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A NOVEL ENANTIOSELECTIVE SYNTHESIS OF ALLENIC ESTERS AND AMIDES

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List of Abbreviations

| | |
|-------------------|---|
| Ar | aryl |
| Bn | benzyl |
| Boc | <i>tert</i> -butyloxycarbonyl |
| Bz | benzoyl |
| Cy | cyclohexyl |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DEAD | diethyl azodicarboxylate |
| DIBAL-H | diisobutylaluminum hydride |
| DIPEA | diisopropylethylamine |
| DMF | <i>N,N</i> -dimethylformamide |
| DYKAT | dynamic kinetic asymmetric transformation |
| <i>ee</i> | enantiomeric excess |
| Equiv. | equivalents |
| Et | ethyl |
| Et ₃ N | triethylamine |
| Et ₂ O | diethyl ether |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| EWG | electron withdrawing group |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrum |
| HWE | Horner-Wadsworth-Emmons |
| <i>i</i> -PrOH | <i>iso</i> -propanol |

| | |
|----------------|---------------------------------------|
| IR | infrared |
| LA | Lewis Acid |
| L | ligand |
| L* | chiral ligand |
| LDA | lithium diisopropylamide |
| <i>m</i> CPBA | <i>meta</i> -chloroperoxybenzoic acid |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| <i>n</i> BuLi | <i>n</i> -butyllithium |
| NaHMDS | sodium hexamethyldisilazane |
| NMM | <i>N</i> -methylmorpholine |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| Ph | phenyl |
| rt | room temperature |
| TBAF | tetrabutylammonium fluoride |
| TBDPS | <i>tert</i> -butyldiphenylsilyl |
| TBS | <i>tert</i> -butyldimethylsilyl |
| <i>t</i> Bu | <i>tert</i> -butyl |
| <i>t</i> -BuOH | <i>tert</i> -butanol |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| X | generic halide |

Abstract

In recent years, allenes have become recognized as useful synthons in organic chemistry. Their unique orthogonal π -bond system can be used in a variety of regio- and stereoselective carbon-carbon bond-forming reactions. Chiral allenes also have the ability to transfer their chirality to one or more new chiral centres. Despite this usefulness, the synthesis of chiral allenes is quite limited. Most methods to synthesize asymmetric allenes require chirality transfer from a pre-formed chiral centre, while only a handful of methods exists which form an asymmetric allene from achiral starting materials.

We have discovered a new method for synthesizing chiral allenes using achiral 3-alkynoates or 3-alkynamides. Treatment of a propargyl carbonyl compound with a catalytic silver source and a chiral Lewis Acid in the presence of a weak amine base results in the formation of chiral allenic esters and amides. Initial reactions with 3-alkynoates lead to the discovery of AgSbF_6 and (*R*)-(*S*)-JOSIPHOS as the ideal catalyst system, and *N*-methylmorpholine as the base. When the reaction was performed in a mixture of methanol/THF, this resulted in the formation of allenes with *ee* values higher than 90%. The reactions did not complete, however, resulting in a mixture of alkynes and allenes which was not separable by chromatography. This problem was solved by applying the same methodology to 3-alkynamides. Within an hour at 0 °C, the reaction was finished, and the alkynes and allenes could easily be separated chromatographically. Nine different allenic amides were synthesized, in 27-95% yield, and 90-99% *ee*.

Once the allenes were synthesized, we determined the absolute stereochemistry, discovering that our methodology formed the (*S*)-allenes. We did this by transforming the allenes to a known butenolide *via* and iodolactonization reaction and removal of the iodine. By comparing the experimental optical rotation to the known optical rotation, we were able to determine the absolute stereochemistry. This was also confirmed by applying the Lowe-Brewster rule, a rule which applies only to allenes. In allenes, the absolute stereochemistry and axial helicity of the compound can be used to predict the direction of the optical rotation, and vice versa.

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First and foremost, I have to thank Keith for his support and guidance through this entire process (and it was definitely a process!). Keith, you were always there when I needed help or advice and you really care about your students and what is best for all of us. No matter how busy you are you make time, and I truly cannot imagine a better supervisor!

Thanks must go out to all members of the Fagnou Factory, past and present. Every one of you has helped me when necessary, and you are without a doubt the most fun and smottest lab ever! The allene dream team – Kayode, Dan, and Ho-Yan – thank you all for working with me on this (not always easy) project. Shoresy (sports, sports, sports, sports...), your help in finishing this thesis was indispensable, although your blind love of Gerber is questionable. The Second Cup crew – Nicole, Sophie (Nicophie!), L-Train and the Big Guy – our daily walks were often the highlight of my day, and you guys always keep me entertained. Dave, we started out together, and you are headed for great things, but I will only remember cottage/sauna Dave. My three bench neighbours - Marc, Derek, and Dan B. – you were all great to work next to, and the help and entertainment along the way was awesome(ish)! D-Lee, thanks for making me feel tall (and for being super cool – but mostly for making me feel tall!). All the Sherbrooke gang – Mégaaaaan, Elisia, David, JP, Méli – you guys are all awesome, even if your lunches made me jealous. Our resident music lovers, Whipp and Malcolm, I wish I had more time in the lab with you two (but not with the scream-o). And of course, our resident grumpy Frenchman, Ben, I personally apologize for Canadian dairy! I will miss all of you.

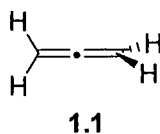
Finally, I need to thank my family and friends who were there for me outside the lab. Most importantly, my parents, who support (almost) every decision I make, and Matt, who believes in me and always makes me laugh. I love you all, and I couldn't have done any of this without you.

1 Introduction

1.1 Introduction to Allenes

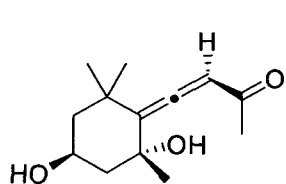
An allene is a unique hydrocarbon compound containing two orthogonal carbon-carbon double bonds. The simplest allene, 1,2-propadiene (**1.1**) is illustrated below.

Figure 1.1. 1,2-Propadiene.

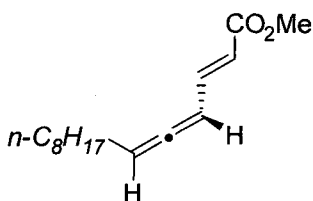


If each terminal carbon of the allene has two different substituents, the allene is axially chiral. The fixed orthogonal double bonds create an axis around which there is no free rotation. When both sides of an allene are unsymmetrically substituted, a system is created where the mirror image of the allene is no longer superimposable on the allene itself, therefore creating a chiral compound (see Figure 1.3 in section 1.1.1).

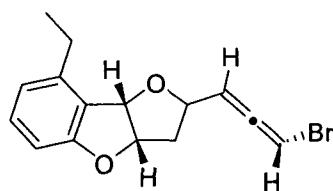
Figure 1.2. A selection of allenic natural products.



Grasshopper Ketone



Insect Pheromone



Panacene

Recently, allenenes have gained popularity in organic chemistry due to their synthetic utility in regio- and stereoselective carbon-carbon bond-forming reactions and their ability to transfer their chirality to one or more new chiral centres. There are also more than 150 known natural products and even some pharmacologically active compounds which contain allenenes, some of which are demonstrated in Figure 1.2. However, despite this

fact, there still remain very few effective methods to synthesize and manipulate optically active allenes.¹

1.1.1 Stereochemistry of Allenes

1.1.1.1 Assigning Stereochemistry

Due to the presence of axial chirality, the determination of the stereochemistry of allenes is slightly different from that of traditional chiral compounds.

Figure 1.3. Assigning stereochemistry to allenes.

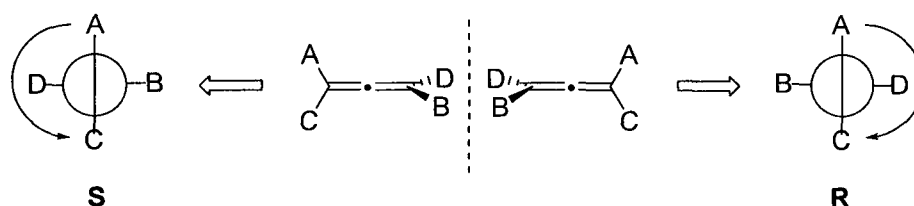


Figure 1.3 shows both enantiomers of an allene with different substituents (A,B,C,D) on each of the terminal carbon atoms. To assign (*R*) or (*S*) to these configurations, they must be viewed from either end, as demonstrated in the Newman projections. *If the priority order of the substituents is $A > B > C > D$, then the two front substituents are ranked 1 (A) and 2 (C), while the back substituents are given rankings of 3 (B) and 4 (D). Even though $B > C$ in priority, the substituents in the front are automatically awarded the top two priority levels. By then treating the allene like any other chiral centre, and placing the 4th priority substituent to the back, the enantiomeric configuration can be assigned based on a clockwise or counterclockwise rotation.*

1.1.1.2 Lowe-Brewster Rule

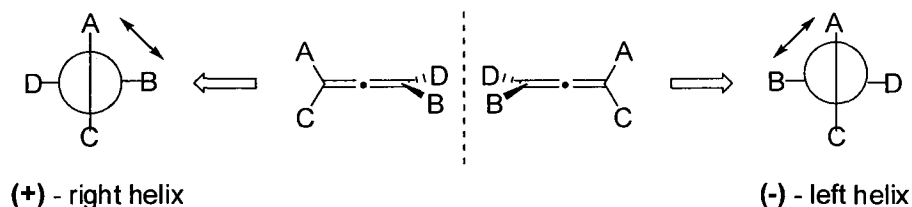
Typically, the absolute stereochemistry of a chiral compound has no bearing on the direction of the optical rotation. With allenes, however, the absolute stereochemistry and axial helicity of the compound can be used to predict the direction of the optical rotation, and vice versa. This is called the Lowe-Brewster Rule.² This rule is demonstrated in Figure 1.4 using the same allene as was used in Section 1.1.1.1.

¹ Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 2933.

² a) Brewster, J.H. *J. Am. Chem. Soc.* **1959**, *81*, 5475

b) Lowe, G. *Chem. Comm.* **1965**, *17*, 411.

Figure 1.4. The Lowe-Brewster Rule.



The Lowe-Brewster rule begins by viewing the allene along its orthogonal axis, with the most polarizable substituent (A) on the uppermost vertical axis. If the more polarizable substituent (B) along the horizontal axis is to the right, then a clockwise, or right-handed helix is obtained, and the enantiomer will be dextrorotatory – as is observed on the left in Figure 1.4. However, if the more polarizable substituent along the horizontal axis is to the left, then a counterclockwise, or left-handed helix is obtained and the enantiomer will be levorotatory, as can be seen on the right of Figure 1.4. Although this rule will seem counterintuitive to most organic chemists, there are numerous examples of its application to the determination and confirmation of the absolute stereochemistry of allenes. It can be used to predict the direction of optical rotation, or to determine the absolute stereochemistry of an allene where the direction of optical rotation is known.

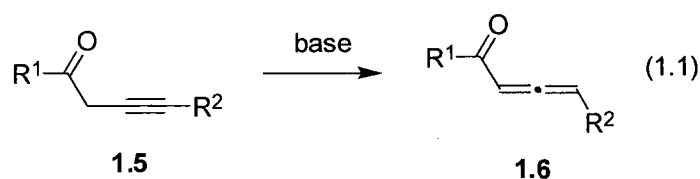
1.2 Acceptor-Substituted Allenes

Allenes directly connected to an electron-withdrawing group (EWG) such as carbonyl groups, nitriles, sulfones, sulfoxides, phosphine oxides and phosphonates are generally referred to as acceptor-substituted allenes. The polarization of the C=C double bond due to the presence of the EWG allows for a diverse range of useful reactions, including nucleophilic additions, heterocycle synthesis and cycloadditions. This usefulness of acceptor substituted allenes has created an increasing interest in their synthesis and reactivity.

1.2.1 Synthesis of Acceptor-Substituted Allenes

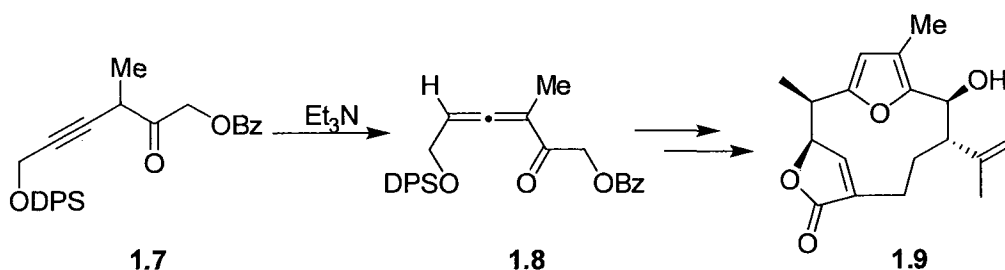
1.2.1.1 Racemic Synthesis

Perhaps the simplest method of synthesizing acceptor-substituted allenes is through the prototropic isomerization of a propargylic acceptor-substituted compound using a weak base.



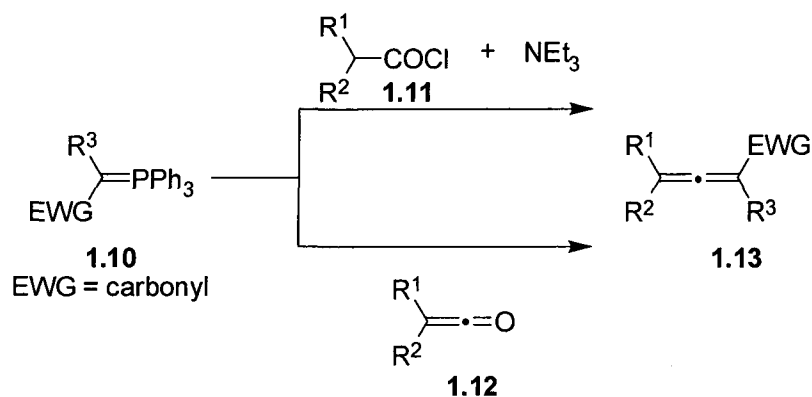
This is effective for the synthesis of allenic ketones, esters, thioesters and amides, and Marshall and Liao used this methodology towards the synthesis of the natural product kallolide A (**1.9**).³

Scheme 1.1. Synthesis of Kallolide A Using Prototropic Isomerization.



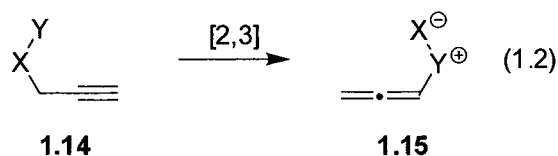
One of the oldest methods of making acceptor-substituted allenes is using the Horner-Wadsworth-Emmons reaction. The reactions of phosphoranes **1.10** with ketenes, either pre-formed (**1.12**) or generated *in situ* from acid chlorides (**1.11**) and triethylamine, provides an effective synthesis of EWG-substituted allenes **1.13**.

Scheme 1.2. Horner-Wadsworth-Emmons Reaction to Synthesize Allenes.



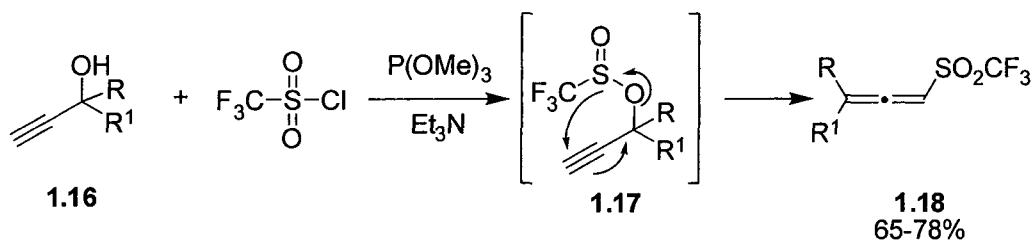
³ Marshall, J.A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962.

Acceptor-substituted allenes can also be formed by [2,3]-rearrangement reactions of propargyl and allyl precursors.



Braverman and co-workers recently used this method to synthesize allenyl trifluoromethyl sulfones (triflones) from propargylic trifluoromethanesulfonates (triflinates).⁴ Treatment of propargyl alcohols **1.16** with trifluoromethanesulfonyl chloride and triethylamine in the presence of reducing agent trimethyl phosphite gave triflinates **1.17**, which rapidly underwent a [2,3]-sigmatropic rearrangement to give allenic triflones **1.18**.

Scheme 1.3. In-situ [2,3]-Rearrangement Forming Allenic Triflones.

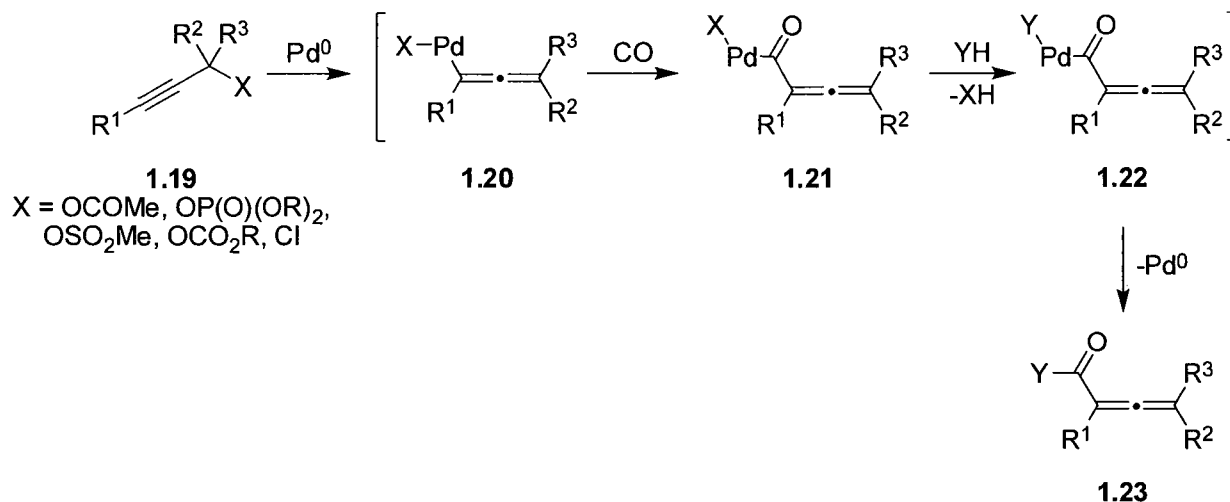


Another method of synthesizing allenic carbonyls is through a palladium-catalyzed carbonylation of propargyl compounds.⁵ Treatment of propargylic compounds **1.19** with palladium(0) results in oxidative addition by an S_N2'-type displacement of the leaving group with palladium(0) to give the allenylpalladium(II) complexes **1.20**. Carbon monoxide insertion into the palladium-carbon bond forms intermediates **1.21**. Exchange of group X for group Y may occur, followed by reductive elimination to yield the allenic carbonyls **1.23** and regenerate the palladium(0) species.

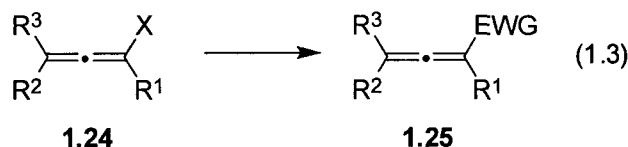
⁴ Braverman, S.; Pechenick, T.; Zafrani, Y. *Tetrahedron Lett.* **2001**, *42*, 1391.

⁵ Tsuji, J.; Mandai, T.; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2589.

Scheme 1.4. Palladium-Catalyzed Carbonylation of Propargyl Compounds.



Finally, acceptor-substituted allenes can be synthesized *via* introduction of the acceptor substituent into an already formed allene.



The simplest example of this type of allene formation is the oxidation of an already present functional group such as a primary or secondary alcohol, thioethers, selenoethers and phosphanes.

1.2.1.2 Enantioselective Synthesis

Many of the above mentioned methods for synthesizing acceptor-substituted allenes racemically can also be performed enantioselectively. These methods will be addressed in more detail in section 1.3, *Enantioselective Synthesis of Allenes*.

1.2.2 Reactions with Acceptor-Substituted Allenes

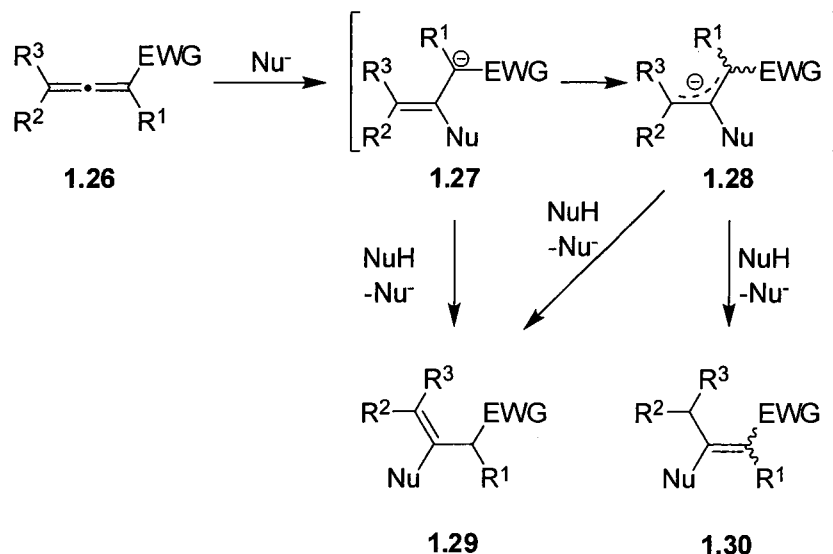
There is a diverse range of reactions which can be performed with acceptor-substituted allenes, including reactions with nucleophiles, electrophiles and cycloaddition reactions. The 'inner' C=C bond adjacent to the EWG is very electron deficient, and therefore

reacts with nucleophiles. It is also an excellent dienophile, and participates in cycloaddition reactions. The more electron-rich 'outer' C=C bond will react with electrophiles, and ring closing reactions are common. There are two types of reactions using acceptor-substituted allenes – reactions which can transfer the chirality of the allenes to the products and reactions in which the chirality is lost, either because the product formed is achiral, or the reaction passes through an achiral transition state. There are many examples of both types of reactions, and only the most common reactions or reactions which are useful to our methodology are presented here. Many more examples can be found in the books *Modern Allene Chemistry*, Volumes 1 and 2.⁶

1.2.2.1 Reactions with Loss of Chirality

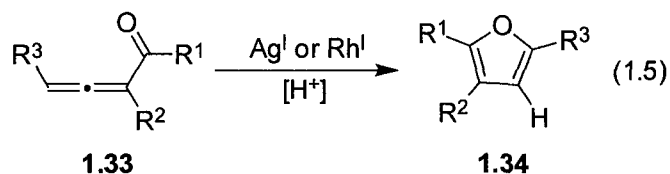
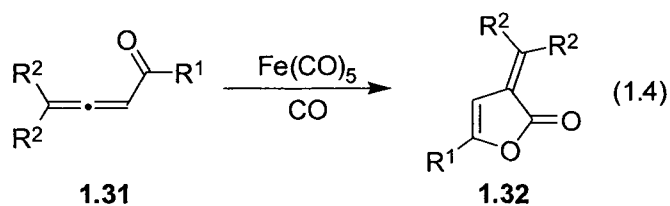
The presence of the EWG makes the 'inner' C=C bond electron-deficient, and thus highly electrophilic. Treatment of acceptor substituted allenes **1.26** with nucleophiles such as alcohols, phenols, carboxylates, amines, thiols, halides, hydride and azides leads to products of type **1.29** and **1.30**. The formation of intermediate **1.27** is kinetically controlled, while the formation of intermediate **1.28** is thermodynamically controlled. Both intermediates are achiral, meaning that it is impossible to transfer chirality from the starting allene to the final products.

Scheme 1.5. 1,4-Nucleophilic Addition on Acceptor-Substituted Allenes.



⁶ Krause, N.; Hashmi, A.S.K. *Modern Allene Chemistry*. 2004, Wiley-VCH, Weinheim, 1127 pp.

The treatment of allenyl ketones or aldehydes with various transition metals results in the formation of furans or achiral lactones.⁷ When allenyl ketones of type **1.31** are treated with $[\text{Fe}(\text{CO})_5]$, cyclic lactones **1.32** form through a metallacyclopentene intermediate (Equation 1.4). Similarly, when treated with Ag^{I} or Rh^{I} , allenyl ketones **1.33** cyclize to form furans **1.34** (Equation 1.5). The transition metal activates the 'outer' alkene, allowing for attack of the ketone and formation of the furan. Similar reactions can also be performed with palladium(II) and gold(III), allowing access to a wide array of furans and cyclic lactones.



1.2.2.2 Reactions with Transfer of Chirality

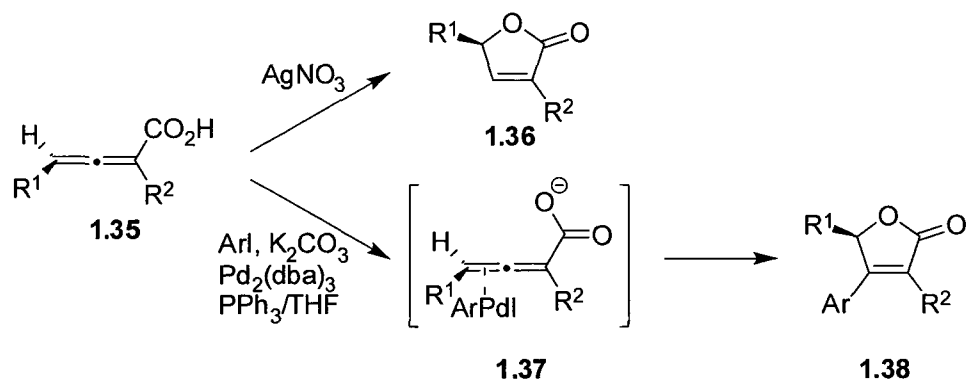
While reactions using acceptor-substituted allenes to form achiral products give access to a range of useful products, of greater interest are reactions where chirality can be transferred from an optically active allene to form optically active products. The most common types of these reactions are ring closing reactions to produce heterocycles. Allenic acids can be cyclized by a variety of different methods, some of which involve effective chirality transfer. In Scheme 1.6, two such examples are illustrated. Treatment of allenic acids **1.35** with silver nitrate results in the formation of butenolides **1.36** in good yields with effective transfer of chirality.⁸ Similarly, ring closure using palladium(0) catalysis in the presence of vinyl or aryl iodides results in cyclization followed by C-C bond formation to form butenolides **1.38**.⁹

⁷ Hashmi, A.S.K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590.

⁸ Marshall, J.A.; Wolf, M.A.; Wallace, E.M. *J. Org. Chem.* **1997**, *62*, 367.

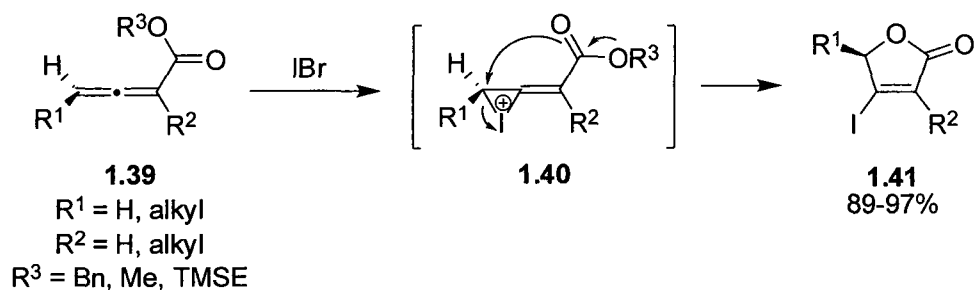
⁹ Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387.

Scheme 1.6. Transfer of Chirality via Cyclization Reactions.



Another example of a cyclization reaction with chirality transfer uses allenic esters. The esters are cyclized to form butenolides. Marshall and co-workers used IBr to perform an iodolactonization with complete retention of stereochemistry.⁸

Scheme 1.7. Iodolactonization with Retention of Stereochemistry.



Treatment of allenic esters **1.39** with IBr results in the formation of iodonium intermediates **1.40**, followed by cyclization. This forms iodobutenolides **1.41** in excellent yields. The ee values of the iodobutenolides are essentially identical to those of the starting allenic esters, indicating a complete transfer of chirality.

1.3 Enantioselective Synthesis of Allenes

Given the attractiveness of allenes as chiral synthons in organic synthesis, the development of synthetic methodologies to create chiral allenes is highly desired. Although the majority of chiral allenes are synthesized by chirality transfer from

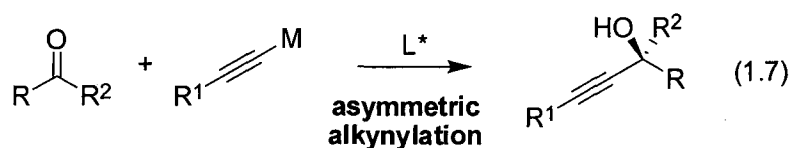
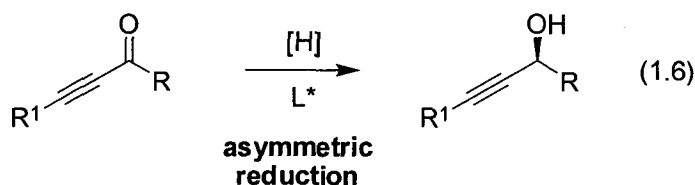
enantioenriched starting materials, recent work has been done to synthesize allenes from achiral starting materials, either by the use of chiral reagents or chiral catalysts.

1.3.1 Enantioselective Synthesis of Allenes *via* Chirality Transfer

The most commonly used method to synthesize chiral allenes is by chirality transfer from an enantioenriched starting material. This is an efficient method which produces optically active allenes in high enantioselectivities, but it often adds extra steps, since it involves first synthesizing the chiral starting material and then performing a reaction to form the allene itself. This chirality transfer typically comes from a chiral propargylic or allylic compound.

1.3.1.1 Chirality Transfer from Propargylic Compounds

The synthesis of chiral allenes from chiral propargylic compounds is the single most used method to make allenes enantioselectively. Before the allene can be made, however, initial steps must be performed to synthesize the enantioenriched propargyl compound. Most of these propargyl compounds originate from chiral propargylic alcohols, which are generally prepared in two ways – asymmetric reduction of an ynone (Equation 1.6), or asymmetric metal catalyzed alkylation of a carbonyl (Equation 1.7). These propargylic alcohols are either used directly to synthesize the allenes, or further transformed to the desired allene precursors.

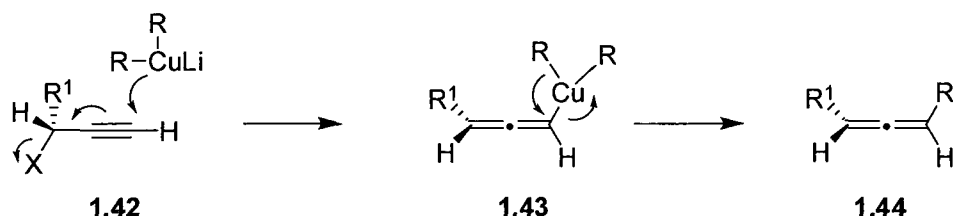


1.3.1.1.1 S_N2' Reactions

One of the most common methods used to synthesize chiral allenes is the S_N2' displacement of a chiral propargyl alcohol derivative with an organometallic nucleophile, typically an organocuprate. The generally accepted mechanism for this process is the

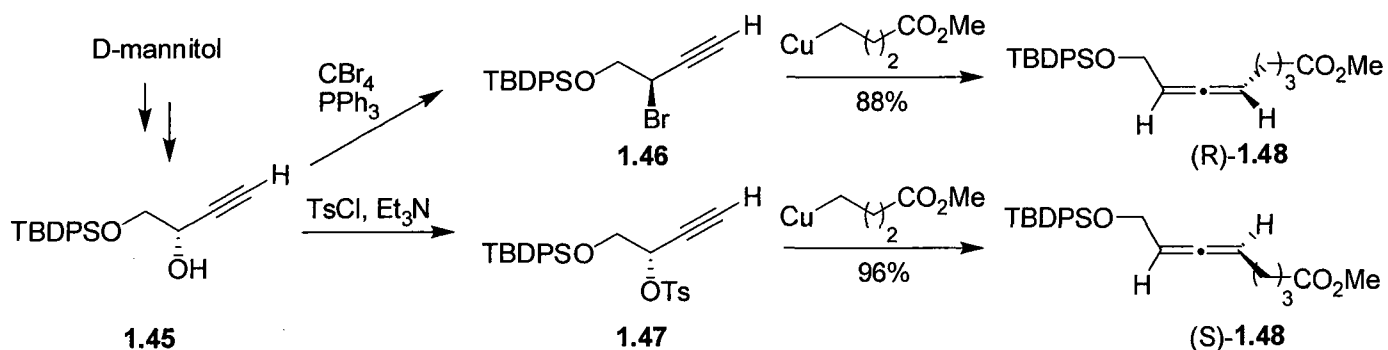
formation of a Cu^{III} intermediate resulting from an anti $\text{S}_{\text{N}}2'$ attack of the Cu^{I} nucleophile, followed by reductive elimination of the intermediate with retention of configuration to give the allene.¹⁰

Scheme 1.8. General Mechanism for $\text{S}_{\text{N}}2'$ Displacement.



Gooding and co-workers demonstrated the utility of this methodology by synthesizing both enantiomers of an antifungal constituent of *Sapium japonicum* (**1.48**).¹¹ Conversion of D-mannitol to the chiral propargyl alcohol **1.45** is followed by tosylate **1.47** or bromide **1.46** formation. Reaction of the propargyl compounds with the necessary organocopper reagent gives enantiomers (*R*)-**1.48** and (*S*)-**1.48** of the same allene. Deprotection of the (*R*) enantiomer with TBAF afforded the required natural product in >94% ee.

Scheme 1.9. Synthesis of Both Enantiomers of *Sapium japonicum*.



This methodology can also be used to form haloallenes by using halocuprate species HCuX_2 . Chiral haloallenes can be used to perform organocopper-mediated substitutions, palladium-catalyzed cross-coupling reactions and the creation of

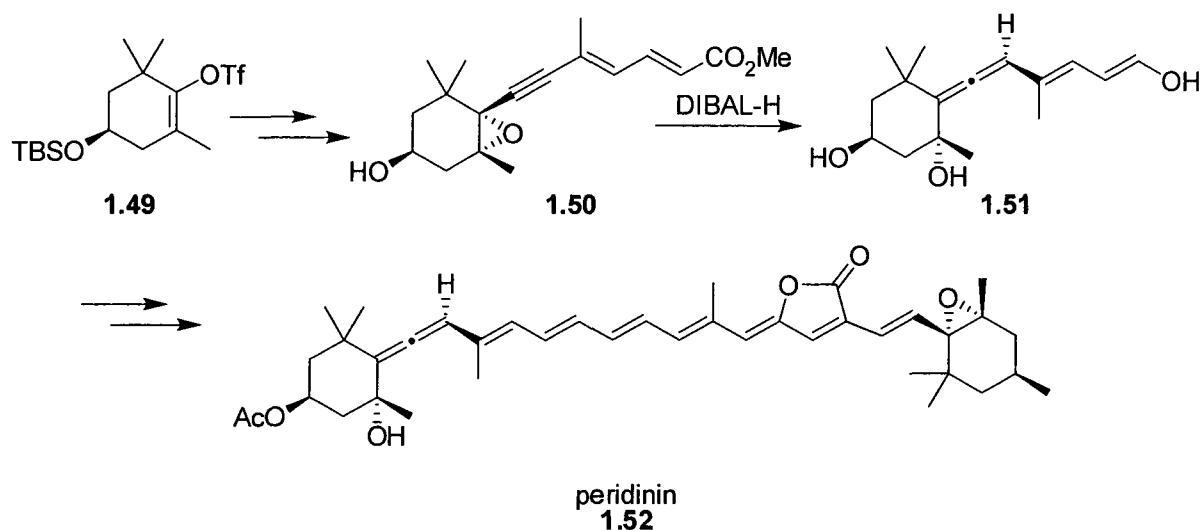
¹⁰ Dollat, J.M.; Luche, J.L.; Crabbe, P.J. *J. Chem. Soc., Chem. Commun.* **1977**, 761.

¹¹ Gooding, O.W.; Beard, C.C.; Jackson, D.Y.; Wren, D.L.; Cooper, G.F. *J. Org. Chem.* **1991**, *56*, 1083.

nucleophilic allenylmetal reagents. As well, many allenic natural products are haloallenes.

The nucleophilic ring-opening of asymmetric propargyl epoxides and related compounds is another convenient method to stereospecifically synthesize allenes. Furuichi and co-workers recently applied this methodology to the stereocontrolled synthesis of the natural product peridinin (**1.52**).¹² Starting from known vinyltriflate **1.49**, the epoxide is installed enantioselectively through a Sharpless epoxidation. Further steps give chiral epoxide **1.50** and treatment with DIBAL-H opens the epoxide stereospecifically to give chiral allene **1.51**. Coordination of the aluminum hydride to the epoxide delivers the hydride stereospecifically. Additional transformations completed the synthesis of peridinin.

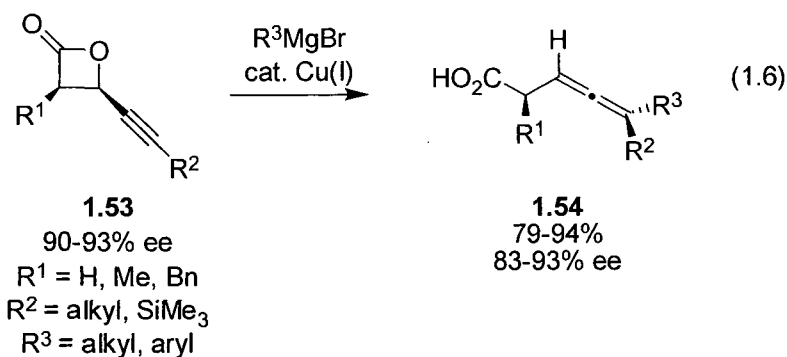
Scheme 1.10. Stereocontrolled Synthesis of Peridinin.



Wan and Nelson have reported the use of chiral propargyl β -lactones as precursors to chiral allenes.¹³ Copper-catalyzed S_N2' reactions on β -lactones **1.53** with Grignard reagents gives chiral allenes **1.54** in consistently high yields and enantioselectivities. The reaction gives essentially complete chirality transfer from the stereogenic centre of the lactone to the axially chiral allene.

¹² Furuichi, N.; Hara, H. Osaki, T.; Nakano, M.; Mori, H; Katsumara, S. *J. Org. Chem.* **2004**, *69*, 7949.

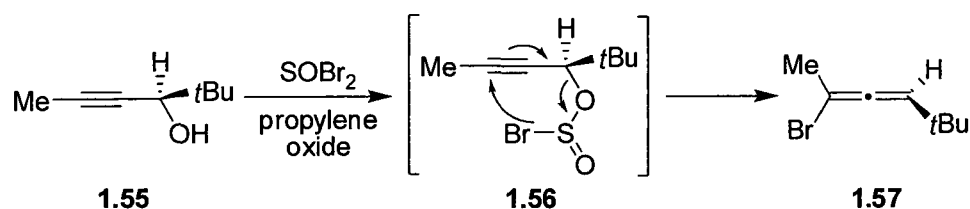
¹³ Wan, Z.; Nelson, S.G.; *J. Am. Chem. Soc.* **2000**, *122*, 10470.



1.3.1.1.2 Rearrangement Reactions

Another common method to synthesize optically active allenes from propargyl compounds is by rearrangement reactions. In this method, a chiral propargyl alcohol is transformed into a derivative which then rearranges to the allene. The first example of this type of reaction, reported in 1963, was the reaction of propargylic alcohols with thionyl chloride,¹⁴ and a similar reaction with thionyl bromide was reported in 1984 by Corey and Boaz (Scheme 1.11).¹⁵ In this reaction, chiral propargyl alcohol **1.55** is treated with SOBr₂ to give intermediate **1.56**, which quickly rearranges to give optically active allene **1.57**.

Scheme 1.11. Chiral Allene Formation via a Rearrangement Reaction.



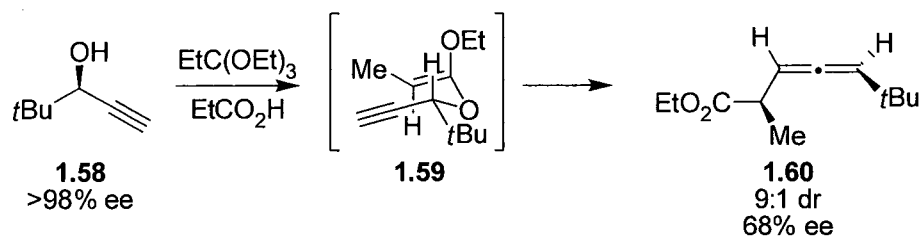
The [3,3] sigmatropic rearrangement reaction can also synthesize allenes with transfer of chirality. In 1988, Henderson and Heathcock reported the first synthesis of asymmetric allenes by an orthoester Claisen rearrangement.¹⁶ Chiral propargyl alcohol **1.58** was treated with triethyl orthopropionate and propionic acid to create the (*E*)-ketene acetal intermediate **1.59**. An orthoester Claisen rearrangement ensues, giving allene **1.60** with good diastereo- and enantioselectivity.

¹⁴ Evans, R.J.D.; Landor, S.R; Smith, R.T. *J. Chem. Soc.* **1963**, 1506.

¹⁵ Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1984**, 25, 3055.

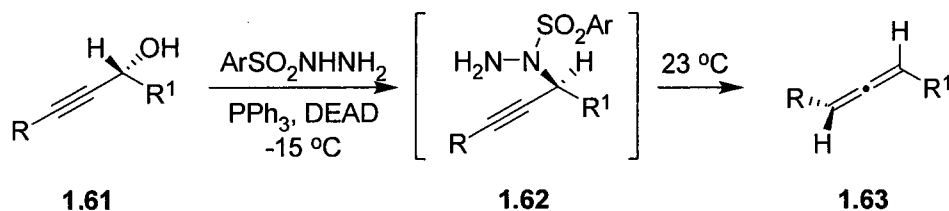
¹⁶ Henderson, M.A.; Heathcock, C.H. *J. Org. Chem.* **1988**, 53, 4736.

Scheme 1.12. Chiral Allene Formation via a [3,3] Sigmatropic Rearrangement.



Myers and Zheng reported another rearrangement-type synthesis using chiral propargyl alcohols. The reaction of propargyl alcohols **1.61** with an arylsulfonylhydrazine in the presence of PPh_3 and DEAD leads to the enantioselective synthesis of allenes **1.63**.¹⁷ An initial Mitsunobu reaction forms intermediate **1.62**, which thermally decomposes to form the chiral allene.

Scheme 1.13. One-Pot Mitsunobu/Rearrangement Reaction to Form Chiral Allenes.

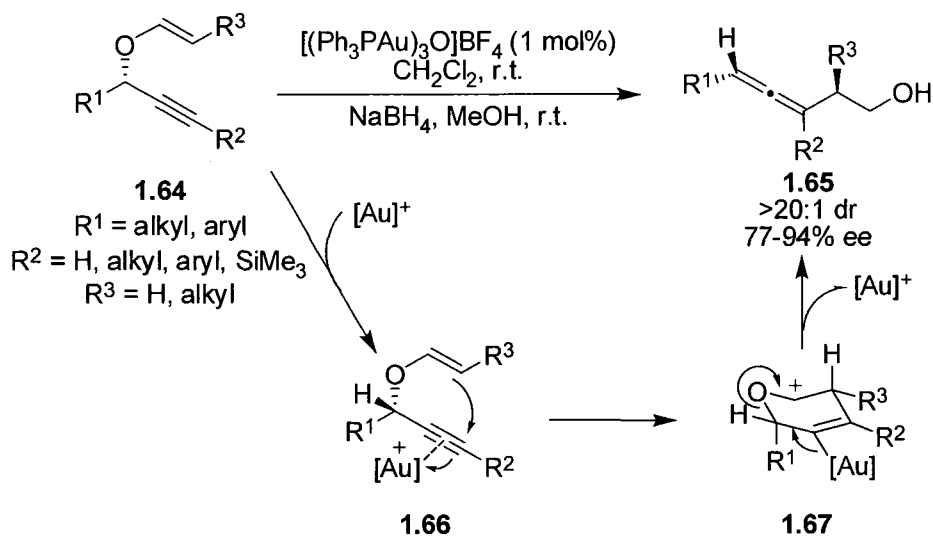


Recently, Toste and Sherry reported a gold(I)-catalyzed propargyl Claisen rearrangement to form optically active allenes.¹⁸ Treatment of chiral propargyl alcohol derivatives **1.64** with a gold(I) catalyst (1 mol%) forms gold(I)-alkyne complex **1.66**. This activation of the alkyne by the electrophilic gold(I) allows a 6-*endo*-dig cyclization of the enol ether, giving cyclic intermediate **1.67**. Grob-type fragmentation of **1.67** gives the allenic product **1.65**. Chirality is almost completely transferred, with a maximum loss of 4% ee from the starting propargyl alcohol. The reaction is also highly diastereoselective, which can be attributed to the minimization of strain in the transition state. The R^3 group adopts a pseudoequatorial position to minimize sterics, and the R^1 group adopts a pseudoequatorial position to minimize $\text{A}^{1,2}$ strain with the vinyl gold substituent.

¹⁷ Myers, A.G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

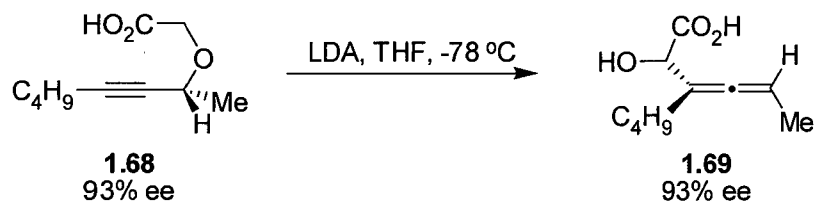
¹⁸ Sherry, B.D.; Toste, F.D. *J. Am. Chem. Soc.* **2004**, *126*, 15978.

Scheme 1.14. Gold Catalyzed Claisen Rearrangement.



[2,3]-Sigmatropic rearrangements can also be used to transform asymmetric propargyl substrates into asymmetric allenes. Marshall and co-workers used the [2,3]-Wittig rearrangement to synthesize α -hydroxyallenes.¹⁹ Treatment of optically active propargyl ether **1.68** with LDA deprotonates next to the carboxylic acid, leading to a rearrangement to give the chiral allene **1.69**. This reaction occurs with complete retention of chirality, providing useful access to asymmetric allenyl carbinols.

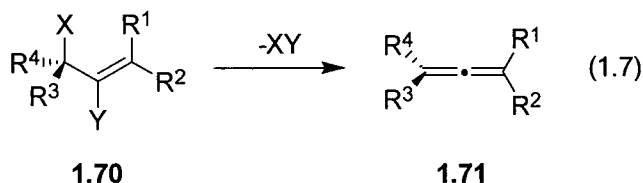
Scheme 1.15. [2,3]-Wittig Reaction to Form Chiral Allenes.



¹⁹ Marshall, J.A.; Robinson, E.D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854.

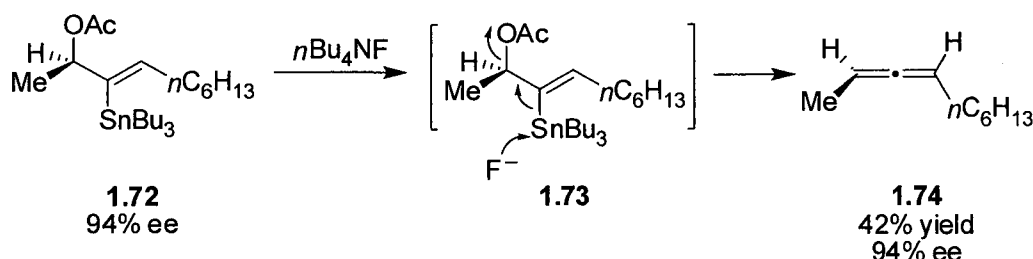
1.3.1.2 Chirality Transfer from Elimination Reactions of Allylic Compounds

Elimination reactions of chiral allylic compounds can give chiral allenes. Chirality at the allylic position is transferred to axial chirality of allenes *via* β -elimination.



Konoike and Araki utilized this methodology to the synthesis of chiral allenes from optically active stannyl allylic acetates.²⁰ Chiral β -stannyl allylic acetate **1.72** is treated with tetrabutylammonium fluoride, and the resultant allene **1.74** is formed with complete retention of enantiomeric excess. The β -elimination occurs with complete *anti*-selectivity to allow for proper orbital overlap.

Scheme 1.16. Elimination Reaction Using Chiral Stannyl Allylic Acetates.



Chiral allenes can also be formed by β -elimination of an allylic compound which is achiral at the allylic position but has a chiral leaving group. Uemura and co-workers reported the synthesis of chiral selenoxides and subsequent β -elimination to form chiral allenes.²¹ Chiral ferrocenyl vinyl selenides **1.75** are formed by the reaction of ethyl propionate derivatives with chiral diferrocenyl diselenide (*S,R*)-**1.78** in the presence of NaBH₄. Diastereoselective oxidation of the chiral selenides using *m*CPBA gives chiral

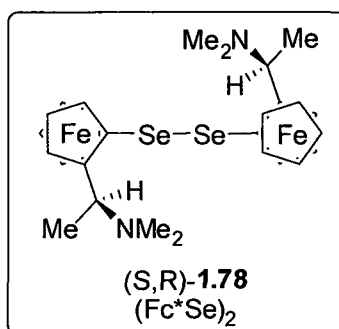
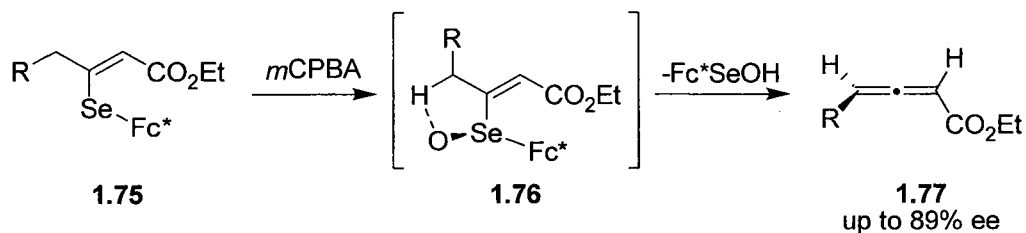
²⁰ Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093.

²¹ a) Nishibayashi, Y.; Singh, J.D.; Uemura, S. *Tetrahedron Lett.* **1994**, *35*, 3697.

b) Nishibayashi, Y.; Singh, J.D.; Fukuzawa, S.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4114.

selenoxides **1.76**, which eliminate spontaneously to give allenic esters **1.77** in good enantioselectivities.

Scheme 1.17. Using a Chiral Leaving Group.



1.3.2 Enantioselective Synthesis of Allenes from Achiral Starting Materials

Although the synthesis of allenenes by chirality transfer can be very effective, it requires the synthesis of optically active starting materials. This adds extra steps to a synthesis, and also relies on the ease of synthesis of these asymmetric starting materials. An ideal method of synthesizing chiral allenenes is through the reaction of a prochiral substrate with an external chiral reagent or catalyst.

1.3.2.1 Allene Synthesis with Chiral Reagents

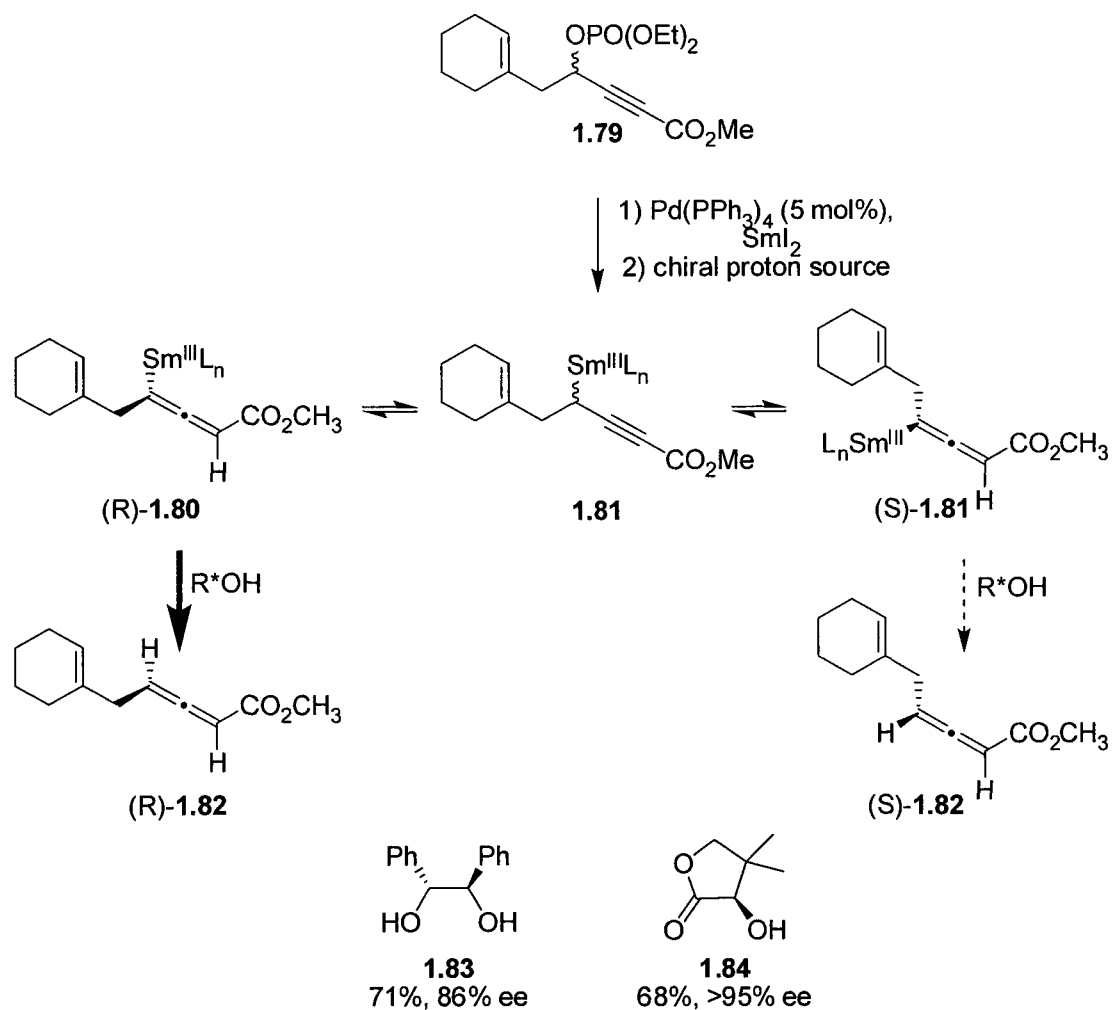
One method of synthesizing chiral allenenes from achiral starting materials is to use a stoichiometric equivalent of a chiral reagent. Although this is technically a method which uses achiral starting materials, at some point in the process at least one equivalent of a chiral compound is necessary.

1.3.2.1.1 Asymmetric Deprotonation-Protonation

In 1997, Mikami and Yoshida reported an asymmetric synthesis of allenic esters via enantioselective protonation of racemic allenylmetal compounds.²² Achiral propargylic phosphate **1.79** is treated with Pd(0) (5 mol%) and SmI₂ to form propargylic samarium(III) intermediate **1.81**. This rapidly isomerizes to the enantiomeric allenylsamarium(III) intermediates (*R*)-**1.80** and (*S*)-**1.80**, and treatment with a chiral proton source (1.1 equiv.) gives allenic ester (*R*)-**1.82** in good yields and enantioselectivities. Different chiral proton sources were tested, and (*R,R*)-(+)-hydrobenzoin (**1.83**) and (*R*)-(-)-pantolactone (**1.84**) were the best, giving 86% and >95% ee, respectively.

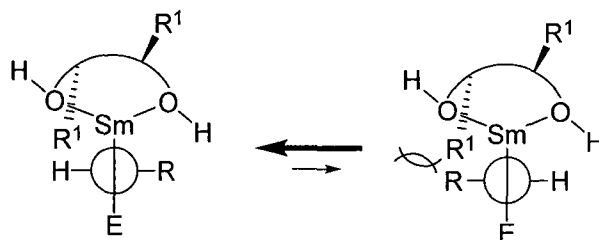
²² Mikami, K.; Yoshida, A. *Angew. Chem, Int. Ed. Engl.* **1997**, *36*, 858.

Scheme 1.18. Asymmetric Deprotonation-Protonation.



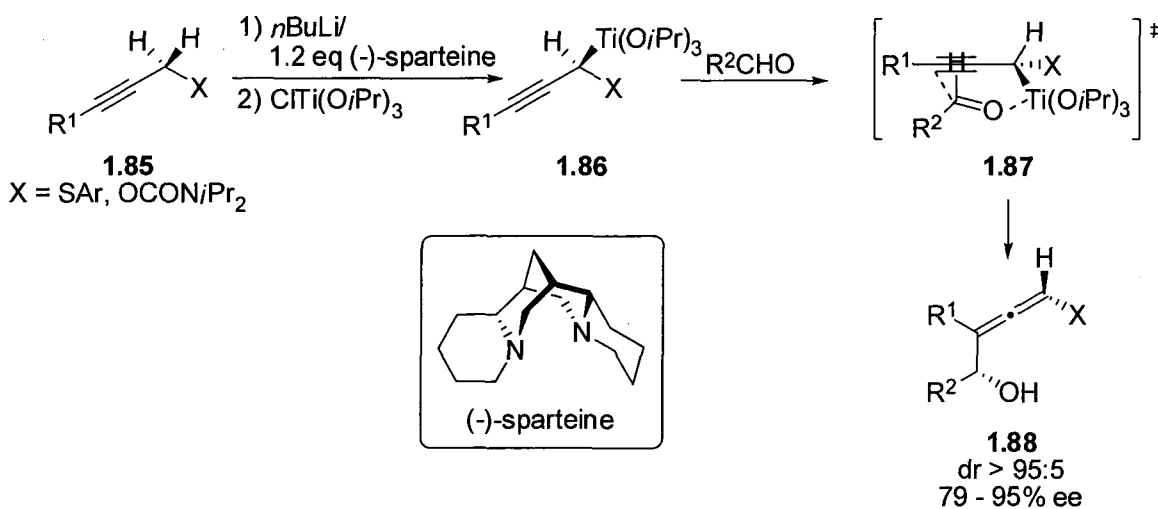
The selective protonation of one enantiomer is proposed to occur through a transition state model in which steric repulsion between the alkyl groups on the allenylsamarium(III) species and the chiral proton source hinders protonation of (S)-1.82 and favours protonation of (R)-1.82.

Figure 1.5. Transition State Model for Deprotonation-Protonation.



The Hoppe group has reported an enantio- and diastereoselective synthesis of allenes by (-)-sparteine-mediated lithiation of alkynyl carbamates and aryl sulfides.²³ In this reaction, prochiral alkynes **1.85** are treated with *n*BuLi in the presence of (-)-sparteine (1.2 equiv.), giving a chiral anion through an enantioselective deprotonation of one of the protons. Transmetalation of the lithium anion with ClTi(O*i*Pr)₃, followed by the addition of an aldehyde leads to the formation of allyl alcohols **1.88**. The stereoselectivity of the reaction comes from a Zimmerman-Traxler transition state (**1.87**), which requires a suprafacial addition, and efficiently transfers the established chirality enantio- and diastereoselectively.

Scheme 1.19. Enantioselective Deprotonation Using (-)-Sparteine.



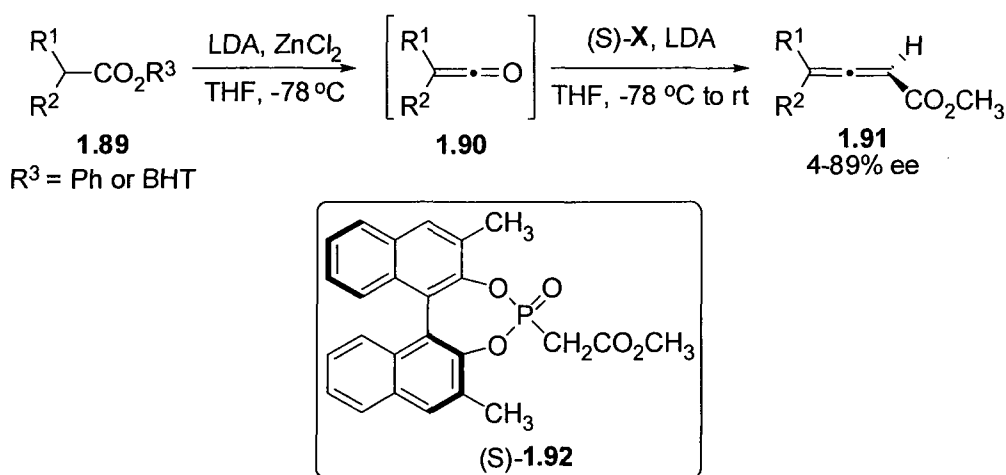
²³ a) Schultz-Fademrecht, C.; Wibbeling, B.; Frohlich, R.; Hoppe, D. *Org. Lett.* **2001**, 3, 1221.

b) Otte, R.; Wibbeling, B.; Frohlich, R.; Nakamura, S.; Shibata, N.; Toru, T.; Hoppe, D. *Tetrahedron Lett.* **2007**, 48, 8636.

1.3.2.1.2 Asymmetric Horner-Wadsworth-Emmons Reactions

A recent method developed to synthesize chiral allenic esters is the asymmetric Horner-Wadsworth-Emmons (HWE) reaction. The first example of this reaction was published by Tanaka and co-workers in 1996.²⁴ In this reaction aryl acetates **1.89** are treated with LDA in the presence of ZnCl₂ to create ketenes **1.90**. Further treatment with the optically active phosphonoacetate reagent (*S*)-**1.92** (1 equiv.) and LDA gives the desired allenic esters **1.91** in low to good enantioselectivities.

Scheme 1.20. Asymmetric Horner-Wadsworth-Emmons Reaction.

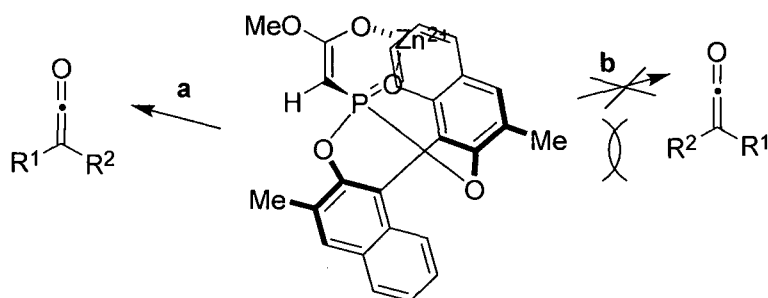


Enantioselectivity in this and other chiral HWE reactions is based on two factors - a significant difference in size between R¹ and R², and the fact that the chiral phosphonate effectively blocks one side of the ylide. Assuming R¹ is bigger than R², the less hindered face of the ylide will approach the ketene from the side with the smaller R² group. As R¹ and R² approach each other in size, the enantiomeric excess decreases.

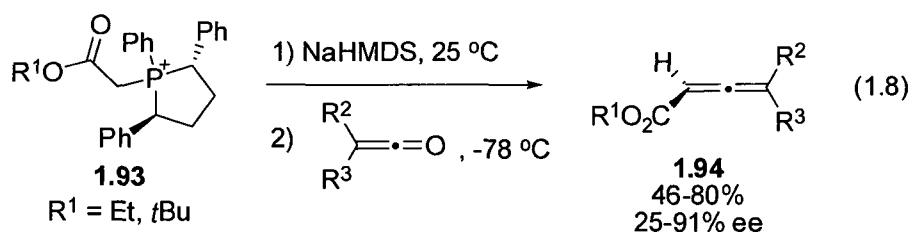
²⁴ a) Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *37*, 3735.

b) Yamazaki, J.; Watanbe, T.; Tanaka, K. *Tetrahedron: Asymm.* **2001**, *12*, 669.

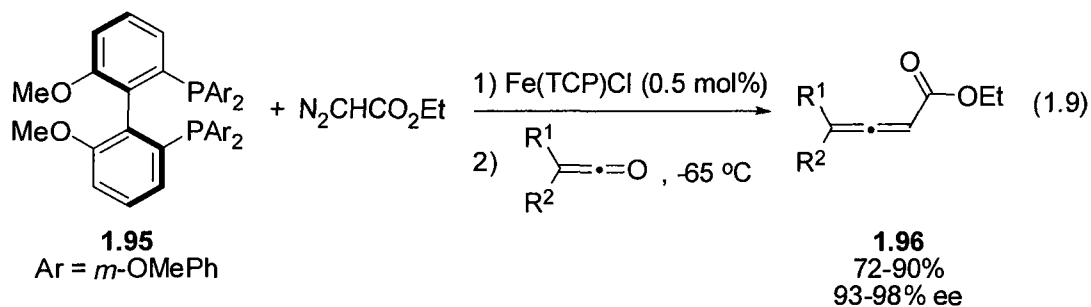
Figure 1.6. Mechanistic Explanation for Observed Enantioselectivity in Chiral HWE.



More recently, Li and co-workers have reported a similar HWE method for the preparation of allenic esters, amides, ketones and nitriles.²⁵ Deprotonation of chiral phosphonium salt **1.93** with NaHMDS creates an ylid, which reacts with ketenes to give allene **1.94** in low to good enantioselectivities.



Li and co-workers have also recently published a HWE-like synthesis of chiral allenic esters from tetra(*p*-chlorophenyl)porphyrin iron chloride (Fe(TCP)Cl), chiral phosphine and ethyl diazoacetate.²⁶



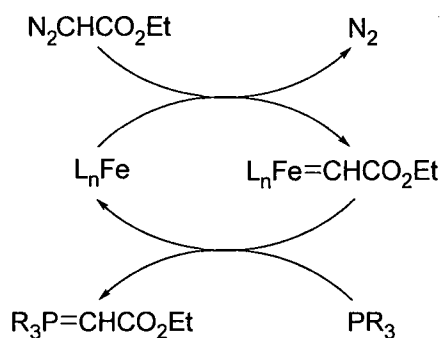
²⁵ a) Li, C.; Sun, X.; Jing, Q.; Tang, Y. *Chem. Commun.* **2006**, 28, 2980.

b) Li, C.; Zhu, B.; Ye, L.; Jing, Q.; Sun, X.; Tang, Y.; Shen, Q. *Tetrahedron.* **2007**, 63, 2007.

²⁶ Li, C.; Wang, X.; Sun, X.; Tang, Y.; Zheng, J.; Xu, Z.; Zhou, Y.; Dai, L. *J. Am. Chem. Soc.* **2007**, 129, 1494.

As can be seen in Figure 1.7, the iron complex reacts with the ethyl diazoacetate to generate an iron(II) carbene species. This carbene ligand is then transferred to chiral phosphine **1.95** to generate an asymmetric HWE reagent, which can then react with the ketene to generate the chiral allene **1.96**. This gives the chiral phosphine oxide as a byproduct which cannot be recycled; meaning that at least 1 equivalent of the chiral phosphine reagent must be used.

Figure 1.7. Iron-Catalyzed HWE Synthesis of Chiral Allenes.



Reactions such as asymmetric deprotonation-protonation and asymmetric HWE reactions form chiral allenes from achiral starting materials. However, at least one equivalent of chiral reagent is used in the process, so the reaction is not really different from those with chiral starting materials. This eliminates the need to synthesize a chiral starting material, but is still wasteful of chiral materials. The only method which does not require some type of stoichiometric chiral reagent is the use of an external chiral catalyst.

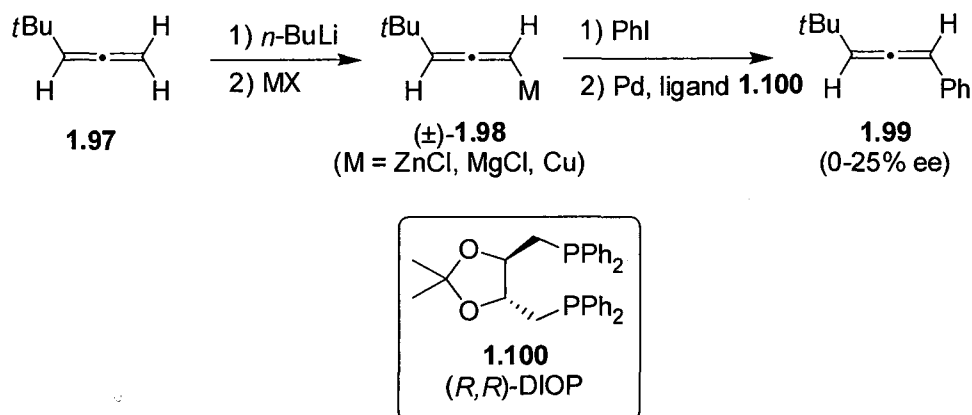
1.3.2.2 Allene Synthesis Using a Chiral Catalyst

1.3.2.2.1 Synthesis from non-Allenic Starting Materials

The formation of optically active allenes from achiral starting materials using an external chiral catalyst is an area which has only been recently explored. Only a handful of examples of this type of catalysis have been discovered, and the efficacy of these reactions is moderate at best.

The first example of the formation of chiral allenes by asymmetric catalysis was reported by De Graaf and co-workers in 1989.²⁷ Deprotonation of monosubstituted allene **1.97** with *n*BuLi, followed by treatment with a metal source gives racemic allenylmetal reagent (\pm)-**1.98**. A cross-coupling reaction with a chiral ligand and iodobenzene in the presence of palladium and a chiral ligand yields disubstituted allene **1.99** in low enantiomeric excess. The best results were observed with zinc chloride as the metal source, palladium chloride and (*R,R*)-DIOP (**1.100**) as the chiral ligand. While the obtained enantiomeric excess of 25% is modest, it is significant as this is the first reported allene synthesis using a chiral catalyst.

Scheme 1.21. The First Reported Asymmetric Allene Synthesis Using a Chiral Catalyst.



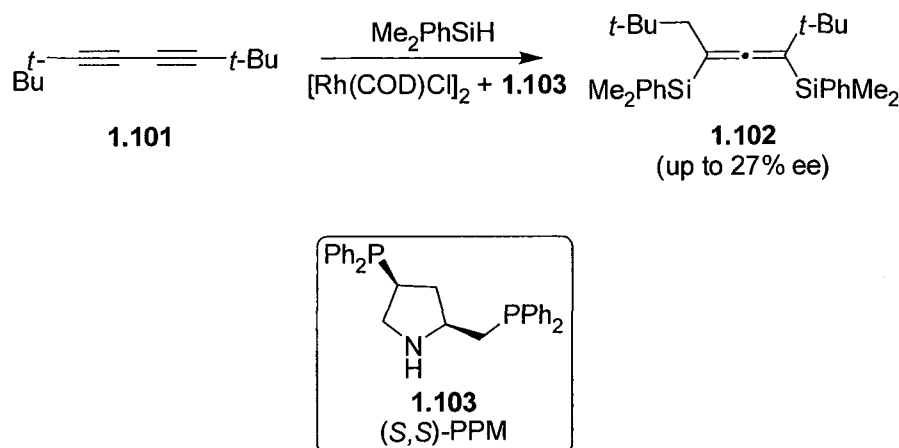
A second example of the synthesis of optically active allenes by chiral catalysis was not published until ten years later. In 1999, Tillack and co-workers reported the formation of allenylsilanes in modest enantiomeric excess *via* the hydrosilylation of butadiynes.²⁸ Over 30 chiral phosphine ligands were tested in combination with [Rh(COD)Cl]₂ (1 mol%), and the best results were observed with (*S,S*)-PPM (**1.103**) (2 mol%) as the ligand. Hydrosilylation of butadiyne **1.101** with the asymmetric rhodium catalyst gives allenylsilane **1.102** in 27% *ee*. Reactions using other metals such as Ni, Ir, Pd and Pt were less effective.

²⁷ De Graaf, W.; Boersma, J.; van Koten, G.; Elsevier, C.J. *J. Organomet. Chem.* **1989**, 378, 115.

²⁸ a) Tillack, A.; Michalik, D.; Koy, C.; Michalik, M. *Tetrahedron Lett.* **1999**, 40, 6567.

b) Tillack, A.; Koy, C.; Michalik, D.; Fischer, C. *J. Organomet. Chem.* **2000**, 603, 116.

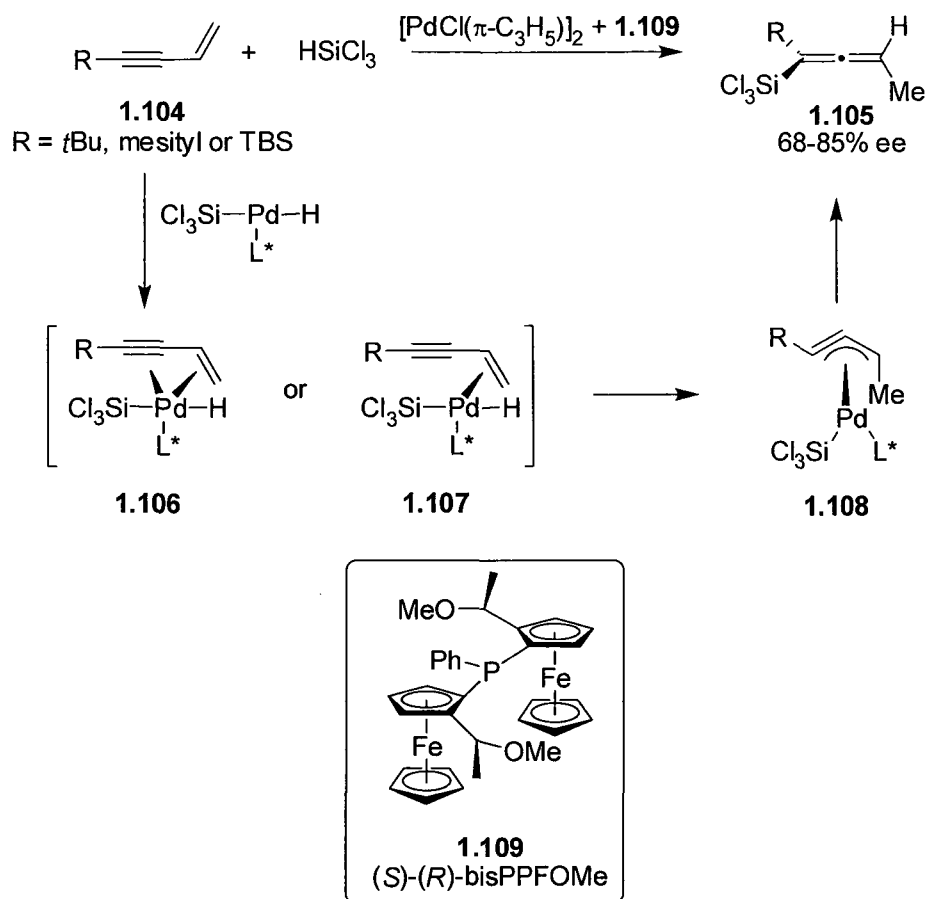
Scheme 1.22. Enantioselective Hydrosilylation of Butadienes.



In 2001, Hayashi and co-workers published two unique approaches to the synthesis of chiral allenes by asymmetric palladium catalysis. The first approach was a synthesis of chiral allenylsilanes *via* a palladium catalyzed asymmetric hydrosilylation of 1,3-enynes.²⁹ The treatment of enynes **1.104** with trichlorosilane in the presence of a palladium complex formed from $[\text{PdCl}(\pi\text{-C}_3\text{H}_5)]_2$ (1 mol%) and the chiral ligand **1.109** (2.2 mol%) gives allenylsilanes **1.105** in yields of 40-90% and enantiomeric excesses of 68-85%. However, a key limitation to this methodology is that the R group on the enyne must be a bulky group (*ie* *t*Bu, mesityl or TBS), or else there is minimal selectivity. The reaction is proposed to pass through a catalytic cycle involving hydropalladation of the terminal alkene, forming a π -propargyl(silyl)palladium intermediate (Scheme 1.23). The necessity of a sterically bulky R group appears to be important to slow down the hydropalladation of the alkyne as opposed to the alkene.

²⁹ Han, J.W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915.

Scheme 1.23. Palladium-Catalyzed Hydrosilylation of 1,3-Enynes.

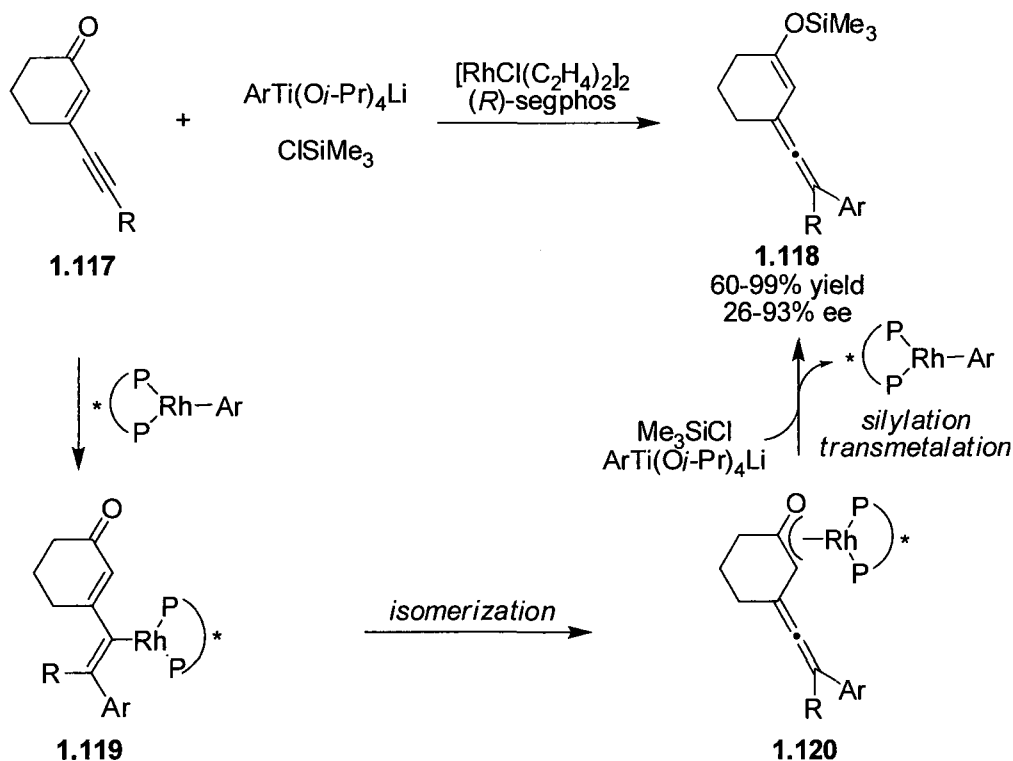


The second approach published by the Hayashi group in 2001 involves a palladium-catalyzed formal $\text{S}_{\text{N}}2'$ reaction of achiral conjugated dienes.³⁰ Treatment of dienes **1.110**, which are easily derived from aldehydes, with an asymmetric Pd/(*R*)-BINAP catalyst (**1.112**, 10 mol%) in the presence of a base and a soft nucleophile gives the disubstituted allene products **1.111** in moderate to high enantioselectivities.

³⁰ Ogasawara, M.; Ikeda, H.; Nagano, T; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089.

Hayashi and co-workers published a third approach towards the synthesis of axially chiral allenes in 2004.³² 1,6-Addition of aryltitanate reagents to 3-alkynyl-2-en-1-ones **1.117** in the presence of chlorotrimethylsilane, a rhodium catalyst (10 mol%) and the chiral ligand (*R*)-segphos (20 mol%) gives axially chiral allenylalkenyl silyl enol ethers **1.118** in high yields and enantioselectivities. The reaction is thought to proceed through the catalytic cycle shown in Scheme 1.27, where the alkyne inserts into the rhodium-aryl bond forming alkenylrhodium **1.119**. This intermediate then isomerizes to the more stable oxa- π -allylrhodium intermediate **1.120**, followed by transmetalation, giving the silyl enol ether **1.118** and reforming the rhodium-aryl intermediate.

Scheme 1.26. Rhodium-Catalyzed Asymmetric Synthesis of Allenes.



These examples are the only known methods of synthesizing chiral allenes catalytically from non-allenic achiral starting materials. Although important, none of these methods consistently yields chiral allenes in synthetically useful enantioselectivities.

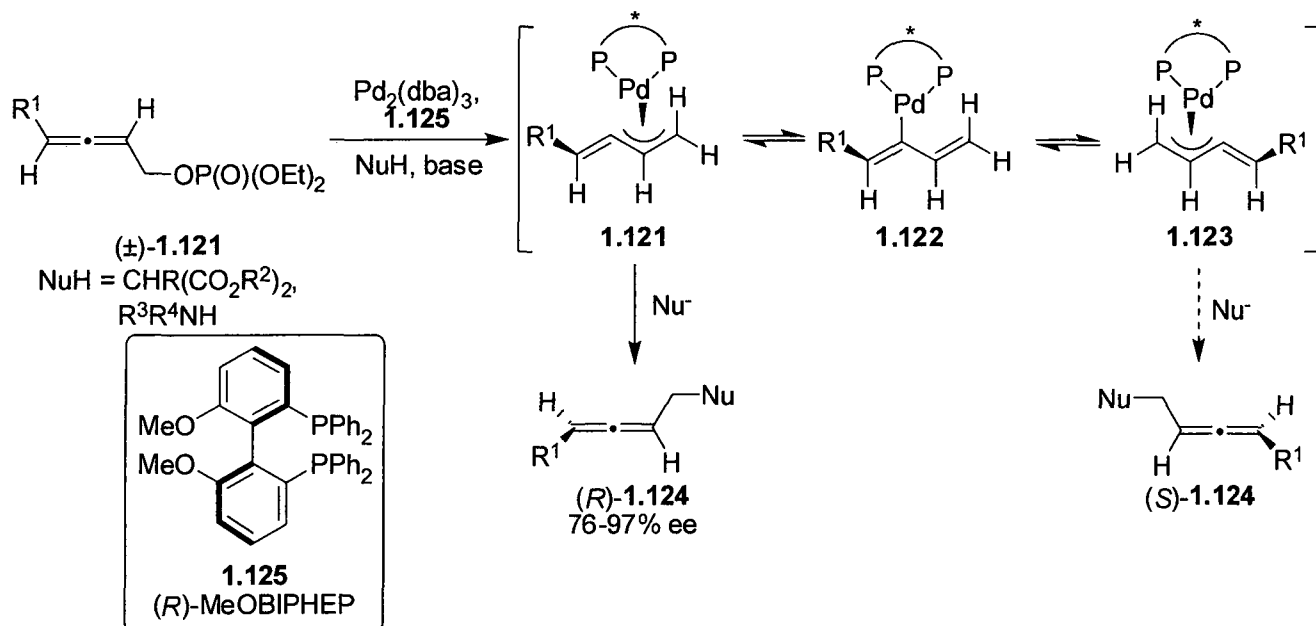
³² Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305.

1.3.2.2.2 Synthesis From Racemic Allenic Starting Materials

Two groups have recently reported formation of chiral allenes by a catalytic dynamic kinetic asymmetric transformation (DYKAT) of racemic allenic starting materials. In this approach, racemic allenes are synthesized, and through a catalytic asymmetric reaction they are transformed into axially chiral allenes.

Murahashi and co-workers used this strategy to perform asymmetric alkylation of racemic allenes.³³ Treatment of racemic alkadienyl phosphates (\pm)-**1.121** with soft nucleophiles in the presence of $\text{Pd}_2(\text{dba})_3$ (1 mol%), chiral ligand **1.125** (4 mol%) and base gives the allenic product (*R*)-**1.124** preferentially. An equilibrium is formed between the two diastomeric π -allylpalladium complexes **1.121** and **1.123**. It is proposed that nucleophilic attack occurs preferentially on intermediate **1.121** from the face opposite the palladium to give the optically active allenes (*R*)-**1.124**.

Scheme 1.27. DYKAT Synthesis of Chiral Allenes.



The Trost group reported a very similar DYKAT approach to the synthesis of chiral allenes.³⁴ Treatment of racemic allenic acetates (\pm)-**1.126** with $\text{Pd}(0)$ (2.5 mol%) and

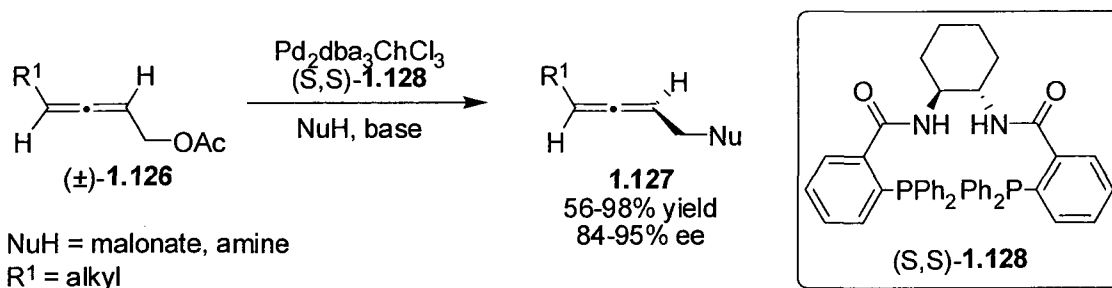
³³ a) Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S. *Chem. Lett.* **2002**, 140.

b) Imada, Y.; Nishida, M.; Kutsuwa, K.; Murahashi, S.; Naota, T. *Org. Lett.* **2005**, *7*, 5837.

³⁴ Trost, B.M.; Fandrick, D.R.; Dinh, D.C. *J. Am. Chem. Soc.* **2005**, *127*, 14186.

chiral ligand (*S,S*)-**1.128** (7.5 mol%) in the presence of a soft nucleophile and base gives allenes **1.127** in high yields and enantioselectivities. As in the previous reaction, an equilibrium between diastereomeric π -allyl Pd(II) intermediates is established, and nucleophilic attack is favoured on only one intermediate by the presence of the chiral ligand.

Scheme 1.28. A Second DYKAT Approach to Chiral Allenes.

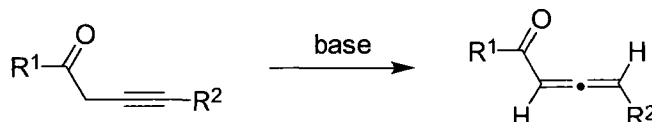


These DYKAT approaches give chiral allenes in useful yields and enantioselectivities, but they still require synthesis of the racemic allene before chirality can be imparted. This can potentially add undesirable extra steps to the transformation. An ideal method for synthesis of a chiral allene would be a catalytic asymmetric transformation of a non-allenic starting material, yielding the allene in high yields and enantioselectivities.

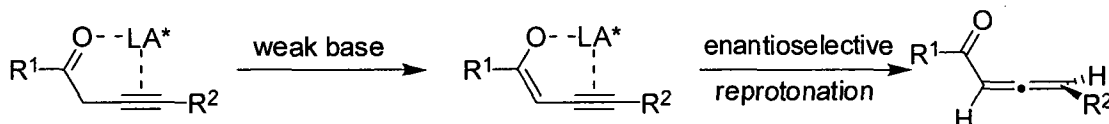
2 Synthesis of Chiral Allenes

2.1 Project Goals

One of the simplest allene-forming reactions known is the base catalyzed isomerization of a propargylic carbonyl.



This reaction is commonly known, but only forms allenes racemically. There are no known applications of this methodology to form chiral allenes. We proposed that this reaction could be performed enantioselectively using a chiral Lewis acid. Treatment of the alkyne in the presence of a Lewis Acid and a chiral ligand should increase the acidity of the α -protons. This would allow the alkyne to be deprotonated by a base which is too weak to perform the deprotonation without Lewis Acid activation, diminishing the possibility of a background reaction.



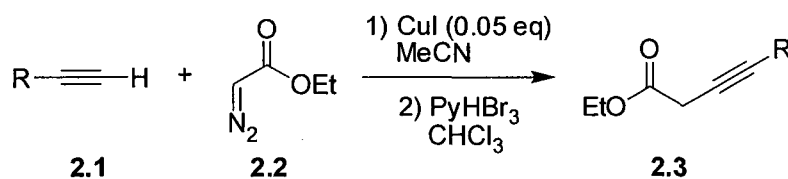
Our goals for this project were to find an effective Lewis Acid, chiral ligand and weak base to perform this reaction with high yields and enantioselectivities. If the reaction was possible, we wanted to then optimize to get the highest enantioselectivities possible, and determine the absolute stereochemistry. Finally, we wanted to explore possible reactions which could be performed with the allenes which transfer the chirality to the products.

2.2 Synthesis of Chiral Allenic Esters

2.2.1 Synthesis of Alkyne Starting Materials

The 3-alkynoate starting materials were prepared using a CuI-catalyzed coupling of terminal alkynes (**2.1**) with diazoesters (**2.2**), as reported by Suárez and Fu (Table 2.1).³⁵ Reaction of ethyl diazoacetate with copper(I) iodide results in the formation of a copper carbene, which subsequently inserts into the terminal alkyne. This reaction forms mostly alkyne (**2.3**), but a small amount of the undesired racemic allene is formed. This allene is removed by a reaction with pyridinium tribromide, which leaves only the desired alkyne as the product.

Table 2.1. Synthesis of 3-alkynoate starting materials.^a



| Entry | R | Yield |
|-------|---|-------|
| 1 | Ph | 72 |
| 2 | | 56 |
| 3 | CH ₂ OBn | 55 |
| 4 | CH ₂ OTBS | 26 |
| 5 | CH ₂ OTIPS | 62 |
| 6 | CH ₂ CH ₂ CH ₂ CH ₃ | 74 |

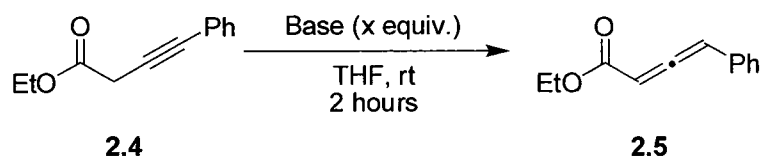
^aConditions: **2.1** (1.0 equiv.) and **2.2** (1.0 equiv.) are stirred in the presence of CuI (0.05 equiv) for 16 h. After NMR determination of the yield of the allene, pyridinium tribromide is added and the reaction is stirred overnight.

³⁵ Suárez, A.; Fu, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3580.

2.2.2 Base and Lewis Acid Screen

In order to determine which base to use, we tested bases containing a wide range of pK_b values. We were looking for a base which could not perform the isomerization reaction to the allene without Lewis acid assistance as to limit background reactivity in enantioselective reactions. As can be seen in Table 2.2, bases with pK_b's lower than 7.5 had minimal background reaction, and would be suitable to use for test reactions. We initially decided to use 2,6-di-*tert*-butyl-4-methylpyridine (Entry 3) to test Lewis Acid catalysis, since it had the lowest pK_b value and was therefore the least likely to cause any background reaction.

Table 2.2. Effect of pK_b on Uncatalysed Isomerisation of Propargyl Esters.^a



| Entry | Base | pK _b ^c | Conversion ^b |
|-------|------|------------------------------|-------------------------|
| 1 | | 10.6 | 25 |
| 2 | | 11.05 | 8 |
| 3 | | 4.95 | 0 |
| 4 | | 7.38 | 1.6 |
| 5 | | 5.20 | 0 |
| 6 | | 11.49 | 59 |

^aConditions: **2.4** (1 equiv.) in THF (0.05 M) is stirred with 0.2 equiv. of each base for 2h.

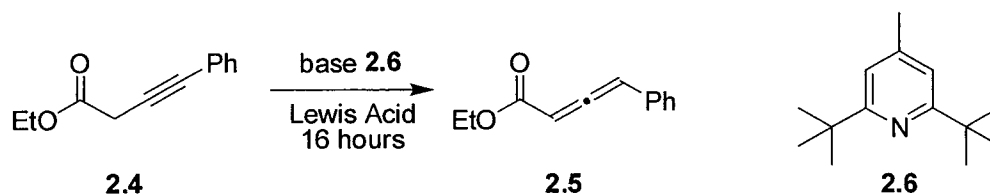
^bDetermined by HPLC.

^cObtained from Evans' pK_a tables

Once the base was selected, we reacted the propargyl ester with base in the presence various soft Lewis Acids. The reaction was performed overnight, and conversion to the

allene was observed in the presence of silver and copper. Since we know the base does not perform the reaction on its own, all reaction is due to Lewis Acid activation.

Table 2.3. Lewis Acid Screen for the Isomerization Reaction.^a



| Entry | Lewis Acid | % conversion ^b |
|-------|----------------------|---------------------------|
| 1 | Ag(OTf) | 55 |
| 2 | Cu(OTf) ₂ | 80 |
| 3 | Sc(OTf) ₃ | 0 |
| 4 | Yb(OTf) ₃ | 0 |

^aConditions: **2.4** (1 equiv.) in THF (0.05 M) is stirred with 0.2 equiv. of each base for 16h.

^bDetermined by HPLC.

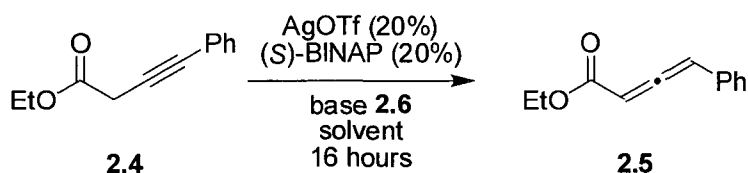
We then attempted to perform the reaction asymmetrically, using silver or copper triflate and a chiral ligand. All attempts to perform asymmetric copper catalysis showed no conversion to product, so we turned our attention to silver. A recent publication by Momiyama and Yamamoto discussed enantioselective reactions using a silver-BINAP complex.³⁶ Using their methodology, we attempted the isomerization reaction with AgOTf (20 mol%) and BINAP (20 mol%). Stirring the reaction overnight in dichloromethane in the presence of base **2.6** gave the allene in 63% ee, but only 2% conversion (Entry 1). Although the conversion was very low, the good enantioselectivity gave a good starting point for optimization.

³⁶ Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360.

2.2.3 Solvent Screen

Various solvents were then screened in order to assess the solvent effect on conversion and enantioselectivity (Table 2.4).

Table 2.4. Effect of Solvent on the Lewis Acid Catalyzed Isomerization.^a



| Entry | Solvent | % ee ^b | % conversion ^b |
|-------|----------------------------------|-------------------|---------------------------|
| 1 | DCM | 63 | 2 |
| 2 | THF | 3.5 | 5 |
| 3 | DCE | - | 0 |
| 4 | Toluene | - | 0 |
| 5 | Ether | 0 | 3.5 |
| 6 | Dimethoxymethane | 62 | 32 |
| 7 | <i>t</i> -BuOH | 77 | 18 |
| 8 | MeOH | 67 | 7 |
| 9 | EtOH | 60 | 15 |
| 10 | <i>i</i> -PrOH | 79 | 20 |
| 11 | ethylene glycol diethyl ether | - | 0 |
| 12 | F ₆ - <i>i</i> -PrOH | 0 | 82 |

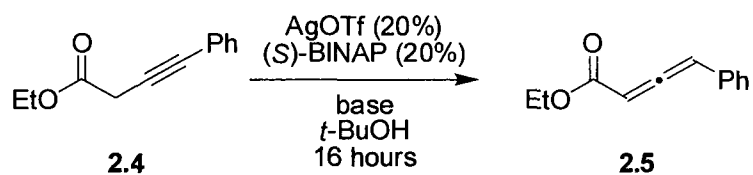
^aConditions: Silver (0.2 equiv.) and (S)-BINAP (0.2 equiv.) are stirred in solvent (0.05 M) for 2h. **2.4** (1 equiv.) and **2.6** (0.2 equiv.) are added and stirred for 16h.

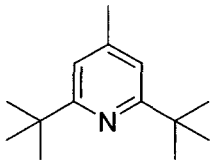
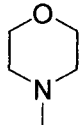
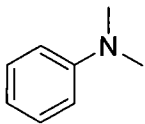
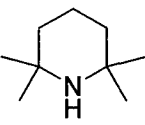
^bDetermined by HPLC.

It became clear that protic solvents were best for the reaction, both in terms of enantioselectivity and conversion. This is likely because they aid in the re-protonation

step of the reaction. However, if the solvent is too good of a proton source, such as hexafluoro-2-propanol (Entry 12), the reaction occurs racemically. Further studies were performed using the alcoholic solvents, the first of which was to do a second base scan. The conversions were very low, and this is likely due to the fact that 2,6-di-*tert*-butyl-4-methylpyridine (**2.6**) is not a very strong base. We decided to test many of the bases which were previously tested, but this time in the presence of the chiral silver complex. We performed the reaction overnight in *t*-BuOH in the presence of various bases with differing pK_b values, and some of the best results are highlighted in Table 2.5.

Table 2.5. Effect of Base on the Lewis Acid Catalyzed Isomerization in *t*-BuOH.^a



| Entry | Base | % ee ^b | % conversion ^b |
|-------|---|-------------------|---------------------------|
| 1 |  | 77 | 10 |
| 2 |  | 33 | 60 |
| 3 |  | 63 | 33 |
| 4 |  | 0 | 85 |

^aConditions: Silver (0.2 equiv.) and (S)-BINAP (0.2 equiv.) are stirred in *t*-BuOH (0.05 M) for 2h. **2.4** (1 equiv.) and base (0.2 equiv.) are added and stirred for 16h.

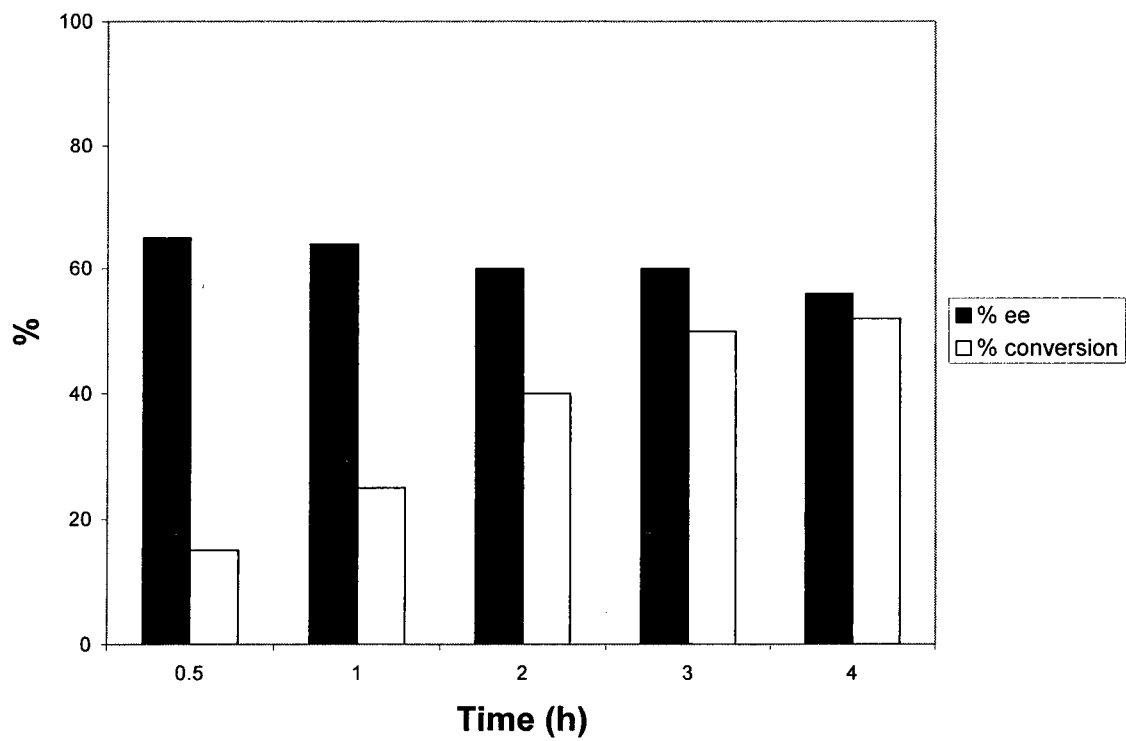
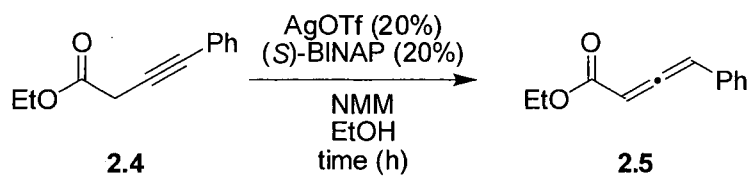
^bDetermined by HPLC.

Although the reaction had significantly higher enantioselectivity with 2,6-di-*tert*-butyl-4-methylpyridine (Entry 1), the conversion was too low. *N*-methylmorpholine (Entry 2) had the highest conversion rate, but a much lower *ee* value. However, *N*-methylmorpholine ($pK_b = 7.38$) is a stronger base than 2,6-di-*tert*-butyl-4-methylpyridine ($pK_b = 4.95$), so there is the possibility of a background reaction which causes racemization.

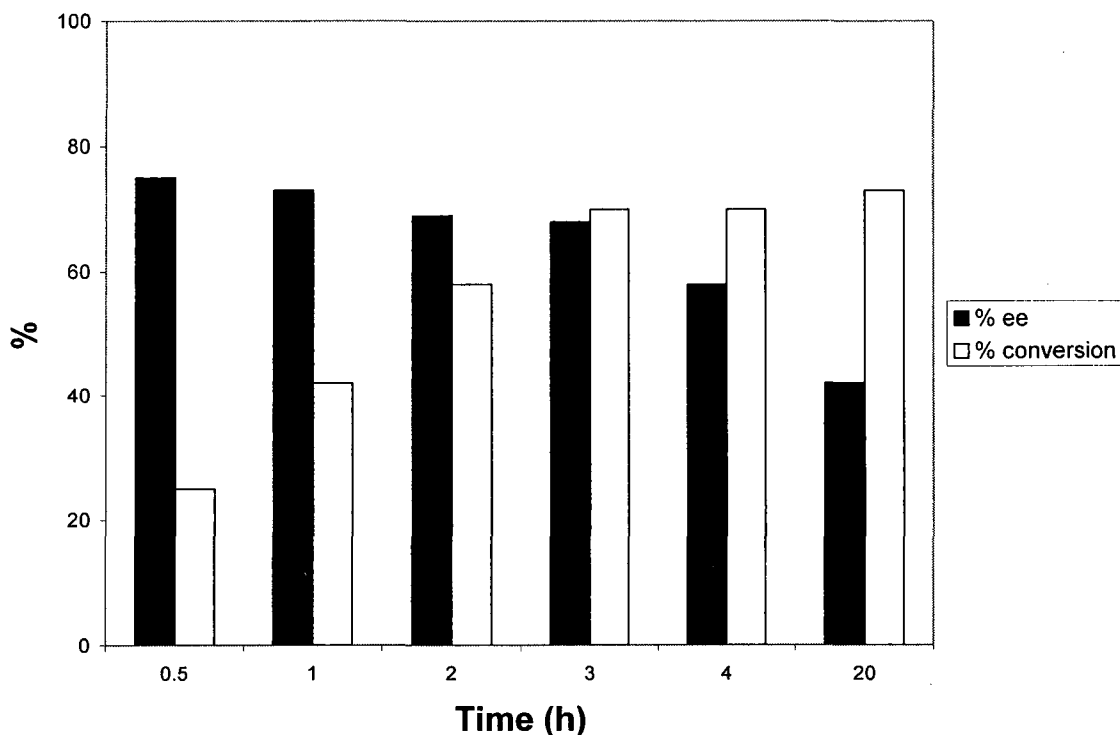
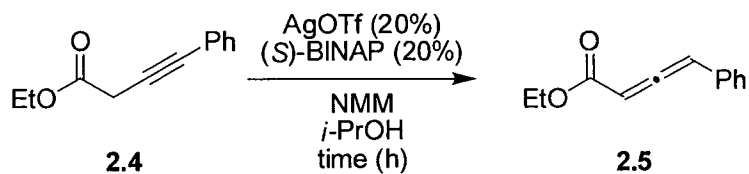
2.2.4 The Effect of Time on the Isomerization Reaction

Since *N*-methylmorpholine (NMM) is a stronger base, there is the possibility that the reaction could be completed in a shorter period of time. The isomerization reaction was performed with the chiral silver-BINAP complex (20 mol%) using *N*-methylmorpholine (10 mol%) as the base and monitored over time. The reaction was performed in both EtOH and *i*-PrOH, and the results are summarized in Schemes **2.1** and **2.2**.

Scheme 2.1. Time-Monitored Reaction Using *N*-methylmorpholine in Ethanol.



Scheme 2.2. Time-Monitored Reaction Using *N*-methylmorpholine in *iso*-Propanol.

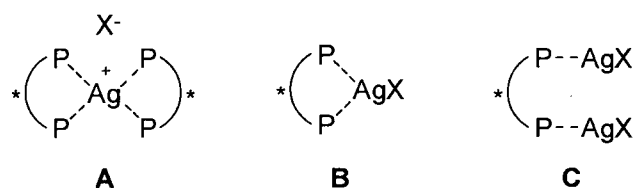


In both solvents the reactions appeared to be complete in terms of conversion after about three hours. After that point, enantioselectivity was lost fairly quickly. *i*-PrOH was the better solvent in terms of both enantioselectivity and conversion, so it was adopted as the solvent for any further reactions.

2.2.5 Silver-BINAP Ratios

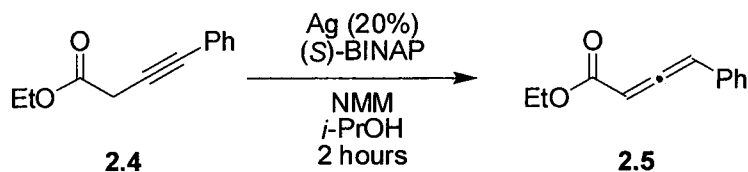
Momiyama and Yamamoto discovered the presence of three different silver-BINAP complexes which were dependent on the ratio of metal to ligand: **A**, **B**, or **C**.³⁶ By using a 2:1 ratio of BINAP to silver triflate, complex **A** was formed. By using a 1:2.5 ratio of BINAP to silver triflate, complex **C** was formed. The use of a 1:1 ratio of silver triflate to BINAP resulted in a 21:63:16 ratio of **A**:**B**:**C**. Switching to silver acetate as the silver source resulted in formation of only complex **B**.

Figure 2.1. Three Unique Silver-BINAP Complexes.



Using this information, we performed the isomerization reaction using different silver:BINAP ratios. The best ratio in terms of both conversion and enantioselectivity was 2.5:1 silver:BINAP. This means that complex **C**, where two silver atoms are chelated to one molecule of ligand, is the most effective at performing the reaction. The 1:2 ratio did not give any enantioselectivity, and the use of silver acetate was not successful. This may be because the acetate anion is basic enough to perform the reaction itself.

Table 2.6. Effects of Silver-BINAP Ratios on Isomerization.^a



| Entry | Silver source | mol% BINAP | Silver:BINAP | % ee ^b | % conversion ^b |
|-------|---------------|------------|--------------|-------------------|---------------------------|
| 1 | AgOTf | 20 | 1:1 | 50 | 14 |
| 2 | AgOTf | 8 | 2.5:1 | 66 | 20 |
| 3 | AgOTf | 40 | 1:2 | 0 | 9 |
| 4 | AgOAc | 20 | 1:1 | 4 | 25 |

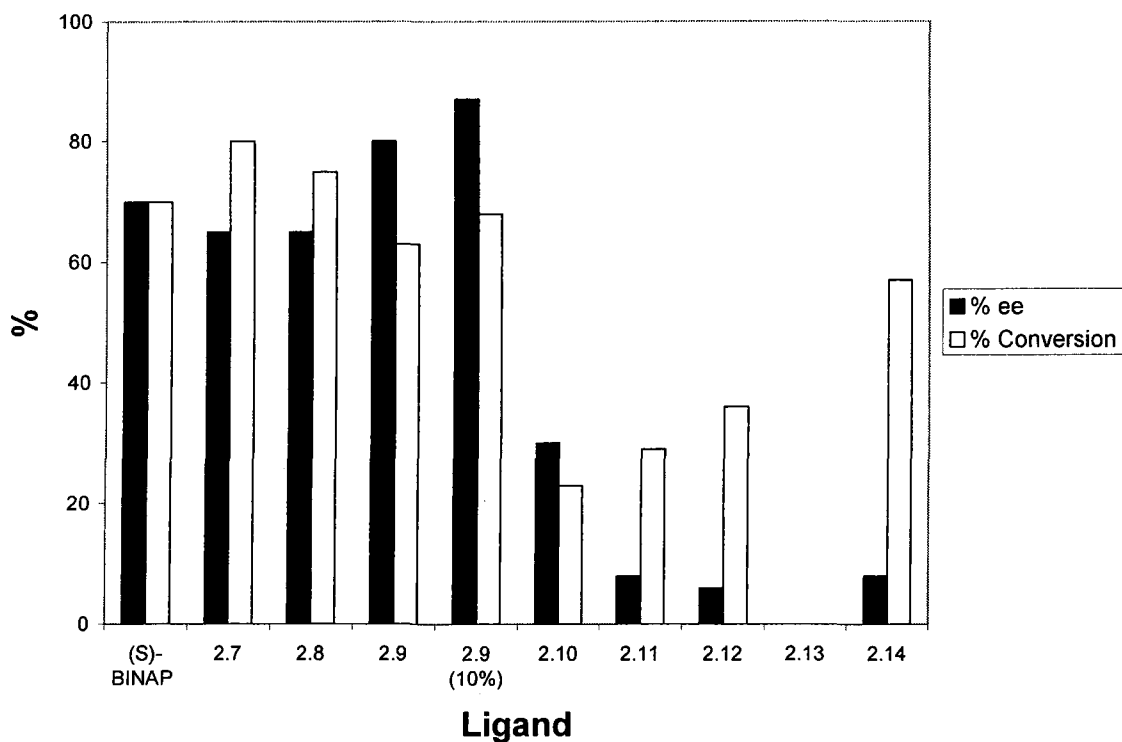
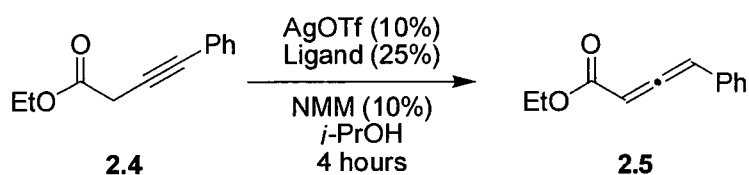
^aConditions: Silver (0.2 equiv.) and (S)-BINAP are stirred in *i*-PrOH (0.05 M) for 2h. **2.4** (1 equiv.) and base (0.2 equiv.) are added and stirred for 16h.

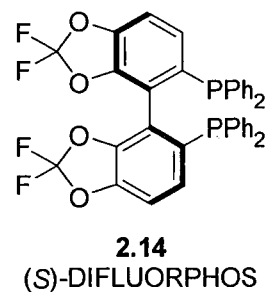
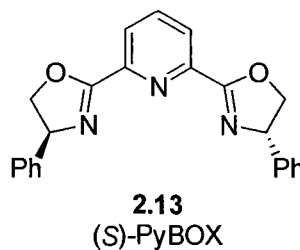
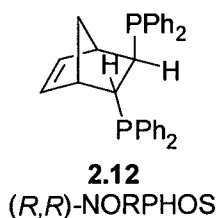
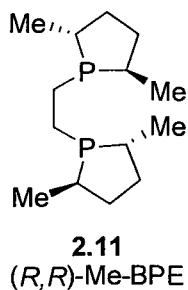
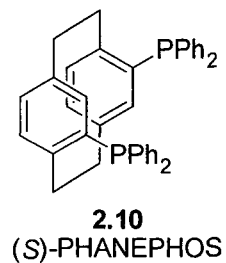
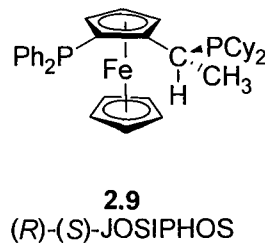
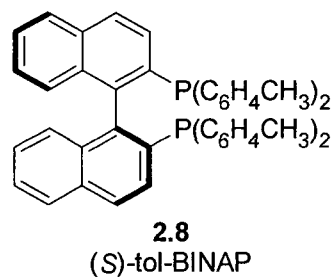
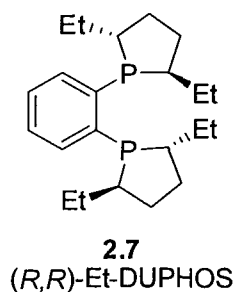
^bDetermined by HPLC.

2.2.6 Ligand Screen

It became apparent that a bidentate ligand was necessary to perform the reaction successfully, and we then analyzed a variety of different bidentate ligands. The different ligands worked with varying degrees of success. The (*S*)-PyBOX (**2.13**) ligand gave no conversion to the allene, indicating that nitrogen-chelating ligands would, in all likelihood, not be useful. (*R,R*)-Et-DUPHOS (**2.7**) and (*S*)-tol-BINAP (**2.8**) gave similar results to the initial (*S*)-BINAP ligand, which is to be expected since they are all similar ligands. The best result came from the use of the (*R,S*)-JOSIPHOS ligand (**2.9**), which was significantly more enantioselective than any other ligand. When a 1:1 ratio of silver triflate to ligand was used, the allene was formed in 87% *ee*.

Scheme 2.3. Ligand Screen for the Isomerization Reaction.^a





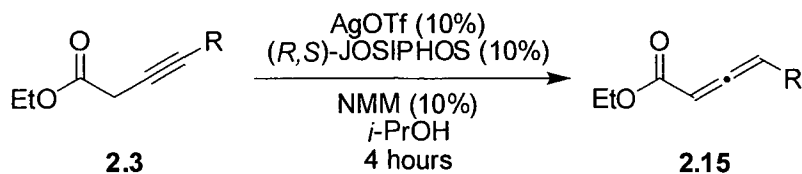
^aConditions: AgOTf (10 mol%) and ligand (25 mol%) are stirred in solvent for 2h. **2.4** (1 equiv.) and *N*-Methylmorpholine (10 mol%) are added and the reaction is stirred at room temperature for 4h.

The *(R,S)*-JOSIPHOS ligand gave the allene product in excellent enantioselectivity, but the conversion was still not exceptional, at 68%. We needed to find a way to keep high enantioselectivities, but increase the conversion. The alkyne cannot be separated from the allene chromatographically, so the reaction needs to go to 100% conversion to obtain the pure chiral allene.

2.2.7 Scope of the Reaction

Before exploring other ways to increase the conversion, we tried the reaction on four different alkyne substrates to test if our methodology was applicable to more than one substrate. The results of the scope test are in Table 2.7.

Table 2.7. Scope of the Isomerization Reaction using AgOTf and JOSIPHOS.^a



| Entry | R | % ee ^b | % conversion ^b |
|-------|---|-------------------|---------------------------|
| 1 | Ph | 87 | 47 |
| 2 | CH ₂ OBn | 47 | 56 |
| 3 | | 93 | 53 |
| 4 | | 93 ^c | 95 ^c |
| 5 | CH ₂ CH ₂ CH ₂ CH ₃ | 69 | 60 |

^aConditions: AgOTf (0.1 equiv.) and (R,S)-JOSIPHOS are stirred in *i*-PrOH (0.05 M) for 2h. **2.3** (1 equiv.) and *N*-methylmorpholine (0.1 equiv.) are added and stirred for 4h.

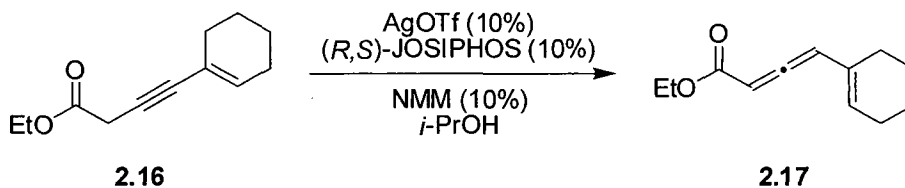
^bDetermined by HPLC.

^cReaction was performed with 20 mol% catalyst and base

The reaction worked on four different substrates with varying degrees of success. The enantioselectivities ranged from moderate to excellent, but the conversions were all too low. If the catalyst loading was increased to 20%, we observed near completion in the reaction while maintaining high enantioselectivity. We felt this catalyst loading was too high, however, and decided to look for a better way to increase the conversion of the reaction. Another base scan using our newly optimized catalyst was performed to see if we could find a base which would perform the reaction with higher conversion while maintaining or increasing the enantioselectivity. We tested a range of bases which have a similar pK_b value to *N*-methylmorpholine, and the results are summarized in Table 2.8. Unfortunately, the best results were still obtained using *N*-methylmorpholine.

2.2.8 Further Investigation of Effect of Bases and Ligands

Table 2.8. Base Scan of the Isomerization Reaction with AgOTf and JOSIPHOS.^a



| Entry | Base | pKb | 2 hours | | 5 hours | |
|-------|------|------|-------------------|---------------------------|-------------------|---------------------------|
| | | | % ee ^b | % conversion ^b | % ee ^b | % conversion ^b |
| 1 | | 7.38 | 100 | 36 | 91 | 56 |
| 2 | | 8.36 | 84 | 42 | 79 | 55 |
| 3 | | 10.7 | 74 | 94 | 55 | 95 |
| 4 | | 8.30 | 91 | 23 | 85 | 45 |
| 5 | | 10 | 72 | 84 | 57 | 90 |
| 6 | | 6.95 | - | 0 | - | 0 |

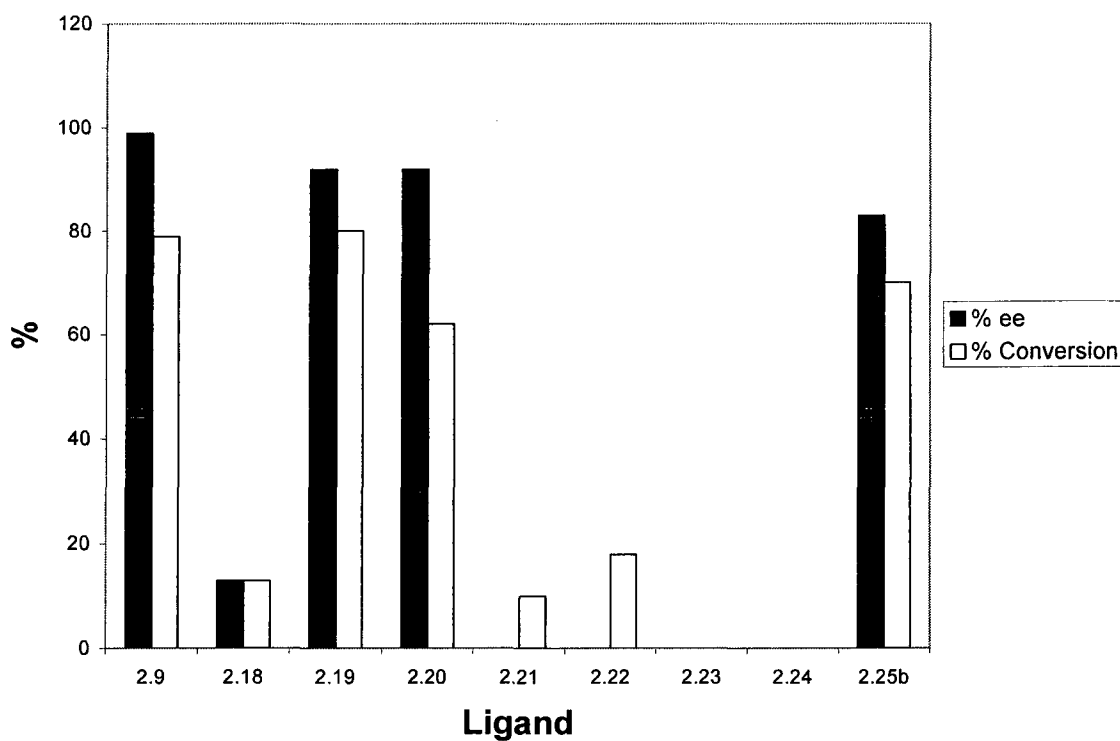
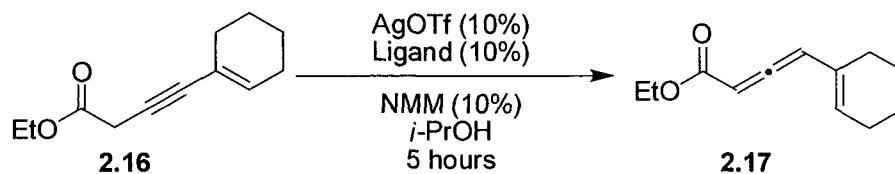
^aConditions: AgOTf (0.1 equiv.) and (R,S)-JOSIPHOS are stirred in *i*-PrOH (0.05 M) for 2h. **2.16** (1 equiv.) and base (0.1 equiv.) are added and stirred for 4h.

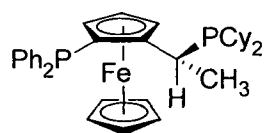
^bDetermined by HPLC.

Using *N*-methylmorpholine we then examined other ligands in the same structural class as (R)-(*S*)-JOSIPHOS since this catalyst lead to significantly higher enantioselectivities than other ligand classes. As can be seen in Scheme 2.4, some of the ligands had

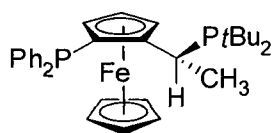
similar reactivity and selectivity to (*R*)-(*S*)-JOSIPHOS, but none of them were more efficient. We decided to remain with (*R*)-(*S*)-JOSIPHOS as our ligand.

Scheme 2.4. Ligand Scan With Ferrocene-Based Ligands.

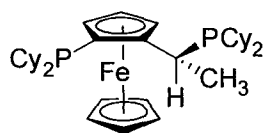




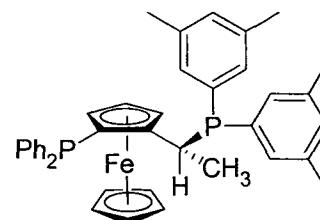
2.9
(*R*)-(*S*)-JOSIPHOS



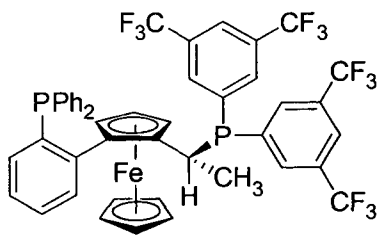
2.18
(*R*)-(*S*)-PPF-PtBu₂



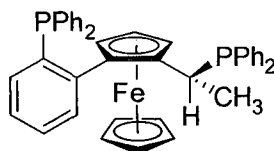
2.19
(*R*)-(*S*)-cy₂PF-Pcy₂



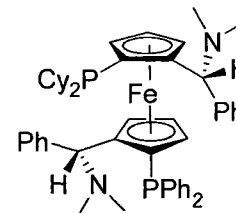
2.20
(*R*)-(*S*)-PPF-Pxyl₂



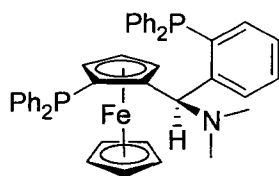
2.21
(*R*)-(*R*)-Ph₂PPhFcCHCH₃P(3,5-CF₃Ph)₂



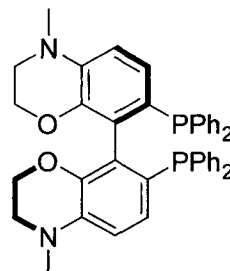
2.22
(*R*)-(*R*)-Ph₂PPhFcCHCH₃PPh₂



2.23
(*R*)-(*S*)-NMe₂-PPh₂-MANDYPHOS



2.24
(*S*)-(*R*)-TANIAPHOS



2.25
(*R*)-SOLPHOS

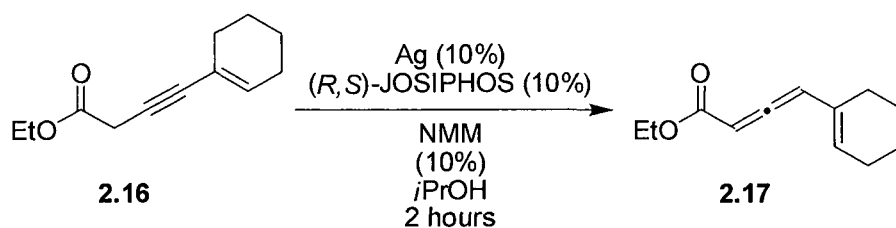
^aConditions: AgOTf (10 mol%) and ligand (10 mol%) are stirred in solvent for 2h. Substrate **2.16** and *N*-methylmorpholine (10 mol%) are added and the reaction is stirred at room temperature for 4h.

^b25 mol % AgOTf used.

2.2.9 Silver Sources

Given the observation that silver acetate led to good conversions and poor ee, we hypothesized that the silver counterion would have an impact on the reaction. Silver sources in which the anion was weakly chelating were screened in order to improve the efficiency of the reaction. The anion also needed to not be basic, as to minimize any racemic background reaction similar to the acetate. From this screen, silver hexafluoroantimonate gave excellent results – very high enantioselectivity and conversion.

Table 2.9. Silver Scan of the Isomerization reaction with (*R,S*)-JOSIPHOS.^a



| Entry | Silver Source | % ee ^b | % conversion ^b |
|-------|--------------------|-------------------|---------------------------|
| 1 | AgOTf | 92 | 53 |
| 2 | AgPF ₆ | 86 | 24 |
| 3 | AgBF ₄ | 81 | 36 |
| 4 | AgSbF ₆ | 96 | 91 |

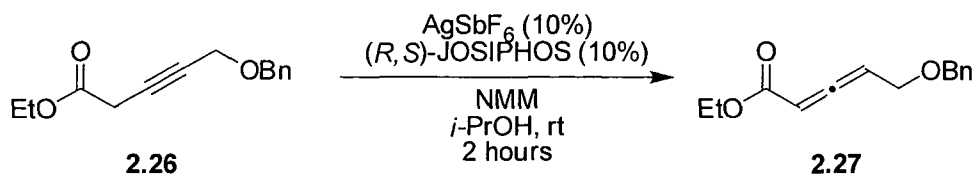
^aConditions: AgOTf (0.1 equiv.) and (*R,S*)-JOSIPHOS are stirred in *i*-PrOH (0.05 M) for 2h. **2.16** (1 equiv.) and *N*-methylmorpholine (0.1 equiv.) are added and stirred for 2h.

^bDetermined by HPLC.

2.2.10 Base Equivalents

Up until this point we had been using 10 mol% of base – equal amounts of base and catalyst. In a final round of optimization we evaluated the impact of the base to substrate ratio on enantioselectivity or conversion. Reactions were done with the benzyl alkyne (**2.26**) which gave the lowest enantioselectivity in the reactions with silver triflate. When the amount of base was increased higher than 10 mol%, the selectivity of the reaction quickly decreased. However, decreasing the amount of base from 10 mol% to 5 mol% increased the enantioselectivity by 9% without affecting the conversion.

Table 2.10. Effect of Base Equivalents on Isomerization Reaction.^a



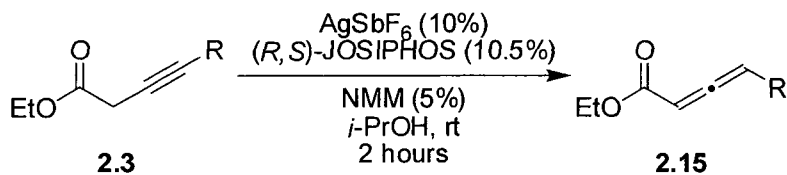
| Entry | mol% base | % ee ^b | % conversion ^b |
|-------|-----------|-------------------|---------------------------|
| 1 | 100 | 44 | >95 |
| 2 | 50 | 52 | >95 |
| 3 | 20 | 65 | >95 |
| 4 | 10 | 70 | >95 |
| 5 | 5 | 79 | >95 |
| 6 | 1 | - | 0 |

^aConditions: AgSbF_6 (0.1 equiv.) and (R,S) -JOSIPHOS (0.1 equiv.) are stirred in *i*-PrOH (0.05 M) for 2h. **2.26** (1 equiv.) and *N*-methylmorpholine are added and stirred for 2h.

^bDetermined by HPLC.

2.2.11 Scope of the Reaction with new Silver Source

The scope of the isomerization with the new catalyst system was evaluated with different alkyne substrates. The results are summarized in Table 2.11, and show that the system gives good to excellent enantioselectivity for all substrates. The conversions are good, with the exception of the substrate with the bulky TIPS group, but we were again limited by the inability to separate the product from the starting material. The conversions all needed to be >95% in order to have the method be synthetically useful.

Table 2.11. Scope Table for Isomerization Reaction with AgSbF_6 .^a

| Entry | R | % ee ^b | % conversion ^b |
|-------|--|-------------------|---------------------------|
| 1 | Ph | 89 | 85 |
| 2 | | 96 | 90 |
| 3 | CH_2OBn | 79 | >95 |
| 4 | $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ | 89 | 70 |
| 5 | CH_2OTBS | 85 | >95 |
| 6 | CH_2OTIPS | >98 | 40 |

^aConditions: AgSbF_6 (0.1 equiv.) and (*R,S*)-JOSIPHOS (0.1 equiv.) are stirred in *i*-PrOH (0.05 M) for 2h. **2.3** (1 equiv.) and *N*-methylmorpholine (0.05 equiv.) are added and stirred for 2h.

^bDetermined by HPLC.

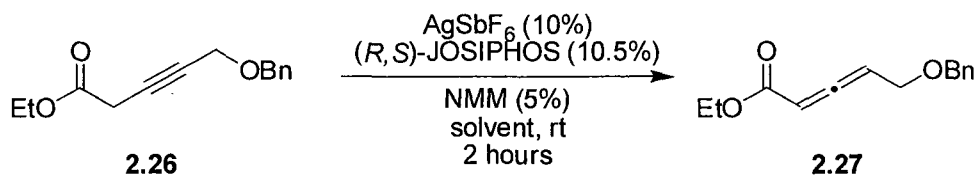
2.2.12 Solubility Issues

2.2.12.1 Solvent Scan

Silver hexafluoroantimonate was selected as the best silver source, but this introduced solubility issues. With silver triflate, the solution was completely homogeneous, indicating that all of the catalyst was in solution. With silver hexafluoroantimonate, however, the solution was heterogeneous due to the presence of an orange precipitate. This indicated that not all of the catalyst was in solution, so the reaction was not performing at maximum efficiency. We decided to test different solvents and concentrations to try to make the catalyst completely soluble while still maintaining enantioselectivity. The results are summarized in Table 2.12. No matter what volume of *i*-PrOH was used, the catalyst was not soluble (Entries 1 – 5). The reaction also proceeded essentially identically in all volumes of solvent, indicating that it is basically concentration independent. THF solubilized the catalyst, and the reaction proceeded

fairly well. When the reaction was run in *i*-PrOH/THF (Entry 6), it completed but the enantioselectivity was lower than before at 68%. Since the catalyst is completely soluble, it is probable that the reaction is faster than before, and cooling the solution could increase the selectivity. Indeed, cooling the solution to 0 °C (Entry 7) increased the selectivity to 75% ee while maintaining high conversion. This was better, but still no improvement over what was previously observed with the insoluble catalyst. A change of the protic solvent to methanol while maintaining the lower temperature, however, increased the enantioselectivity to 93% and preserved the high conversion (Entry 14). This was the best enantioselectivity we had ever observed, and this result was very exciting.

Table 2.12. Solvent Scan to Improve Solubility in Isomerization Reaction.^a



| Entry | Solvent | Solubility | % ee ^b | % conversion ^b |
|-------|---|------------|-------------------|---------------------------|
| 1 | <i>i</i> -PrOH (0.5 mL) | insoluble | 79 | >95 |
| 2 | <i>i</i> -PrOH (1.0 mL) | insoluble | 79 | >95 |
| 3 | <i>i</i> -PrOH (2.0 mL) | insoluble | 85 | 85 ^c |
| 4 | <i>i</i> -PrOH (3.0 mL) | insoluble | 84 | 79 ^c |
| 5 | <i>i</i> -PrOH (4.0 mL) | insoluble | 83 | 88 ^c |
| 6 | 1:1 <i>i</i> -PrOH:THF | soluble | 68 | >95 |
| 7 | 1:1 <i>i</i> -PrOH:THF ^d | insoluble | 75 | >95 |
| 8 | 1:1 <i>i</i> -PrOH:toluene | insoluble | 60 | 40 |
| 9 | 1:1 <i>i</i> -PrOH:DCM | soluble | - | 0 |
| 10 | 1:1 <i>i</i> -PrOH:MeCN | soluble | - | 0 |
| 11 | 1:1 <i>i</i> -PrOH:DMF | soluble | 40 | 28 |
| 12 | 1:1 <i>i</i> -PrOH:acetone ^e | soluble | 79 | 85 |
| 13 | 2:3 MeOH:THF | soluble | 50 | >95 |
| 14 | 2:3 MeOH:THF ^d | soluble | 93 | >95 |
| 15 | MeOH ^d | insoluble | 91 | >95 |

^aConditions: AgSbF₆ (0.1 equiv.) and (R,S)-JOSIPHOS (0.1 equiv.) are stirred in solvent (0.05 M) for 0.5h. **2.26** (1 equiv.) and *N*-methylmorpholine (0.05 equiv.) are added and stirred for 2h.

^bDetermined by HPLC.

^cAfter four hours the reaction was complete with good enantioselectivity.

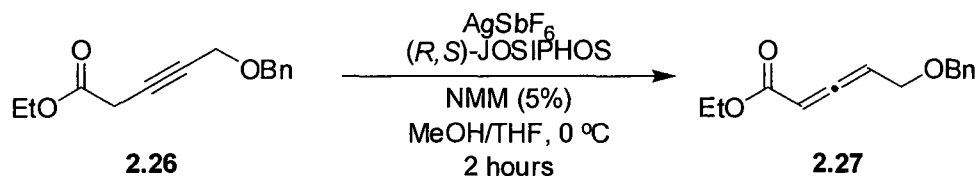
^dReaction performed at 0 °C.

^eResults with acetone as a solvent were inconsistent and often irreproducible.

2.2.12.2 Catalyst Loading

The discovery of this new solvent system appeared to improve the reactivity substantially. We decided to attempt lowering the catalyst loading below 10% to see if the reaction would still work. Using the benzyl substrate, the reaction was performed at 10%, 5% and 2% catalyst loading. All of the catalyst loadings gave excellent enantioselectivities – the lower catalyst loadings were slightly better. The conversion rates were repeatedly inconsistent, however, with 2% catalyst loading giving a much better conversion rate than 5%. This result was strange, but showed that the catalyst loading can be lowered if necessary, although the accuracy of the results may not be guaranteed. We decided to stay with 10% catalyst loading to ensure consistent results.

Table 2.13. Catalyst Loading for the Isomerization Reaction.^a



| Entry | Catalyst Loading (mol%) | % ee ^b | % conversion ^b |
|-------|-------------------------|-------------------|---------------------------|
| 1 | 10 | 93 | >95 |
| 2 | 5 | 96 | 57 |
| 3 | 2 | 97 | 91 |

^aConditions: AgSbF_6 (X equiv.) and (*R,S*)-JOSIPHOS (X equiv.) are stirred in MeOH/THF (0.05 M) for 0.5h. **2.26** (1 equiv.) and *N*-methylmorpholine (0.05 equiv.) are added and stirred for 2h.

^bDetermined by HPLC.

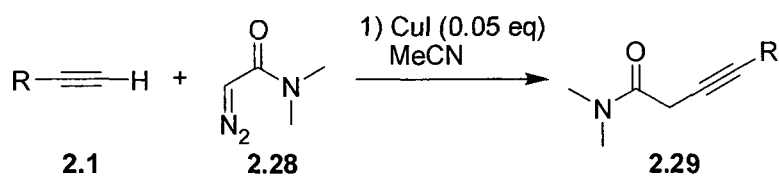
2.3 Synthesis of Chiral Allenic Amides

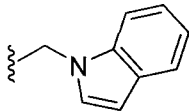
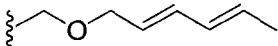
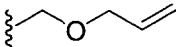
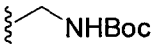
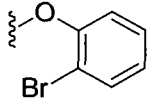
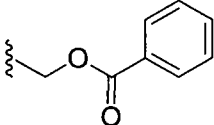
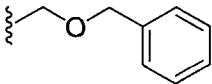
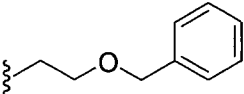
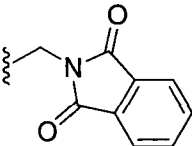
2.3.1 Synthesis of Amide Alkyne Starting Materials.

We now had a system which performed very well, but we were still faced with the problem of incomplete conversion. Unless every substrate completes 100%, we cannot use this method, since the alkyne and allene cannot be separated. This problem had been addressed previously by Suárez and Fu while making these alkyne substrates.³⁵ They noted that if amides are used in the place of esters, the alkynes and allenes are

easily separated by flash chromatography. We tried synthesizing some of these amides, and discovered that the amides which contained a propargylic heteroatom were indeed separable by chromatography (Table **2.14**).

Table 2.14. Synthesis of Amide Starting Materials.^a



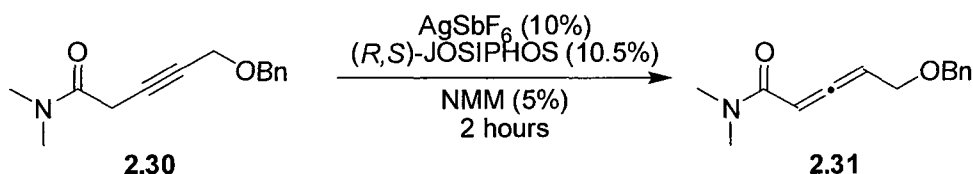
| Entry | R | Yield Alkyne | Yield Allene |
|-------|---|--------------|--------------|
| 1 |  | 60 | 22 |
| 2 |  | 46 | 40 |
| 3 |  | 35 | 49 |
| 4 |  | 57 | 28 |
| 5 |  | 55 | 30 |
| 6 |  | 25 | 62 |
| 7 |  | 61 | 29 |
| 8 |  | 92 | 0 |
| 9 |  | 41 | 43 |

^aConditions: **2.1** (1.0 equiv.) and **2.28** (1.0 equiv.) are stirred in the presence of CuI (0.05 equiv) for 16 h. The allene is isolated by chromatography

2.3.2 Test of Conditions Already Developed

Initial attempts were made to perform the isomerization reaction on the amide alkyne using some of the successful conditions previously developed (Table 2.15).

Table 2.15. Isomerization Reaction on Allenic Amides.^a



| Entry | Solvent | Temperature | % ee ^b | % conversion ^b |
|-------|----------------|-------------|-------------------|---------------------------|
| 1 | <i>i</i> -PrOH | 22 | 67 | 77 |
| 2 | 2:3 MeOH:THF | 22 | 70 | 81 |
| 3 | 2:3 MeOH:THF | 0 | 90 | 80 |

^aConditions: AgSbF_6 (0.1 equiv.) and (R,S) -JOSIPHOS (0.1 equiv.) are stirred in MeOH/THF (0.05 M) for 0.5h. **2.30** (1 equiv.) and *N*-methylmorpholine (0.05 equiv.) are added and stirred for 2h.

^bDetermined by HPLC.

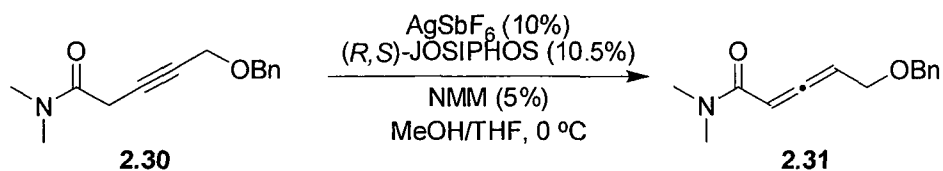
The reaction gave results similar to those with the ester alkynes – excellent enantioselectivities and conversions. The conversion was slightly lower than the related ester alkyne, but the allene can be isolated chromatographically. We did the reaction on a larger scale and actually isolated the product, successfully obtaining the allene in 75% yield and 93% ee. This was the first time we had managed to obtain a completely purified, enantiomerically enriched allene.

2.3.3 Further Base Investigation

The conversion was lower than the conversion of the related ester alkyne, which can be explained by the pKa difference between the ester and the amide. The α -proton of the amide will be about 5 pKa units higher than that of the ester, and thus harder to deprotonate. We decided to again test bases with a slightly higher pKb value to see if we could increase the conversion. Due to the decreased acidity, we hypothesized that less of a background reaction would occur and the high enantioselectivity could be maintained by using a stronger base. The results of the base scan, seen in Table 2.16,

indicate that the reaction can tolerate slightly stronger bases such as morpholine (Entry 3), with no change in enantioselectivity. Stronger bases, such as triethylamine (Entry 1) and diisopropylethylamine (Entry 2) perform the reaction with lower enantioselectivity without increasing the conversion. This indicates that the reaction reaches an equilibrium between the alkyne and the allene, and higher conversion is not possible. If left for a longer period of time, the enantioselectivity consistently decreases without increasing yield. It appears that the maximum conversion is reached after one hour, so performing the reaction for more than one hour is futile.

Table 2.16. Base Scan of Reaction with Amides.^a



| Entry | Base | pK _b | 1 hour | | 3 hours | |
|-------|-------------------|-----------------|-------------------|---------------------------|-------------------|---------------------------|
| | | | % ee ^b | % conversion ^b | % ee ^b | % conversion ^b |
| 1 | Et ₃ N | 10.6 | 81 | 85 | 70 | 85 |
| 2 | DIPEA | 11.05 | 81 | 85 | 60 | 85 |
| 3 | | 8.36 | 92 | 78 | 87 | 80 |
| 4 | | 7.38 | 90 | 80 | 84 | 83 |
| 5 | | 11.49 | 85 | 81 | 68 | 82 |

^aConditions: AgSbF_6 (0.1 equiv.) and (R,S)-JOSIPHOS (0.105 equiv.) are stirred in *i*-PrOH (0.05 M) for 0.5h. **2.30** (1 equiv.) and base (0.05 equiv.) are added and stirred.

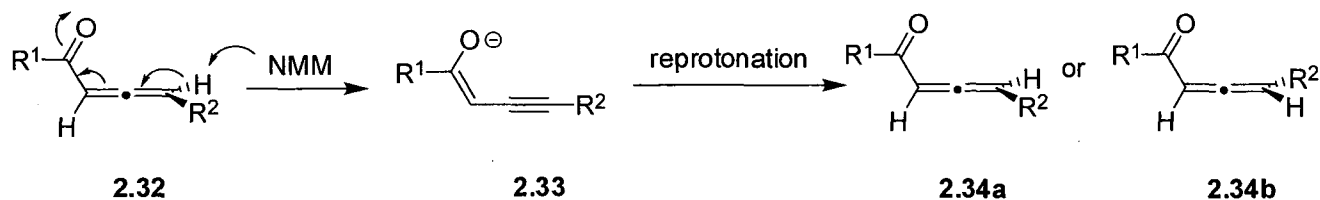
^bDetermined by HPLC.

2.3.4 Loss of Enantiomeric Excess

As was discussed in section 2.2.4 and 2.3.3, once the reaction reaches maximum conversion the ee gradually decreases as the reaction continues. The allenes themselves are stable to chromatography on silica gel, and once isolated they can be stored for a long time without racemization, indicating that the products are fairly stable and it is the specific reaction conditions which are causing the decrease in ee. If the product/alkyne mixture is isolated and re-exposed to the reaction conditions, the same

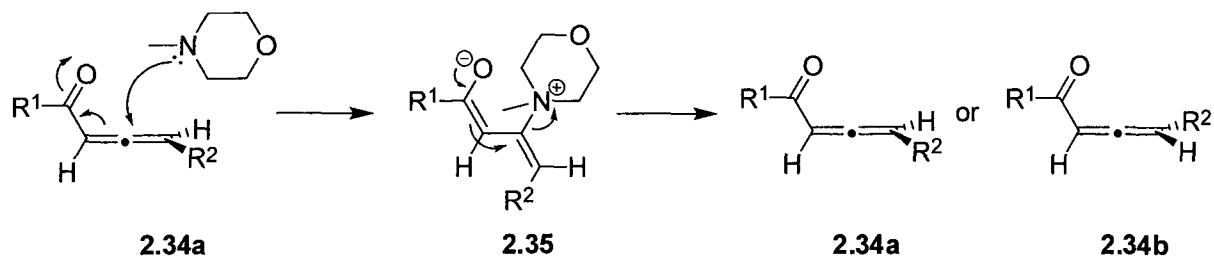
loss of ee is still observed. The fact that the reaction reaches its maximum conversion before any loss of ee is observed indicates gradual reversibility of the reaction with reformation of a racemic allene. It would have to be a process which is much slower than the initial isomerization, which progresses gradually over time leading to racemization. This could be due to simple deprotonation of allene **2.32** with the N-methylmorpholine present in the reaction mixture to give intermediate **2.33**, which could then reprotonate to form the racemic allenes **2.34a** and **2.34b** (Scheme 2.5).

Scheme 2.5. Racemization *via* Reversibility of the Isomerization.



A second possibility, is shown in Scheme 2.6, where the N-methylmorpholine does a 1,4-nucleophilic attack on allene **2.34a**, forming achiral intermediate **2.35**. When the intermediate collapses to re-form allenes **2.34a** and **2.34b**, enantioselectivity is lost. As demonstrated in scheme 1.5, the acceptor-substituted allenes are very susceptible to 1,4-nucleophilic attack, and these products would be no exception, making this mechanism a possibility.

Scheme 2.6. Racemization *via* 1,4-Nucleophilic Attack.

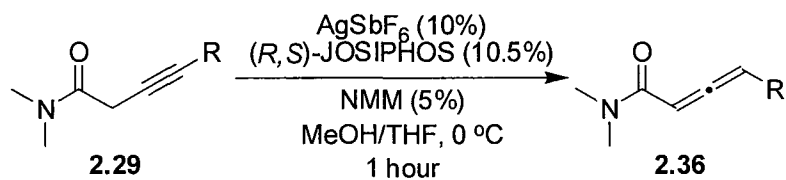


Both of these are hypothetical mechanisms for the racemization of the allene product. The actual mechanism of racemization is not known and was not investigated since the loss of ee is easily controlled by stopping the reaction as soon as it is complete.

2.3.5 Scope of the Reaction with Amides

We decided to stay with *N*-methylmorpholine as the base, since it has a lower pK_b value and is still less likely to perform any background reaction. Using the optimal conditions, we prepared many different allenes via the isomerization reaction. It was also discovered that lowering the temperature to -10 °C increased the ee if so desired, without significant effect on the yield (Entries 5 – 7). All of the allenes formed were isolated by chromatography.

Table 2.17. Scope of the Isomerization Reaction with Amides.^a



| Entry | R | % ee ^b | % yield ^d |
|-------|---|-----------------------|----------------------|
| 1 | | 90 | 95 |
| 2 | | 96 ^c | 72 |
| 3 | | 96 | 68 |
| 4 | | 91 | 73 |
| 5 | | 80 91 ^c | 81 60 |
| 6 | | 83 91 ^c | 76 60 |
| 7 | | 90 95 ^c | 80 73 |
| 8 | | >99 | 27 |
| 9 | | 40 | 60 |

^aConditions: AgSbF₆ (0.1 equiv.) and (R,S)-JOSIPHOS (0.1 equiv.) are stirred in MeOH/THF (0.05 M) for 0.5h. **2.29** (1 equiv.) and *N*-methylmorpholine (0.05 equiv.) are added and stirred for 1h.

^bDetermined by HPLC.

^cReaction performed at -10 °C

^dRemainder of mass balance is unreacted starting material.

3 Determination of Absolute Stereochemistry

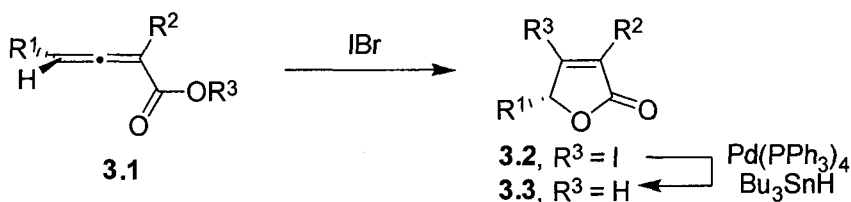
After discovering this effective synthesis of allenic esters and amides, the determination of absolute stereochemistry was crucial. The initial idea was to get a crystal structure, but all the allenes prepared were oils. Attempts at synthesizing a crystalline allene were unsuccessful. While many publications use the Lowe-Brewster rule as the sole method of determining the absolute stereochemistry of allenes, we decided to try to determine the absolute stereochemistry of our allenes using chemical transformations, to see if the application of the Lowe-Brewster rule was truly reliable with our substrate class.

3.1 Manipulation of Chiral Allenes

3.1.1 Precedent for Iodobutenolide Formation

Attempts at transforming one of the allenes into a chiral product which is already known and characterized were hypothesized. If this reaction can be done with chirality transfer, we could determine the stereochemistry of the allene by comparing the experimental optical rotation of the product to the known optical rotation. We initially attempted to reduce the ester or amide to an allenic alcohol, but the allenes were incredibly base and acid sensitive, and racemized under reducing conditions. We then decided to try cyclization of the amide using IBr. The literature precedent for this cyclization reaction is shown in Scheme 3.1. Marshall *et al.* used IBr to cyclize chiral allene **3.1**, forming iodobutenolide **3.2**.³⁷ The iodide can then be removed by treatment with palladium and tin to form butenolide **3.3**

Scheme 3.1. Butenolide Formation Performed by Marshall and coworkers.

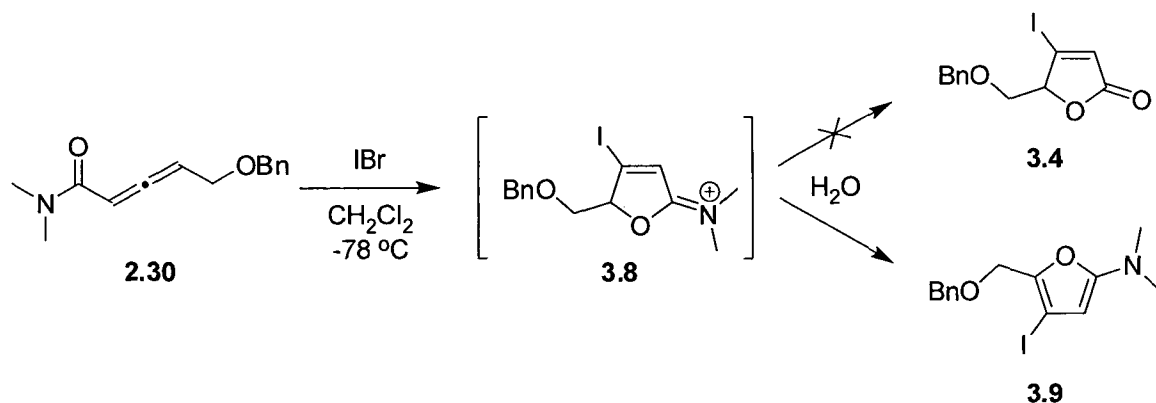


Many of these butenolides are known compounds, so if this reaction could be performed successfully with transfer of chirality, we could use the optical rotation of the butenolide to retroactively determine the absolute stereochemistry of the allene. We decided to

³⁷ Marshall, J.A.; Wolf, M.A.; Wallace, E.M. *J. Org. Chem.* **1997**, *62*, 367.

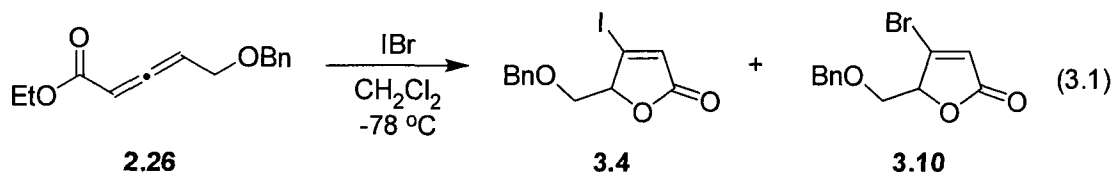
This reaction would go through intermediate **3.8**, and water would theoretically attack the iminium ion, followed by dimethylamine elimination to yield the desired product. Instead, however, it appears that water deprotonated the iminium intermediate, yielding furan **3.9** in 60% yield. Since this is an achiral product, it is no help in the determination of absolute stereochemistry.

Scheme 3.4. Actual Reaction of Allenic Amide with IBr – Formation of Furan.



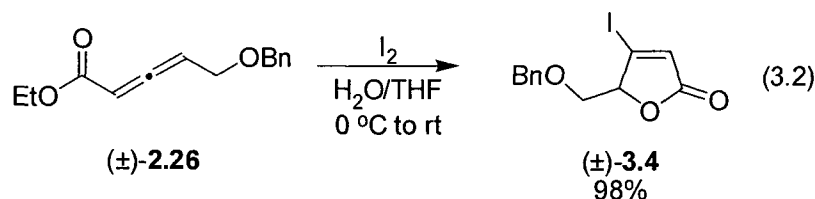
3.1.3 Reactions Using Racemic Allenic Esters

Since the cyclization of the amide yielded an achiral product, we decided to attempt the reaction using the allenic ester instead. Since Marshall and co-workers used esters when performing the reaction, this was more likely to be successful. We tried the reaction with the ethyl ester version of the same allene. Treatment of the allenic ester with IBr at -78 °C formed some of the desired product, but it appeared to form in an approximately 1:1 ratio with the bromobutenolide **3.10**, with an overall yield of 78%. These two products were very difficult to separate chromatographically, which made this reaction difficult to work with.



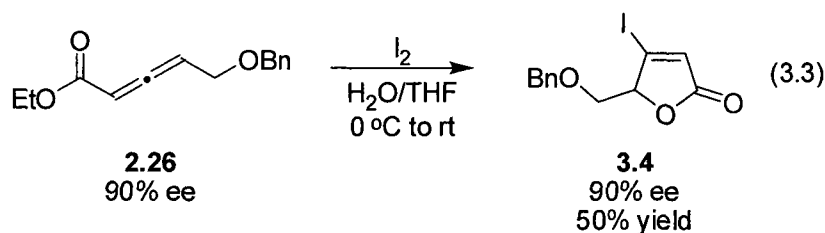
Since the IBr gave a mixture of iodinated and brominated products, we then decided to try the reaction with iodine, so only the iodinated product was possible. Treatment of

allenic ester **2.26** with iodine in a 1:1 mixture of THF:H₂O yielded the desired iodobutenolide **3.4** in 98% yield.



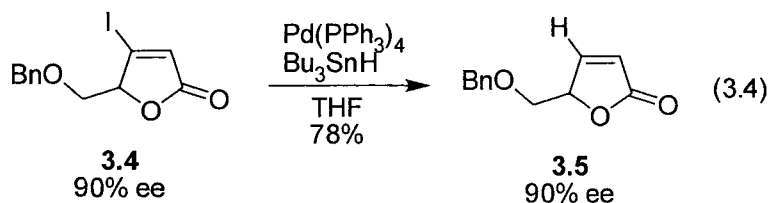
3.1.4 Reactions Using Chiral Allenic Esters

This cyclization result with the iodine was promising, but the reaction was performed on a racemic allene. The next step was to attempt this reaction on a chiral allenic amide and see if the enantiopurity could be retained. The reaction was attempted on the chiral allenic ester with an ee of 90%. The allene was reacted as a mixture of approximately 85% allene, 15% alkyne (since we were using the ester, we could not separate the alkyne from the allene). The iodolactonization reaction gave the iodobutenolide with complete retention of stereochemistry. The iodobutenolide was obtained in 90% ee. The yield was significantly lower than the racemic version of the reaction, but this could be due to the contamination from the alkyne.



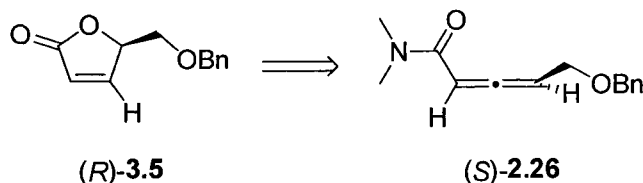
3.1.5 Removal of Iodine and Final Determination of Absolute Stereochemistry

Now that we had the chiral iodobutenolide, the only remaining step was to remove the iodine to yield the known butenolide **3.5**. This reaction was performed using palladium(0) and tributyltin hydride. This reaction worked well, giving the desired product in 78% yield without affecting the enantiopurity of the compound.



Once we had formed the desired butenolide **3.5**, we measured the optical rotation. The optical rotation was positive, which from the literature corresponds to (*R*)-5-hydroxymethyl-5H-furan-2-one ((*R*)-**3.5**).³⁸ As was previously determined, the (*R*)-butenolide is formed from the cyclization of the (*S*)-allene (*S*)-**2.26** (Figure 3.1).

Figure 3.1. Determination of Absolute Stereochemistry.



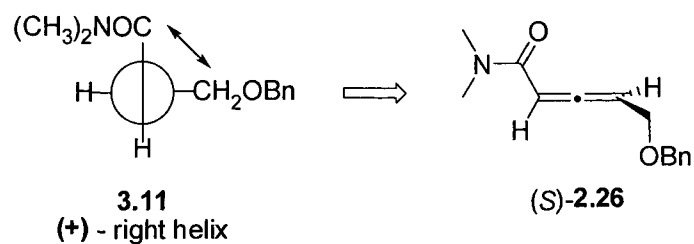
Since all of the allenes are similar, and are synthesized by an identical method using the same silver source and ligand, we can assume that the enantiomer which is formed preferentially in this case will be the enantiomer which is formed in every case. This means that the reaction forming the allenic esters and amides using AgSbF₆ and (*R*)-(*S*)-JOSIPHOS always forms the (*S*) enantiomer of the allene.

3.2 The Lowe-Brewster Rule

The Lowe-Brewster rule states that the absolute stereochemistry of an allene can be determined by the sign of the optical rotation.² All of the allenes we synthesized are dextrorotatory, which suggests that the allenes would all be a right-handed helix. The Lowe-Brewster rule begins by viewing the allene along its orthogonal axis, with the most polarizable substituent (the amide) on the uppermost vertical axis, as can be seen in Figure 3.2. Since we know the compound is dextrorotatory, that means that the more polarizable substituent (CH₂OBn) is along the horizontal axis is to the right – as is observed in the Newman diagram 3.11. This would mean that all of the allenes have an (*S*) conformation, as is illustrated in compound (*S*)-**2.26**.

³⁸ Fazio, F.; Schneider, M.P. *Tetrahedron: Asymm.* **2000**, 1869.

Figure 3.2. Illustration of the Lowe-Brewster Rule.



The prediction of an (*S*) conformation by the Lowe-Brewster rule matches with the absolute stereochemistry already determined *via* chemical transformation. The combination of the butenolide formation and the Lowe-Brewster rule allows us to conclusively determine the absolute stereochemistry of the allenes formed.

4 Conclusion

3-Alkynoates and 3-alkynamides were synthesized according to literature procedure. They were then isomerized into chiral asymmetric allenic esters and amides using AgSbF_6 as a catalyst, (*R*)-(*S*)-JOSIPHOS as a chiral ligand, and *N*-methylmorpholine as a catalytic base. The reaction reached an equilibrium between the allene and alkyne, and did not go to completion. The allenic esters could not be separated from the alkynes chromatographically, but the amides could be separated relatively easily. The reaction was performed in good yields (27-95%) and excellent enantioselectivities (90-99% *ee*). The absolute conformation of the reaction was determined to be (*S*) by two methods – chemical transformation to a known compound, and application of the Lowe-Brewster rule.

5 Supporting Information

5.1 General Methods

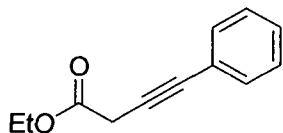
All experiments were carried out under an atmosphere of argon. ^1H and ^{13}C NMR were recorded in CDCl_3 using a Bruker AVANCE 400 spectrometer with Me_4Si as an internal standard. High-resolution mass spectra were obtained on a Kratos Concept IIH. Infra-Red analysis was performed with a Bruker EQUINOX 55. Chiral HPLC data was obtained on a Waters 2695 equipped with a Waters PDA detector 2996. HPLC Grade THF, Et_2O , benzene, toluene and CH_2Cl_2 were dried and purified via MBraun SP Series solvent purification system. Silver salts and Phosphonium ligands were purchased from Strem or Aldrich and stored and weighed out in a glove box. Unless otherwise indicated, all other reagents were purchased from commercial sources and used without further purification.

5.2 Characterization of Products

Starting Materials

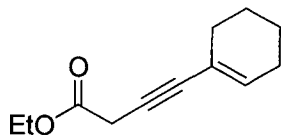
All of the 3-alkynoates and 3-alkynamides were synthesized as previously reported by Suárez and Fu as reported in the literature.³⁵

Table 2.1, entry 1



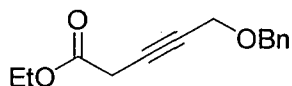
Ethyl 4-phenylbut-3-ynoate (2.4): Synthesized according to literature procedure using 2.0 grams of alkyne, and exhibited spectral data identical to previous reports (2.4 g, 72%).³⁵

Table 2.1, entry 2



Ethyl 4-cyclohexenylbut-3-ynoate (2.16): Synthesized according to literature procedure using 2.0 grams of alkyne, and exhibited spectral data identical to previous reports (1.89 g, 56%).³⁵

Table 2.1, entry 3



Ethyl 5-(benzyloxy)pent-3-ynoate (2.26)³⁹: Synthesized according to the literature procedure using 2.0 grams of alkyne (1.10 g, 55%).

¹H NMR (400 MHz, CDCl₃): δ 1.29 (t, J = 7.2 Hz, 3H), 3.34 (s, 2H), 4.20 (t, J = 2.4 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 4.61 (s, 2H), 7.27 – 7.36 (m, 5H)

¹³C NMR (100 MHz, CDCl₃): δ 14.1 (CH₃), 26.1 (CH₂), 57.5 (CH₂), 61.6 (CH₂), 71.5 (CH₂), 78.5 (C), 79.3 (C), 127.8 (CH), 128.1 (CH), 128.4 (CH), 137.4 (C), 168.1 (C)

IR (ν_{max} /cm⁻¹): 2982.7, 2856.6, 2234.8, 1742.6, 1261.5, 1184.9, 1028.2

HRMS: calculated for C₁₁H₁₁O (M^+ - 73): 159.0810; Found: 159.0844

R_f: 0.37 on silica gel (15% Et₂O in Hexanes)

Table 2.1, entry 4



Ethyl 5-(tert-butyldimethylsilyloxy)pent-3-ynoate³⁹: Synthesized according to the literature procedure using 2.0 grams of alkyne. (0.78 g, 26%).

¹H NMR (400 MHz, CDCl₃): δ 0.10 (s, 6H), 0.89 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H), 2.38 (t, J = 2.4 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.32 (t, J = 2.4 Hz, 2H)

¹³C NMR (100 MHz, CDCl₃): δ -5.2 (CH₃), 14.0 (CH₃), 18.2 (C), 25.8 (CH₃), 26.1 (CH₂), 51.8 (CH₂), 61.5 (CH₂), 76.5 (C), 81.9 (C), 168.1 (C)

IR (ν_{max} /cm⁻¹): 2957.8, 2930.3, 2858.1, 1748.9, 1258.4, 1186.5, 1083.3

HRMS: calculated for C₁₁H₁₁O (M^+ - 73): 159.0810; Found: 159.0844

R_f: 0.48 on silica gel (10% Et₂O in Hexanes)

Table 2.1, entry 5



Ethyl 5-(triisopropylsilyloxy)pent-3-ynoate³⁹: Synthesized according to the literature procedure using 2.0 grams of alkyne. (1.74 g, 62%).

³⁹ Characterization helped by Daniel Shore

¹H NMR (400 MHz, CDCl₃): δ 1.08 – 1.16 (m, 21H), 1.28 (t, *J* = 7.2 Hz, 3H), 3.82 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.64 (s, 2H)

¹³C NMR (100 MHz, CDCl₃): δ 12.0 (CH₂), 14.1 (CH), 17.9 (CH₃), 46.7 (CH₂), 61.4 (CH₂), 67.1 (CH₂), 111.9 (C), 126.3 (C), 166.2 (C)

IR (ν_{max}/cm⁻¹): 2943.9, 2867.1, 2235.8, 1739.7, 1260.5, 1180.5, 1098.0, 882.9

HRMS: calculated for C₁₁H₁₁O (M⁺ - 73): 159.0810; Found: 159.0844

R_f: 0.48 on silica gel (10% Et₂O in Hexanes)

Table 2.1, entry 6



Ethyl oct-3-ynoate³⁹: Synthesized according to the literature procedure using 2.0 grams of alkyne. (3.03 g, 74%).

¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.36 – 1.53 (m, 4H), 2.20 (tt, *J* = 2.4, 6.8 Hz, 2H), 3.24 (t, *J* = 2.4 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H)

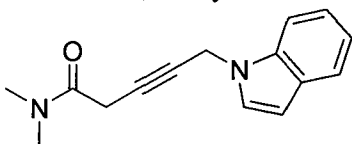
¹³C NMR (100 MHz, CDCl₃): δ 13.6 (CH₃), 14.1 (CH₃), 18.4 (CH₂), 21.9 (CH₂), 26.1 (CH₂), 30.8 (CH₂), 61.4 (CH₂), 71.4 (C), 83.8 (C), 169.0 (C)

IR (ν_{max}/cm⁻¹): 2966.9, 2934.8, 2873.9, 2215.9, 1745.4, 1261.1, 1180.5, 1031.2

HRMS: calculated for C₈H₁₁O₂ (M⁺ - 29): 139.0759; Found: 139.0715

R_f: 0.28 on silica gel (20% Et₂)

Table 2.14, Entry 1



5-(1H-Indol-1-yl)-N,N-dimethylpent-3-ynamide: Synthesized according to the literature procedure using 0.75 grams alkyne (0.70 g alkyne, 60% and 0.26 g allene, 22%).

¹H NMR (400 MHz, CDCl₃): δ 2.90 (s, 6H), 3.24 (br s, 2H), 4.85 (br s, 2H), 6.49 (d, *J* = 3.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H)

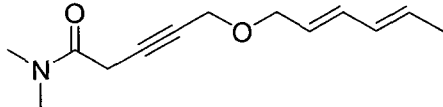
¹³C NMR (100 MHz, CDCl₃): δ 26.3 (CH₂), 35.8 (CH₃), 36.2 (CH₂), 37.7 (CH₃), 77.6 (C) 78.0 (C), 101.6 (CH), 109.3 (CH), 109.6 (C), 119.6 (CH), 120.9 (CH), 121.6 (CH), 127.3 (CH), 135.6 (C), 166.6 (C)

IR (ν_{max}/cm⁻¹): 2929.1, 2233.6, 1656.9, 1462.8, 1398.3

HRMS: calculated for C₁₅H₁₆N₂O₁ (M⁺): 240.1263; Found: 240.1275

R_f: 0.33 on silica gel (EtOAc)

Table 2.14, Entry 2



5-((2E,4E)-Hexa-2,4-Dienyloxy)-N,N-dimethylpent-3-ynamide³⁹: Synthesized according to the literature procedure using 1.0 grams alkyne (0.74 g alkyne, 46% and 0.65 g allene, 40%).

¹H NMR (400 MHz, CDCl₃): δ 1.66 (br d, *J* = 6.8 Hz, 3H), 2.86 (s, 3H), 3.00 (s, 3H), 3.23 (t, *J* = 2.4 Hz, 2H), 3.96 (t, *J* = 6.4 Hz, 2H), 4.05 (t, *J* = 2.4 Hz, 2H), 5.50 (dt, *J* = 6.4, 15.2 Hz, 1H), 5.62 (dq, *J* = 6.8, 14.8 Hz, 1H), 5.96 (ddq, *J* = 1.6, 10.4, 14.8 Hz, 1H), 6.12 (dd, *J* = 10.4, 15.2 Hz, 1H)

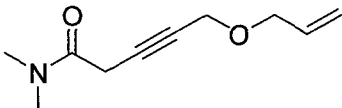
¹³C NMR (100 MHz, CDCl₃): δ 17.8 (CH₃), 26.1 (CH₂), 35.4 (CH₃), 37.5 (CH₃), 56.9 (CH₂), 69.6 (CH₂), 78.7 (C), 79.3 (C), 125.4 (CH), 130.0 (CH), 130.4 (CH), 133.6 (CH), 166.6 (C)

IR (ν_{max}/cm⁻¹): 3019.7, 2933.7, 2853.3, 2231.0, 1651.6, 1263.3, 1126.4, 1069.8

HRMS: calculated for C₁₃H₁₉N₁O₂ (M⁺): 221.1416; Found: 221.1411

R_f: 0.32 on silica gel (20% Hexanes in EtOAc)

Table 2.14, Entry 3



5-(Allyloxy)-N,N-dimethylpent-3-ynamide³⁹: Synthesized according to the literature procedure using 1.0 grams of alkyne (0.66 g alkyne, 35% and 0.92 g allene, 49%).

¹H NMR (400 MHz, CDCl₃): δ 2.96 (s, 3H), 3.10 (s, 3H), 3.33 (t, *J* = 2.4 Hz, 2H), 4.05 (dt, *J* = 1.2, 5.6 Hz, 2H), 4.17 (t, *J* = 2.4 Hz, 2H), 5.21 (dq, *J* = 1.6, 10.4 Hz, 1H), 5.30 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.90 (ddt, *J* = 5.6, 10.4, 17.2 Hz, 1H)

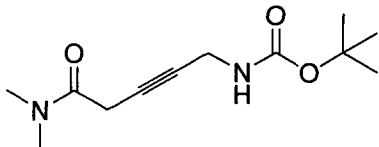
¹³C NMR (100 MHz, CDCl₃): δ 26.4 (CH₂), 35.6 (CH₃), 37.7 (CH₃), 57.6 (CH₂), 70.4 (CH₂), 78.9 (C), 79.4 (C), 117.6 (CH₂), 133.9 (CH), 166.8 (C)

IR (ν_{max}/cm⁻¹): 2936.6, 2856.9, 2226.0, 1652.9, 1132.4, 1077.3

HRMS: calculated for C₃H₆N₁O₁ (M⁺ - 109): 72.0449; Found: 72.0456

R_f: 0.33 on silica gel (25% Hexanes in EtOAc)

Table 2.14, Entry 4



tert-Butyl 5-(dimethylamino)-5-oxopent-2-ynylcarbamate: Synthesized according to the literature procedure using 0.5 grams of alkyne (0.44 g alkyne, 57% and 0.22 g allene, 28%).

¹H NMR (400 MHz, CDCl₃): δ 1.41 (s, 9H), 2.92 (s, 3H), 3.04 (s, 3H), 3.24 (t, *J* = 2.4 Hz, 2H), 3.89 (brt, *J* = 2.4 Hz, 2H), 4.70 (brs, 1H)

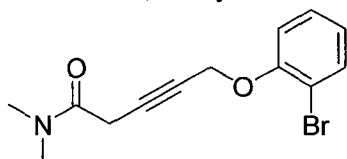
¹³C NMR (100 MHz, CDCl₃): δ 26.3 (CH₂), 28.3 (CH₃), 30.7 (CH₂) 35.7 (CH₃), 37.8 (CH₃), 75.7 (C), 79.8 (C), 155.2 (C), 155.3 (C), 167.0 (C)

IR (ν_{max}/cm⁻¹): 3322.2, 2976.9, 2932.5, 2287.8, 1710.2, 1649.7, 1517.4, 1250.9, 1169.7

HRMS: calculated for C₈H₁₁N₂O₃ (M⁺ - 56): 184.0848; Found: 184.0852

R_f: 0.27 on silica gel (EtOAc)

Table 2.14, Entry 5



5-(2-Bromophenoxy)-N,N-dimethylpent-3-ynamide: Synthesized according to the literature procedure using 0.5 grams of alkyne (0.40 g alkyne, 55% and 0.22 g allene, 30%).

¹H NMR (400 MHz, CDCl₃): δ 2.93 (s, 3H), 2.98 (s, 3H), 3.31 (t, *J* = 2.4 Hz, 2H), 4.80 (t, *J* = 2.4 Hz, 2H), 6.87 (td, *J* = 1.6, 7.2 Hz, 1H), 7.06 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.26 (ddd, *J* = 1.6, 7.2, 8.0 Hz, 1H), 7.54 (dd, *J* = 1.6, 8.0 Hz, 1H)

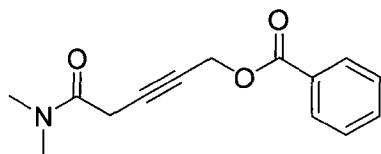
¹³C NMR (100 MHz, CDCl₃): δ 26.5 (CH₂), 35.7 (CH₃), 37.7 (CH₃), 57.2 (CH₂) 78.0 (C), 80.9 (C), 112.3 (C), 114.2 (CH), 122.6 (CH), 128.3 (CH), 133.4 (CH), 154.0 (C), 166.5 (C)

IR (ν_{max}/cm⁻¹): 2929.1, 2231.3, 1655.3, 1478.5, 1397.7, 1279.4, 1229.6, 1133.3

HRMS: calculated for C₁₃H₁₄N₁O₂Br (M⁺): 295.0208; Found: 295.0197

R_f: 0.36 on silica gel (20% Hexanes in EtOAc)

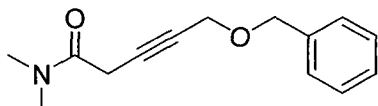
Table 2.14, Entry 6



5-(Dimethylamino)-5-oxopent-2-ynyl benzoate: Synthesized according to the literature procedure using 1.0 grams of alkyne (0.38 g alkyne, 25% and 0.95 g allene, 62%).

¹H NMR (400 MHz, CDCl₃): δ 2.95 (s, 3H), 3.06 (s, 3H), 3.34 (t, *J* = 2.4 Hz, 2 H), 4.94 (t, *J* = 2.4 Hz, 2H), 7.42-7.46 (m, 2H), 7.57 (tt, *J* = 1.2, 7.6 Hz, 1H), 8.04-8.07 (m, 2H)
¹³C NMR (100 MHz, CDCl₃): δ 26.1 (CH₂), 35.6 (CH₃), 37.5 (CH₃), 52.7 (CH₂), 77.4 (C), 79.6 (C), 128.1 (CH), 129.3 (C), 129.4 (CH), 133.0 (CH), 165.5 (C), 166.0 (C)
IR (ν_{max}/cm⁻¹): 2938.3, 2242.7, 1723.0, 1657.4, 1269.6, 1107.9, 1070.8
HRMS: calculated for C₁₄H₁₅N₁O₃ (M⁺): 245.1052; Found: 245.1054
R_f: 0.28 on silica gel (20% Hexanes in EtOAc)

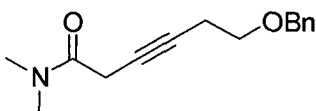
Table 2.14, Entry 7



5-(Benzyloxy)-*N,N*-dimethylpent-3-ynamide: Synthesized according to the literature procedure using 0.65 grams of alkyne (0.66 g alkyne, 61% and 0.31 g allene, 29%).

¹H NMR (400 MHz, CDCl₃): δ 2.93 (s, 3H), 3.05 (s, 3H), 3.31 (t, *J* = 2.4 Hz, 2H), 4.16 (t, *J* = 2.4 Hz, 2H), 4.55 (s, 2H), 7.27-7.34 (m, 5H)
¹³C NMR (100 MHz, CDCl₃): δ 26.4 (CH₂), 35.7 (CH₃), 37.7 (CH₃), 57.5 (CH₂), 71.5 (CH₂), 79.2 (C), 79.4 (C), 127.7 (CH), 127.92 (CH), 128.3 (CH), 137.4 (C), 166.8 (C)
IR (ν_{max}/cm⁻¹): 2934.1, 2227.1, 1655.9, 1397.4, 1131.0, 1071.4
HRMS: calculated for C₁₄H₁₇N₁O₂ (M⁺): 231.1259; Found: 231.1223
R_f: 0.39 on silica gel (20% Hexanes in EtOAc)

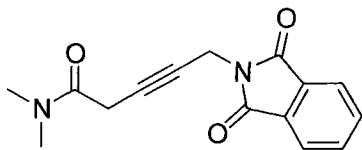
Table 2.14, Entry 8



6-(Benzyloxy)-*N,N*-dimethylhex-3-ynamide³⁹: Synthesized according to the literature procedure using 1.0 grams of alkyne (1.53 g alkyne, 92%, 0% allene).

¹H NMR (400 MHz, CDCl₃): δ 2.51 (tt, *J* = 2.4, 7.2 Hz, 2H), 2.94 (s, 3H), 3.06 (s, 3H), 3.24 (t, *J* = 2.4 Hz, 2 H), 3.57 (t, *J* = 7.2 Hz, 2H), 4.54 (s, 2H), 7.26-7.37 (m, 5H)
¹³C NMR (100 MHz, CDCl₃): δ 20.2 (CH₂), 26.5 (CH₂), 35.7 (CH₃), 37.8 (CH₃), 68.5 (CH₂), 72.9 (CH₂), 73.5 (C), 80.6 (C), 127.6 (CH), 127.7 (CH), 128.4 (CH), 138.1 (C), 167.6 (C)
IR (ν_{max}/cm⁻¹): 2931.8, 2858.0, 2232.2, 1659.6, 1388.0, 1258.1, 1131.2, 1066.3, 991.6
HRMS: calculated for C₁₂H₁₃O₁ (M⁺ - 72): 173.0966; Found: 173.0961
R_f: 0.33 on silica gel (20% Hexanes in EtOAc)

Table 2.14, Entry 9



5-(1,3-Dioxisoindolin-2-yl)-N,N-dimethylpent-3-ynamide³⁹: Synthesized according to the literature procedure using 0.5 grams of alkyne. (0.30 g alkyne, 41% and 0.31 g allene, 43%).

¹H NMR (400 MHz, CDCl₃): δ 2.94 (s, 3H), 3.07 (s, 3H), 3.25 (t, $J = 2.4$ Hz, 2H), 4.47 (t, $J = 2.4$ Hz, 2H), 7.74 (dd, $J = 2.8, 5.2$ Hz, 2H), 7.88 (dd, $J = 2.8, 5.2$ Hz, 2H)

¹³C NMR (100 MHz, CDCl₃): δ 26.5 (CH₂), 27.4 (CH₂), 35.8 (CH₃), 37.9 (CH₃), 75.9 (C), 77.3 (C), 123.5 (CH), 132.0 (C), 134.2 (CH), 166.7 (C), 167.1 (C)

IR (ν_{max} /cm⁻¹): 2929.9, 2245.8, 1770.7, 1717.7, 1652.9, 1394.4, 1113.2, 723.9

HRMS: calculated for C₁₅H₁₄N₂O₃ (M⁺): 270.1004; Found: 270.1000

R_f: 0.27 on silica gel (EtOAc)

Melting Point: 132 – 134 °C

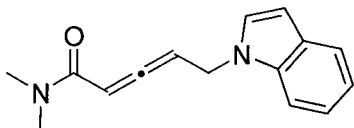
Allene Synthesis

General Procedure:

This reaction is very air sensitive, and it is imperative that all solids are weighed under an inert atmosphere, and all liquids and oils (including reagents) are degassed using nitrogen or argon before being added to the reaction mixture.

(*R*)-(*S*)-JOSIPHOS (0.105 equiv.) is weighed out in a 4 mL screw-cap vial under an inert atmosphere and degassed THF (0.6 mL) is added. A solution of AgSbF₆ (0.1 equiv., weighed under an inert atmosphere) in degassed MeOH (0.2 mL) is added, and the mixture is stirred at room temperature under an inert atmosphere for 30 minutes. A degassed solution of 0.04 g of alkyne **2.29** (1.0 equiv.) in MeOH (0.2 mL) is added, and the mixture is cooled to 0 °C over 20 minutes. *N*-methylmorpholine (0.05 equiv.) is added, and the reaction is stirred at 0 °C for 1 hour. Hexanes are added to the reaction until a precipitate forms (approx. 2 mL), and the solution is filtered through silica using EtOAc as the eluant. The filtrate is concentrated, and the product is purified by column chromatography.

Table 2.17, Entry 1



5-(1H-Indol-1-yl)-N,N-dimethylpenta-2,3-dienamide: Synthesized according to the general procedure (0.038 g, 95%).

¹H NMR (400 MHz, CDCl₃): δ 2.86 (s, 3H), 2.95 (s, 3H), 4.84 (dd, *J* = 2.8, 6.0 Hz, 2H), 5.74 (q, *J* = 6.4, 1H), 5.97 (dt, *J* = 2.8, 6.0 Hz, 1H), 6.50 (dd, *J* = 0.8, 3.2 Hz, 1H), 7.11 (td, *J* = 0.8, 8.0 Hz, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 7.21 (td, *J* = 1.2, 7.2 Hz, 1H), 7.35 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.61 (br d, *J* = 8.0 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): δ 35.7 (CH₃), 37.8 (CH₃), 44.2 (CH₂), 90.2 (CH), 92.2 (CH), 101.8 (CH), 109.5 (CH), 119.5 (CH), 120.9 (CH), 121.6 (CH), 127.7 (CH), 128.7 (C), 135.9 (C), 164.3 (C), 209.5 (C)

IR (ν_{max}/cm⁻¹): 2929.0, 1963.0, 1632.6, 1463.0, 1378.8, 743.1

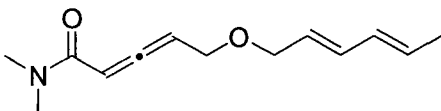
HRMS: calculated for C₁₅H₁₆N₂O₁ (M⁺): 240.1263; Found: 240.1264

R_f: 0.21 on silica gel (EtOAc)

HPLC: The ee was determined to be **90%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 220 nm. Retention times in 10% isopropanol in hexanes were 38 min and 50 min.

[α]_D^{rt} = +160.1, (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 2



5-((2E,4E)-Hexa-2,4-dienyloxy)-N,N-dimethylpenta-2,3-dienamide³⁹: Synthesized according to the general procedure, except the reaction was carried out at -10 °C (0.028 g, 72%).

¹H NMR (400 MHz, CDCl₃): δ 1.75 (d, *J* = 6.8 Hz, 3H), 2.99 (s, 3H), 3.10 (s, 1H), 4.04 (d, *J* = 6.4 Hz, 2H), 4.10 (dd, *J* = 2.4, 6.4 Hz), 5.56 – 5.72 (m, 3H), 6.01 (dt, *J* = 2.4, 6.0 Hz, 1H), 6.04 – 6.08 (m, 1H), 6.21 (dd, *J* = 10.4, 15.3 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): δ 17.9 (CH₃), 35.6 (CH₃), 37.9 (CH₃), 66.0 (CH₂), 70.1 (CH₂), 88.4 (CH), 92.2 (CH), 125.9 (CH), 129.9 (CH), 130.6 (CH), 133.5 (CH), 164.5 (C), 209.7 (C)

IR (ν_{max}/cm⁻¹): 2928.5, 1962.0, 1638.4, 1495.2, 1395.6, 1260.3, 1131.9

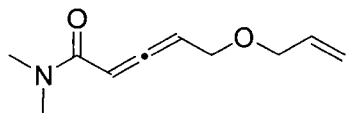
HRMS: calculated for C₁₃H₁₉N₁O₂ (M⁺): 221.1416; Found: 221.1385

R_f: 0.21 on silica gel (20% Hexanes in EtOAc)

HPLC: The ee was determined to be **96%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 228. Retention times in 10% isopropanol in hexanes were 15.2 and 20.0 minutes.

[α]_D^{rt} = +62.4 (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 3



5-(Allyloxy)-N,N-dimethylpenta-2,3-dienamide³⁹: Synthesized according to the general procedure (0.027 g, 68%).

¹H NMR (400 MHz, CDCl₃): δ 3.00 (s, 3H), 3.10 (s, 3H), 4.04 (br d, *J* = 6.0 Hz, 2H), 4.13 (dd, *J* = 2.4, 6.8 Hz, 2H), 5.19 (dq, *J* = 1.2, 10.4 Hz, 1H), 5.29 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.64 (q, *J* = 6.4 Hz, 1H), 5.90 (ddt, *J* = 5.6, 10.4, 17.2 Hz, 1H), 6.02 (dt, *J* = 2.4, 6.4 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): δ 35.8 (CH₃), 38.0 (CH₃), 66.4 (CH₂), 70.8 (CH₂), 88.6 (CH), 92.3 (CH), 117.4 (CH₂), 134.2 (CH), 164.6 (C), 209.9 (C)

IR (ν_{max}/cm⁻¹): 2932.8, 2961.9, 1961.7, 1635.4, 1260.4, 1081.9

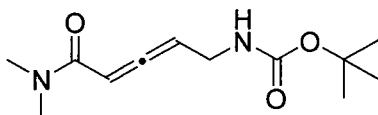
HRMS: calculated for C₁₀H₁₅N₁O₂ (M⁺): 181.1103; Found: 181.1085

R_f: 0.19 on silica gel (25% Hexanes in EtOAc)

HPLC: The ee was determined to be **95%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 210 nm. Retention times in 10% isopropanol in hexanes were 11.7 and 14.3 minutes.

[α]_D^{rt} = +1.25, (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 4



tert-Butyl 5-(dimethylamino)-5-oxopenta-2,3-dienylcarbamate: Synthesized according to the general procedure (0.029 g, 73%).

¹H NMR (400 MHz, CDCl₃): δ 1.44 (s, 9H), 3.00 (s, 3H), 3.10 (s, 3H), 3.84 (br dd, 2H), 4.96 (br s, 1H), 5.63 (q, *J* = 6.0 Hz, 1H), 6.04 (dt, *J* = 3.2, 6.4 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): δ 28.3 (CH₃), 35.7 (CH₃), 37.9 (CH₃), 38.3 (CH₂), 79.4 (C), 89.9 (CH), 93.3 (CH), 155.6 (C), 164.6 (C), 209.2 (C)

IR (ν_{max}/cm⁻¹): 3331.9, 2977.6, 2936.8, 1963.8, 1701.2, 1629.9, 1511.8, 1252.1, 1164.8, 1057.7, 859.7

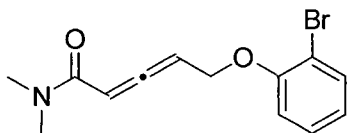
HRMS: calculated for C₈H₁₁N₂O₂ (M⁺ - 73): 167.0821; Found: 167.0826

R_f: 0.20 on silica gel (EtOAc)

HPLC: The ee was determined to be **91%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 210 nm. Retention times in 10% isopropanol in hexanes were 9.63 min and 11.05 min.

[α]_D^{rt} = +76.3 (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 5



5-(2-Bromophenoxy)-*N,N*-dimethylpenta-2,3-dienamide: Synthesized according to the general procedure, except the reaction was performed at -10 °C (0.024 g, 60%).

¹H NMR (400 MHz, CDCl₃): δ 3.00 (s, 3H), 3.08 (s, 3H), 4.75 (dd, *J* = 2.4, 6.4 Hz, 2H), 5.81 (q, *J* = 6.4 Hz, 1H), 6.06 (dt, *J* = 2.4, 6.4 Hz, 1H), 6.85 (td, *J* = 1.2, 7.6 Hz, 1H), 6.94 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.26 (ddd, *J* = 1.6, 7.6, 8.4 Hz, 1H), 7.53 (dd, *J* = 1.6, 7.6 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): δ 35.8 (CH₃), 38.2 (CH₃), 65.6 (CH₂), 90.0 (CH), 91.4 (CH), 112.38 (C), 114.0 (CH), 122.4 (CH), 128.4 (CH), 133.4 (CH), 154.4 (C), 164.2 (C), 209.9 (C)

IR (ν_{max}/cm⁻¹): 2929.6, 2103.8, 1965.9, 1635.6, 1478.3, 1278.8, 1242.6, 1142.7

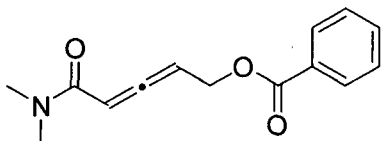
HRMS: calculated for C₁₃H₁₄N₁O₂ (M⁺): 295.0208; Found: 295.0237

R_f: 0.25 on silica gel (20% Hexanes in EtOAc)

HPLC: The ee was determined to be **90%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 210 nm. Retention times in 10% isopropanol in hexanes were 24.5 min and 33.4 min.

[α]_D^{rt} = +93.1, (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 6



5-(Dimethylamino)-5-oxopenta-2,3-dienyl benzoate: Synthesized according to the general procedure, except the reaction was performed at -10 °C (0.024 g, 60%).

¹H NMR (400 MHz, CDCl₃): δ 2.99 (s, 3H), 3.07 (s, 3H), 4.92 (ddd, *J* = 0.8, 1.2, 2.4, 6.4 Hz, 2H), 5.83 (q, *J* = 6.4, 1H), 6.09 (dt, *J* = 2.4, 6.4 Hz, 1H), 7.42-7.46 (m, 2H), 7.56 (tt, *J* = 1.2, 7.6 Hz, 1H), 8.03-8.06 (m, 2H)

¹³C NMR (100 MHz, CDCl₃): δ 35.7 (CH₃), 38.0 (CH₃), 61.1 (CH₂), 89.7 (CH), 90.8 (CH), 128.3 (CH), 129.5 (CH), 129.7 (C), 133.0 (CH), 164.1 (C), 166.0 (C), 210.0 (C)

IR (ν_{max}/cm⁻¹): 2943.0, 1965.6, 1720.1, 1637.7, 1271.8, 1109.3, 714.3

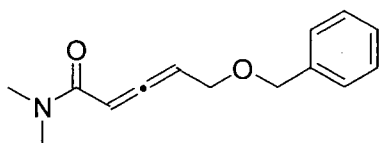
HRMS: calculated for C₁₄H₁₅N₁O₃ (M⁺): 245.1052; Found: 245.1054

R_f: 0.18 on silica gel (20% Hexanes in EtOAc)

HPLC: The ee was determined to be **90%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 220 nm. Retention times in 10% isopropanol in hexanes were 21 min and 26 min.

[α]_D^{rt} = +74.7, (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 7



5-(Benzyloxy)-*N,N*-dimethylpenta-2,3-dienamide (2.31): Synthesized according to the general procedure, except the reaction was performed at -10 °C (0.029 g, 73%).

¹H NMR (400 MHz, CDCl₃): δ 3.00 (s, 3H), 3.08 (s, 3H), 4.17 (dd, *J* = 2.4, 6.4 Hz, 2H), 4.57 (s, 2H), 5.68 (q, *J* = 6.4 Hz, 1H), 6.02 (dt, *J* = 2.4, 6.4 Hz, 1H), 7.27-7.34 (m, 5H)

¹³C NMR (100 MHz, CDCl₃): δ 35.8 (CH₃), 38.0 (CH₃), 66.5 (CH₂), 71.9 (CH₂), 88.7 (CH), 92.3 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 137.8 (C), 164.6 (C), 209.9 (C)

IR (ν_{max}/cm⁻¹): 2928.8, 2861.3, 2104.2, 1961.8, 1635.1, 1261.9, 1144.1, 1074.4

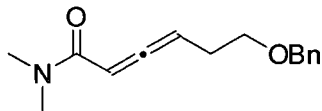
HRMS: calculated for C₁₄H₁₇N₁O₂ (M⁺): 231.1259; Found: 231.1249

R_f: 0.29 on silica gel (20% Hexanes in EtOAc)

HPLC: The ee was determined to be **95%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 210 nm. Retention times in 10% isopropanol in hexanes were 18.9 and 22.1 minutes.

[α]_D^{rt} = +65.5 (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 8



6-(Benzyloxy)-*N,N*-dimethylhexa-2,3-dienamide³⁹: Synthesized according to the general procedure (0.011 g, 27%).

¹H NMR (400 MHz, CDCl₃): δ 2.44 (ddd, *J* = 2.8, 6.8, 13.6 Hz, 2H), 2.97 (s, 3H), 3.05 (s, 3H), 3.59 (t, *J* = 6.8 Hz, 2H), 4.51 (s, 2H), 5.59 (q, *J* = 6.8, 1H), 6.09 (dt, *J* = 2.8, 6.4 Hz, 1H), 7.26-7.36 (m, 5H)

¹³C NMR (100 MHz, CDCl₃): δ 28.3 (CH₂), 35.7 (CH₃), 38.0 (CH₃), 69.1 (CH₂), 72.9 (CH₂), 87.9 (CH), 91.5 (CH), 127.5 (CH), 127.6 (CH), 128.2 (CH), 138.2 (C), 165.2 (C), 209.8 (C)

IR (ν_{max}/cm⁻¹): 2928.3, 1955.8, 1700.1, 1639.1, 1275.1, 1112.5

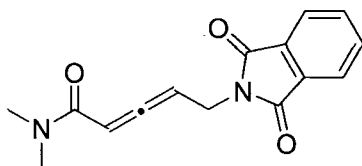
HRMS: calculated for C₁₅H₁₉N₁O₂ (M⁺): 245.1416; Found: 245.1387

R_f: 0.18 on silica gel (20% Hexanes in EtOAc)

HPLC: The ee was determined to be **99%** using HPLC analysis on a CHIRALCEL OD-H column, λ = 210 nm. Retention times in 10% isopropanol in hexanes were 16.3 and 20.5 min.

[α]_D^{rt} = +19.0, (c = 1.00, CH₂Cl₂)

Table 2.17, Entry 9



5-(1,3-Dioxisoindolin-2-yl)-N,N-dimethylpenta-2,3-dienamide: Synthesized according to the general procedure (0.024 g, 60%).

¹H NMR (400 MHz, CDCl₃): δ 2.95 (s, 3H), 3.04 (s, 3H), 4.39 (dd, *J* = 2.4, 6.4 Hz, 2H), 5.66 (q, *J* = 6.4 Hz, 1H), 6.00 (dt, *J* = 2.4, 6.4 Hz, 1H), 7.72 (dd, *J* = 2.8, 5.6 Hz, 2H), 7.85 (dd, *J* = 2.8, 5.6 Hz, 2H)

¹³C NMR (100 MHz, CDCl₃): δ 35.6 (CH₂), 35.8 (CH₃), 38.2 (CH₃), 90.3 (CH), 90.3 (CH), 123.4 (CH), 132.0 (C), 134.1 (CH), 164.1 (C), 167.6 (C), 209.4 (C)

IR (ν_{max}/cm⁻¹): 1967.1, 1717.7, 1627.8

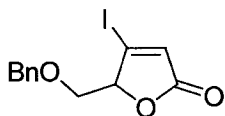
HRMS: calculated for C₁₅H₁₄N₂O₃ (M⁺): 270.1004; Found: 270.1013

R_f: 0.20 on silica gel (EtOAc)

HPLC: The ee was determined to be 40% using HPLC analysis on a CHIRALCEL OJ-H column, λ = 220 nm. Retention times in 10% isopropanol in hexanes were 62.3 min and 70.4 min.

Determination of Absolute Stereochemistry

Equation 3.3



5-(Benzyloxymethyl)-4-iodofuran-2(5H)-one (3.4)³⁹: A solution of I₂ (0.098 g, 0.387 mmol) in 1:1 H₂O:THF (2.0 mL) was cooled to 0 °C. Allene **2.27** was added and the reaction was stirred at 0 °C, before warming to room temperature and stirring for 16h. DCM/H₂O was added, and the organic layer was separated. The organic layer was washed with Na₂S₂O₃, dried over MgSO₄, filtered and concentrated. The white solid was purified by column chromatography on silica gel using 20% EtOAc/Hexanes to give **3.4** (0.041 g, 98%).

¹H NMR (400 MHz, CDCl₃): δ 3.79 (dd, *J* = 5.2, 14.8 Hz, 1H), 3.90 (dd, *J* = 4.0, 14.8 Hz, 1H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.61 (d, *J* = 16.0 Hz, 1H), 5.03 – 5.06 (m, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 7.30 – 7.39 (m, 5H)

¹³C NMR (100 MHz, CDCl₃): δ 67.9 (CH₂), 73.8 (CH₂), 87.3 (CH), 120.7 (C), 127.8 (CH), 127.9 (CH), 128.5 (CH), 131.2 (CH), 137.2 (C), 170.8 (C)

IR (ν_{max}/cm⁻¹): 3426.5, 1640.0, 1313.8, 1236.0, 1154.4, 1087.7

HRMS: calculated for C₁₂H₁₁O₃I (M⁺ - 127): 203.0708; Found: 203.0769

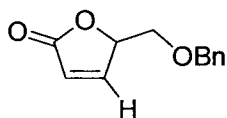
R_f: 0.43 on silica gel (20% EtOAc in Hexanes)

HPLC: The ee was determined to be **71%** using HPLC analysis on a CHIRALCEL OJ-H column, $\lambda = 210$ nm. Retention times in 10% isopropanol in hexanes were 61.7 min and 85.2 min.

$[\alpha]_D^{25}$ = -4.60, (c = 1.00, CH₂Cl₂)

Melting Point: 56 – 58 °C

Equation 3.4



5-(Benzyloxymethyl)furan-2(5H)-one (3.5): Synthesized according to literature procedure using 0.056 g of **3.4** and exhibited spectral data identical to previous reports (0.027 g, 78%).³⁸

Appendix

Selected ^1H and ^{13}C NMR Spectra.

The spectra for all compounds which have not been previously reported in the literature are attached.

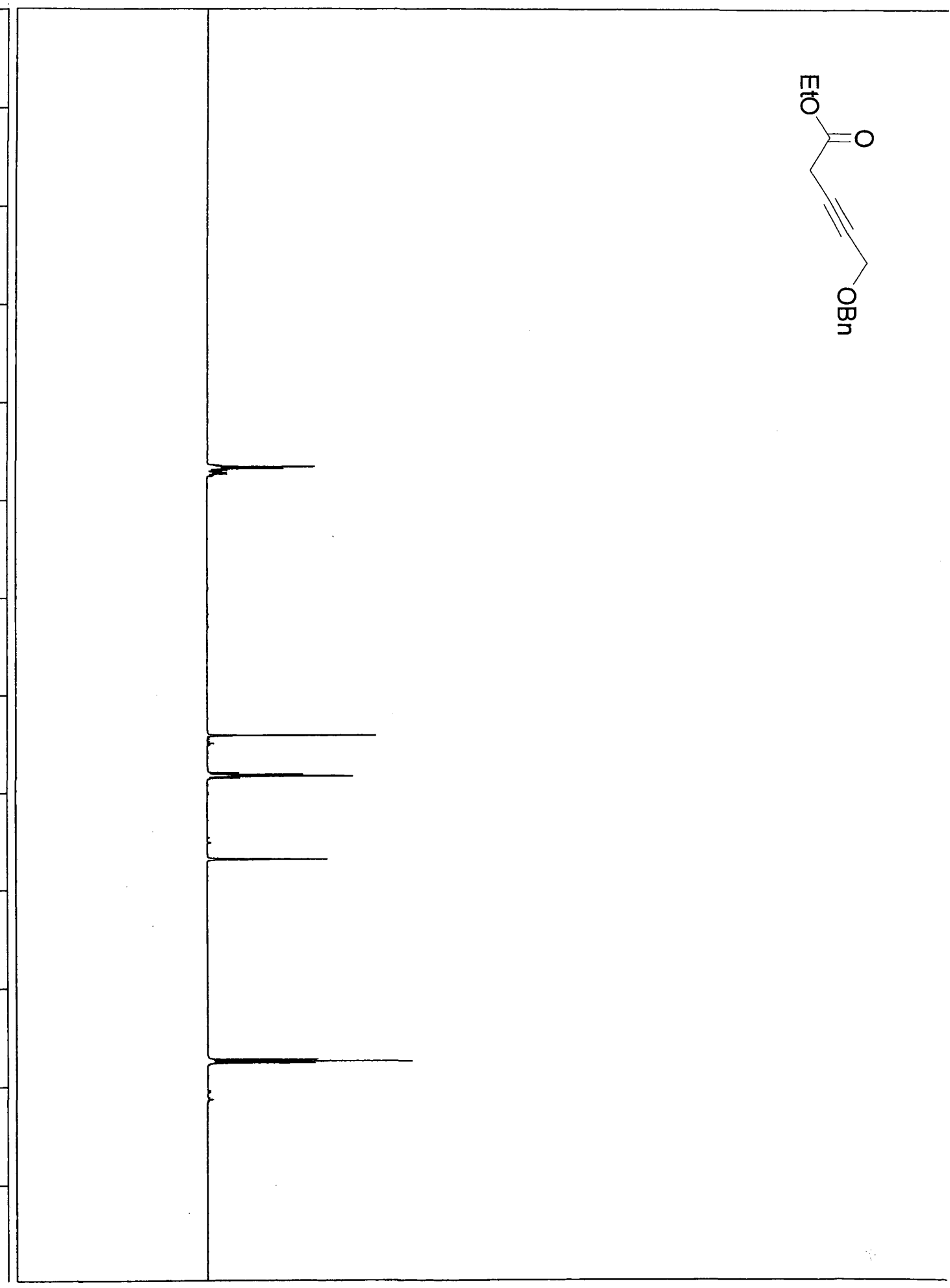


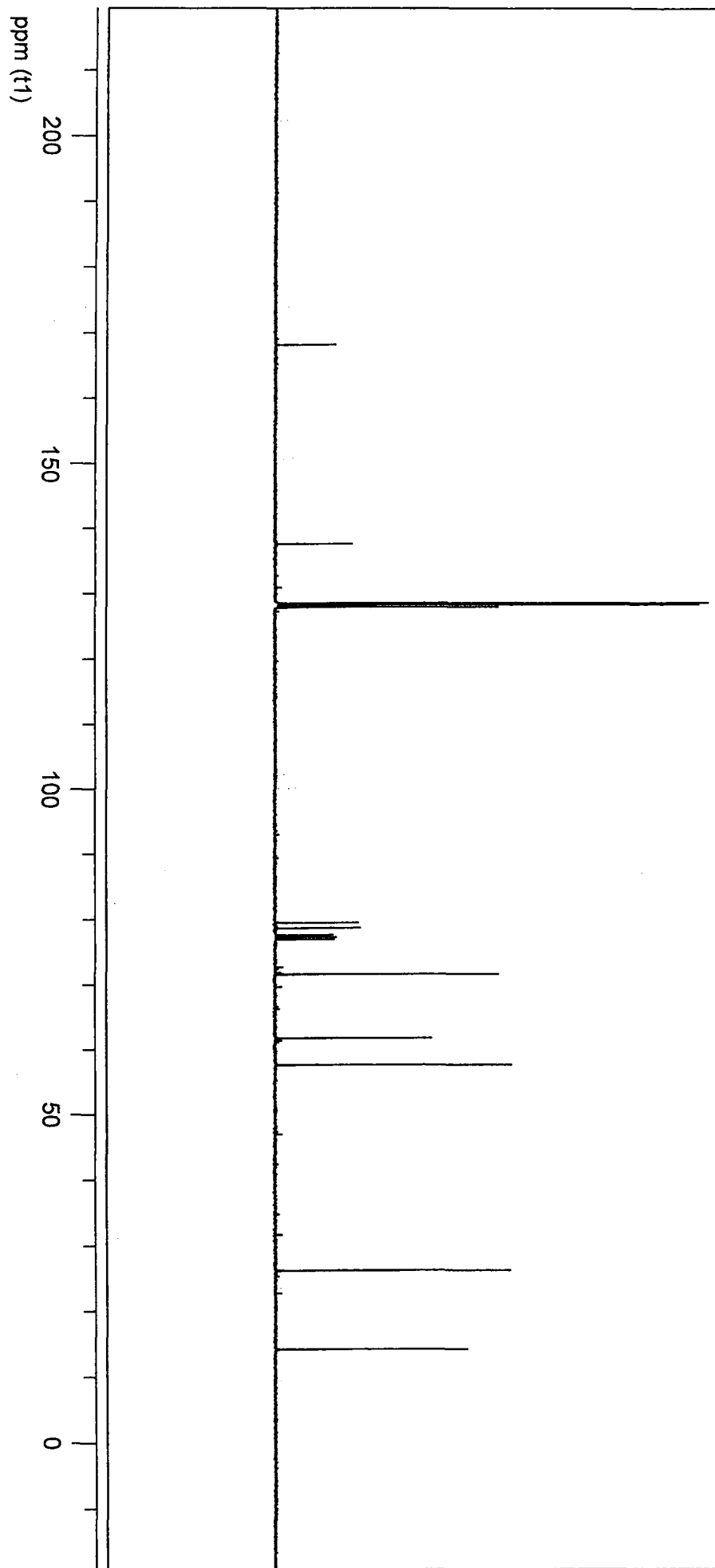
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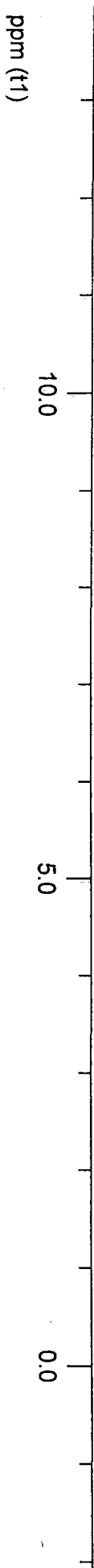
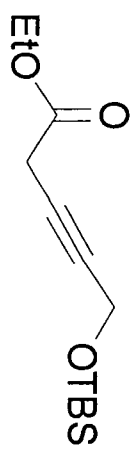
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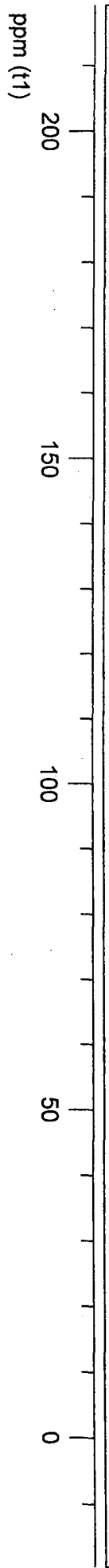
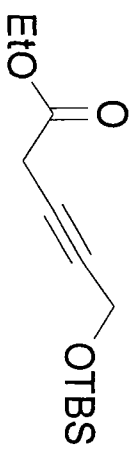
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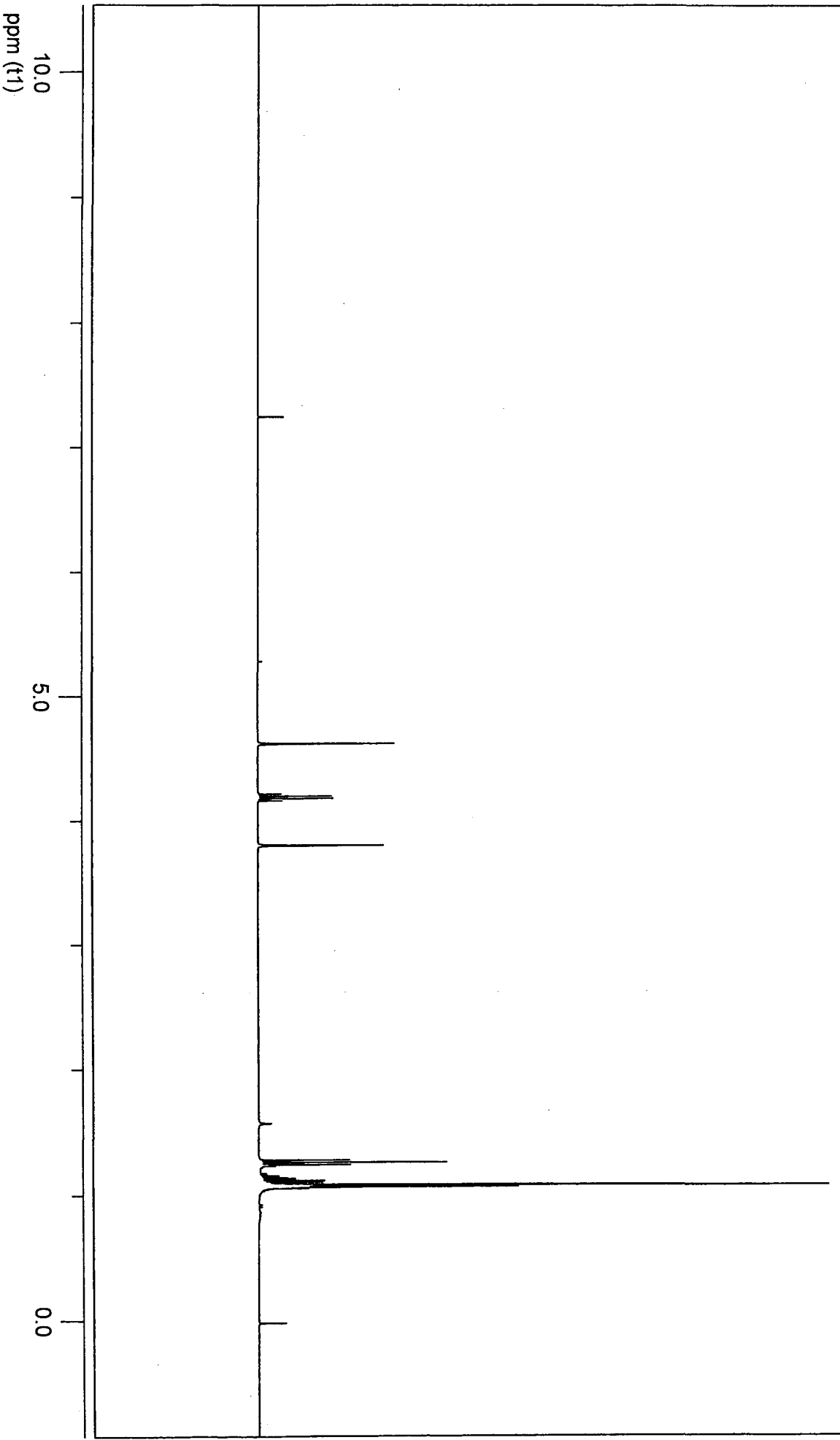
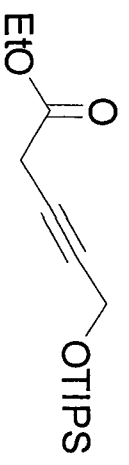
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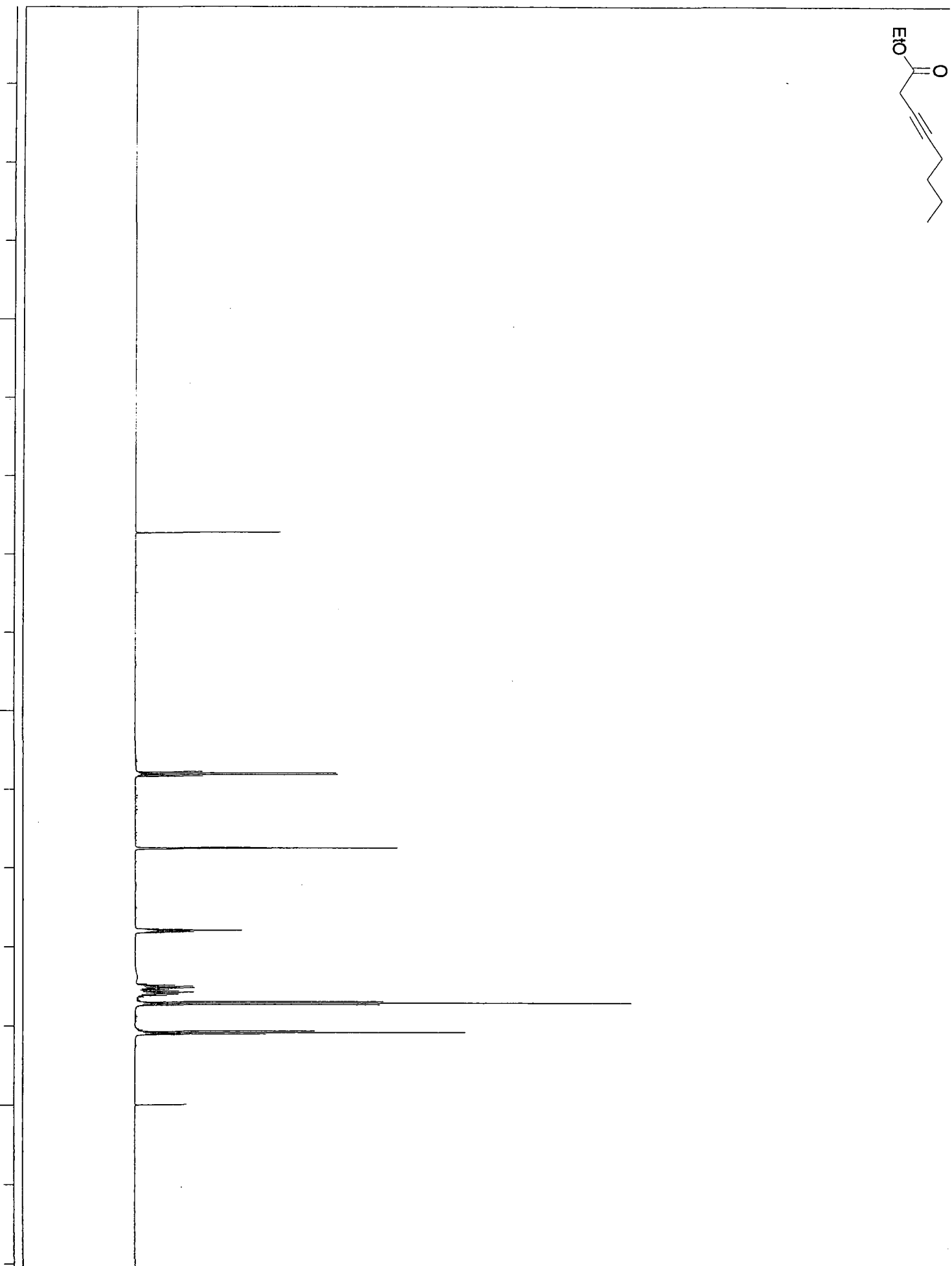


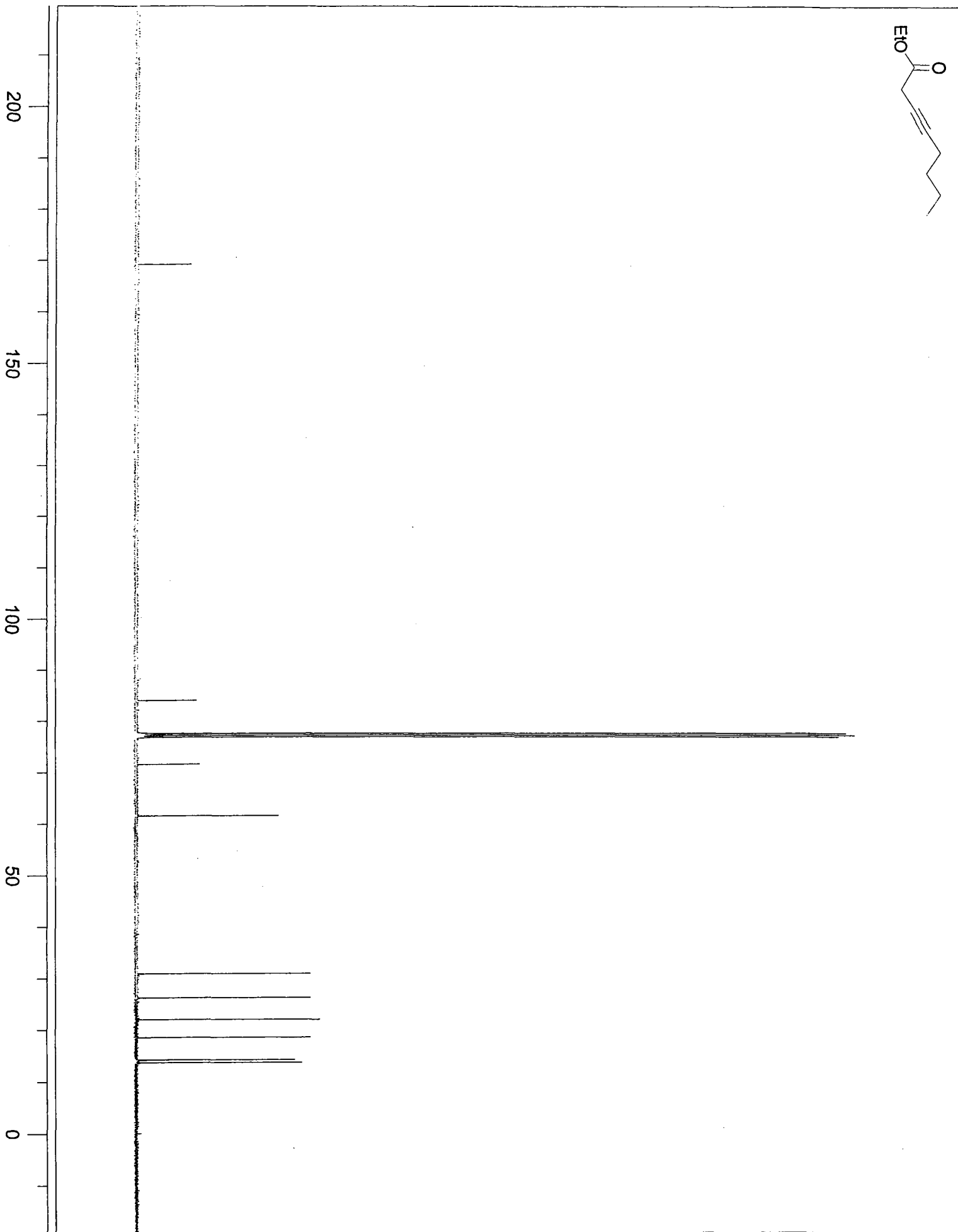


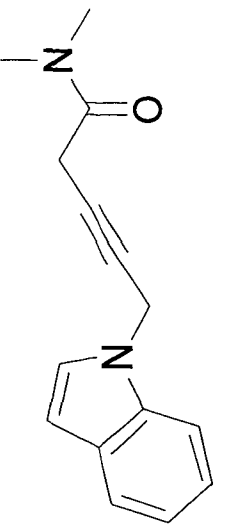
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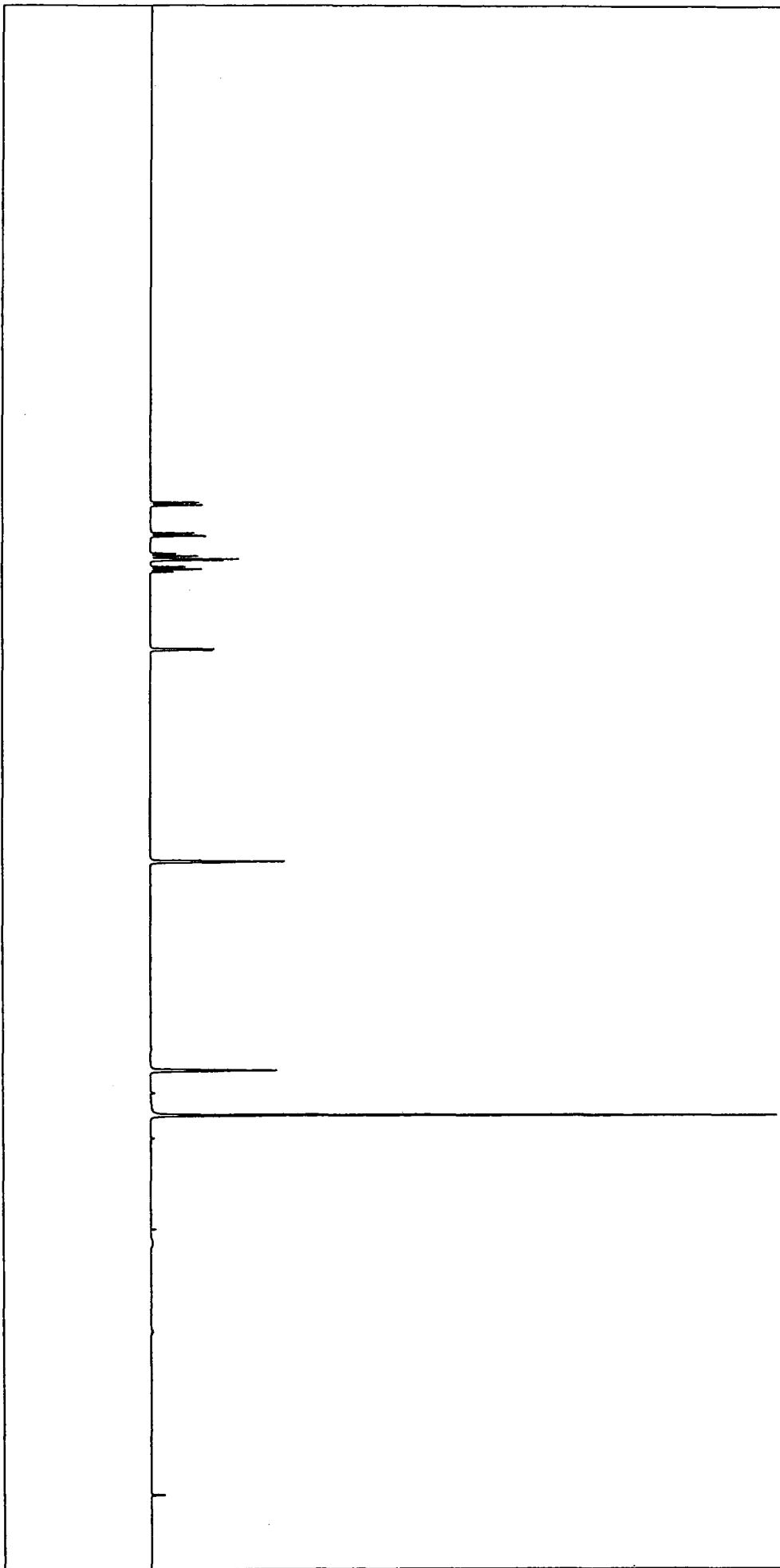


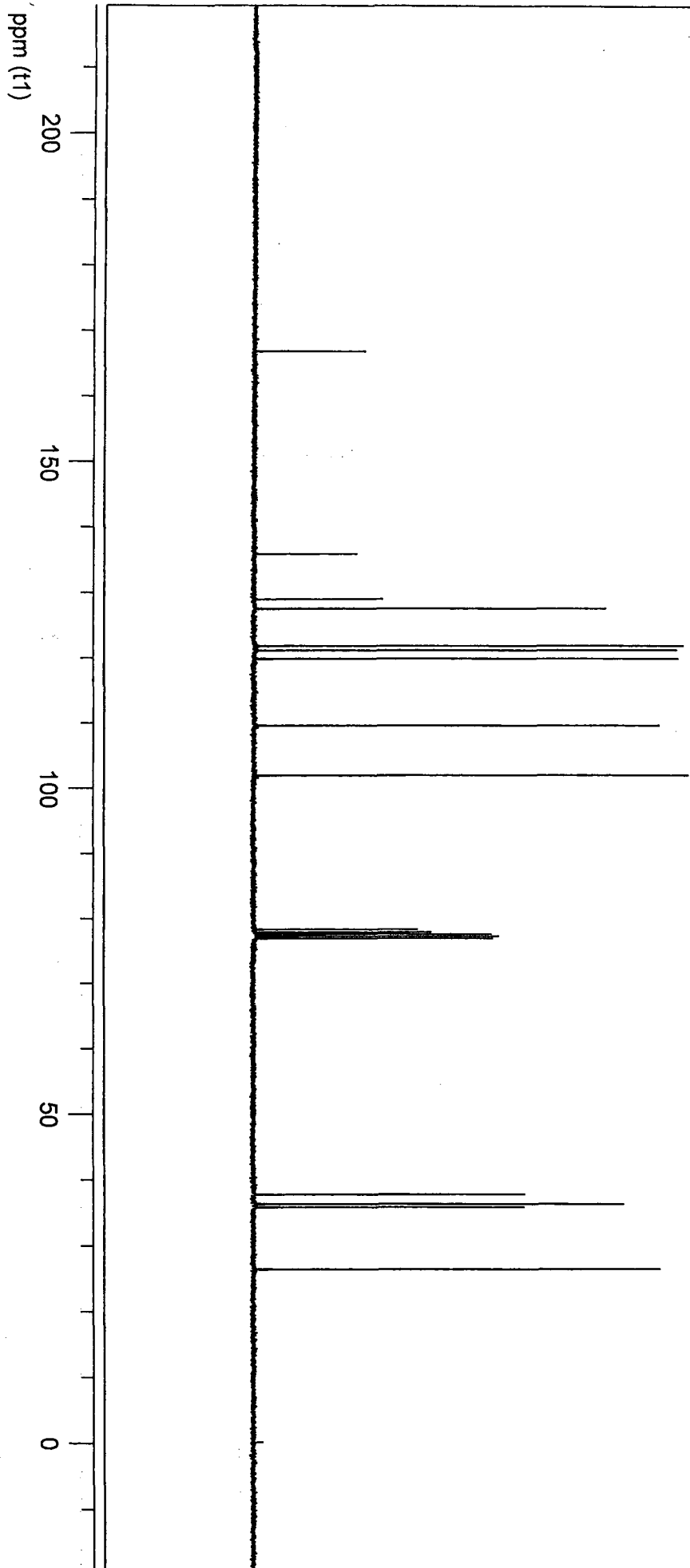
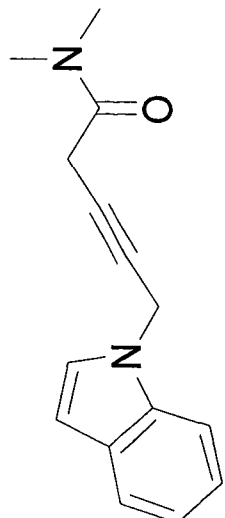
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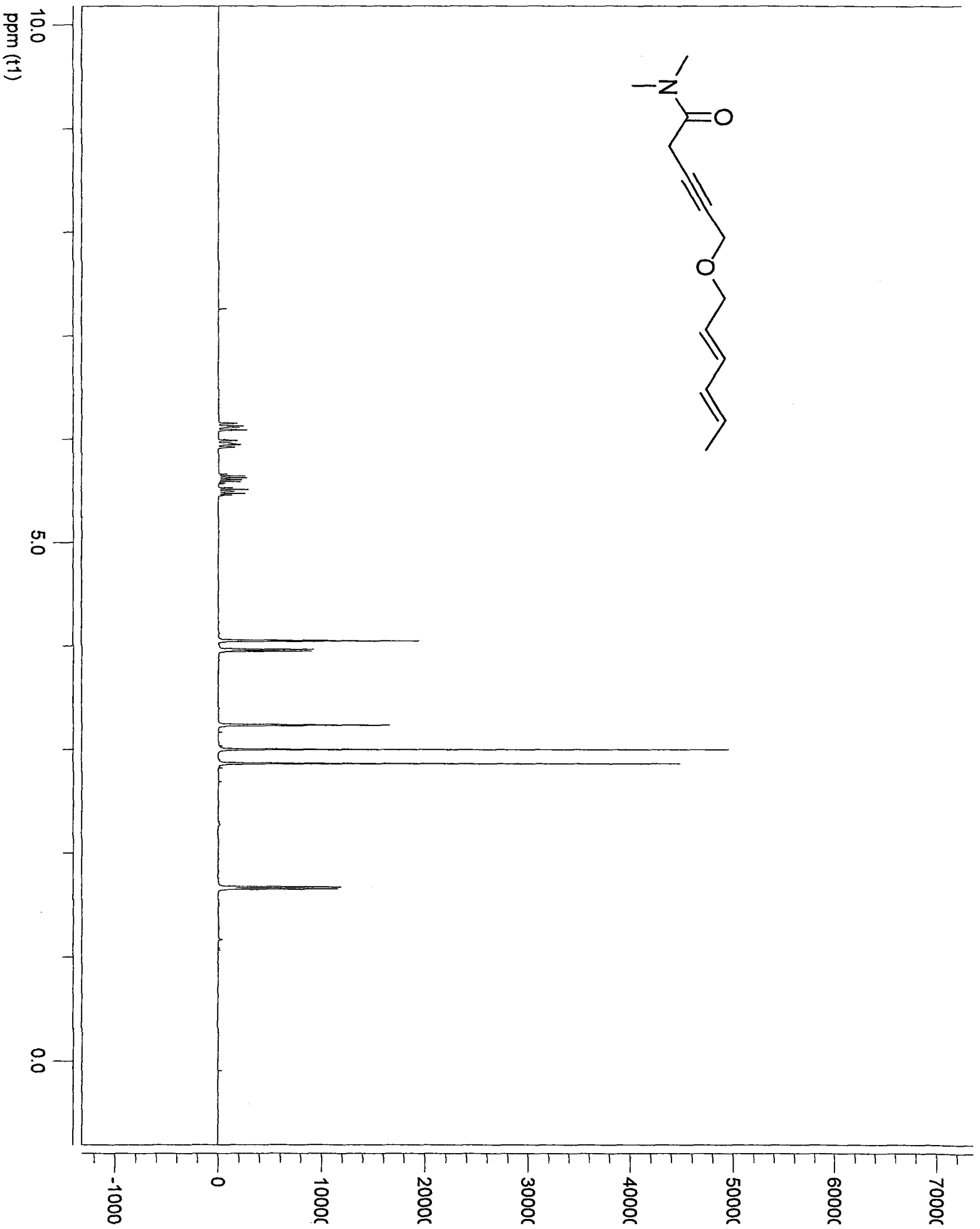
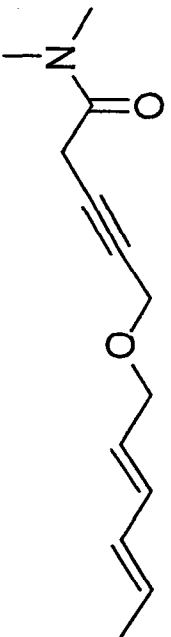
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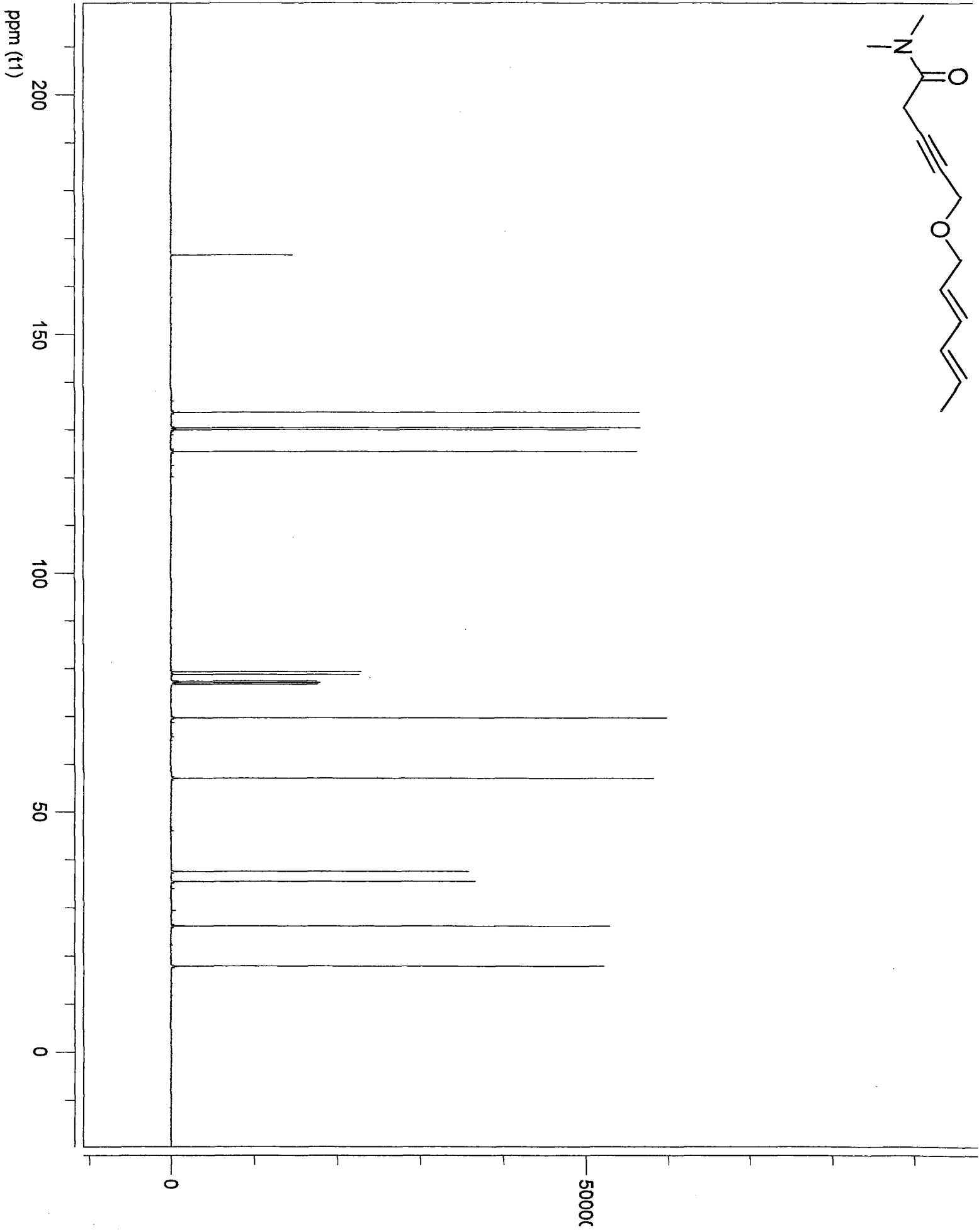
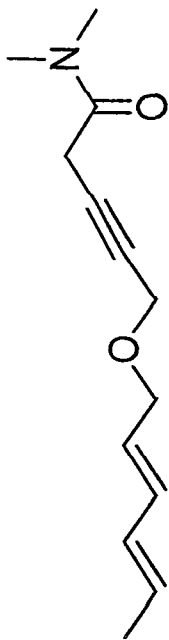
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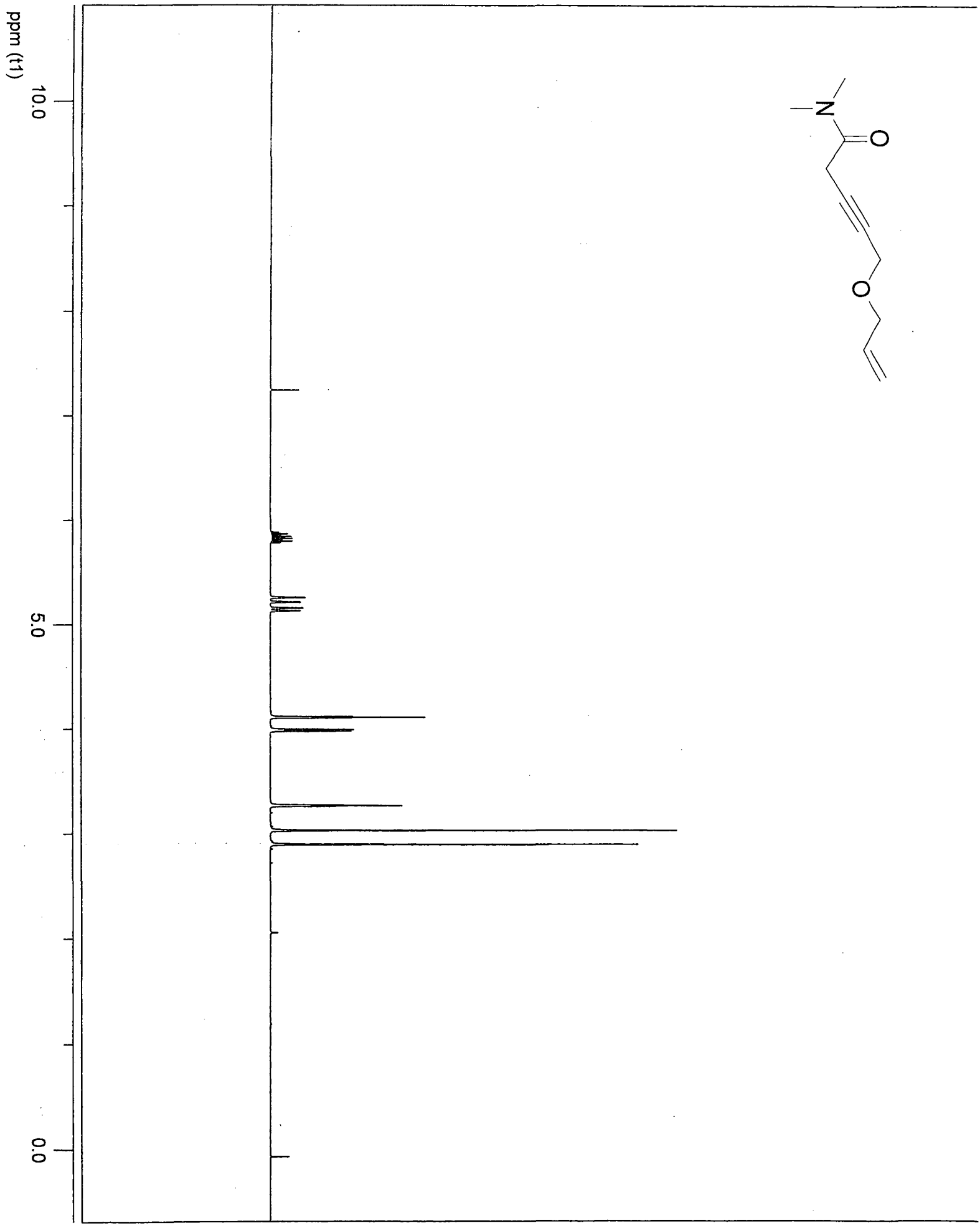
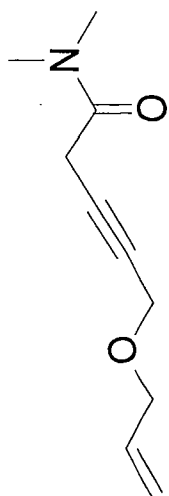
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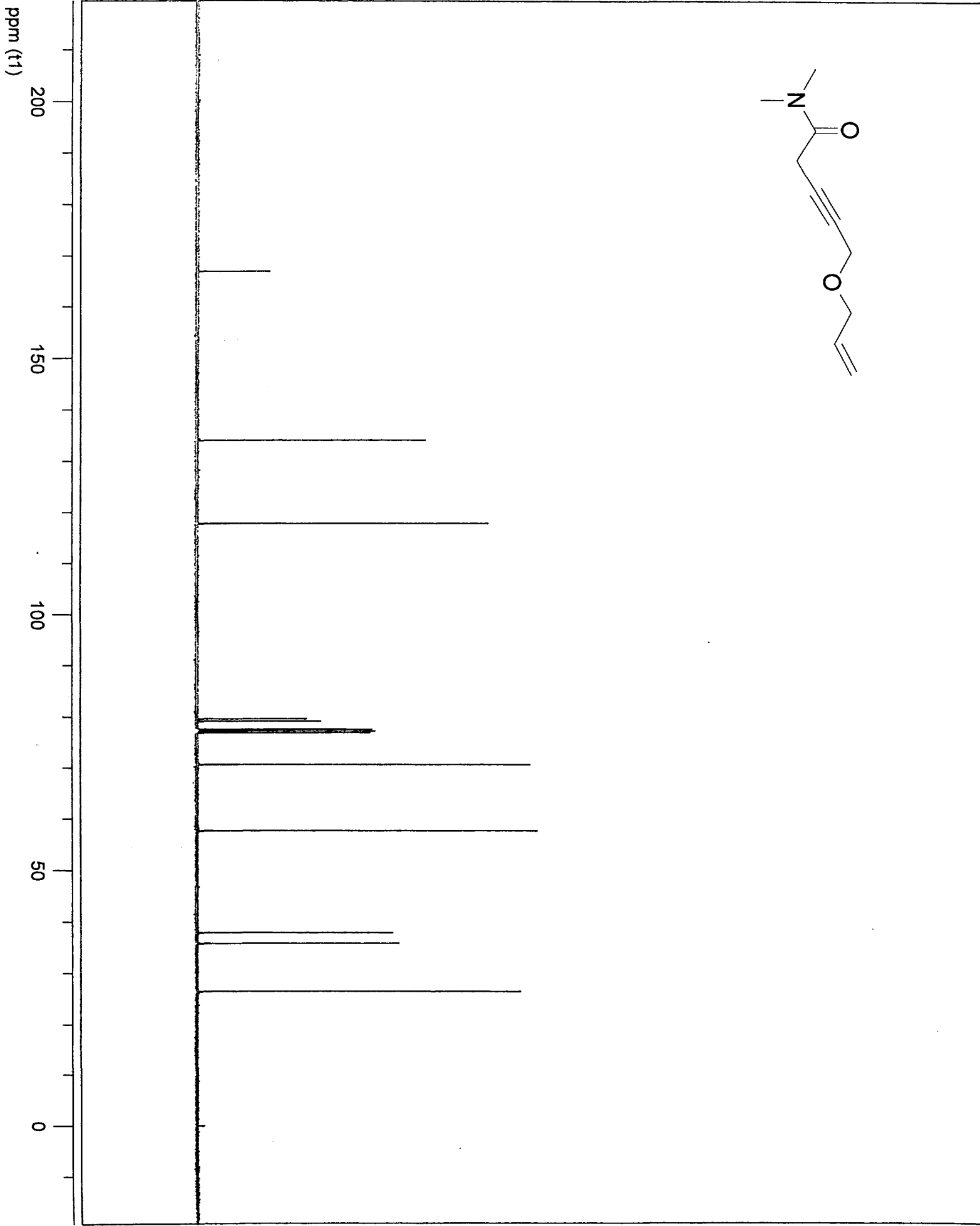
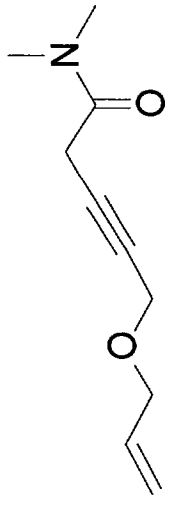


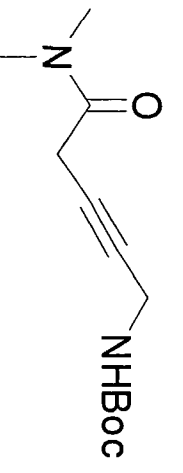












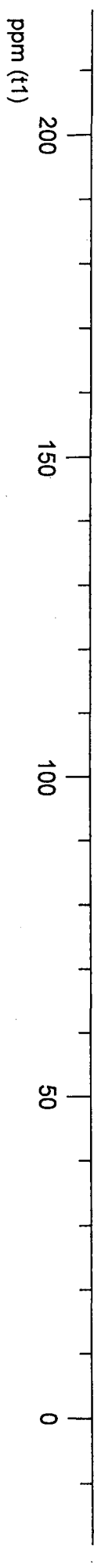
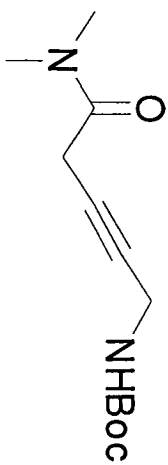
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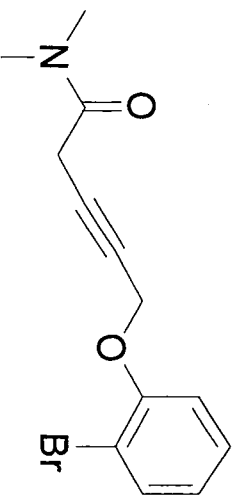
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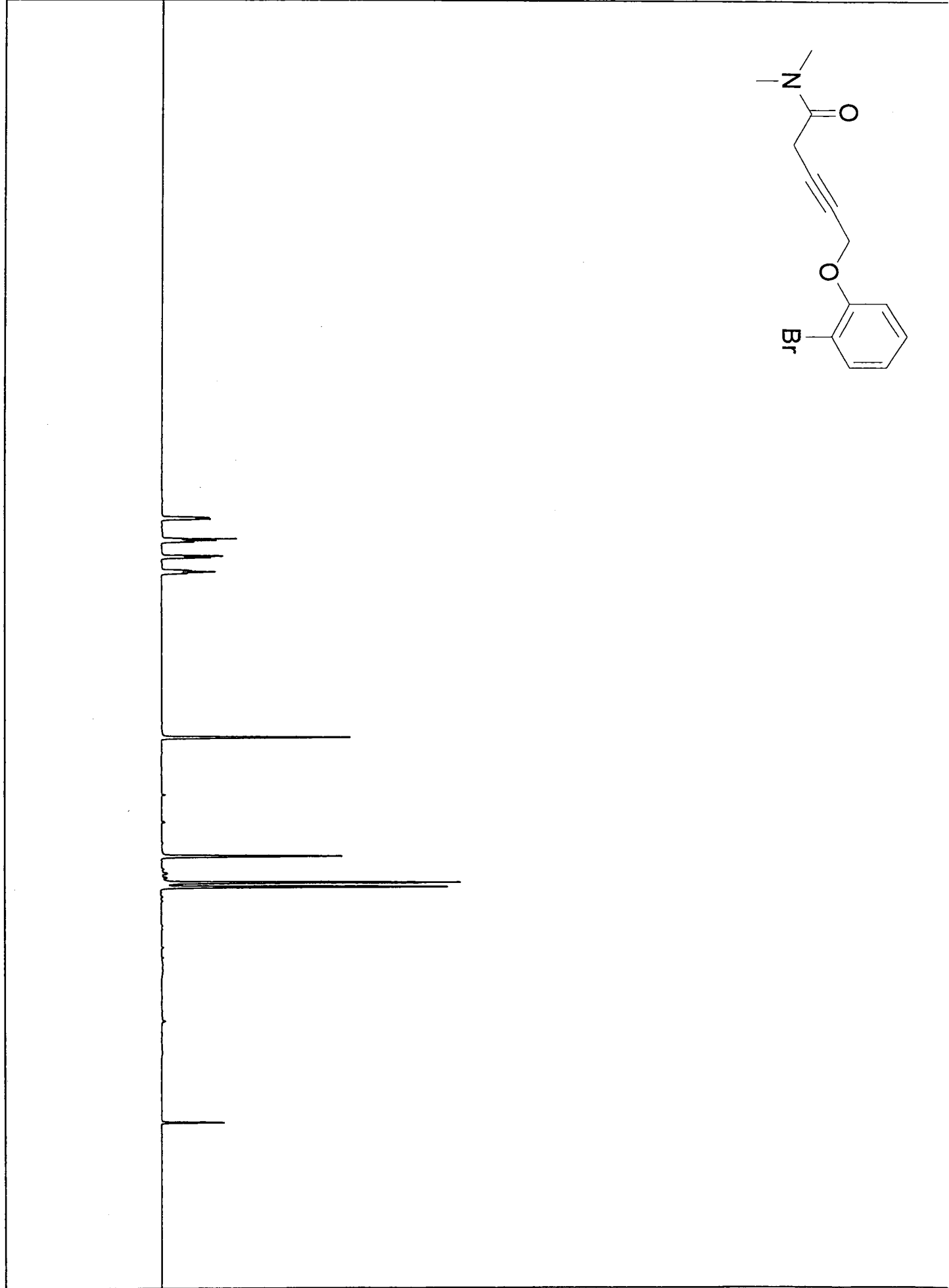


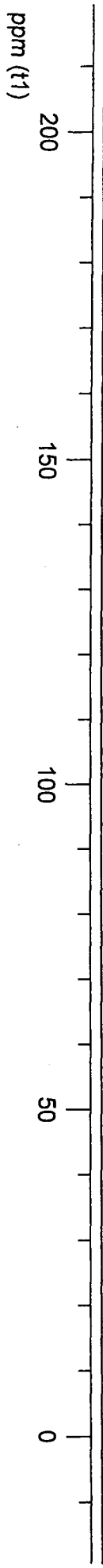
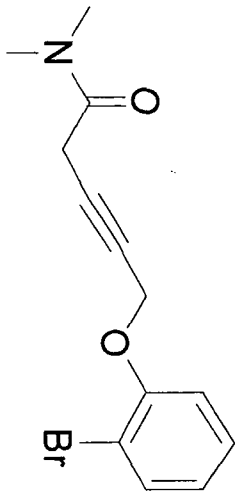
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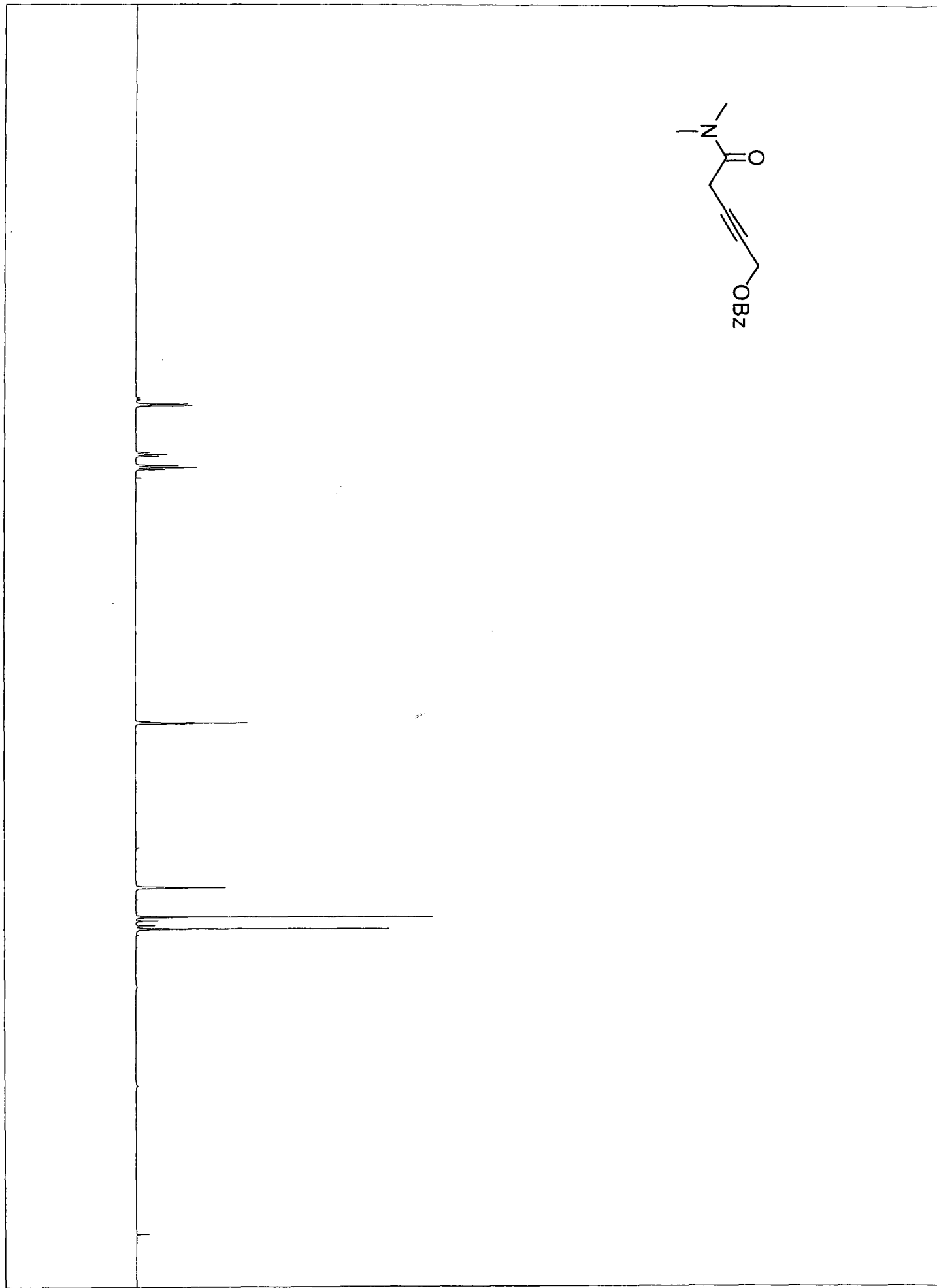


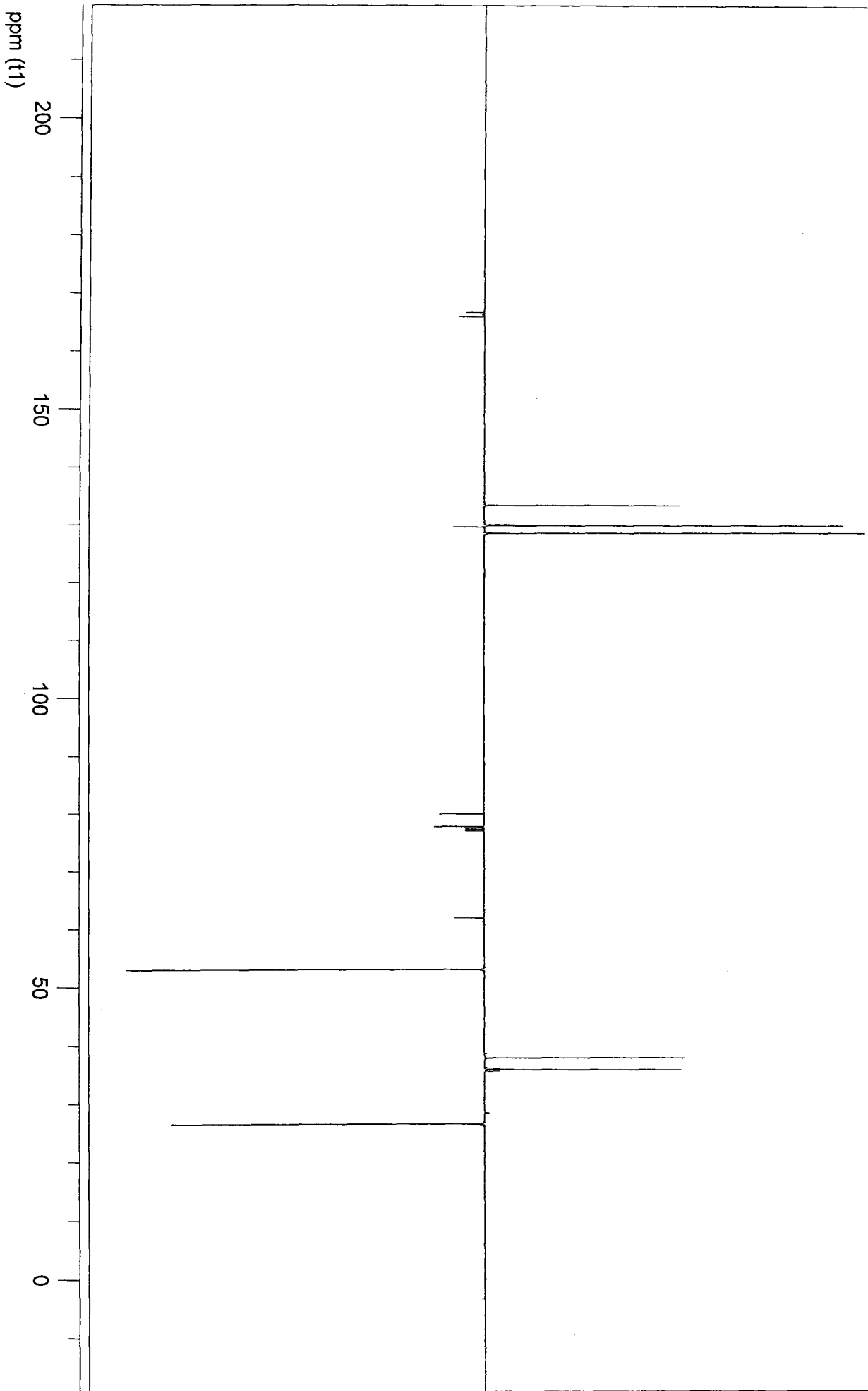
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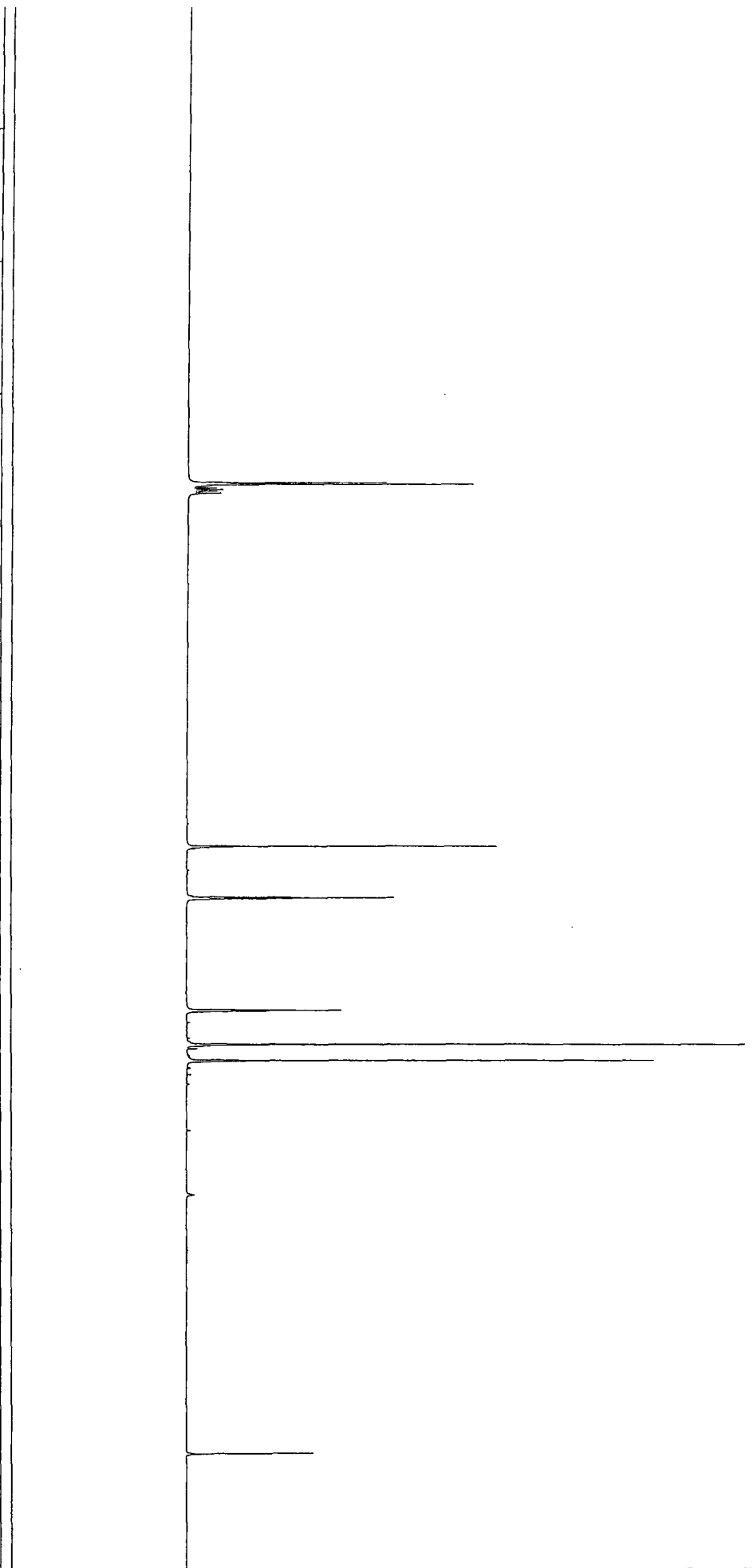




ppm (19,0

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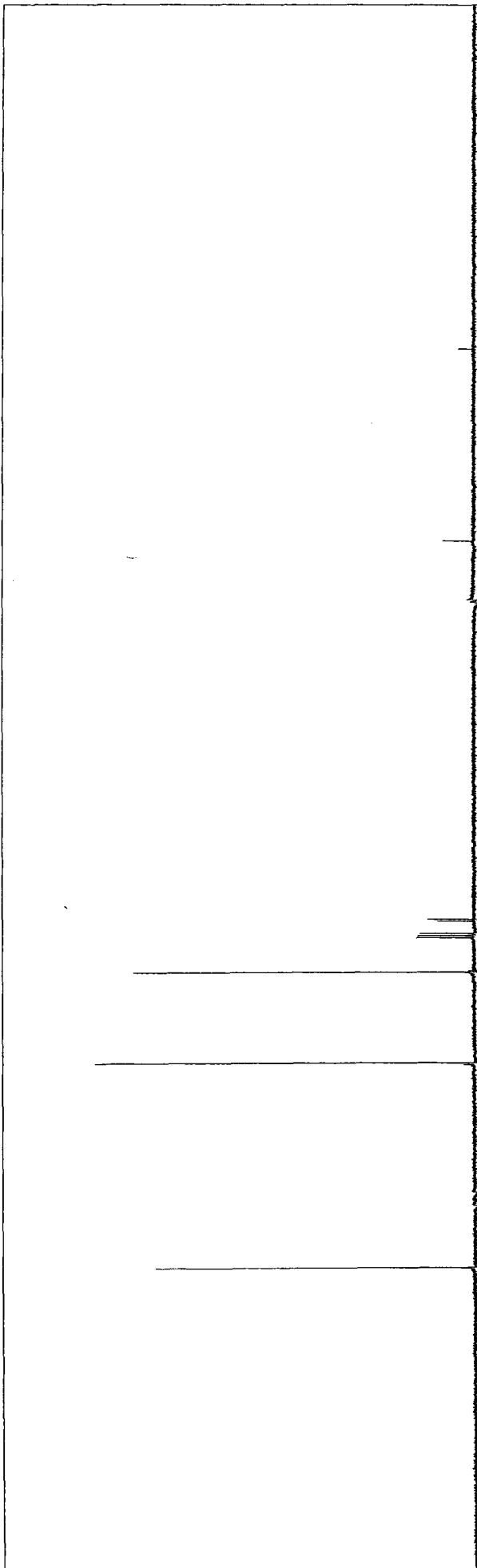
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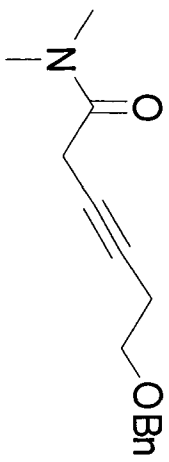
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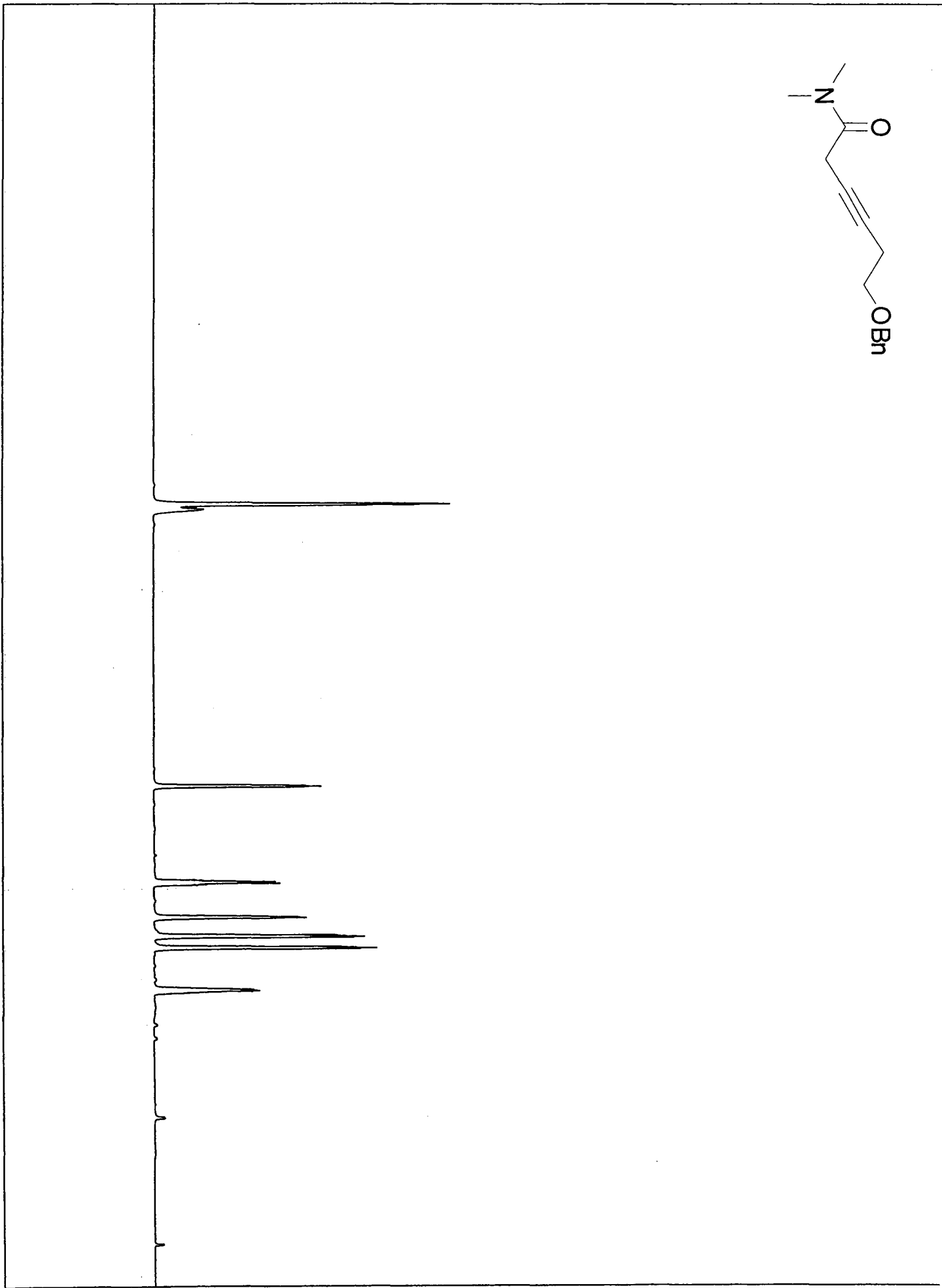


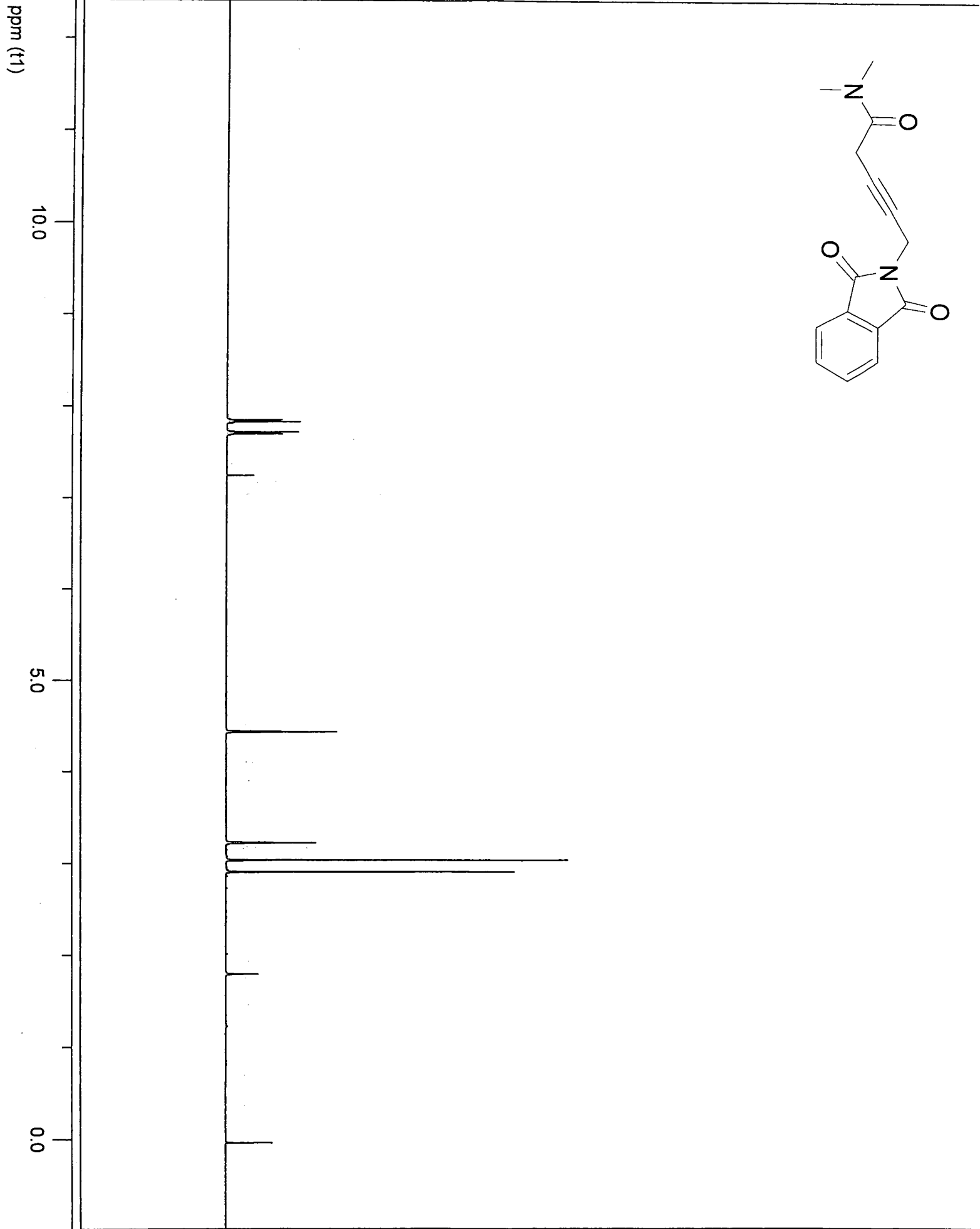
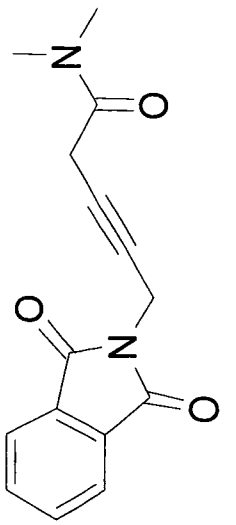
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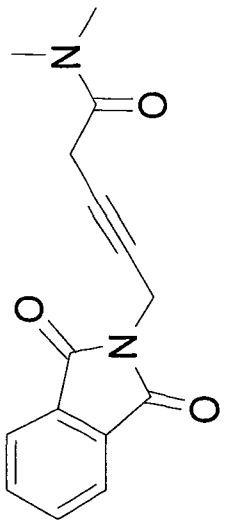
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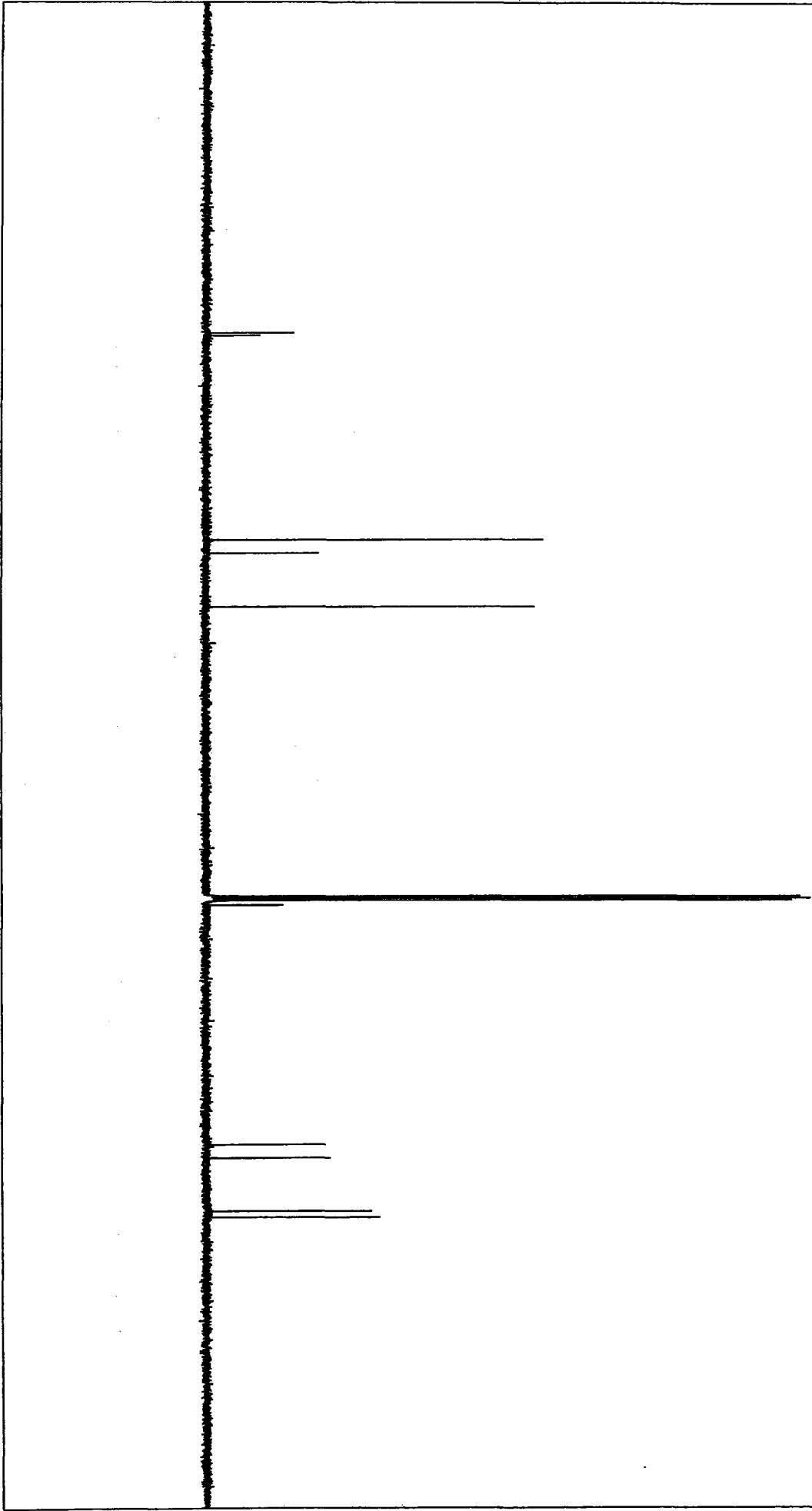
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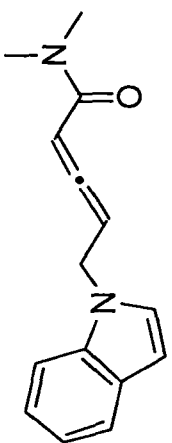
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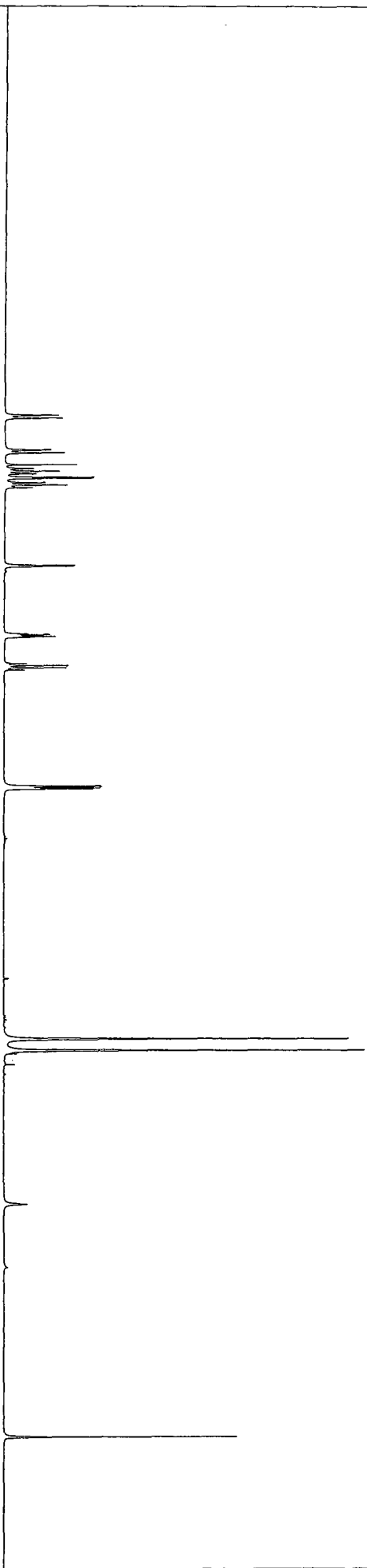
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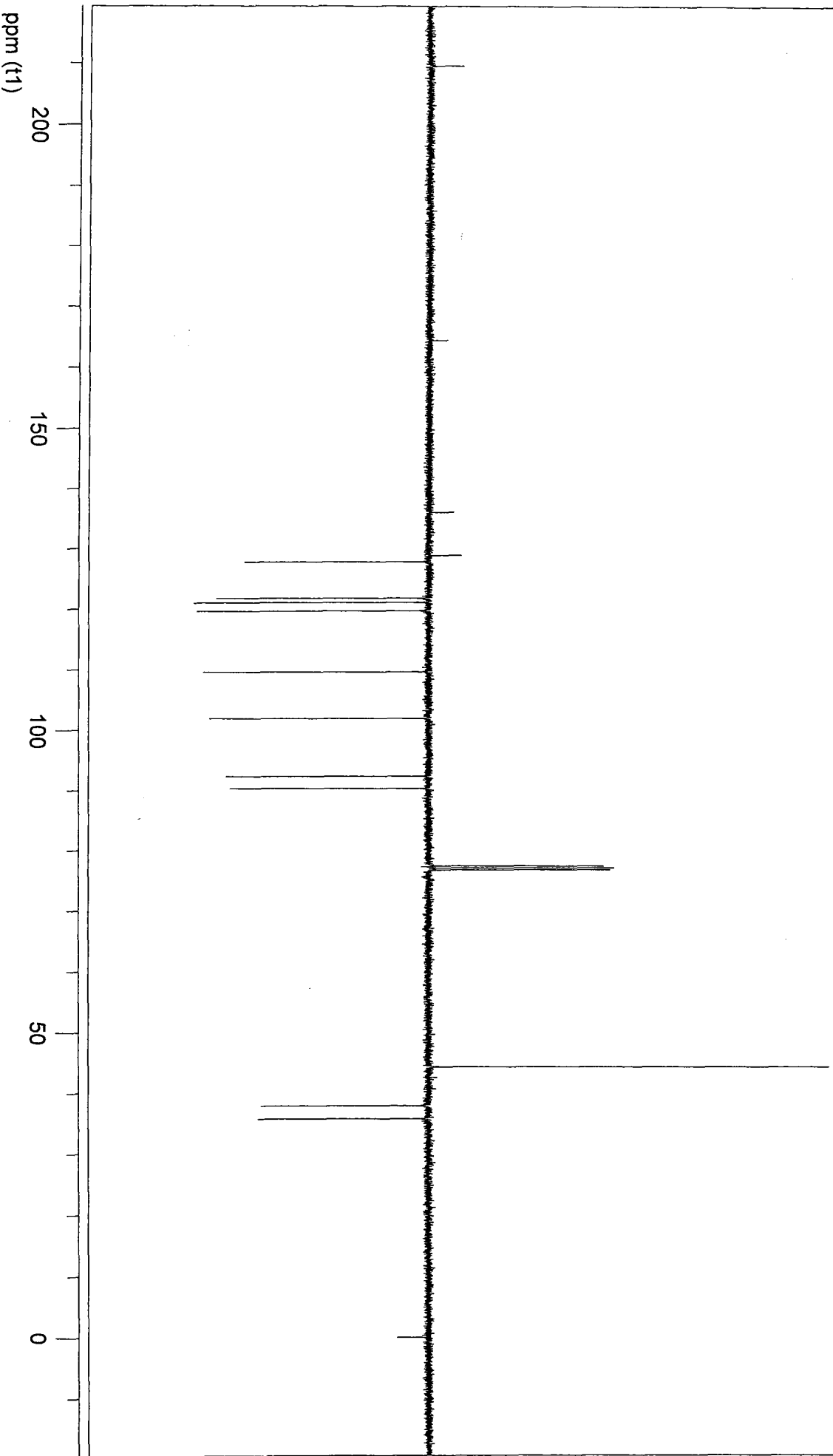
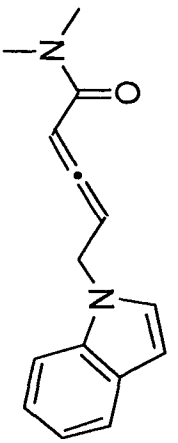
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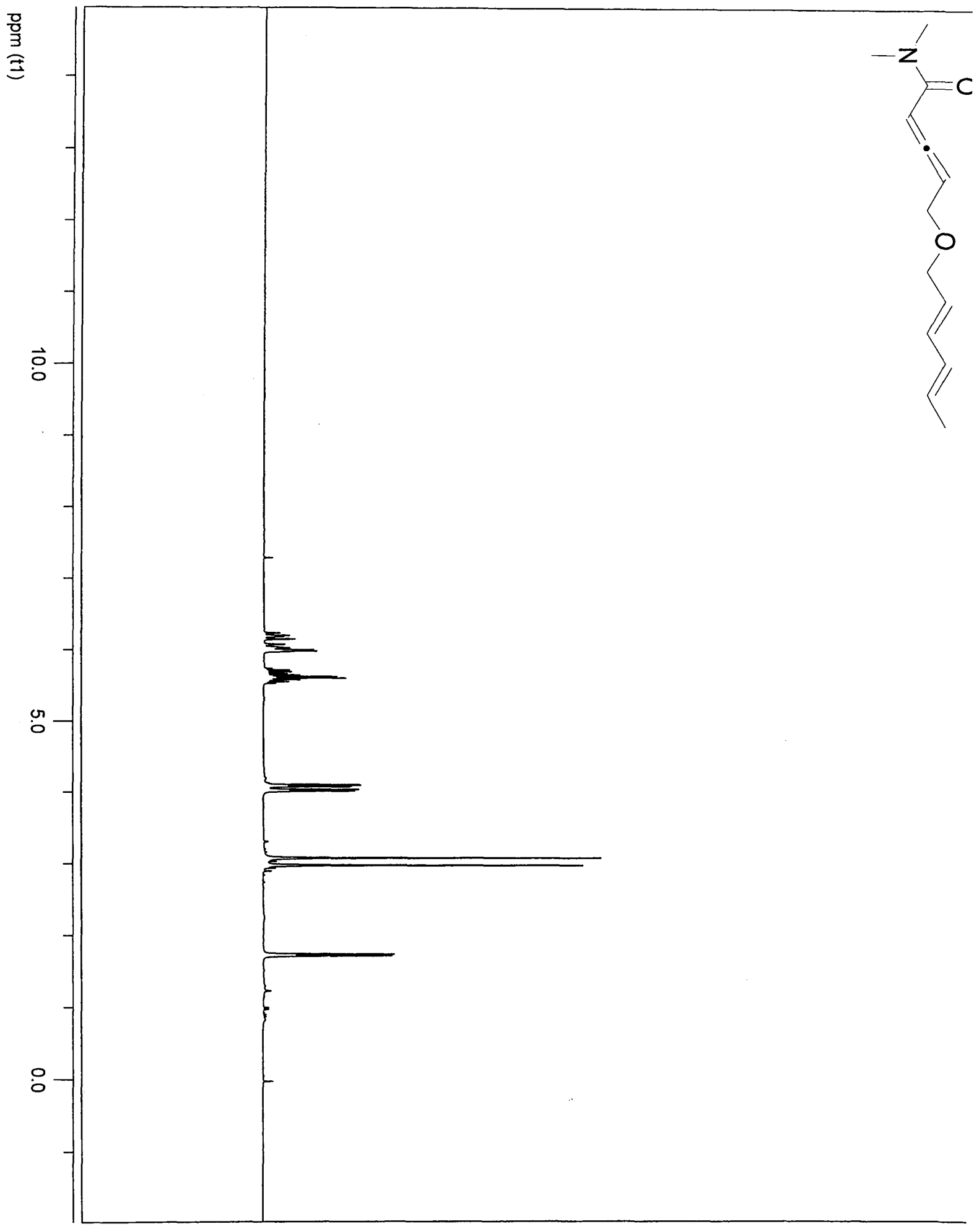
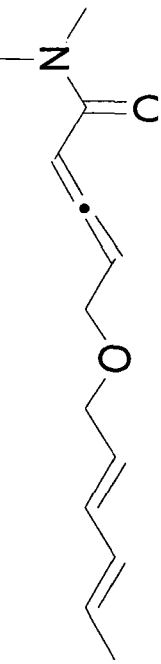


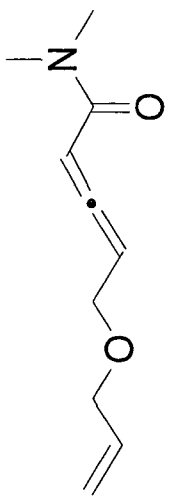


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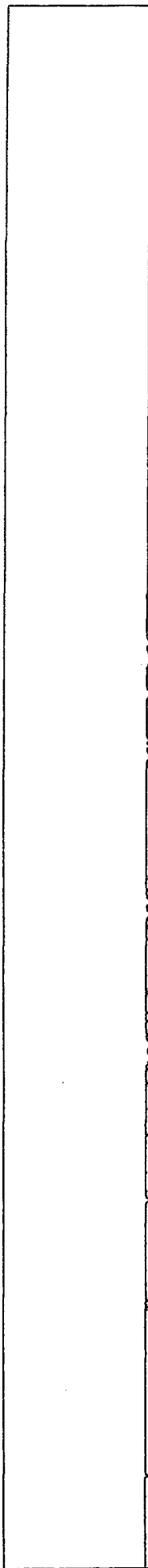


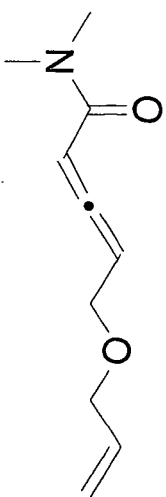






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ppm (t_1)

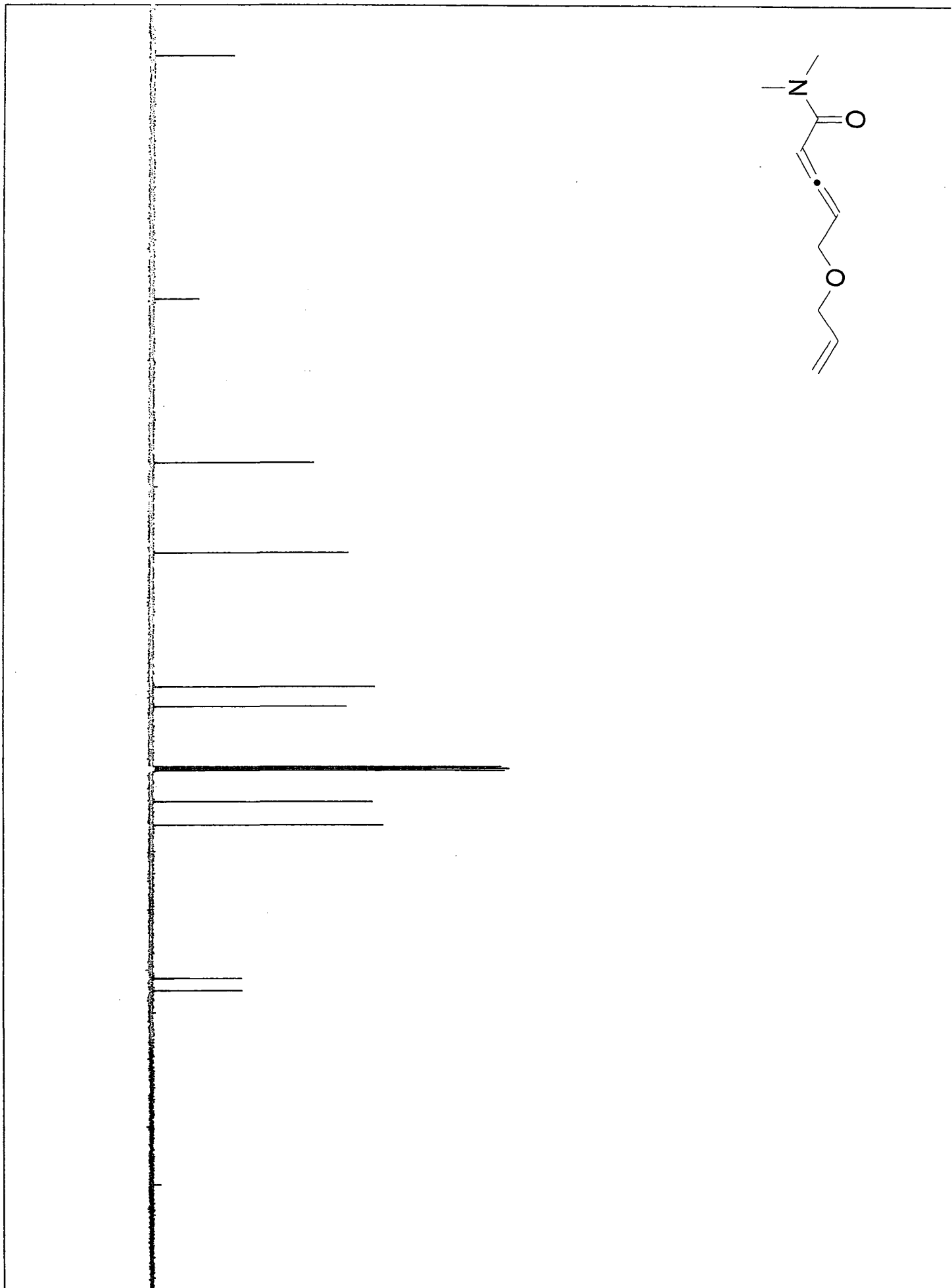
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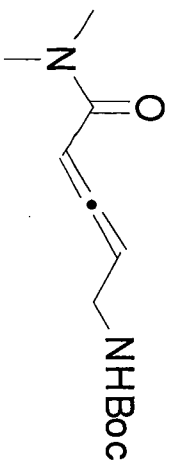
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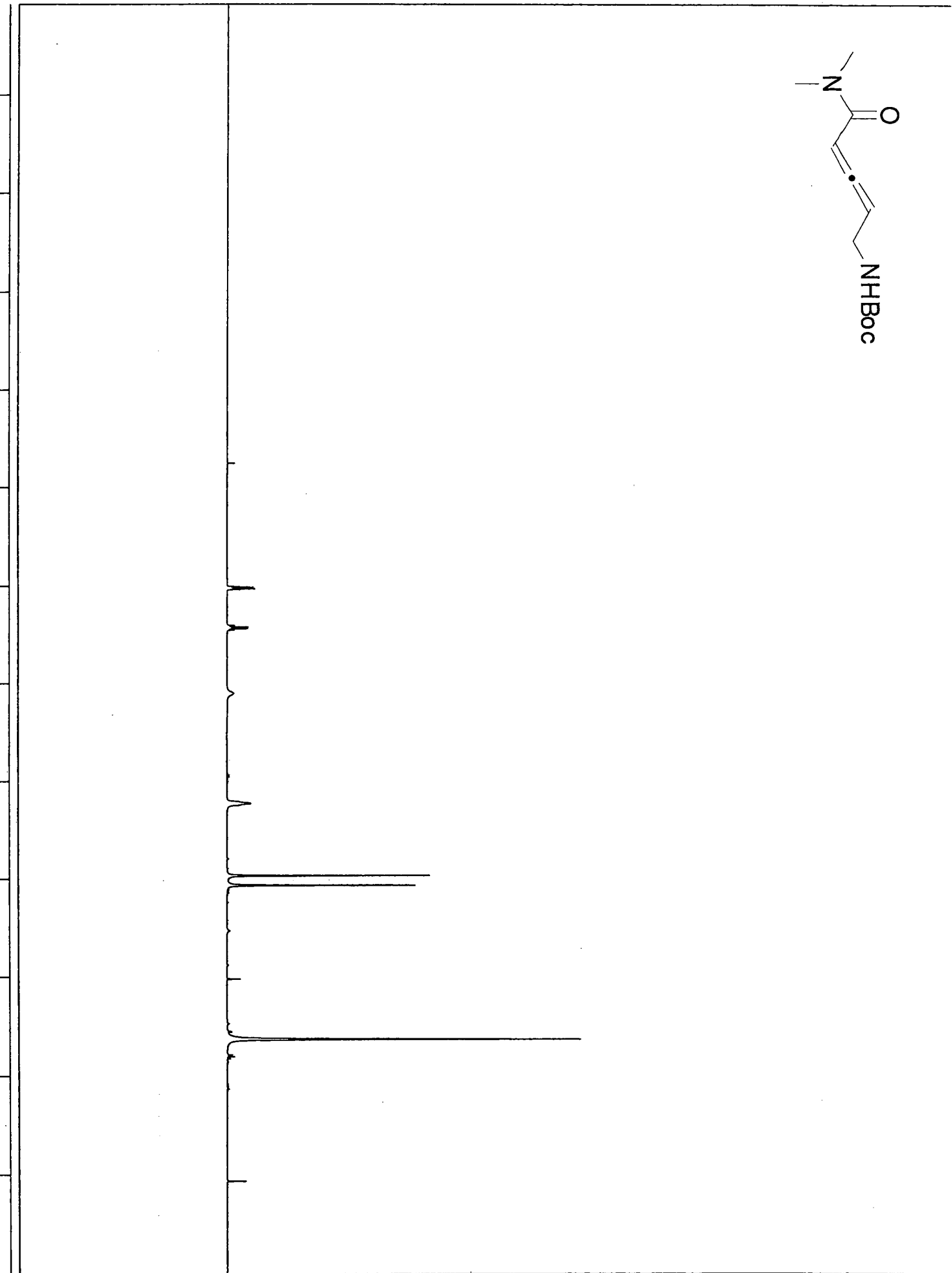


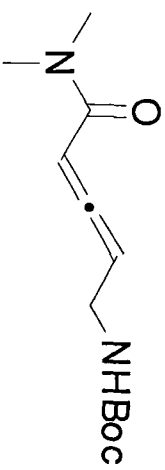
ppm (t1)

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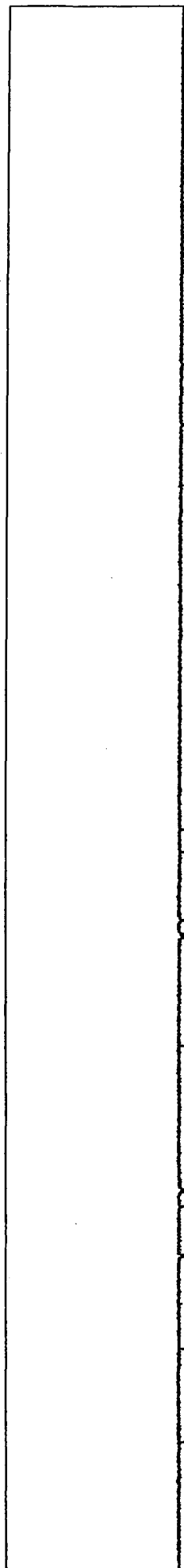
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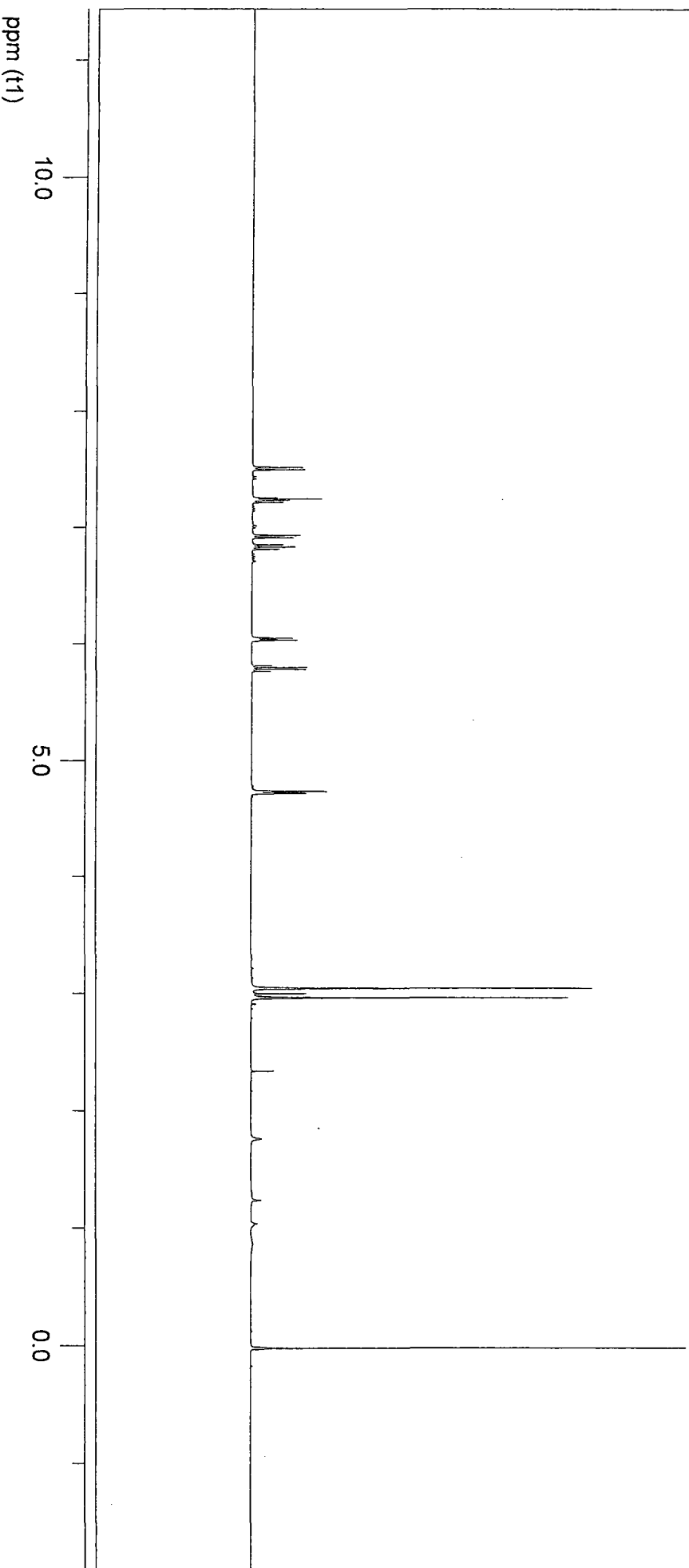
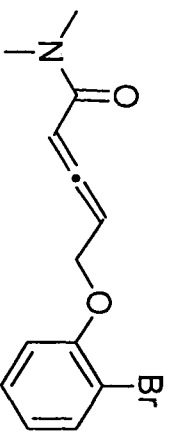
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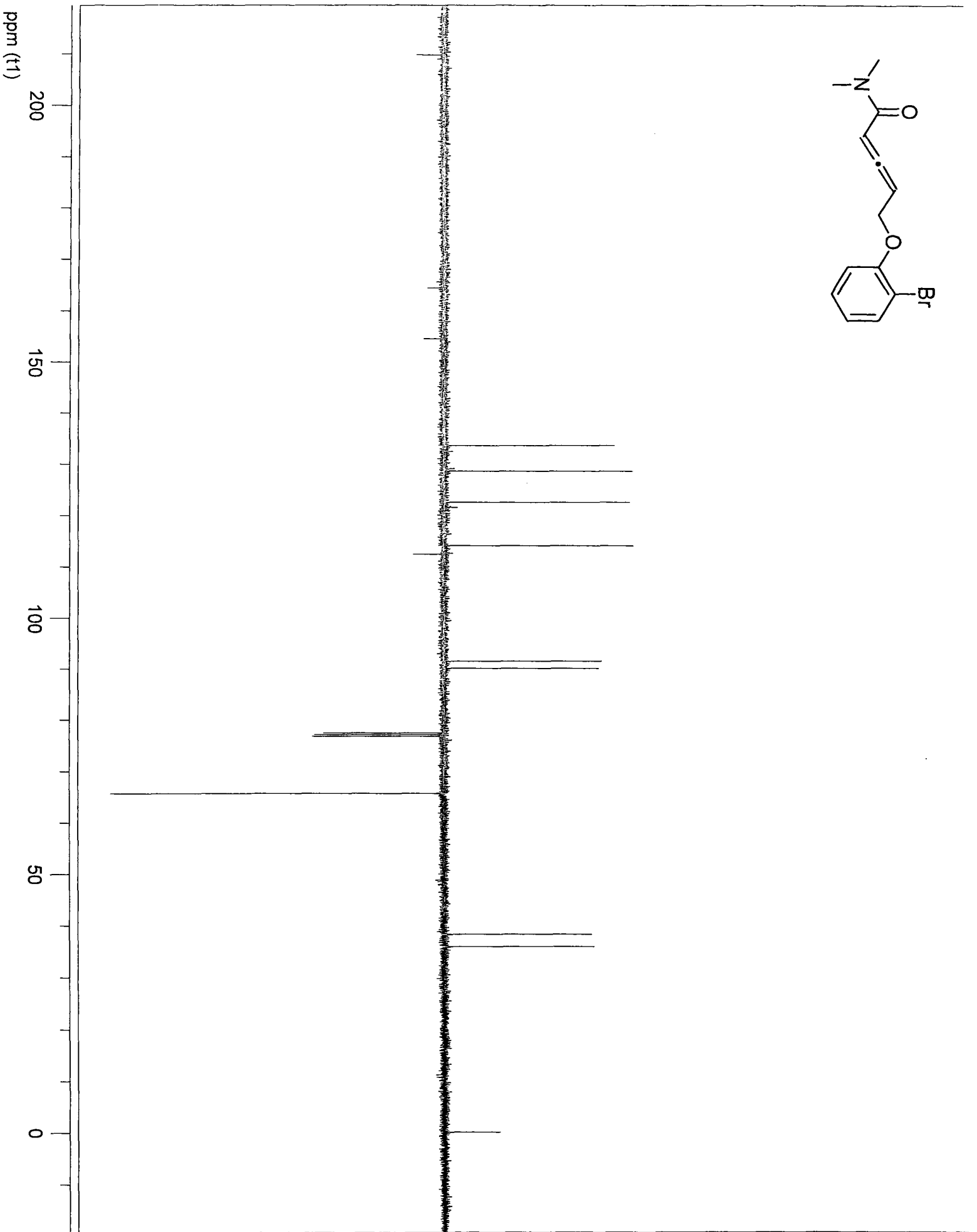
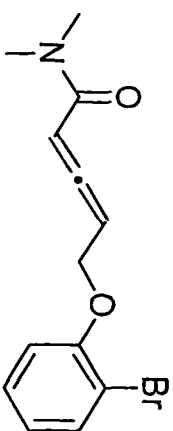
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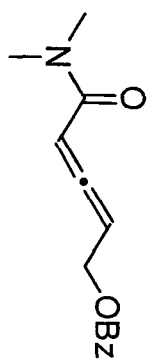
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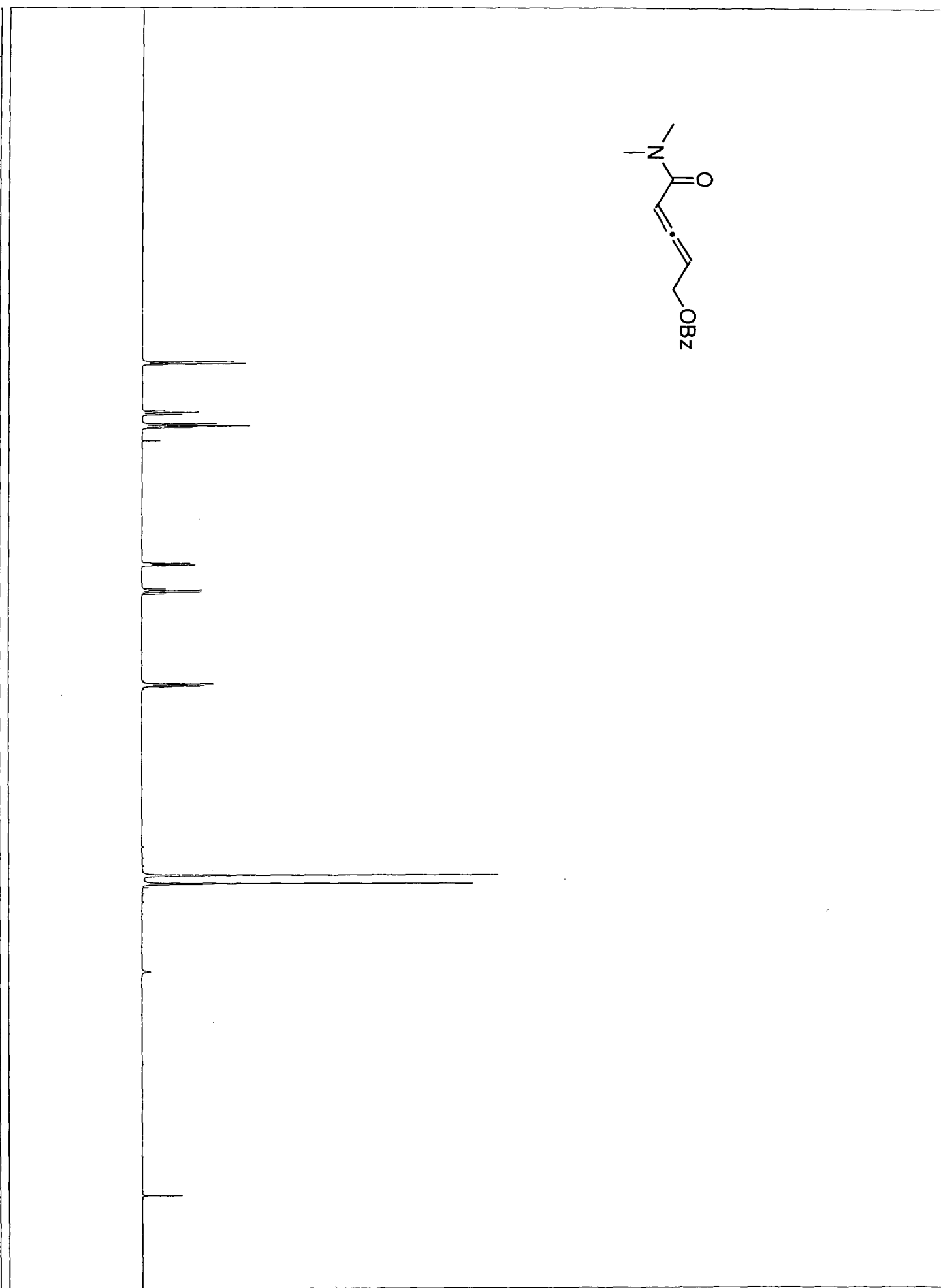


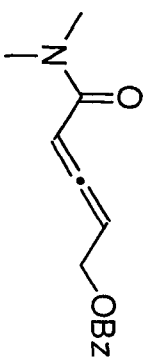
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5.0

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ppm (t_1)

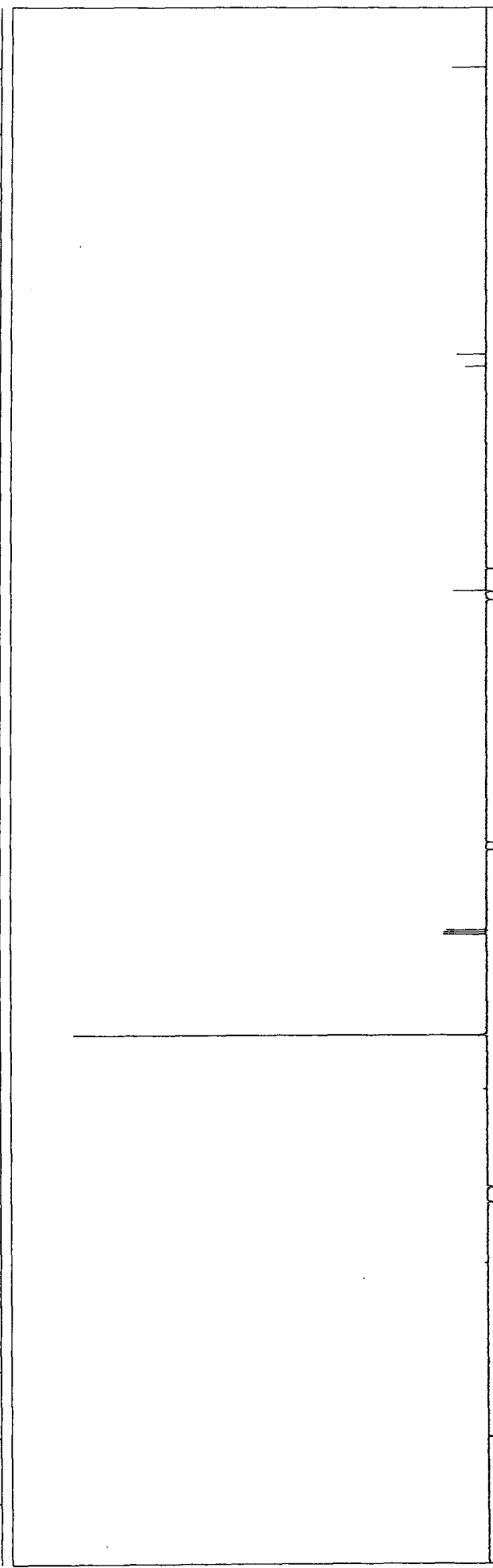
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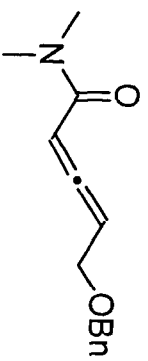
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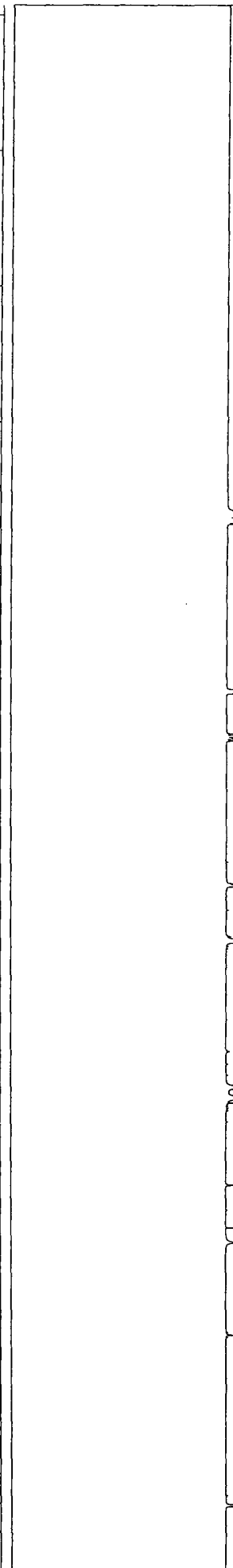


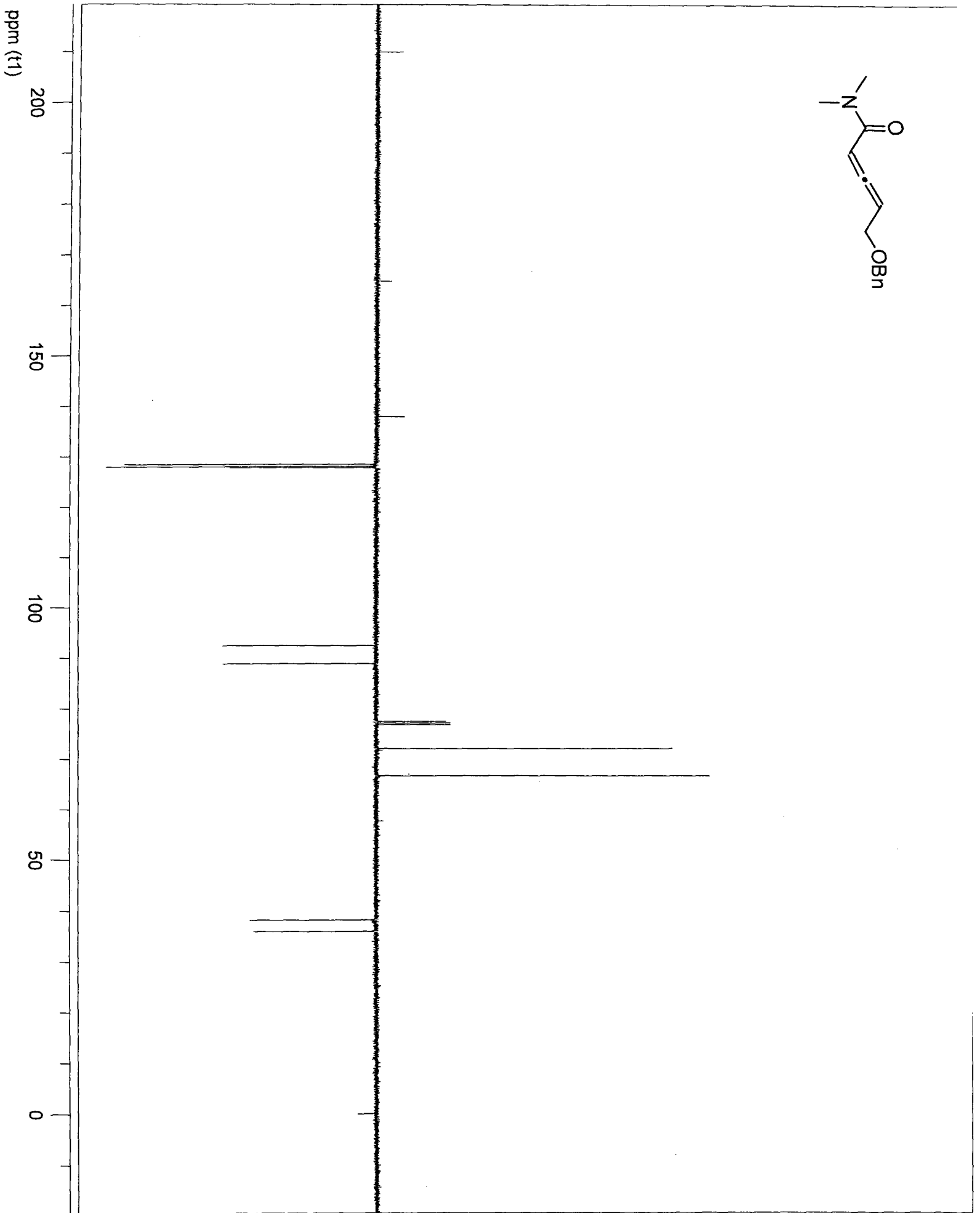
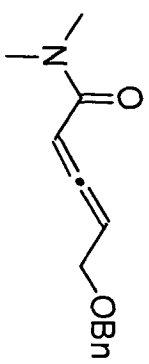
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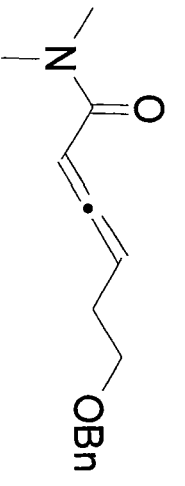
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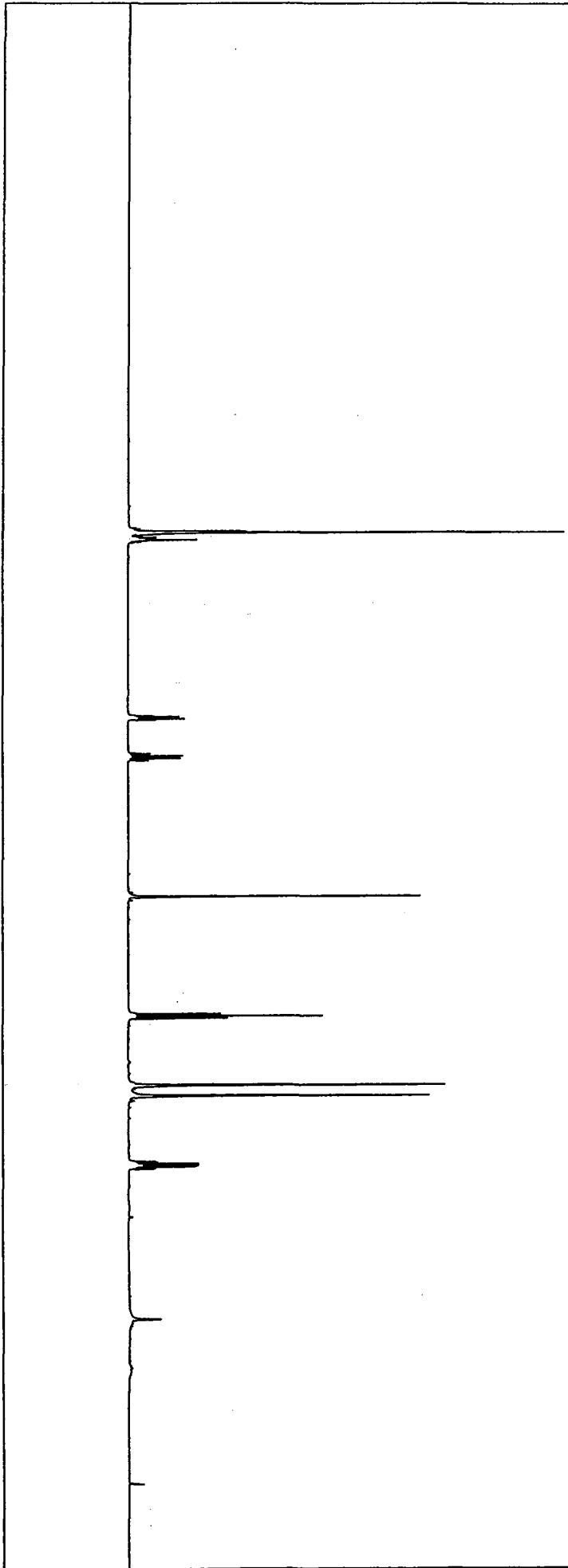
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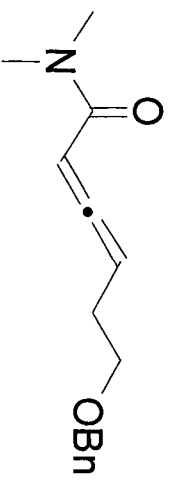






ppm (t1) 10.0 5.0 0.0





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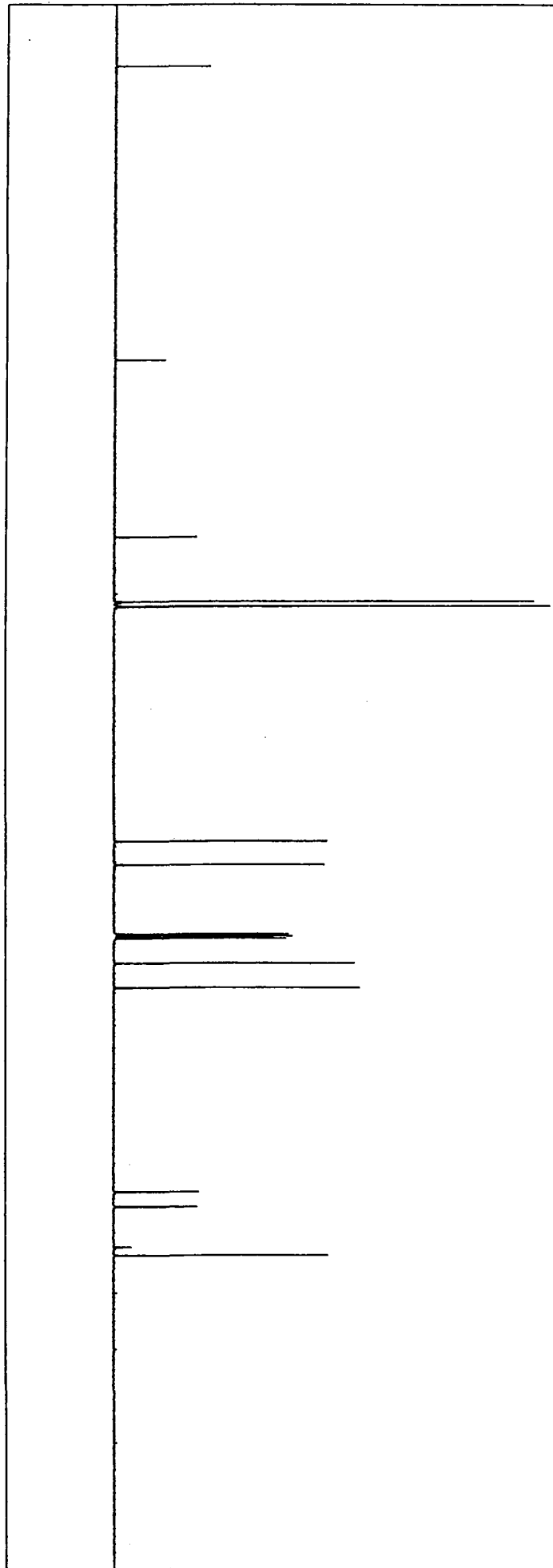
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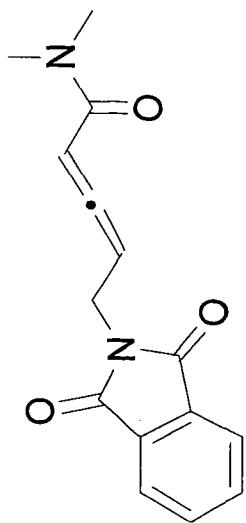
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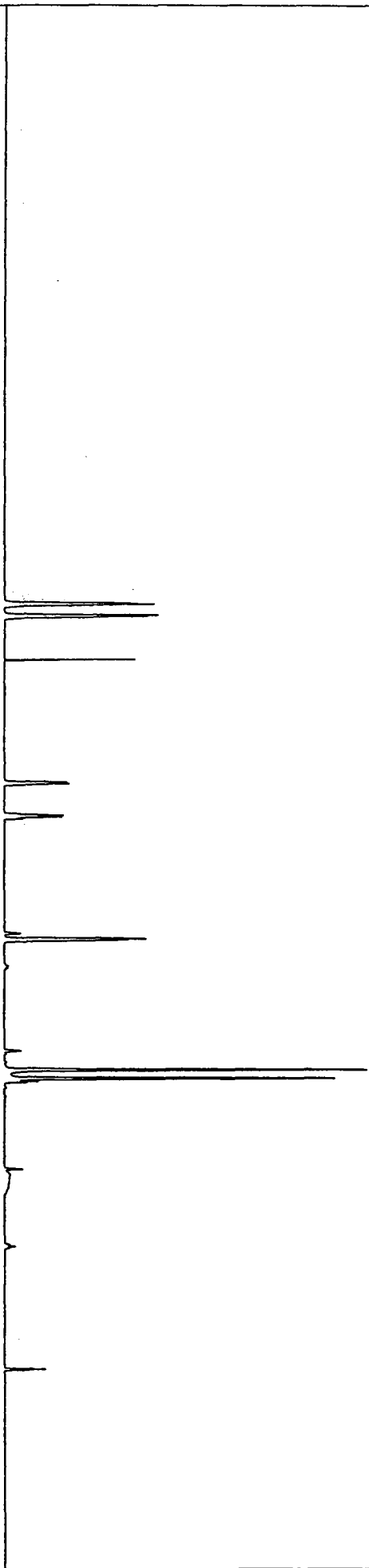


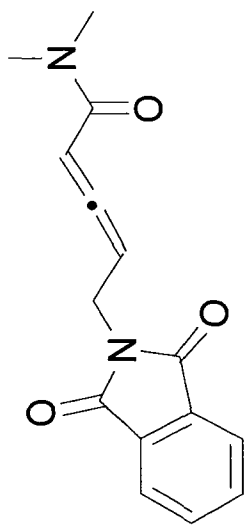
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5.0

0.0





ppm (t1)

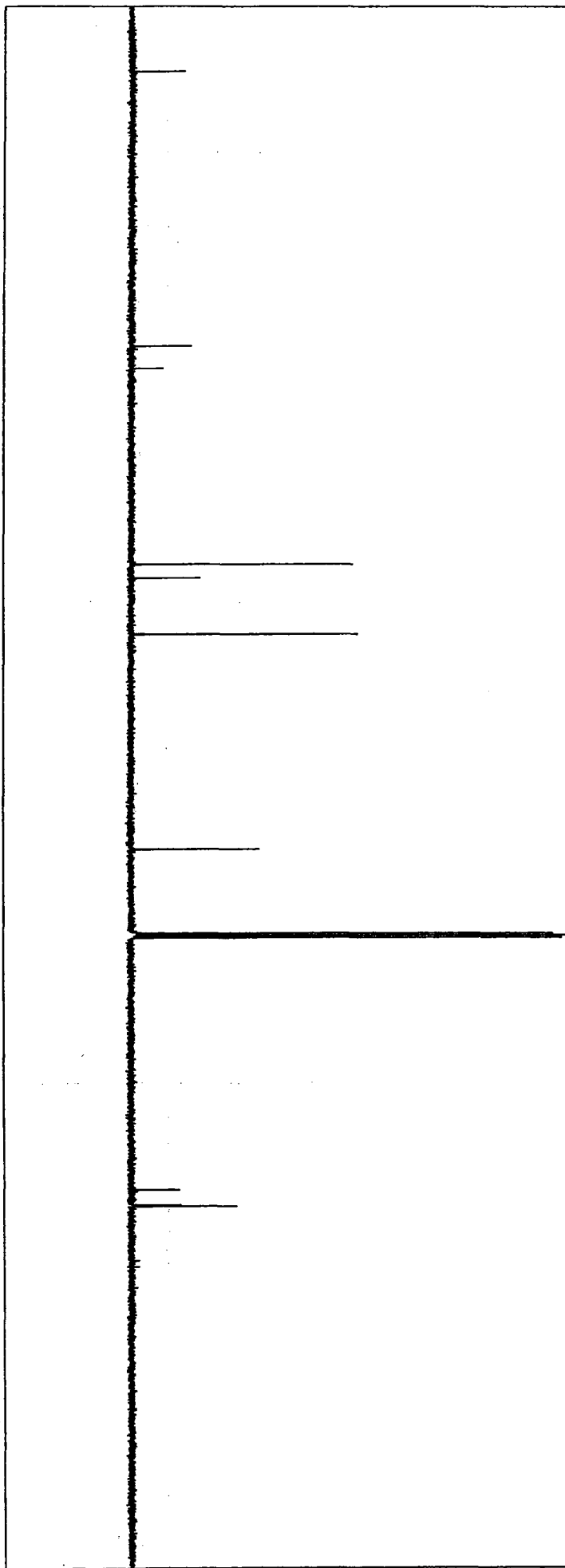
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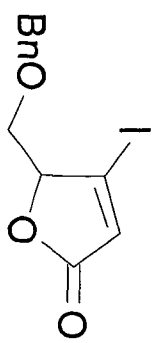
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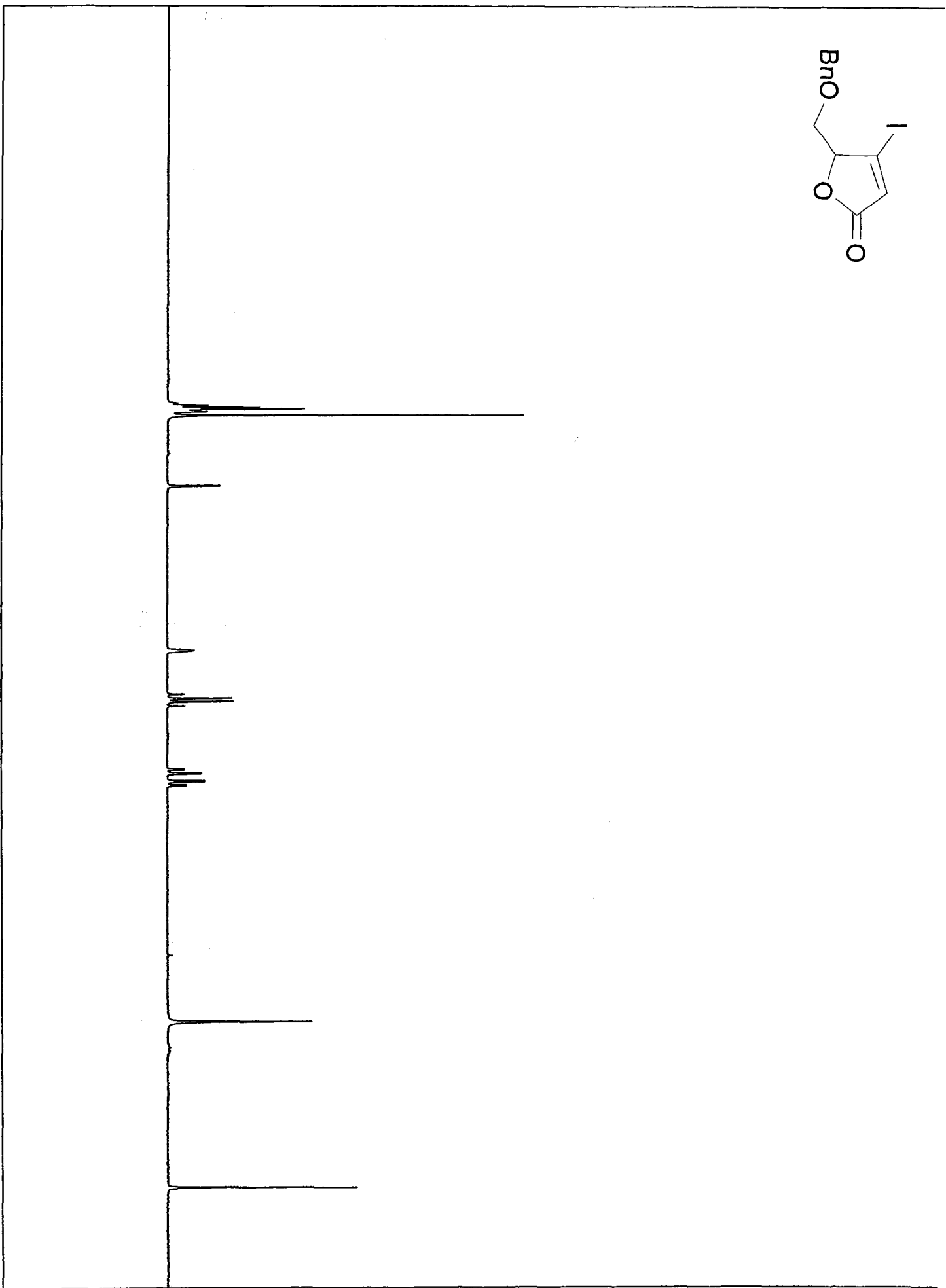


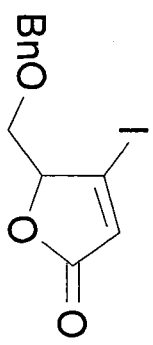
ppm (t1)

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5.0

0.0





ppm (t1)

200

150

100

50

0

