STUDIES TOWARDS A CATALYTIC ASYMMETRIC ISOMERIZATION OF MANGANESE COMPLEXED ALKYNES TO ALLENES USING CHIRAL BASES

by

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This thesis was prepared under the direction of the candidate's thesis advisor, Dr. Salvatore D. Lepore, Department of Chemistry and Biochemistry, and has been approved by the members of his supervisory committee. It was submitted to the faculty of the Charles E. Schmidt College of Science and was accepted in partial fulfillment of the requirements for the degree of Master of Science.

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Abstract

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Title: Studies Towards a Catalytic Asymmetric Isomerization of Manganese Complexed Alkynes to Allenes using Chiral Bases

Institution: Florida Atlantic University

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The conversion of alkynyl carbonyls to allenyl carbonyls via manganese mediated coordination followed by a base-catalyzed isomerization was carried out using a range of chiral and achiral amine bases. Chiral amidine and chiral DBU derivatives were synthesized to carry out the isomerization enantioselectively. We employed HPLC equipped with a chiral column to determine the enantiomeric excess. We also proved that the mechanism of that the manganese-coordinated alkyne/allene rearrangement reaction involved an intermediate cumenolate. It was also confirmed that amine base with *p*Ka lower than that of DBU (*p*Ka = 13.6) would not carry out the isomerization. Alkoxy base were also used in isomerization and the mechanism was also investigated.

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Abbreviations

^{13}C NMR-	Carbon nuclear magnetic resonance
^{1}H NMR-	Proton nuclear magnetic resonance
HPLC-	High-performance liquid chromatography
TLC-	Thin-layer chromatography
MS-	Mass spectrometry
CSP-	Chiral stationary phase
LDA-	Lithium diisopropylamide
TMSCl-	Trimethylsilyl chloride
CAN-	Ceric ammonium nitrate
DCM-	Methylene chloride
TEA-	Triethyl amine
MMT-	Cyclopentadienylmanganese tricarbonyl
DBU-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN-	1,5-Diazabicyclo[4.3.0]non-5-ene
THF-	Tetrahydrofuran
TBAF-	Tetra-n-butylammonium fluoride
TBS-	tert-Butyldimethylsilyl
THP-	Dihydro-2H-pyran

Chapter 1

Introduction

1.1 Background

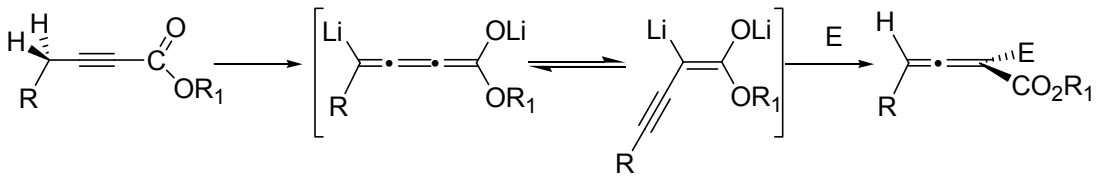
Allenes are a class of compounds containing the 1,2 diene grouping. Allenic hydrocarbons serve as extremely useful precursors in organic synthesis. Allenes have a unique chemistry that has been successfully applied to the preparation of pharmaceuticals, dyes, and polymeric materials as well as highly complex and strained molecules synthesized specifically for the investigation of their physical properties and reactivity.[1] Allenes containing different substituents at the 1-and 3-postitions exhibit the property of planar chirality. Reactions using these optically active substrates usually result in the transfer of chirality to the respective products and are therefore desirable in transformations leading to natural products.[2]

Although allenes are much more reactive than alkenes or alkynes, their selectivity is more difficult to control. While studying allene chemistry, researchers found they can achieve regioselectivity and in some cases stereoselectivity by introducing various functionalities α- to allene to differentiate the two cumulated double bonds chemically.[3] We are interested in the

stereoselective synthesis of allenes conjugated to electron-withdrawing groups with eventual application in total synthesis. The attractive feature of this class of allenes is that they provide an otherwise unattainable chemical reactivity and regioselectivity.[4]

1.2 Synthesis of Allenyl Carbonyls

Due to the lack of dependable methods in the synthesis of allenyl carbonyls, we investigated two particular reactions already in use in our lab group, which showed promise for large-scale production and allenyl carbonyl diversity. Lepore et al. reported a base-promoted conversion of alkynyl esters to α-substituted allenyl esters.[5] They found that at -98 °C, alkynyl esters can be deprontonated using two equivalents of an amide base (lithium diisopropylamide, LDA), and the dianion intermediate which can subsequently be trapped with an electrophile such as trimethylsilyl chloride (TMSCl), or tributyltin chloride (Bu_3SnCl) (Scheme 1). This reaction was improved by the addition of one equivalent lithium chloride (LiCl). In general, adding a metal halide salt addition, such as LiCl, to an enolate forming reaction has been shown to favor the formation of a lithio-enolate/LiCl heterodimer over the lithio-enolate homodimer species. This mixed dimer is frequently responsible for improved product yields and selectivity of the reaction.[6]

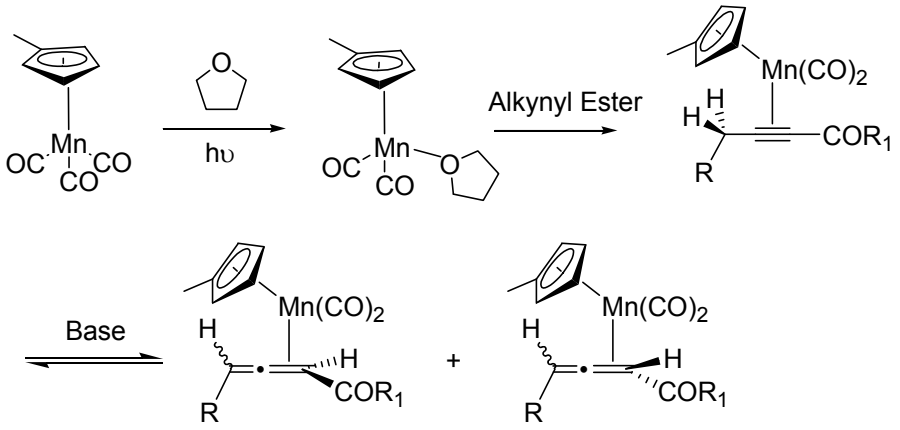


R=alkyl
E=electrophile

Scheme 1. Base-promoted conversion to α-substituted allenyl ester.

The problem with this strong base method of producing allenyl carbonyls is that the reaction is limited to esters, as it requires alkylation at the α-position. In order to investigate the synthesis of other allenyl carbonyls, the manganese-mediated isomerization of alkynes to allenes presented in the 1979 Franck-Neumann paper can be employed.[7] Neumann reported the synthesis of allenes from electrophilic acetylenes using allene-manganese complexes and this method is useful in the production of unsubstituted allenyl carbonyls. According to Franck-Neumann, methyl manganese dicarbonyl complexes obtained from the irradiation of methyl manganese tricarbonyl (MMT) complexes in THF can be coordinated to alkynyl esters, ketones and aldehydes to produce the corresponding allenyl carbonyl complexes via base isomerization. In 1994, Franck-Neumann illustrated that electrophilic alkynes with a second substituent bearing of at least one α-hydrogen can be transformed into electrophilic allenes without the formation of other isomerization products (Scheme 2), if the base-catalyzed isomerization is performed on their dicarbonyl (methylcyclopentadienyl) manganese complexes.[8] These dicarbonyl methylcyclopentadienyl manganese complex allenes are stable compounds. They can easily be handled in air or in

the presence of water. They can be isolated or purified using common small-molecule procedures such as flash chromatography.[9]



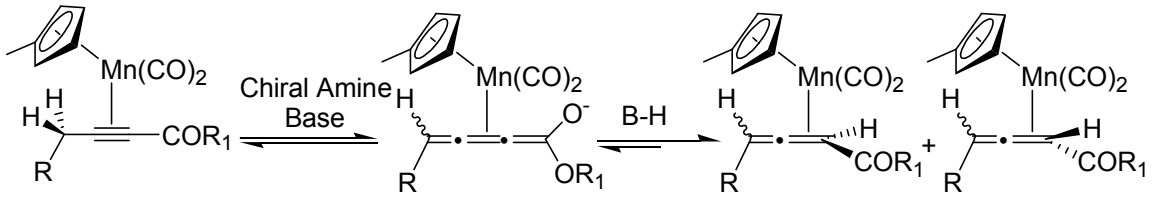
Scheme 2. Manganese-mediated isomerization of alkynes to allenes.

Complete conversion of the alkynyl complex to the allenyl complex can be accounted for by the thermodynamic stability of the allenyl complex over the alkynyl complex. This partiality may be due to the destabilization of the 18-electron alkyne complexes of cyclopentyl manganese dicarbonyl. This destabilization occurs through the repulsive interaction of the π* orbital of the alkyne with the filled d-orbital, which is not seen in the allenyl complex; hence, favoring the more stable allene.[8]

1.3 Mechanistic Investigations for Isomerization Reaction

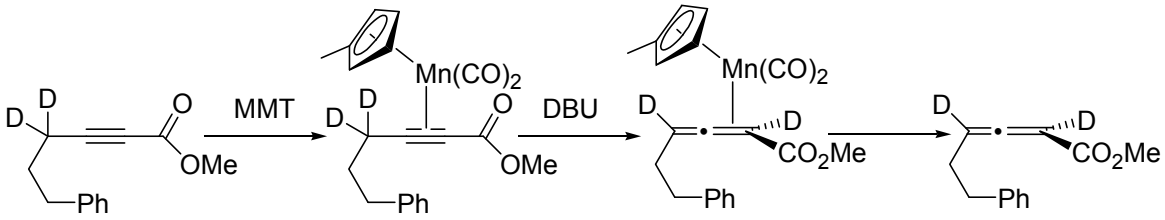
At present, no mechanistic investigations have been reported for cymantrene-mediated alkyne/allene reactions. Our current hypothesis related to this rearrangement reaction is that it involves the intermediacy of cumenolate. In

this conception, the amine base deprotonates at the γ-position to give cumenolate, which is a planar species. Subsequent protonation of prochiral cumenolate at the α-position gives allene, which is thermodynamically-favored since a stable manganese/allene η2-bond is formed (Scheme 3).



Scheme 3. Manganese-mediated isomerization of alkynes to allenes.

If the subsequent protonation at α-position were accomplished by sources other than the conjugate acid of the chiral base then the reaction would be unlikely to lead to a non-racemic product. To answer this mechanistic question, a labeled compound similar in structure to alkynyl esters was synthesized to create a manganese-mediated isomerization reaction (Scheme 4).



Scheme 4. Synthesis of deuterium labeled methyl 6-phenylhexa-2,3-dienoate.

A ^{1}H NMR analysis of deuterium, labeled methyl 6-phenylhexa-2,3-

dienoate, clearly indicates the presence of the α-deuterium. The di-deuterio product would indicate that the proton source is from the γ-position, which gives cumenolate. It is subsequently transferred to the α-position to produce allene.

Based on this hypothesis, it was thought that if a chiral amine base were used, then the reprotonation step would be asymmetric, as it would involve a chiral ammonium species.

1.4 Use of Amine Base Catalytically

Previous reports indicated that the alkyne/allene rearrangement reaction is not catalytic with respect to the base. In all cases, it was found that more than one equivalent of DBU was needed for the isomerization reaction. All attempts to carry out the reaction using a catalytic amount of DBU failed. We hypothesized that more than one equivalent of base is needed because one equivalent acts as an electron pair donor and is coordinated to manganese. The other equivalent acts as a thermodynamic base, deprotonating and reprotonating. If the cumenolate mechanism is operative, as previously indicated, then a catalytic amount of a chiral amine base should induce asymmetry in the reprotonation step that could potentially lead to non-racemic allenes.

We examined the influence of chiral tertiary amine bases such as sparteine, brucine, strychnine and cinchonidine (Figure 1) on the enantioselectivity of alkyne/allene rearrangement reactions. The amount of base used in the

proposed alkyne/allene rearrangement varied from stoichiometic to catalytic quantities.

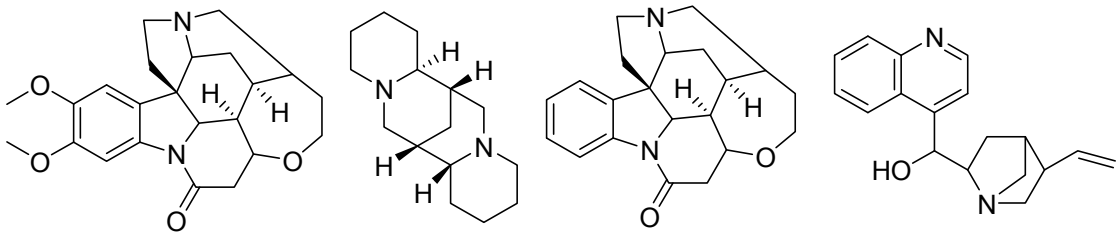


Figure 1. Chiral amine bases used for isomerization reaction.

All attempts to carry out isomerization using stoichiometic and catalytic amounts of a chiral amine base failed. It was thought that the first equivalent of base coordinates the manganese producing a steric encumbrance that potentially makes it difficult for the second equivalent of base to access the γ-position. With that in mind, it was thought that if the coordinating bases were small and the kinetic bases were large, then the isomerization might proceed. Several small weak bases, as shown in Figure 2, thought to be electron pair donors were used in 2 equivalents to determine if they would act as bases. We observed that no isomerized product resulted after several days of reaction time.

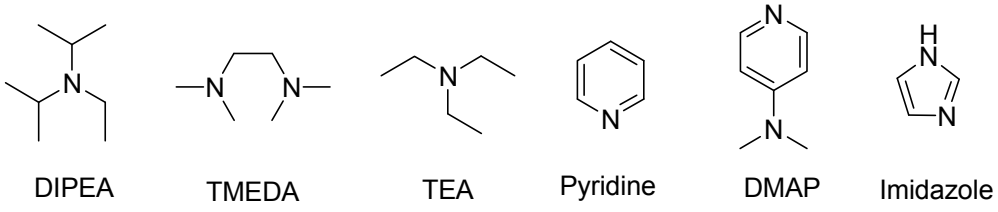
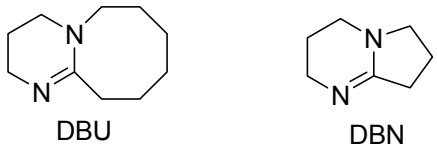


Figure 2. Weak achiral bases used in isomerization reaction.

Nevertheless, whenever DBU/DBN (Figure 3) was used, isomerization took place. Upon examining the properties of based used, all of the chiral and non-chiral bases used had a pKa of 6-9 whereas the DBU had a pKa of 13.6.[10] It was deliberated that the pKa value of the base plays a large role in the deprotonation and reprotonation processes.



DBU DBN

Figure 3. DBU and DBN.

The goal of my project is to synthesize some chiral DBU/DBN derivatives with the same pKa as bases to develop an asymmetric synthesis of enantiopure allenes.

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Chapter 2

Improved Manganese-mediated Isomerization of Alkynyl Carbonyls to the Corresponding Allenes

2.1 UV Reactor with Dimensions

One limiting factor in the synthesis of the allenyl carbonyls is that the reactions are performed on a small scale (~0.1 g of starting material) in a borosilicate glass vial (which allows the irradiation light wavelength to pass freely into the vial).[11] In order to obtain larger quantities of the manganese-coordinated allenyl carbonyls, a UV reactor was redesigned (Figure 4) thus increasing the capacity of the reactor. The reactor had an injection port through which the alkyne was introduced once the reactor was sealed from the air. The cold finger (Figure 5), which circulated water around the lamp to keep the reactor cool, was placed as far into the reactor as possible to allow the stir bar to spin without being trapped on the sides. The yield from the reactor was comparable with that of the vials, but took longer to react depending on the substrate.

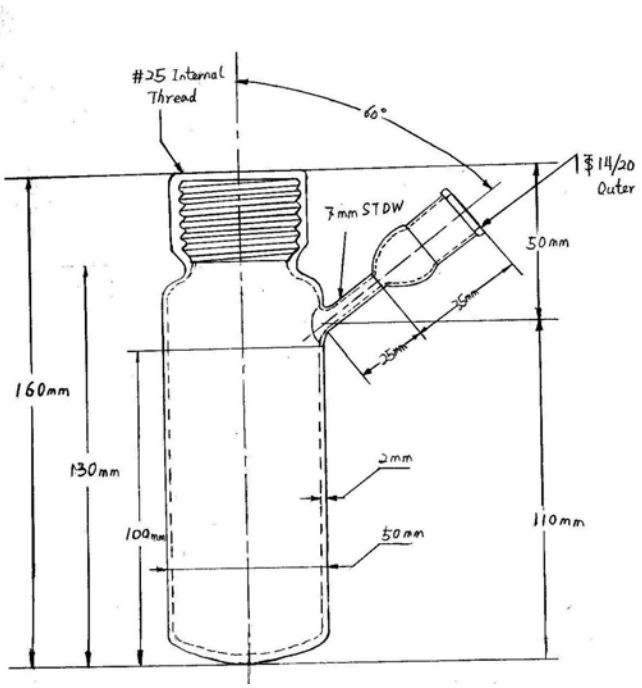


Figure 4. UV reactor for manganese complexation reactions.

Figure 5. Cold finger.

The light source was placed inside the reactor within a water-cooled finger. The vessel was sealed off from the air with a plastic threaded cap on the major arm. The side arm was sealed using Teflon® and Parafilm, so that it was airtight throughout the reaction. An O-ring was used to control the depth of the cold finger as well as to properly seal off the plastic threaded cap from the atmosphere. Argon atmosphere could be introduced via the side arm from a manifold (Figure 6).

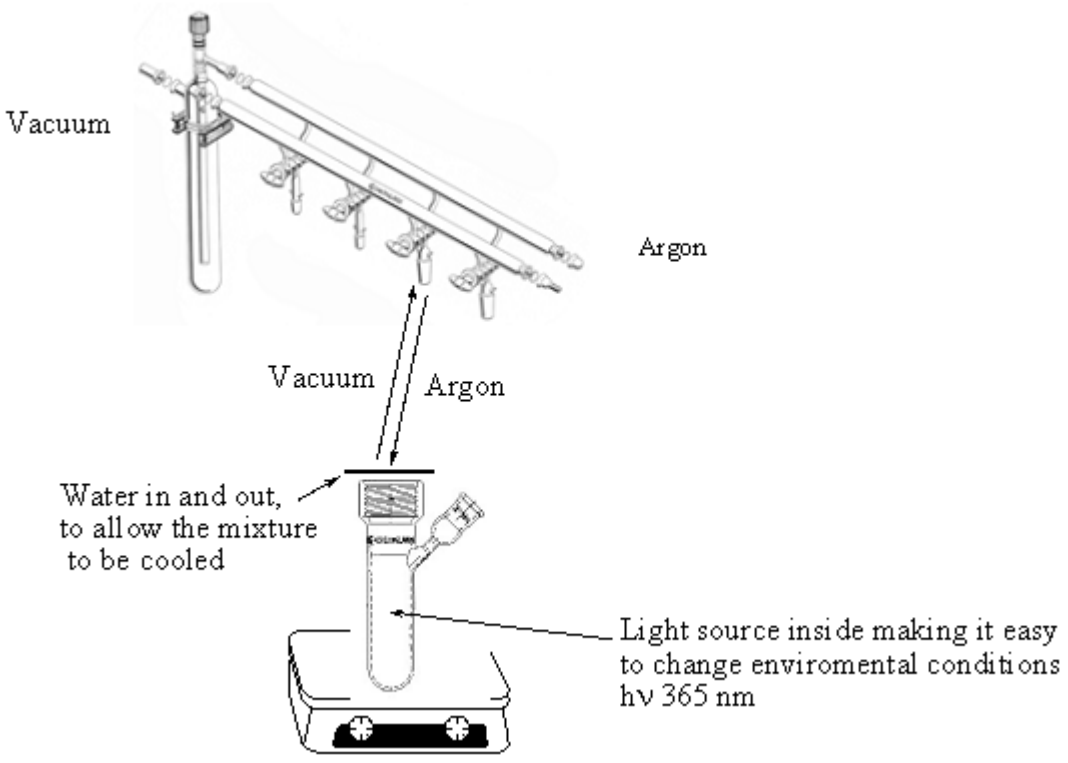
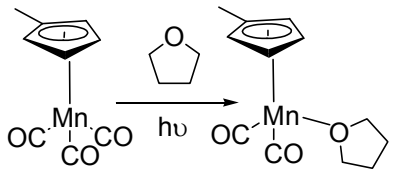


Figure 6. Set-up for the UV reactor.

This reactor could hold a maximum of 180 mL of solvent, so that we could do the isomerization reaction with more than 5g of starting material.

The first step of the manganese-mediated isomerization reaction involved breaking the manganese-carbonyl bond and then putting the manganese-THF complex under UV light irradiating in THF solution (Scheme 5).[7, 12]



Scheme 5. Formation of manganese-THF complex under UV irradiation**.**

In order to obtain the best absorption of UV light, a UV spectroscopy of MMT was done. The wavelength maximum of MMT was 329nm (Figure 7). Normally, there are two kinds of pen-ray UV lamps available commercially: 254nm and 365nm. The former one was used in our lab. For better results, a 365nm pen-ray UV lamp was utilized for the isomerization reaction. The enhancement of UV light strength helped increased the percentage yield by about 10%.

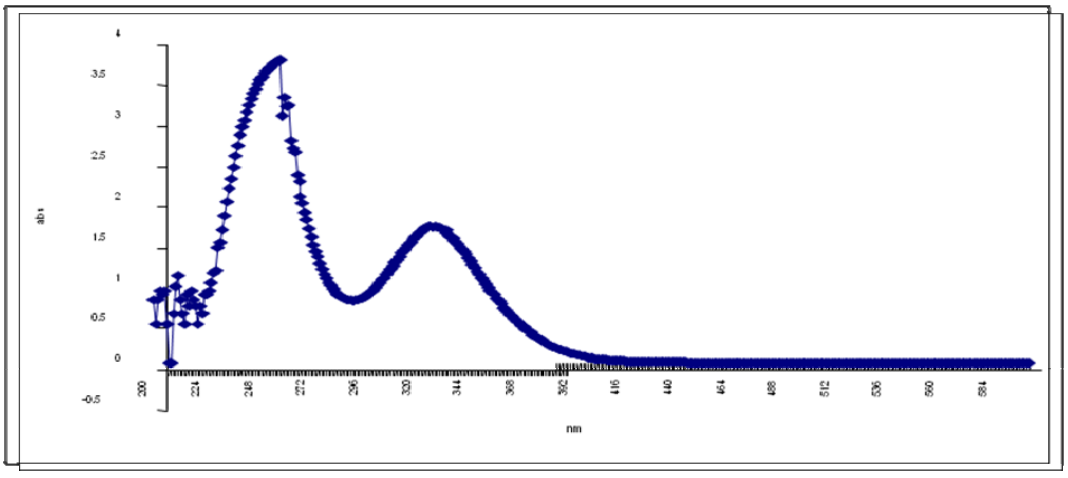
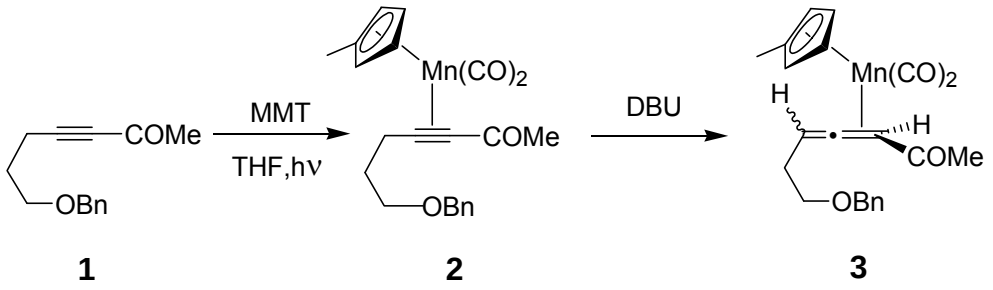


Figure 7. UV-Vis spectroscopy of MMT.

2.2 Optimization Study of Manganese-mediated Isomerization Reaction.

The other limiting factor in the synthesis of the allenyl carbonyls was that the percentage yield of the isomerization reactions was not very high, especially when the starting material was ketone or aldehyde alkyne. For these, there was only a 55% yield.[11] In the optimization study of the manganese-mediated isomerization reaction, we embarked on a detailed investigation to determine the scale of the reactants, the radio of the reagents, irradiation time and concentration of MMT, and reaction temperature using alkynyl ketone **1** as the starting material to give the corresponding manganese complex allene **3** (Scheme 6).[13]



1 **2** **3**

Scheme 6. Synthesis of manganese complex alkynyl methyl ketone (**3**)**.**

2.2.1 Scale effect on the isomerization using UV reactor

A small-scale reaction (0.1g) can be conducted successfully in the small vial. This has already been proved by this experiment. Then, a set of reactions were done to figure out the issue of scalability in the UV reactor. We used 1.4

equivalent of MMT and irradiated the MMT-THF solution for 0.5 hours. Different scales of alkynyl methyl ketone were investigated from 0.1g to 1g (Table 1).

Table 1. Effect of scale on the isomerization reaction**.**

Entry	Scale(g)	Equiv. (S.M.:MMT)	Irradition time (h)	% yield
1	1	1:1.4	0.5	42
2	0.5	1:1.4	0.5	41
3	0.25	1:1.4	0.5	45
4	0.1	1:1.4	0.5	47

The isolated percentage yield showed that there was almost no obvious change with the yield even though we increased the scale of alkynyl ketone from 0.1g to 1g. Therefore, it was estimated that there would be no problem with the big-scale reaction in the UV reactor.

2.2.2 Irradiation time effect on the isomerization reaction

Frank-Newmann's procedure for the coordination reaction involved a reaction of cymantrene with the alkynyl carbonyl under constant UV irradiation.[7(a)] First, cymantrene was dissolved in THF and stirred under constant UV irradiation for 30 to 40 minutes in an oxygen-free environment, during which time the yellow

colored solution turned wine red. Previous reports indicated that this was due to the molecule of THF coordinating to manganese, at the same time eliminating a molecule of carbon monoxide.

It was found that stirring for more than 45 minutes gave unsatisfactory results. To double-check this finding, the irradiation time of MMT with THF solution was also examined. This confirmed the earlier report, as shown in Table 2.

Table 2. Effect of irradiation time on the isomerization reaction**.**

Entry	Scale(g)	Equiv. (S.M.:MMT)	Rxn time (h)	% yield
1	1	1:1.4	0.5	42
2	1	1:1.4	1	41
3	1	1:1.4	2	36
4	1	1:1.4	3	36

Data analysis showed that longer irradiation time did not give a better yield; however, the percentage yields became a little lower than before. It is supposed that the longer irradiation time results in the decomposition of cymantrene, so the best irradiation time would be around 30 to 40 minutes.

2.2.3 Irradiation time effect on the isomerization reaction

The concentration of MMT in THF solution is another issue with the isomerization reaction. Compared with the concentration of MMT in THF in the small-scale reaction (0.1g, 0.08 mM), 0.16, 0.32, and 0.64 mM of MMT in THF was also tested using the UV reactor as shown as Table 3.

Table 3. Effect of concentration of MMT on the isomerization reaction**.**

Entry	Solvent(ml)	Concentration	% yield
1	8	0.08	56
2	8	0.16	49
3	8	0.32	22
4	8	0.64	23

The percentage yield decreased significantly from 56% to 23% when the concentration of MMT in THF increased from 0.08 mM to 0.64 mM. It proved that too much MMT in THF does not help the isomerization reaction and the concentration of MMT is better when it is not over 0.08 mM.

2.2.4 Reaction temperature effect on the isomerization reaction

Frank-Newmann's procedure for the coordination reaction involves a low temperature (-20 ^{o}C) reaction of cymantrene with the alkynyl carbonyl[7(a)]. However, in our hands, the coordination proceeded smoothly at room

temperature overnight under UV irradiation. For further determination of the temperature effect on the isomerization reaction, we increased the reaction temperature to 50 ^{o}C to see if it would accelerate the reaction. However, the reaction gave a lower yield as shown in Table 4. The reason, perhaps, is that the manganese complex is less stable in higher temperatures, especially the manganese alkyne complex **2**. It is even much less stable than the manganese allene complex in solvent.

Table 4. Effect of reaction temperature on the isomerization reaction**.**

Entry	Scale(g)	Equiv. (S.M.:MMT)	Temp	% yield
1	1	1:1.4	RT	42
2	1	1:1.4	50	12

2.2.5 Equivalent of MMT effect on the isomerization reaction

The use of one equivalent of MMT in this reaction gave only a 42% yield of the manganese alkynyl allene complex; we also examined the effect of the ratio of MMT on the isomerization reaction (Table 5).

Interestingly, the isolation yield was increased significantly to 79% when using 10 equivalents MMT. We reasoned that the MMT-THF complex is not stable in the THF solution, so more than one equivalent of MMT needs to be

used to make the MMT-THF complex. In addition, a bigger equivalent of MMT-THF complex should force the isomerization reaction to the product side to obtain more products. However, when the equivalent of MMT is over 10, the yield does not change too much. Our conclusion is that at least 8 to 10 equivalent of MMT needs to be used in this kind of reaction.

Table 5. Effect of ratio of MMT on the isomerization reaction**.**

Entry	Scale(g)	Equiv. (S.M.:MMT)	Irradiation time (h)	% yield
1	1	1:1	0.5	42
2	1	1:3	0.5	59
3	1	1:5	0.5	69
4	1	1:10	0.5	79
5	1	1:15	0.5	73
6	1	1:20	0.5	79

2.2.6 Summary of optimal condition study

We have identified the conditions for the manganese-mediated isomerization reaction in synthetically useful scales and yields. A key factor in this conversion is the use of more equivalent of MMT in the first step. The concentration of the MMT in the reaction mixture was also found to be crucial,

giving optimal yields at 0.08 mM. The optimized conditions resulting from our study of this reaction establishes this method as a viable synthetic tool for the production of unsubstitued allenyl ester/aldehyde/ketone. In general, optimal conditions for this conversion of conjugated alkynyl ketone to conjugated allenyl ketone are:

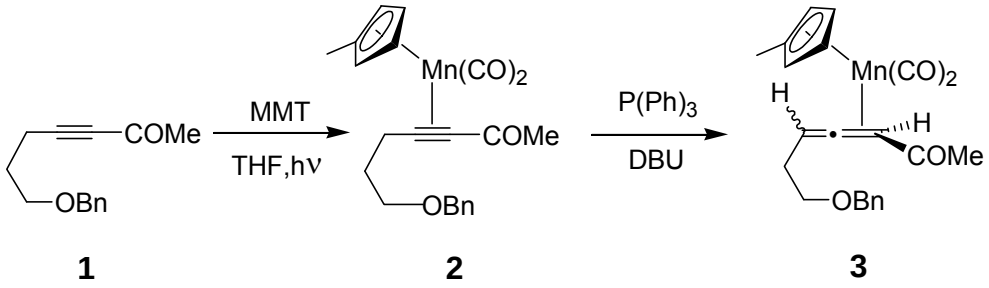
1) UV wavelength : λ=365 nm
2) Irradiation time : 30 minutes
3) Temperature : Room temperature
4) MMT Concentration : 0.08 mm
5) Ratio (Alkyne : MMT) : 1:10

We can do big-scale reactions with as much as 5g in the new UV reactor and get an 84% yield when using DBU as a base under these optimal conditions.

2.2.7 Use of DBU as a catalyst

From pervious findings, it was determined that 1 equivalent of the base (DBU) coordinates with manganese and the other equivalent transfers the proton forming the allene as a catalytic base.[11] It was contemplated that when using a strong electron pair donor coordinated to manganese that the kinetic base as the DBU can work as a catalyst to conduct the isomerization reaction. Triphenylphosphine was considered as the coordinate base because it is neutral; two electron donors bind to transition metals through its lone pairs.[14] Triphenylphosphine was added 1 hour before the DBU to coordinate to complex

alkyne and then a catalytic amount of DBU was added to give the corresponding allenyl ketone (Scheme 7).[15]



1 **2** **3**

Scheme 7. Using DBU as a catalytic kinetic base**.**

Different amounts of DBU have been used in the isomerization reaction as shown in Table 6. Coordination and isomerization were carried out as indicated before. Even using 2% DBU achieved an acceptable yield of 62%. It proved our hypothesis that before DBU can work as a catalyst and the cumenolate mechanism is operative.

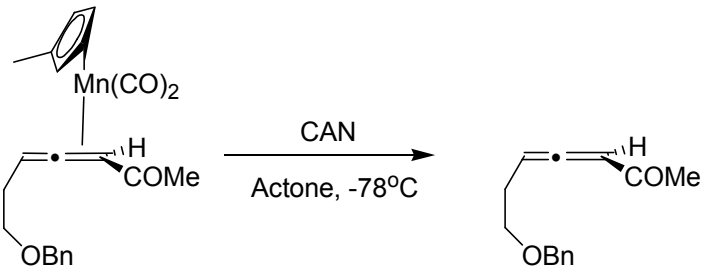
Table 6. Effect of ratio of DBU on the isomerization reaction.

Entry	Scale(g)	Equiv. (S.M.:MMT)	Equiv. (DBU)	% yield
1	1	1:10	2	84
2	1	1:10	0.4	83
3	1	1:10	0.1	65
4	1	1:10	0.05	69
5	1	1:10	0.02	62

2.3. New Oxidative Protocols for Manganese Removal

Previously in the Lepore research group, various known methods were used, but failed to give the free allene with good yields such as iron trichloride ($FeCl_3$), PCC and m-chloroperoxybenzoic acid (*m*CPBA).[16]. The photolytic decomplexation of an alkene, demonstrated by Top et al.[17] gave poor yield after chromatography purification, using a 2:1 methanol to ether solution.

Franck-Neumann reported that the use of cerium (IV) ammonium nitrate (CAN) in a solution of acetone at 0°C for 0.5 hours gives the decomplexed allenyl carbonyl results in good yields (Scheme 8).[16,18] However, the CAN oxidation method in our lab did not give reasonable yields even after extensive optimization.



3 **4**

Scheme 8. CAN decomplexation of allenyl methyl ketone.

The CAN oxidation method conditions were not successful in producing a sufficient yield of the alkynyl methyl ketone. For the methyl ketone allene **4**, the yield is only 36%. More than 1 equivalent of CAN (1.8 equivalent) needs to be used to complete the reaction, but excess CAN will destroy the allene product in the workup condition. Repeated attempts were made to remove the effect of excess CAN. The reaction was performed drop-wise using a syringe pump over one hour at 0 °C and slow addition at a lower temperature of -98 °C. The ratio of CAN was adjusted from 1 equivalent to 3 equivalents. The workup used water/dichloromethane as a two-phase condition. We quenched the reaction mixture with sodium thiosulphate to destroy the excess CAN. We also plugged (filter through silica gel in a Buchner fritted funnel) the reaction mixture. All attempts failed to give a successful yield.

The conditions for the CAN oxidation method may vary for different substrates. For better and reliable results, we tried milder oxidants to remove the manganese from manganese-coordinated allenes like Br_2, $FeCl_3$, *m*CPBA, MnO_2, PCC, PDC, Chromic acid, Urea, IBX, DDQ, Ferrocenium hexafluorophosphate

and so on. All of them gave a poor yield of allene products and had a normal amount of byproducts.

Otherwise, the use of $CuCl_2$ and iodophenyl diacetate as oxidants produced rewarding results. $CuCl_2$ gave a clean and acceptable 50% yield, but the reaction can take several days to complete. Iodophenyl diacetate gave better results; the reaction will complete in two hours and gave the free allene in moderate yields of 71%.

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Chapter 3

Synthesis of Chiral Amidine Bases

3.1 Potential Chiral DBU/DBN Derivatives

Bicyclic amidines are organic super bases utilized in various synthetic transformations. Asymmetric reactions with chiral derivatives of bicyclic amidines[19] have not been widely studied, possibly because of the difficulty of synthesizing chiral bicyclic amidines. 1, 8-Diazabicyclo [5.4.0] undec-7-ene (DBU) and, 1, 5-diazabicyclo [4.3.0] non-5-ene (DBN) have attracted considerable interest due to their importance as non-nucleophilic strong organic bases in promoting several types of organic transformations, such as isomerization, esterification, alkylation, Michael addition, condensation, and protection. The nucleophilic character of these kinds of bicyclic amidines[19b, 20], further broadens their utility as catalysts. Accordingly, it is easy to imagine that the introduction of a chiral center onto the DBU/DBN skeleton could provide an efficient entry to novel enantiopure organic base catalysts.

Initially, two sets of bicyclic amidines were considered as the chiral bases for the isomerization reaction as show in Figures 8 and 9.

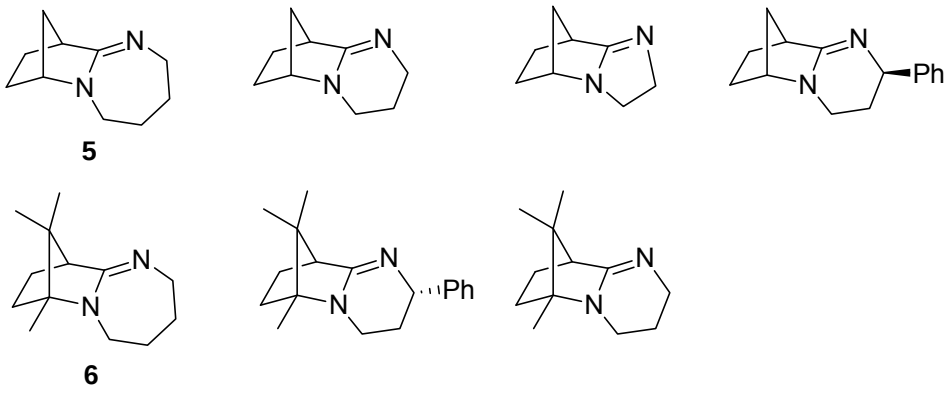


Figure 8. Bridge bicyclic amidines.

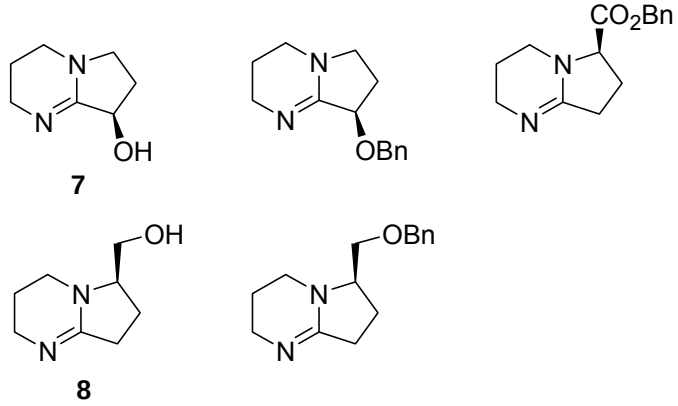


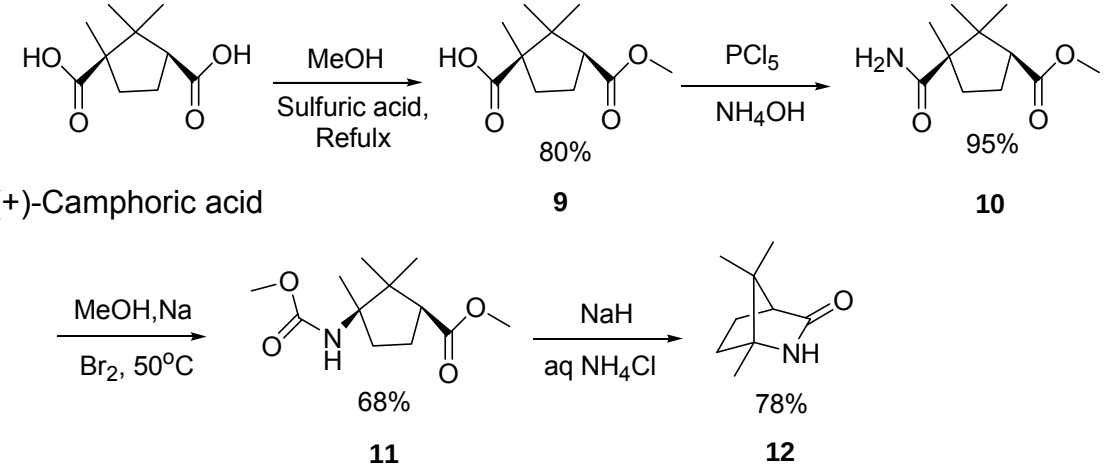
Figure 9. Chiral DBN derivatives.

The synthesis of chiral amidines 5, 6, 7, 8 was our initial target because they have simpler structures compared to the other chiral amidines.

3.2 Synthesis of Bridge Bicyclic Amidines

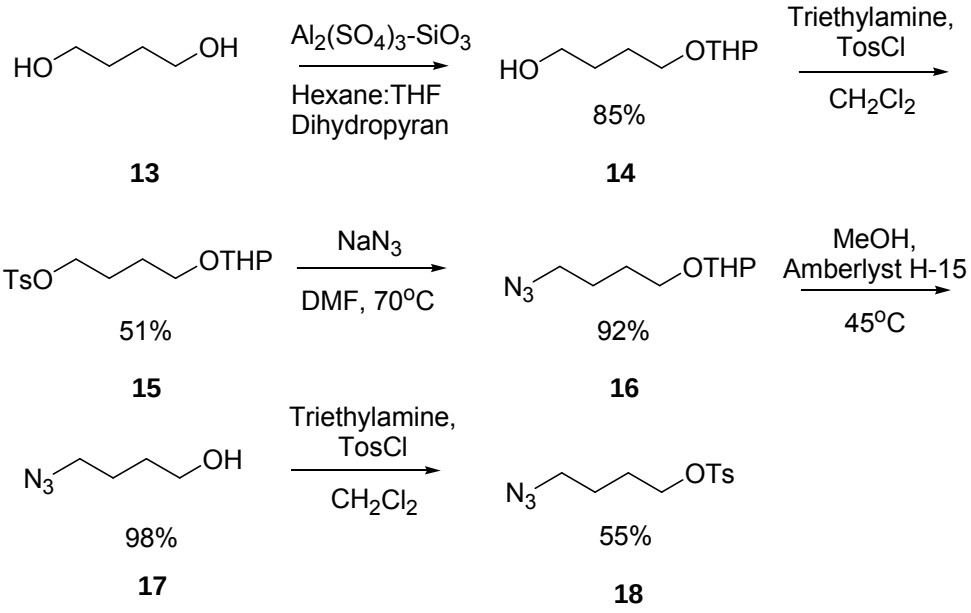
Unfortunately, very few examples of the synthesis of chiral DBU/DBN derivatives have been reported so far.[21] The Kotsuki group in Japan described a

synthesis of sterically hindered DBU/DBN-related organic bases. Their synthetic strategy toward the target molecule **6** was accomplished by constructing amidine functionality to be used in the intramolecular condensation of ω-amino-N-alkylated thiolactam,[22] which can be prepared from (+)-camphor lactam, readily available from (+)-camphoric acid.[23]



Scheme 9. Synthesis of (+) camphor lactam (**12**).

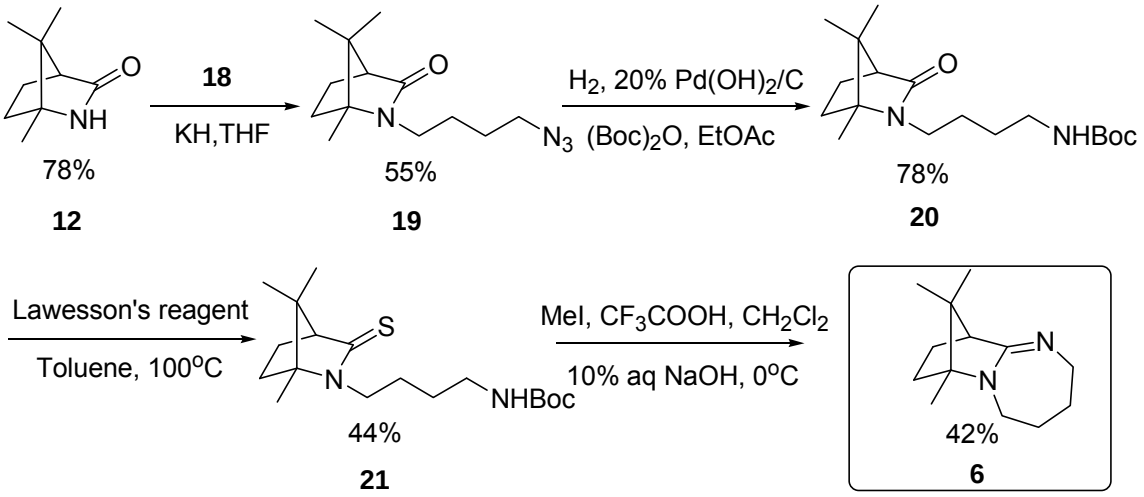
(+) Camphor lactam was prepared in four steps (Scheme 9) starting with the appropriate antipode of camphoric acid[24, 25] which was monomethylated in methanol and sulfuric acid under reflux to give **9** with an 80% yield. Subsequent amination was carried out using phosphorus pentachloride and aqueous ammonium hydroxide to give **10** with 95% yields. The corresponding product **11** was obtained by a Hoffmann rearrangement and cyclized using sodium hydride and aqueous ammonium chloride to give the desired lactam **12** in 78% yields.



Scheme 10. Synthesis of tosylated azide.

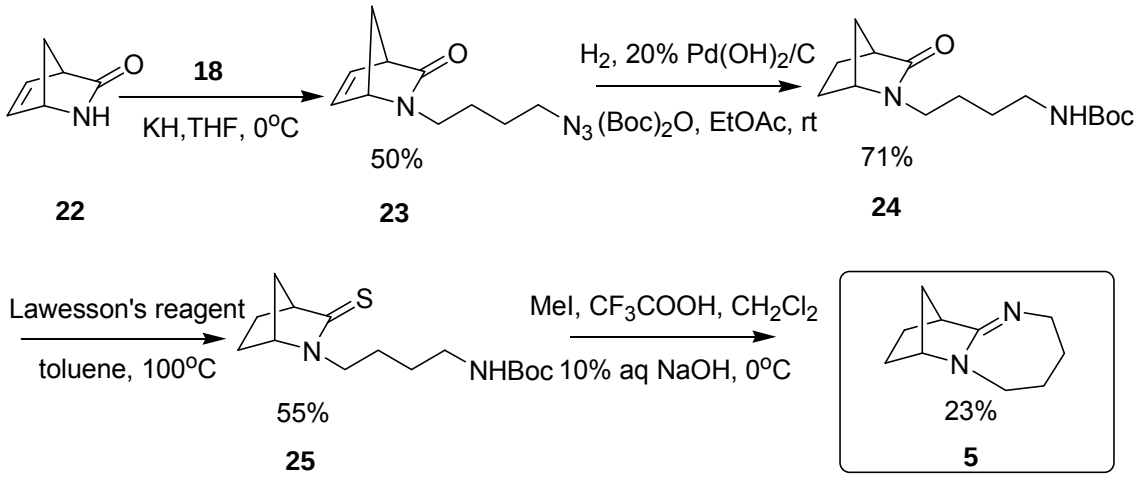
Synthesis of **18** was carried out starting from 1,4-butanediol (Scheme 10). Nishiguchi and Kawamine[26] reported that a highly selective monacylation of 1,*n*-diols could be achieved by transesterififcation, catalyzed by metallic sulphates supported on chromatographic silica gel [$M_m(SO_4)_n$-SiO_2]. That study suggested that selective reactions such as monacylation might occur when the polarity successively decreases from the starting material to the final product and the polarity of the solvent is suitable.[26] By using the solvent system of hexane/THF with 1.5:1 ratio, the reaction gave a monoprotected product **14** with an 85% yield. Tosylation of monoprotected THP-butanol **14** was achieved using p-toluene sulfonyl chloride in the presence of triethylamine to give the tosylated product **15** with a 51% yield.[27] Tosylated **15** was treated with sodium azide in water or DMF under microwave irradiation to afford the corresponding azide **16** with a 92%

yield.[28] Synthesis of fragment **18** was achieved via THP deprotection followed by tosylation.[27]



Scheme 11. Synthesis of (1R,8S)-2,6-Diaza-1,11,11-trimethyltricyclo[7.2.1.0]tridec-6-ene (**6**).

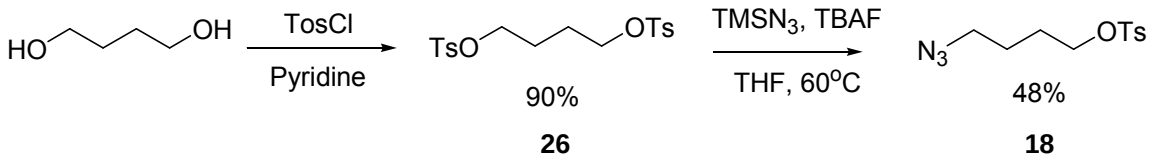
Coupling of tosylated azide **18** with (+) camphor lactam **12,** which was prepared by KH-mediated alkylation of the lactam nitrogen, gave compound **19** with a 55% yield. Reductive transformation of the terminal azido group to the corresponding *N*-(*tert*-butoxycarbonyl)-protected amines **20** and under catalytic hydrogenation conditions, followed by treatment with Lawesson's reagent in toluene at 100°C, gave thiolactam **21**. Finally, treatment of the thiolactam **21** with excess MeI, followed by deprotection of Boc group with trifluoroacetic acid in methylene chloride at 0°C, afforded the corresponding ammonium salt which, upon exposure to excess, 10% of the aqueous NaOH, cyclized to give the desired amidines **6** with a yield of 42% (Scheme 11).



Scheme 12. Synthesis of (1R,8S)-2,6-Diaza-tricyclo[7.2.1.0]dec-6-ene (**5**).

However, before the synthesis of camphor lactam, it was thought that it was available commercially and in place of it, 2-azabicyclo [2.2.0] hept-5-en-3-one **22** was purchased which also coupled with tosylated azide to give **23** with a 50% yield. We considered that the use of compound **22** used in place of the (+) camphor lactam could save a few steps in the synthesis if the reactivity of compound **22** is the same as (+) camphor lactam **12**. The total synthesis of **5** using commercially available lactam **22** is shown in Scheme 12.

The synthesis of tosylated azide **18** took five steps with a 21.5% total yield using Nishiguchi and Kawamine's method of starting from 1,4-butanediol. We developed a two-step method to synthesize it shown in Scheme 13, resulting in a total yield of 43.2%.



Scheme 13. Synthesis of 4-azidobutyl 4-methylbenzenesulfonate (**18**)

1,4-butanediol was dissolved in pyridine and added drop-wise to the tosylated chloride solution in pyridine to give the bistosylated compound **26** with a 90% yield. Then, the bistosylated compound **26** was treated with azidotrimethylsiliane and TBAF in THF solution at 60°C to give the desired product, tosylated azide **18,** with 48% yields. Some optimizations were done for the second step of the synthesis of tosylated azide **18** as shown in Table 7. Traditional methods using sodium azide in different polar solvents and different temperatures all failed to give the desired product. Only TBAF and $TMFN_3$, reacting with bistosylate compound **26,** gave the mono-substitute product with a 48% yield.

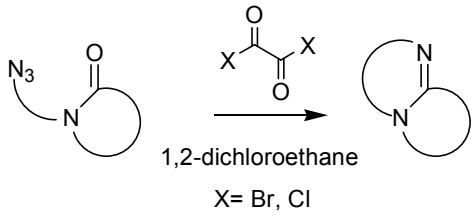
Table 7. Optimization of synthesis of tosylated azide **18.**

Entry	Reagent	Solvent	Temp (°C)	% yield
1	NaN_3	DMF	70	X
2	NaN_3	H_2O/Acetone	RT	X
3	NaN_3	DMF/18-Crown-6	RT	X
4	TiF_4, $TMSN_3$	DCM	RT	X
5	$TMSN_3$, TBAF	THF	60	48

Isomerization and coordination using synthesized chiral DBU derivatives **5** and **6** were carried out as before. However, no isomerization was observed. The cause for the non-reactivity could be due to the fact that the basicity of these two chiral bicyclic amidines is lower than the DBU/DBN and the isomerization reaction needs a stronger base like DBU to carry on. This suggests that new kinds of chiral DBU/DBN derivatives need to be synthesized with a similar *p*Ka as DBU/DBN to proceed with the reaction.

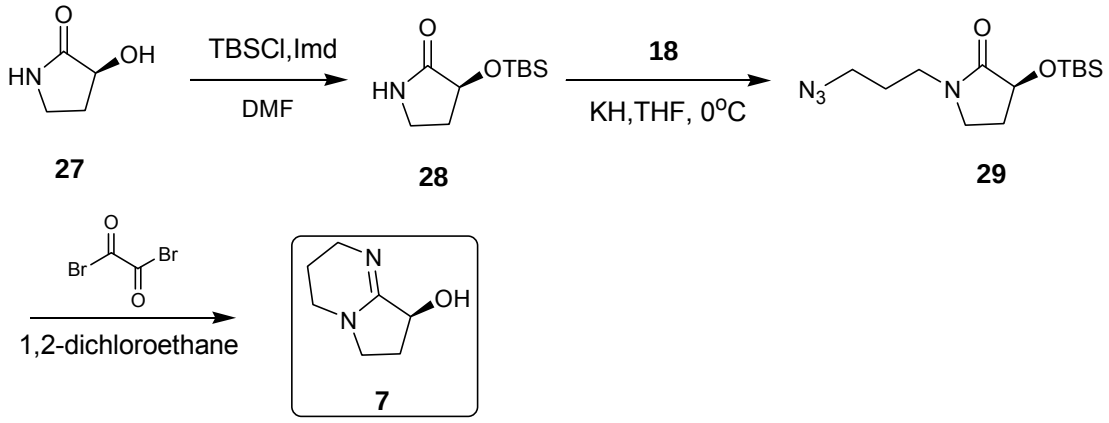
3.3 Synthesis of Bridge Bicyclic Amidines

According to the Kotsuki group's[23] method of forming bicyclic amidines, the starting material should have two nitrogen-containing functionalities that can assemble intramolecular to form an amandine core at the ring junction. However, for this method, too many steps involve readily available organic materials. In addition, the reaction conditions are mild and the total yield is very low. The Kumagai group in Japan reported a concise synthetic procedure for forming bicyclic amidines starting from readily available tethered azido lactams and using intromolecular cyclization (Scheme 14). This approach provides easy access to various achiral and chiral amidines under mild reaction conditions.[29] The direct use of an azido function, instead of an amino group, plays a key role in this synthesis.

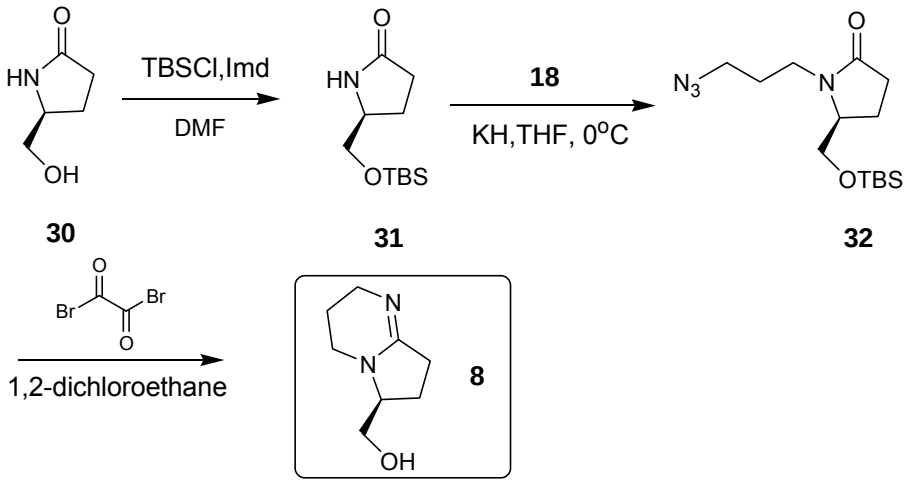


Scheme 14. Strategy for the formation of bicyclic amidines.

This method focused on the direct use of an azido group as the nucleophile in the intramolecular cyclization.[30, 31] This enables chemo-selective activation of the amide because the azido unit is not affected by the many kinds of electrophilic reagents. Using this method, we focused on the synthesis of two chiral DBN derivatives, **7** and **8** (Scheme 15, 16)**.**



Scheme 15. Synthesis of (*S*)-7-Hydroxy-1,5-diazabicyclo[4.3.0]non-5-ene (**7**).



Scheme 16. Synthesis of (*S*)-9-Hydroxymethyl-1,5-diazabicyclo[4.3.0]non-5-ene (**8**).

Syntheses of bicyclic amidines were carried out starting with the commercially available lactams **27**/**30**. The hydroxyl groups of lactams were protected by the TBS group. We coupled the tosylated azide **18** with TBS-protected compounds **28/31** that were prepared by KH-mediated alkylation of the lactam nitrogen, to give azido lactams **29/32**. Finally, adding oxalyl bromide drop-wise to the azido lactams, **29/32**, in dichloroethane solution, followed by quenching the reaction mixture with anisole and MeOH at 0°C and extracting with HCl, afforded the desired amidines, **7/8**.

This one-step reaction from the azido lactam to the final product was supposed to have a very high yield of about 90%. However, we did not obtain the desired yield or the purity of the final products in the reaction. This suggests that we need to optimize our reaction conditions to get the acceptable results for the isomerization reaction.

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Chapter 4

Method Development for Analysis of Enantiomeric Excess

4.1 HPLC Method Developments

A key aspect of this research involved the development of an HPLC method to determine enantiomeric excess. Several broad-range chiral columns available in the lab failed to resolve both the complexed and decomplexed allenyl compounds. Designed to distinguish between the enantiomers of compounds having certain common structural features, the chiral selector used in the chiral stationary phase (CSP) can be used. Typically, those who wish to chromatographically separate the enantiomers of some substance by using a chiral stationary phase (CSP), seek a suitable CSP by trial and error. CSPs derived from biopolymers typically contain multiple types of binding sites and are of such mechanistic complexity as to presently defy a detailed understanding of how they differentiate between enantiomers. In contrast, brush-type CSPs have been prepared using low molecular-weight selectors, which have been designed to contain only those interaction sites essential for the differentiation of the enantiomers. CSP 1 shown in Figure 10 contains a cleft-like binding site that preferentially binds that enantiomer which, without departing substantially from a

low-energy conformation, can undergo simultaneous face-to-face and face-to-edge π-π interactions as well as a hydrogen bonding interaction with the CSP.

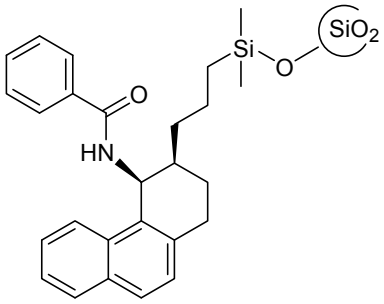
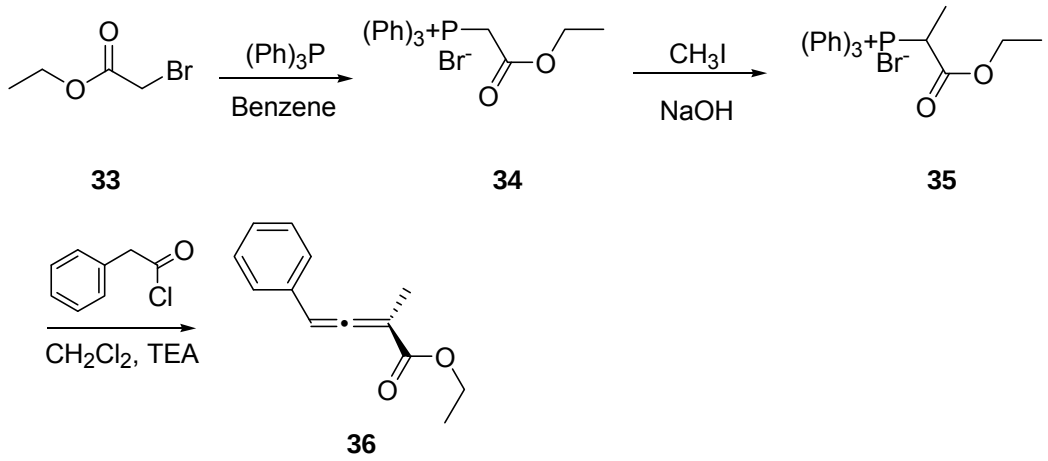


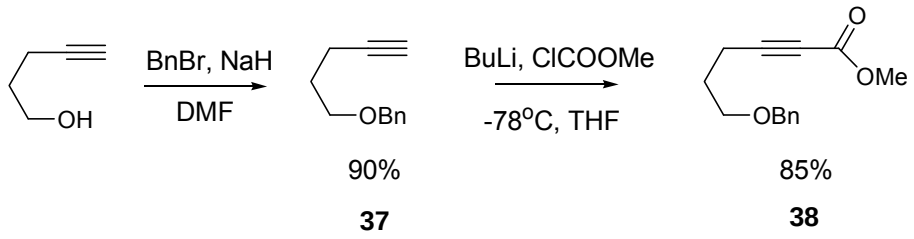
Figure 10. Synthetic chiral stationary phase used in this study CSP 1.

Analytes containing a π-basic group and hydrogen bond acceptor site near a stereogenic center are candidates for enantiodifferentiation by this CSP 1.[32] These work for relatively well-defined reasons and are commercially available. This particular CSP 1 (a (R,R) Whelk-O 1 brush –type HPLC column (25cm x 4.6 5µm spherical silica particles of 10/100Å pore size) available from Regis Technologies, Morton Grove, IL) was used to separate chiral aromatic allenic acid and esters such as **36**. The analytes used in the study were prepared according to literature methods outlined in Scheme 17. Aromatic allenic ester **36** was prepared as a standard in developing conditions for the chiral column.



Scheme 17. Synthesis of Ethyl 2-methyl-4-phenylpenta-2,3-dienoate (**36**).

In the process of method development, it was thought that if the alkynyl ester **38** was converted to the corresponding allene that it would form diastereomers because of the chiral center in the pyran moiety. With that in mind, a benzyl-protecting group was used and coupled with methyl ester to prepare an alkynyl ester model compound **38** by a straightforward method as shown in Scheme 18.



Scheme 18. Synthesis of Methyl 6-(benzyloxy)hex-2-ynoate (**38**).

Methyl 6-(benzyloxy)hex-2-ynoate (**38**) was successfully coordinated and isomerized using DBU (90%) to give the manganese-coordinated allene product. Then, free allene was isolated by removing the manganese. The manganese

complexed and decomplexed allenyl carbonyls were both resolved using this chiral column under the conditions of utilizing 95:5 hexane/isopropanol mobile phase and 2mL/min flow rate. The HPLC spectra are shown in Figures 11 and 12.

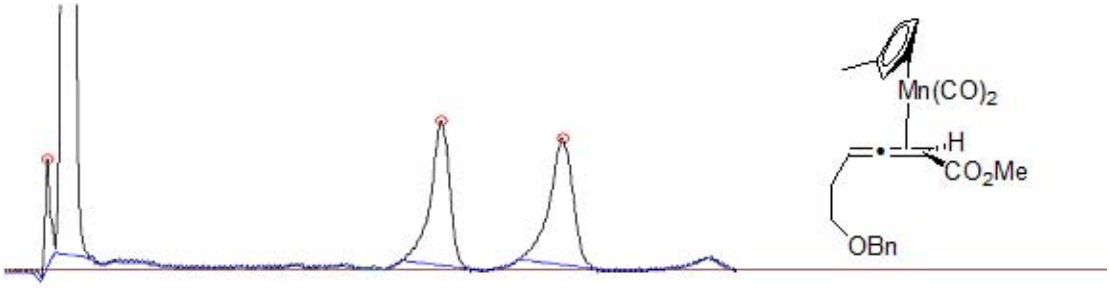


Figure 11. HPLC spectroscopy of Manganese complex alkynyl allene.

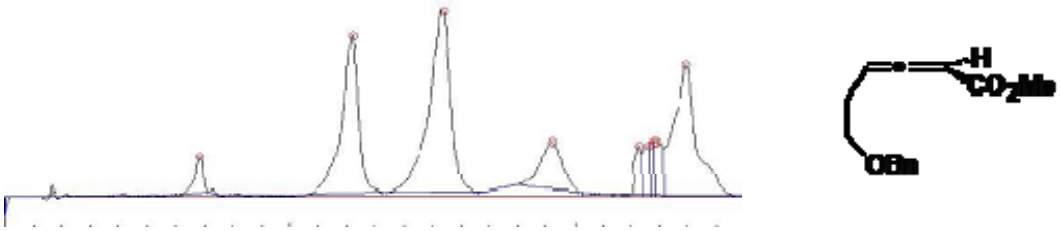


Figure 12. HPLC spectroscopy of free alkynyl allene.

4.2 NMR Method Developments

The isomerized-coordinated allenyl carbonyl products were identified via TLC analysis before in our lab as an orange spot that generally has a lower R_f than that of the coordinated alkyne. The identity of allenyl carbonyls was

inferred by spectroscopic analysis of the allene products obtained after manganese decomplexation. ^{1}HNMR spectroscopy of these manganese allenyl carbonyl complexes was not easy to obtain and interpret, as manganese, which has paramagnetic properties, causes broadening of all the peaks (Figure 13).

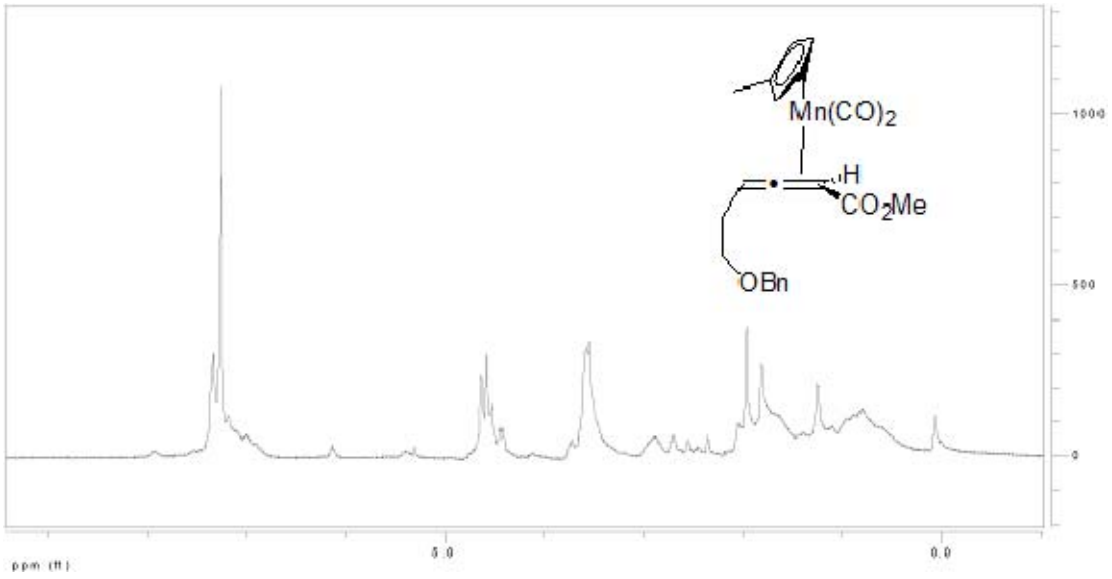


Figure 13. ^{1}H NMR of manganese complex allene

For obtaining better results with the NMR analysis, we pretreated the NMR solvent before the NMR measurement by flushing the NMR solvent with argon. We then filtered the solvent on Millipore membranes (GS 0.22m) to remove the small particles in it. Finally, we scanned the sample with a long scan to give an acceptable ^{13}C spectrum (Figure 14).

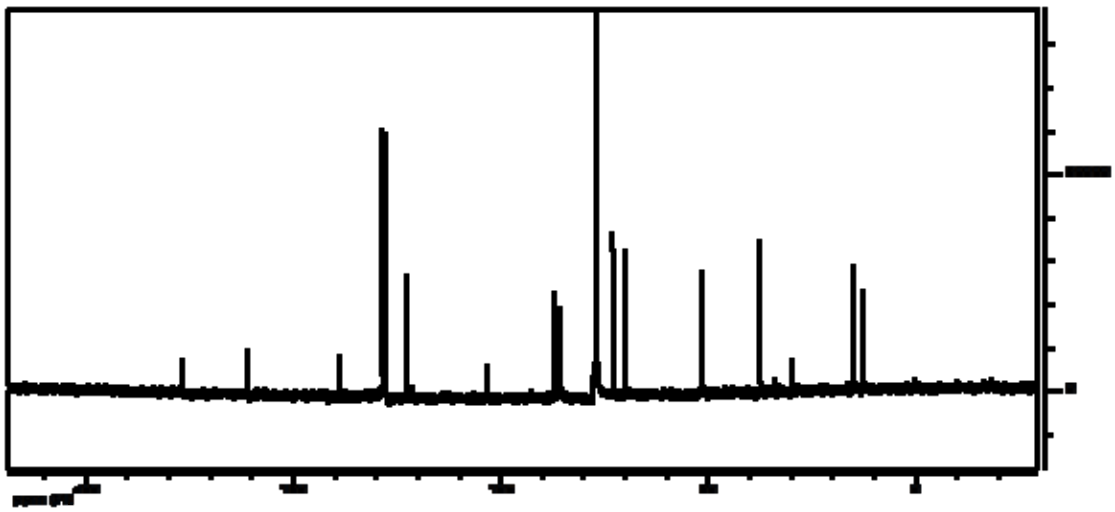


Figure 14. ^{13}C NMR of manganese complex allene

4.3 IR Method Developments

IR analysis is the other way to analyze the manganese-coordinated compounds. We examined the IR spectra of manganese-coordinated alkynyl ester and manganese-coordinated allenyl ester shown in Figures 15 and 16.

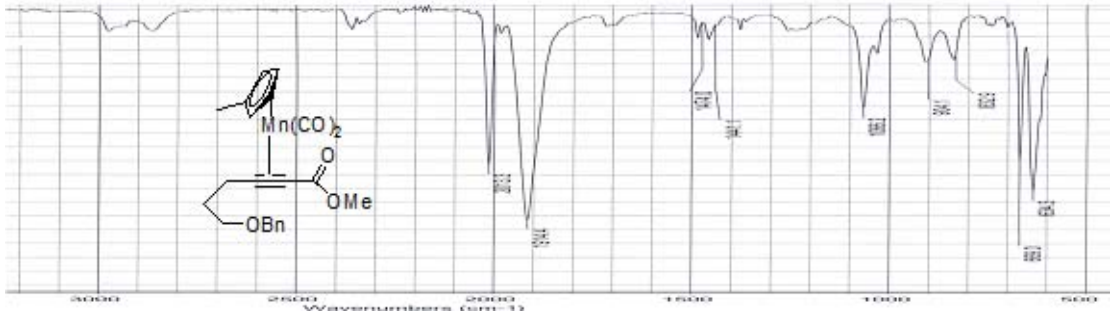


Figure 15. IR spectrum of manganese-coordinated alkynyl ester.

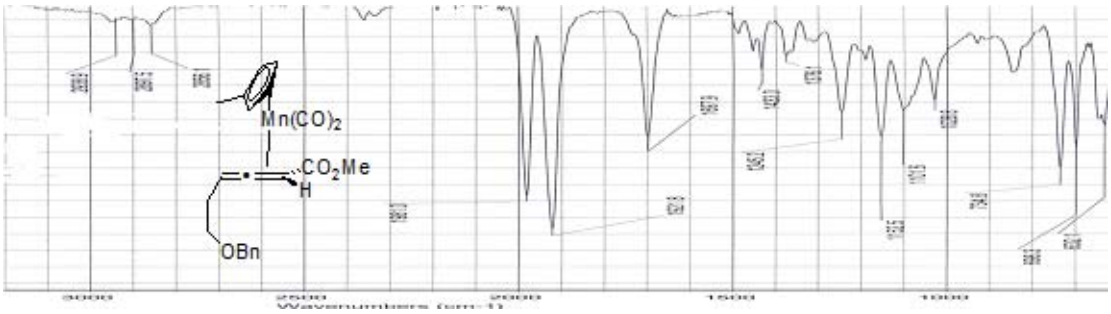


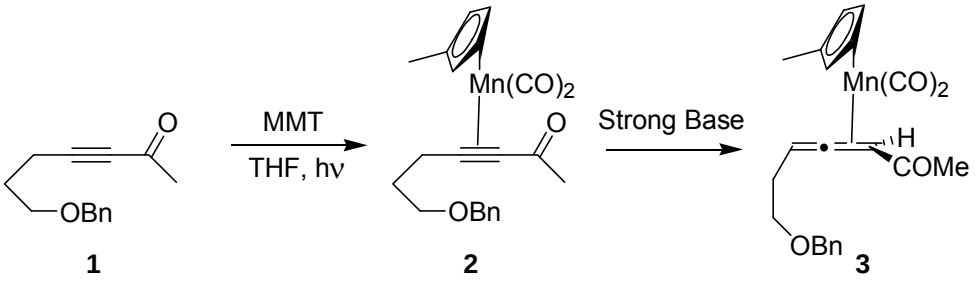
Figure 16. IR spectrum of manganese-coordinated allenyl ester.

We can see that the carbonyls groups from the MMT shift a little bit from the manganese-coordinated alkynyl ester to the manganese-coordinated allenyl ester. We can use these kinds of differences to indentify the manganese-coordinated compounds.

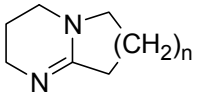
4.4 Use of Strong Bases

As discussed above, our hypothesis regarding the *p*Ka of bases plays a key role in the isomerization reaction. We also proved in a published paper that potassium *tert*-butoxide worked in this kind of reaction as a strong base.[33] To double-check the importance of the basicity of bases in the isomerization reaction, we also examined some bases with a bigger *p*Ka value to prove this theory (Table 8).

Table 8. Use of a strong base in the isomerization reaction.



1 **2** **3**

Entry	Reagent	*p*Ka	Reaction time (h)	% yield
1		~13	24	84
2	NaH/KH	~37	1	80
3	tBuOK	~19	1	62
4	MeONa	~17	72	50

Data showed that strong bases, NaH/KH, also worked very well by completing the reaction in an hour and obtaining an 80% yield. Sodium methoxide was also used, but only a yield of 50% of isomerized allene was observed after 3 days. These results again prove that we need stronger bases for the isomerization reaction.

Based on these results, we also examined some chiral alcohols as bases. Alkoxy bases were considered because their *p*Ka is greater than DBU and chiral derivatives are available commercially. A series of chiral alcohols were

evaluated as alkoxide bases for their effect on the reactivity and asymmetric influence on the isomerization reaction (Figure 17).

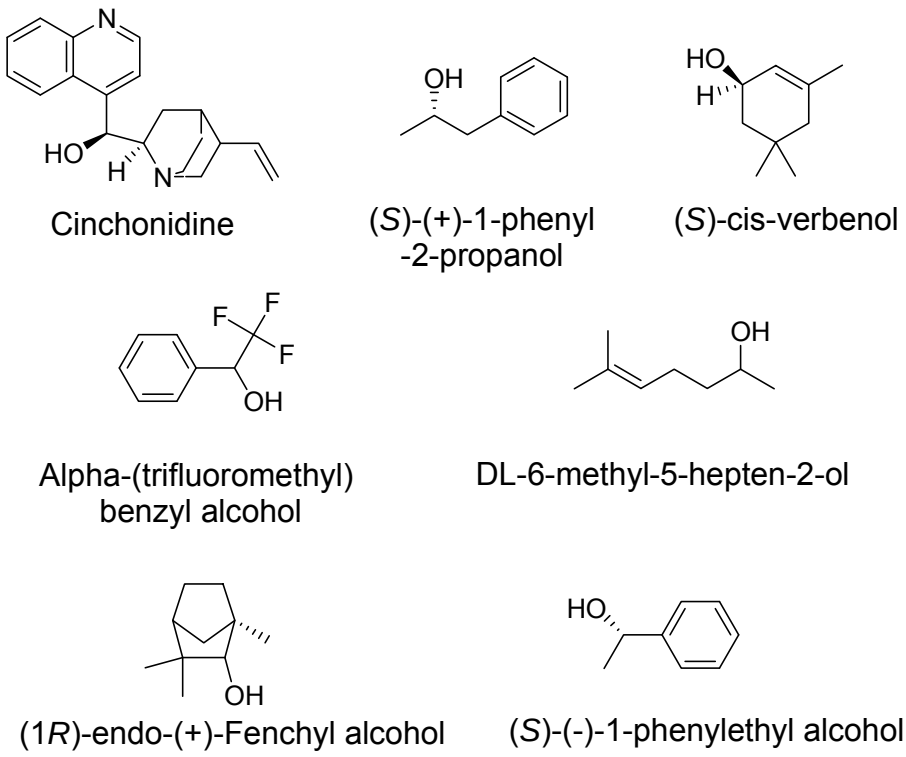
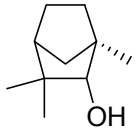
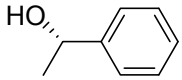


Figure 17. Chiral alcohols used as alkoxide bases.

Only (1R)-endo-(+)-Fenchyl alcohol and (S)-(-)-1-phenylethyl alcohol showed their reactivity as shown in Table 9, but there was no particular asymmetric influence on the isomerization reaction.

Table 9. Working chiral alcohol in the isomerization reaction.

Reagent	Reaction time	%Yield
 (1*R*)-endo-(+)-Fenchyl alcohol	2h	30
 (*S*)-(-)-1-phenylethyl alcohol	7d	56

4.5 Mechanistic Studies of Enantiomeric Excess

One interesting fact came out of our analysis of the HPLC chromatograms of MMT-coordinated allenyl carbonyl. We always got 0% e.e. of two enantiomers of complexed allenyl ester (Figure 18) when we used DBU/DBN as the base; but always-got 20% e.e. of these two when we used any other strong bases like NaH/KH or alkoxide bases (Figure 19).

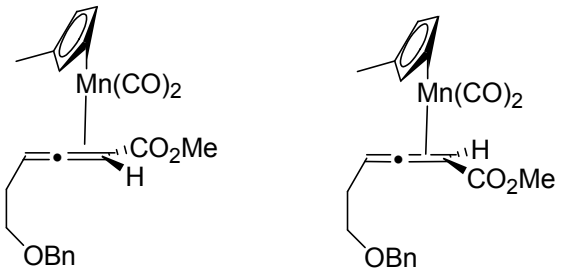


Figure 18. Two enantiomers of manganese-coordinated alkynyl ester.

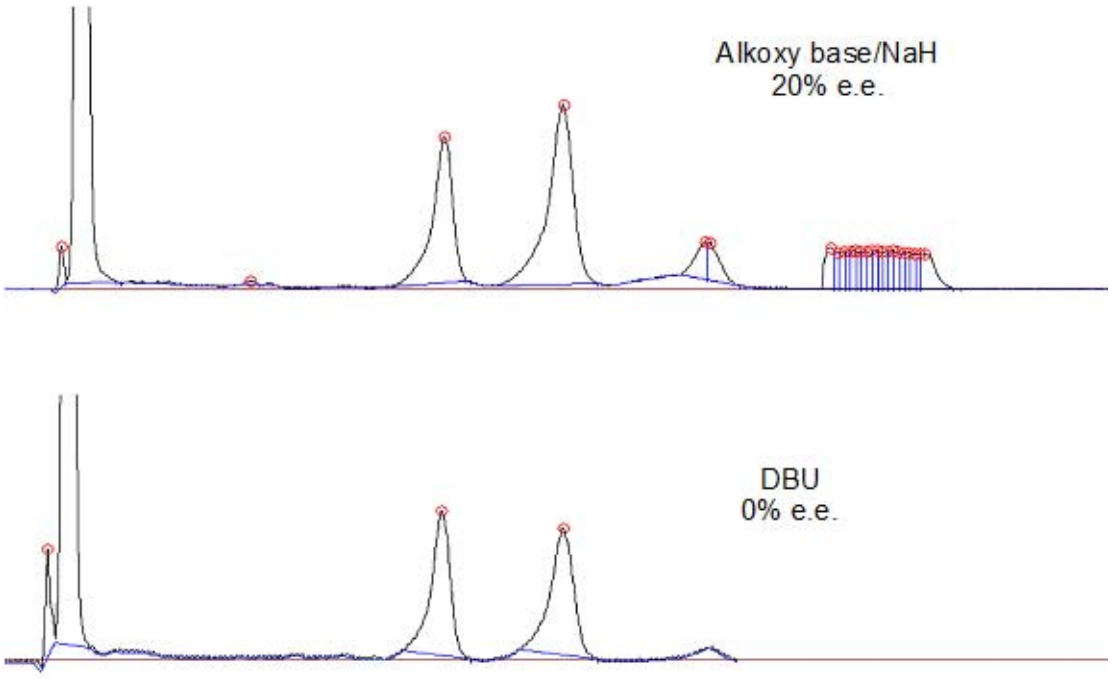


Figure 19. HPLC spectra of manganese-coordinated alkynyl ester.

Because there were no chiral reagents involved in the isomerization reaction, we wondered where the 20% e.e. came from. To answer this question, we set up a set of experiments using NaH and DBU as bases to determine the effects of workup conditions (Table 10).

Table 10. Workup condition effect on the e.e.

Base	Workup	Column	e.e.
DBU	-	Yes	4
DBU	H_2O	No	5
DBU	-	No	0
NaH	-	No	20
NaH	H_2O	No	16.5
NaH	HCl	No	22
NaH	HCl	Yes	16

From the HPLC analysis, we found that the workup conditions have nothing do with the e.e. It did not matter if we used the aqueous/acid workup conditions or applied the flush column. We could conclude that the e.e. is not from the workup conditions. To further prove this hypothesis, we also quenched the isomerization reaction with different kinds of chiral acid, but we still got the same results (Table 11).

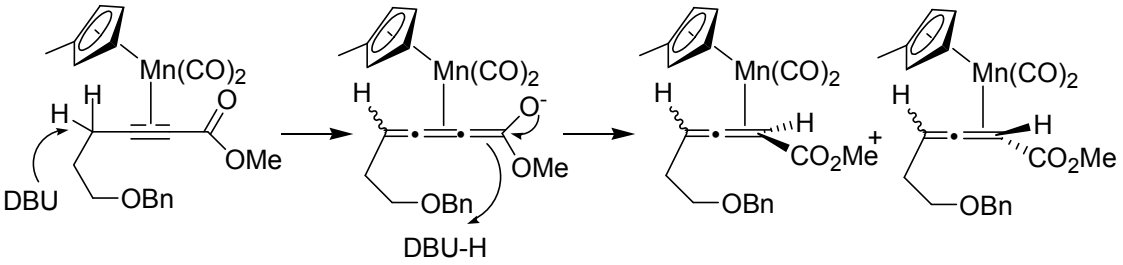
Table 11. Chiral acid quenching effect on the e.e.

Base	Workup	e.e.[a]
NaH	D(+)-(+)-Camphorsulfonic acid	24
	L(-)-(-)-Camphorsulfonic acid	23
	D-Proline	22
	L-Proline	24
	D-Tyrodine	19
	L-Tyrodine	20
	D-Camphorsulfonic acid	30
	L-Camphorsulfonic acid	33

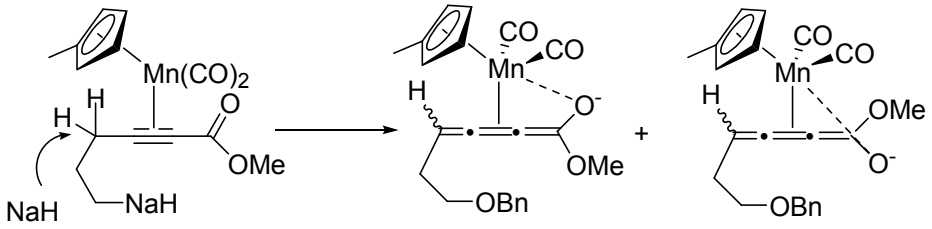
[a] e.e. were obtained before and after column chromatography

Our current hypothesis for the difference of e.e. is that there are two kinds of mechanisms involved in the isomerization reaction when using DBU and NaH as kinetic bases. When using DBU as base, the amine base deprontonated at the γ-position to give cumenolate. Then, subsequent protonation of prochiral cumenolate at the α-position gives allene complex at the same time (Scheme 19). However, when using NaH as the strong base, after deprotonation at the γ-position, no reprotonation at the α-position occurs in the reaction. Instead, the oxygen from the ester group coordinates with the manganese to give two diastereomers (Scheme 20). Therefore, the 20% enantiomer excess is actually

diastereomer excess. These two diastereomers should be very stable in the workup conditions and the general flush column.



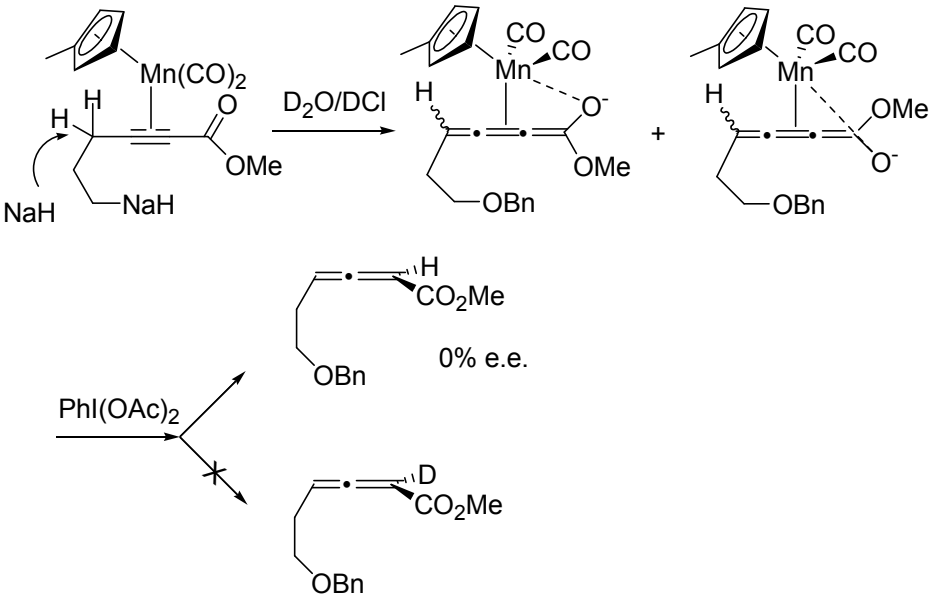
Scheme 19. Proposed mechanism for isomerization reaction using DBU as the base.



Scheme 20. Proposed mechanism for isomerization reaction using NaH as the base.

With this hypothesis, we did further investigation to prove this mechanism. We quenched the isomerization reaction with D_2O/DCl and did not find the deuterium in the free allene after removal of manganese from the manganese-coordinated allenyl ester. This means that deuterium quenching does not give the deuterium at the α-position. In addition, the analysis of the HPLC spectrum

of free allene showed that we got 0% e.e. back again, doubly proving our hypothesis (Scheme 21).



Scheme 21. Deuterium quenching using NaH as the base.

In order to break the oxygen-manganese bond, we tried adding a set of metal chelators an hour before adding NaH (Table 12). It was thought that if a strong electron pair donor were coordinated to manganese then the oxygen-manganese bond would be weakened by the manganese donating electron density back to the alkynyl system and lowering the acidity of protons at the γ-position. However, no attempts changed the results. The reason, perhaps, is that the bond constant of manganese and oxygen is bigger than the bond constant of manganese and phosphors.

Table 12. Metal chelators using NaH as the base.

Base	Metal Chelator	e.e.
NaH	PPh_3	20
	$P(OEt)_3$	20
	PMe_3	20
	TMSCl	22
	PPh_3+TMSCl	23

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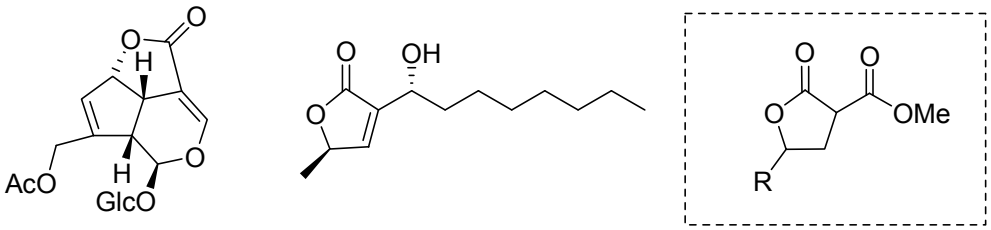
Chapter 5

Synthesis of Lactone and Further Research

5.1 Synthesis of Lactone

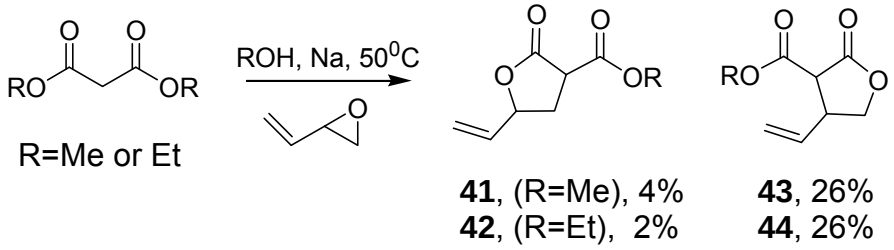
One area of our research focused on the total synthesis of pyran-containing natural products that exhibit important biological activities such as Asperuloside **39**[34] and (-) Acaterin **40**[35]. Chemically synthesizing these natural products enables the molecules to be produced on a larger scale for pharmacological studies as well as allowing for manipulation of the molecules in an effort to improve the biological activity and stability. By manipulating various portions of these molecules, it may be possible to improve the effectiveness of these molecules as clinical drugs for treatment of HIV, cancer and tumors. For the total synthesis of these natural products, we required a reliable and scalable procedure for the preparation of the lactone intermediate **41**[36] (Figure 20).



Asperuloside **39** (-)Acaterin **40** Lactone intermediate **41**

Figure 20. Natural products and their lactone intermediate.

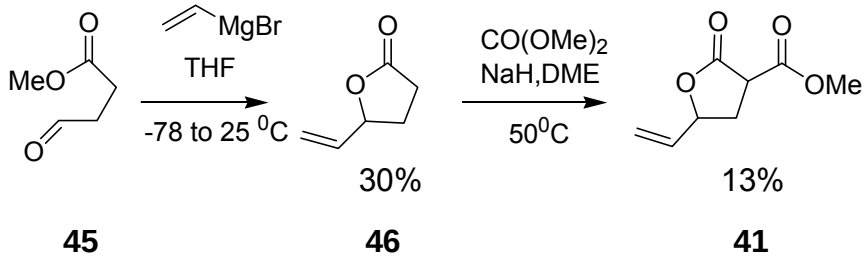
Initial attempts to prepare **41** centered on a reported one-step procedure for the synthesis of ethyl ester analog **42** involving the condensation of diethyl malonate with butadiene monoxide.[37] However, repeated attempts to condense malonate ester with butadiene monoxide, following the reported protocol, led to the formation of undesired regioisomers **43/44** as the major products (Scheme 22).[38] These data suggest that the structure of the lactone product described in earlier reports was incorrectly assigned.



41, (R=Me), 4% **43**, 26%
42, (R=Et), 2% **44**, 26%

Scheme 22. Condensation of butadiene monoxide with dimethyl and diethyl malonate.

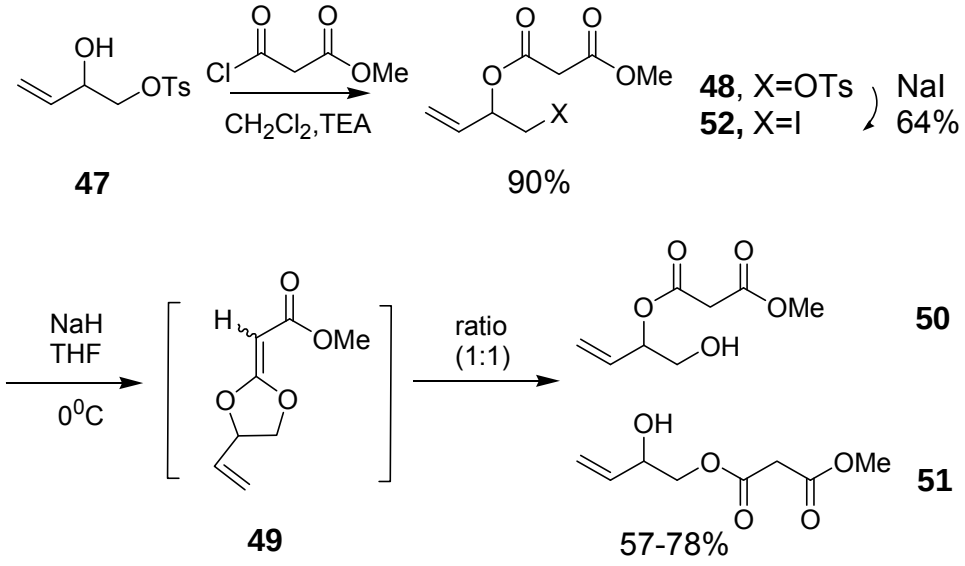
We initially envisioned a two-step approach for the preparation of **41** beginning with the addition of vinyl Grignard to commercially available aldehyde ester **45** to give lactone **46** following a related procedure.[39] Subsequent methoxycarbonylation would be expected to yield **41** (Scheme 23).[40] Although the addition of Grignard reagents to **45** has been previously described,[39a] we were not able to obtain the desired lactone in reasonable yields even after extensive optimization.



Scheme 23. Two-step synthesis of **41**.

We next attempted a three-step synthesis of **41** starting from 3,4-dihydroxybutene that is commercially available as the racemate and in non-racemic form. Mono-tosylation of 3,4-dihydroxybutene[41] to give **47** was followed by the formation of malonate ester **48**.[42] The addition of sodium hydride to **48** failed to give an intramolecular C-C bond formation leading to **41**. Instead, malonic esters **50** and **51** were isolated as a mixture (1:1) after aqueous workup of the reaction. We hypothesize that these two regioisomers arise from ketene acetal intermediate **49** formed by O-alkylation which is rapidly hydrolyzed to afford observed products **50** and **51** (Scheme 24). Alternatively, intermediate **49**

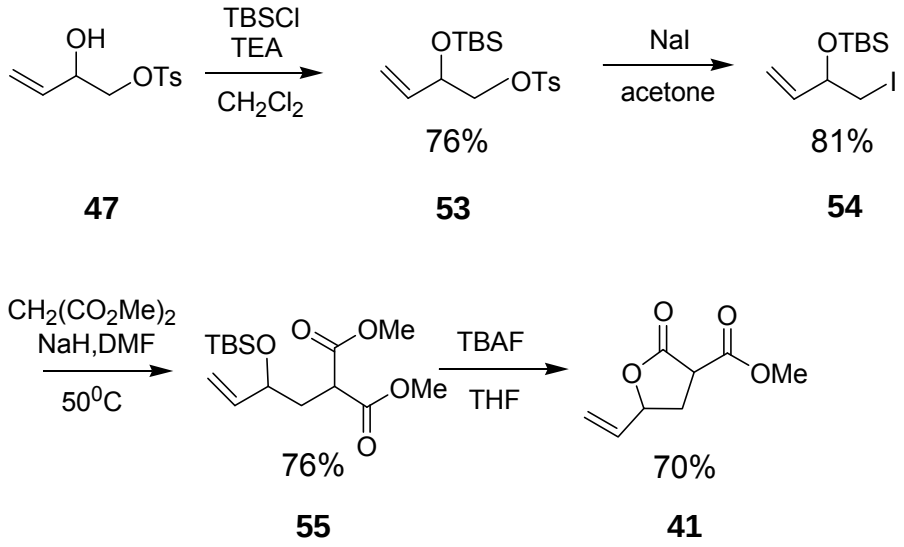
may be hydrolyzed under workup conditions to afford either product **50** or **51,** which are subsequently equilibrated to the observed 1:1 mixture via an acyl migration mechanism. In an attempt to increase the likelihood of C-alkylation, the tosylated leaving group of malonate **48** was converted to the softer iodide in intermediate **52**.[43] However, attempts to cyclize iodide **52** under basic conditions also led to the exclusive formation of **50** and **51** (1:1) in similar yields.



Scheme 24. Attempted intramolecular synthesis of 1a from 3,4-dihydroxybutene.

To accomplish an intermolecular malonate addition to **47**, the secondary hydroxyl group of **47** was protected using TBSCl to give ether **53** using standard conditions (Scheme 25).[44] An attempt to condense the tosylated **53** with dimethylmalonate using sodium hydride as a base in DMF at 90ºC failed to yield the desired condensation product. Further alkylation attempts involving the use

of a variety of solvents and added crown ether catalysts also failed to yield the desired alkylation product. However, conversion to iodide **54** followed by condensation with dimethyl malonate (9 equiv.) using sodium hydride as a base in DMF successfully yielded coupling product **55** with a 76% yield.[45] This intermediate was then converted to the desired lactone **41** as a 1:1 mixture of diastereomers with a 70% yield in the presence of TBAF.



Scheme 25. Intermolecular synthesis of **41**.

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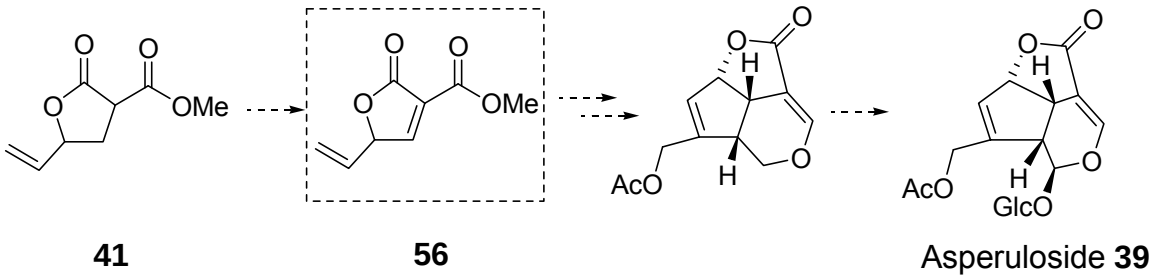
In conclusion, we have explored alternative synthetic approaches and identified a reliable synthesis of **41** starting from 3,4-dihydroxybutene. Given the accessibility of non-racemic 1,2-diols through highly selective catalytic asymmetric dihydroxylation, the optimized procedure might be used to obtain a variety of γ-butyrolactones containing π-conjugating substituents at the γ-position. In addition, the present work provides a correction to earlier reports involving malonate additions to vinyl oxirane.

5.2 Further Research on the Synthesis of Lactone with Double Bond

For the total synthesis of the natural product, Asperuloside **39**, we needed to add a double bond to the lactone **41** to make the other intermediate **56** (Scheme 26)**.** With our first attempt, we obtained a set of enantiomers, **57** or **58**, with an acceptable ratio when we added the selenium phenyl group to lactone **41** (Scheme 27).



41 **56** Asperuloside **39**

Scheme 26. Strategy of synthesis of Asperuloside **39**.

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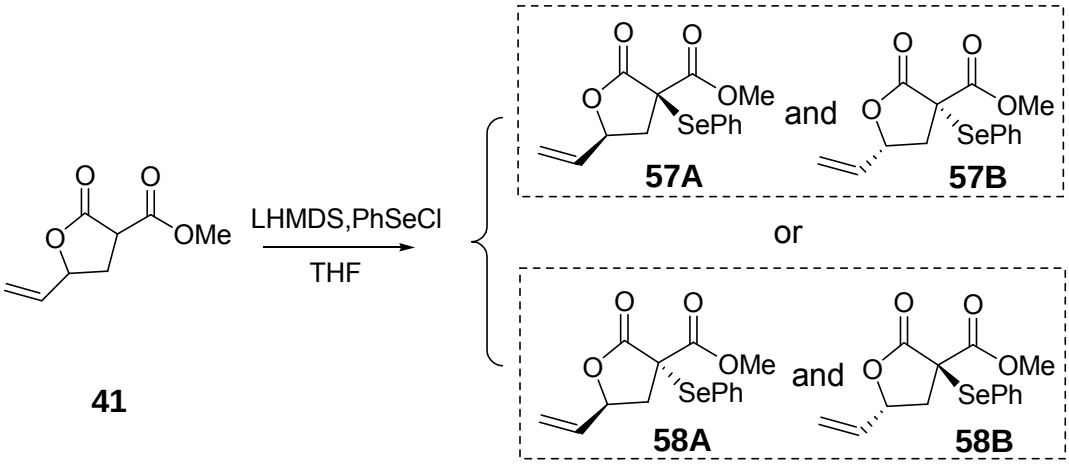


41 **57A** **57B** **58A** **58B**

Scheme 27. Synthesis of enantiomers **57** and **58**.

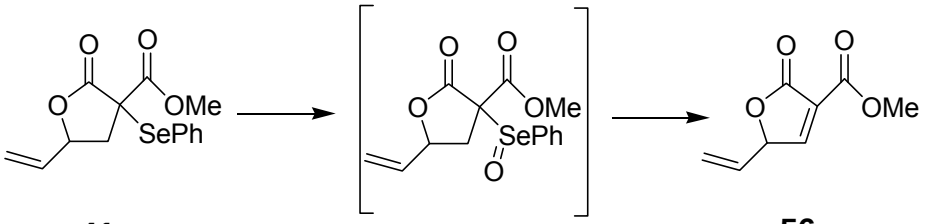
Table 13. Kinetically controlled deprotonation of lactone **41**.

Base	Temp (^{o}C)	Time (min)	Equiv[a]	%Yield	Result
LHMDS	-78	60 [b]	1:1:1	70	1:2.9
LHMDS	-78	10	1:1:5	31	1:2.0
SHMDS	-78	10	1:1:1	41	1:2.0
LHMDS	-98	10	1:1:1	64	1:3.0
SHMDS	-98	10	1:1:1	50	1:1.6
LHMDS	-98	10	1:1:5	63	1:2.3
SHMDS	-98	10	1:1:5	41	1:2.0

[a] Lactone:Base:PhSeBr; [b] Slow addition

First, we attempted a kinetically controlled deprotonation of the lactone **41** with PhSeCl in the presence of a weak base under cold temperatures. However, the best result we got was the ratio 1:3 shown in Table 13.

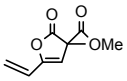
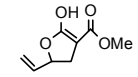
The next step was oxidative elimination of the lactone compound **57/58** to afford the desired double bond lactone **56** (Scheme 28). After extensive optimization of the reaction conditions, we still could not obtain the desired lactone **56** (Table 14).



41 **56**

Scheme 28. Synthesis of lactone **56**.

Table 14. Elimination reaction of lactone **57**/**58**.

Solvent	Temp (^oC)	Oxidizer	Base	Equiv	Result
CH_2Cl_2	0	m-CPBA		1:2	N/A
CH_2Cl_2	0	m-CPBA	DEA	1:2:3	N/A
CH_2Cl_2	0	H_2O_2	Pyridine	1:4:8	N/A
THF	0	H_2O_2	AcOH	1:2:1	
CH_2Cl_2	0	H_2O_2	AcOH	1:2:1	
MeOH	0	$NaIO_4$		1:15	N/A
MeOH	0	$NaIO_4$		1:2	N/A
CH_2Cl_2	25	SeO_2	TEA	1:1.2:1.1	N/A
CCl_4	25	SO_2Cl_2	$NaHCO_3$	1:1.4	N/A
CH_2Cl_2	25		t-BuOOH	1:1	N/A
Toluene	25	O_2	TEA	1:2	

Other attempts including trying to use a leaving group other than selenium phenyl or directly eliminating the reaction to form the double bond all failed to

give the desired lactone **56**. It is supposed that the structure of lactone **56** is not a stable form. We need to develop a new synthesis strategy to achieve the total synthesis of the natural product, Asperuloside **39**.

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Chapter 6

Experimental

All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury plus 400 MHz nuclear magnetic resonance spectrometer. The chemical shifts of ^{1}H and ^{13}C NMR were expressed in parts per million relative to chloroform (δ=7.26). All spectra were analyzed using Mestre-C NMR Software version 4.4.1.0 and were treated using the 'Full FT', 'Automatic Phase APT', and 'Full Auto Baseline Correction' processing options. Mestre-C was also used to integrate the peaks to produce normalized peak areas for each compound.

Mass spectra were obtained from the University of Florida's Mass Spectroscopy Services. Low-resolution electron impact (EI) or chemical ionization (CI) spectra were obtained using a Finnigan 4000 mass spectrometer, while high-resolution mass spectra were obtained using a Kratos MS-50 instrument.

HPLC analyses were collected using a Hitachi-L4200H UV-Vis Detector, Hitachi-L-6200A Intelligent Pump Model-Gradient, and Hitachi (EM-Science) D-2500 Chromato-Integrator. A (R,R) Whelk-O I brush type HPLC column (25cm x 4.6 5μm spherical silica particles of 10/100A pore size) which is available from Regis Technologies Morton Grove, IL, was used to determine the enantiomer

ratios and to help identify compounds as possible allenes. HPLC samples were prepared by dissolving aliquots of sample in 95% Isopropanol in Hexanes.

Air-sensitive reactions were performed under a positive pressure of argon unless otherwise indicated. Air and moisture-sensitive reagents were introduced via syringe or cannula through a rubber septum. THF was distilled prior to use using a THF still, purchased from Solv-Tek. All reagents were purchased from Aldrich or Acros and used without further purification.

Purification by flash column was carried out in the indicated solvent system using 70-230 mesh silica gels. TLC analysis was conducted on 5 x 20cm Selecto Flexible-Backed Silica Gel TLC Plates with a Fluorescent Indicator. The developed plates were visualized by UV light (254nm) and/or stained using potassium permanganate, ceric ammonium molybdate (CAM), and phosphorus molybdic acid (PMA).

7-phenoxyhept-3-yn-2-one (1)

We placed a solution of the tetrahydropyranyl ether 2-prop-2-ynyloxy-tetrahydro-pyran in freshly distilled THF, which was stirred for 15 minutes under argon. We put the reaction mixture in a dry ice and acetone bath (-78^{o}C) for 10 minutes. We then slowly added an n-butyl lithium hexane solution (2.5M). When the addition was completed, the reaction mixture was stirred continually at -78^{o}C for 1 hour. Then, freshly distilled methylchloroformate was added. The final reaction mixture was stirred for 1 hour at -78^{o}C and then warmed to room temperature. Saturated aqueous ammonium chloride (NH_4Cl) was added and the resulting mixture was extracted with ether 3 times. Ether layers were

combined and washed with water and brine. We separated them and made a TLC analysis, dried over Na_2SO_4. The oil was purified using a flash column and a gradient eluant 0~10% EtOAc in hexanes to give **1** with a 76% yield. ^{1}H NMR ($CDCl_3$) δ 1.88 (2H, m), 2.3 (3H, s), 3.51(2H, t), 3.56(2H, t), 4.52 (2H,s), 7.34 (5H, m).

Cyclopentadienylmanganese dicarbonyls coordinate methyl ketone (2-3)

MMT was added to a reactor with a stir bar. The air was removed by high vacuum and flushed with argon. Then, 70ml of THF was added. The reactor was sealed with a septum, paraffin and Teflon tape. The mixture was irradiated with UV-light (wavelength λ=364nm) for 30 minutes and then flushed with Argon again for 10 minutes. The methyl ketone was added with 10 ml of THF and left to react under constant hv. The reaction was left 12 hours to give intermediate **2**. The UV-light was turned off at this point and the reactor was covered completely with aluminum foil to prevent light from entering. Then, a base was added for isomerization and allowed to react overnight at room temperature. TLC analysis indicated that isomerization had completely taken place. The reaction mixture was purified using silica gel using 0%-20% Ethyl acetate/Hexanes to give **3** with an 84% yield. No ^{1}H NMR was obtained because Mn causes considerable band broadening.

7-Benzyloxy-hepta-3,4-dien-2-one (4)

A round-bottomed flask containing MMT-coordinated methyl 6-benzyloxy-hexa-2,3-dienoate (**3**) (480 mg, 1.13 mmol) dissolved in acetone (10 mL) in an argon atmosphere was cooled to -78 ºC for 5 minutes. Cerium ammonium nitrates

(2.00 g, 3.66 mmol) was dissolved in acetone (70 mL), and added drop-wise to the flask via a syringe. The resulting reaction mixture was stirred at -78 ºC for an additional 1.5 hours. The reaction mixture was then concentrated in vacuo and passed through a plug of silica gel (90 g) to remove excess cerium salts flushing with EtOAc. Following solvent removal, the crude oil was purified via flash column chromatography using silica (40 g, 3 x 11 cm) with gradient elution (0-10% EtOAc/hexanes) to yield a colorless oil (53 mg, 36%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5 H), 5.75-5.66 (m, 2H), 4.52 (s, 2H), 3.61 (t, J = 6.2 Hz, 2H), 2.48 (m, 2H), 2.19 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 213.7, 199.2, 138.0, 128.4, 127.7, 98.1, 92.3, 73.1, 68.7, 28.4, 26.5; HRMS (CI) [M+H]+ = 217.1232, calculated for $C_{14}H_{16}O_2$ [M+H]+ = 217.1229.

(1S,9R)-2,7-Diazatricyclo[7.2.1.0^{2,8}]dodec-7-ene (5)

A solution of azabicycloheptenon (**21**) in MeI was stirred under N_2 for 15 hours at room temperature in the dark (covered with alumina foil). After concentration, the crude product was dissolved in DCM and trifluoroacetic acid was added at 0^{o}C. After stirring at 0^{o}C for 4 hours, the mixture was quenched by adding ice and 10% NaOH. The reaction solution was stirred for an additional 4 hours. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried (K_2CO_3), and concentrated. The residue was purified by alumina column chromatography using 9:1 EtOAc/MeOH to give **5** with a 10% yield. ^{1}H NMR ($CDCl_3$) δ 1.14-1.20 (m, 1 H), 1.27 (d, 1H), 1.43-1.67 (m, 3H), 1.74-1.90 (m, 5H), 2.57 (ddd, 1H), 2.78 (brs,1H), 2.97-3.05 (m, 2H), 3.57 (brs, 1H), 3.6-3.65 (m,

1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 25.8 28.6 29.1 38.7 47.7, 48.0 50.7 65.2, 168.9; HRMS (FAB) [M+H]+ = 165.1396, calculated for $C_{10}H_{16}N_2$ [M+H]+ = 165.1396.

(1R,8s)-2,6-Diaza,1,11,11-trimethyltricyclo[6.2.1.0<2,7>]undec-6-ene (6)

In a similar manner, **6** was prepared from **21** (5%) as pale yellow oil. ^1H NMR ($CDCl_3$) δ 0.95 (s, 6 H), 1.26 (s, 3H), 1.56-1.89 (m, 4H), 1.96-2.11 (m, 2H), 2.15-2.22 (m, 1H), 3.09 (ddd,1H), 3.35-3.46 (m, 2H), 3.54 (d, 1H), 3.75 (ddd, 1H); ^{13}C NMR ($CDCl_3$) δ 12.1, 17.8 18.1, 24.6, 26.5, 26.7, 31.7, 44.1, 45.7, 51.1, 53.5, 76.9, 173.0; HRMS calculated for $C_{13}H_{22}N_2$ [M+H]+ = 207.1861.

(S)-7-Hydroxy-1,5-diazabicyclo[4.3.0]non-5-ene (7)

To a solution of azido lactam (**29**, 0.1M) in 1, 2-dichloroethane in an argon atmosphere was added a solution of orally bromide in dichloromethane (2M) drop-wise at 0^oC. After the reaction mixture was stirred at 0^oC for 1 hour, it was warmed to room temperature and stirred for 4 hours. The resulting mixture was quenched with anisole (2 equiv) and MeOH (1/5 volume of 1, 2- dichloroethane) at 0^oC and stirred for 30 minutes at room temperature. The resulting mixture was concentrated to half of the original volume and extracted with 1M aq HCl. The aqueous extract was washed with CH_2Cl_2 and concentrated under reduced pressure. The residue was passed through Amberlite IRA400 (OH-) with MeOH as the eluent. The evaporation of the solvent gave amidine **7**. ^1H NMR ($CDCl_3$) δ 1.63-1.77 (m, 2H), 1.84-1.91 (m, 1H), 2.15-2.22 (m, 1H), 3.06-3.16 (m, 4H), 3.21-3.25 (m, 1H), 3.30 (ddd,1H), 4.41 (dd, 1H), 6.35 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 29.3, 42.6, 43.0, 48.4, 70.4, 163.0; ESI-MS m/z [M+H]+ = 141.

(S)-9-Hydroxymethyl-1,5-diazabicyclo[4.3.0]non-5-ene (8)

^{1}H NMR (C_6D_6) δ 1.31-1.50 (m, 2H), 1.60 and 1.75 (m, 2H), 2.32 (ddd, 1H), 2.60 (dt, 1H), 2.72 (dt, 1H), 3.14 (m,1H), 3.07 (m, 1H), 3.20-3.27 and 3.34-3.39 (2H), 4.43 (dd, 1H), 3.55 (dd, 1H); ^{13}C NMR (C_6D_6) δ 20.6, 22.3, 30.1, 41.2, 43.3, 61.8, 64.0, 161.0.

(1R,3S)-3-(methoxycarbonyl)-1,2,2-trimethylcyclopentanecarboxylic acid (9)

To a solution of 3g (14.98mmol) of (+)-camphoric acid in 17ml of anhydrous methanol was added 1.197ml of concentrated sulfuric acid. The mixture was heated at reflux for 30 minutes and then left standing at 0^{o}C overnight. The resultant solid was collected by decantation; the solid was dissolved in a minimum amount of satd. $NaHCO_3$ (60ml) and washed with ether. The aqueous layer was acidified with conc. HCl to pH 3; whereupon the acid ester was precipitated. The white crystalline solid was collected by filtration to give **9** with a yield of 76.62%. ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, s), 1.25 (3H, s), 1.27 (3H, s), 1.55 (2H, m) 1.83 (1H, m), 2.22 (1H, m), 2.55 (1H, m), 2.83(1H, t), 3.70(3H, s); ^{13}C NMR ($CDCl_3$) 21.50, 21.80, 22.70, 22.80, 32.50, 46.80, 51.55, 53.00, 56.40, 58.54, 174.50; R_f = .6 in 30% E/H.

(1S,3R)-methyl 3-carbamoyl-2,2,3-trimethylcyclopentanecarboxylate (10)

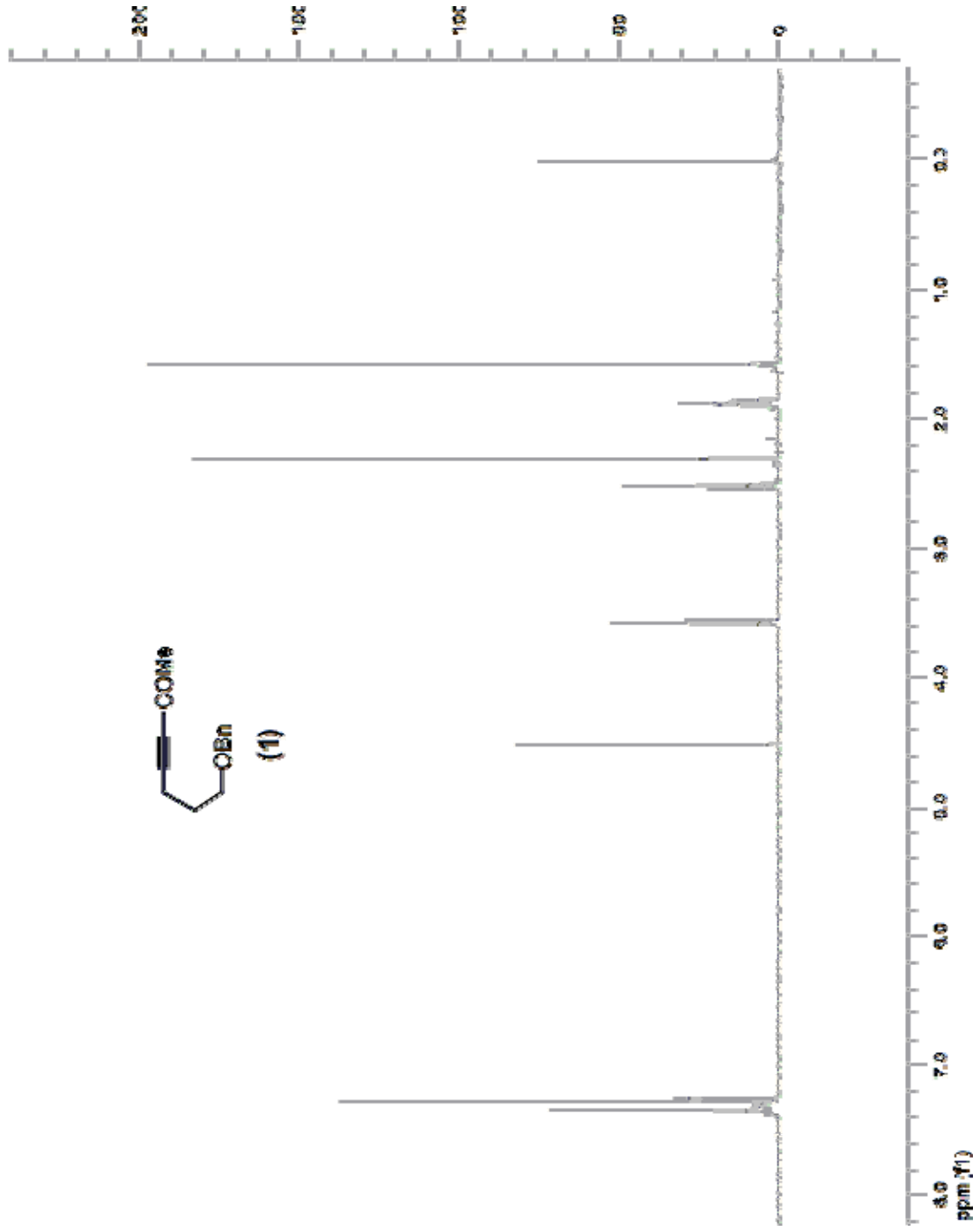
To a solution of the acid ester (**9**), (3g, 14.00mmole) dissolved in 9ml of hexane and PCl_5 (3.79g, 18.20mmole) was added in small portions. The resultant homogeneous solution was stirred for 1.5 hours at room temperature and then transferred to a dropping funnel. The acid chloride was added drop-wise over 1 hour to an ice-cold solution of saturated NH_4OH (9 ml). The resultant precipitate

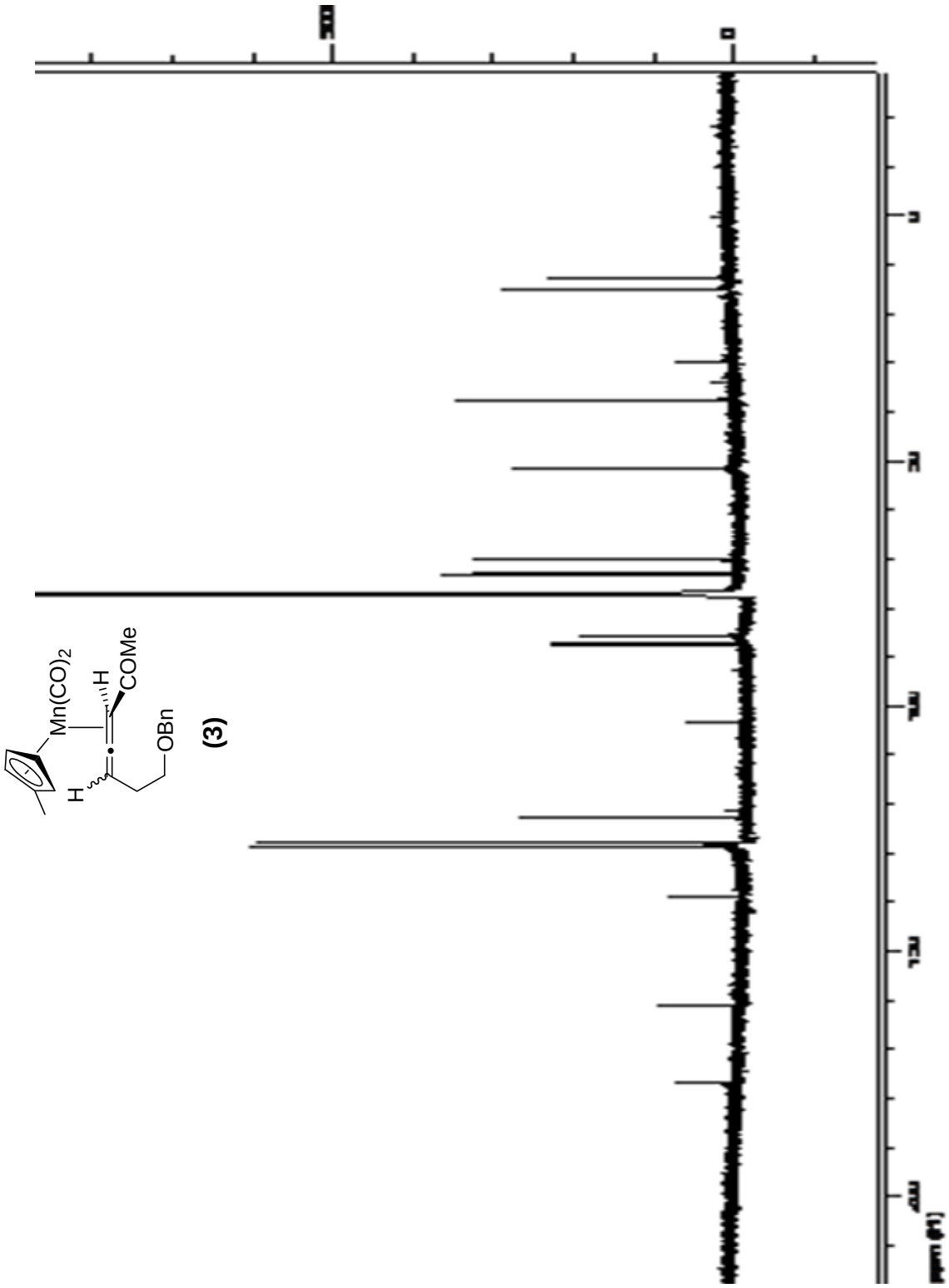
was collected by filtration and washed with Di-water until all the NH_4OH was completely washed away to give **10** as a white solid with a yield of 95%. ^1H NMR ($CDCl_3$) 0.85 (3H, s), 1.23 (3H, s), 1.55 (2H, m), 1.85 (1H, m), 2.25 (1H, m), 2.40 (1H, m), 2.82 (1H, m) 3.70 (3H, s), 5.35 (1H, broad s) 5.53 (1H, brs).

Methyl (1R,3S)-3-(Methoxycarbonyl)-1,2,2-trimethylcyclopentylcarmata (11)

Sodium metal (0.218g, 9.47mmole) was dissolved in absolute MeOH (20ml). To the solution, bromide (0.598g, 3.74mmole) was added drop-wise at -60^oC via syringe, and the reaction mixture was stirred for 10 minutes. To the resulting white slurry, was carefully added a solution of amide ester (**10**) (0.613g, 2.87mmole) in absolute MeOH (20ml) while ensuring that the internal temperature of the solution remained <-50^oC. The resulting colorless, homogeneous solution was then slowly warmed to 0^oC over 2 hours and then heated up to 55^0C for 3 hours. When cooled to room temperature, the reaction mixture was acidified to pH 5 with 2N-HCl. After removal, most of the solvent and the remaining slurry were dissolved in a minimum amount of water. The solution was extracted with ether and the combined organic extracts were dried over Na_2SO_4 to give (**11**) with a yield of 68%. ^1H NMR ($CDCl_3$) 0.88 (3H, s), 1.11 (3H, s) 1.38 (3H, s) 1.90 (2H, m) 2.10 (2H, m), 2.70 (1H, q), 3.62 (3H, s) 3.70 (3H, s), 5.20 (1H, brs).

Chapter 7 Selected Spectra





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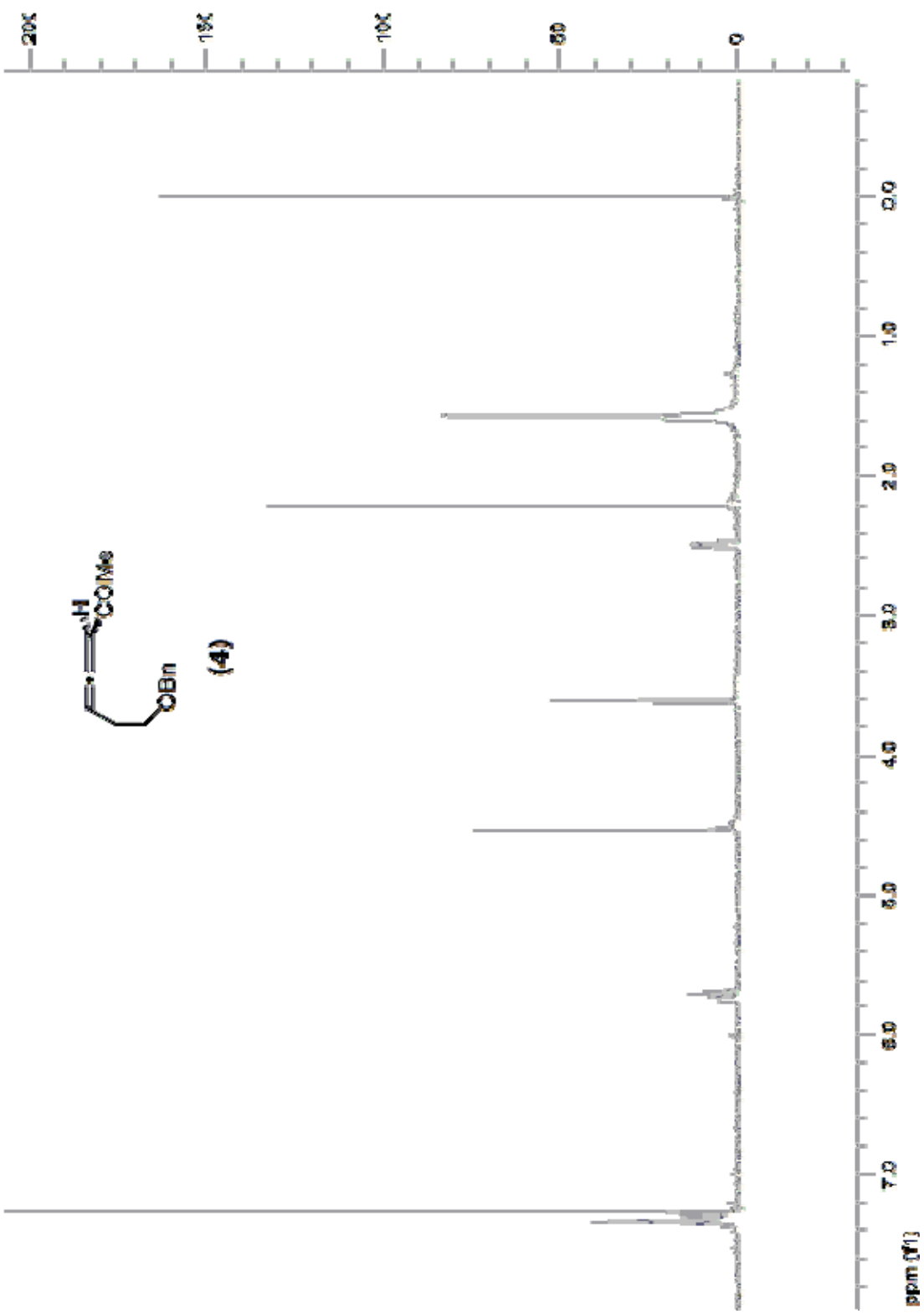
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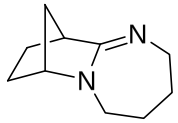

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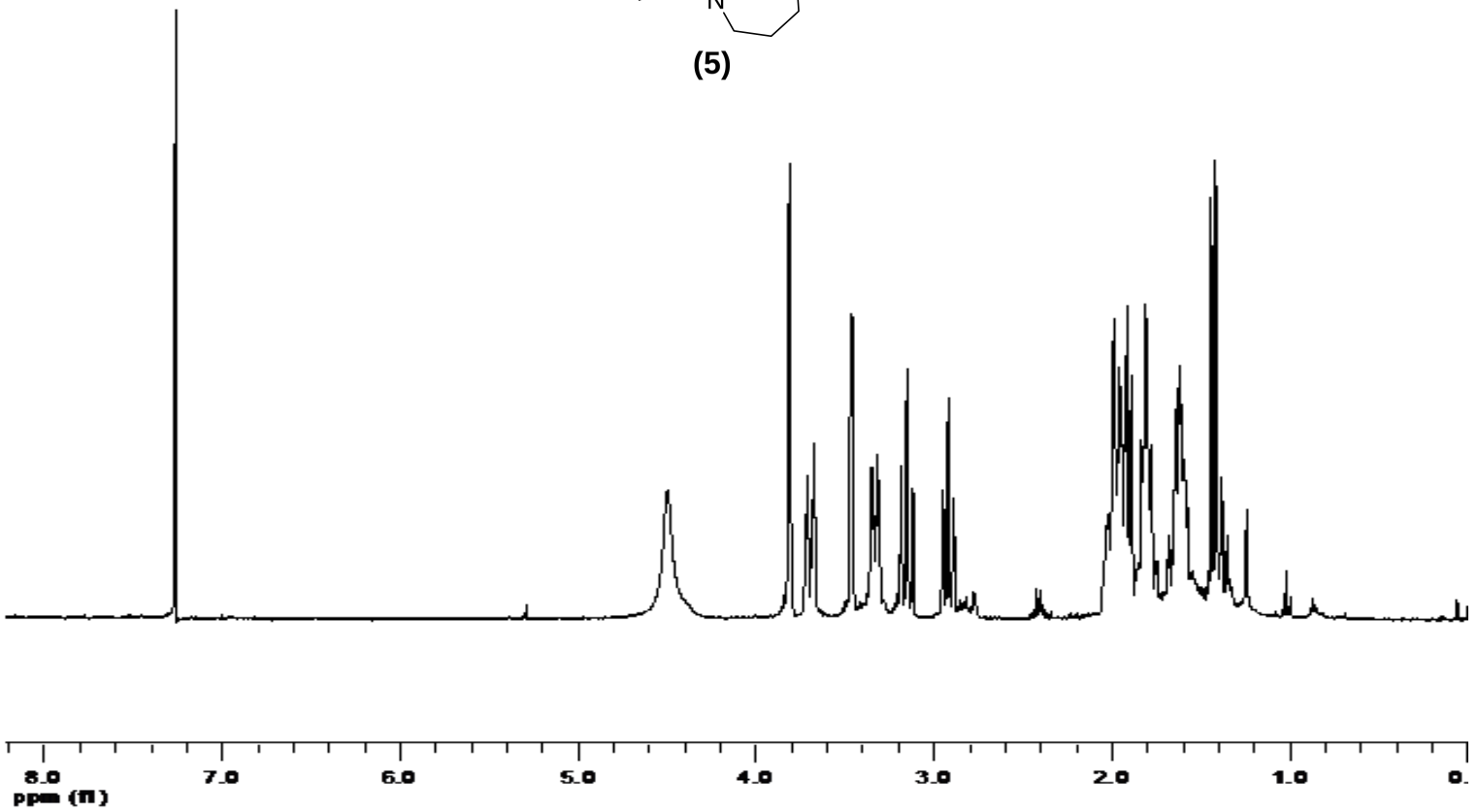

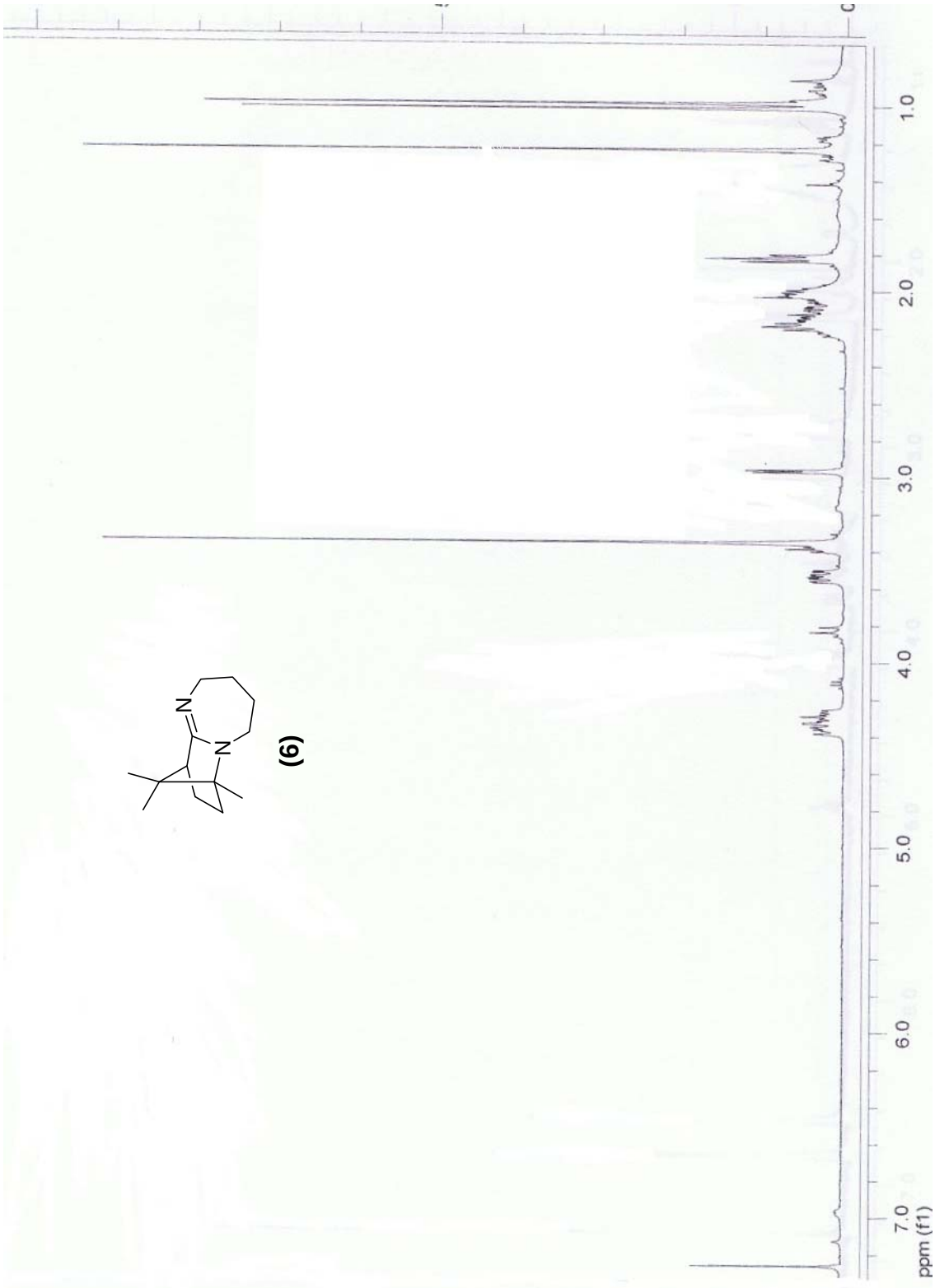
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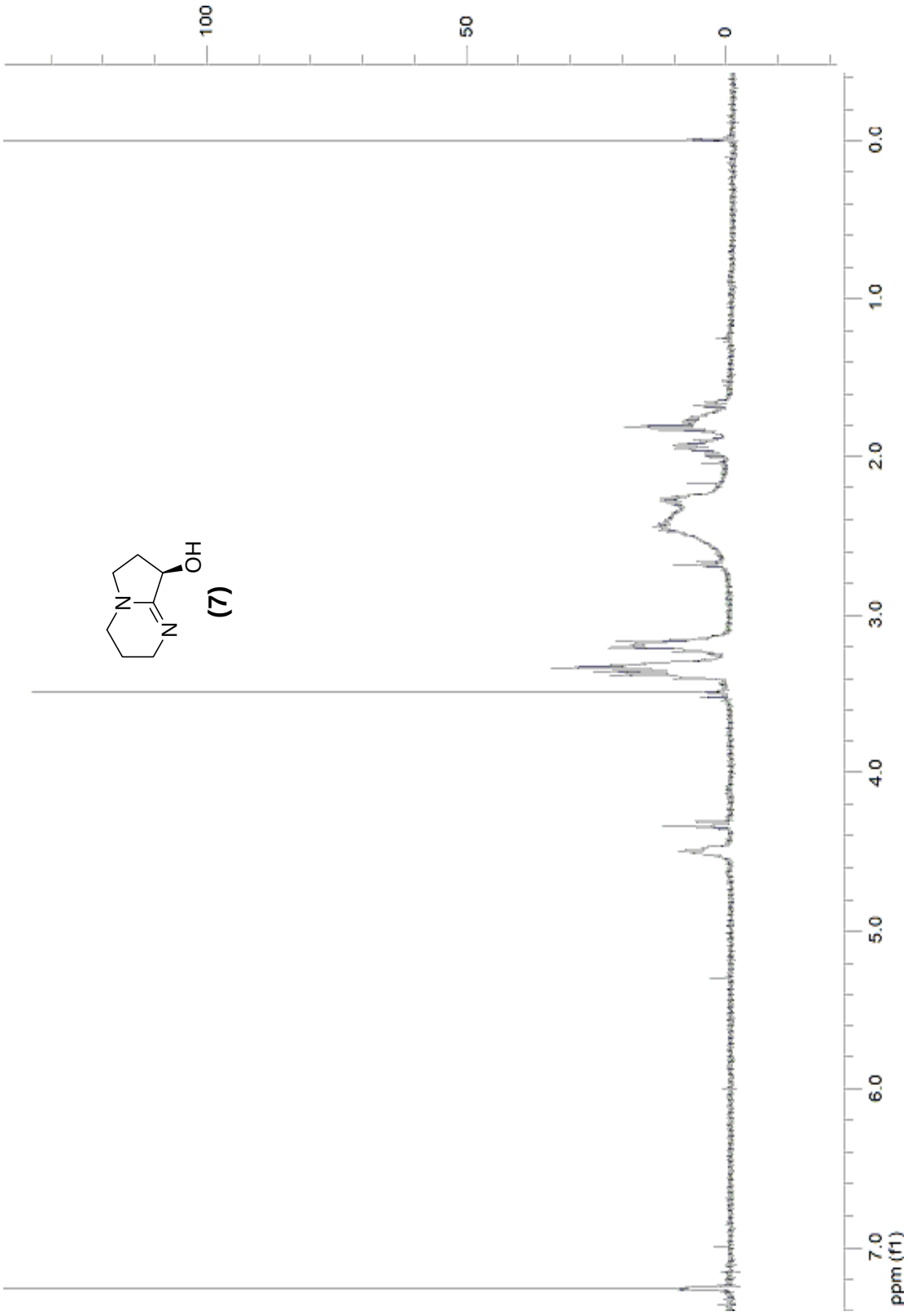
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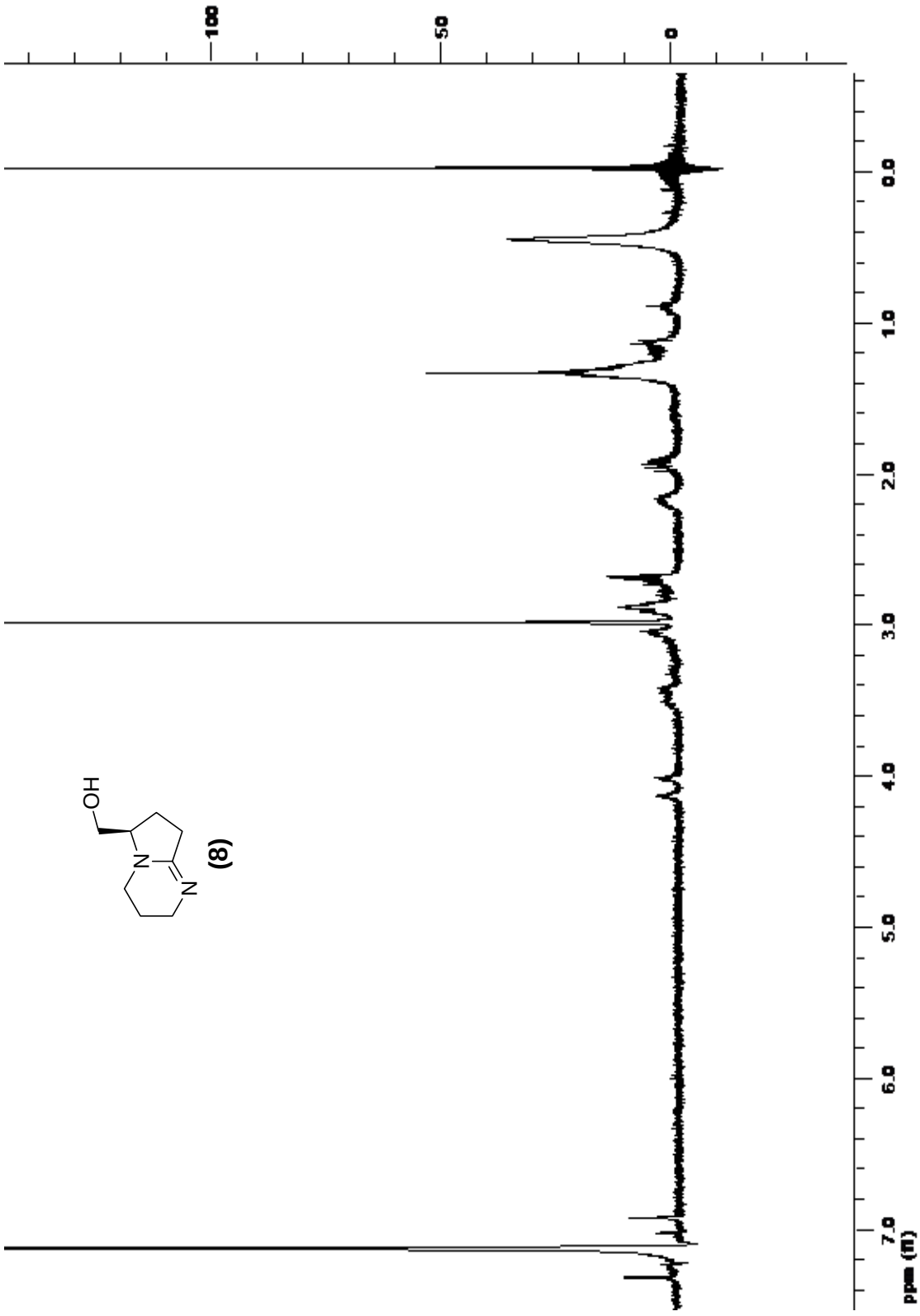
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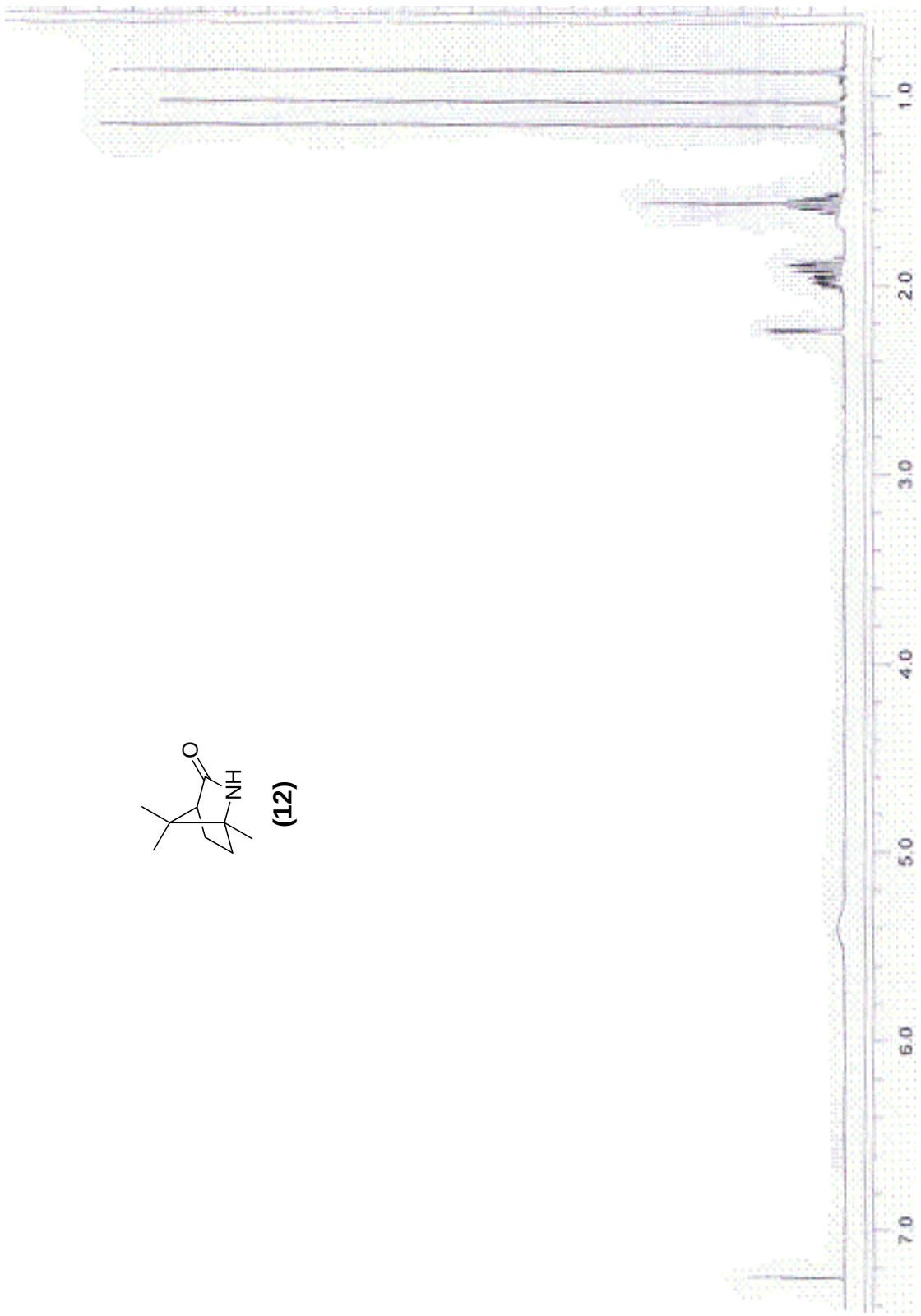

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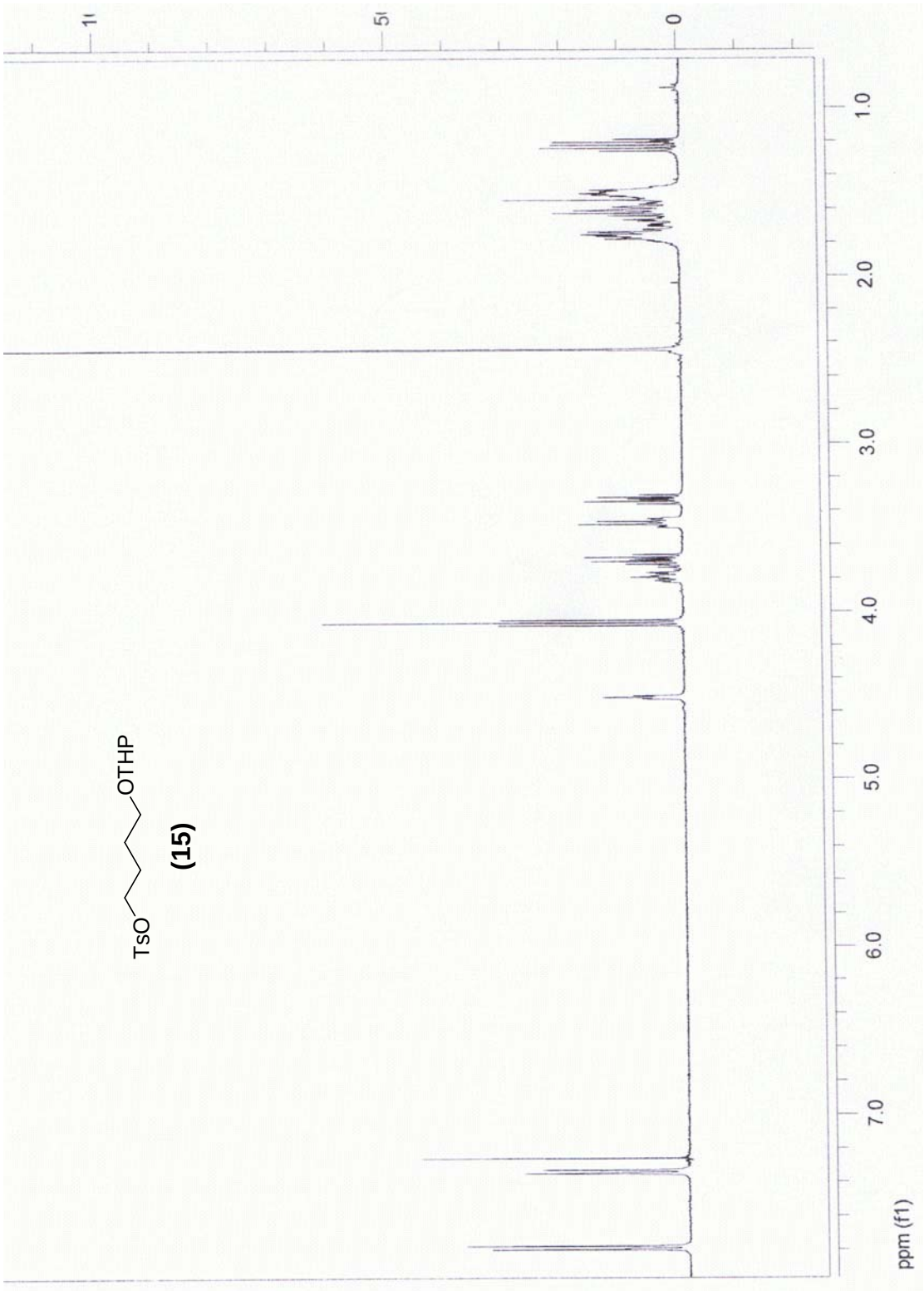
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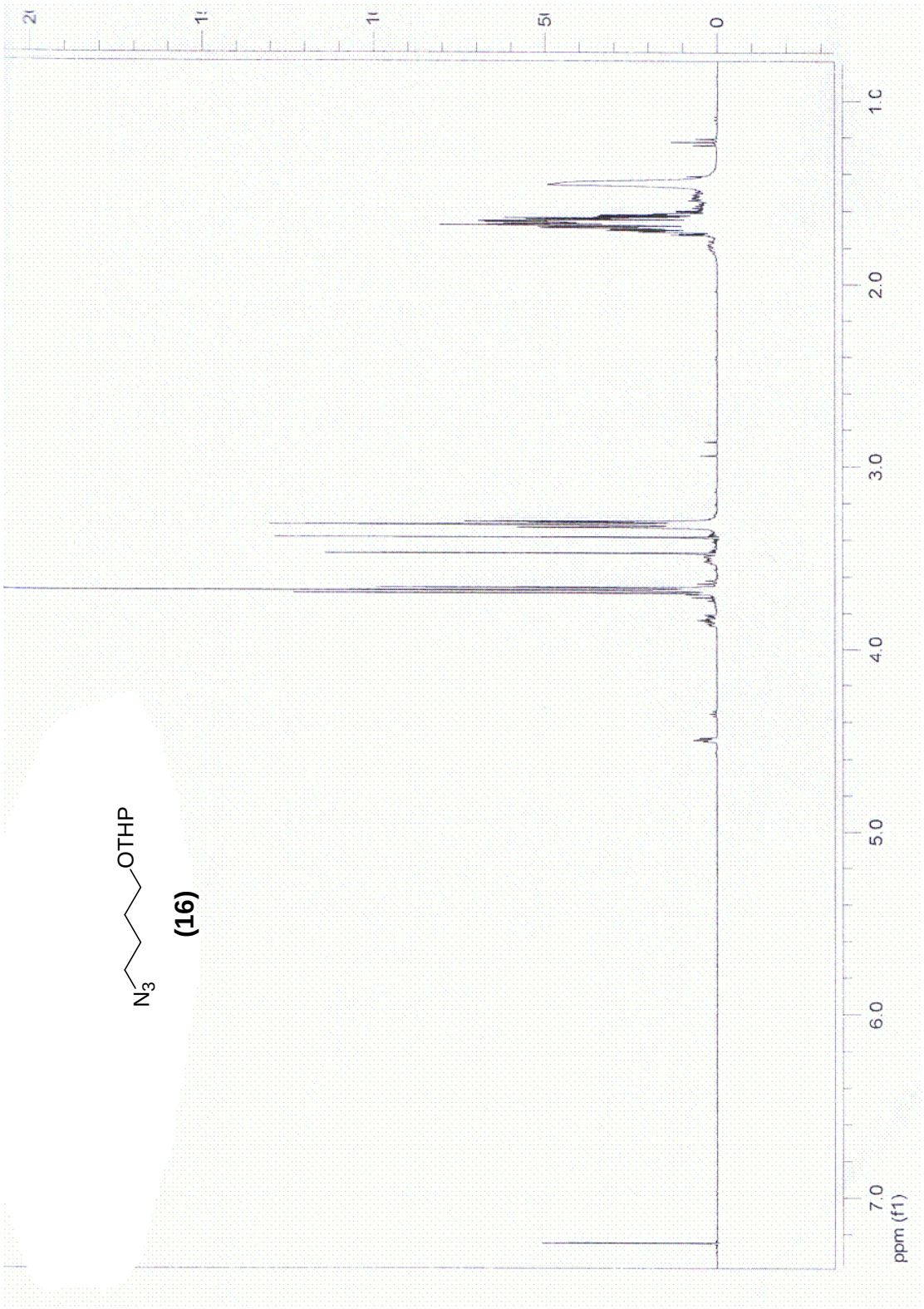
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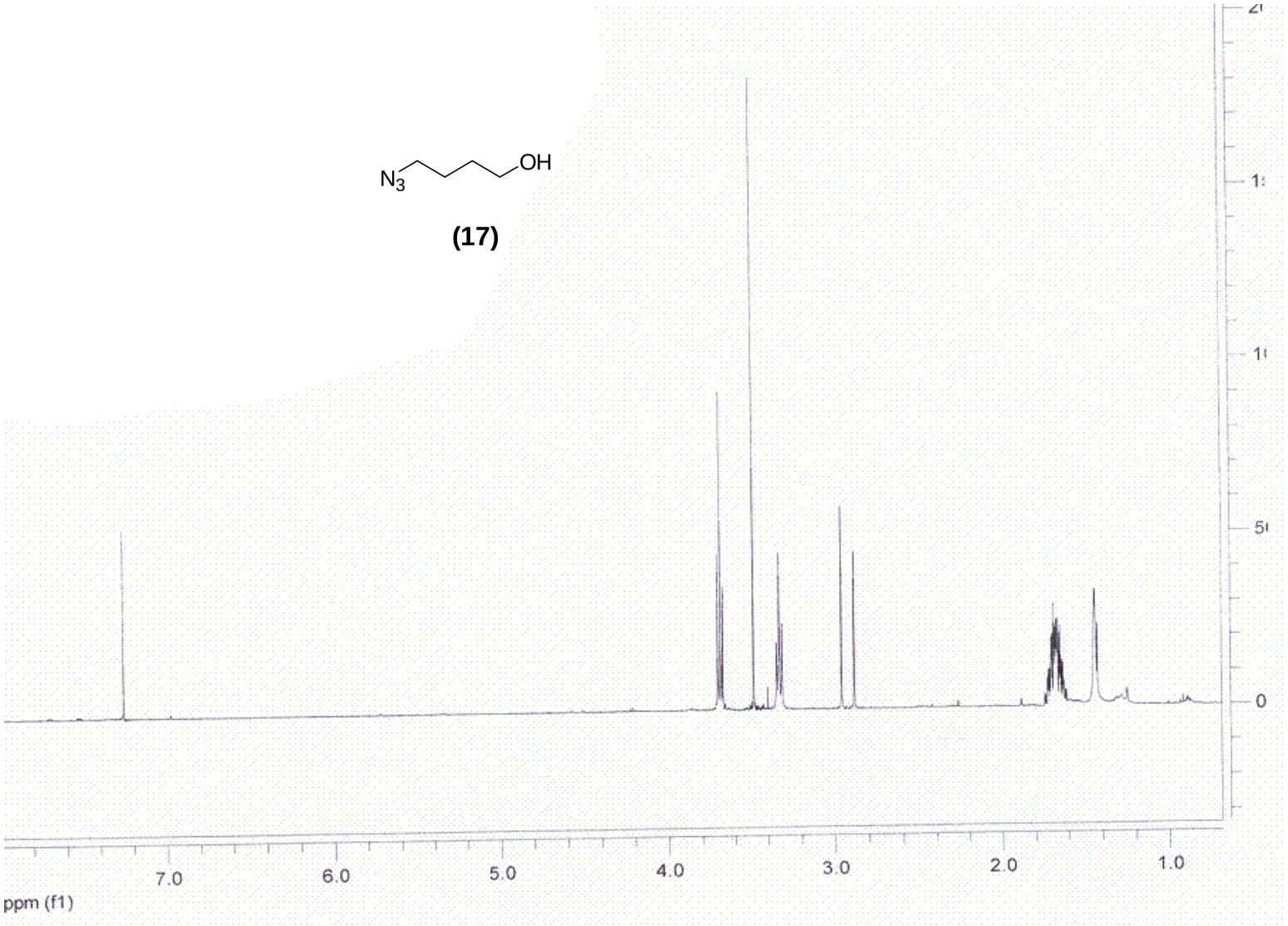

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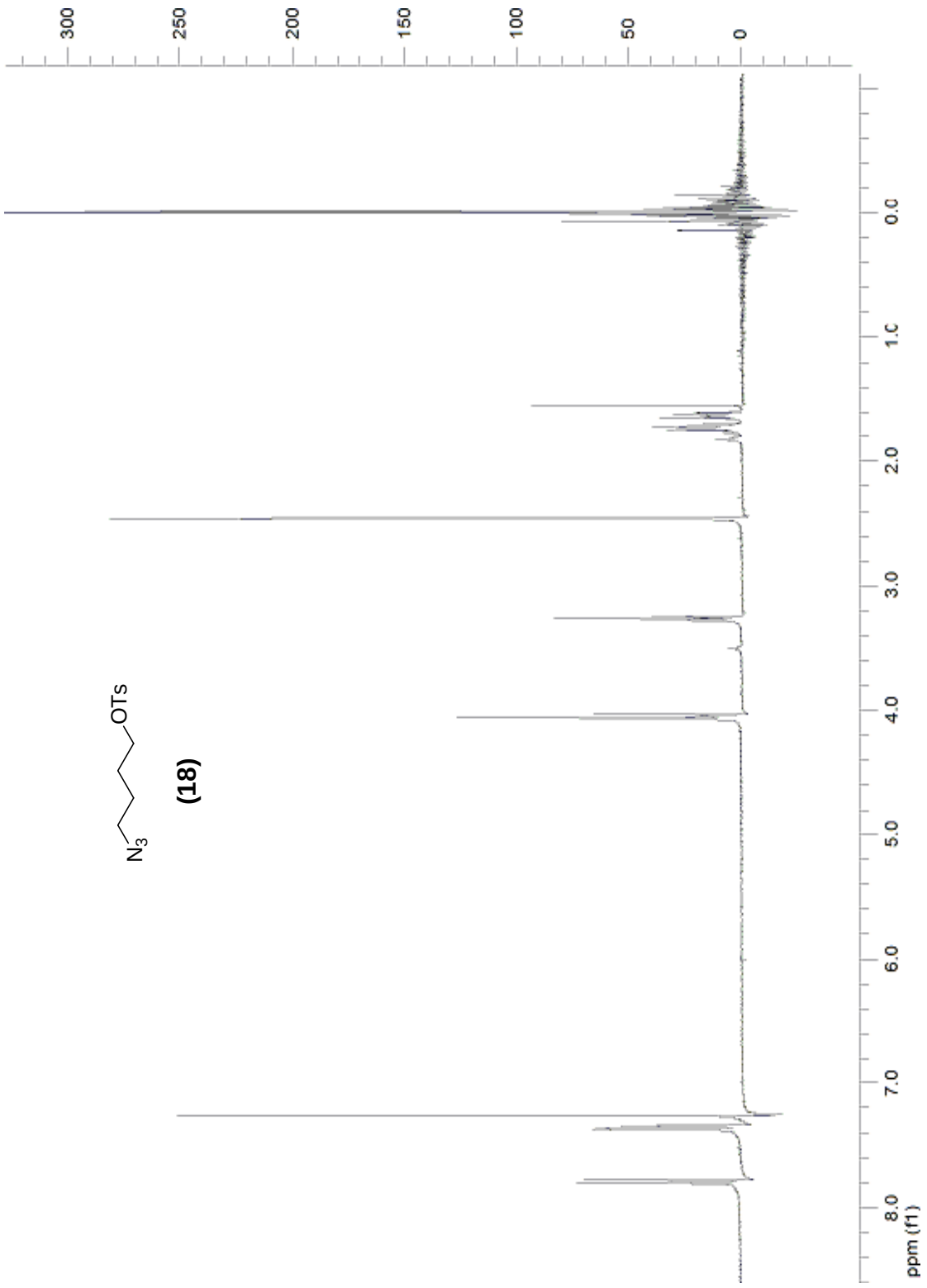
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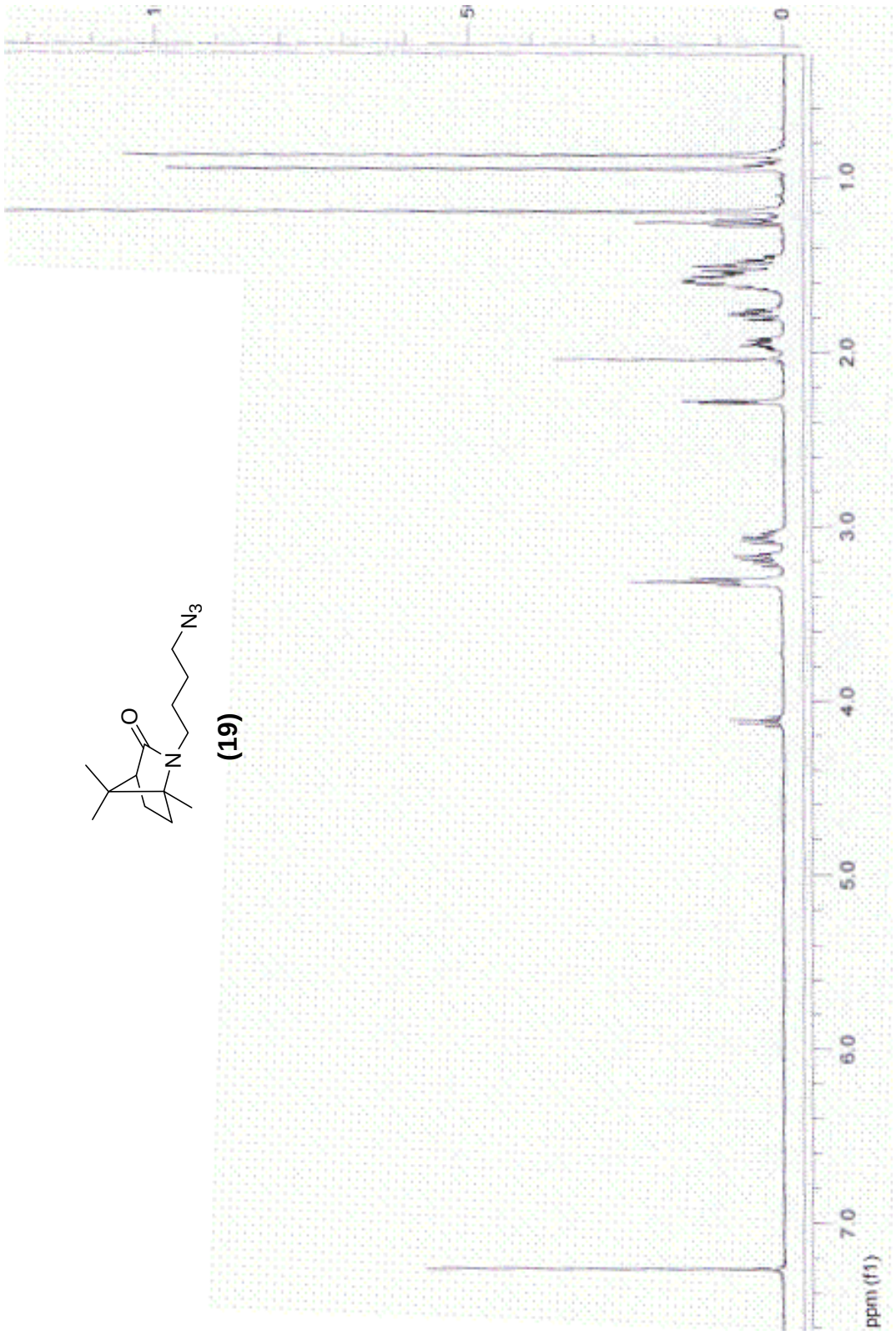

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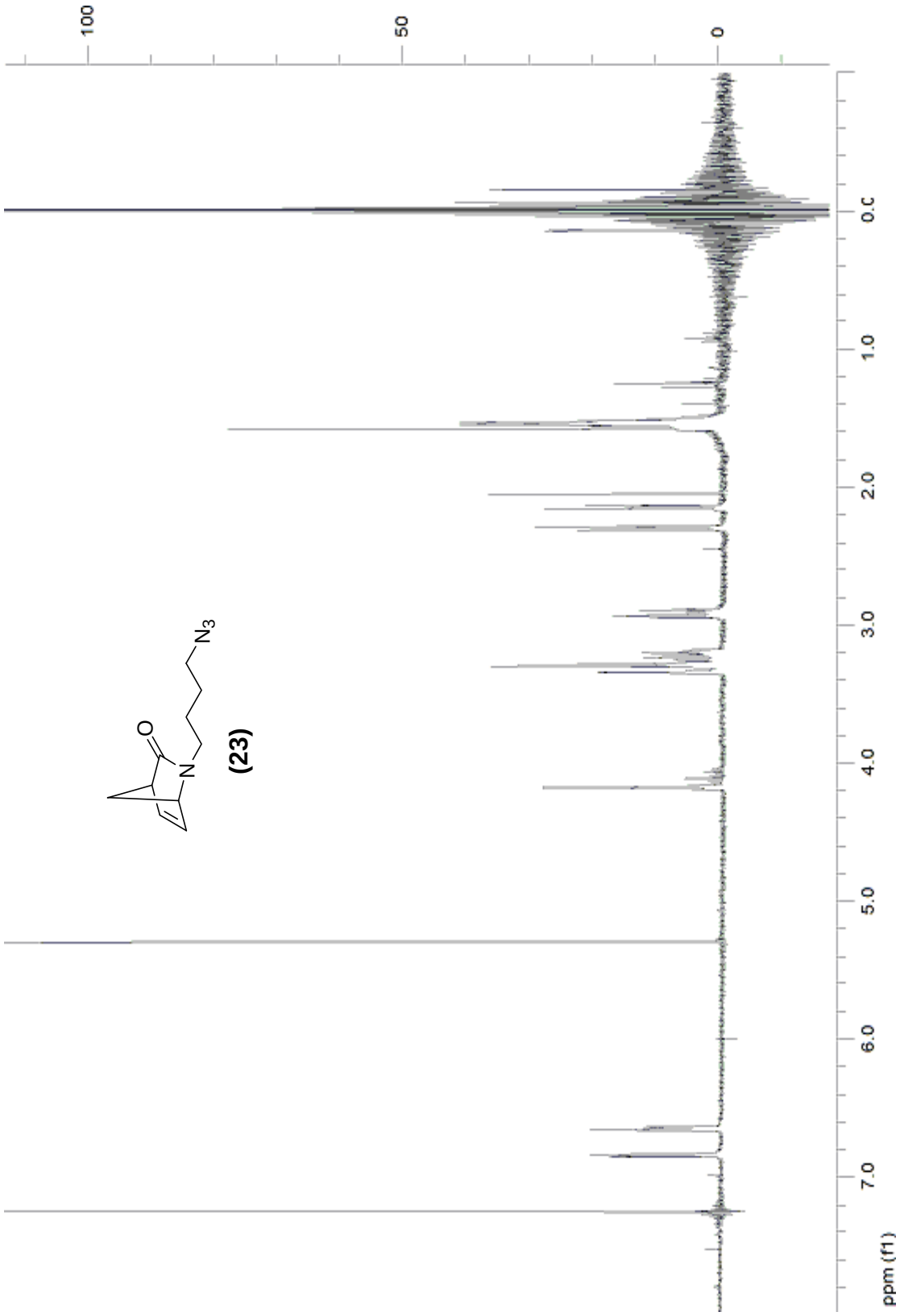

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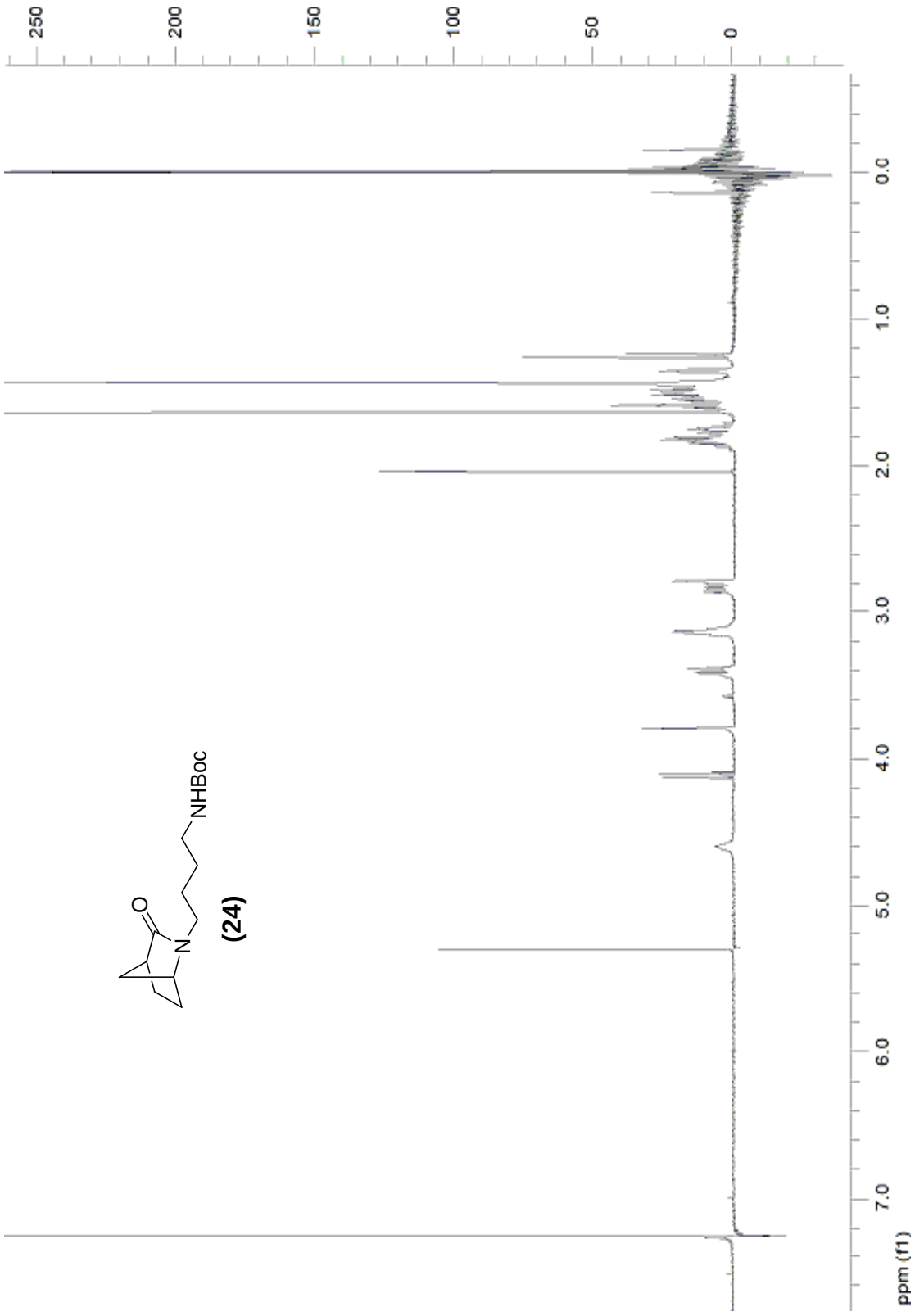
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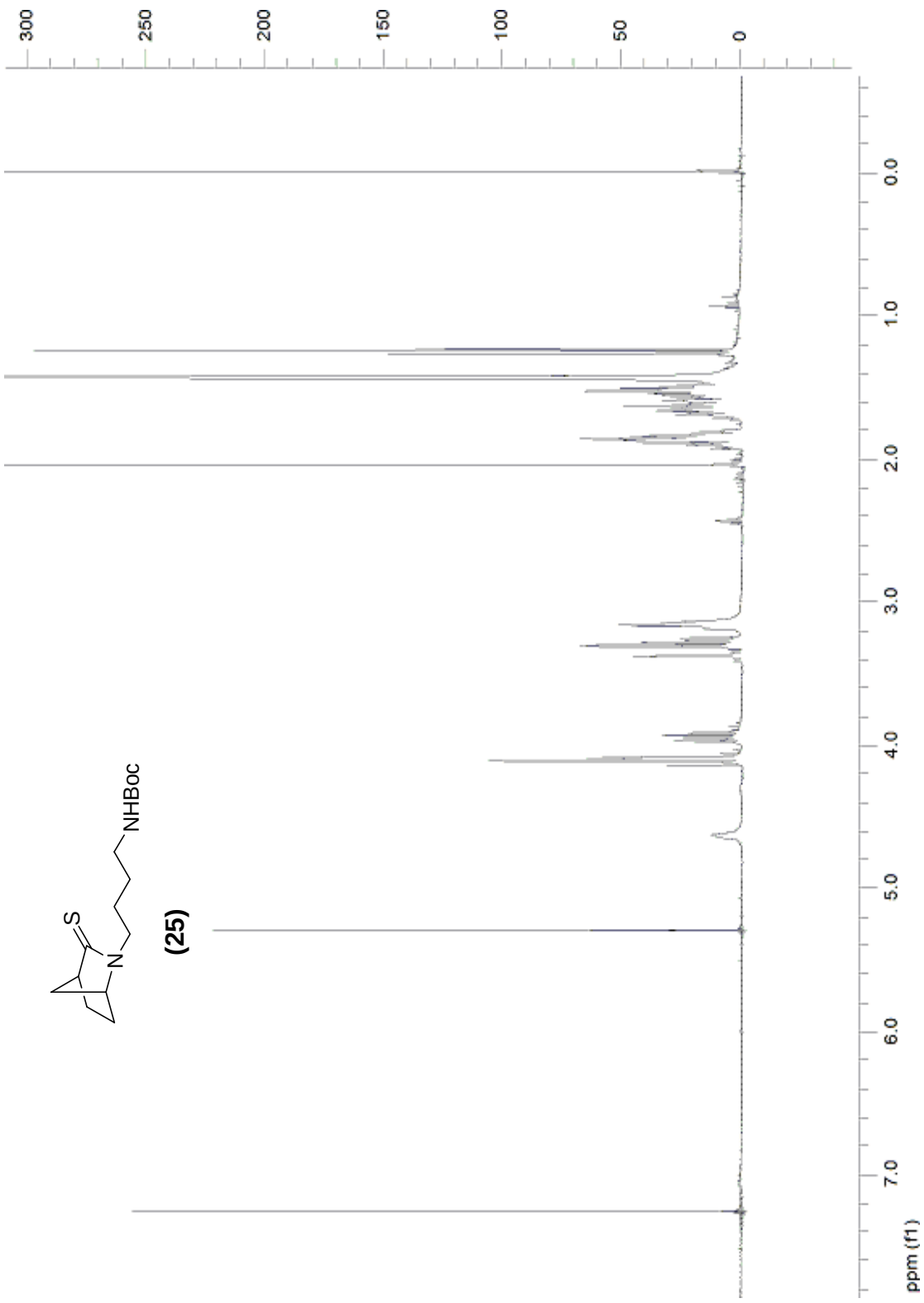

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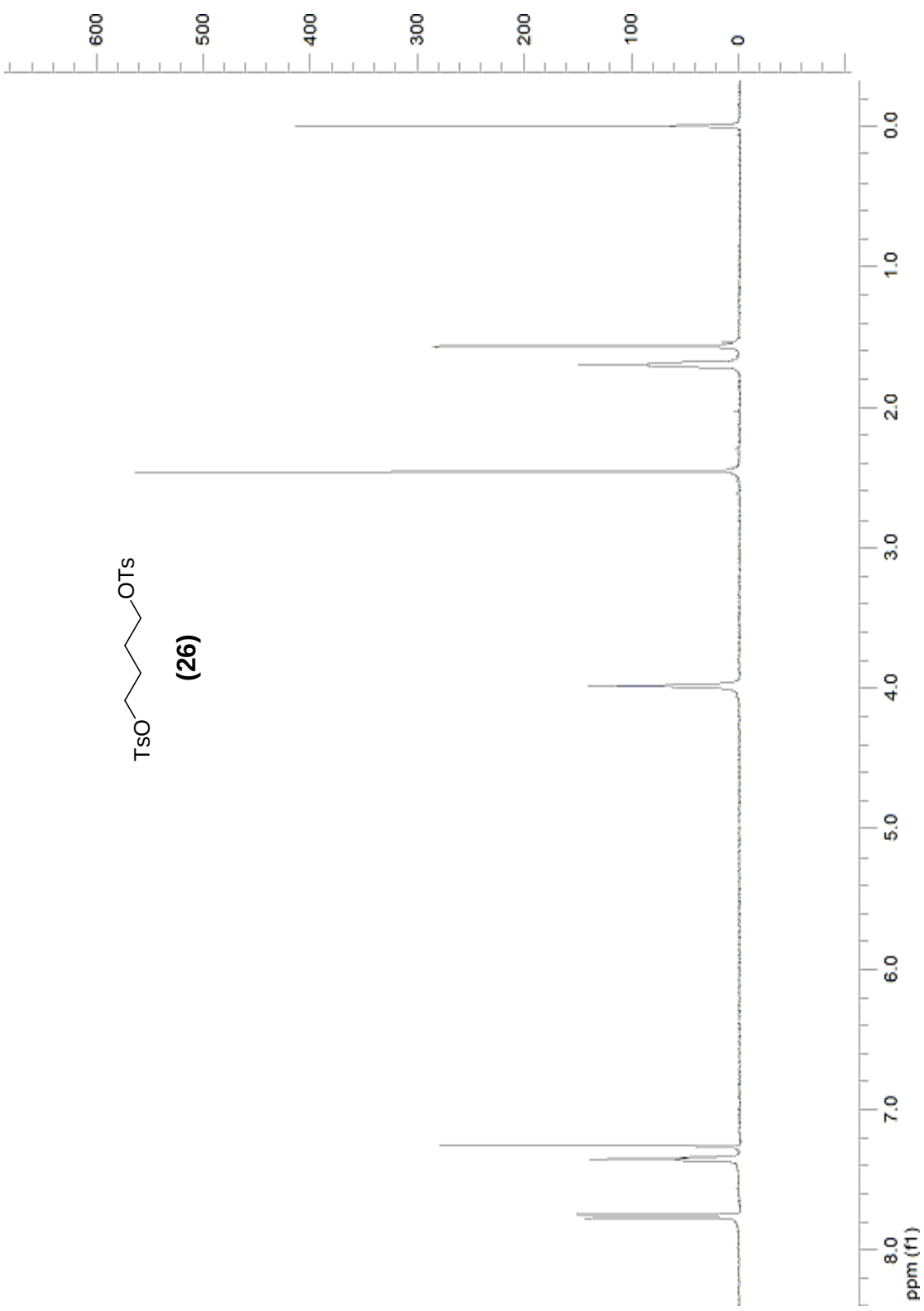

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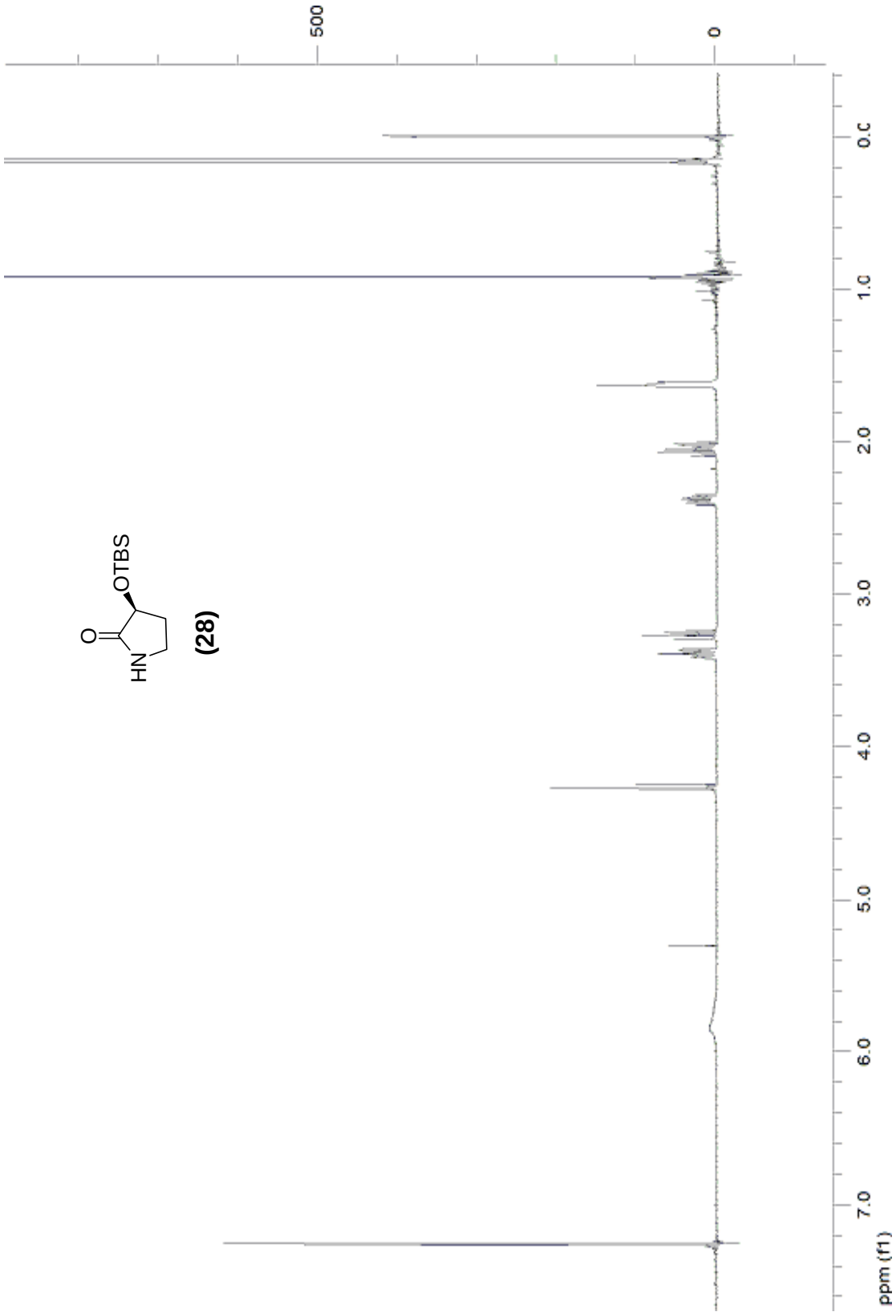
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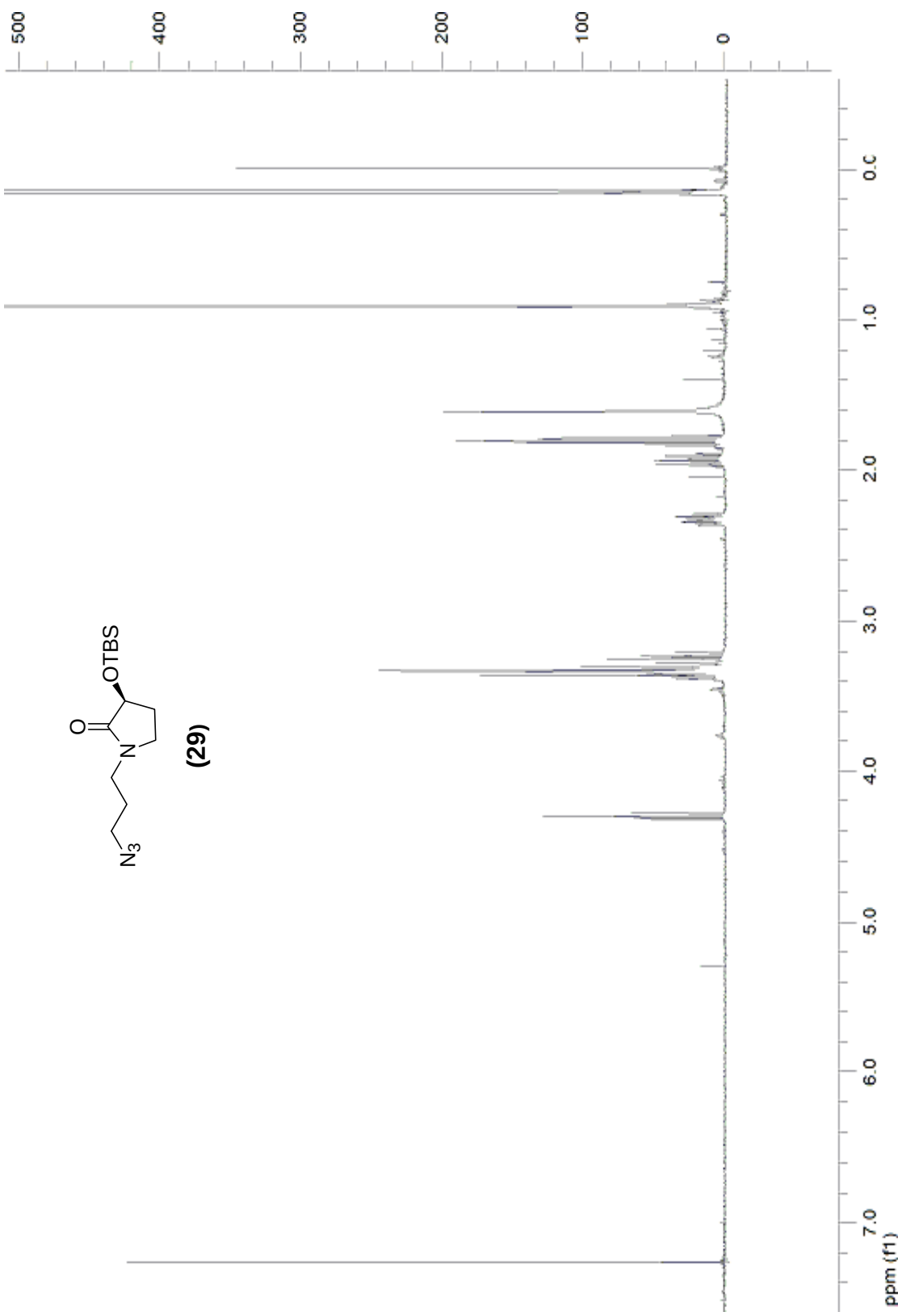
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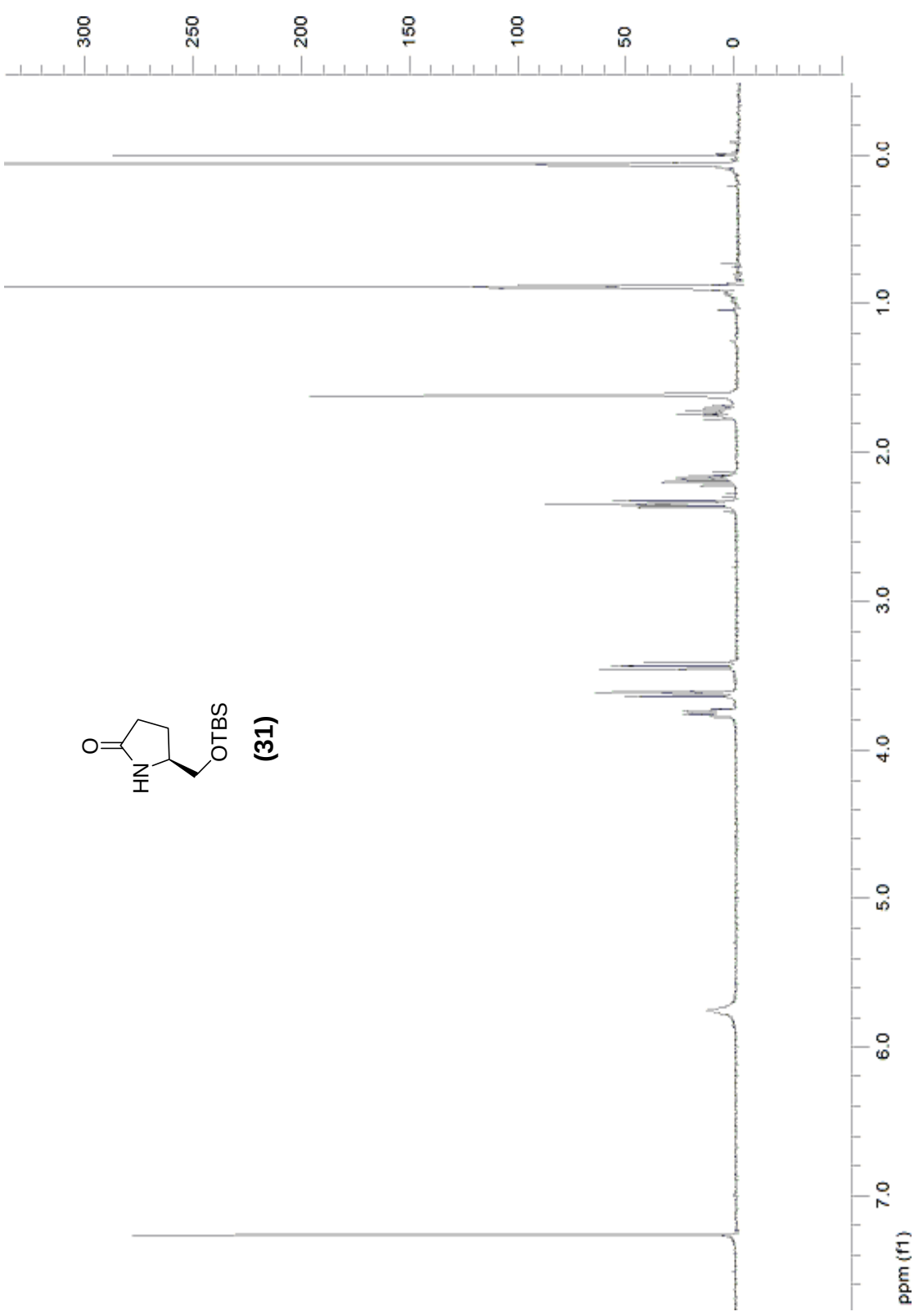

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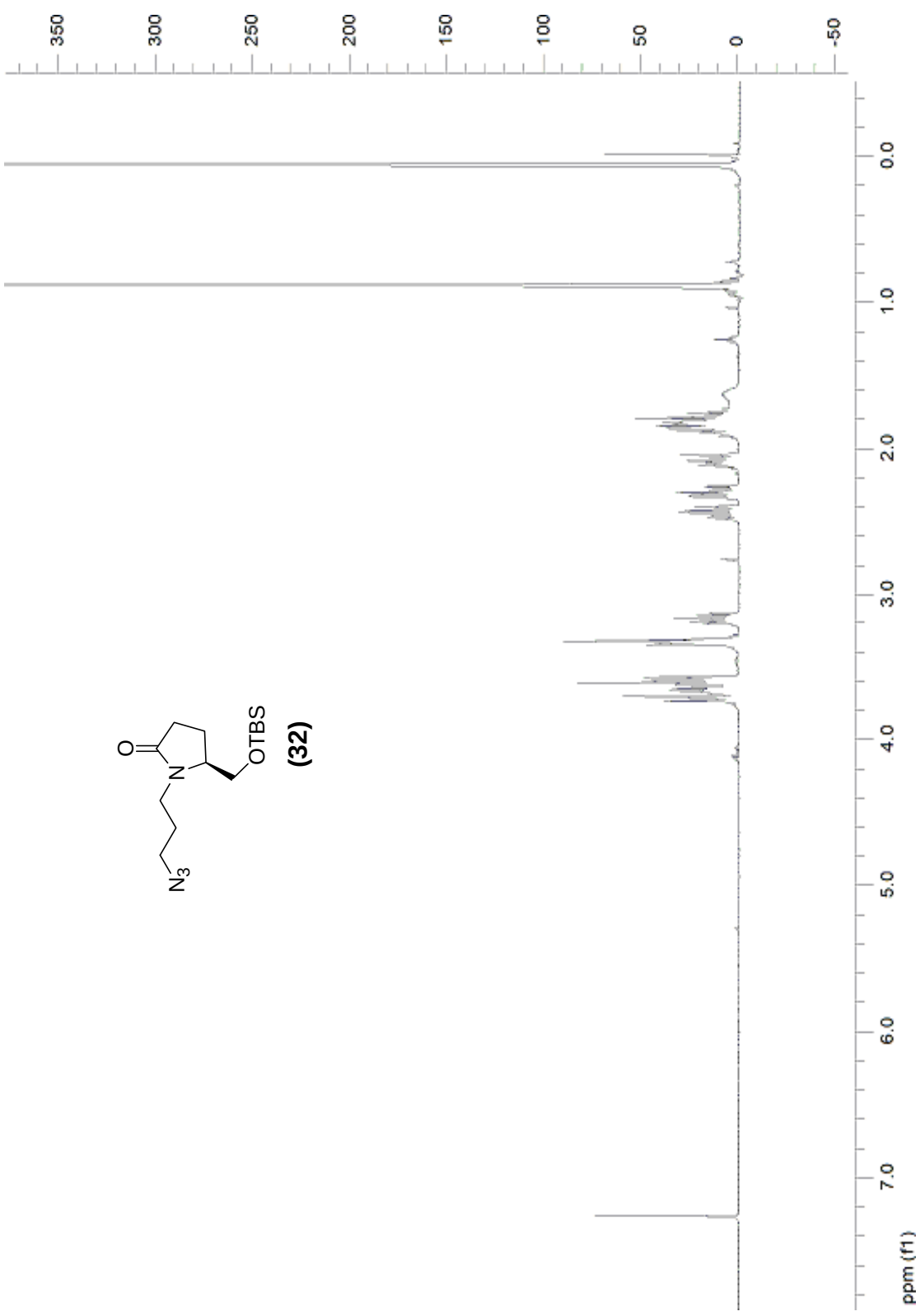
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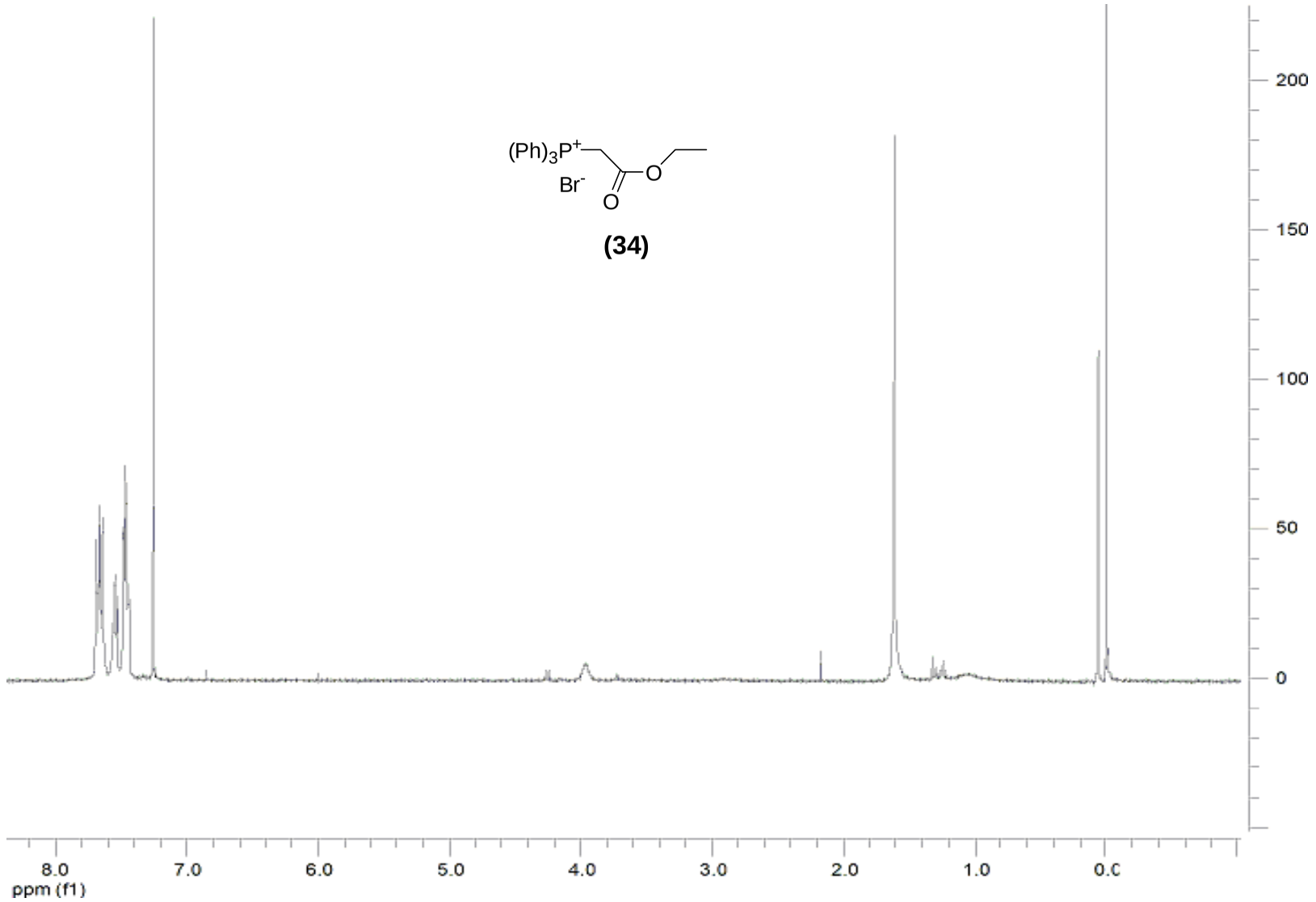

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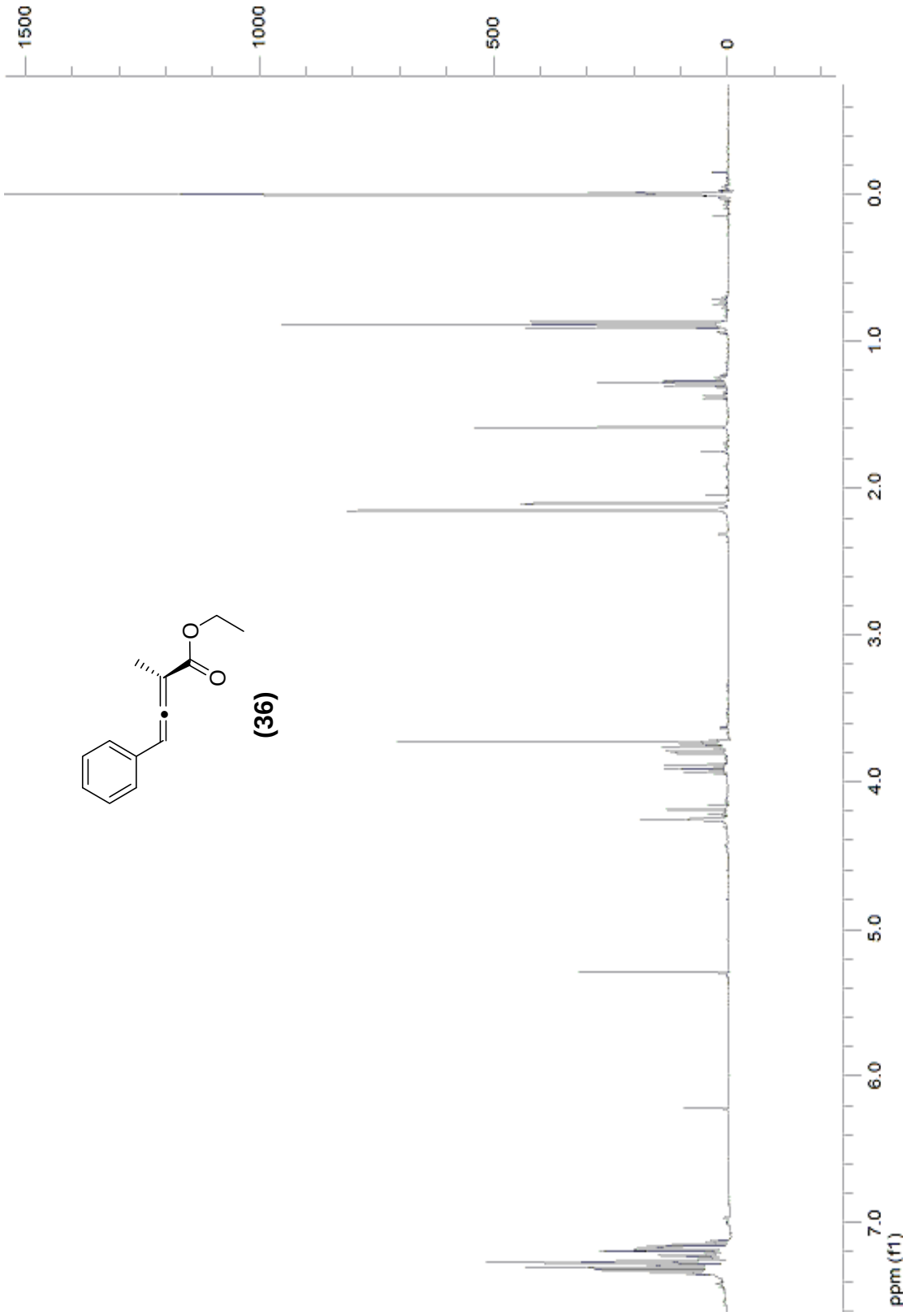

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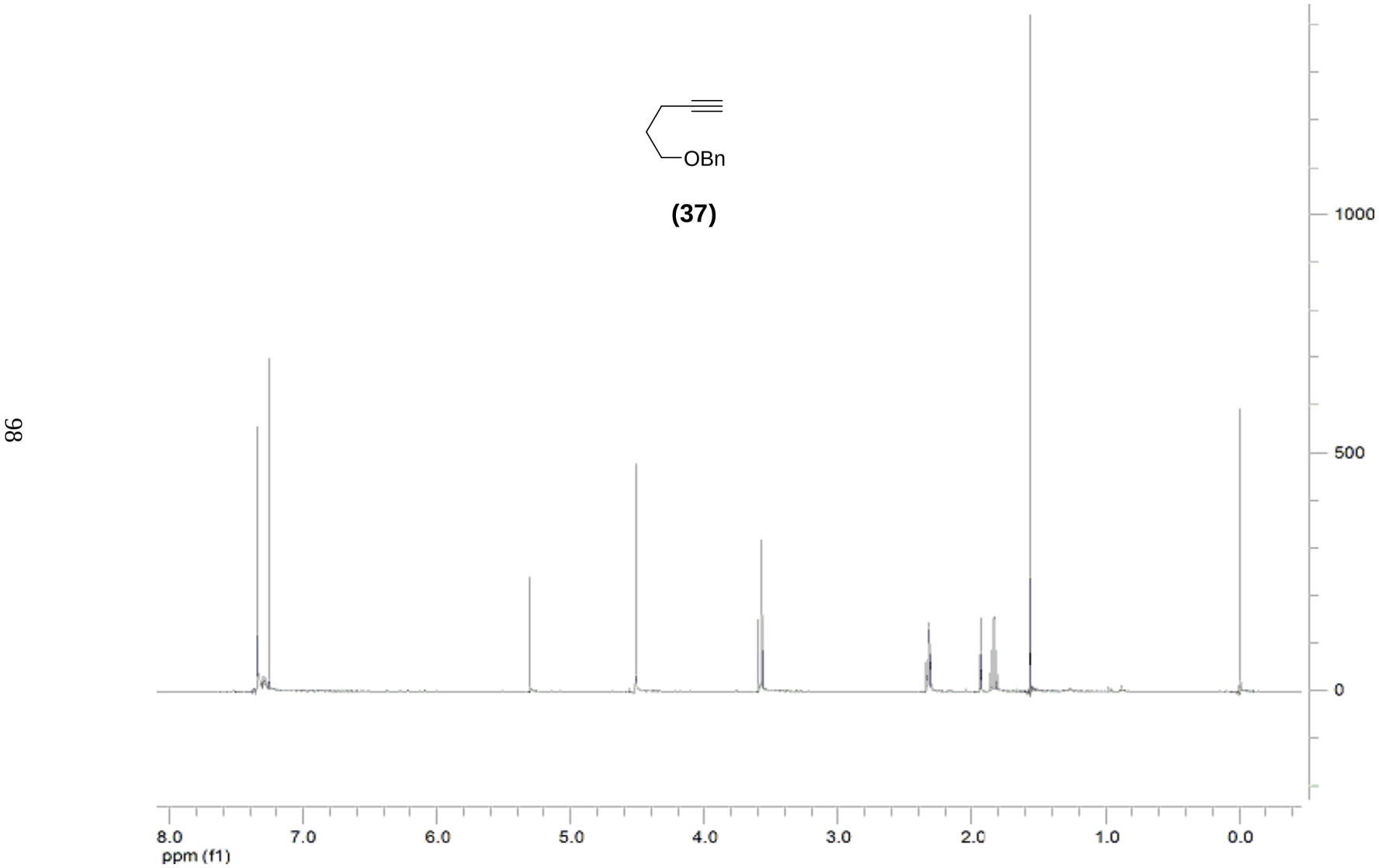

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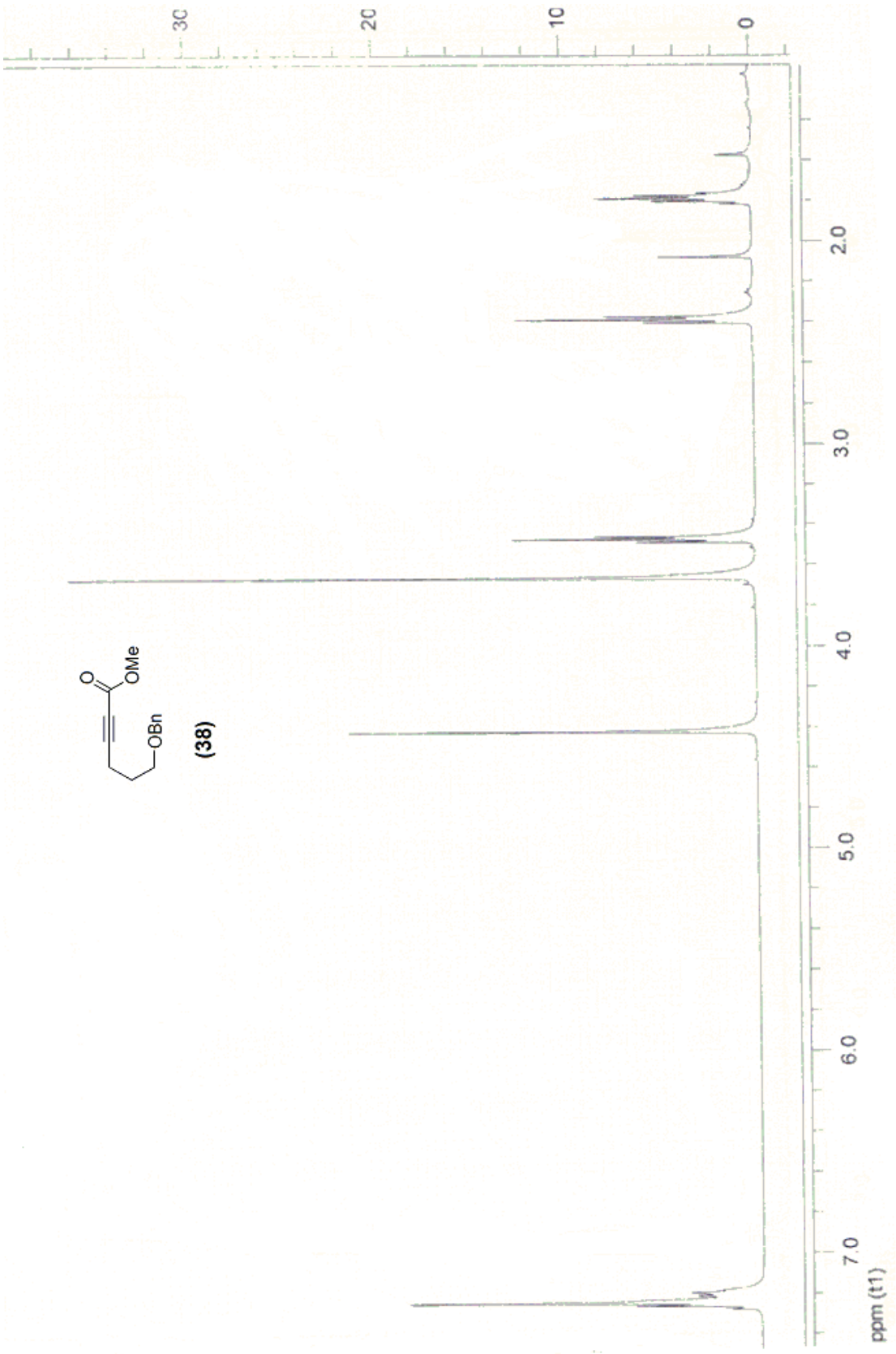
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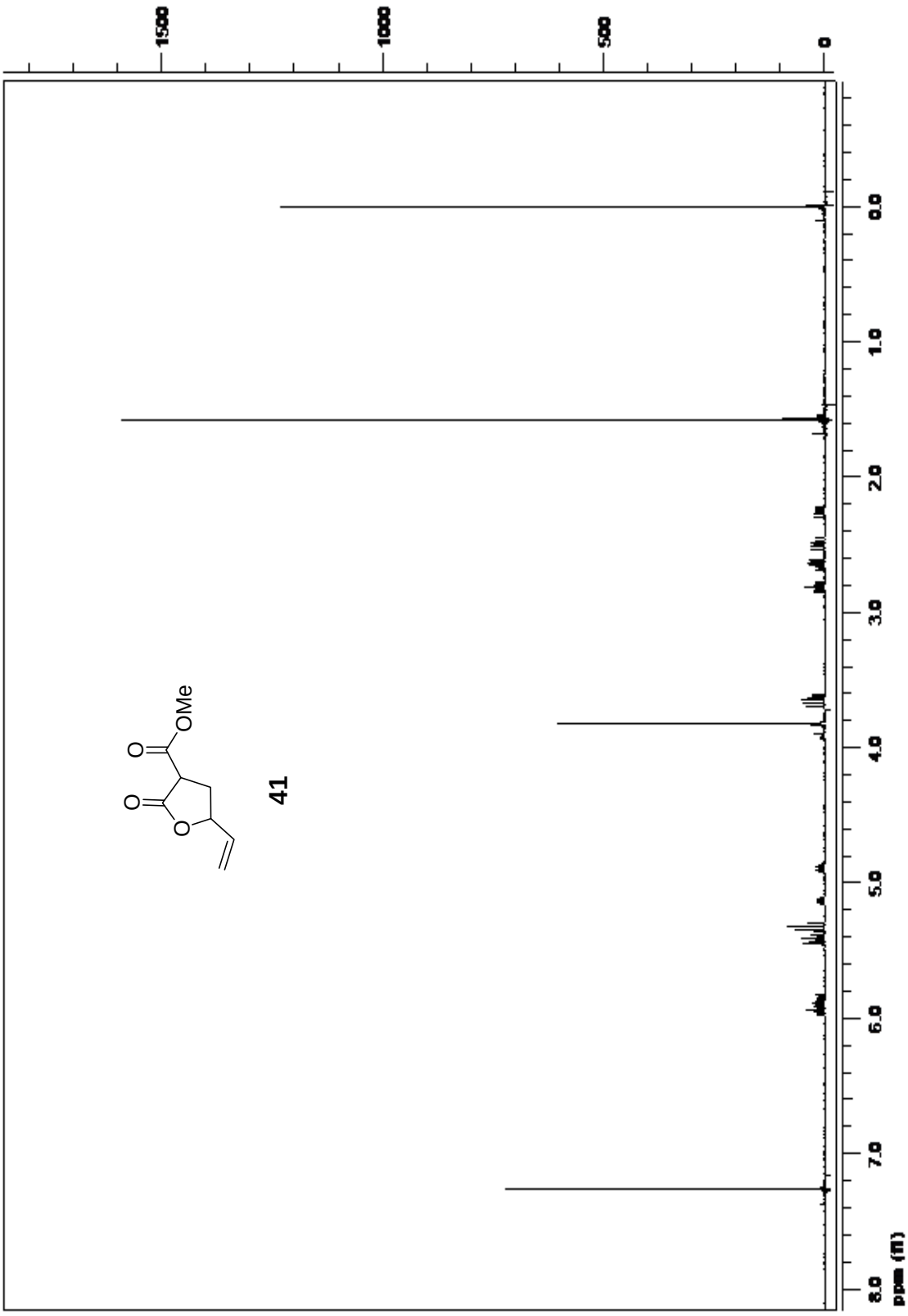
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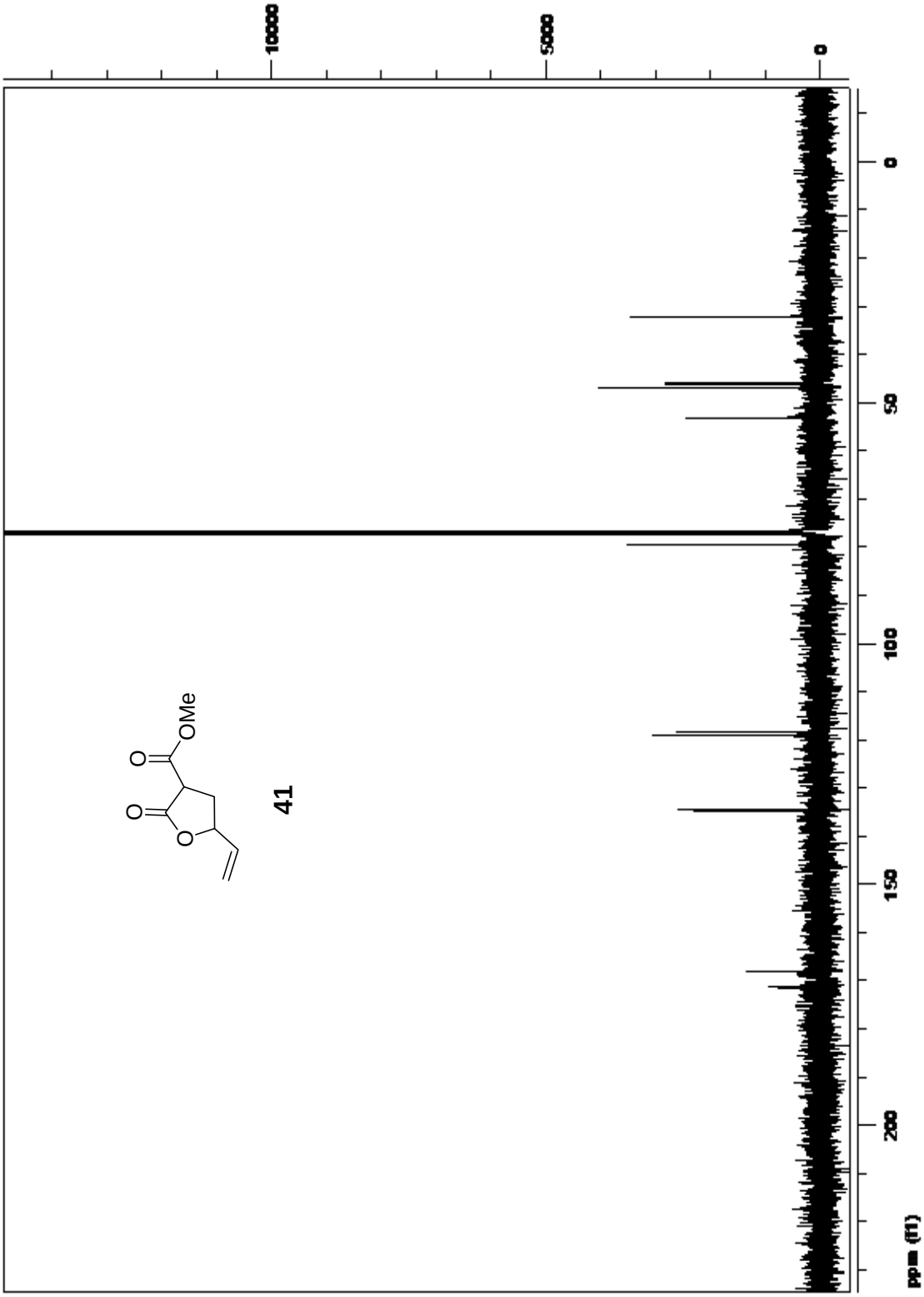

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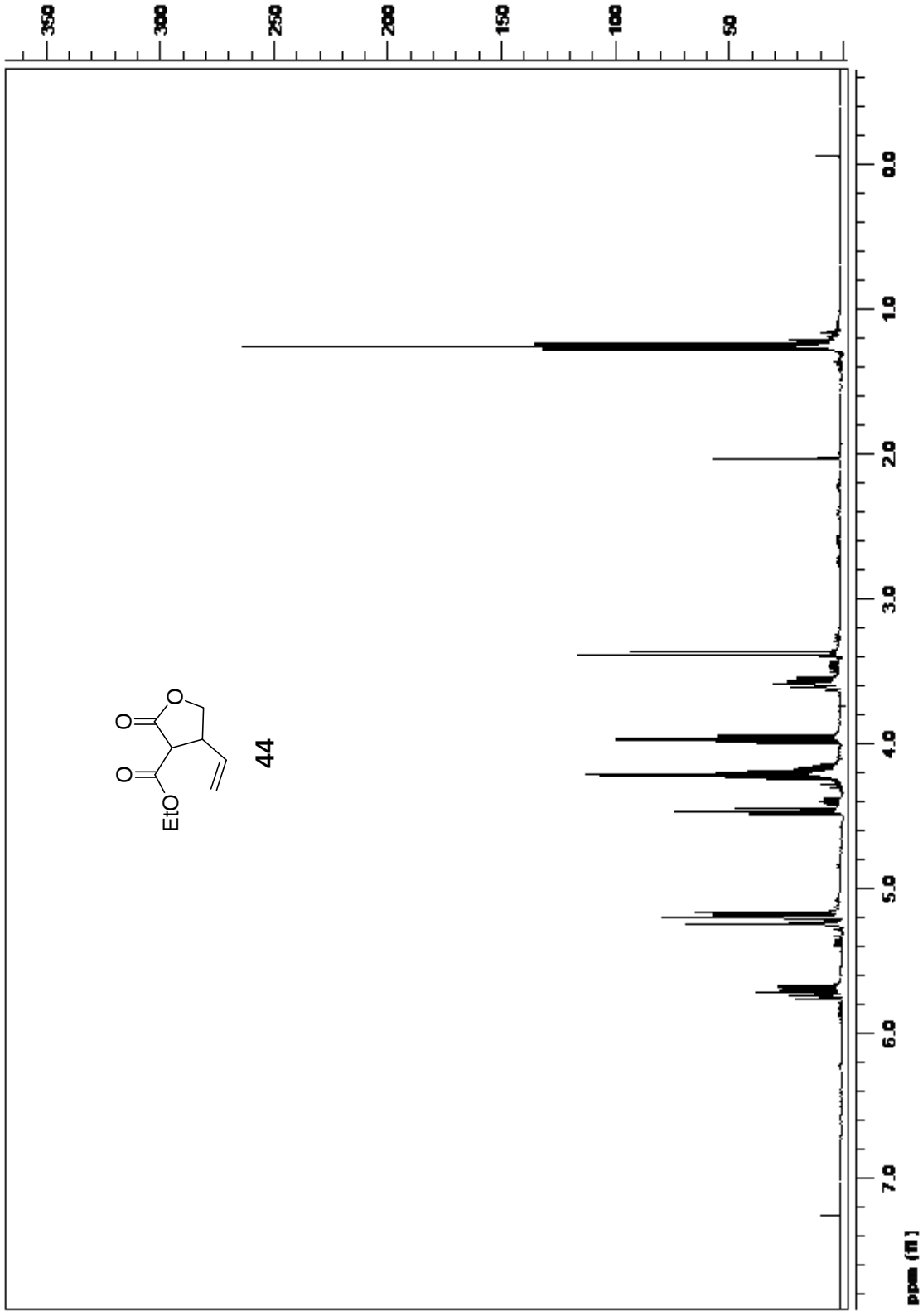
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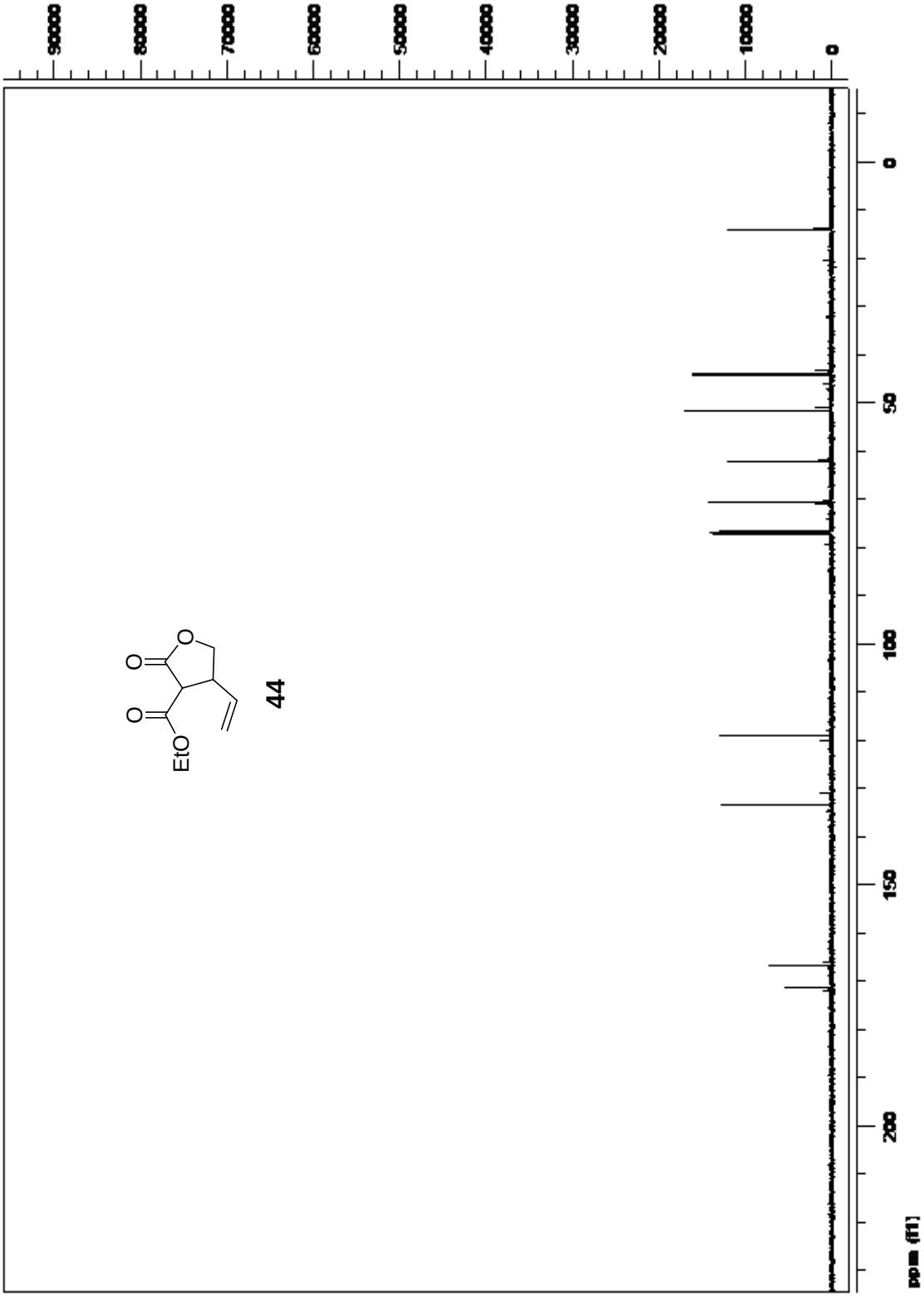
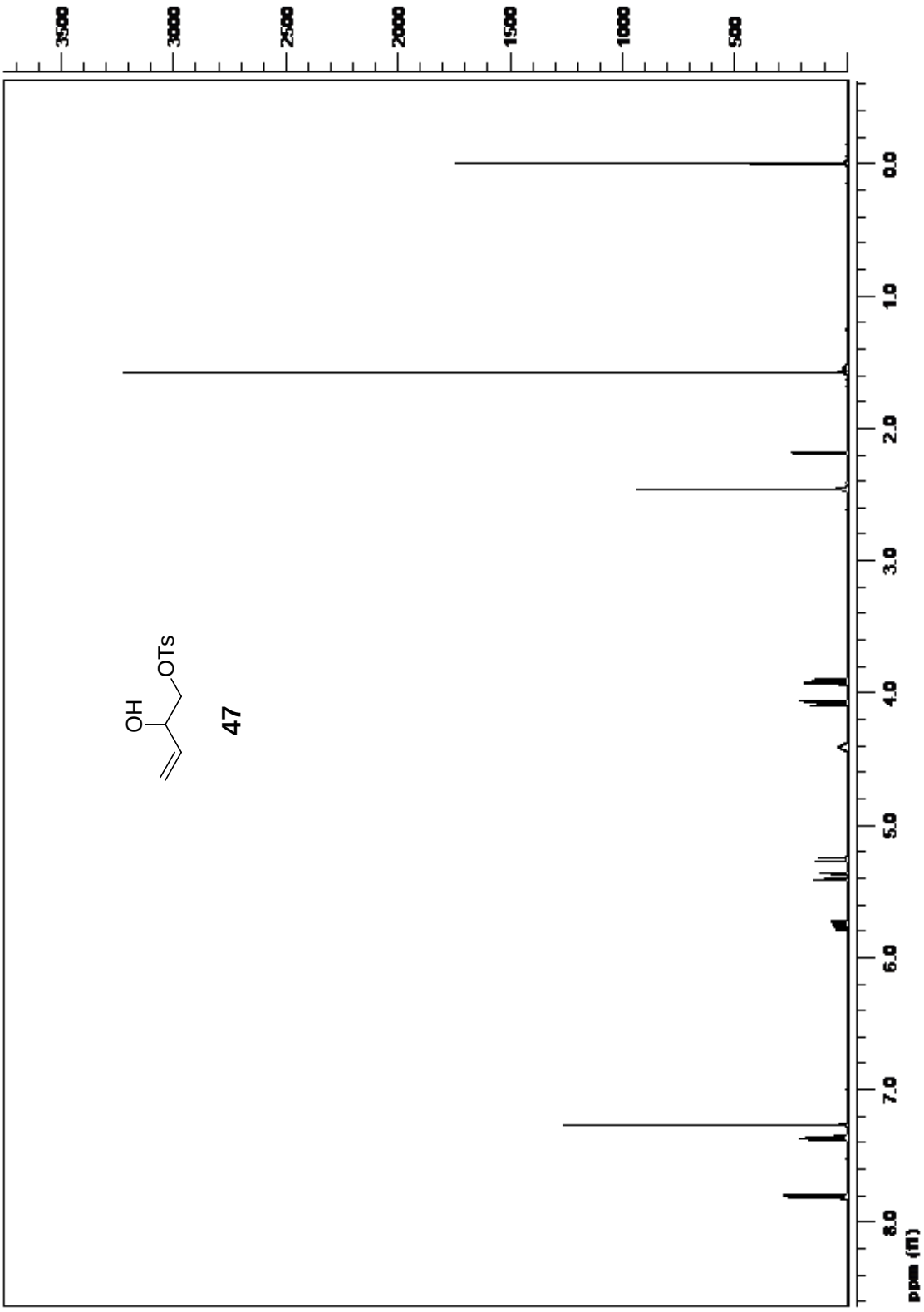
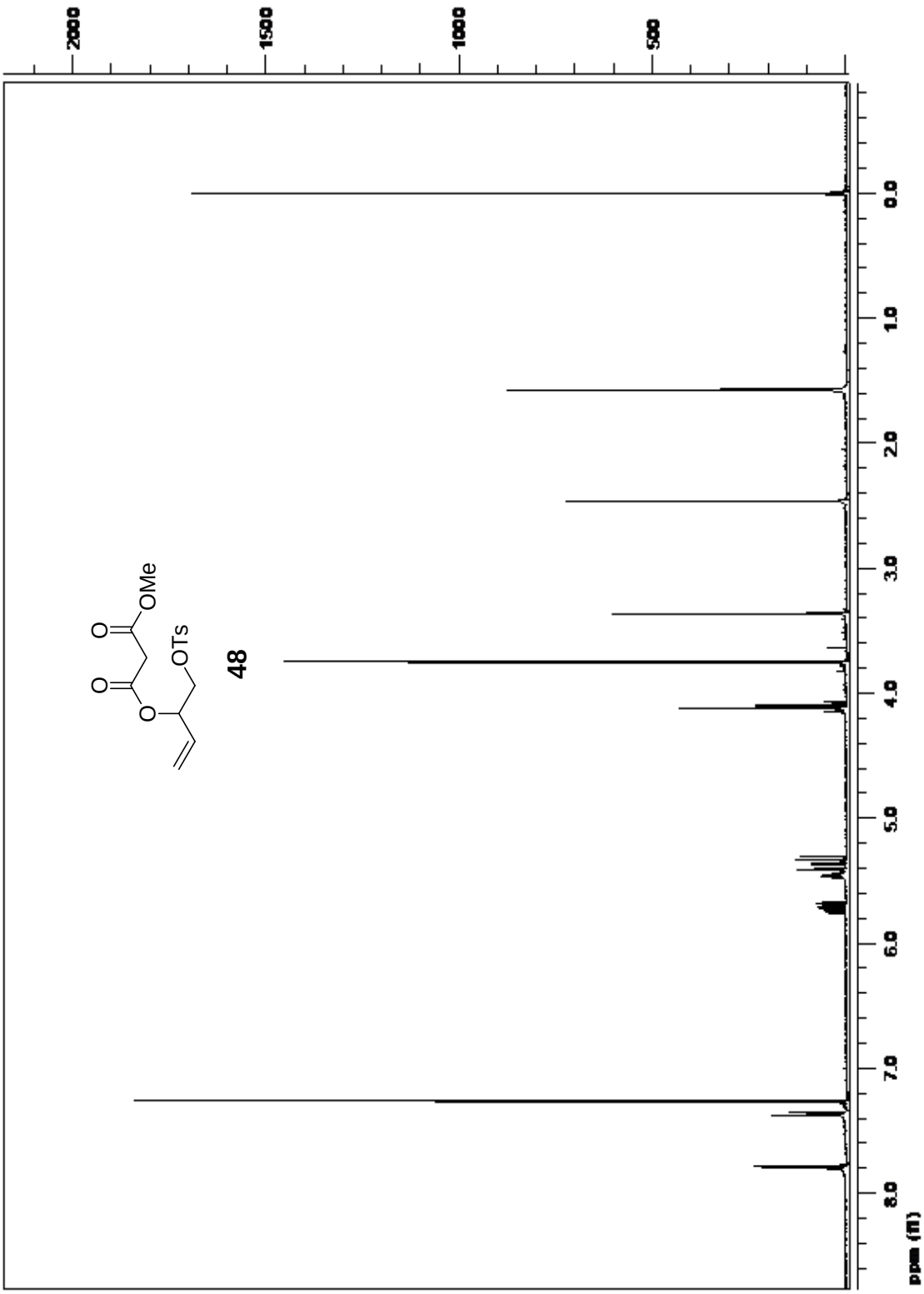
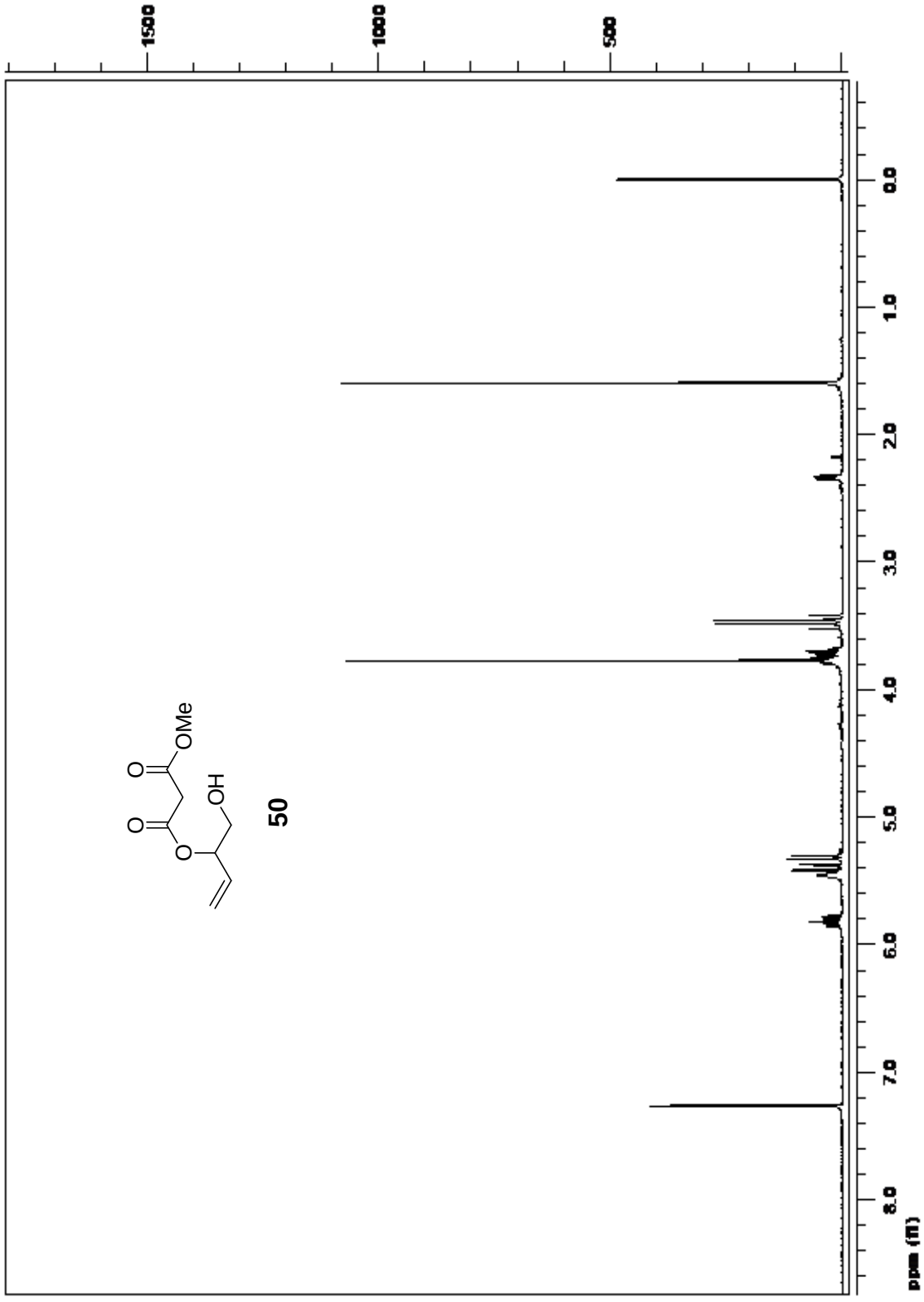
EtO
44


90000
80000
70000
60000
50000
40000
30000
20000
10000
0
0
50
100
150
200
ppm (f1)
O
O
O
EtO

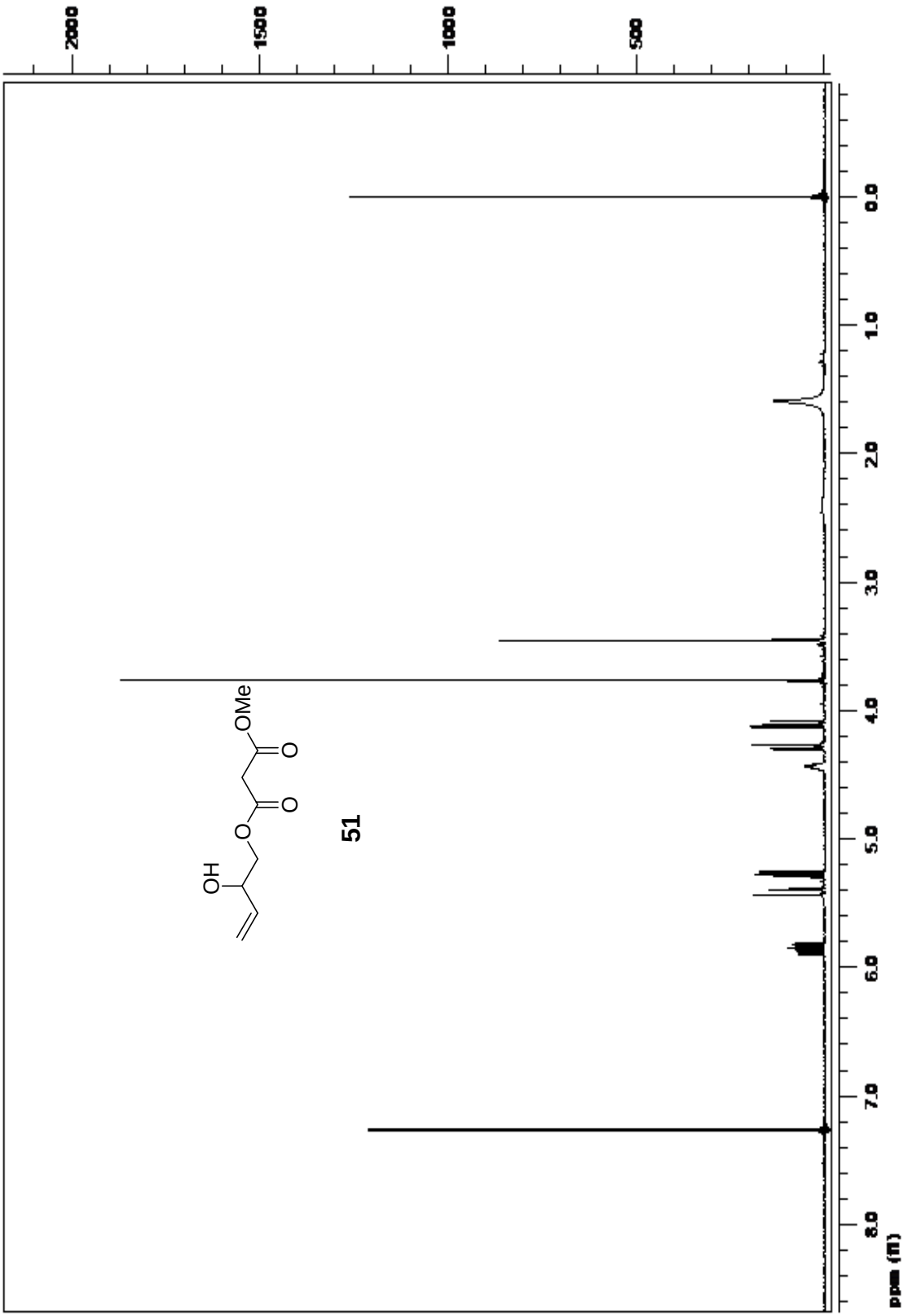
44

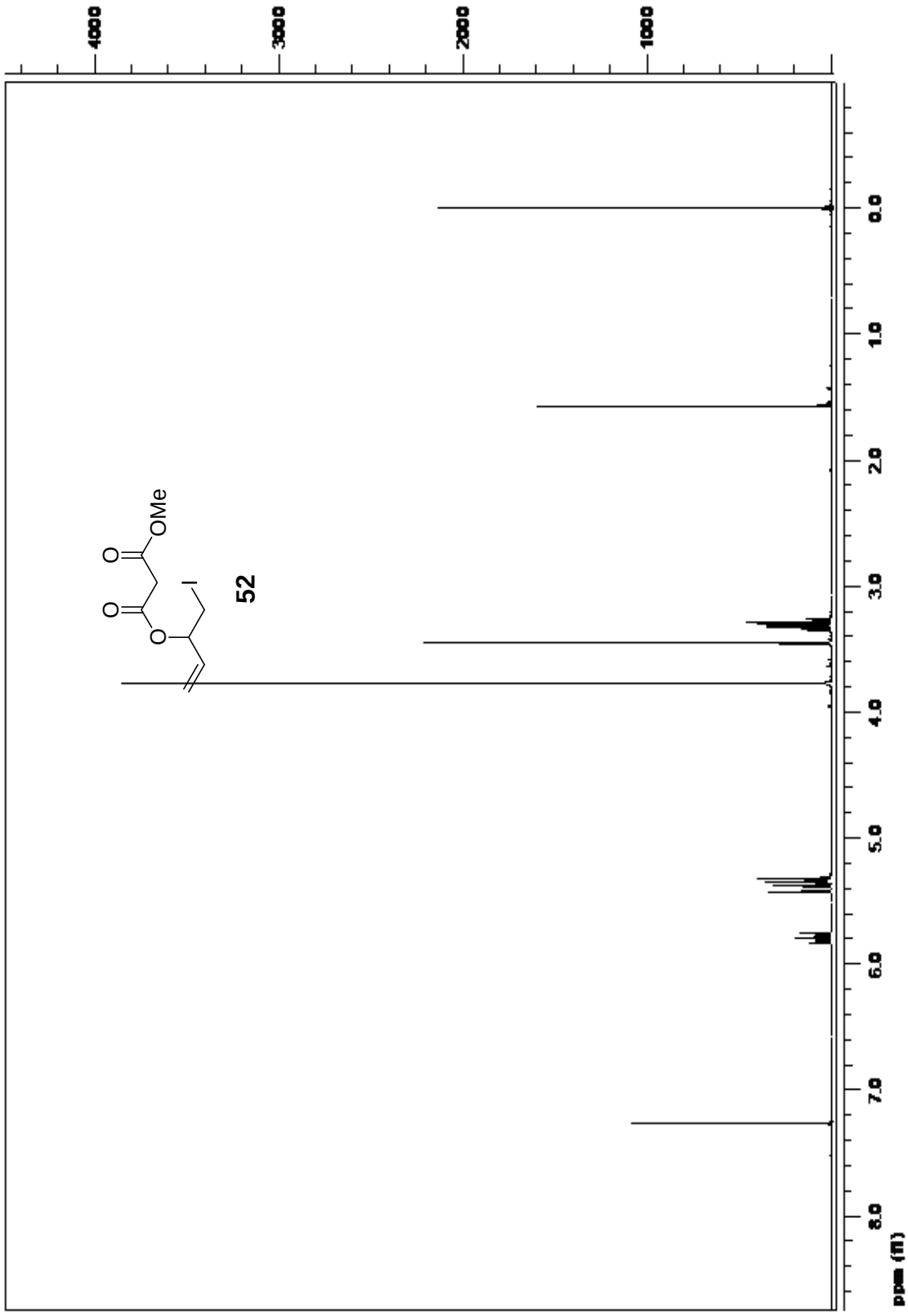

OH
OTs
47
3500
3000
2500
2000
1500
1000
500
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

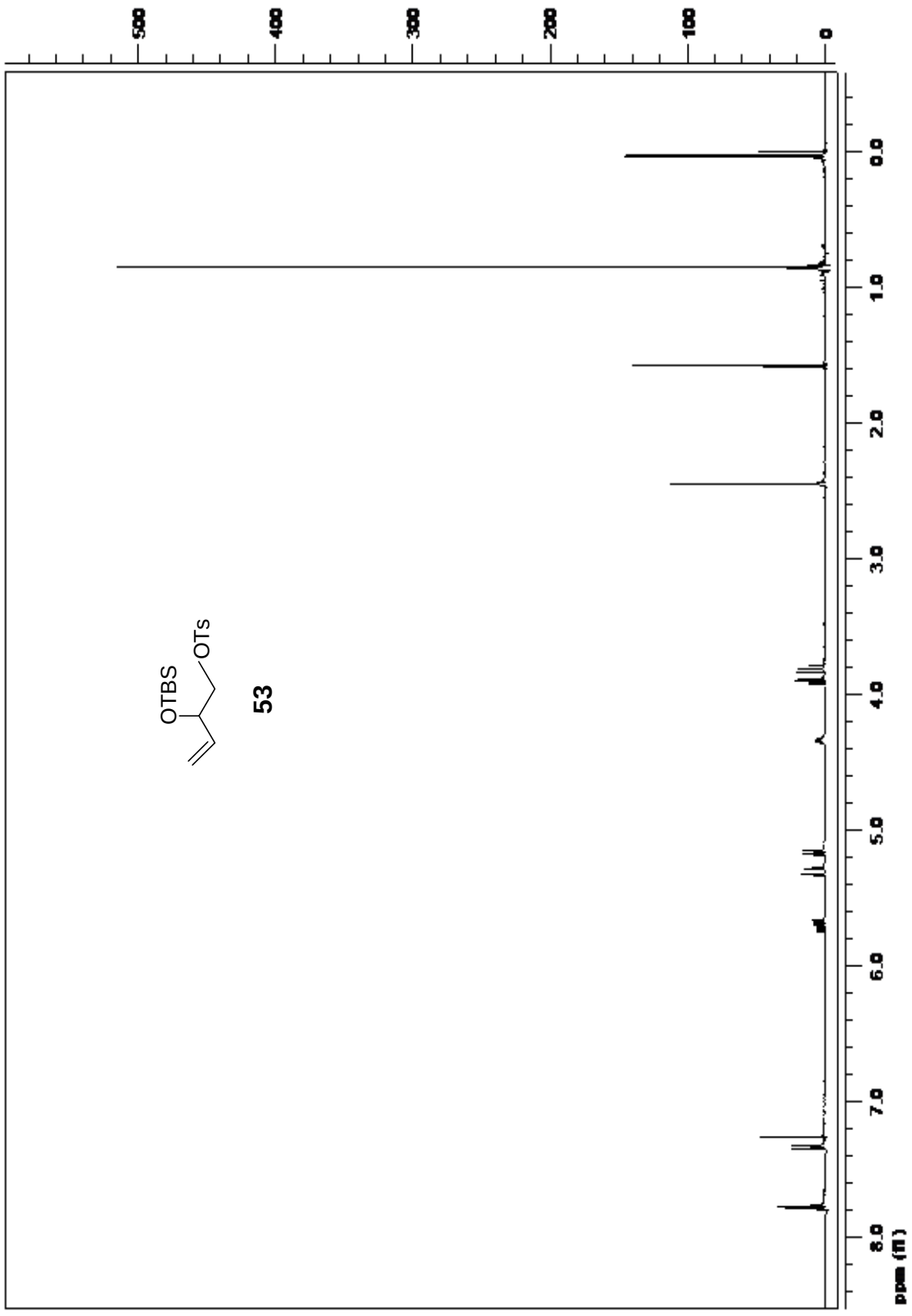

2000
1500
1000
500
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)
O
OMe
O
OTs
O
48

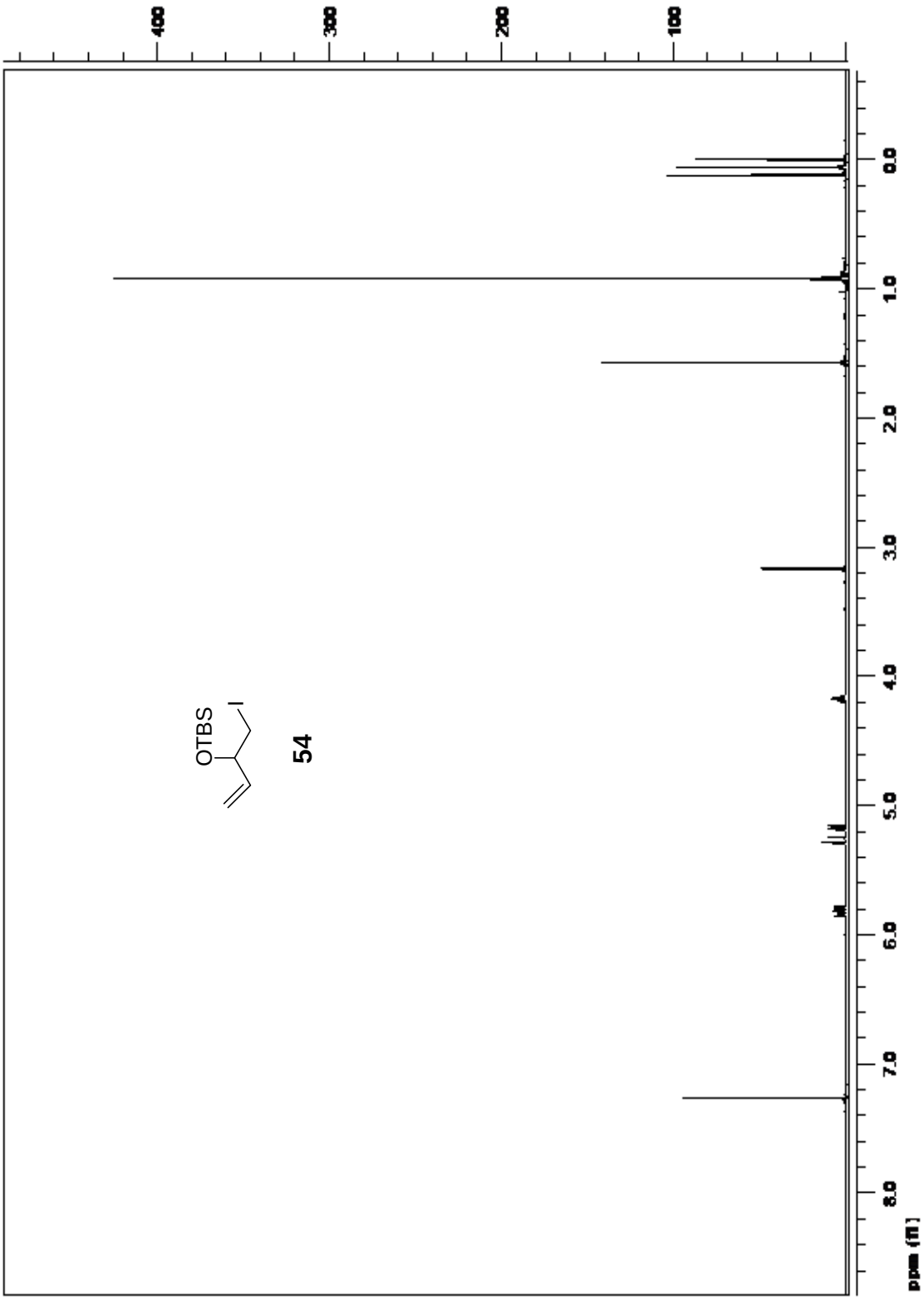


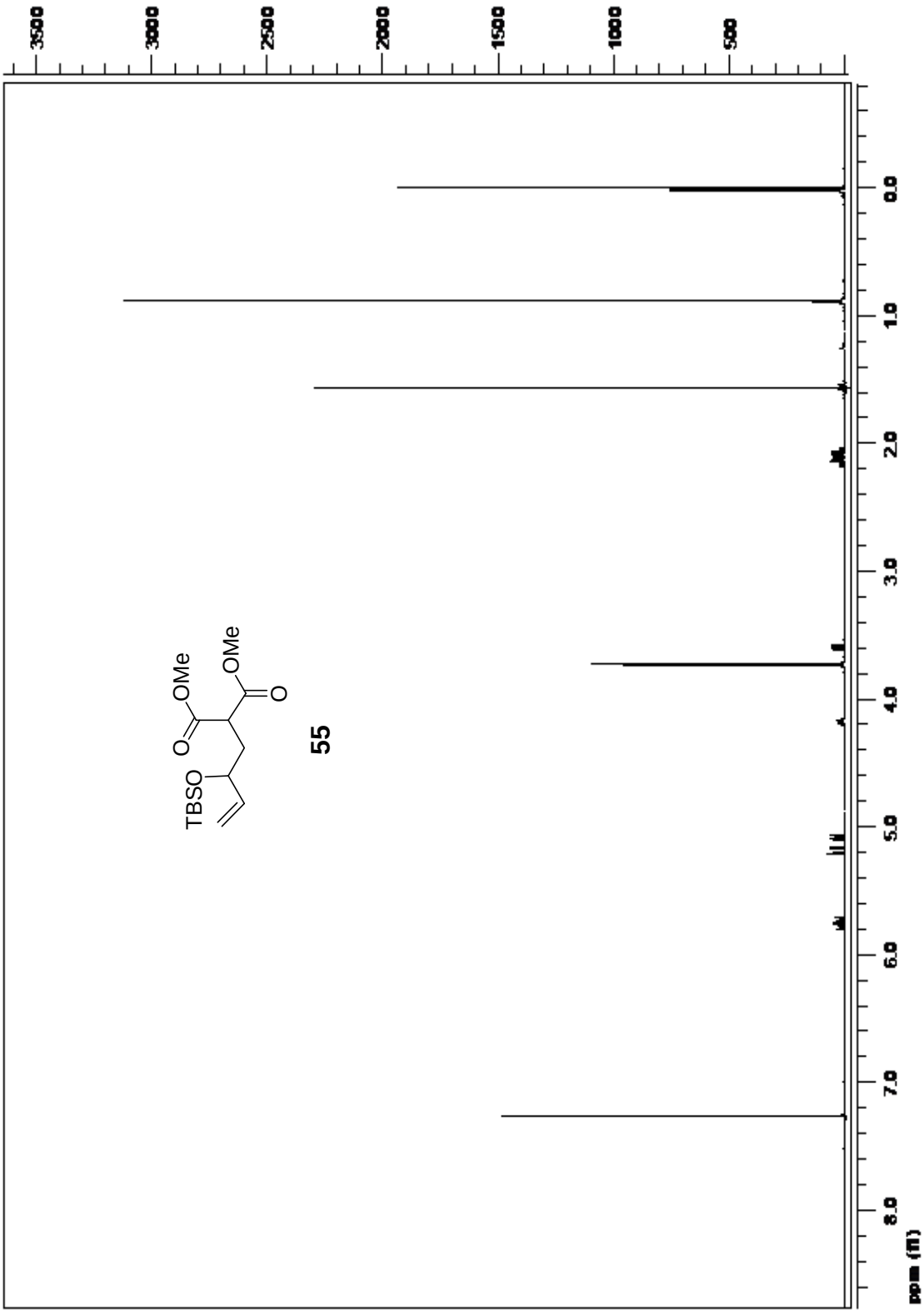
50


2000
1500
1000
500
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)
OMe
O
O
O
OH
51


4000
3000
2000
1000
OMe
O
O
O
I
52
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


OTBS
OTs
53
500
400
300
200
100
0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OTBS
I
54
400
300
200
100
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


3500
3000
2500
2000
1500
1000
500
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)
OMe
OMe
O
O
TBSO

55