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Efforts Towards the Total Synthesis of Natural product Alkaloids (±) Lycorine and Gracilamine, Gold-Catalyzed Diene Formation, and Oxy-Cope/Ene/Claisen/Diels-Alder Reactions to form the Homo-Steroid Skeleton

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Efforts Towards the Total Synthesis of Natural Product Alkaloids (±) Lycorine and Gracilamine, Gold-Catalyzed Diene Formation, and Oxy-Cope/Ene/Claisen/Diels-Alder Reactions to Form the Homo-Steroid Skeleton

By

ANIK MICHELLE CHARTRAND

B.Sc. (Honors), University of Ottawa, 2007

A Thesis submitted to the School of Graduate Studies and Research in Partial Fulfillment
Of the Requirements for the Degree of Master of Science

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<<It is the time you have wasted for your rose that makes your rose so important.

Antoine de Saint-Exupery

À Johanne et Pierre....

Abstract

The *amaryllidaceae* family is an attractive source of alkaloids, which are valuable targets for total synthesis. This thesis describes the ingenious approach to the synthesis of two *amaryllidaceae* alkoids: (±)-lycorine and gracilamine. Utilization of the phenylbutadiene and pyrroline intramolecular push-pull Diels-Alder reaction for lycorine and of the intramolecular 1,3-dipolar cycloaddition for gracilamine is described. A route was developed to give access to advanced intermediates required for both syntheses. However the existing methodology did not fully accommodate the complete core structure of the targets.

Development of a new novel gold-catalyzed reaction is also depicted. A facile and quick method to generate dienes from propargylic acetates and pyvaloates has been developed. The scopes and limitations of this methodology are discussed. The application of the newly discovered $Au(PPh_3)Cl$ and acid catalyst system was examined.

Finally, we investigated the 1-alkynyl-2-vinyl-cyclohexanols for the formation of multi-cyclic skeletons found in natural products. Our goal was to develop a way to easily access the steroid and/or carbocyclic core in one tandem reaction sequence. To this end, the use of a tandem oxy-cope/Claisen/ene/Diels-Alder reaction was developed. The tandem oxy-Cope/Claisen/ene/Diels-Alder reaction can produce up to 9 contiguous stereogenic centers where two are quaternary. In addition, this domino process provides the steroid core possessing much exploitable functionality.

Acknowledgements

First, I would like to thank Dr. Louis Barriault for this amazing opportunity. During my undergraduate years, he was always there to guide me in the right direction, and to answer my many questions. His motivation and great competence in chemistry made working in his lab a wonderful learning experience. His projects have proven to be very motivating and interesting, making the last 3 years a great journey... His passion and commitment to his students makes Dr. Barriault a great professor and mentor, making him one of Ottawa University's greatest assets. Please accept my sincerest thank you, for having me in your lab; you dynamism, motivation, patience and passion for the world of chemistry was a key aspect in my flourishment as a chemist.

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Throughout my studies, I have met many incredible people, some of which I remain friends with today. The outings, parties, movie nights, in-depth conversations etc., were all instrumental in my success. I must acknowledge that my university years would not have been the same without the presence of Michelle. Although we had to part ways in third year, (damn biology!) you were always a phone call away when I needed encouragement, a night off from studying or even just a good laugh. Those first few years of university were truly the best for me.

It all goes without saying that my years in lab would not have been the same without my lab mates. I would like to thank Christiane for imparting on me some great technical

skills and for answering my many questions at the beginning on my degree. Thank you to my first bay partner, Maxime, we had some great talks, and my second bay partner, Francis, I will never forget you. Thank you to all the other graduate students that I encountered in the lab: Steve, Jason, Kass, Eric, Marie-Christine, Effiette, you all played an instrumental part in making this a great experience. I wish you all the best and great success in your future endeavors.

I would like to thank all the students who have worked for me: Anna, Anne-Catherine, and Byron. I hope that your time in the laboratory was as enriching for you as it was for me. During the last couple of years, I have had the opportunity to work with many other undergraduate students. Your presence made the lab a livelier and fun place to work (and sometimes dangerous :P). Thank you to all of you; Patrick, Gabriel, J-F, Joel) for all the laughs.

Finally yet importantly, I would like to thank all the technical support staff at the University of Ottawa (Dr. Glenn Facey, Cheryl McDowall and Prof. Clem Kasakoff)

Table of Contents

Schemes

Figures

Tables

Chapter 1

Introduction

1.1 Natural Product synthesis

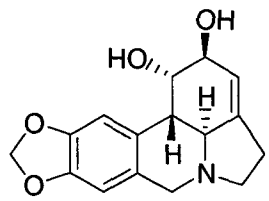
Natural product synthesis is the art and science of constructing the molecules of nature in the laboratory.[1] From the birth of the discipline in 1828 when Friedrich W□hler synthesized urea from ammonium cyanate, to its growth and advancements seen today as a powerful method for the development of complex molecules, the total synthesis of naturally occurring substances is without doubt the foundation and driving force of organic chemistry.[2] During the last century, the field of natural product synthesis has grown enormously: target size, complexity, efficiency, minimization of the number of steps etc.

Existing trends in the field include the synthesis of complex molecules using a minimal amount of steps, protecting groups, as well as performing multiple reactions in one pot to achieve the desired product. Such trends have been seen by Baran's protection group free total synthesis[3] of alkaloids hapalindol U and ambiguine H as well as Paquette's total synthesis[4] of (±)-pentalenene using the squarate ester cascade.

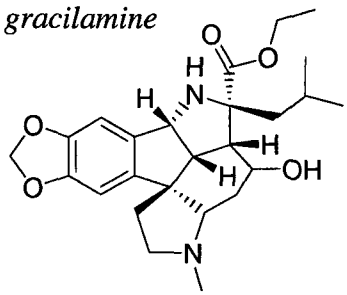
In spite of all the new synthetic methods developed in the last century, the total synthesis of natural products remains a challenge. One of the main difficulties is the formation of C-C bonds. The execution of such steps with high enantioselectivity and diastereoselectivity is an even greater challenge. Aware of such challenges we embarked on

a journey to construct such carbon-carbon bonds through the synthesis of two known *Amaryllidaceae* alkaloids: lycorine (**1.1**) and gracilamine (**1.2**).

***Figure 1.1**: lycorine and gracilamine*



1.1



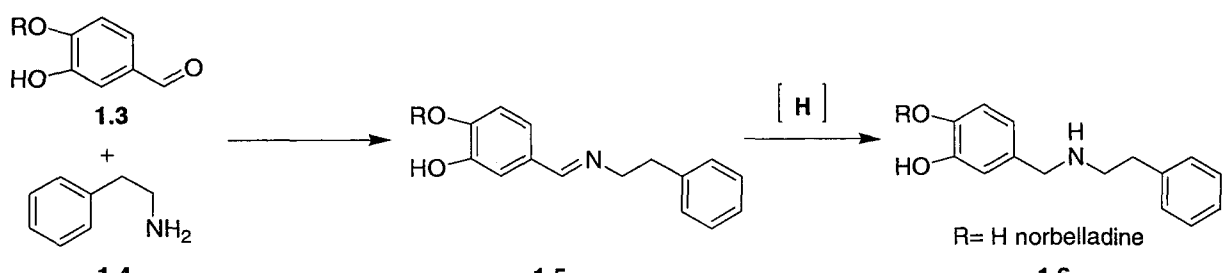
1.2

1.2 Amaryllidaceae Alkaloïds

Since the beginning of time, herbal medicine has been used in the treatment of disease. Many plant families have been investigated against various diseases in hopes of finding a therapeutic solution. Plants of the *Amaryllidaceae* family, including *ca.*65 genera and about 860 species, are amongst the top 20 in the most widely applied medicinal plant families.[5] A number of pharmacologically active compounds, including alkaloids, phenols peptides, etc., have been isolated and characterized from this family. *Amaryllidaceae* alkaloids are known for their potentially useful pharmacological properties such as analgesic[6], antiviral[7] and anti-neoplastic activities.[8,9]

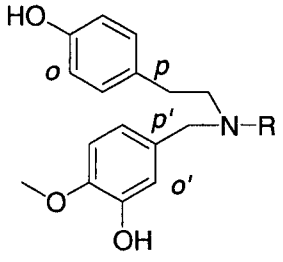
The *Amaryllidaceae* family of alkaloids is not only attractive for their bioactivities but they also prove to be an important target for total synthesis due to their unique structural architectures and limited supply in nature. They are believed to be biogenetically derived from norbelladine derivatives (**1.6**), which are produced in plants from aromatic aldehydes (**1.3**) and tyramine (**1.4**)[5] (Scheme 1.1).

***Scheme 1.1**: Biosynthetic pathway*



The biosynthesis of the wide variety of compounds that comprise the *Amaryllidaceae* family can then be accommodated by the biogenetic hypothesis that the carbon skeletons are produced by oxidative phenolic coupling. Node et al.[10] propose that the alkaloids are, in the metabolic pathway, synthesized at least by three different types of intramolecular phenol coupling. That is the coupling between the positions of *p-o'*, *p-p'*, and *o-p'* (phenol-*O*-methylcathecol) in the *O*-methylnorbelladine (**1.7**). For example, lycorine (**1.1**) is generated via the *o-p'* coupling and gracilamine (**1.2**) from the p-p' type coupling.

***Figure 1.2**: Structures of the Amaryllidaceae family of alkaloids*



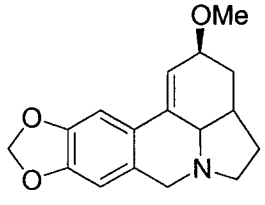
R=H : O-methylnorbelladine

1.7

1.2.1 Lycorine

Lycorine (**1.1**) constitutes up to 1% of the dry weight of daffodil bulbs and is considered to be the most abundant of the nitrogen bases of the *Amaryllidaceae*.[11] It was the first *Amaryllidaceae* alkaloid isolated in 1877 from Narcissus pseudonarcissus.[12] It is a toxic crystalline alkaloid found in several plant species, such as the bush lily (*Clivia miniata*), Lycoris, and Narcissus. The determination of the structure of this compound rests, in large measure, on the outstanding efforts of several Japanese groups started in the mid-1930s and which included degradation work whereby lycorine was converted into derivative (**1.8**).[13,14]

***Figure 1.3**: Degradation derivative of lycorine*

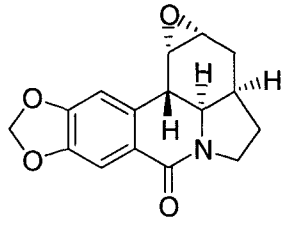


1.8

Lycorine (**1.1**) contains a ABCD tetracyclic α-lycorane core. It may be highly poisonous, if not lethal, when ingested in certain quantities but in lower doses is useful medicinally. For example, it is known to inhibit protein and DNA synthesis and was also found to inhibit mouse tumor cell apoptosis induced by polymorphonuclear leukocyte-derived calprotectin (EC_{50}= 0.1-0.5 μg/mL).[15] Lycorine is one of the most explored Amaryllidaceae alkaloids, and this not only because of its large range of potential biological activities[16] (antiviral[17], antineoplastic activity[18], growth inhibition in higher plants as well as in yeast[19] and an effective antifeedant activity[20]) but because it has been an attractive target to explore new synthetic methodologies.[21]

Various synthetic studies[22] have been directed towards the synthesis of lycorine (**1.1**). Unfortunately, most of the syntheses lead to the racemic form of the alkaloid.[23] In 1975 Tsuda and co-workers[23a] developed a relay type synthesis of the natural product were they were able to compare multiple intermediates, such as the epoxide intermediate (**1.9**), in their synthesis to the naturally occurring oxide that were available in good quantities from naturally occurring lycorine (**1.1**).

***Figure 1.4**: Tsuda and cowowers' epoxide intermediate*

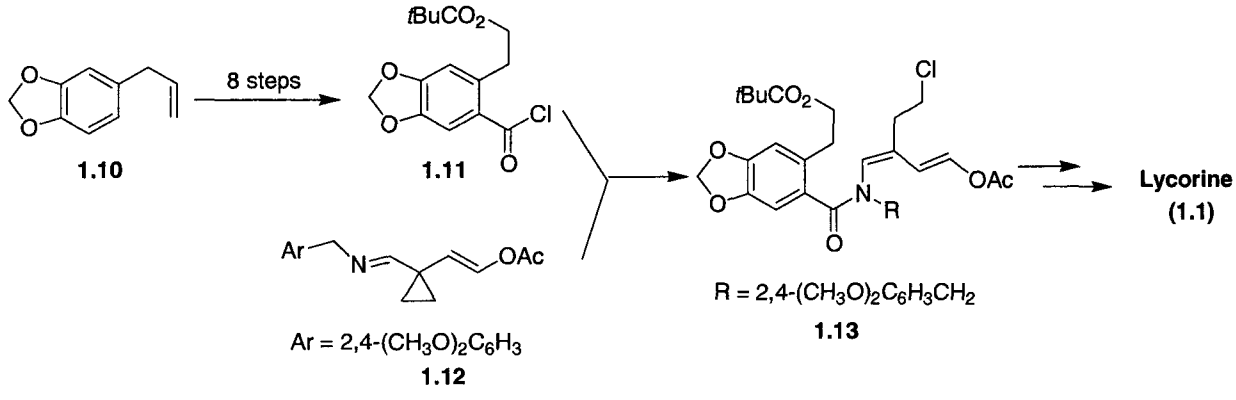


1.9

Boechmann and coworkers[23e] published an interesting route to the synthesis of (±)-lycorine (**1.1**) using the cyclopropyl acylinium ion rearrangement. The utilization of the rearrangement was useful in setting the right stereochemistry and oxidation state of the C ring substituents early in the synthesis; a process that proved lengthy and difficult in other approaches. Their thirteen steps synthesis, began with the elaboration of acyl chloride (**1.11**) from safrole (**1.10**) in eight steps. The key coupling/rearrangement was then done between the acyl chloride (**1.11**) and the imine cyclopropane (**1.12**) to give the (*Z,E*) dieneamine in a

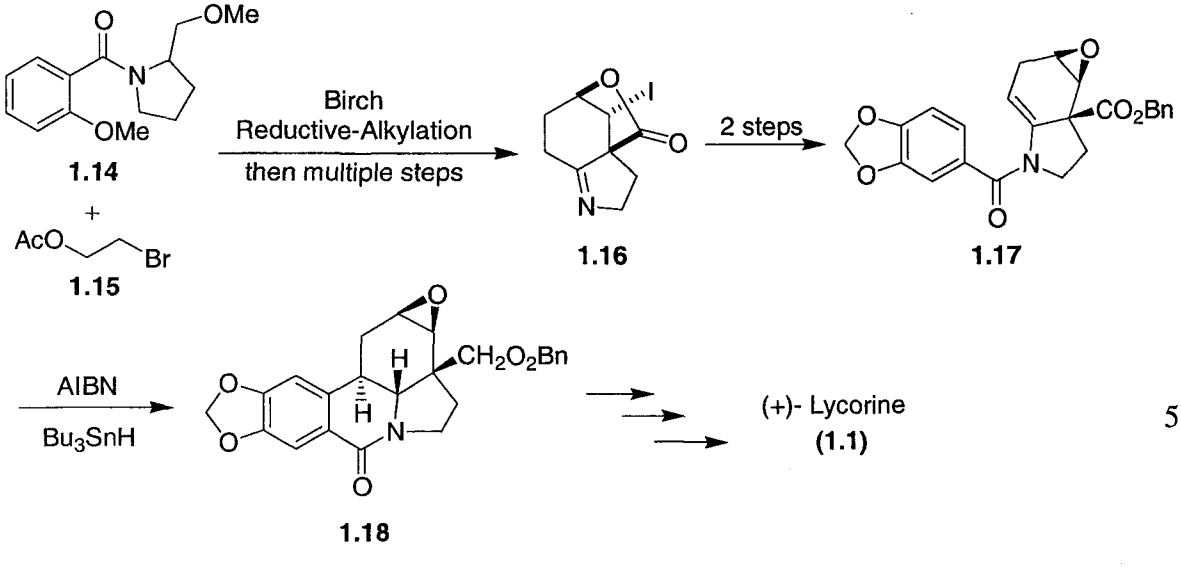
reasonable yield (56%). After isomerisation to the required (*E, E*) enamine and further separation, recycling and synthetic steps developed by Tsunda et al.[24] they achieved the synthesis of the (±)-lycorine (**1.1**) (Scheme 1.2).

***Scheme 1.2**: Boechmanns cyclopropyl acylium rearrangement*



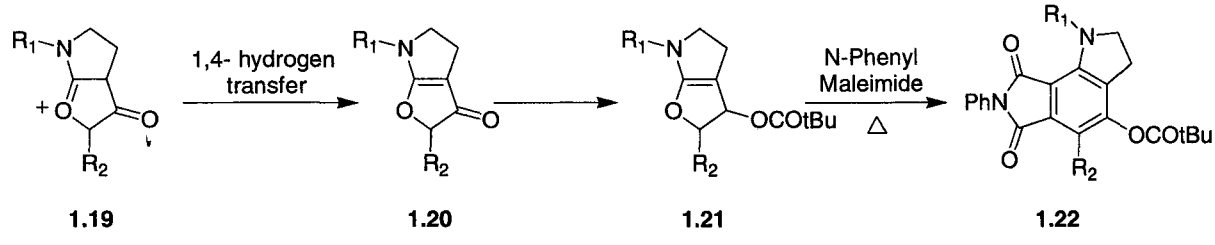
In 1996, Schultz and co-workers[25] reported the preparation of *ent*-lycorine and *ent*-1-deoxylycorine in thirteen to fifteen steps using the Birch-reductive alkylation of a chiral benzamide as a key transformation. The stereoselective formation of the C ring centered on the reductive alkylation of the chiral benzamide (**1.14**) with the two-carbon alkylation reagent (**1.15**) to give a 1,4-cyclohexadiene (**1.16**). Multiple synthetic steps to functionalize the substrate then followed. Closure of the BD ring was done by complete region- and stereoselective radical cyclization of (**1.17**).

***Scheme 1.3**: Schultz route to lycorine via the reductive alkylation*



Padwa and coworkers[22h] studied a different approach to the synthesis of lycorine. Although many approaches to the lycorine family dealt with intermolecular and intramolecular Diels-Alder reaction they sought out to develop the first example of a push pull carbonyl-ylide cycloaddition approach. Based on key retro-synthetic disconnections, they chose a disubstituted dipyrrolidinone core to generate a tricyclic intermediate. During the initial model study, they found that an intramolecular 1,4-hydrogen transfer occurred more readily then the expected inter- or intra-cycloaddition process (Scheme 1.4). Nevertheless, they envisioned the use of this new intermediate to perform a Diels-Alder reaction via an amido furan intermediate. This attractive approach to the total synthesis of lycorine has, to this day, never been published by the group, but was applied to other alkaloid synthesis.

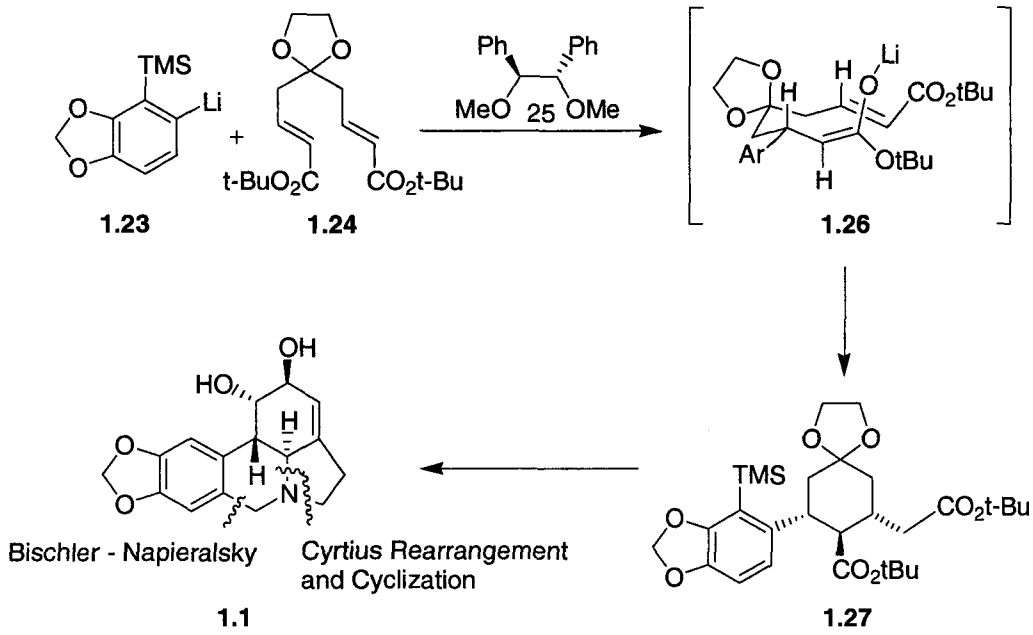
Scheme 1.4: *1,4-Hydrogen transfer and Diels-Alder reaction*



1.19 **1.20** **1.21** **1.22**

Recently, Tomioka and co-workers[26] described the first asymmetric total synthesis of (-)-lycorine using a chiral ligand-controlled cascade conjugate addition reaction.[14] There strategy includes the use of a chiral ligand (**1.25**) which mediates the conjugate addition reaction of aryllithium **1.23** in one pot to give the chiral cyclohexane intermediate **1.27**. Further steps to derive the lycorine skeleton include a Curtius rearrangement and cyclization, as well as a Bischler-Napieralski reaction with the symmetric Micheal acceptor (**1.24**) to afford, enantioselectively, the lithium enolate (**1.26**) which can the undergo a subsequent diastereoselective intramolecular Michael addition. This enabled the formation of two carbon-carbon bonds and tree stereogenic centers

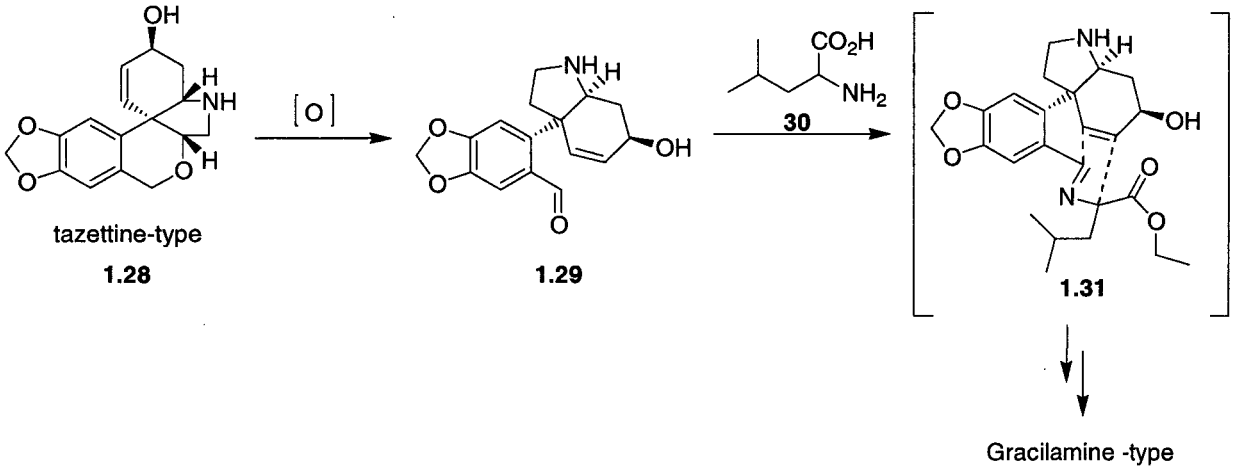
***Scheme 1.5**: Tamioka's total synthesis of (-)-lycorine using a chiral ligand-controlled cascade conjugate addition reaction*



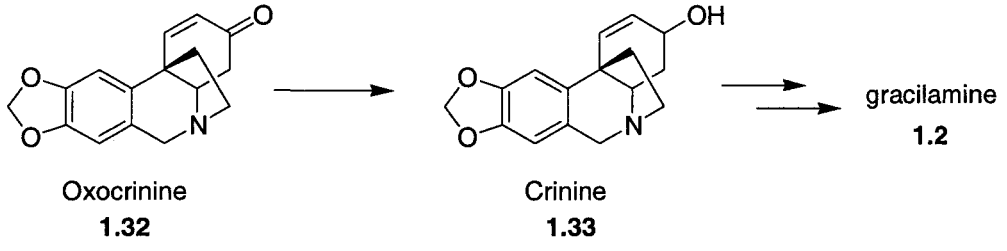
1.2.1 Gracilamine

The genus *Galanthus* of the *Amaryllidaceae* family has proven to be a promising source of alkaloids with diverse structures, which recently provided a novel subgroup, the graciline-type alkaloids.[5] In 2005, during the course of a phytochemical investigation on the species *G.gracillis*, a new member of the graciline subgroup of *Amaryllidaceae* alkaloids was identified. This novel pentacyclic dinitrous alkaloid, (±)-gracilamine (**1.2**), was characterized by Ünver and Kaya.[27] To date, (±)-gracilamine (**1.2**) has yet to be synthesized.[28] A common feature shared by the majority of the compounds in this family is the above mentioned pentacyclic dinitrogenous skeleton; as such, the biogenic pathway to (±)-gracilamine (**1.2**) parallels that of other *Amaryllidaceae* alkaloids. Ünver and Kaya[27] stipulated that (±)-gracilamine's pentacyclic skeleton was produced by oxidative opening of a tazettine-type alkaloid (**1.28**) to form an aldehyde (**1.29**), followed be a cyclization with the amino acid leucine (**1.30**) (Scheme 1.6). It has also been proposed that (±)-crinine (**1.33**), a derivative of (±)-oxo-crinine (**1.32**), is a possible intermediate in the biogenic pathway to (±)-gracilamine (**1.2**) (Scheme 1.7).

***Scheme 1.6**: Proposed biosynthetic pathway for gracilamine*

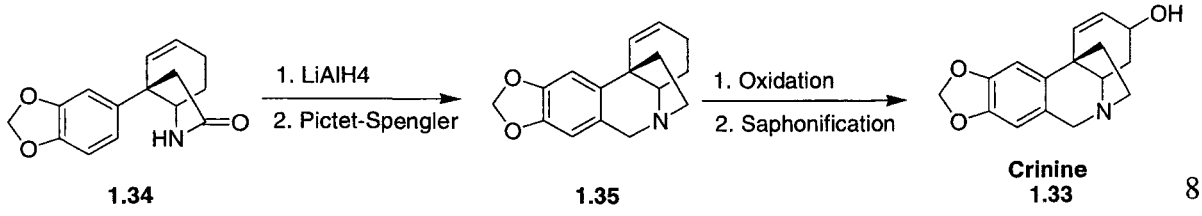


***Scheme 1.7**: Other proposed biosynthetic pathway to gracilamine*



The synthesis of (±)-oxocrinine (**1.32**) is well documented.[29] The first synthesis of (±)-oxocrinine (**1.32**) was reported in 1966.[28a] Lactam **1.34** was reduced with lithium aluminium hydride followed by a Pictet-spengler cyclization to (±)-α-desoxycrinine (**1.35**). This intermediate is oxidized with selenium dioxide followed by saphonification of the resulting acetate to give (±)-crinine (**1.33**); further oxidation with chromium trioxide-pyridine affords oxocrinine (**1.32**).

***Scheme 1.8**: First synthesis of crinine and oxo-crinines*

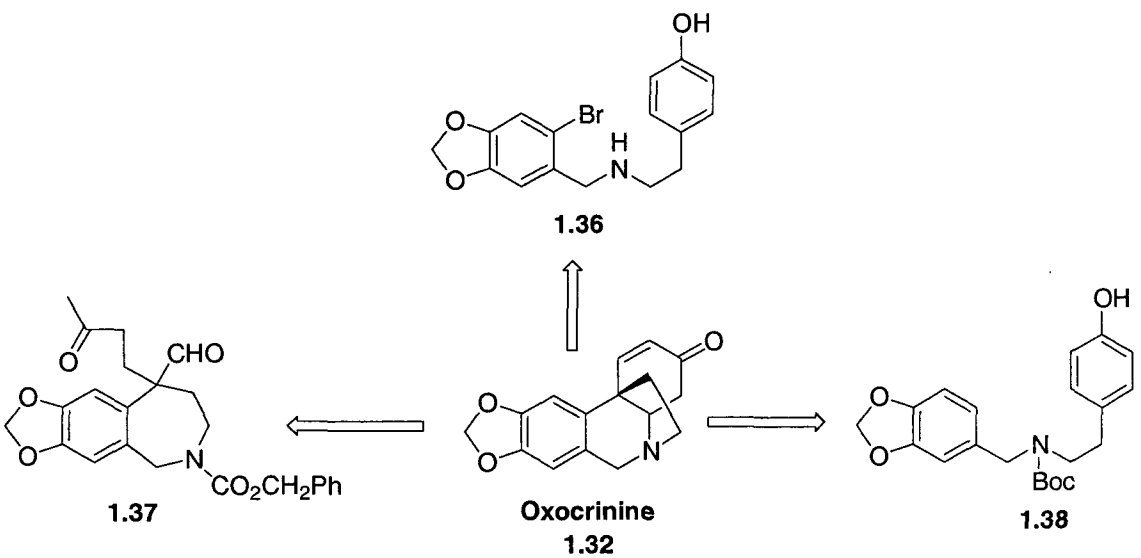


In 1971, a one-step synthetic method for the isoquinoline crinine ring system via protochemical intramolecular cyclization of bromo-aromatic compounds **1.36** (Figure 1.5) was published by Fukumoto and coworkers.[28b] This method, however, is not a viable route to the natural product due extremely to low yields (3.3 %).

Subsequent syntheses focused on the cyclization of precursors containing rings B and C, in order to simplify the synthesis of the spirocyclohexadienone system. Sanchez et al.[28c] proposed a route, where keto aldehyde **1.37** (Figure 1.5) is cyclized and dehydrated to a 5,10-ethanophenanthridine intermediate, which undergoes an intramolecular 1,4-addition of the secondary amine to the spiro enone system to afford (±)-dihydrooxocrinine, following, the removal of the N-(carbobenzoxy) protecting group, under boron trifluoride catalyst. Despite the good yields of these two steps, 85% and 92% respectively, the synthetic of this precursor to (±)-oxocrinine consist of 11 steps.

The most efficient method to obtain the (±)-oxocrinine, is based on the intramolecular oxidative phenol coupling of protected amine **(1.38).**[28d-f] Oxidation of the phenol moiety can be achieved with a variety of oxidizing agents. An example seen in Figure 1.5 uses a phenyl iodide(III)bis(trifluoroacetate) reagent to do the phenol coupling on molecule **1.38.**[10]

***Figure 1.5**: Pathways to the synthesis of (±)oxo-crinine (1.32)*



For the purpose of this synthesis of (±)-gracilamine (**1.2**), we chose the latter approach to the synthesis of oxocrinine.

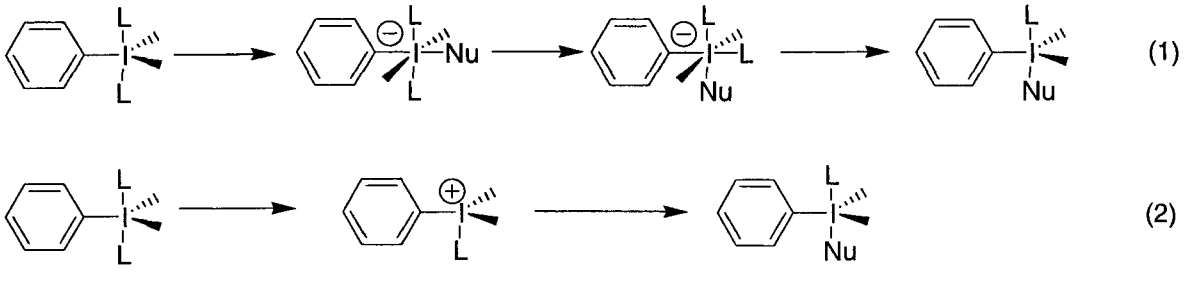
1.3 Phenol coupling using phenyliodine (III) bis(trifluoroacetate)- PIFA

Intramolecular oxidative phenolic coupling reactions are important key steps in the biosynthesis of many natural products.[30] A number of biogenetic-type phenolic coupling reactions have been investigated using heavy metallic oxidizing reagents such as Ti^{III} or V^{V} salts.[31] These reagents are, however, highly toxic and care must be taken in handling them. To solve these problems, oxidative phenolic coupling reactions using hypervalent iodine(III) reagents, which are safe and useful synthetic reagents, were examined and developed by Kita and coworkers.[32]

Phenyl iodide(III) bis(trifluoroacetate), PIFA, is a trivalent iodine compound with reactivity trends similar to those of heavy metal reagents and anodic oxidation.[32] This reagent has a pseudotrigonal bipyramidal geometry: the central iodine atom has a partial positive charge, while the oxygen atoms of the two trifluoroacetate ligands carry partial negative charge.

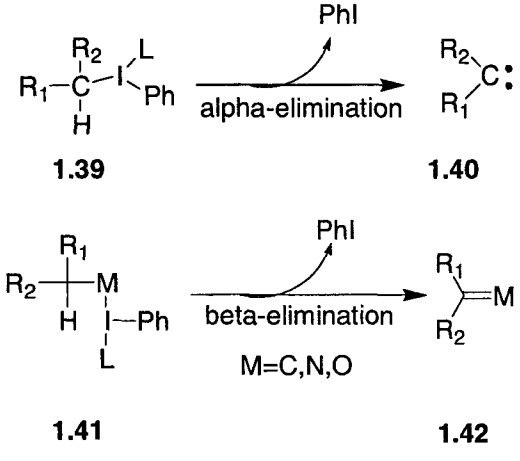
The mechanism for the PIFA mediated oxidation can be divided into two steps: ligand exchange and reductive elimination. In the first step, one of the two heteroatoms ligands is liberated by the addition of a nucleophile. The ligand exchange can occur in either an associative or dissociative fashion (Figure 1.6). No experimental results are available to indicate that the dissociative pathway (eq.2) is a viable mechanism for this process; this may be due to the highly energetic nature of the iodonium intermediate. Examples of intermediate species of associative ligand exchange have been isolated and characterized.[33]

***Figure 1.6**: Associative (1) and dissociative (2) pathways for ligand exchange of trivalent iodine compounds*



The second heteroatom ligand is expelled during the reductive elimination step, where a β- or α-proton is removed to afford the oxidation product, and the trivalent iodine is reduced to its monovalent state (Scheme 1.9). This reaction is not catalytic and the oxidizing agent is degraded to TFA and iodobenzene, which can be recycled to PIFA thus minimizing the waste generated.[34]

***Scheme 1.9**: α- and β- reductive elimination of the trivalent iodine species*



1.39 **1.40**

1.41 **1.42**

Our strategy for the synthesis of lycorine (**1.1**) and gracilamine (**1.2**) described herein, is to follow a route that parallels the biogenic pathway to the natural product. Thus, a biomimetic pathway was envisioned. This strategy comprises the use of a phenolic coupling in both syntheses as part of the formation of the core of the molecules.

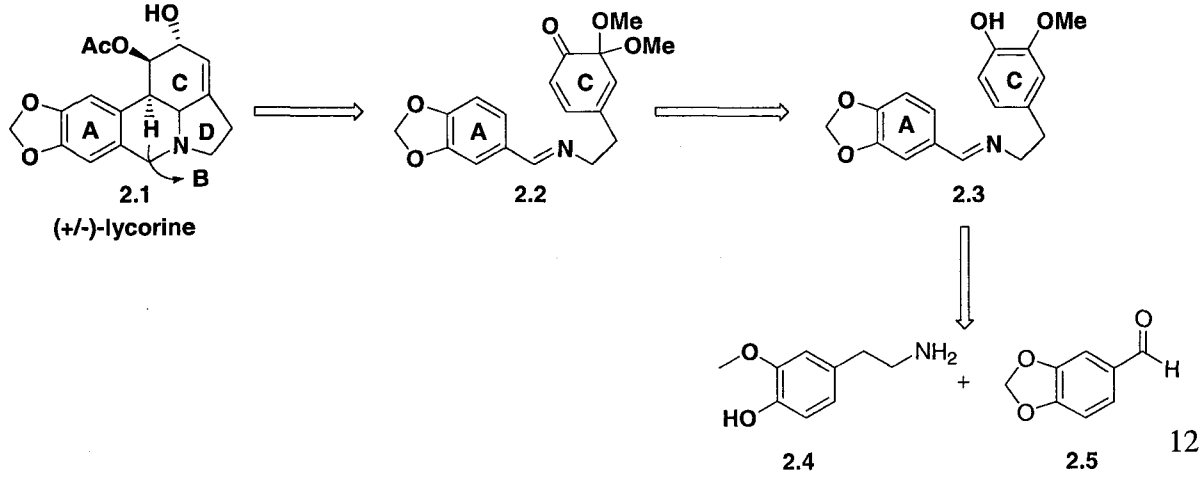
Chapter 2

Towards the Synthesis of (±)-Lycorine

2.1 First Attempt Towards the Synthesis of Lycorine

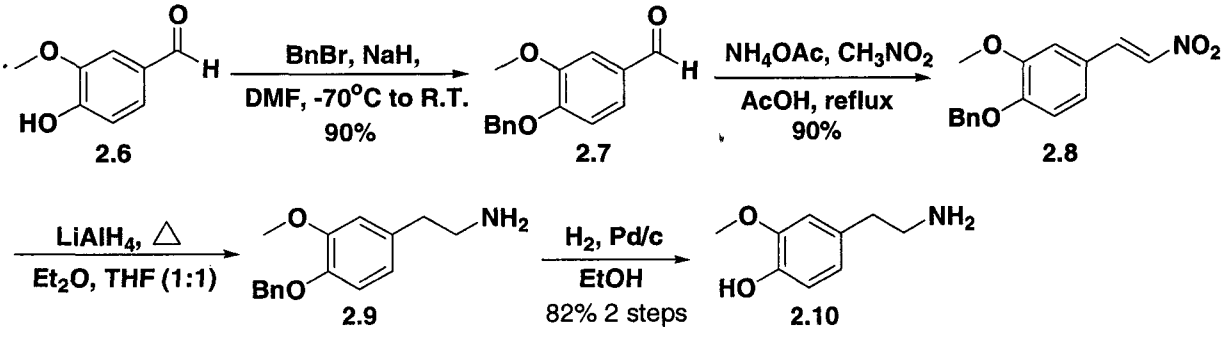
Our retrosynthetic outline is shown in Figure 2.1, where the B cycle would be closed via a [4+2] cycloaddition reaction between the A and C cycle. The diene **2.2** for this reaction would be formed via a phenolic oxidation of **2.3**. Compound **2.3** would come from a condensation of the tyramine like derivative **2.4** and piperidine **2.5**.

***Figure 2.1**: Retrosynthetic outline of plan #1*



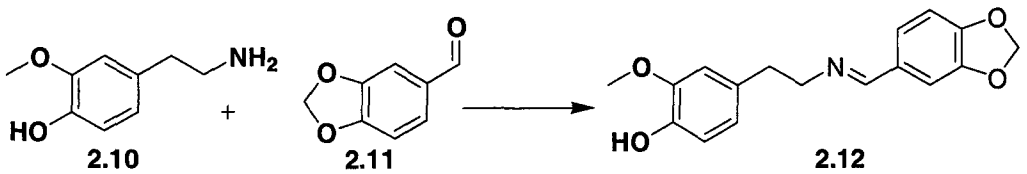
To start the synthesis we first need to construct the tyramine-like intermediate **2.10**. To accomplish this we commenced by benzylating vanilline **2.6** to give **2.7** in a 90% yield. We were then able to work construct the amine portion of our molecule by reacting the aldehyde with CH_3NO_2 and NH_4OAc[35] to give the nitro compound **2.8** in a 90 % yield. Intermediate **2.8** was then reduced using lithium aluminum hydride in refluxing conditions[34] and deprotected with hydrogen and the palladium on carbon catalyst to give our desired tyramine-like intermediate **2.10**. Previous conditions tried to do this reduction were the use of DDQ in a 18 to 1 solution of DCM and H_2O[36], and refluxing ammonium formate in MeOH with Pd/c.[37] The use on DDQ degraded our compound, while the use of ammonium formate gave the desired product in a quantitative yield. We decided to use the H_2 gas over the ammonium formate because the reaction was much cleaner by NMR.

Scheme 2.1** : Formation of the tyramine-like intermediate **2.10



The next step was the coupling of piperonal (**2.11**) and **2.10** to give the enamine **2.12**. Many conditions were explored[38] as seen in Table 2.1. We first refluxed the mixture in MeOH containing dry molecular sieves to trap the H_2O formed during the reaction (entry 1). Unfortunately, the reaction did not proceed accordingly and no product was formed. A variety of solvents were also used, in combination with various drying agents, while refluxing in a Dean-Stark apparatus (entries 2-7). Unfortunately, the reactions did not go to completion. In fact, we obtained, at most, a 50 % conversion to the product by NMR. It seems that the water formed in situ was not trapped resulting in equilibrium between the desired product and coupling reagents.

Table 2.1**: Coupling of piperonal and amine **2.11



2.10 2.11 2.12

Entry	Solvent	Drying agent	Conditions	Product[b]
1	MeOH	4A mol sieves	reflux[a]	50%
2	MeOH	$MgSO_4$	Dean-Stark	50%
3	Toluene	N/A	Dean-Stark	50%
4	Toluene	4A mol sieves/$MgSO_4$	Dean-Stark	50%
5	Benzene	N/A	Dean-Stark	50%
6	DCM	4A mol sieves	Dean-Stark	50%
7	DCM	4A mol sieves/$MgSO_4$	Dean-Stark	50%

[a] Only condition that did not yield any product. [b] 1:1 Mixture of 2.11 and 2.12

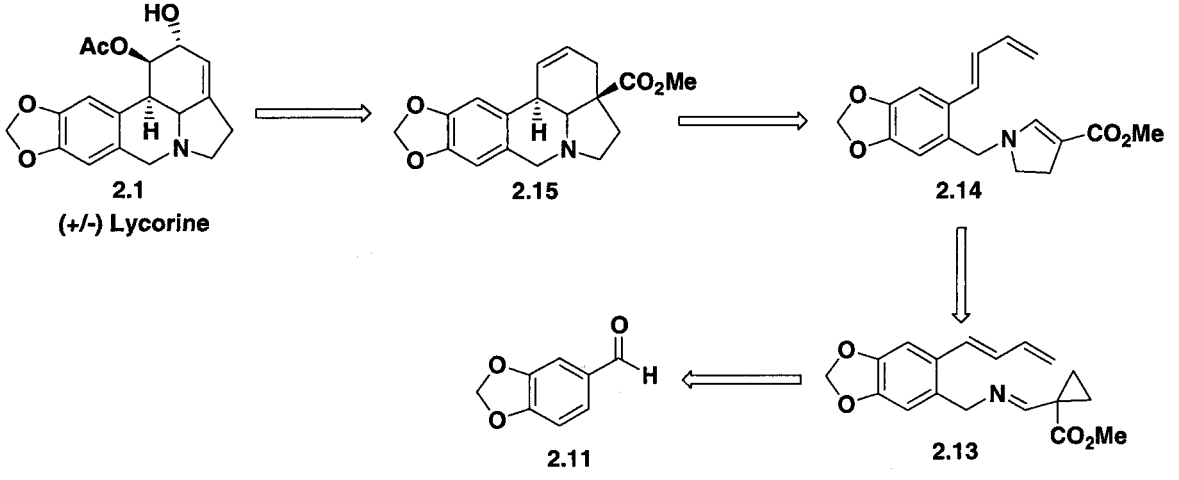
Despite our low conversion to the enamine **2.12**, we decided to separate the mixture. Unfortunately, the separation was not possible; hydrolysis of the enamine to the starting material was always observed. We then opted to move on with our mixture and try the phenolic oxidation step using PIDA at –78°C in DCM to create our diene, which would be perfectly aligned for the subsequent cycloaddition. Two attempts were made, and by NMR it seemed that there might be some product formation. Alas, too much piperidine left over from the previous step and the presence of the labile enamine moiety, made the optimizing task difficult forcing us to review our synthesis plan.

2.2 Second Attempt Towards the Synthesis of Lycorine

The new plan consists of a 12-step synthesis, starting with the commercially available piperonal (**2.11**). We envisaged that piperonal (**2.11**) would be functionalized to give the cyclopropane- containing compound **2.13,** which could undergo a cyclopropyl iminium ion rearrangement to give the 2-pyrrolidine intermediate **2.14**. The pyrrolidine moiety is functionalized in a way to act as a push pull dienophile and undergo a intramolecular [4+2]

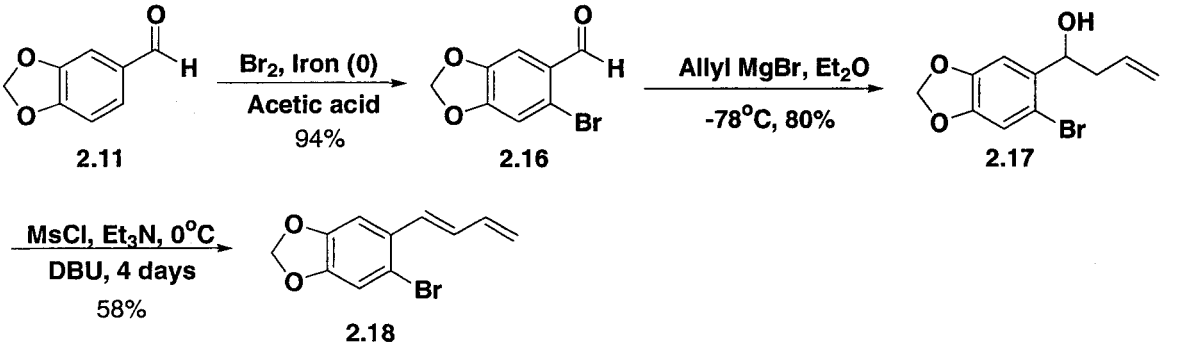
cycloaddition reaction. This would complete the pentacyclic core of lycorine (**1.1**) to give **2.15**, which would be an attractive precursor for lycorine **2.1**.

Figure 2.2: *Retrosynthetic outline of plan #2*



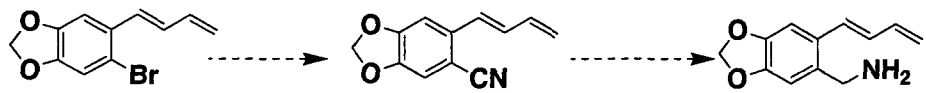
The synthesis started by bromination of the commercially available piperonal (**2.11**) using Iron(0) and Br_2 in glacial acetic acid[39] to give **2.16** in a 94% yield after re-crystallization. The brominated piperonal (**2.16**) was then alkylated with the allyl magnesium bromide Grignard reagent[40] to give **2.17** in 80% isolated yield. We latter was treated with MsCl, Et_3N and DBU, as reported by Danishefski et al.[36], to give the corresponding diene **2.18** in a 58 % yield.

Scheme 2.2: *Formation of the Diene*



Our next goal was to generate the benzylic amine **2.20** directly from the bromine intermediate **2.18** using copper cyanide (Scheme 2.3). Three different sets of conditions [41] were tried but only starting material was observed: i. CuCN, DMF, 80°C, 16 hrs ; ii. CuCN, DMF, 100°C in the microwave (250 psi), 20 min.; and iii. CuCN, DMF, 100°C in the microwave (250 psi), 60 min.

Scheme 2.3: *Benzylic amine formation using copper cyanide*



2.18 **2.19** **2.20**

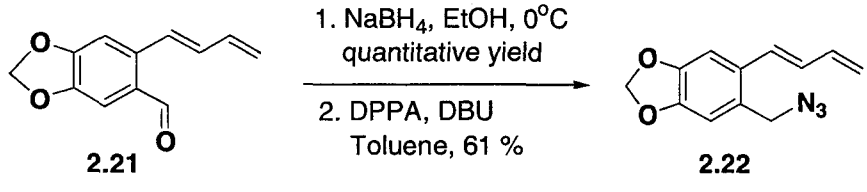
Based on these results, we contemplated the generation of the benzylic amine via the formation of the aldehyde generated by a metal halogen exchange. All the conditions tried to form the aldehyde **2.21** are listed in Table 2.2. Our first attempt was using *t*-Buli at -78°C. The reaction was stirred for 45 minutes before adding DMF and then the reaction mixture was let warmed to room temperature and worked-up. Because of the low yield and high amounts of degradation observed, we tried the reaction at -40°C, in two different solvents, without letting the reaction warm to room temperature (entry 2 and 3). To our dismay, both attempts provided degradation products. Attempted to generate the benzylic alcohol by addition of paraformaldehyde[42], instead of DMF, were not fruitful (entry 4-6). Various other reactive electrophiles where tried (methyl chloroformate and dimethyl carbonate) in combination with different nucleophiles at various temperatures (entry 7-10) but our attempts lead us to the recovery on starting material or degradation product. It was thought that by having the reaction proceed at a lower temperature and on a longer time period we would diminish the amount of degradation and formation of protonated benzene (entries 11-13). To prevent the formation of the protonated benzene we used DMF distilled on $MgSO_4$[43] where the fresh distillate was collected in a flame-dried flask also containing a little amount of $MgSO_4$. The mixture of the freshly distilled DMF/$MgSO_4$ solution was then added via cannula to the reaction mixture to give the desired aldehyde **2.21** (R=H) in and optimized reaction yield of 81% (entry 13).

***Table 2.2**: Formation of the aldehyde-type intermediate*

Entry	Metal Halogen Exchange	Temperature	Quench	Result
1	*t*-BuLi (2eq), THF	-78°C	DMF	27 %
2	*t*-BuLi (2eq), Ether	-40°C	DMF	Degradation
3	*t*-BuLi (2eq), THF	-40°C	DMF	Degradation
4	*n*BuLi, THF	-78°C	Paraformaldehyde	S.M and Protonated benzene
5	Mg, THF,	65°C	Paraformaldehyde	Protonated benzene
6	*t*-BuLi, THF	-78°C	Paraformaldehyde	Degradation
7	*t*-BuLi, THF,	0°C	Dimethyl carbonate	S.M
8	*t*-BuLi, THF,	0°C	Methyl chloroformate	S.M
9	Mg, THF,	65°C	Methyl chloroformate	S.M
10	Mg, THF,	65°C	Dimethyl carbonate	S.M
11	*t*-BuLi (2eq), THF	-90°C to -100°C	DMF	46- 50 %
12	*t*-BuLi (2eq), THF	-90°C to -100°C	Paraformaldehyde	Protonated benzene
13	*t*-BuLi (2eq), THF	-90°C to -100°C	DMF + $MgSO_4$	81%

Having the aldehyde **2.21** (R=H) in hand, we were now ready to convert it to the benzylic amine. First, a reductive amination reaction using NH_2OH/HCl in methanol and water[44] was performed. Unfortunately, no desired product was observed, only starting material was recovered. Based on this result, we envisaged the formation of the benzylic amine **2.23** via reduction of the azide moiety. To this end, the aldehyde was reduced to the corresponding alcohol, followed by treatment with DPPA[45] to give the desired product in a moderate yield of 61% (Scheme 2.4).

***Scheme 2.4**: Azide formation using DPPA*



Many conditions were tried[46] to reduce the azide to the benzilic amine as seen in Table 2.3. Unfortunately, entries 1-6 gave little or no desired product. When treating the azide with a source of tin hydride (entry 7) in refluxing benzene, we were pleased to isolate the desired amine in a 57 % yield.

***Table 2.3**: Reduction of the Azide*

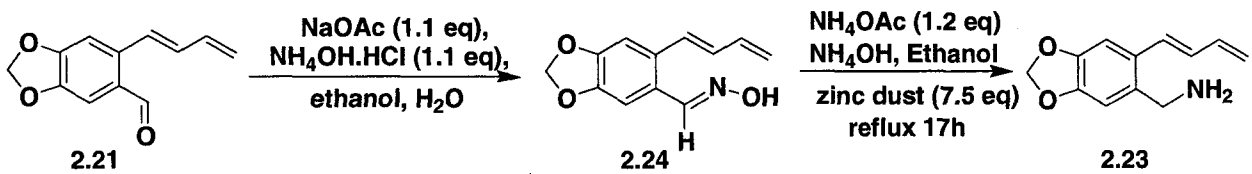
2.22 **2.23**

Entry	Reagent	Yield (%)
1	PPh_3, H_2O, 0°C, 3days	S.M.*
2	PPh_3, H_2O, R.T, 3days	S.M.*
3	$(t\text{-Bu})_3P$, Et_2O, R.T	S.M.*
4	$LiAlH_4$, THF, 0°C to R.T 1.5 hrs	10
5	$NaBH_4$, MeOH/*i*-PrOH, 0°C, 2.5hrs	S.M.*
6	PBu_3, THF, H_2O_2, reflux, $_2$hours	S.M.*
7	*n*-BuSn-H, benzene,reflux, O.N	57

* Only S.M was observed by ^1H NMR of crude

At the same time some milder conditions were being tested (Scheme 2.5); formation of the amine via the oxime **2.24**.[47] Pleasingly, this new milder conditions provided us with the benzylic amine 54 in a 97% yield over 2 steps.

***Scheme 2.5**: Benzylic amine formation via oxime*



2.21 **2.24** **2.23**

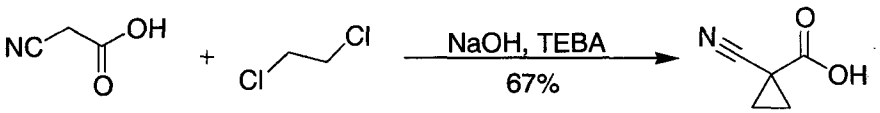
The next step of the synthesis consists of a coupling reaction of the benzylic amine **2.23** and the cyclopropyl substrate **2.25**. To this end, the synthesis of ethyl 1-formylcyclopropanecarboxylate (**2.25**) was attempted.

***Scheme 2.6**: Coupling of the cyclopropyl moiety and the benzyl amine*

2.23 **2.25** **2.13**

We envisioned creating the 1-cyanocyclopropanecarboxilic acid **2.28**, which would then be reduced to the 1-formylcyclopropylcarboxylic acid. The latter, could be easily converted to the ester **2.25**. We started by trying reaction conditions published by Danishefsky et al.[48] where they used ethyl cyano acetate in combination with sodium hydroxide, the di-halogen alkyl and trietylbenzylammonium chloride (TEBA - phase transfer agent). The cyclopropane **2.28** was isolated in a 67% yield.

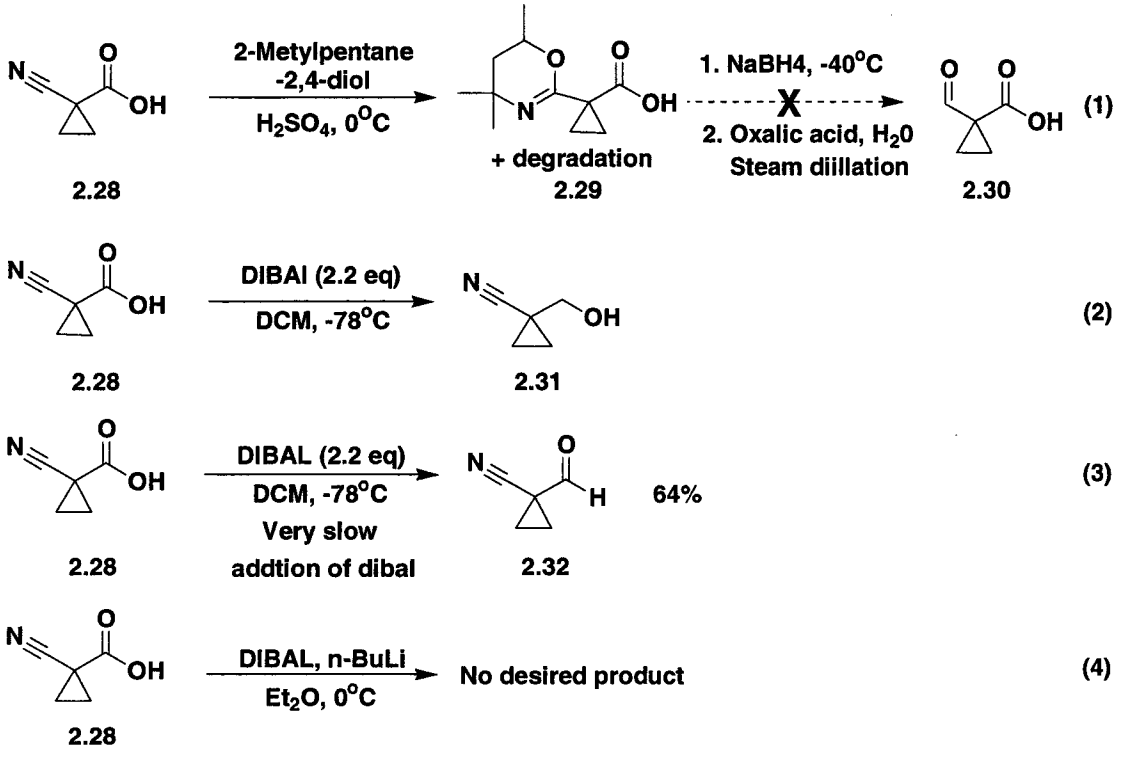
Scheme 2.7**: Synthesis of 1-cyanocyclopropanecarboxilic acid **2.28



2.26 **2.27** **2.28**

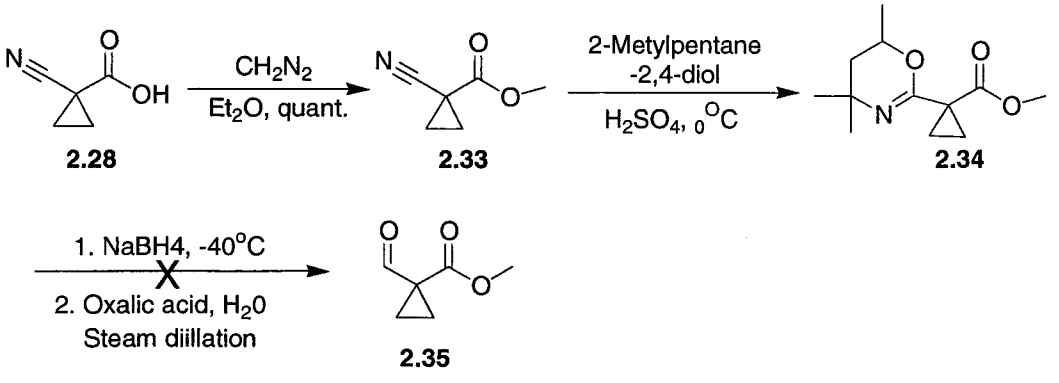
Following a procedure reported by Stevens et al.[49] the nitrile group was transformed into the 5-membered oxazine ring **2.29** (Scheme 2.8, equation 1). However, the reaction proved capricious and **2.29** was obtained in a low yield and was contaminated with by-products. We subsequently turned to various DIBAL-H reduction conditions tried by previous lab mates (equations 2-4), but no desired product was obtained.

***Scheme 2.8**: Reduction of the cyano moiety*



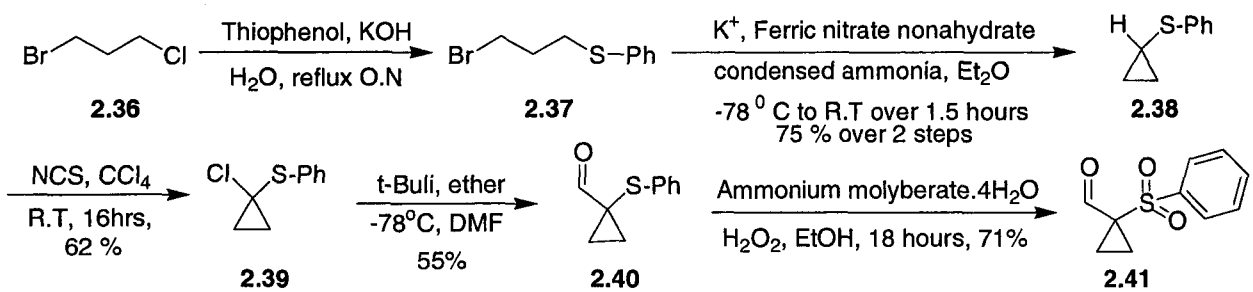
It occurred to us that the carboxylic acid group might be interfering in the formation of the oxazine. To overcome this problem, the carboxylic acid group was transformed to the corresponding ester **2.33** (scheme 2.9). The later was treated in standard conditions. Unfortunately, no desired product **2.35** was obtained.

***Scheme 2.9**: Cyclopropane formation via the ester*



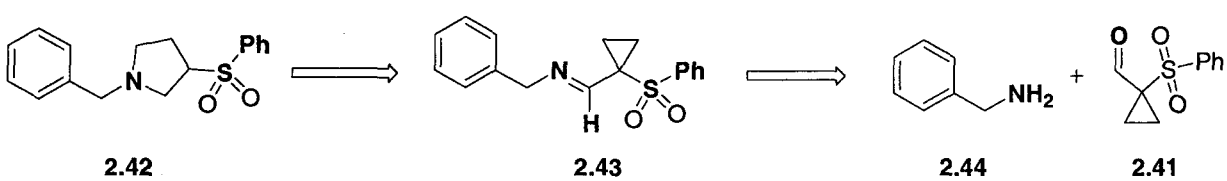
At this point, we decided to change our target cyclopropane to the 1-(phenylsulfonyl) cyclopropanecarbaldehyde (**2.41**). The use of the phenyl sulfonyl moiety can actually be a great advantage in our synthesis. Such moieties as the sulfone (or even the sulfoxide) can be prepared as the chiral version, which would allow us to do an enantioselective synthesis of lycorine. Scheme 2.10 represents the reaction sequence used to obtain this product.

***Scheme 2.10**: Preparation of 1-(phenylsulfonyl)cyclopropanecarbaldehyde*



1-Bromo-3-chloropropane **2.36** was first converted to the thiophenol (**2.37**). The crude product was pure enough to perform the cyclization using potassium, iron and ammonia[50] to give **2.38** in 75% yield (over 2 steps). The latter was chlorinated[51] using *n*-chloro succinimide to afford **2.39** in 62% yield. A halogen metal exchange using *t*-followed by a quench with DMF provided aldehyde **2.40** in a 55% yield. The thio-phenol **2.40** was oxidated to the corresponding sulfone to give the final desired product **2.41.** At this point, a model study was put in place to test the following two steps of our reaction; the condensation of the amine with the cyclopropyl aldehyde, and the rearrangement of the 3-membered ring into a 5-membered ring (Figure 2.3).

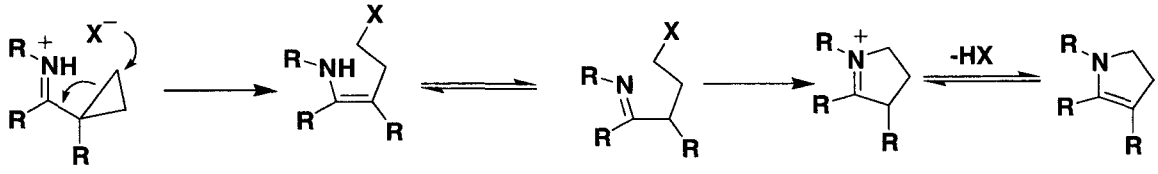
***Figure 2.3**: Proposed model study – retrosyntetic analysis*



2.2.1 Model study

Condensation of amine **2.44** and aldehyde **2.41** provided imine **2.43** quantitative yield. We were then ready to perform the rearrangement reaction. The mechanism proposed for the synthesis of the 2-pyrrolidines such as **2.42** by Stevens[52] is shown in Scheme 2.11. Their studies clearly demonstrate that this rearrangement is not a purely thermal process, an acid catalyst is required.

***Scheme 2.11**: Proposed mechanism for the rearrangement of the substituted cyclopropyl imines to for the substituted 2-pyrrolines by Stevens.*



Many halohydrogen acids were tried and did in fact catalyze the reaction but Stevens et al.[47] found that the ammonium halides were more effective and provided a superior yield.

Having imine **2.43**, we explored various reaction conditions[53] (Table **2.4**) to promote the rearrangement of the 3-membered ring to the 5-membered ring. Heating 2.43 in xylene in the presence of ammonium chloride for multiple hours, gave no desired product, only starting material was seen by ^{1}H NMR of the crude reaction mixture (entries 1-3). Various acids and conditions (high temperatures, microwave irradiation etc.) were also tried. Again, no desired product was observed. We subsequently hypothesized that our five member ring could be forming in small quantities and quickly decomposing. To try to elevate that problem we attempted to trap it with a Diels-Alder reaction, mimicking the tandem rearrangement/Diels-Alder sequence in our synthesis.

Lewis acids such as triflic acid (entry 7) and Gold tri-chloride (entry 8) were tried to catalyze the Diels-Alder reaction. Unfortunately, no cycloaddition product or 5-membered ring rearrangement product was observed. We then tried to catalyze the reaction using freshly made TMSI (entry 10) and were satisfied to see the desired product was present in a

57% yield isolated yield. Conditions using neat ammonium chloride (1 eq.) in a sealed tube with the product heated at 160°C to promote the rearrangement were tried, (entry 11) and we were delighted to isolate our product in quantitative yield.

Table 2.4: *Development of the conditions for the rearrangement reaction*

2.43 **2.42**

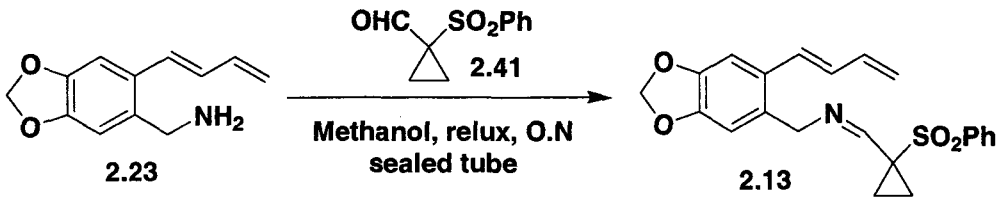
Entry	Salt	Temperature	Time	Sovent	Concentration	Yield
1	NH_4Cl cat.	reflux	3 hours	Xylene	0.1 M	0 %
2	NH_4Cl cat.	110°C	2hours	Xylene	0.1 M	0 %
3	NH_4Cl (1.2 eq)	reflux	5hours	Xylene	0.1 M	0 %
4	HBr cat.	reflux	4hours	Xylene	0.1 M	0 %
5	HCl in dioxane cat.	110°C microwave	15min	Xylene	----	0 %
6	HCl in dioxane cat	110°C microwave	20 min	THF	----	0%
7	TfOH/t-Bu_4NCl	110°C	1hrs	DCM/Mol.Sieves	0.1 M	0%**
8	$AuCl_3$, t-Bu_4NCl	110°C	1hrs	MeOH/Mol.Sieves	0.1M	0%**
9	NH_4Cl (1.2 eq)	110°C	2.5 hours	Toluene/Mol.Sieves	0.1 M	0%
10	TMSI	110°C	1hr	ACN	0.1 M	57%
11	NH_4Cl (1 eq)	160°C	1hr	toluene	1 drop	100%

** A diene was added in situ to promote the Diels-Alder reaction

2.2.2 Proof of principle: Application of the Rearrangement Condition to the Synthesis

Having developed an efficient way to conduct the rearrangement we were ready to try it on our actual substrate. To this end, we first condensed diene (**2.23**) with sulphonyl cyclopropane substrate (**2.41**) to give imine **2.13**. Refluxing a one to one mixture of the two in a sealed tube overnight (Scheme 2.12) gave the product in a quantitative yield, however the product proved to be whimsical during purification. For that reason, it was not isolated or purified.

***Scheme 2.12**: Coupling reaction to make the pre-rearrangement substrate*

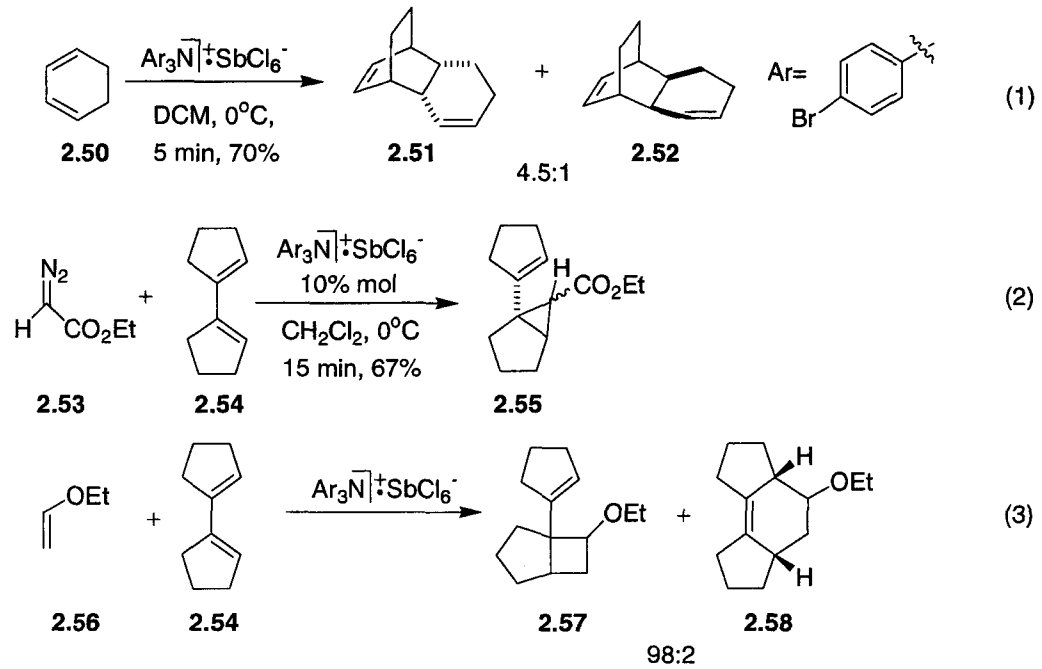


The crude product was then concentrated, ammonium chloride and toluene were added, and the mixture was heated at 160°C for one hour. Unfortunately, no desired product was observed. After repeating the reaction 3 times and always obtaining degradation ofimine **2.13**, we opted to use TMSI. To our surprise, no desired product was observed. We decided to try the initial conditions (developed with our model study) using either TMSI or NH_4Cl, but this time at a lower temperature, to see if it would eliminate some of the degradation. Unfortunately, the same results were obtained as with the higher temperatures. Attempts to perform the rearrangement in the microwave for various lengths of time and temperatures were met with failure. We then resorted to try some of the previously tried conditions in the model study. On the basis of those results, we modified our synthetic plan.

2.3 Third Attempt Towards the Synthesis of Lycorine

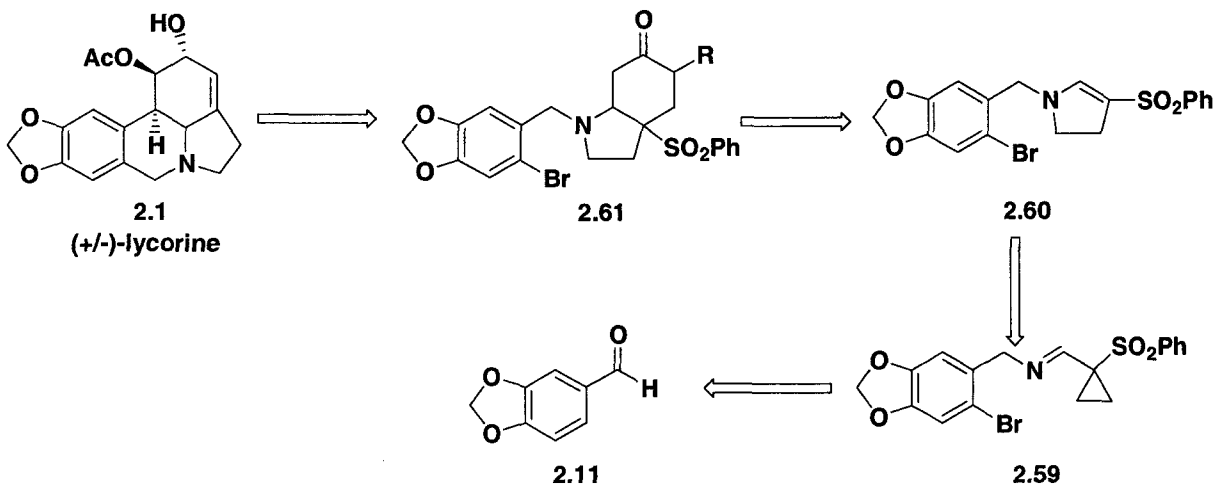
The last approach was plagued by problems when performing the rearrangement reaction to generate the pyrroline ring. We hypothesize that the rearrangement reaction was affect by the presence of the diene moiety since, in the model study lacking the diene, we observed the rearrangement in excellent yields. To avoid this problem we modified the route to omit the diene moiety. Drawing inspiration from the works of Nathan Bauld and coworkers on radical cation Diels-Alder reactions[54] (Scheme 2.13, eq. 1), chain cyclopropanation[55] (eq. 2), and cross addition reactions[56] (eq. 3), we envisioned a radical cation Micheal-type addition reaction for our key step.

***Scheme 2.13**: Radical Cation chemistry by Bauld and cowokers*



The formation of the BCD rings, in lycorine, via a cation radical Michael addition reaction onto the pyrroline substrate (Figure 2.4) would come from the direct rearrangement of the cyclopropane moiety, which, in turn, would arise from the commercially available piperonal (**2.11**).

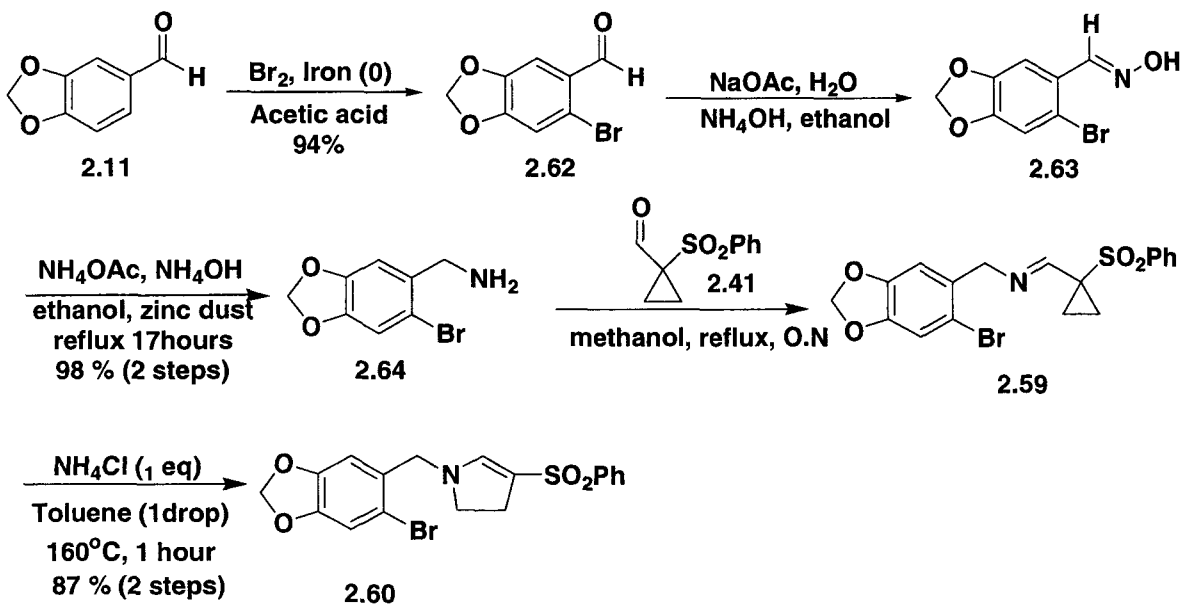
***Figure 2.4** : Retrosynthetic outline of the attempt # 3*



There exist many methods to generate cationic radicals (chemical, photochemical, electrochemical oxidation and radiolytic oxidation). Bauld and coworkers focused their efforts on the "chemical version" of the radical generators. Such one-electron oxidants having a suitable oxidation potential to match the potential of the substrate were chosen and reacted in inert solvents. Having a radical chain character, only a catalytic amount of the oxidants were needed, making them an interesting choice. Bauld preferred using the chemical cation radical generators within the triarylamminium salts catalyst/initiators. Coincidentally when evaluating their oxidizing potential with our substrates we found them to be a good match.

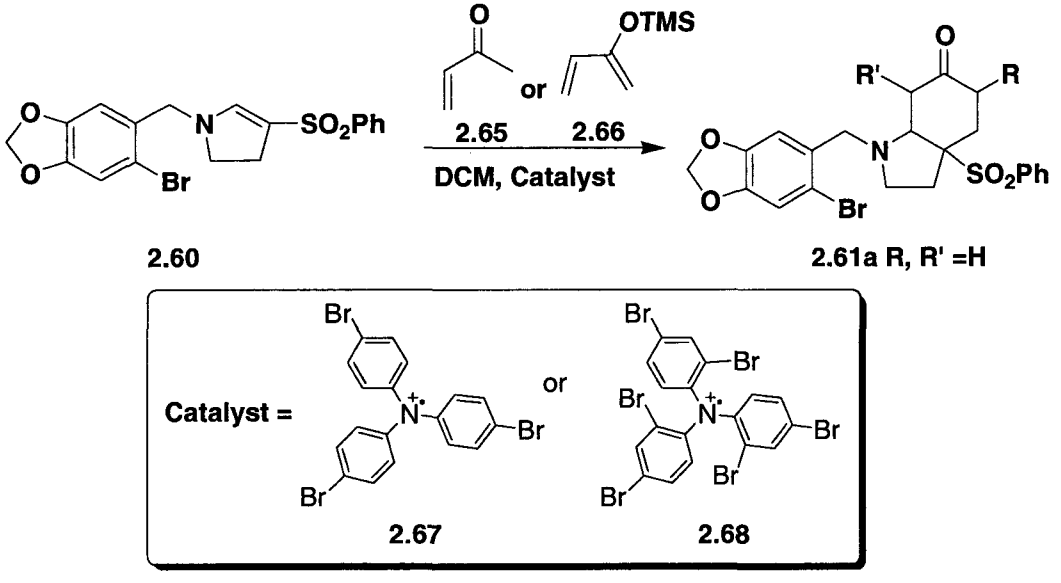
The synthesis began with the bromination of piperonal[35] **2.11** in 94% yield. The aldehyde would then be converted to an amine via the oxime[43] **2.63** in 98 % yield over 2 steps. Afterward, we were able to couple the cyclopropane moiety (**2.41**) and initiate the rearrangement to give **2.60** in a 87% yield after work-up (over 2 steps). Here the rearrangement of the 3-membered ring into the 5-member ring was done smoothly validating our hypothesis as to the interference of the diene, in the previous route.

***Scheme 2.14**: Synthesis of the five membered-ring enamine*



The next step was the cationic cyclization using metal vinyl ketone (**2.65**) or vinyl ether **2.66**. The reactions were initiated by addition, over a 5-minute period, of 10% mol of the catalyst to the solution of pyrroline and **2.65** or **2.66**. Multiple combinations of two different catalyst (tris(4-bromophenyl)aminium hexachloroantimonate and the more potent single electron acceptor tris(2,4-dibromophenyl)aminium hexachloroantimonate[57]), substrates **2.65** and **2.66** and different temperatures (0°C, R.T., -78°C) were tried. Nonetheless, no desired product was seen, only starting material, degradation or a combination of both was obtained.

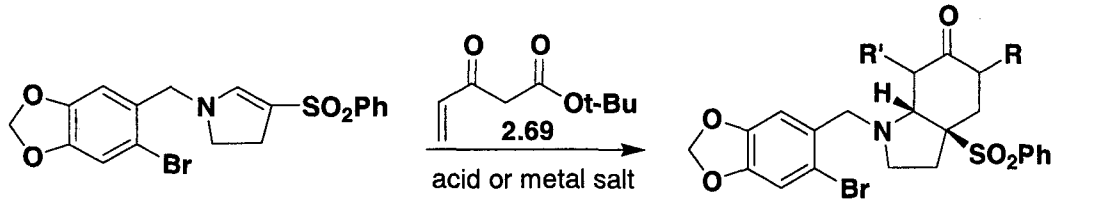
***Scheme 2.15**: Cation radical Michael-like addition to the pyrroline ring*



We envisioned the use of oxidative addition of carbon-centered radicals to the tert-butyl 3-oxopent-4-enoate (**2.69**) mediated by metal salts. Manganese(III) acetate and ceric(IV) ammonium nitrate (CAN) have been used most efficiently in the literature do to such reactions. Recently CAN-mediated oxidative cycloaddition of 1,3-dicarbonyl compounds to alkenes, vinyl acetates, enol silyl ethers, and enol ethers has been studied extensively.[58] At this point, we planned on to react tert-butyl 3-oxopent-4-enoate (**2.69**) in the presence of an activating agent, such as the metal salts or acid, to produce the 5 and 6-membered ring bicycle (**2.70**). Acid catalysis (using PTSA in CAN, refluxed for 1 hour) and radical cyclization (CAN/$NaHCO_3$ at various temperatures and lengths[59] of time as well as

$Mn(OAc)_3.H_2O$ in MeOH refluxed for 24hrs[60]) were explored. However, no desirable product was observed, only S.M and degradation was seen by ^1H NMR of the crude product.

***Scheme 2.16**: Addition of tert-butyl-3-oxopen-4-enoate to the pyrrolidine ring*

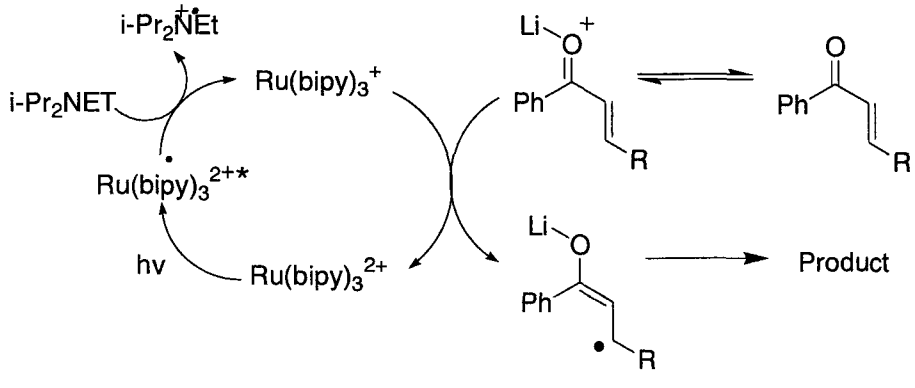


2.60

2.61b R = H
R' = CO_2t-Bu

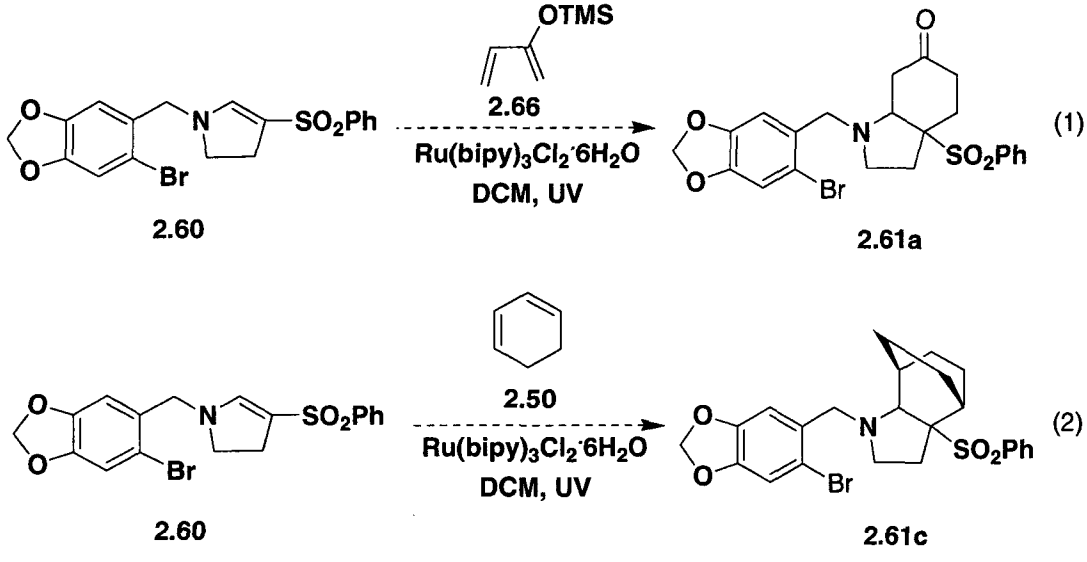
Subsequently, we came upon an article published by Yoon and coworkers[61] were he describes an efficient photocatalysis of [2+2] cycloaddition. In particular, he studied the effects of the $Ru(bipy)_3^{2+}$. Irradiation of this chromophore can produce a photoexcited state $(Ru(bipy)_3^{2+})^*$ that is a powerful photoredox catalyst able to either oxidize or reduce a variety of organic molecules. During their control experiments they confirmed the necessity of the $LiBF_4$ (forms $Ru(bipy)_3(BF_4)_2$ which produces a homogeneous solution, presumably because of the increase in solubility) as well as the presence of the *i*-Pr_2Net. These results led to propose the mechanism outlined in Scheme 2.17. Consequently, we considered the use of this chromophone to initiate a photoredox reaction between a diene and our pyrrolinone substrate, in hopes of creating product **2.61b**.

***Scheme 2.17**: Photoredox mechanism of $Ru(bipy)_3^{2+}$ by Yoon and coworkers*



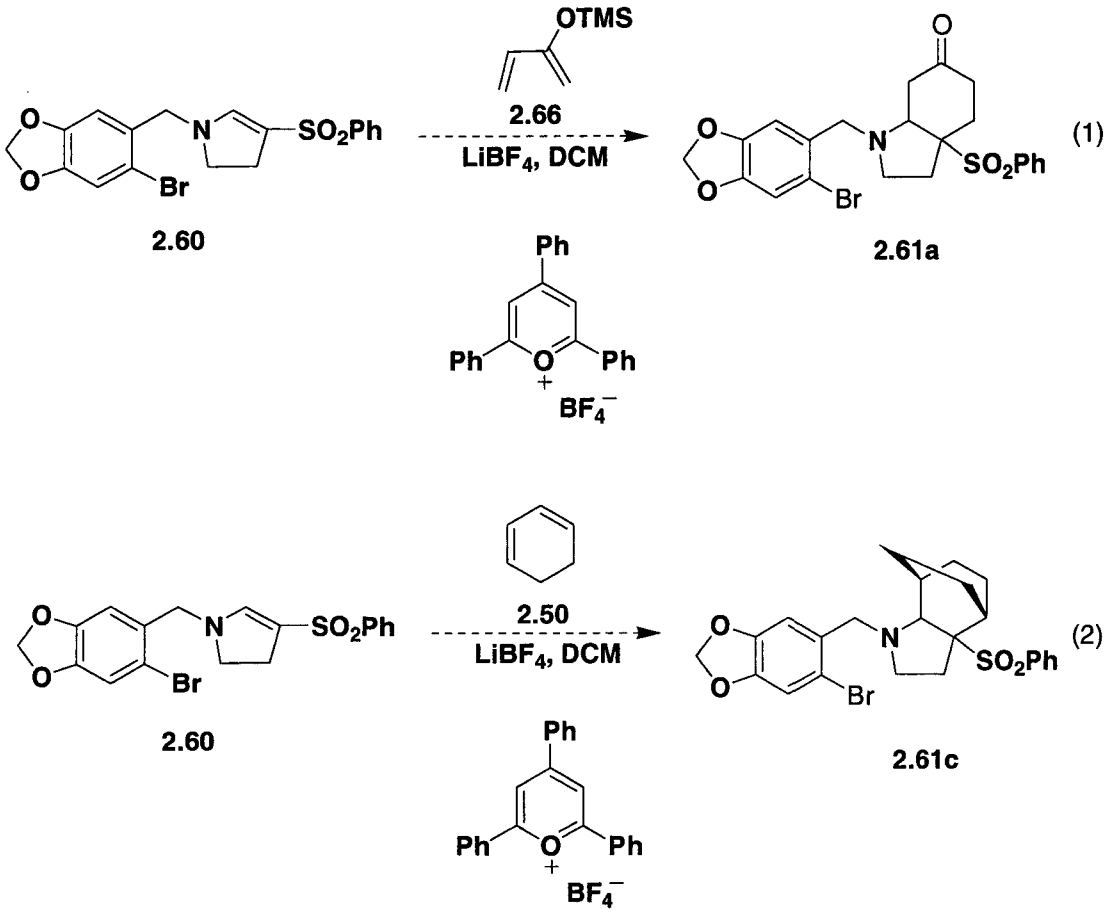
We combined $Ru(bipy)_3Cl_2 \cdot 6H_20$ (5 % mol) , $LiBF_4$ (10% mol) and our substrates (**2.60** and in degassed DCM in a flamed dried sealed tube and irradiated with water-cooling (10-15^{0}C) for 3 hours. Six experiments were tried were the combination of 2 dienes and tree different wavelengths (UVA, UVB, UVC) were used in those conditions. To our dismay no product was obtained, only starting material and degradation was recovered.

***Scheme 2.18**: UV catalyzed reactions*



Photosensitized electron transfer (PET) initiators can also be used to do such reactions. PET initiators provide similar results and are especially advantageous in the case were the substrates involved contain very sensitive functionalities. For this reason, we decided to perform the same experiments by replacing the ruthenium catalyst with the PET catalyst TPP (triphenylpyrilium). The same experimental method was used were the $Ru(bipy)_3Cl_2 \cdot 6H_20/LiBF_4$ was replaced by 5 mol % of TPP. Eight experiments were conducted were the same two dienes (**2.50** and **2.66**) were used in combination with different wavelengths (UVA and UVB) and different time periods (4 to 24 hrs). In all cases, only starting material was recovered along with some degradation.

Scheme 2.19: Reaction utilizing a PET initiator



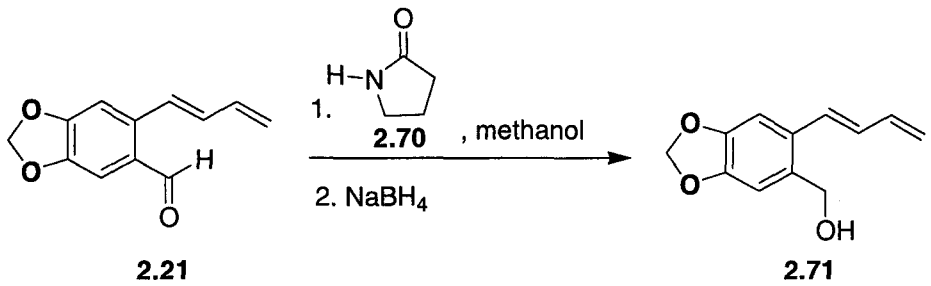
After further consideration we decided to go back to our route # 2 substrate were the diene was already incorporated in the molecule and focus on a new way to generate the pyrrolidine ring moiety.

2.4 Fourth Attempt Towards the Synthesis of Lycorine

The objective of this fourth attempt toward the synthesis of the natural product lycorine (2.1) was to develop a method for the construction of the pyroline five-membered ring onto our already existing substrate **2.21** developed in route #2. We first envisaged the formation of the five membered ring to come from the coupling of 2-pyrrolidinone **2.68** and our aldehyde substrate **2.21**. Therefore, we first tried to couple 2-pyrrolidinone with

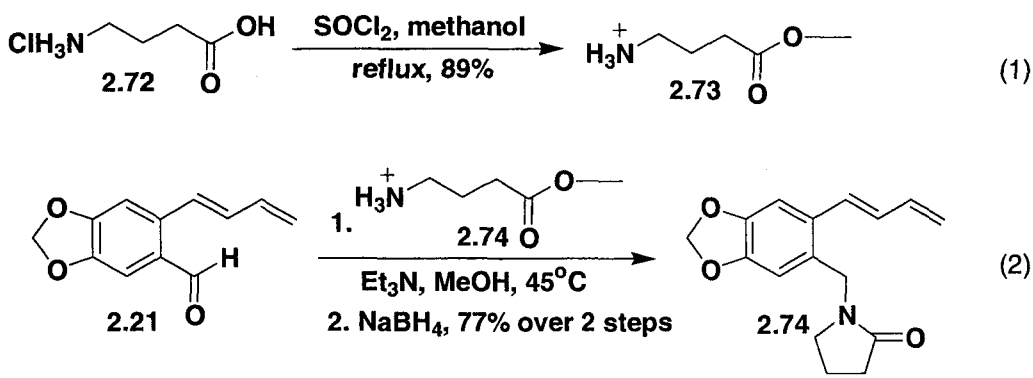
aldehyde **2.21** and reduced the iminium in situ by adding $NaBH_4$ sequentially (Scheme 2.20) We were well aware that the presence of the amide functionality rendered the nitrogen less nucleophilic and could potentially complicate the coupling. In fact, that is exactly what happened, no desired product was observed, only the reduced aldehyde was isolated after column chromatography.

***Scheme 2.20**: Sequential one pot condensation and reduction reaction*



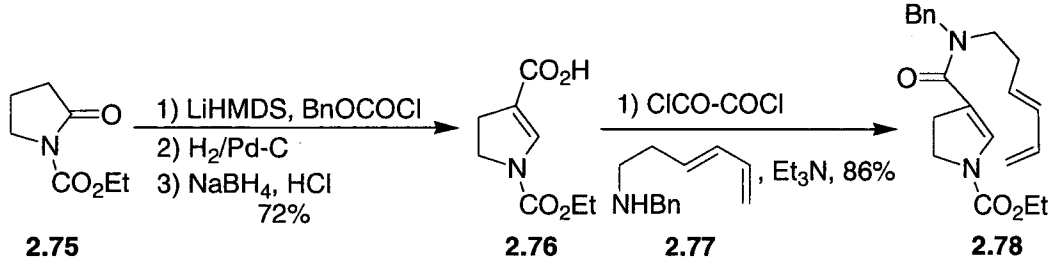
The next method tried was the formation of the five membered ring pyrroline by a reductive amination/lactimization reaction. The 4-amino methyl ester (**2.74**) was prepared by esterification of the 4-aminobutyric acid (**2.72**) using thionyl chloride and methanol in refluxing conditions[62] (Scheme 2.21, equation 1). Then ester **2.73** was combined with aldehyde **2.21** in the presence of $NaBH_4$ to afford the desired amide **2.74** in 77% yield.

***Scheme 2.21**: Reductive amination/lactimization reaction to form pyrroline 2.74*



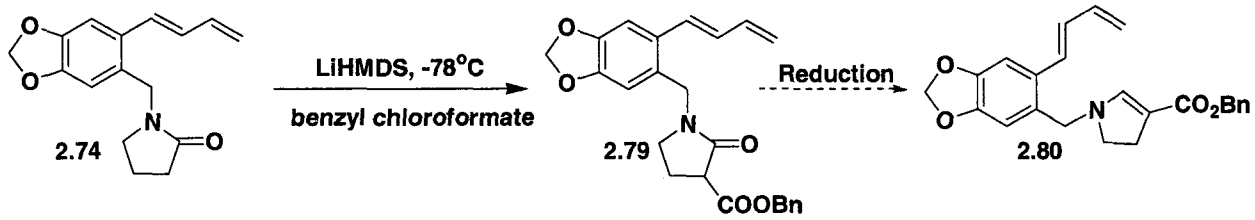
Having succeeded in the formation of the five-membered ring amino ester we then revised our synthesis plan for the next steps to come. We were inspired by the works of Martin and coworkers,[63] where they fabricated the dienophile component **2.76** from **2.75** via a straightforward sequence of reactions. After this, the dienophile was coupled via its acid chloride with **2.77** to give the trienic substrate **2.78** used in the enantioselective synthesis of manzamine A and related alkaloids.

***Scheme 2.22** : Inspirational work done by Martin and coworkers*



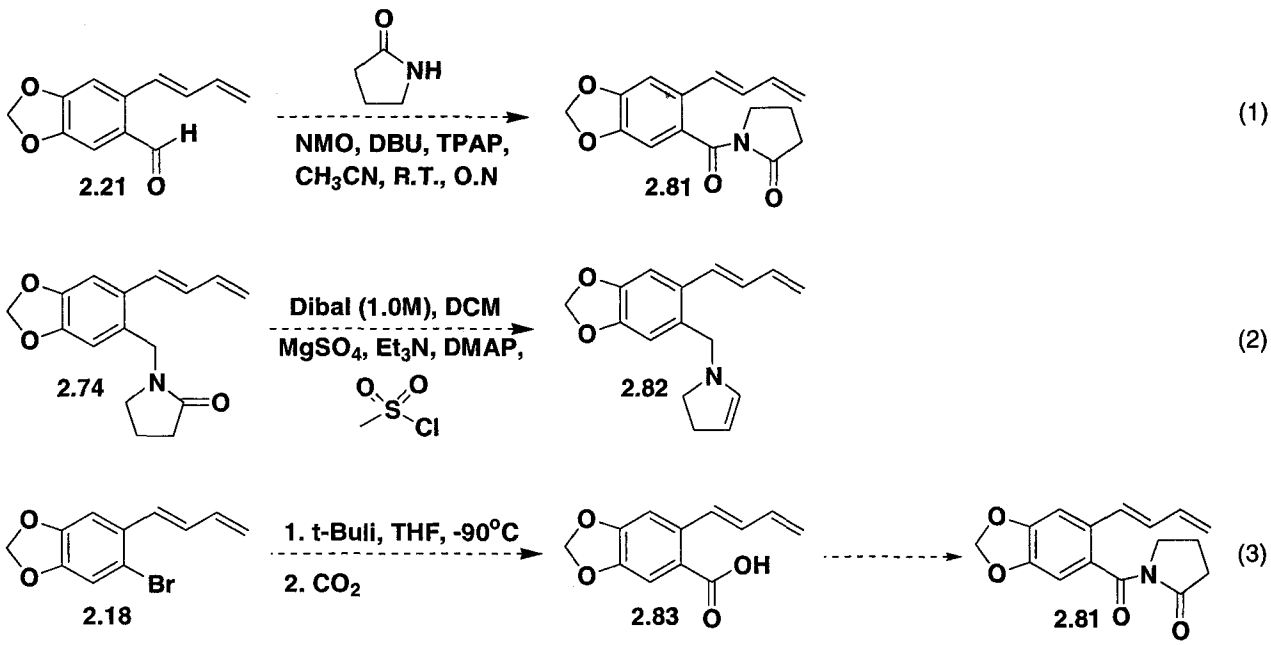
To this end, **2.74** was first treated with LiHMDS to form the enolate, followed by a reaction with benzyl chloroformate to give **2.79**. Pleasingly, we observed the desired product **2.79** in a 61% yield. Attempts to do the same reaction using LDA and NaH as a base were ineffective. We anticipated that the reduction using $NaBH_4$ would be selective to the more reactive carbonyl, the ketone, the give the desired product **2.76**. Unfortunately, when attempting the reaction only S.M. and degradation product was formed. Since Martin and coworkers reduced **2.75** to the carboxylic acid, we imagined the same might help in our case. Their use of H_2/Pd-C was not possible in our case due to the presence of olefins on the molecule. Instead, **2.79** was converted to the carboxylic acid using $LiOH{\cdot}H_2O$ in THF/MeOH (3:1). The ^1H NMR of the crude reaction mixture showed the presence of the desired product; for this reason we tried the reduction using $NaBH_4$ once again. To our dismay, no desired product was observed.

Scheme 2.23**: Attempts toward the formation of **2.80



Other attempts to create the lycorine core using the N-acylation of pyrrolidinone[64] (Scheme 2.24, eq.1), reduction of **2.74** to pyrroline **2.82** before alkylation[65] (eq.2) and formation of the carboxylic acid **2.83** followed by coupling via various coupling agents such as HBTU, DCC, EDC, DIC etc. has proven to be unsuccessful. The latter was the most promising but formation of the carboxylic acid proves to be very difficult and low yielding.

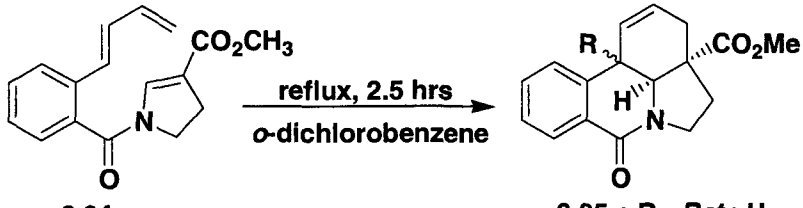
***Scheme 2.24** : Other attempts for the formation of the lycorine core*



In summary, a successful synthesis of a key precursor to the core of lycorine has been described. To our surprise, the anticipated approach via the [4+2] cycloaddition was validated upon our discovery of an article published by Stork and coworkers[66] detailing

efforts towards the synthesis of the core ring system of lycorine via an intramolecular Diels-alder cycloaddition between the pyrrolidine ring and the diene. It is important to note that their approach provided a poor stereochemical outcome when executing the cycloaddition reaction due to the fact that 2 endo effects are possible.

***Scheme 2.25** : Intramolecular Diels-Alder Approach to lycorine by Stork and coworkers*

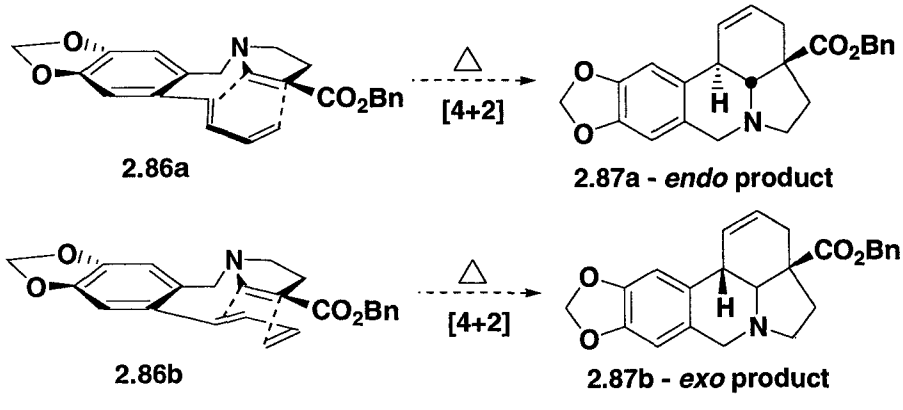


2.84

2.85 a R= *Beta*-H
2.85 b R= *Alpha*-H
(0.84 : 1)

Nevertheless, our system, being slightly different by the substitution on the pyrroline ring and by the absence of the benzylic ketone, can be the key to the desired stereochemical selectivity needed during that key step. In fact, in our case only one endo effect and one exo effect is possible. Moreover, our system can be validated by the synchronisity which entails that the shorter bond of the cycloaddition will usually be trans. As a result, we are enthoused that our synthesis will be successful.

***Scheme 2.26:** 3-D view of our Diels-Alder approach to the total synthesis of lycorine*



2.86a

2.87a - *endo* product

2.86b

2.87b - *exo* product

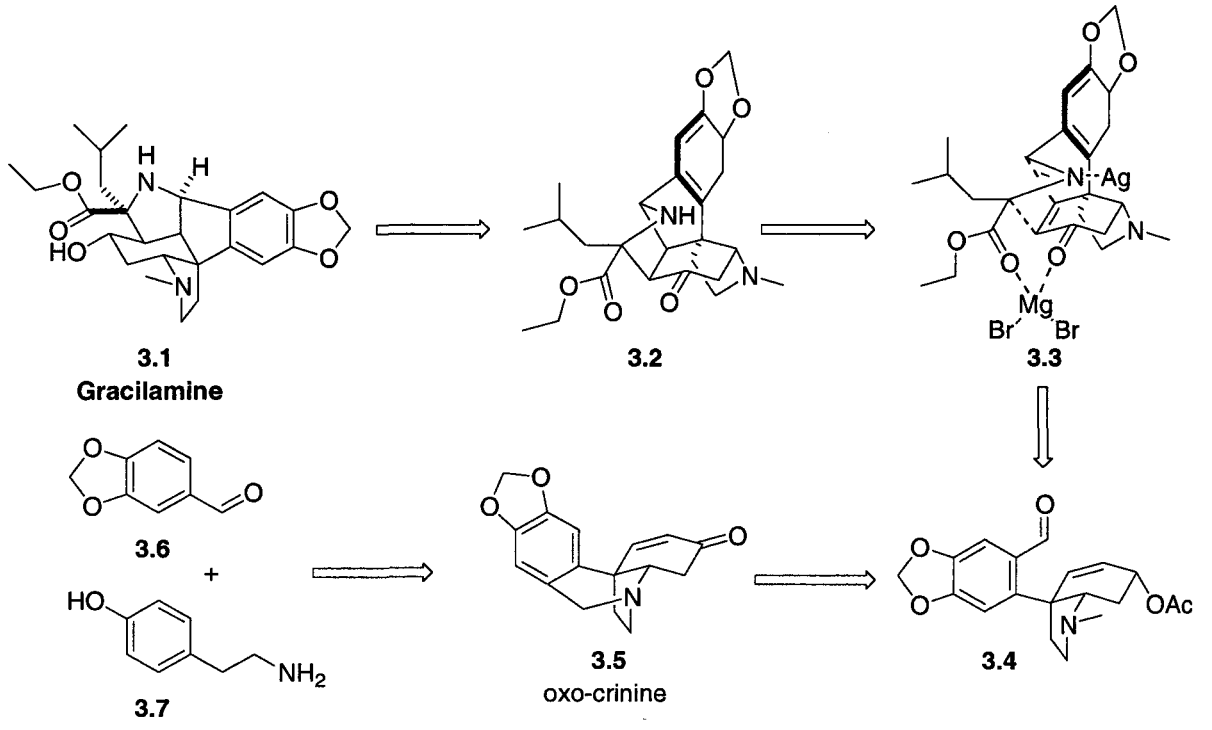
In summary, a successful synthesis of a key precursor to the core of lycorine has been described. Our anticipated approach via the [4+2] cycloaddition was validated upon our discovery of an article published by Stork and coworkers[66] detailing efforts towards the synthesis of the core ring system of lycorine via an intramolecular Diels-alder cycloaddition between the pyrrolidine ring and the diene. Their pyrrolidine system provided poor stereochemical outcome when doing the cycloaddition reaction. Nevertheless, our systeme, being slightly different by the substitution on the pyrrolidine ring, can be the key to the desired stereochemical selectivity needed during that key step. As a result, we are enthoused that our synthesis will be successful.

Chapter 3

Towards the Synthesis of Gracilamine

In 2005, during the course of a phytochemical investigation on the species *G.gracillis*, a new member of the graciline subgroup of *Amaryllidaceae* alkaloids was identified. This novel pentacyclic dinitrous alkaloid, (±)-gracilamine (**3.1**), was characterized by Ünver and Kaya.[67] To date no total synthesis of gracilamine has been reported. It's pentacyclic core and functionalizations made this natural compound an interesting challenge for total synthesis. We envisaged a synthesis consisting of 8 to 12 step synthesis depending on the protecting groups needed. Figure 3.1 details our retrosyntetic outlook where Gracilamine would first come from a reduction of **3.2** which in turn arises from our key step; a silver catalyzed intramolecular 1,3-dipolar cycloaddition reaction of imino ester **3.3**. It is envisioned that under AgOTf catalysis, the azoethine ylide **3.3** will be formed and undergo a 1,3-dipolar cycloaddition onto the electron poor cyclohexadienone olefin to afford **3.2.**

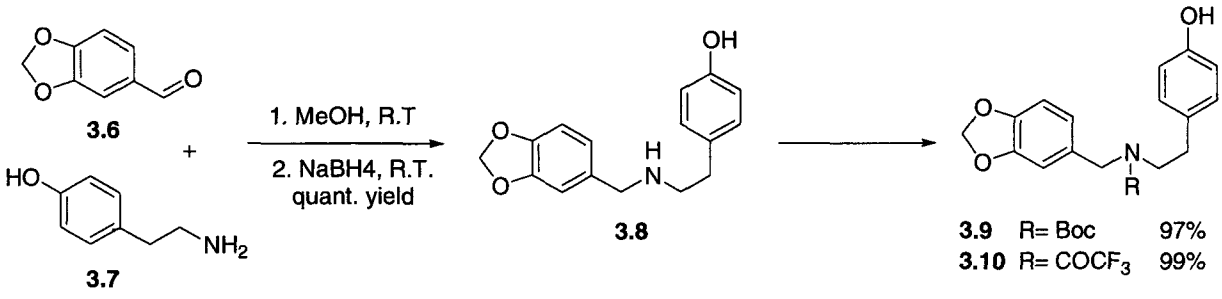
***Figure 3.1**: Retrosynthetic outlook of the proposed Gracilamine (**3.1**) synthesis*



The 1,3-dipolar cycloaddition substrate would be synthesized from the oxo-crinine **3.5** which would be converted to the aldehyde by oxidative Kornblum-type opening of the piperidine ring at the benzylic position. The aldehyde (**3.4**) could then be coupled with the desired amine to afford **3.3**. In turn, oxo-crinine (**3.5**) can be developed via the reductive amination of cheap commercially available piperonal **3.6** and tyramine **3.7**.[10]

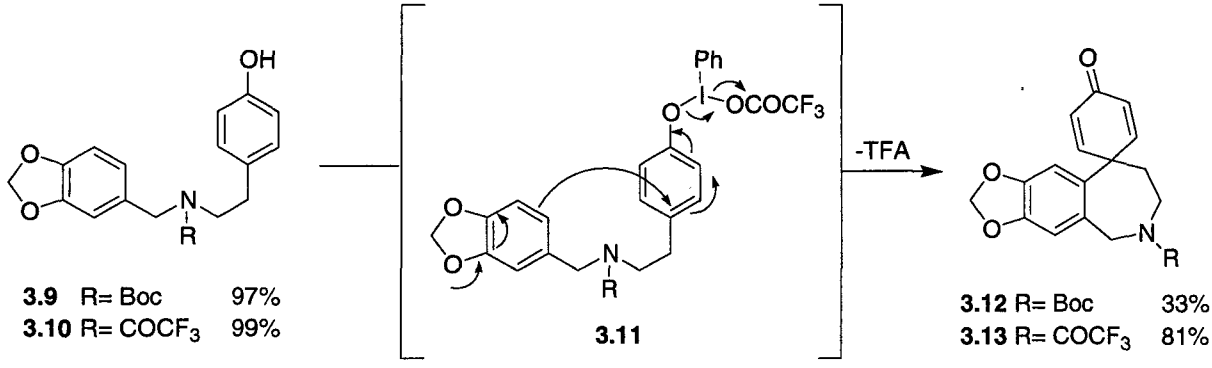
To begin, the synthesis N-3',4'-methylenedioxyphenylmethyl-[2-(4-hydroxy-phenyl)]ethylamine (**3.9/3.10**) was prepared by coupling piperonal (**3.6**) and tyramine (**3.7**) in methanol followed by reduction of the resulting imine with $NaBH_4$ (Scheme 3.1) to give **3.8** in quantitative yield.[10] The free amine (**3.8**) was subjected to protection conditions without further purification. The Boc-protected amine **3.9** was obtained in good yields after refluxing in MeOH with Boc_2O and Et_3N; the trifluoroacetyl-protected amine **3.10** was also synthesized[10] with 99% yield.

***Scheme 3.1** : Synthesis of intermediates **3.9** and **3.10**.*



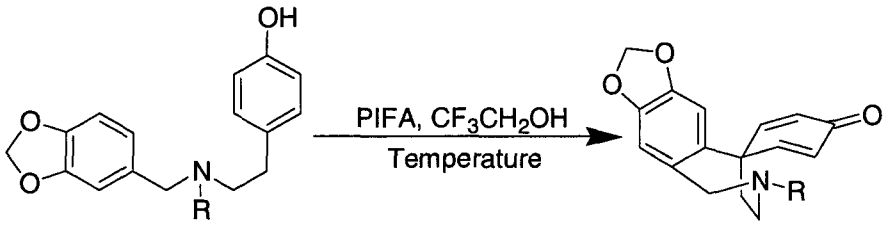
To attain the spirocyclic system of (±) oxocrinine (**3.5**), an oxidative spiro-annulation reaction was carried out on both **3.9** and **3.10** with PIFA in 2,2,2-trifluoroethanol to afford the cross-conjugated cyclohexadienone derivatives **3.12** and **3.13**, respectively (Scheme 3.2).[67] Initial attempts to cyclize the Boc-protected amine **3.9** at 0°C under inert atmosphere were unsuccessful; no desired product was isolated from the complex product mixture. Although separation and analysis of the side products was not possible, it can be stipulated that the trace presence of water may have resulted in the degradation of the PIFA reagent by nucleophilic competition with the phenolic alcohol in the ligand exchange step of the oxidation reaction. In order to minimize unwanted reactivity, the reaction flask was flame dried, 2,2,2-trifluoroethanol was treated with $NaHCO_3$ prior to the addition of the PIFA and the reaction temperature was decreased to -40°C. These modifications attained the desired result and the cross-conjugated cyclohexadienone could be isolated in yields ranging from 29-33%; the reaction did not proceed to completion and stating material could be isolated by flash column chromatography. The trifluoroacetyl-protected amine **3.13** was also cyclized using the optimized oxidation conditions; the yield was significantly comparable to those reported in the literature[10], but on larger scale the reaction could not be brought to completion.

Scheme 3.2**: Formation of cross-conjugated cyclohexadienone derivatives **3.12** and **3.13



A more direct route to (±) oxo-crinine (**3.5**) has also been investigated. Treatment of free amine **3.8** with excess PTSA or TFA to form the ammonium salt has been stipulated as a method to promote selective oxidation of the phenol without the addition of protecting groups. This is an attractive method, as it reduces the synthesis of intermediate **3.5** by two steps; however, this transformation has yet to be carried out successfully (Table 3.1, entries 4-6) .A summary of the conditions tried are seen below in Table 1.

Table 3.1: *Conditions tried for the direct route, no protection, to oxo-crinine (**3.5**)*



R= Boc (**3.9**)
R= $COCF_3$ (**3.10**)
R= H (**3.10a**)

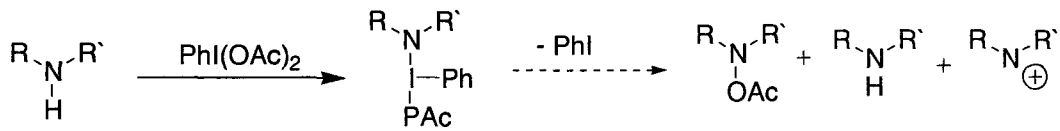
R= Boc (**3.12**)
R= $COCF_3$ (**3.13**)
R= H (**3.13a**)

Entry	R=	Acid	Temperature	Yield
1	Boc	N/A	0°C	0
2	Boc	N/A	-40°C	33
3	$COCF_3$	N/A	-40°C	81
4	H	PTSA	0°C	0
5	H	TFA	-40°C	0
6	H	PTSA	-40°C	0

* Acid was aded to entries 4-6 in hopes to get the oxo-crinine directly

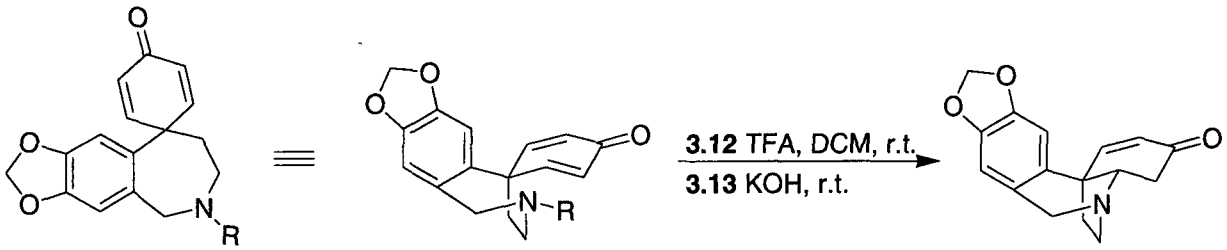
A possible explanation for the low yields when using Boc as a protecting group is that amines can react with PIFA to form unstable intermediates including radicals and nitrenium ions (Scheme 3.3)[30e], which can lead to a wide range of unwanted side products.

Scheme 3.3: *Possible reactive side products of PIFA oxidation of free amine*



Following the formation of the cross-conjugated cyclohexadienones **3.12** and **3.13**, de-protection[68] of the amine resulted in an intramolecular nucleophilic conjugate addition of the amine on the cyclohexadienone to afford (±)-oxo-crinine (**3.5**); in 71% and 82% yields respectively (Scheme 3.4).

Scheme 3.4: *Deprotection of intermediates* ***3.12*** *and* ***3.13*** *to afford (±)-oxo-crinine (****3.5****)*



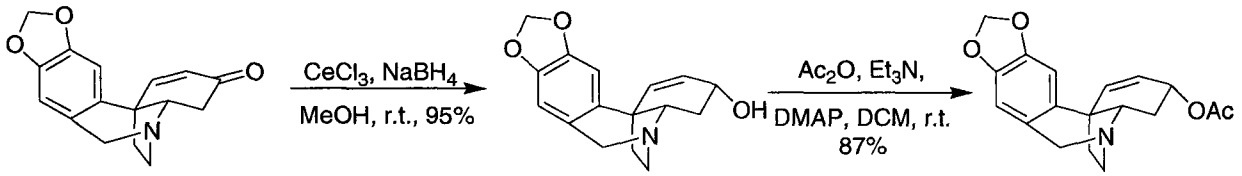
3.12 R= Boc
3.13 R= $COCF_3$

33 %
81 %

3.5
71 %
82 %

A Luche reduction[69] was then carried out on the (±)-oxo-crinine (**3.5**) to selectively afford the 1,2-reduction product **3.14**; this compound is also naturally occurring alkaloid, (±) epivittatine (**3.14**) that is acylated to give (±) krepowine (**3.15**) (Scheme 3.5). This reaction sequence was carried out with good yields, and no side products were observed.

Scheme 3.5: *Reduction and protection of (±)-oxo-crinine (****3.5****) to (±)-krepowine (****3.15****) via (±)- epivittatine (****3.14****).*

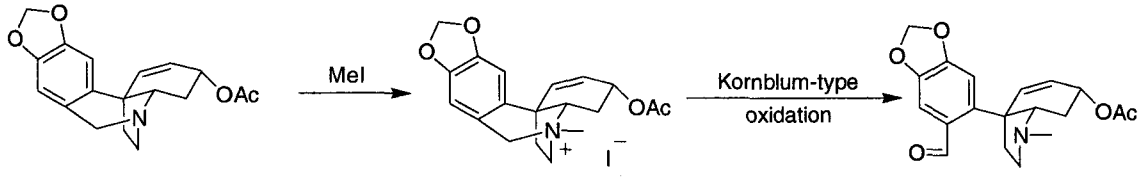


3.5 **3.14** **3.15**

The subsequent reaction scheme is unprecedented in the literature. In an attempt to mimic the biogenic intermediate **3.4** (Scheme 3.6), it was proposed to carry out a modified Kornblum oxidation of the quaternized amine (**3.16**) resulting in oxidative ring opening of (±) krepowine (**3.15**). Methyl iodide was chosen as the alkylating agent for the synthesis of **3.4**. Initial attempts to quaternarize the tertiary amine by using 1 eq. MeI in DCM at room temperature were unsuccessful; ^{1}H and ^{13}C NMR analysis was inconclusive and gave no

proof that the ammonium salt had been formed. Treatment of the product mixture with base (Et_3N) and DMSO, however, resulted in the formation of an unknown product, indicating that quaternization of trace amounts of tertiary amine **3.16** were achieved. However, no aldehyde peak was discernable by ^1H NMR analysis, which indicated that the Kornblum-type oxidation did not afford the desired product **3.4.**

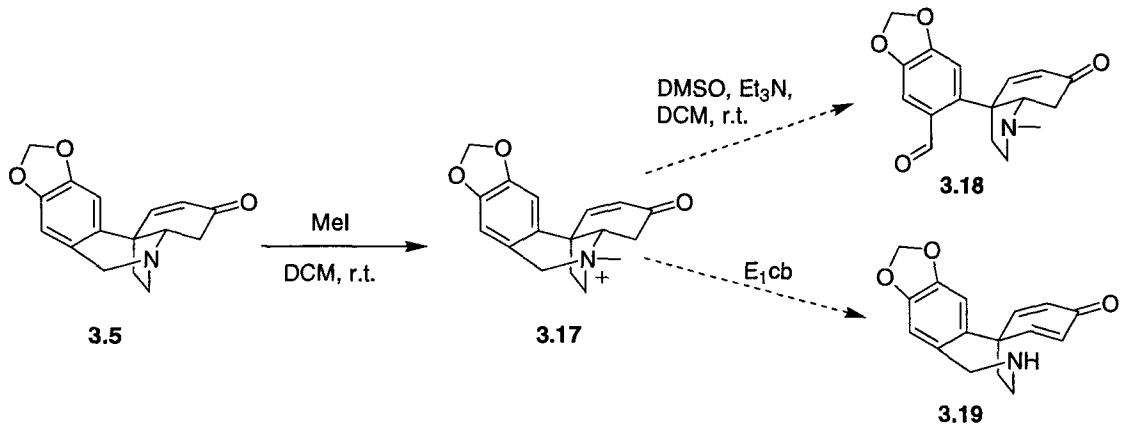
Scheme 3.6**: Quaternization of (±)-kreptowine (**3.15**) followed by ring opening via Kornblum oxidation-type reaction to aldehyde **3.4



3.15 **3.16** **3.4**

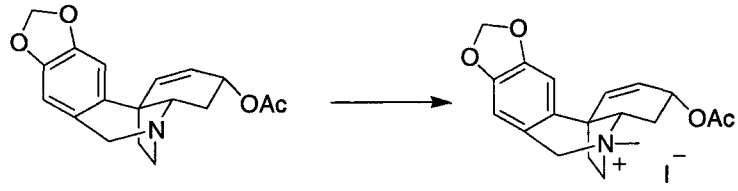
The above quaternization conditions were also applied to (±) oxo-crinine (**3.3**) (Scheme 3.7). This reaction was carried out to compare the relative efficacy of this transformation on synthetic intermediates **3.16** and **3.17.** Although oxidative ring opening of **3.17** is a faster route to intermediate **3.28**, the formation of **3.19** via and E_1CB mechanism could be a competitive pathway. Quaternization of the amine **3.5** to give **3.17** could not be confirmed by ^1H and ^{13}C NMR analysis, however upon treatment with base and DMSO an unknown product was formed. The absence of the aldehyde peak in the 9-10 ppm region of the ^1H spectrum indicated that aldehyde **3.18** was not formed; the characteristic splitting pattern in the 2,40-4,80 ppm region denoting the formation of the cross-conjugated cyclohexadienone system was also absent, which indicated that the elimination to **3.19** did not occur.

***Scheme 3.7**: Route to **3.18** and possible side product from the quaternization of oxo-crinine (**3.5**)*



Alternate reaction conditions for the alkylation of amine **3.15** were investigated; the amine was subjected to MeI (1.5 eq.) in *i*-PrOH at room temperature[70] to give partial conversion to an unknown intermediate. The reaction was not taken further. The amine **3.15** was refluxed in acetone in the presence of KOH, followed by reflux with MeI which resulted in complete conversion of the starting material into a single product. Unfortunately, the ^{1}H NMR (DMSO-d_6) was not conclusive. Two products were formed. A variety of N-alkylation reagents and conditions were then tried[71] on substrate **3.15**. These conditions are summarized bellow in Table 3.2.

Table 3.2: Quaternization *of amine* ***3.15***



3.15 **3.16**

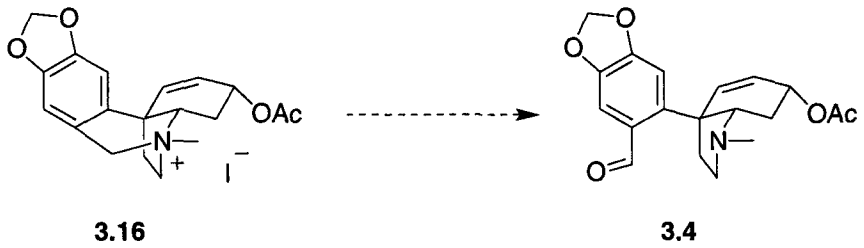
Entry	Alkylation agent	Solvent	Temperature	Time	Yield
1	MeI (1.2 eq)	Acetone	R.T.	3 hrs	0%
2	MeI (5 eq)	DMF	0^0C to R.T.	20 hrs	0%
3	CH_2N_2	DCM	R.T.	20 minutes	0%
4	CF_3SO_3Me (10 eq)	DCM	R.T.	3 hrs	0%
5	Dimethyl carbonate (10 eq)/ DBU (1eq)	DCM	90°C	1 hrs	0%
6	Dimethyl carbonate (10 eq)/ DBU (1eq)	DCM	160°C	50 minutes	0%
7	Dimethyl Sulfate (1.5 eq)	DCM	0°C to R.T.	3 hrs	0%
8	Meerwein Salt (1eq)	DCM	R.T	1hrs	100 %*

* crude

Analysis of the products derived from entries **1** to **7** in Table 3.2 showed no sign of the desired product. However, exposure of **3.15** (entry **8**) to the Meerwein salt for 60 minutes gave a white solid in quantitative yield. ^{1}H, ^{13}C, DEPT, and HRMS confirmed the structure of the desired product **(3.16).**

After obtaining **3.16**, we then envisioned the opening of the ring at the benzylic carbon (Scheme 3.8). To this end, we first tried Kornblum modification conditions[72] unfortunately, no desired product was observed. Five other set of conditions[73] were explored (1. KOH(1N), DMSO, 2hrs, R.T.; 2. CAN (3eq), ACN/H_2O (1:1), 2hrs, R.T.; 3. Cerium triflate (2eq), ACN, 3hrs, R.T.; 4. CrO_3 (5eq), AcOH/H_2O (10%), 2.5hrs, R.T.; 5. CrO_3/H_5IO_6, ACN, 5hrs, R.T.), alas, none gave the desired aldehyde only a complex mixture of products was observed.

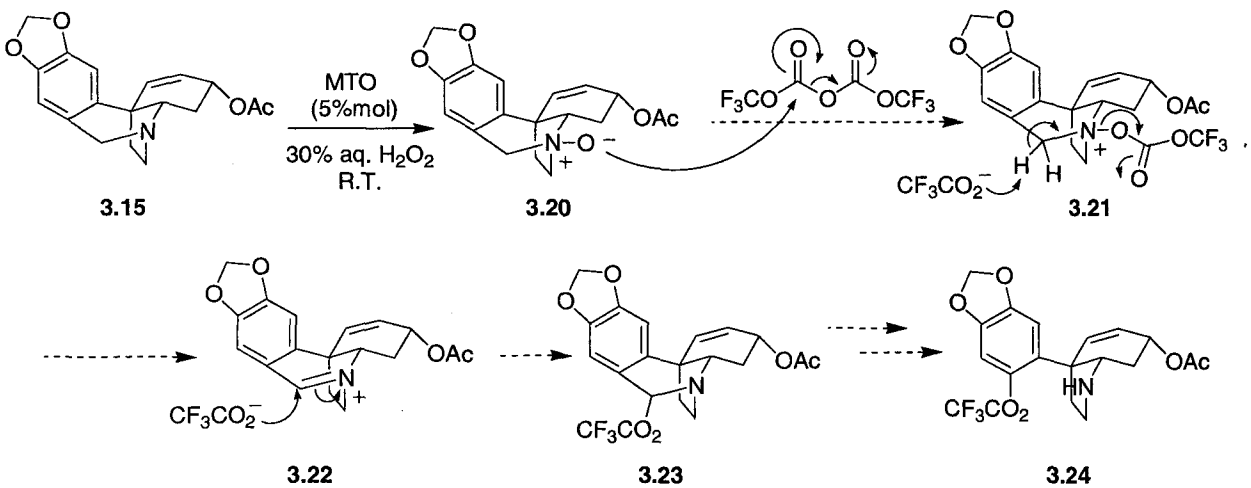
***Scheme 3.8**: Oxidative opening of benzylic C-N bond*



3.16 **3.4**

We then envisioned the opening of the ring at the benzylic position via a Polonovski-Pottier type reaction (Scheme 3.9). The Polonoski-Pottier reaction is a modification of the Polonovski reaction where trifluoroacetic anhydride is used to acetylate the N-Oxide (**3.20**). The left over acid would then deprotonate the acidic benzylic proton to form imine **3.22**, which can react to give **3.23**. Opening of the ring at the benzylic position would be favored to give **3.24**.

***Scheme 3.9:** Proposed route for the opening of the ring at the benzylic position via the Polonovski-Pottier reaction*



3.15 **3.20** **3.21**

3.22 **3.23** **3.24**

To this end, we synthesized N-Oxide **3.20** using MTO (5%mol) and aq. H_2O_2.[74] Various conditions[75] were tried to open the ring at the benzylic position: (a) TFAA, DCM, -30°C to R.T., 1hr; (b) TFAA DCM, R.T., 2 hrs; (c) TFAA, DCM, reflux, 1hrs; (d) TFAA, DMAP, R.T., 2hrs; (e) Ac_2O, DCM, -30°C to R.T., 1hr; (f) Ac_2O, DCM, R.T., 4hrs; (g)

$FeSO_4$-$7H_2O$/H_2SO_4 (0.5N), MeOH, R.T., 40hrs; (h) $FeSO_4$-$7H_2O$/H_2SO_4 (0.5N), MeOH, 100°C, 4hrs; (i) t-BuOK/t-BuOH, 150°C, 3hrs; (j) t-BuOK/t-BuOH 80°C, 3hrs; (k) CrO_3, pyridine, 50°C, 20hrs, but unfortunately none were successful. It is possible that the N-oxide intermediate and N-methyl intermediate are too stable to undergo reaction, although all literature evidence points towards the fact that they should react. At this point further literature research is needed to find the appropriate conditions.

3.1 Future Perspective to Complete the First Total Synthesis of Gracilamine

To complete the synthesis of (±)-gracilamine, the reaction conditions for the preparation of aldehyde **3.18** must be optimized. This includes optimization of the (±) oxo-crinine (**3.5**) synthesis by investigating the PIFA oxidation of the ammonium salt of free amine **3.8**, as well as the direct oxidative ring opening the (±)-oxo-crinine (**3.5**). These improvements would allow for the continuation of the synthesis by providing a viable route to the imino ester (**3.3**) necessary to carry out this synthesis key step.

The intramolecular 1,3-dipolar cycloaddition reaction of imino ester **3.3** is believed to by catalyzed by AgOTf. The selectivity of this reaction has been extensively documented in the literature[76], demonstrating that the dipolarophile (in this case, the cyclohexadienone double bond) will approach the ylide with the electron withdrawing group oriented toward the metal center, thus resulting in the formation of the *endo* product. A simple reduction of the cycloaddition product **3.2** would afford the natural product gracilamine **3.1**.

In summary, a simple and innovative strategic synthesis of (+/-)-gracilamine has been proposed and is currently underway. If successful, we will have the first and total synthesis of the gracilamine natural product.

Chapter 4

Synthesis of 1-Acetoxy-Dienes via Gold (I) Catalyzed-Rearrangement of Propargylic Acetate

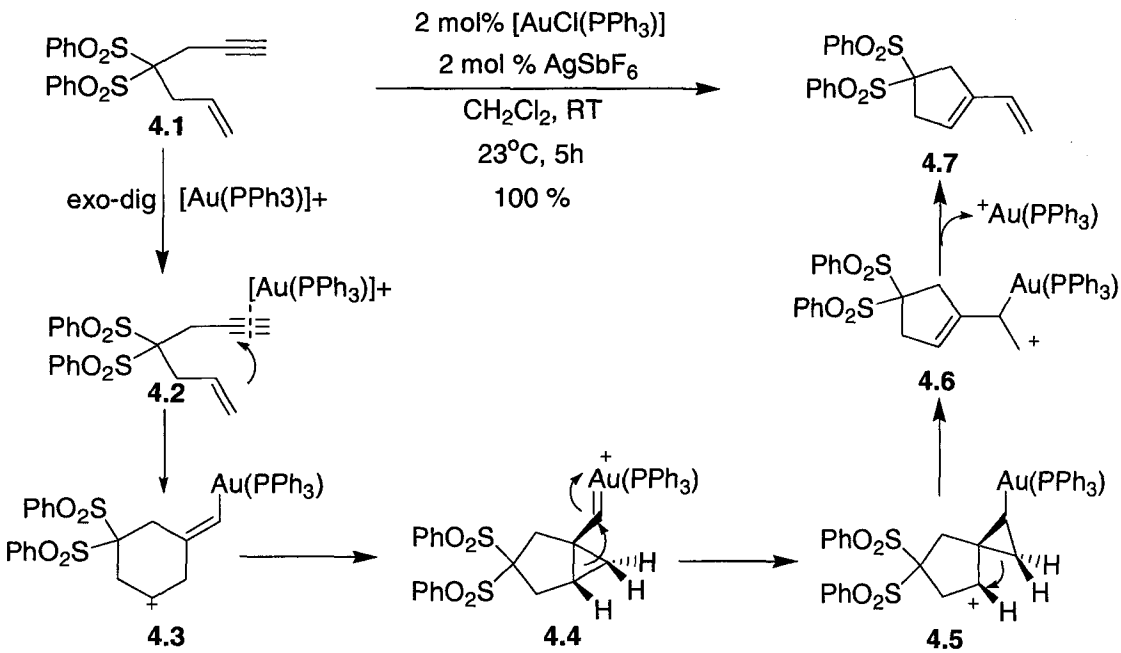
Introduction to Gold Catalyzed Transformation Reactions via Alkyne Activation

Gold has been known since ancient times, its discovery dating back to at least 5000BC[77] and although it is a rare element, it is more abundant then platinum, rhodium, and palladium. Applications of gold and gold salts in heterogeneous catalysis evolved at the beginning of the last century, and nowadays they belong to the most active catalysts for such diverse reactions as the low temperature oxidation of carbon monoxide and the hydrochlorination of ethyne.[78] Gold catalysis proceeds under very mild conditions, has a high affinity for alkynes, arenes, allenes and alkenes and can even act simultaneously as a Lewis Acid. Because of their ability to activate carbon-carbon double and triple bonds as

soft carbophilic Lewis acids (alkynophile), gold homogeneous catalyst prove to be versatile methods of generating C-C, C-O, C-N and C-S bonds.[79]

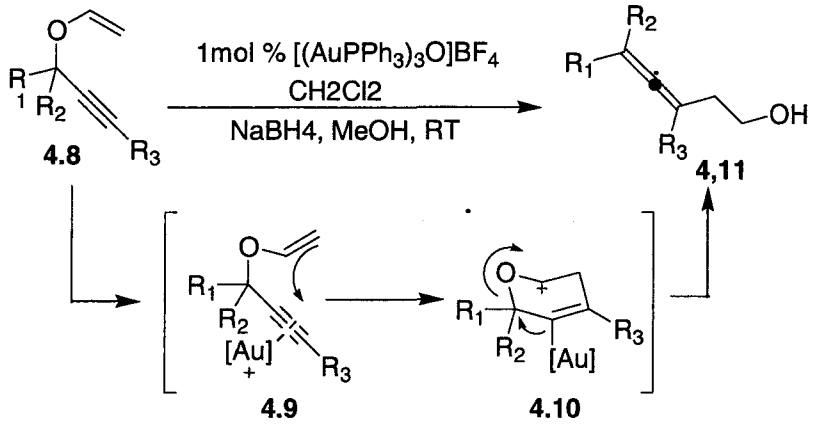
Alkyne activation by Lewis-Acid gold salts is becoming more and more popular every day, and already has a very widespread application. For instance, it has been shown[80] that $Au(I)^+$ can be used to perform intramolecular cycloisomeration of enyne to produce dienes such as depicted in Scheme 4.1. Here the cationic gold species activates the alkyne by coordination to give compound **4.2**, which then undergoes a 6-*endo*-dig cyclization to give **4.3**. This is then followed by the cyclopropanation of **4.3** to give compound **4.4**, which undergoes bond rearrangements to give **4.6**. The desired diene product **4.7** is formed by release of the cationic gold species.

Scheme 4.1: *Proposed mechanism for the enyne metathesis with gold*



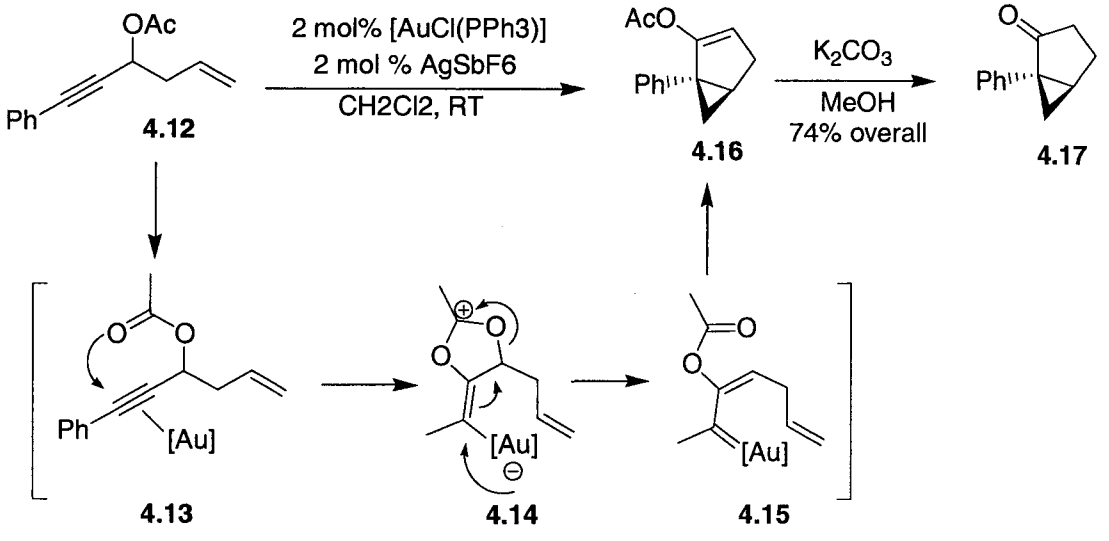
Sherry and Toste[81] discovered that the treatment of a propargylic vinyl with a catalytic amount of $[\{Au(PPh_3)\}_3O]BF_4$ induced a rearrangement giving allenol **4.11**.[81] The proposed mechanism goes via cationic intermediate **4.10.**

Scheme 4.2: *Proposed mechanism for the formation of 3,4-allenol products via gold catalysis*



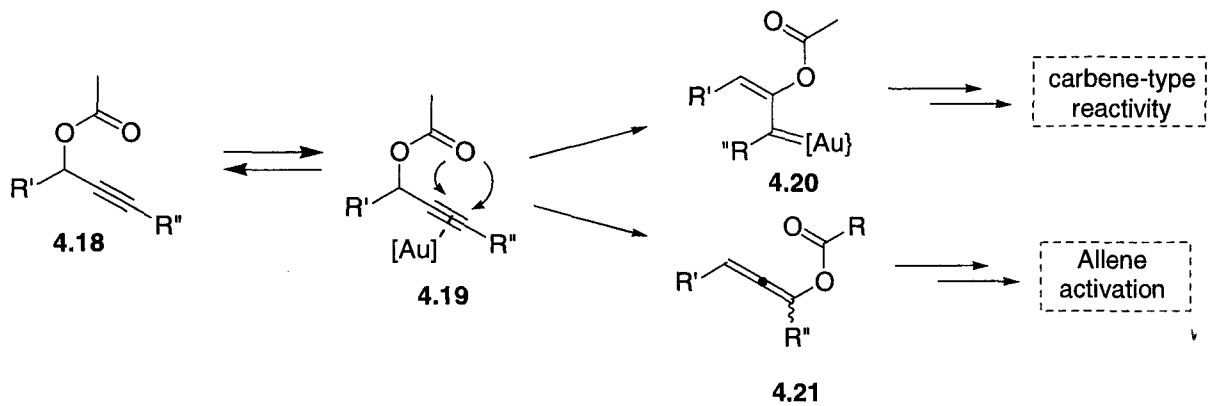
Propargylic acetates have also been used in the synthesis of the natural product sesquicarene (Scheme 4.3). The cationic gold (I) complexes bind to the alkyne and induce the intramolecular nucleophilic attack of the carbonyl oxygen onto the alkyne affording a zwitterionic vinylic gold intermediate which is then converted to a carbene intermediate by subsequent cleavage of the C-O bond.[74] Then an intramolecular cyclopropanation can occur to give the final bicyclic product **4.16**.

Scheme 4.3: *Synthesis of sesquicarene-like intermediate via gold mediated cyclopropanation*



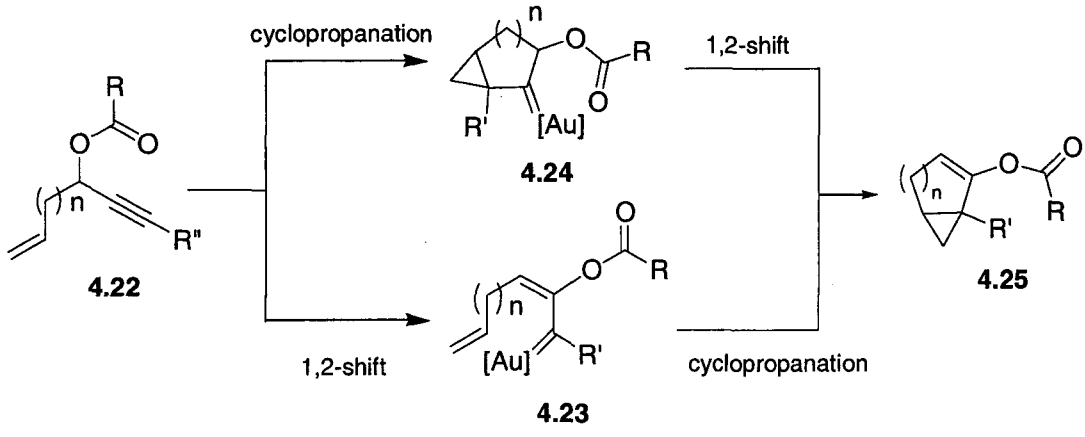
Due to their high reactivity in gold catalysis studies on the squeletal rearrangement of propargylic esters were performed. However, to this day, many mechanistic problems remain unsolved including the nature of the acyl shift which is still under debate.[82] The propargylic esters reactivity permits the opportunity to have a great diversity of compounds due to the fact that they can undergo a 1,2- and 1,3- acyl shift (Figure 4.1). The 1,2- acyl migration will give a Au-carbene intermediate and the 1,3- acyl migration give a Au-allene intermediate; both react to give different products.

Figure 4.1: *1,2 and 1,3-acyl shift of propargylic esters*



Furstner and his group showed that cationic gold(I), obtained by the silver-induced abstraction of the chloride from $Au(PPh_3)Cl$, was an efficient catalyst do to cycloisomeration. They report that cyclopropanation then migration mechanism occurs allowing the stereogenic information at the propargylic position to be transferred to the product (Scheme 4.5).[83] Toste *et al.* report the opposite sequence where the stereogenic information is consistent with a migration then cyclopropanation sequence (Figure 4.2).[84]

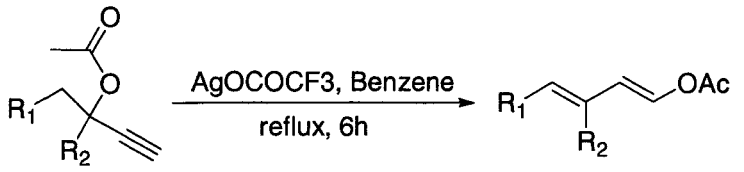
Figure 4.2: *Two reported mechanistic sequences for the cyclopropanation and 1,2-acyl shift*



Propargylic esters can also undergo a 1,3-acyl shift rearrangement. The transformation of propargylic esters into allenyl esters is a common process since it is an example of a [3,3] sigmatropic rearrangement.[75] In addition, the gold catalyst can activate the allene moiety, in a mild fashion, permitting the intermediate to undergo further reactivity. This concept has permitted the production of 2,3-indoline-fused-cyclobutanes,[85] indenes,[86] cyclopentadienylic esters and corresponding cyclopentanones,[87] conjugated dienes[88] by protodesilation, dihydrofurans[89] and finally α-ylidene β-ketones[90] if no nucleopghilic groups are present at the propargylic position.

Later, Cookson et.al[91] demonstrated an improved way of making the allenyl acetates by copper catalyzed reactions, which gave the desired product in a quantitative yield. While investigating different conditions they found that heating of various propargylic acetates (**4.26a-d**) in refluxed benzene with silver trifluoroacetate or platinum chloride gave the diene (**4.27a-d**) as a sole product in a (7:1 trans:cis) ratio (Scheme 4.4). Formation of the allenyl acetate intermediate seen above by metal catalyzed rearrangement has been well documented,[92] but none by gold. The resulting dienes where exposed to dienophiles such as maleic anhydride, N-phenylmaleimide, ethyl acrylate etc., to give the corresponding cycloadduct in yields ranging from 52-91 %.

Scheme 4.4: *Diene formation by a silver catalyzed reaction*



4.26 **4.27**

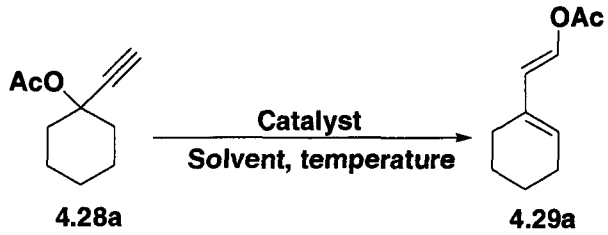
a: R_1 = H, R_2 = Me
b: R_1R_2 = $[CH_2]_4$
c: R_1R_2 = $[CH_2]_3$
d: R_1= H, R_2 = 4-methylcyclohex-3-enyl

Taking these studies into account, we envisaged the development of a new gold(I) catalyzed reaction for the formation of dienes using propargylic esters. Demonstrating the chemioselectivity of the gold-acid catalyzed diene formation by rearrangement of propargyl pivaloates and by cycloisomerization is also one of our objectives.

Initial discovery

This project was initially started during my undergraduate degree as a partial fulfillment for my BSc. and was later continued by Anne-Catherine Bédard, a COOP and part-time undergraduate worker in our laboratory, under my guidance. Acetic acid 1-ethynyl-cyclohexyl ester (**4.28a**) was first treated with $Au(PPh_3)Cl$ (5% mol) and AgOTf (5 % mol) in dry dichloromethane at room temperature. Please note that all reactions documented in this thesis using AgOTf were run in the dark because of AgOTf's sensitivity to light. After stirring for 2.5 hours at 25°C diene **4.29a** was isolated in a 50 % yield as the major product (Table 4.1, entry 1). To optimize the reaction conditions, the temperature, solvent and catalyst loading was varied.

Table 4.1: *Initial optimization of Au and Ag(I)-catalyzed diene synthesis*



4.28a **4.29a**

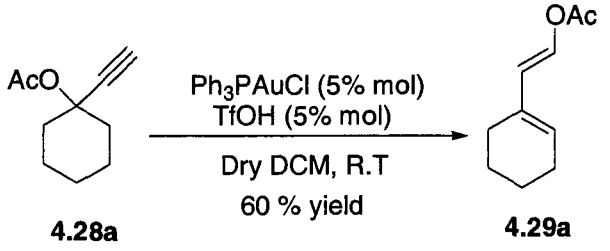
Entry	Catalyst	Solvent[d]	Temperature	Yield (%)[a]
1	5% $Au(PPh_3)Cl$, 5% AgOTf	DCM	R.T	50
2	5% $Au(PPh_3)Cl$, 5% AgOTf	DCM	0°C	17[c]
3	5% $Au(PPh_3)Cl$, 5% AgOTf	DCM	-23°C	0[b]
4	2.5 % $Au(PPh_3)Cl$, 2.5 % AgOTf	DCM	R.T	0[b]
5	0.1 % $Au(PPh_3)Cl$, 0.1% AgOTf	DCM	R.T	0[b]
6	5% $Au(PPh_3)Cl$, 5% AgOTf	ACN	R.T.	0[b]
7	5% $Au(PPh_3)Cl$, 5% AgOTf	MeOH	R.T.	0[b]
8	5% $Au(PPh_3)Cl$, 5% AgOTf	DCM	R.T.	0[b]

[a] Isolated Yield, [b] Un-Identified product, [c]NMR conversion, [d]all solvents used were dry except for entries 7 and 8. Note that reaction times varied between 20 minutes to 2.5 hours.

Changing the temperature to 0°C gave the desired product in a 17% yield (entry 2). When further lowering the temperature of the reaction to –23°C (entry 3), no desired product was obtained. A reduction of catalyst loading to 2.5 mol % (entry 4) of $Au(PPh_3)Cl$ and AgOTf, and 0.1 mol % of $Au(PPh_3)Cl$ and AgOTf (entry 5) lead to the formation of un-identified products. Experiments employing different solvents such as dry acetonitrile (entry 6), methanol (entry 7), and non-anhydrous dichloromethane (entry 8) also did not yield to any desired product.

To further explore and optimise the reaction, the conditions reported by Christiane M. Grise and Louis Barriault[93] were tried. They reported the use of catalyst system generated by $AuPPh_3Cl$ and TfOH to perform benzannulations. This catalyst system was tried (Scheme 4.5) using a 5% loading, and generated the desired diene **4.29a** in a 60 % yield.

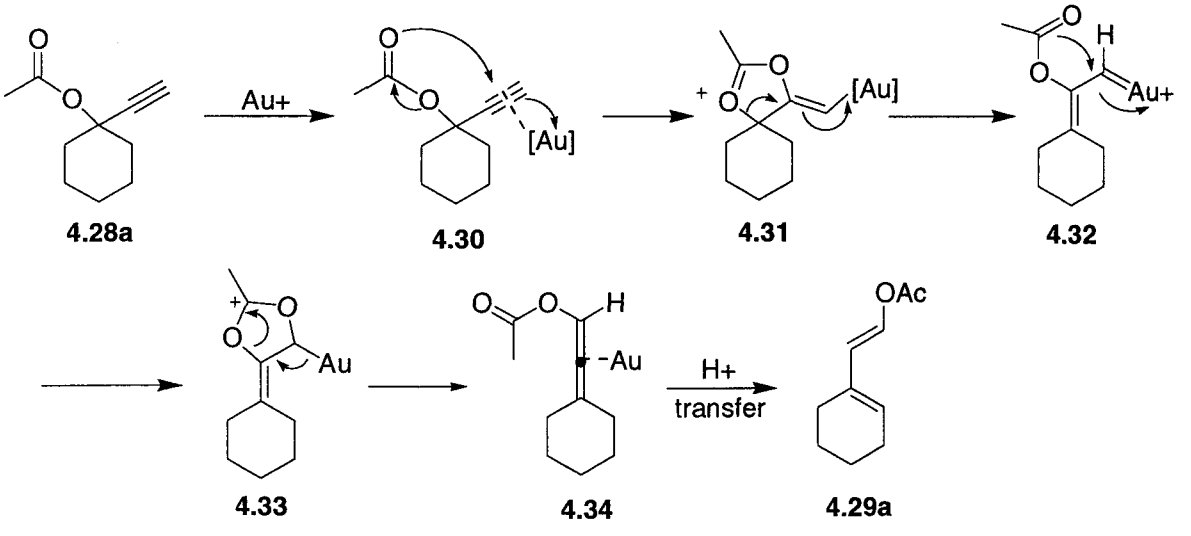
Scheme 4.5: *Diene formation using conditions developed by L. Barriault and C.M. Grisé*



In the midst of our promising preliminary results, we decided to further investigate the reaction at hand and to minimize the major hydrolysis side product.

We proposed the following mechanism depicted in Scheme 4.6. The propargylic acetate **4.28a** undergoes complexation with the gold (I) species to form **4.30**. The acetate can react with the electron-activated alkyne in a 5-exo-dig fashion to give **4.31**, which will rearrange in the allylic carbene **4.32**. The allylic acetate **4.32** can then cyclize to give **4.33** followed by migration of the gold species to produce intermediate **4.34**. Finally, a proton migration occurs to yield the desired diene **4.29a**.

Scheme 4.6: *Proposed mechanism*

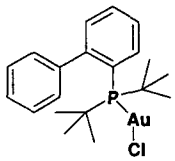
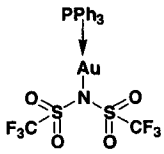
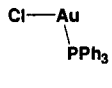
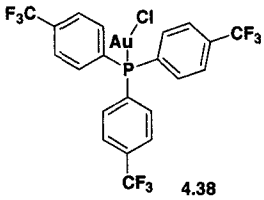


Optimization

First, different catalyst/co-catalyst/solvent combinations were investigated via a high throughput scan to find the optimal conditions. To this end, we utilized the SYMYX located in the Center for Catalyst Research and Innovation (CCRI) at the University of Ottawa. The workflows are specially designed to run a large number of reactions (96 well plates) on a very small scale (200-800 μl) in a fully automated fashion. Plates maybe run at high-pressures (up to 1500 psi.), temperatures up to 200°C, stirring speeds up to 1000rpms and analysis of the results can be done via GC (FID and MS), SFC and HPLC each with an auto-sampler. Therefore, this is process minimizes cost, time and experimental error.

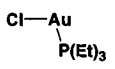
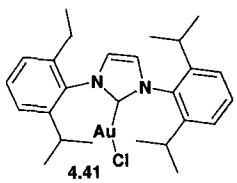
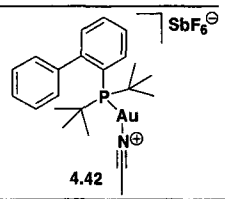
Our scanning process included eight different catalysts, which were each tested with or without a silver co-catalyst. Three silver co-catalysts were chosen ($AgSbF_6$, $AgBF_4$, AgOTf). Each combination of gold catalyst/co-catalyst was tested in five different solvents (DCM, DCE, benzene, toluene, chlorobenzene) bringing the total reaction count with co-catalyst to ninety different combinations and fifteen different combinations with no co-catalyst present. The training, setup and analysis for this process took two days; establishing itself to be an efficient catalyst scanning process. A list of all the reactions tried and their results are seen in Tables 4.2 and 4.3.

***Table 4.2:** SYMYX scan for optimized reaction conditions**

		 4.35	 4.36	 4.37	 4.38
no silver	DCM	-	Product/Degradation	-	-
	DCE	-	Product/Degradation	-	-
	Benzene	-	Product/Degradation	-	-
	Toluene	-	Product/Degradation	-	-
	Chlorobenzene	-	Product/Degradation	-	-
$AgSbF_6$	DCM	Product/Degradation	-	Product/Degradation	Product/Degradation
	DCE	Product/Degradation	-	Product/Degradation	Product/Degradation
	Benzene	Product/Degradation	-	Product/Degradation	Product/Degradation
	Toluene	Product/Degradation/SM	-	Product/Degradation	Product/Degradation
	Chlorobenzene	Product/Degradation	-	Product/Degradation	Product/Degradation
$AgBF_4$	DCM	Product/Degradation	-	Product/Degradation	Product/Degradation
	DCE	Product/Degradation	-	Product/Degradation	Product/Degradation
	Benzene	Product/Degradation	-	Product/Degradation	Product/Degradation
	Toluene	Product/Degradation	-	Product/Degradation/SM	Product/Degradation
	Chlorobenzene	Product/Degradation	-	Product/Degradation	Product/Degradation
AgOTf	DCM	Product/SM	-	SM	SM
	DCE	Product/SM	-	SM	SM
	Benzene	Product/SM	-	SM	SM
	Toluene	Product/SM	-	SM	SM
	Chlorobenzene	Product/SM	-	SM	SM

[a] Reaction time = 1h at r.t., [b] Reaction scale = 5mg, [c] All reagents were combined in a glove box. [d] Catalyst were dispensed as DCM solution and the solvent s were concentrated before the starting material was added. [e] SM = Acetic acid 1-ethynyl-cyclohexyl ester. * Done by Anne-Catherine Bédard.

***Table 4.3:** SYMYX scan for optimized reaction conditions (cont.)**

		 4.39	$AuCl_3$ 4.40	 4.41	 4.42
no silver	DCM	-	Product	-	Product/Degradation
	DCE	-	Product/SM	-	Product/Degradation
	Benzene	-	Product/SM	-	Product/Degradation
	Toluene	-	Product/SM	-	Product/Degradation
	Chlorobenzene	-	Product/SM	-	Product/Degradation
$AgSbF_6$	DCM	Product/Degradation	Product	Product/Degradation	-
	DCE	Product/Degradation	Product/Degradation/SM	Product/Degradation	-
	Benzene	Product/Degradation	Product/Degradation/SM	Product/Degradation	-
	Toluene	Product/Degradation	Product/Degradation/SM	Product/Degradation	-
	Chlorobenzene	Product/Degradation	Product/Degradation/SM	Product/Degradation	-
$AgBF_4$	DCM	Product/Degradation/SM	Product/Degradation/SM	Product/Degradation	-
	DCE	Product/Degradation	SM	Product/Degradation	-
	Benzene	Product/Degradation/SM	Product/Degradation/SM	Product/Degradation	-
	Toluene	Product/Degradation/SM	Product/SM	Product/Degradation	-
	Chlorobenzene	Product/Degradation	Product/SM	Product/Degradation	-
AgOTf	DCM	SM	Product/SM	Product/SM	-
	DCE	SM	Product/SM	Product/SM	-
	Benzene	SM	Product/SM	Product/SM	-
	Toluene	SM	Product/SM	Product/SM	-
	Chlorobenzene	SM	Product/SM	Product/SM	-

[a] Reaction time = 1h at r.t., [b] Reaction scale = 5mg, [c] All reagents were combined in a glove box. [d] Catalyst were dispensed as DCM solution and the solvent s were concentrated before the starting material was added. e SM = Acetic acid 1-ethynyl-cyclohexyl ester. * Done by Anne-Catherine Bédard.

To set up the reaction, all reagents were weighed in a glove box and a solution of the catalyst and co-catalyst were prepared in DCM. The automated distributor dispensed the catalyst and co-catalyst as a DCM solution into the appropriate oven dried reaction vials. The solvents were then concentrated and then the starting material was dispensed into the reaction flask as a solution in the chosen solvent. Reactions were run for one hour at room temperature and on a five-milligram scale. It should be noted that each reaction plate contained control reactions; each gold catalyst without its co-catalyst, each co-catalyst without gold. Additionally, previously made product was added to the plate to test degradation by each catalyst system; these reactions were only tested in DCM.

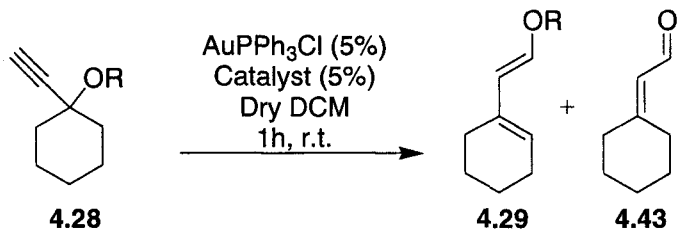
Analysis of all the reactions was done by TLC by an automated liquid dispensing robot. Each TLC plate contained the results of six reactions as well as non-reacted starting material and product to ease the analysis. The TLC's were analyzed via relative quantitative product/starting material/degradation products. The best results obtained were the catalyst combinations of **4.35**/$AgBF_4$ in DCE, $AuCl_3$ in DCM, **4.41**/$AgSbF_4$ in DCE, **4.41**/$AgBF_4$ in DCE and **4.42** in DCE. These reactions were re-done individually in the laboratory several times to get the isolated yields, but none of the isolated yields were better than our initial catalyst combination of $AuPPh_3Cl$/AgOTf in DCM. Nevertheless, this experiment was fruitful in identifying other strong candidates for our transformation.

Another aspect we wanted to optimize was the presence of hydrolysis product (**4.43**). We suspected that hydrolysis products were being formed via a trace amount of water present in the solvents (even if they were distilled) (Table 4.4). Our first task was to determine optimal reaction conditions to eliminate this side product. To this end, freshly distilled solvents were used and every precaution was taken to ensure dry reaction conditions (catalyst were kept in the glove box, flask were flame dried twice, solvents were distilled twice, etc.). Even so, a variable amount of the hydrolysis product was observed each time. The only modification that would reduce the hydrolysis of our product was the use of molecular sieves, but it significantly reduced the speed of the reaction (reaction now took days to complete). At that point we decided to investigate the use of a different protecting

group on the alcohol. The use of a pivaloate instead of an acetate protecting group would, to our knowledge, render the hydrolysis reaction more difficult.

The pivaloyl substrate was reacted using the standard conditions (5 % mol of $AuPPh_3Cl$ and AgOTf). We were pleased to see that the reaction yields were optimized and a reduction in hydrolysis product was observed (see Table 4.4).

***Table 4.4**: Propargyl acetates vs. propargyl pivaloates- a reduction in hydrolysis product formation*



4.28 **4.29** **4.43**

R	Catalyst	Yield (4.29)	Hydrolysis product (4.43)
Piv	AgOTf	79%	2-5%
	TfOH	52%	
Ac	AgOTf	70%	10-75%
	TfOH	60%	

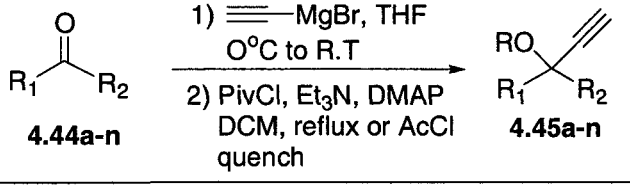
Now that we had obtained satisfactory results concerning the reduction of side product formation for the isolated product yield of both the acid and silver co-catalyzed gold reactions, we were then ready to investigate the scope of the reaction.

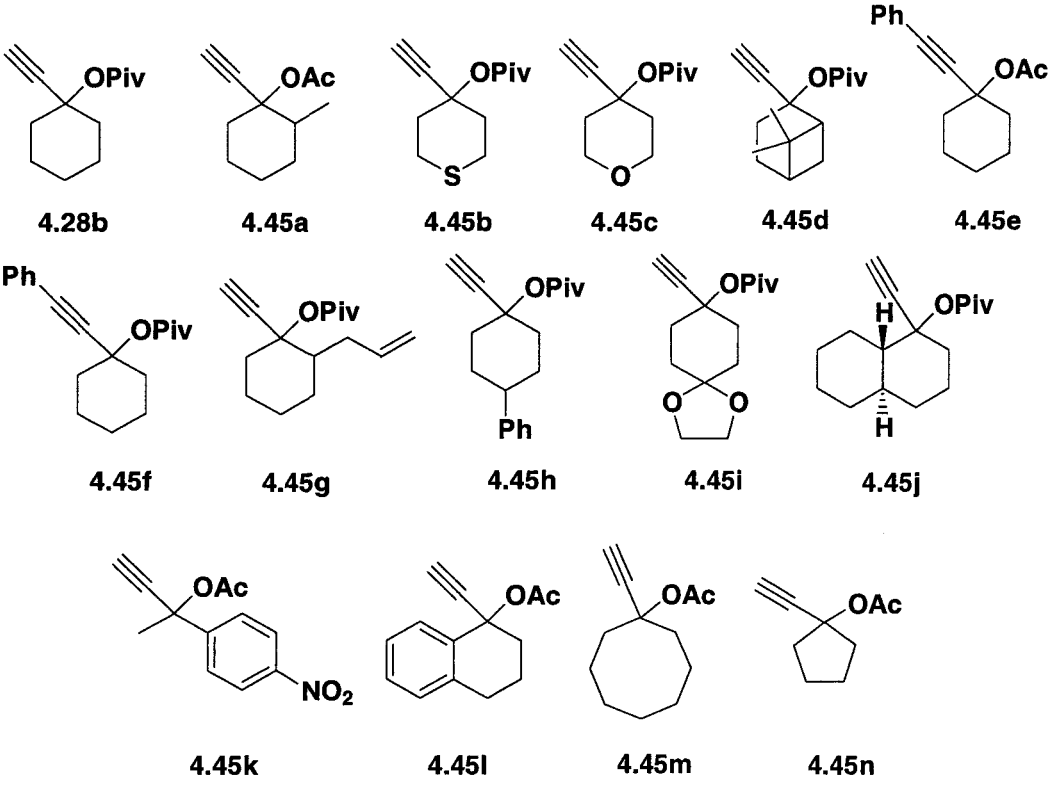
Scope and Limitations of the Gold Catalyzed Rearrangement of Propargylic Acetate to Dienes

Having found the optimal reaction conditions we decided to explore the substrate scope of our reaction. First, varieties of propargyl pivaloates were prepared using conventional methods to test our best reaction conditions. Starting with the corresponding ketone (**4.44a-n**) by treatment with ethynyl magnesium bromide in dry ether at 0°C and

quench with water afforded the corresponding propargyl alcohol in good yield. Subsequent protection of the alcohol moiety with pivaloylchloride afforded the desired protected substrate in all cases with reasonable to excellent yields (Table 4.5). Some substrates, previously synthesized, with the acetate protecting group were also examined.

***Table 4.5**: Substrate scope for the formation of the diene*

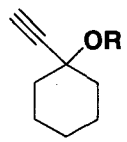
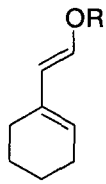
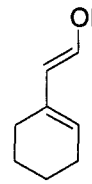
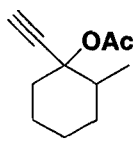
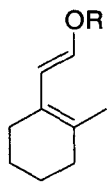
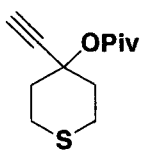
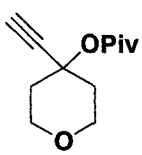
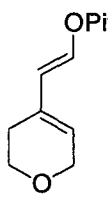
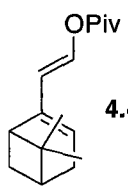
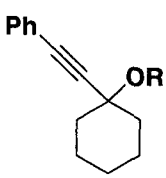
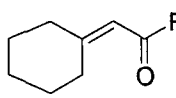
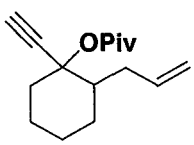




We submitted all our compounds to our two best reactions conditions which are the use of either AgOTf or TfOH as co-catalyst to $AuPPh_3Cl$ in DCM at room temperature. All experiments were monitored by TLC. Our results are summarized in Tables 4.6 and 4.7.

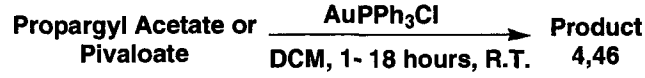
***Table 4.6**: Results of the gold catalyzed diene formation of propargylic acetates and pivaloates*

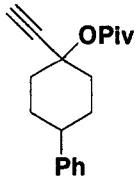
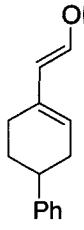
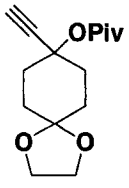
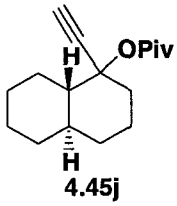
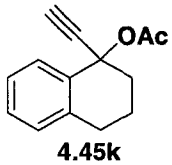
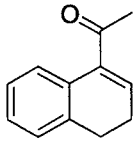
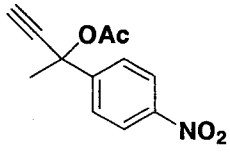
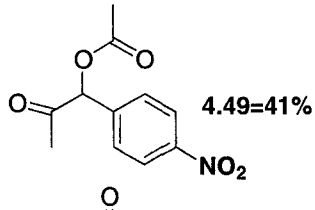
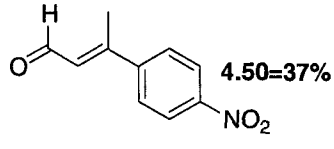
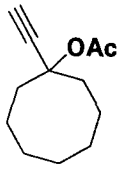
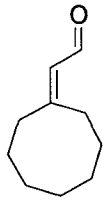
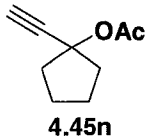
Propargyl Acetate or Pivaloate $\xrightarrow[\text{DCM, 1- 18 hours, R.T.}]{\text{AuPPh}_3\text{Cl}}$ **Product 4.46**

Entry	Substrate	Co-Catalyst: AgOTf	Co-Catalyst: TfOH
1	 **4.28a,b**	 Piv (**4.29b**) = 79% Ac (**4.29a**) = 70%	 Piv (**4.29b**) = 79% Ac (**4.29a**) = 52%
2	 **4.45a**	 **4.46a** = 36 %	No desired product **
3	 **4.45b**	No desired product **	N/A
4	 **4.45c**	 **4.46c** = 71%	No desired product **
5	 **4.45d**	 **4.46d** = 7 % conversion*	N/A
6	 **4.45e,f**	Ac (**4.47**) =  56% Piv (**4.46f**) = no desired product **	Ac = no desired product ** Piv = no desired product **
7	 **4.45g**	Traces of both product and hydrolyzed product	No desired product**

* By ^{1}H NMR ** Only degradation was observed

***Table 4.7**: Results of the gold catalyzed diene formation of propargylic acetates and pivaloates (cont.)*



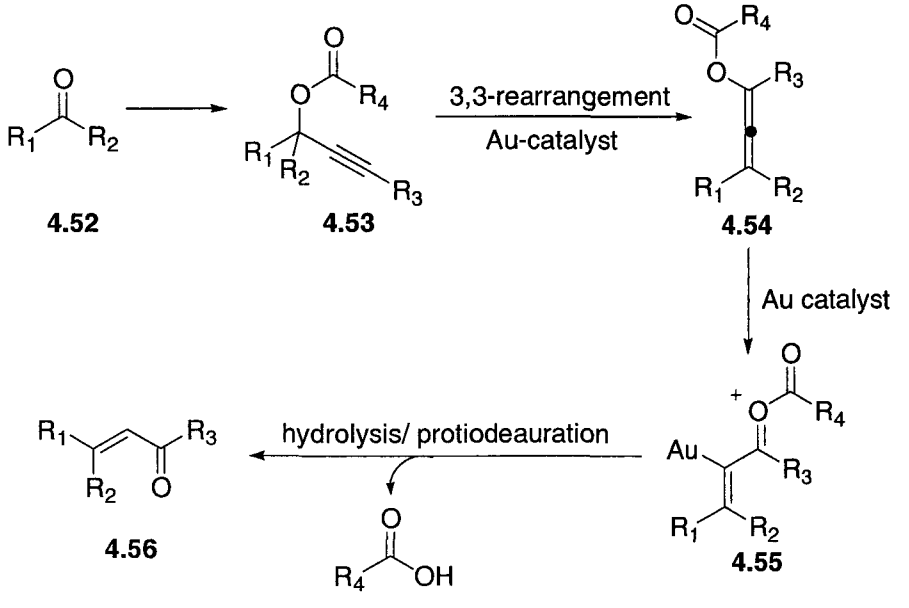
Entry	Substrate	Co-Catalyst: AgOTf	Co-Catalyst: TfOH
8	 **4.45h**	 **4.46h** = 53%	No desired product**
9	 **4.45i**	3 % conversion* and hydrolysis product (1:3)	11 % conversion* and hydrolysis product
10	 **4.45j**	No desired product **	No desired product **
11	 **4.45k**	 **4.48= 73%**	N/A
12	 **4.45l**	 **4.49=41%**	 **4.50=37%**
13	 **4.45m**	 **4.51** 26% conversion*	No desired product**
14	 **4.45n**	S.M	S.M

* By ^{1}H NMR ** Only degradation was observed

We were pleased to observed product formation for **4.28a, b** and **4.46 a, c, h** when using the silver co-catalyst. Unfortunately, no product was obtained when trying our gold and triflicacid conditions. Entries 5 and 9 showed some conversion by 1H NMR but all optimization efforts were fruitless to increase the yields. As for entry 14, it is possible the carbon-carbon angles forming the five-member ring might be too small for the formation of the diene via this method. However, this is unclear to us and further investigation into mechanistic aspect of the diene formation will be undertaken. Hydrolysis and/or degradation products were observed for the remaining entries.

Zhang *et al.* have recently published a possible mechanism for the Au- catalyzed formation of α,β-unsaturated ketones from propargylic esters (Scheme 4.7).[38a] They speculated that the gold(I) catalyzed formation of the carboxyallene **4.55** can be followed by the hydrolysis/protiodeauration (by water located *in situ*) to give the corresponding ketone **4.55**.

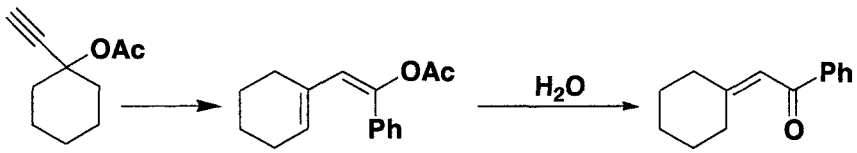
Scheme 4.7: *proposed mechanism for the Au-catalyzed formation of α,β-unsaturated ketones*



Taking this into account we propose, for example, the formation of **4.57** via a similar proposed mechanism. We propose that the diene formation is followed by the hydrolysis to

give **4.47** (no water is located *in situ* in our reaction system) (Scheme 4.8). Therefore, if we could find conditions eliminating the formation of hydrolysis products we would obtain many more desired dienes.

***Scheme 4.8:** Proposed route to hydrolysis product*



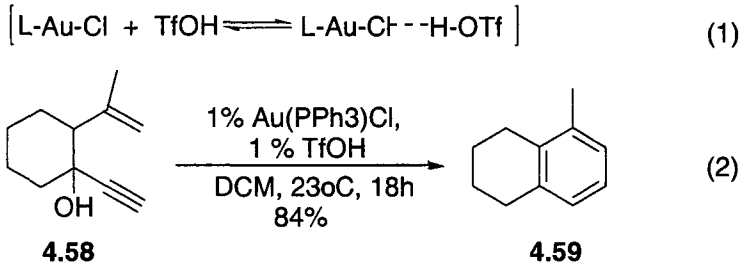
4.28a **4.57** **4.47**

In summary, the synthesis of various types of dienes was attempted, however only the cyclohexane-type propargyl acetates or pivaloates underwent the desired reaction. Other ring sizes were not compatible with the reaction at hand. In addition, certain functional groups, such as the presence of sulfur, hindered the reactions presumably by binding the gold catalyst irreversibly.

Rearrangement of 1,6-Enynes Catalyzed by $AuPPh_3Cl$ and Acid

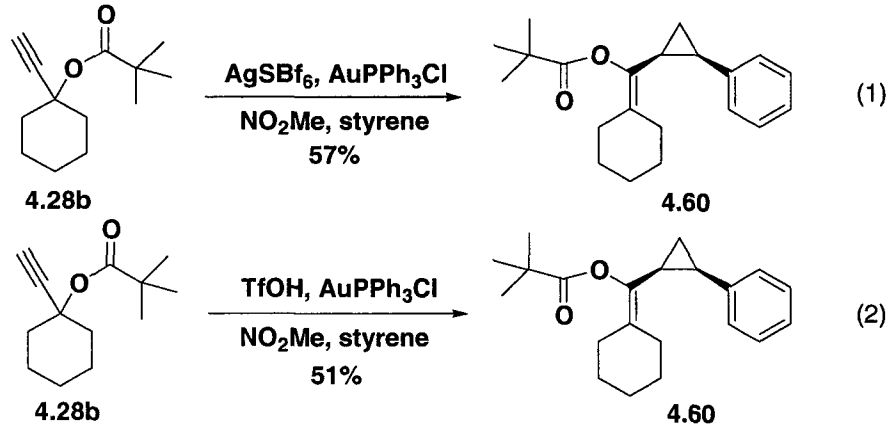
During the past few of years, gold chemistry has become a key research subject in our laboratory. Barriault et al. demonstrated that they could promote a gold-catalyzed benzannulation reaction using the $AuPPh_3Cl/AgOTf$ catalyst system. They also found that the use of $AuPh_3Cl$ and TfOH catalyzed the benzannulation reaction, and in most cases in a better yield (Scheme 4.9, eq. 2). One might assume that a trace of triflic acid could be present in the typical reaction conditions due to the presence of silver triflate, nevertheless this was an interesting discovery. They speculate that an unknown species was in equilibrium with $Au(PPh_3)Cl/TfOH$ and this species was responsible for the observed reaction (Scheme 4.9, eq.1).

Scheme 4.9: *Au/acid catalyzed benzannulation reaction*



Interestingly, the $AuPPh_3Cl$/Bronsted acid catalyst system has been used in our lab in the context of other reactions. For example, that catalyst system has been demonstrated to be applicable to a known novel reaction system otherwise catalyzed by the cationic gold species. In fact, Toste and coworkers[94] have demonstrated the gold-catalyzed transformation of propargylic pivaloate **4.28b** into product **4.60** (Scheme 4.10, eq.1) in 58% yield. In our case, treatment of the same substrate with 5 mol% of $Au(PPh_3)Cl$ and TfOH furnished the desired product in 51% yield (Scheme 4.10, eq. 2).

Scheme 4.10: *Gold(I) catalyzed stereoselective olefin cyclopropanation*

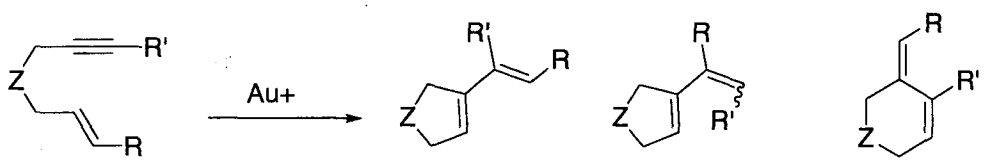


Afterwards, two undergraduate students, Eric Rodrique and Catherine Séquin, worked on the application of the previously developed gold-catalyzed reaction conditions on reactions other than the benzannulation of 3-hydroxy-1,5-enynes. The rearrangement of 1,6-enynes was chosen due to the ease of synthesis of the required substrates.

Three different products can arise from the rearrangement of 1,6-enynes: the single *exo*-cleavage product **4.62**, the double *exo*-cleavage product **4.63** and the single *endo*-

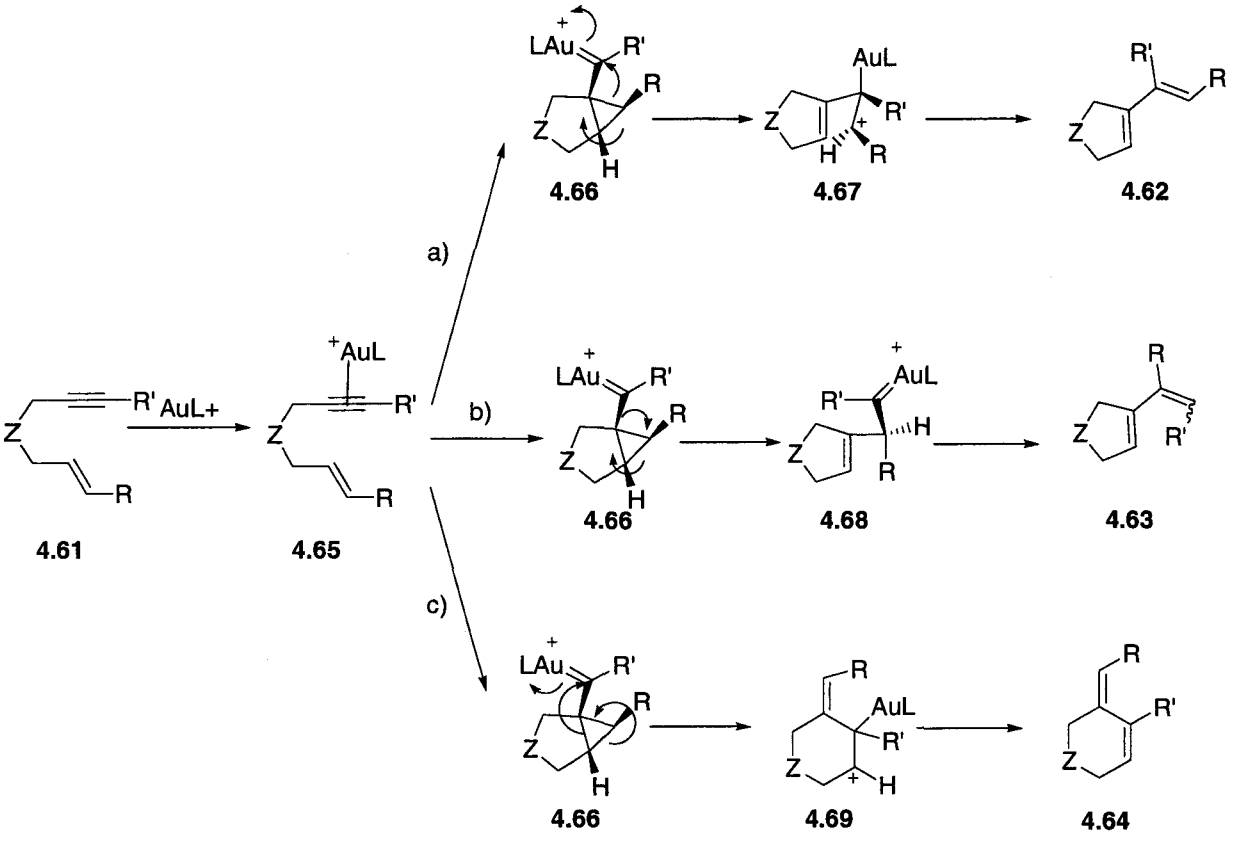
cleavage product **4.64**[95] (Scheme 4.11). The proposed mechanism for this type of rearrangement is depicted in Figure 4.3 where the product distribution is said to be influenced by the catalyst used for the reaction as well as substituent R and R'. The cationic gold catalyst, generated by the activation of the neutral LAuCl pre-catalyst with a silver salt, activates the alkyne which can, along with the alkene, react in a 5-*exo*-dig manner to produce cyclopropyl gold carbene **4.65**. Even though it has been demonstrated that these type of intermediates have carbene-like properties.[96] However, it has recently been proposed that these types of intermediates might also be of carbocationic nature.[97] Intermediate **4.66** can rearrange following three possible pathways depending on the substitution pattern. In pathway *a*, the cyclopropyl carbene intermediate **4.66** rearranges to generate carbocation **4.67** followed by metal elimination to affords diene **4.62**. In the double cleavage pathway (b), a diotropic rearrangement[98] occurs to form carbene **4.68** that gives **4.63** after a hydride shift and a de-metallation sequence. For the formation of endocyclic product **4.64**, the cyclopropyl carbene intermediate rearranges to produce cation **4.69** which can then undergo a metalelimination.

***Scheme 4.11**: Possible products arising from 1,6-enyne rearrangement*



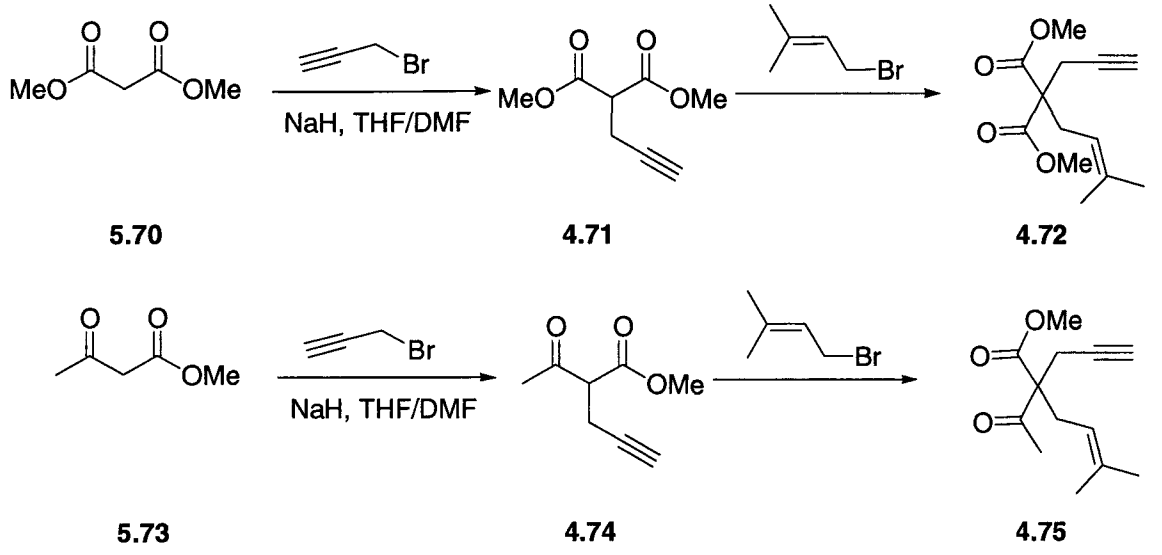
4.61 **4.62** **4.63** **4.64**

Figure 4.3: *Proposed mechanism for the 1.6-enyne rearrangement*



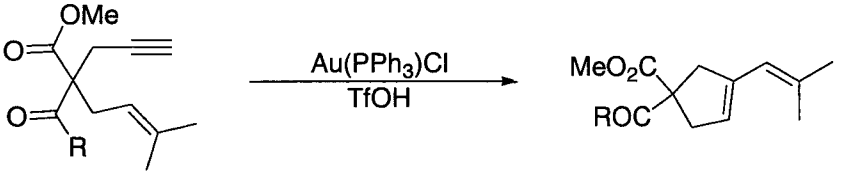
To study the skeletal rearrangement of 1,6-enynes with $Au(PPh_3)Cl$ and an acid, substrates that cyclize to give products of the type **4.62** were selected. Thus, known substrate **4.72** was synthesized in two steps from commercially available dimethylmalonate and, substrate **4.75** was also synthesized in a similar way.

Scheme 4.12: *Substrate synthesis for the 1,6-enyne rearrangement*



In a preliminary trial, substrate **4.72** was treated with 2.5 mol% of each, $Au(PPh_3)Cl$ and TfOH in dichloroethane at room temperature. The reaction went to completion and it was possible to isolate the desired product (**4.76**) in 70% yield. Moreover, the $Au(PPh_3)Cl$/TfOH catalyzed cycloisomerization of **4.75** gave **4.77** in 60% yield. Even though the optimization of the reaction conditions was done for the benzannulation, we wanted to study the effect of the different acids on the rearrangement of 1,6-enynes. The goal of this investigation was to find other Bronsted acids than TfOH that could catalyze the reaction in the presence of $AuPPh_3Cl$.[99]

Scheme 4.13: *Preliminary trial for the 1,6-enyne rearrangement*



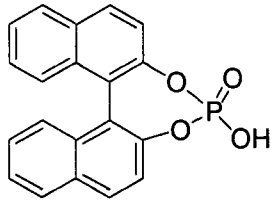
4.72, R=OMe
4.75, R=Me

4.76, R=OMe 70%
4.77, R=Me 60%

After, scanning a variety of different acids (acetic acid, PPTS, trichloroacetic acid, PTSA, *N,N'*-Di(4-fluorophenyl)urea, TFA etc.) they found that different acids could in fact

be used in combination with $AuPPh_3Cl$ to promote the reaction. TfOH, TFA and phosphoric acid **4.78** (Figure 4.4) and PTSA were all compatible with the reaction although the reaction went to completion only in the case of TfOH, PTSA and TFA.[100]

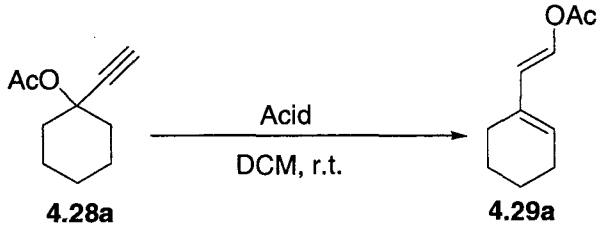
***Figure 4.4**: 1,1'-binaphthyl-2,2'-diylhydrogenphosphate*



4.78

Knowing that the cycloisomerization reaction could be catalyzed by other acid we now wanted to research the other potential acids to catalyze the diene formation from cyclohexane propargylic acetate and pivaloate. One can imagine that if the two types of reactions can be catalyzed by different acids one can promote selective sequential diene formation. The following Table 4.8 entails the acids tested for the diene formation.

***Table 4.8** : Acid scope for the diene formation of propargylic acetates*



4.28a **4.29a**

Entry	Acid	Yield (%)[a]
1	5% $Au(PPh_3)Cl$, 5% PTSA[b]	0
2	5% $Au(PPh_3)Cl$, 5% Phosphoric Acid A[c]	0[d]
3	5% $Au(PPh_3)Cl$, 5% TFA	5[d]
4	5 % $Au(PPh_3)Cl$, 5 % H_3PO_4	0
5	5 % $Au(PPh_3)Cl$, 5% TfOH	60[d]
6	5% $Au(PPh_3)Cl$, 5% TMSOTf	0[d]

[a] Isolated Yield, [b] p-toluene sulfonic acid, [c] 1,1'-binaphthyl-2,2' diylhydrogenphosphate, [d] Decomposition product recovered

Entries 1, 2, 4 and 6 did not catalyze the rearrangement reaction. A trace amount of product was observed when catalyzing the reaction with TFA however, we observed once again formation of our desired diene in good yields using TfOH as the co-catalyst. Since the conversion was low in the case of **4.28a** with TFA, it is believed that a cationic gold species was not generated in this case. To confirm that that reaction was catalyzed by a combination of $Au(PPh_3)Cl$ and an acid, control experiments were performed. There was no desired product observed when the reaction was done in the presence of only $Au(PPh_3)Cl$, or only the co-catalyst (acid).

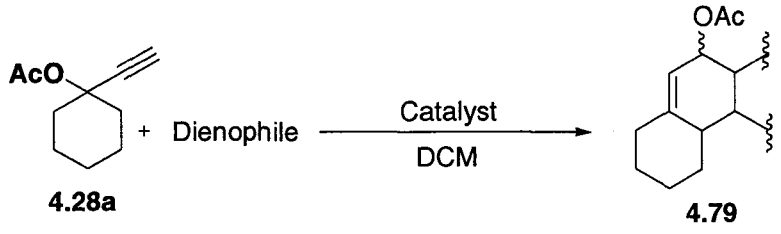
Interestingly, the 1,6-enyne and the propargylic acetate/pivaloates rearrangement are catalyzed by different acid co-catalyst. In fact, the rearrangement of propargyl pivaloates to give a diene needs a strong acid whereas the cycloisomerization would proceed in good yield with a weaker acid. Such methods for the chemeo-selective creation of dienes could be very useful in synthetic chemistry when developing substrates, or even in total synthesis.

Outlook

The novel discovery of the diene formation via a gold-catalyzed rearrangement of propargylic acetates and pivaloates is very interesting. In the past, such systems were converted to dienes by heating for many hours in the presence of a silver lewis acid. The fact that we can do the exact reaction within 1 hour at room temperature makes our system much more appealing.

One could also imagine the development of a one-pot cascade reaction where the diene could be formed and react in situ with a chosen dienophile. Such reaction would form, in one step, a functionalized bicycle amendable to be used in the synthesis of many natural products and hormones.

Figure 4.5: *One pot cascade reaction of diene formation/Diels-Alder reaction.*



Conclusion

In brief, a novel and effective method for the development of dienes from propargylic acetates and pivaloates has been developed. Using 5 mol% each of $Au(PPh_3)Cl$ and silver triflate, the acetoxy- and pivaloxy-dienes are obtained in good yields. It was found that the same rearrangement could be catalyzed by $Au(PPh_3)Cl$ and triflic acid in equal to better yields. Some optimization still needs to be done to minimize the presence of hydrolysis product. Such optimization will require a detail look into the mechanistic aspects of the reaction at hand.

In addition, the use of the acid co-catalyst has been showed to be useful for many reactions developed in our laboratory. Furthermore, chemeoselectivity can be achieved by using the appropriate acid catalyst to promote a specific gold catalyzed reaction.

Chapter 5

Efforts towards the Development of the Tandem Oxy-Cope/Ene/ Claisen/Diels-Alder Reaction

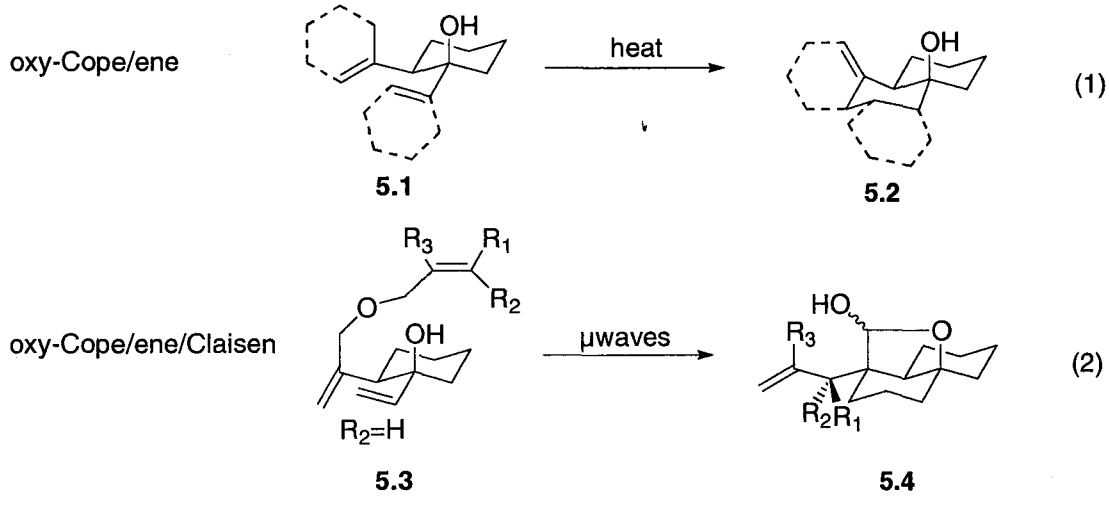
Introduction to Cascade Reactions

During the past century, the world of chemistry has evolved immensely. Nonetheless, the development of efficient synthetic methods, especially for the formation of carbon-carbon bonds, remains a challenge. In the last decade, cascade reactions have started to emerge as strong powerful tools for the formation of multiple C-C bonds, maximizing the efficiency and accessibility to complex molecules. Cascade reactions (or domino reactions)

consists of a consecutive series of reactions in a defined order,[101] where no additional reagents are added.

In our laboratory, such cascade reactions have been developed utilizing pericyclic reactions to access polycyclic compounds such as diterpenes. In fact, in 2000 Barriault and Warrington[102] published a rapid method for the preparation of advanced polycyclic intermediate via a cascading oxy-Cope/ene reaction of 1,2-divinylcyclohexanols. This methodology was then applied to the total synthesis of (+)-arteannuin M.[103] Further research lead to the development of the tandem oxy-Cope/transannular-ene/Claisen reaction sequence that generated up to four continuous stereogenic centers including two quaternary carbons.[104] This highly diastereoselective synthesis of decalin type cores was used towards the total synthesis of tetrodecamycin.[105]

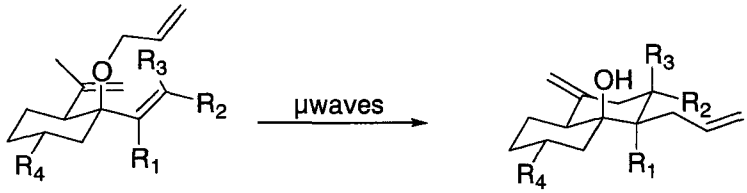
***Scheme 5.1**: Cascading pericyclic reactions – initial discoveries*



Additional research in the laboratory permitted the development of the oxy-Cope/Claisen/ene reaction. In 2004, Barriault and Sauer reported the highly efficient transfer of chirality from the macrocyclic conformation arising from the tandem oxy-Cope/Claisen/ene reaction. Here, the 10-membered ring macrocycle formed by the oxy-Cope rearrangement can adopt a few conformations. The conformational preference of the macrocycle at the transition state for the Claisen and ene reactions control the stereochemical outcome thus forming decalins with two consecutive quaternary centers.[106] This newly

developed methodology was applied, as a key synthetic step, towards the total synthesis of two natural products: wiedemannic acid[107] and teucrolivin A.[108]

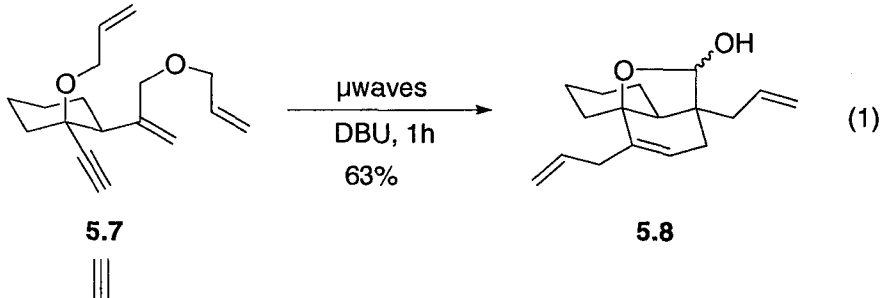
Scheme 5.2: *Cascading reaction – Oxy-Cope/Claisen/Ene*



5.5 **5.6**

Another cascade reaction developed in our lab, this time un-expectedly was the oxy-Cope/Claisen/ene/Claisen domino reaction. Dr. Jeff Warrington discovered this reaction and Danny Gauvreau then worked on studying its scope and limitations.[109] He found that the reaction was very sensitive to certain functional groups, but could be optimized when using DBU (Scheme 5.3, equation 1) as a base instead of the initially used triethylamine (equation 2). At the time, a master student in the lab, Roxanne Clement, investigated related functionalities to the above-mentioned systems **5.7** and **5.9**. Unfortunately, the substrates sensitivity lead to a limited scope and applications compelling her to investigate other tandem sequences such as the oxy-Cope/Claisen/ene/hydroxyl-directed Diels-Alder reaction.[110]

Scheme 5.3: *Oxy-Cope/Claisen/Ene/Claisen reaction*

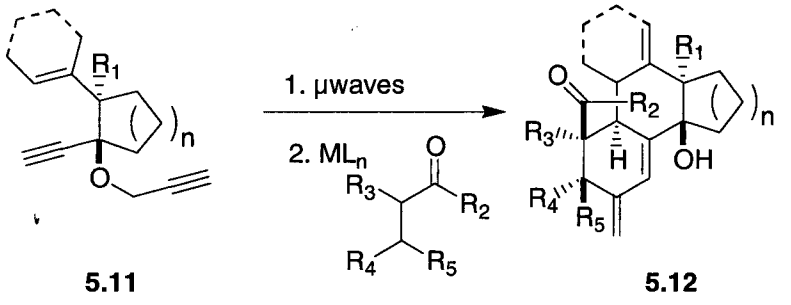


5.7 **5.8**

5.9 **5.10**

This very efficient domino reaction proved to be an efficient way to access carbocycles from easily synthesized substrates. The first three tandem reactions form a diene, which can react with a dienophile to undergo the hydroxyl-directed Diels-Alder reaction. This novel reaction was of great importance since it selectively generated one carbocycle having up to four new continuous chiral centers. Further optimization by Clément and later Grisé-Bard led to the development of the powerful synthetic process that could be used to generate complex polycyclic molecules (Scheme 5.4).[111] In fact, this methodology was used towards the synthesis of digitoxin.[94] The synthesis of this natural product is still under progress by Jason Poulin.

***Scheme 5.4**: Oxy-Cope/Claisen/Ene/HDDA reaction*



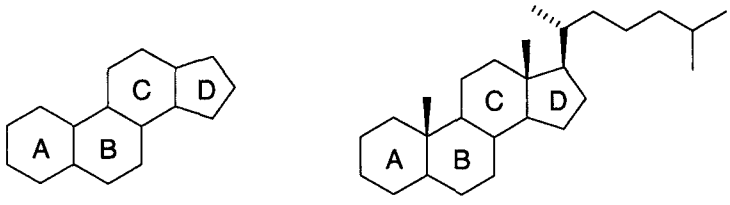
5.11 **5.12**

It is evident that cascade reactions have numerous advantages, notably the fact that by performing many reactions at once the yield is typically higher due to less purification steps. To this end, the utilization of such reactions was envisioned to synthesize steroids.

Steroids

A steroid is a terpenoid characterized by its sterane nucleus. They consist of a four-ring core usually distinguished by the letters A, B, C, D. The four-ring core is always composed of a five-membered ring and three six-membered rings (Figure 5.1). Steroids are distinguished by the functional groups attached to these rings as well as the oxidation states of the rings. They are essential to many life forms and are widely distributed in nature occurring naturally in plants, fungi and animals.

***Figure 5.1**: Steroid core structure*

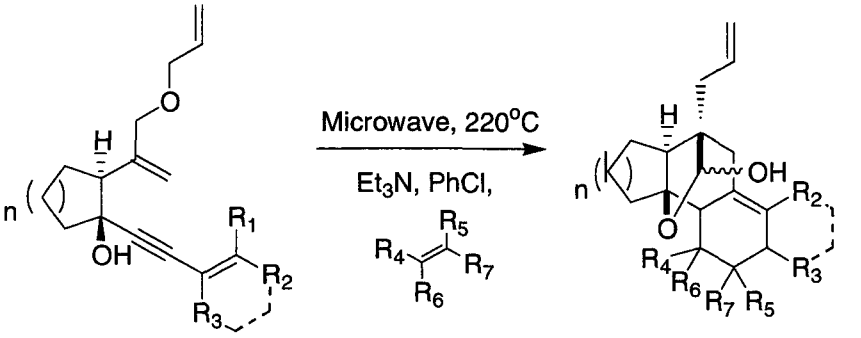


Basic Core 1 **Basic Core 2**

Many steroids have proved to be valuable drugs. In fact, they are used to treat patients who have hormonal deficiencies, autoimmune diseases, as well as patients that undergo organ transplants to suppress immune response.[112] Steroid drugs have also been known to be used in cancer therapy[113] but the most widely used steroids are the synthetic estrogen and progesterone used in birth control pills. Simple steroids are known to be easily synthesized via microbial methods but more complex steroids require more attention.

The total synthesis of steroids is undoubtedly one of the most important achievements in organic chemistry. Bachmann, Coles and Wilds[114] published the first synthesis of the simplest of sex hormones, equilenin, in 1939. In 1952 came the first synthesis of cholesteron and of the sex and adrenocorticol hormones by Woodward[115] and Robinson in addition to many more milestones reported thereafter. The enormous strides observed in the advancement of steroid synthesis over the years are mainly due to the advancement in organic chemistry. The number of specifically directed reaction constantly increases easing the synthesis of these complex polycycle molecules. Industrial production of steroid hormones has always been a complex task since it requires stereoselective reactions and convergence of the synthesis. Our goal is to develop a way to easily access the steroid core in one tandem reaction sequence. To this end, we envisioned the use of a tandem oxy-Cope/Claisen/ene/Diels-Alder reaction. The tandem oxy-Cope/Claisen/ene/Diels-Alder reaction (Scheme 5.5) can produce up to 9 (including the lactol) contiguous stereogenic center where two are quaternary. In addition, this domino process provides the steroid core or diterpene possessing much exploitable functionality.

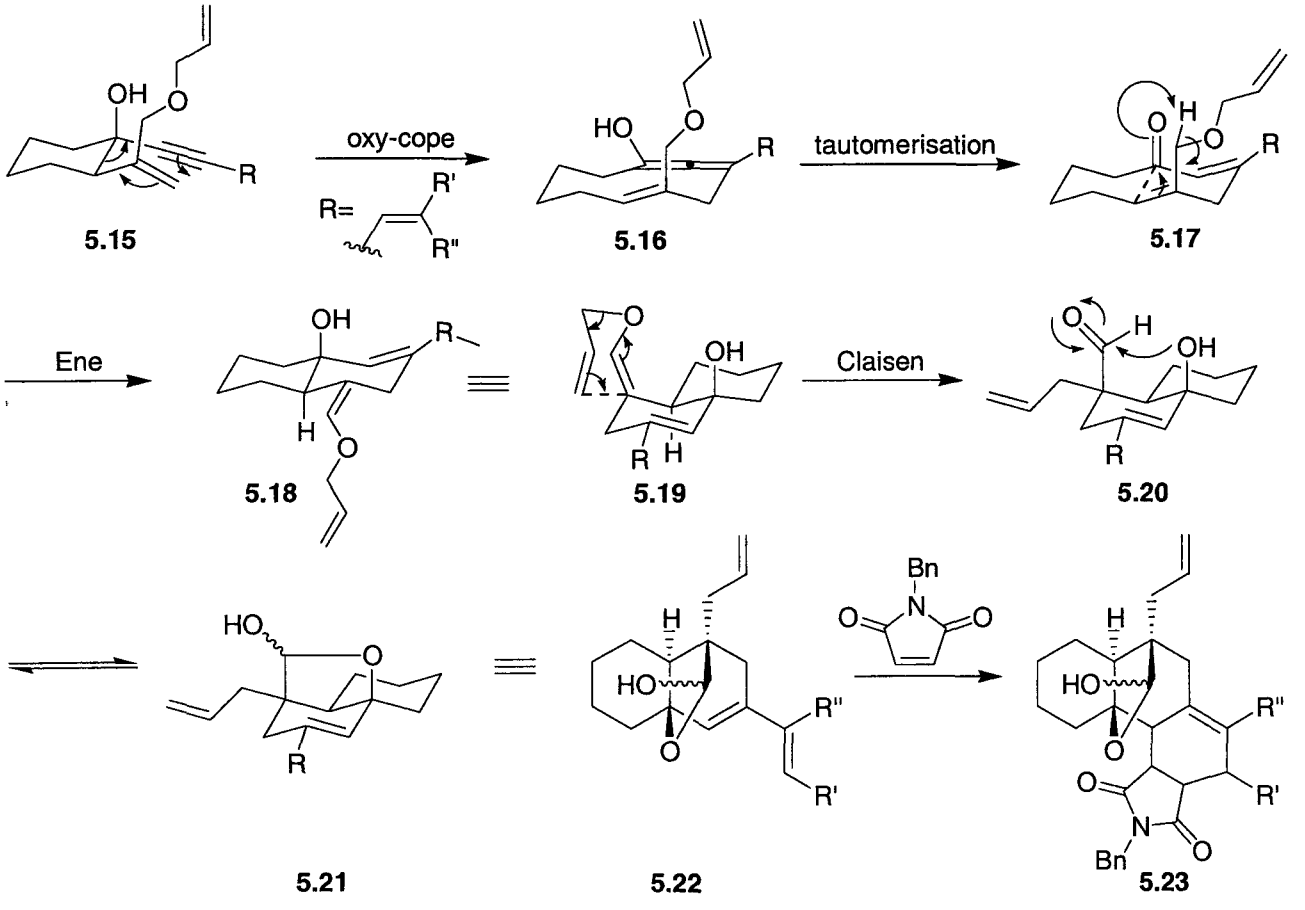
Scheme 5.5: *Oxy-Cope/Claisen/Ene/Diels-Alder*



5.13 **5.14**

The proposed mechanism for this tandem reaction is illustrated in the scheme below (Scheme 5.6).

Scheme 5.6: *Proposed mechanism for the tandem oxy-Cope/Claisen/ene reaction*



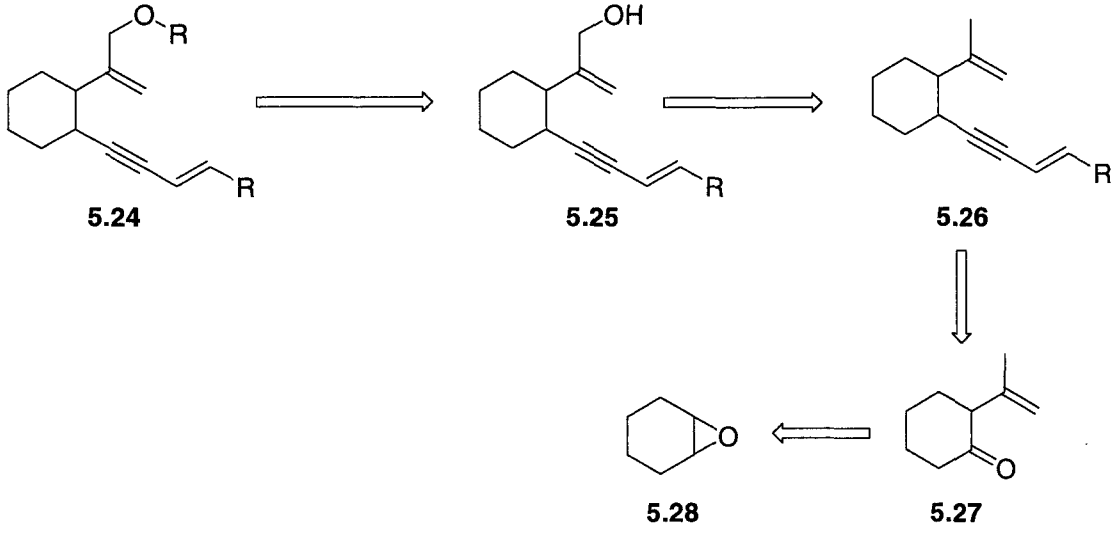
5.15 **5.16** **5.17** **5.18** **5.19** **5.20** **5.21** **5.22** **5.23**

To begin, the process is triggered by a [3,3] sigmatropic rearrangement of **5.15** where both chains are in an equatorial position. If the chains were not both in the equatorial position, there would not be proper orbital alignment for the sigmatropic rearrangement. The sigmatropic rearrangement (or oxy-Cope reaction in this case) provides us with the diol **5.16** which easily undergoes tautomerization to afford **5.17**. The latter is poised to undergo a transannular ene reaction leading to the formation of intermediate **5.18** as a *Z* conformer. Decaline **5.18** can subsequently undergo another [3.3] sigmatropic rearrangement, the Claisen rearrangement, to provide **5.19** as a sole product. The γ-hydroxyl group can readily attack the newly formed aldehyde to form the lactol ring in **5.21**. We speculate that under the high temperatures of the reaction, formation and opening of the lactol ring is in fact in equilibrium providing an equal mixture of lactol diastereomers. It is important to note that the triple bond on the alkyl chains (R_1) is crucial to the formation of the diene. Without the triple bond there would be no remaining olefin following the oxy-Cope reaction.

Substrate Preparation for the Oxy-Cope/Claisen/Ene/Diels-Alder Reaction

To verify our proposal the development of the tandem oxy-Cope/Claisen/ene/Diels-Alder reaction was first commenced as a collaboration between Boubacar Sow, Olivier Gagné, Daniel Newbury, and Jason Poulin. The substrates envisioned for the tandem reaction were synthesized via the following retrosynthetic outline (Figure 5.2).

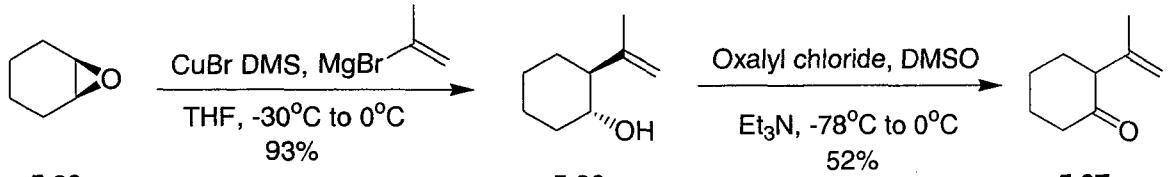
***Figure 5.2**: Retrosynthetic outline for the synthesis of the substrates*



5.24 **5.25** **5.26** **5.28** **5.27**

The synthesis began by an epoxide opening of the commercially available cyclohexane oxide with *iso*-propenyl magnesium bromide in the presence of CuBr·DMS in THF to give **5.30** in 93% yield. The latter was converted to ketone **5.27** via a Swern oxidation.

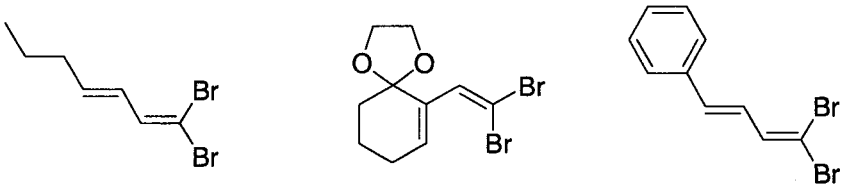
***Scheme 5.7**: Synthesis of 5.27*



5.29 **5.30** **5.27**

The next step of the synthesis was a Corey-Fuchs reaction, but first the reagents themselves, had to be synthesized. Three different Corey-Fuchs reagents were synthesized as seen in Figure 5.3.

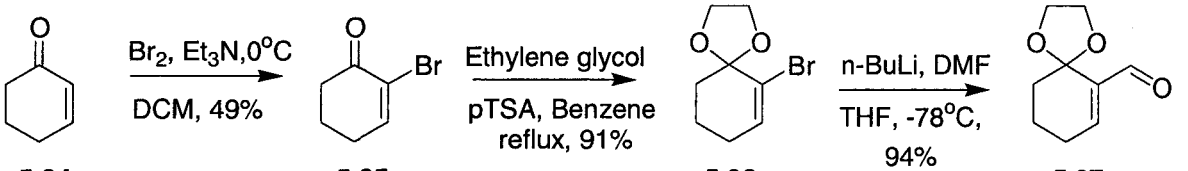
***Figure 5.3**: Corey-Fuchs reagents of choice*



5.31 **5.32** **5.33**

Commercially available cinamaldehyde and trans-2-hexanal were used to synthesize the dibromo intermediates **5.31** and **5.33**, but intermediate **5.32** was synthesized in four steps from cyclohexenone. To that end, we started with an α-bromination of cyclohexenone **5.34** to give crystalline α-bromo ketone **5.35** in 49% yield. Treatment of **5.35** with ethylene glycol and *p*TSA afforded **5.36** in 91% yield. Subsequently a lithium halogen exchange using *n*-BuLi in THF at -78°C was done followed by a quench with DMF to provide aldehyde **5.37a** in 94% yield.

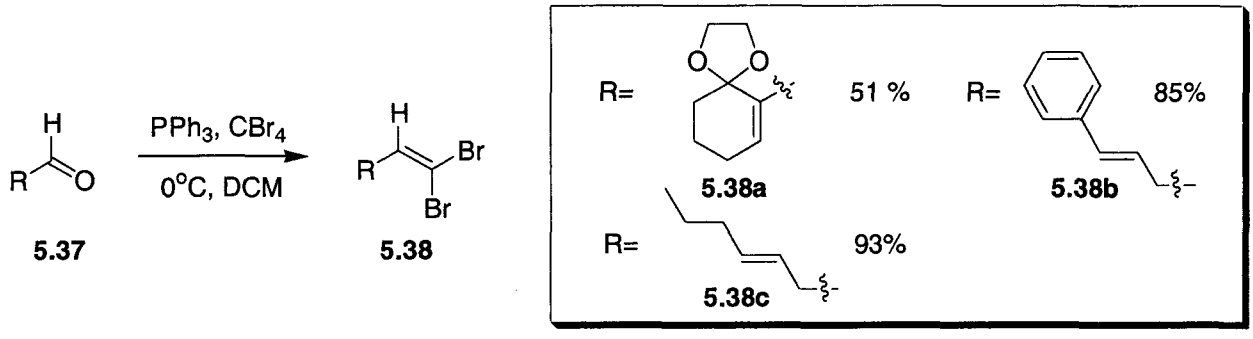
***Scheme 5.8**: Synthesis of the Corey-Fuchs reagents **5.37a**.*



5.34 **5.35** **5.36** **5.37a**

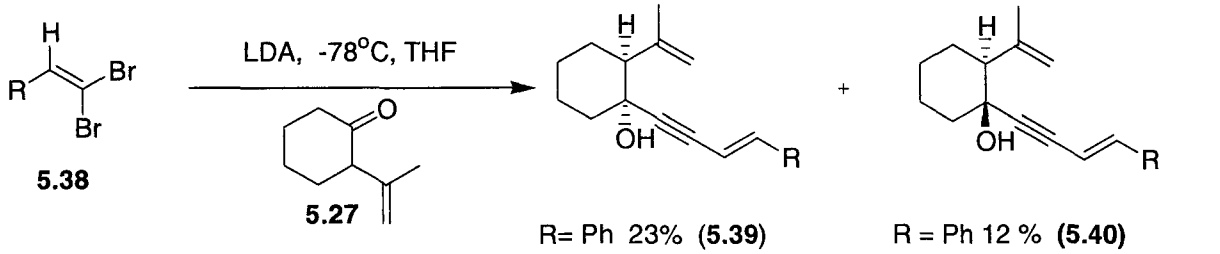
All three aldehydes were then treated with CBr_4 in a solution of PPh_3 in DCM to afford the corresponding dibromo products.

***Scheme 5.9** : Final preperations of the Corey-Fuchs reagents.*



Having all the required components in hand, **5.38a, b** and **c** would now serve as alkylating agents onto ketone **5.27** to give the desired Corey-Fuchs product. The usual Corey-Fuchs conditions developed by Ross Maclean[116] as well as other condition involving dry Cerium Chloride ($CeCl_3$) and HMPA with the alkyne instead of the dibromo substrates were investigated; however many products were observed. Subsequently, conditions using LDA as the base were tried. Pleasingly, we obtained the desired product as a mixture of *cis* and *trans*. Unluckily both diastereoisomers were very close together on the TLC plate when using a eluent composed of ethylacetate and hexanes, nevertheless we were delighted to discover that we can separate the two products with a eluent composed of a one to one mixture of CH_2Cl_2 and toluene.

***Scheme 5.10:** Optimal conditions for the Corey-Fuchs reaction*



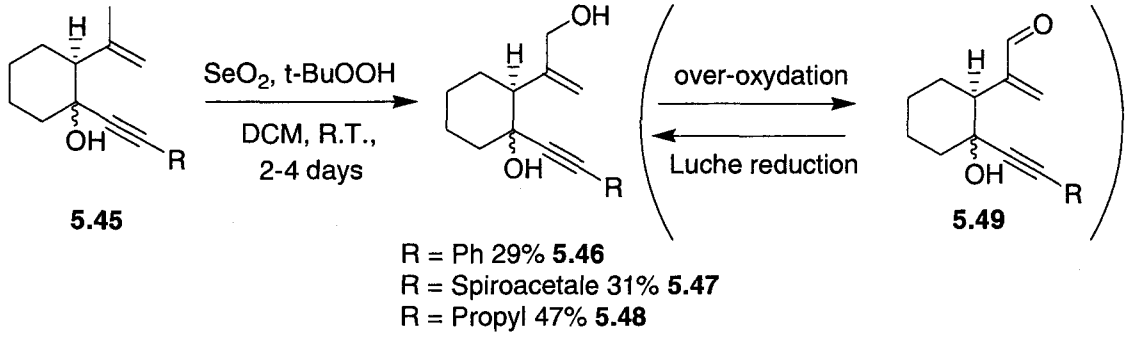
R= Ph 23% (**5.39**)
R= spriroacetal 37% (**5.41**)
R= propyl 39% (**5.43**)

R = Ph 12 % (**5.40**)
R = spiroacetale 35% (**5.42**)
R= propyl 41% (**5.44**)

The next step, consist of an allylic oxidation to install the terminal hydroxyl group followed by an alkylation to give the final substrates. The allylic oxidation took 2-4 days to

complete. Unfortunately, in some cases over-oxidation was observed. It follows that the over-oxidation product was reduced back to the allylic alcohol via a Luche reduction.

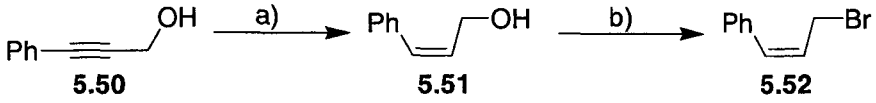
***Scheme 5.11**: Allylic oxidation to form the diol*



R = Ph 29% **5.46**
R = Spiroacetale 31% **5.47**
R = Propyl 47% **5.48**

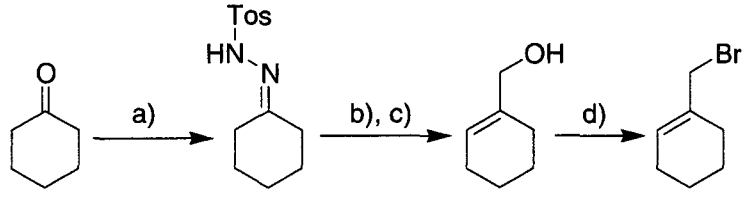
Diol in hand we were now able to couple a variety of substrates to the allylic alcohol position. One could envision that, depending on the substitution pattern of allyl ether **5.66**, additional quaternary and tertiary carbon center could be introduced. In order to investigate the scope of the oxy-Cope/Claisen/ene/Diels-Alder reaction allyl ethers with various degrees of substitution at the terminal double bond were prepared via esterification of diols **5.46**, **5.47** and **5.48** with the corresponding allyl halides. All allyl halides, except for commercially available cinnamyl bromide **5.57** and allyl bromide **5.58** (Scheme 5.12), were prepared from the corresponding alcohols via bromination with CBr_4/Ph_3P in CH_2Cl_2. Due to their instability on the silica gel allyl bromides were used in the etherification reaction without purification.

Scheme 5.12: *Synthesis of allyl bromides*



5.50 **5.51** **5.52**

a) Lindlard catalyst/H_2, quinoline, hexanes, 79%; b) CBr_4, PPh_3, Ch_2Cl_2, R.T.,10min.



5.53 **5.54** **5.55** **5.56**

a) p-toluenesulfonhydrazide, ethanol, reflux 3h, 100%; b) 4 eq. t-BuLi, TMDA, 5 h, then DMF, 76% b) DIBAL-H, THF, -78 °C, 66%, c) CBr_4, Ph_3P, CH_2Cl_2, 10 min

5.57 **5.58**

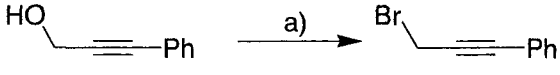
a) both are commercially available from Aldrich

Propargyl esters were also synthesized to introduce new type of functionality and substitution patterns. 1-bromo-2-pentyne (**5.65**) and propargyl bromide (**5.64**) were both commercially available however, propargylic ester **5.61** and **5.63** were synthesized (Scheme 5.13).

Scheme 5.13 *: Synthesis of propargylic esters*

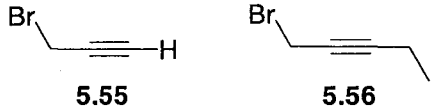
5.50 **5.51** **5.52**

a) NaH, BnBr, THF, 45%; b) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt, 95%.



5.53 **5.54**

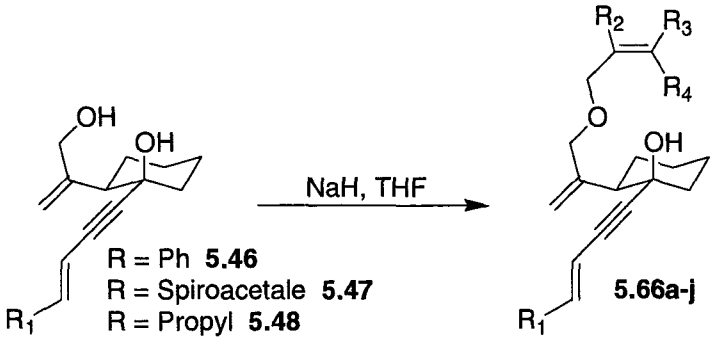
a) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt., 98%

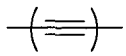
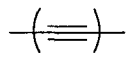
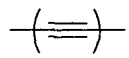
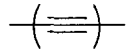


5.55 **5.56**

a) both are commercially available from Aldrich

***Table 5.1**: Synthesis of substituted diol substrates*



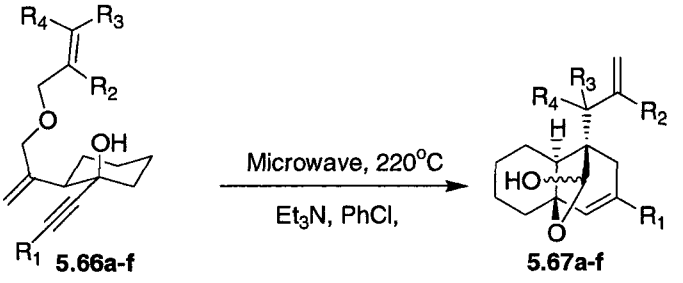
Entry	R_1	Allyl/propargyl bromide	R_2	R_3	R_4	Product	Yield %
1	Spiro acetal	**5.58**	H	H	H	**5.66a**	64%
2	Ph	**5.58**	H	H	H	**5.66b**	48%
3	Propyl	**5.58**	H	H	H	**5.66c**	86%
4	Propyl	**5.57**	H	Ph	H	**5.66d**	75%
5	Propyl	**5.52**	H	H	Ph	**5.66e**	59%
6	Propyl	**5.56**	$-(CH_2)_4-$		H	**5.66f**	58%
7	Propyl	**5.64**			H	**5.66g**	71%
8	Propyl	**5.65**			CH_2CH_3	**5.66h**	77%
9	Propyl	**5.63**			Ph	**5.66i**	57%
10	Propyl	**5.61**			OBn	**5.66j**	74%

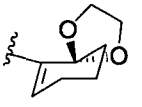
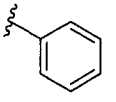
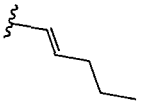
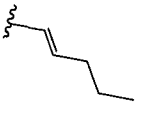
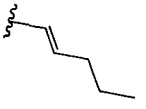
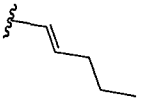
All allyl and propargyl ethers were then dissolved in chlorobenzene and 5 eq of Et_3N in a quartz tube, degassed for 20 minutes and irradiated. The microwave quartz tube had been previously treated in a base bath to avoid any traces of acid, which could lead to product decomposition. Irradiation was done for 3-5 hours at 220°C and the crude product was concentrated and purified by column chromatography. At this point, we did not add any dienophile to the reaction mixture since our objective was to first isolate the Oxy-Cope/Claisen/Ene diene product. We planned to attempt the four-tandem reactions once we are certain that the first three tandem reactions formed the desired diene.

Irradiation of **5.66 a** and **c** gave the desired diene while irradiation of **5.66b** gave only decomposition product. Interestingly, only the major anomer was observed for the microwave reaction of **5.66a**. Unfortunately, **5.66b** has proven to be more difficult to

synthesize compared to its related structures due to low yields and so, the reaction was only tried once. Please note substrates **5.66d-f** are related to **5.66c** by the same side chain, they only differ by their allylic substitution. To our dismay, they did not yield the corresponding diene, only degradation was observed. This may be owing to the high temperatures and pressure used to instigate the reaction. Optimization of these conditions are currently underway.

Table 5.2: *Results for the microwave reaction*



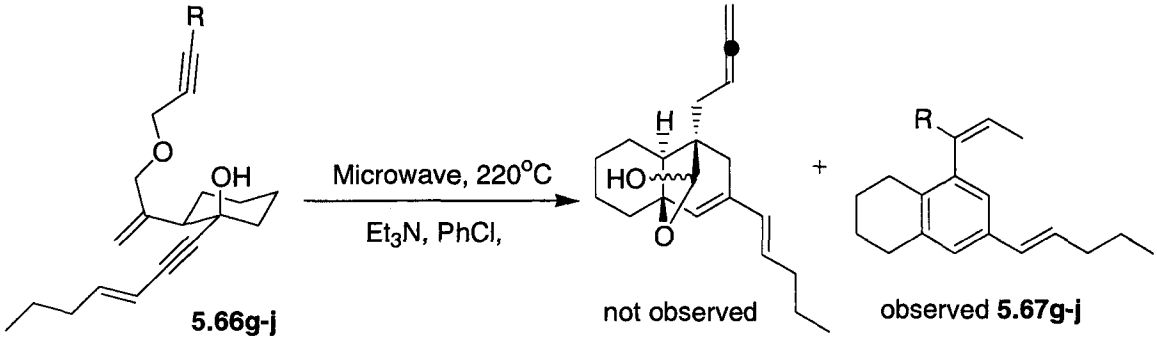
		Product					
Entry	**Starting material**	**R_1**	**R_2**	**R_3**	**R_4**		**Yield %**
1	**5.66a**		H	H	H	**5.67a**	62
2	**5.66b**		H	H	H	**5.67b**	0
3	**5.66c**		H	H	H	**5.67c**	73
4	**5.66d**		H	Ph	H	**5.67d**	N/A*
5	**5.66e**		-(CH_2)-		Ph	**5.67e**	N/A*
6	**5.66f**		H	H	H	**5.67f**	N/A*

* Trace amount by ^{1}H NMR.

Table 5.3 consist of the microwave reaction of the propargylic esters. To our surprise, none of the expected diene products were observed or isolated. However, we

observe a new aromatic compound. In all four cases, we observe aromatic compounds resembling each other in moderate yields. The structures were elucidated by ^{1}H, ^{13}C, DEPT 135, COSY, and HMQC magnetic resonance.

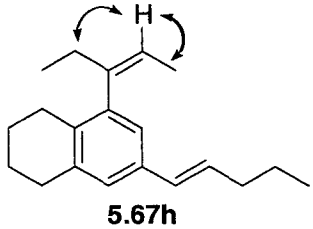
***Table 5.3**: Results of the microwave reaction of the propargylic esters*



		Product		
Entry	**Starting material**	**R**		**Yield %**
1	**5.66g**	H	**5.67g**	32%
2	**5.66h**	CH_2CH_3	**5.67h**	64%
3	**5.66i**	Ph	**5.67i**	42%
4	**5.66j**	OBn	**5.67j**	40%

In all cases, only the *E* isomer was observed. This was determined by NOESY and 1D nOe.

***Figure 5.4**: 1D nOe results*

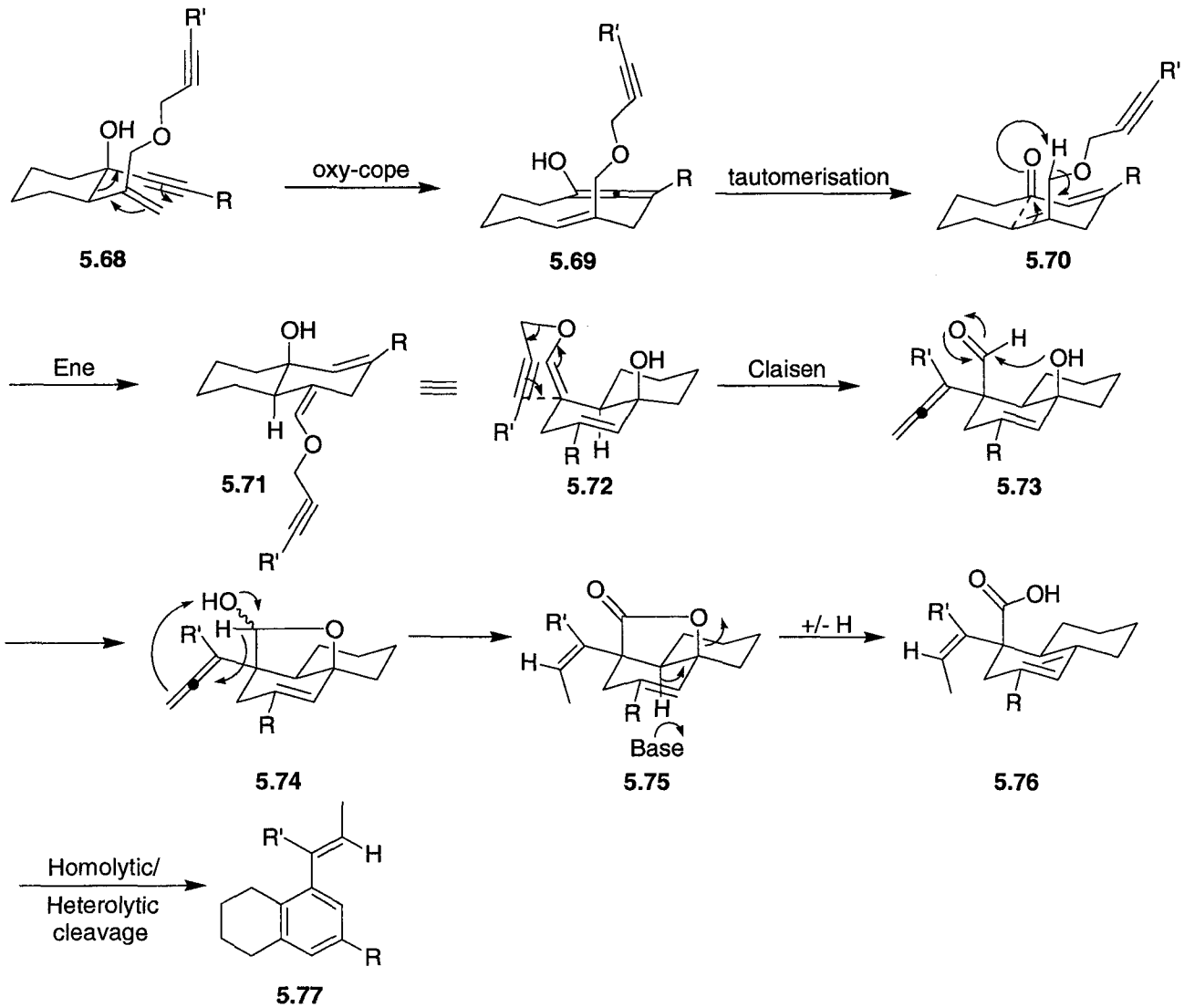


5.67h

The unexpected formation of the aromatic product **5.67g-j** were observed in each case using a propargyl ether. Although the presence of a triple bond for the oxy-Cope

reaction was necessary to yield the diene, it appears that the presence of a addition triple bond affects the reactivity of the compound. We envisage that the aromatic compound is generated via the proposed mechanism depicted in Scheme 5.14. Substrate **5.68** would first undergo the oxy-Cope reaction followed by tautomerisation and the ene reaction as depicted for the formation of the desired dienes in Scheme 5.14. The Claisen rearrangement occurs subsequent to the ene reaction this time giving rise to allene **5.73.** The allene is formed due to the rearrangement of the triple bond. The hydroxyl group can readily attack the newly formed aldehyde to form the lactol ring in **5.74.**

***Scheme 5.14**: Proposed mechanism for the formation of the newly discovered aromatic compounds.*



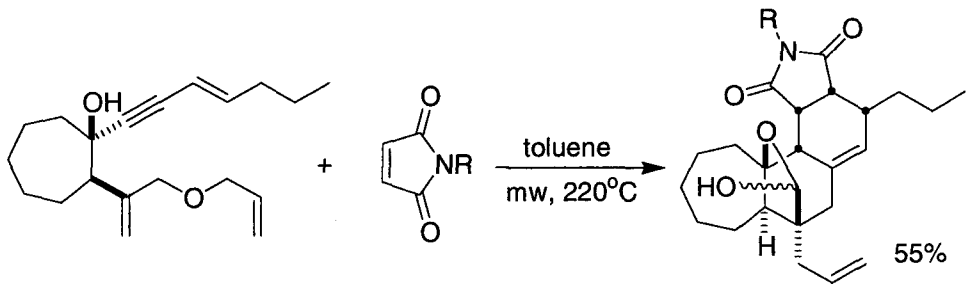
5.68 **5.69** **5.70** **5.71** **5.72** **5.73** **5.74** **5.75** **5.76** **5.77**

We then theorize an intramolecular hydride shift to generate intermediate **5.75**. Olefination can transpire afterwards to promote the opening of the lactol, which can subsequently eliminate via a hemolytic or heterolytic pathway. The detailed mechanism for the formation of such compounds is currently under investigation.

Incorporation of the Diels-Alder Reaction in the Tandem Sequence

Jason Poulin attempted the tandem Oxy-Cope/Claisen/ene/Diels-alder reaction with the seven membered ring substrate **5.78**. We were very pleased to observe the desired four tandem reaction product in 55% yield.

Scheme 5.15**: Tandem oxy-Cope/Claisen/ene/Diels-Alder with the seven membered ring substrate **5.78



5.78 **5.79** **5.80**

Further studies to develop the tandem oxy-Cope/Claisen/ene/Diels-Alder reaction are on there way.

Future outlook

In summary, a successful synthesis of the key precursors to the tandem oxy-Cope/Claisen/ene/Diels-Alders reaction has been described. Promising results were obtained when attempting the tandem reaction with the allyl ethers. The oxy-Cope reaction provides evidence to have reacted solely in the chair like conformation placing the bulky substituents

in the equatorial position to minimize steric effects. The ene reaction was poised to react generating the desired intermediate ready to undergo a Claisen rearrangement producing a single product. Once the aldehyde was formed, lactimization by NMR would confirm the *cis* arrangement of the latter and the hydroxyl group.

The oxy-Cope/Claisen/ene reaction of the propargyl ethers have, to our surprise, generated tetrahydro-naphtalenes. Mechanistic studies to determine the specific pathway to the generation of such substrates are currently under investigation. At this moment, only preliminary conditions were developed in the lab permitting the addition of the Diels-Alder reaction to the tandem reaction forming a homo-steroid core. The Diels-Alder reaction is key to generate molecular complexity in a stereoselective fashion.

The results obtained and their applicability to future work are significant. The Diels-Alder product of the envisaged tandem reaction bears a lactol group existing in equilibrium with its open form. Such functionality can permit functionalization of the core via a vast repertoire of reactions. The same reactions can also be performed on 5-membered ring ketones to get the desired steroid core. Undoubtedly, the potential and possibilities are endless.

Claims to Original Research

1. Investigations into the synthesis of the core of (±)-lycorine using an cyclopropyl iminium rearrangement followed by the intramolecular Diels-Alder reaction.
2. Development of a route to a useful intermediate in the synthesis of gracilamine.
3. Synthesis of dienes using the gold-catalyzed rearrangement of propargylic acetates and pivaloates.
4. Optimization of the oxy-Cope/Claisen/ene/Diels-Alder reaction.
5. Investigations of the oxy-Cope/Claisen/ene/Diels-Alder reaction on allyl and propargyl ether precursors.
6. Formation of the tetrahydronaphtalene product via the oxy-Cope/Claisen/ene/Diels-Alder reaction.
7. Demonstration that the activation of $Au(PPh_3)Cl$ using an acid is applicable to known example in the literature.

Presentations from this Work

Poster: "**Progress Towards the Synthesis of 1-Acetoxy-Dienes via Gold(I) Catalyzed-Rearrangement of Propargylic Acetates and pyvaloates"** Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, Toronto, Canada. November 2008.

Poster: "**Progress Towards the Synthesis of 1-Acetoxy-Dienes via Gold(I) Catalyzed-Rearrangement of Propargylic Acetates**" University of Ottawa Synthesis Day, Ottawa, Canada. Poster. June 2008.

Chapter 6

Experimental

General Experimental

All reactions were performed under argon in flame-dried glassware equipped with a magnetic stir bar and a rubber septum unless otherwise indicated. Solvents used were freshly distilled prior to use: ether and THF over sodium and benzophenone; dichloromethane, toluene and DMF over calcium hydride. Triethylamine was distilled, over calcium hydride, prior to use. All other commercial reagents were used without purification unless specified.

Microwave reactions were preformed using a CEM Model ESP-1500 Plus microwave oven equipped with a pressure monitoring device and an EST-300 Plus fiber optic temperature probe or the CEM Discovery microwave. The reaction vessel was a quartz tube, and in indicated cases carboflon^{TM} was added to aid in the absorption of microwave radiation.

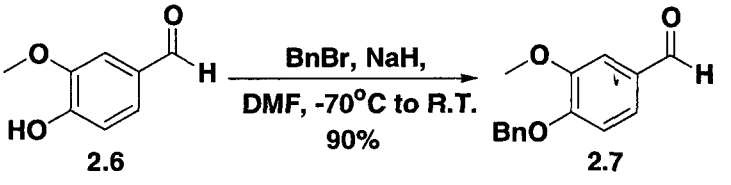
Reactions were monitored by TLC analysis using glass plates precoated (250 μm thickness) with silica gel 60 F_{254} (E. Merck) or aluminum sheets precoated with silica gel 60

F254, cut to size. TLC plates were viewed using UV light, *p*-anisaldehye staining solution, phosphomolybdic acid staining solution or potassium permanganate staining solution. Flash chromatography was carried out on 230-400 mesh silica gel 60.

^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX 300 MHz, and Bruker AMX 400 MHz spectrometers in the specified deuterated solvent. Data are reported as multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sext. =sextet, m = multiplet), integration and coupling constant(s) in Hz. High-resolution mass spectra were recorded on a Kratos-Concept IIH instrument operated by the Ottawa-Carleton Mass Spectrometry Centre. IR spectra were recorded on a Bomen Michaelson 100 FTIR spectrometer and melting points were recorded using a Gallenkamp P1106G Melting Point Apparatus.

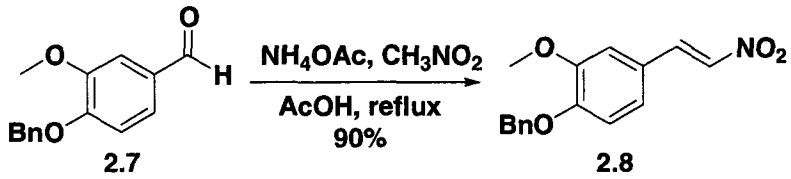
Procedures-Chapter 2

Detailed experimental



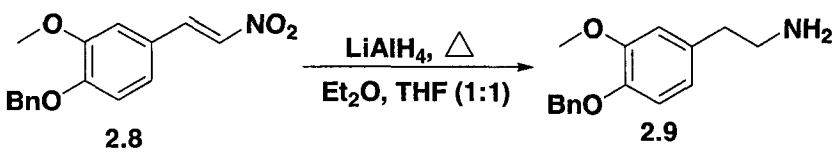
2.6 2.7

4-Benzyloxy-3-methoxy-benzaldehyde (2.7). Vanilline (2g, 13.15 mmol) was dissolved in DMF (25 ml), and cooled to –78°C. Subsequently, benzyl bromide (1.8ml, 15.78 mmol) was added dropwise at that temperature and the reaction was let warm to 0°C while mixing for 90 minutes. Reaction was quenched with water and extracted once with DCM. The organic layer was then washed 3X with water, dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (15 % ethyl acetate in hexanes) to afforded **2.7** as a light brown powder (2.18 g, 90 % yield). IR (neat, cm^{-1}) 3069 (w), 2945 (w), 2835 (w), 2734 (w), 1681 (s), 1587 (s), 1510 (s), 1426 (m), 1386 (m), 1265 (s), 1138 (s), 1027(m), 729 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.81 (s, 1H), 7.46-7.28 (m, 7H), 6.96 (d, J= 8.2 Hz, 1H), 5.20 (s, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 191.0 (C_4), 153.7 (CH), 150.1 (CH), 136.0 (CH), 130.3 (CH), 128.8 (CH), 128.3 (CH), 127.3 (CH), 126.6 (CH), 112.4 (CH) 109.4 (CH), 70.9 (CH_2), 56.12 (CH_3); HRMS (EI) m/z calcd for $C_{15}H_{14}O_3$ $(M)^+$ 242. 2970, found 242.0949.



2.7 2.8

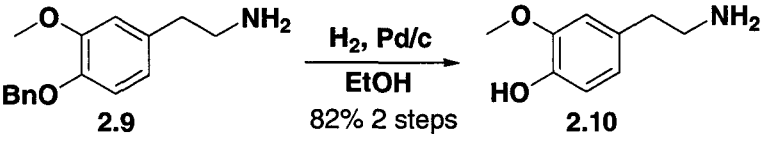
1-Benzyloxy-2-methoxy-4-(2-nitro-vinyl)-benzene (2.8). A mixture of NH_4OAc (257.62 mg, 2.97 mmol), CH_3NO_2 (0.36 ml, 6.69) and benzylated vanilline (0.9g, 3.72 mmol) in AcOH (10 ml) was refluxed for 7 hours. The reaction was let cool to room temperatur for 30 minutes then evaporated to give a yellow (mustard collored) powder. The powder was then washed with methanol to give **2.8** as a yellow powder. (720 mg, 90 % yield). Full characterization can be found in the literature.[35] IR (neat, cm^{-1}) 3113 (w), 2945 (w), 1626 (s), 1599 (s), 1493 (s), 1340 (m), 1262 (s), 1141 (s), 1031 (m), 968 (m), 812 (m), 746(m), 692 (m); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, J= 13.1 Hz, 1H), 7.50 (d, J=13.5 Hz, 1H), 7.43-7.32 (m, 5H), 7.10 (dd, J= 3.16, 8.33Hz, 1H), 7.01 (d, J= 3.6 Hz, 1H), 6.91 (d, J= 8.3 Hz, 1H), 5.22 (s, 2H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 150.1 (C_4), 139.4 (CH), 136.1 (C_4), 135.2 (CH), 128.3 (CH), 127.2 (CH), 125.5 (CH), 123.2 (C_4), 113.6 (CH), 110.9 (CH), 71.1 (CH_2), 56.3 (CH_3); HRMS (EI) m/z calcd for $C_{16}H_{15}NO_4$ $(M)^+$ 285.2946, found 285.1008.



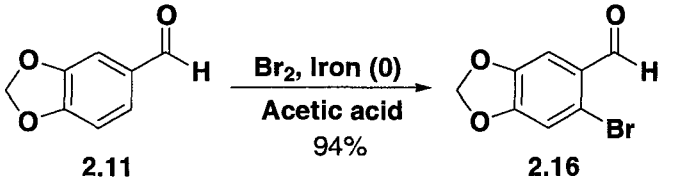
2.8 2.9

2-(4-Benzyloxy-3-methoxyphenyl)ethylamine (2.9). To a stirred solution of this nitrostyrene **2.8** (2.0 g, 7.02 mmol) in 50 mL of anhydrous Et_2O/THF (1:1) was slowly added $LiAlH_4$ (0.8 g, 21.05 mmol). The solution was refluxed for 2 h and then stirred overnight at room temperature. To this solution were added water (2 mL), 15% NaOH (2 mL), and then water (6 mL), and the solution was stirred 30 min before filtering. The phases were separated, and the aqueous layer was extracted with ether (3 X 20 mL); the ether washes were combined and concentrated. The oily residue was dissolved in 10% HCl (3 mL) and washed with ether (10 mL); the aqueous layer was made basic and extracted with ether

(2 X 20 mL). These two ether washes were combined and washed with water and brine before drying over K_2CO_3. Removal of the solvent produced the titled compound **2.9** as an orange oil (1.28 g, 71%). The crude product was used in the next step.

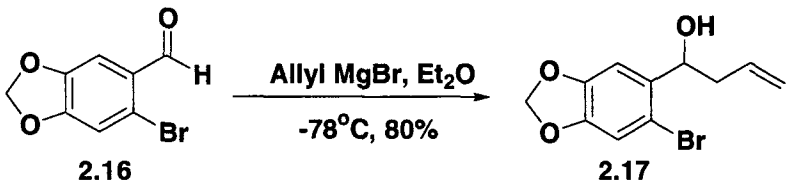


4-(2-Amino-ethyl)-2-methoxy-phenol (2.10). Substrate **2.9** (162mg, 0.630mmol) was dissolved in ethanol and Pd/C (5% mol) was then added. A balloon filled with H_2, attached to a valve, was used. The reaction was purged 3 times with argon, then 3 times with hydrogen gas before submitting the reaction to the hydrogen gas filled ballon. Reaction was stirred at room temperature until completions (1hour), filtered through celite and concentrated to give the desired product as a light yellow oil. Crude product was used in next step. Caracterization is in accord with the literature.[35]



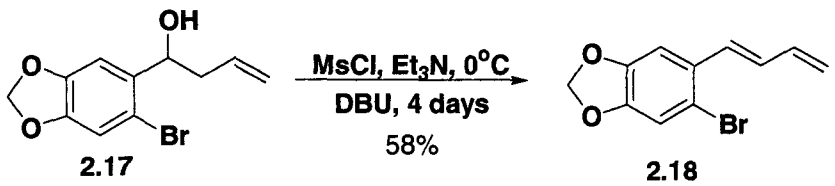
6-Bromopiperonal (2.16). To a vigorously stirred suspension of iron(0) fillings (3.12 g, 405 mmol) in 75 mL of glacial acetic acid is added Br_2, (4.65 ml, 679 mmol) at a steady rate, care being taken to avoid an exotherm. Following addition, the solution is stirred 20 min before dropwise addition of piperonal (6 g, 399 mmol) in 15 mL of acetic acid. After the solution is stirred for 5 min, Br_2, (2.8 ml, 405 mmol) is added dropwise and the reaction mixture stirred for several days until all starting material is reacted by TLC determination (periodic addition of 34% excess Br_2 may help maintain reaction rate). The reaction mixture is diluted with 1 L of $CHCl_3$, and filtered through Celite. The solution is washed with 250-mL portions of saturated $Na_2S_2O_3$ until all excess bromine is reduced (the aqueous layer remains colorless) followed by washes with 250 mL of 10% Na_2C0_3 and 250 mL of

saturated NaCl. The solution is dried ($MgSO_4$) and filtered and the solvent removed to give a tan solid. Recrystallization from 95% EtOH affords aryl bromide **2.16** (9.34g, 94%) as off-white needles. Procedure and characterization are in accordance to the literature.[117]

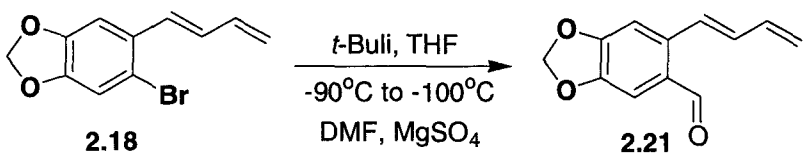


2.16 **2.17**

1-(6-Bromo-benzo[1,3]dioxol-5-yl)-but-3-en-1-ol (2.17). Procedure taken from Danichefsky et al.[38] To a solution of allyl magnesium bromide (20.96 ml, 20.96 mmol) at –78°C was added dropwise the 6-bromopiperonal (4g, 17.47 mmol) dissolved in diethyl ether/tetrahydrofuran (1:1) (50ml). The reaction was monitored by TLC till completion (3 hours) and then was quenched with NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated *in vaccuo*. Purification by flash chromatography (20 % ethyl acetate in hexanes) afforded **2.17** as a white solid (3.8 g, 80 % yield). IR (neat, cm^{-1}) 3184 (br), 2950 (m), 2855 (m), 1484 (s), 11240 (s), 1113 (s), 1042 (s), 933 (s), 840 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25 (s, 1H), 7.06 (s, 1H), 5.97 (dd, J= 1.5, 2.8 Hz, 2H), 5.92-5.81 (m, 1H), 5.22-5.17 (m, 1H), 5.16 (s, 1H), 5.06-5.01 (m, 1H), 2.61-2.53 (m, 1H), 2.36-2.28 (m, 1H), 2.06, (d, J= 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1 (C_4), 136.2 (C_4), 134.2 (CH), 118.7 (CH_2), 112.4 (CH), 112.0 (C_4), 107.3 (CH), 101.7 (CH_2), 77.2 (C_4), 71.8 (CH), 42.3 (CH_2); HRMS (EI) m/z calculated for $C_{11}H_{11}O_3Br$ $(M)^+$ 269.9892 found 269.9886.

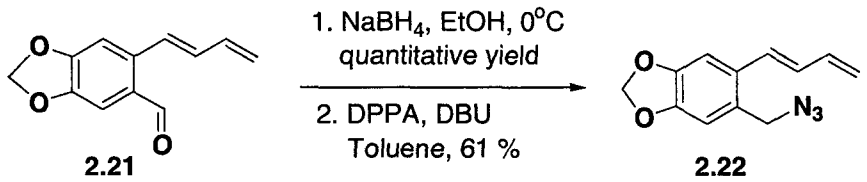


5-Bromo-6-buta-1,3-dienyl-benzo[1,3]dioxole (2.18). Alcohol **2.17** (3.0 g, 11.07 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. To this solution was added Et_3N (2.3 mL, 16.6 mmol) and methanesulfonyl chloride (1.0 mL, 13.3 mmol), respectively; then, the ice bath was removed. Afterall alcohol **2.17** had reacted (TLC monitoring), DBU (1.65 mL, 11.07 mmol) was added to the reaction mixture. In addition, 2 X 1.0 mL of DBU was added over the course of 4 days. The mixture was diluted with CH_2CI_2 (30 mL) and washed with saturated NaHCO, (2 X 10 mL) and brine. It was dried over Na_2S0_4, and the solvent was evaporated *in vacuo*. Purification by flash chromatography, (10% EtOAc/hexane) gave (1.6 g, 58 %) of diene **2.18** as a white solid: mp 103-105 °C. IR (neat, cm^{-1}) 3082 (w), 3000 (w), 2898 (w), 1806 (w), 1603 (w), 1509 (m), 1481 (s), 1239 (s), 1110 (m), 1038 (m), 1006 (m), 937 (m), 855 (m), 843 (m), 675 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.04 (s, 1H), 7. 00 (s, 1H), 6.84 (d, J= 15.4 Hz, 1H), 6.62-6.49 (m, 2H), 5.97 (s, 2H), 5.34 (d, J= 10.0, 1H), 5.20 (d, J=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 147.9 (C_4), 147.7 (C_4), 137.1 (CH), 131.2 (CH), 130.7 (CH), 130.2 (C_4), 118.2 (CH_2), 115.2 (C_4), 112.7 (CH), 105.7 (CH), 101.8 (CH_2); HRMS (EI) m/z calculated for $C_{11}H_9O_2Br$ $(M)^+$ 251.0920 found 251.9806.



6-Buta-1,3-dienyl-benzo[1,3]dioxole-5-carbaldehyde (2.21). A solution of bromine **2.18** (200mg, 0.790 mmol) in THF (10 ml) was cooled to -90°C/-100°C in a bath of hexane cooled with liquid nitrogen. A fresfly titrated solution of *t*-Buli (1.14ml, 1.580 mmol) was then added dropwise via cannula. The reaction misture was let stir at that same temperature for 30 min during which was distilled the DMF. The trick here is to distill the DMF using

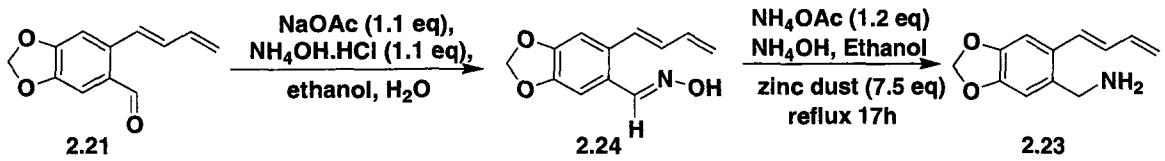
$MgSO_4$ as a drying agent and to have some $MgSO_4$ in the distillat receiving flask. The room temperature solution of DMF (30ml) is then added by cannula to the reaction mixture and stirred for 30 minutes. The solution is then quenched with water and extracted 3X with EtOAc. Organic phases are combined, dried with $MgSO_4$ and concentrated *in vaccuo* to obtain the desired produc in a 50 to 80% yield. IR (neat, cm^{-1}) 2921 (m), 1674 (s), 1614 (m), 1480 (s), 1258 (s), 1038 (s), ^1H NMR ($CDCl_3$, 400 MHz) δ 10.19 (s, 1H), 7.31 (d, J= 15.5Hz, 1H), 7.27 (s, 1H), 7.00 (s, 1H), 6.66-6.49 (m, 2H), 6.04 (s, 2H), 5.38 (d, J= 17.9, 1H), 5.25 (d, J= 11.9, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 189.7 (CH), 152.6 (C_4), 147.9 (C_4), 137.6 (C_4), 136.8 (CH), 134.3 (CH), 128.2 (C_4), 127.4 (CH), 119.7 (CH_2), 108.5 (CH), 106.4 (CH), 102.0 (CH_2); HRMS (EI) m/z calculated for $C_{12}H_{10}O_3$ $(M)^+$ 202.2060 found 202.0621.



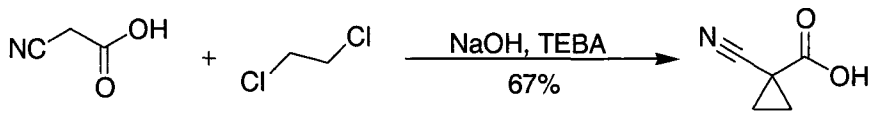
2.21 **2.22**

5-Azidomethyl-6-buta-1,3-dienyl-benzo[1,3]dioxole (2.22).[43] To a solution of aldehyde **2.21** (250 mg, 1.23 mmol) in 99% EtOH (30 ml) cooled at 0°C was added $NaBH_4$ (53mg, 1.36 mmol) and stired at at that temperature for 45 minutes. Reaction mixture was quenched with water (30ml) and the acqueous layer was extractd 3X with ethyl acetate (15 ml). Organic layers were combined, dried with $MgSO_4$, filtered and concentrated *in vaccuo* to obtain the desired benzyl alcohol in quantitative yield. The crude benzyl alcohol was dissolved in toluene (2ml), treated with DBU (0.25 ml, 1.59 mmol), and diphenyl phophoryl azide (DPPA) (0.33 ml, 1.47 mmol) and stired at room temperature for 14 hrs. After acqueous work-up with NH_4Cl aq, extraction with EtOAc and dried over $MgSO_4$, the product was purified by column chromatography to yield 2.22 in a 61% yield over 2 steps. IR (neat, cm^{-1}) 2923 (m), 2167 (s), 2080 (m), 1480 (s), 1258 (s), 1038 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.05 (s, 1H), 6.74 (s, 1H), 6.71-6.68 (m, 3H), 6.05 (s, 2H), 5.97 (s, 2H), 5.32 (d, *J*= 16.5Hz, 1H), 5.17 (d, *J*= 9.5Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.3 (C_4), 147.3 (C_4), 137.6 (CH), 131.2 (C_4), 130.7 (CH),

128.4 (CH), 126.4 (C_4), 118.5 (CH_2), 110.2 (CH), 105.9 (CH), 101.5 (CH_2), 62.5 (CH_2); HRMS (EI) m/z calculated for $C_{12}H_{11}N_3O_2$ $(M)^+$ 229.2346 found 229.0877.

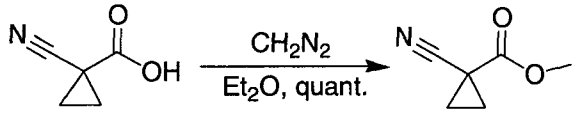


C-(6-Buta-1,3-dienyl-benzo[1,3]dioxol-5-yl)-methylamine (2.23).[47] A solution of sodium acetate (44.7 mg, 0.544 mmol) in water (1 ml) was added to a solution of hydroxylamine-HCl (37.8 mg, 0.544 mmol) in water (1ml) and the mixture was added to a warm (35°C) solution of the aldehyde in ethanol (3.5ml). A precipitate was formed, the 5 ml of water was added, and the mixture was stirred at room temperature ovrernight. The reaction was concentrated *in vaccuo* to remove the ethanol, and then extracted with DCM (3X). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated to yield the corresponding crude oxime **2.24**. A mixture of the oxime (50 mg, 0.23 mmol), ammonium acetate (21.29 mg, 0.276 mmol), zinc dust (113.3 mg, 1.733 mmol), concentrated aqueous ammonia (1.5 ml) and ethanol (1.5 ml) was heated under argon atmosphere for 17hrs. The solvents were then removed *in vaccuo* and the residue was stired for 1hr with aqueous potassium hydroxide (35% w/v, 1.5 ml). The reaction mixture was extracted with ether and the extract was dried and concentrated to give the desired product **2.23** (97% over 2 steps). IR (neat, cm^{-1}); 3482 (br), 2924 (w), 2855 (w), 1503 (m), 1484 (s), 1249 (m), 1040(s); ^1H NMR ($CDCl_{36}$, 400 MHz) δ 7.03 (s, 1H), 6.80 (s, 1H), 6.78 (d, *J*= 14.6 Hz, 1H), 6.64-6.47 (m, 2H), 5.94 (s, 2H), 5.31 (d, *J*= 14.6 Hz, 1H), 5.15 (d, *J*= 10.13 Hz, 1H), 3.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 147.0 (C_4), 137.4 (CH), 132.8 (C_4), 130.3 (CH), 129.3(C_4), 128.9 (CH), 117.5 (CH_2), 108.7 (CH), 105.5 (CH), 101.1 (CH_2), 43.9 (CH_2), 29.6 (CH_2); HRMS (EI) m/z calculated for $C_{12}H_{13}NO_2$ (M^+): Calculated 203.2371, found 203.0924.



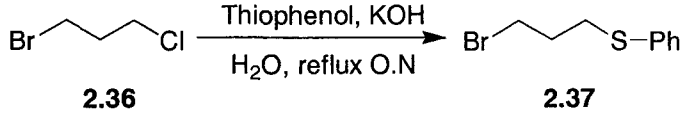
2.26 **2.27** **2.28**

1-Cyano-cyclopropanecarboxylic acid (2.28). To a stirred solution of 20ml of 50% aqueous sodium hydroxide was added TEBA (10.07g, 0.044 mol) and a mixture of ethyl cyanoacetate (5g, 0.044 mol) and 1,2-dichloroethane (7.65 ml, 0.088 mol). Evolution of heat was noted and the ambient temperature was maintained by external cooling. Stiring was continued for 2 hours and the solution was diluted with 100 ml of water. The mixture was extracted with ether and the aqueous layer was acidified with 25 ml of concentrated HCl and then extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. The product was concentrated invaccuo to give the desired product 2.28 in 67% yield. Caracterization of product coincides with the literature.[48]



2.28 **2.33**

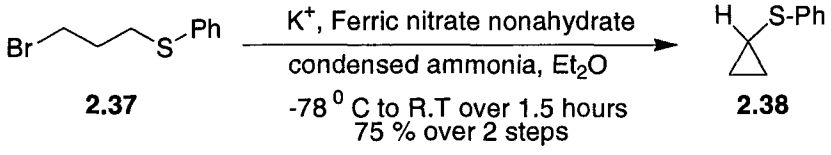
1-Cyano-cyclopropanecarboxylic acid methyl ester (2.33). To a solution of acid 2.28 (100mg, 0.877 mmol) in ether (10ml) was added CH_2N_2 dropwise until the mixture became yellow. Silica was added to the mixture (3ml) until the yellow color disappeared. The mixture was filtered and concentrated *in vaccuo* to afford **2.33** in quantitative yield. Caracterization is in accordance to the published literature.[118]



2.36 **2.37**

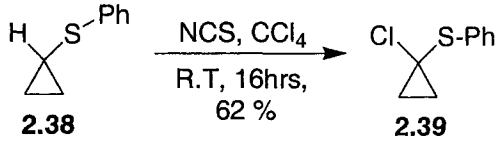
(3-Bromo-propylsulfanyl)-benzene (2.37). A solution of 1-bromo-3-chloropropane (20g, 0.127 mol) in water containing KOH (7.12g, 0.127 mol) was stirred rapidly as the thiophenol (13.04 ml, 0.127 mol) was slowly added over 30 min. The reaction mixture

was refluxed overnight, then cooled and extracted (3X) with ether. The organic layers were combined and washed with water (3X), dried with $MgSO_4$, filtered and concentrated. The crude product was used in the next step. Caracterization is in accordance with the literature.[119]



2.37 **2.38**

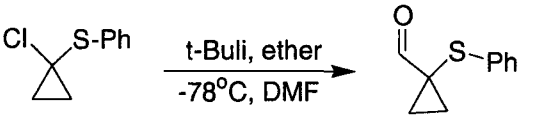
Cyclopropylsulfanyl-benzene (2.38). Potasium metal (4.35g, 0.229 mol) was dipped in hexane and then the top surface layer was pealed off and he remaining cube was cut in smaller pieces dipped in hexane and then left in THF. Potassium metal was added in small pieces to a rapidly stirred solution of ferric nitrate nonahydrate (0.25g, 0.620 mmol) in 125 ml of condensed ammonia cooled at -78°C. After the blue color has disappeared, the thiophenol (9.5g, 0.051 mol) was added to the reaction mixture via cannula as a solution in 125ml of ether. The acetone/dry ice bath was then removed and the reaction was let warm to room temperature over 1.5hrs to evaporate the ammonia. The reaction was the refluxed for 3 hours. Upon cooling, the reaction micture was hydrolyzed slowly with an aqueous solution of $NaHCO_3$ then water. Subsequently the mixture was filtered, the aqueous phase was extracted with ether, the organic layers were combined and dried with $MgSO_4$, filtered and concentrated in vaccuo. Purification by column chromatography (0-5% EtOAc in hexanes) afforded the desired product **2.38** in (3.72g, 75%) yield over 2 steps. Caraterization is in accordance to the literature.[116]



2.38 **2.39**

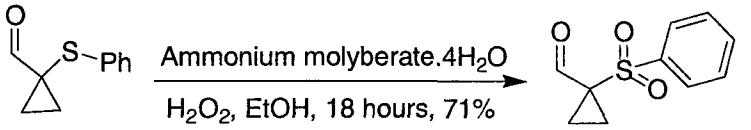
(1-Chloro-cyclopropylsulfanyl)-benzene (2.39). A solution of cyclopropane **2.38** (500mg, 3.32 mmol) in CCl_4 (8ml) was stirred with N-Chlorosuccinimide (577.7 mg,

4.33 mmol) at room temperature overnight. The precipitate was filtered and the solvent was evaporated to give the crude product. Purification by column chromatography (0-5% EtOAc in hexanes) afforded the desired product in (497mg, 62%). Caracterization is in accordance with the literature.[120]



2.39 **2.40**

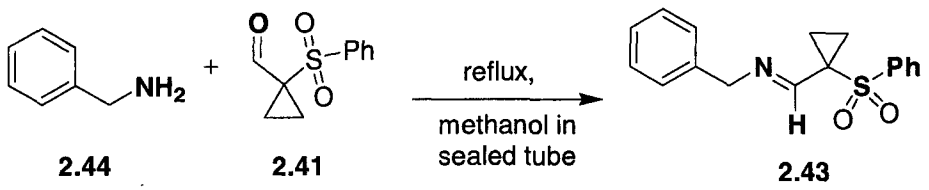
1-Phenylsulfanyl-cyclopropanecarbaldehyde (2.40). To a -78°C solution of 1-chlorocyclopropylphenylsulfide (100mg, 0.542mmol) in ether (5 ml) was added over a 20 minute period *t*-Buli (70.8µl, 1.083mmol) in pentane (1.53M). The mixture turned milky before complete addition of the *t*-Buli. After being stirred at that temperature for 2 hours, freshly distilled DMF was added rapidly and stirring continued for 30 minutes. The cold mixture was then pourd into 10% aq.HCl solution, the phases were separated, the organic phase was washed with brine, dried with $MgSO_4$, and concentrated in vaccuo to obtain **2.40** in a (48mg, 55%) yield afterpurification by column chromatography (0-7% EtOAc in hexanes). Caracterization is in accordance to the literature.[121]



2.40 **2.41**

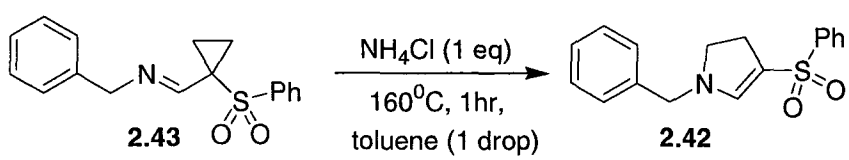
1-Benzenesulfonyl-cyclopropanecarbaldehyde (2.41).[122] A solution of ammonium molybdate (26.82mg, 0.0217 mmol) in hydrogen peroxide 30% (0.01ml, 0.33 mmol) was added into a solution of sulfide (22mg, 0.087 mmol) in ethanol (3 ml) at 25°C and the heterogeneous mixture was stirred overnight. Water was added and ethanol was removed in vaccuo. The acqueous residue was extracted with DCM (3X) and the collecting organic phases were washed with water, brine and dried over $MgSO_4$. The solvent was removed under vaccuo and the residue was purified by flash chromatography to afford the desired produc in 71% yield. IR (neat, cm^{-1}); 2982 (w), 1701 (s), 1308 (s), 1273 (m), 1142(s),

722(m), 602 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.85 (s, 1H), 7.94 (dd, *J*= 3.4, 5,4 Hz, 2H), 7.69 (ddd, *J*= 4.1, 7.9, 14.6 Hz, 1H), 7.59 (ddd, 4.5, 7.8, 14.7 Hz, 2H), 1.99 (dd, *J*= 4.8, 8.3 Hz, 2H), 1.67 (dd, *J*= 4.4, 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 193.1 (CH), 139.7 (C_4), 134.2 (CH), 129.7 (CH), 128.2 (CH), 51.0 (C_4), 18.5 (CH_2); HRMS (EI) m/z calculated for $C_{10}H_{10}O_3S$ (M^+): Calculated 210.2496, found [M^+- $PhSO_2$] 125.0115.



2.44 2.41 2.43

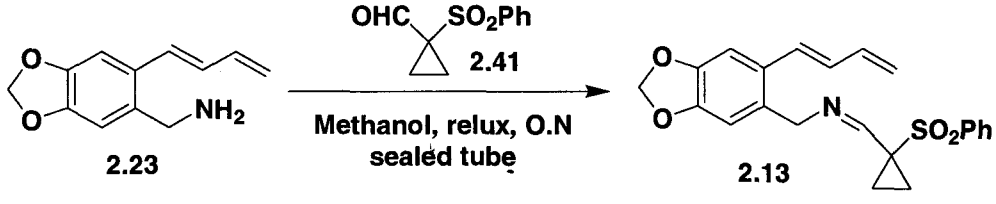
(1-Benzenesulfonyl-cyclopropylmethylene)-benzo[1,3]dioxol-5-ylmethyl-amine (2.43). Benzylamine 2.44 (0.08ml, 0.28 mmol), cyclopropane 2.41 (50mg, 0.28mmol) and methanol (5ml) are combined in an oven dried sealed tube and heated overnight at 100°C. The reaction mixted is concentrated to give the desired producy in quantitative yield. IR (neat, cm^{-1}) 3080 (w), 2889 (m), 1651 (s), 1506 (s), 1440 (s), 1249 (s), 1023 (m), 927 (s), 726 (s), 605 (s); ^{1}H NMR (400 MHz, C_6D6): δ 7.54 (s, 1H), 7.23 (d, *J*= 9.2 Hz, 2H), 7.05 (dd, *J*= 11.3 Hz, 1H), 6.96 (dd, *J*=9.9 Hz, 2H), 6.15 (d, *J*= 9.89 Hz, 1H), 5.98-5.95 (m, 3H) 5.42 (s, 2H), 4.07(s, 1H), 1.53 (dd, J= 5.6, 9.9 Hz, 2H), 1.35(dd, *J*= 5.6, 9.9 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 158.1 (CH), 147.2 (C_4), 139.1 (C_4), 133.7 (CH), 132.0 (C_4), 129.4 (CH), 128.2 (CH), 121.0 (CH), 108.4 (CH), 108.1 (CH), 100.0 (CH_2), 63.7 (CH_2), 45.7 (C_4), 16.1 (CH_2); (EI) *m/z* $C_{17}H_{17}NO_2S$ (M^+): Calculated 343.3969, found 343.0875.



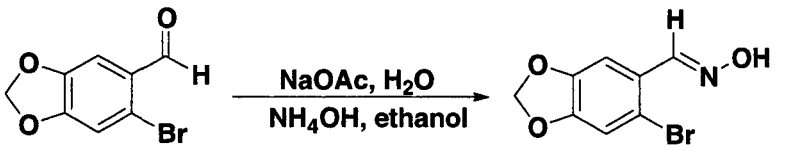
2.43 2.42

4-Benzenesulfonyl-1-benzyl-2,3-dihydro-1H-pyrrole (2.42). Substrate 2.43 (40 mg, 0.12 mmol), NH_4Cl (1.37 mg, 0.26 mmol), toluene (1 drop) was added to an oven dried sealed

tube. The reaction tube was degased with argon for 10 minutes, sealed and heated at 160°C for 1 hrs. Once cooled, the reaction mixture was dissolved in DCM (3ml) and washed with water. Subsequently, the organic layer is dried with MgSO4, filtered, and concentrated to give the desire dproduc t in quantitative yield. IR (neat, cm^{-1}) 3350 (br), 2925 (s), 2848 (m), 2343 (w), 1749 (s), 1652 (m), 11456 (s), 1230 (s), 1097 (s), 1024 (s), 696 (s); ^1H NMR (400 MHz, C_6D6): δ 7.54 (s, 1H), 7.23 (d, *J*= 9.2 Hz, 2H), 7.05 (dd, *J*= 11.3 Hz, 1H), 6.96 (dd, *J*=9.9 Hz, 2H), 6.15 (d, *J*= 9.89 Hz, 1H), 5.98-5.95 (m, 4H) 5.42 (s, 2H) 1.53 (dd, *J*= 5.6, 9.9 Hz, 2H), 1.35 (dd, *J*=5.4, 9.8 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 158.1 (CH), 147.2 (C_4), 139.1 (C_4), 133.7 (CH), 132.0 (C_4), 129.4 (CH), 128.2 (CH), 121.0 (CH), 108.4 (CH), 108.1 (CH), 100.0 (CH_2), 63.7 (CH_2), 45.7 (C_4), 16.1 (CH_2); (EI) *m/z* $C_{17}H_{17}NO_2S$ (M^+): Calculated 343.3969, found 343.0875.

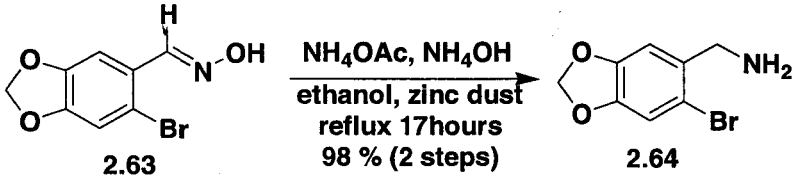


(1-Benzenesulfonyl-cyclopropylmethylene)-(6-buta-1,3-dienyl-benzo[1,3]dioxol-5-ylmethyl)-amine (2.13). Benzylamine **2.23** (25mg, 0.12 mmol), cyclopropane **2.41** (25.8 mg, 0.12 mmol) and methanol (2ml) are combined in an oven dried sealed tube and heated overnight at 100°C. The reaction mixted is concentrated to give the desired produc in quantitative yield. IR (neat, cm^{-1}) 3341 (br), 2923 (s), 2839 (m), 2327 (w), 1749 (s), 1651 (m), 1456 (s), 1230 (s), 1097 (s), 1020 (s), 696 (s); ^1H NMR (400 MHz, C_6D6): δ 8.41 (s, 1H), 8.00 (d, *J*= 11.6 Hz, 2H), 7.75 (dd, *J*=9.5 Hz, 1H), 7.62 (dd, *J*=10.2 Hz, 2H), 6.56 (d, *J*=11.5 Hz, 1H), 6.30 (d, *J*=11.5Hz, 4H), 5.59 (s, 2H), 0.40(q, *J*=6.1 Hz, 2H), 0.05 (dd, *J*=6.7 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 158.1 (CH), 146.8 (C_4), 139.6 (C_4), 133.7 (CH), 132.0 (C_4), 129.4 (CH), 128.2 (CH), 121.0 (CH), 108.4 (CH), 108.1 (CH), 100.9 (CH_2), 77.1 (CH), 634.1 (CH_2), 45.7 (C_4), 16.1 (CH_2); (EI) *m/z* $C_{22}H_{21}NO_4S$ (M^+): Calculated 395.4725, found 395.1842.



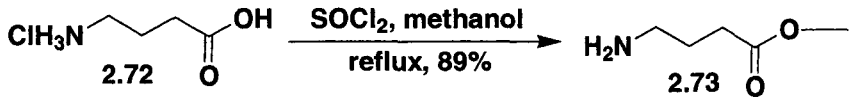
2.62 2.63

6-Bromo-benzo[1,3]dioxole-5-carbaldehyde oxime (2.63). A solution of sodium acetate (588 mg, 7.17 mmol) in water (15 ml) was added to a solution of hydroxylamine-HCl (498 mg, 7.17 mmol) in water (5ml) and the mixture was added to a warm (35°C) solution of the aldehyde (1.5g, 6.5 mmol) in ethanol (10 ml). A precipitate was formed, the 5 ml of water was added, and the mixture was stirred at room temperature overnight. The reaction was concentrated *in vaccuo* to remove the ethanol, and then extracted with DCM (3X). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated to yield the corresponding crude oxime **2.63** in a 94% yield (1.49g, 6.5 mmol). Spectral analysis is in accordance to that in the literature.[123]

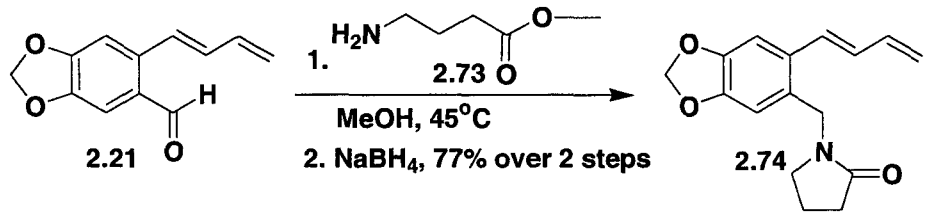


2.63 2.64

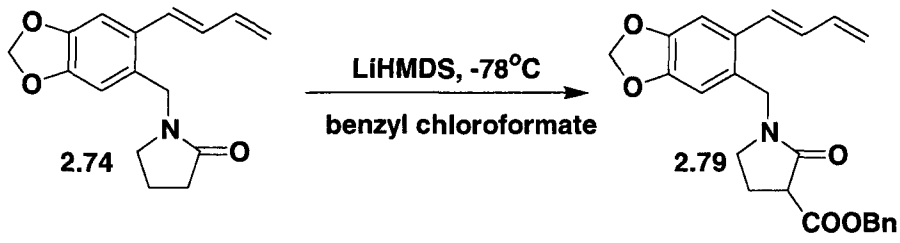
C-(6-Bromo-benzo[1,3]dioxol-5-yl)-methylamine (2.64). A mixture of the oxime **2.63** (1.43g, 5.86 mmol), ammonium acetate (542 mg, 7.03 mmol), zinc dust (2.87g, 43.9 mmol), concentrated aqueous ammonia (30 ml) and ethanol (30 ml) was heated under argon atmosphere for 17hrs. The solvents were then removed *in vaccuo* and the residue was stirred for 1hr with aqueous potassium hydroxide (35% w/v, 15 ml). The reaction mixture was extracted with ether and the extract was dried and concentrated to give the desired product **2.23** (98% over 2 steps).[118]



4-Amino-butyric acid methyl ester (2.73). Thionyl chloride (6.92g, 58.18mmol) was added dropwise to a stirred solution od the amino acid (2g, 19.39 mmol) and methanol (10ml) at 0°C. The resulting solution was then heated to reflux in methanol overnight. The solvent and thionyl chloride were then removed under reduced pressure to afford the desired product in a 89% yield of the crude product. Spectal analysis of **2.73** is in accordance with the litterature.[124]



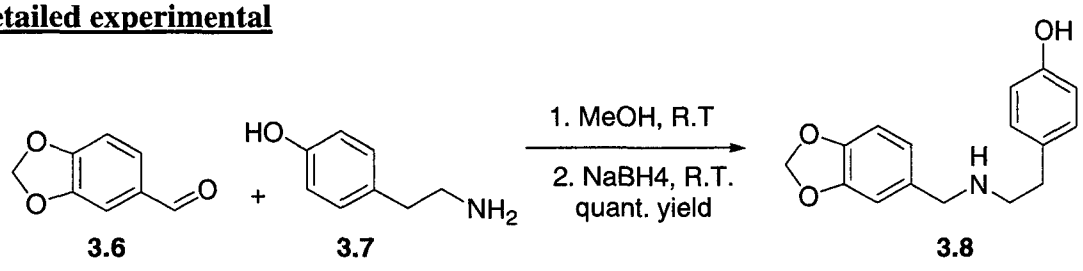
1-(6-Buta-1,3-dienyl-benzo[1,3]dioxol-5-ylmethyl)-pyrrolidin-2-one (2.74). A mixture of benzaldehyde **2.21** (50 mg, 0.25 mmol) in CH_3OH was treated with triethylamine (0.05ml. 0.32 mmol) followed by 5-aminovalerate **2.75** (45.6 mg, 0.297 mmol) and allowed to stir for 30 minutes to form the imine. After treatment with $NaBH_4$ (12.17 mg, 0.32 mmol) the reaction was stired for 19 hours at 45°C. The reaction was worked up by quenching with water and the product was extracted with DCM (3X). The organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (2-10% EtOAc in hexanes) to afford the desired product in 77% over 2 steps. IR (neat, cm^{-1}) 2921 (br), 2360 (w), 1676(s), 1503 (m), 1485(m), 1260 (m), 1030 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.81-6.76 (m, 3H), 6.71 (s, 1H), 5.98 (s, 2H), 5.32 (d, *J*= 14.7 Hz, 1H), 5.17 (d, *J*=9.9Hz, 1H), 4.48 (s, 2H), 3.16 (t, *J*=7.1, 2H), 2,41 (t, *J*=8.8 Hz, 2H), 1.96 (quint. *J*= 7.6Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.4(C_4), 147.7(C_4), 147.2(C_4),137.6 (CH), 130.6 (C_4), 130.3 (CH), 129.2 (CH), 127.9 (C_4), 117.4 (CH_2), 109.8 (CH), 105.5 (CH), 101.3 (CH_2),46.3 (CH_2), 44.2 (CH_2), 30.9 (CH_2),17.7 (CH_2); (EI) *m/z* $C_{15}H_{17}NO_3$ (M^+): Calculated 271.3111, found 271.1196.[63]



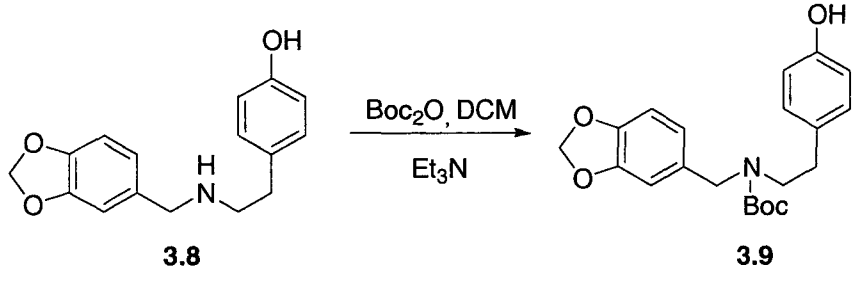
1-(6-Buta-1,3-dienyl-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester (2.79). A solution of LiHMDS was prepared from *n*-Buli (0.06ml, 0.11mmol) and hexamethyldisilane (0.025ml, 0.11mmol) in THF (2 ml) at 0°C and cooled to -78°C, whereupon a solution of **2.74** in THF (3ml) was added over 10 minutes. The mixture was stirred at -78°C for 40 minutes and freshly distilled methyl chloroformate (5.12mg, 0.054 mmol) was added dropwise. The mixture was then allowed to warm slowly to room temperature and stirred overnight. Saturated aqueous NH_4Cl and water were added and the mixture was extracted with DCM (3X). The combined organic fractions were dried with $MgSO_4$, and concentrated under reduced pressure, and the residue was purified by flash chromatography to yield the desired product in 61% yield. IR (neat, cm^{-1}) 2924 (br), 2364 (w), 2341(w), 1737 (s), 1689(s), 1485 (m), 1266 (m), 1163(m),1036(m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 5H), 7.01 (s, 1H), 6.74 (d, *J*=13.7 Hz, 1H), 6.69 (s, 1H), 6.57-6.44 (m, 2H), 5.28 (d, *J*= 16.7 Hz, 1H), 5.21 (s, 2H), 5.15-5.11 (m, 1H), 4.53 (d, *J*= 15.3Hz, 1H), 4.42 (d, *J*= 14.3Hz, 1H), 3.49 (dd, *J*= 7.4, 9.8 Hz,1H), 3.31-3.25 (m, 1H), 3.14-3.08 (m, 1H), 2.37-2.28 (m, 1H), 2.23-2.14 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.0(C_4), 169.2(C_4), 147.8(C_4), 147.4(C_4), 137.4 (CH), 135.7 (C_4), 130.6 (C_4), 130.5 (CH), 129.0 (CH), 128.6 (CH), 128.3(CH), 128.1(CH), 127.2 (C_4), 117.6 (CH_2), 109.9 (CH), 105.5 (CH), 101.3 (CH_2), 67.2 (CH_2), 48.5 (CH), 44.9 (CH_2), 44.6 (CH_2), 22.2 (CH_2); (EI) *m/z* $C_{24}H_{23}NO_5$ (M^+): Calculated 405.4432, found 405.1550.

Procedures-Chapter 3

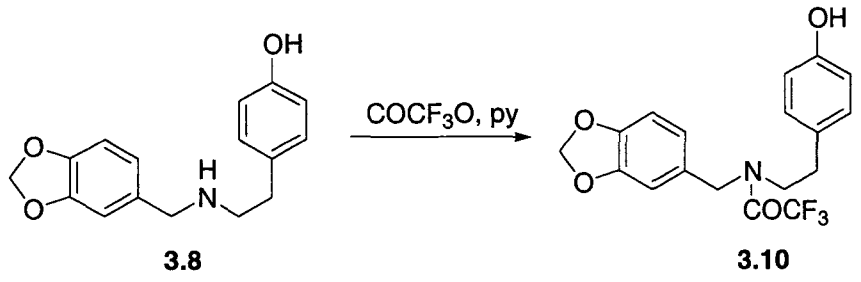
Detailed experimental



N-3',4'-methylenedioxyphenylmethyl-[2-(4-hydroxyphenyl)] ethylamine (3.8), A flask was charged with a stir bar, piperonal **3.6** (2.0g, 13.3 mmol) and tyramine **3.7** (2.2g, 16.0 mmol) in methanol (32 ml). The reaction was let stir at room temperature for 1 hr. $NaBH_4$ (553 mg, 14.6 mmol) was added to the solution and stirred at room temperature for 1 hr. The reaction mixture was condenced *in vacuo*, washed with water and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **3.8** as a flaky beige solid (4.25 g, 103%). The product was treated for further reaction without purification. Prepared and characterized according to the procedure by Kadoma et al.[10]

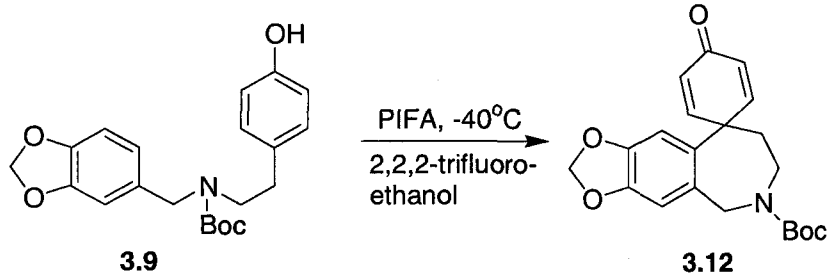


***N*-Boc-*N*-3',4'-methylenedioxyphenylmethyl-[2-(4-hydroxyphenyl)] ethylamine (3.9).** A flask was charged with a stir bar, amine **3.8** (92.9mg, 0.34 mmol), Boc_2O (90.0 mg, 0.51 mmol) and Et_3N (0.95ml, 0.68mmol) in DCM (3 mL). The reaction was refluxed for 8 hrs, and concentrated in *vacuo*. The residue was purified by flash column chromatography (0 to 2% MeOH in DCM) to afford **3.9** as a yellow oil (120 mg, 97%). Spectral data were in accord with those publiched[10].



3.8 **3.10**

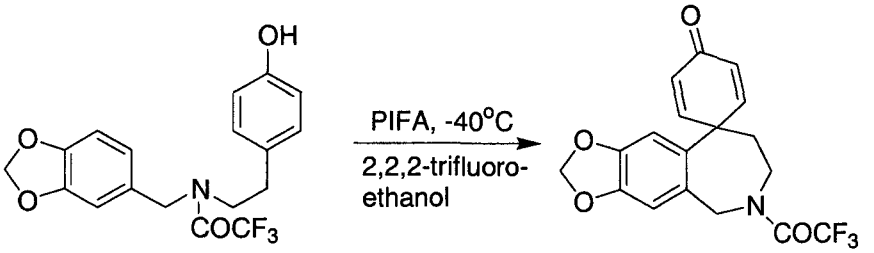
***N*-Trifluoroacetyl-*N*-3',4'-methylenedioxyphenylmethyl-[2-(4-hydroxyphenyl)] ethylamine (3.10).** Prepared according to the procedure by Kadoma et *al.*[10] A flask was charged with a stir bar, free amine 3.8 (67.4 mg, 0.492 mmol) in pyridine (1mL). The solution was cooled to 0°C in an ice bath, then trifluoroacetic anhydride (215.1 mg, 1.02 mmol) was added dropwise and the reaction mixture was let stir at 0°C for 2hrs. The reaction mixture was diluted with MeOH condensed in vacuo and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo* and purified by flash column chromatography (50 to 65% EtOAc in hexanes) to afford **3.10** as beige solide in (175.2 mg, 99%). Spectral data are in accord with those published.[125]



3.9 **3.12**

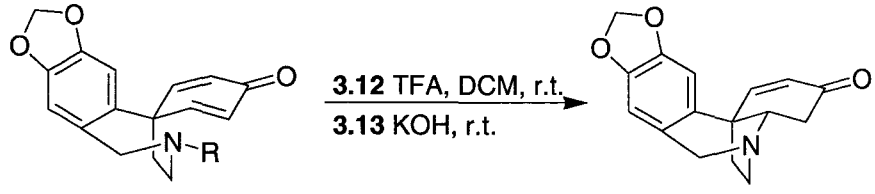
Spiro ketone – Boc protected amine (3.12). Prepared according to the procedure by Kadoma.[10] A round bottom flask was charged with a stir bar and flame dried under reduced pressure. A solution of amine **3.9** (2.0g, 5.38 mmol) was in dry 2,2,2-trifluoroethanol (30 mL) was purged with argon and cannulated into the flame-dried vessel and cooled to –40°C. PIFA (2.54g, 5.92 mmol) was dissolved in dry 2,2,2-trifluoroethanol (15 mL), the solution was purged with argon and added by cannulation to the amine **3.9** solution. The reaction mixture was stirred for 40 minutes at –40°C, and then concentrated in *vacuo*. The residue

purified by flash column chromatography (5 to 30% EtOAc in hexanes) to afford **3.12** as beige solid (650 mg, 33%. Spectral data were in accord with those published.[10]



3.9 **3.13**

Spiro ketone – $COCF_3$ protected amine (3.13). Prepared according to the procedure by Kadoma.[10] A round bottom flask was charged with a stir bar and flame dried under reduced pressure. A solution of amine **3.9** (20mg, 0.054 mmol) was in dry 2,2,2-trifluoroethanol (1 mL) was purged with argon and cannulated into the flame-dried vessel and cooled to –40°C. PIFA (25.76 mg, 0.06 mmol) was dissolved in dry 2,2,2-trifluoroethanol (1 mL), the solution was purged with argon and added by cannulation to the amine **3.9** solution. The reaction mixture was stirred for 40 minutes at –40°C, and then concentrated in *vacuo*. The residue purified by flash column chromatography (5 to 30% EtOAc in hexanes) to afford **3.13** as beige solid as 81% yield. Spectral data were in accord with those published.[126]



3.12 R= Boc
3.13 R= $COCF_3$

3.8
71 %
82 %

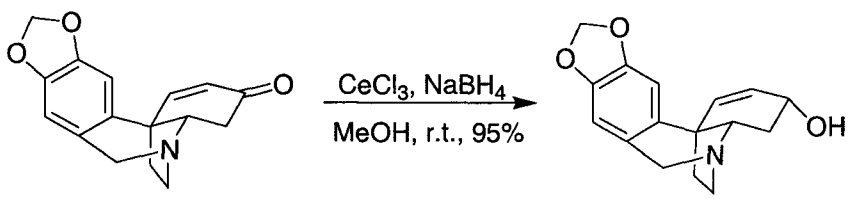
Formation of 3.5 from 3.12.

(±) Oxocrinine (3.5). Compound **3.12** (29.5mg, 0.081mmol) was dissoleved in DCM (1ml) anda few drops of TFA was added at room temperature. The reaction was let stir for 2hrs and then quenched with sat. $NaHCO_3$ solution and extracted with DCM. The

combined organic layers were dried over $MgSO_4$ and concentrated in vaccuo. The crude mixture was purified by column chromatography (50%EtOAc in hexanes). The desired product **3.5** was isolated in a (21.6mg, 71% yield)

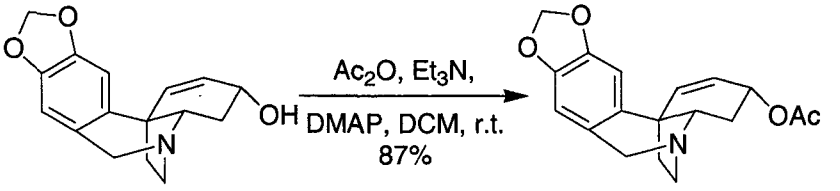
Formation of 3.5 from 3.13

(±) Oxo-crinine (3.5). Prepared according to the procedure by Bru[67]. A flask was charged with a stir bar, amine **3.13** (50mg, 0.14 mmol) in MeOH (0.5mL) A 10% aq. Solution of KOH (15.7 mg, 0.28 mmol) was added and the reaction misture was let stir for 9 hrs at room temperature. The reaction mixture concentrated *in vacuo* and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and condensed *in vacuo*. The residue was purified by flash column chromatography (0 to 3% MeOH in DCM) to give **3.5** as a mixture of diastereomers, as a white solid (41 mg, 82%). Spectral data were in accord with those published.[77]



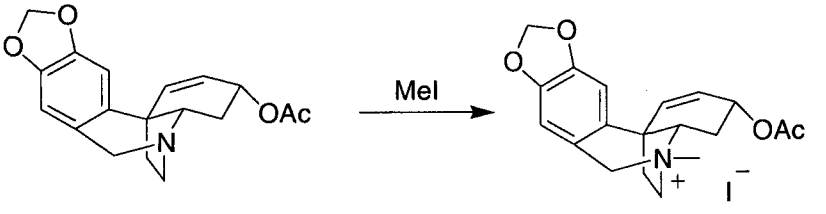
3.8 **3.14**

(±) Epivittatine (3.14). Prepared according to the procedure by Henninger.[68] A round bottom flask was charged with a stir bar and (±) oxo-crinine (**3.5**) (45.5mg, 0.169 mmol) in MeOH (0.7 mL). $CeCl_3$ (28.4mg, 0.169 mmol) and $NaBH_4$ (7.04mg, 0.186 mmol) were added and the reaction mixture was stirred at room temperature for 40 minutes. The reaction solution was diluted with water and extracted with EtOAc. The combine organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to give **3.14** as a mixture of diastereomers, as a white solid (43.7mg, 95.3%). The product was treated for further reaction without purification. Spectral data were in accord with those published.[127]



3.14 **3.15**

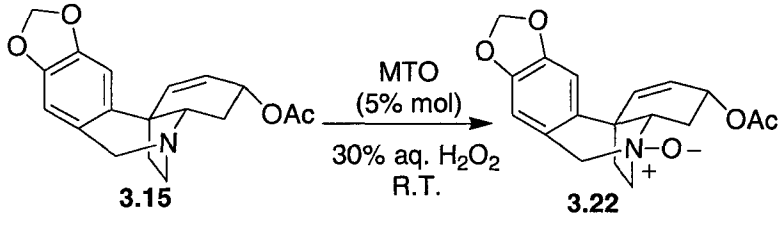
(±) Krepowine (3.15). Prepared according to the procedure by Henninger.[68] A round bottom flask was charged with a stir bar and **(±)** epivittatine (**3.14**) (38.7 mg, 0.142 mmol) in DCM (1.5 mL). The solution was cooled to 0°C and Et_3N (26µl, 0.185 mmol), DMAP (5% mol) and acetic anhydride (16µl, 0.170 mmol) were added, and the solution was stirred at 0°C for 2hrs. MeOH was added, and stirring was continued for 10 minutes. The solution was washed with 1 N HCl, saturated aq. NaHCO3, and brine and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (0 to 3% MeOH in DCM) to give **3.15** as a mixture of diastereomers, as a white solid (38.6 mg, 87%). Spectral data were in accord with those published.[68]



3.15 **3.16**

Kreptowine with quaternary amine (3.16). Amine **3.15** (100mg, 0.319mmol) was dissolved in DCM (10ml) and Meerwein salt (47.2mg, 0.319mmol) was added slowly at room temperature. The reaction mixture was stirred for 30 minutes during which the mixture became cloudy and a white precipitate was formed. The crude mixture was concentrated to give the desired crude product **3.16** in quantitative yield. IR (neat, cm^{-1}) 2947 (m), 2855 (m), 1743 (s), 1494 (s), 1243 (s), 1040 (s), ^1H NMR (DMSO-D_6, 400 MHz) δ 7.21 (s, 1H), 6.87 (s, 1H), 6.66 (dd, *J*= 2.0, 11.8 Hz, 1H), 6.04 (s, 2H), 5.79 (d, *J*= 10.1 Hz, 1H), 5.46-5.39 (m,

1H), 4.83 (d, *J*= 13.8 Hz, 1H), 4.74 Hz (d, J= 15.2, 1H), 4.27 (dd, *J*= 4.2, 13.3 Hz, 2H), 3.99-3.91 (m, 2H), 3.25 (s, 3H), 2.59- 2.52 (m, 1H), 2.42-2.28 (m, 2H), 2.10 (s, 3H), 2.07-1.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 170.4 (C_4), 148.3 (C_4), 147.1 (C_4), 133.6 (C_4), 128.5 (CH), 128.0 (CH), 119.9 (C_4), 106.9 (CH), 104.4 (CH), 102.2 (CH_2), 72.3 (CH), 69.40 (CH_2), 68.7 (CH), 62.8 (CH_2), 48.1 (CH_3), 46.5 (CH), 41.93 (CH_2), 25.9, (CH_2), 21.3 (CH_3); HRMS (ESI) m/z calculated for $C_{19}H_{22}NO_4$ $(M)^+$ 328.1549 found 328.1785.



N-Oxide kreptowine derivative (3.22). A mixture of amine **3.15** (49 mg, 0.16 mmol) and MTO (2 mg, 0.008 mmol) was dissolved in distilled DCM (5ml) and then treated with 30% ac. H_2O_2 an stirred at room temperature for 8 hours. The biphasic reaction was then treated with a catalytic amount of MnO_2 ans stirred until oxygen evolution ceased. Following phase separation the aqueous phase was extracted with DCM (3X), combined, dried over $MgSO_4$, filtered and concentrated to give the desired product in 88% yield. IR (neat, cm^{-1}) 3412 (w), 2984 (m), 1732 (s), 1646 (m), 1504 (s), 1488 (s), 1375 (m), 1244 (s), 1036 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.56 (s, 1H), 6.29 (dd, J= 2.4, 10.17 Hz, 1H), 5.94 (d, *J*= 6.1Hz, 2H), 5.81 (d, *J*= 8.6 Hz, 1H), 5.50-5.43 (m, 1H), 4.79 (q, *J*= 17.2Hz, 2H), 3.96-3.88 (m, 2H), 3.67-3.63 (m, 1H), 3.45 (s, 1H), 3.17-3.11 (m, 1H), 2.45-2.40 (m, 1H), 2.19-2.12 (m, 1H), 2.08 (s, 3H), 1.92-1.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 147.9 (C_4), 147.2 (C_4), 134.5 (C_4), 129.3 (CH), 127.7 (CH), 121.2 (C_4), 106.6 (CH), 102.8 (CH), 101.4 (CH_2), 76.2 (CH), 68.9 (CH), 68.14 (CH_2), 46.6 (CH_2), 40.8 (CH_2), 26.1 (CH_2), 14.2 (CH_3); HRMS (ESI) m/z calculated for $C_{18}H_{19}NO_5$ $(M)^+$ 329.3472 found $(M^+ - O)$ 313.1279.

Procedures-Chapter 4

General procedure

A) Synthesis of propargyl acetates

The ketone (1 eq) is dissolved in dry THF (0.1 M). The solution was then cooled to 0°C and then ethynyl magnesium bromide (2eq) was added drop wise over 30 minutes. The reaction is then warmed to room temperature and stirred till completion. The reaction was then cooled to 0°C and quenched with acyl chloride (1.2eq), then extracted with ethyl acetate (3X). The organic layers where combined and dried over $MgSO_4$, filtered and concentrated *in vaccuo* to afford a dark brown oil as a crude product. Purification by flash chromatography affords the corresponding propargyl acetate.

B) Synthesis of propargyl pivaloates

The ketone (1 eq) is dissolved in dry THF (0.1 M). The solution was then cooled to 0°C and then ethynyl magnesium bromide (2eq) was added drop wise over 30 minutes. The reaction is then warmed to room temperature and stirred till completion. The reaction was then cooled to 0°C and quenched with water. The reaction mixture is then extracted with ethyl acetate (3X). The organic layers where combined and dried over $MgSO_4$, filtered and concentrated to afford a dark purple oil as a crude alcohol.

PivCl (1.5 equiv.), Et_3N (1.75 equiv.) and DMAP (0.75 equiv.) were dissolved in DCM and combined in a flame dried flask equipped with a stirbar and a condensor. The alcohol (1 equiv.) was added via cannula as a DCM solution (1M). The mixture was refluxed overnight. The crude reaction was cooled down and quenched with water. The mixture was extracted with EtOAc (3x) and dried over $MgSO_4$, filtered, concentrated *in vaccuo*. Purification by flash chromatography affords the corresponding propargyl pivaloate.

C) Using the catalyst combination $Au(PPh_3)Cl$ and AgOTf.

$Au(PPh_3)Cl$ (5 mol %) and AgOTf (5 mol %) was weighed in the glove box and transferred to a flamed dried flask with a magnetic stirrer. The solution of dry dichloromethane (1mL) and our propargyl acetate or pivaloate (1 eq) was then added via cannula. The resulting black solution was then stirred for 2.5 hours, filtered through celite, evaporated *in vaccuo* and purified by flash column chromatography to afford the corresponding product.

D) Using the catalyst combination $Au(PPh_3)Cl$ and TfOH.

$Au(PPh_3)Cl$ (5% mol) was weighed in the glove box and transferred to a flamed dried flask with a magnetic stirrer. Then was added the 1M solution of TfOH (5% mol) in dry dichloromethane followed by the solution of dry dichloromethane (1 mL) and the propargyl acetate or pivaloate is then added via cannula. The resulting dark brown solution was then stirred for 2.5 hours, filtered through celite and washed with Na_2CO_3 (3X). Organic layers were combined, dried over $MgSO_4$, evaporated *in vaccuo* and purified by flash column chromatography to afford the corresponding product.

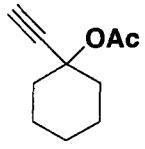
E) SYMYX experiments

Stock solutions of the gold and silver catalyst were made in dry DCM (0.1M). To this end, the catalysts were weighed in the glove box in oven dried vials and dry DCM was added via cannula. . Stock solutions of the starting material and the product were also made in dry DCM, dry benzene, dry toluene, dry chlorobenzene and dry DCE (0.0605M). All the stock solutions were put in the SYMYX glove box with plates containing oven dried vials and stir bars. Using the SYMYX syringe the gold and silver catalyst were added, as a DCM solution, to the vials, and the DCM was evaporated *in vaccuo* in the glovebox. To the now dry catalyst was added the substrate as a solution in the corresponding solvent that was tried for each reaction. The plate was then sealed with Teflon and a rubber sheet, taken out of the glovebox

to be stirred at room temperature for 1h. After 1 h the seal was opened and the automated SYMYX machine took TLC's of the reactions.

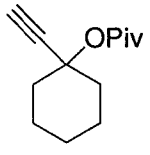
Detailed Experimental

Synthesis of propargyl acetate and pivaloates:



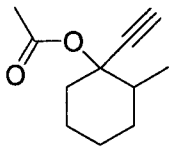
4.28a

Acetic acid 1-ethynyl-cyclohexyl ester (4.28). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.28a (2.35g, 69%) as a yellow oil. IR (neat, cm^{-1}) 3285 (br), 2937 (s), 2862 (m), 1745 (s), 1447 (w), 1368 (m), 1230 (s), 1025 (s); ^1H NMR (400 MHz, $CDCl_3$): δ2.59 (s, 1H), δ2.12 (m, 2H), δ2.03 (s, 3H), δ1.84 (m, 2H), δ1.61 (m, 4H), δ1.50 (m, 1H), δ1.32 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ169.3, (CO), 83.7 (C_4), 75.1 (C_4), 74.2 (CH), 36.9 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 21.9 (CH_3); HRMS (EI) *m/z* M^+ ($C_{10}H_{14}O_2$): Calculated 166.2169, found 166.0970.



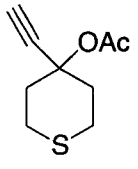
4.28b

2,2-Dimethyl-propionic acid 1-ethynyl-cyclohexyl ester (4.28b). Synthesized following the general procedure B. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.28b (1.7g, 83%). IR (film; cm^{-1}): 3271, 2975, 2937, 2868, 2166, 2120, 1737, 1480, 1136; ^1H NMR (400 MHz, $CDCl_3$) δ2.55(s, 1H), δ2.05-1.92 (m, 4H), δ1.60-1.58 (m, 4H), δ1.44-1.42 (m, 2H). δ1.23 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.5(C_4), 84.1 (C_4), 74.2 (C_4), 73.5(CH), 39.2(C_4), 36.7(CH_2), 28.8 (CH_3), 25.6 (CH_2), 22.2 (CH_2); HRMS (EI) *m/z* M^+ ($C_{13}H_{20}O_2$): Calculated 208.1463, found 208.1451.



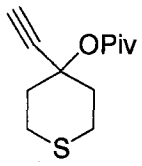
4.40a

Acetic acid 1-ethynyl-2-methyl-cyclohexyl ester (4.40a). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) gave 4.40a (0.85g, 63%). IR (neat, cm^{-1}) 3272 (m), 2935 (s), 2861 (m), 1746 (s), 1449 (m), 1369 (m), 1240 (s), 1018 (s), 958 (m), 876 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.23 (m, 1H), 2.53 (s, 1H), 2.05 (s, 3H), 1.87-1.77 (m, 1H), 1.65- 1.17 (m, 7H), 1.05 (d, *J*= 3.4, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 169.6 (C_4), 84.1 (C_4), 80.7 (C_4), 76.2 (CH), 40.8 (CH), 35.9 (CH_2), 31.4 (CH_2), 25.1 (CH_2), 22.0 (CH_3), 21.2 (CH_2), 16.1 (CH_3); HRMS (EI) m/z calculated for $C_{11}H_{16}O_2$ $(M)^+$ 180.2435 found $[M-C_2H_30]^+$ 137.0973.



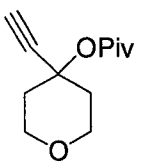
4.40b$_2$

Acetic acid 4-ethynyl-tetrahydro-thiopyran-4-yl ester (4.40b$_2$). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) gave 4.40b$_2$ (0.62g, 87%). IR (neat, cm^{-1}) 3274 (br), 2955 (s), 2923 (s), 2832 (m), 2115 (m), 1756 (s), 1431 (m), 1369 (m), 1149 (m), 1018 (m), 670 (s); ^1H NMR (400 MHz, $CDCl_3$): δ2.60-2.55 (m, 2H), δ2.45-2.39 (m, 2H). δ2.19-2.13 (m, 2H), δ1.96-1.89 (m, 2H), δ1.83 (s, 3H), δ1.64 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ167.8 (C_4), 81.5(C_4), 73.1(CH), 62.3(C_4), 37.0(CH_2), 24.1(CH_2), 20.5(CH_3); HRMS (EI) *m/z* M^+ ($C_9H_{12}O_2S$) : Calculated 184.0558, found 184.0582.



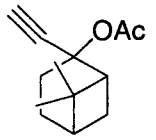
4.40b

2,2-Dimethyl-propionic acid 4-ethynyl-tetrahydro-thiopyran-4-yl ester (4.40b). Synthesized following the general procedure B. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40b (0.43g, 77%). IR (neat, cm^{-1}) 3279 (br), 2971 (m), 2922 (m), 2873 (m), 2112 (w), 1739 (s), 1481 (m), 1272 (m), 1148 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ2.78-2.63 (m, 4H), 2.62 (s, 1H), δ2.37-2.22 (m, 4H), 1.22 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.3 (C_4), 82.6 (C_4), 73.1(CH), 39.2(C_4), 37.6(CH_2), 27.1 (CH_3), 26.9(C_4), 24.6(CH_2); HRMS (EI) *m/z* M^+ ($C_9H_{12}O_2S$): Calculated 226.1028, found 226.1001.



4.40c

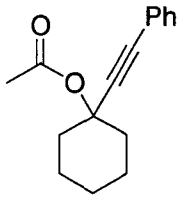
2,2-Dimethyl-propionic acid 4-ethynyl-tetrahydro-pyran-4-yl ester (4.40c). Synthesized following the general procedure B. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40c (0.68 g, 79%). IR (neat, cm^{-1}) 3273 (br), 2967 (s), 2937 (s), 2863 (s), 2116 (w), 1739 (s), 1480 (s), 1281 (m), 1048 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84-3.72 (m, 4H), 2.63 (s, 1H), δ2.23-2.02 (m, 4H), 1.21 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.3 (C_4), 82.5 (C_4), 75.1 (CH), 71.5 (C_4), 64.8 (CH_2), 39.4 (C_4), 37.08(CH_2), 27.4 (CH_3); HRMS (EI) *m/z* M^+ ($C_{12}H_{18}O_2$) : Calculated 210.1256, found [M^+- Piv] 126.0685.



4.40d$_2$

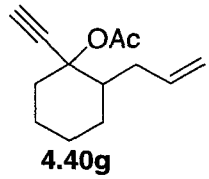
Acetic acid 2-ethynyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-yl ester (4.40d$_2$). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40d$_2$ (1.02 g, 91%). IR (neat, cm^{-1}) 3288 (br), 2926 (s), 2871 (s), 2116 (w), 1751 (s), 1463 (s), 1208 (s), 1041 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ2.66-2.55 (m, 2H), δ2.47 (s, 1H), δ2.38-2.23 (m, 2H), δ2.02 (s, 3H). δ2.00-1.84 (m, 3H), δ1.37 (d, *J*= 12.3 Hz, 1H), δ1.24 (s, 3H), δ0.99 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ168.7 (C_4), 85.57(C_4), 78.8 (C_4), 70.6(CH), 50.6(CH), 39.9(CH), 37.4(C_4), 30.6 (CH_2), 27.3(CH_2), 26.8(CH_3), 24.0(CH_2), 22.6(CH_3), 22.1(CH_3); HRMS (EI) *m/z* M^+ ($C_{13}H_{18}O_2$): Calculated 206.1307, found [M^+-Ac] 191.1066.

2,2-Dimethyl-propionic acid 2-ethynyl-6,6-dimethyl-bicyclo[3.1.1]hept-2-yl ester (2.40d). Synthesized following the general procedure B. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40d (1.14 g, 76%). IR (neat, cm^{-1}) 3288 (br), 2926 (s), 2871 (s), 2116 (w), 1751 (s), 1463 (s), 1208 (s), 1041 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ2.67-2.60 (m, 1H), 2.49 (dd, *J*= 4.6, 7.4 Hz, 1H), 2.4 (s, 1H), 2.39-2.33 (m, 1H), 2.27-1.19 (m, 1H), 2.20-1.87 (m, 3H), 1.37 (d, *J*= 11.0 Hz, 1H), 1.24 (s, 3H), δ1.18 (s, 9H), 0.99 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ168.7 (C_4), 85.57(C_4), 78.8 (C_4), 70.6(CH), 50.6(CH), 39.9(CH), 37.4(C_4), 30.6 (CH_2), 27.3(CH_2), 26.8(CH_3), 24.0(CH_2), 22.6(CH_3), 22.1(CH_3); HRMS (EI) *m/z* M^+ ($C_{16}H_{24}O_2$): Calculated 208.1776, found [M^+-Piv] 163.0744.



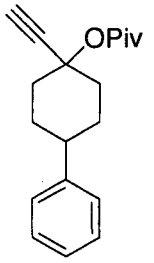
4.39e

Acetic acid 1-phenylethynyl-cyclohexyl ester (4.40e). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40e (1.12 g, 90%). IR (CH_2Cl_2): 3468(w), 2932 (s), 2859 (s), 2229(s), 1741 (s), 1612 (w), 1491(m), 1219(m), 1070(m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 3H), 7.44 (m, 2H), 2.23 (m, 2H); 2.06 (s, 3H), 1.91 (m, 2H), 1.67 (m, 4H), 1.55 (m, 1H), 1.33 (m, 1H); ^{13}C NMR (400 MHz, CDCl3): δ169.4 (CO), 131.9(CH), 128.2(CH), 122.8 (CH), 89.2(C_4), 86.4(C_4), 76.0(C_4), 37.1(CH_2), 25.4 (CH_2), 22.8 (CH_2), 22.0 (CH_3); HRMS (EI) *m/z* M^+ ($C_{16}H_{18}O_2$) , calculated 242.3130, found 242.1323.



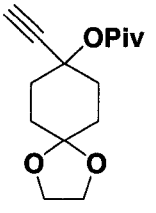
4.40g

Acetic acid 2-allyl-1-ethynyl-cyclohexyl ester (4.40g). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40g (0.88 g, 79%). IR (film): 3473, 3291, 3077, 2972, 2940, 2860, 2105, 1751, 1733, 1641, 1447, 1232; ^1H NMR (400 MHz, $CDCl_3$): δ5.77-5.66 (m, 1H), 5.01-4.95 (m, 2H), 2.74-2.67 (m, 1H), 2.64-2.50 (m, 2H), 2.01 (s, 1H), 1.99 (s, 1H), 1.94-1,12 (m, 10H); ^{13}C NMR (400 MHz, $CDCl_3$): δ169.0 (C_4), 137.1 (CH), 115.9 (CH_2), 83.7(C_4), 80.5(C_4), 76.5(CH), 45.6(CH), 36.0 (CH_2), 34.7(CH_2), 27.8(CH_2), 25.7(CH_2), 24.8(CH_2), 21.2 (CH_3); HRMS (EI) *m/z* M^+ ($C_{13}H_{18}O_2$): Calculated 206.1307, found [M^+-Ac] 164.1203.



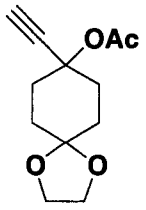
2.40h

2,2-Dimethyl-propionic acid 1-ethynyl-4-phenyl-cyclohexyl ester (2.40h). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40h (0.48g, 55%). IR (film; cm^{-1}): 3284, 3028, 2936, 2864, 2120, 1737, 1494, 1480, 1453, 1283, 1160; ^1H NMR (400 MHz, $CDCl_3$): δ7.32-7.18(m, 5H), 2.68 (s, 1H), 2.57-2.53 (m, 3H), 1.99-1.90 (m, 4H). 1.76-1.69 (dt, J_1=5.5Hz, J_2=12Hz, 2H), 1.21 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ176.6 (C_4), 146.0 (C_4), 128.4 (CH_2), 127.0 (CH_2), 126.8 (C_4), 82.9 (C_4), 76.8 (C_4), 75.1 (CH), 43.4(C_4), 39.1(CH), 37.2 (CH_2), 30.9 (CH_2), 26.9 (CH_3); HRMS (EI) *m/z* M^+ ($C_{19}H_{24}O_2$): Calculated 284.1776, found 284.1760.



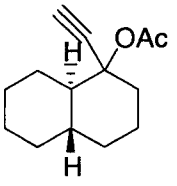
4.40i

2,2-Dimethyl-propionic acid 8-ethynyl-1,4-dioxa-spiro[4.5]dec-8-yl ester (4.39i). Synthesized following the general procedure B. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40i (0.19g, 43%). IR (film): 3264, 2959, 2872, 2116, 1735, 1151, 1105, 929; ^1H NMR (400 MHz, $CDCl_3$): δ3.91 (s, 4H), 2.53 (s, 1H), 2.24-2.11 (m, 4H), 1.79-1.66 (m, 4H). 1.17 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): 176.56 (C_4), 107.48(C_4), 83.09(C_4), 73.66 (CH), 72.73(C_4), 64.34(CH_2), 39.23(C_4), 34.16 (CH_2), 30.77(CH_2), 27.07(CH_3); HRMS (EI) *m/z* M^+ ($C_{15}H_{22}O_4$): Calculated 266.1518, found: 266.1499.



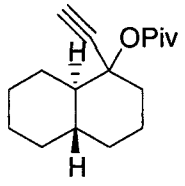
4.40i$_2$

Acetic acid 8-ethynyl-1,4-dioxa-spiro[4.5]dec-8-yl ester (4.40i$_2$). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40i$_2$ (0.28g, 75%). IR (film): 3264 (br), 2962 (s), 2882 (s), 2115 (m), 1751 (s), 1446(s), 1371 (s), 1245(s); ^{1}H NMR (400 MHz, $CDCl_3$): δ3.83 (s, 4H), 2.53 (s, 1H), 2.24-2.11 (m, 4H), 1.94 (m, 3H), δ1.74-1.56 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ168.9 (C_4), 107.1(C_4), 82.5(C_4), 74.1 (CH), 73.2(C_4), 64.1 (CH_2), 33.9(CH_2), 30.6 (CH_2), 21.5(CH_3); HRMS (EI) *m/z* M^+ ($C_{11}H_{16}O_4$): Calculated 224.1049, found [M^+-Piv] 182.0895.



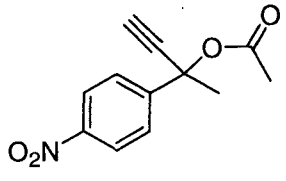
4.40j$_2$

Acetic acid 1-ethynyl-decahydro-naphthalen-1-yl ester (4.40j$_2$). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40j$_2$ as a (1:1) mixture of diastereomers (0.48g, 55%). IR (film): 3270, 2930, 2853, 2112, 1746, 1447; ^{1}H NMR (400 MHz, $CDCl_3$): δ2.92-2.88 (m, 0.5 H), 2.75-2.72 (m, 0.5 H), 2.55 (s, 0.5 H), 2.46 (s, 0.5H). 1.98 (s, 1.5 H), 1.94 (s, 1.5H),.90-0.81 (m, 7.5H); ^{13}C NMR (400 MHz, $CDCl_3$): δ169.1(C_4), 169.0(C_4),, 83.5(CH), 81.0(CH), 79.3(CH), 76.0(C_4), 75.9(C_4), 73.1(CH), 51.5(CH_2), 50.6(CH_2), 38.1(CH), 36.3(CH), 36.2(CH_2), 35.1(CH_2), 34.2(CH_2), 33.7(CH_2), 33.2(CH_2), 26.4(CH_2), 26.2(CH_2), 26.0(CH_2), 25.9(CH_2), 25.7(CH_2), 25.6(CH_2), 22.6(CH_2), 22.1(CH), 21.9(CH), 19.7(CH_2); HRMS (EI) *m/z* M^+ ($C_{14}H_{20}O_2$): Calculated 220.1463, found 220.1449.



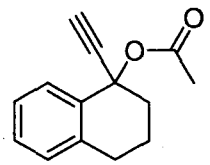
4.40j

2,2-Dimethyl-propionic acid 1-ethynyl-decahydro-naphthalen-1-yl ester (4.40j). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40j as a (1:1) mixture of diastereomers (0.48g, 55%). IR (film) : 3397 (w), 3295(w), 2931 (s), 2854(m), 1739(s), , 1479(m); ^{1}H NMR (400 MHz, $CDCl_3$): δ2.94 (d, *J*=17.5Hz, 0.5 H), 2.81 (d, *J*= 17.1 Hz, 0.5 H), δ2.56 (s, 0.5 H), 2.45 (s, 0.5H). 2.11-0.87 (m, 12 H); ^{13}C NMR (400 MHz, $CDCl_3$): δ176.5(C_4), 176.3(C_4), 83.8(CH), 81.3(CH), 78.9(CH), 75.7(C_4), 73.0(C_4), 52.12 (CH), 51.5(CH), 39.63(CH), 39.3(CH), 38.2(CH_2), 36.8(CH_2), 36.4(CH_2), 34.4(CH_2), 33.9(CH_2), 33.3(CH_2), 27.4(CH_2), 27.2(CH_3), 26.7(CH_2), 26.6(CH_2), 26.3(CH_2), 26.1(CH_2), 25.9(CH_2), 22.6(CH_2), 22.1(CH), 21.9(CH), 19.7(CH_2); HRMS (EI) *m/z* M^+ ($C_{17}H_{26}O_2$): Calculated 262.1933, found 262.1957.



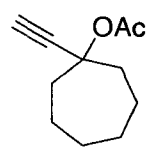
4.40k

Acid 1-methyl-1-(4-nitro-phenyl)-prop-2-ynyl ester (4.40k). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40k (0.07g, 85%). IR (neat, cm^{-1}) 3281 (w), 2932 (s), 2858 (m), 1748 (m), 1601 (w), 1520 (s), 1346 (m), 1222 (m), 1061 (w), 850 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, *J*= 9.7 Hz, 2H), 7.74 (d, *J*= 9.7 Hz, 2H), 2.88 (s, 1H), 2.12 (s, 3H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 168.9 (C_4), 145.8 (C_4), 126.0 (CH), 123.8 (CH), 94.4 (C_4), 32.0 (CH_3), 21.5 (CH_3); HRMS (EI) m/z calculated for $C_{12}H_{11}NO_4$ $(M)^+$ 233.2200, found 233.0701.



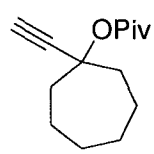
4.40l

Acetic acid 1-ethynyl-1,2,3,4-tetrahydro-naphthalen-1-yl ester (4.40l). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40l (0.35g, 80%). IR (neat, cm^{-1}) 3284 (m), 2937 (m), 2870 (w), 1743 (s), 1490 (m), 1367 (m), 1235 (s), 1012 (m), 942 (m), 761 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.74-7.70 (m, 1H), 7.24-7.21 (m, 2H), 7.12-7.07 (m, 1H), 2.88-2.79 (m, 2H), 2.71 (s, 1H), 2.60-2.45 (m, 2H), 2.04 (s, 3H), 1.96-1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 169.3 (C_4), 136.5 (C4), 135.9 (C_4), 129.1 (CH), 128.7 (CH), 128.6 (CH), 126.3 (CH), 84.2 (C_4), 75.2 (CH), 74.7 (C_4), 34.9 (CH_2), 28.9 (CH_2), 22.2 (CH_3), 19.3 (CH_2); HRMS (EI) m/z calculated for $C_{14}H_{14}O_2$ $(M)^+$ 214.2598 found 214.0992.



4.40m

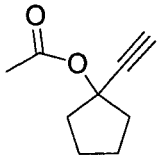
Acetic acid 1-ethynyl-cycloheptyl ester (4.40m). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40m (0.48g, 55%). Spectral data is in accord with those published.[128]



4.40m$_2$

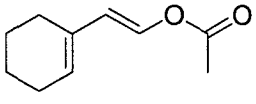
2,2-Dimethyl-propionic acid 1-ethynyl-cycloheptyl ester (4.40m$_2$). Synthesized following the general procedure B. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.39m$_2$ (0.31g, 59%). IR (neat, cm^{-1}) 3284 (m), 2937 (m), 2870 (w), 1743 (s), 1490 (m), 1367 (m), 1235 (s), 1012 (m), 942 (m), 761 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.51 (s,

1H), 2.24-2.05 (m, 4H), 1.60-1.49 (m, 6H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 176.5(C_4), 84.8(CH), 77.9 (C_4), 73.2(C_4), 40.2(C_4), 34.7(CH_2), 27.8(CH_2), 26.8(CH_3), 24.6(CH_2), 21.7(CH_2); HRMS (EI) m/z calculated for $C_{14}H_{22}O_2$ $(M)^+$ 222.3233 found 222.1695.



4.40n

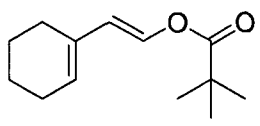
Acetic acid 1-ethynyl-cyclopentyl ester (4.40n). Synthesized following the general procedure A. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40n (01.45g, 80%) as a clear oil. Spectral data were in accord with those published.[129]



4.29a

Acetic acid 2-cyclohex-1-enyl-vinyl ester (4.29a). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) yielded 4.29a (20mg, 70%) as a clear yellow oil.

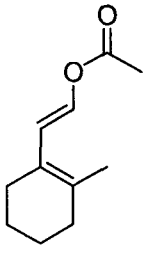
Acetic acid 2-cyclohex-1-enyl-vinyl ester (4.29a). Synthesized following the general procedure D. Purification by flash chromatography (5% EtOAc/Hexanes) yielded 4.29a (41 mg, 60%) as a clear yellow oil.IR (CH_2Cl_2): 2915 (s), 1726 (s), 1257 (s), 1141 (s), 963(s); ^1H NMR (400 MHz, CDCL3): δ 7.27 (d, *J*=13.56Hz, 1H), 6.02 (d, *J*=13.56Hz, 1H), 5.69 (s, 1H), 2.13 (s, 3H). 2.11 (m, 4H), 1.63 (m, 4H); ^{13}C NMR (400 MHz, CDCl3): δ 133.68 (CH), 132.16 (C_4), 129.13 (CH), 118.97 (CH), 25.74 (CH_2), 24.66(CH_2), 22.28 (CH_2), 20.98(CH_2); HRMS (EI) *m/z* M^+ ($C_{10}H_{14}O_2$),



4.29b

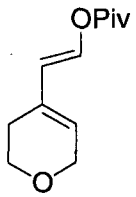
(1E)-2-cyclohexenylvinyl pivalate (4.29b). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.29b(61 mg, 79%) as a clear yellow oil.

(1E)-2-cyclohexenylvinyl pivalate (4.29b). Synthesized following the general procedure D. Purification by flash chromatography (5% EtOAc/Hexanes) yielded 4.29b (41 mg, 52%) as a clear yellow oil.IR (film): 3101, 2931, 2861, 1744, 1135; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.28 (d, J = 12.7 Hz, 1H), 6.05 (d, J = 12.8 Hz, 1H), 5.70 (m, 1H), 2.11-2.10 (m, 4H). 1.70-1.62 (m, 2H), δ1.62-1.57 (m, 2H), δ1.24 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ175.7, 134.0, 132.2, 128.7, 118.8, 38.7, 27.0, 25.8, 24.6, 22.4, 22.3; HRMS (EI) *m/z* M^+ ($C_{13}H_{20}O_2$): Calculated 208.1463, found: 208.1465.



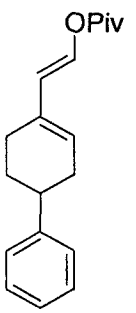
4.41a

Acetic acid 2-(2-methyl-cyclohex-1-enyl)-vinyl ester (4.41a). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) yielded 4.41a (7.2 mg, 36%) as a clear yellow oil. IR (neat, cm^{-1}) 2927 (m), 2859 (w), 1756 (s), 1622 (w), 1370 (m), 1218 (s), 1120 (m), 914 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J=12.6 Hz, 1H), 6.50 (d, J= 13.5 Hz, 1H), 2.14 (s, 3H), 2.12-2.02 (m, 4H), 1.73 (s, 3H), 1.67-1.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 168.4 (C_4), 134.3 (CH), 133.3 (C_4), 124.1 (C_4), 114.6 (CH), 32.8 (CH_2), 25.7 (CH_2), 22.9 (CH_2), 22.6 (CH_2), 20.9 (CH_3), 19.4 (CH_3); HRMS (EI) m/z calculated for $C_{11}H_{16}O_2$ $(M)^+$ 180.2435 found 180.1150.



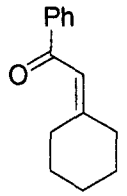
4.41c

(E)-2-(3.6-dihyro-2H-pyran-4-yl)vinyl pivalate (4.41c). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.41c (62.2 mg, 71%) as a clear yellow oil. IR (neat, cm^{-1}) 341 (br), 2971 (m), 2930 (m), 2869 (m), 1732 (s), 1143 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (d, *J*= 12Hz, 1H), 6.05 (d, *J*= 14.3 Hz, 1H), 5.65 (m, 1H), 4.2 (m, 2H), 3.82(t, *J*=5.1Hz, 2H), 2.23 (m, 2H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 175.5 (C_4), 135.2 (CH), 130.7 (C_4), 126.6 (CH), 117.0 (CH), 65.6 (CH_2), 63.9 (CH_2), 38.7(C_4), 26.9 (CH_3), 22.6 (CH_2); HRMS (EI) m/z calculated for $C_{12}H_{18}O_3$ $(M)^+$ 210.1256 found $[M^+ - C_2H_6]$ 167.0351.



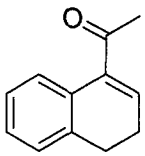
4.41h

2,2-Dimethyl-propionic acid 2-(4-phenyl-cyclohex-1-enyl)-vinyl ester (4.41h). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.41h (42.2 mg, 53%) as a clear yellow oil. IR (neat, cm^{-1}) 3097(w), 2964 (m), 2926 (m), 2880 (m), 1736 (s), 1478 (m), 11.34(s); ^1H NMR (400 MHz, $CDCl_3$): δ7.34-7.29 (m, 3H), 7.26-7.19 (m, 3H), 6.12 (d, J=12.4 Hz, 1H), 5.79 (d, *J*=2.4 Hz, 1H), 2.85-2.78 (m, 1H), 2.46-2.39 (m, 1H), 2.31-2.24 (m, 3H), 2.06-2.00 (m, 1H), 1.86-1.76 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ175.7, 146.6, 134.5, 132.1, 128.4, 128.0, 126.8, 126.0, 118.2, 40.0, 38.7, 34.0, 29.7, 29.4, 27.0, 25.2. HRMS (EI) m/z calculated for $C_{19}H_{24}O_2$ $(M)^+$ 284.1698 found $[M^+]$ 284.1774.



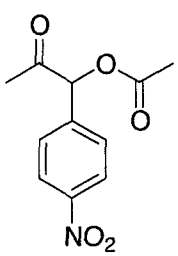
4.42

2-Cyclohexylidene-1-phenyl-ethanone (4.42). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.40o (427.8 mg, 51%) as a clear yellow oil. Spectral data in in accod with the literature.[130]



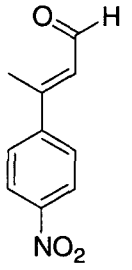
4.43

1-(3,4-Dihydro-naphthalen-1-yl)-ethanone (4.43). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.43 (19.3 mg, 73%) as a clear yellow oil. IR (neat, cm^{-1}) 3064 (w), 2938 (m), 2830 (m), 1673 (s), 1258 (2), 766(m); ^1H NMR (400 MHz, $CDCl_3$): δ7.68 (d, J= 8.2Hz, 1H), 7.26-7.14 (m, 3H), 7.01 (t, *J*=12.4 Hz, 1H), 2.75 (d, *J*= 7.4 Hz, 2H), 2.47 (s, 3H), 2.43 (t, *J*= 7.8 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ199.8(C_4), 139.2 (CH), 136.4(C_4), 130.9(C_4), 127.7(CH), 127.6(CH), 126.6(CH), 126.5(CH), 29.9(CH_2), 27.9(CH_2), 23.8(CH_3). HRMS (EI) m/z calculated for $C_{12}H_{12}O_1$ $(M)^+$ 172.2231 found [M] 172.0894.



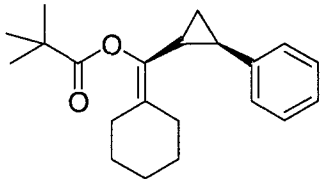
4.44

Acetic acid 1-(4-nitro-phenyl)-2-oxo-propyl ester (4.44). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.44 (53 mg, 41%) as a clear yellow oil. Spectral data is in accordance with the literature.[131]



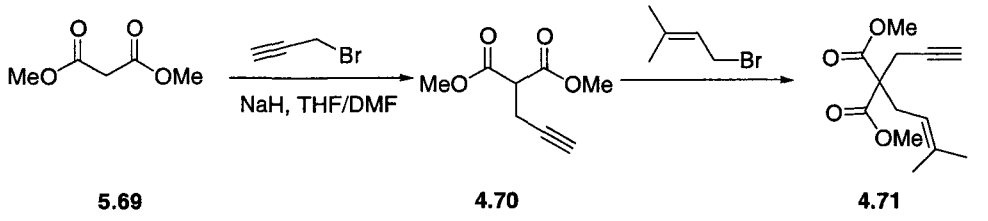
4.45

3-(4-Nitro-phenyl)-but-2-enal (4.45). Synthesized following the general procedure C. Purification by flash chromatography (5% EtOAc/Hexanes) afforded 4.45 (16 mg, 37%) as a clear yellow oil. Spectral data is in accordance with the literature.[132]



4.59

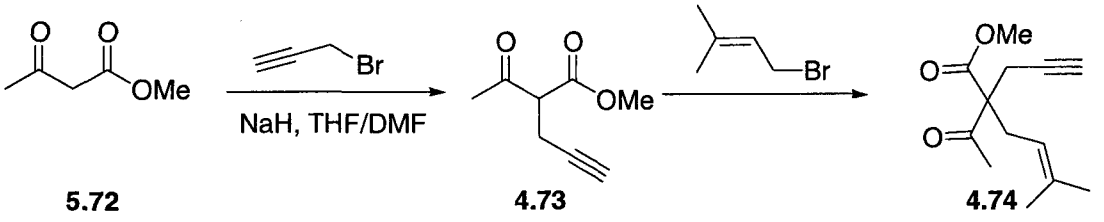
1-Cyclohexylidene-4,4-dimethyl-1-(2-phenyl-cyclopropyl)-pentan-3-one (4.59). The gold catalyst (3.5 mg, 0.007 mmol) and TfOH (1μl, 1M solution of NO_2Me_3) was weight in the glove box in a flamed dried round bottom flask with stir bar. After allowing the catalyst mixture to sit without stirring for 10 minutes, styrene (60 mg, 0.57 mmol) was added. To this mixture was added a solution of the propargylic ester (29.0 mg, 0.14 mmol)in NO_2Me_3 (0.5 ml). The resulting mixture was monitored by TLC until all starting material was consumed (approx. 1hr). The reaction mixture was concentrated and loaded directly onto a silica column. Purification by flash chromatography (10 % ethyl acetate in hexanes) afforded **4.59** as a clear oil (25 mg, 57% yield). IR (neat, cm^{-1}) 2966 (m), 2929 (m), 2854 (m), 1741 (s), 1497 (w), 1479(w), 1461 (w), 1448(w), 1284 (w), 1129 (s), 699 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.19 (m, 2H), 7.13-7.10 (m, 1H), 7.02-7.00 (m, 2H), 2.23 (dd, *J*= 9.93, 10.13 Hz, 2H), 2.12-1.88 (m, 3H), 1.74 (dddd, *J*= 6.45, 11.97 Hz, 1H), 1.62-1.27 (m, 6H), 1.24 (s, 9H), 1.26-1.02 (m, 2H), 0.89 (d, J= 14.2 Hz, 1H), 0.48-0.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 176.9 (C_4), 139.6 (C_4), 135.0 (C_4), 130.4 (C_4), 127.5 (CH), 127.3 (CH), 125.5 (CH), 39.0 (C_4), 28.7 (CH_2), 27.3 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 24.4 (CH), 21.7 (CH), 11.8 (CH_2); HRMS (EI) m/z calculated for $C_{21}H_{28}O_2$ $(M)^+$ 312.4458, found 312.2092.



5.69 4.70 4.71

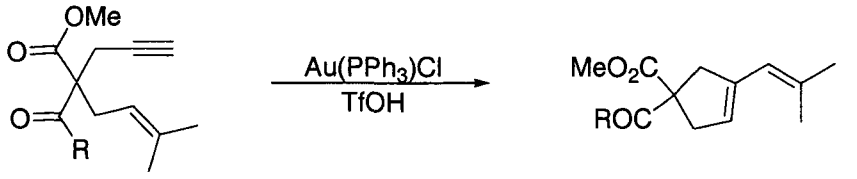
2-(3-Methyl-but-2-enyl)-2-prop-2-ynyl-malonic acid dimethyl ester (4.71)

Compound was synthesized by the method reported by Echavarren.[133]



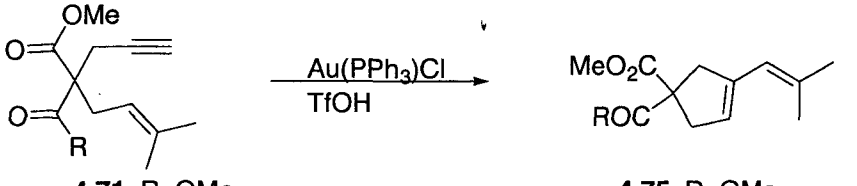
5.72 4.73 4.74

2-Acetyl-5-methyl-2-prop-2-ynyl-hex-4-enoic acid methyl ester (4.74). NaH (0.465g, 11.6 mmol) was added to a flame-dried flask containing 18.5 mL of THF. Once this solution had been cooled to 0°C, methyl acetoacetate (1.20 mL, 11.1 mmol) was added dropwise. The resulting mixture was then stirred at room temperature for an hour before distilled propargyl bromide (1.35 mL, 12.2 mmol) was added. At that point, the resulting solution was stirred at room temperature until completion by TLC. The reaction was quenched with NH_4Cl and the mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Cs_2CO_3 (5.43 g, 16.6 mmol) was added to a flame-dried flask in the glovebox. A solution of **4.65** (crude) in acetone (42.6 mL) was cannulated into the flask. After stirring the solution for 10 minutes, 3,3-dimethyl-allylbromide (2.56 mL, 22.2 mmol) was added dropwise. The resulting mixture is then stirred until completion by TLC. Once completed, the solution was filtered through celite, then concentrated *in vacuo*. Purification by flash chromatography (6:1 pet ether/ether) afforded **4.74** (539.3 mg, 28%) as a colorless oil. Caracterization is in accord with that published in Christiane Grisé-Bard thesis.[97]



4.74, R=Me **4.76**, R=Me

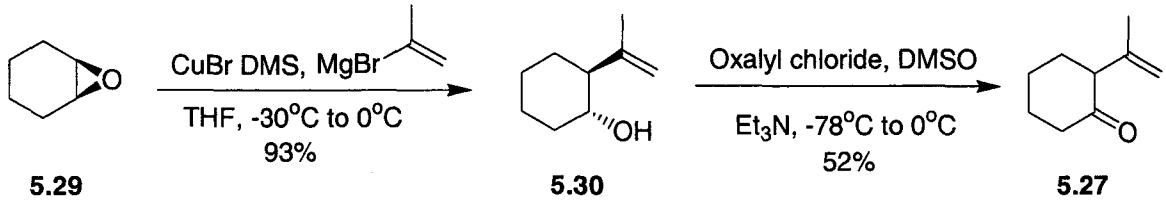
1-Acetyl-3-(2-methyl-propenyl)-cyclopent-3-enecarboxylic acid (4.76). $Au(PPh_3)Cl$ (1.0 mol%) was weighed in the glovebox and dissolved by a portion of the DCE. Then, a solution of TfOH (1.0 mol%) (0.01 M in ether) was added. Subsequently, the substrate in dichloroethane (0.1 M based on the alcohol) was cannulated. The resulting dark solution Stirred at room temperature till completion by TLC. The reaction mixture was cooled to room temperature and quenched with $NaHCO_3$. The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography 6:1 pet ether/ether) afforded **4.76** (25.4 mg, 60%) as a colorless liquid. Caracterization is in accord with that published in Christiane Grisé-Bard thesis.[97]



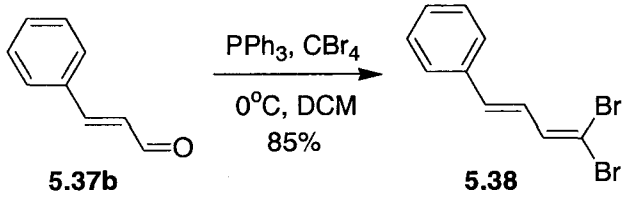
4.71, R=OMe **4.75**, R=OMe

3-(2-Methyl-propenyl)-cyclopent-3-ene-1,1-dicarboxylic acid dimethyl ester (4.75). $Au(PPh_3)Cl$ (2.5 mol%) was weighed in the glovebox and dissolved by a portion of the DCE. Then, a solution of TfOH (2.5 mol%) (0.01 M in ether) was added. Subsequently, the substrate in dichloroethane (0.1 M based on the alcohol) was cannulated. The resulting dark solution was stirred at room temperature until completion by TLC. The reaction mixture was cooled to room temperature and quenched with $NaHCO_3$. The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (20% ether/80% petroleum ether) afforded diene **4.75** (22.0 mg, 70%). Characterization was available through the literature.[126]

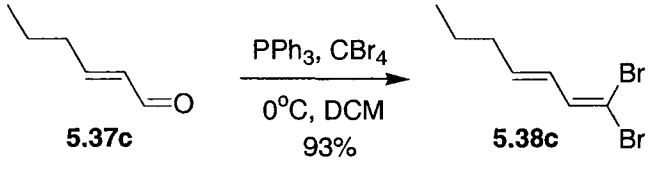
Procedures-Chapter 5



(±)-2-Isopropenyl-cyclohexanone (5.27) Compound was synthesized by the method reported by Roxanne Clément.[109]

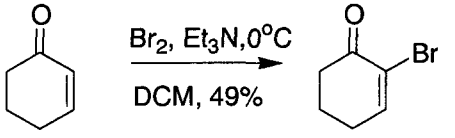


(4,4-Dibromo-buta-1,3-dienyl)-benzene (5.38). A dry 250 round bottom was charged with triphenylphosphine (40.37g, 153.9 mmol) in DCM (75 ml). The solution was cooled to 0°C and CBr_4 (22.68g, 68.4 mmol) was added slowly. After stirring for 30 minutes, a solution of cinnemaldehyde (4.3 ml, 34.2 mmol) in DCM (40 ml) was added. The solution was stirred overnight and diluted with diethyl ether (300 ml) and filtered through celite. The solid residue remaining was washed thoroughly with DCM (200 ml). The solution was concentrated to 100 ml and extracted in $NaHCO_3$, H_2O and brine. Organic phase was then dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (hexane) yielded **5.38** (8.3761g, 85%) as white crystals. Spectral data in agreement with literature.[134]



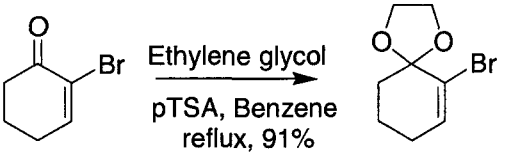
1,1-Dibromo-hepta-1,3-diene (5.28c). To a solution of PPh_3 (3.6g, 13.75mmol) in DCM (10ml) is slowly added CBr_4 (2.05g, 6.11 mmol) at 0°C and stirred for 30 minutes. A

solution of the aldehyde (0.35ml, 3.06mmol) in DCM (5 ml) is then slowly added by cannula. The reaction is then stired for 40 minutes while warming slowly. Monitoring is done by TLC (100% Hexanes as eluent). Water was then add dropwise at 0°C once the reaction was done until the reddish/brown color disappears. The reaction mixture was concentrated to ½ the volume and the suspended mixture was dissolved in hexanes and ether. Filtration (3X) by eluting through a silica pad and washing with ether gave the desired product as a crude yellow oil (720 mg, 93%).



5.34 **5.35**

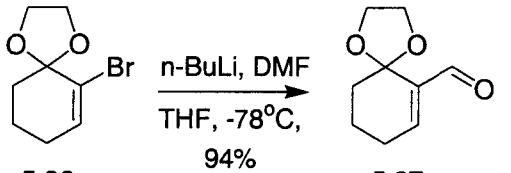
2-Bromo-cyclohex-2-enone (5.35). To a dry 2000 ml round bottom was added cyclohexenone (21.5 ml, 0.224 mol) in DCM (500 ml). A solution of bromine (12.0 ml, 0.234 mol) in DCM (250 ml) was slowly added via cannula to the round bottom flask cooled at 0°C. After 1.5 hours of stirring, Et_3N (4.6ml, 0.36mmol) was added dropwise and the mixture was stirred overnight at room temperature. The solution was washed with a 1M HCl solution (2x) followed by brine. Activated carbon was added to the organic phase. The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vaccuo.* Recristallisation in hot EtOAc and cold hexane yielded **5.35** (18.79 g, 49%) of white fluffy crystals. Spectral data in agreement with literature. [135]



5.35 **5.36**

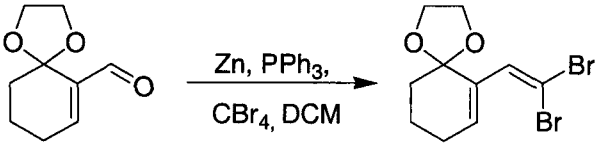
6-Bromo-1,4-dioxa-spiro[4.5]dec-6-ene (5.36). To a dry 2000 ml round bottom flask was added ethylene glycol (12.3 ml, 0.221 mol), pTSA (1.05g, 5.51 mmol), and **5.35** (19.31g, 0.110mol) in bulk grade benzene (1200 ml). The solution was refluxed under a Dean Stark setup overnight. Solution was concentrated to 500 ml, and the water phase extracted with

DCM (3x). Purification by flash chromatography (50% Et_2O in hexane) yielded **5.36** (22.09 g, 91%). Spectral data in agreement with literature.[136]



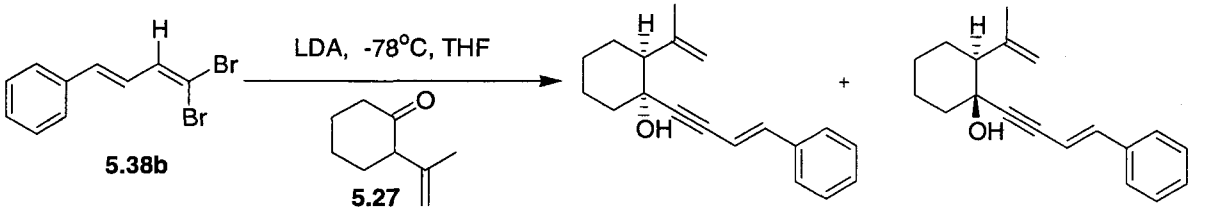
5.36 **5.37a**

1,4-Dioxa-spiro[4.5]dec-6-ene-6-carbaldehyde (5.37a). To a dry 50 ml round bottom was added **5.26** (0.9975g, 4.55mmol) in THF (20ml). Addition of *n*-BuLi (2.55 ml, 4.998 mmol) at -78°C (acetone/dry ice bath), and DMF (390 µl, 5.01 mmol) was added subsequently. The solution was stirred for 10 minutes and was rapidly brought to room temperature to quench with a minimum of NH_4Cl (sat.aq.). The mixture was concentrated and rapidly purified by flash chromatography to yield **5.37a** (564.0 mg, 100%) as a yellow oil. Spectral data in agreement with literature.[137]



5.37a **5.38a**

6-(2,2-Dibromo-vinyl)-1,4-dioxa-spiro[4.5]dec-6-ene (5.38a). Compound was synthesized by the method reported by Peter Ross Maclean.[115]

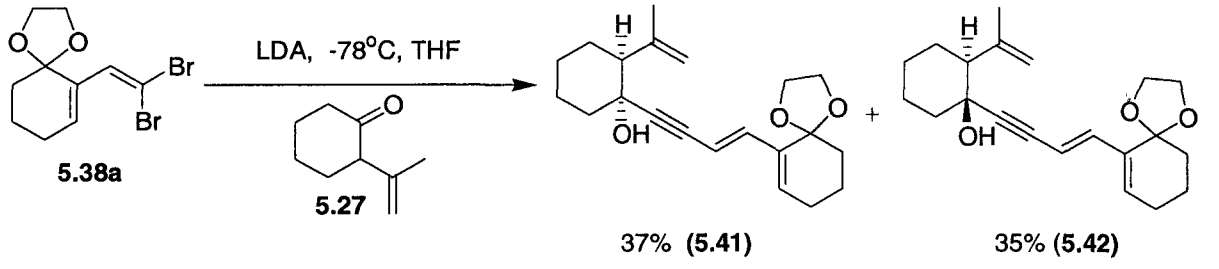


5.38b **5.27** 23% **(5.39)** 12 % **(5.40)**

(1R, 2R)-1-((E)-4-phenylbut-3-en-1-ynyl)-2-(prop-1-en-2-yl) cyclohexanol (5.39). A dry 50 ml round bottom was charged with **5.38b** (506.9 mg, 1.76 mmol) in THF (2ml) and stirred at -78°C. A solution of LDA was made by diluting distilled DIPA (260 µl) in THF

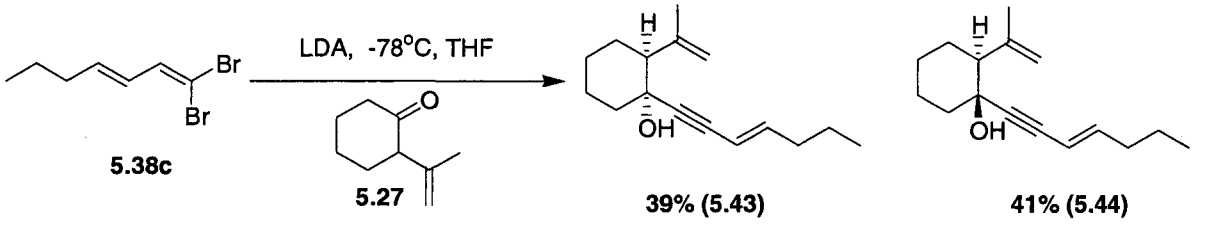
(0.5 ml) and titrating it with *n*-Buli (845 µl, 1.76 mmol). The LDA solution was added via cannula to the round bottom and stirred 45 minutes at -78°C. A solution of ketone **5.27** (110.8 mg, 0.80 mmol) in THF (2 ml) was cannulated into round bottom. Solution was stirred for an hour and bath was removed. Stirred for an hour and quenched with NH_4Cl (sat. aq). Extracted in water with DCM (3X) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (10% EtOAc in hexane) yielded **5.39** (475.3 mg, 12%) as a yellow oil. Spectral data in agreement with that reported by Peter Ross Maclean. [116]

(1S,2R)-1-((E)-4-phenylbut-3-en-1-ynyl)-2-(prop-1-en-2-yl)cyclohexanol (5.40). Compound **5.40** was synthesized as seen above for 5.29. Spectral data in agreement with that reported by Peter Ross Maclean. [116]



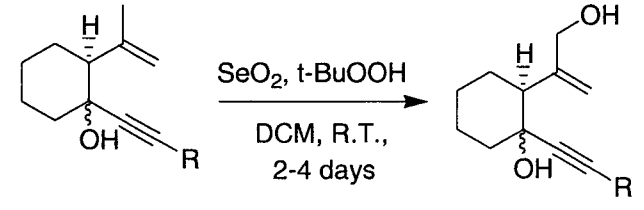
(1R,2R)-1-(1,4-dioxaspiro[4.5]dec-6-en-6-ylethynyl)-2-(prop-1-en-2-yl)cyclohexanol (5.41). A dry 50 ml round bottom flask was loaded with freshly synthesized dibromo **5.38a** (2.3512 g, 8.398 mmol) in THF (10ml). A solution of LDA was made by diluting distilled DIPA (2.6 ml) in THF (10 ml) and titrating it with *n*-Buli (8.19 ml, 16.8 mmol) at -78°C. The LDA solution was added via cannula to the round bottom flask and stirred 45 minutes at -78°C. A solution of ketone **5.27** (920 mg, 6.69 mmol) in THF (10 ml) was added via cannula ansd the solution was stirred for an hour. After that the bath was removed, stirred for an hour and quenched with NH_4Cl (sat. aq). The mixture was extracted in water with EtOAc (3x) and the combined organic layers were dried with $MgSO_4$, filtered and *concentrated in vaccuo*. Purification by flash chromatography (20% EtOAc in hexane) yielded **5.41** (713.8 mg, 35%) as a yellow oil. Spectral data in agreement with that of Peter Ross Maclean.[116]

(*1S,2R*)-1-(1,4-dioxaspiro[4.5]dec-6-en-6-ylethynyl)-2-(prop-1-en-2-yl)cyclohexanol (5.42). See above procedure. Compound **5.42** was also obtained as a yellow oil (745.2 mg, 37%). Spectral data in agreement with that of Peter Ross Maclean. [116]



(1R,2R)-1-Hept-3-en-1-ynyl-2-isopropenyl-cyclohexanol (5.43). Compound was synthesized by the method reported by Peter Ross Mclean. [116]

(1S,2R)-1-Hept-3-en-1-ynyl-2-isopropenyl-cyclohexanol (5.44). Compound was synthesized by the method reported by Peter Ross Mclean. [116]



R = Ph **5.39**
R = Spiroacetale **5.41**
R = Propyl **5.43**

R = Ph 29% **5.46**
R = Spiroacetale 31% **5.47**
R = Propyl 47% **5.48**

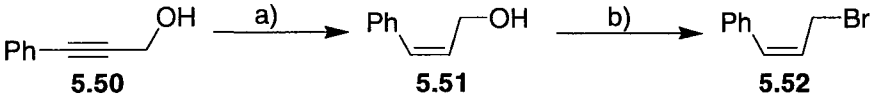
General procedure for the allylic oxidation: A dry round bottom flask was charged with the alcohol (1eq) in DCM (0.1M). Addition of t-BuOOH (2.0eq) and SeO_2 (0.5eq.) followed. The reaction was stirred at room temperature for 2-4 days while being monitored by TLC. Subsequently, it was quenched with $NaHCO_3$ (sat. aq), the organic phase was washed with $NaHCO_3$, H_2O (2x) and brine. The combined organic phases were dried with $MgSO_4$,

filtered and concentrated *in vaccuo*. Purification by flash chromatography (10% EtOAc in hexane) yielded the corresponding diol.

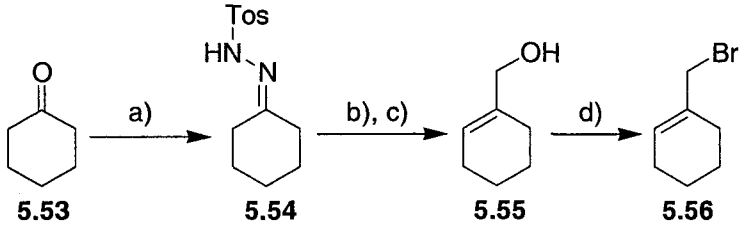
(1R,2R)-2-(3-hydroxyprop-1-en-2-yl)-1-((E)-4-phenylbut-3-en-1-ynyl)cyclohexanol (5.46). Spectral data in agreement with that reported in the thesis of Peter Ross Maclean.[116]

(1R,2R)-1-(1,4-dioxaspiro[4.5]dec-6-en-6-ylethynyl)-2-(3-hydroxyprop-1-en-2-yl)cyclohexanol (5.47). Spectral data in agreement with that reported in the undergraduate thesis of Olivier Gagné.[138]

1-Hept-3-en-1-ynyl-2-(1-hydroxymethyl-vinyl)-cyclohexanol (5.48). Spectral data in agreement with that reported in the PhD. thesis of Irina Dessinova. [139]

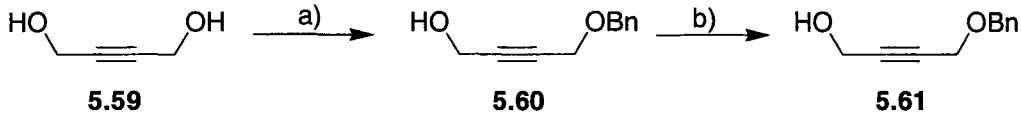


(3-Bromo-propenyl)-benzene (5.52). Compound was synthesized by the method reported by Irina Dessinova.[139]



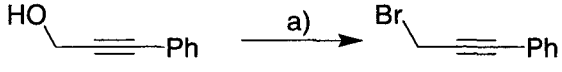
a) p-toluenesulfonhydrazide, ethanol, reflux 3h, 100%; b) 4 eq. t-BuLi, TMDA, 5 h, then DMF, 76% b) DIBAL-H, THF, -78 °C, 66%, c) CBr_4, Ph_3P, CH_2Cl_2, 10 min

1-Bromomethyl-cyclohexene (5.56). Compound was synthesized by the method reported by Irina Dessinova.[139]



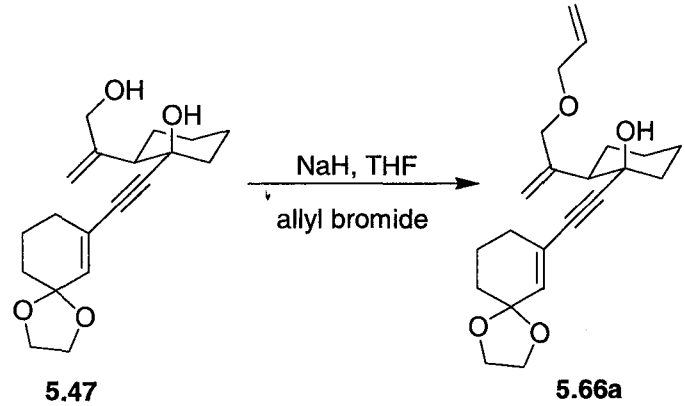
5.59 **5.60** **5.61**

4-Benzyloxy-but-2-yn-1-ol (5.61). Compound was synthesized by the method reported by Irina Dessinova.[139]



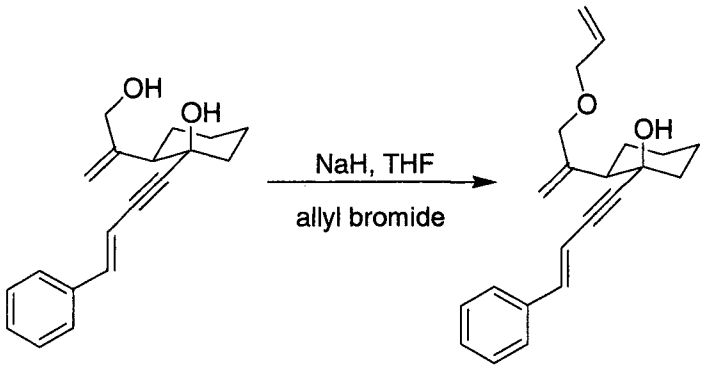
5.62 **5.63**

(3-Bromo-prop-1-ynyl)-benzene (5.63). Compound was synthesized by the method reported by Irina Dessinova.[139]



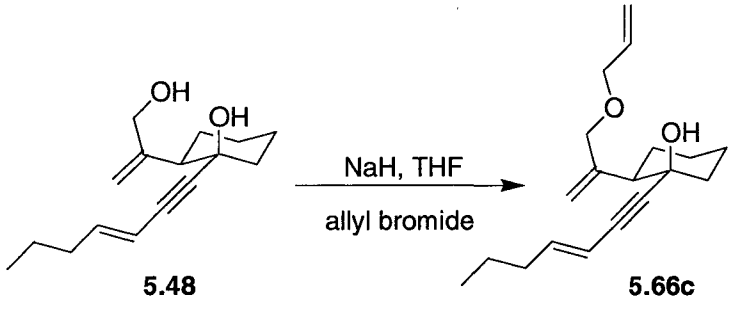
5.47 **5.66a**

2-[2-Allyloxy-2-(1,4-dioxa-spiro[4.5]dec-6-en-7-ylethynyl)-cyclohexyl]-prop-2-en-1-ol (5.66a) To a suspension of NaH (88.4 mg, 2.21 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.47** (275.9 mg, 0.8665 mmol) in 27 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of freshly distilled allyl bromide (120 µl, 1.39 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over MgSO4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66a** (199.6 mg, 64%) as a yellowish oil. Product was synthesized by Olivier gangé. [138]



5.46 **5.66b**

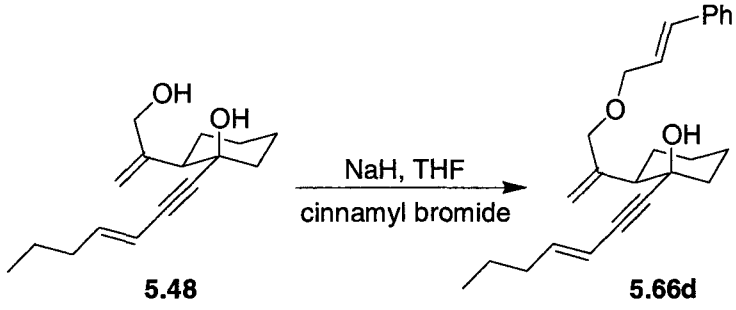
2-[2-Allyloxy-2-(4-phenyl-but-3-en-1-ynyl)-cyclohexyl]-prop-2-en-1-ol (5.66b). To a suspension of NaH (54.9 mg, 1.37 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.46** (171.6 mg, 0.608 mmol) in 17 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of freshly distilled allyl bromide (80 µl, 0.924 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66b** (93.7 mg, 55%) as a yellowish oil. Spectral data is in accordance with those published in the thesis of Peter Ross Maclean.[116]



5.48 **5.66c**

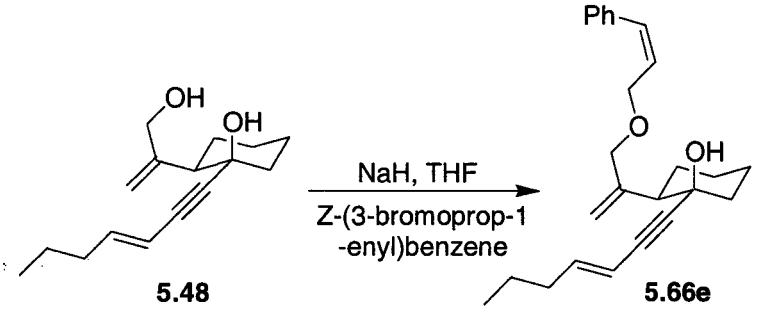
2-(2-Allyloxy-2-hept-3-en-1-ynyl-cyclohexyl)-prop-2-en-1-ol (5.66c). To a suspension of NaH (64.4 mg, 1.61 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (100 mg, 0.403 mmol) in 20 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of freshly distilled allyl bromide (69 µl, 0.924 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts

were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66c** (91.9 mg, 86%) as a yellowish oil. Caracterization in accord with that of Ross Maclean.[116]



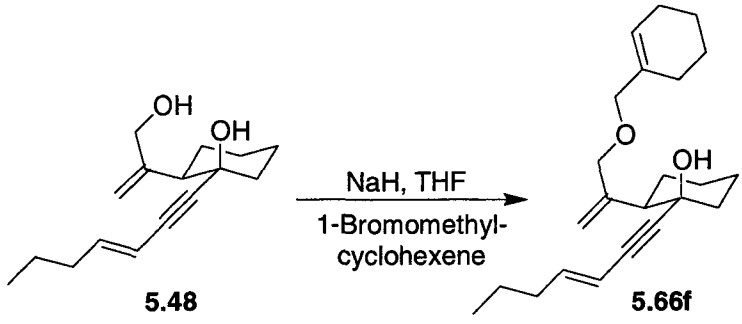
5.48 **5.66d**

2-[2-Hept-3-en-1-ynyl-2-(3-phenyl-allyloxy)-cyclohexyl]-prop-2-en-1-ol (5.66d). To a suspension of NaH (128.8 mg, 5.367 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (200 mg, 0.805 mmol) in 40 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of cinnamyl bromide (317.3 mg, 1.61 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66d** (222.3g, 75%) as a yellowish oil. IR (neat, cm^{-1}) 3390 (m), 2936 (s), 2854 (s), 1641 (w), 1494 (w), 1451(m), 1187 (w), 1068(m), 961 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.32 (m, 2H), 7.31-7.24 (m, 2H), 7.24-7.17 (m, 1H), 6.59 (d, J = 15.9 Hz, 1H), 6.27 (dt, J=6.0, 16.1 Hz, 1H), 60.4 (dt, *J*= 7.1, 15.9, 1H), 5.43 (dt, *J*= 1.6, 15.8 Hz, 1H), 5.18 (m 2H), 4.28 (ddd, *J*= 1.48, 5.8, 12.4, 1H), 4.20 (dd, *J*= 0.6, 12.09 Hz, 1H), 4.13 (s, 1H), 4.08 (ddd, *J*= 1.4, 6.4, 12.4, 1H), 3.93 (d, *J*= 12.2, 1H), 2.37 (dd, J= 9.5, 13.1Hz, 1H), 2.14-2.11 (m, 1H), 2.02 (qd, *J*= 1.5, 7.2 Hz, 2H), 1.88-1.59 (m, 4H), 1.51-1.40 (m, 2H), 1.35(q, *J*= 7.5, 2H), 1.31-1.23 (m, 1H), 0.86 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ145.8 (C_4), 144.2 (CH), 136.6 (C_4), 133.0 (CH), 128.5 (CH), 127.7 (CH), 126.6 (CH), 125.4 (CH), 118.7 (CH_2), 109.4 (CH), 92.63 (C_4), 82.4(C_4), 72.1(CH_2), 70.2(CH_2), 67.8(C_4), 52.6(CH), 39.7 (CH_2), 35.1(CH_2), 26.2(CH_2), 25.9(CH_2), 21.9(CH_2), 20.7(CH_2), 13.6(CH_3); HRMS (EI) m/z calculated for $C_{25}H_{32}O_2$ $(M)^+$ 364.5204, found 364.2383.



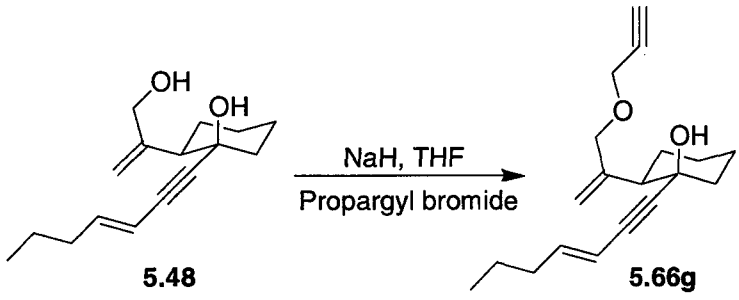
5.48 **5.66e**

2-[2-Hept-3-en-1-ynyl-2-(3-phenyl-allyloxy)-cyclohexyl]-prop-2-en-1-ol (5.66e). To a suspension of NaH (70.87 mg, 1.77 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (200 mg, 0.81 mmol) in 20 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of cinnamyl bromide (285.56 mg, 1.45 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66e** (174.4g, 59%) as a yellowish oil. IR (neat, cm^{-1}) 2943 (s), 2864 (m), 1640 (w), 1444 (w), 1179 (w), 1089(m), 957 (m), 917(m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.29 (m, 2H), 7.26-7.22 (m, 2H), 7.18-7.16 (m, 1H), 6.59 (d, *J* = 11.8 Hz, 1H), 6.00 (dt, *J*= 7.1, 16.0 Hz, 1H), 5.84 (dt, *J*= 5.7, 12.6, 1H), 5.37 (dt, *J*= 1.8, 16.2 Hz, 1H), 5.11 (m 2H), 4.36 (ddd, *J*= 2.0, 5.7, 12.6, 1H), 4.29 (ddd, *J*= 1.5, 7.1, 12.4 Hz, 1H), 4.18 (d, *J*=12.4Hz, 1H), 3.85 (d, *J*= 12.2, 1H), 2.36 (dd, *J*= 3.7, 13.1 Hz, 1H), 2.15-2.09 (m, 1H), 2.02 (qd, *J*= 5.8, 7.4 Hz, 2H), 1.83-1.47 (m, 5H), 1.40-1.22 (m, 2H), 1.36(q, *J*= 7.4, 2H), 0.85 (t, J= 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ145.6 (C_4), 144.1 (CH), 136.6 (C_4), 131.8 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.2 (CH), 118.7 (CH_2), 109.4 (CH), 92.5 (C_4), 82.4 (C_4), 72.2(CH_2), 67.8(C_4), 66.3(CH_2), 52.6(CH), 39.7 (CH_2), 35.1(CH_2), 26.1(CH_2), 25.9(CH_2), 21.9(CH_2), 20.7(CH_2), 13.6(CH_3); HRMS (EI) m/z calculated for $C_{25}H_{32}O_2$ $(M)^+$ 364.5204, found 364.2374.



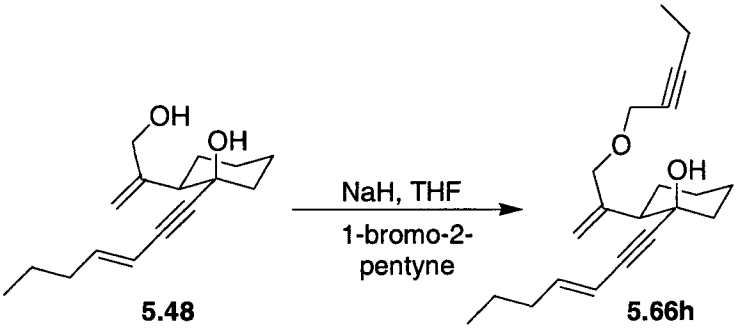
5.48 **5.66f**

2-[2-(Cyclohex-1-enylmethoxy)-2-hept-3-en-1-ynyl-cyclohexyl]-prop-2-en-1-ol (5.66f). To a suspension of NaH (70.87 mg, 1.77 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (200 mg, 0.81 mmol) in 20 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of 1-bromoethyl-cyclohexene (253.8 mg, 1.21 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66f** (159.7g, 58%) as a yellowish oil. IR (neat, cm^{-1}) 2930 (s), 2861 (m), 2363 (w), 1644 (m), 1444 (m), 1258 (w), 1080(m), 971 (m); ^1H NMR (C_6D_6, 400 MHz) δ 6.02 (dt, *J*= 7.2, 15.9 Hz, 1H), 5.73-5.61 (m, 1H), 5.43 (dt, *J*= 1.7, 16.0 Hz, 1H), 5.13 (m 2H), 4.11 (d, *J*=11.3Hz, 1H), 3.95 (d, *J*= 10.7, 1H), 2.79 (d, *J*= 12.5 Hz, 1H), 3.74 (d, *J*=11.9, 1H), 2.40-2.29 (m, 1H), 2.17-1.92 (m, 9H), 1.18-1.57 (m, 8H), 1.37 (q, *J*= 7.2, 2H), 1.32-1.19 (m, 1H), 0.87 (t, *J*= 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ145.4 (C_4), 143.4 (CH), 134.6 (C_4), 128.1 (CH), 125.3(CH), 118.4 (CH_2), 110.3 (CH), 92.5 (C_4), 82.4 (C_4), 74.5(CH_2), 71.5(CH_2), 68.0(C_4), 53.5(CH), 40.2 (CH_2), 35.0(CH_2), 26.4(CH_2), 26.2(CH_2), 26.1(CH_2), 25.09(CH_2), 22.7(CH_2), 22.5(CH_2), 22.0(CH_2), 20.9(CH_2), 13.4(CH_3); HRMS (EI) m/z calculated for $C_{23}H_{34}O_2$ $(M)^+$ 342.5149, found [M^+-methylcyclohexene] 247.1689.



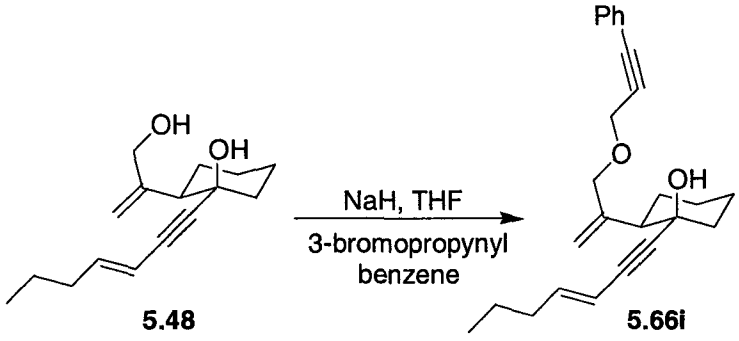
5.48 **5.66g**

2-(2-Hept-3-en-1-ynyl-2-prop-2-ynyloxy-cyclohexyl)-prop-2-en-1-ol (5.66g). To a suspension of NaH (23.3 mg, 0.583 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (69 mg, 0.28 mmol) in 10 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of propargyl bromide (46μg, 0.42 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66g** (54mg, 71%) as a yellowish oil. IR (neat, cm^{-1}) 3458 (br), 2929 (w), 1712 (s), 1644 (m), 1437 (m), 1398 (m), 1348(m), 1140 (w), 836 (w), 700.0(w); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.04 (dt, J= 7.4, 16.3 Hz, 1H), 5.43 (dt, *J*= 1.4, 15.6 Hz, 1H), 5.20 (d, *J*=18.2 Hz, 2H), 4.27-4.09 (m, 3H), 4.04 (d, *J*=12.2Hz, 1H), 3.51 (d, *J*= 2.0, 1H), 2.42 (t, *J*= 2.6 Hz, 1H), 2.35 (dd, *J*=3.4, 12.9, 1H), 2.17-2.07 (m, 1H), 2.02(dq, *J*= 1.8, 7.2 Hz, 2H), 1.89-1.60 (m, 3H), 1.51-1.41 (m, 2H), 1.37 (sext., *J*= 7.4, 2H), 1.28-1.19 (m, 2H), 0.87 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ145.3(C_4), 144.4 (CH), 118.8 (CH_2), 109.3 (CH), 92.4 (C_4), 82.6 (C_4), 79.3 (CH), 74.7 (CH), 71.7(CH_2), 67.7(C_4), 56.4(CH_2), 51.9(CH), 39.7(CH_2), 35.1(CH_2), 26.3(CH_2), 25.6(CH_2), 21.9(CH_2), 20.6(CH_2), 13.6(CH_3); HRMS (EI) m/z calculated for $C_{19}H_{26}O_2$ $(M)^+$ 286.4085, found 286.1855.



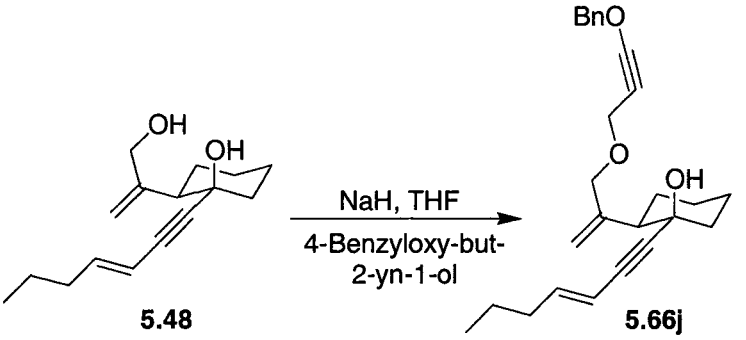
5.48 5.66h

2-(2-Hept-3-en-1-ynyl-2-pent-2-ynyloxy-cyclohexyl)-prop-2-en-1-ol (5.66h). To a suspension of NaH (13.33 mg, 0.333 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (39 mg, 0.14 mmol) in 5 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of 1-bromo-2-pentyne (22µl, 0.22 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66h** (32mg, 77%) as a yellowish oil. IR (neat, cm^{-1}) 3408 (br), 2943 (s), 2854 (s), 2235(w), 1712 (w), 1451 (m), 1068 (m), 971 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.08 (dt, J= 7.6, 16.1 Hz, 1H), 5.49 (dt, J= 1.2, 15.9 Hz, 1H), 5.20 (d, J=19.5 Hz, 2H), 4.29 (d, I=18.9, 1H), 4.15 (dt, J=2.1, 5.6Hz, 2H), 4.07 (d, *J*= 11.2Hz, 1H), 3.86 (d, *J*= 1.6 Hz, 1H), 2.44 (m, 2H), 1.98-1.57 (m, 8H), 1.35 (tt, *J*= 3.7, 16.3 Hz, 2H), 1.12 (sext., *J*= 7.2, 3H), 0.91 (t, J=5.7Hz, 3H), 0.71 (t, J= 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ145.9(C_4), 143.6 (CH), 118.3 (CH_2), 110.0 (CH), 93.5 (C_4), 82.4 (C_4), 75.3 (CH), 74.3 (CH), 71.2(CH_2), 67.8 (C_4), 56.7(CH_2), 52.7(CH), 40.0(CH_2), 34.9(CH_2), 26.5(CH_2), 26.0(CH_2), 21.8(CH_2), 20.7(CH_2), 13.5(CH_3), 13.2(CH_3), 12.2(CH_2); HRMS (EI) m/z calculated for $C_{21}H_{30}O_2$ $(M)^+$ 314.4617, found 314.2170.



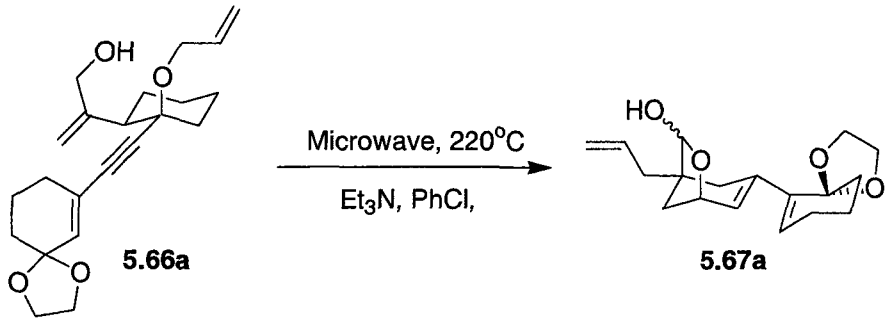
5.48 5.66i

2-[2-Hept-3-en-1-ynyl-2-(3-phenyl-prop-2-ynyloxy)-cyclohexyl]-prop-2-en-1-ol (5.66i). To a suspension of NaH (70.87 mg, 1.77 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (200 mg, 0.80 mmol) in 20 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of 3-bromopropynyl benzene (235.59mg, 1.21 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66i** (167mg, 57%) as a yellowish oil. IR (neat, cm^{-1}) 3413 (br), 2933 (s), 2861 (m), 1487(w), 1444 (m), 1080 (m), 968 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44-7.40 (m, 2H), 7.31-7.27 (m, 3H), 6.05 (dt, I= 7.3, 16.1 Hz, 1H), 5.43 (dt, *J*= 1.8, 15.6 Hz, 1H), 5.28 (s, 1H), 5.20(s, 1H), 4.40 (q, *J*=15.9 Hz, 2H), 4.29 (d, *J*=12.4, 1H), 4.13 (d, *J*= 13.1Hz, 1H), 3.61 (d, *J*=1.5Hz, 1H), 2.39 (dd, *J*= 3.4, 12.8Hz, 1H), 2.13-2.01 (m, 1H), 2.01 (dq, *J*= 5.4, 7.4 Hz, 2H), 1.87-1.59 (m, 4H), 1.49-1.41 (m, 1H), 1.35 (sext., *J*= 7.6, 2H), 1.23-1.18 (m, 2H), 0.86 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ145.1(C_4), 144.4 (CH),131.8(CH), 128.5(CH), 128.3(CH), 127.5(C_4), 118.7(CH_2), 109.3(CH), 93.7 (C_4), 84.7 (C_4), 77.2 (CH), 71.8(CH_2), 67.8 (C_4), 57.2(CH_2), 51.9(CH), 39.7(CH_2), 35.1(CH_2), 26.3(CH_2), 25.8(CH_2), 21.9(CH_2), 20.7(CH_2), 13.7(CH_3), 13.2(CH_3), 12.2(CH_2); HRMS (EI) m/z calculated for $C_{25}H_{30}O_2$ $(M)^+$ 362.5045, found 362.2245.

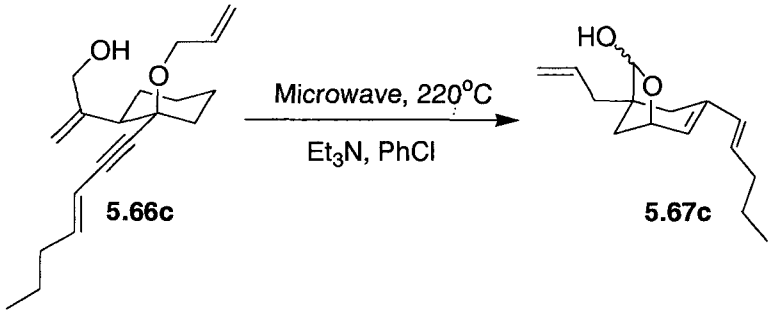


5.48 **5.66j**

2-[2-(3-Benzyloxy-prop-2-ynyloxy)-2-hept-3-en-1-ynyl-cyclohexyl]-prop-2-en-1-ol (5.66j). To a suspension of NaH (56.4 mg, 1.41 mmol, 60% in oil) in THF was transferred by cannula a solution of diol **5.48** (159.3 mg, 0.64 mmol) in 20 ml of THF at 0°C. The resulting mixture was stirred for 5 minutes followed by addition of 3-bromopropynyl benzene (230.1 mg, 0.96 mmol). The reaction was stirred overnight and quenched with a saturated acqeous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **5.66j** (179 mg, 79%) as a yellowish oil. IR (neat, cm^{-1}) 3423 (br), 2940 (s), 2864 (m), 1641(w), 1462 (m), 1348 (m), 1061 (m), 968 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.737.24 (m, 4H), 6.03 (dt, *J*= 7.6, 16.7 Hz, 1H), 5.43 (dt, *J*= 1.9, 16.1 Hz, 1H), 5.20 (d, *J*=17.7 Hz, 2H), 4.58 (s, 2H), 4.30-4.17 (m, 5H), 4.04 (d, *J*=12.7Hz, 1H), 3.61 (s, 1H), 2.36 (d, *J*=4.1, 12.4 Hz, 1H), 2.10 (d, *J*= 12.9 Hz, 1H), 2.02 (dq, *J*= 1.7, 6.7 Hz, 2H), 1.85-1.38 (m, 6H), 1.35 (sext., *J*= 12.0 Hz, 2H), 1.28-1.20 (m, 1H), 0.86 (t, *J*= 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ145.3(C_4), 144.4 (CH), 137.4(C_4), 128.4(CH), 128.1(CH), 127.9(CH), 118.9(CH_2), 109.3(CH), 92.4 (C_4), 82.7(C_4), 82.4(C_4), 82.1(C_4), 71.7(CH_2), 71.6(CH_2), 67.8 (C_4), 57.4(CH_2), 56.7(CH_2), 51.9(CH), 39.7(CH_2), 35.1(CH_2), 26.3(CH_2), 25.7(CH_2), 21.9(CH_2), 20.6(CH_2), 13.6(CH_3); HRMS (EI) m/z calculated for $C_{27}H_{34}O_3$ $(M)^+$ 406.5571, found $[M^+$-Bn] 315.1956.

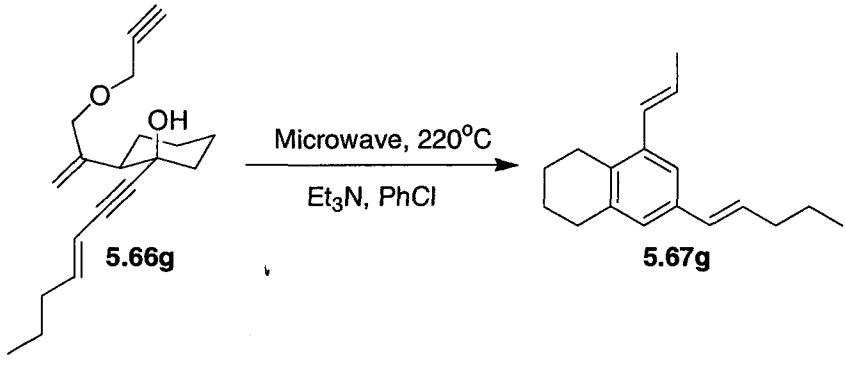


1-Allyl-3-(1,4-dioxa-spiro[4.5]dec-6-en-6-yl)-6-oxa-bicyclo[3.2.1]oct-3-en-7-ol (5.67a). To a flamed dried and base bathed vial was measured **5.66a** (28.4 mg, 79.3 mmol) and dissolved in distilled chlorobenzene (3 ml). The solution was added by cannula to a flamed dried base bathed microwave tube, and the solvent was degassed for 20 minutes with Argon. Triethylamine (55 µl, 395 mmol) was added. Microwave tube was then capped under Argon and heated in a microwave oven for 7 hours at 220°C. The solution was concentrated and purified by flash chromatography to obtain **5.67a** (17.6 mg, 62%) as a sandy yellow oil. Caracterization done by Olivier Gagné. [138]



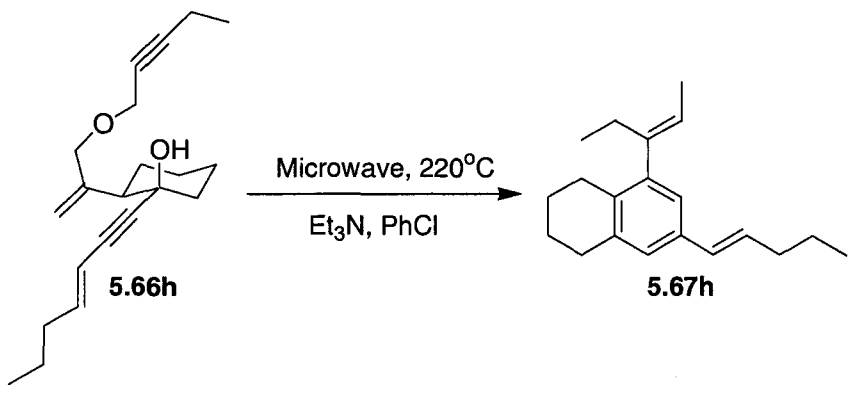
1-Allyl-3-pent-1-enyl-6-oxa-bicyclo[3.2.1]oct-3-en-7-ol (5.67c). To a flamed dried and base bathed vial was measured **5.66c** (70 mg, 0.2427 mmol) and dissolved in distilled chlorobenzene (3 ml). The solution was added by cannula to a flamed dried base bathed microwave tube, and the solvent was degassed for 20 minutes with Argon. Triethylamine (156 µl, 1.21 mmol) was added. Microwave tube was then capped under Argon and heated in a microwave oven for 4 hours at 220°C. The solution was concentrated and purified by flash chromatography to obtain **5.67c** (51 mg, 73%) as a yellow oil (as a mixture of the

opened and closed acetal). IR (neat, cm^{-1}) 3405 (br), 2930 (s), 2864 (m), 1648(m), 1441 (m), 1147 (m), 1108 (m), 968 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.10 (dd, J= 7.2, 16.3Hz, 1H), 5.92-5.70 (m, 2H), 5.67 (d, J= 10.9 Hz, 1H), 5.26 (d, J= 6.3 Hz, 1H), 5.21-5.08 (m, 2H), 2.73 (d, J= 17.2Hz, 1H), 2.51-2.02 (m, 5H), 1.90-1.62 (m, 4H), 1.56-0.97 (m, 6H), 0.91 (q, J= 8.95 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 170.6(C_4), 136.0(CH), 135.3(CH), 134.9(C_4), 134.6(CH), 131.8(CH), 130.0(CH), 117.1(CH_2), 104.9(CH), 103.7(CH), 78.5 (C_4), 49.4(CH), 46.8(CH), 38.1(CH_2), 37.7(CH_2), 35.7(CH_2), 35.1(CH_2), 33.1(CH_2), 32.8(CH_2), 25.2(CH_2), 24.9(CH_2), ,23.4(CH_2), 23.3(CH_2), 22.7(CH_2), 21.3(CH_2), 21.2(CH_2), 13.7(CH_3); HRMS (EI) m/z calculated for $C_{26}H_{19}$ $(M)^+$ 286.4085, found 286.1956



7-Pent-1-enyl-5-propenyl-1,2,3,4-tetrahydro-naphthalene (5.67g). To a flamed dried and base bathed vial was measured **5.66g** (30.0 mg, 0.105 mmol) and dissolved in distilled chlorobenzene (3 ml). The solution was added by cannula to a flamed dried base bathed microwave tube, and the solvent was degassed for 20 minutes with Argon. Triethylamine (73 µl, 0.524 mmol) was added. Microwave tube was then capped under Argon and heated in a microwave oven for 4 hours at 220°C. The solution was concentrated and purified by flash chromatography to obtain **5.67g** (7.7 mg, 32%) as a yellow oil. IR (neat, cm^{-1}) 3441 (br), 3013 (m), 2926 (s), 2859 (m), 1646(m), 1458 (m), 957 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98 (s, 2H), 6.95 (s, 1H), 6.37 (d, *J*= 11.6 Hz, 1H), 6.30 (d, *J*= 15.9 Hz, 1H), 6.13 (dt, J= 6.7, 16.1 Hz, 1H) 5.82-5.74 (m, 1H), 2.74 (t, *J*= 6.2Hz, 2H), 2.57 (t, *J*= 5.4 Hz, 2H), 2.15 (q, *J*=6.8Hz, 1H), 1.80-1.70 (m, 5H), 1.46 (sex., *J*= 7.4 Hz, 2H), 1.24(s, 2H), 0.92 (t, J= 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 198.7 (CH), 150.7(C_4), 128.8(CH), 128.7(CH),

127.9(CH), 102.7(CH_2), 45.4 (C_4), 45.3(C_4), 44.0(CH), 35.0(CH_2), 33.1(CH), 30.2(CH_2), 28.2(CH), 25.6(CH_2), 23.4(CH_2), 22.6(CH_2), 21.8(CH_2), 13.8(CH_3); HRMS (EI) m/z calculated for $C_{18}H_{24}$ $(M)^+$ 240.3822, found $[M^+]$ 240.1863.



5-(1-Ethyl-propenyl)-7-pent-1-enyl-1,2,3,4-tetrahydro-naphthalene (5.67h). To a flamed dried and base bathed vial was measured **5.66h** (30.0 mg, 0.096 mmol) and dissolved in distilled chlorobenzene (3 ml). The solution was added by cannula to a flamed dried base bathed microwave tube, and the solvent was degassed for 20 minutes with Argon. Triethylamine (67 µl, 0.478 mmol) was added. Microwave tube was then capped under Argon and heated in a microwave oven for 4 hours at 220°C. The solution was concentrated and purified by flash chromatography to obtain **5.67h** (19.2 mg, 64%) as a yellow oil. IR (neat, cm^{-1}) 2962 (s), 2929 (s), 2857 (m), 1578(w), 1458 (m), 964 (m);

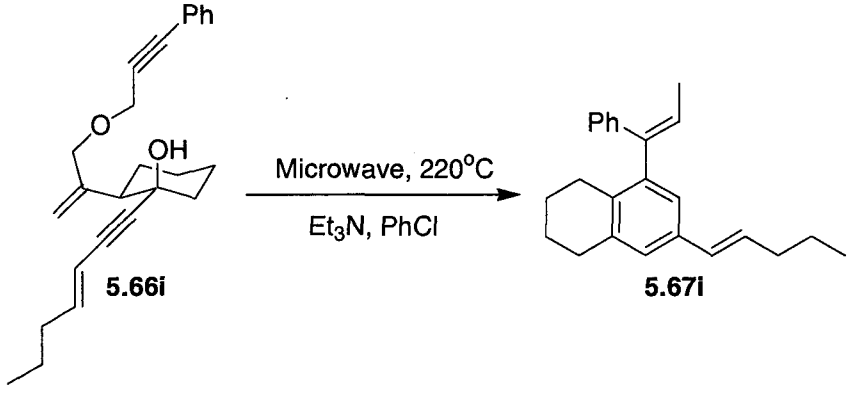
^1H NMR (400 MHz, $CDCl_3$)

H	Chemical shift (δ)	COSY	HMQC	NOESY
A	6.96 (s, 1H)	B, F,G(w)	126.4	C, D, F, (w)
B	6.77 (s, 1H),	A, F	124.9	C, D
C	6.30 (d, *J*= 16.6 Hz, 1H),	D, H	129.9	H
D	6.14 (dt, *J*= 6.8, 15.9 Hz, 1H)	C, H	129.7	H
E	5.47 (q, *J*= 6.8Hz, 1H)	J	119.5	G, H, I
F	2.76 (t, *J*= 5.9Hz, 2H)	G, I	31.9	A, I
G	2.49 (t, *J*= 6.3 Hz, 2H)	F, I	30.0	I, J, K(w), N
H	2.24-2.11 (m, 4H)	J. L	35.2	J, L, E, C, A

I	1.80-1.67 (m, 5H)	G, F	26.4, 23.4, 23.2	F, G
J	1.40 (sext., *J*= 12.2 Hz, 2H),	N, H	22.7	H, D, N
K	1.35 (d, *J*=3.8 Hz, 3H)	N	14.5	F
L	0.98 (t, *J*= 7.4 Hz, 3H)	H	13.8	H
M	0.92 (t, *J*= 7.7Hz, 3H)	K	12.6	B(w), E, G, H
N	0.85 (q, *J*= 7.3 Hz, 2H)	H, J	22.6	J

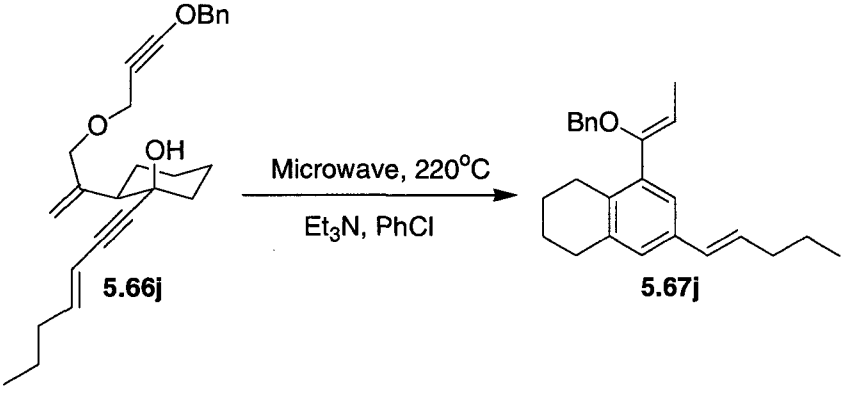
(w)=weak interaction

NOE (1D, $CDCl_3$, 400 MHz) Irradiation of proton at 5.47 ppm shows 3.5% and 2.9 % of protons at 1.35 and 0.98 ppm respectively. ^{13}C NMR ($CDCl_3$, 400 MHz) δ 142.9(C_4), 141.4(C_4), 137.1(C_4), 134.6(C_4), 133.6(C_4), 129.92(CH), 129.7(CH), 124.8(CH), 123.7 (CH), 119.5(CH), 35.2(CH_2), 31.5(CH_2), 30.0(CH_2), 29.7(CH_2), 26.4(CH_2), 23.4(CH_2), 23.2(CH_2), 22.7(CH_2), 14.5(CH_3), 13.8(CH_3), 12.6(CH_3); HRMS (EI) m/z calculated for $C_{20}H_{28}$ $(M)^+$ 268.2191, found 268.2172.



7-Pent-1-enyl-5-(1-phenyl-propenyl)-1,2,3,4-tetrahydro-naphthalene (5.67i). To a flamed dried and base bathed vial was measured **5.66i** (30.0 mg, 0.083 mmol) and dissolved in distilled chlorobenzene (3 ml). The solution was added by cannula to a flamed dried base bathed microwave tube, and the solvent was degassed for 20 minutes with Argon. Triethylamine (58 µl, 0.414 mmol) was added. Microwave tube was then capped under Argon and heated in a microwave oven for 4 hours at 220°C. The solution was concentrated

and purified by flash chromatography to obtain **5.67i** (12.1 mg, 40%) as a yellow oil. IR (neat, cm^{-1}) 3031 (m), 2926 (s), 2856 (m), 1657(w), 1457 (m), 964 (m), 908(m), 733(m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.14 (m, 5H), 7.04 (s, 1H), 6.89 (s, 1H), 6.31 (d, *J*= 15.9 Hz, 1H), 6.26 (q, *J*= 6.9 Hz, 1H), 6.16 (dt, *J*= 7.2, 15.7 Hz, 1H), 2.78 (t, *J*= 6.3Hz, 2H), 2.45 (dt, *J*= 6.6, 17.5 Hz, 1H), 2.24 (dt, *J*= 6.7, 12.3 Hz, 1H), 2.14 (q, *J*= 7.5 Hz, 2H), 1.72-1.61 (m, 2H), 1.58 (d, *J*= 6.9Hz, 3H), 1.44 (sext., *J*= 7.2 Hz, 2H), 0.92 (t, *J*= 7.2 Hz, 3H), 0.88-0.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 141.4(C_4), 141.3(C_4), 139.3(C_4), 137.5(C_4), 134.9(C_4), 134.5(C_4), 129.8(CH), 129.8(CH), 128.2(CH), 126.6 (CH), 125.8(CH), 125.5(CH), 125.1(CH), 123.6(CH), 35.2(CH_2), 30.6(CH_2), 29.7(CH_2), 26.6(CH_2), 23.3(CH_2), 23.1(CH_2), 22.6(CH_2), 15.5(CH_3), 13.8(CH_3); HRMS (EI) m/z calculated for $C_{24}H_{28}$ $(M)^+$ 316.4791, found 316.2186.



5-(1-Benzyloxy-propenyl)-7-pent-1-enyl-1,2,3,4-tetrahydro-naphthalene (5.67j). To a flamed dried and base bathed vial was measured **5.66j** (30.0 mg, 0.074 mmol) and dissolved in distilled chlorobenzene (3 ml). The solution was added by cannula to a flamed dried base bathed microwave tube, and the solvent was degassed for 20 minutes with Argon. Triethylamine (52 µl, 0.478 mmol) was added. Microwave tube was then capped under Argon and heated in a microwave oven for 4 hours at 220°C. The solution was concentrated and purified by flash chromatography to obtain **5.67j** (12.5 mg, 42%) as a yellow oil. IR (neat, cm^{-1}) 3089 (m), 2937(m), 2855 (m), 1697(w), 1457 (m), 1102(w), 918 (s), 742(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.25 (m, 5H), 6.97 (s, 1H), 6.85 (s, 1H), 6.38 (d, *J*= 15.6 Hz, 1H), 6.12 (dt, J= 6.9, 15.9 Hz, 1H), 5.85 (q, *J*= 7.0 Hz, 1H), 4.54 (q, *J*= 11.4Hz, 2H),

4.05 (q, *J*= 12.7 Hz, 2H), 2.76 (t, *J*= 5.3 Hz, 2H), 2.51 (t, J= 5.7Hz, 2H), 2.14 (q, *J*= 7.6 Hz, 2H), 1.73-1.62 (m, 4H), 1.48-1.41 (m, 3H), 0.94 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 138.6(C_4), 138.5(C_4), 137.9(C_4), 137.2(C_4), 134.8(C_4), 134.0(C_4), 129.8(CH), 129.8(CH), 128.3(CH), 127.5(CH), 127.4(CH), 125.6(CH), 124.1(CH), 123.4(CH), 74.5(CH_2), 72.3(CH_2), 35.2(CH_2), 30.0(CH_2), 26.5(CH_2), 23.4(CH_2), 23.1(CH_2), 22.8(CH_2), 22.6(CH_2), 14.3(CH_3), 13.8(CH_3); HRMS (EI) m/z calculated for $C_{25}H_{30}O$ $(M)^+$ 346.2297, found $[M^+$-OBn] 252.1885.

Glossary of Abbreviations

Ac	acetate
ACN	acetonitrile
AIBN	azobisisobutyronitrile
BRSM	based on recovered starting material
Bn	benzyl
Bu	butyl
BuLi	*n*-butyllithium
CAN	Ceric(IV) ammonium nitrate
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIC	N,N'-Diisopropylcarbodiimide
DIBAL-H	diisobutylaluminumhydride
DIPEA	*N,N,N*-diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ent	enantiomer

equiv	equivalents
Et	ethyl
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
HDDA	hydroxy-directed Diels-Alder
HMDS	hexamethyldisilazane or bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation
HRMS	high resolution mass spectrum
imid.	imidazole
LDA	lithiumdiisopropylamide
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
mp	melting point
ms	molecular sieves
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
O^{t}Bu	*tert*-butoxide
OTf	trifluoromethylsulfonate
OTs	toluenesulfonate
PCC	pyridiniumchlorochromate
Pd/C	palladium on carbon
PDC	pyridinium dichromate
PET	photosensitized electron transfer
Ph	phenyl
PIDA	phenyl iodide diacetate
Piv	pivaloyl $(CH_3)_3C$-CO
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate

PTSA	*para*-toluenesulfonic acid
py	pyridine
quant.	quantitative yield (i.e. >98%)
R.T.	room temperature
SM	starting material
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethyl silyl
TEBA	benzyl triethyl ammonium chloride
t-BuLi	*tert*-butyllithium
Tf	Trifluoromethanesulfonic
TFA	trifluoroacetic acid
TLC	Thin-layer chromatography
TMEDA	Tetramethylethylenediamine
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPP	Triphenylpyrilium
UVA	ultraviolet A
UVB	ultraviolet B
UVC	ultraviolet C

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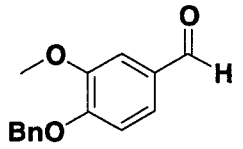
Supporting Information

Supporting Information



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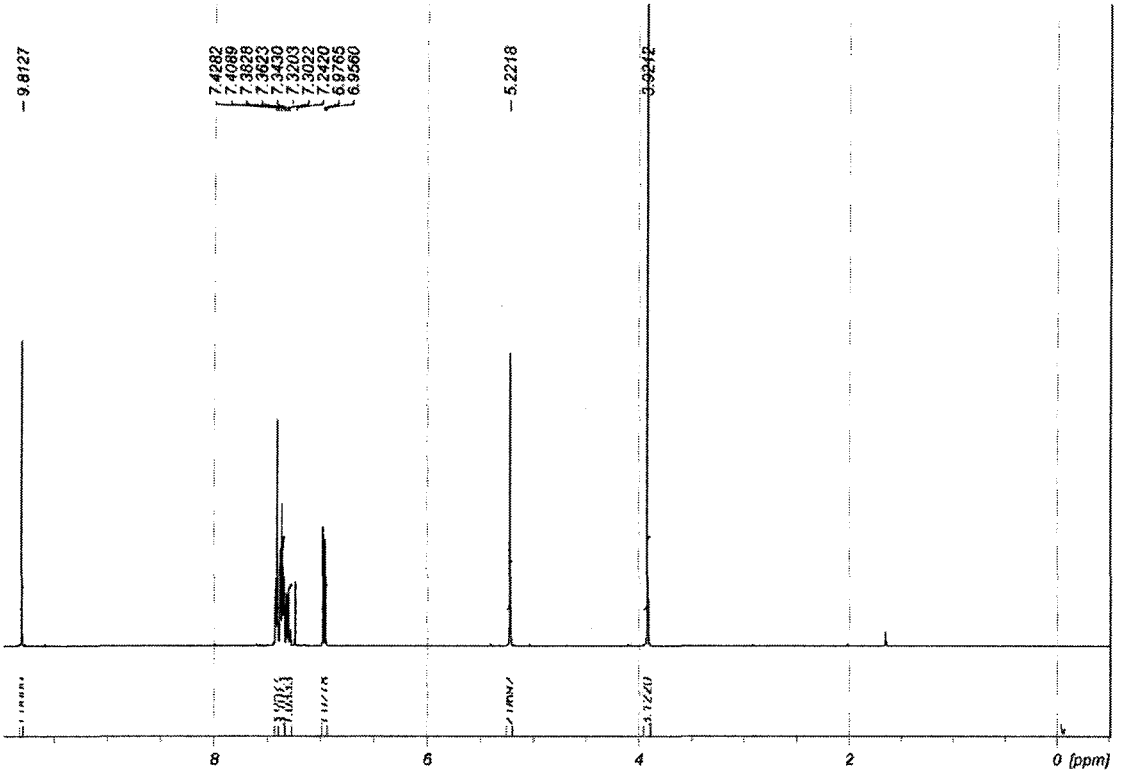

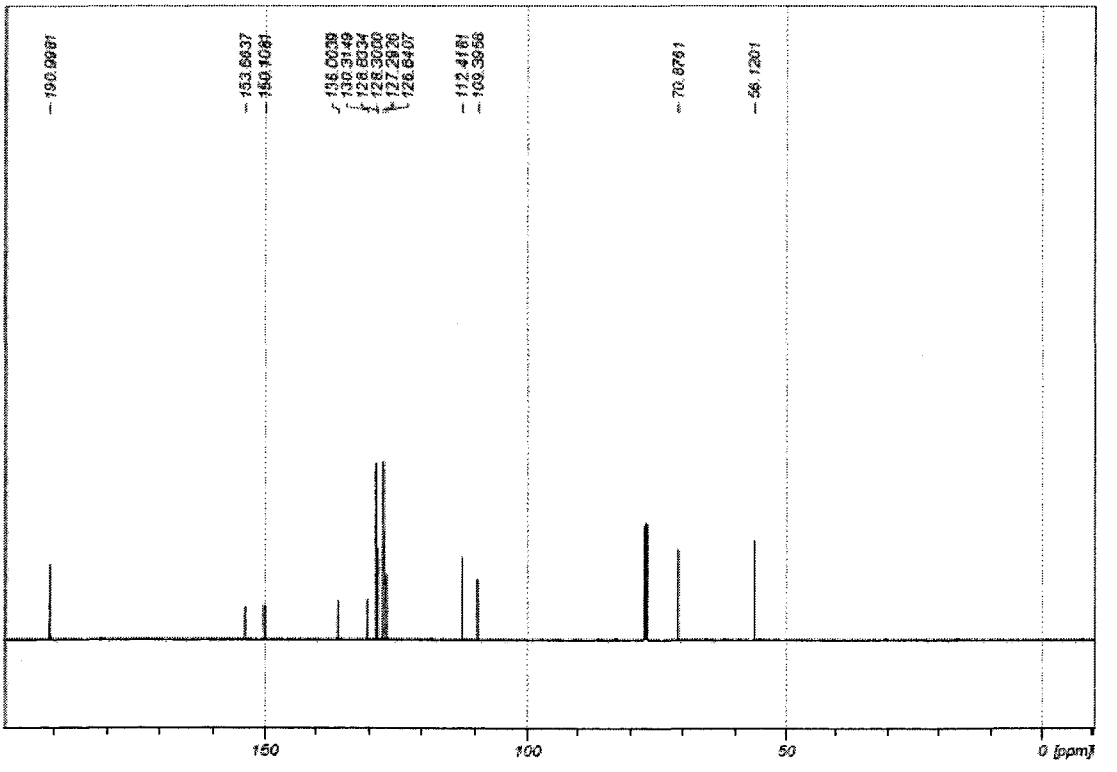

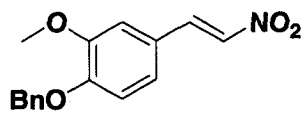
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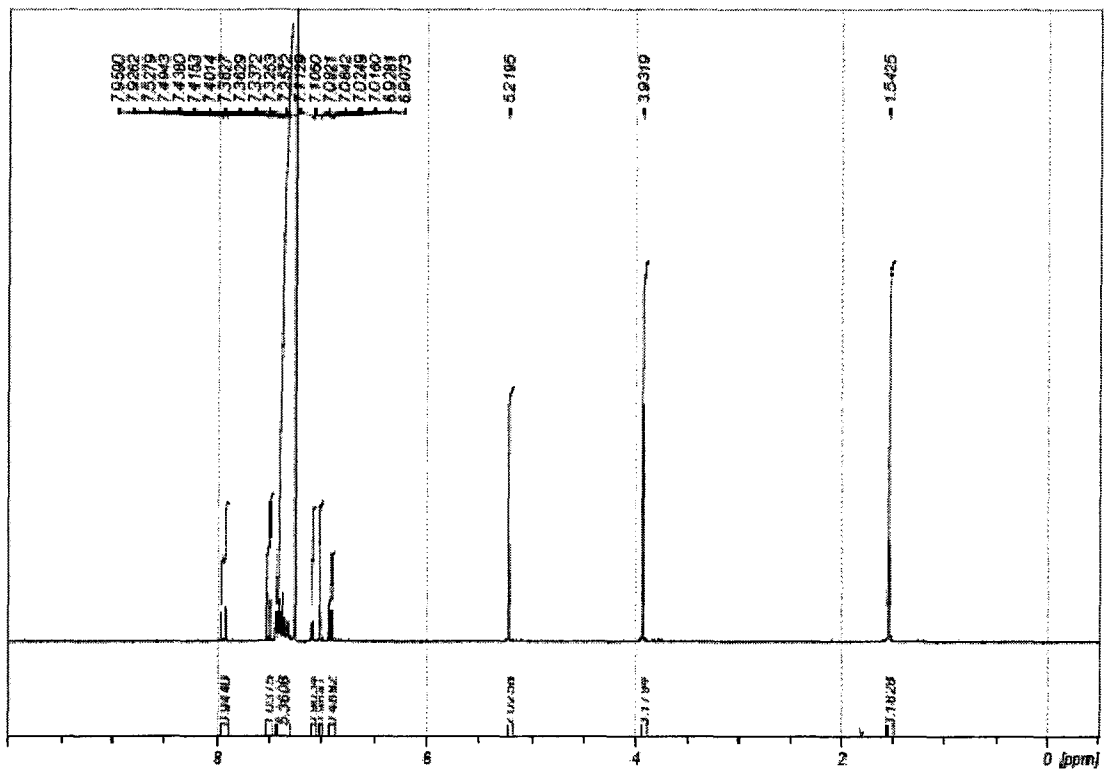
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4
2
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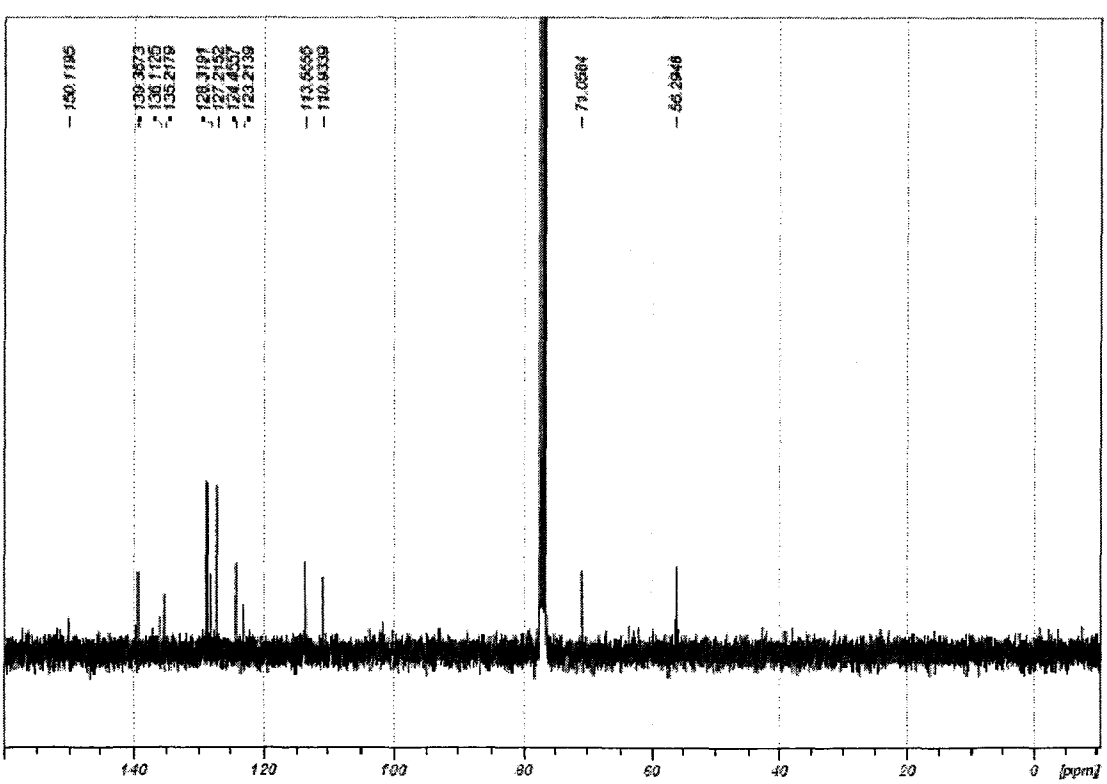
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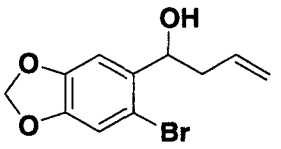
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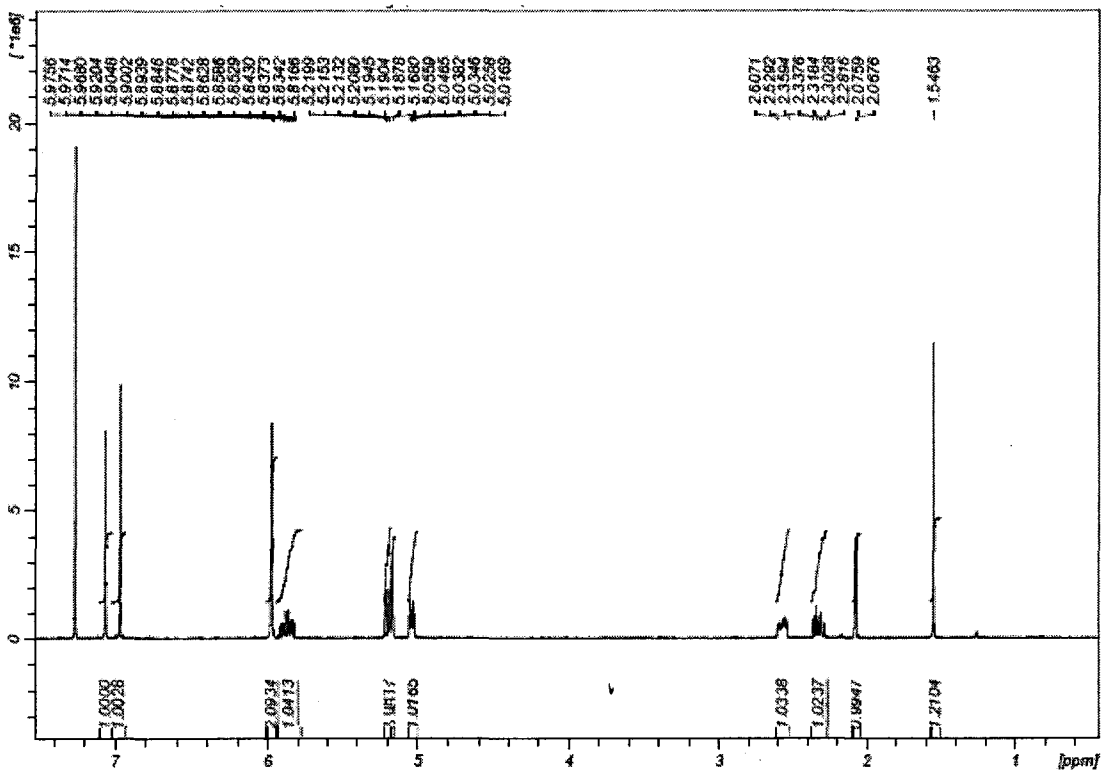
2.17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5.1680
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5.0382
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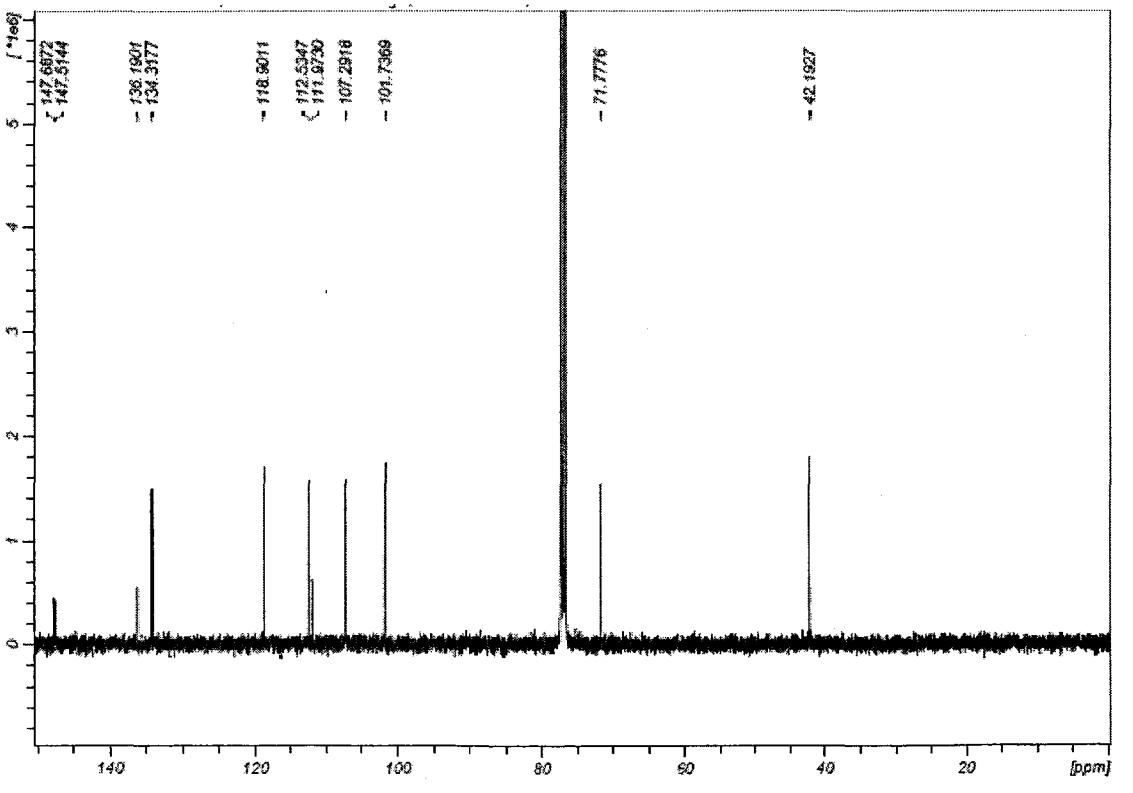
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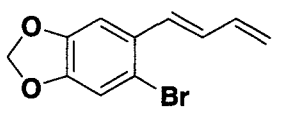
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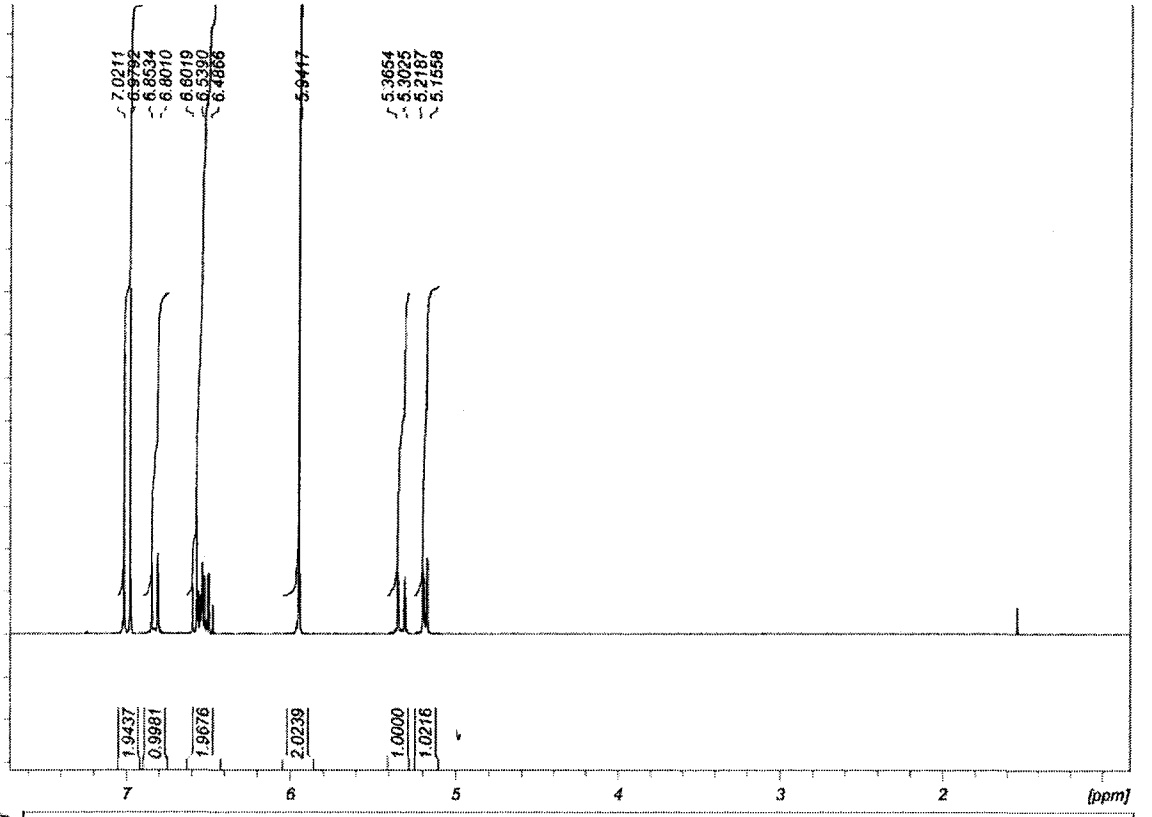
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6
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4
3
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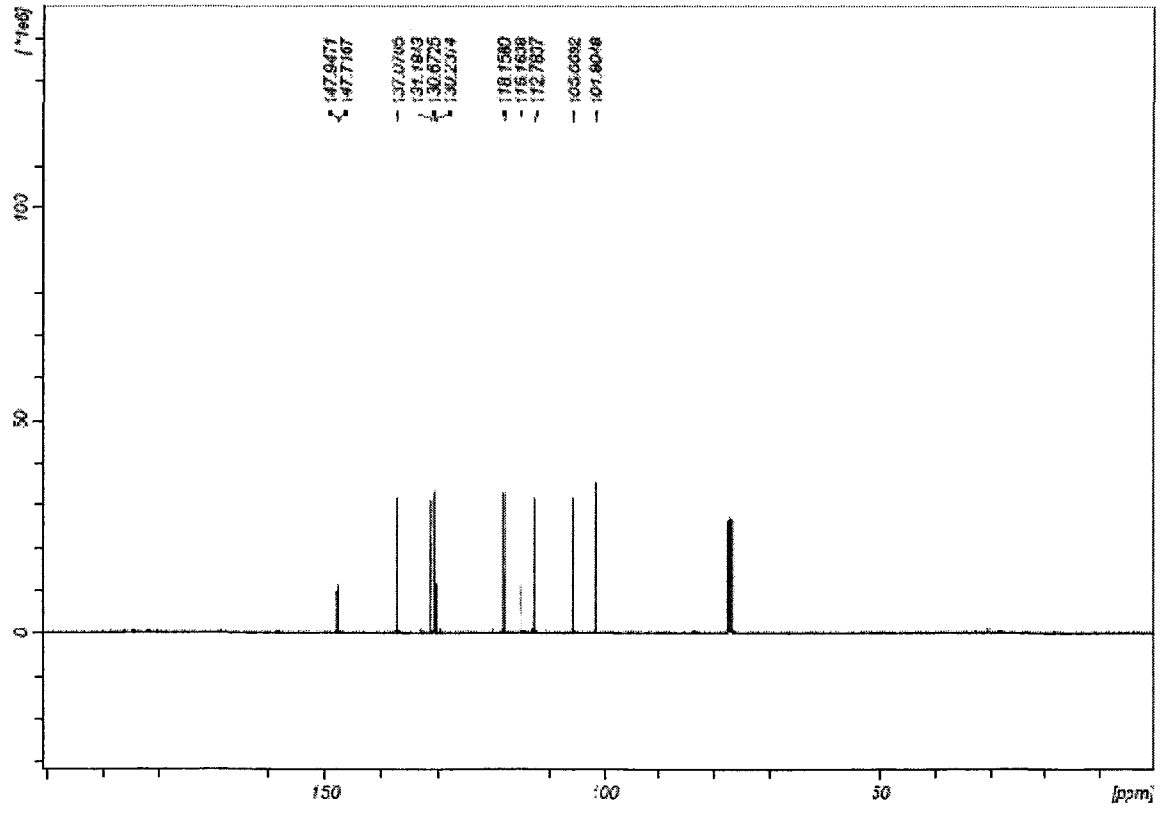
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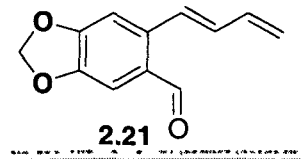

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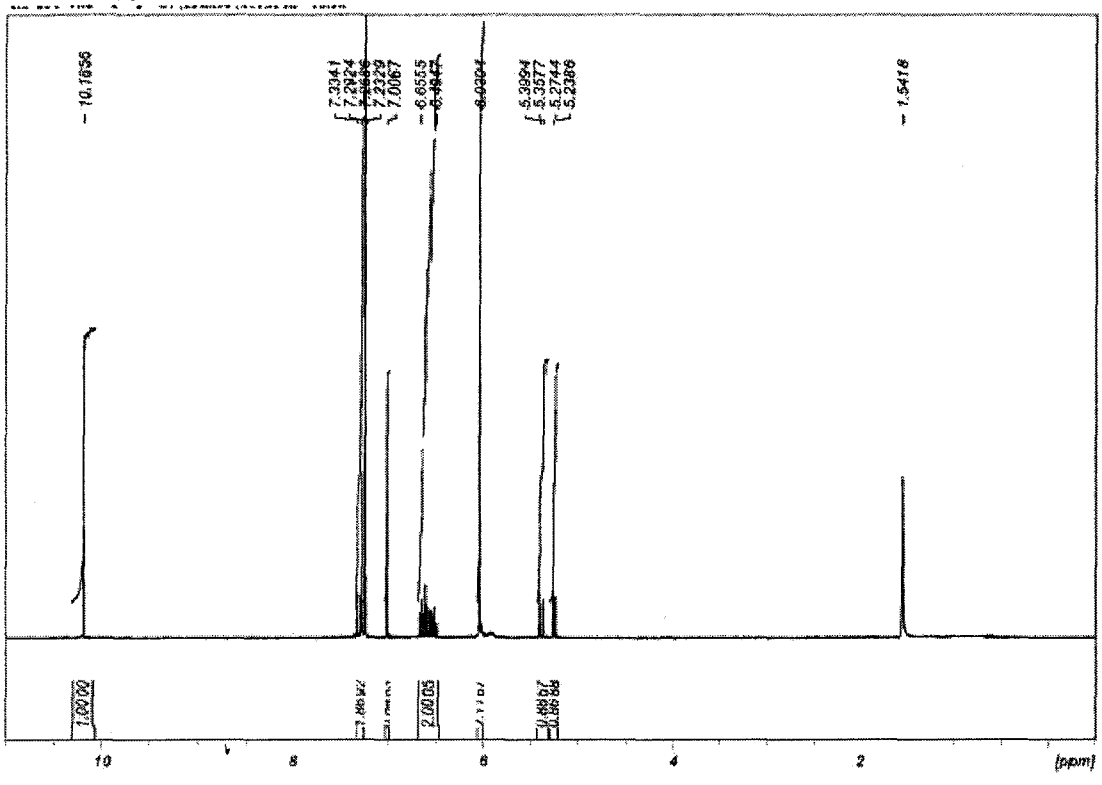
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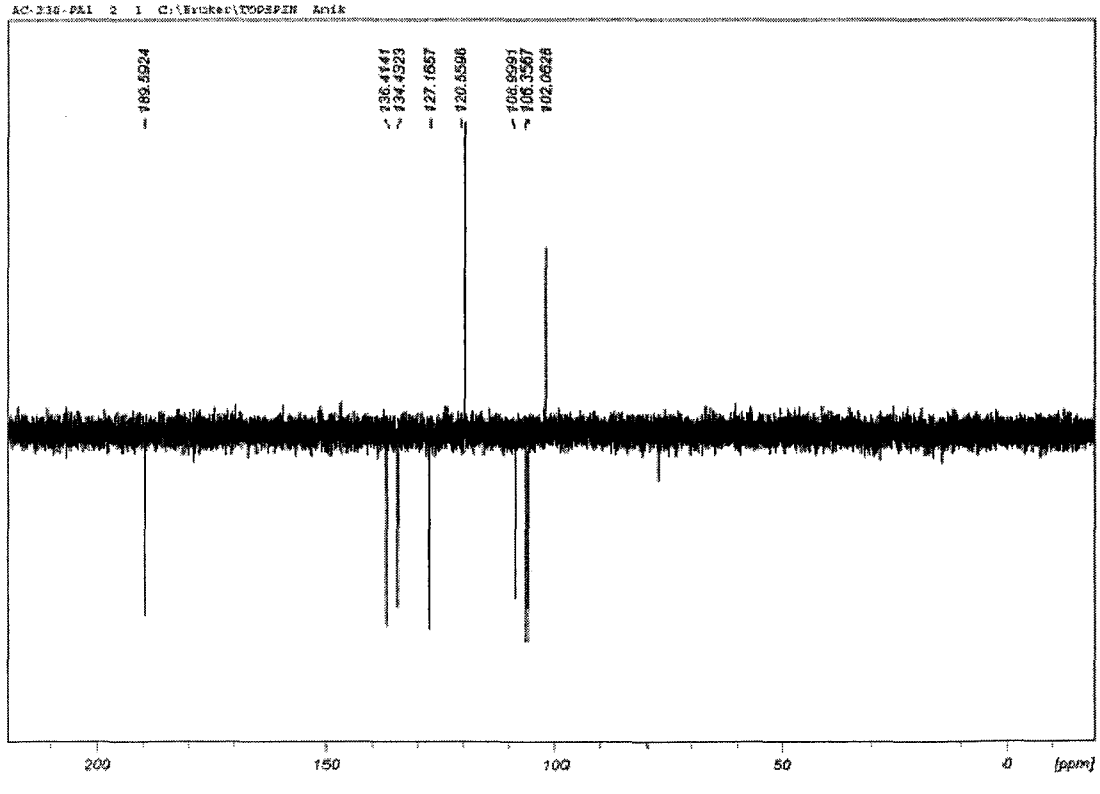
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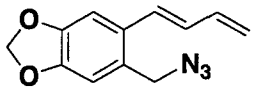

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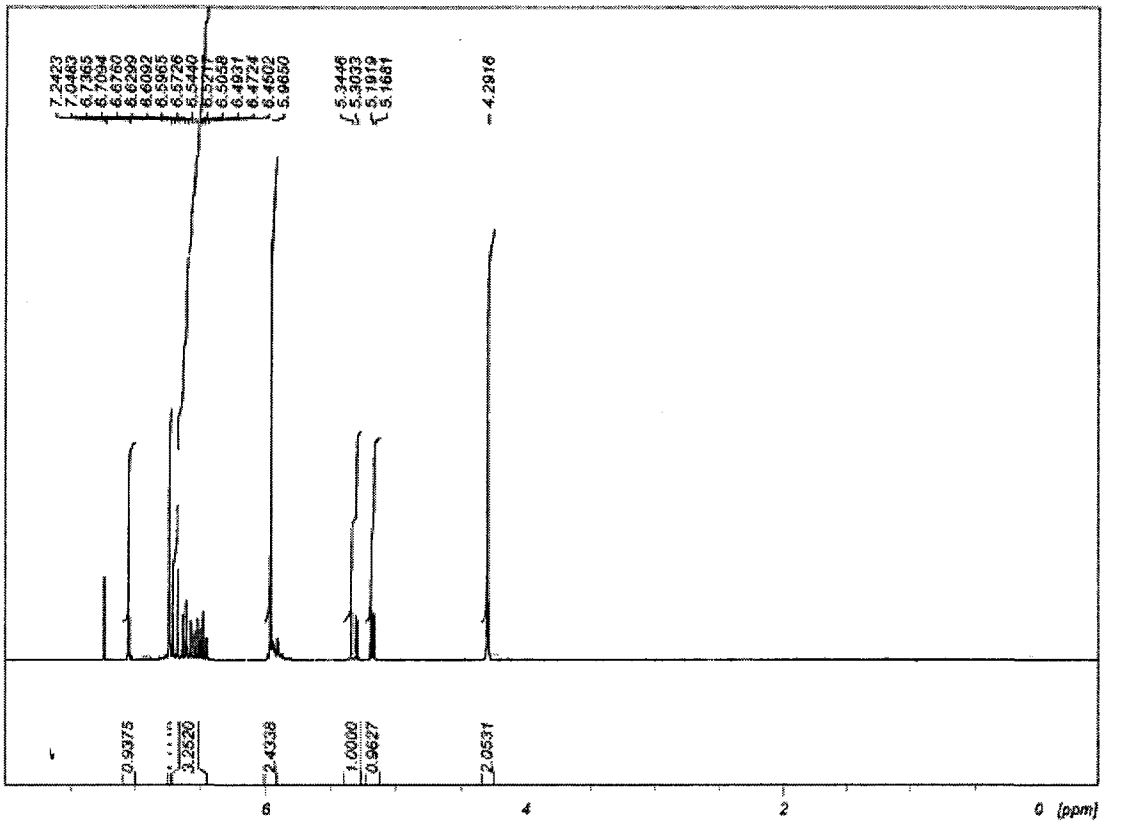
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6.4931
6.4724
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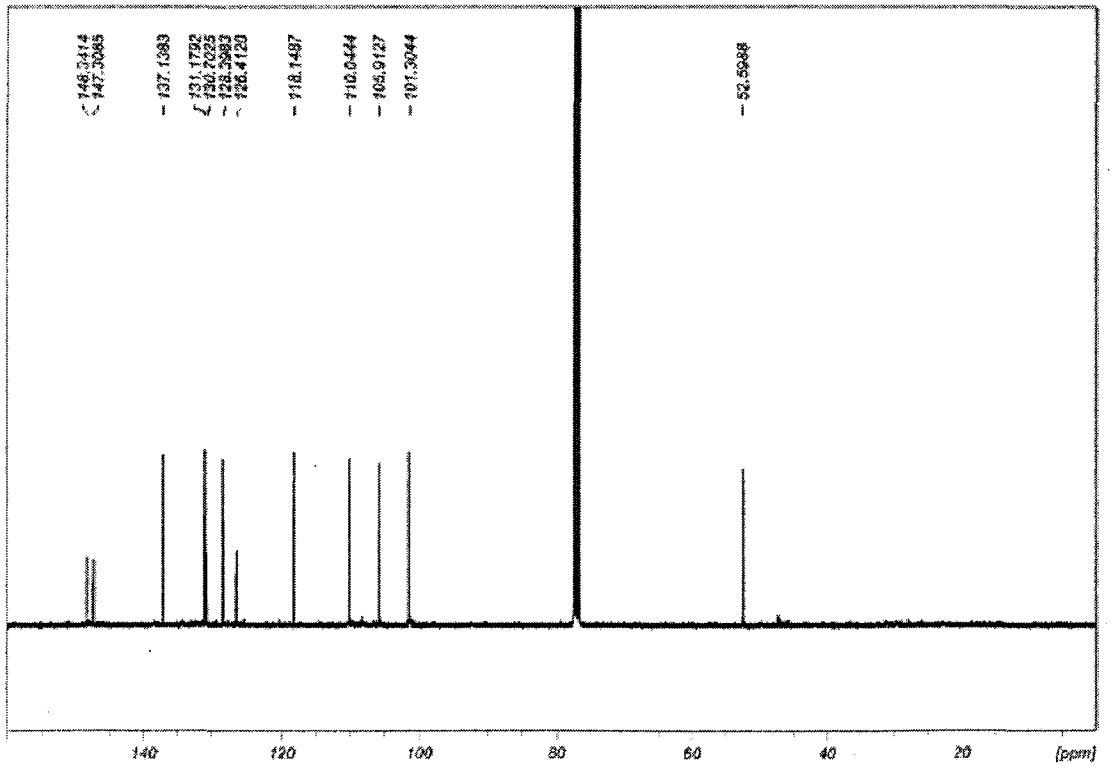
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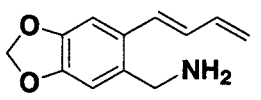

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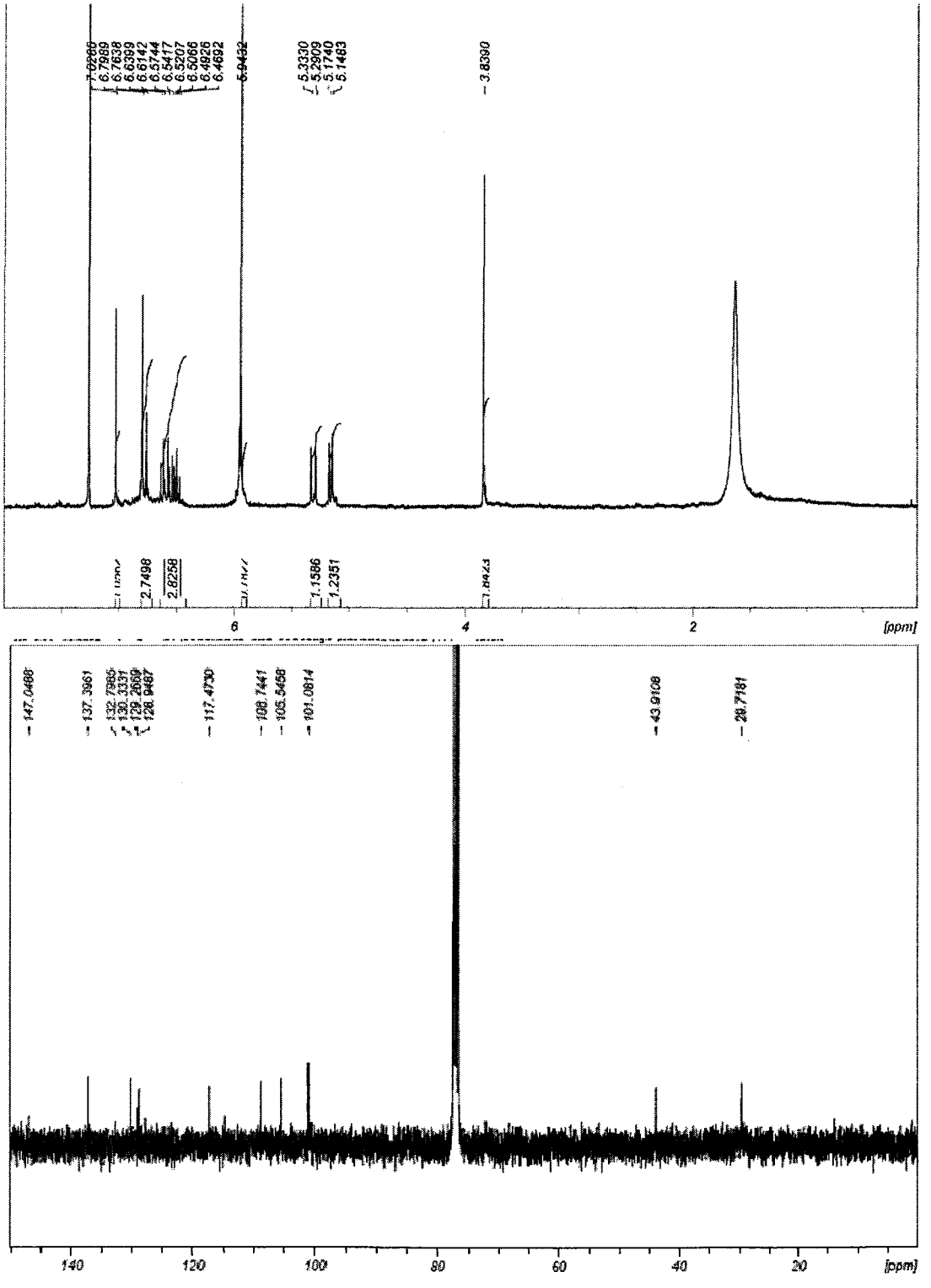
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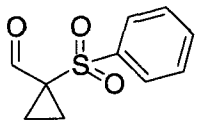

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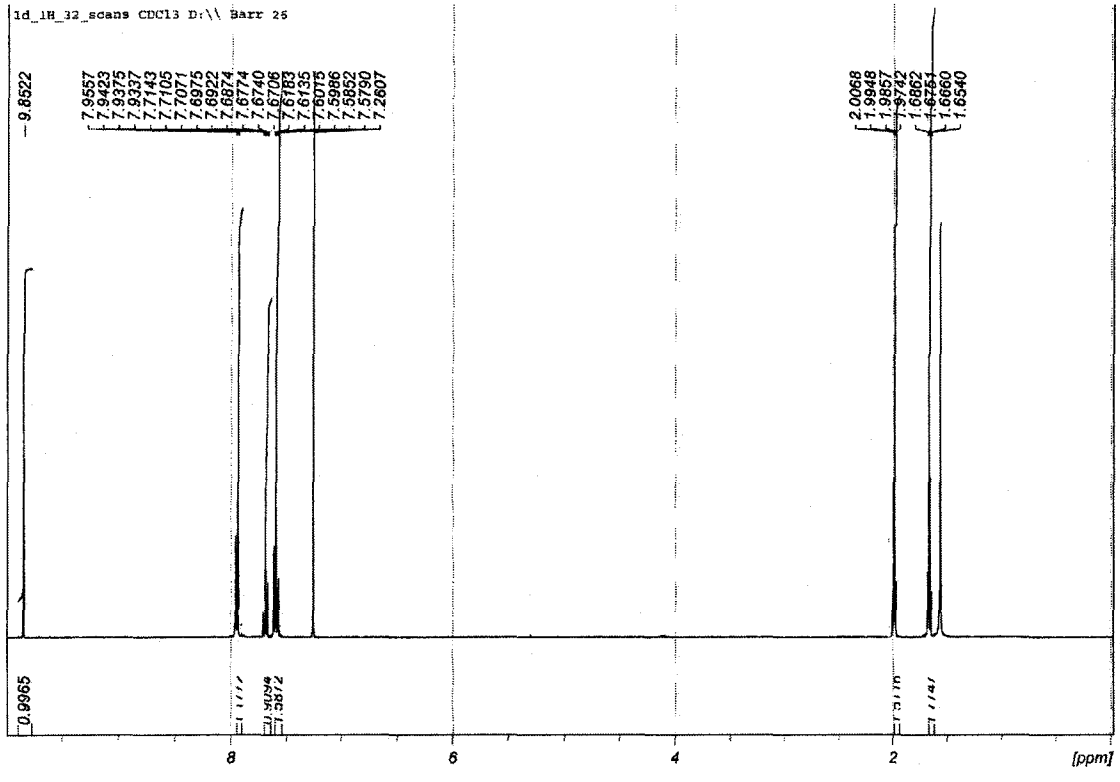
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7.6183
7.6135
7.6075
7.5986
7.5852
7.5790
7.2607
2.0068
1.9948
1.9857
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1.6662
1.6581
1.6660
1.6540
0.9965
8
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4
2
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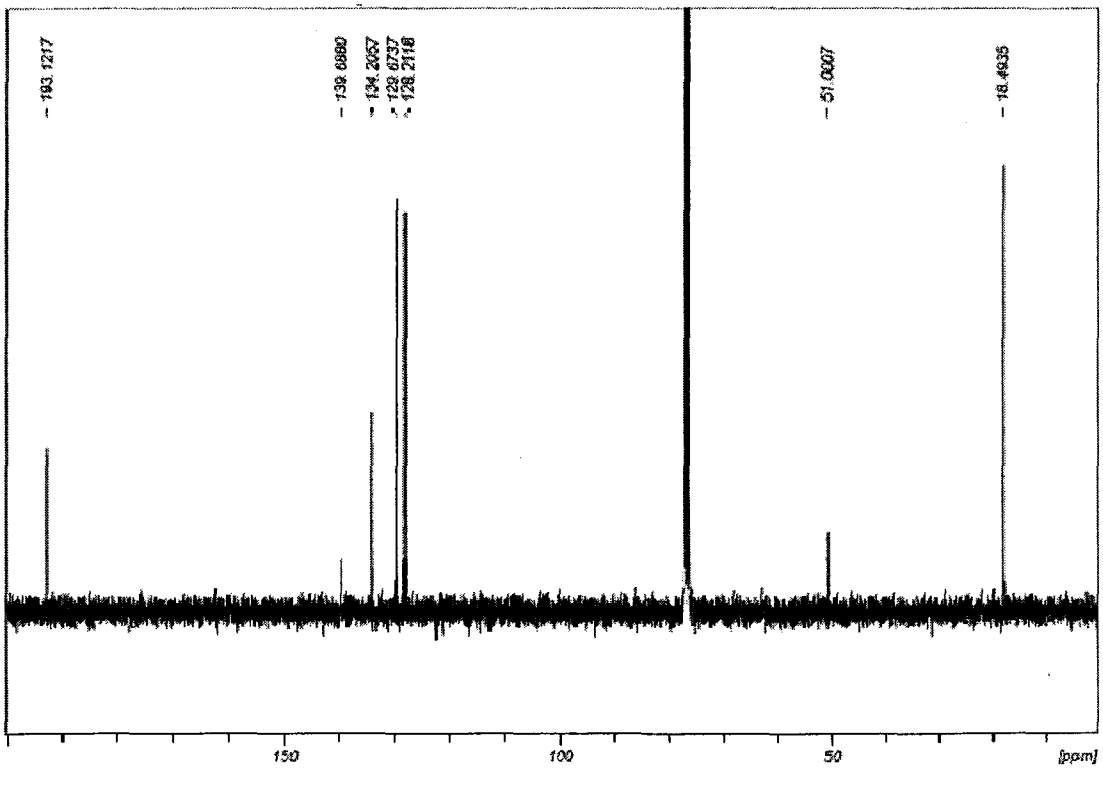
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128.2118
51.0807
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100
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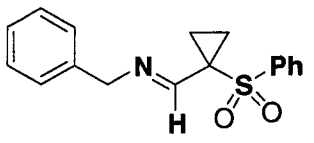
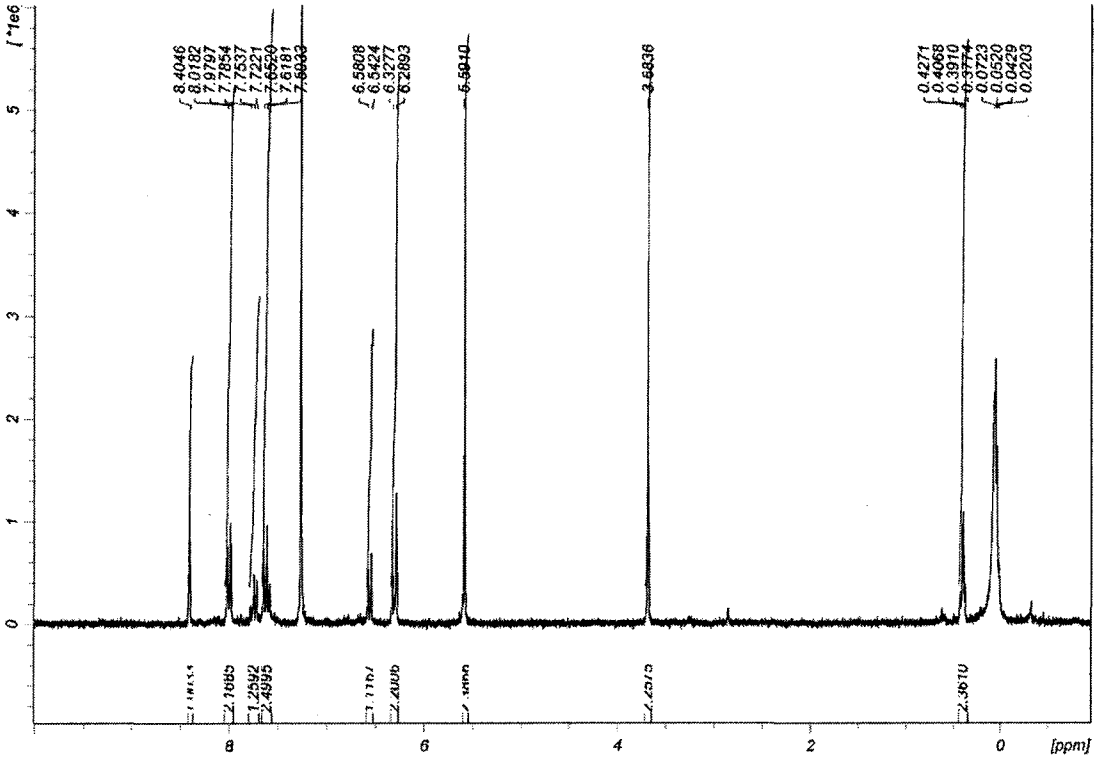

N
Ph
S
O
O
H

2.43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7.9797
7.7854
7.7537
7.7221
7.6529
7.6181
7.6033
6.5808
6.5424
6.3277
6.2893
5.5810
3.6836
0.4271
0.4068
0.3910
0.3774
0.0723
0.0520
0.0429
0.0203
2.1885
1.2592
2.4995
2.3610
8
6
4
2
0
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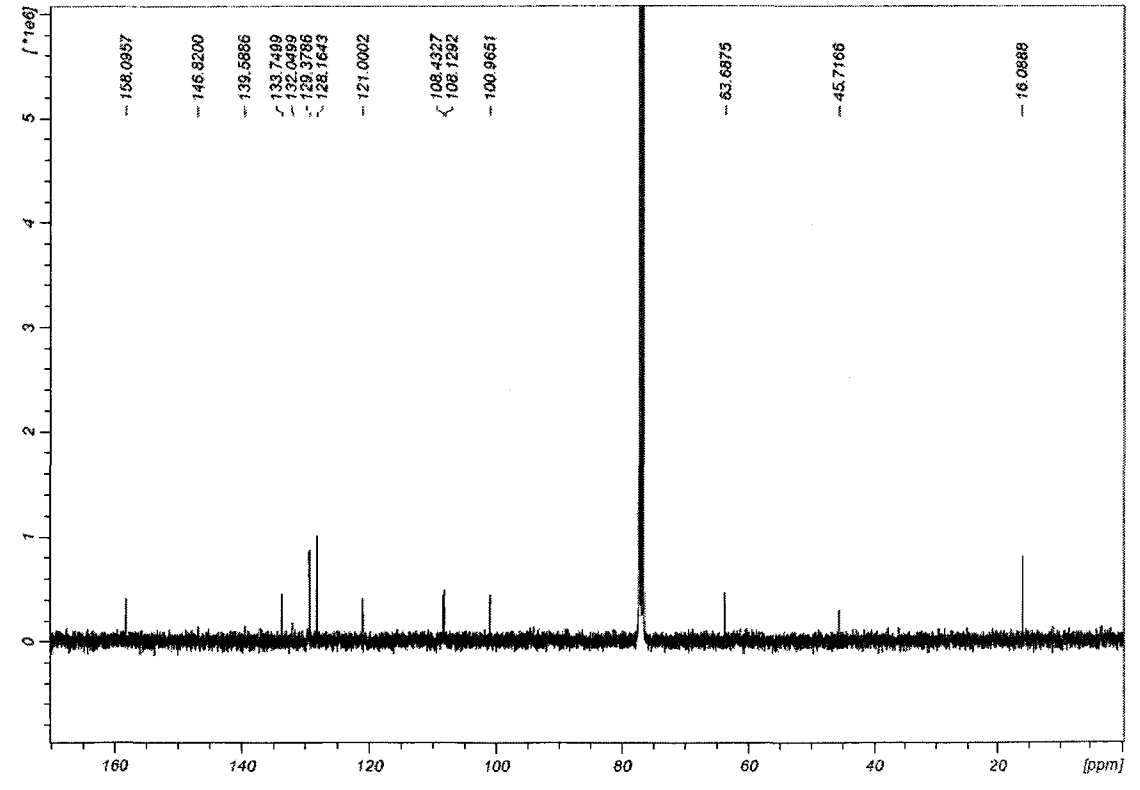
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146.8200
139.5886
133.7499
132.0499
129.3786
128.1643
121.0002
108.4327
108.1292
100.9651
63.6875
45.7166
16.0888
160
140
120
100
80
60
40
20
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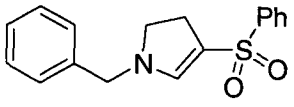
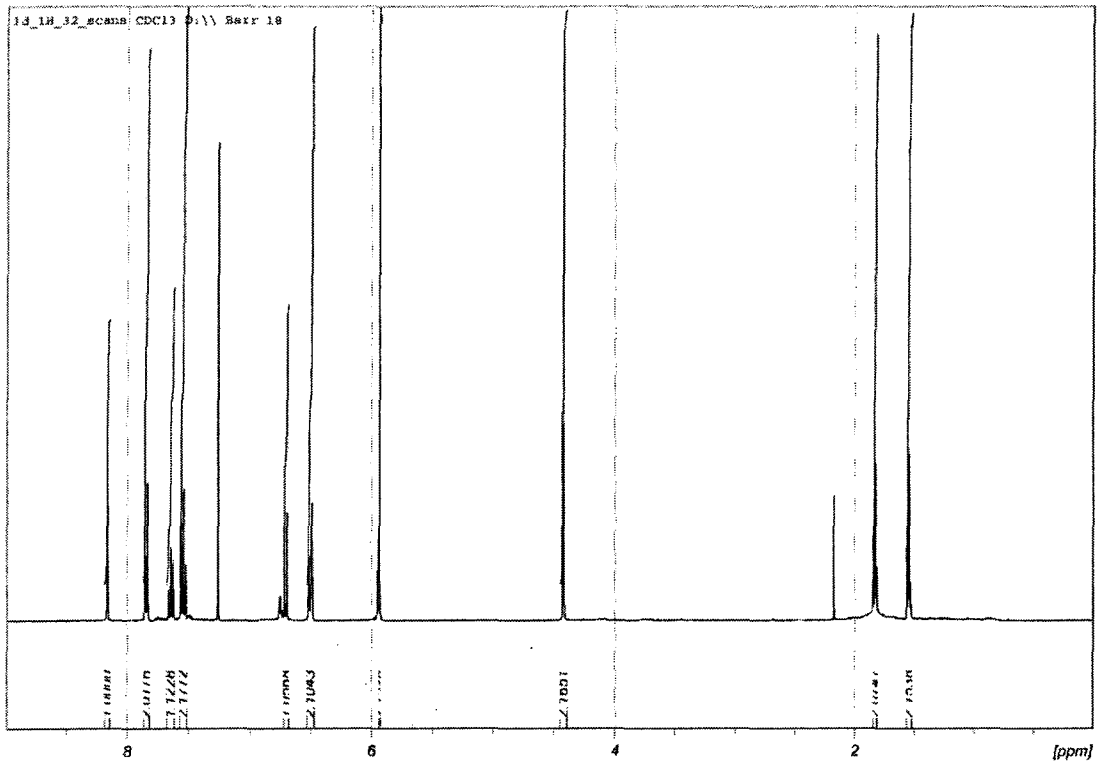
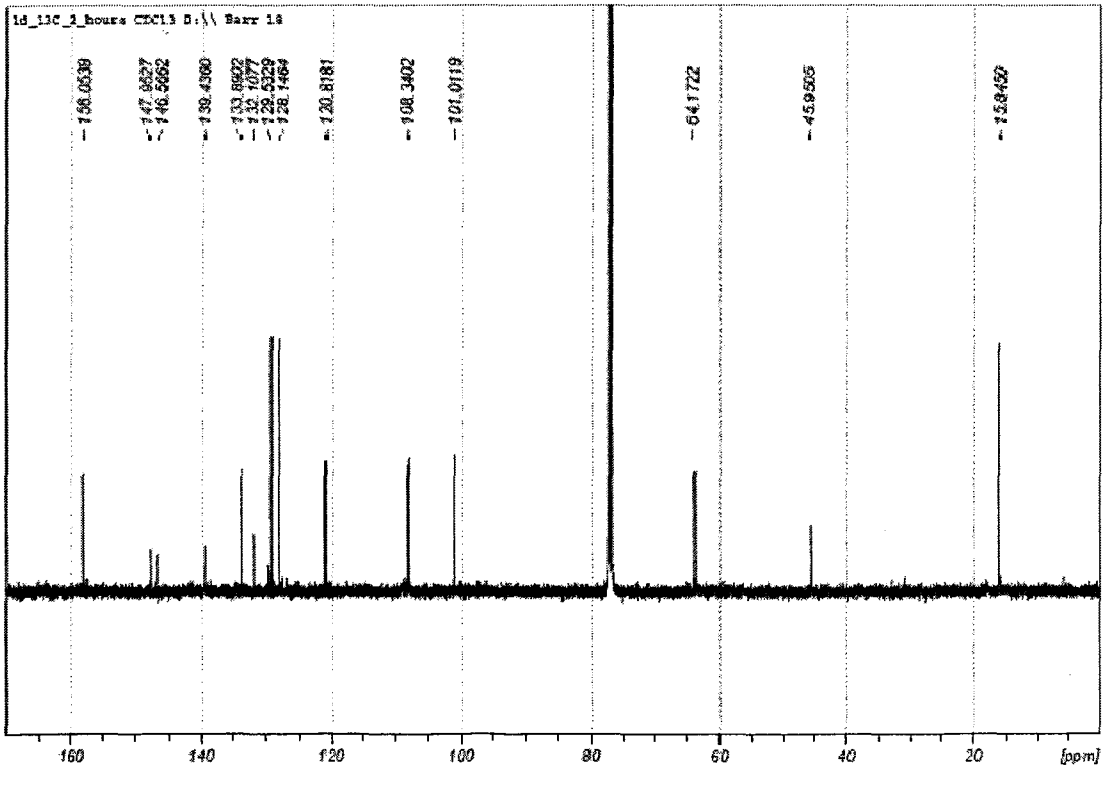

Ph
S
O
O
N

2.42


8
6
4
2
[ppm]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146.5662
139.4360
133.8922
132.1077
129.5329
128.1464
120.8181
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64.1722
45.9505
15.8452
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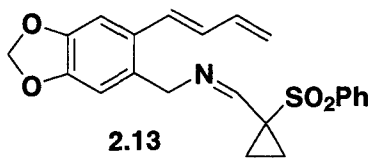
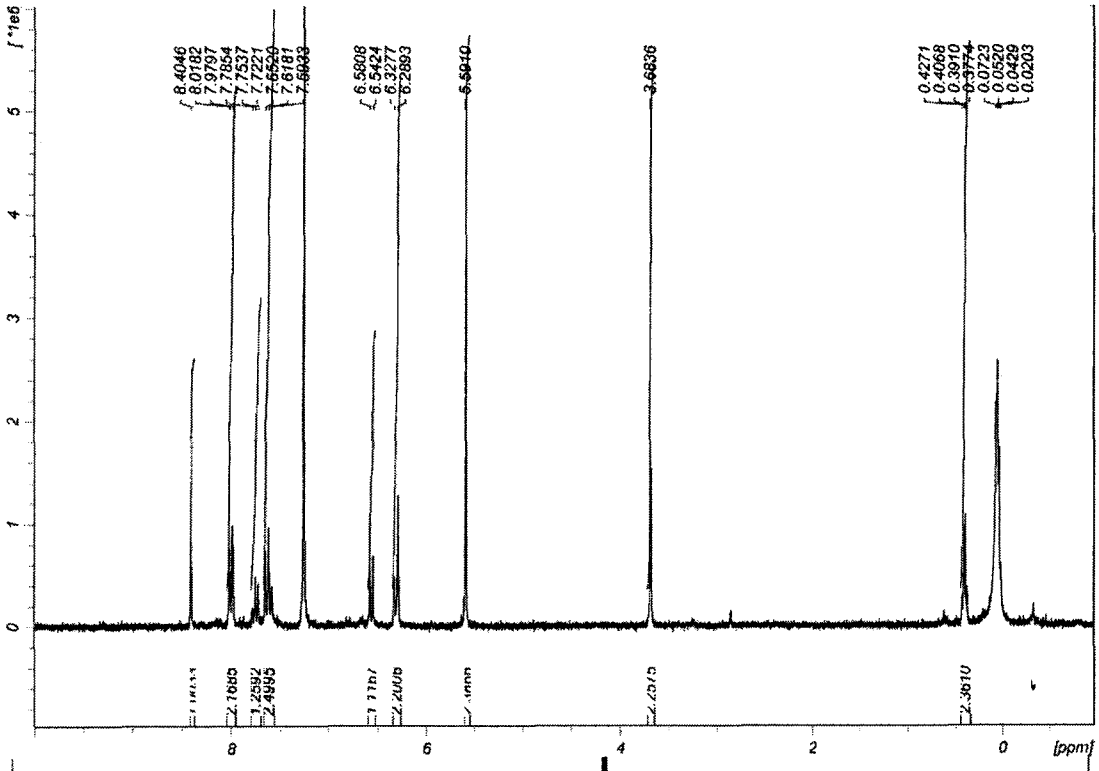
140
120
100
80
60
40
20
[ppm]


O
O
N
SO2Ph

2.13


[*1e6
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8.0182
7.9797
7.7854
7.7537
7.7221
7.6530
7.6181
7.5833
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6.5424
6.3277
6.2893
5.5610
3.6836
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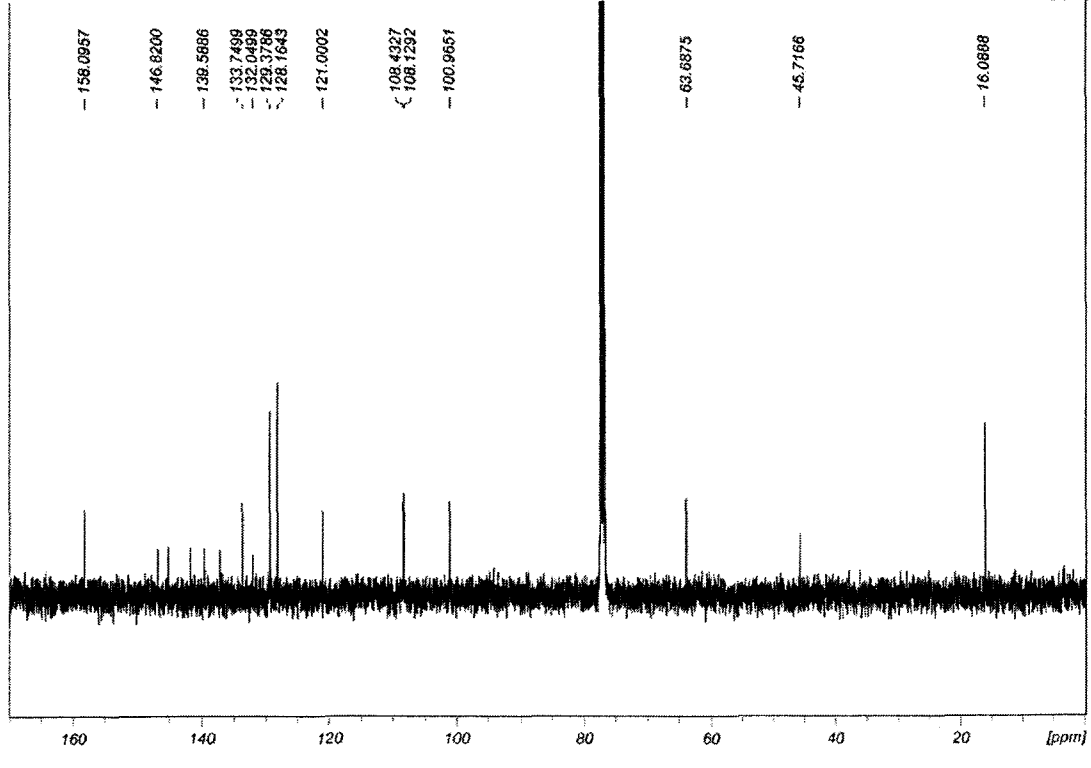
0.4068
0.3910
0.3774
0.0723
0.0520
0.0429
0.0203
[ppm]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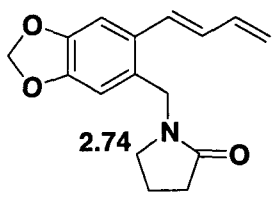
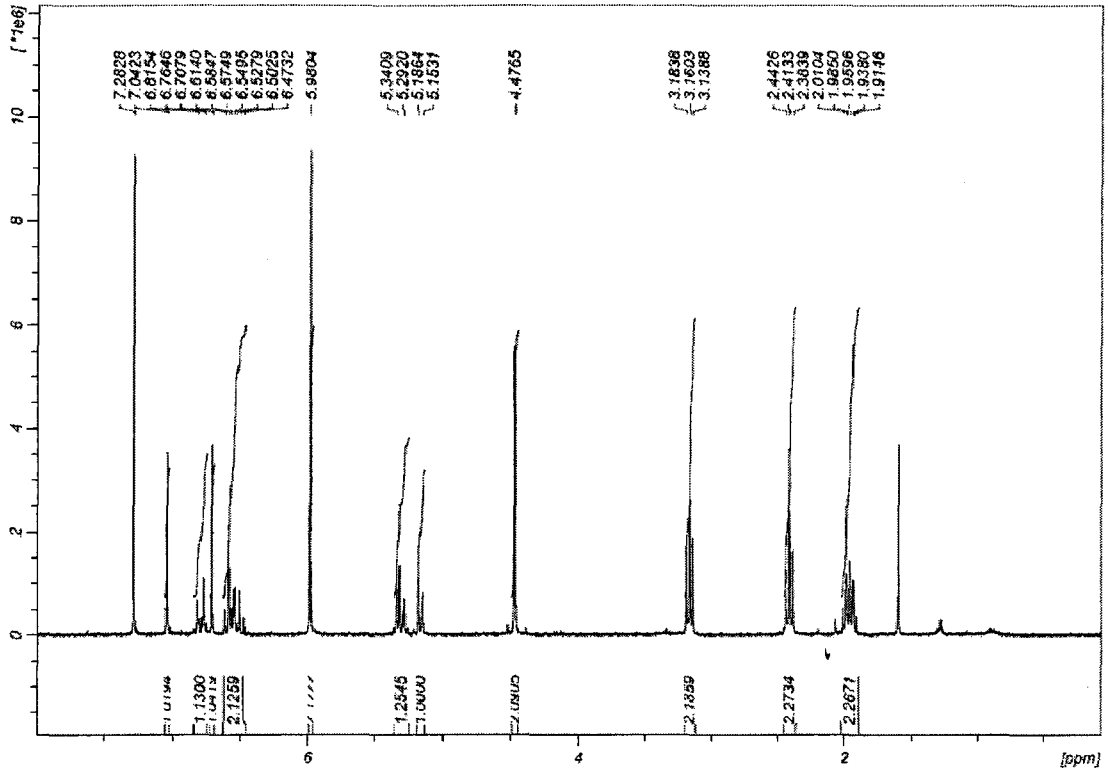
139.5886
133.7499
132.0499
129.3766
128.1643
121.0002
108.4327
108.1292
100.9651
63.6875
45.7166
16.0888
[ppm]


O
O
2.74
N
O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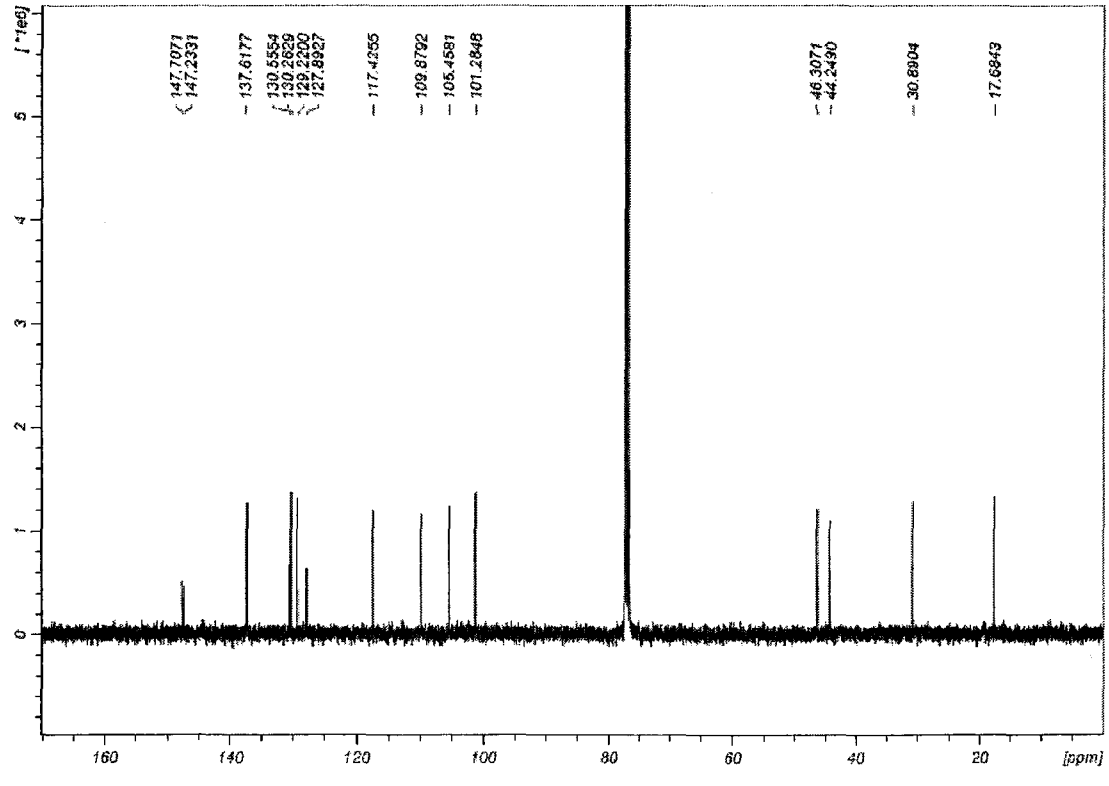
7.0423
6.8154
6.7646
6.7079
6.6140
6.5847
6.5749
6.5495
6.5279
6.5025
6.4732
5.9804
5.3409
5.2920
5.1864
5.1531
4.4765
3.1838
3.1603
3.1388
2.4426
2.4133
2.3839
2.0104
1.9850
1.9596
1.9380
1.9146
1.1300
2.1259
1.2545
2.1859
2.2734
2.2671
[ppm]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130.2629
129.2200
127.8927
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109.8792
105.4581
101.2848
46.3071
44.2490
30.8904
17.6843
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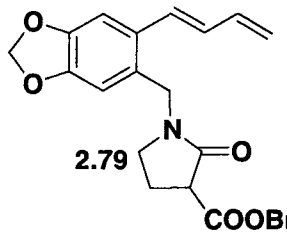
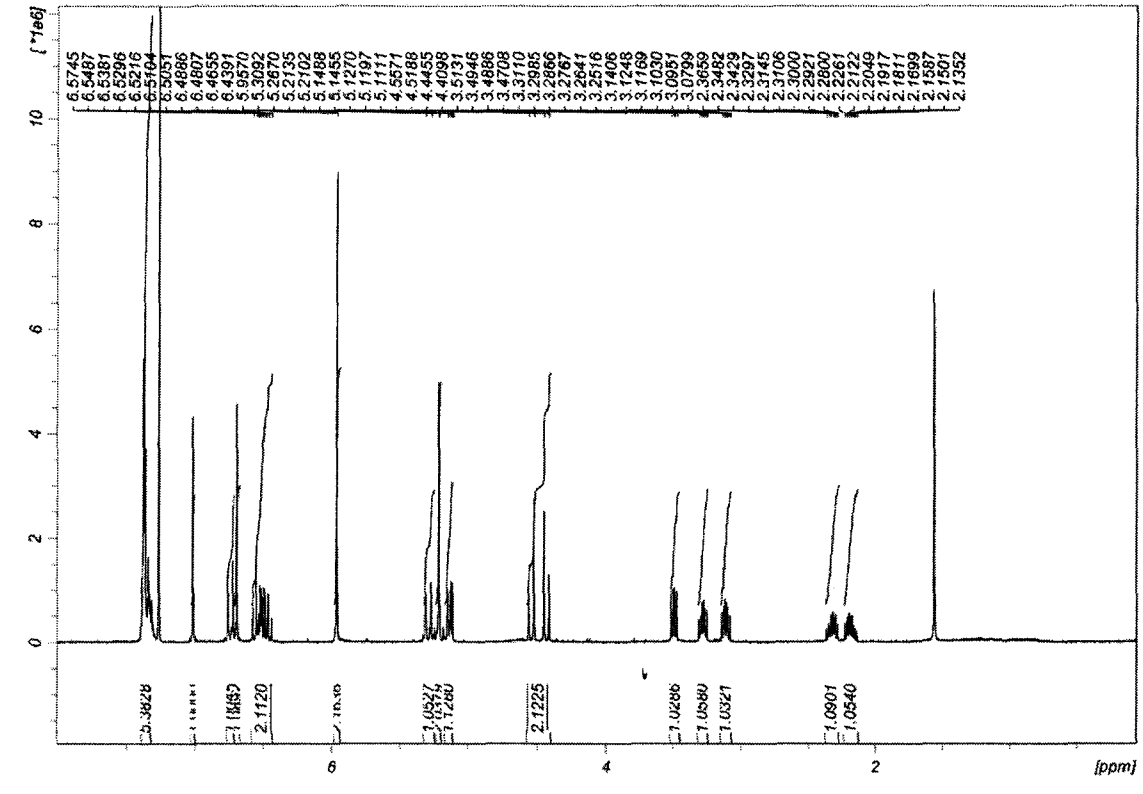

O
O
N
O
COOBn

2.79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6.5487
6.5381
6.5296
6.5216
6.5164
6.5051
6.4886
6.4807
6.4655
6.4391
5.9570
5.3092
5.2670
5.2135
5.2102
5.1468
5.1455
5.1270
5.1197
5.1111
4.5571
4.5186
4.4455
4.4098
3.5131
3.4946
3.4886
3.4708
3.3110
3.2985
3.2866
3.2767
3.2641
3.2516
3.1406
3.1248
3.1169
3.1030
3.0951
3.0799
2.3659
2.3482
2.3429
2.3297
2.3145
2.3106
2.3000
2.2921
2.2800
2.2261
2.2122
2.2049
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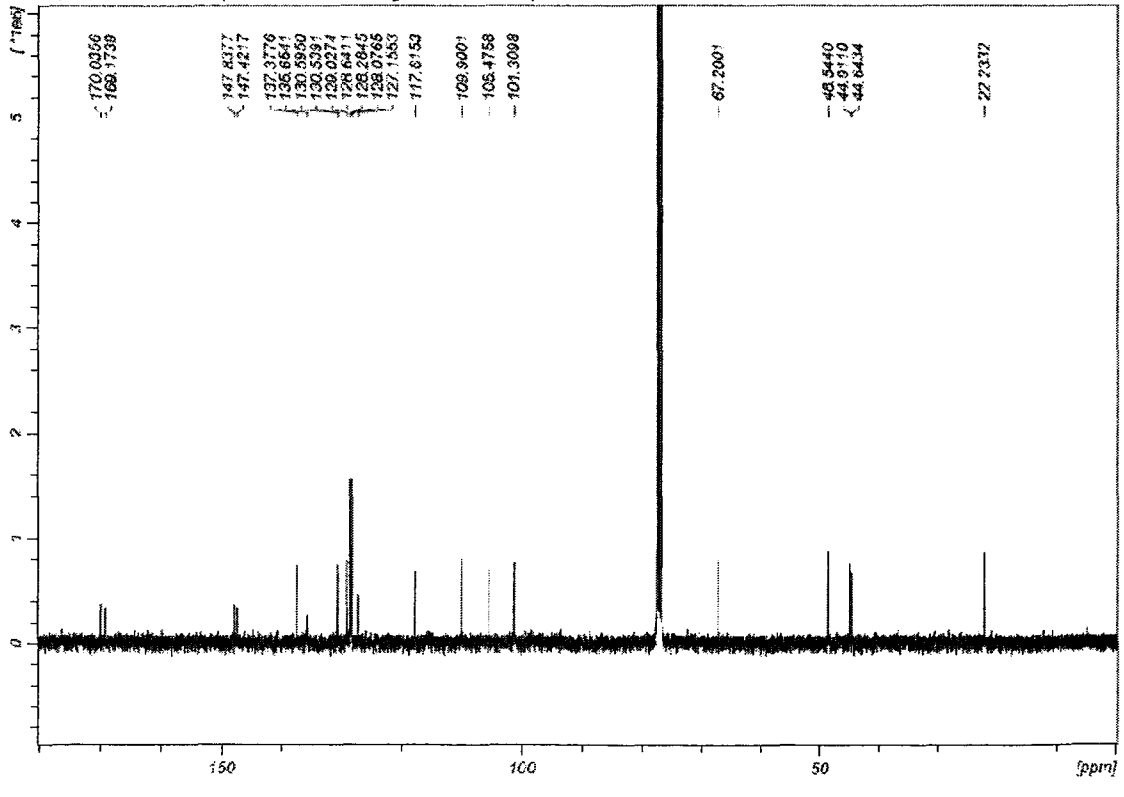
2.1811
2.1699
2.1587
2.1501
2.1352
2.1120
2.1225
[*1e6]
[ppm]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147.4217
137.3776
135.6641
130.5950
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128.0274
128.6411
128.2845
128.0765
127.1553
117.6153
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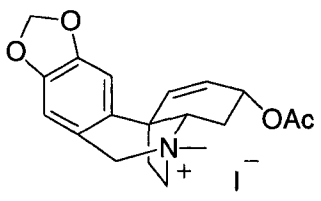
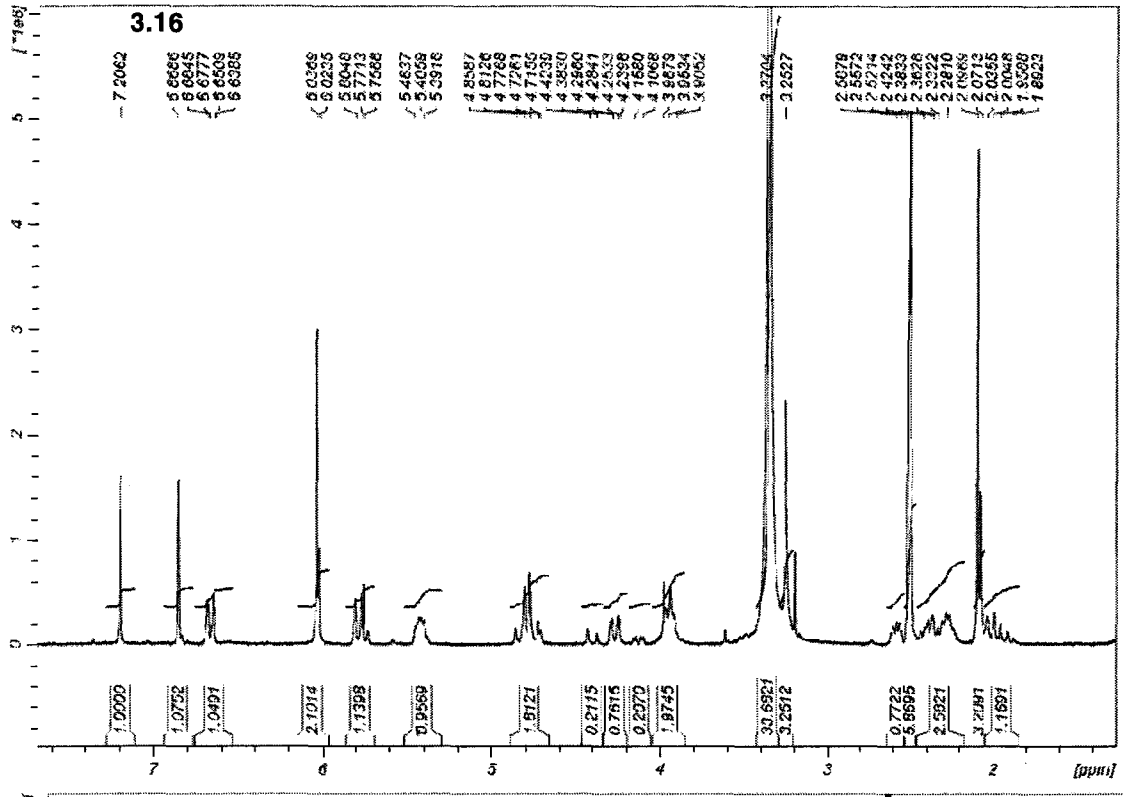
44.9110
44.6434
22.2312
[*1e6]
[ppm]


O
O
OAc
N
+
I
−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7.2062
3.2527
1.0000
1.0752
1.0491
2.1014
1.1398
0.9569
1.8121
0.2115
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1.8745
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3.2512
0.7732
5.9595
2.5927
1.1691
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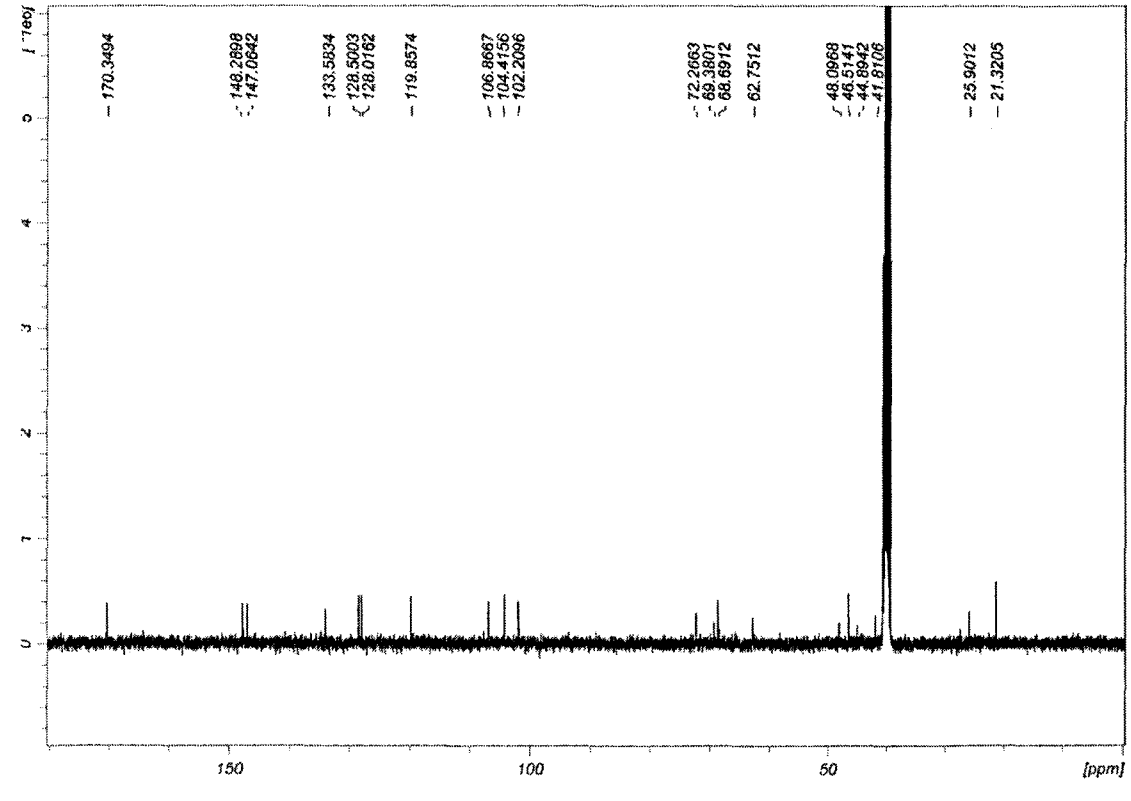
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128.5003
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119.8574
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104.4156
102.2096
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69.3801
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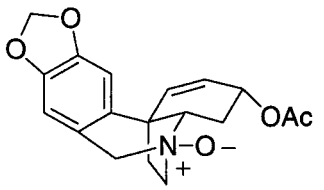
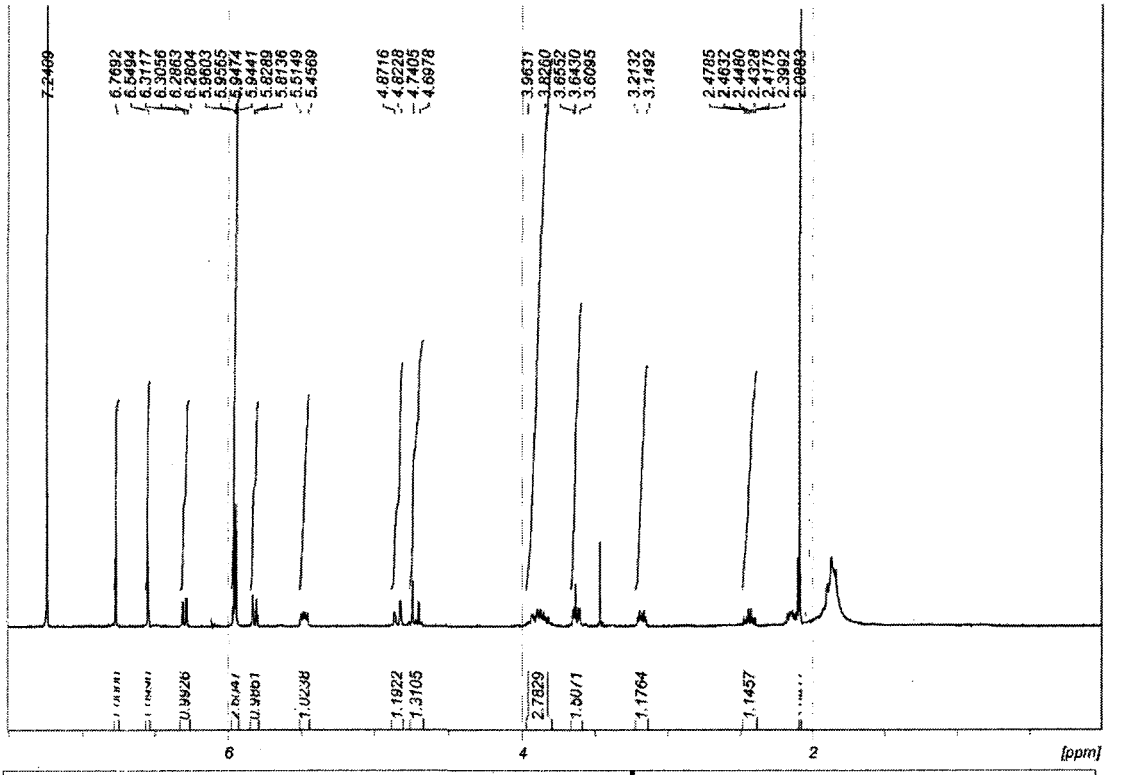
62.7512
48.0968
46.5141
44.8942
41.8106
25.9012
21.3205
150
100
50
[ppm]


O
O
OAc
N–O–
+

3.22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6.5494
6.3117
6.3056
6.2863
6.2804
5.9803
5.9565
5.9474
5.9441
5.8289
5.8136
5.5149
5.4569
4.8716
4.8228
4.7405
4.6978
3.9631
3.8260
3.6552
3.6430
3.6095
3.2132
3.1492
2.4785
2.4632
2.4480
2.4328
2.4175
2.3992
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0.9926
1.0238
1.1922
1.3105
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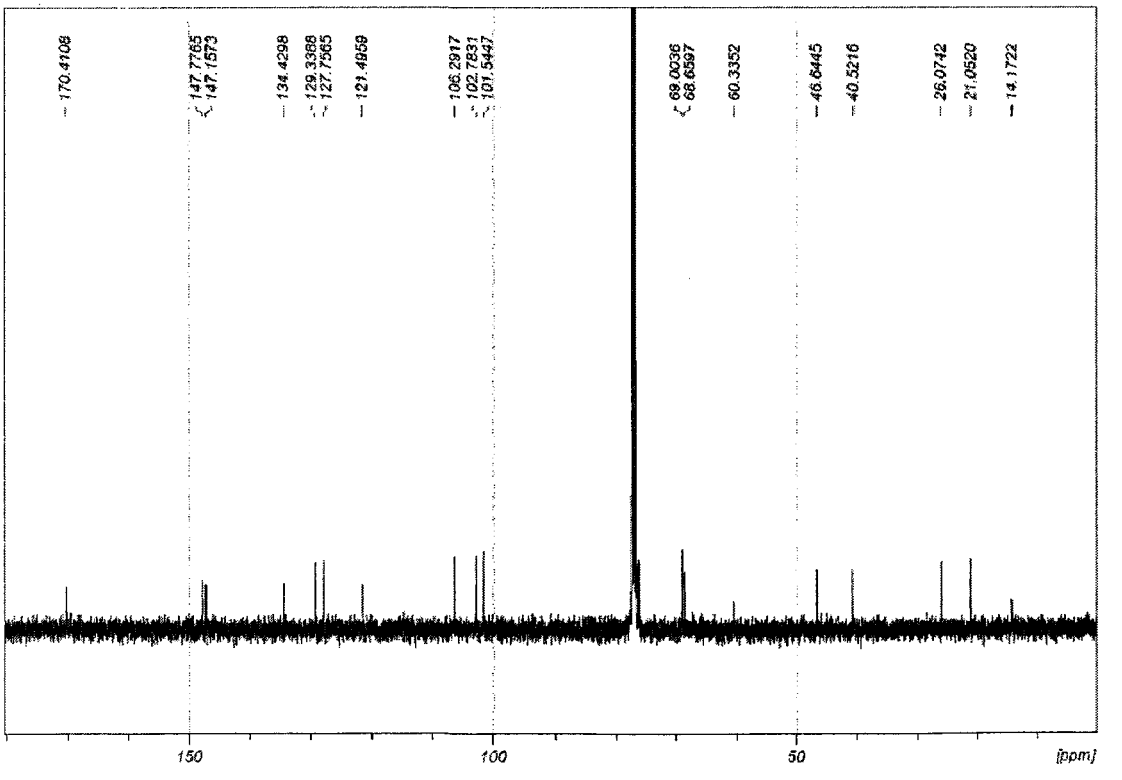
1.1764
1.1457
6
4
2
[ppm]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102.7831
101.5447
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60.3352
46.6445
40.5216
26.0742
21.0520
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100
50
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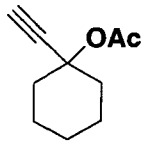
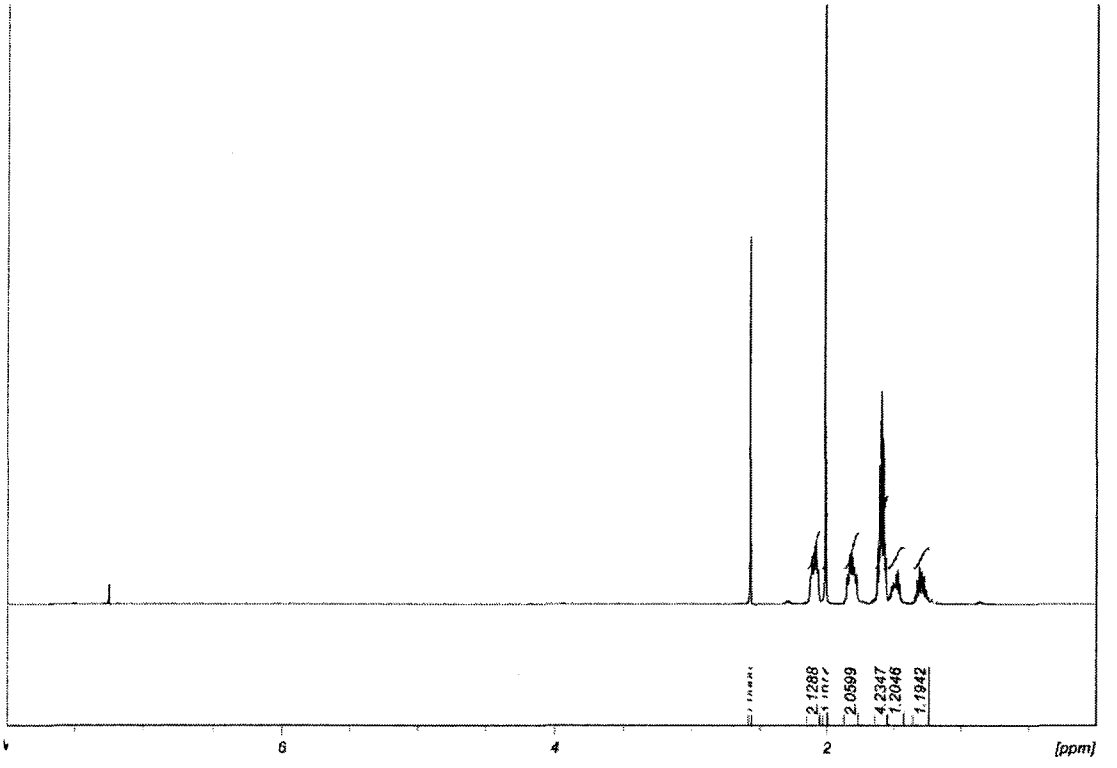

OAc

4.28a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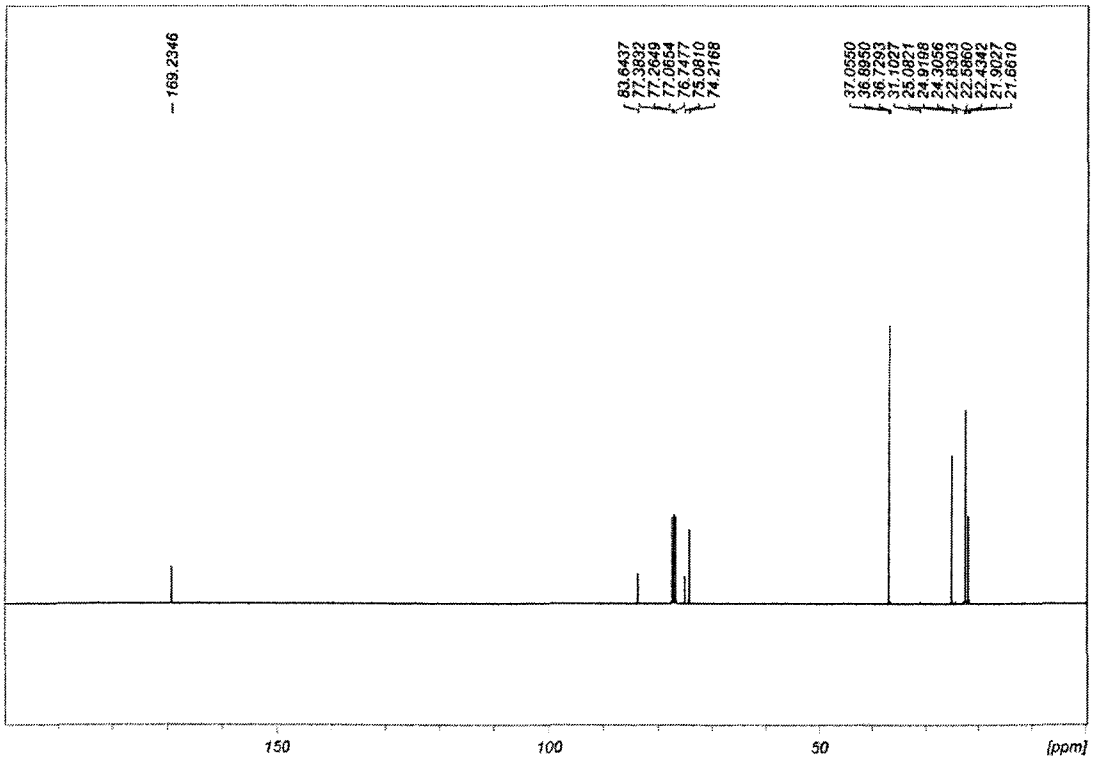
1.2046
1.1942
6
4
2
[ppm]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77.2649
77.0654
76.7477
75.0810
74.2168
37.0550
36.8950
36.7293
31.1027
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22.8303
22.5860
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100
50
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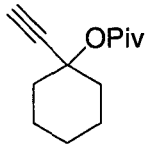
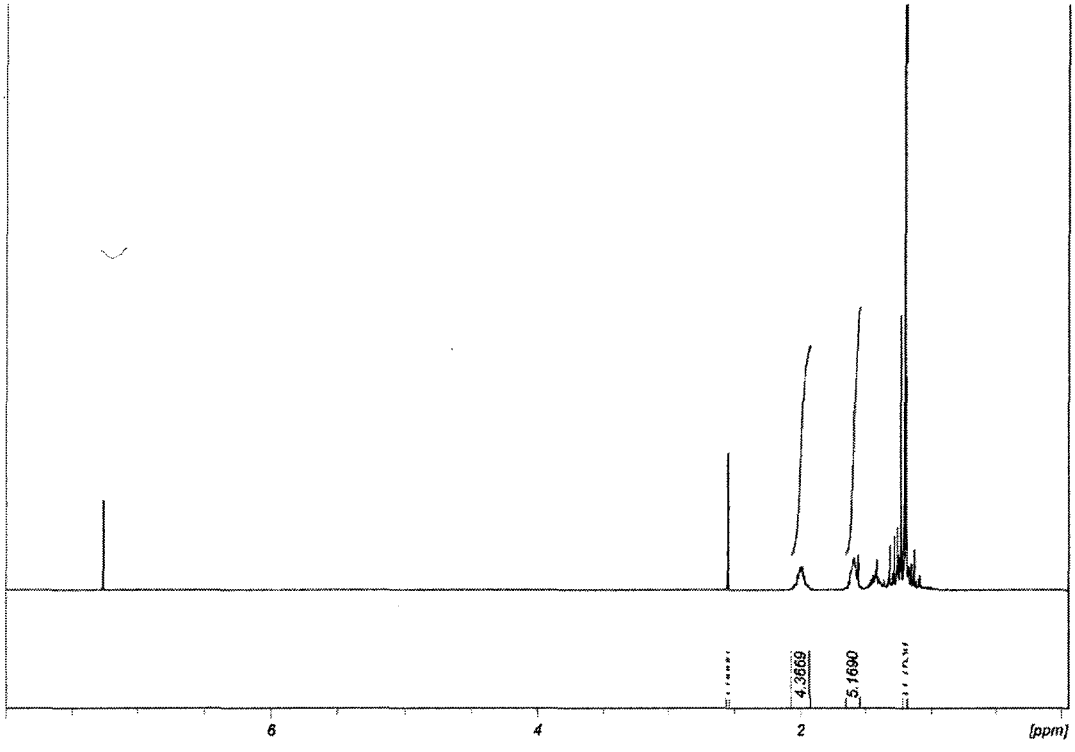

OPiv

4.28b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4
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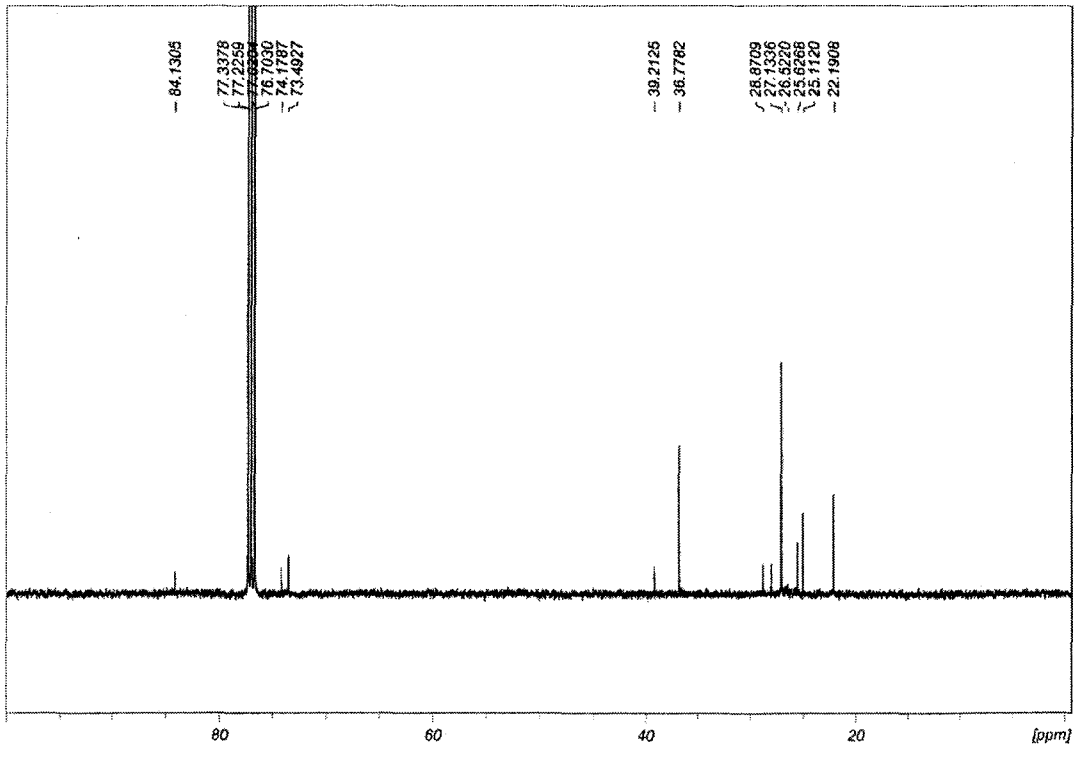
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76.7030
74.1787
73.4927
39.2125
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22.1908
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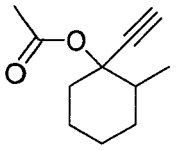
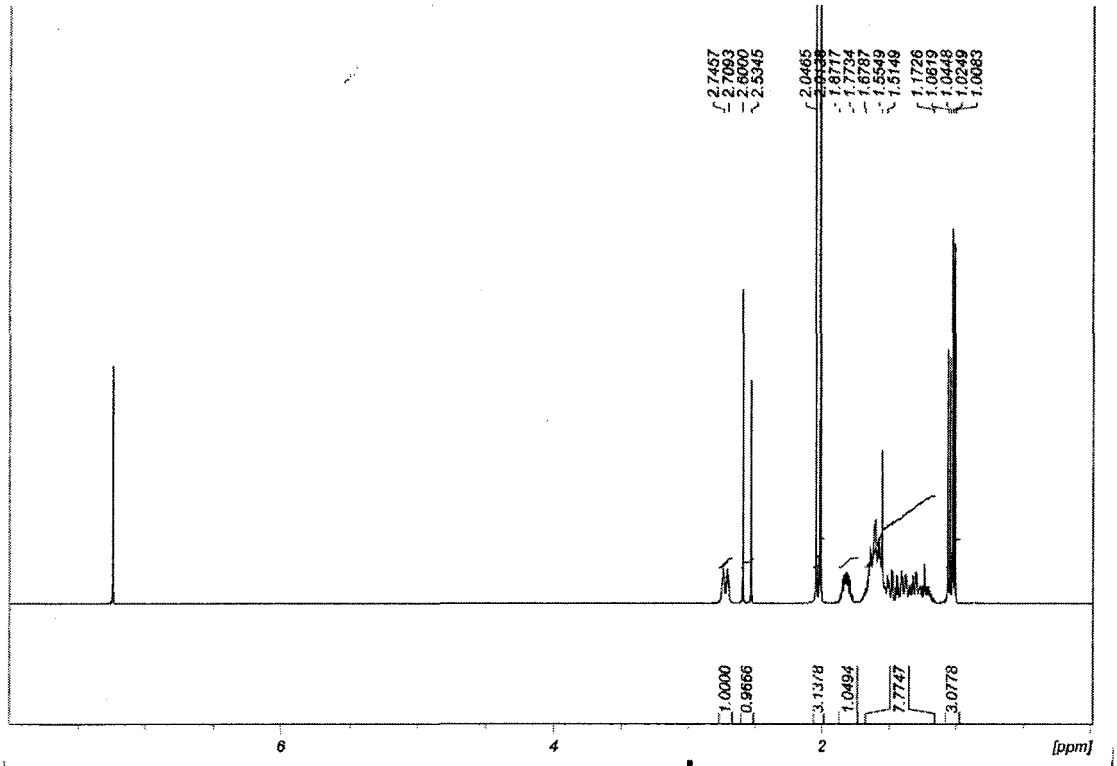
40
20
[ppm]



4.40a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1.7734
1.6787
1.5549
1.5149
1.1726
1.0619
1.0448
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1.0000
0.9666
3.1378
1.0494
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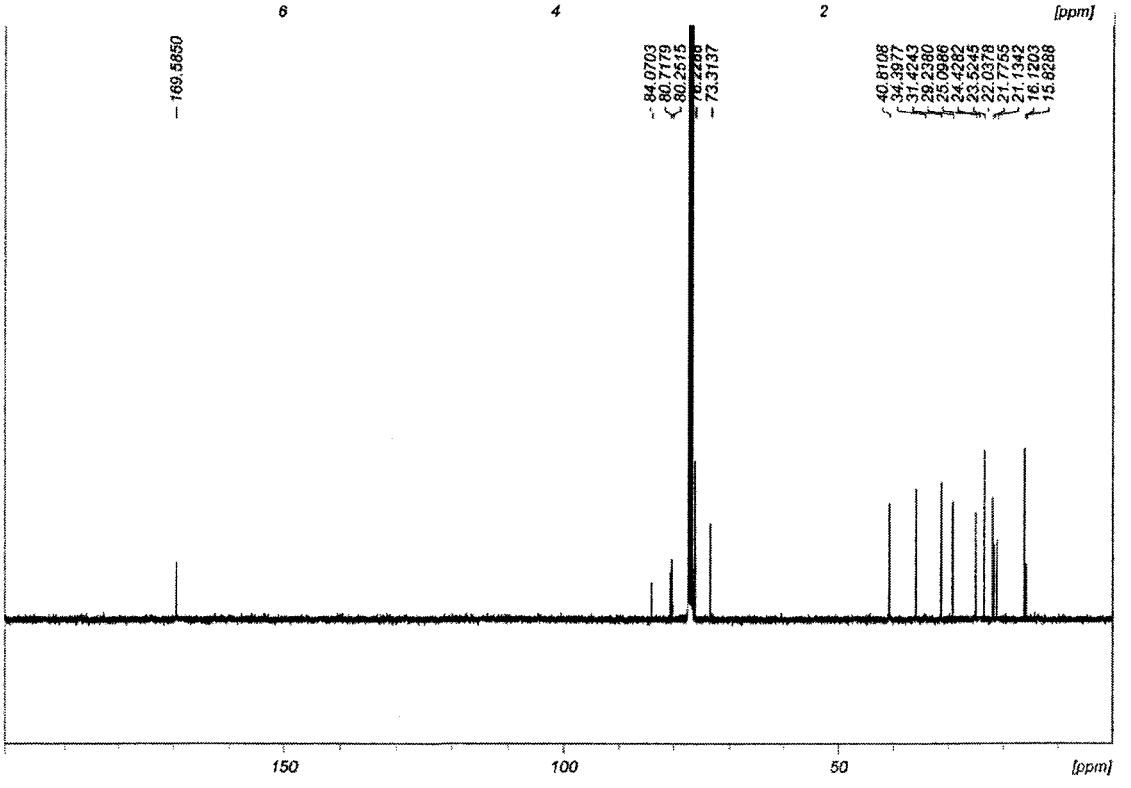
3.0778
6
4
2
[ppm]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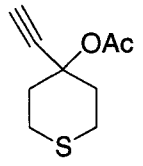
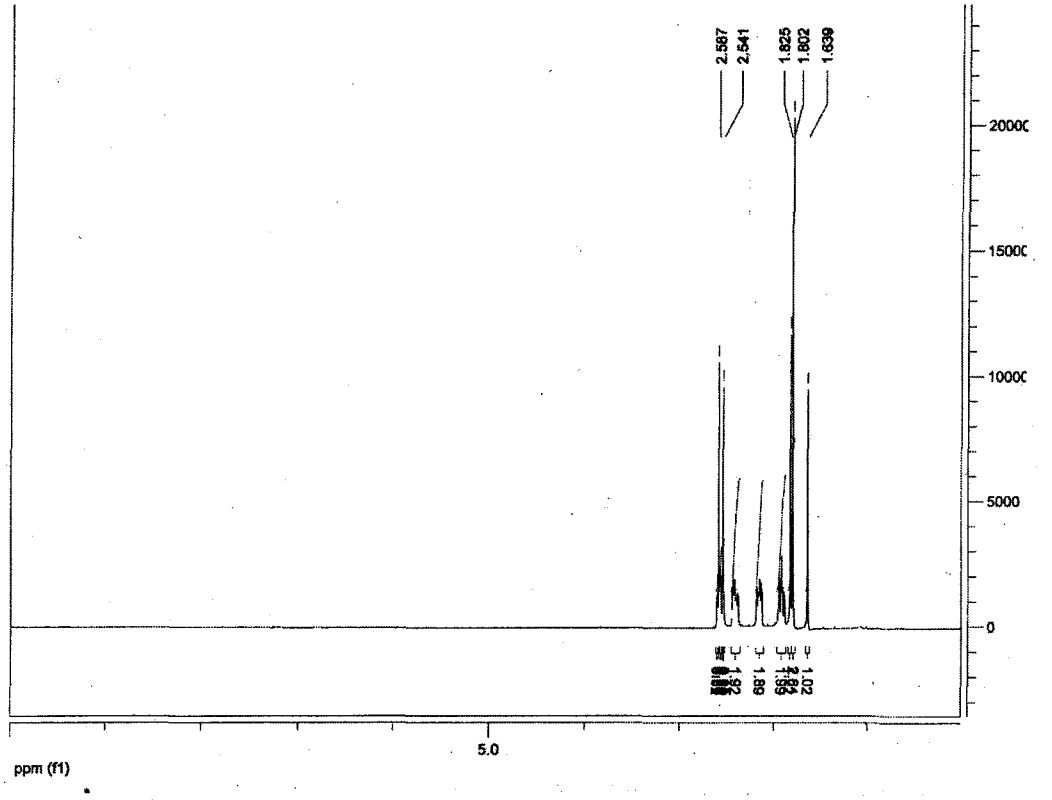
80.2515
73.3137
40.8108
34.3977
31.4243
29.2380
25.0986
24.4282
23.5245
22.0378
21.7755
21.1342
16.1203
15.8288
150
100
50
[ppm]


OAc
S

4.40b$_2$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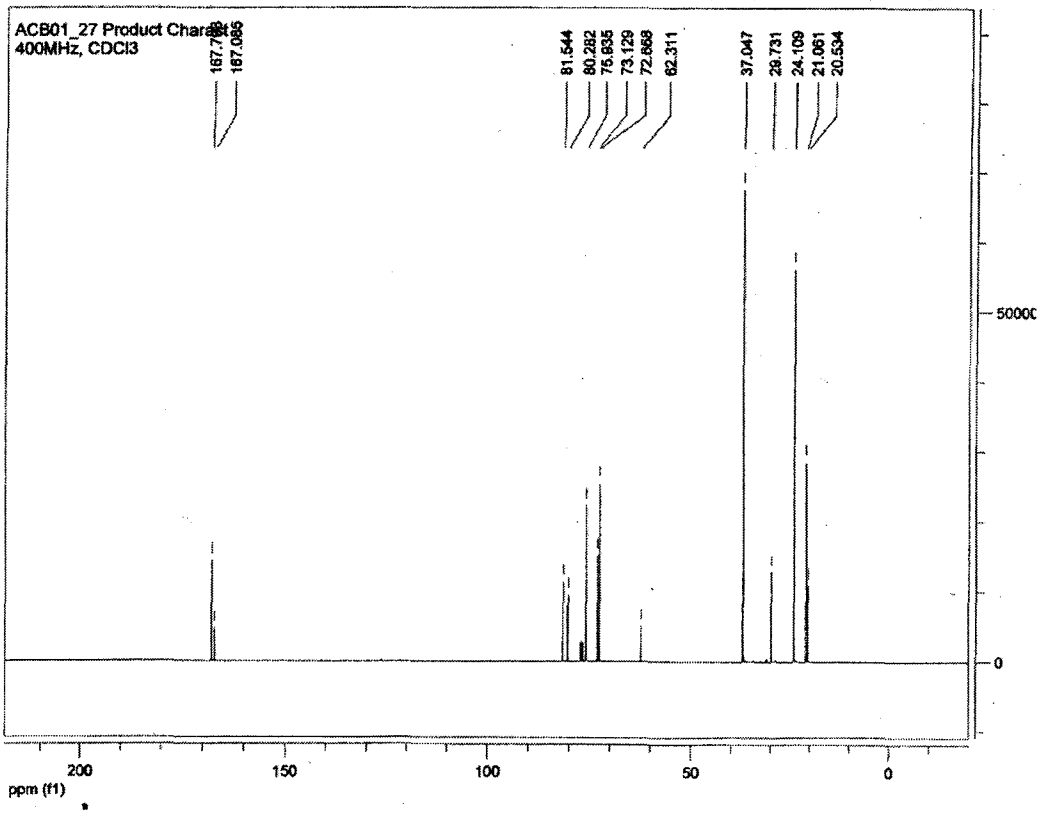
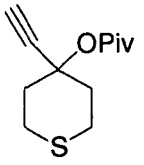
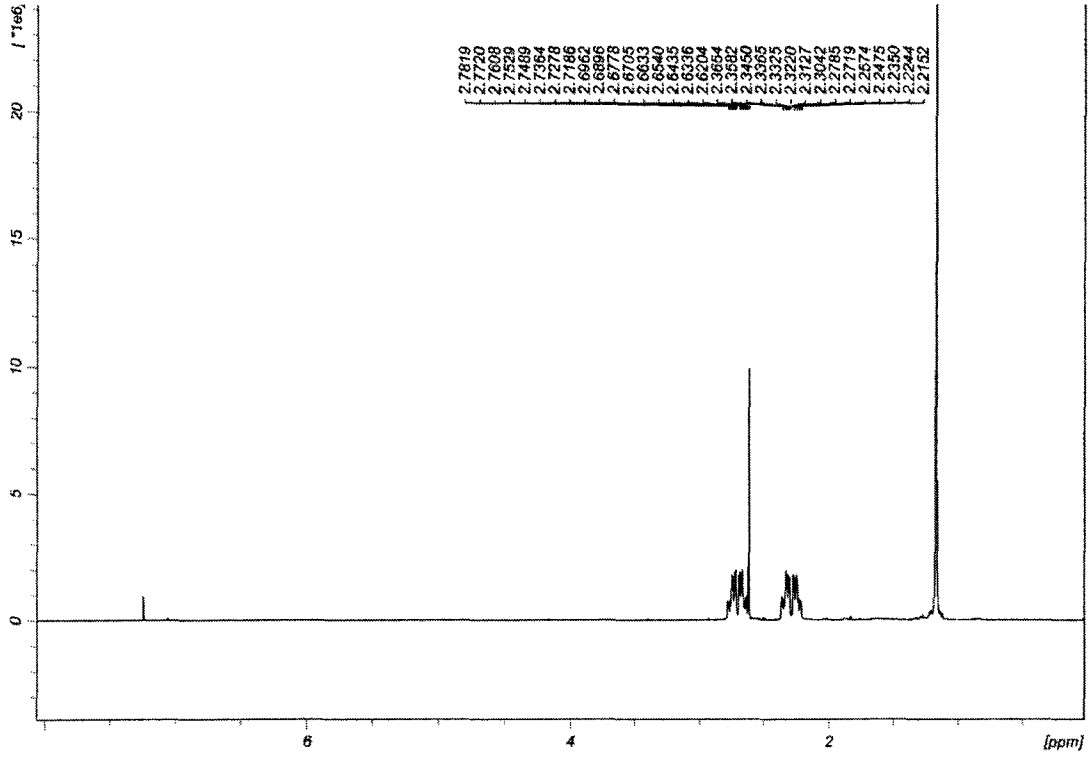
1.825
1.802
1.639
20000
15000
10000
5000
0
5.0
ppm (f1)


ACB01_27 Product Charac
400MHz, CDCl3
167.786
167.085
81.544
80.282
75.635
73.129
72.668
62.311
37.047
29.731
24.109
21.061
20.534
50000
0
200
150
100
50
0
ppm (f1)


OPiv
S

4.40b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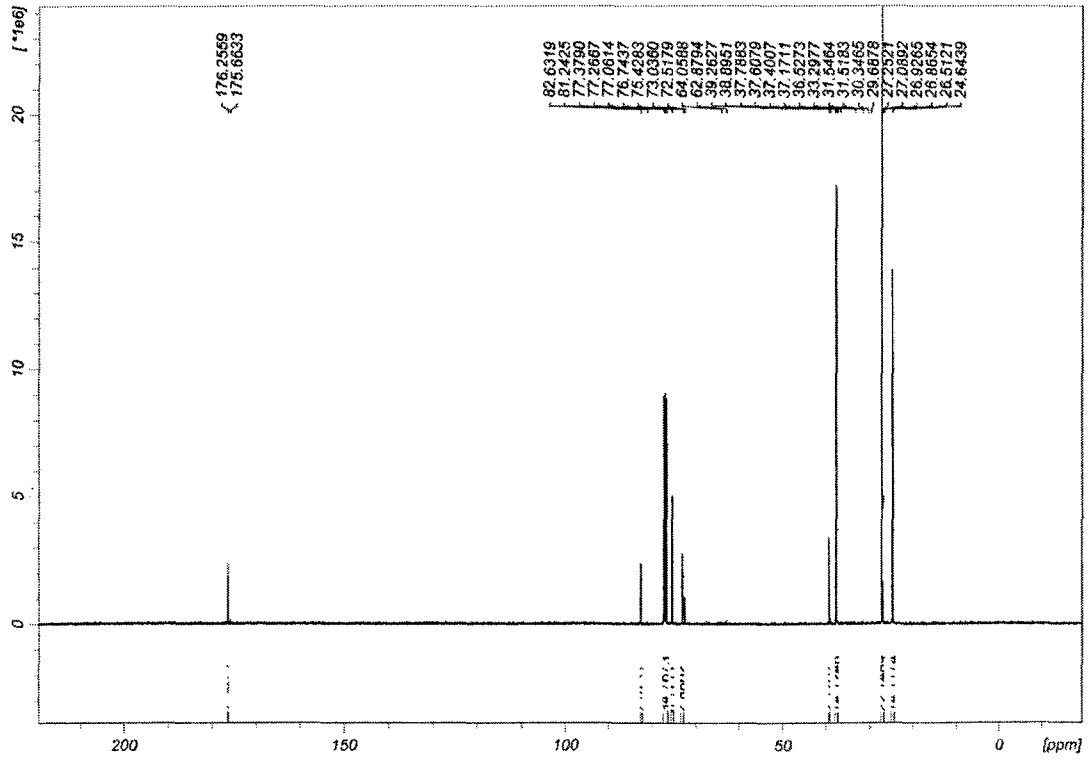
2.7529
2.7489
2.7364
2.7278
2.7186
2.6962
2.6896
2.6778
2.6705
2.6633
2.6540
2.6435
2.6336
2.6204
2.3654
2.3582
2.3450
2.3365
2.3325
2.3220
2.3127
2.3042
2.2785
2.2719
2.2574
2.2475
2.2350
2.2244
2.2152
[ppm]


[*1e6]
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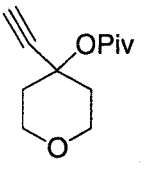
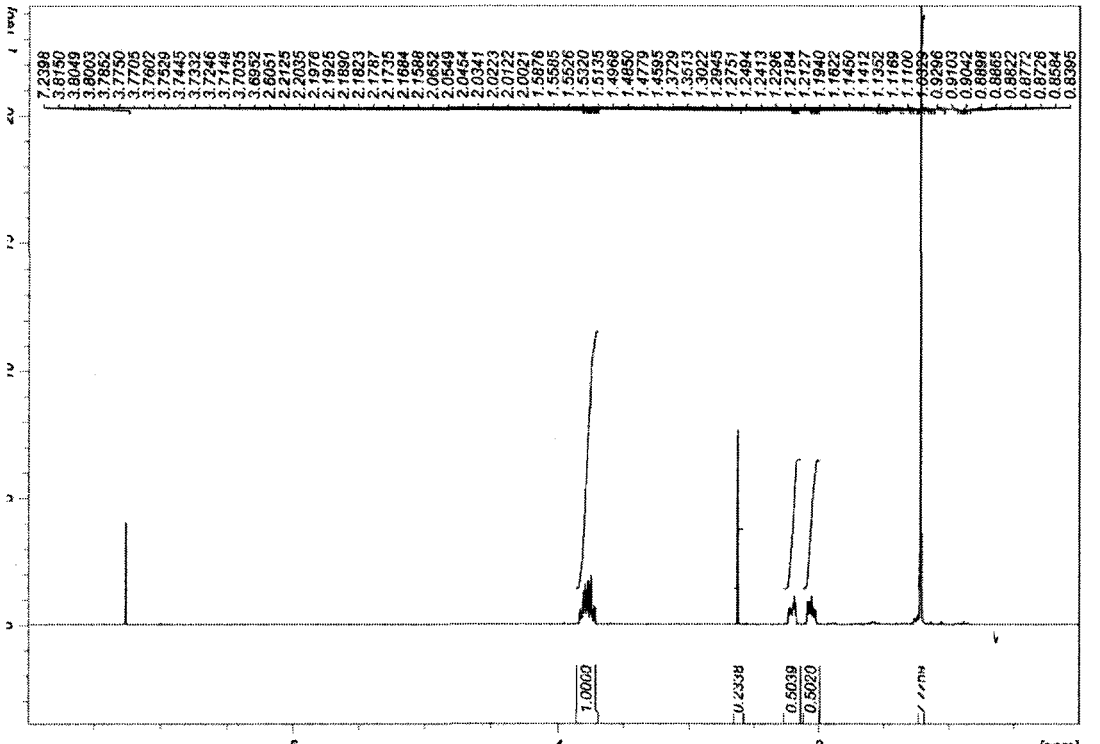
175.8633
82.6319
81.2425
77.3790
77.2687
77.0614
76.7437
76.4263
73.0360
72.5179
64.0588
62.8794
39.2627
38.8951
37.7883
37.6079
37.4007
37.1711
36.5273
33.2977
31.5464
31.5183
30.3465
29.6578
27.2327
27.0892
26.9265
26.8654
26.5121
24.6439
[ppm]


OPiv
O

4.40c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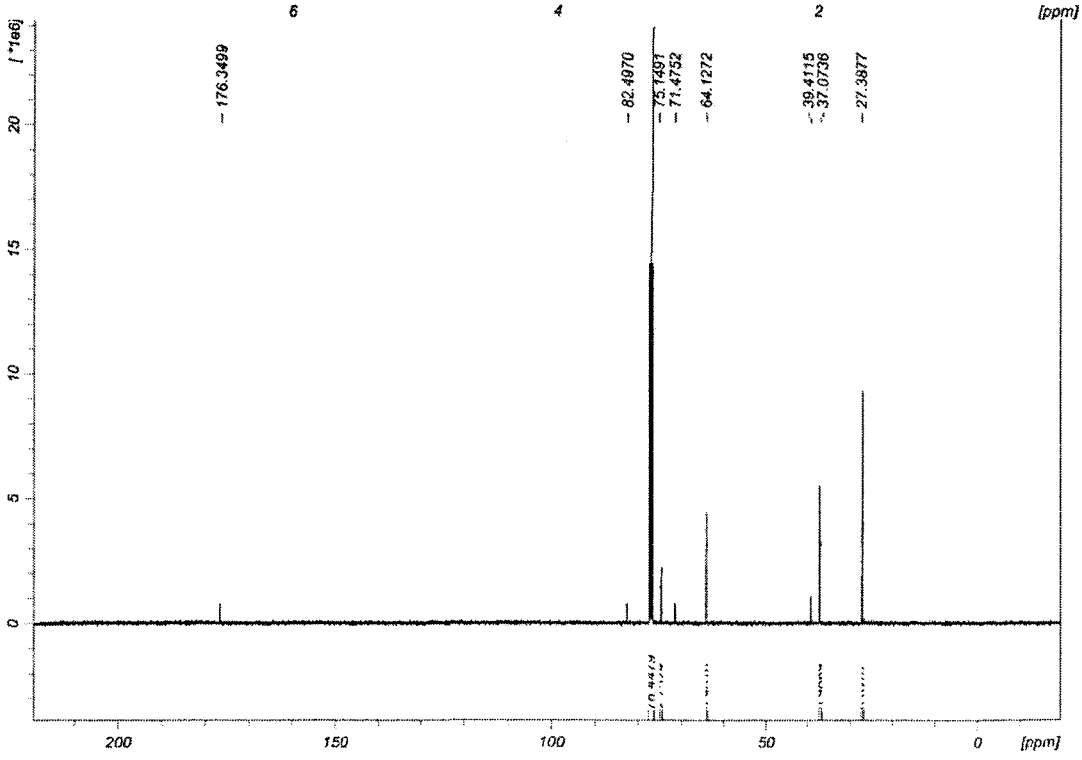
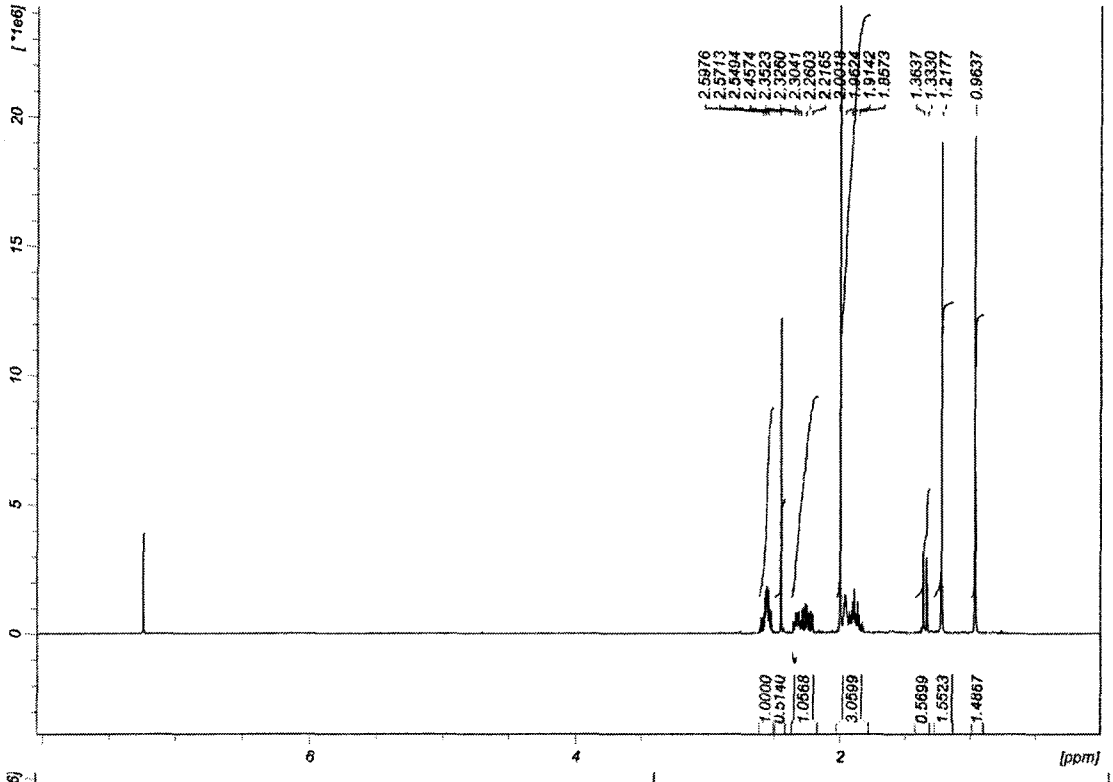
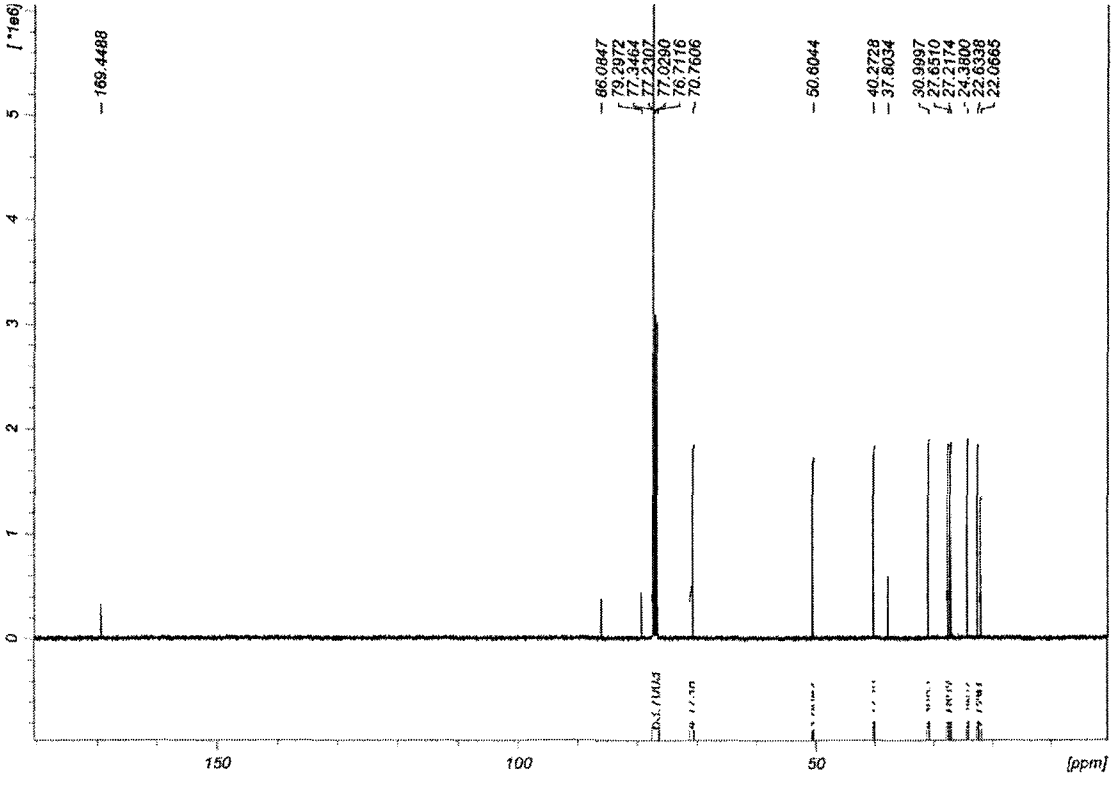
3.8049
3.8003
3.7852
3.7750
3.7705
3.7602
3.7529
3.7445
3.7332
3.7246
3.7149
3.7035
3.6952
2.6051
2.2125
2.2035
2.1976
2.1925
2.1890
2.1823
2.1787
2.1735
2.1684
2.1588
2.0652
2.0549
2.0454
2.0341
2.0223
2.0122
2.0021
1.5876
1.5585
1.5526
1.5320
1.5135
1.4968
1.4850
1.4779
1.4595
1.3729
1.3513
1.3022
1.2845
1.2751
1.2494
1.2413
1.2296
1.2184
1.2127
1.1940
1.1822
1.1450
1.1412
1.1352
1.1169
1.1100
0.9296
0.9103
0.9042
0.8898
0.8865
0.8822
0.8772
0.8726
0.8584
0.8395
1.0000
0.2338
0.5039
0.5020
6
4
2
[ppm]

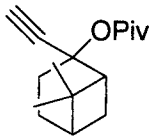

176.3499
82.4970
75.1491
71.4752
64.1272
39.4115
37.0736
27.3877
[*1e6]
200
150
100
50
0
[ppm]


OAc

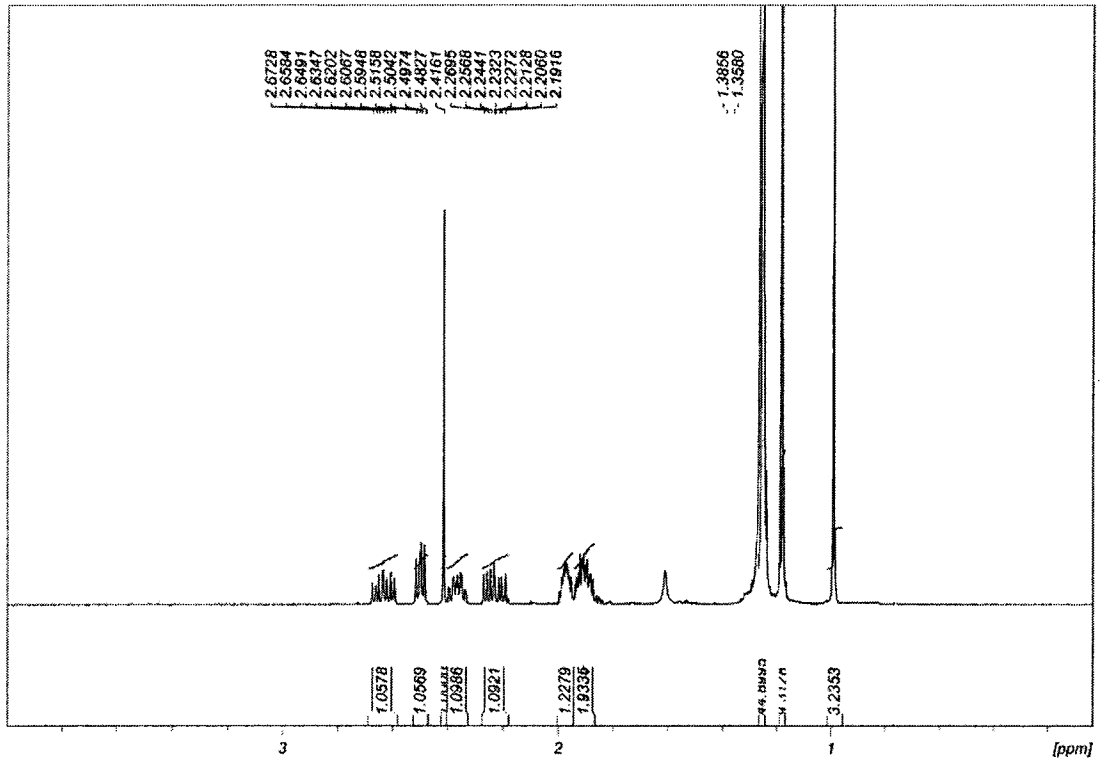
4.40d$_2$

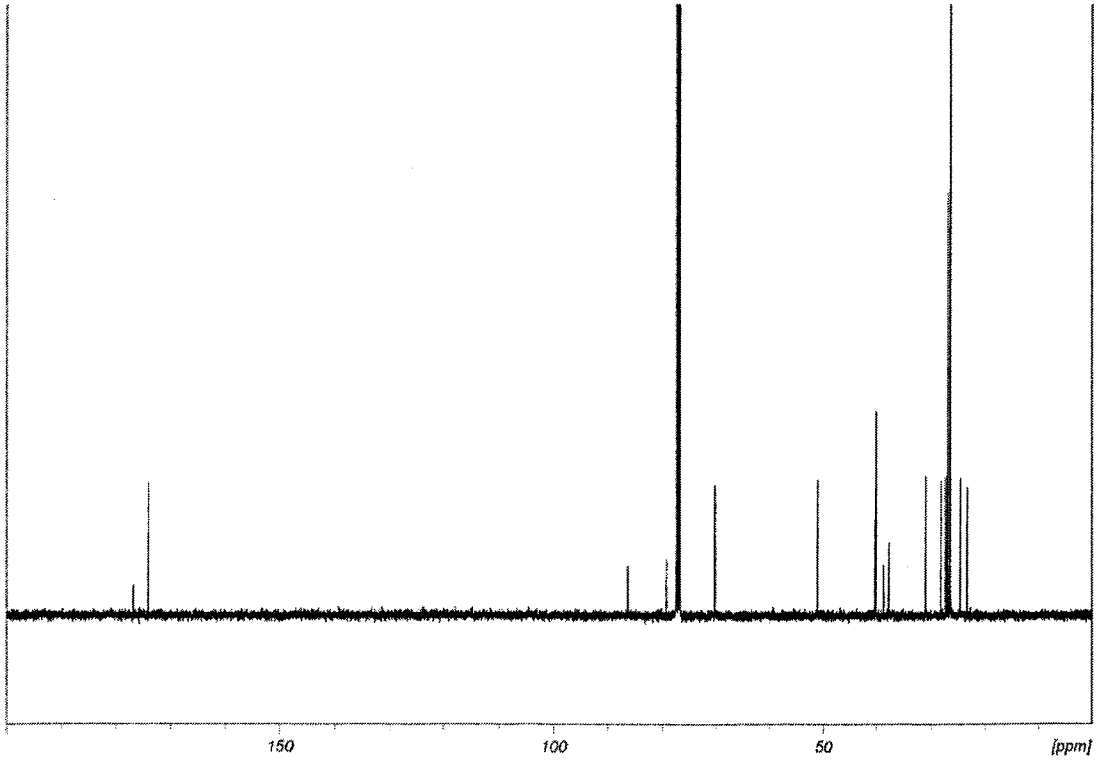

[*1e6]
2.5976
2.5713
2.5404
2.4574
2.3523
2.3260
2.3041
2.2603
2.2165
2.0018
1.9624
1.9142
1.8573
1.3637
1.3330
1.2177
0.9637
1.0000
0.5140
1.0568
3.0599
0.5699
1.5523
1.4867
[ppm]

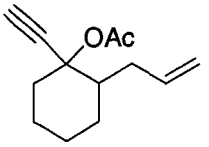

[*1e6]
169.4488
86.0847
79.2972
77.3464
77.2307
77.0290
76.7116
70.7606
50.8044
40.2728
37.8034
30.9997
27.6510
27.2174
24.3800
22.6338
22.0665
[ppm]


OPiv

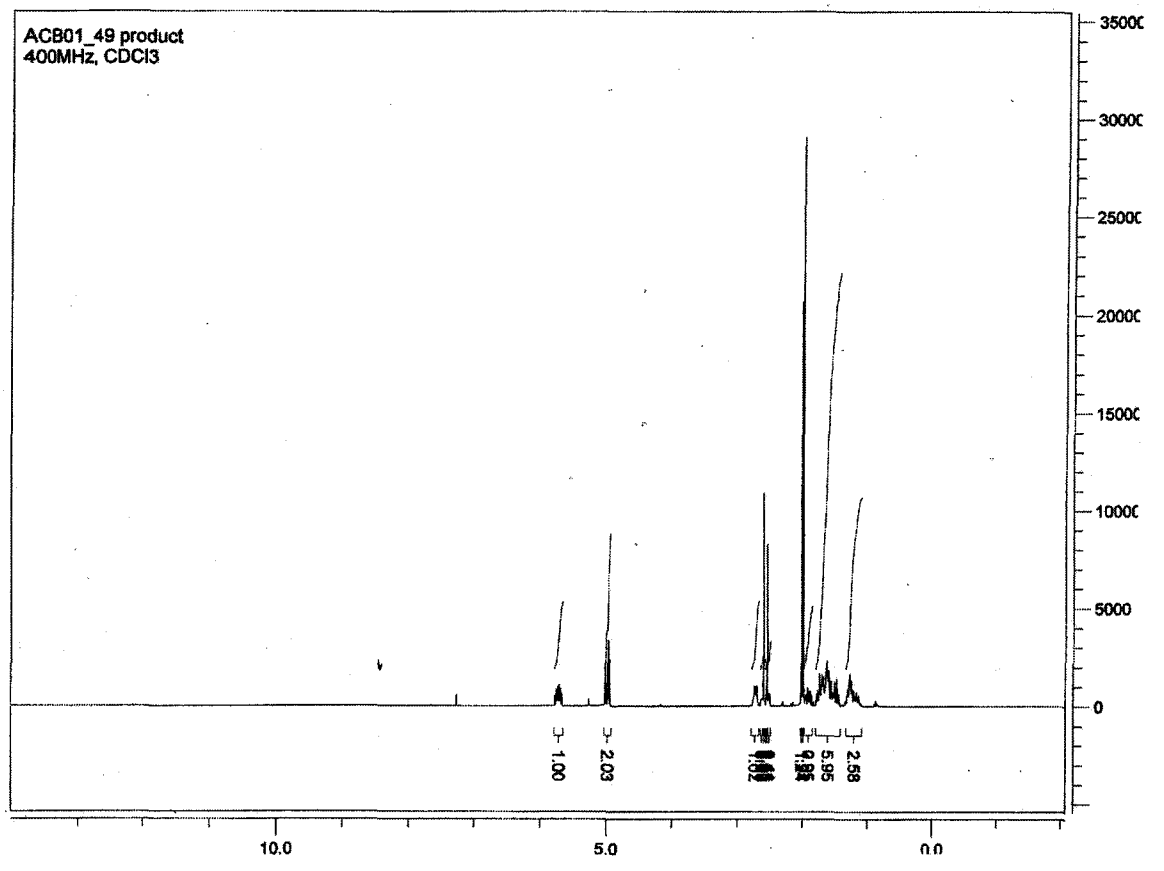
4.40d


2.6728
2.6584
2.6491
2.6347
2.6202
2.6067
2.5948
2.5158
2.5042
2.4974
2.4827
2.4161
2.2695
2.2566
2.2441
2.2323
2.2272
2.2128
2.2060
2.1916
1.3856
1.3580
1.0578
1.0569
1.0988
1.0921
1.2279
1.9336
3.2353
3
2
1
[ppm]


150
100
50
[ppm]


OAc

4.40g


ACB01_49 product
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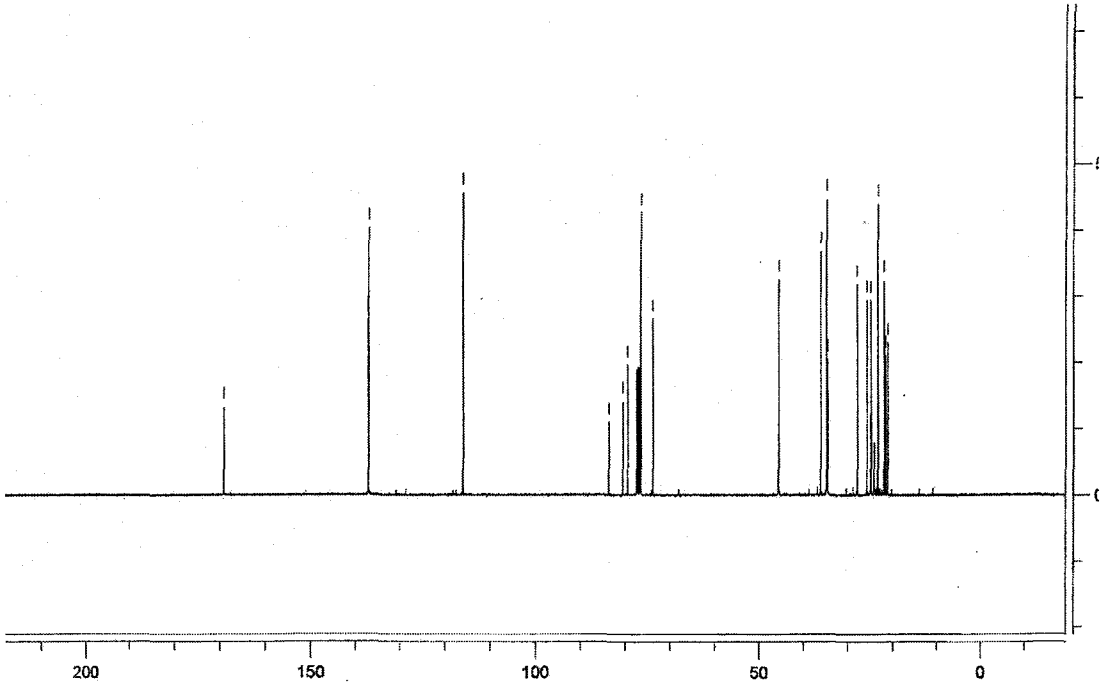
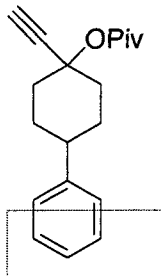
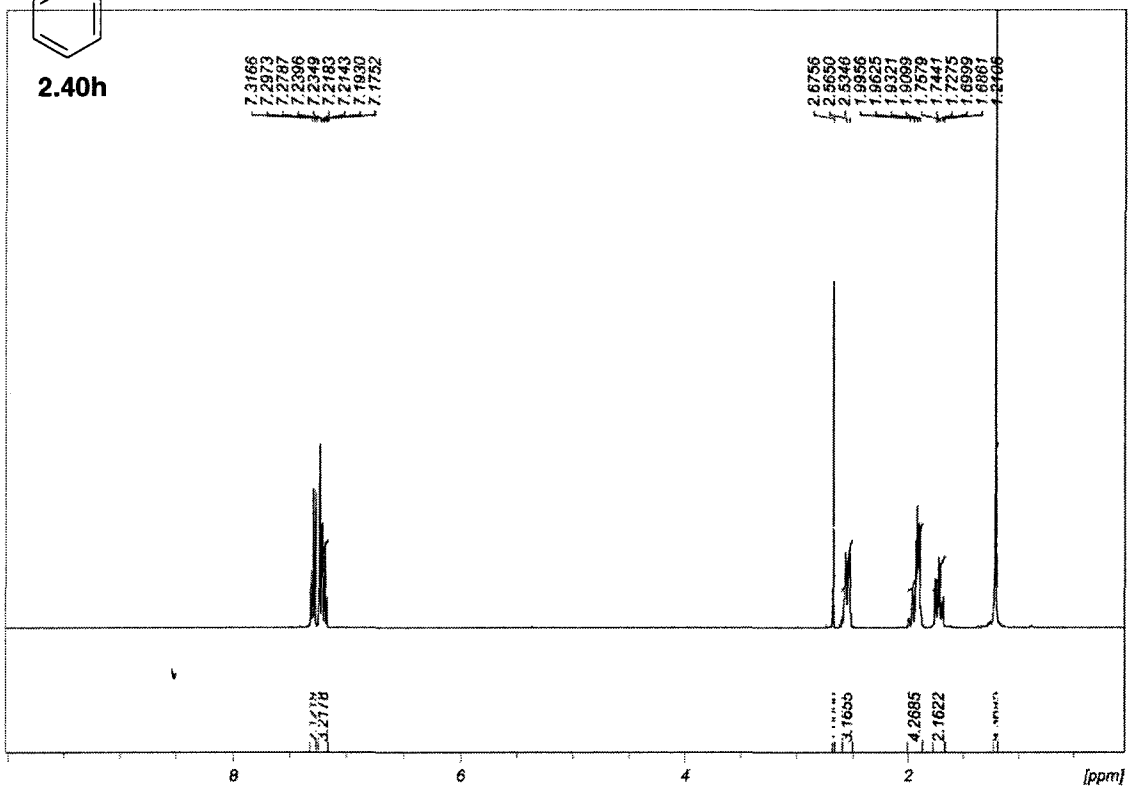
2.03
5.95
2.58
10.0
5.0


200
150
100
50
0


OPiv

2.40h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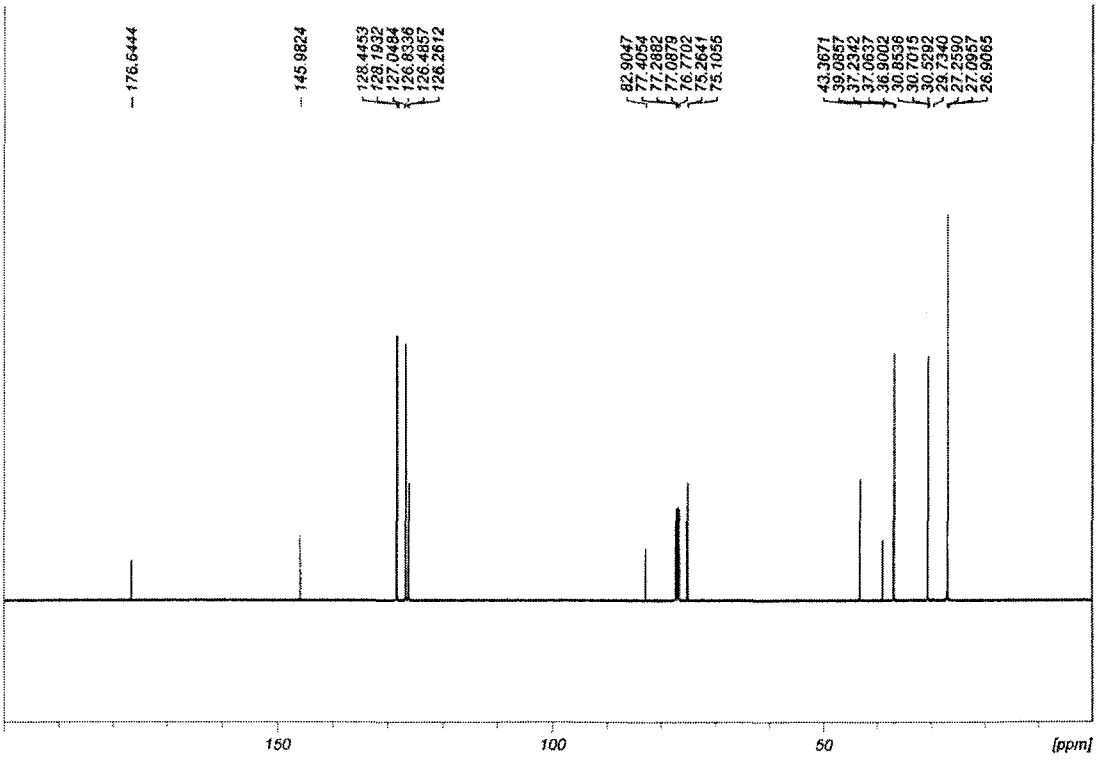
7.2973
7.2787
7.2596
7.2349
7.2183
7.2143
7.1930
7.1752
2.6756
2.5650
2.5346
1.9956
1.9625
1.9321
1.9009
1.7579
1.7441
1.7275
1.6999
1.6861
1.2406
4.2718
3.1635
4.2685
2.1622
8
6
4
2
[ppm]


176.6444
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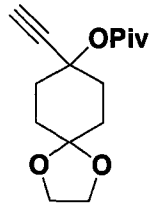
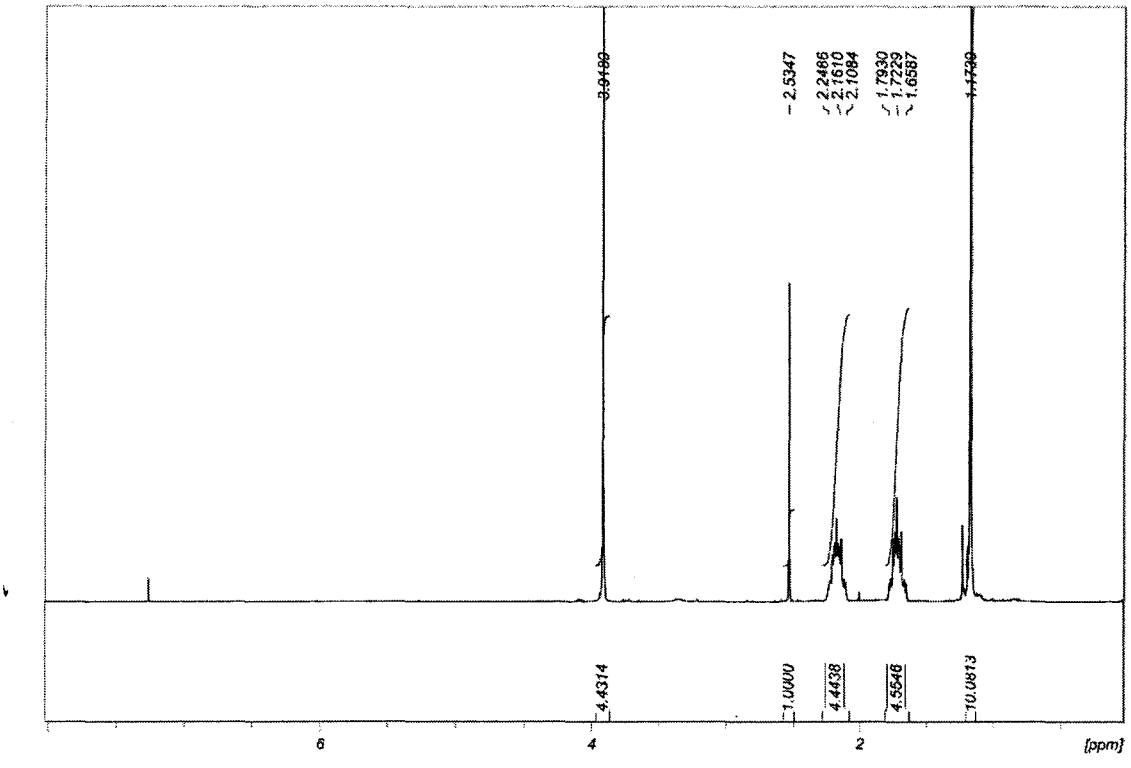
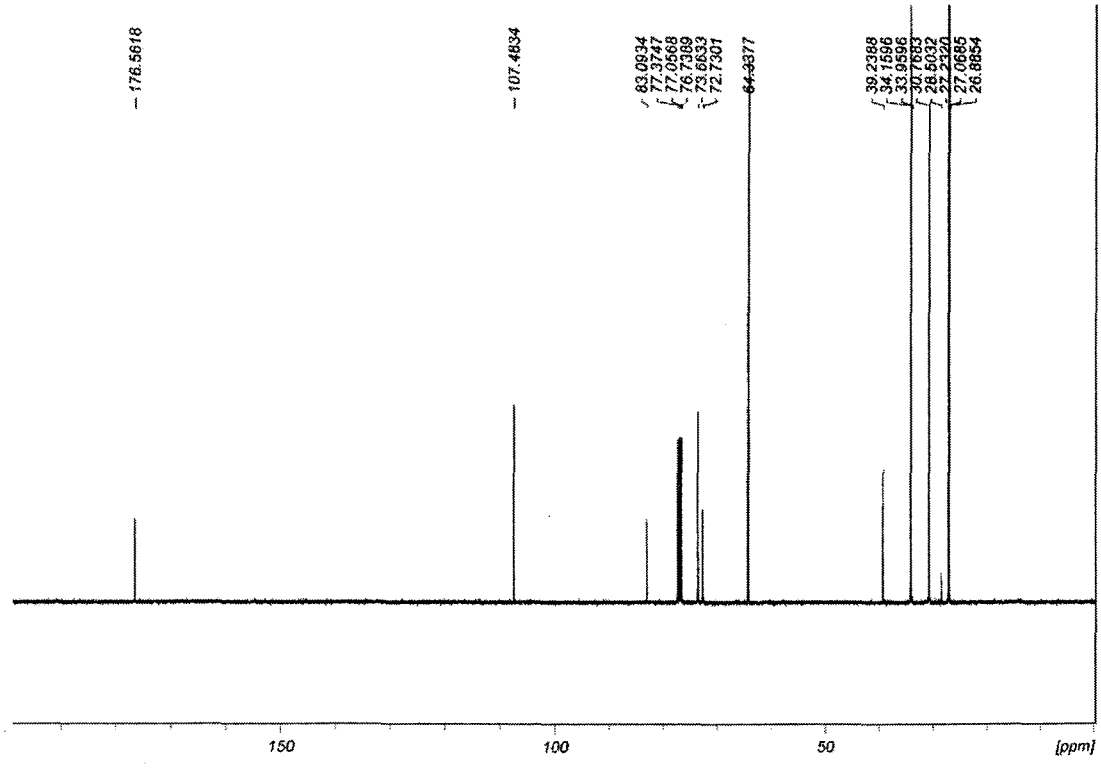
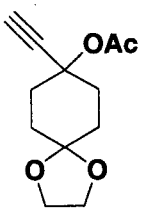
128.4453
128.1932
127.0484
126.8336
126.4857
126.2612
82.9047
77.4054
77.2882
77.0879
76.7702
75.2641
75.1055
43.3671
39.0857
37.2342
37.0637
36.9002
30.8536
30.7015
30.5292
29.7340
27.2590
27.0957
26.9065
150
100
50
[ppm]


OPiv
O
O

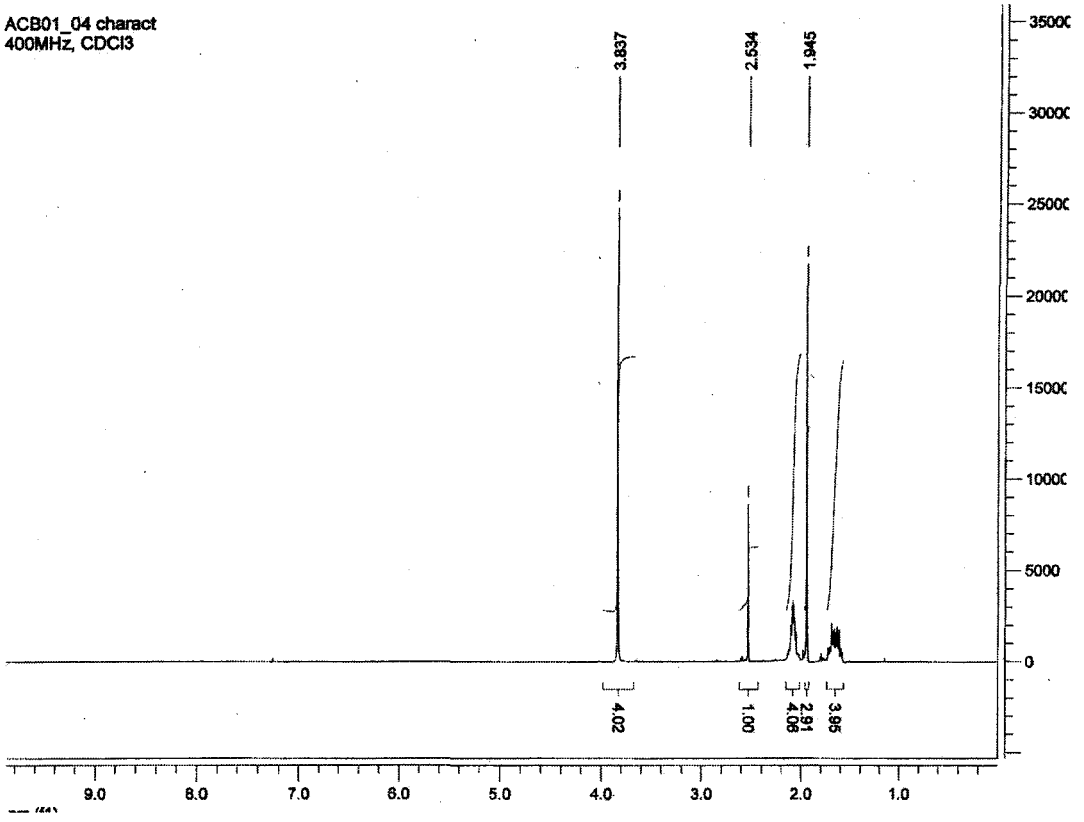
4.40i

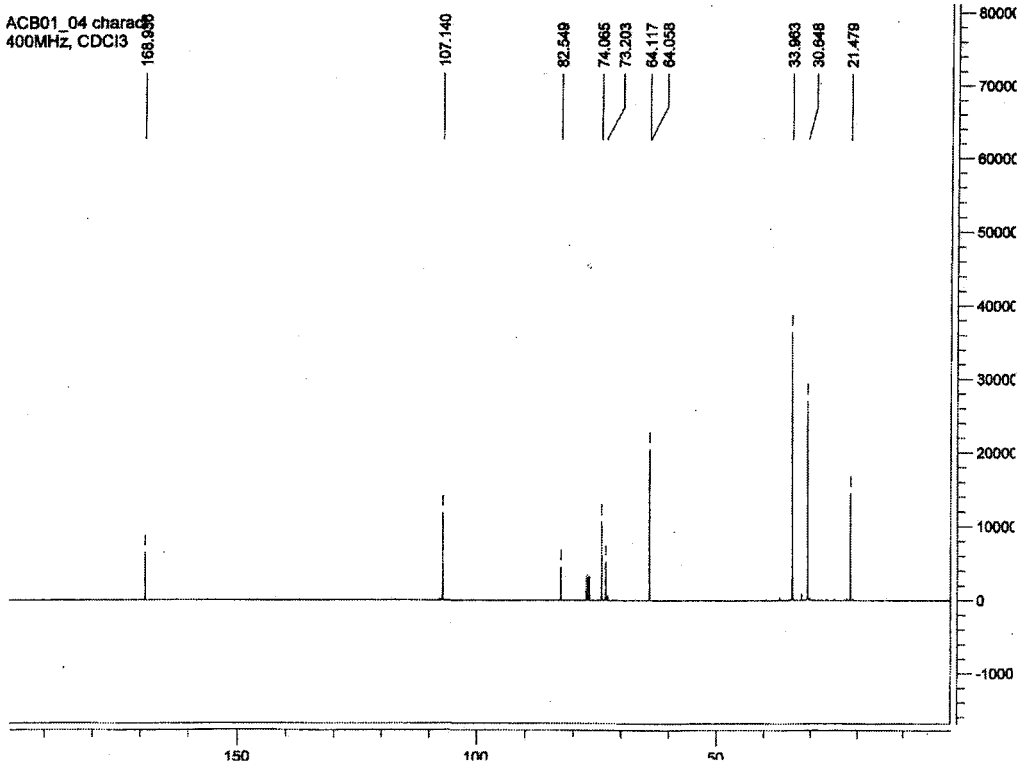

3.0490
2.5347
2.2466
2.1610
2.1084
1.7930
1.7229
1.6587
1.1730
4.4314
1.0000
4.4438
4.5546
10.0813
6
4
2
[ppm]


176.5618
107.4834
83.0934
77.3747
77.0568
76.7389
73.6633
72.7301
64.3377
39.2388
34.1596
33.9596
30.7683
28.5032
27.2320
27.0685
26.8854
150
100
50
[ppm]


OAc
O
O

4.40i$_2$


ACB01_04 charact
400MHz, CDCl3
3.837
2.534
1.945
4.02
1.00
4.08
2.91
3.95
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


ACB01_04 charac
400MHz, CDCl3
168.936
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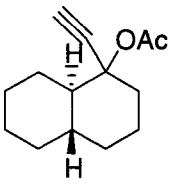
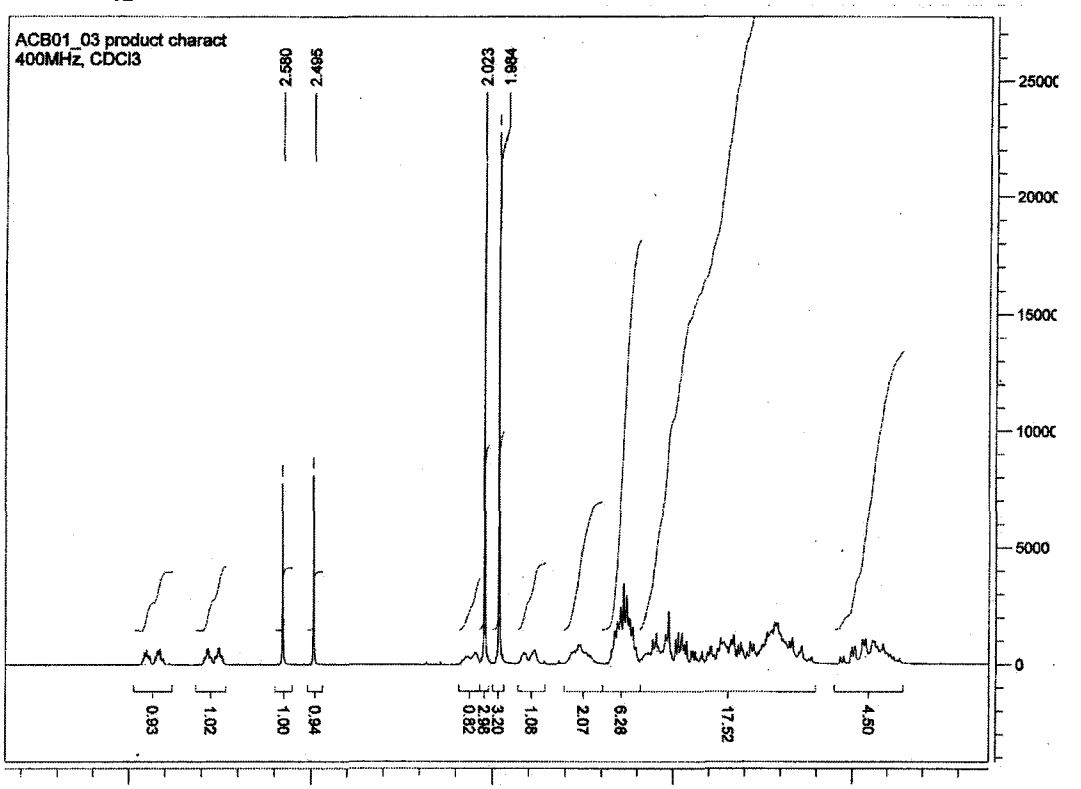
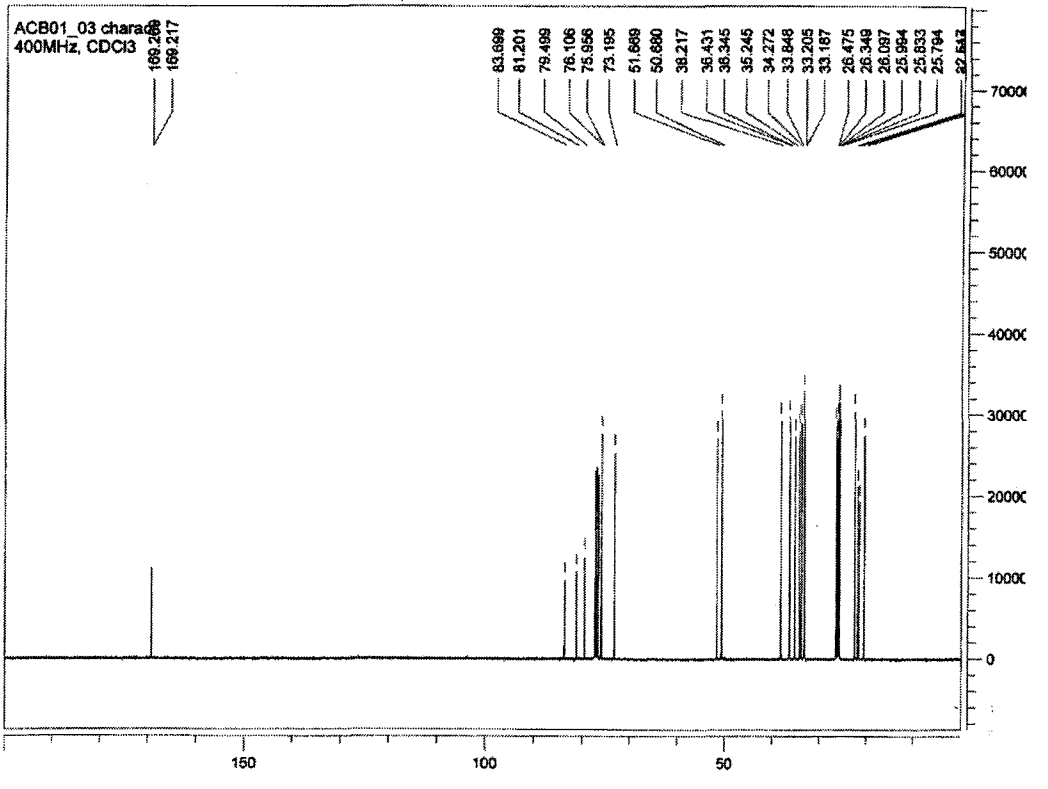
82.549
74.065
73.203
64.117
64.058
33.963
30.648
21.478
150
100
50


OAc
H
H

4.40j$_2$


ACB01_03 product charact
400MHz, CDCl3
2.580
2.495
2.023
1.984
0.83
1.02
1.00
0.94
0.82
2.88
3.20
1.08
2.07
6.28
17.52
4.50
3.00
2.50
2.00
1.50
1.00


ACB01_03 charac
400MHz, CDCl3
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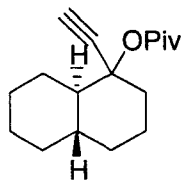
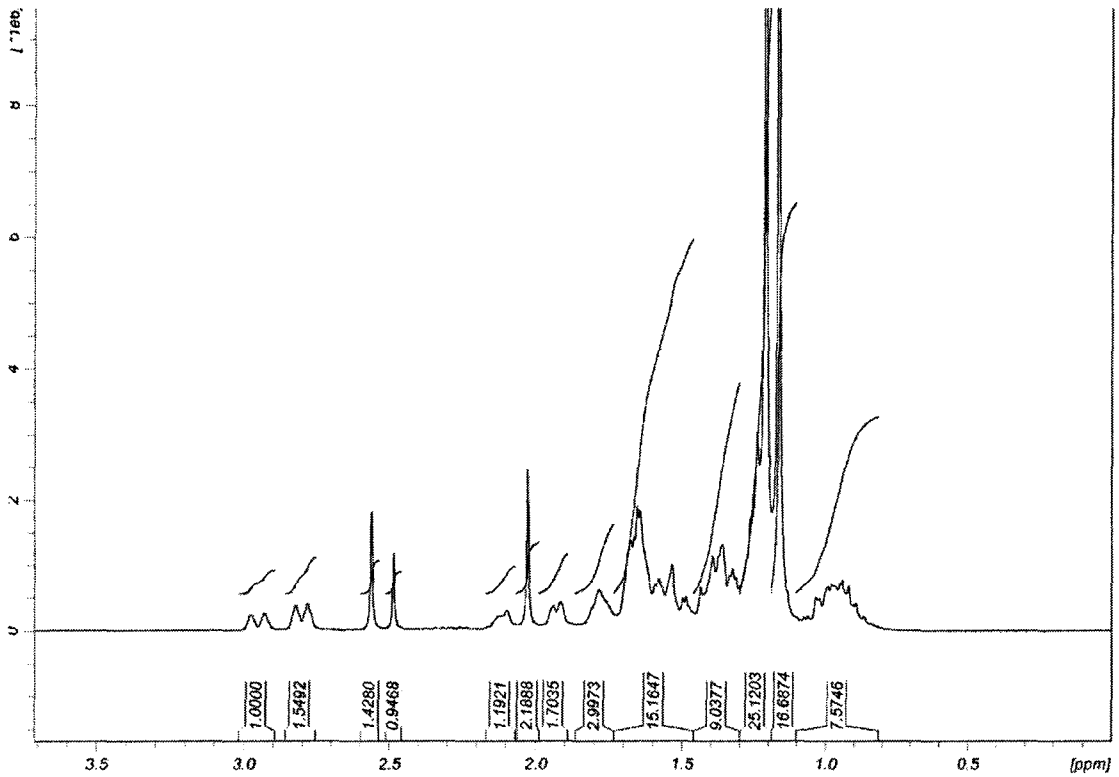
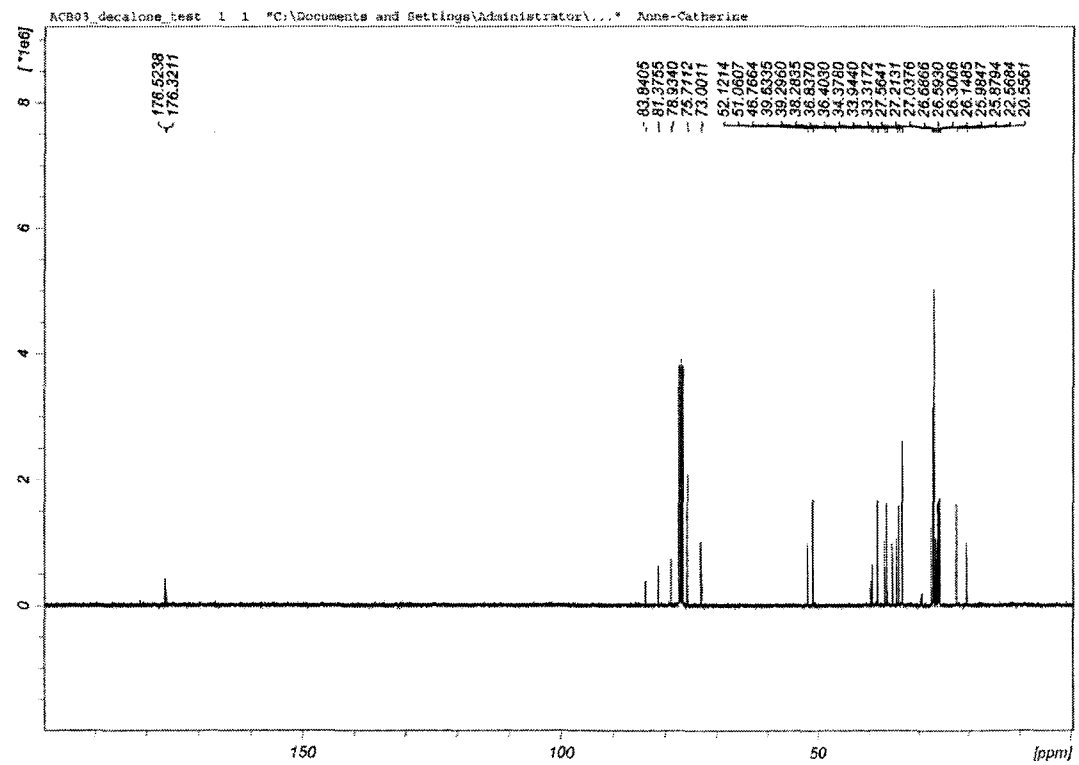
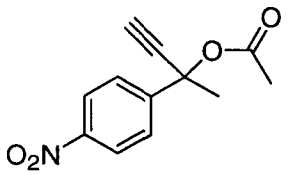
79.499
76.106
75.956
73.195
51.669
50.880
38.217
36.431
36.345
35.245
34.272
33.848
33.205
33.187
26.475
26.349
26.097
25.994
25.833
25.794
150
100
50


OPiv
H
H

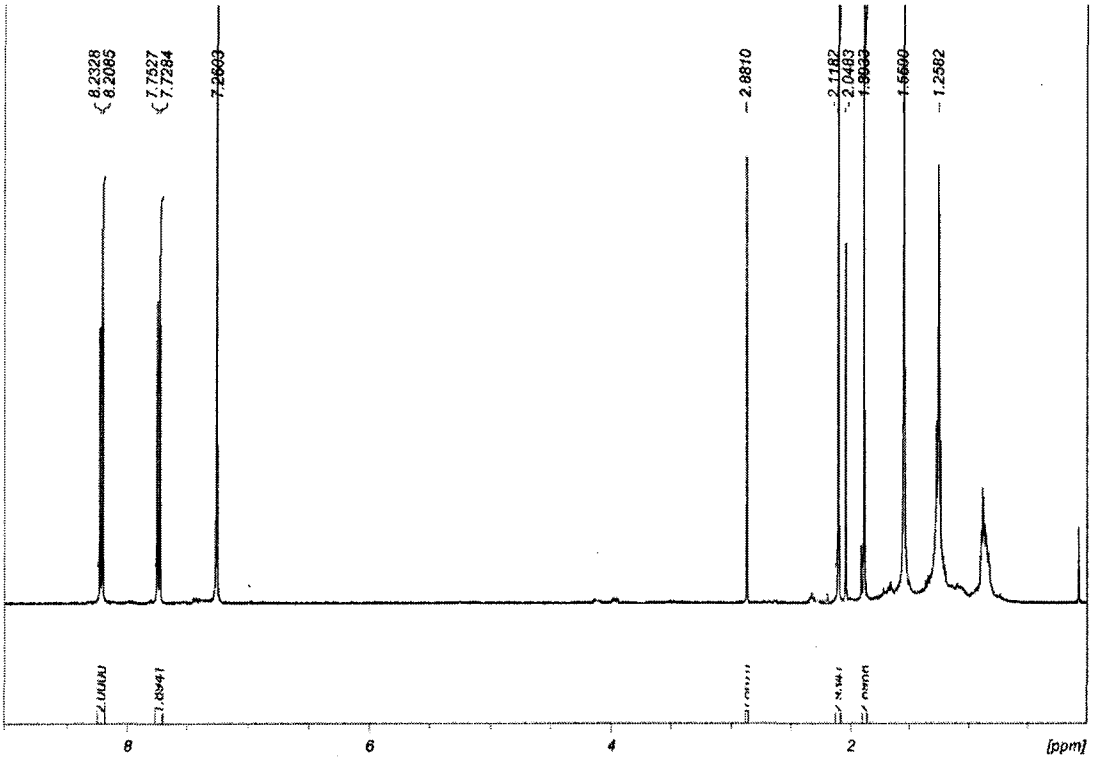
4.40j

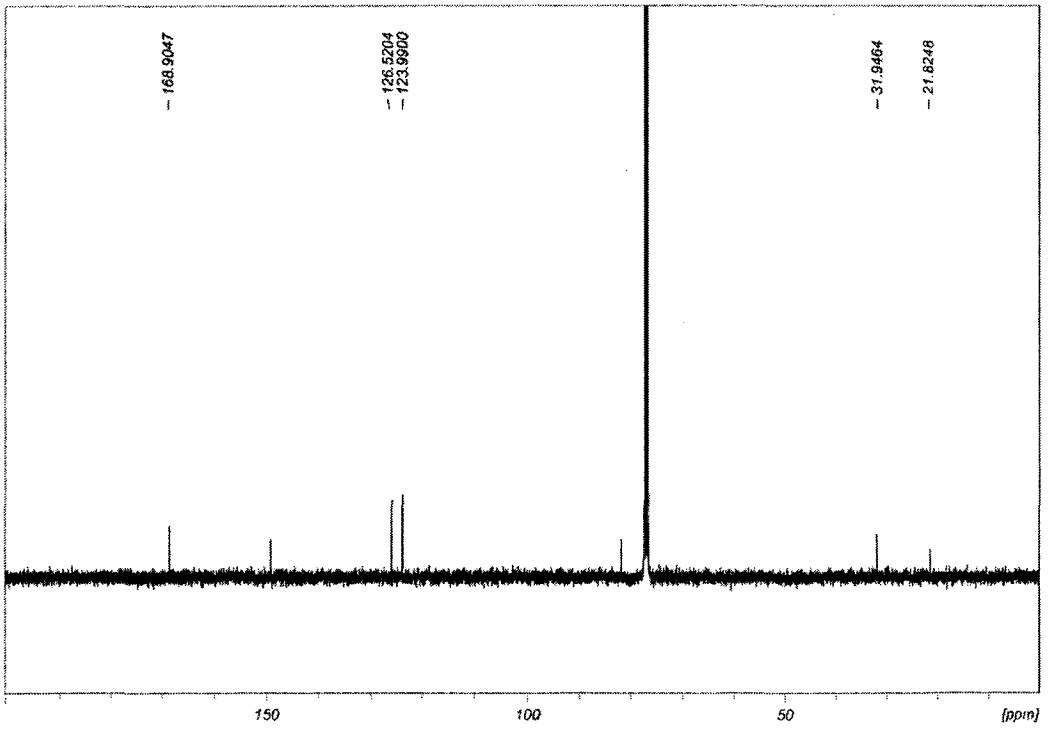

1.0000
1.5492
1.4280
0.9468
1.1921
2.1688
1.7035
2.9973
15.1647
9.0377
25.1203
16.6874
7.5746
3.5
3.0
2.5
2.0
1.5
1.0
0.5
[ppm]

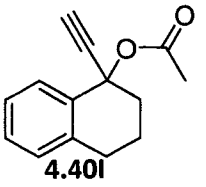

ACB03_decalone_test 1 1 "C:\Documents and Settings\Administrator\...\ Anne-Catherine
176.5238
176.3211
83.8405
81.3755
78.9340
75.7112
73.0011
52.1214
51.0607
46.7664
39.6335
39.2960
38.2835
36.8370
36.4030
34.3780
33.9440
33.3172
27.5641
27.2131
27.0376
26.6866
26.5930
26.3006
26.1485
25.9847
25.8794
22.5684
20.5561
150
100
50
[ppm]



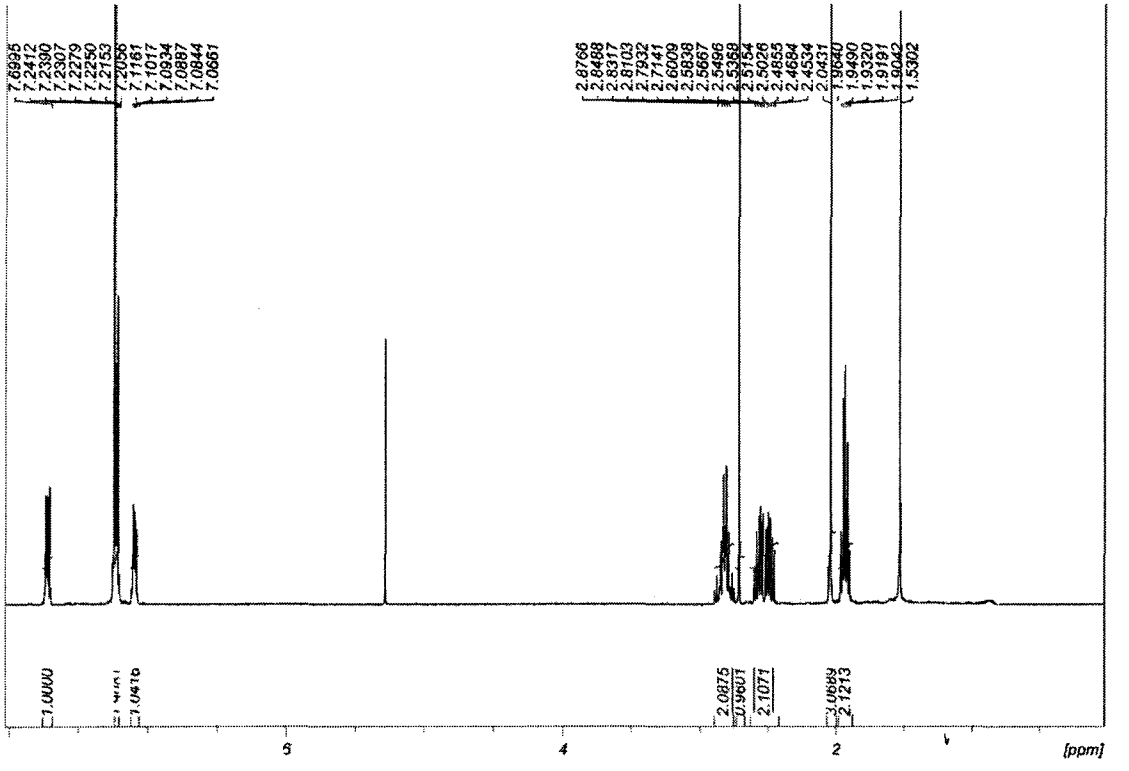
4.40k


8.2328
8.2085
7.7527
7.7284
7.2603
2.8810
2.1182
2.0483
1.5600
1.2582
8
6
4
2
[ppm]


168.9047
126.5204
123.9900
31.9464
21.8248
150
100
50
[ppm]



4.40l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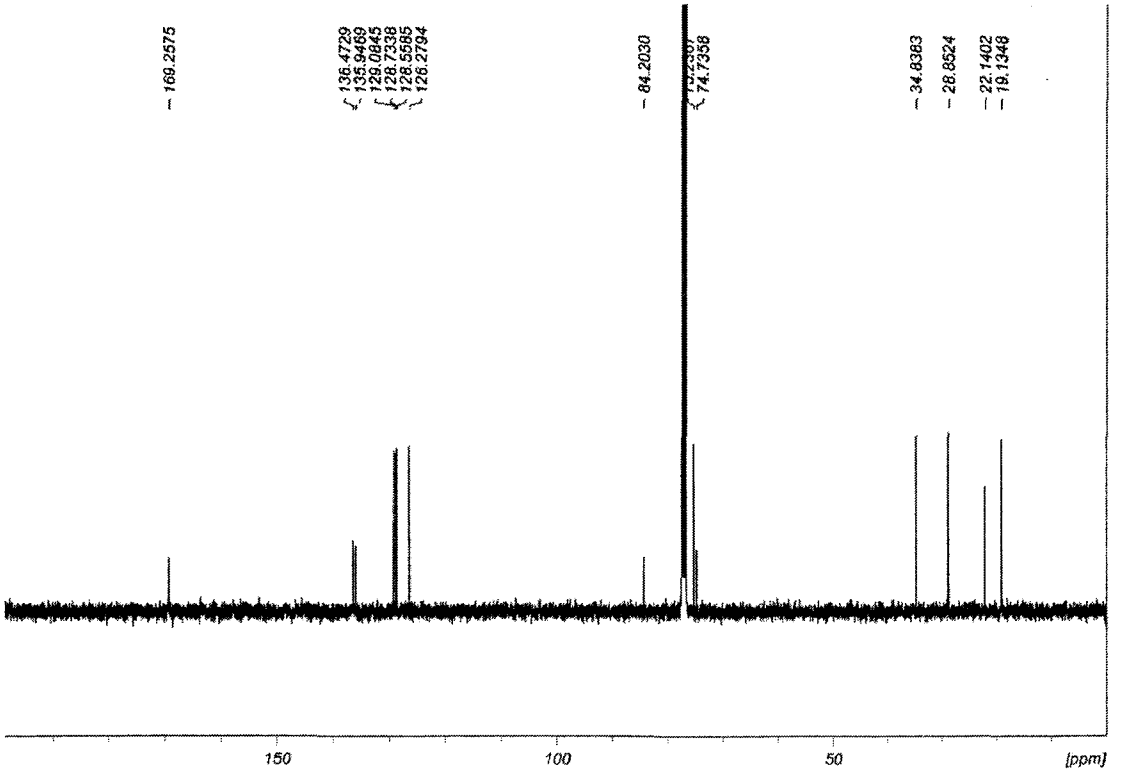
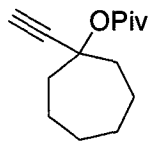
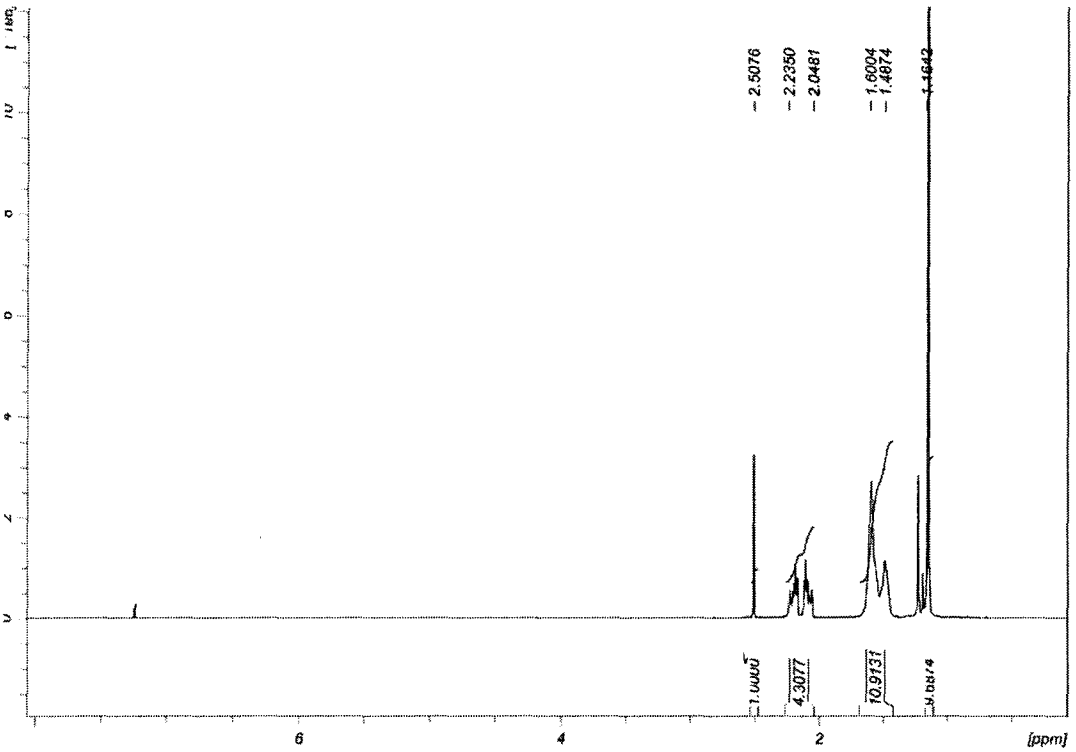
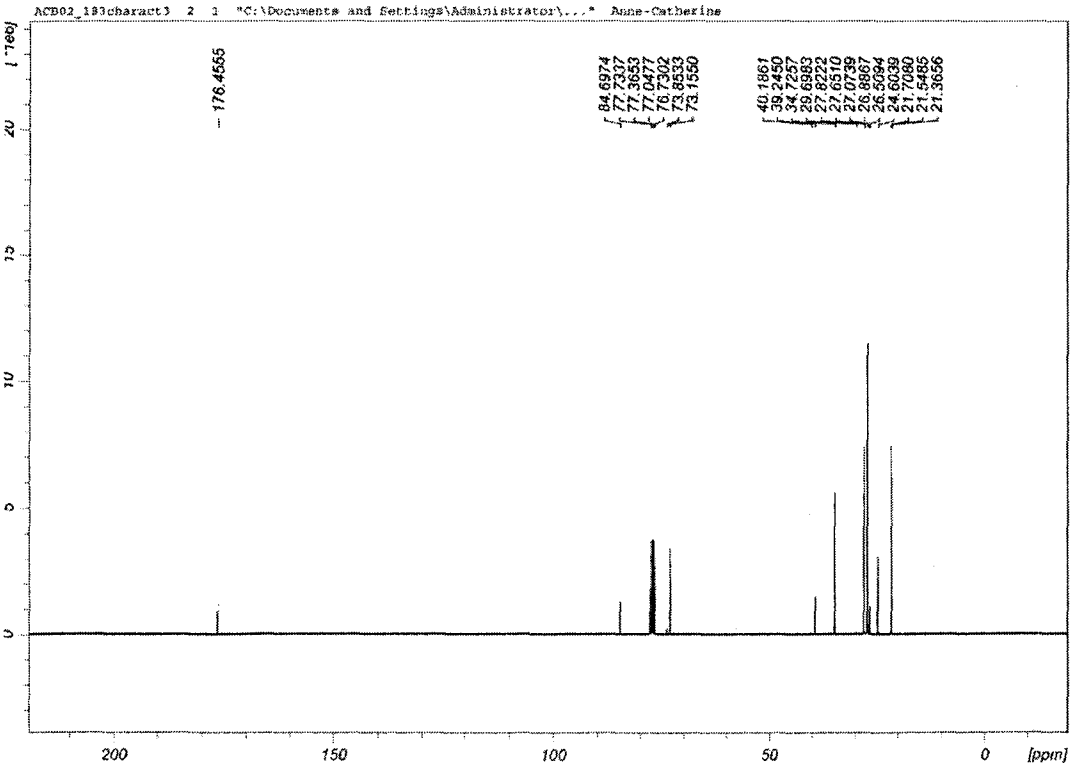
7.2412
7.2390
7.2307
7.2279
7.2250
7.2153
7.2056
7.1161
7.1017
7.0934
7.0887
7.0844
7.0661
2.8766
2.8488
2.8317
2.8103
2.7932
2.7141
2.6009
2.5838
2.5667
2.5496
2.5368
2.5154
2.5026
2.4855
2.4684
2.4534
2.0431
1.9540
1.9490
1.9320
1.9191
1.9042
1.5302
1.0000
1.0476
2.0875
0.9607
2.1071
3.0889
2.1213
5
4
2
[ppm]


169.2575
136.4729
135.9469
129.0845
128.7338
128.5585
126.2794
84.2030
74.7358
34.8383
28.8524
22.1402
19.1346
150
100
50
[ppm]


OPiv

4.40m$_2$


2.5076
2.2350
2.0481
1.6004
1.4674
1.1642
1.0000
4.3077
10.9131
6
4
2
[ppm]


ACB02_183charact3 2 1 "C:\Documents and Settings\Administrator\..." Anne-Catherine
176.4555
84.6974
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77.3653
77.0477
76.7302
73.8533
73.1550
40.1861
39.2450
34.7257
29.6983
27.8222
27.6510
27.0739
26.8867
26.5094
24.6038
21.7080
21.5485
21.3656
200
150
100
50
0
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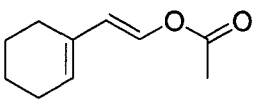
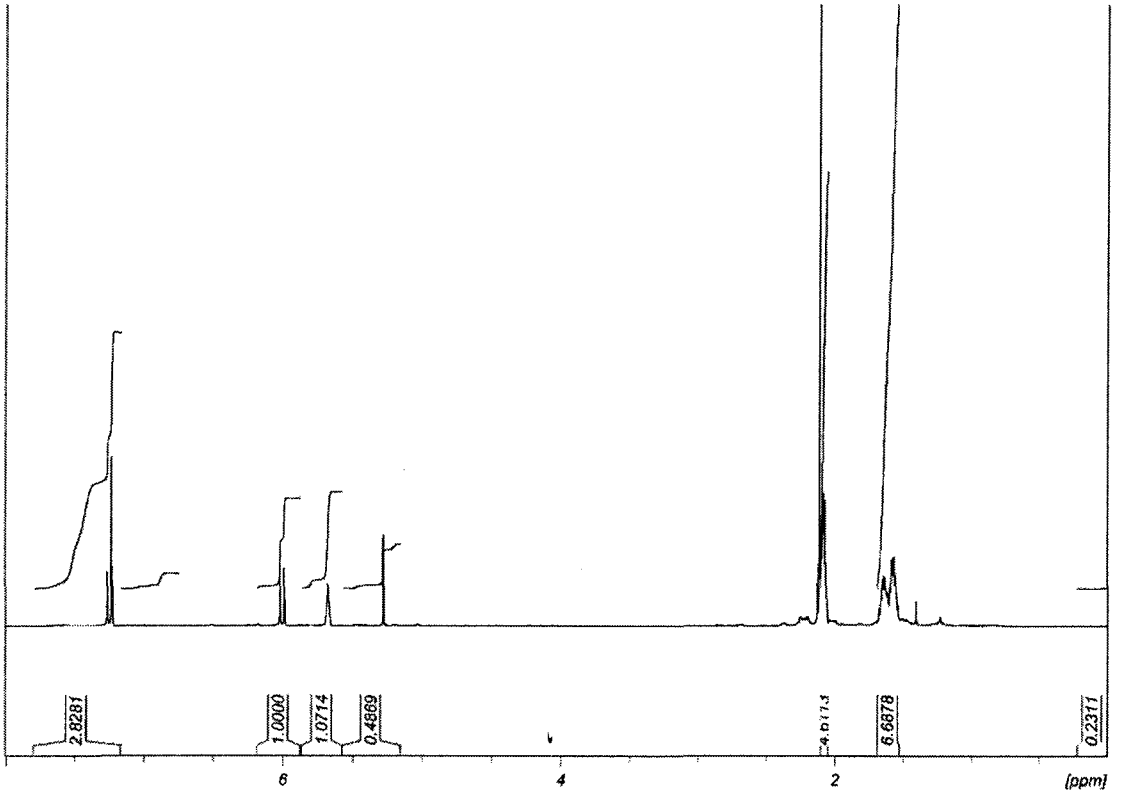
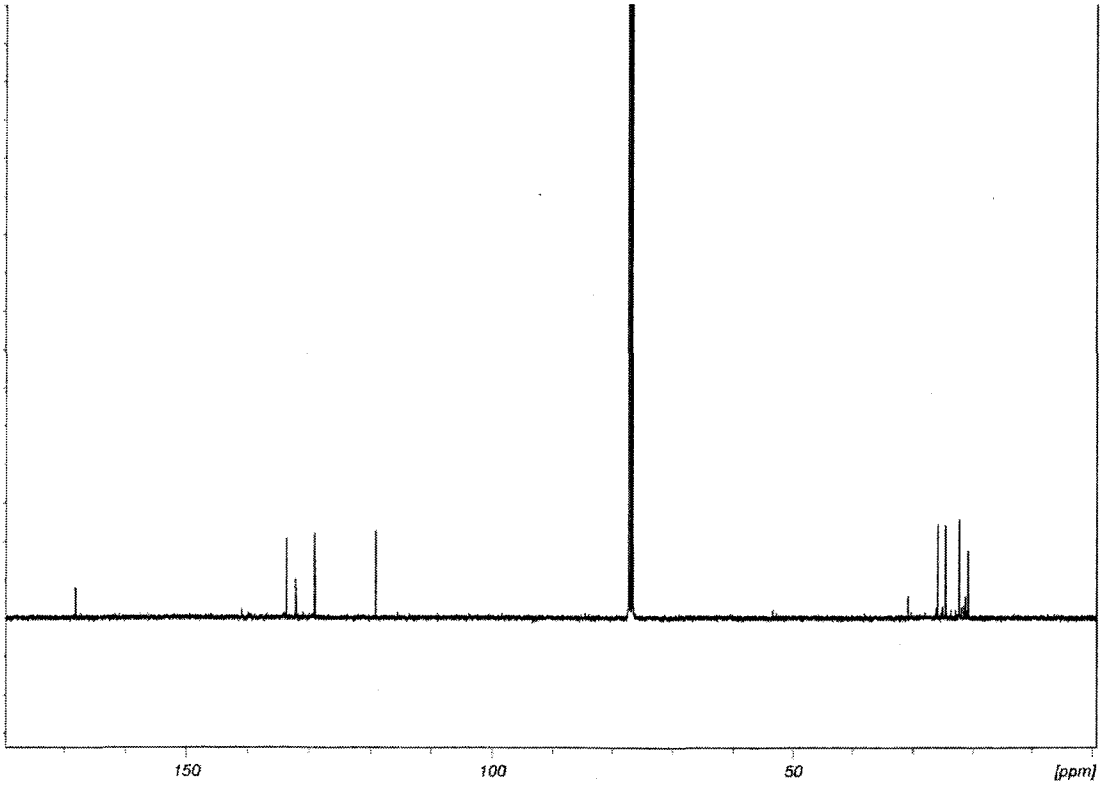
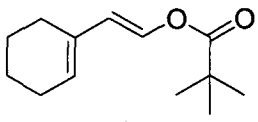


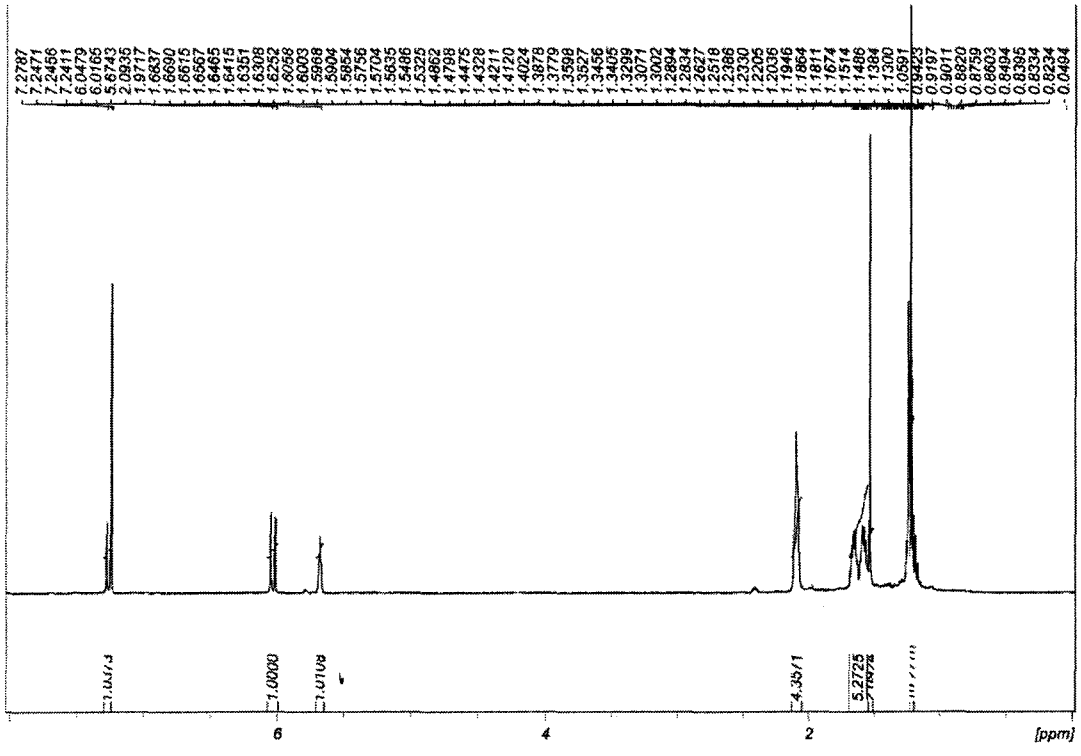
4.29a







4.29b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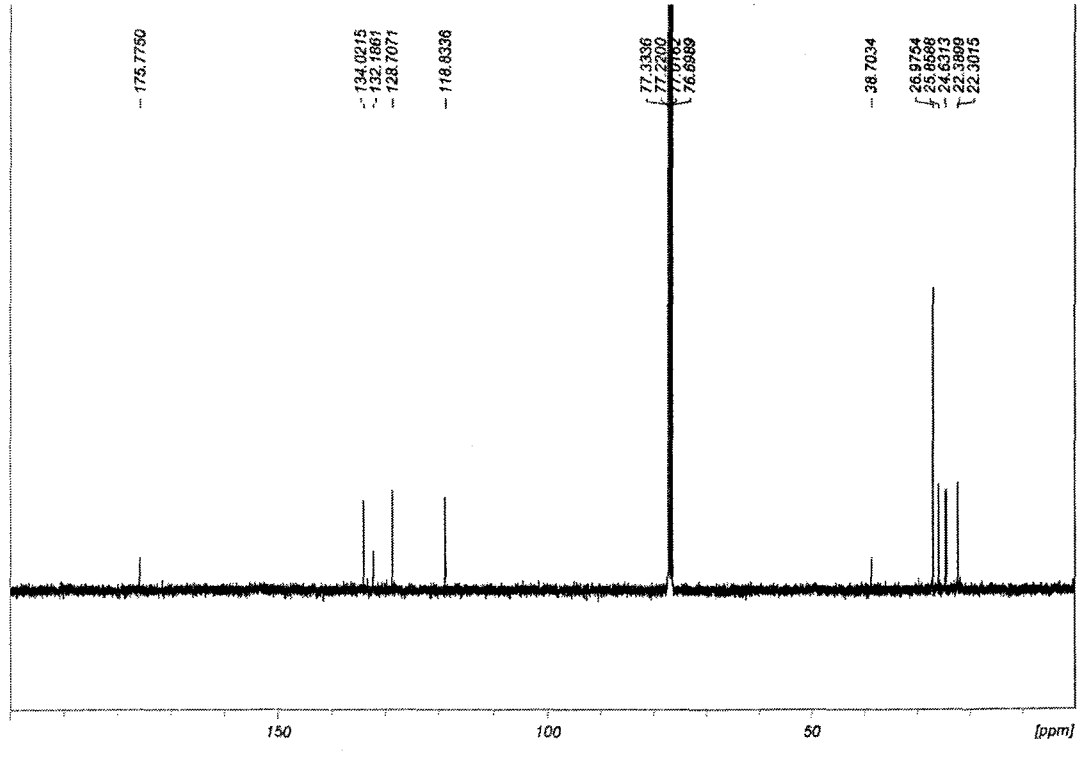
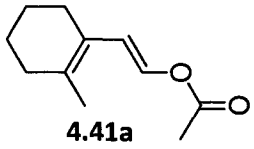
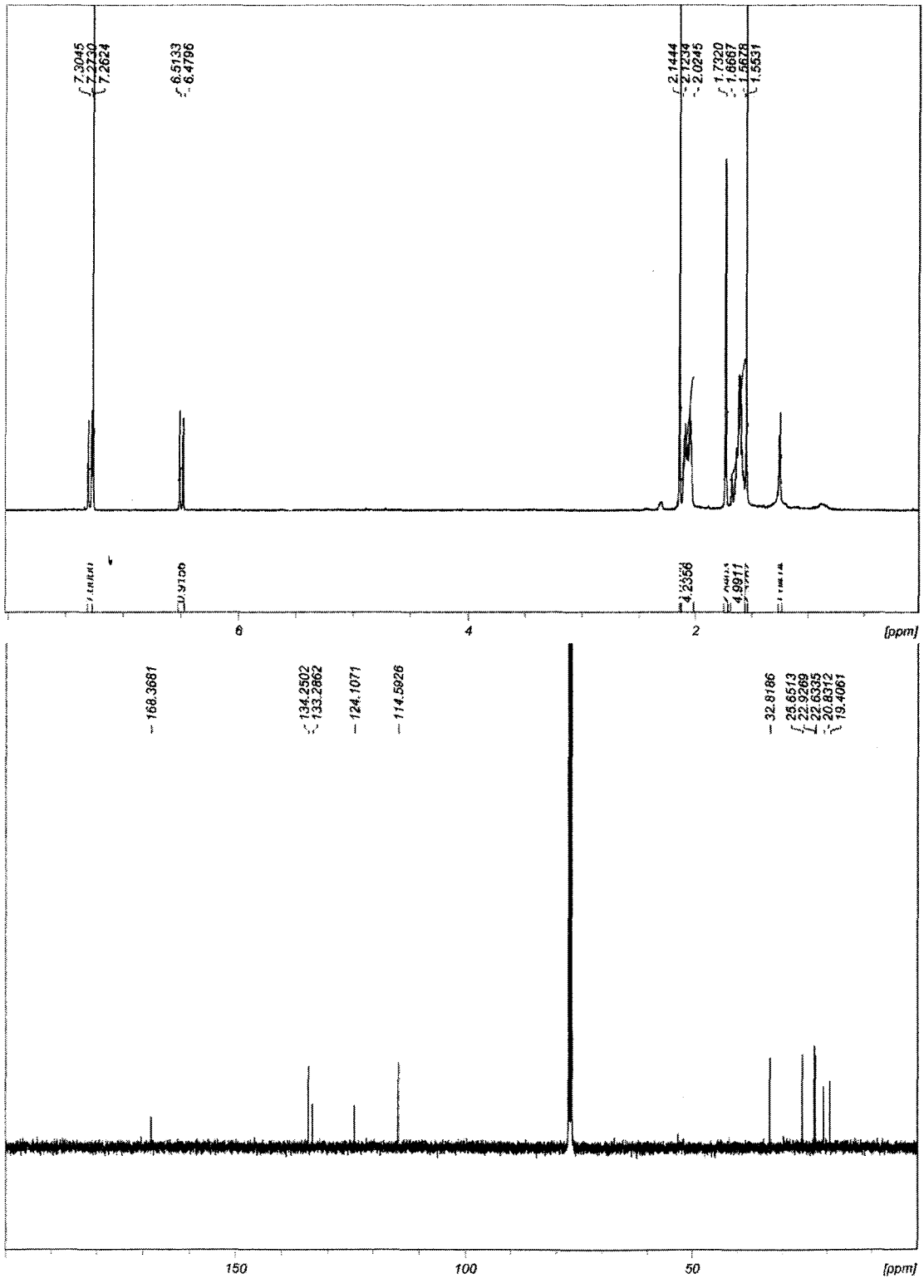
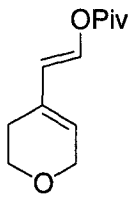
7.2456
7.2411
6.0479
6.0165
5.6743
2.0936
1.9717
1.6837
1.6690
1.6615
1.6567
1.6465
1.6415
1.6351
1.6308
1.6252
1.6058
1.6003
1.5968
1.5904
1.5854
1.5756
1.5704
1.5635
1.5486
1.5325
1.4862
1.4798
1.4475
1.4328
1.4211
1.4120
1.4024
1.3878
1.3779
1.3598
1.3527
1.3456
1.3405
1.3299
1.3071
1.3002
1.2894
1.2834
1.2627
1.2518
1.2386
1.2330
1.2205
1.2036
1.1946
1.1864
1.1811
1.1674
1.1514
1.1486
1.1384
1.1300
1.0591
0.9423
0.9197
0.9011
0.8820
0.8759
0.8603
0.8494
0.8395
0.8334
0.8234
-0.0494
1.0000
4.3511
5.2725
6
4
2
[ppm]


175.7750
134.0215
132.1661
128.7071
118.8336
77.3336
77.2200
77.0162
76.6989
38.7034
26.9754
25.8688
24.6313
22.3899
22.3015
150
100
50
[ppm]

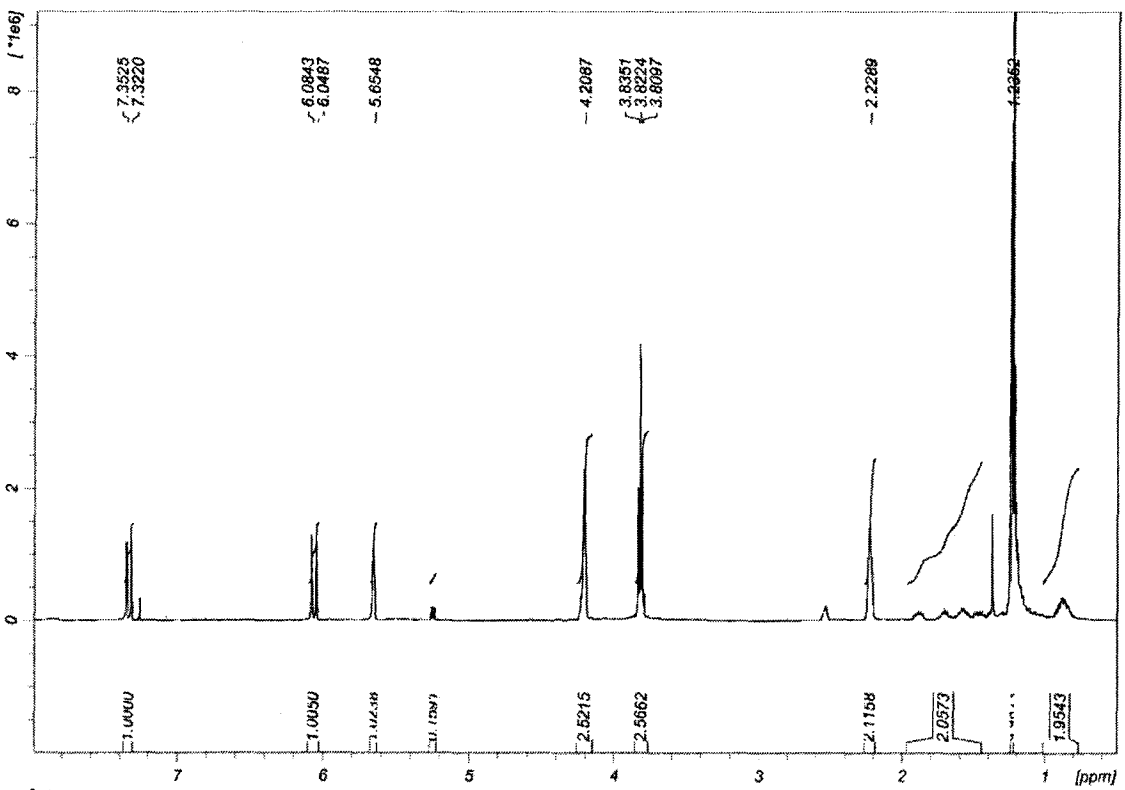


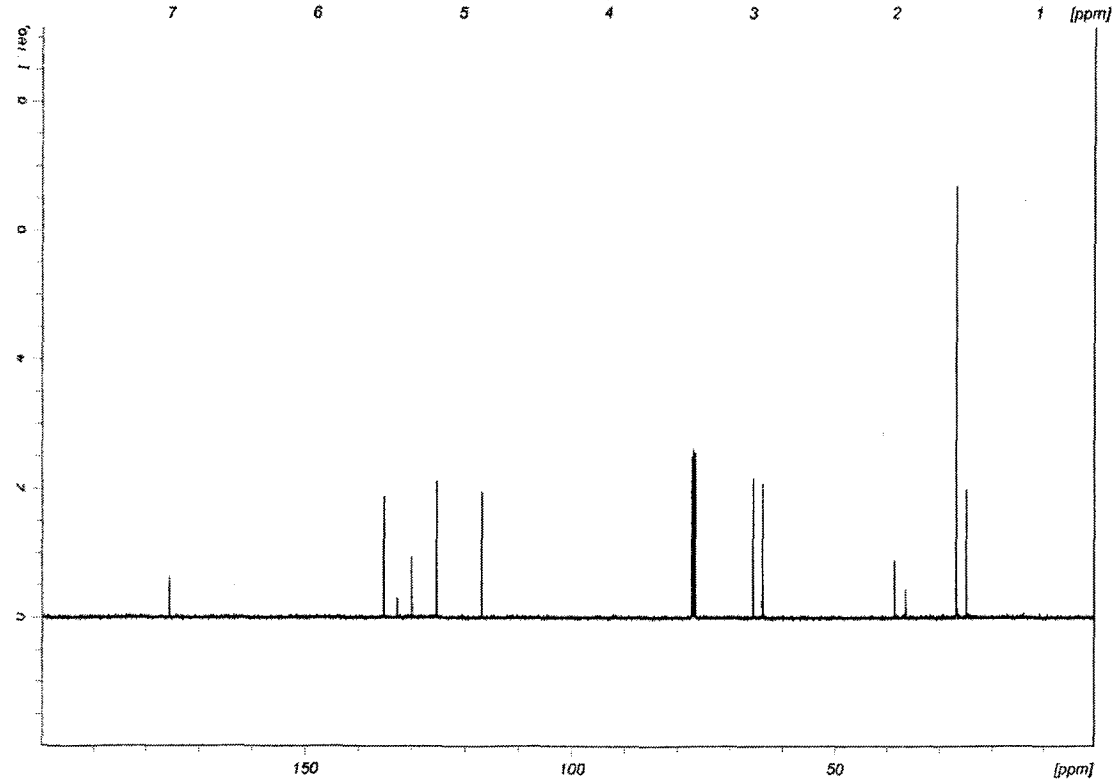
4.41a

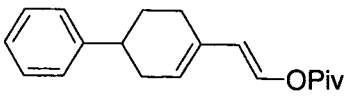

7.3045
7.2730
7.2624
6.5133
6.4796
2.1444
2.1234
2.0245
1.7320
1.6667
1.6628
1.5531
4.2356
4.9911
6
4
2
[ppm]
168.3681
134.2502
133.2862
124.1071
114.5926
32.8186
29.6513
22.9269
22.6335
20.8312
19.4061
150
100
50
[ppm]


OPiv
O

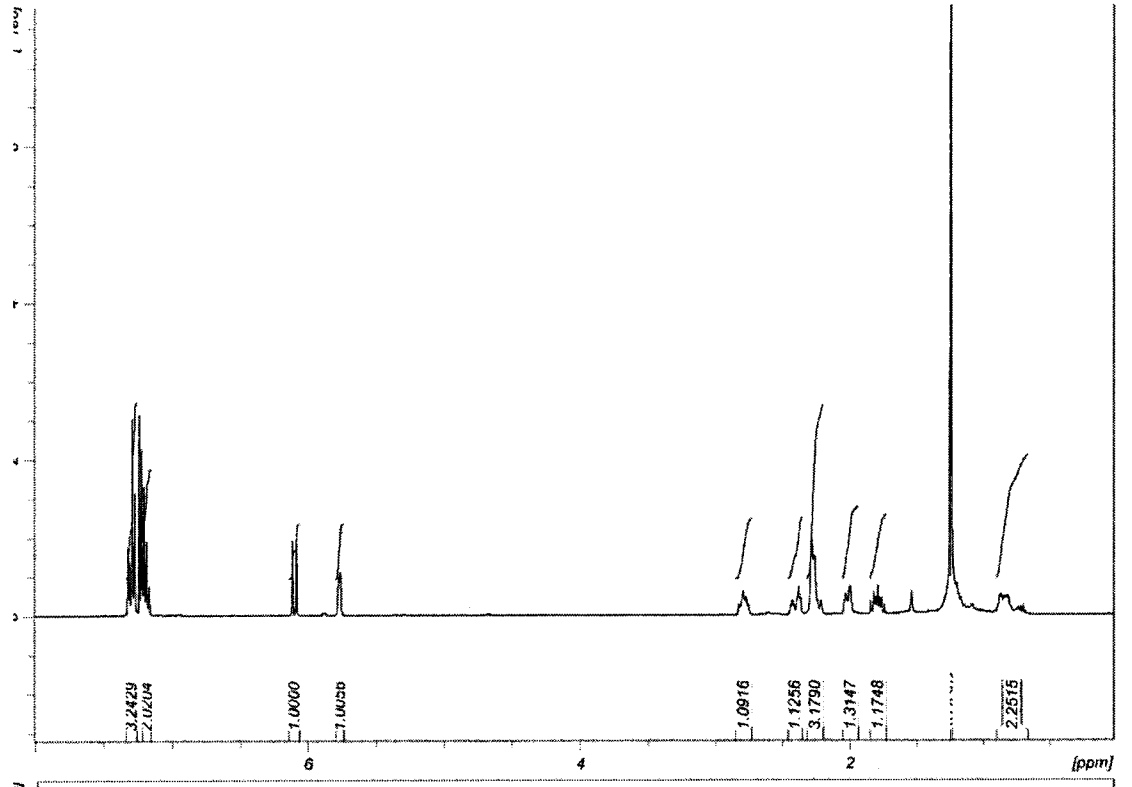
4.41c


7.3525
7.3220
6.0843
6.0487
5.6548
4.2087
3.8351
3.8224
3.8097
2.2269
1.2962
1.0000
1.0050
2.5215
2.5662
2.1158
2.0573
1.9543
[ppm]


150
100
50
[ppm]


OPiv

4.41h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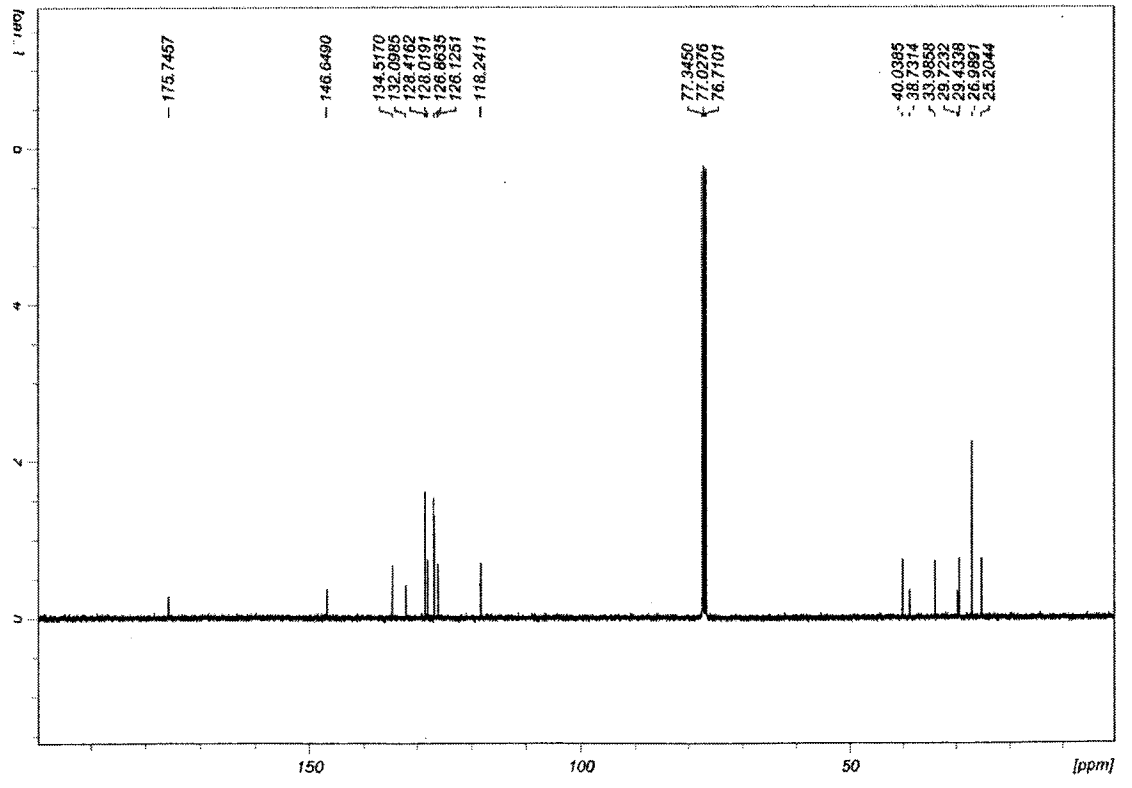
1.0000
1.0038
1.0916
1.1256
3.1790
1.3147
1.1748
2.2516
6
4
2
[ppm]


175.7457
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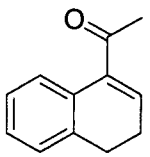
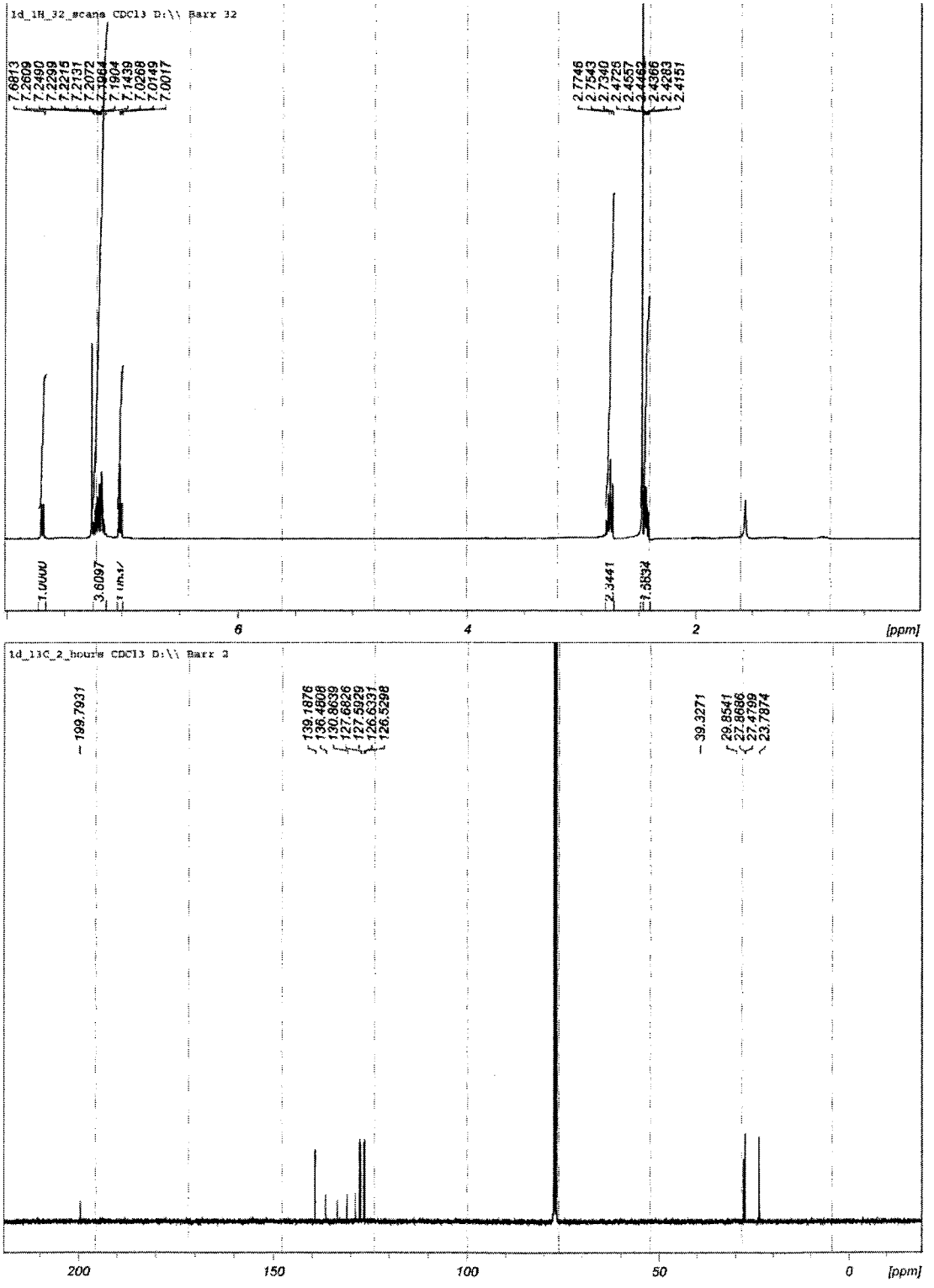
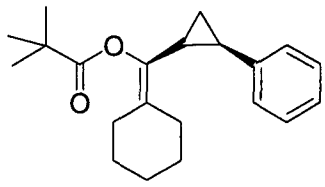
134.5170
132.0985
128.4162
128.0191
126.8835
126.1251
118.2411
77.3450
77.0276
76.7101
40.0385
38.7314
33.9858
29.7232
29.4338
26.9891
25.2044
150
100
50
[ppm]

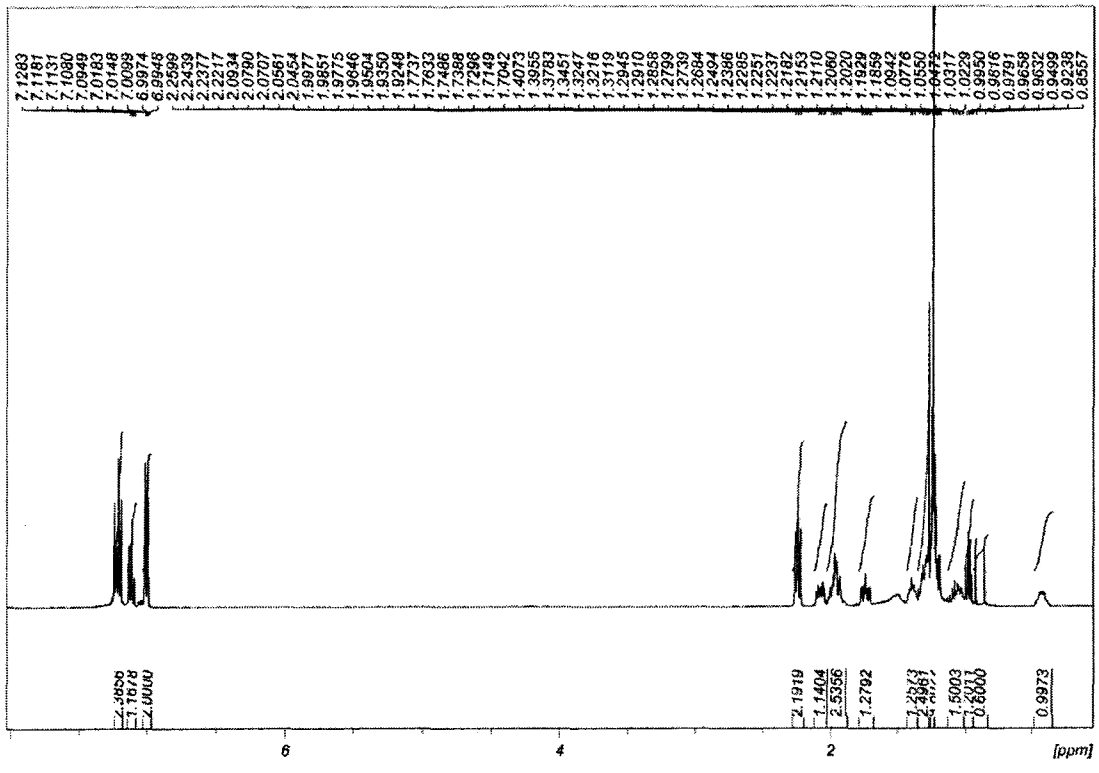


4.43


1d_1H_32_scans CDCl3 D:\\ Barr 32
7.6813
7.2609
7.2490
7.2299
7.2215
7.2131
7.2072
7.1964
7.1904
7.1439
7.0268
7.0149
7.0017
2.7746
2.7543
2.7340
2.4726
2.4557
2.4462
2.4366
2.4283
2.4151
1.0000
3.6097
2.3441
1.8834
6
4
2
[ppm]
1d_13C_2_hours CDCl3 D:\\ Barr 2
199.7931
139.1876
136.4608
130.8639
127.6826
127.5929
126.6331
126.5298
39.3271
29.8541
22.8686
22.4799
23.7874
200
150
100
50
0
[ppm]



4.59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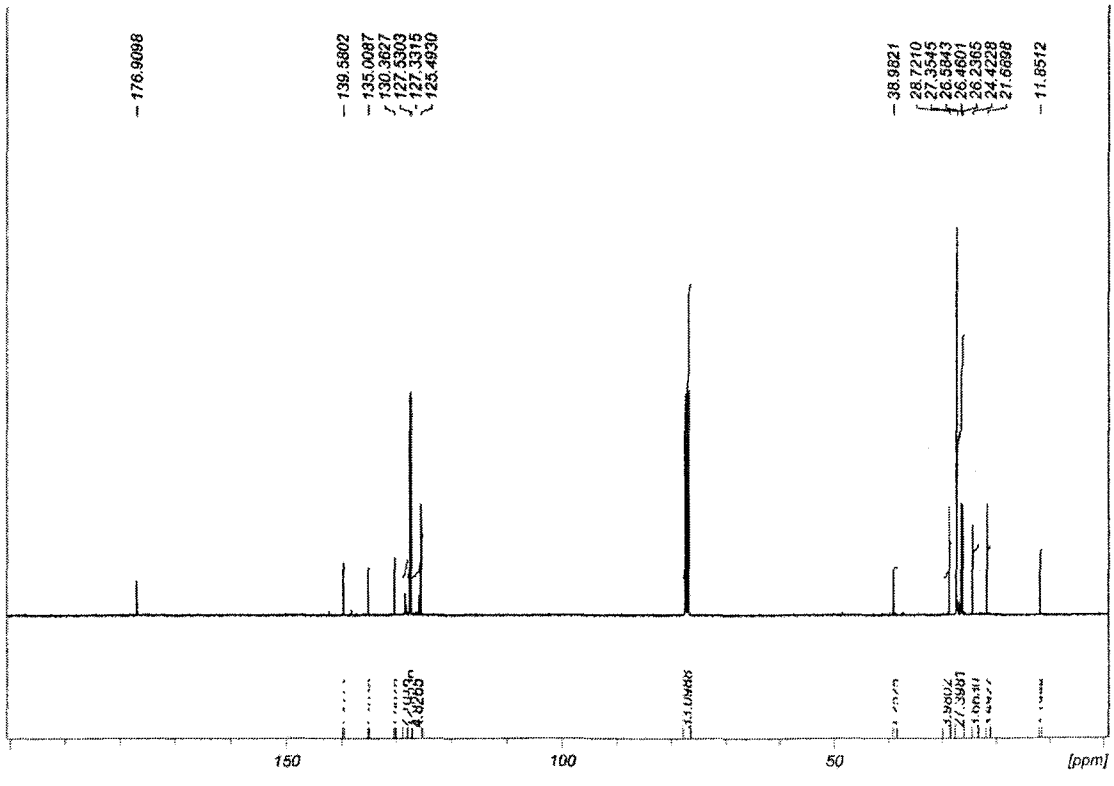
7.1181
7.1131
7.1080
7.0949
7.0183
7.0148
7.0099
6.9974
6.9948
2.2599
2.2439
2.2377
2.2217
2.0834
2.0780
2.0707
2.0561
2.0454
1.9977
1.9851
1.9775
1.9646
1.9504
1.9350
1.9248
1.7737
1.7633
1.7486
1.7388
1.7296
1.7149
1.7042
1.4073
1.3955
1.3783
1.3451
1.3247
1.3216
1.3119
1.2945
1.2910
1.2858
1.2799
1.2739
1.2684
1.2494
1.2386
1.2285
1.2251
1.2237
1.2182
1.2153
1.2110
1.2060
1.2020
1.1929
1.1859
1.0942
1.0776
1.0550
1.0317
1.0229
0.9950
0.9816
0.9791
0.9658
0.9632
0.9499
0.9238
0.8557
2.1919
1.1404
2.5356
1.2792
1.5003
0.6000
0.9973
6
4
2
[ppm]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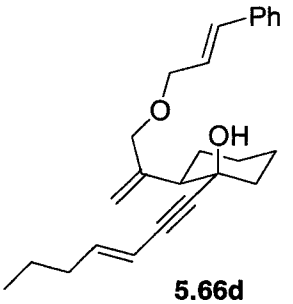
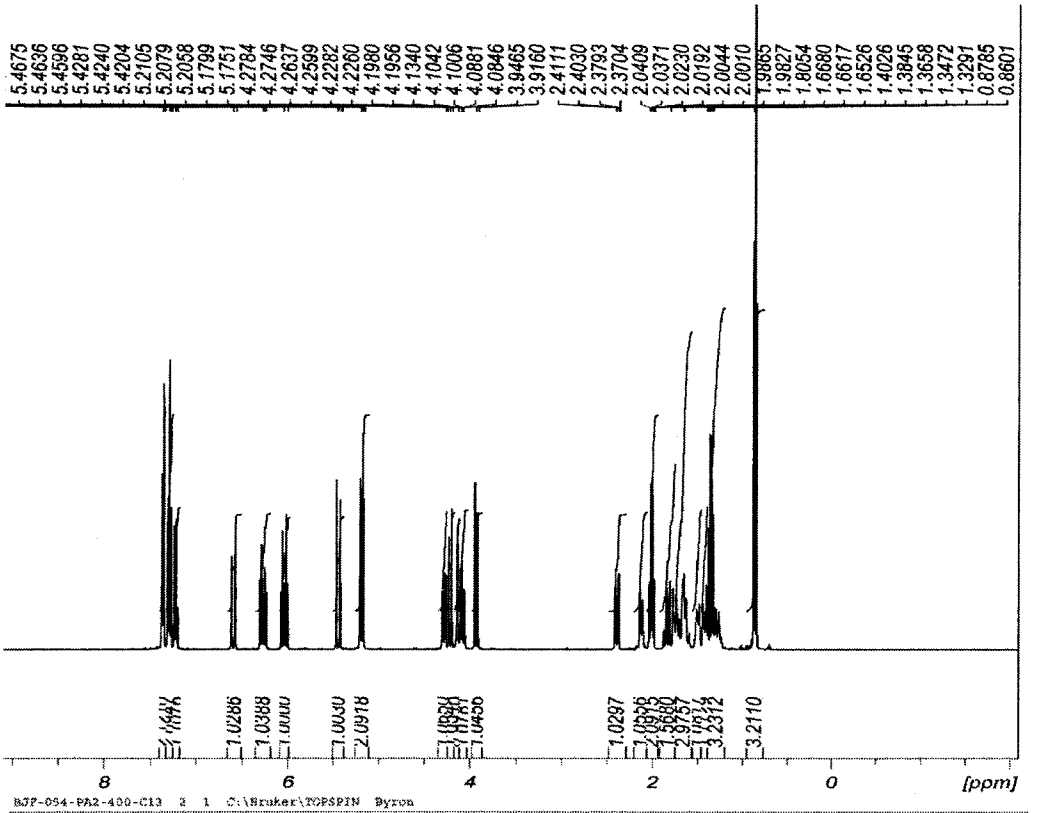
135.0087
130.3627
127.5303
127.3315
125.4930
38.9821
28.7210
27.3545
26.5843
26.4601
26.2365
24.4228
21.6698
11.8512
150
100
50
[ppm]


Ph
O
OH

5.66d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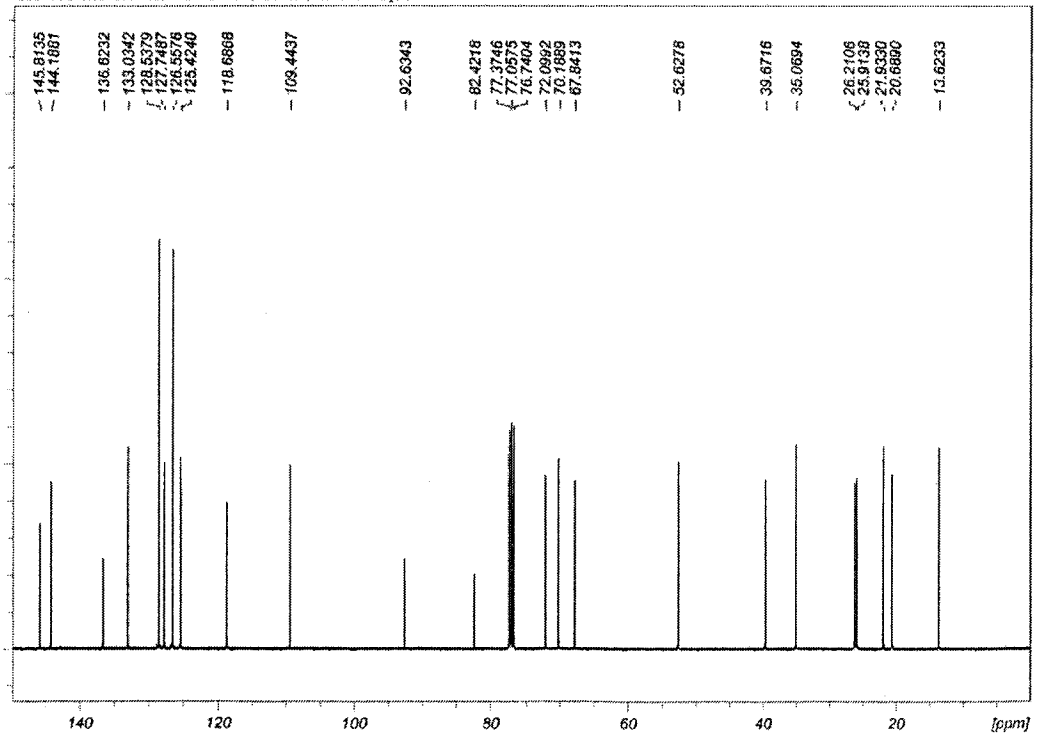
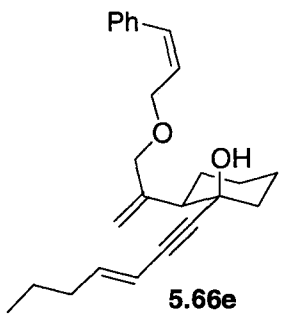
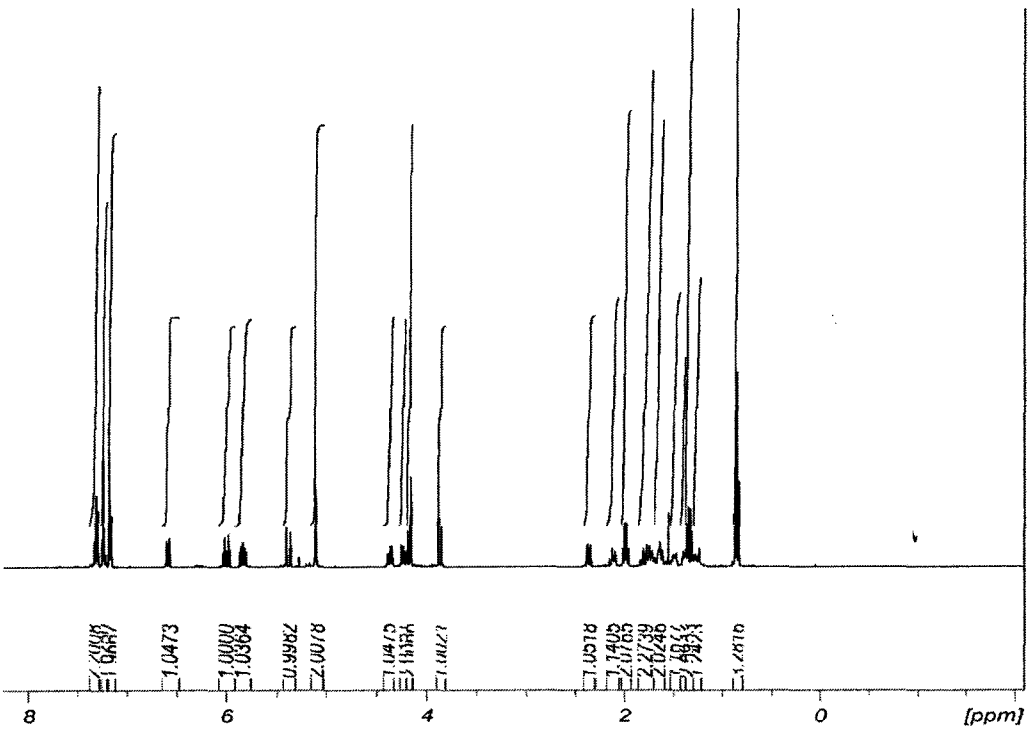
5.4636
5.4596
5.4281
5.4240
5.4204
5.2105
5.2079
5.2058
5.1799
5.1751
4.2784
4.2746
4.2637
4.2589
4.2282
4.2260
4.1980
4.1956
4.1340
4.1042
4.1006
4.0881
4.0846
3.9465
3.9160
2.4111
2.4030
2.3793
2.3704
2.0409
2.0371
2.0230
2.0192
2.0044
2.0010
1.9865
1.9827
1.8054
1.6680
1.6617
1.6526
1.4026
1.3845
1.3658
1.3472
1.3291
0.8785
0.8601
1.0286
1.0388
1.0000
1.0030
2.0918
1.0297
3.2312
3.2110
8
6
4
2
0
[ppm]


BJF-054-PA2-400-C13 2 1 C:\Bruker\TOPSPIN Byron
145.8135
144.1881
136.8232
133.0342
128.5379
127.7487
126.5576
125.4240
118.6868
109.4437
92.6343
82.4218
77.3746
77.0575
76.7404
72.0992
70.1889
67.8413
52.6278
39.6716
35.0694
26.2106
25.9138
21.9330
20.6880
13.6233
140
120
100
80
60
40
20
[ppm]


Ph
O
OH

5.66e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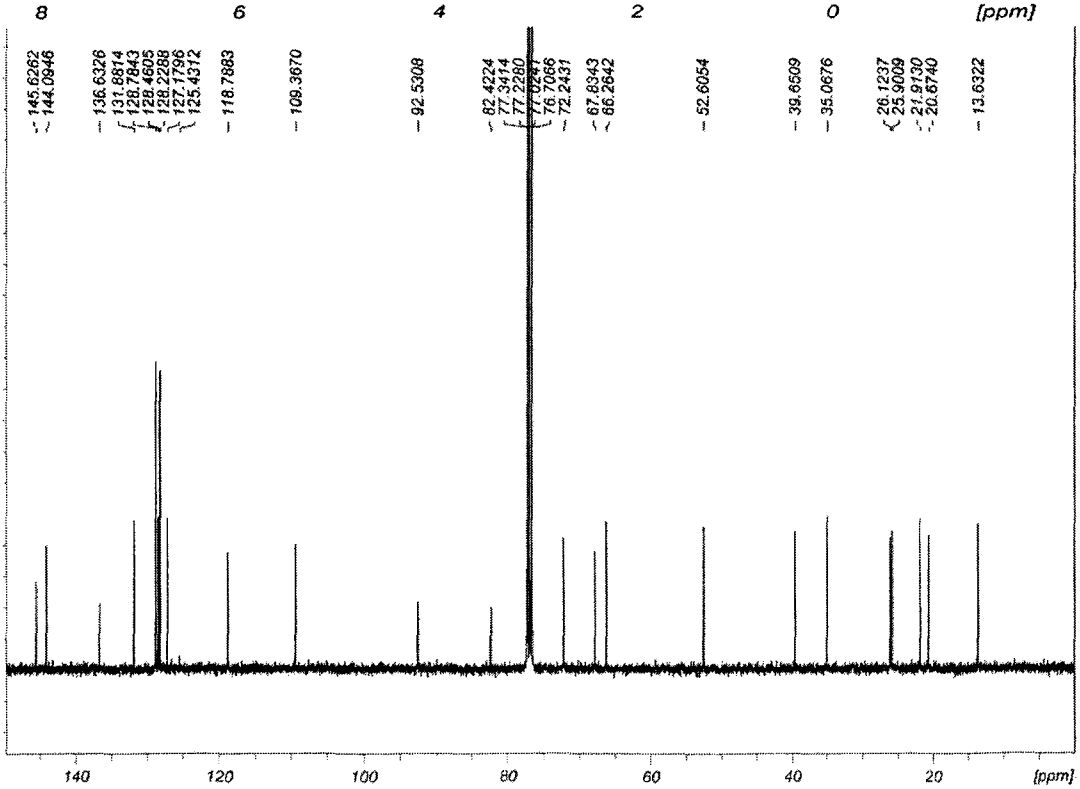
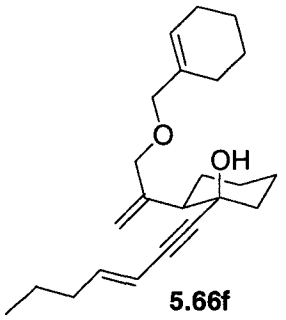
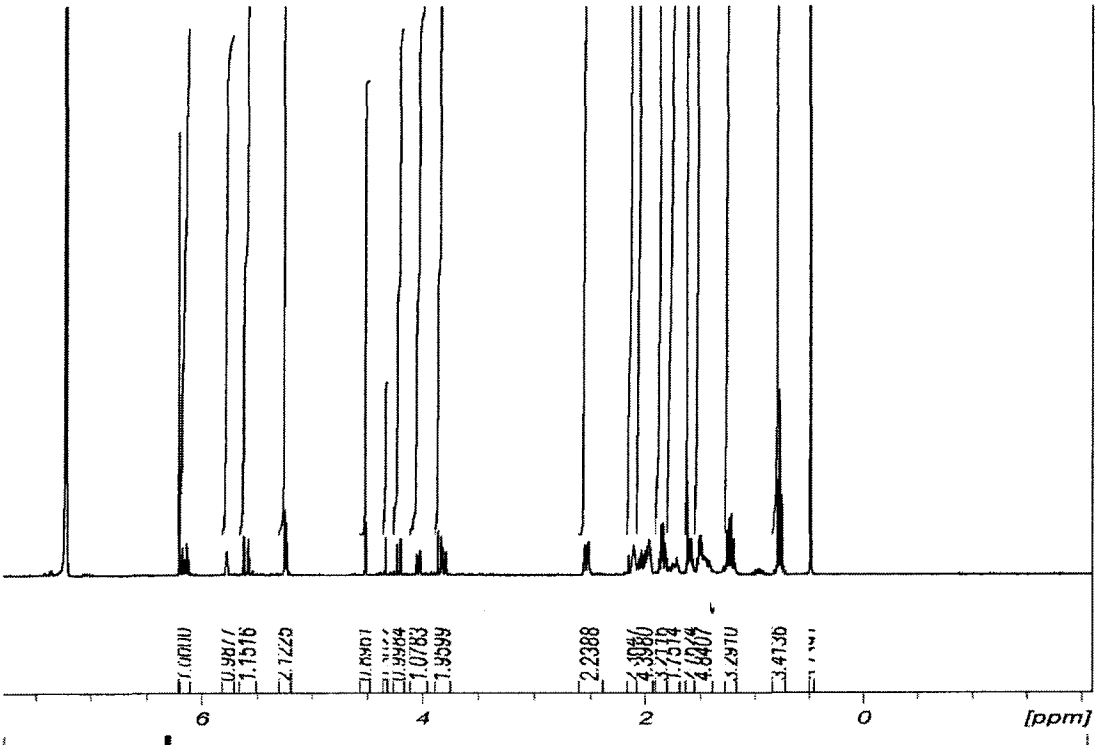
1.0364
0.9982
2.0078
8
6
4
2
0
[ppm]


145.6262
144.0946
136.6326
131.8814
128.7843
128.4605
128.2288
127.1796
125.4312
118.7883
109.3670
92.5308
82.4224
77.3414
77.2280
76.7066
72.2431
67.8343
66.2642
52.6054
39.6509
35.0676
26.1237
25.9009
21.9130
20.6740
13.6322
140
120
100
80
60
40
20
[ppm]


O
OH

5.66f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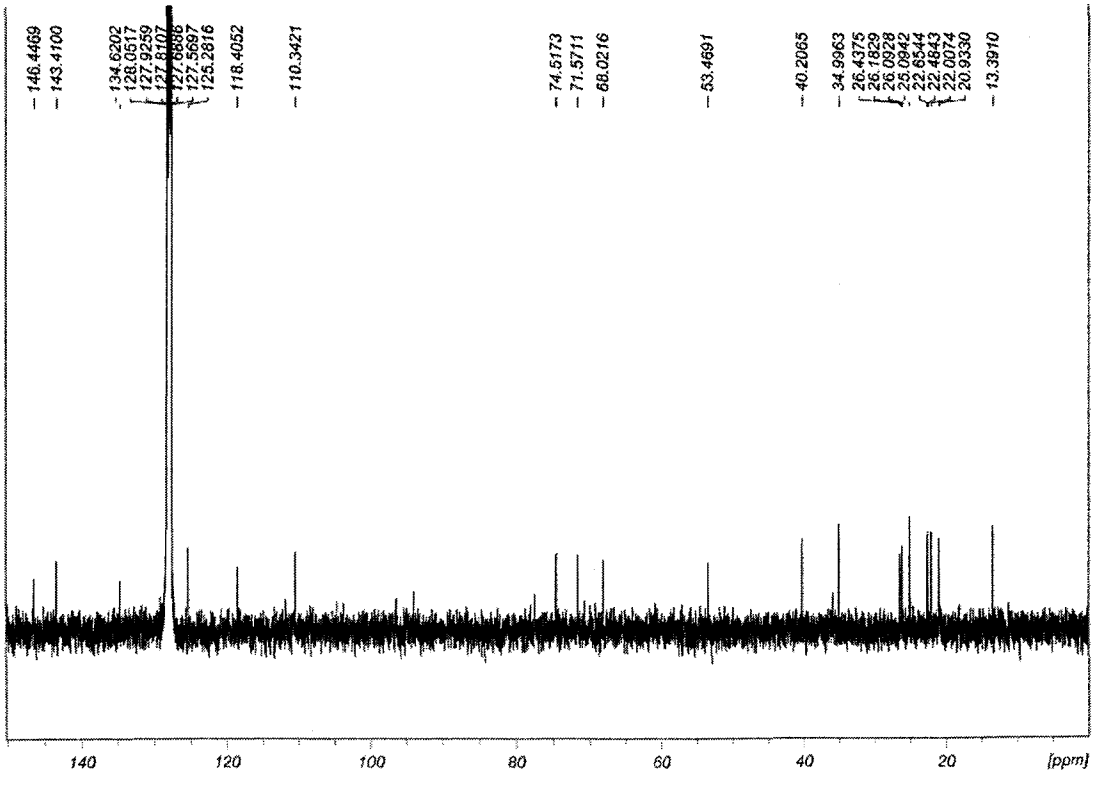
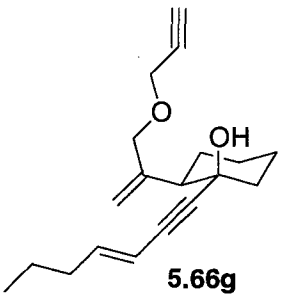
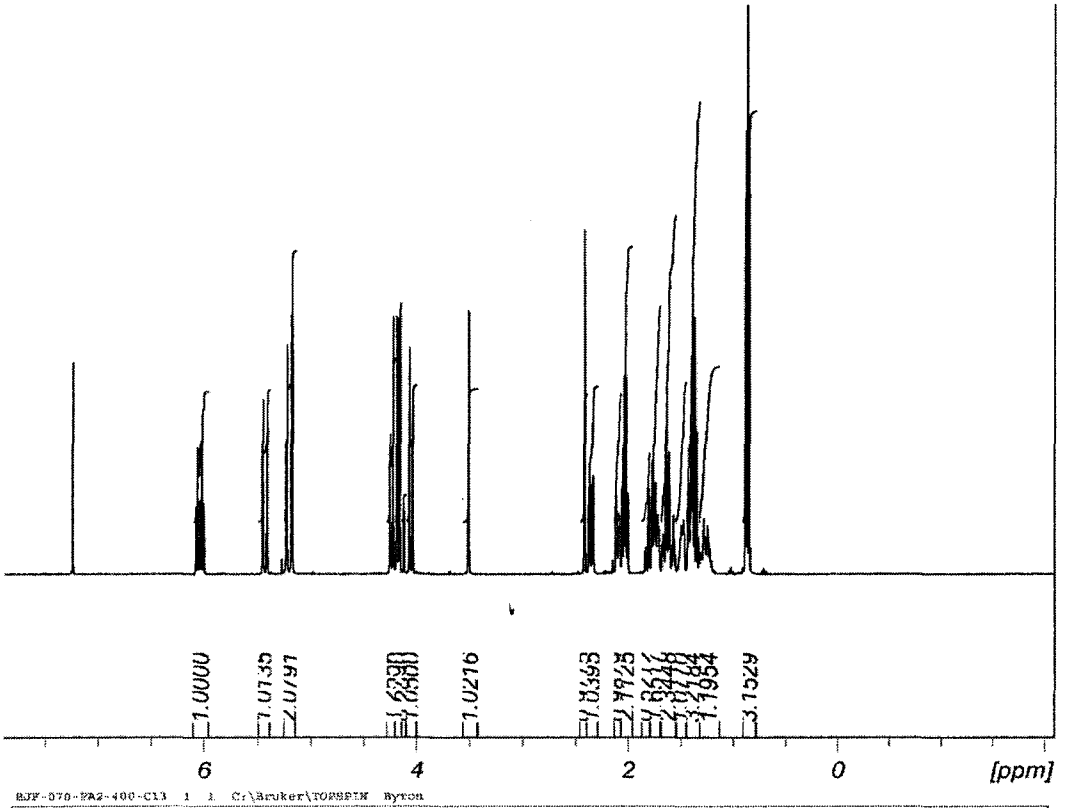
1.1516
2.1225
1.8901
0.9964
1.0783
1.9599
2.2388
4.3980
3.7514
4.8407
3.4136
6
4
2
0
[ppm]


146.4469
143.4100
134.6202
128.0517
127.9259
127.8107
127.5697
125.2616
118.4052
110.3421
74.5173
71.5711
68.0216
53.4691
40.2065
34.9963
26.4375
26.1829
26.0928
25.0942
22.6544
22.4843
22.0074
20.9330
13.3910
140
120
100
80
60
40
20
[ppm]


O
OH

5.66g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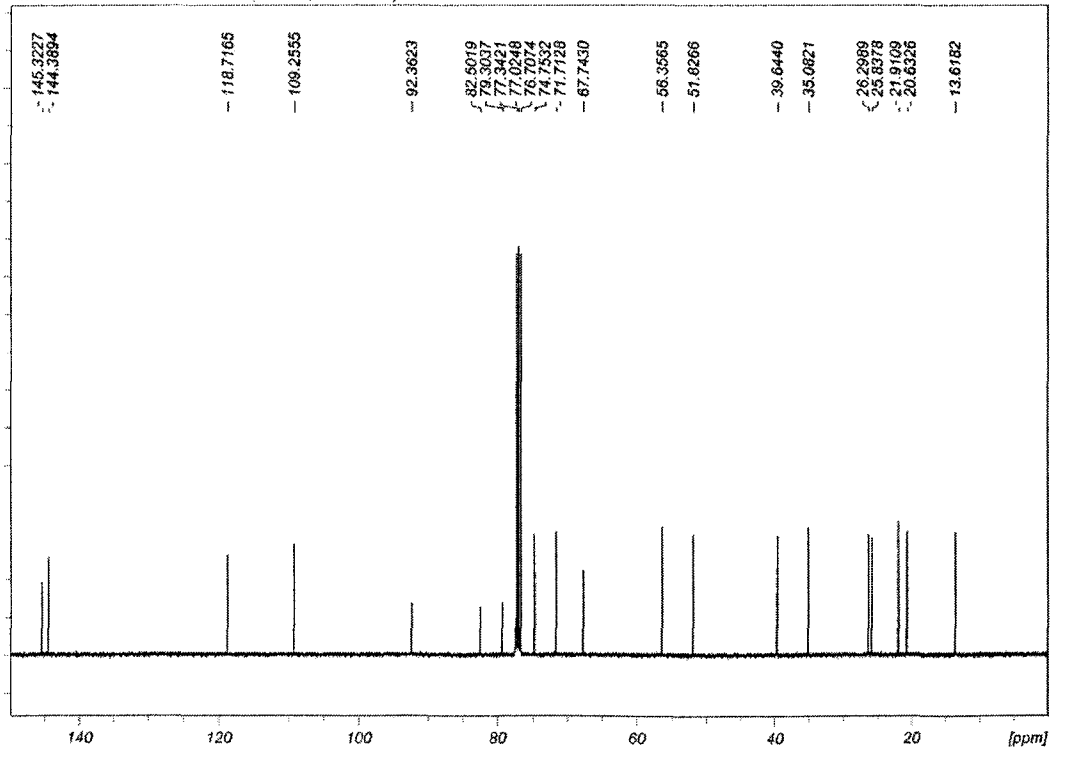
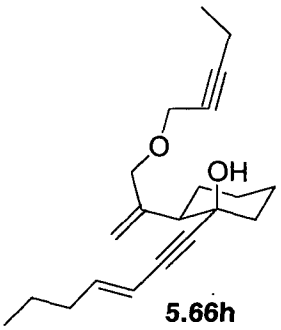
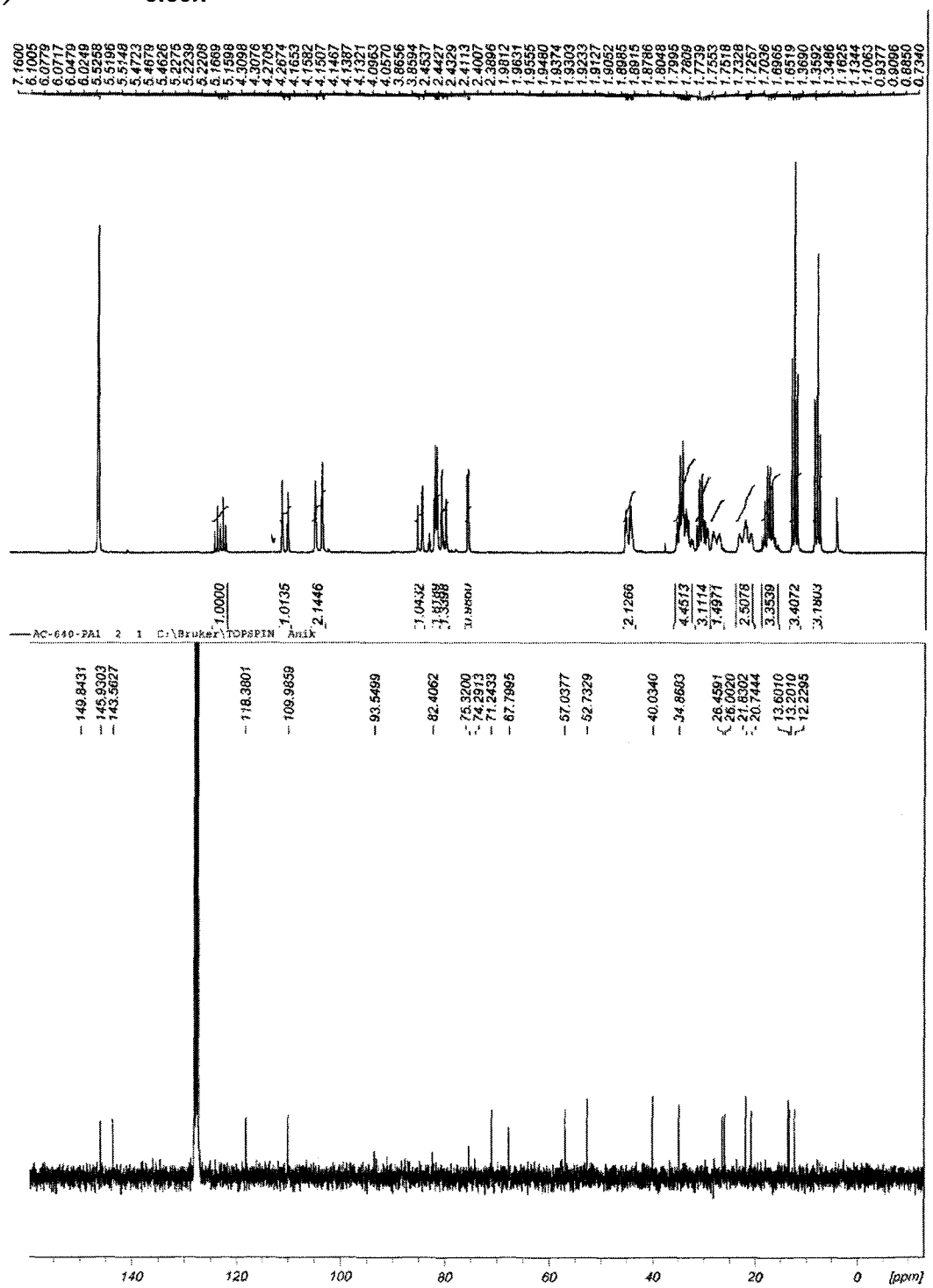
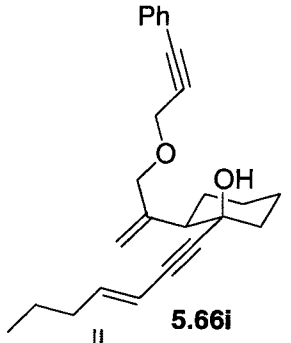
1.0216
7.0393
2.7923
3.1529
6
4
2
0
[ppm]


BJF-070-PA2-400-C13 1 1 C:\Bruker\TOPSPIN Byron
145.3227
144.3894
118.7165
109.2555
92.3623
82.5019
79.3037
77.3421
77.0248
76.7074
74.7532
71.7128
67.7430
56.3565
51.8266
39.6440
35.0821
26.2999
25.8378
21.9109
20.6326
13.6182
140
120
100
80
60
40
20
[ppm]

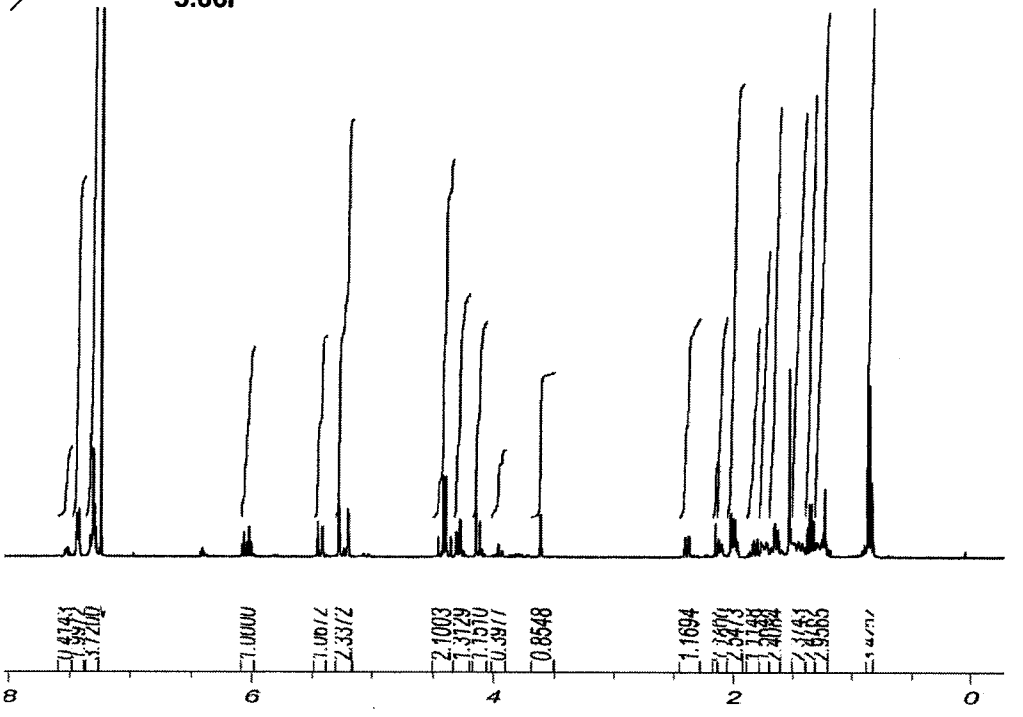

O
OH

5.66h


AC-640-PA1 2 1 C:\Bruker\TOPSPIN Anik
140
120
100
80
60
40
20
0
[ppm]


Ph
O
OH

5.66i


1.0000
2.3372
2.1003
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1.1510
0.8548
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4
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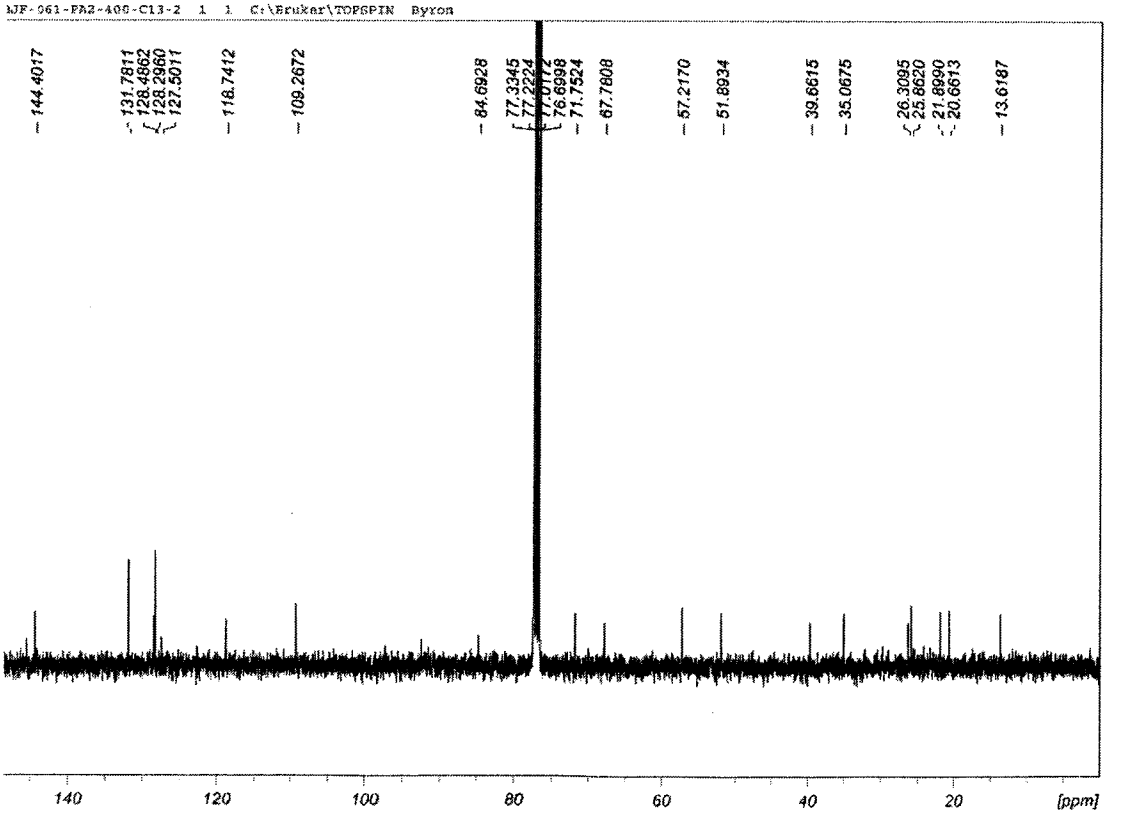
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127.5011
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77.0172
76.6998
71.7524
67.7808
57.2170
51.8934
39.6615
35.0675
26.3095
25.8620
21.8990
20.6613
13.6187
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80
60
40
20
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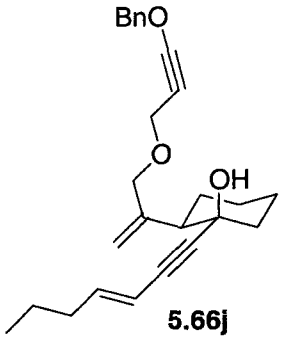
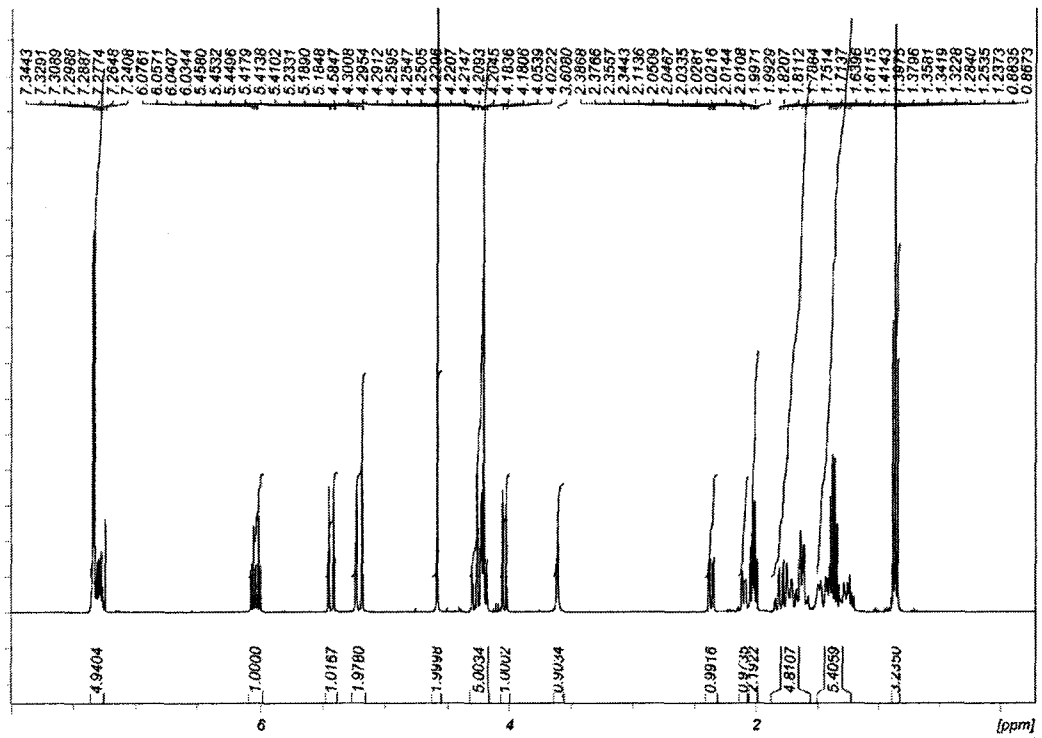

BnO
O
OH

5.66j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6.0407
6.0344
5.4580
5.4532
5.4496
5.4179
5.4138
5.4102
5.2331
5.1890
5.1648
4.5947
4.3008
4.2954
4.2912
4.2595
4.2547
4.2505
4.2206
4.2207
4.2147
4.2083
4.2035
4.1838
4.1806
4.0539
4.0222
3.6080
3.6068
2.3766
2.3557
2.3443
2.1136
2.0569
2.0467
2.0335
2.0281
2.0216
2.0144
2.0108
1.9971
1.9929
1.8207
1.8112
1.7084
1.7514
1.7137
1.6308
1.6115
1.4143
1.3579
1.3581
1.3419
1.3228
1.2840
1.2555
1.2373
0.8835
0.8673
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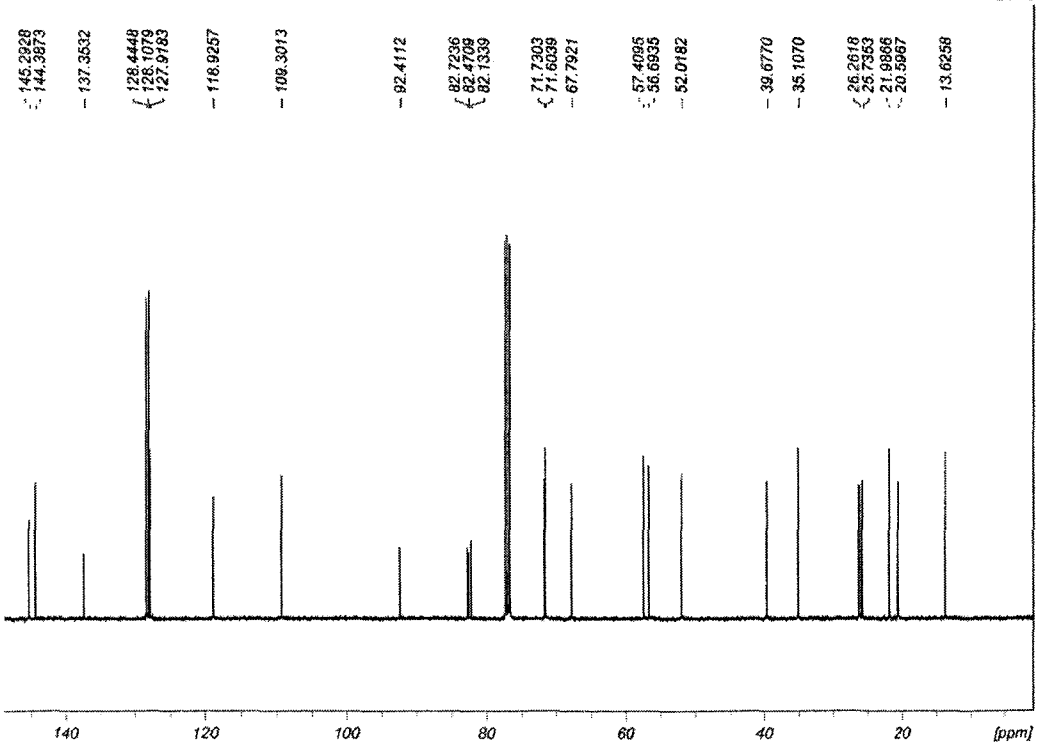
1.0167
1.9780
5.0034
0.9916
4.8107
5.4059
6
4
2
[ppm]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92.4112
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82.4709
82.1339
71.7303
71.6039
67.7921
57.4095
56.6935
52.0182
39.6770
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26.2618
25.7353
21.9866
20.5967
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140
120
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20
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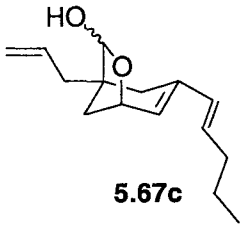
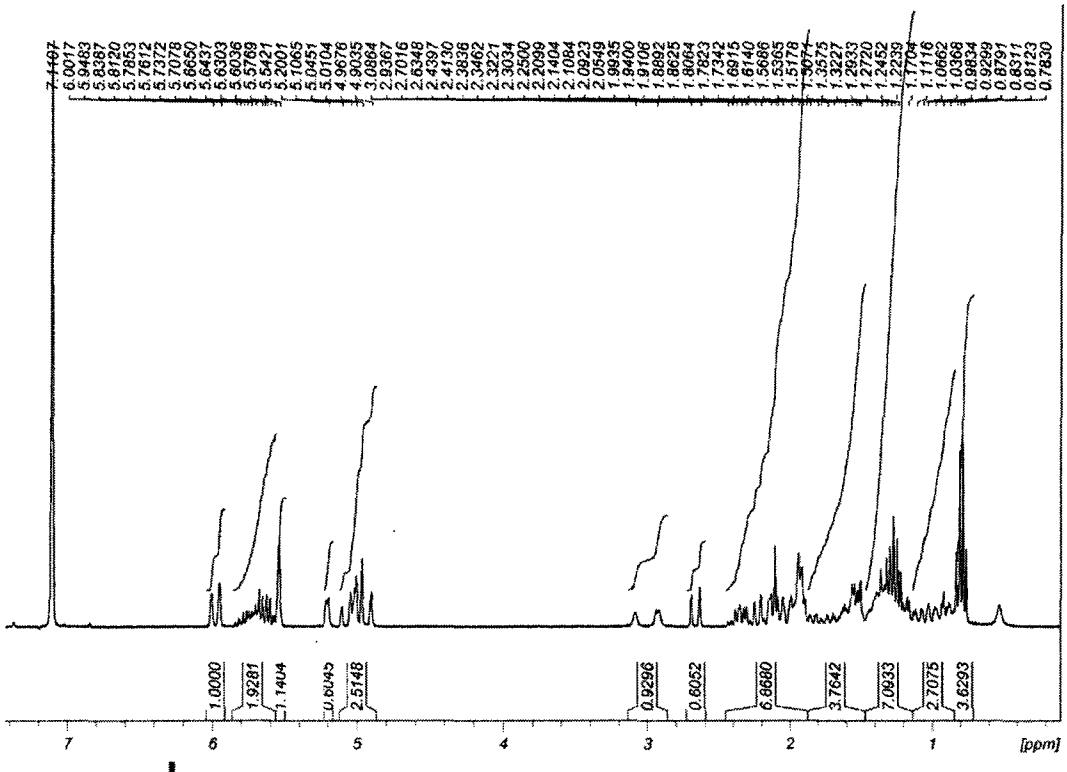

HO
O

5.67c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5.5769
5.5421
5.2001
5.1065
5.0451
5.0104
4.9676
4.9035
3.0864
2.9367
2.7016
2.6348
2.4397
2.4130
2.3838
2.3462
2.3221
2.3034
2.2500
2.2099
2.1404
2.1084
2.0923
2.0549
1.9935
1.9400
1.9106
1.8892
1.8625
1.8064
1.7823
1.7342
1.6915
1.6140
1.5686
1.5305
1.5178
1.3074
1.3575
1.3227
1.2933
1.2720
1.2452
1.2239
1.1704
1.1116
1.0662
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0.9289
0.8791
0.8311
0.8123
0.7830
1.0000
1.9281
1.1404
0.6045
2.5148
0.9296
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3.6293
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1
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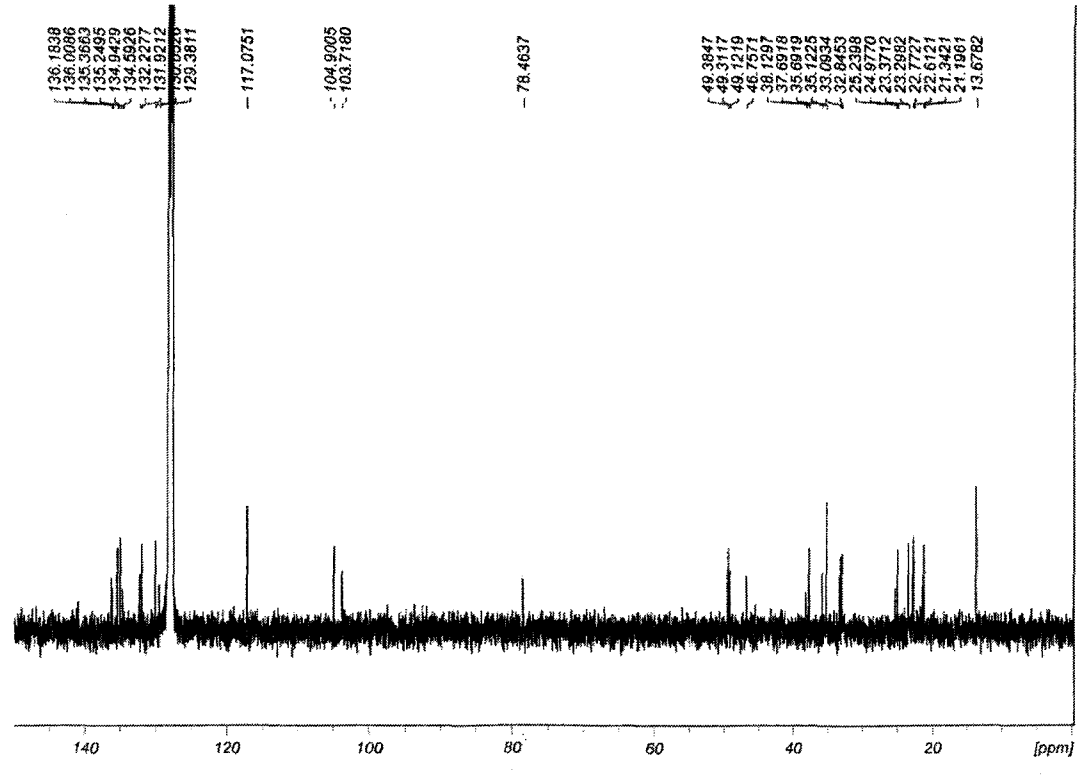
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117.0751
104.9005
103.7180
78.4637
49.3847
49.3117
49.1219
46.7571
38.1297
37.6918
35.6919
35.1225
33.0934
32.8453
25.2398
24.9770
23.3712
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60
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20
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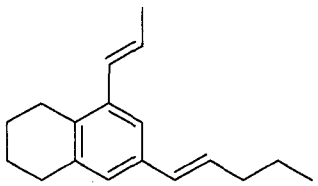
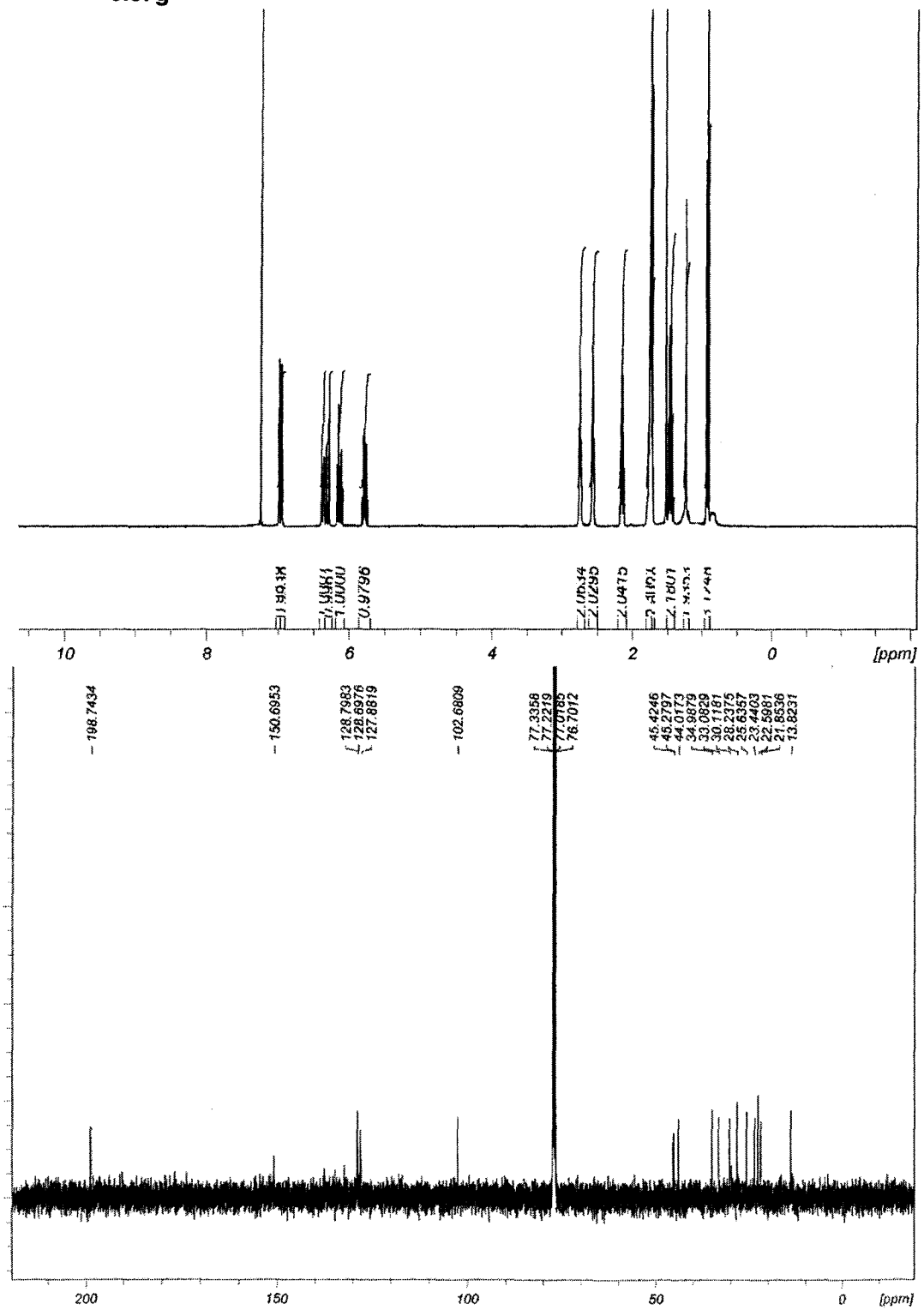


5.67g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77.2219
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76.7012
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44.0173
34.9879
33.0829
30.1181
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23.4403
22.5981
21.8536
13.8231
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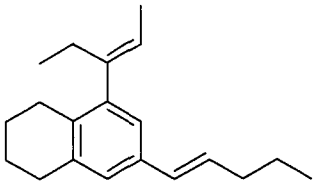
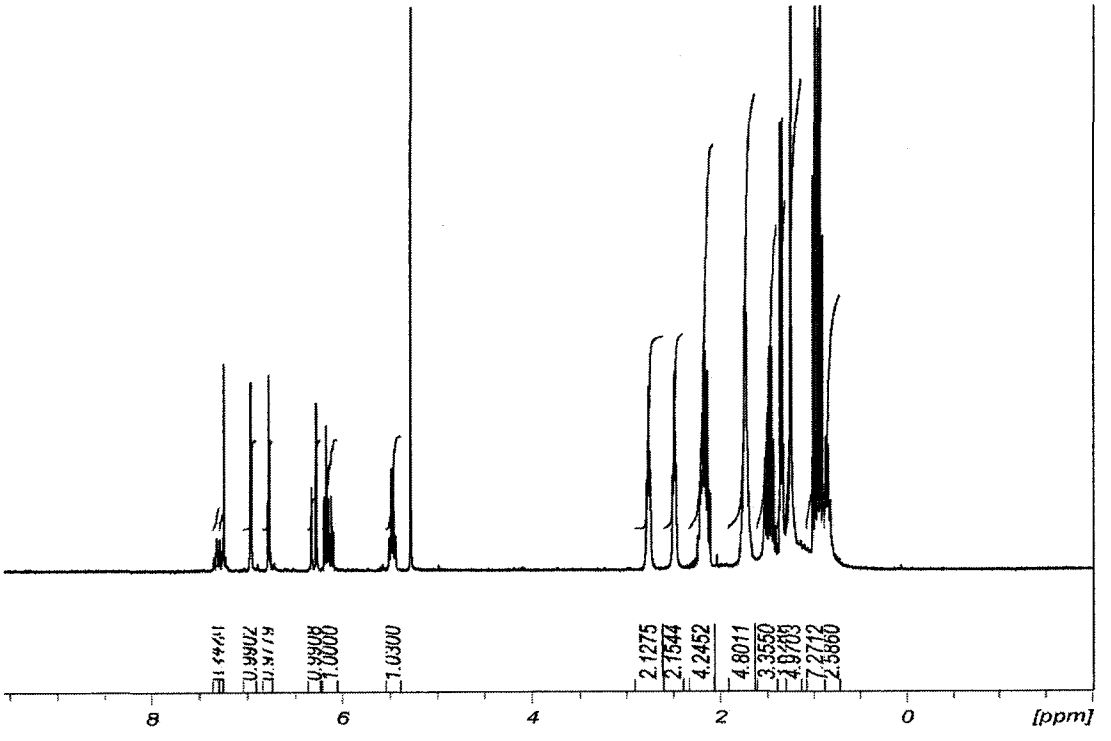


5.67h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4.8011
3.3550
7.2712
2.3660
8
6
4
2
0
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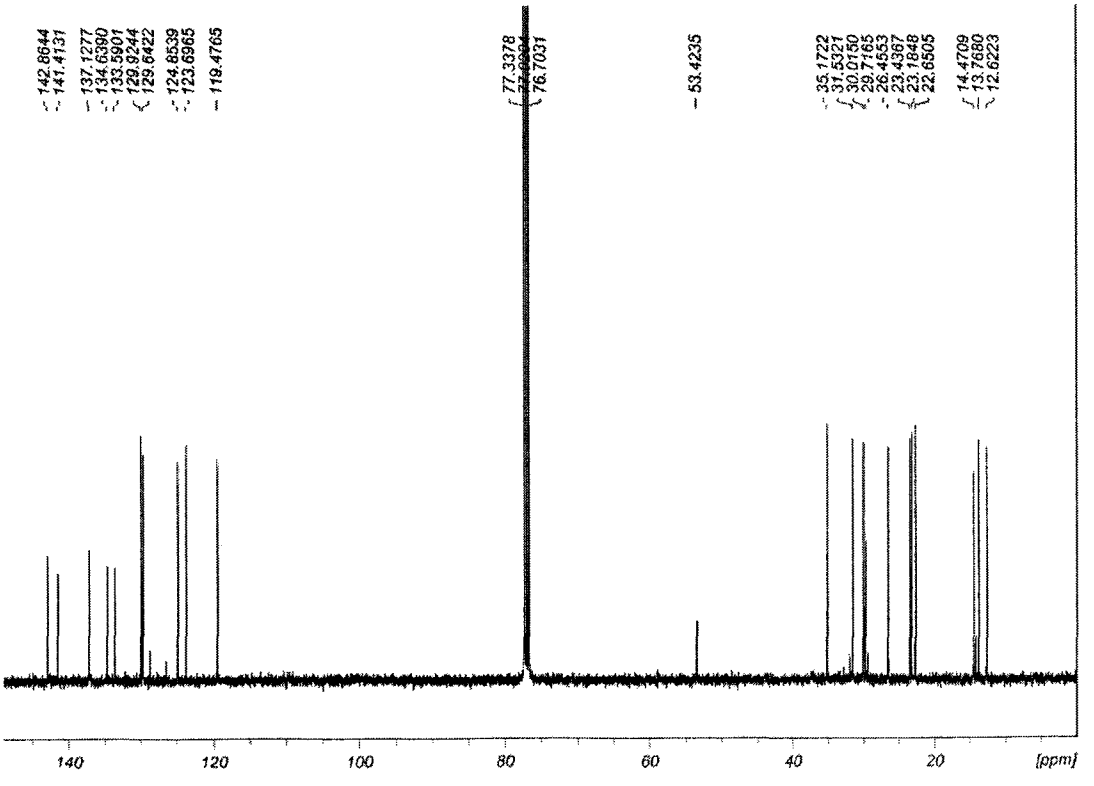
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119.4765
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26.4553
23.4367
23.1848
22.6505
14.4709
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12.6223
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80
60
40
20
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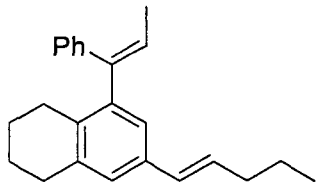
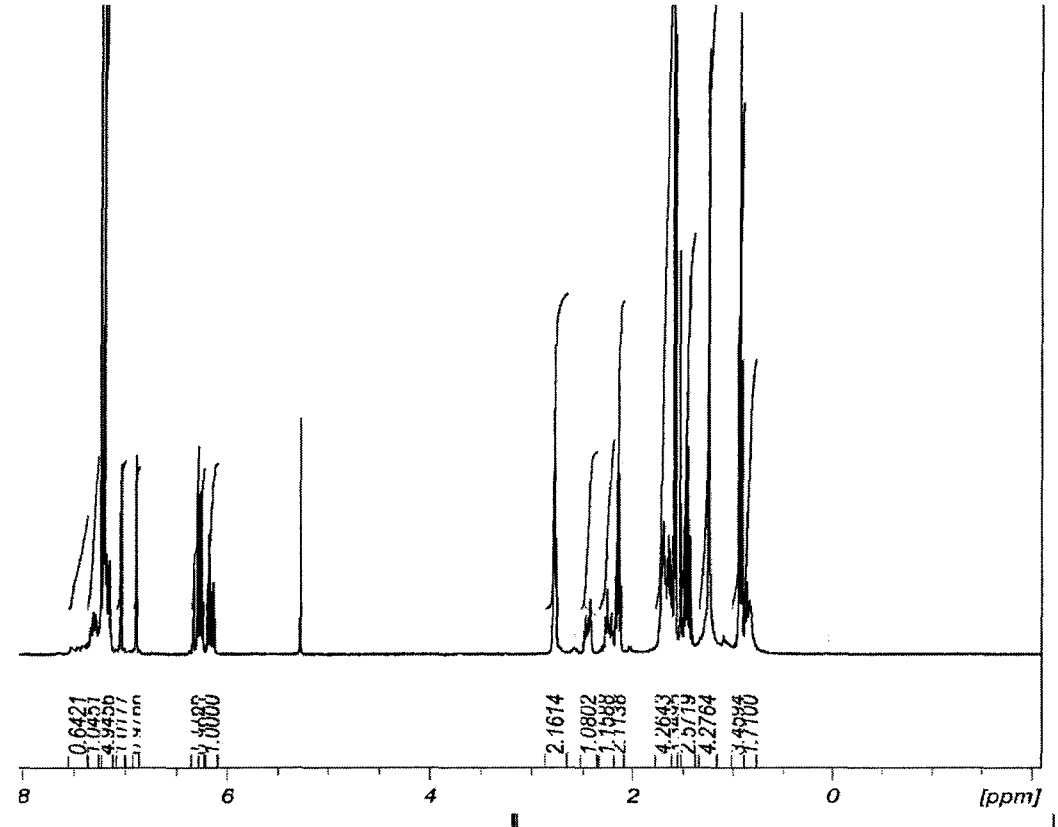

Ph

5.67i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4.2764
3.4944
1.7100
8
6
4
2
0
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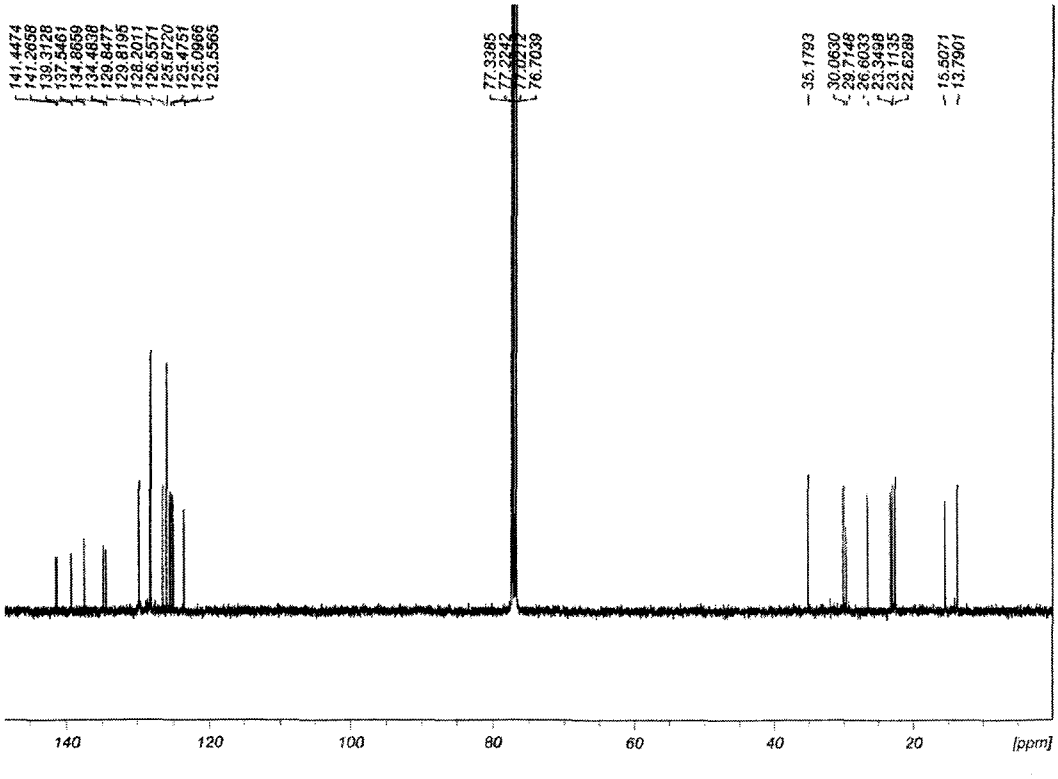
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125.4751
125.0966
123.5565
77.3385
77.2242
76.7039
35.1793
30.0630
29.7148
26.6033
23.3498
23.1135
22.6289
15.5071
13.7901
140
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100
80
60
40
20
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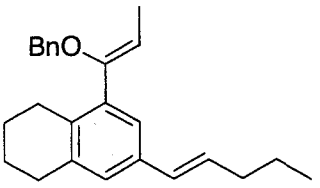
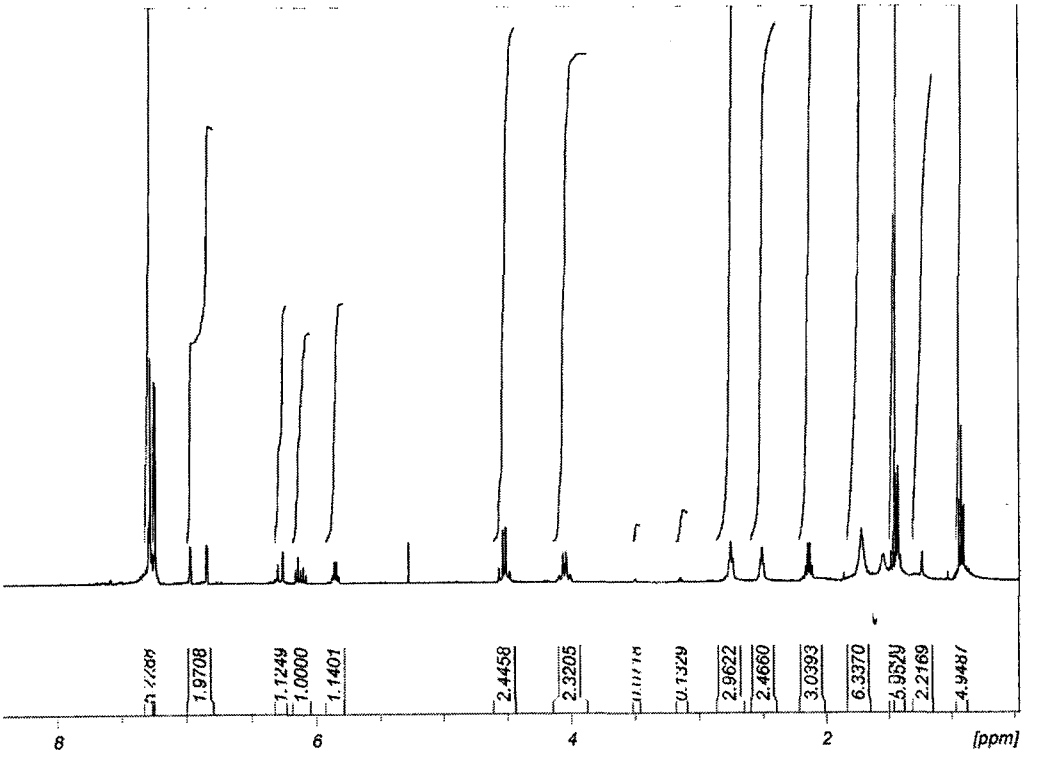

BnO

5.67j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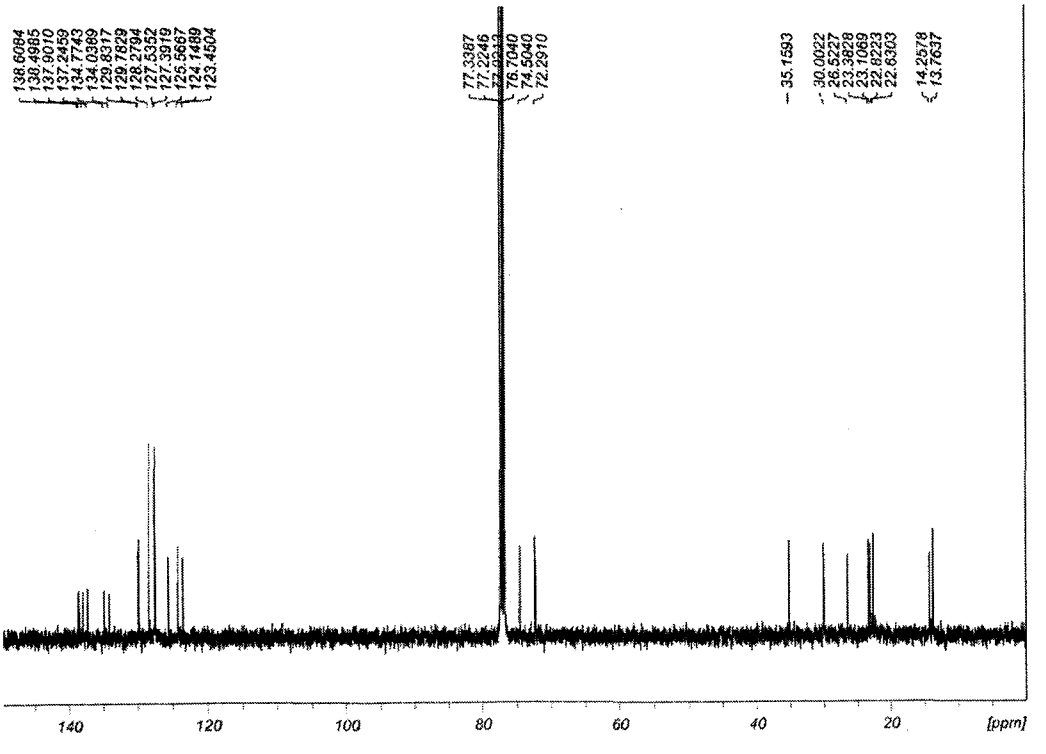
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76.7040
74.5040
72.2910
35.1593
30.0022
26.5227
23.3828
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22.6303
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13.7637
140
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80
60
40
20
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