Development of new methods for catalytic enantioselective olefin metathesis

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DEVELOPMENT OF NEW METHODS FOR CATALYTIC ENANTIOSELECTIVE OLEFIN METATHESIS

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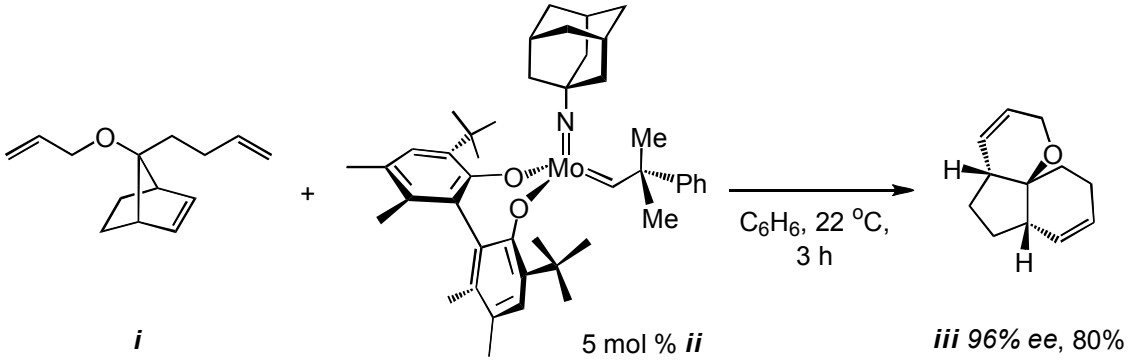
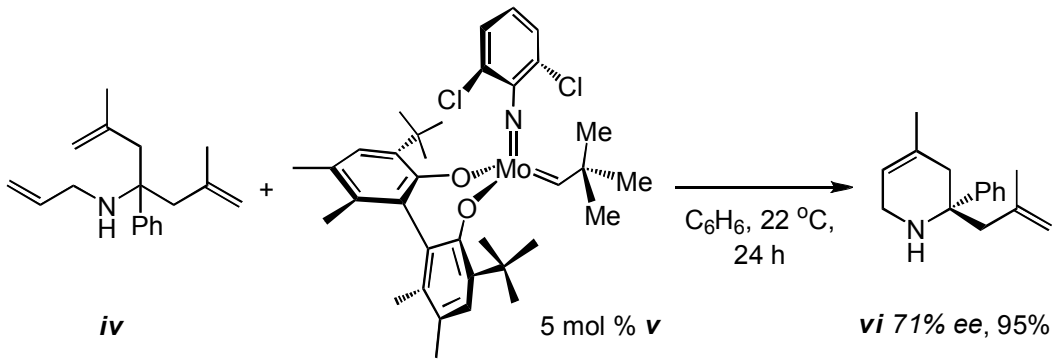
Abstract

♦ **Chapter One.** The synthesis of enantioenriched polycycles (in up to *>98% ee*) was accomplished through Mo-catalyzed asymmetric ring-opening/ring-closing metathesis (AROM/RCM) reactions of achiral norbornyl trienes. As a representative example, Mo complex ***ii*** catalyzes the formation of polycycle ***iii*** in *96% ee* and 80% yield from triene ***i*** (shown below). These investigations were the first to show that an adamantylimido Mo alkylidene complex (***ii***) is capable of efficiently and selectively catalyzing enantioselective olefin metathesis transformations. These studies also provided insight into plausible catalytic reaction pathways for this class of metathesis transformations.



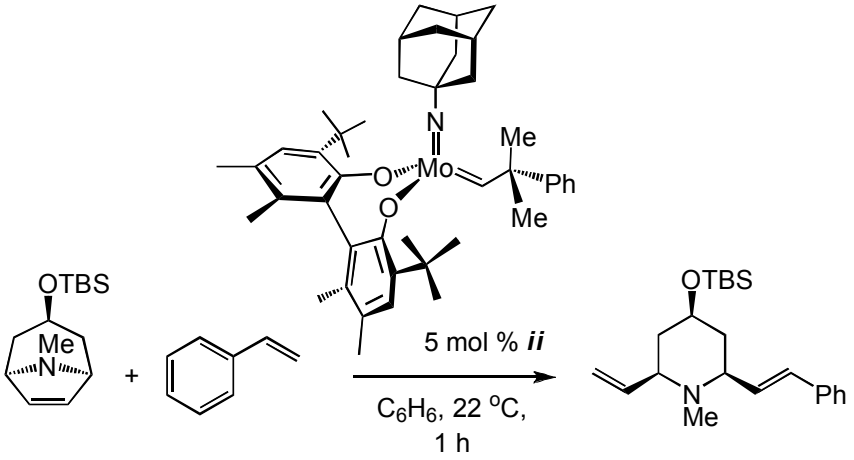
i 5 mol % ***ii*** ***iii*** *96% ee*, 80%

♦ **Chapter Two.** The preparation of chiral amines (up to *97% ee*) was realized through the Mo-catalyzed asymmetric ring-closing metathesis (ARCM) reactions of achiral polyene precursors. These studies resulted in the development of methods to provide chiral cyclic amine products that contain readily removable protecting groups on nitrogen. Although generally considered sensitive to heteroatom functional groups, the Mo complexes in these studies were found to be tolerant of certain unprotected amine substrates (shown below). Mo complex ***v*** catalyzes the desymmetrization of secondary amine ***iv*** to provide cyclic amine ***vi*** in *71% ee* and 95% yield.



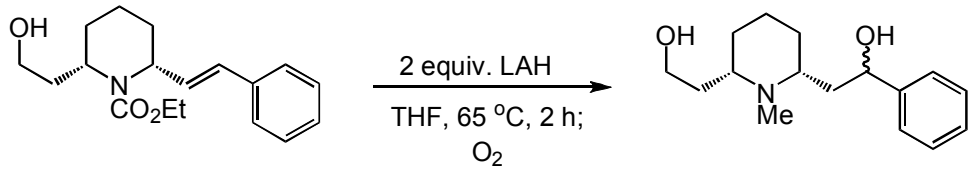
iv 5 mol % ***v*** ***vi*** *71% ee*, 95%

♦ **Chapter Three.** Efforts resulting in the enantioselective synthesis of piperidines (up to *>98% ee*) through the Mo-catalyzed asymmetric ring-opening/cross-metathesis (AROM/CM) reactions of various *meso* azabicyclic substrates are discussed in this chapter. As an illustrative example, Mo complex ***ii*** catalyzes the desymmetrization of azabicycle ***vii*** with styrene to provide *N*-Me piperidine ***viii*** in *94% ee* and 95% yield after 1 h. Enantioenriched carbamate-protected piperidines can also be prepared by this method, and moreover, these studies showed that a variety of aryl-olefin cross-partners can be employed for the desymmetrization reactions of azabicycles.



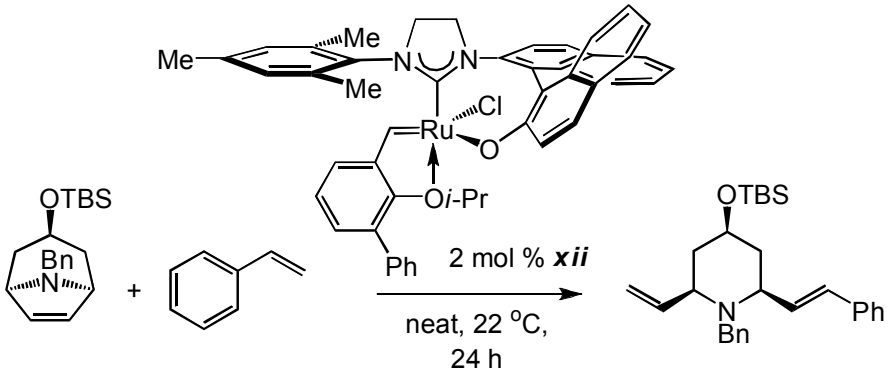
vii 10 equiv. ***viii*** *94% ee*, 95%

♦ **Chapter Four.** In this chapter we provide details of our investigations into the functionalization of piperidine products formed through asymmetric ring-opening/cross-metathesis (AROM/CM) reactions. Experiments were initially directed toward the synthesis of two biologically active piperidine alkaloids. These studies resulted in the discovery of a unique directed hydroalumination of styrenyl olefins. As shown below, this process was used to install oxygen functionality at a benzylic position by converting carbamate-protected piperidine ***ix*** to *N*-Me piperidine ***x*** in 45% yield. Additionally, studies were conducted to shed light into the mechanism of this novel transformation.



ix ***x*** 45%

♦ **Chapter Five.** In this chapter we describe studies undertaken to compare the ability of chiral Ru and Mo complexes to catalyze the formation of enantioenriched pyrans and piperidines. A representative example of the reactions studied is shown below. Ru complex ***xii*** catalyzed the AROM/CM reaction of *N*-Bn azabicycle ***xi*** with styrene to afford *N*-Bn piperidine ***xiii***. In this example, Ru complex ***xii*** was found to be the optimal catalyst for the synthesis of ***xiii***; a screen of available chiral Mo complexes resulted in the formation of ***xiii*** with <20% ee. In contrast, Mo complexes proved to be the optimal catalyst in the formation of *N*-Me piperidines (see above, synthesis of ***viii***); Ru complexes provided ***viii*** in *30% ee* and 20% yield. These investigations encompass the first direct comparison of chiral Ru and Mo complexes for asymmetric olefin metathesis.



xi 20 equiv. ***xiii*** *>98% ee*, 80%
<20% ee with Mo complexes

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CHAPTER 4: FUNCTIONALIZATION OF PIPERIDINE PRODUCTS

CHAPTER 5: COMPARISON OF MOLYBDENUM AND RUTHENIUM COMPLEXES FOR CATALYTIC ASYMMETRIC RING-OPENING CROSS-METATHESIS REACTIONS

Chapter One

MOLYBDENUM-CATALYZED ENANTIOSELECTIVE SYNTHESIS OF POLYCYCLES THROUGH ASYMMETRIC RING-OPENING/RING-CLOSING METATHESIS REACTIONS

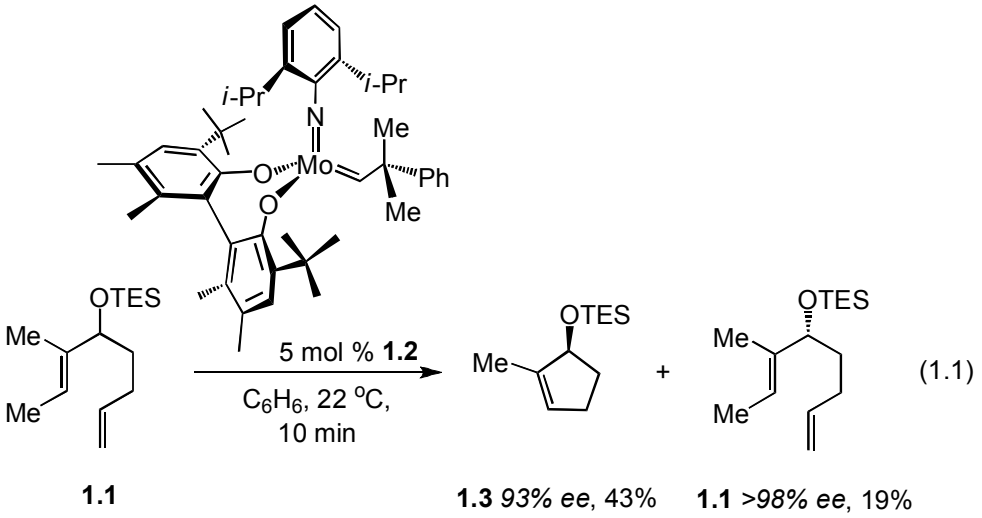
1.1 Introduction

My research endeavors during my doctoral candidacy were largely focused on the development of new methods involving catalytic enantioselective olefin metathesis. When I began my graduate career efforts were focused on the application of chiral Mo-based complexes to enantioselective olefin metathesis. The advent of chiral Ru-based catalysts for olefin metathesis, which occurred as I was starting my graduate work, allowed me the opportunity to (in the latter part of my graduate career) study these complexes in addition to Mo-based complexes. With this in mind, I decided to begin this introduction by providing a timeline of Mo-catalyzed enantioselective olefin metathesis reactions that were developed by the collaborative work between the Schrock and Hoveyda groups. It is hoped that this timeline will enlighten the reader as to the progression of asymmetric olefin metathesis, from its inception to the time when my research began. In doing so, the hope is also that the reader will acquire an understanding of attributes innate to chiral Mo-based complexes employed for olefin metathesis. This discussion should also facilitate an understanding of concepts to be presented in future chapters relating to comparative studies between chiral Mo- and Ru-based complexes for olefin metathesis.

1.1a Enantioselective Synthesis of Cyclopentenes and Dihydrofurans. Our first collaborative report of a Mo-catalyzed enantioselective olefin metathesis process was published in 1998.[1] Initial studies involved the kinetic resolution of 1,6-dienes through ring-closing metathesis reactions. The metathesis of 1,6-dienes was chosen partly because it was well documented that Mo complexes were efficient at performing such ring closures; products and byproducts of the reactions were known and could be readily identified.[2] Furthermore, the olefin substitution patterns of such 1,6-dienes were easily

(1) "Catalytic Enantioselective Ring-Closing Metathesis by a Chiral Biphen-Mo Complex," Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042.
(2) "Synthesis of Cycloalkenes Via Alkylidene-mediated Olefin Metathesis and Carbonyl Olefination," Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800–3801.

modified, and allowed us to predict the site of initiation by Mo complexes. The biphenol-containing catalyst **1.2** was previously prepared by the Schrock group and chosen for these studies due to its efficiency in controlling the stereochemistry of ring-opening metathesis polymerization (ROMP) reactions of norbornenes.[3] A representative example of the outcome from these studies is illustrated in eq. 1.1. Exposure of 1,6-diene **1.1** to 5 mol% Mo complex **1.2** delivers cyclopentene **1.3** in *93% ee* (k_{rel} = 58)[4] and 43% yield after a reaction time of only 10 min.[5] Enantioenriched 1,6-diene **1.1** is isolated in *>98% ee* and 19% yield.



A mechanistic model accounting for formation of cyclopentene **1.3** is shown in Figure 1.1. Mo alkylidene **1.2** likely reacts at the terminal olefin of the starting 1,6-diene and adopts a pseudo-chair conformation prior to the subsequent metathesis that furnishes **1.3**. It is clear from this mechanistic model that the major enantiomer that forms has a lower activation energy barrier ($\Delta G^{\dagger\dagger}$) in its transition state than the minor enantiomer. If reaction with the slower-reacting (minor) enantiomer were to occur, severe steric repulsion would be present between the pendant silyl ether and the catalyst complex.

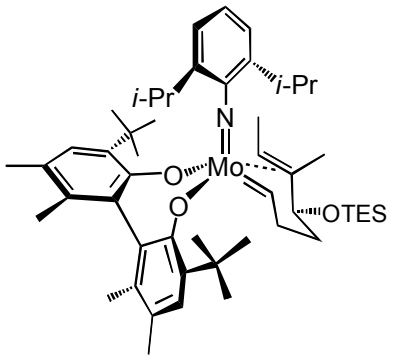


Figure 1.1 Proposed Transition State Model for Kinetic Resolution

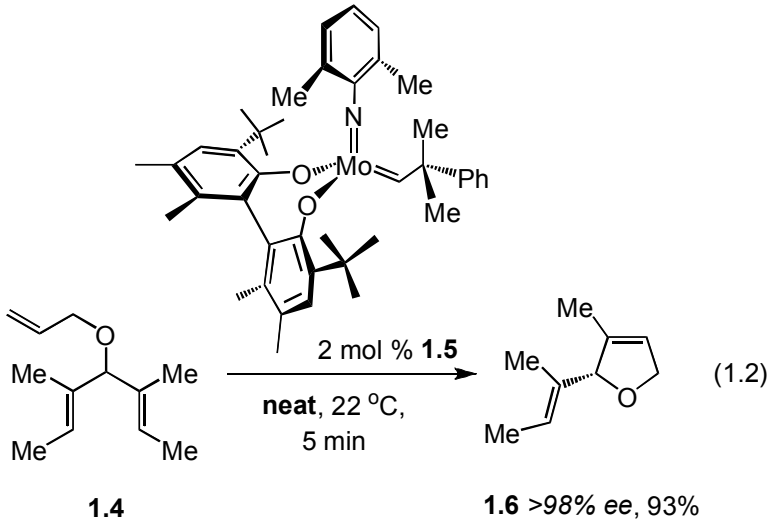
(3) "Ring Opening Metathesis Polymerization with Binaphtholate or Biphenolate Complexes of Molybdenum," Totland, K. M.; Boyd, T. J.; Lavoie, G. G.; Davis, W. M.; Schrock, R. R. *Macromolecules* **1996**, *29*, 6114–6125.

(4) The value for k_{rel} is calculated by the equation reported by Kagan, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.

(5) After ten minutes the reaction has proceeds to 81% conversion to product. The facility of this ring-closure attests to the high reactivity of these high-oxidation state metal complexes.

Although highly effective in the kinetic resolution to form cyclopentene products, this method was not amenable to the formation of cyclohexene products; kinetic resolution of 1,7-dienes proceeds to k_{rel} values <11.[6] These limitations of this method made it imperative that more selective chiral complexes be developed. Additionally, since these were the first ventures into asymmetric olefin metathesis it remained unknown what other classes of asymmetric transformations could be efficiently and selectively catalyzed by Mo complex **1.2**.

After studying kinetic resolution reactions, we focused on to investigate the desymmetrization reactions of meso 1,6-dienes. In general, catalytic desymmetrization processes are more atom-economical than kinetic resolutions. In a desymmetrization reaction the product can be isolated in up to 100% yield, in contrast to a maximum yield of 50% in a kinetic resolution. One major goal of these studies was to determine whether chiral Mo complexes could differentiate between enantiotopic olefins in a *meso* compound. To this end, we studied the Mo-catalyzed desymmetrization of meso 1,6-trienes such as the representative example shown in eq. 1.2.[7] Treatment of triene **1.4** with 2 mol % Mo complex **1.5** in the *absence of solvent* leads to the formation of dihydrofuran **1.6** in >*98% ee* and 93% yield within 5 min.



(1.2)

1.4 **1.6** >*98% ee*, 93%

Several facets of this chemical transformation deserve discussion. First, the reaction involves minimal waste production. The metathesis can be performed without

(6) Values of k_{rel} >50 are generally required if products of high enantiomeric purity are to be obtained in useful yield, see: "Practical Considerations in Kinetic Resolution Reactions," Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26.

(7) "Mo-Catalyzed Asymmetric Synthesis of Dihydrofurans. Catalytic Kinetic Resolution and Enantioselective Desymmetrization through Ring-Closing Metathesis," La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720–9721.

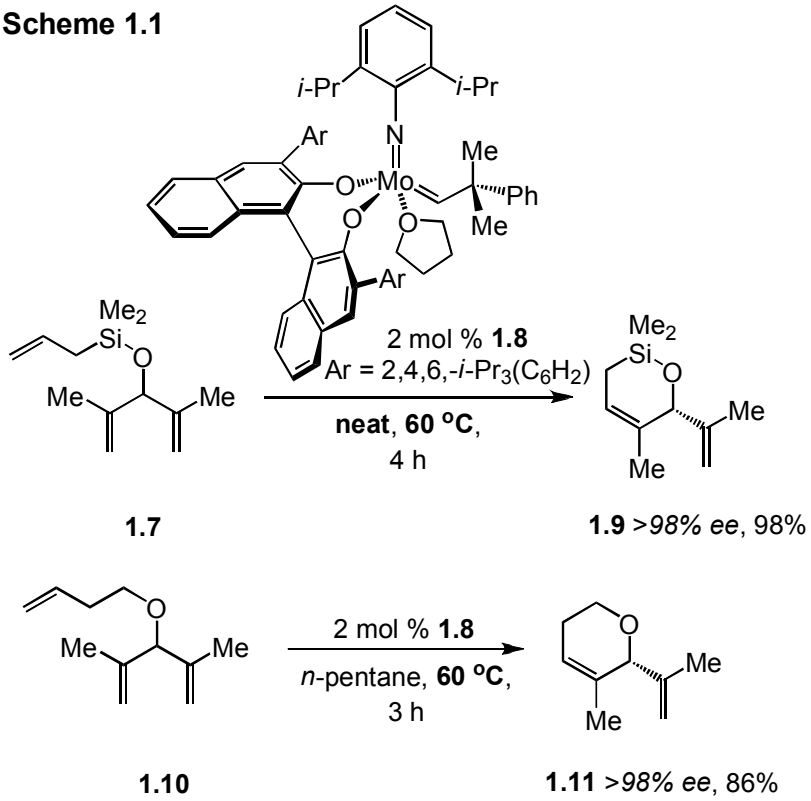
solvent and the only byproduct from the reaction is propene, a volatile and easily removable gas. Second, the optimal catalyst for the reaction (**1.5**) is a chiral Mo complex that was newly developed; previously discussed Mo complex **1.2** provides **1.6** in *>98% ee*, however, in only 32% conversion after 9 h. These results show that subtle differences in catalyst structure, in this case changing the imido ligand from 2,5-*i*-Pr_2 in catalyst **1.2** to 2,5-Me_2 in catalyst **1.5**, lead to significant reactivity differences. In short, these observations highlighted the need to have available a family of various structurally dissimilar, yet highly reactive, chiral Mo complexes. Most importantly, these studies provided a new method for the enantioselective synthesis of heterocyclic compounds. Heterocyclic compounds are invaluable intermediates for therapeutics[8] and this method allows for the preparation of enantiopure 2-substituted dihydrofuran, intermediates not easily accessible by other known methods.

1.1b Enantioselective Synthesis of Six-membered Ring Compounds through Catalytic Metathesis. The next set of studies involved desymmetrization reaction protocols for the formation of six-membered ring heterocycles, exemplified in Scheme 1.1 (see below).[9] As previously mentioned, difficulties were encountered in trying to perform desymmetrization transformations of 1,7-dienes. Mo complex **1.8**, a new catalyst construct containing a bidentate binaphtholate ligand, was prepared in response to the potential need for catalyst architecture different from that of biphenol-based Mo complexes **1.2** and **1.5**. Utilizing this catalyst, exposure of siloxy-containing triene **1.7** to 2 mol % of Mo complex **1.8** in the absence of solvent at *60 °C* produces silyl ether **1.9** in *>98% ee* and 98% yield after 4 h. Under identical reaction conditions, dihydropyran **1.11** is isolated in *>98% ee* and 86% yield after 3 h. As in the synthesis of chiral dihydrofurans, Mo-catalyzed reactions were performed in the absence of solvent. Notably, reactions proceed to high levels of enantioselectivity even at elevated temperature. These experiments revealed that Mo-catalyst **1.8** was the best catalyst for the synthesis of chiral six-membered ring intermediates; Mo complexes **1.2** and **1.5** generate the desired products with lower efficiency and in lower selectivity than complex **1.8**. Although complex **1.8** was found to be the optimal catalyst for the desymmetrization of 1,7-dienes, the complex was less effective for the desymmetrization of 1,6-dienes such as formation of **1.6** (see eq. 1.2 above), again highlighting the advantage of sustaining a

(8) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. in *Heterocycles in Life and Society*, Wiley–VCH, Weinheim, Germany, **1997**; Edition 1.
(9) "Chiral Mo-Binol Complexes: Activity, Synthesis, and Structure. Efficient Enantioselective Six-Membered Ring Synthesis through Catalytic Metathesis," Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251–8259.

family of chiral Mo complexes. After achieving success in various asymmetric ring-closing metathesis transformations, we moved on to study a completely different class of olefin metathesis reactions, namely, the ring-opening/cross-metathesis reaction of meso norbornenes.

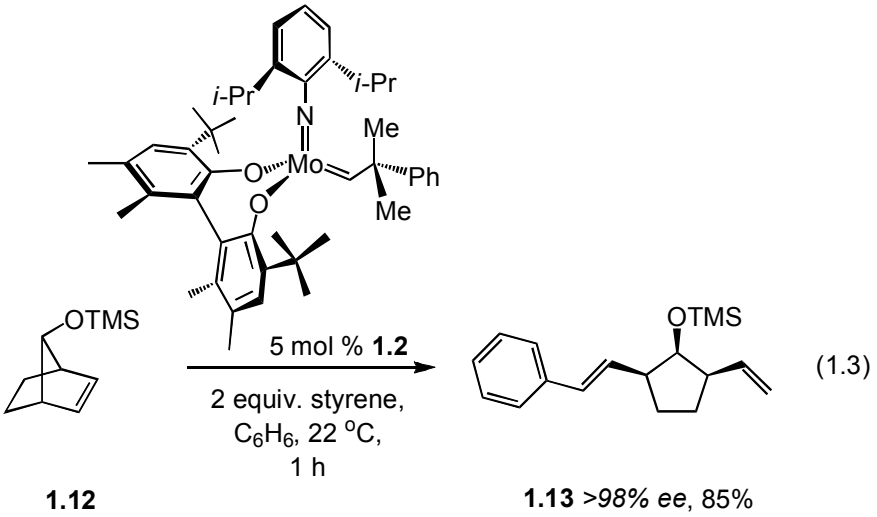
Scheme 1.1



1.1c Asymmetric Ring-Opening Metatheses Processes. A beautiful feature–if not the most–of the olefin metathesis reaction is the number of possible permutations of metatheses that can be performed under the right reaction conditions. A highly strained norbornene, for example, in the presence of Mo-catalysts typically undergoes polymerization reactions; polymerization reactions of norbornenes are well-studied and have received much attention from chemists in recent years.[10] It is generally accepted that the primary driving force for ring-opening reactions of norbornenes is release of ring strain. In the presence of an appropriate olefin donor, however, polymerization reactions of norbornenes can be prevented and instead lead to the formation of cyclopentanes through ring-opening/cross-metathesis reactions.[11] To explore this possibility with chiral

(10) For a review of ring-opening metathesis polymerization reactions, see: Black, G.; Maher, D.; Risse, W. in *Handbook of Metathesis* (Ed: R. H. Grubbs), Wiley–VCH, Weinheim, Germany, **2003**; vol. 3, pp. 2–71.
(11) For a review of catalytic ring-opening olefin metathesis reactions, see: Schrader, T. O.; Snapper, M. L. in *Handbook of Metathesis* (Ed: R. H. Grubbs), Wiley–VCH, Weinheim, Germany, **2003**; vol. 2, pp. 205–237.

Mo complexes we studied the desymmetrization of meso norbornyl ethers; a representative example of these studies is shown in eq. 1.3. In the presence of two equivalents of styrene and 5 mol % of Mo complex **1.2**, norbornyl ether **1.12** is desymmetrized to form enantioenriched cyclopentane **1.13** in *>98% ee* and 85% yield after 1 h. From an initial inspection it would appear that this is a facile reaction, however, it should be noted that ring-opening/cross-metathesis reactions are often difficult to control and predict. Ring-opening/cross-metathesis reactions are bimolecular reactions that suffer from formation of byproducts that would not be present in other metathesis processes, for example ring-closing metathesis reactions.



(1.3)

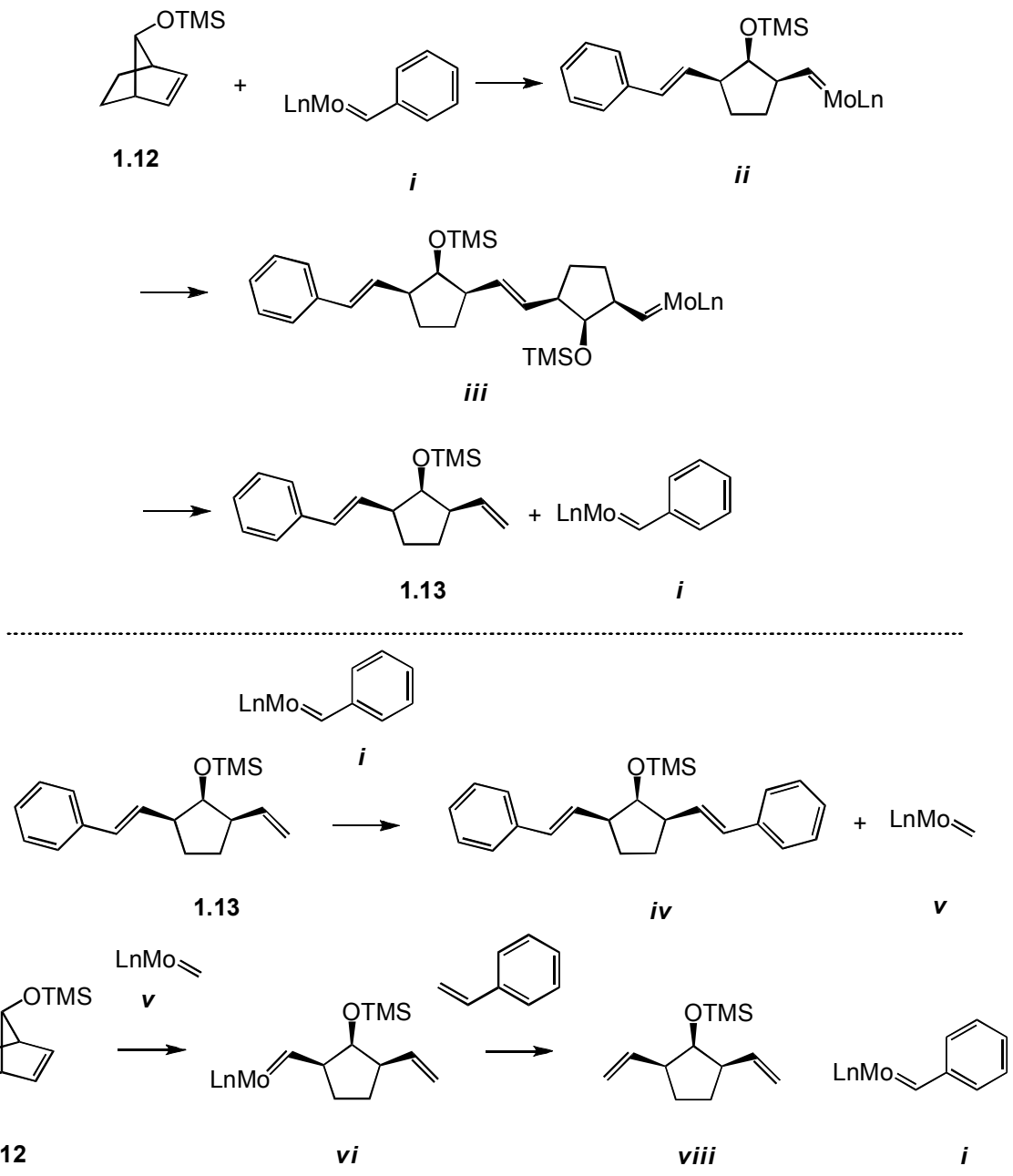
1.12 **1.13** *>98% ee*, 85%

Difficulties encountered in developing ring-opening cross-metathesis reactions can be better appreciated through a discussion of potential and observed mechanistic pathways; the Mo intermediates and potential byproducts involved in the desymmetrization of norbornene **1.12** are shown in Scheme 1.2 (see below). Initially, Mo benzylidene ***i*** is formed through reaction of the Mo pre-catalyst neopentylidene (**1.2** in eq. 1.3) with styrene. Studies from our group have shown that Mo benzylidenes are slow to react with another equivalent styrene, as evident from minimal stillbene formation in the absence of another olefin cross partner (norbornene in this example). Ring-opening of norbornene **1.12** with Mo benzylidene ***i*** thus leads to formation of Mo alklylidene ***ii***. This newly generated alkylidene can react with another equivalent of norbornene or styrene. Reaction with norbornene would form Mo alkylidene ***iii***, which represents an intermediate that would be involved in norbornene polymerization. Alternatively, reaction of alkylidene ***ii*** with styrene furnishes cyclopentane **1.13**, the observed product of the reaction, and regenerates Mo benzylidene ***i***. At this point, if benzylidene ***i*** reacts at the terminal olefin of the newly generated cyclopentene **1.13**, then *bis*-cross metathesis product ***iv*** would be formed along with Mo methylidene ***v***. Studies

from the Shrock group have shown that Mo methylidene intermediates are highly reactive (in relation to benzylidene ***i***) and have been implicated in catalyst decomposition pathways.[12] In addition to catalyst decomposition, Mo methylidene intermediates can be involved in non-productive metathesis pathways; if Mo methylidene ***v*** were to react with norbornene **1.12**, the result would be formation of Mo alkylidene ***vi***. Intermediate ***vi*** in turn could react with another equivalent of norbornene **1.12** and provide a Mo alkylidene similar to that of ***iii*** (this intermediate would have a terminal olefin in place of a styrenyl olefin at its terminus). Alternatively, alkylidene ***vi*** could react with styrene leading to *meso* cyclopentane ***viii*** and regenerate Mo benzylidene ***i***. It should be noted that in the ring-opening/cross-metathesis being discussed (eq. 1.3, see above) byproducts ***iv*** and ***viii*** are not observed; formation of non-chiral cyclopentanes such as ***iv*** and ***viii*** are sensitive to the identity of the starting norbornene and *meso* intermediates of this type have been observed in other ring-opening cross-metathesis reactions. In concluding this discussion on the mechanism of ring-opening cross-metathesis reactions, it should also be noted that not all potential pathways were shown. Pathways leading to other byproducts, such as oligomers or products arising from an initial ring-opening of a Mo pre-catalyst neopentylidene have also been observed in other reactions.

(12) "Reduction of Molybdenum Imido-alkylidene Complexes in the Presence of Olefins to Give Molybdenum (IV) Complexes," Robbins, J.; Bazan, G. C.; Murdzek, J. S.; O'Regan, M. B.; Schrock, R. R. *Organometallics* **1991**, *10*, 2902–2907.

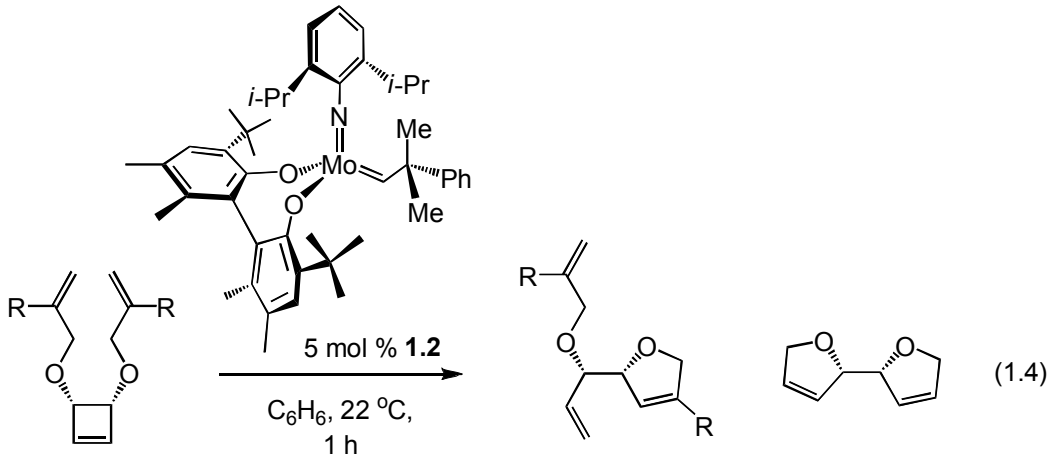
Scheme 1.2



1.1d Tandem Ring-Opening/Ring-Closing Metathesis Reactions. The next class of asymmetric reactions developed was the ring-opening/ring-closing metathesis of cyclobutenes for the formation of enantioenriched dihydrofurans.[13] Hitherto, enantioenriched dihydrofurans were prepared through asymmetric ring-closing

(13) "Tandem Catalytic Asymmetric Ring-Opening Metathesis/Ring-Closing Metathesis," Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829.

metathesis reactions. A different approach to this class of chiral compounds is through a skeletal rearrangement exemplified in eq. 1.4. Treatment of cyclobutene **1.14a** with 5 mol % Mo complex **1.2** delivers dihydrofuran **1.15a** in *92% ee* and 69% yield after 1 h. When the metathesis of a related cyclobutene, terminal olefin containing **1.14b**, was studied the desired product is formed in *>98% ee*, however, in only 10% yield. The major product from the reaction of **1.14b** is *meso* double ring-closed product **1.15c**. This difference in product distribution highlights the sensitivity of Mo complexes to the olefin substitution pattern of metathesis substrates.



(1.4)

1.14a R = Me

1.14b R = H

1.15a *92% ee*, 69%

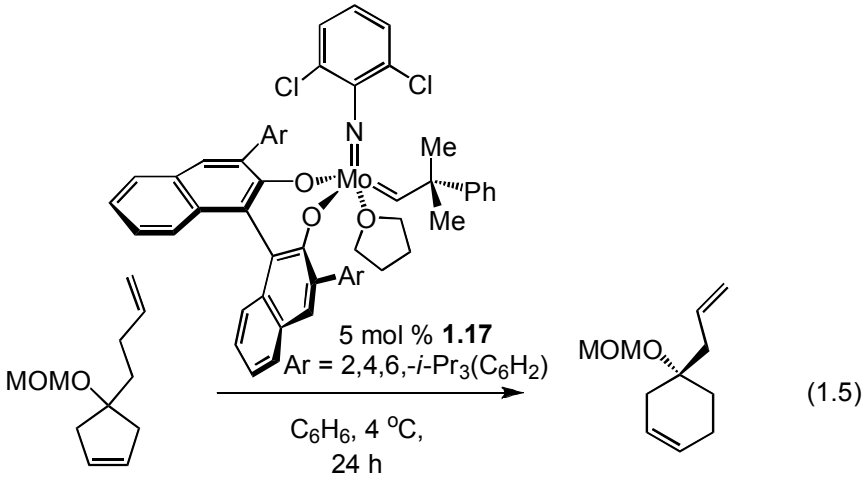
1.15a *>98% ee*, 10%

1.15c

As previously mentioned, the release of strain in a molecule can serve to energetically favor a metathesis reaction. Along these lines, after the desymmetrization of cyclobutenes we moved on to study the ring-opening/ring-closing rearrangement of cyclopentenes to deliver cyclohexenes; a representative example of this class of asymmetric transformations is shown in eq. 1.5 (see below). Exposure of cyclopentene **1.16** to 5 mol % of Mo complex **1.17** delivers enantioenriched cyclohexene **1.18** in *78% ee* and >98% conversion (consumption of substrate as monitored by 1H NMR analysis) after 24 h.[14] In light of the moderate selectivity observed in this reaction (*78% ee*) we examined various additives in attempts to improve the enantioselectivity of this reaction. Previous studies with Mo complexes, in particular studies with **1.17**, revealed that Lewis basic additives such as THF were capable of altering the equilibrium between syn and anti benzylidene isomers. It was hoped that the altering this equilibrium could be beneficial to the selectivity of the reaction. When 2 equiv. of THF are used as an additive

(14) "Enhancement of Enantioselectivity by THF in Asymmetric Mo-Catalyzed Olefin Metathesis. Catalytic Enantioselective Synthesis of Cyclic Tertiary Ethers and Spirocycles," Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779–10784.

in this reaction **1.18** is isolated in *85% ee* and >98% conversion. When the optimal amounts of THF additive (10 equiv.) are used for this reaction the product **1.18** is isolated in *92% ee*, >98% conversion, and 93% isolated yield after 24 h. As we have seen, our studies up to this point have shown that a wide variety of factors must be taken into consideration when developing a catalytic enantioselective olefin metathesis method; this in effect teaches and challenges us as chemists to "not leave a stone unturned" when trying to solve problems in organic chemistry.



(1.5)

1.16 **1.18**

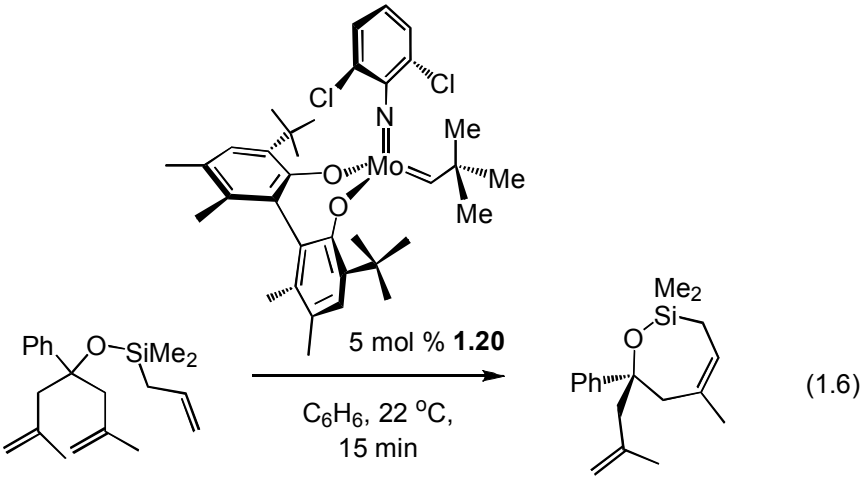
no THF *78% ee*, >98% conv.
2 equiv. THF *85% ee*, >98% conv
10 equiv. THF 92% *ee*, >98% conv. 93%

1.1e Enantioselective Synthesis of Medium-size Rings. Our next investigations dealt with the preparation of enantioenriched seven-membered ring heterocycles, intermediates previously inaccessible through Mo-catalyzed olefin metathesis.[15] One of the difficulties in performing ring-closing metathesis reactions of larger ring sizes is the tendency of metathesis catalysts to undergo cross-metathesis reactions, delivering substrate homodimers, instead of the desired ring-closed products. A way of circumventing this problem is by relying on the reversibility of cross-metathesis reactions, since cyclic olefins of low strain energy are less likely to undergo a reversible ring-opening metathesis reaction. In particular, the problem of troublesome ring-closures of macrocycles has been solved in this manner. [16] It is more difficult to get around the

(15) "Enantioselective Synthesis of Medium-Ring Heterocycles, Tertiary Ethers, and Tertiary Alcohols by Mo-Catalyzed Ring-Closing Metathesis," Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868–2869.

(16) "Applications of Zr-Catalyzed Carbomagnesation and Mo-Catalyzed Macrocyclic Ring Closing Metathesis in Asymmetric Synthesis. Enantioselective Total Synthesis of Sch 38516 (Fluvirucin B_1)," Xu,

problem of cross-metathesis when medium size rings are the desired metathesis products. The approach we took to solve this problem, which has also been used by others for related ring-closures,[17] was to incorporate functional groups in the substrate molecule that would induce a Thorpe-Ingold effect,[18] and thus facilitate a ring-closing metathesis to occur. Toward this end, treatment of triene **1.19** with 5 mol % of Mo complex **1.20** in benzene delivers seven-membered heterocycle **1.21** in *87% ee* and 95% yield after 15 min. Two additional aspects of this reaction merit mention: (1) the reaction was performed with 1 g of substrate, demonstrating that reactions with Mo complexes can be scaled to multi-millimol quantities (3.2 mmol in this example). Second, the product can be subjected to proteo-desilylation reaction conditions to provide an enantioenriched tertiary alcohol (not shown) that would otherwise be difficult to prepare.



(1.6)

1.19 (1.0 g)

1.21 87% *ee*, 95%

1.2 Mo-catalyzed Enantioselective Synthesis of Bicycles and Tricycles

And this is where my story, of the contributions I made to catalytic enantioselective olefin metathesis reactions, begins. It was a cold winter day, on January 1st, 2002, when I entered the labs of Professor Amir H. Hoveyda to begin my graduate career. Gabriel Weatherhead, an utmost thoughtful chemist, greeted me and it was only a matter of

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Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.

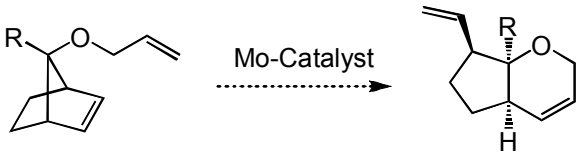
(17) "A Concise Total Synthesis of Dactylol via Ring Closing Metathesis," Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746–8749.

(18) The Thorpe-Ingold effect, or gem-dimethyl effect or angle compression, is phenomena observed in organic chemistry where increasing the size of two substituents on a tetrahedral arrangement around a center leads to enhanced reactions between parts of the other two substituents. For the original publication on this effect, see: (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080–1106. For additional discussion on this topic, see: (b) "Conformational Analysis. IX. The Gem-Dimethyl Effect," Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701–704.

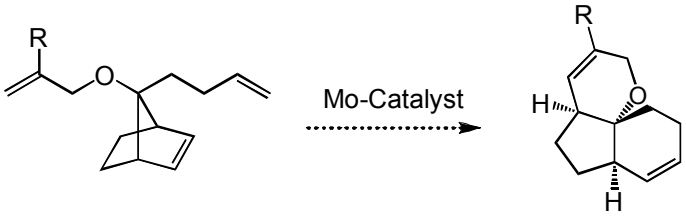
moments before our objectives were clearly defined and we began our search for chemicals with which to commence our studies; I was to work with Gabe on the development of a new class of tandem ring-opening/ring-closing metathesis reactions.

1.2a Desymmetrization Reactions of Meso-Norbornenes. Our attention was focused on the possibility of performing asymmetric ring-opening/ring-closing metathesis (AROMRCM) reactions of *meso*-norbornenes. Previous work had showed that norbornenes were compatible substrates for ring-opening/cross-metathesis reactions (*vide supra*). But what if instead of having an intermolecular reaction between a norbornene and olefin-cross partner, we had an achiral norbornene with a tethered olefin that could react in an intramolecular fashion, would it be possible to perform tandem ring-opening/ring-closing metathesis reactions? The substrates chosen to answer these questions are shown in Scheme 1.3. Our goal was to prepare substrate types, exemplified by substrate **1.22** and **1.24**, which could lead to the formation of structurally complex bicycles (**1.23**) or tricycles (**1.25**).

Scheme 1.3



1.22 R = H or alkyl **1.23 R = H or alkyl**



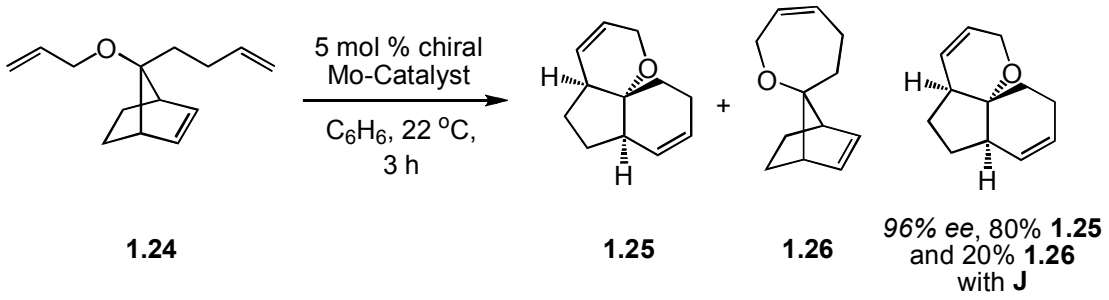
1.24 R = H or alkyl **1.25 R = H or alkyl**

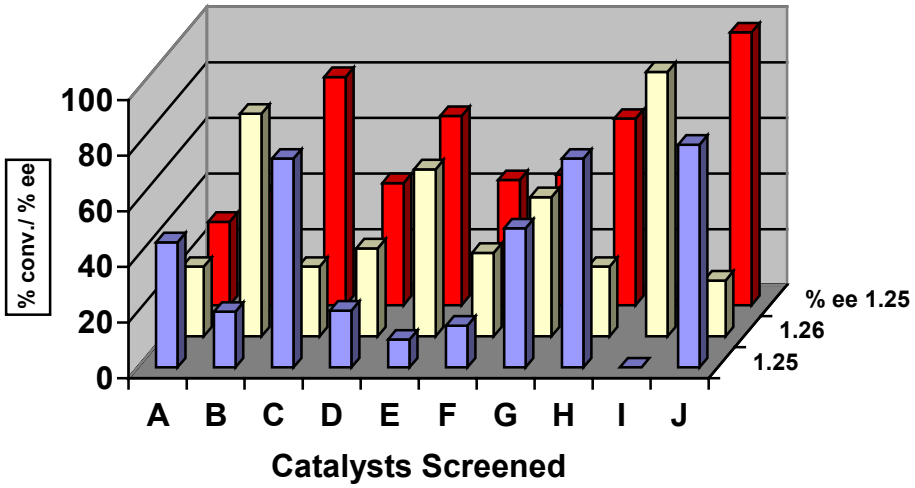
1.2b AROM/RCM of Norbornyl Trienes. As illustrated in Scheme 1.4 (see below), our studies began by investigating the desymmetrization of norbornyl triene **1.24** to provide tricycle **1.25**.[19] Initial screening conditions employed 5 mol % of chiral Mo-complexes (see Chart 1 below for catalysts screened)[20] and reactions were quenched after 3 h. As previously discussed, one potential drawback to olefin metathesis transformations is for nonproductive reaction pathways to occur. A byproduct observed during our screen is achiral seven-membered ring **1.26**, arising from the ring-closing

(19) The synthesis of **1.28** and all other substrates is described in the experimental section of this chapter.
(20) For convenience, from this point forward chiral Mo catalysts are numbered alphabetically.

metathesis between the two terminal olefins in substrate **1.24**. As illustrated by the graph in Scheme 1.4, Mo-catalysts demonstrate varying levels of selectivity and reactivity for the desymmetrization of **1.24**. Two notable examples of such differences are exemplified by catalysts **I** and **J**. Whereas **I** exclusively catalyzes formation of achiral **1.26**, the major product formed in the reaction with **J** is the desired tricycle **1.25**. Under optimized reaction conditions with Mo complex **J**, tricycle **1.25** is isolated in *96% ee* and 80% yield.[21] At the time complex **J** was the newest addition to our family of chiral Mo complexes and these studies resulted in the first example of complex **J** catalyzing a highly selective olefin metathesis reaction. Complex **J** is structurally very different from previous Mo complexes in that **J** possesses an adamantylimido ligand, in contrast to earlier complexes that contain arylimido ligands.

Scheme 1.4





(21) "An Enantiomerically Pure Adamantylimido Molybdenum Alkylidene Complex. An Effective New Catalyst for Enantioselective Olefin Metathesis," Tsang, W. C. P.; Jernelius, J. A.; Cortez, G. A.; Weatherhead, G. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2591–2596.

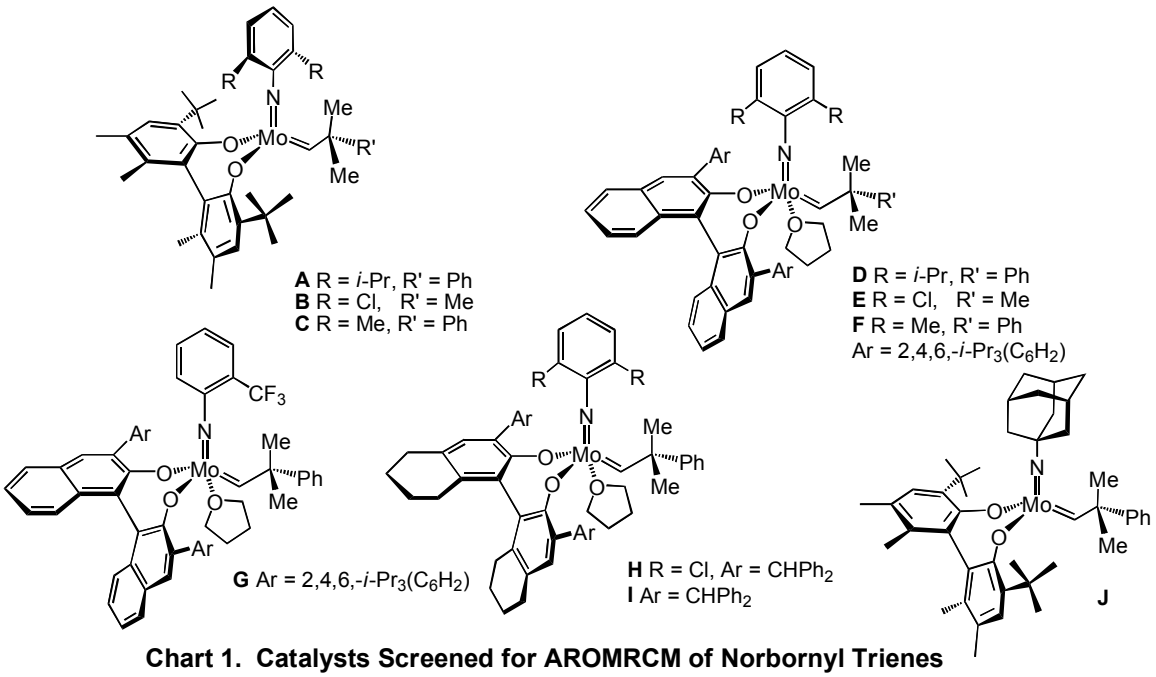
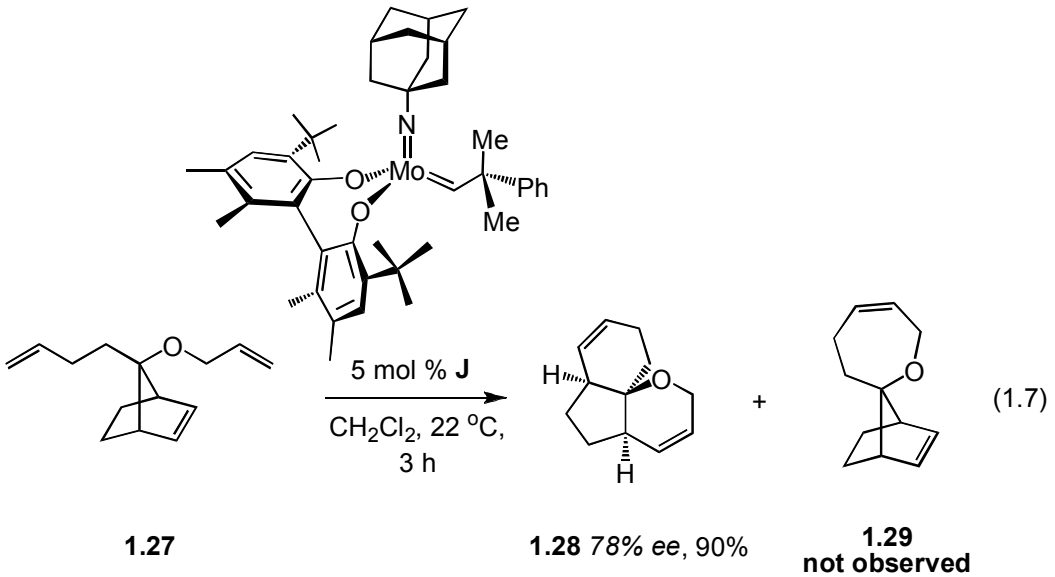


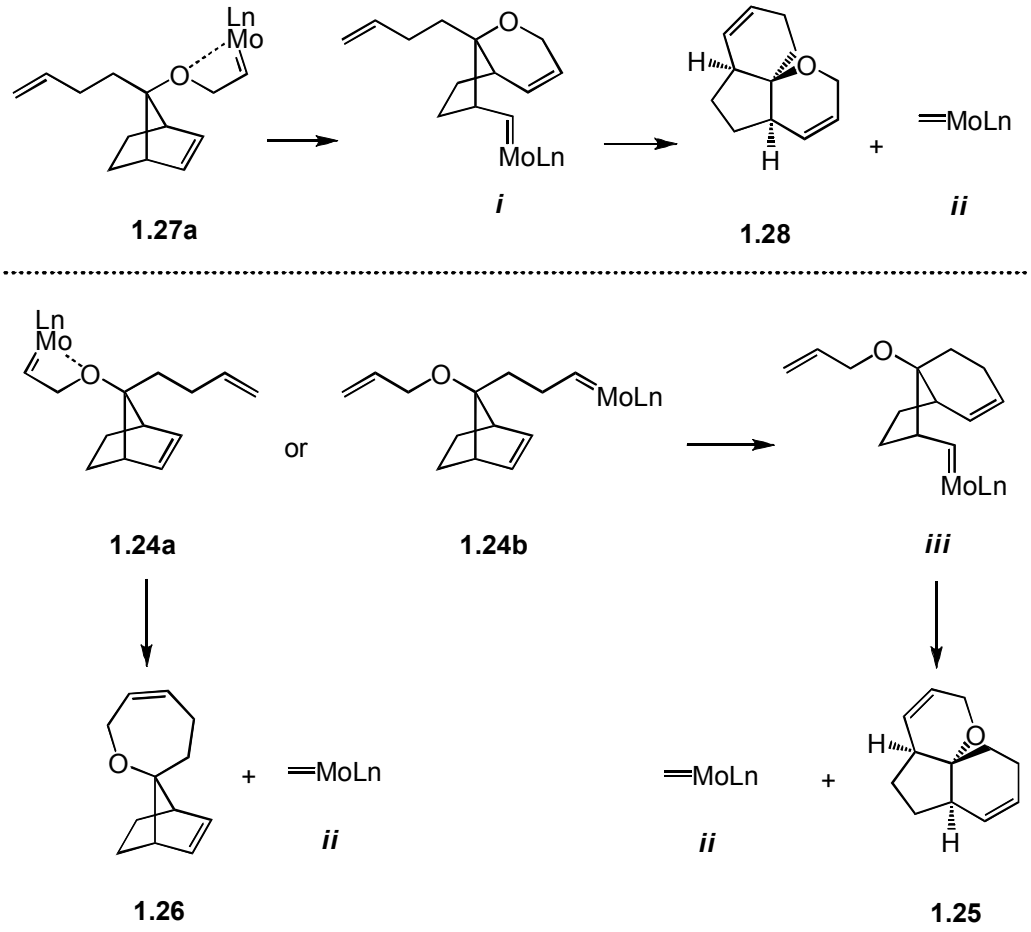
Chart 1. Catalysts Screened for AROMRCM of Norbornyl Trienes

The next substrate studied was norbornyl triene **1.27**, a diastereomer of **1.24**. As shown in eq. 1.7, after screening available chiral Mo-catalysts, the optimal catalyst for the desymmetrization of **1.27** was again adamantylimido Mo complex **J**. Exposure of **1.27** to 5 mol % of **J** provides tricycle **1.28** in *78% ee* and 90% isolated yield after 3 h. One notable difference in the formation of **1.28** (vs. **1.25**) is that the desired product is formed in lower enantioselectivity (*78% ee* for **1.28** vs. *96% ee* for **1.25***)*. Another notable difference is that the achiral byproduct **1.29**, which would form through a ring-closing metathesis of the terminal olefins, is not observed. These results highlight the difficulties in predicting the outcome of any given metathesis reaction.



1.2c Mechanistic Model for AROM/RCM of Norbornyl Trienes. A mechanistic rationale for the product distribution difference between the desymmetrization of **1.24** and **1.27** is shown in Scheme 1.5.

Scheme 1.5



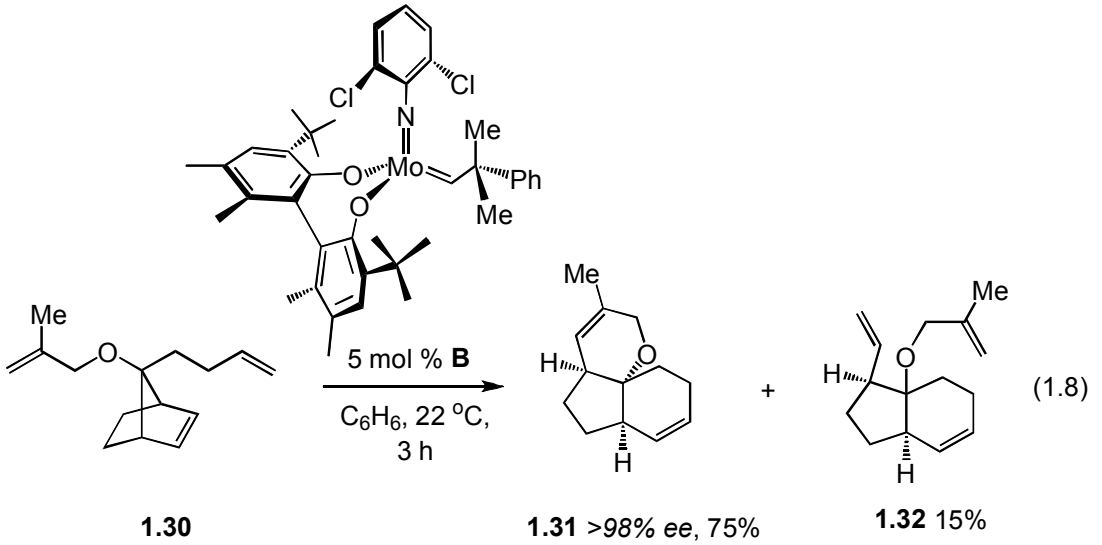
Studies from several groups, including ours, have described the chelating effect of proximal heteroatoms in metathesis reactions.[22] Presumably, the active Mo catalyst first reacts with the allylic ether olefin in **1.27** resulting in intermediate **1.27a** where an O→Mo chelation is present. The alkylidene of **1.27a** then reacts with the norbornyl olefin to provide intermediate ***i***, furnishing one of the fused six membered rings present in **1.28**. Finally, ring-closure with the pendant terminal olefin provides tricycle **1.28** along with Mo-methylidene ***ii***. Based on the preceding supposition that a Mo-alkylidene

(22) (a) "Reaction of Neopentylidene Complexes of the Type M(CH-t-Bu)(N-2,6-C6H3-i-Pr2)(OR)2 (M = W, Mo) with Methyl Acrylate and N,N-dimethylacrylamide To Give Metallacyclobutane Complexes," Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260–2265. (b) Dolman, S. New Chiral Molybdenum Metathesis Catalysts; Application To The Enantioselective Preparation of Cyclic Amines. Ph. D. Dissertation, Massachusetts Institute of Technology, Cambridge, MA, June 2004.

preferentially reacts at an allylic ether olefin over an alkyl olefin, in the reaction of **1.24** with Mo complex **J**, two alkylidene intermediates are possible, **1.24a** and **1.24b**. Intermediate **1.24b** would follow a reaction pathway similar to that of **1.27a**, by first providing ***iii*** and ultimately delivering **1.25** along with Mo-methylidene ***ii***. In intermediate **1.24a**, the spatial distance separating the norbornyl olefin and the reactive alkylidene make it unlikely that the two can undergo metallacyclobutane formation. It is at this point that reaction of the alkylidene in **1.24a** with the pendant terminal olefin likely occurs resulting in the formation of seven-membered ring product **1.26**. This mechanistic proposal would require the alkylidene in **1.24a** to undergo a different metathesis reaction, such as reaction with another molecule of **1.24** to arrive at **1.24b**. Based on this mechanistic analysis, we decided to prepare a substrate with a disubstituted allylic ether olefin distal to the norbornyl olefin. We reasoned that steric differentiation should favor reaction of the Mo alkylidene at the terminal olefin (similar to formation of **1.24b**) and thus prevent seven-membered ring product formation.

1.3 An Example of a Dynamic Asymmetric Process

1.3a Observation of a Bicyclic Ring-Opening/Ring-Closing Product. To this end, we prepared and studied the desymmetrization of norbornyl triene **1.30** (eq. 1.8). Upon screening of available chiral catalysts, we found Mo complex **B** to be the optimal catalyst in the desymmetrization of **1.30**: Treatment of **1.30** with 5 mol % Mo catalyst **B** furnishes tricycle **1.31** in *>98% ee* and 75% yield after 3 h. Mo complex **J** was also selective in the formation of **1.31** *(>98% ee*); however, the product is isolated in only 60% yield.



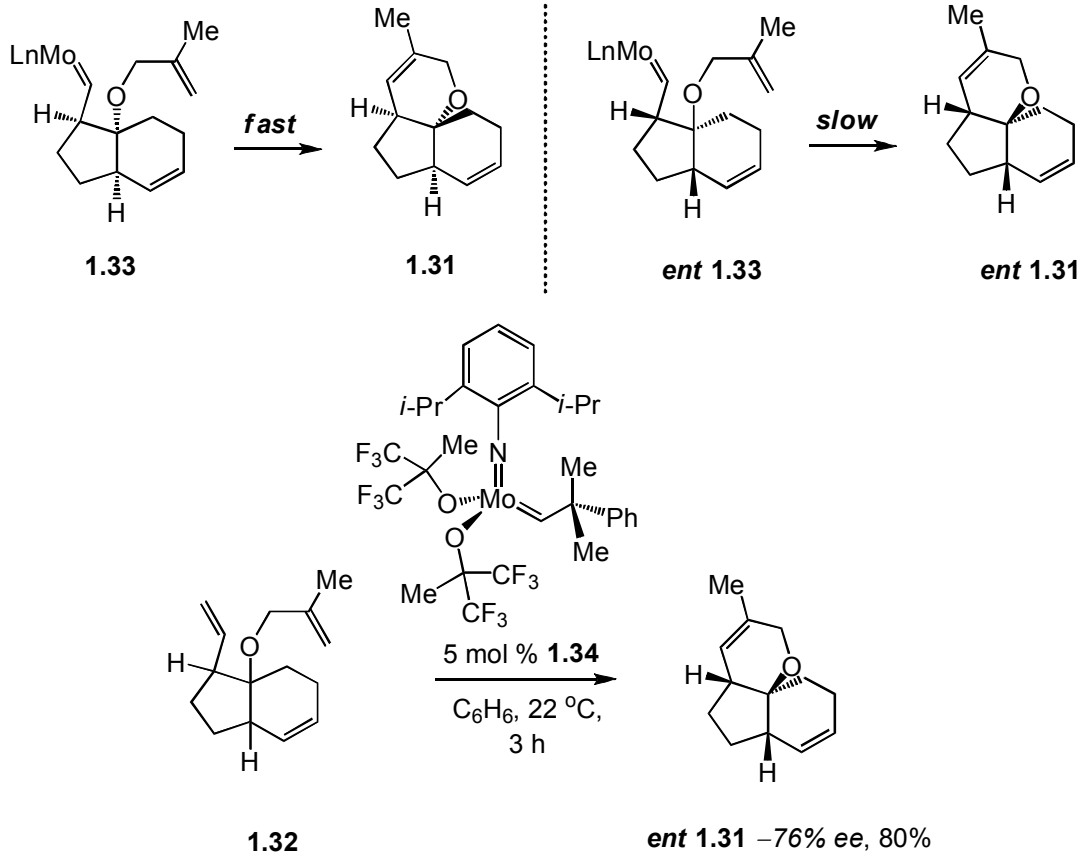
1.30 **1.31** *>98% ee*, 75% **1.32** 15%

As predicted, increasing the substitution at the allylic ether olefin disfavors formation of a seven-membered ring product; however, a different byproduct, bicycle **1.32**, is

isolated in 15% yield (complex **J** provides **1.32** in 40% yield). This was not surprising since the metathesis to form cyclic tri- and tetrasubstituted olefins is generally sluggish; in comparison to reactions for the formation of cyclic disubstituted olefins. These results, at least in part, substantiate our mechanistic proposal for the AROM/RCM of this class of norbornyl trienes.

1.3b Determination of a Catalytic Dynamic Asymmetric Process. Given the high selectivity in the formation of **1.31** and the formation of **1.32**, we speculated as to whether or not this reaction was an example of a matched vs. miss-matched enantioselective process (Scheme 1.6). If, based on our mechanistic model, the initial Mo alkylidene reacts at the terminal olefin, followed by ring-opening of the norbornene, an intermediate such as **1.33** should be formed along the reaction coordinate. Is it possible that the ring-closure of **1.33** is faster than the ring-closure of **ent 1.33**, the enantiomer of **1.33**? If the ring-closure of **ent 1.33** is slow and instead leads to formation of bicycle **1.32**, then the enantiopurity of **1.31** should be high, as we have observed. To address this question we would have to determine the enantiomeric excess of **1.32**. Ring-closure of **1.32** to tricycle **1.31** would provide the answer to this question. Indeed, when **1.32** is treated with 5 mol % of achiral Mo complex **1.34**, **ent 1.31** is isolated in *–76% ee* and 80% yield.

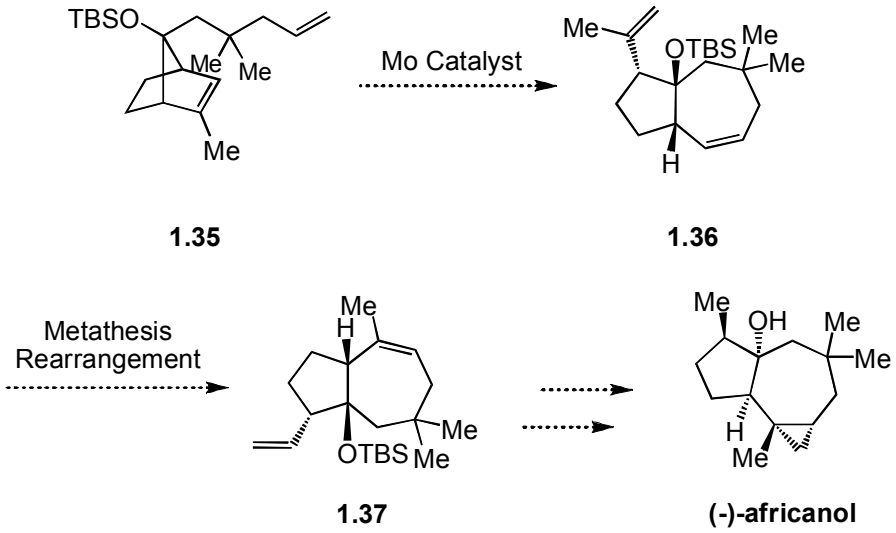
Scheme 1.6



1.4 Limitation of Mo-catalyzed AROM/RCM Method

1.4a Kinetic Resolution Approach to Natural Product Synthesis. To demonstrate the practicality of our newly developed method, we undertook the synthesis of the sesquiterpene natural product africanol, isolated from the marine invertebrate *Lemnalia africana*.[23] During our studies, Gabe and I took two different approaches toward africanol. My studies involved the kinetic resolution of norbornene **1.35** to access bicycle **1.36** (Scheme 1.7). We postulated that the kinetic product of this ring-opening/ring-closing rearrangement should be **1.36**, which would posses an exocyclic 1,1-disubstituted olefin. Then, under the proper reaction conditions a metathesis rearrangement should allow for the formation of the thermodynamic product **1.37**, which would possess an endocyclic trisubstituted olefin. Functional group manipulations would then provide (−)-africanol. Unfortunately, under various reaction conditions we were never able to perform the desired kinetic resolution of norbornene **1.35**; in all cases the starting material was recovered in >98% mass recovery.

Scheme 1.7

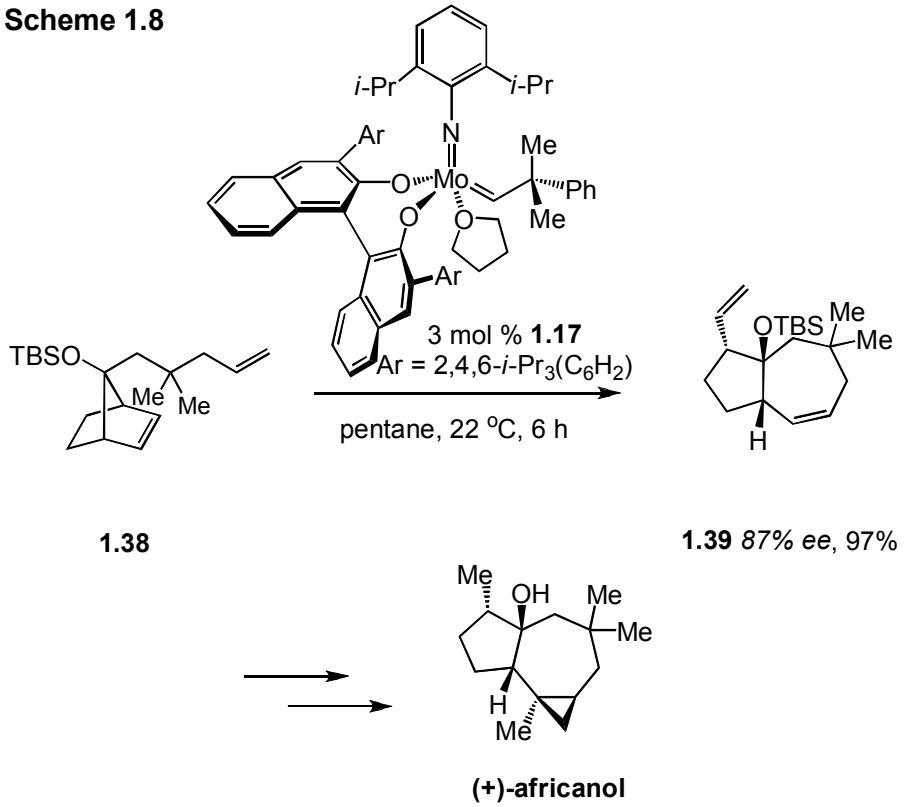


1.4b Desymmetrization Approach to Natural Product Synthesis. The alternative approach to africanol proved to be more fruitful (Scheme 1.8, see below). This approach involved the desymmetrization of norbornene **1.38**. To this end, Gabe found that treatment of norbornene **1.38** with 3 mol % of Mo complex **1.17** in pentane delivers the

(23) "Chemical studies of marine invertebrates. VIII africanol, an unusual sesquiterpene from Lemnalia africana (Coelenterata, Octocorallia, Alcyonacea)," Tursch, B.; Braekman, J. C.; Daloze, D.; Fritz, P.; Kelecom, A.; Karlsson, R.; Losmon, D. *Tetrahedron Lett.* **1974**, *15*, 747−750.

desired bicycle **1.39** in *87% ee* and 97% yield after 6 h.[24] After several functional group manipulations, Gabe was able to arrive at an intermediate that was previously reported en route toward a total synthesis of africanol,[25] constituting an enantioselective formal synthesis.

Scheme 1.8



1.5 Conclusions

These studies resulted in the development of a variety of Mo-catalyzed tandem asymmetric ring-opening/ring-closing metathesis reactions. Previously, norbornenes had only been substrates in asymmetric ring-opening/cross-metathesis reactions to deliver cyclopentanes. With these investigations, we were able to show that olefin metathesis can take a single class of substrates, *meso* norbornenes, and form a variety of enantioenriched products (bicycles and tricycles), demonstrating the versatility of olefin metathesis for organic synthesis. These studies also demonstrate for the first time that a Mo alkylimido alkylidene complex (**J**, see above) is capable of efficiently and selectively catalyzing olefin metathesis reactions. In addition to developing new methods for olefin metathesis, these studies provided insight into the reaction mechanism of such

(24) "Mo-catalyzed asymmetric olefin metathesis in target-oriented synthesis: Enantioselective synthesis of (+)-africanol," Weatherhead, G. S.; Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5805–5809.
(25) Fan, W.; White, J. B. *J. Org. Chem.* **1993**, *58*, 3557–3562.

transformations. Arguably, the most important aspect of this work was that it demonstrated that catalytic olefin metathesis is applicable to complex natural product synthesis.

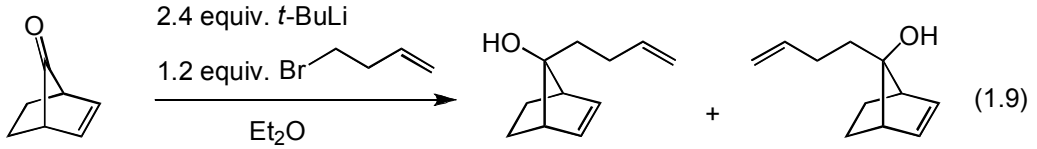
1.6 Experimental Section

Materials and Reagents.[26] All reactions were conducted in oven- (135 ^{o}C) or flame-dried glassware under an inert atmosphere of dry N_2 unless otherwise stated. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) or weak (w). ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal reference ($CDCl_3$: δ 7.26, C_6D_6: δ 7.16). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or combinations thereof), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal reference ($CDCl_3$: δ 77.16, C_6D_6: δ 128.10). Enantiomer ratios were determined by chiral HPLC (Chiral Technologies Chiralpak OD column, Chiralpak AD, Chiralcel OJ, and Chiralcel OB-H (4.6 mm x 250 mm)). High-resolution mass spectrometry was performed at the University of Illinois Mass Spectrometry Laboratories (Urbana-Champaign, IL). Elemental microanalyses were performed by Robertson Microlit Laboratories (Madison, N. J.). Optical rotation values were recorded on a Rudolph Research Analytical Autopol IV polarimeter.

Solvents were purged with argon and then purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: CH_2Cl_2 was passed through activated alumina columns; benzene was passed successively through activated Cu and alumina columns. Tetrahydrofuran was purified by distillation from sodium benzophenone ketal immediately prior to use. All reagents were purchased from Aldrich Chemical Company, Lancaster Synthesis, or Strem Chemicals, Inc., and purified by appropriate methods prior to use. Lithium aluminum hydride was purchased in powder form and was stored in a N_2-filled glovebox. Mo complex **J** was prepared according to published procedures.[16] Mo complexes were handled under an inert atmosphere in a N_2-filled glovebox. Substrates employed in Mo-catalyzed reactions were dried by repeated (three times) azeotropic distillation of water with benzene under high vacuum unless otherwise stated. Ru complexes **1a-2b** were prepared according to published

(26) This section on materials and reagents applies to subsequent chapters as well.

procedures.[27] All reactions were allowed to stir with a magnetic stir bar and performed at 22 °C, unless otherwise stated. All filtrations involved gravity filtration; gravity filtrations were conducted with Whatman® filter papers. All reagent solvents were purchased from Doe and Ingalls.



1.40 **1.41** **1.42**

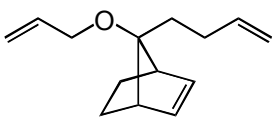
Synthesis of acohols **1.41** and **1.42.** Alcohols **1.41** and **1.42** were prepared from norbornenone[28] as shown in eq. 1.8. A two-neck 500-mL round-bottom flask, fitted with an addition funnel, was charged with 4-bromobutene (3.08 mL, 30.4 mmol, 1.2 equiv.), Et_2O (250 mL), and the reaction vessel was cooled to −78 °C in a dry ice/acetone bath. To this solution was added *t*-butyllithium (33.22 mL, 60.80 mmol, 1.83 M solution in hexane) dropwise over a period of 2 h. At this time, the reaction vessel was warmed to 0 °C and allowed to stir for 1 h, after which time it was cooled to −78 °C and allowed to stir a further 4 h. At this moment, norbornenone **1.40** (2.70 g, 25.0 mmol) was added to this mixture by cannula, after which time the cooling bath was removed and the reaction mixture was allowed to stir for 12 h. The reaction was quenched by the addition of H_2O (50 mL), the layers were separated, and the aqueous layer was washed with Et_2O (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting dark brown residue was purified by $AgNO_3$-impregnated silica gel chromatography (gradient elution, 1:6 to 1:3 Et_2O:hexanes) to give **1.41** as colorless oil (0.918 g, 5.59 mmol, 22%) and **1.42** as colorless oil (0.890 g, 5.40 mmol, 20%); the identity of **1.41** was confirmed by nOe analysis. Norbornene **1.41**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (dd, *J* = 2.0, 2.0 Hz, 2H), 5.86 (dddd, *J* = 17.2, 10.4, 6.8, 6.8 Hz, 1H), 5.03 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 4.93 (dddd, *J* = 10.4, 1.2, 1.2, 1.2 Hz, 1H), 2.61–2.57 (m, 2H), 2.20–2.13 (m, 2H), 1.80–1.75 (m, 2H), 1.62–1.58 (m, 2H),

(27) (a) "A Recyclable Chiral Ru Catalyst for Enantioselective Olefin Metathesis. Efficient Catalytic Asymmetric Ring-Opening/Cross Metathesis in Air," Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (b) "A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions," Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

(28) Norbornenone was prepared in five steps through known chemical procedures. "The Chemistry of 7-Substituted Norbornenes," Gassman, P. G.; Pape, P. G. *Tetrahedron Lett.* **1963**, *4*, 9–12.

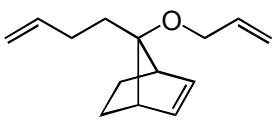
0.96 (dd, *J* = 10.4 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 132.0, 129.2, 63.0, 47.5, 29.4, 25.9, 23.8. Norbornene **1.42**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (dd, *J* = 2.4, 2.4 Hz, 2H), 5.81 (dddd, *J* = 16.8, 10.0, 6.4, 6.4 Hz, 1H), 5.01 (dddd, *J* = 16.8, 1.6, 1.6, 1.6 Hz, 1H), 4.92 (dddd, *J* = 10.0, 2.0, 1.2, 1.2 Hz, 1H), 2.43 (ddd, *J* = 4.0, 2.0, 2.0 Hz, 2H), 2.12–2.06 (m, 2H), 1.98–1.92 (m, 2H), 1.80–1.75 (m, 2H), 0.97 (dd, *J* = 11.2, 3.6 Hz, 2H).

Allylation of alcohols **1.41** and **1.42** provided metathesis substrates **1.24**, **1.27**, and **1.30**.



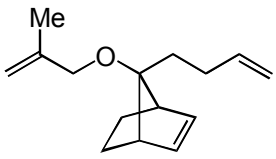
1.24

Norbornene **1.24**: IR (Neat): 2967 (m), 2942 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.00 (dd, *J* = 2.0, 2.0 Hz, 2H), 5.90–5.79 (m, 2H), 5.19 (dddd, *J* = 17.2, 2.0, 1.6, 1.6 Hz, 1H), 5.06 (dddd, *J* = 10.4, 2.0, 1.2, 1.2 Hz, 1H), 5.01 (dddd, *J* = 17.2, 3.6, 1.6, 1.6 Hz, 1H), 4.92 (dddd, *J* = 10.0, 2.0, 1.2, 1.2 Hz, 1H), 3.72 (ddd, *J* = 2.8, 1.6, 1.6 Hz, 2H), 2.66 (ddd, *J* = 3.6, 2.0, 2.0 Hz, 2H), 2.14–2.07 (m, 2H), 1.70–1.67 (m, 2H), 2.14–2.07 (m, 2H), 1.57 (ddd, *J* = 8.4, 4.8, 4.8 Hz, 2H), 0.98 (ddd, *J* = 13.6, 2.8, 2.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5, 135.6, 134.8, 115.8, 113.9, 96.5, 64.0, 46.8, 29.8, 25.8, 23.4. Elem. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found C, 82.11; H, 9.99.



1.27

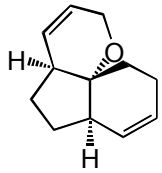
Norbornene **1.27**: ^{1}H NMR (400 MHz, C_6D_6): δ 5.81–5.71 (m, 4H), 5.25 (dddd, *J* = 17.2, 4.0, 2.0, 2.0 Hz, 1H), 5.00–4.91 (m, 2H), 4.90 (dddd, *J* = 10.0, 2.0, 1.2, 1.2 Hz, 1H), 3.53 (ddd, *J* = 3.6, 1.6, 1.6 Hz, 2H) 2.41 (ddd, *J* = 3.6, 3.6, 2.0 Hz, 2H), 2.06–1.98 (m, 4H), 1.73–1.69 (m, 2H), 0.86 (ddd, *J* = 9.6, 3.2, 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5, 135.7, 132.6, 116.2, 114.2, 97.5, 67.1, 46.7, 28.4, 28.3, 23.0. Elem. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found C, 82.17, H, 10.00.



1.30

Norbornene **1.30:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (dd, *J* = 2.0, 2.0 Hz, 2H), 5.80 (dddd, *J* = 16.8, 10.0, 6.4, 6.4 Hz, 1H), 5.10–4.95 (m, 2H), 4.89 (dddd, *J* = 10.4, 2.4, 1.6, 1.6 Hz, 1H), 4.85–4.83 (m, 1H), 3.67 (br s, 2H), 2.62 (dd, *J* = 3.6, 2.0 Hz, 2H), 2.05–1.98 (m, 2H), 1.96–1.91 (m, 2H), 1.90–1.76 (m, 5H), 0.90 (ddd, *J* = 10.8, 3.6, 3.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 139.5, 134.8, 113.9, 111.1, 96.3, 66.7, 46.8, 29.9, 25.8, 23.4, 20.0. Elem. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found C, 82.49, H, 10.27.

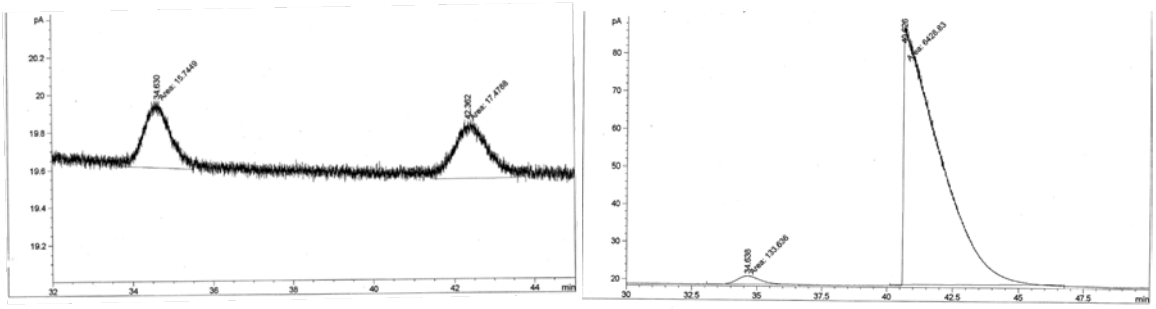
Representative procedure for tandem Mo-catalyzed AROM/RCM; synthesis of tricycle 1.25 and *meso* 1.26. In a N_2-filled glovebox, a 4-mL vial was charged with triene **1.24** (25.0 mg, 0.122 mmol) and C_6H_6 (1.20 mL). To this solution was added **J** (5.0 mg, 0.0061 mmol, 0.05 equiv) and the vial was fitted with a teflon lined cap. The

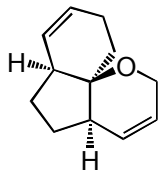


1.25

reaction mixture was allowed to stir at 22 °C for 3 h. At this time, the vial was removed from the glovebox, and the volatiles were removed in vacuo. The resulting brown residue was purified by silica gel chromatography (40:1 pentane:Et_2O) to give **1.25** as colorless oil (17.7 mg, 0.0976 mmol, 80%) and **1.26** as colorless oil (4.3 mg, 0.024 mmol, 20%). Tricycle **1.25**. IR (Neat): 3024 (m), 2955 (m), 1465 (w), 1440 (w); ^{1}H NMR (400 MHz, C_6D_6): δ 5.78–5.70 (m, 3H), 5.30 (dddd, *J* = 10.0, 5.6, 2.4, 2.4 Hz, 1H), 4.18 (dddd, *J* = 17.6, 5.6, 2.8, 2.8 Hz, 1H), 4.01 (dddd, *J* = 17.6, 4.4, 2.4, 2.4 Hz, 1H), 2.64–2.54 (m, 1H), 2.24–2.06 (m, 2H), 1.91–1.77 (m, 3H), 1.55–1.47 (m, 1H), 1.26–1.00 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.1, 126.3, 126.1, 125.9, 64.1, 45.2, 43.0, 29.9, 29.1, 23.5, 21.7, 19.1. Elem. Calcd $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found C, 81.84; H, 9.26. *Meso* **1.26**. IR (Neat): 2961 (m), 2936 (m). ^{1}H NMR (400 MHz, C_6D_6): δ 5.82 (s, 2H), 5.70–5.60 (m, 1H), 5.42–5.38 (m, 1H), 3.91 (s, 2H), 2.49 (s, 2H), 2.16 (d, *J* = 3.6 Hz, 2 H), 2.02 (s, 2H), 1.40–1.20 (m, 2H), 0.98 (d, *J* = 3.2 Hz, 1H), 0.85 (dd, *J* = 2.8, 2.8 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 135.3, 131.9, 129.2, 97.6, 63.0, 47.4, 29.4, 25.9, 23.7). The optical purity of **1.25** was determined by chiral GC analysis in comparison with authentic racemic material, shown below: CDGTA column, 105 °C, 20 psi, $[\alpha]_D^{20}$ –75.91 (*c* = 1.2, $CHCl_3$) for a sample of *96% ee*.

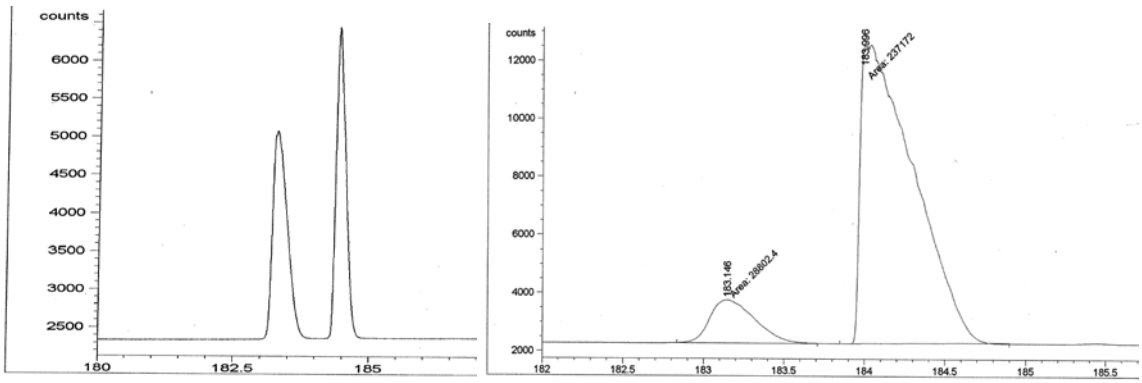
1.26

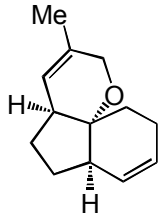




1.28

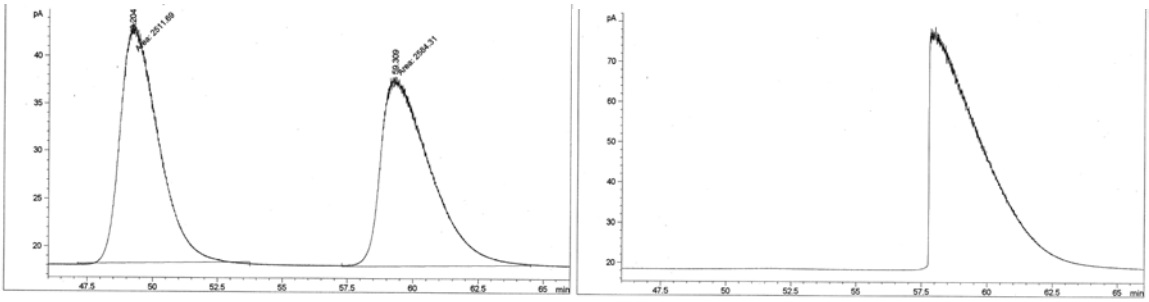
Tricycle **1.28**. ^{1}H NMR (400 MHz, C_6D_6): δ 5.82–5.68 (m, 3H), 5.43–5.39 (m, 1H), 3.96–3.84 (m, 2H), 2.25–2.13 (m, 2H), 2.12–1.97 (m, 2H), 1.96–1.74 (m, 1H), 1.73–1.58 (m, 2H), 1.28–1.14 (m, 2H), 0.92–0.84 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 127.2, 126.3, 124.5, 77.1, 65.9, 60.6, 48.1, 41.2, 30.7, 26.5, 26.3, 24.3. The optical purity of **1.28** was determined by chiral GC analysis in comparison with authentic racemic material, shown below: CDGTA column, 70 °C for 180 min and then 140 °C 10 min thereafter (increasing at the rate of 70 °C/min), 20 psi, for a sample of *78% ee*.

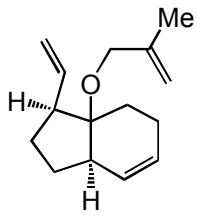




1.31

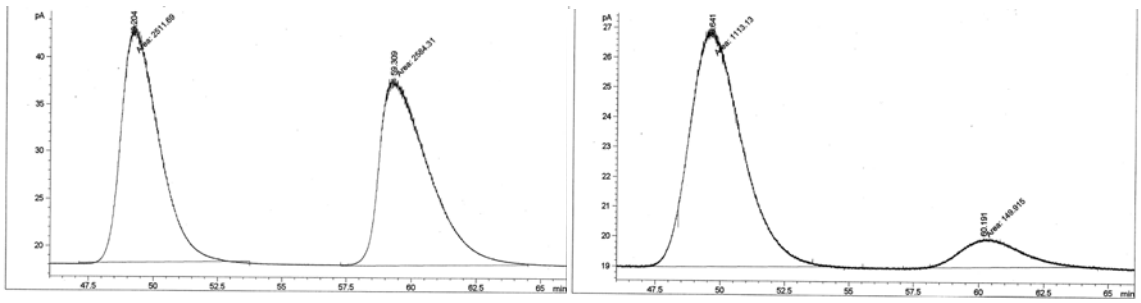
Tricycle **1.31**. ^{1}H NMR (400 MHz, C_6D_6): δ 5.80–5.76 (m, 2H), 5.44 (dddd, *J* = 5.6, 4.0, 2.0, 2.0 Hz, 1H), 4.08 (dddd, *J* = 17.2, 3.2, 2.4, 1.2 Hz, 1H), 3.97–3.90 (m, 1H), 2.64–2.59 (m, 1H), 2.34–2.21 (m, 2H), 1.98–1.72 (m, 3H), 1.58–1.1.50 (m, 1H), 1.32–1.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.5, 129.1, 126.2, 121.0, 67.4, 45,3, 42.7, 29.5, 23.6, 21.6, 19.1, 18.2. Elem. Calcd $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found C, 82.0; H, 9.66. The optical purity of **1.31** was determined by chiral GC analysis in comparison with authentic racemic material, shown below: CDGTA column, 105 °C for, 20 psi, for a sample of *>98% ee*.





1.32

Bicycle **1.32**. ^{1}H NMR (400 MHz, C_6D_6): δ 5.86–5.77 (m, 1H), 5.72–5.68 (m, 1H), 5.65–5.61 (m, 1H), 5.18–5.17 (m, 1H), 5.05–5.03 (m, 1H), 5.01–4.99 (m, 1H), 4.89–4.87 (m, 1H), 3.82 (dd, *J* = 12.4, 12.4 Hz, 2H), 2.75 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.50–2.42 (m, 1H), 2.30–2.21 (m, 1H), 2.10–1.53 (m, 3H), 1.53 (s, 3H), 1.46–1.22 (m, 4H). The optical purity of **ent 1.31**, isolated from the reaction shown in Scheme 1.6, was determined by chiral GC analysis in comparison with authentic racemic material, shown below: CDGTA column, 105 °C, 20 psi, for a sample of *–76 ee*.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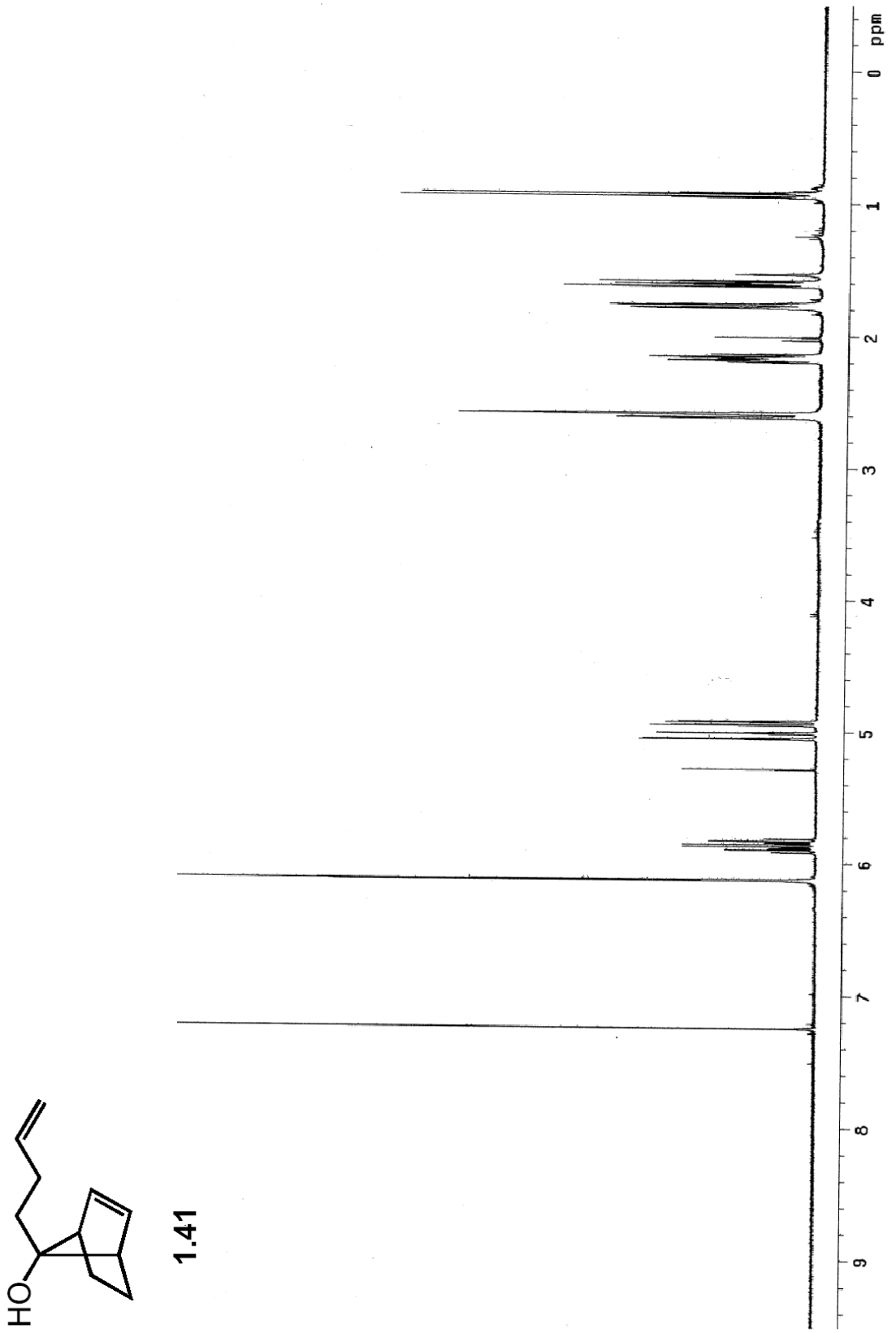
50
52.5
55
57.5
60
62.5
65 min
pA
47.5
50
52.5
55
57.5
60
62.5
65 min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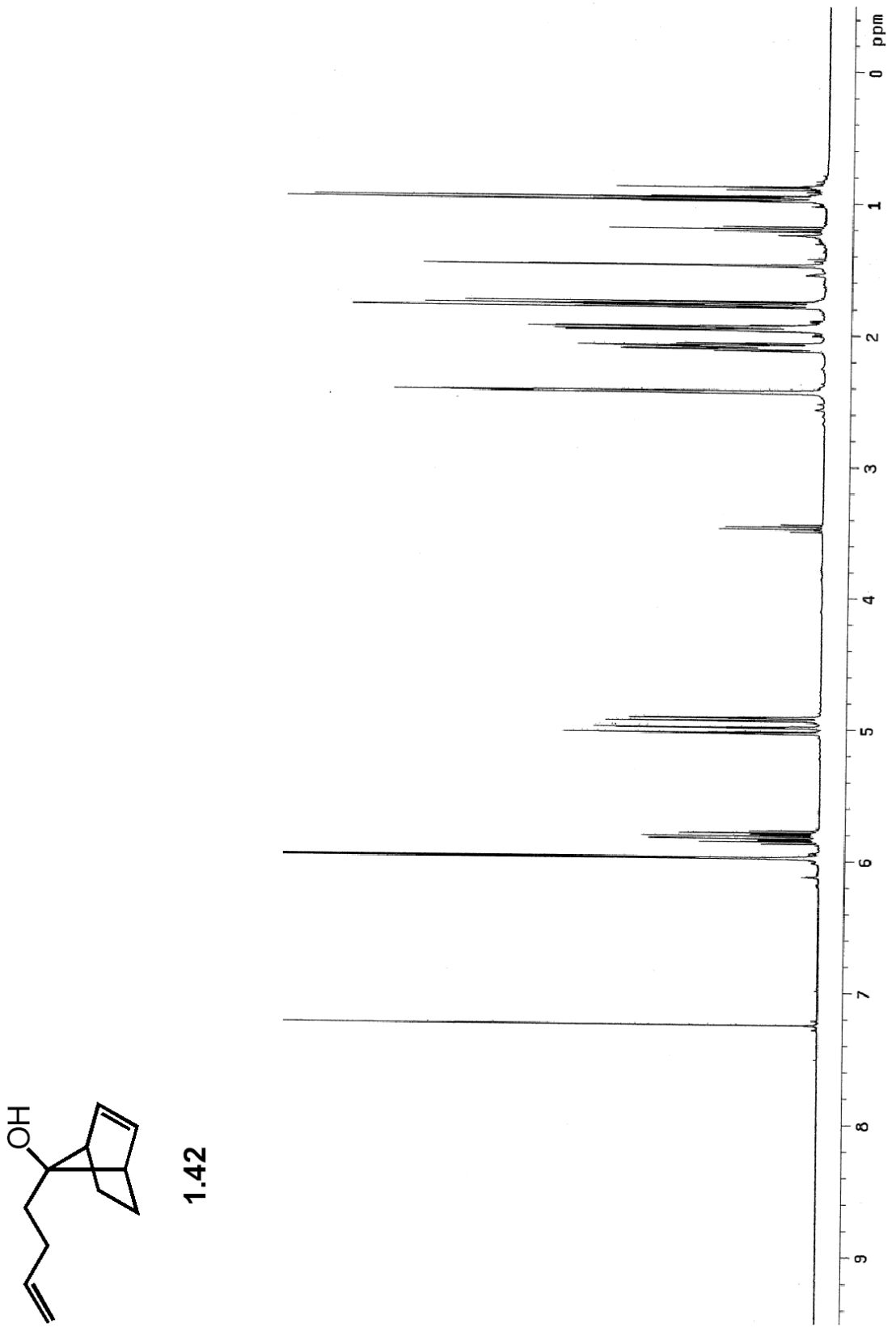
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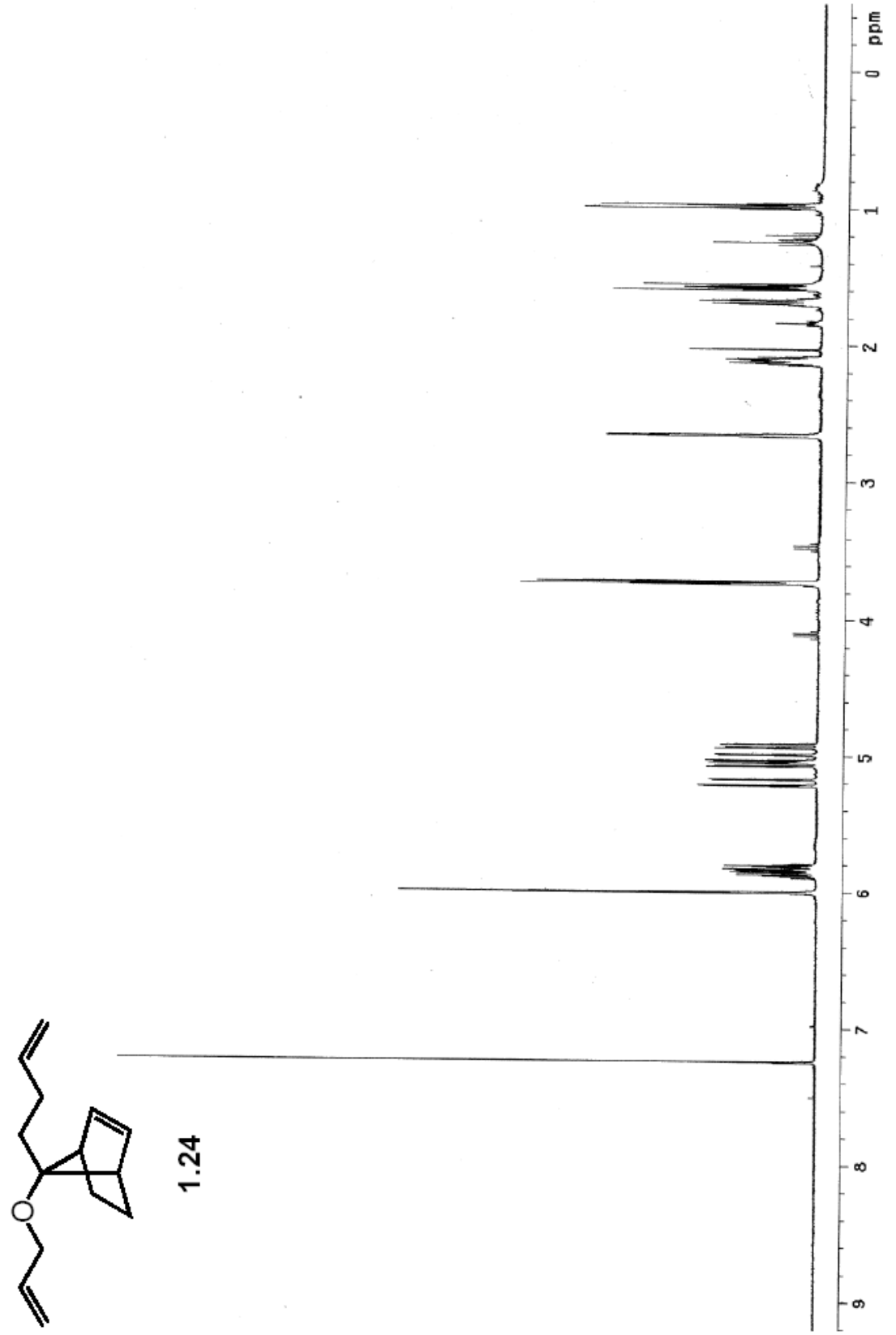
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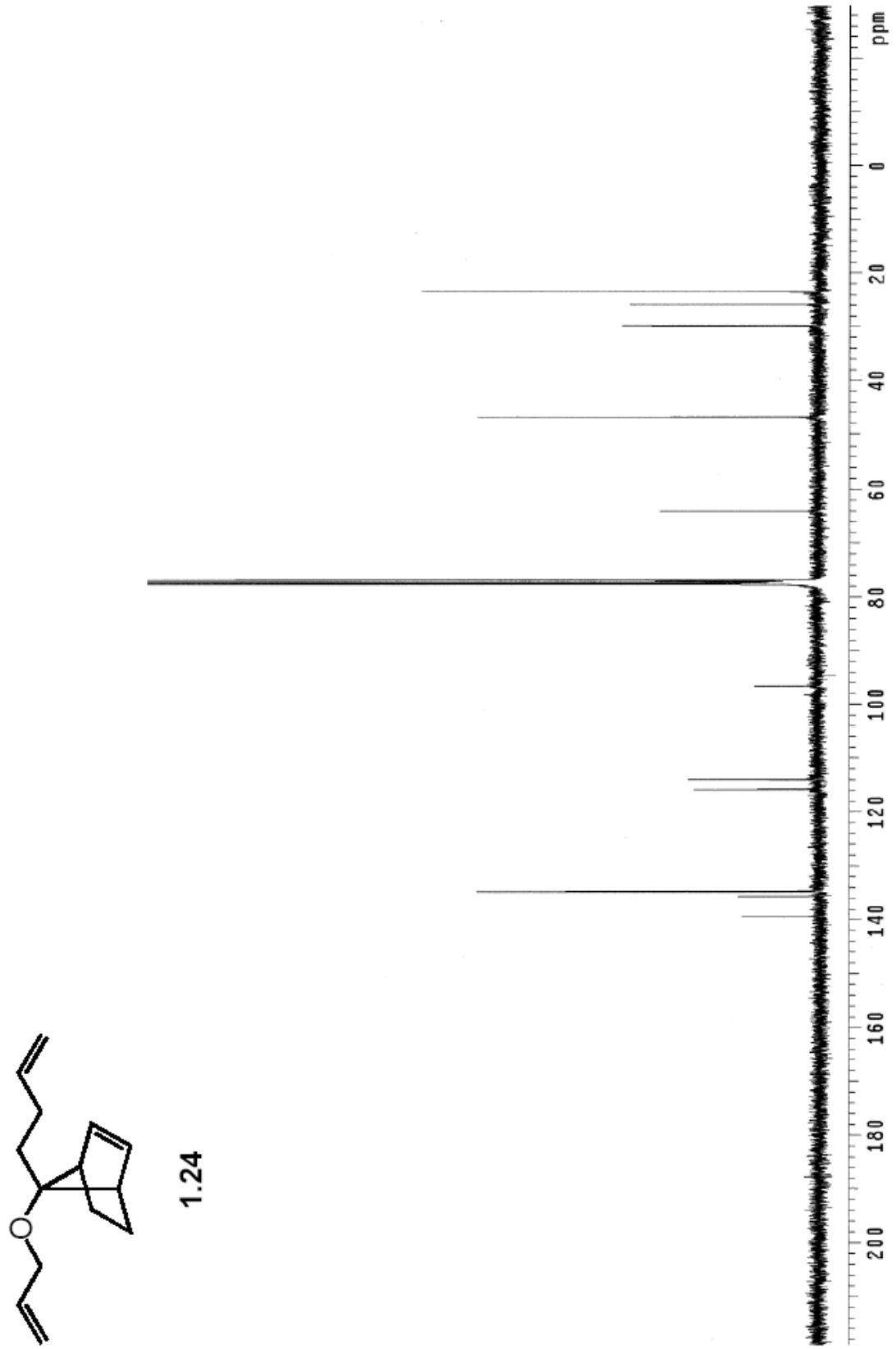

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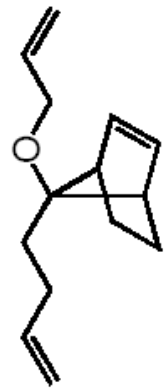
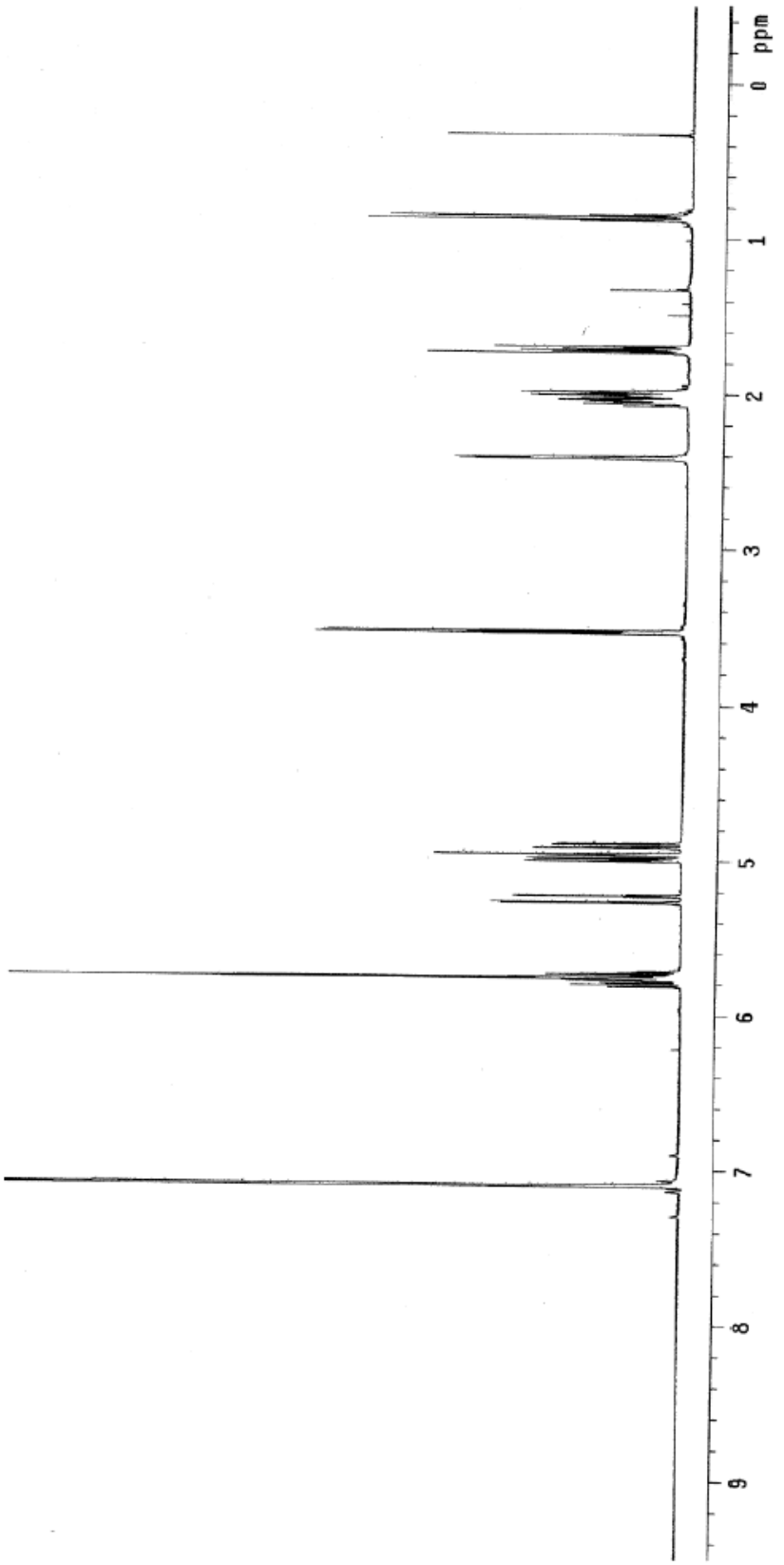
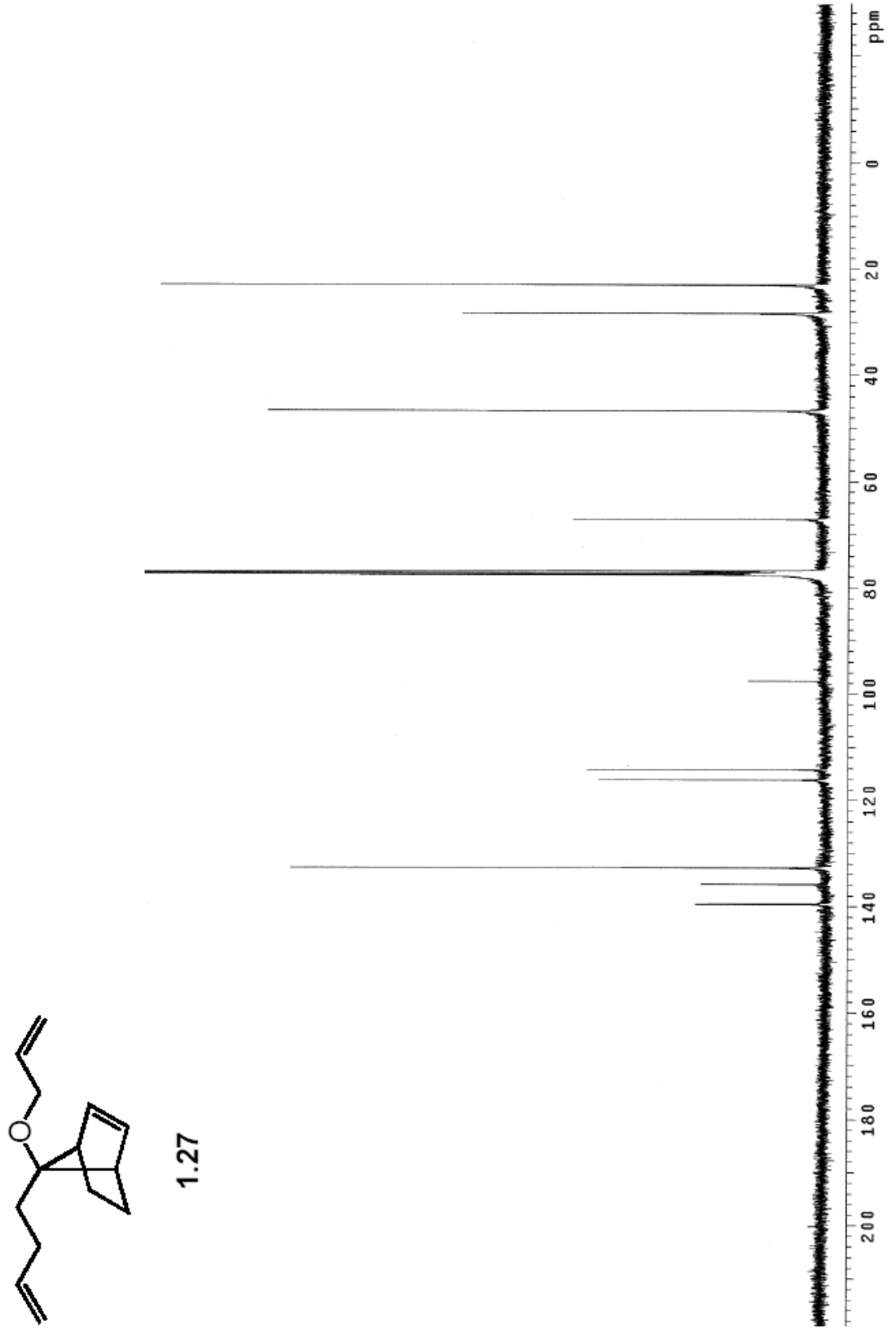


1.27





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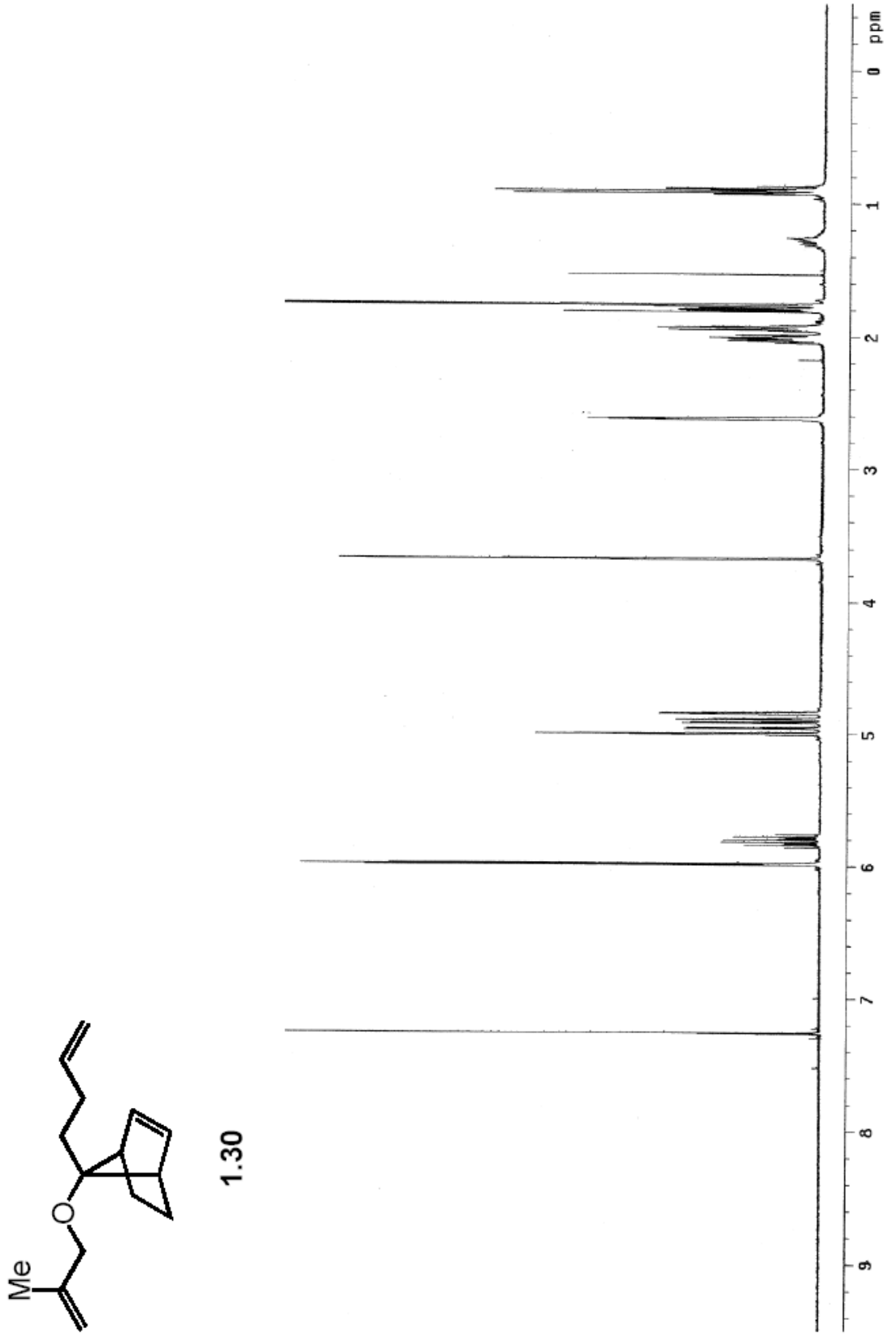
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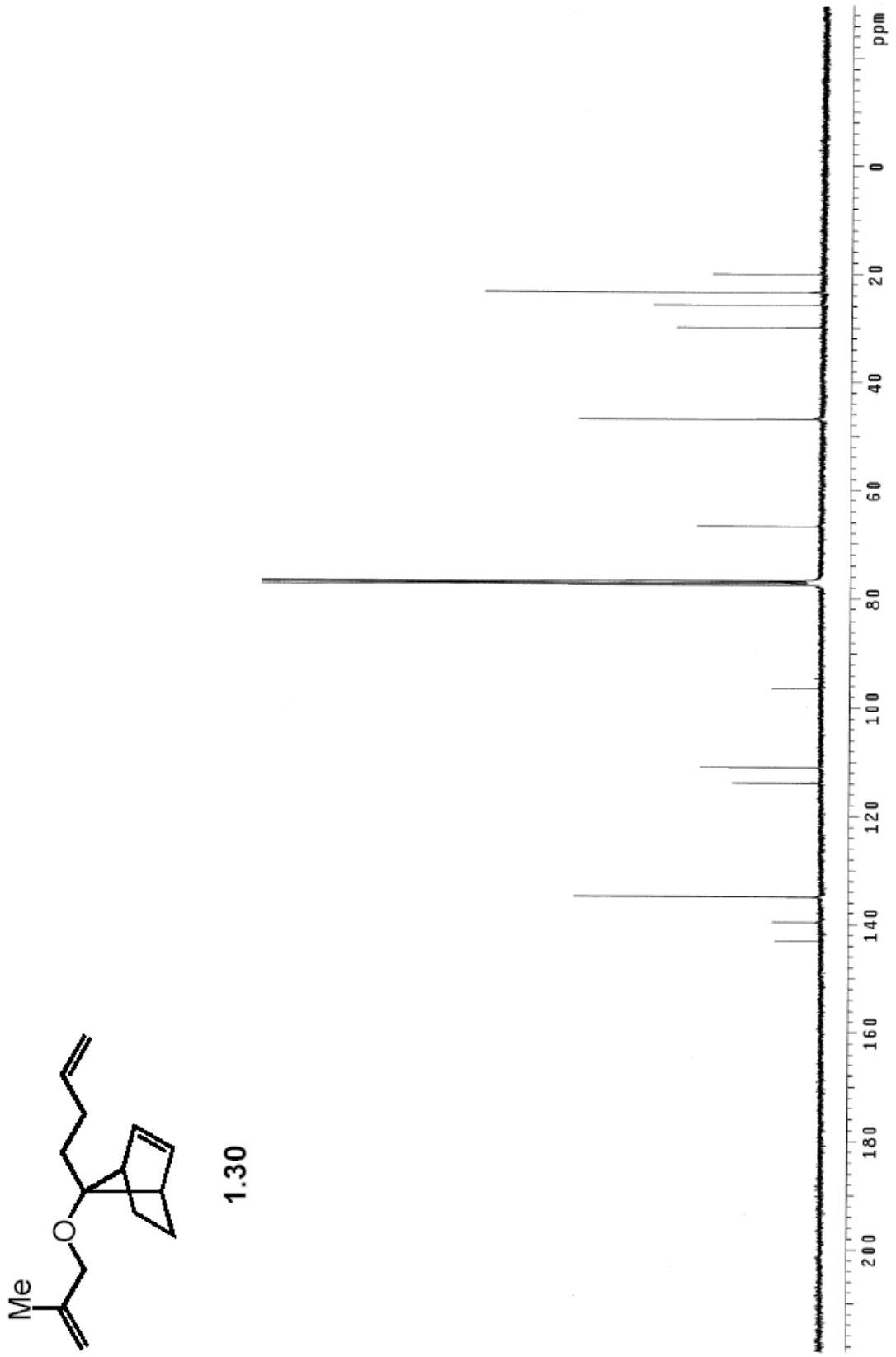
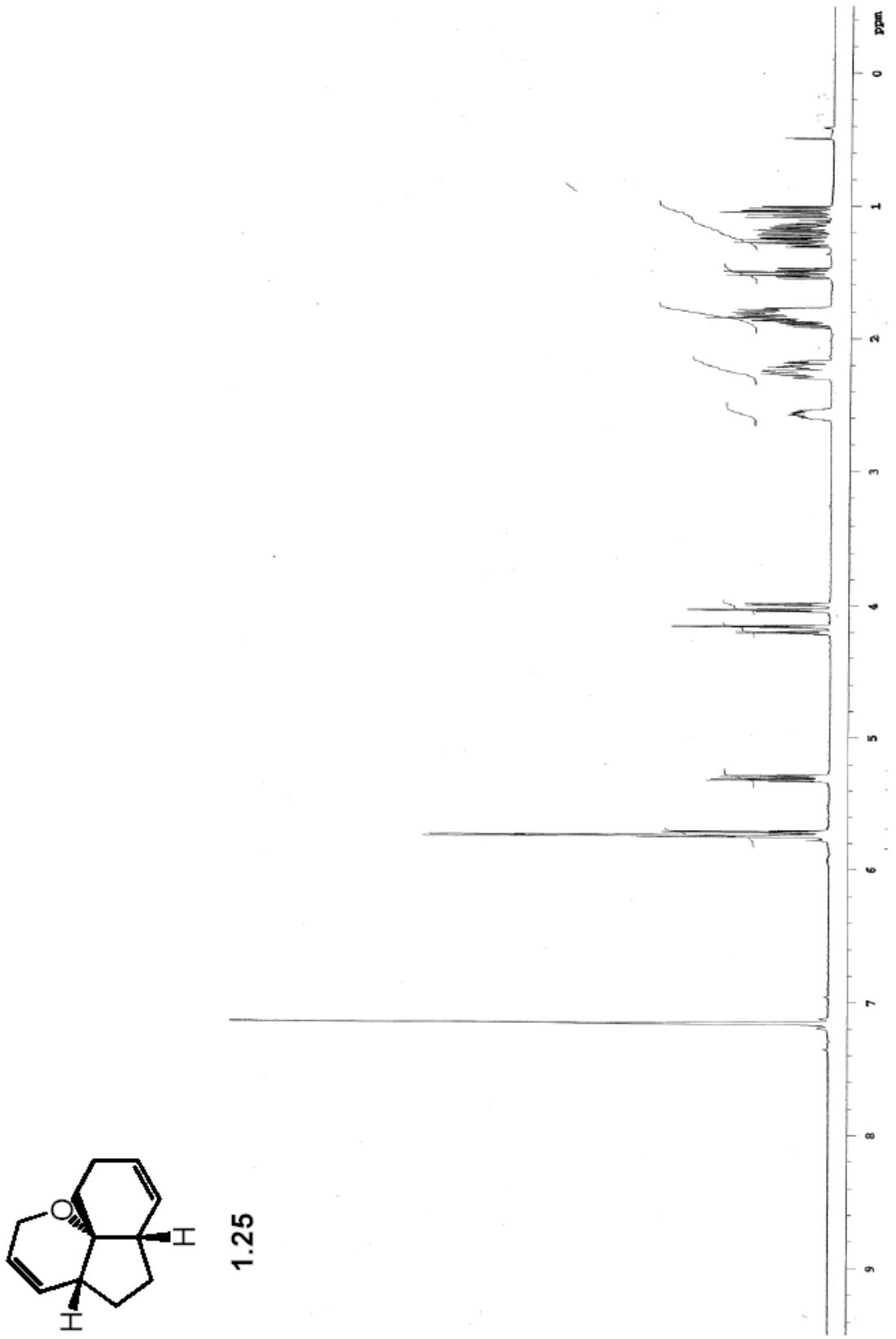


1.30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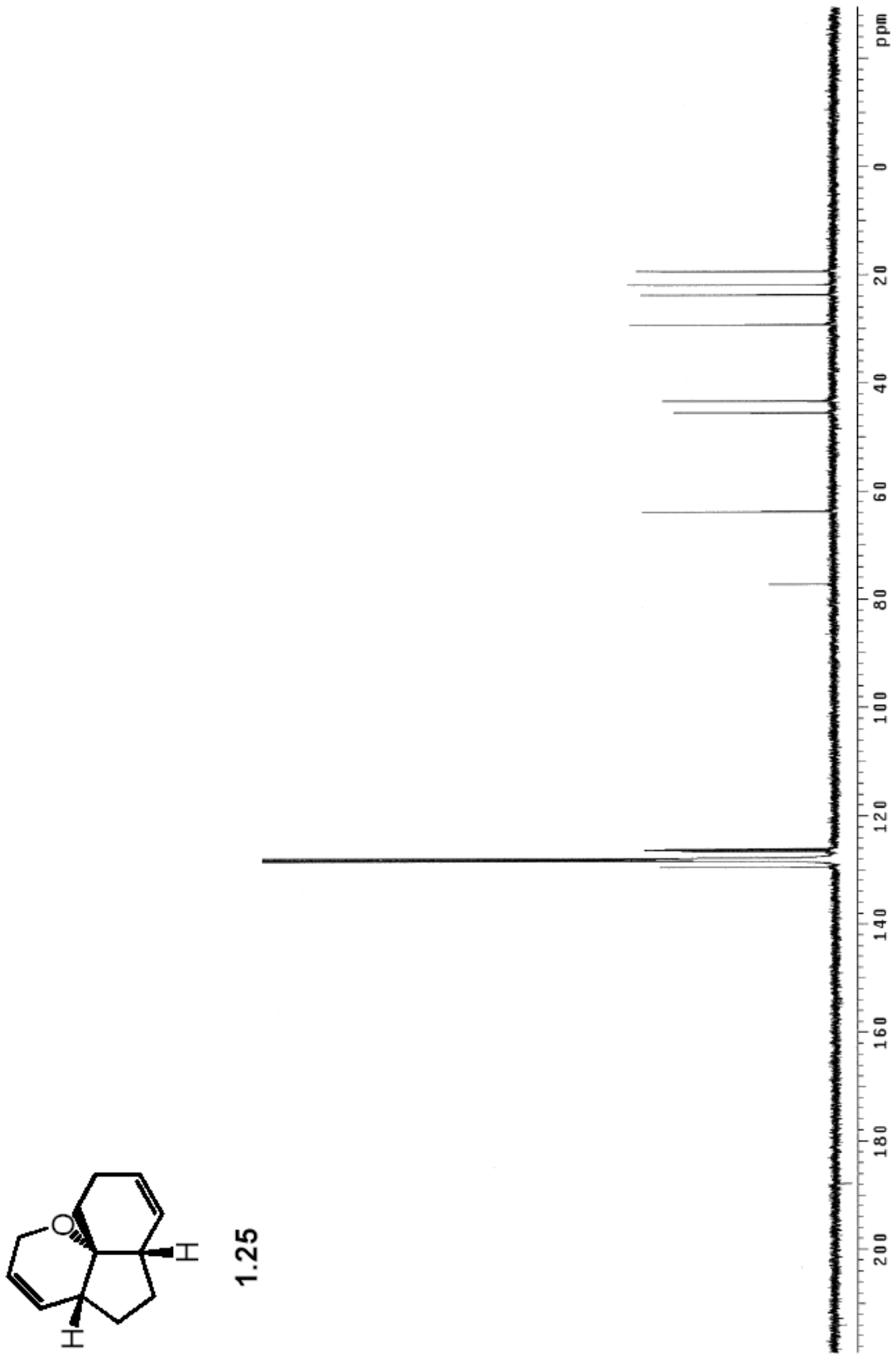

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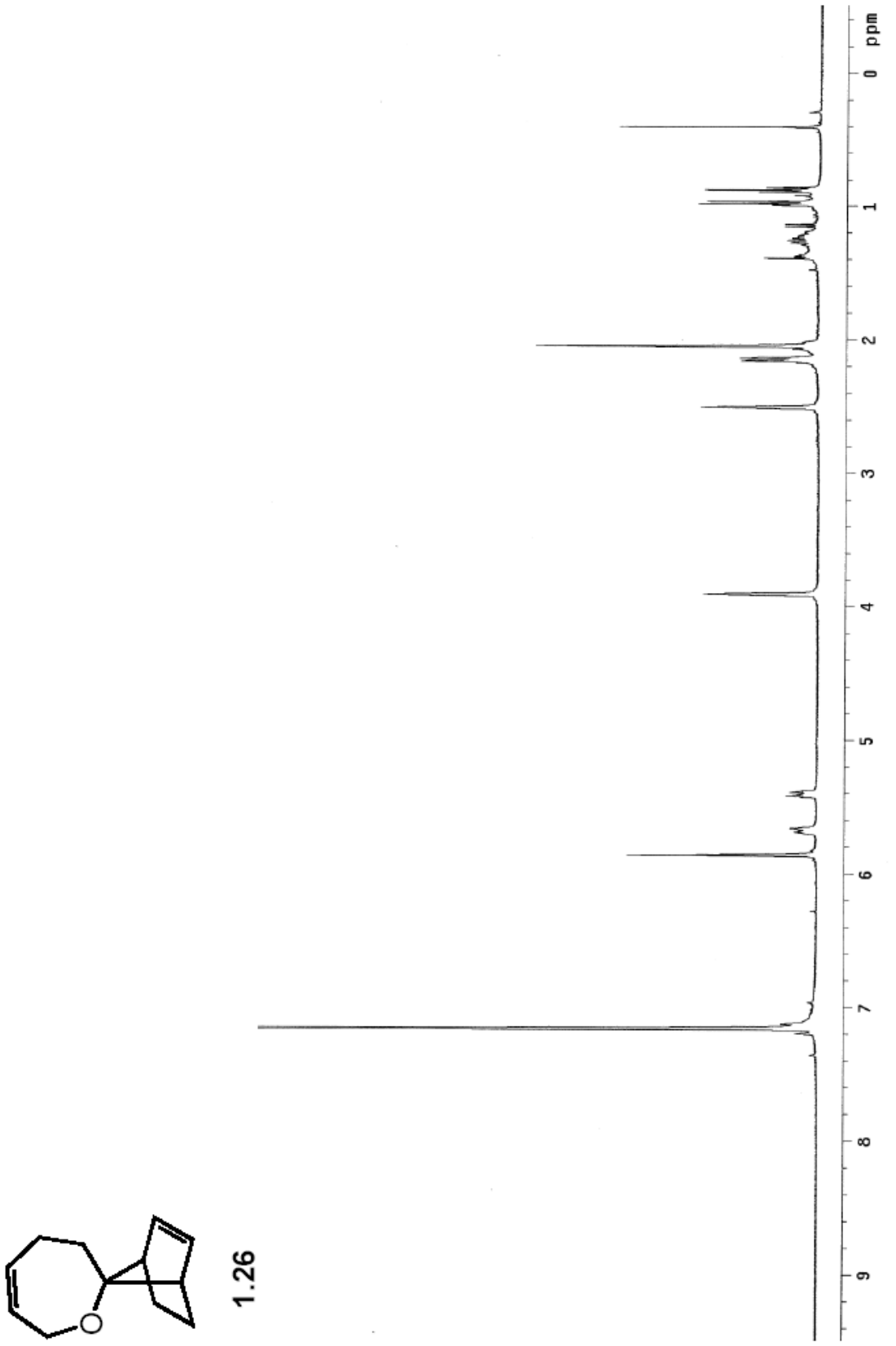
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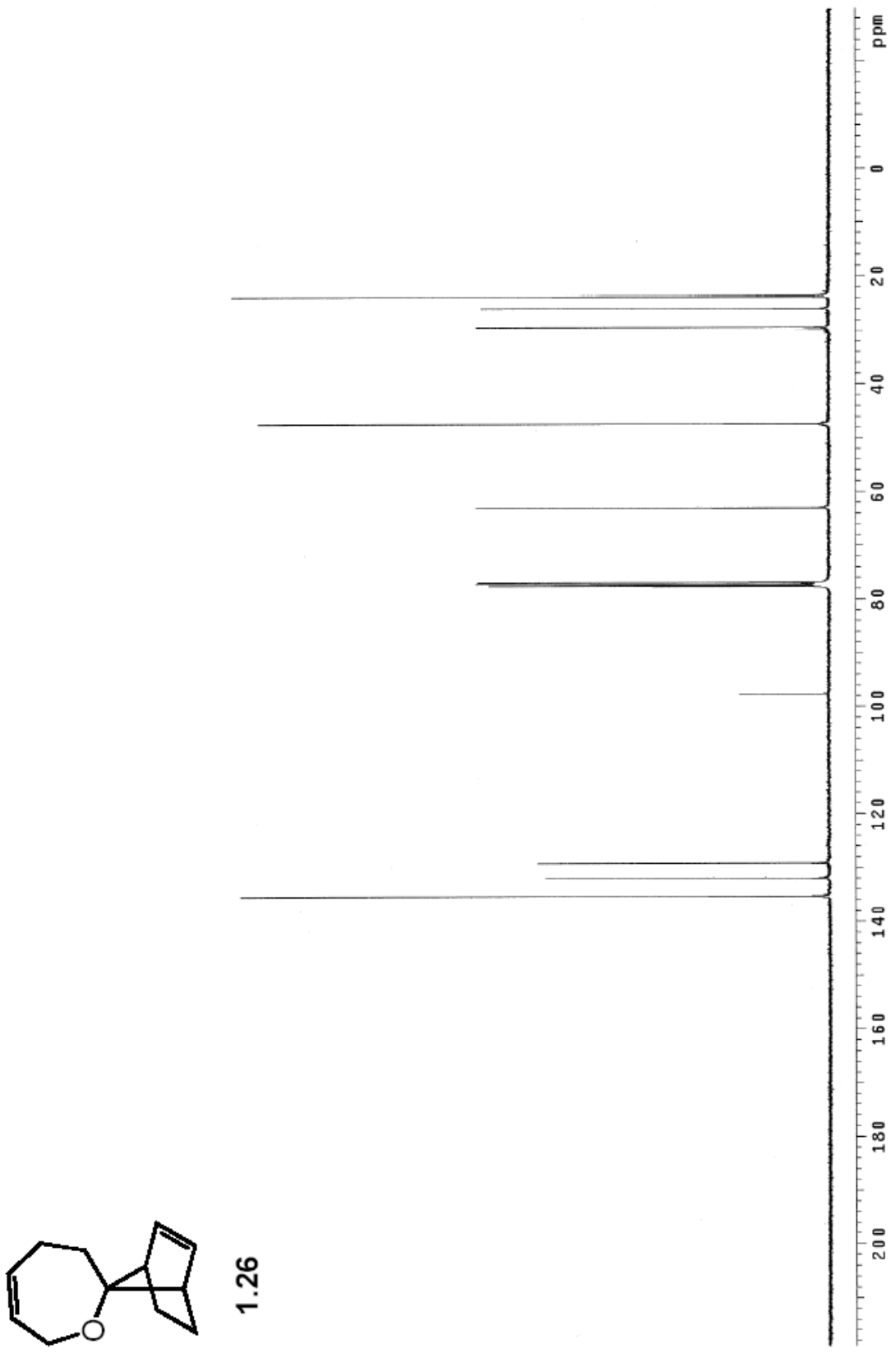

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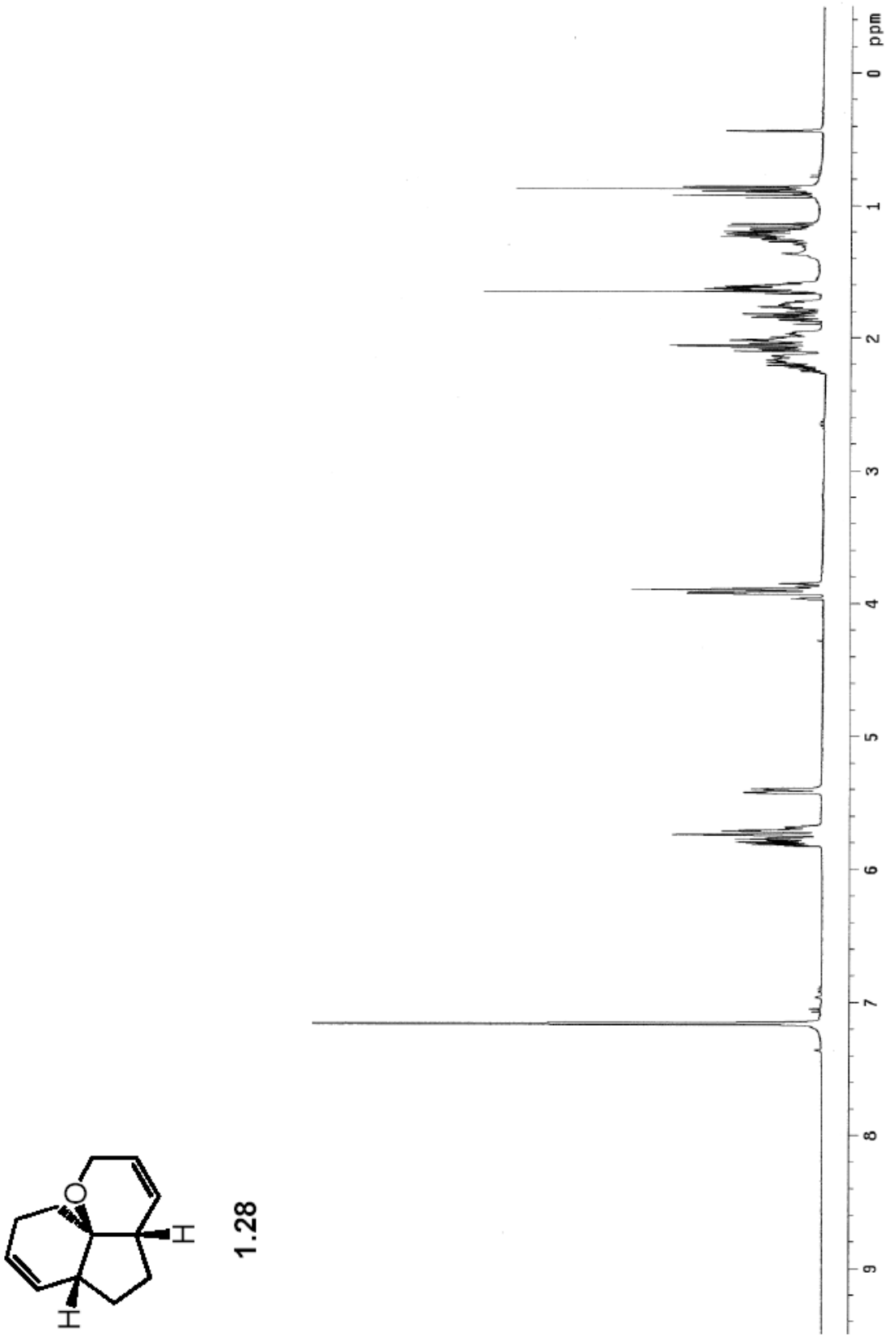
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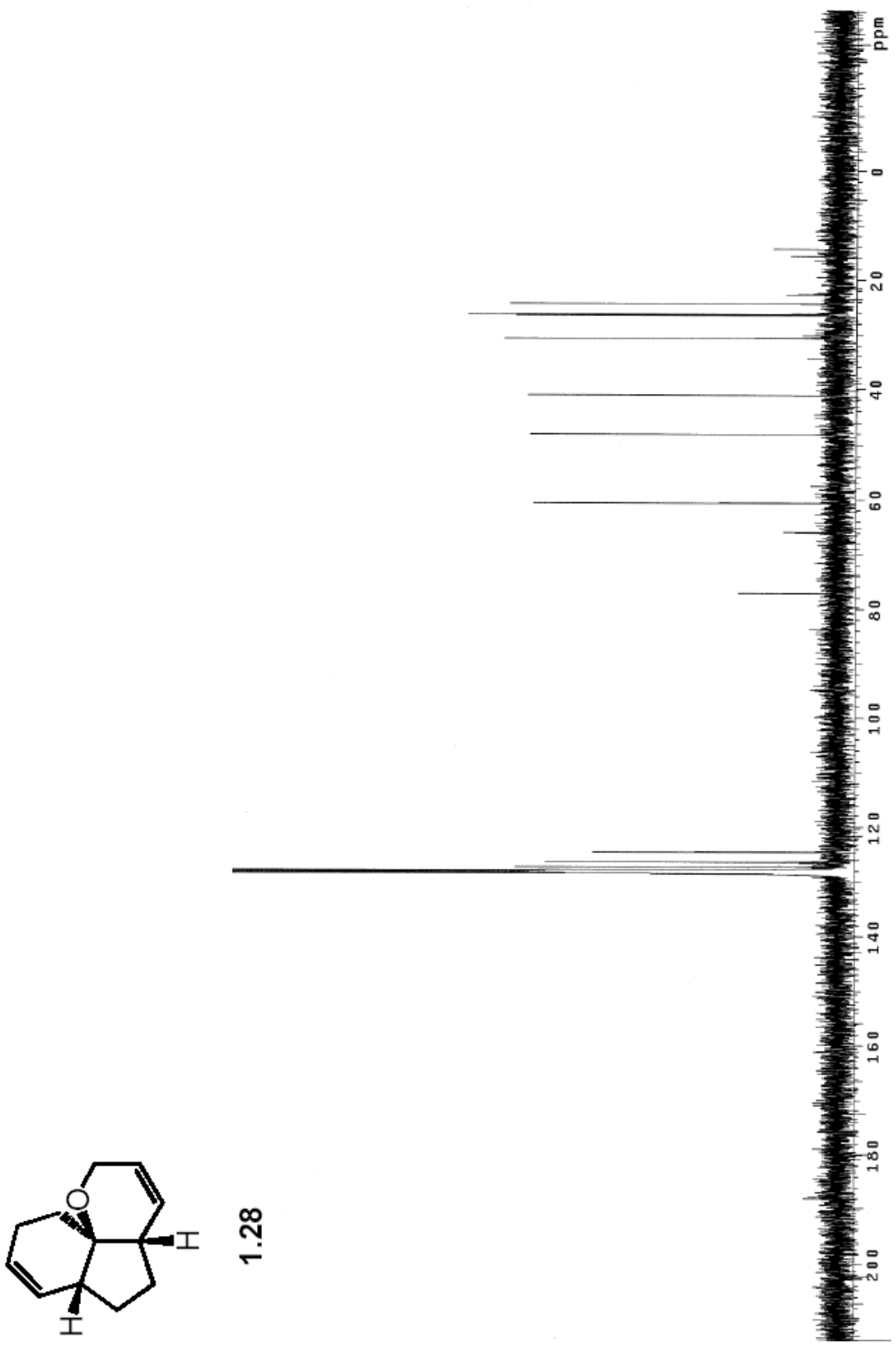
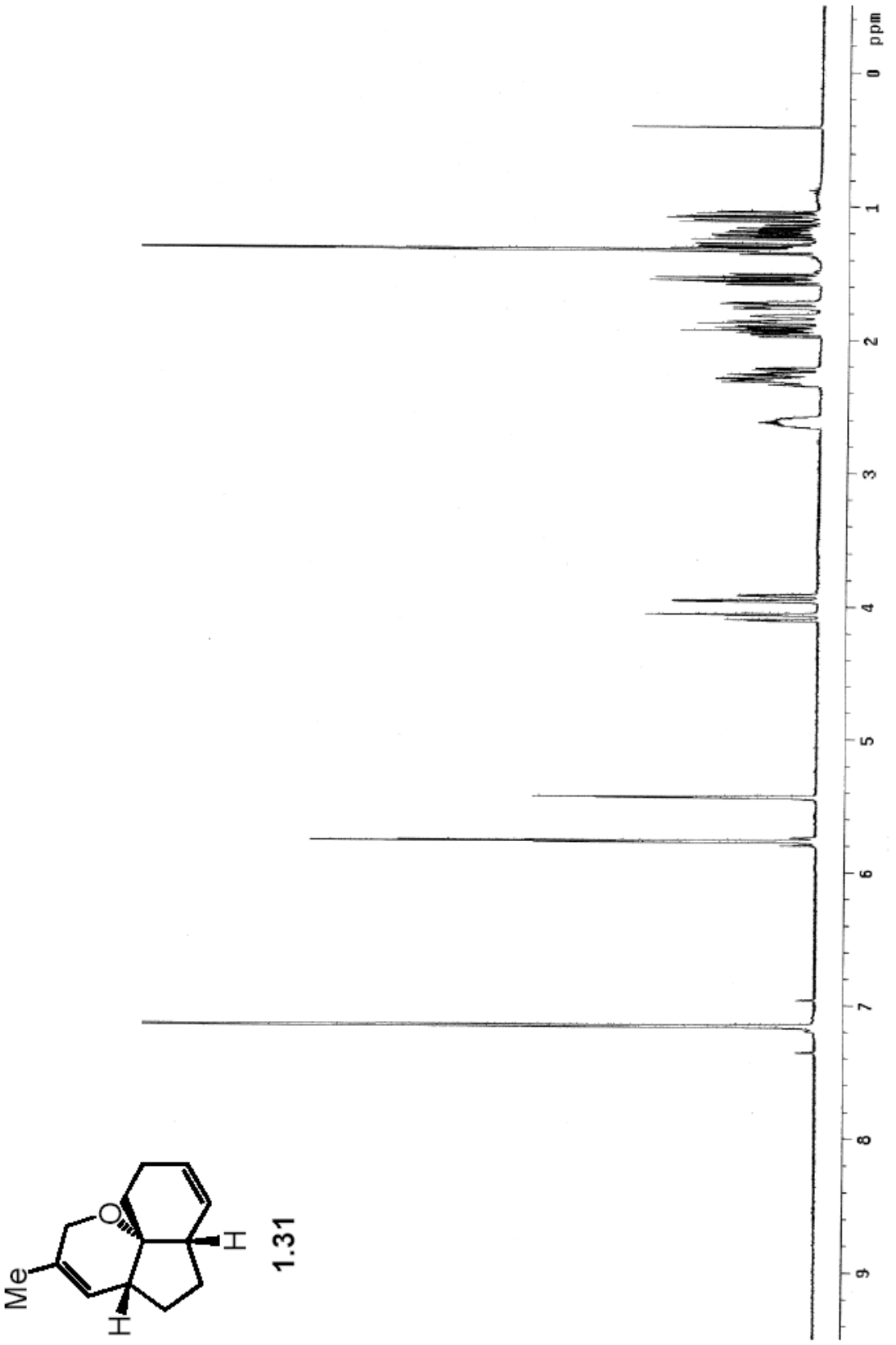


1.28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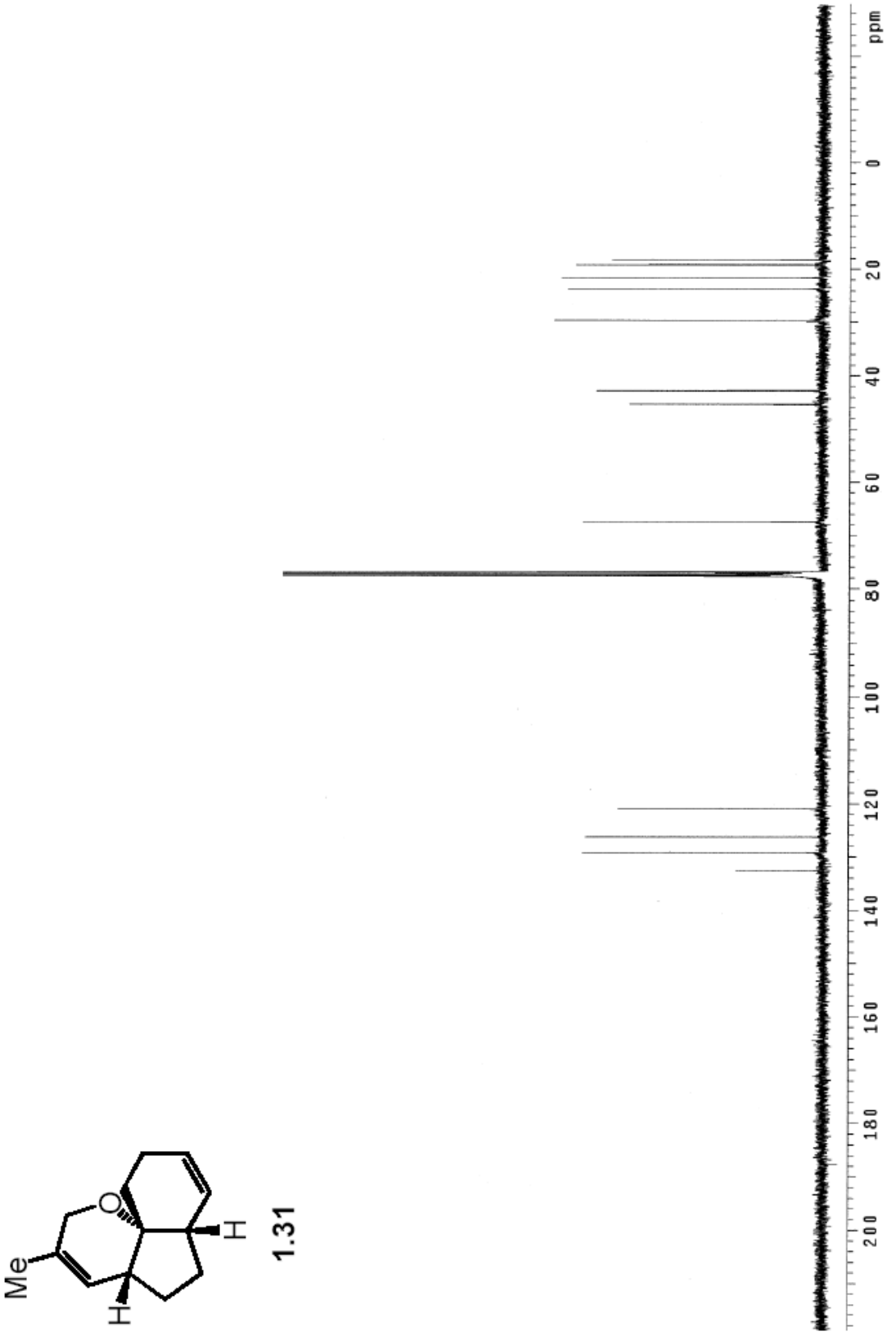
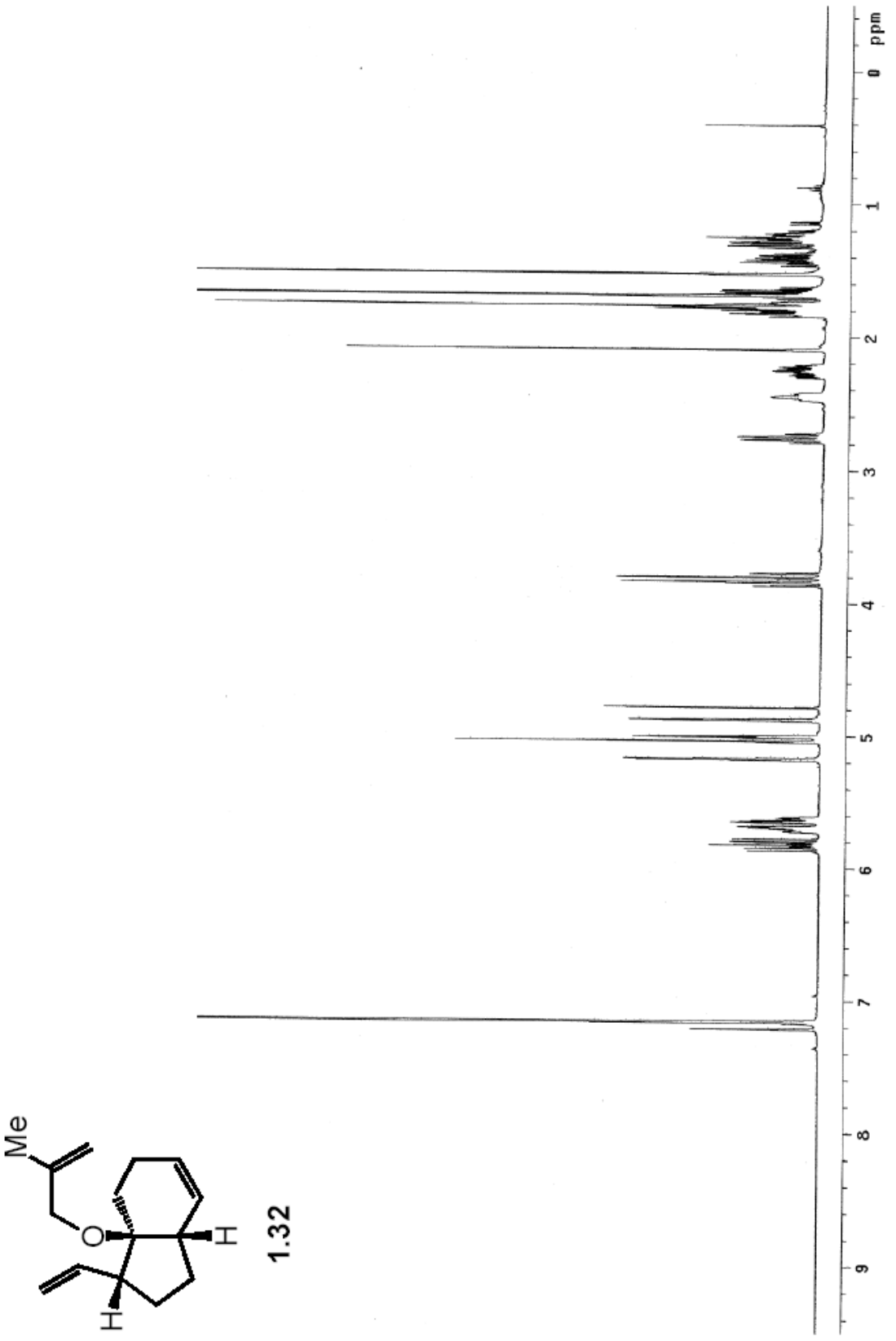


1.31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9

Chapter Two

MO-CATALYZED ENANTIOSELECTIVE SYNTHESIS OF *N*-CONTAINING HETEROCYCLES THROUGH ASYMMETRIC RING-CLOSING METATHESIS

2.1 Introduction

After being involved with a successful effort aimed at developing methods for the catalytic enantioselective synthesis of polycycles, I focused my attention to the development of methods for the catalytic enantioselective synthesis of heterocyclic amines.[29]

2.1a First Example of a Ring-Closing Metathesis of a Tertiary Amine Containing Substrate. Grubbs and Fu were the first to publish on the Mo-catalyzed ring-closing metathesis of tertiary amines and a representative example of this work is shown in eq. 2.1 (see below).[30] Treatment of tertiary amine **2.1** with 4 mol % achiral Mo complex **2.2** affords heterocycle **2.3** in 73% yield after 1 h. Importantly, Mo catalysts typically outperform Ru-based complexes in olefin metathesis reactions involving substrates with tertiary amine functional groups.[31]

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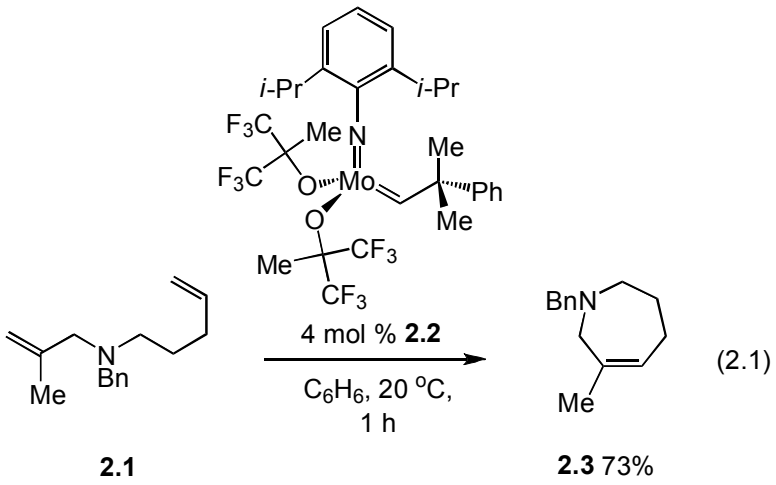
(29) (a) "Efficient Catalytic Enantioselective Synthesis of Unsaturated Amines: Preparation of Small- and Medium-Ring Cyclic Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis in the Absence of Solvent," Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991–6997. (b) "Enantioselective Synthesis of Cyclic Secondary Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis (ARCM)," Dolman, S. J.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2003**, *5*, 4899–4902.

(30) "Synthesis of Nitrogen Heterocycles via Catalytic Ring-Closing Metathesis of Dienes," Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.

(31) (a) "Catalytic Ring-Closing Metathesis of Functionalized Dienes by a Ruthenium Carbene Complex," Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857. (b) "Novel entry to the Ergot alkaloids via ring closing metathesis," Lee, K. L.; Goh, J. B.; Martin S. F. *Tetrahedron Lett.* **2001**, *42*, 1635–1638. (c) "An Efficient Approach to *Aspidosperma* Alkaloids via [4 + 2] Cycloadditions of Aminosiloxydienes: Stereocontrolled Total Synthesis of (±)-Tabersonine. Gram-Scale Catalytic Asymmetric Syntheses of (+)-Tabersonine and (+)-16-Methoxytabersonine. Asymmetric Syntheses of (+)-Aspidospermidine and (–)-Quebrachamine," Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.



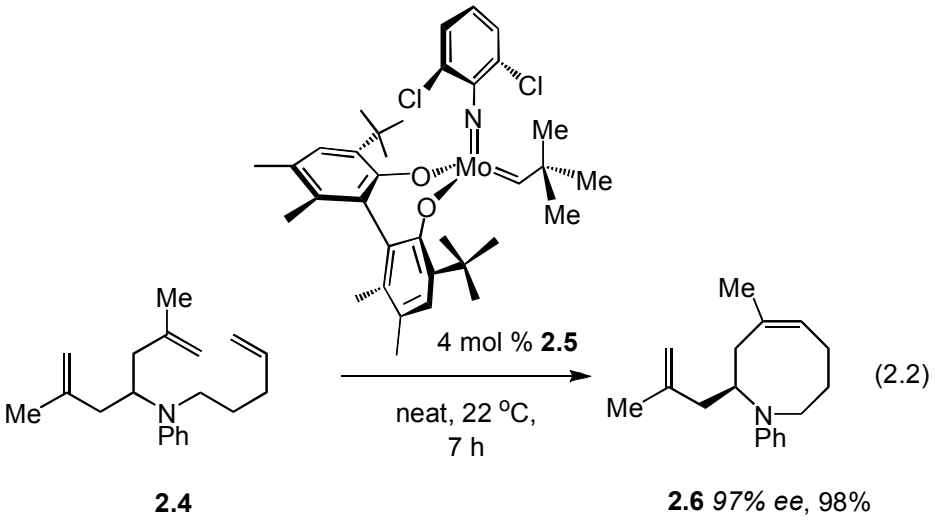
2.1 **2.3** 73%

Mo complexes for olefin metathesis exist at the highest possible oxidation state, that of VI, at the metal center. This makes Mo complexes highly Lewis acidic and sensitive to Lewis basic functional groups such as carbonyls and alcohols. Ru complexes, conversely, are in a low oxidation state at the metal center, that of $^{+}$II, and are tolerant of Lewis basic functionalities. A priori, it would be expected for Mo complexes to be sensitive to tertiary amines, which are a class of Lewis basic compounds; Ru complexes, in turn would be expected to be tolerant of such functional groups. Tertiary amines, however, serve as compatible ligands for and tend to inhibit the metathesis activity of Ru complexes. Nonbonding electrons on tertiary amines have a high electron density coefficient (high lying Highest Occupied Molecular Orbital-HOMO) and have a greater affinity toward the less electropositive Ru complexes (low lying Lowest Unoccupied Molecular Orbital-LUMO) than toward the more electropositive Mo complexes (high lying LUMO).[32] This discussion of functional group compatibility also serves to explain why compounds of high lying HOMOs (such as phosphines and *N*-heterocyclic carbenes) are good ligands for Ru complexes, whereas compounds of low lying HOMOs (such as alkoxides) are good ligands for Mo complexes. Based on the supposition that Mo complexes would be tolerant of tertiary amine functional groups, we initiated studies into the enantioselective synthesis of amine containing heterocycles.

2.1b Mo-catalyzed Asymmetric Ring-Closing Metathesis of Aniline Substrates. In collaboration with the Schrock group, we previously published on the first Mo-catalyzed enantioselective synthesis of amines. Initial efforts focused on the desymmetrization of aniline containing trienes and a representative example is shown in eq. 2.2 (see below).[33]

(32) For a discussion of HOMO-LUMO interactions, see: Fleming, I. in *Frontier Orbitals and Organic Chemical Reactions*, John Wile & Sons, Ltd. Chichester, England, **1976**; Edition 1 pp 34–84.
(33) "Efficient Catalytic Enantioselective Synthesis of Unsaturated Amines: Preparation of Small- and Medium-Ring Cyclic Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis in the Absence

Exposure of aniline **2.4** to 4 mol % of Mo complex **2.5** delivers azocine **2.6** in *97% ee* and 98% yield after 7 h.



(2.2)

2.4 **2.6** *97% ee*, 98%

One notable feature of this reaction is that the metathesis reaction can be performed in the absence of solvent; exclusion of solvent from metathesis reactions minimizes waste production. Additionally, an eight-membered ring heterocycle can be prepared in high optical purity; in ring-closing metathesis reactions it is typically more difficult to form rings of greater size than six atom units (see Ch1, 1.1 Introduction).

2.1c Mo-catalyzed Asymmetric Ring-Closing Metathesis of Secondary Aniline Substrates. The next set of studies in Mo-catalyzed enantioselective syntheses of *N*-containing heterocycles involved the desymmetrization of anilines such as **2.7**, illustrated in eq. 2.3 (see below).[34] These studies were aimed at determining whether a desymmetrization reaction could be performed to deliver an enantioenriched heterocycle that contains a fully substituted carbon stereocenter. Thus, treatment of aniline **2.7** with 2 mol % of Mo complex **2.8** furnishes azepine **2.9** in *93% ee* and 75% yield after 3 h. An attractive feature of this class of transformations is that the enantioenriched products would otherwise be difficult to access by other known catalytic enantioselective methods. Another aspect of this reaction worthy of mention is that the isolated product, aniline **2.9**, contains a free N-H moiety. Mo complexes, due to the high reactivity at the alkylidene carbon, are typically not tolerant of functional groups containing Brønsted acids such as alcohols and carboxylic acids. In the presence of Brønsted acid functional groups, Mo

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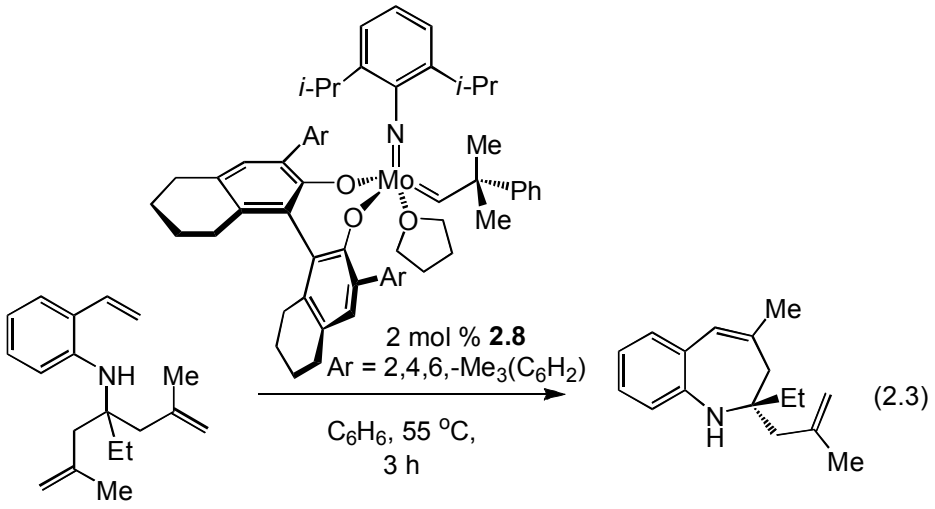
of Solvent," Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991–6997.

(34) "Enantioselective Synthesis of Cyclic Secondary Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis (ARCM)," Dolman, S. J.; Hoveyda, A. H.; Schrock, R. R. *Org. Lett.* **2003**, *5*, 4899–4902.

complexes decompose through protonation at the alkylidene carbon. These experiments demonstrated that chiral Mo complexes are more functional group tolerant than previously believed.



2.7 **2.9** *93% ee*, 75%

At this point in my graduate career I became involved in a group effort that included Elizabeth Sattely (then a graduate student) and David Moebius (then an undergraduate student), aimed at further developing Mo-catalyzed asymmetric ring-closing metathesis reactions amines. We sought to study the desymmetrization reaction of non-aryl amines. Previous work was able to furnish a variety of arylamine chiral compounds, however, the phenyl group is not typically considered a protecting group for nitrogen.[35] Within this context, we prepared and investigated the desymmetrization of protected amine trienes typified by **2.10** that would deliver enantioenriched cyclic amines such as **2.11** (eq. 2.4).

2.10
P = protecting group
R = alkyl

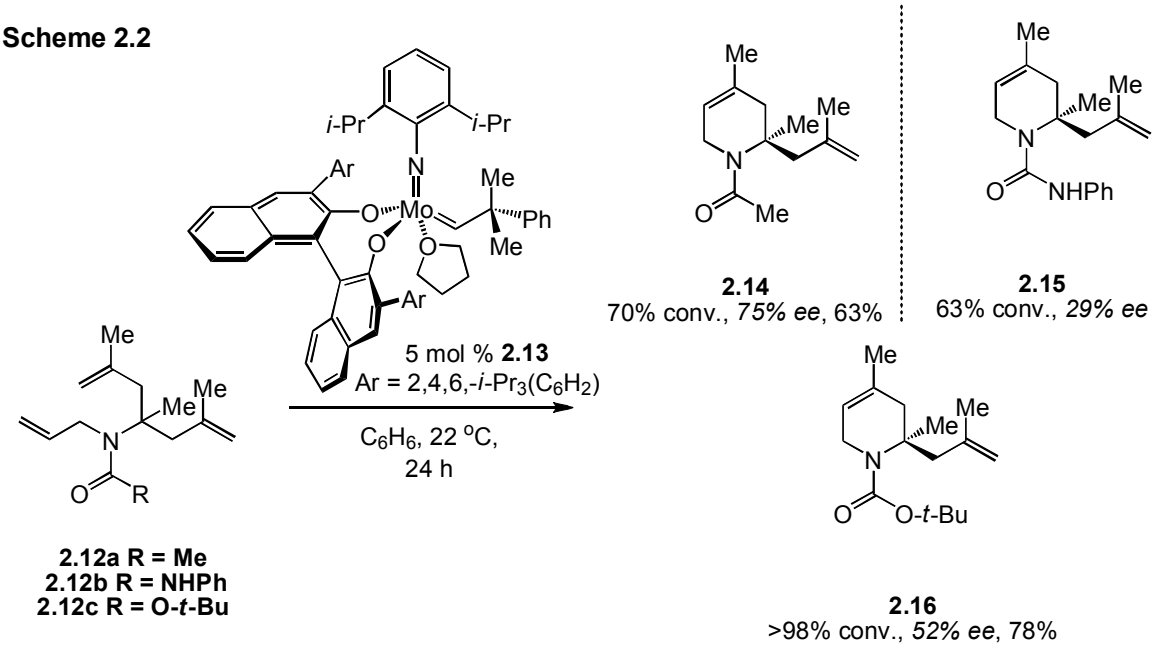
2.11

(35) Conversion of arylamines to the derived unprotected amines remains an inefficient procedure and few examples have been reported in the literature; for a representative example, see: "Bradsher Cycloaddition of 4-Alkoxyisoquinolinium Salts as a Route to a Fully Functionalized B Ring of the Angucycline Antibiotics," Nicolas, T. E.; Franck, R. W. *J. Org. Chem.* **1995**, 60, 6904–6911.

2.2 Asymmetric Ring-Closing Metathesis of Protected Amines

2.2a Catalytic Asymmetric Ring-Closing Metathesis of Protected Amines. Our first goal was to study the desymmetrization reactions of differentially protected amines **2.12a-c** (Scheme 2.2, see below).[36] Our decision to study these protecting groups was twofold: (1) The acetate (**2.12a**), *tert*-butyl carbamate (**2.12b**), and urea (**2.12c**) groups would have orthogonal deprotection reaction conditions for the derived cyclic products. (2) The choice of protecting groups would provide insight into the functional group tolerance of chiral Mo complexes.

Scheme 2.2

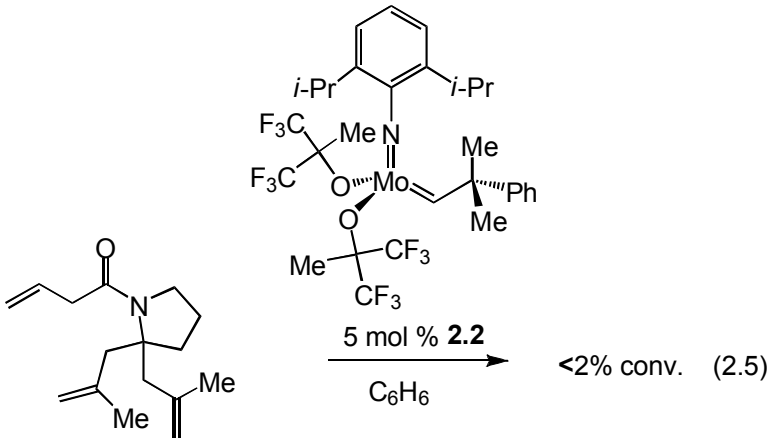


To this end, we found Mo complex **2.13** to be the optimal catalyst in the conversion of trienes **2.12a-c** to heterocycles **2.14**, **2.15**, and **2.16**. We were gratified to find that a single catalyst was compatible with all three protecting groups; this allowed us to directly compare the outcome of all three catalytic reactions. Treatment of amines **2.12a-c** with 5 mol % of Mo complex **2.13** delivers enantioenriched heterocycles **2.14** (70% conversion, *75% ee* and 63% yield),[37] **2.15** (63% conversion and *29% ee*), and **2.16** (>98% conversion, *52% ee* and 78% yield) after 24 h. As the data in Scheme 2.2 illustrates, reactions to form acetate-protected heterocycle **2.14** and urea-protected heterocycle **2.15** proceed with comparable conversion to product (70% conversion and 63% conversion, respectively). The reaction to form *tert*-butyl carbamate-protected

(36) For the preparation of all metathesis substrates and metathesis substrate precursors please see the Experimental section 2.6.

(37) The % conversion represents formation of product from consumption of substrate as monitored by ^{1}H NMR of the unpurified reaction mixture. Undesired byproducts were typically not observed in these reactions. This holds true for all remaining conversions given in this thesis, unless otherwise mentioned.

heterocycle **2.16**, however, proceeds to >98% conversion of desired product. This difference in conversion to product could be attributed to the *tert*-butyl carbamate serving as a better protecting group for nitrogen (in comparison to the acetate and urea groups) since it is sterically bulkier. Furthermore, the carbonyl oxygens of the amide and urea protecting groups are more nucleophilic, than the *tert*-butyl carbamate protecting group, likely favoring chelation to the metal center and decreasing catalyst activity.



2.17

2.2b Evidence for Mo Complex Sequestration and Metathesis Deactivation. Evidence for catalyst sequestration and deactivation comes from our observation of a chelated Mo alkylidene intermediate. During the course of our studies we found that in the presence of Mo complexes, the metathesis of amide-containing triene **2.17** did not proceed to appreciable levels of conversion to desired product (eq. 2.5). Even in the presence of achiral Mo complex **2.2**, which is typically more reactive than chiral Mo complexes, < 2% of the desired product was formed. To garner insight into this lack of reactivity, we monitored this metathesis reaction by ^{1}H NMR and observed formation of a new triplet (J = 4.7 Hz) at δ 11.97 ppm, corresponding to the chelated alkylidene intermediate shown in Figure 2.1. This notion of catalyst deactivation by chelation is also supported by the observation that ring-closing metathesis reactions of carbonyl containing substrates require longer reaction times than reactions with substrates lacking carbonyl moieties; reactions in Scheme 2.2 require 24 h, whereas reactions in eq. 2.2 and eq. 2.3 require 7 h and 3 h, respectively (see above).

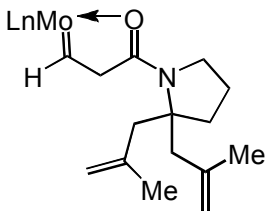


Figure 2.1 Observation of Chelated Alkylidene

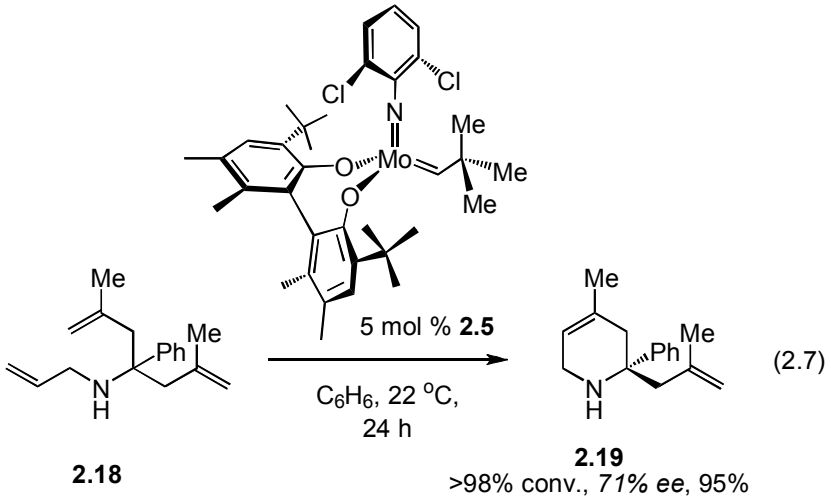
2.3 Asymmetric Ring-Closing Metathesis of Unprotected Secondary Amines

2.3a Studies of Sterically Encumbered Amine Metathesis Substrate. The next phase of our studies involved the enantioselective synthesis of amines that would contain alkyl substituents other than a methyl group at the nascent stereogenic center to be formed. When we prepared secondary amine **2.18**, however, we encountered difficulties in protecting the nitrogen group (eq. 2.6, see below).[38] Placing a phenyl group in place of a methyl group caused significant steric congestion adjacent to the nitrogen and impeded our attempts at protection of the amine. Based on this consideration, we decided to investigate the enantioselective synthesis of heterocycle **2.19**; the idea was that the nitrogen would possibly be to sterically hindered to diminish the activity of Mo complexes.

(2.6)

2.18 **2.19**

2.3b Enantioselective Synthesis of an Unprotected Amine Heterocycle. Screening of available chiral Mo complexes revealed Mo complex **2.5** to be the optimal catalyst for the desymmetrization of amine **2.18** (eq. 2.7). To this result, exposure of amine **2.18** to 5 mol % of Mo complex **2.5** delivers enantioenriched heterocycle **2.19** in *71% ee* and 95% yield after 24 h. In addition, the reaction proceeds to >98% conversion of desired product. Encouraged by the efficient and selective synthesis of **2.19**, we pursued the desymmetrization of related sterically hindered unprotected secondary amines.



(2.7)

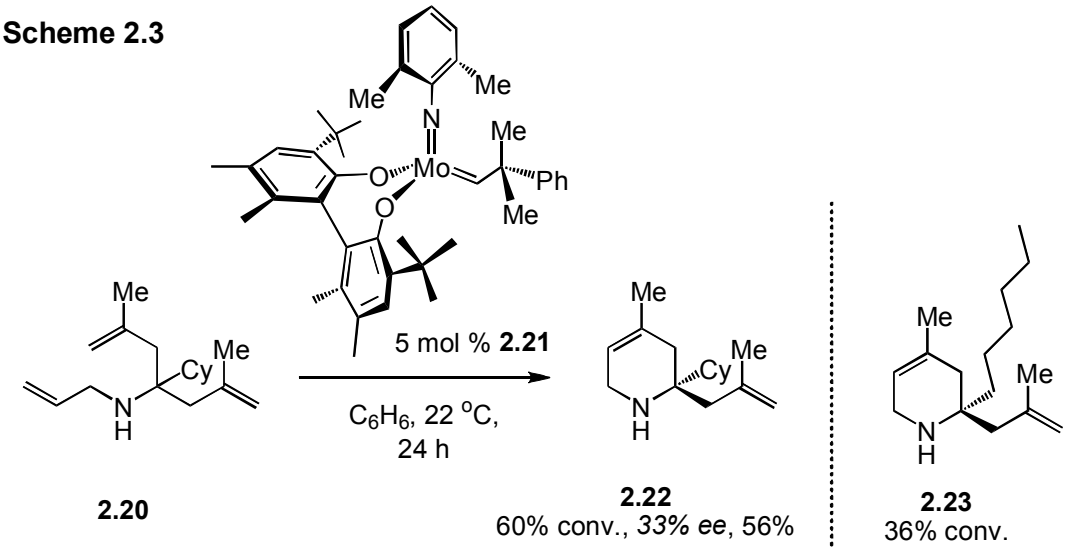
2.18

2.19
>98% conv., *71% ee*, 95%

(38) For the synthesis of **2.18**, see the Experimental section 2.6.

As shown in Scheme 2.3 (see below), the next substrate under study was unprotected secondary amine **2.20**, which contained a cyclohexyl group at the carbon adjacent to the amine (vs. phenyl in amine **2.18**, eq. 2.7). Exposure of amine **2.20** to 5 mol % of Mo complex **2.21** affords heterocycle **2.22** in *33% ee* and 56% yield after 24 h. Interestingly, this reaction only proceeds to 60% conversion of desired product. In studying the enantioselective synthesis of related heterocyle **2.23**, where we replaced the cyclohexyl group with a hexyl group, the reaction proceeds to only 36% conversion to desired product. Unfortunately, we were unable to determine the enantioselectivity of **2.23**.[39] The asymmetric metathesis to form **2.22** is less selective than the reaction to form **2.19**, pointing to the influence of substitution at the stereogenic center on catalyst enantioinduction.

Scheme 2.3



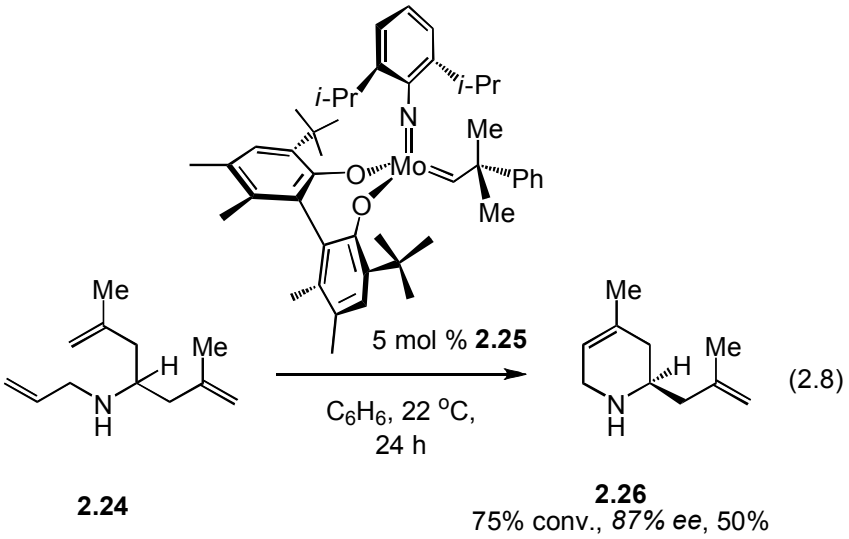
2.20

2.22
60% conv., *33% ee*, 56%

2.23
36% conv.

2.3c Influence of Substrate Substitution on Enantioselectivity. As discussed, in changing a phenyl to a cyclohexyl group, at the stereogenic center in heterocyclic products (**2.19** in eq. 2.7 to **2.22** in Scheme 2.3), we observed decrease in the enantioselectivities of these products, begging the question "would a smaller substitution at the stereogenic center, such as a proton, lead to product formation in even lower enantioselectivity?" To address this question we studied the desymmetrization of secondary amine **2.24** (eq. 2.8, see below). Treatment of amine **2.24** with 5 mol % of Mo complex **2.25** delivers enantioenriched heterocycle **2.26** in *87% ee* and 50% yield after 24 h; the reaction proceeds to 75% conversion of desired product. This result contradicted our initial hypothesis about the mechanistic details of this class of catalytic reactions.

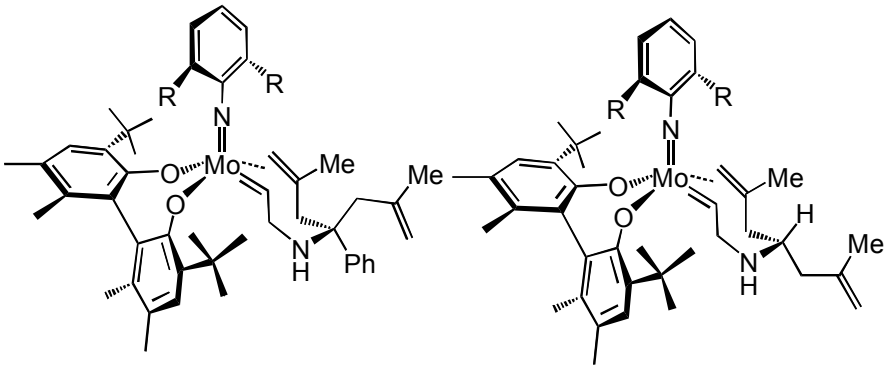
(39) Attempts were made to separate enantiomers by chiral GC and HPLC. The enantiomers of amide and carbamate derivatives of **2.23** also did not separate by the above methods.



2.24

2.26
75% conv., *87% ee*, 50%

2.3d Proposed Transition State Model for Asymmetric Ring-Closing Metathesis. From an initial analysis, it appears that no correlation can be made between the substitution pattern at the stereogenic center and enantioinduction. If a direct steric effect influences enantioinduction, we would expect **2.26** to form in lower enantioselectivity (vs. **2.19** in eq. 2.7 and **2.22** in Scheme 2.3, see above). After closer consideration, we devised a preliminary transition state model, shown in Figure 2.2, which serves to explain the enantioselectivities observed. It should be mentioned that further data is required to further support this model. Presumably, the Mo pre-catalyst initiates at the terminal olefin of the substrate molecule and then adopts a twist-chair conformation being either **2.27** or **2.28**, depending on the substitution at the stereogenic center (shown in Figure 2.2, see below). This would be followed by coordination to one of the pendant enantiotopic olefins prior to metallacyclobutane formation. If the catalyst coordinates with the olefin illustrated by intermediate **2.27**, the remaining alkyl-olefin containing side chain would occupy a psuedo-axial orientation and the phenyl group a pseudo-equatorial orientation. This would be highly preferred since a large size difference exists between the olefin side chain and the phenyl group. Relating this analysis to intermediate **2.28**, where the

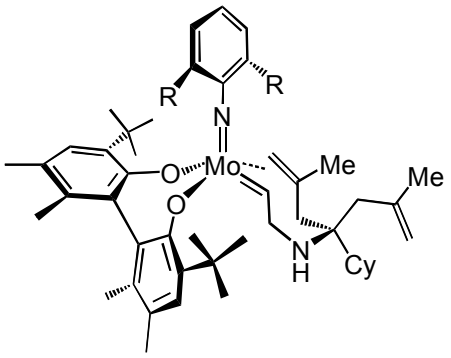


2.27 **2.28**

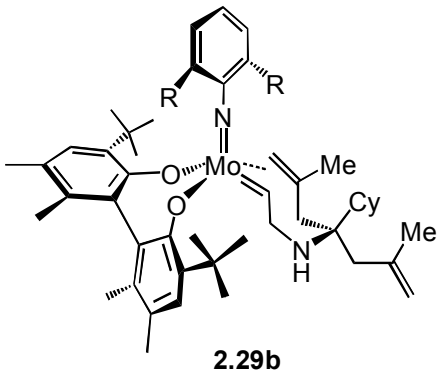
Figure 2.2 Proposed Transition State Model

stereogenic center would contain a proton instead of a phenyl group, it is likely that the olefin side chain occupies a pseudo-equatorial orientation. Intermediates **2.27** and **2.28** thus lead to products of appreciable enantioselectivity, *71% ee* and *87% ee*, respectively.

If the stereogenic center contains an alkyl group of similar size to the alkyl-olefin containing side chain, the difference in energy between the two possible enantiotopic transition states would be minimal and the product would likely form in low enantioselectivity; this is observed when the stereogenic center contains a cycohexyl group. As illustrated in Figure 2.3, the transition state energy of the diastereomeric transition states **2.29a** and **2.29b** would be close in value and the product would thus form in low enantioselectivity, as we do observe (*33% ee*). The difference in size between substituents at the stereogenic carbon and alkyl-olefin side chain can be reasoned by comparing "Winstein-Holness" A-values.[40] If we take the A-value of the olefin-containing side chain to be close to that of an ethyl group (1.75 kcal/mol) and compare it to the A-value of a cyclohexyl group (2.15 kcal/mol) we see a difference of only ~0.40 kcal/mol. If we compare the difference in A-value energy between the olefin-containing side chain with that of a phenyl group (3.0 kcal/mol) we see a difference of 1.25 kcal/mol. Moreover, the difference in energy between the olefin-containing side chain and a proton is ~2.15 kcal/mol. Thus, as is observed, the product containing a proton at the stereogenic carbon (**2.26** *87%ee*, eq. 2.8) is formed with greater enantioenrichment than the product containing a phenyl (**2.19** *71% ee*, eq. 2.7), followed by the product containing the lowest A-value difference in the transition state, cyclohexyl (**2.22** *33% ee*, Scheme 2.3).



2.29a



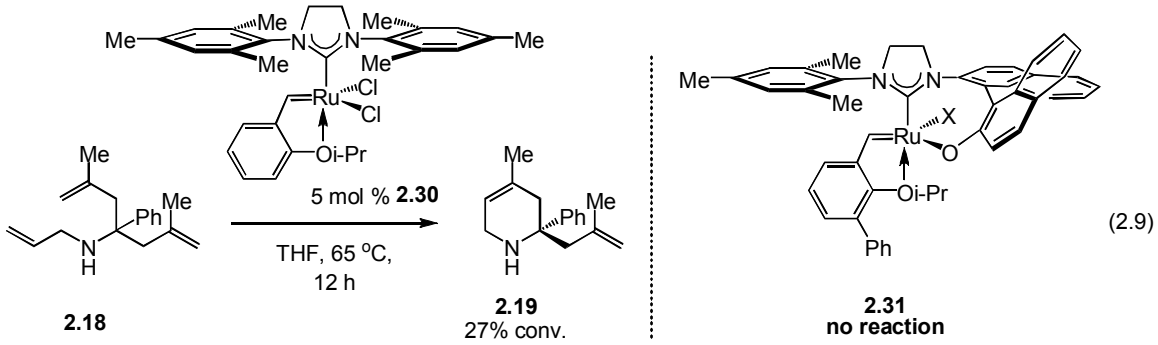
2.29b

Figure 2.3 Proposed Transition State Model

(40) Hirsch, J. A. *Top. in Stereochem.* **1967**, *1*, 199–222.

2.4 Reactivity of Ru Complexes With Amine-Containing Substrates

2.4a Comparison of Ru Complexes for Asymmetric Ring-Closing Metathesis. Before concluding this chapter, it is important to emphasize the advantage of utilizing Mo complexes over Ru-based counterparts for this class of olefin metathesis transformations; the results in eq. 2.9 are illustrative. Treatment of amine **2.18** with 5 mol % of achiral Ru catalyst **2.30** in THF, and monitoring the reaction by thin layer chromatography after 5 h reveals that the desired product **2.19** does not form. Heating the reaction mixture to 65 ^{o}C, quenching the reaction after 12 h, does not promote formation of desired product. Analysis of the crude reaction mixture by ^{1}H NMR analysis reveals that the reaction proceeds to only 27% conversion of desired product, whereas reaction with chiral Mo complex **2.5** proceeds to >98% conversion (compare with eq. 2.7, see above). Reaction of amine **2.18** with chiral Ru complex **2.31** is even less efficient, with isolation of starting amine **2.18** in >98% yield.



2.18

2.19
27% conv.

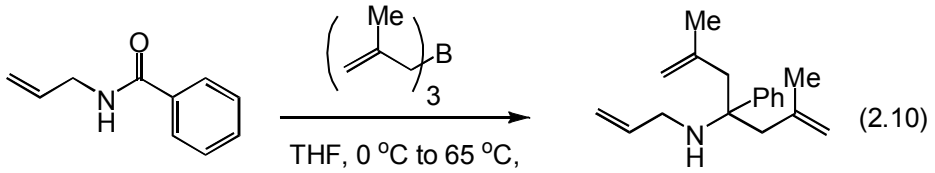
2.31
no reaction

(2.9)

2.5 Conclusions

These investigations discussed in this chapter resulted in the development of methods for the Mo-catalyzed enantioselective synthesis of heterocyclic amine compounds. These studies revealed that Mo complexes are sensitive to the substituents on nitrogen in olefin metathesis substrates with regards to efficiency and selectivity. Importantly, we were able to show for the first time that Mo complexes are tolerant of sterically hindered secondary amine substrates. These studies further demonstrated that Mo complexes are preferred for the olefin metathesis of amine containing substrates, over Ru-based counterparts.

2.6 Experimental Section[41]

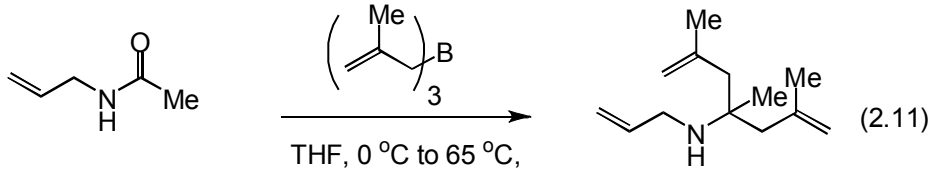


2.32 **2.18** 37% (2.10)

Synthesis of unprotected secondary amine **2.18.** Amide **2.32** was prepared according to previously published literature procedures.[42] The trimethallyl borane reagent was prepared (85% yield, 44 mmol) and purified according to a previously reported procedure used for the synthesis of triallyl borane; herein we employed BF_3OEt_2, methallyl chloride, and Mg turnings in Et_2O.[43] Amine **2.18** was prepared through a slight modification of a previously reported reductive bisalkylation of lactams as shown in eq. 2.10.[44] A 15-mL round-bottom flask was charged with amide **2.32** (513 mg, 3.18 mmol), THF (1.00 mL), and the reaction vessel was cooled to 0 °C in an ice-bath. To this solution was added dropwise trimethyallyl borane (0.800 mL, 3.18 mmol), after which time the cooling was removed and the reaction mixture was allowed to warm to ambient temperature. At this time, the reaction vessel was fitted with a reflux condenser and the reaction mixture set to reflux at 65 °C. After allowing the reaction mixture to stir for 12 h, the heating bath was removed and the mixture was allowed to cool to ambient temperature. At this time, MeOH (3 mL) was added to the mixture and it was set to reflux a further 1 h, after which time the heating bath was removed and the resulting mixture was allowed to reach ambient temperature. At this point, a 5 M aqueous solution of NaOH (3 mL) was added to the mixture and allowed to stir for 30 min., after which time layers were separated, and the aqueous layer was washed with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (20 mL), dried (Na_2CO_3), filtered, and the volatiles removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (CH_2Cl_2) to give **2.18** as yellow oil (0.300 g, 1.17 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.43 (m, 2H), 7.32–7.37 (m, 2H), 7.21–7.16 (m, 1H), 5.97 (tdd, *J* = 16.0, 10.0, 5.6 Hz, 1H), 5.25 (ddd, *J* = 17.2, 2.0, 1.6 Hz, 1H), 5.08

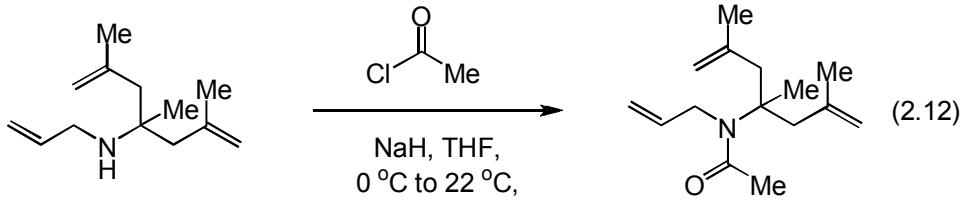
(41) For the spectral traces of compounds **2.12a**, **2.24**, **2.26**, and **2.14** please see: Dissertation of Dr. Elizabeth Sattely.
(42) "Synthesis of Cyclopropylpyrrolidines via Reaction of *N*-Allyl-*N*-propargylamides with a Molybdenum Carbene Complex. Effect of Substituents and Reaction Conditions," Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268–2272.
(43) "Organoboranes. 44. A convenient, highly efficient synthesis of triorganylboranes via a modified organometallic route," Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1986**, *51*, 427–432.
(44) "A Convenient Synthesis of 2,2-Diallylated Nitrogen Heterocycles by Allylboration of Lactams," Bubnov, Y. N.; Pastukhov, F. V.; Yampolsky, I. V.; Ignatenko, A. V. *Eur. J. Org. Chem.* **2000**, 1503–1505.

(ddd, J = 10.4, 1.6, 1.2 Hz, 1H), 4.77 (td, J = 4.0, 1.6 Hz, 2H), 4.61 (s, 2H), 3.20 (td, J = 5.6, 1.2 Hz, 2H), 2.66 (d, J = 14.0 Hz, 2H), 2.52 (d, J = 14.0 Hz, 1H), 1.57 (s, 1H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 142.6, 137.4, 128.0, 127.0, 126.3, 115.2, 114.7, 61.1, 46.2, 45.1, 24.9.



2.33 **2.34** 47%

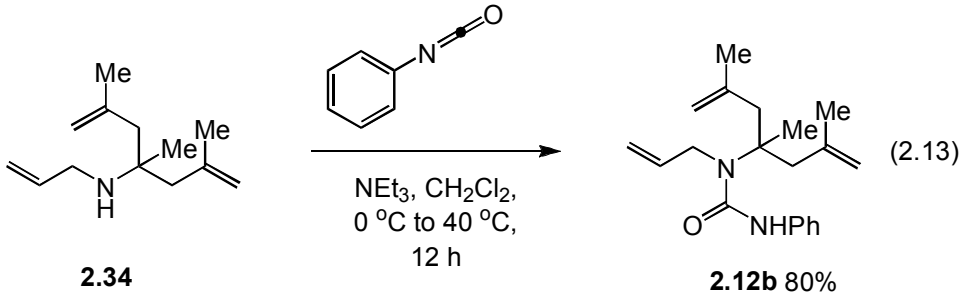
Synthesis of **2.34**, the amine precursor to protected secondary amines **2.12a-c.** Amine **2.34** was prepared in 47% yield by the same procedure used to synthesize amine **2.18** (eq. 2.10), however, allyl acetamide **2.33** was employed as the starting material for the reductive bisalkylation, shown in eq. 2.11. Protected amines **2.12a-c** were prepared from secondary amine **2.34**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (dddd, J = 11.6, 10.4, 5.6, 5.6 Hz, 1H), 5.17 (ddd, J = 17.2, 3.6, 1.6 Hz, 1H), 5.04 (ddd, J = 10.0, 2.8, 1.2 Hz, 1H), 4.97 (ddd, J = 4.0, 3.2, 1.6 Hz, 2H), 4.70–4.68 (m, 2H), 3.21 (ddd, J = 5.6, 1.2, 1.2 Hz, 2H), 2.16 (dd, J = 13.6, 13.6 Hz, 2H), 1.83 (s, 6H), 1.07 (s, 3H).



2.34 **2.12a** 44%

Synthesis of amide **2.12a**. To a stirring solution of NaH (168 mg, 7.00 mmol) in 70 mL THF in a 100-mL round-bottom flask was added **2.34** (1.35 g, 7.00 mmol) by cannula transfer with a total of 10 mL THF. After allowing this mixture to stir for 1 h,the reaction vessel was cooled to 0 °C in an ice-bath. At this time, to this mixture was added acetylchloride (495 μL, 7.00 mmol) dropwise by syringe. The resulting mixture was allowed to stir for 12 h, at which point the reaction was quenched by the addition of H_2O, (50 mL), and the resulting biphasic layers were separated. The aqueous layer was washed with Et_2O (3 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting yellow residue was purified by silica gel chromatography (20:1 CH_2Cl_2:Et^2O) to give **2.12a** as colorless oil (725 mg, 3.08 mmol). IR (neat): 3087 (w), 2980 (m), 1671 (s), 1470 (m), 1401 (s), 1212 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddt, J = 17.2, 11.0, 5.5 Hz, 1H), 5.19–5.12 (m, 2H), 4.87 (dq, J = 2.5, 1.1 Hz, 2H), 4.68–4.67 (m, 2H), 3.83 (dt, J = 5.5, 1.8 Hz, 2H), 3.34 (d,

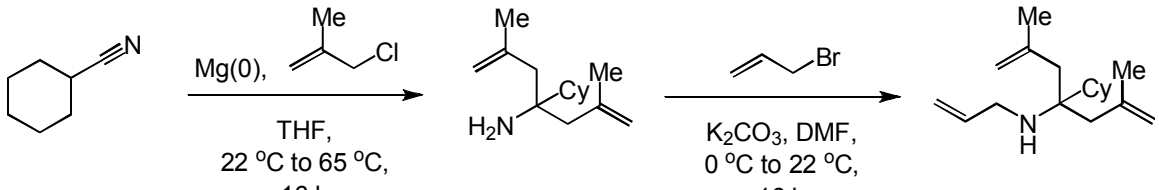
J = 13.2 Hz, 2H), 2.17 (d, *J* = 13.2 Hz, 2H), 2.07 (s, 3H), 1.73 (s, 6H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 143.0, 136.2, 116.3, 115.4, 63.3, 49.8, 45.8, 25.5, 25.0, 24.6. HRMS ES (*m/z*) Calcd for $C_{15}H_{25}NO$ 236.2014 $(M+H)^+$, Found 236.2011.



2.34 **2.12b** 80%

Synthesis of amide **2.12b**. A 25-mL round-bottom flask was charged with amine 2.34 (50.0 mg, 0.259 mmol), triethyl amine (36.0 μL, 0.259 mmol), CH_2Cl_2 (2.6 mL), and the reaction vessel was cooled to 0 °C in an ice-bath. To this solution was added phenyl isocyanate (28.0 μL, 0.259 mmol) by syringe, after which time the ice-bath was removed and the reaction mixture was allowed to reach ambient temperature. At this time, the reaction vessel was fitted with a reflux condenser and the reaction mixture set to reflux at 40 °C. After allowing the reaction mixture to stir for 12 h, the heating bath was removed and the mixture was allowed to cool to ambient temperature. At this time, CH_2Cl_2 (5 mL) followed by a saturated aqueous solution of NH_4Cl (5 mL) was added to the reaction mixture. The resulting biphasic layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The yellow residue was purified by silica gel chromatography (50:1 CH_2Cl_2:NEt_3) to give **2.12b** as yellow oil (65.0 mg, 0.208 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.25 (m, 4H), 7.02–6.98 (m, 1H), 5.94 (dddd, *J* = 17.2, 10.0, 5.2, 5.2 Hz, 1H), 5.45 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.34 (ddd, *J* = 10.4, 1.6, 1.6 Hz, 1H), 4.92 (ddd, *J* = 4.4, 3.2, 1.6 Hz, 2H), 4.76–4.75 (m, 2H), 3.91 (ddd, *J* = 4.0, 2.0, 2.0 Hz, 2H), 3.40 (d, J = 12.8 Hz, 2H), 2.18 (d, *J* = 12.8 Hz, 2H), 1.81 (s, 6H), 1.38 (s, 3H).

Scheme 2.4



2.35 **2.36** 82% **2.20** 65%

Synthesis of metathesis substrate **2.20**. Metathesis substrate **2.20** was prepared through a slight modification of a known literature procedure, illustrated in Scheme 2.4.[45] A 500-mL three-neck round-bottom flask, fitted with an addition funnel and reflux condenser, was charged with cyclohexanecarbonitrile **2.35** (3.30 mL, 27.5 mmol), magnesiu turnings (2.50 g, 103 mmol), and THF (200 mL). Methallyl chloride (6.80 mL, 68.7 mmol) and THF (68 mL) was slowly added to this solution by addition funnel, whilst heating the reaction vessel with a heat gun. After circa 10 mL of the methallyl chloride solution was added the mixture became olive green in color, signifying initiation of the reaction.[46] At this moment, the reaction vessel was no longer heated with a heat gun and the remaining methallyl chloride solution was slowly added over a period of 1 h, at which point the reaction mixture was set to reflux at 65 ^{o}C. After 16 h, the heating bath was removed, the mixture was allowed to reach ambient temperature and then cooled to 0 ^{o}C in an ice-bath. At this point, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (100 mL) and the resulting biphasic layers were separated. The organic layer was concentrated in vacuo to remove the majority of THF. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL), dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (20:1 CH_2Cl_2:MeOH) to give primary amine **2.36** as yellow oil (5.00 g, 22.6 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (dd, *J* = 2.4, 1.2 Hz, 2H), 4.72 (dd, *J* = 2.4, 1.2 Hz, 2H), 2.20 (d, *J* = 13.2 Hz, 2H), 2.05 (d, *J* = 13.2 Hz, 2H), 1.81 (s, 6H), 1.79–1.6 (m, 2H), 1.40–1.00 (m, 9H). A 50-mL round-bottom flask was charged with amine **2.36** (0.50 g, 2.3 mmol), potassium carbonate (0.31 g, 2.3 mmol), DMF (13 mL), allyl bromide (0.20 mL, 2.3 mmol), and the resulting solution was allowed to stir for 16 h. At this time, the reaction mixture was diluted with Et_2O (50 mL), washed with H_2O (6 x 25 mL), dried ($MgSO_4$), filtered and the volatiles removed in vacuo. The resulting brown residue was purified by silica gel chromatography (20:1 CH_2Cl_2:MeOH) to give secondary amine **2.20** as yellow oil (0.40 g, 1.5 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (tdd, *J* = 18.0, 11.6, 6.0 Hz, 1H), 5.21 (ddd, *J* = 17.2, 3.6, 2.0 Hz, 1H), 5.16 (ddd, *J* = 17.2, 3.6, 2.0 Hz, 1H), 5.04 (dd, *J* = 3.6, 2.0 Hz, 1H), 5.01 (dd, *J* = 3.6, 2.0 Hz, 1H), 4.85 (dd, *J* = 2.4, 1.2 Hz, 2H), 4.75 (dd, *J* = 2.4, 1.2 Hz, 2H), 3.22 (m, 2H), 2.16 (s, 3H), 1.86 (s, 3H), 1.82–1.09 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 137.7, 114.6, 114.5, 60.6, 45.9, 42.9, 27.6, 27.5, 27.0, 25.5.

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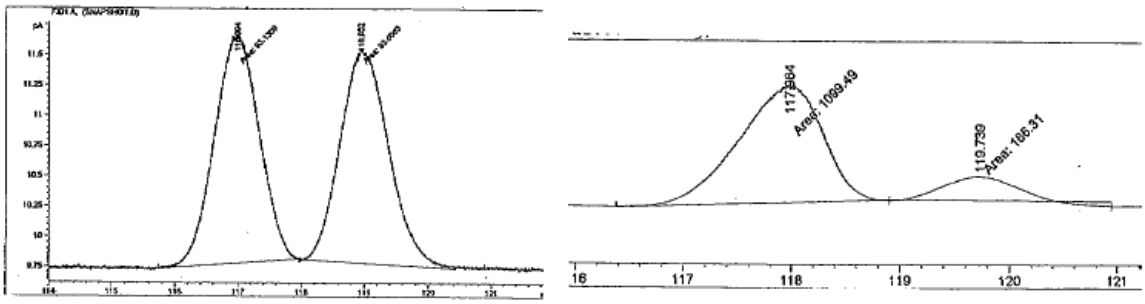
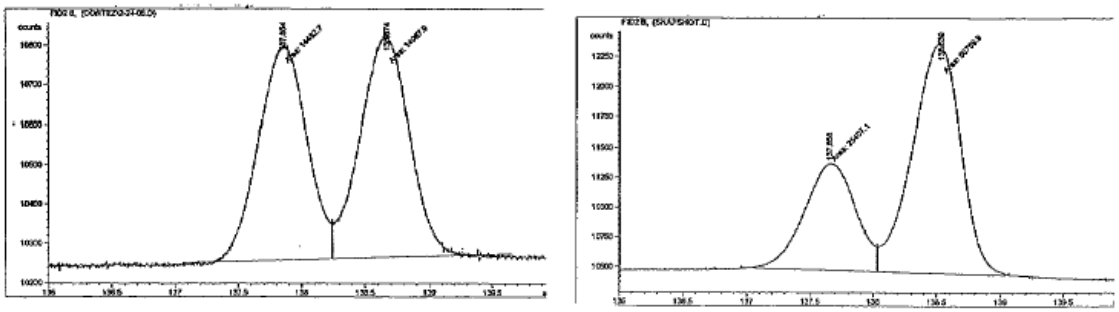
(45) "Tertiary Alkyl Primary Amines, RR'R//CNH2. II," Henze, H. R.; Allen, B. B.; Leslie, W. B. *J. Am. Chem. Soc.* **1943**, *65*, 87–89.
(46) Caution should be taken as the reaction is highly exothermic at this point.

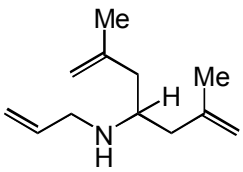
Representative procedure for tandem Mo-catalyzed Asymmetric Ring-Closing Metathesis; synthesis of amine 2.19. In a N_2-filled glovebox, a 4-mL vial was charged with triene **2.18** (20.0 mg, 0.0783 mmol) and C_6H_6 (783 μL). To this solution was added **2.5** (3.2 mg, .0039 mmol) and the vial was fitted with a teflon lined cap. The reaction mixture was allowed to stir at 22 °C for 24 h, after which time the vial was removed from the glovebox and the volatiles were removed in vacuo. The resulting brown residue was purified by silica gel chromatography (50:1 MeOH:CH_2Cl_2) (20.6 mg, 0.0744 mmol, 95%). IR (neat): 3383 (br), 2961 (m), 2917 (s), 2848 (m), 2369 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 4H), 7.23–7.18 (m, 1H), 5.30 (s, 1H), 4.77 (s, 1H), 4.60 (s, 1H), 3.29 (d, *J* = 20.0 Hz, 1H), 3.03 (d, *J* = 20.0 Hz, 1H), 2.55–2.24 (m, 4H), 1.75 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 146.0, 142.8, 131.4, 128.4, 127.3, 126.8, 121.5, 115.2, 57.5, 51.9, 42.6, 39.2, 24.9, 24.0. HRMS ES (*m/z*) Calcd for $C_{16}H_{21}N$ 228.1752 $(M+H)^+$, Found 228.1747. Enantiomeric excess was determined by GLC analysis of the derived acetamide. Acetyl-protected **2.19-Ac**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.14 (m, 5H), 5.60 (s, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 4.20–3.56 (m, 3H), 2.84 (t, *J* = 12.0 Hz, 2H), 2.18 (d, *J* = 16.0 Hz, 1H), 2.03 (s, 3H), 1.63 (s, 3H), 1.54 (s, 3H). The optical purity of **2.19-Ac** was determined by GC analysis in comparison with authentic racemic material, shown below: β-dex chiral column, 130 °C, 15 psi, for a sample of *71% ee*.



Synthesis of amine **2.22**. General procedure for ARCM was followed. Silica gel chromatography (1:1 Et_2O:hexanes) was used for purification of **2.22**, which was isolated as yellow oil (0.076 mmol, 56%). IR (neat): 2924 (m), 2855 (m), 1734 (w), 1639 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 3.30 (dd, *J* = 41.6, 16.8 Hz, 2H), 2.32–1.98 (m, 4H), 1.84 (s, 3H), 1.66 (s, 3H), 1.48–0.87 (m, 11H). ^{13}C NMR (100 MHz, C_6D_6): δ 131.3, 127.9, 120.0, 114.6, 42.8, 42.0, 40.7, 36.1, 27.5, 27.4, 27.3, 27.2, 25.5, 24.1. HRMS ES (*m/z*) Calcd for $C_{16}H_{27}N$ 234.2222 $(M+H)^+$, Found 234.2224. Enantiomeric excess was determined by GLC analysis of the derived acetamide. Acetyl-protected **2.22-Ac**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 1H), 4.73 (s, 1H), 4.65 (s, 1H), 3.82–3.00 (m, 2H), 3.52–3.46 (m, 1H), 2.75–2.65 (m, 1H), 2.20–2.10 (m, 1H), 2.10 (s, 3H), 2.10–2.00 (m, 1H), 1.78 (s, 3H), 1.62 (s, 3H), 1.45–0.82

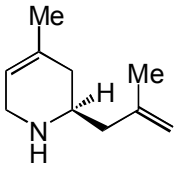
(m, 11H). The optical purity of **2.22-Ac** was determined by GC analysis in comparison with authentic racemic material, shown below: α-dex chiral column, 130 °C, 15 psi, for a sample of *33% ee*.





2.24

Synthesis of amine **2.24**. A reductive alkylation of allylformamide[47] with trimethallylborane was performed according to the procedure for the synthesis of **2.34** (see eq. 2.11). Silica gel chromatography (4:1 CH_2Cl_2:hexanes washed with 1% v/v concentrated NH_4OH) was used for purification of **2.24**, which was isolated as yellow oil (8.5 mmol, 71%). The amine can be further purified by Kugelrohr distillation under vacuum to give colorless oil. IR (neat): 3087 (m), 2980 (m), 2936 (s), 1652 (m), 1457 (m), 1381 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (dddd, *J* = 16.8, 10.3, 6.2, 6.2 Hz, 1H), 5.15 (ddd, *J* = 17.2, 3.3, 1.5 Hz, 1H), 5.08 (d(br), *J* = 10.3 Hz, 1H), 4.81 (s(br), 2H), 4.75 (s(br), 2H), 3.26 (d, *J* = 5.9 Hz, 2H), 2.82 (dddd, *J* = 6.6, 6.6, 6.6, 6.6 Hz, 1H), 2.15 (dd, *J* = 13.9, 7.3 Hz, 2H), 2.07 (dd, *J* = 13.9, 6.2 Hz, 2H), 1.72 (s, 6H), 1.28 (s(br), 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 137.2, 116.0, 113.1, 52.0, 50.1, 43.4, 22.6. HRMS ES (*m/z*) Calcd for $C_{12}H_{21}N$ 180.1752 $(M+H)^+$, Found 180.1751.

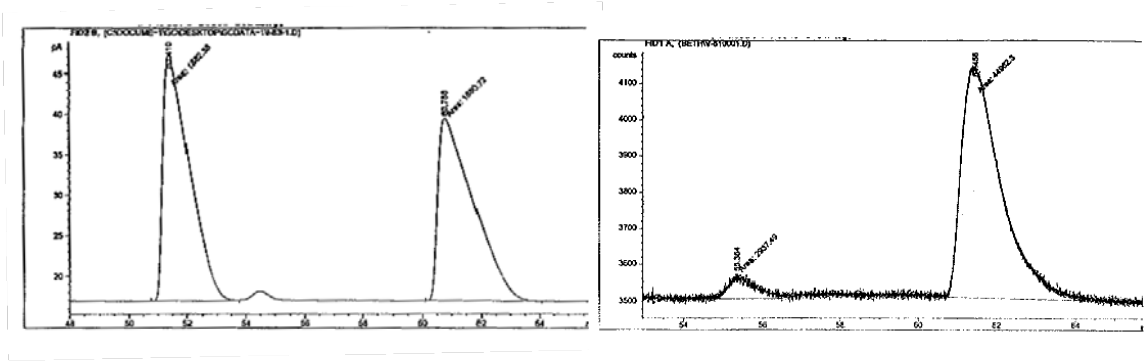


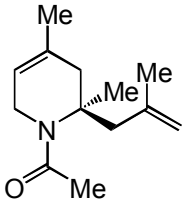
2.26

Synthesis of amine **2.26**. General procedure for ARCM was followed. Silica gel chromatography (20:1 CH_2Cl_2:MeOH washed with 2% v/v concentrated NH_4OH) was used for purification of **2.26**, which was isolated as yellow oil (0.027 mmol, 50%, product is volatile). IR (neat): 3270 (w), 3075 (m), 2917 (s), 1659 (m), 1451 (s), 1381 (m), 890 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.41 (s(br), 1H), 4.83 (s(br), 1H), 4.78 (s(br), 1H), 3.35 (s(br), 2H), 2.85 (dddd, *J* = 9.5, 7.7, 5.9, 4.4 Hz, 1H), 2.17–2.13 (m, 2H), 1.90–1.72 (m, 3H), 1.74 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 132.9, 120.1, 112.9, 50.4, 45.6, 45.3, 37.3, 23.4, 22.5. HRMS ES (*m/z*) Calcd for $C_{10}H_{17}N$ 152.1439 $(M+H)^+$, Found 152.1436. $[\alpha]_D$ +7.7 (*c* = 1). Enantiomeric excess was determined by GLC analysis of the derived acetamide: ^{1}H NMR (400 MHz, $CDCl_3$,

(47) Prepared according to literature procedure, see: "Acid-catalyzed cyclization reactions. IX. Formation of oxazolinium and thiazolinium cation from N-allyl and substituted N-allylamides, -urethans, -ureas, and –thioureas," McManus, S. P.; Carroll, J. T.; Piiman Jr., C. U. *J. Org. Chem.* **1970**, *35*, 3768–3774.

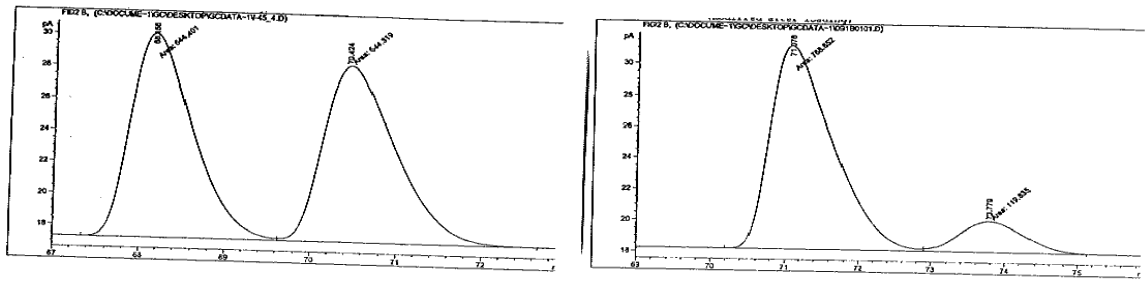
25 C), ~2:3 mixture of amide rotamers: δ 5.39 (s(br), 0.4H), 5.33 (s(br), 0.6H), 5.10 (dd, *J* = 14.6, 7.3 Hz, 0.6H), 4.83 (s(br), 0.4H), 4.73 (s(br), 0.6H), 4.70 (s(br), 0.4H), 4.65 (s(br), 0.6H), 4.58 (d(br), *J* = 19.0 Hz, 0.4H), 4.08 (dd, *J* = 13.6, 6.6 Hz, 0.4H), 3.91 (d(br), *J* = 17.6 Hz, 0.6H), 3.73 (d(br), *J* = 17.6 Hz, 0.4H), 3.39 (d(br), *J* = 19.0 Hz, 0.4H), 2.38–2.20 (m, 2.4H), 2.11 (s, 1.2H), 2.10–2.07 (m, 0.6H), 2.04 (s, 1.8H), 1.93–1.79 (m, 1H), 1.78 (s, 1.8H), 1.77 (s, 1.2H), 1.71 (br s, 3H). The optical purity of **2.26-Ac** was determined by GC analysis in comparison with authentic racemic material, shown below: CDGTA chiral column, 120 °C, 15 psi, for a sample of *87% ee*.



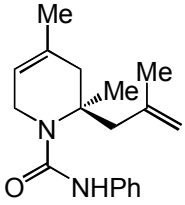


2.14

Synthesis of amine **2.14**. General procedure for ARCM was followed. Silica gel chromatography (15:1 CH_2Cl_2:Et_2O) was used for purification of **2.14**, which was isolated as colorless oil (0.140 mmol, 63%). IR (neat): 3068 (m), 2968 (s), 2923 (s), 2861 (m), 1646 (s), 1694 (s), 1243 (m), 1168 (m), 897 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (s(br), 1H), 4.83 (s, 1H), 4.66 (s, 1H), 3.85 (dd, *J* = 15.7, 4.8 Hz, 1H), 3.68 (dd, *J* = 15.7, 1.5 Hz, 1H), 3.02 (d, *J* = 13.6 Hz, 1H), 2.34 (d, *J* = 14.6 Hz, 1H), 2.30 (d, *J* = 13.6 Hz, 1H), 2.06 (s, 3H), 1.87 (d, *J* = 15.7 Hz, 1H), 1.74 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 143.3, 136.2, 117.6, 114.9, 58.7, 45.2, 44.8, 42.5, 26.9, 25.5, 24.2, 23.0. HRMS ES (*m/z*) Calcd for $C_{13}H_{21}NO$ 208.1701 $(M+H)^+$, Found 208.1698. The optical purity of **2.14** was determined by GC analysis in comparison with authentic racemic material, shown below: CDGTA chiral column, 140 °C, 15 psi, for a sample of *75% ee*.

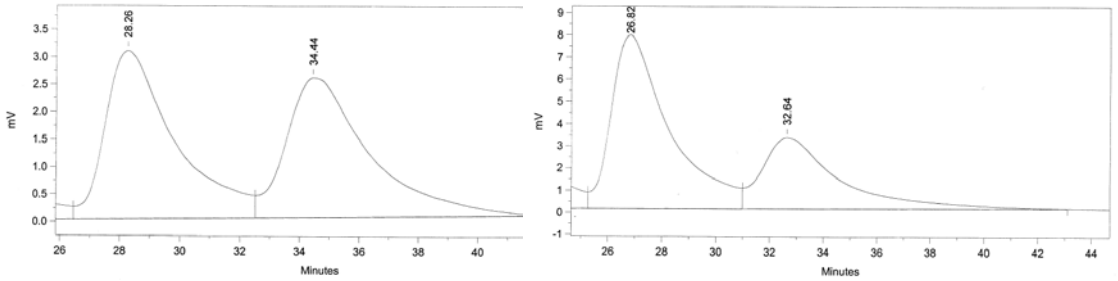


Synthesis of amine **2.15** (Scheme **2.2**). General procedure for ARCM was followed. An optimized isolated yield was not obtained for amine **2.15**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.25 (m, 4H), 7.03–6.99 (m, 1H), 6.34 (br s, 1H), 5.47 (br s, 1H), 4.88 (ddd, *J* = 4.0,

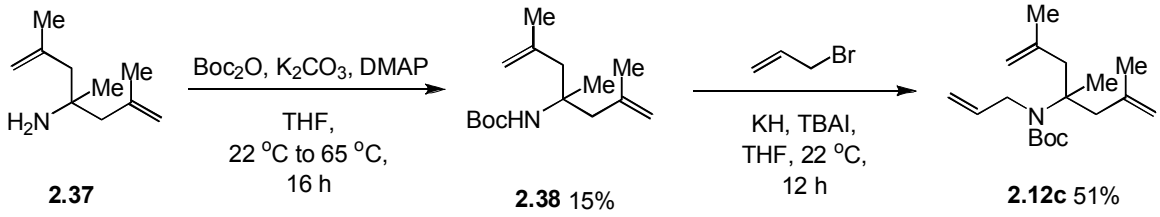


2.15

2.8, 1.2 Hz, 1H), 4.74–4.73 (m, 1H), 4.0–3.80 (m, 2H), 2.76 (d, *J* = 14.0 Hz, 1H), 2.54 (d, *J* = 13.6 Hz, 1H), 2.29 (d, *J* = 15.6 Hz, 1H), 1.99 (d, *J* = 16.8 Hz, 1H), 1.80 (s, 3H), 1.76 (s, 3H), 1.25 (s, 3H). The optical purity of **2.15** was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak AD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, for a sample of *29% ee*.



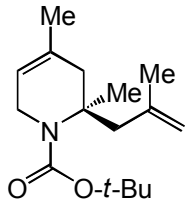
Scheme 2.5



2.37 **2.38** 15% **2.12c** 51%

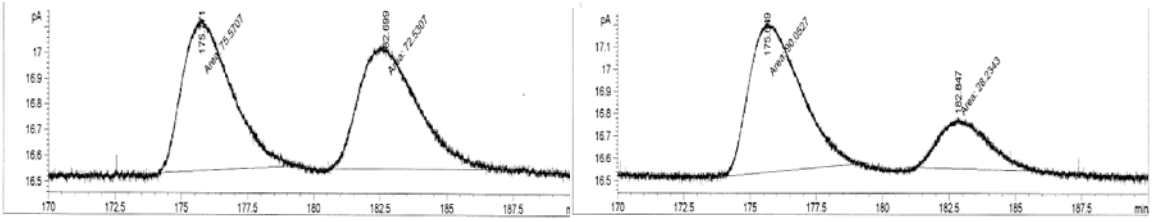
Synthesis of Metathesis Substrate **2.12c**. Metathesis substrate **2.12** was prepared according to the procedure shown in Scheme 2.5. Amine **2.37** was prepared in 40% yield by the same procedure used to synthesize amine **2.36** (Scheme 2.4), however, acetonitrile was employed as the starting material for the bisalkylation. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (br s, 2H), 4.64 (br s, 2H), 3.37 (br s, 4H), 2.04 (s, 3H), 1.73 (s, 6H), 1.46 (br s, 2H). A 250-mL round-bottom flask was charged with amine **2.37** (1.00 g, 6.52 mmol), potassium carbonate (1.35 g, 9.79 mmol), dimethylaminopyridine (39.8 mg, 0.326 mmol), and THF 65 mL). The reaction vessel was then fitted with a reflux condenser and the reaction mixture was set to reflux at 65 °C. After allowing the reaction mixture to stir for 16 h, the heating bath was removed, and the mixture was allowed to cool to ambient temperature. At this point, H_2O (50 mL) was added to the mixture and the resulting biphasic layers were separated. The organic layer was concentrated in vacuo to remove a majority of the THF. The resulting mixture was diluted with Et_2O, after which time it was washed with a saturated aqueous solution of NaCl (50 mL), H_2O (50 mL), dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting brown residue was purified by silica gel chromatography (50:1 hexanes:Et_2O) to provide *tert*-butyl carbamate **2.38** as colorless oil (256 mg, 1.01 mmol, 15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90 (ddd, *J* = 3.6, 2.8, 1.2 Hz, 2H), 4.70–4.69 (m, 2H), 4.40 (br s, 1H), 2.77 (d, *J* =

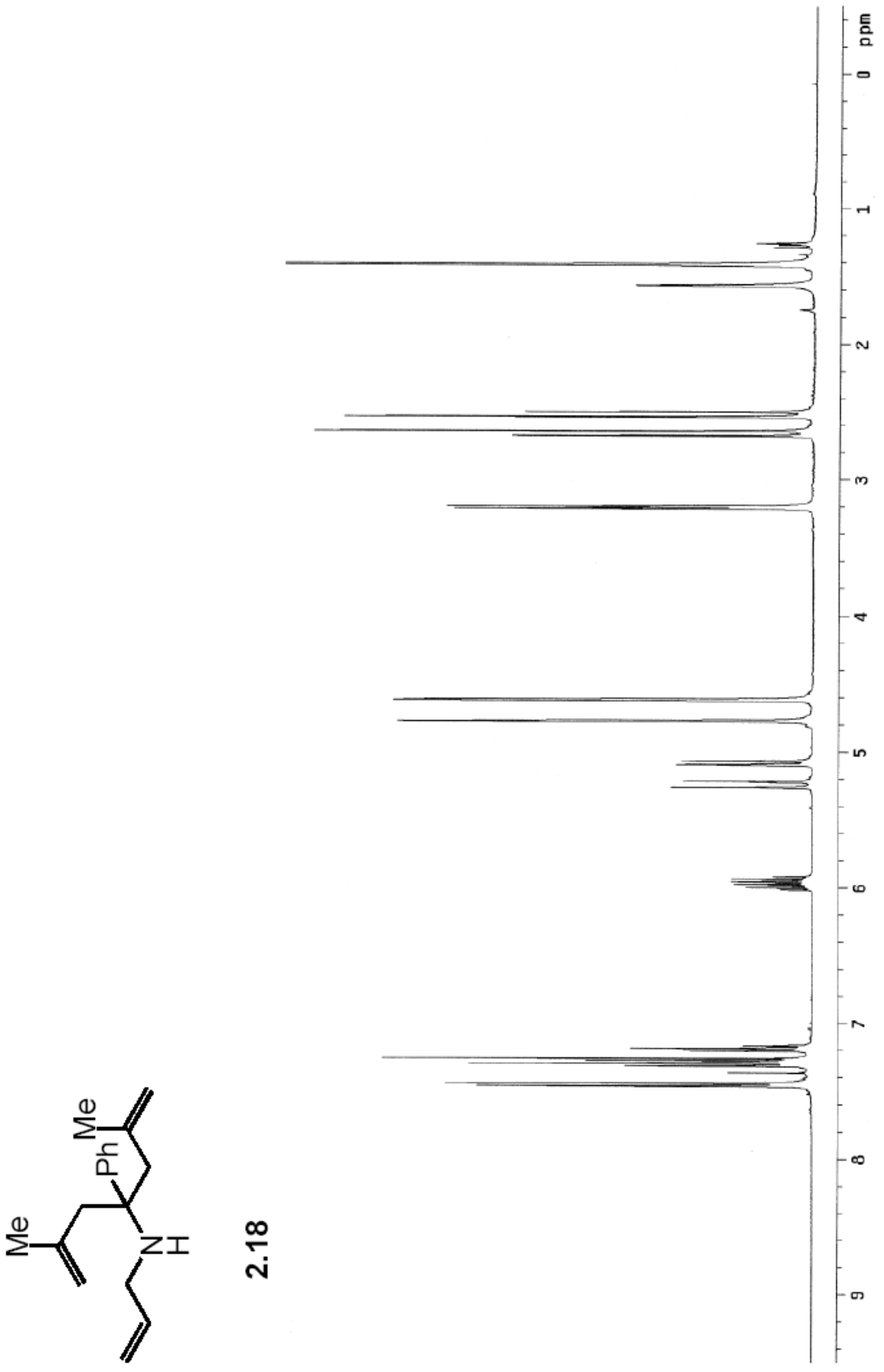
13.6 Hz, 1H), 2.16 (d, *J* = 13.6 Hz, 1H), 1.80 (s, 6H), 1.43 (s, 9H), 1.17 (s, 3H). A 100-mL round-bottom flask was charged with **2.38** (256 mg, 1.01 mmol), potassium hydride (135 mg, 3.37 mmol), tetrabutylammonium iodide (18.7 mg, 0.0505 mmol), allyl bromide (0.300 mL, 3.45 mmol), and THF (20 mL). This mixture was allowed to stir for 12 h, after which time H_2O (50 mL) was added to the mixture and the resulting biphasic layers were separated. The organic layer was concentrated in vacuo to remove a majority of the THF. The resulting mixture was diluted with Et_2O, after which time it was washed with a saturated aqueous solution of NaCl (50 mL), H_2O (50 mL), dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting brown residue was purified by silica gel chromatography (25:1 hexanes:Et_2O) to provide metathesis substrate **2.12c** as colorless oil (150 mg,0.0511 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (dddd, *J* = 16.8, 10.0, 6.0, 6.0 Hz, 1H), 5.03 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.97 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.85 (br s, 2H), 4.65 (br s, 2H), 3.75 (d, *J* = 6.0 Hz, 1H), 3.20 (d, *J* = 12.8 Hz, 1H), 2.00 (d, *J* = 13.2 Hz, 1H), 1.72 (s, 6H), 1.44 (s, 9H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 142.9, 137.3, 115.3, 115.2, 114.9, 79.3, 61.6, 48.7, 46.9, 28.6, 24.7.



2.16

Synthesis of amine **2.16**. General procedure for ARCM was followed. Silica gel chromatography (20:1 Et_2O:hexanes) was used for purification of **2.16**, which was isolated as colorless oil (0.0159 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50 (br s, 1H), 4.84 (ddd, *J* = 4.0, 2.8, 1.6 Hz, 1H), 4.68–4.67 (m, 1H), 4.08–4.03 (m, 1H), 3.62–3.56 (m, 1H), 2.76 (d, *J* = 17.6 Hz, 1H), 2.28–2.21 (m, 3H), 1.91 (d, *J* = 16.0 Hz, 2H), 1.76 (s, 6H), 1.73 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 143.6, 134.5, 119.3, 115.3, 79.8, 57.4, 45.9, 44.0, 43.3, 29.0, 28.2, 24.6, 23.4. The optical purity of **2.16** was determined by GC analysis in comparison with authentic racemic material, shown below: CDGTA chiral column, 130 °C, 15 psi, for a sample of *52% ee*.





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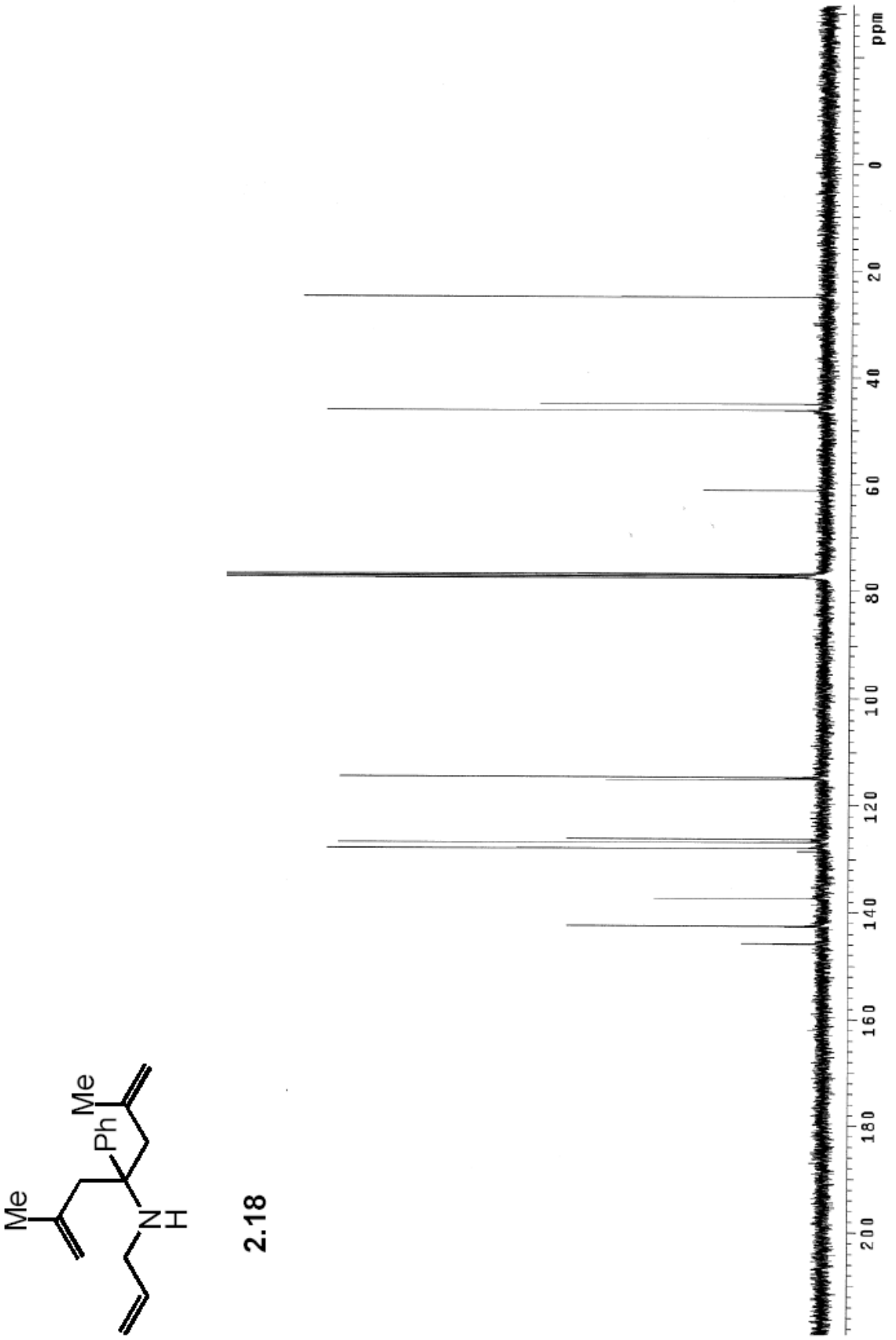

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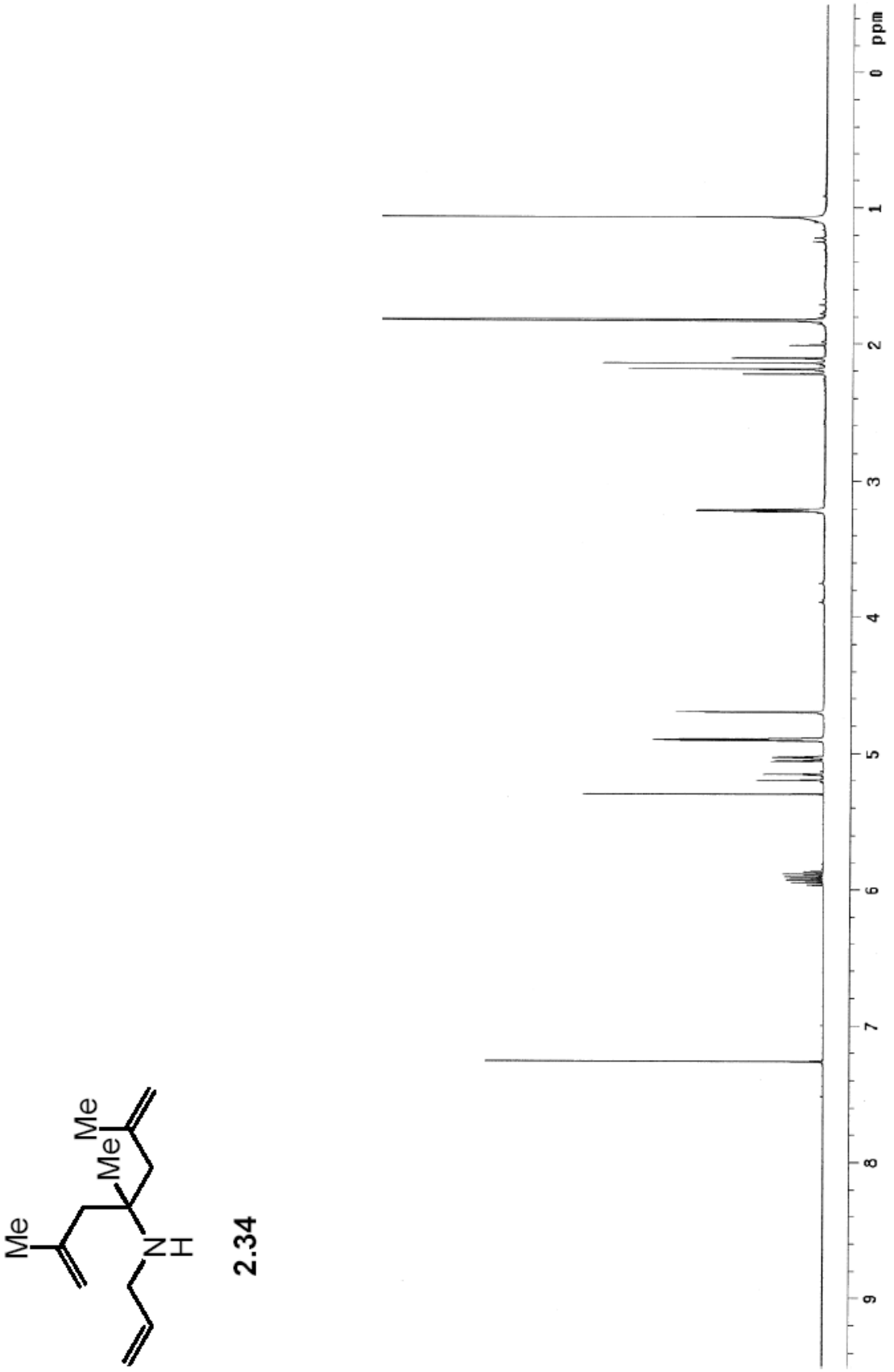

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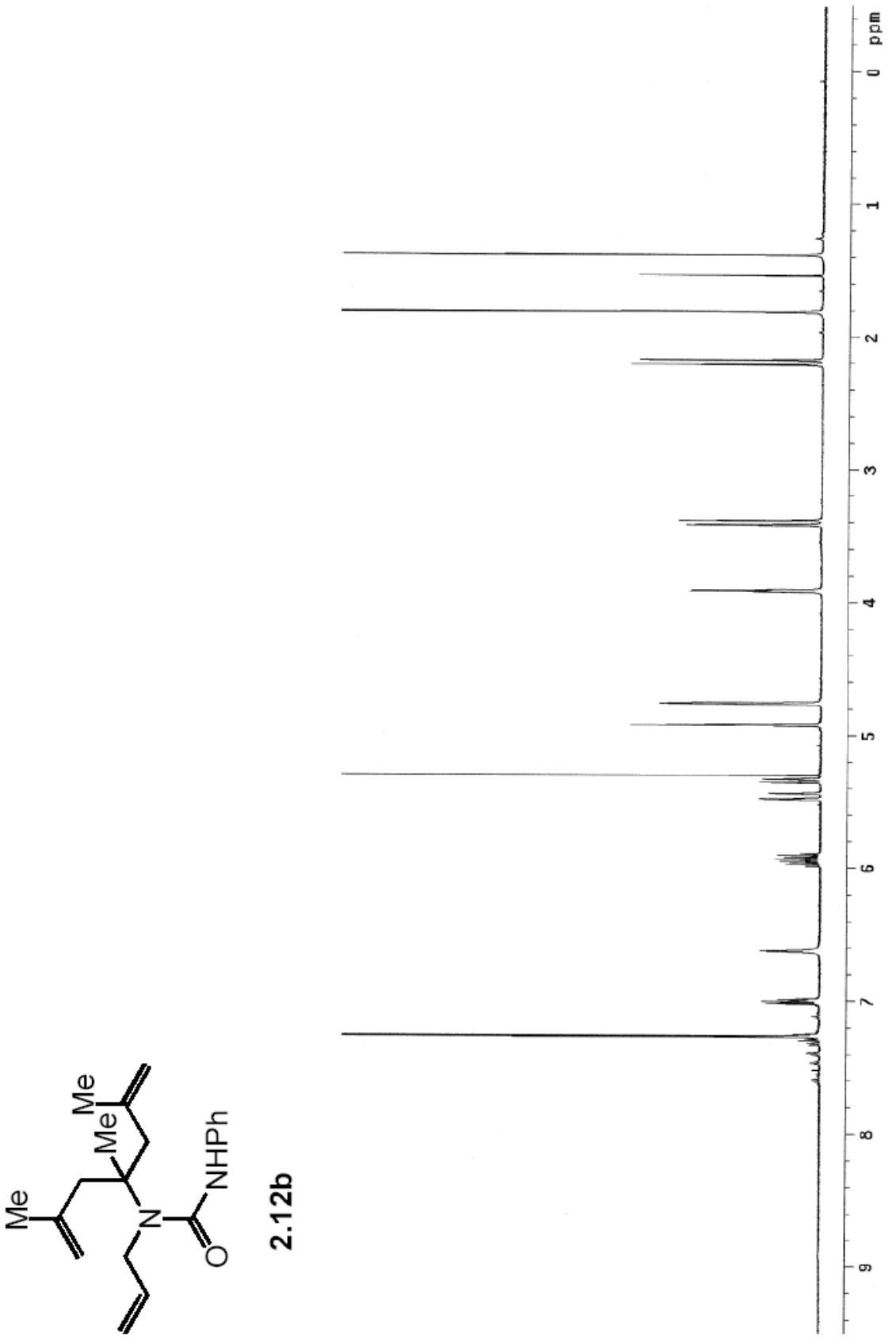
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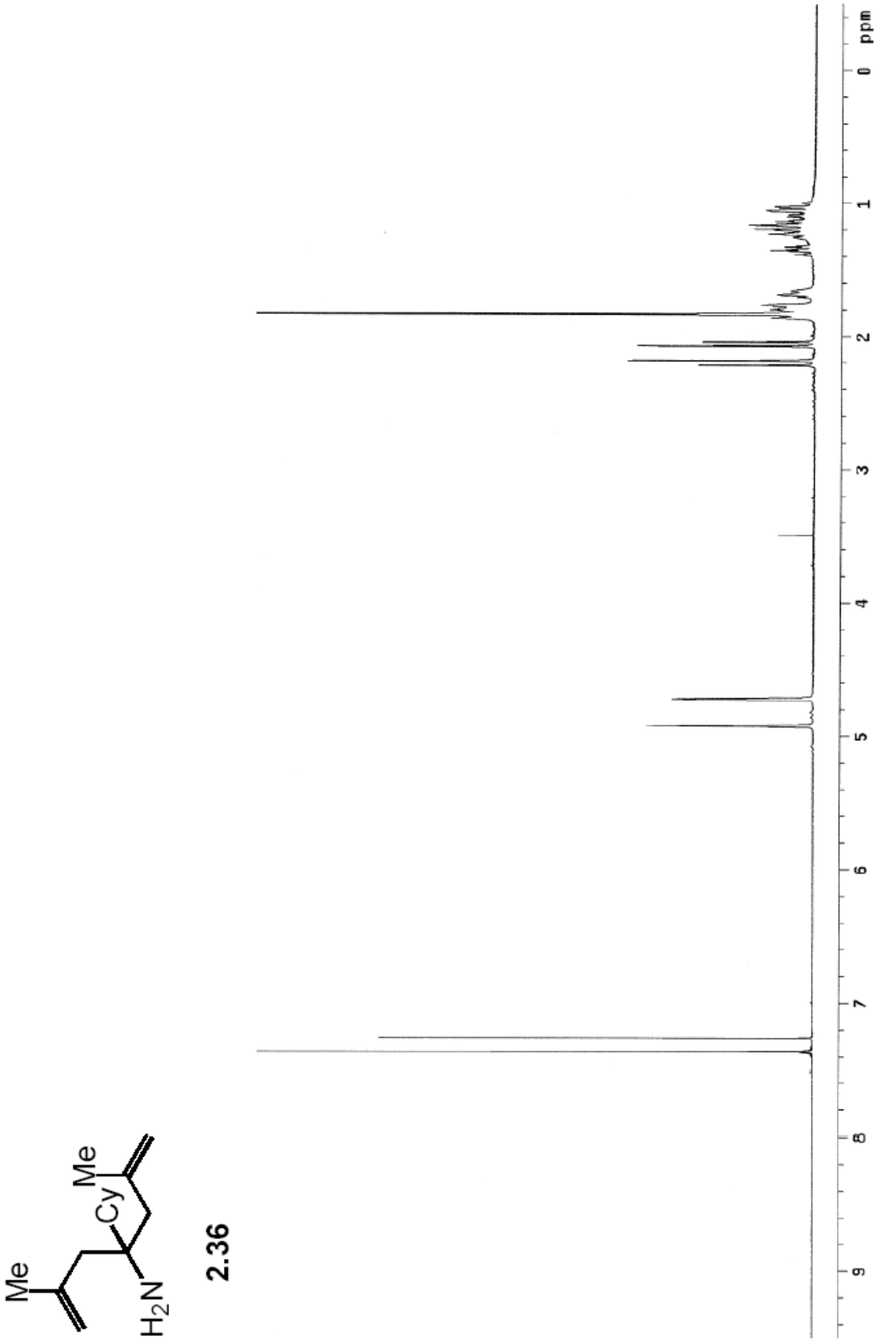
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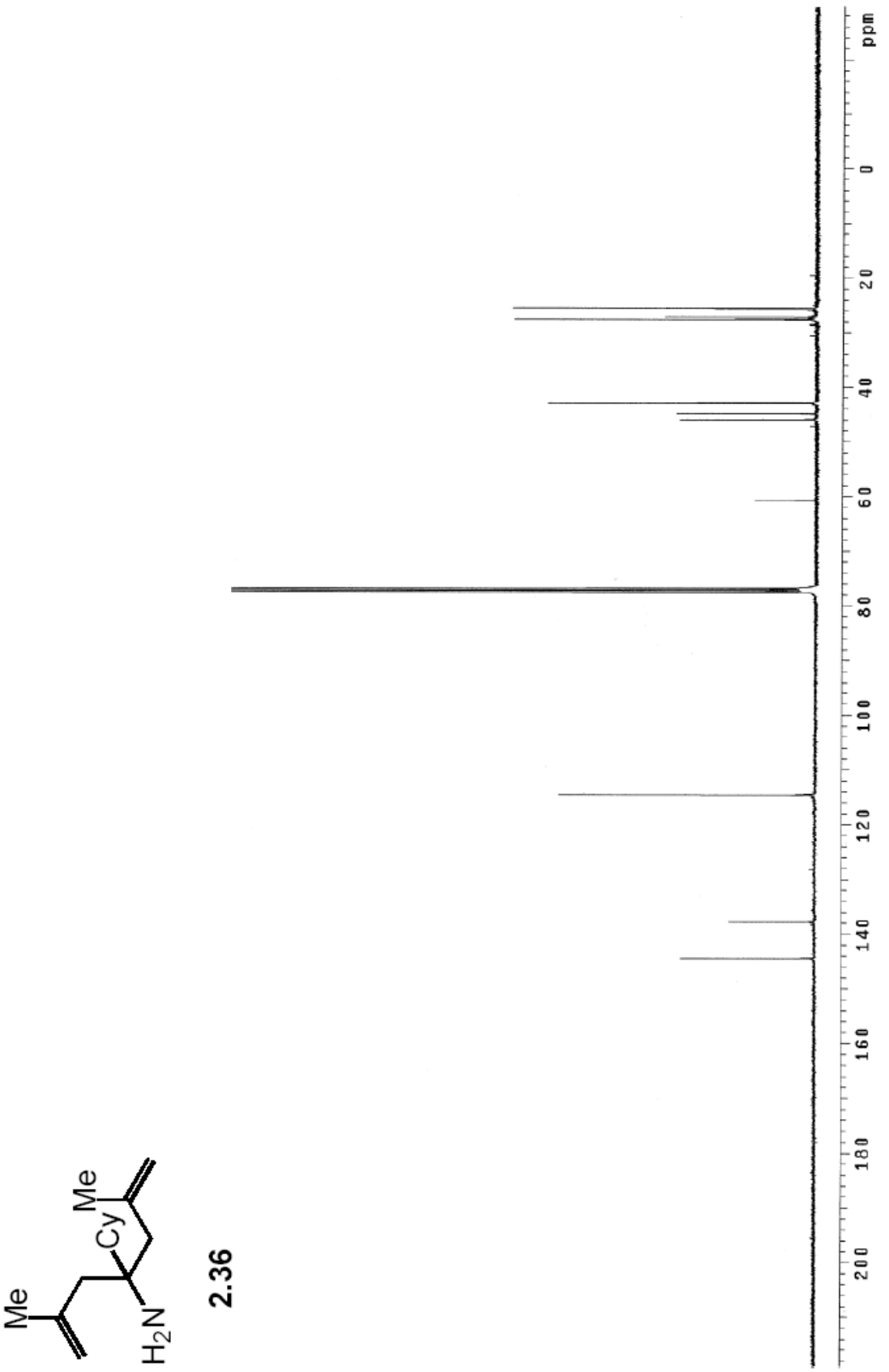

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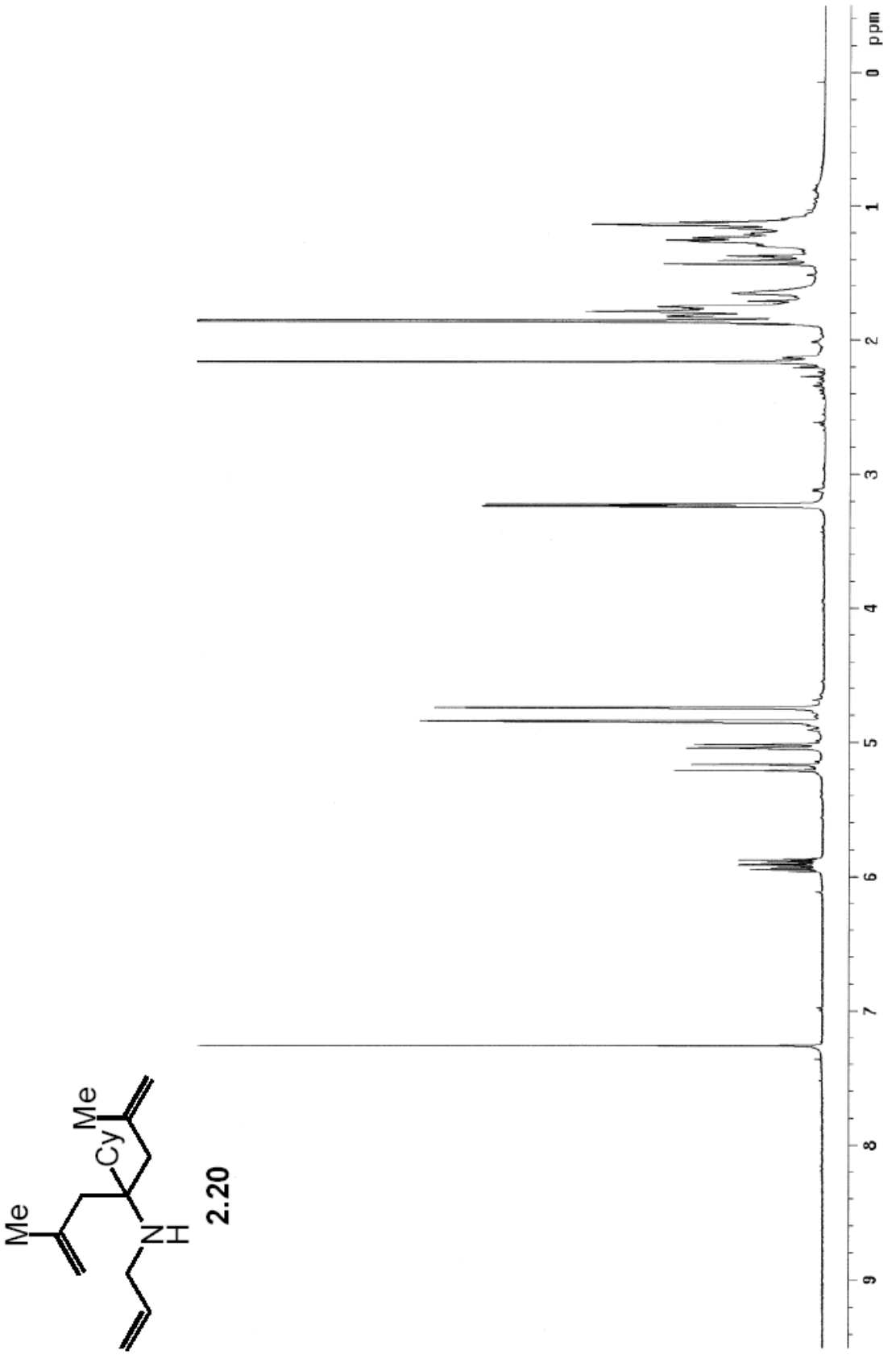
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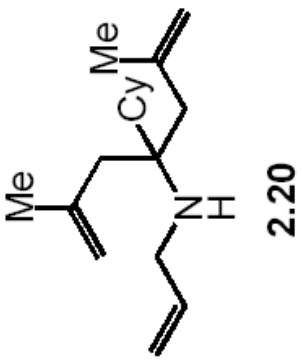

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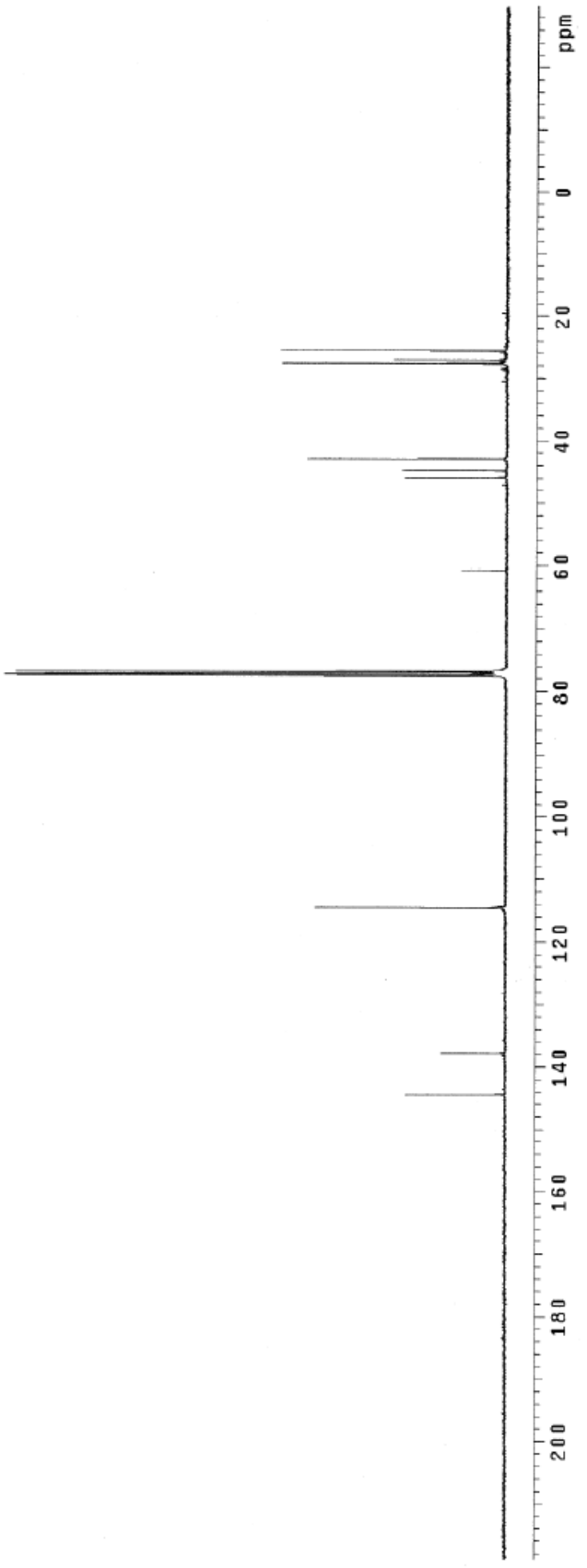

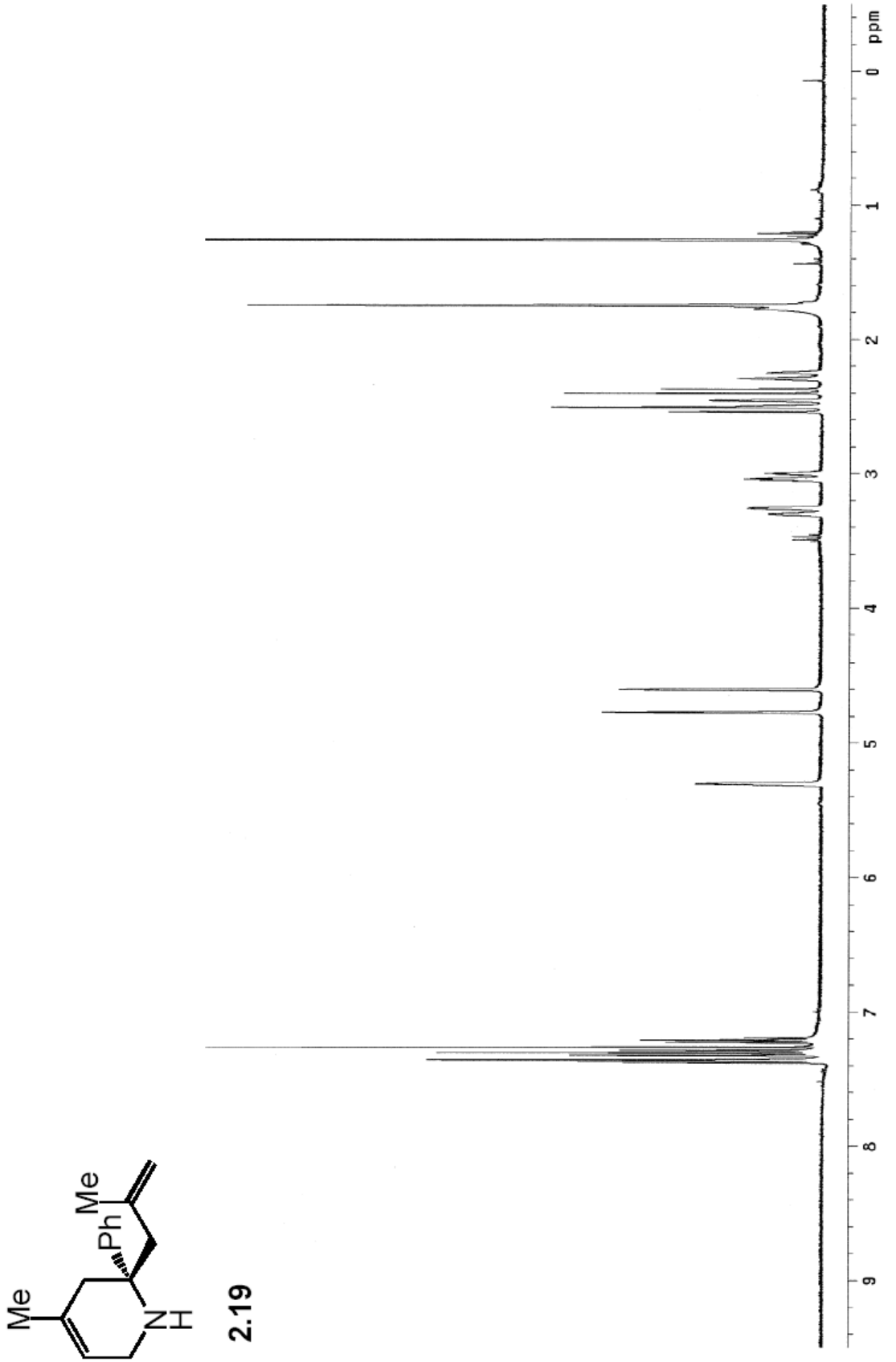
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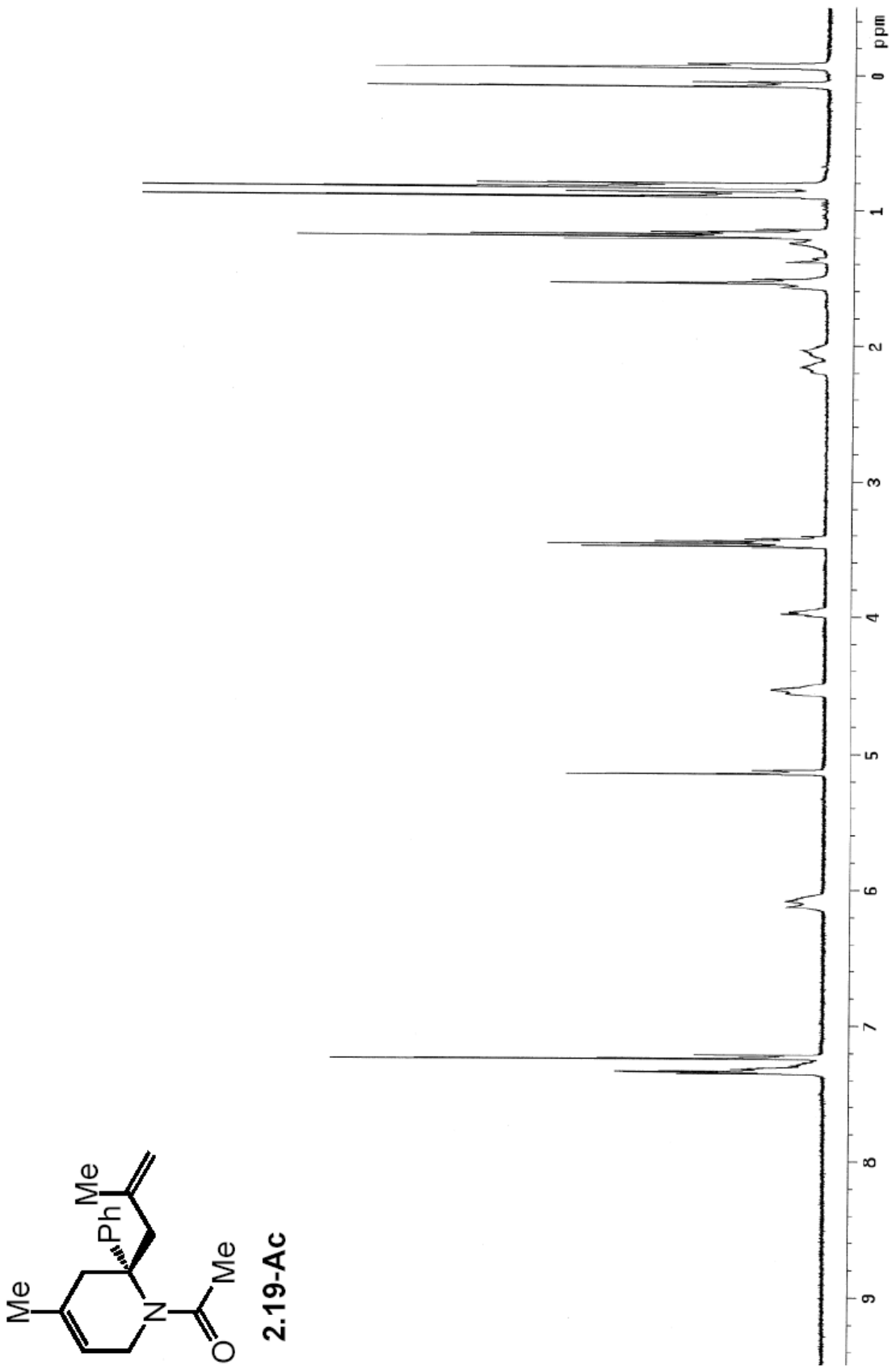
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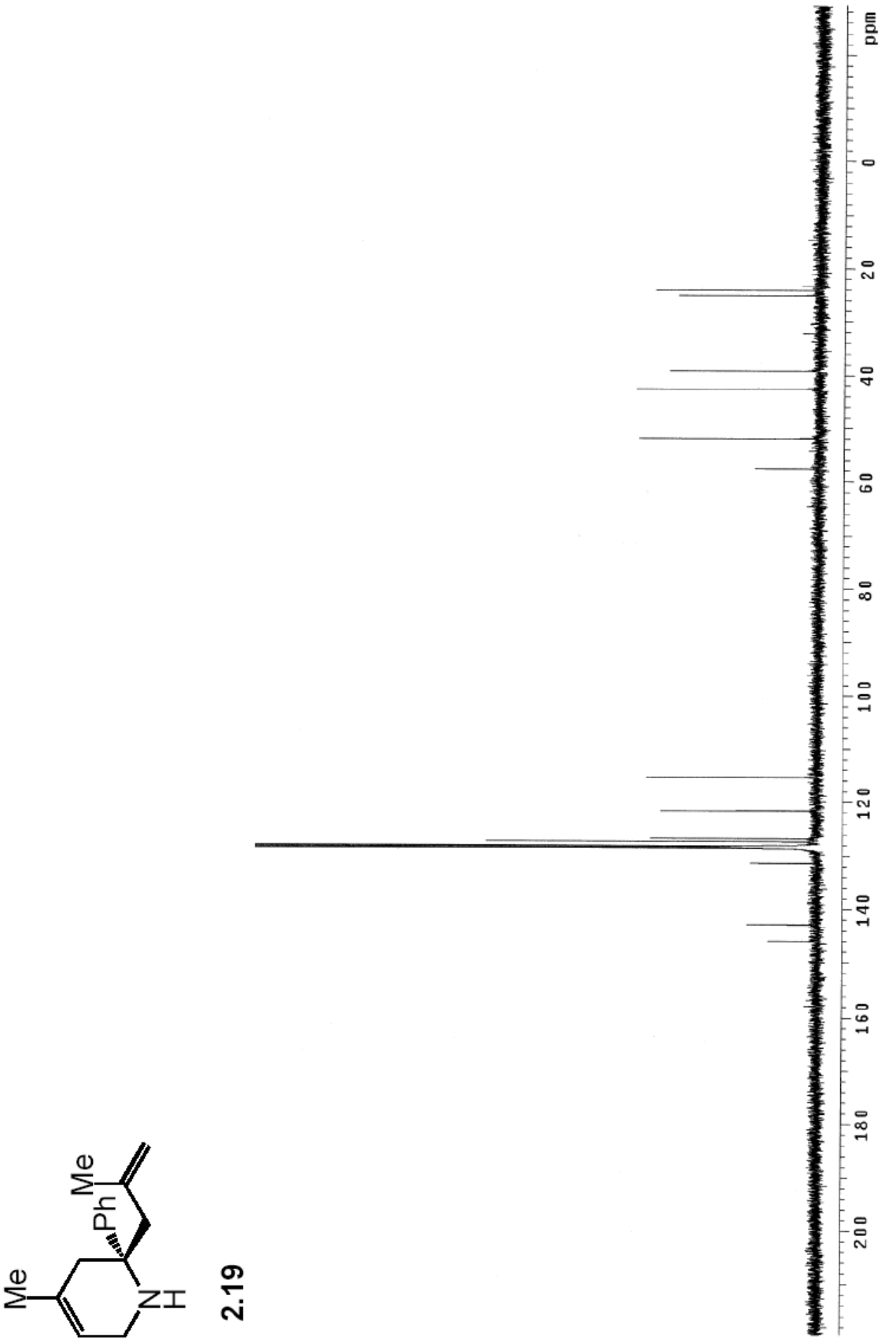

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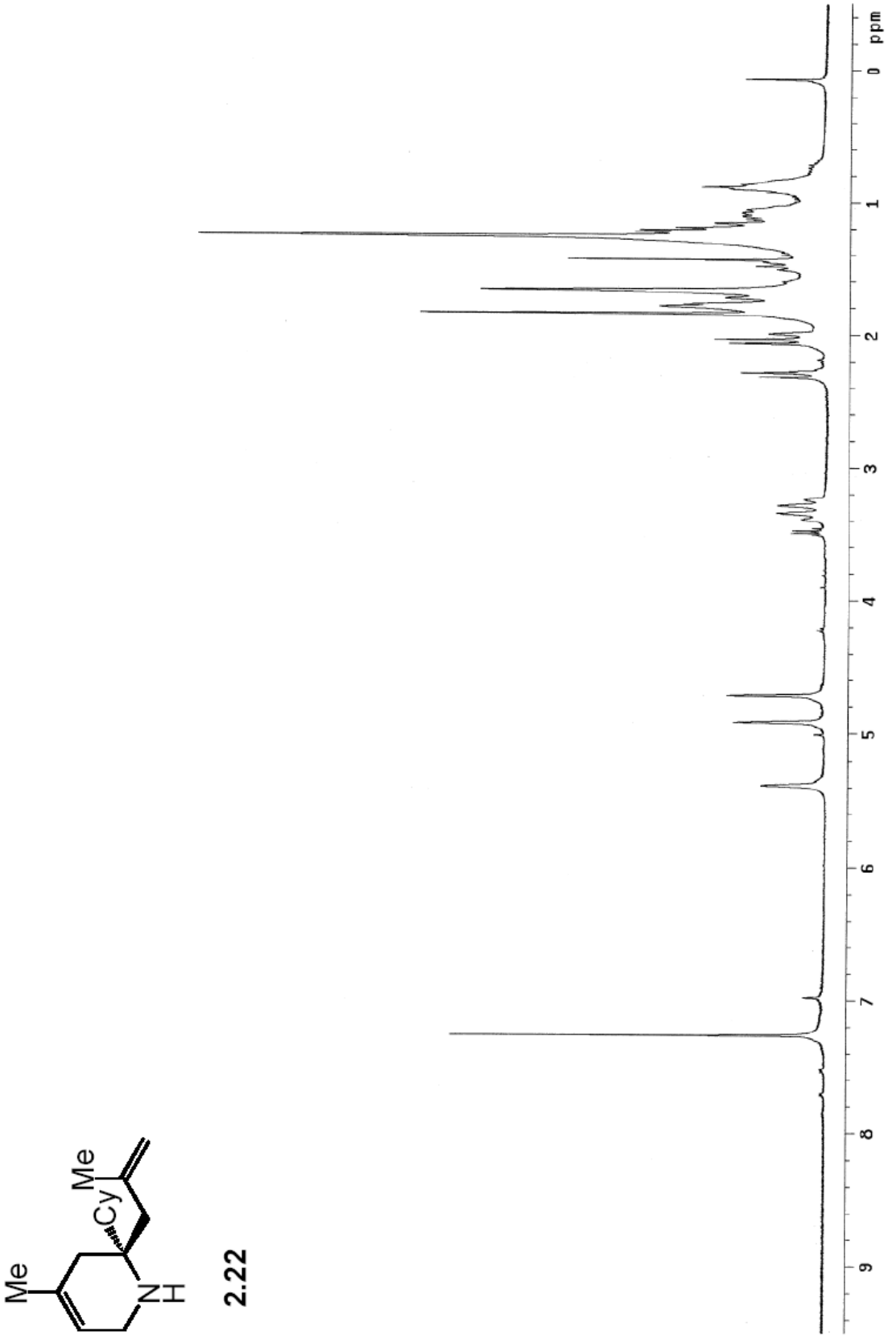
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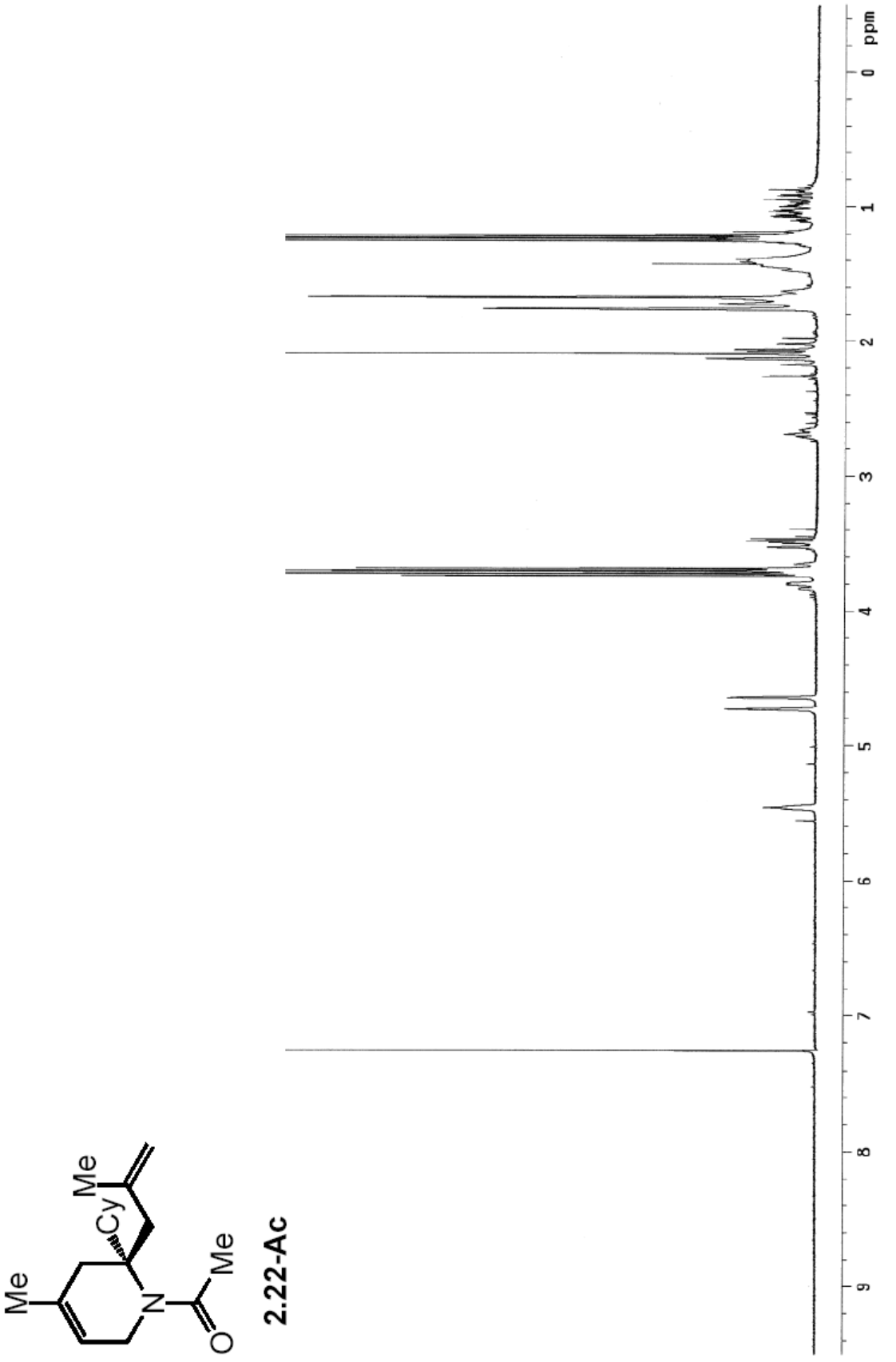
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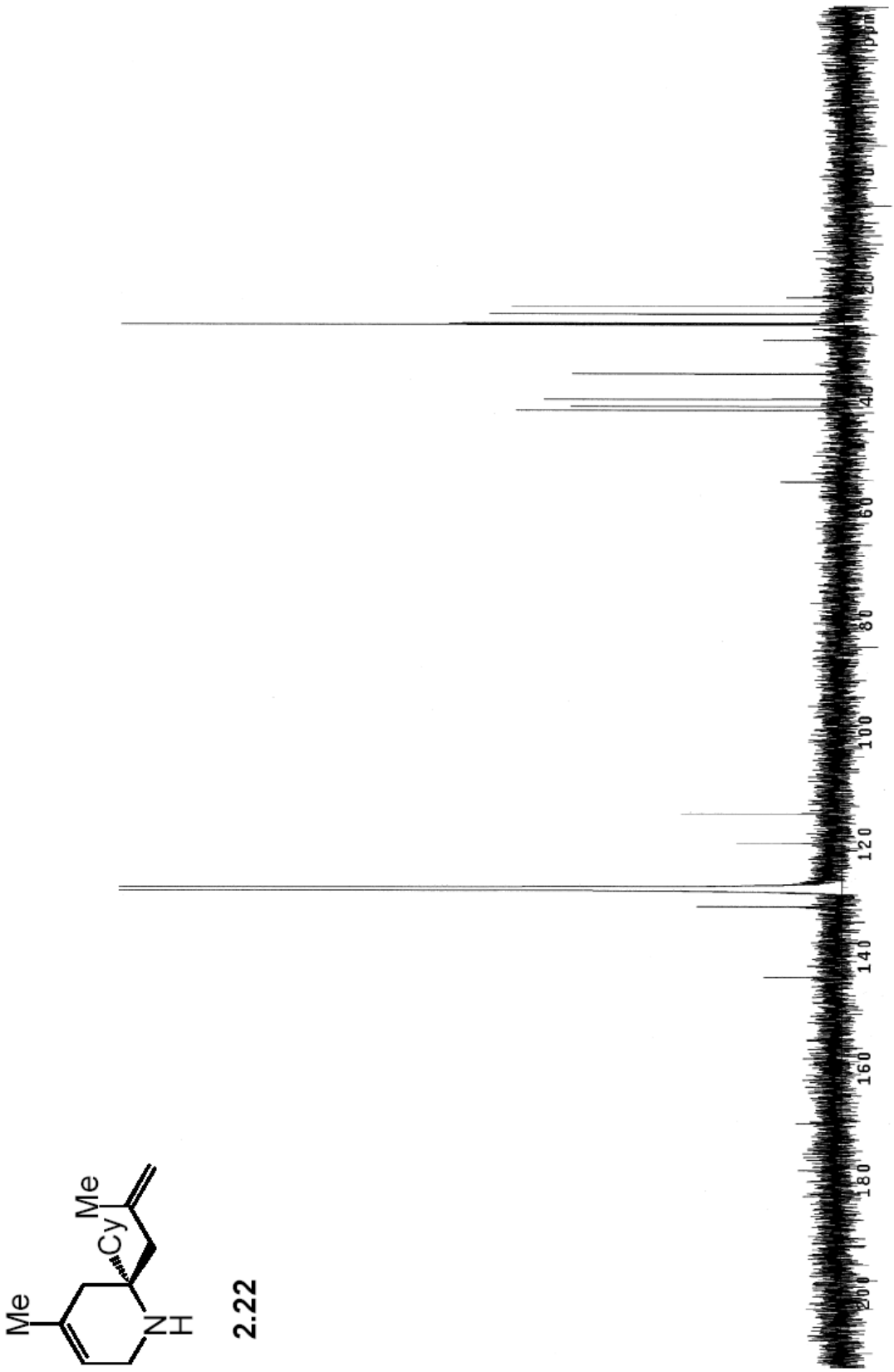
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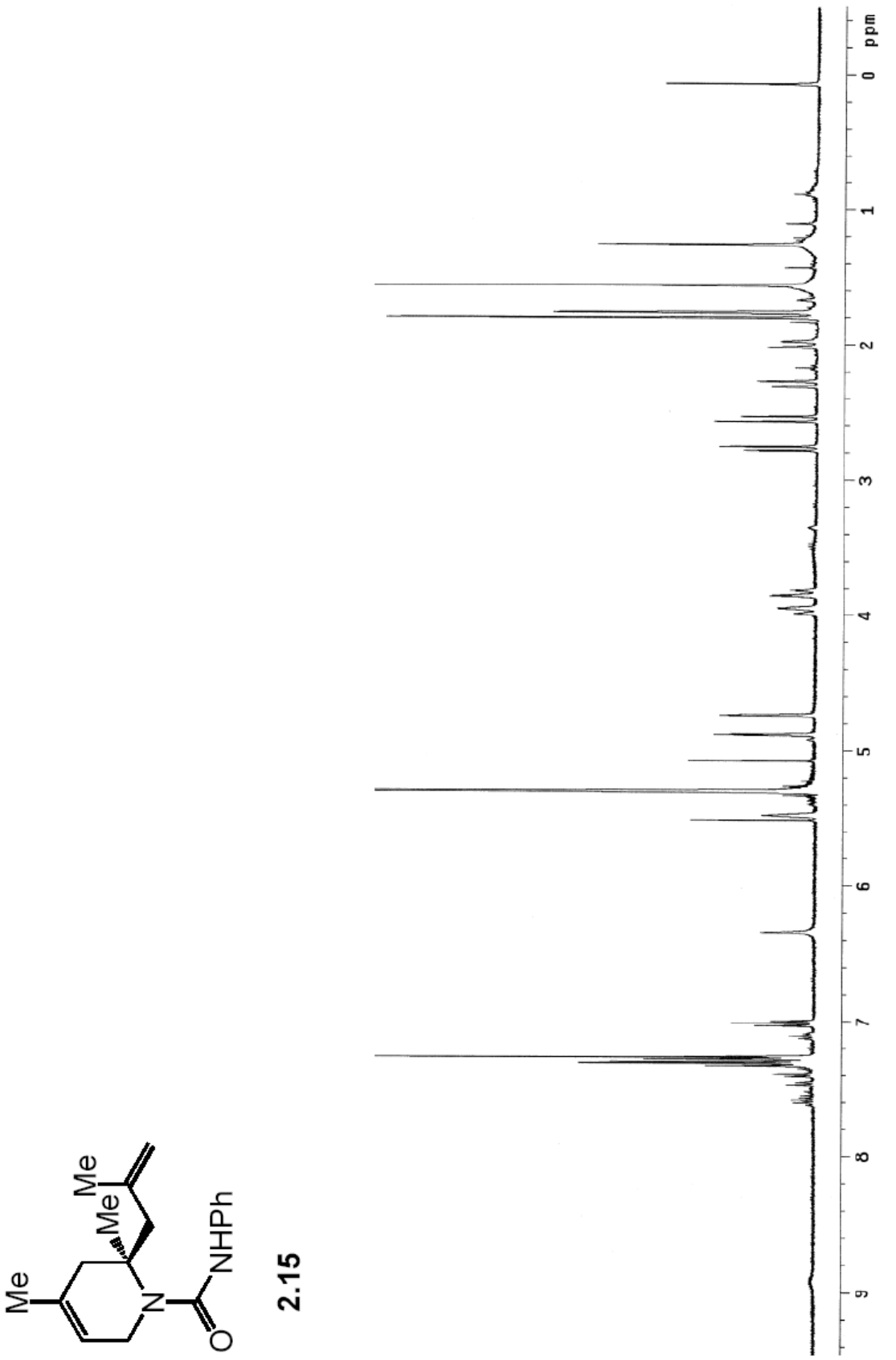

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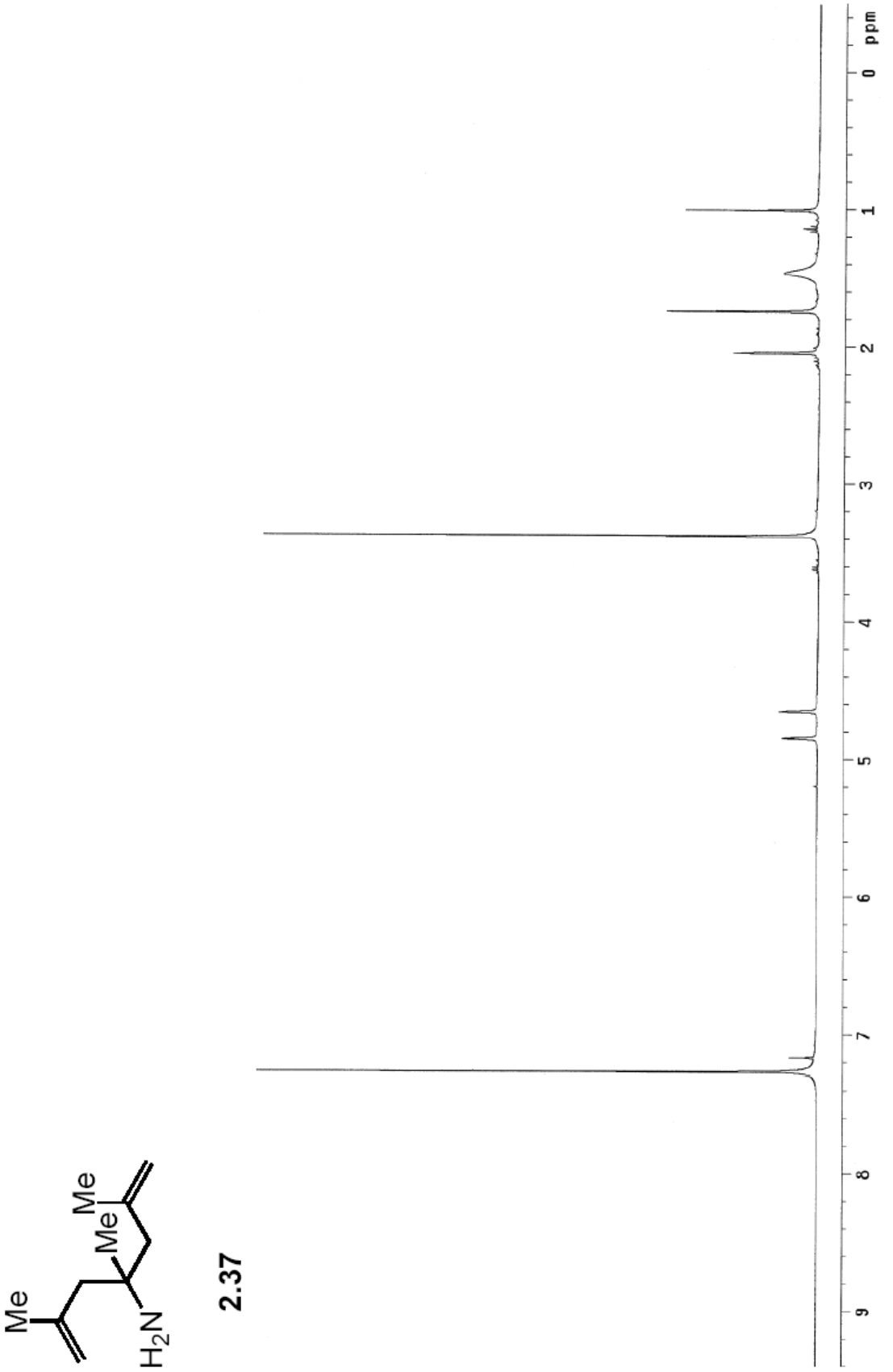
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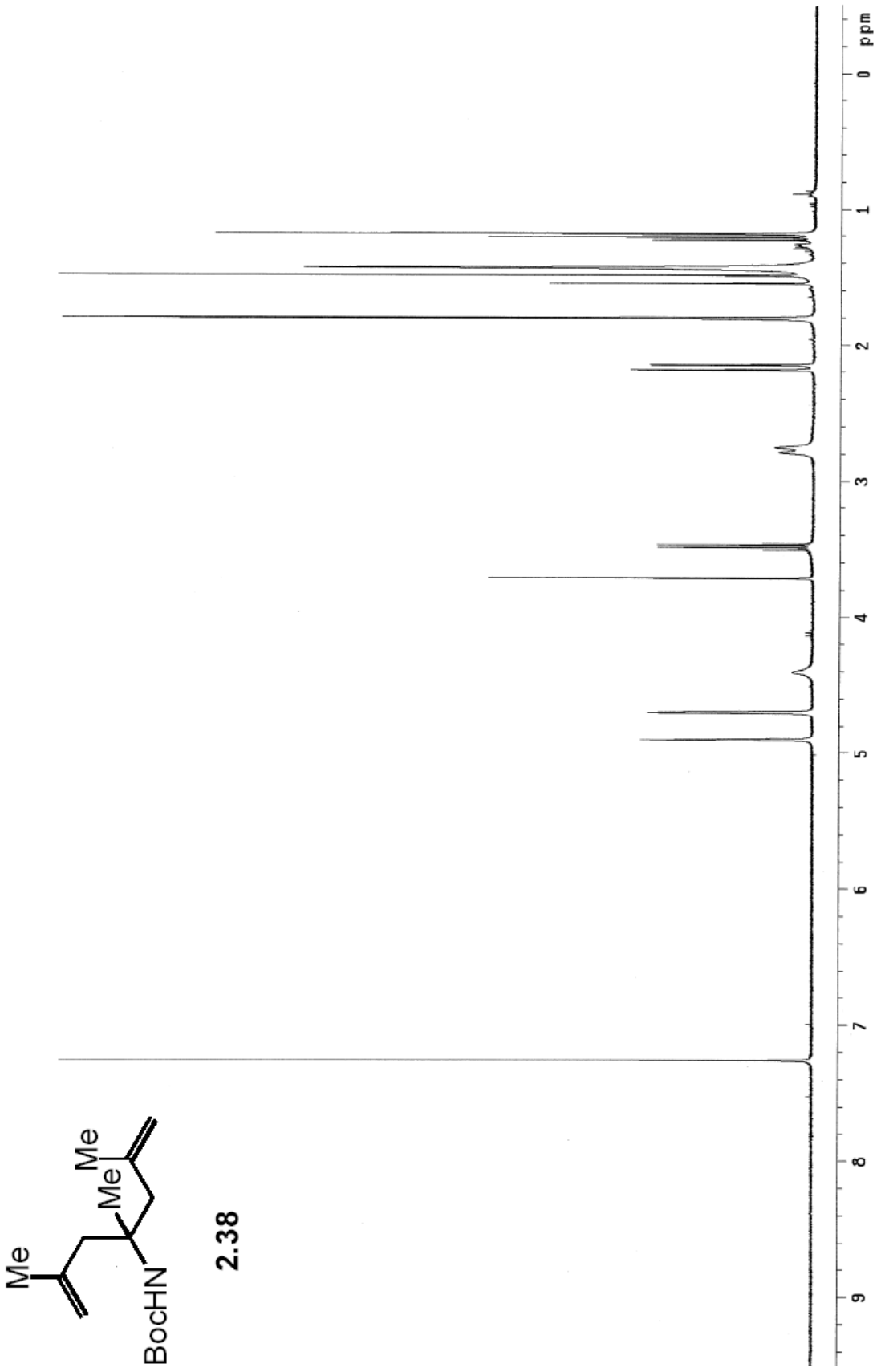
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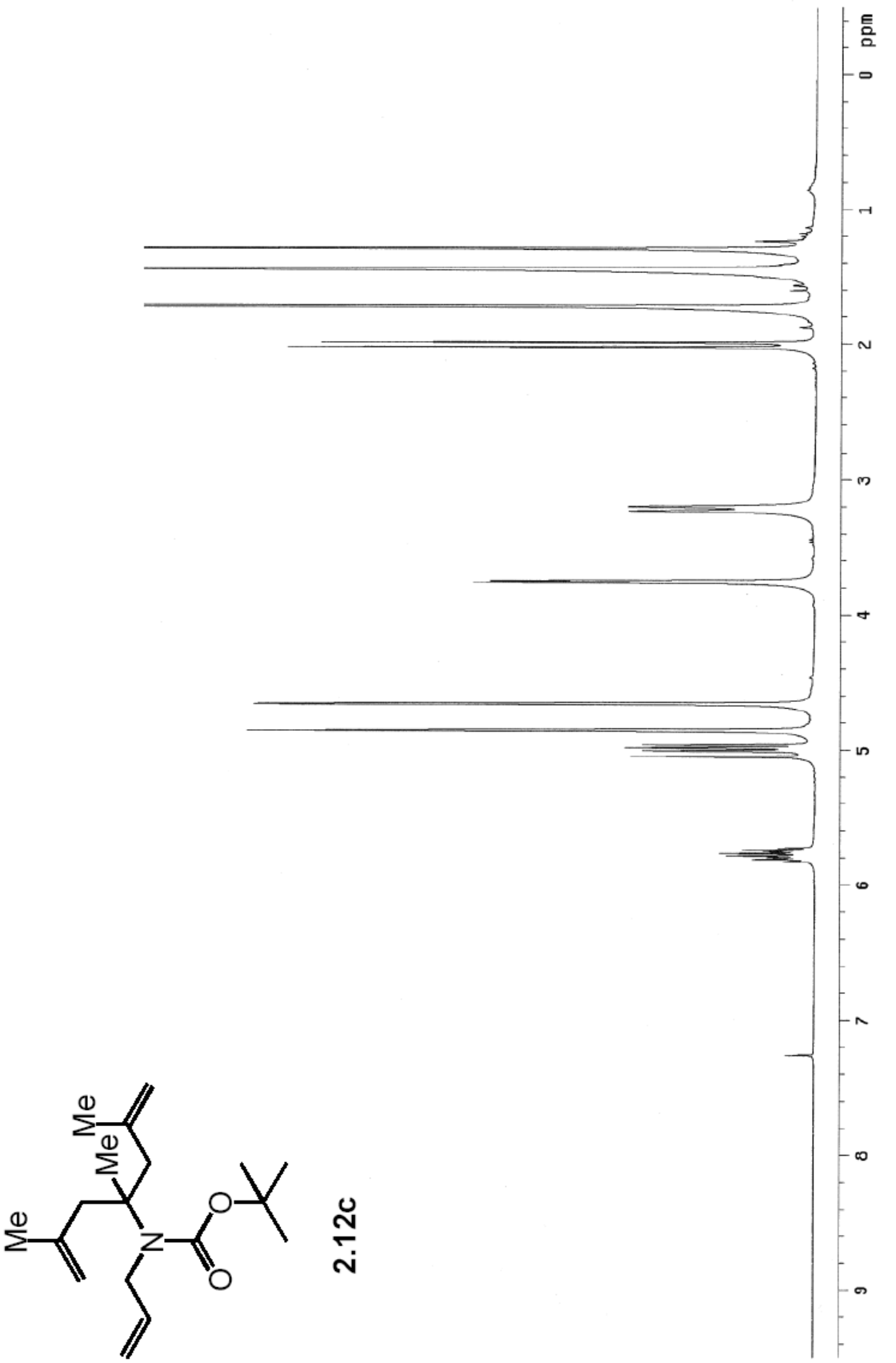
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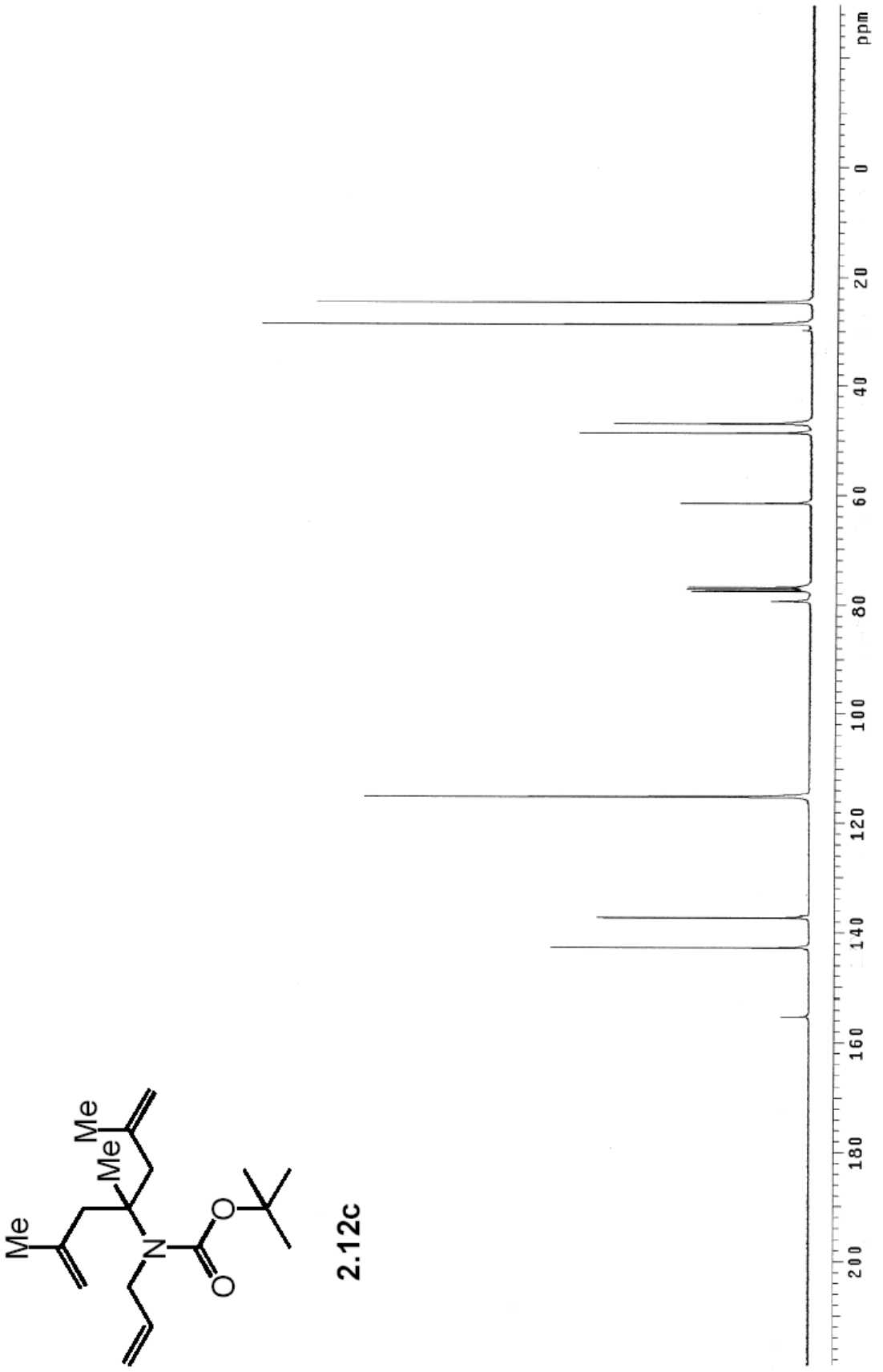

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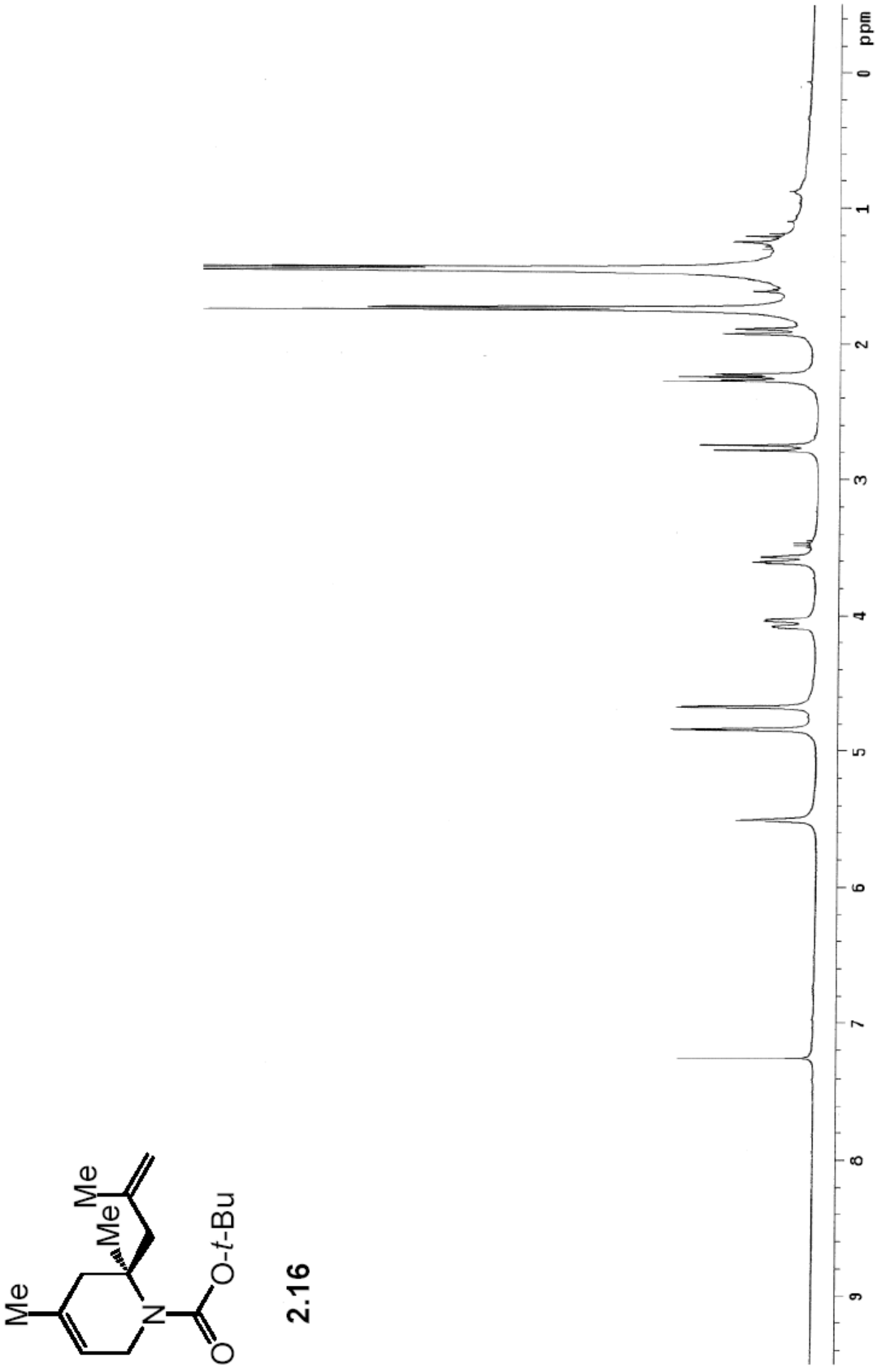
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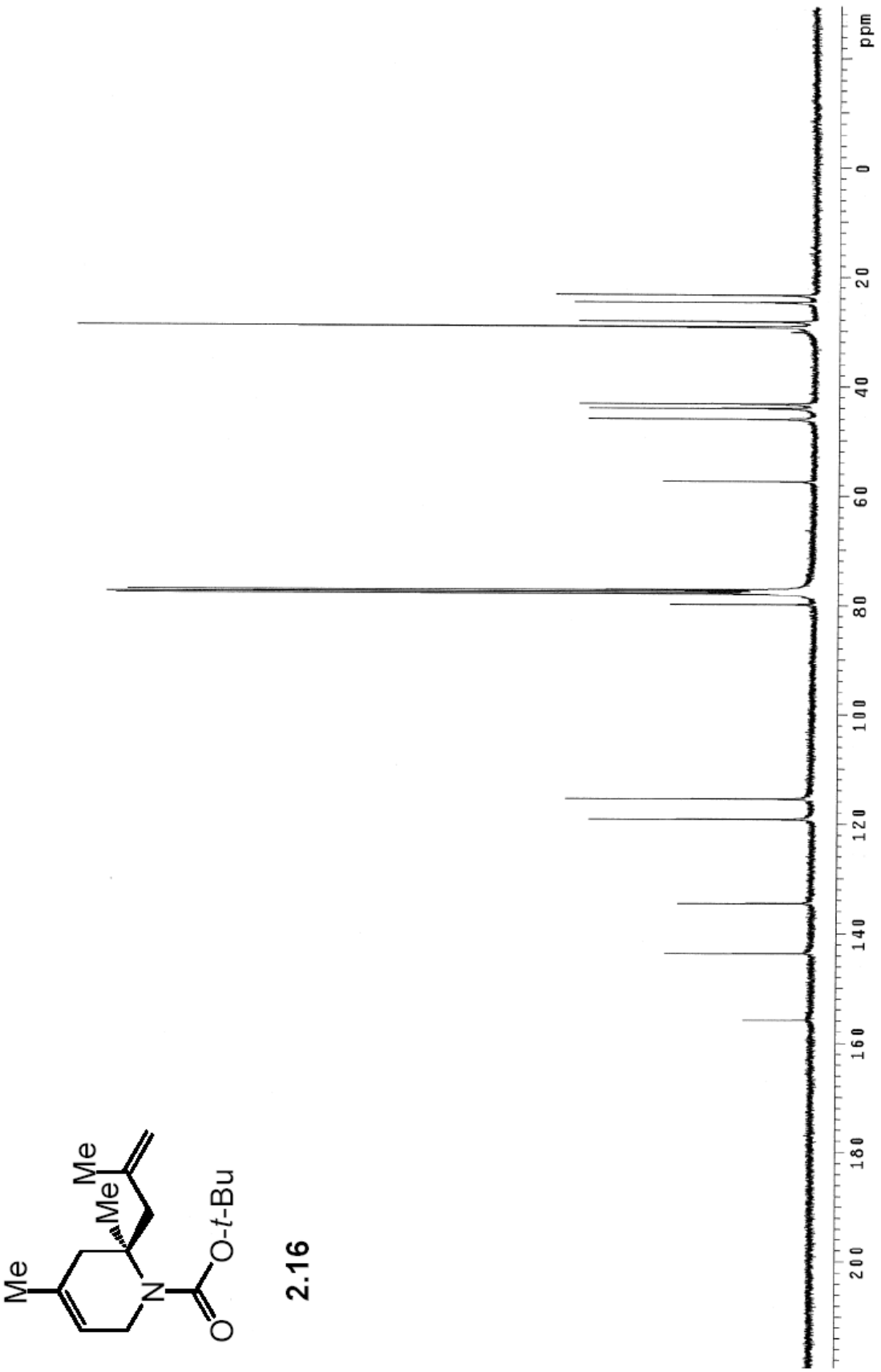


2.16

Chapter Three

Mo-CATALYZED ENANTIOSELECTIVE SYNTHESIS OF PIPERIDINES THROUGH ASYMMETRIC RING-OPENING/CROSS-METATHESIS

3.1 Introduction

Arguably, one of the most important reasons for researching organic chemistry is to develop methods that can be applied to the synthesis of agents of therapeutic value. Often times the inspiration for these methods are natural products that possess biological activity. Within this context, the next class of catalytic olefin metathesis reactions we developed was the asymmetric ring-opening/cross-metathesis (AROM/CM) of [3.2.1]-azabicycles for the enantioselective synthesis of 2,6-cis-disubstituted piperidines.

3.1a Piperidine Natural Products. Illustrated in Figure 3.1 are representative naturally occurring piperidine compounds that have demonstrated biological activity.

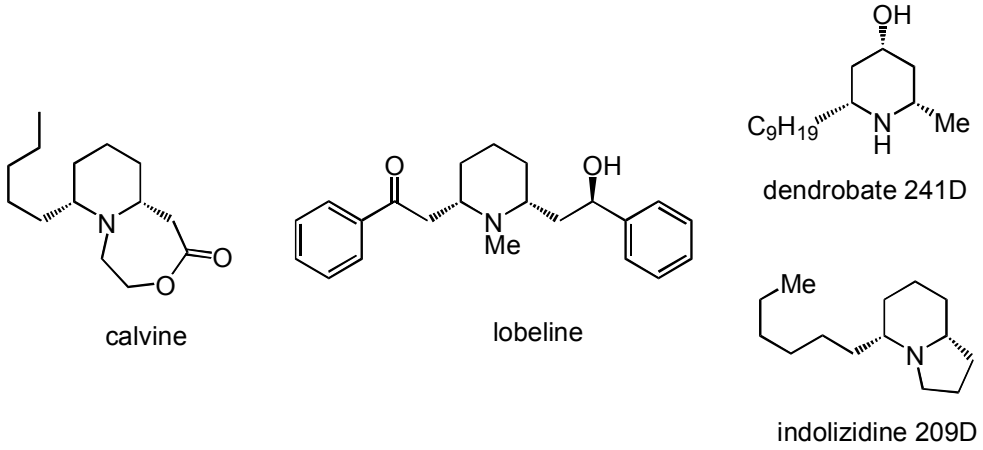


Figure 3.1 Bioglogically Active Piperidine Natural Products

Fascinatingly, despite sharing similar structural architecture, these piperidine natural products have been isolated from very dissimilar organisms. A common structural feature of these natural products is *syn*-substitution at the 2- and 6-position of the piperidine core. Calvine[48] is a bicyclic piperidine that contains a seven-membered ring lactone and is isolated from coccinellid beetles belonging to the genus *Calvia*. This alkaloid is secreted when the beetles are disturbed and is a well-described process known

(48) "New Piperidine Alkaloids from Two Ladybird Beetles of the Genus *Calvia* (Coccinellidae)," Braekman, J-C,; Charlier, A.; Daloze, D.; Heilporn, S.; Pasteels, J.; Plasman, V.; Wang, S. *Eur. J. Org. Chem.* **1999**, 1749–1755.

as "reflex bleeding", which serves to protect the beetles from predators.[49] Lobeline[50] is an *N*-Me-containing piperidine isolated from *lobelia inflata*, which is generally found in eastern parts of North America and belongs to the lobelia family of alkaloids. Lobeline was originally referred to as Indian tobacco because the leaves of the plant were smoked by native Americans. Most recently, lobeline has been studied as a smoking deterrent and for the treatment of amphetamine addiction.[51] Indolizidine 209D,[52] belonging to the "bicyclic gephyrotoxin" family of alkaloids, is a 5-6-fused bicyclic piperidine that is isolated from the skin secretion of neotropical frogs. The indolizine alkaloids are a class of non-competative blockers for neuromuscular transmission.[53] And although only one example is shown, dendrodate 241D, another common structural feature of piperidine alkaloids is an alcohol functionality at the 4-position of the piperidine; dendrotate 241D is isolated from the skin of poison dart frogs.[54]

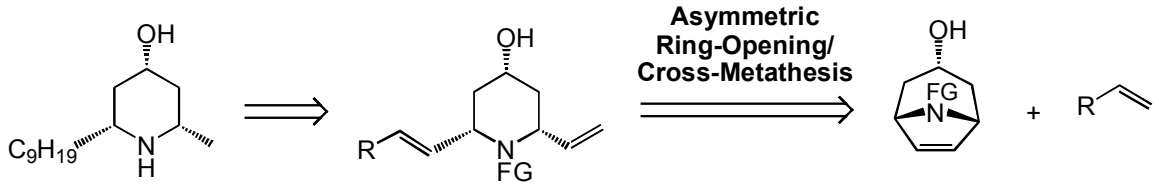
poison dart frog

3.1b Retrosynthetic Analysis of Dendrobate 241D; Substrates for AROM/CM. One set of substrates we studied for the enantioselective synthesis of piperidines were [3.2.1]-azabicycles, typified by **3.2** (Scheme 3.1). As shown in Scheme 3.1, the desymmetrization of an azabicycle such as **3.2** could be employed in the synthesis of piperidine alkaloids such as dendrobate 241D. Retrosynthetically, dendrobate 241D could be prepared from a 2,4,6-trisubstituted piperidine such as **3.1**. Piperidine **3.1** in turn could be accessed from a Mo-catalyzed AROM/CM of azabicycle **3.2** with an appropriate olefin cross-partner **3.3**. Although the free secondary alcohol is shown in azabicycle **3.2**, initial studies involved different hydroxyl protected substrates since Mo complexes are not compatible with alcohol functionalities. Additionally, the functional group on the nitrogen of **3.2** is undefined

(49) "Hemorrhage in a *Coccinellid* Beetle and Its Repellent Effect on Ants," Happ, G. M.; Eisner, T. *Science*, **1961**, *134*, 329–331.
(50) "History, chemistry and biology of alkaloids from *Lobelia inflata*," Felpin, F-X.; Lebraton, J. *Tetrahedron*, **2004**, *60*, 10127–10153.
(51) "Drugs to Fight Addictions," Thayer, A. *Chem. Eng. News* **2006**, *84*, 21–44.
(52) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4. Chapter 1.
(53) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albequerque, E. X. *Neurochemical Res.* **1986**, *11*, 1227.
(54) Daly, J. W.; Garraffo, H. M.; Spande, T. F. Amphibian Alkaloids. In *The Alkaloids*: Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 43. pp. 185–289.

since it was *apriori* not possible to predict what *N*-containing functionalities would be most compatible with chiral Mo complexes.

Scheme 3.1

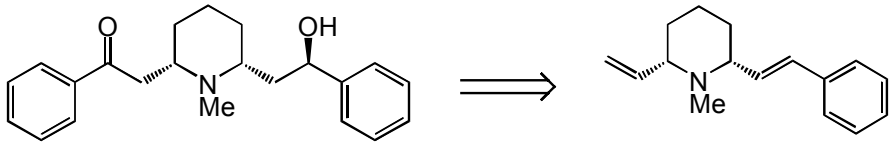


241D **3.1** **3.2** **3.3**

Iobelia inflata

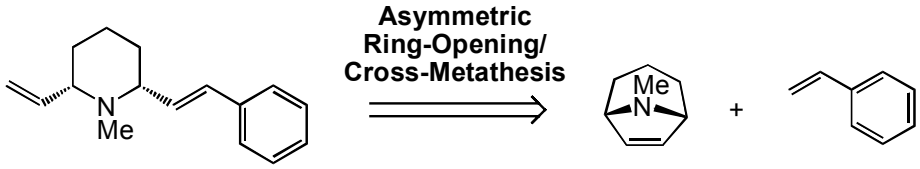
3.1c Retrosynthetic Analysis of Lobeline; Azabicyclic Substrates for the Enantioselective Synthesis of 2,6-syn-Substituted Piperidines. In addition to studying the desymmetrization of azabicycles such as **3.2** (Scheme 3.1, see above), the desymmetrization of [3.2.1]-azabicycles such as trop-6-ene **3.5** (Scheme 3.2) was investigated. Retrosynthetically, the alkaloid lobeline could be accessed from an *N*-Me piperidine such as **3.4**.

Scheme 3.2



Iobeline
isolated from *Lobelia inflata*

3.4



3.4 **3.5**

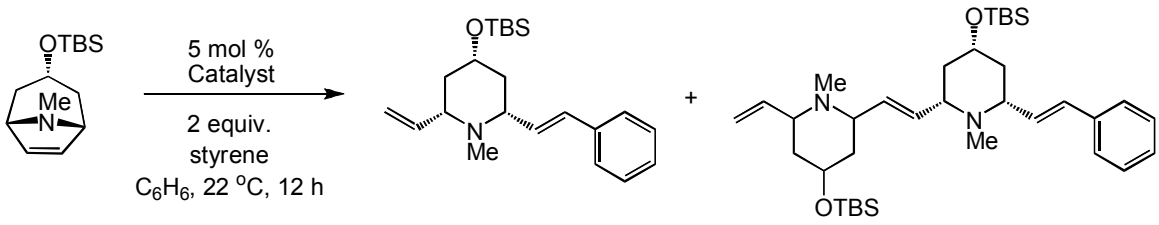
Interestingly, piperidine **3.4** could be accessed through a Mo-catalyzed AROM/CM of trop-6-ene **3.5** with styrene. Two facets of this desymmetrization reaction merit discussion. First, the requisite cross-partner for this desymmetrization is styrene, an olefin donor that we knew was compatible with chiral Mo complexes. Thus, we had reason to be optimistic about the enantioselective reaction. Secondly, the desymmetrization substrate **3.5** would possess a tertiary amine, which based on our

previous experience (see Chapter 2) and literature reports was expected be compatible with Mo complexes.

3.2 AROM/CM approach to *N*-Me Piperidines

3.2a Initial Screen of Mo Catalysts for the Enantioselective Synthesis of N-Me Piperidines. Initial screening for the Mo-catalyzed AROM/CM of azabicycles with styrene is shown in Scheme 3.3.

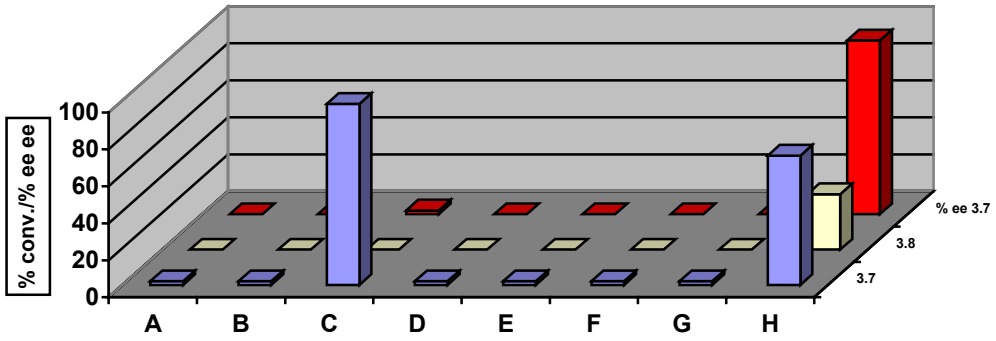
Scheme 3.3



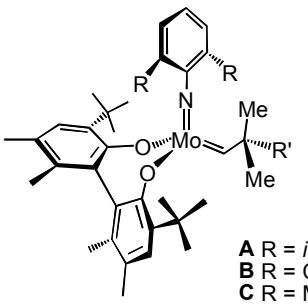
3.6

3.7 70%
>98% *E*:*Z*

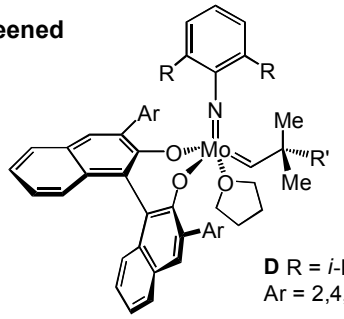
3.8 30%



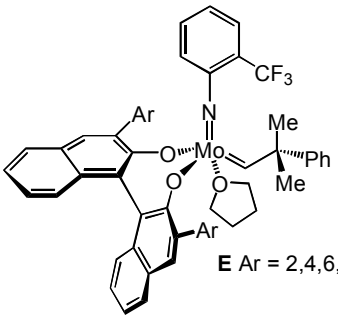
Catalysts Screened



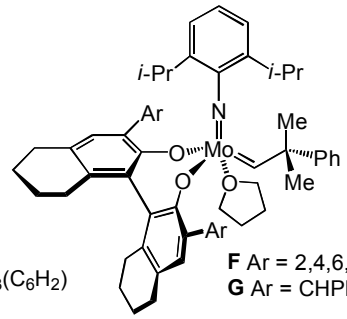
A R = *i*-Pr, R' = Ph
B R = Cl, R' = Me
C R = Me, R' = Ph



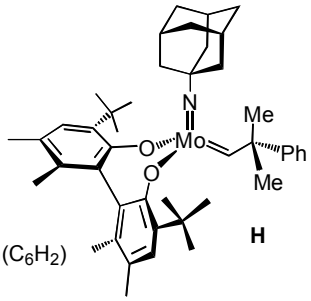
D R = *i*-Pr, R' = Ph
Ar = 2,4,6,-*i*-Pr$_3$(C$_6$H$_2$)



E Ar = 2,4,6,-*i*-Pr$_3$(C$_6$H$_2$)



F Ar = 2,4,6,-*i*-Pr$_3$Ph(C$_6$H$_2$)
G Ar = CHPh$_2$



H

The substrate we first decided to study was azabicycle **3.6**. By studying this particular azabicycle we were able to address the issues of: (1) Preparing piperidines with an alcohol functionality at the 4-position and (2) the feasibility of preparing enantioenriched *N*-Me-containing piperidines. To this end, a screen of available chiral Mo catalysts revealed that two complexes, **C** and **H**, are capable of providing the desired piperidine **3.7**. Chiral Mo complex **C**, however, delivers piperidine **3.7** in racemic form, were as chiral Mo complex **H** affords piperidine **3.7** in *94% ee* an in >98% *E:Z* olefin geometry.[55] The dimeric byproduct **3.8** is also formed during the course of the reaction. The isolated yields in Scheme 3.3, 70% yield for **3.7** and 30% yield for **3.8**, are the results obtained with Mo complex **H**. At this point, our next objective was to optimize the reaction conditions for the enantioselective synthesis of **3.7** and garner insight into the mechanism for this class of desymmetrization reactions.

3.2b Optimization and Mechanistic Studies into the Mo-catalyzed AROM/CM of Azabicycles. Based on previous studies concerning the Mo-catalyzed desymmetrization of norbornenes, we presumed that a Mo benzylidene ***i*** (Scheme 3.4, see below) performs the initial ring-opening of azabicycle **3.6** to provide the Mo alkylidene intermediate ***ii***. From here, reaction of ***ii*** with styrene would deliver the desired product if the Molybdenum alkylidene reacts with another equivalent of styrene. Alternatively, reaction of ***ii*** with another azabicyclic molecule of **3.6** would provide a Mo alkylidene ***iii***, which would lead to alkylidene ***iv***, and ultimately result in the formation of the dimer observed. This mechanistic proposal would be the most likely scenario if azabicyle **3.6** is strained enough to compete with styrene toward reaction with Mo alkylidene **3.9**. To better gauge the reactivity of this azabicyle, we performed a reaction of **3.6** with Mo complex **H** in the absence of styrene and monitored the outcome by ^{1}H NMR analysis. To this end, exposure of azabicycle **3.6** to 5 mol % of Mo complex **H** in deuterated benzene results in a rapid ring-opening metathesis polymerization (ROMP) reaction. As judged by ^{1}H NMR analysis, 75% of the initial azabicycle is polymerized within 30 min. As a comparison, when the reaction is performed with the

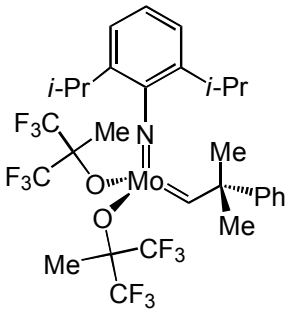
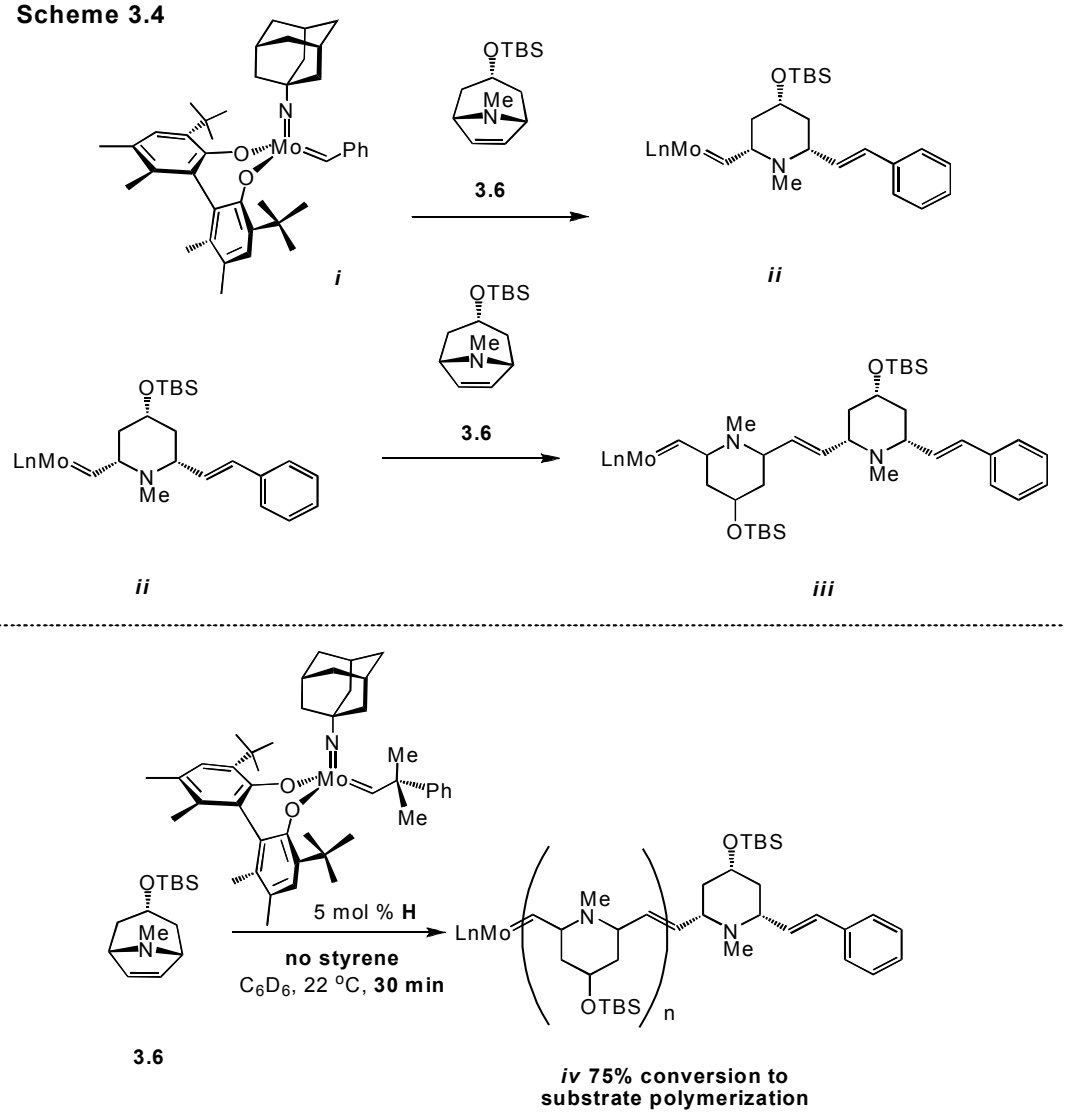


Figure 3.2 polymerization of azabicycle 3.6 within 30 min

(55) All piperidine products in this chapter were isolated with >98% *E:Z* olefin geometry as determined by ^{1}H NMR analysis; large *J*-coupling values, indicative of trans olefins, were found for all styrenyl olefinic protons in piperidine products. For a discussion of this concept, see: Silverstein, R. M.; Webster, F. X. In *Spectrometric Identification of Organic Compound*; Rose, N., Swain, E., Eds.; John Wiley & Sons, Inc. New York, 1998;

achiral Schrock catalyst (Fig. 3.2), azabicycle **3.6** is fully-consumed and polymerized within 30 min.

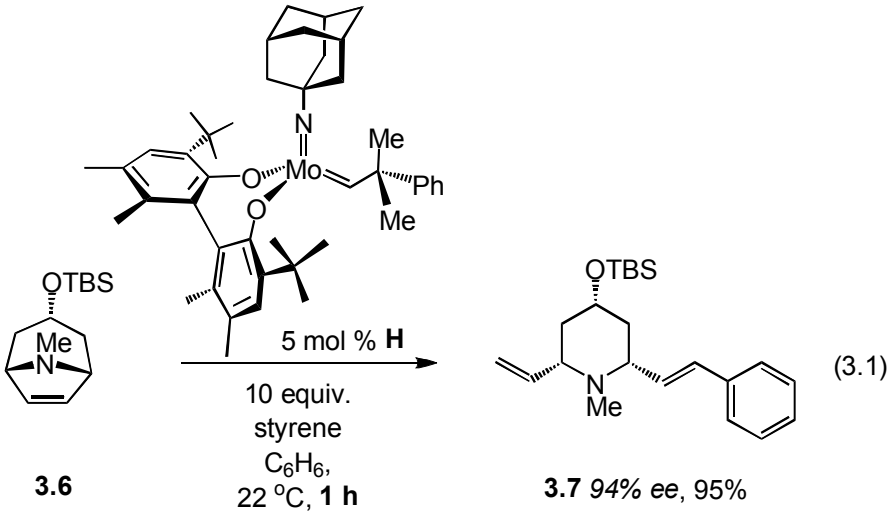
Scheme 3.4



One approach to solving the problem of dimer formation in the desymmetrization of azabicycle **3.6** was to increase the equivalents of styrene in the reaction (eq. 3.1, see below). During our initial screen of chiral catalysts for the AROM/CM of **3.6** we employed 2 equivalents of styrene. From previous experience, we knew that stillbene formation in the presence of Mo complexes is slow.[56] This means that Mo methylidene complexes, that are typically detrimental to ring-openin cross-metathesis reactions,

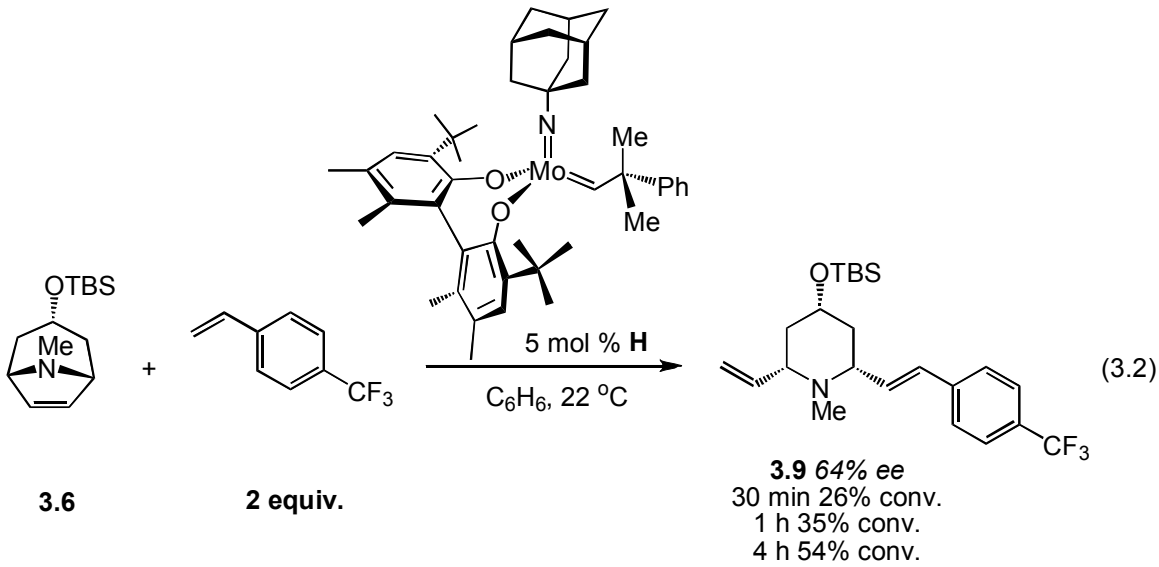
(56) "Catalytic Asymmetric Ring-Opening Metathesis/Cross Metathesis (AROM/CM) Reactions. Mechanism and Application to Enantioselective Synthesis of Functionalized Cyclopentanes," La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock R. R.; Hoveyda A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767–7778.

should not be formed in appreciable levels. Gratifyingly, after screening a variety of styrene equivalents in the desymmetrization of **3.6**, we found that utilizing 10 equivalents of styrene provided the best results for this transformation. Treatment of azabicycle **3.6** with 5 mol % Mo complex **H** in the presence of 10 equivalents of styrene affords piperidine **3.7** in *94% ee* and 95% yield after 1h. These optimized reaction conditions were then employed to study the scope of Mo-catalyzed AROM/CM reactions of a variety of azabicycles with various electronically and sterically modified styrene cross-partners.

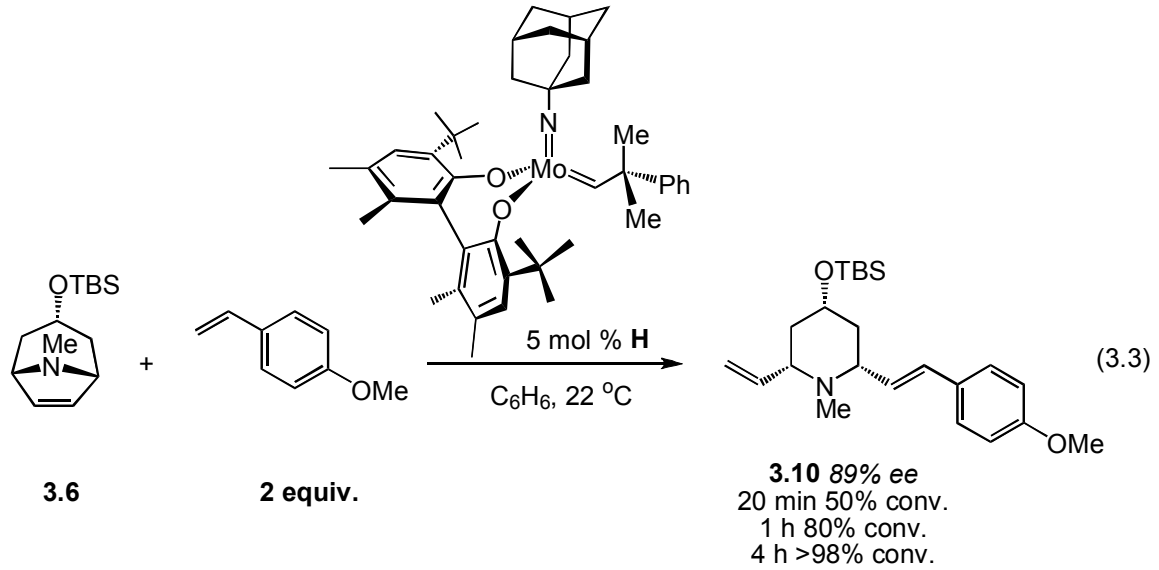


3.6 **3.7** *94% ee*, 95% (3.1)

3.2d Influence of Electron Poor and Electron Rich Styrenes on the Reaction Rate and Enantioselectivity of AROM/CM Reactions. Among one of the most interesting features of this class of catalytic enantioselective olefin metathesis reactions is the effect that the aryl-olefin cross-partner has on the outcome of the transformation. Specifically, we found that in AROM/CM reactions of azabicycles with electron rich and electron poor styrene cross-partners the piperidine products were formed in different rates and selectivities. First, we studied the AROM/CM of azabicycle **3.6** with 2 equivalents of *p*-CF_3-styrene in the presence of 5 mol % **H** (eq. 3.2, see below) and monitored the conversion of the reaction by ^{1}H NMR analysis. Two equivalents of *p*-CF_3-styrene were initially used because we wanted to conduct a direct comparison with the results we observed during our initial screen in the metathesis of **3.6** with styrene (Scheme 3.3, see above). To this end, treatment of azabicycle **3.6** with 5 mol % Mo complex **H** in the presence of 2 equivalents of *p*-CF_3-styrene proceeds to 26% conversion to the desired product **3.9** within 30 min. The reaction proceeds to 35% conversion to the desired product within 1 h and 54% conversion within 4 h. Notably, the product is isolated in only *64% ee*, as opposed to *94% ee* when the olefin cross-partner is styrene.

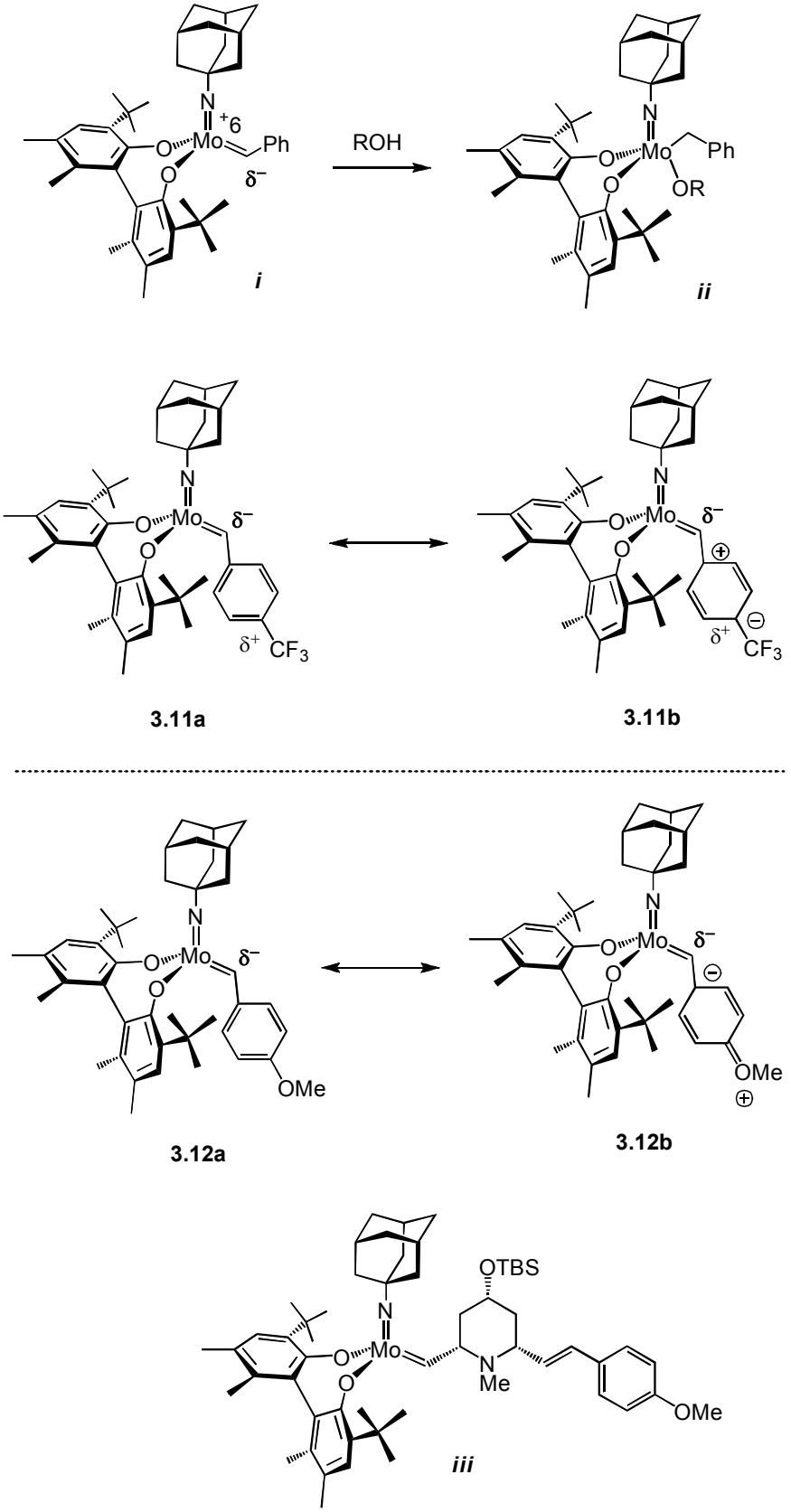


The results obtained in the AROM/CM of azabicycle **3.6** with *p*-CF_3-styrene are in stark contrast to the results observed when an electron rich olefin, *p*-OMe-styrene, is used as an olefin cross-partner. As shown in eq. 3.3, under identical reaction conditions to those used in eq. 3.2, desired piperidine **3.10** is formed at a faster rate and in greater enantiopurity. Treatment of azabicycle **3.6** with 5 mol % of Mo complex **H** in the presence of 2 equivalents of *p*-OMe-styrene proceeds to 50% conversion to the desired product **3.10** within 30 min. The reaction proceeds to 50% conversion to the desired product within 1 h and >98% conversion within 4 h. A proposal for this difference in reactivity follows.



Prior to presenting the following mechanistic proposal it should be noted that there is no definitive evidence for this hypothesis, rather it is an attempt to explain the results observed by way of empirical evidence. As illustrated in Figure 3.2 (see below),

Mo benzylidene intermediates such as ***i*** are highly reactive for olefin metathesis reactions because the benzylidene carbon possesses significant δ^- character and in addition the highly Lewis acidic nature at the metal center ($^+$6) facilitates the coordination of olefins. The drawback to such reactivity is exemplified by what would happen to Mo benzylidene ***i*** in the presence of an alcohol; the benzylidene carbon would undergo protonatation and the complex would possess an additional alkoxy ligand resulting in formation of ***ii***. Now, if we apply these principles to benzylidenes **3.11** and **3.12**, previously discussed in equations 3.2 and 3.3, we can perform an analysis to explain their differences in reactivity with azabicycle **3.6** for AROM/CM reactions. A benzylidene such as **3.11a**, formed from reaction of Mo complex **H** with *p*-CF_3-styrene (see eq. 3.2 above), would decrease the electron density at the benzylidene carbon and therefore decrease electron density at the metal center making it more Lewis acidic and consequently more likely to bind an olefin. This can be more easily seen in **3.11b**, a resonance form of **3.11a**. Since the benzylidene carbon would now donate electron density into the aromatic ring it would be expected to be less reactive in olefin metathesis reactions, and this is what we observed in the AROM/CM shown in eq. 3.2 above. Another way of rationalizing the inherent reactivity of this type of Mo benzylidene is by viewing **3.11a** as a stabilized, and therefore less reactive benzylidene. This electronic effect would be reversed in the case of a Mo benzylidene such as **3.12a**, formed from reaction of Mo complex **H** with *p*-OMe-styrene (see eq. 3.3 above); this effect being more evident in **3.12b**, a resonance form of **3.12a**. In this case, the benzylidene carbon would possess more electron density, and thus be more reactive. Benzylidene **3.12a** can be viewed as a destabilized alkylidene by the repulsive effect of having two δ^- carbon atoms adjacent to each other. Furthermore, if we consider Mo alkylidene ***iii***, the initial product from the ring-opening metathesis of **3.6** with Mo complex **3.12a**, we can see that de-stabilization at the benzylidene carbon would be reduced. In short, it appears that, at least in Mo-catalyzed AROM/CM of azabicycles, electron poor benzylidenes lead to decrease metathesis activity whereas electron rich benzylidenes lead to increased metathesis activity. This mechanistic proposal relies on the rate-determining step of the AROM/CM reaction to be initial ring-opening of the strained azabicyle, rather than formation of the subsequent metallacyclobutane and its break down to generate the piperidine product. However, it is still not clear to us what the rate-determining step is in these reactions.



i *ii*

3.11a **3.11b**

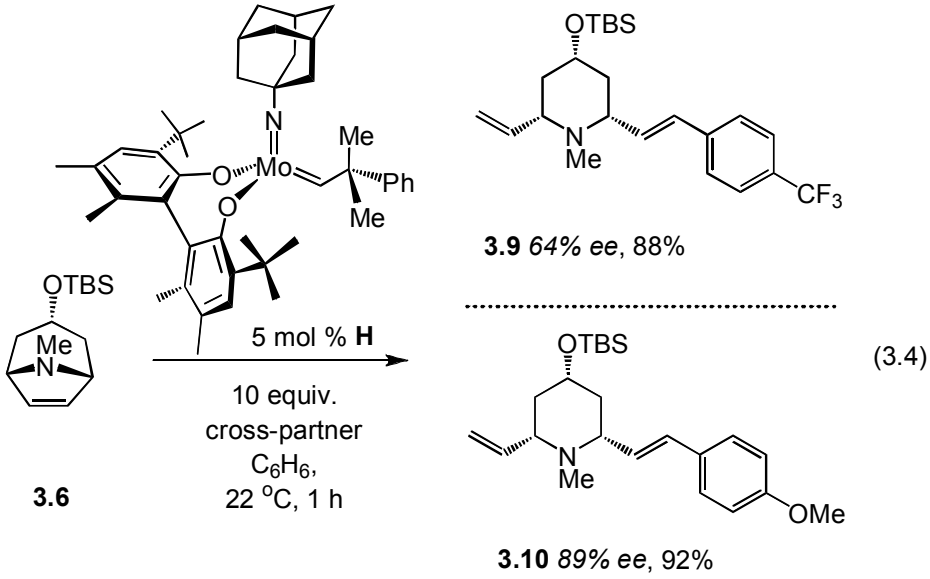
3.12a **3.12b**

iii

Figure 3.2 Electronics of Different Alkylidenes

As we have seen the electronics of aryl olefins plays a crucial role in the rates of olefin metathesis reactions. When we employ optimized reaction conditions, however, we observe that these electronic effects are moot since reactions are complete within the same reaction time (eq. 3.4). To this end, exposure of azabicycle **3.6** to 5 mol % Mo complex **H**, in the presence of *p*-CF_3-styrene (10 equiv.) or *p*-OMe-styrene (10 equiv.) delivers the desired piperidines **3.9** in *64% ee* (88% yield) and **3.10** in *89% ee* (92% yield) within 1h. Since increasing cross-partner equivalents clearly results shorter reaction times these results may suggest that the rate-determing step in these reactions is release of the Mo alkylidene formed after the initial ring-opening metathesis of azabicycles.

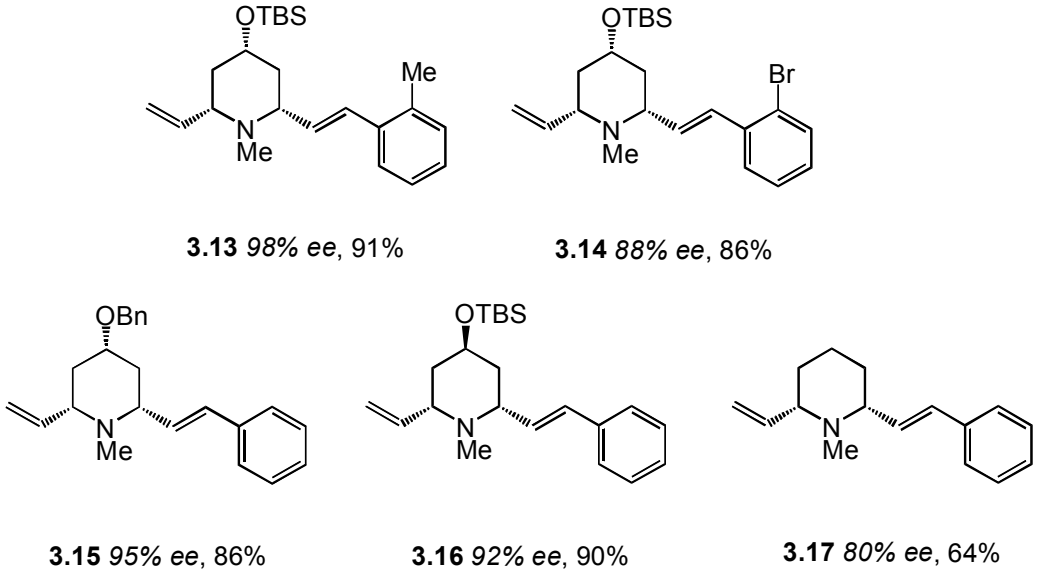
It should be mentioned that at this time it is difficult to put forth a model accounting for the difference in enantioselectivities observed between these two reactions. One explanation, however, is that benzylidenes **3.11** and **3.12** (see Fig 3.2 above) exist in different syn/anti ratios, and thus different selectivity levels; further mechanistic studies are required to support this hypothesis.



3.2e Scope of Aromatic Cross-Partners with N-Me Azabicycles. The next phase of our studies involved expanding the scope of our newly developed method; employing the optimized reaction conditions with Mo complex **H**,[57] we were able to form various enantioenriched *N*-Me piperidines (Figure 3.3, see below). Piperidine **3.14** is isolated in *98% ee* and 91% yield. Of interest in the formation of this piperidine is that *o*-Me-styrene is used as the olefin cross-partner in the metathesis. At the outset we were not

(57) Reaction conditions involved 1 equiv. of the requisite azabicycle, 5 mol % Mo complex **H** and 10 equiv. olefin cross-partner in a 1.0 M solution in C_6H_6 at 22 °C. All reactions were stopped after 1 h.

sure if the metathesis activity of Mo complexes would be inhibited by *o*-substituted styrenes. Piperidine **3.14** is isolated in *88% ee* and 86% yield. Notably, this piperidine is contains an aryl bromide that can be potentially employed in various metal-catalyzed cross-coupling reactions.[58] To show that orthogonal hydroxyl protecting groups can be employed in this class of transformations we utilized an azabicyclic substrate with a benzyl protecting group as opposed to a silyl ether. To this end, piperidine **3.15** is isolated in *95% ee* and 86% yield. To demonstrate the stereochemistry at the hydroxy functionality is not detrimental to the asymmetric reaction we employed an azabicyclic substrate with opposite stereochemistry at the oxygenated carbon. To this result, piperidine **3.16** is isolated in *92% ee* and 90% yield. As was mentioned in the introduction of this chapter, we directed our studies toward the synthesis of 2,4,6-substituted piperidines in addition to the enantioselective synthesis of piperidines lacking substitution at the 4-position. To this end, piperidine **3.17** is isolated in *80% ee* and 64% yield.[59] Unfortunately, in this reaction piperidine **3.17** is isolated in moderate selectivity because this piperidine shares many structural features of previously mentioned alkaloids, for example lobeline.



3.13 *98% ee*, 91% **3.14** *88% ee*, 86%

3.15 *95% ee*, 86% **3.16** *92% ee*, 90% **3.17** *80% ee*, 64%

Figure 3.3 Scope of *N*-Me Piperidine Products

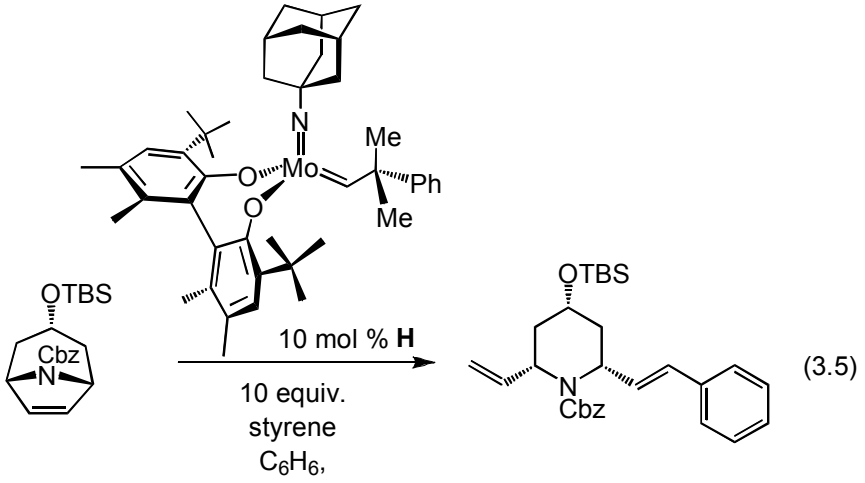
(58) (a) "Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds," Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) "The Heck Reaction as a Sharpening Stone of Palladium Catalysis," Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009–3066. (c) "Selected Patented Cross-Coupling Reaction Technologies," Corbet, J.-P.; Mignani, G. *Chem. Rev*. **2006**, *106*, 2651–2710. (d) "Aryl-Aryl Bond Formation by Transition-Metal-Catalyzed Direct Arylation," Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174–238.

(59) The reason for the low isolated yield of **3.17**, in comparison to other piperidines in Fig. 3.3, is that we found **3.17** to be somewhat volatile.

3.3 Mo-catalyzed AROCM of Carbamate-Protected Azabicycles

3.3a Enantioselective Synthesis of Cbz-protected Piperidines. Next, we turned our attention on the desymmetrization of carbamate-protected azabicycles. One key issue we wanted to address, besides studying different substitution at nitrogen, was whether it would be feasible to perform the ring-opening of sp^2 hybridized azabicycles. The synthesis of carbamate-protected azabicycles, discussed in the experimental section of this chapter, have one interesting caveat; these substrates are prepared by *ring-closing metathesis* reactions of 2,6-divinyl piperidines.[60] These details gave us reason to believe ring-opening reactions of carbamate-protected azabicycles might not be feasible.

To our initial skepticism, we found Mo complexes to be compatible with Cbz-protected azabicycles for the enantioselective synthesis of piperidines (eq. 3.5).



3.18 **3.19** *90% ee*, 93% >98% conversion (3.5)

Treatment of azabicycle **3.18** with 10 mol % Mo complex **H** in the presence of 10 equivalents of styrene affords piperidine **3.19** in *90% ee*, 93% yield, and >98% conversion after 24 h. At this point, a comparison is merited between this reaction and the AROM/CM reactions of *N*-Me azabicycles. First, we found the optimal catalyst loading in formation of **3.19** to be 10 mol % as opposed to the catalyst loadings of 5 mol % used in the desymmetrization of *N*-Me azabicycles; reactions to form **3.19** with 5 mol % of Mo complex **H** proceeded to 45% conversion of **3.19** after 24 h.[61] Second, despite performing the reaction to form **3.19** with 10 mol % of Mo Complex **H**, the reaction is

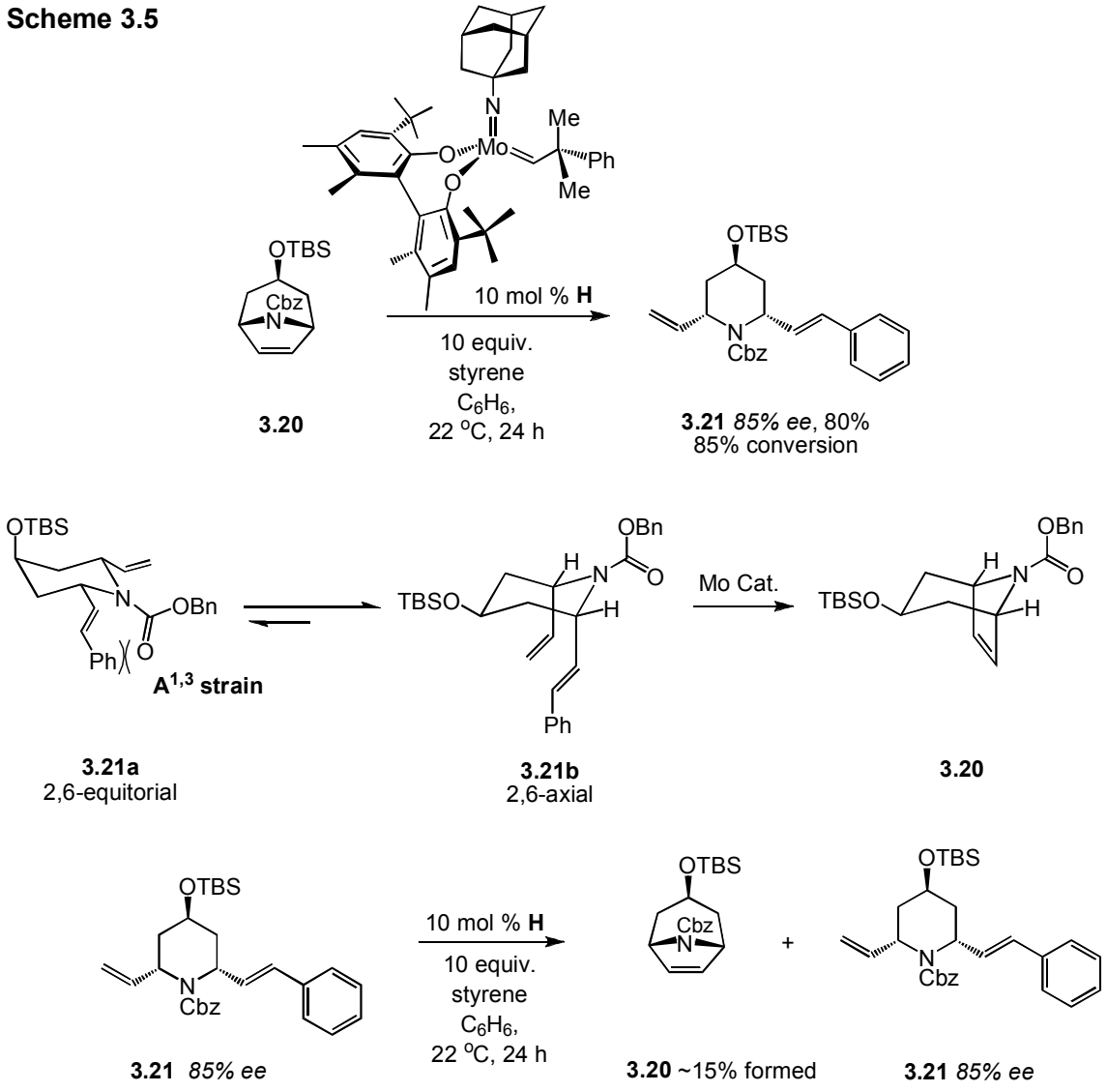
(60) A detailed discussion of the reasons why the ring-closures of carbamate-protected piperidines is included in the following sub-section.

(61) Additionally, The formation of **3.19** with 5 mol % and 10 mol % **H** was monitored by ^{1}H NMR analysis. With 5 mol % of **H**, piperidine **3.19** is formed in <5% conversion after 1 h, ~20% conversion after 3 h, and ~30% conversion after 6 h. With 10 mol % of **H**, piperidine **3.19** is formed in ~25% conversion after 1 h, ~40% conversion after 3 h, and ~56% conversion after 6 h.

complete within 24 h, as opposed to a reaction time of 1 h for the synthesis of *N*-Me azabicycles. Based on these differences, it is likely that carbamate-protected azabicycles are much less strained than their *N*-Me counterparts. An additional point of interest in these enantioselective metathesis reactions is that Mo complex **H** delivers the same antipode of piperidine products; *N*-Me piperidines and *N*-Cbz piperidines are formed with the same absolute stereochemistry. This was verified by chemical correlation; the carbamate of **3.19** was reduced to deliver *N*-Me piperidine **3.7** (see eq. 3.1 above) and was found to have the same sense of enantioinduction.

3.3b Reversibility of Cbz-protected Piperidine. The next substrate we studied was azabicycle **3.20**, a diastereomer of azabicycle **3.18**, and results are summarized in Scheme 3.5.

Scheme 3.5



Treatment of azabicycle **3.20** with 10 mol % of Mo complex **H** in the presence of 10 equivalents of styrene furnishes Cbz-protected piperidine **3.21** in *85% ee*, 85% conversion, and 80% yield after 24 h. A feature of this reaction that quickly struck our attention was that the reaction did not proceed to completion, in contrast to the metathesis of **3.18** (see eq. 3.5 above). In light of this observation we raised the following question: is it possible that this metathesis reaction is reversible by way of the Mo catalyst performing a ring-closing metathesis of piperidine **3.21**? It is well documented that the preferred conformation of sp^2 hybridized piperidines with substituents at the 2- and 6-position is that in which the substituents are positioned in a pseudo-axial and not pseudo-equatorial orientation.[62] These reports have demonstrated that in piperidines, such as **3.21a** in Scheme 3.5 (see above), the sp^2 character of the nitrogen group causes severe $A^{1,3}$-strain which is relieved when the piperidine adopts a conformation such as **3.21b**. From this analysis we can see that the olefins at the 2- and 6-position of this piperidine would be in perfect alignment to undergo a metallacyclobutane formation in the presence of a Mo catalyst and re-form the starting azabicycle **3.20**. To explore this possibility we subjected the isolated piperidine **3.21** to the AROM/CM reaction conditions. Indeed, we found that Mo complex **H** is capable of performing a ring-closing metathesis of **3.21** in roughly 15% conversion with no change in its initial enantiopurity, and in addition delivers azabicycle **3.20** (as judged by ^{1}H NMR and chiral HPLC analysis).

3.3c Scope of Enantioselective Synthesis of Cbz-protected Piperidines. Our subsequent objectives involved studying the scope of enantioenriched Cbz-protected piperidine products we could form through Mo-catalysis, illustrated in Figure 3.4 (see below). In metathesis reactions to form these piperidines we employed the optimized reaction conditions previously discussed.[63] First, we performed the AROM/CM reaction of a Cbz-protected azabicyclic substrate lacking a hydroxyl functionality.

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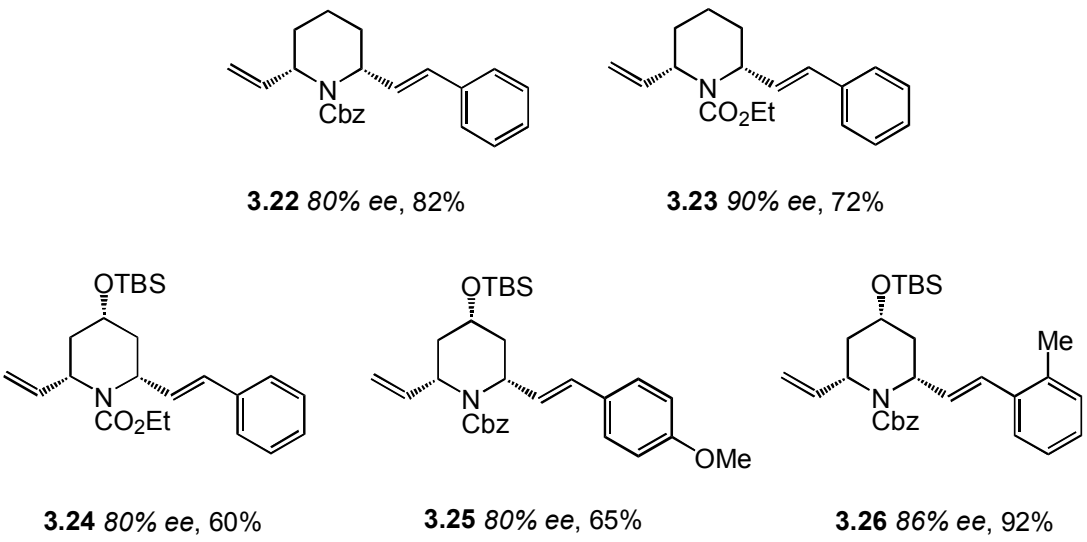
(62) (a) "Allylic strain in six-membered rings," Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413. (b) "The "A" value for the methyl group in 2-methylpiperidines," Fraser, R. R.; Grindley, T. B. *Tetrahedron Lett.* **1974**, *15*, 4169–4172. (c) "Synthesis of 2,6-diacetonylpiperidine. X-ray diffraction analysis of its N-benzoyl derivative," Quick, J.; Mondello, C.; Humora, M.; Brennan, T. *J. Org. Chem.* **1978**, *43*, 2705–2708.

(63) Reaction conditions involved 1 equiv. of the requisite azabicycle, 10 mol % Mo complex **H** and 10 equiv. olefin cross-partner in a 1.0 M solution in C_6H_6 at 22 ^oC. All reactions were stopped after 24 h.



3.22 *80% ee*, 82%

3.23 *90% ee*, 72%

3.24 *80% ee*, 60%

3.25 *80% ee*, 65%

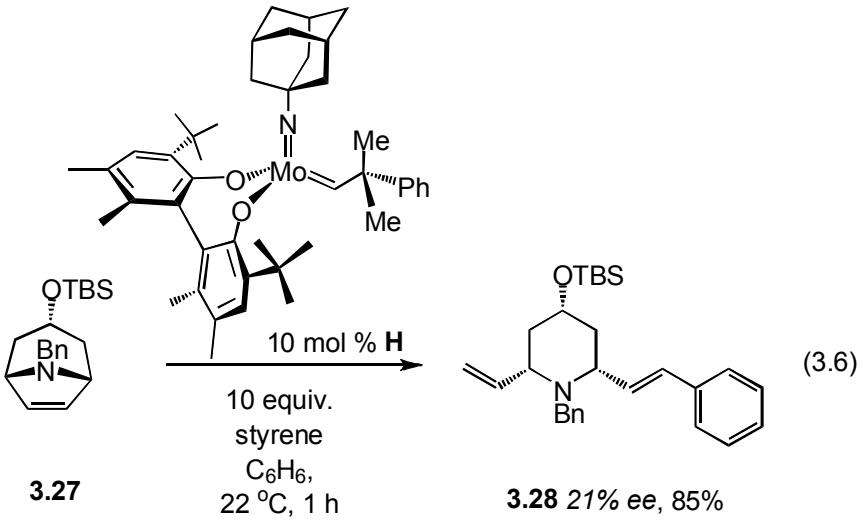
3.26 *86% ee*, 92%

Figure 3.4 Scope of Carbamate Piperidine Products

To this end, piperidine **3.22** is isolated in *80% ee* and 82% isolated yield. We then moved on to study the desymmetrization of an ethyl-carbamate protected azabicycle to see how a different smaller carbamate-protecting group would effect the selectivity of the reaction. This change in the protecting group on nitrogen proved beneficial and we found the metathesis reaction to be more selective with the smaller carbamate. Ethyl-carbamate protected piperidine **3.23** is isolated in *90% ee* and 72% yield (vs. *80% ee* in **3.22**). Next, we performed the AROM/CM on an azabicycle containing a silyl ether. Similar to our first carbamate-protected azabicyclic substrate (see **3.18** in eq. 3.5 above), but with the smaller ethyl-carbamate protecting group. To this result, piperidine **3.24** is isolated in *80% ee* and 60% yield. The results of this reaction proved that the smaller protecting group does not always lead to products of greater selectivity; compare **3.19** of *90% ee* in eq. 3.5 with **3.24** of *80% ee* in Fig. 3.4 (see above). Additional points of mention for this class of AROM/CM reactions include the use of electronically and sterically modified aryl aromatic cross-partners. Piperidine **3.25**, generated with the use of *p*-OMe-styrene as olefin-cross partner in the asymmetric reaction, is isolated in *80% ee* and 65% isolated yield. Finally, with the use of *o*-Me-styrene as the olefin cross-partner, the catalytic enantioselective reaction delivers piperidine **3.26** in *86% ee* and 92% yield.

3.4 Mo-catalyzed AROM/CM of Bn-protected Azabicycles

3.4a Low Selectivity in the Enantioselective Synthesis of N-Bn Piperidines. In our continuing efforts to understand the limits and breadth of enantioenriched piperidine products accessible through olefin metathesis, we investigated the desymmetrization of Bn-protected azabicycles (eq. 3.6, see below).

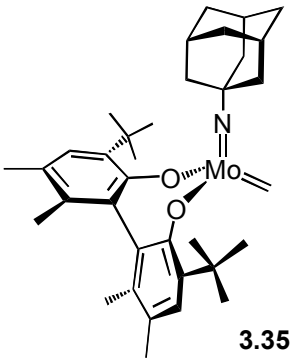


3.27 **3.28** *21% ee*, 85% (3.6)

Unlike previous desymmetrization reactions that delivered *N*-Me and Cbz-protected piperidine products in high enantioselectivity, reactions that provided Bn-protected amines were only slightly selective. Treatment of azabicycle **3.27** with 10 mol % of Mo complex **H** in the presence of 10 equiv. of styrene furnishes piperidine **3.28** in only *21% ee* and 85% yield after 1 h. The origin of this major dissimilarity in selectivity remains unclear. One possibility is that the Lewis basic electrons on nitrogen (in the case of *N*-Me azabicycles) or electrons of the oxygens (in the case of the carbamate-protected azabicycles) serve to direct the Mo complex during the enantiodetermining step of the metathesis reaction. In the case of *N*-Bn-protected azabicycles, the size of the Bn group might diminish the ability of the lone pair electrons on nitrogen to effectively direct the Mo complex during the enantiodetermining step of the metathesis reaction. Despite these observations being a limitation of Mo-catalyzed enantioselective olefin metathesis reactions, they provided impetus for us to study Ru catalysts for this class of transformations (discussed in Ch 5).

3.5 Mo-catalyzed AROM/CM of Azabicycles with Non-Aryl Olefin Cross-Parnters

3.5a Mo-catalyzed AROM/CM Reactions of Alkyl Olefin Cross-partners. After studying AROM/CM reactions of aryl-olefin cross-partners we pursued reactions involving non-aryl olefin cross-partners. During these studies we found that asymmetric reactions with non-aryl olefin cross-partners were generally not as selective and efficient as reactions with aryl-olefins. Illustrated in Scheme 3.6 (see below) are studies we performed on the

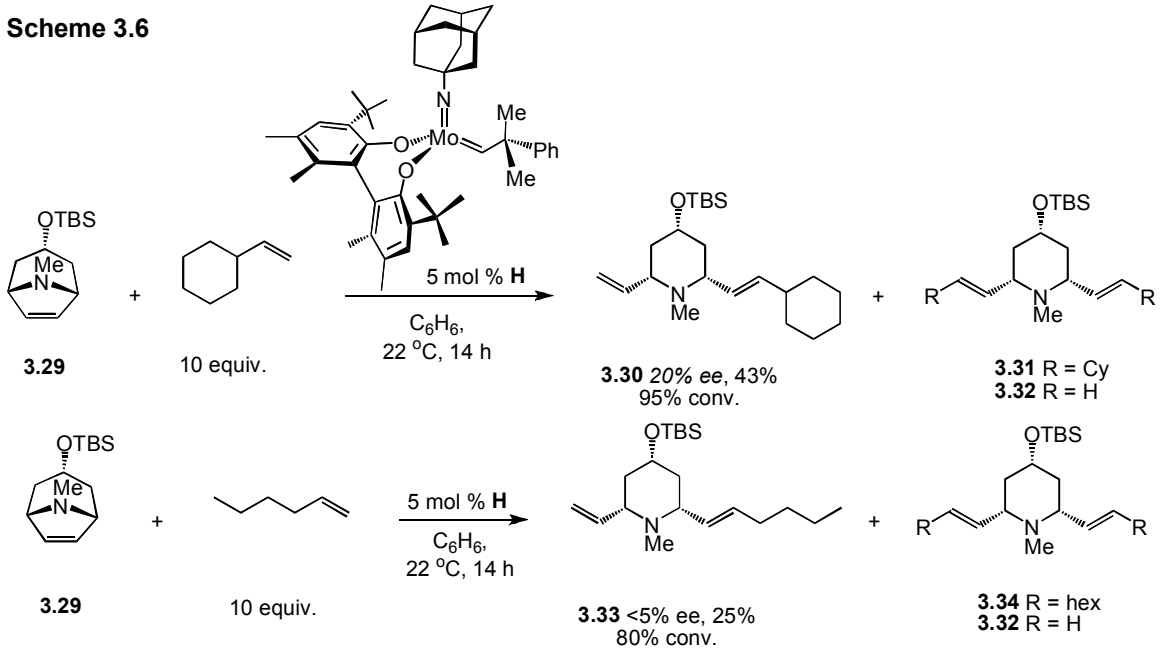


3.35

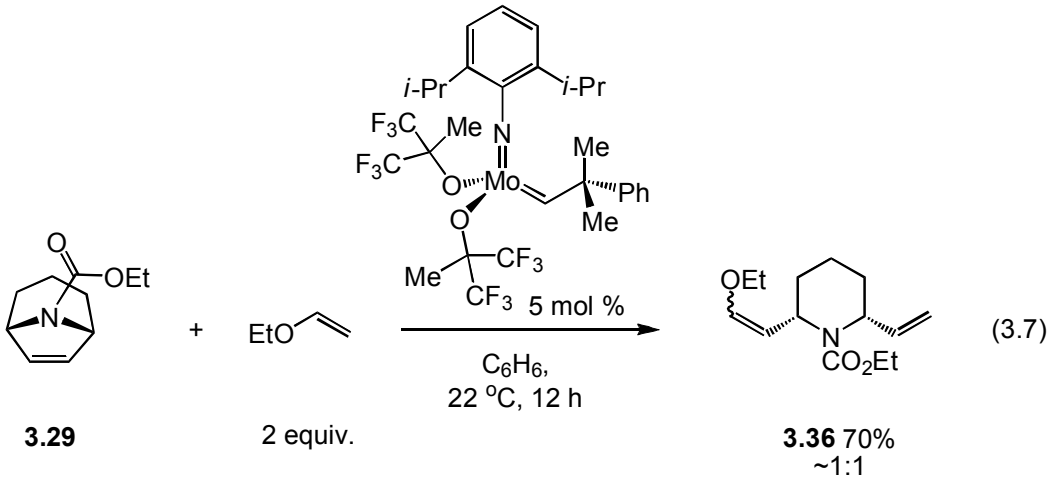
Figure 3.5 Mo Methylidene

AROM/CM of azabicycle **3.29** with alkyl olefins. To this end, exposure of **3.29** to 5 mol % Mo complex **H** and 10 equiv. vinylcyclohexane delivers the desired piperidine **3.30** in *20% ee*, 43% yield, and 95% conversion (consumption of starting material as judged by ^{1}H NMR analysis) after 14 h. And treatment of azabicycle **3.29** with 5 mol % of Mo complex **H** in the presence of 10 equiv. of hexene delivers the desired piperidine **3.33** in *<5% ee*, 25% yield, and 80% conversion (consumption of starting material as judged by ^{1}H NMR analysis) after 14 h. A reason for the low yields in these reactions is the formation of *meso* byproducts arising from a *bis*-cross metathesis of the olefin cross partner, **3.31** in the case of vinyl cyclohexane and **3.34** in the case of hexene. The other *meso* byproduct from the reactions, the 2,6-divinyl piperidine **3.32**, presumably forms from a ring-opening of azabicycle **3.29** with Mo methylidene intermediate **3.35**, shown in Figure 3.5. Mo methylidene **3.35** forms through the homodimerization of either vinylcylohexene and hexene; these homodimers are observe by ^{1}H NMR analysis of the reaction mixture. These undesired side reactions are likely responsible for the low enantioselectivity observed in piperidines **3.30** and **3.33**. It should be noted that the alkyl olefin cross partners would be more readily consumed through dimmerization if less than 10 equiv. of alkyl cross-partners are employed in these reactions. In addition, Mo methylidene intermediates have been shown to undergo decomposition pathways, explaining why these reactions do not proceed to complete consumption of **3.29**.

Scheme 3.6



3.5b Mo-catalyzed AROM/CM Reactions of Miscellaneous Olefin Cross-partners. Moving our attention away from aryl and alkyl olefin cross-partners, we explored the potential of conducting AROM/CM reactions of azabicycles with enol-ether olefin cross-partners (eq. 3.7).



After screening of available Mo complexes we found that only the achiral Schrock Mo complex was compatible with ethyl vinyl ether for the ring-opening cross-metathesis of azabicycle **3.29**. Thus, treatment of azabicycle **3.29** with 5 mol % of the Mo Schrock catalyst in the presence of 2 equiv. of ethyl vinyl ether delivers the desired piperidine product in 70% yield, as a 1:1 mixture of *E*- and *Z*-olefin isomers, within 12 h. This result underlines the need for the development of more active chiral Mo complexes and provides potential future areas of study in asymmetric ring-opening cross-metathesis reactions. Other olefin cross-partner investigated that proved incompatible with either chiral or non-chiral Mo complexes include vinyl trimethoxysilane, vinyl pinocal borane, allyl pinacol borane, and acrylonitrile.

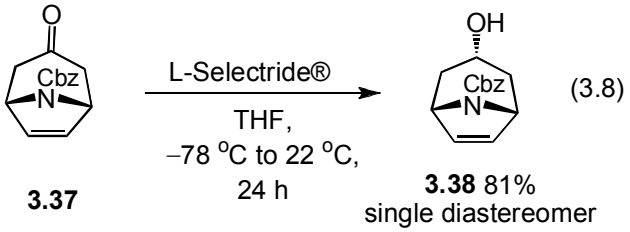
3.6 Conclusions

This chapter disclosed the first examples of Mo-catalyzed asymmetric ring-opening metathesis/cross-metathesis reactions for the enantioselective syntheses of piperidines. It was shown that *N*-Me- and carbamate-containing azabicycles were compatible with Mo complexes for the desymmetrization reactions. These investigations also demonstrated that a variety of aryl-olefin cross-partners can be employed for catalytic enantioselective reactions. Additionally, these studies provided insight into the mechanism of this class of ring-opening/cross-metathesis reactions. Specifically, it was shown that formation of Mo benzylidene complexes is required prior to the initial ring-opening reactions of azabicycles. It was also shown that azabicycles exhibit different reactivities towards electron poor and electron rich aryl-olefins. Furthermore, it was

shown that certain desymmetrization reactions are in equilibrium and that Mo complexes can perform the ring-closing of piperidine products. Importantly, the products formed bear close resemblance to a variety of biologicially naturally occurring alkaloids, pointing to the potential application of this method to natural product synthesis. The shortcomings of this method, namely in the synthesis of *N*-Bn piperidines and cross-metathesis reactions with alkyl olefins underline the need to continue developing novel Mo complexes for asymmetric olefin metathesis.

3.7 Experimental Section[64]

Synthesis and spectral data for azabicyclic substrates that deliver 2,4,6-substituted piperidine products. For the preparation of azabicyclic substrates that provide 2,4,6-substituted piperidines, we utilized intermediate azabicycle **3.37**, which has been previously prepared.[65]

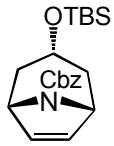


Preparation of azabicycle **3.38** (eq. 3.8). A two-neck 200 mL round-bottom flask, fitted with addition funnel, was charged with **3.37** (1.00 g, 3.89 mmol), THF (40 mL), and cooled to −78 °C in a dry ice/acetone bath. L-Selectride® (a 1.00 M solution in THF, 4.30 mL, 4.28 mmol, 1.1 equiv.) was added to this solution over 10 min by addition funnel, after which time the mixture was warmed to 22 °C, and the resulting mixture was allowed to stir for 1 h. At this period, the reaction mixture was cooled to 0 °C in an ice bath, and the reaction was quenched by the (slow and sequential) addition of a 1.0 M solution of NaOH (20 mL), and a solution of H_2O_2 (37 wt % in H_2O, 20 mL). The resulting mixture was warmed to 22 °C, and was allowed to stir for 15 min. At this time, EtOAc (20 mL), and a 1.0 M solution of HCl (20 mL) were added to this mixture. The resulting mixture was transferred to a 250-mL separatory funnel, and the resulting biphasic layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the volatiles were

(64) In some instances, rotamers of carbamate- and amide-containing azabicycles were observed as determined by variable temperature ^{1}H NMR analysis. Additionally, this is likely the reason that in some instances ^{13}C NMR spectra do not appear to have the correct number of carbon peaks. In these instances the ^{13}C NMR spectra is reported as observed.

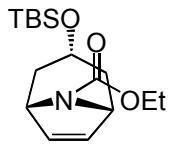
(65) "Synthesis of Bridged Azabicyclic Structures via Ring-Closing Olefin Metathesis," Neipp, C. E.; Martin S. F. *J. Org. Chem.* **2003**, *68*, 8867−8878.

removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (3:2 EtOAc:hexanes) to provide **3.38** as colorless oil and as a single diastereomer (0.811 g, 3.12 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$):[66] 1:1 mixture of carbamate rotamers, δ 7.37–7.31 (m, 5H), 6.43–6.30 (m, 2H), 5.17 (s, 2H), 4.67–4.60 (m, 2H), 3.97–3.91 (m, 1H), 2.34–2.14 (m, 2H), 1.82–1.76 (d, J = 14.8 Hz, 2H).



3.18

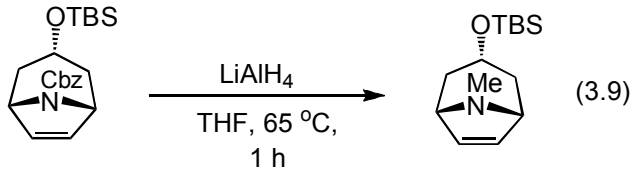
Preparation of azabiycle **3.18**. Azabicycle **3.18** was prepared by TBS protection of the alcohol in azabicycle **3.38**.[67] The relative stereochemistry of the protected hydroxyl group carbon was determined by correlation to nOe analysis of azabicycle **3.20**, the diastereomer of **3.18** (see below). To further verify the identity of these diastereoisomers, a nOe experiment of **3.18** was also performed. IR (neat): 2951 (m), 2920 (m), 2858 (m), 1710 (s), 1412 (m) 1300 (m), 1244 (m), 1089 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers:[68] δ 7.37–7.26 (m, 5H), 6.04–5.99 (m, 2H), 5.18 (s, 2H), 4.68–4.65 (m, 2H), 3.99 (t, J = 5.2 Hz, 1H), 2.25–2.00 (m, 2H), 1.60–1.52 (m, 2H), 0.81 (s, 9H), –0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 137.1, 134.0, 133.6, 128.6, 128.0, 127.9, 66.7, 65.1, 57.4, 36.0, 35.2, 25.8, 17.9, –4.8. HRMS ES (*m/z*) Calcd for $C_{21}H_{31}NO_3Si$ 373.2073 M^+ Found 373.2071.



precursor to piperidine **3.24**

The azabicyclic precursor to **3.24** (shown here on the left) was prepared by utilizing the same sequence to form **3.18**, however, ethylchloroformate was used in the place of CbzCl at the beginning of the synthetic route (This azabicycle was isolated as colorless oil and in comparable yields to those in the preparation of azabicycle **3.18**). IR (neat): 2955 (m), 2923 (m), 2848 (w), 1702 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers:[68] δ 6.18–6.02 (m, 2H), 4.59–4.44 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.99 (t, J = 5.6 Hz, 1H), 2.22–2.02 (m, 2H), 1.56 (d, J =14.4 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H), –0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 133.6, 65.1, 60.9, 57.3, 57.2, 35.9, 35.1, 25.8, 17.9, 15.0, –4.8. HRMS ES (*m/z*) Calcd for $C_{16}H_{29}NO_3Si$ 311.1917 $(M)^+$, Found 311.1923.

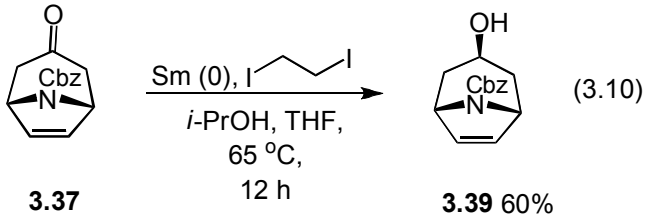
(66) Residual water is present in the ^{1}H NMR spectra of this compound.
(67) "Protection of Hydroxyl Groups as *tert*-butyldimethylsilyl Derivatives," Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
(68) Residual TBSOH is present in the ^{1}H NMR spectra of this compound.



(3.9)

3.38 **3.6** 90%

Synthesis of azabicycle **3.6** (eq. 3.9, see above). Representative procedure for lithium aluminum hydride reduction of carbamate protected azabicycles: In a N_2-filled glovebox, a 4-mL vial was charged with **3.18** (40.0 mg, 0.0800 mmol), THF (0.800 mL), and lithium aluminum hydride (6.1 mg, 0.16 mmol, 2 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and the reaction mixture was allowed to stir for 1 h. At this point, the reaction mixture was cooled to 22 °C over 15 min, the vial was removed from the glovebox, and the reaction was stopped by the slow and sequential addition of H_2O (40.0 μL, 1 μL/mg of **3.18**), a 3.8 M solution of NaOH (0.120 mL, 3 μL/g of **3.18**) and H_2O (40.0 μL, 1 μL/mg of **3.18**. The resulting mixture was subjected to vacuum filtration (to remove Al salts), and eluted with EtOAc. The filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting yellow residue was purified by silica gel chromatography (9:1 CH_2Cl_2:MeOH) to afford **7** as colorless oil (18.2 mg, 0.0720 mmol, 90%). IR (neat): 2930 (s), 2854 (m), 1256 (w), 1067 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 2H), 3.95 (t, J = 5.6 Hz, 1H), 3.34 (br s, 2H), 2.27 (s, 3H), 2.13–2.07 (m, 2H), 1.57 (d, J = 14.0 Hz, 2H), 0.84 (s, 9H), –0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.4, 65.9, 64.2, 41.4, 37.1, 25.5, 17.6, –5.1. HRMS ES (*m/z*) Calcd for $C_{14}H_{27}NOSi$ 253.1857 $(M)^+$, Found 253.1862.

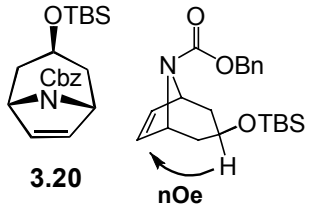


(3.10)

3.37 **3.39** 60%

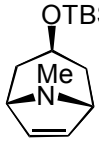
Synthesis of Azabicycle **3.39**, precursor to azabicycle **3.20** (3.10)**.** In a N_2-filled glovebox, a 25-mL round-bottom flask was charged with Sm (132 mg, 0.880 mmol), and 1,2-diiodoethane (248 mg, 0.880 mmol), after which the flask was capped with a rubber septa. The flask was then removed from the glovebox, at which point THF (4.5 mL) was added to the mixture. After the resulting solution became deep blue (*circa* 1 h), a solution of **3.37** (0.100 g, 0.440 mmol) in isopropanol (33.0 μL, 0.440 mmol), and THF (4.0 mL) was added to the deep blue solution. At this moment, a reflux condenser was attached to the flask, and the reaction mixture was allowed to stir at 65 °C for 12 h. At this time, the reaction mixture was cooled to 22 °C, and the reaction was quenched by the

addition of H_2O (10 mL). The resulting mixture was filtered through celite by vacuum filtration, and eluted with EtOAc. The volatiles were removed from the filtrate in vacuo, the resulting mixture was transferred to a 60-mL separatory funnel, and the mixture was washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield yellow oil. This oil was purified by silica gel chromatography (dry load, 1:1 to 1:2 hexanes:EtOAc to 100% EtOAc) to give **3.39** as colorless oil (68.0 mg, 0.260 mmol, 60%). IR (neat): 3404 (br), 2945 (w), 2926 (w), 1685 (s), 1418 (s) 1319 (m), 1288 (m), 1102 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 7.37–7.26 (m, 5H), 6.04–5.99 (m, 2H), 5.18–5.10 (m, 2H), 4.68–4.65 (m, 2H), 3.90 (dddd, *J* = 12.8, 12.8, 6.6, 6.4 Hz, 1H), 1.97 (dd, *J* = 12.8, 6.4 Hz, 2H), 1.86 (s, 1H), 1.64–1.58 (m, 1H), 1.51–1.45 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 136.7, 131.0, 130.8, 128.5, 128.1, 128.0, 66.8, 64.7, 57.2, 34.7, 33.9. HRMS ES (*m/z*) Calcd for $C_{15}H_{17}NO_3$ 259.1208 $(M)^+$, Found 259.1206.



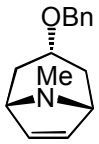
3.20

Azabicycle **3.20** was prepared by TBS protection of the alcohol in azabicycle **3.39**. The relative stereochemistry at the protected hydroxyl group carbon was determined by nOe analysis. IR (neat): 2951 (m), 2920 (m), 2858 (m), 1710 (s), 1412 (m) 1300 (m), 1244 (m), 1089 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 7.37–7.26 (m, 5H), 6.04–5.99 (m, 2H), 5.18–5.10 (m, 2H), 4.68–4.65 (m, 2H), 3.94–3.90 (m, 1H), 1.85–1.77 (m, 2H), 1.72–1.50 (m, 2H), 0.86 (s, 9H), 0.00 (s, 6H) .^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 136.9, 131.1, 130.8, 128.5, 128.3, 128.0, 127.9, 66.7, 65.5, 65.4, 57.3, 57.1, 35.0, 34.9, 34.2, 25.8, 22.3, 18.1, –4.6. HRMS ES (*m/z*) mass Calcd for $C_{21}H_{31}NO_3Si$ 373.2073 $(M)^+$ Found 373.2068.



precursor to piperidine **3.16**

The azabicyclic precursor to **3.16** (shown on the left) was prepared by lithium aluminum hydride reduction of the carbamate in **3.20**; for a representative procedure, see azabicycle **3.6** (eq. 3.9, see above). IR (neat): 2930 (s), 2855 (m), 1470 (w), 1256 (m), 1099 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (s, 2H), 3.74 (dddd, *J* = 13.6, 8.8, 6.8, 6.8 Hz, 1H), 3.47 (br s, 2H), 2.22 (s, 3H), 1.90–1.85 (m, 2H) 1.70–1.60 (m, 2H), 0.82 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.5, 66.5, 65.4, 40.5, 35.8, 25.9, 18.1, –4.4. HRMS ES (*m/z*) Calcd for $C_{14}H_{27}NOSi$ 253.1862 $(M)^+$, Found 253.1866.



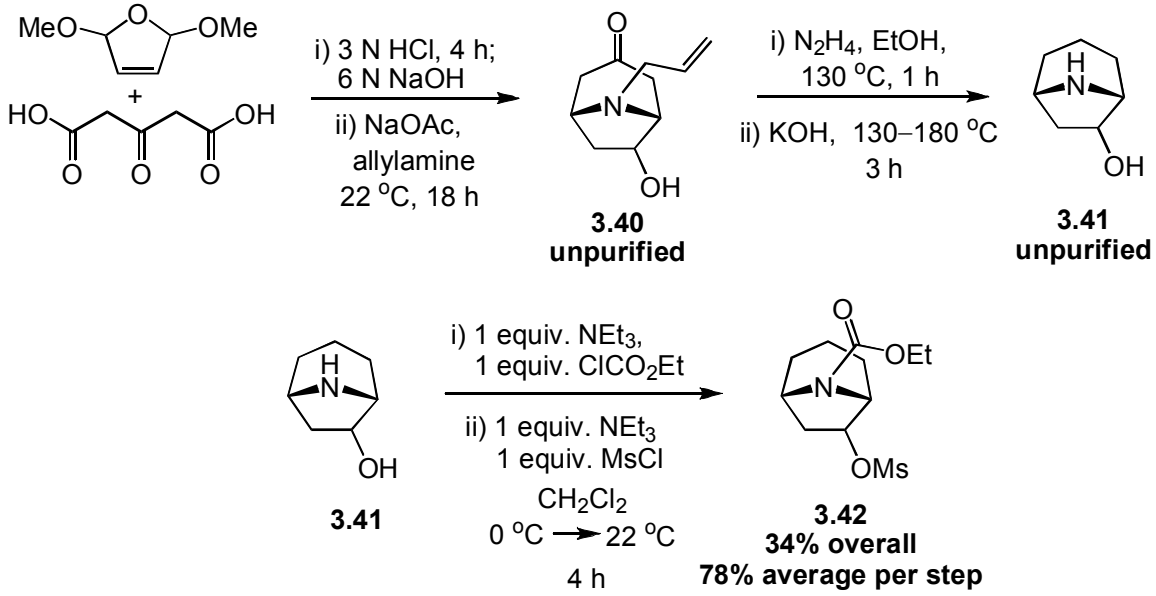
precursor to piperidine **3.15**

The azabicyclic precursor to **3.15** (shown on the left) was prepared by benzyl protection[69] of the alcohol in azabicycle **3.38** (eq. 3.8, see above), followed by lithium aluminum hydride reduction of the carbamate; for a representative procedure, see azabicycle **3.6** (eq 3.9, see above). IR 2930 (s), 2848 (m), 1451 (w), 1067 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.34–7.25 (m, 5H), 6.04 (s, 2H), 4.40 (s, 2H), 3.64 (dd, J = 6.4, 6.4 Hz, 1H), 3.41 (br s, 2H), 2.31 (s, 3H), 2.17–2.11 (m, 2H), 1.86 (d, J = 14.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5, 132.1, 127.3, 127.2, 71.6, 70.1, 66.0, 53.6, 41.8, 33.7. HRMS ES (*m/z*) Calcd for $C_{15}H_{19}NO$ 229.1467 $(M)^+$, Found 229.1461.

Synthesis and spectral data for azabicyclic substrates that deliver 2,6-substituted piperidine products.

Preparation of the azabicyclic precursor to piperidine **3.23** (shown below) was previously reported from azabicycle **3.42** (*vide infra*).[70] However, the cost of the commercially available starting material (6-*exo*-hydroxytropinone, $200/g from Aldrich) and the length of the reported synthetic route prompted us to develop an alternative route to azabicycle **3.42**, shown in Scheme 3.7 (see below).

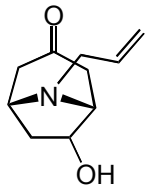
Scheme 3.7



(69) "Nouvelle Methode de Benzylation D'hydroxyles Glucidiques Encombres," Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535–3536

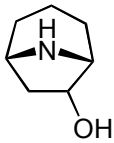
(70) "Synthesis of (±)-Epibatidine and Its Analogues," Bai, S.; Xu, R.; Chu, G.; Zhu, X. *J. Org. Chem.* **1996**, *61*, 4600–4606.

A modified procedure for the Robinson-type annulation[71] of allylamine with 2,5-dimethoxyfuran, and acetonedicarboxylic acid afforded **3.40**, which was used in the subsequent step without purification. Wolff-Kischner reduction of **3.40** provided intermediate **3.41**, which was also taken forward without purification. A two-step, one-pot procedure was then performed to obtain azabicycle **3.42**; a single purification was required in the sequence carried out to arrive at **3.41**. To this end, treatment of **3.41** with ethylchloroformate followed by treatment with mesyl chloride provided pure **3.42** after silica gel chromatography (34% overall yield).[72] It is worth noting that an advantage of our synthesis for **3.42** is that intermediate **3.41** can be utilized to access different azabicyclic derivatives; the amino group in **3.41** can be selectively functionalized prior to derivatization of the carbinol.



3.40

Synthesis of azabicycle **3.40**. Dimethoxyfuran (20.0 g, 0.150 mol) was dissolved in a 3.0 N aqueous solution of HCl (280 mL) in a 500-mL Erlenmeyer flask, and was allowed to stir for 4 h. At this time, a 6.0 N aqueous solution of NaOH (140 mL) was added, and the resulting solution was allowed to stir for 30 min. At this period, the mixture was added to a solution of NaOAc (98.4 g, 1.20 mol, 8 equiv.), allylamine (22.5 mL, 0.300 mol, 2 equiv.), and acetonedicarboxylic acid (43.8 g, 0.300 mol, 2 equiv.) in de-ionized H_2O (2.0 L) in a 4-L Erlenmeyer flask. The reaction mixture was allowed to stir for 18 h. To this mixture was added K_2CO_3 (25 g, 1.25 wt %), NaCl (25 g, 1.25 wt %), and the resulting mixture was allowed to stir for 1 h, after which time it was transferred to a 4-L separatory funnel, and washed with CH_2Cl_2 (6 × 500 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **3.40** as viscous brown oil (20.0 g); **3.40** was used in the subsequent reaction without purification. IR (neat): 3408 (br), 2948 (m), 1709 (s), 1413 (m), 1344 (m). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 5.95 (dddd, *J* = 16.4, 12.8, 10.4, 6.4 Hz, 1H), 5.32–5.25 (m, 2H), 4.07 (dd, *J* = 6.8, 2.4 Hz, 1H), 3.69 (br s, 1H), 3.52–3.40 (m, 5H), 2.68–2.56 (m, 2H), 2.26–1.94 (m, 2H), 1.80 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 135.3, 117.3, 74.9, 66.1, 56.9, 51.2, 44.4, 42.1, 40.7. HRMS ES (*m/z*) Calcd for $C_{10}H_{15}NO_2$ 182.1181 $(M)^+$, Found 182.1175.

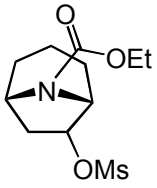


3.41

Synthesis of azabicycle **3.41.** A 500-mL round-bottom flask was charged

(71) "Chemical Synthesis and Pharmacology of 6- and 7-Hydroxylated 2-Carbomethoxy-3-(*p*-tolyl)tropanes: Antagonism of Cocaine's Locomotor Stimulant Effects," Zhao, L.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J.; Kozikowski, A. P. *J. Med Chem.* **2000**, *43*, 3283–3294.
(72) The stereochemistry at the carbon containing a mesyl group of **3.42** was not determined as the next step involves an elimination to an enocyclic olefin.

with azabicycle **3.40** (20.0 g, 0.110 mol), anhydrous EtOH (200 mL), hydrazine hydrate (48.0 mL, 0.990 mol, 9 equiv.), the flask was fitted with a reflux condenser, and the mixture was allowed to stir at 120 °C for 1.5 h. At this time, EtOH was removed in vacuo to yield viscous dark brown oil. To this oil was added powdered KOH (56.0 g, 0.990 mol, 9 equiv.),[73] and the resulting mixture was allowed to stir at 130 °C for 1 h, at 160 °C for 1 h, and at 180 °C for 2.5 h. After this period, the reaction mixture was cooled to 22 °C, and the reaction was quenched by the addition of H_2O (200 mL). The resulting mixture was transferred to a 1-L separatory funnel, and washed with CH_2Cl_2 (6 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give **3.41** as viscous brown oil (14.0 g); **3.41** was used in the next step without purification. IR (neat): 3361 (br), 3261 (br), 2926 (s), 2864 (m), 1635 (w), 1536 (w), 1437 (m). ^{1}H NMR (400 MHz, $CDCl_3$): 5.48 (br s, 2H), 4.25–4.20 (m, 1H), 3.85–3.80 (m, 1H), 3.25 (br s, 1H), 2.20–2.15 (m, 1H), 1.90–1.82 (m, 1H), 1.80–1.65 (m, 2H), 1.62–1.42 (m, 2H), 1.40–1.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.7, 63.5, 55.5, 39.7, 29.5, 27.6, 16.8. HRMS ES (*m/z*) Calcd for $C_7H_{14}NO$ 128.1075 $(M+H)^+$, Found 128.1071.

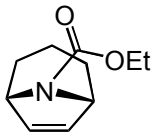


3.42

Synthesis of azabicycle **3.42**. A two-neck 250-mL round-bottom flask, fitted with an addition funnel, was charged with **3.42** (2.20 g, 15.9 mmol), CH_2Cl_2 (100 mL), Et_3N (2.22 mL, 15.9 mmol, 1 equiv.), and cooled to 0 °C in an ice bath. Ethyl chloroformate (1.51 mL, 15.9 mmol, 1 equiv.) was added to this solution dropwise by addition funnel; after the addition was complete the ice bath was removed, and the mixture was allowed to stir for 2 h. To this solution was added Et_3N (2.22 mL, 15.9 mmol, 1 equiv.), and the resulting solution was cooled to 0 °C in an ice bath. To this solution was added methanesulfonyl chloride (1.23 mL, 15.9 mmol, 1 equiv.) dropwise by addition funnel; after the addition was complete the ice bath was removed, and the mixture was allowed to stir for 2 h. At this time, the reaction was quenched by the addition of H_2O (75 mL), the mixture was transferred to a 250-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with a saturated aqueous solution of NaCl (1 x 75 mL), and H_2O (1 x 75 mL), after which time the organic layer was dried ($MgSO_4$), filtered, and the volatiles were removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (gradient elution, 1:1 Et_2O:hexanes followed by 100% Et_2O) to provide **3.42** as colorless oil (2.78 g, 9.00 mmol, 34% yield starting from 2,5-dimethoxyfuran). Compound **3.42** has been prepared previously; the physical and spectral data for **3.42** were identical to those previously reported.[65] ^{1}H NMR (400 MHz,

(73) A mortar and pestle were used to crush KOH granules into a powder.

$CDCl_3$): δ 5.13 (dd, *J* = 6.4, 3.2 Hz, 1H), 4.50–4.35 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.03 (s, 3H), 2.27–2.17 (m, 1H), 1.78–1.23 (m, 7H), 1.20 (t, *J* = 7.2 Hz, 3H).

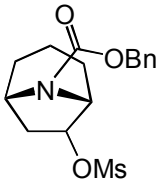


precursor to piperidine **3.23**

Syntheis of the azabicyclic precursor to **3.23** (shown on the left). A 100-mL round-bottom flask was charged with **3.42** (7.21 g, 23.3 mmol), collidine (30 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.20 mL, 27.9 mmol, 1.2 equiv.). The flask was fitted with a reflux condenser, and the reaction mixture was allowed to stir at 160 ^{o}C for 24 h. At this period, the reaction mixture was cooled to 22 ^{o}C, and the reaction was quenched by the addition of H_2O (100 mL). The resulting mixture was transferred to 250-mL separatory funnel, and was washed with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with a 0.5 M aqueous solution of HCl (4 x 50 mL), a solution of saturated aqueous $NaHCO_3$ (50 mL), and a solution of saturated aqueous NaCl (50 mL). The organic layer was dried (Na_2SO_4), filtered, and the volatiles were removed in vacuo. The resulting viscous brown oil was purified by silica gel chromatography (99:1 CH_2Cl_2:MeOH) to provide the precursor to **3.23** as yellow oil (3.50 g, 19.3 mmol, 81% yield). This azabicycle has been prepared previously and full characterization data for were reported; the physical and spectral data for this compound were identical to those previously reported.[64] ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 6.02–5.99 (m, 2H), 4.60–4.44 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.80–1.30 (m, 6H), 1.25 (t, *J* = 7.2 Hz, 3H).

precursor to piperidine **3.17**

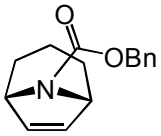
Syntheis of the azabicyclic precursor to **3.17** (shown on the left). This azbicycle was prepared by lithium aluminum hydride reduction of the carbamate in the precursor to **3.23**; for a representative procedure, see azabicycle **3.6** (eq 3.9, see above). This azabicycle has been prepared previously; the physical and spectral data for this compound were identical to those previously reported.[74] ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (s, 2H), 3.40 (s, 2H), 2.20 (s, 3H), 1.80–1.20 (m, 6H).



Synthesis of the azabicyclic precursor to **3.22** (the mesylate shown here on the left) was prepared by utilizing CbzCl, in place of ethylchloroformate, in the carbamate formation of the sequence shown in Scheme 3.7 (*vide supra*). A 25-mL round-bottom flask was charged with this mesylate intermediate (0.220 mg, 0.840 mmol), collidine (4.20 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.120 mL, 1.01 mmol, 1.2 equiv.), the flask was fitted

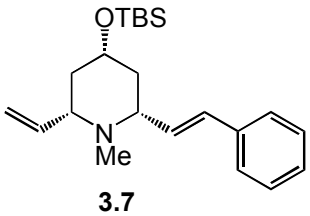
(74) "Manipulation of substituents at nitrogen in tropanes, homotropanes, and dehydro- derivatives," Howarth, N. M.; Smith, C. R.; Malpass, J. R. *Tetrahedron* **1998**, *54*, 10899–10914.

with a reflux condenser, and the reaction mixture was allowed to stir at 160 °C for 24 h. At this time, the reaction mixture was cooled to 22 °C, and the reaction was quenched by the addition of a solution of saturated aqueous NH_4Cl (10 mL). The resulting mixture was transferred to a 50-mL separatory funnel, and washed with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with a 0.5 M solution of HCl (3 x 15 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL), and a solution of saturated aqueous NaCl (15 mL). The organic layer was dried (Na_2SO_4), filtered, and the volatiles were removed in vacuo. The resulting brown residue was purified by silica gel chromatography (gradient elution, 1:9 Et_2O:hexanes followed by 1:1 Et_2O:hexanes) to provide the precursor to **3.22** (shown here on the left) as colorless oil (0.140 g, 0.580 mmol, 70% yield).



IR (neat): 2939 (m), 2858 (w), 1704 (s), 1418 (s), 1306 (s), 1095 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 7.39–7.28 (m, 5H), 6.09–6.01 (m, 2H), 5.17 (s, 2H), 4.60–4.56 (m, 2H), 1.82–1.63 (m, 3H), 1.47–1.43 (m, 1H), 1.35–1.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 137.0, 130.5, 130.1, 128.4, 127.9, 127.8, 66.4, 58.5, 58.5, 24.4, 23.5, 16.3. HRMS ES (*m/z*) Calcd for $C_{15}H_{17}NO_2$ 243.1254 $(M)^+$, Found 243.1259.

Representative procedure for Mo-catalyzed asymmetric ring-opening/cross-metathesis reactions, synthesis of piperidine 3.7: In a N_2-filled glovebox, Mo complex **H** (2.4 mg, 0.0030 mmol, 0.05 equiv.) was dissolved in C_6H_6 (0.250 mL) in a 4-mL vial. Styrene (68.0 μL, 0.593 mmol, 10 equiv.) was added to this solution by syringe. The resulting mixture was allowed to stir for 1 min, and added by syringe to a solution of azabicycle **3.6** (15.0 mg, 0.0592 mmol) in C_6H_6 (0.250 mL) in a 4-mL vial.[75] The reaction mixture was allowed to stir for 1 h. At this time, the vial was removed from the glovebox, and the volatiles were removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (9:1 CH_2Cl_2:MeOH) to afford piperidine **3.7** as colorless oil (20.4 mg, 0.0570 mmol, 95%).



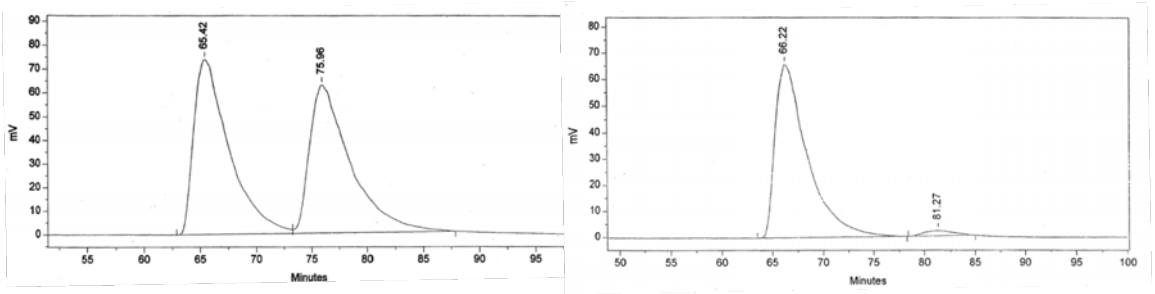
3.7

IR (neat): 2949 (s), 2930 (s), 2772 (s), 2363 (s), 1646 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H), 6.48 (d, J = 15.6 Hz, 1H), 6.15 (dd, J = 15.6, 8.8 Hz, 1H), 5.79 (ddd, J = 17.2, 10.4, 8.8 Hz, 1H), 5.15 (dd, J = 17.2, 1.6 Hz, 1H), 5.05 (dd, J = 10.4, 1.6 Hz, 1H), 3.77–3.68 (m, 1H), 2.77–2.60 (m, 1H), 2.58–2.48 (m, 1H), 2.18 (s, 3H), 1.87–1.78 (m, 2H), 1.60–1.51 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 137.1, 133.4, 130.7, 128.7, 127.6, 126.4, 115.7, 68.7, 67.6, 66.7, 43.0,

(75) Mo complex **6** is pre-treated with styrene to ensure formation of the chiral Mo benzylidene complex.

42.9, 41.5, 25.9, 18.3, –4.39. HRMS EI (*m/z*) Calcd for $C_{22}H_{35}NOSi$ 357.2488 $(M)^+$, Found 357.2482.

Representative procedure for desilylation of secondary alcohols in piperidine product, synthesis of piperidine 37-OH:[76] A 4-mL vial was charged with **3.7** (20.4 mg, 0.0570 mmol), THF (0.500 mL), and TBAF (285 μL, 0.285 mmol, a 1.00 M solution in THF, 5 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and the reaction mixture was allowed to stir for 1 h. At this time, the vial was cooled to 22 °C over 15 min, and the volatiles were removed in vacuo. The resulting yellow residue was purified by silica gel chromatography (4:1 CH_2Cl_2:MeOH) to afford piperidine **37-OH** as colorless oil (13.2 mg, 0.0541 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.21 (m, 5H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.16 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.4, 8.8 Hz, 1H), 5.17 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.07 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.82–3.70 (m, 1H), 2.77–2.60 (m, 1H), 2.58–2.48 (m, 1H), 2.20 (s, 3H), 2.00–1.92 (m, 2H), 1.55–1.43 (m, 3H). $[\alpha]_D^{20}$ –75.2 (*c* = 0.2, $CHCl_3$) for a sample of *94% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99:1 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *94% ee*.



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
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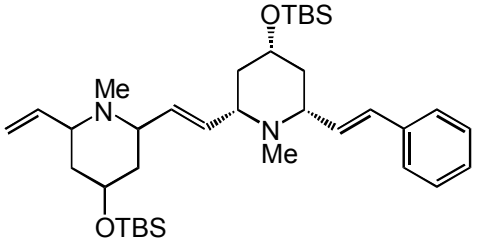
2	81.270		0.0000	0.000	403201.3	2.696	BB	3.380	1988.16	2.930

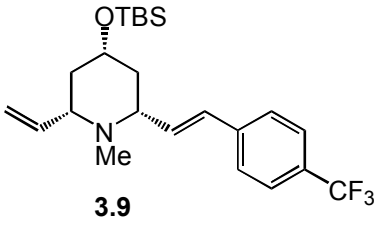


3.8

Piperidine **3.8** (homodimer byproduct). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.13 (dd, *J* = 16.0, 8.8 Hz, 1H), 5.79 (ddd, *J* = 16.0, 10.0, 8.8 Hz, 1H), 5.52–5.47 (m, 2H), 5.13 (dd, *J* = 16.0, 1.6 Hz, 1H), 5.03 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.75–3.62 (m, 2H),

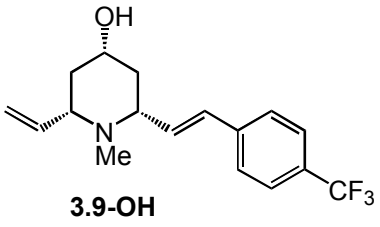
(76) Determination of enantiomeric excess of **8**, and in some other cases, involved the piperidine derived from TBAF deprotection of the secondary alcohol.

2.68–2.60 (m, 1H), 2.58–2.40 (m, 3H) 2.18–2.11 (m, 6H), 1.84–1.20 (m, 8H), 0.87 (s, 18H), 0.05 (s, 12H).



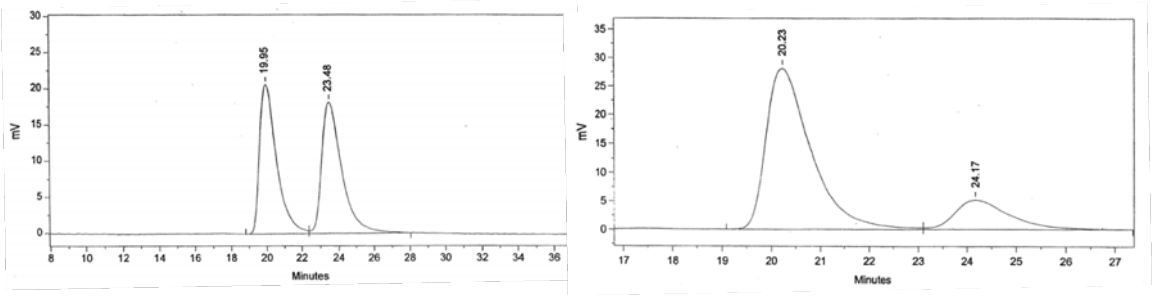
3.9

Piperidine **3.9**. IR (neat): 2949 (s), 2924 (s), 2779 (m), 1615 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.26 (dd, *J* = 8.4, 7.2 Hz, 1H), 5.76 (ddd, *J* = 18.0, 9.6, 9.6 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 3.75–3.67 (m, 1H), 2.69–2.61 (m, 1H), 2.54–2.47 (m, 1H), 2.17 (s, 3H), 1.86–1.74 (m, 2H), 1.62–1.48 (m, 2H), 0.87 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 140.6, 136.2, 129.4, 126.5, 125.7, 125.6, 123.0, 115.9, 68.6, 67.5, 66.6, 42.9, 42.8, 41.5, 25.9, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{23}H_{35}NOF_3Si$ 426.2440 $(M+H)^+$, Found 426.2451. Determination of enantiomeric excess of **3.9** involved the piperidine derived from desilylation of the silyl ether in **3.9**.



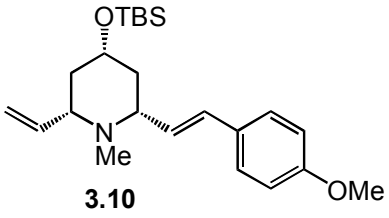
3.9-OH

Piperidine **9-OH**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.26 (dd, *J* = 8.8, 8.0 Hz, 1H), 5.76 (ddd, *J* = 18.0, 9.6 Hz, 1H), 5.18 (d, *J* = 16.4 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 3.81–3.75 (m, 1H), 2.76–2.66 (m, 1H), 2.60–2.50 (m, 1H), 2.19 (s, 3H), 1.99–1.94 (m, 2H), 1.57–1.46 (m, 2H), 1.29–1.20 (br s, 1H). $[\alpha]_D^{20}$ –15.40 (*c* = 0.5, $CHCl_3$) for a sample of *64% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *64% ee*.



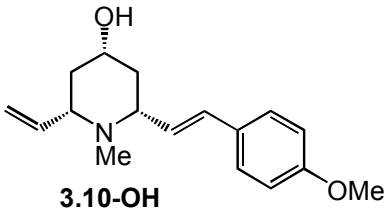
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	20.228		0.0000	0.000	1803209.0	81.866	BV	1.072	28035.64	84.481
2	24.166		0.0000	0.000	399424.8	18.134	VB	1.293	5150.06	15.519

Piperidine **3.10**. IR (neat): 2955 (s), 2923 (s), 2854 (s), 2772 (m), 1508 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 6.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.00 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.0, 8.8 Hz, 1H), 5.18 (d, *J*



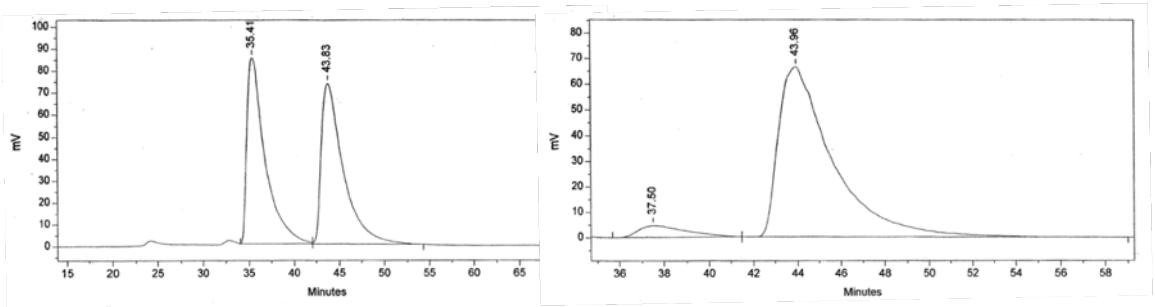
3.10

= 17.2 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.80–3.67 (m, 1H), 2.63–2.55 (m, 1H), 2.55–2.46 (m, 1H), 2.18 (s, 3H), 1.86–1.76 (m, 2H), 1.61–1.48 (m, 2H), 0.85 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 141.9, 131.1, 130.2, 129.9, 127.6, 115.6, 114.2, 68.7, 67.6, 66.8, 55.5, 43.1, 42.9, 41.4, 26.0, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{28}H_{40}NOSi$ 434.2879 $(M+H)^+$, Found 434.2889. $[\alpha]_D^{20}$ –31.99 (*c* = 0.5, $CHCl_3$) for a sample of *89% ee*. Determination of enantiomeric excess of **3.10** involved the piperidine derived from desylilation of the secondary silyl ether in **3.10**.

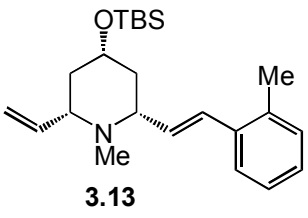


3.10-OH

Piperidine **3.10-OH**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.01 (dd, *J* = 15.2, 8.4 Hz, 1H), 5.78 (ddd, *J* = 17.2, 10.0, 8.8 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.80–3.70 (m, 1H), 2.70–2.60 (m, 1H), 2.60–2.50 (m, 1H), 2.22 (s, 3H), 2.02–1.90 (m, 2H), 1.60–1.44 (m, 3H). The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99:1 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *89% ee*.



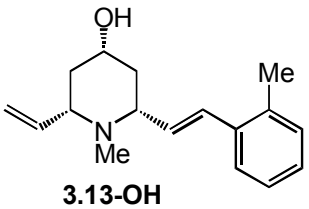
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	37.501		0.0000	0.000	691439.1	5.726	BB	2.510	4591.43	6.475
2	43.961		0.0000	0.000	11384710.0	94.274	BB	2.861	66319.44	93.525



3.13

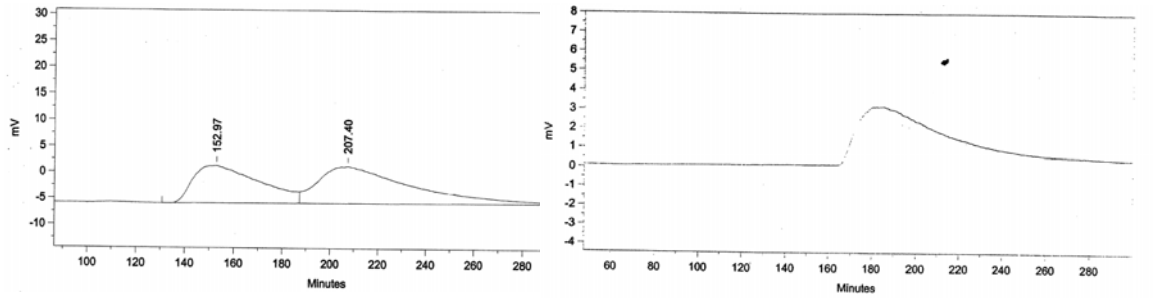
Piperidine **3.13**. IR (neat): 2949 (s), 2930 (s), 2854 (s), 2364 (m), 2338 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.40 (m, 1H), 7.18–7.12 (m, 3H), 6.81 (d, *J* = 16.0 Hz, 1H), 6.03 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.77 (ddd, *J* = 18.4, 10.0, 10.0 Hz, 1H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 3.73 (dddd, *J* = 15.2, 10.4, 4.8 Hz, 1H), 2.68–2.62 (m, 1H), 2.53–2.48 (m, 1H), 2.35 (s, 3H), 2.19 (s, 3H), 1.86–1.76 (m, 2H), 1.63–1.49 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 136.1, 135.3, 134.7, 130.4, 128.5, 127.5, 126.3, 125.8, 115.7, 68.7,

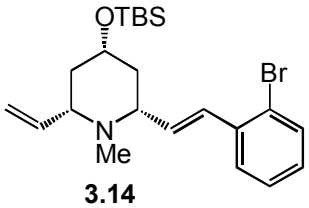
67.6, 67.0, 43.2, 43.0, 41.5, 25.9, 20.0, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{23}H_{38}NOSi$ 372.2723 $(M+H)^+$, Found 372.2728. Determination of the enantiomeric excess of **3.13** involved the piperidine derived from desilylation of the silyl ether in **3.13**.



3.13-OH

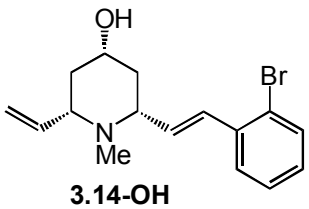
Piperidine **3.13-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.40 (m, 1H), 7.18–7.13 (m, 3H), 6.73 (d, *J* = 15.6 Hz, 1H), 6.11–6.04 (m, 1H), 5.88–5.76 (m, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 9.6 Hz, 1H), 3.85–3.75 (m, 1H), 2.80–2.55 (m, 2H), 2.34 (s, 3H), 2.26 (s, 3H), 2.04–1.95 (m, 2H), 1.70–1.50 (m, 2H), 1.22 (br s, 1H). The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OJ (4.6 x 250 mm), 99.8:0.2 hexanes:*i*-PrOH, 1 mL/min, λ = 254 nm, *>98% ee*.





3.14

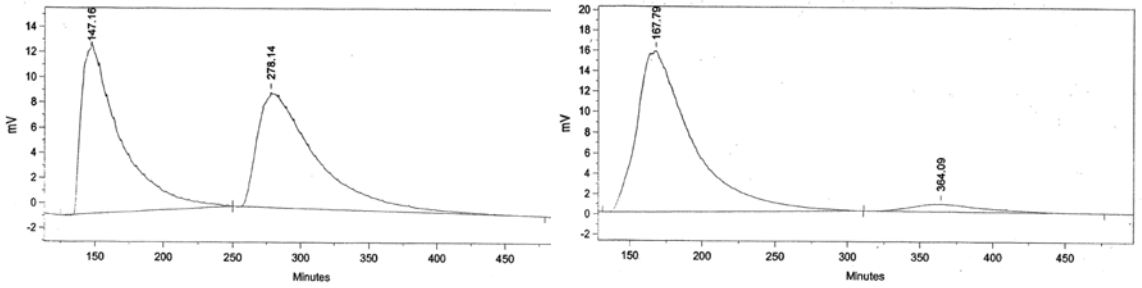
Piperidine **3.14.** IR (neat): 2949 (s), 2924 (s), 2855 (s), 2363 (m), 1463 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.40 (m, 2H), 7.26–7.22 (m, 1H), 7.09–7.05 (m, 1H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.09 (dd, *J* = 8.8, 6.8 Hz, 1H), 5.77 (ddd, *J* = 18.4, 9.6 Hz, 1H), 5.15 (d, *J* = 17.2 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 3.75–3.68 (m, 1H), 2.73–2.67 (m, 1H), 2.53–2.48 (m, 1H), 2.19 (s, 3H), 1.85–1.76 (m, 2H), 1.60–1.47 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 136.9, 136.3, 132.1, 129.5, 128.9, 127.7, 127.1, 123.6, 115.8, 68.6, 67.5, 66.6, 43.0, 42.9, 41.5, 25.9, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{22}H_{35}NOSiBr$ 436.1671 $(M+H)^+$, Found 436.1678. $[\alpha]_D^{20}$ –30.89 (*c* = 0.5, $CHCl_3$) for a sample of *88% ee*. Determination of enantiomeric excess of **3.14** involved the piperidine derived from desilylation of the silyl ether in **3.14**.



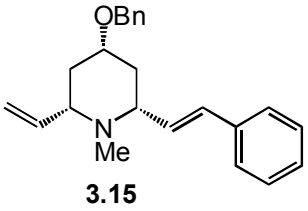
3.14-OH

Piperidine **3.14-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.50 (m, 2H), 7.30–7.24 (m, 1H), 7.11–7.07 (m, 1H), 6.85 (d, *J* = 15.6 Hz, 1H), 6.12 (dd, *J* = 8.8, 6.8 Hz, 1H), 5.77 (ddd, *J* = 18.4, 9.6 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 3.83–3.70 (m, 1H), 2.80–2.70 (m, 1H), 2.62–2.55 (m, 1H), 2.23 (s, 3H), 2.03–1.93 (m, 2H), 1.60–1.52 (m, 2H), 1.40 (br s, 1H). The optical

purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralcel OJ (4.6 x 250 mm), 99.8:0.2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *88% ee*.

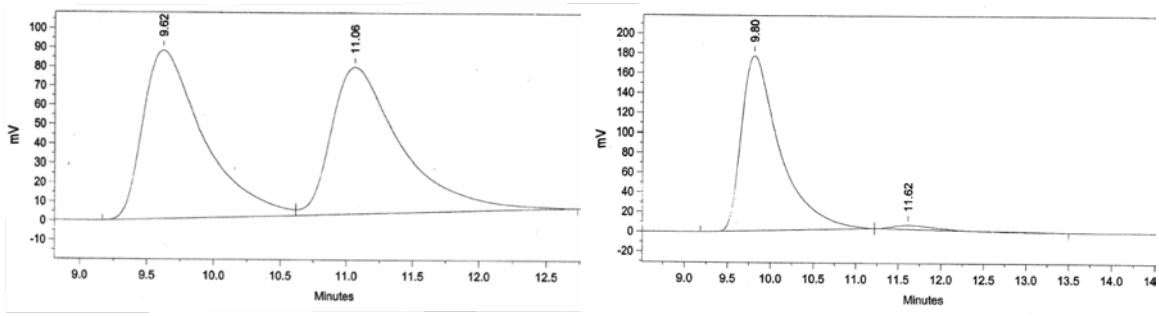


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	167.789		0.0000	0.000	41480400.0	94.113	BB	43.950	15730.24	95.395
2	364.092		0.0000	0.000	2594679.0	5.887	BB	56.947	759.38	4.605

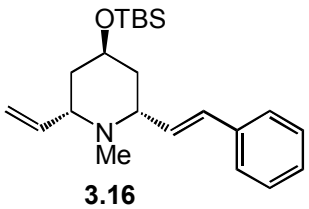


3.15

Piperidine **3.15.** IR (neat): 3030 (m), 2943 (s), 2924 (s), 2773 (s), 1451 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.10 (m, 10H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.10 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.72 (ddd, *J* = 18.8, 10.4, 8.8 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.00 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.48 (s, 2H), 3.48–3.38 (m, 1H), 2.59–2.53 (m, 1H), 2.47–2.41 (m, 1H), 2.12 (s, 3H), 2.04–1.92 (m, 2H), 1.57–1.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 139.8, 137.6, 134.3, 130.6, 128.9, 128.6, 127.7, 127.6, 127.5, 126.7, 114.9, 74.5, 69.6, 67.5, 66.6, 41.6, 40.0, 39.9. HRMS EI (*m/z*) Calcd for $C_{23}H_{28}NO$ 334.2171 $(M+H)^+$, Found 334.2174. $[\alpha]_D^{20}$ –14.80 (*c* = 0.1, $CHCl_3$) for a sample of *96% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *96% ee*.

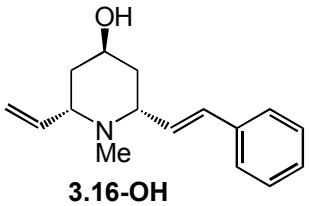


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	9.804		0.0000	0.000	5478271.0	98.076	BV	0.517	176525.90	- 0.002
3	11.615		0.0000	0.000	107475.1	1.924	BB	0.427	4191.67	0.000



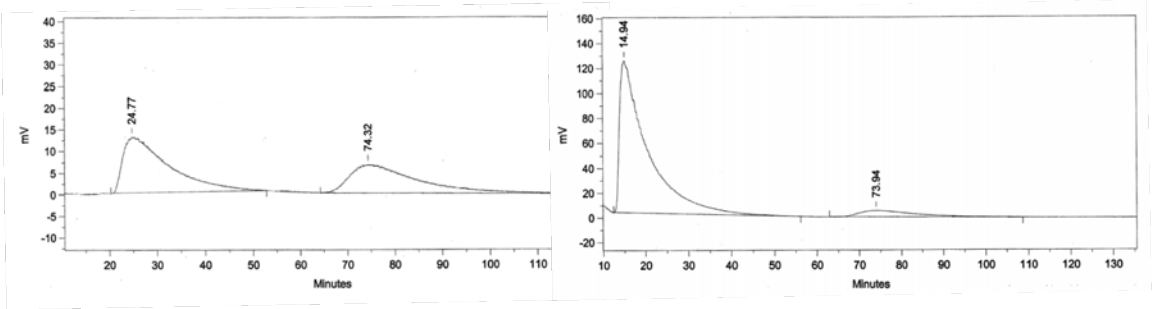
3.16

Piperidine **3.16**. IR (neat): 2961 (s), 2930 (s), 2854 (m), 1256 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.15 (dd, *J* = 9.7, 7.2 Hz, 1H), 5.74 (ddd, *J* = 18.4, 9.6, 9.6 Hz, 1H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 4.07 (br s, 1H), 3.10–3.00 (m, 1H), 2.99–2.90 (m, 1H), 2.20 (s, 3H), 1.80–1.55 (m, 4H), 0.91 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 137.2, 133.7, 130.8, 128.7, 127.5, 126.4, 115.9, 64.9, 63.0, 62.2, 41.8, 40.9, 26.0, 18.3, –4.67, –4.70. HRMS EI (*m/z*) Calcd for $C_{22}H_{36}NOSi$ 358.2566 $(M+H)^+$, Found 358.2571. Determination of enantiomeric excess of **3.16** involved the piperidine derived from desilylation of the silyl ether in **3.16**.

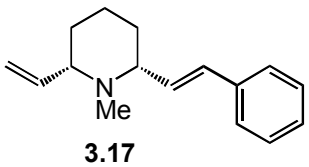


3.16-OH

Piperidine **3.16-OH** ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38–7.20 (m, 5H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.12 (dd, *J* = 16.0, 8.8 Hz, 1H), 5.72 (ddd, *J* = 18.4, 9.6, 9.6 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 16 Hz, 1H), 4.17 (s, 1H), 3.10–3.00 (m, 1H), 2.98–2.90 (m, 1H), 2.25 (s, 3H), 1.80–1.70 (m, 4H). $[\alpha]_D^{20}$ –79.98 (*c* = 0.01, $CHCl_3$) for a sample of *84% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OJ (4.6 x 250 mm), 97:3 hexanes:*i*-PrOH, 1.2 mL/min, λ = 254 nm, *84% ee*.



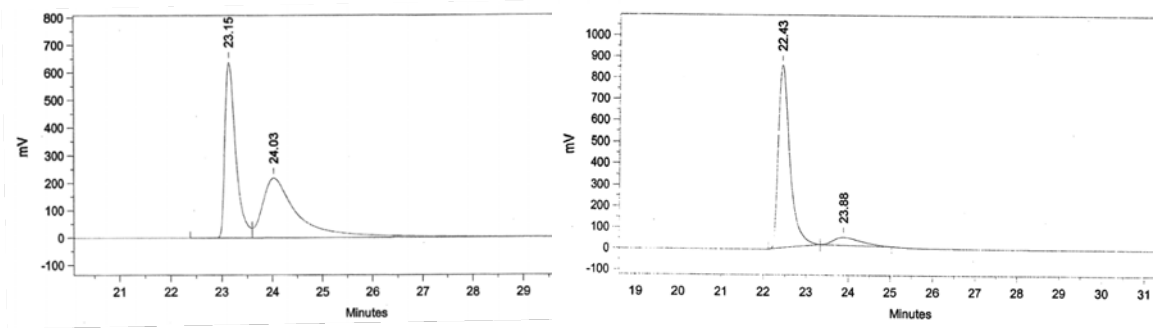
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	14.942		0.0000	0.000	55070540.0	92.332	BB	7.541	121712.40	95.793
2	73.940		0.0000	0.000	4573726.0	7.668	BB	14.259	5345.85	4.207



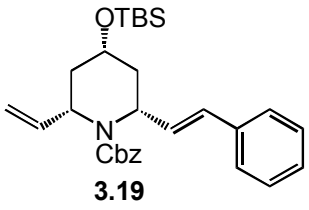
3.17

Piperidine **3.17**. IR (neat): 2930 (s), 2848 (m) 2773 (s), 1445 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.82–5.73 (m, 1H), 5.15 (dd, *J* = 17.6, 2.0 Hz, 1H), 5.03 (dd, *J* = 10.4, 1.6 Hz, 1H), 2.60–2.54 (m, 1H), 2.47–2.42 (m, 1H), 2.21 (s, 3H), 1.80–1.42 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 137.4, 134.3, 130.5, 128.8, 127.5, 126.4, 115.5, 69.4, 68.5, 42.3, 33.9, 33.8, 24.0. HRMS EI (*m/z*) Calcd for $C_{16}H_{21}N$ 227.1674 $(M)^+$, Found

227.1679. $[\alpha]_D^{20}$ –31.19 (*c* = 0.5, $CHCl_3$) for a sample of *80% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *80% ee*.

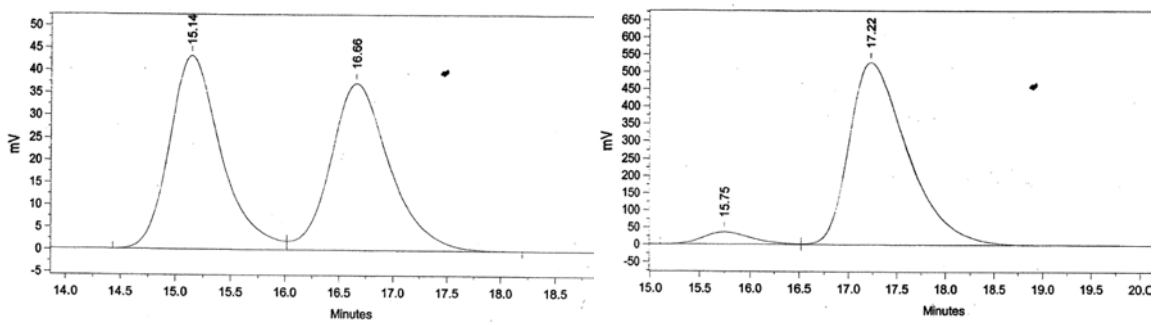


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	22.426		0.0000	0.000	16050500.0	90.266	BB	0.312	856385.20	95.775
2	23.882		0.0000	0.000	1730848.0	9.734	BB	0.764	37781.50	4.225

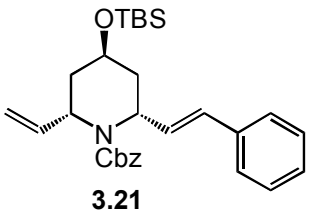


3.19

Piperidine **3.19.** IR (neat): 2955 (m), 2923 (m), 2855 (w), 1697 (s), 1073 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.19 (m, 10H), 6.68 (dd, *J* = 16.0, 8.4 Hz, 1H), 6.40 (d, *J* = 15.2 Hz, 1H), 6.28 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.19–5.01 (m, 4H), 4.98–4.92 (m, 1H), 4.86–4.78 (m, 1H), 4.16 (dddd, *J* = 7.6, 4.4, 4.4, Hz 1H), 2.10–1.84 (m, 4H), 0.89 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 141.5, 137.4, 136.9, 132.8, 130.5, 128.6, 128.5, 128.2, 128.0, 127.3, 126.5, 114.9, 67.4, 64.9, 52.4, 52.3, 36.7, 36.5, 26.0, 18.2, –4.7. HRMS EI (*m/z*) Calcd for $C_{29}H_{39}NO_3Si$ 477.2693 $(M)^+$, Found 477.2699. $[\alpha]_D^{20}$ 92.8 (*c* = 0.08, $CHCl_3$) for a sample of *90% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *90% ee*.

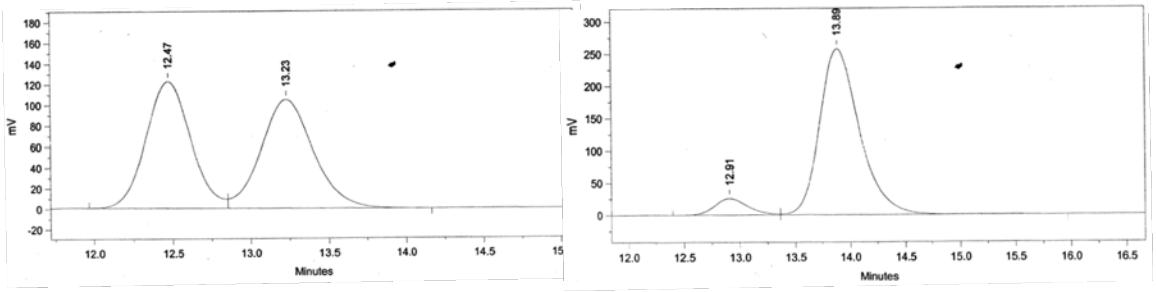


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	15.745		0.0000	0.000	1212583.0	5.205	BV	0.561	36049.54	6.398
2	17.224		0.0000	0.000	22083840.0	94.795	VB	0.698	527388.10	93.602

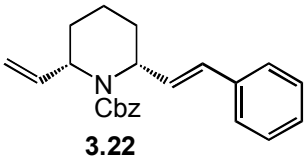


3.21

Piperidine **3.21.** IR (neat): 2955 (s), 2924 (s), 2861 (m), 1697 (s), 1400 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.22 (m, 10H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.93 (ddd, *J* = 16.4, 10.8, 6.0 Hz, 1H), 5.21–5.10 (m, 5H), 5.00–4.98 (m, 1H), 4.17 (dddd, *J* = 11.2, 7.2, 7.2, 4.0 Hz, 1H), 2.10–2.05 (m, 2H), 1.83–1.67 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 139.7, 137.0, 136.8, 130.8, 130.6, 128.7, 128.6, 128.1, 128.0, 127.7, 126.5, 115.5, 67.5, 62.3, 53.6, 53.5, 38.5, 38.0, 26.0, 18.3, –4.37. HRMS EI (*m/z*) Calcd for $C_{29}H_{39}NO_3Si$ 477.2699 $(M)^+$, Found 477.2693. $[\alpha]_D^{20}$ 39.9 (*c* = 0.01, $CHCl_3$) for a sample of *85% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *85% ee*.

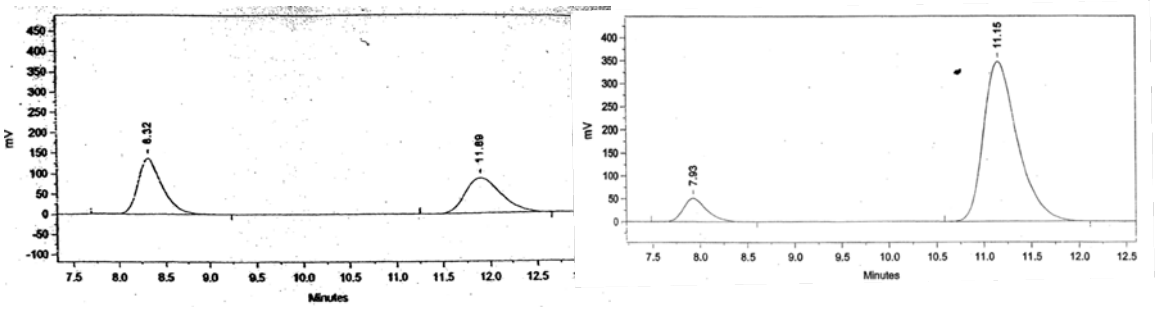


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	12.910		0.0000	0.000	530022.3	7.598	BV	0.343	25752.90	9.093
2	13.886		0.0000	0.000	6445757.0	92.402	VB	0.417	257468.20	90.907

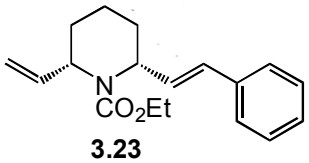


3.22

Piperidine **3.22.** IR (neat): 2936 (w), 1697 (s), 1407 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.21 (m, 10H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.34 (dd, *J* = 16.0, 7.1, Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 5.14–5.10 (m, 2H), 5.05–4.97 (m, 1H), 4.88–4.85 (m, 1H), 1.94–1.72 (m, 5H), 1.60–1.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 139.6, 137.2, 136.9, 130.6, 128.6, 128.5, 128.1, 128.0, 127.5, 126.4, 115.4, 67.3, 53.5, 52.5, 52.4, 29.1, 28.3, 15.1. HRMS EI (*m/z*) Calcd for $C_{23}H_{25}NO_2$ 347.1885 $(M)^+$, Found 347.1892. $[\alpha]_D^{20}$ 53.58 (*c* 0.05, $CHCl_3$) for a sample of *82% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *82% ee*.

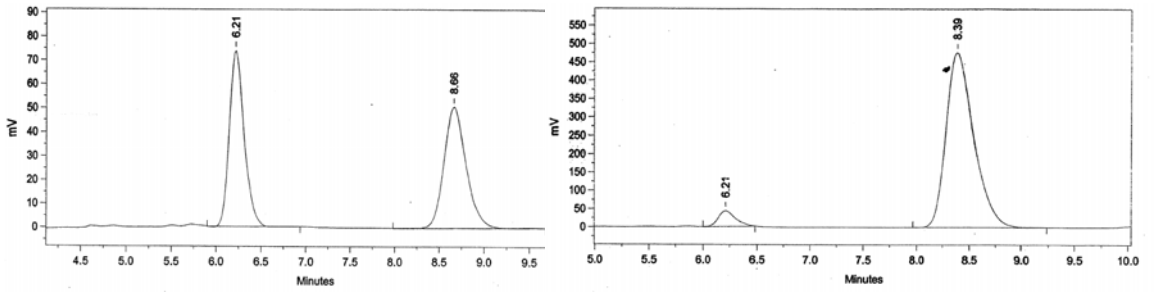


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	7.928		0.0000	0.000	87051: 8	9.133	BB	0.284	51077.28	12.820
2	11.151		0.0000	0.000	8660895)	90.867	BB	0.416	347339.50	87.180

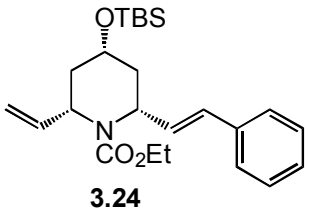


3.23

Piperidine **3.23**. IR (neat): 2936 (w), 2357 (m), 2332 (m), 1690 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.18 (m, 5H), 6.48 (d, *J* = 16.4 Hz, 1H), 6.31 (dd, *J* = 16.4, 9.2 Hz, 1H), 5.95 (ddd, *J* = 17.6, 10.8, 6.0 Hz, 1H), 5.14 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.11 (dd, *J* = 10.8, 1.6 Hz, 1H), 4.97–4.92 (m, 1H), 4.82–4.77 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.92–1.62 (m, 4H), 1.58 (br, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 139.8, 137.4, 131.0, 130.4, 128.6, 127.5, 126.4, 115.3, 61.4, 52.4, 52.2, 29.0, 28.3, 15.2, 14.8. HRMS EI (*m/z*) mass Calcd for $C_{18}H_{23}NO_2$ 285.1728 $(M)^+$, Found 285.1720. $[\alpha]_D^{20}$ 52.87 (*c* = 1.0, $CHCl_3$) for a sample of *90% ee.* The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *90% ee.*



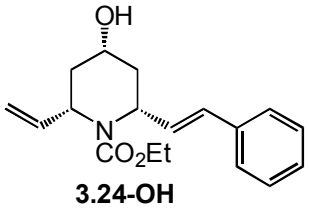
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	6.214		0.0000	0.000	488872.4	5.401	BB	0.188	43369.62	8.327
2	8.389		0.0000	0.000	8562277.0	94.599	BB	0.299	477439.50	91.673



3.24

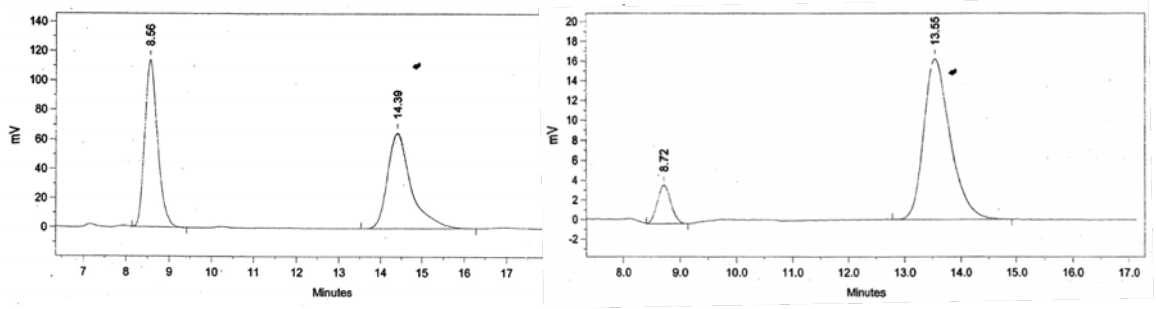
Piperidine **3.24.** IR (neat): 2955 (m), 2930 (m), 2855 (w), 1697 (s), 1073 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.19 (m, 5H), 6.65 (dd, *J* = 15.6 8.4 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.22 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.03 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.96–4.90 (m, 1H),

4.82–4.76 (m, 1H), 4.20–4.09 (m, 2H), 2.02–1.84 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 141.6, 137.5, 133.1, 130.3, 128.5, 127.3, 126.5, 114.7, 64.9, 61.4, 52.2, 52.1, 36.7, 36.5, 26.0, 18.2, 14.8, –4.8. HRMS EI (*m/z*) Calcd for $C_{24}H_{37}NO_3Si$ 415.2543 $(M)^+$, Found 415.2551. Determination of enantiomeric excess of **3.24** involved the piperidine derived from desilylation of the silyl ether in **3.24**.

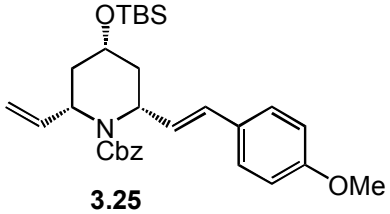


3.24-OH

Piperidine **3.24-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.21 (m, 5H), 6.54–6.48 (m, 2H), 6.20 (ddd, J = 16.8, 10.0, 6.4 Hz, 1H), 5.18 (dd, J = 17.2, 1.2 Hz, 1H), 5.10 (dd, J = 10.0, 1.2 Hz, 1H), 5.00–4.94 (m, 1H), 4.86–4.80 (m, 1H), 4.24–4.20 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.12–1.96 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H). $[\alpha]_D^{20}$ 27.0 (c = 0.1, $CHCl_3$) for a sample of *79% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 90:10 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *79% ee*.



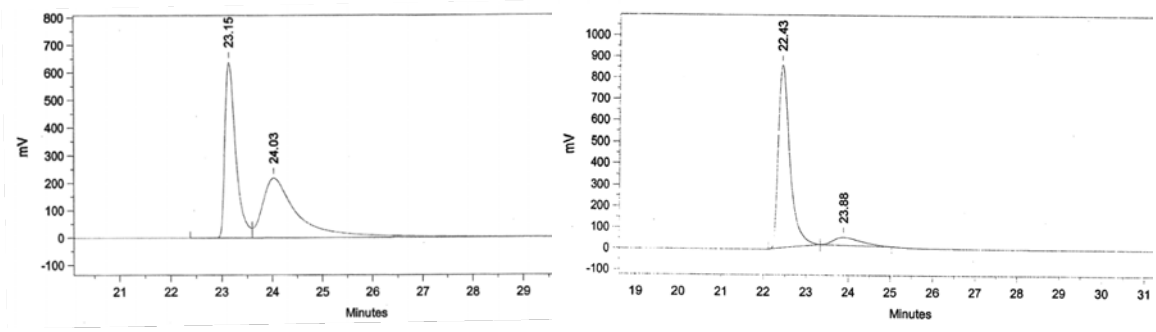
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	8.721		0.0000	0.000	62366.3	10.522	BB	0.266	3910.58	19.444
2	13.551		0.0000	0.000	530377.3	89.478	BB	0.546	16201.38	80.556



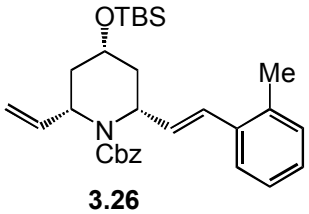
3.25

Piperidine **3.25**. IR (neat): 2949 (s), 2924 (s), 2855 (m), 1697 (s), 1508 (s), 1250 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38–7.30 (m, 7H), 7.22 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.53 (dd, J = 16.0, 8.4 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 6.28 (ddd, J = 17.2, 10.4, 7.6 Hz, 1H), 5.19–5.08 (m, 2H), 5.07–5.06 (m, 1H), 5.01 (dd, J = 12.0, 1.2 Hz, 1H), 4.94–4.90 (m, 1H), 4.84–4.80 (m, 1H) 4.18–4.11 (m, 1H), 3.80 (s, 2H), 2.05–1.85 (m, 4H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 189.7, 158.8, 141.2, 130.4, 129.7, 128.2, 127.8, 127.7, 127.4, 114.5, 113.6, 67.0, 64.7, 55.1, 52.2, 36.5, 36.3, 25.7, 17.9, –0.2, –5.1. HRMS ES (*m/z*) Calcd for $C_{30}H_{42}NO_4Si$ 508.2883 $(M+H)^+$, Found 508.2871. $[\alpha]_D^{20}$ 23.99 (c = 0.1, $CHCl_3$) for a sample of *80%*

ee. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD-R (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *80% ee*.

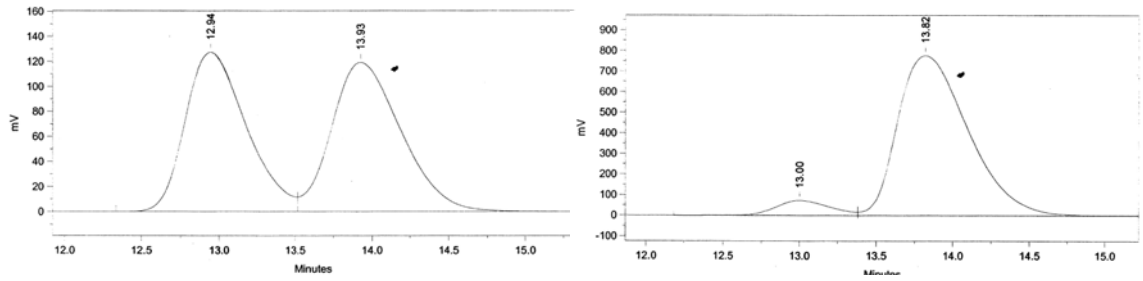


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	22.426		0.0000	0.000	16050500.0	90.266	BB	0.312	856385.20	95.775
2	23.882		0.0000	0.000	1730848.0	9.734	BB	0.764	37781.50	4.225

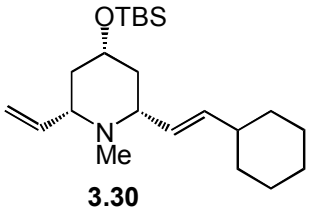


3.26

Piperidine **3.26**. IR (neat): 2949 (s), 2924 (s), 2855 (m), 1697 (s), 1400 (m), 1073 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38–7.26 (m, 7H), 7.20–7.10 (m, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.55 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.28 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.15 (s, 2H), 5.10 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.00–4.96 (m, 1H), 4.84–4.80 (m, 1H), 4.16 (dd, *J* = 8.0, 4.4 Hz, 1H), 2.22 (s, 3H), 2.05–1.87, (m, 4H) 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 141.5, 137.0, 136.4, 135.5, 134.0, 130.2, 128.6, 128.2, 128.1, 128.0, 127.2, 126.0, 125.6, 114.9, 67.4, 65.0, 52.6, 52.4, 36.8, 36.6, 26.0, 19.9, 18.2, –4.8. HRMS ES (*m/z*) Calcd for $C_{30}H_{42}NO_3Si$ 492.2934 $(M+H)^+$, Found 492.2928. $[\alpha]_D^{20}$ 47.99 (*c* = 0.3, $CHCl_3$) for a sample of *86% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD-R (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *86% ee*.

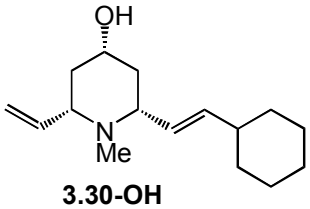


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	13.002		0.0000	0.000	1815532.0	6.861	BV	0.413	73257.07	8.624
2	13.819		0.0000	0.000	24645590.0	93.139	VB	0.529	776164.30	91.376



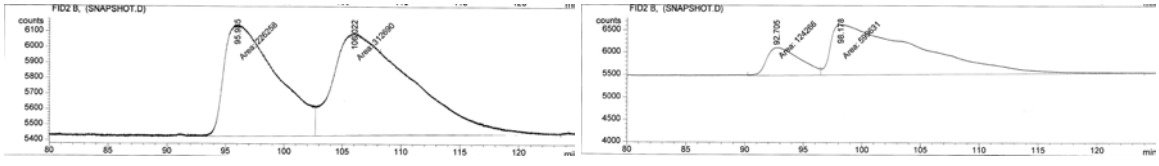
3.30

Piperidine **3.30**. IR (neat): 2924 (s), 2848 (s), 2766 (w), 1099 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddd, *J* = 18.8,10.0, 10.0 Hz, 1H), 5.50 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.28 (dd, *J* = 15.2, 8.8 Hz, 1H), 5.12 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.02 (dd, *J* = 10.0, 1.2 Hz, 1H), 3.65 (dddd, *J* = 15.2, 10.4, 4.4, 4.4 Hz, 1H), 2.43 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.36 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.11 (s, 3H), 1.98–1.86 (m, 1H), 1.80–1.58 (m, 6H), 1.54–1.38 (m, 2H), 1.30–1.00 (m, 6H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.2, 138.0, 130.8, 115.4, 68.8, 67.6, 66.6, 43.3, 43.1, 41.1, 40.3, 33.0, 26.4, 26.2, 26.0, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{22}H_{42}NOSi$ 364.3036 $(M+H)^+$, Found 364.3035. Determination of enantiomeric excess of **3.30** involved the piperidine derived from desilylation of the silyl ether in **30**.



3.30-OH

Piperidine **3.30-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (ddd, *J* = 18.8, 9.2, 9.2 Hz, 1H), 5.51 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.31 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.15 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.05 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.75–3.67 (m, 1H), 2.52–2.40 (m, 2H), 2.14 (s, 3H), 1.98–1.86 (m, 2H), 1.72–1.60 (m, 5H), 1.51–1.36 (m, 2H), 1.25–0.83 (m, 6H). The optical purity of this compound was determined by GC analysis in comparison with authentic racemic material, shown below: β-dex chiral column, 130 °C, 20 psi.



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
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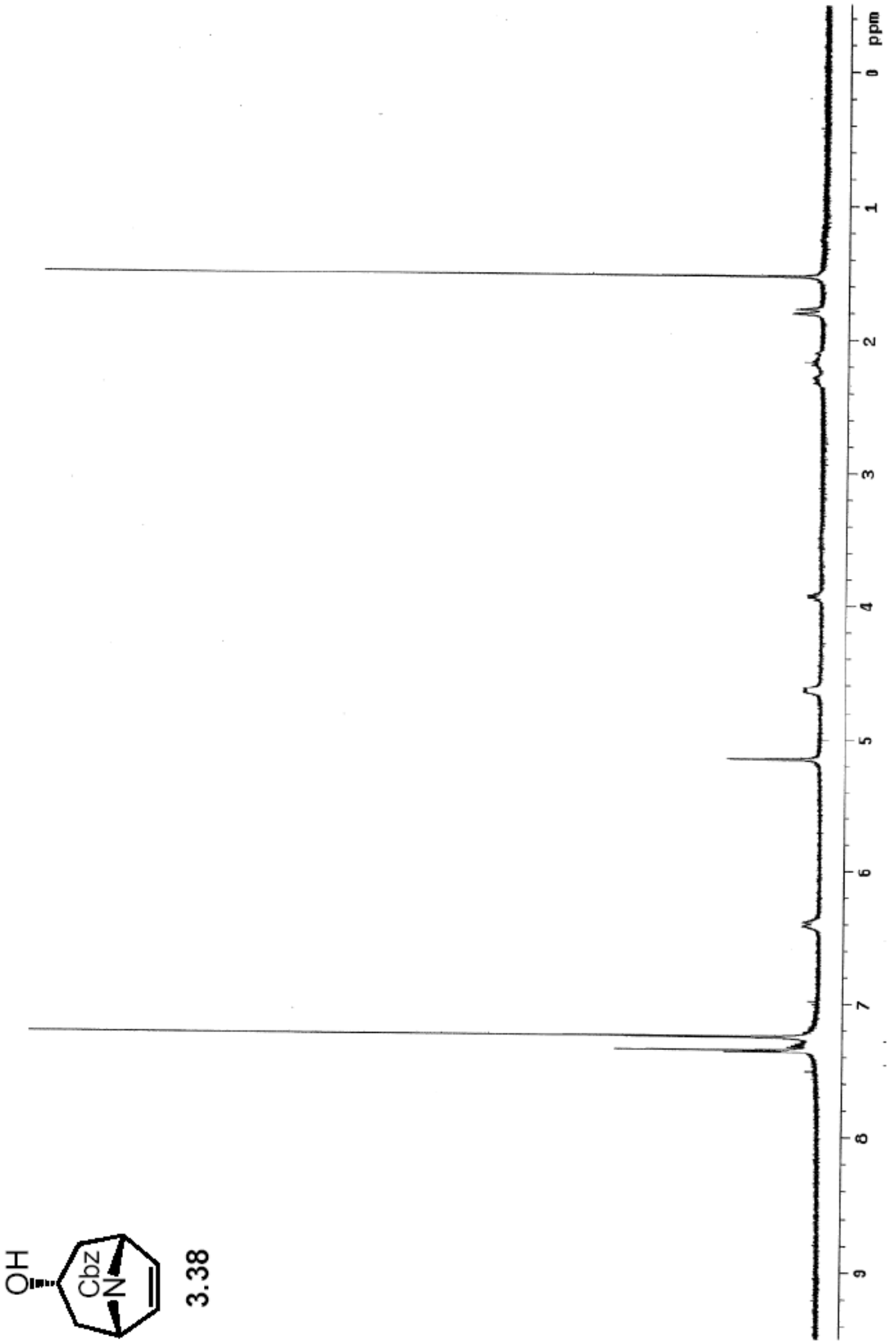
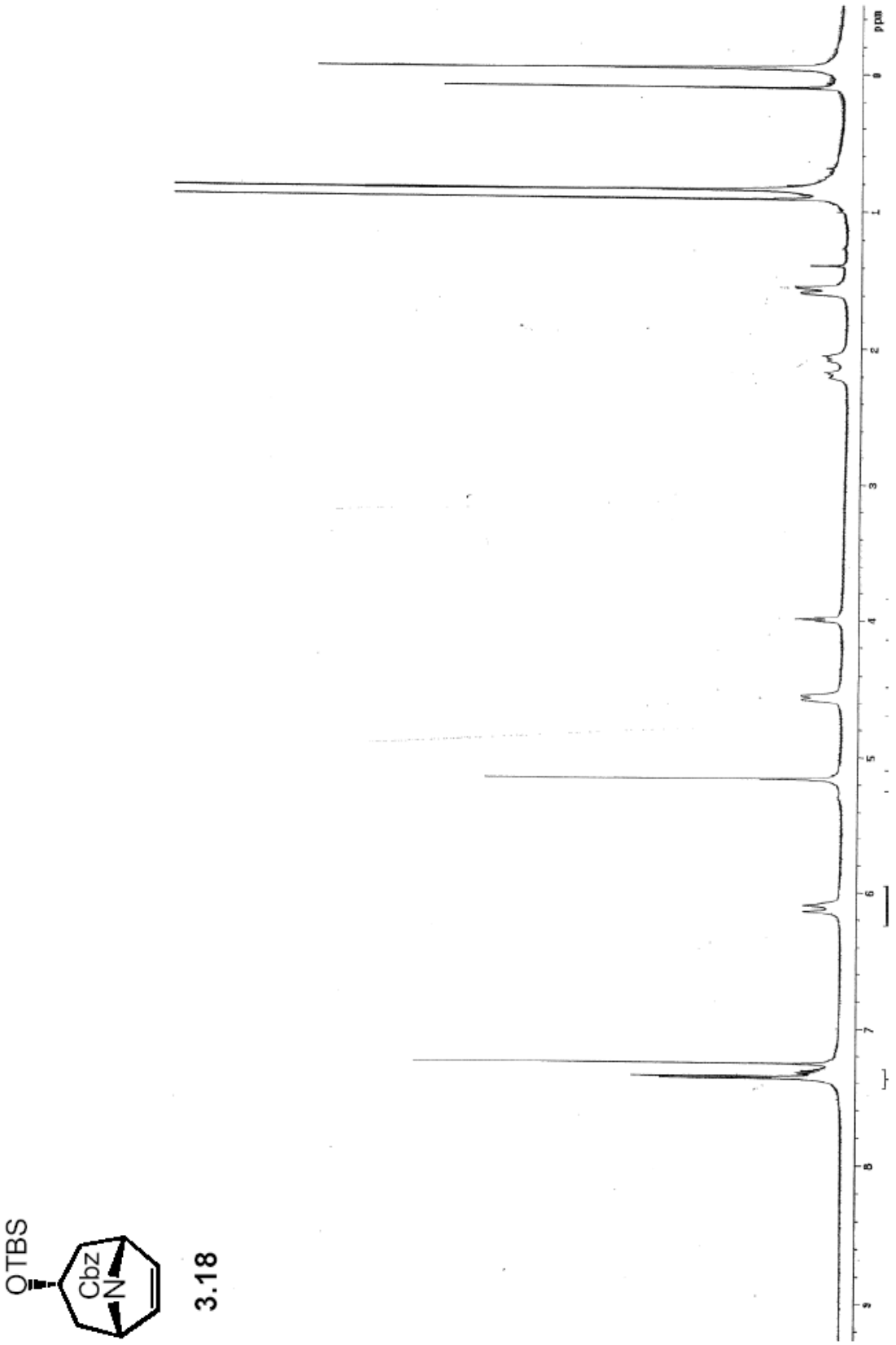
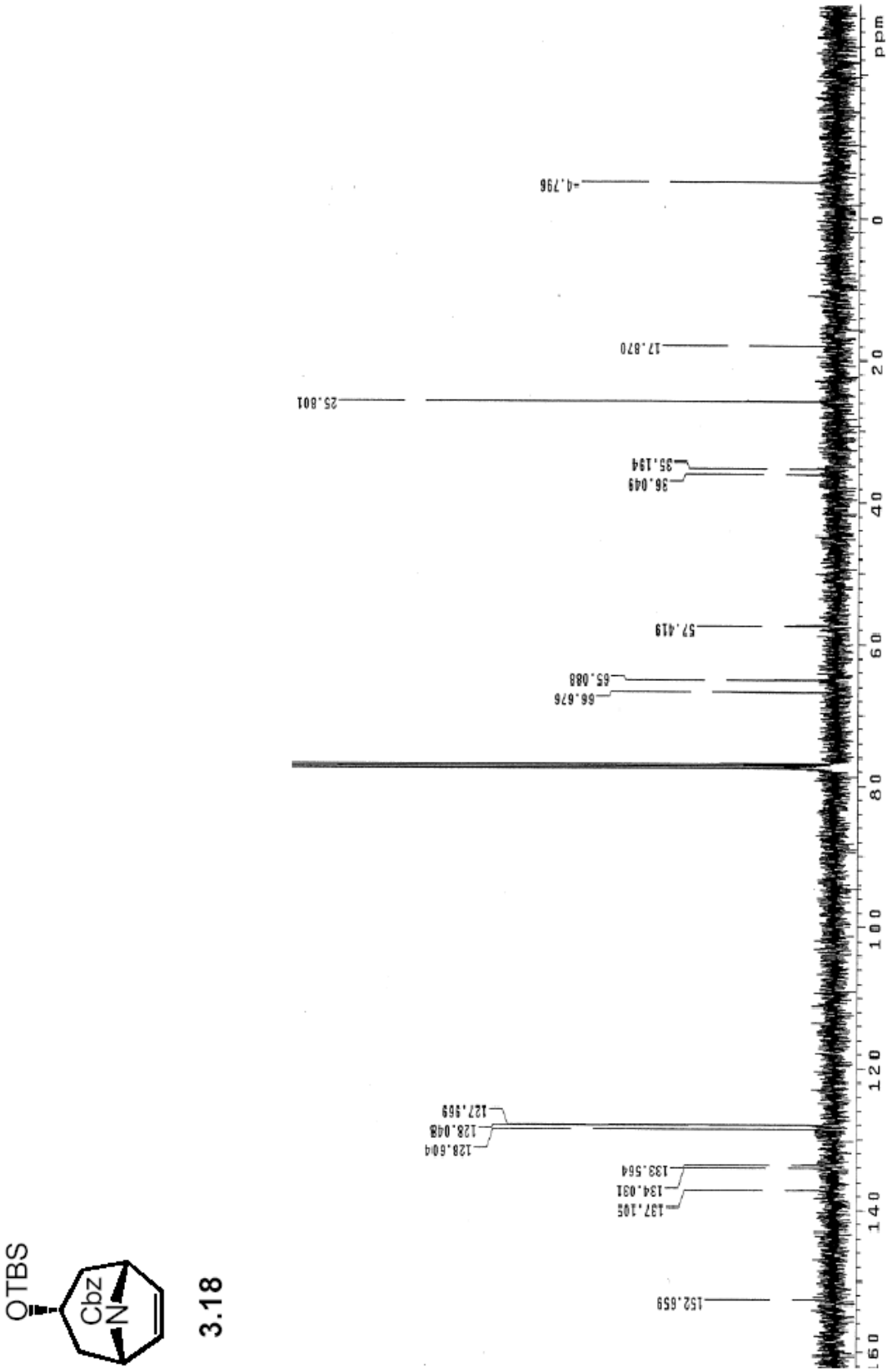
2	106.022	FM	7.8456	3.12690e5	664.26031	58.01861

Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	92.705	MF	3.2765	1.24266e5	632.10815	17.16621
2	98.178	FM	8.7504	5.99631e5	1142.10352	82.83379

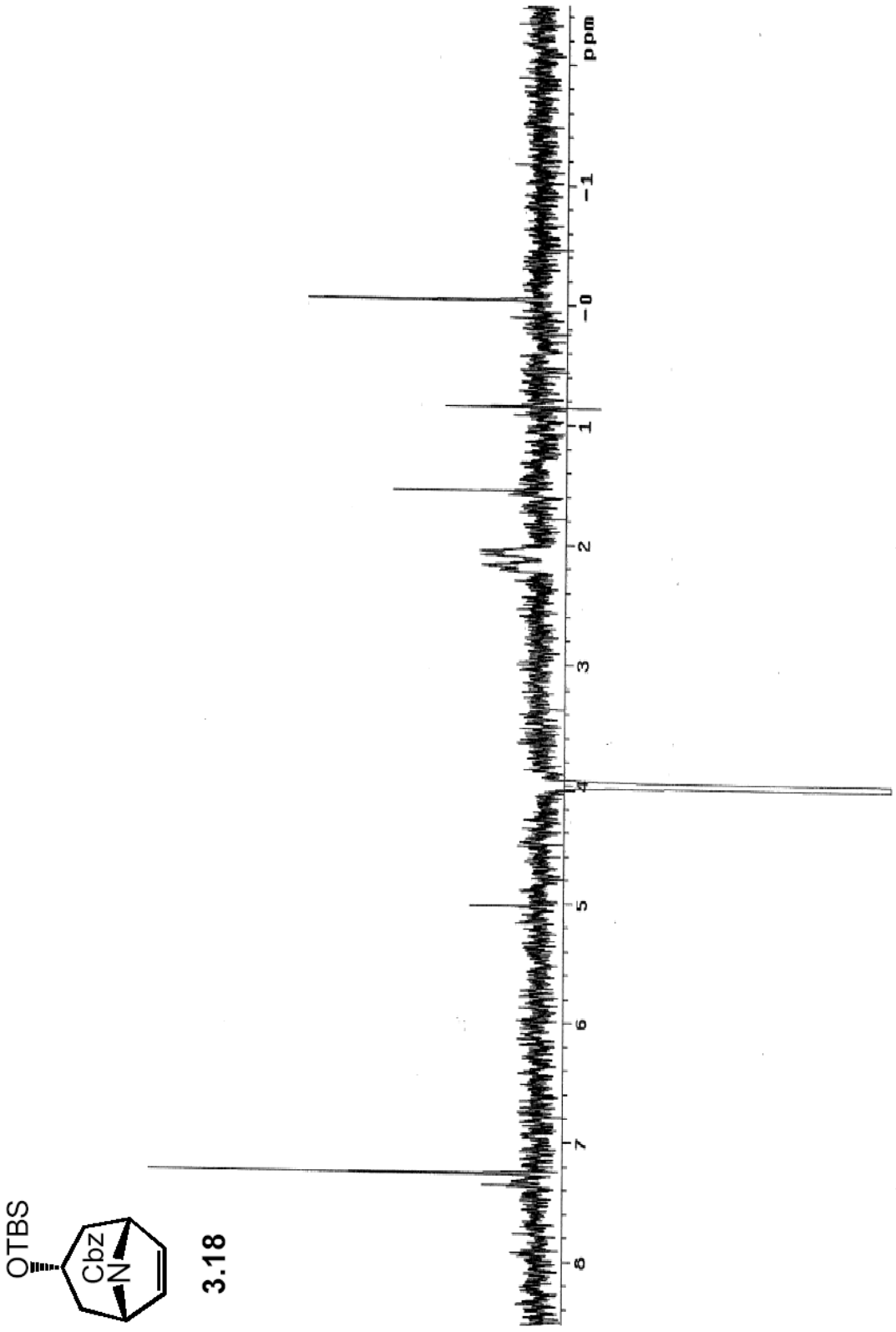

OH
Cbz
N
3.38
9
8
7
6
5
4
3
2
1
0 ppm

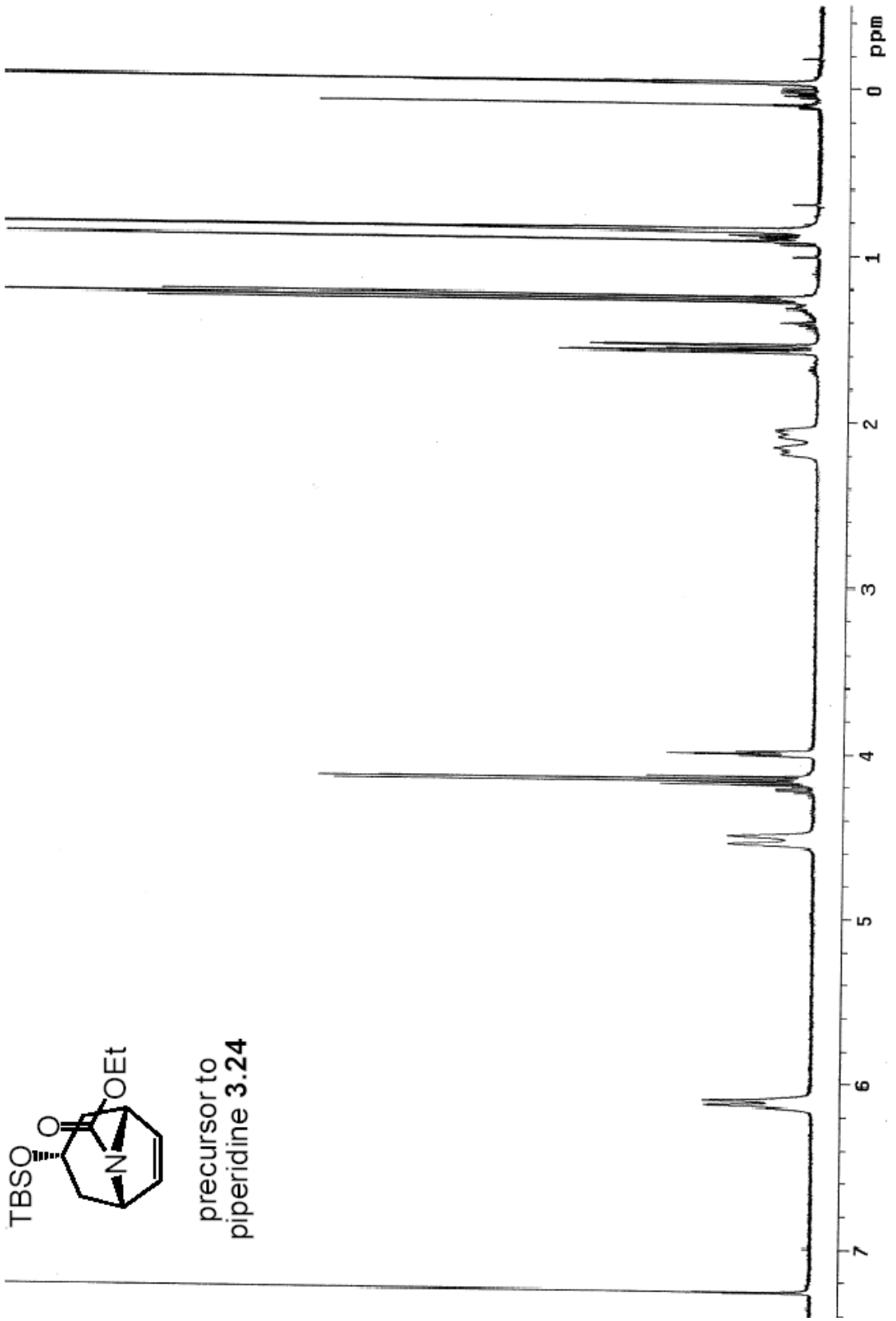


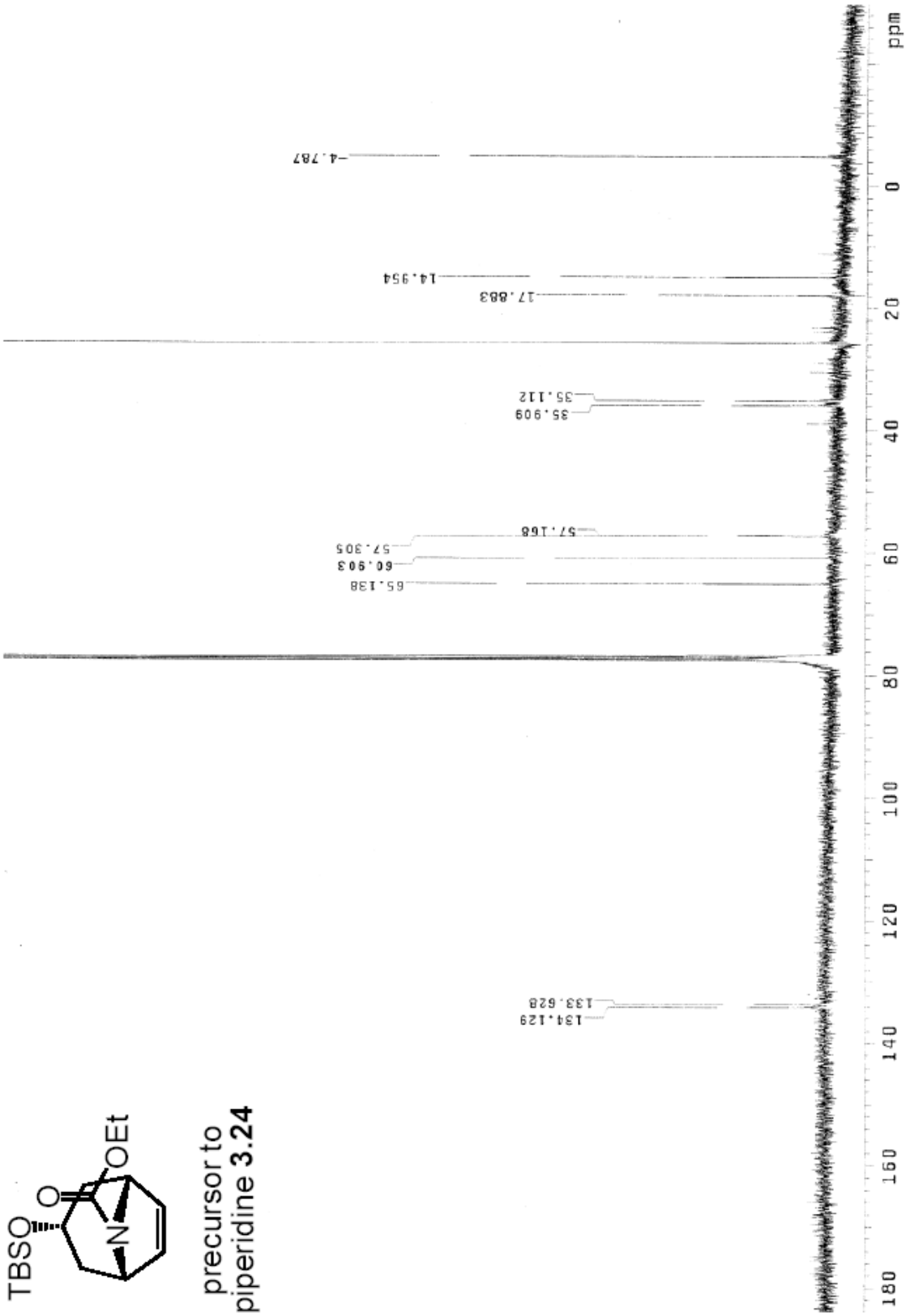
3.18

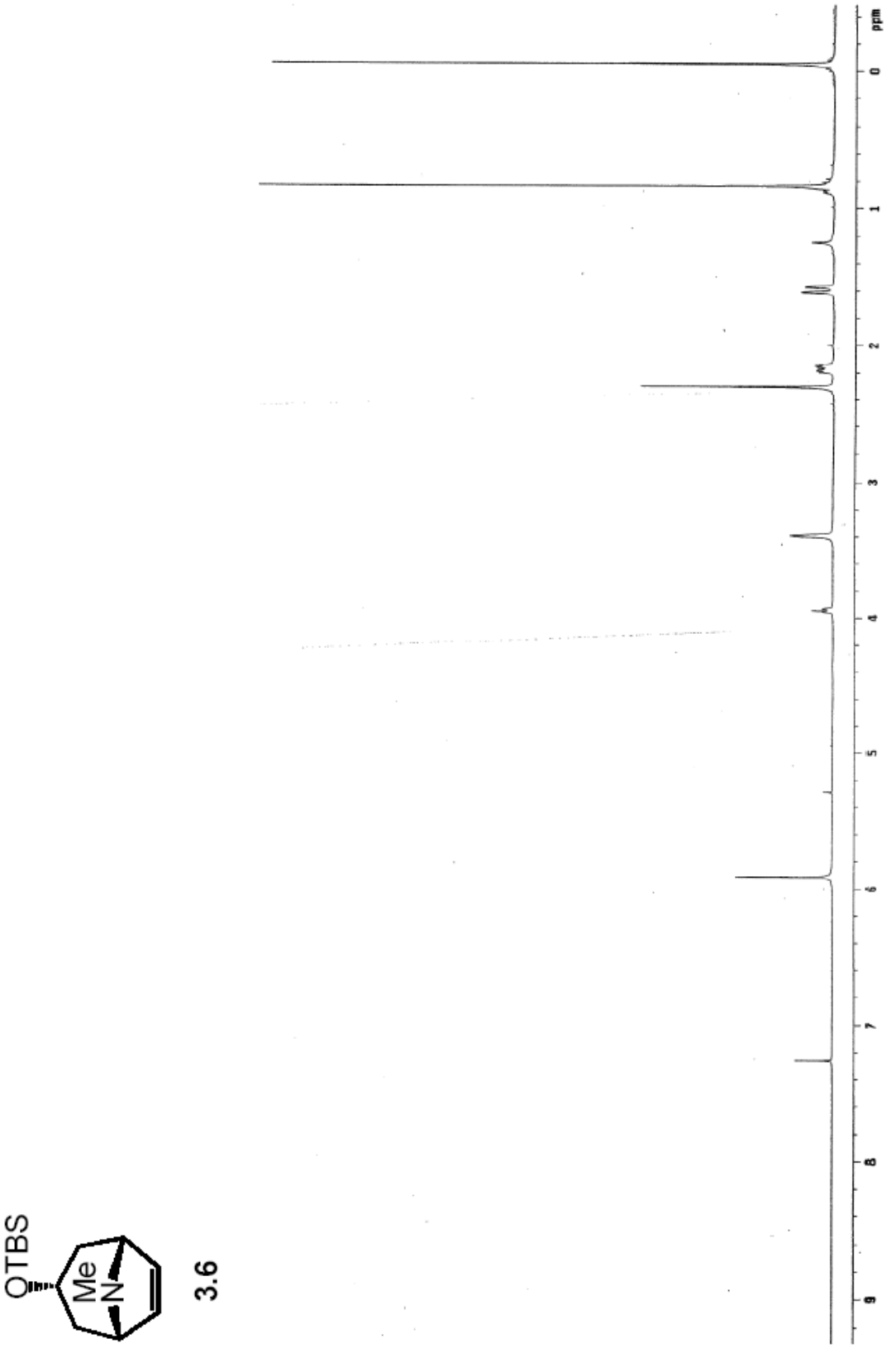

OTBS
Cbz
N
ppm
-4.796
17.870
25.801
35.194
36.049
57.419
65.088
66.676
127.969
128.048
128.604
133.564
134.081
137.105
152.659

3.18

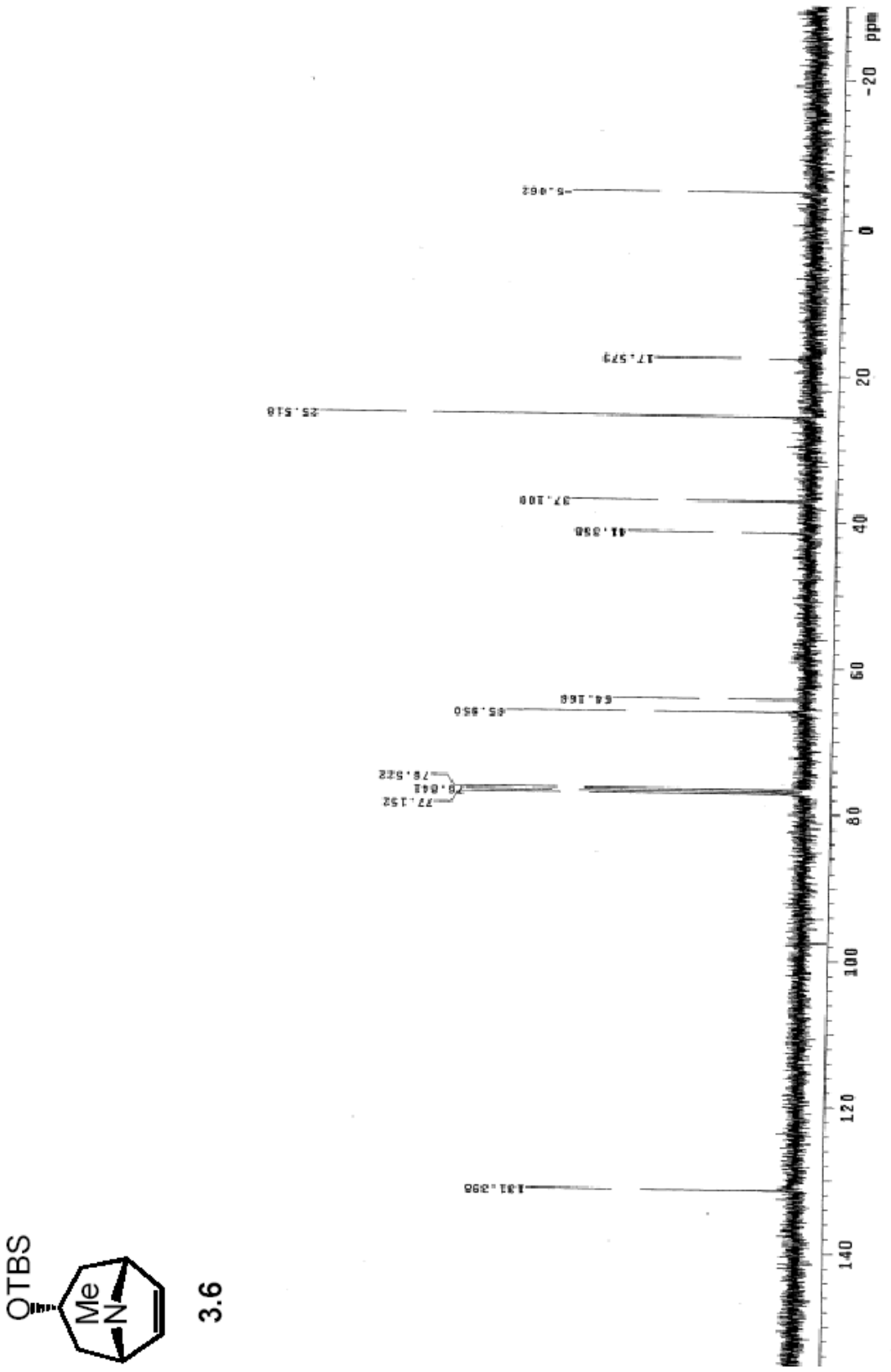

OTBS
Cbz
N
3.18
ppm
8
7
6
5
4
3
2
1
0
−1


TBSO
O
N
OEt
precursor to
piperidine **3.24**
7
6
5
4
3
2
1
0
ppm


TBSO
O
N
OEt
precursor to
piperidine **3.24**
ppm
0
20
40
60
80
100
120
140
160
180
-4.787
14.954
17.883
35.112
35.909
57.168
57.305
60.903
65.138
134.129
133.628



3.6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Me
N
3.6
ppm
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0
20
40
60
80
100
120
140
-5.062
17.579
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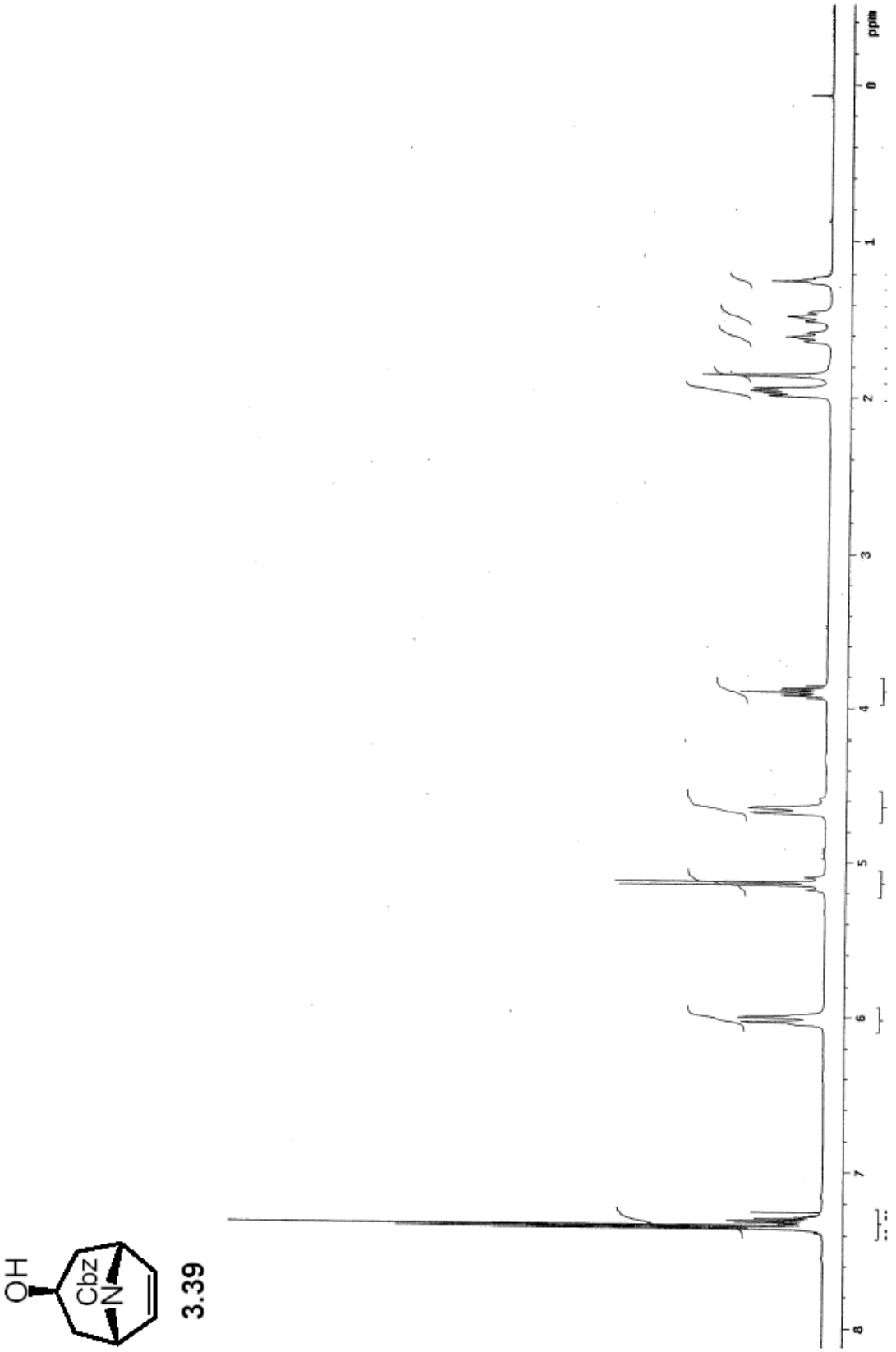
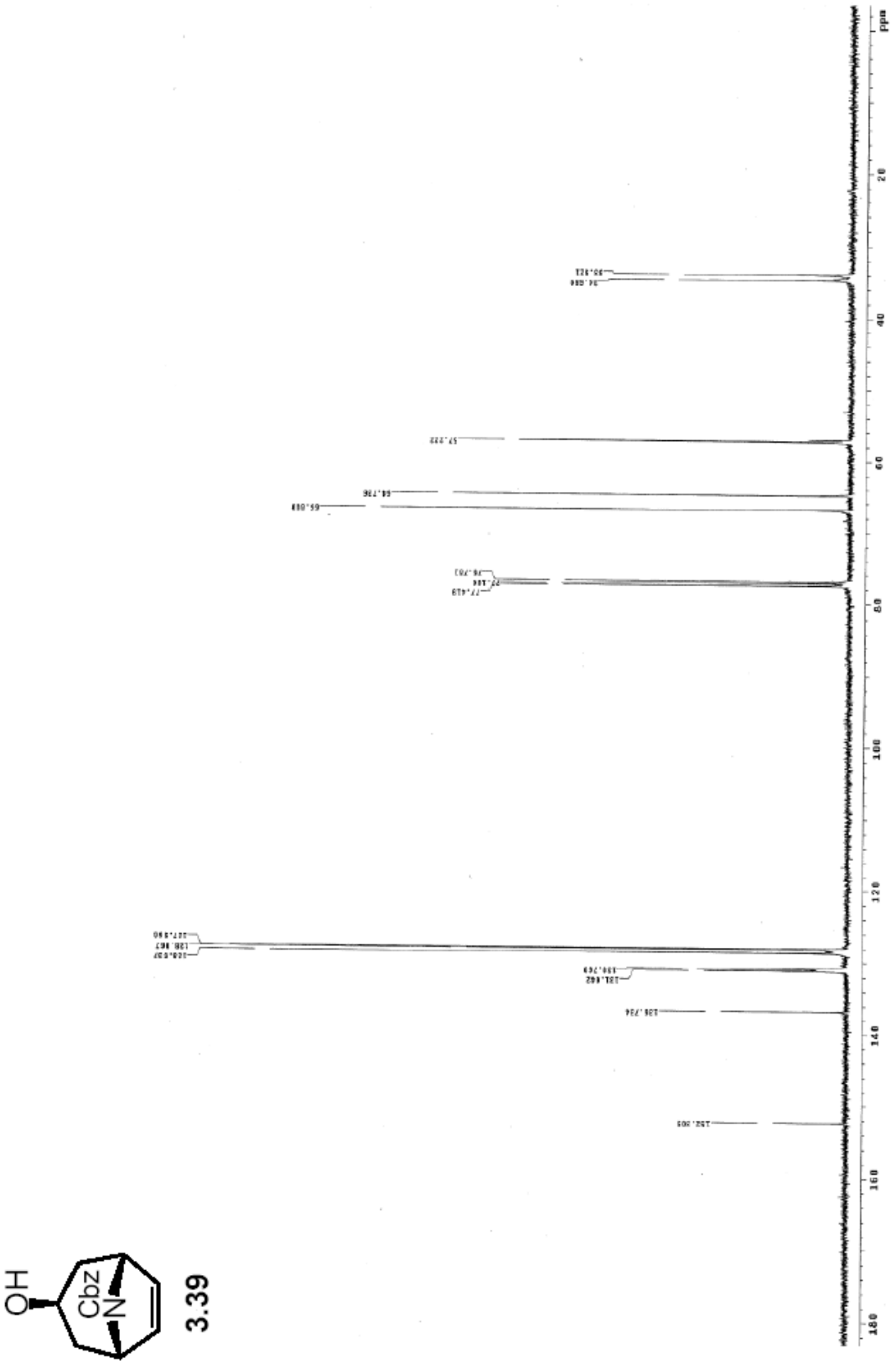
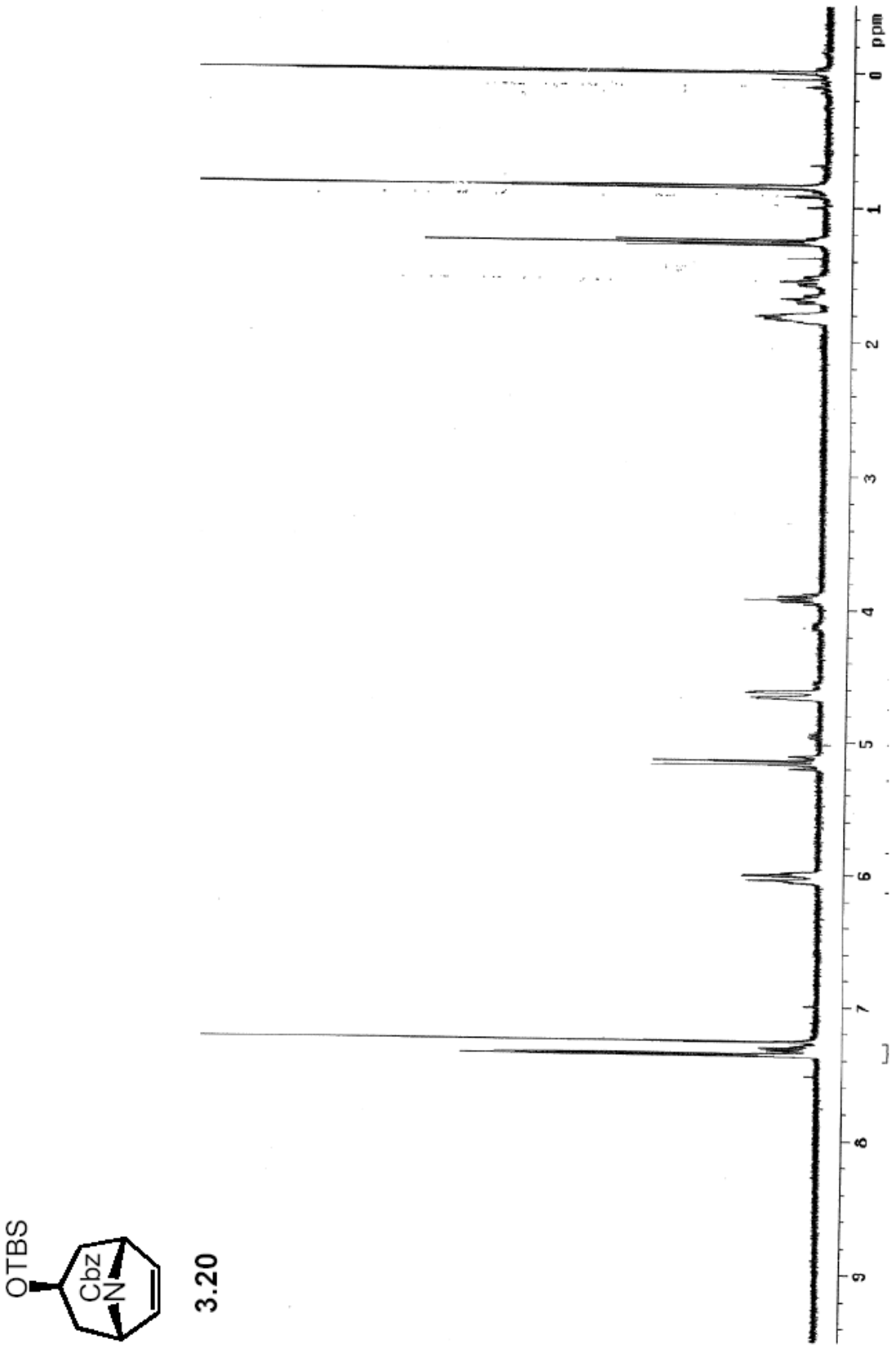
64.168
65.850
77.152
78.041
78.522
131.286

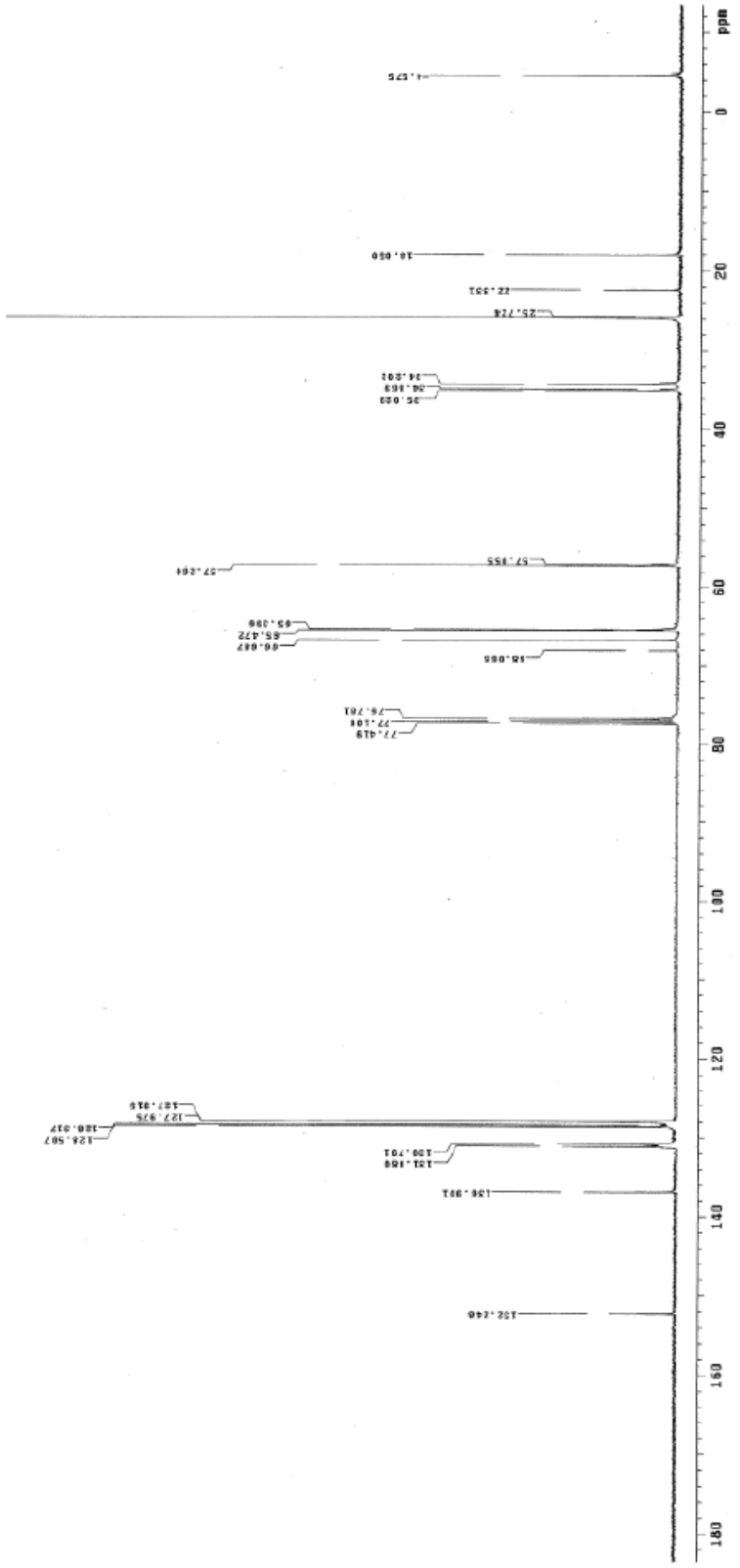

OH
Cbz
N
3.39
ppm
0
1
2
3
4
5
6
7
8

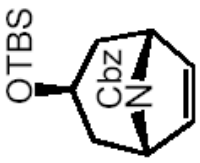


3.39

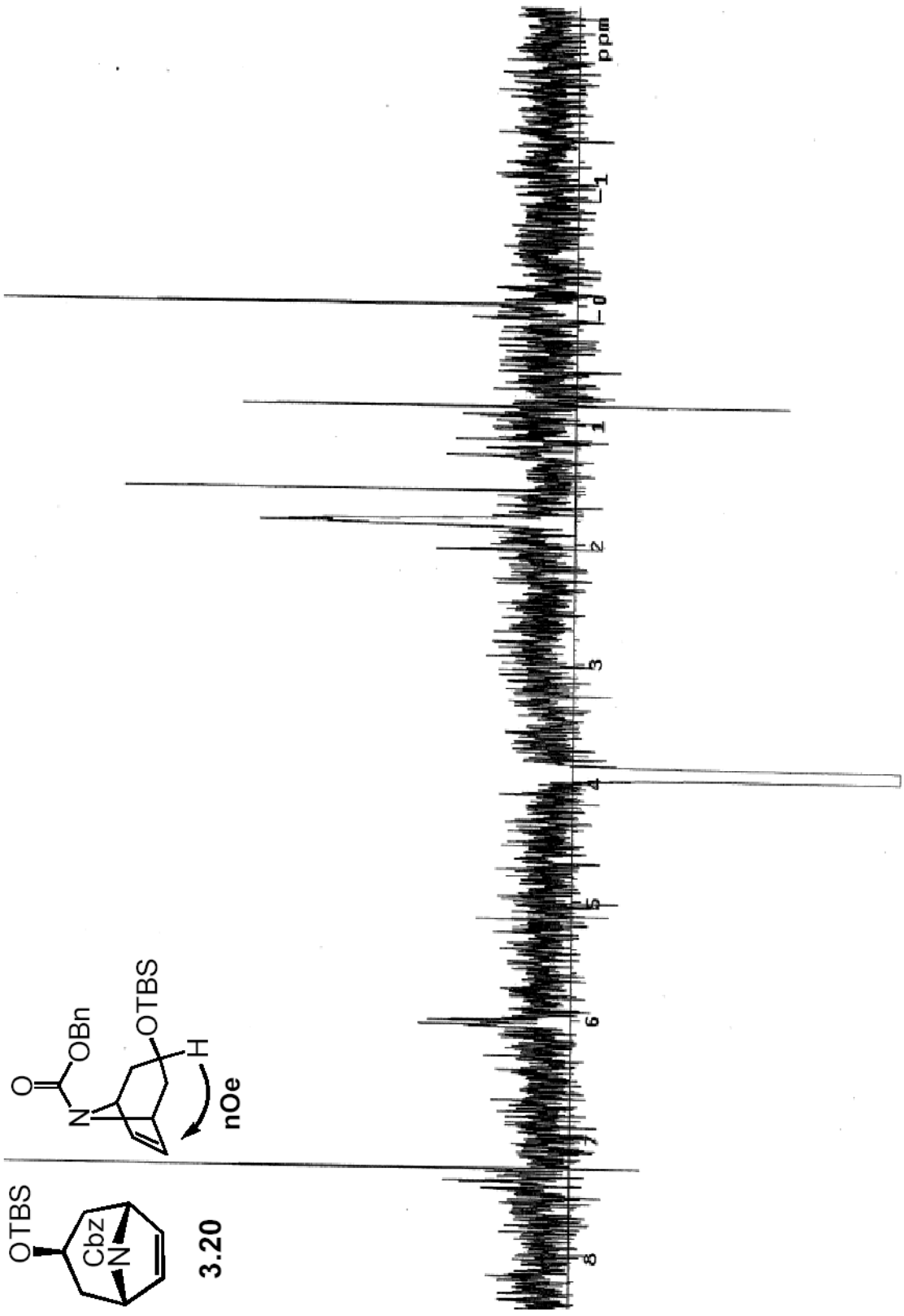


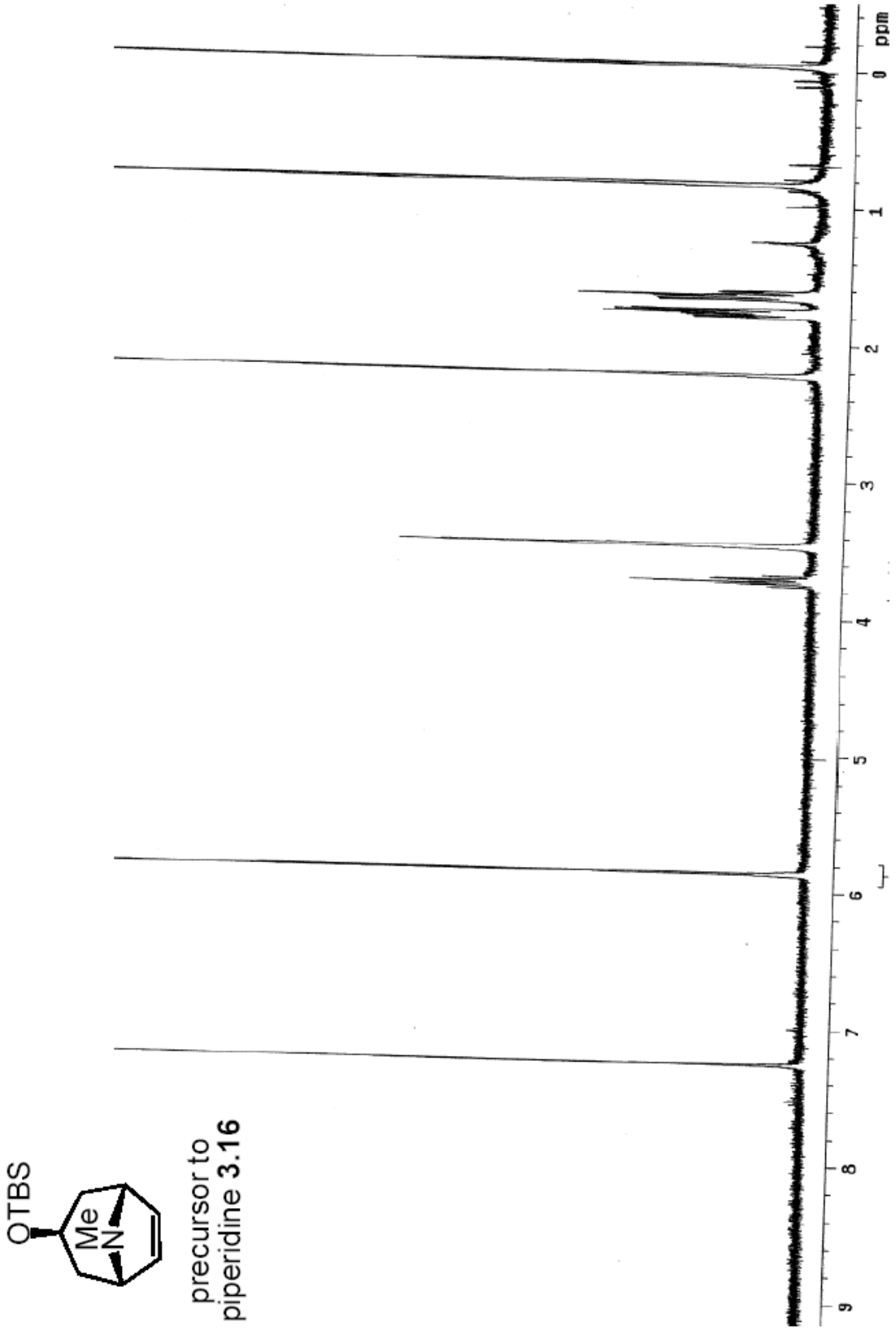
3.20

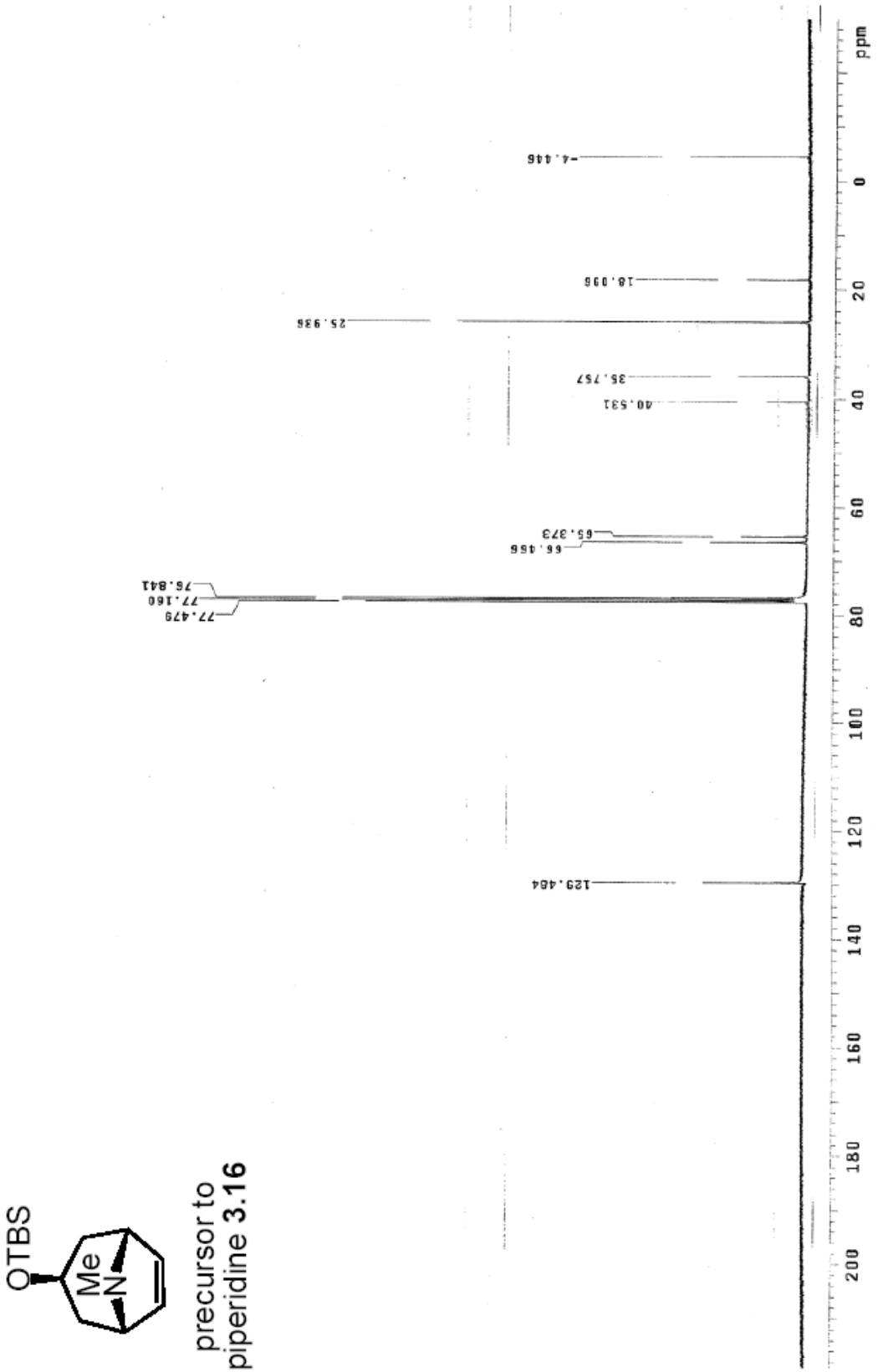


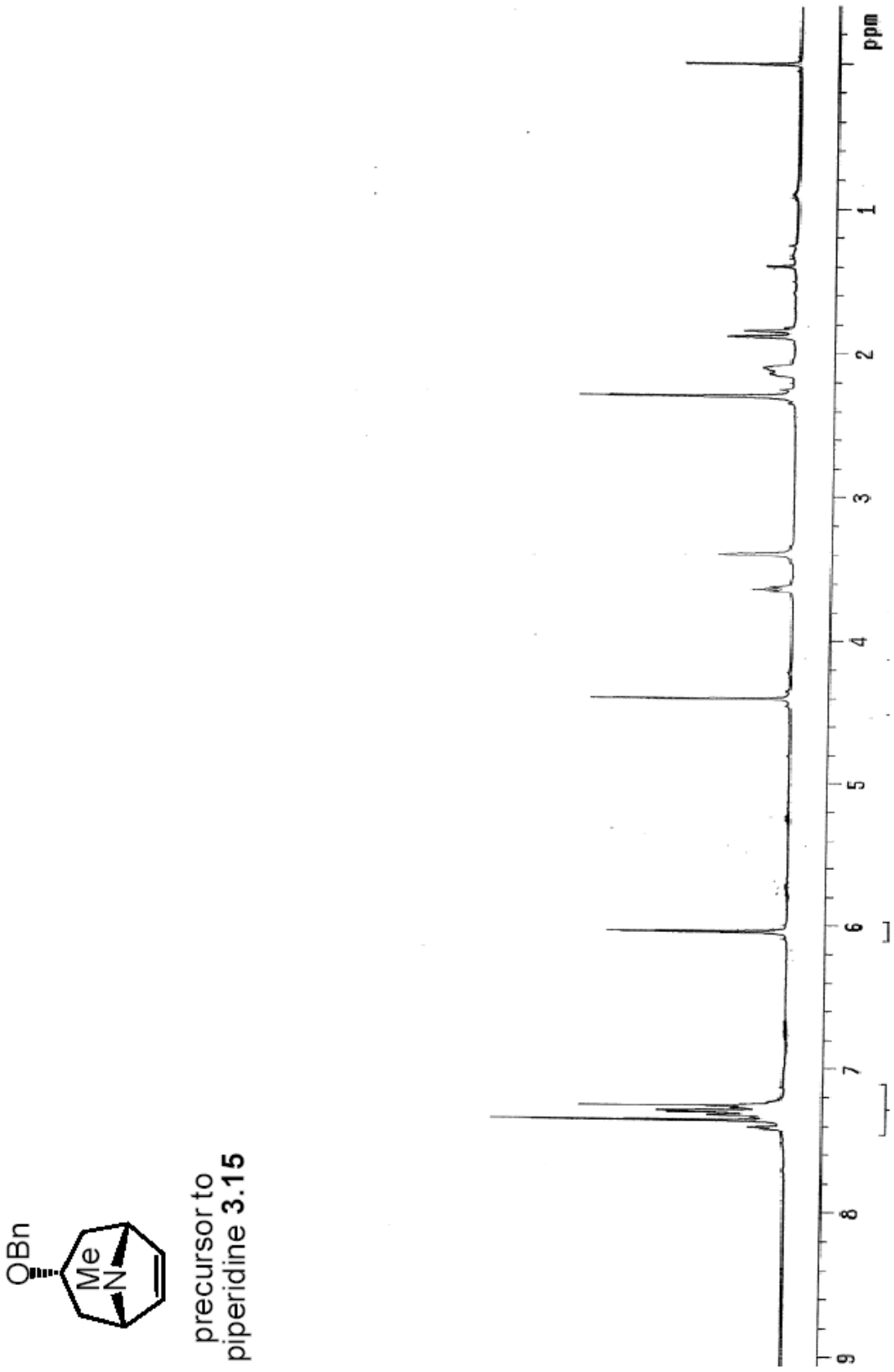


3.20

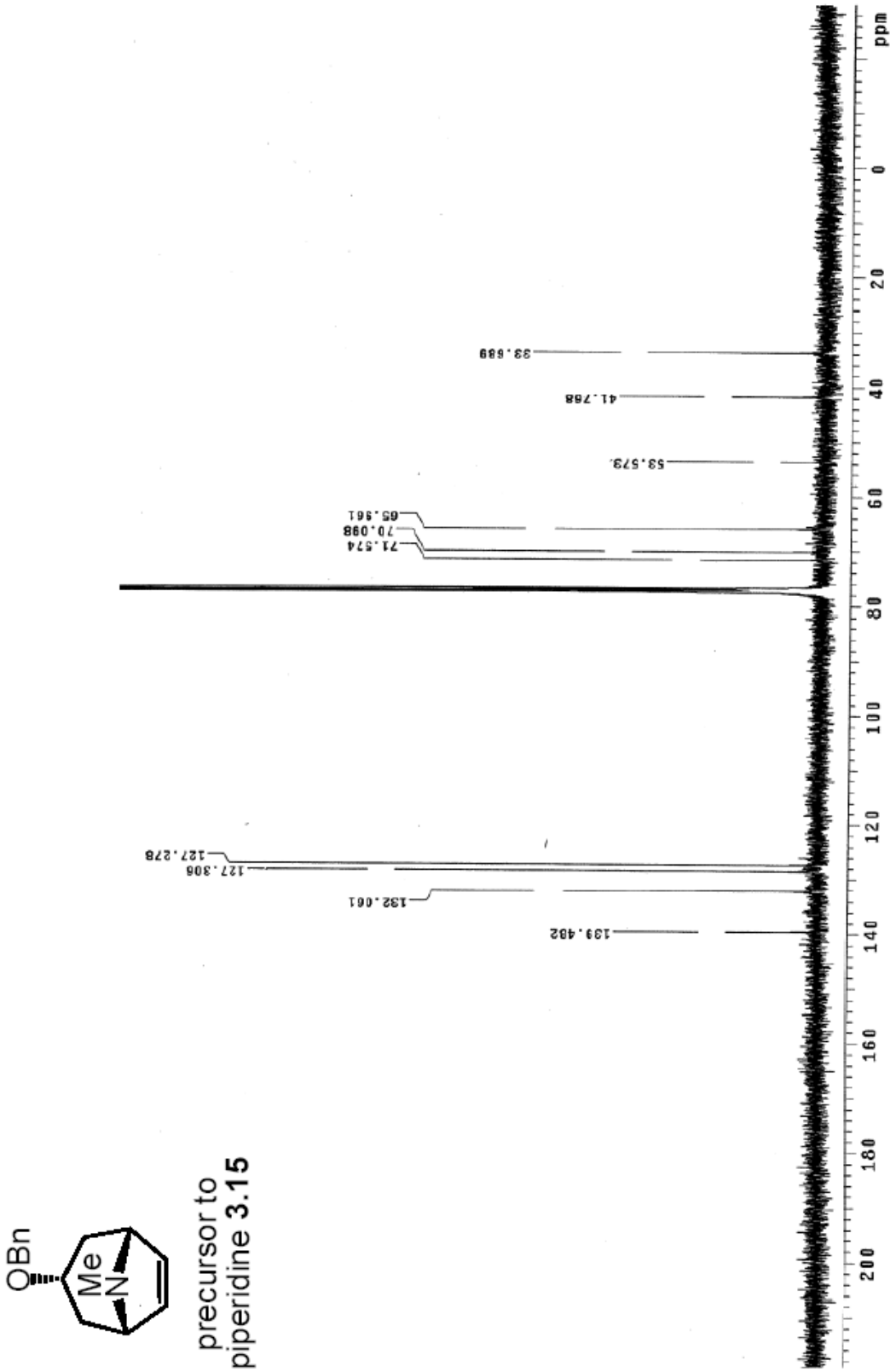

OTBS
Cbz
N
3.20
O
OBn
N
OTBS
H
nOe
ppm
8
7
6
5
4
3
2
1
0

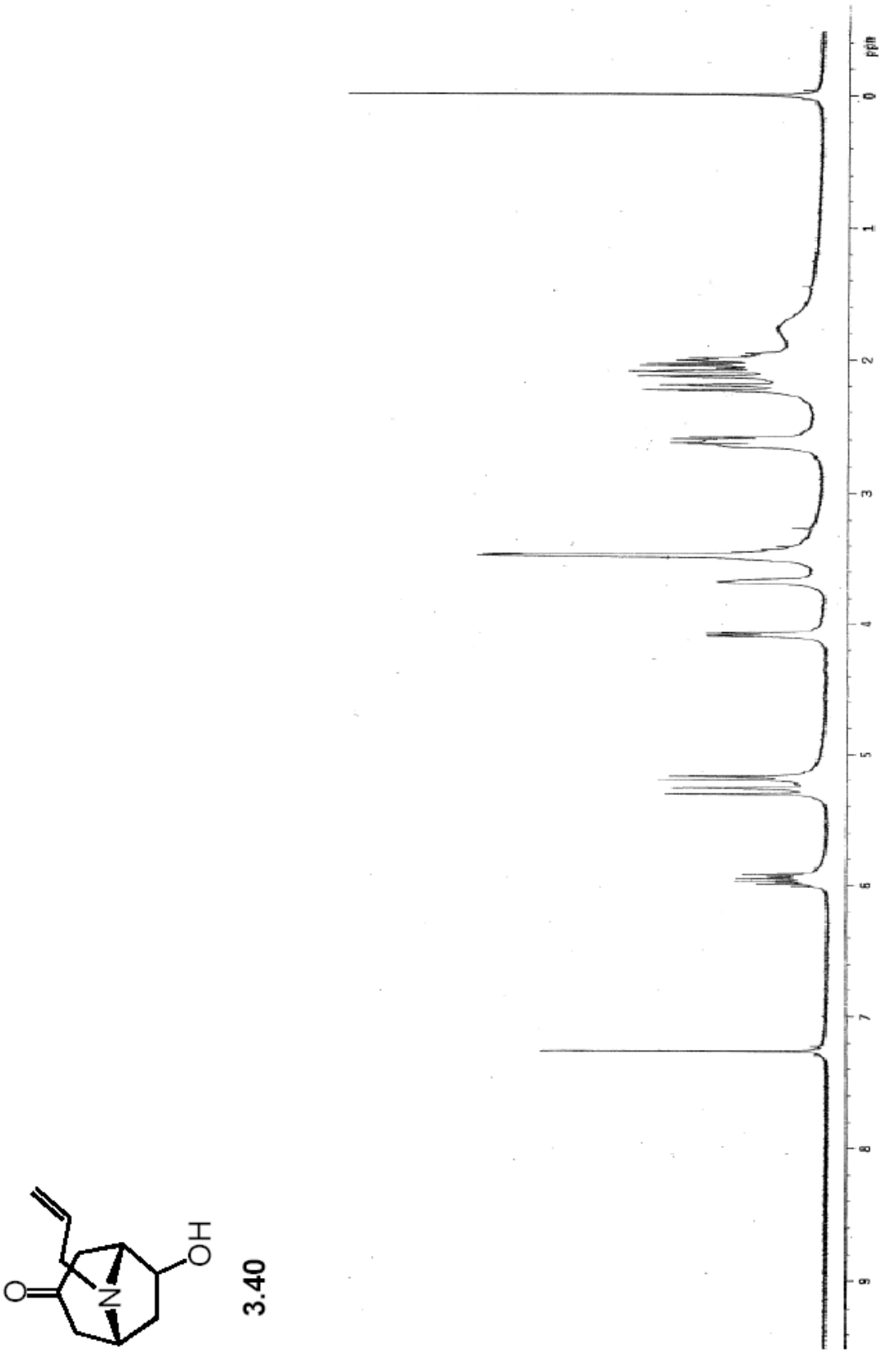

OTBS
Me
N
precursor to
piperidine **3.16**
9
8
7
6
5
4
3
2
1
0 ppm


OTBS
Me
N
precursor to
piperidine **3.16**
-4.446
18.098
25.938
35.757
40.531
65.373
66.466
77.479
77.160
75.841
129.464
ppm
0
20
40
60
80
100
120
140
160
180
200

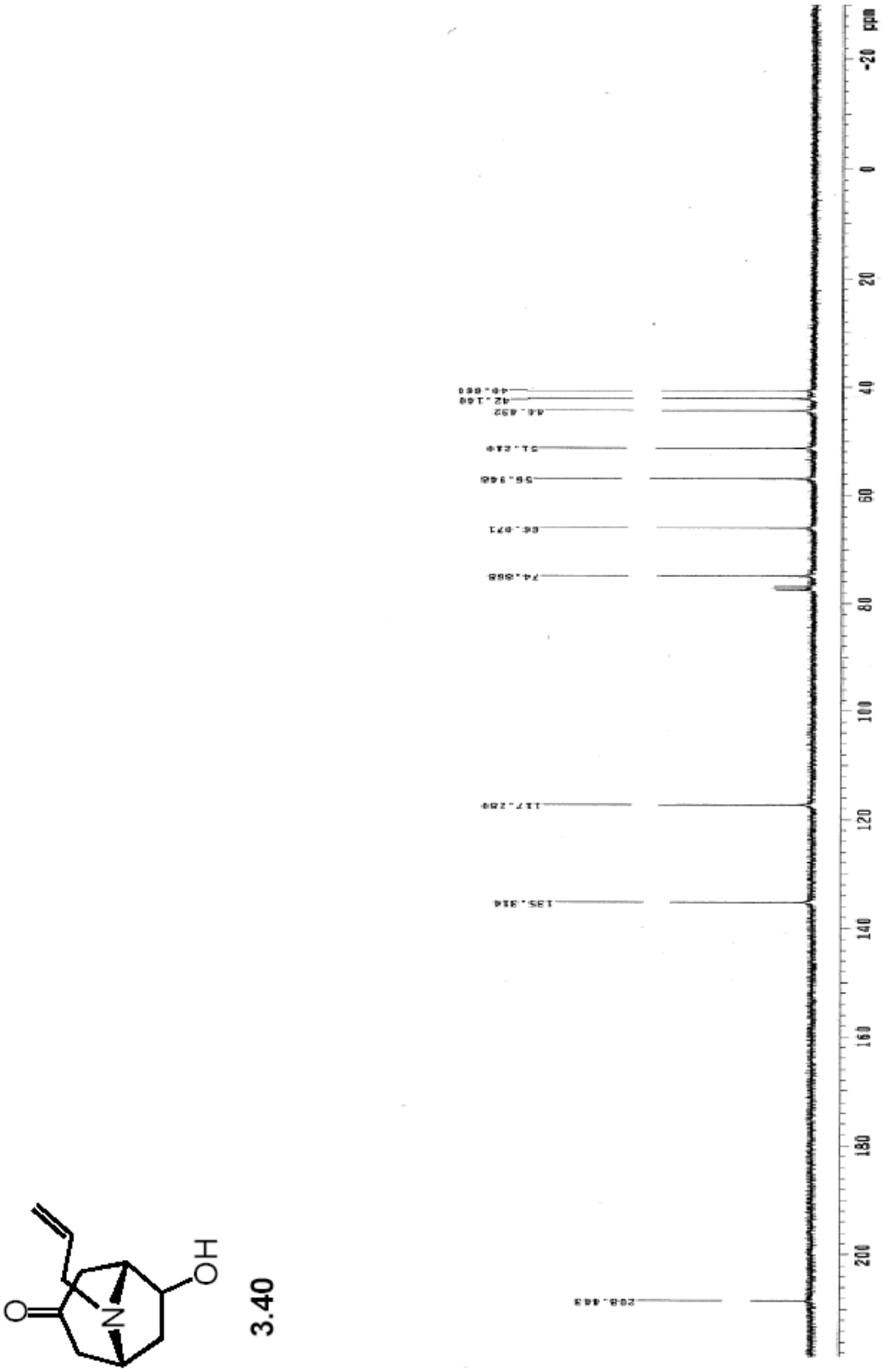


precursor to piperidine **3.15**


OBn
Me
N
precursor to
piperidine **3.15**
33.589
41.768
58.579
65.361
70.098
71.574
127.278
127.306
132.061
139.482
ppm
0
20
40
60
80
100
120
140
160
180
200

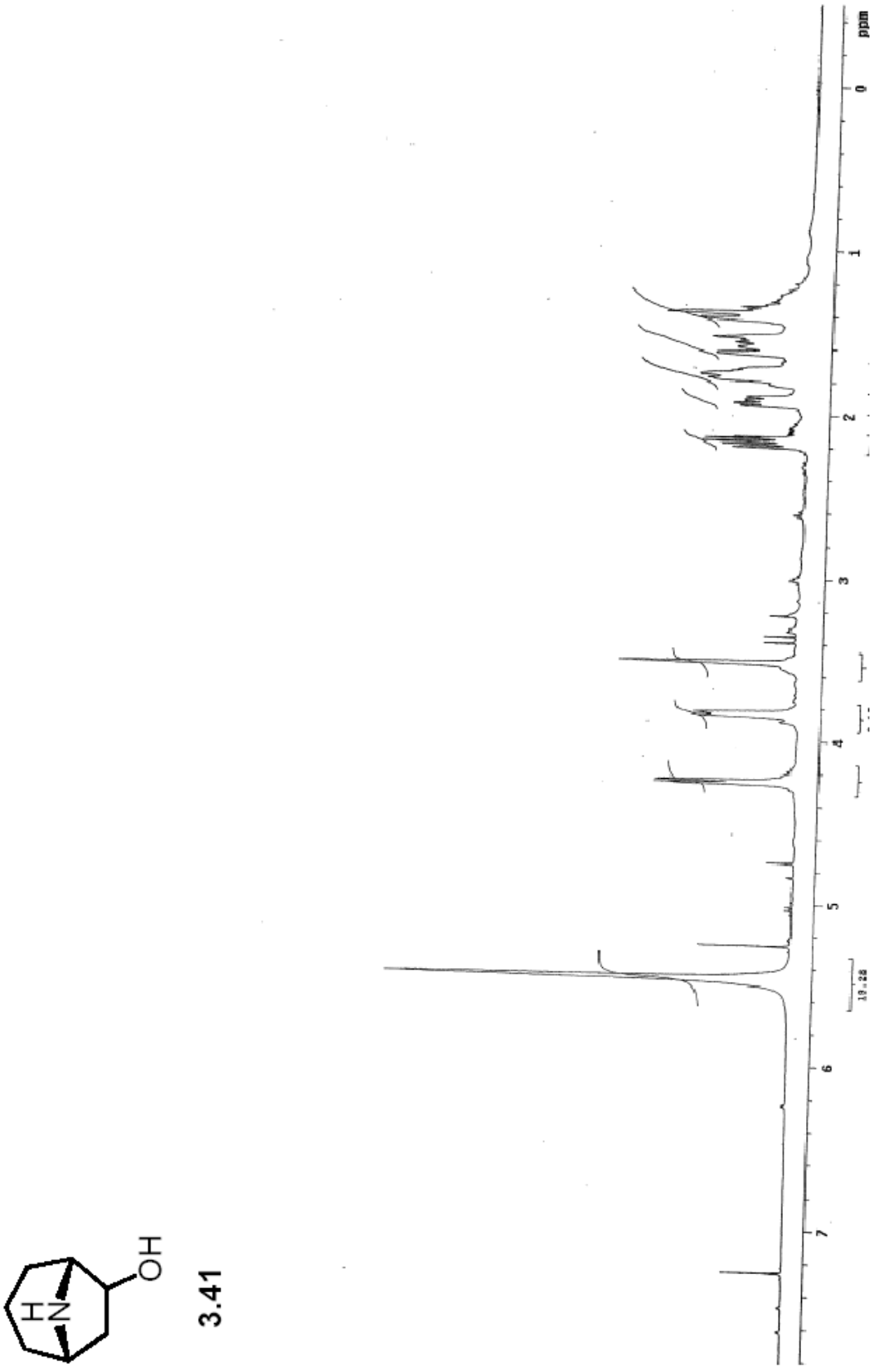


3.40

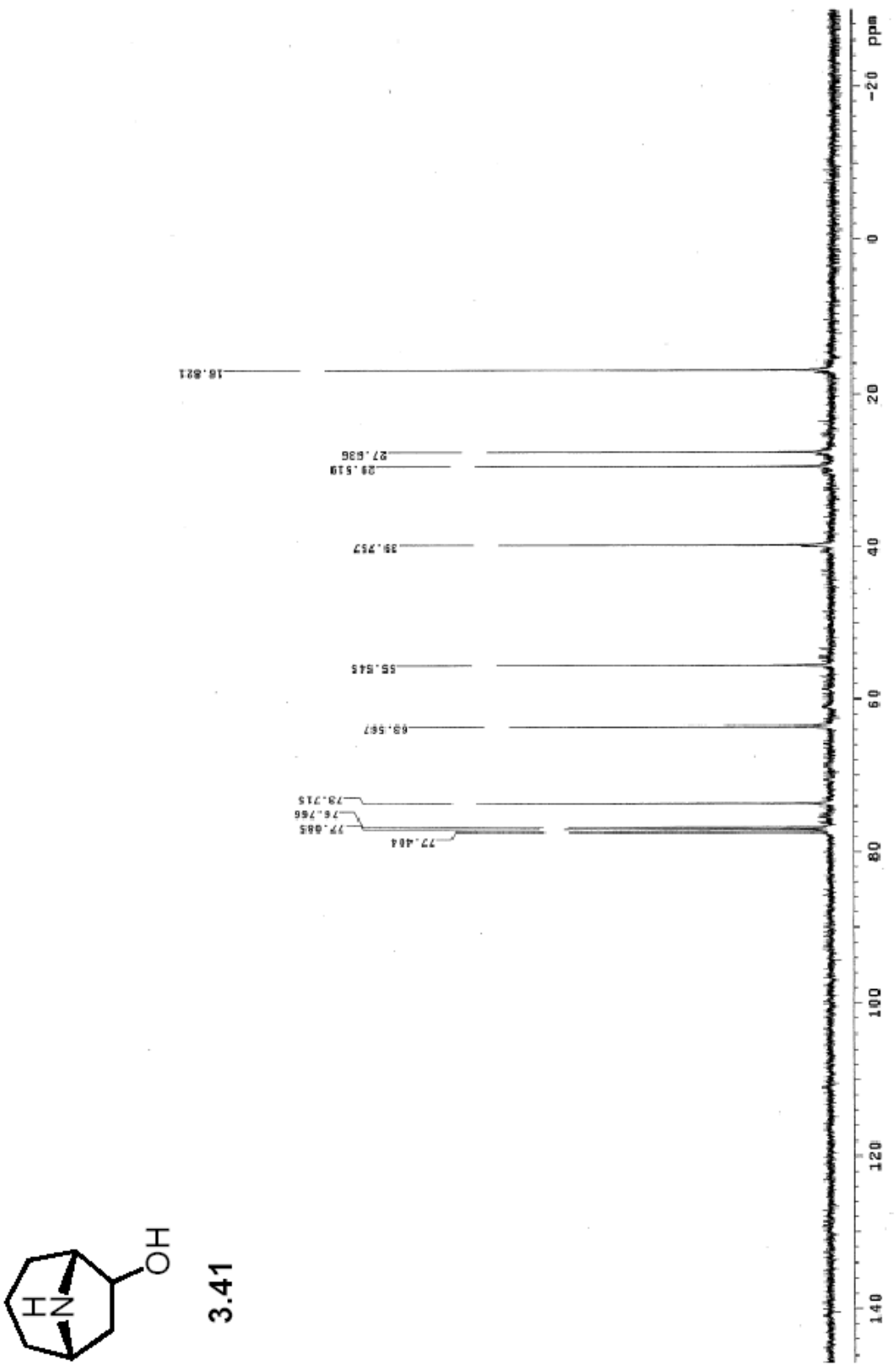

208.443
185.814
117.288
74.688
66.071
56.968
51.248
44.650
42.148
40.868
ppm
-20
0
20
40
60
80
100
120
140
160
180
200

O
N
OH

3.40

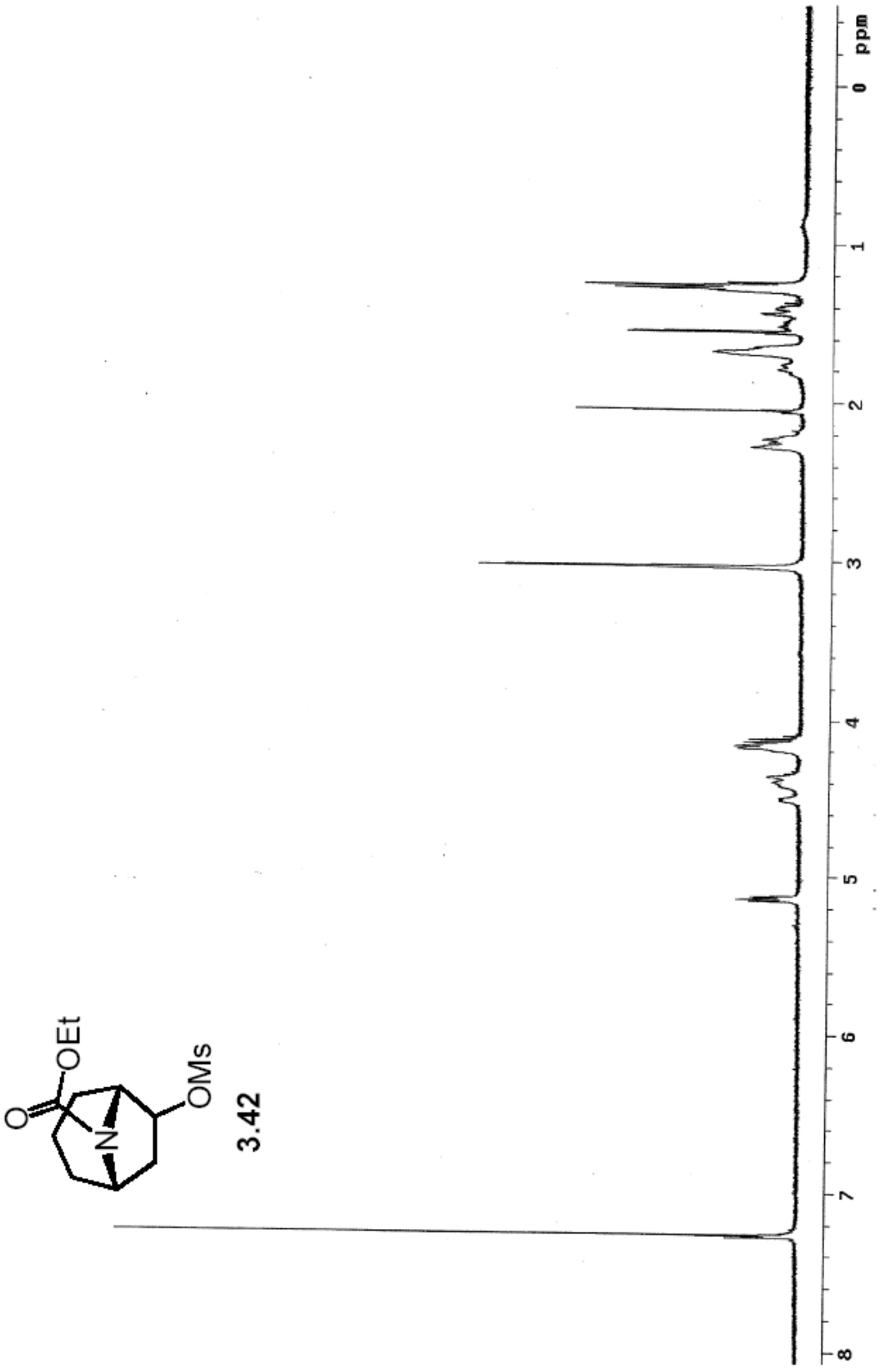


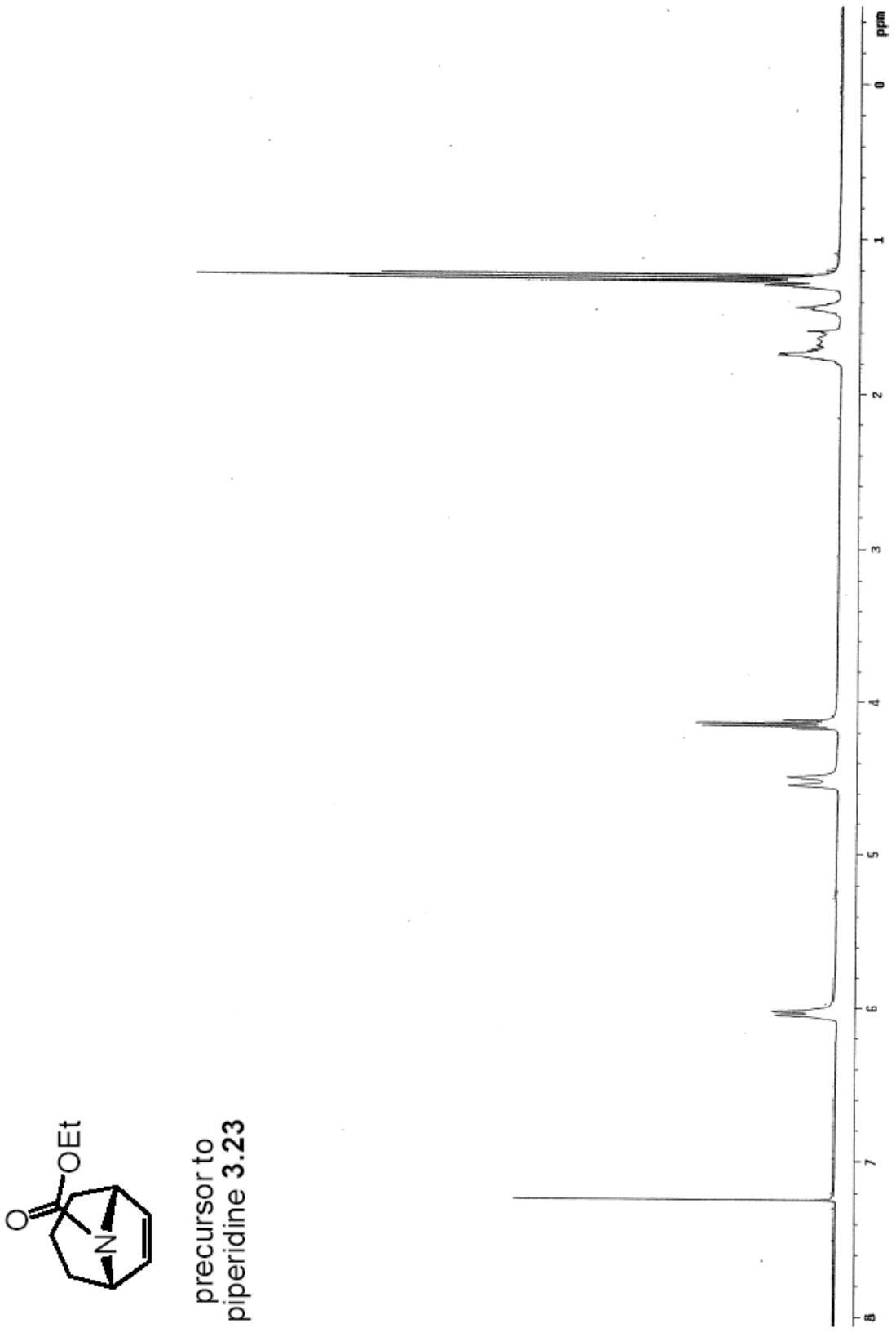
3.41

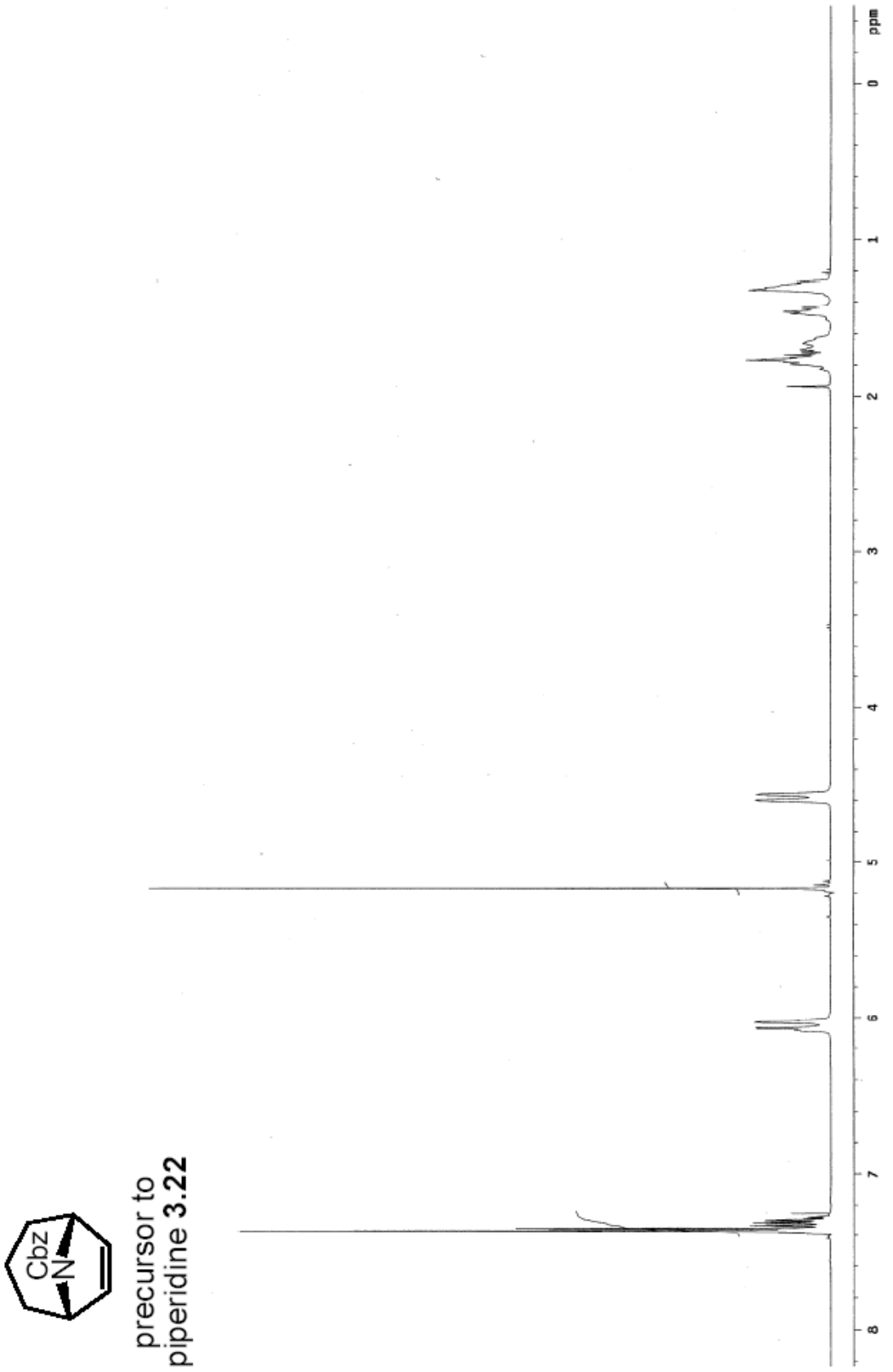

18.821
27.836
29.519
39.757
55.545
69.567
78.715
76.766
77.085
77.404
ppm
-20
0
20
40
60
80
100
120
140

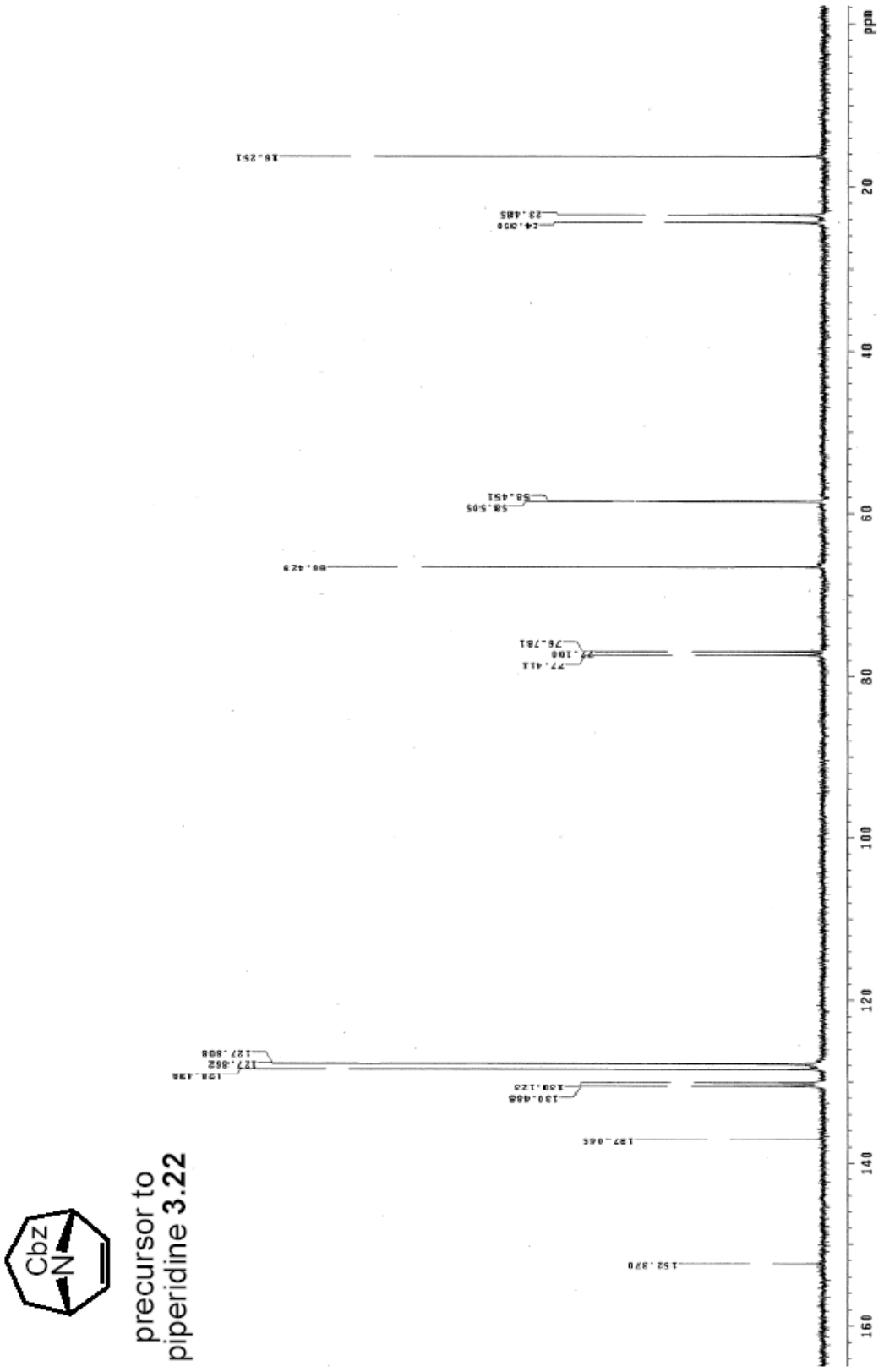
H
N
OH

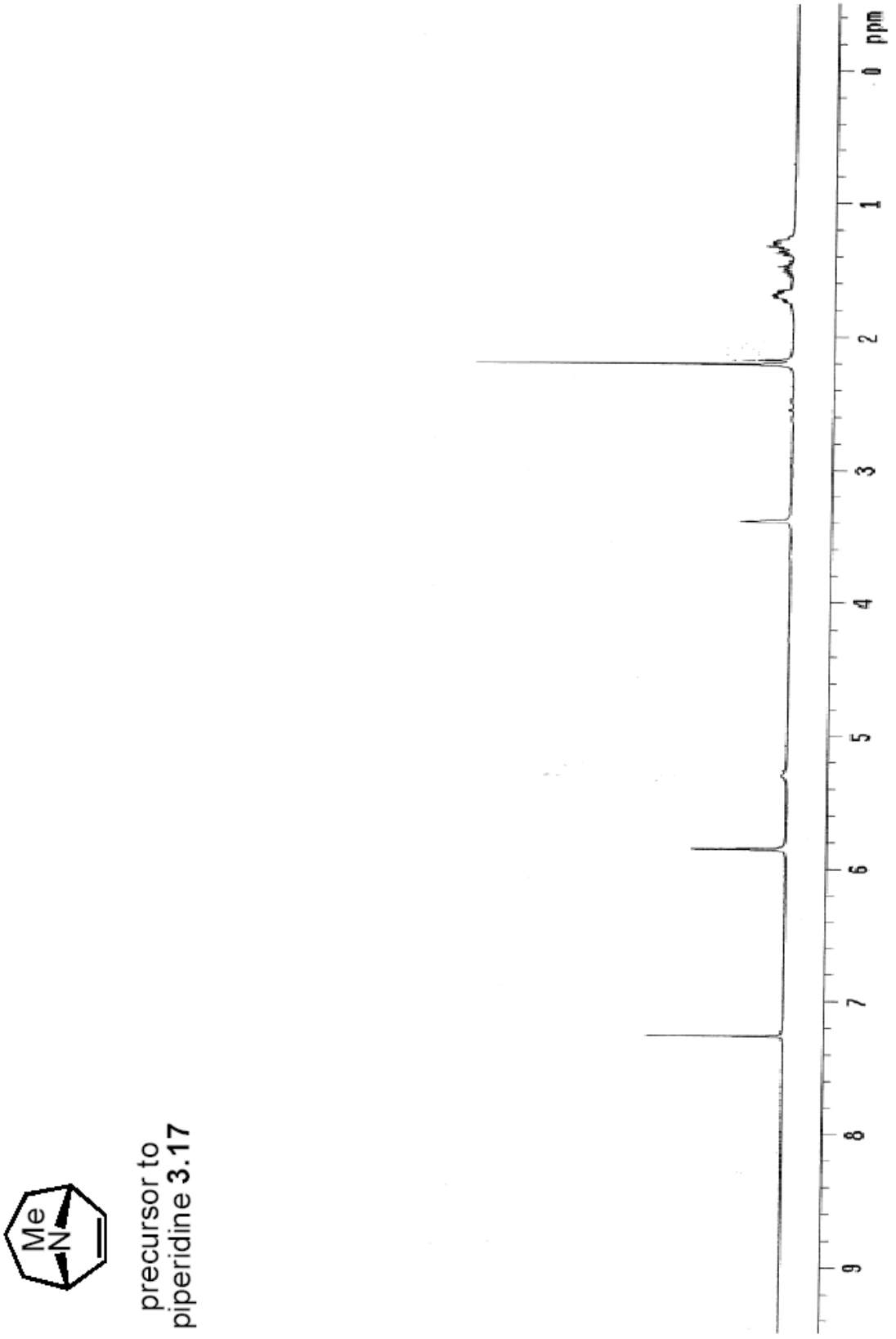
3.41

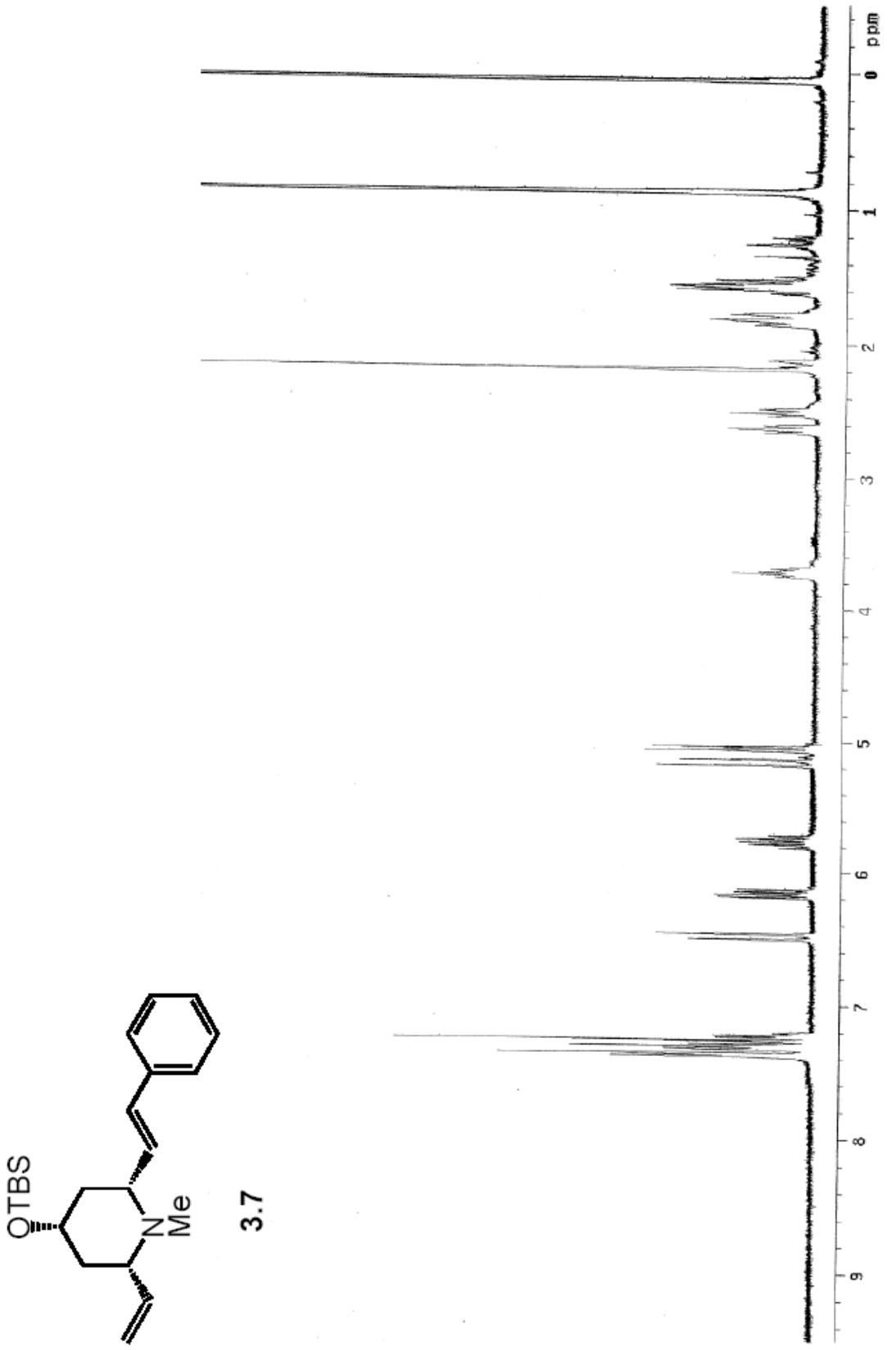

OEt
O
N
OMs
3.42
8
7
6
5
4
3
2
1
0 ppm

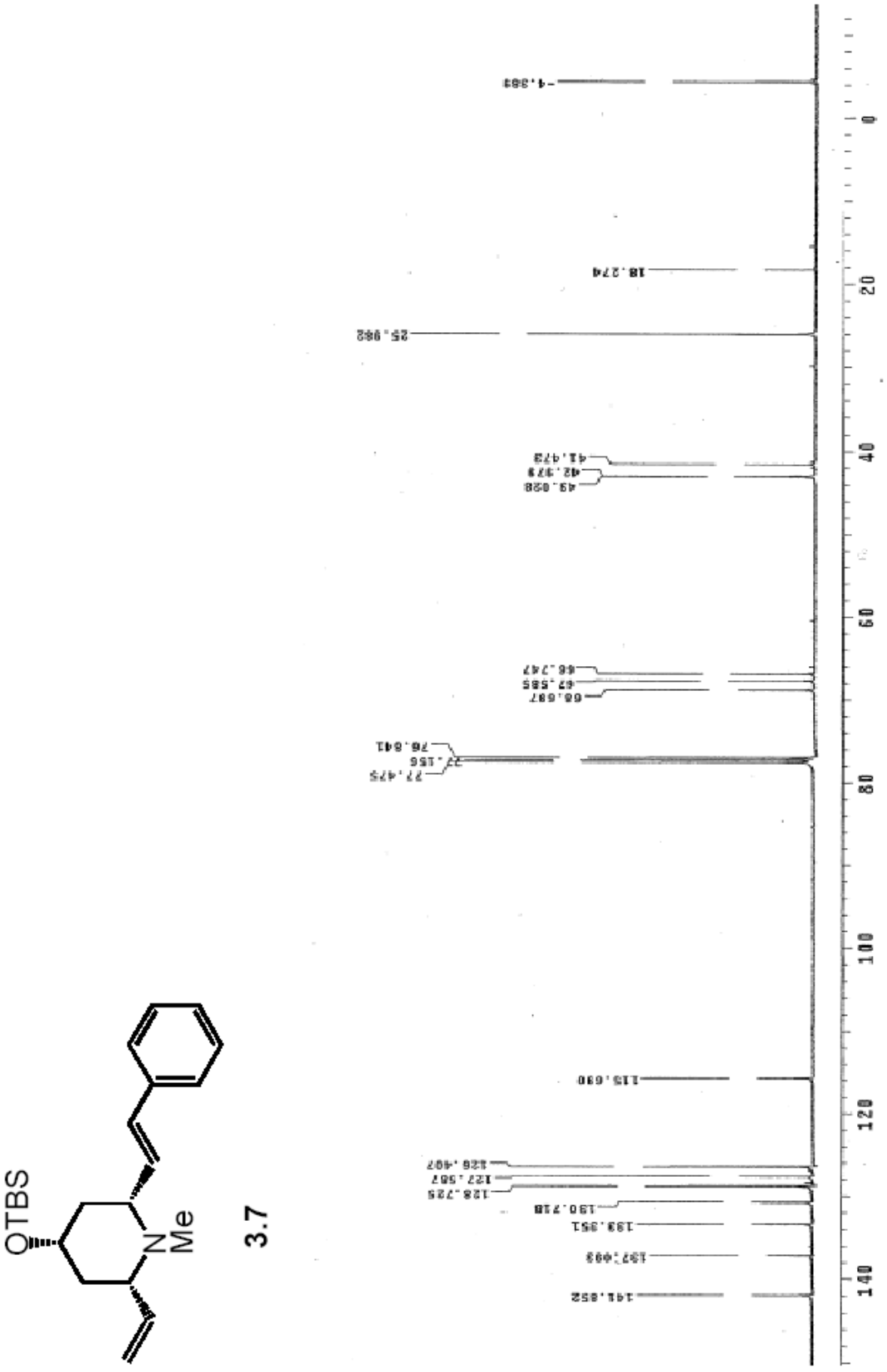

OEt
O
N
precursor to
piperidine **3.23**
ppm
0
1
2
3
4
5
6
7
8

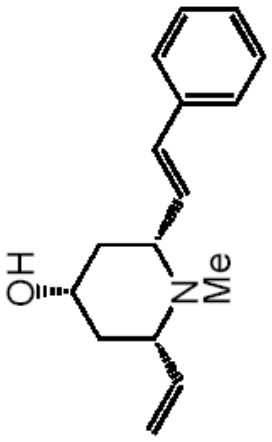

Cbz
N
precursor to
piperidine **3.22**
8
7
6
5
4
3
2
1
0
ppm


Cbz
N
precursor to
piperidine **3.22**
ppm
20
40
60
80
100
120
140
160

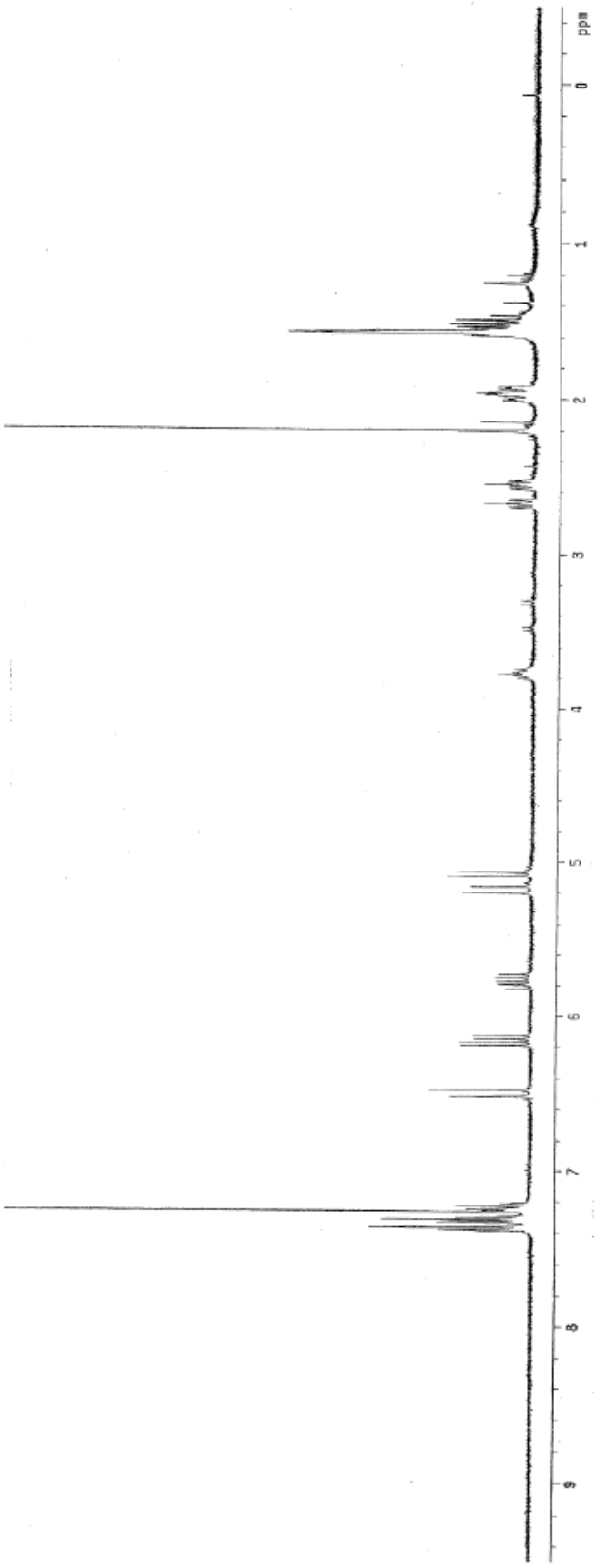

Me
N
precursor to
piperidine **3.17**
9
8
7
6
5
4
3
2
1
0 ppm

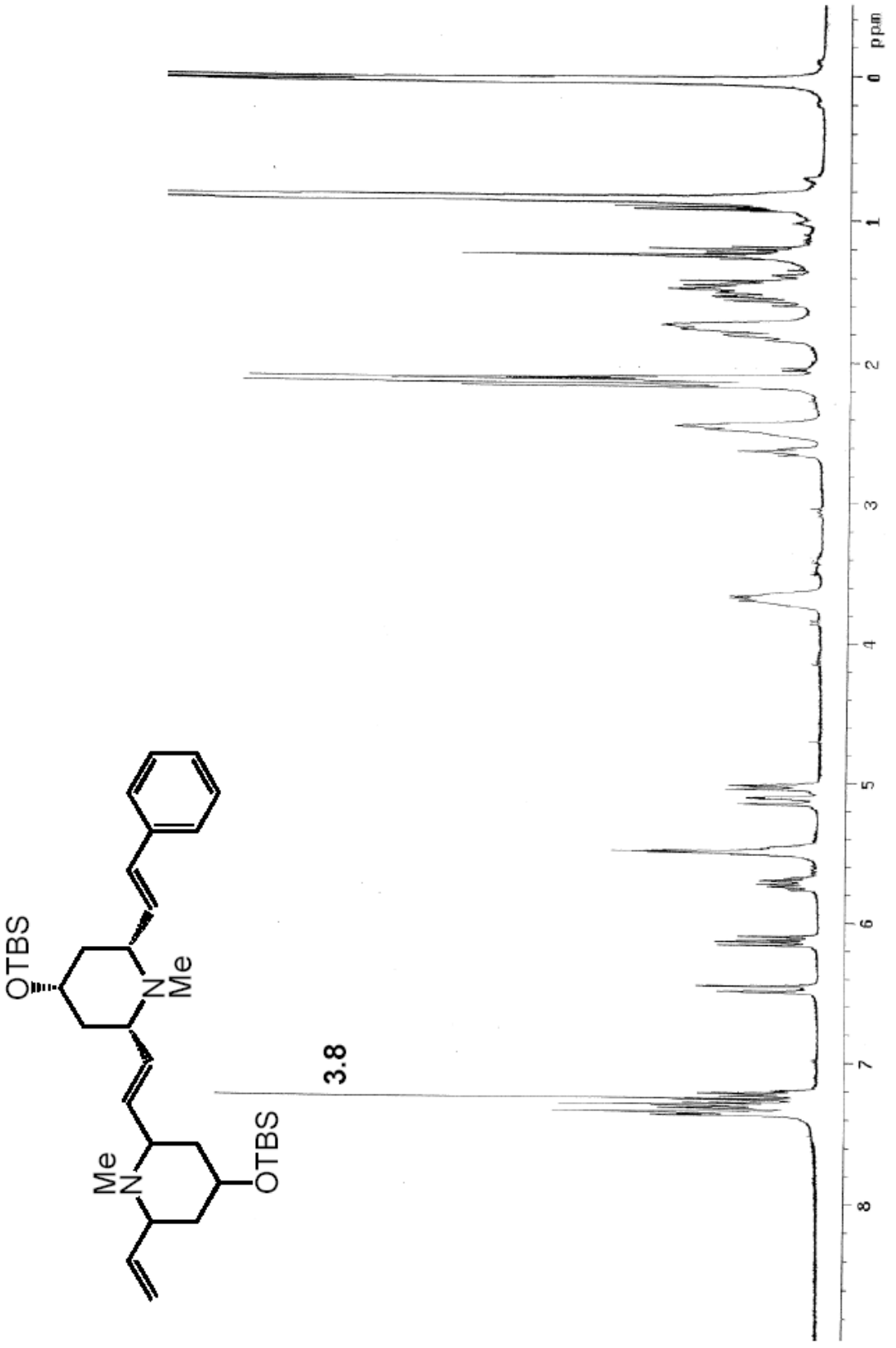

OTBS
N
Me
3.7
9
8
7
6
5
4
3
2
1
0 ppm

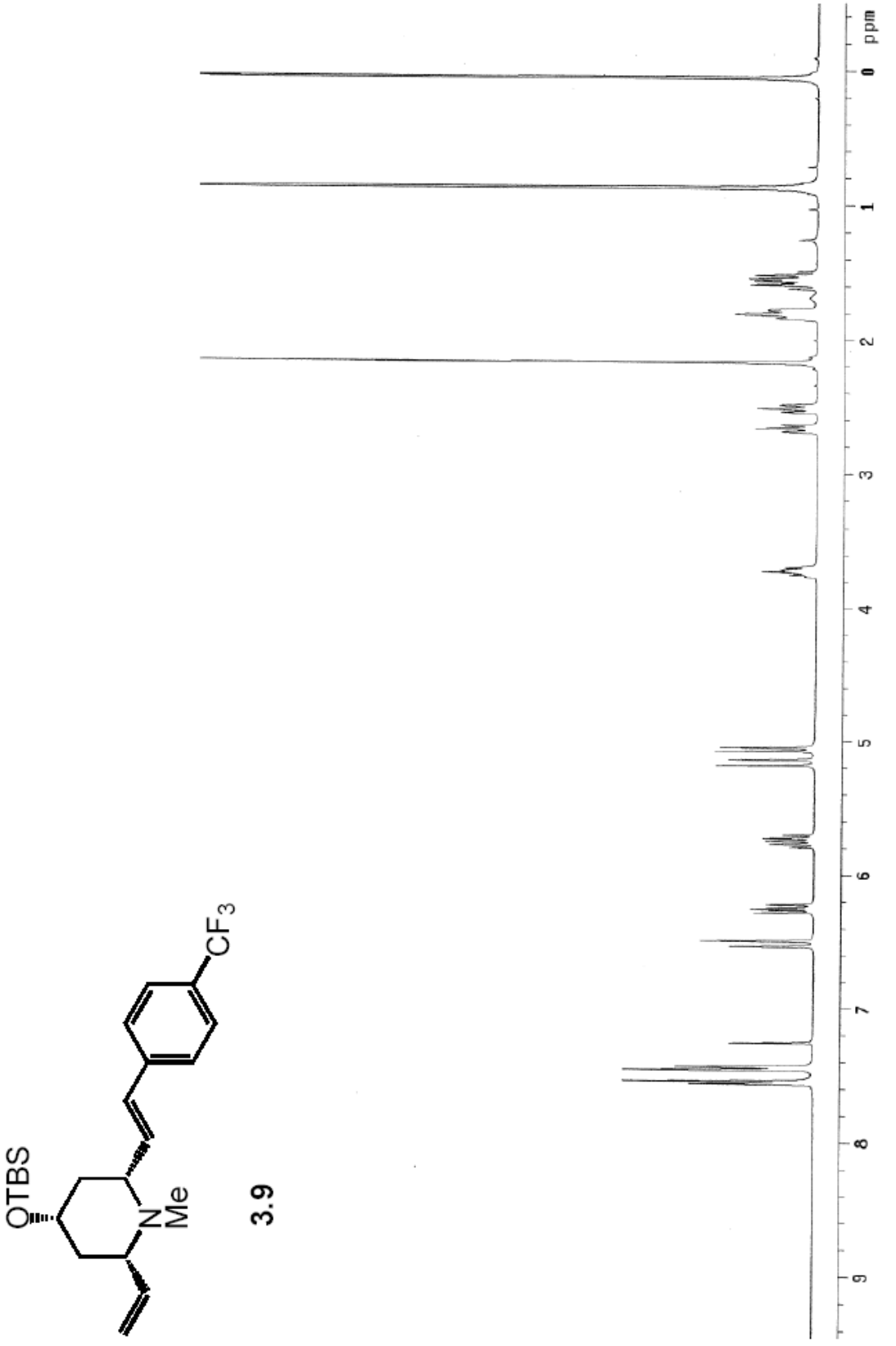

OTBS
N
Me
3.7
-4.383
18.274
25.982
41.978
42.379
43.058
66.747
67.585
68.687
77.475
77.156
78.641
115.690
126.497
127.587
128.725
130.718
133.951
137.099
145.852
0
20
40
60
80
100
120
140

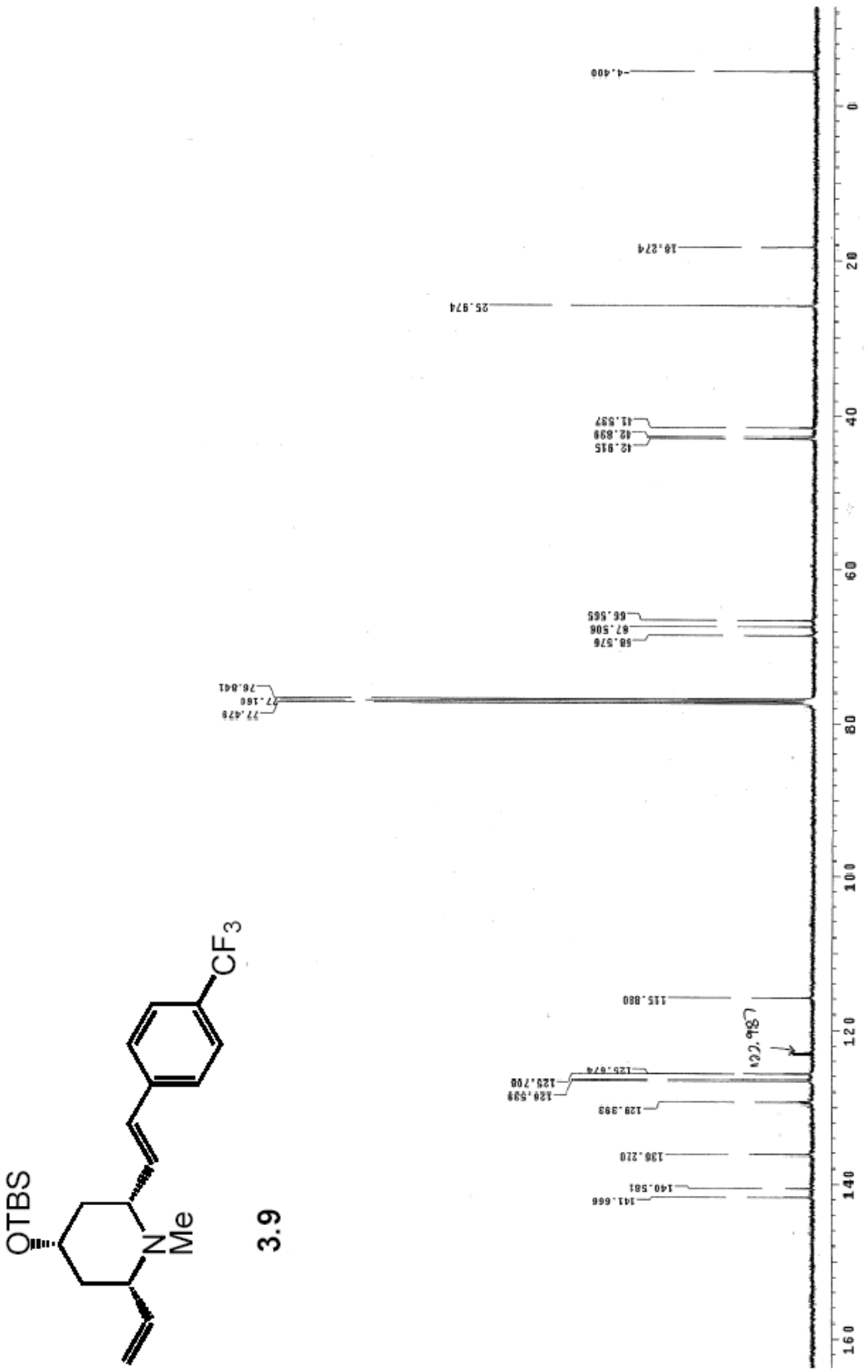


3.7-OH

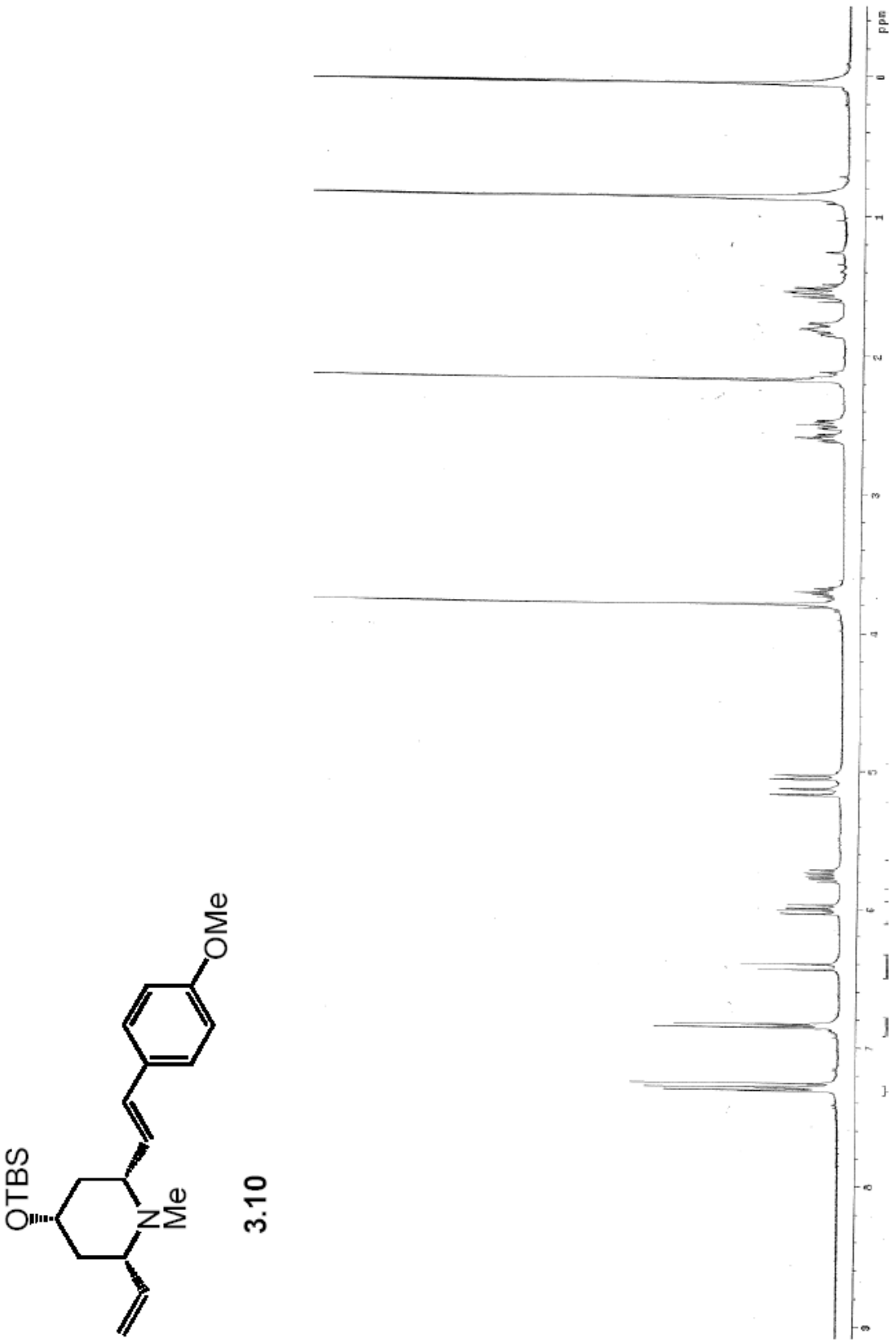



OTBS
N
Me
Me
N
OTBS
3.8
8
7
6
5
4
3
2
1
0
ppm

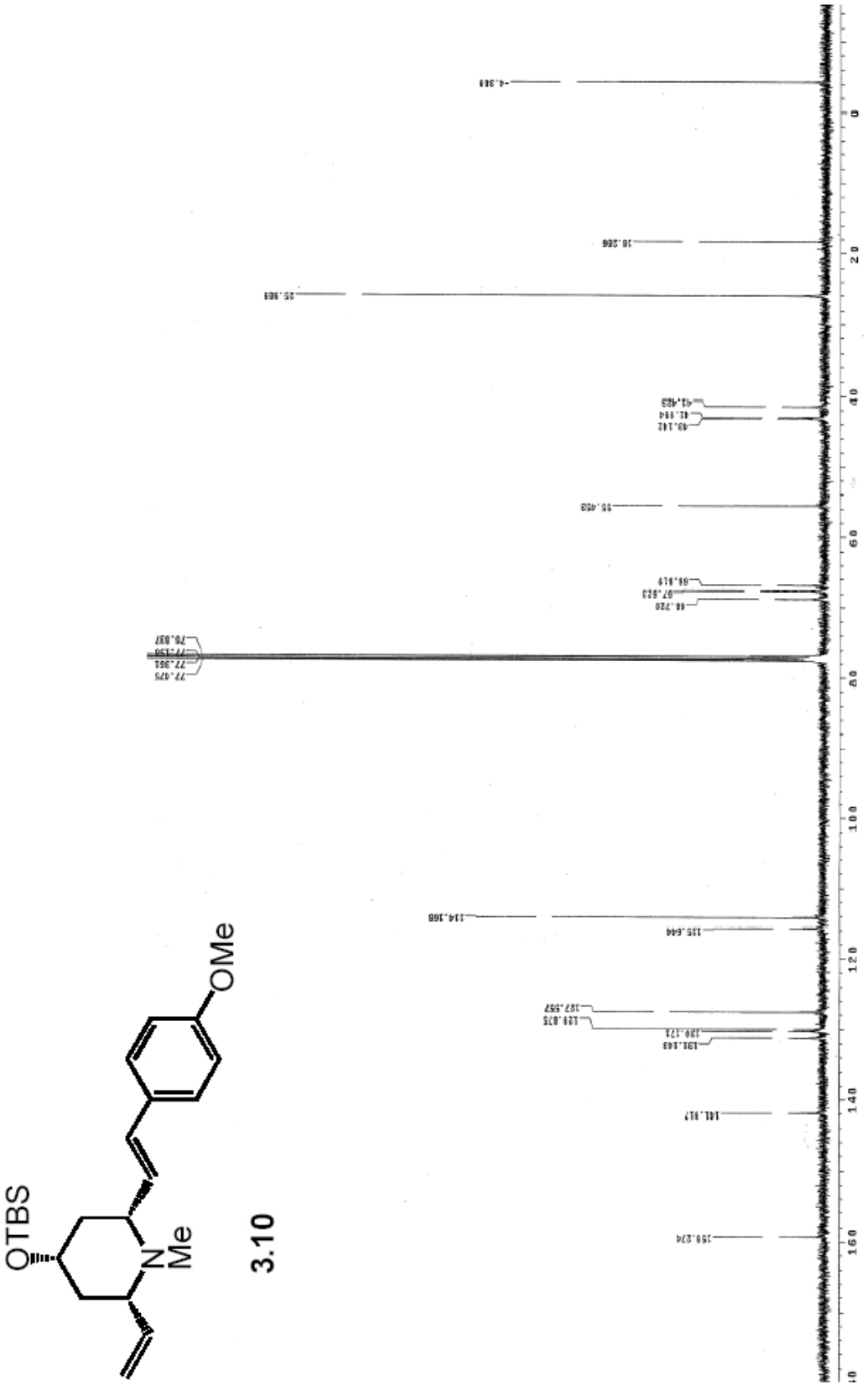

OTBS
N
Me
CF3
3.9
9
8
7
6
5
4
3
2
1
0
ppm


OTBS
N
Me
CF3
3.9
-4.400
18.274
25.974
41.597
42.899
42.915
66.565
67.506
68.576
76.841
77.160
77.479
115.880
122.987
125.674
125.708
129.599
129.993
136.220
140.581
141.666
0
20
40
60
80
100
120
140
160

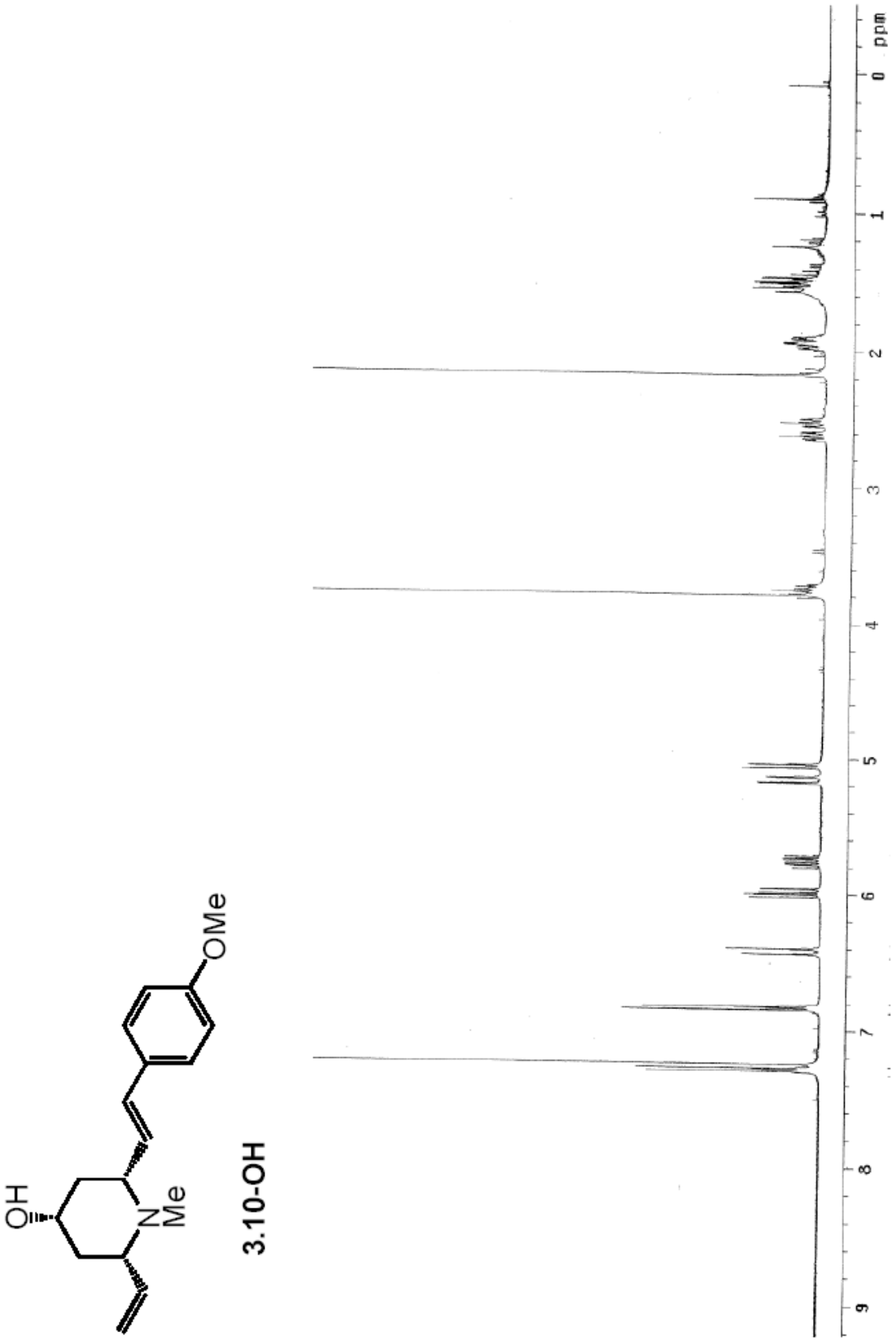

OH
N
Me
CF3
3.9-OH
ppm
0
1
2
3
4
5
6
7
8
9

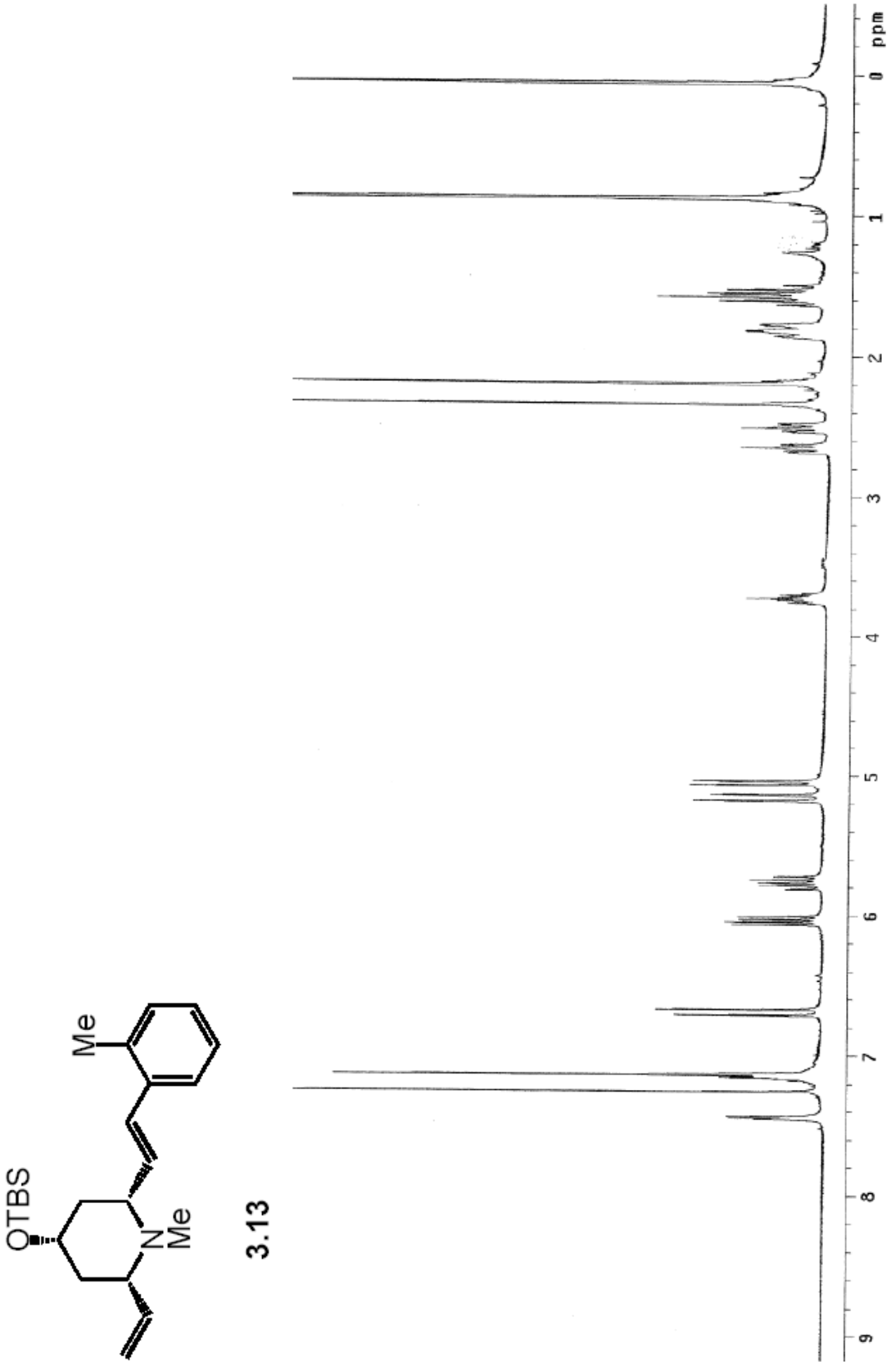


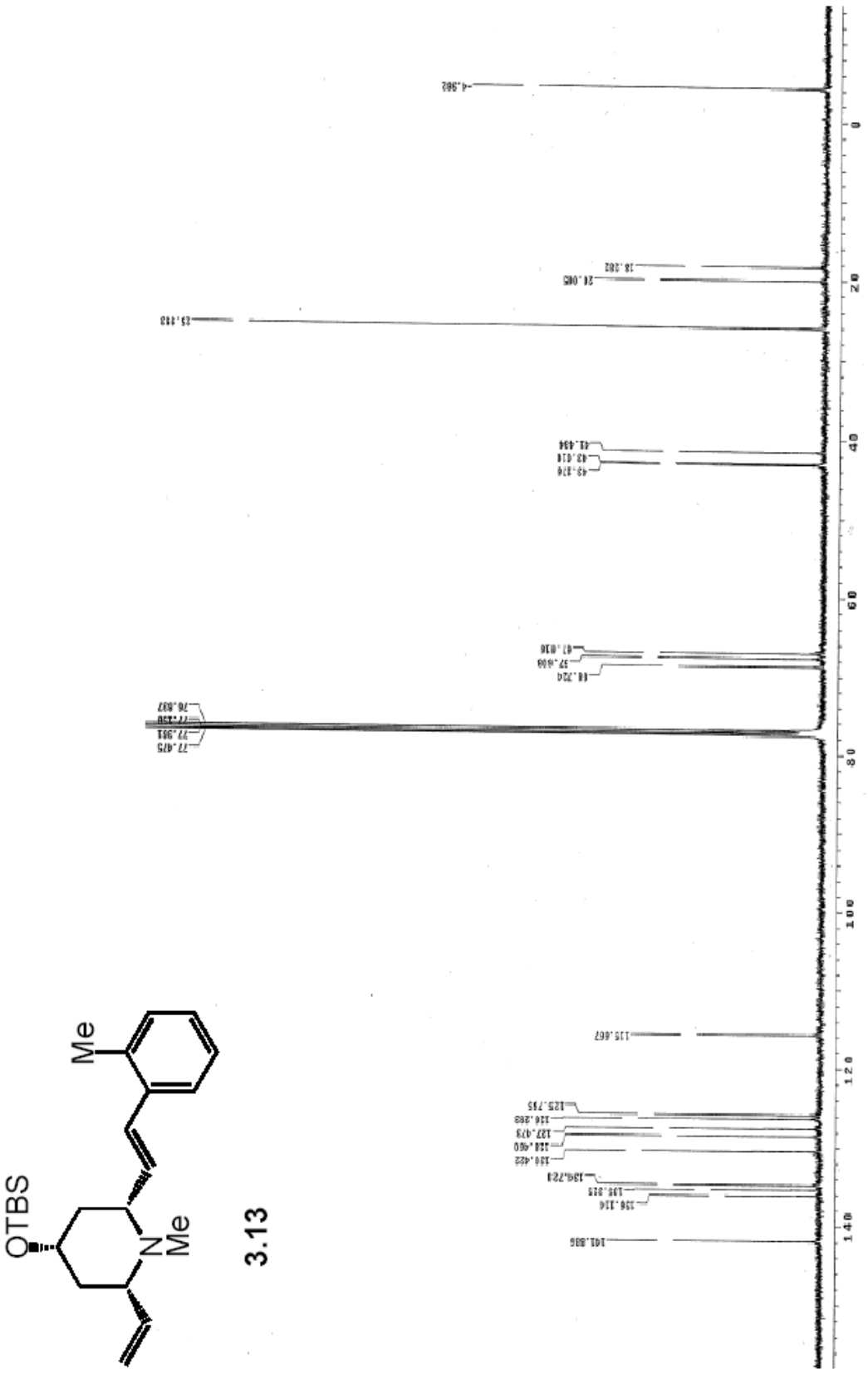
3.10



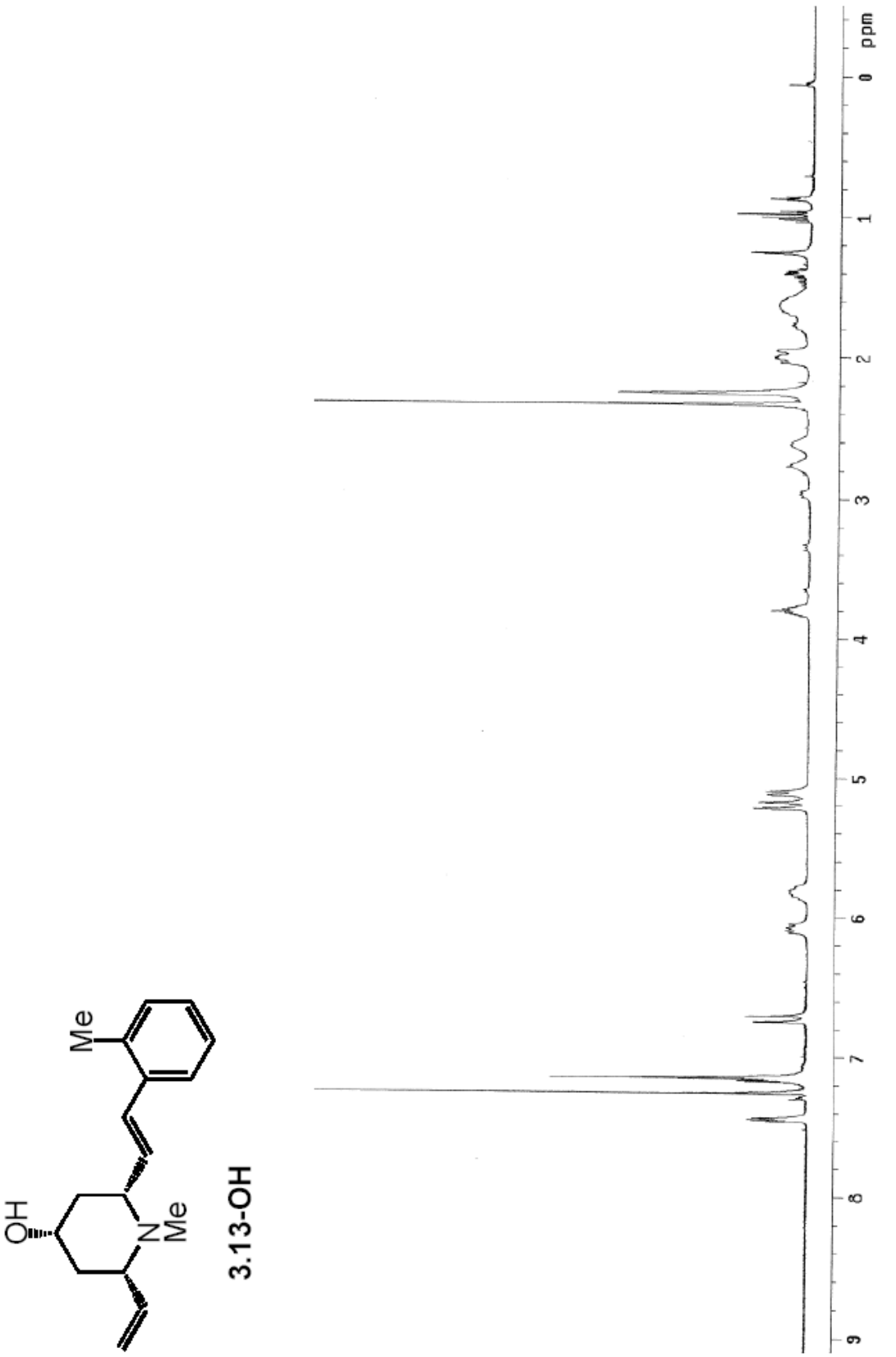
3.10

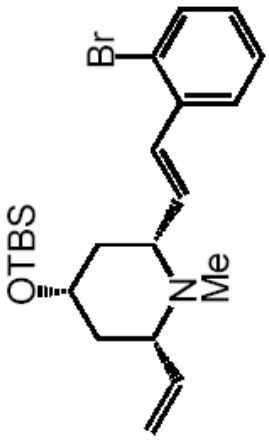

OH
N
Me
OMe
3.10-OH
9
8
7
6
5
4
3
2
1
0
ppm


OTBS
N
Me
Me
3.13
9
8
7
6
5
4
3
2
1
0
ppm

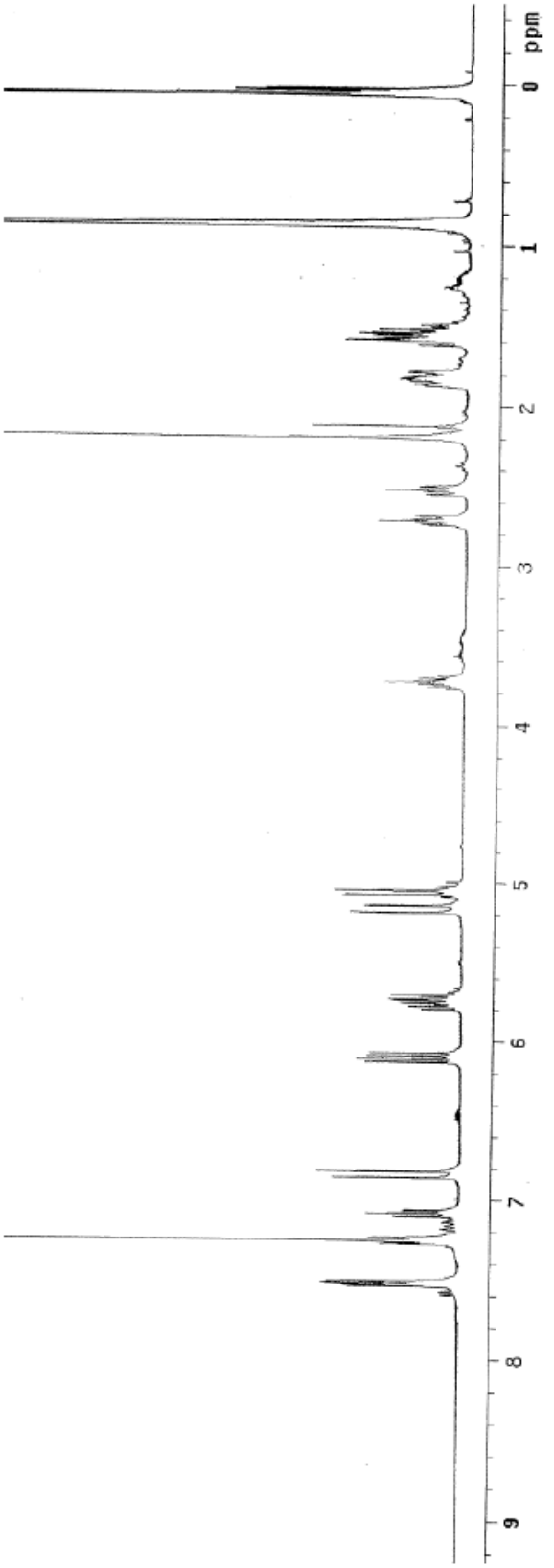


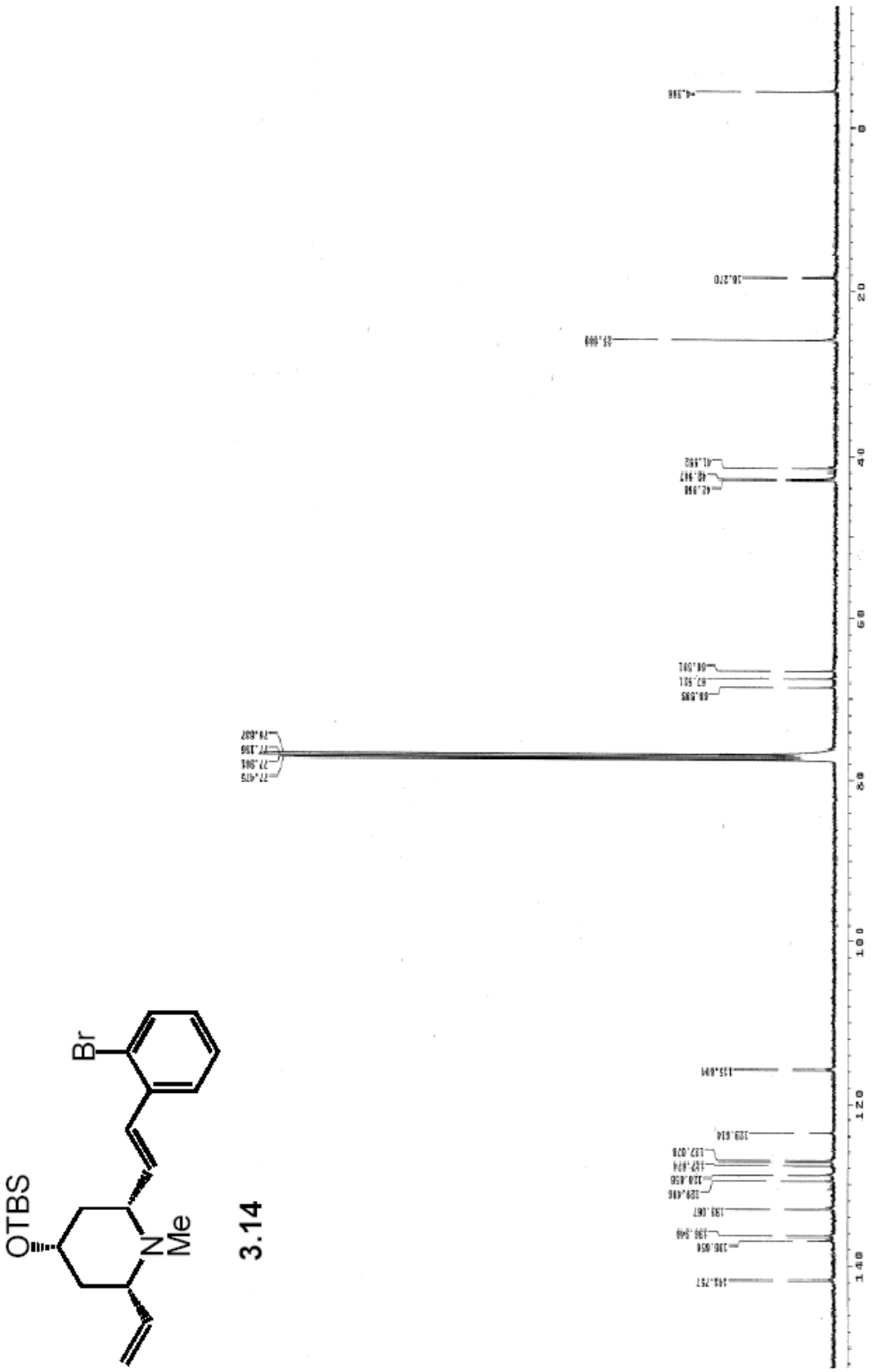
3.13


Me
OH
N
Me
3.13-OH
9
8
7
6
5
4
3
2
1
0
ppm



3.14





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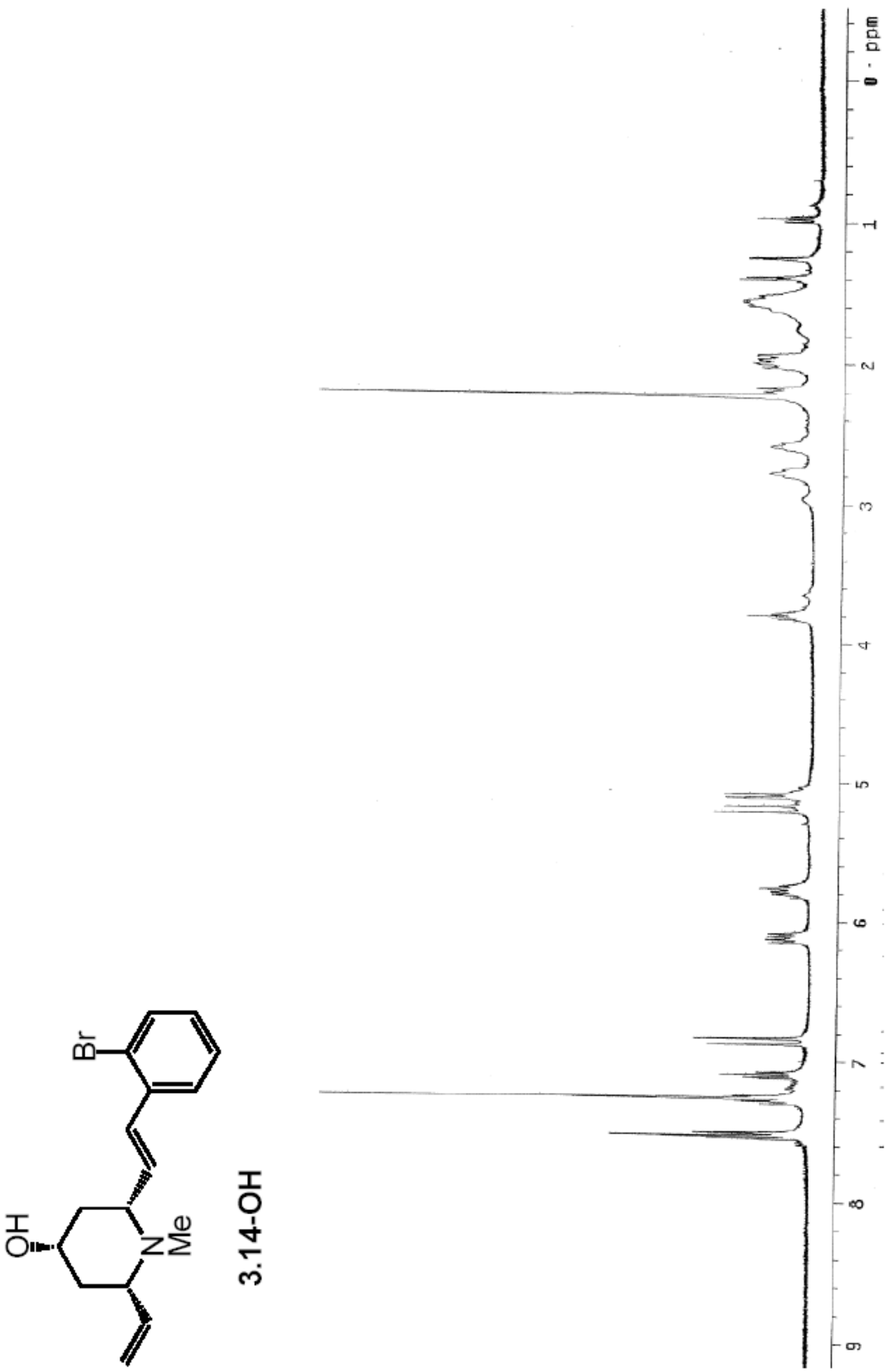
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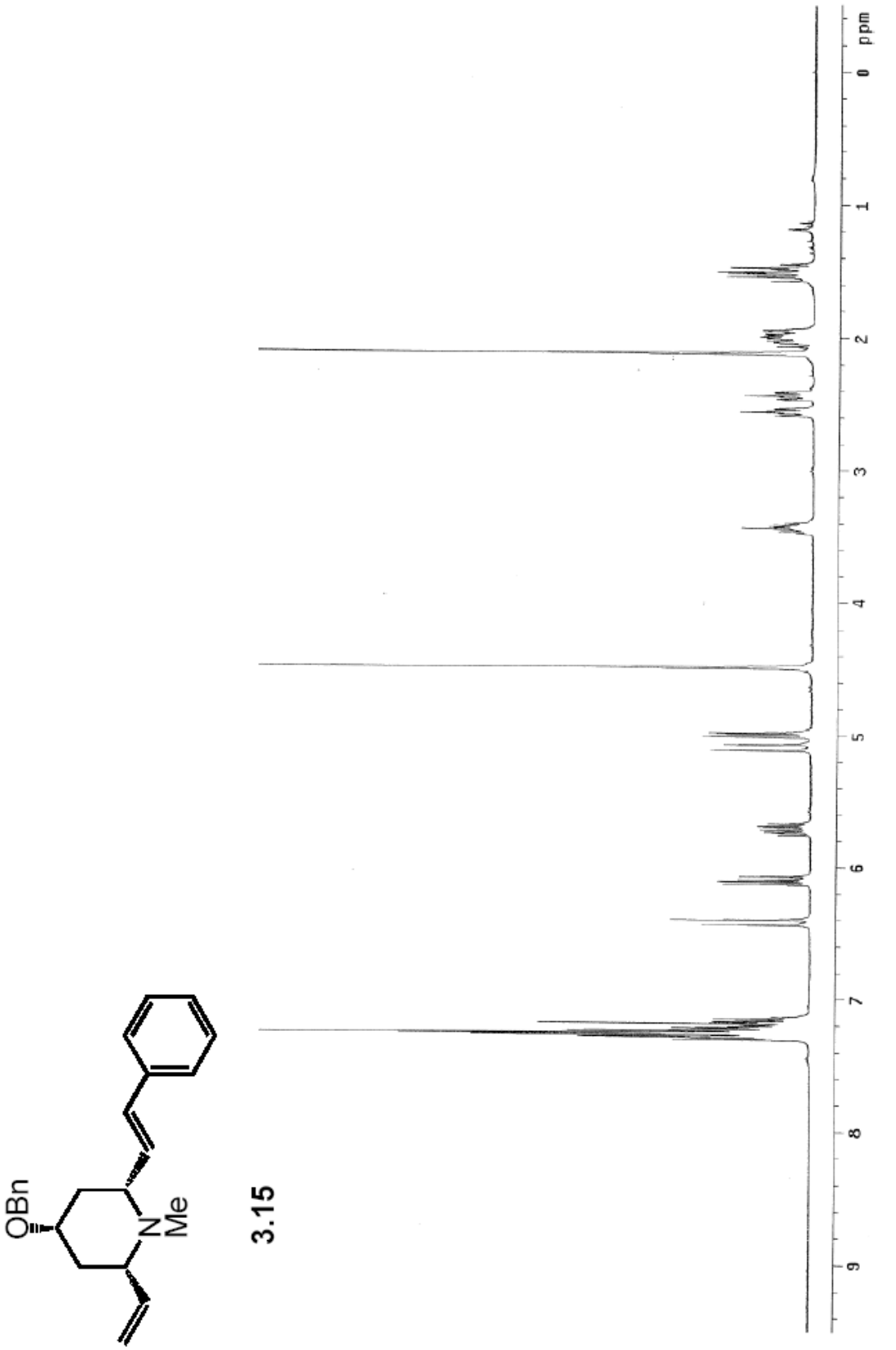
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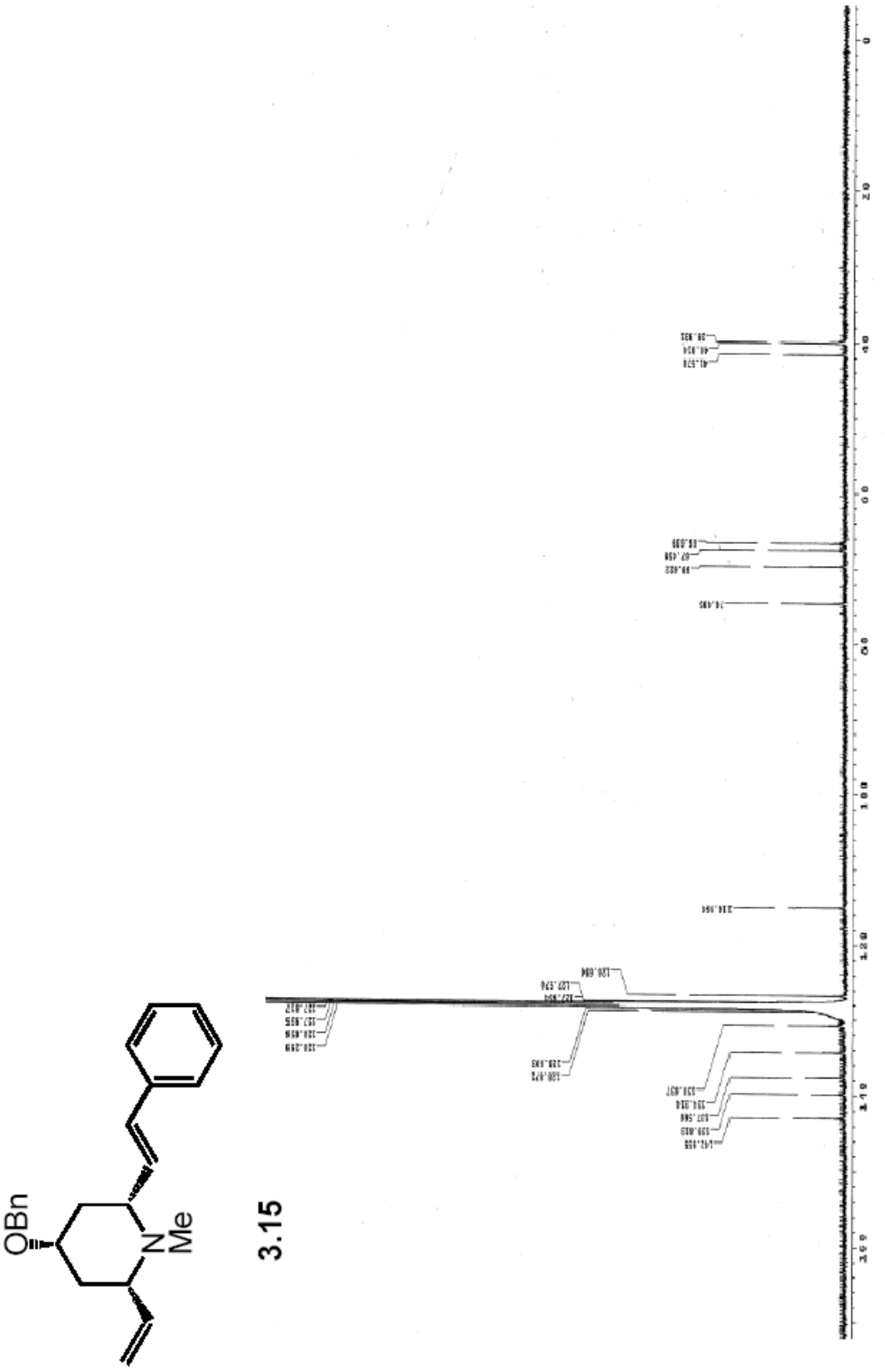

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7
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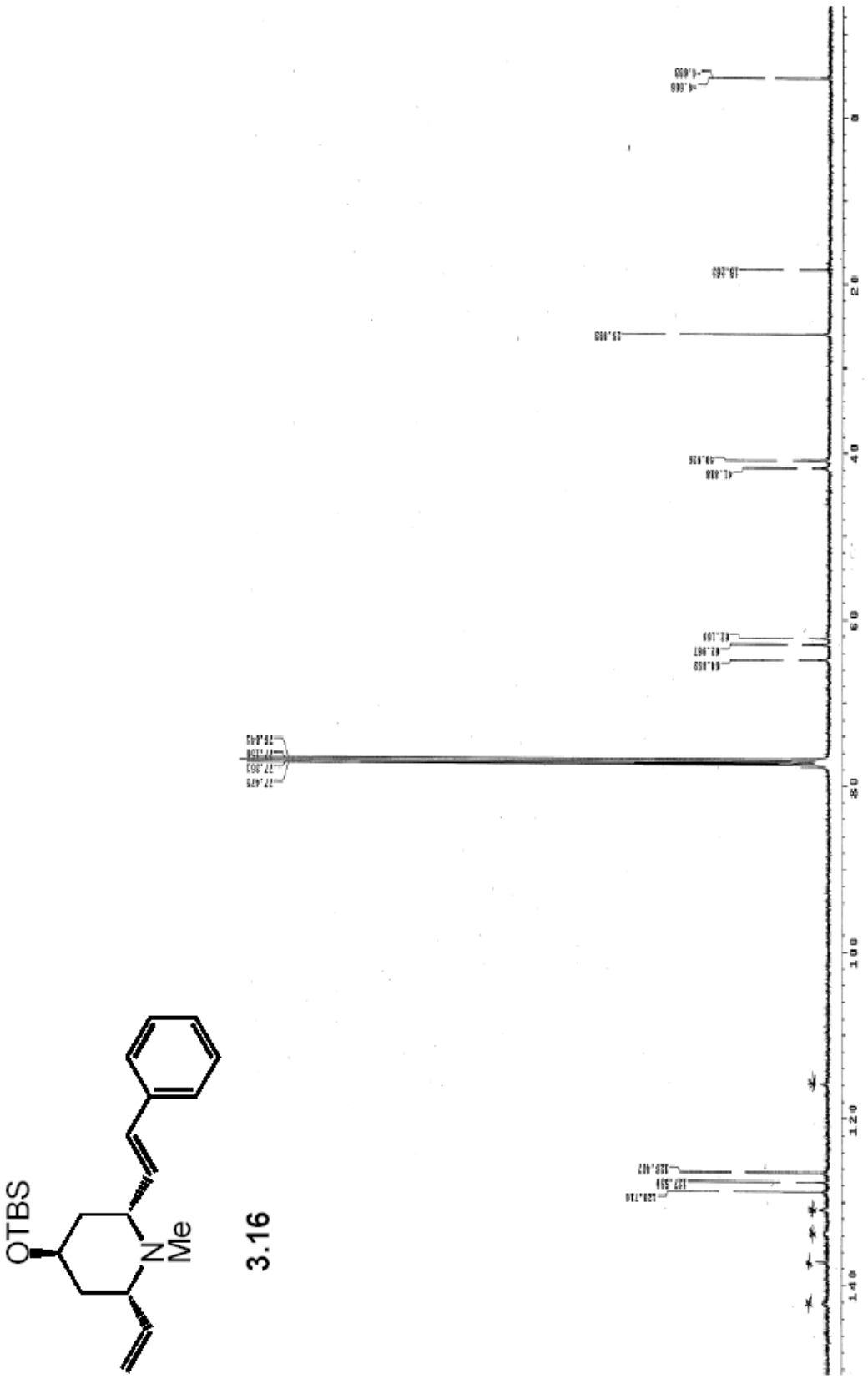

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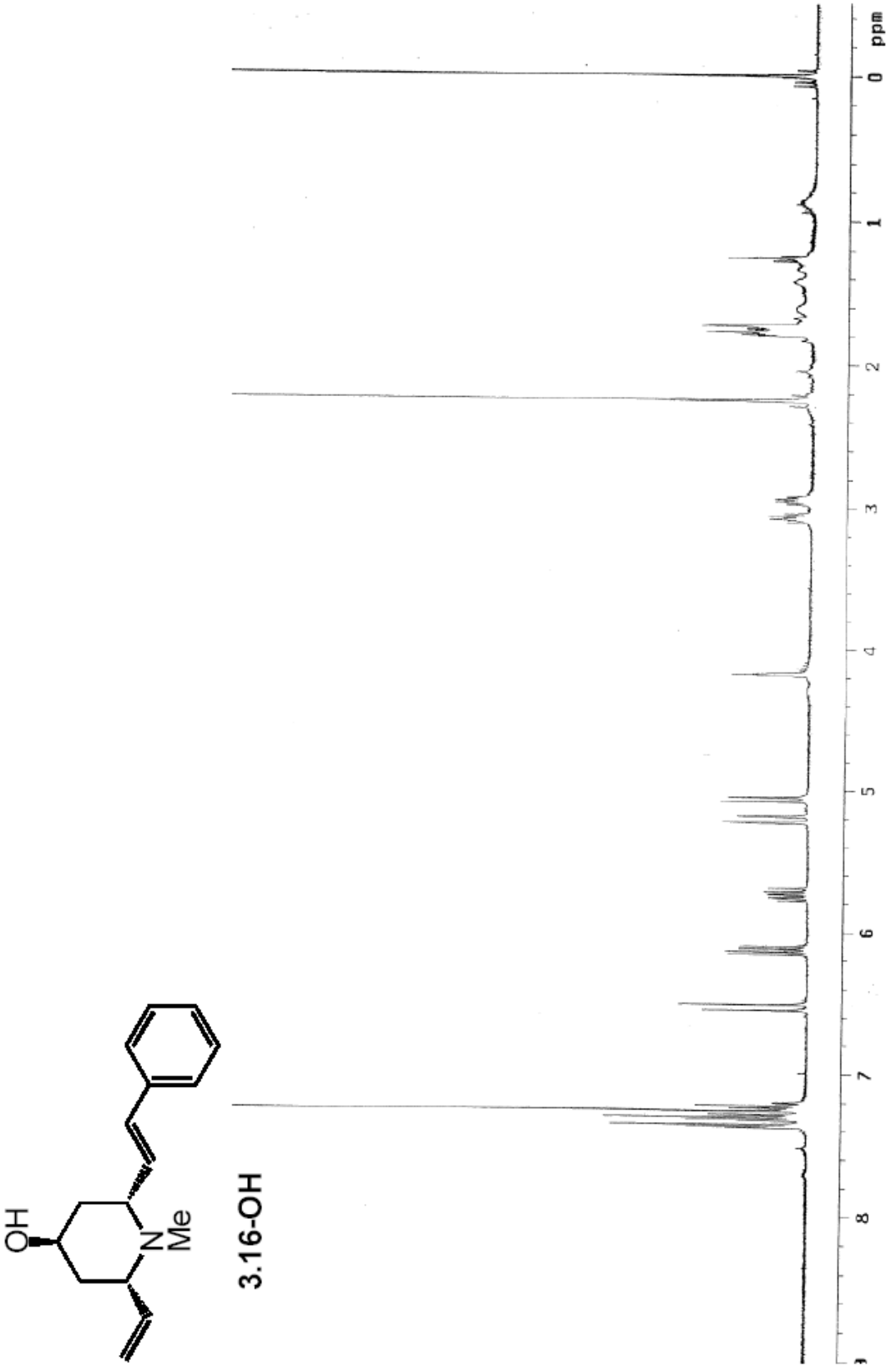
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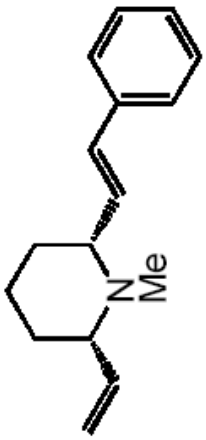

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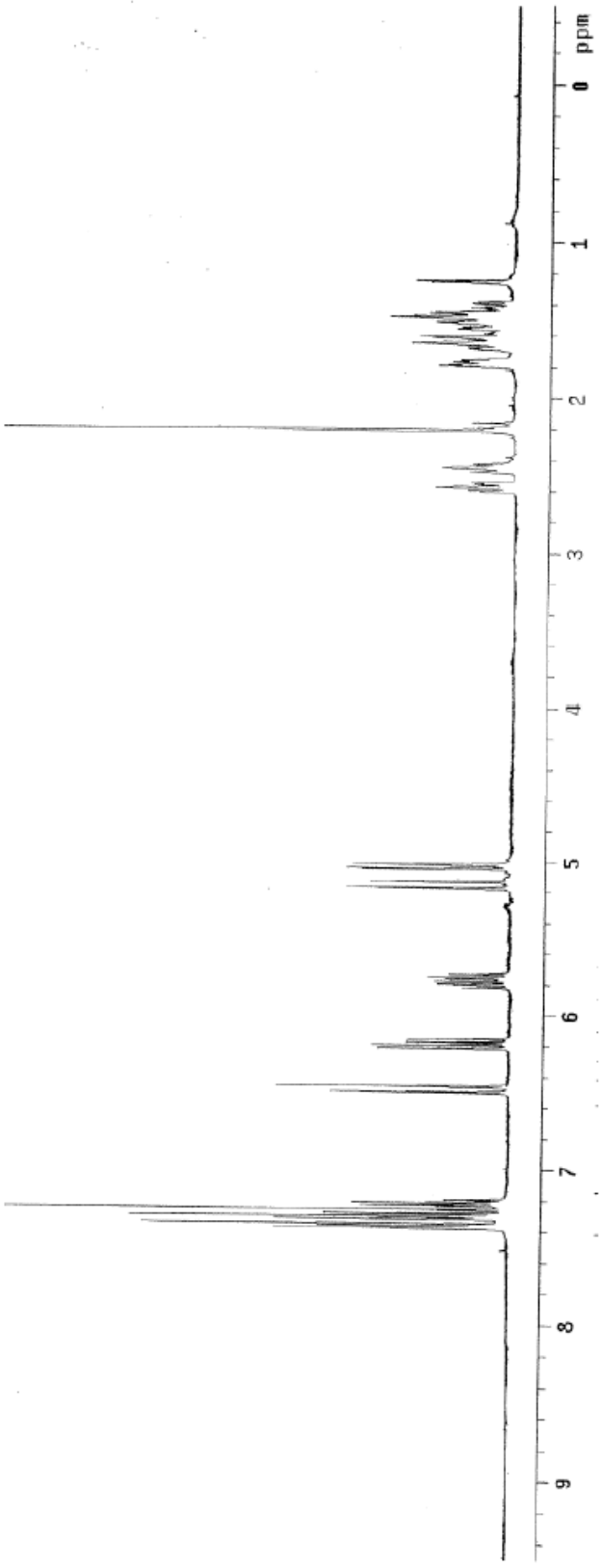

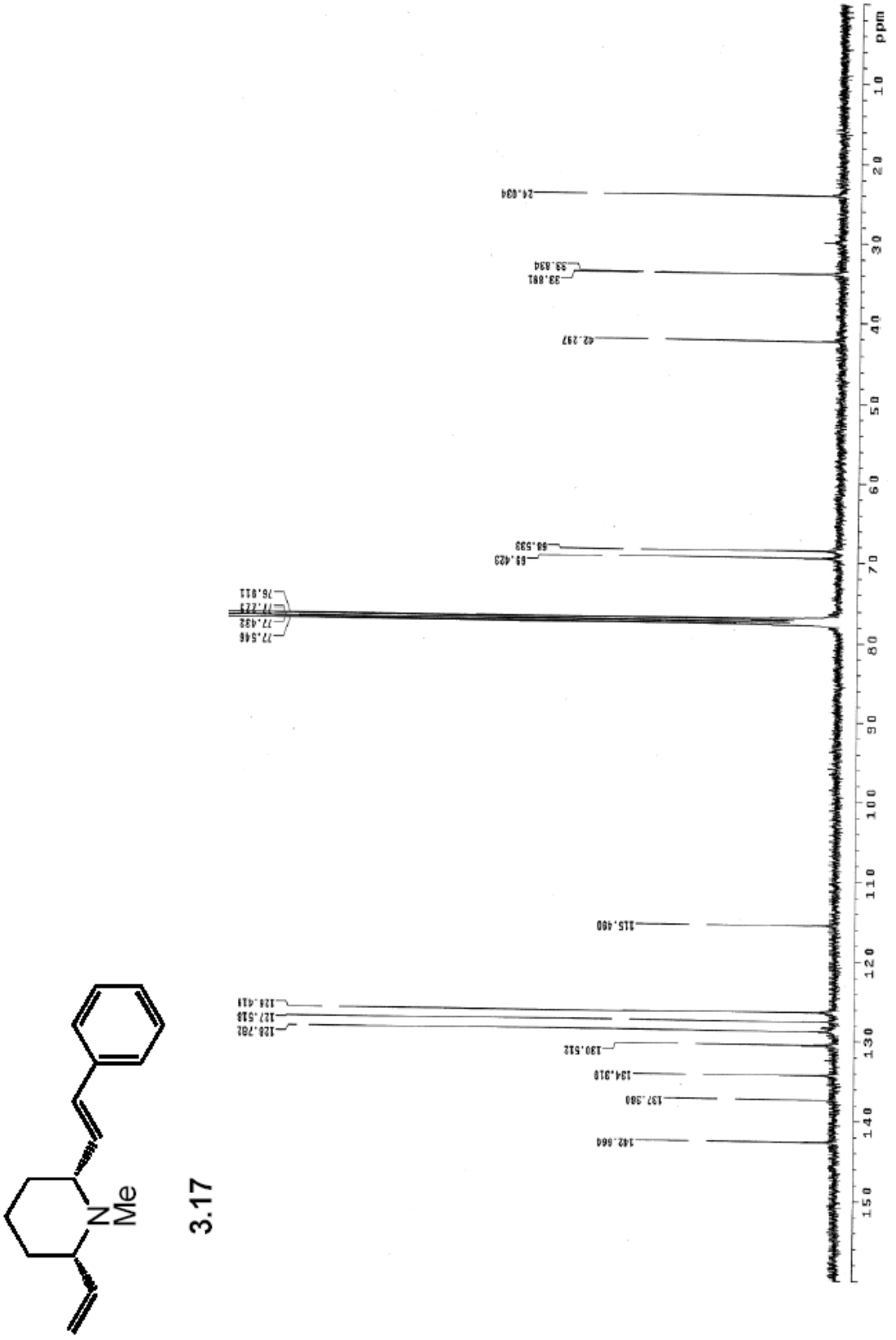
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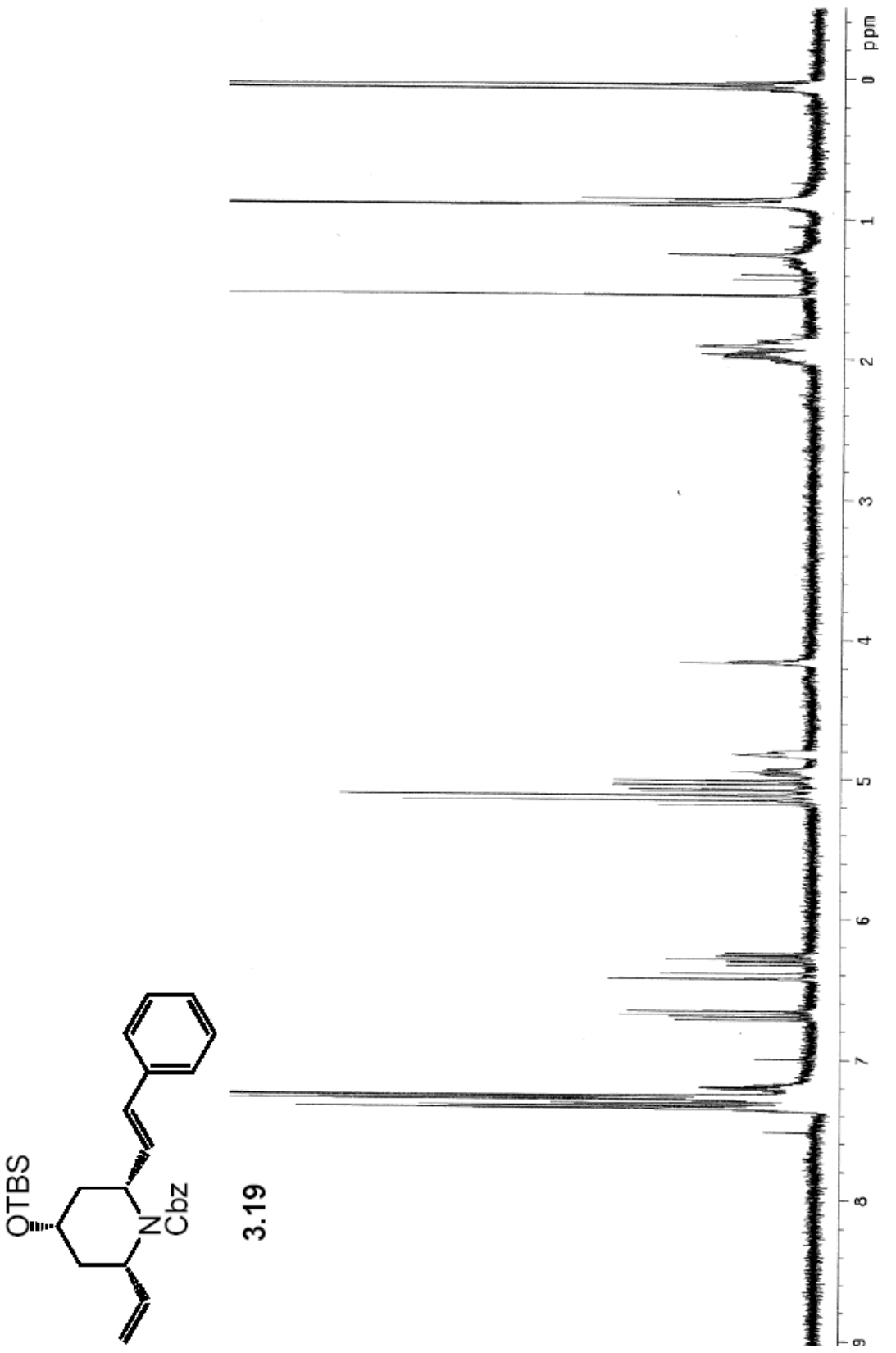
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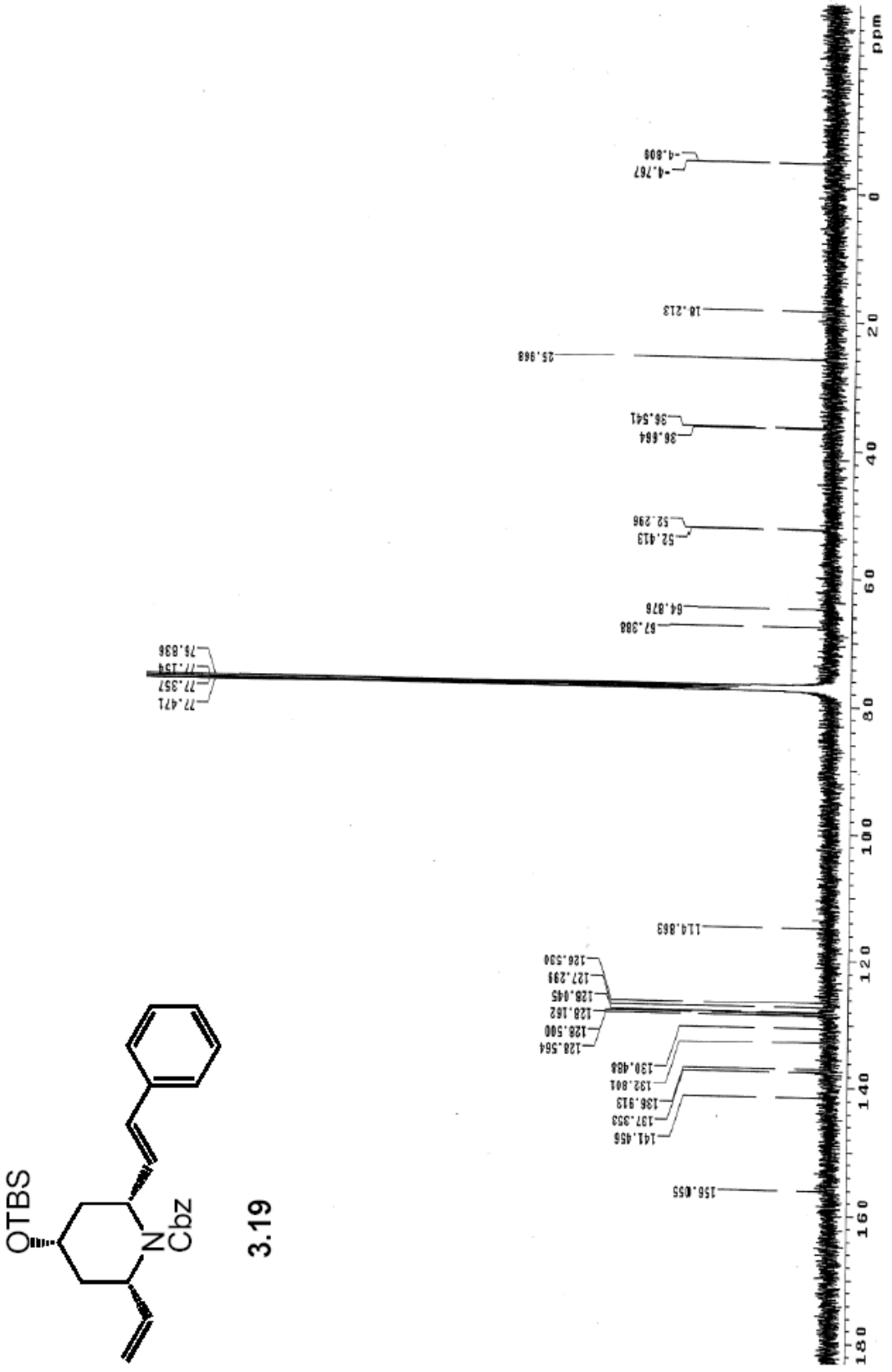
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77.154
79.836
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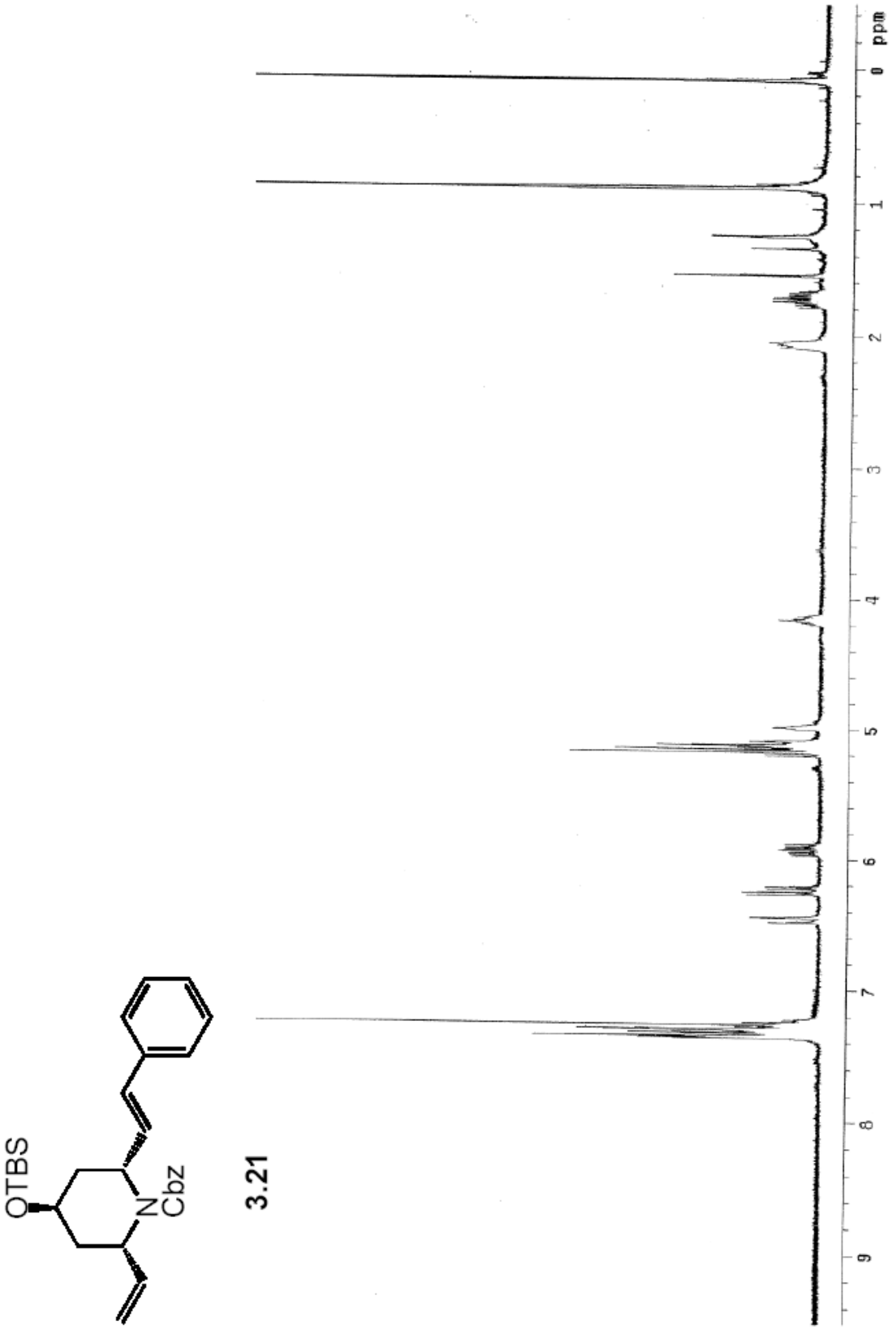
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5
6
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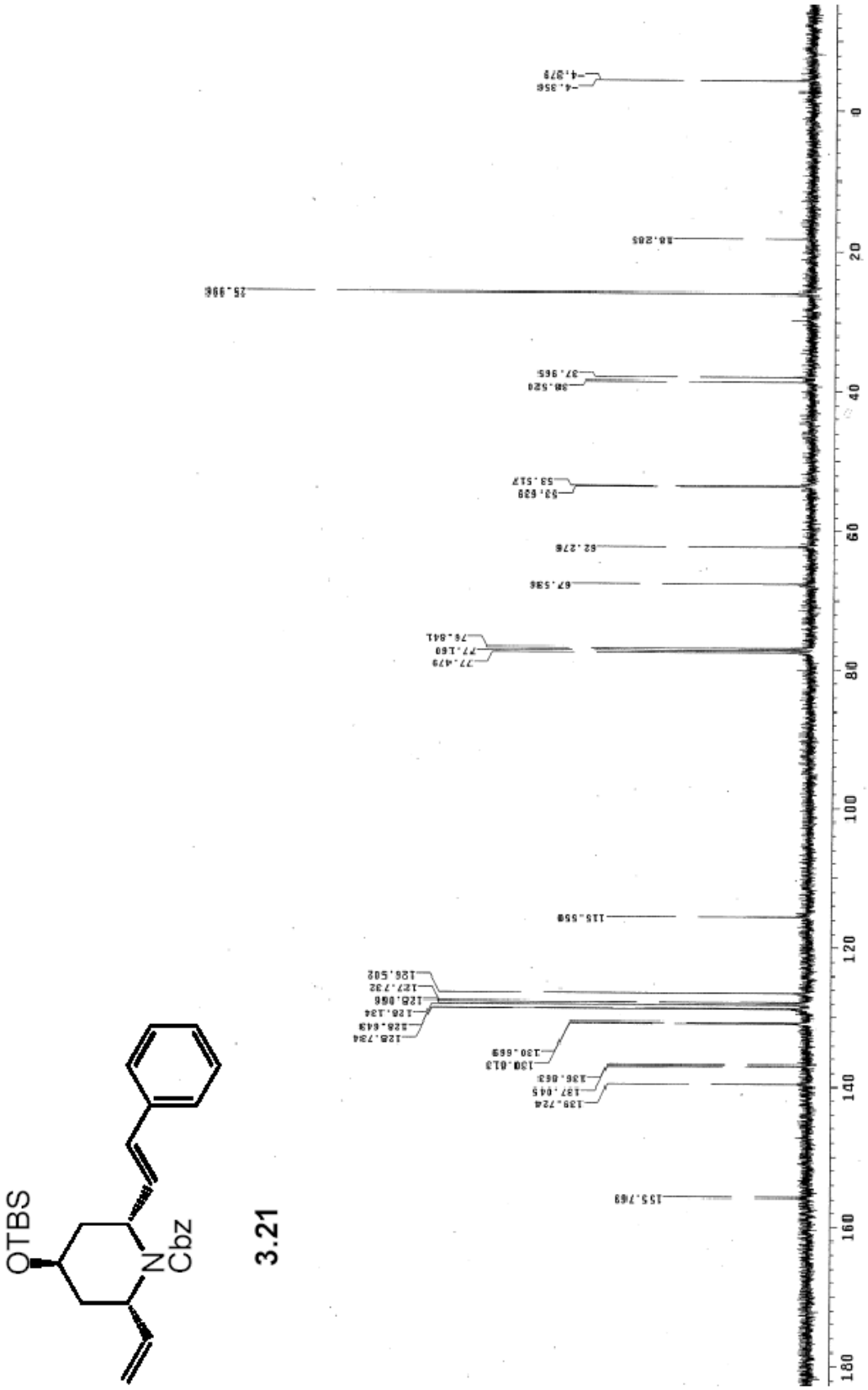
8
9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67.586
76.841
77.160
77.479
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125.502
125.732
125.866
126.134
126.643
126.734
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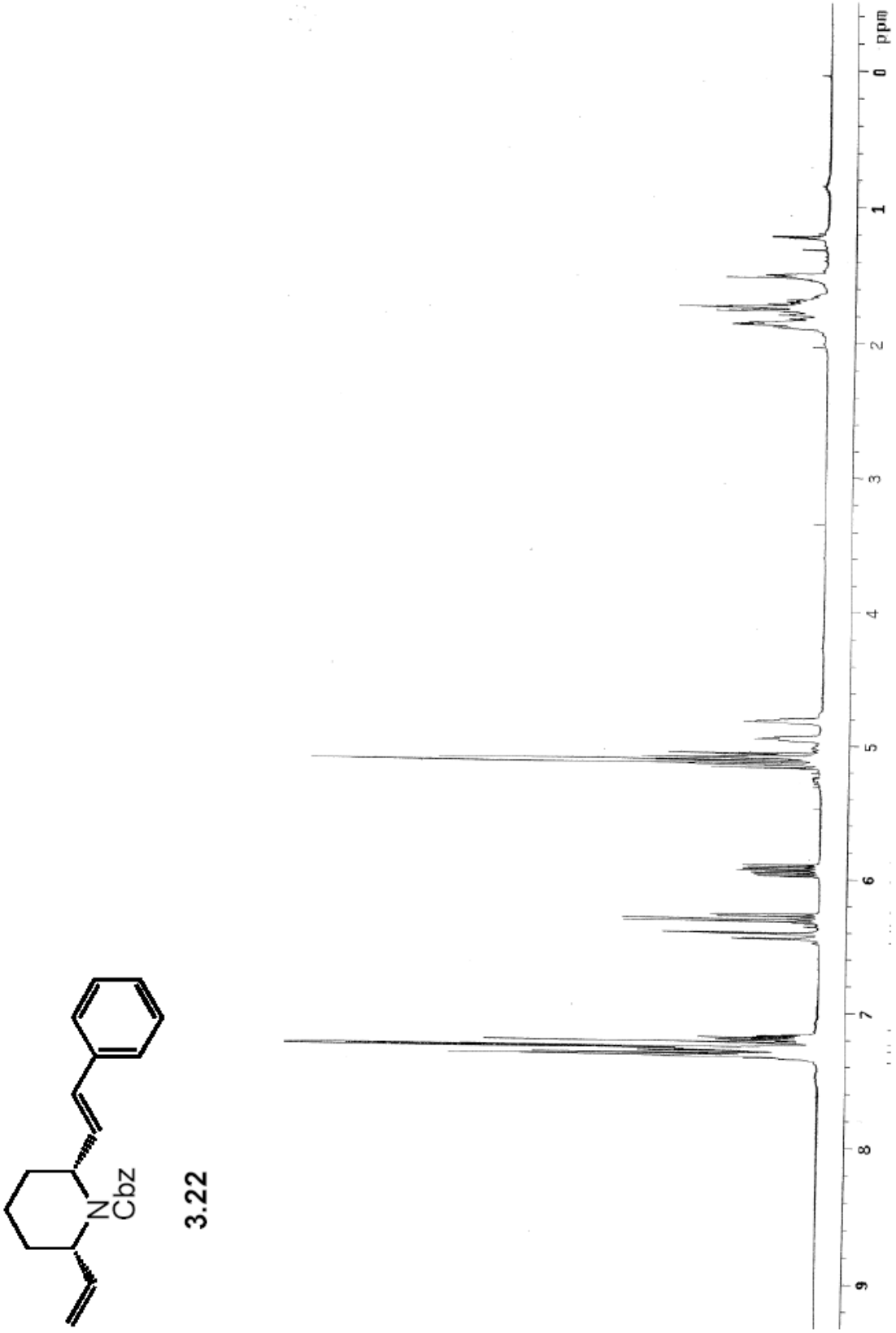

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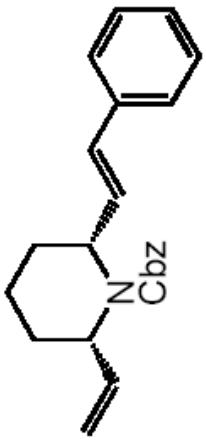
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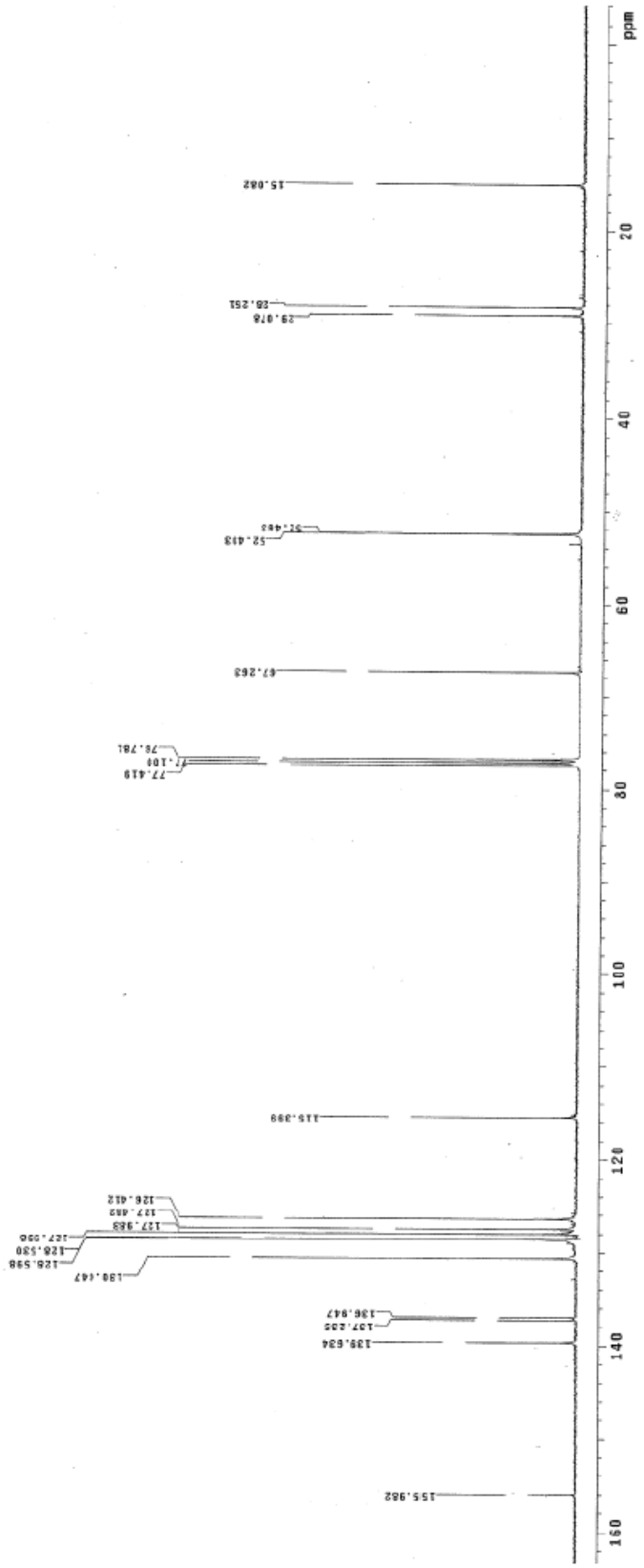
Cbz

3.22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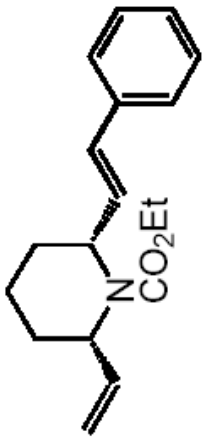

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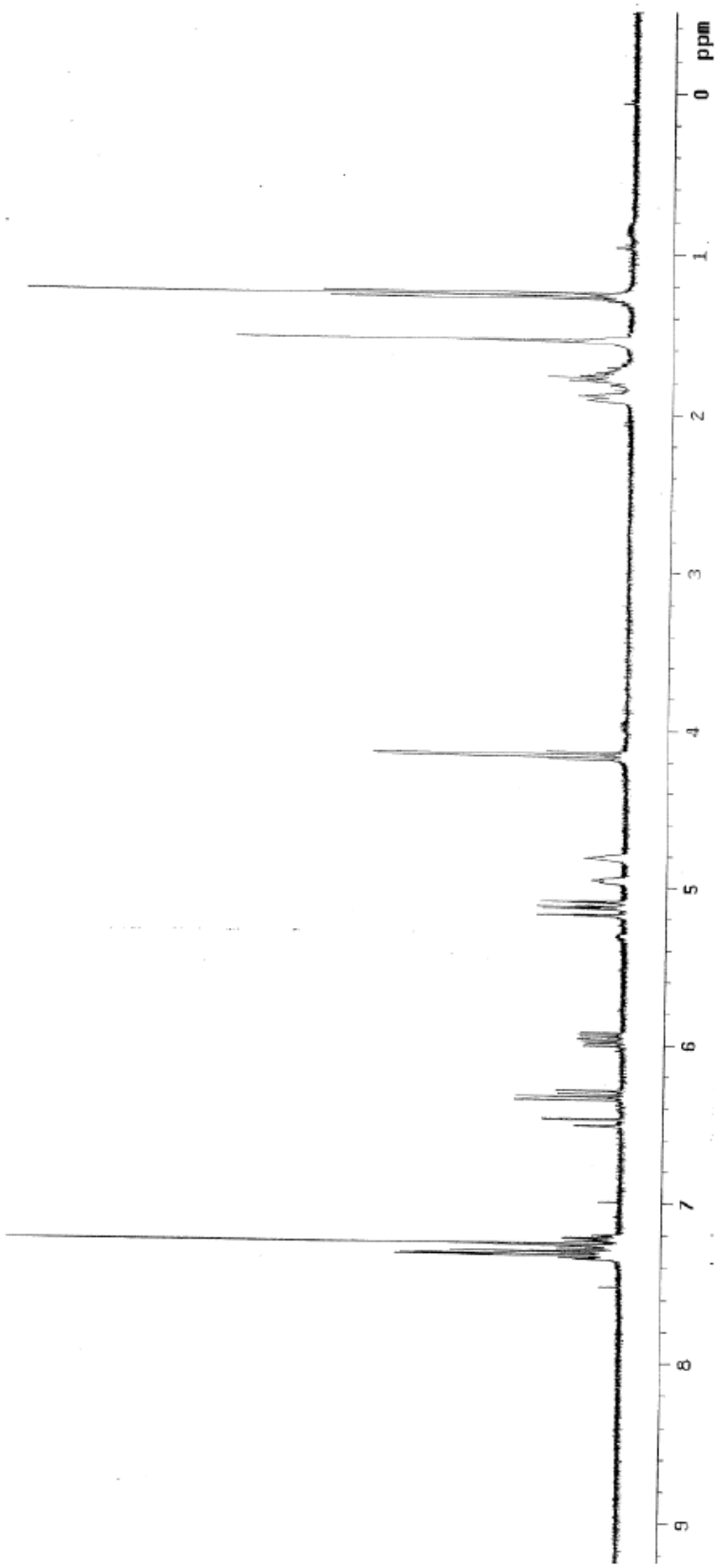

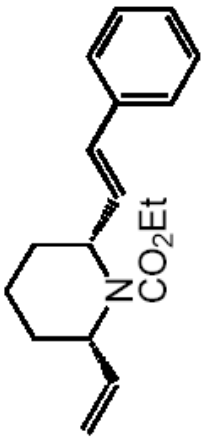

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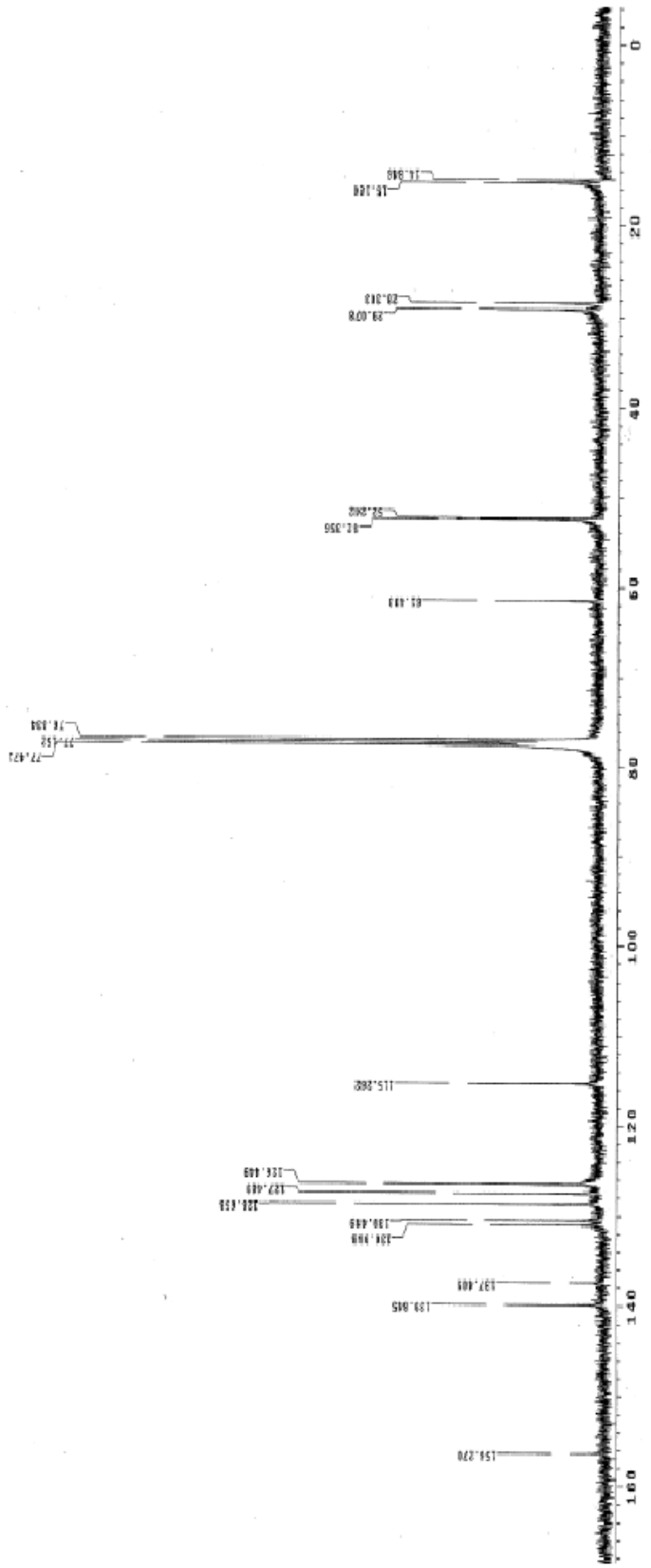

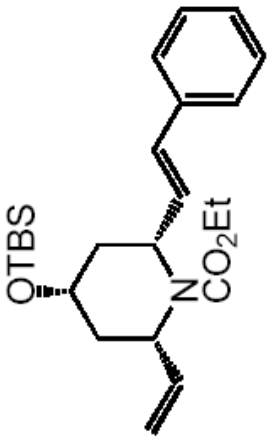

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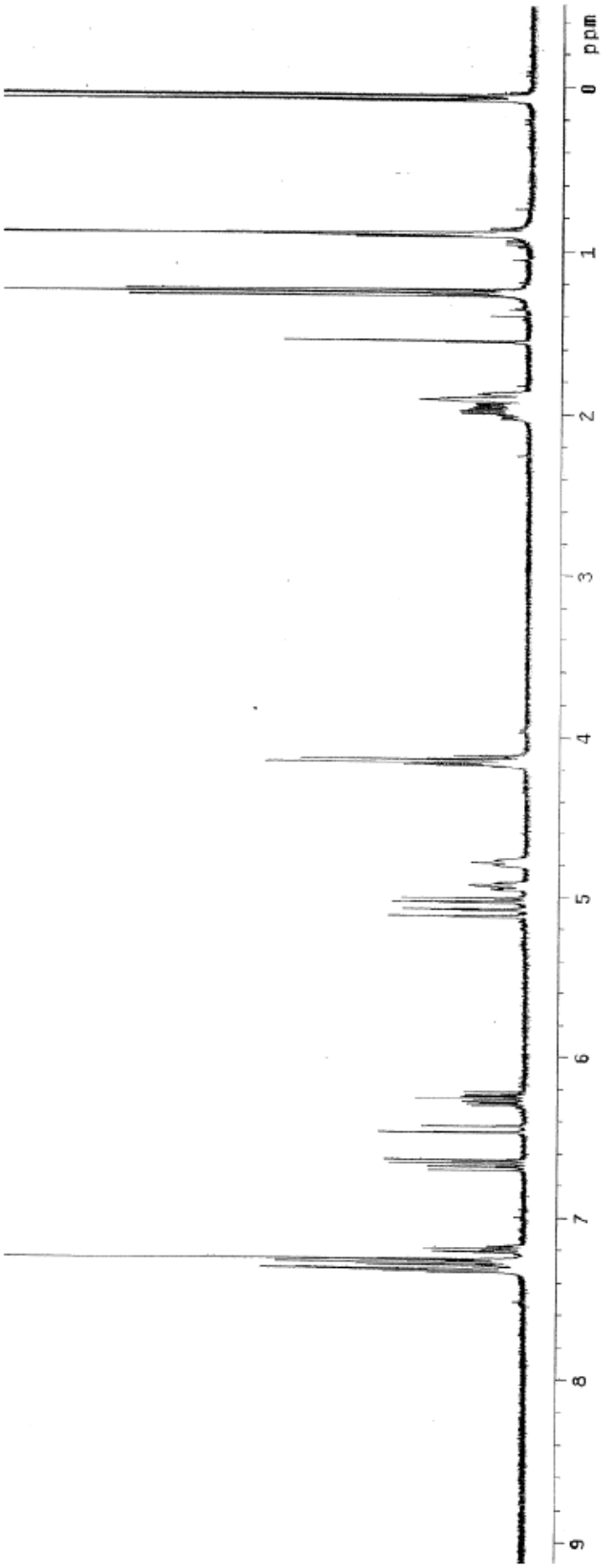

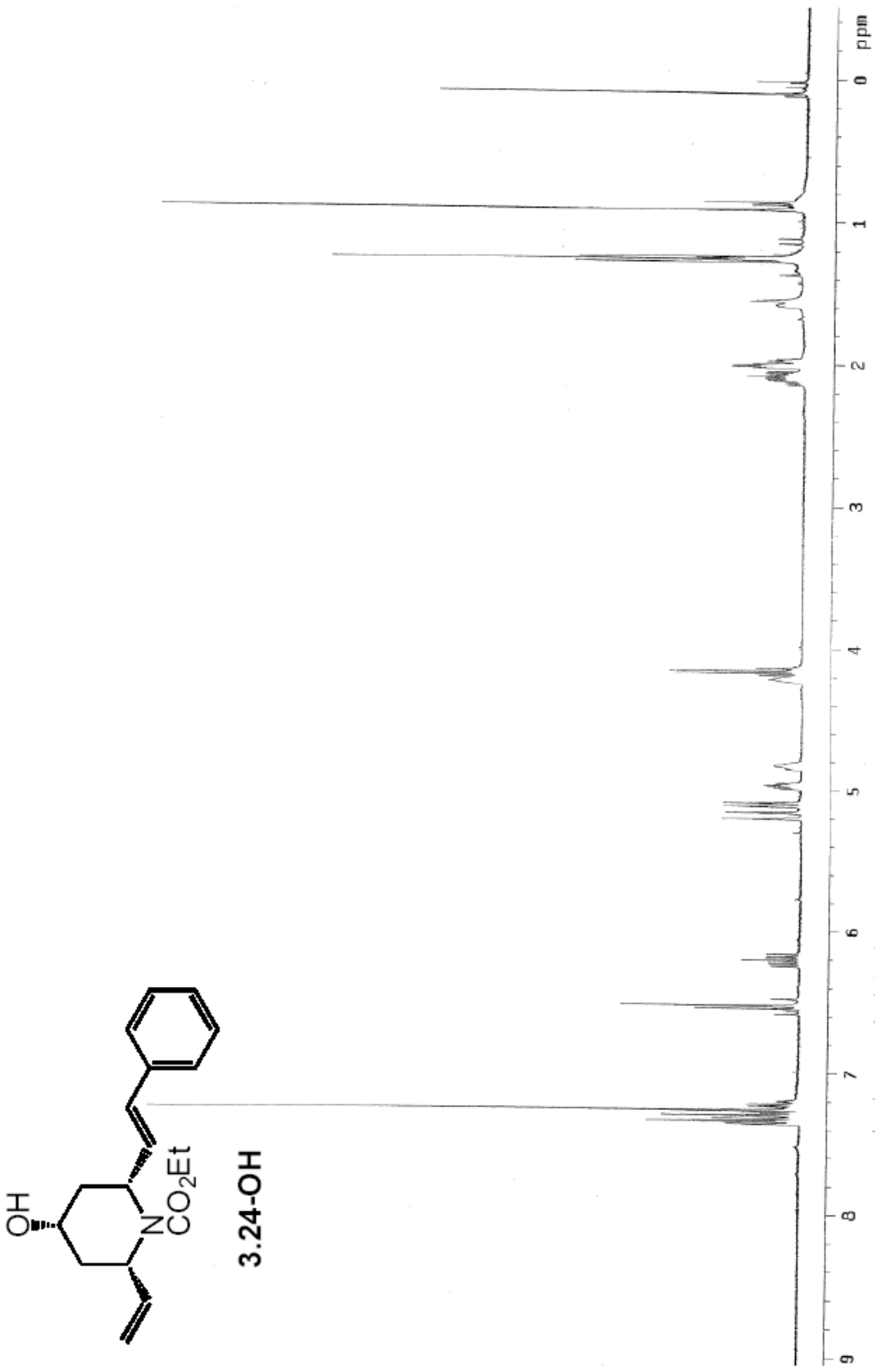
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CO2Et
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7
6
5
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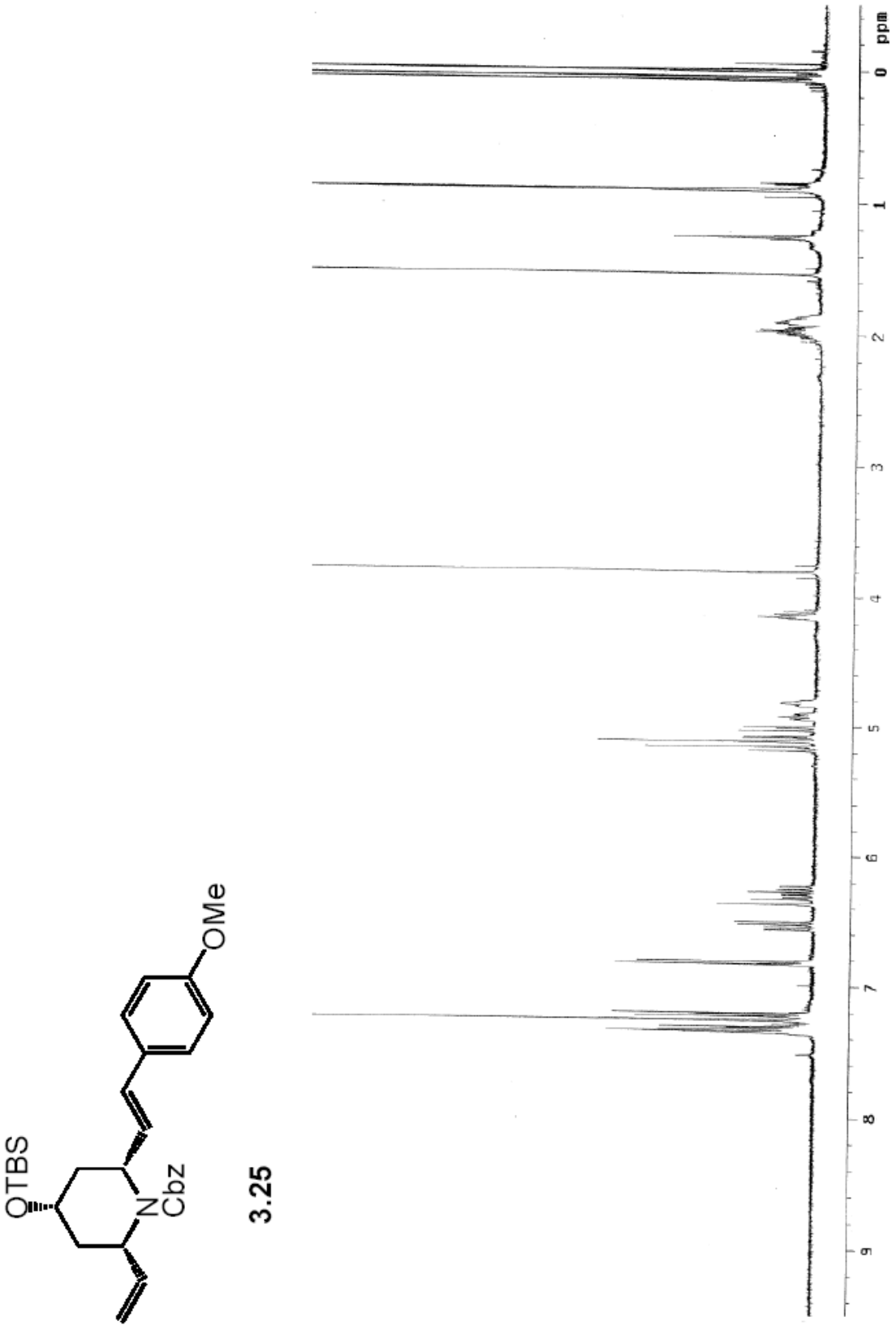
3
2
1
0 ppm



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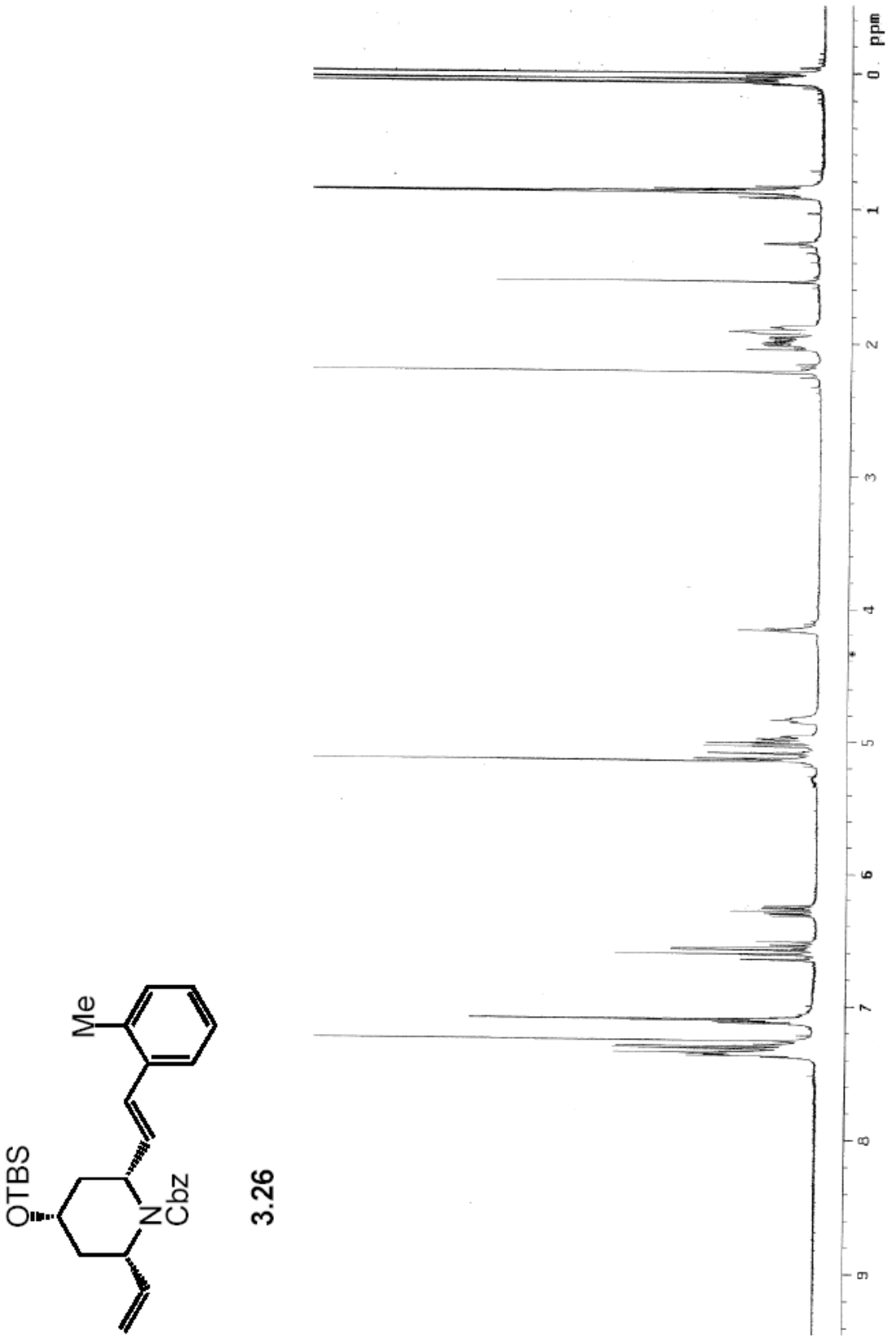

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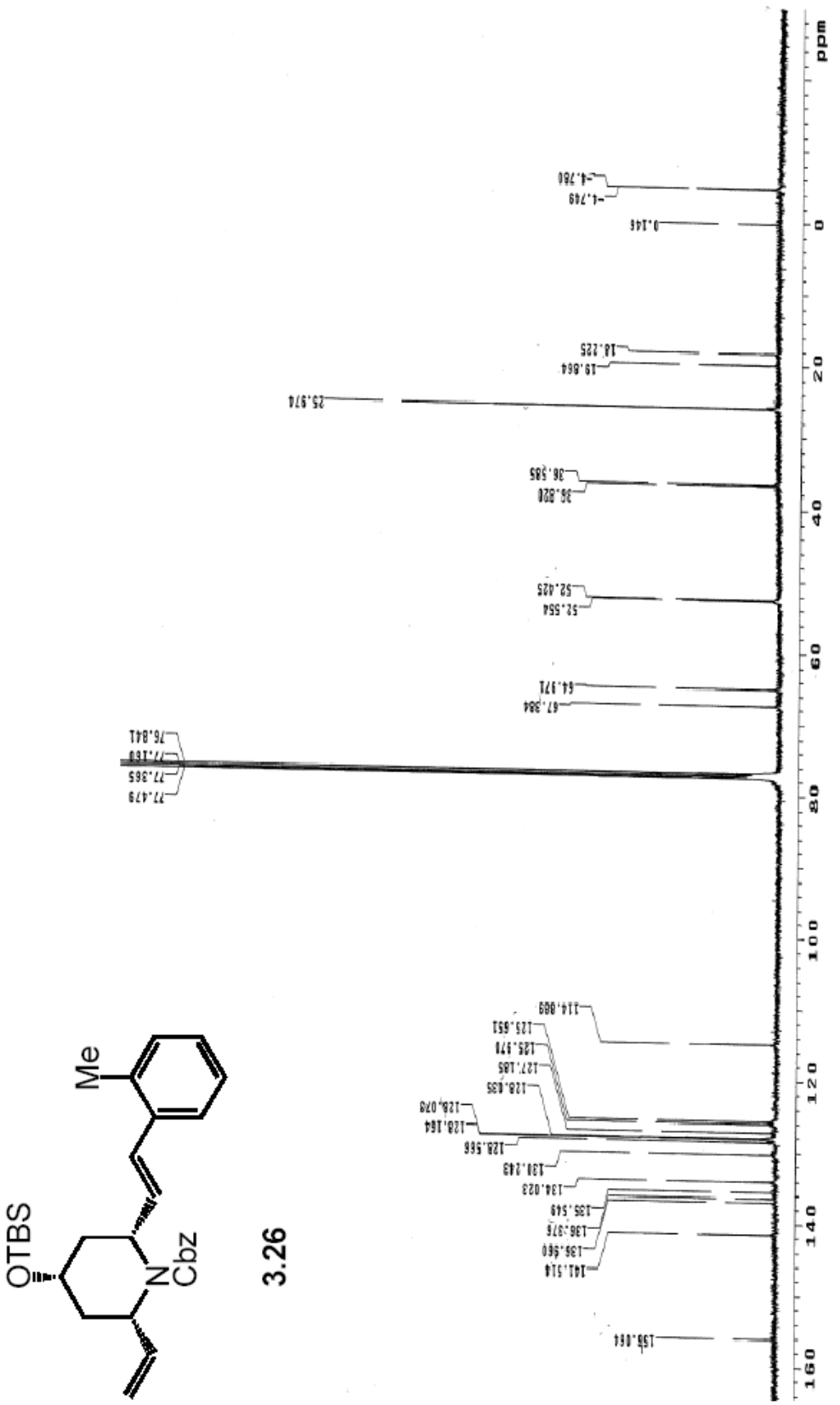
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Cbz
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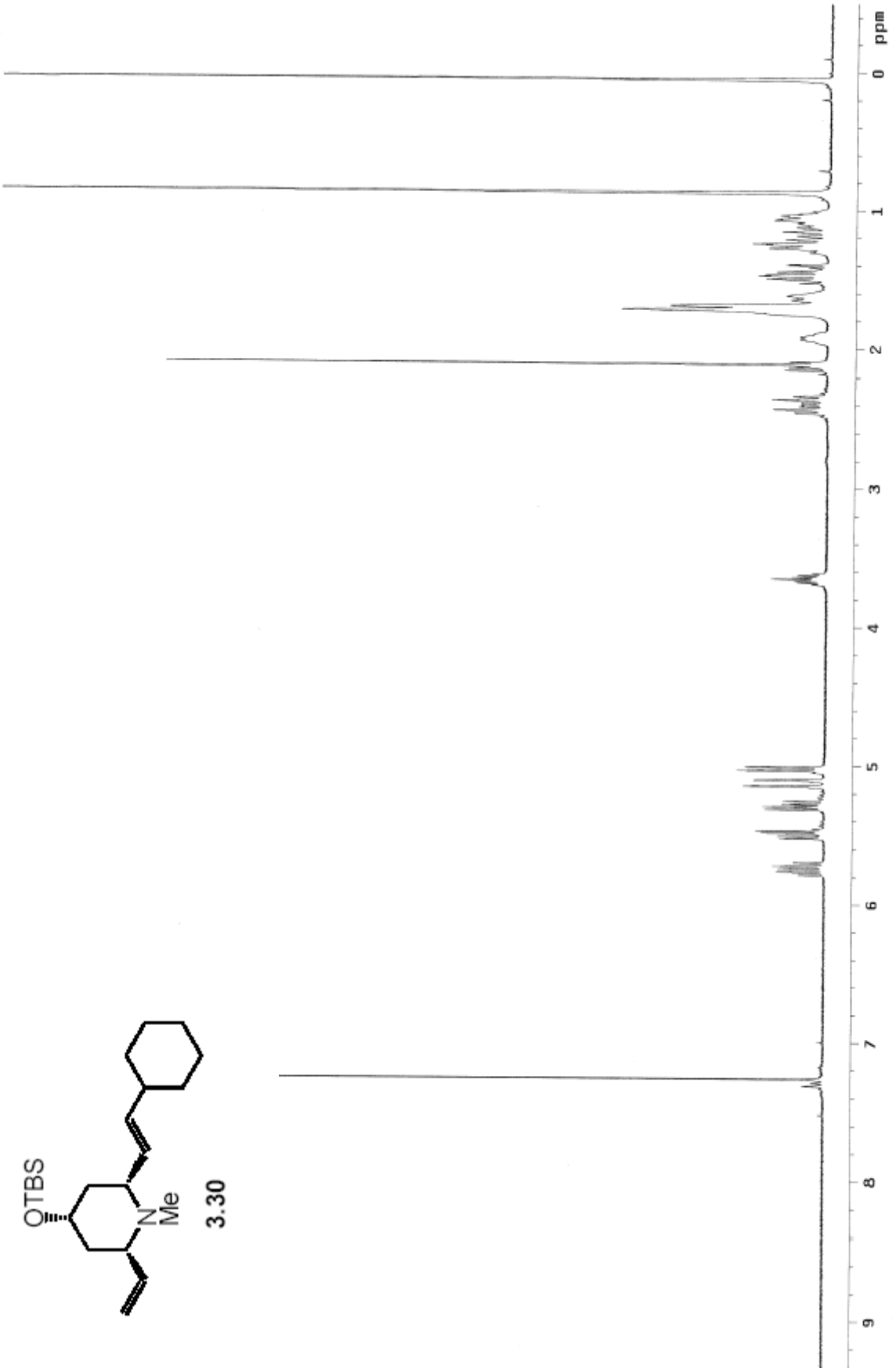
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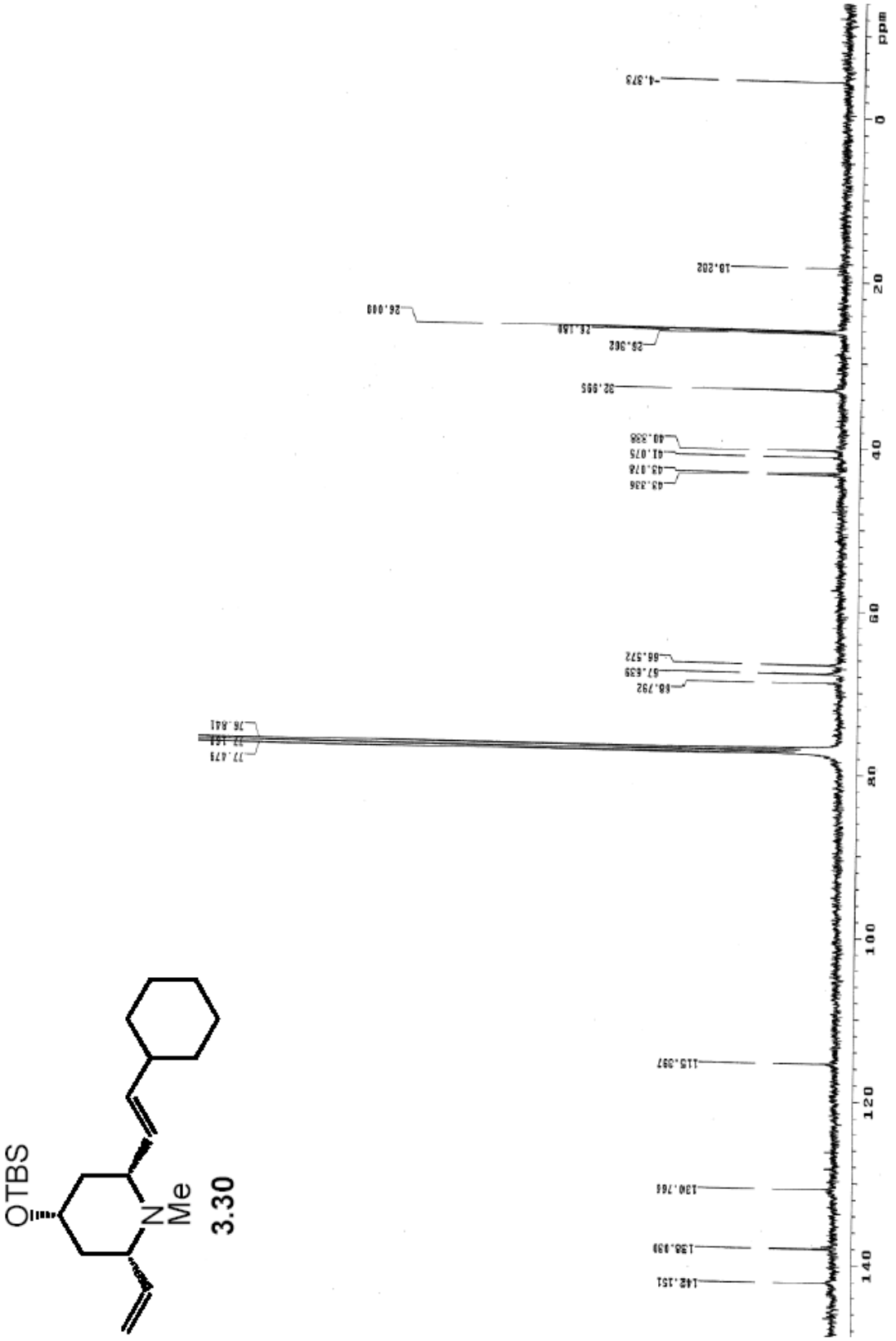
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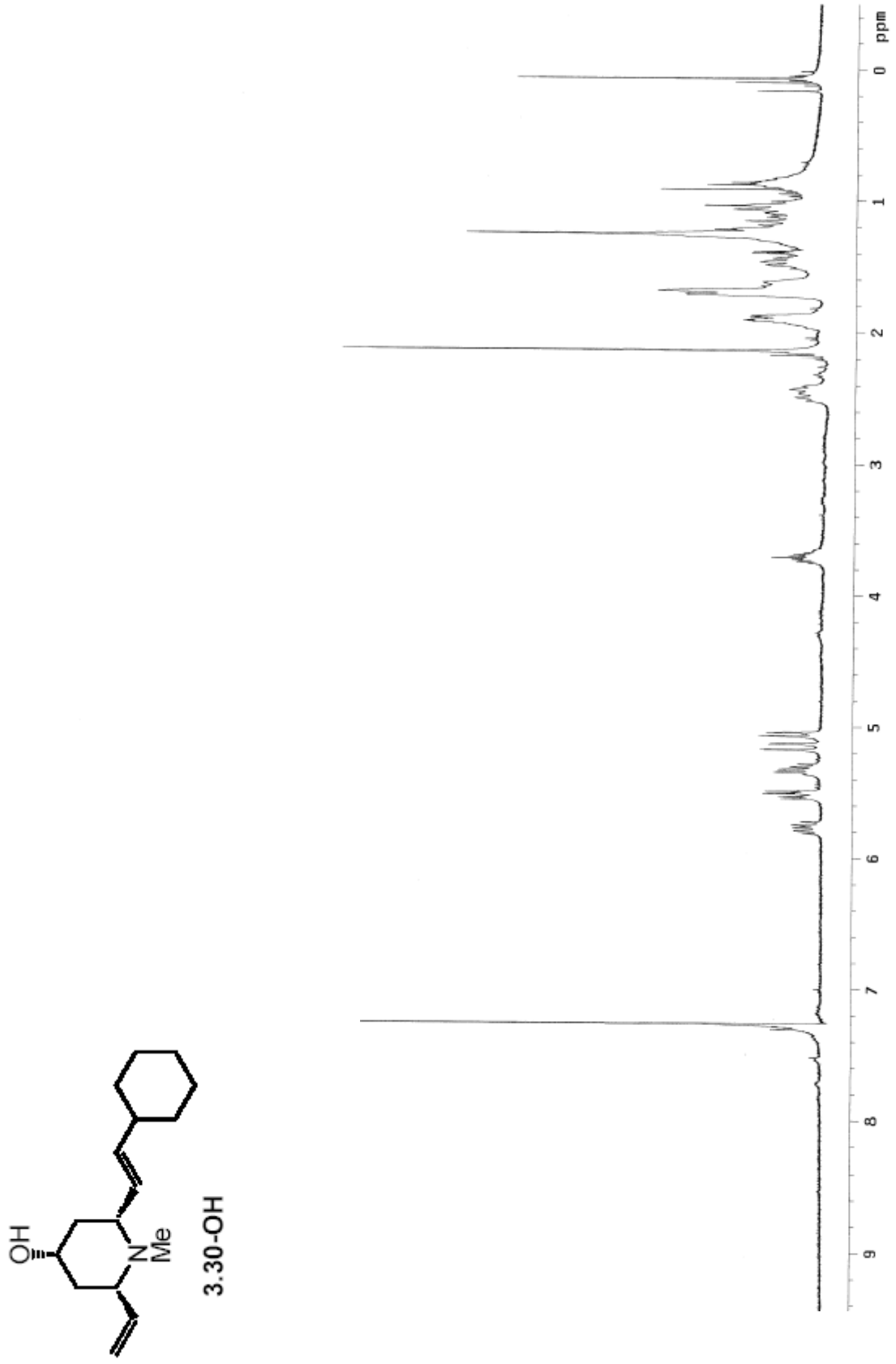
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N
Me
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ppm
0
1
2
3
4
5
6
7
8
9

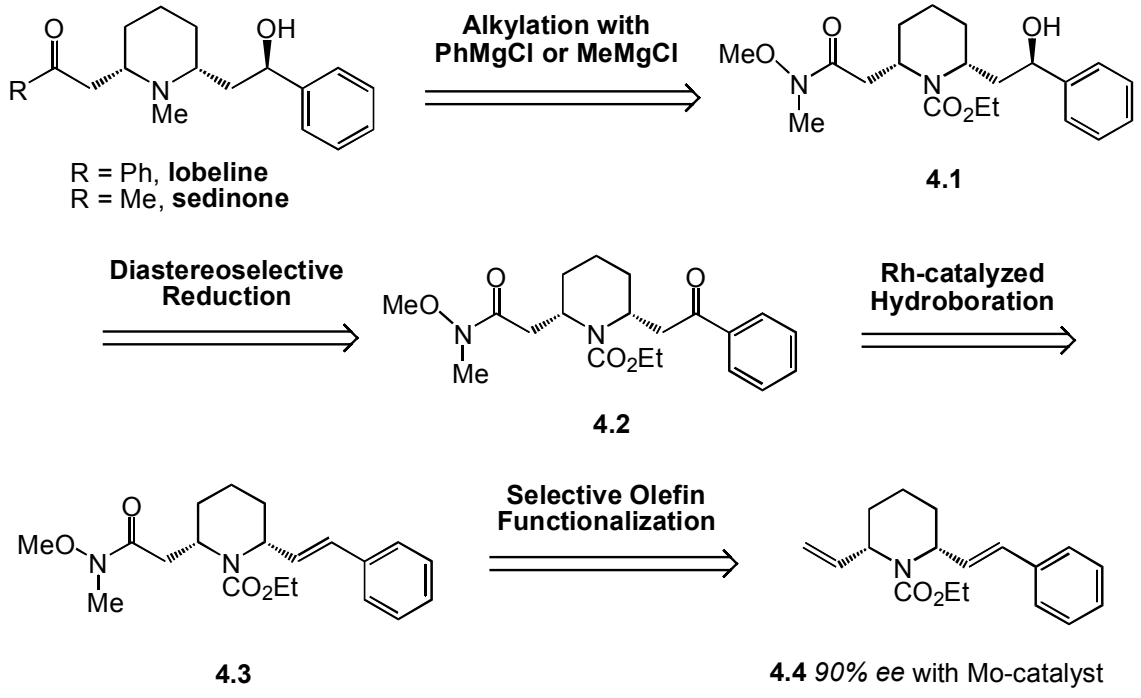
Chapter Four

FUNCTIONALIZATION OF PIPERIDINE PRODUCTS

4.1 Introduction

In the preceding chapter several biologically active alkaloids were presented and discussed as possible targets for natural product synthesis utilizing our newly developed method for the catalytic enantioselective synthesis of piperidines. To demonstrate the utility of such enantioenriched piperidines we undertook studies directed at the functionalization of these products. Our initial goal was to elaborate AROM/CM piperidine products to intermediates that could potentially be applied to the synthesis of the alkaloids lobeline and sedinone[77] (Scheme 4.1). Of special interest to us was that the only structural difference between these two natural products is that lobeline possess a phenyl ketone while sedinone has a methyl ketone. Thus we envisaged an approach where an advanced intermediate could be diverted in one step to either of the two natural products.

Scheme 4.1



(77) "Alkaloids of Some Asian Sedum Species," Kim, J. H.; Hart, H. T.; Stevens, J. F. *Phytochemistry*, **1996**, *41*, 1319–1324.

4.1a Retrosynthetic Analysis of Alkaloid Natural Products. Our initial retrosynthetic analysis of lobeline and sedinone is shown in Scheme 4.1 (see above). We expected to arrive at either natural product from the alkylation of the Weinreb amide in **4.1**. Our plan was to convert the carbamate in **4.1** to an *N*-Me group in the same reaction vessel as the alkylation of the Weinreb amide, given the stability of tetrahedral intermediates formed from Weinreb amide alkylations.[78] We projected that **4.1** would be accessible from benzylic ketone **4.2**. No problems were foreseen in performing a diastereoselective reduction of the benzylic alcohol in **4.2** since stereoselective reduction of benzylic ketones has been well documented in the literature.[79] We anticipated, and found it to be true, that the most difficult functionalization in this synthetic sequence would be conversion of the styrenyl olefin in **4.3** to the benzylic ketone in **4.2**. A known method for the benzylic oxidation of styrenyl olefins is through Rh-catalyzed hydroboration/oxidation reactions.[80] These reports, however, generally relate to the hydroboration reactions of terminal styrenes. We did not know whether these methods would be applicable to a substituted styrene such as the one in **4.3**. The starting point in this synthesis was to be piperidine **4.4**, accessible in *90% ee* through Mo catalysis. We speculated that the terminal olefin moiety in **4.4** could be differentiated from the more substituted styrenyl olefin and converted to the Weinreb amide in **4.3**.

4.2 Initial Approach to Piperidine Alkaloids

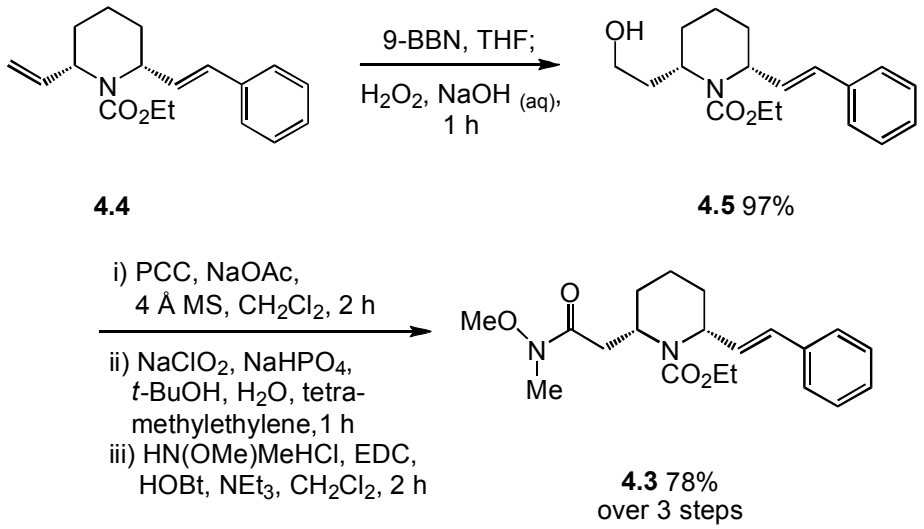
4.2a Synthesis of Weinreb Amide Intermediate. The first objective of preparing Weinreb amide **4.3** was met readily and the sequence to arrive at this intermediate is shown in Scheme 4.2 (see below). To this end, treatment of piperidine **4.4** with [3.3.1]-9-borabicyclononane followed by an oxidative work-up delivers primary alcohol **4.5** in 97% yield. A series of three well-known reactions were then employed to access **4.3**. To this result, oxidation of the primary alcohol in **4.5** to the aldehyde with pyridinium chlorochromate, followed by further oxidation to the carboxylic acid with sodium chlorite, and ultimately peptide coupling with N,O-dimethylhydroxyl amine hydrochloride delivers piperidine **4.3** in 78% yield (over three steps). With this

---

(78) "*N*-methoxy-n-methylamides as Effective Acylating Agents," Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
(79) (a) "Asymmetric Boron-catalyzed Reactions," Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784. (b) "New Chiral Phosphorus Ligands for Enantioselective Hydrogenation ," Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070.
(80) "On the Origin of Regio- and Stereoselectivity in the Rhodium-Catalyzed Vinylarenes Hydroboration Reaction," Daura-Oller, E.; Segarra, A. M.; Poblet, J. M.; Claver, C.; Fernandez, E.; Bo, C. *J. Org. Chem.* **2004**, *69*, 2669–2680.

intermediate in hand we began to study Rh-catalyzed hydroboration/oxidation reactions of the styrenyl olefin moiety.

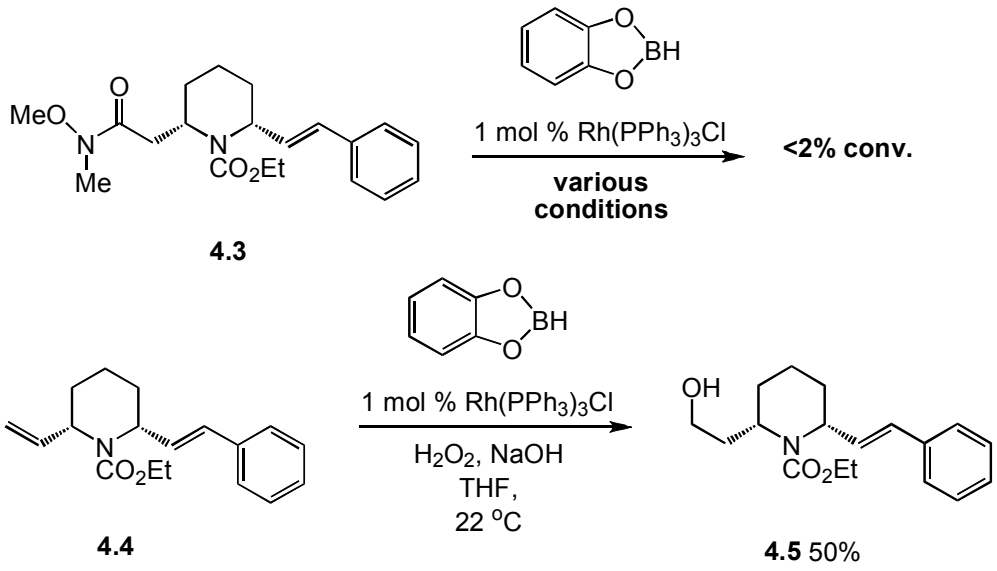
Scheme 4.2



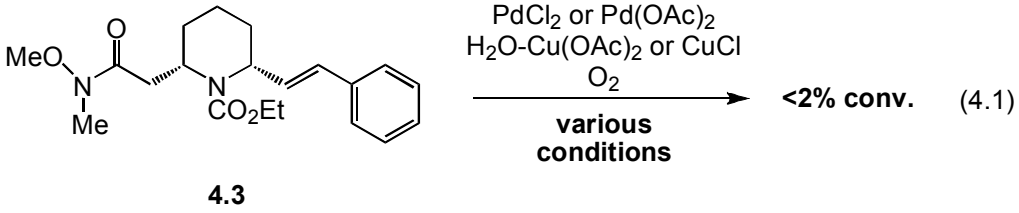
4.2b Hydroboration Attemps of Styrenyl Olefin. Our attempts to perform Rh-catalyzed hydroboration/oxidation reactions of substituted styrenyl olefins are shown in Scheme 4.3 (see below). It is well known that Wilkinson's catalyst can perform the regioselective hydroboration/oxidation of styrenyl olefins to deliver benzylic alcohols.[81] Unfortunately, under a variety of conditions, we found that Wilkinson's catalyst, in the presence of catechol borane, was unreactive toward the styrenyl olefin in **4.3**. To determine whether the Weinreb amide in **4.3** was responsible for this lack of reactivity we studied the hydroboration/oxidation reaction with piperidine **4.4**, hoping to perform a double oxidation. Based on steric considerations, we expected the terminal olefin to be converted to a primary alcohol that could then be converted to a Weinreb amide. As expected, Wilkinson's catalyst cleanly converted the terminal olefin to a primary alcohol. Dauntingly, however, we found that Wilkinson's catalyst was again unreactive toward the styrenyl olefin moiety of the piperidine and found the major product from the reaction to be **4.5**. After these disappointing results, we pursued an alternative approach to the oxidation of the styrenyl olefin in **4.3**.

(81) "Transition-metal promoted hydroborations of alkenes, emerging methodology for organic transformations," Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179–1191.

Scheme 4.3



4.2c Attempts at Wacker Oxidation of a Substituted Styrenyl Olefin. Around this time we came across an earlier report in the literature, in which a tetrahydropyran with a styrenyl substituent at the 2-position underwent a Wacker oxidation to deliver a benzylic ketone.[82] The researchers reporting this reaction proposed that the oxygen directed Pd to the proximal carbon of the styrene, resulting in the formation of a benzylic ketone as the major product. We were hopeful this directing effect would also apply to carbamate-protected piperidines and studied the Wacker oxidation of **4.3**. To our misfortune, the attempts proved unfruitful (eq. 4.1). The reaction conditions screened involved the use of either palladium (II) chloride or palladium (II) acetate as catalytic palladium sources and the use of either copper (II) acetate monohydrate or copper (I) chloride as re-oxidant. A variety of solvent mixtures and temperatures were also screened; in all cases the starting piperidine **4.3** was recovered in >98% yield.

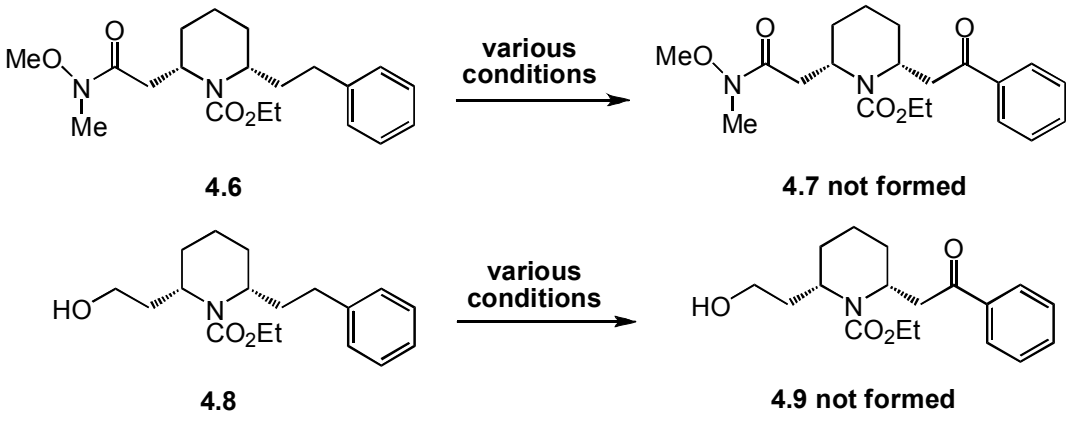


4.2d Attempts at Performing Benzylic Oxidations of Alkyl-arenes . At this point, we decided to pursue a different approach to install an oxygen functionality at the benzylic positon of our piperidine intermediates. Various reports from the literature have

(82) "Organic Synthesis with Enzymes. 3. TBADH-catalyzed Reduction of Chloro Ketones. Total synthesis of (+)-(S,S)-(cis-6-methyltetrahydropyran-2-yl)acetic Acid: A Civet Constituent," Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474–3480.

described the benzylic oxidation of aromatic-alkyl compounds to benzylic ketones. We hydrogenated the styrenyl olefins in piperidines **4.3** and **4.5** and utilized the resulting products (**4.6** and **4.8**) as benzylic oxidation substrates.[83] As shown in Scheme 4.4 under various benzylic oxidation conditions the desired products **4.7** and **4.9** were not formed the starting piperidine was recovered in quantitative yield in all cases. Among the various oxidants investigated were *m*-chloroperoxybenzoic acid,[84a] potassium permanganate supported on montmorillonite K10,[77b] periodinane reagents,[77c] pyridinium chlorochromate,[77d] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[77e]

Scheme 4.4



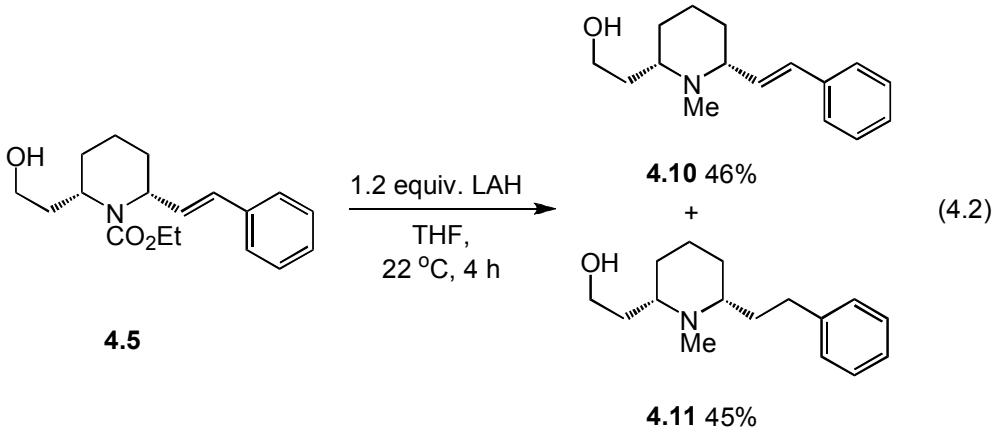
4.3 Discovery of a Unique Directed Hydroalumination

4.3a Observation of an Unexpected Hydroalumination Product. It was at this juncture that we started considering the possibility that the carbamate moiety in **4.3** was responsible for the lack of reactivity of the styrenyl olefin toward Pd and Rh complexes, (and also toward benzylic oxidation conditions in the case of **4.6** and **4.8**) either through an electron withdrawing or steric effect. To address this potential problem we chose to reduce the carbamate group to an *N*-Me. An additional reason for this decision was that

(83) The reaction conditions for the hydrogenation of **4.3** and **4.5** involved 3 equivalents of sodium bicarbonate, 10% by weight to substrate of Pd/C (10% by weight.), as a 1.0 M concentration of substrate in ethanol at 22 ^{o}C under 1atm H_2. Piperidine **4.6** is isolated in 80% yield and piperidine **4.8** is isolated in 85% yield.

(84) (a) "Oxidation of Benzylic Methylene Compounds to Ketones with *m*-Chloroperoxybenzoic Acid and Oxygen," Ma, D.; Xia, C.; Tian, H. *Tetrahedron Lett.* **1999**, *40*, 8915–8917. (b) "Selective Oxidation of Alkylarenes in Dry Media with Potassium Permanganate Supported on Montmorillonite K10," Shaabani, A.; Bazgir, A.; Teimouri, F.; Lee, D. G. *Tetrahedron Lett.* **2002**, *43*, 5165–5167. (c) "Selective Oxidation at Carbon Adjacent to Aromatic Systems with IBX," Nicolaou, K. C.; Baran, P. S.; Zhong, Y-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183–3185. (d) "Orthocyclophanes. 1. Synthesis and Characterization of [14]- and [15]orthocyclophanes and Bicyclic Biscyclophanes," Lee, W. Y.; Park, C. H.; Kim, Y. D. *J. Org. Chem.* **1992**, *57*, 4074–4079. (e) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in Acetic Acid, a Convenient New Reagent for the Synthesis of Aryl Ketones and Aldehydes via Benzylic Oxidation," Lee, H.; Harvey, R. G. *J. Org. Chem.* **1988**, *53*, 4587–4589.

the alkaloid targets both possess an *N*-Me group which we would need to eventually unveil in the course of the synthesis. First, the conversion of primary alcohol-containing piperidine **4.5** to *N*-Me piperidine **4.10** was explored (eq. 4.2). Treatment of piperidine **4.5** with 1.2 equivalents of lithium aluminum hydride delivers the desired *N*-Me piperidine **4.10** in 46% yield, but to our astonishment also delivers the *unexpected piperidine* **4.11** in 45 % yield, in which the styrenyl olefin has been saturated. To our knowledge, this is a chemical transformation without precedence.[85] Strained olefins in close proximity to amines and propargylic amines have been shown to undergo directed hydroaluminations; however, no allylic amines of this type have been shown to undergo this type of reaction. This reaction piqued my curiosity and was one of my fondest moments in graduate school. I was fortunate throughout my graduate career in starting with set goals that I was able to bring to fruition, namely to develop new catalytic methods that turned out to be highly selective and efficient, but this discovery was different. My personal feelings are that, as a scientist, one of the most exciting and romantic moments a person can have is when nature presents them with a gift such as this. I felt that nature, at that moment in my life, had enticed me to pursue and explore its never-ending secrets.



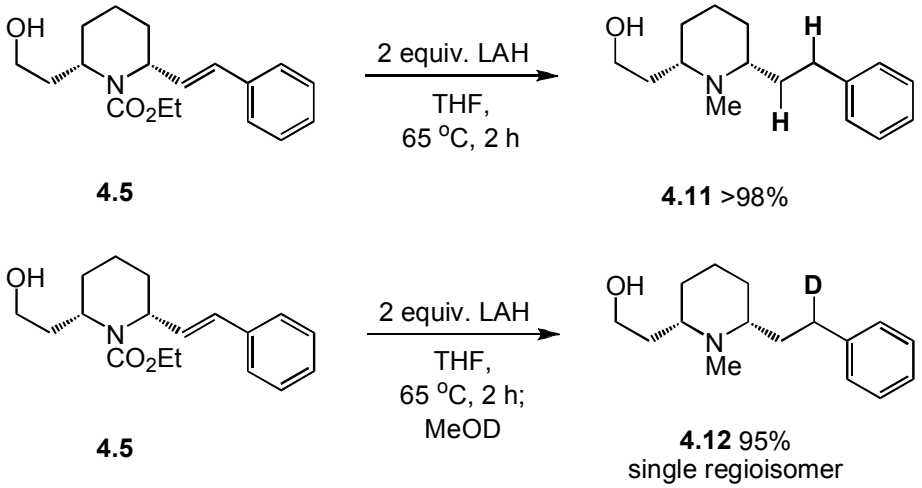
(4.2)

4.3b Optimization and Deuterium Labeling Experiments of the Hydroalumination Reaction. The first question to be answered was whether it was possible to perform this reduction reaction under conditions to deliver **4.11** as the major product (Scheme 4.5, see below). Treatment of piperidine **4.5** with two equivalents of lithium aluminum hydride at 65 °C provides *N*-Me piperidine **4.11** in quantitative yield. The next issue to be

(85) For amine directed hydroalumination reactions, see: (a) "Anomalous Lithium Aluminum Hydride Reduction of Carbon—Carbon Double Bonds in 7-azabicyclo(2.2.1)heptenyl Systems," Marchand, A. P.; Allen, R. W. *Tetrahedron Lett.* **1975**, *16*, 67–70. (b) "An Unusual Lithium Aluminum Hydride Reduction of an Isolated Olefin in a 1,2-diamine System," Szmuszkovicz, J.; Musser, J. H.; Laurian, L. G. *Tetrahedron Lett.* **1978**, *19*, 1411–1412. (c) "Stereoselective trans-reduktion tert. Propargylamine mit DIBAH zu (E)-Allylaminen," Granitzer, W.; Stütz, A. *Tetrahedron Lett.* **1979**, *20*, 3145–3148.

addressed was whether this reduction was regioselective. It was still unknown if an organoalane or radical carbon intermediate was being formed in the reaction. To answer this, deuterium labeling experiments were conducted by quenching the reaction with >99.9% deuterated methanol. In doing so, we found that *N*-Me piperidine **4.12** is formed in 95% yield as a single regioisomer and appears to be a single diastereomer, as determined by ^{2}H NMR studies. The fact that a single regioisomer is formed in the reaction suggests that the reducing agent is directed and that a stabilized C–Al bond forms in the course of the reaction.

Scheme 4.5

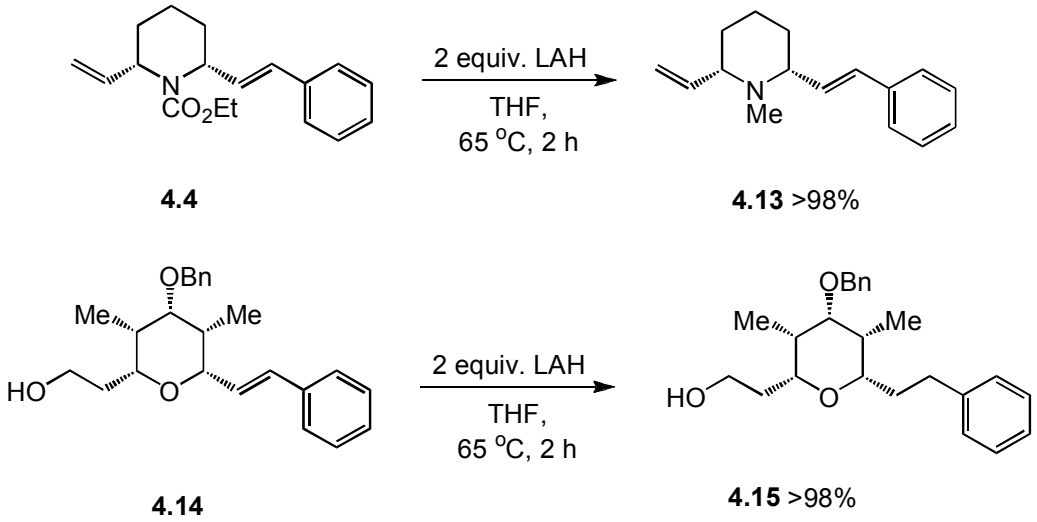


4.3c Investigations into Directing Group-Effect of Hydroalumination. The next question asked was what functional group is responsible for the directing effect in this reaction; is the hydroalumination of the styrenyl olefin being directed by the hydroxy group or the amino group? To address the former part of this question, we investigated the reduction of piperidine **4.4**, which lacks a primary alcohol (Scheme 4.6, see below). To this end, exposure of **4.4** to lithium aluminum hydride at 65 °C provides *N*-Me piperidine **4.13** in quantitative yield. This result made it clear that the hydroxy group is important for the reduction of the styrenyl olefin, but it did not negate the requirement for the amino group to participate. For this reason we studied the reduction of pyran **4.14**,[86] which contains a primary alcohol and styrenyl olefin (Scheme 4.6). Treatment of pyran **4.14** with two equivalents of lithium aluminum hydride at 65 °C provides pyran **4.15**, wherein the styrenyl olefin has been reduced, in quantitative yield. Together, these results provide strong evidence that the hydroxy group and not the amino group is

(86) This compound was prepared from an intermediate that is discussed in Chapter 5.

responsible for this unique directed hydroalumination reaction.[87] It is interesting to note that this reaction can be applied to pyrans as well as piperidines and, although not studied, it would be curious to know whether this reaction could be applied to other six-membered ring hetero- or carbocycles.

Scheme 4.6



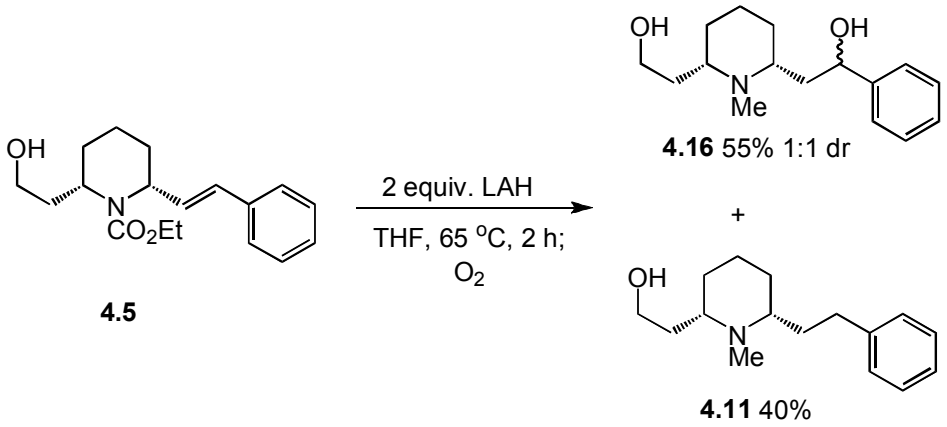
4.4 **4.13** >98%

4.14 **4.15** >98%

4.3d Investigations into Trapping of Organoalane Intermediate. After these mechanistic investigations were completed, we focused our, efforts on performing a directed hydroalumination reaction of piperidine **4.5** followed by trapping of the organoalane intermediate formed in the reaction with an electrophilic oxygen source. The natural products lobeline and sedinone both possess a benzylic alcohol functionality and we felt this would be a unique way of introducing this functional group to this class of piperidines. And we came to the conclusion that the best electrophilic oxygen source would be anhydrous oxygen gas, given practicality and atom economy of using this reagent. The outcome of these studies is shown in eq. 4.3. To this end, treatment of piperidine **4.5** with two equivalents of lithium aluminum hydride at 65 °C followed by exposure of the resulting mixture to anhydrous oxygen gas provides *N*-Me piperidine **4.16** in 55% yield and *N*-Me **4.11** in 40% yield. We were content that the desired product **4.16**, wherein oxygen is incorporated at the benzylic position, is formed in the reaction.

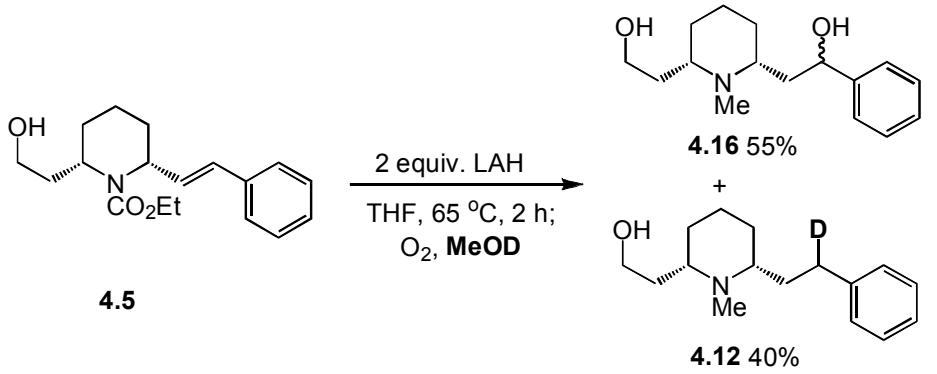
(87) For a review of substrate-directed reactions, see: (a) "Substrate-directable Chemical Reactions," Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. For examples of hydroxyl-directed hydroalumination reactions, see: (b) "Stereochemical Control of Reductions. 6. The Hydroxymethyl Group as a Hinge for Internal Reagent Delivery," Thompson, H. W.; McPherson, E. *J. Org. Chem.* **1977**, *42*, 3350–3353. (c) "α-Ketoketene Dithioacetal Chemistry. 1. Alternate Modes of Lithium Aluminum Hydride Reduction. Regio- and Stereospecific vs. Reduction-alkylation-fragmentation," Gammill, R. B.; Gold, P. M.; Mizsak, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 3095–3100. (d) "Hydroxy-directed Hydroaluminations: A Stereoselective Approach to Cycloalkanols From β-aryl Enones," *Tetrahedron Lett.* **1994**, *35*, 1137–1140.

Unfortunately, the reaction is not stereoselective and **4.16** is isolated as a 1:1 mixture of epimers at the benzylic position. This result was in contrast to our previous deuterium labeling studies, in which the product appears to be a single diastereomer (see eq. 4.2 above). It is probable that in the formation of **4.16** oxygen is incorporated *via* a radical mechanism. We also became concerned with incomplete oxygen incorporation in the reaction and under a variety of conditions were not able to prevent the formation of **4.11**.



(4.3)

To nullify the possibility that an adventitious proton source was responsible for the formation of **4.11**, we performed the electrophilic oxygen trapping reaction with a deuterium quench (eq. 4.4). Treatment of piperidine **4.5** with lithium aluminum hydride at 65 °C, exposure of the resulting mixture to anhydrous oxygen gas and then treatment with >99.9% deuterated methanol again deliverer *N*-Me piperidine **4.16** in 55% yield and the deuterium-incorporated product **4.12** in 40% yield. This result provided proof that an advantitious proton source is not responsible for formation of **4.11**. Most likely, organoaluminum intermediates aggregate during the course of the reaction, which prevents full oxygen incorporation at the benzylic position.

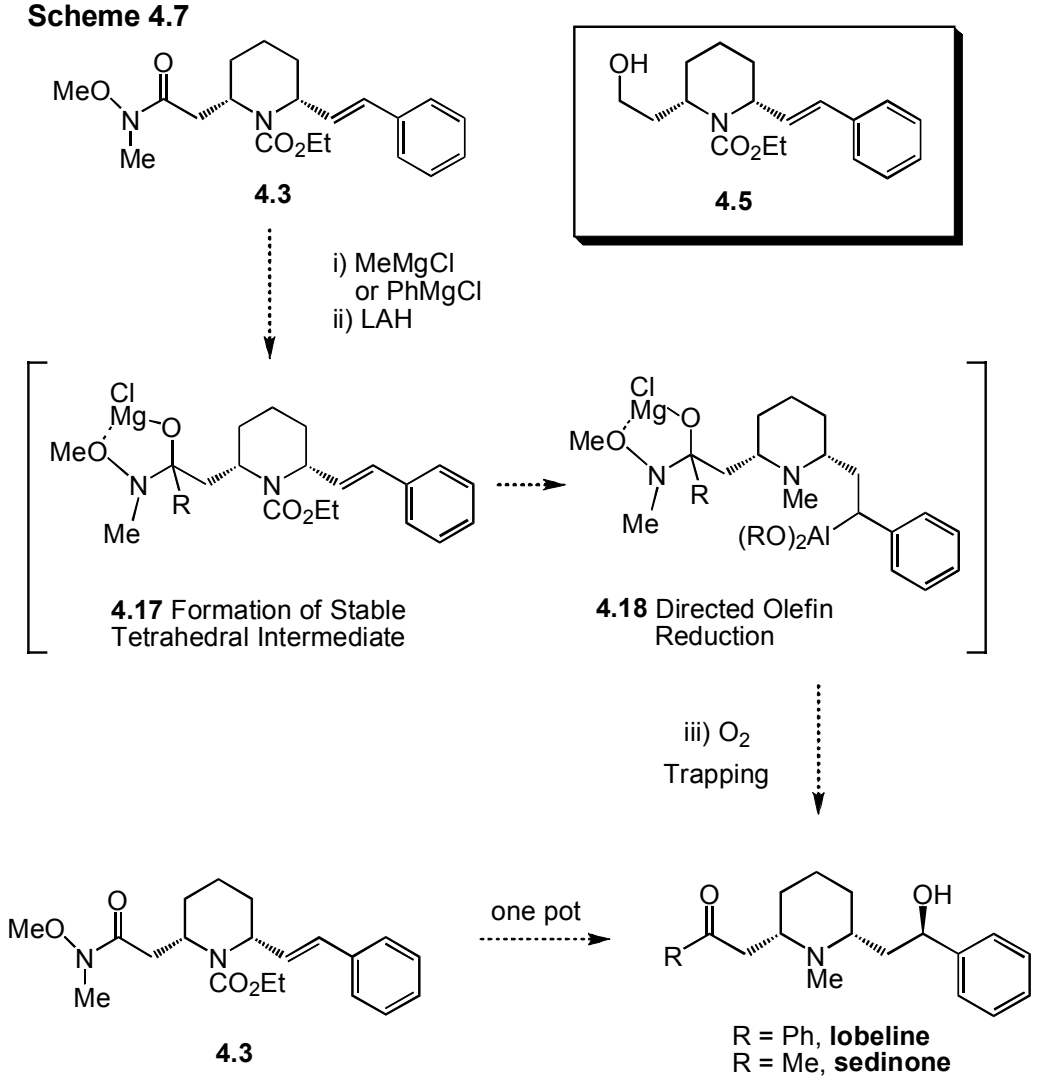


(4.4)

4.4 Alternative ApproachTo Piperidine Alkaloids

4.4a Tandem Alkylation-Reduction/Hydroalumination-Oxygen Trapping of Piperidine Intermediates. Despite being unable to fully incorporate oxygen in the directed hydrometallation of **4.5**, we were optimistic that we could still use this unique reaction and devised a new strategy toward the alkaloids lobeline and sedinone (Scheme 4.7).

Scheme 4.7

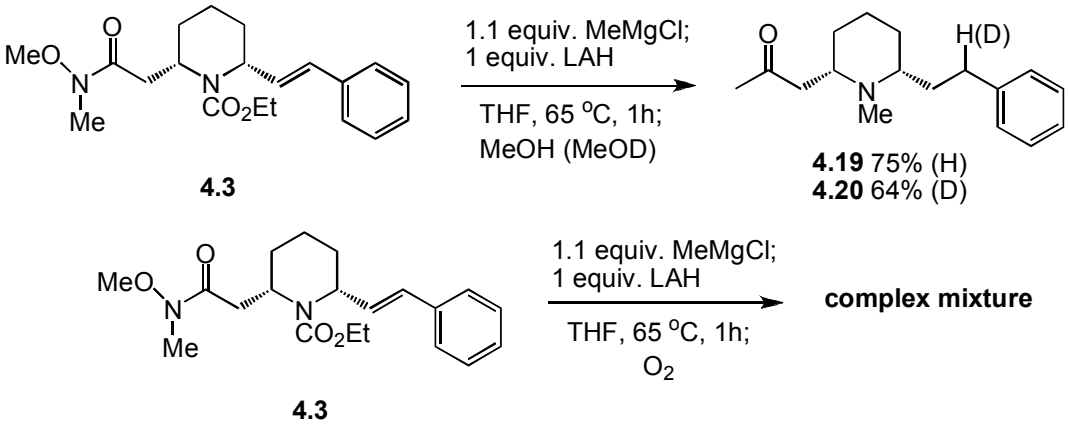


This approach involved a multi-component, one-pot cascade of reactions starting from piperidine **4.3**. Due to the stability of Weinreb amide tetrahedral intermediates, we hypothesized that alkylation of the Weinreb amide in **4.3** could be performed with either a methyl or phenyl nucleophile, resulting in the likely robust intermediate **4.17**. Then, treatment of this intermediate with lithium aluminum hydride would result in the reduction of the carbamate in **4.17**, followed by the directed hydroalumination to generate

organoalane intermediate **4.18**. Treatment of this intermediate with anhydrous oxygen followed by standard work-up conditions was then expected to furnish either lobeline or sedinone.

4.4b Studies into Multicomponent Reactions of a Weinreb Amide-containing Piperidine. Investigations into this multi-component transformation began with determining the feasibility of performing an alkylation of the Weinreb amide in **4.3** followed by reduction of the ethyl-carbamate group to an *N*-Me group (Scheme 4.8). Toward this objective, treatment of piperidine **4.3** with 1.1 equiv. of methylmagnesium chloride followed by treatment with 1 equiv. of lithium aluminum hydride at 65 ^{o}C delivers the desired piperidine **4.19** in 75% yield after 1 h. If more than 1 equiv. of lithium aluminum hydride is used in the reaction, undetermined side products begin to form. Additionally, the stereogenic center β to the methyl ketone undergoes a facile epimerization resulting in a mixture of 2,6-*syn* and 2,6-*anti* piperidines.[88] To ensure the fidelity of the directed hydrometallation we performed the reaction with a deuterium quench and were able to isolate the desired product **4.20** in 64% yield. Next, we pursued the multi-component reaction sequence with the inclusion of an oxygen gas trapping after the alkylation/directed hydrometallation sequence. Unfortunately, under a variety of reaction conditions, desired natural products were not formed; analysis of the reaction mixture by ^{1}H NMR analysis revealed that complex mixtures formed in all cases. These studies suggest that introduction of oxygen results in break down of the tetrahedral intermediate formed from the Weinreb amide.

Scheme 4.8



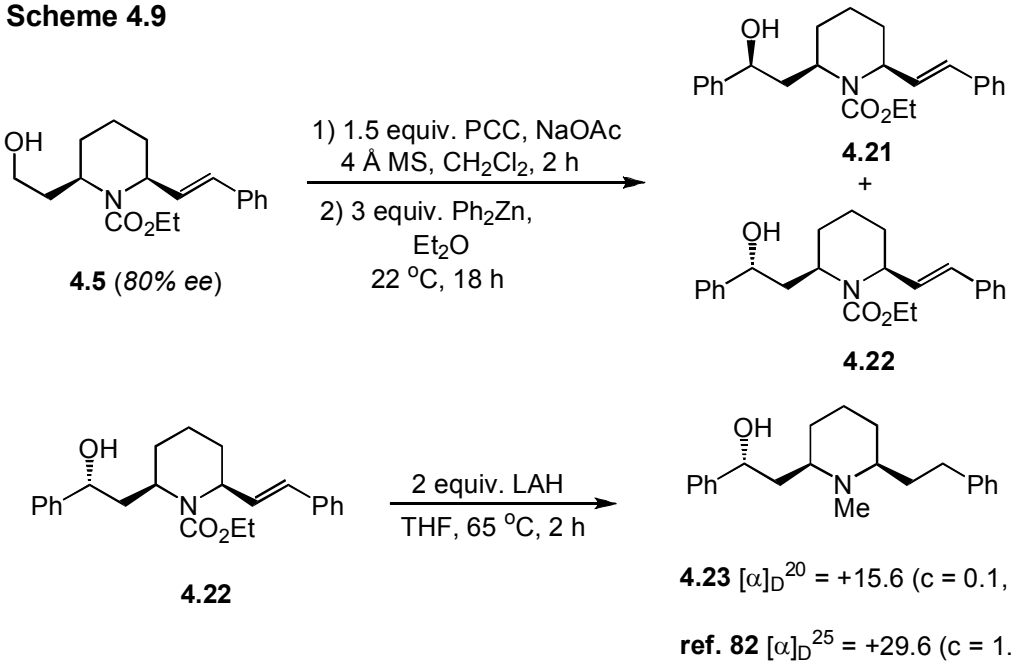
(88) It is well documented that β-amino ketones such as **4.19** undergo facile epimerization, presumably through an elimination/intramolecular conjugate addition process, see: "Syntheses of the Sedum and Related Alkaloids," Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978.

4.5 Miscellaneous Functionalization Reactions of Piperidines

Prior to concluding this chapter several other piperidine funtionalizations will be discussed. Most importantly, the functionalizations performed to determine the absolute stereochemistry of the piperidine products in the Mo-catalyzed asymmetric ring-opening/cross-metathesis reactions of azabicycles will be discussed.

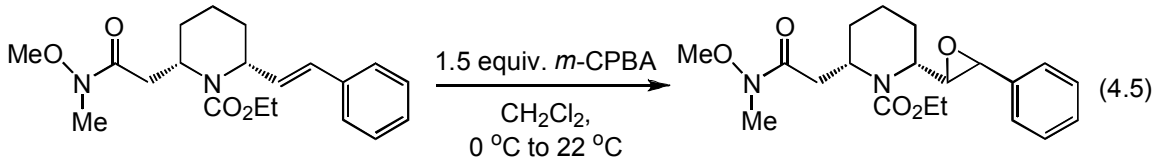
4.5a Absolute Stereochemistry Determination for Piperidine Products. The absolute stereochemistry for piperidine products was determined by chemical correlation to a piperidine product of known absolute stereochemistry (Scheme 4.9).[89] The stereoproof began with piperidine **4.5** of *80% ee*.[90] Oxidation of **4.5** to the corresponding aldehyde with PCC, followed by alkylation with diphenylzinc provides a mixture of alcohols **4.21** and **4.22** that is separable by silica gel chromatography. Treatment of piperidine **4.22** with lithium aluminum hydride then affords piperidine **4.23**,[91] of known absolute stereochemistry. The calculated enantiomeric excess for a sample of **4.23** of $[\alpha_D]^{20}$ = +15.6 (c = 0.1, $CHCl_3$) is *76% ee*, correlating to our observed value of *80% ee*. The absolute stereochemistry of all piperidine products was assigned by inference based on the absolute stereochemistry of piperidine **4.5**, which was obtained from the enantioenriched piperidine **4.4**.

Scheme 4.9



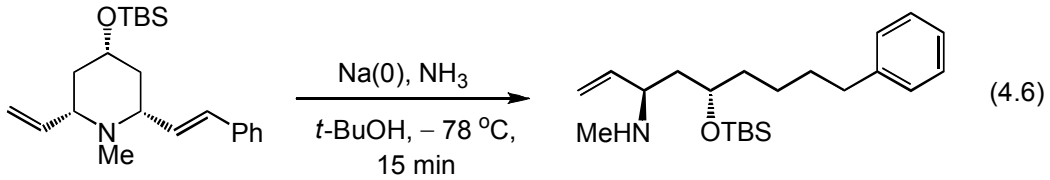
(89)"Lobeline: Structure-Affinity Investigation of Nicotinic Acetylcholinergic Receptor Binding," Flammia, D.; Dukat, M.; Damaj, M. I.; Martin, B.; Glennon, R. A. *J. Med. Chem*. **1999**, *42*, 3726–3731.
(90) In the optimized reaction conditions for AROM/CM, piperidine **4.4** was obtained in *90% ee*, see Ch 3.
(91) The spectral data for **4.23** has been previously published, see ref. 82.

4.5b Epoxidation of Substituted Styrene Intemediate. One functionalization of these piperidine products involved the epoxidation of the styrenyl olefin in piperidine **4.3** (eq. 4.5). Treatment of piperidine **4.3** with 1.5 equivalents of *m*-chloroperoxybenzoic acid in methylene chloride delivers expoxide **4.24** in 64% yield as a 1:1 mixture of epoxide diastereomers. It was hoped that the opening of the epoxide could be performed regioselectively with a hydride source through a directing effect from the ethyl-carbamate en route towards the total synthesis of lobeline and sedinone. Unfortunately, several hydride sources resulted in hydride attack at the benzylic position due to electronic stabilization.



4.3 **4.24** 64% (4.5)

4.5c Dissolving Metal Vinylogous Opening of an N-Me Piperidine to a 1,3-Aminoalcohol. Another functionalization of piperidine products involved the conversion of *N*-Me piperidine **4.25** to 1,3-aminoalcohol **4.26** (eq. 4.6). Previously, we described the dissolving metal opening of related pyrans to 1,3-diols.[92] We found this reaction can also be applied to styrenyl olefin containing piperidines. Treatment of piperidine **4.25** with sodium dissolved in liquid ammonia delivers 1,3-aminoalcohol **4.26** in 85% yield after 15 min.



4.25 **4.26** 85% (4.6)

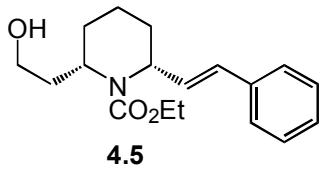
4.6 Conclusions

This chapter described several methods for the functionalization of enantioenriched piperidine products that were derived from Mo-catalyzed asymmetric ring-opening/cross-metathesis reactions of azabicycles. Initially, efforts were directed toward the total synthesis of piperidine alkaloids and it was shown that terminal olefins can be easily differentiated from styrenyl olefins. The difficulties encountered in functionalizing the styrenyl olefin of piperidine intermediates underlines the need for new

(92) "Efficient Enantioselective Synthesis of Functionalized Tetrahydropyrans by Ru-Catalyzed Asymmetric Ring-Opening Metathesis/Cross-Metathesis (AROM/CM)," Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290.

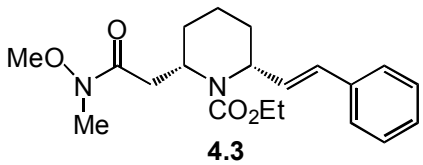
methods to be developed for reactions of substituted styrenes of molecular complexity. Nevertheless, these investigations resulted in the discovery and development of a novel regioselective hydroalumination reaction of styrenyl olefins. Various studies, including deuterium labeling experiments, were conducted to shed insight into the mechanism of this reaction. Furthermore, it was shown that this novel transformation can be employed as a benzylic oxidant by the trapping of an organoalane with an electrophilic oxygen source. Another set of important funcionalization reactions resulted in the preparation of a piperidine that established the absolute stereochemistry of piperidines derived from Mo-catalyzed AROM/CM reactions.

4.7 Experimental Section



4.5

Synthesis of primary alcohol-containing piperidine **4.5**. A 25-mL round-bottom flask was charged with piperidine **4.4**[93] (0.250 g, 0.876 mmol), THF (9.0 mL), 9-borabicyclo[3.3.1]nonane (0.130 g, 1.10 mmol, 1.25 equiv.), and allowed to stir for 1 h. At this time, the reaction mixture was cooled to −10 °C in a NaCl/ice bath, and the reaction was quenched by the (slowly and sequentially) addition of a 30% aqueous solution of H_2O_2 (0.880 mL, 1 mL/mmol of **4.4**), and a 1.0 M solution of NaOH (0.880 mL, 1 mL/mmol of **4.4**). The resulting mixture was warmed to 22 °C over 30 min, after which time it was transferred to a 60-mL separatory funnel. At this point, EtOAc (15 mL), and a saturated aqueous solution of NaCl (10 mL) were transferred to the separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with H_2O (2 × 10 mL), dried ($MgSO_4$), filtered, and the volatiles were removed in vacuo. The resulting colorless residue was purified by silica gel chromatography (1:1 EtOAc:hexanes) to deliver **4.5** as colorless oil (0.258 mg, 0.850 mmol, 97%). IR (neat): 3446 (br), 2943 (m), 2867 (m), 1659 (s), 1413 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.20 (m, 5H), 6.52 (d, J = 16.0 Hz, 1H), 6.19 (dd, J = 16.0, 6.8 Hz, 1H), 5.00–4.92 (br, 1H), 4.52–4.44 (m, 1H), 4.28–4.14 (m, 2H), 3.62–3.42 (m, 2H), 1.98–1.55 (m, 8H), 1.25 (t, J = 9.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 136.8, 130.8, 130.1, 128.6, 127.6, 126.2, 61.9, 60.4, 58.8, 51.1, 46.7, 37.1, 29.4, 28.3, 21.0, 14.8, 14.7, 14.2. HRMS EI (*m/z*) Calcd for $C_{18}H_{25}NO_3$ 303.1834 $(M)^+$, Found 303.1833.

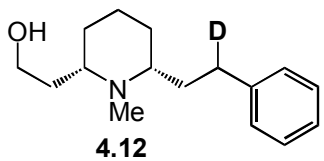


4.3

Synthesis of piperidine **4.3**. A 25-mL round-bottom flask was charged with **4.5** (317 mg, 1.05 mmol), CH_2Cl_2 (10.5 mL), NaOAc (85.0 mg, 1.05 mmol, 1

(93) For the characterization data of piperidine **4.4** please see the experimental section of Ch 3.

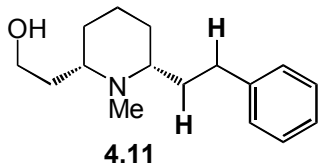
equiv.), powdered 4Å molecular sieves (15.9 mg, 5 wt. %), PCC (339 mg 1.58 mmol, 1.5 equiv.), and the mixture was allowed to stir for 2 h. To the reaction mixture was added Et_2O (5.0 mL), and resulting mixture was allowed to stir for 15 min. At this time, the mixture was filtered through Florisil® by vacuum filtration, eluted with EtOAc, and the filtrate was collected in a 25-mL round-bottom flask. The volatiles were removed in vacuo. The resulting slightly yellow residue was dissolved in *t*-BuOH (5.3 mL), and tetramethylethylene (936 μL, 7.88 mmol, 7.5 equiv.). To this solution was added a solution of $NaClO_2$ (712 mg, 7.88 mmol, 7.5 equiv.), and NaH_2PO_4 (942 mg, 6.83 mmol, 6.5 equiv.) dissolved in H_2O (5.3 mL). The reaction mixture was allowed to stir for 1 h, after which time the volatiles were removed in vacuo. To this mixture was added EtOAc (10 mL), H_2O (10 mL), the mixture was transferred to a 60-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with a saturated aqueous solution of NaCl (10 mL), H_2O (10 mL), dried (Na_2SO_4), filtered, and concentrated to yellow oil. This oil was dissolved in minimal EtOAc, transferred to a 25-mL round-bottom flask, and re-concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10.5 mL). To this solution was added Et_3N (295 μL, 2.10 mmol, 2 equiv.), EDC (301 mg, 1.58 mmol, 1.5 equiv.), HOBt (241 mg, 1.58 mmol, 1.5 equiv.), *N*,*O*-dimethylhydroxylamine hydrochloride (154 mg, 1.58 mmol, 1.5 equiv.), and the mixture was allowed to stir for 2 h. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL), the mixture was transferred to a 60-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with H_2O (2 x 10 mL), dried (Na_2SO_4), and the volatiles were removed in vacuo. The resulting yellow residue was purified through silica gel chromatography (1:1 EtOAc:hexanes) to furnish **4.3** as colorless oil (295 mg, 0.819 mmol, 78% over three steps). IR (neat): 2936 (s), 1690 (s), 1407 (m), 1312 (m), 1268 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.22 (m, 5H), 6.53 (d, J = 16.4 Hz, 1H), 6.32 (dd, J = 16.4, 5.2 Hz, 1H), 5.01 (br, 1H), 4.78 (br, 1H), 4.24–4.10 (m, 2H), 3.52 (s, 3H), 3.13 (s, 3H), 2.96–2.84 (m, 1H), 2.55 (dd, J = 14.8, 3.6 Hz, 1H), 2.05–2.0 (m, 1H), 1.82–1.60 (m, 5H), 1.30–1.22 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 137.5, 137.2, 131.4, 130.1, 128.7, 127.6, 126.3, 61.5, 61.3, 60.5, 50.8, 47.5, 36.1, 32.2, 27.8, 21.2, 14.9, 14.6, 14.3. HRMS EI (*m/z*) mass Calcd for $C_{20}H_{28}N_2O_4Na$ 383.1947 $(M+Na)^+$, Found 383.1928.



4.12

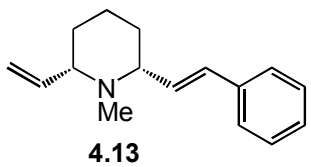
Synthesis of piperidine **4.12**. In a N_2-filled glovebox, a 4-mL vial was charged with piperidine **4.5** (15.0 mg, 0.0494 mmol), THF (0.500 mL), and lithium aluminum hydride (6.0 mg,

0.099 mmol, 2 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and the reaction mixture was allowed to stir for 1 h. At this point, the reaction mixture was cooled to 22 °C over 15 min, the vial was removed from the glovebox, and the reaction was quenched by the slow addition of MeOD[94] (0.500 mL). The resulting mixture was allowed to stir for 12 h. To this mixture was (slowly and sequentially) added H_2O (15.0 μL, 1 μL/mg of **4.5**), a 3.8 M solution of NaOH (45.0 μL, 3 μL/mg of **4.5**), and H_2O (15.0 μL, 1 μL/mg of **4.5**). The resulting mixture was subjected to vacuum filtration (to remove Al salts), and eluted with EtOAc. The filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting colorless residue was purified by neutral alumina gel chromatography (20:1 CH_2Cl_2:MeOH) to provide piperidine **4.12** as colorless oil (11.8 mg, 0.0475 mmol, 95%). IR (neat): 3371 (br), 2930 (s), 2855 (m), 1055 (w). ^{1}H NMR (400 MHz, C_6D_6): δ 7.20–7.10 (m, 5H), 3.92 (ddd, *J* = 10.4, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.52–2.42 (m, 2H), 2.30–2.20 (m, 1H), 2.02 (s, 3H), 1.59–0.86 (m, 8H). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.30–7.18 (m, 5H), 3.92 (ddd, *J* = 10.8, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.82–2.76 (m, 1H), 2.62–2.50 (m, 2H), 2.27 (s, 3H), 1.82–1.24 (m, 8H). ^{13}C NMR (100 MHz, C_6D_6): δ 143.0, 129.0, 128.9, 126.3, 64.4, 62.9, 62.5, 36.3, 33.9, 32.1, 31.9, 31.7, 30.0, 26.2, 26.0, 25.4. HRMS EI (*m/z*) Calcd for $C_{16}H_{25}DNO$ 249.2077 $(M+H)^+$, Found 249.2015. ^{2}H NMR (400 MHz, $CDCl_3$): δ 2.50–2.40 (br s).



4.11

Synthesis of piperidine **4.11**. The procedure to synthesize piperidine **4.11** was identical to that used for the synthesis of **4.12**, however, MeOH was used to quench the reaction mixture. IR (neat): 3390 (br), 2930 (s), 2855 (m), 1457 (w), 1055 (w). ^{1}H NMR (400 MHz, C_6D_6): δ 7.30–7.18 (m, 5H), 3.92 (ddd, *J* = 10.8, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.62–2.50 (m, 3H), 2.31–2.25 (m, 1H), 2.00 (s, 3H), 1.70–1.60 (m, 1H), 1.59–1.21 (m, 5H), 1.17–0.80 (m, 4H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.25 (m, 3H), 7.20–7.14 (m, 2H), 3.92 (ddd, *J* = 10.4, 5.2, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.84–2.76 (br, 1H), 2.68–2.55 (m, 3H), 2.02 (s, 3H), 1.85–1.72 (m, 3H), 1.70–1.60 (m, 3H), 1.58–1.40 (m, 3H), 1.30–1.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_6$): δ 142.6, 128.5, 125.8, 64.6, 63.2, 62.6, 36.1, 32.6, 32.0, 26.0, 25.7, 24.9. HRMS EI (*m/z*) Calcd for $C_{16}H_{26}NO$ 248.2014 $(M+H)^+$, Found 248.2015.



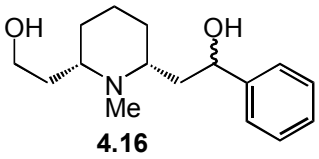
4.13

Synthesis of piperidine **4.13**. The procedure to synthesize piperidine **4.13** was identical to that used for the synthesis of **4.12**, however, MeOH was used to quench the reaction mixture.

(94) Deuterated methanol was taken from a freshly opened ampule of 99.95 atom % D.

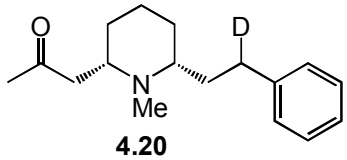
IR (neat): 2930 (s), 2848 (m) 2773 (s), 1445 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.82–5.73 (m, 1H), 5.15 (dd, *J* = 17.6, 2.0 Hz, 1H), 5.03 (dd, *J* = 10.4, 1.6 Hz, 1H), 2.60–2.54 (m, 1H), 2.47–2.42 (m, 1H), 2.21 (s, 3H), 1.80–1.42 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 137.4, 134.3, 130.5, 128.8, 127.5, 126.4, 115.5, 69.4, 68.5, 42.3, 33.9, 33.8, 24.0. HRMS EI (*m/z*) Calcd for $C_{16}H_{21}N$ 227.1674 $(M)^+$, Found 227.1679.

Synthesis of piperidine **4.15**. The procedure to synthesize piperidine **4.15** was identical to that used for the synthesis of **4.12**, however, MeOH was used to quench the reaction mixture.



4.16

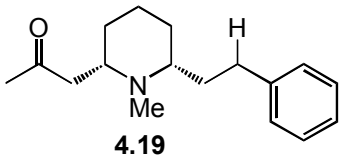
Synthesis of piperidine **4.16**. In a N_2-filled glovebox, a 4-mL vial was charged with piperidine **4.5** (40.0 mg, 0.130 mmol), THF (1.30 mL), and lithium aluminum hydride (10.0 mg, 0.260 mmol, 2 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and the mixture was allowed to stir for 1 h. At this moment, the reaction mixture was cooled to 22 °C over 15 min, the vial was removed from the glovebox, and O_2 (balloon passed through drying tube filled with P_2O_5) was bubbled through the reaction mixture for 1 h. To this mixture were slowly and sequentially added H_2O (40.0 μL, 1 μL/mg of **4.5**), a 3.8 M solution of NaOH (0.120 mL, 3 μL/mg of **4.5**), and H_2O (40.0 μL, 1 μL/mg of **4.5**). The resulting mixture was subjected to vacuum filtration (to remove Al salts), and eluted with EtOAc. The filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting colorless residue was purified by neutral alumina gel chromatography (10:1 CH_2Cl_2:MeOH) to provide piperidine **4.16** as colorless oil (18.8 mg, 0.0715 mmol, 55%). IR (neat): 3370 (br), 2930 (s), 2855 (m), 1451 (w), 1055 (w). Isolated as a 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.39–7.23 (m, 5H), 5.00 (dd, *J* = 6.0, 6.0 Hz, 0.5H), 4.92 (dd, *J* = 10.0, 3.6 Hz, 0.5H), 3.82–3.64 (m, 2H), 3.14–3.00 (m, 1H), 2.84–2.60 (m, 1H), 2.34 (s, 1.5H), 2.28 (s, 1.5H), 2.00–1.20 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 145.4, 128.8, 127.6, 127.4, 126.2, 126.0, 75.6, 72.2, 64.1, 63.2, 62.9, 62.6, 61.6, 61.3, 61.0, 60.9, 41.0, 40.8, 35.8, 35.4, 32.8, 30.3, 30.2, 26.7, 25.4, 25.3, 25.0, 24.2, 24.0. HRMS EI (*m/z*) mass Calcd for $C_{16}H_{25}NO_2$ 263.1885 $(M)^+$, Found 263.1883.



4.20

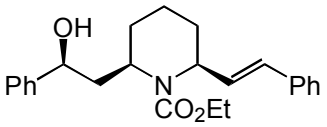
Synthesis of piperidine **4.20**. A 4-mL vial was charged with **4.3** (20.0 mg, 0.0555 mmol), and THF (555 μL). Methylmagnesium chloride (a 2.40 M solution in THF, 25.4 μL, 0.0610 mmol, 1.1 equiv.) was added to this solution by

syringe, and the mixture was allowed to stir for 30 min. At this time, the vial was relocated into a N_2-filled glovebox. To this mixture was added lithium aluminum hydride (2.1 mg, 0.055 mmol, 1 equiv.), the vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and allowed to stir for 1 h. At this point, the mixture was cooled to 22 °C over 15 min, the vial was removed from the glovebox, and the reaction was quenched by the slow addition of MeOD[5] (500 μL). The resulting mixture was allowed to stir for 12 h. To this mixture were slowly and sequentially added H_2O (20 μL, 1 μL/mg of **4.3**), a 3.8 M solution of NaOH (60 μL, 3 μL/mg of **4.3**), and H_2O (20 μL, 1 μL/mg of **4.3**). The mixture was filtered under vacuum (to remove Al salts), and eluted with EtOAc. The resulting filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting yellow residue was purified by neutral alumina gel chromatography (20:1 CH_2Cl_2:MeOH) to provide piperidine **4.20** as colorless oil (10.8 mg, 0.0415 mmol, 75%).[95] IR (neat): 2930 (s), 2855 (s), 1709 (s), 1451 (m). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.30–7.17 (m, 5H), 2.70–2.40 (m, 4H), 2.32 (s, 3H), 2.15 (s, 3H), 1.80–1.25 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 133.6, 128.6, 128.5, 128.4, 125.9, 62.8, 59.6, 56.2, 55.0, 52.5, 50.5, 38.9, 38.1, 36.0, 32.3, 32.2, 31.8, 29.8, 27.4, 26.9, 24.7, 24.6, 19.7. HRMS EI (*m/z*) mass Calcd for $C_{17}H_{24}NOD$ 260.2018 $(M)^+$, Found 260.2014. ^{2}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s), 2.14 (s).

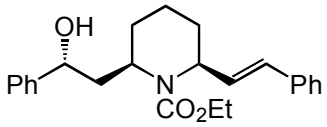


4.19

Piperidine **4.19**.[92] IR (neat): 2923 (s), 2855 (s), 1709 (s), 1602 (m), 1451 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.22 (m, 2H), 7.20–7.15 (m, 3H) 2.70–2.40 (m, 4H), 2.34 (s, 3H), 2.20 (s, 3H), 2.16 (d, J = 7.2 Hz, 2H), 1.80–1.25 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 129.1, 128.9, 128.8, 126.7, 57.4, 54.1, 47.5, 36.8, 32.1, 30.8, 30.1, 29.8, 23.8, 23.6. HRMS EI (*m/z*) mass Calcd for $C_{17}H_{25}NO$ 259.1936 $(M)^+$, Found 259.1935.



4.21

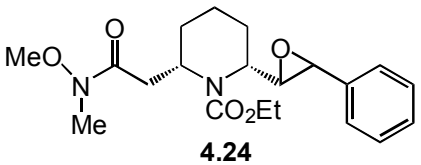


4.22

Synthesis of piperidines **4.21 and 4.22**. In a N_2-filled glovebox, diphenylzinc (22.0 mg, 0.0990 mmol, 3 equiv.) was added to a solution of the aldehyde derived from **4.5** (10.0 mg, 0.0330 mmol, 1 equiv.) in Et_2O (0.400 mL) and the reaction mixture was allowed to stir for 18 h. At this time, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2 mL) and diluted with Et_2O (2 mL), the mixture was transferred to a 30-mL separatory funnel, and the

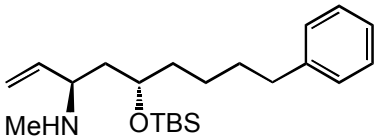
(95) This compound exists as a mixture of 2,6-*syn* and *anti* isomers, resulting in ^{13}C NMR spectra that does not appear clean, see ref. 85 of this Chapter.

resulting biphasic layers were separated. The organic layer was washed with H_2O (2 x 10 mL), dried (Na_2SO_4), and the volatiles were removed in vacuo. The resulting colorless residue was purified through silica gel chromatography (1:5 EtOAc:hexanes) to furnish **4.21** as colorless oil (5.0 mg, 0.013 mmol, 40%, TLC R_f = 0.35) and **4.22** as colorless oil (5.0 mg, 0.013 mmol, 40%, TLC R_f = 0.2). ^{1}H NMR of **4.21** (400 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 7.13–7.09 (m, 5H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.38 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.08–4.26 (m, 3H), 4.24–4.18 (m, 2H), 2.20 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.00–1.90 (m, 1H), 1.84–1.70 (m, 2H), 1.66–1.1.50 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.90–0.78 (m, 2H). ^{1}H NMR of **4.22** (400 MHz, $CDCl_3$): δ 7.36–7.21 (m, 10H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 7.2 Hz, 1H), 4.96–4.86 (m, 1H), 4.70–4.64 (m, 1H), 4.46–4.40 (m, 1H), 4.25–4.13 (m, 2H), 2.26–1.90 (m, 2H), 1.80–1.70 (m, 2H), 1.60–1.54 (m, 2H), 1.34–1.22 (m, 3H), 0.90–0.80 (m, 2H).



4.24

Synthesis of epoxide **4.24**. A 5-mL round-bottom flask was charged with piperidine 4.3 (27.0 mg, 0.0750 mmol, 1 equiv.), CH_2Cl_2 (0.750 mL), and the reaction vessel was cooled to 0 °C in an ice-bath. To this mixture was slowly added *m*-chloroperbenzoic acid (20.0 mg, 0.110 mmol, 1.5 equiv.). At this point the flask was removed from the ice-bath, the reaction mixture was allowed to stir at 22 °C for 2 h after which time it was transferred to a 30-mL separatory funnel. At this time H_2O (5 mL) and CH_2Cl_2 (5 mL), was transferred to the separatory funnel and the resulting biphasic layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting colorless residue was purified through silica gel chromatography (2:3 EtOAc:hexanes) to deliver **4.24** as colorless oil (18.0 mg, 0.0478 mmol, 64%, mixture of *circa* 1:1 expoxide diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$):[96] δ 7.33–7.21 (m, 5H), 4.80–4.70 (m, 1H), 4.57–4.52 (m, 0.5H), 4.32–4.26 (m, 0.5H), 4.20–4.08 (m, 2H), 3.93 (s, 0.5H), 3.78 (s, 0.5H), 3.44 (s, 3H), 3.18–3.02 (m, 4H), 2.90–2.78 (m, 1H), 2.58–2.42 (m, 1H), 1.90–1.50 (m, 6H), 1.30–1.20 (m, 3H).

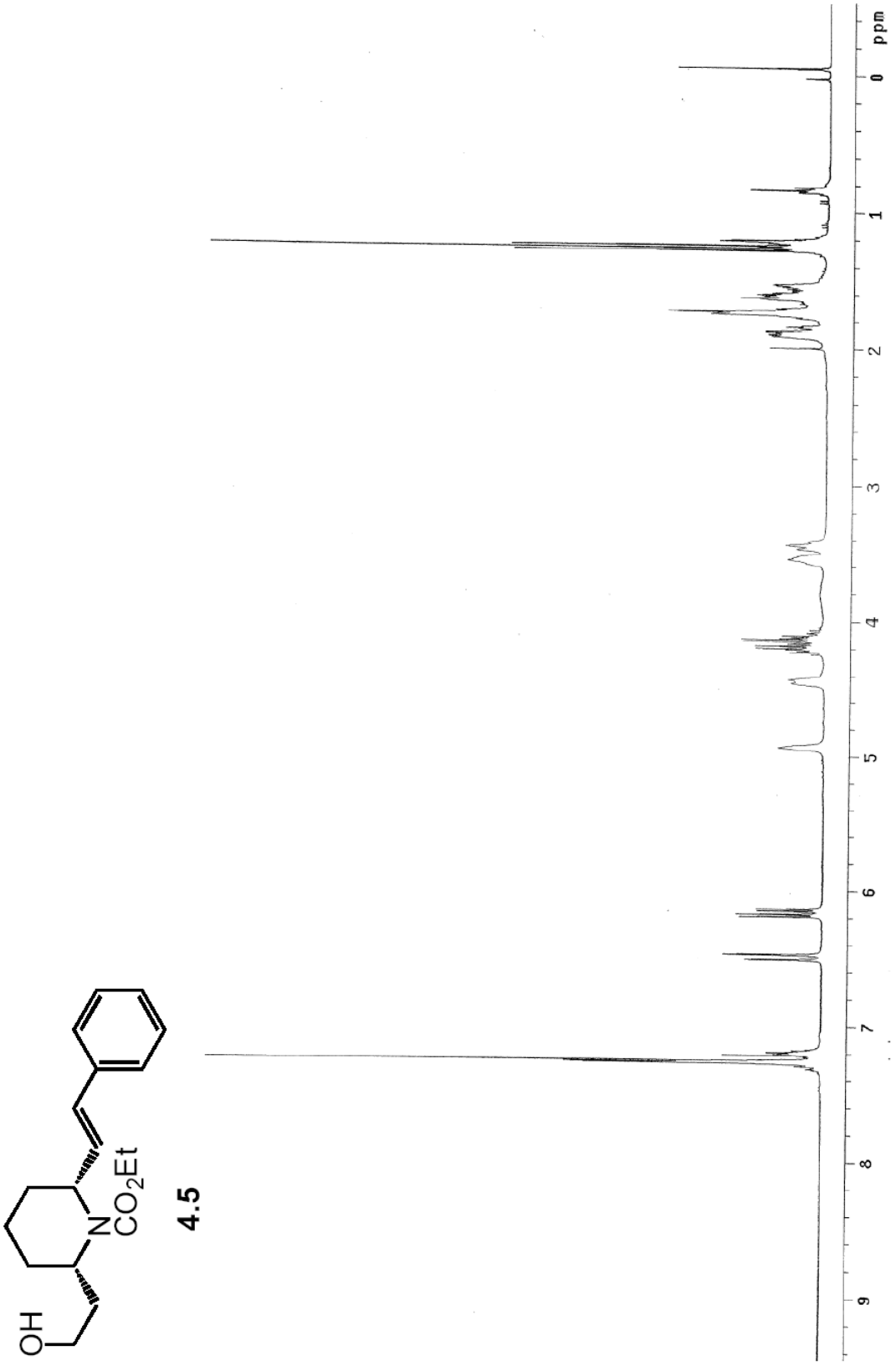


4.26

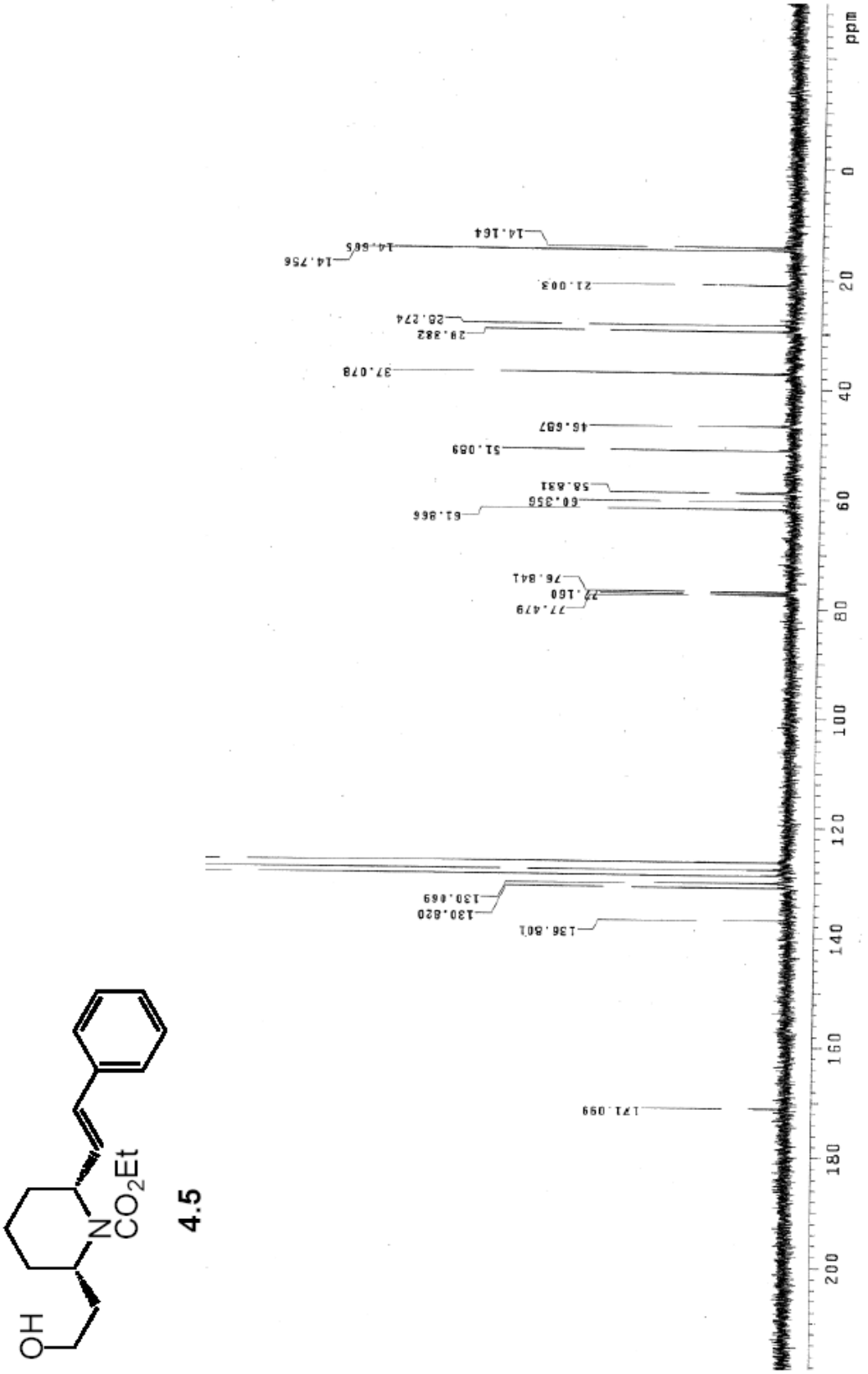
Synthesis of 1,3-aminoalcohol **4.26**. A 25-mL round-bottom flask was charged with Na (40.0 mg, 1.74 mmol, 48 equiv.), the flask was fitted with a cold-finger condenser, and the reaction vessel was cooled to –78 °C in a dry ice/acetone bath. Ammonia gas (*circa* 5 mL) was condensed into the flask; upon dissolution of Na in liquid ammonia the solution became deep blue in appearance. A

(96) The 1H NMR spectra shown contains residual EtOAc.

solution of piperidine **4.25** (13.0 mg, 0.0360 mmol, 1 equiv.) in *t*-BuOH (0.120 mL), and Et_2O (2.0 mL) was added to this solution by syringe. The reaction mixture was allowed to stir at –78 °C for 15 min, after which time the reaction was quenched by the addition of CH_2Cl_2 (10 mL), and the cold bath was removed. The resulting mixture was allowed to warm to 22 °C over 15 min, and then transferred to a 60-mL separatory funnel. At this instance, H_2O (10 mL) was transferred to the separatory funnel, and the resulting biphasic layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to deliver analytically pure amino alcohol **4.26** as yellow oil (11.0 mg, 0.0304 mmol, 85%). IR (neat): 2949 (s), 2924 (s), 2855 (m), 2773 (w), 1105 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.25 (m, 3H), 7.20–7.15 (m, 2H) 5.77 (ddd, *J* = 17.6, 10.4, 8.4 Hz, 1H), 5.12 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.04 (dd, *J* = 10.4, 0.8 Hz), 3.65–3.59 (m, 1H), 2.78–2.70 (m, 1H), 2.61–2.50 (m, 1H), 2.18 (s, 3H), 2.05–1.42 (m, 9H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5, 128.4, 125.9, 115.4, 69.3, 67.3, 66.0, 61.5, 42.0, 40.2, 38.5, 35.7, 31.3, 29.8, 26.0, 18.3, 15.4, –4.40. HRMS ES (*m/z*) mass Calcd for $C_{22}H_{37}NOSi$ 359.2644 $(M–H_2)^+$, Found 359.2647.



4.5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14.756
21.003
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29.382
37.078
46.687
51.089
58.831
60.356
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77.160
77.479
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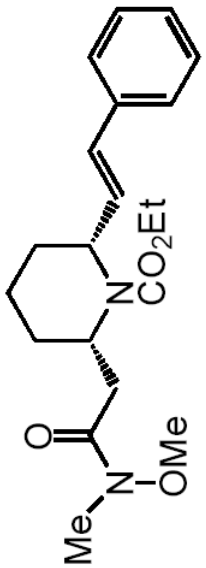
CO2Et

4.5



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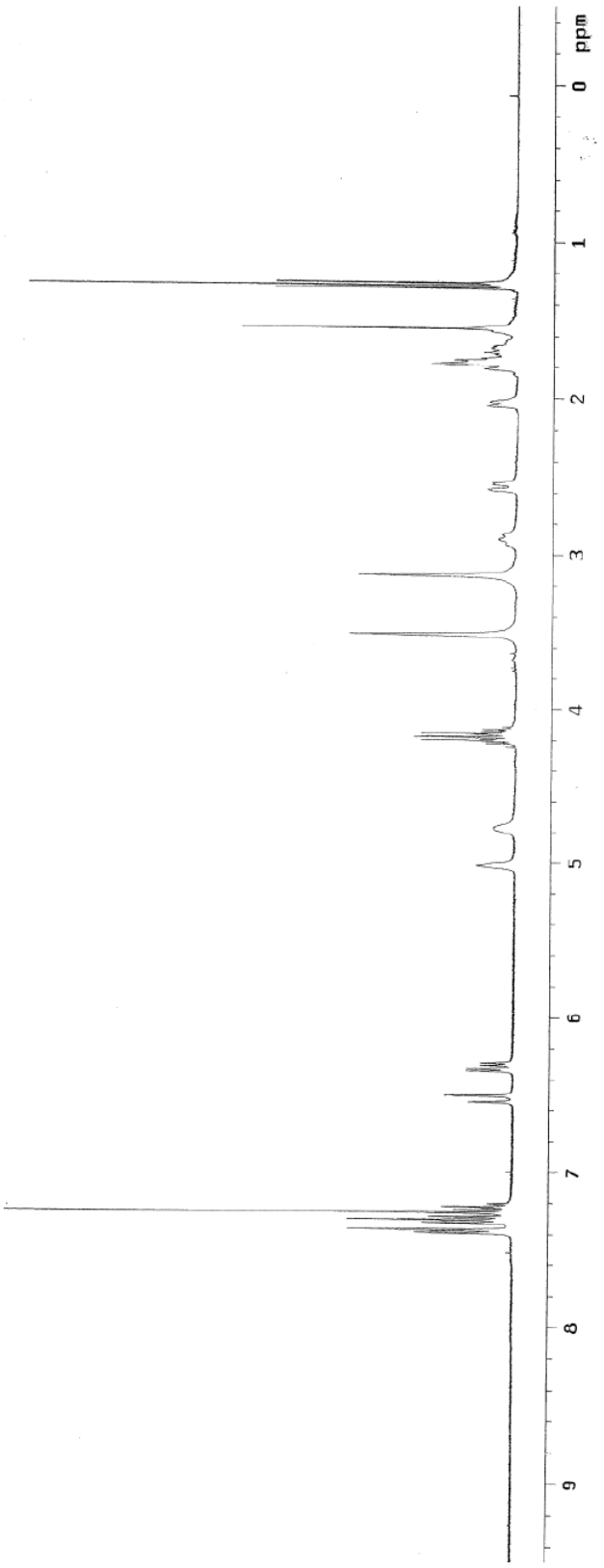

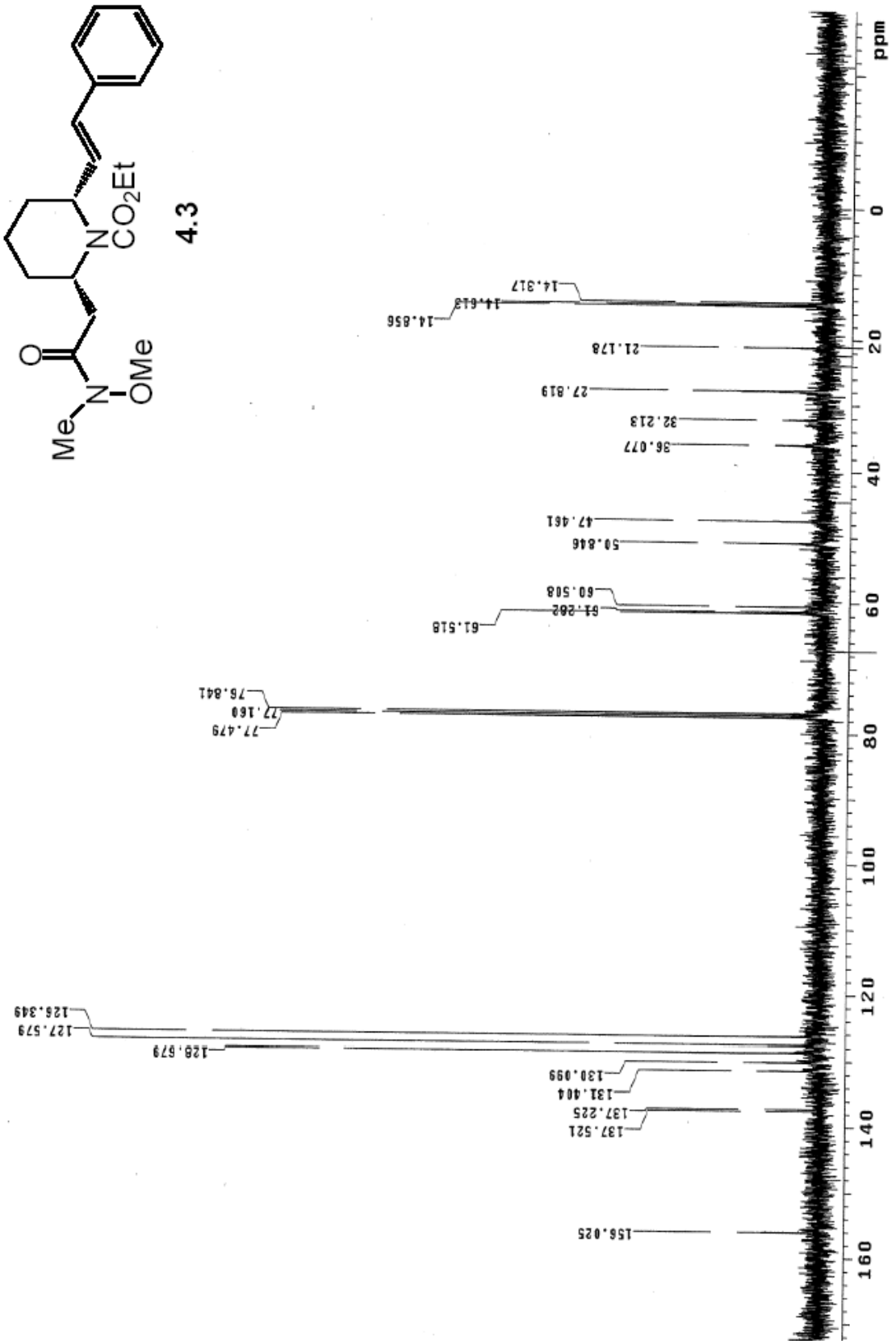
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32.213
36.077
47.461
50.846
60.508
61.262
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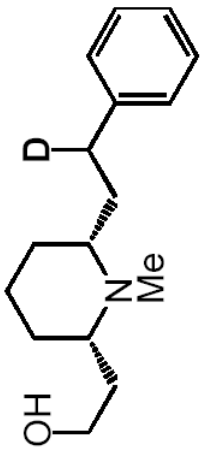

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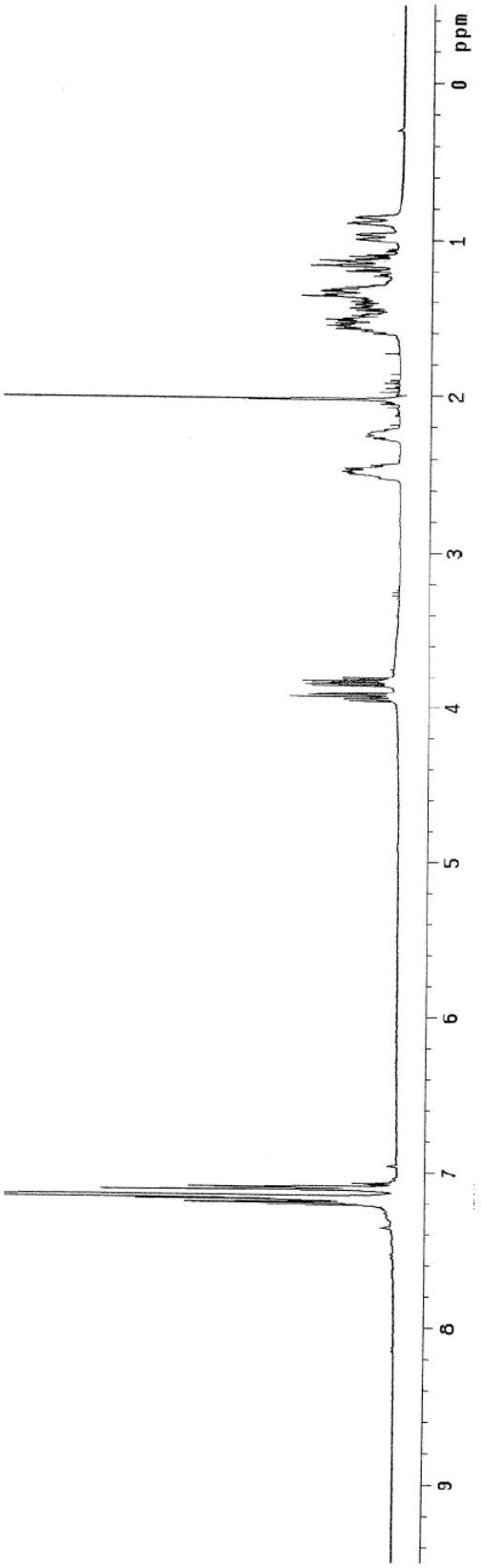

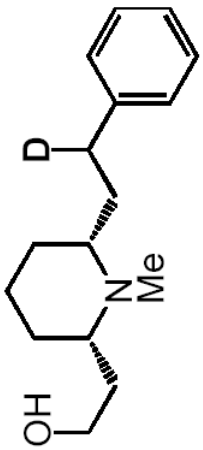

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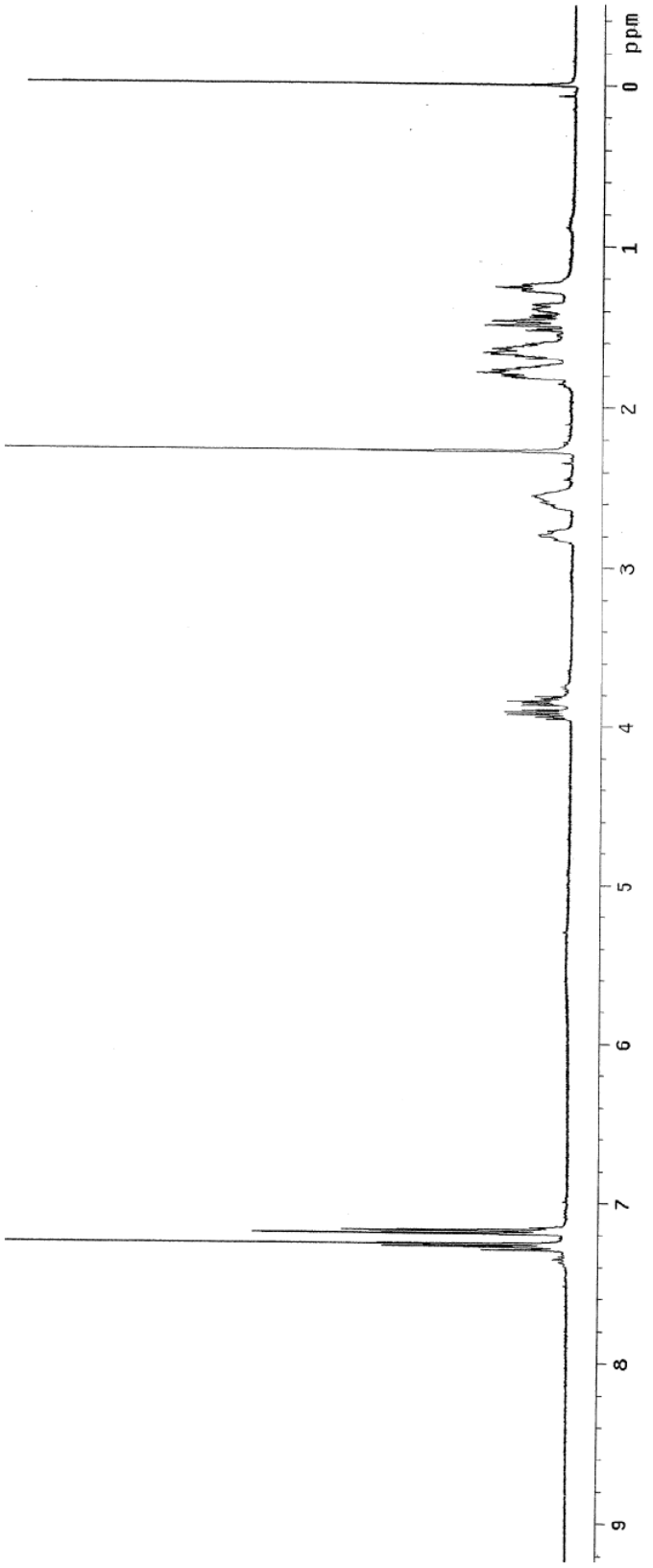

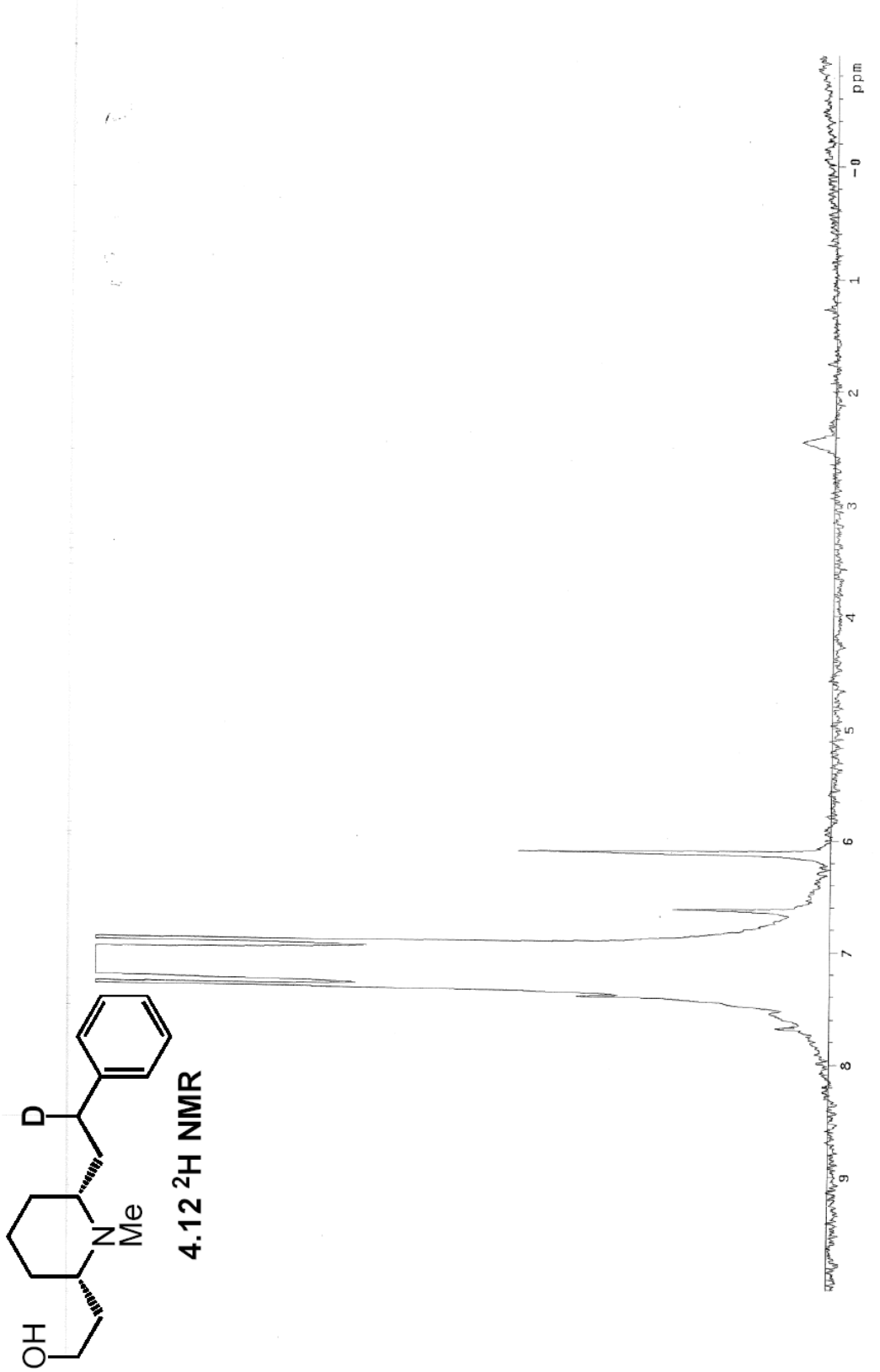

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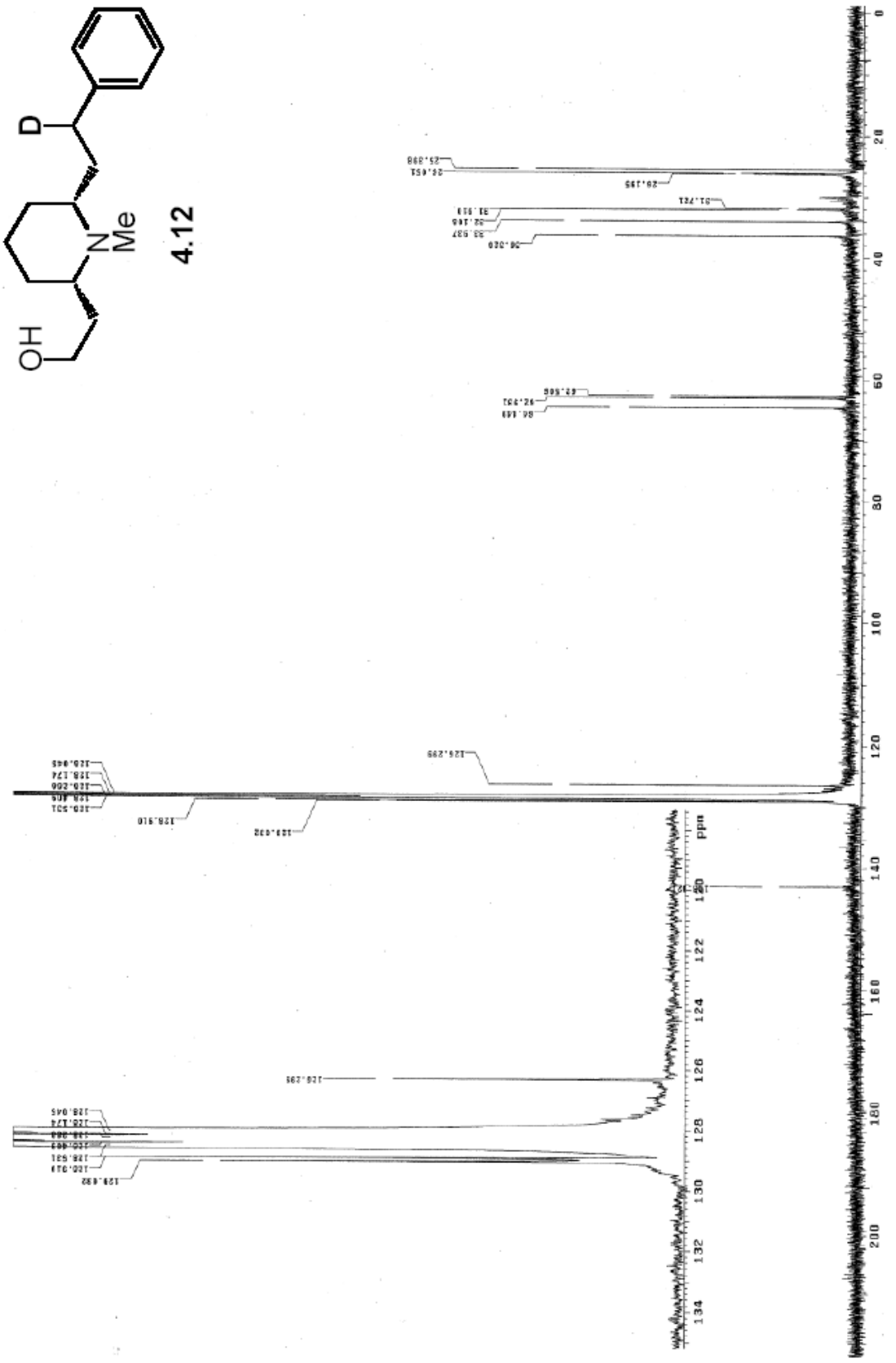
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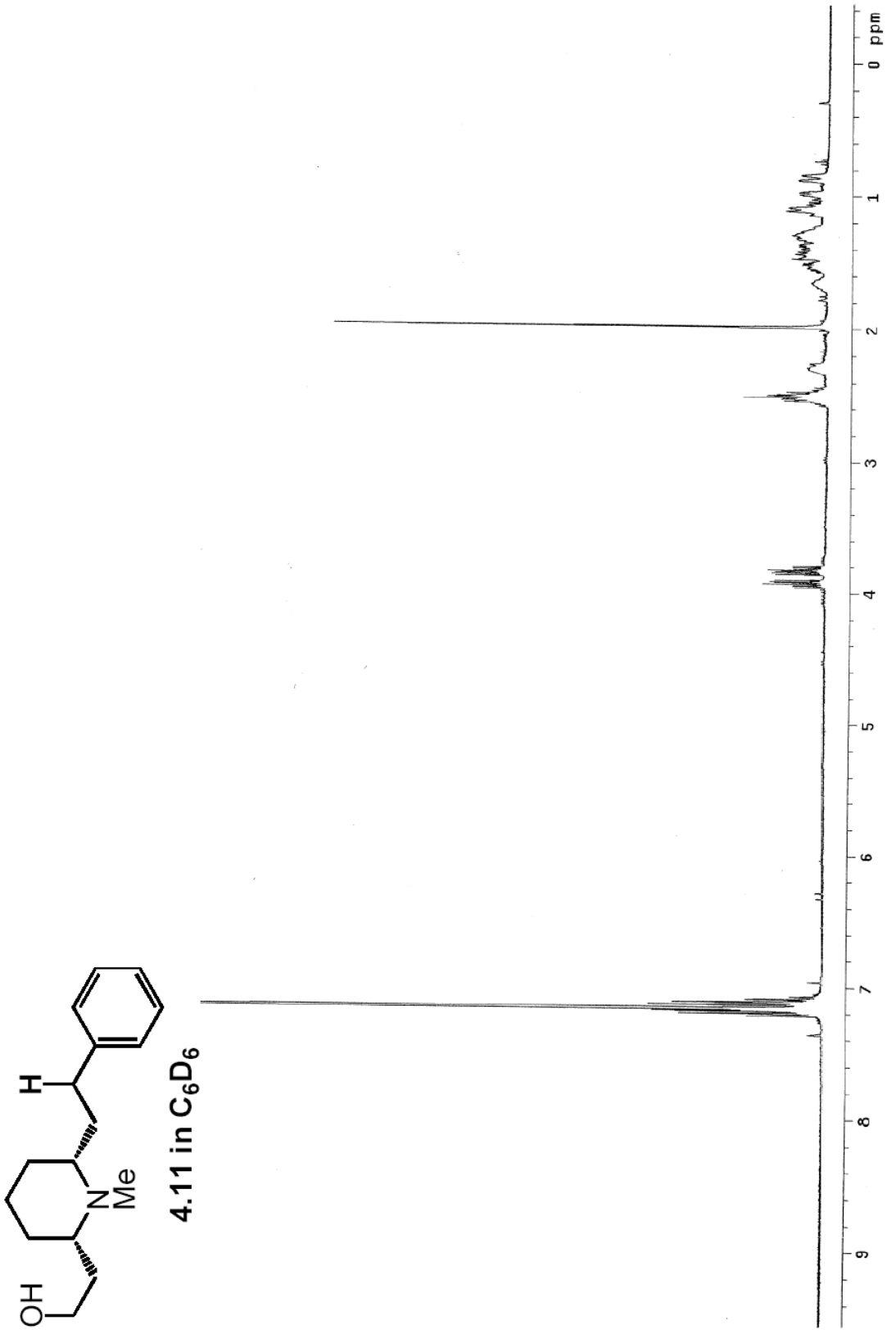
ppm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4.11 in C_6D_6
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6
5
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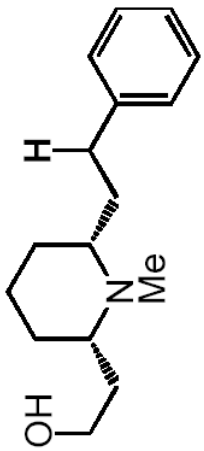

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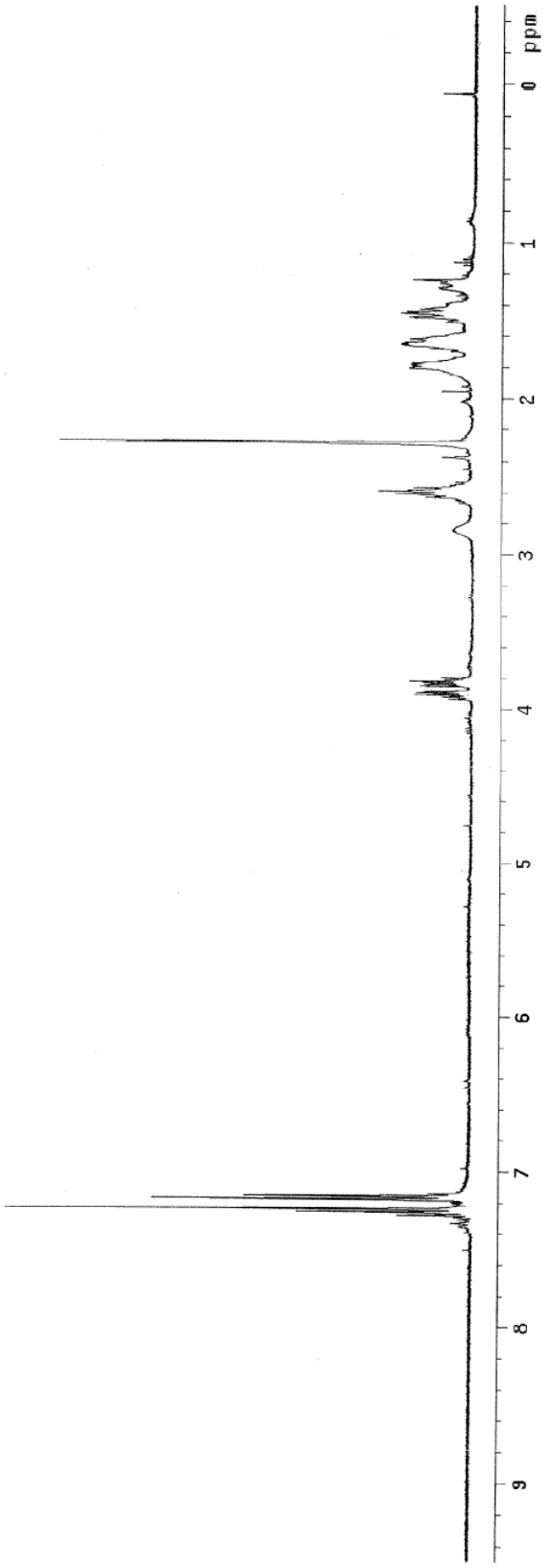

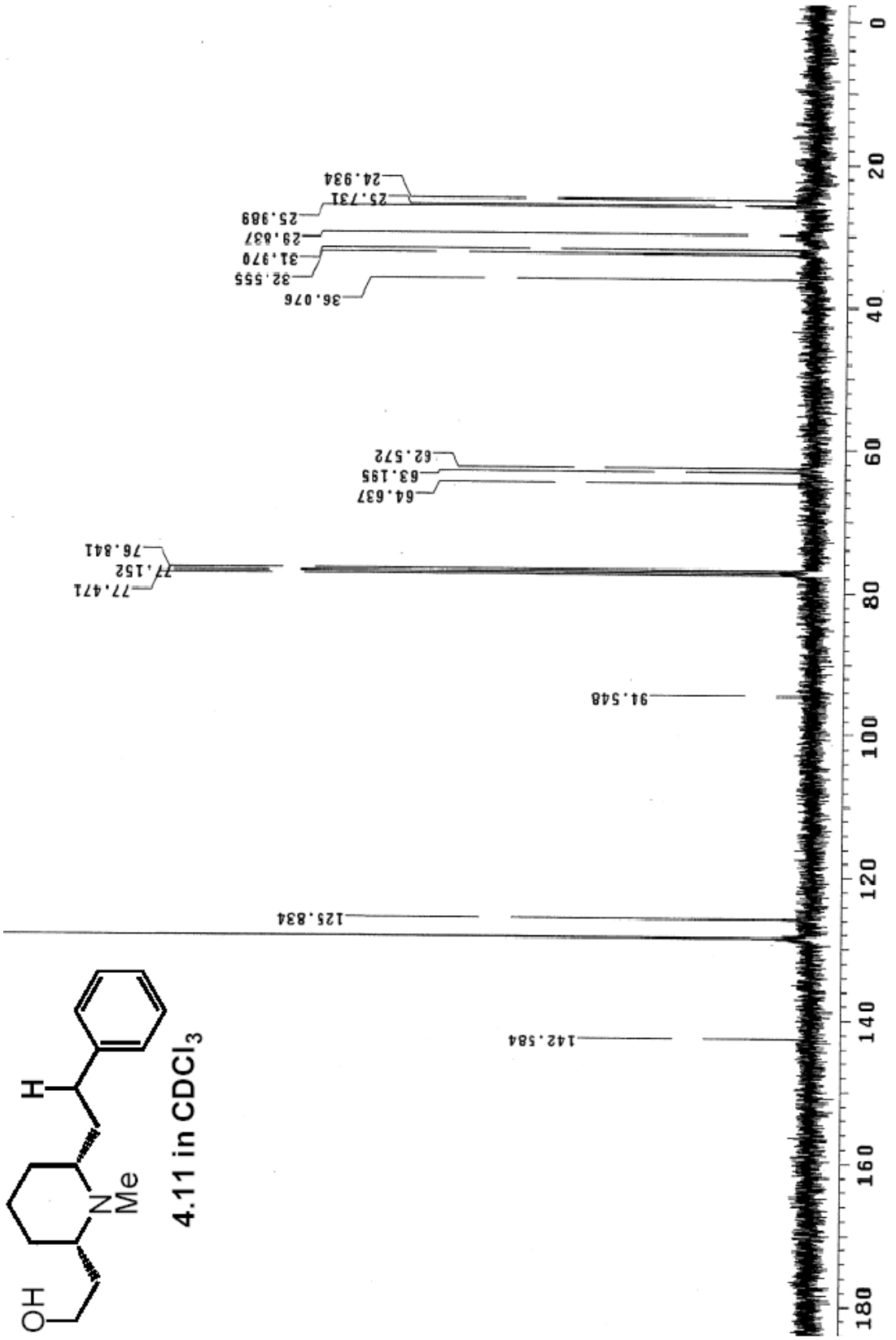
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25.989
25.731
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60
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140
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4.11 in $CDCl_3$
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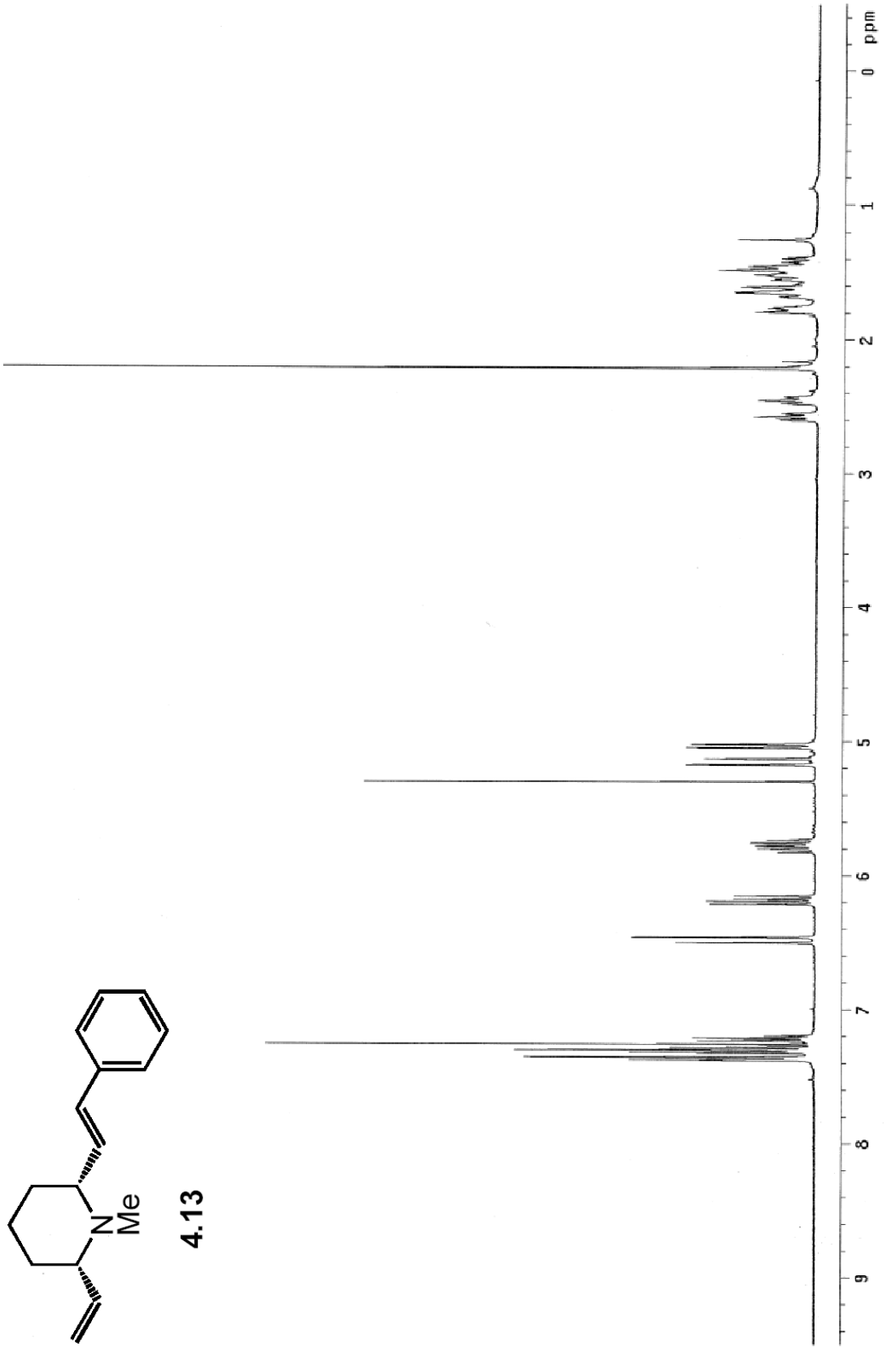
Me
H
OH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7
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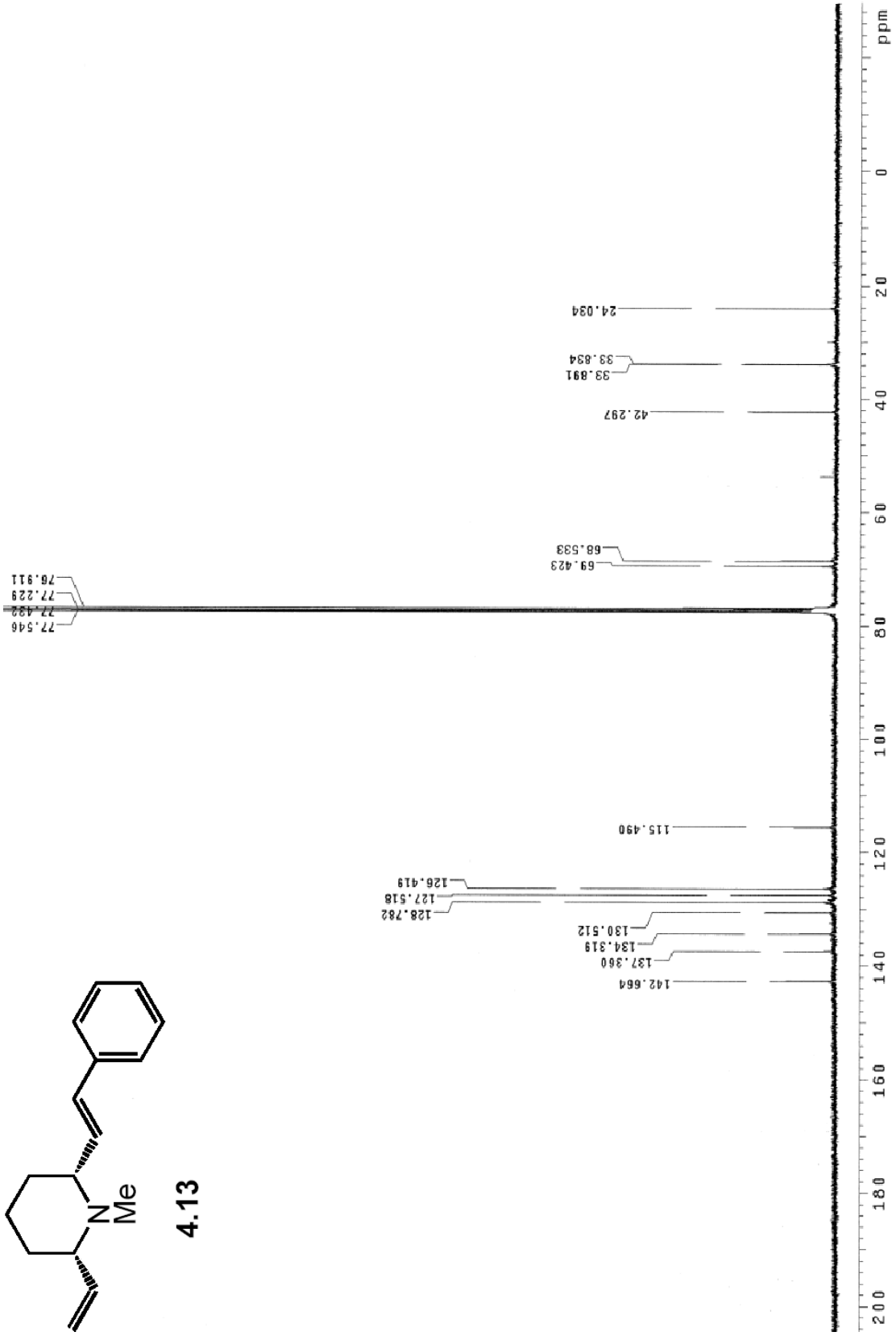
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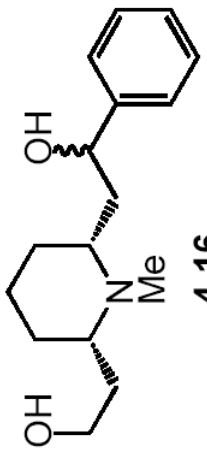
Me

4.13



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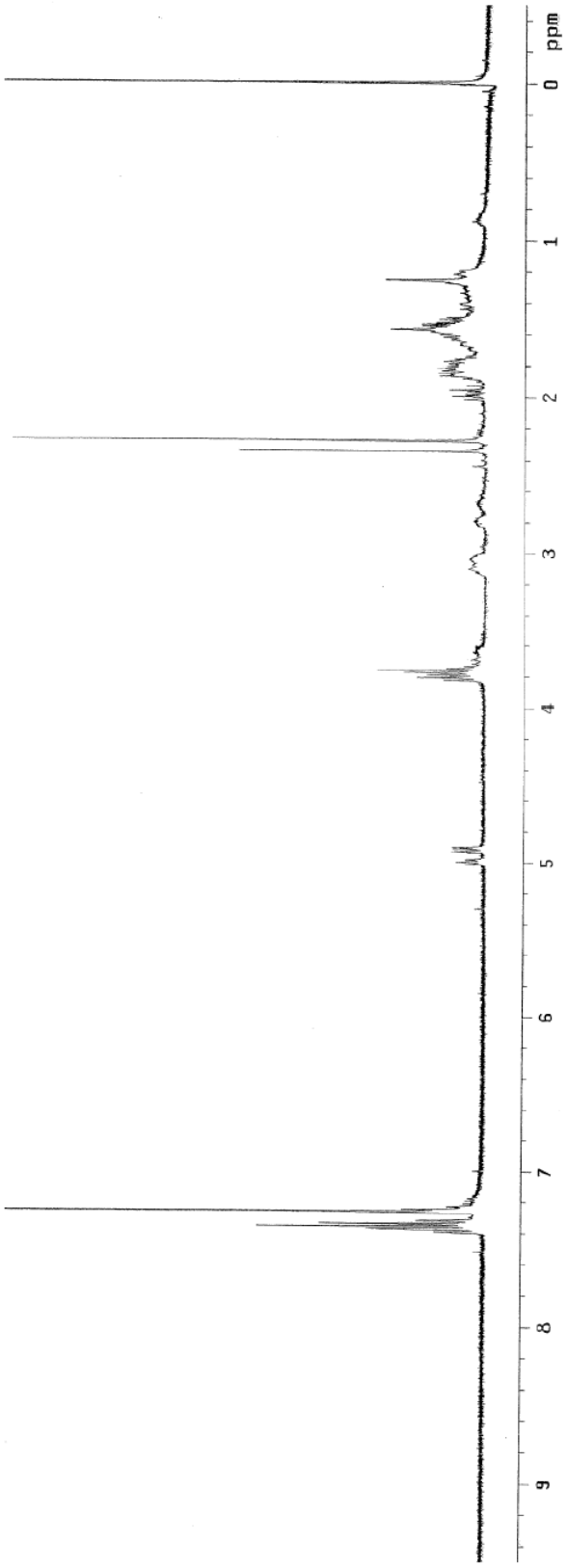

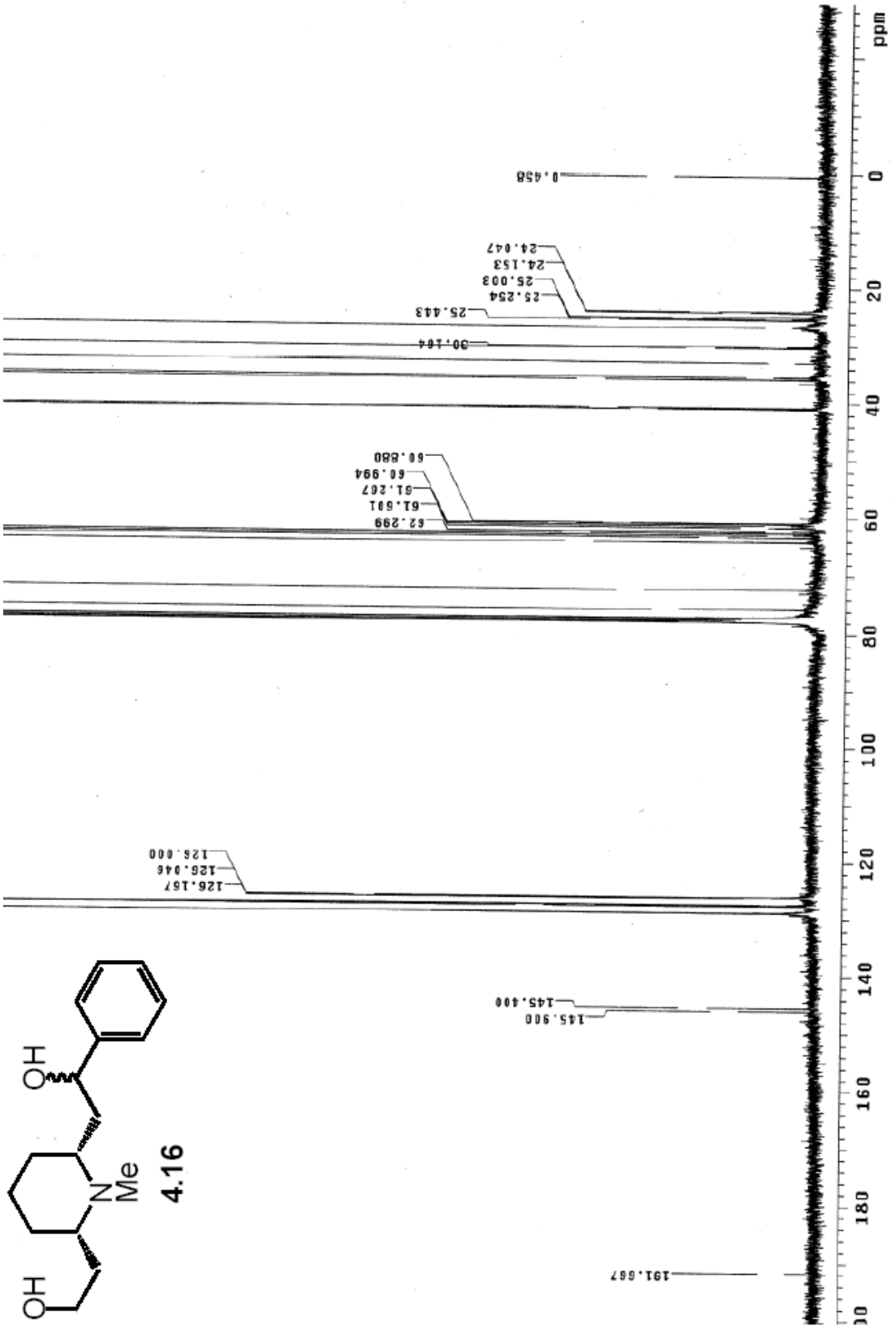
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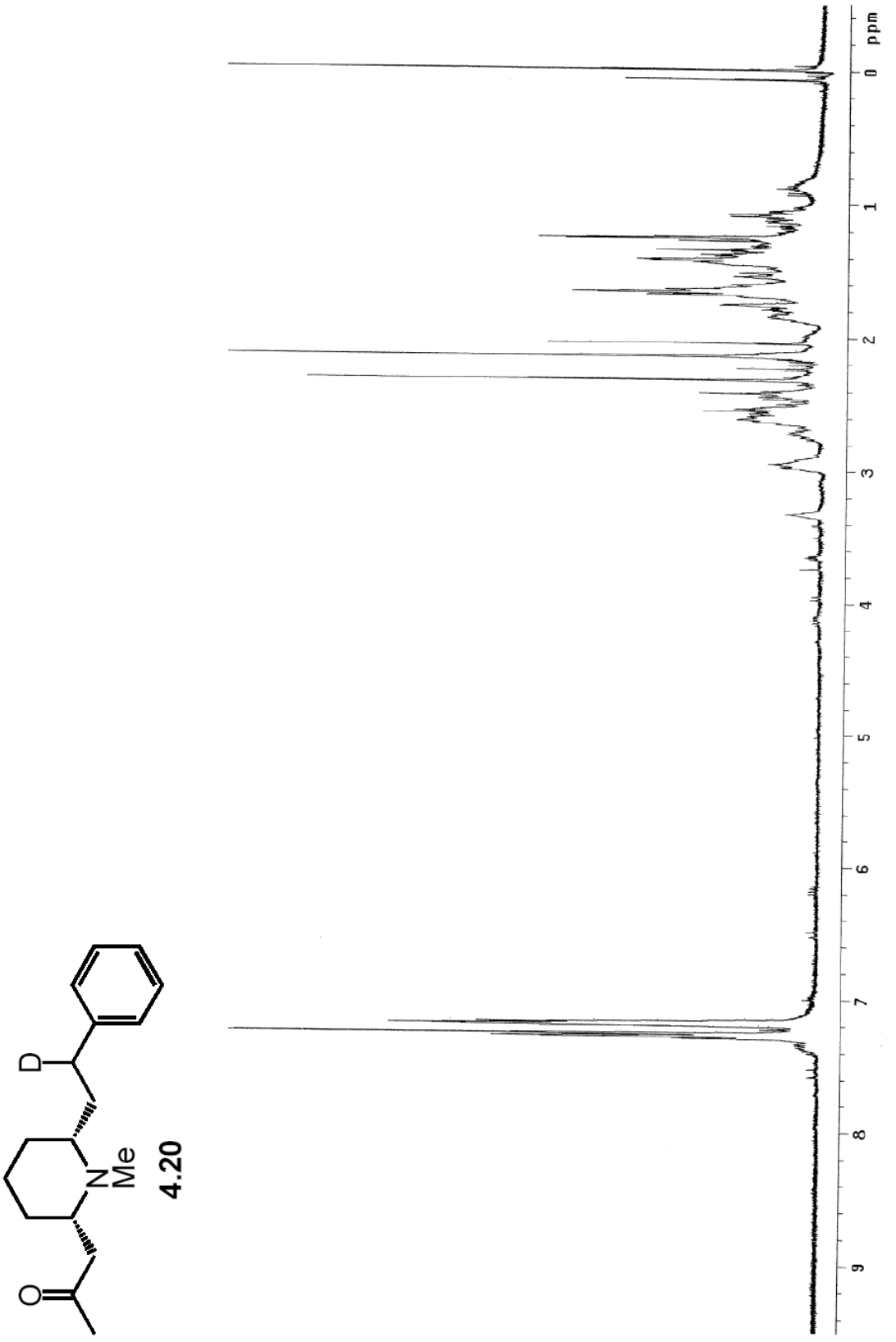

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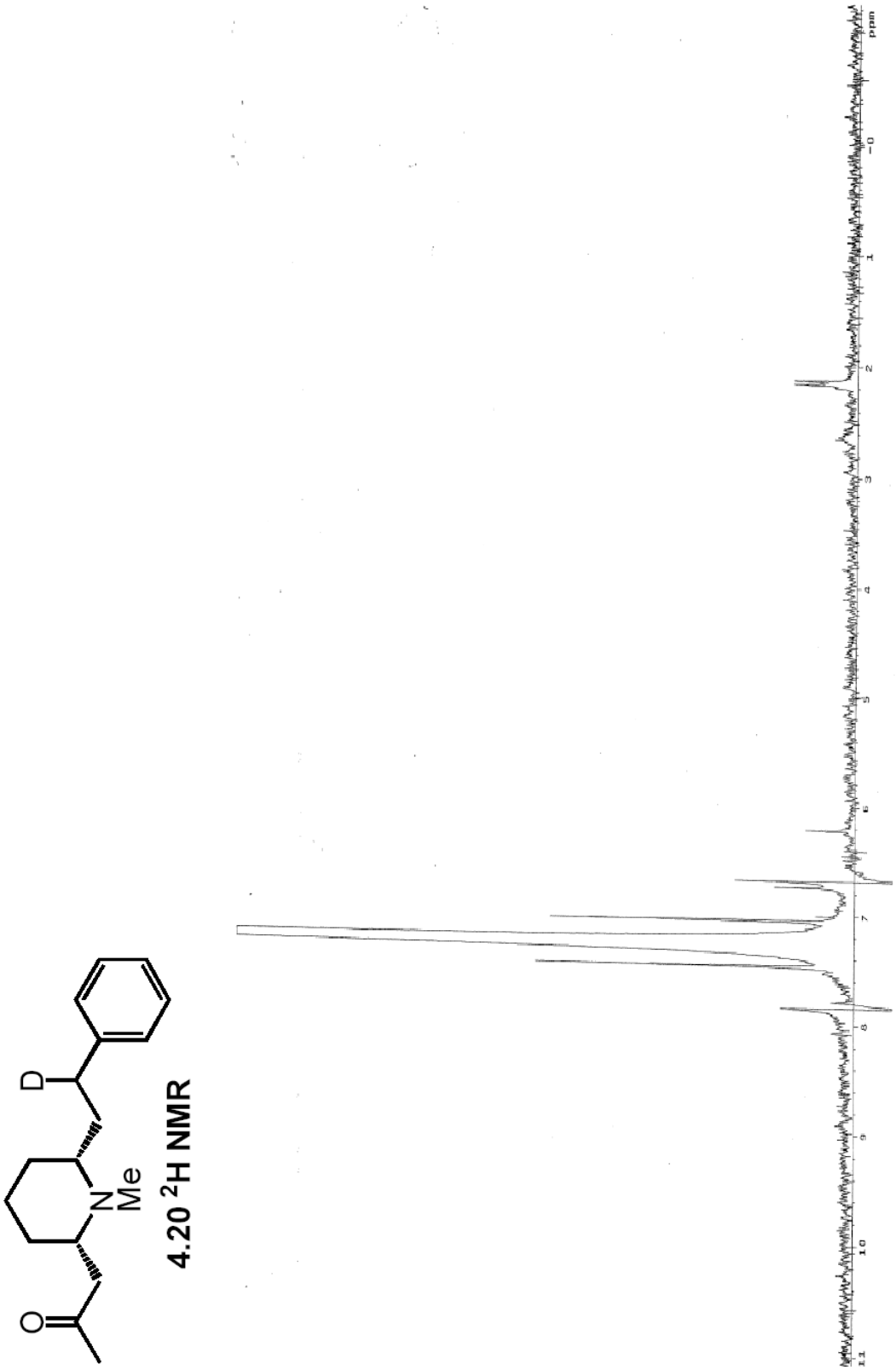

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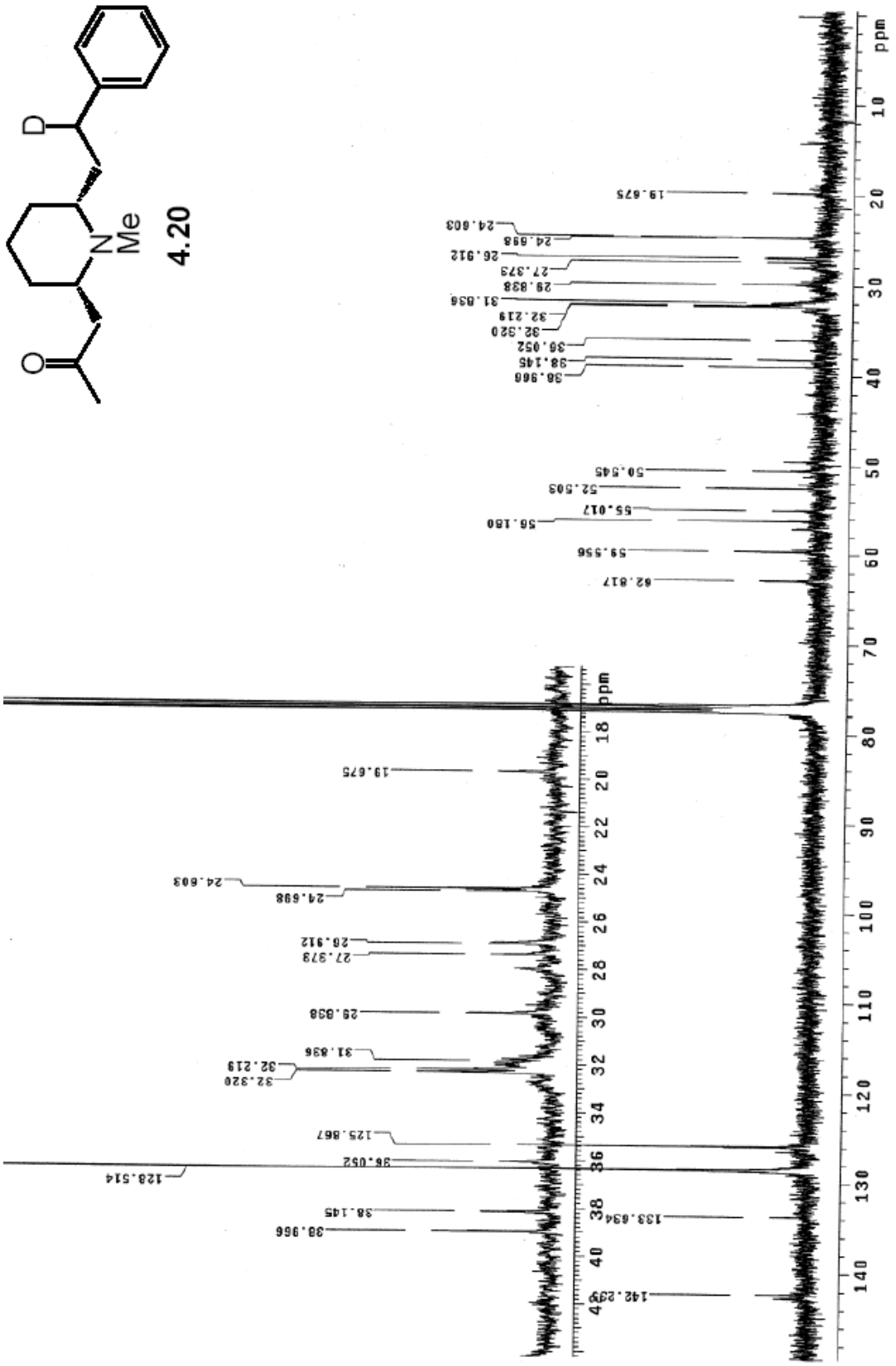
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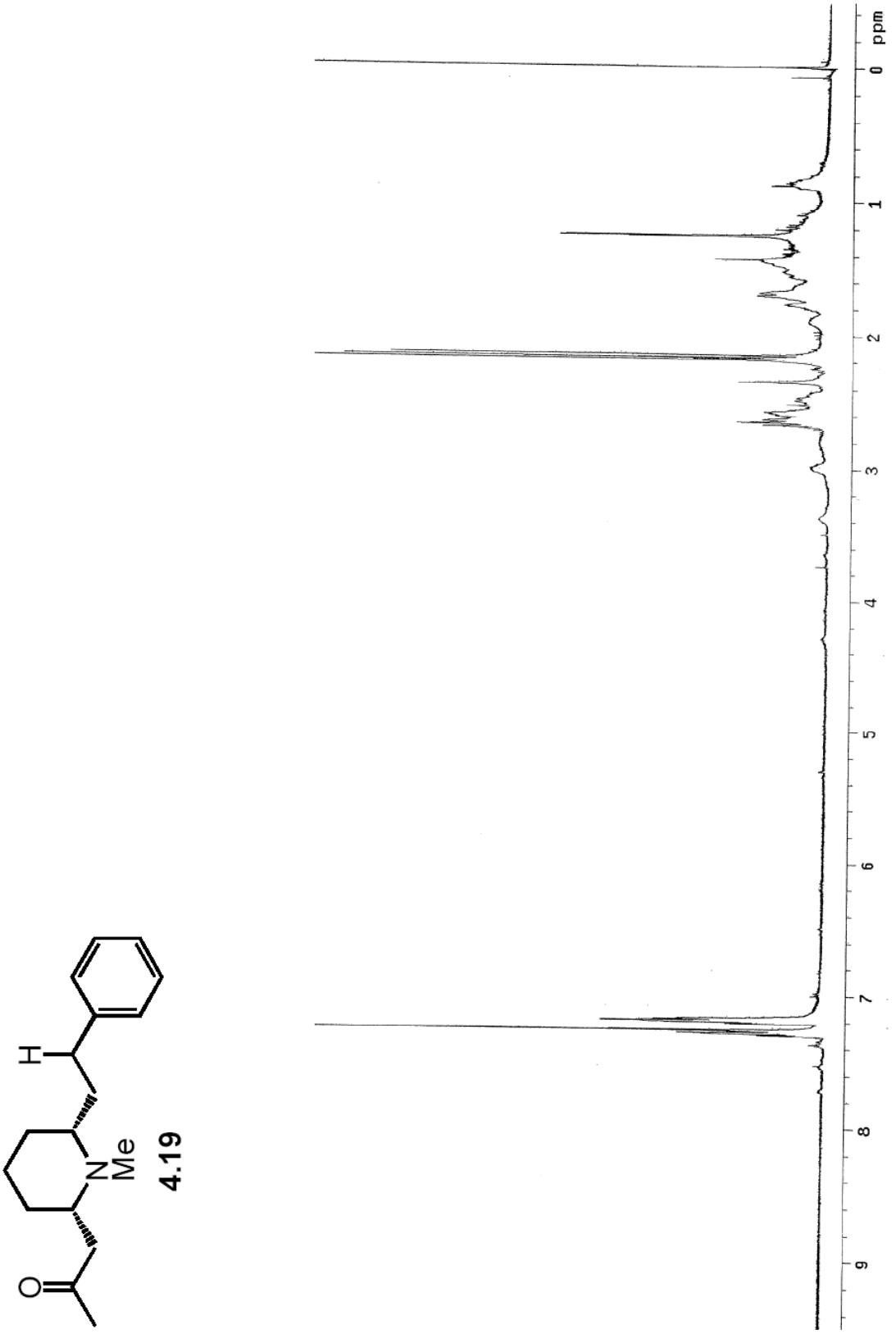

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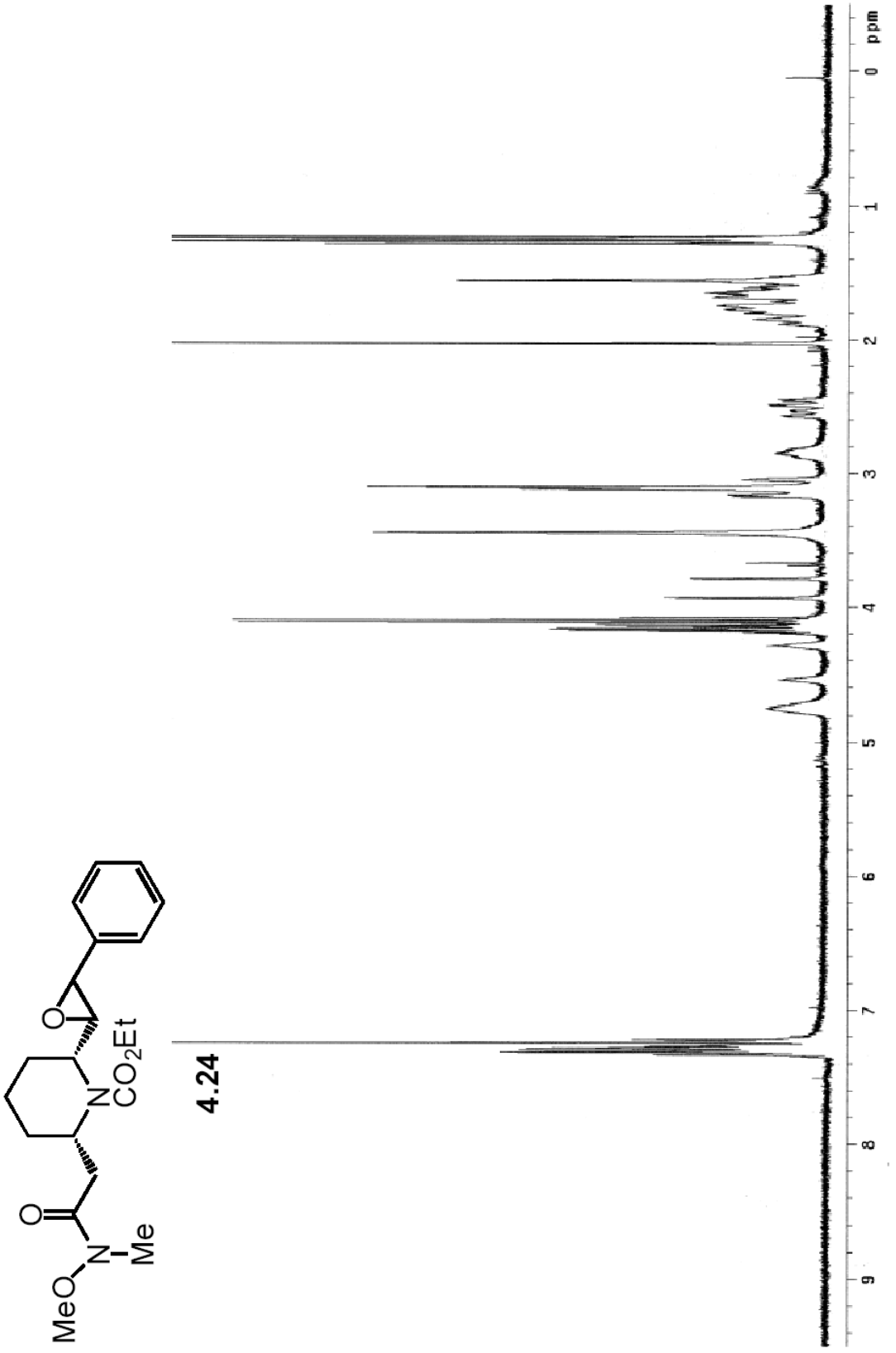
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O
O
N
CO2Et
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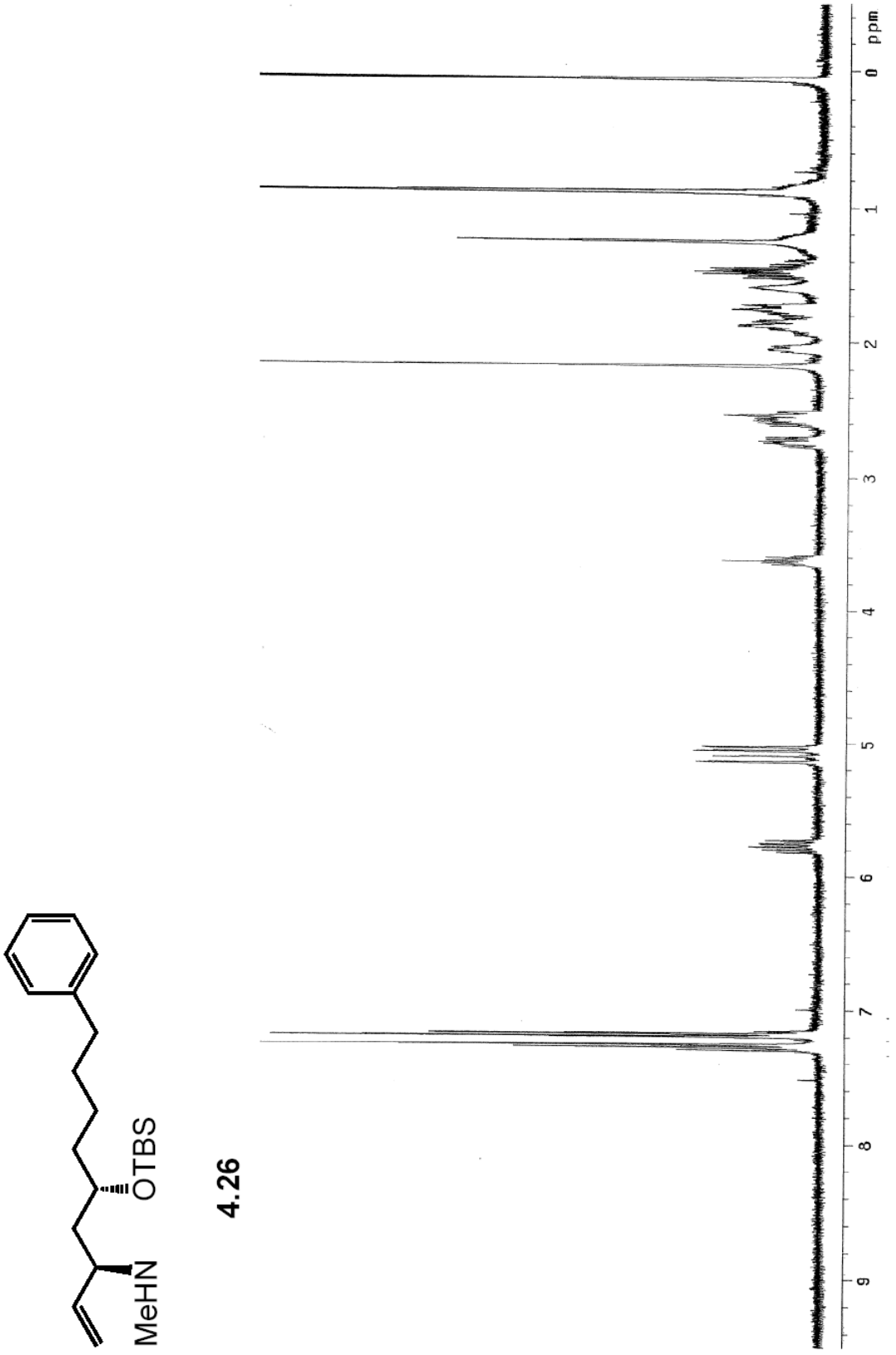
8
7
6
5
4
3
2
1
0
ppm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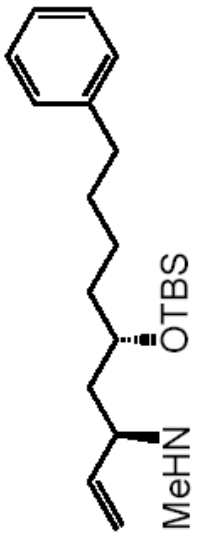
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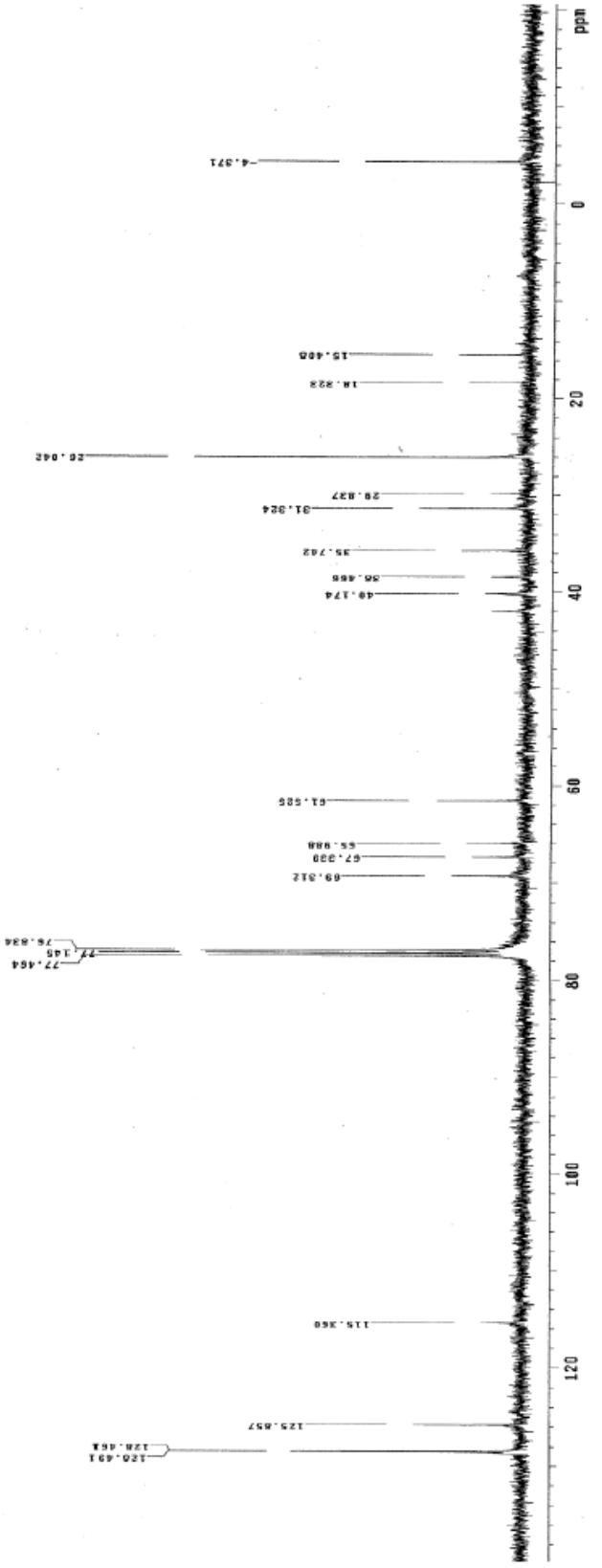
OTBS

4.26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40.174
61.585
67.328
69.312
77.464
120.691
125.857
115.360

Chapter Five

COMPARISON OF MOLYBDENUM AND RUTHENUIM COMPLEXES FOR CATALYTIC ASYMMETRIC RING-OPENING CROSS-METATHESIS REACTIONS

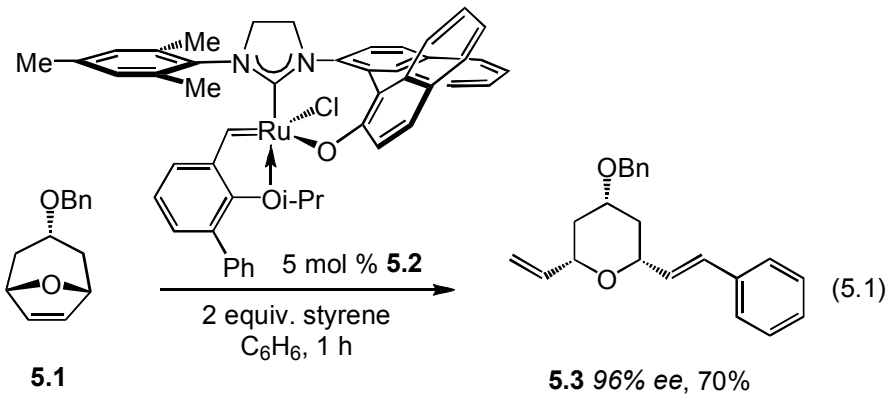
5.1 Introduction

In Chapter Two I alluded to the reactivity difference between Mo and Ru complexes for olefin metathesis. This difference affords chiral Mo complexes an advantage over chiral Ru complexes for the asymmetric ring-closing metathesis of tertiary amines; chiral Ru complexes were inefficient at performing asymmetric ring-closing metathesis reactions of amines. Nonetheless, we did find one example where Mo complexes were inefficient; namely the desymmetrization reaction of *N*-Bn azabicycles. Would chiral Ru complexes be efficient for this type of transformation? How general are reactivity and selectivity differences between chiral Mo and Ru complexes? These were among several considerations that lead us to undertake the first set of studies involving a comparison of Mo and Ru-based chiral complexes for olefin metathesis. There are relatively few reports in the literature of direct comparisons between Mo and Ru complexes for olefin metathesis. Moreover, these reports generally relate to reactivity and not selectivity.

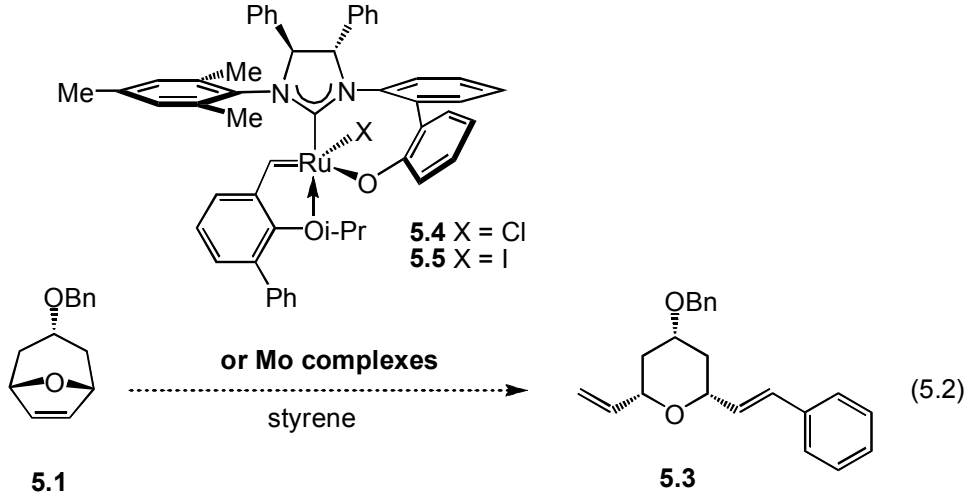
5.1a Ru-catalylzed Enantioselective Synthesis of Pyrans. Previously we reported on the Ru-catalyzed enantioselective synthesis of 2,4,6-substituted pyrans through the ring-opening metathesis reactions of *meso* oxabicycles.[97] Since Ru complexes proved to be highly selective for this class of reactions this was to be the starting point of our comparative studies between Mo and Ru complexes. A representative example of this Ru-catalyzed process is shown in eq. 5.1 (see below). Exposure of oxabicycle **5.1** to 5 mol % of Ru complex **5.2** in the presence of two equivalents of styrene affords pyran **5.3** in *96% ee* and 70% yield after 1 h. We refer to Ru complex **5.2** as a first generation chiral Ru catalyst. First generation Ru complexes possess a bidentate *N*-heterocyclic carbene ligand that is derived from a biaryl N,O-binapthyl intermediates. Another structural characteristic of these complexes is that they posses one alkoxy and one halide ligand, in contrast to the early achiral Ru complexes that typically have two halide ligands.

---

(97) "Efficient Enantioselective Synthesis of Functionalized Tetrahydropyrans by Ru-Catalyzed Asymmetric Ring-Opening Metathesis/Cross-Metathesis (AROM/CM)," Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2004**, *126*, 12288–12290.

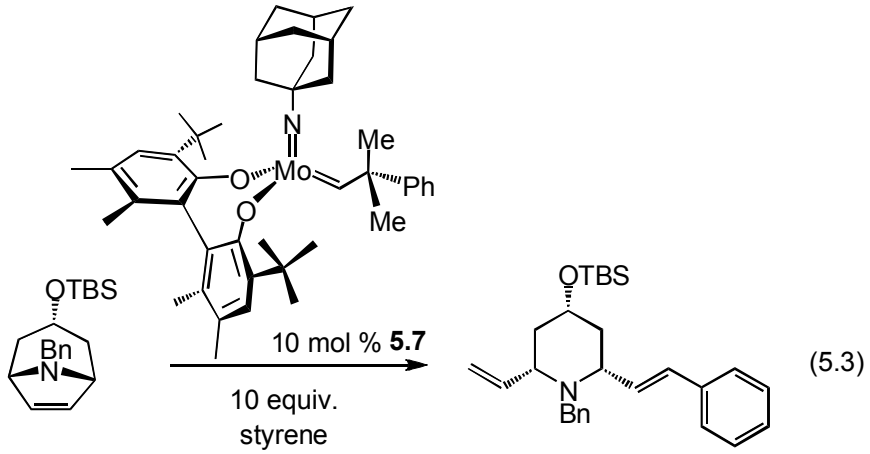


After completing our studies into the Ru-catalyzed enantioselective synthesis of pyrans our group developed a different class of chiral Ru complexes. In order to rigorously compare Mo and Ru complexes we first had to study the desymmetrization reactions of oxabicycles with our newly developed Ru catalysts **5.4** and **5.5** (eq. 5.2). These complexes, referred to as second generation chiral Ru complexes, are structurally very different from first generation Ru complexes. For one, the chirality of these complexes is derived from a C_2-symmetric chiral diamine backbone. Morevoer, the bidentate N-heterocyclic carbene ligands are derived from biphenyl intermediates, and not binapthyls as in the first generation complexes. An additional note about both classes of Ru complexes is that the halide ligand on the metal can be either a chloride (**5.4**) or an iodide (**5.5**). After understanding how both classes of Ru complexes behave in desymmetrization reactions of oxabicycles we would be able to make a comparison with Mo complexes for this class of transformations.



5.1b Ru-catalyzed Enantioselective Synthesis of Piperidines. The next phase of our comparative studies would entail studying Ru complexes for the desymmetrization of azabicycles. Of particular interest would be reactions where Mo complexes were found to be nonselective such as the enantioselective synthesis of *N*-Bn protected piperidines

(eq. 5.3, see below) where Mo complex **5.7** delivers piperidine **5.8** in only *21% ee*. Other reactions of interest would include the desymmetrization reactions of carbamate-protected azabicycles. We expected the metathesis activity of Ru complexes would not be diminished by carbamate functional groups.



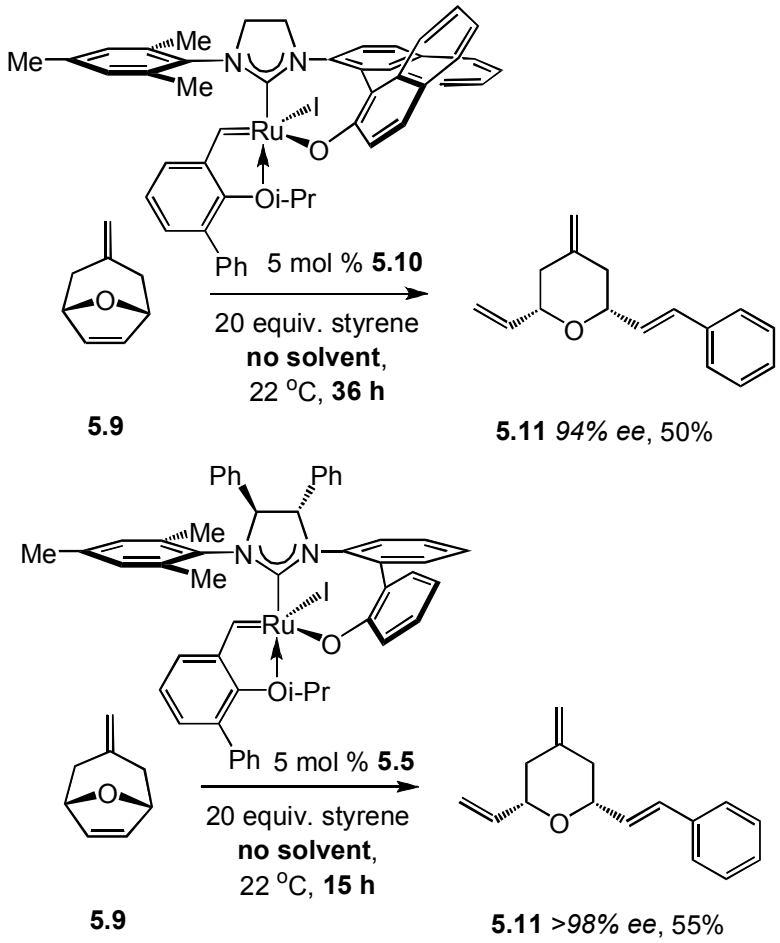
5.2 Second Generation Ru Catalyst for the Enantioselective Synthesis of Pyrans

5.2a Comparison of Ru Catalysts for the Desymmetrization of Oxabicycles. During our investigations of Ru-catalyzed ring-opening/cross-metathesis reactions of oxabicycles we quickly took note of the reactivity differences between first and second generation Ru catalysts. Second generation Ru complexes were found to be more reactive than first generation complexes for this class transformations and this reactivity difference is exemplified in Scheme 5.1 (see below). Ru complex **5.10** catalyzes the ring-opening/cross-metathesis of oxabicycle **5.9** with styrene to provide pyran **5.11** in *94% ee* and 50% yield after an extended reaction time of 36 h. This reaction must be carried out in the absence of solvent; if the reaction is performed with solvent <2% of the desired product is formed. We attribute this low reactivity to the lower strain energy of oxabicycle **5.9**, in comparison to the desymmetrization of oxabicycle **5.1** that can be carried out in solvent (see eq. 5.1 above). Under identical reaction conditions, Ru complex **5.5** delivers the desired pyran in higher selectivity and significantly shorter reaction time. Treatment of oxabicycle **5.9** with 5 mol % of Ru complex **5.5** in twenty equivalents of styrene delivers pyran **5.11** in *>98% ee* and 55% yield.[98] An additional note about these reactions is that iodide-containing Ru complexes were employed because in the reactions with chloride-containing complexes (**5.2** in eq. 5.1 and **5.4** in eq.

(98) The low yields in the formation of **5.11** are due to the volatility of the pyran.

5.2, see above), pyran **5.11** is formed in lower enantioselectivity.[99] This trend in the reactivity of Ru complexes remained the same when we studied different oxabicyclic substrates. Although, it cannot be generalized that second generation catalysts are more selective than first generation catalysts for the enantioselective synthesis of pyrans.

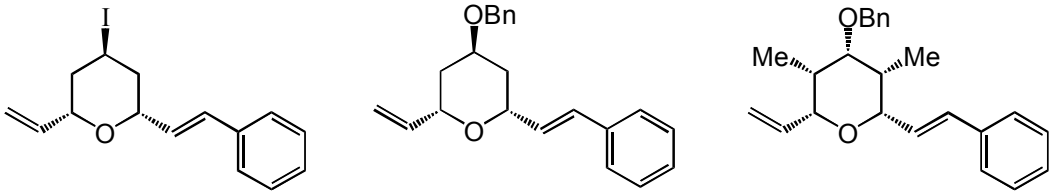
Scheme 5.1



5.2b Comparison of First and Second Generation Ru Catalysts in the Preparation of Enantioenriched Pyrans. Illustrated in Figure 5.1 (see below) are the results we obtained in comparing Ru catalysts for the enantioselective synthesis of other pyran products. Ru complex **5.10** catalyzes the formation of iodide-containing pyran **5.12** in *93% ee* and 65% yield after 4 h. In comparison, Ru complex **5.5** catalyzes the formation of pyran **5.12** in *82% ee* and 70% yield after 1h. Here, the first generation Ru complex is the catalyst of choice delivering the desired pyran in greater selectivity. An advantage of

(99) The increase in selectivity for iodide-containing Ru complexes over chloride-containing complexes has been noted previously for a different class of chiral Ru complexes, see: "Enantioselective Ruthenium-Catalyzed Ring-Closing Metathesis," Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228.

second generation Ru complexes over first generation complexes is that since reactions proceed at a faster rate, the temperature of certain reactions can be lowered to improve selectivity without having extended reaction times. As an example, Ru complex **5.10** furnishes pyran **5.13** in *90% ee* and 85% yield after a reaction time of 36 h. Whereas Ru complex **5.5** provides pyran **5.13** in *>98% ee* and 84% yield after a reaction time of 15 h at –15 °C; at 22 °C pyran **5.13** is isolated in *92% ee*. Clearly, performing this reaction at lower temperature with the first generation Ru complex would be impractical. Another example of the advantages in employing second generation Ru complexes, over first generation complexes, is in the preparation of fully substituted pyran **5.14**. Ru complex **5.10** delivers pyran **5.14** in *80% ee* and 44% yield after a long reaction time of 44 h. At a reaction temperature of –15 °C, second generation Ru complex **5.5** provides pyran **5.14** at *89% ee* and 64% yield in 15 h; significantly shorter reaction time than with the first generation Ru complex. This pyran product is of special interest since it was employed by our group in the total synthesis of the natural product baconipyrone C.[100]



5.12 *93% ee*, 65%, 4 h
2 mol % **5.10**

5.12 *82% ee*, 70%, 1 h
2 mol % **5.5**

5.13 *90% ee*, 85%, 36 h
2 mol % **5.10**

5.13 *>98% ee*, 84%, 15 h
2 mol % **5.5**
at –15 °C

5.14 *80% ee*, 44%, 44 h
5 mol % **5.10**

5.14 *89% ee*, 64%, 15 h
2 mol % **5.5**
at –15 °C

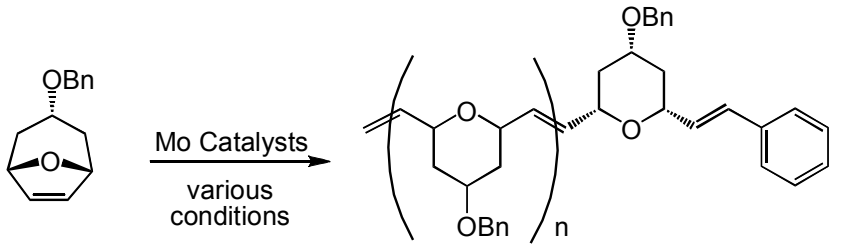
Figure 5.1. Comparison of Ru Complexes in the Enantioselective Synthesis of Pyrans

5.3 Mo Complexes for the Enantioselective Synthesis of Pyrans

5.3a Mo Complexes Prove to be Overly Reactive with Highly Strained Oxabicycles. The first oxabicyclic substrate we studied with chiral Mo complexes was oxabicycle **5.1** (eq. 5.4, see below), the strained oxabicycle that was readily desymmetrized by Ru complexes even in the presence of solvent. When performing a screen of Mo catalysts for this desymmetrization reaction we found that in all cases the starting oxabicycle underwent a ring-opening metathesis polymerization to deliver

(100) "Chiral N-Heterocyclic Carbenes in Natural Product Synthesis: Application of Ru-Catalyzed Asymmetric Ring-Opening/Cross-Metathesis and Cu-Catalyzed Allylic Alkylation to Total Synthesis of Baconipyrone C," Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864.

polymer **5.15**. We performed this reaction under a variety of reaction conditions and were unable to prevent this polymerization from occurring.

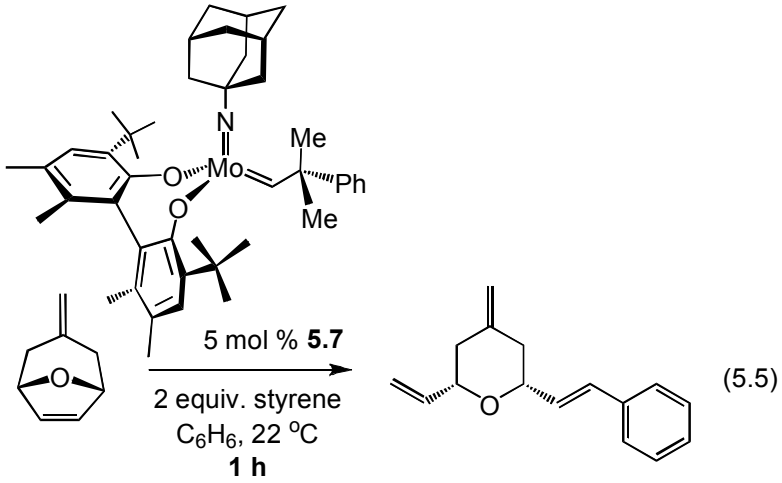


(5.4)

5.1

5.15
substrate polymerization

5.3b Mo-catalyzed Asymmetric Ring-Opening Cross-Metathesis of a Less Strained Oxabicycle. Since Mo complexes generally exhibit greater reactivity than Ru complexes, we turned our attention toward desymmetrization reactions of oxabicycles that Ru complexes could only perform in the absence of solvent. We postulated that less strained oxabicycles would not be polymerized by Mo complexes and were gratified to find that this was indeed the case. The initial substrate under investigation was exocyclic-olefin containing oxabicycle **5.9**. After a screen of available chiral Mo complexes we found the optimal catalyst to be adamantylimido alkylidene **5.7** and the metathesis with optimized reaction conditions is shown in eq. 5.5. Treatment of oxabicycle **5.9** with 5 mol % of Mo complex **5.7** in the presence of two equivalents of styrene delivers pyran **5.11** in *97% ee* and 55% yield. The selectivity observed in this reaction was comparable with selectivities observed in reactions with Ru complexes (see Scheme 5.1 above), but due to the greater reactivity exhibited by Mo complexes the reaction was complete within significantly less reaction time (1 h with Mo complex **5.7** vs. 15 h and 36 h with Ru complexes).

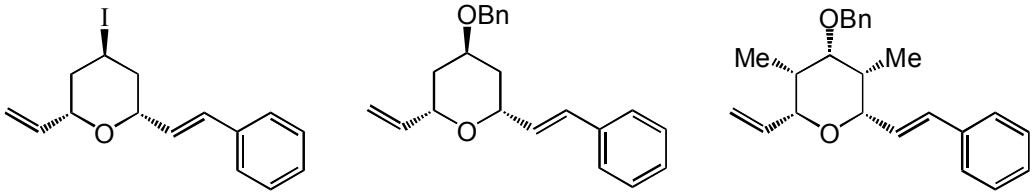


(5.5)

5.9

5.11 *97% ee*, 55%

5.3c Mo-catalyzed Enantioselective Synthesis of Pyrans; Comparison of Reactions with Ru Complexes. Illustrated in Figure 5.2 are the results obtained when we studied the desymmetrization reactions of other less-strained oxabicycles with Mo complex **5.7**. The optimal results with Ru complexes are also shown for comparison. As previously discussed, the first generation Ru complex **5.10** was the optimal catalyst for the formation of pyran **5.12**, delivering the product in *93% ee*. Mo complex **5.7** delivers pyran **5.12** in comparable selectivity of *96% ee*, but within a slightly shorter reaction time of 1 h vs. 4 h with Ru complex **5.10**. This is a case in which chiral Mo and Ru complexes exhibit similar reactivity and selectivity profiles. Next, we compared the enantioselective synthesis of pyran **5.13**, in which the second generation Ru catalyst **5.5** was the optimal for the reaction delivering the desired pyran in *>98% ee* within 15 h at –15 °C. Mo complex **5.7** is outperformed by Ru complex **5.5** in this particular reaction. Mo complex **5.7** delivers pyran **5.13** in *90% ee* and 81% yield within 1 h at 22 °C. Clearly, the Ru catalyst would be the catalyst of choice in this transformation given the greater selectivity, despite the reaction being complete in shorter reaction time with the Mo complex. When we compared the enantioselective synthesis of fully-substituted pyran **5.14** we found again that the Ru complex outperformed the Mo complex. Second generation Ru complex **5.5** provides pyran **5.14** in *89% ee* within 15 h at –15 °C. Mo complex **5.7** delivers pyran **5.14** within shorter reaction time at 22 °C (6 h vs. 15 h), however, the product is isolated in only *67% ee* (vs. *89% ee* with Ru complex **5.5**). These studies into the enantioselective synthesis of pyrans were key in providing us with further insight into the intrinsic differences and similarities between Ru and Mo complexes.



5.12 *93% ee*, 65%, 4 h
2 mol % **5.10**

5.13 *>98% ee*, 84%, 15 h
2 mol % **5.5**
at –15 °C

5.14 *89% ee,* 64%, 15 h
5 mol % **5.5**
at –15 °C

5.12 *96% ee*, 76%, 1 h
2 mol % **5.7**

5.13 *90% ee*, 81%, 1 h
5 mol % **5.7**

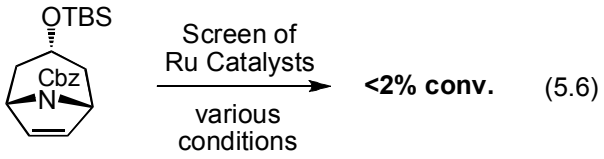
5.14 *67% ee*, 70%, 6 h
5 mol % **5.7**

Figure 5.2. Comparison of Mo and Ru Complexes for the Enantioselective Synthesis of Pyrans

Most distinguishing, these investigations revealed for the first time that Mo and Ru complexes complement each other for the same set of enantioselective olefin metathesis transformations. Before concluding this section it should be noted that in all cases the asymmetric reactions with Mo and Ru complexes delivered the opposite antipodes of pyran products.[101] To avoid confusion and for clarity of comparison enantioselectivites are always given as positive.

5.4 Ru Complexes for the Enantioselective Synthesis of Carbamate-protected Piperidines

5.4a Ru Complexes Prove Inefficient for the Synthesis of 2,4,6-substituted Carbamate-protected Piperidines. After comparing Mo and Ru complexes for the enantioselective synthesis of pyrans, we turned our focus to comparing these complexes for the enantioselective synthesis of piperidines. As previously noted, Mo complexes proved quite efficient and selective for the synthesis of various enantioenriched piperidines. The first desymmetrization substrate we studied with Ru complexes was Cbz-protected azabicycle **5.16** (eq. 5.6). Screening of available chiral complexes under a variety of reaction conditions revealed that this substrate was incompatible with Ru complexes for the asymmetric ring-opening/cross-metathesis with styrene; in all cases azabicycle **5.16** was isolated in >98% yield. Furthermore, the diastereomer of **5.16**, which contains the opposite stereochemistry at the hydroxy group carbon was also found to be incompatible with Ru complexes.



(5.6)

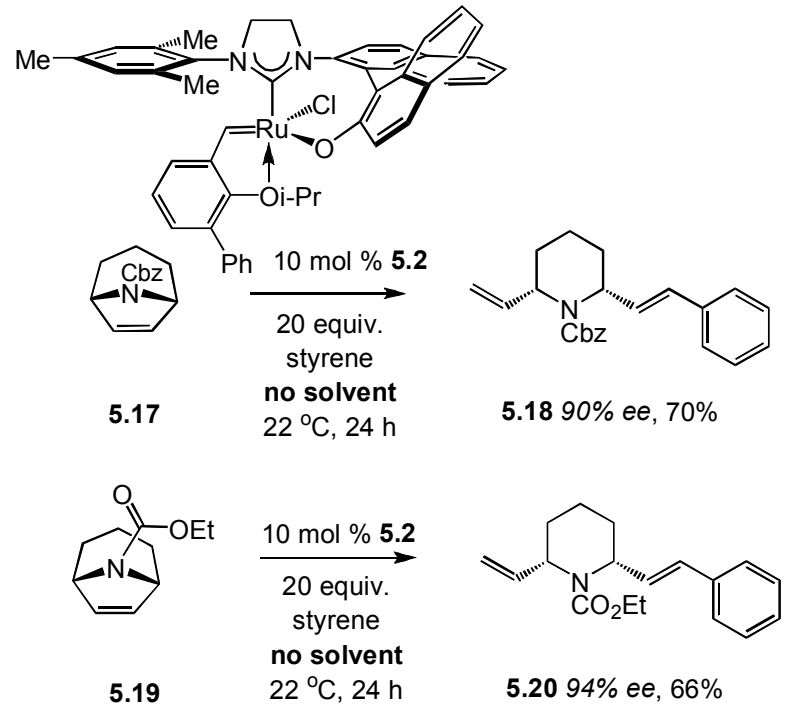
5.16

5.4b Ru Complexes Prove to be Selective for the Synthesis of 2,6-substituted Carbamate-protected Piperidines. Undaunted by the initial lack of reactivity of Ru complexes with azabicyclic substrates, we explored the desymmetrization of other carbamate-protected azabicycles. We discovered that Ru complexes are compatible with azabicycles that deliver 2,6-substituted piperidines and results are shown in Scheme 5.2 (see below). To this end, first generation Ru complex **5.2** was the optimal catalyst for the desymmetrization of azabicycles **5.17** and **5.19**. Treatment of azabicycle **5.17** with 10 mol % Ru catalyst **5.2** in 20 equivalents of styrene delivers piperidine **5.18** in *90% ee* and 70% yield after 24 h. And treatment of azabicycle **5.19** with 10 mol % Ru catalyst **5.2** in

(101) See the experimental section of this chapter for HPLC traces of pyran products.

20 equivalents of styrene furnishes piperidine **5.20** in *94% ee* and 66% yield. Several aspects of these reactions, in comparison with reactions Mo complexes, merit mention. For one, similar to the desymmetrization reactions of less strained oxabicycles, reactions with Ru complexes require that they be performed in the absence of solvent. Additionally, these reactions with Ru complexes require a catalyst loading of 10 mol %, in comparison with Ru catalyst loadings as low as 2 mol % for the synthesis of pyrans (Fig. 5.1, see above). The reaction times obtained in these reactions are comparable with the desymmetrization reactions employing Mo complexes (24 h). In both of these reactions Ru complex **5.2** delivers the product in greater enantioselectivity than the optimal Mo complex (*82% ee* for **5.18** and *90% ee* for **5.20**, see Ch 3 Fig 3.4 above). An advantage the optimal Mo complex has over the optimal Ru complex for these reactions is that with the Mo complex a catalyst loading of 5 mol % is sufficient for the reaction to proceed, as opposed to a catalyst loading of 10 mol % with the Ru complex.

Scheme 5.2



5.4c Mechanistic Rationale for the Difference in Reactivity of Ru Complexes with Different Carbamate Protected Azabicycles. In order to understand the reasons for differences in the reactivity of Ru complexes toward different azabicycles we conducted energy minimization calculations of the azabicyclic substrates.[102] Our analysis indicates that the conformations of hydroxy-substituted carbamates **5.16** and **5.21** prevent Ru

(102) Energy minimization calculations were performed on Spartan version 5.0.

complexes from reacting with the norbornyl olefins because of distortions of the [3.2.1]-azabicycle caused by the large *tert*-butyldimethylsilyl ethers (Fig. 5.3, see below). In line with previous studies involving ring-opening/cross-metathesis reactions of norbornenes and oxabicycles it is likely that the initial approach of a Ru catalyst toward azabicyclic olefins is from the exocyclic face. This is shown for the azabicycle **5.17**, which is compatible with Ru complexes. Now, in the case of azabicycle **5.16**, the bulky *tert*-butyldimethylsilyl group causes an increase in the bond angle shown bringing the carbamate group on the nitrogen to be in closer proximity to the azabicyclic olefin. This most likely prevents Ru complexes from forming the metallacyclobutane necessary for the initial ring-opening metathesis of the substrate. This effect is even more prominent in the case of azabicycle **5.21**, where a *syn*-pentane interaction is present between the *tert*-butyldimethylsilyl group and the olefinic carbons. This steric repulsion causes the olefinic carbons to be in closer proximity to the carbamate group; just as in azabicycle **5.16**. The difficulties encountered in trying to desymmetrize **5.16** and **5.21** underline the need to develop new chiral Ru complexes, either smaller or more reactive, that can overcome these metathesis inhibiting effects

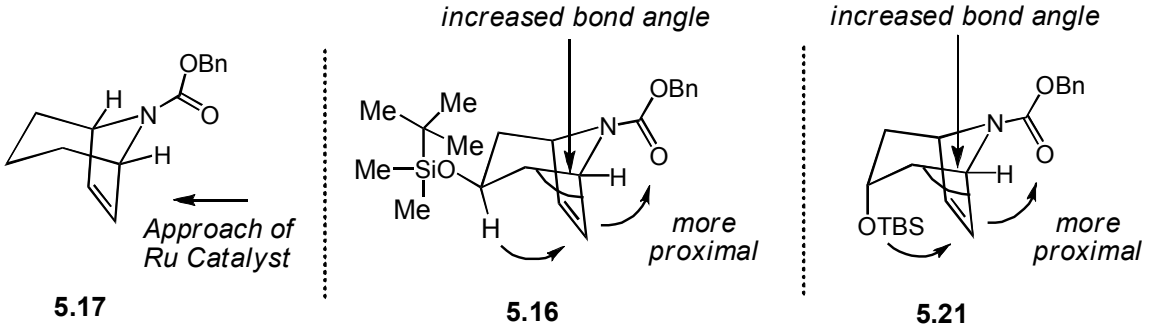
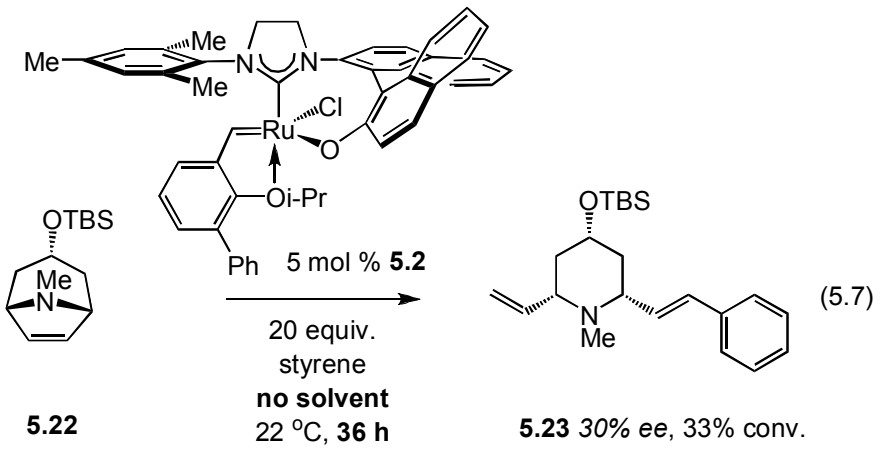


Figure 5.3. Rationale for Reactivity of Ru Complexes Toward Azabicycles

5.5 Ru Complexes for the Enantioselective Synthesis of N-alkyl Piperidines

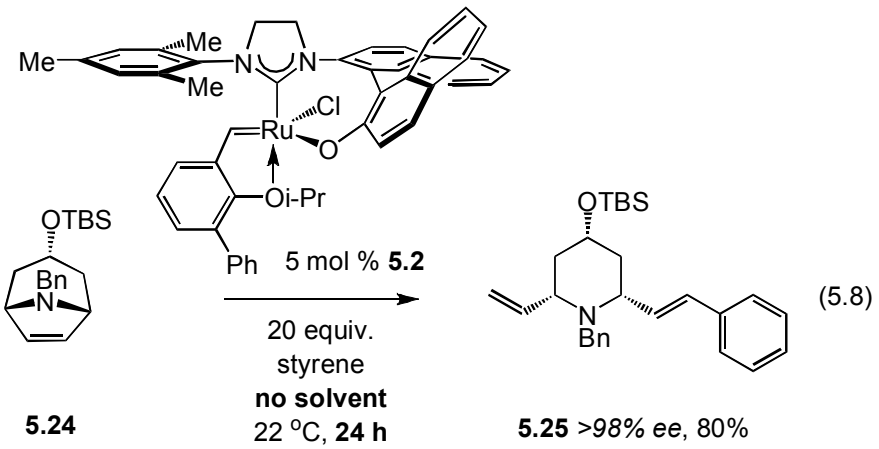
5.5a Ru-catalyzed Asymmetric Ring-Opening/Cross-Metathesi of N-Me Azabicycles. Our next efforts involved the Ru-catalyzed desymmetrization reaction of *N*-Me-containing azabicycle **5.22** (eq. 5.7).



5.22 **5.23** *30% ee*, 33% conv.

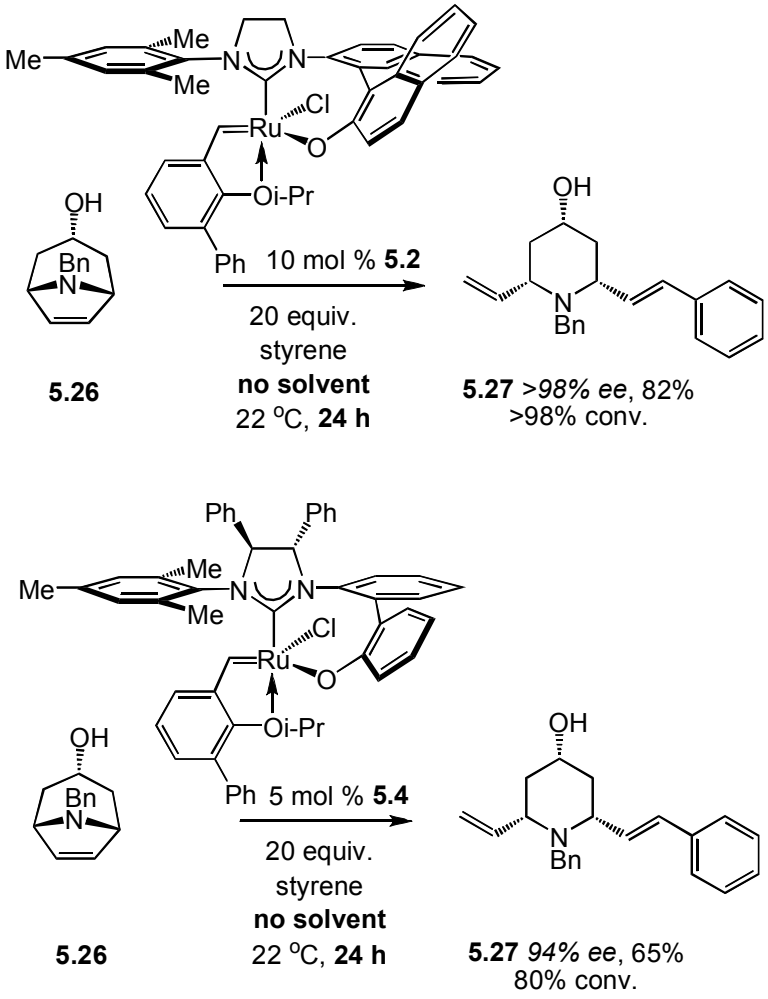
Previously, we demonstrated that this substrate was readily and efficiently desymmetrized by Mo complexes. Ru complexes, on the other hand, were found to be inefficient at performing this transformation. Treatment of azabicycle **5.22** with 5 mol % of Ru catalyst **5.2** in 20 equivalents of styrene delivers piperidine **5.23** in only *33% ee* and 30% conversion to desired product after a reaction time of 36 h. This result was not surprising since earlier studies revealed Ru complexes to be incompatible with amine-containing ring-closing metathesis substrates.

5.5b Ru-catalyzed Asymmetric Ring-Opening/Cross-Metathesis of N-Bn Azabicycles. The next azabicyclic substrate we studied with Ru complexes was *N*-Bn-containing azabicycle **5.24** (eq. 5.8). These investigations resulted in one of the most intriguing differences we had yet to observe between Mo and Ru complexes. Previously we found that Mo complexes catalyzed the desymmetrization of **5.24** in low enantioselectivity and to our surprise we found Ru complexes were more selective at performing this transformation. Toward this end, treatment of *N*-Bn azabicycle **5.24** with 5 mol % of Ru complex **5.2** in twenty equivalents of styrene delivers desired piperidine **5.25** in *>98% ee* and 80% yield after 24 h. It is likely that in the case of *N*-Me azabicycles, the nitrogen binds to the Ru metal center and inhibits metathesis activity; this is evident from the low conversion to desired product (see eq. 5.7 above). The benzyl group is most likely large enough to prevent the nitrogen from binding to Ru, as strongly as in the case of the *N*-Me, and thus allows the catalyst to perform the reaction.



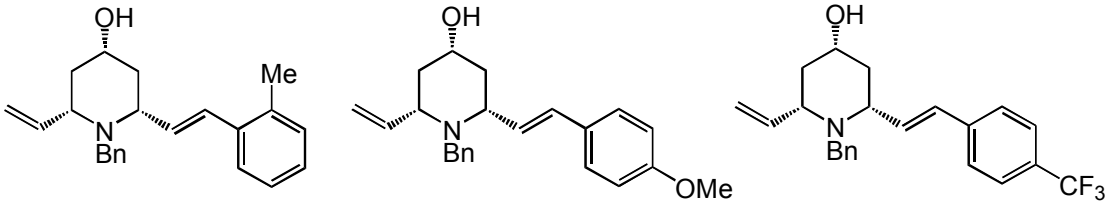
5.5c Ru-catalyzed Desymmetrization Reactions of Alcohol-containing Azabicycles. The next logical step for us to take was to study the desymmetrization reaction of *N*-Bn azabicycles that contained secondary alcohols, in place of previously studied silyl-protected alcohols. As mentioned earlier, Ru complexes unlike Mo complexes are tolerant of alcohol functionalities. To this end, we studied the desymmetrization reaction of azabicycle **5.26** with first gerneration and second generation chiral Ru catalysts, **5.2** and **5.4**, respectively (Scheme 5.3, see below). Treatment of *N*-Bn azabicycle **5.26** with 5 mol % of first generation Ru complex **5.2** in twenty equivalents of styrene delivers the desired piperidine **5.27** in *>98% ee*, >98% conversion to desired product, and 82% yield after 24 h. Treatment of *N*-Bn azabicycle **5.26** with 5 mol % of second generation Ru complex **5.4** in twenty equivalents of styrene delivers desired piperidine **5.27** in *94% ee*, 80% conversion to desired product, and 65% yield after 24 h. As displayed by these results, the first generation Ru complex is the optimal catalyst delivering the product with greater efficiency, albeit both complexes deliver the desired product in comparable levels of selectivity. This distinction in reactivity difference between the first and second generation Ru complexes holds true in desymmetrization reactions of azabicycle **5.26** with other aryl olefin cross-partners.

Scheme 5.3



5.5d Comparison of Ru Complexes in the Desymmetrization of Alcohol-containing Azabicycles with Various Aryl Olefin Cross-Partners. Illustrated in Figure 5.3 (see below) are results obtained when we performed the desymmetrization of azabicycle **5.26** with electronically and sterically modified styrene cross-partners. First we studied the desymmetrization reaction with *o*-Me-styrene. Ru complex **5.2** delivers piperidine **5.28** in *>98% ee* and 81% yield. Ru complex **5.4** provides piperidine **5.28** in *>98% ee* and 60% yield. Next, we studied the desymmetrization reaction of **5.26** with electron rich *p*-OMe-styrene. Ru complex **5.2** delivers piperidine **5.29** in *>98% ee* and 67% yield. Ru complex **5.4** provides piperidine **5.29** in *96% ee* and 38% yield. Last, we studied the desymmetrization reaction of **5.26** with electron poor *p*-CF_3-styrene. Ru complex **5.2** delivers piperidine **5.30** in *97% ee* and 78% yield. Ru complex **5.4** provides piperidine **5.30** in *96% ee* and 63% yield. It is clear from these results that the first generation Ru complex **5.2** is the catalyst of choice for the desymmetrization of *N*-Bn-containing

azabicycles. It should be noted that these desymmetrization reactions were performed with the chloride-containing Ru complexes since the enantioenriched piperidines were isolated in high selectivity.



5.28 *>98% ee*, 81%
>98% conv.
5 mol% **5.2**

5.28 *>98% ee*, 60%
95% conv
5 mol % **5.4**

5.29 *>98% ee*, 67%
87% conv.
5 mol% **5.2**

5.29 *96% ee*, 38%
50% conv.
5 mol% **5.4**

5.30 *97% ee*, 78%
>98% conv.
5 mol% **5.2**

5.30 *96% ee*, 63%
85% conv.
5 mol% **5.4**

Figure 5.3. Scope of AROM/CM with Various Cross-Partners

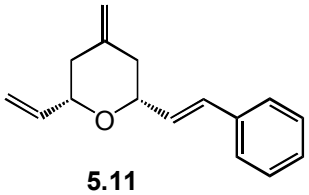
5.6 Conclusions

This chapter detailed the first direct comparison of chiral Mo and Ru complexes for asymmetric olefin metathesis. Our studies clearly indicate the importance of having families of both classes of chiral complexes due to their complementarity in reactivity and selectivity. Ru complexes are the preferred complexes for the desymmetrization of highly strained oxabicycles given that Mo complexes tend to polymerize these type of substrates. When it comes to the desymmetrization of less strained oxabicycles, the nature of the substrate dictates whether a Mo or Ru complex will be the optimal catalyst. A pronounced distinction between these two classes of complexes was observed in the desymmetrization reactions of azabicycles. Mo complexes outperformed Ru complexes for the enantioselective synthesis of 2,4,6-substituted carbamate-protected piperidines. Whereas Ru complexes proved to deliver 2,6-substituted carbamate-protected piperidines in comparable levels of selectivity. The most striking difference between Mo and Ru complexes was in the desymmetrization reactions of *N*-alkyl azabicycles. Mo complexes efficiently and selectively deliver a variety of *N*-Me-containing piperidine products. In contrast, Ru complexes appear to be incompatible with *N*-Me azabicycles, delivering products in low selectivity and efficiency. The ability of each complex to selectively furnish *N*-Bn azabicycles was reversed from that of *N*-Me azabicycles. Ru complexes delivered products in higher enantioselectivity than their Mo counterparts. In conclusion, these studies are of utmost importance in our continuing pursuit to understand the

fundamental intricacies of Mo and Ru complexes, as well as guiding us toward future endeavors.

5.7 Experimental Section[103]

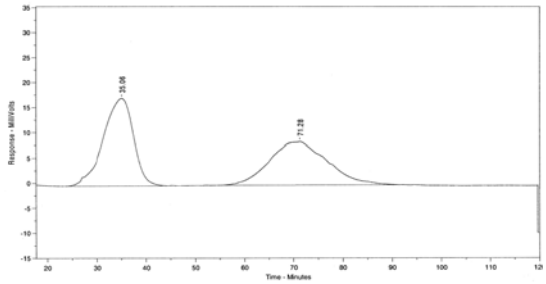
Characterization data for pyran products: All oxabicycles were prepared according to published literature procedures and characterization data for all pyrans was previously reported.[104]



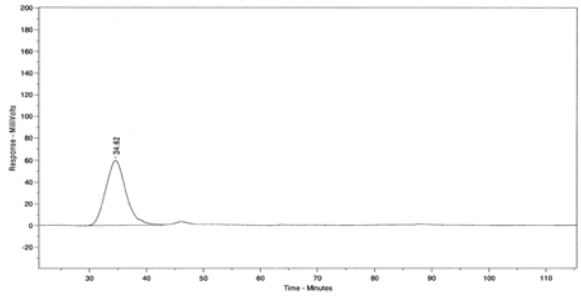
5.11

Pyran **5.11**. The enantiomeric purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OB-H (4.6 x 250 mm), 99.8:0.2 hexanes:*i*-PrOH, 0.5 mL/min, λ = 254 nm.

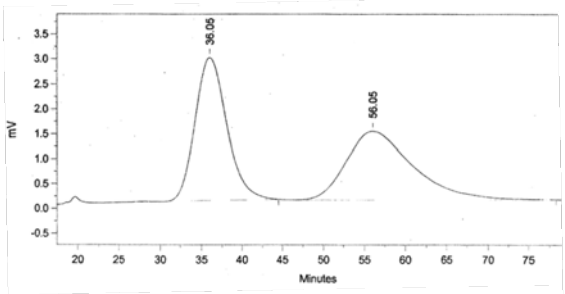
Authentic racemic



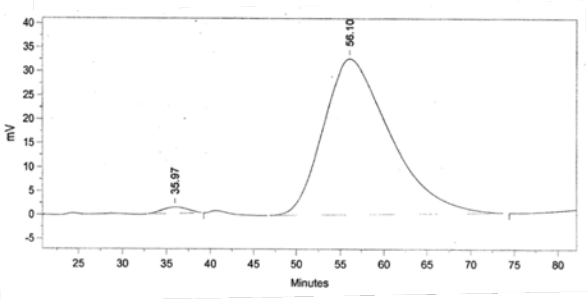
>*98% ee* with Ru catalyst 5.5



Authentic racemic



***97% ee* with Mo catalyst 5.7**

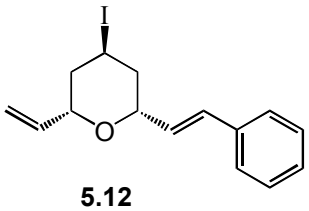


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	35.967		0.0000	0.000	266301.7	1.507	BB	3.333	1331.49	3.932
2	56.105		0.0000	0.000	17399460.0	98.493	BB	8.914	32531.87	96.068

(103) In some instances, rotamers of carbamate- and amide-containing azabicycles were observed as determined by variable temperature ^{1}H NMR analysis. Additionally, this is likely the reason that in some instances ^{13}C NMR spectra do not appear to have the correct number of carbon peaks. In these instances the ^{13}C NMR spectra is reported as observed.

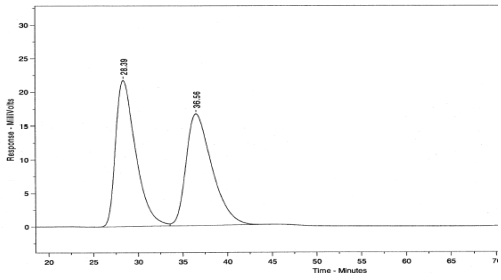
(104) For HPLC traces of pyrans with Ru complex **5.2**, the trace of pyran **5.12** with Ru complex **5.10**, and the trace of pyran **5.14** with Ru complex **5.5**, see supporting information in: "Efficient Enantioselective Synthesis of Functionalized Tetrahydropyrans by Ru-Catalyzed Asymmetric Ring-Opening Metathesis/Cross-Metathesis (AROM/CM)," Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2004**, *126*, 12288−12290.

Pyran **5.12**. The enantiomeric purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OJ (4.6 x 250 mm), 99.8:0.2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm.



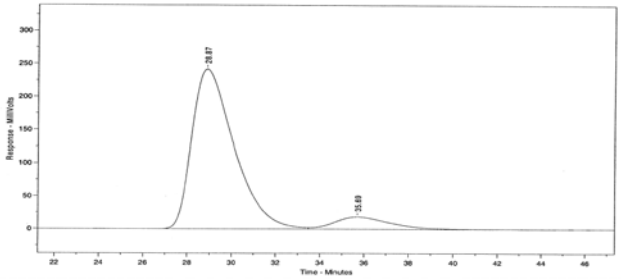
5.12

Authentic racemic



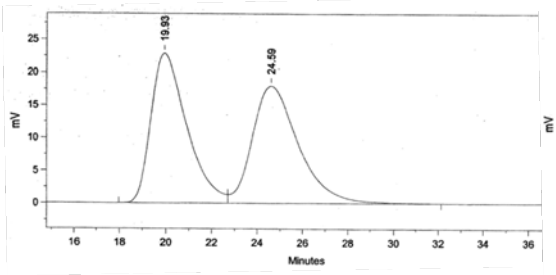
Peak #	Ret. Time	Name	Amount
1	28.87		0.00
2	35.69		0.00

***82% ee* with Ru catalyst 5.5**

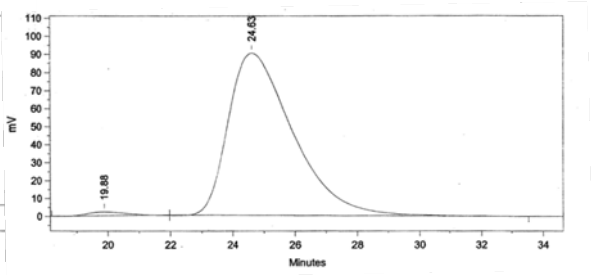


Amt %	Area	Area %	Type	Width
N/A	32209810	90.785	BV	2.03
N/A	3269509	9.215	VB	2.64

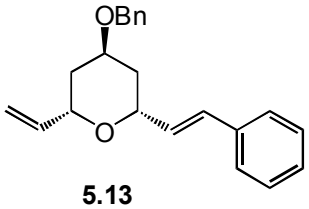
Authentic racemic



***97% ee* with Mo catalyst 5.7**



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	19.885		0.0000	0.000	171181.5	1.300	BB	1.309	2179.52	2.364
2	24.629		0.0000	0.000	12998170.0	98.700	BB	2.407	90001.13	97.636

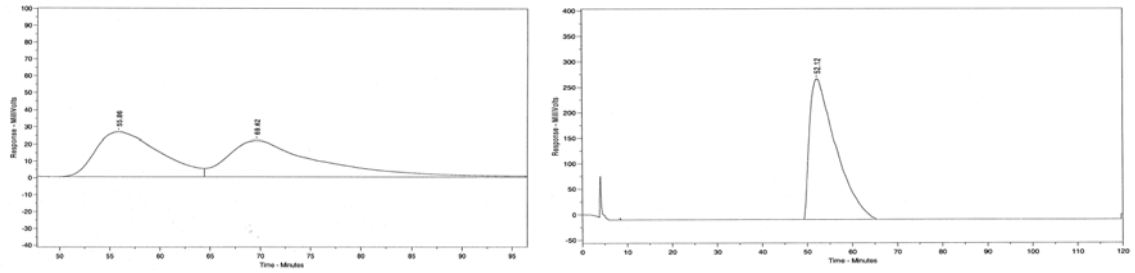


5.13

Pyran **5.13**.[105] The enantiomeric purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OJ (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm.

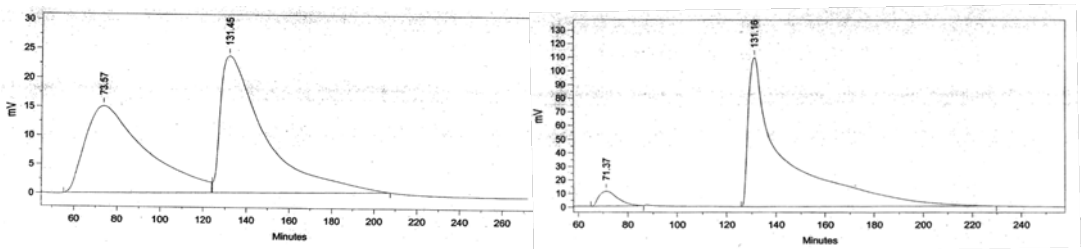
(105) Two sets of conditions for HPLC separation of enantiomers are shown because the data was acquired at different times.

Authentic racemic **>*98% ee* with Ru catalyst 5.5 at –15 °C**

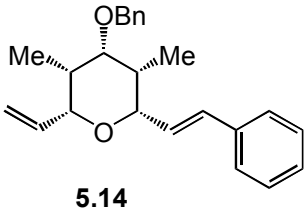


Chiralpak AD (4.6 x 250 mm), 99.9:0.1 hexanes:*i*-PrOH, 0.2 mL/min, λ = 254 nm.

Authentic racemic ***90% ee* with Mo catalyst 5.7**



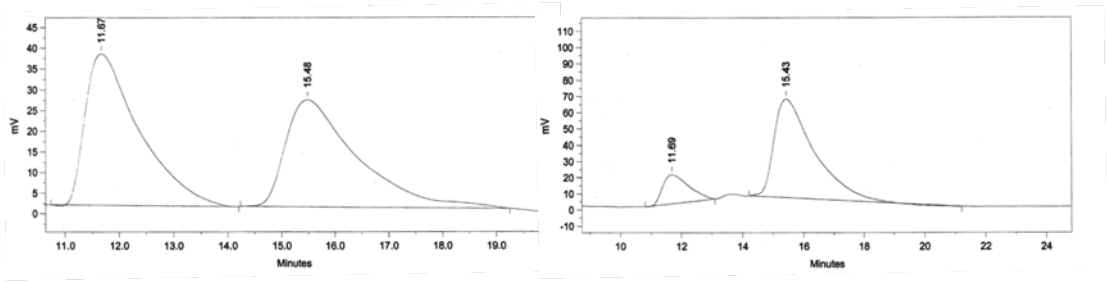
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	71.370		0.0000	0.000	5889050.0	4.923	BB	9.004	10900.20	9.071
2	131.162		0.0000	0.000	113736400.0	95.077	BB	17.349	109264.90	90.929



5.14

Pyran **5.14**. The enantiomeric purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak AD (4.6 x 250 mm), 96:4 hexanes:*i*-PrOH, 0.8 mL/min, λ = 210 nm.

Authentic racemic ***67% ee* with Mo catalyst 5.7**



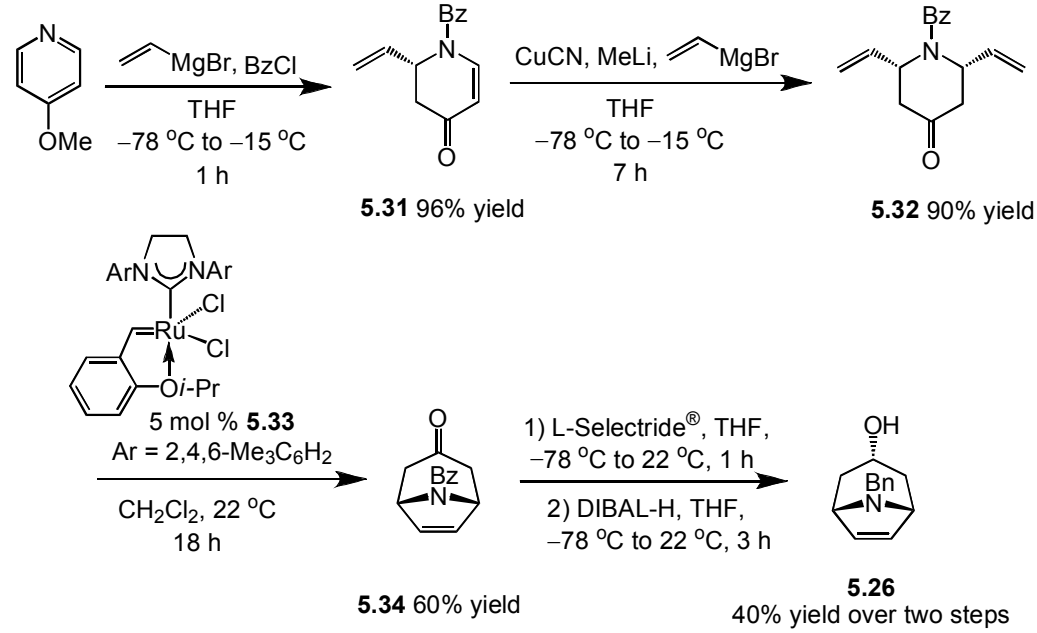
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	11.692		0.0000	0.000	1074356.0	16.229	BB	0.999	17931.63	22.811
2	15.435		0.0000	0.000	5545654.0	83.771	BB	1.523	60679.14	77.189

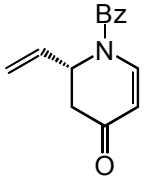
Synthesis of Azabicycles: The synthesis of *N*-Me azabicycle **5.22** was reported earlier.[106] The synthetic route used to form **5.22** was modified and employed for the

(106) See the experimental section of Ch 3.

preparation of azabicycle **5.26**, shown in Scheme 5.4 (see below). Alkylation of *p*-methoxypyridine with vinylmagnesium bromide in the presence of benzoyl chloride provides piperidinone **5.31**. Conjugate addition to **5.31** with a mixed vinyl hight-order cuprate reagent then delivers divinyl piperidinone **5.32**. Then, ring-closing metathesis of **5.32** with Ru catalyst **5.33**[107] furnishes azabicycle **5.34**. Selective reduction of the carbonyl in **5.34** with L-Selectride® followed by reduction of the benzamide to the tertiary benzyl amine ultimately furnishes metathesis substrate **5.26**.

Scheme 5.4. Synthesis of Azabicycle 5.26



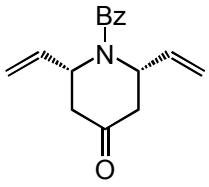


5.31

Synthesis of Piperidinone **5.31**. A 250-mL round-bottom flask, fitted with an addition funnel, was charged with *p*-methoxypyridine (5.00 g, 46.2 mmol), THF (46 mL), and the reaction vessel was allowed to cool to –78 °C in a dry ice/acetone bath. To this solution was added vinylmagnesium bromide (55.5 mL, 55.5 mmol, 1.0 M in THF) dropwise over a period of 10 min, after which time the resulting mixture was allowed to warm to –15 °C in a cooling bath. To this mixture was added benzoyl chloride (8.48 mL, 69.4 mmol) dropwise over a period of 10 min. The mixture was allowed to stir at –15 °C for 20 min, after which time the flask was removed from the cooling bath and the reaction was quenched by the addition of a 2.0 M aqueous solution of HCl (75 mL). The resulting solution was allowed to stir at 22 °C for 15 min, after which point it was washed with Et_2O (4 × 100 mL). The combined organic layers were washed with a 1.0 M aqueous solution of NaOH (25 mL),

(107) "Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts," Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

a saturated aqueous solution of NaCl (50 mL), dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (dry load, 1:1 to 3:1 Et_2O:hexanes) to give **5.31** as slight yellow solid (10.05 g, 44.20 mmol, 96%). mp: 40–43 °C. IR (neat): 3081 (w), 2995 (w), 1666 (s), 1598 (s), 1393 (m), 1331 (s), 1288 (s), 1213 (s), 1145 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.56–7.45 (m, 6H), 5.87 (ddd, *J* = 17.2, 10.6, 4.9 Hz, 1H), 5.44–5.40 (m, 1H), 5.30–5.27 (m, 2H), 5.21 (dd, *J* = 17.2, 1.6 Hz, 1H), 2.98 (dd, *J* = 16.7, 6.6 Hz, 1H), 2.68 (d, *J* = 16.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 172.0, 142.8, 132.9, 132.7, 131.8, 128.9, 128.5, 118.0, 107.8, 54.4, 40.2. HRMS ES (*m/z*) Calcd for $C_{14}H_{14}NO_2$ 228.1025 $(M + H)^+$, Found 228.1024.

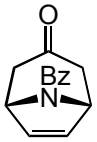


5.32

Synthesis of *cis*-2-vinylpiperidine **5.32**. A 500-mL round bottom flask, fitted with an addition funnel, was charged with CuCN (2.96 g, 33.1 mmol), THF (51 mL), and the reaction vessel was allowed to cool to –78 °C in a dry ice/acetone bath. To this solution was added MeLi (21.4 mL, 33.1 mmol, 1.54 M in Et_2O) dropwise over a period of 10 min. At this time, the reaction flask was removed from the dry ice bath and placed in an ice bath at 0 °C for 1 min, after which time the flask was allowed to cool to –78 °C in a dry ice/acetone bath. To this mixture was added vinylmagnesium bromide (34.0 mL, 33.1 mmol, 0.97 M) in THF, dropwise over a period of 15 min and the mixture was allowed to stir at –78 °C for 10 min. The mixture was then charged with a solution of **5.31** (5.00 g, 22.0 mmol, as a solution in 20 mL) of THF in a dropwise fashion over a period of 40 min, and the resulting orange mixture was allowed to stir at –78 °C for 5 h (it is critical to add **5.31** slowly to prevent formation of the *trans* product). At this time, the mixture was poured into a solution consisting of a saturated aqueous solution of NH_4Cl and a saturated aqueous solution of NH_4OH (9:1, 250 mL)[108] at 22 °C. The mixture was allowed to stir for 12 h, after which time the solution was washed with EtOAc (3 × 250 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (150 mL), dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (dry load, 4:1 to 1:1 hexanes:EtOAc) to provide **5.32** as colorless oil (5.05 g, 19.8 mmol, 90%). IR (neat): 3081 (w), 2974 (w), 2905 (w), 1722 (s), 1634 (s), 1394 (s), 1338 (s), 1224 (m), 916 (m), 702 (m). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.48–7.41 (m, 5H), 5.98 (ddd, *J* = 17.2, 10.6, 5.1 Hz, 2H), 5.23–5.18 (m, 6H), 2.69 (d, *J* = 5.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 172.0, 138.2, 136.1, 130.2, 128.9, 128.7, 126.6, 117.2,

(108) Caution should be taken as this part of the procedure is exothermic.

54.7, 43.2. HRMS ES (*m/z*) mass Calcd for $C_{16}H_{18}NO_2$ 256.1338 $(M+H)^+$, Found 256.1340.



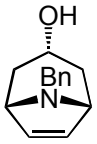
5.34

Synthesis of Azabicycle **5.34**. A 100-mL round-bottom flask was charged with **5.32** (610 mg, 2.39 mmol), CH_2Cl_2 (25 mL), and Ru catalyst **5.33** (75 mg, 0.12 mmol, 5 mol %) at 22 °C. The reaction mixture was allowed to stir for 18 h, after which time the volatiles were removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (dry load, 4:1 to 1:1 hexanes:EtOAc) to give **5.34** (323 mg, 1.42 mmol, 60%) as slight brown oil. IR (neat): 3057 (w), 2976 (w), 2901 (w), 1716 (s), 1635 (s), 1412 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): reported as a 1:1 mixture of amide rotamers, δ 7.55–7.42 (m, 5H), 6.33 (br s, 1H), 6.21 (br s, 1H), 5.35 (br s, 1H), 4.74 (br s, 1H), 3.05–2.95 (m, 1H), 2.58–2.44 (m, 2H), 2.38–2.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1, 168.1, 134.8, 134.6, 133.4, 130.8, 128.8, 127.3, 58.7, 55.0, 46.7, 45.6. HRMS ES (*m/z*) mass Calcd for $C_{14}H_{14}NO_2$ 228.1025 $(M+H)^+$, Found 228.1018.

Synthesis of Azabicyclic Precursor to **5.26** (shown here on the left).[109] A 200-mL round-bottom flask was charged with **5.34** (1.35 g, 5.94 mmol), THF (59 mL), and the reaction vessel was allowed to cool to −78 °C in a dry ice/acetone bath. To this solution was added L-Selectride® (6.53 mL, 6.53 mmol, 1.00 M in THF) dropwise over a period of 10 min, after which time the flask was removed from the dry ice batch and the mixture was allowed to stir at 22 °C for 1 h. The reaction vessel was allowed to cool to 0 °C in an ice-bath and the reaction was quenched by the sequential slow addition of a 1.0 M solution of NaOH (20 mL) and H_2O_2 (37 wt % in H_2O, 20 mL). At this point, the flask was removed from the ice-bath and the mixture was allowed to stir at 22 °C for 15 min, after which time a 1.0 M solution of HCl (20 mL) was added. The resulting solution was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The remaining yellow residue was purified by silica gel chromatography (dry load, 2:1 to 1:2 hexanes:EtOAc) to deliver the precursor to **5.26** as colorless oil (1.09 g, 4.75 mmol, 80%). IR (neat): 3408 (br), 2974 (w), 2945 (m), 2943 (m), 1621 (s) 1451 (s) 1067 (s), 696 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.50–7.39 (m, 5H), 6.51 (dd, *J* = 5.9, 2.0 Hz, 1H), 6.36 (dd, *J* = 5.9, 2.0 Hz, 1H), 5.14 (br s, 1H), 4.47 (br s, 1H), 4.05–4.01 (m, 1H), 2.50–2.44 (m, 1H), 2.24 (d, *J* = 9.7 Hz, 1H), 2.14–2.08 (m, 1H), 1.91 (d, *J* = 14.8

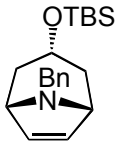
(109) The precursor to **5.26** is the azabicycle containing a secondary alcohol derived from hydride reduction of the carbonyl in **5.34**. The diastereomeric identity of this alcohol (endo vs. exo) was assigned by correlation to related azabicyclic substrates. See the experimental section of Ch 3.

Hz, 1H), 1.79 (d, J = 14.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 136.7, 135.6, 133.2, 130.3, 128.6, 127.3, 65.7, 60.1, 55.8, 37.3, 35.5. HRMS ES (*m/z*) mass Calcd for $C_{14}H_{15}NO_2$ 229.1098 $(M)^+$, Found 229.1102.



5.26

Synthesis of Olefin Methathesis Substrate **5.26**. A 200-mL round-bottom flask, fitted with an addition funnel, was charged with the azabicyclic precursor to **5.26** (1.09 g, 4.75 mmol), THF (48 mL), and the mixture was allowed to cool to −78 °C in a dry ice/acetone bath. To this solution was added DIBAL-H (16.9 mL, 23.8 mmol, 20% by volume in hexane) dropwise over a period of 15 min. The resulting mixture was allowed to stir at –78 °C for 10 min, after which time the flask was removed from the dry ice bath and the mixture was allowed to stir at 22 °C for 2 h. At this time, the mixture was allowed to cool to 0 °C in an ice-bath and the reaction was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (20 mL). At this point, the flask was removed from the ice-bath and the mixture was allowed to stir at 22 °C for 15 h, after which time it was washed with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the volatiles removed in vacuo. The dark brown residue was purified by silica gel chromatography (CH_2Cl_2 to 94:5:1 CH_2Cl_2:MeOH:NEt_3) to provide **5.26** as slight yellow solid (510 mg, 2.37 mmol, 50%). mp: 102–104 °C. IR (neat): 3408 (br), 2930 (s), 2836 (w), 1489 (m) 1438 (m), 1042 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.26–7.21 (m, 5H), 6.29 (s, 2H), 3.90–3.85 (m, 1H), 3.53 (s, 2H), 3.50 (br s, 2H), 2.28 (br s, 1H), 2.24 (dd, J = 6.0, 3.7 Hz, 1H), 2.20 (dd, J = 6.0, 3.7 Hz, 1H), 1.81–1.80 (m, 1H), 1.78–1.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 135.3, 128.6, 128.3, 126.8, 66.1, 64.0, 57.8, 37.8. HRMS ES (*m/z*) mass Calcd for $C_{14}H_{18}NO$ 216.1388 $(M+H)^+$, Found 216.1399.

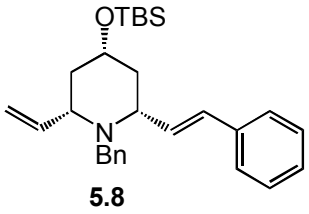


5.24

Synthesis of Olefin Metathesis Substrate **5.24**.[110] Azabicycle **5.24** was prepared by TBS protection of the alcohol in **5.26**. IR (neat): 2925 (s), 2853 (w), 1252 (w), 1065 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.24 (d, J = 7.2 Hz, 2H), 5.98 (br s, 2H), 4.00 (dd, J = 5.2 Hz, 1H), 3.60 (br s, 2H), 3.46 (br s, 2H), 2.14 (br s, 2H), 1.56 (d, J = 12.0, 2H), 0.85 (s, 9H), –0.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7, 132.6, 128.8, 126.8, 65.2, 64.1, 57.7, 37.5, 25.9, 17.9, 0.02, –4.7. HRMS ES (*m/z*) mass Calcd for $C_{20}H_{31}NOSi$ 329.2175 $(M)^+$, Found 329.2184.

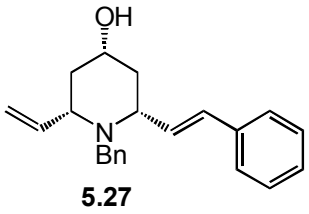
(110) For the TBS protection of a related azabicycle see the experimental section of Ch 3.

Representative procedure for Ru-catalyzed asymmetric ring-opening metathesis/cross-metathesis reactions of azabicycles, synthesis of piperidine 5.8: Ru complex **5.2** (3.8 mg, 0.0046 mmol) was dissolved in styrene (106 μL, 0.930 mmol) in a 4-mL vial. The resulting mixture was added by syringe to a solution of azabicycle **5.6** (20.0 mg, 0.0930 mmol) in styrene (106 μL, 0.930 mmol) in a 4-mL vial. The mixture was allowed to stir for 24 h, upon which time the volatiles were removed in vacuo. The resulting dark brown residue was purified by silica gel column chromatography (98:2 CH_2Cl_2:MeOH) to give piperidine **5.8** as colorless oil (23.8 mg, 0.0744 mmol, 80%). IR (neat): 3363 (s), 2955 (m), 2930 (m), 2338 (s), 1104 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.12 (m, 10H), 6.44 (d, *J* = 15.9 Hz, 1H), 5.99 (dd, *J* = 15.9, 8.6 Hz, 1H), 5.81 (ddd, *J* = 17.6, 10.0, 8.8 Hz, 1H), 5.18 (dd, *J* = 17.2, 0.9 Hz, 1H), 5.04 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.92 (d, *J* = 15.3 Hz, 1H), 3.73 (d, *J* = 15.3 Hz, 1H), 3.69–3.64 (m, 1H), 3.07 (ddd, *J* = 14.4, 9.2, 2.8 Hz, 1H), 3.01 (ddd, *J* = 11.2, 8.8, 2.4 Hz, 1H), 1.80–1.76 (m, 2H), 1.62–1.51 (m, 2H), 0.86 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ. 142.7, 140.1, 137.2, 134.6, 130.0, 129.3, 128.5, 127.8, 127.3, 126.3, 126.2, 115.6, 68.6, 64.4, 64.0, 55.2, 43.4, 43.4, 25.9, 18.2, –4.5. HRMS EI (*m/z*) mass Calcd for $C_{28}H_{40}NOSi$ 434.2879 $(M+H)^+$, Found 434.2889. $[\alpha]_D^{20}$ –63.52 (*c* = 0.5, $CHCl_3$) for a sample of *94% ee*. Determination of enantiomeric excess of **5.25** involved piperidine **5.27**, derived from TBAF deprotection of the secondary alcohol in **5.25**.



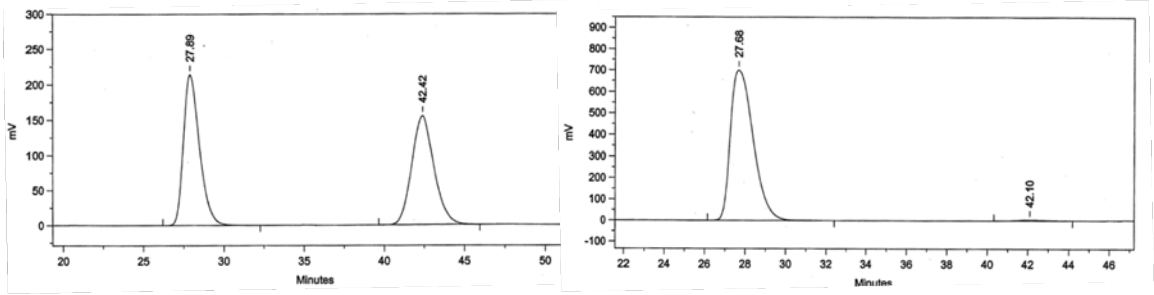
5.8

Piperidine **5.27**. IR (neat): 3333 (br), 3024 (w), 2936 (m), 2911 (m), 1495 (m), 1457 (m). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.30–7.09 (m, 10H), 6.45 (d, *J* = 15.9 Hz, 1H), 5.98 (dd, *J* = 15.9, 8.6 Hz, 1H), 5.82 (ddd, *J* = 17.2, 10.1, 8.4 Hz, 1H), 5.21 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.07 (dd, *J* = 10.1, 1.5 Hz, 1H), 3.94 (d, *J* = 15.5 Hz, 1H), 3.74 (d, *J* = 15.5 Hz, 1H), 3.76–3.68 (m, 1H), 3.11 (ddd, *J* = 11.6, 8.8, 2.8 Hz, 1H), 3.05 (ddd, *J* = 11.2, 8.4, 2.8 Hz, 1H), 1.96–1.90 (m, 2H), 1.64 (br s, 1H), 1.58–1.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 140.1, 137.1, 134.2, 130.2, 129.2, 128.5, 127.9, 127.4, 126.3, 126.2, 115.9, 68.0, 64.4, 64.1, 55.2, 43.0. HRMS EI (*m/z*) mass Calcd for $C_{22}H_{25}NO$ 319.1936 $(M)^+$, Found 319.1938. The enantiomeric purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm.



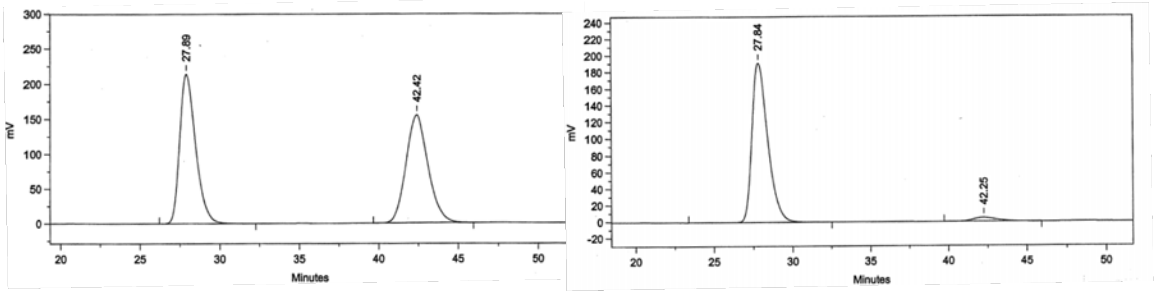
5.27

Authentic racemic **>98% *ee* with Ru catalyst 5.2**



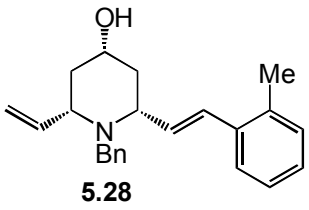
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	27.677		0.0000	0.000	54585420.0	99.247	BB	1.300	699891.60	99.341
2	42.096		0.0000	0.000	414404.3	0.753	BB	1.489	4639.53	0.659

Authentic racemic ***94% ee* with Ru catalyst 5.4**



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	27.837		0.0000	0.000	13339090.0	96.811	BB	1.163	191217.20	97.695
2	42.245		0.0000	0.000	439441.7	3.189	BB	1.623	4512.16	2.305

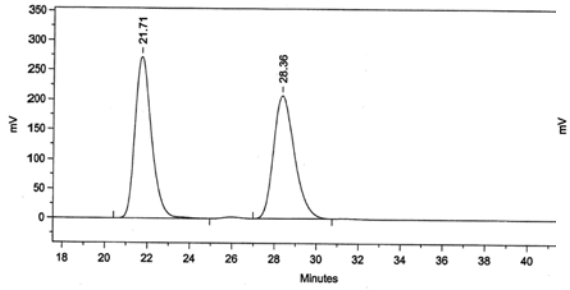
Characterization data for piperidine products:



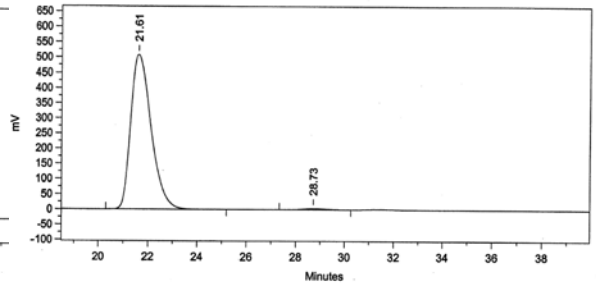
5.28

Piperidine **5.28.** IR (neat): 3333 (br), 2930 (w), 2917 (w), 2836 (w), 1483 (w), 1451 (m), 1086 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.32 (d, *J* = 7.0 Hz, 2H), 7.27–7.17 (m, 3H), 7.10-7.03 (m, 3H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 5.90 (dd, *J* = 15.8, 8.6 Hz, 1H), 5.83 (ddd, *J* = 17.4, 10.1, 8.4 Hz, 1H), 5.21 (dd, *J* = 17.4, 0.9 Hz, 1H), 5.07 (dd, *J* = 10.1, 1.3 Hz, 1H), 3.97 (d, *J* = 15.4 Hz, 1H), 3.78 (d, *J* = 15.4 Hz, 1H), 3.77–3.70 (m, 1H), 3.13 (ddd, *J* = 11.2, 8.6, 2.3 Hz, 1H), 3.06 (ddd, *J* = 11.2, 8.4, 2.6 Hz, 1H), 2.31 (s, 3H), 1.97–1.91 (m, 2H), 1.64 (br s, 1H), 1.60–1.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 140.0, 136.2, 135.6, 135.1, 130.1, 129.1, 128.1, 127.9, 127.3, 126.3, 126.1, 125.9, 115.9, 68.0, 64.3, 64.2, 55.1, 43.2, 43.0, 19.8. HRMS ES (*m/z*) mass Calcd for $C_{23}H_{28}NO$ 334.2171 $(M+H)^+$, Found 334.2176. $[\alpha]_D^{25}$ –106.2 (*c* 1.0, $CHCl_3$) for a sample of *>98% ee*. The enantiomeric purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm.

Authentic racemic

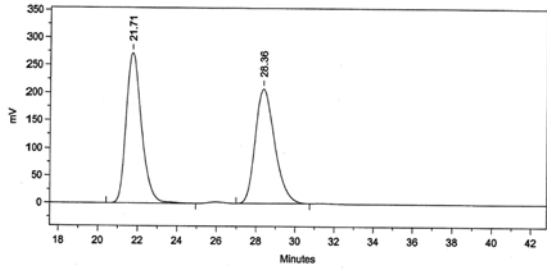


***98% ee* with Ru catalyst 5.2**

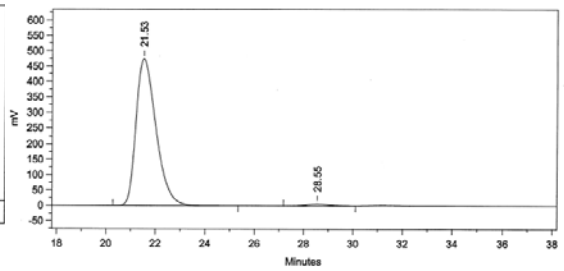


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	21.608		0.0000	0.000	29053440.0	99.105	BV	0.954	507718.20	99.197
2	28.727		0.0000	0.000	262247.7	0.895	VB	1.064	4107.74	0.803

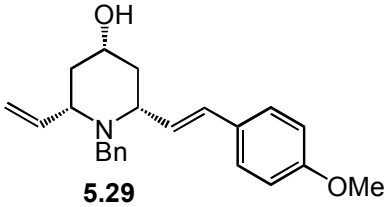
Authentic racemic



***98% ee* with Ru catalyst 5.4**



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	21.530		0.0000	0.000	26457090.0	98.769	BV	0.933	472780.70	98.909
2	28.554		0.0000	0.000	329741.9	1.231	VB	1.054	5212.81	1.091



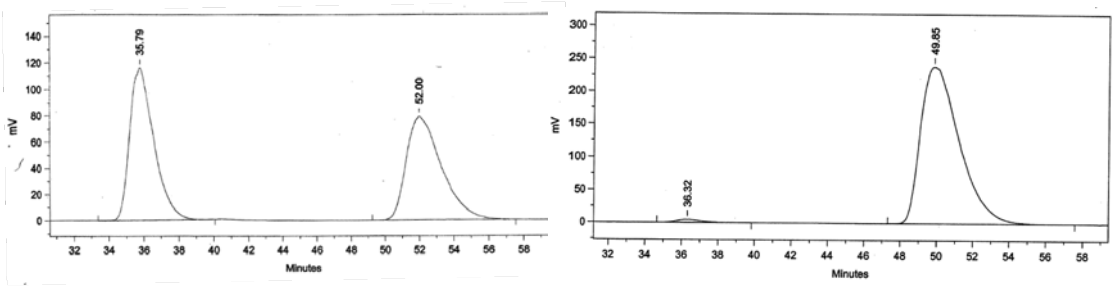
5.29

Piperidine **5.29**.[111] Method A for Ru-catalyzed AROM/CM was followed. IR (neat): 3355 (br), 2920 (m), 2839 (m), 1604 (m), 1511 (s), 1251 (m). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.28–7.14 (m, 5H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.38 (d, *J* = 15.9 Hz, 1H), 5.83 (dd, *J* = 15.9, 8.6 Hz, 1H), 5.81 (ddd, *J* = 17.4, 10.3, 8.4 Hz, 1H), 5.19 (dd, *J* = 17.4, 0.9 Hz, 1H), 5.05 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.93 (d, *J* = 15.4 Hz, 1H), 3.78 (s, 3H), 3.75–3.67 (m, 1H), 3.73 (d, *J* = 15.4 Hz, 1H), 3.07 (ddd, *J* = 11.2, 8.6, 2.4 Hz, 1H), 3.03 (ddd, *J* = 11.2, 8.4, 2.6 Hz, 1H), 1.94–1.90 (m, 2H), 1.62 (br s, 1H), 1.57–1.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 142.5, 140.3, 132.1, 130.0, 129.7, 129.3, 127.9, 127.6, 126.3, 115.9, 114.0, 68.1, 64.5, 64.2, 55.4, 55.2, 43.2, 43.2. HRMS ES (*m/z*) mass Calcd for $C_{23}H_{28}NO_2$ 350.2120 $(M+H)^+$, Found 350.2118. $[\alpha]_D^{25}$ –158.0 (*c* 1.0, $CHCl_3$) for a sample of *98% ee*. The enantiomeric purity of this compound was

(111) The ^{1}H NMR spectra of this compound contains residual water.

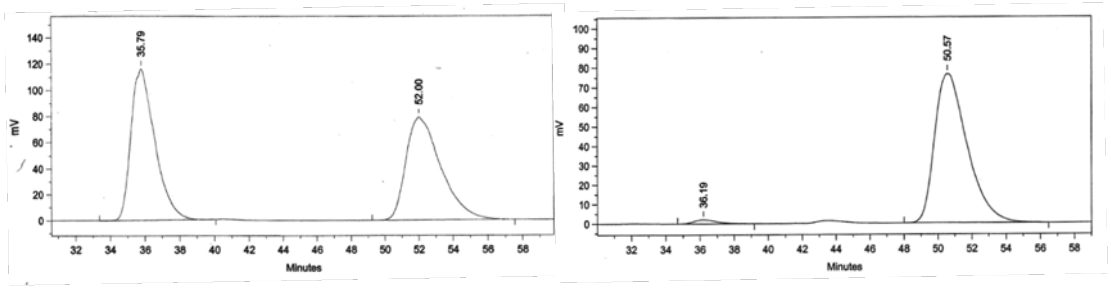
determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm.

Authentic racemic ***98% ee* with Ru catalyst 5.2**



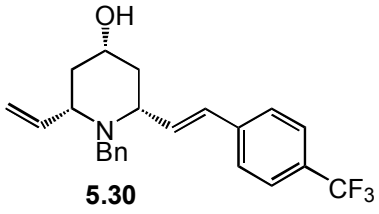
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	36.316		0.0000	0.000	430324.9	1.194	BB	1.551	4624.56	1.894
2	49.852		0.0000	0.000	35616210.0	98.806	BB	2.478	239586.60	98.106

Authentic racemic ***96% ee* with Ru catalyst 5.4**



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	36.190		0.0000	0.000	191776.8	1.838	BB	1.542	2072.18	2.633
2	50.572		0.0000	0.000	10243310.0	98.162	BB	2.228	76631.08	97.367

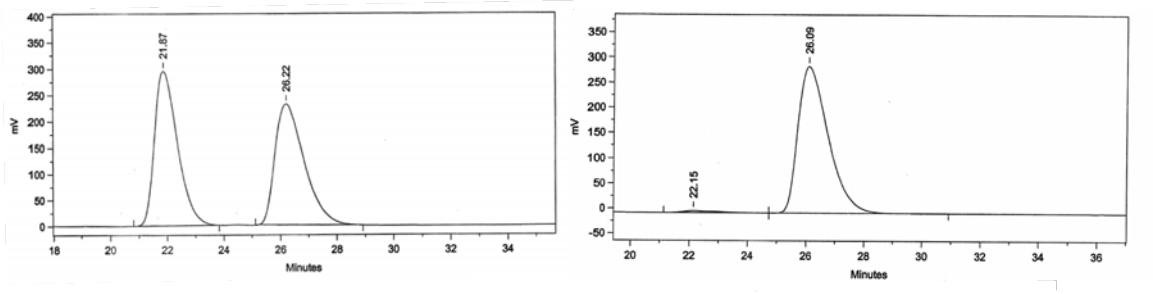
Representative procedure for Ru-catalyzed asymmetric ring-opening metathesis/cross-metathesis reactions, synthesis of piperidine 5.30: Ru complex **5.2** (2.8 mg, 0.0035 mol) was dissolved in toluene (37.0 μL) in a 4-mL vial. The resulting mixture was added by syringe to a solution of azabicycle **5.26** (15.0 mg, 0.0697 mmol), and *p*-trifluoromethylstyrene (51.0 μL, 0.350 mmol) in a 4-mL vial. The resulting solution was allowed to stir for 12 h, at which time another portion of Ru complex **5.2** (2.8 mg, 0.0035 mmol) was added. The resulting mixture was allowed to stir for a further 12 h, upon which time the volatiles were removed in vacuo. The resulting dark brown residue was purified by silica gel column chromatography (99:1 CH_2Cl_2:MeOH) to furnish piperidine **5.30** as colorless oil (21.0 mg, 0.0540 mmol, 78%). IR (neat): 3358 (br), 2936 (w), 2848 (w), 1608 (w), 1325 (s), 1155 (m), 1124 (m). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.46 (d, *J*



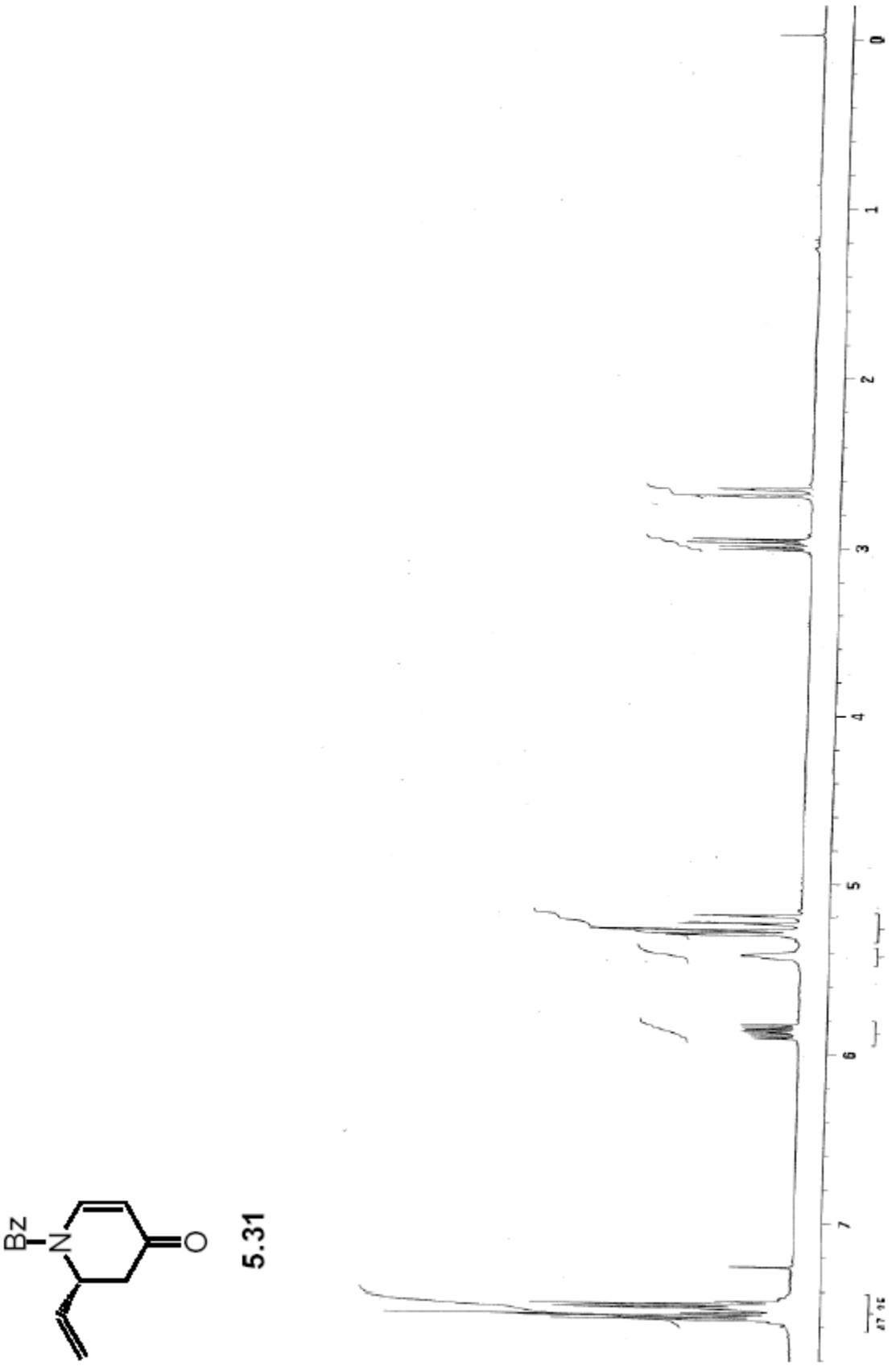
5.30

= 8.3 Hz, 2H), 7.28–7.16 (m, 5H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.44 (d, *J* = 16.1 Hz, 1H), 5.99 (dd, *J* = 16.1, 8.8 Hz, 1H), 5.83 (ddd, *J* = 17.3, 10.2, 8.4 Hz, 1H), 5.21 (dd, *J* = 17.3, 0.6 Hz, 1H), 5.08 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.98 (d, *J* = 15.4 Hz, 1H), 3.75–3.70 (m, 1H), 3.62 (d, *J* = 15.4 Hz, 1H), 3.11 (ddd, *J* = 11.2, 8.8, 2.6 Hz, 1H), 3.04 (ddd, *J* = 11.2, 8.4, 2.6 Hz, 1H), 1.97–1.89 (m, 2H), 1.57 (br s, 1H), 1.59–1.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 140.6, 140.4, 137.1, 129.0, 128.6, 128.0, 126.5, 126.3, 125.4, 125.3, 116.2, 68.0, 64.6, 64.6, 55.7, 42.9 42.7, –5.1. HRMS ES (*m/z*) mass Calcd for $C_{23}H_{25}F_3NO$ 388.1888 $(M+H)^+$, Found 388.1878. $[\alpha]_D^{25}$ –72.9 (*c* 0.5, $CHCl_3$) for a sample of *97% ee*. The enantiomeric purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm.

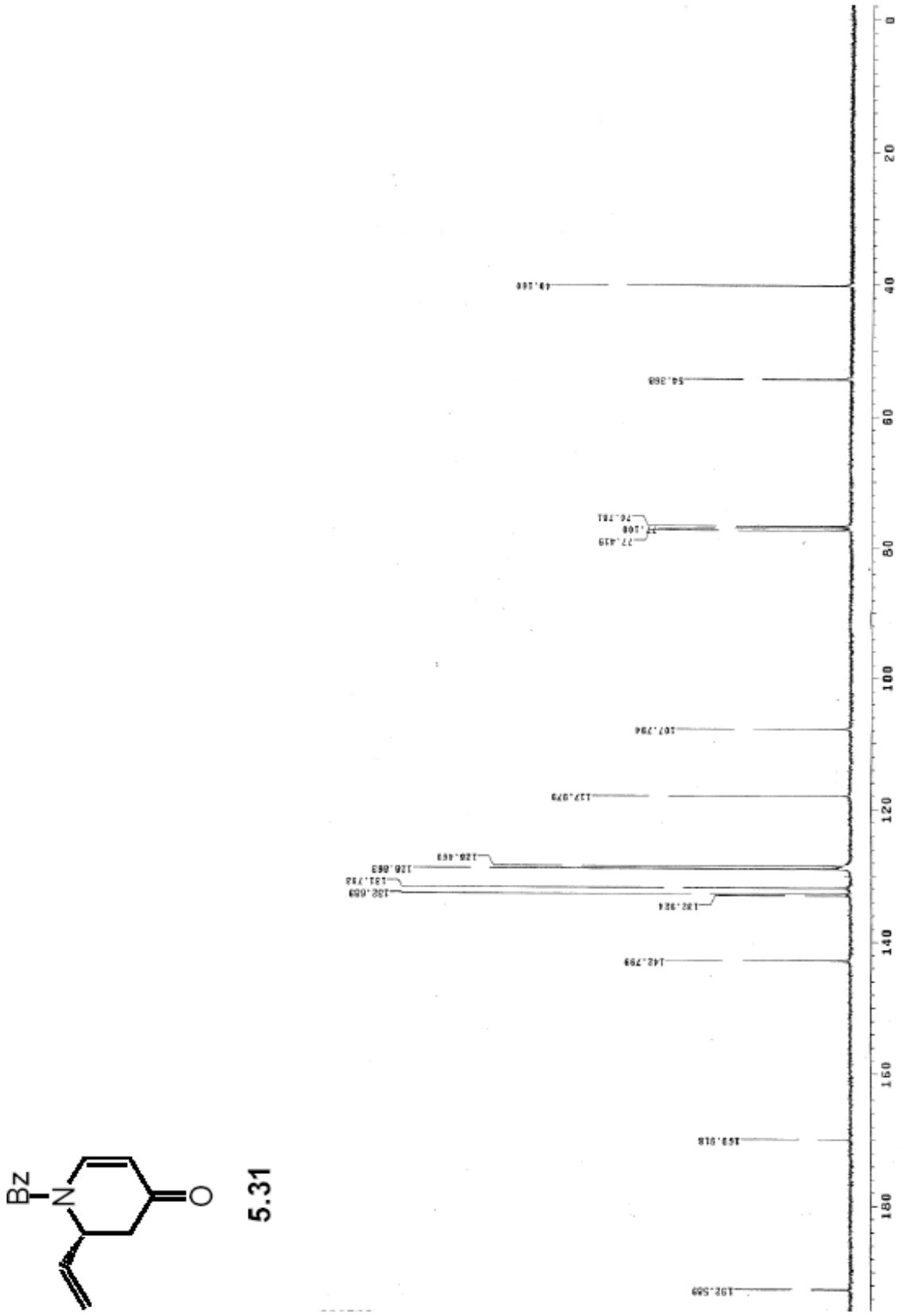
Authentic racemic **97% ee with Ru catalyst 5.2**



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%	
2	22.149		0.0000	0.000	296507.6	0.000	BV	1.255	3936.79	0.000	1.4
3	26.094		0.0000	0.000	21046120.0	0.000	VB	1.201	292004.50	0.000	98.6



5.31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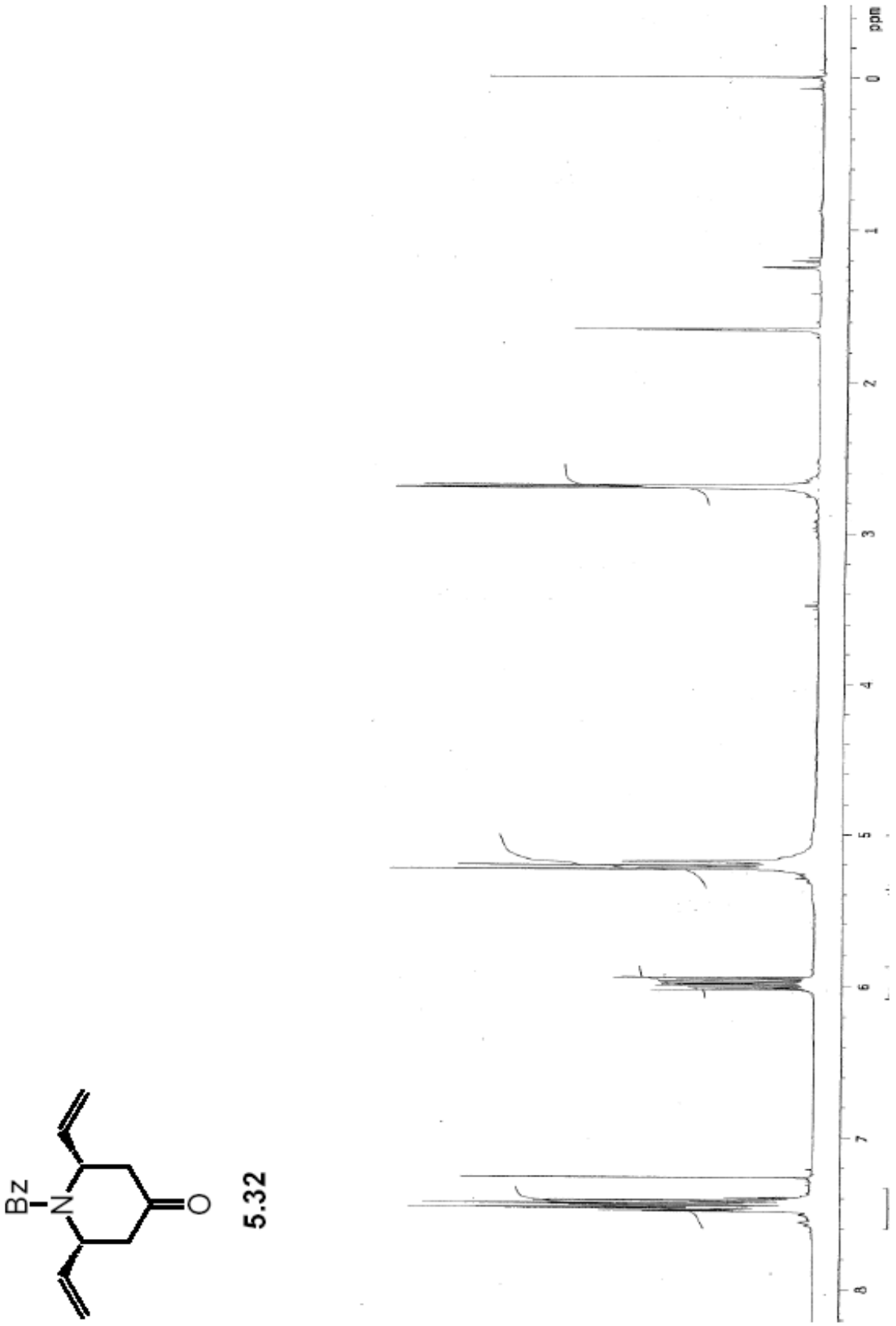
80
100
120
140
160
180



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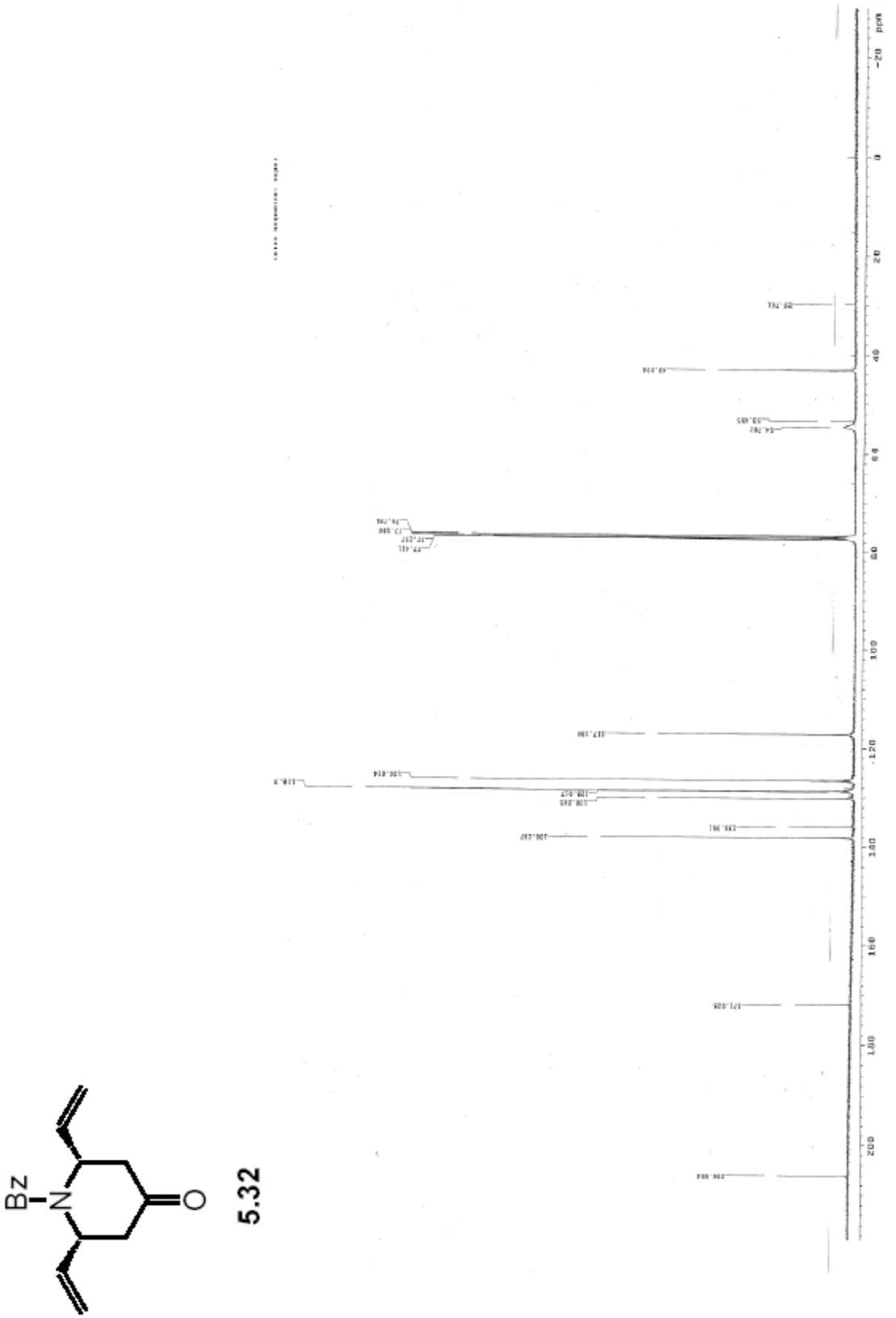
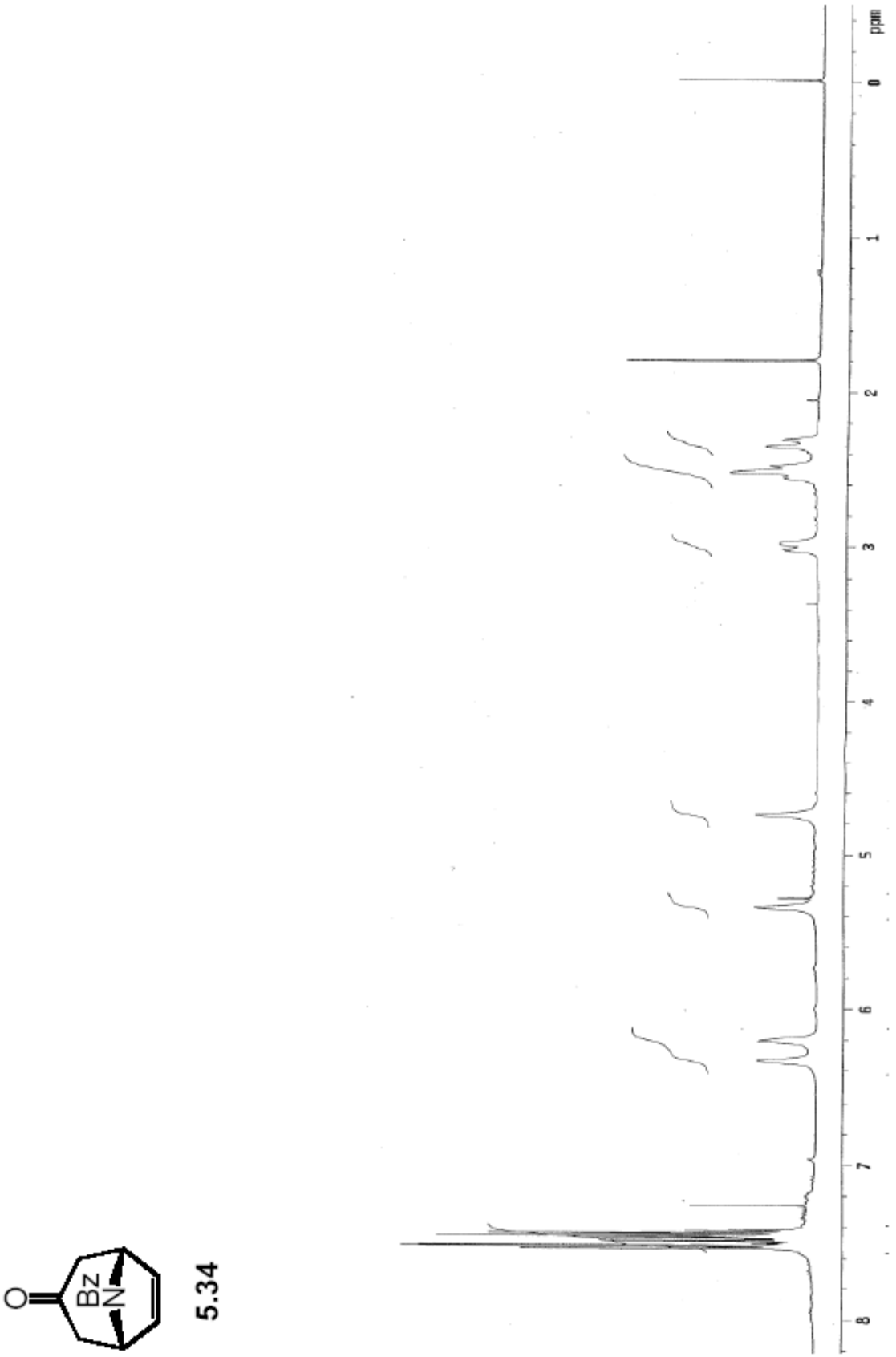


5.32



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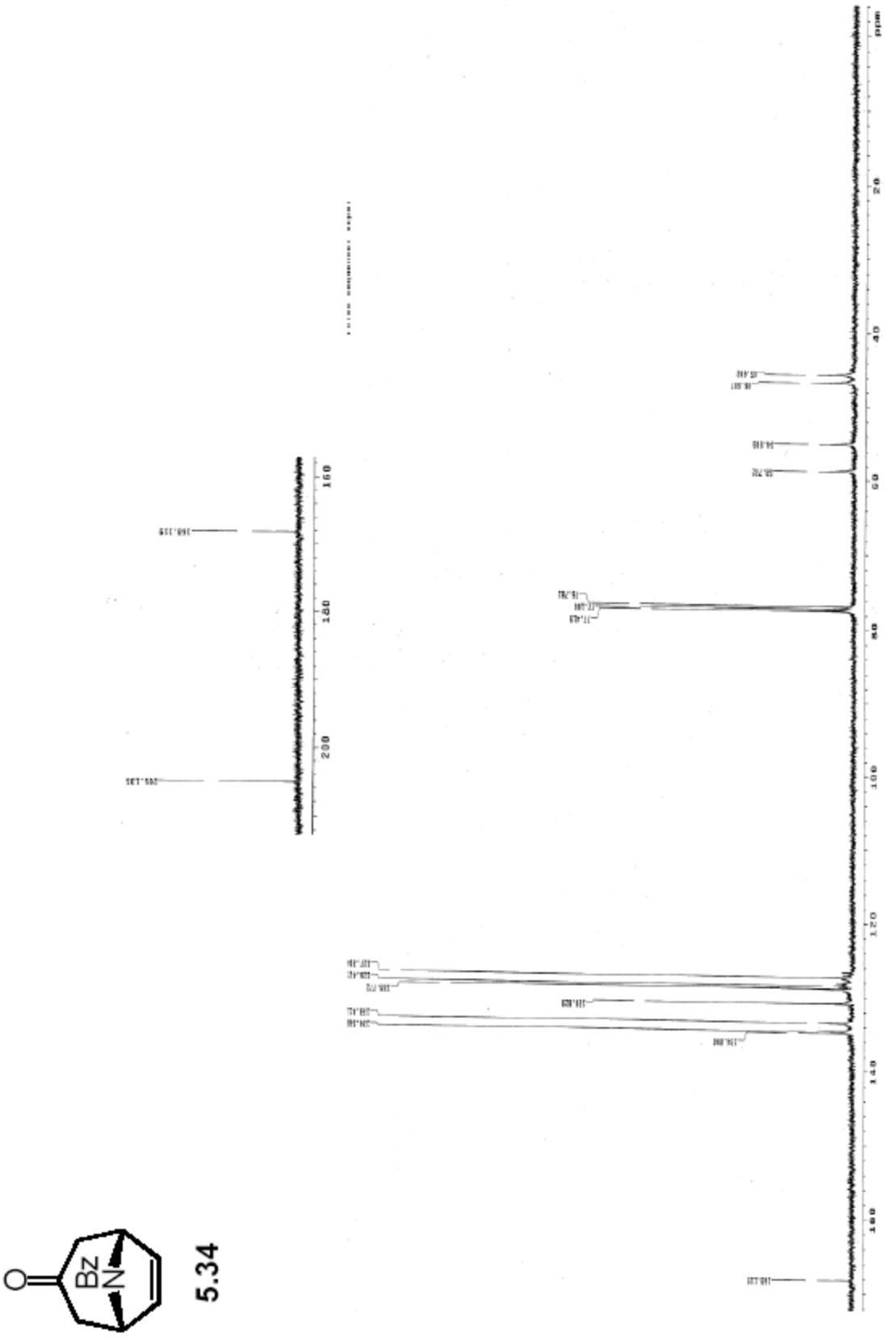

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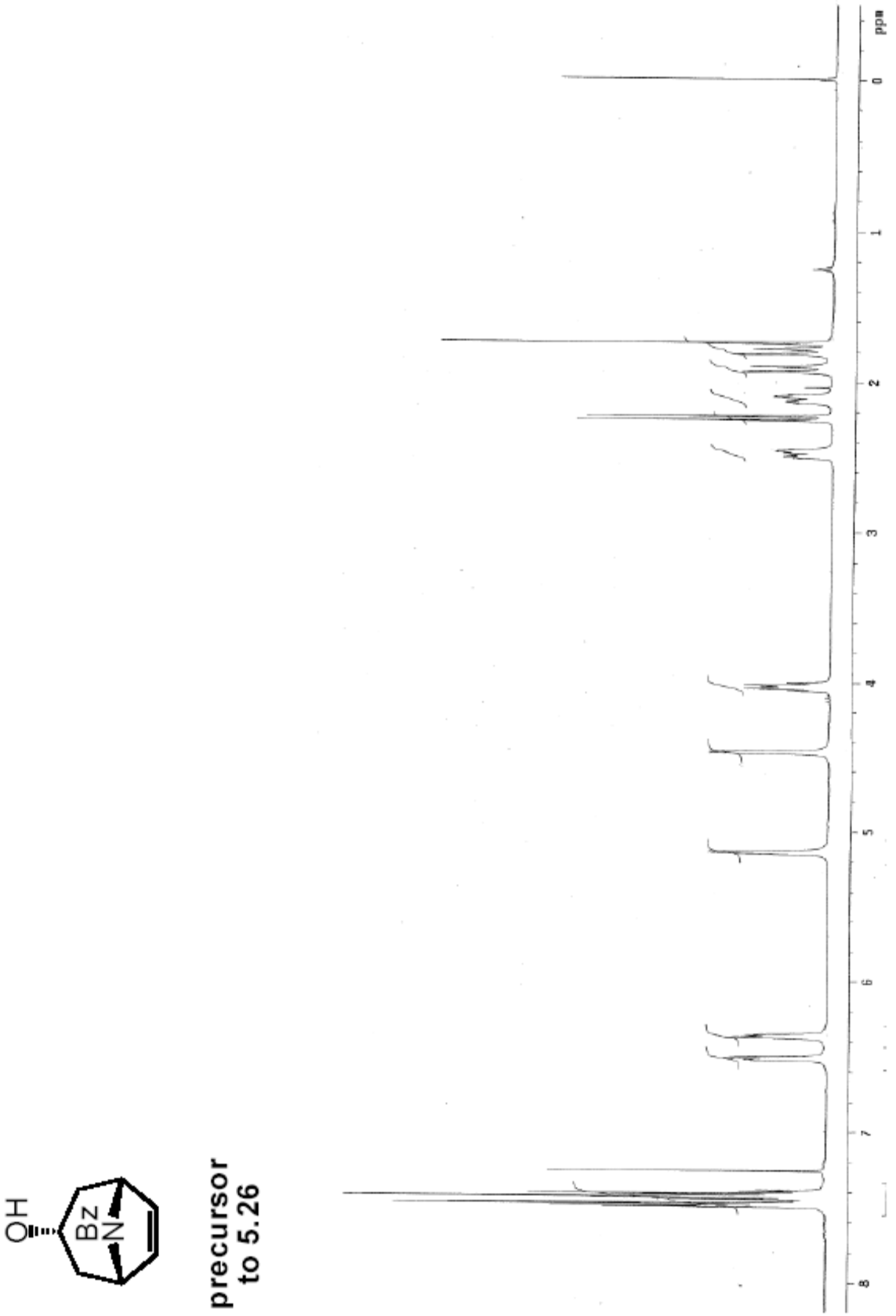
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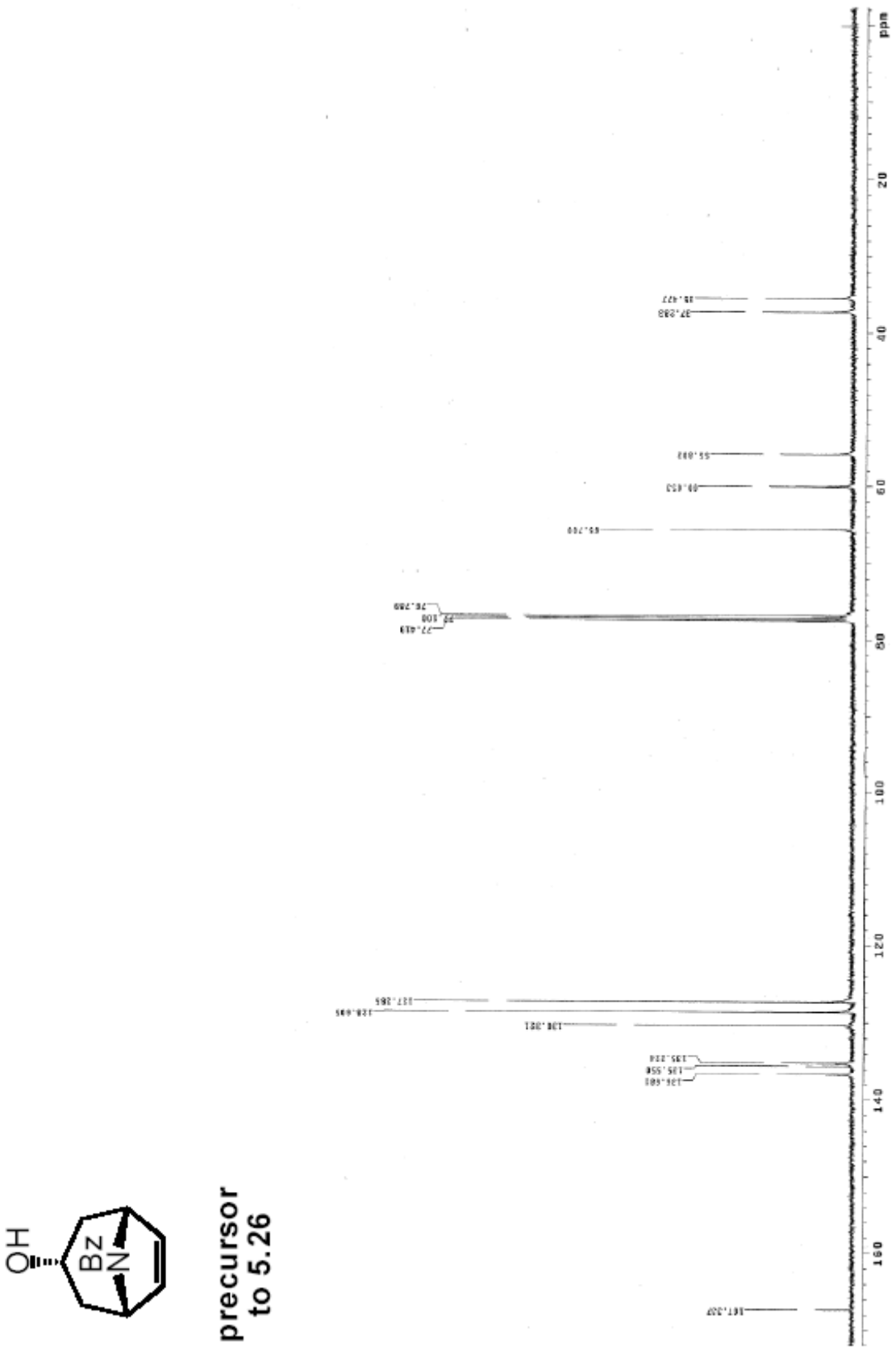
7
8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precursor
to 5.26
ppm
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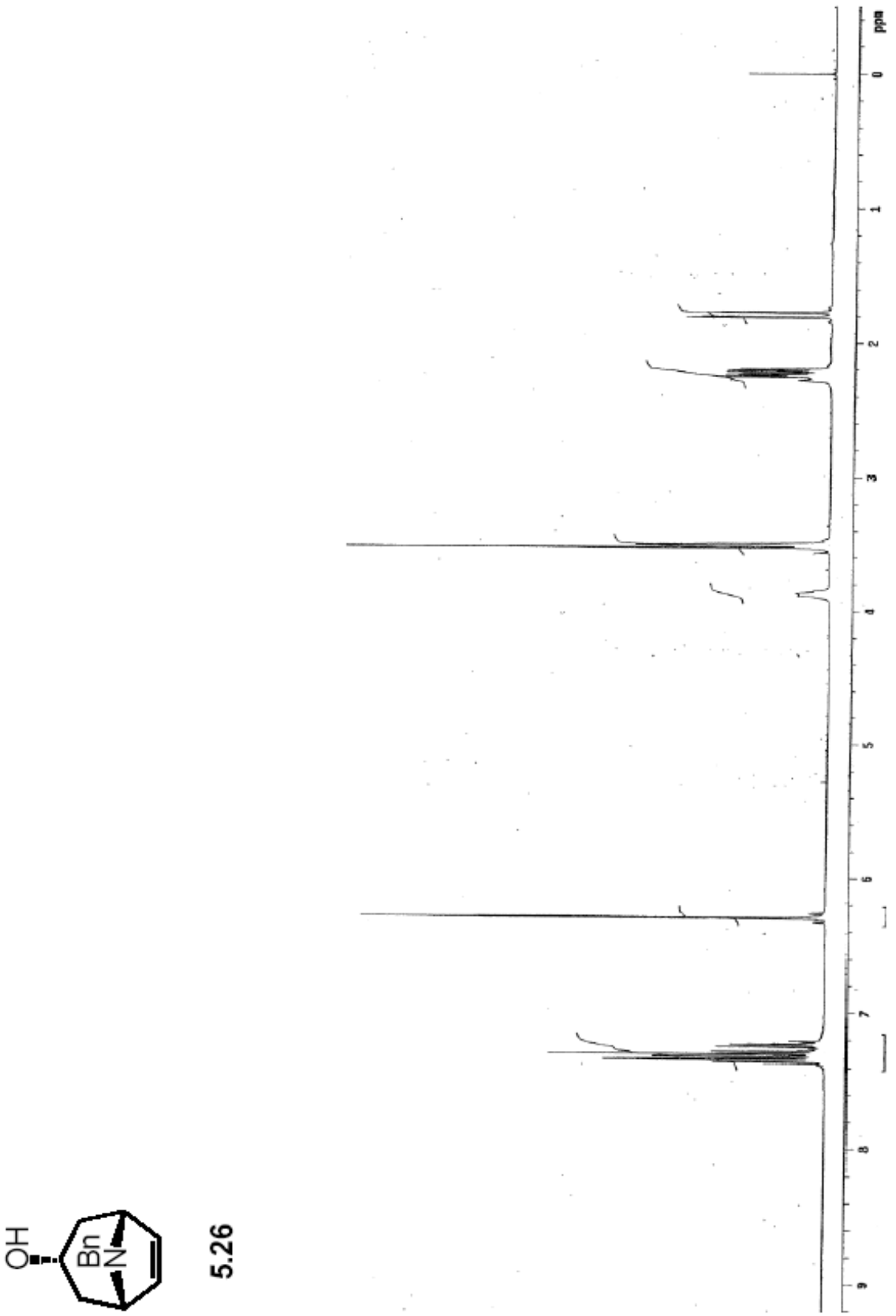
60
80
100
120
140
160



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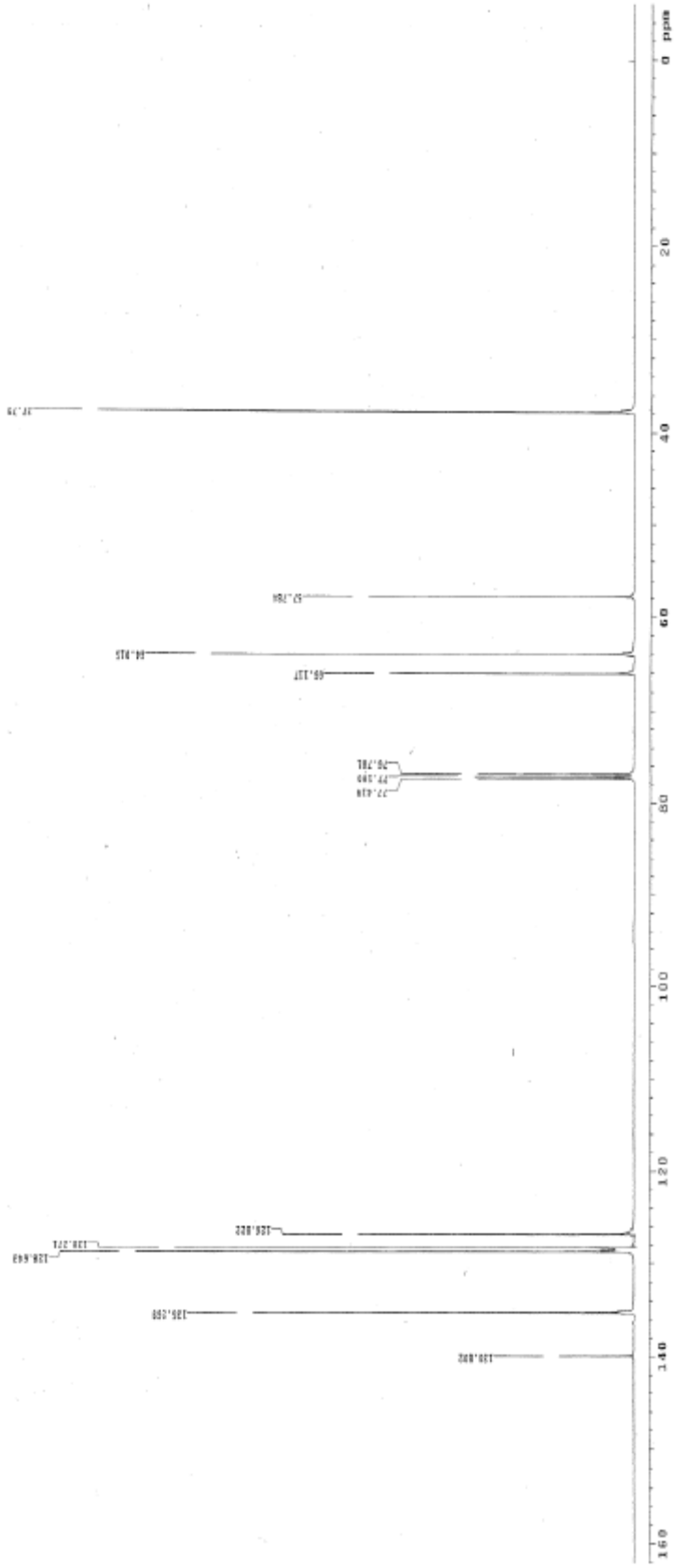
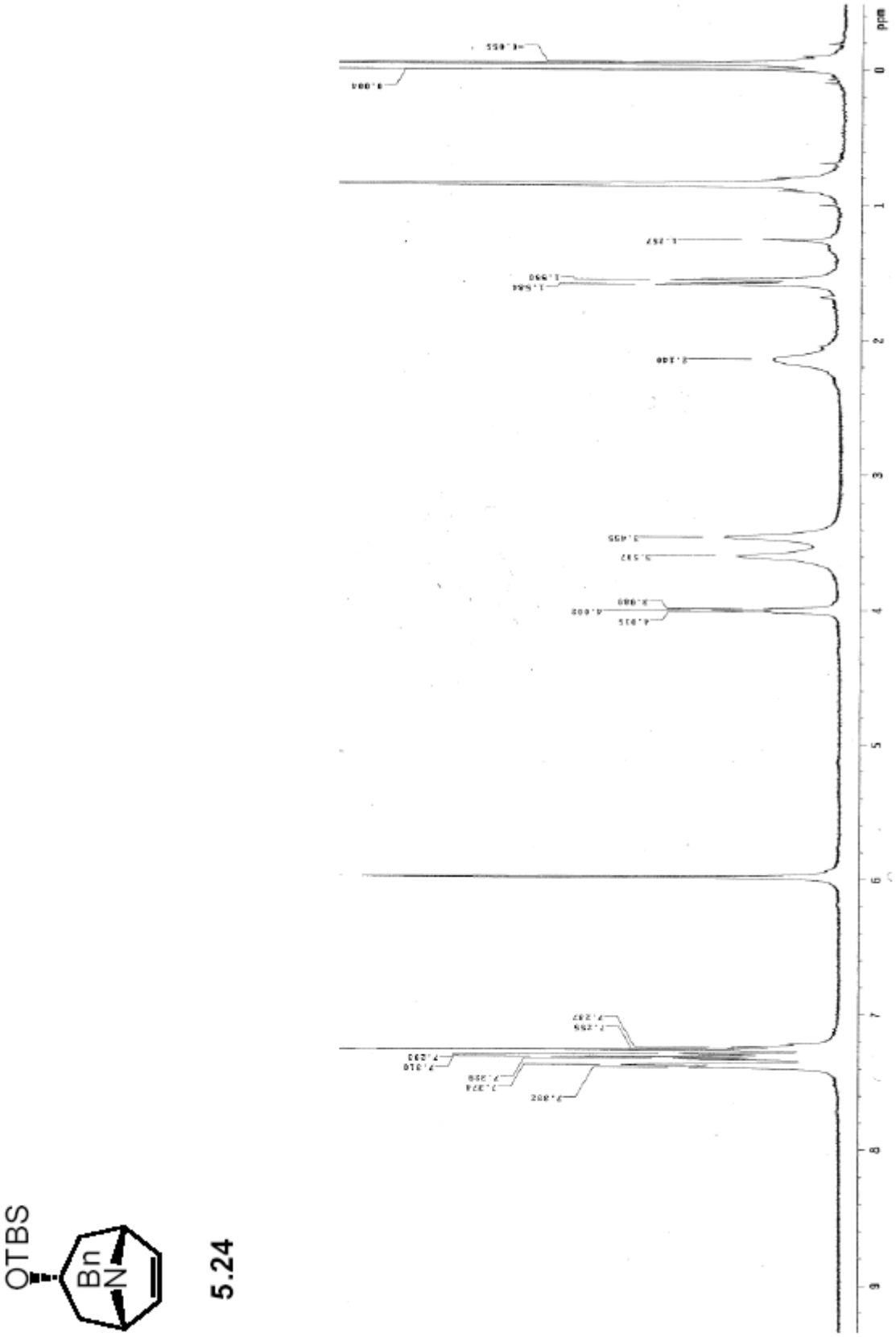
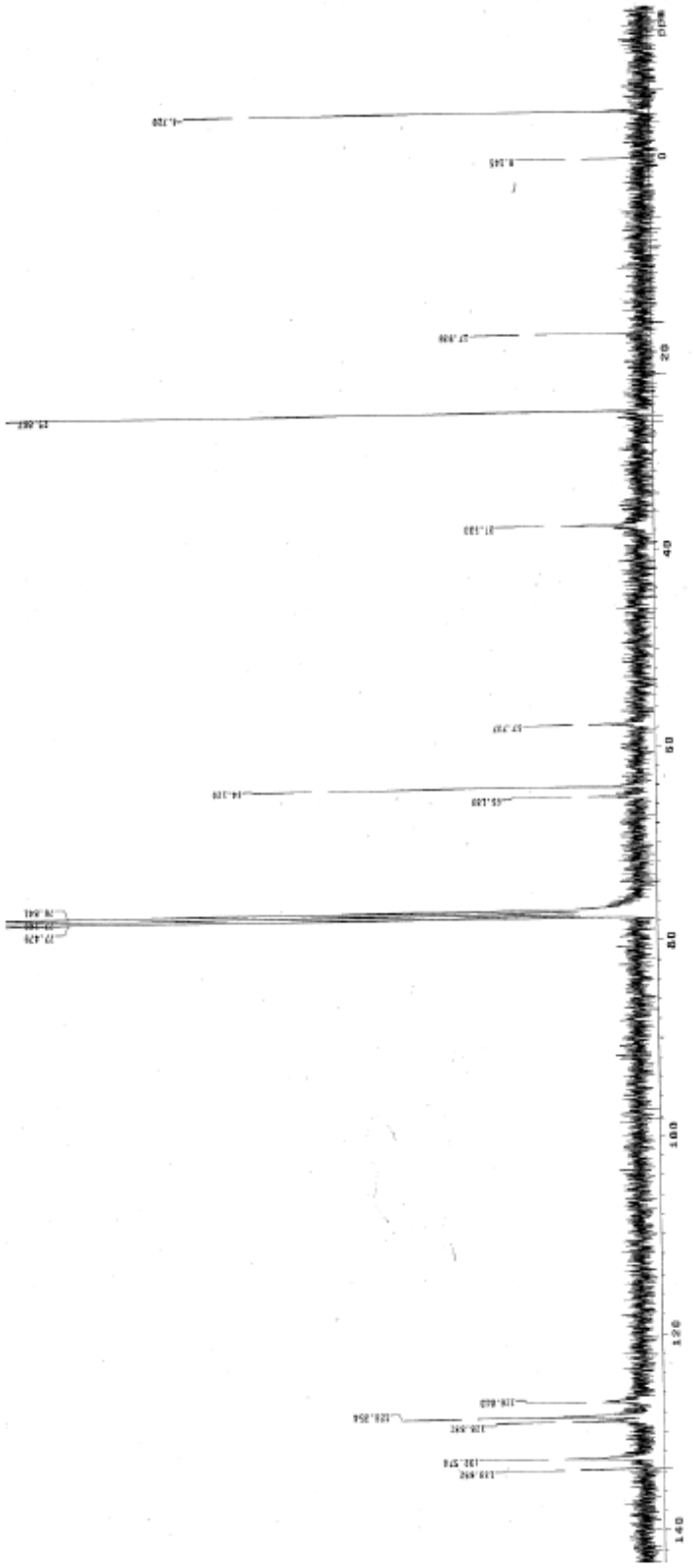


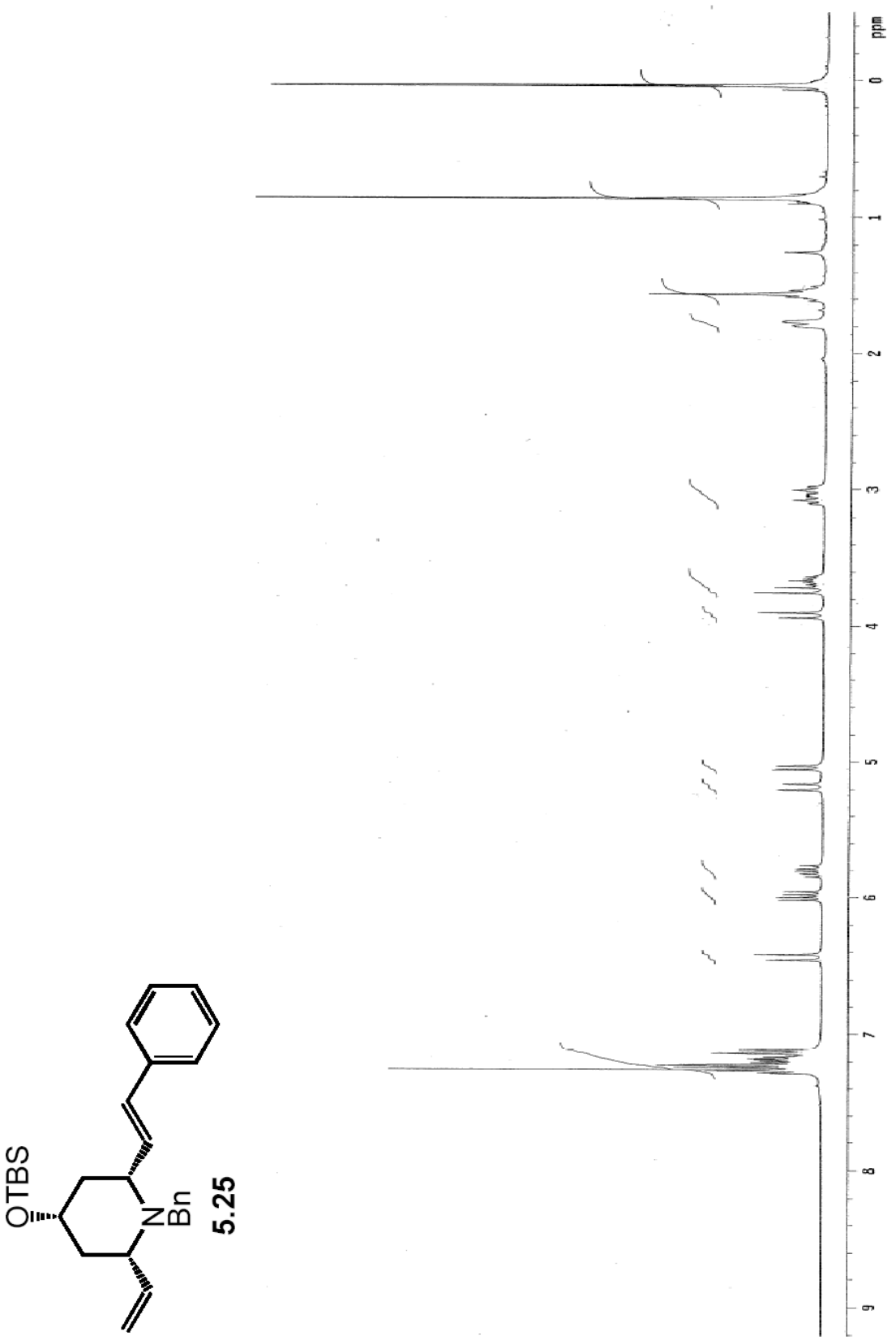
5.26



5.24

5.24

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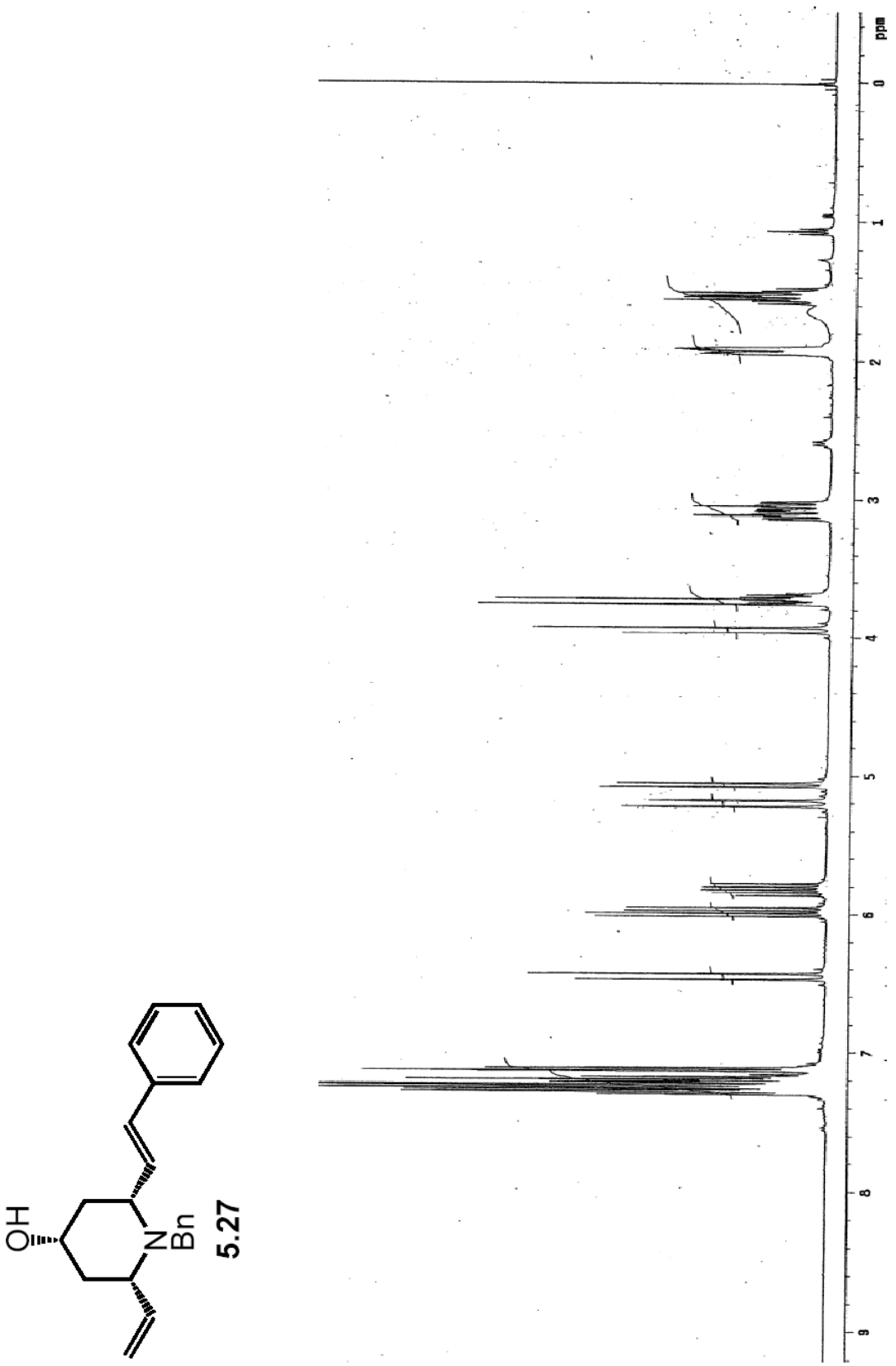
6
7
8
9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Bn
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ppm
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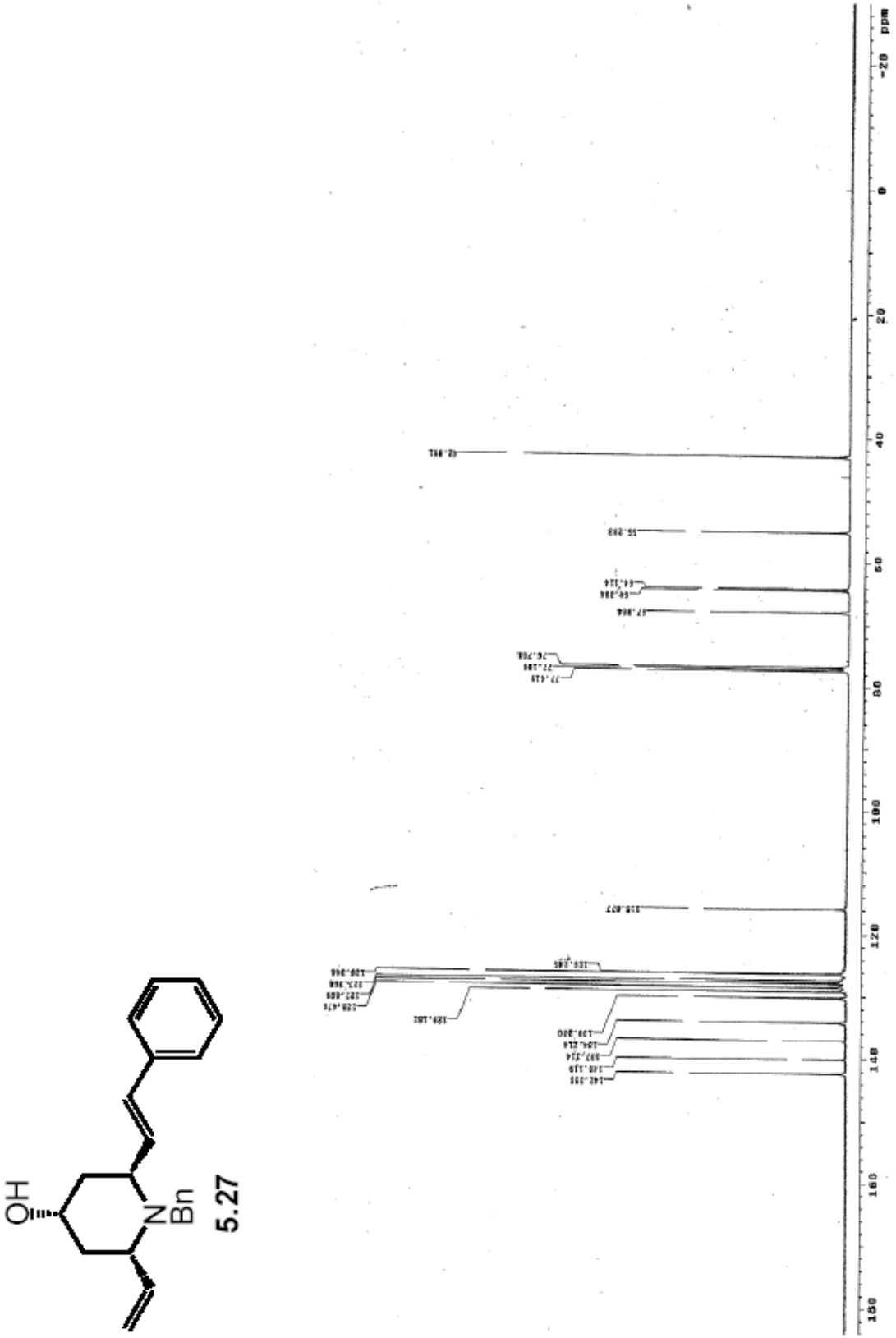
5
6
7
8
9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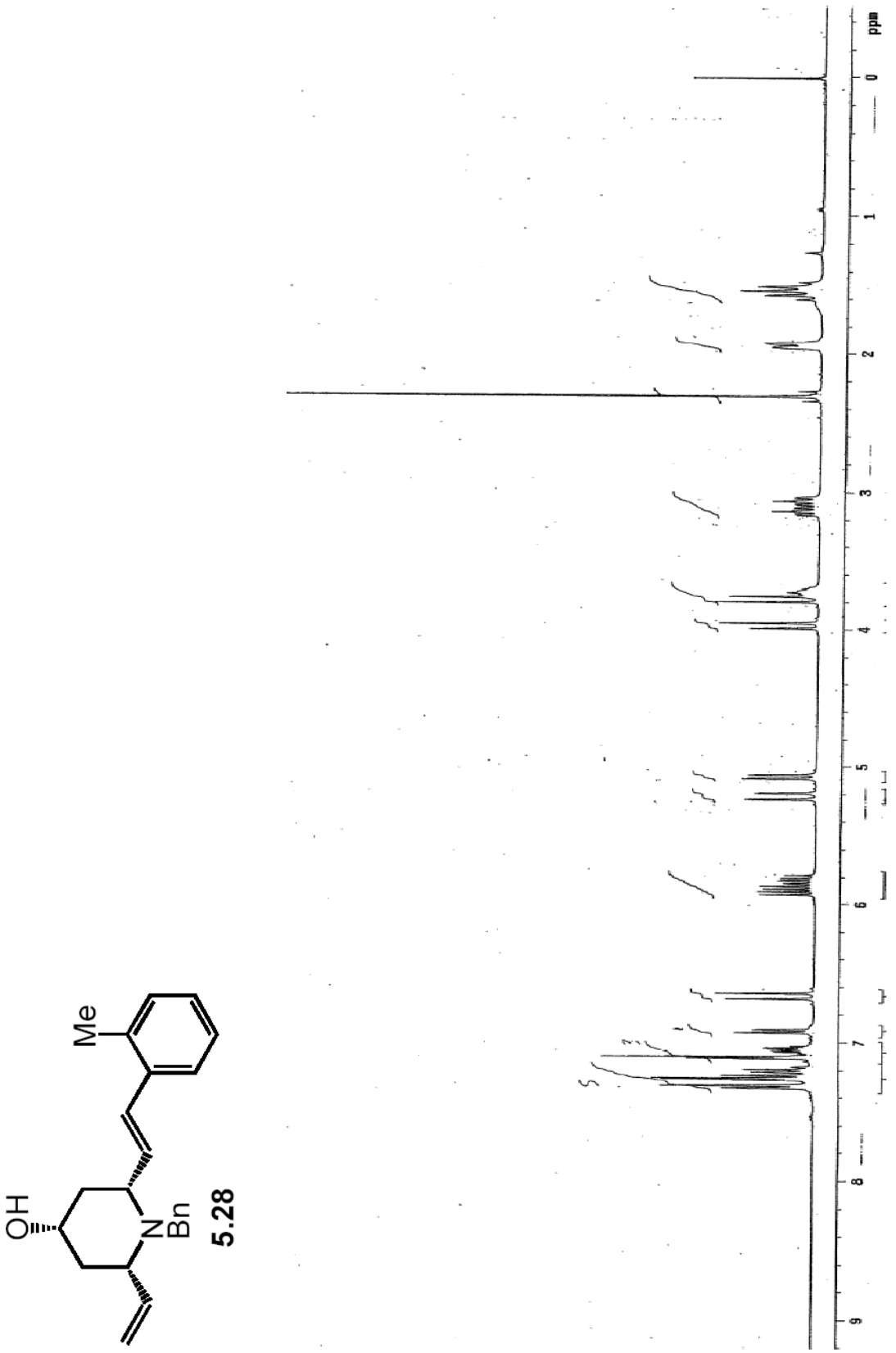
Bn
5.27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Bn
5.28
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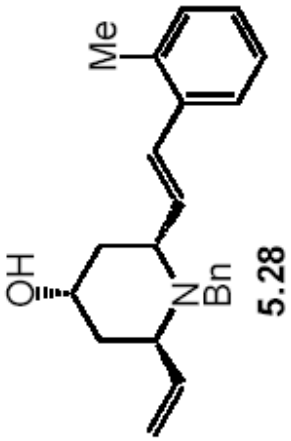
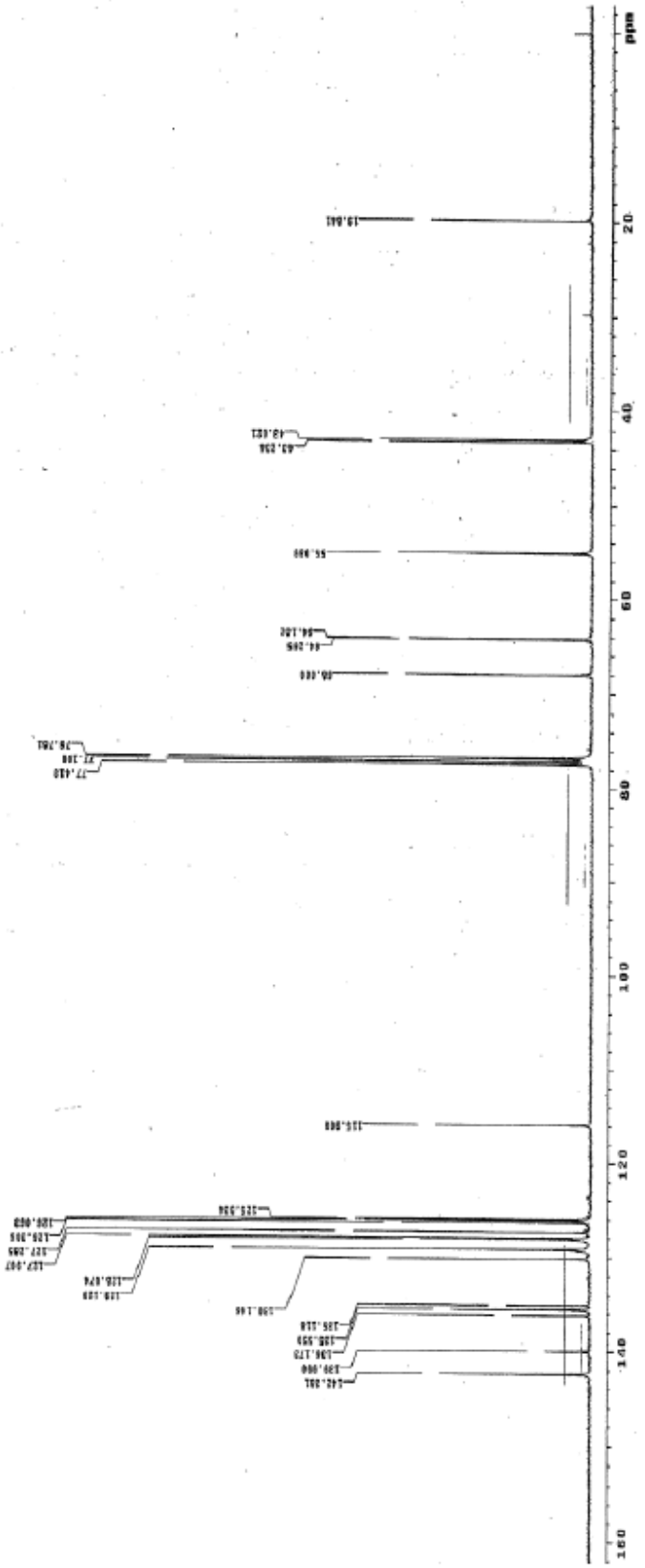
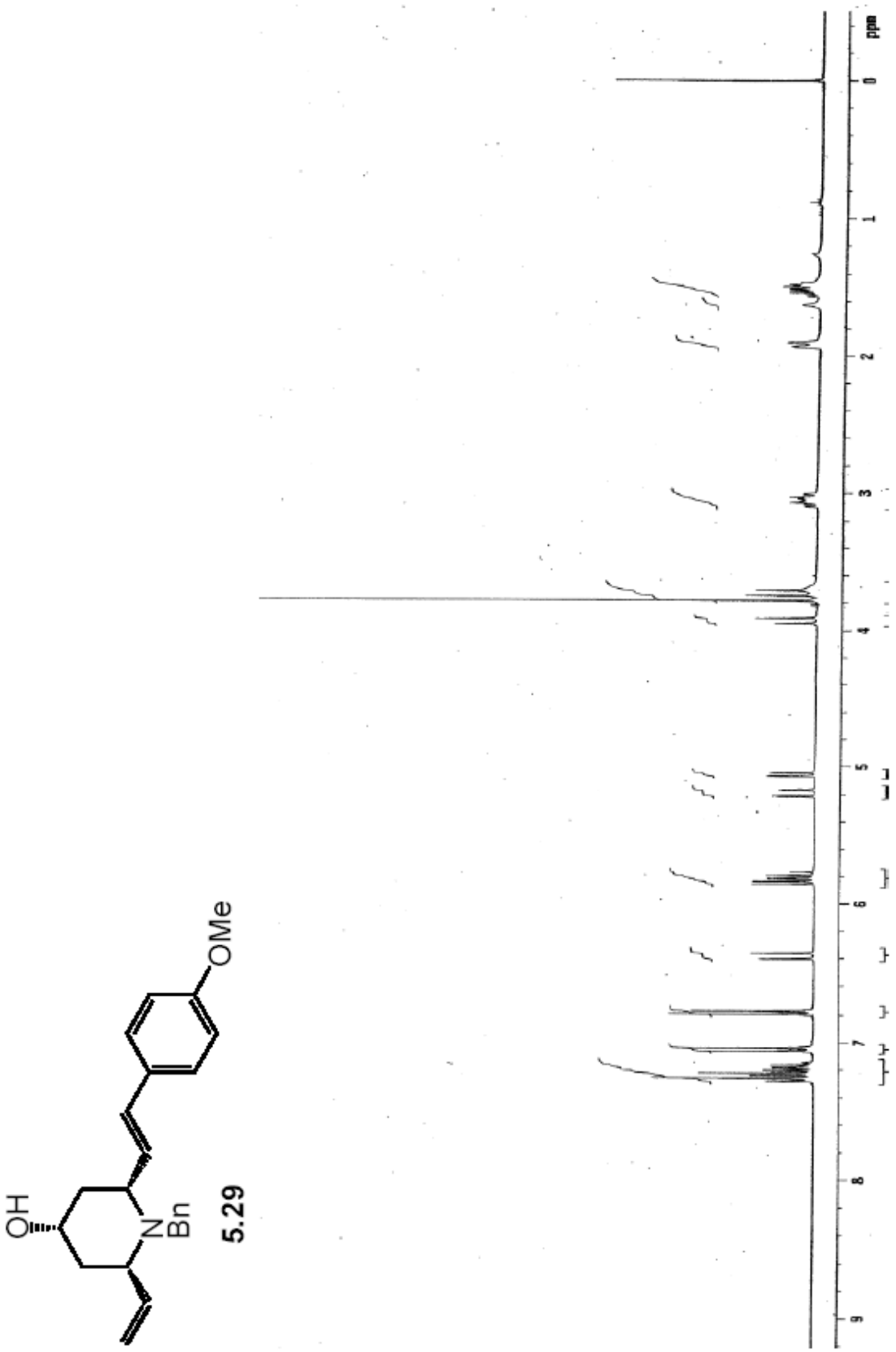
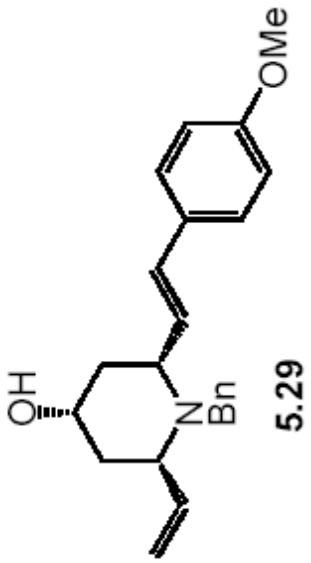


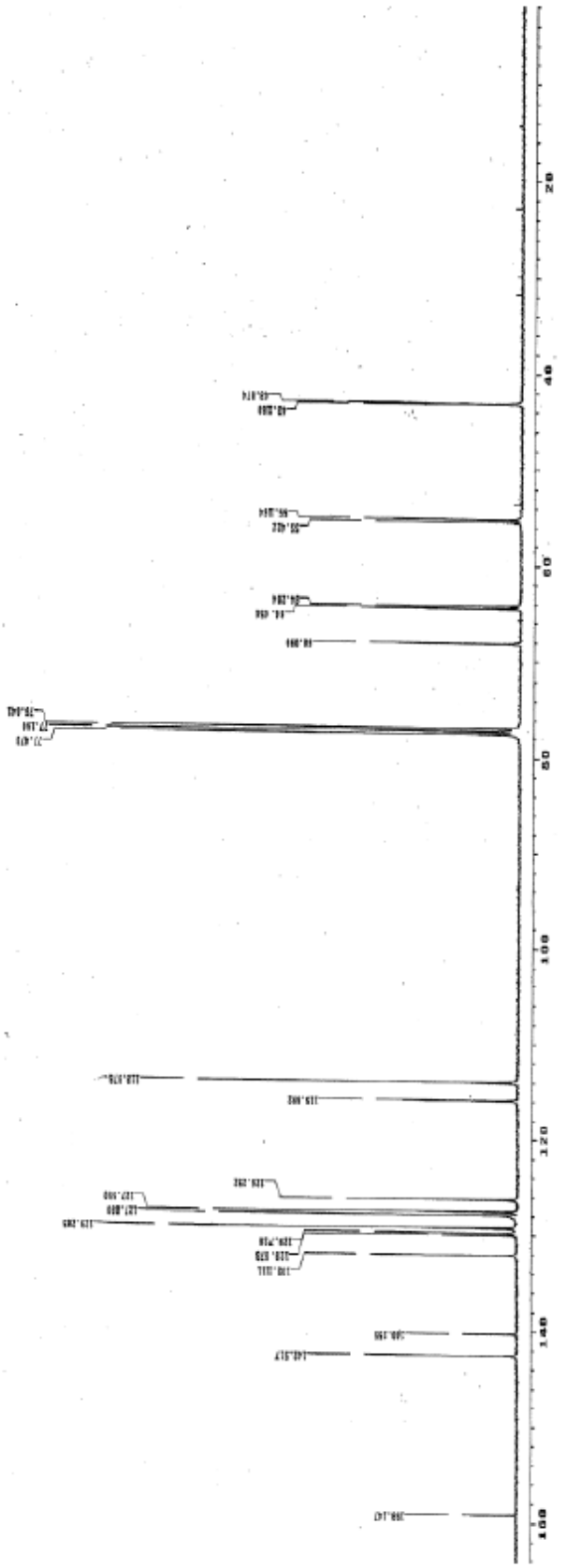
5.28

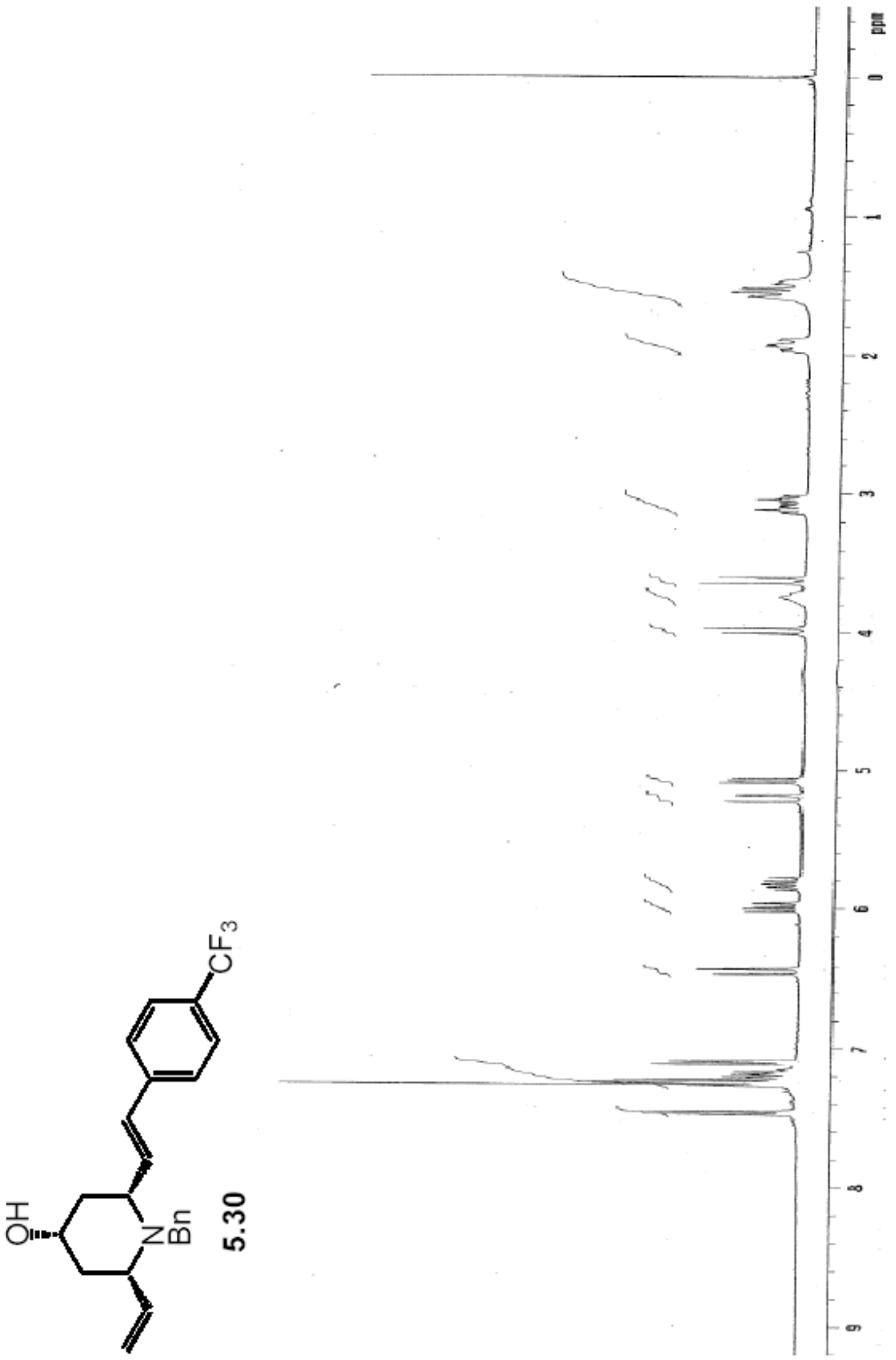



OMe
OH
N
Bn
5.29
ppm



5.29

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Bn
CF3
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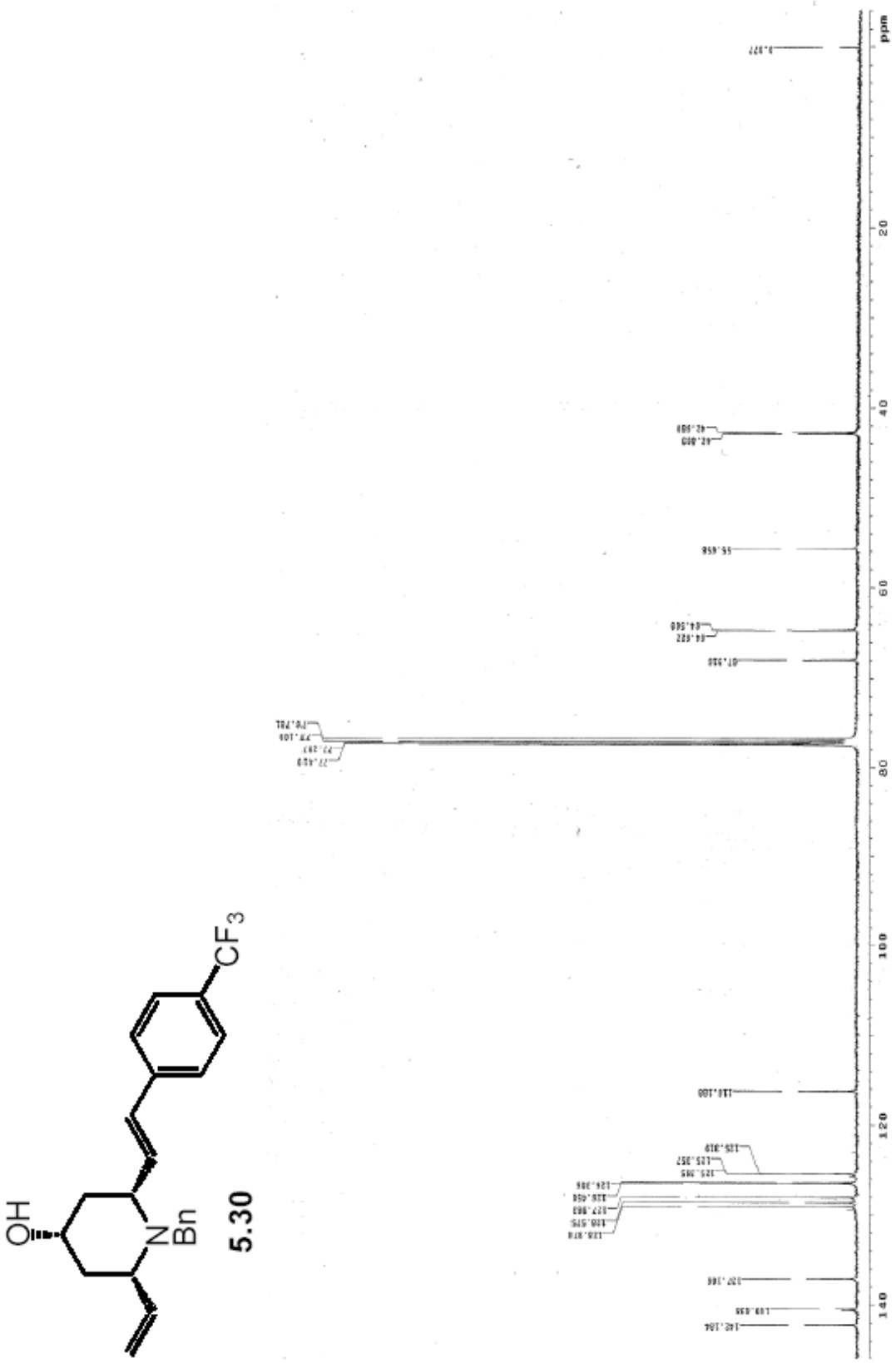
ppm


OH
N
Bn
CF3
5.30
ppm
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