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An Exploration of Novel Metal-Mediated Vinylcyclopropane Reactivity

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An Exploration of Novel Metal-Mediated Vinylcyclopropane Reactivity

by

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Abstract

Vinycyclopropanes (VCPs) are an important building block for synthetic and medicinal chemistry as they can undergo a variety of useful cycloaddition reactions to rapidly prepare complex molecular frameworks. Although VCPs contain ring strain, useful energy to drive chemical reactions, they typically still require activation to induce cycloadditions. The activation of vinylcyclopropanes using first row transition metal catalysis is not broadly studied and may offer opportunities for novel reactivity. First row transition metals were used to study the reactivity of three different vinylcyclopropanes toward cycloadditions. This thesis describes the results of screening these unactivated vinylcyclopropanes with Cu, Co, Ni and Fe catalysts. Subsequently, vinycyclopropane-containing natural products were screened for their reactivity toward cycloaddition reactions. Monoterpenes sabinene and 2-carene were utilized as starting materials for these annulations which were tested via rhodium catalysis. Also explored, was the induction of a 1,4-sigmatropic rearrangement reaction with first row transition metal catalysis. The Derksen group has previously reported a photomediated rearrangement in which 6:3:5 and 7:3:5 vinylcyclopropane ring systems were quickly introduced. The synthesis of these materials in good yields and selectivity provides rapid access to polycyclic vinycyclopropanes that offer opportunities for further reactivity. This thesis describes the screening of this transformation via Mn, Ti, Cu, Co, Ni and Fe catalysis rather than photochemical conditions.

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List of Abbreviations, Symbols and Nomenclature

Symbol	Definition
Å	Angstrom (1 Å = 10^{-10} m)
$AgPF_6$	silver hexafluorophosphate
B_2Pin_2	bis(pinacolato)diboron
BnBr	benzyl bromide
$CHCl_3$	chloroform
DCM	dichloromethane
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMAPP	dimethylallyl pyrophosphate
DMSO	dimethyl sulfoxide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
El	electrophile
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram
GPP	geranyl diphosphate
IPP	isopentenyl pyrophosphate
K_2CO_3	potassium carbonate
KOH	potassium hydroxide
LA	lewis acid
MeOH	methanol
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NaOMe	sodium methoxide
Na_2SO_4	sodium sulfate
nBuLi	n-butyllithium
NEt_3	triethylamine
NMR	nuclear magnetic resonance
Nu	nucleophile
m	multiplet
mg	milligram
$MgSO_4$	magnesium sulfate
rt	room temperature
SET	single electron transfer
SiO_2	silica gel
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography

VCP	vinylcyclopropane
δ	chemical shift in parts per million (ppm) downfield from tetramethylsilane

Chapter One: Types, reactivity and synthesis of vinylcyclopropanes and their uses in chemistry

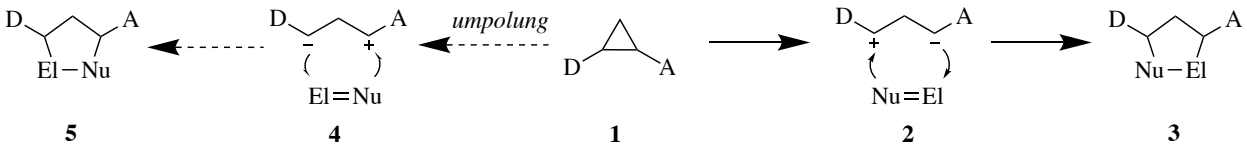
Organic chemists have a strong interest in building blocks with unique reactivity that can give rise to complex products with minimal steps. One such building block is a class of 3-membered carbocycles known as vinylcyclopropanes (VCP). With the first reaction being performed on a VCP taking place in 1959, the interest in these starting materials has only grown over the past 61 years.[1] Vinycyclopropanes are of interest because of their inherent ring strain, 27 kcal/mol for cyclopropane group, useful energy to drive a variety of different reactions to rapidly prepare complex molecular frameworks.[2] Ring opening reactions, isomerizations, cycloadditions and thermal rearrangement reactions are just a few examples of the versatility of these starting materials.[3-5] Due to the possibilities these reactions provide, as well as their prominence in both natural products and biologically active molecules, VCPs are a natural starting point to study synthetic methodology. However, even with their extensive presence in literature, there is still much to be learned and developed in terms of the reactivity of these moieties; including limiting pre-requisite activation, exploring reactivity with earth abundant catalysts further, as well as working towards utilizing naturally-occurring vinylcylopropanes existing in nature.

1.1 Donor-acceptor vinycyclopropanes and their reactivity

Although vinycyclopropanes are strained systems, which makes them reactive as the release of this energy is a driving force for transformations, they often still require activation in order to induce desired reactivity.[3,6-7] One such reactivity relies on the installation of donor-acceptor groups onto the VCP. This modification induces a 1,3-dipole in which the vinyl group can act as a donor, and therefore delocalize a positive charge, while the acceptor group, such as geminal diester groups, can stabilize negative charges.[6,8] A good example of the formation of this dipole and its

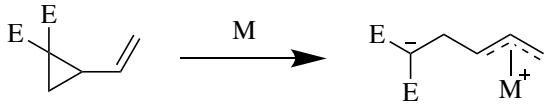
interaction with substrates is shown by Moran et.al. in their demonstration of a method to create an inversion of the standard observed polarity (Scheme 1).[6]

Scheme 1. Normal donor acceptor cyclopropane reactivity forming cyclopentane 3 vs. umpolung reactivity to form cyclopentane 5 from Moran et.al[6]



From Scheme 1 it can be seen that the stabilized positive charge on intermediate **2** in the normal reactivity pathway can be trapped by the partial negative charge on the nucleophile (Nu) of the coupling partner, and vice versa for the electrophile, giving rise to a substituted cyclopentane. The reverse is true for the developed umpolung method, where the stabilized negative charge by the donor group on intermediate **4** can attack the partial positive of the electrophile (El), and vice versa, giving rise to the regioisomeric cyclopentane. While this example shows the formation of a dipole from these moieties, in the case of vinycyclopropanes, this ring opening step is normally caused by the activation of a transition metal or a Lewis acid.[3,9] In a review from Brownsey et.al., this dipole formation via transition metal catalysis is summarized (Scheme 2).

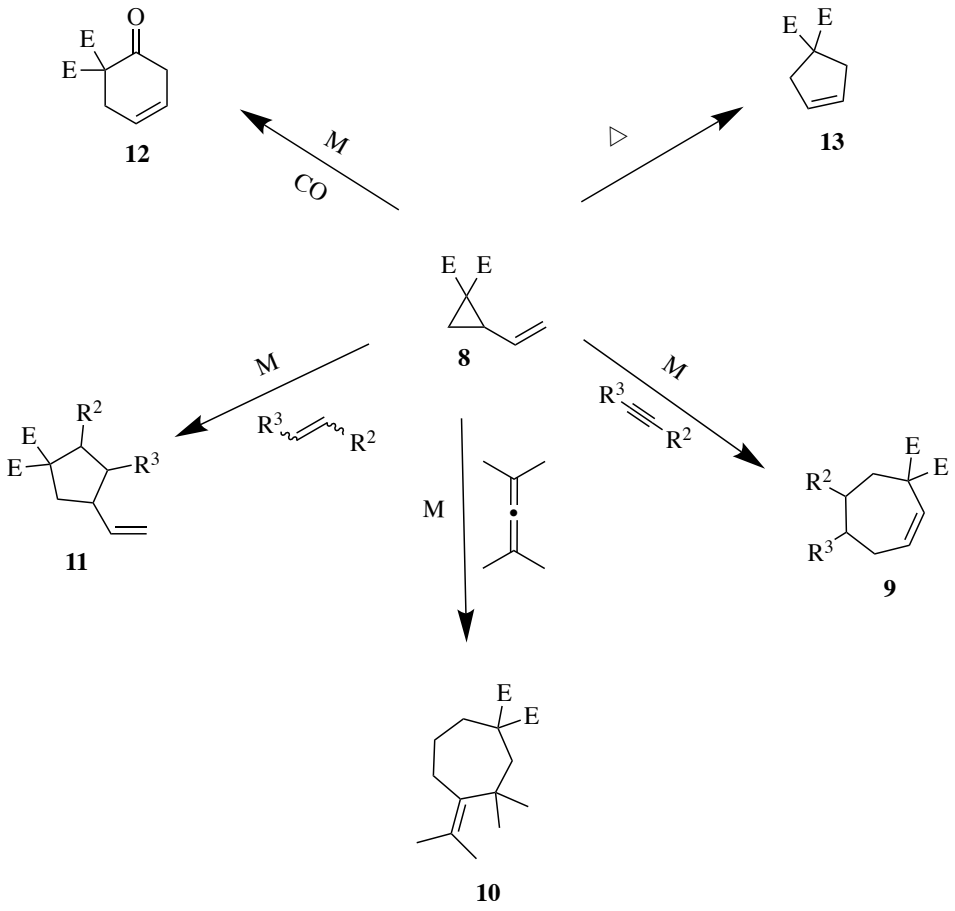
Scheme 2. Transition metal activated dipole formation via metal coordination followed by ring opening from Brownsey et.al.[3]



From this schematic depicting the vinyl group as the donor, with the acceptor group being illustrated as disubstituted groups labeled with 'E', as in donor acceptor vinylcyclopropane chemistry the acceptor group is most commonly geminal diester groups.[3, 10-14] The insertion of this metal source allows for general compound **7** to then undergo a variety of different reactions

rather than just cyclopentane formation, including a variety of cycloaddition reactions as well as substitution reactions.[4] Some examples of the transition metal mediated reactions of these substituted moieties are shown in Scheme 3. The induction of these reactions is caused primarily by transition metals such as palladium, or Lewis acid (LA) catalysts, as the LA coordinates to one or more of the ester groups causing the cyclopropane bonds to be weakened.[3-4, 9]

Scheme 3. Examples of donor acceptor VCP annulation and rearrangement reactions



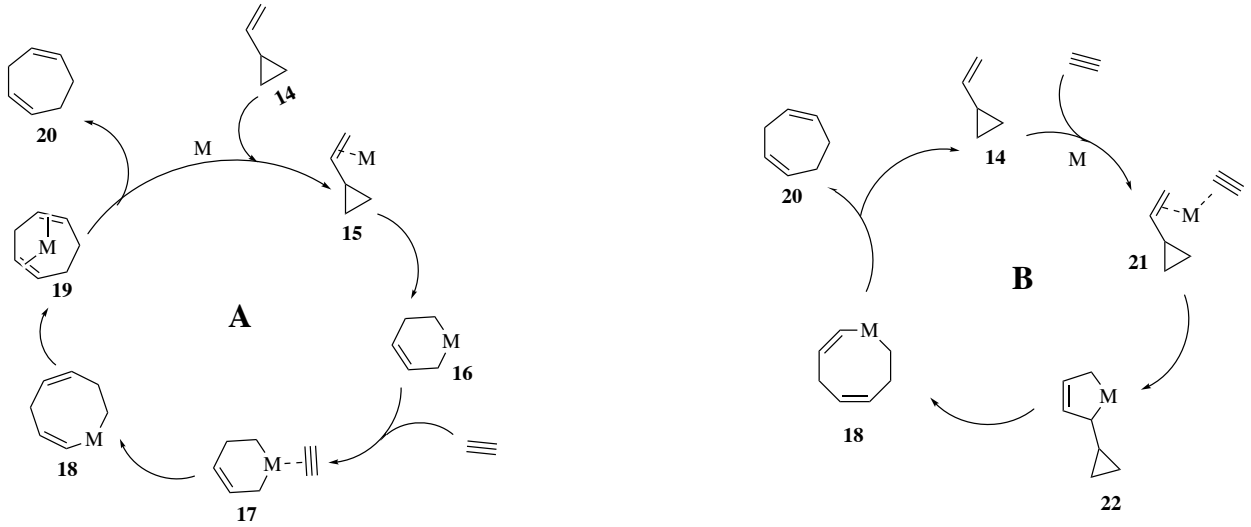
As it can be seen from Scheme 3, donor acceptor vinycyclopropanes have a wide variety of utility giving rise to versatile products.[3-4] Specifically, the direct access to seven membered rings, such as the generic example shown through the [5+2] cycloaddition with a substituted alkyne giving product **9**. The access to seven membered rings is a particularly interesting reaction as the synthesis of medium sized rings is an active problem in organic chemistry due to the large entropic penalty

associated with these transformations.[15] Although donor-acceptor vinylcyclopropanes show why the annulation reactions of these molecules are interesting and need to be explored by quickly accessing medium sized rings and complex materials, the substitution of these starting materials can be detrimental to the efficient access of many target compounds. As most natural product, or biologically active targets, do not contain geminal diester or these activating groups, further removal of these groups is required moving forward with the syntheses.[3,16-17] Therefore, it is of interest to explore the reactivity of unactivated vinylcyclopropanes which can give rise to carbocyclic skeletons directly.

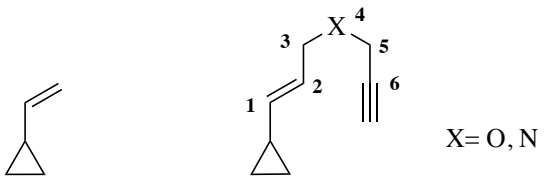
1.2 Unactivated vinylcyclopropane reactivity with transition metal catalysis

Unactivated vinycyclopropanes, or those with reduced activation, have been found to undergo annulation reactions in the presence of transition metals.[3-4,18-19] Unlike donor-acceptor VCPS, however, the lack of activating groups causes this reaction pathway of a 1,3-dipole in the presence of metals such as palladium to be less favourable. instead, the main step being the formation of a metallocycle intermediate in the presence of metals such as rhodium, ruthenium, iridium, iron,

Scheme 4. Reaction pathways 'A' and 'B' for the formation of 7 membered products through transition metal coordination and metallocycle intermediates



nickel and cobalt (Scheme 4)[1]. While reactions with the former, heavier metals, are well established reactions with unactivated substrates, reactions with the latter first row transition metals have much fewer literature examples.[3-4] Depending on the metal catalyst used, the reaction can follow different reactive pathways (Scheme 4). The most common general pathway, pathway A, is through the insertion of metal catalyst through ring opening oxidative addition of the VCP, giving rise to intermediate **16**. This is followed by complexation to the coupling partner shown in intermediate **17**, insertion and finally reductive elimination providing seven membered ring **20**.[4] However different metals, or oxidation states of metals, can follow pathway B, in which first oxidative cyclometallation of the coupling partner with the vinyl group of the VCP is undergone providing intermediate **21**, keeping the cyclopropane intact and forming a metallacycle.[4] The cyclopropane then undergoes ring opening and reductive elimination in order to give rise to the product **20**.[4] Generally, both intramolecular and intermolecular vinylcyclopropane reactions follow the first reaction pathway.[3] While intermolecular cycloaddtions involve a vinylcyclopropane such as the general structure shown in Figure 1 with an external coupling partner, intramolecular vinylcyclopropane reactivity involves the use of a compound containing a VCP group with a coupling partner directly included in the moiety such as shown in the same figure. The most common example of intramolecular vinylcyclopropane starting materials used in literature are 1,6-enyne VCPs where there is a heteroatom substituent at that four position, like



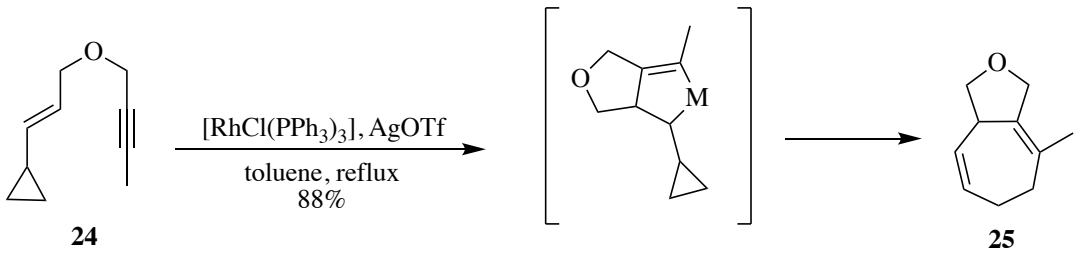
14 **23**

Figure 1. General examples of VCP cores used for intermolecular and intramolecular cycloadditions

compound **23**, which give rise to 5,7-fused products (Figure 1). [3,10-12,20-22] As there are a variety of different cycloadditions these unactivated VCPs could undergo, such as [5+1], [5+2], [5+2+1], and [3+2] depending on substituents or coupling partners, and each metal source providing a different reaction mechanism, the reactivity of each case has been studied extensively with different substrates. Specifically, unactivated vinylcyclopropane cycloaddition reactions involving late transition metals have been studied in depth.[3-4 10-12,18-22]

Unactivated vinylcyclopropanes can undergo a variety of intermolecular and intramolecular cycloaddition reactions with alkynes, alkenes, allenes, and different reactions with carbon monoxide, with the vast majority of literature precedent for these reactions being performed with rhodium catalysts.[3-4,10-13,18] The majority of these annulation reactions being performed with rhodium catalysis is due not only to the fact that it was the first reported case of [5+2] intermolecular cycloadditions of VCPs out of the Wender group, but also due to its versatility in catalyzing these annulation reactions (Scheme 5).[23]

Scheme 5. The first rhodium catalyzed [5+2] vinylcyclopropane annulation reaction from the Wender group[23]

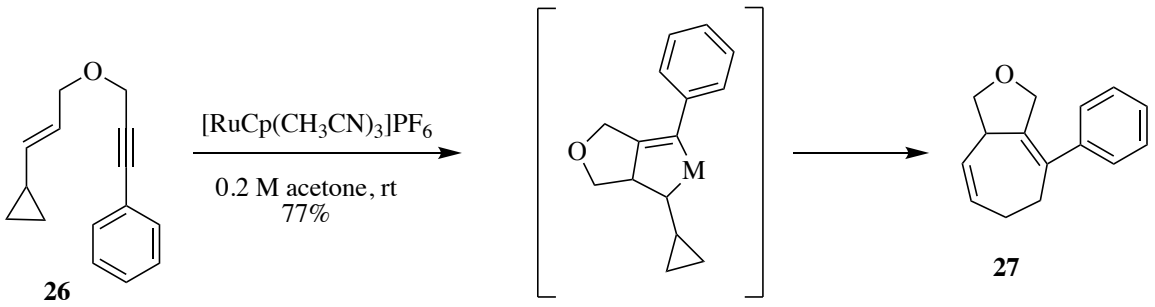


24 **25**

Rhodium has since been shown to be an effective catalyst for [5+2], [5+2+1], [5+1], [3+2] cycloadditions of both intramolecular and intermolecular VCPs.[3-4,10-13,18-34] For a complete account of vinylcylcopropane reactivity with rhodium catalysis, multiple reviews exist.[3-4,35-37] While the vast majority of literature VCP annulation reactions involve rhodium catalysis, there are also many accounts of this reactivity being induced with ruthenium and iridum catalysis.[14,20,38-40] With the

first report of ruthenium catalyzed [5+2] cycloaddtion being reported by the Trost group, they aimed to use milder temperature conditions, along with cheaper ruthenium catalysts in comparison to the previous reports using rhodium (Scheme 6).[39]

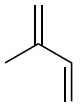
Scheme 6. The first ruthenium catalyzed [5+2] vinylcyclopropane annulation reaction from the Trost group[39]



These discoveries sparked interest in the use of transition metal catalysis for vinylcyclopropane cycloaddition reactions, particularly [5+2] annulations to access seven membered rings. Still, however, limited examples of these annulation reactions with first row transition metals exist, with the majority of the examples using these metals using intramolecular reactivity rather than intermolecular reactivity. [14,20,38-40] As such, research is still required into the reactivity of intramolecular and intermolecular vinylcyclopropane annulation reactions with first row transition metals.

1.3 Terpenes in chemical synthesis

Terpenes are a class of natural products that constitute a huge area of chemical space with over 55,000 members.[41-43] These compounds are widely recognized for their versatility in everyday life, with utility as fragrance sources in perfumes, flavours in food, in biofuel products and a variety of different medicines.[42-43] Terpenes are classified primarily by being composed of 5 carbon isoprene building blocks (Figure 2).[41-42]

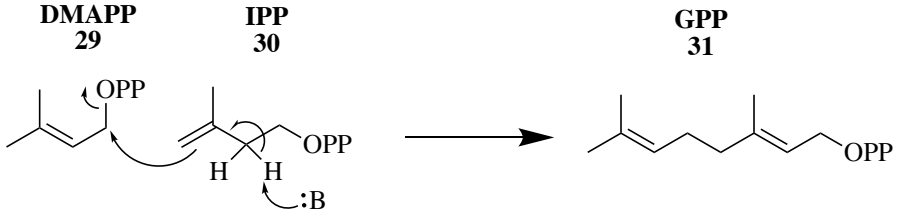


Isoprene
28

Figure 2. Structure of 2-methyl-1,3-butadiene or isoprene

From these isoprene units, all terpenes are formed through reactions with DMAPP and IPP.[42,45-46,48] The general reaction pathway, shown in Scheme 7, involves a head-tail condensation reaction between DMAPP and IPP to form a geranyl diphosphate.[42,45-46,47-48]

Scheme 7. Condensation reaction between DMAPP and IPP to form GPP



The number of additional IPP units that are subsequently added to the GPP dictates the class of terpene that is formed.[42,45,46-47] Following the additions of IPP, GPP then undergoes a cyclization reaction which gives rise to the isoprene units embedded in the terpenes, which simultaneously characterizes them as one of the many classes within these natural products.[47-49]Although being synthesized in the same way, not all members of the terpene class have the same biological effects or utility; so it is important to differentiate the different subclasses.[41,43] Amongst this class of natural products are seven distinct classes of terpenes.[49] The general structures are classified by the isoprene units in the back bone, as well as the number of carbons. From one isoprene unit in hemiterpene (C_5) increasing to 8 isoprene units in tetraterpene (C_{40}).[49] Among the classes of terpenes, one of the most studied is monoterpenes. This is due to not only their structural simplicity comparatively, but their bioactivity; with multiple examples being tested and showing anticarcinogenic potential.[50]

1.3.1 Monoterpenes

Monoterpenes, classified as having a $C_{10}H_{16}$ skeleton with two isoprene units, have been studied in literature for a variety of different biological and chemical uses.[50-51] Originating from a variety of sources including essential oils, these natural products are most commonly found as products from the secondary metabolism of plants and extracted from leaves, fruits, barks and roots; it is possible, however, for this class of terpenes to be isolated from animals or micoorganisms as well.[52] While the term monoterpene was cultivated to encompass hydrocarbon backbones, the term monoterpenoid, which will be used interchangeably here on out, was coined in order to encompass heteroatom substituted derivatives.[49] The three main types of monoterpenoids are acyclic, monocyclic and bicyclic.[53] Examples of acyclic monoterpenoids include, but are not limited to, aforementioned GPP, linalool **32**, geraniol **33**, ocimene **34** and myrcene **35** (Figure 3).[54]

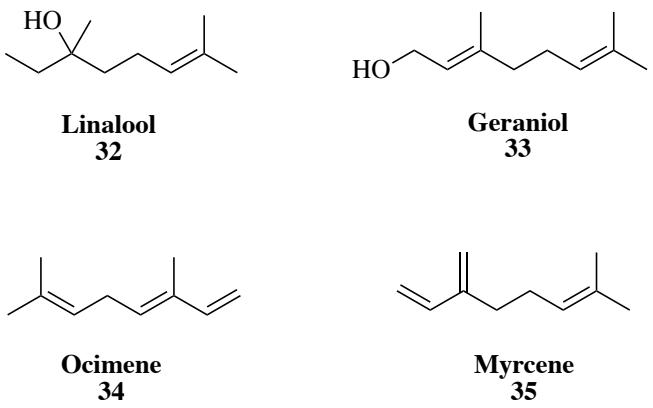
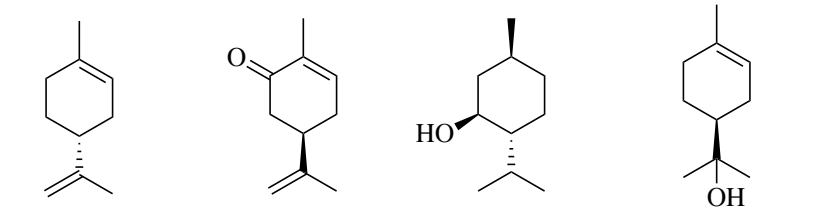


Figure 3. Structures of acyclic monoterpenes linalool, geraniol, ocimene and myrecene

Of these acyclic monoterpenes, linalool is a molecule with many functions in both industry and in terms of biological activity.[55] Being a key compound in the synthesis of fragrance compounds, as well as vitamins, makes this compound of interest to perfumes and flavouring.[55] On the biological side, linalool has been shown to have anticancer, anti-inflammatory, anti-oxidant and antimicrobial activity, along with having effects on the central nervous system.[55-56] Similarly, both ocimene and geraniol are used as flavouring for foods, but have been tested positively for their antimicrobial

and antibacterial activity.[56-58] Myrcene has been tested as an antimicrobial and antibacterial agent, and more recently investigated for its activity at transient receptor channel TRPV1.[56,59]

Monocyclic monoterpenes are recognized as having a large potential in the pharmaceutical industry as they can treat a variety of different diseases.[60] Monoterpene examples include (+)-limonene **36**, (+)-carvone **37**, (+)-menthol **38** and (+)-α-terpineol **39** (Figure 4).[54,56] With all of these compounds showing antibacterial effects to some degree, limonene specifically has been studied for its antitumor, antiviral and anti-inflammatory bioactivity.[56, 60-63]



(+)-Limonene 36 **(+)-Carvone 37** **(+)-Menthol 38** **(+)-α-Terpineol 39**

Figure 4. Structures of monocyclic monoterpenes (+)-limonene, (+)-carvone, (+)-menthol and (+)-α-terpineol

The third and final subclass of monoterpenes is bicyclic terpenes including (+)-thujene **40**, (+)-sabinene **41**, (+)-α-pinene **42**, (+)-3-carene **43** and (1*R*)-(+)-camphor **44** (Figure 5).[54] Of these bicyclic compounds, both α-pinene and 3-carene show antifungal and antibacterial effects, with the former also being antiviral and the latter being a local anesthetic.[56] Similarly, sabinene and thujene have been shown to have antibacterial activity, while thujene has also been tested for its antioxidant and antimicrobial properties.[64-65] Finally, camphor has been tested for a variety of biological activities, including an analgesic agent, antitussive as well as an antiviral and antimicrobial agent.[66]

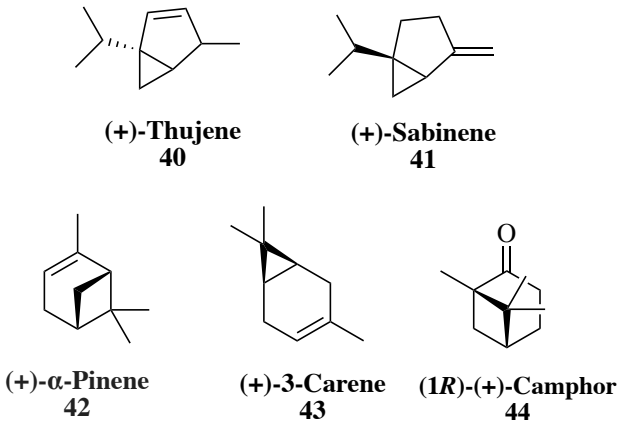


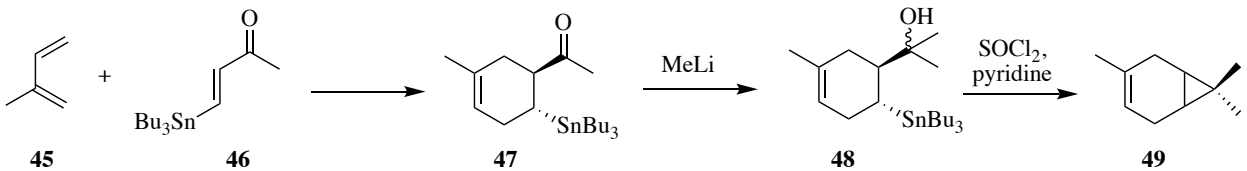
Figure 5. Structures of bicyclic monoterpenes (+)-thujene, (+)-sabinene, (+)-α-pinene, (+)-3-carene and (1*R*)-(+)-camphor

As with many natural products, particularly those with biological activity, there is a lot of interest from both chemists and biologists to both utilize these compounds in syntheses as well as having them as synthetic targets.

1.3.2 Monoterpenes in total synthesis

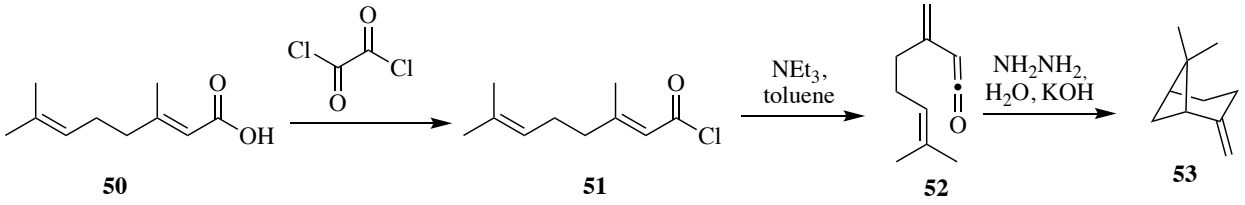
With the many different functions of monoterpenes, it is natural that they often show up in syntheses. Since the main form of biosythensis of these compounds is within plants, small quantitates are produced which can make it difficult for biological testing.[52] Therefore, there are many examples of syntheses in literature with monoterpene targets.[48] One such example comes from Johnson et al where they were able to synthesize bicyclic monoterpene 3-carene in just 3 steps (Scheme 8).[48,67] Through a Diels-Alder reaction between diene **45** and vinyl ketone **46**, intermediate **47** was synthesized. This was followed by methyl addition to give alcohol

Scheme 8. Synthesis of 3-carene from Johnson et al.[67]



intermediate **48** and finally using thionyl chloride to form the cyclopropane ring, 3-carene **49** was able to be accessed; although this synthesis also provided the methyl regioisomer, it provided a quick and useful synthesis of this monoterpene.[48,67] In another nice monoterpene synthesis, Snider et al. were able to prepare β- pinene **30** from geranic acid in 4 steps (Scheme 9).[48,68] The first step of their synthesis involved converting **50** to the acid chloride intermediate **51**, which was then converted to ketene intermediate **52**. This single regioisomer ketene was then able to undergo a [2+2] cycloaddition with the corresponding alkene which then underwent a Wolff-Kishner reduction in order to produce β- pinene **53**. The authors were also able to synthesize another monoterpene, chyrsanthenone, through the isomerization of intermediate **52**.[68]

Scheme 9. Synthesis of β- pinene from geranic acid by Snider et al.[68]



50 **51** **52** **53**

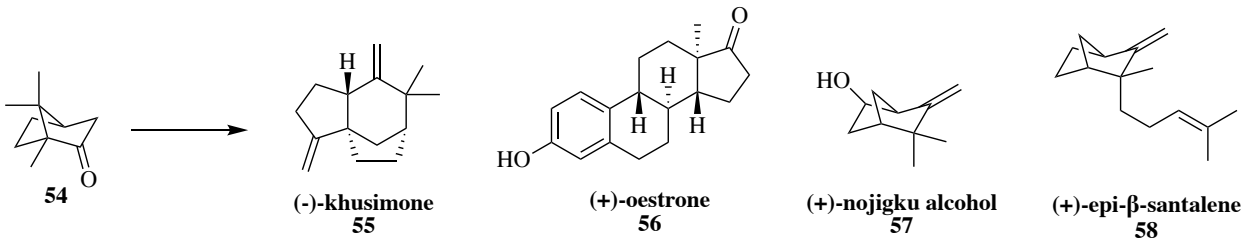
Accessing natural products via chemical synthesis is a very large area of organic chemistry; equally as large is using these natural products as readily available starting materials in order to prepare other targets. As it has been shown that these monoterpene compounds are able to be accessed efficiently, more recently chemists have grown interested in using these frameworks as starting materials to access more complex materials.[48]

1.3.3 Monoterpenes as starting materials in chemical synthesis

Although a more recent effort, much like the total synthesis of monoterpenes, there are a vast number of examples of using monoterpenes as starting materials.[48,69-70] One figure from Jarchow-Choy et al. illustrates the ability of just one monoterpene, (+)-camphor **54**, to be used to access more complex materials (Scheme 10).[48] The products that were able to be synthesized using this

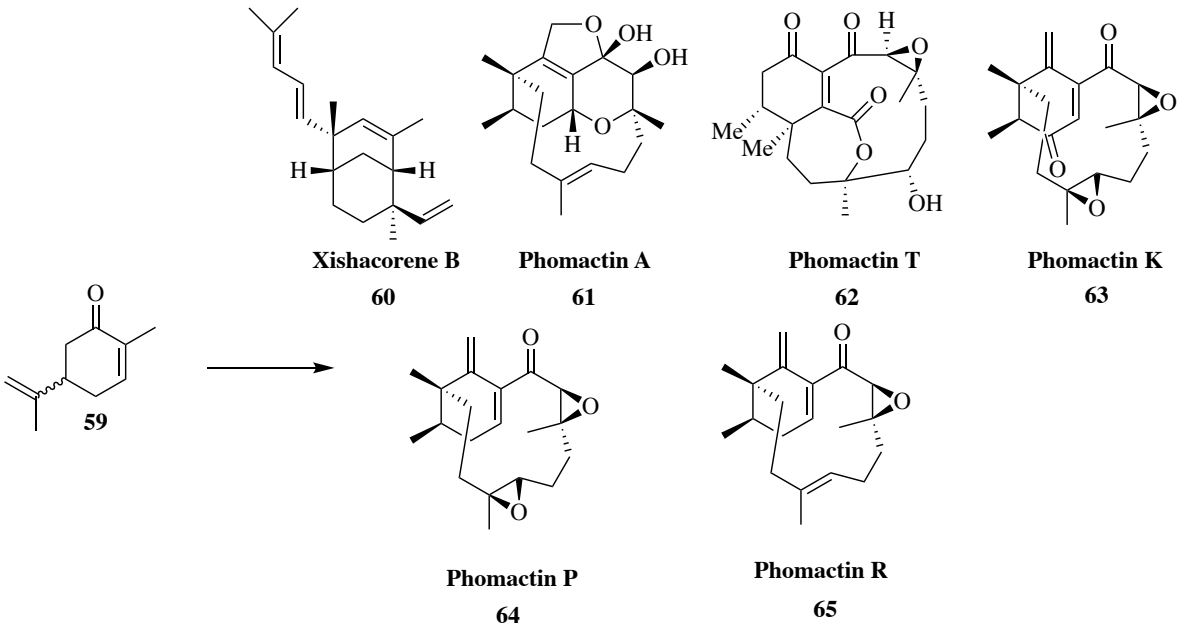
monoterpene include estrogen (+)-oestrone **56**, (-)-khusimone **55** and (+)-nojigku alcohol **57**, natural scents and (+)-epi-β-santalene **58** a natural flavouring.

Scheme 10. Synthesis of complex materials accessed using (+)-camphor as a starting material



The Sarpong group out of Berkeley university has many examples of using monoterpenes as starting materials in complex material synthesis, specifically using carvone **59**.[69,70] In two different instances, the group was able to utilize carvone in total syntheses to produce both (-)-xishacorene B as well as more complex terpenoids phomactins A, K, P, R and T (Scheme 11).[70] These diterpenoids were then able to be studied for their biological activity, and give access to derivatives that may not be able to be produced in nature.[70]

Scheme 11. Complex materials accessed using (R),(S)-carvone as a starting material

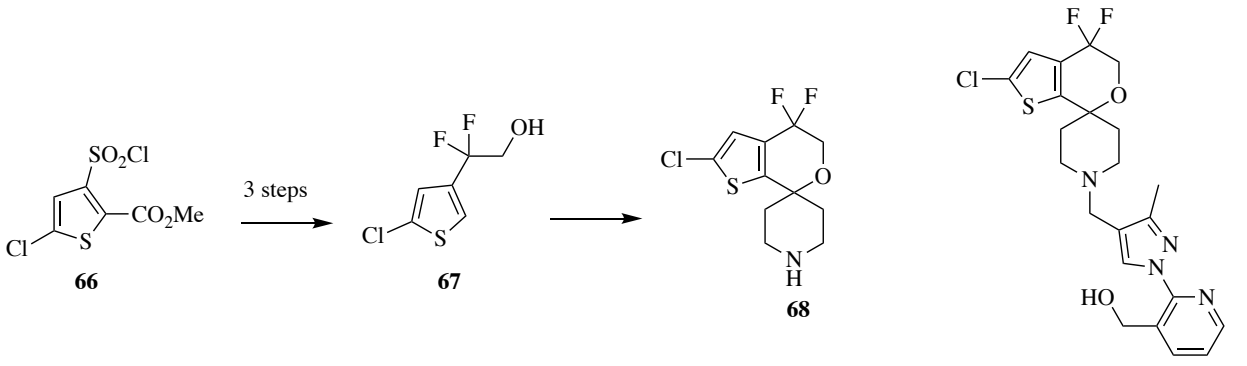


Monoterpenes continue to be studied as both starting materials and total synthesis products, as well as tested biologically as pharmaceuticals and industrially relevant compounds. Other emerging methods of introducing vinylcyclopropane moieties, such as photochemical conditions, are of interest as they similarly provide quick and efficient access to complex products.

1.4 Light-mediated rearrangement reactions

Light-mediated reactions are an advancing area of chemistry, rising in literature precedent due to their versatility and functional group tolerance.[71-72] Ease of reaction set-ups, along with mild reaction conditions can often make light-mediated reactions a more attractive approach than their transition metal catalyzed or thermal reaction counterparts.[73] With a shift towards green chemistry in recent years, visible-light mediated reactions are at the forefront of this initiative as they use inexpensive and readily available light sources, but require the use of photocatalysts.[74] While the presence of photocatalysts can help catalyze reactions, they can be expensive or difficult to remove, and such reactions that occur in the absence are of interest.[74-75] With over 71 reviews on organic reactions catalyzed by visible light, it would be impossible to summarize the scope of this field, however the remainder of this chapter will cover interesting contributions to medicinal

Scheme 12. The synthesis of late stage spriocycle intermediate toward ORL-1 antagonist from Eli Lilly and Stephenson[76-77]

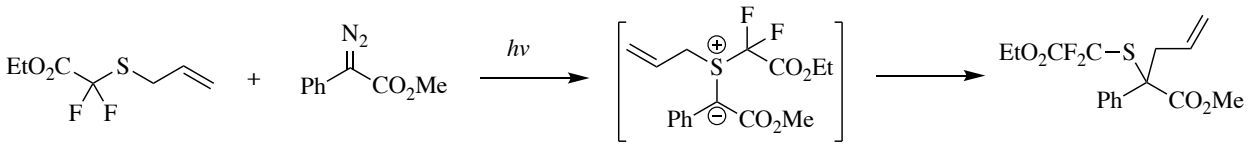


66 **67** **68** **ORL-1 antagonist 69**

chemistry with the absence of photocatalysts.[74] One such example emerged from the collaboration between Eli Lilly and the Stephenson group in which a visible light-mediated radical Smiles rearrangement was used to prepare a fluorinated intermediate with the intention of using it towards the synthesis of a complex ORL-1 antagonist (Scheme 12).[71,76-77] The synthesis shows the conversion of starting material **66** to intermediate **67** which occurs through a 3 step process, with the final step being the conversion via a light-mediated reaction; details of the synthesis can be found in references 76-77. Intermediate **67** was then converted to spirocycle **68**, assembling a large part of the core of ORL-1 antagonist **69**, on up to a 100 g scale.

With ethyl α,α-difluoroacetate sulfanylgroups having a presence in biologically relevant molecules such as anti-ulcer drugs, antibiotics and insecticides, Jana and Koenings sought to synthesize these moieties through a Doyle-Kirmse rearrangement reaction.[78] They were able to catalyze this rearrangement with rhodium on a number of substrates, as well as with visible light, in good yields (Scheme 13).

Scheme 13. Visible light induced metal free Doyle-Kirmse reaction[78]



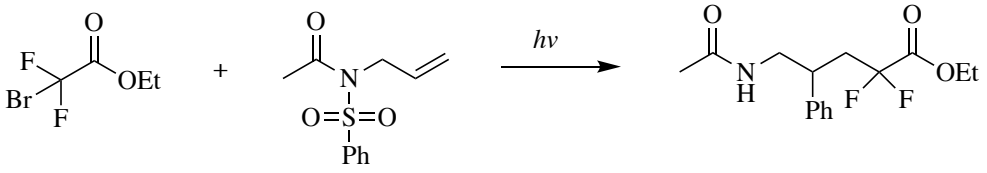
70 **71** **72**

In this metal free reaction, it is proposed that substrate **71** forms a carbene that can then form a ylide intermediate with substrate **70**. This reaction gives rise to product **72** with an ethyl α,α-difluoroacetate sulfanylgroup in place, along with a terminal alkene available for further functionalization.[78]

In another example from Whalley et al. a Truce-Smiles rearrangement was able to be performed under visible-light mediated conditions, in the absence of a photocatalyst.[79] This reaction is significant because it is a rearrangement based on light, but also involves the migration of aryl

rings, which opens the door for aryl starting materials to be converted to higher value, less readily available products.[79] Their process involved the addition of an unactivated alkene with a sulfonamide group **74** to a bromodifluoracetate **73** (Scheme 14). This reaction would go through a stable secondary radical intermediate, to give rise to arylated product **75**.

Scheme 14. Truce-Smiles rearrangement reaction from Whalley et al.[79]



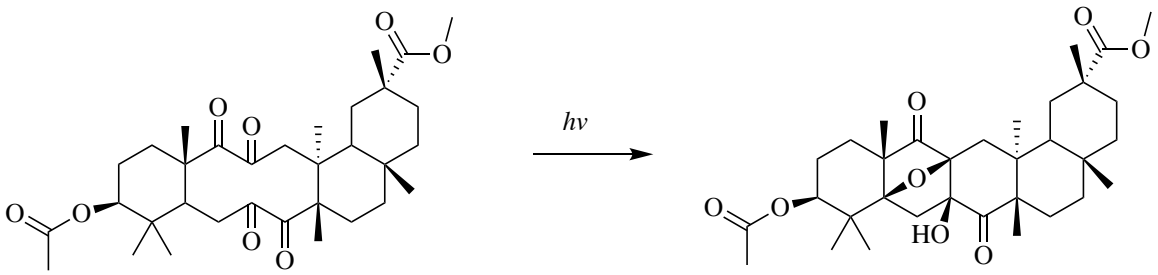
73 **74** **75**

Among the most popular of light mediated rearrangement reactions are photocyclization reactions, as they give rise to cyclic frameworks that may be harder to achieve through other synthetic routes.

1.4.1 Photocyclization reactions

Photocyclization reactions have been a staple to form ring systems in literature for over a decade, with the first example being published by Stobbe in 1905.[80] Since, these reactions have been staples in chemistry for forming ring systems. This chemistry is ever growing, especially in the synthesis of natural products or pharmaceuticals.[81-83] Providing rapid cyclization and access to strained systems which would otherwise be hard to achieve is a big draw to photocyclization reactions.[81] One example of beneficial photocyclization in respect to natural products is Ignatenko's synthesis using medicinally relevant tripterpenoids via Norrish-Yang photocyclization.[81,84-85] In this reaction, a derivative of trierpenoid byrolic acid **76** was irradiated and through an unexpected reaction pathway gave rise to product **77**, a 6/6/6/-fused structure to be added to the library of triperenoid analogues, with a complex backbone that would be difficult to access otherwise (Scheme 15).[81]

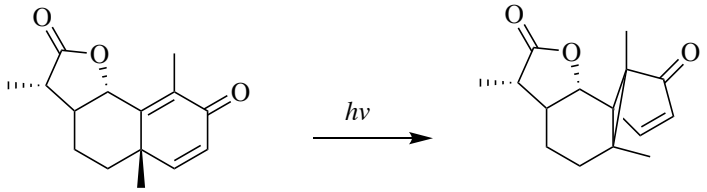
Scheme 15. Unexpected photocylization product of a byrolic acid derivative by Ignatenko[81]



76 **77**

Another example of these reactions relating to natural products, is the photochemical rearrangement of (-)-α-santonin **78** to lumisantonin **79**.[83, 86-90] This high yielding reaction provides a one-step synthetic route to sesquiterpene **79** from readily available starting material **78** (Scheme 16). As lactone containing sesquiterpenes exhibit a variety of biological activities and are subsequently found in a variety of natural medicinal sources, reactions involving these moieties are useful to the pharmaceutical and medicinal chemistry industries.[91]

Scheme 16. The photochemical conversion of (-)-α-santonin to lumisantonin



(-)-α-santonin
78

lumisantonin
79

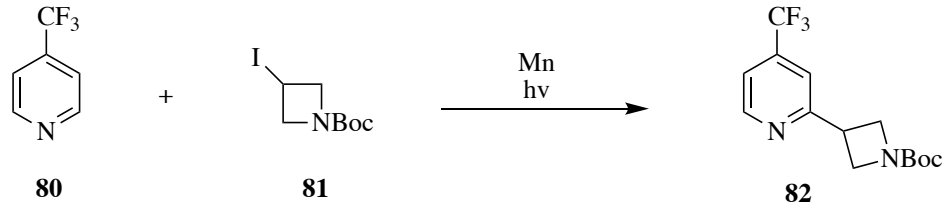
Another exciting area of photochemistry is the coupling of light with transition metal catalyzed reactions in order to improve the quality of these reactions.

1.4.2 Light mediated reactions coupled with transition metal catalysis

An area emerging from photochemistry is the C-C bond formation reactions, coupling light and transition metal catalysis.[92] Cooperative or dual catalysis, has been found to proceed through single electron transfer from the photocatalysts to the transition metal to break and form bonds.[92-94] as mentioned, photocatalysts can be expensive or unstable, and therefore even more recently has been

works developing these bond forming reactions with metal complexes of Mn, Co, Cu and Pd.[92,95] Some interesting reactions with these metals are outlined, showing potential applications of combining these two areas of chemistry. Primarily, Frenette and Fadeyi reported a light-mediated, Mn catalyzed Minisci reaction to obtain akylated quinolines.[92,96] In this reaction, a Mn catalyst radical is formed via a photochemical reaction, which then undergoes a SET reaction with alkyl iodide **81**.[92,96] This radical then attacks the heteroaromatic substrate **80** at the electron deficient position and subsequent SET transfer gives rise to alkylated quinoline **82** without the need for a traditional photocatalyst (Scheme 17).[92,96]

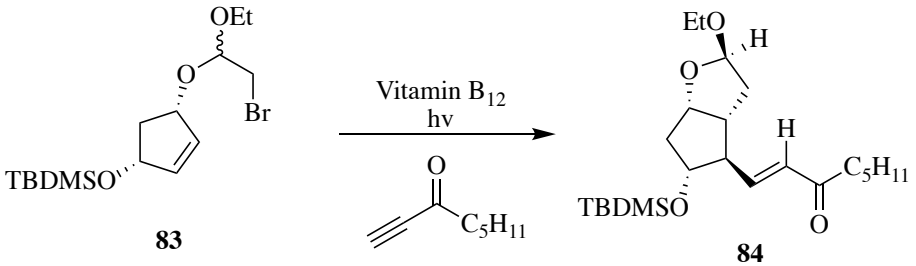
Scheme 17. Light-mediated Mn catalyzed Minisci reaction from Frenette and Fadeyi[96]



80 **81** **82**

An interesting example from Scheffold et al. utilizes vitamin B_{12} as a cobalt catalyst in order to synthesize the core of prostaglandin $F_{2\alpha}$.[92,97] The combination of cobalt catalyst with visible light provided a SET process yielding **84** as a mixture of isomers (Scheme 18).[92,97]

Scheme 18. Vitamin B_{12} as a cobalt catalyst for the synthesis of prostaglandin $F_{2\alpha}$ from Scheffold et al.[97]

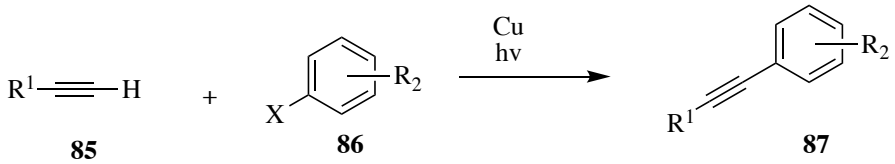


83 **84**

Finally, there are multiple examples in the literature that illustrate Cu catalyzed visible light mediataed Sonogashira coupling reactions.[92,98-99] Scheme 19 from Kanchelra et al. summarizes

Hwang's work towards the first visible-light mediated Sonogashira coupling reaction.[92,98] In this example, the authors use only CuCl as a catalyst, with no additional ligands, and visible light in order to couple aryl iodides and bromides to substituted terminal alkynes.[92,98]

Scheme 19. Hwang's work towards a Cu catalyzed Sonogashira coupling reaction with visible-light[98]



While this works focuses on the coupling of first row transition metals with visible-light to induce reactivity, there are also plenty of examples of reactivity induced via Pd catalysis under similar conditions.[92, 99-104]

1.5 Conclusion

The synthesis of natural products and complex molecules requires the use of intricate starting materials and chemistry. Vinycyclopropanes, both with activating groups and unactivated with transition metal catalysts are good starting materials for the formation of complex products through cycloaddition reactions.[1-40] Similarly, terpenes provide good starting materials as they are readily available, already complex molecules, that can undergo reactions to quickly form more complex structures.[41-70] Finally, light-mediated reactions are continually evolving to make standard reactions, and complex materials, in an inexpensive and efficient way.[71-104] All of these tactics can be employed in order to work towards building new complex targets of interest.

1.6 Chapter summaries and role of contributors

Chapter One introduces various methods of synthesizing complex materials. Cycloadditions of both activated and unactivated vinylcyclopropanes are introduced. Terpene natural products as

starting materials and products, as well as light-mediated, specifically photocyclization reactions, are discussed as means to reach target molecules.

Chapter Two aims to introduce both intramolecular and intermolecular vinylcyclopropanes and their syntheses. Both Dr. Ben Rowley and Anna Tang assisted in completing syntheses of target molecules **95** and **133** respectively via literature precedent reactions. Dr. Evgueni Gorobets and Dr. Jeffrey Vanhumbeck provided synthesized ligands **97** and **96** respectively to be included in reaction screening. The chapter covers the optimization of substrate development before reaching target molecules, as well as the screening of three compounds for their cycloaddition reactivity. Chapter two also covers novel reactivity found via 1,6-enyne vinylcyclopropanes with rhodium catalysis.

Chapter Three introduces the idea of using vinylcyclopropane containing monoterpenes as starting materials for cycloaddition reactions. The chapter summarizes the unexpected major product formation, and reaction optimization attempts in order to induce the preferred reaction pathway for two monoterpenes.

Chapter Four introduces the work of Dr. Evgueni Gorobets in the photocyclization of a divinylketone in order to synthesize natural product analogues.[86] The work in this chapter is complementary with an unsubstituted core in order to try and induce the reactivity that was observed with light sources, with transition metal catalysis. Reaction screening of a divinyl ketone starting material was performed and summarized with the assistance of Dr. Evgueni Gorobets in preparation of starting material following his literature protocol.[86]

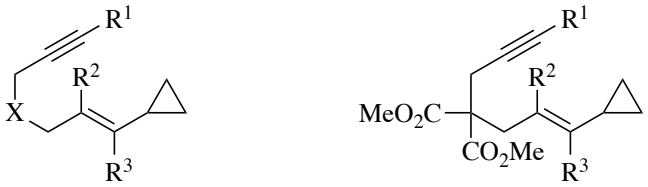
Chapter 5 summarizes future work to be undergone in relation to the projects discussed in this thesis. The novel reactivity of 1,6-enynes will be further investigated in order to fully understand the mechanism. A second round of screening for light-mediated rearrangement reactions with

transition metal catalysis is underway and will be undertaken by another member of the Derksen group.

Chapter Two: Investigating the reactivity of unactivated vinylcyclopropanes

2.1 Synthesis of an unactivated enyne vinylcyclopropane

As discussed in chapter one, intramolecular [5+2] cycloadditions of activated vinylcyclopropanes, usually contains geminal diester groups, such as **89**, are well known reactions.(Scheme 3).[3, 10-14] Interestingly, less activated enynes have been found to undergo these cycloadditions, utilizing a heteroatom at the 4 position, such as compound **88** (Figure 6). [3,10-12,20-22] While these substrates are less activated, like stated in chapter one, they typically require the use of heavier metals such as rhodium, ruthenium and iridium.[3-4,10-14,18-34, 38-40]

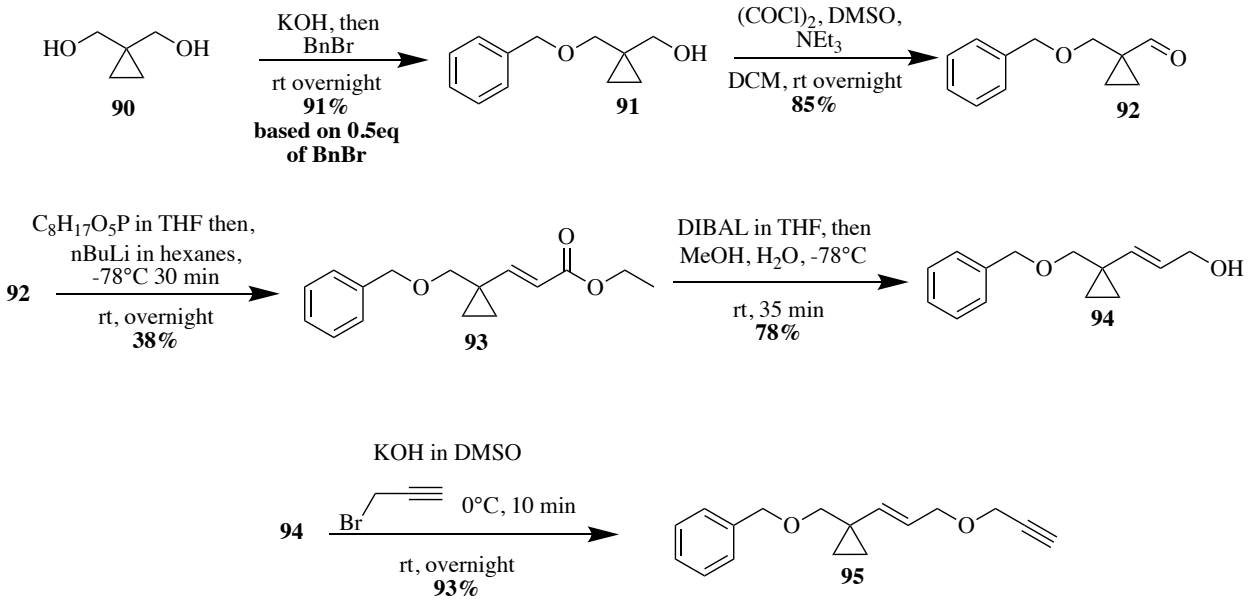


88 **89**

Figure 6. Examples of commonly synthesized 1,6-enyne vinylcyclopropanes

One of the focuses in the Derksen research group is to study the reactivity of 1,6-enyne vinylcyclopropanes without the use of activating groups, and with more abundant first row transition metal catalysts. As it has been shown that enyne vinylcyclopropanes can be intermediates in natural product synthesis, the development of these cycloaddition reactions without the need for further removal of activating groups, with earth abundant catalysts, is of interest. The synthesis of **95** was carried out by Anna Tang, which could then be used for high-throughput reaction condition screening in order to test reactivity (Scheme 20**)**. Beginning with a monobenzylation of readily available starting material 1,1-bis(hydroxymethyl)cyclopropane, a series of generally high yieleding reactions were able to be performed in order to produce gram scale quantities of 1,6 enyne vinylcyclopropane **95**.

Scheme 20. Synthesis followed to produce 1,6-enyne 95



2.1.1 High-throughput screening of unactivated enyne vinylcyclopropane reactivity

As the intramolecular reactivity of this vinylcyclopropane had not been studied before, reaction conditions were chosen to cover a variety of reactivity pathways. Conditions were chosen in order to cover as much variability as possible, assess what combinations induce reactivity and analyze those components in depth, in order to avoid running every reaction combination; which would take ample time and resources. For metal sources, first row transition metals were chosen based on availability and ease of use, i.e. metal sources with high air sensitivity were not chosen to make scalable syntheses realistic. For ligands, a variety of monodentate, bidentate and polydentate ligands were used in order to get a variety of complexation with metal sources to create different catalysts. Both **L1** and **L2** were synthesized at University of Calgary, with **L1** (Figure 8) being provided by the Van Humbeck lab and **L2** (Figure 8) being synthesized in the Derksen lab by Dr. Evgueni Gorobets. Finally, for intramolecular reactivity, an additive was used, consisting of a variety of acids, bases, oxidants and reductants; the premise behind using additives being to cover the basis of all different kinds of reactive intermediates and essentially trapping these products.

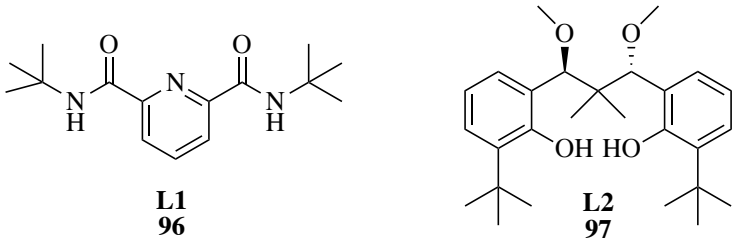


Figure 7. Ligands provided by Dr. Jeffrey Van Humbeck and Dr. Evgueni Gorobets used in reaction screening

With a variety of components chosen, high-throughput screening for substrate **95** began with a 24 reaction screen (Table 1). After 2 hours, these reactions were analyzed by GCMS to look for absence of starting material or presence of a new prominent peak which does not correspond to any of the components present in the initial reaction mixture. From this screen, reaction 1 seemed to exhibit the formation of new products via GC-MS and were therefore scaled up in order to try and identify these products. Following running this reaction on a 40 mg scale and running reverse phase SiO_2 column chromatography, the only identifiable product was starting material and the result was therefore abandoned.

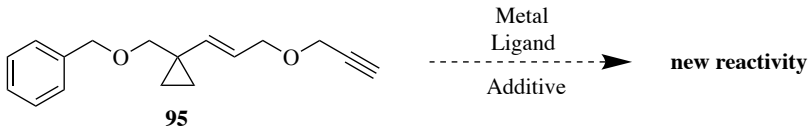


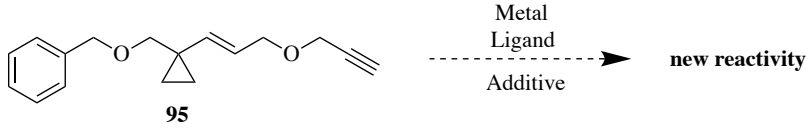
Table 1. Reaction screen of intramolecular VCP cycloadditions via substrate 95[a]

Reaction	Metal	Ligand	Additive	Results
1	$CuBr_2$	Xphos	benzoic acid	NR
2	$CoBr_2$	Xphos	piperidine	NR
3	$FeCl_2$	Xphos	cyclohexadiene	NR
4	$NiCl_2$	Xphos	benzoic acid	NR
5	$CuBr_2$	phenanthroline	formic acid	NR
6	$CoBr_2$	phenanthroline	imidazole	NR
7	$FeCl_2$	phenanthroline	$AgPF_6$	NR
8	$NiCl_2$	phenanthroline	piperidine	NR
9	$CuBr_2$	DPPF	TFA	NR
10	$CoBr_2$	DPPF	none	NR
11	$FeCl_2$	DPPF	B_2Pin_2	NR

12	$NiCl_2$	DPPF	cyclohexadiene	NR
13	$CuBr_2$	BINOL	none	NR
14	$CoBr_2$	BINOL	K_2CO_3	NR
15	$FeCl_2$	BINOL	DDQ	NR
16	$NiCl_2$	BINOL	formic acid	NR
17	$CuBr_2$	L1	piperidine	NR
18	$CoBr_2$	L1	cyclohexadiene	NR
19	$FeCl_2$	L1	benzoic acid	NR
20	$NiCl_2$	L1	imidazole	NR
21	$CuBr_2$	L2	imidazole	NR
22	$CoBr_2$	L2	$AgPF_6$	NR
23	$FeCl_2$	L2	formic acid	NR
24	$NiCl_2$	L2	$AgPF_6$	NR

[a] Reactions were performed on a 0.04 mmol scale, with 10 mol% metal, 15 mol% ligand and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

After not finding any tangible new results from the scaled-up reactions, a second reaction screen was performed on substrate **95**. The second screen contained 24 more reactions, with different combinations of the same reaction components (Table 2). From this screen, no reactions showed promising formation of new products that could be isolated, and reactions were not scaled up.



95

Table 2. Second reaction screen of intramolecular VCP cycloadditions via substrate 95[a]

Reaction	Metal	Ligand	Additive	Results
1	$CuBr_2$	Xphos	none	NR
2	$CoBr_2$	Xphos	B_2Pin_2	NR
3	$FeCl_2$	Xphos	TFA	NR
4	$NiCl_2$	Xphos	TFA	NR
5	$CuBr_2$	phenanthroline	K_2CO_3	NR
6	$CoBr_2$	phenanthroline	DDQ	NR
7	$FeCl_2$	phenanthroline	none	NR
8	$NiCl_2$	phenanthroline	none	NR
9	$CuBr_2$	DPPF	cyclohexadiene	NR
10	$CoBr_2$	DPPF	benzoic acid	NR
11	$FeCl_2$	DPPF	piperidine	NR
12	$NiCl_2$	DPPF	B_2Pin_2	NR
13	$CuBr_2$	BINOL	$AgPF_6$	NR
14	$CoBr_2$	BINOL	formic acid	NR

15	$FeCl_2$	BINOL	imidazole	NR
16	$NiCl_2$	BINOL	none	NR
17	$CuBr_2$	L1	B_2Pin_2	NR
18	$CoBr_2$	L1	TFA	NR
19	$FeCl_2$	L1	none	NR
20	$NiCl_2$	L1	K_2CO_3	NR
21	$CuBr_2$	L2	DDQ	NR
22	$CoBr_2$	L2	none	NR
23	$FeCl_2$	L2	K_2CO_3	NR
24	$NiCl_2$	L2	DDQ	NR

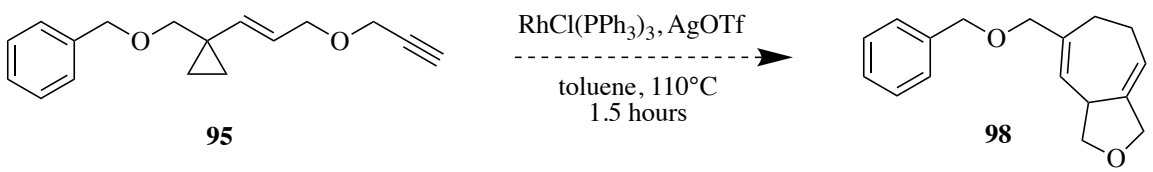
[a] Reactions were performed on a 0.04 mmol scale, with 10 mol% metal, 15 mol% ligand and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

After two reaction screens, it was deemed that with the small scales of these reactions, along with the complex nature these reactions seemed to proceed through (i.e. formation of many by-products), isolating and identifying new products may be more difficult than anticipated. Therefore, a new approach was proposed to synthesize the known reaction product of an intramolecular cycloaddition using rhodium catalysis and use this product as a standard. Moving forward, only the reactions that contained that standard peak would need to be analyzed and scaled up, thus eliminating the crux of sorting through data which wasn't of interest.

2.1.2 Synthesis of [5+2] cycloaddition product via literature conditions

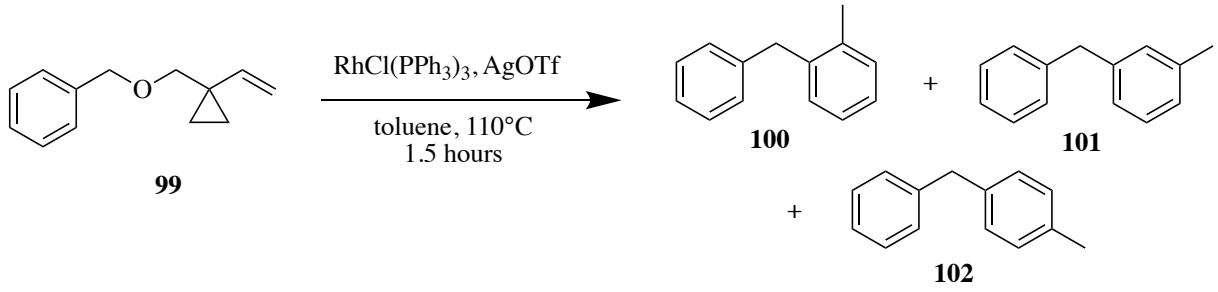
To synthesize a GCMS standard of the expected intramolecular cycloaddition of substrate **95**, literature procedure from Wender et.al. was followed.[10] Although the literature substrate did not contain a benzyl protected alcohol, and instead had a terminal alcohol, it was thought that it would react in the same manner. The proposed product was that of an intramolecular [5+2] cycloaddition giving product **98** (Scheme 21).

Scheme 21. Proposed cycloaddition using literature conditions from Wender et. al.[10]



When the reaction was worked up after 1.5 hours and purified, however, the components did not seem to match either the proposed product or the VCP starting material by ^{1}H NMR spectroscopy analysis. It was noted by Anna Tang that none of the components appeared to contain the diagnostic benzyl methylene peak found in both of the starting material and product by ^{1}H NMR spectroscopy. This led to the hypothesis that the benzyl protecting group was falling off during the reaction and participating in the formation of a new product. To test this theory, another reaction was performed with a simpler VCP whose synthesis could be done in a timely manner, but still contained a benzyl protecting group, and therefore should give the same by-product if this deprotection was indeed occurring (Scheme 22).

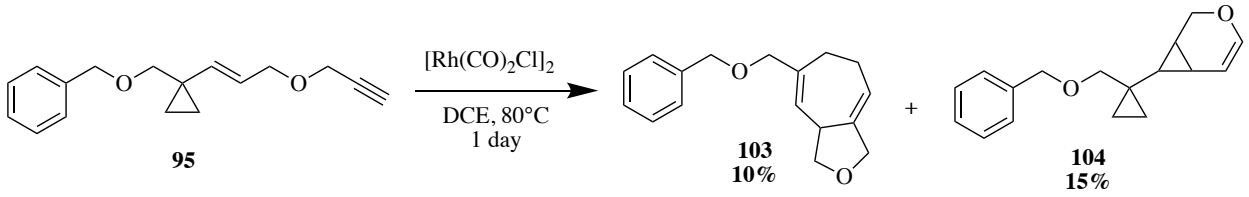
Scheme 22. Experiment to test the durability of the benzyl protecting group



99 **100** **101** **102**

From this reaction, it was clear to see that the same product was being formed via GC-MS analysis using the unknown product peak as a standard. Through mass analysis of this peak, it was deduced that the benzyl group was indeed falling off, but not interacting with another part of the molecule as originally hypothesized; instead, the benzyl group was deprotecting, and interacting with the solvent, toluene. This interaction gives rise to the main products of the reaction, the isomers shown in Scheme 22. With this information it was clear that a change of solvent needed to be undergone. It can be noted that in the original Wender paper, reaction conditions were changed from toluene to DCE with a complimentary change in rhodium catalyst rhodium catalyst without justification. This second set of reaction conditions was then

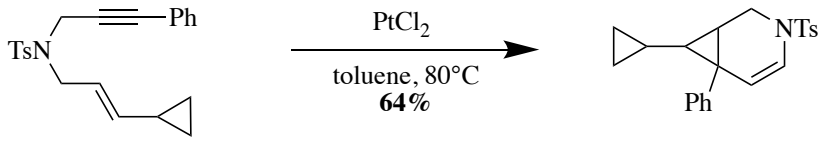
Scheme 23. Cycloaddition reaction with second set of reaction conditions



tried in order to synthesize the expected cycloaddtion product (Scheme 23). Following a solvent change from toluene to DCE, as well as a change to the rhodium catalyst, the by-product seen in the previous reaction was seen to be alleviated via GC-MS analysis. Although the reaction took 1-day vs the 1.5-hour reaction time of the previous attempt, it was seen through ^{1}H NMR spectroscopy that the product **103** was indeed being formed. Notably, however, is that the product was only being formed in a 10% yield and was not the major product. The major product, when examined by ^{1}H NMR spectroscopy, appeared to the diagnostic peaks for both the cyclopropane and alkene from the VCP starting material, however the chemical shifts and coupling patterns were different. Notably, the alkyne peak was absent, indicating that some sort of rearrangement had taken place, which was worthwhile deciphering as this was the favourable pathway of the reaction. Upon extensive analysis of both 1D NMR and 2D NMR spectroscopy including COSY, HMBC, HSQC and mass analysis, substrate **104** was deduced as the major product of the reaction. As this new bi-cyclopropyl structure was unexpected, and an intriguingly complex structure, it was of interest to explore its literature precedent.

Upon a substructure search of the product, a paper was found from Chung et.al where a very similar structure was used as a starting material for a $Rh^{(I)}$-catalyzed cycloisomerization reaction. The general procedure for the synthesis of the starting materials used for these cycloisomerization reactions used 1,6-enynes with a platinum catalyst (Scheme 24).[21]

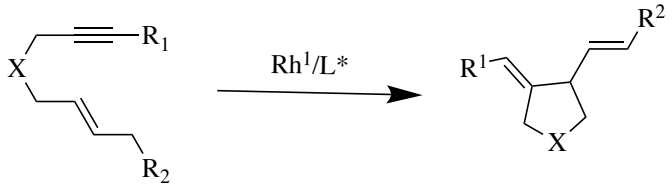
Scheme 24. Literature precedent for synthesis of bi-cyclopropyl substrates from 1,6-enynes



105 **106**

Having a precedent for these substrates initiated a literature search, showing that 1,6-enynes can actively undergo these rearrangement reactions to provide bi-cyclopropyl products, however authors report these reactions happening with platinum and gold catalysis.[21-22] When these enyne substrates are subjected to rhodium and ruthenium catalysts in literature, they are noted to give access to different cyclized products such as the general product shown in Scheme 25 proposed by Zhang et.al.[105]

Scheme 25. Rhodium cyclization reactions of 1,6-enynes by Zhang et. al.[105]

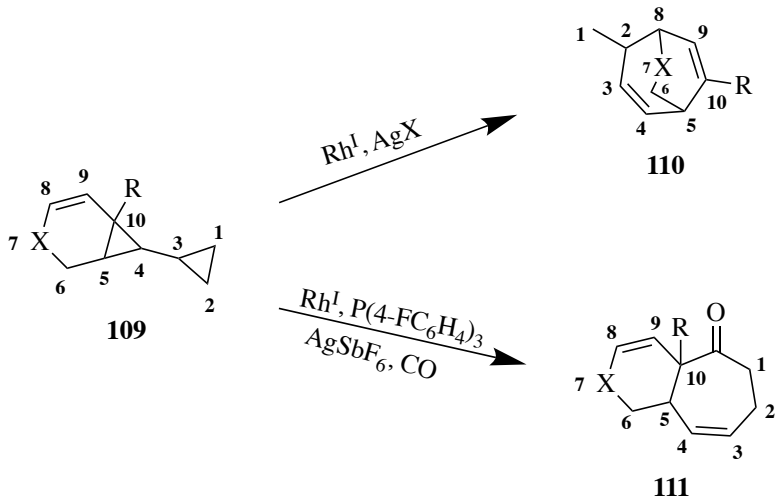


107 **108**

Another interesting contrast of the witnessed reactivity versus the literature precedent reactivity is the lack of substitution on the terminal alkyne of substrate **95**. In all of the found literature examples of these VCP enyne cyclization reactions with Pt or Ag resembling the substrate, there was a requirement of a substituent on the alkyne.[21-22] Therefore, the observed reactivity seemed to be first in class in more way than one, which sparked the question of what these cyclized products are used for. Interestingly, these products are used primarily in rhodium catalysis to further induce cyloisomerzation reactions. These are useful reactions because when performed with a rhodium catalyst and silver salt, they can give rise to heterobicylces such as compound **110** shown in Scheme 26, which can be found in natural alkaloids.[21-22] When the same reaction is performed, but

trapped with carbon monoxide, these substrates can give rise to 6-7 fused ring systems such as **111** shown in Scheme 26.[21-22] These products are of interest as accessing substituted 7 membered rings is an inherit challenge in chemical synthesis, but an important one as these substituted ring systems are prominent in natural products.[15]

Scheme 26. Rhodium cycloisomerization reactions with bi-cyclopropyl substrates



As it was shown that these structures can give rise to chemically and biologically interesting products, this serendipitous discovery was analyzed to decide the next experiment to be performed. It was proposed that since the bi-cyclopropyl product was able to be synthesized using rhodium catalysis, and the cycloisomerization reactions require the same component, that this reaction would be able to be performed in a one pot synthesis from 1,6-enyne to either bicycles or 6,7-ring system.

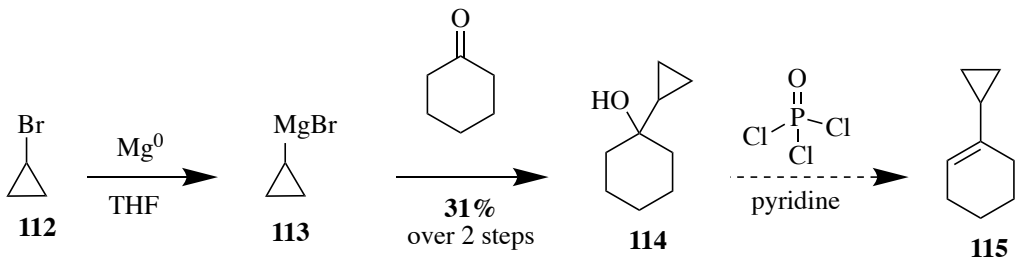
2.2 Synthesis of unactivated endo- and exocyclic vinylcyclopropanes

With some reactivity being shown with the intramolecular vinycyclopropane **95** using first row transition metals, it was proposed that similar reactivity may be observed with intermolecular cycloadditions. While [5+2] cycloadditions of intermolecular VCPs with alkynes have been broadly studied, there are less examples of this reactivity being induced without the use of

activating groups such as donor acceptor substituents, as mentioned in Chapter One.[3-6] The examples of these reactions that do use unactivated substrates, much like the intramolecular reactions, favour the use of heavier metals.[3-6] With it being known that intermolecular cycloaddition reactions can provide access to medium sized rings, with some level of variability depending on the alkyne used, the Derksen research group was interested in testing the reactivity of endo- and exocyclic unactivatived vinylcyclopropanes with alkynes using first row transition metal catalysts.

The first step to building this program was the development of a scalable and cost-effective synthesis of endo- and exocyclic VCP substrates that could be used in high-throughput reaction screening. The first generation of endocyclic vinylcyclopropane was proposed as an all carbon substrate available through a 3 step, 2 pot synthesis (Scheme 27). The synthesis was attempted and intermediate **114** was able to be accessed in a 31% yield via a Grignard reaction. Problems arose with the last step of the synthesis, with multiple elimination reaction conditions being tried, however the substrate experienced issues with volatility. With the final product being too volatile, no appreciable amount of material was able to be isolated, and therefore was not a realistic target for a scalable synthesis.

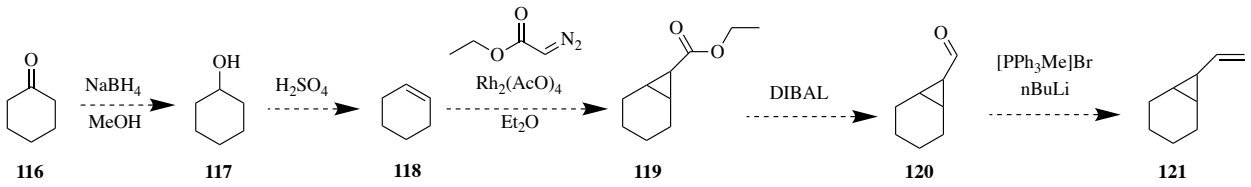
Scheme 27. Proposed synthesis for the first generation endocyclic vinylcyclopropane



The first generation of exocyclic vinylcyclopropane was similarly designed as an all carbon target available through a short synthesis with cost effective reagents (Scheme 28). However, since

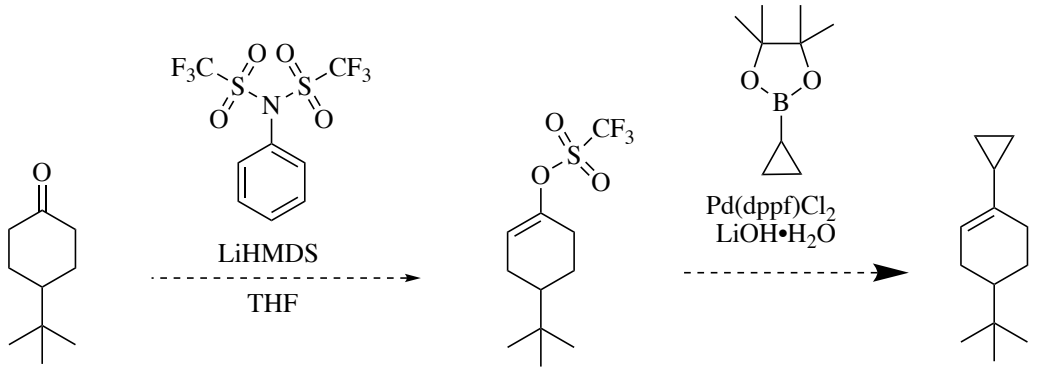
problems had arisen with the volatility of the endocylic substrate, it was deemed likely that the same problems would occur with the exocyclic target and the synthesis was not attempted. Instead, for scalability and consistency between substrates, both proposed syntheses were reworked to include substrates with a higher molecular weight.

Scheme 28. Proposed synthesis for the first generation exocyclic vinylcyclopropane



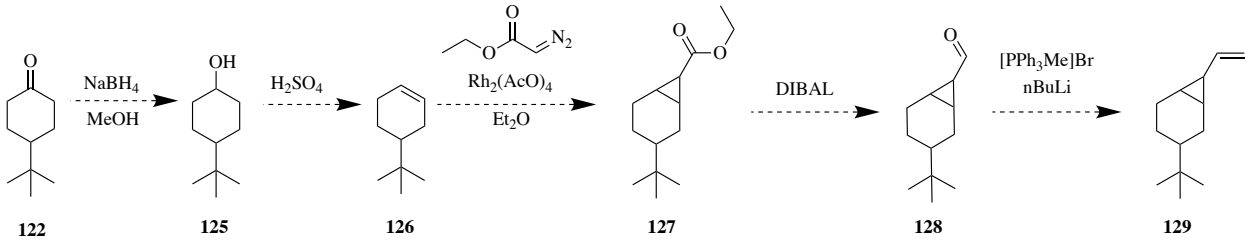
The second generation of endocyclic vinylcyclopropane was another all carbon skeleton, with the addition of a tert-butyl group para to the cyclopropane in order to increase the molecular weight and help with volatility without introducing activating groups. After attempting the same general proposed synthesis as the first endocyclic VCP and having issues with yields, the proposed synthesis was adjusted to include a vinyl triflate **123** intermediate (Scheme 29). While the first step of the reaction was still low yielding, due to availability of the starting material, gram scales of **123** were still able to be obtained. Obtaining the product through a cross coupling reaction proved to be difficult as problems arose during the purification step. Due to the extreme non-polar nature of the target, even slow normal phase column chromatography in a non-polar mobile phase (100% hexanes) was not enough to separate any by-products. Silver nitrate impregnated silica gel is precedented as being helpful for difficult separations such as isomers, so this was also tried. However all attempts at purification failed to give a pure product; this coupled with the non-UV

Scheme 29. Proposed synthesis for the second generation endocyclic vinylcyclopropane



active nature of the product deemed it unfit for a scalable synthesis. The second generation of exocyclic vinycyclopropane was much the same as the first generation, with the exception of tert-butyl cyclohexanone **122** as a starting material in order to increase molecular weight and decrease volatility (Scheme 30). However, with the purification issues of the counter endocyclic vinylcyclopropane, the synthesis was stopped after optimization of the first step was underway. Instead, the synthetic route was re-evaluated in an attempt to fix some key problems: the substrates needed to be UV active, non-volatile, and include heteroatoms in order to help with purification and reaction monitoring, without introducing activation to the targets.

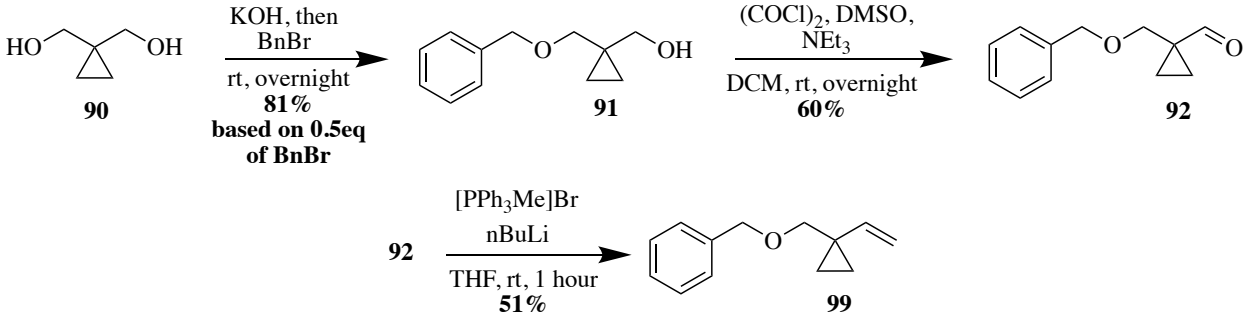
Scheme 30. Proposed synthesis for the second generation exocyclic vinylcyclopropane



For the third generation of vinylcyclopropane, the starting material was a cyclopropane diol that was found commercially to be cost effective and compatible with a scalable synthesis. As the starting material was not easily translatable to a ring system, the exocyclic and endocyclic VCP starting materials were abandoned, and instead two new synthetic routes were designed. The first

advantage to using the commercial diol, is that mono-benzyl protecting to give intermediate **91** covers two of the primary concerns from previous strategies, as it provides a UV handle as well as upping the molecular weight to address volatility. From this intermediate, two subsequent steps provide **99** in a high yielding synthesis that allows for gram scale quantities to be prepared, by Anna Tang, for high-throughput reaction screening (Scheme 31).

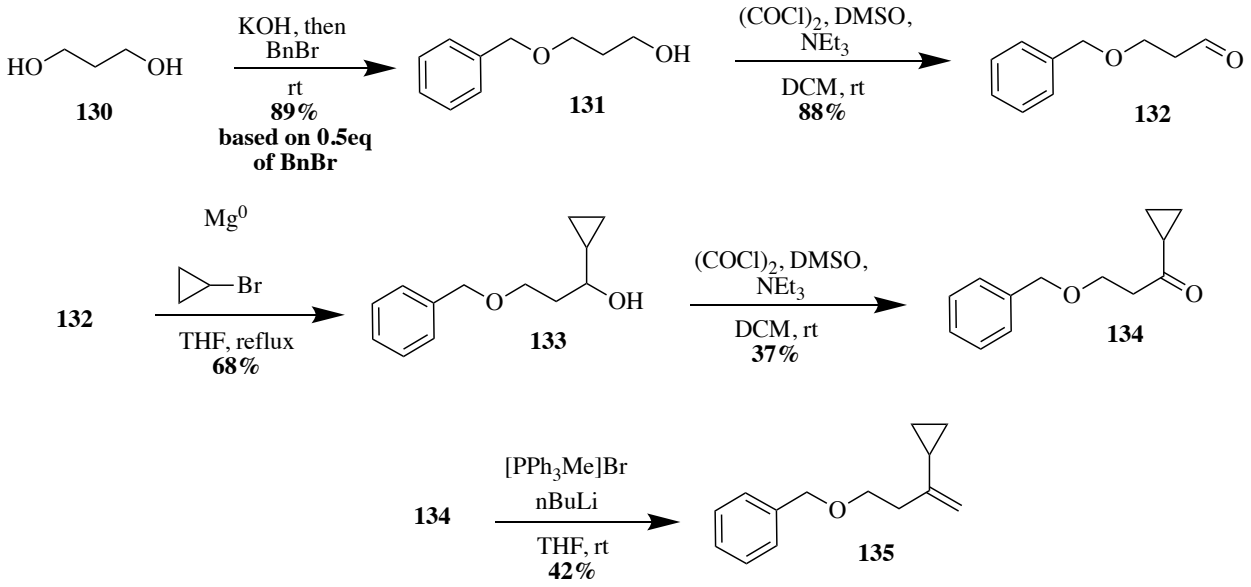
Scheme 31. Synthetic route to provide final vincylcylopropane 99



Although endocyclic and exocyclic VCPs were abandoned, the interest in making two complementary substrates was still there. The use of a symmetric diol was still of interest, as it provided the characteristics of interest in one easy, high yielding step. Instead of starting with the same diol, however, a search of commercial sources provided cost effective **99** which could be used in a complementary synthesis. In the synthesis of the second substrate performed by Dr. Ben Rowley, well known and generally high yielding reactions can be used in order to produce **135** in a five-step synthesis (Scheme 32).

While these substrates initially seemed to fit all the criteria needed for a scalable synthesis that can be used for reaction screening, it was later noted that substrate **135** could present problems in this

Scheme 32. Synthetic route to provide final vinylcyclopropane 135

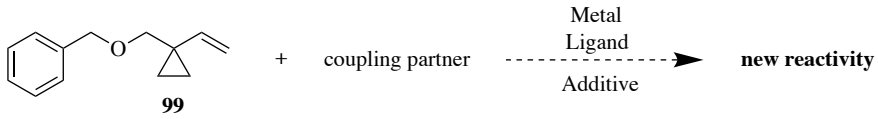


setting. As the placement of the double bond in this vinylcyclopropane allows for isomerization, this could make reaction screens more complicated by giving what looks like a new compound, but not one of interest. Nevertheless, both compound **99** and **135** were subjected to high-throughput screening in order to test their reactivity.

2.2.1 High-throughput screening of unactivated intermolecular vinylcyclopropane cycloadditions

Similarly, to the intramolecular VCP reactivity, metal sources, ligands and additives for screening were chosen based on cost effectiveness and variability to cover different reaction pathways. As substrates **99** and **135** were investigated for intermolecular reactivity, another component was required to be added to the reaction screen: coupling partner. As VCPs can undergo a variety of different cycloadditions, including but not limited to [3+2] and [5+2], a variety of alkenes and alkynes were included to account for these reaction pathways. [3-6] The first reaction screen was performed on substrate **99** and included 8 reactions which were analyzed by GC-MS (Table 3).

From this screen, reaction 3 appeared to be giving a new product peak and was therefore scaled up and run on a 30 mg scale. However, due to the small scale and



99

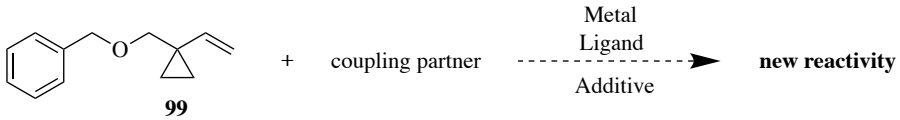
Table 3. Reaction screen of intermolecular cycloadditions via substrate 99[a]

Reaction	Metal	Ligand	Coupling partner	Additive	Results
1	$CuBr_2$	Xphos	benzaldehyde	benzoic acid	NR
2	$CoBr_2$	Xphos	methyl acrylate	piperidine	NR
3	$FeCl_2$	Xphos	benzyl bromide	cyclohexadiene	new peak
4	$NiCl_2$	Xphos	phenyl acetylene	benzoic acid	NR
5	$CuBr_2$	phenanthroline	allyl TMS	formic acid	NR
6	$CoBr_2$	phenanthroline	benzaldehyde	imidazole	NR
7	$FeCl_2$	phenanthroline	methyl acrylate	$AgPF_6$	NR
8	$NiCl_2$	phenanothroline	benzyl bromide	piperidine	NR

[a] Reactions were performed on a 0.03 mmol scale, with 10 mol% metal, 15 mol% ligand, 1.0 eq of coupling partner and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

complexity of the reaction, no tangible or reproducible results were able to be obtained and this result was abandoned to do another larger screen

The second reaction screen on substrate **99** was comprised of 20 reactions, yielding two interesting results via GC-MS analysis, reaction 11 and reaction 14 (Table 4). Both reactions were scaled up and rerun on a 50 mg scale in order to separate the components and identify the new products formed. For reaction 11, reproducible results were not able to be obtained and this result was deemed a false positive. For reaction 19, upon separation of components, a product was obtained whose mass seemed to correlate to that of the cycloadditions products (276 g/mol).



99

Table 4. Second reaction screen of intermolecular cycloadditions via substrate 99[a]

Reaction	Metal	Ligand	Coupling partner	Additive	Results
1	$CuBr_2$	$Ph_2P(CH_2)_3PPh_2$	phenyl acetylene	TFA	NR

2	$CoBr_2$	$Ph_2P(CH_2)_3PPh_2$	allyl TMS	none	NR
3	$FeCl_2$	$Ph_2P(CH_2)_3PPh_2$	benzaldehyde	B_2Pin_2	NR
4	$NiCl_2$	$Ph_2P(CH_2)_3PPh_2$	methyl acrylate	cyclohexadiene	NR
5	$CuBr_2$	BINOL	benzyl bromide	none	NR
6	$CoBr_2$	BINOL	phenyl acetylene	K_2CO_3	NR
7	$FeCl_2$	BINOL	allyl TMS	DDQ	NR
8	$NiCl_2$	BINOL	benzaldehyde	formic acid	NR
9	$CuBr_2$	L1	methyl acrylate	piperidine	NR
10	$CoBr_2$	L1	benzyl bromide	cyclohexadiene	NR
11	$FeCl_2$	L1	phenyl acetylene	benzoic acid	new peak
12	$NiCl_2$	L1	allyl TMS	imidazole	NR
13	$CuBr_2$	L2	benzaldehyde	imidazole	NR
14	$CoBr_2$	L2	methyl acrylate	$AgPF_6$	new peak
15	$FeCl_2$	L2	benzyl bromide	formic acid	NR
16	$NiCl_2$	L2	phenyl acetylene	$AgPF_6$	NR
17	$CuBr_2$	Xphos	allyl TMS	none	NR
18	$CoBr_2$	Xphos	benzaldehyde	B_2Pin_2	NR
19	$FeCl_2$	Xphos	methyl acrylate	TFA	NR
20	$NiCl_2$	Xphos	benzyl bromide	TFA	NR

[a] Reactions were performed on a 0.05 mmol scale, with 10 mol% metal, 15 mol% ligand, 1.0 eq of coupling partner and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

With reaction 14 in hand that seemed to give access to a cycloaddition product, another screen was performed with these conditions (Table 5). This screen was meant to show what components of this reaction are essential to giving the product being chased, and therefore 8 reactions were performed: reaction 7 being a rerun of the original for reproducibility, and 1-7 leaving out one component and monitoring if the reaction product was still formed. These reactions were performed and purified by prep TLC in order to be able to quickly analyze products. From this screen, it was found that the metal source seemed to be giving little to no contribution to the reaction, as reaction 2 gave the same results as reactions in which the metal was included. The same could be said for the coupling partner, as when methyl acrylate was removed, the reaction still proceeded. Both ligand and additive seemed to play a vital role in the reaction, as when these components were removed reactivity was shut down and only starting materials were shown via TLC. Finally, when the VCP was removed reactivity was shut down and starting materials were

shown unreacted via TLC, showing that it was taking part in the reaction pathway. Although the cycloaddition reaction that was presumed to being undergone was ruled out with this screen as methyl acrylate was nonessential, it was still of interest to explore what reaction was taking place.

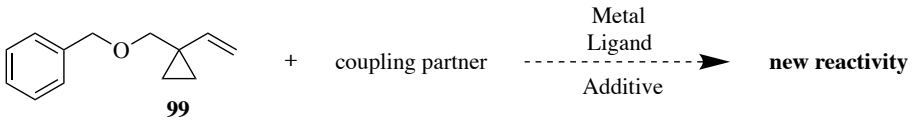


Table 5. Reaction screen with conditions from the hit reaction[a]

Reaction	Metal	Ligand	Coupling partner	Additive
1	$CoBr_2$	L2	**none**	$AgPF_6$
2	**none**	L2	methyl acrylate	$AgPF_6$
3	$CoBr_2$	**none**	methyl acrylate	$AgPF_6$
4	$CoBr_2$	L2	methyl acrylate	**none**
5[b]	$CoBr_2$	L2	methyl acrylate	$AgPF_6$
6	$CoBr_2$[c]	L2	methyl acrylate	$AgPF_6$
7	$CoBr_2$	L2[d]	methyl acrylate	$AgPF_6$
8	$CoBr_2$	L2	methyl acrylate	$AgPF_6$

[a] Reactions were performed on a 0.13 mmol scale, with 10 mol% metal, 15 mol% ligand, 1.0 eq of coupling partner and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours.[b] The VCP (**90**) was not used in this reaction. [c] 1 equivalent of metal was used. [d] 1 equivalent of ligand was used.

As it was found that only three components were vital to the reaction pathway that was being undergone, a screen was performed in the same manner, performing a rerun in reaction 1 and leaving one component out for reactions 2-4 (Table 6). Unfortunately, these reactions when analyzed by GC-MS gave a large number of by-product peaks and made it nearly impossible to obtain any tangible data. From this screen it was found that the ligand seemed to be decomposing creating a very complex GC-MS chromatograph. It was decided to leave this hit behind and shift focus to substrate **135**.

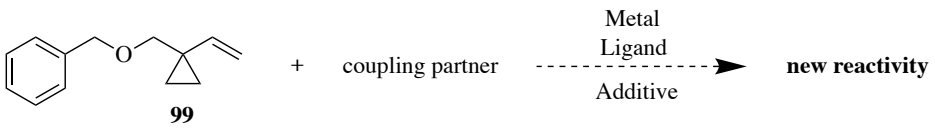


Table 6. Reaction screen performed with substrate 99, L2 and $AgPF_6$[a]

Reaction	VCP	Ligand	Additive
1	90	L2	$AgPF_6$
2	**none**	L2	$AgPF_6$
3	90	**none**	$AgPF_6$
4	90	L2	**none**

[a] Reactions were performed on a 0.26 mmol scale, with 10 mol% metal, 15 mol% ligand and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours.

The first reaction screen performed on substrate **135** contained 24 reactions with the same reaction conditions, in different combination, as substrate **99** (Table 7). From this screen, reaction 1 seemed to give a new product and was therefore scaled up and run on a 50 mg scale. Upon column chromatography, it was observed that the reaction gave many different products in negligible amounts in terms of being able to characterize them. At the same time, it was deemed that substrate **133** can undergo isomerization of the double bond, and therefore cause more issues with GC-MS analysis and false positive hits, so this substrate was abandoned.

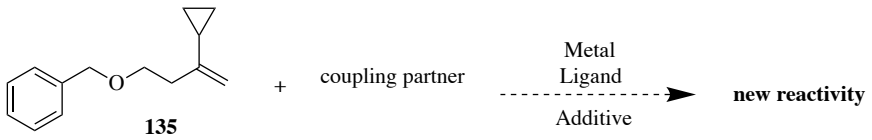


Table 7. Reaction screen of intermolecular cycloadditions via substrate 135[a]

Reaction	Metal	Ligand	Coupling partner	Additive	Results
1	$CuBr_2$	Xphos	benzaldehyde	benzoic acid	new peak
2	$CoBr_2$	Xphos	methyl acrylate	piperidine	NR
3	$FeCl_2$	Xphos	benzyl bromide	cyclohexadiene	NR
4	$NiCl_2$	Xphos	phenyl acetylene	benzoic acid	NR
5	$CuBr_2$	phenanthroline	allyl TMS	formic acid	NR
6	$CoBr_2$	phenanthroline	benzaldehyde	imidazole	NR
7	$FeCl_2$	phenanthroline	methyl acrylate	$AgPF_6$	NR
8	$NiCl_2$	phenanthroline	benzyl bromide	piperidine	NR
9	$CuBr_2$	$Ph_2P(CH_2)_3PPh_2$	phenylacetylene	TFA	NR
10	$CoBr_2$	$Ph_2P(CH_2)_3PPh_2$	allyl TMS	none	NR

11	$FeCl_2$	$Ph_2P(CH_2)_3PPh_2$	benzaldehyde	B_2Pin_2	NR
12	$NiCl_2$	$Ph_2P(CH_2)_3PPh_2$	methyl acrylate	cyclohexadiene	NR
13	$CuBr_2$	BINOL	benzyl bromide	none	NR
14	$CoBr_2$	BINOL	phenyl acetylene	K_2CO_3	NR
15	$FeCl_2$	BINOL	allyl TMS	DDQ	NR
16	$NiCl_2$	BINOL	benzaldehyde	formic acid	NR
17	$CuBr_2$	L1	methyl acrylate	piperidine	NR
18	$CoBr_2$	L1	benzyl bromide	cyclohexadiene	NR
19	$FeCl_2$	L1	phenyl acetylene	benzoic acid	NR
20	$NiCl_2$	L1	allyl TMS	imidazole	NR
21	$CuBr_2$	L2	benzaldehyde	imidazole	NR
22	$CoBr_2$	L2	methyl acrylate	$AgPF_6$	NR
23	$FeCl_2$	L2	benzyl bromide	formic acid	NR
24	$NiCl_2$	L2	phenyl acetylene	$AgPF_6$	NR

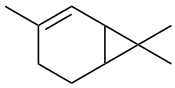
[a] Reactions were performed on a 0.05 mmol scale, with 10 mol% metal, 15 mol% ligand, 1.0 eq of coupling partner and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

After 7 different reaction screens of both intermolecular and intramolecular cycloadditions, and three different substrates, the project was re-evaluated. It was determined that without any standards of different cycloaddition products to use on GC-MS in order to filter through reactions, the project was not giving reproducible results and was ultimately taken in another direction. With the crux of the project being vinycyclopropanes and their reactivity, this was looked at in different cases where less variables were pitted against the reactivity of these substrates.

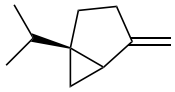
2.3 Reactivity of vinycyclopropane containing monoterpenes

As mentioned in Chapter One, terpenes are a class of compounds that are produced naturally by a from a variety of sources.[41-70] They often have strong odours and are therefore used in a variety of perfumes and scents. There is a strong interest in organic chemistry to use natural products as starting materials in synthesis, as they are readily available and actively produced.[50-60] This interest is actively shown when looking at terpenes as starting materials; they have long been known to be great building blocks to access both more complex terpenes, as well as other complex natural products that can be difficult to synthesize.[60-70] As the Derksen group has an active interest in both using natural products as building blocks, as well as having synthetic access to complex natural

product targets, terpenes are a natural fit in synthetic programs. Specifically, multiple monoterpenes contain vinylcyclopropanes in their ring systems, such as 2-carene, 4-carene, sabinene, α-thujene and β-thujene (Figures 5&8). As the compounds are all carbon skeletons, they inherently have no pre-activation, and therefore prove a natural starting point for testing the reactivity of unactivated vinylcyclopropanes.



2-carene
136



(+)-Sabinene
41

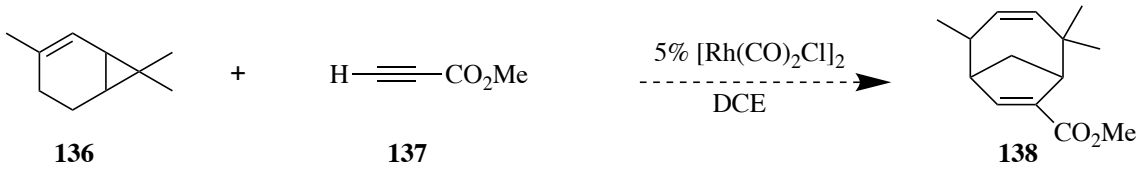
Figure 8. Structures of vinycyclopropane containing monoterpenes

At the time of experiments, sabinene and 2-carene were the most readily available and inexpensive of the vinylcyclopropane containing monoterpenes. Also, they existed as complementary starting materials for testing cycloaddition reactivity as they covered both endocyclic and exocyclic double bonds and were therefore chosen as starting materials.

The reactivity of sabinene and 2-carene as vinylcyclopropane starting materials has not been reported in literature. As such, the focus of the Derksen group was to induce this reactivity and provide naturally occurring, unactivated VCP starting materials that can undergo cycloadditions to form more complex targets. Therefore, known literature conditions for cycloadditions of unactivated vinycyclopropane starting materials were first looked at, with the proposal of then trying these cycloaddition reactions with first row transition metals after they show reactivity.

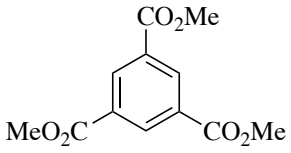
These starting materials contain endo- and exocyclic double bonds and would undergo intermolecular cycloaddition reactions. As such, it was decided to follow literature procedure from Wender et.al. targeting [5+2] cycloaddition reactions using methyl propiolate as a coupling partner.[19] The reactivity of 2-carene was first tested, with the expected reaction pathway of [5+2] cycloaddition show in Scheme 33.

Scheme 33. Proposed cycloaddition reaction of 2-carene with literature conditions



136 **137** **138**

This reaction was attempted and run for 2 hours, giving a major product by TLC as well as multiple minor products. When these products were analyzed by GC-MS, the starting material was mainly maintained, and the major product did not involve a reaction of 2-carene. Instead, the main reaction that took place was a [2+2+2] cycloaddition of methyl propiolate with itself, in order to form an alkyne trimerizations product shown in Figure 9.



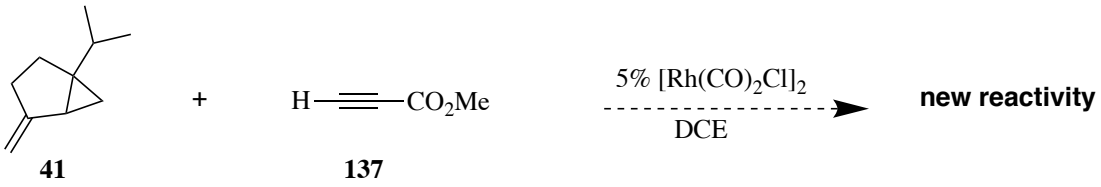
139

Figure 9. Structure of alkyne trimerization by-product

In order to alleviate the formation of this unwanted cycloaddition product, the reaction was attempted using a syringe pump to add the alkyne slowly, in order to induce reactivity with 2-carene rather than itself. Reactions were attempted using addition of the alkyne over 2, 4, 6, 12 and 24 hours, but no difference was seen in the major product. In lieu of this, different literature reaction conditions were attempted using an iridium catalyst rather than rhodium, with the addition of the syringe pump addition of methyl propiolate as standard conditions. Unfortunately, the major product did not change and the desired cycloaddition product was not able to be accessed in appreciable enough yields to get full characterization; this showing that a scalable synthesis would not be possible with these conditions. As 2-carene contains a sterically hindered endocyclic alkene, while sabinene has an exocyclic alkene, it was hypothesized that sabinene may be more reactive

and therefore the efforts were turned to this starting material. Much like 2-carene, sabinene was tested for a [5+2] cycloaddition reaction with methyl propiolate using a rhodium catalyst in DCE (Scheme 34).

Scheme 34. Proposed reaction of sabinene with literature conditions



41 **137**

The same measures were taken as with 2-carene and a syringe pump was used to add the alkyne over various time frames, and unfortunately the same alkyne trimerization product was observed. As a last effort, the reaction was tried with iridium catalyzed conditions along with syringe pump addition of methyl propiolate, to no appreciable success.

2.4 Summary and conclusions

Toward the goal of discovering new vinylcyclopropane reactivity with first row transition metal catalysis, the Derksen group developed syntheses for both intramolecular and intermolecular cycloaddition reactions: a VCP 1,6- enyne **95**, as well as two alkyl vinylcyclopropane substrates **99** and **135**. These compounds were subjected to high-throughput screening to find optimal reaction conditions, and 112 reactions were performed to this end. A new cycloisomerization reaction pathway was found via 1,6-enyne **95** with rhodium catalysis and is currently being examined further. Additionally, in an effort to utilize vinylcyclopropane containing monoterpenes as a starting material for cycloaddition reactions, sabinene and 2-carene were subjected to literature reaction conditions of unactivated VCPs.

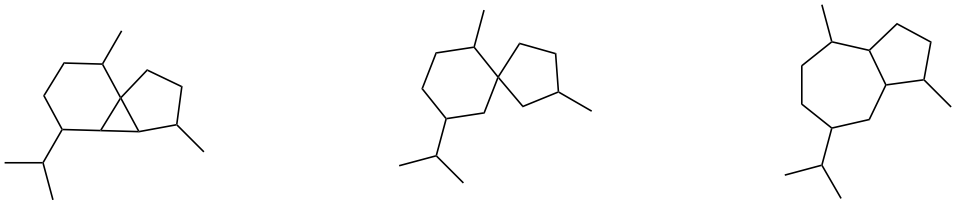
As previously mentioned in Chapter 2, these compounds experienced problems with by-product formation and the small-scale synthesis made it difficult to isolate any product of appreciable

amount in order to undergo a thorough characterization. The synthesis of product standards was introduced and is being applied further in order to continue the screening process. For monoterpene vinylcyclopropanes, the conditions needed to be optimized in this case due to the inherent non-reactive nature of the starting material, which made [2+2+2] cycloadditions of the alkyne coupling partner more energetically favourable than a [5+2] cycloaddition. The introduction of a syringe pump to add the coupling partner over time periods minimized this trimerization but could not alleviate it enough to get appreciable amounts of product. In moving forward with this program, trying different alkynes that may be less reactive towards trimerization may help to improve desired reactivity.

Chapter Three: 1,4-Sigmatropic rearrangements into vinylcyclopropane containing targets

3.1 Synthesis of divinylketone substrate

As mentioned in Chapter One, photocyclization reactions are an important tool in an organic chemists toolbox, as they can give rise to many rearrangement products in minimal steps.[71] In the Derksen research group, this chemistry was employed in line with the interest of accessing natural products in order to test their interactions with transient receptor channels.[86] For this program, the aim was to access sesquiterpene frameworks with ease in order to synthesize and test analogues, inspired by the photochemical rearrangement of (-)-α-santonin mentioned in Chapter One.[83,86-90] Initially, Dr. Evgueni Gorobets began this focus by retro synthetically analyzing cubebane, spiroxane and guaiane, and from here synthesized a starting matreial that could undergo 1,4-sigmatropic rearrangement and form these sesquiterpenes in minimal steps (Figure 10).[86] With the target substrate in hand, Dr. Gorobets was able to synthesize the required precursor in 3 steps. For more information on this work, see the previous publication from our lab.[86]



cubebane
140

sprioaxane
141

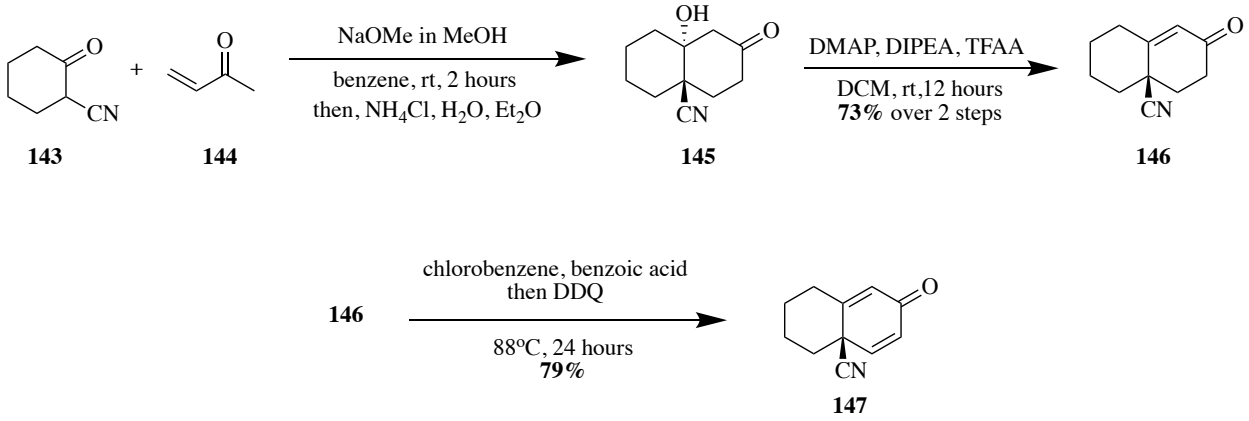
guaiane
142

Figure 10. Structures of sesquiterpene natural products

With a synthetic pathway in hand to target these divinyl ketone starting materials in order to test their photocyclization properties, Dr. Gorobets sought to synthesize an unsubstituted framework in order to attempt to work through selectivity issues as well as gain insight into the general mechanism of action. The synthesis beings with the addition of **144** to **143** followed by a

cyclization to give intermediate **145**. An elimination reaction to give intermediate **146** followed by generation of an alkene gives product **147** in good yield.

Scheme 35. Synthesis of (*R*)-7-oxo-1,2,3,4,4a,7-hexahydronaphthalene-4a-carbonitrile preformed by Dr. Evgueni Gorobets



With the substrate **147** being accessible in minimal steps, its photocyclization properties could be tested in order to work through selectivity issues.

3.1.1 Light mediated rearrangement using various wavelengths

In undergoing the initial exploration UV-A, UV-B, UV-C and visible light sources were tested for their ability to induce these photocyclization reactions. This reaction can give rise to 2 major products, a 6:3:5 and a 7:3:5 rearrangement product. For the substrate **147** chosen in this work, those products would be product **148** and **149** (Figure 11).

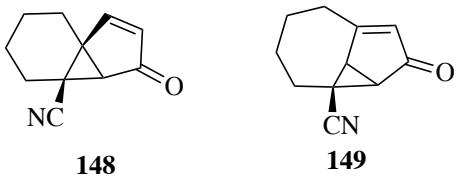


Figure 11. Products from the photocyclization reaction of 147

Product **148** is of interest because it is just steps away from being both cubebol, a cubebane derivative, and a spiroxane derivative. Product **149** is just steps away from forming a guianane

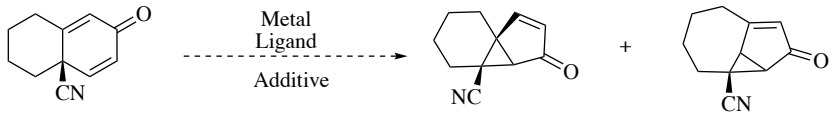
derivative. Due to the interest in testing products from both cyclization pathways, selectivity of this reaction is of importance in order to be able to access each individually. In order to test selectivity and yield, the formation of each product was monitored with the use of each of the light sources previously mentioned. It was found that UV-C light produced the product with the best selectivity (9:1) in the shortest amount of time (2 hours).[86] While this discovery was encouraging, UV-C is not an optimal light source as its harsh conditions require the use of quartz cuvette in order to be subjected. UV-A, UV-B and visible light resulted in between a 3:1 and 4:1 selectivity after 2 hours. In order to try and induce higher selectivity with less harsh conditions, the reaction screening of substrate **147** began with metal catalyzed conditions with earth abundant metal sources, rather than light mediated rearrangement.

3.1.2 Reaction screening using metal catalyzed conditions in the absence of a light source

With both the 6:3:5 and 7:3:5 products being synthesized via the aforementioned light-mediated rearrangement reactions, a standard sample was available so that a standard peak could be obtained by GC-MS analysis. With a standard peak in hand, reactions could be analyzed quickly for product formation, allowing reaction screening to be small scale and high throughput, while avoiding issues surrounding the need to have substantial product amounts for characterization experienced in Chapter 2. In order to test the compatibility of these rearrangement reactions with metal catalyzed conditions, a variety of metal sources, ligands and additives were chosen in order to accommodate the various reaction pathways this divinyl ketone **147** could undergo. As the rearrangement reaction proceeds via a single electron process[96], metal sources were chosen based on their ability to take part in such processes. As first row transition metals are known to be suitable catalysts for single electron processes, Ni(II), Fe(II), Co(II) and Cu(II) used in reaction screening in Chapter two were the starting point for screening conditions. Additionally, first row transition

metals Ti(IV) and Mn (IV) were added to the conditions in order to increase metal variety. Ligands were chosen to cover monodentate, bidentate, tridentate and polydentate in order to have a variety of binding characteristics. Finally, reductants, oxidants and other additives were designed in order to cover various different reaction pathways. With reaction conditions in hand, high throughput screening was performed with the goal of scaling up interesting reactions in order to both find significant formation of products without the use of light sources, but moreover to induce a high amount of selectivity between the 6:3:5 and 7:3:5 products that was not seen when using light.

The first reaction screen involved 30 reactions generated from the chosen reaction conditions mentioned. Although previous rearrangement reactions involving light were performed in CH_3CN, metal catalyzed reactions were performed under the screening conditions that had been previously used which included DCE as a solvent. An experiment was performed with visible light, known to give a standard 5% conversion to product, with both DCE and CH_3CN in order to make sure no difference was obtained. Of this screen, two reactions seemed to be interesting and were therefore chosen to be scaled up. Reaction 5, which appeared to give a small conversion to product via GC-MS analysis, as well as reaction 30 in which all of the starting material had been consumed in the reaction, albeit giving a new product by GC-MS analysis, not the standard product peak.



147 **148** **149**

Table 8. Reaction screen of rearrangement via metal catalysis[a]

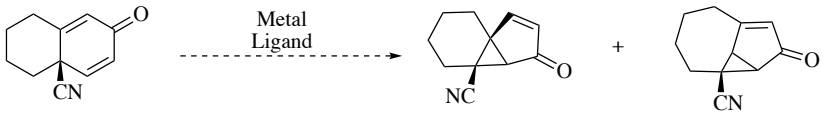
Reaction	Metal	Ligand	Additive	Results
1	Cp_2TiCl_2	phenanthroline	DDQ	NR
2	$NiCl_2$	BINOL	cyclohexadiene	NR
3	MnO_2	DPPF	MeOH	NR
4	$FeCl_2$	Xphos	$AgPF_6$	NR
5	$CuBr_2$	L1	none	new product peak
6	$CoCl_2$	phenanthroline	formic acid	NR

7	$ZnBr_2$	BINOL	DDQ	NR
8	Cp_2TiCl_2	DPPF	cyclohexadiene	NR
9	$NiCl_2$	Xphos	MeOH	NR
10	MnO_2	L1	$AgPF_6$	NR
11	$FeCl_2$	phenanthroline	none	NR
12	$CuBr_2$	BINOL	formic acid	NR
13	$CoCl_2$	DPPF	DDQ	NR
14	$ZnBr_2$	Xphos	cyclohexadiene	NR
15	Cp_2TiCl_2	L1	MeOH	NR
16	$NiCl_2$	phenanthroline	$AgPF_6$	NR
17	MnO_2	BINOL	none	NR
18	$FeCl_2$	DPPF	formic acid	NR
19	$CuBr_2$	Xphos	DDQ	NR
20	$CoCl_2$	L1	cyclohexadiene	NR
21	$ZnBr_2$	phenanthroline	MeOH	NR
22	Cp_2TiCl_2	BINOL	$AgPF_6$	NR
23	$NiCl_2$	DPPF	none	NR
24	MnO_2	Xphos	formic acid	NR
25	$FeCl_2$	L1	DDQ	NR
26	$CuBr_2$	phenanthroline	cyclohexadiene	NR
27	$CoCl_2$	BINOL	MeOH	NR
28	$ZnBr_2$	DPPF	$AgPF_6$	NR
29	Cp_2TiCl_2	Xphos	none	NR
30	$NiCl_2$	L1	formic acid	starting material consumed

[a] Reactions were performed on a 0.14 mmol scale, with 10 mol% metal, 15 mol% ligand and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

Both scaled up reactions were run on a 200 mg scale in order to isolate and quantify reaction yields and selectivity. Unfortunately, upon running reaction 5 a second time, no change was seen and starting material was recovered. Similarly, with reaction 30, no change was seen, however it was noted that formic acid was unintentionally left out of this reaction. Reaction 30 was therefore reattempted with the standard conditions; however, no reproducible result was obtained, and this result was abandoned as it did not appear to be giving the rearrangement product regardless. Although reaction 5 did not give reproducible results in the duplicate reaction, as it appeared to be giving some product via GCMS analysis, it was reattempted. In addition to reattempting this reaction, a 7-reaction screen was conducted. As reaction 5 seemed to show conversion using a

metal source and ligand with no additive, reactions were performed in which this metal source (Cu(II)) was combined with each of the ligands, as well and the ligand (L1) combined with other metal sources in order to find the maximum conversion (Table 9). Although each ligand was tested with the metal, only 2 metals were tested due to availability of starting material. These reactions showed no product formation, although reaction 1 was a triplicate run of reaction 5 from Table 8. When the vials were analyzed, reaction 1 showed material precipitated, with the majority of its contents being crystals. The crystals were attempted to be analyzed by NMR spectroscopy, but were insoluble in every solvent attempted, and therefore this reaction was abandoned.



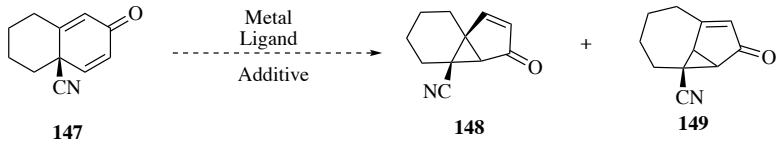
147 **148** **149**

Table 9. Reaction screen based off of hit reaction conditions[a]

Reaction	Metal	Ligand
1	$CuBr_2$	L1
2	$CuBr_2$	Xphos
3	$CuBr_2$	phenanthroline
4	$CuBr_2$	BINOL
5	$CuBr_2$	DPPF
6	MnO_2	L1
7	$ZnBr_2$	L1

[a] Reactions were performed on a 0.14 mmol scale, with 10 mol% metal and 15 mol% ligand in 1.0 mL of DCE at 85°C for 2 hours.

With problems arising with reproducibility, screen 1 was dismissed and another 30-reaction screen was performed (Table 10). No conversion was apparent in any of the reactions performed in screen 2, so conditions were revaluated before moving on to screen 3.



147 148 149

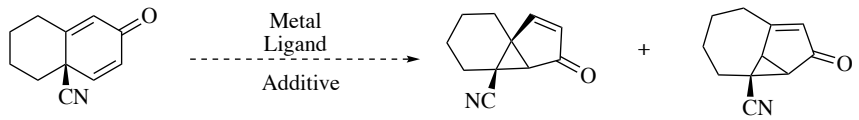
Table 10. Second reaction screen of rearrangement with metal catalysis[a]

Reaction	Metal	Ligand	Additive	Results
1	Cp_2TiCl_2	BINOL	cyclohexadiene	NR
2	$NiCl_2$	DPPF	MeOH	NR
3	MnO_2	Xphos	$AgPF_6$	NR
4	$FeCl_2$	L1	none	NR
5	$CuBr_2$	phenanthroline	formic acid	NR
6	$CoCl_2$	BINOL	DDQ	NR
7	$ZnBr_2$	DPPF	cyclohexadiene	NR
8	Cp_2TiCl_2	Xphos	MeOH	NR
9	$NiCl_2$	L1	$AgPF_6$	NR
10	MnO_2	phenanthroline	none	NR
11	$FeCl_2$	BINOL	formic acid	NR
12	$CuBr_2$	DPPF	DDQ	NR
13	$CoCl_2$	Xphos	cyclohexadiene	NR
14	$ZnBr_2$	L1	MeOH	NR
15	Cp_2TiCl_2	phenanthroline	$AgPF_6$	NR
16	$NiCl_2$	BINOL	none	NR
17	MnO_2	DPPF	formic acid	NR
18	$FeCl_2$	Xphos	DDQ	NR
19	$CuBr_2$	L1	cyclohexadiene	NR
20	$CoCl_2$	phenanthroline	MeOH	NR
21	$ZnBr_2$	BINOL	$AgPF_6$	NR
22	Cp_2TiCl_2	DPPF	none	NR
23	$NiCl_2$	Xphos	formic acid	NR
24	MnO_2	L1	DDQ	NR
25	$FeCl_2$	phenanthroline	cyclohexadiene	NR
26	$CuBr_2$	BINOL	MeOH	NR
27	$CoCl_2$	DPPF	$AgPF_6$	NR
28	$ZnBr_2$	Xphos	none	NR
29	Cp_2TiCl_2	L1	formic acid	NR
30	$NiCl_2$	phenanthroline	DDQ	NR

[a] Reactions were performed on a 0.14 mmol scale, with 10 mol% metal, 15 mol% ligand and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

Although the initial reaction conditions were chosen based on a one electron process and components that could accommodate this type of reaction, the first two reaction screens relied

solely on the use of first row transition metals with a 2+ oxidation state. Moving forward with screen 3, first row transition metals were retained, however different oxidation states were tried (Table 11). The addition of Fe(III) and Cu(I) to reaction screening ensured more representation of metal sources. It should be noted that Ni(0) and Co(III), were not included in the initial oxidation states screen due to availability issues, but future work would look at these metal sources as well.



147 **148** **149**

Table 11. Third reaction screen of rearrangement with different oxidation states[a]

Reaction	Metal	Ligand	Additive	Results
1	$NiCl_2$	Xphos	MeOH	NR
2	$FeCl_2$	L1	$AgPF_6$	NR
3	$FeCl_3$	phenanthroline	none	NR
4	CuCl	BINOL	formic acid	NR
5	$CuBr_2$	DPPF	DDQ	NR
6	$CoCl_2$	Xphos	cyclohexadiene	NR
7	$NiCl_2$	phenanthroline	$AgPF_6$	NR
8	$FeCl_2$	BINOL	none	NR
9	$FeCl_3$	DPPF	formic acid	NR
10	CuCl	Xphos	DDQ	NR
11	$CuBr_2$	L1	cyclohexadiene	NR
12	$CoCl_2$	phenanthroline	MeOH	NR
13	$NiCl_2$	DPPF	none	NR
14	$FeCl_2$	Xphos	formic acid	NR
15	$FeCl_3$	L1	DDQ	NR
16	CuCl	phenanthroline	cyclohexadiene	NR
17	$CuBr_2$	BINOL	MeOH	NR
18	$CoCl_2$	DPPF	$AgPF_6$	NR
19	$NiCl_2$	L1	formic acid	NR
20	$FeCl_2$	phenanthroline	DDQ	NR
21	$FeCl_3$	BINOL	cyclohexadiene	NR

[a] Reactions were performed on a 0.09 mmol scale, with 10 mol% metal, 15 mol% ligand and 1.0 eq of additive in 1.0 mL of DCE at 85°C for 2 hours. NR= no reaction

From the 21 reactions performed in screen 3, no product formation was observed. With the lack of product forming reactions from screens 1-3, it was concluded that metal catalysis by itself would

not be a suitable replacement for the best performing conditions in the light mediated rearrangement reactions. Instead, since visible light has been shown to give 5% product conversion as stated earlier in Chapter 4, it was hypothesized that the coupling of metal catalysis with visible light may increase this conversion. If using metal catalysis and visible light increases the conversion to greater than 50% as seen with UV-C, it would provide opportunities for better control for the rearrangement reaction.

3.2 Summary and conclusions

Towards the goal of inducing a 1,4-sigmatropic rearrangement observed with light mediated conditions with transition metal catalysis, the Derksen group developed a synthesis for substrate **147**. This substrate was subjected to numerous reaction conditions in order to observe 6:3:5 or 7:3:5 reaction products.

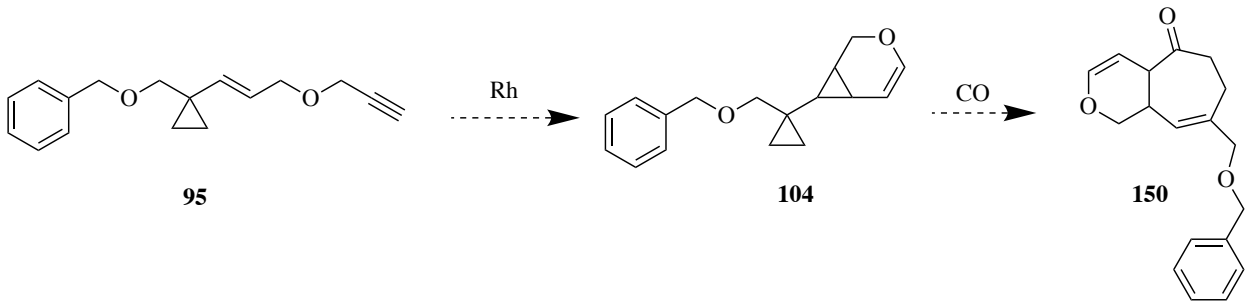
As previously discussed in Chapter Four, issues arose with reproducibility when it came to scaling up “hit” reactions. These issues can be avoided by minimizing time as much as possible between reaction completion and GCMS analysis of reactions.

Chapter 4. Future plans for the vinylcyclopropane and rearrangement projects

4.1 Cycloisomerization reactions of 1,6-enynes with rhodium

There have been scarce, but existent methods developed that outline the synthesis of bis-cyclopropyl materials from 1,6-enyne starting materials.[20-21] These methods, however have been limited to the use of gold and platinum as catalysts.[20-21] With these substrates typically undergoing different reaction pathways with rhodium catalysis, our group made the discovery of the formation of these products with the unexpected catalyst. Our goal was to work to develop a one pot synthesis, from 1-6 enyne to 7-6 fused ring systems through a bis bicyclopropyl intermediate, as these intermediates are known to undergo ring expansion reactions with rhodium catalysts and the introduction of carbon monoxide.[20-21] Our approach to achieve this reactivity is outlined in Scheme 36.

Scheme 36. Steps involved to make a one pot synthesis of 7-6 fused rings from 1,6-enyne vinylcyclopropanes

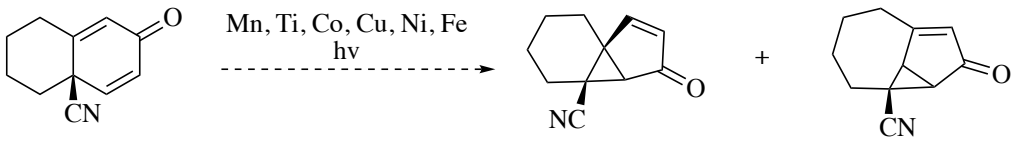


As mentioned in Chapter Two, structure elucidation of this strained system took time, and therefore the testing of this reactivity was unable to be achieved. The utilization of this intermediate remains of interest to the Derksen group and will be followed up with by another member moving forward.

4.2 Rearrangment reactions with visible-light mediated transition metal catalysis

As described in Chapter Four, the light-mediated photocyclization of a divnylketone in order to give access to natural product derivatives was developed in the Derksen group.[86] With this reaction, the highest selectivity between 6:3:5 and 7:3:5 was seen with UV-C light source.[86] In hopes to induce better selectivity, as well as study mechanistic insights, an unsubtituted divinyl ketone core was synthesized by Dr. Evgueni Gorobets. With this substrate, reaction screening was undergone with first row transition metal catalysts in order to try and create a selective system, while maintaining an inexpensive route to product formation. As seen, transition metal catalysts alone were unable to form any amount of either product after multiple reaction screens were performed. With many accounts of visible-light assisting in increasing reaction efficiency catalyzed with Mn, Co and Cu outlined in Chapter One, our goal was to couple a visible-light with our previously performed transition metal catalyzed reaction screens in order to increase the yield from 5% previously seen with visible light and alter selectivity (Scheme 37).

Scheme 37. Proposed reaction to induce selectivity of 6:3:5 and 7:3:5 rearrangement products



147 **148** **149**

From the coupling of these techniques, the goal was to find a metal and light system that worked to give selectively the 6:3:5 rearrangement product, and subsequently find another system to selectively give the 7:3:5 product. We await the screening of these conditions and the results of formation of products from the Derksen group in the future.

Appendix A: Supporting Information

A.1. General considerations

Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without additional purification. $CDCl_3$ was stored over 4 Å molecular sieves. Anhydrous solvents were prepared by standard methods (Na/benzophenone for THF, LAH for ether and CaH_2 for DCM, CH_3CN, HMPA and benzene). "DriSolv" EMD Millipore grade DMF was used. Chloroform stored over K_2CO_3 was used for work with acid sensitive compounds. Column chromatography was preformed using silica gel (technical grade, pore size 60 Å, 230-400 mesh particle size, 40-63 μm particle size). Automatic column chromatography was carried out using a Biotage Isolera Prime instrument with UV detector (version 3.0, build number 10387, operating system 5.0-i386-69, serial number ISPS1602108) ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 MHz (^1H), 100 MHz (^{13}C) with tetramethylsilane as an internal standard. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ and the chemical shifts (in ppm) are relative to the $CHCl_3$ peak (7.26 ppm for ^1H, 77.16 ppm for ^{13}C). Coupling constants (*J* values) are reported in Hz. Infrared spectra were recorded on a Nexus 470 FT-IR spectrometer. GenTech 5890 Series II SSQ 7000 and Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS instruments were used for LR MS and HR MS analyses respectively at the University of Calgary. Elemental analyses were performed on PerkinElmer Series II CHNS/O 2400 instrument at the University of Calgary. All melting points are uncorrected. A LZC-4V photoreactor (Luzchem Research Inc.) was used for irradiation of the divinyl ketones and equipped with:

1. 14x8W Sylvania S818 lamps (cool white light) for vis light irradiation
2. 14x8W Hitachi FL8BL-B lamps (1.2W UV Output) for UV-A irradiation
3. 14x8W *Sankyo Denki G8T5E* lamps (1.6W UV Output) for UV-B irradiation
4. 14x7.2W USHIO G8T5 lamps (2.2W UV Output) for UV-C irradiation

A 5 mm *Wilmad*® quartz NMR tube was used for simultaneous samples irradiation and the reaction monitoring when small amounts (less than 10 mg) of the irradiated starting materials were used. A 4 ml and 9 ml cylindric quartz reactors were used for the irradiation up to 400 mg of starting materials or 100 (200) ml quartz RBF were used for reactions with up to 5 g.

A.2. General procedures I-VI followed in Chapter Two

*A.2.1 General Procedure I: Mono-benzyl protection of diol*s

KOH pellets (1.0 eq) and the diol (1.0 eq) were placed in an oven dried round bottom flask with a magnetic stir bar. The reaction mixture was purged under an inert atmosphere and stirred for 5 mins at room temperature. Benzyl bromide (0.5 eq) was added in one portion. After stirring overnight, the mixture was quenched with water and extracted 3 times with EtOAc. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography eluting with a mixture of EtOAc and hexanes.

A.2.2 General Procedure II: Swern oxidation of alcohols

Oxalyl chloride (7.7 eq) in DCM was transferred to an over-dried round bottom flask with a magnetic stir bar at -78°C and purged under an inert atmosphere. DMSO (5.0 eq) in DCM was added into the flask dropwise and stirred for 5 minutes at -78°C. The alcohol (1.0 eq) was added over a period of 5 minutes at -78°C and stirred for 15 minutes. Dry NEt_3 (9.7 eq) was added dropwise into the reaction mixture which was then warmed to room temperature. After stirring overnight at room temperature, the reaction was quenched with water, extracted 3 times with DCM and washed with brine. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography eluting with a mixture of EtOAc and hexanes. Reactions were typically carried out at a 0.3-0.35 M concentration, for specific concentrations see detailed procedures.

A.2.3 General Procedure III: Cycloisomerization reaction procedure

$[Rh(CO)_2Cl]_2$ (10 mol%) was transferred to an oven dried round bottom flask with a magnetic stir bar and purged under an inert atmosphere. DCE and **5** (1 eq) were added to the flask and heated to 80°C. The reaction stirred overnight at 80°C and after cooling to room temperature was filtered through a silica plug and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography eluting with a mixture of EtOAc and hexanes. Reactions were run on a 0.2 M concentration.

A.2.4 General Procedure IV: Wittig reaction of aldehydes and ketones

Methyltriphenylphosphonium bromide (2.2 eq) dissolved in THF was transferred to an oven dried round bottom flask with a magnetic stir bar. The flask was purged under an inert atmosphere, and cooled to -78°C. nBuLi(2.5 eq, 2.5 M solution in hexanes), was added dropwise to the reaction mixture and allowed to warm to room temperature and stir for 30 minutes. The aldehyde (1.0 eq) was added in dropwise at room temperature and stirred for another 30 minutes. The reaction mixture was quenched with water, extracted 3 times with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography eluting with a mixture of EtOAc and hexanes. Reactions were run at a 0.09 M concentration.

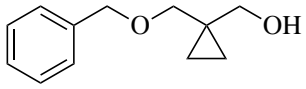
A.2.5 General Procedure V: Vinylcyclopropane screening conditions

VCP (1.0 eq), metal source (10 mol%), ligand (15 mol%) and coupling partner (1.0 eq) were added to a 2-dram vial. An additive (1 eq) in DCE (0.33 mL) was added to the mixture along with an internal standard (15 mol%) and a magnetic stir bar. DCE (0.66 mL) was added to the mixture and vials were allowed to stir for 2 hours at 85°C. After warming to room temperature, reactions were quenched with a 1M sodium citrate solution and run through a silica plug with 1.6 mL of absolute ethanol.

A.2.6 General Procedure VI: Addition of a cyclopropane to ketones/aldehydes

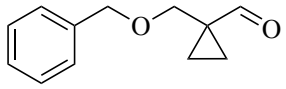
Magnesium turnings (1.1 eq) were ground using a mortar and pestle and added to a round bottom flask with a magnetic stir bar and a crystal of iodine. Cyclopropyl bromide (1.0 eq) in dry THF was added dropwise to the flask under nitrogen and allowed to stir at reflux for an hour to form a Grignard reagent. Cyclohexanone (1.1 eq) was added to the mixture at 0°C. The reaction was allowed to warm to room temperature and stir overnight. The reaction was protonated with a saturated ammonium chloride solution and extracted with diethyl ether. The combined organic layers was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography eluting with a mixture of EtOAc and hexanes. Reactions were run at a 0.5 M concentration.

A.3. Chapter Two experimental



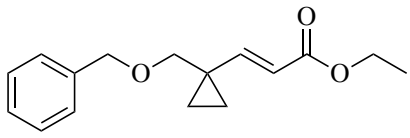
(1-((benzyloxy)methyl)cyclopropyl)methanol (91)

General procedure I was followed for the protection of 1,1-bis(hydroxymethyl)cyclopropane (10.03 g, 98.2 mmol) with benzyl bromide (0.5 eq, 5.8 mL) in the presence of KOH pellets (1.0 eq, 5.494 g). The reaction was carried out at room temperature overnight and after workup, SiO_2 colum chromatography in 30% EtOAc/hexanes afforded 7.94 g (91%) of **63**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.27 (m, 5H), 4.55 (s, 2H), 3.57 (s, 2H), 3.46 (s, 2H), 2.25 (s, 1H) 0.57 – 0.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 128.6, 127.8, 127.7, 73.2, 69.3, 14.3, 9.0.



1-((benzyloxy)methyl)cyclopropanecarbaldehyde (92)

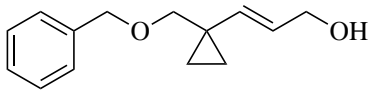
General procedure II was followed for the oxidation of **91** (6.80 g, 35.4 mmol) with oxalyl chloride (7.7 eq, 23.5 mL) and DMSO (5.0 eq, 12.5 mL) in the presence of NEt_3 (9.7 eq, 48 mL) in DCM (100 mL). The reaction was carried out overnight at room temperature and after workup, SiO_2 column chromatography in a 15-25% EtOAc/hexanes gradient afforded 5.70 g (85%) of **92**.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 7.35 – 7.27 (m, 5H), 4.56 (s, 2H), 3.70 (s, 2H), 1.25 – 1.10 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 138.2, 128.5, 127.8, 73.2, 69.6, 32.5, 12.9.



(*E*)-ethyl 3-(1-((benzyloxy)methyl)cyclopropyl)acrylate (93)

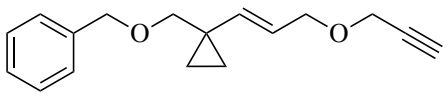
Triethyl phosphonoacetate (2.0 eq, 8.26 mL) dissolved in THF (45 mL) was transferred to an oven dried round bottom flask with a magnetic stir bar and purged under an inert atmosphere. The flask was cooled to -78°C and nBuLi (2.0 eq, 2.33 M in hexanes, 17.8 mL) was added dropwise to the solution. The reaction mixture stirred at -78°C for 30 minutes. **92** (20.8 mmol, 4.0 g) dissolved in THF (15 mL) was added slowly over a period of 10 minutes. The reaction mixture was warmed to

room temperature and after stirring overnight was quenched with NH_4Cl (15 mL) and extracted with ethyl acetate (3x15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography in 20% EtOAc/hexanes affording 2.05 g (38%) of **93.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 5H), 6.64 – 6.60 (d, 1H), 5.92 – 5.88 (d, 1H), 4.54 (s, 2H), 4.19 – 4.16 (q, 2H), 3.47 (s, 2H), 1.30 – 1.26 (t, 3H), 0.96 – 0.87 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 153.3, 138.1, 128.5, 127.9, 127.8, 117.8, 73.8, 73.0, 60.2, 22.9, 14.7, 14.4.



(*E*)-3-(1-((benzyloxy)methyl)cyclopropyl)prop-2-en-1-ol (94)

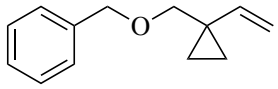
DIBAL (4.0 eq, 1.5 M in toluene, 21.0 mL) in THF (25 mL) was transferred to an oven dried round bottom flask with a magnetic stir bar and purged under an inert atmosphere. **93** (7.88 mmol, 2.05 g) in THF (10 mL) was added in dropwise over a period of 20 minutes at -78°C. Methanol (6 mL) was added at -78°C, followed by water (3 mL). After warming to room temperature, the reaction mixture stirred for 15 minutes. Water (3 mL) was added, followed by 15% w/w NaOH and filtered to remove the crashed-out aluminum salt and the filtrate was concentrated *in vacuo*. The crude product was washed with water (15 mL) and extracted with ethyl acetate (3x15 mL). The organic layer was concentrated *in vacuo* to afford 1.34 g (78.2%) of **94.** ^{1}H NMR (400 MHz, $CDCl_3$):z δ 7.35 – 7.27 (m, 5H), 5.74 – 5.67 (dt, 1H), 5.55 – 5.50 (dt, 1H), 4.53 (s, 2H), 4.13 – 4.09 (m, 2H), 3.42 (s, 2H), 1.28 – 1.24 (t, 1H), 0.74 – 0.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 136.5, 128.5, 127.9, 127.7, 126.2, 75.3, 72.9, 64.0, 21.7, 12.9.



(*E*)-(((1-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)cyclopropyl)methoxy)methyl) benzene (95)

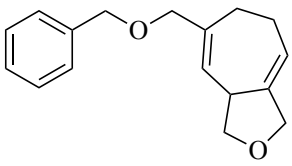
KOH pellets (6.0 eq, 2.11 g) dissolved in DMSO (8 mL) were transferred to an oven-dried round bottom flask with a magnetic stir bar. The reaction mixture was then purged under an inert atmosphere. **94** (6.16 mmol, 1.34 g) dissolved in DMSO (1.5 mL) was added in dropwise at 0°C and stirred for 10 minutes. Propargyl bromide (12.5 eq, 5.8 mL) was added in dropwise at 0°C and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with

water (15 mL) and the resulting precipitate was filtered and washed with diethyl ether, while the filtrate was extracted with diethyl ether (3x15 mL). The organic layers were combined, washed with brine (2 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography in a 5-15% EtOAc/hexanes gradient to afford 1.47 g (93%) of **95**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 5H), 5.62 – 5.60 (m, 2H), 4.53 (s, 2H), 4.13 – 4.12 (d, 2H), 4.05 – 4.04 (m, 2H), 3.43 (s, 2H), 2.42 – 2.41 (m, 1H), 0.75 – 0.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.4, 128.3, 127.7, 127.5, 122.5, 79.9, 75.0, 74.3, 72.7, 70.4, 56.7, 21.7, 12.8.



(((1-vinylcyclopropyl)methoxy)methyl)benzene (99)

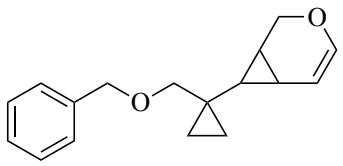
General procedure IV was followed for the Witting reaction of **92**. **92** (5.26 mmol, 1.00 g). methyltriphenylphosphonium bromide (2.2 eq, 4.07 g) and nBuLi (2.5 eq, 2.5 M in hexanes, 5.2 mL) in THF (58 mL) were allowed to react at room temperature for 30 minutes. Following work up and SiO_2 colum chromatography in a 0-5% EtOAc/ hexanes gradient, 0.24 g (25%) of **99** was afforded. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 5H), 5.73 – 5.66 (dd, 1H), 5.10 - 5.05 (dd, 1H), 5.00 – 4.97 (dd, 1H), 4.55 (s, 2H), 3.46 (s, 2H), 0.75 – 0.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 138.6, 128.4, 127.8, 127.6, 111.5, 75.1, 72.9, 22.7, 12.7.



5-((benzyloxy)methyl)-3,3a,6,7-tetrahydro-1H-cyclohepta[c]furan (103)

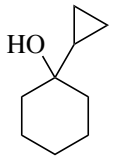
General procedure III for the cycloisomerization reaction of **95** (0.39 mmol, 100 mg) catalyzed by $[Rh(CO)_2Cl]_2$ (10 mol%, 10 mg) in DCE (2 mL) was followed. The reaction was carried out at 80°C overnight and following workup, SiO_2 column chromatography in 5% EtOAc/ hexanes afforded 10 mg (10%) of **103**. ^{1}H NMR (401 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 4H), 5.64 – 5.62 (m, 1H), 5.54 – 5.51 (m, 1H), 4.49 (s, 2H), 4.39 – 4.35 (m, 1H), 4.26 – 4.21 (m, 2H), 3.93 – 3.92 (m, 2H), 3.76 (s, 1H), 3.55 – 3.51 (m, 1H), 2.68 – 2.61 (m, 1H), 2.34 – 2.25 (m, 1H), 2.21 – 2.10 (m,

2H). ^{13}C NMR (101 MHz, $CDCl_3$): ^{13}C NMR (100 MHz, CDCl3) δ 141.1, 140.1, 138.5, 128.5, 127.8, 127.7, 126.9, 118.7, 74.7, 74.6, 72.6, 72.0, 40.6, 27.4, 25.2.



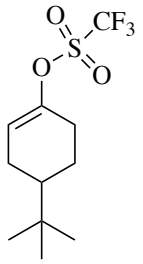
7-(1-((benzyloxy)methyl)cyclopropyl)-3-oxabicyclo[4.1.0]hept-4-ene (104)

General procedure III for the cycloisomerization reaction of **95** (0.39 mmol, 100 mg) catalyzed by $[Rh(CO)_2Cl]_2$ (10 mol%, 10 mg) in DCE (2 mL) was followed. The reaction was carried out at 80°C overnight and following workup, SiO_2 column chromatography in 5% EtOAc/ hexanes afforded 15 mg (15%) of **104**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 5H), 6.16 – 6.15 (d, 1H), 5.21 – 5.18 (m, 1H), 4.54 (s, 2H), 4.03 – 4.00 (dd, 1H), 3.78 – 3.75 (dd, 1H), 3.39 – 3.30 (dd, 2H), 1.59 – 1.57 (m, 1H), 1.23 – 1.18 (m, 1H), 0.96 – 0.91 (m, 1H), 0.40 – 0.27 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 138.8, 128.4, 127.6, 127.5, 105.8, 77.4, 72.8, 62.4, 29.4, 21.1, 20.3, 10.8, 8.3, 8.1.



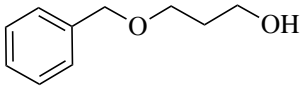
1-cyclopropyl-1-cyclohexanol (114)

General procedure VI was followed for the addition of a cyclopropyl group to cyclohexanone (1.1 eq, 4.7 mL) via a Grignard reagent formed with magnesium turnings (1.1 eq, 1.11 g) and cyclopropyl bromide (41.33 mmol, 3.3 mL) in dry THF (70 mL). The reaction proceeded at room temperature overnight and following work up and SiO_2 column chromatography in 10% EtOAc/hexanes, 1.78 g (31%) of **114** was afforded. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33-2.28 (m, 1H), 1.73-1.67 (m, 1H), 1.62-1.47 (m, 6H), 1.41-1.37 (m, 2H), 1.28-1.17 (m, 1H), 0.96-0.84 (m, 1H), 0.33-0.27 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$): δ -0.2, 21.7, 21.9, 24.9, 25.8, 26.9, 37.2, 41.8, 69.3.



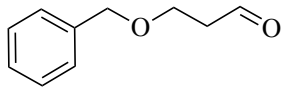
1-trifluoromethanesulfonyloxy-4-t-butylcyclohexene (123)

To an oven-dried round bottom flask with a magnetic stir bar was added t-butyl cyclohexanone (19.4 mmol, 2.97 g) and dry THF (30 mL) under nitrogen. Following cooling to -78°C, lithium bistrimethyl silyl amine (1.0 eq, 19 mL) was added over 30 minutes via a syringe pump. The solution was allowed to stir for 1 hour and N-phenyl trifluoromethane sulfonamide (1.0 eq, 6.80 g) in THF (24 mL) was added over 30 minutes via a syringe pump. The solution was allowed to stir for 2 hours at -78°C before warming to room temperature and reacting overnight. The reaction mixture was extracted with ethyl acetate (3x15 mL), washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography in 1% EtOAc/hexanes affording 0.90 g (16%) of **122**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75-5.73 (m, 1H), 2.44-2.32 (m, 2H), 2.25-2.16 (m, 1H), 1.99-1.90 (m, 2H), 1.42-1.28 (m, 2H), 0.89 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 118.4, 113.2 (q, CF_3), 42.9, 32.0, 31.6, 28.5, 27.1, 25.3, 24.1, 22.6, 14.0.



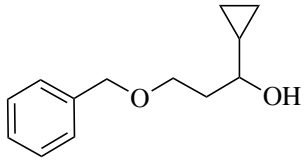
3-(benzyloxy)propan-1-ol (131)

General procedure I was followed for the protection of 1,3-propane diol (7.12 g, 93.6 mmol) with benzyl bromide (0.5 eq, 5.6 mL) in the presence of KOH pellets (1.0 eq, 5.25 g). The reaction was carried out at room temperature until the disappearance of benzyl bromide by TLC and after workup, SiO_2 colum chromatography in 25% EtOAc/hexanes afforded 6.91 g (89%) of **129**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 – 7.3 (m, 5H), 4.5 (s, 2H), 3.8 (td, J = 5.8, 1.0 Hz, 2H), 3.7 (td, J = 5.8, 1.0 Hz, 2H), 1.9 (p, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 128.5, 127.7, 127.7, 73.3, 69.5, 62.0, 32.1. HRMS (EI$^+$, TOF): *m/z* $[M]^{+\bullet}$ calcd. for $C_{10}H_{14}O_2$ 166.0993, Found 166.0994.



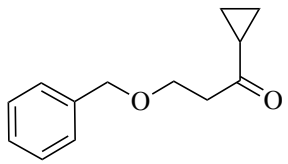
3-benzyloxypropanal (132)

General procedure II was followed for the oxidation of 3-(benzyloxy)propan-1-ol (6.80 g, 40.9 mmol) with oxalyl chloride (7.7 eq, 7.0 mL) and DMSO (5.0 eq, 11.6 mL) in the presence of NEt_3 (9.7 eq, 34.2 mL) in DCM (200 mL). The reaction was carried out until the disappearance of starting material at room temperature and after workup, SiO_2 column chromatography in a 43% EtOAc/hexanes afforded 5.91 g (88%) of **130**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (t, *J* = 1.8 Hz, 1H), 7.4 – 7.3 (m, 5H), 4.5 (s, 2H), 3.8 (t, *J* = 6.1 Hz, 2H), 2.7 (td, *J* = 6.1, 1.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 138.0, 128.6, 127.9, 127.9, 73.4, 64.0, 44.0. HRMS (EI^+, TOF): *m/z* $[M]^{+\bullet}$ calcd. for $C_{10}H_{12}O_2$ 164.0837, Found 164.0843.



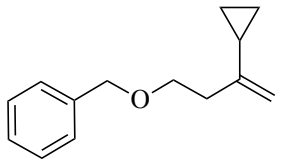
1-cyclopropyl-3-phenylmethoxypropan-1-ol (133)

General procedure VI was followed for the addition of a cyclopropyl group to 3-benzyloxypropanal (1.1 eq, 4.30 g) via a Grignard reagent formed with magnesium turnings (1.1 eq, 2.23 g) and cyclopropyl bromide (41 mmol, 3.0 mL) in dry THF (70 mL). The reaction proceeded at room temperature until the disappearance of starting material by TLC and following work up and SiO_2 column chromatography in 66% EtOAc/hexanes, 3.65 g (68%) of **131** was afforded. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.29 (m, 5H), 4.53 (s, 2H), 3.79 – 3.63 (m, 2H), 3.12 (dt, *J*=8.3, 6.0, 1H), 1.93 (q, *J*=6.0, 2H), 0.92 (qt, *J*=8.3, 5.0, 1H), 0.58 – 0.43 (m, 2H), 0.35 (dtd, *J*=8.3, 5.0, 3.7, 1H), 0.24 – 0.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 128.4, 127.7, 127.6, 75.5, 73.2, 68.7, 36.5, 17.4, 2.8, 2.0. HRMS (EI^+, TOF): *m/z* $[M]^{+\bullet}$ calcd. for $C_{13}H_{18}O_2$ 206.1300, Found 206.1307.



1-cyclopropyl-3-phenylmethoxypropan-1-one (134)

General procedure II was followed for the oxidation of 1-cyclopropyl-3-phenylmethoxypropan-1-ol (3.53 g, 17.1 mmol) with oxalyl chloride (7.7 eq, 3.67 mL) and DMSO (5.0 eq, 4.86 mL) in the presence of NEt_3 (9.7 eq, 9.54 mL) in DCM (53 mL). The reaction was carried out until the disappearance of starting material by TLC at room temperature and after workup, SiO_2 column chromatography in a 43% EtOAc/hexanes afforded 1.30 g (37%) of **132**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.26 (m, 5H), 4.54 (s, 2H), 3.78 (t, *J*=6.4 Hz, 2H), 2.86 (t, *J*=6.4 Hz, 2H), 1.98 (tt, *J*=7.9, 4.6, 1H), 1.11 – 1.02 (m, 2H), 0.92 – 0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0, 138.2, 128.4, 127.7, 127.6, 73.2, 65.3, 43.4, 20.9, 10.9. HRMS (EI^+, TOF): *m/z* $[M]^{+\bullet}$ calcd. for $C_{14}H_{18}O$ 204.1150, Found 204.1155.



1-cyclopropyl-3-phenylmethoxypropan-1-ene (135)

General procedure IV was followed for the Witting reaction of 1-cyclopropyl-3-phenylmethoxypropan-1-one. 1-cyclopropyl-3-phenylmethoxypropan-1-one (5.87 mmol, 1.20 g). methyltriphenylphosphonium bromide (2.2 eq, 4.20 g) and nBuLi (2.5 eq, 2.5 M in hexanes, 5.14 mL) in THF (65 mL) were allowed to react at room temperature until disappearance of starting material by TLC. Following work up and SiO_2 colum chromatography in a 25% EtOAc/ hexanes, 0.50 g (42%) of **133** was afforded. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 5H), 4.72 – 4.70 (m, 2H), 4.55 (s, 2H), 3.65 (t, *J*=7.1 Hz, 2H), 2.38 (t, *J*=7.1 Hz, 2H), 1.33 (m, 1H), 0.66 – 0.61 (m, 2H), 0.48 – 0.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 138.5, 128.4, 127.7, 127.5, 73.0, 69.3, 36.0, 16.2, 6.0. HRMS (EI^+, TOF): *m/z* $[M]^{+\bullet}$ calcd. for $C_{14}H_{18}O$ 202.1357, Found 202.1407.

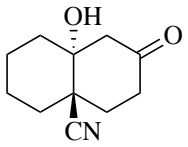
A.4. General procedure VII followed in Chapter Three

A.4.1 General Procedure VII: Divinylketone screening conditions

109 (1.0 eq), metal source (10 mol%), ligand (15 mol%) and internal standard (15 mol%) were added to a 2 dram vial. An additive (1 eq) in DCE (0.33 mL) was added to the mixture along with a magnetic stirring bar. DCE (0.66 mL) was added to the mixture and vials were allowed to stir

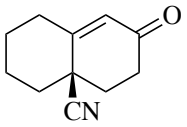
for 2 hours at 85°C. After warming to room temperature, reactions were quenched with a 1M sodium citrate solution and run through a silica plug with 1.6 mL of absolute ethanol.

A.5. Chapter Three experimental



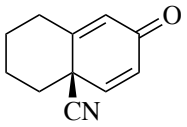
4a*S*,8a*R*)-8a-hydroxy-2-oxodecahydronaphthalene-4a-carbonitrile (145)

To a solution of the 1-cyano-cyclohexanone (18.87 g, 153 mmol) and methylvinylketone (13.4 g, 15.6 mL, 191 mmol) in dry benzene (300 ml) at rt was added a freshly prepared solution of NaOMe (6.25 mL, 15 mmol, 0.1 eq., 2.4 M) in methanol over 5 min. The mixture was stirred for 2 h (until the starting nitrile and intermediate Michael addition products were consumed by ^{1}H NMR spectroscopy). A solution of NH_4Cl (aq, sat., 20 mL), water (10 mL) and Et_2O (40 mL) were added to the reaction mixture and stirred vigorously for 15 min. The white powder was filtered up, washed consequently with benzene (2x30 ml), water (2x25 ml) and dried *in vacuo* to give 16.67 g of the target product **2**. The combined biphasic liquor was separated, and the aqueous layer was extracted with $CHCl_3$ (3x75 mL). The combined organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was subjected to SiO_2 column chromatography in a 25-40% $Et_2O/CHCl_3$ gradient furnishing additional amount of **143** (1.12 g, 60% combined yield) and 7.6 g (26% yield) of the target product **145** of 95% purity. mp: 186-187 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (d, *J*=14.9 Hz, 1H), 2.76 (dt, *J*=13.9 Hz, *J*=6.7 Hz, 1H), 2.55-2.48 (m, 1H), 2.36 (dd, *J*=15.2 Hz, *J*=2.3 Hz, 1H), 2.23 (dt, *J*=13.6 Hz, *J*=4.8 Hz, 1H), 2.08-1.95 (m, 3H), 1.88-1.55 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5 (C=O), 122.3 (CN), 74.0 (C), 52.8 (CH_2), 43.5 (C), 38.6 (CH_2), 36.1 (CH_2), 31.7 (CH_2), 30.7 (CH_2), 22.5 (CH_2), 23.3 (CH_3), 19.6 (CH_2); IR (film, cm^{-1}) 3369, 2934, 2861, 2233, 1705, 1453, 1413, 1197, 997, 971; LRMS (EI) 193 [M$^+$] (80), 175 (10), 166 (18), 150 (17), 136 (100), 124 (80), 108 (48), 93 (22), 81 (21), 71 (32), 58 (53), 47 (62); Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.01, H, 7.73; N, 7.15.



(*R*)-7-oxo-1,2,3,4,4a,5,6,7-octahydronaphthalene-4a-carbonitrile (146)

To a solution of alcohol **145** (17.71 g, 91.8 mmol), DMAP 12.2 g, 100 mmol) and DIPEA (46.6 g, 64 ml, 367 mmol) in DCM (400 ml) at 0 °C was added TFAA (42 g, 28 ml, 200 mmol). After 15 min, the reaction mixture was allowed to warm up and stirred at rt for 16 hs. All the volatile components were removed *in vacuo* and the residue was diluted with toluene (360 ml) and after 30 min of stirring at rt the mixture was moved into fridge. After 12 hs the white powder (ca. 26 g, consisted mostly of TFA*DMAP and TFA*DPEA salts) was filtered up. The filtrate was diluted with Et_2O (300 mL) and toluene in the amount enough to get ca. 1000 mL of total volume. The solution was passed through SiO_2 plug (300 g) to get rid of very polar compounds. Additional amount (300 mL) of the 30% Et_2O/toluene mixture was used to take all the target product off the SiO_2. The solvents were removed *in vacuo* and crystallization of the residue (21.7 g) from 5% hexanes/EtOAc mixture, (500 mL, slow cooling technique) furnished 11.9 g of the target **146**. SiO_2 column chromatography in a 4-6% $Et_2O/CHCl_3$ gradient of the concentrated mother liquor gave additionally 4.7 g of **146** of 95% purity. It was combined with the product (7.6 g) of the same quality from previous step and recrystallized from 5% hexanes/EtOAc mixture to furnish 7.4 g of pure **146** (19.3 g in total, 73% yield after 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96(s, 1H, CH=C), 2.73-2.64 (m, 1H), 2.56-2.48 (m, 3H), 2.43 (ddd, *J*=13.8 Hz, *J*=8.3 Hz, *J*=4.7 Hz, 1H), 2.30 (dq, *J*=11.5 Hz, *J*=2.4 Hz, 1H), 2.05-1.96 (m, 2H), 1.94-1.85 (m, 2H), 1.54-1.38 (m, 2H). All other data are in agreement with the published ones[1].

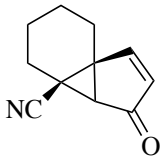


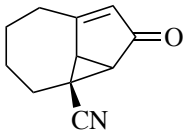
(*R*)-7-oxo-1,2,3,4,4a,7-hexahydronaphthalene-4a-carbonitrile (147)

To a solution of **146** (10.45 g, 59 mmol) in dry chlorobenzene (200 mL) was added benzoic acid (14.4 g, 120 mmol) followed by DDQ (24 g, 106 mmol) and the mixture was stirred at 88°C for

[1] Liu, H-J.; Ly, T-W.; Tai, C-L.; Wu, J-D.; Liang, J-K.; Guo, J-C.; Tseng, N-W.; Shia, K-S. *Tetrahedron* **2003**, *59*, 1209-1226.

24 hours. After cooling down to rt the solid by-products were filtered up and the organic solution was concentrated *in vacuo* and the residue was redissolved in EtOAc (300 mL) and the solution was washed with 1:1 mixture (5x80 mL) of $NaHCO_3$ (aq, sat) solution and water to remove the leftover of benzoic acid and the biggest part of the corresponding hydroquinone derivative of DDQ. After drying over Na_2SO_4 and filtering the organic solution was concentrated *in vacuo*, the residue was redissolved in toluene (200 mL) and subjected to two consecutive SiO_2 column chromatographies in a 20-30% Et_2O/toluene gradient and 30% EtOAc/hexanes to furnish 8.25 g (79% yield) of the target **147** as a yellowish oil solidifying in course of storage. mp: 42-43°C; UV-Vis: 229.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (d, *J*=9.8 Hz, 1H, C<u>H</u>=CH), 6.40 (dd, *J*=9.8 Hz, *J*=1.7 Hz, 1H, CH=C<u>H</u>), 6.24 (s, 1H, CH=C), 2.68-2.55 (m, 2H), 2.53-2.45 (m, 1H), 2.16-2.10 (m, 1H), 2.10-1.90 (m, 2H), 1.51-1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.4 (C=O), 156.3 (<u>C</u>=CH), 143.8 (<u>C</u>H=CH), 130.1 (CH=C), 125.8 (C=<u>C</u>H), 117.1 (CN), 41.0 (C), 39.3 (CH_2), 33.3 (CH_2), 29.2 (CH), 27.4 (CH_2), 22.5 (CH_2); IR (film, cm^{-1}) 2940, 2860, 2229, 1665, 1635, 1609, 1446, 1393, 1260, 878; LRMS (EI) 173 $[M]^+$ (100), 158 (44), 144 (71), 130 (64), 117 (69), 103 (59), 89 (25), 76 (22), 67 (20); LRMS (CI) 174 $[M+H]^+$; Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.08, H, 6.39; N, 8.19.



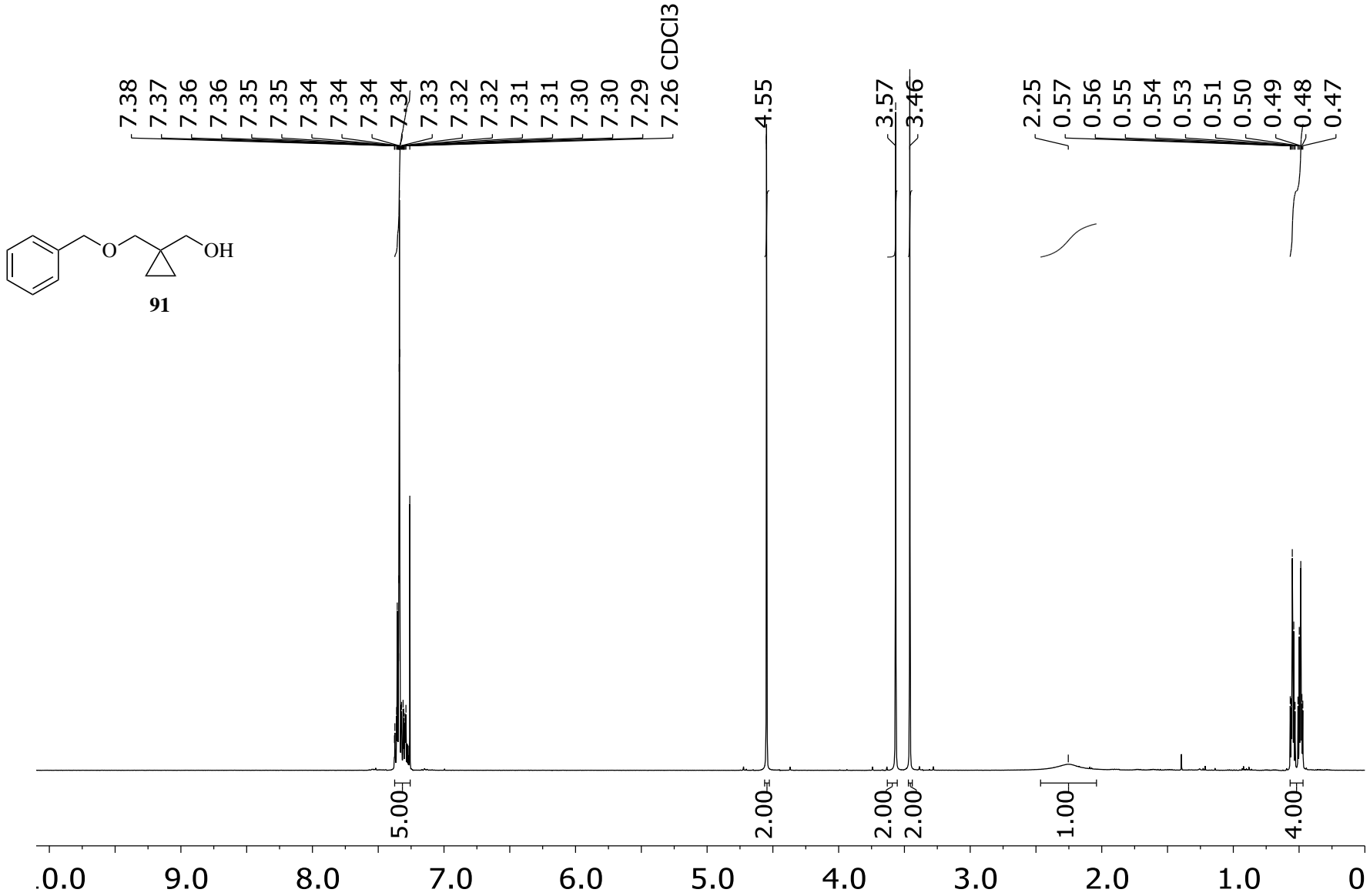


(3b*R*)-3-oxo-3a,3b,4,5,6,7-hexahydro-3H-cyclopenta[1,3]cyclopropa[1,2]benzene-3b-carbonitrile (148) and (2b*S*)-2-oxo-2,2a,2a1,2b,3,4,5,6-octahydrocyclopropa[cd]azulene-2b-carbonitrile (149). A solution of **147** (3.33 g, 19.2 mmol) in dry CH_3CN (90 ml) in quartz flask (200 mL) was UV-C irradiated under stirring in LZC-4V photoreactor for 6 hours. A solution containing **147**, **148** and **149** in 1:1:1 ratio (by ^{1}H NMR) was concentrated, and the residue was redissolved in 20% Et_2O in benzene mixture (100 mL) and passed through short plug of SiO_2 to eliminate polar by-products. Additional amount (200 mL) of the same solvent mixture was used to take off all the valuable compounds from SiO_2. The combine solution was concentrated, the residue (3.10 g) was redissolved in CH_3CN (90 mL) and UV-C irradiated for 6 hours more to give a solution containing **147**, **148** and **149** in 0.4:1.25:1 ratio (by ^{1}H NMR, 85% conversion). According to TLC run in 7% Et_2O/benzene the reaction mixture showed two spots with R_f 0.45

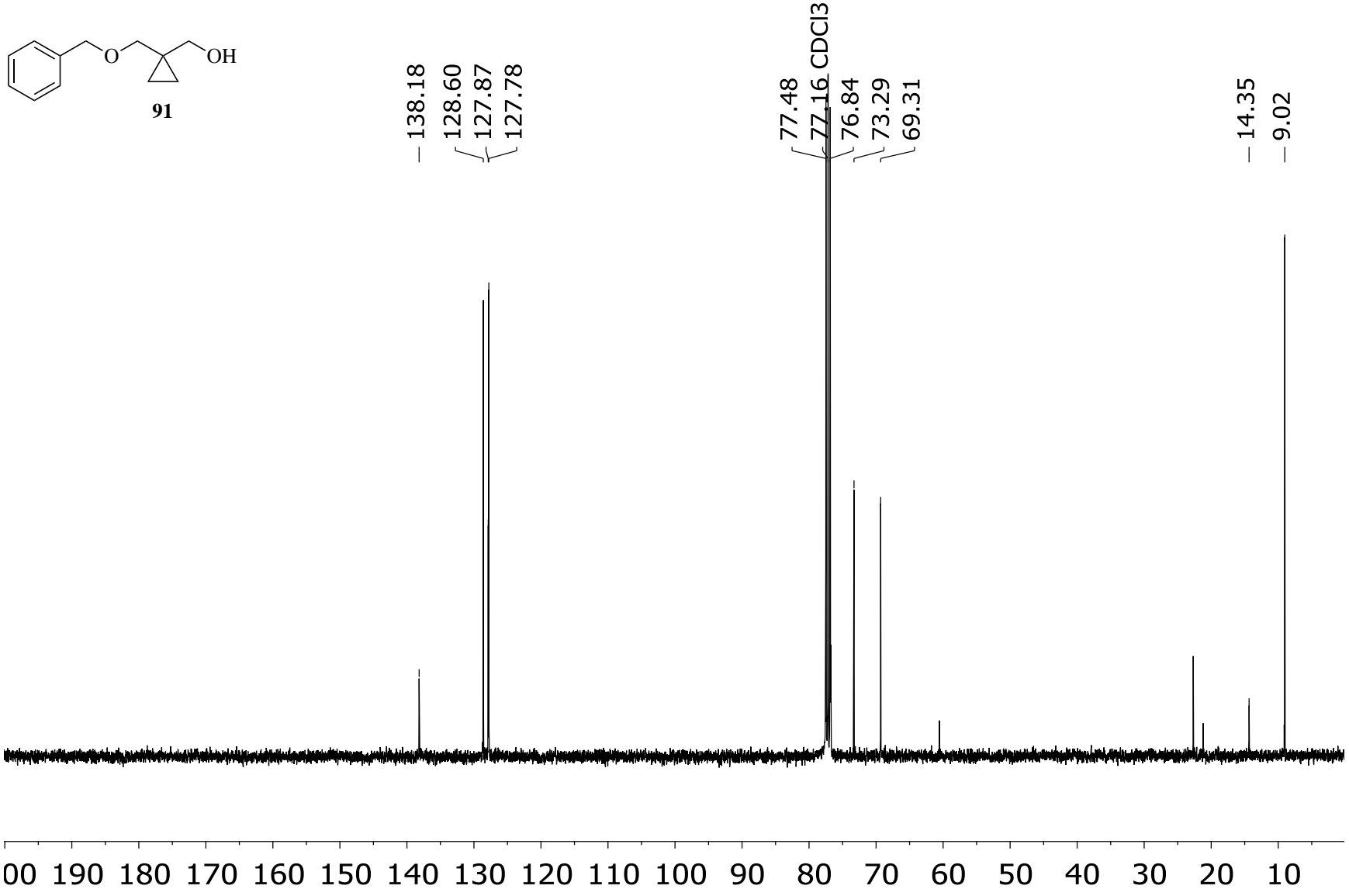
and 0.35 (after 3 runs). The first spot (R_f 0.45) represented target product **148**. The second spot consisted of two components, namely, starting material **147** and target product **149**. So that after the reaction mixture was concentrated, SiO_2 column chromatography in a 7-9% Et_2O/benze gradient of the residue furnished 1.17 g of the target product **148** and 1.63 g of the mixture containing **147**, **148** and **149** in 0.37:0.10:1.0 ratio. In order to separate the starting material from the target products (mostly **149**) in this mixture column chromatography exploiting Aluminum oxide instead of Silica gel was used. Et_2O/Benzene system for chromatography was also substituted with $CHCl_3$/hexanes one. According to TLC (Aluminum oxide, 1:1 $CHCl_3$/hexanes) the second combined fraction from the previous column chromatography showed two spots with R_f 0.41 and 0.35 (after 3 runs). The first spot (R_f 0.41) represented the starting material **147**. The second spot consisted of target product **149** contaminated with target product **148**. So that the mixture was forwarded to the Aluminum oxide column chromatography in a 1:1-2:1% $CHCl_3$/hexanes gradient to furnish 0.38 g of the starting material **147**, 0.25 g of the mixed fraction and 0.93 g of the target product **149** containing ca. 1 % of **147**. Recrystallization from hexane/EtOAc gave analytically pure sample. **148**: viscous oil; UV-Vis: 223.3, 260.9 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, *J*=5.6 Hz, *J*=1.1 Hz, 1H, CH=CH), 6.00 (dd, *J*=5.6 Hz, *J*=1.1 Hz, 1H, CH=CH), 2.35-2.26 (m, 1H), 2.25-2.08 (m, 2H), 2.20 (s, 1H), 1.98-1.91 (m, 1H), 1.63-1.55 (m, 1H), 1.51-1.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1 (C=O), 162.7 (<u>C</u>H=CH), 131.2 (CH=C<u>H</u>), 119.9 (CN), 40.6 (C), 39.2 (C), 38.3 (CH), 29.7 (CH_2), 23.1 (CH_2), 20.5 (CH_2), 19.9 (CH_2); IR (film, cm^{-1}) 3399, 3056, 2931, 2861, 2236, 1702, 1442, 1333, 1164, 878, 821, 742, 490; LRMS (EI) 173 [M^+] (100), 158 (8), 145 (12), 130 (8), 117 (10), 103 (7); HRMS (ESI) calcd. for $C_{11}H_{11}NO$ 173.0841, found 173.0842. **149**: mp: 58-59 °C (Hexane/ EtOAc); UV-Vis: 220.0, 261.1, 330.2 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (s, 1H, CH=C), 3.21 (d, *J*=4.8 Hz, 1H, C^{1}H), 3.04-2.88 (m, 1H), 2.69 (d, *J*=4.8 Hz, 1H, C^{2}H), 2.38 (dd, *J*=15.4 Hz, *J*=7.0 Hz, 1H), 2.28 (dt, *J*=12.0 Hz, *J*=5.4 Hz, 1H), 2.17-2.15 (m, 1H), 2.01-1.95 (m, 1H),), 1.50 (dq, *J*=15.1 Hz, *J*=2.4 Hz, 1H), 1.39 (dd, *J*=11.9 Hz, *J*=10.6 Hz, 1H), 1.12-1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4 (C=O), 172.7 (<u>C</u>=CH), 129.0 (<u>C</u>H=C), 120.6 (CN), 39.3 (CH), 37.9 (CH), 32.9 (C), 32.3 (CH_2), 29.1 (CH_2), 27.3 (CH_2), 25.9 (CH_2); IR (film, cm^{-1}) 3372, 3067, 2944, 2858, 2237, 1751, 1692, 1596, 1456, 1276, 1180, 1067, 1040, 908, 878, 566; LRMS (ESI) 196 [M+Na^+]; HRMS (ESI) calcd. for $C_{11}H_{11}NaNO$ 196.0733, found 196.0732; Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.18, H, 6.41; N, 8.21.

A.6. Chapter Two spectra

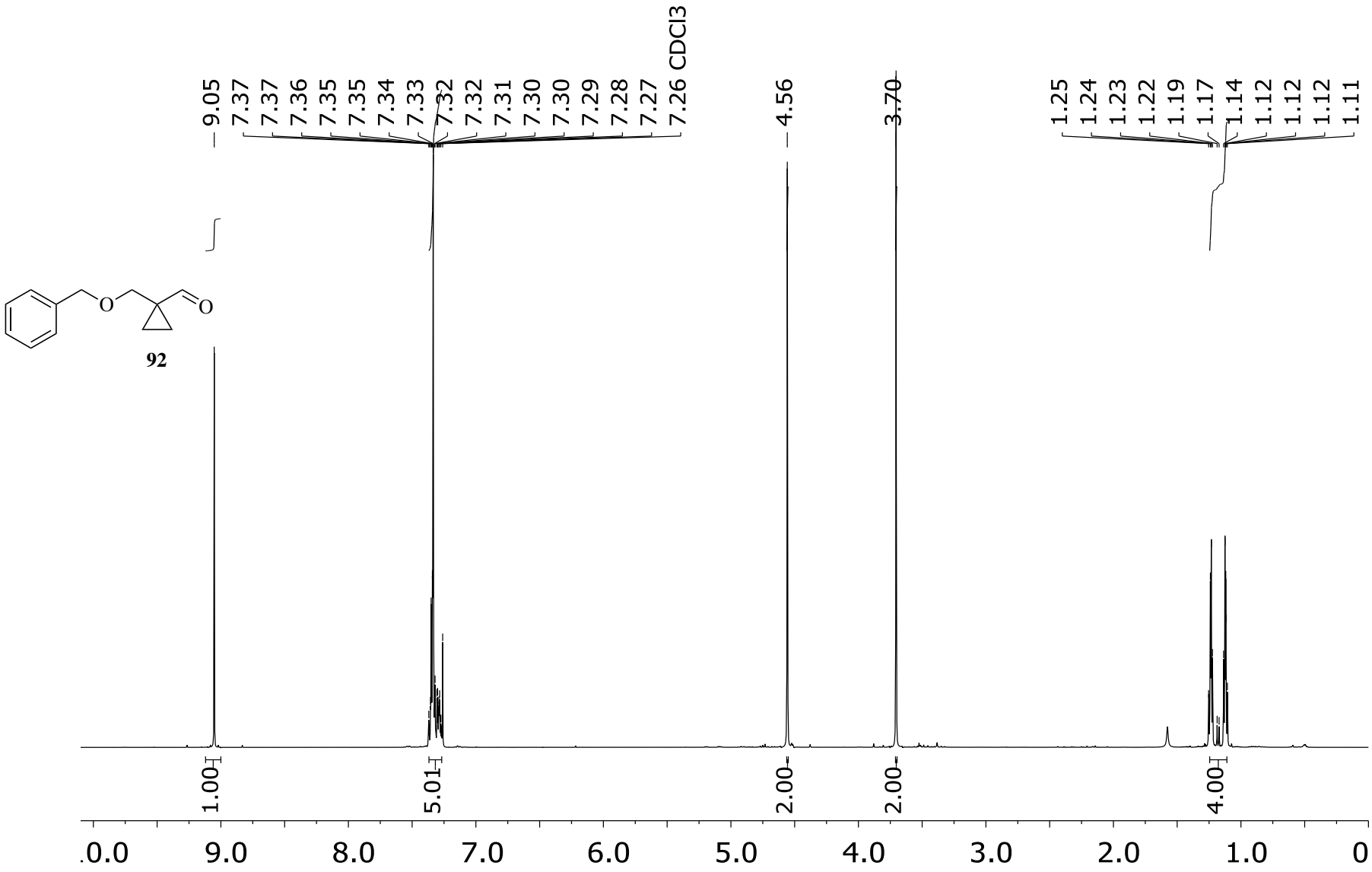
A.6.1. Chapter Two spectra pages 71-90



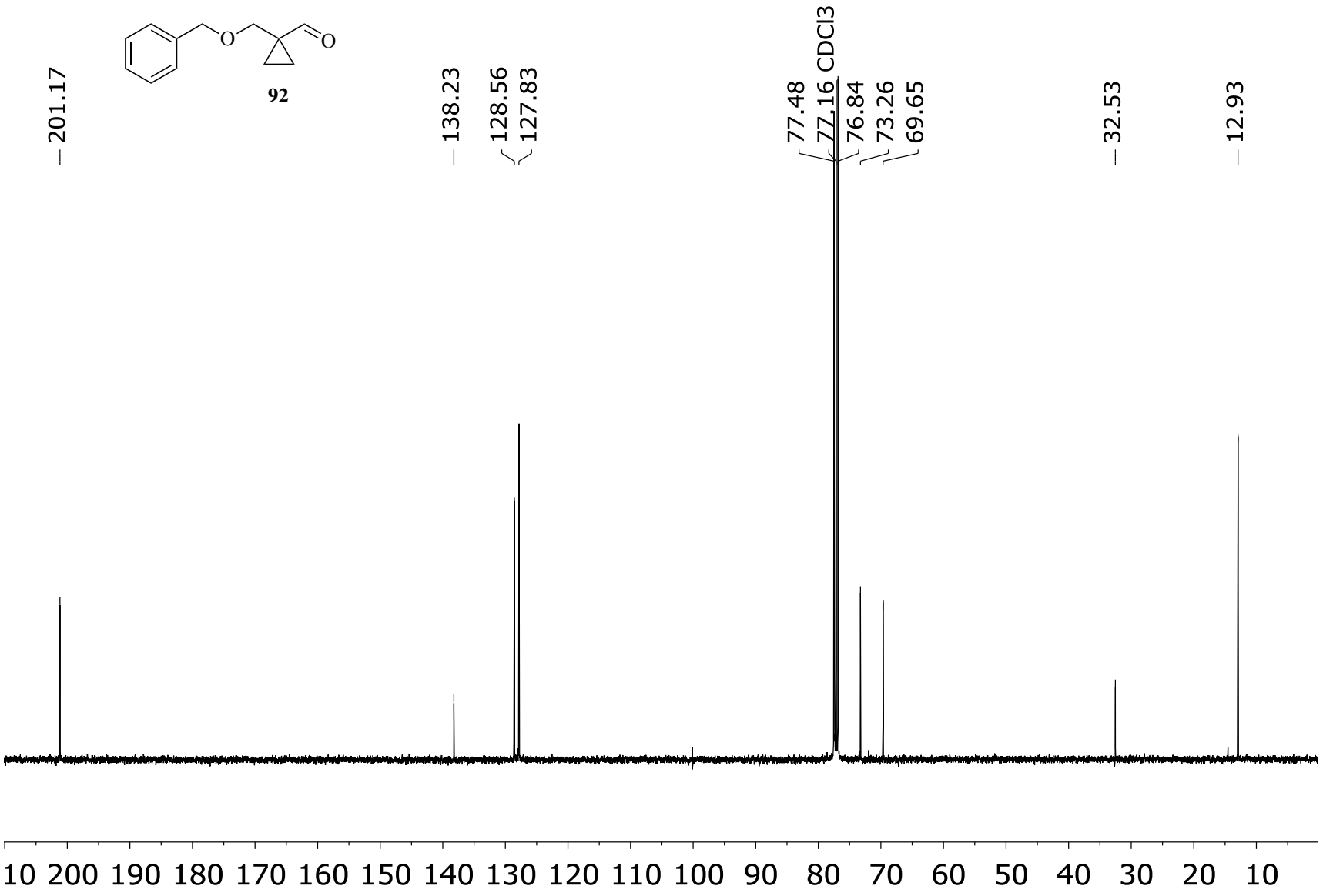
^{1}H NMR spectrum for compound **91**



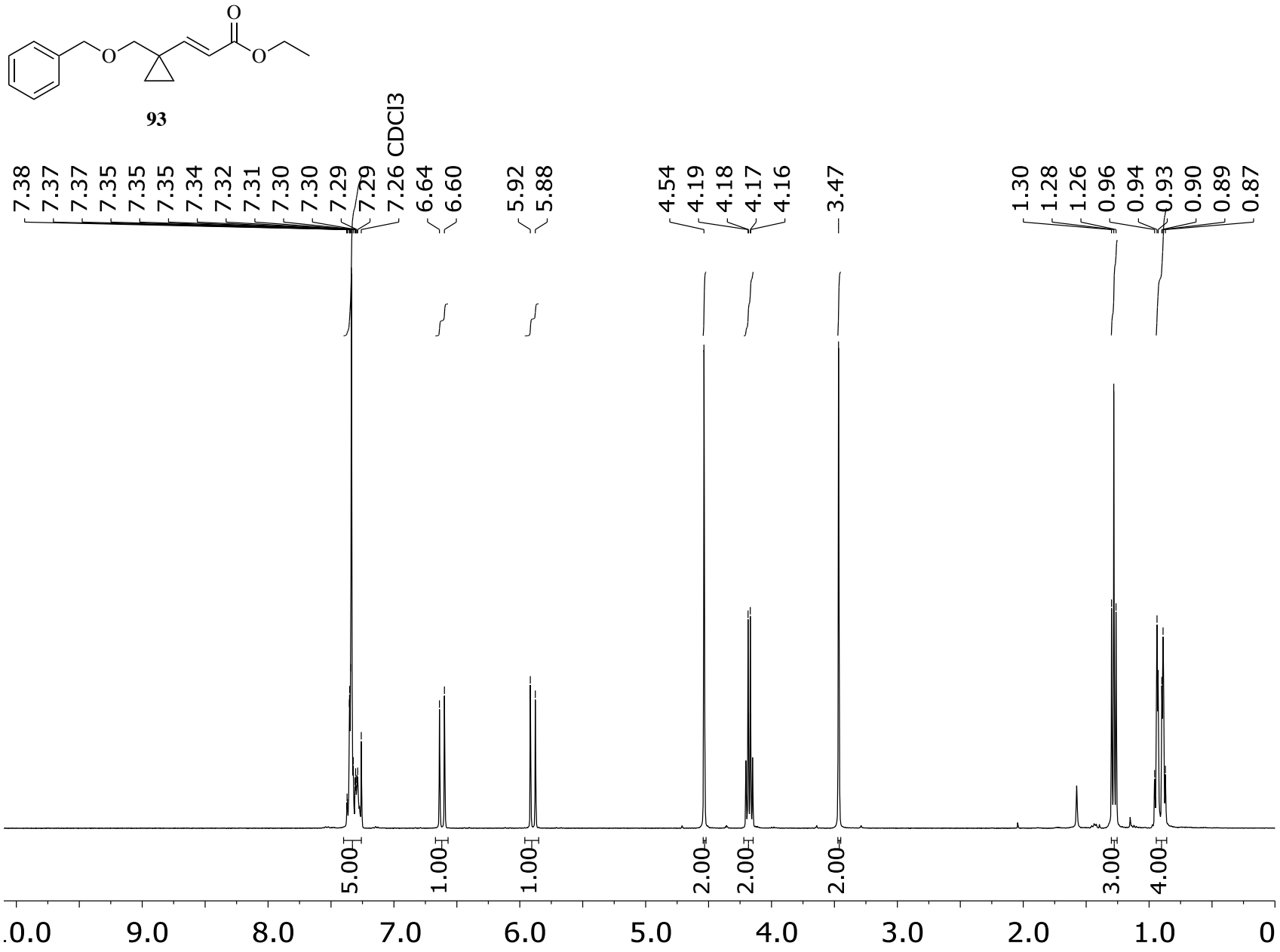
^{13}C NMR spectrum for compound **91**



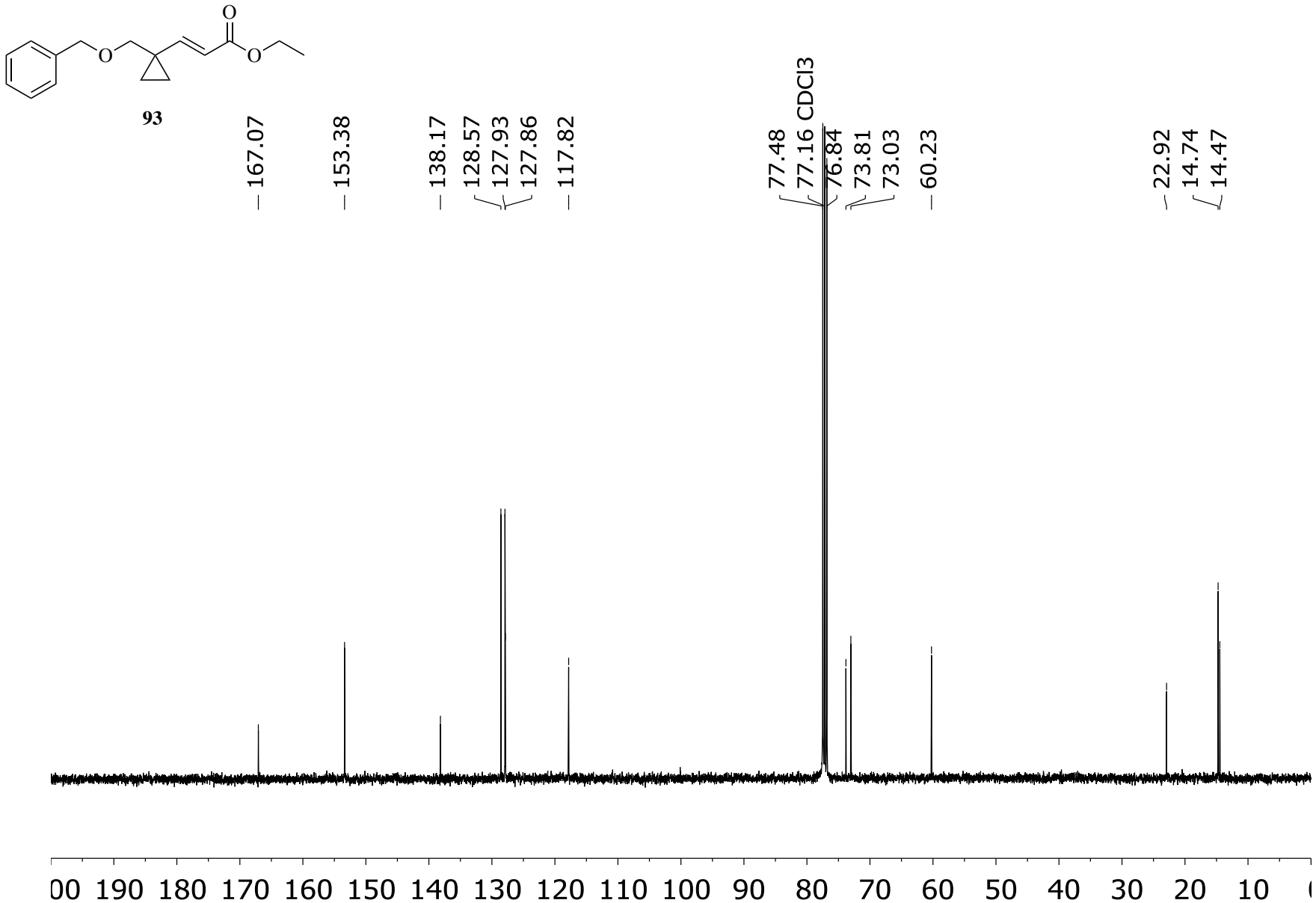
^{1}H NMR spectrum for compound **92**



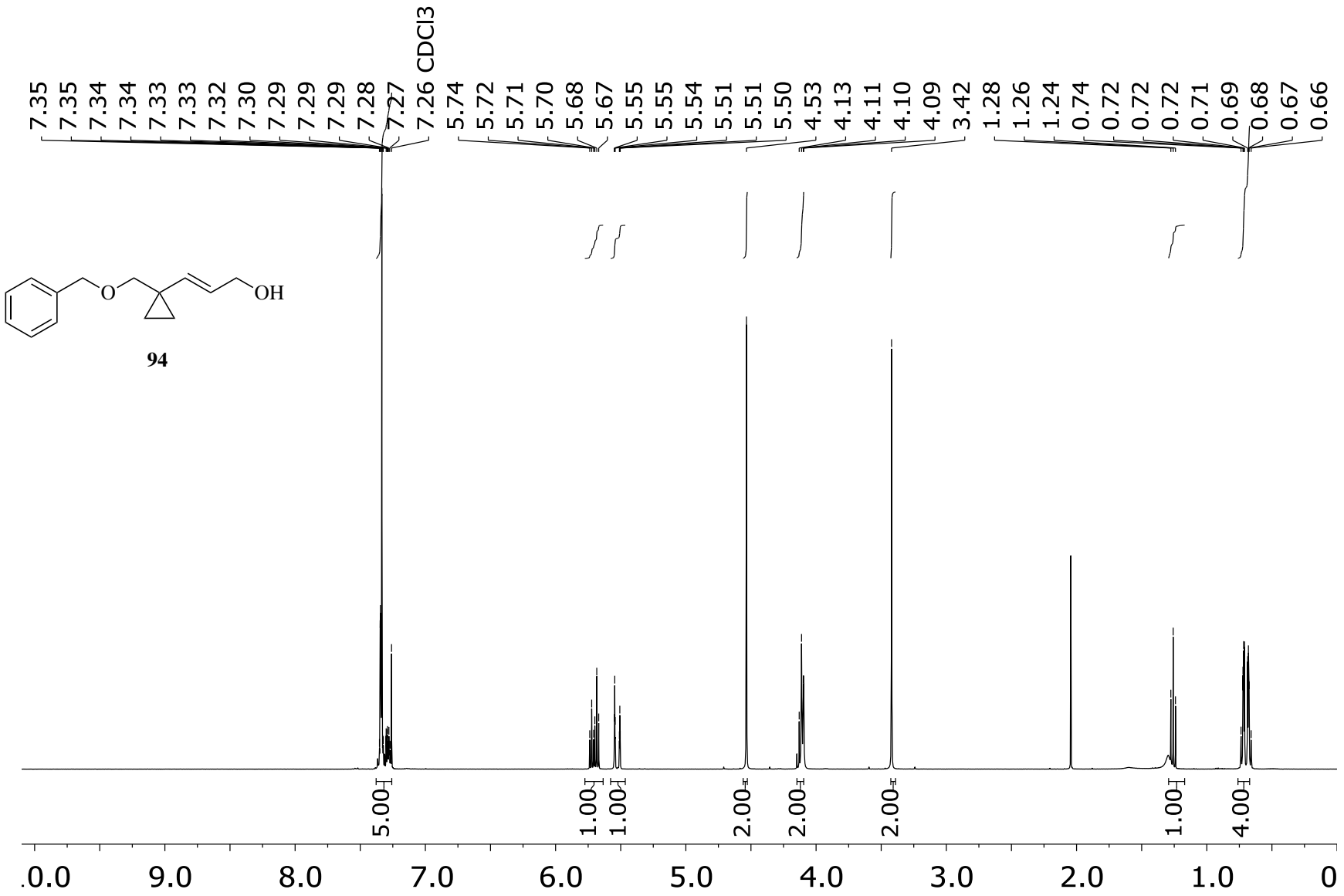
^{13}C NMR spectrum for compound **92**



^{1}H NMR spectrum for compound **93**

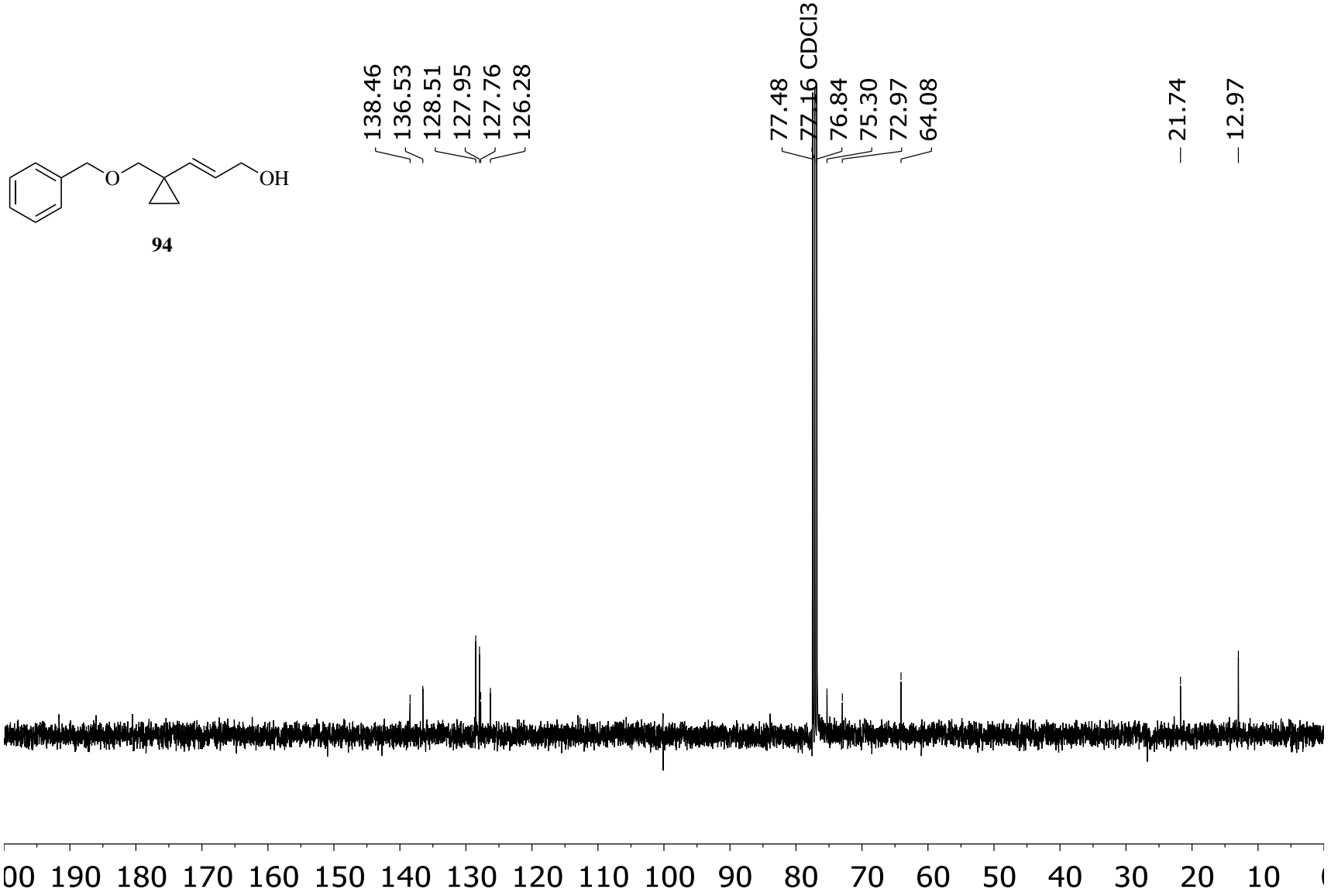


^{13}C NMR spectrum for compound **93**

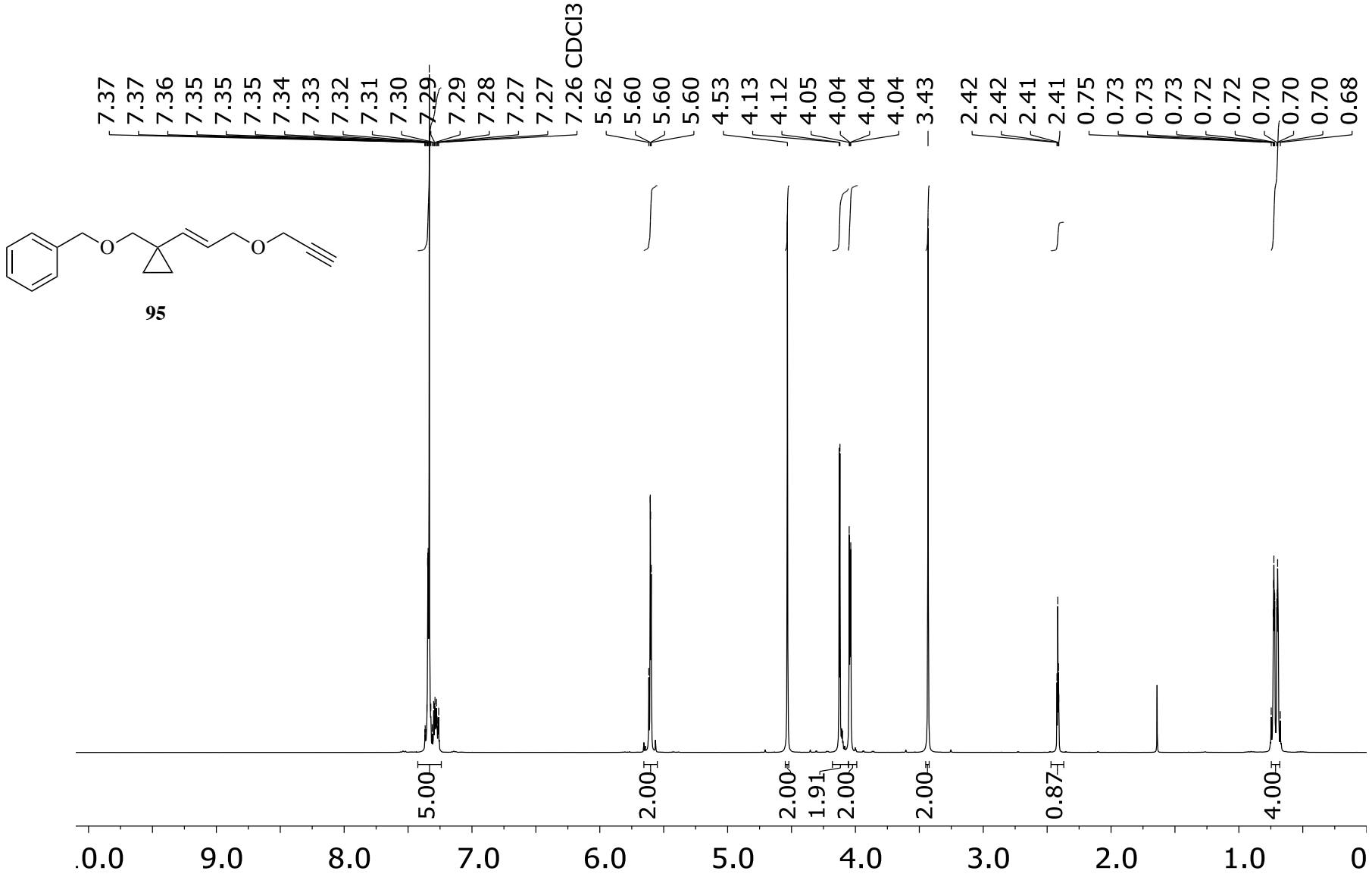


94

^{1}H NMR spectrum for compound **94**

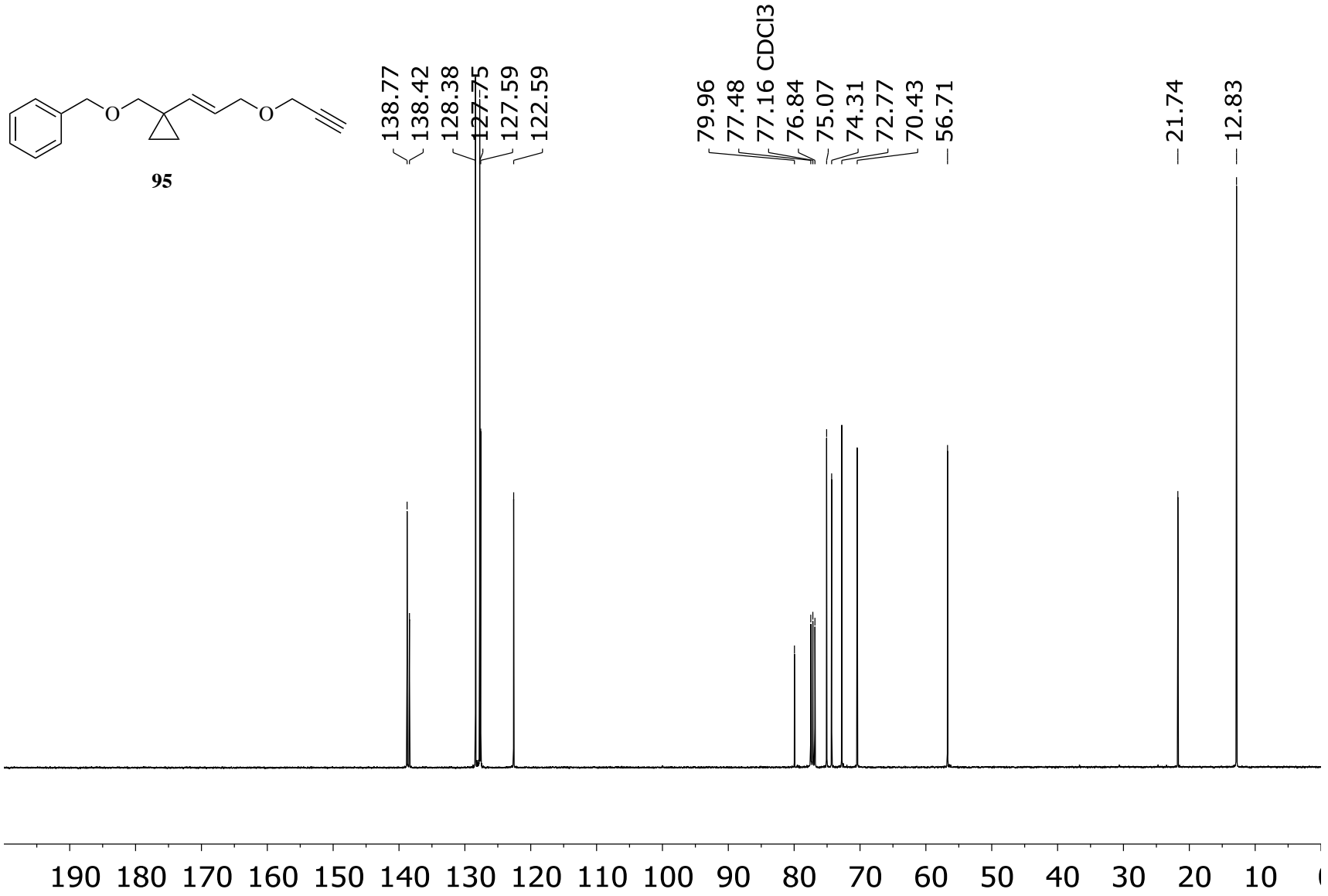


^{13}C NMR spectrum for compound **94**

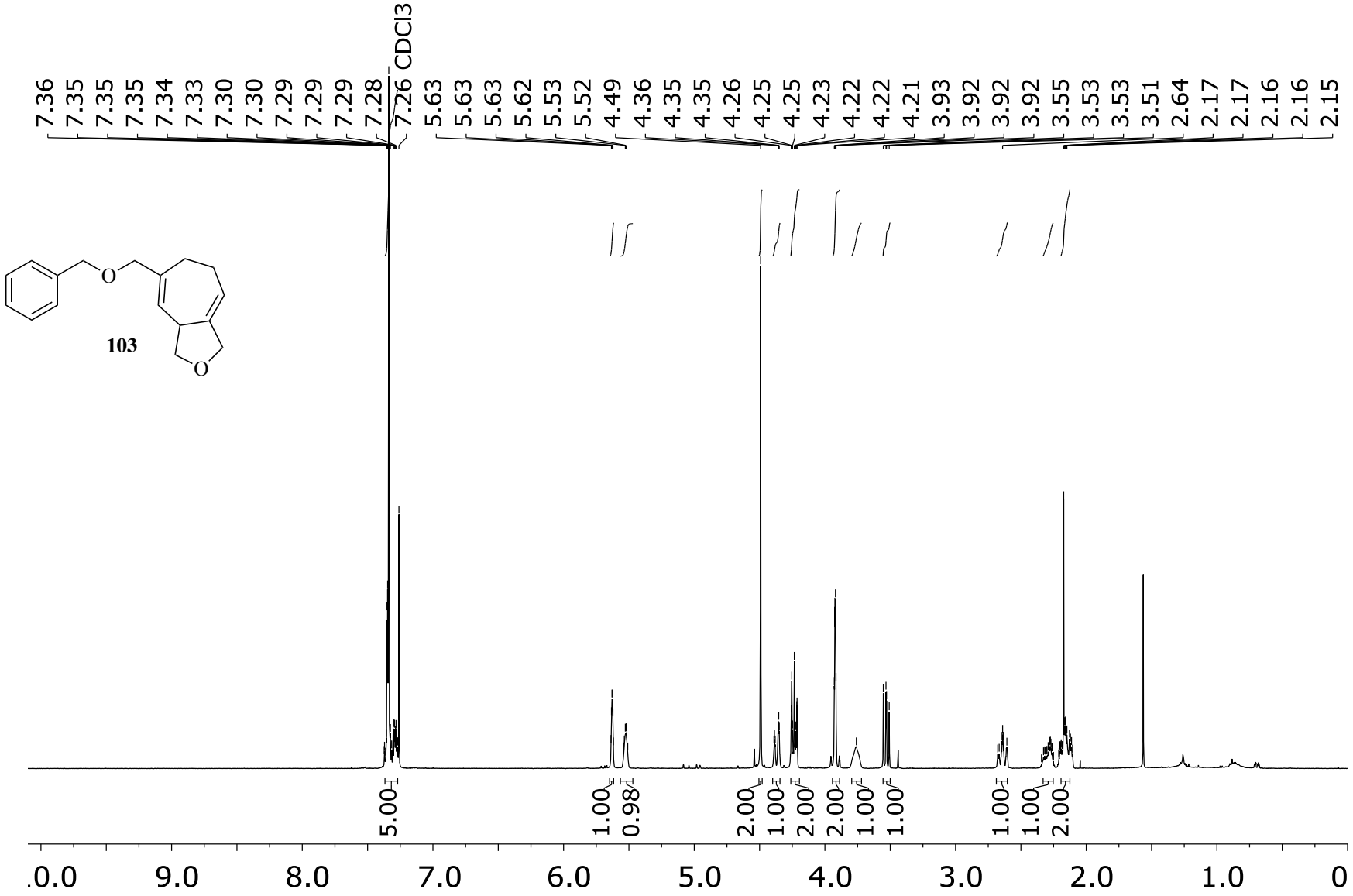


95

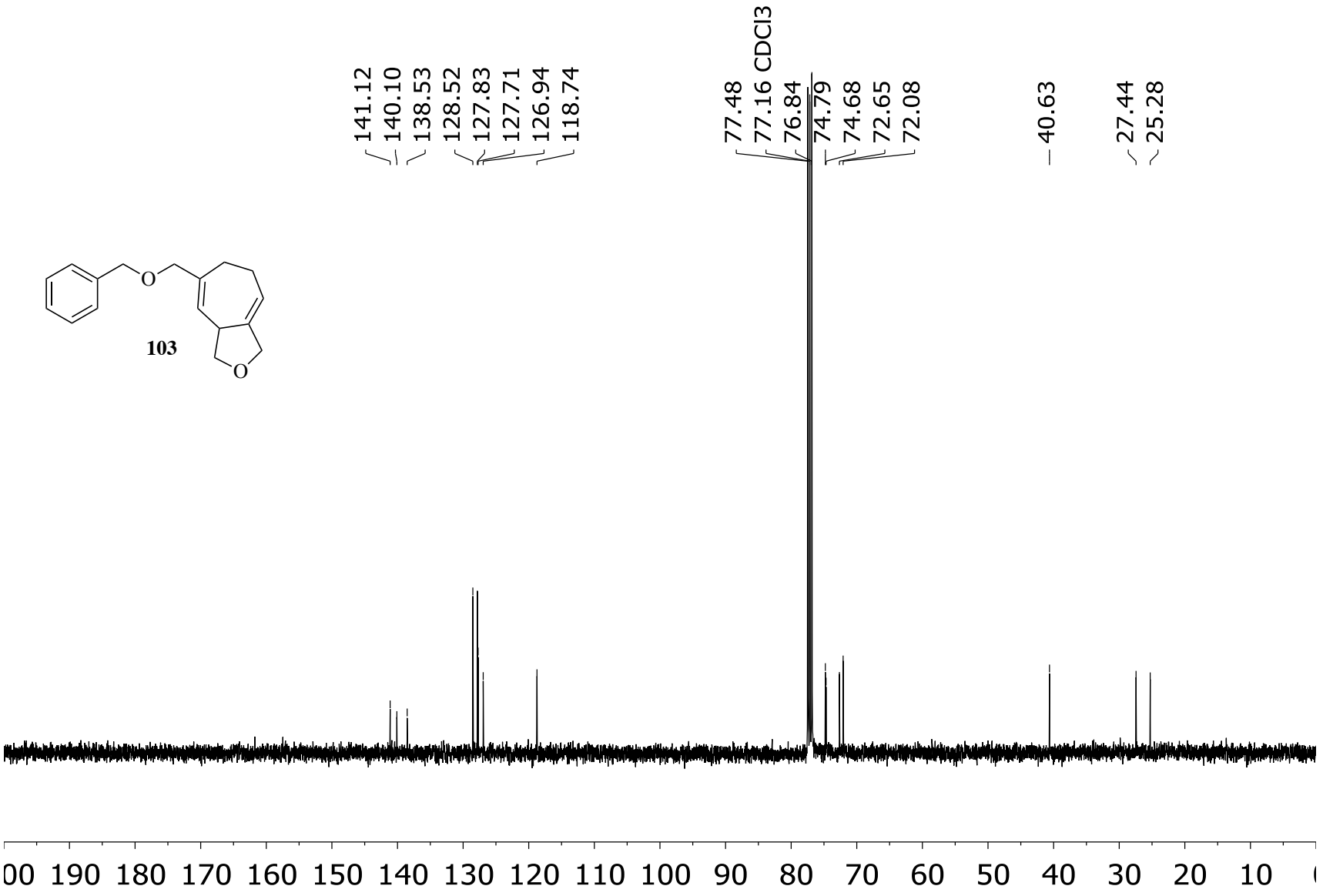
^{1}H NMR spectrum for compound **95**



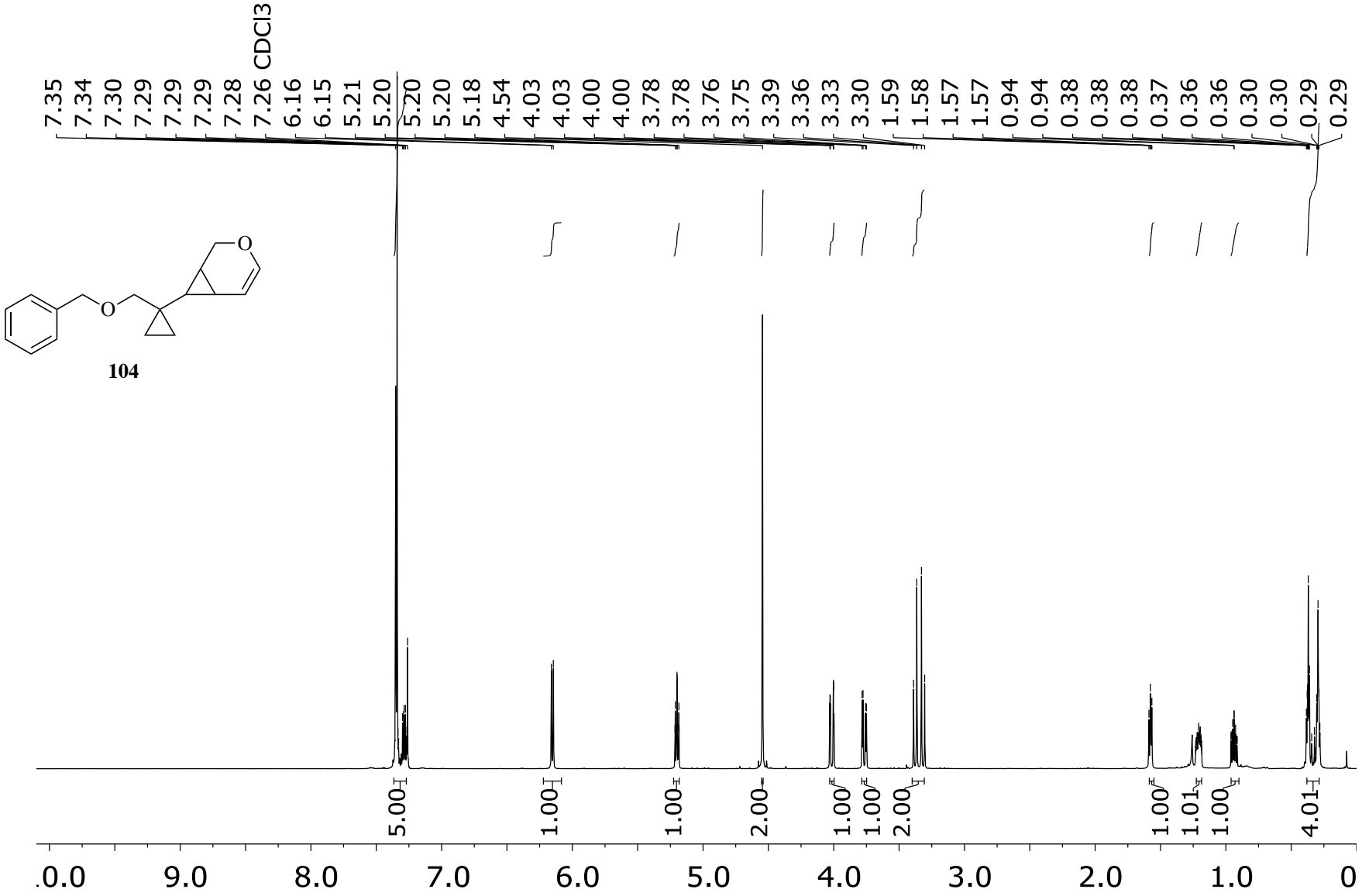
^{13}C NMR spectrum for compound **95**



^{1}H NMR spectrum for compound **103**

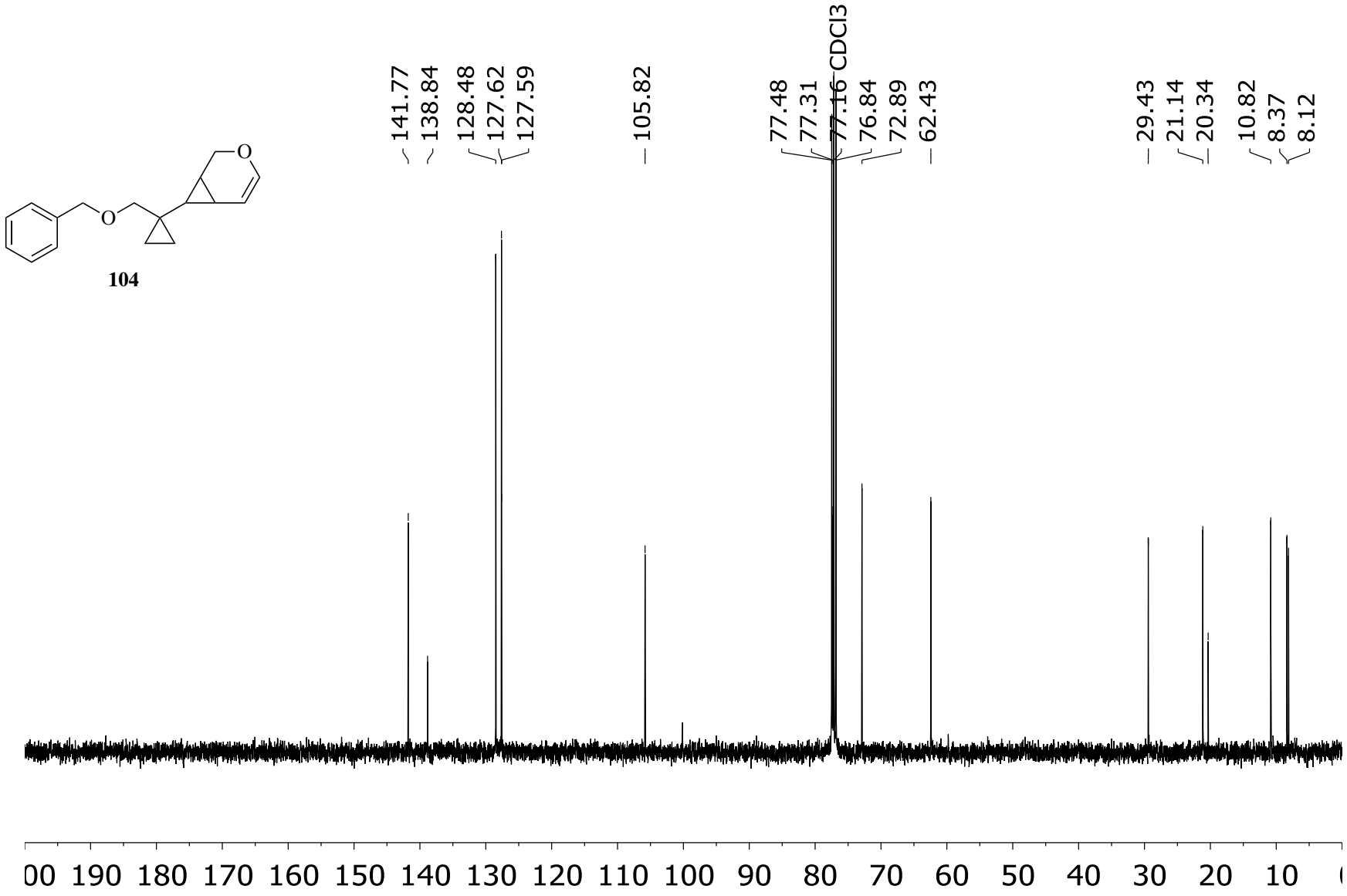


^{13}C NMR spectrum for compound **103**

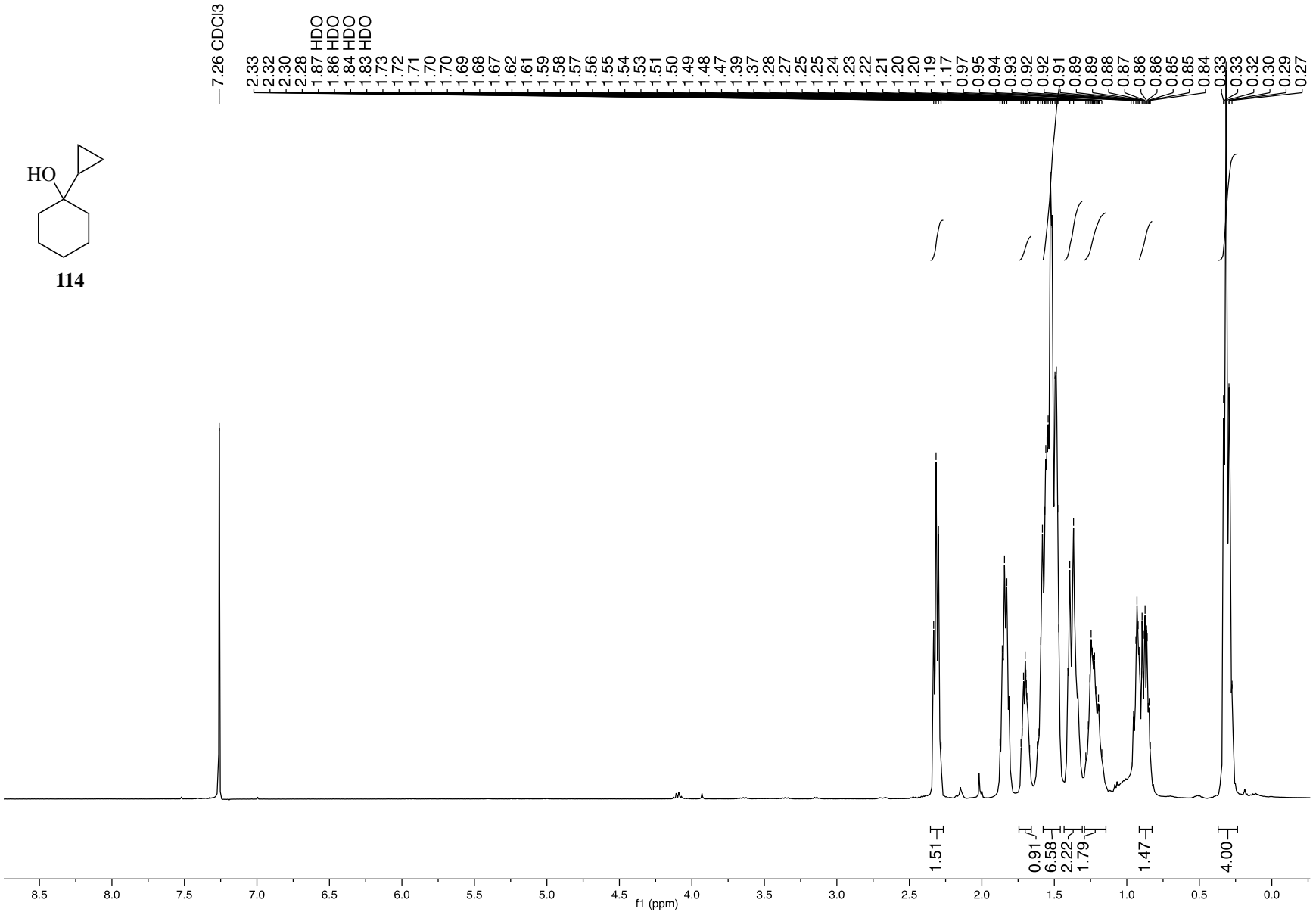


104

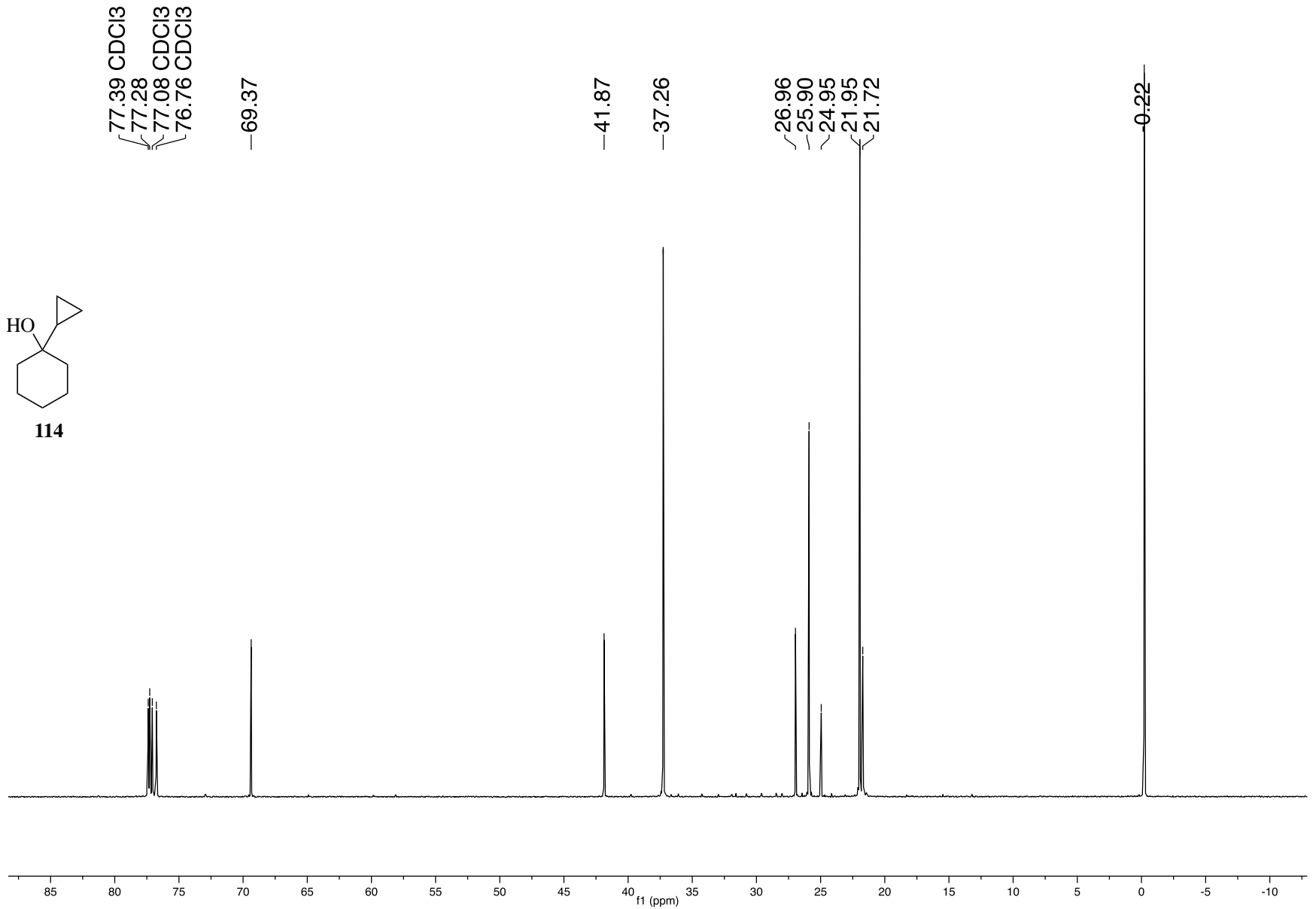
^{1}H NMR spectrum for compound **104**



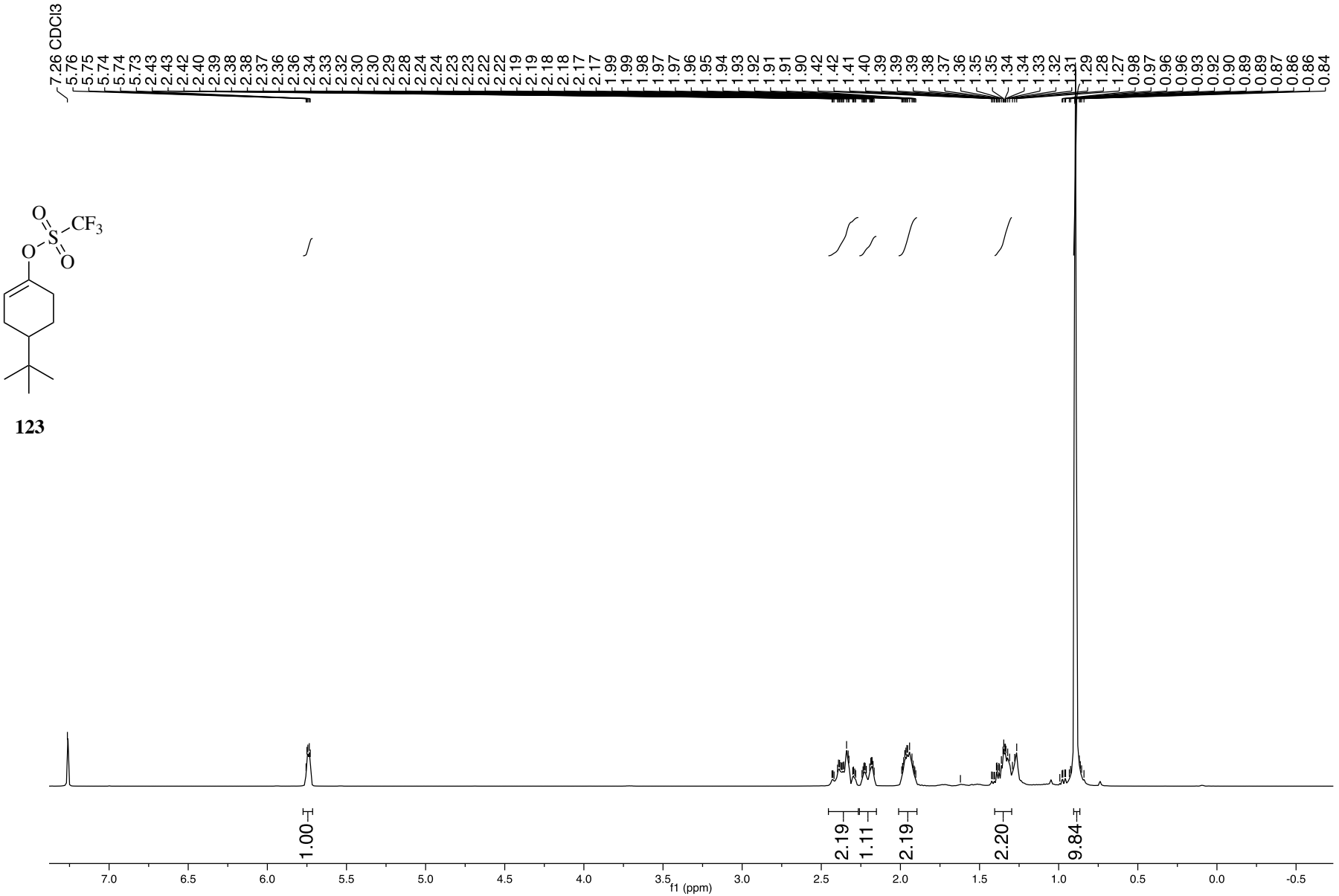
^{13}C NMR spectrum for compound **104**



^{1}H NMR spectrum for compound **114**

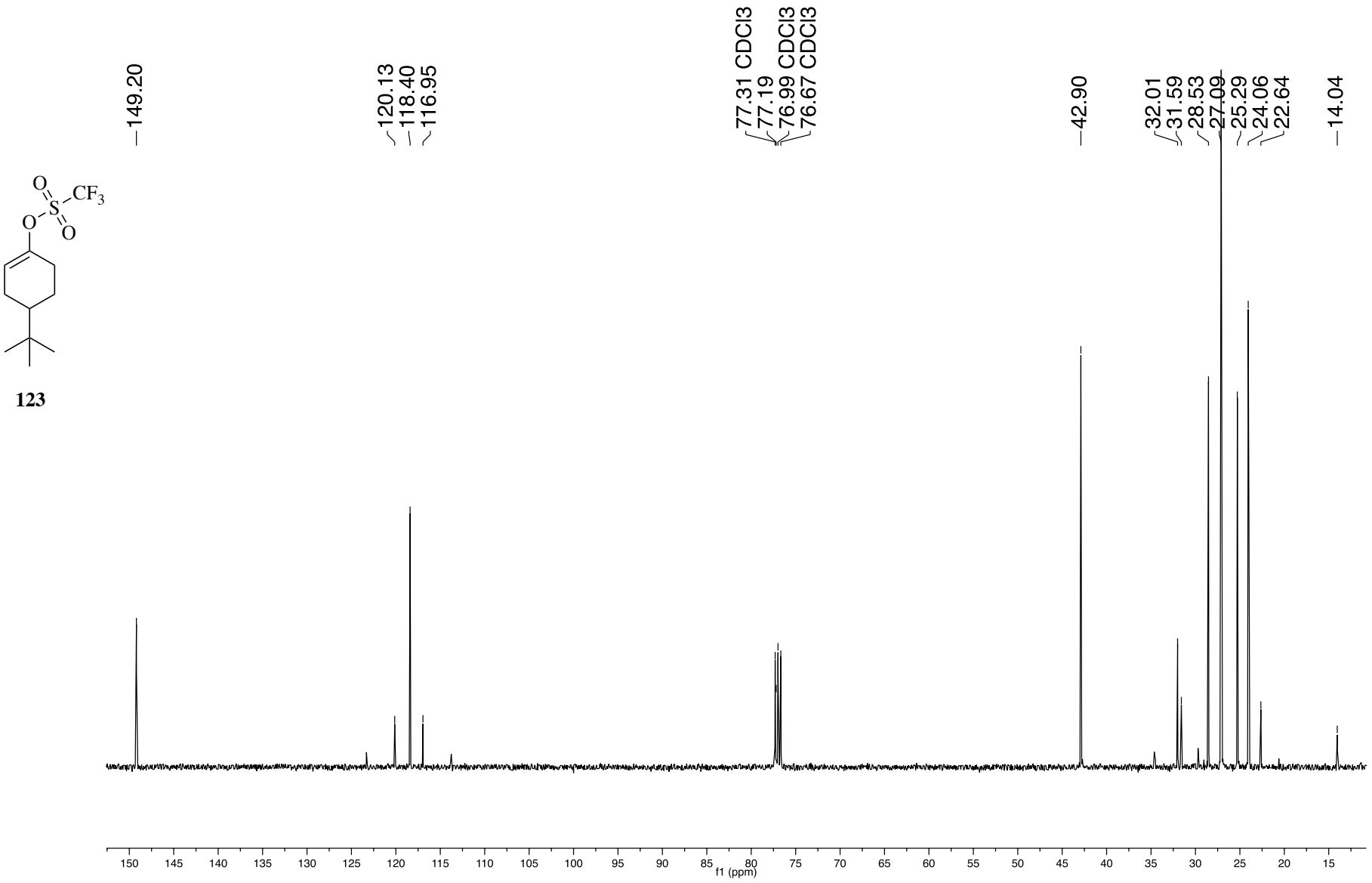


^{13}C NMR spectrum for compound **114**



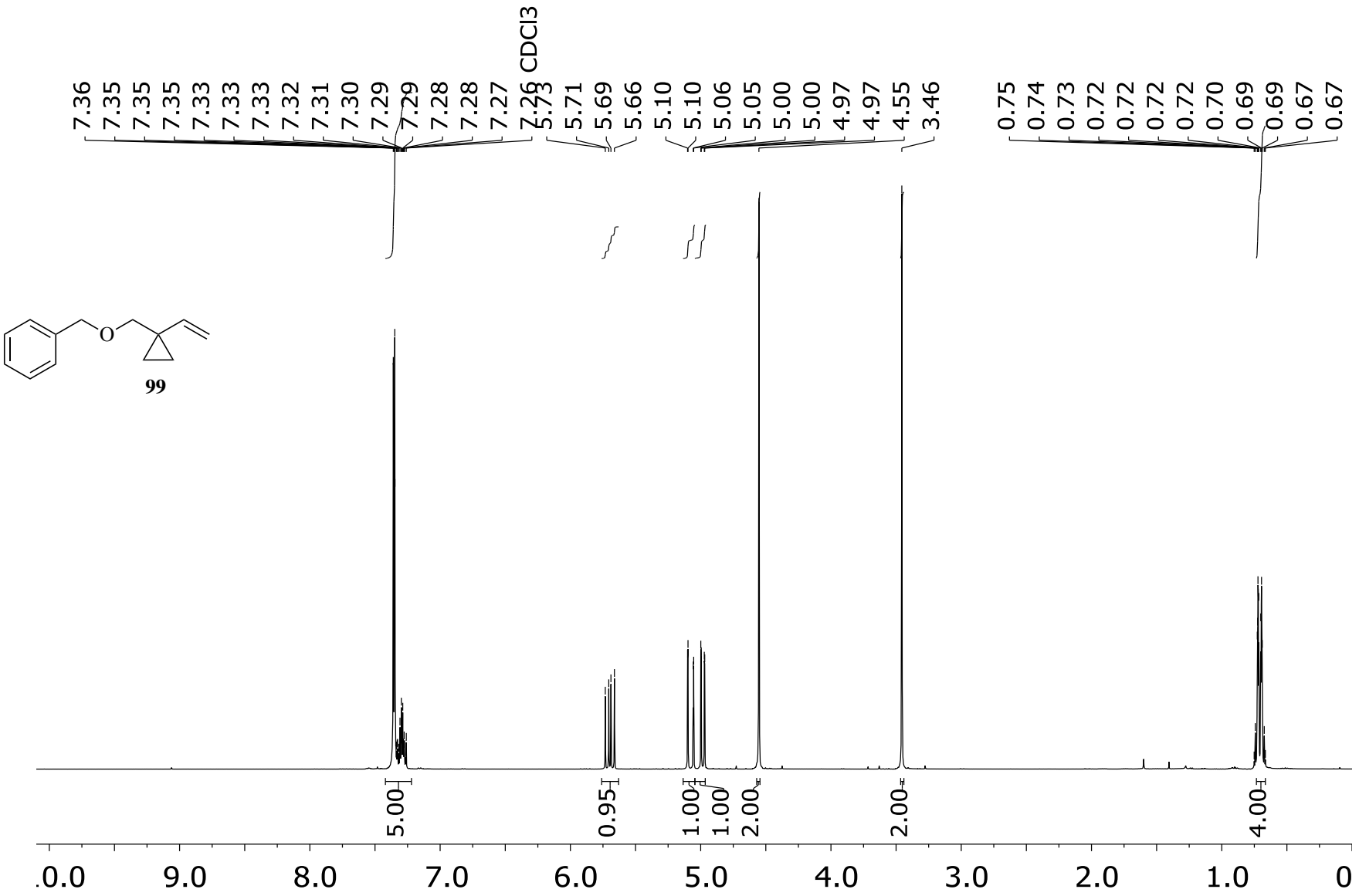
123

^{1}H NMR spectrum for compound **123**

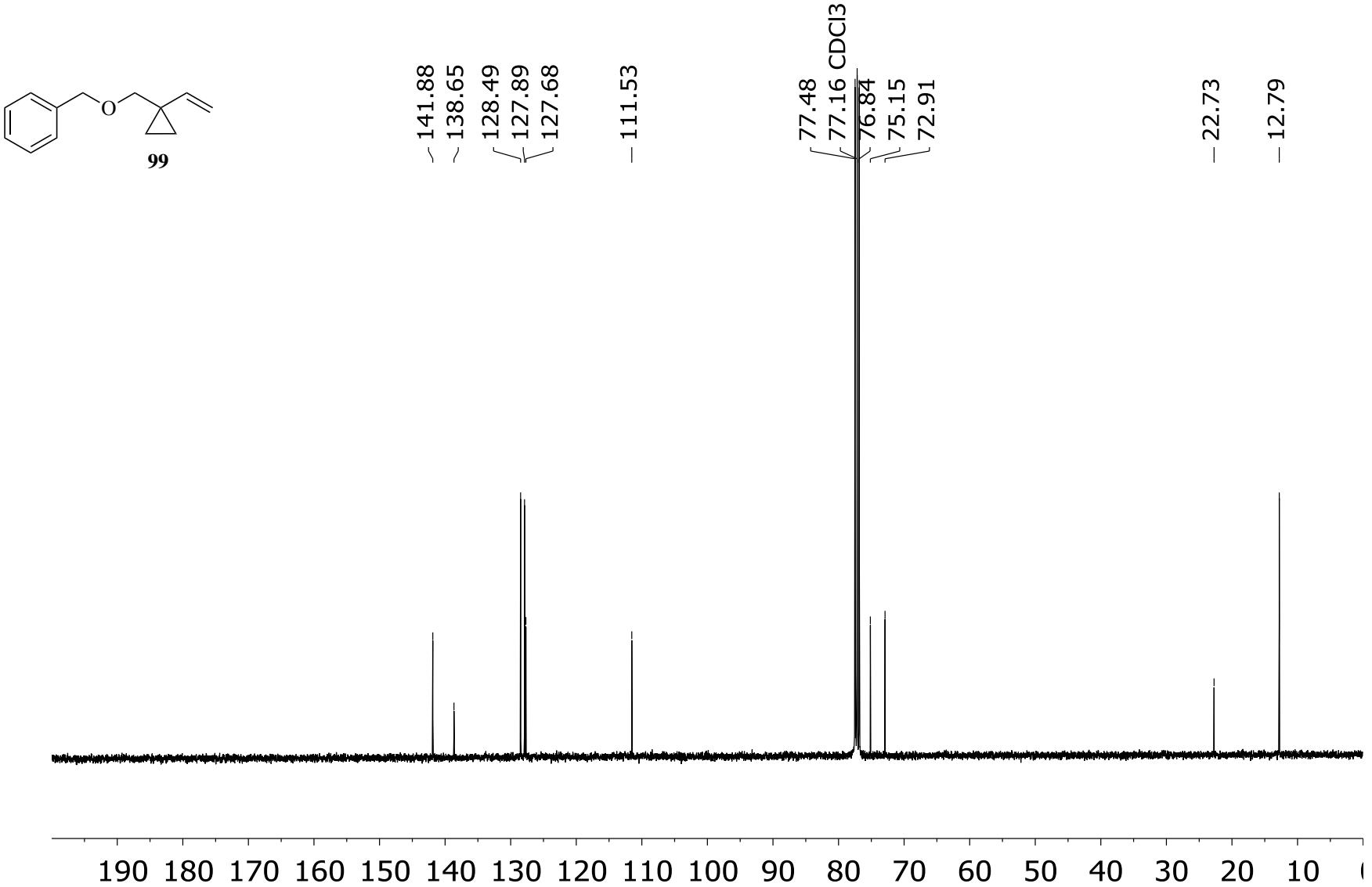


123

^{13}C NMR spectrum for compound **123**



^{1}H NMR spectrum for compound **99**



^{13}C NMR spectrum for compound **99**

References

(1) Z. Wang, in *Comprehensive oranic name reactions and reagents*, ed. N. J. Hoboken, John Wiley, NJ, 2009.
(2) T.Dudev and C. Lim, *J. Am. Chem. Soc*, 1998, **120**, 4450-4458.
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