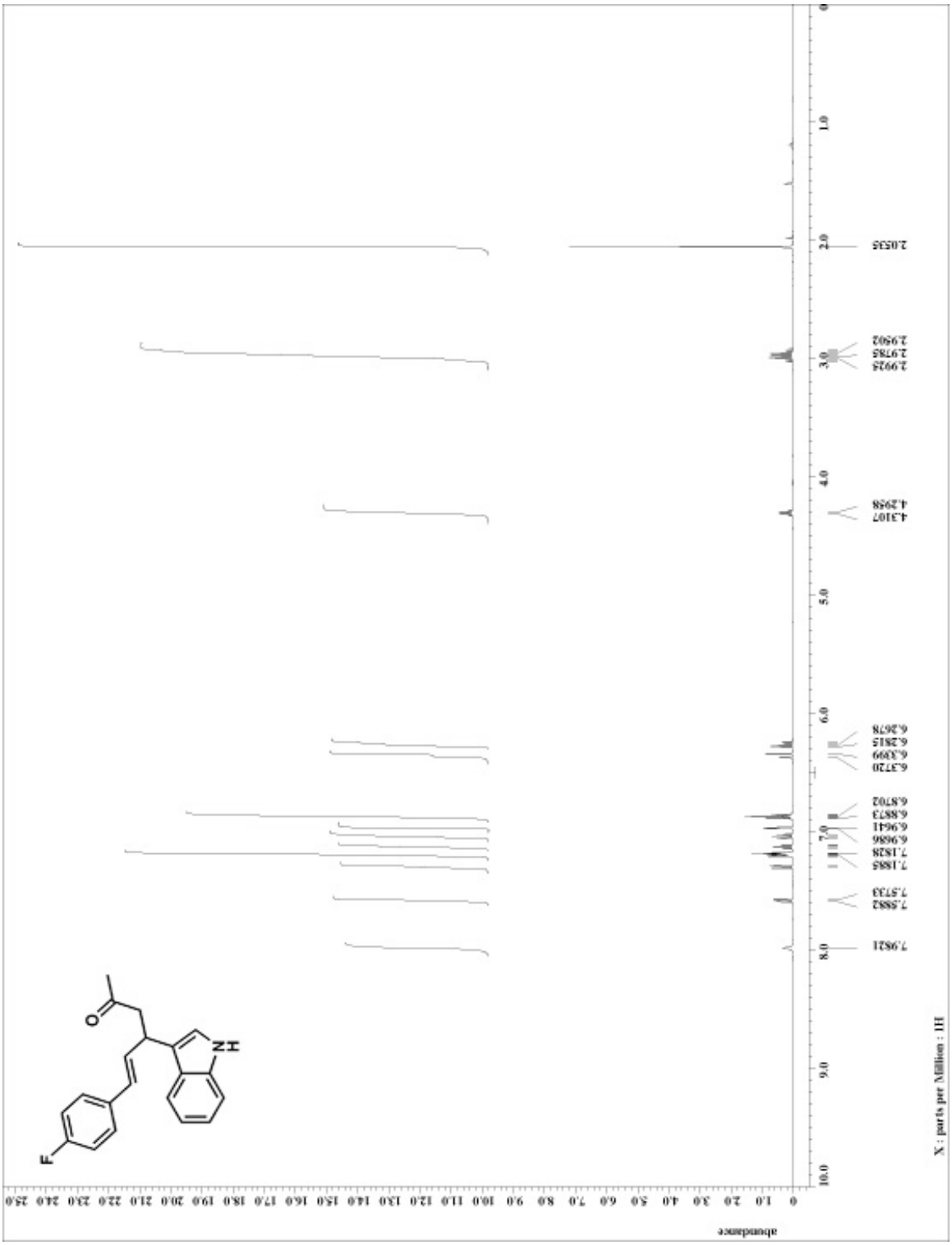


Figure A.1.87 ^{1}H NMR for compound **80**

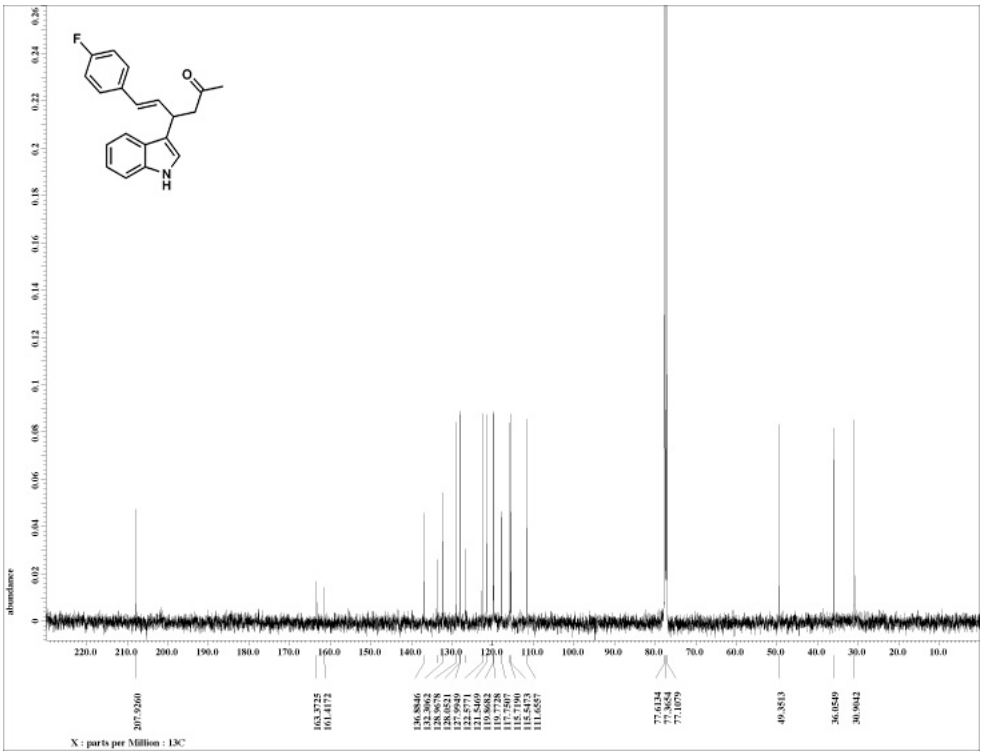


Figure A.1.88 ^{13}C NMR for compound **80**

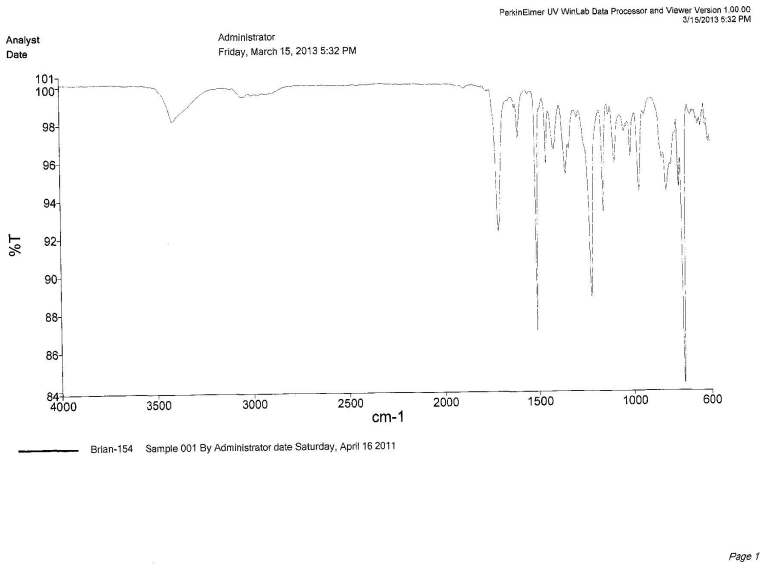
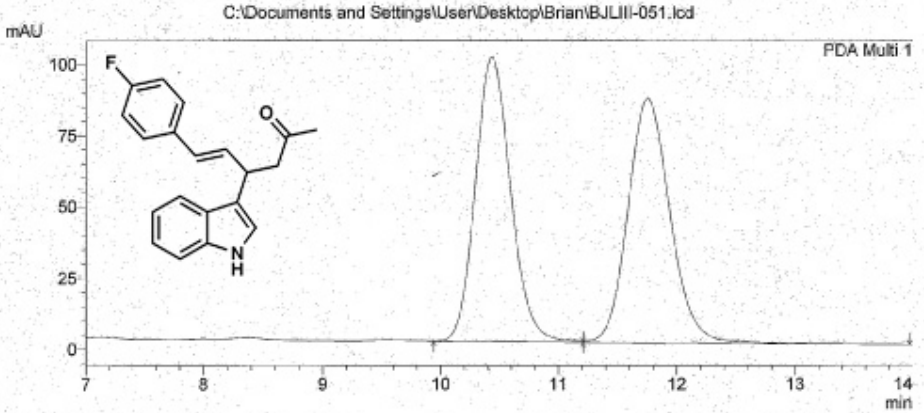


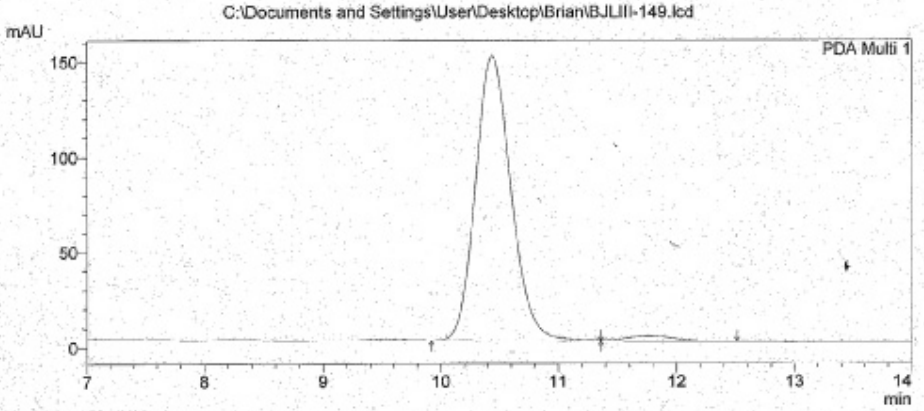
Figure A.1.89 IR spectra for compound **80**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.432	2097288	99936	49.691	53.781
2	11.749	2123378	85886	50.309	46.219
Total		4220666	185823	100.000	100.000



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.432	3146075	149332	97.668	98.108
2	11.767	75131	2880	2.332	1.892
Total		3221205	152213	100.000	100.000

Figure A.1.90 HPLC trace for compound **80**

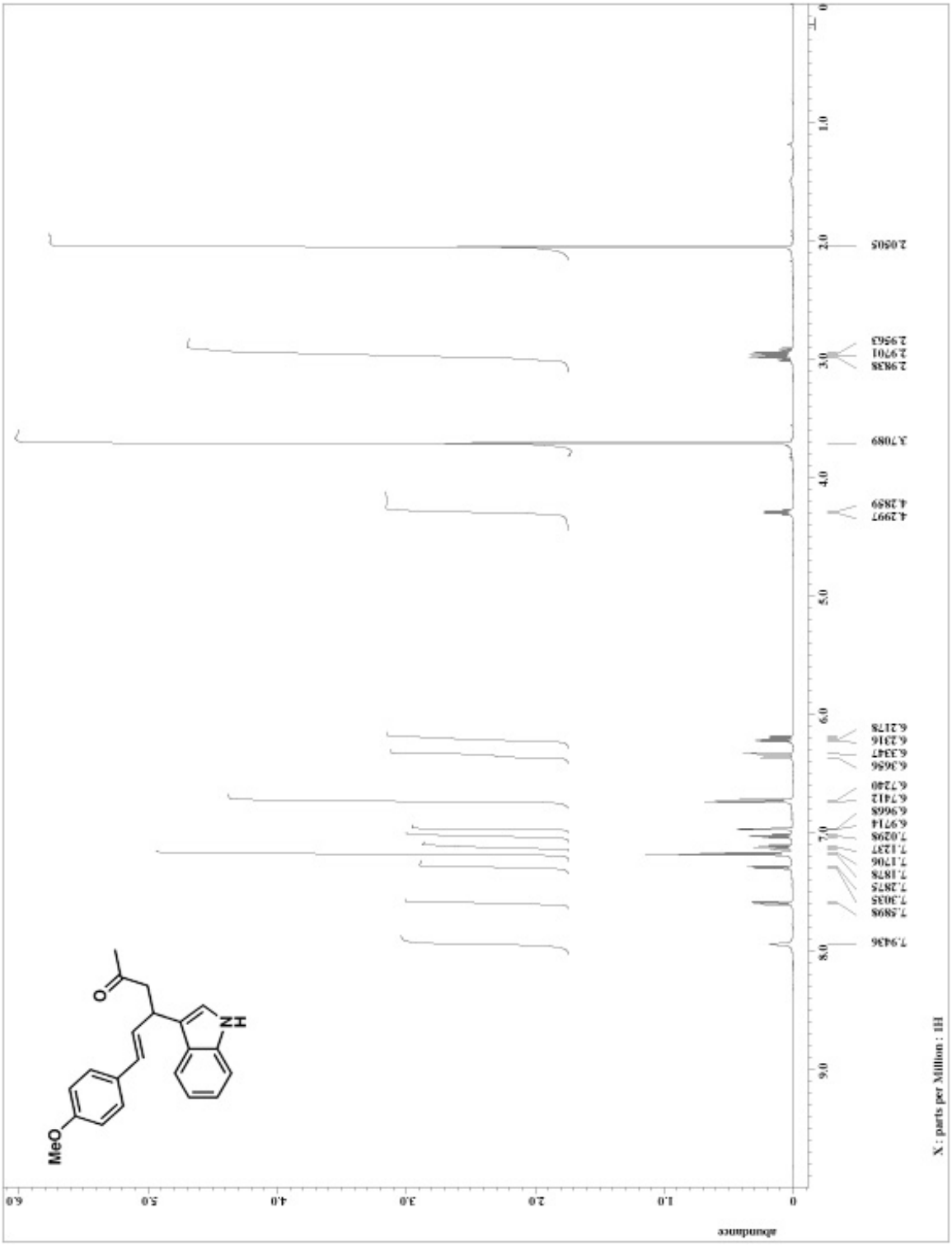


Figure A.1.91 ^{1}H NMR for compound **81**

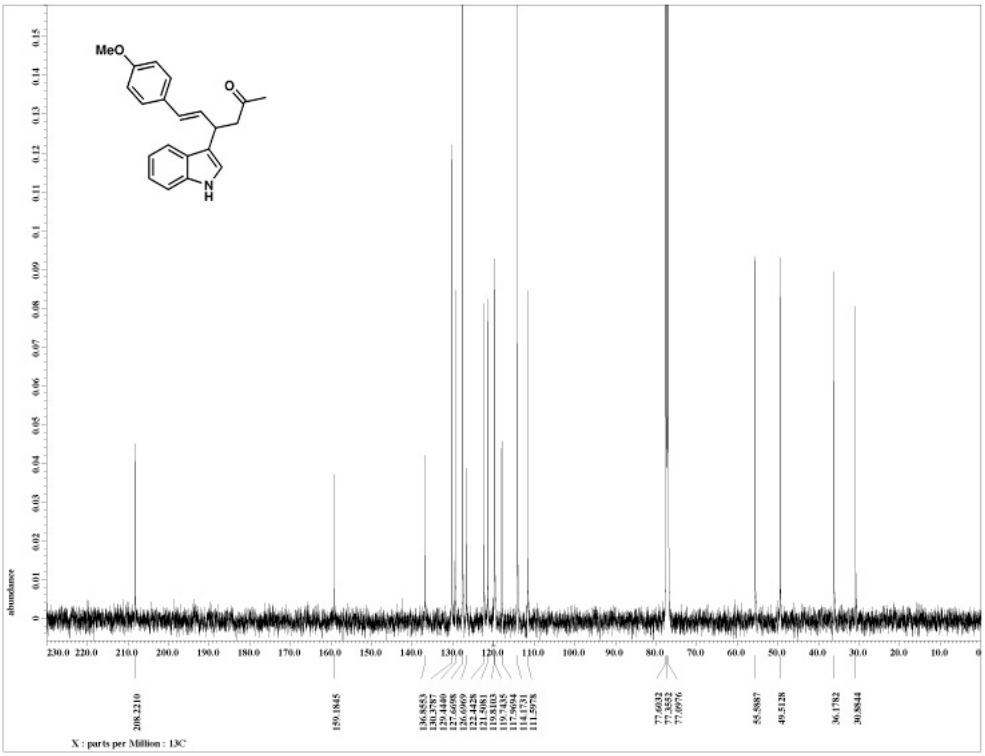


Figure A.1.92 ^{13}C NMR for compound **81**

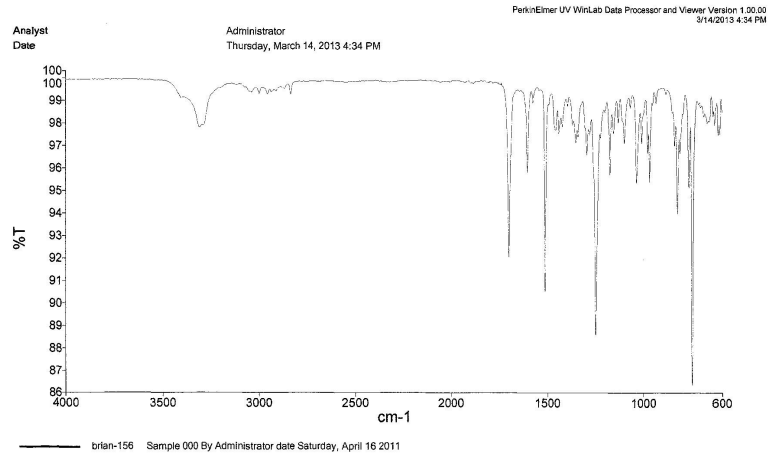
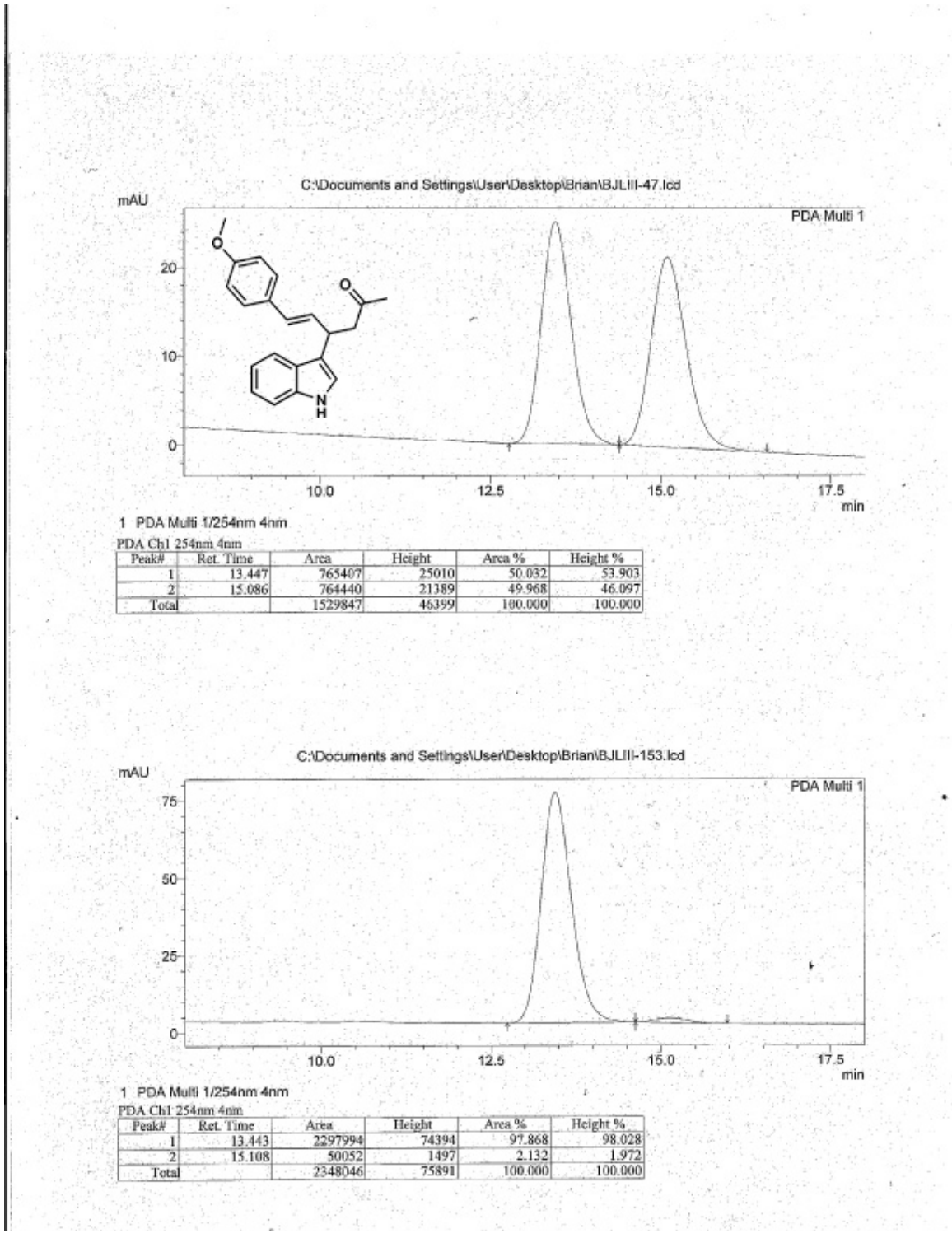


Figure A.1.93 IR spectra for compound **81**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.447	765407	25010	50.032	53.903
2	15.086	764440	21389	49.968	46.097
Total		1529847	46399	100.000	100.000

1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.443	2297994	74394	97.868	98.028
2	15.108	50052	1497	2.132	1.972
Total		2348046	75891	100.000	100.000

Figure A.1.94 HPLC trace for compound **81**

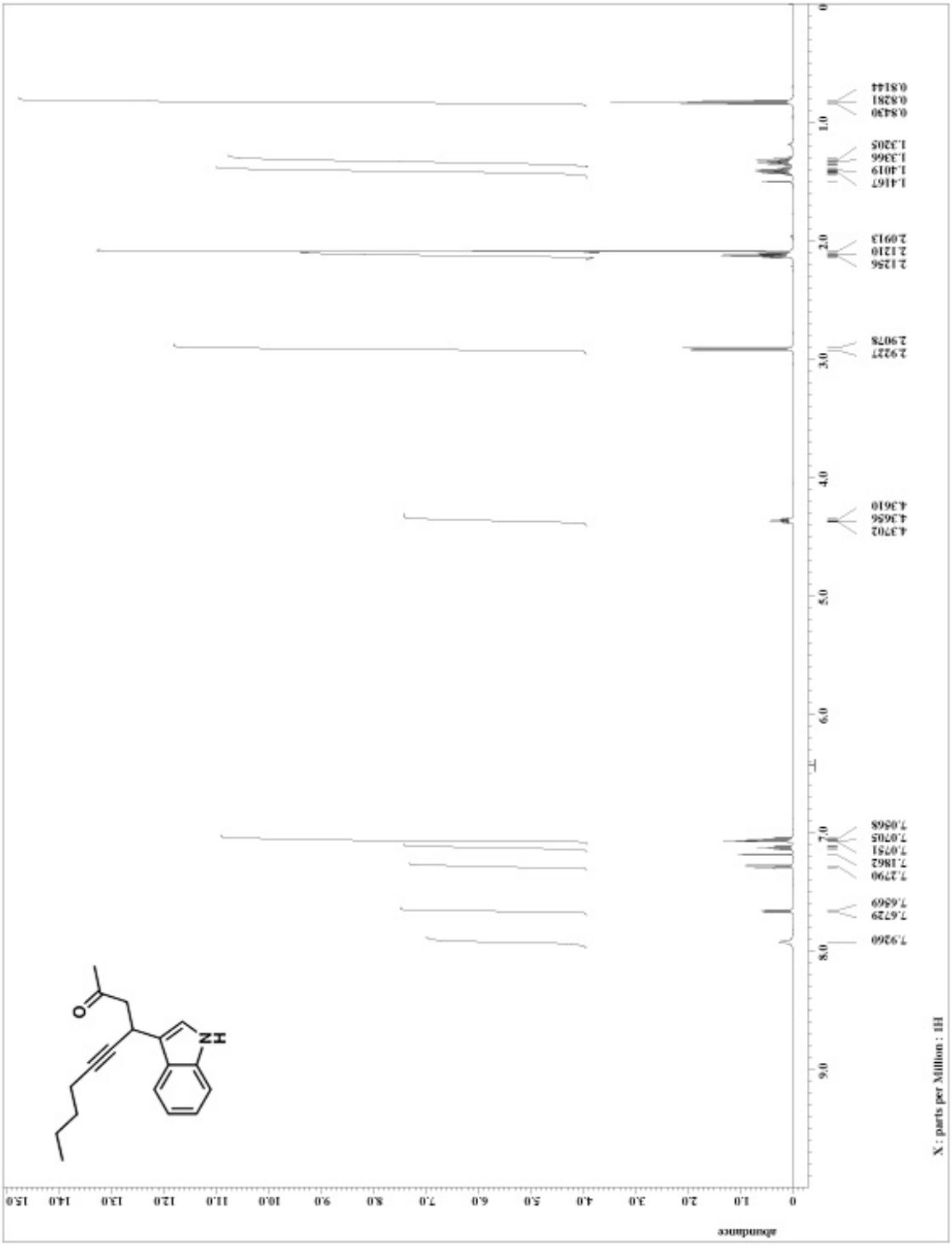


Figure A.1.95 ^{1}H NMR for compound **82**

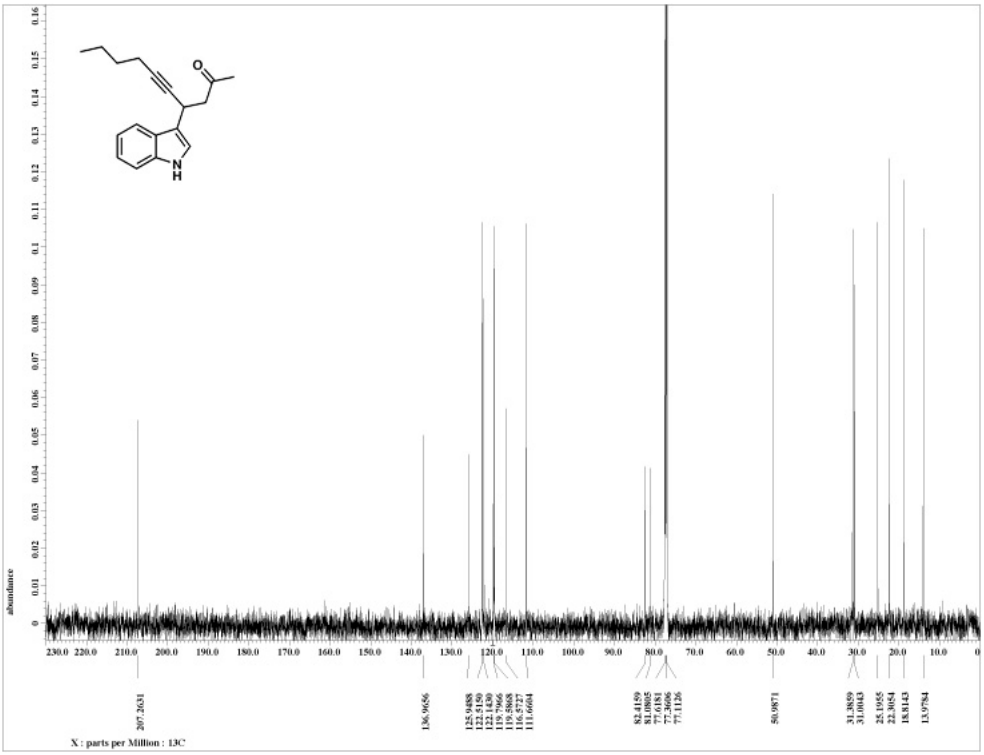


Figure A.1.96 ^{13}C NMR for compound **82**

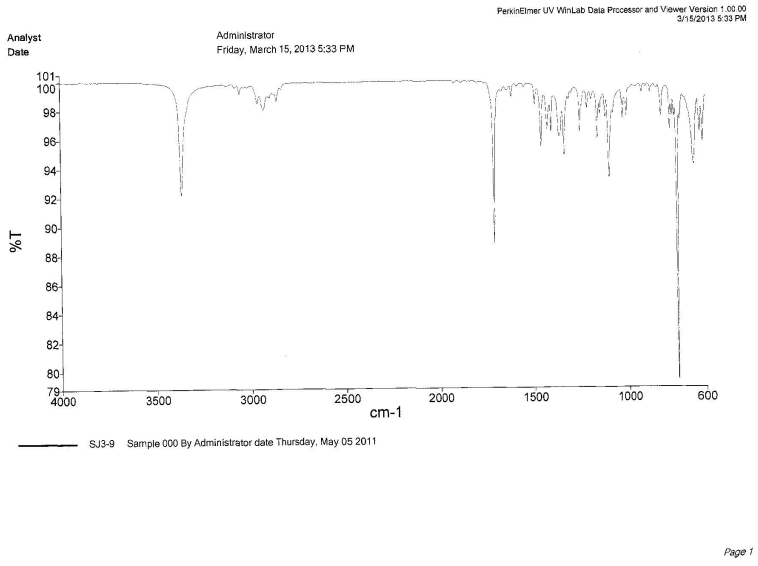
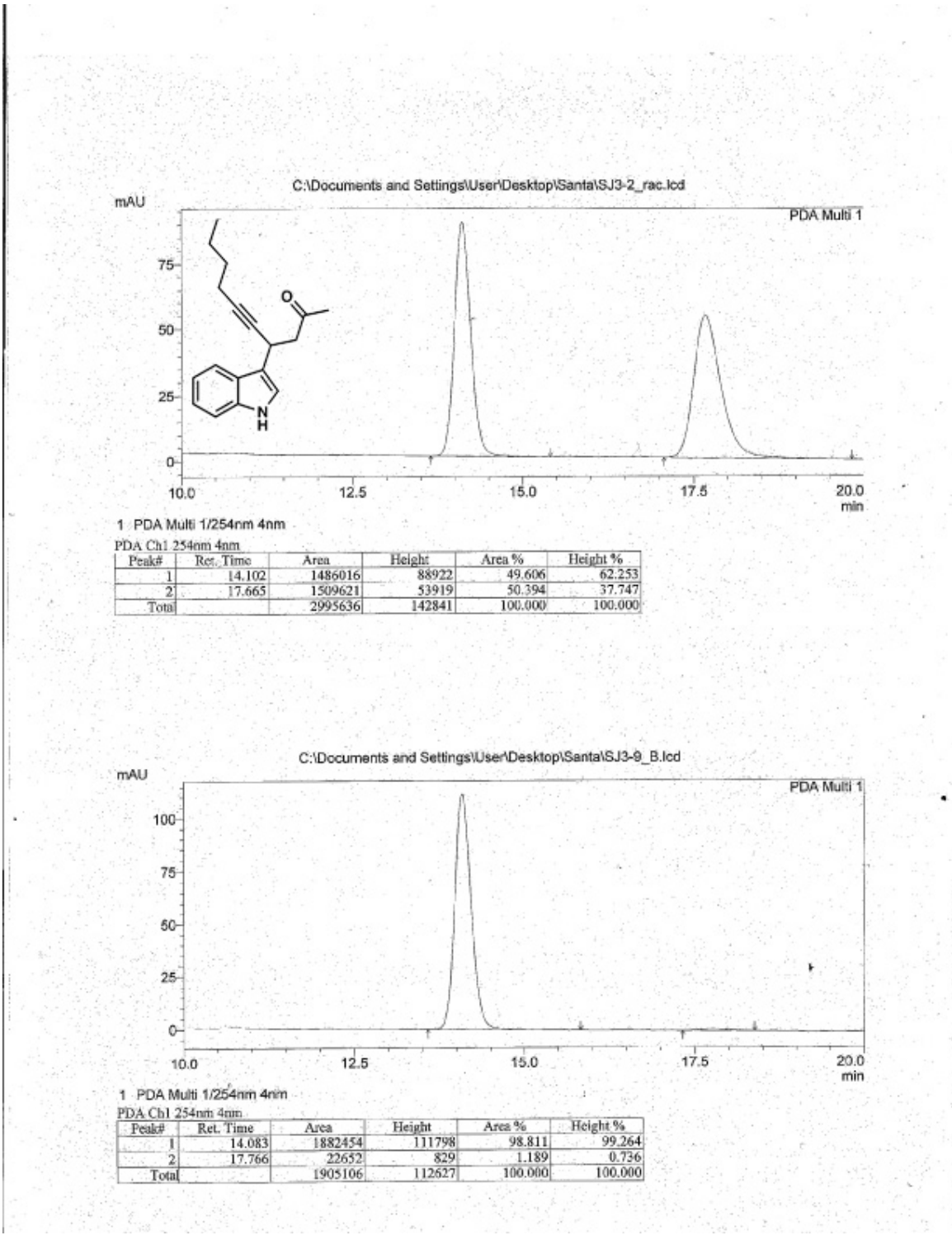


Figure A.1.97 IR spectra for compound **82**



1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.102	1486016	88922	49.606	62.253
2	17.665	1509621	53919	50.394	37.747
Total		2995636	142841	100.000	100.000

1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.083	1882454	111798	98.811	99.264
2	17.766	22652	829	1.189	0.736
Total		1905106	112627	100.000	100.000

Figure A.1.98 HPLC trace for compound **82**

Chapter Three

The Aplykurodin Family of Natural Products

3.1 Introduction

The total synthesis of natural products is a vital field in chemistry as it has led to many advances in disease treatment.[1-3] The purpose of being able to synthesis these natural products in a lab is to help obtain a large quantity of the needed compound, whereas isolation from the natural source typically yields very little product from samples of the supplying organism. In addition, the synthesis of natural products is typically not limited to solely one naturally existing compound. Many natural products are members of families of several structurally similar compounds that can also be targeted after the development of a synthetic strategy for the original compound. In addition, with any naturally occurring compound, the functional groups of the compound can be modified to look for increased potencies and selectivities of its biological properties. This chapter will provide a background to the aplykurodin family as well as the approach to the synthetic route to one of its members, aplykurodinone 1.

3.2 Aplykurodin Family of Natural Products

The four members of the family that will be discussed in this section are aplykurodinone 1 (**83**), aplykurodin B (**84)**, aplykurodinone B (**85**), and 3-*epi*-aplykurodinone B (**86**), all of which are shown in Figure 3.2. The family member that is the main target and will receive most of the discussion in the following sections and chapter is aplykurodinone 1.

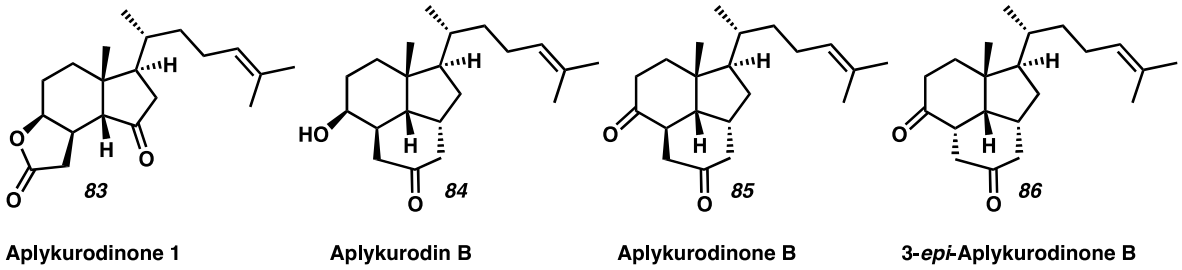


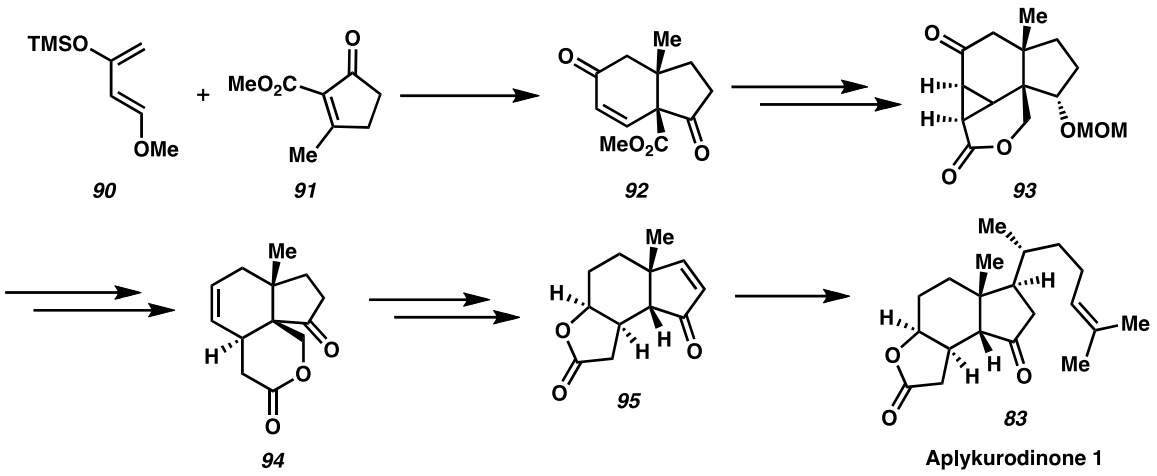
Figure 3.2 Aplykurodin family

Aplykurodinone 1 (**83**) was isolated by Gavagnin et al. off the coasts of Greece from the marine anaspidean *Syphonota geographica. Syphonota g.* is a sea slug that belongs to the Aplysiidea family that got its name due to the map like markings on the body. They are found in shallow waters and typically feed on algae, which leads to isolation of many secondary metabolites found in the animals. However, they also have chemicals that are suspected to have resulted from metabolism by the animal such as degraded sterols, polypropionates, and oxylipins. The exact function of aplykurodinone 1 is not known. It was originally suspected of being part of a defense mechanism of the species because it was isolated from the skin of the slug, however it didn't have the same icthyotoxic properties of the some other reported aplykurodins.[4] Aplykurodin B (**84**) is another compound that was isolated from animals belonging to the Aplysiidae family, the sea hare *Aplysia kurodai.*[5] Aplykurodinone B (**85**) was isolated from the external parts of the mollusk *Aplysia fasciata.* When **85** was isolated it was determined to have structural properties very similar to other previously isolated aplykurodins, therefore it was also classified in this same family of natural products. It was found to be toxic to the mosquito fish *Gambusia affinis* at 10 ppm. It also showed feeding deterrence at a concentration of 60 μg/cm^2 for the fish *Carassius auratus.* As with other members of the family it is

speculated that the function of the compound is for defense of the species. This conclusion is made based on the feeding deterrence properties as well as the isolation of aplykurodinone B in the outer portion of the creature.[6] The last aplykurodin derivative that will be discussed is 3-*epi*-aplykurodinone B (**86**), which also might be the most promising member of the family in terms of biological activity. 3-*epi*-aplykurodinone B was also isolated from *Aplysia fasciata.* It was isolated in the intertidal zone of Rio San Pedro, Cadiz, Spain and was subsequently tested against tumor cell lines, along with aplykurodinone B. It was determined that 3-*epi*-aplykurodinone B showed mild in vitro cytotoxicity with ED_{50} values of 2.5 μg/mL against P-388 mouse lymphoma, A-549 human lung carcinoma, HT-29 human colon carcinoma, and MEL-28 human melanoma.[7] As previously mentioned, this promising activity against tumor cell lines in addition to the interesting structure of this family of natural products attracted our attention to attempt to synthesize it, starting with aplykurodinone 1.

3.3 Danishefsky Approach to Aplykurodinone 1

Aplykurodinone 1 was synthesized in 2010 by the Danishefky lab at Columbia University as shown in Scheme 3.3.

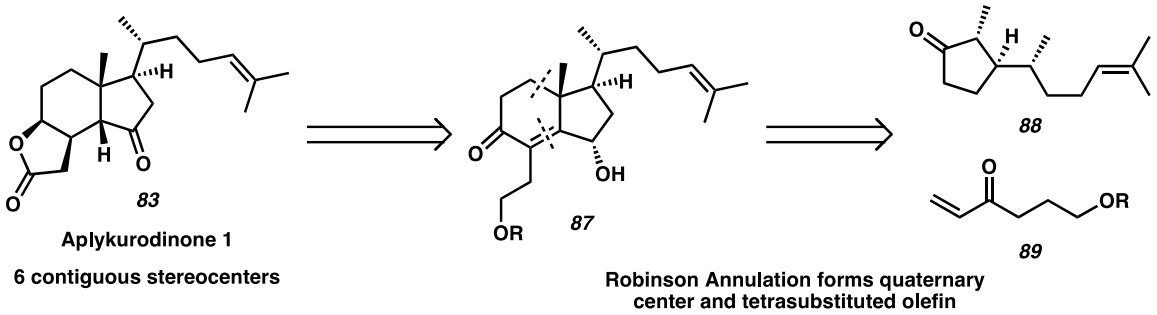


Scheme 3.3 Danishefsky's synthetic route toward aplykurodinone 1

Starting with Danishefsky's diene (**90**) and cyclopentenone **91**, they were able to effect a cycloaddition to form bicyclic intermediate **92** in 73% yield. In 7 steps, intermediate **92** was converted to cyclopropyl intermediate **93** in 21% overall yield. Keto-lactone **94** was then formed in 5 steps from cyclopropane **93** in 5% overall yield. The tricyclic core of aplykurodinone 1, shown in intermediate **95,** was then formed in 4 steps from keto-lactone **94** in 51% overall yield. With compound **95**, the last transformation was to install the isoprene side chain of aplykurodinone 1. This was done in 5 steps with a yield of 22% to form the target compound **83**. By Danishefksy's synthetic route, aplykurodinone 1 was synthesized in 22 steps with an overall yield of 0.9%.[8] This is the only published synthetic route toward aplykurodinone 1.

3.4 May Lab Approach to Aplykurodinone 1

Some of the challenges that can be seen in the structure of aplykurodinone 1 include 6 contiguous stereocenters, as well as a quaternary carbon at the ring fusion. Our retrosynthetic approach to the total synthesis of the compound can be seen in Scheme 3.4.



Scheme 3.4 Retrosynthetic analysis for the approach to aplykurodinone 1

Our synthetic route involves the formation of late stage intermediate **87**. The hydroxyl group in this intermediate will be installed by the oxidation of an enone in the γ-position potentially by the formation of an extended enolate followed by the addition of an electrophilic oxidant. This is a challenging transformation due to the presence of the olefin in the isoprene side chain of the molecule. A chemoselective oxidation procedure will need to be used to get exclusive oxidation at the position γ- to the enone while not causing oxidation of the other olefin as well as prevention of allylic oxidation on the side chain. The immediate precursor to intermediate **87** is the bicyclic enone prior to the hydroxyl oxidation. This intermediate can be formed by a Robinson annulation reaction of synthons **88** and **89**. The proposed Robinson annulation would form a quaternary carbon center as well as a tetra-substituted olefin. The Michael addition followed by the aldol condensation that the Robinson annulation encompasses will be attempted in a one-

pot reaction. The formation of ketone **88** will start with commercially available cyclopentadiene and methylcrotonate. It also has previously been made by the Taber research group. The synthesis of ketone **88** and enone **89** will be discussed in more detail in the next chapter.

3.5 Conclusion

The aplykurodin family has been shown to have promising anti tumor activity in addition to an interesting structural make-up. These two factors attracted our attention to attempt to synthetically make aplykurodinone 1, with the key steps to our synthesis being a Robinson annulation reaction to form the bicyclic core followed by γ-oxidation to install the needed oxidation state. The precursors to the Robinson annulation reaction will be discussed in exhaustive detail in the next chapter. Our goal is to improve on the efficiency of the published route by the Danishefsky group by improving the overall yield, as well as decreasing the step count. The next chapter gets into detail of our synthetic route to aplykurodinone 1.

3.6 Notes and References

[1] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477.

[2] Wilson, R. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 6032–6056.

[3] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311–335.

[4] Gavagnin, M.; Carbone, M.; Nappo, M.; Mollo, E.; Roussis, V.; Cimino, G. *Tetrahedron* **2005**, *61*, 617–621.

[5] Miyamoto, T.; Higuchi, R.; Komori, T.; Fujioka, T.; Mihashi, K. *Tetrahedron Lett.* **1986**, *27*, 1153–1156.

[6] Spinella, A.; Gavagnin, A.; Crispino, A.; Cimino, G.; Martinez, E.; Ortea, J.; Sodano, G. *J. Nat. Prod.* **1992**, *55,* 989–993.

[7] Ortega, M. J.; Zuiba, E.; Zalva, J. *J. Nat. Prod.* **1997**, *60*, 488–489.

[8] Zhang, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 9567–9569.

Chapter Four

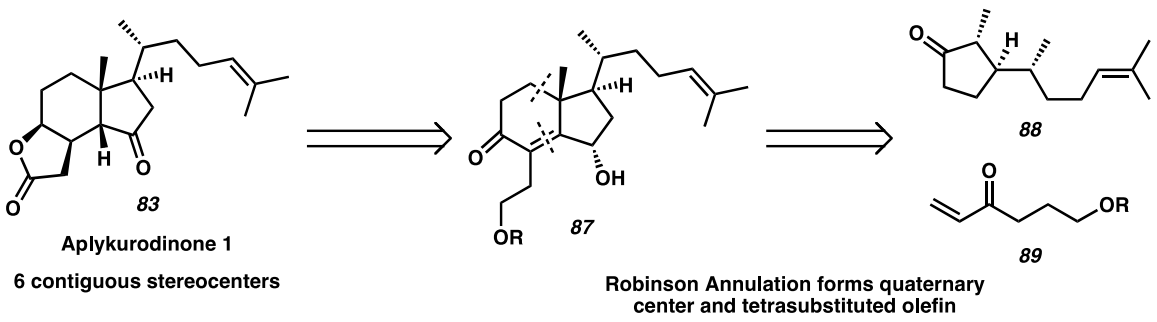
Synthetic Developments Toward Aplykurodinone 1

4.1 Introduction

As mentioned in the previous chapter, a variety of aplykurodin derivatives have been isolated from sea animals of the family Aplysiidae. Most are thought to function as defense mechanisms; however one member of the family was shown to have some activity against cancer cell lines. For this reason, and because of the interesting structure, our lab decided to pursue the total synthesis of aplykurodinone 1. The short-term goal of the project is to efficiently synthesize the natural product. The long-term goal is to modify the late stage synthetic steps in order to have easy access to derivatives which may exhibit other biological activity. In this chapter, the work toward the synthesis of aplykurodinone 1 will be discussed in detail.

4.2 Synthesis of Ketone 88

Our lab evaluated two different routes to ketone **88**. One was a strategy previously used by the Taber[1] lab and the other was designed in our lab. Both routes will be discussed, but it will be shown that stereoselectivity issues in the key step of Taber's route decrease its effectiveness, and the route that will best allow access to aplykurodinone 1 will be the formation of ketone **88**, shown in Scheme 4.2, by the method devised in our lab.



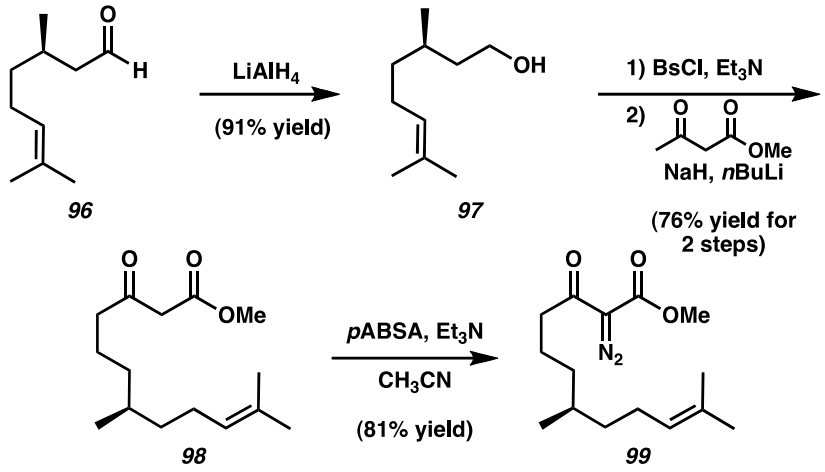
Scheme 4.2 Retrosynthetic analysis for the approach to aplykurodinone 1

4.2.1 Taber Lab Route to Ketone 88[1]

In 2001, the Taber Group published a synthesis of (-)-astrogorgiadiol, forming a late stage intermediate by way of a Robinson annulation reaction of ketone **88** and another compound prepared in their lab. The approach with which they went about this is reminiscent of how we plan to synthesize aplykurodinone 1. The ketone **88** used by Taber is the same ketone that we plan to use for our synthesis, so naturally the route was attempted. It did present a problem with the key step of the ketone formation, which involved a rhodium catalyzed C-H insertion that will be discussed below.

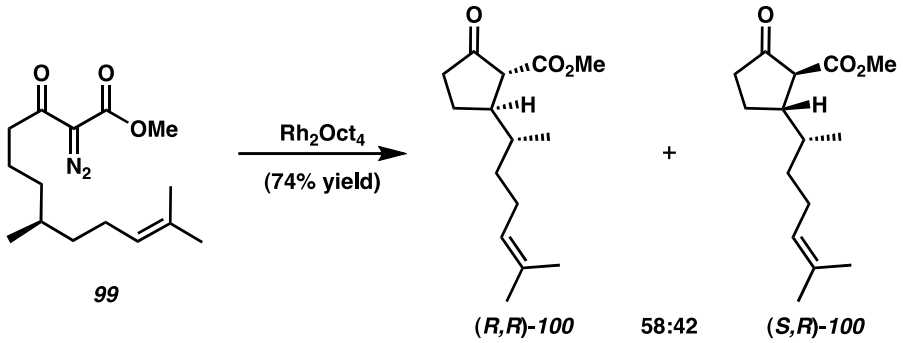
The Taber route starts with commercially available and inexpensive (*R*)-citronellal (**96**), which was converted to citronellol (**97**) by way of $LiAlH_4$ reduction in 91% yield shown in Scheme 4.2.1.1. From there, the alcohol was then converted to the benzesulfonate using benzensulfonyl chloride with triethylamine. That transformation was followed by homologation with methyl acetoacetate using the dianion to form β-keto-ester citronellal derivative **98** in 76% yield for the 2 steps.[2] With the β-keto-ester **98** in hand, the next step yielded the diazo-compound **99** using *p*ABSA with triethylamine in

acetonitrile in 81% yield to form the intermediate for the key step in the ketone sequence, the rhodium-catalyzed C-H insertion.[3]



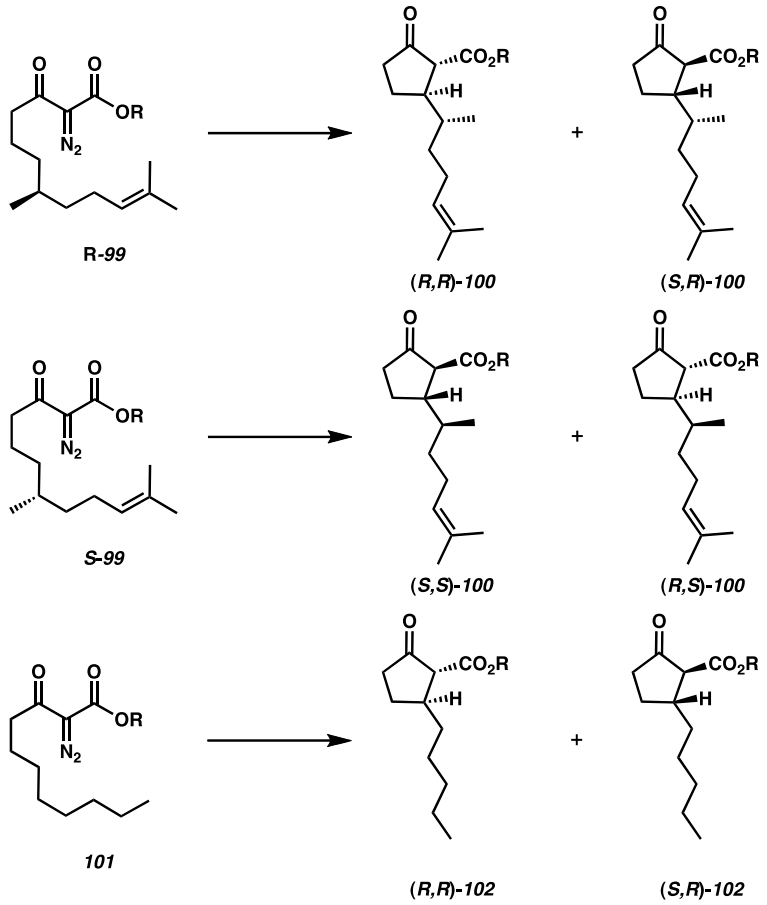
Scheme 4.2.1.1 Initial steps of the Taber group's synthesis of ketone **89**

The initial attempt of the C-H insertion made by the Taber group used rhodium octanoate and resulted in a 74% yield of the diastereomeric mixture with only a moderate excess of the needed diastereomer, (*R-R)*-**100**, resulting in a 14% de as shown in Scheme 4.2.1.2.[4] At this point, a greater selectivity was needed for the desired diastereomer to make the reaction useful, so several different catalysts were tried including rhodium acetate, Doyle's MEPY catalyst,[5] Hashimoto's PTPA catalyst,[6] and Davies' DOSP and BiTISP catalysts.[7]



Scheme 4.2.1.2 Initial attempt at rhodium catalyzed C-H insertion by Taber's group

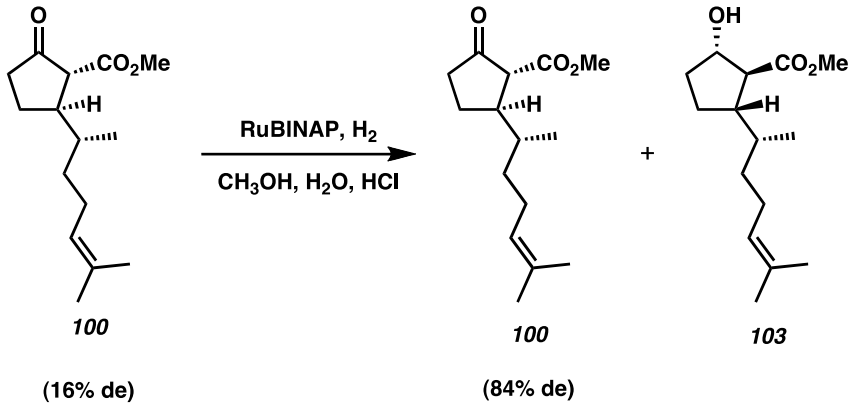
To optimize this reaction the Taber lab used multiple different substrates (Table 4.2.1.1) in addition to the already mentioned catalysts. Table 4.2.1.1 has the results from the optimization attempts done by the Taber group. Using rhodium acetate as the catalyst, yields were excellent ranging from 91% to 99%, however, the greatest diastereomeric excess exhibited by the catalyst was 22%. When they used (*R*)-PTPA, the yields once again were excellent, however, again the stereoselectivity was poor with the greatest excess being 56%. Using the (5*S*)-MEPY catalyst both the yield and stereoselectivity was not great in any of the trials. (*S*)-DOSP provided great yields as high as 99%, but similar to the acetate and (*R*)-PTP, (*S*)-DOSP furnished poor selectivity with the greatest excess of diastereomer being 46%. (*S*)-BiTISP was another catalyst that performed poorly in both selectivity and yield.[1]



entry	substrate	acetate	(*R*)-PTPA	(5S)-MEPY	(S)-DOSP	(S)-BiTISP
1	*R*-99a	57:43 (92%)[a]	74:26 (98%)[a]	57:43 (66%)[b]	64:36 (94%)[a]	79:21 (38%)[c]
2	*R*-99b	61:39 (99%)[a]	78:22 (89%)[a]	57:43 (48%)[b]	73:27 (95%)[a]	67:33 (12%)[d]
3	*S*-99a	45:55 (92%)[a]	31:69 (92%)[a]	42:58 (64%)[b]	46:54 (95%)[a]	75:25 (32%)[c]
4	*S*-99b	38:62 (91%)[a]	23:77 (88%)[a]	38:62 (44%)[b]	35:65 (96%)[a]	40:60 (10%)[d]
5	101a	50:50 (98%)[a]	60:40 (99%)[a]	51:49 (82%)[b]	51:49 (95%)[a]	
6	101b	50:50 (99%)[a]	61:39 (98%)[a]	50:50 (75%)[b]	48:52 (95%)[a]	

Table 4.2.1.1 Optimization attempts for C-H insertion, a, R= Me, b, R=2,4-Dimethyl-3-pentyl. Isolated yields are in parenthesis. [a] Reaction run for 2 h at 20 ºC. [b] Reaction run for 16 h at 60 ºC. [c] Reaction run for 2 h at 60 ºC. [d] Reaction run for 4 h at 60 ºC

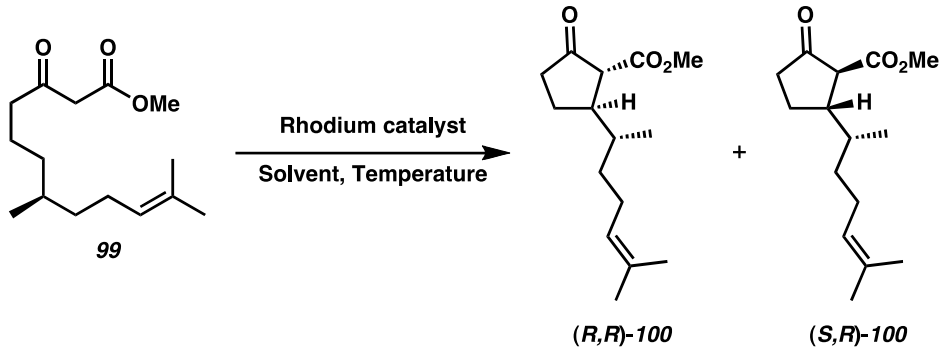
As can be seen from Table 4.2.1.1, none of the catalysts used were able to provide the desired diastereomer with high selectivity, while most cases were able to provide the mixture in high yields. Therefore the method they selected to continue on with the synthesis involved the use of the PTPA catalyst followed by kinetic resolution using Ru-BINAP hydrogenation. They were able to start with diazo-compound **99**, and obtain a mixture of diastereomers of **100** in 98% yield with 16% de. From there as shown in Scheme 4.2.1.3, they used the hydrogenation conditions to obtain the desired diastereomer in 84% excess, with 66% recovery of the desired diastereomer.[8,9] Alcohol **103** was consequently obtained, but was easily purified away.



Scheme 4.2.1.3 Kinetic resolution done by Taber's group

Based on the results from Taber's attempts to optimize the reaction and increase the selectivity, our group also decided to try a few more recently developed catalysts in an attempt to increase the efficiency of the reaction and make this route to ketone **88** more attractive. The reactions were run at different temperatures and in a variety of

solvents to further attempt to increase the efficiency of the rhodium catalyzed C-H insertion to form keto-ester **100**. Table 4.2.1.2 shows the results from the trials.



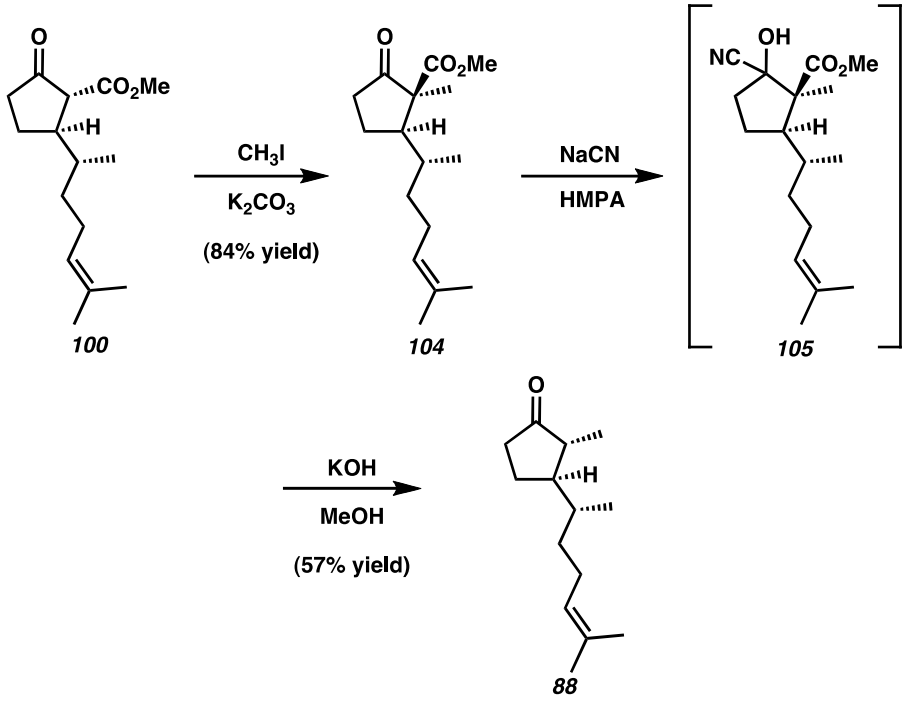
solvent/Temp.	*S*-PTAD	*R*-PTAD	Tetrakis	$(CF_3COO)_2$
Benzene/R.T.	3.1:1 (99%)	3.9:1 (78%)	—	—
Hexane/R.T.	3.4:1 (92%)	4.2:1 (99%)	—	—
CF_3CH_2OH/R.T.	Multiple Products	Multiple Products	—	—
CH_2Cl_2/R.T.	3.3:1 (92%)	—	1.7:1 (98%)	—
CH_2Cl_2/0 °C	3.5:1 (70%)	4.1:1 (71%)	—	1:1 (67%)
CH_2Cl_2/-10 °C	3.0:1.0 (63%)	4.1:1 (73%)	—	—

Table 4.2.1.2 Attempts to further the optimization of the C-H insertion. Product distribution is ratio of r,r to s,r diastereomers. Isolated yields are in parenthesis.

We were unable to find a catalyst that gives a useful diastereomeric ratio. Using rhodium(II) tetrakis[1-[(4-tert-butylphenyl)sulfonyl]-(2S)-pyrrolidinecarboxylate as a catalyst we obtained a product ratio of 1.7:1. Having such a poor selectivity this attempt was the only one that was made with this specific catalyst and no other temperatures or solvents were tried. Rhodium trifluoroacetate also gave only a 1:1 mixture of

diastereomers therefore no other attempts were made with this catalyst either under the premise that it was not a productive catalyst for this reaction. The two different PTAD enantiomers were the catalysts that proved to be the most successful; however, they showed only moderate selectivity. The best results obtained for *S*-PTAD was with dichloromethane as solvent at 0 ºC obtaining a product ratio of 3.5:1 and a yield of 70%. The best results obtained using the *R*-PTAD catalyst was with hexane at room temperature resulting in a diastereomer ratio of 4.2:1 and a yield of 99%.

After the formation of keto-ester **100** the next step, as shown in Scheme 4.2.1.4, is the methylation of **100** using methyl iodide and potassium carbonate at the α-position to both the ketone and ester to form intermediate **104** in 84% yield. Following the methylation is the decarboxylation by cyano-addition to the ketone forming **105**, followed by addition of base to form ketone **88** in 57% yield.



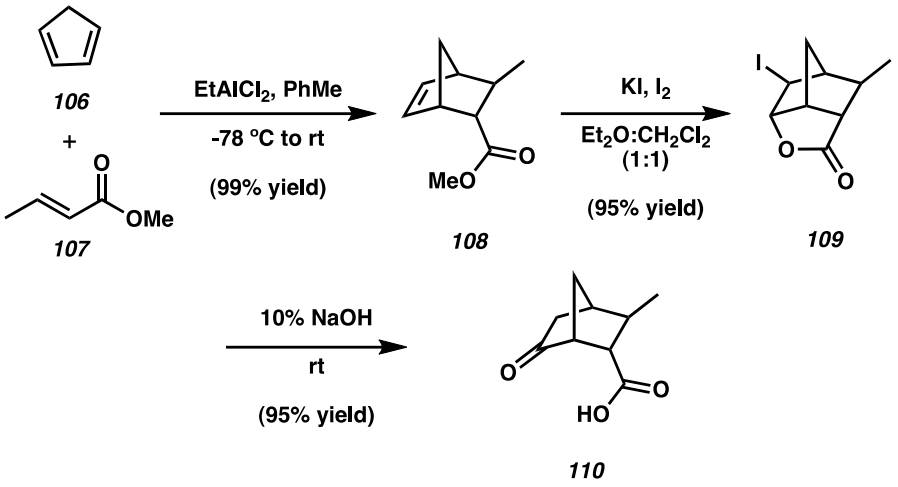
Scheme 4.2.1.4 Final steps for the Taber route to ketone **88**

Using Taber's route to the ketone it is 7 steps with an overall percent yield of 17%. As can be seen from Tables 4.2.1.1 and 4.2.1.2 the key step for his synthesis, the rhodium catalyzed C-H insertion, is problematic resulting in less than desirable diastereomeric ratios and causing loss of material at this step. For this reason, we explored an alternative route to enable us to have a higher overall yield of ketone **88**. This newly devised route will be described in the next section.

4.2.2 May Lab Route to Ketone 88

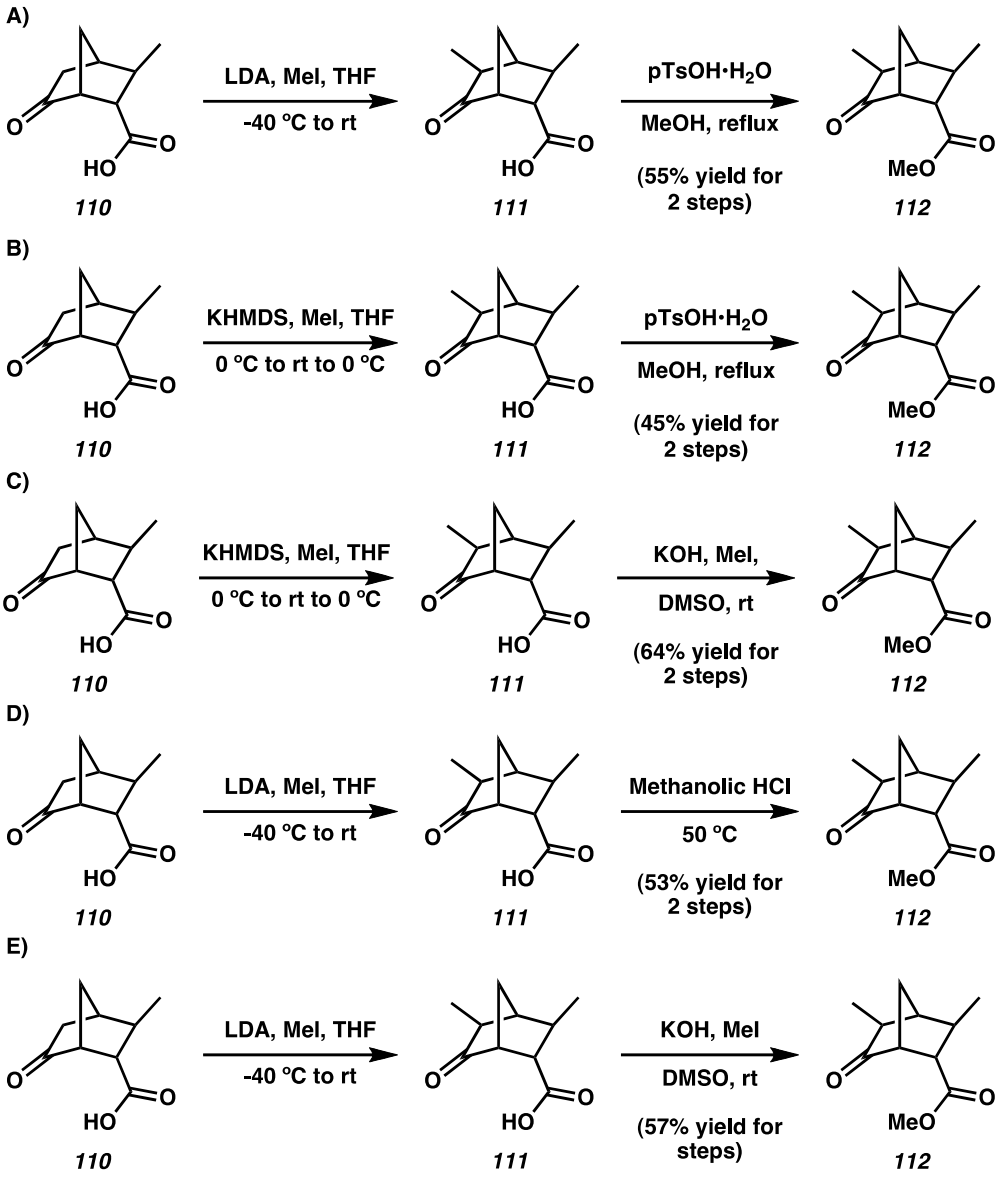
This route to form ketone **88** starts with dicyclopentadiene shown in Scheme 4.2.2.1, which must be cracked and distilled at around 200 ºC. Cyclopentadiene will dimerize back to dicyclopentadiene readily, so it must be stored at -78 ºC. Cyclopentadiene (**106**) underwent a Diels-Alder cycloaddition with methylcrotonate (**107**) using $EtAlCl_2$ as a Lewis acid catalyst.[10] Initially, $MeAlCl_2$ was used, but it's commercial production has been discontinued. However, $EtAlCl_2$ seems to work a little better and is easily obtained. One problem with the initial Diels-Alder reaction is that some polymer was formed during the reaction that must be precipitated and filtered off using acetone to get a clean product. It appeared that less polymer was formed using $EtAlCl_2$. After the formation of ester **108** by Diels-Alder conditions, it was then subjected to KI and I_2 to form iodolactone **109** in very good yield.[11] Following iodolactonization was base hydrolysis, also in excellent yield, to form keto-acid **110**. The next step was a methylation in the α-position to the ketone using LDA followed by acid catalyzed esterification. It will be shown however that the yield for this two-step sequence was

uncharacteristically low, therefore a few different methods will be used to try to perform this two-step sequence with increased efficiency.



Scheme 4.2.2.1 Formation of keto-ester **110**

Shown in Scheme 4.2.2.2 is the two-step methylation/esterification sequence. The yield for the original two-step sequence was 55% (entry A). It was initially surmised that the problem lay in the acid catalyzed esterification step due to the possibility of rearrangements and the formation of nonclassical cations resulting in different side products forming. Therefore, a few different reaction types were tried for this two-step process in the attempt to increase the yield.

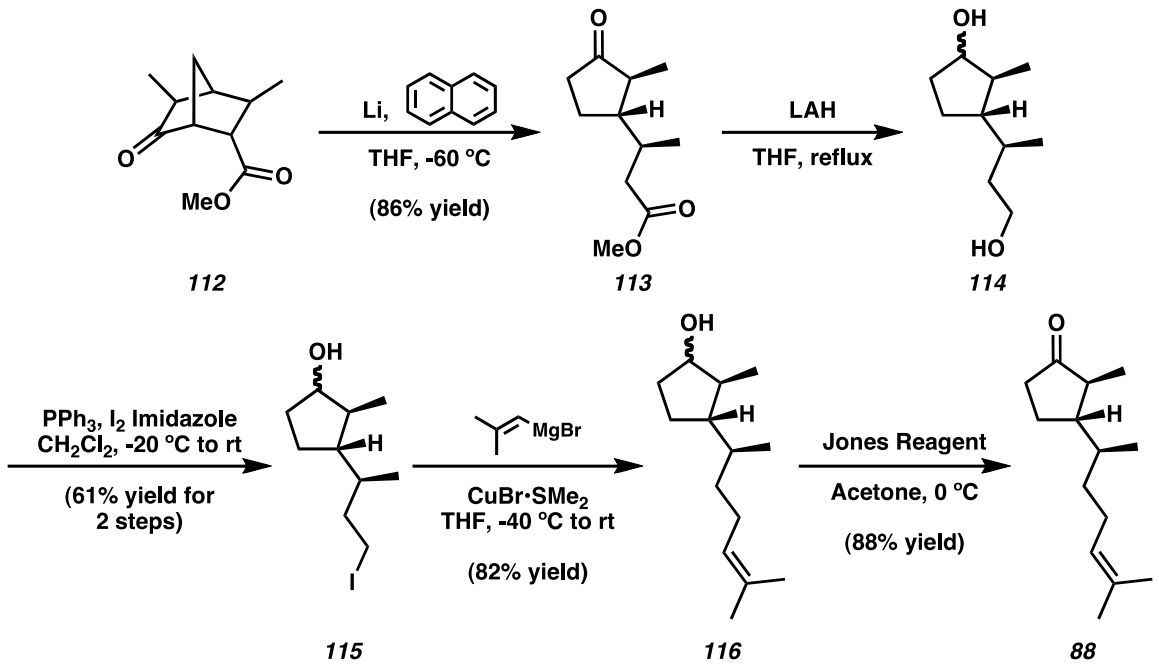


Scheme 4.2.2.2 Different routes to methylated keto-ester **112**

Scheme 4.2.2.2 shows many different variations of methylation and esterification sequences to try to find one that would work in higher yields. All of the attempts produced somewhat similar yields. The lowest two-step yield was 45% when KHMDS and MeI followed by pTsOH•H_20 in MeOH was used (entry B). The highest yield was

64% when KHMDS and MeI were used followed by esterification with KOH and MeI in DMSO (entry C). However, the sequence that has continued to be used is the LDA methylation forming intermediate **111** followed by the pTsOH•H_20 in MeOH esterification conditions resulting in **112** which is reaction A,[12] mainly due to the cost of reagents as well as the ability to use the acid catalytically.

Once the methylated keto-ester **112** had been formed, lithium naphthalenide was used to perform a single electron reductive cleavage of the bicyclic core, resulting in the pentanone intermediate **113** in 86% yield (Scheme 4.2.2.3). Formation of the lithium naphthalenide was observed as a very deep green coloration that took over the reaction mixture.[12] $LiAlH_4$ reduction of **113** reduced both the ketone and the ester to their respective alcohol oxidation states, resulting in diol **114**. Diol **114** was then used without purification in Mitsunobu type conditions to form the 1º iodide selectively over the 2º and provide monoiodinated intermediate **115** in 61% for the two-step sequence.[13] The low temperature and careful addition of I_2 in multiple portions allowed for the chemoselectivity. If I_2 was added too quickly or all at once, then the doubly iodinated product formed as the major product. A Corey-House[14] coupling of an alkyl Grignard to the terminal iodide extended the carbon chain and introduced the tertiary olefin of **116** in 82% yield.[15] In order to prevent any isomerization of the olefin, the organo-cuprate must be generated at low temperatures. The final step in forming ketone **88** was the Jones oxidation of **116** with a yield of 83%. By this synthetic method, ketone **88** can be synthesized in 10 steps with an overall yield of 19%.

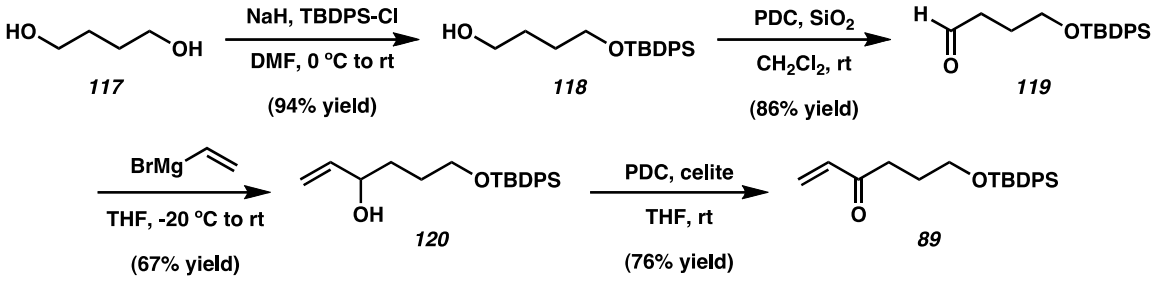


Scheme 4.2.2.3 Final steps of the synthesis to ketone **88**

4.3 Formation of Enone 89

Formation of enone **89** began with commercially available 1,4-butanediol **117** as seen in Scheme 4.3. It was monoprotected in 94% yield using TBDPS-Cl as the limiting reagent to prevent the protection of both hydroxyl groups from occurring. This was the only protection step planned in the synthesis, which increases the efficiency by limiting step count relative to using many different protecting/deprotecting steps. With monoprotected intermediate **118** in hand; the next step was to oxidize the free hydroxyl group to the aldehyde using PDC with silica gel as the solid support for the oxidant forming aldehyde **119**. This oxidation was done in 97% yield. With the aldehyde in place, the molecule is ready for a Grignard addition to extend the carbon chain to the number of carbons needed. Vinyl Grignard was used to do this to form enal **120** in 66% yield. After

this step was the first and only chromatographic purification that takes place in route to forming enone **89**, which is a testament to the practicality of the route. The final step was oxidation of **120**, again using PDC, with the solid support being celite. This was done in 76% yield to form enone **89** to be used in the Robinson annulation reaction to be described later. The synthesis of the enone required 4 steps with an overall yield of 56%.

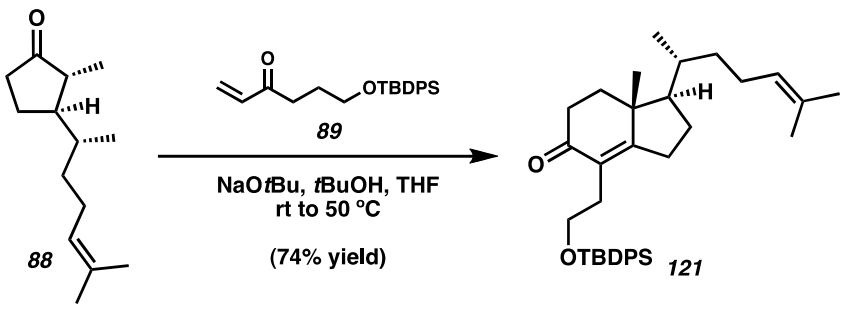


Scheme 4.3 Synthesis of enone **89**

The two intermediates needed, ketone **88** and enone **89**, were synthesized in preparation of a Robinson annulation reaction to form the bicyclic core of aplykurodinone 1. These two compounds were prepared with few purification steps and only one protecting group. The next section will discuss the Robinson annulation reaction.

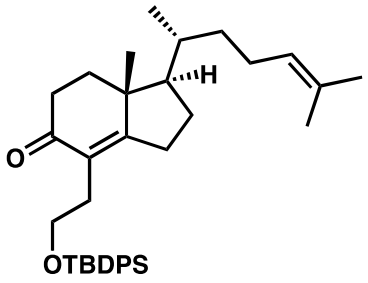
4.4 Robinson Annulation Reaction

The key step for our synthesis is a Robinson annulation to assemble the bicyclic core structure of aplykurodinone 1 as shown in Scheme 4.4.1.

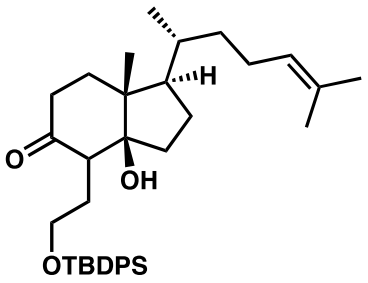


Scheme 4.4.1 Robinson annulation

The Robinson annulation reaction was successfully performed in a one-pot reaction using the conditions as shown in Scheme 4.4.1.[16] However, the need for improvement remained. We realized some interesting effects that depended on the condition of our solvent, *t*BuOH. If unaltered *t*BuOH straight from the bottle was used as shown in entry 1 in Table 4.3, we only obtained the aldol product, **122**. If freshly distilled *t*BuOH was used as seen in entry 2, then the correct product is obtained, **121**; however the yield tends to be lower than desired. However, when *t*BuOH that is shaken and stored with $MgSO_4$ overnight was used, the correct enone product was formed in the highest yield (entry 3). Therefore, it was hypothesized that some form of Mg^{2+} is helping to catalyze the reaction. However, if $MgSO_4$ was directly added into the reaction mixture we obtained no product as shown in entry 4. Some additives were then tried to see if any of them would increase the yield of the reaction. As seen in Table 4.4, only 2 of the additives resulted in any kind of product formation, Cs_2CO_3 and $Mg(OtBu)_2$ (entries 5 and 6), but they only formed **122** in low yields. The other additives as seen in entries 7-12 yielded no major products.



121



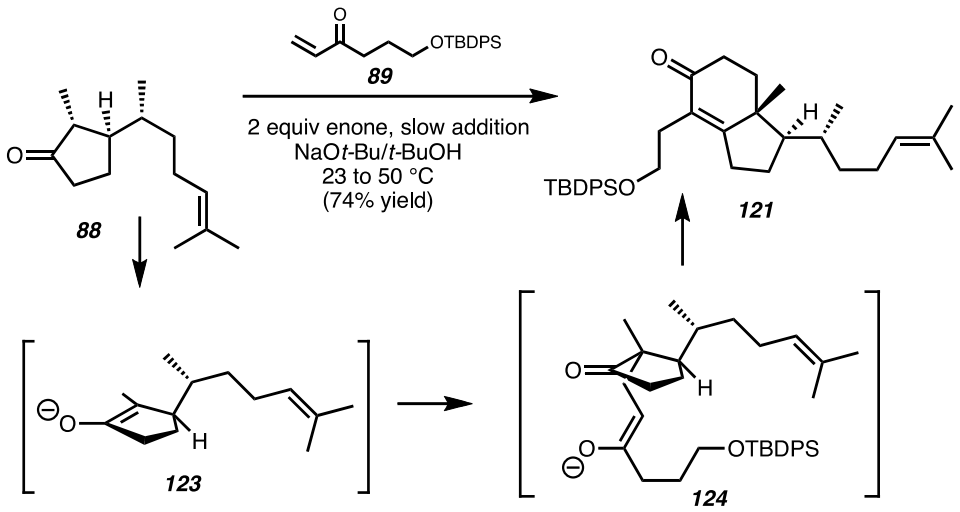
122

entry	conditions	product(s)	yield
1	unaltered *t*BuOH (from bottle)	*122*	49%
2	freshly distilled *t*BuOH	*121*	52%
3	$MgSO_4$ dried *t*BuOH	*121*	74%
4	freshly distilled *t*BuOH w/ $MgSO_4$	none	—
5	freshly distilled *t*BuOH w/ Cs_2CO_3	*122*	16%
6	freshly distilled *t*BuOH $Mg(OtBu)_2$	*122*	22%
7	freshly distilled *t*BuOH $MgBr_2$	none	—
8	freshly distilled *t*BuOH ZnI_2	none	—
9	freshly distilled *t*BuOH $CuBr_2$	none	—
10	freshly distilled *t*BuOH $CaCl_2$	none	—
11	freshly distilled *t*BuOH $TiOiPr_2$	none	—
12	freshly distilled *t*BuOH $Al(OtBu)_2$	none	—

Table 4.4 Additives screened under Robinson annulation conditions

The explanation for the stereochemistry in the product can be seen in Scheme 4.4.2. After deprotonation of the ketone forming the thermodynamic enolate **123**, the enone approaches the ketone from the bottom due the large isoprenyl side chain blocking the top of the ketone, causing the methyl group of the ketone to be pushed toward the top

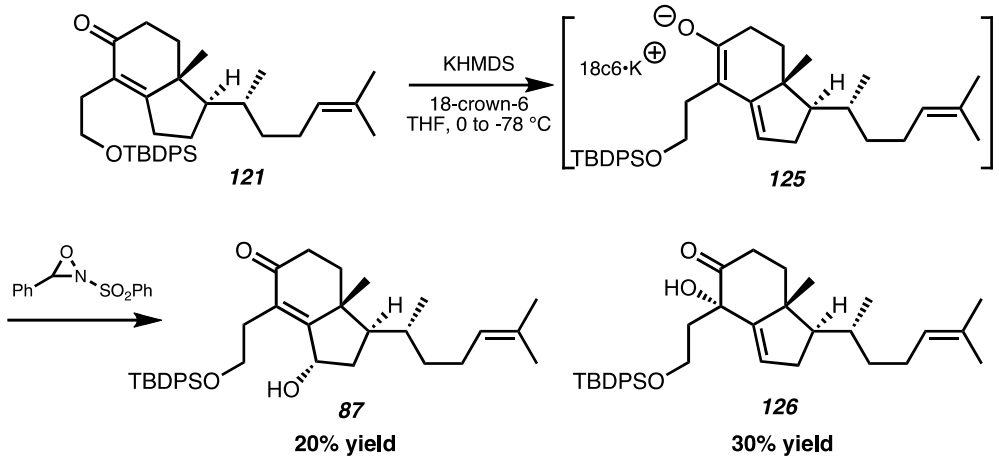
face during C-C bond formation as seen in intermediate **124**. Consequently, the closing of the second ring of the bicycle by the aldol condensation occurs on the bottom face of the ketone forming **122**.



Scheme 4.4.2 Stereochemical explanation of Robinson annulation

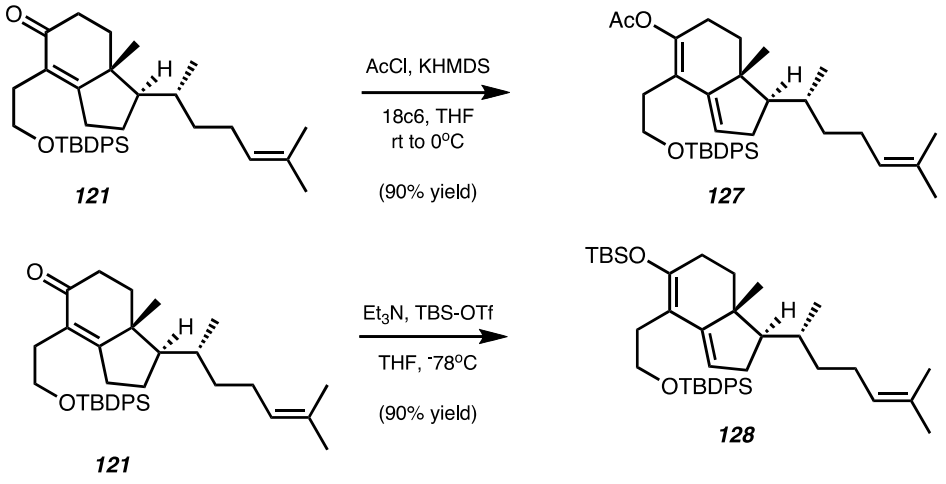
Section 4.5 Gamma Oxidation Of Enone 121

Many attempts have been made to oxidatively hydroxylate enone **121** at the λ-position; however, very few conditions yielded any kind of product whatsoever. The best result came from using the electrophilic oxidant Davis oxaziridine[17] to install a hydroxyl group in the λ-position as shown in Scheme 4.5.1. KHMDS was used to form the extended enolate (**125**) using potassium trapped in 18-crown-6 as a counter ion to add bulk around the enolate oxygen in efforts to force the oxidant to the λ-position. The yield of the reaction was at best less than desirable at around 20% of the desired λ-product. Unfortunately, this method was not reproducible and reliable. The product with the hydroxyl group in the α-position, **126**, was also observed.



Scheme 4.5.1 λ-Oxidation using Davis oxaziridine

In addition, the extended enolate was formed and trapped with TBS-Cl as well as AcCl shown in Scheme 4.5.2. This was done to prove that the extended enolate could be formed as well as forming another intermediate to attempt to oxidize with electrophilic oxidants. However, all attempts to oxidize the two intermediates have been unsuccessful so far. Therefore, while some λ-oxidation product has been formed overall, it has been very inconsistent.

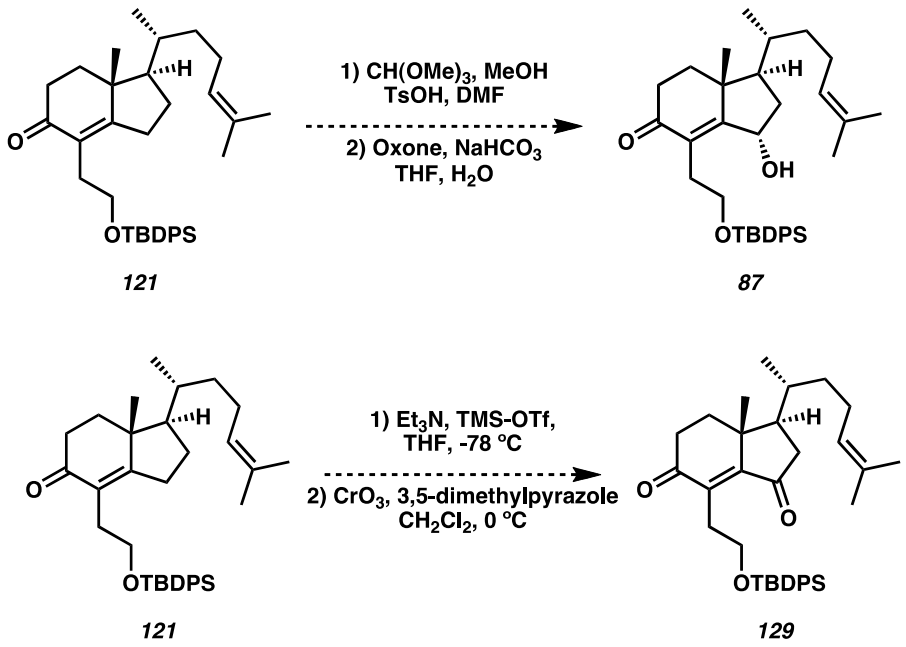


Scheme 4.5.2 Formation of the extended enolate trapping with TBS-Cl and AcCl

Some of the other methods that were attempted to form product **87** included forming intermediate **127** then oxidizing with NMO and OsO_4; however, that failed to produce any product. Another method that was attempted was to oxidize using 20% aq. KOH and O_2, but that failed as well. Using benzoyl peroxide as an electrophilic oxidant was also unsuccessful, as well as using *m*CPBA on **128**. A couple of other methods to try to effect the desired oxidation are shown in the next section.

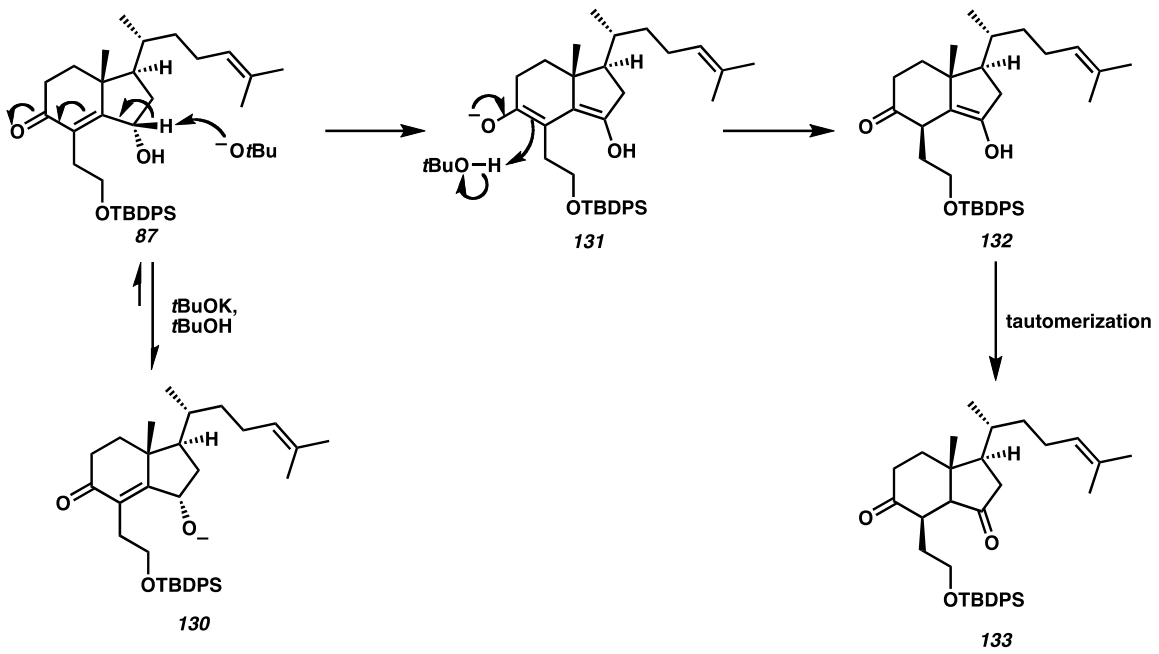
4.6 Proposed Completion of Aplykurodinone 1

There have been a couple of new methods found in the literature that show great promise in the ability to oxidize the γ-position of an enone **121**. The first method comes from the Bonjoch group in their synthesis of (+)-Xylarenal A and *ent*-Xylarenal A.[18] It involves forming a dienol ether followed by use of oxone to instill the hydroxyl in the desired position. The other proposed method is based on work from the Carreira group in the synthesis of (±)-Gomerone C.[19] This method forms a silyl enol ether that when subjected to CrO_3 forms dienol **129** which can also be a useful intermediate. These methods are promising for the oxidation of enone **121** (Scheme 4.6.1).



Scheme 4.6.1 Alternate methods to oxidize in the γ-position

After the successful formation of **87**, the next step will be a redox isomerization to form diketone **133**[20] as shown in Scheme 4.6.2. The deprotonation of the hydroxyl group (**130**) is in equilibrium with formation of the enolate shown in intermediate **131.** Protonation of the enolate to form **132** followed by tautomerization forms the diketone product **133.**



Scheme 4.6.2 Mechanism for the base-catalyzed rearrangement proposed

After the formation of **133,** the use of a reductant such as L-selectride will be used in attempts to direct the stereochemistry based on the sterics and the conformation of the molecule to reduce only the cyclohexanone to form **134** as can be seen in Scheme 4.6.3. The cyclohexanone ring will be in a boat conformation. Therefore, the molecule will be concave in that the cyclopentanone carbonyl will be in the interior preventing reduction from occurring at the bottom face. The large isoprenyl side will block the top face of this ketone preventing reduction from occurring on the top face as well. The cyclohexanone carbonyl will be blocked from the top face by the TBDPS side chain; however, due to the boat conformation of this ring the carbonyl will point upward exposing the bottom face for hydride attack. The 3-D conformation of **133** can be seen in Figure 4.6.

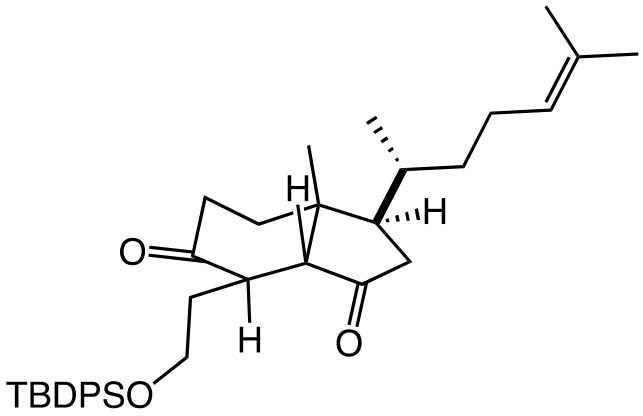
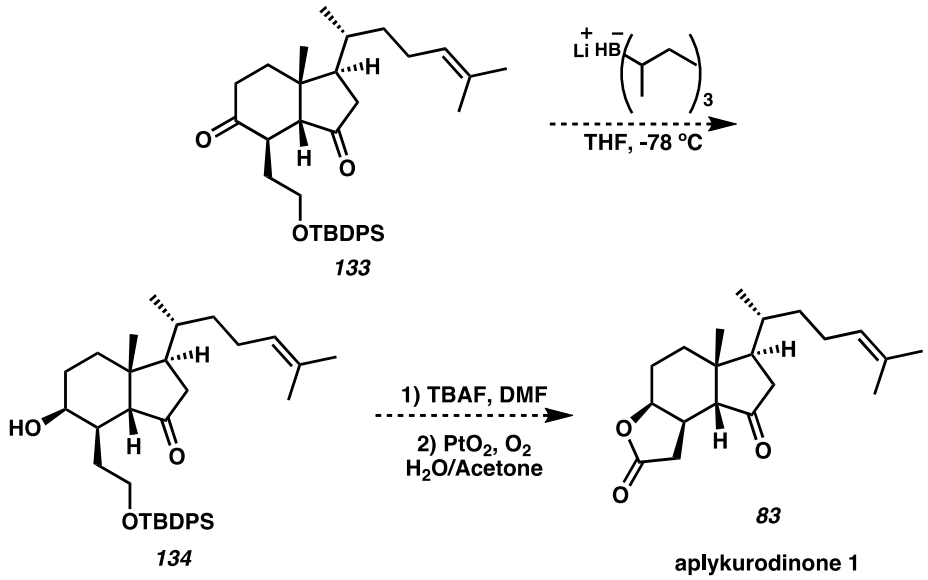


Figure 4.6 3-D conformation of **133** to explain selective reduction

After selective reduction takes place the next step is to remove the TBDPS group freeing the primary hydroxyl of **134** as shown in Scheme 4.6.3. After the deprotection, PtO_2 with O_2 will be used to selectively oxidize the primary alcohol to the lactone and complete the structure of aplykurodinone 1.



Scheme 4.6.3 Proposed final steps toward aplykurodinone 1

4.7 Conclusion

Discussed in this chapter is the advancement toward the synthesis of aplykurodinone 1. The structural intricacies, such as 6 contiguous stereocenters and a quaternary bridgehead carbon, make it an interesting natural product. It also belongs to a family that has shown potential biological activity against tumor cell lines. The key step of our synthesis is a Robinson annulation reaction that forms the structural core of aplykurodinone 1; however, the λ-oxidation step has proved to be a problematic bottleneck to this point. In addition, the proposed final steps of the synthetic strategy illustrate how that the natural product will be completed in the near future.

4.8 Experimental Section

4.8.1 General Considerations

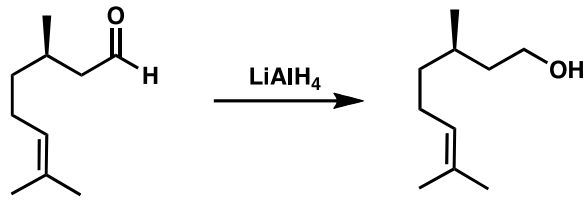
All of the reactions were performed in flame- or oven-dried glassware. THF, Et_2O, toluene, MeCN, and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash column chromatography was performed on 60Å silica gel (Sorbent Technologies). The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using TMS or residual solvent peak as an internal standard. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm.

4.8.2 Materials

Commercially available compounds were purchased from Aldrich, Acros, or Alfa Aesar and were used without further purification.

4.8.3 Experimentals for Taber Ketone Synthesis

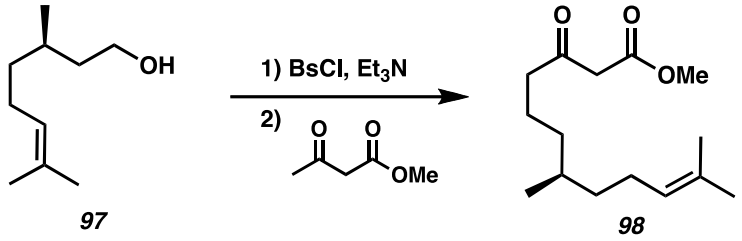
4.8.3.1 Synthesis of (R)-Citronellol (97)



96 *97*

To a flame-dried flask was added $LiAlH_4$ (636 mg, 16.7 mmol, 0.5 equiv) and THF (128 mL) and cooled to 0 ºC. (R)-Citronellal (**96**) (6 mL, 33.1 mmol, 1.0 equiv) was then added neat over 15 minutes and it was stirred rapidly at 0 ºC. After completion, 600 µL of H_2O, 600 µL of 3M NaOH, and a solution of 1.8 mL of H_2O in 1.8 mL of THF were added to the reaction mixture. The crude reaction mixture was then run through a plug of celite with MTBE as the eluent. The solvent was then removed via rotary evaporation (4.72 g, 30.2 mmol, 91% yield). All spectral properties were in accordance to the published values.[1]

4.8.3.2 Synthesis of (*S*)-methyl 7,11-dimethyl-3-oxododec-10-enoate (98)



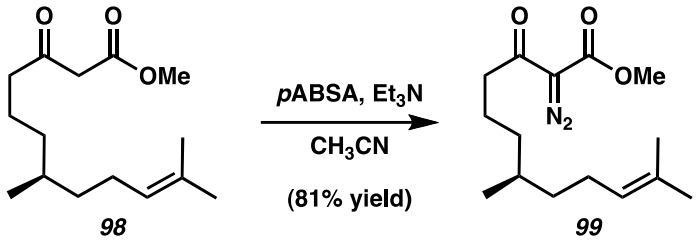
97 *98*

To a flame-dried flask with **97** (4.72 g, 30.2 mmol, 1.0 equiv) was added CH_2Cl_2 (62 mL) and cooled to 0 ºC. Et_3N (9.3 mL, 66.4 mmol, 2.2 equiv) was then added in one portion followed by DMAP (313 mg, 0.25 mmol, 0.0085 equiv) Benzenesulfonyl chloride (6.66 g, 37.7 mmol, 1.25 equiv) was then added dropwise. The reaction was allowed to stir for 2 h at 0 ºC. It was then quenched with 3M HCl and extracted with Et_2O. The organic layer was then washed with brine solution and dried with Na_2SO_4. The reaction was then filtered and the solvent was removed via rotary evaporation (8.91g, 30.0 mmol, 99% yield). All spectral properties were in accordance to the published values.[1]

The product was then used directly without purification in the next step. To a flame-dried flask was added NaH (4.7 g, 60% in mineral oil, 117.5 mmol, 4.0 equiv) followed by THF (63 mL). The reaction was then cooled to 0 ºC and allowed to stir rapidly. Methyl acetoacetate (7.0 mL, 64.6 mmol, 2.2 equiv) was then added. After addition, the reaction was allowed to stir for 10 minutes before *n*-BuLi (24 mL, 2.5 M in hexanes, 60 mmol, 2.0 equiv) was added. The reaction was allowed to stir at 0 ºC for 10 minutes before starting material (8.91 g, 30 mmol, 1.0 equiv) was added as a solution in THF (16 mL) via cannula. The mixture stirred at room temperature for 1 h before carefully being quenched with NH_4Cl. It was then extracted with MTBE and the organic

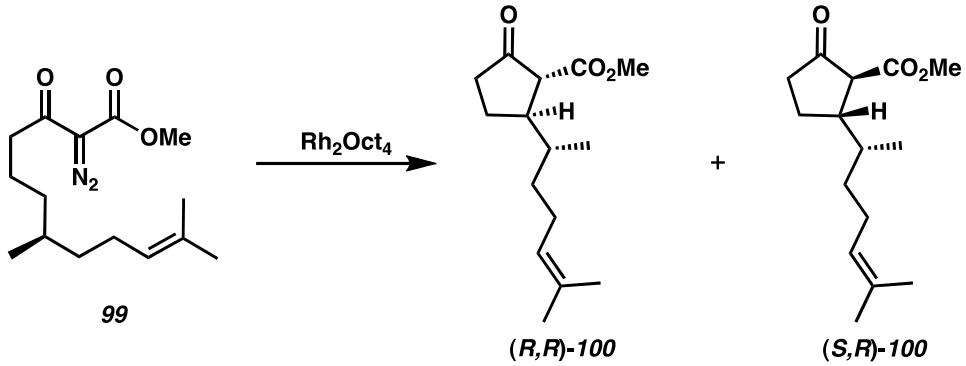
layer was washed with brine solution. The solvent was then removed via rotary evaporation (5.91 g, 23.2 mmol, 76% yield). All spectral properties were in accordance to the published values.[1]

4.8.3.3 Synthesis of (*S*)-methyl 2-diazo-7,11-dimethyl-3-oxododec-10-enoate (99)



To a flame-dried flask with **98** (4.12 g, 16.2 mmol, 1.0 equiv) was added CH_3CN (17 mL). Et_3N (5.5 mL, 39.6 mmol, 2.5 equiv) was then added followed by pABSA (4.74 g, 19.7 mmol, 1.2 equiv) and allowed to stir at room temperature overnight. After completion of the reaction, it was quenched with 3M NaOH and then extracted with Et_2O. The organic layer was then washed with brine solution. The solvent was then removed via rotary evaporation. The crude product was purified via column chromatography with a 2.5-10% gradient of ethyl acetate in hexanes (3.68 g, 13.1 mmol, 81% yield). All spectral properties were in accordance to the published values.[1]

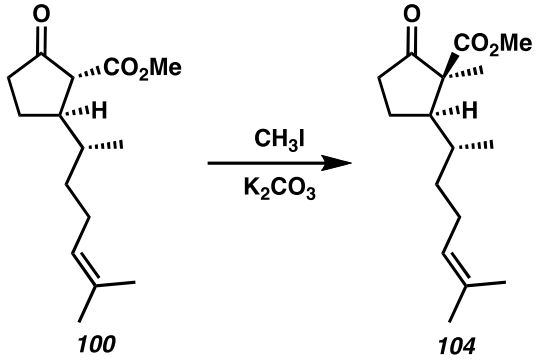
4.8.3.4 General Procedure for the Synthesis of methyl 2-(6-methylhept-5-en-2-yl)-5-oxocyclopentanecarboxylate (100)



99 (*R,R*)-*100* (*S,R*)-*100*

To a flame-dried flask with **99** (500 mg, 1.78 mmol, 1.0 equiv) was added CH_2Cl_2 (19 mL). Rhodium catalyst (0.56 mol %) was then added and the reaction was allowed to stir rapidly. After completion, the solvent was removed by rotary evaporation resulting in a green residue. The residue was purified by column chromatography with a 2.5-10% gradient of ethyl acetate in hexanes. The purified compound is a mixture of the diastereomers that can be separated by recrystallization. Minimal but equal amounts of ethanol and water were added and it was heated to 50 ºC. More ethanol can be added to the mixture at this temperature until all of the oil is dissolved. The mixture is then cooled to room temperature to afford the diastereomerically pure compound. All spectral properties were in accordance to the published values.[1]

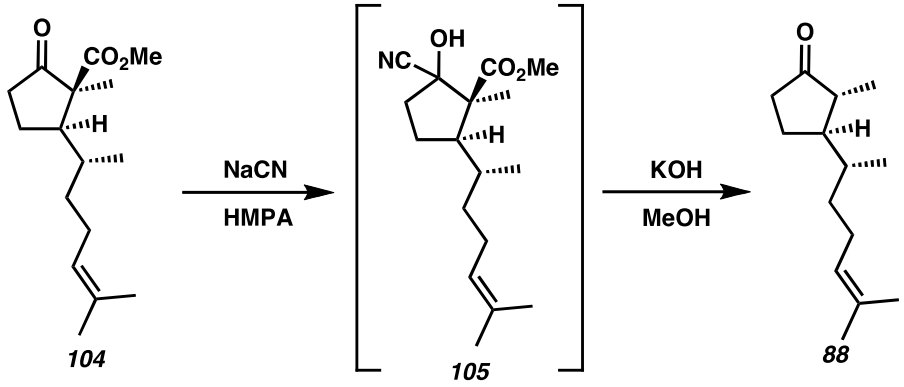
4.8.3.5 Synthesis of (1*S*,2*R*)-methyl 1-methyl-2-((*R*)-6-methylhept-5-en-2-yl)-5-oxocyclopentanecarboxylate (104)



100 *104*

To a flame-dried flask with **100** (100 mg, 0.39 mmol, 1.0 equiv) was added acetone (2 mL). Methyl iodide (49 μL, 0.78 mmol, 2.0 equiv) was then added followed by K_2CO_3 (194 mg, 1.40 mmol, 3.6 equiv). The reaction was then heated to reflux for 5 h before being cooled to room temperature. It was then quenched with saturated aq. NH_4Cl. The organic layer was extracted with ethyl acetate and dried with Na_2SO_4. The mixture was then filtered and the solvent was removed via rotary evaporation. The resulting crude oil was then purified via column chromatography with a 2.5-10% gradient of ethyl acetate in hexanes (88 mg, 0.33 mmol, 84% yield). All spectral properties were in accordance to the published values.[1]

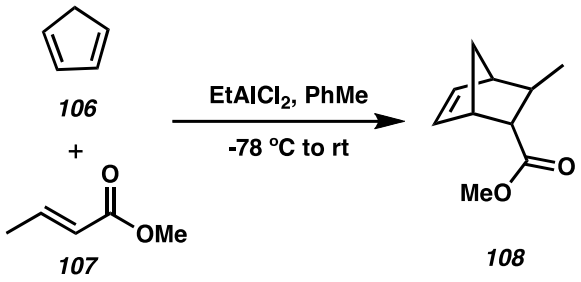
4.8.3.6 Synthesis of (2*R*,3*R*)-2-methyl-3-((*R*)-6-methylhept-5-en-2-yl)cyclopentanone (88)



To a flame-dried flask with **104** (192 mg, 0.72 mmol, 1.0 equiv) was added HMPA (7 mL). NaCN (71 mg, 1.44 mmol, 2.0 equiv) was then added and the reaction mixture was then warmed to 80 ºC for 5 h. The organic layer was extracted with MTBE, and then washed with saturated aq. $NaHCO_3$ followed by H_2O. The solvent was then removed via rotary evaporation. The residue was diluted with 2 mL of 10% KOH in MeOH and allowed to stir for 10 minutes at room temperature. It was then extracted with Et_2O and washed with brine solution followed by H_2O. The organic layer was dried with Na_2SO_4 and filtered. The solvent was then removed via rotary evaporation. The crude product was purified by column chromatography with a 2.5-10% gradient of ethyl acetate in hexanes (104 mg, 0.57 mmol, 57% yield). All spectral properties were in accordance to the published values.[1]

4.8.4 Experimentals for May Lab Ketone Synthesis

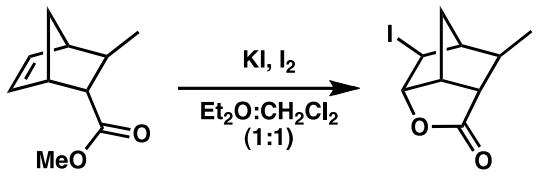
4.8.4.1 Synthesis of (1*S*,2*S*,4*R*)-methyl 3-methylbicyclo[2.2.1]hept-5-ene-2-carboxylate (108)



To a flame-dried flask was added toluene (43 mL) and cooled to -78 ºC. Methyl crotonate (**107**) (8.6 mL, 80.7 mmol, 1.0 equiv) was then added. Cyclopentadiene (**106**) (10.2 mL, 121.0 mmol, 1.5 equiv) was then added to the bottom of the reaction flask while stirring rapidly. $EtAlCl_2$ (1.0M in hex, 14 ml, 14 mmol, 0.175 equiv) was then added via cannula as a solution in toluene (10 mL) to the bottom of the reaction flask with rapid stirring. The reaction was then allowed to slowly warm to room temperature and stir overnight. After completion, it was cooled to 0 ºC and quenched slowly with Rochelle's salt. It was then extracted with CH_2Cl_2 and the organic layer was dried with $MgSO_4$. The mixture was filtered and the solvent was removed via rotary evaporation. Any polymer that may have formed during the reaction can be precipitated out with acetone and then filtered off. The acetone is then removed via rotary evaporation (13.3 g, 79.8 mmol, 99% yield, 92:8 endo:exo). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.26 (dd, J = 5.73, 3.44 Hz, 1H), 5.98 (dd, J = 5.73, 2.86 Hz, 1H), 3.61 (s, 1H), 3.09 (bs, 1H), 2.46 (bs, 1H) 2.36 (t, J = 4.01 Hz, 1H), 1.84-1.79 (m, 1H), 1.53 (app. d, J = 8.59 Hz, 1H), 1.42 (dq, J = 8.59, 1.72 Hz, 1H), 1.17 (d, J = 6.87 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 175.3, 138.8, 133.4, 52.5, 51.5, 48.9, 46.1, 46.0, 38.0, 21.0 ppm. IR (neat): 2960, 2872, 1736, 1435, 1321, 1273, 1196, 1173, 1025 cm^{-1}. R_F: 0.65 in 20% ethyl acetate in hexanes.

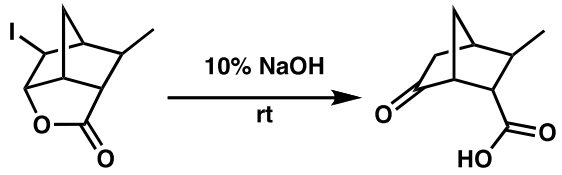
4.8.4.2 Synthesis of Iodolactone (109)



108 *109*

To a flame-dried flask with **108** (1.4 g, 8.42 mmol, 1.0 equiv) was added Et_2O (23 mL) and CH_2Cl_2 (46 mL). I_2 (3.2 g, 12.6 mmol, 1.5 equiv) and KI (1.4 g, 8.42 mmol, 1.0 equiv) were then added and the reaction was allowed to stir overnight at room temperature after being covered with foil. After completion, Et_2O (23 mL) was then added and the reaction was washed with 1:1 mixture of aq. 10% $Na_2S_2O_3$ and aq. 10% $NaHCO_3$. The organic layer was then dried with $MgSO_4$ and filtered. The solvent was then removed via rotary evaporation. The resulting product was then run through a silica plug with 50% ethyl acetate in hexanes (2.22 g, 7.99 mmol, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.08 (d, *J* = 5.15 Hz, 1H), 3.84 (d, *J* = 2.29 Hz, 1H), 3.13 (app. t, *J* = 5.15 Hz, 1H), 2.43 (bs, 1H), 2.27 (dd, *J* = 12.03, 1.15 Hz, 1H), 2.12 (m, 2H), 2.02 (dd, *J* = 12.49, 1.49 Hz, 1H), 1.12 (d, *J* = 6.87 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 178.8, 88.5, 53.2, 46.5, 45.9, 42.5, 34.3, 30.1, 20.8 ppm. IR (neat): 2978, 1785, 1473, 1343, 1170, 1152, 1007 cm^{-1}. R_F: 0.36 in 20% ethyl acetate in hexanes.

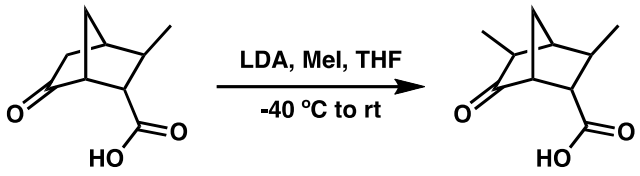
4.8.4.3 Synthesis of (1*R*,2*S*,4*R*)-3-methyl-6-oxobicyclo[2.2.1]heptane-2-carboxylic acid (110)



109 *110*

To a flask with **109** (10.5 g, 37.7 mmol, 1.0 equiv) was added 10% NaOH (738 mL) and allowed to stir rapidly at room temperature for 1 h. It was first extracted with Et_2O 1x to remove any starting material that remains. Then it was acidified with 6M HCl and extracted with EtOAc. The organic layer was then dried with $MgSO_4$ and filtered. The solvent was then removed via rotary evaporation (5.98 g, 35.5 mmol, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.87 (d, *J* = 3.44 Hz, 1H), 2.48 (app. s, 1H), 2.33 (app. s, 1H), 2.20-2.11 (m, 2H), 2.00-1.86 (m, 2H), 1.72 (d, *J* = 10.31 Hz, 1H), 1.18 (d, *J* = 6.87 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 178.6, 177.5, 54.0, 51.5, 45.0, 41.7, 39.4, 35.7, 21.3 ppm. IR (neat): 2972, 1746, 1694, 1431, 1304, 1222, 1149, 1016 cm^{-1}.

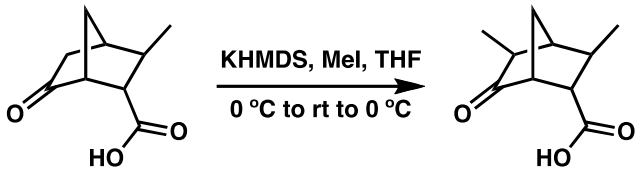
4.8.4.3 Procedures for the Synthesis of (1*R*,2*S*,3*R*,4*S*,5*S*)-3,5-dimethyl-6-oxobicyclo[2.2.1]heptane-2-carboxylic acid (111)



110 *111*

To a flame-dried flask was added HN*i*Pr$_2$ (23 mL, 164 mmol, 5.0 equiv) followed by THF (249 mL) and then cooled to -20 ºC. *n*BuLi (40 mL, 2.5M in hexanes, 100 mmol,

3.0 equiv) and the reaction was allowed to stir for 10 minutes. The reaction was then cooled to -40 ºC and **110** (6.93 g, 41.2 mmol, 1.0 equiv) was added as a solution in THF (30 mL) via cannula over 20 minutes. The reaction was then warmed up to -20 ºC and stirred for 30 minutes, then at room temperature for 30 minutes. The reaction was then cooled back down to 0 ºC and MeI (23.5 mL, 377 mmol, 11.5 equiv) was added rapidly. The reaction was stirred at 0 ºC for 30 minutes then at room temperature for 1.5 h. It was quenched with 3M HCl and the organic layer was extracted with Et_2O. The organic layer was then washed with brine, dried with $MgSO_4$, and filtered. The solvent was then removed via rotary evaporation (7.37 g, 40.4 mmol, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.77 (d, *J* = 3.38 Hz, 1H), 2.46 (app. s, 1H), 2.18 (app. d, *J* = 5.15 Hz, 1H), 2.02-1.97 (m, 2H), 1.87-1.80 (m, 2H), 1.19 (d, *J* = 6.87 Hz, 3H), 1.08 (d, *J* = 7.45 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 178.8, 53.9, 51.2, 48.3, 47.9, 40.6, 32.9, 21.4, 14.2 ppm. IR (neat): 3704, 3656, 2975, 2863, 1743, 1706, 1228, 1055, 1010 cm^{-1}. R_F: 0.19 in 50% ethyl acetate in hexanes.

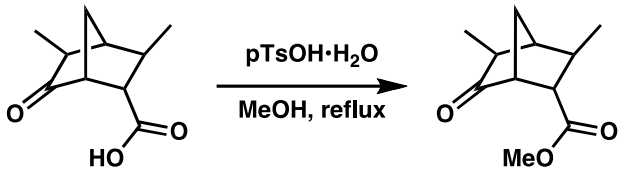


110 ***111***

To a flask with **110** (100 mg, 0.59 mmol, 1.0 equiv) was added THF (4.5 mL) and cooled to 0 ºC. KHMDS (3 mL, 0.5M in toluene, 1.48 mmol, 2.5 equiv) was then added dropwise and the reaction was allowed to stir at 0 ºC for 10 minutes, then at room temperature for 20 minutes. It was then cooled back down to 0 ºC and MeI (338 μL, 5.42

mmol, 9.2 equiv) was added. It was allowed to slowly warm to room temperature. After completion it was quenched with 3M HCl and the organic layer was extracted with Et_2O. The organic layer was washed with brine and dried with $MgSO_4$. The reaction was then filtered and the solvent was removed via rotary evaporation (100 mg, 0.55 mmol, 93% yield).

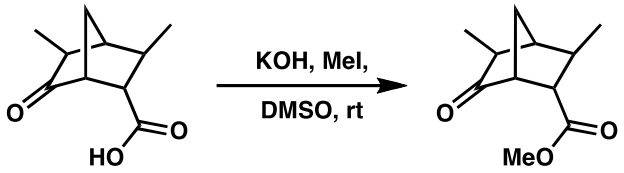
4.8.4.4 Procedures for the Synthesis of (1*R*,2*S*,3*R*,4*S*,5*S*)-methyl 3,5-dimethyl-6-oxobicyclo[2.2.1]heptane-2-carboxylate (112)



111 *112*

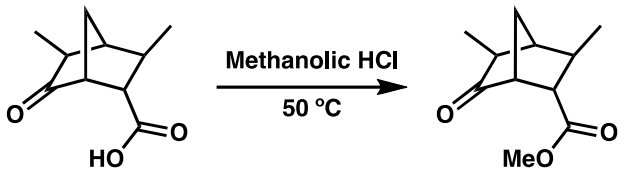
To a flask with **111** (7.37 g, 40.0 mmol, 1.0 equiv) was added MeOH (147 mL) and pTsOH•H_2O (152 mg, 0.80 mmol, 2 mol %). The reaction was warmed to reflux and allowed to stir for 2 h. After completion, it was quenched with 10% $NaHCO_3$ and extracted with Et_2O. The organic layer was then washed with brine solution and dried with $MgSO_4$. The reaction was filtered and the solvent was removed via rotary evaporation. The crude product was then purified via column chromatography with a 10–30% gradient of ethyl acetate in hexanes (3.59 g, 18.3 mmol, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (s, 3H), 2.73 (app. d, J = 4.58 Hz, 1H), 2.43 (t, J = 4.58 Hz, 1H), 2.23-2.16 (m, 1H), 2.02-1.97 (m, 2H), 1.85-1.77 (m, 2H), 1.16 (d, J = 7.45 Hz, 3H), 1.07 (d, J = 7.45 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 217.6, 173.9, 54.2, 52.2,

51.4, 48.3, 47.9, 40.2, 32.9, 21.5, 14.2 ppm. IR (neat): 2969, 1752, 1736, 1437, 1285, 1201, 1176 cm^{-1}. R_F: 0.62 in 50% ethyl acetate in hexanes.



111 *112*

To a flask with **111** (250 mg, 1.37 mmol, 1.0 equiv) in anhydrous DMSO (5.5 mL) was added KOH (81 mg, 1.44 mmol, 1.05 equiv). The reaction mixture stirred for 25 minutes, and then MeI (94 µL, 1.51 mmol, 1.1 equiv) was added. The reaction was allowed to stir overnight at room temperature. After completion, H_2O and Et_2O were added and the organic layer was extracted with Et_2O. The organic layer was then washed with brine solution and dried with $MgSO_4$. The mixture was filtered and the solvent was removed via rotary evaporation. The crude product was then purified by column chromatography with a 10–30% gradient of ethyl acetate in hexanes (168 mg, 0.856 mmol, 62% yield).

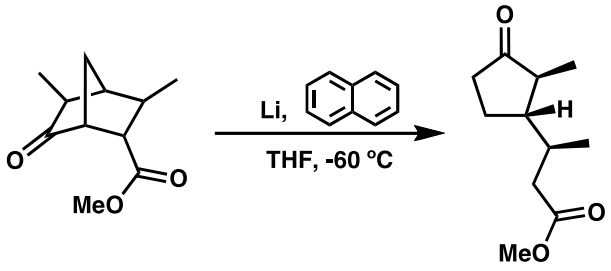


111 *112*

To a flask with **111** (55 mg, 0.302 mmol, 1.0 equiv) was added methanolic HCl (0.5M, 18 mL). The reaction was heated to 50 ºC and allowed to stir for 2 h. It was then quenched by adding aq. $NaHCO_3$ and the organic layer was extracted with Et_2O. The organic layer was then washed with brine solution and dried with $MgSO_4$. It was filtered

and the solvent was removed via rotary evaporation. The crude product was then purified via column chromatography with a 10-30% gradient of ethyl acetate in hexanes (32 mg, 0.163 mmol, 54% yield).

4.8.4.5 Synthesis of (*S*)-methyl 3-((1*S*,2*S*)-2-methyl-3-oxocyclopentyl)butanoate (113)

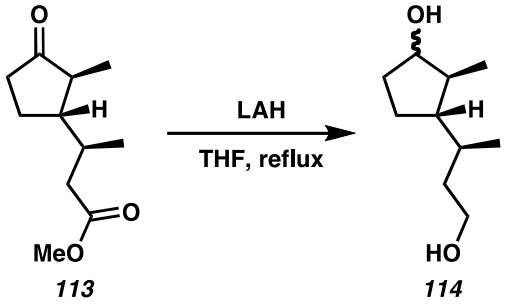


112 *113*

To a flame-dried flask was added naphthalene (2.25 g, 17.5 mmol, 3.0 equiv) and THF (30 mL). Lithium wire (118 mg, 17.0 mmol, 2.9 equiv) was rinsed with hexanes and added to the reaction. The mixture was then sonicated at room temperature for 2 h until all of the lithium was consumed. The reaction mixture was then cooled to -60 ºC and **112** (1.15 g, 5.86 mmol, 1.0 equiv) was added as a solution in THF (1.6 mL) via cannula. The reaction was allowed to stir at -60 ºC for 30 minutes before being quenched with 3M HCl at room temperature. The organic layer was extracted with EtOAc and washed 2x with brine solution. The organic layer was then dried with $MgSO_4$, filtered, and the solvent was removed via rotary evaporation. The crude mixture was then purified via column chromatography with a gradient of 5-30% ethyl acetate in hexanes (1.0 g, 5.04 mmol, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 (s, 3H), 2.45-2.33 (m, 2H), 2.26-2.19 (m, 1H), 2.16-2.08 (m, 2H), 2.05-1.97 (m, 1H), 1.86-1.79 (m, 1H), 1.74-1.66 (m, 1H), 1.50-1.41 (m, 1H), 1.10 (d, *J* = 6.87 Hz, 3H), 1.04 (d, *J* = 6.87 Hz, 3H) ppm. ^{13}C NMR

(125.77 MHz, $CDCl_3$): δ 220.8, 173.6, 51.7, 49.6, 47.1, 37.9, 37.3, 32.4, 23.7, 18.3, 14.2 ppm. IR (neat): 2966, 2887, 1736, 1434, 1300, 1170 cm^{-1}. R_F: 0.25 in 20% ethyl acetate in hexanes.

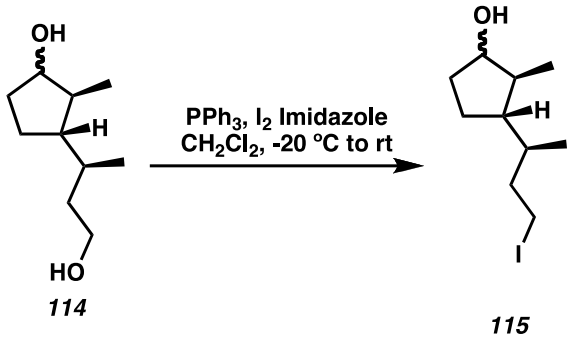
4.8.4.6 Synthesis of (2*S*,3*S*)-3-((*S*)-4-hydroxybutan-2-yl)-2-methylcyclopentanol (114)



113 *114*

To a flame-dried 3-neck flask fitted with a condenser on the middle arm was added **113** (1.03 g, 5.19 mmol, 1.0 equiv) and THF (26 mL). The reaction was then cooled to 0 ºC and LAH (354 mg, 9.34 mmol, 1.8 equiv) was added in 3 portions. The reaction was allowed to warm to room temperature while stirring, then heated to reflux for 1 h. Then 350 µL of H_2O, 350 µL of 15% NaOH, 1.2 mL of H_2O, 26 mL of Et_2O, and $MgSO_4$ were added in sequential order and the mixture was allowed to stir for 1 h at room temperature. The mixture was then filtered through a celite plug with EtOAc as the eluent and the solvent was removed via rotary evaporation (894 mg, 5.14 mmol, 99% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 3.75-3.67 (m, 2H), 3.65-3.60 (m, 1H), 1.86-1.80 (m, 1H), 1.74-1.58 (m, 3H), 1.55-1.45 (m, 2H), 1.36-1.27 (m, 3H), 1.01 (d, J = 6.87 Hz, 3H), 0.93 (d, J = 6.87, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 80.8, 61.6, 51.2, 45.5, 36.5, 33.5, 32.8, 25.8, 18.9, 18.3 ppm. IR (neat): 3346, 2952, 2876, 1459, 1375, 1053, 734 cm^{-1}. R_F: 0.08 in 40% ethyl acetate in hexanes.

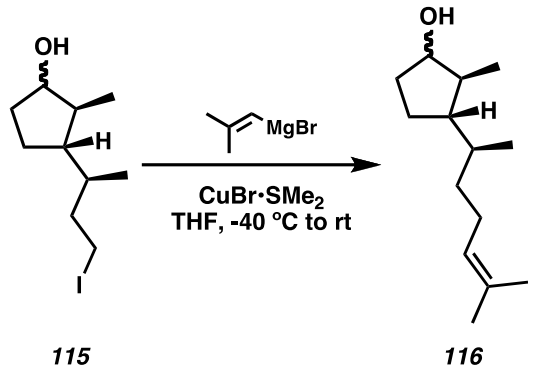
4.8.4.7 Synthesis of (2*S*,3*S*)-3-((*S*)-4-iodobutan-2-yl)-2-methylcyclopentanol (115)



114 *115*

To a flame-dried flask with **114** (894 mg, 5.19 mmol, 1.0 equiv) was added CH_2Cl_2 (105 mL), PPh_3 (1.49 g, 5.71 mmol, 1.1 equiv), and Imidazole (388 mg, 5.71 mmol, 1.1 equiv) and cooled to -20 ºC. I_2 (1.32 g, 5.19 mmol, 1.0 equiv) slowly added in multiple portions with rapid stirring, adding each portion after 30 minutes of stirring in between. After additions, reaction slowly warmed to room temperature. After completion the reaction was quenched with H_2O. The organic layer was extracted with Et_2O and dried with $MgSO_4$. The mixture was then filtered and the solvent was removed via rotary evaporation. The crude product was then purified via column chromatography using a gradient of 10-30% ethyl acetate in hexanes (882 mg, 3.15 mmol, 61% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (app. q., J = 5.15 Hz, 1H), 3.37-3.29 (m, 1H), 3.10 (app. q., J = 8.02 Hz, 1H), 2.02-1.95 (m, 1H), 1.87-1.78 (m, 1H), 1.69-1.43 (m, 7H), 1.38-1.28 (m, 1H), 1.01 (d, J = 6.87, 3H), 0.90 (d, J = 6.32 Hz, 3H). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 80.7, 50.6, 45.4, 37.6, 37.1, 33.5, 25.9, 18.9, 17.3, 5.9 IR (neat): 3346, 2954, 2871, 1457, 1377, 1242, 1180, 1071 cm^{-1}. R_F: 0.44 in 40% ethyl acetate in hexanes.

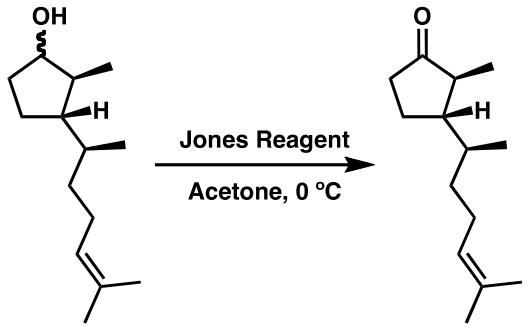
4.8.4.8 Synthesis of (2*S*,3*S*)-2-methyl-3-((*S*)-6-methylhept-5-en-2-yl)cyclopentanol (116)



115 *116*

To a flame-dried flask was added CuBr•SMe_2 (1.56 g, 7.58 mmol, 1.1 equiv) and cooled to -40 ºC. Grignard reagent (69 mL, 0.5M in THF, 34.4 mmol, 5.0 equiv) was then added dropwise. Next, a solution of **115** (1.93 g, 6.89 mmol, 1.0 equiv) in THF (18 mL) was added via cannula dropwise. The reaction mixture was then allowed to warm to room temperature slowly. It was then quenched with NH_4Cl and the organic layer was extracted with Et_2O. The organic layer was then dried with $MgSO_4$. It was then filtered and the solvent was removed via rotary evaporation. The crude product mixture was then purified via column chromatography using a gradient of 5–30% ethyl acetate in hexanes (1.18 g, 5.60 mmol, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10-5.07 (m, 1H), 3.70 (app. q, *J* = 5.73 Hz, 1H), 2.10-2.01 (m, 1H), 1.90-1.78 (m, 2H), 1.73-1.61 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.54-1.38 (m, 2H), 1.33-1.27 (m, 2H), 1.10-1.05 (m, 1H), 1.00 (d, *J* = 6.30 Hz, 3H), 0.90 (d, *J* = 6.87 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 131.3, 125.0, 81.0, 51.1, 45.5, 35.9, 33.6, 26.0, 25.8, 25.8, 18.9, 18.1, 17.7 ppm. IR (neat): 3335, 2960, 2929, 2875, 1461, 1376, 1073 cm^{-1}. R_F: 0.33 in 20% ethyl acetate in hexanes.

4.8.4.9 Synthesis of (2*S*,3*S*)-2-methyl-3-((*S*)-6-methylhept-5-en-2-yl)cyclopentanone (88)



116 *88*

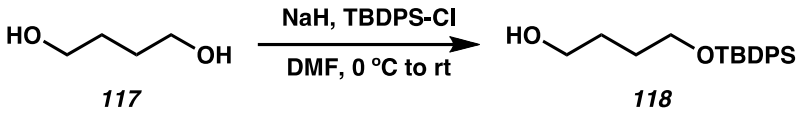
To a vial with CrO_3 (2.0 g, 20.02 mmol, 1.0 equiv) was added H_2O (5.8 mL) and the solution turned orange. The mixture was then cooled to 0 ºC and H_2SO_4 (1.7 mL) was then added resulting in a 2.67M solution of Jones reagent.

To a flask with **116** (894 mg, 4.25 mmol, 1.0 equiv) was added acetone (45 mL) and cooled to 0 ºC. Jones reagent was added dropwise until the reaction mixture turned and sustained an orange color and reaction completion was visualized by TLC. After completion, 19 mL H_2O was added along with 54 mL of Et_2O. The organic layer was extracted with Et_2O and washed with brine solution. The organic layer was then dried with $MgSO_4$, filtered, and the solvent was removed via rotary evaporation. The crude reaction mixture was then run through a silica plug using 30% ethyl acetate in hexanes (781 mg, 3.75 mmol, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 (m, 1H), 2.30 (dd, *J* = 18.43, 8.53 Hz, 1H), 2.10 (m, 2H), 2.0-1.8 (m, 3H), 1.7-1.6 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.6-1.4 (m, 2H), 1.15 (m, 1H), 1.08 (d, *J* = 6.83 Hz, 3H), 1.00 (d, *J* = 6.49 Hz, 3H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 222.0, 131.8, 124.6, 50.3, 47.0, 37.4,

34.2, 32.5, 26.0, 25.8, 23.3, 17.7, 14.0 ppm. IR (neat): 2967, 2933, 2873, 1742, 1459, 1384, 1159 cm^{-1}. R_F: 0.54 in 20% ethyl acetate in hexanes.

4.8.5 Experimentals for Enone Synthesis

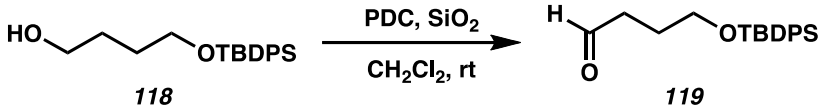
4.7.5.1 Synthesis of 4-(*tert*-butyldiphenylsilyloxy)butan-1-ol (118)



117 *118*

To a flask with NaH (60% in mineral oil, 4.44 g, 108.45 mmol, 1.25 equiv) was added DMF (148 mL) and the mixture was cooled to 0 ºC. Diol **117** (10mL, 112.85 mmol, 1.3 equiv) was added dropwise and the reaction was allowed to stir at 0 ºC for 15 minutes. It then slowly warmed to room temperature and stirred for 16 h. The reaction was then cooled back down to 0 ºC and TBDPS-Cl (22 mL, 86.8 mmol, 1.0 equiv) was added dropwise. The mixture then stirred at room temperature for 4 h. After completion H_2O and Et_2O were added and the organic layer was then extracted with Et_2O. The organic layer was washed with 1:1 brine solution to H_2O, and dried with $MgSO_4$. The mixture was then filtered and the solvent was removed via rotary evaporation (27.34 g, 83.31 mmol, 94% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (m, 4H), 7.40 (m, 6H), 3.67 (m, 4H), 1.65 (m, 5H), 1.06 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 135.7, 134.9, 129.7, 127.8, 64.1, 62.9, 30.0, 29.4, 26.9, 19.2 ppm. IR (neat): 3359, 3071, 2857, 1667, 1472, 1427, 1389, 1111 cm^{-1}. R_F: 0.50 in 40% ethyl acetate in hexanes.

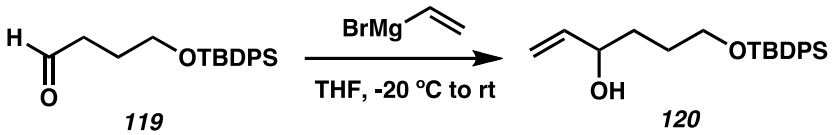
4.8.5.2 Synthesis of 4-(*tert*-butyldiphenylsilyloxy)butanal (119)



118 *119*

To a flask with **118** (5.0 g, 15.23 mmol, 1.0 equiv) was added CH_2Cl_2 (156 mL) and SiO_2 (24.40 g). PDC (11.5 g, 30.5 mmol, 2.0 equiv) was then added and the mixture was allowed to stir overnight at room temperature. After completion, the solvent was removed via rotary evaporation. The mixture was then passed through a silica plug using 20% ethyl acetate in hexanes (4.28 g, 13.12 mmol, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.67-7.63 (m, 4H), 7.44-7.36 (m, 6H), 3.74-3.64 (m, 2H), 2.62-2.50 (m, 2H), 1.93-1.84 (m, 2H), 1.04 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 202.7, 135.6, 133.6, 129.8, 127.8, 63.0, 40.9, 26.9, 25.3, 19.3 ppm. IR (neat): 2957, 2931, 2858, 1709, 1428, 1110, 701 cm^{-1}. R_F: 0.73 in 40% ethyl acetate in hexanes.

4.8.5.3 Synthesis of 6-(*tert*-butyldiphenylsilyloxy)hex-1-en-3-ol (120)



119 *120*

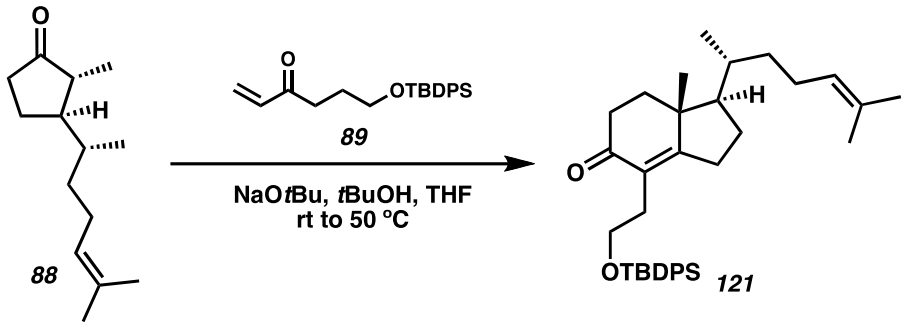
To a flame-dried flask with **119** (2.84 g, 8.71 mmol, 1.0 equiv) was added THF (43 mL) and the mixture was cooled to -20ºC. Grignard reagent (1.0M in THF, 10.5 mL, 10.5 mmol, 1.2 equiv) was then added dropwise and the reaction was allowed to slowly warm to room temperature. After completion, it was quenched with aq. NH_4Cl and Et_2O. The organic layer was extracted with Et_2O and then washed with brine solution. The organic layer was then dried with $MgSO_4$ and filtered. The solvent was then removed via

rotary evaporation. The crude mixture was then purified via column chromatography using a gradient of 5-15% ethyl acetate in hexanes (2.05 g, 5.78 mmol, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.39 (m, 6H), 5.87 (m, 1H), 5.23 (app d, J = 17.18 Hz, 1H), 5.10 (app d, J = 10.31 Hz, 1H), 4.31 (bs, 1H), 3.68 (t, J = 5.73 Hz, 2H), 2.18 (d, J = 4.58 Hz, 1H), 1.66 (m, 4H), 1.04 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 141.2, 135.7, 133.7, 129.7, 127.7, 114.6, 72.9, 64.1, 34.0, 28.5, 26.9, 19.3 ppm. IR (neat): 3377, 2931, 2858, 1472, 1427, 1389, 1110 cm^{-1}. R_F: 0.32 in 20% ethyl acetate in hexanes.

4.8.5.4 Synthesis of 6-(*tert*-butyldiphenylsilyloxy)hex-1-en-3-one (89)

To a flame-dried flask with **120** (2.05 g, 5.78 mmol, 1.0 equiv) was added CH_2Cl_2 (60 mL) and celite (8.6 g). PDC (4.3 g, 11.56 mmol, 2.0 equiv) was then added and the reaction was allowed to stir overnight at room temperature. After completion, the solvent was reduced in vacuo and the mixture was then run through a silica plug with 20% ethyl acetate in hexanes as the eluent. The solvent was then removed via rotary evaporation (1.55 g, 4.40 mmol, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, J = 8.02, 1.72 Hz, 4H), 7.39 (m, 6H), 6.34 (dd, J = 17.76, 10.31 Hz, 1H), 6.21 (dd, J = 17.76, 1.15 Hz, 1H), 5.82 (dd, J = 10.88, 1.15 Hz, 1Hz), 3.69 (app. t, J = 6.30 Hz, 2H), 2.71 (t, J = 7.45 Hz, 2H), 1.87 (m, 2H), 1.04 (s, 9H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 200.9, 136.7, 135.6, 134.9, 133.9, 129.7, 128.1, 127.7, 63.1, 36.0, 26.9, 19.3 ppm. IR (neat): 2931, 2857, 1682, 1428, 1110, 701 cm^{-1}. R_F: 0.50 in 20% ethyl acetate in hexanes.

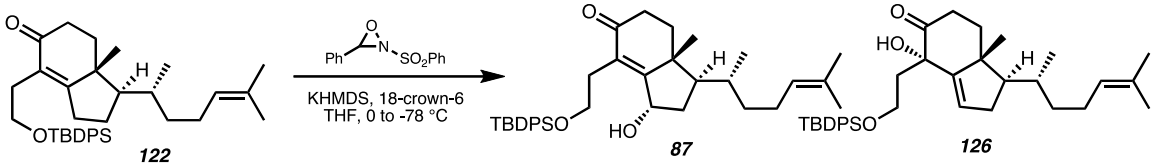
4.8.6 Synthesis of (1*R*,7a*R*)-4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-7a-methyl-1-((*R*)-6-methylhept-5-en-2-yl)-2,3,7,7a-tetrahydro-1*H*-inden-5(6*H*)-one (121)



To a flame-dried flask with **88** (40 mg, 0.192 mmol, 1.0 equiv) was added *t*BuOH (4 mL, that was dried and stored over $MgSO_4$) and NaO*t*Bu (18.5 mg, 0.192 mmol, 1.0 equiv). H_2O (35 μL, 1.94 mmol, 10 equiv) was then added and the mixture was allowed to stir at room temperature for 10 min. **89** (135 mg, 0.383 mmol, 2.0 equiv) was then added over 4.5 h using a syringe pump as a solution in THF (286 μL) and *t*BuOH (286 μL) that was dried and stored over $MgSO_4$. After addition, it was then allowed to stir overnight at room temperature then heated to 50 ºC for 5 h. After completion it was quenched with NH_4Cl and the organic layer was extracted with Et_2O. The organic layer was washed with brine solution, and then dried with $MgSO_4$. It was then filtered and the solvent was removed via rotary evaporation. The crude reaction mixture was then purified via column chromatography with a gradient of 1-10% of ethyl acetate in hexanes (77 mg, 0.142 mmol, 74% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67-7.60 (m, 4H), 7.42-7.31 (m, 6H), 5.10-5.07 (m, 1H), 3.69-3.57 (m, 2H), 2.58-2.44 (m, 6H), 2.33 (dd, *J* = 17.76, 1.72 Hz, 1H), 2.20 (dd, *J* = 13.17, 1.72 Hz, 1H), 2.05-2.00 (m, 1H), 1.96-1.86 (m, 1H), 1.83-1.76 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.57-1.35 (m, 1H), 1.20-1.19 (m,

1H), 1.07-0.91 (m, 18 H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 198.2, 175.9, 135.7, 134.0, 131.4, 129.6, 128.1, 127.7, 124.8, 62.7, 56.2, 45.4, 36.7, 35.7, 33.9, 29.5, 28.1, 27.2, 26.9, 25.8, 24.6, 19.2, 18.9, 17.8, 16.7, 10.1 ppm. IR (neat): 2959, 2930, 2857, 1739, 1660, 1643, 1471, 1427, 1111, 701 cm^{-1}. R_F: 0.26 in 10% ethyl acetate in hexanes.

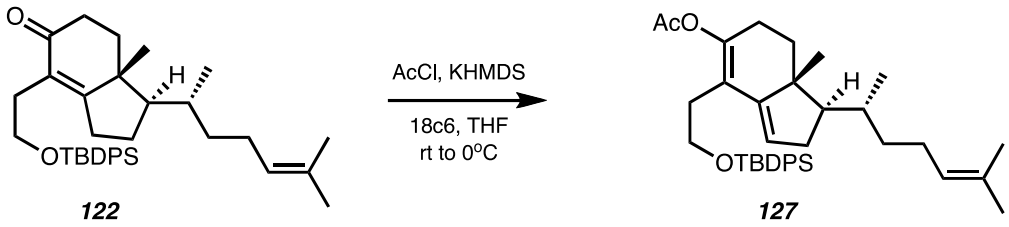
4.8.7 Synthesis of (1*R*,3*S*,7a*R*)-4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-3-hydroxy-7a-methyl-1-((*R*)-6-methylhept-5-en-2-yl)-2,3,7,7a-tetrahydro-1*H*-inden-5(6*H*)-one (87) and (126)



To a flame-dried flask with **122** (77 mg, 0.142 mmol, 1.0 equiv) was added THF (13.9 mL) and 18-crown-6 (48.7 mg, 0.185 mmol, 1.3 equiv) and the mixture was cooled to 0 ºC. ½ KHMDS (254 µL, 0.5M in toluene, 0.127 mmol, 0.9 equiv) was added dropwise of 2 minutes and then allowed stir for 5 minutes. Then the other ½ of the KHMDS (254 µL, 0.5M in toluene, 0.127 mmol, 0.9 equiv) was added dropwise over 2 minutes and the reaction mixture stirred at 0 ºC for 10 minutes, then at -78 ºC for 10 minutes. Davis oxaziridine (55.7 mg, 0.252 mmol, 1.8 equiv) was then added quickly dropwise as a solution in THF (473 µL). The mixture was then stirred at -78 ºC for 1 h. Me_2S (77 µL) was then added at -78 ºC then the mixture was warmed up to room temperature. It was quenched with aq. NH_4Cl and aq. $Na_2S_2O_3$ and stirred for 10 minutes at room temperature. The organic layer was then extracted with Et_2O and dried with $MgSO_4$. The solvent was then removed via rotary evaporation and the crude mixture was

purified via column chromatography with a gradient of 2.5-15% ethyl acetate in hexanes (26 mg, 4.67 mmol, 33% yield) and (18 mg, 3.22 mmol, 23% yield).

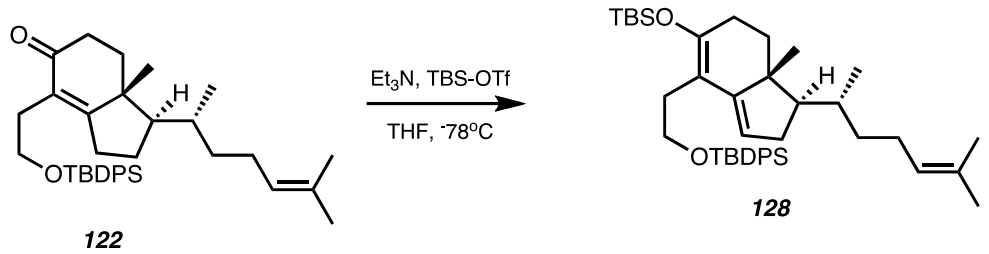
4.8.8 Synthesis of (1*R*,7a*R*)-4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-7a-methyl-1-((*R*)-6-methylhept-5-en-2-yl)-2,6,7,7a-tetrahydro-1*H*-inden-5-yl acetate (127)



122 ***127***

To a flame-dried flask with **122** (30 mg, 0.055 mmol, 1.0 equiv) was added THF (2.3 mL) and 18c6 (30 mg, 0.11 mmol, 2.0 equiv).The mixture was then cooled to 0 ºC and ½ of the KHMDS (110 µL, 0.5M in toluene, 0.055 mmol, 1.0 equiv) was added dropwise and the reaction was allowed to stir for 5 minutes. The other ½ of KHMDS (110 µL, 0.5M in toluene, 0.055 mmol, 1.0 equiv) was then added and the mixture was allowed to stir for 10 minutes. AcCl (10 µL, 0.14 mmol, 2.5 equiv). After completion, Et_2O and aq. NH_4Cl were added and the layers were separated. The organic layer was then washed with brine solution 1x and the solvent was then removed via rotary evaporation. The crude mixture was then purified via column chromatography with a gradient of 5-20% ethyl acetate in hexanes (29 mg, 0.049 mmol, 90% yield). R_F: 0.44 in 10% ethyl acetate in hexanes.

4.8.9 Synthesis of *tert*-butyl(2-((1*R*,7a*R*)-5-(*tert*-butyldimethylsilyloxy)-7a-methyl-1-((*R*)-6-methylhept-5-en-2-yl)-2,6,7,7a-tetrahydro-1*H*-inden-4-yl)ethoxy)diphenylsilane (128)



122 *128*

To a flame-dried flask with **122** (30 mg, 0.055 mmol, 1.0 equiv) was added THF (1.2 mL). The solution was then cooled to -78 ºC and Et_2NH (23 μL, 0.22 mmol, 4.0 equiv) was then added. TBS-OTf (25 μL, 0.11 mmol, 2.0 equiv) was then added dropwise and the reaction mixture was allowed to stir rapidly. After completion, the mixture warmed to room temperature and aq. $NaHCO_3$ was added followed by hexanes. The organic layer was washed with aq. $NaHCO_3$ 2x and brine solution 1x. The organic layer was then dried with Na_2SO_4 and the solvent was the removed via rotary evaporation (32 mg, 0.049 mmol, 90% yield). R_F: 0.58 in 5% ethyl acetate in hexanes.

4.9 Notes and References

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APPENDIX TWO

Spectra Relevant to Chapter 4:

Synthetic Developments Toward Aplykurodinone 1

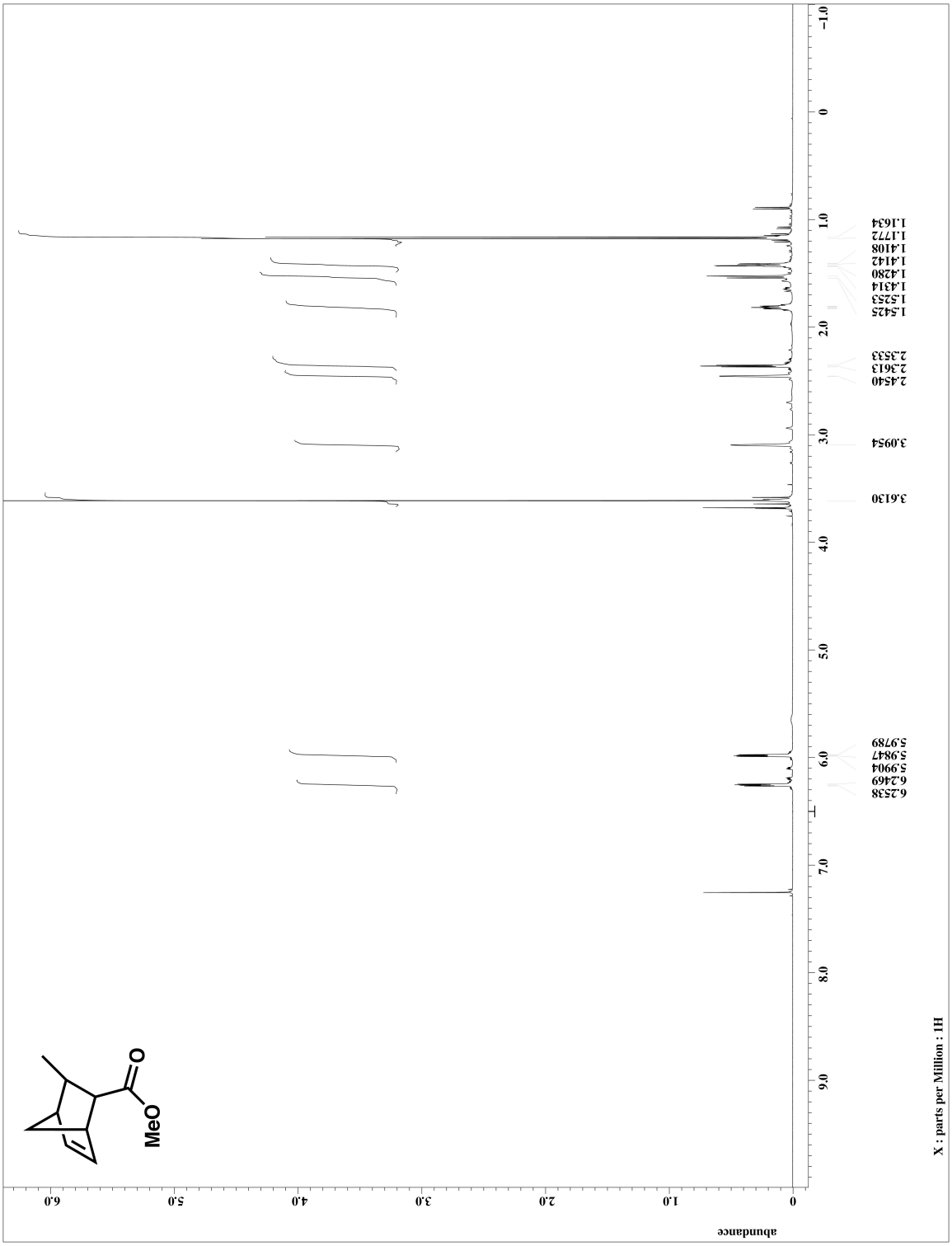


Figure A.2.1 ^{1}H NMR for compound **108**

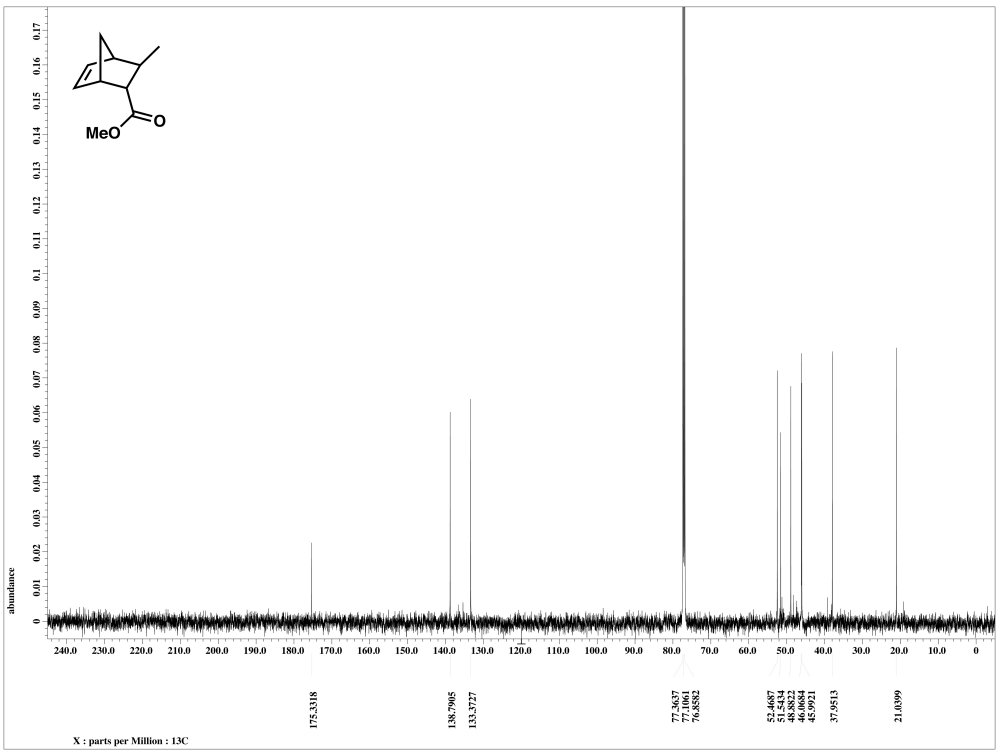


Figure A.2.2 ^{13}C NMR for compound **108**

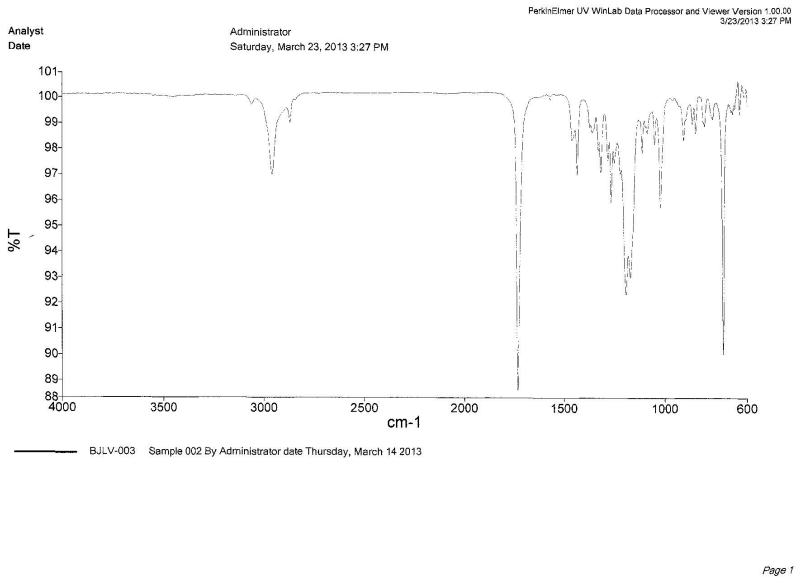


Figure A.2.3 IR spectra for compound **108**

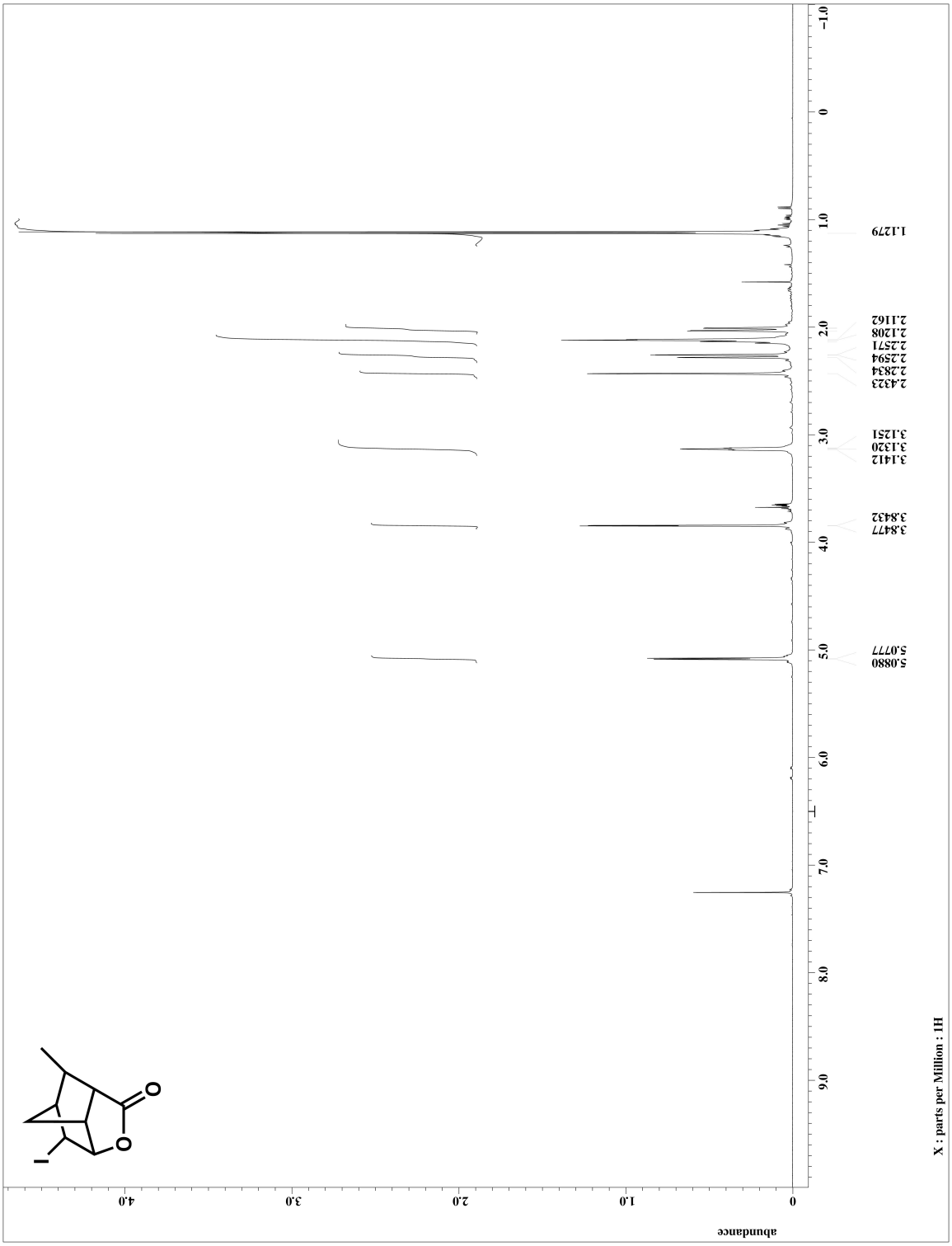


Figure A.2.4 ^{1}H NMR for compound **109**

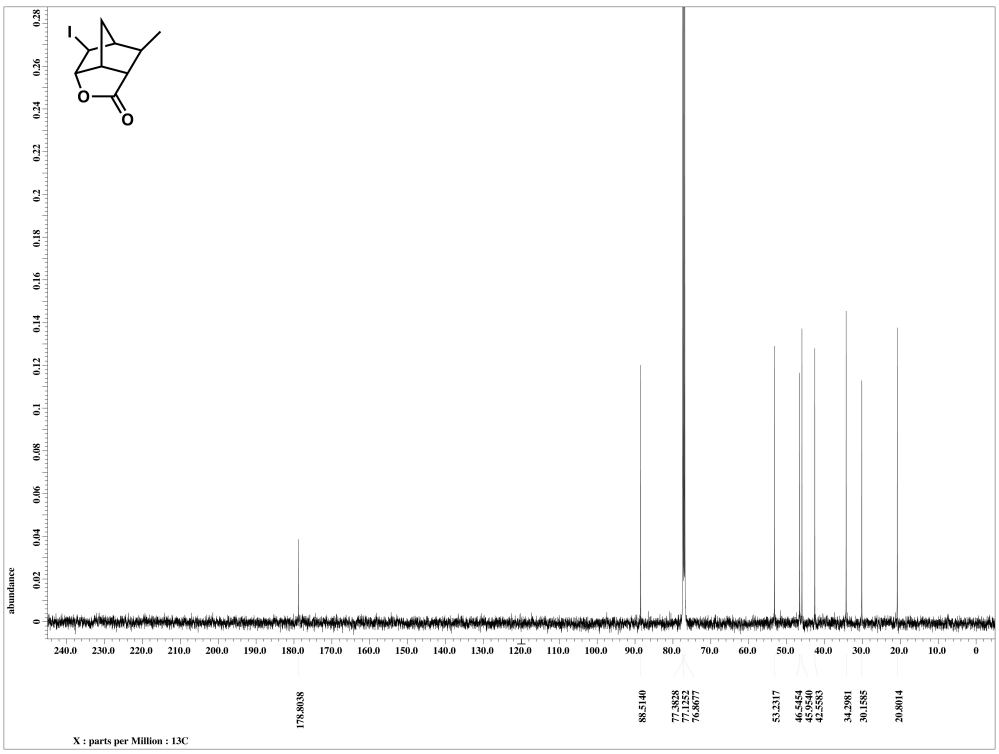


Figure A.2.5 ^{13}C NMR for compound **109**

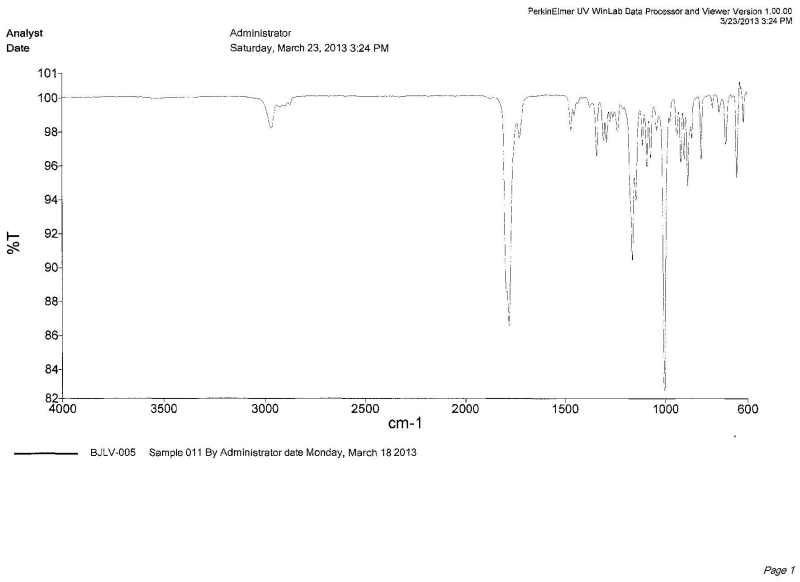


Figure A.2.6 IR spectra for compound **109**

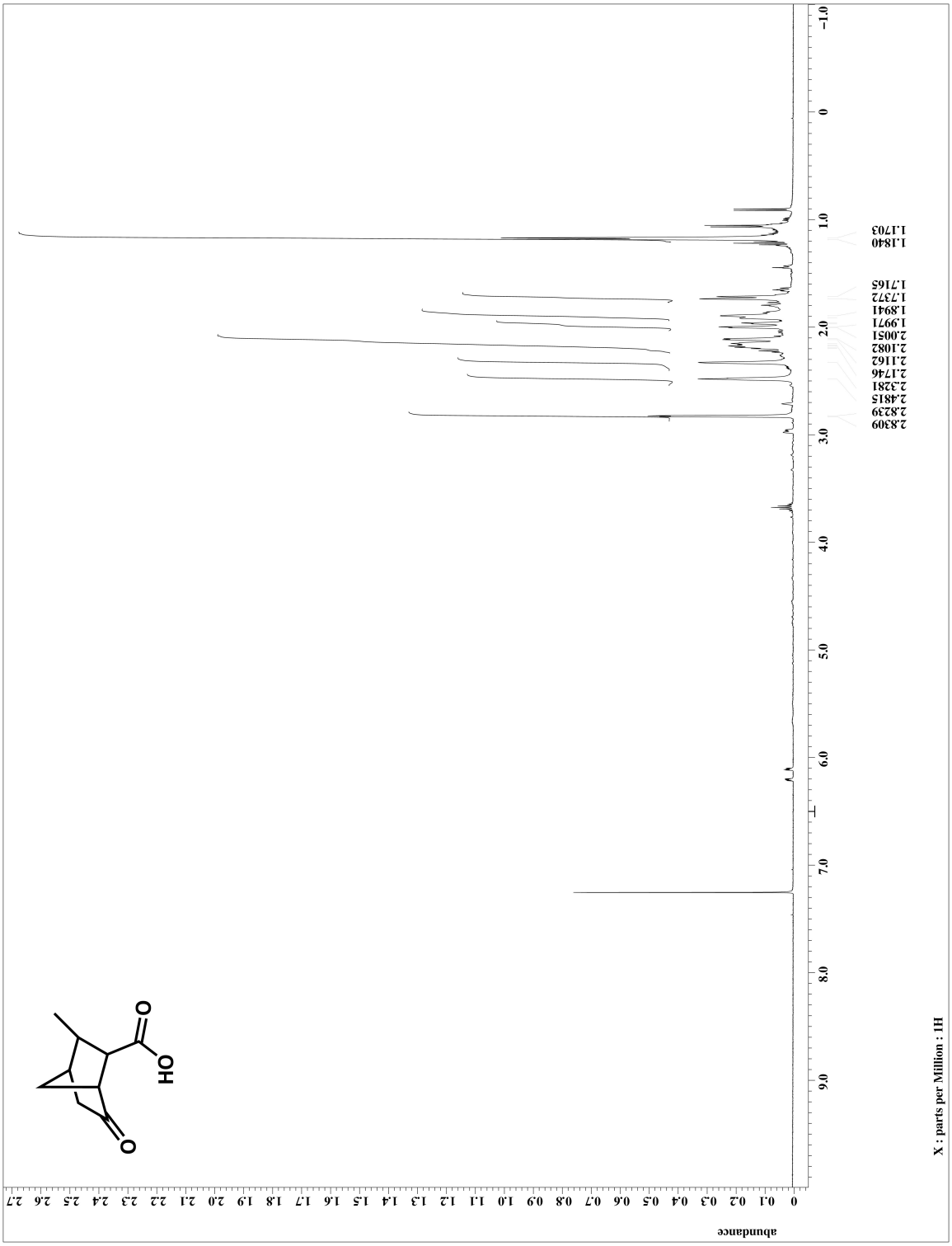


Figure A.2.7 ^{1}H NMR for compound **110**

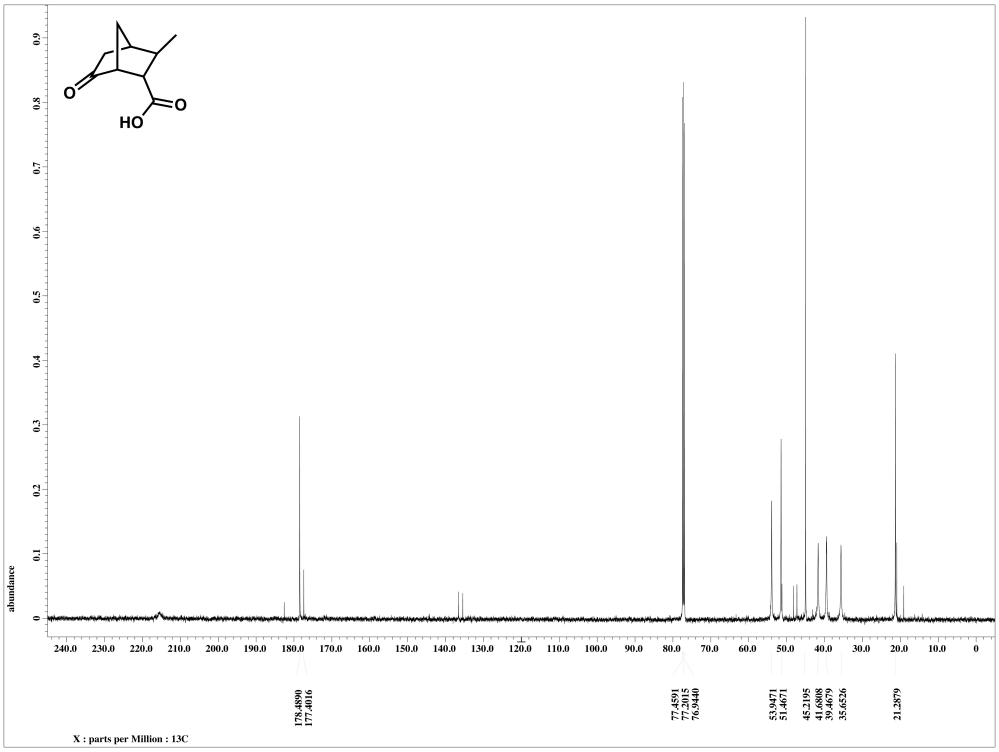


Figure A.2.8 ^{13}C NMR for compound **110**

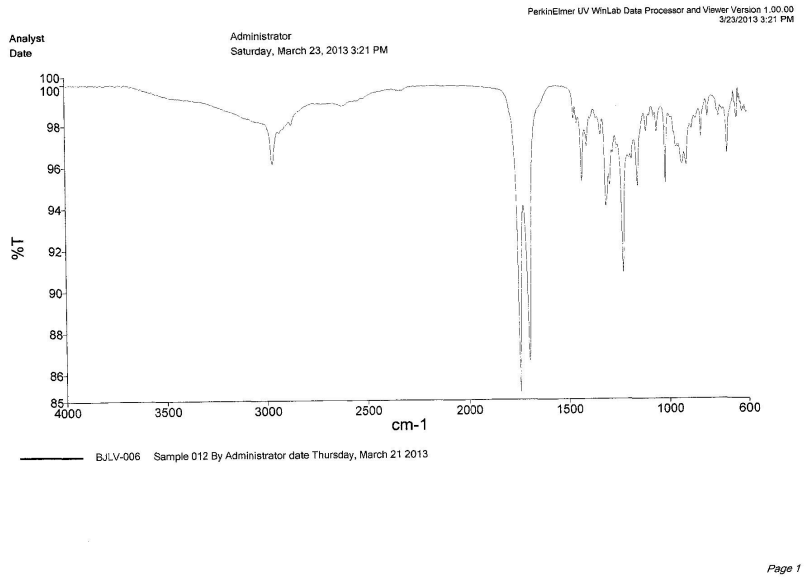


Figure A.2.9 IR spectra for compound **110**

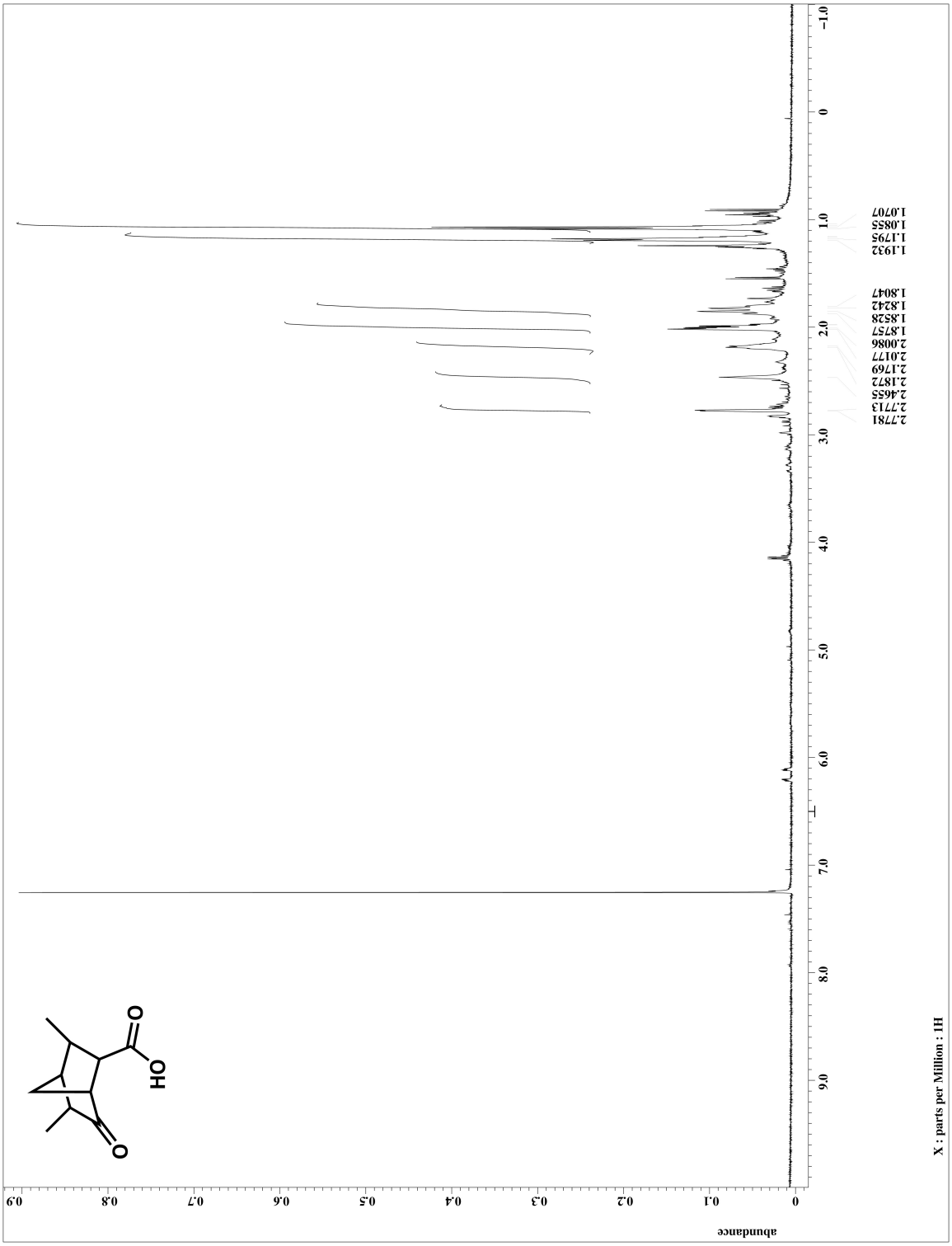


Figure A.2.10 ^{1}H NMR for compound **111**

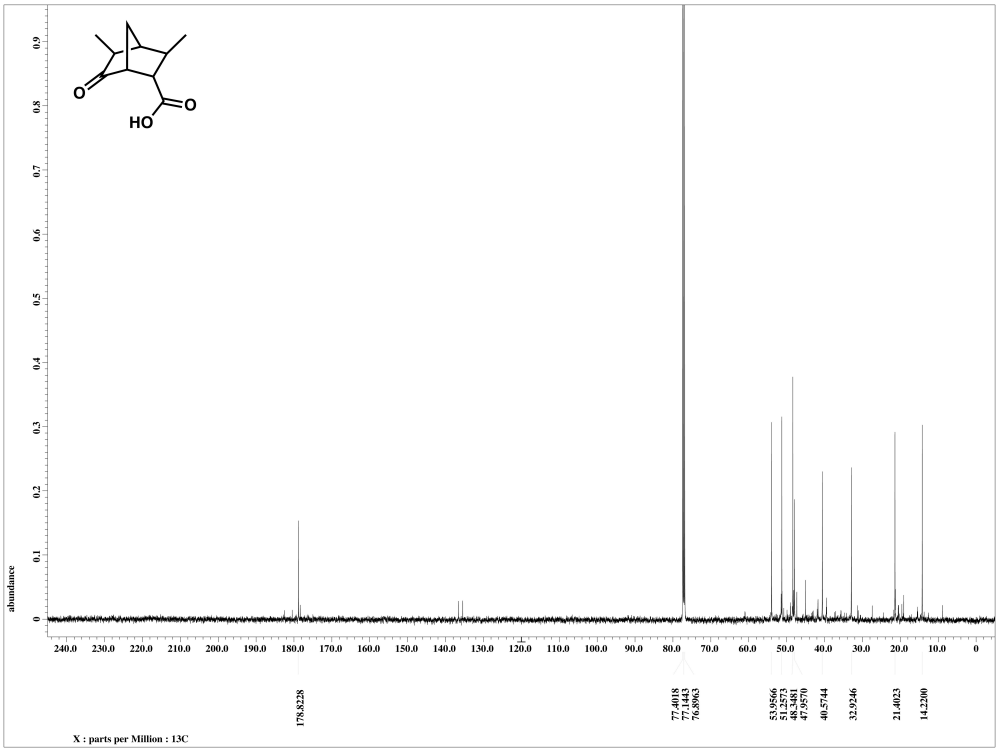


Figure A.2.11 ^{13}C NMR for compound **111**

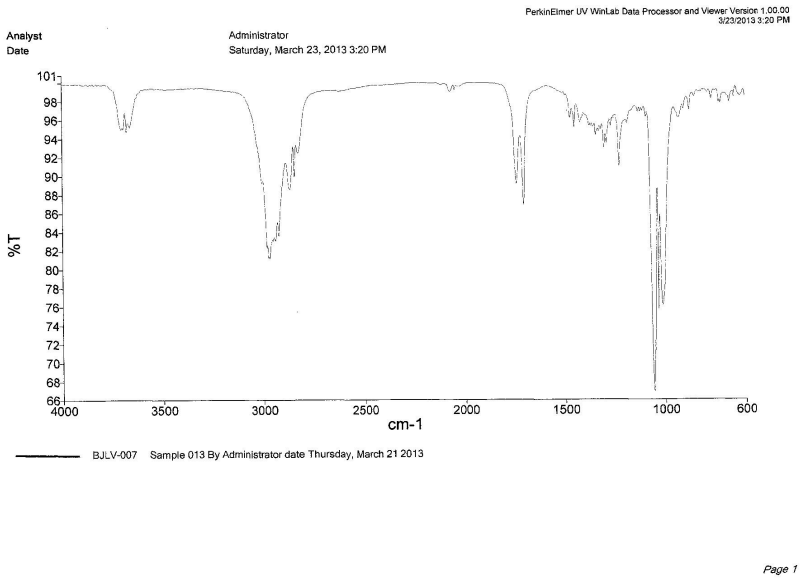


Figure A.2.12 IR spectra for compound **111**

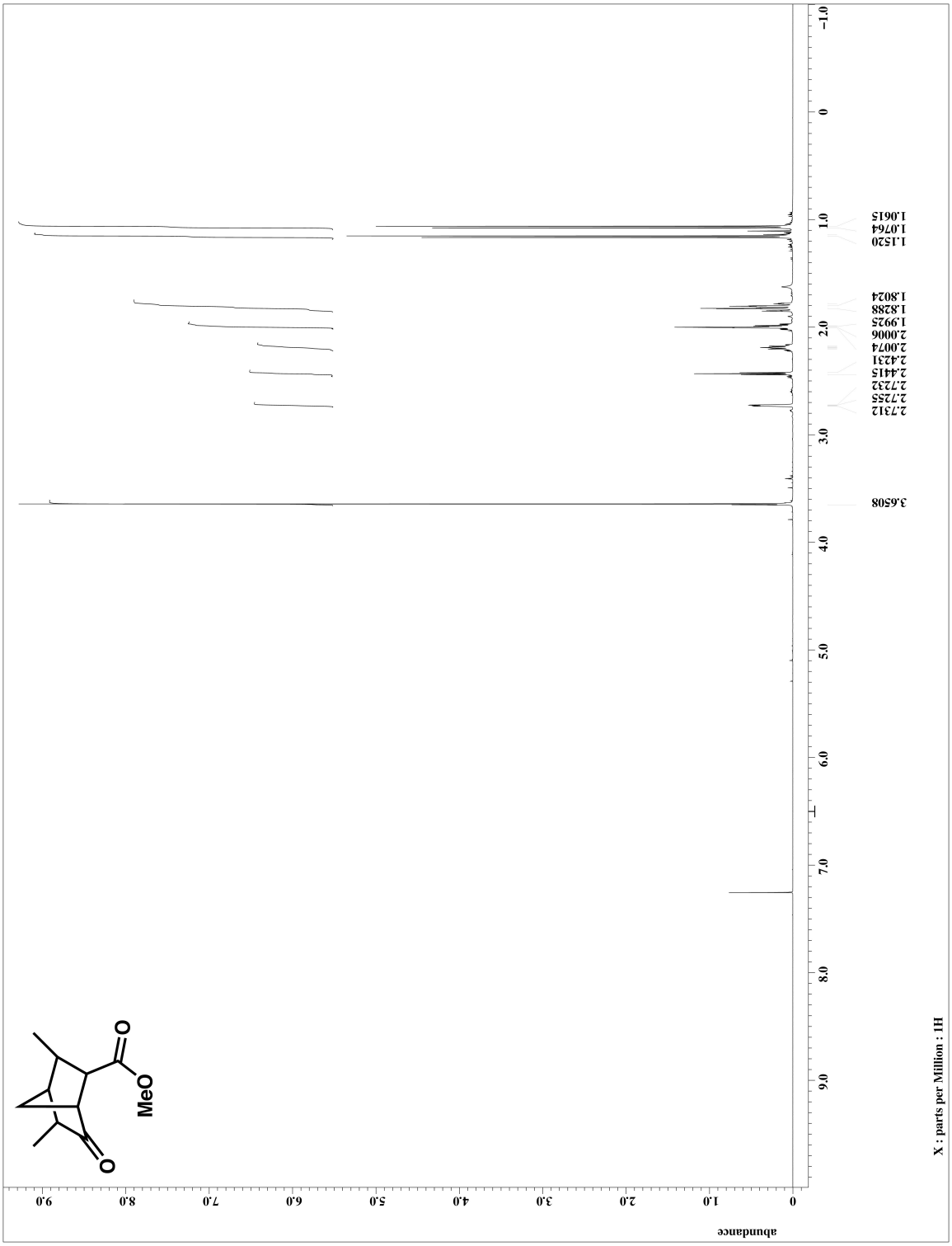


Figure A.2.13 ^{1}H NMR for compound **112**

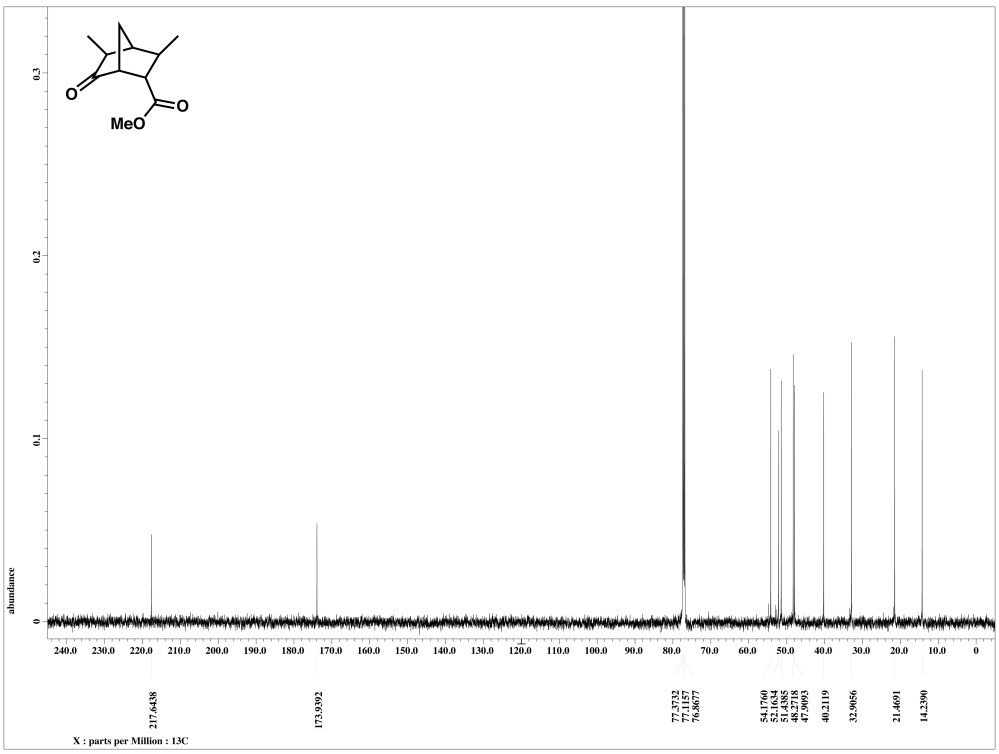


Figure A.2.14 ^{13}C NMR for compound **112**

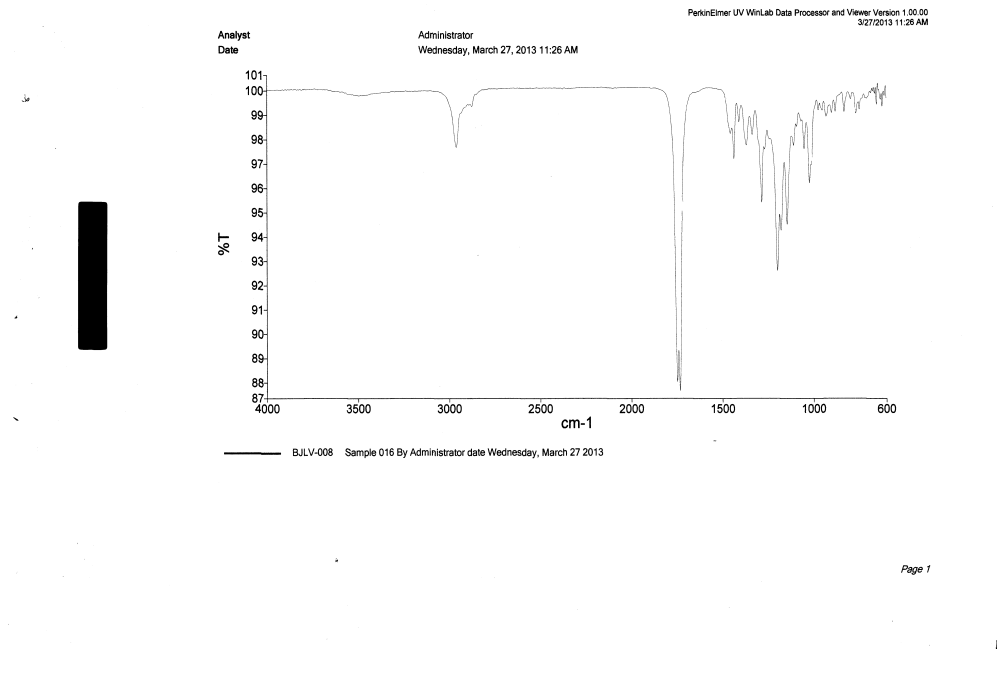


Figure A.2.15 IR spectra for compound **112**

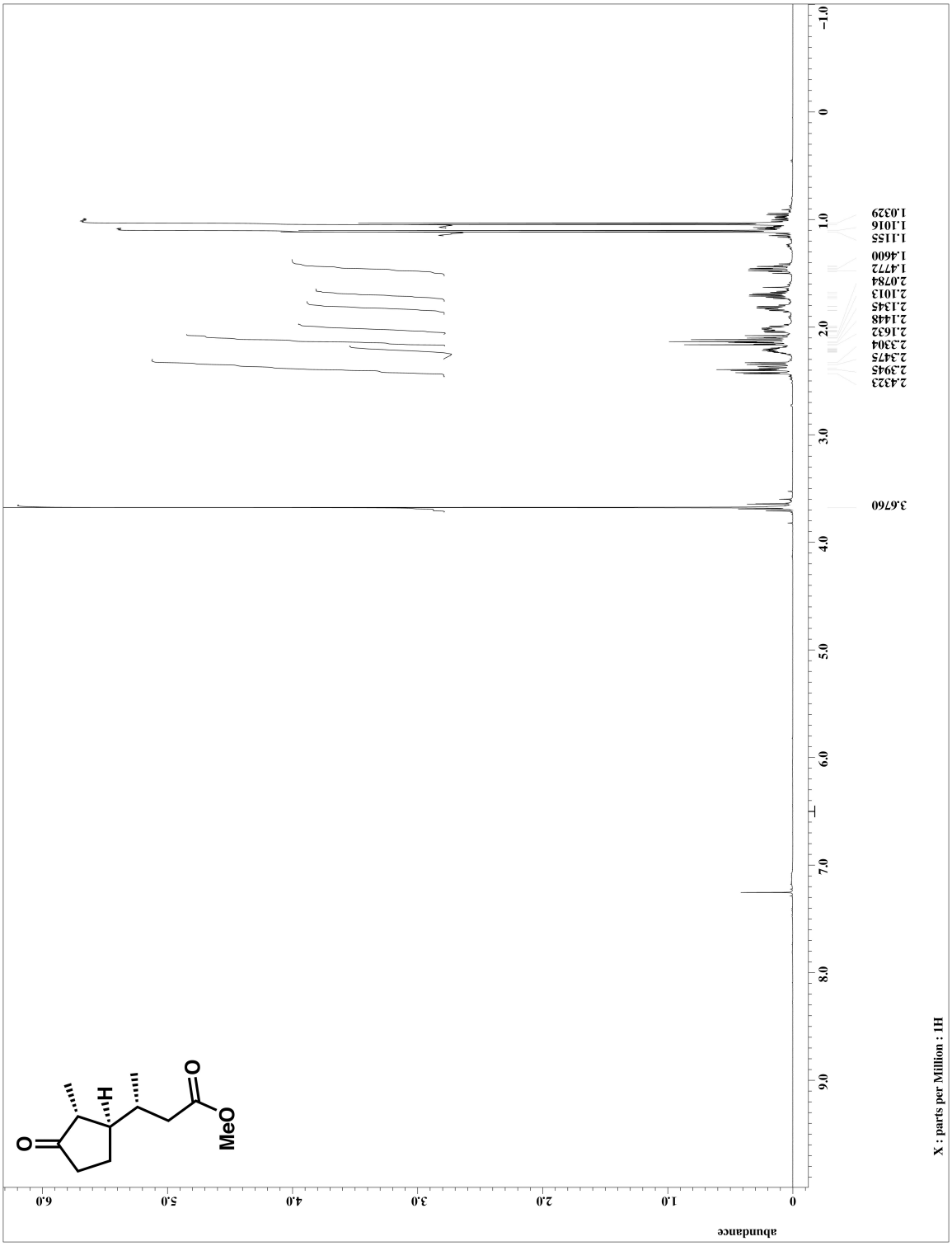


Figure A.2.16 ^{1}H NMR for compound **113**

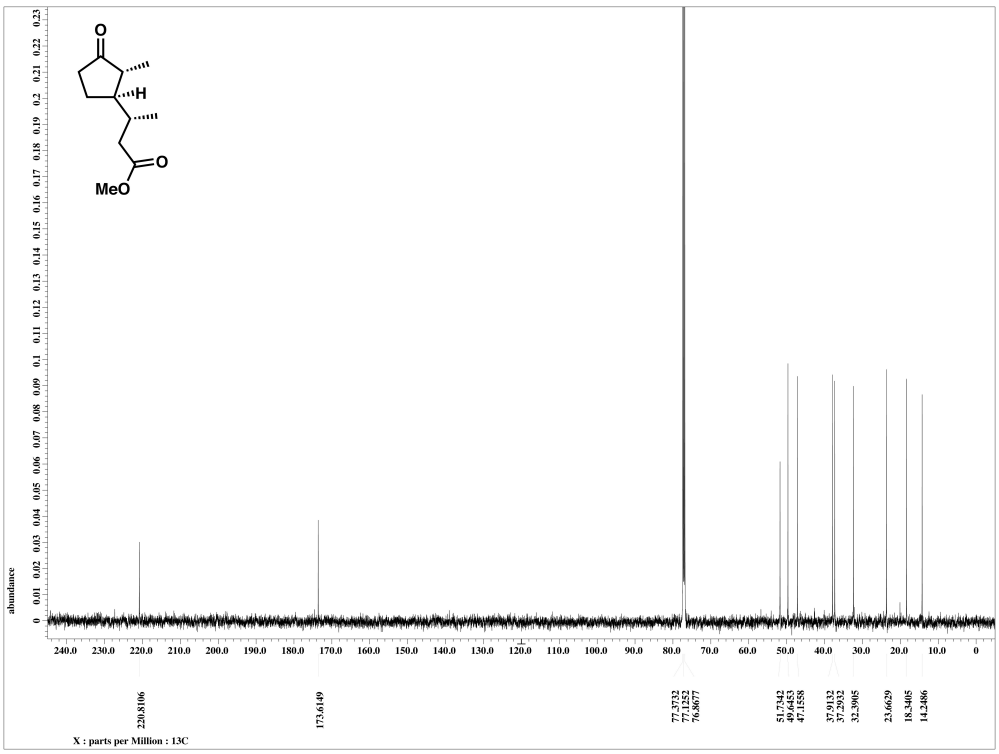


Figure A.2.17 ^{13}C NMR for compound **113**

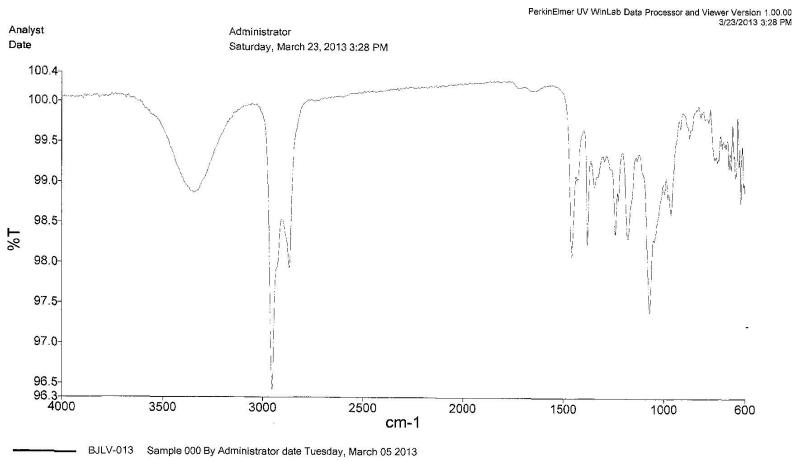
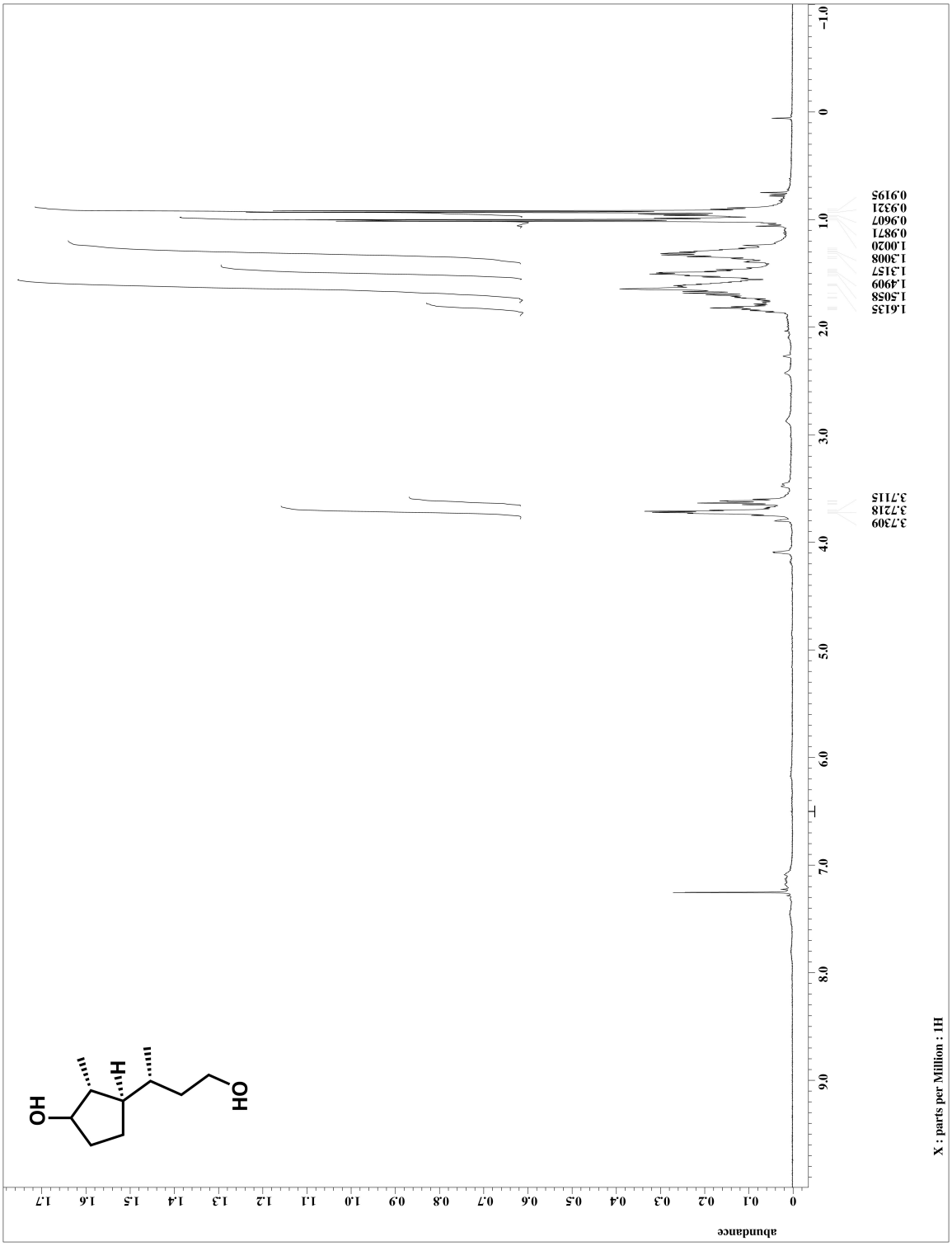


Figure A.2.18 IR spectra for compound **113**



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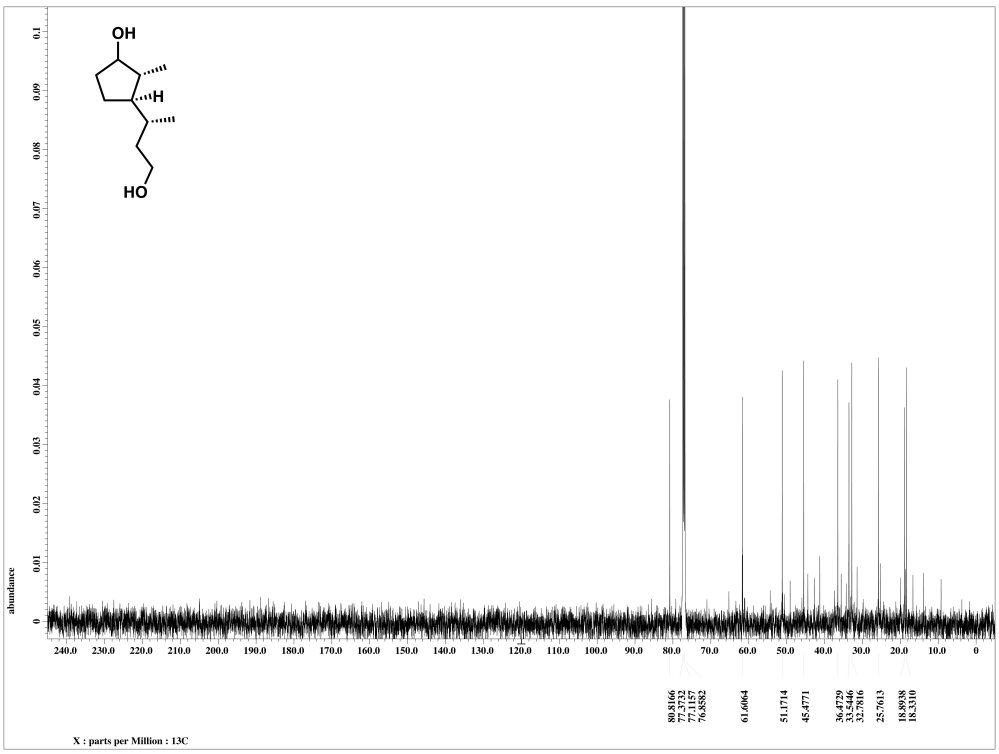


Figure A.2.20 ^{13}C NMR for compound **114**

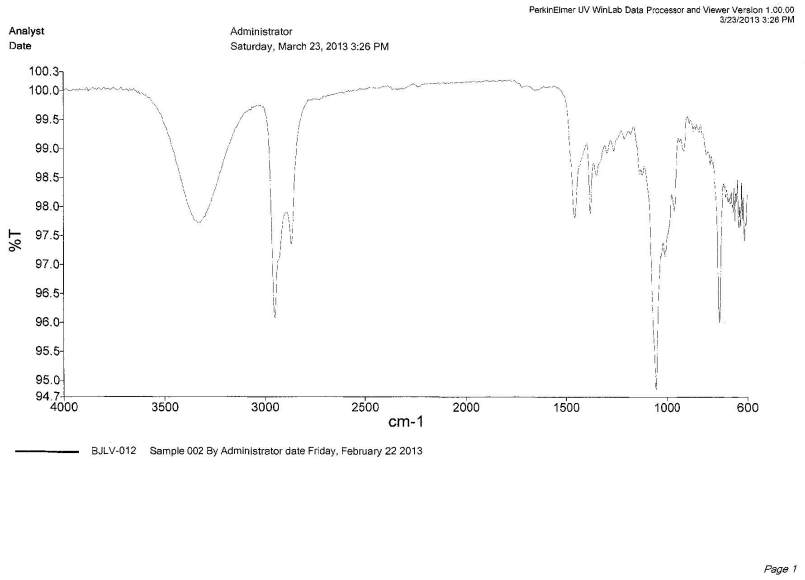


Figure A.2.21 IR spectra for compound **114**

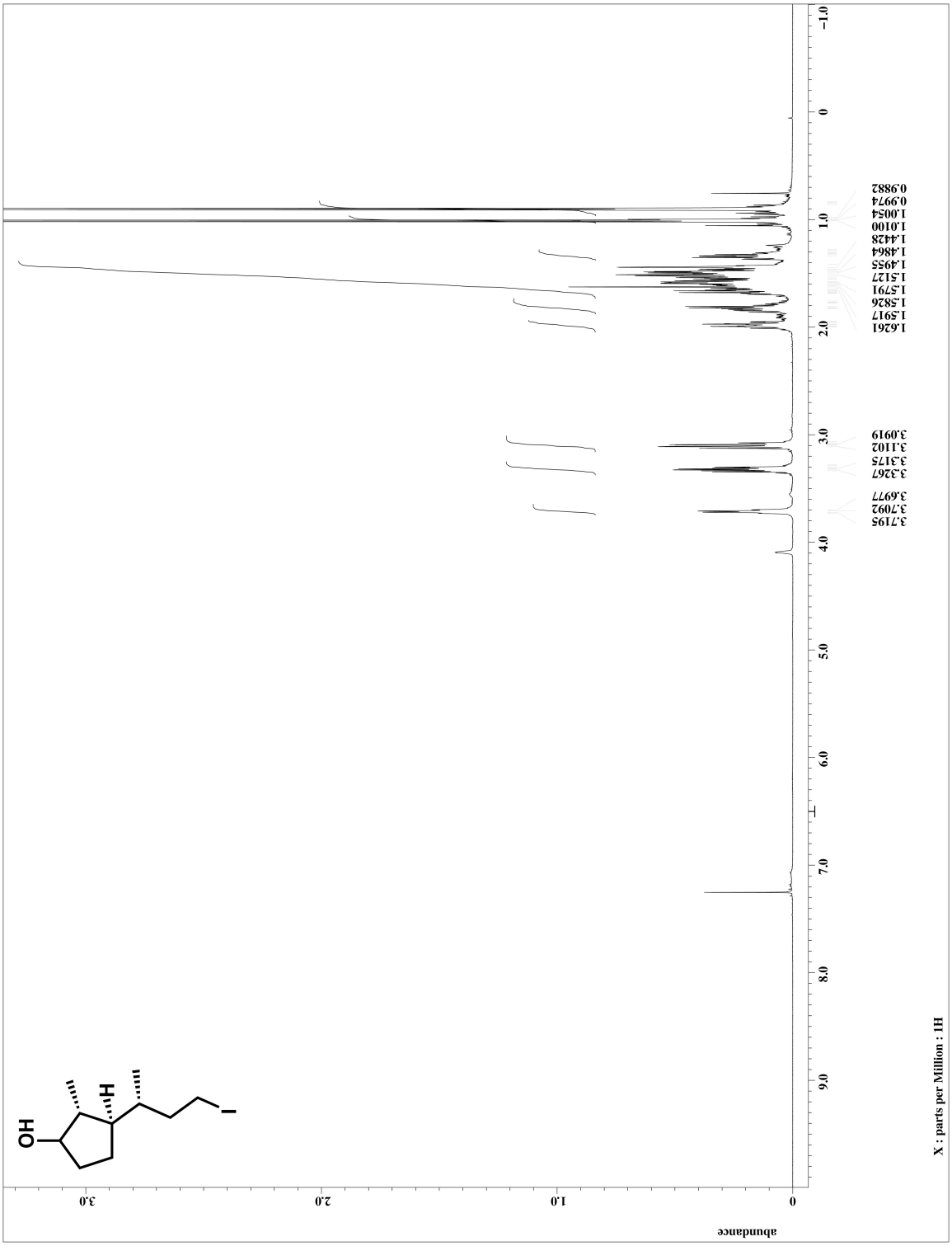


Figure A.2.22 ^{1}H NMR for compound **115**

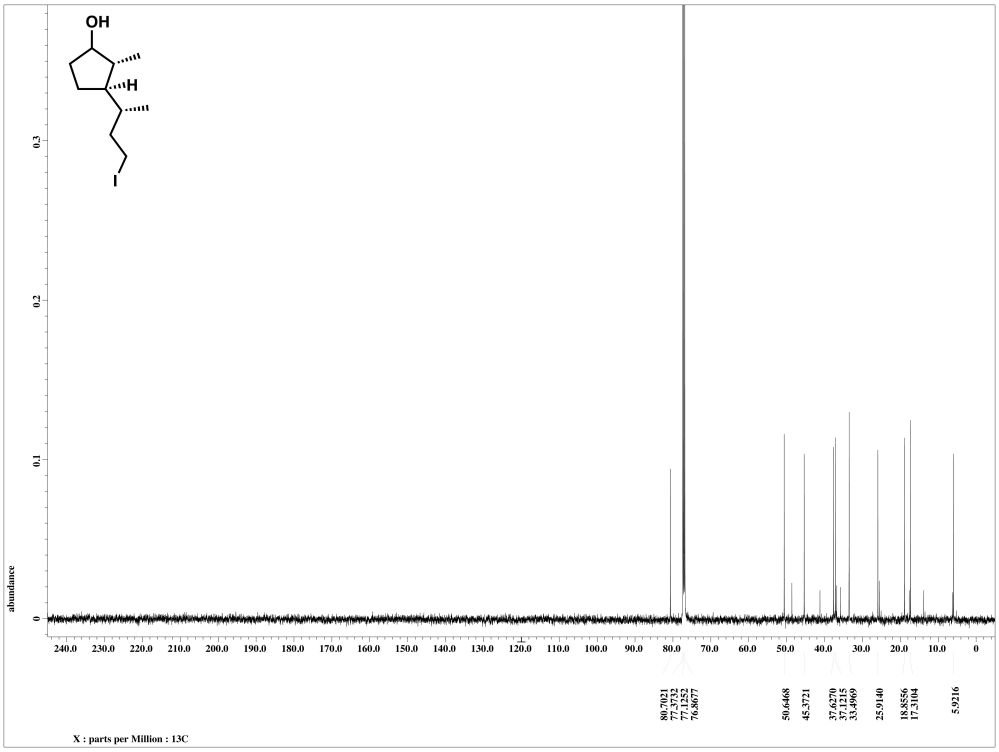


Figure A.2.23 ^{13}C NMR for compound **115**

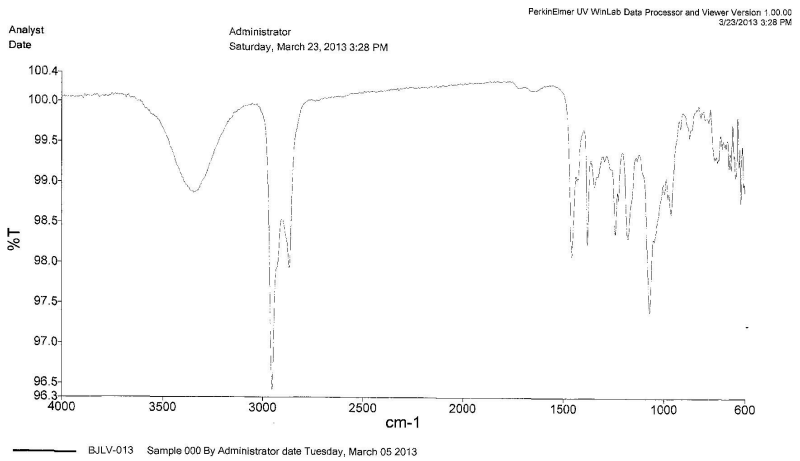


Figure A.2.23 IR spectra for compound **115**

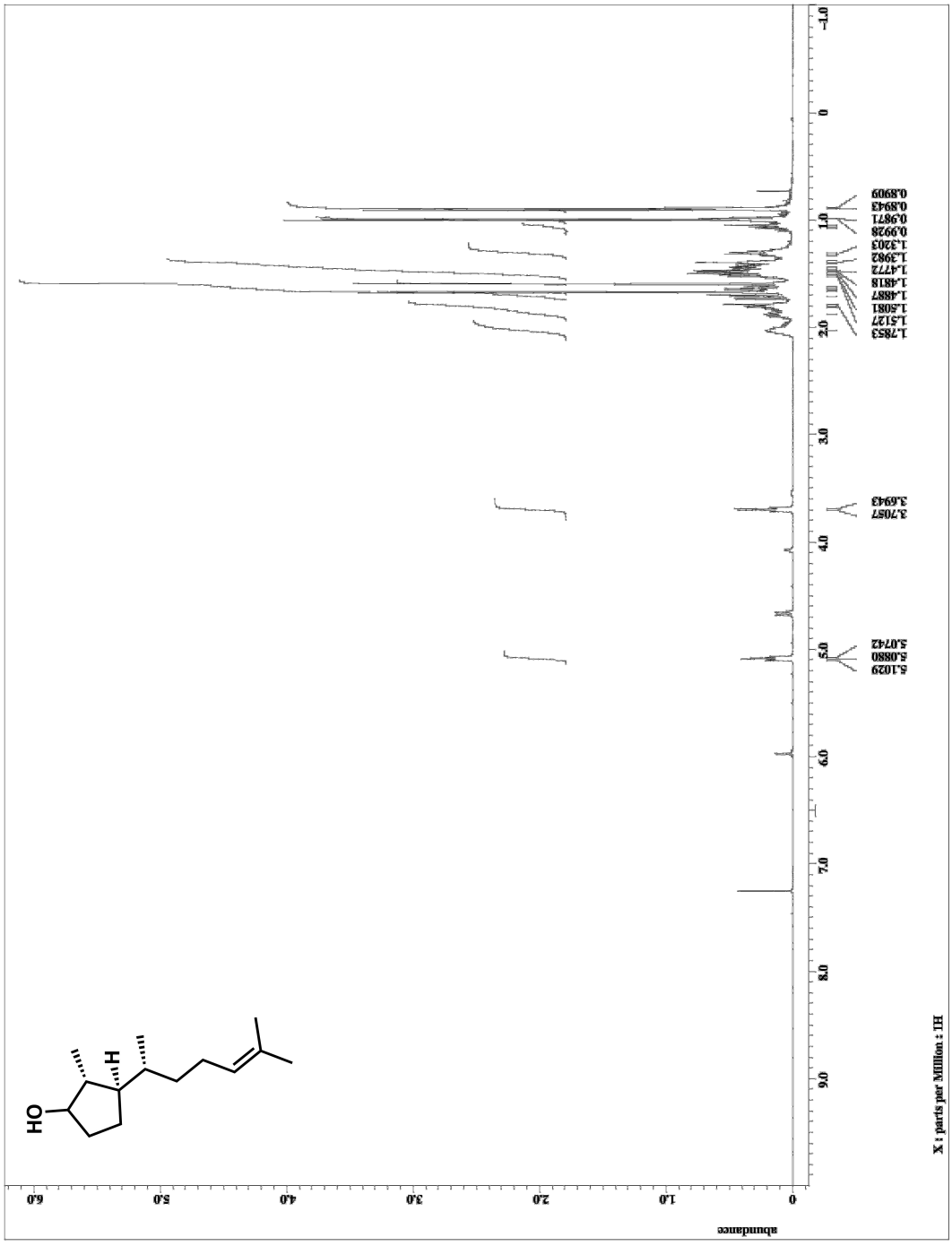


Figure A.2.24 ^{1}H NMR for compound **116**

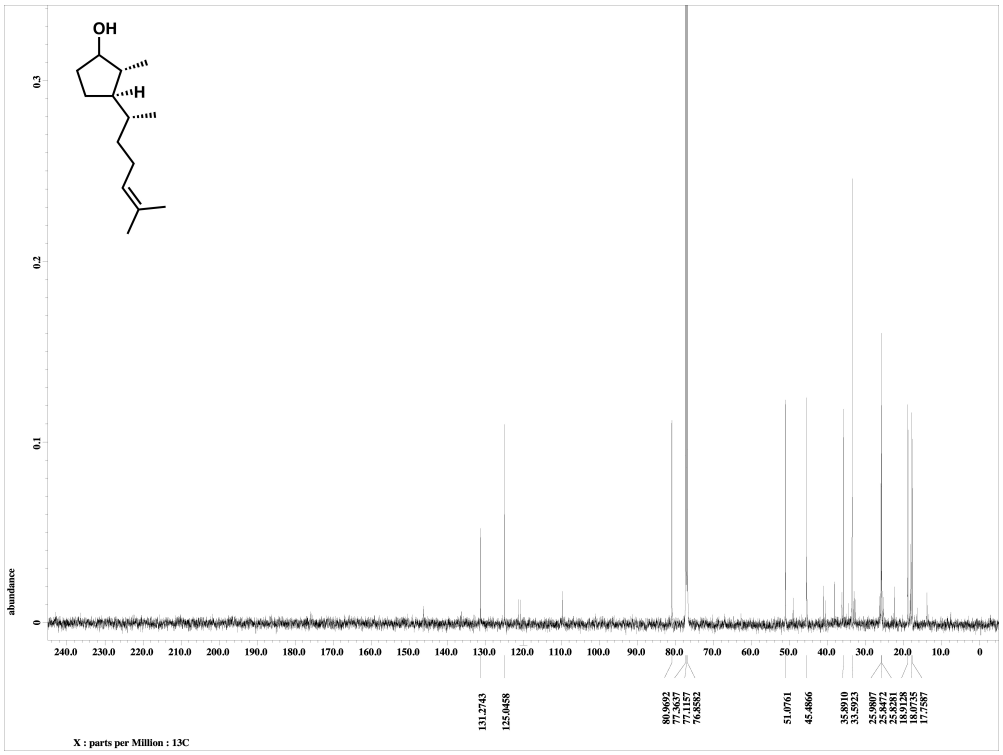
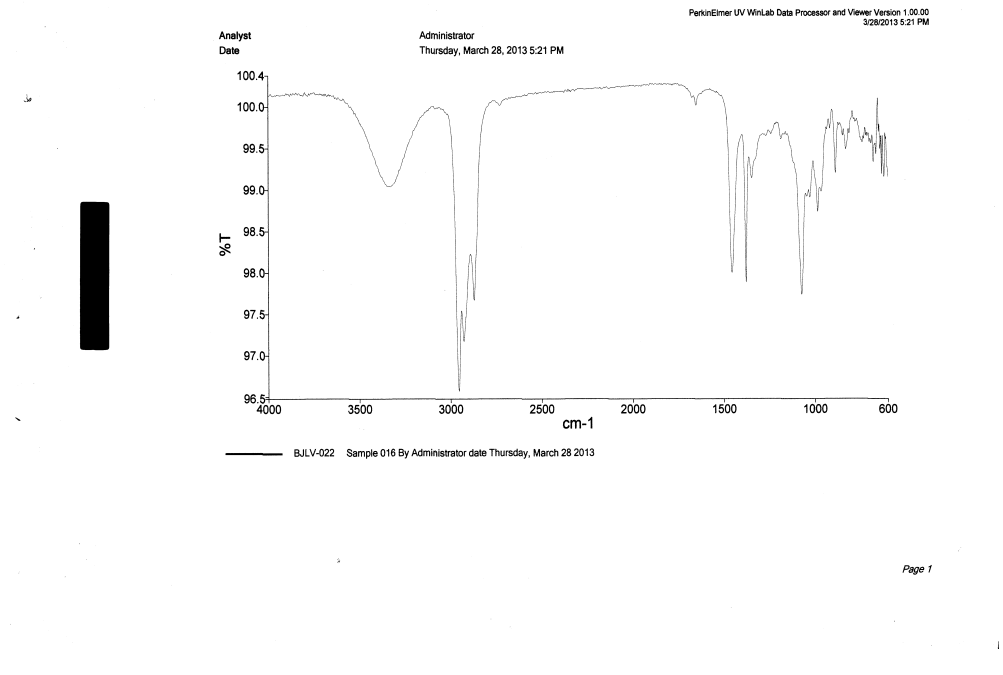


Figure A.2.25 ^{13}C NMR for compound **116**



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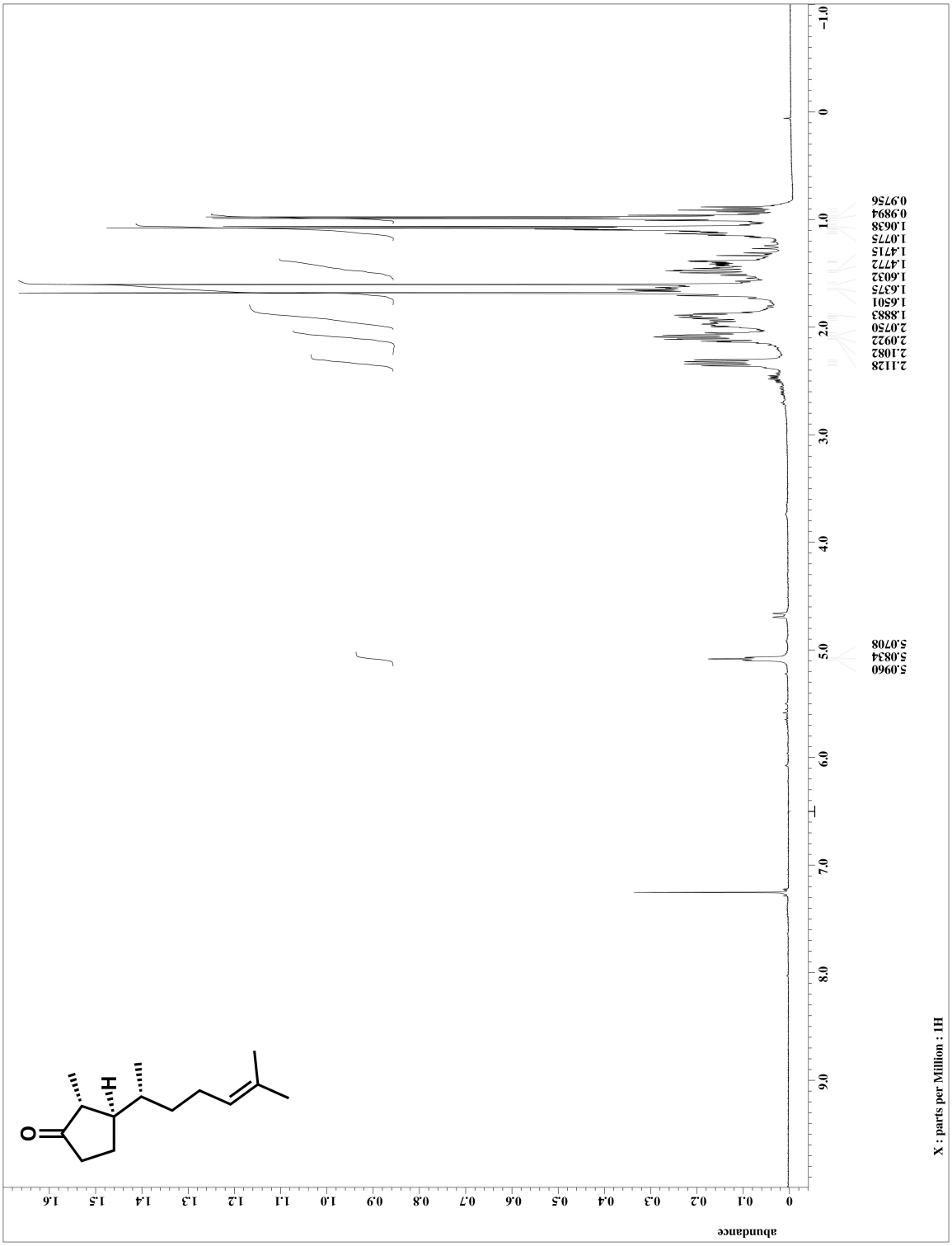

Figure A.2.27 ^{1}H NMR for compound **88**

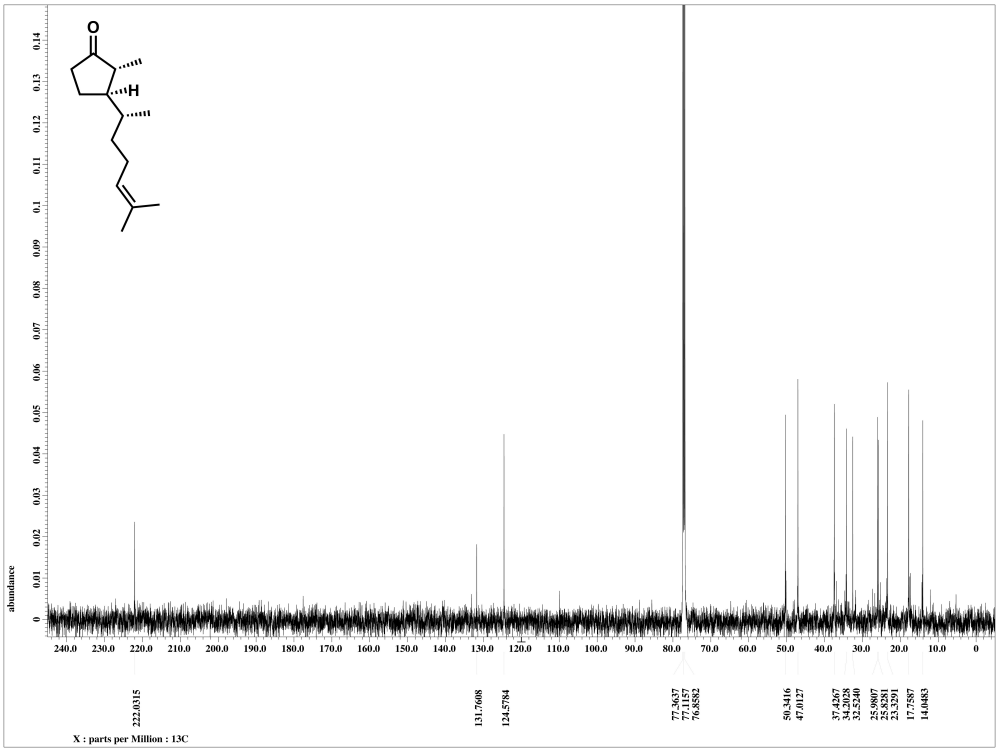

Figure A.2.28 ^{13}C NMR for compound **88**

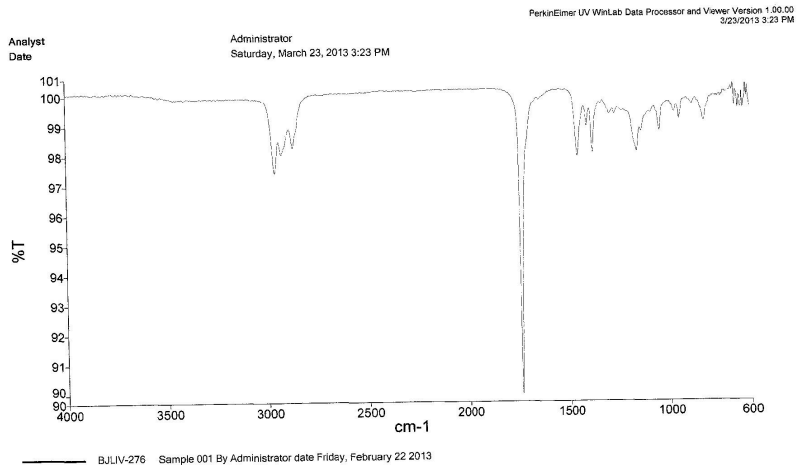

Figure A.2.29 IR spectra for compound **88**

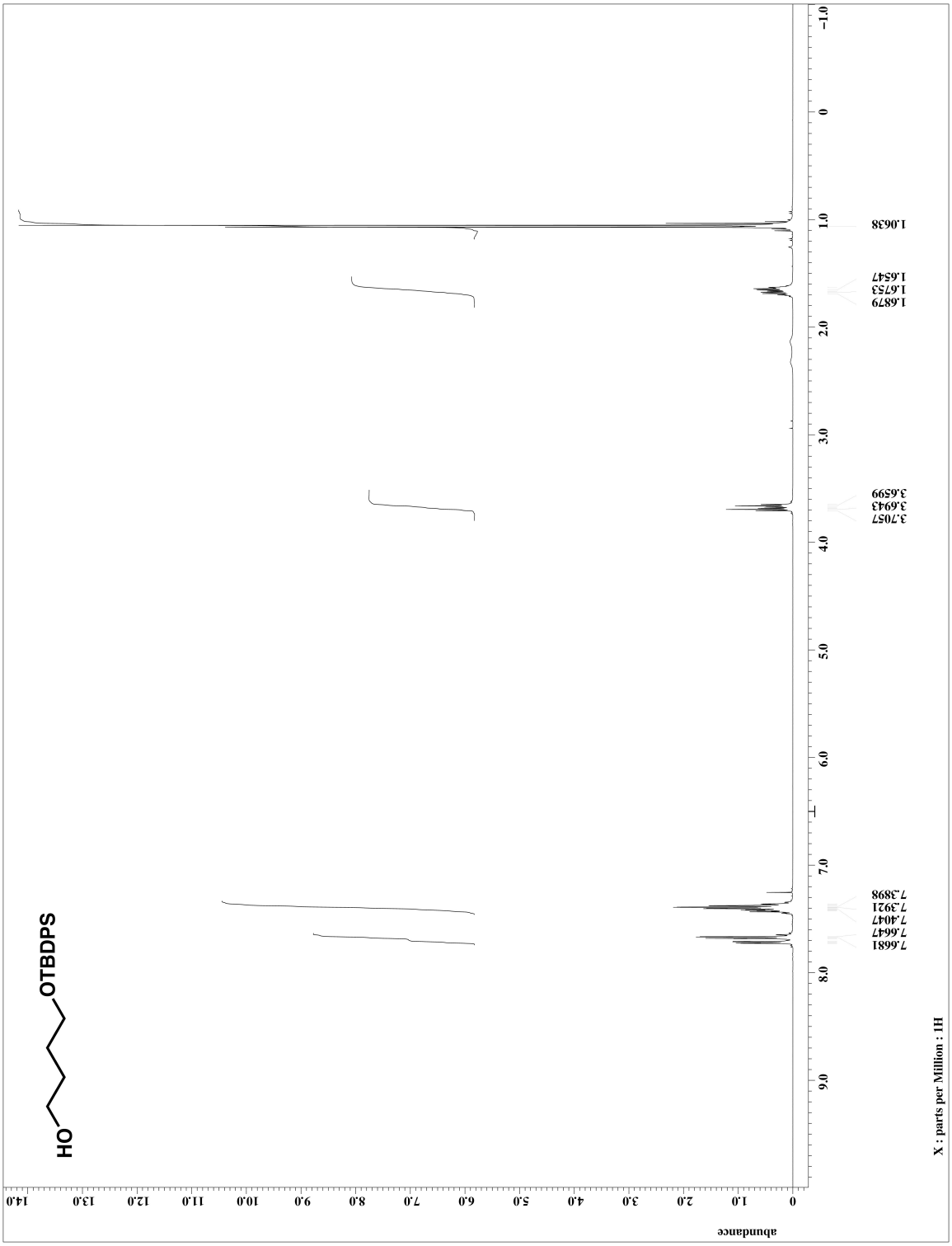

Figure A.2.30 ^{1}H NMR for compound **118**

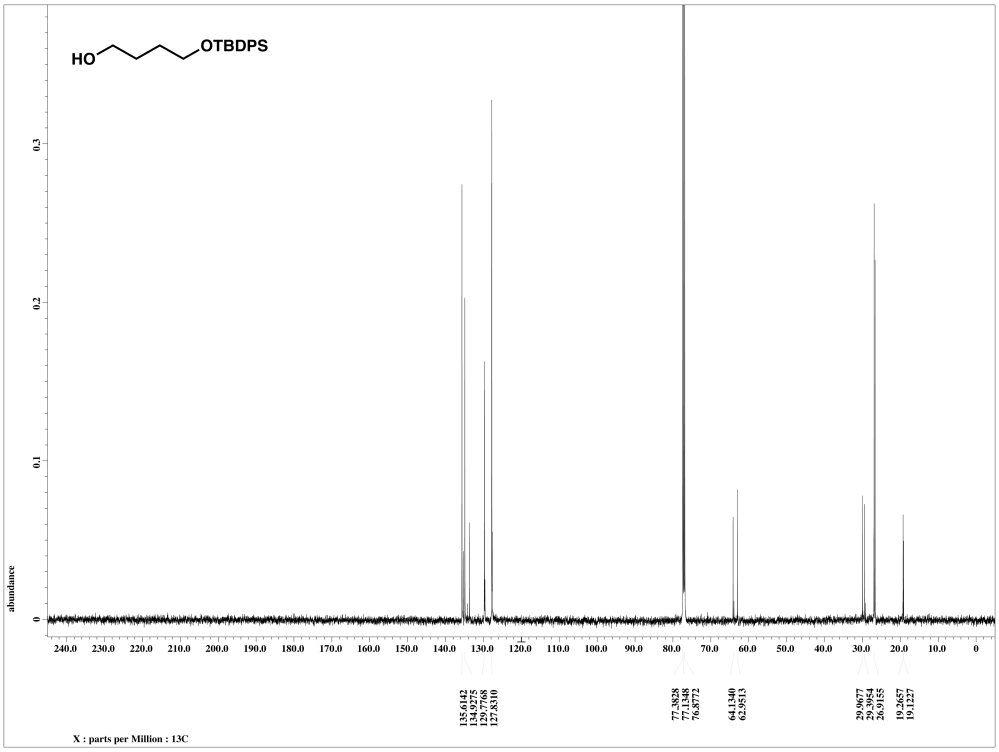

Figure A.2.31 ^{13}C NMR for compound **118**

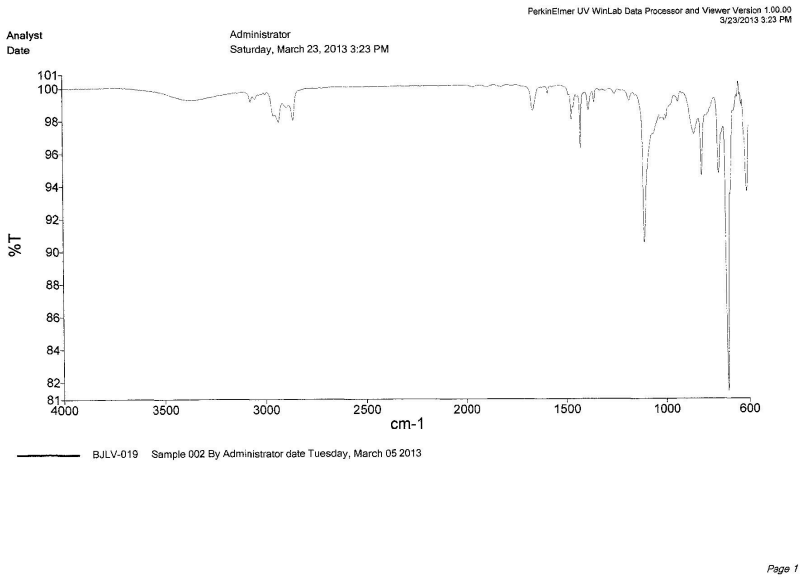

Figure A.2.32 IR spectra for compound **118**

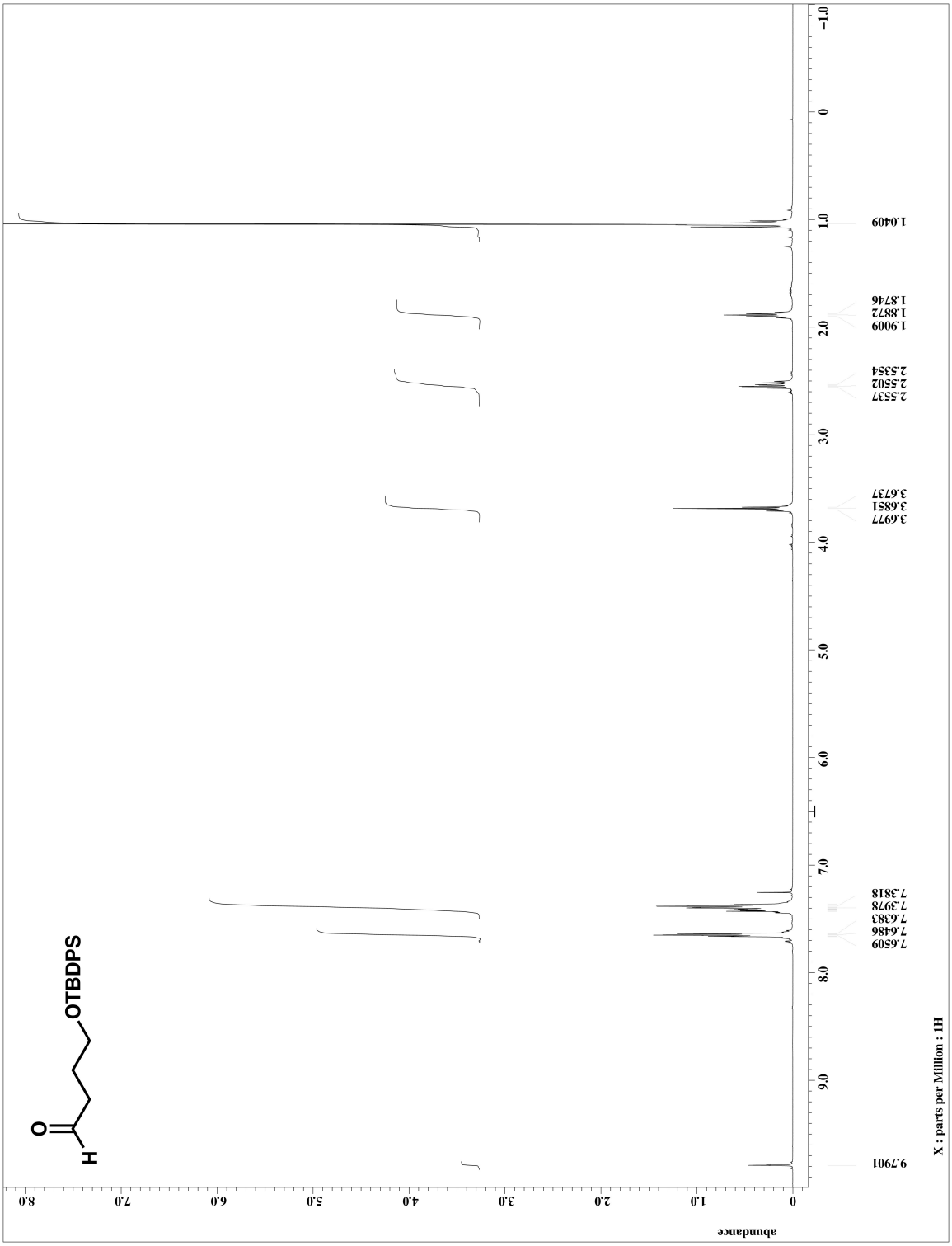

Figure A.2.33 ^{1}H NMR for compound **119**

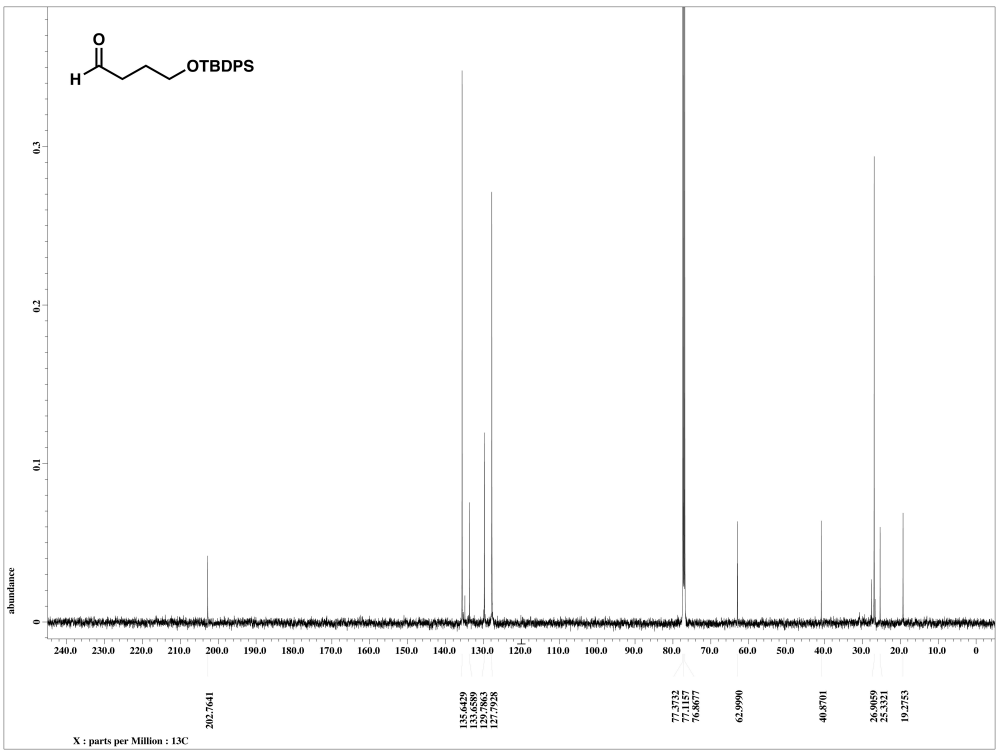

Figure A.2.34 ^{13}C NMR for compound **119**

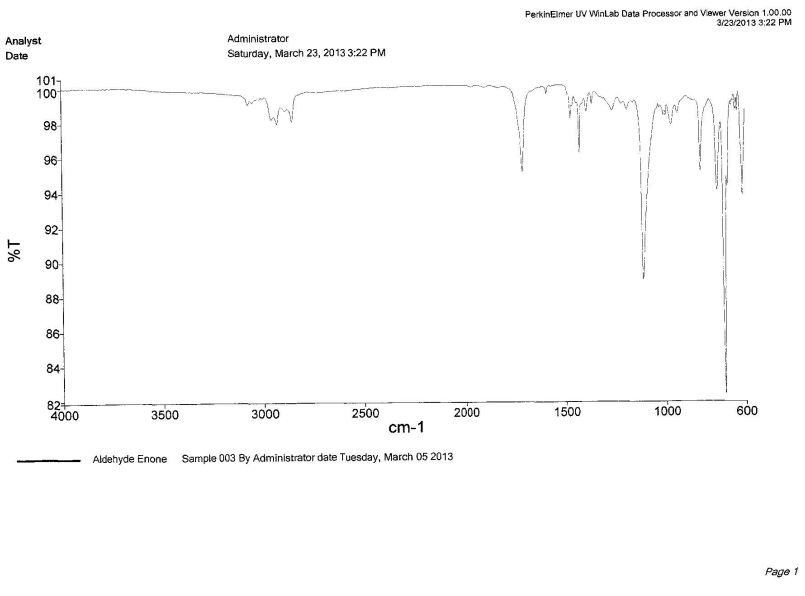

Figure A.2.35 IR spectra for compound **119**

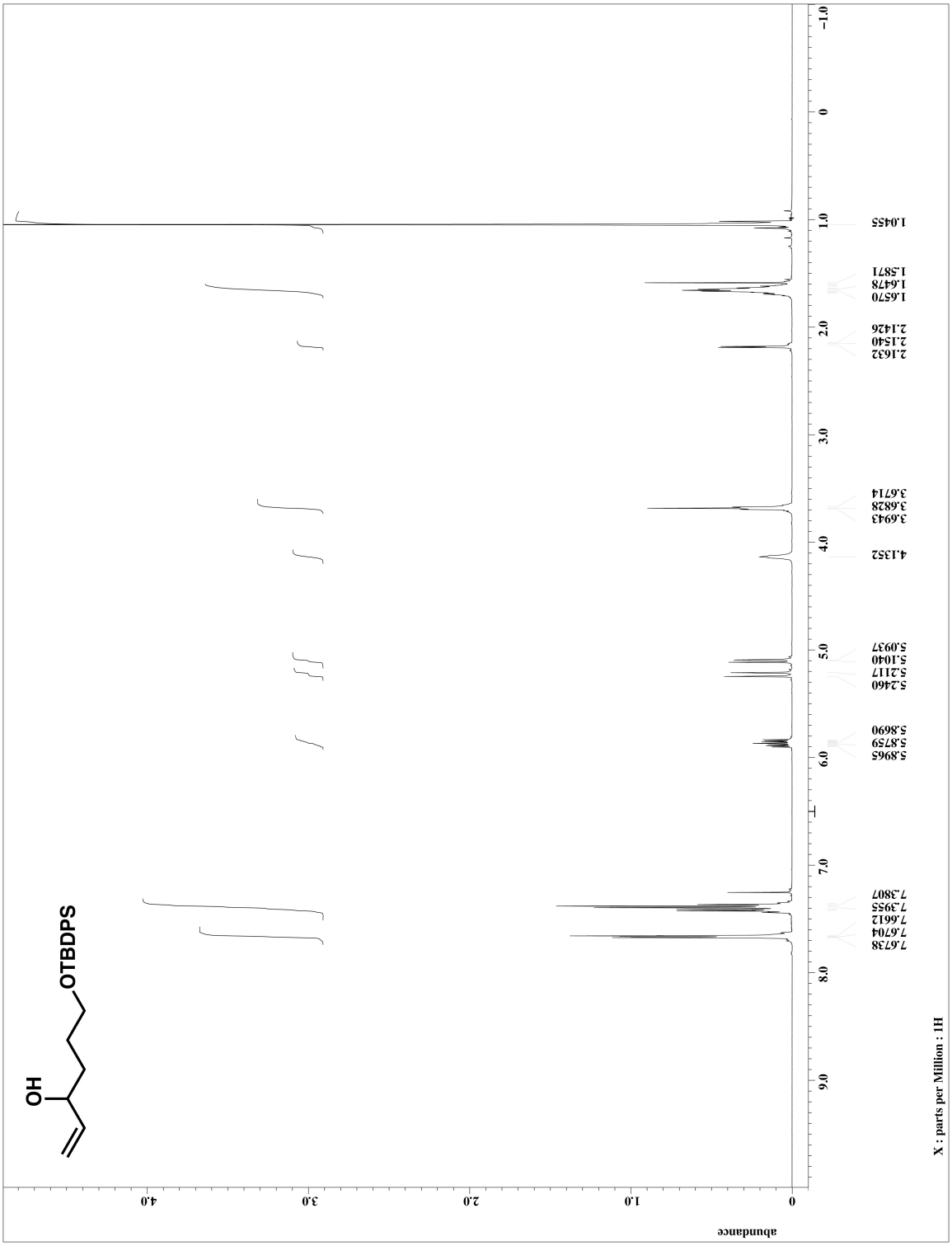

Figure A.2.36 ^{1}H NMR for compound **120**

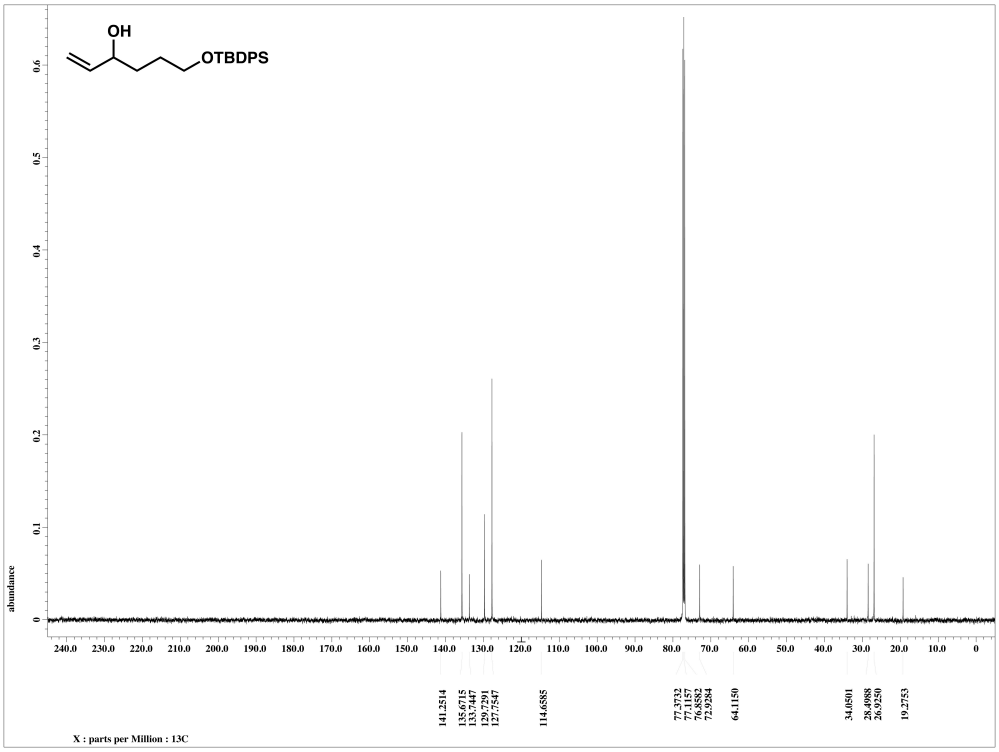

Figure A.2.37 ^{13}C NMR for compound **120**

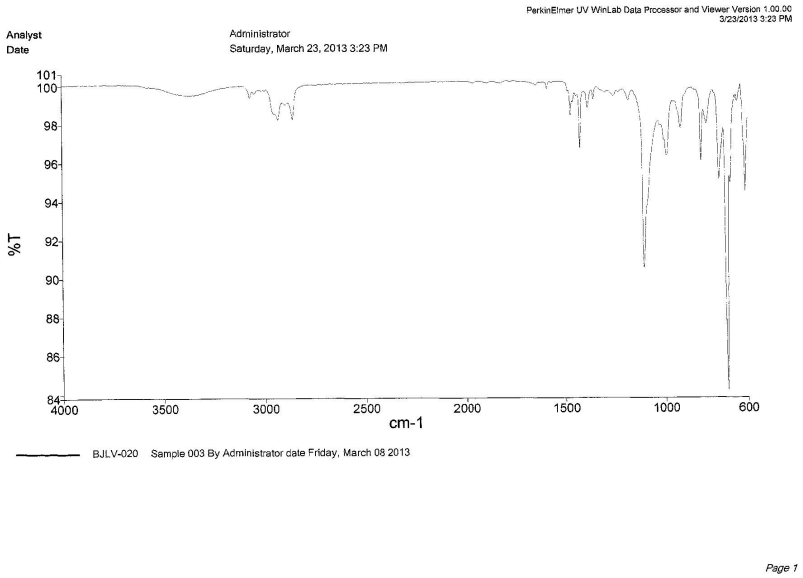

Figure A.2.38 IR spectra for compound **120**

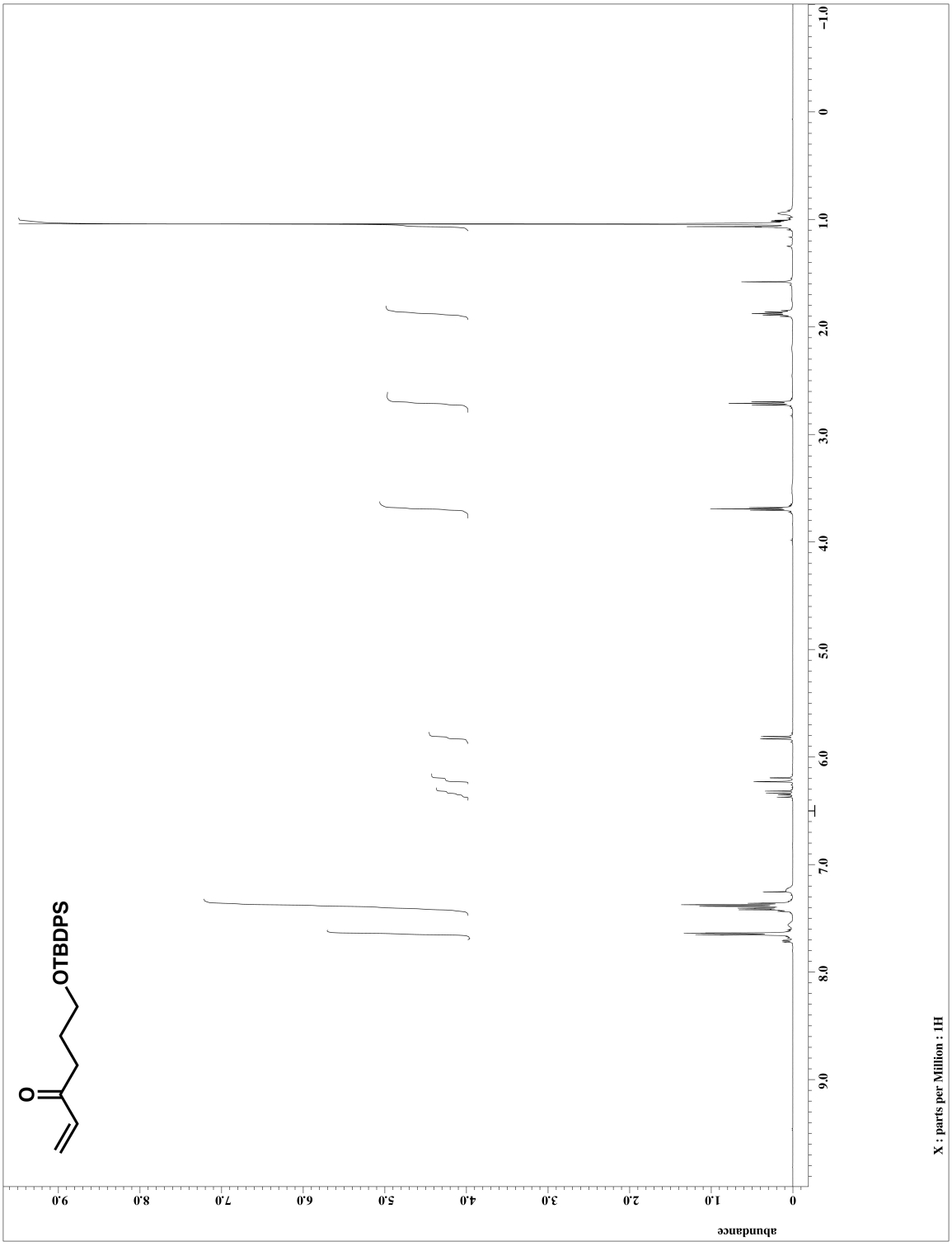

Figure A.2.39 ^{1}H NMR for compound **89**

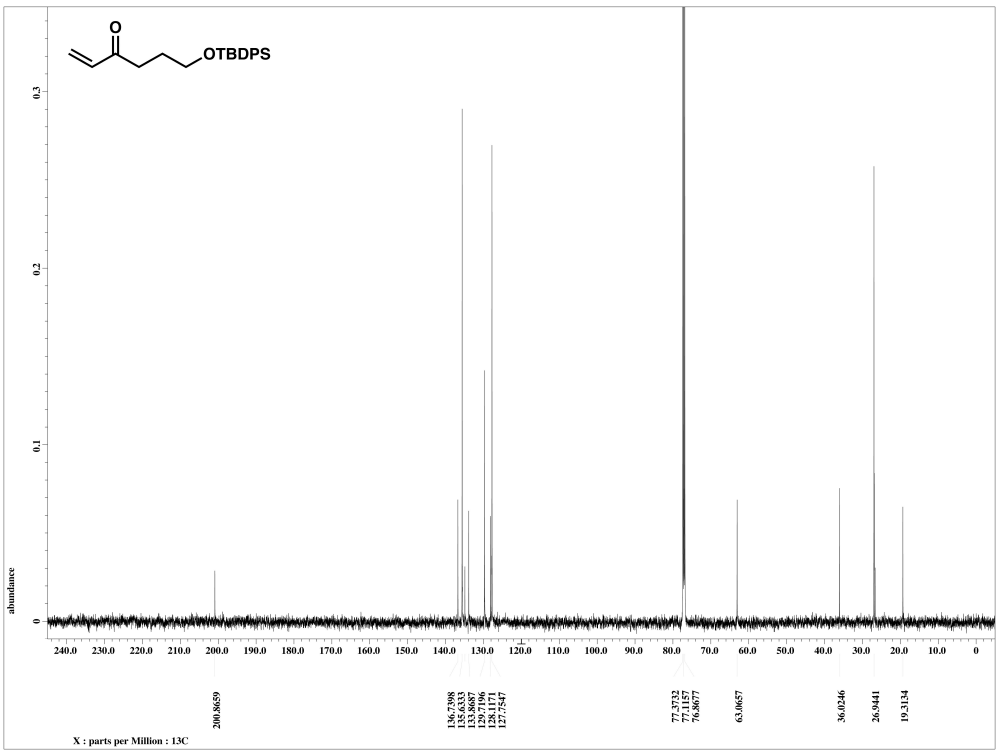

Figure A.2.40 ^{13}C NMR for compound **89**

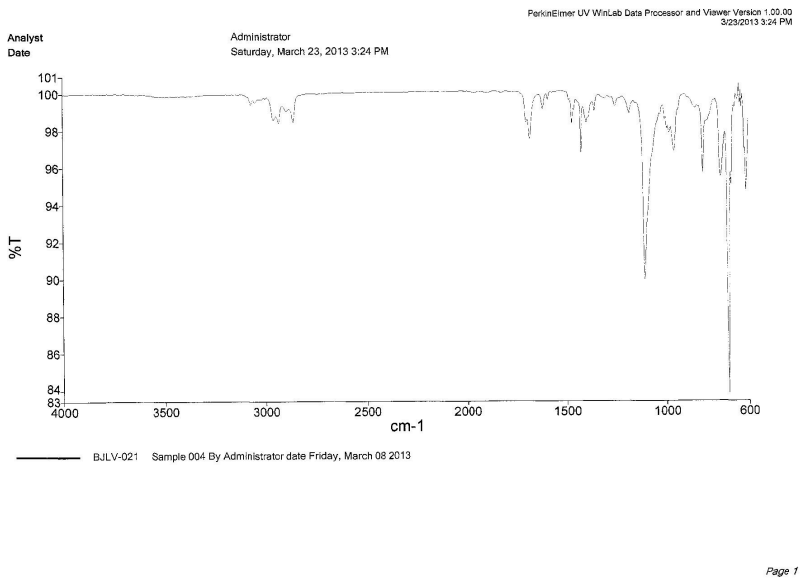

Figure A.2.40 IR spectra for compound **89**

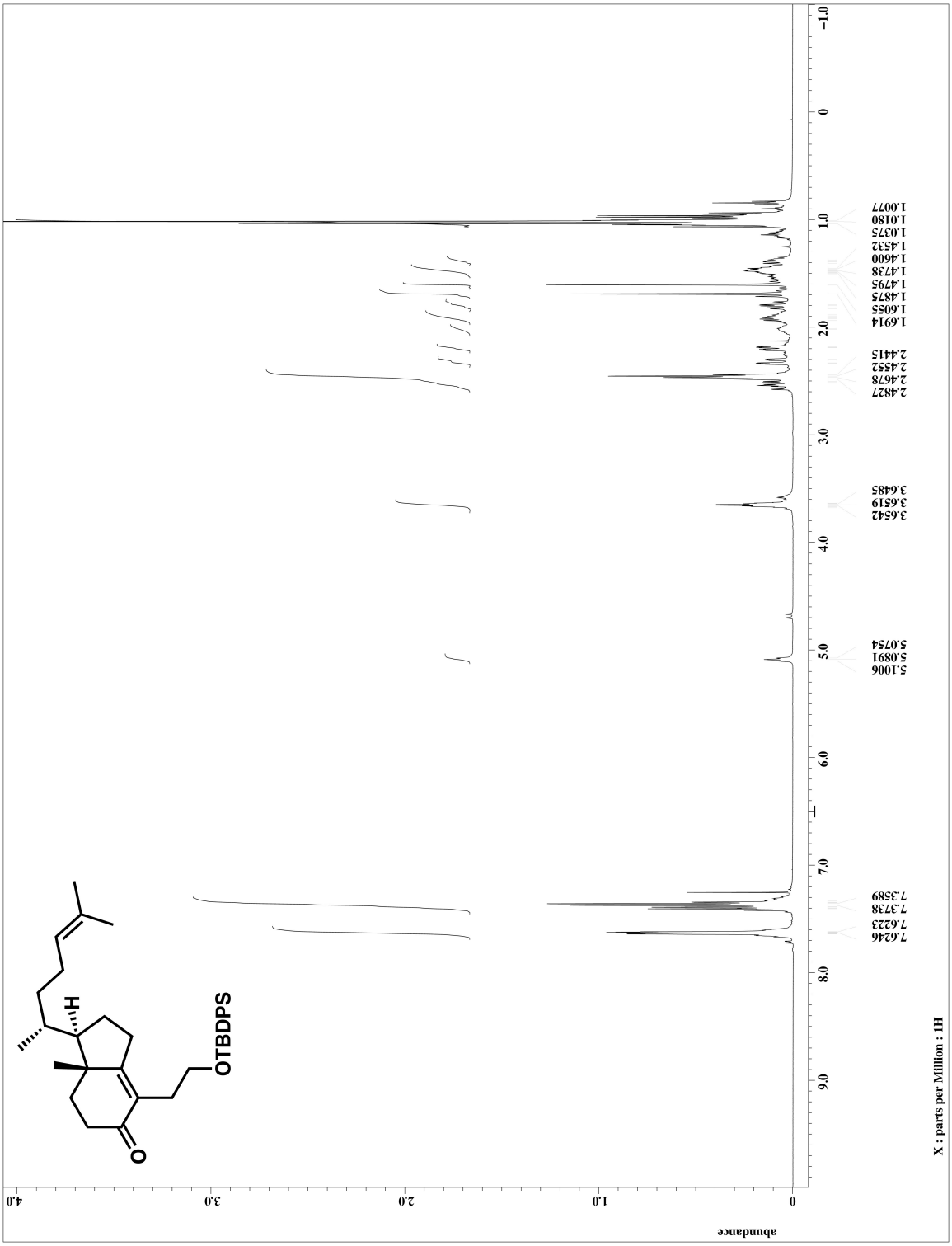

Figure A.2.41 ^{1}H NMR for compound **121**

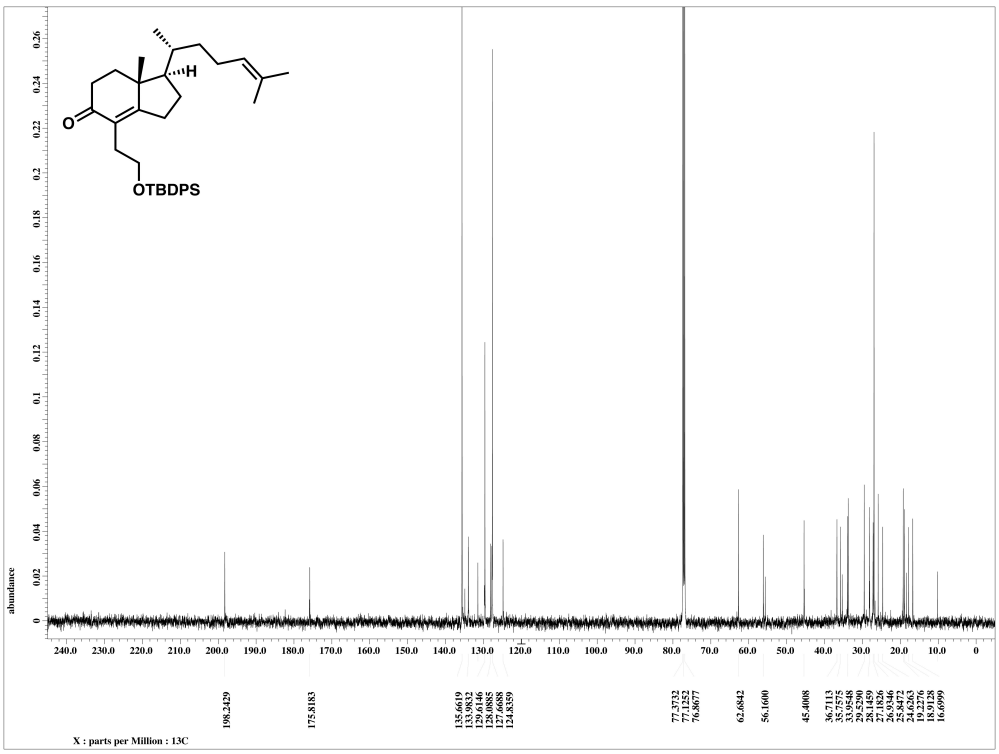

Figure A.2.42 ^{13}C NMR for compound **121**

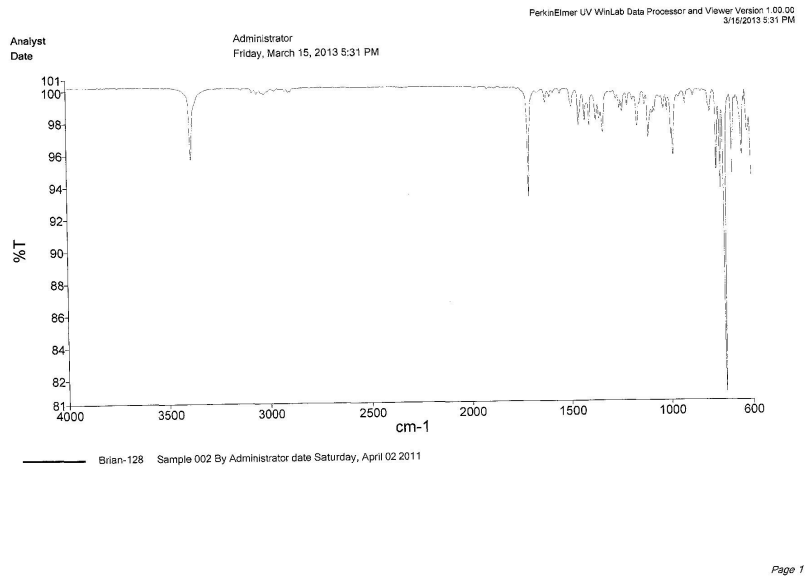

Figure A.2.43 IR spectra for compound **121**

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