Construction of the Polycyclic Structure of Mangicols from Chiral Propargylic Alcohols

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Abstract

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Chiral propargylic alcohols are versatile synthetic components in asymmetric synthesis. The asymmetric alkynylzinc addition to aldehydes is an efficient method to access chiral propargylic alcohols. Pauson-Khand cyclization-based domino reactions of chiral propargylic alcohol derivatives can conveniently construct the multicyclic structure of complex molecules.

Mangicols, isolated from the marine fungus *Fusarium heterosporum* by Fenical and coworkers in 2000, are new type of sesterterpenoid metabolites with unprecedented spirotricyclic skeletal components. They represent a novel class of multicyclic natural products that could potentially be made by using the transformations of chiral propargylic alcohols.

A one-pot Rh-catalyzed domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition was developed to generate an optically active polycyclic compound possessing the core fragment of mangicols. Other related polycyclic compounds were also synthesized through the same strategy. Further conversions of the polycyclic compound were investigated to facilitate the synthesis of mangciols.

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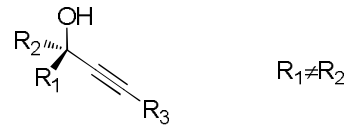
Chapter 1. Asymmetric Alkyne Addition and Applications of Chiral Propargylic Alcohols

1. Asymmetric alkynylzinc additions to aldehydes

1.1 Introduction

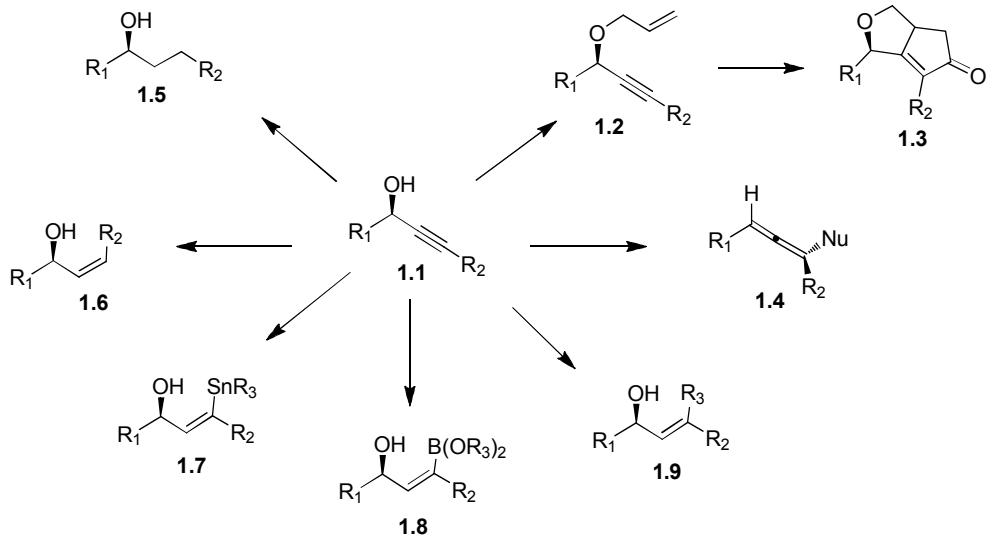
A propargylic alcohol is defined as an alkyne unit connected to a carbon bearing a hydroxyl group. Chiral propargylic alcohols possess chirality at the propargylic carbon (Figure 1.1) and have found broad applications in asymmetric synthesis.[1] A variety of transformations can be achieved from propargylic alcohols **1.1** due to the reactions of the alcohol and alkyne functionalities (Figure 1.2). For example, the hydroxyl group can undergo S_N2 substitutions to afford allylic ethers **1.2** which can be further transformed to cyclic compounds **1.3** via Pauson-Khand reaction. Optically active allenes **1.4** can be obtained by reaction with nucleophiles. The triple bond can be reduced completely to give alkanes **1.5**, or partially to give alkenes **1.6**. Metal-catalyzed hydrostannation and hydroboration can produce vinyl stannanes **1.7** and vinyl borates **1.8**, respectively.[2,3] These vinyl stannanes **1.7** and borates **1.8** can be utilized in metal-catalyzed cross coupling reactions to afford functionalized olefins **1.9**.

Figure 1.1. Chiral propargylic alcohol.



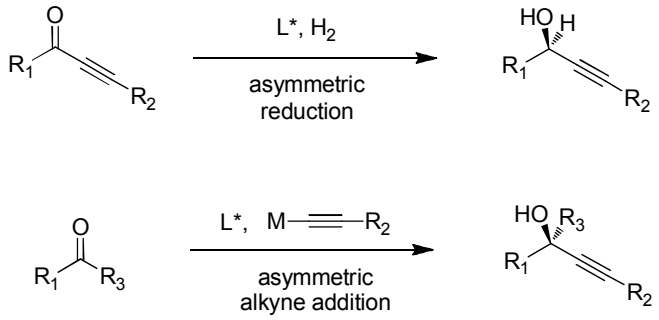
Chiral propargylic alcohol

Figure 1.2. Transformations of propargylic alcohols.



Optically active propargylic alcohols have generally been prepared through two synthetic routes: asymmetric ynone reduction and asymmetric metal-catalyzed alkyne additions to carbonyl compounds (Figure 1.3).[1] Although both methods have been investigated and used successfully, the asymmetric alkyne addition strategy gains several inherent advantages over ynone reduction. Ynone compounds are not easy to synthesize which adds more steps to access the desired propargylic alcohols. In addition, tertiary propargylic alcohols can not be obtained through ynone reduction. However, asymmetric alkyne addition produces a carbon-carbon bond and a new stereogenic center in one step, which makes it more efficient to give the chiral propargylic alcohols. In addition, tertiary propargylic alcohols can be obtained when ketones are treated with alkynyl metal reagents.[4]

Figure 1.3. Two synthetic routes to access chiral propargylic alcohols.



1.2. Asymmetric alkynylzinc additions to aldehydes

Among the asymmetric alkyne additions to aldehydes, alkynylzinc reagents have been most widely studied and used. There are many advantages for the use of alkynylzinc reagents in comparison with other alkynyl metal reagents. First of all, alkynylzinc reagents can be conveniently prepared in situ under mild conditions. Secondly, alkynylzinc reagents can tolerate many functional groups such as esters, amides, nitro groups, halogens, silyl groups and nitriles. Alkynylzinc reagents also show a slow rate of addition to carbonyl compounds in the absence of a catalyst, which will minimize the non-enantioselective background reaction.[5,6] A few representative catalyst systems are discussed below.

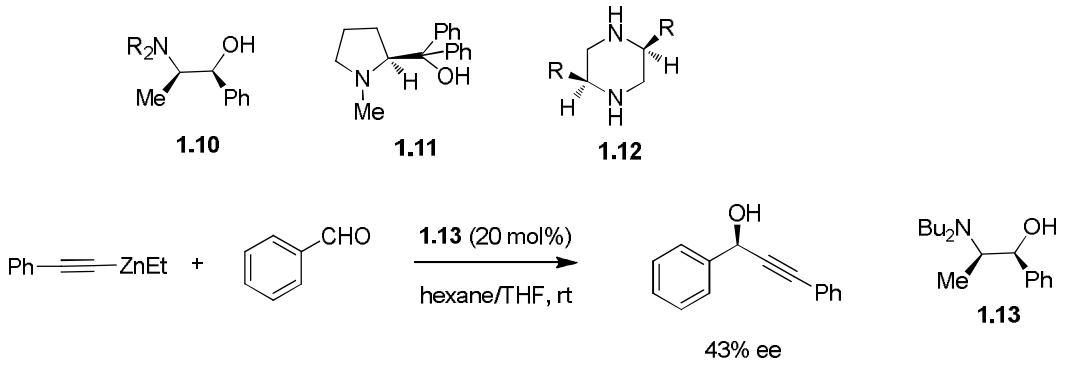
1.2.1. Nitrogen–containing ligands

a. Amino alcohol and amine ligands

In the asymmetric alkynylzinc additions to aldehydes, chiral amino alcohols are investigated first. In 1990, Soai and coworkers reported the first catalytic enantioselective alkynylzinc addition to aldehydes by using the chiral amino alcoh

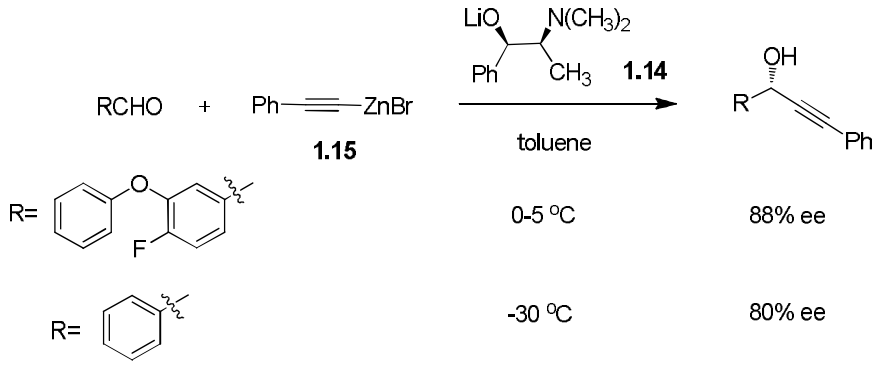
and amines **1.10-1.12**.[7] The highest ee (43%) was observed when 20 mol% of the chiral amino alcohol **1.13** was employed to catalyze the reaction of benzaldehyde with the alkynylzinc derived from phenylacetylene and Et_2Zn (Scheme 1.1). Other chiral amino alcohols and amines gave lower enantioselectivities.

Scheme 1.1. Soai's amino alcohol and amine catalyzed alkynylzinc addition.



Tombo found that using stoichimetric amounts of the chiral amino alcohol lithium salt **1.14** increased ee up to 88% for alkynylzinc additions to aldehydes in 1990.[8] The reaction was conducted at 0-5 ^oC in toluene in the presence of 1 eq of ligand **1.14** and 2 eq of the alkynylzinc reagent **1.15**. Also, benzaldehyde reacted with **1.15** to generate the chiral proparylic alcohol with 80% ee at -30 ^oC (Scheme 1.2).

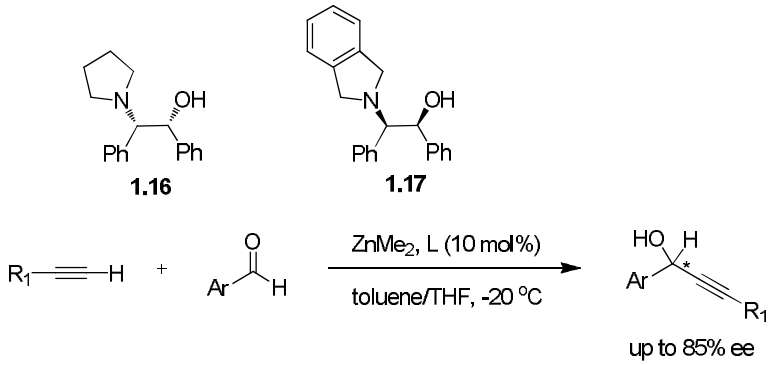
Scheme 1.2. Tombo's amino alcohol lithium salt catalyzed alkynylzinc addition.



In the same year, Li demonstrated that the amino alcohols **1.16** and **1.17** catalyzed the addition of terminal alkynes to aromatic aldehydes with up to 85% ee (Sche

1.3).[9] $ZnMe_2$ was used to form alkynylzinc in this method.

Scheme 1.3. Li's amino alcohol catalyzed alkynylzinc addition.

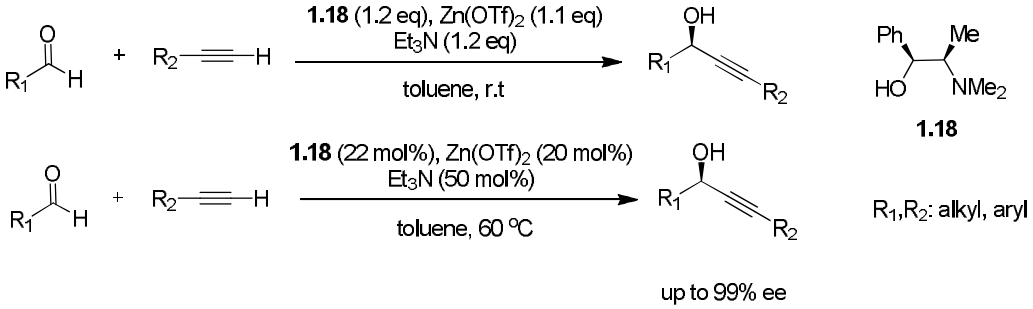


A great progress in asymmetric alkynylzinc additions to aldehydes was made by Carreira and co-workers in 2000 (Scheme 1.4).[10] They discovered an efficient catalytic system to control the stereoselective reaction of terminal alkynes with aldehydes. A stoichiometric amount of the chiral aminol alcohol **1.18** was used in the presence of 1.1 eq $Zn(OTf)_2$ and 1.2 eq Et_3N to catalyze the asymmetric addition reactions that produced the propargylic alcohols with up to 99% ee at room temperature. This system worked well for both aliphatic and aromatic aldehydes, which significantly extended the scope of the alkynylzinc additions to aldehydes in comparison with the previous research. In 2001, Carreria found the reaction could be carried out using catalytic amount of **1.18** and $Zn(OTf)_2$ when increasing the temperature to 60 ^oC.[11]

Besides the high enantioselectivities this catalytic system provided, several advantages could be highlighted. First, all reagents were commercially available and inexpensive. No prior preparation was required for the reagents. Secondly, the system was effective when using various alkynes and aldehydes. Finally, these reactions w
able to tolerate air and moisture, which made this method more convenient a

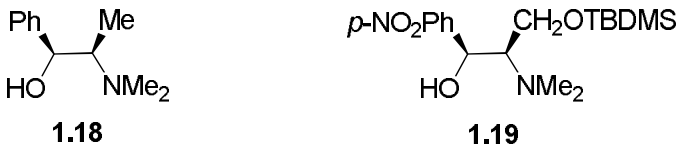
practical. One limitation of the system was low yield obtained when benzaldehyde was involved because of the Cannizaro reaction. The catalytic conditions were also not applicable to the linear aliphatic aldehydes.

Scheme 1.4. Amino alcohol catalyzed alkynylzinc addition.



On the basis of Carreria's catalytic system, Jiang modified the structure of the amino alcohol **1.18** and prepared a new zinc reagent, $Zn(OSO_2CF_2H)$ in 2002.[12,13] The amino alcohol **1.19** was used in the presence of $Zn(OSO_2CF_2H)$ and Et_3N for the asymmetric alkynylzinc addititons to give chiral propargylic alcohols with up to 99% ee (Figure 1.4).

Figure 1.4. Jiang's amino alcohols.



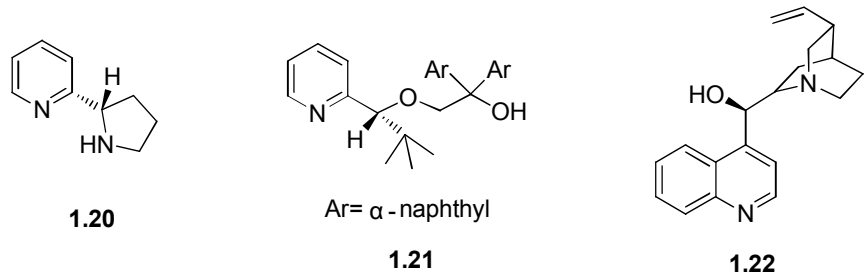
b. Pyridyl and alkaloid ligands

Other nitrogen-containing ligands like pyridyl and alkaloid ligands have been examined (Figure 1.5). In 1991, Falorni used the pyridyl amine ligand **1.20** to catalyze the addition of $(^nBuCC)_2Zn$ to benzaldehyde and got the propargylic alcohol with 16% ee.[14] The pyridyl alcohol ligand **1.21** was employed in the addition

alkynylzinc to aldehydes by Ishizaki in 1994.[15] The reaction gave up to 95% ee for aromatic aldehydes but much lower ee for aliphatic aldehydes.

In 2003, Kamble and Singh found the alkaloid ligand **1.22** catalyzed the reaction of phenylacetylene with aromatic and aliphatic aldehydes with 62-85% ee in the presence of $Ti(O^iPr)_4$.[16]

Figure 1.5. Pyridyl and alkaloid ligands.



1.20 **1.21** **1.22**

1.2.2. BINOL/ H8BINOL ligands

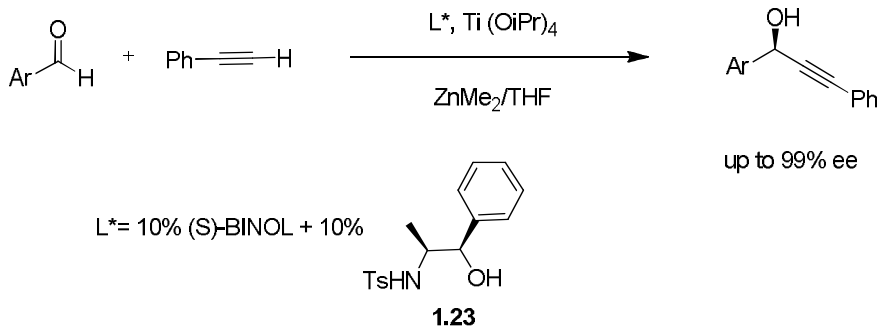
Chiral 1,1'-bi-2-naphthol (BINOL) and its derivatives have been studied and widely used in asymmetric synthesis.[17-19] Catalytic systems using optically active BINOL and its derivatives in the alkynylzinc addtions to aldehydes have also been investigated over the past decade.[5]

In 2002, our research group[20,21] and that of Chan[22,23] independently reported their work on the use of BINOL for the asymmetric alkynylzinc additions. In their study, the BINOL-$Ti(O^iPr)_4$ system was introduced to catalyze alkynylzinc additions to aldehydes with high enantioselectivities. Different alkylzinc precursors and experimental procedure were employed in their work.

Chan and co-workers used BINOL or its partially hydrogenated derivative H_8BINOL in combination with $Ti(O^iPr)_4$ and Me_2Zn for the asymmetric additions phenylacetylene to aromatic aldehydes with high enantioselectivities (Scheme 1.5)

In their procedure, phenylacetylene (1.3 eq) was added to a toluene solution of Me_2Zn (1.2 eq) at 0 ^oC for 15 min. To this solution, the titanium complex, prepared from $Ti(O^iPr)_4$ (1.5 eq) and ligand (20 mol%), was added at 0 ^oC and the solution was stirred for 15 min. An aldehyde was then added and the mixture was maintained at 0 ^oC overnight before acidic work up. High enantioselectivities were obtained for the additions to *para* and *meta*-substituted aromatic aldehydes, but reduced enantioselectivities for *ortho*-substituted aromatic and aliphatic aldehydes. It was later found the use of sulfonamide **1.23** as a co-catalyst improved the enantioselectivities for all aldehydes.[23]

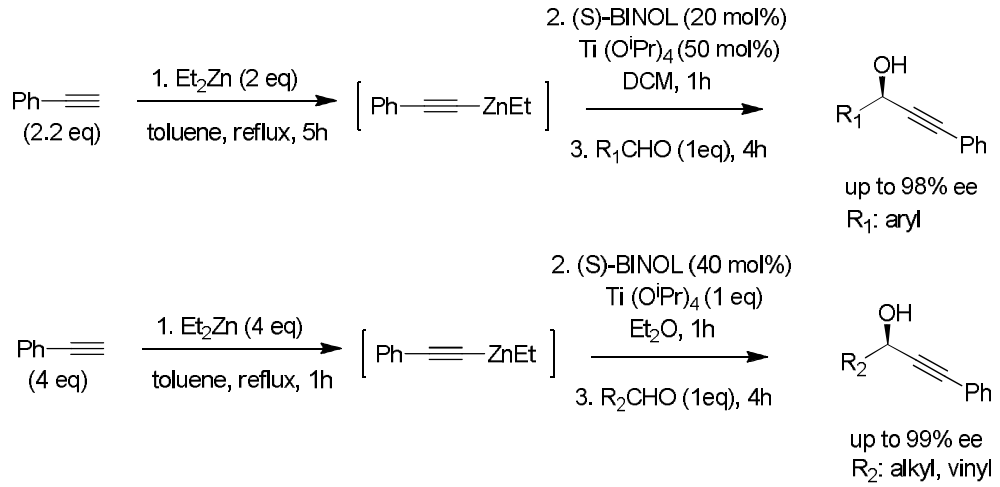
Scheme 1.5. Chan's BINOL catalytic system for alkynylzinc addition.



Our lab utilized Et_2Zn to form the alkynylzinc reagent.[20] The typical procedure consisted of three steps. First of all, phenylacetylene (2.2 eq) and Et_2Zn (2 eq) were added to a toluene solution under nitrogen and the solution was heated under reflux for 5 h during which a white precipitate was formed. Secondly, the solution was cooled to room temperature. Then (S)-BINOL (20 mol%), $Ti(O^iPr)_4$ (50 mol%) in dichloromethane were added and the mixture was stirred for 1 h. Finally, an aldehyde (1 eq) was added and the reaction mixture was stirred for 4h to give the desi propargylic alcohol. High enantioselectivities up to 98% were achieved for

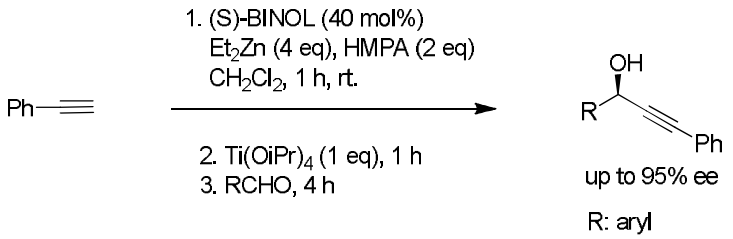
additions to various aromatic aldehydes including *ortho*, *meta* and *para*-substituted aromatic aldehydes. Using a different procedure, high enantioselectivities up to 99% were observed for the additions of alkynylzinc to aliphatic and α,β-unsaturated aldehydes.[21] In a typical experiment, to a toluene solution was added phenylacetylene (4 eq) and Et_2Zn (4 eq). The mixture was heated under nitrogen for 1 h. Then, (S)-BINOL (40 mol%), Et_2O and $Ti(O^iPr)_4$ (1 eq) were added sequentially at room temperature and stirred for 1 h. An aldehyde (1 eq) was added and the mixture was stirred for 4 h (Scheme 1.6).

Scheme 1.6. Pu's BINOL catalytic system for alkynylzinc addition.



Although the method was applied to various aldehydes in high yields and enantioselectivities, it was limited to the high temperature for the formation of the alkynylzinc reagents. In 2004, our lab found a new method to form the alkynylzinc under mild condition, which extended the generality in the asymmetric alkynylzinc additions to aldehydes.[24] HMPA as a Lewis base additive was employed in the BINOL-Et_2Zn-$Ti(O^iPr)_4$ system that catalyzed the reactions at room temperature with up to 95% ee for aromatic aldehydes (Scheme 1.7).

Scheme 1.7. Our BINOL catalytic system employing HMPA as an additive.

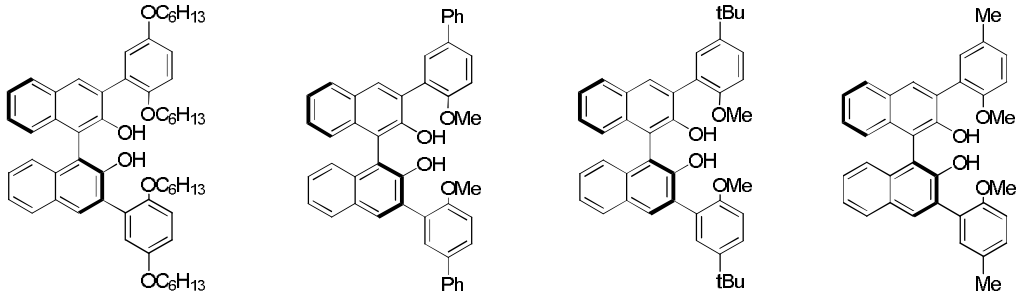


1.2.3. BINOL based derivatives

a. 3,3'-substituted BINOL ligands

Our group also conducted a significant amount of research to explore the use of 3,3'-substituted BINOL ligands for asymmetric alkylnylation additions. Ligand **1.24** was found to be highly effective for the additions of dialkylzincs to various aldehydes including aromatic and aliphatic aldehydes.[25] In 2002, ligand **1.24** and other derivatives were investigated for the asymmetric additions of alkylnylzinc to aldehydes (Figure 1.6).[26] The paper showed ligand **1.24** and a series of derivatives with electron-withdrawing groups on benzene rings were not good for the reactions of phenylacetylene with benzaldehyde in the presence of Et_2Zn. However, ligand **1.25** was found to catalyze the asymmetric additions more effectively with 80% ee. The steric effect was examined by synthesizing and testing another two ligands **1.26** and **1.27**. The ligand **1.26** with the bulkier t-Bu group at the *para* position of the 3,3'-anisyl group improved the enantioselectivity to 89%. The ligand **1.27**, which has smaller methyl group substituents, gave lower ee compared to ligand **1.26**. Interestingly, ligand **1.26** could facilitate the formation of the alkynylzinc at room temperature without Lewis base additives, which would become a feature of the 3,3'-substituted BINOL ligands.

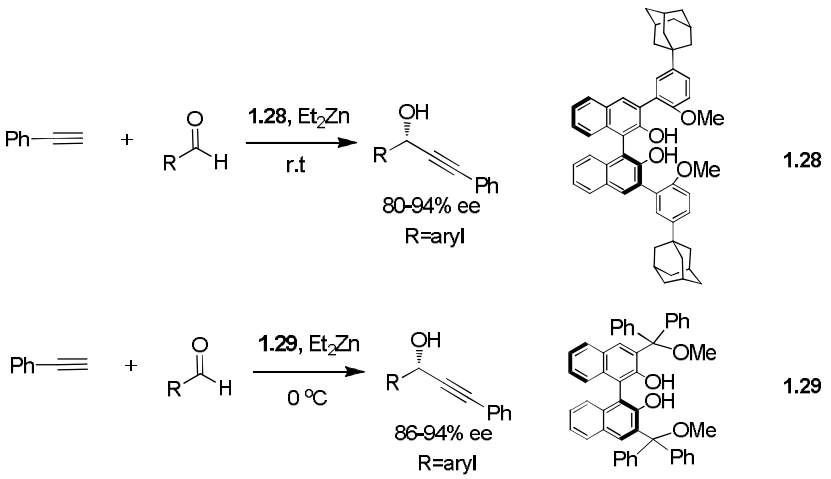
Figure 1.6. 3,3'-substituted BINOL ligands **1.24-1.27**.



1.24 **1.25** **1.26** **1.27**

Encouraged by previous results, more bulkier adamantyl group was introduced to the *para* position of the 3,3'-anisyl group and ligand **1.28** was obtained. It was found to catalyze the reaction of a terminal alkyne with various aromatic aldehydes under mild conditions to generate chiral propargylic alcohols with up to 94% ee.[27] $Ti(O^iPr)_4$ was not required and alkynylzinc could be formed at room temperature in this procedure. It was hypothesized that the catalytic efficiency may be improved if the bulky group was closer to the chiral center. With that in mind, ligand **1.29** was synthesized and tested. It showed high enantioselectivities (86-94% ee) without using $Ti(O^iPr)_4$ and a Lewis base additive for the reactions of phenylacetylene with aromatic aldehydes in the presence of Et_2Zn (Scheme 1.8).[28]

Scheme 1.8. 3,3'-substituted BINOL ligands **1.28-1.29** catalyzed alkynylzinc addition

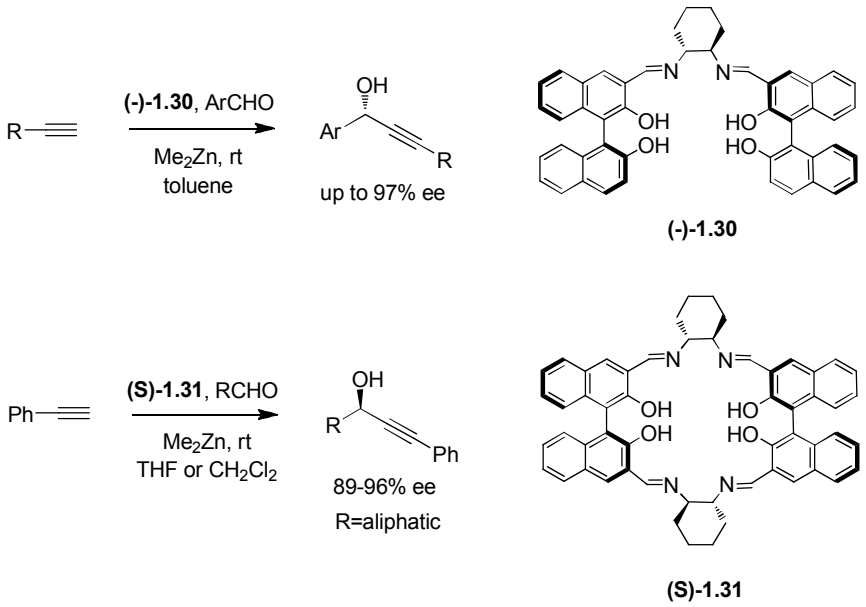


b. BINOL-amine/imine ligands

BINOL-amine/imine ligands have also been employed in the asymmetric alkynylzinc additions to aldehydes (Scheme 1.9).[29] In 2004, the BINOL-imine ligand **1.30** was designed by our group to catalyze the additions of terminal alkynes to aromatic aldehydes at room temperature with up to 97% ee. However, low enantioselectivities were observed for the additions of aliphatic aldehydes. The catalytic system featured the mild condition and no addition of $Ti(O^iPr)_4$.

Our lab also reported that the BINOL-imine macrocycle ligand **1.31** could improve enantioselectivities for the alkyne additions to aliphatic aldehydes.[30] 89-96% ee's were obtained for the addition of phenylacetylene to aliphatic aldehydes to give chiral propargylic alcohols in the presence of ligand **1.31** and Me_2Zn. The reactions could be conducted at room temperature without the use of $Ti(O^iPr)_4$.

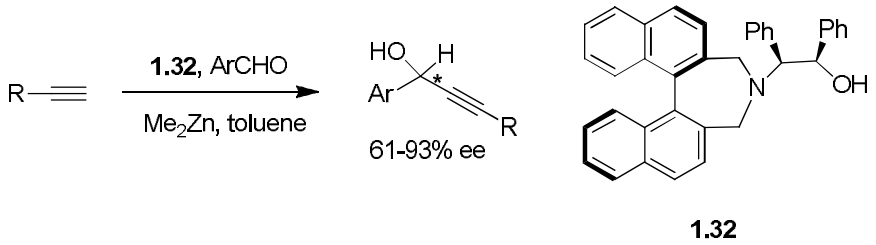
Scheme 1.9. BINOL-imine ligands **1.30-1.31** catalyzed alkynylzinc addition.



The BINOL-amine ligand **1.32** was designed by Chan in 2001 and was found effectively catalyze the addition of alkynylzinc to aromatic aldehydes to give

corresponding chiral propargylic alcohols with 61-93% ee (Scheme 1.10).[31]

Scheme 1.10. BINOL-amine ligand **1.32** catalyzed alkynylzinc addition.

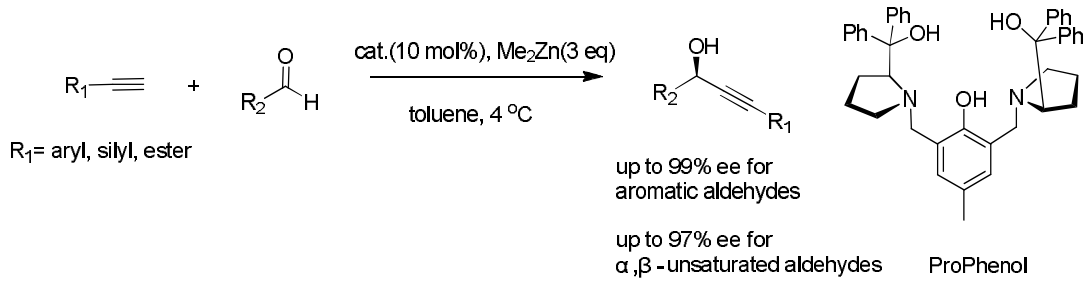


1.32

1.2.4. Other notable ligands

Besides chiral amino alcohols and BINOLs, many other catalytic systems have been developed for the addition of alkynylzinc to aldehydes. Trost's ProPhenol catalyst and Wolf's bisoxazolidine ligand are the most attractive. In 2006, Trost developed a proline-derived dinuclear zinc catalyst system (ProPhenol catalyst) to catalyze the alkynylation of aromatic and α,β-unsaturated aldehydes with high enantioselectivities (Scheme 1.11).[32] 10 mol% ProPhenol catalyst and Me_2Zn (3 eq) were used in this system. More importantly, the ProPhenol system for asymmetric alkynylzinc addition has been employed successfully by Trost in the total synthesis of several natural products including (+)-spriolaxine methyl ether, (-)-ushikulide A and (-)-adociacetylene B.[33-35]

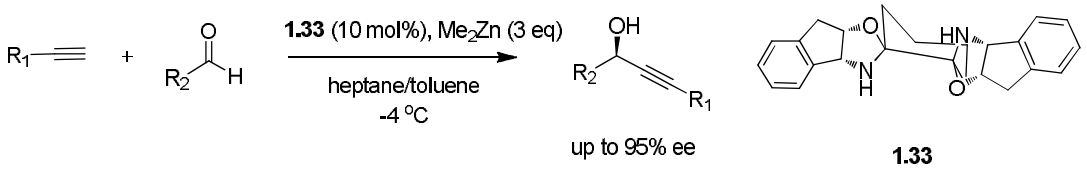
Scheme 1.11. ProPhenol catalyzed alkynylzinc addition.



First bisoxazolidine ligand **1.33** was prepared and applied in the asymmet

alkynylzinc addition to various aromatic aldehydes in high yields and enantioselectivities by Wolf in 2006 (Scheme 1.12).[36] Ligand **1.33** was synthesized in one step in a high yield from commercially available and inexpensive amino indanol. However, low enantioselectivities were obtained for aliphatic aldehydes.

Scheme 1.12. Bisoxazolidine catalyzed alkynylzinc addition.



1.3. Summary

Many highly effective catalytic systems for asymmetric alkynylzinc additions to aldehydes have been developed over the decades. Chiral amino alcohols and BINOLs represent two important classes of catalytic systems. Among these methods, Carreira's amino alcohol system and the BINOL-based catalytic system of our lab are the most effective and attractive in their practical use. Additionally, another novel and notable ligand, Trost's ProPhenol catalyst, has been proven to be highly effective and employed in the total synthesis of several natural products.

While great advances have been made, there is still much room for improvement as no catalytic system is effective for every type of alkynes and aldehydes. Traditionally, aliphatic aldehydes are the most challenging substrates in this area. The use of chiral propargylic alcohols in organic synthesis will continue to promote the exploration of more effective and general catalytic systems.

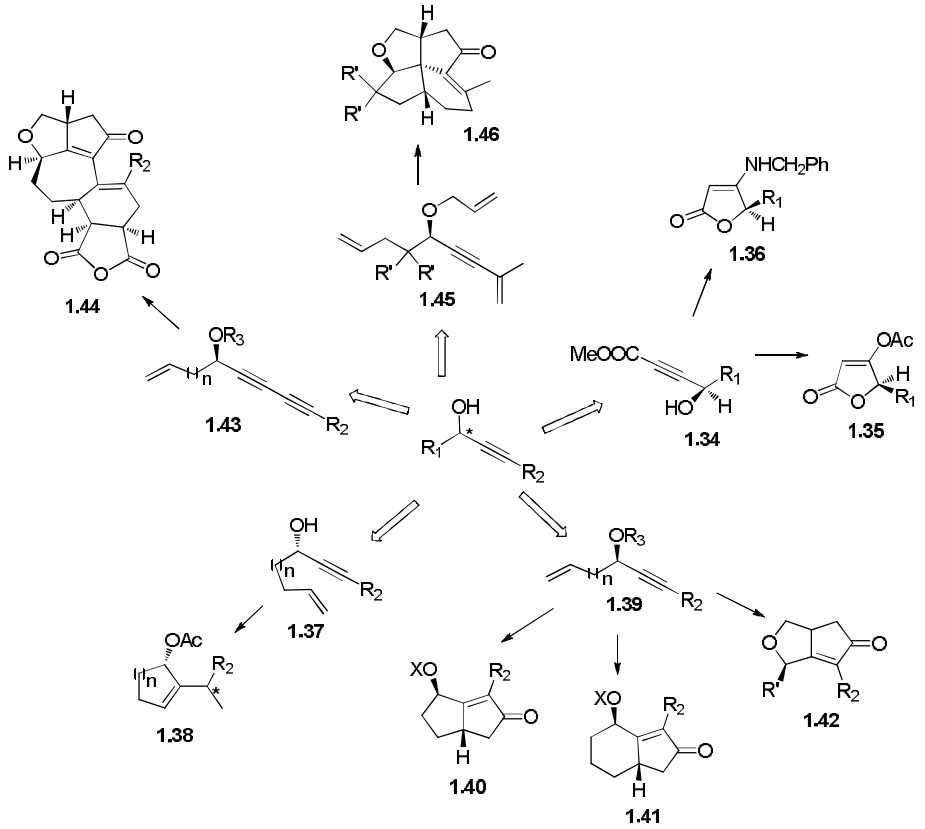
2. Synthesis of polycyclic compounds from chiral propargylic alcohols based on Pauson-Khand reaction

2.1. Transformations of chiral propargylic alcohols

As many effective methods have been developed for the asymmetric addition of alkynes to aldehydes, diverse chiral propargylic alcohols are readily available for the synthesis of complex chiral compounds. Thus, the application of chiral propargylic alcohols in organic synthesis is further under investigation.

Our lab has reported various transformations of the chiral propargylic alcohols generated from the BINOL-Ti(O^iPr)$_4$-Et_2Zn system (Figure 1.7).[1,9,10] A type of functionalized propargylic alcohols **1.34** could be converted to optically active tetronic acids **1.35**[37] and aminofuranones **1.36**.[38] Also, functionalized cycloalkenes **1.38** could be generated from propargylic alcohol based enynes **1.37** utilizing ring-closing metathesis.[39] Propargylic alcohol based enynes **1.39** could undergo intramolecular Pauson-Khand reaction to access bicyclic products **1.40-1.42**.[40] Polycyclic compounds **1.44** could be constructed via Pauson-Khand reaction of propargylic alcohol based dienediynes **1.43** followed by enyne metathesis and intermolecular [4+2] cycloaddition.[41] Finally, a domino Pauson-Khand and Diels-Alder reaction was used to generate tetracyclic compounds **1.46** from propargylic alcohol based trienynes **1.45**.[42,43]

Figure 1.7. Transformations of chiral propargylic alcohols.



Among all these transformations, Pauson-Khand reaction was one of the most attractive methods for the construction of cyclopentenone rings. Polycyclic compounds could be obtained conveniently through Pauson-Khand reaction in tandem with other reactions such as [4+2] cycloaddition.

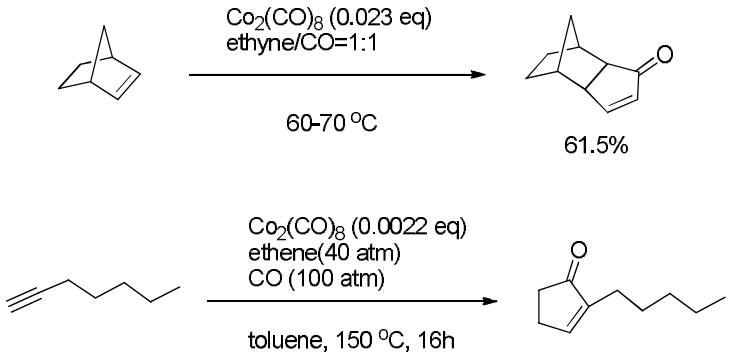
2.2. Pauson-Khand reaction

2.2.1. Introduction

Pauson-Khand reaction is a formal [2+2+1] cycloaddition of an alkyne, alkene and carbon monoxide, which is a powerful way for making cyclopentenone rings.[44-49] The reaction was first reported by Pauson and Khand in the early 1970s.[50,51] The classical Pauson-Khand reaction was considered to be a stoichiometric reaction a

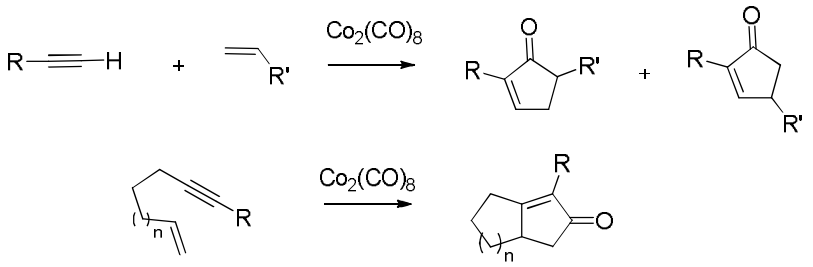
the alkene substrate was limited to strained alkenes such as norbornene, norbonadiene and cyclopropenes. In 1973, Pauson and coworkers reported the first example of catalytic intermolecular Pauson-Khand reaction employing 0.023 eq of $Co_2(CO)_8$.[52] In 1991, Rautenstrauch and coworkers utilized 0.0022 eq of $Co_2(CO)_8$ to catalyze intermolecular Pauson-Khand reaction of unconstrained alkenens (Scheme 1.13).[53]

Scheme 1.13. Catalytic intermolecular Pauson-Khand reaction.



Intermolecular Pauson-Khand reaction is regioselective with respect to alkyne, and the CO group is normally found next to the bulkier R group of the alkyne. But the regioselectivity with respect to alkene is limited. To control the orientation of the alkene, extra coordination positions with the metal are needed. The better way to solve the regioselectivity issue is to make enynes as substrates that can undergo intramolecular Pauson-Khand reaction. In 1981, Schore and coworkers discovered the first intramolecular Pauson-Khand reaction of simple enynes.[54] Strained alkenes were not necessary for this reaction. Therefore, the intramolecular Pauson-Khand reaction becomes a powerful and efficient strategy to establish polycyclic ring systems of structurally complex compounds from simple enyne precursors (Scheme 1.14).

Scheme 1.14. Intermolecular and intramolecular Pauson-Khand reaction.



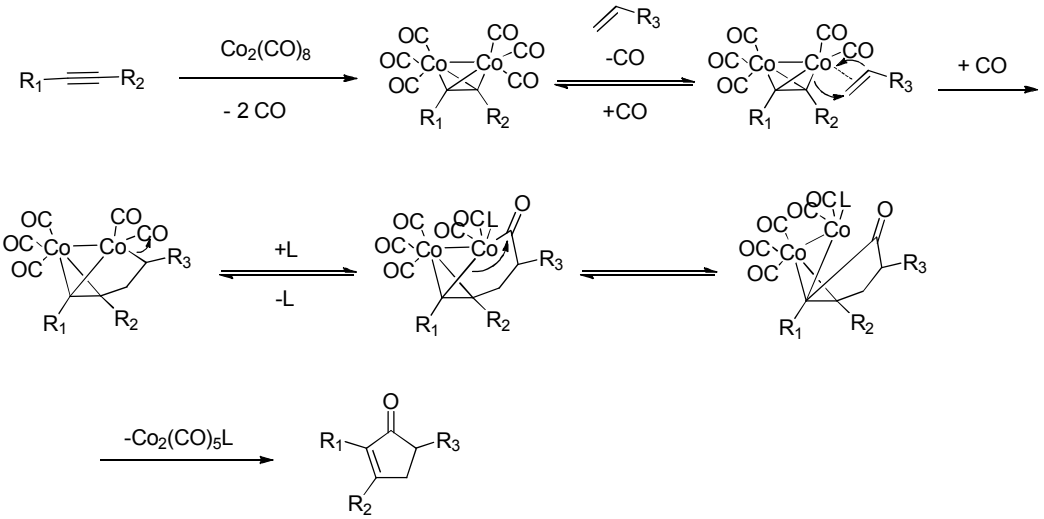
While Pauson-Khand reaction is shown to tolerate many functional groups such as esters, ethers, thioethers, amides, nitriles and alcohols, it still has some limitations. Classical Pauson-Khand reactions are performed in two steps. Firstly, a cobalt-alkyne complex is formed at room temperature upon treatment of alkyne with $Co_2(CO)_8$. Secondly, temperature is increased to promote the cyclization. However, high temperature often leads to decomposition of substrates or products. In order to circumvent high temperature and slow reaction rate, many improvements have been made for the Pauson-Khand reaction.

2.2.2. Exploration and improvement of Pauson-Khand reaction

To better understand and improve the reaction, a mechanism has been proposed based on observations of regio- and stereochemistry for many examples (Scheme 1.15).[44-46] While no solid mechanistic data or all intermediates were obtained, this mechanism has been generally accepted. The only intermediate that has been isolated is the initial alkyne-$Co_2(CO)_6$ complex from the complexation of the alkyne with $Co_2(CO)_8$, releasing two molecules of CO. The next step involves dissociation of a CO and alkene coordination. Then the alkene can insert into one of the cobalt-carb bonds to generate the resulting cobaltacycle, which is thought to be a rate-determini

step in the reaction. In the intermolecular Pauson-Khand reaction, the alkene will insert at the less sterically hindered cobalt-carbon bond, resulting in the observed regioselectivity with respect to the alkyne. However, the regioselectivity, which depends on the orientation of the alkene, can not be predicted. Then, migratory insertion of a CO ligand bound to cobalt to form the carbonyl moiety and subsequent reductive elimination and decomplexation of dicobalt complex generate the cyclopentenone product.

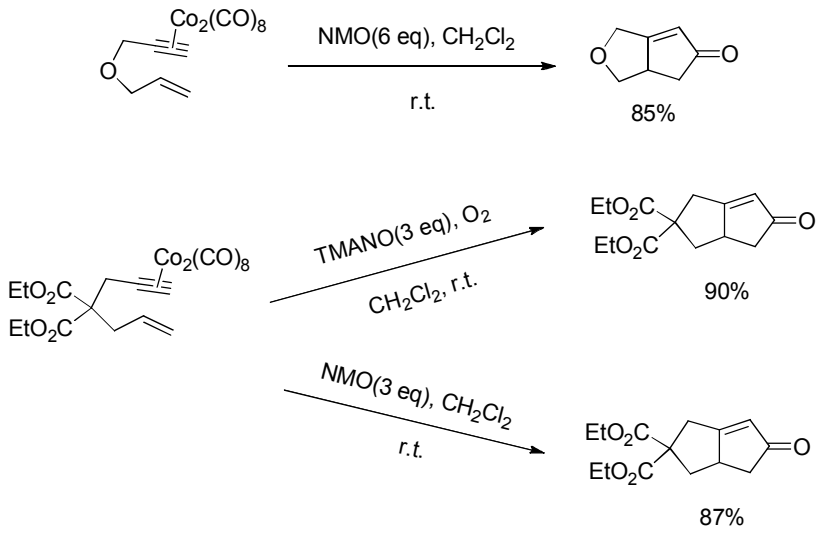
Scheme 1.15. A Proposed mechanism for the Pauson-Khand reaction.



From the studies of this mechanism, the dissociation of a CO ligand to open a coordination site for the alkene is determined to be crucial. It is assumed that harsh conditions such as elevated temperature promoted the dissociation of CO for the Pauson-Khand reaction. A great breakthrough was made by Schreiber[55] and Jeong[56] in the early 1990s when they independently found that tertiary amine *N*-oxides were effective in promoting the Pauson-Khand reaction at room temperature. Among the amine *N*-oxides, the most commonly used are *N*-methylmorpholine-*N*-oxide (NM discovered by both Schreiber and Jeong, and trimethylamine *N*-oxide (TMAN

introduced by Jeong (Scheme 1.16). The amine *N*-oxides are most likely to function by oxidizing a CO ligand from the metal, liberating a CO_2 and opening a coordination site for the alkene. The discovery of these amine *N*-oxides made the Pauson-Khand reaction proceed under milder conditions, which greatly expanded the scope of substrates and utilities of the reaction in organic synthesis.

Scheme 1.16. Tertiary amine *N*-oxides as promoters for the Pauson-Khand reaction.



In addition to the most attractive and widely used amine *N*-oxides, other promoters such as silica, amines, amides, sulfides and molecular sieves have also been explored to improve the Pauson-Khand reaction (Scheme 1.17). In 1986 Smit and Caple reported that thermolysis on silica under oxygen was a mild method for promoting the Pauson-Khand reaction.[57] It is hypothesized that absorption of the metal on the silica facilitates ligand exchange, and that hydrogen bonding of the ether oxygen to the solid surface serves to force the hydrophobic portions of the molecule together to promote the reaction. The alkyne-cobalt **1.47** underwent the reaction smoothly at 45 ^{o}C within 30 min to give the cyclized product in 75% yield.

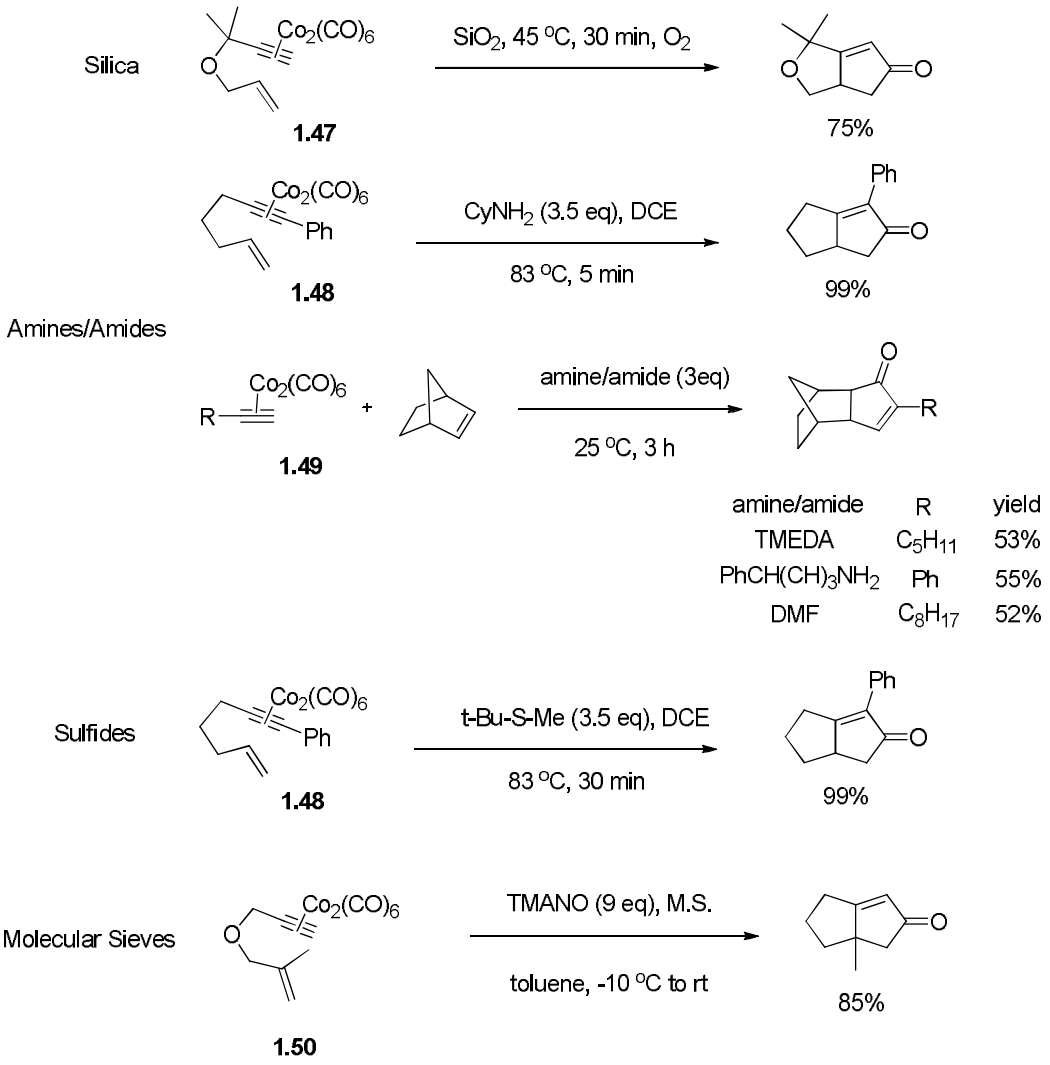
Primary amines such as cyclohexylamine ($CyNH_2$) were found to effectiv

accelerate the Pauson-Khand reaction by Sugihara in 1997.[58] The alkyne-cobalt **1.48** was treated with $CyNH_2$ at 83 ^oC to produce the cyclized product in quantitative yield within 5 min. It was later found by the same group that sulfides such as n-butyl methyl sulfide could also facilitate the Pauson-Khand reaction efficiently.[59]

Amines and amides including tetramethylethylenediamine (TMEDA), α-methylbenzylamine and dimethylformamide (DMF) were introduced to promote the Pauson-Khand reaction of alkyne-cobalt complexes **1.49** with norbornene by Periasamy in 1998.[60] The amines and amides function by displacing one of the CO ligands and coordinating with the metal.

The combination of molecular sieves, TMANO amine oxide and zeolite introduced by Pérez-Castells In 1999 promoted the Pauson-Khand reaction efficiently.[61] The alkyne-cobalt **1.50** was reacted with 9 eq TMANO in the presence of 4Å molecular sieves at room temperature to give the bicyclic product in 85% yield. Molecular sieve is assumed to adsorb the enyne and stabilize a pretransition state or accelerate ligand exchange.

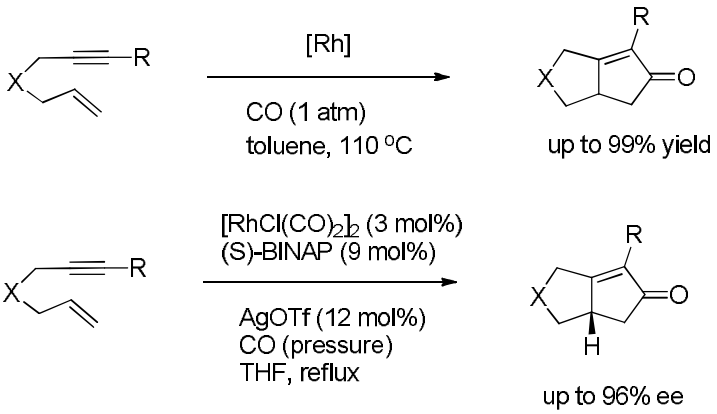
Scheme 1.17. Promoters for the Pauson-Khand reaction.



In addition to the Co catalysts, other transition metal catalysts based on Fe[62], Ni[63], Ti[64-66], Zr[67,68], Ru[69,70], Rh[71] and Ir[72] have also been investigated for the Pauson-Khand reaction. Among these metal catalysts, Rh based catalysts are the most attractive and commonly used. The Rh(I)-catalyzed intramolecular Pauson-Khand reaction was realized for the first time in 1998 by Jeong and coworkers (Scheme 1.18).[71] A few of Rh (I) catalysts such as $RhCl(PPh_3)_3$, *trans*-$RhCl(CO)(PPh_3)_2$, RhCl(CO)(dppe) and *trans*-$[RhCl(CO)(dppp)]_2$ were found to be effective for this cyclization. A variety of *C*-, *O*- and *N*-tethered 1,6-enynes gave good to excellent yields. In 2000 they report

the first successful Rh-catalyzed asymmetric intramolecular Pauson-Khand-type reaction utilizing a catalytic system comprising $[RhCl(CO)_2]_2$ and (S)-BINAP.[73]

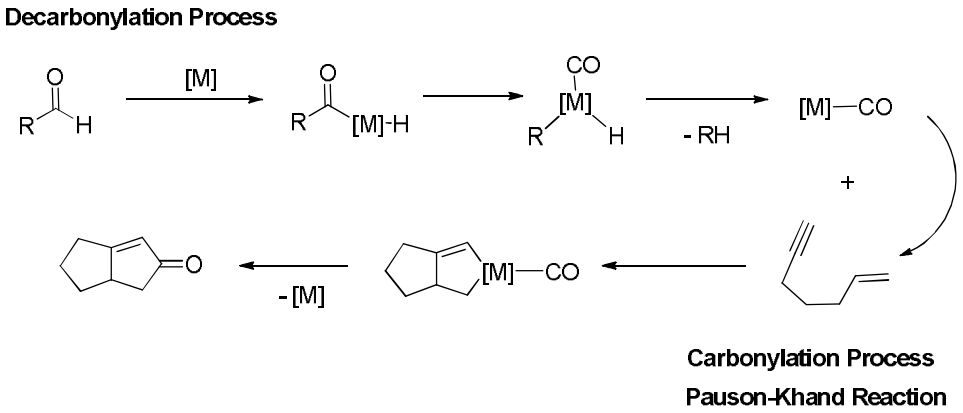
Scheme 1.18. Rh(I)-catalyzed intramolecular Pauson-Khand reaction.



Various Rh catalytic systems have been further explored since the first Rh(I) catalyzed Pauson-Khand reaction was reported. It was shown that $Rh(dppp)_2Cl$ or $[Rh(COD)Cl]_2$ or $[Rh(CO)_2Cl]_2$ tuned by phosphine ligands were widely used to effectively catalyze intra- and intermolecular Pauson-Khand and related reactions.[49] Chiral ligands were needed in these catalytic systems for the asymmetric Pauson-Khand reactions.

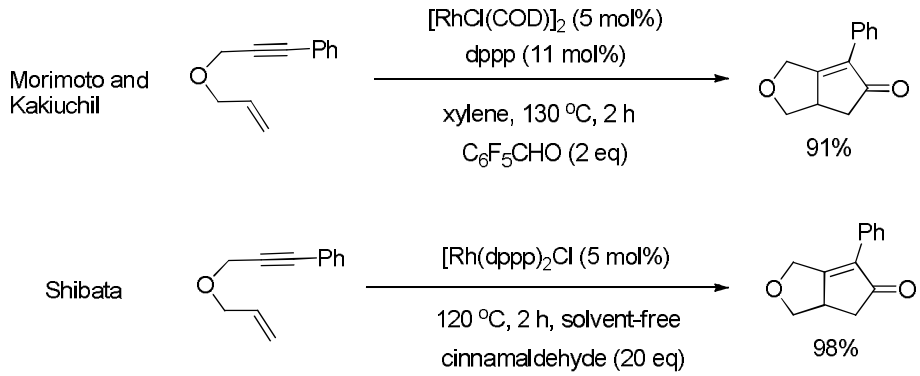
Highly poisonous carbon monoxide is usually employed in the Pauson-Khand reaction, which constitutes a drawback to the previous methodologies. In 2002, Morimoto and Kakiuchi[74] and Shibata[75] independently reported a conceptual evolution on the use of metal carbonyl systems to allow the Pauson-Khand reaction in the absence of CO gas. Since Rhodium complexes could catalyze both the decarbonylation of aldehydes and the Pauson-Khand reaction, it would be possible to introduce aldehydes as CO source to the reaction system (Scheme 1.19).

Scheme 1.19. Decarbonylation of aldehyde and the Pauson-Khand reaction.



Morimoto and Kakiuchi utilized pentafluorobenzaldehyde as an efficient CO surrogate for the Pauson-Khand reaction, whereas Shibata employed cinnamaldehyde as CO source (Scheme 1.20).

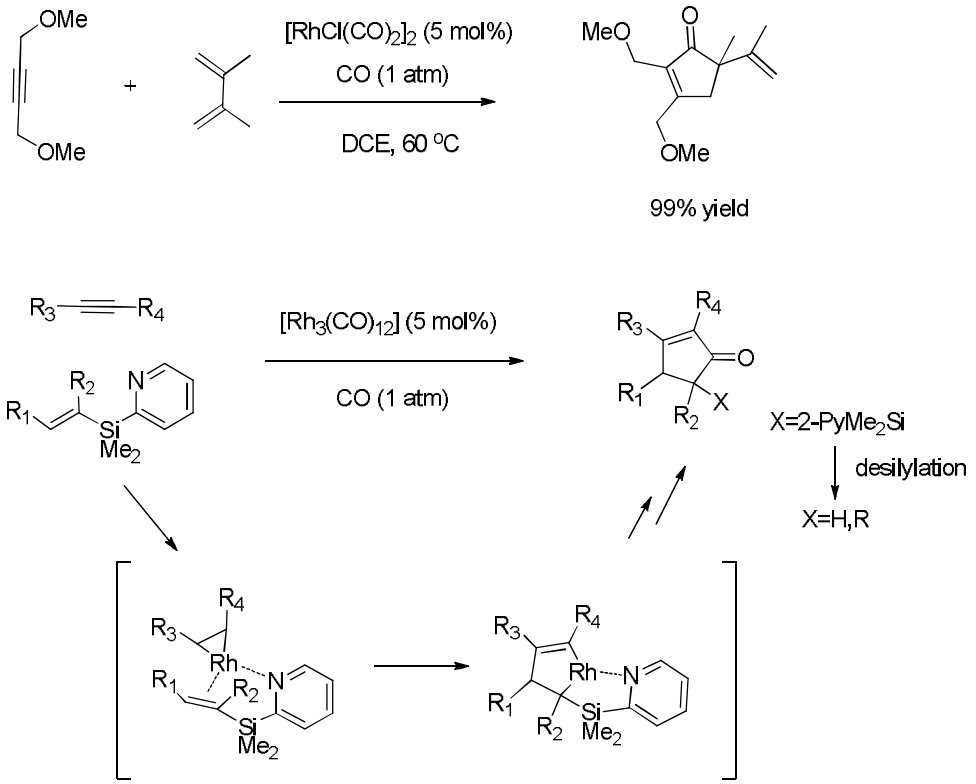
Scheme 1.20. Aldehydes as CO surrogates for the Pauson-Khand reaction.



In addition to simple *C*-, *O*- and *N*-tethered enynes which are suitable for intramolecular Pauson-Khand and related reactions, the scope of alkene substrates in intermolecular Pauson-Khand reaction have also been widened by introducing alkene equivalents. In 2004, Wender reported the first example of Rh-catalyzed intermolecular dienyl Pauson-Khand reaction (Scheme 1.21).[76] 2,3-disubstituted 1,3-dienes reacted with various alkynes to generate the alkenyl cyclopentenones with excellent regioselectivities and yields under mild conditions. In 2002, Itami a Yoshida introduced a pyridylsilyl group to control regioselectivities of alke

substrates, which greatly expanded the scope of intermolecular Pauson-Khand reaction (Scheme 1.21).[77] The pyridylsilyl group was able to coordinate with metal center to control regioselectivity and could be readily removed later via desilylation.

Scheme 1.21. Widen the scope of intermolecular Pauson-Khand reaction.



2.3. Pauson-Khand based domino reactions

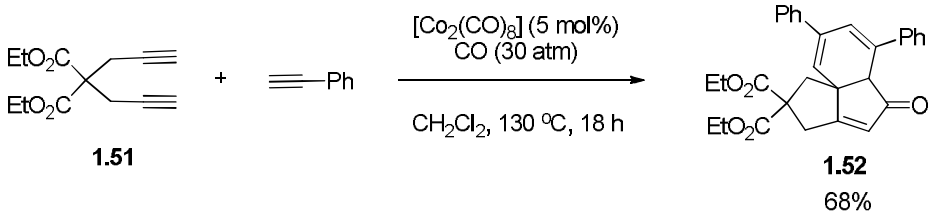
Transition-metal-mediated reactions have been widely studied and applied in organic synthesis for several decades.[78] However, the use of transition metals in the synthesis of complex molecules is often limited to one chemical transformation. The synthetic efficiency can be greatly improved if a single catalyst is used to mediate two or more transformations in a selective manner in one operation.[79] domino reaction becomes a powerful and efficient method to construct the skeleton of comp compounds.[80-82]

Pauosn-Khand reaction is a useful way to access cyclopentenone ring bearing two double bonds which can be potentially utilized in the following reactions such as Diels-Alder reaction.[46] Chung and co-workers have been active for decades in the area of Pauson-Khand based domino reactions. A variety of complex polycyclic compounds have been readily synthesized by their catalytic system.

2.3.1. Co-catalyzed intermolecular Pauson-Khand based domino reactions

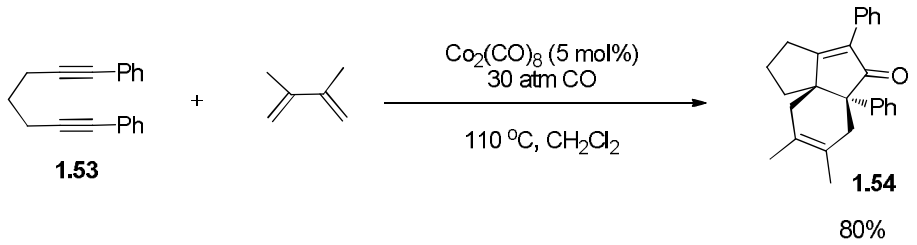
In 2000, they reported a Co-catalyzed domino [2+2+1] and [2+2+2] cycloaddition reaction of diynes with two phenylacetylenes in the presence of 30 atm CO (Scheme 1.22).[83] The first [2+2+1] cycloaddition is a Co-catalyzed Pauosn-Khand type reaction employing 1,6-diyne **1.51** as substrate, whose product is trapped through the second Co-catalyzed [2+2+2] cycloaddition with phenylacetylene to generate the tricyclic compound **1.52**.

Scheme 1.22. Co-catalyzed domino [2+2+1] and [2+2+2] cycloaddition.



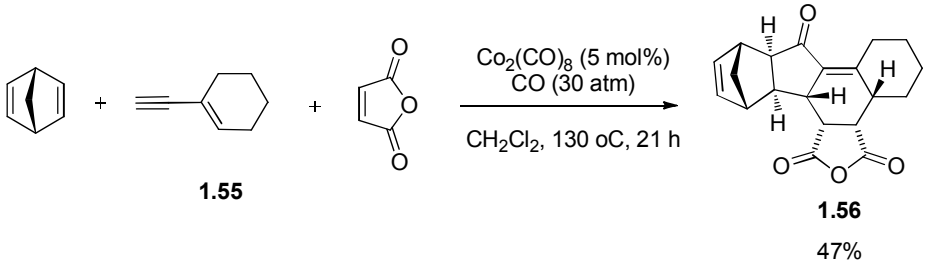
Chung also studied Co-catalyzed domino [2+2+1] and [4+2] cycloaddition reaction between diyne and diene.[84] Treatment of the diyne **1.53** and dimethyl-1,3-butadiene with $Co_2(CO)_8$ (5 mol%) in CH_2Cl_2 at 110 °C under 30 atm CO for 18 h afforded the tricyclic compound **1.54** (Scheme 1.23).

Scheme 1.23. Co-catalyzed domino [2+2+1] and [4+2] cycloaddition.



In 2005, they demonstrated that complex compounds were easily obtained from three components through a one-pot Co-catalyzed domino Pauson-Khand and Diels-Alder reaction.[85] The enyne **1.55** was treated with norbornene, maleic anhydride and $Co_2(CO)_8$ (5 mol%) in CH_2Cl_2 at 130 °C under 30 atm CO for 21 h to generate compound **1.56** in 47% yield (Scheme 1.24).

Scheme 1.24. One-pot Co-catalyzed domino Pauson-Khand and Diels-Alder reaction.



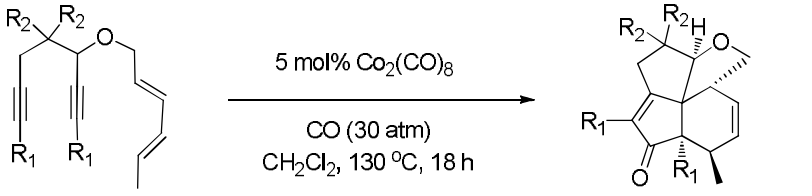
2.3.2. Co-catalyzed intramolecular Pauson-Khand based domino reactions

Intramolecular Pauson-Khand based domino reactions have also been proved effective to construct polycyclic ring systems. In 2002, Chung developed a one-pot synthesis of fenestrane derivatives from dienediynes by the Co-catalyzed domino intramolecular Pauson-Khand-type reaction and [4+2] cycloaddition.[86] The dienediynes **1.57** were treated with $Co_2(CO)_8$ (5 mol%) in CH_2Cl_2 at 130 °C in the presence of 30 atm CO for 18 h to form fenestrane derivatives **1.58** (Scheme 1.2

Later they reported the synthesis of new tetracyclic compounds **1.60** from anotl

type of dienediynes **1.59** employing the same method (Scheme 1.26).[87]

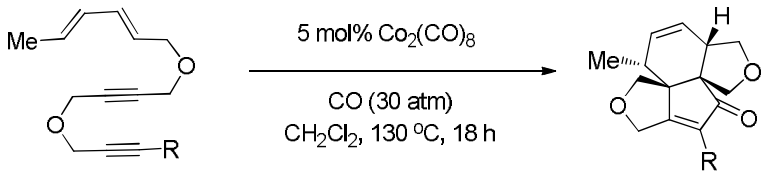
Scheme 1.25. One-pot synthesis of fenestrane derivatives from dienediynes.



1.57 **1.58**

R_1=Ph, R_2=Me 84%
R_1=Ph, R_2=H 74%
R_1=R_2=H 51%

Scheme 1.26. Synthesis of tetracyclic compounds **1.60** from dienediynes **1.59**.

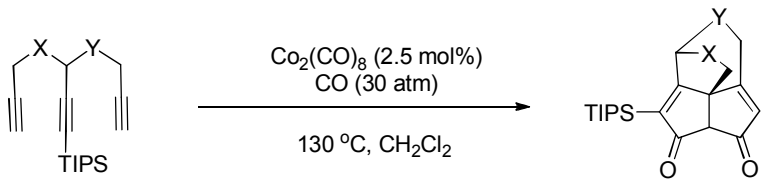


1.59 **1.60**

R=H, 19%
R=Me, 64%
R=nBu, 57%
R=Ph, 73%

Triynes could also be appropriate precursors for the construction of tetracycles through intramolecular Pauson-Khand based domino reactions. $Co_2(CO)_8$ (2.5 mol%) catalyzed the triynes **1.61** under 30 atm CO at 130 °C for 18 h to give the tetracyclic compounds **1.62** in poor to good yields (Scheme 1.27).[88]

Scheme 1.27. Synthesis of the tetracyclic compounds **1.62** from triynes **1.61**.



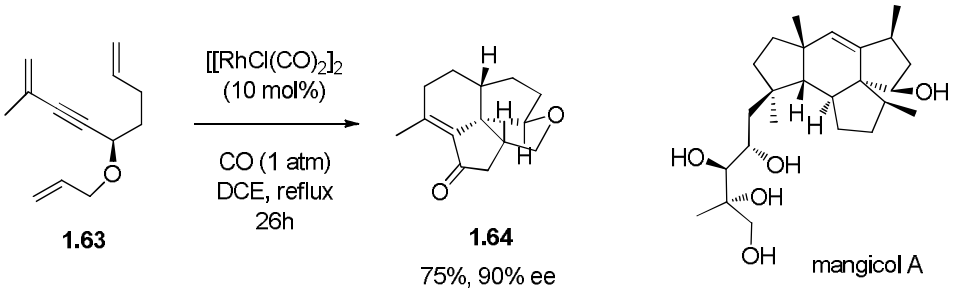
1.61 **1.62**

X=O, Y=O, 75%
X=O, Y=CH_2, 71%
X=CH_2, Y=N-Bn, 74%
X=O, Y=$C(CH_3)_2$, 10%

2.3.3. Rh-catalyzed intramolecular Pauson-Khand based domino reactions

Recently, our lab developed an efficient Rh(I)-catalyzed domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition to access the spirotricyclic compounds.[42,43] When the chiral trieneyne **1.63** was treated with $[[RhCl(CO)_2]_2$ (10 mol%) under 1 atm CO in refluxing 1,2-dichloroethane (DCE), the tetracyclic compound **1.64** was obtained with 75% yield and 90% ee (Scheme 1.28). Compound **1.64** represents an analogue of the core fragment of mangicol A after the opening of its hydrofuran ring.

Scheme 1.28. Rh(I)-catalyzed domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition.



2.4. Summary

Chiral propargylic alcohols have found extensive applications in organic synthesis. Diverse transformations could be achieved from chiral propargylic alcohols to prepare cyclic compounds. Among these transformations, Pauson-Khand reaction is one of the most efficient methods to access cyclopentenone ring bearing two double bonds which can be employed in the following reactions to construct complex polycyclic compounds. Pauson-Khand reaction has been studied for several deca

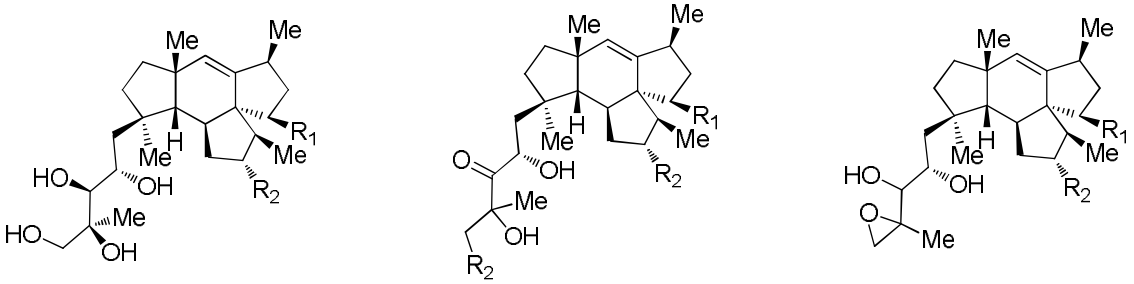
since it was first discovered in 1970s. Promoters, transition metal catalysts, CO surrogates and the scope of substrates have been widely explored. In the synthesis of complex molecules, domino Pauson-Khand-type reaction and other reactions such as [4+2] cycloaddition are found to be highly effective and convenient. One-pot Co or Rh-catalyzed Pauson-Khand based domino reactions have been demonstrated by Chung and our lab respectively to access a variety of polycyclic compounds.

3. Mangicols and neomangicols

3.1. Introduction

Mangicols represent a novel class of multicyclic natural products that could potentially be made by using the transformations of chiral propargylic alcohols. Mangicol A-G (Figure 1.8), isolated from the marine fungus *Fusarium heterosporum* by Fenical and coworkers in 2000, are new type of sesterterpenoid metabolites with unprecedented spirotricyclic skeletal components.[89] In a test against the National Cancer Institutes 60 cell line panel, the mangicols showed weak to modest cytotoxicities with no specificity towards any particular cancer cell evaluation. However, mangicol A and C displayed significant anti-inflammatory activity in a phorbol myristate acetate-induced edema assay (81% and 57% reduction in edema, respectively), which was comparable to a commercially available anti-inflammatory reagent, indomethacin (71% reduction).[89] The mangicols may be potentially promising in this therapeutic application.

Figure 1.8. Mangicols A-G.



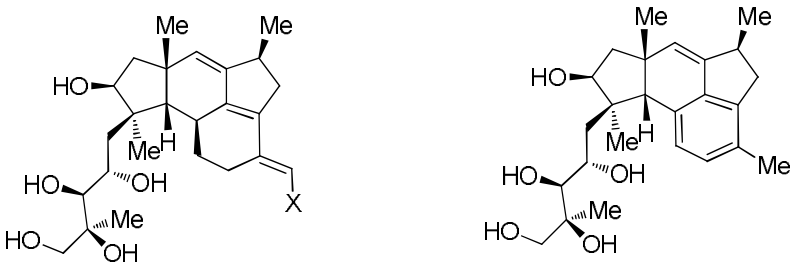
Mangicol A, R_1 = OH, R_2 = H
Mangicol B, R_1 = H, R_2 = OH
Mangicol D, R_1 = H, R_2 = H

Mangicol C, R_1 = OH, R_2 = H
Mangicol E, R_1 = H, R_2 = OH
Mangicol F, R_1 = H, R_2 = H

Mangicol G

Neomangicols A-C (Figure 1.9), isolated from the same organism, also represent a new class of sesterterpenenes possessing a related and intriguing framework to the mangicols.[90] Neomangicol A and B are the first examples of halogenated sestererpenoids natural products although halogenated terpenoid natural products are ubiquitous. It was found that neomangicol A was active against MCF-7 (human breast carcinoma) (IC_{50} = 4.9 uM) and CACO-2 (human colon carcinoma) (IC_{50} = 5.7 uM) cell lines. Neomangicol B showed less potent towards cancer cell lines but significant antibacterial activity against the gram-positive bacterium *Bacillus subtilus*, which was comparable to the known antibiotic, gentamycin. Neomangicol C, an isolation artifact from aromatization of neomangicol A or B, had no specific biological activities.

Figure 1.9. Neomangicols A-C.



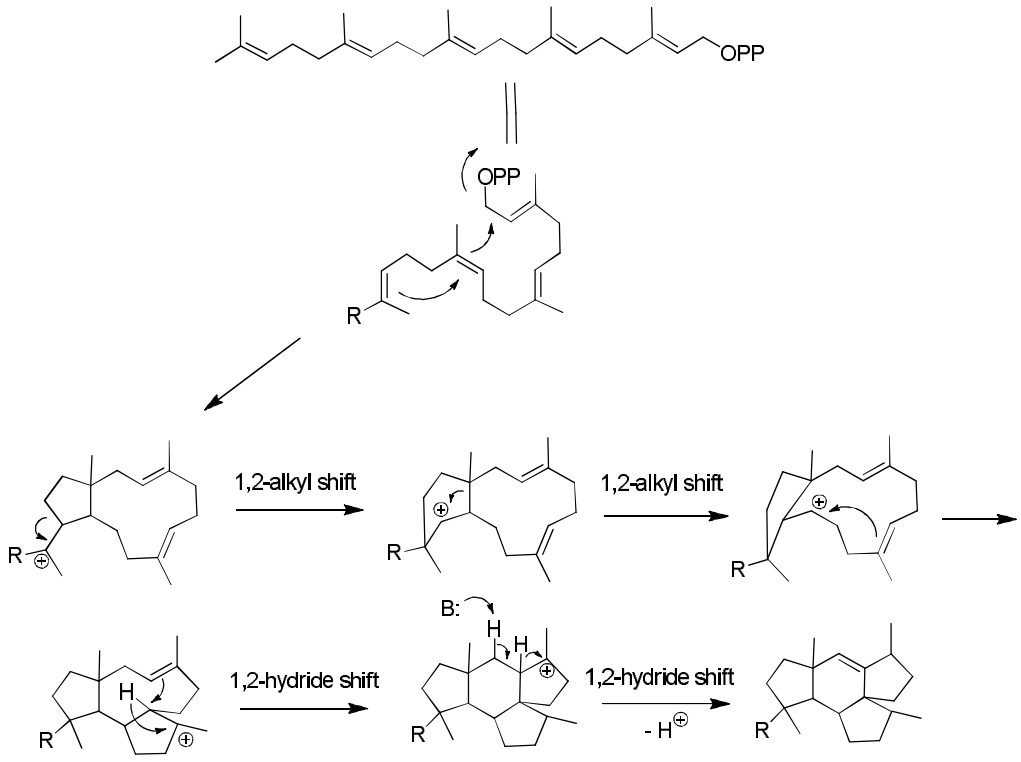
Neomangicol A, X = Cl
Neomangicol B, X = Br

Neomangicol C

3.2. Biosynthesis of the mangicols and neomangicols

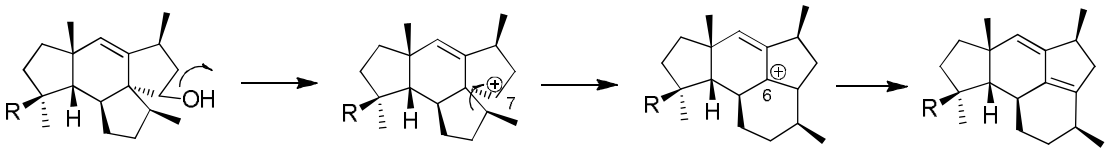
Mangicols and Neomangicols belong to terpenoid family that consists of isoprene units.[91] On the basis of feeding experiments, Fenical proposed geranylfarnesyl diphosphate was a biogenetic precursor for C_{25} sesterterpenes.[89] Three of the five isoprene units kept intact and the remaining two isoprene units were rearranged through two 1,2-alkyl shift. Similar to the biosynthesis of the humulene skeleton in another fungal terpenoid, the 11-membered ring was formed by the initial cyclolization of geranylfarnesyl diphosphate (Scheme 1.29).[92] A 1,2-alkyl shift generated a secondary carbocation, followed by another 1,2-alkyl shift to give 5-membered ring with a new secondary carbocation. Macrocycle underwent a cation-reduced cyclization, two 1,2-hydride shift and deprotonation to give the mangicol core.

Scheme 1.29. Proposed biosynthesis of the mangicol core.



The labeling patterns observed also indicated that the neomangicol carbon skeleton was derived from a mangicol skeleton precursor (Scheme 1.30).[89] It would be a reasonable explanation that a C-7 carbocation in the mangicol skeleton initiated a 1,2-alkyl migrations to generate more stable tertiary carbocation at C-6 and completed the establishment of the neomangicol core. Subsequent modifications including halogenation could afford neomangicol A and B.

Scheme 1.30. Transformation from the mangicol core to the neomangicol core.

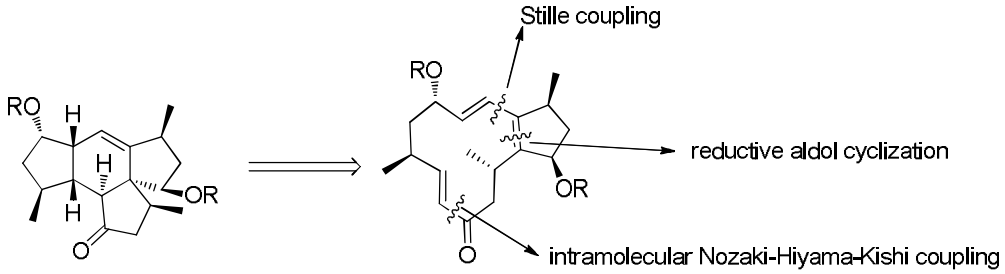


3.3. Approaches to the mangicols and neomangicols

3.3.1. Uemura's approach to mangicols

In 2004, Uemura reported an effective synthetic way to establish the core fragment of mangicols by employing a transannular Diels-Alder (TADA) reaction.[93] The strategy featured reductive aldol cyclization, Stille coupling and intramolecular Nozaki-Hiyama-Kishi coupling for the preparation of the precursor of TADA reaction (Scheme 1.31).

Scheme 1.31. Retrosynthetic analysis of the mangicol core.

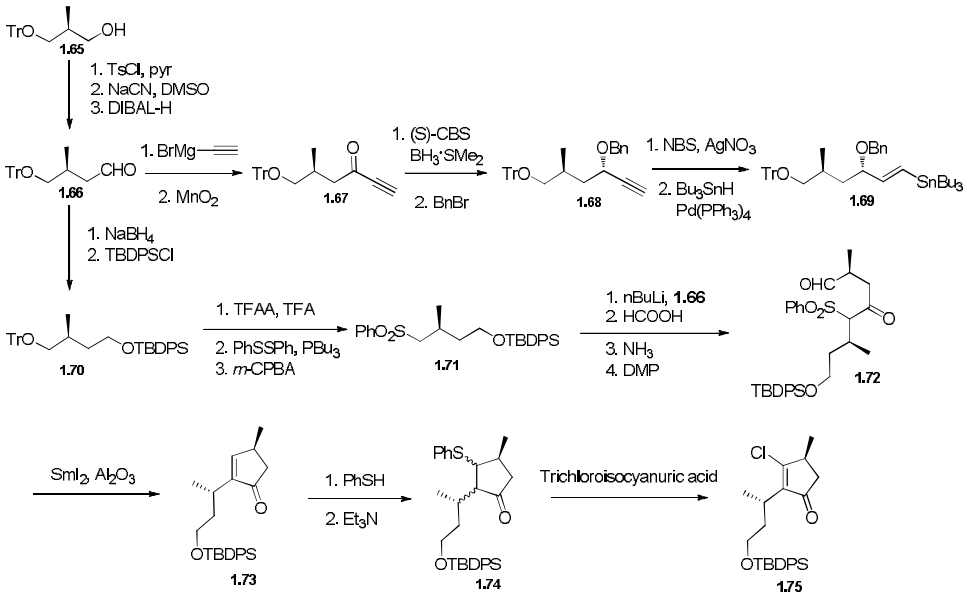


Chiral alcohol **1.70** served as the starting material for both Stille coupli

partners **1.69** and **1.75** (Scheme 1.32). Tosylation of **1.65** and substitution with cyanide generated the nitrile, which was reduced with DIBAL-H to give aldehyde **1.66**. Ketone **1.67** was formed by the addition of ethylnylmagnesium bromide to aldehyde **1.66** and subsequent MnO_2 oxidation. Diastereoselective reduction and benzylation gave benzyl ether **1.68**, which underwent bromination and hydrostannylation to afford vinyl stannane **1.69**.

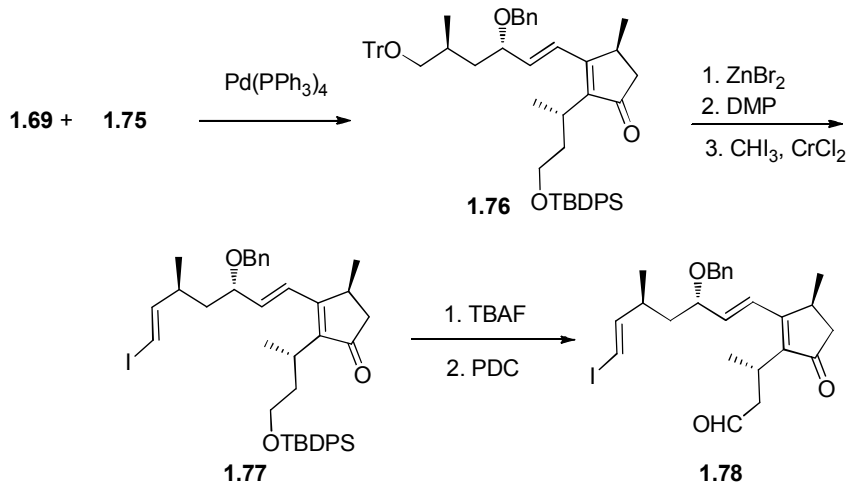
Aldehyde **1.66** was also used for the synthesis of another partner **1.75**. It was reduced with $NaBH_4$ and substituted by TBDPS group to form ether **1.70**. Subsequent removal of the trityl protecting group, elaboration of sulfide and oxidation led to sulfone **1.71**. Deprotonation, nucleophilic addition to aldehyde **1.66**, removal of the trityl protecting group and Dess-Martin oxidation gave ketoaldehyde **1.72**. Reductive aldol cyclization mediated by SmI_2 and treatment with Al_2O_3 afforded cyclopentenone **1.73**. Michael addition with thiophenol led to thioester **1.74**. Partner **1.75** was obtained through oxidative chlorination with trichloroisocyanuric acid.

Scheme 1.32. Synthesis of Stille coupling partners **1.69** and **1.75**.



Stille coupling of partner **1.69** and **1.75** gave dienone **1.76** in excellent yield. After the trityl group was removed with $ZnBr_2$, subsequent Dess-Martin oxidation and Takai olefinantion afforded vinyl iodide **1.77**. Then TBDPS group was removed with TBAF and the resultant alcohol was oxidized by PDC to generate aldehyde **1.78** (Scheme 1.33).

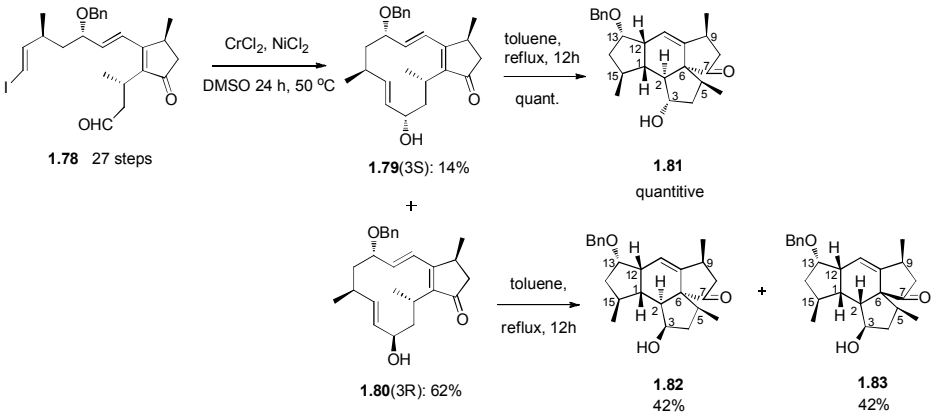
Scheme 1.33. Synthesis of Nozaki-Hiyama-Kishi coupling precursor **1.78**.



Aldehyde **1.78** was prepared in 27 steps. Intramolecular Nozaki-Hiyama-Kishi coupling of **1.78** generated two diastereomeric macrocycles **1.79** (3S) and **1.80** (3R). The minor diastereomer **1.79** (3S) underwent the thermal transannular Diels-Alder reaction to produce a single diastereomer **1.81** quantitatively. The major diastereomer **1.80** (3R) was converted to compounds **1.82** and **1.83** each in 42% yield under the same conditions (Scheme 1.34).

Compounds **1.81** and **1.82** contain many structural features of the core fragment of mangicol A. However, many more synthetic steps are required to elaborate some chiral centers like C3, C7, C12, C13, C15 and introduce a polyol side chain.

Scheme 1.34. Transannular Diels-Alder reaction to form the mangicol core.

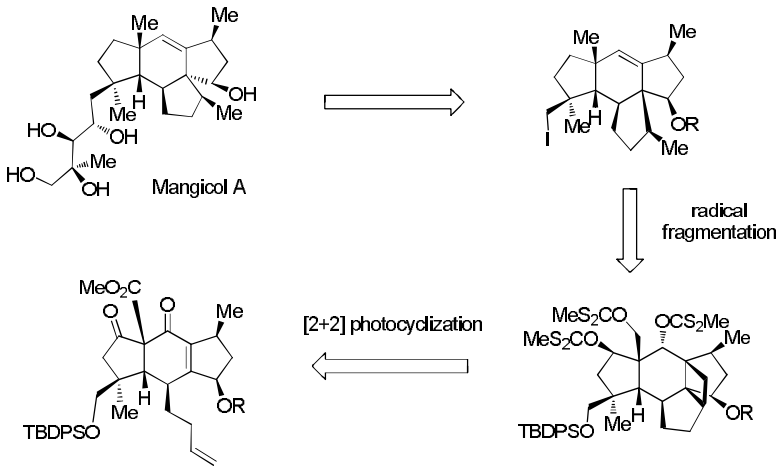


3.3.2. Paquette's approaches to mangicols

In 2006, Paquett reported two synthetic strategies for the synthesis of mangicol A.[94,95] Although both of the strategies were unsuccessful to access the natural product skeleton, they were expected to facilitate the exploration of the synthesis of mangicols.

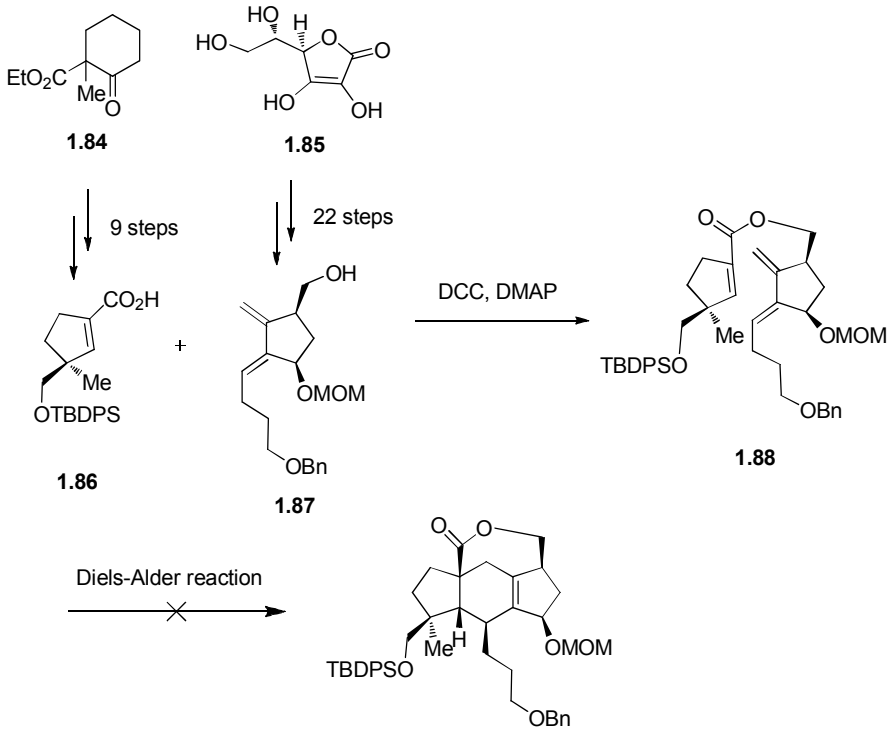
The first strategy was keyed to the availability of tricyclic compound through Diels-Alder reaction, which could undergo [2+2] photocyclization and radical fragmentation to access the fundamental skeleton of mangciols (Scheme 1.35).[94]

Scheme 1.35. Retrosynthetic analysis of mangicol A.



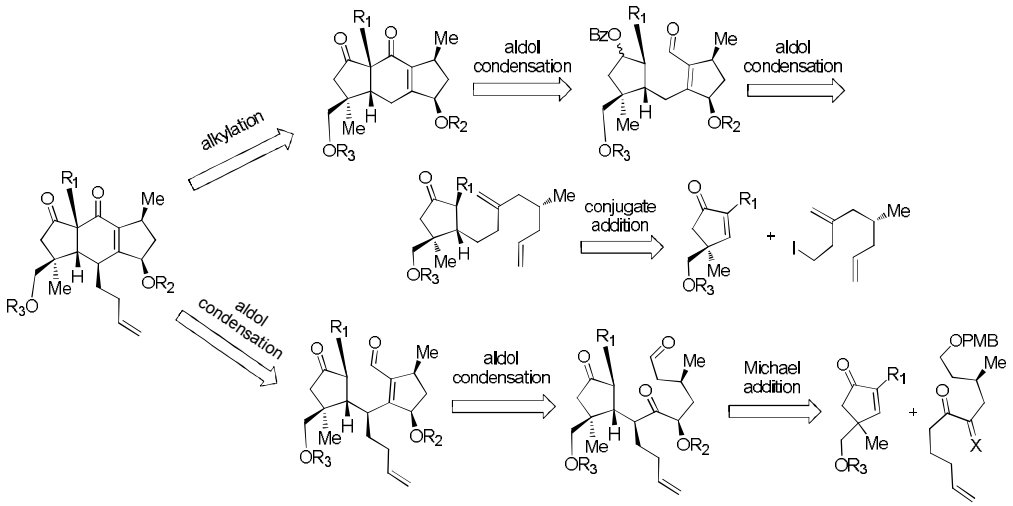
Dienophile **1.86** and diene **1.87** were synthesized in nine steps from β-ketoester **1.84** and twenty-two steps from ascorbic acid **1.85**, respectively. The precursor **1.88** was formed through DCC-mediated esterification with excellent yield. But subsequent attempts to promote intramolecular Diels-Alder reaction were unsuccessful under many classical conditions. The reactivity of dienophile and diene components was also investigated and optimized. Unfortunately, no desired Diels-Alder cycloadducts were obtained (Scheme 1.36).

Scheme 1.36. Paquette's first strategy.



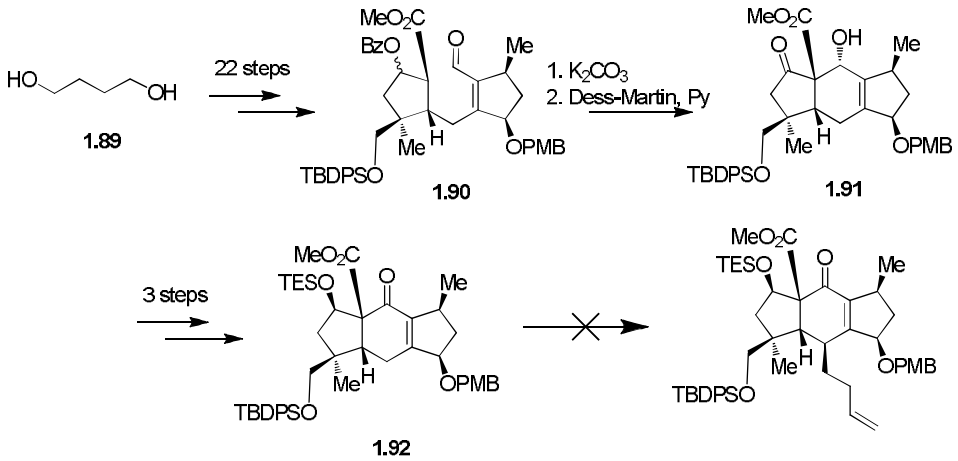
The second strategy was alternative routes to access the tricyclic compound that featured several conjugate additions and aldol condensation.[95] They proposed two synthetic routes which were mainly distinguished from the order of alkylation and sequential aldol condensation (Scheme 1.37).

Scheme 1.37. Retrosynthetic analysis of the tricyclic compound.



The first route was to construct the tricyclic structure via sequence aldol condensation and incorporate the side chain at late stage via alkylation. Compound **1.90** was prepared in 22 steps from commercially available 1,4-butanediol **1.89**. After the benzoyl group was cleaved, DMP oxidation and subsequent cyclization gave the tricycilic compound **1.91** with high stereoselectivity. Elaboration over 3 steps generated compound **1.92**, which failed to undergo alkylation due to the instability under base condition (Scheme 1.38).

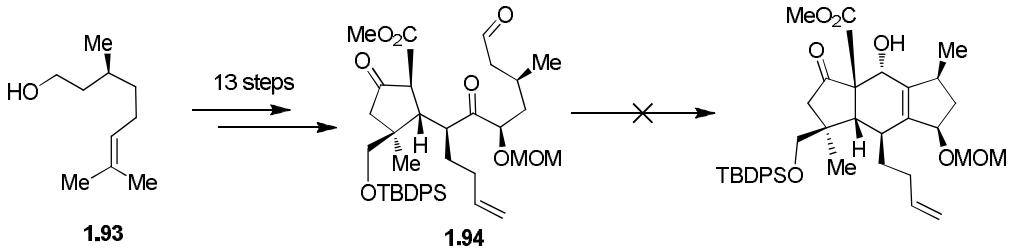
Scheme 1.38. First synthetic route.



The second route was then examined. 13 steps conversion from (S)-(-)-citronel

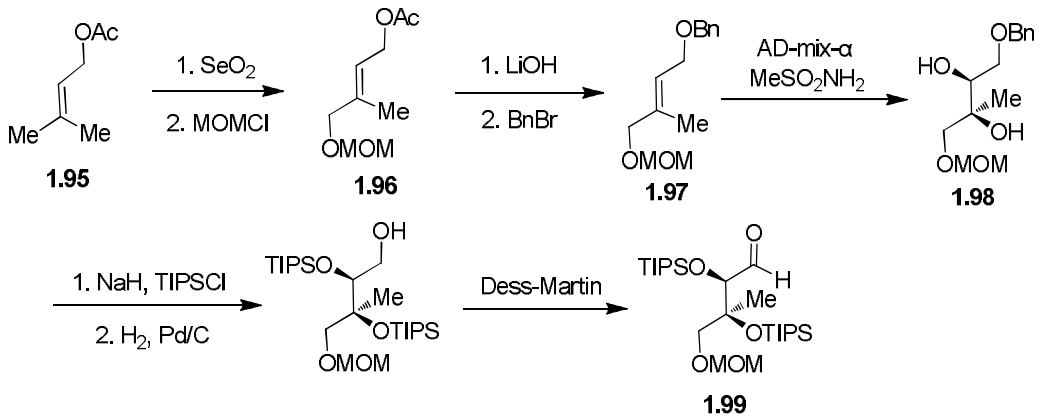
1.93 generated highly functionalized diketo aldehyde **1.94**. Unfortunately, no desired tricyclic compound was obtained via aldol condensation under a variety of conditions (Scheme 1.39).

Scheme 1.39. Second synthetic route.



Although the construction of the mangicol core fragment was unsuccessful, they developed an efficient way to access the side chain. Starting from commercially available prenyl acetate **1.95**, SeO_2 oxidaiton and MOM protection afforded compound **1.96**, which was transformed to **1.97** via deacetylation followed by benzylation. Sharpless asymmetric dihydroxylation with AD-mix-α led to the formation of **1.98**. TIPS protection, chemoselective debenzylation and Dess-Martin oxidation generated the final protected aldehyde **1.99** (Scheme 1.40).

Scheme 1.40. Synthesis of the side chain **1.99**.

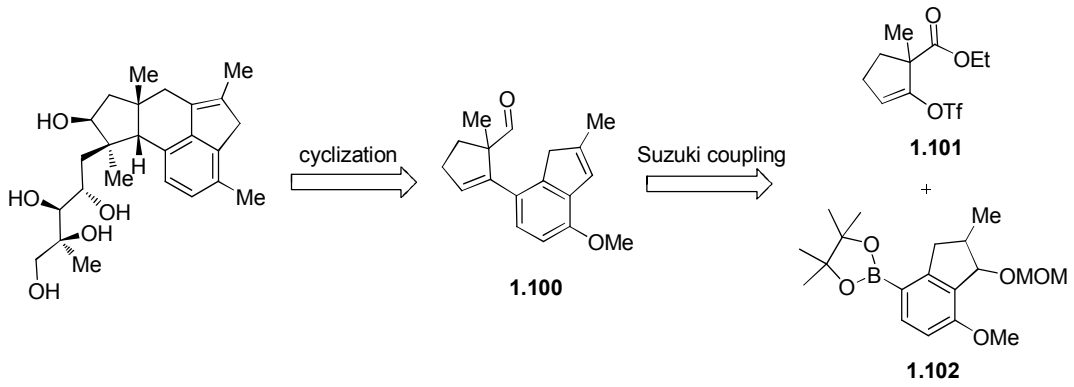


3.3.3. Sarpong's approach to neomangicols

In 2009, Sarpong reported the first approach to the tetracyclic core of the neomangicols via a late-stage indene alkylation reaction.[96] As neomangicol carbon skeleton may derive from a mangicol skeleton precursor, the establishment of the core fragment of neomangicol C will promote the synthesis of neomangicols and mangicols.

The strategy features a late-stage alkylation of indene **1.100**, which could led to the construction of the tetracyclic core fragment. Compound **1.100** could be synthesized through Suzuki cross-coupling of vinyl triflate **1.101** with boronic ester **1.102** (Scheme 1.41).

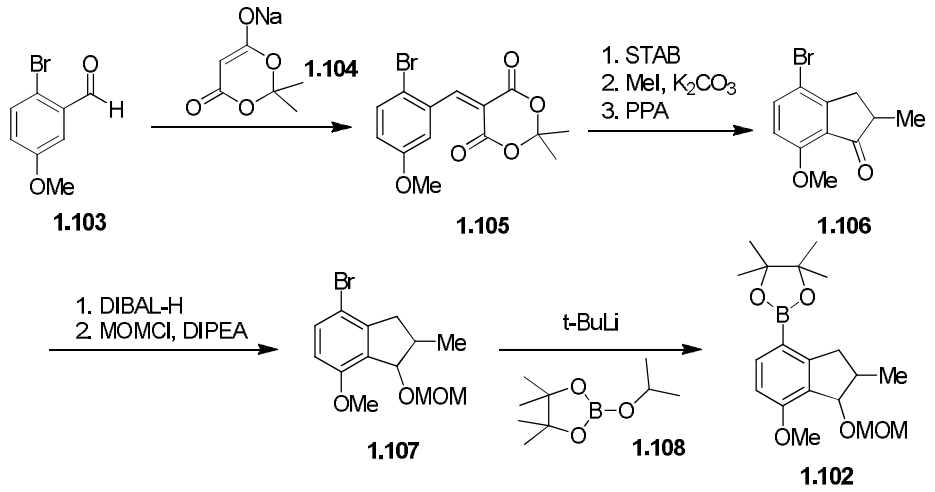
Scheme 1.41. Retrosynthetic analysis of the neomangicol core



Boronic ester **1.102** was prepared in seven steps starting from 2-bromo-5-methoxybenzaldehyde **1.103** (Scheme 1.42). Knoevenagel condensation of 2-bromo-5-methoxybenzaldehyde **1.103** and the sodium salt **1.104** afforded compound **1.105**, which underwent sequential conjugate reduction, methylation and Friedel-Crafts acylation to access indanone **1.106**. Ether **1.107** was obtained via DIBAL-H reduction and MOM protection. Halogen-metal exchange with t-Bu

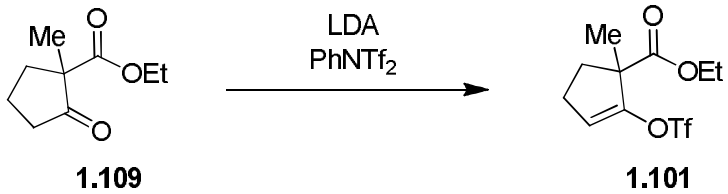
followed by reacting with dioxaborolane **1.108** gave boronic ester **1.102**.

Scheme 1.42. Synthesis of boronic ester **1.102**.



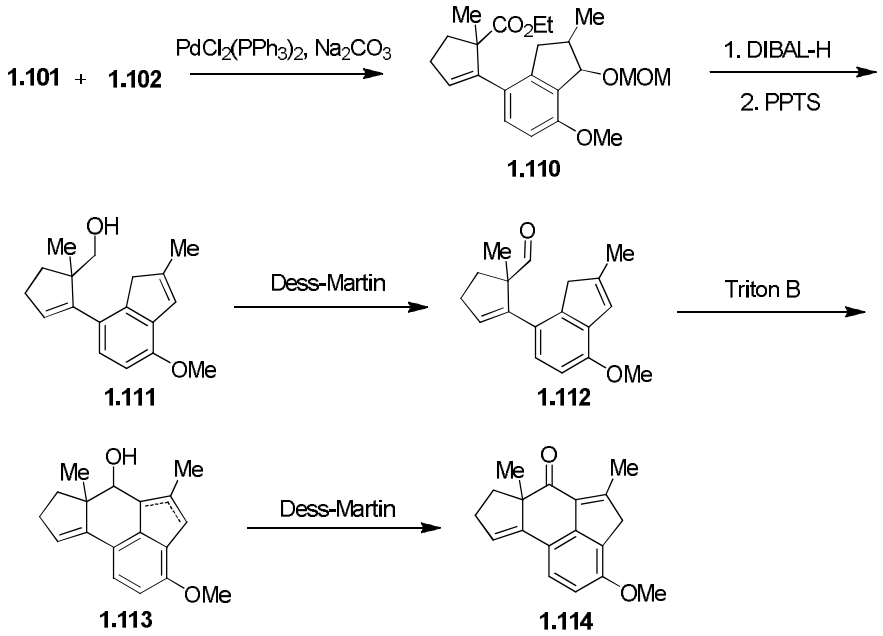
Another partner vinyl triflate **1.101** was easily available from β-ketoester **1.109** via enolate formation and triflation (Scheme 1.43).

Scheme 1.43. Synthesis of vinyl triflate **1.101**.



Suzuki cross-coupling of vinyl triflate vinyl **1.101** and boronic ester **1.102** gave compound **1.110**. Reduction of **1.110** upon treatment with DIBAL-H and elimination with pyridinium *p*-toluenesulfonate (PPTS) led to alcohol **1.111**. Dess-Martin oxidation of alcohol **1.111** provided the precursor **1.112** for cyclization. After the screening of a series of base conditions for indene alkylation, they found triton B effectively converted **1.112** to the tetracyclic compound **1.113**. Subsequent Dess-Martin oxidation generated compound **1.114** possessing the core structure of neomangicol C and functional groups for further elaboration (Scheme 1.44).

Scheme 1.44. Synthesis of the neomangicol core **1.114**.



3.4. Summary

Several approaches have been described here to review the previous synthetic work towards mangicols and neomangicols. Uemura reported a synthesis of the core structure of mangicols in 29 steps employing transannular Diels-Alder reaction. Paquett reported two synthetic strategies for the synthesis of mangicol A but neither of them could access the core fragment. Sarpong successfully completed the synthesis of core structure of neomangicols. No total synthesis of mangicols and neomangicols has been achieved to date while substantial progress has been made toward their preparation.

In our laboratory, we are interested in developing efficient synthetic strategies to access this class of compounds. In the following chapter, we will describe our efforts to use the Pauson-Khand cyclization-based domino reactions of chiral propargylic alcohol derivatives to construct the multicyclic core of mangicols.

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Chapter 2. Attempted Synthesis of the Core Structure of Mangciol A by a Rh-catalyzed domino Pauson-Khand/[4+2] Cycloaddition

1. Introduction

Mangicol A, isolated by Fenical in 2000 from the marine fungus *Fusarium heterosporum*, is a new type of sesterterpenoids with a novel carbon framework that exhibits cytotoxic and anti-inflammatory activities.[1] Intrigued by the challenging structure and potential biological activities, several attempts have been reported for the synthesis of this class of compounds but no total synthesis has been achieved to date.[2-5] Uemura reported a synthesis of the core structure of mangicols in 29 steps by employing a transannular Diels-Alder reaction.[2]

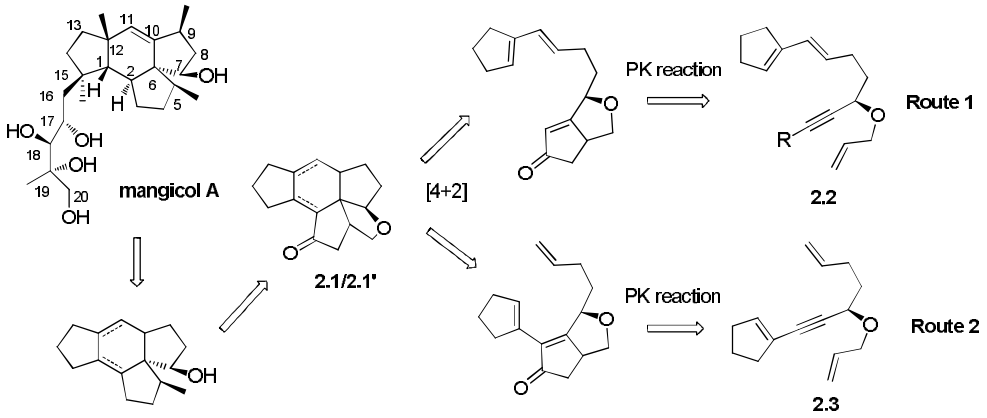
We have used the Rh(I)-catalyzed domino intramolecular Pauson-Khand and [4+2] cyclizations of chiral propargylic alcohols to synthesize the multicyclic core structure of mangicols. The optically active starting materials were prepared by using the asymmetric alkyne addition to aldehydes in the presence of the BINOL-Ti(O^iPr)$_4$-Et_2Zn-Cy_2NH catalytic system previously developed in our laboratory. This work is described below.

2. Exploration of synthesis of the core structure of mangciol A

Encouraged by our previous results, we hypothesized that the ring system of mangicol A could be constructed by employing the Rh(I)-catalyzed domino Pauson-Khand reaction and [4+2] cycloaddition. Two synthetic routes were desigr

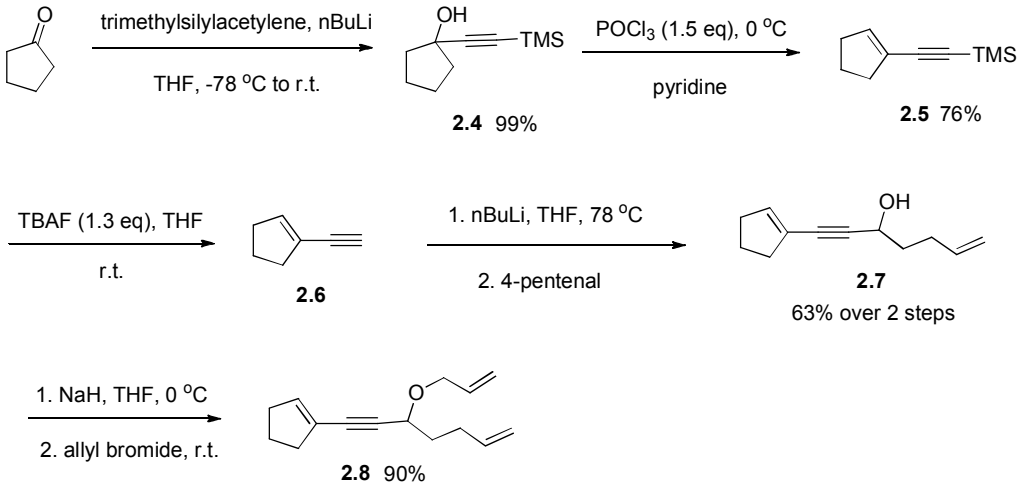
to access the key intermediates **2.1/2.1'** from triene-yne **2.2** and **2.3**, respectively (Scheme 2.1).

Scheme 2.1. Retrosynthetic analysis of the mangicol core.



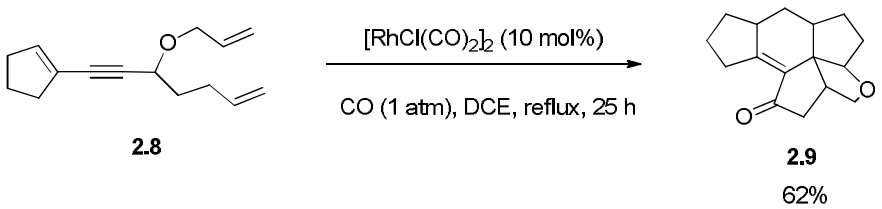
After preliminary investigation, route 1 met some difficulties in the synthesis of the intermediate **2.1**, which will be elaborated in chapter 3. Encouragingly, route 2 was proven to access the corresponding intermediate **2.1'** effectively. To test the domino Pauson-Khand reaction and [4+2] cycloaddition, racemic triene-yne **2.8** was prepared in 5 steps starting from cyclopentanone (Scheme 2.2). Deprotonation of trimethylsilylacetylene with nBuLi followed by addition to cyclopentanone gave alcohol **2.4** in 99% yield. Alcohol **2.4** underwent dehydration in the presence of phosphorus oxychloride and pyridine to generate enyne **2.5** in 76% yield. With the removal of TMS group by TBAF, the resulting enyne **2.6** was deprotonated and reacted with 4-pentenal to give alcohol **2.7** in 63% yield over 2 steps. Racemic triene-yne **2.8** was obtained in 90% yield through allylation of alcohol **2.7**.

Scheme 2.2. Synthesis of racemic triene-yne **2.8**.



With the racemic triene-yne **2.8** in hand, $[Rh(CO)_2Cl]_2$ (10 mol%) was introduced in refluxing 1,2-dichloroethane (DCE) under 1 atm CO to catalyze the domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition. Pleasantly, the desired polycyclic compound **2.9** was formed in a moderate yield (62%) within 25 h (Scheme 2.3). Reducing the loading of catalyst to 2% lowered the yield (44%). This strategy gave a quick access to the fundamental ring structure of mangicol A in short steps.

Scheme 2.3. Domino Pauson-Khand reaction and [4+2] cycloaddition of **2.8**.



3. Synthesis of the optically active polycyclic compound

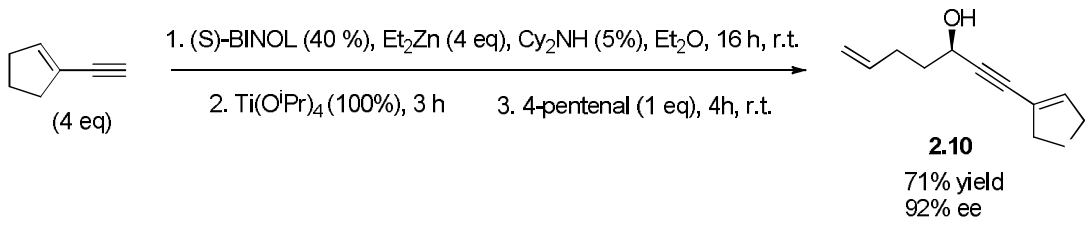
With the success achieved in the synthesis of the racemic polycyclic compound **2.9**, the optically active compound was prepared from the optically active propargy

alcohol-based triene-yne by using the same domino Pauson-Khand/[4+2] cyclizations.

3.1. Synthesis of the optically active propargylic alcohol

In recent years, significant progress has been made in the development of catalytic systems for the asymmetric alkyne addition to aldehydes to access chiral propargylic alcohols. Our lab developed the BINOL-Et_2Zn-$Ti(O^iPr)_4$-Cy_2NH catalytic system for the asymmetric alkynylzinc addition to aldehydes.[8] The chiral propargylic alcohol **2.10** was prepared with 71% yield and 92% ee from the reaction of the enyne **2.6** with 4-pentenal at room temperature. Reducing the amount of the enyne (2.5 eq) and Et_2Zn (2.5 eq) lowered the yield (51%) and eroded the enantioselectivity (86%). The procedure consisted of three steps. Firstly, to a solution of (S)-BINOL (40%) in Et_2O was added the enyne (4 eq), Cy_2NH (5%) and Et_2Zn (4 eq) sequentially under nitrogen at room temperature and the mixture was stirred for 16 h. Secondly, $Ti(O^iPr)_4$ (100%) was added and stirred for 3 h. Finally, 4-pentenal (1 eq) was added and the reaction was completed within 4 h. This procedure was a little different from the one in previous work that combined step 2 and 3 into one step.[7] Very low ee (10%-20%) was obtained if $Ti(O^iPr)_4$ was added followed by the addition of 4-pentenal immediately. Extra time (3 h) in step 2 was required to achieve the high stereoselectivity after $Ti(O^iPr)_4$ was added (Scheme 2.4).

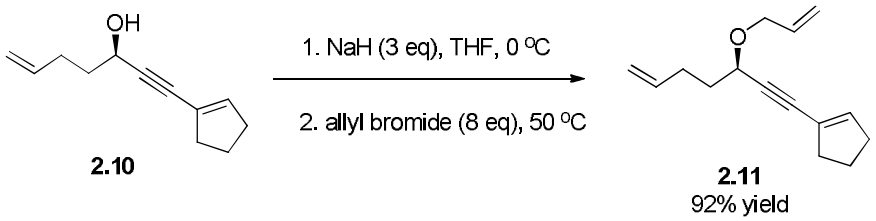
Scheme 2.4. Synthesis of the chiral propargylic alcohol **2.10**.



3.2. Synthesis of the optically active triene-yne

With the chiral propargylic alcohol **2.10** in hand, the optically active triene-yne **2.11** was readily prepared in 92% yield by treatment with NaH (3 eq) and allyl bromide (8 eq) at 50 °C (Scheme 2.5).

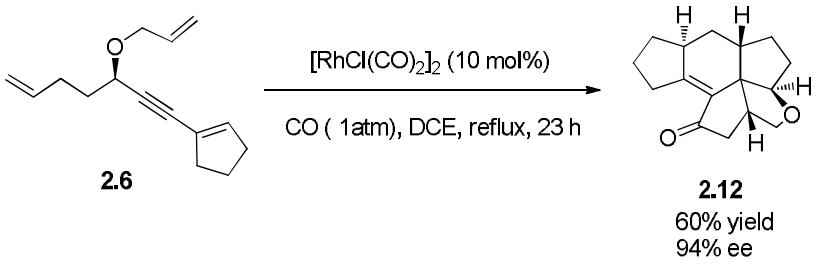
Scheme 2.5. Synthesis of the optically active triene-yne **2.11**.



3.3. Synthesis of the optically active polycyclic compound

When the chiral triene-yne **2.11** was treated with $[Rh(CO)_2Cl]_2$ (10 mol%) under 1 atm CO in refluxing 1,2-dichloroethane (DCE), the polycyclic compound **2.12** was obtained with 60% yield and 94% ee (Scheme 2.6). In compound **2.12**, four new chiral carbon centers were created whose formation was controlled by the original chiral propargylic center of **2.11**. The Rh(I)-catalyzed domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition proceeded smoothly to give **2.12** with high chemoselectivity and stereoselectivity.

Scheme 2.6. Synthesis of the optically active polycyclic compound **2.12**.

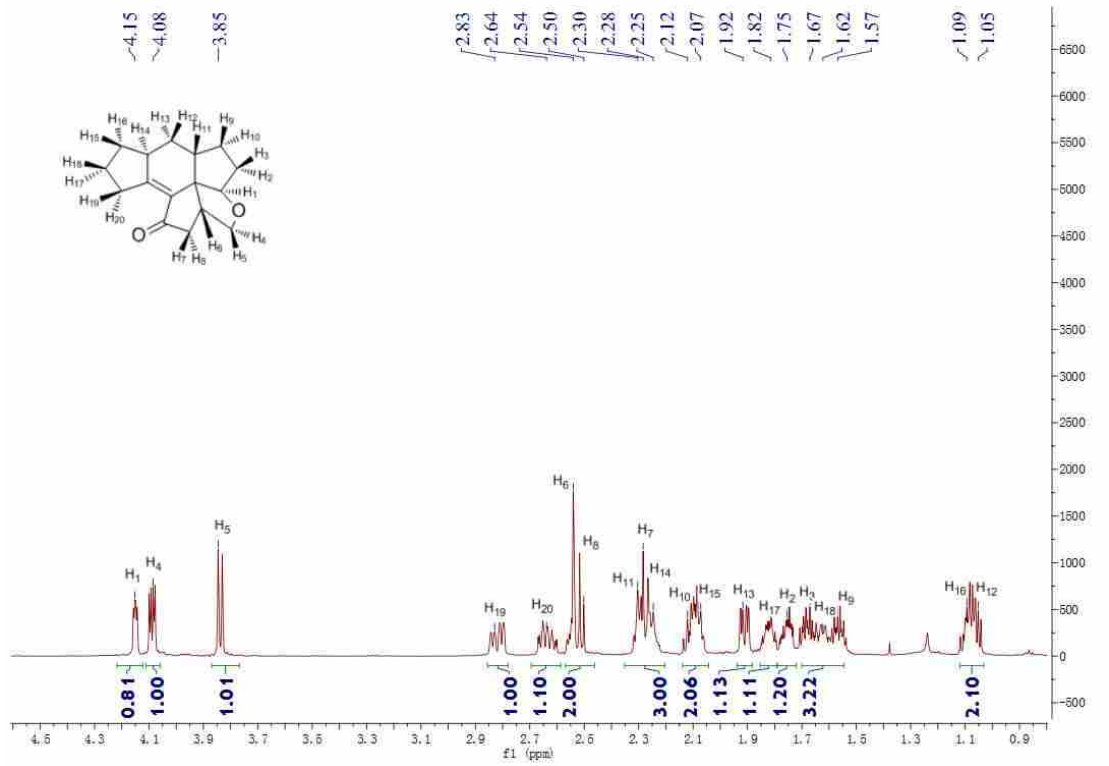


The structure of **2.12** was determined by high-resolution mass spectrosco

analysis and various ^{1}H and ^{13}C NMR spectroscopic analysis including COSY, NOESY, HSQC and DEPT-135. The ^{1}H NMR signal assignments for **2.12** are shown below (Figure 2.1). The signal at δ 4.15 was assigned to be H_1 on the basis of DEPT-135 and HSQC. The signal at δ 1.75 was assigned to be H_2 since it showed stronger NOE effect with H_1 than the signal at δ 1.67 which was assigned to be H_3. The signals at δ 4.08 and 3.85 were assigned to be H_4 and H_5 on the basis of DEPT-135, HSQC and stronger NOE effect (H_4) with H_1. The signal at δ 2.54 was assigned to be H_6 because of COSY correlation with H_4/H_5 and HSQC. The configuration of H_6 was assigned to be *up* based on its NOE effect with H_5. The signals at δ 2.28 and 2.50 were assigned to be H_7 and H_8 on the basis of COSY correlation with H_6, HSQC and NOE effect (H_7) with H_5. The signal at δ 2.12 was assigned to be H_{10} since it showed stronger NOE effect with H_4 than the signal at δ 1.57 which was assigned to be H_9. The signal at 2.30 was assigned to be H_{11} according to COSY correlation with H_9/H_{10}, HSQC and DEPT-135. The configuration of H_{11} was assigned to be *up* based on its strong NOE effect with H_6. The signal at 2.25 was assigned to be H_{14} on the basis of HSQC and DEPT-135. The configuration of H_{14} was assigned to be *down* due to its strong NOE effect with H_1. The signals at δ 1.05 and 1.92 were assigned to be H_{12} and H_{13} on the basis of COSY correlation with H_{11}, HSQC and NOE effect (H_{13}) with H_{14}. Tracing the COSY, HSQC and NOE correlation with H_{14} allowed the assignment of H_{15} and H_{16} at δ 2.07 and at 1.09. On the basis of COSY correlation with H_{15}/H_{16} and HSQC, the signal at δ 1.82 was assigned to be H_{17} as it showed strong NOE effect with H_2 and the signal at δ 1.

was assigned to be H_{18}. The signals at δ 2.83 and 2.64 were assigned to be H_{19} and H_{20} on the basis of COSY correlation, HSQC and NOE effect (H_{19}) with H_{18}.

Figure 2.1. ^{1}H NMR signal assignments of **2.12**.

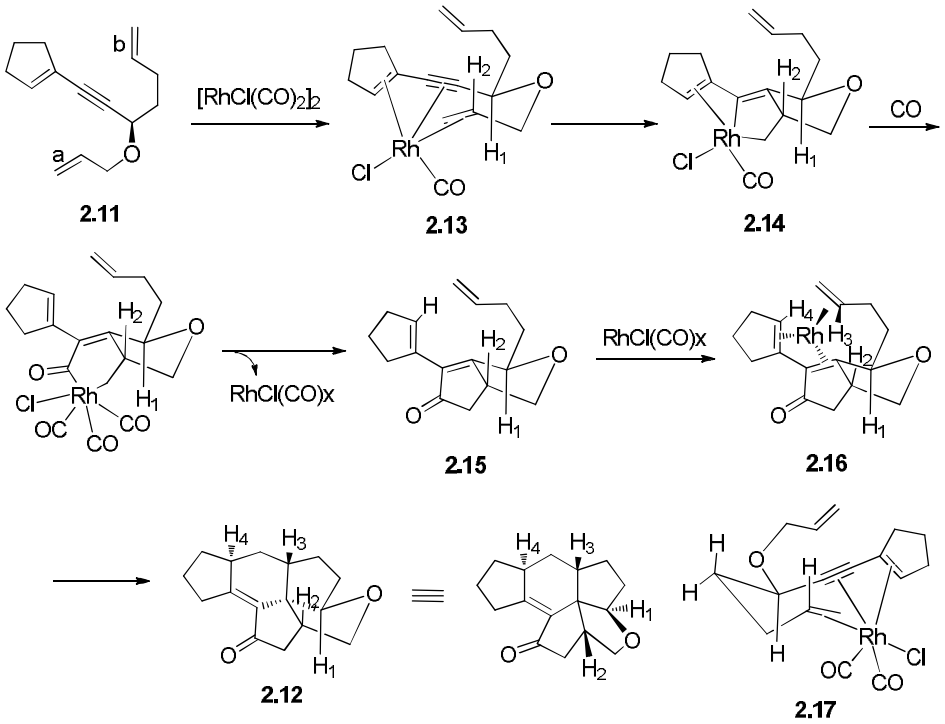


On the basis of the previous studies on the Rh-catalyzed Pauson-Khand reaction and [4+2] cycloaddition, a mechanism has been proposed to illustrate the formation of the compound **2.12** (Scheme 2.7).[6,7] **2.11** can coordinate with the metal center of the catalyst to generate the intermediate **2.13**. Oxidative coupling of the coordinated triple bond and double bond of **2.13** gives **2.14**. In this step, the newly formed bridgehead hydrogen H_2 is *trans* with respect to the proton H_1 from the chiral triene-yne **2.11**. Migratory insertion of **2.14** with CO followed by reductive elimination gives the PK cycloaddition product **2.15**. Then a Rh-catalyzed [4+2] cycloaddition of **2.15** via the intermediate **2.16** gives the product **2.12** with the observed *exo*-Diels-Alder reacti stereochemistry. In this step, the newly formed bridgehead hydrogen H_3 is *cis* w

respect to H_2, whereas H_4 is *trans* with respect to H_2.

When **2.11** is treated with the catalyst, **2.17** is another possible intermediate in which the double bond *b* is coordinated instead of the double bond *a*. **2.17** is less favorable probably due to the greater 1,3,-diaxial interaction. The difference of the electronic effect in the formation of an ether ring verses a carbocycle should be an important factor for the reaction pathway.

Scheme 2.7. A proposed mechanism for the formation of **2.12**.

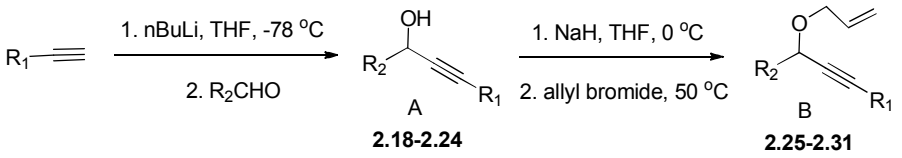


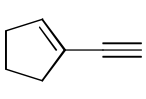
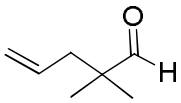
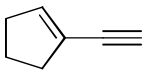
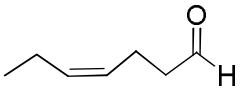
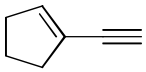
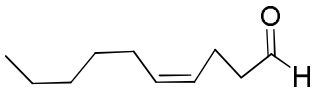
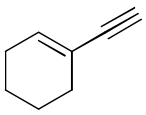
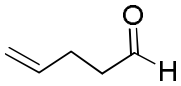
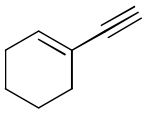
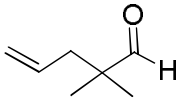
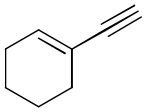
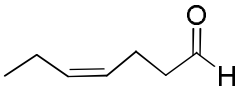
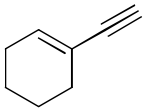
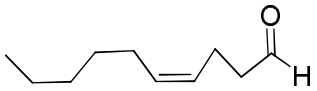
4. Synthesis of other related polycyclic compounds

The formation of compound **2.12** proved the efficiency of the Rh(I)-catalyzed domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition. To investigate the generality of this powerful strategy, a couple of racemic substrates were synthesized and tested. The racemic triene-ynes B **2.25-2.31** were readily prepared in high yields via alkyne additions to aldehydes followed by allylati

(Scheme 2.8).

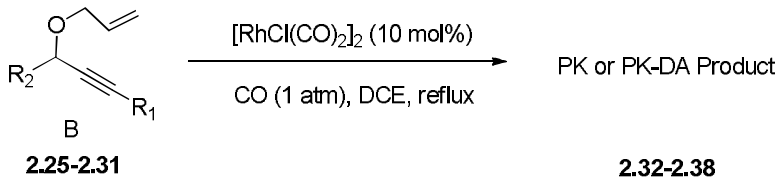
Scheme 2.8. Synthesis of the racemic triene-ynes B **2.25-2.31**.

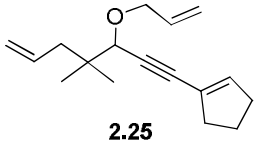
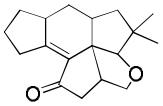
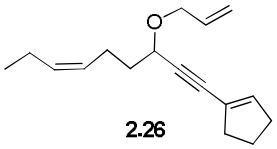
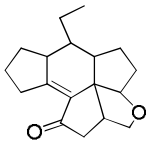
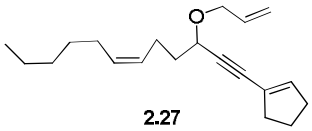
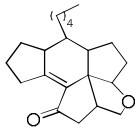
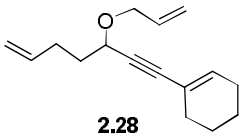
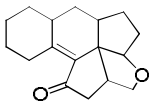
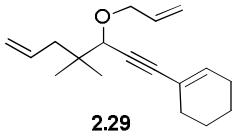
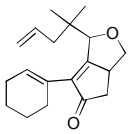
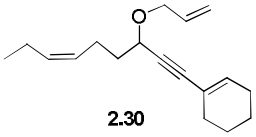
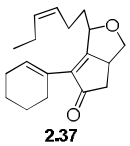
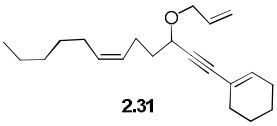
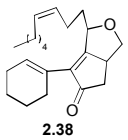


Entry	Alkyne	Aldehyde	A Yield (%)	B Yield (%)
1			73	97
2			84	93
3			74	96
4			64	97
5			79	91
6			77	91
7			79	67

Triene-ynes B **2.25-2.31** were treated with $[Rh(CO)_2Cl]_2$ (10 mol%) under 1 atm CO in refluxing 1,2-dichloroethane (DCE) to give the PK (Pauson-Khand) products (entry 1-4, **2.32-2.35**) or PK-DA (Pauson-Khand and Diels-Alder) products (entry 5-7, **2.36-2.38**) in moderate yields (38%-64%) (Scheme 2.9).

Scheme 2.9. Synthesis of other related polycyclic compounds.



Entry	Triene-yne B	Type	Product	Time (h)	Yield (%)
1	 **2.25**	PK-DA	 **2.32**	23	49
2	 **2.26**	PK-DA	 **2.33**	47	56
3	 **2.27**	PK-DA	 **2.34**	37	38
4	 **2.28**	PK-DA	 **2.35**	28	45
5	 **2.29**	PK	 **2.36**	21	57
6	 **2.30**	PK	 **2.37**	26	44
7	 **2.31**	PK	 **2.38**	26	64

Treating the PK product **2.36** (entry 5) with $[Rh(CO)_2Cl]_2$ (10 mol%) under N_2 in refluxing toluene didn't promote the Diels-Alder reaction. The failure of the Diels-Alder reaction for the PK products **2.36-2.38** (entry 5-7) might be attributed

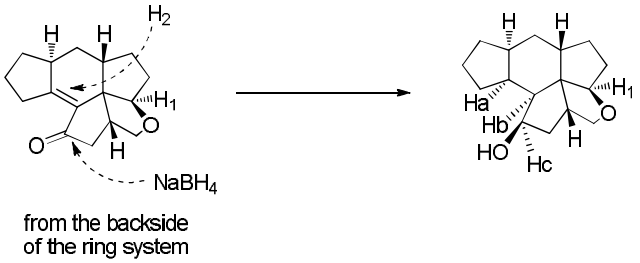
the steric hindrance of dienophile system since triene-yne **2.28** (entry 4) was transformed to the PK-DA product smoothly.

Although triene-ynes **2.36-2.38** (entry 5-7) were not able to undergo the Diels-Alder reactions, the strategy showed its efficiencies in the synthesis of the polycyclic compounds **2.32-2.35**. Other catalysts are under investigation now to promote the Diels-Alder reactions for **2.36-2.38** (entry 5-7).

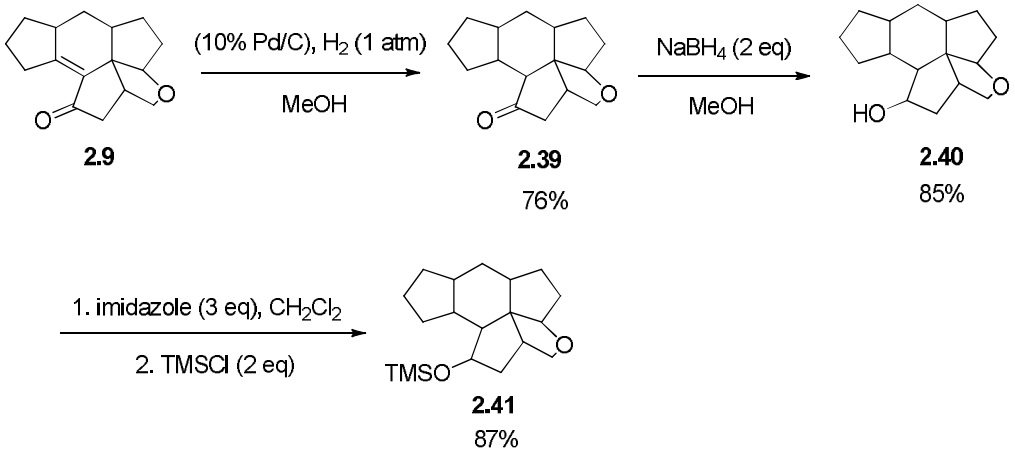
5. Further conversions of the polycyclic compound 2.9

With the polycyclic compound **2.9** in hand, the next work was to open its hydrofuran ring. Considering the functional groups in **2.9** (C-C double bond and carbonyl group) might be sensitive to ring opening reagents, further elaborations were made before the cleavage of the hydrofuran ring (Scheme 2.10). Compound **2.9** was reduced under 1 atm H_2 with Pd/C to give compound **2.39** in 76% yield. Treatment of **2.39** with $NaBH_4$ afforded compound **2.40** in 85% yield.[9] Excellent diastereoselectivities were achieved in these reduction steps. H_2 and $NaBH_4$ attacked the C-C double bond and carbonyl group respectively from the backside of ring system and generated H_a, H_b, H_c that are *cis* with respect to H_1 (Figure 2.2). Compound **2.41** was obtained in 87% yield with the protection of hydroxyl group.

Figure 2.2. Diastereoselective hydrogenation and carbonyl reduction.



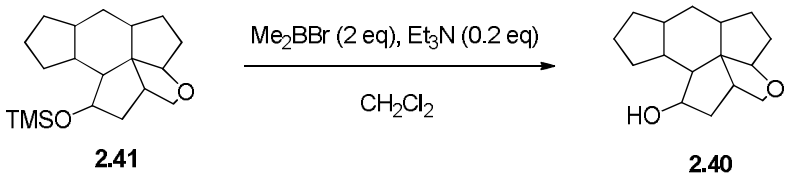
Scheme 2.10. Further conversions.



2.9 **2.39** 76% **2.40** 85% **2.41** 87%

We envisioned that after the hydrofuran ring of **2.41** was cleaved, a polyol side chain could be introduced to TMS position to access an analogue of mangciol A which might have potential biological activities. Compound **2.41** was then reacted with Me_2BBr (2 eq) and Et_3N (0.2 eq).[10] Instead of giving the desired hydrofuran ring opening product, the TMS group fell off to regenerate the alcohol **2.40** (Scheme 2.11).

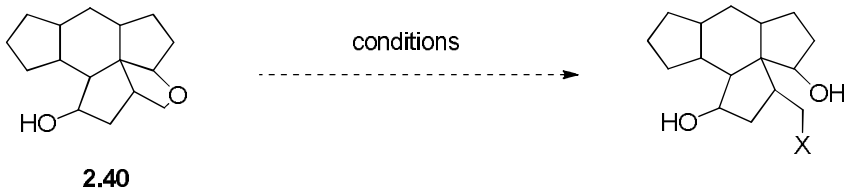
Scheme 2.11. Test of ring cleavage of **2.41**.



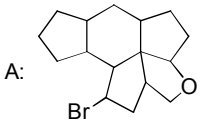
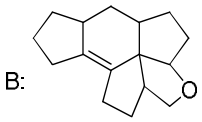
2.41 **2.40**

Jatczak and co-workers disclosed that simple unprotected ether could undergo ring opening reaction.[11] Compound **2.40** was then tested in a couple of ring opening conditions with different Lewis acids and nucleophiles employed (Scheme 2.12).[11-19]

Scheme 2.12. Test of a couple of conditions for ring cleavage of **2.40**.



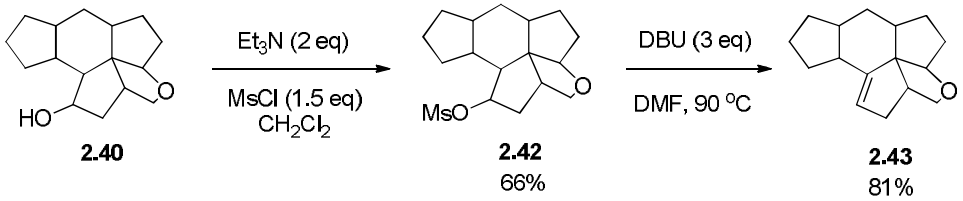
2.40

Entry	Condition	Result
1	$Me_2BBr/Et_3N/CH_2Cl_2$	No reaction
2	BBr_3/CH_2Cl_2	No reaction
3	Et_4NBr/BF_3-$Et_2O/CHCl_3$	No reaction
4	LiBr/*p*-$MeC_6H_4SO_3H$/DMF	No reaction
5	TMSBr/ BF_3-Et_2O/ CH_2Cl_2	No reaction
6	HBr/dioxane	Major: starting material Byproduct A: 14% 
7	$AlCl_3$/NaI/MeCN	Major: starting material Byproduct B: 25% 
8	Me_3SiCl/NaI/MeCN	No reaction
9	TBAI/BF_3-$Et_2O/CHCl_3$	No reaction

Br nucleophiles were examined first (entry 1-6). No reaction occurred under the conditions in entry 1-5. In entry 6, a small amount of possible byproduct A (14% yield) was generated when compound **2.40** was treated with HBr in dioxane at 85 ^{o}C overnight. With the failure of Br nucleophiles, we turned to stronger I nucleophiles. The conditions in entry 8-9 couldn't cleave the hydrofuran ring of **2.40**. In entry 7, compound **2.40** was reacted with $AlCl_3$/NaI/MeCN at 95 ^{o}C to give a possil elimination byproduct B in 25% yield.

As no methods were able to cleave the hydrofuran ring of **2.40**, it was thought that Lewis acids might be trapped by the hydroxyl group. Removal of the hydroxyl group might promote the ring opening reaction. Then compound **2.43** was prepared through sulfonylation with MsCl and elimination under DBU condition (Scheme 2.13).[20,21]

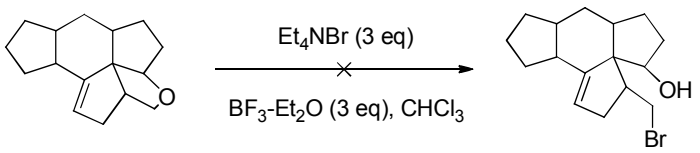
Scheme 2.13. Synthesis of compound **2.43**.



2.40 **2.42** 66% **2.43** 81%

Then compound **2.43** was examined under Et_4NBr/BF_3-$Et_2O/CHCl_3$ condition which had been previously tested to be effective for simple tetrahydrofuran. Disappointingly, this method failed to convert compound **2.43** to the desired product **2.44**. No reaction occurred when the temperature was gradually increased to reflux (Scheme 2.14).

Scheme 2.14. Test of ring cleavage of **2.43**.

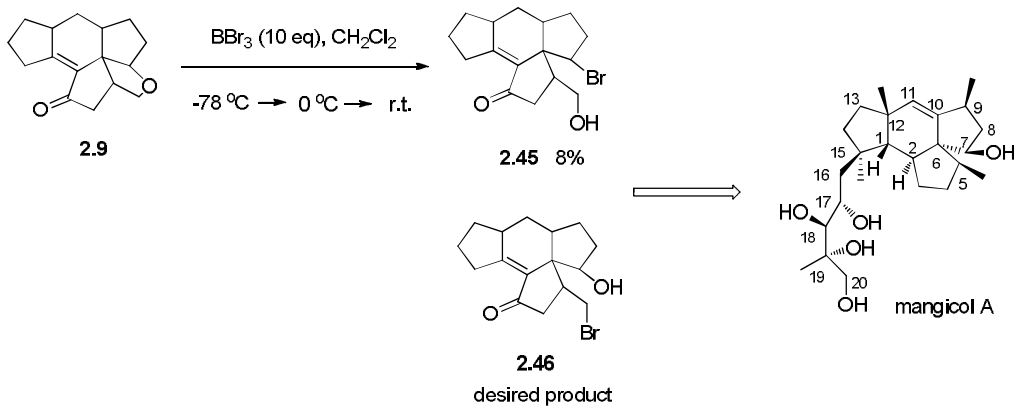


2.43 **2.44**

After many methods were not successful to open the hydrofuran ring of compound **2.40**, **2.41** and **2.43**, we went back to test compound **2.9** without any modification. Excess BBr_3 (10 eq) was reacted with **2.9** at -78 °C for 2 h. Then the system was warmed to 0 °C for 3 h and room temperature overnight. Encouragingly, another type of ring opening product **2.45** was obtained in low yield (8%) althougl

was not the desired product **2.46**. Besides, 46% starting material was recovered and some unidentified byproducts were formed (Scheme 2.15). The structure of **2.45** was determined by ^{1}H, ^{13}C NMR and high-resolution mass spectroscopic analysis. We were pleased that BBr_3 didn't affect two functional groups (C-C double bond and carbonyl group) in the ring system. Compared to **2.46**, more steps are required for **2.45** to construct chiral centers C5 and C7. However, compound **2.45** is still useful in the synthesis if a high yield could be achieved.

Scheme 2.15. Test of ring cleavage of **2.9**.

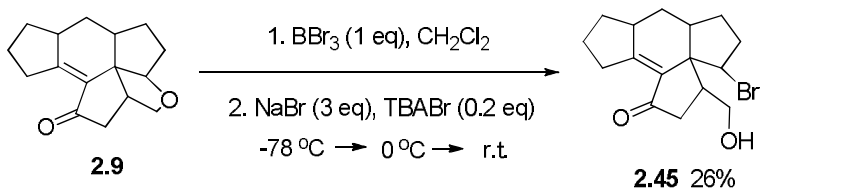


Our next task was to improve the yield by optimizing the BBr_3 condition. This reaction was limited to the incomplete conversion of starting material and some side reactions. We were trying to improve the conversion and inhibit the side reactions.

When BBr_3 (10 eq) was employed, extending the reaction time at room temperature didn't help the conversion. Gradually increasing the temperature to 50 ^{o}C promoted the decomposition of compounds. Decreasing the temperature to 0 ^{o}C lowered the conversion and the side reactions still occurred. Reducing the amount of BBr_3 (1 eq) were not able to inhibit the side reactions while some product was formed. NaBr with catalytic tetrabutylammonium bromide (TBABr) had been reported

promote the ring opening reaction and improve the conversion.[22] After NaBr (3 eq) and TBABr (0.2 eq) were introduced to the system at room temperature, more products were obtained while the yield was still not high (26%) (Scheme 2.16). No further conversion was observed when increasing temperature to 45 °C. Adding extra BBr_3 (1 eq) to the system also failed to improve the conversion.

Scheme 2.16. NaBr/TBABr promoted ring cleavage of **2.9**.



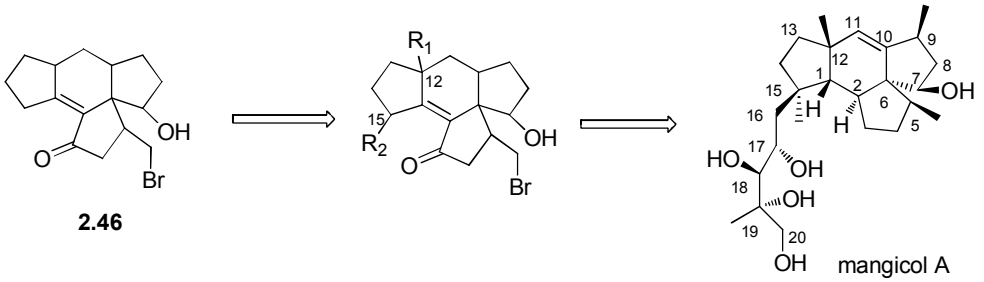
2.9 **2.45** 26%

recovered starting material: 30%

The formation of compound **2.45** indicated that the reaction might undergo S_N1 process. The resulting secondary carbocation combined with Br^- to give **2.45**. In addition, some side reactions such as elimination might have occurred.

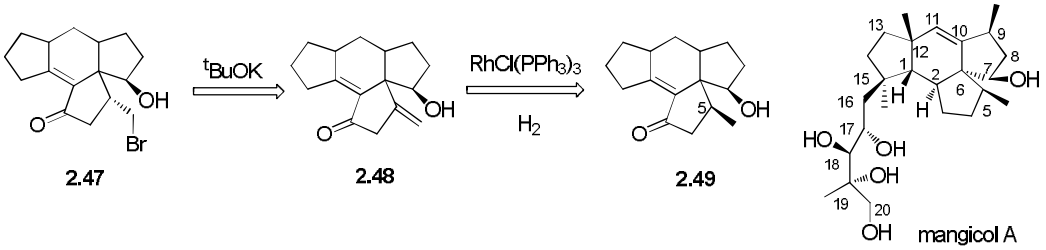
Now we are investigating other reaction conditions to open the hydrofuran ring of compound **2.9**. The desired ring opening products such as compound **2.46** could serve as a good precursor for further modification in the synthesis of mangciol A. The allylic positions (C12 and C15) could be deprotonated with base such as LDA, which offer opportunities to form a quaternary carbon C12 and introduce a polyol side chain at C15 (Scheme 2.17).

Scheme 2.17. Introduction of a quartenary carbon C12 and a side chain.



In addition, optically active **2.47** could be achieved after ring cleavage based on the stereochemistry of **2.12**. Compound **2.47** could be eliminated in treatment with a bulky base like ^{t}BuOK to give compound **2.48**. The stereochemistry of the hydroxyl group in **2.48** could direct the hydrogenation of the adjacent double bond by using Wilkinson' s catalyst $RhCl(PPh_3)_3$ to give compound **2.49** with a desired chiral center C5 (Scheme 2.18).

Scheme 2.18. Formation of a chiral center C5.



Moreover, the C-C double bond and carbonyl group could be modified at a later stage to establish the desired chiral centers C1 and C2.

6. Summary

In conclusion, we have demonstrated a one-pot Rh-catalyzed domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition to access the chiral polycyclic compound **2.12** with high yield (60%) and enantioselectivity (94%
Compound **2.12** represents the fundamental core structure of mangciol A after

cleavage of its hydrofuran ring. The completion of the synthesis of the racemic polycyclic compounds **2.32-2.35** showed great efficiency and generality of this strategy. Other catalysts are under investigation to promote the PK products **2.36-2.38** to undergo [4+2] cycloaddition. After exploration and optimization of the conditions for ring opening, an undesired ring opening compound **2.45** was obtained in a low yield. Now we are focused on investigating other conditions to open the hydrofuran ring of **2.9** and obtain the desired products such as compound **2.46** that has many potential uses in further elaboration of the mangicol core.

Experimental and Characterization

1. Analytical Instruments

NMR: Varian 300 MHz, Bruker 600 MHz and Bruker 800 MHz.

HPLC: Water 600 Pump and Waters 486 Tunable Absorbance Detector, Chiralcel OD, OD-H, or Chiralpak AD, AD-H column.

Polarimeter: Jasco Digital Polarimeter P-2000.

High resolution mass spectra were obtained by EI [70-VSE(C)] or ESI (Q-TOf) analysis.

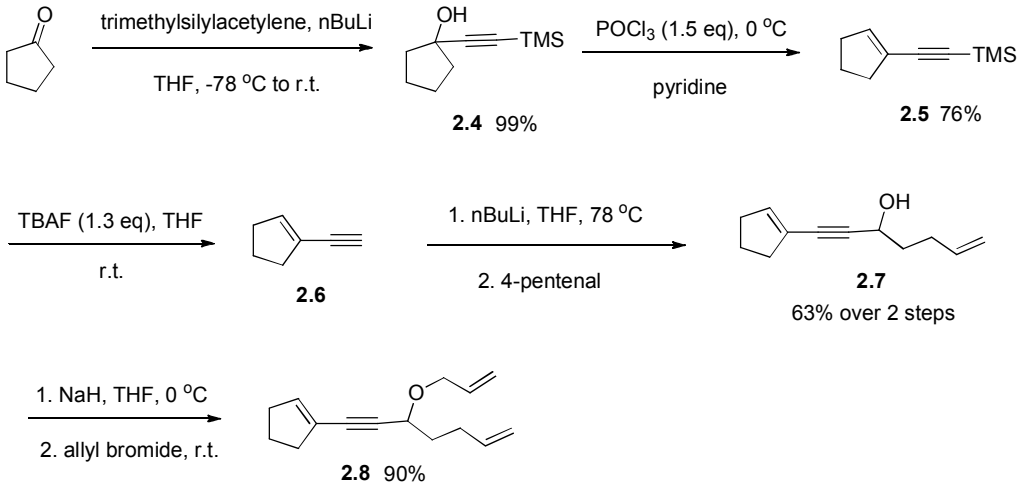
2. General Data

All commercial chemicals were used without further purification unless otherwise noted. All catalysts were purchased and stored in dry nitrogen atmosphere. Tetrahydrofuran was distilled over sodium and benzophenone under nitrogen. Diethyl ether and methylene chloride were dried by passing through activated alumina columns under nitrogen. All the NMR spectra were obtained in $CDCl_3$ unless indicated otherwise.

3. General Procedures

3.1. Exploration of synthesis of the core structure of mangciol A

a. Synthesis of racemic triene-yne 2.8.



1-((trimethylsilyl)ethynyl)cyclopentanol, 2.4

Trimethylsilylacetylene (15 g, 153 mmol, 1.5 eq) was dissovled in THF (20 mL) and cooled to -78 °C under nitrogen. nBuLi (48.9 mL, 122.4 mmol, 2.5 M in hexane, 1.2 eq) was added and the mixture was stirred for 30 min. Then cyclopentenone (9 mL, 102 mmol, 1 eq) was added and the system was warmed to room temperature. After 4 h, the reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=15:1) to furnish the compound **2.4** (18.3 g, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (m, 4H), 1.73 (m, 4H), 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.8, 87.3, 75.0, 42.8, 23.8, 0.21.

(cyclopent-1-en-1-ylethynyl)trimethylsilane, 2.5

To a solution of alcohol **2.4** (18.3 g, 100.5 mmol, 1 eq) in CH_2Cl_2 (20 mL) v

added pyridine (20 mL) under nitrogen. The system was cooled to 0 ^{o}C and phosphoryl chloride (13.8 mL, 150.8 mmol, 1.5 eq) was added dropwise. Then the mixture was kept at 0 ^{o}C for 30 min and warmed to room temperature for 2 h. The reaction was quenched with small pieces of ice at 0 ^{o}C, neutralized by 2 M HCl and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography eluted with hexanes to give **2.5** as yellow oil (12.5 g, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (t, 1H, J=3 Hz), 2.46-2.41 (m, 4H), 1.88 (m, 2H), 0.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 124.8, 102.8, 95.5, 36.6, 33.5, 25.6, 0.26.

1-(cyclopent-1-en-1-yl)hept-6-en-1-yn-3-ol, 2.7

To a solution of **2.5** (0.89 g, 5.42 mmol, 1 eq) in THF (10 ml) was added TBAF (7 mL, 7 mmol, 1 M in THF, 1.3 eq) dropwise at room temperature under nitrogen. The mixture was stirred for 4 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with Et_2O three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation at 0 ^{o}C and purified by flash column chromatography eluted with *n*-hexanes to furnish compound **2.6** (498 mg).

2.6 (498 mg, 5.4 mmol, 1.25 eq) was dissovled in THF (10 mL) and cooled to -78 ^{o}C under nitrogen. n-BuLi (1.94 mL, 4.86 mmol, 2.5 M in hexane, 1.13 eq) was added and the mixture was stirred for 30 min. Then 4-pentenal (425.6 uL, 4.32 mmol, 1 e

was added and stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=15:1) to give compound **2.7** (480.4 mg, 63% over two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (t, 1H, J=3 Hz), 5.84 (m, 1H), 5.06 (m, 1H), 4.98 (d, 1H, J=12 Hz), 4.52 (t, 1H, J=6 Hz), 2.42 (m, 4H), 2.23 (m, 2H), 2.03 (s, 1H), 2.03-1.80 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.0, 124.1, 115.4, 91.2, 82.7, 62.7, 37.1, 36.6, 33.4, 29.7, 23.5.

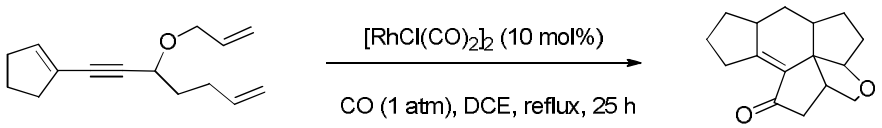
1-(3-(allyloxy)hept-6-en-1-yn-1-yl)cyclopent-1-ene, 2.8

To a solution of NaH 60% w/w (3.5 g, 87.6 mmol, 3 eq) in THF (20 mL) was added alcohol **2.7** (5.14 g, 29.2 mmol, 1 eq) in THF (10 mL) at 0 ^{o}C under nitrogen and stirred for 30 min. Then allyl bromide (20.2 mL, 233.6 mmol, 8 eq) was added and the mixture was warmed to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=25:1) to give compound **2.8** (5.68 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (t, 1H, J=3 Hz), 5.86 (m, 2H), 5.30 (dd, 1H, J=18, 3 Hz), 5.17 (d, 1H, J=9 Hz), 5.04 (dd, 1H, J=18, 3 Hz), 4.96 (d, 1H, J=18 Hz), 4.25 (m, 2H), 3.95 (dd, 1H, J=12, 6 Hz), 2.42 (m, 4H), 2.23 (m, 2H), 1.86 (m, 4H). ^{1}

NMR (75 MHz, $CDCl_3$) δ 138.2, 138.0, 134.8, 124.3, 117.4, 115.2, 89.3, 83.5, 69.8, 68.9, 36.7, 35.2, 33.4, 29.8, 23.5. HRMS (ESI) for $C_{15}H_{19}O$ (MH+) Cacld: 215.14360, Found: 215.14395.

b. Synthesis of racemic PK-DA product 2.9.



2.8 **2.9**
62%

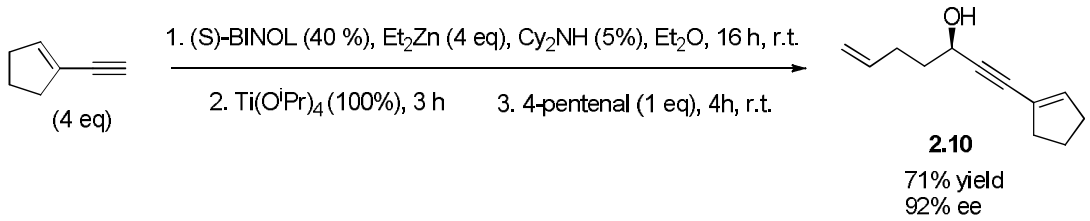
Under nitrogen, **2.8** (58.5 mg, 0.272 mmol, 1 eq) and $[Rh(CO)_2Cl]_2$ (10.5 mg, 0.10 eq) were weighed into a tared two-necked round bottom flask and dissolved in DCE (5 mL). The flask was fitted with reflux condenser fit with a septum and the side arm of the flask was also fitted with septum. The solution was bubbled with CO gas for 2 minutes through the side arm fitted with septum and a vent needle in the septum of the reflux condenser. Then, the solution was placed under CO atmosphere by using a balloon. After the reaction mixture was heated at 70 ^oC to reflux temperature for 25 h, it was cooled to room temperature and the CO was released cautiously in the hood. The reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel (hexane:EtOAc=20:1 to 8:1) to give compound **2.9** (40.7 mg, 62%).

^1H NMR (600 MHz, $CDCl_3$) δ 4.15 (m, 1H), 4.09 (dd, 1H, J=6, 3 Hz), 3.84 (d, 1H, J=6 Hz), 2.82 (dd, 1H, J=9, 3 Hz), 2.64 (m, 1H), 2.52 (m, 1H), 2.28 (m, 3H), 2,09 (m, 2H), 1.91 (dd, 1H, J=6, 3 Hz), 1.82 (m, 1H), 1.75 (m, 1H), 1.71-1.54 (m, 3H), 1.07

2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.0, 160.6, 132.4, 91.2, 73.0, 62.9, 47.5, 43.1, 42.4, 39.8, 35.7, 32.8, 32.6, 32.0, 31.6, 24.9. HRMS (ESI) for $C_{16}H_{21}O_2$ (MH+) Cacld: 245.1542, Found: 245.1544.

3.2. Synthesis of chiral polycyclic compound 2.12

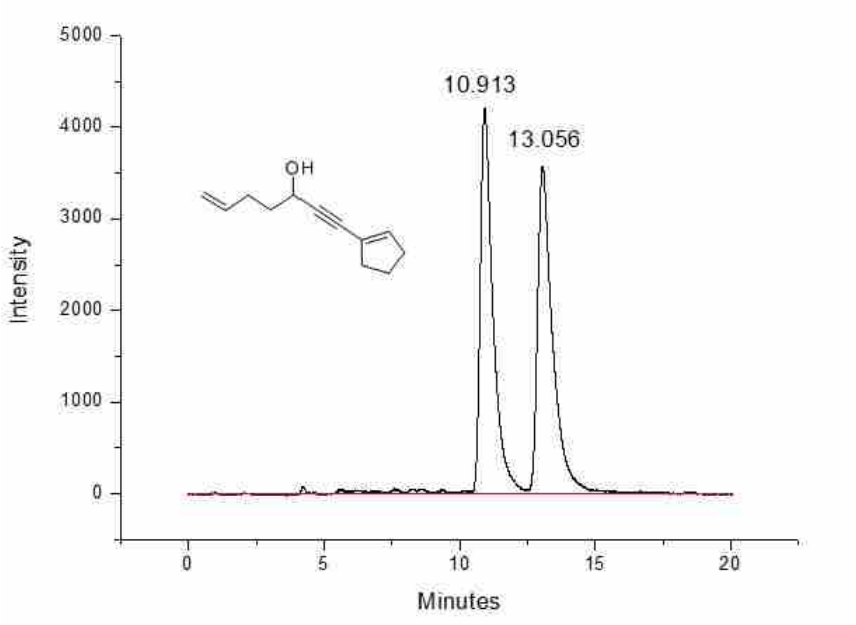
a. Synthesis of chiral propargylic alcohol 2.10.



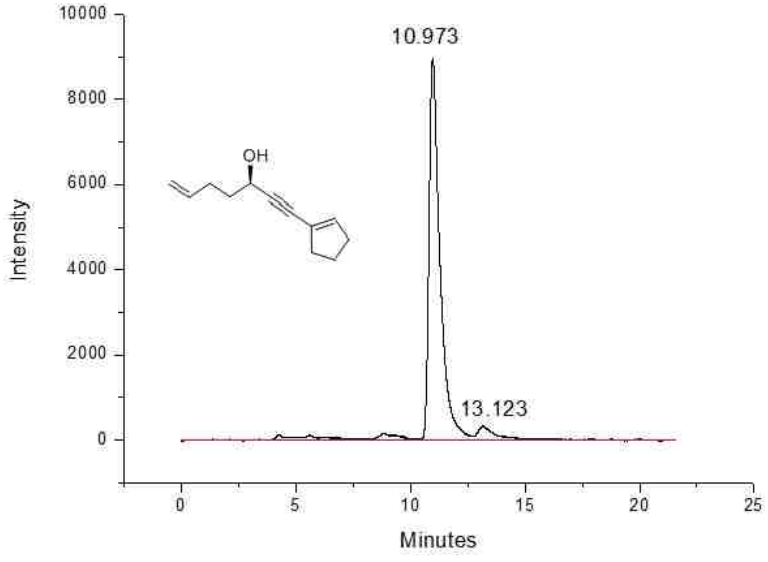
Under nitrogen atmosphere, (S)-BINOL (28.6 mg, 40%) was weighted into a tared flask and dissolved in Et_2O (3 mL). An alkyne (92 mg, 4 eq), Cy_2NH (2.5 uL, 5%) and Et_2Zn (102 uL, 4 eq) were added and the mixture was stirred for 16 h at room temperature. Then, $Ti(OiPr)_4$ (73.9 uL, 100%) was added and stirring continued for 3 h. 4-pentenal (24.6 uL, 0.25 mmol, 1 eq) was added and the mixture was stirred for another 4 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4 and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel (hexane:EtOAc=20:1 to 10:1) to give compound **2.10** in 71% yield and 92% ee determined by HPLC analysis: Chiralpak OD column, 98:2 hexanes: ^{i}PrOH, flow rate= 1.0 mL/min, λ= 254 nm, retention time: t_{major}= 10.973 min, t_{minor}= 13.123 min. $[\alpha]^{24}_{D}$= -18.996 (c= 0.455, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (t, 1H, J=3 Hz), 5.84 (m, 1H), 5.06 (

1H), 4.98 (d, 1H, J=12 Hz), 4.52 (t, 1H, J=6 Hz), 2.42 (m, 4H), 2.23 (m, 2H), 2.03 (s, 1H), 2.03-1.80 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.0, 124.1, 115.4, 91.2, 82.7, 62.7, 37.1, 36.6, 33.4, 29.7, 23.5.

HPLC plots for determination of Enantiomeric Excess

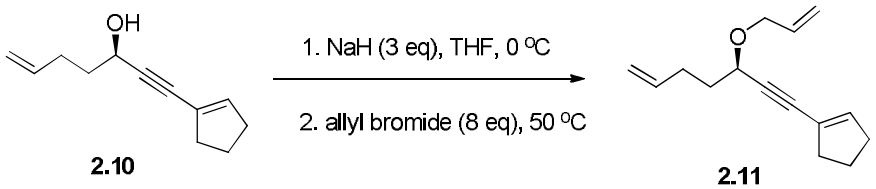


	Retention Time (min)	Area	%Area
1	10.913	2288	50.08%
2	13.056	2280	49.92%



	Retention Time (min)	Area	%Area
1	10.973	4955	95.86%
2	13.056	214	4.14%

b. Synthesis of chiral triene-yne 2.11.

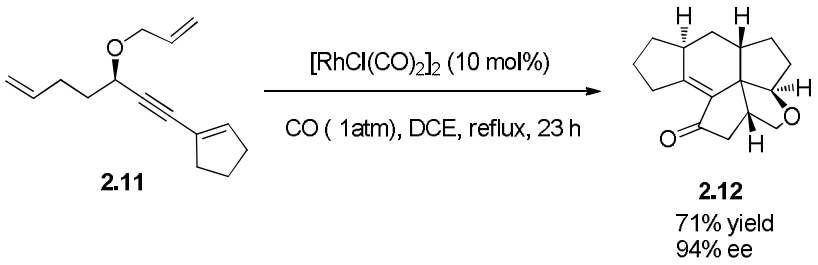


2.10 **2.11**
92% yield

To a solution of NaH 60% w/w (8.7 mg, 3 eq) in THF (2 mL) was added alcohol **2.10** (21.3 mg, 0.121 mmol, 1 eq) in THF (2 mL) at 0 °C under nitrogen and stirred for 30 min. Then allyl bromide (83.8 uL, 8 eq) was added and the mixture was warmed to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=25:1) to give compound **2.11** (24 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (t, 1H, J=3 Hz), 5.86 (m, 2H), 5.30 (dd, 1H, J=18, 3 Hz), 5.17 (d, 1H, J=9 Hz), 5.04 (dd, 1H, J=18, 3 Hz), 4.96 (d, 1H, J=18 Hz), 4.25 (m, 2H), 3.95 (dd, 1H, J=12, 6 Hz), 2.42 (m, 4H), 2.23 (m, 2H), 1.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 138.0, 134.8, 124.3, 117.4, 115.2, 89.3, 83.5, 69.8, 68.9, 36.7, 35.2, 33.4, 29.8, 23.5. HRMS (ESI) for $C_{15}H_{19}O$ (MH+) Cacld: 215.14360, Found: 215.14395.

c. Synthesis of chiral PK-DA product 2.12.

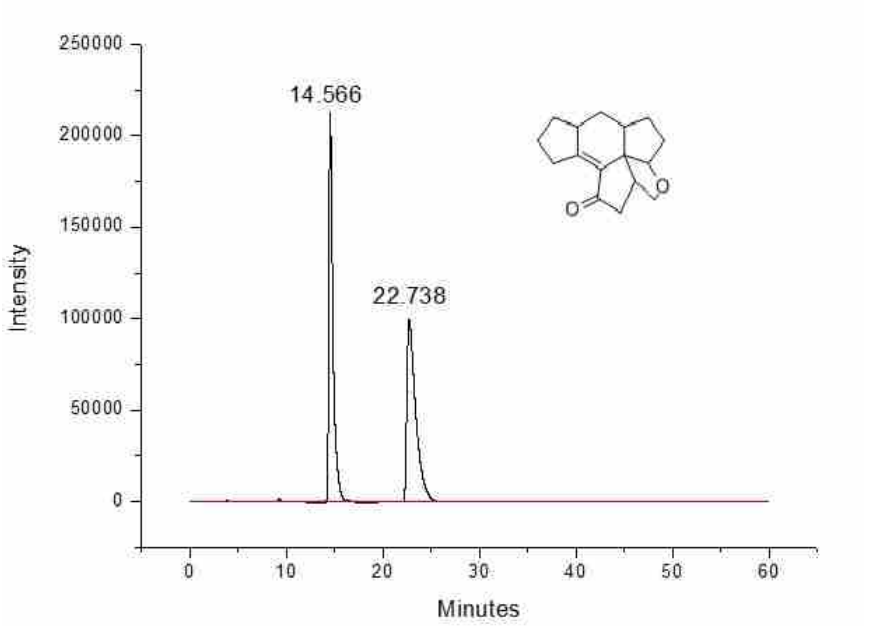


Under nitrogen, **2.11** (24 mg, 0.111 mmol, 1 eq) and $[Rh(CO)_2Cl]_2$ (4.3 mg, 0.10 eq) were weighed into a tared two-necked round bottom flask and dissolved in DCE (3 mL). The flask was fitted with reflux condenser fit with a septum and the side arm of the flask was also fitted with septum. The solution was bubbled with CO gas for 2 minutes through the side arm fitted with septum and a vent needle in the septum of the reflux condenser. Then, the solution was placed under CO atmosphere by using a balloon. After the reaction mixture was heated at 70 ^{o}C to reflux temperature for 23 h, it was cooled to room temperature and the CO was released cautiously in the hood. The reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel (hexane:EtOAc=20:1 to 5:1) to give compound **2.12** in 60 % yield (16.3 mg) and 94% ee determined by HPLC analysis: Chiralpak AD-H column, 98:2 hexanes: ^{i}PrOH, flow rate= 1.0 mL/min, λ= 254 nm, retention time: t_{major}= 22.773 min, t_{minor}= 14.591 min. $[\alpha]^{23}_{D}$= -103.63 (c= 0.815, $CHCl_3$).

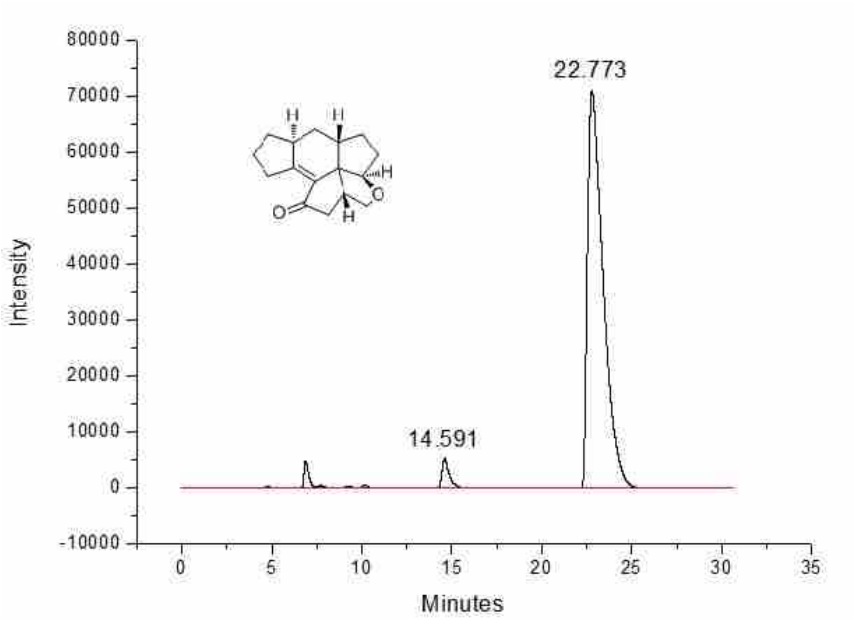
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.15 (m, 1H), 4.09 (dd, 1H, J=6, 3 Hz), 3.84 (d, 1H, J=6 Hz), 2.82 (dd, 1H, J=9, 3 Hz), 2.64 (m, 1H), 2.52 (m, 1H), 2.28 (m, 3H), 2,09 (m, 2H), 1.91 (dd, 1H, J=6, 3 Hz), 1.82 (m, 1H), 1.75 (m, 1H), 1.71-1.54 (m, 3H), 1.07 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.0, 160.6, 132.4, 91.2, 73.0, 62.9, 47.5, 4

42.4, 39.8, 35.7, 32.8, 32.6, 32.0, 31.6, 24.9. HRMS (ESI) for $C_{16}H_{21}O_2$ (MH+) Cacld: 245.1542, Found: 245.1544.

HPLC plots for determination of Enantiomeric Excess



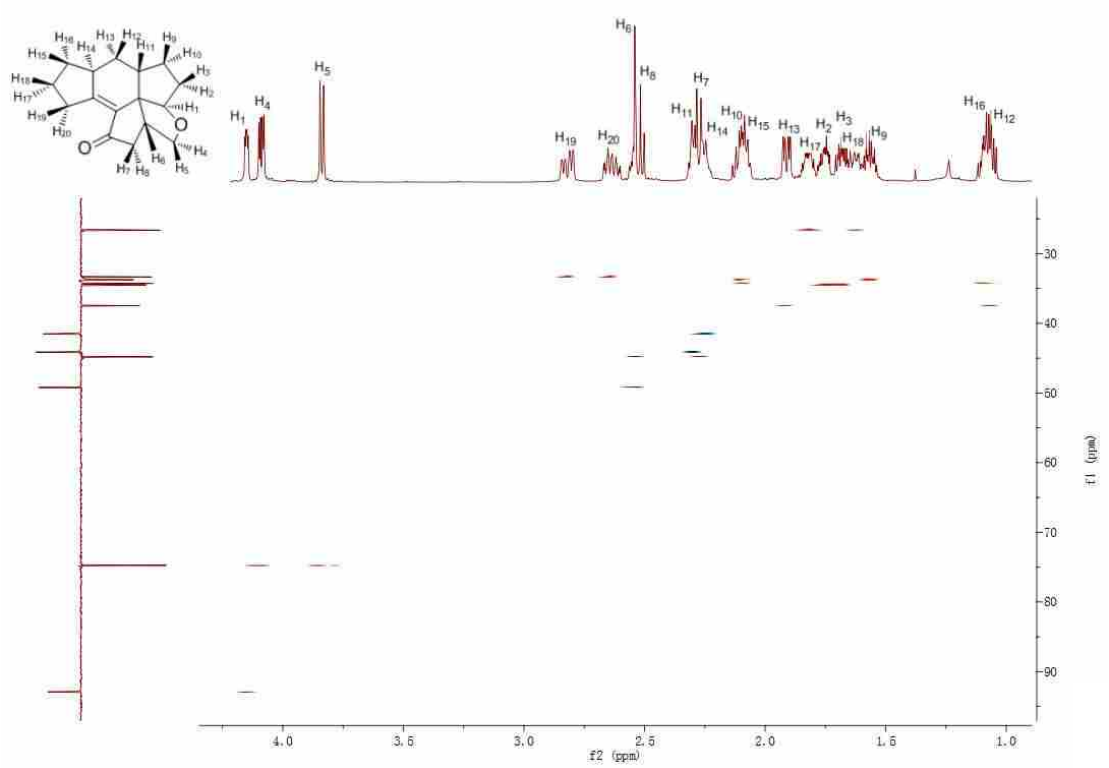
	Retention Time (min)	Area	%Area
1	14.566	105651	50.14%
2	22.738	105045	49.86%



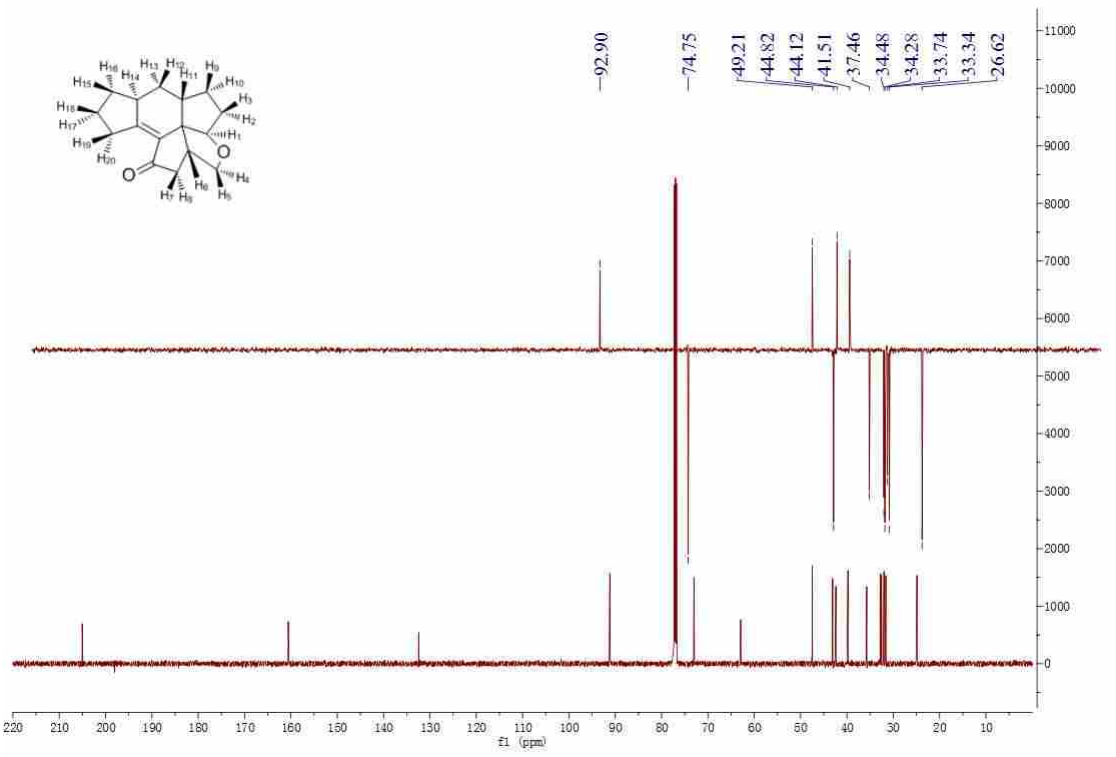
	Retention Time (min)	Area	%Area
1	14.591	2336	3.17%
2	22.773	71392	96.83%

2D NMR Spectra of 2.12

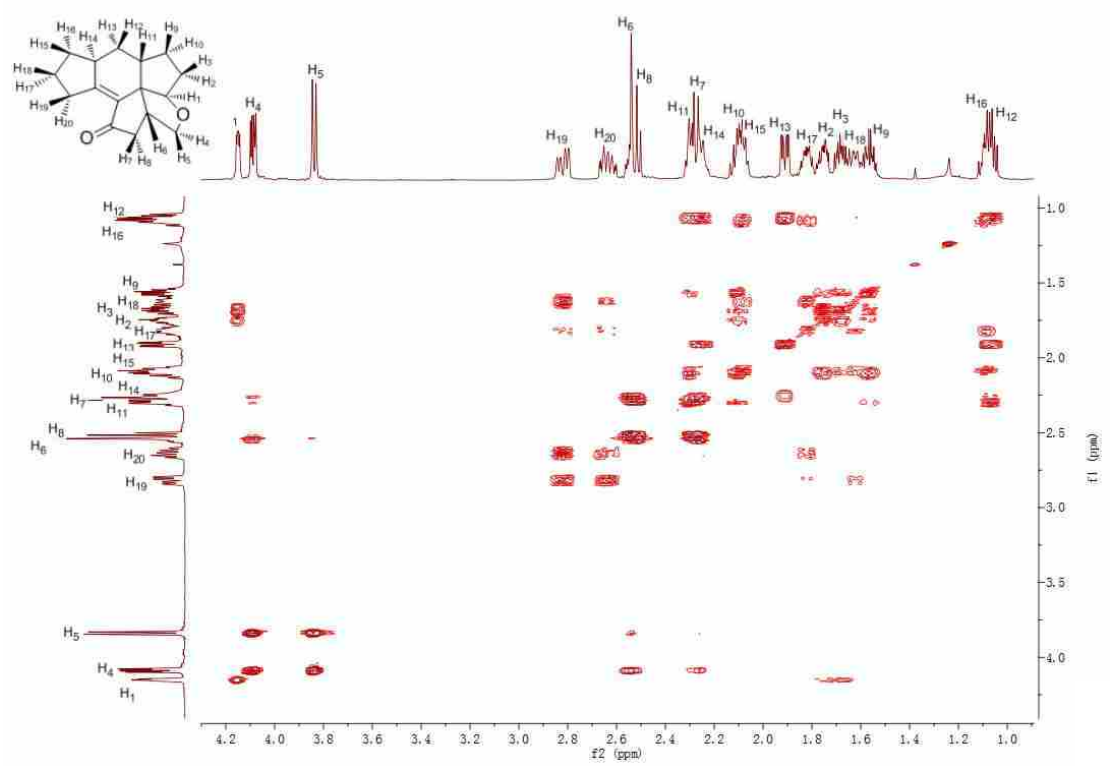
HSQC spectra of **2.12**



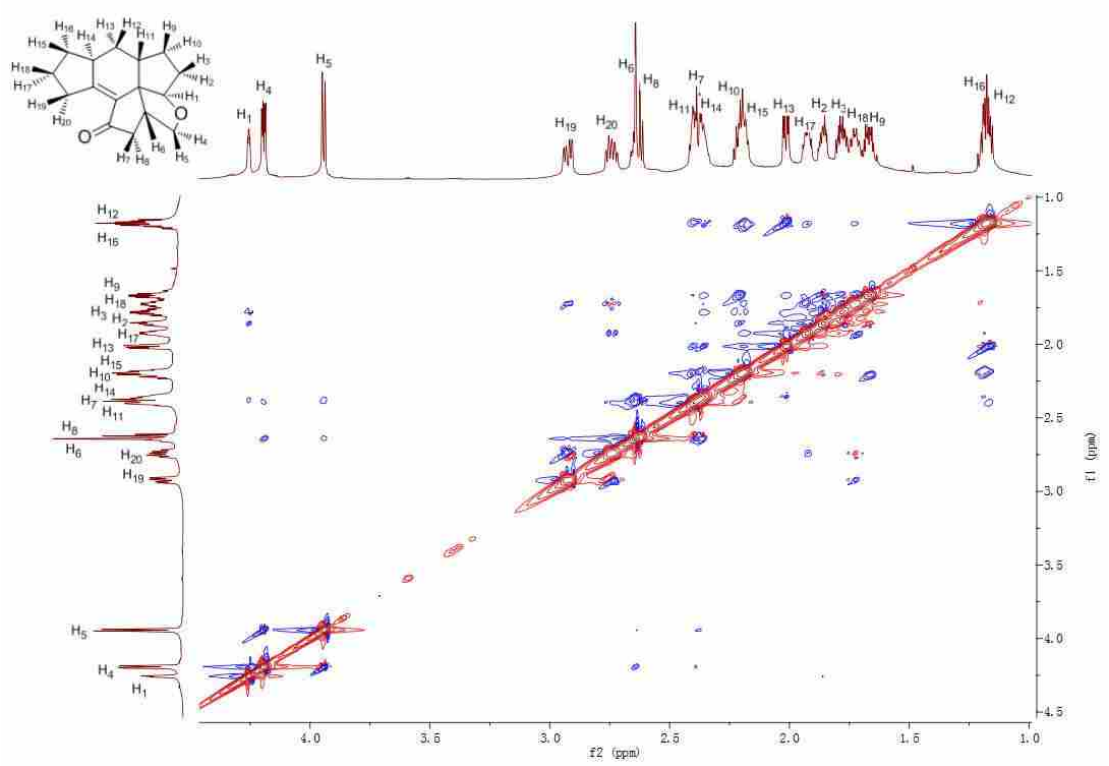
Comparison of DEPT-135 and ^{13}C NMR of **2.12**



COSY spectra of **2.12**



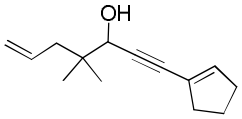
NOSEY spectra of **2.12**



3.3. Synthesis of racemic derivatives

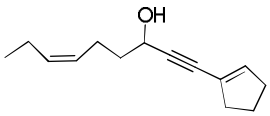
a. General Procedure for the preparation of racemic propargylic alcohols 2.18-2.24

Under nitrogen, an alkyne (1.5 eq) was dissovled in THF (5 mL) and cooled to -78 ^{o}C under nitrogen. nBuLi (1.2 eq) was added and the mixture was stirred for 30 min. Then an aldehyde (1 eq) was added and the system was stirred for 3 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by column chromatography on silica gel.



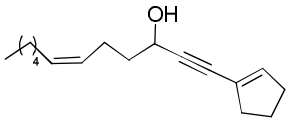
1-(cyclopent-1-en-1-yl)-4,4-dimethylhept-6-en-1-yn-3-ol, 2.18

73% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (t, 1H, J=3 Hz), 5.84 (m, 1H), 5.08 (dd, 1H, J=6, 3 Hz), 5.04 (s, 1H), 4.19 (d, 1H, J=6 Hz), 4.96 (d, 1H, J=18 Hz), 2.42 (m, 4H), 2.14 (m, 2H), 1.90 (m, 3H), 0.97 (s, 3H), 0.96 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 135.2, 124.2, 117.9, 90.0, 83.7, 70.9, 43.0, 39.1, 36.6, 33.4, 23.5, 22.9, 22.8.



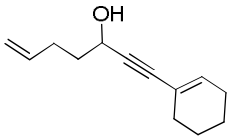
(*Z*)-1-(cyclopent-1-en-1-yl)non-6-en-1-yn-3-ol, 2.19

84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (m, 1H), 5.37 (m, 2H), 4.51 (m, 1H), 2.41 (m, 4H), 2.20 (m, 2H), 2.04 (m, 3H), 1.88 (m, 2H), 1.76 (m, 2H), 0.95 (t, 3H, J=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 133.0, 128.0, 124.2, 91.3, 82.6, 62.8, 37.9, 36.6, 33.4, 23.5, 23.2, 20.8, 14.6.



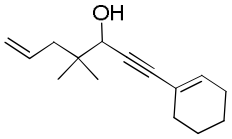
(*Z*)-1-(cyclopent-1-en-1-yl)dodec-6-en-1-yn-3-ol, 2.20

74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.39 (m, 2H), 4.51 (m, 1H), 2.42 (m, 4H), 2.21 (m, 2H), 2.06 (m, 2H), 1.89 (m, 3H), 1.78 (m, 2H), 1.29 (m, 6H), 0.88 (t, 3H, J=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 131.5, 128.5, 124.1, 91 82.6, 62.9, 38.0, 36.6, 33.4, 31.8, 29.6, 27.4, 23.5, 23.3, 22.8, 14.3.



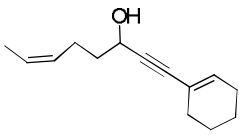
1-(cyclohex-1-en-1-yl)hept-6-en-1-yn-3-ol, 2.21

64% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (m, 1H), 5.83 (m, 1H), 5.08 (dd, 1H, J=18, 3 Hz), 4.98 (dd, 1H, J=9, 3 Hz), 4.49 (t, 1H, J=6 Hz), 2.22 (m, 2H), 2.08 (m, 4H), 2.00 (s, 1H), 1.80 (m, 2H), 1.59 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 135.5, 120.3, 115.4, 87.4, 87.2, 62.6, 37.2, 29.7, 29.4, 25.8, 22.5, 21.7.



1-(cyclohex-1-en-1-yl)-4,4-dimethylhept-6-en-1-yn-3-ol, 2.22

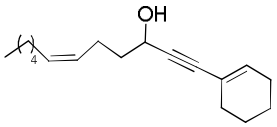
79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (m, 1H), 5.83 (m, 1H), 5.08 (m, 1H), 5.03 (m, 1H), 4.16 (s, 1H), 2.10 (m, 6H), 1.04 (s, 1H), 1.59 (m, 4H), 0.96 (m, 3H), 0.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 135.2, 120.4, 117.8, 88.1, 86.1, 70.8, 43.0, 39.1, 29.4, 25.8, 22.9, 22.8, 22.5, 21.7.



(*Z*)-1-(cyclohex-1-en-1-yl)non-6-en-1-yn-3-ol, 2.23

77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (m, 1H), 5.35 (m, 2H), 4.46 (m, 1H), 2.18 (m, 3H), 2.07 (m, 6H), 1.74 (m, 2H), 1.58 (m, 4H), 0.94 (t, 3H, J=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 132.9, 128.1, 120.3, 87.5, 87.0, 62.7, 38.0, 29

25.8, 23.2, 22.5, 21.7, 20.8, 14.6.

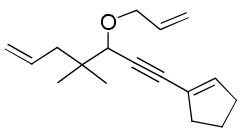


(*Z*)-1-(cyclohex-1-en-1-yl)dodec-6-en-1-yn-3-ol, 2.24

79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (m, 1H), 5.35 (m, 2H), 4.45 (m, 1H), 2.34 (d, 1H, J=3 Hz), 2.18 (m, 2H), 2.06 (m, 6H), 1.73 (m, 2H), 1.57 (m, 5H), 1.27 (m, 6H), 0.85 (t, 3H, J= 6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 131.3, 128.6, 120.4, 87.6, 87.0, 62.7, 38.0, 31.8, 29.6, 29.4, 25.8, 23.4, 22.8, 22.5, 21.7, 14.3.

b. General Procedure for the preparation of racemic triene-ynes 2.25-2.31

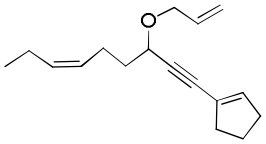
To a solution of NaH 60% w/w (3 eq) in THF was added an alcohol (1 eq) in THF at 0 ^{o}C under nitrogen and stirred for 30 min. Then allyl bromide (8 eq) was added and the mixture was warmed to 50 ^{o}C overnight. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography.



1-(3-(allyloxy)-4,4-dimethylhept-6-en-1-yn-1-yl)cyclopent-1-ene, 2.25

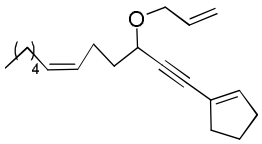
97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.86 (m, 2H), 5.30 (m, 1H 5.17 (m, 1H), 5.04 (m, 2H), 4.30 (ddt, 1H, J=12, 6, 3Hz), 3.93 (m, 1H), 3.87 (s, 1H

2.45 (m, 4H), 2.16 (m, 2H), 1.90 (m, 2H), 0.99 (s, 3H), 0,97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 135.3, 135.0, 124.5, 117.6, 117.0, 88.3, 84.3, 77.2, 70.3, 43.4, 38.7, 36.7, 33.4, 29.9, 23.5, 23.2.



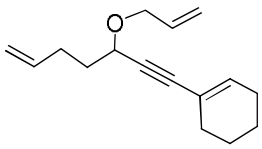
(*Z*)-1-(3-(allyloxy)non-6-en-1-yn-1-yl)cyclopent-1-ene, 2.26

93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.92 (m, 1H), 5.36 (m, 3H), 5.16 (m, 1H), 4.23 (m, 2H), 3.97 (ddt, 1H, J=12, 6, 3Hz), 2.42 (m, 4H), 2.20 (m, 2H), 2.06 (m, 2H), 1.89 (m, 2H), 1.79 (m, 2H), 0.95 (t, 3H, J=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 134.8, 132.8, 128.1, 124.3, 117.4, 89.5, 83.4, 69.8, 69.0, 36.6, 36.0, 33.4, 23.5, 23.3, 20.7, 14.6.



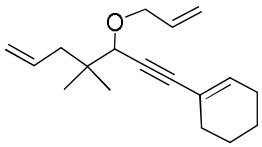
(*Z*)-1-(3-(allyloxy)dodec-6-en-1-yn-1-yl)cyclopent-1-ene, 2.27

96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.92 (m, 1H), 5.36 (m, 3H), 5.18 (m, 1H), 4.23 (m, 2H), 3.97 (ddt, 1H, J=12, 6, 3Hz), 2.43 (m, 4H), 2.21 (m, 2H), 2.03 (m, 2H), 1.90 (m, 2H), 1.79 (m, 2H), 1.29 (m, 8H), 0.88 (t, 3H, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 134.8, 131.2, 128.6, 124.3, 117.3, 89.5, 83.4, 69.8, 69.1, 36.7, 36.0, 33.4, 31.8, 29.6, 27.4, 23.5, 23.4, 22.8, 14.6. HRMS (ESI) for $C_{20}H_{30}ONa$ (MNa+) Cacld: 309.2194, Found: 309.2191.



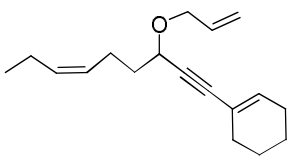
1-(3-(allyloxy)hept-6-en-1-yn-1-yl)cyclohex-1-ene, 2.28

97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (m, 1H), 5.93 (m, 1H), 5.79 (m, 1H), 5.30 (m, 1H), 5.17 (m, 1H), 5.04 (m, 1H), 4.97 (m, 1H), 4.22 (m, 2H), 3.97 (ddt, 1H, J=15, 6, 3Hz), 2.22 (m, 2H), 2.09 (m, 4H), 1.84 (m, 2H), 1.60 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 135.1, 134.9, 120.4, 117.4, 115.2, 88.0, 85.4, 69.7, 68.9, 35.2, 29.8, 29.5, 25.8, 22.5, 21.7.



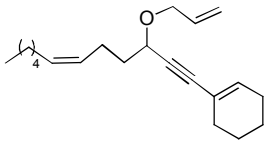
1-(3-(allyloxy)-4,4-dimethylhept-6-en-1-yn-1-yl)cyclohex-1-ene, 2.29

91% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (m, 1H), 5.87 (m, 2H), 5.30 (m, 1H), 5.17 (m, 1H), 5.03 (m, 2H), 4.29 (ddt, 1H, J=12, 6, 3 Hz), 3.90 (m, 1H), 3.85 (s, 1H), 2.13 (m, 6H), 1.60 (m, 4H), 0.98 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 135.1, 134.7, 120.7, 117.5, 116.9, 88.8, 84.4, 77.1, 70.2, 43.4, 38.7, 29.9, 29.6, 25.8, 23.5, 23.2, 22.5, 21.7. HRMS (ESI) for $C_{18}H_{27}O$ (MH+) Cacld: 259.2062, Found: 259.2066.



(*Z*)-1-(3-(allyloxy)non-6-en-1-yn-1-yl)cyclohex-1-ene, 2.30

91% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (m, 1H), 5.91 (m, 1H), 5.35 (m, 2H), 5.29 (m, 1H), 5.17 (m, 1H), 4.27 (ddt, 1H, J=12, 6, 3 Hz), 4.18 (t, 1H, J=6 Hz), 3.96 (ddt, 1H, J=12, 6, 3 Hz), 2.21 (q, 2H, J=6 Hz), 2.08 (m, 6H), 1.78 (m, 2H), 1,61 (m, 4H), 0.95 (t, 3H, J=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 134.9, 132.8, 128.1, 120.5, 117.3, 87.9, 85.6, 69.8, 69.0, 36.1, 29.5, 25.8, 23.3, 22.5, 21.7, 20.7, 14.6. HRMS (ESI) for $C_{18}H_{27}O$ (MH+) Cacld: 259.2062, Found: 259.2061.



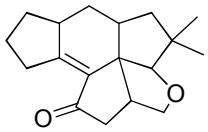
(*Z*)-1-(3-(allyloxy)dodec-6-en-1-yn-1-yl)cyclohex-1-ene, 2.31

67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (m, 1H), 5.92 (m, 1H), 5.38 (m, 2H), 5.30 (m, 1H), 5.17 (m, 1H), 4.27 (ddt, 1H, J=9, 6, 3 Hz), 4.18 (t, 1H, J=6 Hz), 3.96 (ddt, 1H, J=15, 6, 3 Hz), 2.21 (q, 2H, J=6 Hz), 2.10 (m, 6H), 1.78 (m, 2H), 1,59 (m, 4H), 1.29 (m, 6H), 0.88 (t, 3H, J=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 134.9, 131.2, 128.7, 120.5, 117.3, 88.0, 85.6, 69.7, 69.0, 36.1, 31.8, 29.7, 29.5, 27.4, 25.8, 23.4, 22.8, 22.5, 21.7, 20.7, 14.3. HRMS (ESI) for $C_{21}H_{33}O$ (MH+) Cacld: 301.2531, Found: 301.2532.

c. General Procedure for tandem Pauson-Khand and [4+2] cycloaddition

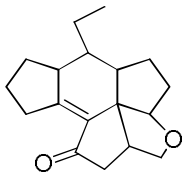
Under nitrogen, a triene-yne (1 eq) and $[Rh(CO)_2Cl]_2$ (0.10 eq) were weighed into a tared two-necked round bottom flask and dissolved in DCE (3 mL). The flask was fitted with reflux condenser fit with a septum and the side arm of the flask w

also fitted with septum. The solution was bubbled with CO gas for 2 minutes through the side arm fitted with septum and a vent needle in the septum of the reflux condenser. Then, the solution was placed under CO atmosphere by using a balloon. After the reaction mixture was heated at 70 ^{o}C to reflux temperature for 21-47 h, it was cooled to room temperature and the CO was released cautiously in the hood. The reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel.



PK-DA product, 2.32

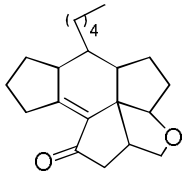
49% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.05 (m, 1H), 3.87 (d, 1H, J=6 Hz), 3.76 (s, 1H), 2.83 (dd, 1H, J=12, 6 Hz), 2.61 (m, 1H), 2.46 (m, 3H), 2.26 (m, 1H), 2.11 (m, 1H), 1.91 (m, 2H), 1.84 (m, 1H), 1.63 (m, 1H), 1,58 (m, 1H), 1.51 (m, 1H), 1.25 (m, 1H), 1.06 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.8, 158.7, 134.2, 96.2, 72.6, 64.0, 47.6, 45.9, 43.0, 40.9, 40.2, 38.3, 32.9, 32.7, 31.7, 29.1, 24.8, 24.5. HRMS (ESI) for $C_{18}H_{25}O_2$ (MH+) Cacld: 273.1855, Found: 273.1850.



PK-DA product, 2.33

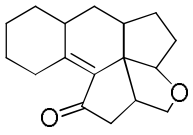
56% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.21 (t, 1H, J=3 Hz), 4.04 (dd, 1H, J=6, 3 Hz), 3.86 (d, 1H, J= 3 Hz), 2.86 (dd, 1H, J=9, 3 Hz), 2.52 (m, 3H), 2.30 (m, 3H), 2. (m, 2H), 1.88 (m, 1H), 1.82 (m, 2H), 1.61 (m, 3H), 1.48 (m, 1H), 1,28 (m, 1H), 1.

(m, 2H), 0.94 (t, 3H, J=3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 159.3, 133.9, 91.4, 72.3, 64.2, 47.3, 46.3, 44.9, 44.7, 43.5, 32.4, 32.3, 31.4, 25.3, 24.9, 24.5, 12.5. HRMS (ESI) for $C_{18}H_{25}O_2$ (MH+) Cacld: 273.1855, Found: 273.1855.



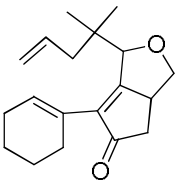
PK-DA product, 2.34

38% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (t, 1H, J=6 Hz), 4.03 (m, 1H), 3.84 (d, 1H, J= 9 Hz), 2.86 (dd, 1H, J=21, 9 Hz), 2.47 (m, 3H), 2.26 (m, 2H), 2.11 (m, 2H), 1.83 (m, 3H), 1.53 (m, 5H), 1.28 (m, 6H), 1.05 (m, 2H), 0.89 (t, 3H, J=6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.7, 158.6, 133.2, 90.7, 71.6, 63.5, 46.6, 44.5, 44.2, 43.7, 42.8, 32.0, 31.8, 31.7, 30.9, 30.6, 26.7, 24.5, 24.3, 22.5, 14.0. HRMS (ESI) for $C_{21}H_{31}O_2$ (MH+) Cacld: 315.2297, Found: 315.2323.



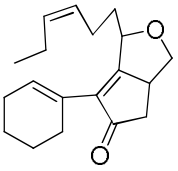
PK-DA product, 2.35

45% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.21 (d, 1H, J=3 Hz), 3.97 (dd, 1H, J=6, 3 Hz), 3.82 (m, 1H), 3.76 (d, 1H, J=3 Hz), 2.66 (dd, 1H, J=12, 6 Hz), 2.46 (m, 1H), 2.18 (m, 3H), 2.01 (m, 2H), 1.85 (m, 2H), 1.74 (m, 3H), 1.61 (m, 1H), 1.50 (m, 2H), 1.28 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 154.0, 132.6, 90.0, 72.3, 62.6, 45.7, 44.7, 40.4, 37.6, 35.2, 34.4, 32.8, 32.7, 28.8, 27.5, 25.8. HRMS (ESI) for $C_{17}H_{23}O_2$ (MH+) Cacld: 259.1698, Found: 259.1699.



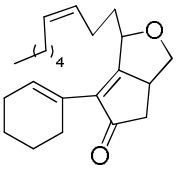
PK product, 2.36

57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (m, 1H), 5.69 (s, 1H), 5.06 (s, 1H), 5.01 (d, 1H, J=6 Hz), 4.54 (s, 1H), 4.30 (t, 1H, J=6 Hz), 3.14 (m, 2H), 2.61 (dd, 1H, J=18, 6 Hz), 2.45 (d, 1H, J=12 Hz), 2.05 (m, 5H), 1.61 (m, 4H), 1.23 (s, 1H), 0.89 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 176.8, 140.5, 134.7, 130.1, 128.6, 118.0, 82.8, 71.7, 43.6, 43.5, 39.5, 29.9, 27.4, 25.4, 23.5, 23.4, 22.6, 22.0. HRMS (ESI) for $C_{19}H_{27}O_2$ (MH+) Cacld: 287.2011, Found: 287.2006.



PK product, 2.37

44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (m, 1H), 5.37 (m, 2H), 4.74 (m, 1H), 4.31 (m, 1H), 3.19 (m, 2H), 2.65 (dd, 1H, J=18, 6 Hz), 2.28-2.00 (m, 9H), 1.82-1.57 (m, 6H), 0.95 (t, 3H, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 176.7, 137.1, 133.2, 130.4, 129.2, 127.9, 76.1, 71.7, 42.4, 40.0, 35.9, 29.9, 27.8, 25.7, 23.4, 22.8, 22.0, 20.8, 14.5. HRMS (ESI) for $C_{19}H_{27}O_2$ (MH+) Cacld: 287.2011, Found: 287.2007.



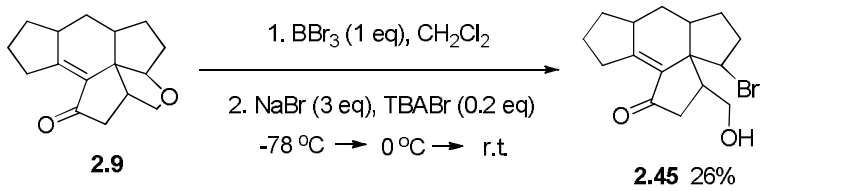
PK product, 2.38

64% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (m, 1H), 5.39 (m, 2H), 4.74 (m, 1l

4.31 (m, 1H), 3.19 (m, 2H), 2.65 (dd, 1H, J=18, 6 Hz), 2.27-2.09 (m, 6H), 2.01 (m, 2H), 1.80-1.59 (m, 6H), 1.34-1.24 (m, 7H), 0.87 (t, 1H, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 176.7, 137.1, 131.6, 130.4, 129.2, 128.4, 76.1, 71.7, 42.4, 40.0, 35.9, 31.7, 29.9, 29.6, 27.8, 27.4, 25.7, 23.5, 22.8, 22.0, 14.3. HRMS (ESI) for $C_{22}H_{33}O_2$ (MH+) Cacld: 329.2481, Found: 329.2480.

3.4 Further modification and exploration

a. Ring-opening reaction



2.9 **2.45** 26%

recovered starting material: 30%

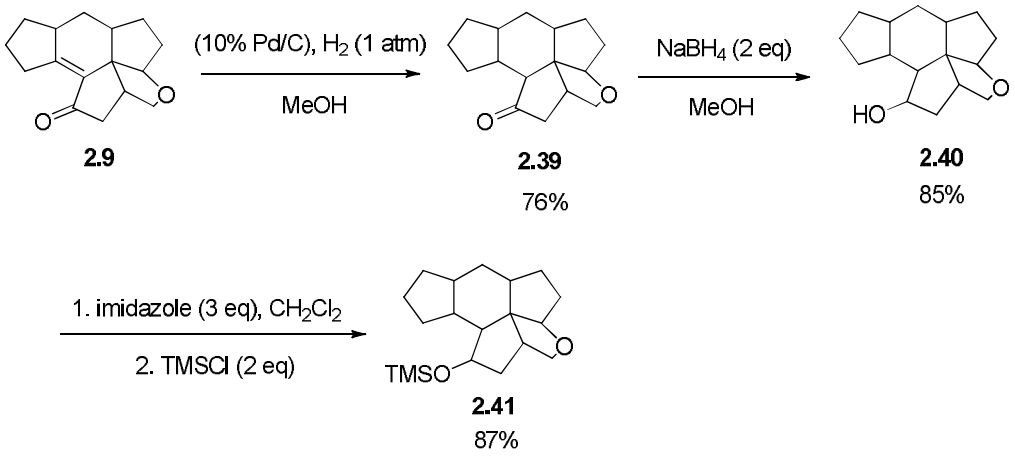
Ring-opening product, 2.45

To a solution of **2.9** (43.7 mg, 0.179 mmol, 1 eq) in CH_2Cl_2 (10 mL) was added BBr_3 (17 uL, 1 eq) in CH_2Cl_2 (5 mL) dropwise at -78 °C under nitrogen. The mixture was kept at -78 °C for 2 h and warm to 0 °C overnight. Then NaBr (55.2 mg, 3 eq) and TBABr (13 mg, 0.2 eq) in CH_2Cl_2 (5 mL) were added at room temperature and stirred overnight. The reaction was quenched by slow addition of saturated sodium bicarbonate solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by column chromatography on silica gel (CH_2Cl_2:MeOH=150:1) to give compound **2.45** (15 mg, 26%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (t, 1H, J=6 Hz), 3.91 (dd, 2H, J=6, 3 Hz), 2.94 (

1H), 2.63 (m, 2H), 2.33 (m, 3H), 2.10 (m, 2H), 1.90 (m, 6H), 1.67 (m, 2H), 1.04 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.5, 161.9, 135.9, 62.8, 57.4, 57.3, 55.8, 46.1, 41.3, 39.8, 38.9, 34.9, 32.4, 31.7, 29.4, 24.7. HRMS (ESI) for $C_{16}H_{22}O_2Br$ (MH+) Cacld: 325.0803, Found: 325.0805.

b. Further elaborations before ring-opening.



2.9 → **2.39** 76% → **2.40** 85% → **2.41** 87%

Compound 2.40

A suspension of **2.9** (73.2 mg, 0.3 mmol, 1 eq) and 10% Pd/C (7.3 mg) in MeOH (3 mL) was hydrogenated with H_2 (1 atm) for 18 h. The reaction mixture was filtrated over Celite and the residue was concentrated by rotavapor and purified by column chromatography on silica gel (hexane:EtOAc=15:1 to 10:1) to give compound **2.39** (55.8 mg, 76%).

A solution of **2.39** (55.8 mg, 0.230 mmol, 1 eq) and $NaBH_4$ (17.4 mg, 2 eq) in MeOH (3 mL) was stirred for 11 h at room temperature. The reaction was quenched by water and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by fl column chromatography (hexane:EtOAc=5:1 to 3:1) to afford compound **2.40** (4

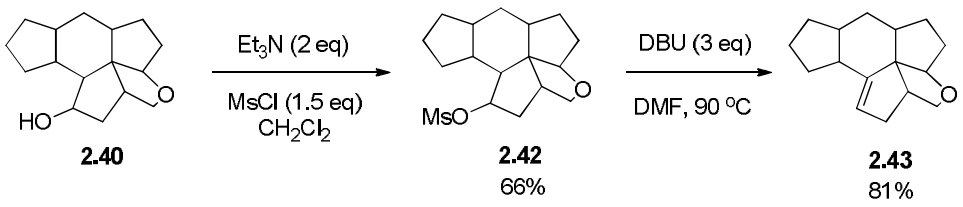
mg, 85%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.54 (q, 1H, J=6 Hz), 4.09 (dd, 1H, J=6, 3 Hz), 3.92 (dd, 1H, J=12, 6 Hz), 3.68 (dd, 1H, J=12, 6 Hz), 2.28 (m, 1H), 2.23 (t, 1H, J=6 Hz), 2.16 (m, 1H), 2.08 (m, 1H), 1.99 (m, 1H), 1.95 (m, 1H), 1.91 (m, 1H), 1.83 (m, 2H), 1.77 (m, 4H), 1.59 (m, 1H), 1.41 (m, 3H), 1.31 (m, 1H), 1.24 (m, 1H), 1.17 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.5, 76.6, 74.9, 62.3, 49.7, 47.8, 41.3, 41.1, 37.2, 34.4, 32.6, 32.2, 32.0, 30.8, 30.0, 25.5. HRMS (ESI) for $C_{16}H_{25}O_2$ (MH+) Cacld: 249.1855, Found: 249.1681.

Compound 2.41

To a solution of **2.40** (105.2 mg, 0.424 mmol, 1 eq) in CH_2Cl_2 (5 mL) was added imidazole (86.5 mg, 3 eq) and TMSCl (73 uL, 2 eq) at 0 ^{o}C sequentially. The reaction mixture was stirred at 0 ^{o}C for 1 h and warmed to room temperature. After 2.5 h, the reaction was quenched by water, neutralized by 2 M HCl and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=25:1) to give compound **2.41** (117.8 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (q, 1H, J=6 Hz), 4.09 (dd, 1H, J=9, 3 Hz), 3.92 (dd, 1H, J=9, 6 Hz), 3.68 (d, 1H, J=9 Hz), 2.24 (m, 1H), 2.12 (m, 2H), 1.97 (m, 3H), 1.86 (m, 2H), 1.63 (m, 5H), 1.39 (m, 3H), 1.21 (m, 3H), 0.08 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.7, 76.5, 74.8, 61.9, 49.6, 48.5, 41.5, 41.3, 37.7, 34.4, 32.7, 32.2, 32.1, 30.8, 29.6, 25.4, 0.32.



2.40 **2.42** 66% **2.43** 81%

Compound 2.42

To a solution of **2.40** (110.8 mg, 0.447 mmol, 1 eq) in CH_2Cl_2 (5 mL) was added Et_3N (124 uL, 2 eq) and MsCl (51.8 uL, 1.5 eq) at 0 °C sequentially. The reaction mixture was stirred at 0 °C for 2 h and warmed to room temperature overnight. Then the reaction was quenched by water, neutralized by 2 M HCl and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=10:1) to give compound **2.42** (96.8 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (q, 1H, J=6 Hz), 4.16 (dd, 1H, J=6, 3 Hz), 3.92 (dd, 1H, J=9, 6 Hz), 3.72 (d, 1H, J=9 Hz), 3.01 (s, 3H), 2.12 (m, 2H), 2.54 (t, 1H, J=6 Hz), 2.28 (m, 2H), 2.17 (m, 2H), 2.00 (m, 4H), 1.78 (m, 4H), 1.61 (m, 1H), 1.44 (m, 3H), 1.25 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.2, 83.5, 76.1, 61.6, 48.6, 46.8, 40.8, 38.3, 38.1, 37.5, 34.2, 32.6, 32.2, 31.9, 30.4, 29.3, 25.2.

Compound 2.43

To a solution of **2.42** (24.2 mg, 0.074 mmol, 1 eq) in DMF (3 mL) was added DBU (22.1 uL, 2 eq) under nitrogen. The mixture was heated to 90 °C and stirred for 19 h. Then the system was cooled to room temperature, quenched by water, neutralized by 2 M HCl and extracted with CH_2Cl_2 three times. The organic layer v washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation a

purified by flash column chromatography (hexane:EtOAc=15:1) to give compound **2.43** (13.7 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (m, 1H), 4.26 (m, 1H), 4.06 (dd, 1H, J=9, 6 Hz), 3.54 (dd, 1H, J=9, 3 Hz), 2.53 (m, 3H), 2.14 (m, 3H), 1.92 (m, 2H), 1.82 (m, 2H), 1.66 (m, 4H), 1.49 (m, 3H), 1.16 (m, 1H). GCMS (EI) for $C_{16}H_{22}O$ (M+) Found: 230.

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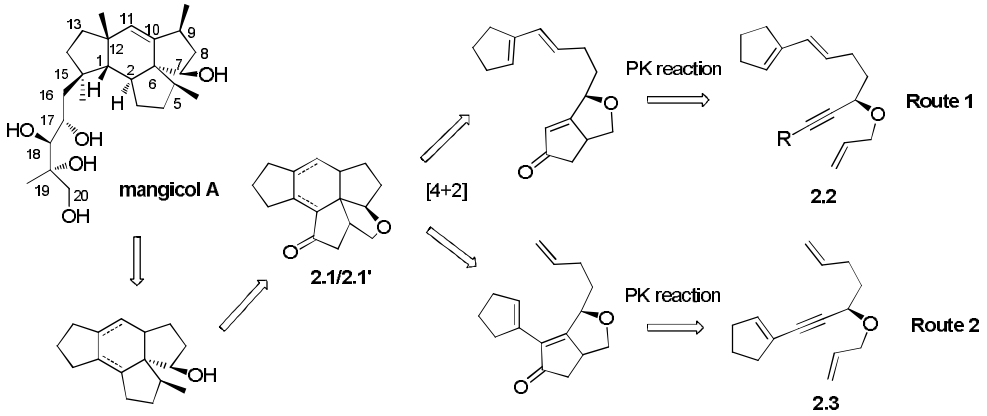
Chapter 3. Other methods attempted

1. Investigation of route 1.

Before route 2 was found to effectively access the fundamental ring system of mangicol A, we had made much efforts on the investigation of route 1. However, there were some issues in the synthesis of the corresponding intermediate **2.1**, which made route 1 unsuccessful (Scheme 3.1).

Scheme 3.1. Retrosynthetic analysis of the mangicol core.



In the previous synthetic proposal, the intermediate **2.1** could be prepared through domino Pauson-Khand reaction and [4+2] cycloaddition from the optically active triene-yne **2.2**. To test this strategy, a couple of related racemic substrates were synthesized from corresponding aldehydes.

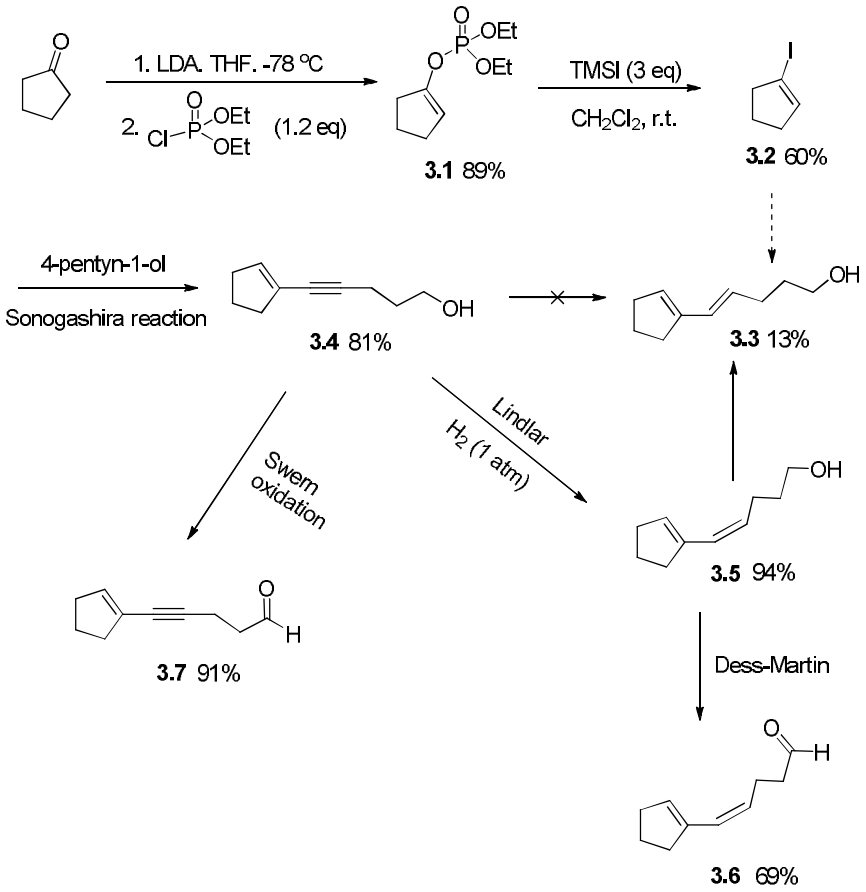
These aldehydes could be prepared as shown in Scheme 3.2. Deprotonation of cyclopentanone followed by substitution of diethyl chlorophosphate generated compound **3.1** in 89% yield.[1] Treatment of **3.1** with TMSI led to iodide **3.2** in 60% yield.[2] Heck coupling of iodide **3.2** with 4-pentenal or 4-penten-1-ol failed to affo the corresponding trans dienes. Suzuki coupling of iodide **3.2** with the correspondi

borate gave trans compounds in low yields under several classical conditions. Fortunately, reaction of iodide **3.2** with 4-pentyn-1-ol under Sonogashira coupling condition resulted in enyne **3.4** in 81% yield.[3] Trans reduction in treatment with LAH or Red-Al failed to give trans diene **3.3**. Pleasantly, exposing enyne **3.4** to Lindlar catalyst (10 mol%) under 1 atm H_2 generated cis diene **3.5** as a major isomer (cis:trans=10:1) in 94% yield.[4,5]

However, Lindlar hydrogenation was difficult to control in which a small amount of over-reduction byproduct was formed. The byproduct could not be removed by column chromatography. Adding of extra quinoline (1eq or 2 eq) failed to inhibit the formation of the byproduct. In addition to Lindlar catalyst, Nickel boride was used for cis reduction but the byproduct was still generated.[6]

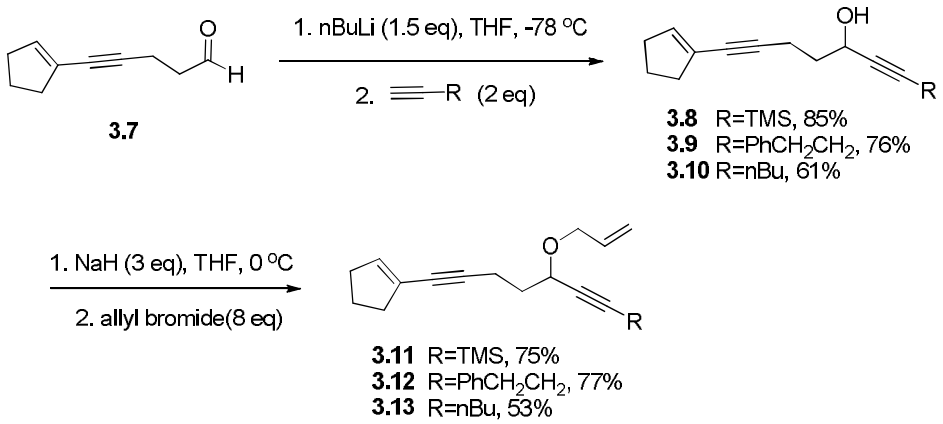
Although cis triene-yne is less likely to undergo domino Pauson-Khand reaction and [4+2] cycloaddition because of the steric effect compared to trans triene-yne, we continued to prepare cis triene-yne to test the strategy. Then cis diene **3.5** was treated with Dess-Martin reagent to give aldehyde **3.6** in 69% yield.[7] Besides, aldehyde **3.7** was prepared from enyne **3.4** via Swern oxidation in 91% yield.[8] Moreover, isomerization of cis diene **3.5** at 40 ^{o}C in the presence of iodine dissolved in cyclohexane/$CHCl_3$ generated trans diene **3.3** (trans:cis=12:1) in low yield (13%).[9]

Scheme 3.2. Synthesis of aldehyde **3.6** and **3.7**.

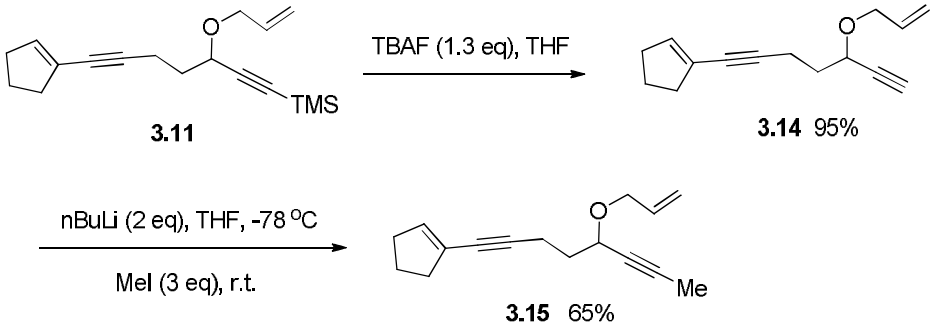


A series of precursors **3.11-3.13** were synthesized in good yields from aldehyde **3.7** via alkyne addition followed by allylation (Scheme 3.3). Compound **3.14** was prepared in 95% yield from **3.11** after the removal of TMS group by TBAF.[10] Subsequent methylation led to compound **3.15** in 65% yield (Scheme 3.4).[11]

Scheme 3.3. Synthesis of precursors **3.11-3.13**.

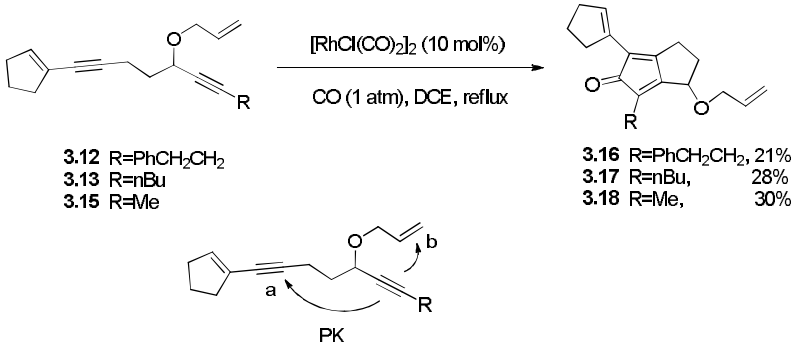


Scheme 3.4. Synthesis of precursors **3.14** and **3.15**.



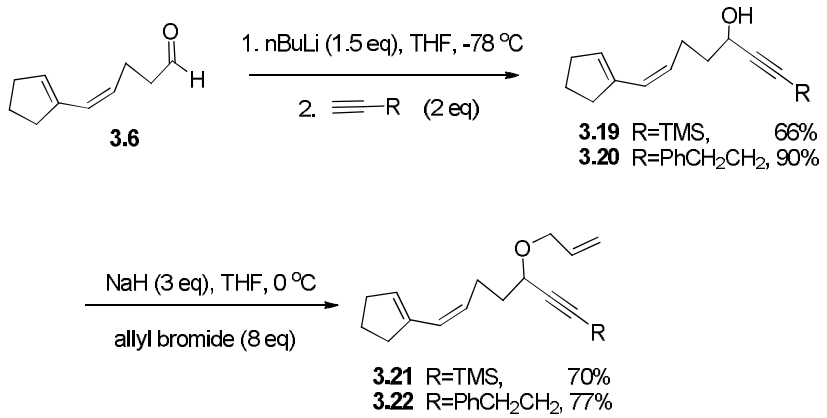
Then substrates **3.11-3.15** were utilized to test domino intramolecular Pauson-Khand reaction and [4+2] cycloaddition. We hypothesized that reduction could be conducted after the formation of the desired ring system. No reaction occurred when TMS substituted compound **3.11** was treated with $[Rh(CO)_2Cl]_2$ (10 mol%) under 1 atm CO in refluxing 1,2-dichloroethane (DCE). Increasing CO pressure to 40 atm still didn't initiate the reaction. The steric hindrance of TMS group might retard the cyclization. Terminal alkyne substrate **3.14** decomposed under the same condition (1 atm CO). Interestingly, it was likely that alkyl substituted compounds **3.12**, **3.13** and **3.15** underwent Pauson-Khand-type reaction of two triple bonds (pathway *a*) instead of triple-double bonds (pathway *b*) to generate possible compounds **3.16**, **3.17** and **3.18**, respectively (Scheme 3.5). However, the yields were low and pure compounds were not obtained for further characterization.

Scheme 3.5. Pauson-Khand-type reaction (pathway *a*).

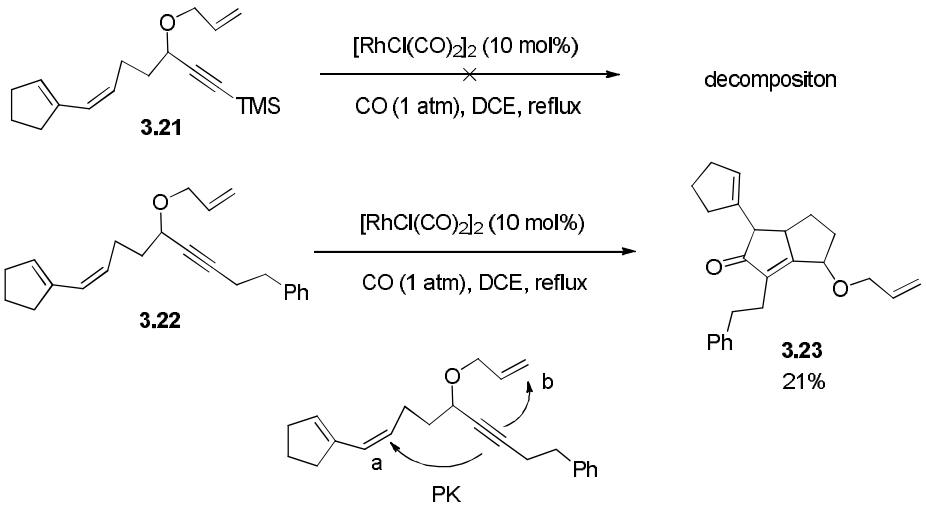


From aldehyde **3.6**, another type of precursors **3.21** and **3.22** were prepared in two steps in good yields (Scheme 3.6). Compound **3.21** underwent decomposition in the presence of the Rh catalyst under 1 atm CO. A possible compound **3.23** was obtained in 21% yield when **3.22** was treated with same condition. It was likely that compound **3.23** was generated via Pauson-Khand reaction in pathway *a* instead of desired pathway *b* (Scheme 3.7).

Scheme 3.6. Synthesis of precursors **3.21** and **3.22**.



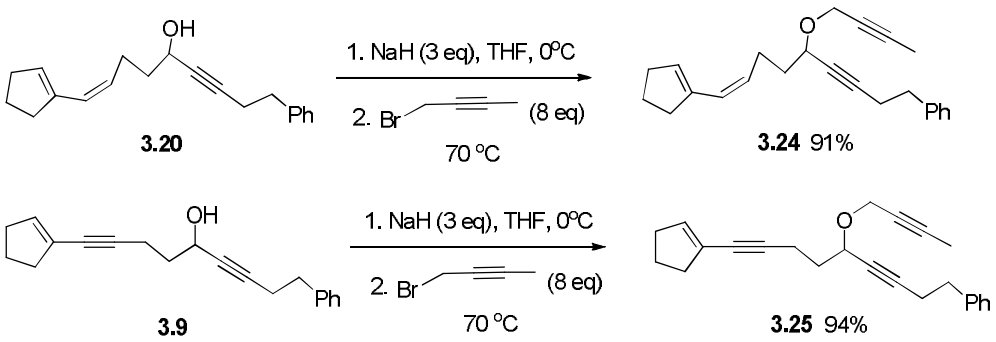
Scheme 3.7. Pauson-Khand reaction (pathway *a*).



Chung reported that under 30 atm Co at 130 °C, $Co_2(CO)_8$ catalyzed the domino cyclization of racemic diene-diynes to generate muticyclic products.[12,13] Thus,

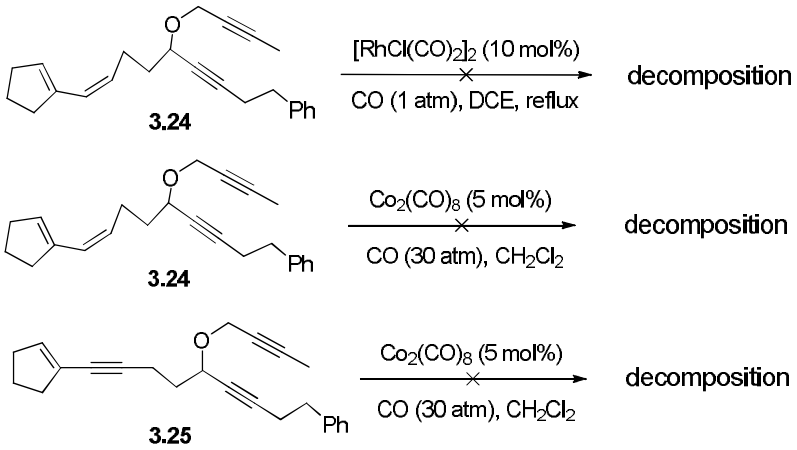
prepared a structurally similar diene-diyne **3.24** and ene-triyne **3.25** for Co-catalyzed domino cyclization (Scheme 3.8).

Scheme 3.8. Synthesis of diene-diyne **3.24** and ene-triyne **3.25**.



Dienediyne **3.24** was investigated with the Rh catalyst but it decomposed in the reaction. Chung's method was employed for diene-diyne **3.24** and ene-triyne **3.25**. Disappointingly, even if we gradually increased the temperature from 70 °C to 130 °C, no valuable compounds were generated (Scheme 3.9).

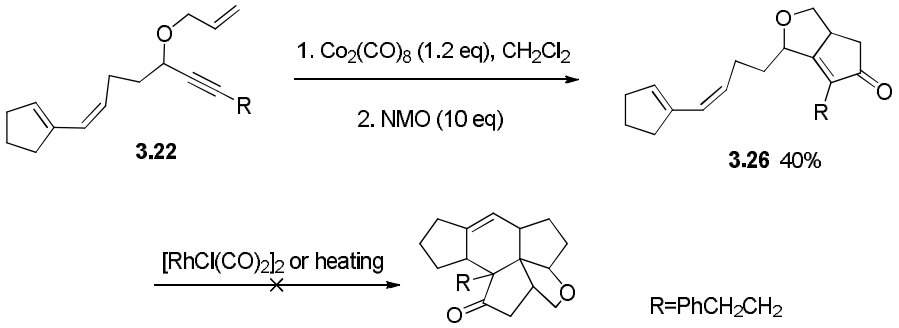
Scheme 3.9. Test of diene-diyne **3.24** and ene-triyne **3.25**.



With the failure of domino cyclization, we tended to construct the ring system by independent Pauson-Khand reaction and [4+2] cycloaddition. Diene-diyne **3.22** was treated with $Co_2(CO)_8$ and NMO to generate the Pauson-Khand product **3.26** in 40% yield.[14] However, [4+2] cycloaddition in the next step could not be initiated by the

catalyst or heating (Scheme 3.10).

Scheme 3.10. Formation of the Pauson-Khand product **3.26** employing $Co_2(CO)_8$.



2. Summary

We made much effort to investigate route 1 but failed to synthesize the key intermediate **2.1** that contains the core fragment of mangicol A. There were several issues in route 1. First of all, reduction of enyne **3.4** failed to give trans diene **3.3** and coupling reaction could afford trans compounds in low yields, which made us turn to synthesize cis diene **3.5**. Secondly, Lindlar hydrogenation generated cis diene **3.5** with a small amount of over-reduction byproduct. This byproduct could not be removed and made the spectra of subsequent compounds messier. In addition, the Pauson-Khand reaction of **3.12**, **3.13**, **3.15** and **3.22** underwent in undesired pathways. The yields were low and pure compounds were not obtained for further characterization. Finally, the Rh catalyst or heating were not able to promote the [4+2] cycloaddition of **3.26**.

Experimental and Characterization

1. Analytical Instruments

NMR: Varian 300 MHz, Bruker 600 MHz and Bruker 800 MHz.

HPLC: Water 600 Pump and Waters 486 Tunable Absorbance Detector, Chiralcel OD, OD-H, or Chiralpak AD, AD-H column.

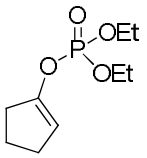
Polarimeter: Jasco Digital Polarimeter P-2000.

High resolution mass spectra were obtained by EI [70-VSE(C)] or ESI (Q-TOf) analysis.

2. General Data

All commercial chemicals were used without further purification unless otherwise noted. All catalysts were purchased and stored in dry nitrogen atmosphere. Tetrahydrofuran was distilled over sodium and benzophenone under nitrogen. Diethyl ether and methylene chloride were dried by passing through activated alumina columns under nitrogen. All the NMR spectra were obtained in $CDCl_3$ unless indicated otherwise.

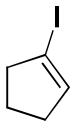
3. General Procedures and Characterization



Cyclopent-1-en-1-yl diethyl phosphate, 3.1

In a 100 mL flask under nitrogen, cyclopentanone (2.64 mL, 30 mmol, 1 eq) was dissolved in THF (30 mL) and cooled to -78 ^{O}C. LDA (1 eq) freshly prepared from diisopropylamine (4.2 mL, 30 mmol, 1 eq) and (12 mL, 30 mmol, 2.5M in hexane, 1 eq) was added and the reaction was stirred for 1 h. Diethyl chlorophosphate (5.19 mL, 36 mmol, 1.2 eq) was then added at -78 ^{O}C. The mixture was warmed to room temperature and stirred for another 2 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine and dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=5:1) to furnish the compound **3.1** (5.86 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (m, 1H), 4.12 (q, 4H, J=7.5 Hz), 2.40 (m, 2H), 2.28 (m, 2H), 1.89 (q, 2H, J=7.5 Hz), 1.31 (t, 6H, J=7.2 Hz).

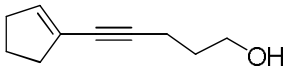


1-iodocyclopent-1-ene, 3.2

To a solution of **3.1** (5.73 g, 26.1 mmol, 1 eq) in anhydrous CH_2Cl_2 (20 mL) was added TMSI (11 mL, 3 eq) dropwise. After stirring for 15 min at room temperature, the reaction mixture was quenched by addition of saturated $NaHCO_3$ and satura Na_2SO_3 solution. The organic layer was separated and the aqueous layer was extrac

with CH_2Cl_2 three times. The combined organic solution was dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography using *n*-pentane as an eluent to give **3.2** (3.02 g, 60%).

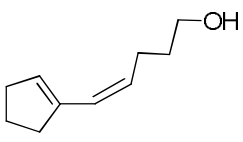
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (t, 1H, J=2.4 Hz), 2.60 (m, 2H), 2.31 (m, 2H), 1.92 (t, 2H, J=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 92.9, 44.0, 34.2, 24.1.



5-(cyclopent-1-en-1-yl)pent-4-yn-1-ol, 3.4

To a stirred solution of $Pd(PPh_3)Cl_2$ (296 mg, 5%), CuI (157.4 mg, 10%) and iodide **3.2** (1.604 g, 8.27 mmol, 1 eq) in anhydrous NEt_3 (8 mL) and THF (8 mL), 4-pentyn-1-ol (0.92 mL, 9.93 mmol, 1.2 eq) dissolved in THF (5 mL) was added under nitrogen. The mixture was stirred at 50 ^{o}C for 3 h, then diluted with CH_2Cl_2, neutralized by 2M HCl, extracted with CH_2Cl_2 three times and washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane:EtOAc=8:1) to give compound **3.4** (1.007g, 81%).

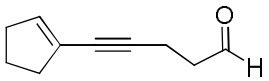
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H), 3.76 (t, 2H, J=6.2 Hz), 2.45 (t, 2H, J=7.2 Hz), 2.36-2.45 (m, 4H), 1.60 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 124.9, 90.6, 78.6, 62.1, 36.8, 33.3, 31.6, 23.5, 16.3.



(*Z*)-5-(cyclopent-1-en-1-yl)pent-4-en-1-ol, 3.5

A solution of **3.4** (157.5 mg, 0.7 mmol 1 eq) in MeOH (20 mL) was treated with Lindlar catalyst (225 mg, 10%) and hydrogenated at balloon pressure for 20 h at room temperature. The suspension was filtered through Celite, concentrated and purified by flash chromatography (hexane:EtOAc=6:1) to give compound **3.5** (148.7 mg, 94 %) (cis:trans=10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, 1H, J=12 Hz), 5.68 (s, 1H), 5.34 (m, 1H), 3.67 (m, 2H), 2.56 (m, 2H), 2.35 (m, 2H), 1.91 (m, 2H), 1.67 (m, 2H), 1.40 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 131.9, 130.1, 126.2, 62.8, 35.3, 33.3, 32.3, 25.5, 24.2.

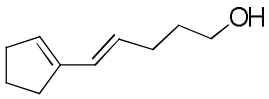


5-(cyclopent-1-en-1-yl)pent-4-ynal, 3.7

To a stirred solution of $(COCl)_2$ (378.7 uL, 1.5 eq) in CH_2Cl_2 (3 mL) at -78 ^{O}C was added DMSO (651 uL, 3 eq). The resulting mixture was stirred for 15 min before a solution of compound **3.4** (443 mg, 2.97 mmol, 1 eq) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 25 min before Et_3N (2.53 mL, 6eq) was added. The resulting mixture was warmed to room temperature before it was quenched with H_2O. The layers were separated and aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane:EtOAc=15:1) afforded compound **3.7** (402.2 mg, 91 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 5.93 (s, 1H), 2.66 (m, 4H), 2.37 (t, 4

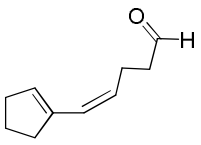
J=9 Hz), 1.85 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 137.2, 124.7, 89.0, 78.9, 42.9, 36.7, 33.3, 23.4, 13.0.



(*E*)-5-(cyclopent-1-en-1-yl)pent-4-en-1-ol, 3.3

To a solution of cis-diene **3.5** (cis:trans=10:1) (137.3 mg, 0.91 mmol, 1 eq) in 3 mL of a solvent (cyclohexane: chloroform=20:1) was added 1.5 mL of iodine solution (0.5% w/v in the solvent described above) and allowed to stand in dark at 40 ^{O}C for 20 h. The reaction was detected by NMR to determine the completion of the reaction. The mixture was diluted with ether and washed with sodium thiosulfate three times and brine, and dried. Purification by chromatography (hexane:EtOAc=20:1) afforded compound **3.3** (trans:cis= 12:1) (17.1 mg, 13%).

^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, 1H, J=15 Hz), 5.55 (m, 2H), 3.68 (m, 2H), 2.39 (t, 4H, J=6 Hz), 2.19 (m, 2H), 1.90 (m, 2H), 1.68 (m, 2H), 1.29 (m, 1H).



(*E*)-5-(cyclopent-1-en-1-yl)pent-4-enal, 3.6

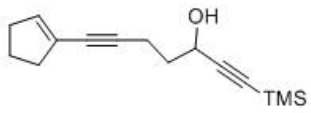
To a solution of **3.5** (199.6 mg, 1.31 mmol, 1 eq) in CH_2Cl_2 (5 mL) was added Dess-Martin reagent (668.2 mg, 1.2 eq) at room temperature. After 2 h, the reaction was quenched with water and extracted with CH_2Cl_2 three times. The combin organic layers were washed with brine, dried over Na_2SO_4, and concentrat

Purification by column chromatography (hexane:EtOAc=25:1) afforded compound **3.6** (138 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.05 (d, 1H, J=12 Hz), 5.69 (s, 1H), 5.27 (m, 1H), 2.57 (m, 6H), 2.36 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 141.3, 132.5, 128.0, 127.1, 44.5, 35.3, 32.4, 24.2, 21.9.

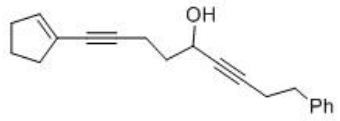
General Procedure for the preparation of racemic propargylic alcohols

Under nitrogen, an alkyne (1.5 eq) was dissovled in THF (5 mL) and cooled to -78 ^{o}C under nitrogen. nBuLi (1.2 eq) was added and the mixture was stirred for 30 min. Then an aldehyde (1 eq) was added and the system was stirred for 3 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by column chromatography on silica gel.



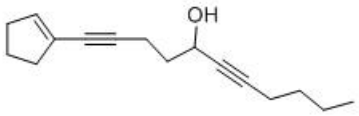
7-(cyclopent-1-en-1-yl)-1-(trimethylsilyl)hepta-1,6-diyn-3-ol, 3.8

85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (s, 1H), 4.52 (t, 1H, J=6 Hz), 2.50 (m, 2H), 2.39 (m, 4H), 1.91 (m, 5H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 124.8, 106.1, 90.2, 90.1, 78.8, 62.0, 36.8, 36.7, 33.3, 23.5, 15.8, 0.08.



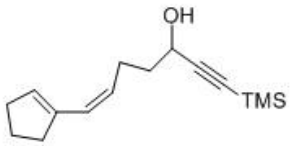
1-(cyclopent-1-en-1-yl)-9-phenylnona-1,6-diyn-5-ol, 3.9

76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.95 (s, 1H), 4.50 (m, 1 H), 2.82 (t, 2H, J=6 Hz), 2.50 (m, 3H), 2,41 (m, 5H), 1.86 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 136.8, 128.7, 128.6, 126.6, 124.9, 90.3, 85.5, 81.5, 78.7, 61.9, 37.0, 36.8, 35.2, 33.3, 23.5, 21.2, 15.8.



1-(cyclopent-1-en-1-yl)undeca-1,6-diyn-5-ol, 3.10

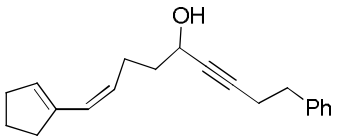
61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 1H), 4.52 (tt, 1H, J=6, 3 Hz), 2.49 (m, 2H), 2.39 (m, 4H), 2.20 (m, 2H), 1,96 (s, 1H), 1.88 (m, 4H), 1.44 (m, 4H), 0.90 (t, 3H, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 124.9, 90.3, 86.3, 80.6, 78.7, 61.9, 37.2, 36.8, 33.3, 30.9, 23.5, 22.2, 18.6, 15.8, 13.8.



(*Z*)-7-(cyclopent-1-en-1-yl)-1-(trimethylsilyl)hept-6-en-1-yn-3-ol, 3.19

66% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (d, 1H, J=12 Hz), 5.70 (s, 1H), 5.33 (m, 1H), 4.39 (m, 1H), 2.59 (m, 2H), 2.41 (m, 4H), 1.91 (m, 2H), 1.80 (m, 4H), 1. (m, 1H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 132.2, 129.4, 126

106.7, 90.0, 62.7, 38.2, 35.2, 32.3, 24.9, 24.3, 0.09.

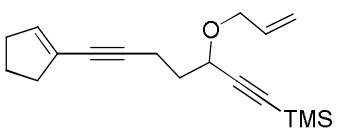


(*Z*)-1-(cyclopent-1-en-1-yl)-9-phenylnon-1-en-6-yn-5-ol, 3.20

90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 6.07 (d, 1H, J=9 Hz), 5.70 (s, 1H), 5.33 (m, 1H), 4.37 (m, 1H), 2.83 (t, 2H, J=6 Hz), 2.59 (m, 2H), 2.51 (m, 2H), 2.40 (m, 4H), 1.92 (m, 3H), 1.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 140.8, 132.0, 129.6, 168.7, 128.6, 126.6, 126.4, 85.2, 82.1, 62.5, 38.7, 35.3, 35.2, 32.3, 25.0, 24.3, 21.2.

General Procedure for the preparation of racemic esters

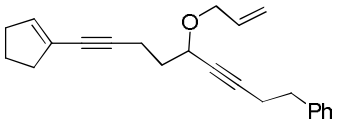
To a solution of NaH 60% w/w (3 eq) in THF was added an alcohol (1 eq) in THF at 0 ^{o}C under nitrogen and stirred for 30 min. Then allyl bromide (8 eq) was added and the mixture was warmed to 50 ^{o}C and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography.



(3-(allyloxy)-7-(cyclopent-1-en-1-yl)hepta-1,6-diyn-1-yl)trimethylsilane, 3.11

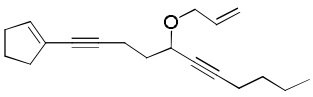
75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (m, 2H), 5.30 (dd, 1H, J=18 Hz), 5.

(dd, 1H, J=9 Hz), 4.24 (m, 2H), 3.98 (ddt, 1H, J=15, 9, 3 Hz), 2.49 (m, 2H), 2.40 (m, 4H), 1.90 (m, 4H), 0.17 (s, 9H).



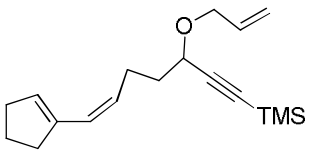
(5-(allyloxy)-9-(cyclopent-1-en-1-yl)nona-3,8-diyn-1-yl)benzene, 3.12

77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.94 (s, 1H), 5.87 (m, 1H), 5.27 (dd, 1H, J=18 Hz), 5.17 (dd, 1H, J=9 Hz), 4.16 (m, 2H), 3.90 (dd, 1H, J=12, 6 Hz), 2.83 (t, 2H, J=6 Hz), 2.52 (t, 3H, J=6 Hz), 2.43 (m, 5H), 1.90 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 136.4, 134.8, 128.7, 128.6, 126.5, 125.1, 117.3, 90.6, 86.1, 79.6, 78.4, 69.7, 67.8, 36.8, 35.3, 35.2, 33.3, 23.5, 21.2, 15.8.



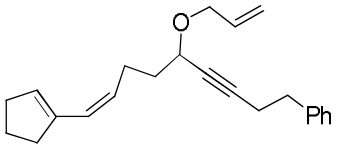
1-(5-(allyloxy)undeca-1,6-diyn-1-yl)cyclopent-1-ene, 3.13

53% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 2H), 5.30 (d, 1H, J=18 Hz), 5.17 (d, 1H, J=9 Hz), 4.22 (m, 2H), 3.96 (dd, 1H, J=9, 6 Hz), 2.49 (m, 2H), 2.40 (m, 4H), 2.21 (m, 2H), 1.90 (m, 4H), 1.46 (m, 4H), 0.91 (t, 3H, J=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 134.8, 125.1, 117.3, 90.6, 90.0, 78.6, 78.3, 69.7, 67.9, 36.8, 35.4, 33.3, 31.0, 23.5, 22.2, 18.6, 15.9, 13.8.



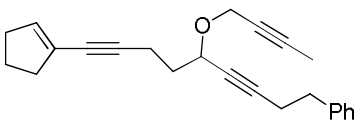
(*Z*)-(3-(allyloxy)-7-(cyclopent-1-en-1-yl)hept-6-en-1-yn-1-yl)trimethylsilane, 3.21

70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, 1H, J=12 Hz), 5.91 (m, 1H), 5.69 (s, 1H), 5.30 (m, 2H), 5.18 (d, 1H, J=9 Hz), 4.26 (dd, 1H, J=12, 6 Hz), 4.08 (m, 1H), 3.95 (dd, 1H, J=12, 6 Hz), 2.59 (m, 2H), 2.39 (m, 2H), 1,91 (m, 2H), 1.79 (m, 2H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 134.7, 132.0, 129.6, 126.4, 117.5, 106.4, 104.7, 69.8, 68.9, 36.2, 35.2, 32.3, 25.0, 24.3, 0.16.



(*Z*)-(5-(allyloxy)-9-(cyclopent-1-en-1-yl)non-8-en-3-yn-1-yl)benzene, 3.22

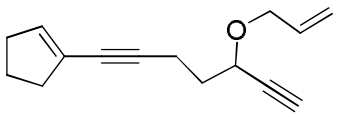
77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 6.05 (d, 1H, J=12 Hz), 5.89 (m, 1H), 5.69 (s, 1H), 5.32 (m, 1H), 5.24 (m, 1H), 5.17 (d, 1H, J=9 Hz), 4.18 (dd, 1H, J=12, 3 Hz), 4.06 (m, 1H), 3.88 (dd, 1H, J=15, 6 Hz), 2.84 (t, 2H, J=9 Hz), 2.55 (m, 4H), 2.38 (m, 4H), 1.91 (m, 2H), 1.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 140.8, 134.9, 131.8, 129.8, 128.7, 128.6, 126.5, 126.3, 117.3, 85.8, 80.0, 69.6, 68.6, 36.6, 35.3, 35.2, 32.3, 25.1, 24.3, 21.2.



(5-(but-2-yn-1-yloxy)-9-(cyclopent-1-en-1-yl)nona-3,8-diyn-1-yl)benzene, 3.25

94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.94 (s, 1H), 4.34 (m, 1H), 4.24 (m, 1H), 4.08 (m, 1H), 2.83 (t, 2H, J=6 Hz), 2.52 (m, 2H), 2.41 (m, 6H), 1.93 (4H), 1.85 (t, 1H, J=3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 136.4, 128.7, 128

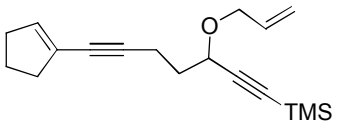
126.6, 125.1, 90.6, 86.5, 82.6, 78.9, 78.4, 75.2, 67.3, 56.5, 36.8, 35.2, 35.1, 33.3, 23.5, 21.2, 15.8, 3.94.



1-(5-(allyloxy)hepta-1,6-diyn-1-yl)cyclopent-1-ene, 3.14

To a solution of **3.11** (66.5 mg, 0.233 mmol, 1 eq) in THF (3 mL) was added TBAF (0.34 mL, 1 M in THF, 1.3 eq) at room temperature. The reaction was stirred for 40 min, diluted in ether and washed with saturated ammonia chloride solution. Repeated extraction of the aqueous phase with ether, drying of the combined organic layers (Na_2SO_4), evaporation of the solvent and flash chromatography eluted with *n*-hexanes afforded compound **3.14** (47.3 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 2H), 5.32 (d, 1H, J=15 Hz), 5.20 (d, 1H, J=9 Hz), 4.26 (m, 2H), 3.98 (dd, 1H, J=12, 6 Hz), 2.51 (m, 2H), 2.40 (m, 4H), 1.94 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 134.4, 125.0, 117.7, 90.1, 82.5, 78.6, 74.2, 70.0, 67.3, 36.8, 34.9, 33.3, 23.5, 15.8.



(3-(allyloxy)-7-(cyclopent-1-en-1-yl)hepta-1,6-diyn-1-yl)trimethylsilane, 3.15

To a solution of **3.14** (11.8 mg, 0.055 mmol, 1 eq) in THF (2 mL) was added nBuLi (43,7 uL, 2 eq) at -78 ^{o}C under nitrogen. The mixture was stirred for 1 h and MeI (10.3 uL, 3 eq) was added. Then the system was warmed to room temperatı

and continued stirring overnight. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography (hexane:EtOAc=25:1) to furnish the compound **3.15** (8.2 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 2H), 5.30 (d, 1H, J=18 Hz), 5.18 (d, 1H, J=12 Hz), 4.21 (m, 2H), 3.95 (dd, 1H, J=12, 6 Hz), 2.49 (m, 2H), 2.40 (m, 4H), 1.92 (m, 4H), 1.85 (d, 3H, J=3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 134.8, 125.0, 117.4, 90.5, 82.3, 78.4, 77.9, 69.8, 67.9, 36.8, 35.3, 33.3, 23.5, 15.9, 3.9.

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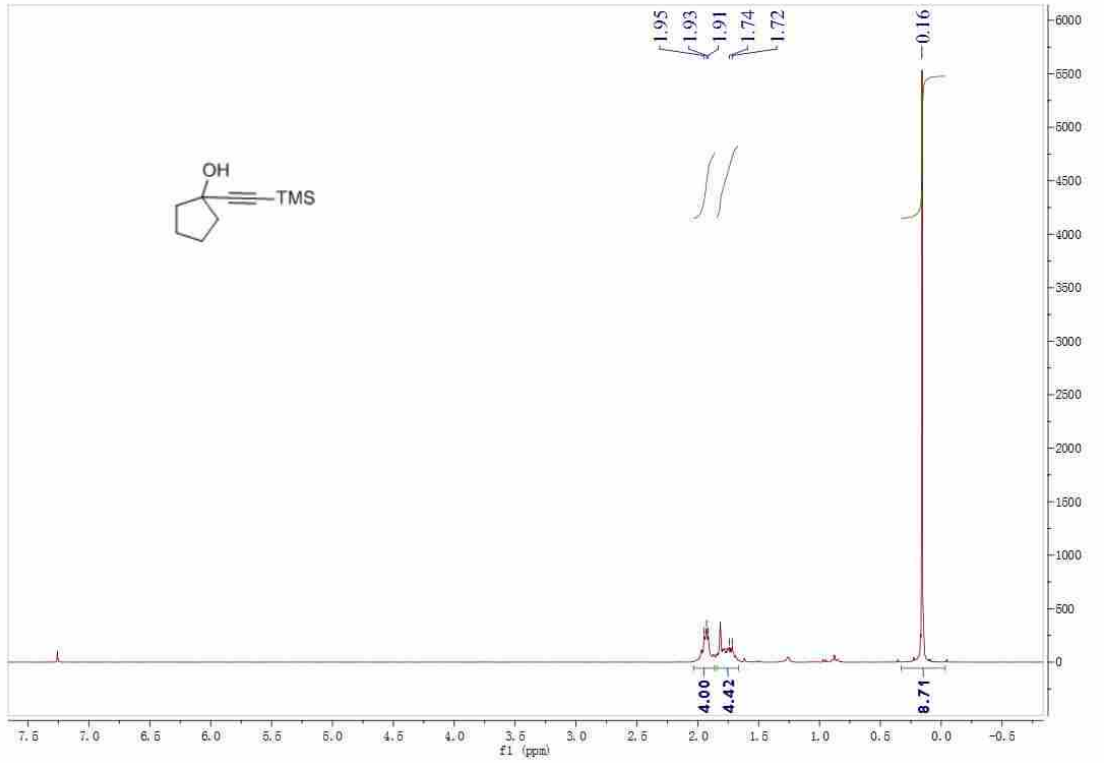
Appendix

^{1}H NMR



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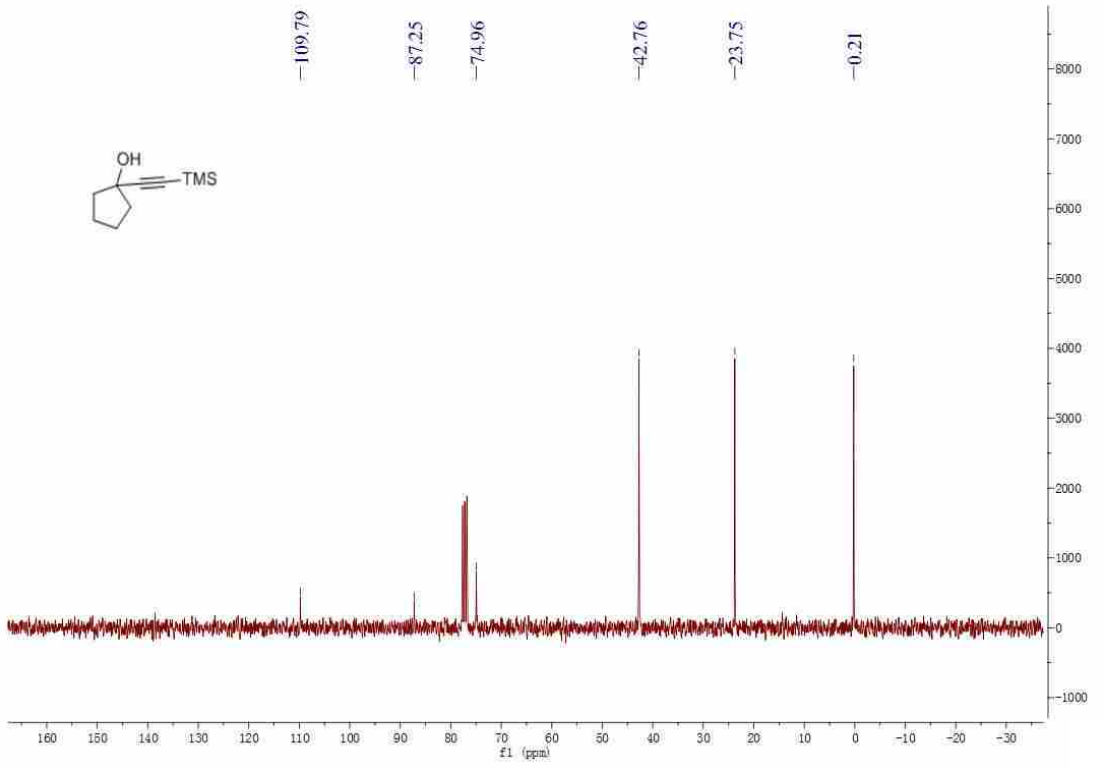
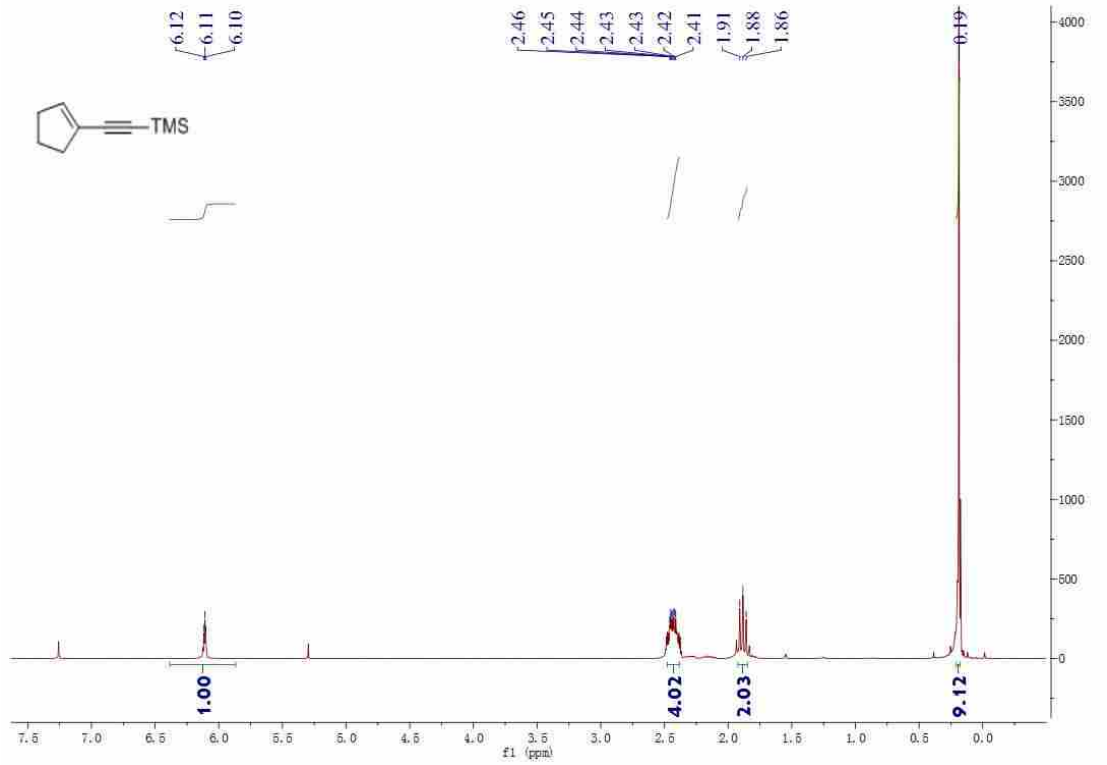


^{1}H NMR



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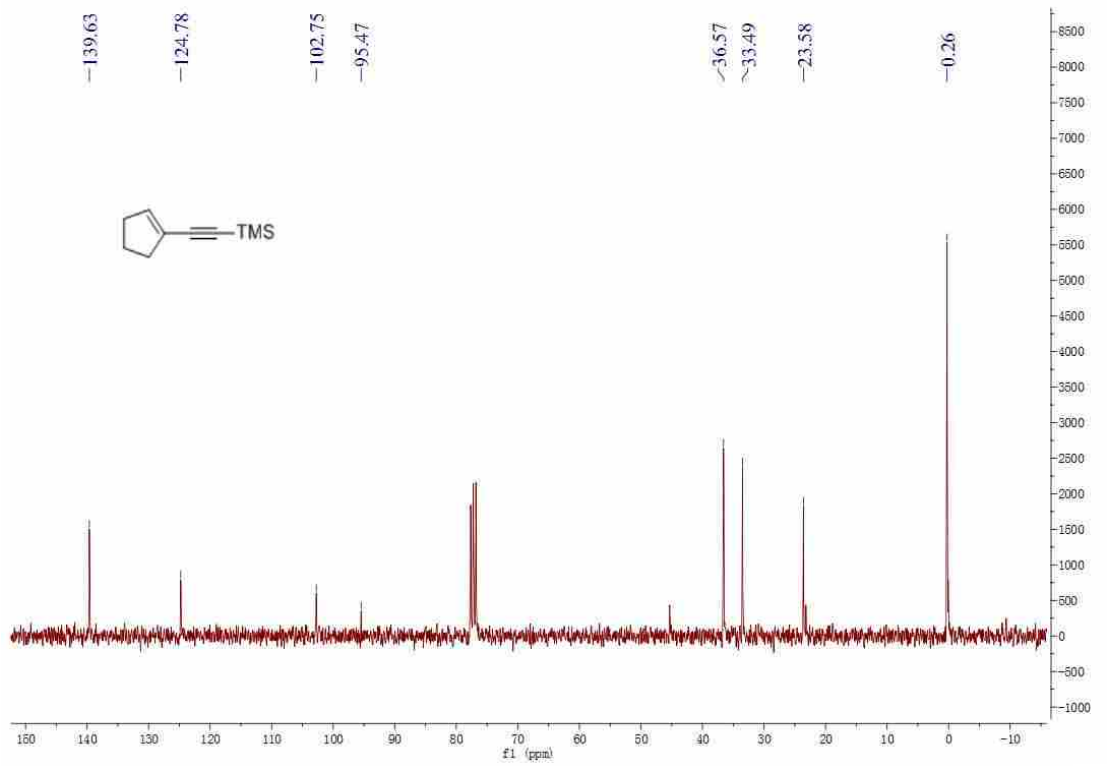
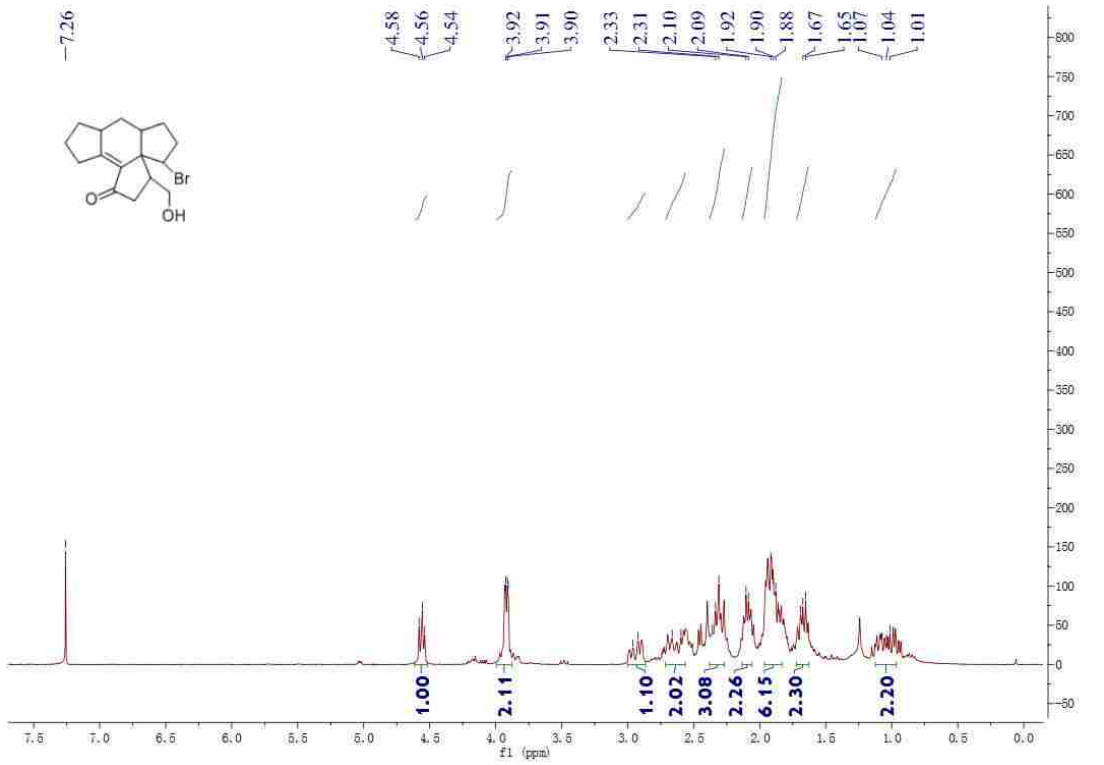


^{1}H NMR



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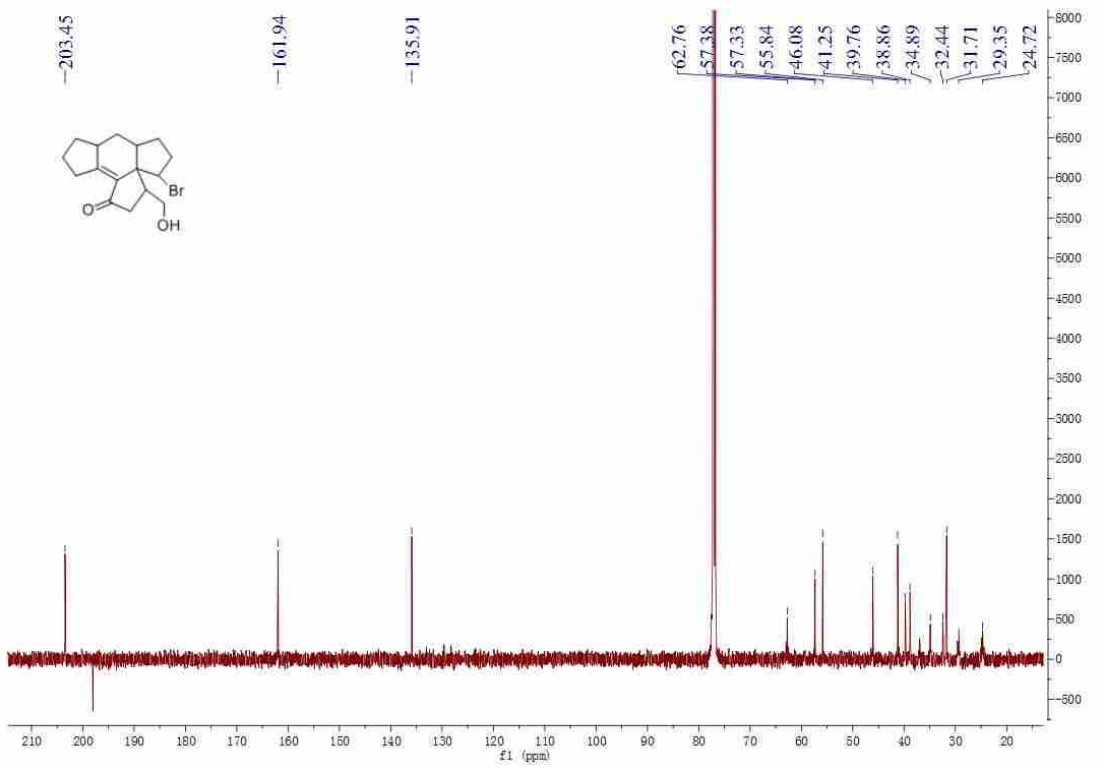
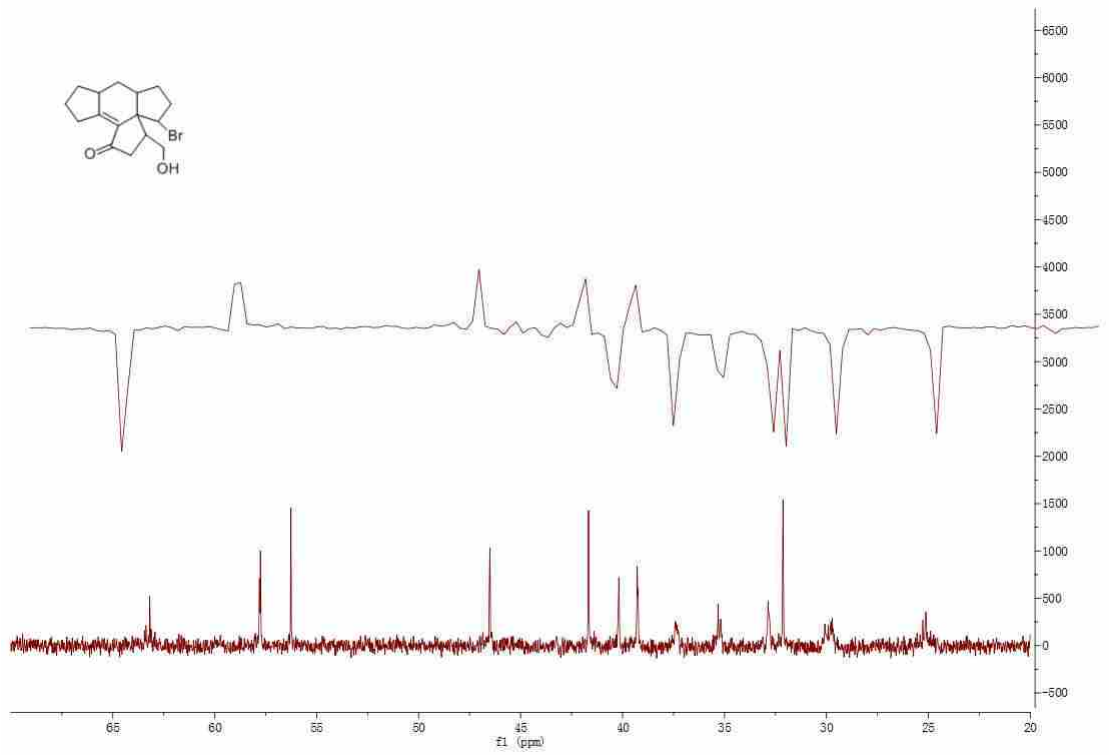


^{13}C NMR and DEPT-135



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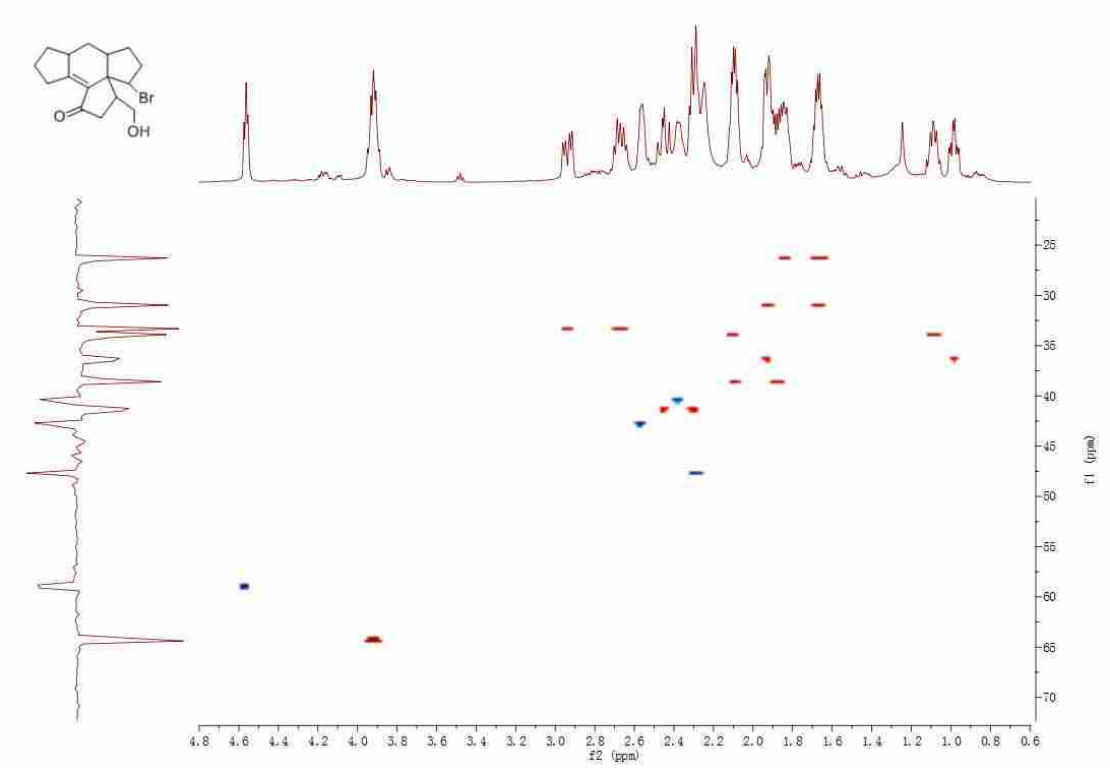
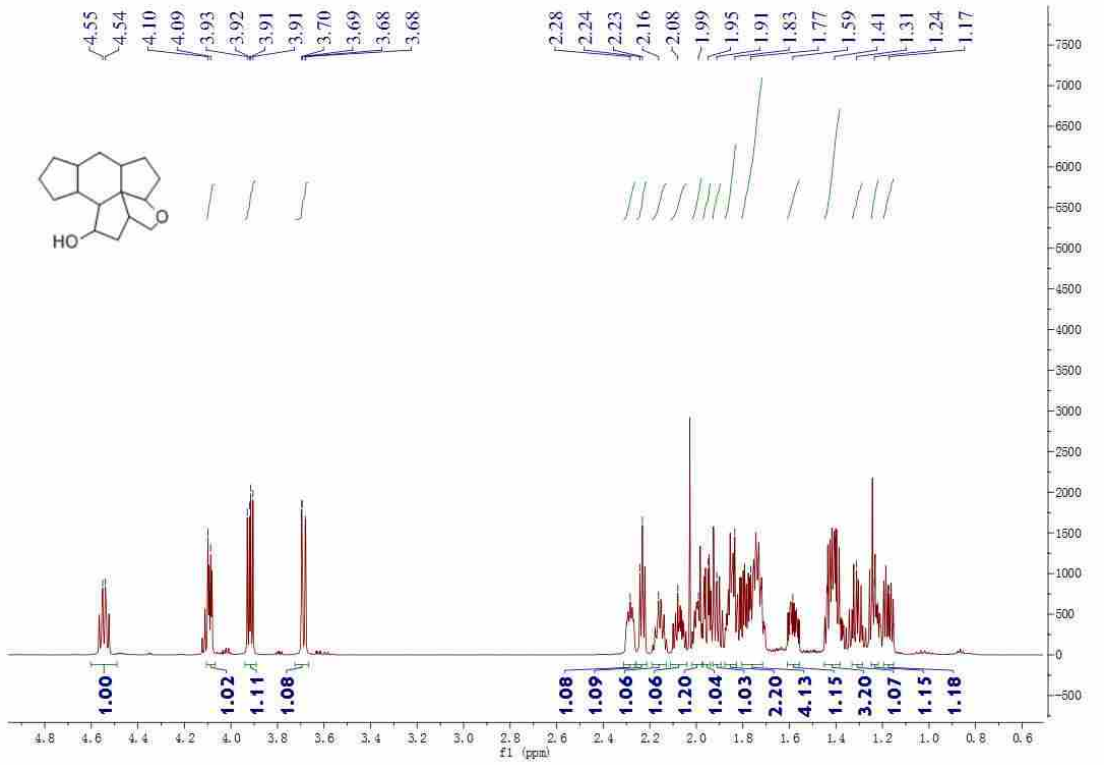
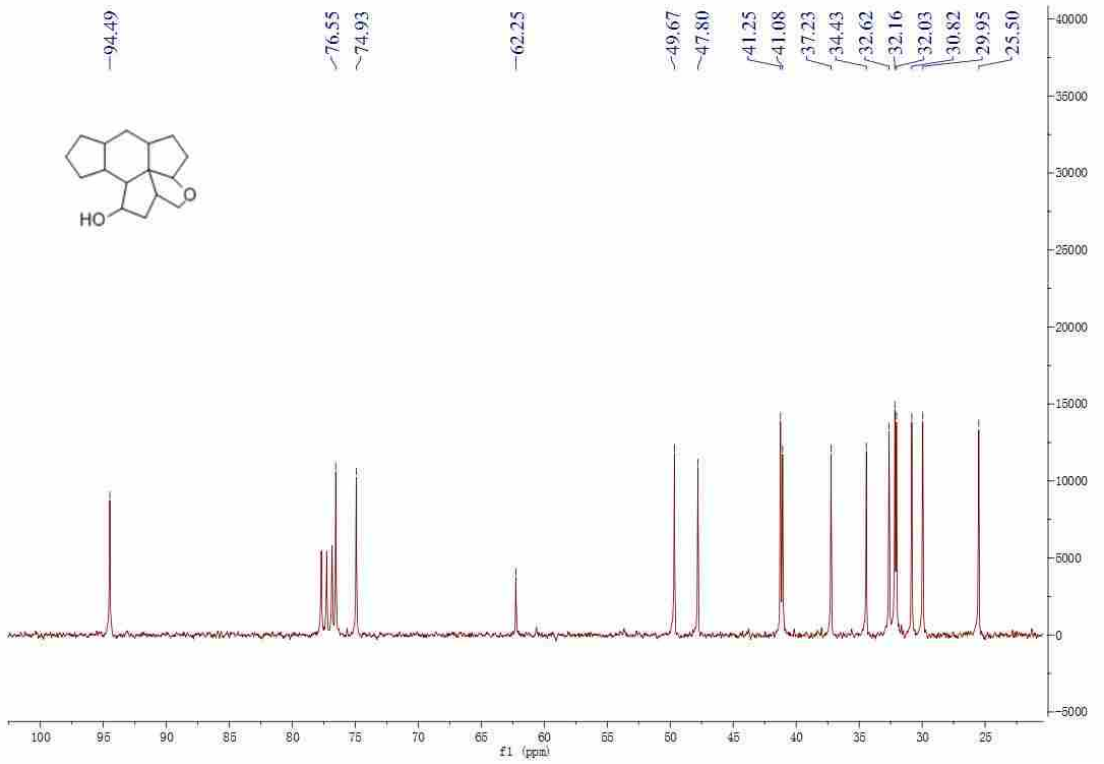


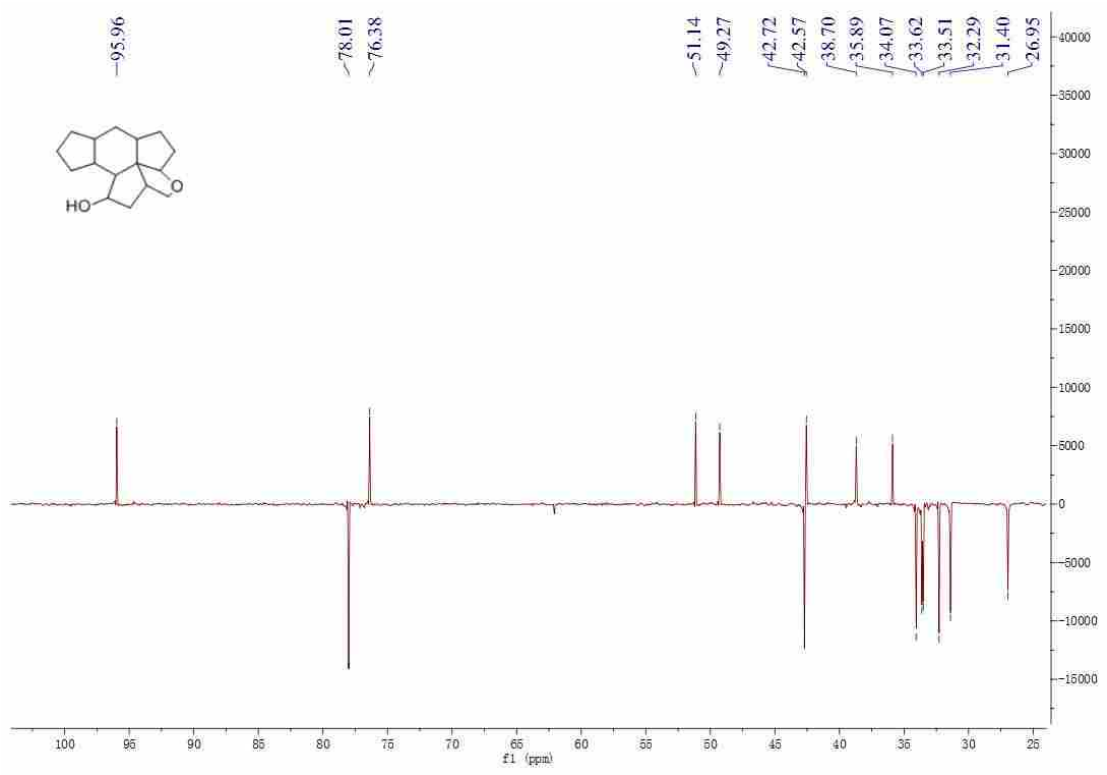
^{1}H NMR



^{13}C NMR



DEPT-135



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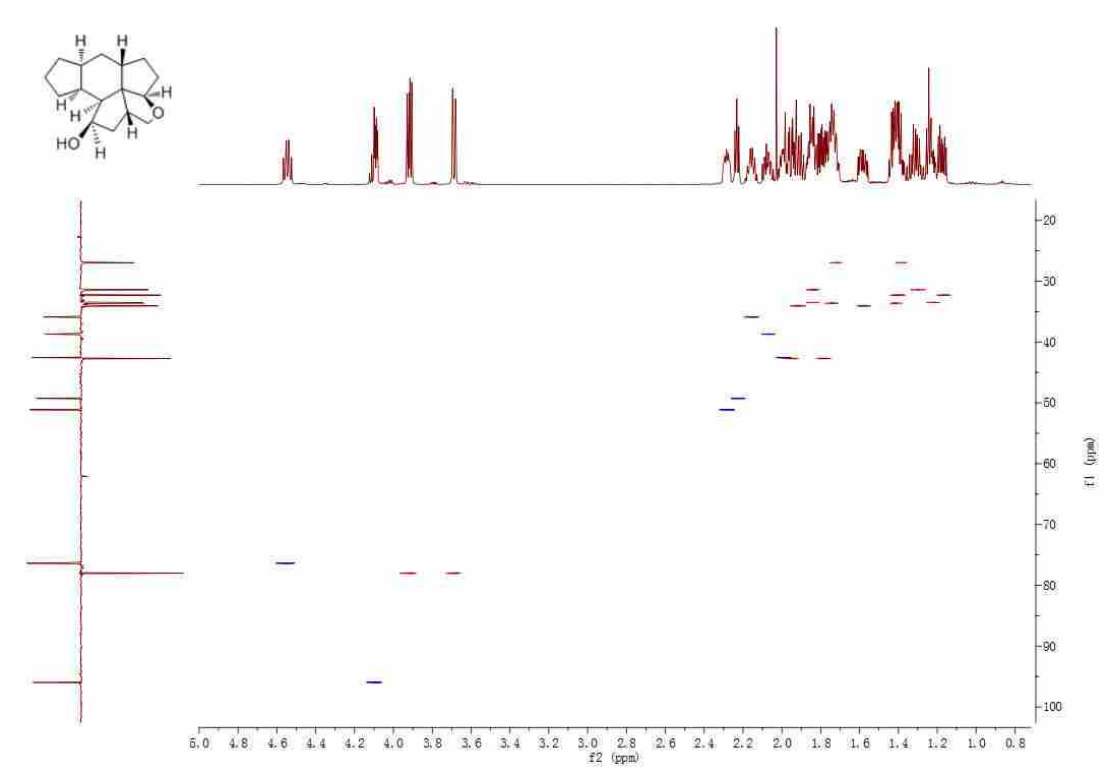
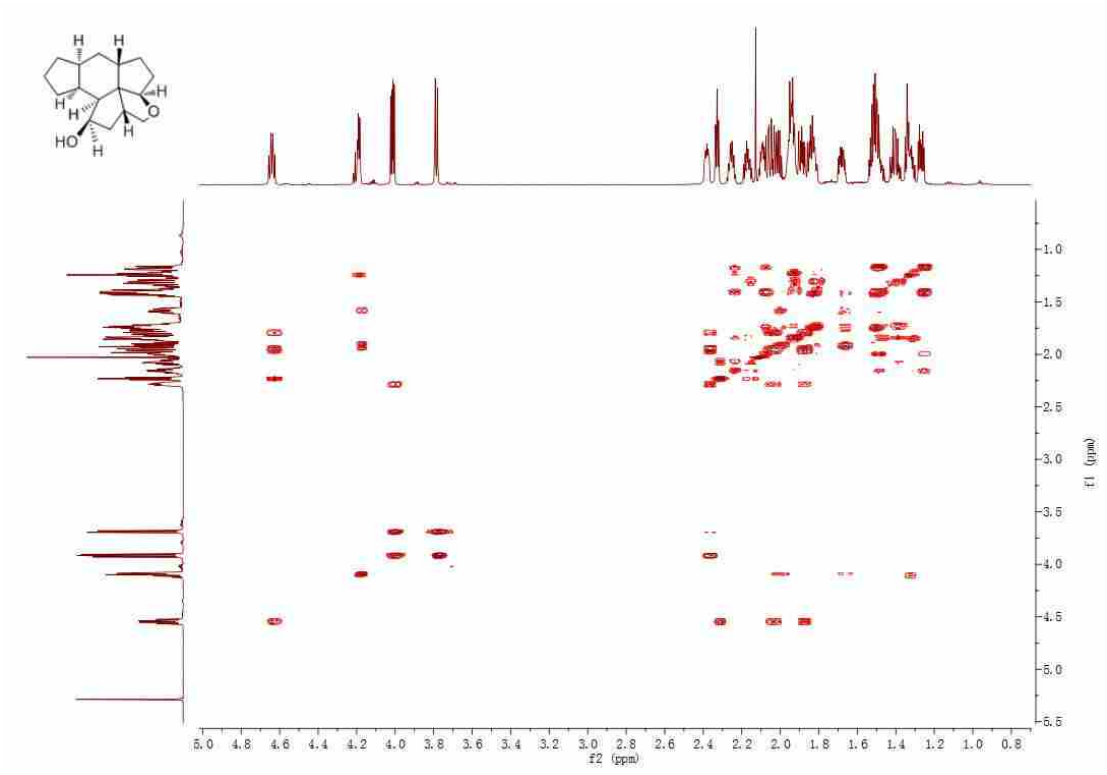
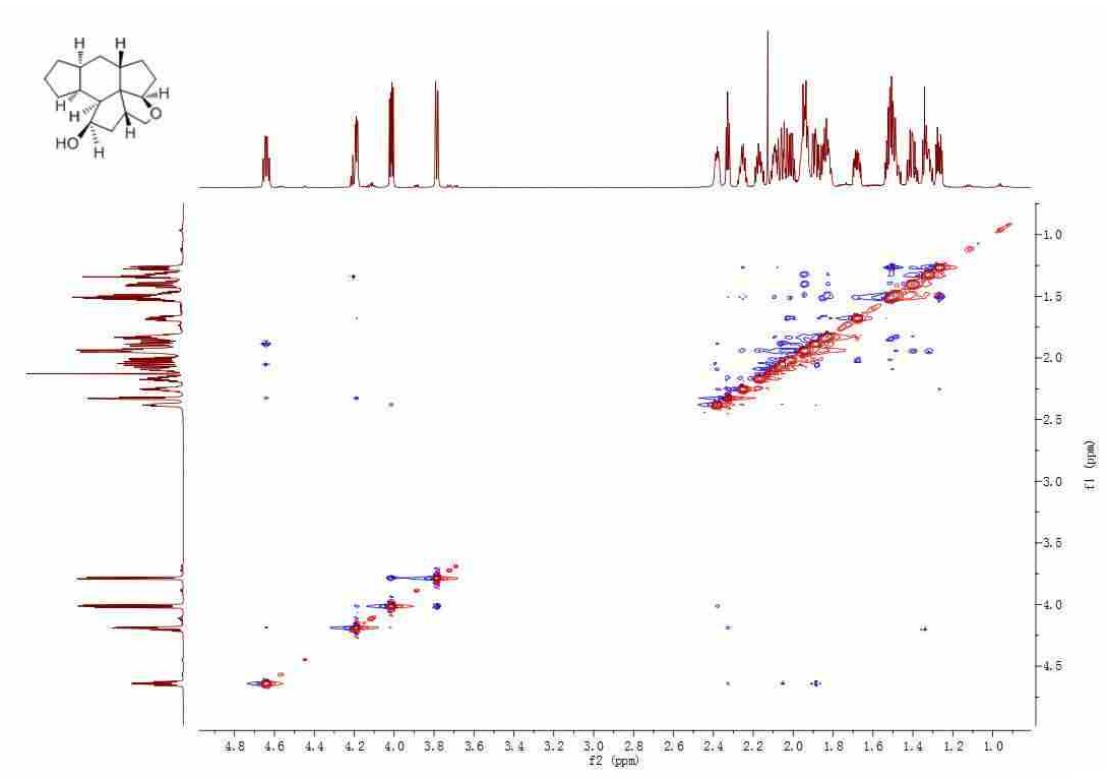


COSY



NOESY



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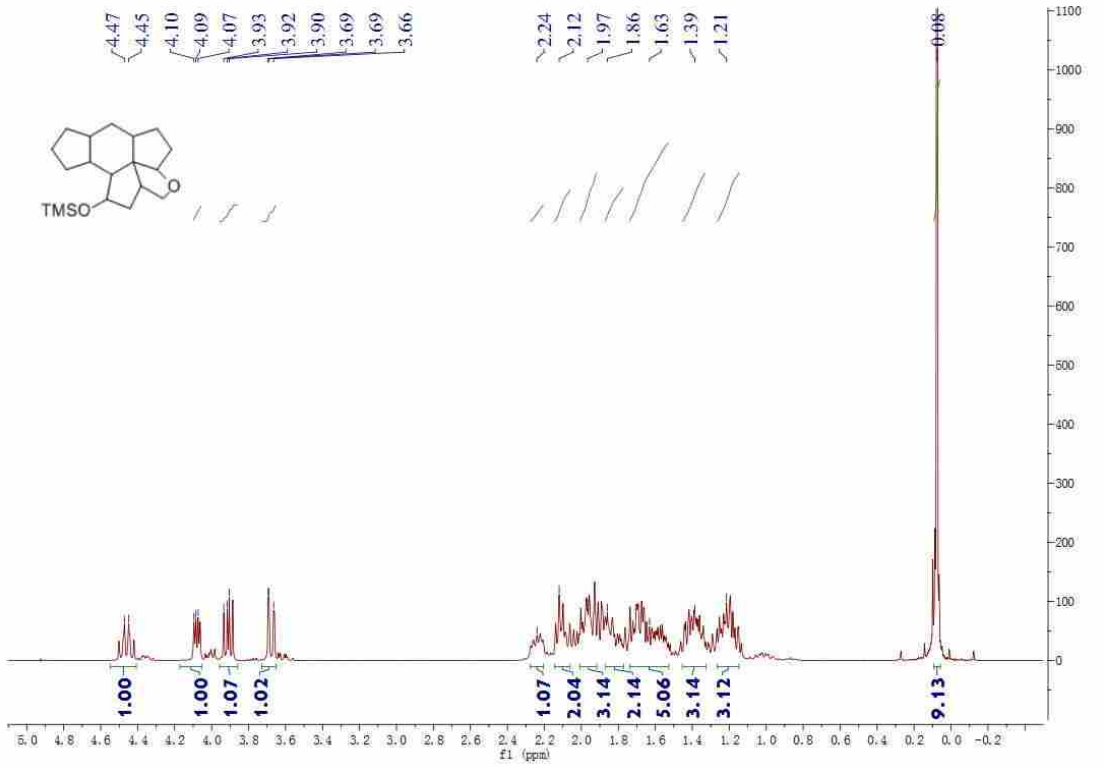

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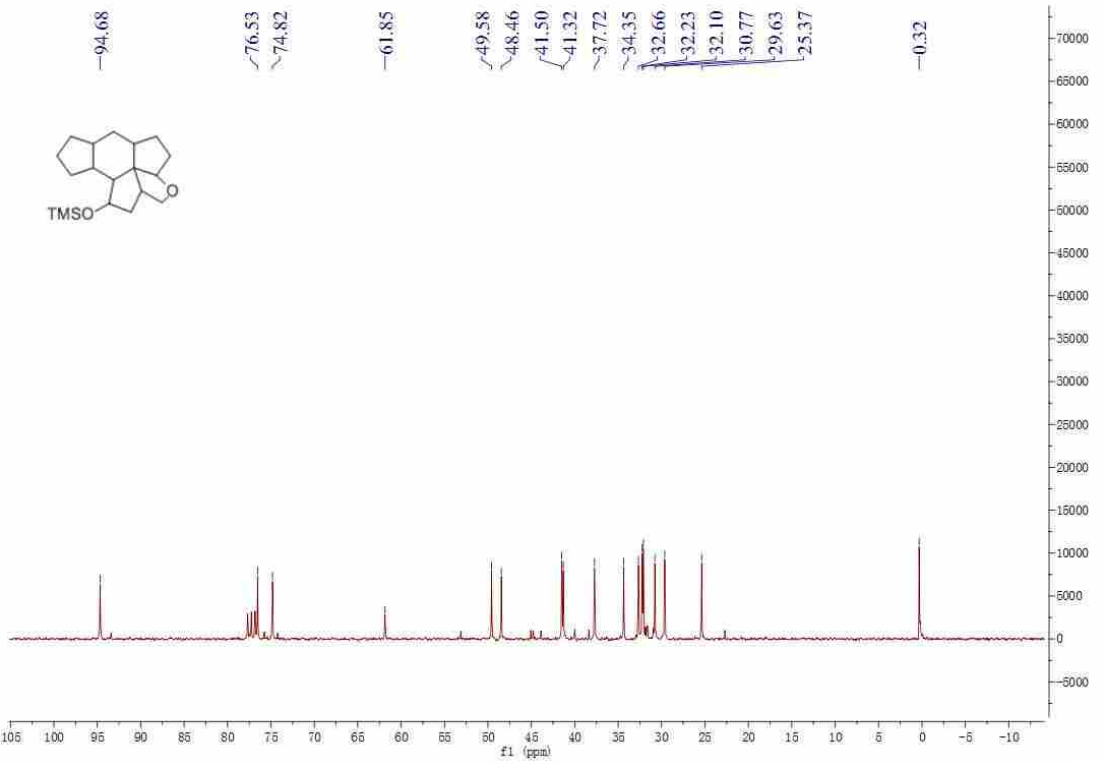

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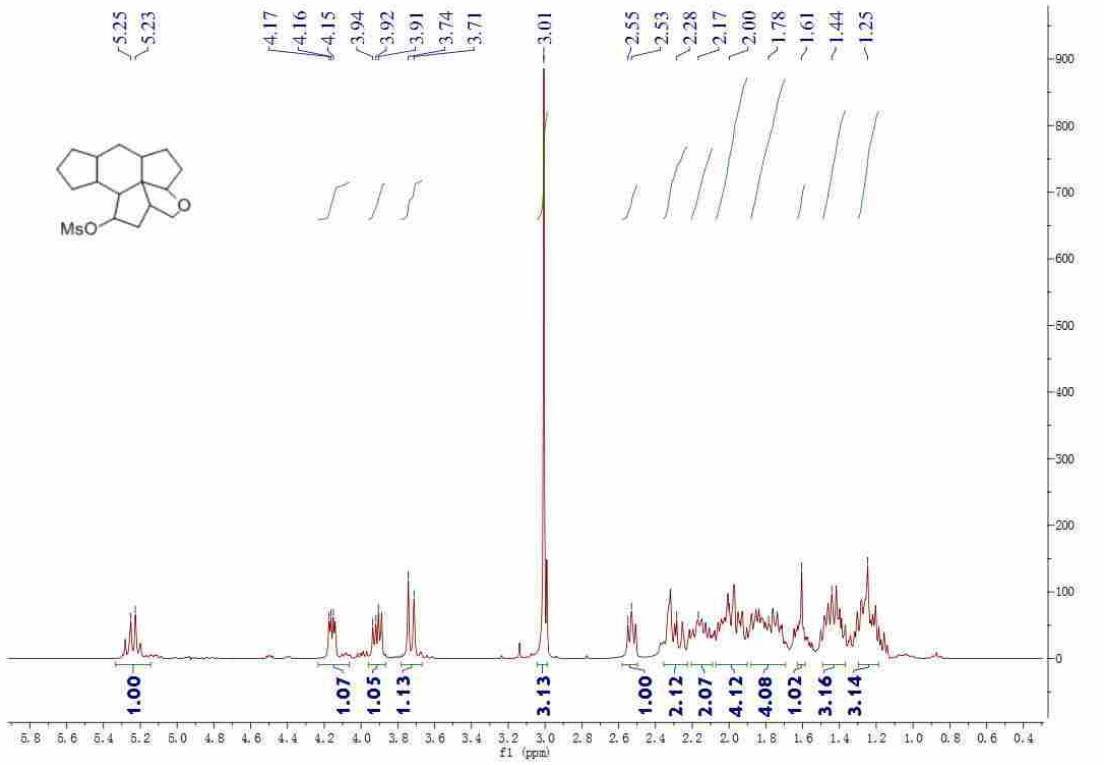

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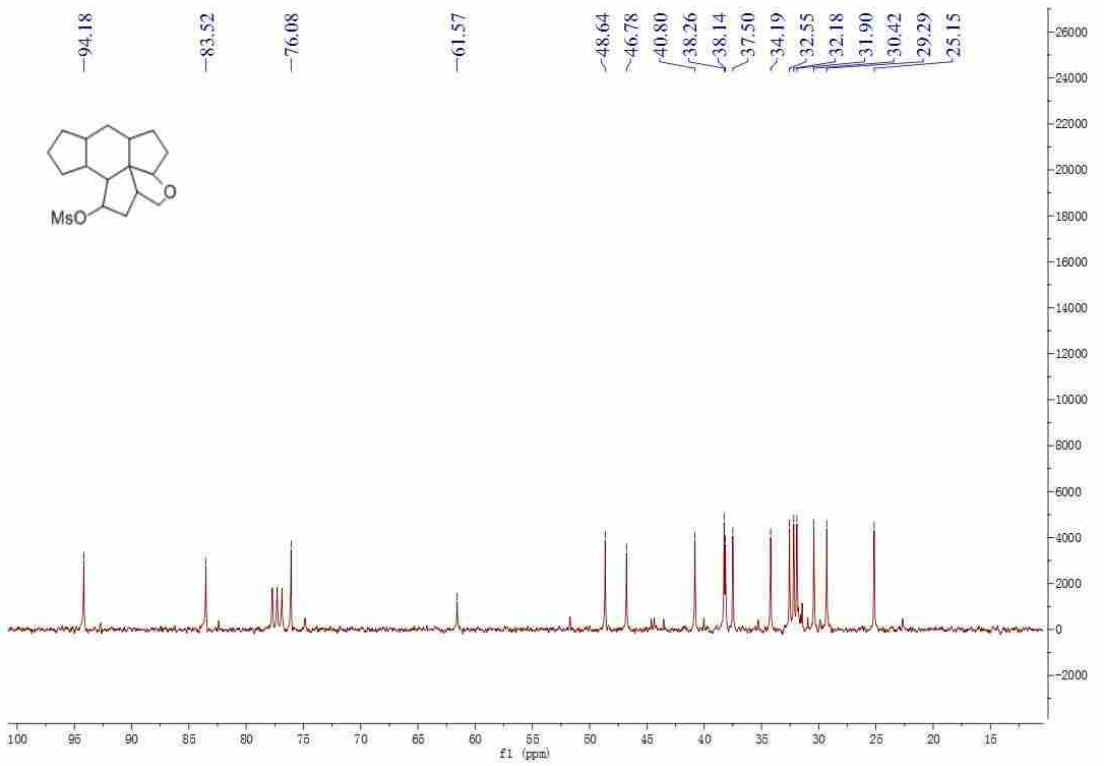

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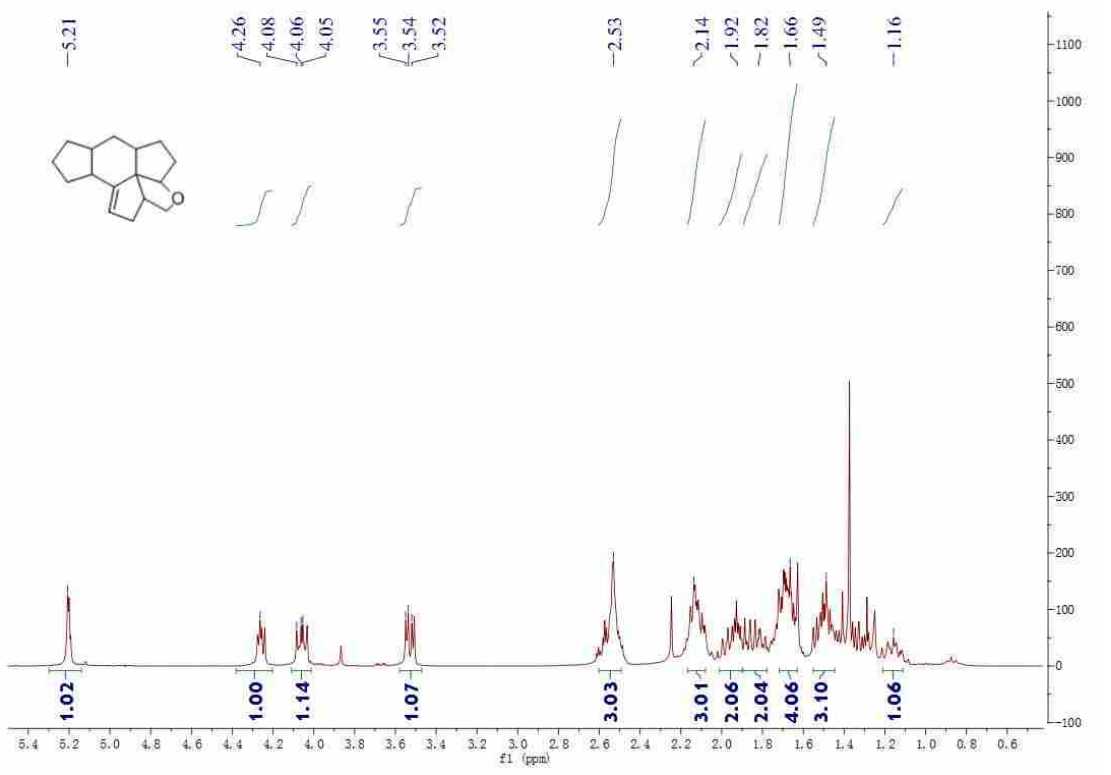
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3.55
3.54
3.52
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2.14
1.92
1.82
1.66
1.49
1.16
1.02
1.00
1.14
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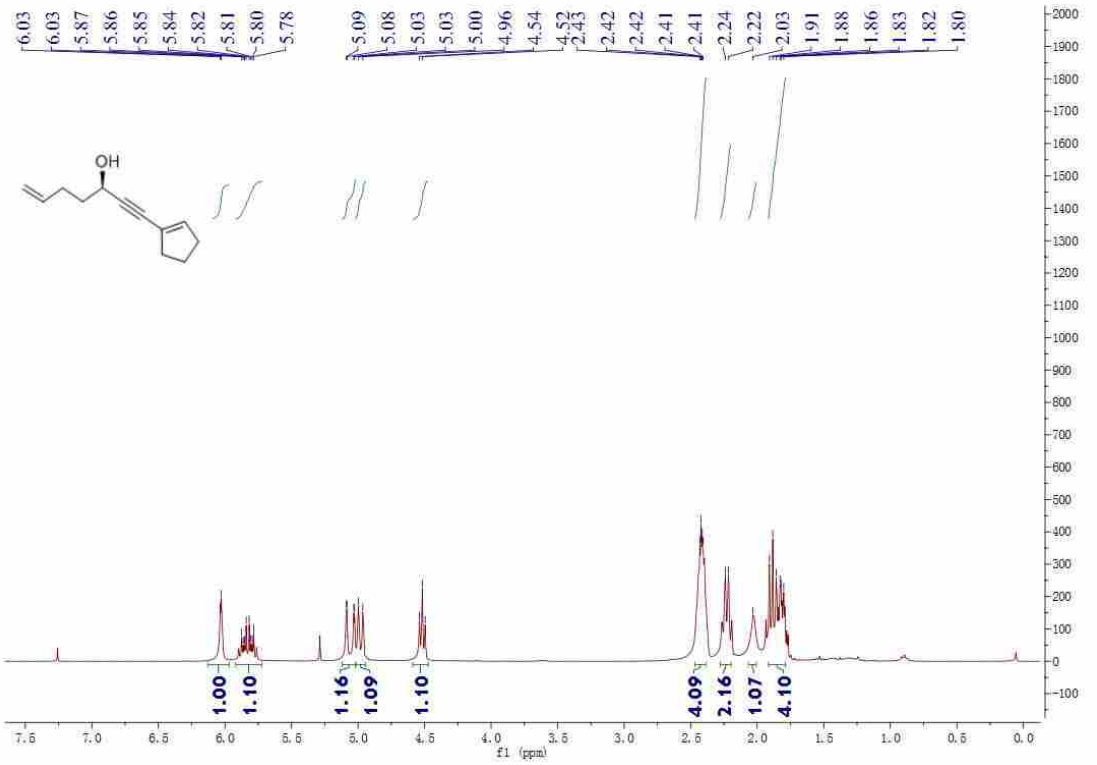
3.03
3.01
2.06
2.04
4.06
3.10
1.06
f1 (ppm)

^{1}H NMR



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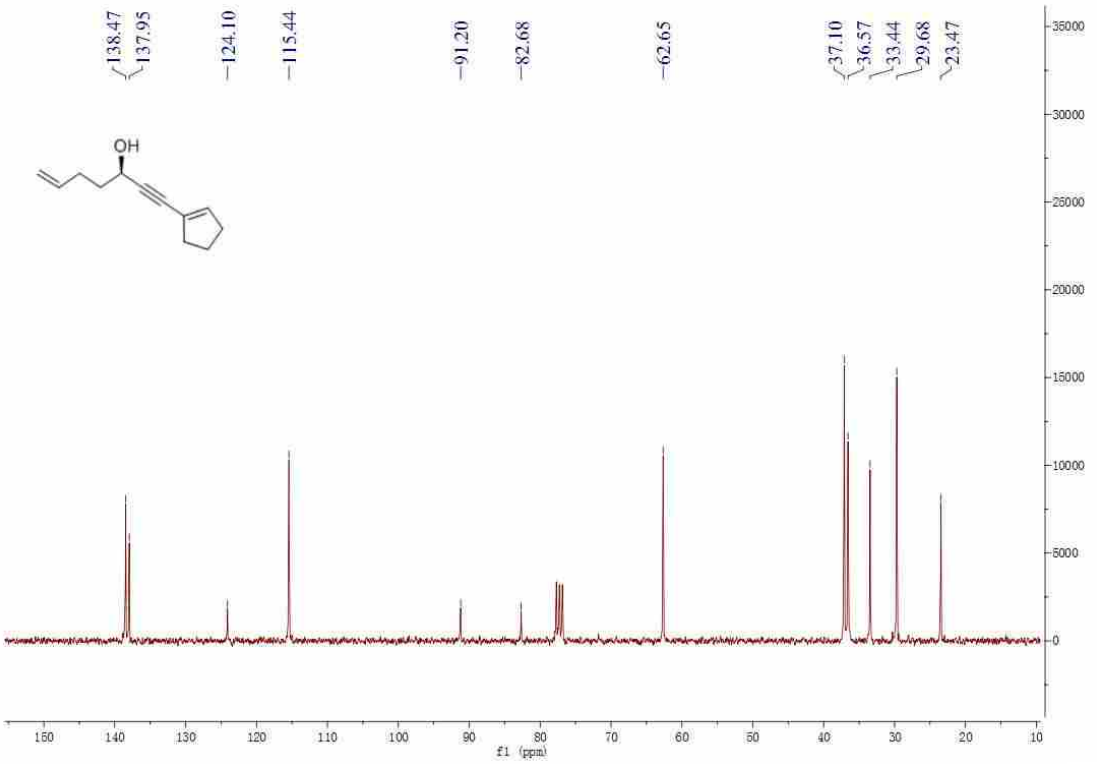

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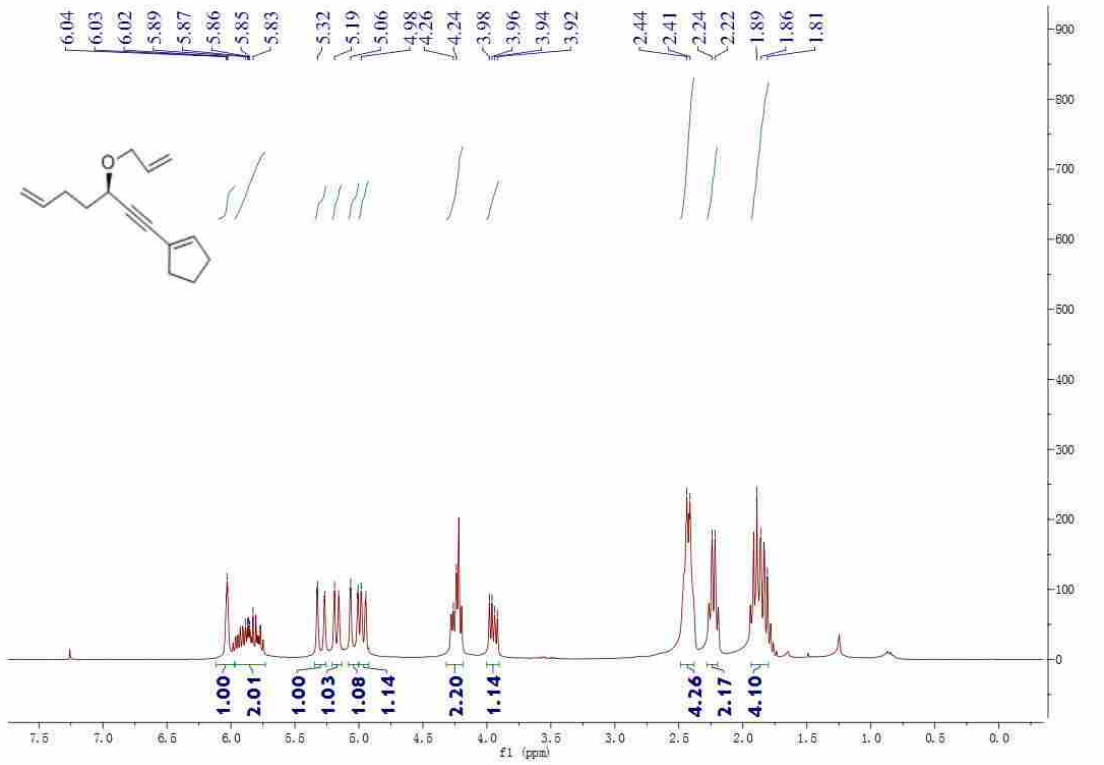

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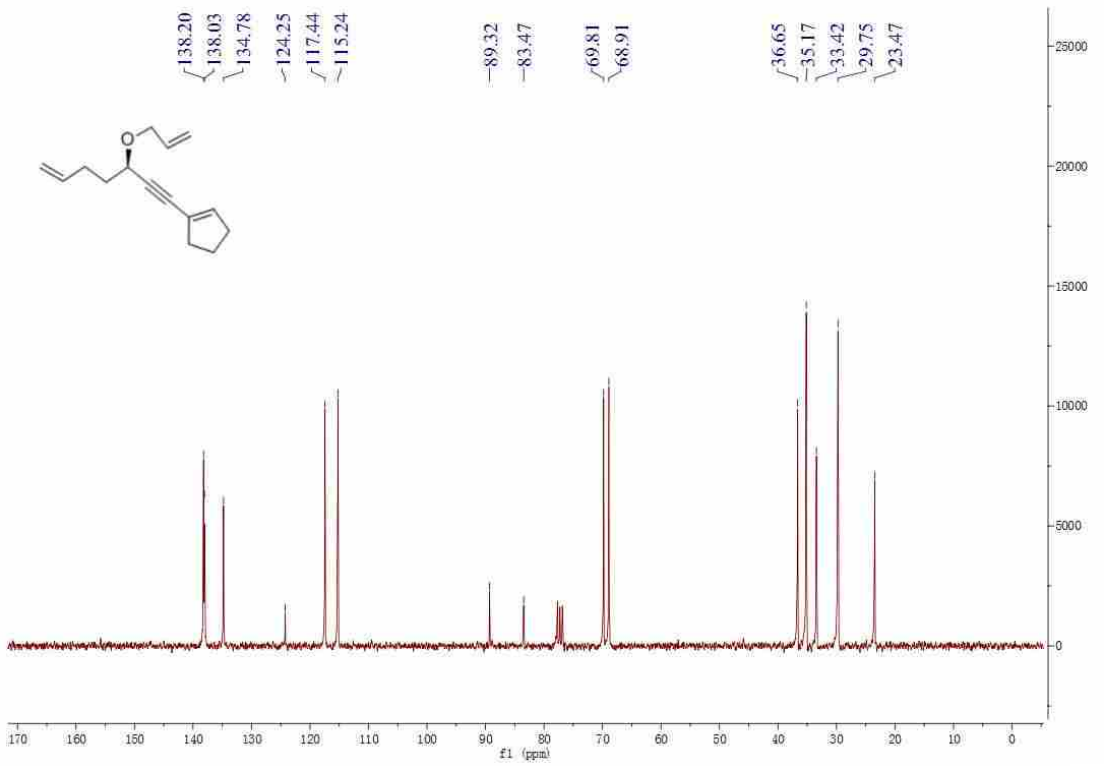

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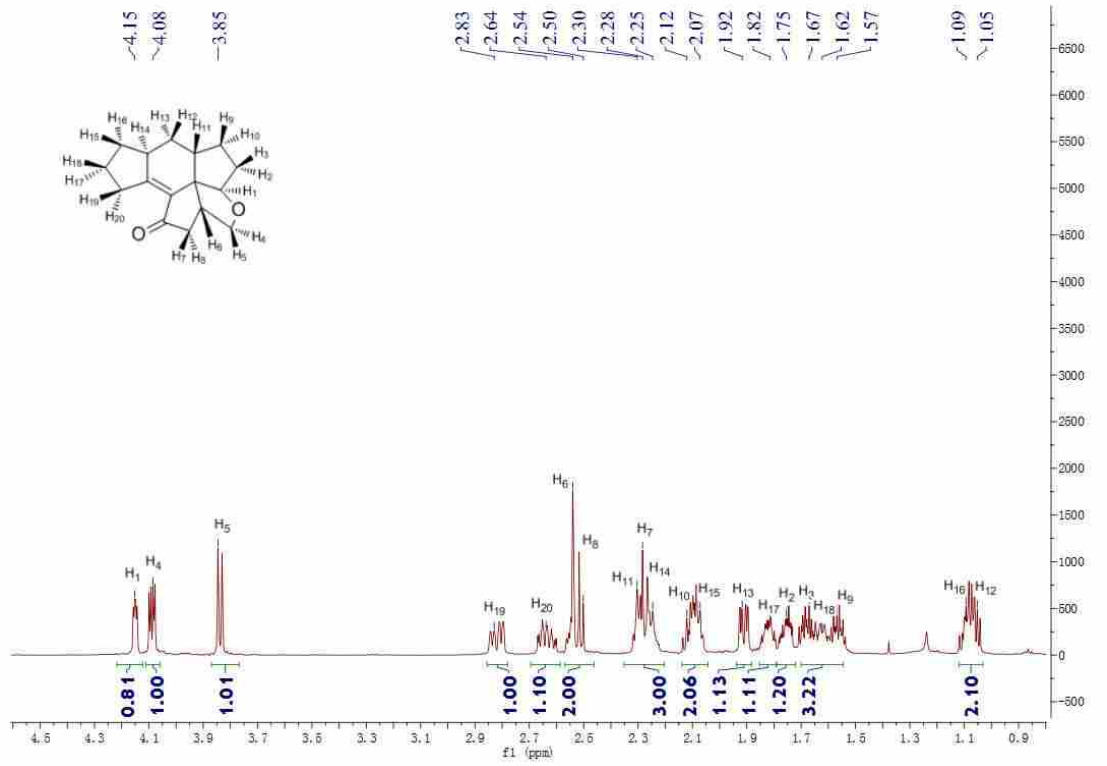

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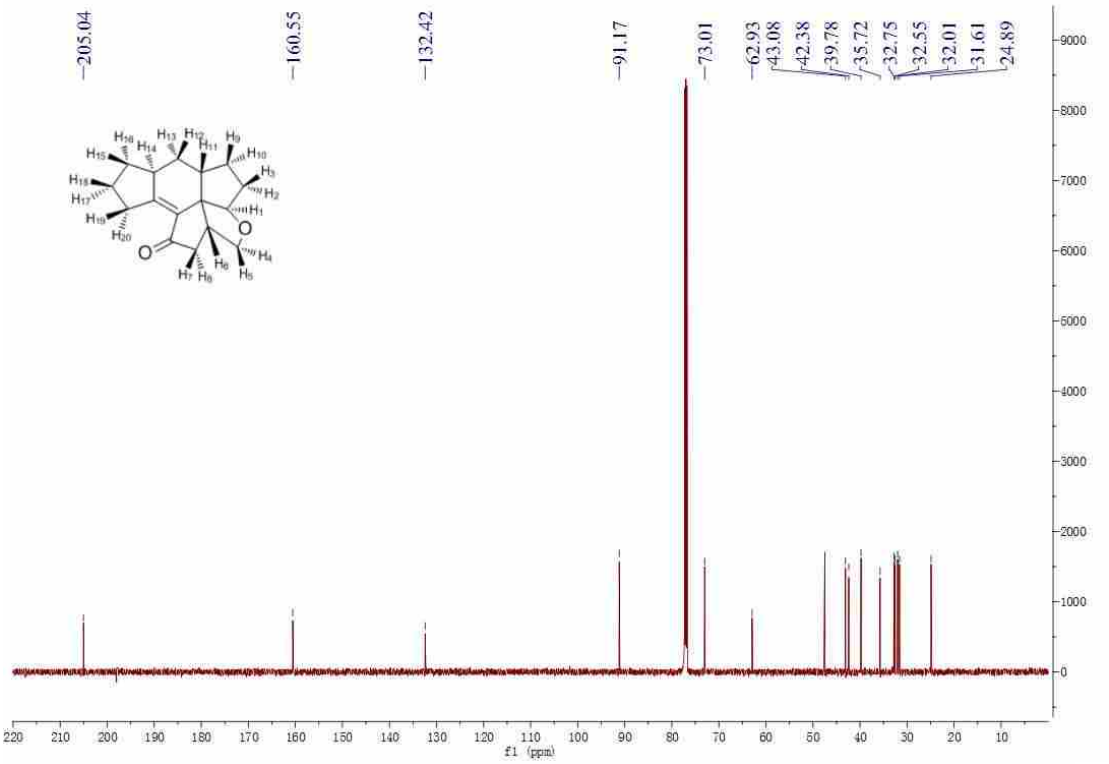

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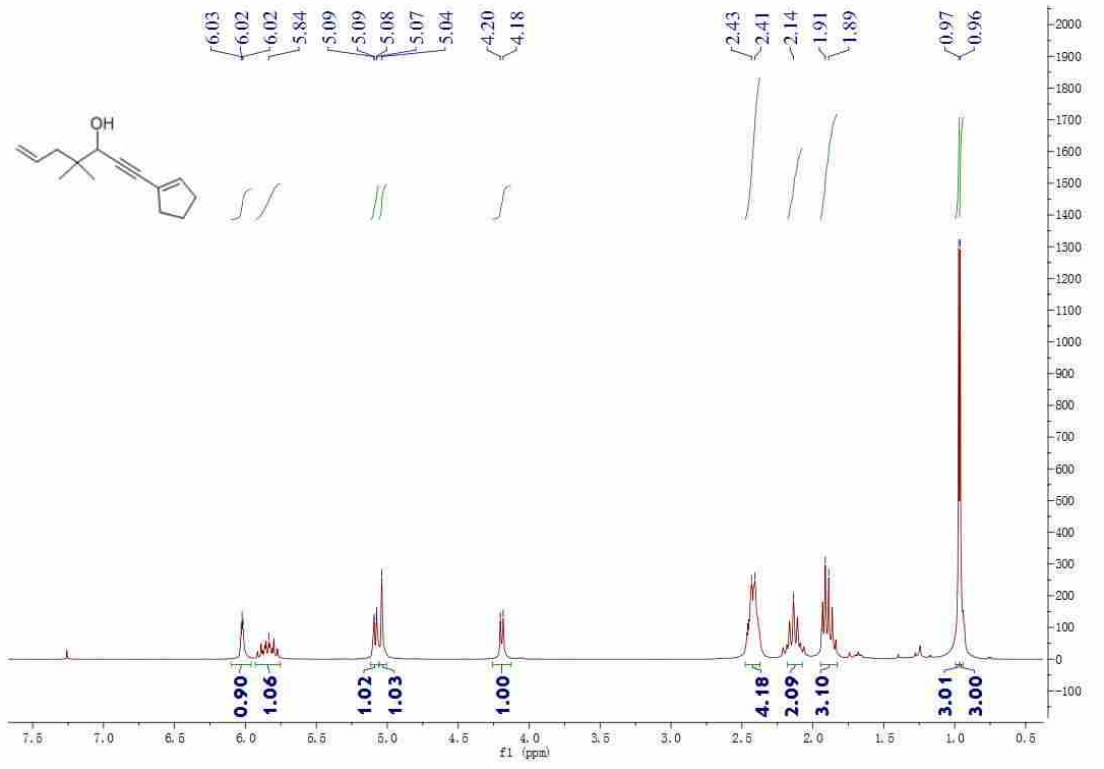

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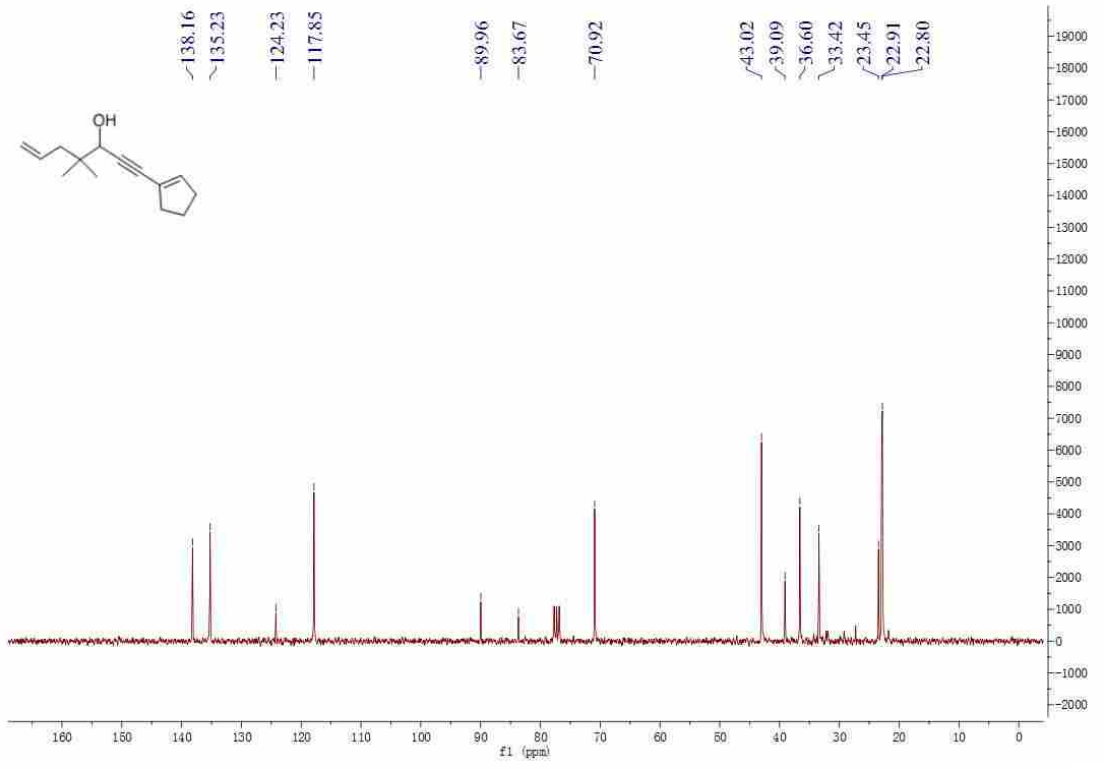

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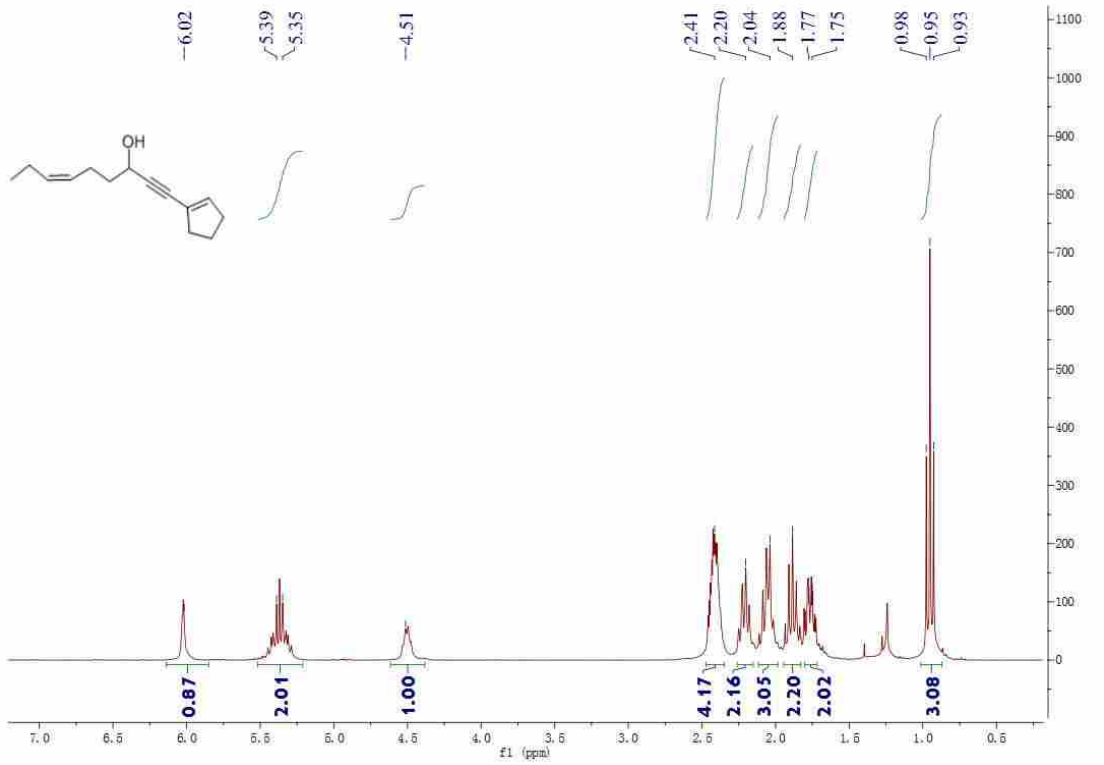

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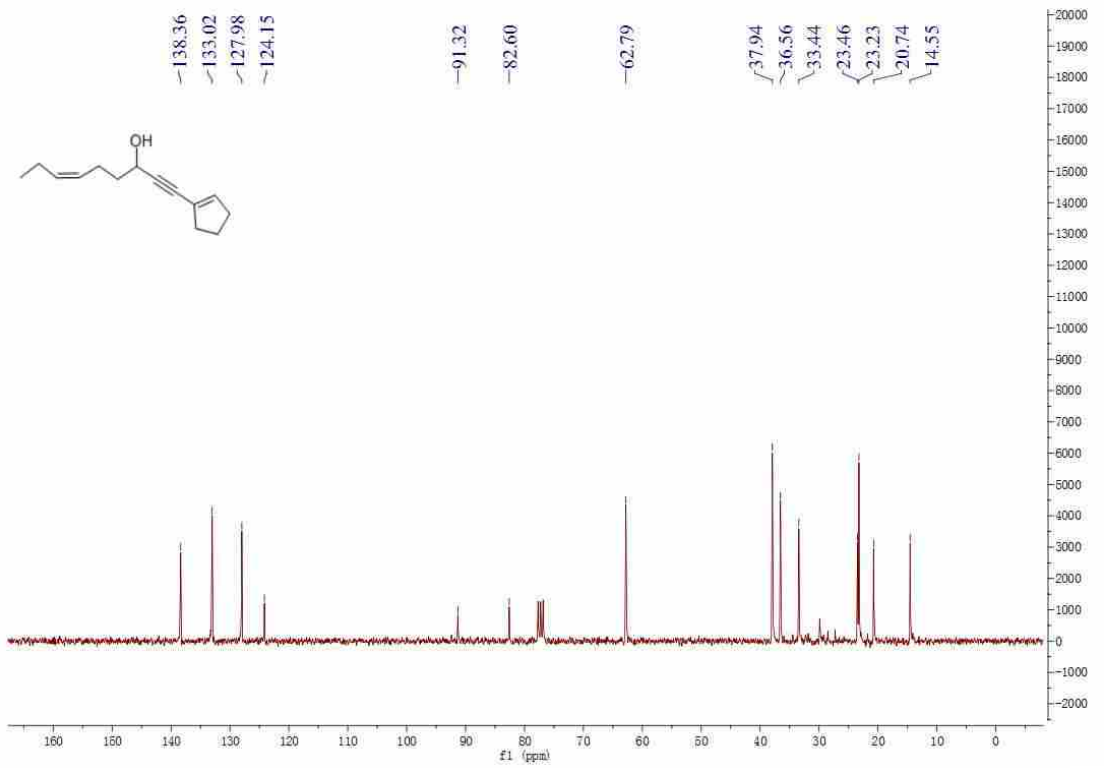

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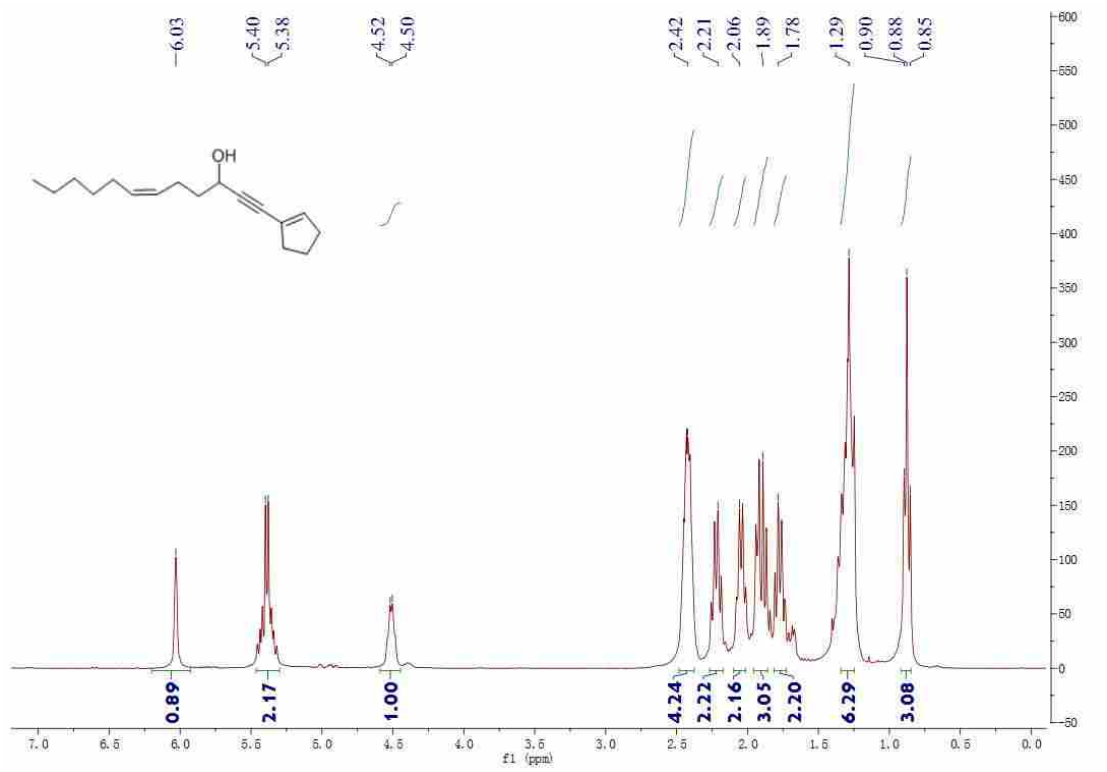

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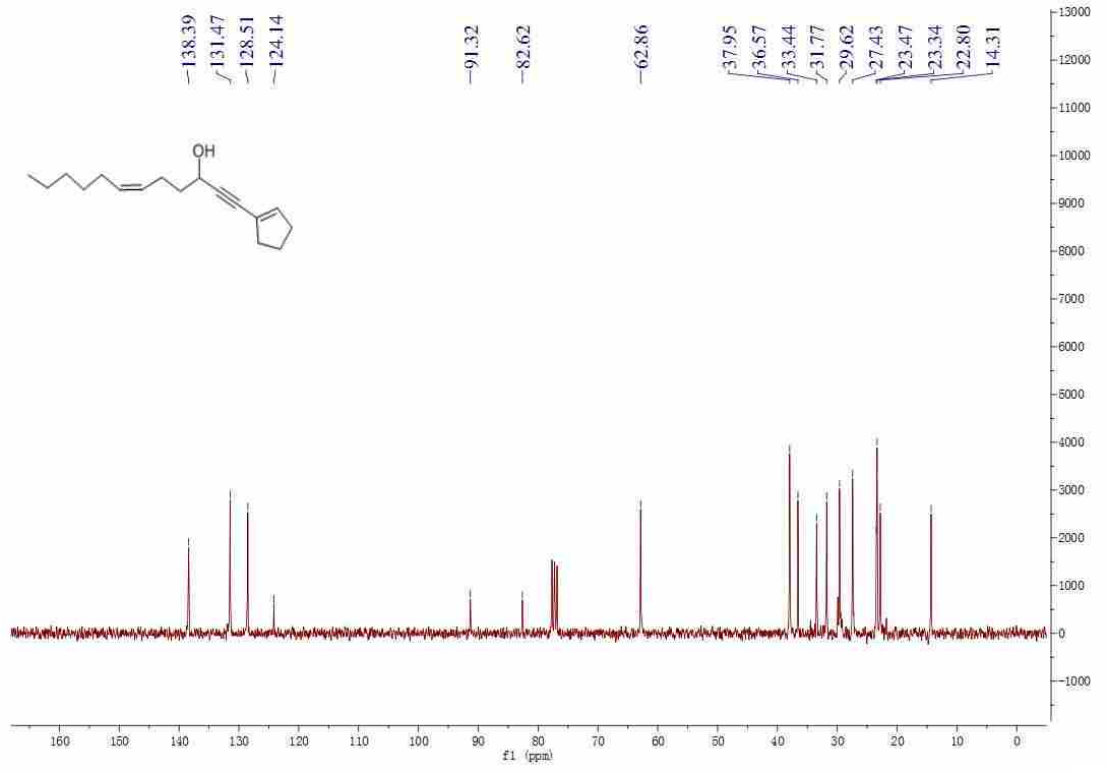

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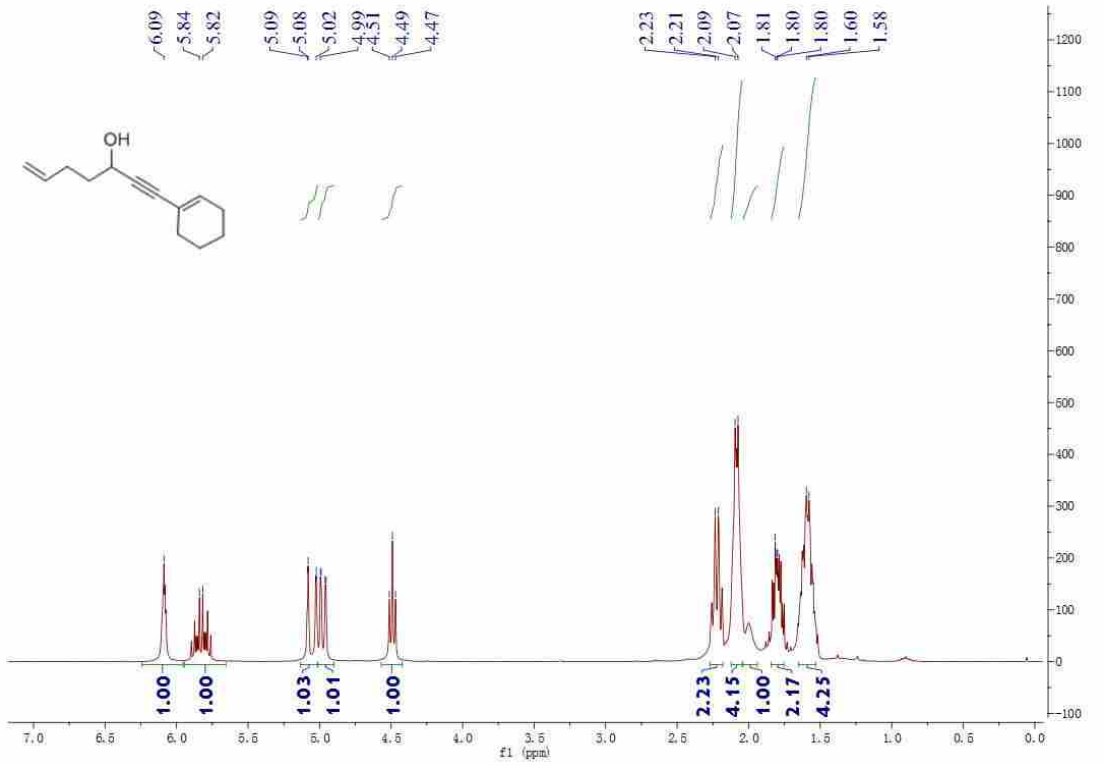

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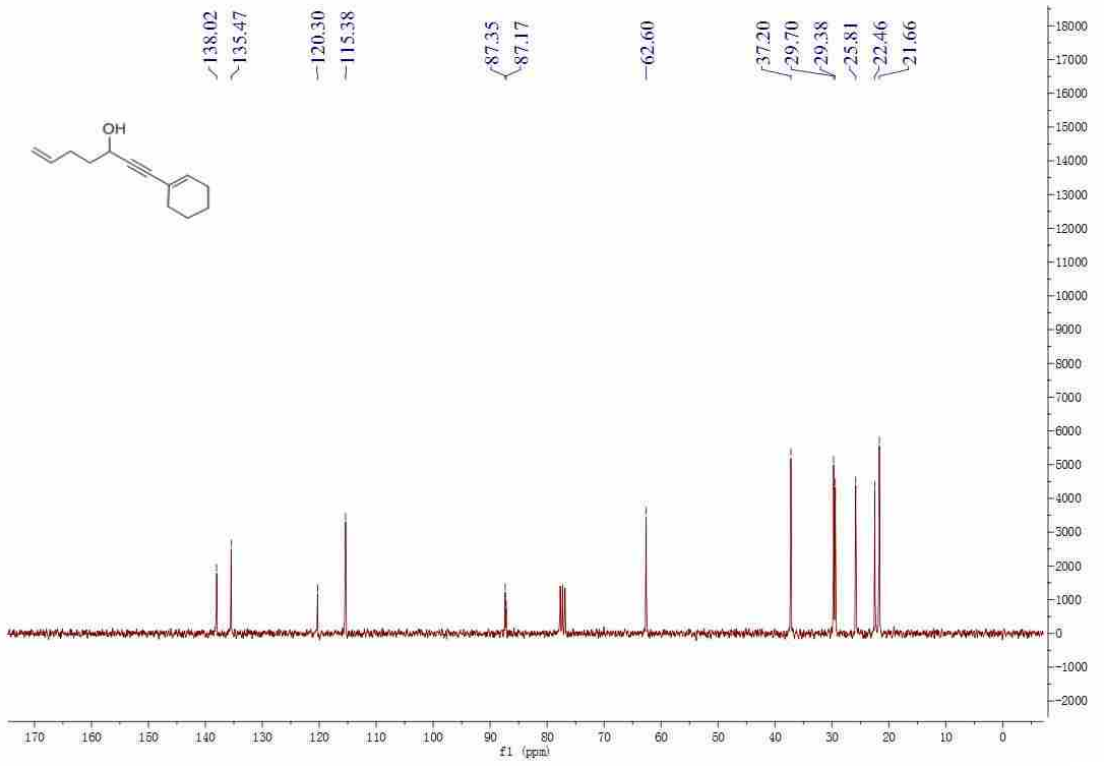

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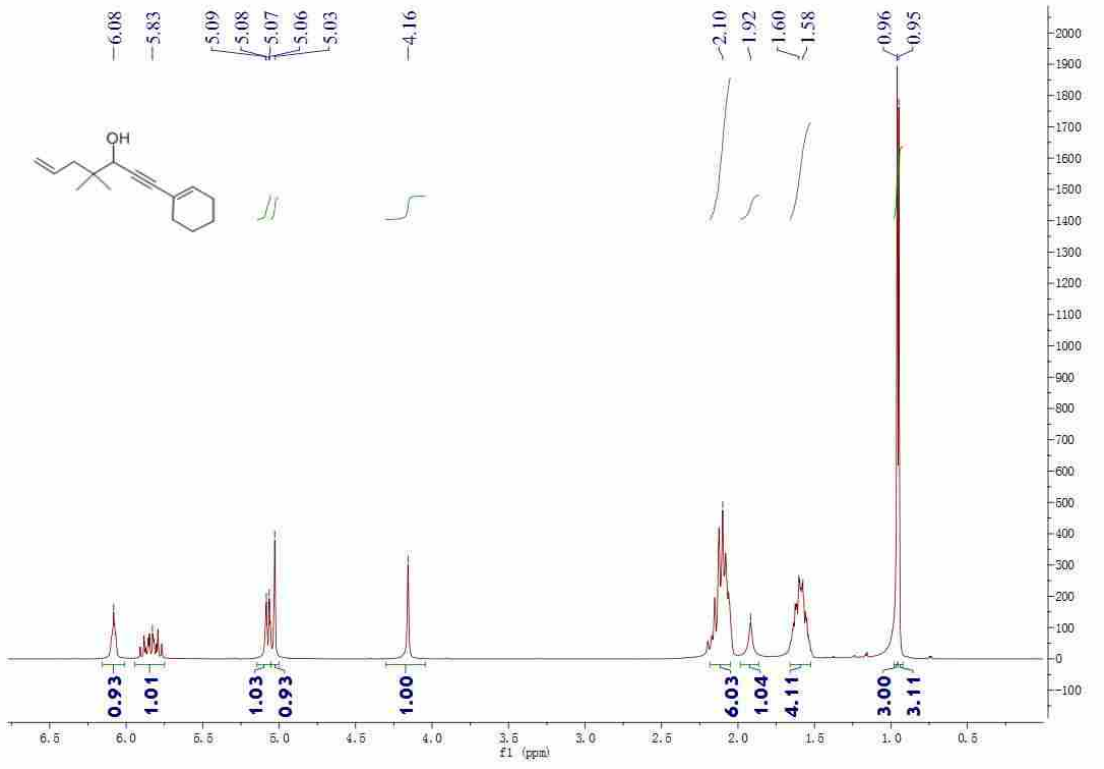

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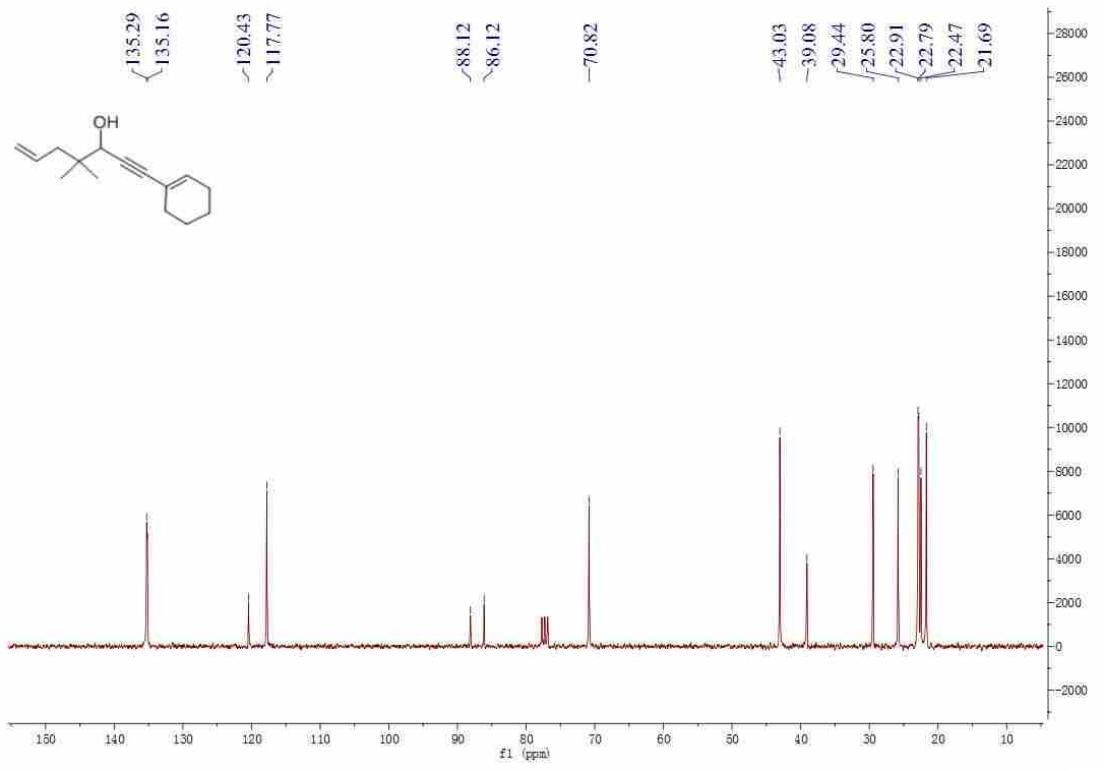

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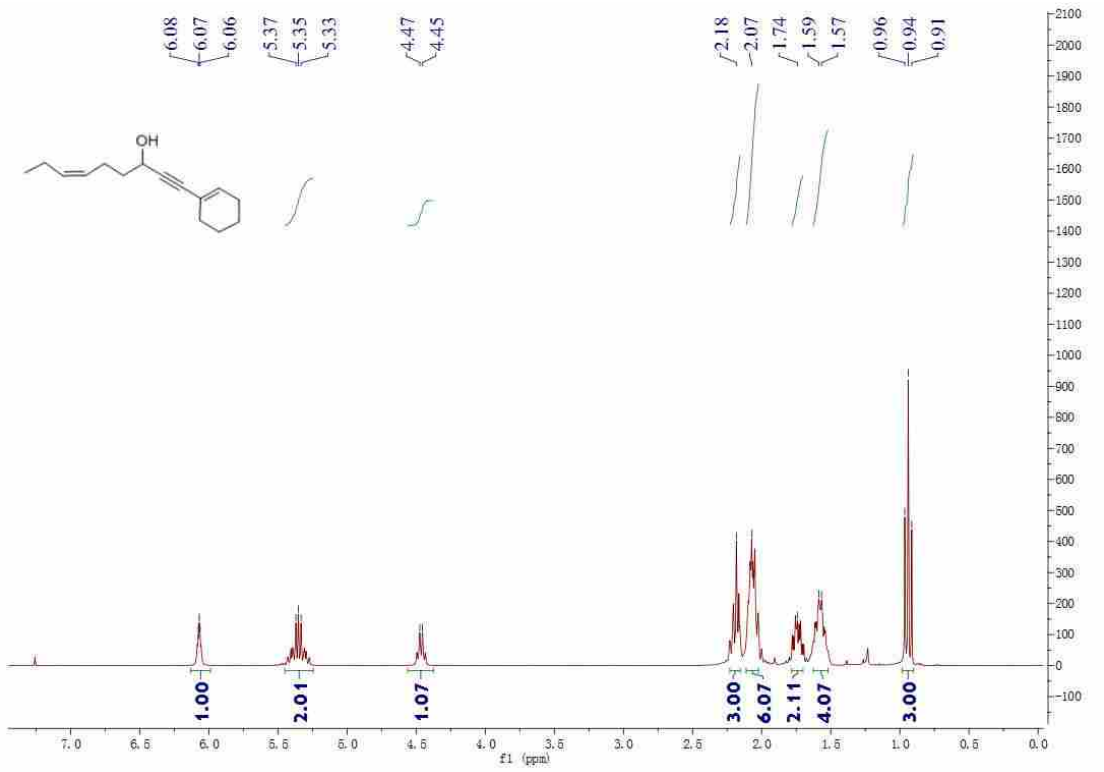

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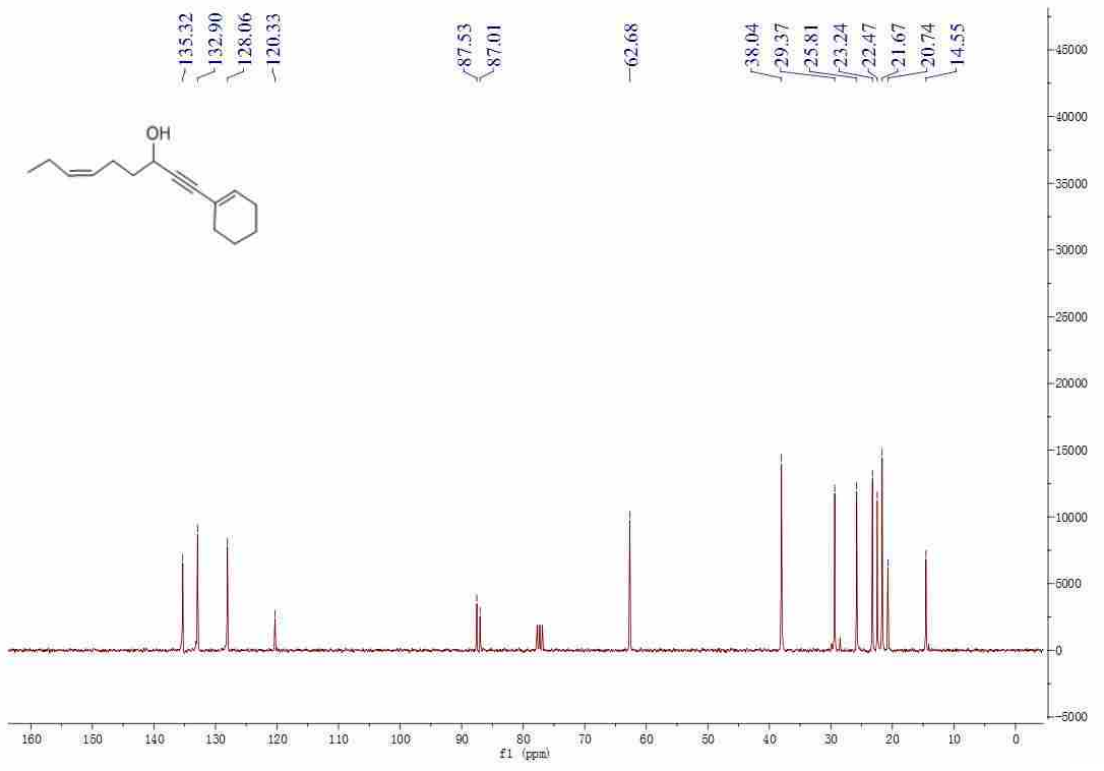

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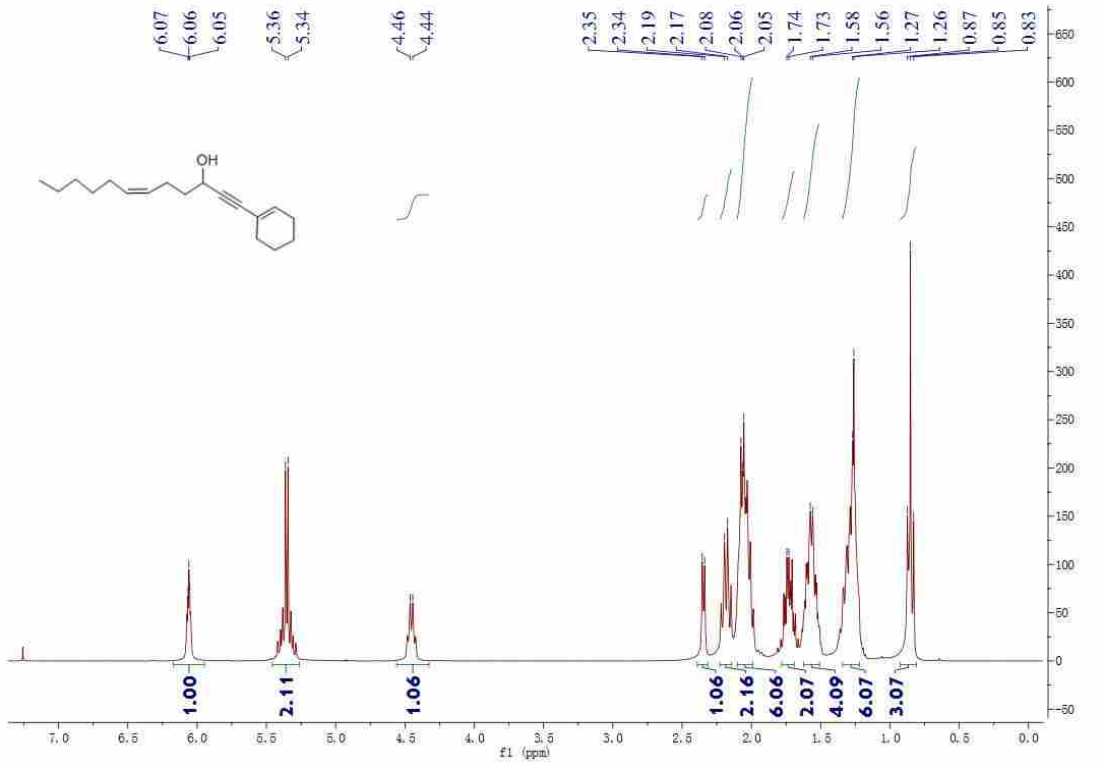

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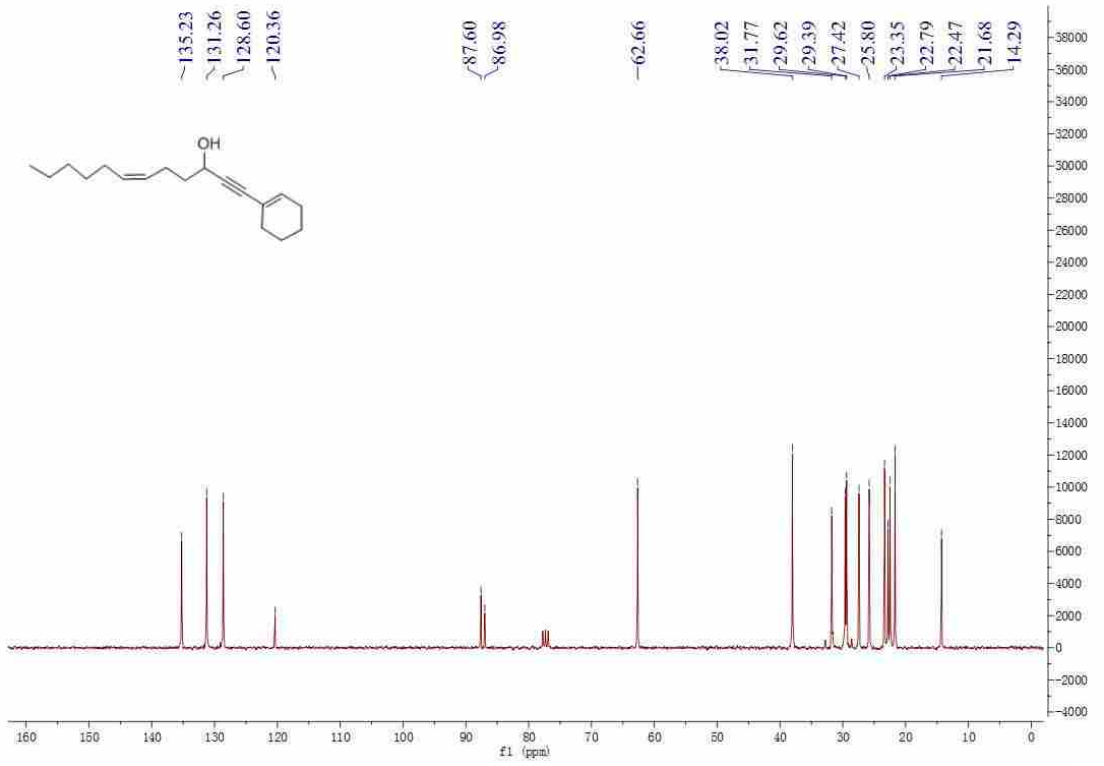

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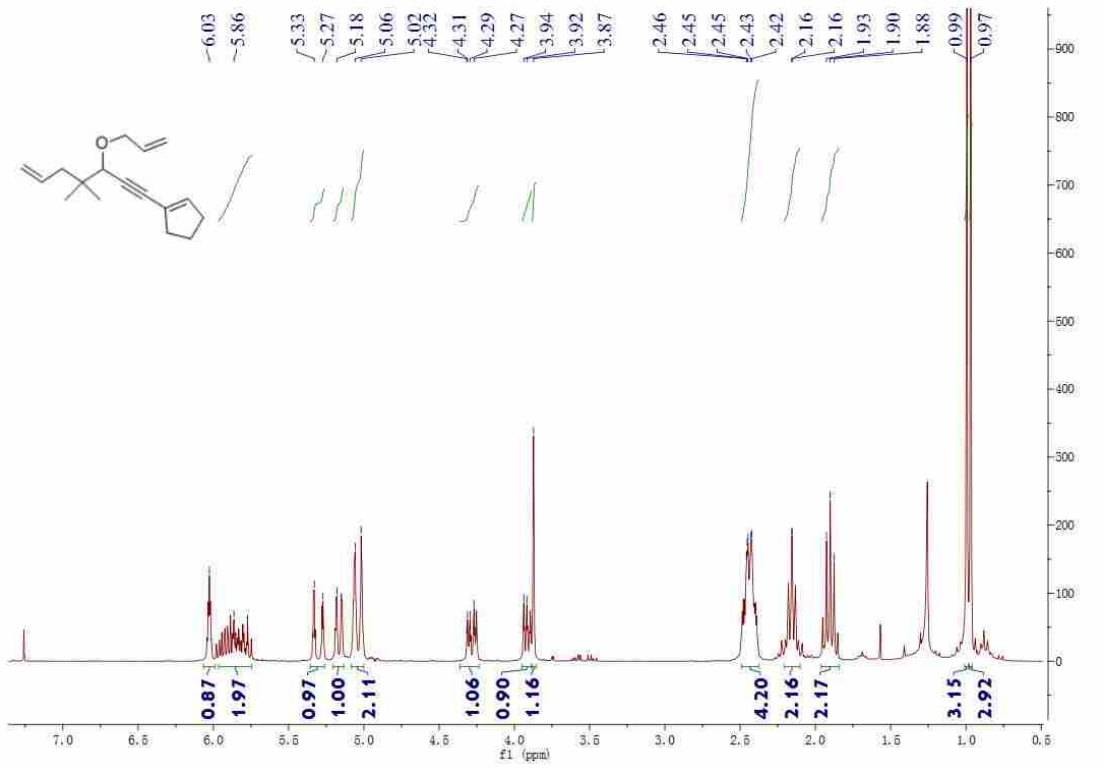

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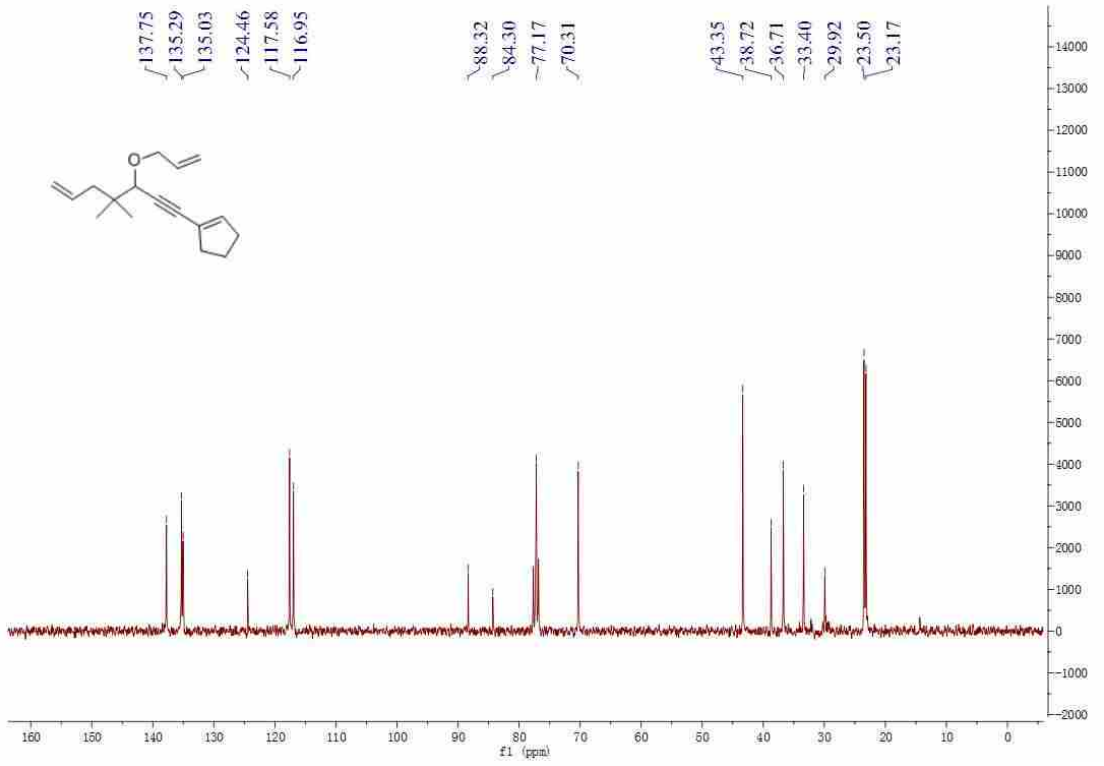

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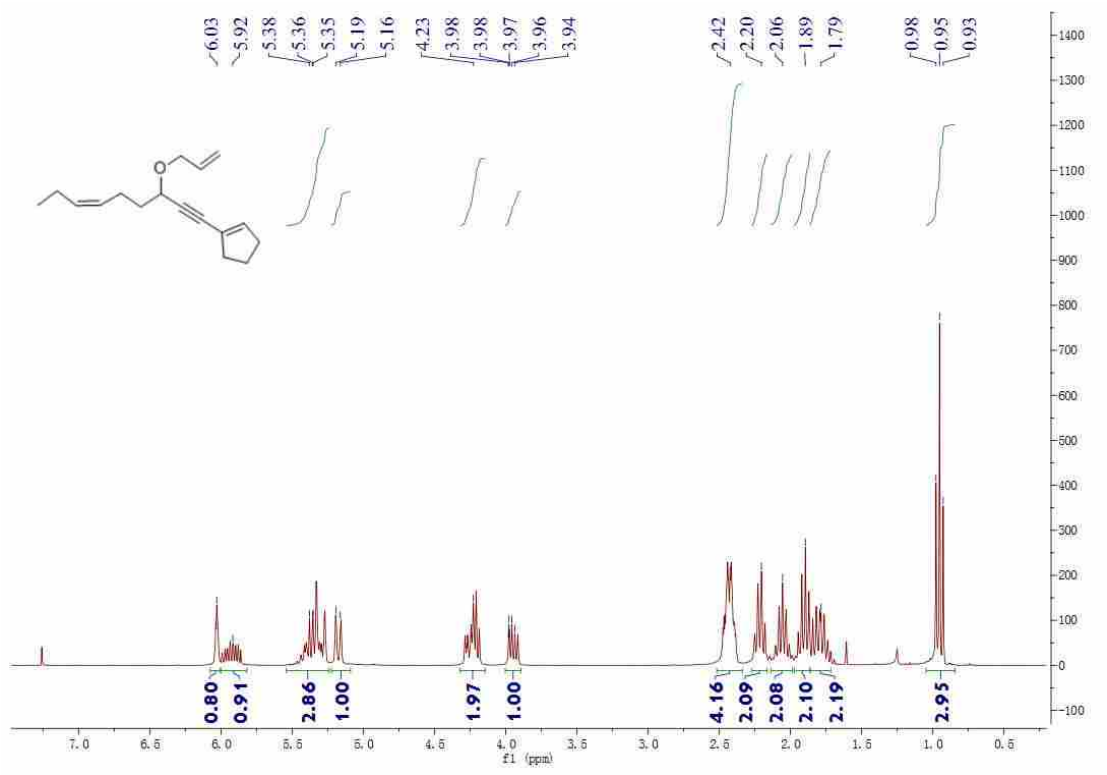

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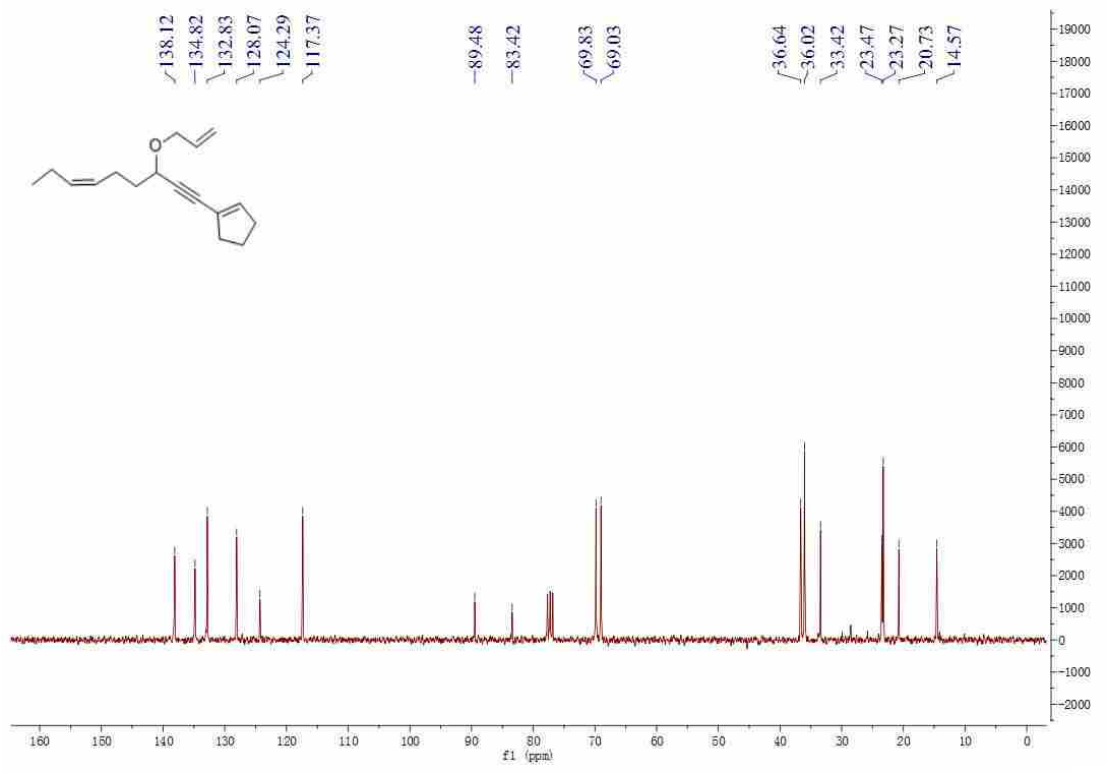

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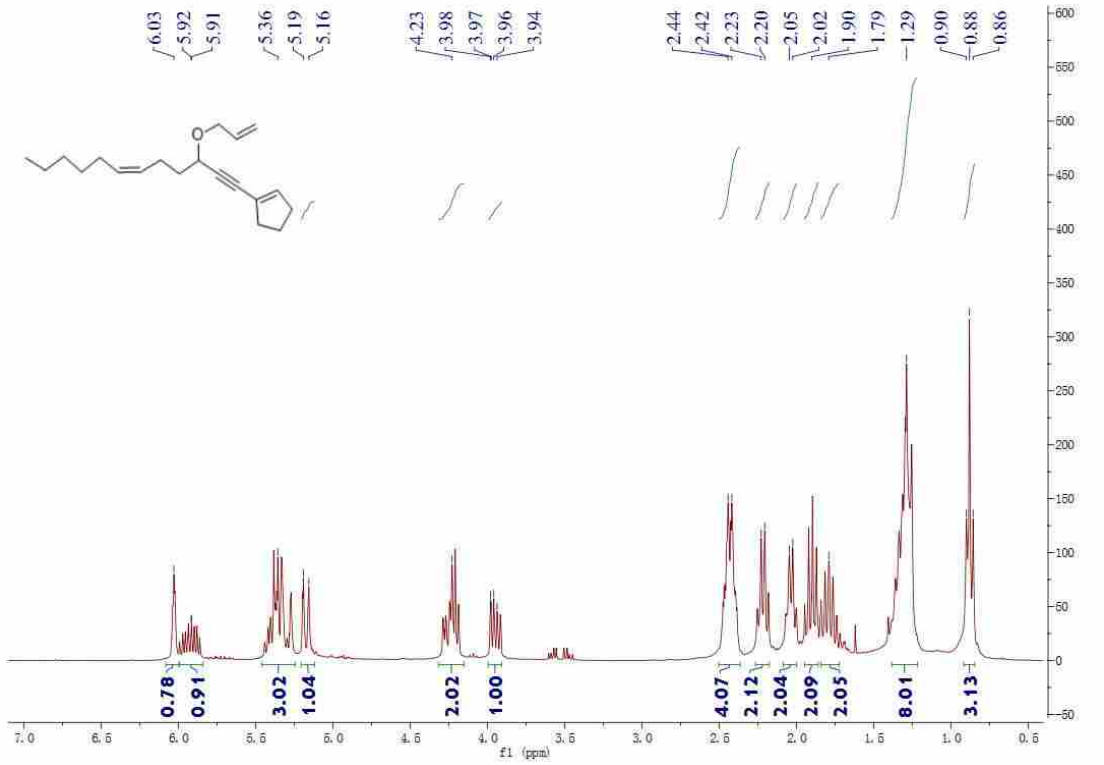

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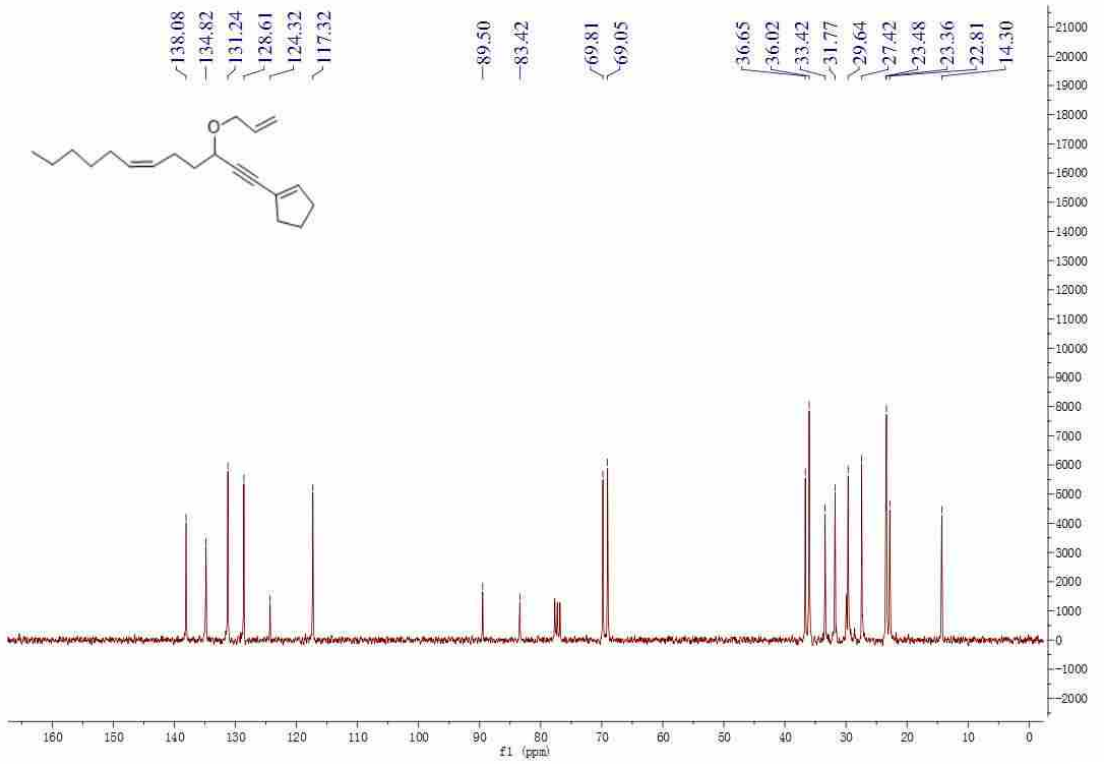

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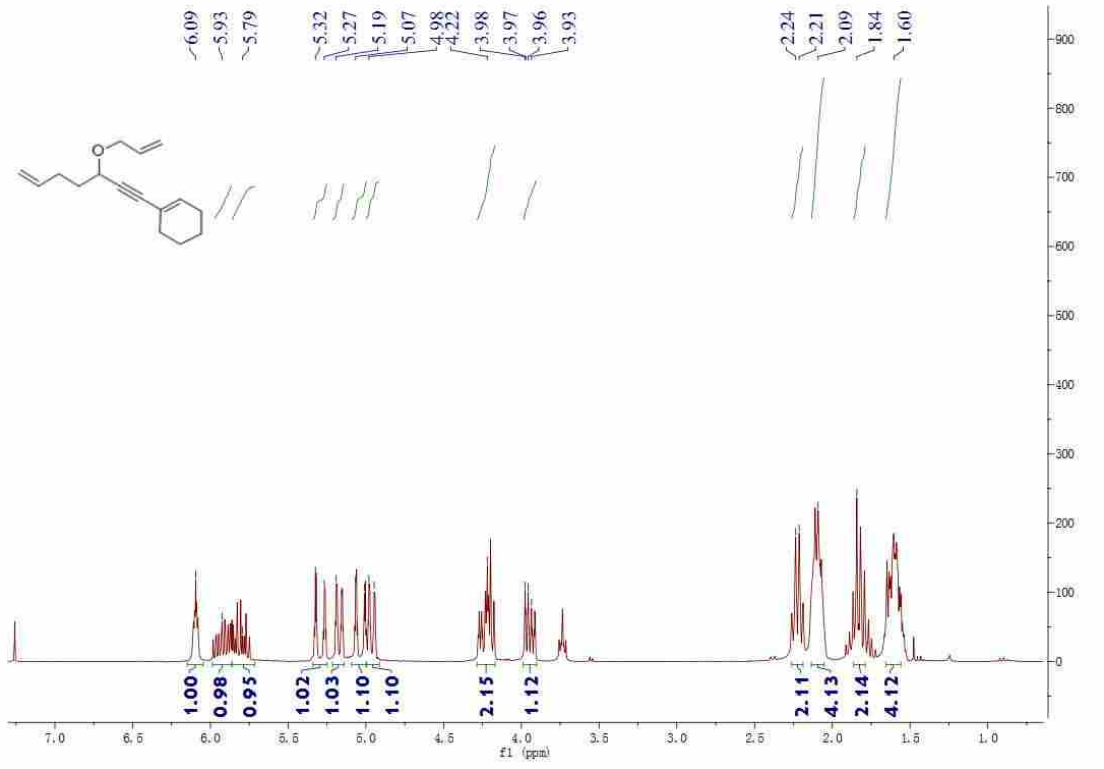

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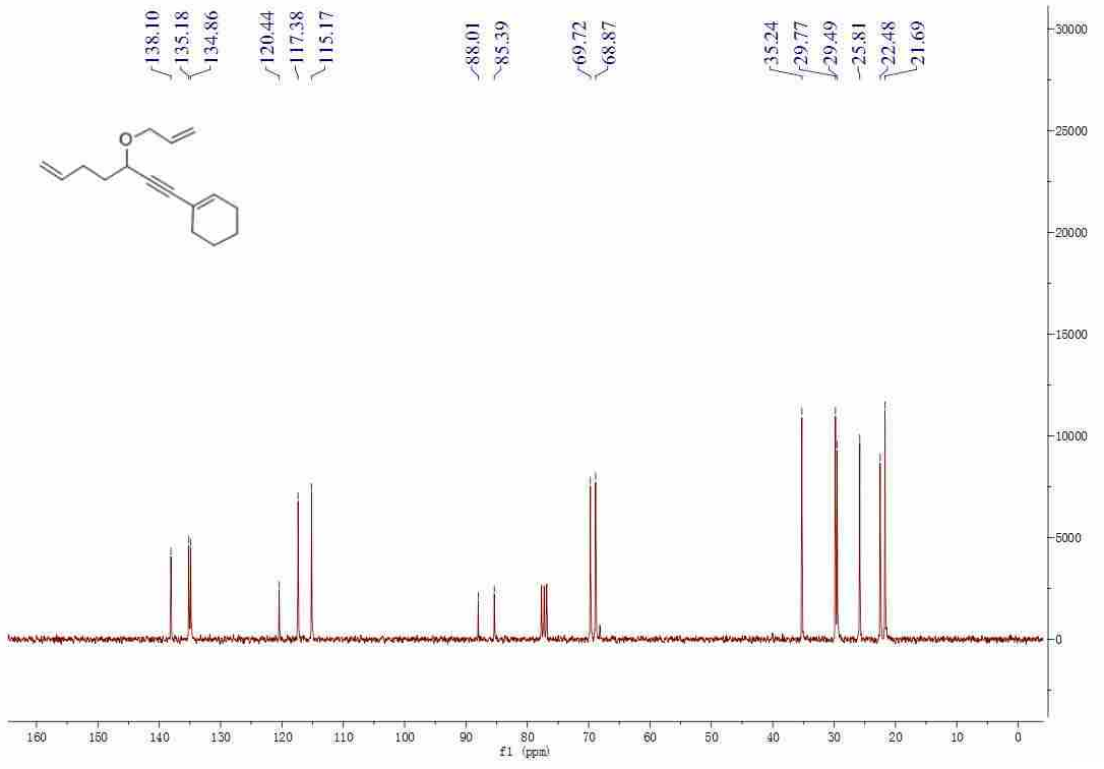

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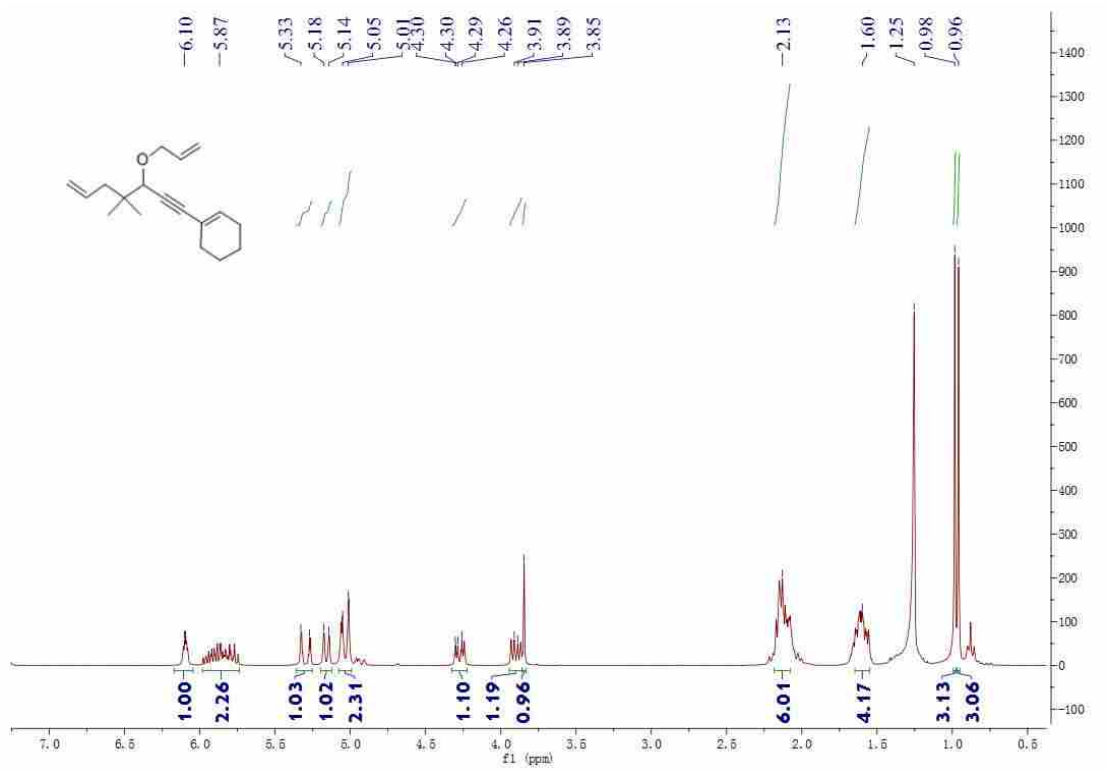

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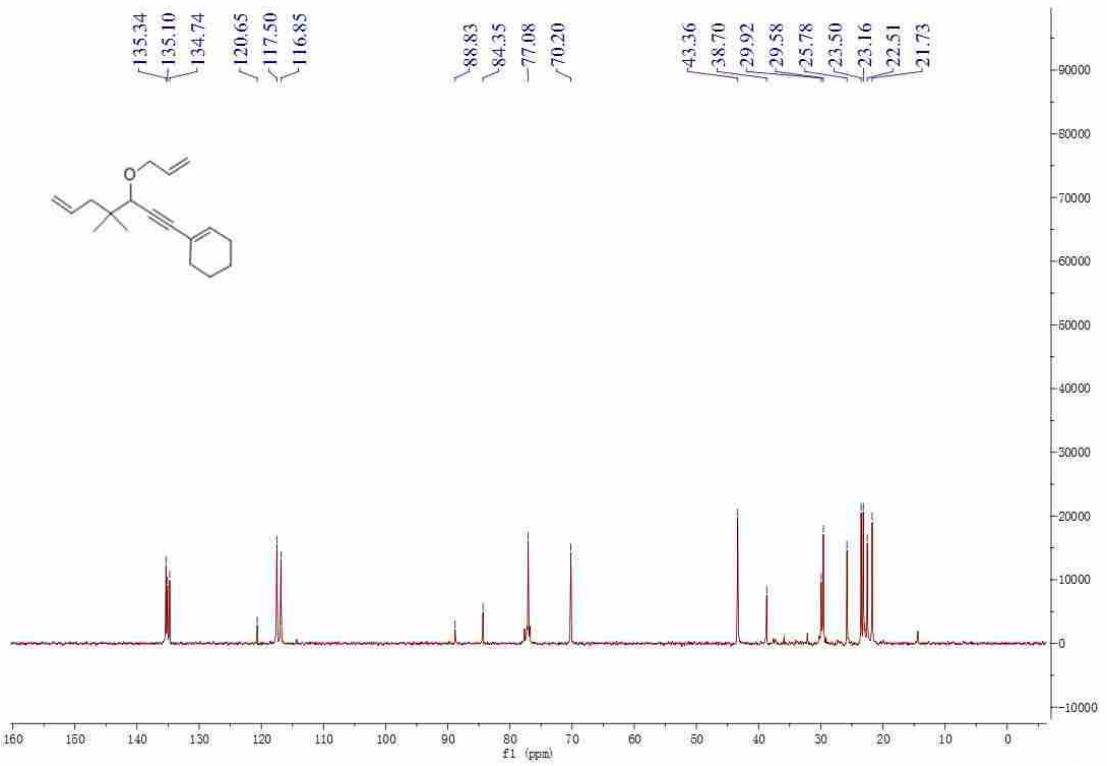

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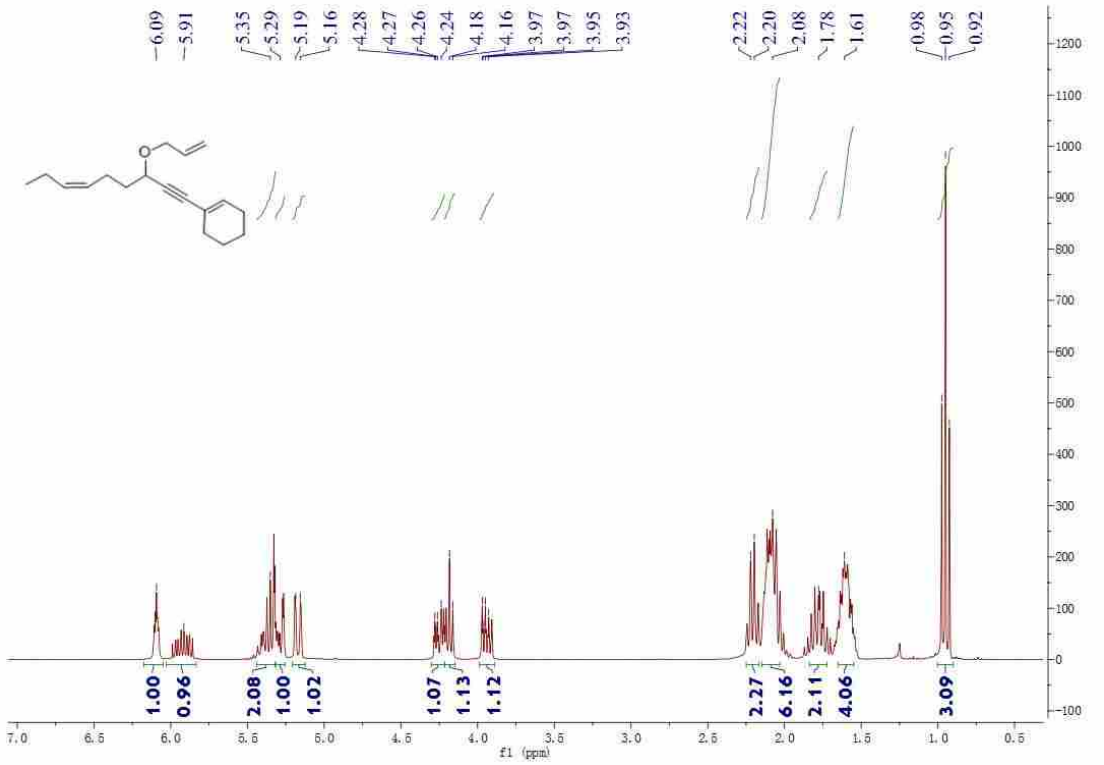

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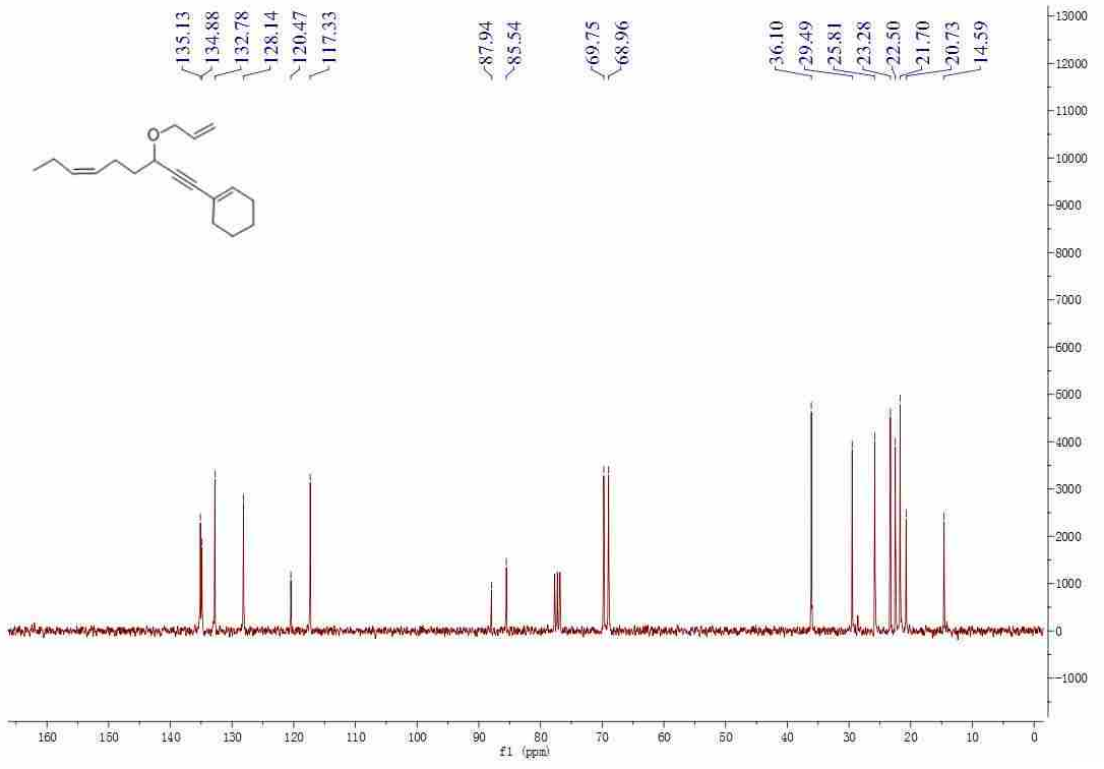

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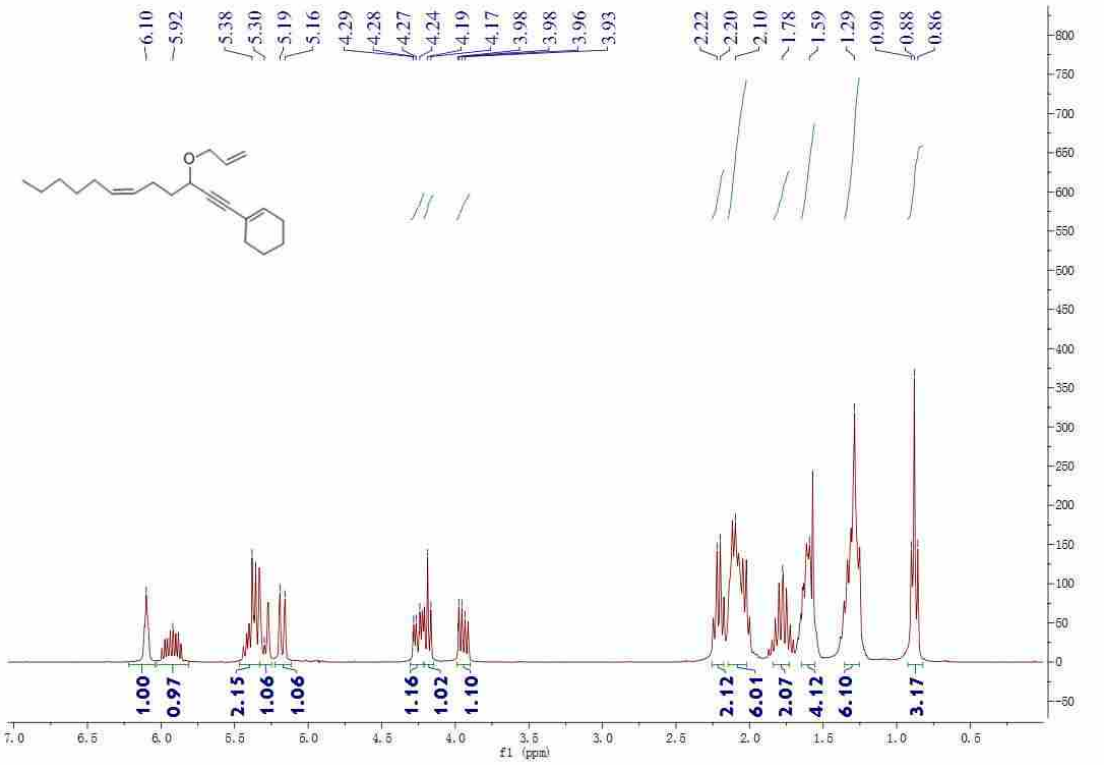

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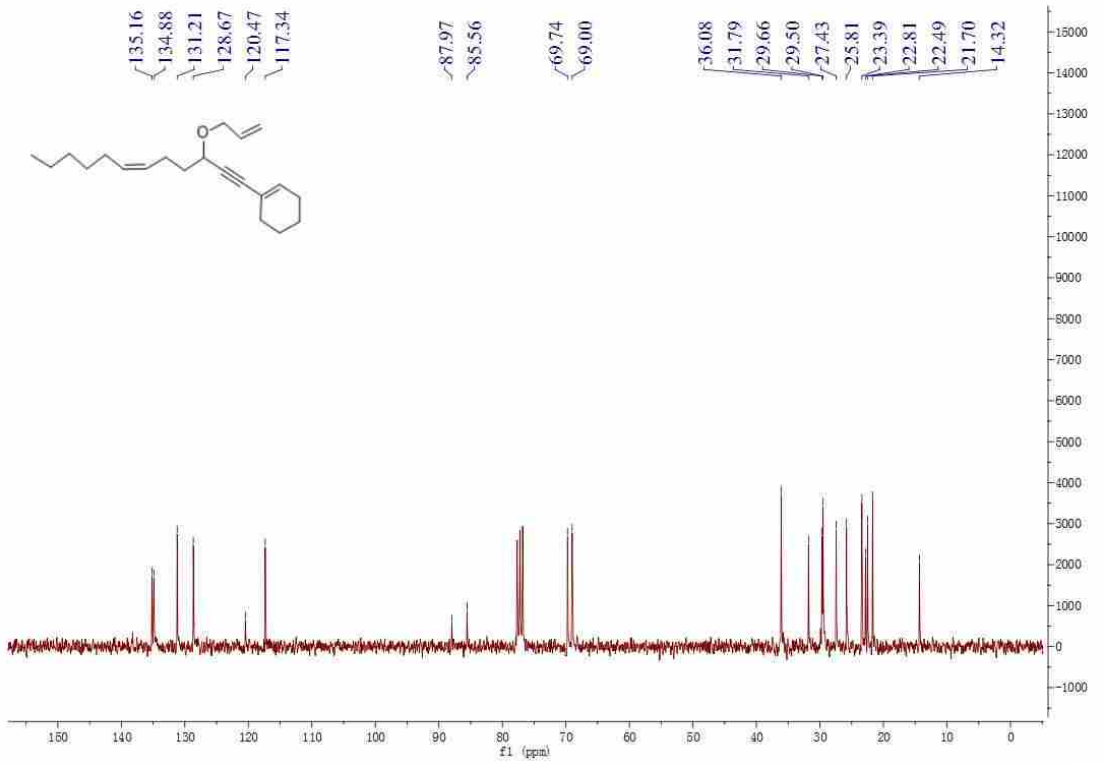

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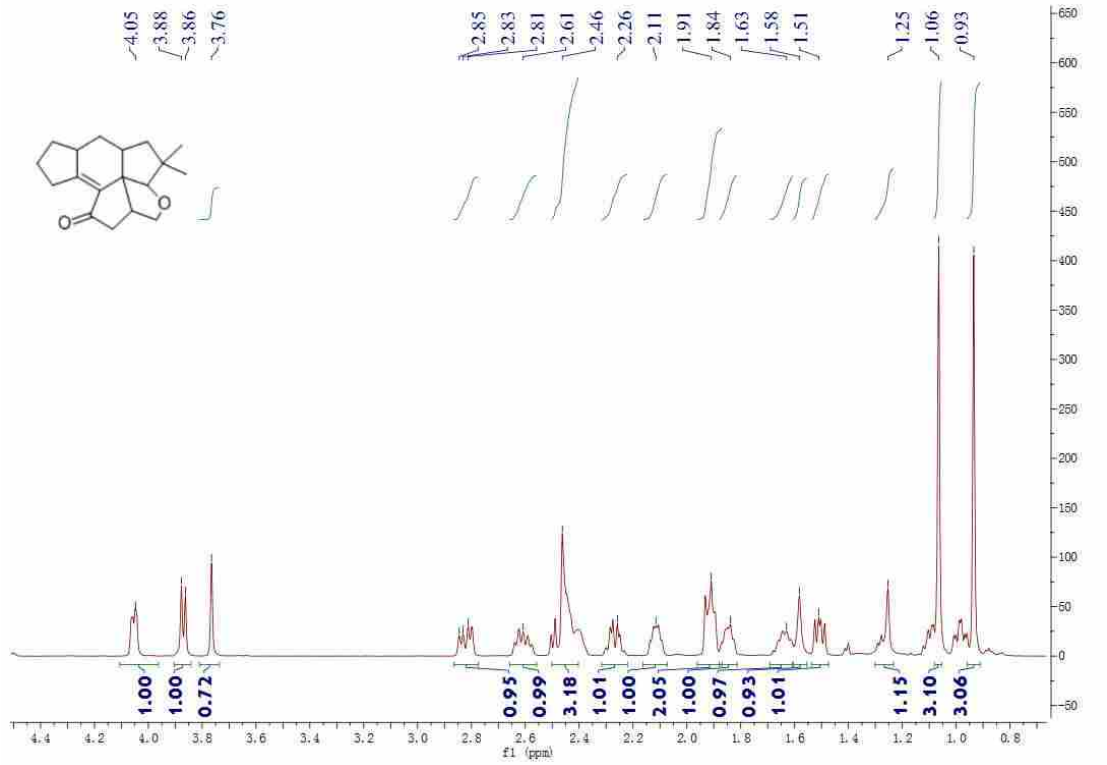

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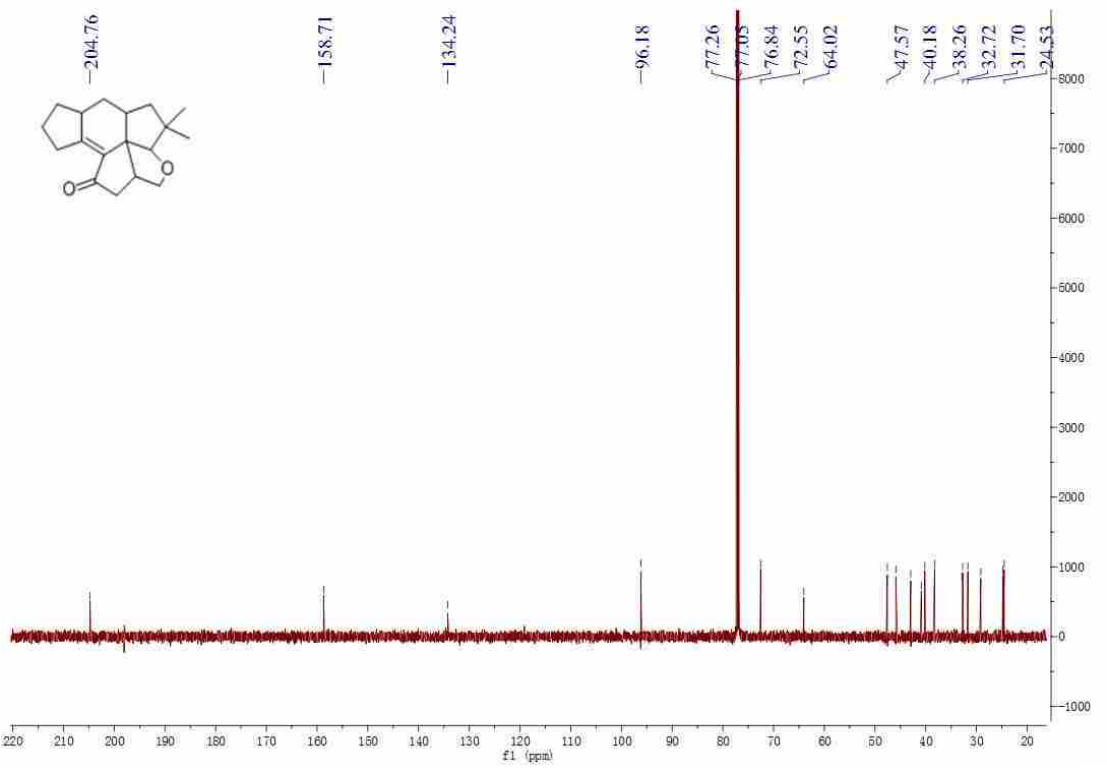

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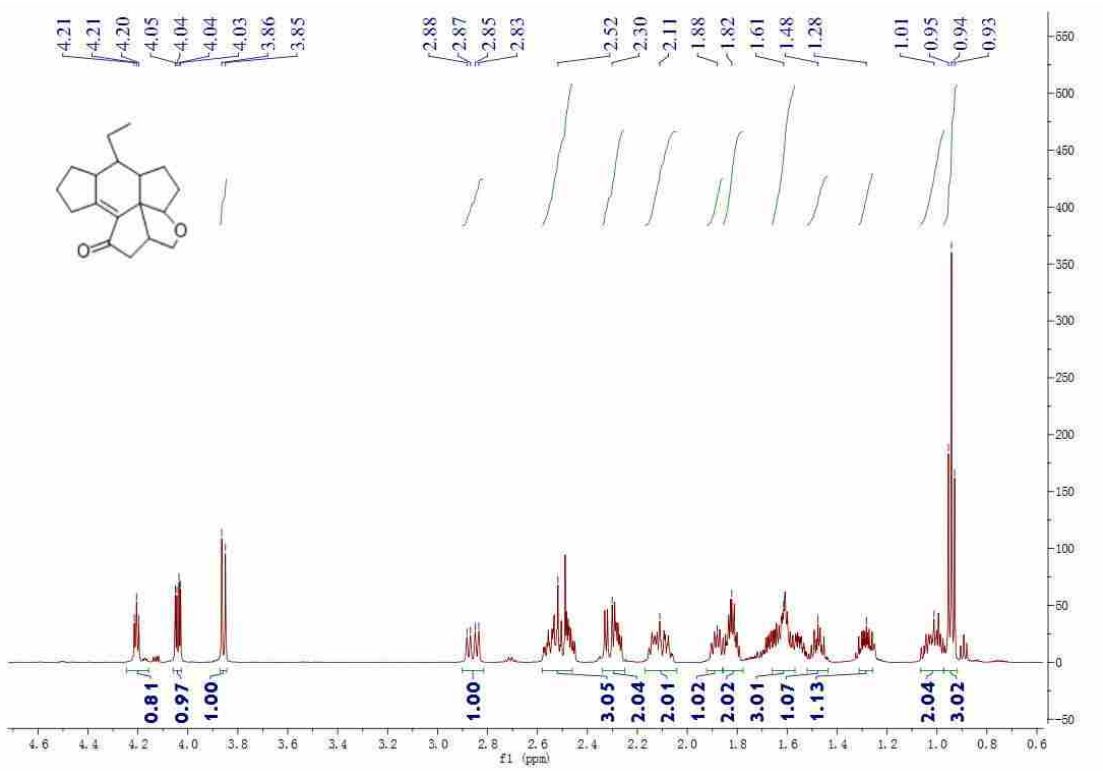

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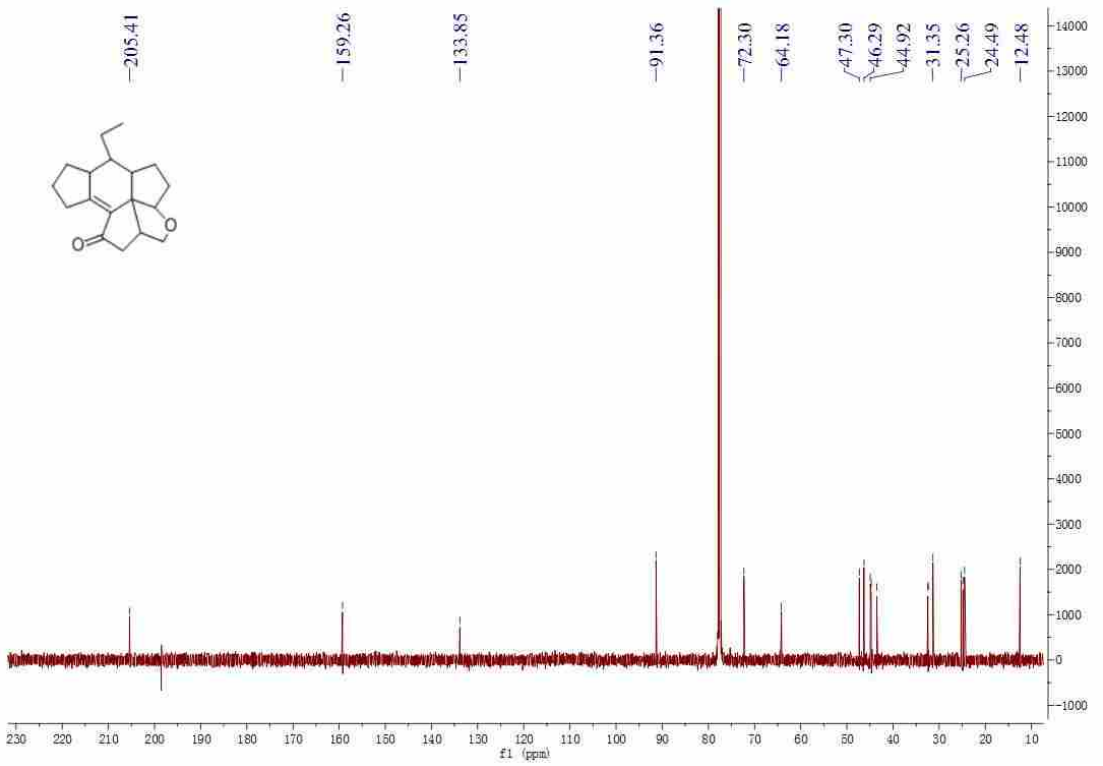

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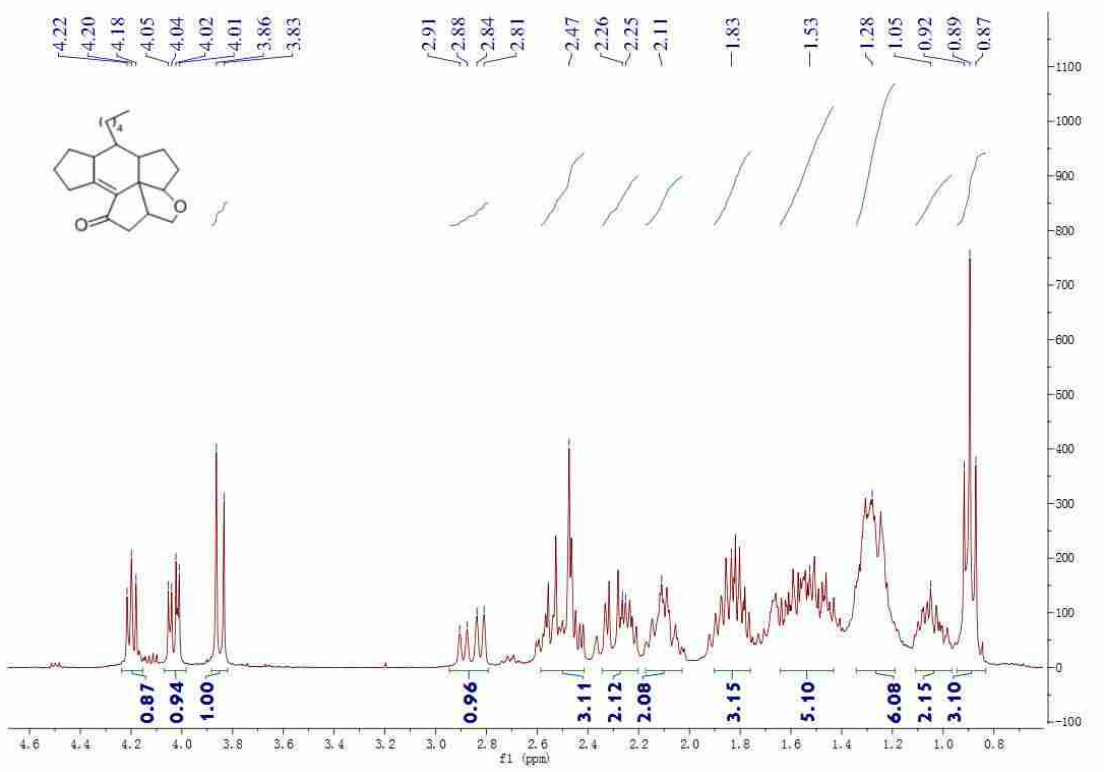

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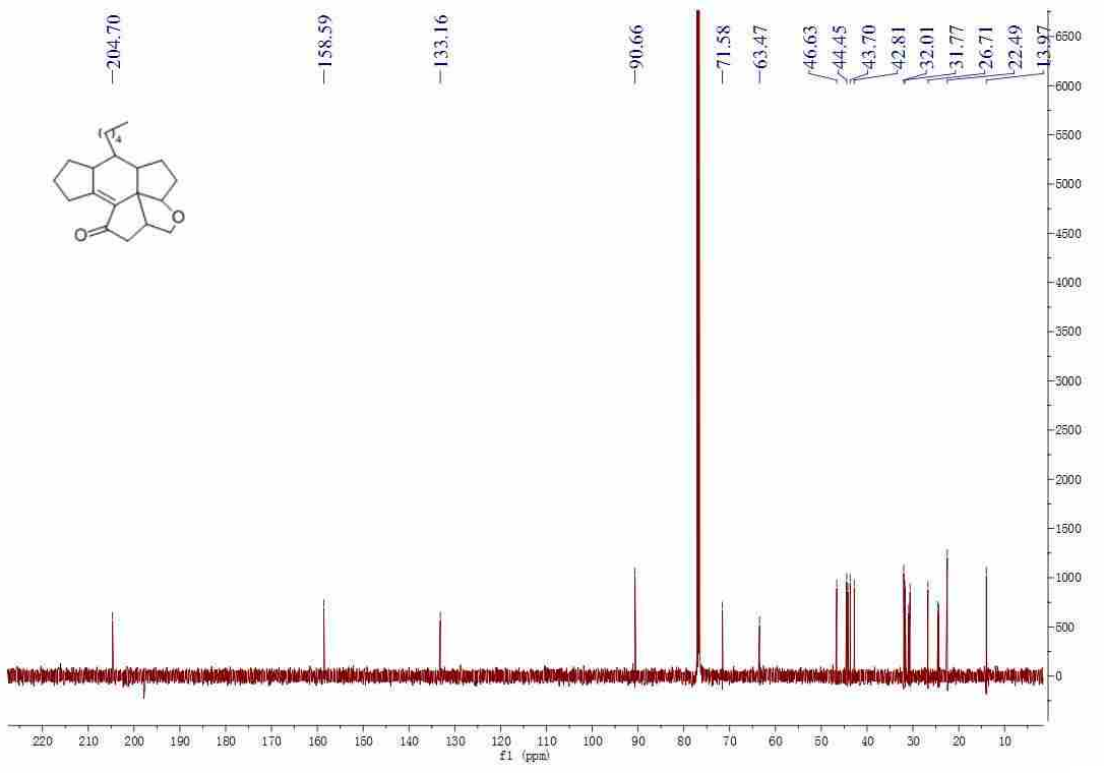

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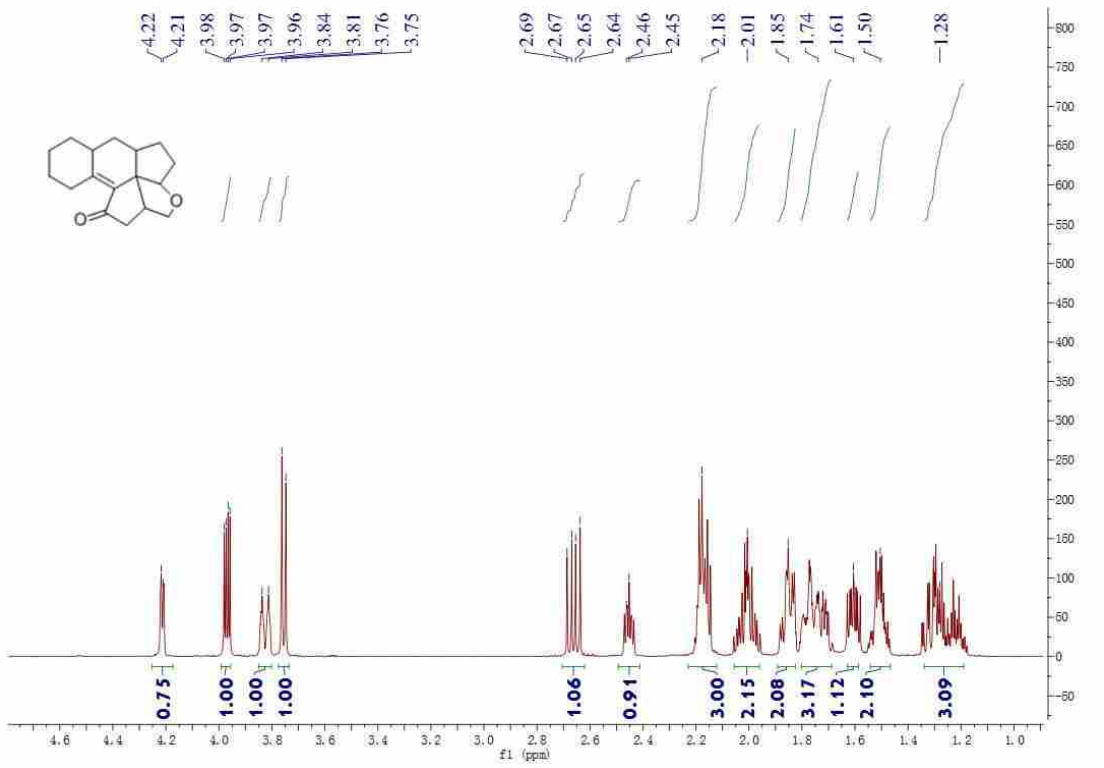

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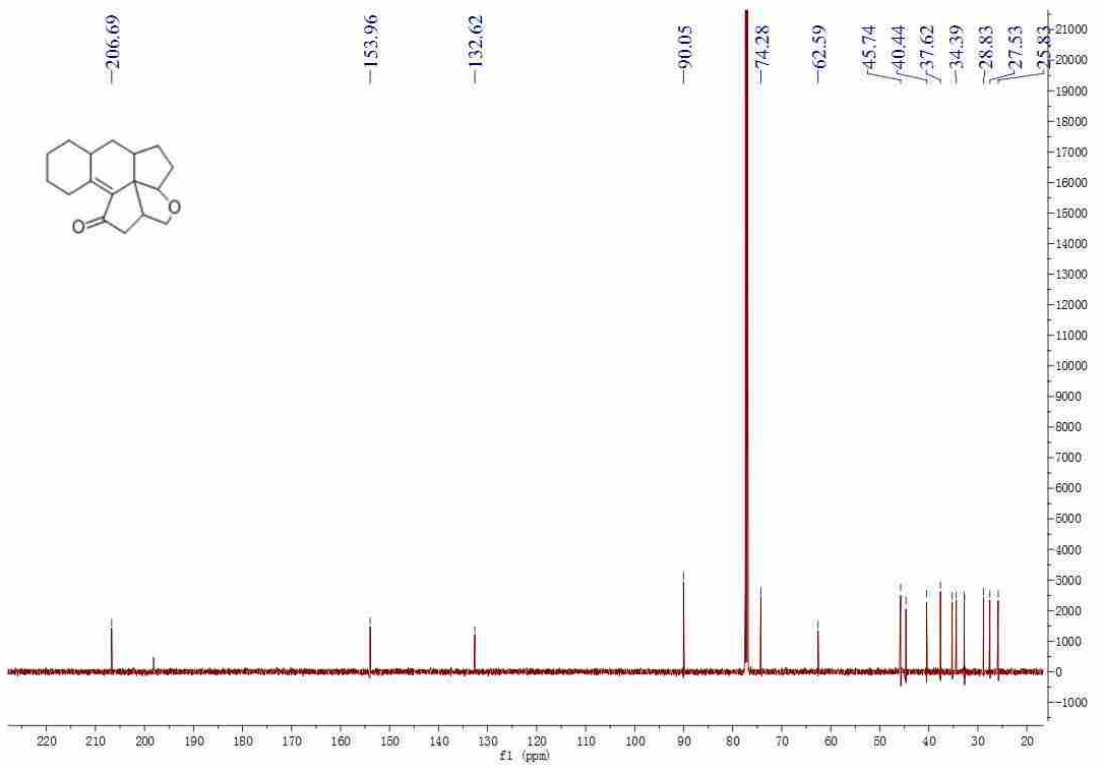

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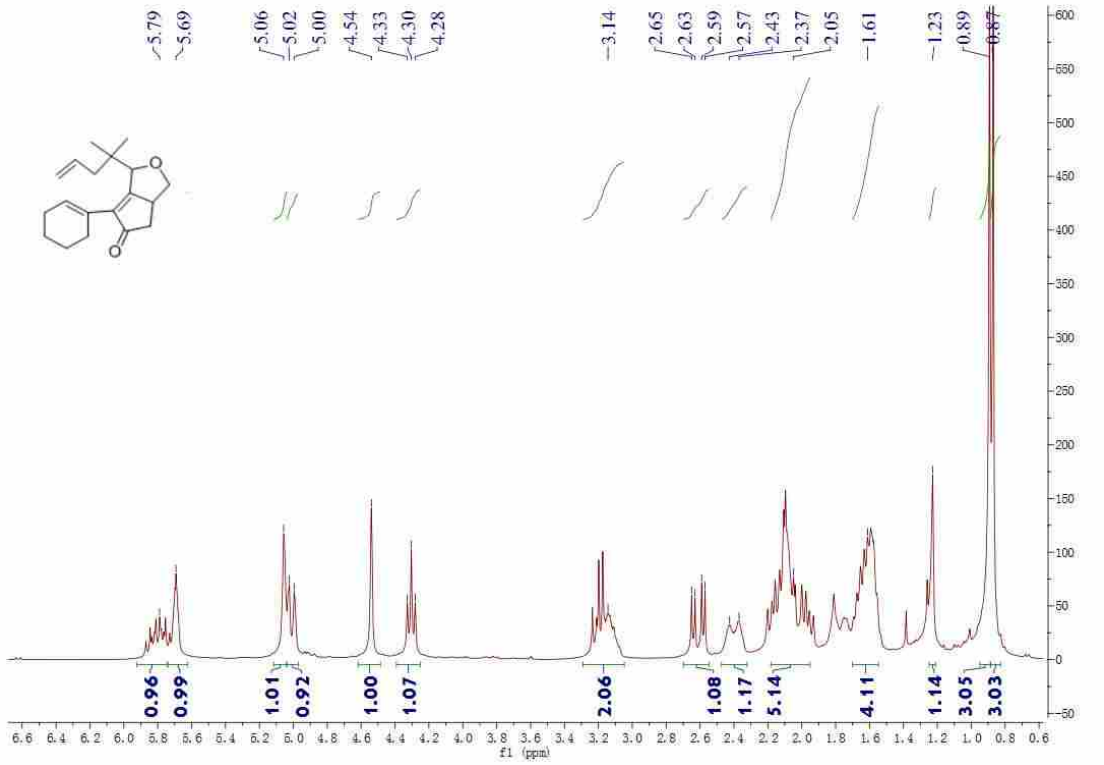

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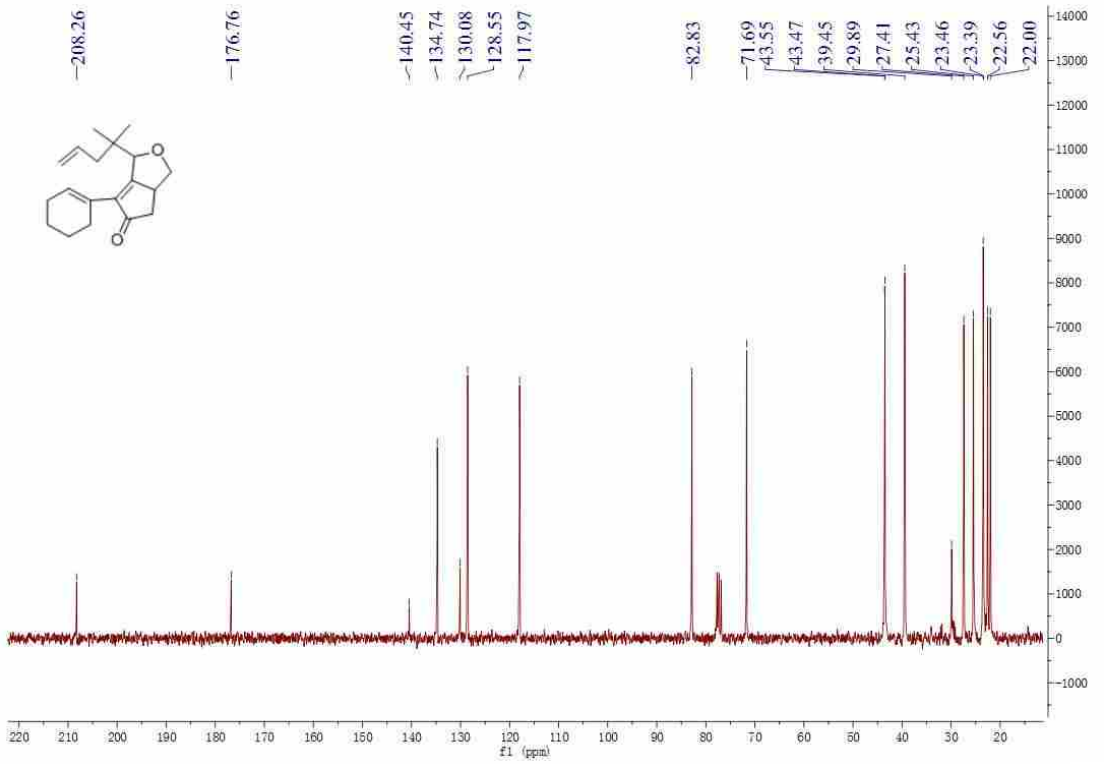

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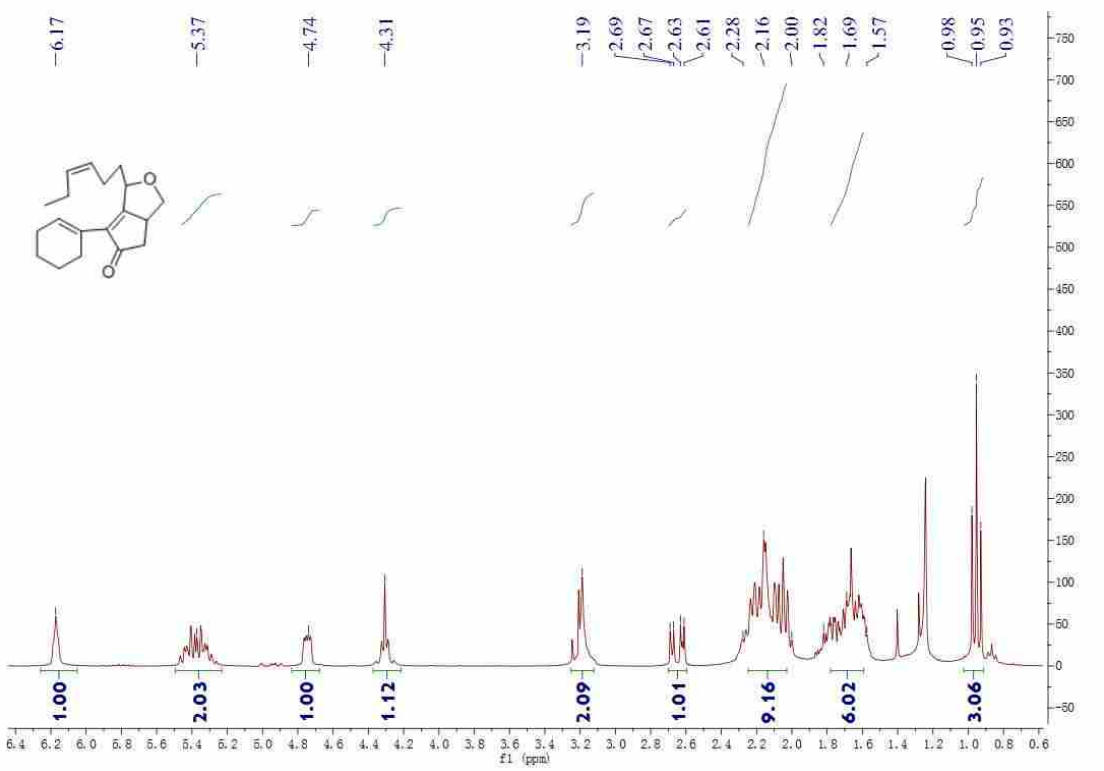

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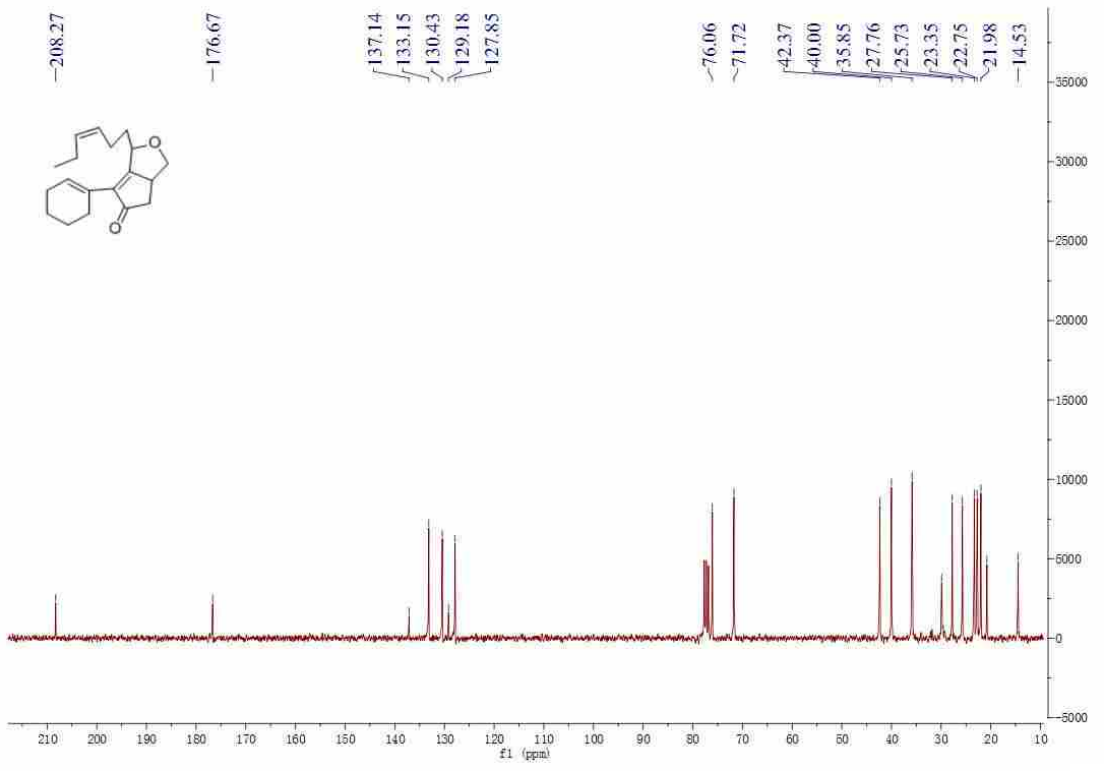

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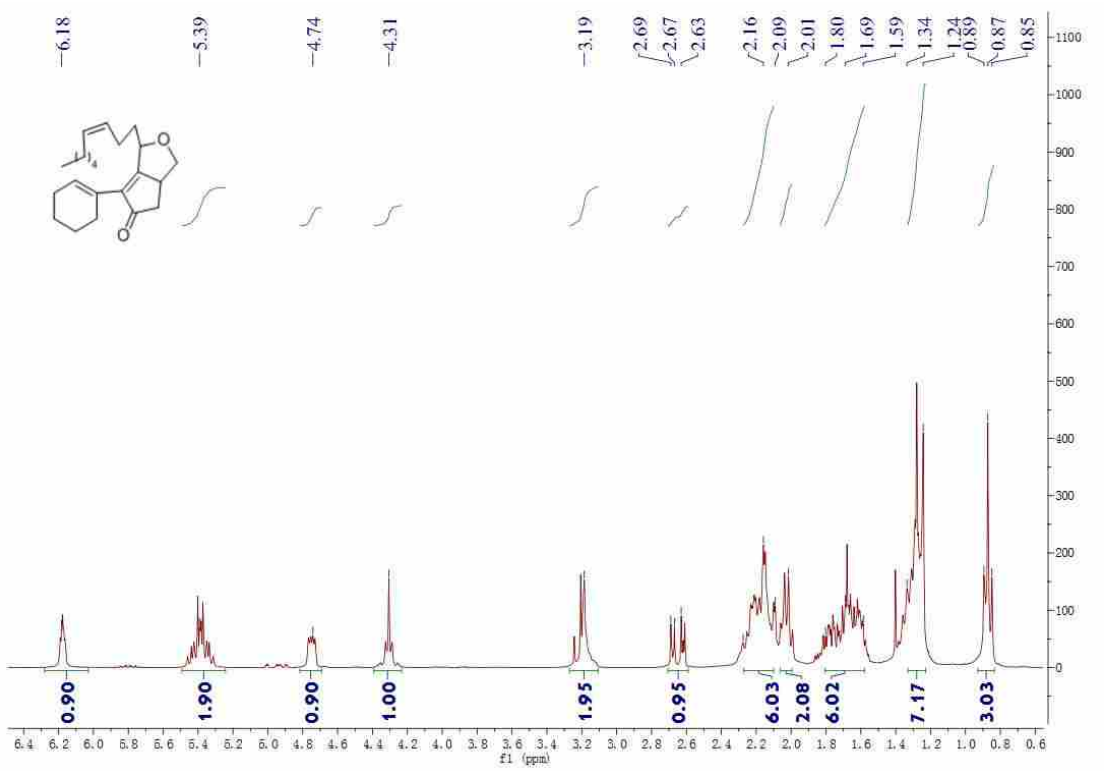

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