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Oxidative Cyclizations of Tertiary Pentenols and the Synthesis of β-Carboline Alkaloids

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Chemistry

OXIDATIVE CYCLIZATIONS OF TERTIARY PENTENOLS AND THE SYNTHESIS OF β-CARBOLINE ALKALOIDS

(Thesis format: Monograph)

by

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Abstract and Key Words

This thesis describes the work carried out on two projects. The first chapter of the thesis discusses the application of the second generation $Co(nmp)_2$ catalyst towards the oxidative cyclization of tertiary pentenols through a modified Mukaiyama aerobic oxidative cyclization procedure.

The second chapter describes the progress made towards the synthesis of β-carboline alkaloids. The total synthesis of the alkaloid natural product cyclocapitelline is detailed along with the formal synthesis of the natural product chrysotricine.

Key Words: Mukaiyama aerobic oxidative cyclization, *trans*-2,5,5-tetrahydrofurans, natural product, chrysotricine, cyclocapitelline, cross-metathesis.

Acknowledgments

I would like to thank my family for their support in all of my endeavors. I would also like to thank my colleagues for all of their support and friendship during my time as a graduate student.

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List of Abbreviations

10-CSA	10-camphorsulfonic acid
Å	angstrom
OAc	acetyl
BAIB	bis(acetoxy)iodobenzene
Bn	benzyl
Bz	benzoyl
CAM	cerium ammonium molybdate
*m*CPBA	meta-chloroperbenzoic acid
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
EtOAc	ethyl acetate
EI	electron impact ionization
Et	ethyl
L-Selectride®	Lithium tri-*sec*-butylborohydride
Me	methyl
Ms	mesyl
MS	molecular sieves
mmol	millamole(s)
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile

Ph	phenyl
PPTS	pyridinium p-toluenesulfonate
RCM	ring-closing metathesis
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyl diphenylsilyl
TBS	*tert*-butylsilyl
*t*BuOOH	*tert*-butylhydroperoxide
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropyl silyl
TLC	thin layer chromatography

Chapter One: Synthesis of *trans*-2,5,5-tetrahydrofurans

1.0 Introduction

The tetrahydrofuran (THF) ring is a 5 membered cyclic ether which is one of the most commonly used organic solvents. THF is much more than a simple solvent however, as substitution about the ring provides access to a multitude of products with differing regio and stereochemical arrangements. These derivatives represent a prominent structural motif within the chemistry of natural products and pharmaceuticals as there are an ever growing number of natural products being isolated which contain the THF moiety. Many of these compounds possess biological activity and the potential to be advanced within the pharmaceutical development process.[1] This chapter will outline progress towards the synthesis of *trans*-2,5,5-THFs through a Mukaiyama aerobic oxidative cyclization procedure employing a second generation cobalt catalyst.[1] The research in this chapter was carried out in collaboration with colleagues Dr. Andrew Stevens and Mr. Cory Palmer. Results are those generated by the author unless otherwise attributed.

1.1 Common Methods for THF Synthesis

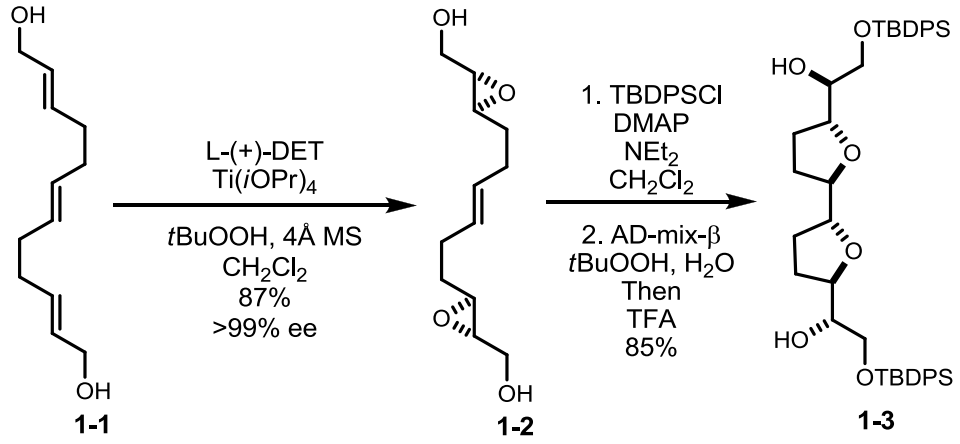
The prevalence of the THF ring in natural products chemistry has driven considerable synthetic efforts towards the synthesis of THFs. A multitude of procedures can be applied to forming THFs with some having broad substrate applicability and others finding more niche applications.[2]

When considering the asymmetric synthesis of THFs, it is often beneficial to make use of prochiral starting materials, which enable the synthesis of chiral material either directly or in a stepwise manner. Prochiral olefins can be asymmetrically epoxidized through methods such as Sharpless or Shi epoxidations and then opened either intra or intermolecularly. This strategy is often amenable to cascade reactions sequences allowing for the synthesis of several THFs in one

[1] *trans*-2,5,5-THFs have been named according to the Cahn-Ingold-Prelog priorities of the substituents at the 2 and 5 positions of the THF ring. The orientation of the highest priority substituents at these positions dictates the *cis* or *trans* label indicated for the THF.

process. Hoye employed such a procedure in his synthesis of the natural product (+)-Parviflorin (Scheme 1.0). The synthesis made use of a double Sharpless epoxidation and Sharpless dihydroxylation sequence to form the bis THF core of the natural product as a single diastereomer **1-3**.[3]

Scheme 1.0. Synthesis of (+)-Parviflorin core.



Reactions of this type can be tuned with different electrophilic and nucleophilic partners in order to accommodate synthetic goals. The disadvantage of this method is that specific substrate classes and multistep formation of asymmetric material are required. In addition, the stereochemistry of both nucleophilic and electrophilic partners must be set initially to achieve optimal diastereoselectivity.

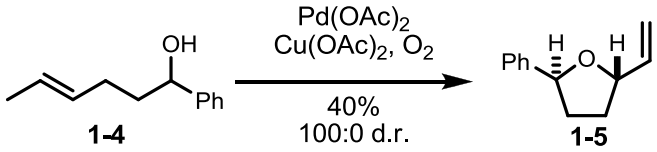
It is beneficial to conduct one pot THF forming reactions from prochiral molecules rather than employing multiple synthetic steps designed to set stereocenters before THF formation. Such transformations require fewer stereochemical setting steps because stereochemistry is set during the course of the reaction. The oxidative cyclization of unsaturated alcohols to form THFs is a one pot product forming procedure frequently employed in synthesis.

The advantages to this method are its high substrate tolerance, the general simplicity of preparing starting materials, and the high degree of diastereoselectivity in product formation.

Oxidative cyclizations of unsaturated alcohols make use of catalytic amounts of transition metal complexes in the presence of stoichiometric oxidants, to convert bishomoallylic alcohols into THFs with varying degrees of substitution.

Some early work in this area was conducted by Hosokawa who developed a method for the oxidative cyclization of vinyl pentenols to afford 2-vinyltetrahydrofurans in low yield but with good to excellent diastereoselectivity (Scheme 1.2).[4]

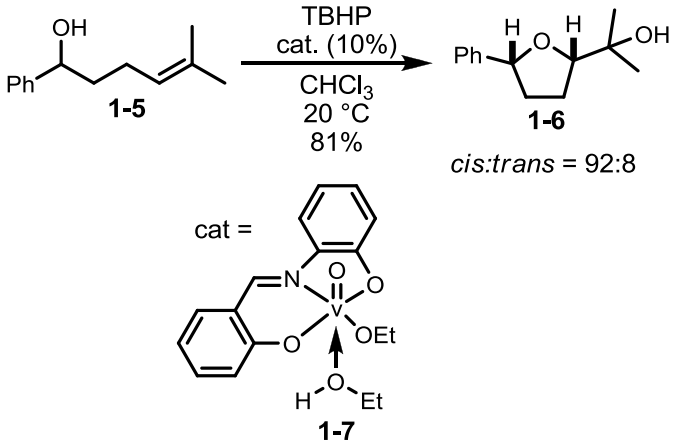
Scheme 1.2. Hosokawa oxidative cyclization.



This methodology employed $Pd(OAc)_2$ catalyst with oxygen acting as the stoichiometric oxidant. $Cu(OAc)_2$ was present in a stiochiometric amount in order to re-oxidize the Pd(0) to the active Pd(II) catalyst. The use of oxygen as a stoichiometric oxidant is another advantage to this methodology as it is a cheap, readily available reagent which lowers the amount of waste being produced in such reactions. Later optimizations with Pd species would allow for the removal of the Cu oxidant and limit waste production even further.[5]

Palladium catalyzed oxidative cyclizations can be replaced with less expensive alternatives while still maintaining good yields and high levels of diastereoselectivity. The Hartung group has demonstrated this with the development of Schiff-base vanadium complexes, which have been used in conjuction with *tert*-butyl hydroperoxide as the stoichiometric oxidant to effect the formation of *cis* 2,5-THFs (Scheme 1.3).[6]

Scheme 1.3. Hartung's synthesis of *cis*-2,5-THFs.

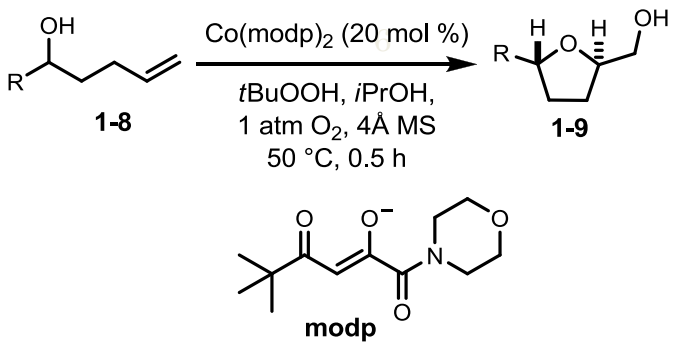


Given that there are a number of oxidative cyclization reactions capable of forming THFs, the method to be employed in a synthesis is dependent upon the diastereoselectivity of the method, the potential for higher yields and the substrate tolerance of the transformation.

1.2 The Mukaiyama Aerobic Oxidative Cyclization

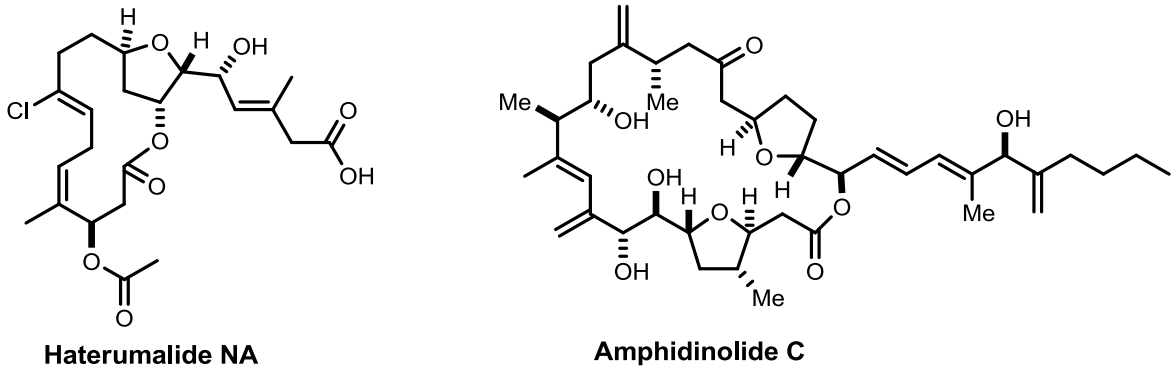
Within the area of THF chemistry, the Mukaiyama aerobic oxidative cyclization stands out as prominent transformation for the formation of THFs bearing substituents with *trans* stereochemistry at the 2 and 5 positions.[7] The methodology developed by Mukaiyama and co-workers employs a Co catalyst and oxygen as a stoichiometric oxidant to convert bishomoallylic alcohols into *trans*-2,5-THFs (Scheme 1.4) in good yield and excellent levels of diastereoselectivity (>99:1 dr).

Scheme 1.4. The Mukaiyama aerobic oxidative cyclization.



THF rings bearing *trans* stereochemistry at the 2 and 5 positions can be found in a range of natural products. Some notable examples include the amphidinolide family of natural products, along with the haterumalides and the biselides (Figure 1.0). Several members of these large families possess biological activities including haterumalide NA which was found to be cytotoxic towards leukemia cell line (P338) and Amphidinolide C which exhibits potent cytotoxicity against murine lymphoma and human epidermoid carcinoma cells.[8] The biologically active nature of these natural products make their synthesis more than just a synthetic challenge, but also a practical endeavor from a pharmaceutical standpoint.

Figure 1.0. Natural products containing *trans*-2,5-THFs.

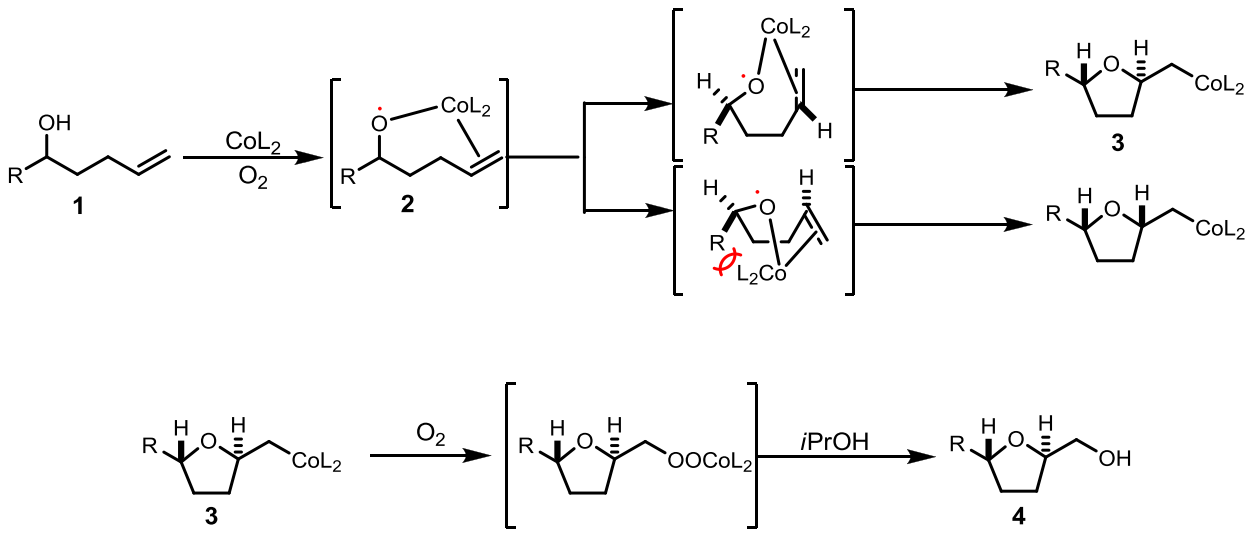


The original Mukaiyama procedure was effective for the cyclization of a wide variety of bishomoallylic alcohols bearing diverse functionalities and was very selective in the formation of *trans* stereochemistry at the 2 and 5 positions of the resulting products (>99% *trans*). The primary alcohol formed in the cyclization also acts as a useful synthetic handle for further transformations. Unfortunately, the original Mukaiyama procedure did come with setbacks to its applicability. The original modp catalyst was difficult to separate through conventional flash chromatography, making purification of substrates challenging. Yields of the cyclized products were moderate to good but left room for improvement and a stoichiometric amount of *tert*-butyl hydroperoxide was required for optimal yields and reaction times.

1.3 Mechanistic Investigation of the Oxidative Cyclization

The origin of *trans* selectivity in the Mukaiyama cyclization was examined by Mukaiyama in his original publication on the method (Scheme 1.5).[7] He proposed that pentenol **1** interacts with oxygen and $Co(modp)_2$ to form a radical coordination compound **2**. This coordination compound then cyclizes via radical cyclization to form Co species **3** with *trans* orientation at the 2 and 5 positions. The *trans* stereochemistry arises from the R group and CoL_2 adopting a *trans* orientation at the 2 and 5 positions in order to avoid steric interactions. Oxygen then inserts into the Co-C bond of **3** forming a cobalt peroxide intermediate. Reductive cleavage by the *i*PrOH solvent affords the THF methanol product **4**.

Scheme 1.5. Mukaiyama's proposed mechanism.

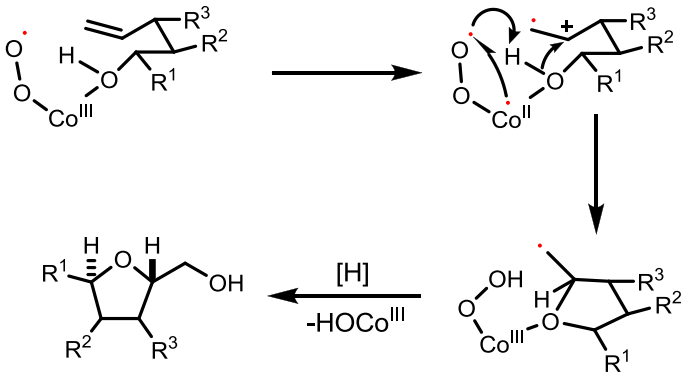


The Mukaiyama mechanism serves to explain the origin of the *trans* stereochemistry in the products but is limited in its explanation of radical formation, and regeneration of the Co catalyst following reductive cleavage.

The role of *t*BuOOH remains unclear, however Mukaiyama speculates that the peroxide may accelerate the formation of the radical intermediate **2**. It may also assist in re-oxidizing the cobalt catalyst.

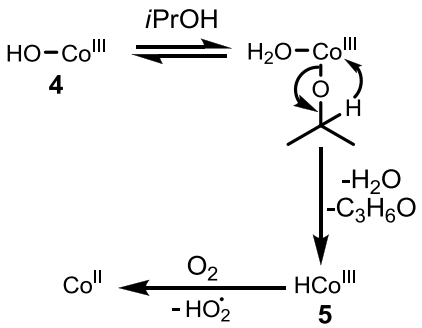
A publication by Hartung shed new light on the mechanistic pathway of the Mukaiyama cyclization (Scheme 1.6).[9] In the mechanism, Hartung proposes that the Co(II) catalyst, in the presence of oxygen is oxidized to a radical Co(III) species able to coordinate to the pentenol oxygen forming **1**. Single electron oxidation of the pendant alkene provides radical cation **2**. 5-*exo* attack of the hydroxyl group onto the carbocation forms THF methyl radical **3**. The observed *trans* stereochemistry of the products arises during the ring closure step where a chair like transition state forces substituents at the 2 and 5 positions into a *trans* orientation to limit steric interactions. In the presence of an H atom donor radical THF species **3** will afford THF methanol product and hydroxy cobalt(II) complex **4.**

Scheme 1.6. Hartung mechanism for the Mukaiyama oxidative cyclization.



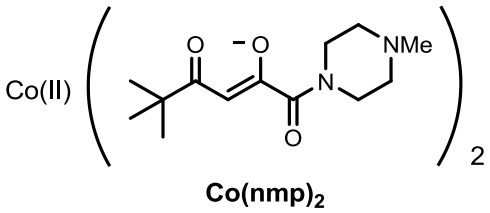
Catalyst regeneration is proposed to occur via coordination of a solvent molecule to hydroxy cobalt complex **4**. A hydride shift from the solvent molecule would then produce hydridocobalt(III) complex **5** releasing water and acetone as byproducts. In the presence of oxygen, cobalt complex **5** can then be converted to Co(II) which is then able to re-enter the catalytic cycle (Scheme 1.7).

Scheme 1.7. Completion of catalytic sequence.



1.4 The $Co(nmp)_2$ Catalyst

Many of the problems associated with the original Mukaiyama catalyst and cyclization procedure were addressed by the Pagenkopf group through the development of a second generation Co catalyst.[10] The $Co(nmp)_2$ catalyst (Figure 1.2) was more easily separated than the $Co(modp)_2$ catalyst thereby greatly simplifying purification. $Co(nmp)_2$ could be removed through extraction using a pH 4 phosphate buffer wash of the organic layer. With acid sensitive substrates the N-methyl nitrogen could be quaternized with methyl iodide allowing for the catalyst to be removed through extraction. It was also discovered that the catalyst could be removed through a simple filtration through a silica plug with excess solvent.

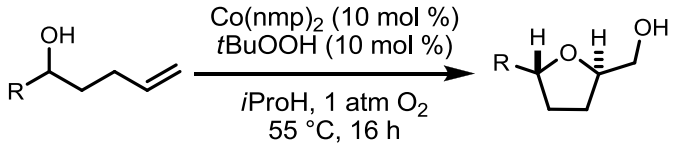


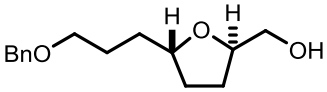
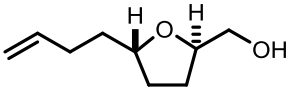
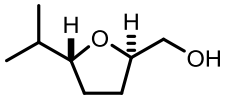
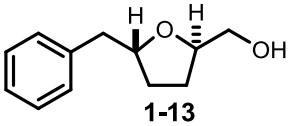
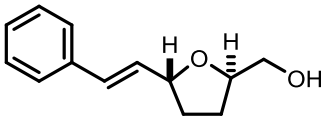
$Co(nmp)_2$

Figure 1.2. $Co(nmp)_2$

The $Co(nmp)_2$ catalyst was found to be more active than Co(modp), providing *trans*-2,5-THFs in higher yields than the original system while still achieving excellent levels of diastereoselectivity (Table 1.0). A lower catalyst loading 10% $Co(nmp)_2$ vs 20% $Co(modp)_2$ was effective at catalyzing the oxidative cyclizations and stoichiometric amounts of *tert*-butyl hydroperoxide were not required. $Co(nmp)_2$ has also been employed in the total synthesis of several natural products including Pagenkopf's syntheses of the C(1)-C(9) fragment of amphidinolide C, and Fürstner's total synthesis of amphidinolide F.[11]

Table 1.0. Comparrison of $Co(nmp)_2$ to $Co(modp)_2$ in the synthesis of *trans*-2,5-THFs.

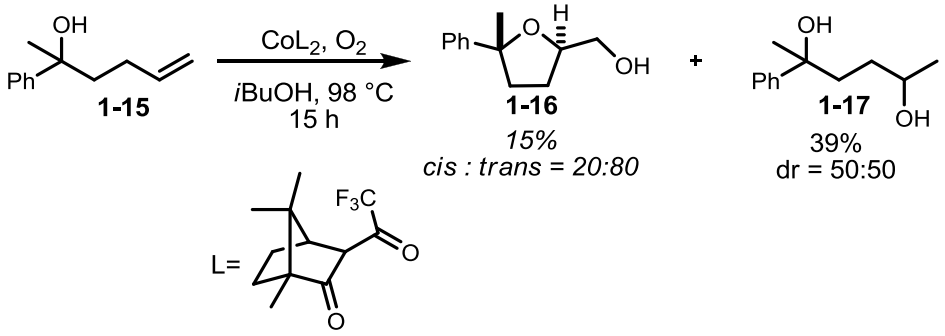


Entry	Product	$Co(modp)_2$ yield (%)	$Co(nmp)_2$ yield (%)
1	 **1-10**	58	90
2	 **1-11**	57	95
3	 **1-12**	76	91
4	 **1-13**	70	90
5	 **1-14**	42	88

1.5 Synthesis of *trans*-2,5,5-THFs

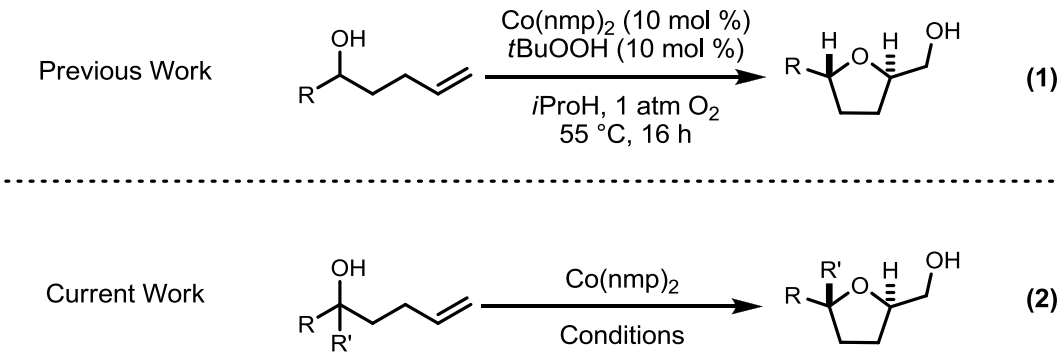
Like *trans*-2,5-THFs, related *trans*-2,5,5-THFs are also frequently found in natural products. Methods for their synthesis under oxidative cyclization conditions have seen limited exposure within the literature. Work by the Hartung group has shown that such transformations can be accomplished under catalysis with a bis[3-trifluoroacetylcampherato(−1)]cobalt(II) complex although the diastereoselectivity and yield of the product THFs were limited (Scheme 1.8).

Scheme 1.8. Hartung's synthesis of *trans*-2,5,5-THFs.



In an effort to extend the methodology originally developed by Mukaiyama as well as expand on the scope of $Co(nmp)_2$ catalyzed oxidative cyclizations the Pagenkopf group chose to apply $Co(nmp)_2$ to the cyclization of tertiary bishomoallylic alcohols (Equation 2, Scheme 1.9).

Scheme 1.9. Oxidative cyclizations of secondary and tertiary bishomoallylic alcohols.

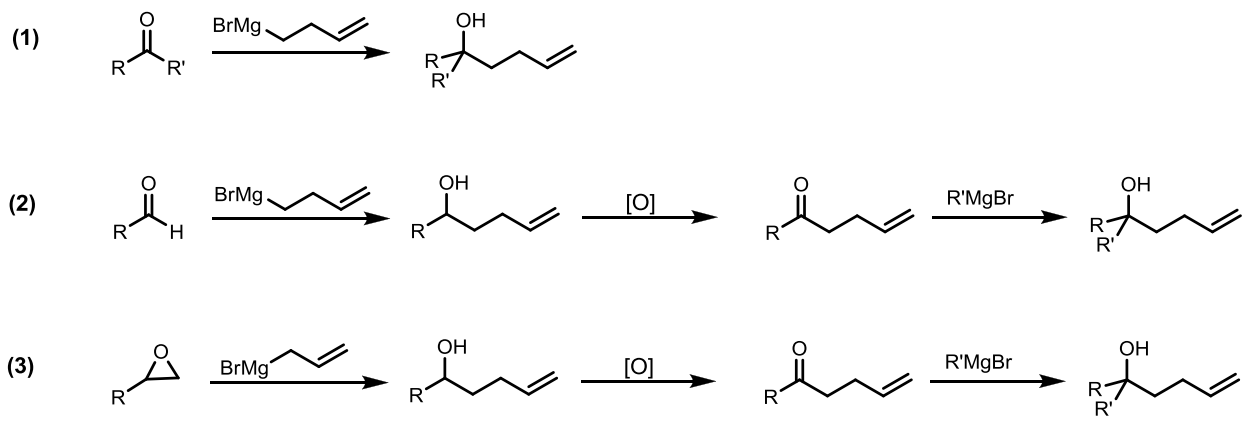


1.6 Results and Discussion

The synthesis of the cyclization substrates was carried out with Grignard additions to ketones, aldehydes, or epoxides (Scheme 1.10, equations 1, 2, 3 respectively). In the first case (eq 1), the addition of the Grignard reagent formed from 4-bromo-1-butene with a variety of ketones allowed quick access to the corresponding tertiary pentenols. Although this approach

produced several different pentenols, the use of enolizable ketones proved problematic and hindered product formation in some cases. To overcome this problem, additions of the Grignard reagent of 4-bromo-1-butene were carried out on a variety of aldehydes followed by an oxidation and second Grignard addition to the resulting ketone (eq 2). When the appropriate terminal epoxide could be synthesized epoxide openings were carried out employing allyl magnesium bromide to afford secondary pentenols. These pentenols were then oxidized to the corresponding ketone followed by a second Grignard addition to access the tertiary pentenol (eq 3).

Scheme 1.10. Synthesis of cyclization substrates.



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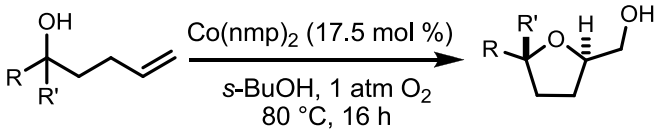
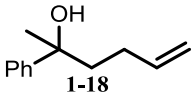
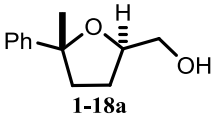
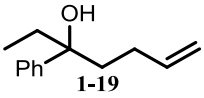
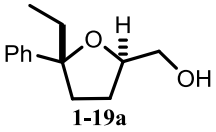
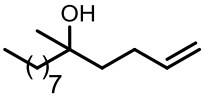
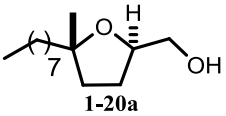
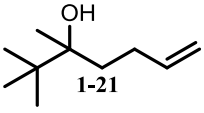
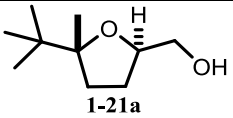
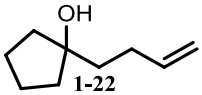
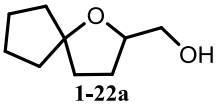
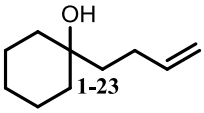
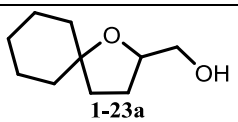
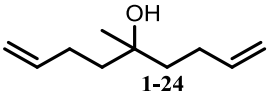
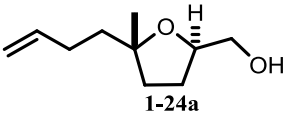
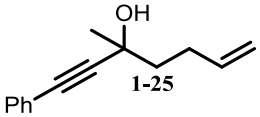
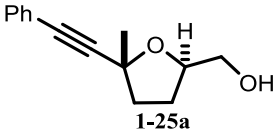
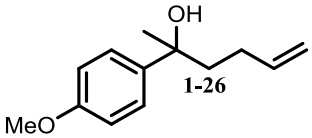
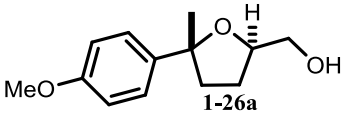
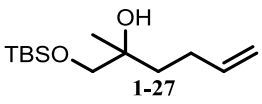
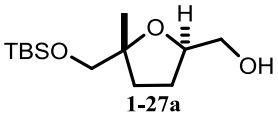
Initial efforts towards the cyclization of tertiary bishomoallylic alcohols to form *trans*-2,5,5-THFs were begun by co-workers Dr. Andrew Stevens and Mr. Cory Palmer. They found that the conditions established for the synthesis of secondary bishomoallylic alcohols proved to be ineffective when applied to tertiary alcohols. This problem was circumvented by the establishment of a modified procedure wherein the $Co(nmp)_2$ catalyst was pre-oxidized with *t*BuOOH under oxygen atmosphere prior to substrate introduction. The pre-oxidized catalyst was found to be more active and was able to catalyze the cyclization of tertiary pentenols. Stevens and Palmer found that optimal conditions were achieved with a pre-oxidized catalyst loading of 17.5% in *sec*-butanol (0.5 M with respect to starting material) with heating to 80 °C for a period of 16 h. With the optimized set of conditions in hand, a substrate scope was investigated (Table 1.1).

Table 1.1. Initial Substrate Scope.



Entry	Starting Material	Product	Yield % (*)[a]	d.r.
1	 1-18	 1-18a	63 (72)	7:1
2	 1-19	 1-19a	42 (48)	5:1
3	 1-20	 1-20a	36 (69)	3:1
4	 1-21	 1-21a	25 (32)	2:1
5	 1-22	 1-22a	44 (50)	-
6	 1-23	 1-23a	39 (73)	-
7	 1-24	 1-24a	38 (45)	2:1
8	 1-25	 1-25a	19 (20)	5:1
9	 1-26	 1-26a	44 (50)	2:1

10	 **1-27**	 **1-27a**	45 (57)	2:1

[a] Yield based on recovered starting material. Yeilds for **1-20a-1-21a, 1-23a**, and **1-25a** reported by Cory Palmer.

The cyclization proved to be tolerant of a wide range of tertiary pentenols providing products in poor to moderate yields. Substrates with less steric bulk at the tertiary alcohol generally gave higher yields and better diastereotopic ratios. This can be seen when comparing **1-18a** (entry 1) and its one carbon homologue **1-19a** (entry 2) where there is a drop in yield and selectivity and again when comparing spirocyclic products **1-22a** and **1-23a** (entries 5 and 6). Greater steric bulk at the alcohol oxygen may effect catalyst coordination resulting in poorer levels of conversion and lower yields. Steric crowding at the alcohol may also result in *trans* orientation at the 2 and 5 positions becoming less favourable thus leading to a greater percentage of an alternate diastereomer

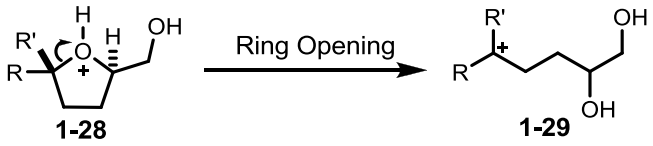
The major diastereomer was expected to arise from *trans* stereochemistry at the 2 and 5 positions as the oxidative cyclization is selective for *trans* stereochemistry on a steric basis. The configuration of the minor diastereomeric constituent was unclear however it was likely a result of a *cis* orientation at the 2 and 5 positions. NOE analysis of the diastereomeric mixtures proved inconclusive and the nature of the stereochemical arrangement of the products would not be confirmed until later work on the synthesis of β-Carboline alkaloids (see chapter 2).

The isolated yields of the tri-substituted THF products were lower than those acquired when cyclizing secondary pentenols. Analysis of crude material from the cyclization of secondary alcohols showed consumption of starting material with in many cases the ability to acquire pure product following filtration.

When tertiary pentenols were cyclized the reaction did not go to completion and starting material remained however mass recovery was generally quantitative. Taking the remaining starting material into account, the isolated yields of the tri-substituted THFs following flash chromatography were lower than expected based on the yields of product calculated from NMR analysis of crude material. The application of a mesitylene internal standard confirmed that the crude yields were in fact reliable.

We speculated that such a loss could be the result of product decomposition during silica gel chromatography. The tri-substituted ether at the 5 position the THF product presents a possible site for ring opening on exposure to acidic media such as silica gel through the formation of a stable tertiary carbocation **1** (Scheme 1.11).

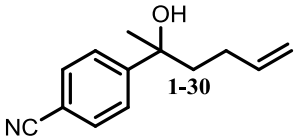
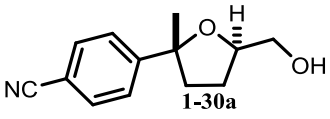
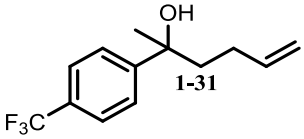
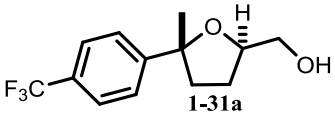
Scheme 1.11. Possible Ring Opening Mechanism.



The application of alternative purification methods such as the use of alumina, basic alumina, and reverse phase silica gel were ineffective at preventing loss of product on purification.

With the idea that electronics and ring opening were the problem we chose to synthesize THFs bearing electron withdrawing substituents at the 5 position in the hopes that the electron withdrawing effect would limit ring opening and product loss (Table 1.2).

Table 1.2 Substituents bearing electron withdrawing functionalities.

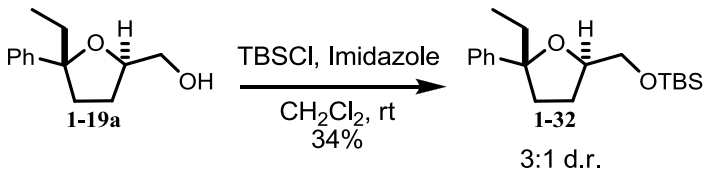
Entry	Starting Material	Product	Yield % (*)[a]	d.r.
1			35 (38)	4:1
2			49 (63)	4:1

[a] Yield based on recovered starting material.

Aryl pentenols **1-30** and **1-31** possessing *para* substituted electron withdrawing groups were cyclized providing THF products **1-30a** and **1-31a** respectively (entries 1 and 2). Unfortunately the yields of these products were in line those of alkyl and even electron rich THFs e.g. **1-26a**.

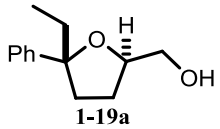
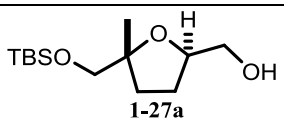
Following these results, we chose to derivatize a crude mixture of **1-19a** as a TBS ether (Scheme 1.12). The goal of this derivatization was to lower the polarity of the cyclized product and thereby limit possible detrimental interactions with the chromatographic solid phases. In addition derivatization might serve to limit deleterious effects arising from the free hydroxyl. Conversion to the TBS ether was carried out successfully, however column chromatography of the crude reaction mixture was still ineffective at isolating the product in high yield.

Scheme 1.12. Derivatization of crude material.



A select few pentenols were cyclized under the standard conditions but with $Co(modp)_2$ as the catalyst in order to make a comparison with the yields obtained with $Co(nmp)_2$ (Table 1.3). As expected, the first generation catalyst was able to catalyze the cyclizations but the yields were substantially lower than the corresponding yields with $Co(nmp)_2$.

Table 1.3. Comparrison to $Co(modp)_2$.

Entry	Product	Yield % $Co(modp)_2$	Yield % $Co(nmp)_2$
1	 **1-19a**	23	56
2	 **1-27a**	27	45

Despite the issues related to purification, the $Co(nmp)_2$ catalyzed oxidative cyclization of tertiary pentenols presents significant advantages over other THF forming reactions. The simplicity of the required cyclization precursors, the ease of application, and the primary alcohol formed in the reaction make THF formation through Mukaiyama oxidative cyclization a viable option for use in organic synthesis.

1.7 Conclusions and Future Work

This chapter has outlined the progress made towards applying the Mukaiyama oxidative cyclization with $Co(nmp)_2$ towards the cyclization of tertiary pentenols. A number of THFs have been synthesized with reasonable to good yields and diastereotopic ratios. This work represents an advancement in the synthesis of *trans*-2,5,5-THFs by oxidative cyclization over previously reported procedures.

There is room for improvement with the methodology in terms of the yields obtained. Future work in this area would seek to improve yields and levels of diastereoselectivity. This could potentially be accomplished through modification to the catalyst system itself in order to more effectively tailor steric and electronic factors in the cyclization process.

Future would also seek to employ the cyclization methodology with $Co(nmp)_2$ in the synthesis of natural products and pharmaceutical agents.

1.8 Experimental

1.8.1 General Experimental Details

All reactions were conducted under Argon atmosphere unless otherwise indicated. All glassware was oven dried and cooled in a desiccator prior to use. Solvents and reagents were purified using standard methods.[12] All reactions were stirred with a magnetic stir bar. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by passing solvents through activated alumina columns. Isopropyl alcohol was used as obtained from Caledon Laboratory Chemicals. All other chemicals were reagent grade and used as obtained from commercial sources unless otherwise noted. The progress of reactions were monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by staining with potassium permanganate or ceric ammonium molybdate (CAM). Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[13]

^{1}H and ^{13}C NMR were acquired on 400 and 600 MHz spectrometers in deuterated chloroform. ^{1}H NMR were referenced to residual chloroform at δ 7.26 ppm and the center peak of the triplet at δ 77(t) ppm for ^{13}C NMR. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; ddt, doublet of doublet of triplets; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. EI mass spectra were obtained on a Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV.

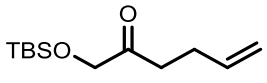
1.82 Experimental Details

General Cyclization Procedure: Previously prepared $Co(L)_2$ (0.175 mmol, 0.175 equiv) was placed under 1 atm O_2 (balloon) and then dissolved in 3 mL *i*PrOH.[14] *tert*-butyl hydroperoxide (5.74 M in isooctane, 0.03 mL, 0.175 mmol, 0.175 equiv) was added and the resulting mixture heated at 50 °C for 1 hr. Solvent was removed under reduced pressure yielding the pre-oxidized catalyst as dark green crystals. To the pre-oxidized catalyst was then added the cyclization precursor (1 mmol, 1 equiv) in 2 mL *sec*-butanol. With a condenser attached the reaction mixture was placed under 1 atm O_2 (balloon) and heated at 80 °C for 16h. The reaction mixture was then concentrated under reduced pressure and the resulting oil diluted with ethyl acetate and filtered through a silica gel (3.5 cm) and Celite (1 cm) bilayer pad. The pad was flushed with excess ethyl acetate (~75 mL) following filtration. The filtrate was concentrated under reduced pressure and then purified by flash chromatography.

1.83 Cyclization Substrates

Compounds **1-18 – 1-26** were prepared by Cory Palmer and Andrew Stevens.

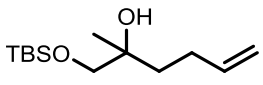
Compound 1-33



To a 250 mL round bottom flask charged with CH_2Cl_2 (50 mL) at 0 °C were combined TBSCl (5.79 g, 38 mmol, 1.2 eq), imidazole (5.3 mL, 96 mmol, 3 eq), and 1 drop of DMF forming an opaque white solution. Glycidol (2.3 mL, 32 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was then introduced. After 1 hr at 0 °C the reaction was poured into half-saturated $NaHCO_3$ (30 mL). The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure to afford TBS protected glycidol (5.05 g, 27 mmol, 1 eq) requiring no purification. The crude material was transferred to a 250 mL round bottom equipped with a condenser and then diluted with ether (125 mL). The resulting solution was cooled to 0 °C. Allylmagenisum bromide (1M in ether, 40.1 mL, 40.1 mmol, 1.5 equiv) was introduced and the condenser rinsed with ether (5 mL). The cooling bath was removed. After 1 h excess Grignard reagent was quenched with half-saturated NH_4Cl (30 mL). The layers were separated and the aqueous extracted with ether (3 x 50 mL). The combined

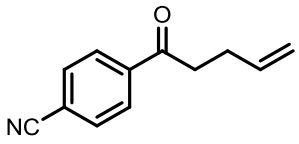
organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The crude residue (6.15 g, 27 mmol, 1 eq) was taken up in CH_2Cl_2 (125 mL). *i*Pr_2NEt (32 mL, 186 mmol, 7 eq) and DMSO (9.4 mL, 133 mmol, 5 eq) were introduced and the solution cooled to 0 °C. SO_3•Pyr complex (12.7 g, 80 mmol, 3 eq) was then introduced and the cooling bath removed. After 30 min half-saturated $NaHCO_3$ (30 mL) was introduced. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/Hexanes) to afford the title compound (5.15 g, 56% over 3 steps) as a clear colourless oil. R_f 0.64 (20% EtOAC/Hexanes); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.82 (dddd, *J* = 16.8, 10.2, 6.6, 6.6 Hz, 1 H), 5.01-5.06 (m, 1 H), 4.96-5.00 (m, 1 H), 4.16 (s, 2 H), 2.61 (t, *J* = 7.0 Hz, 2 H) 2.31-2.37 (m, 2 H), 0.92 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.4, 137.1, 115.2, 69.4, 37.5, 27.2, 25.8, 18.3, -5.5; HRMS *m/z* 229.1618 (calc for $C_{12}H_{24}O_2Si+H^+$, 229.1618).

Compound 1-27



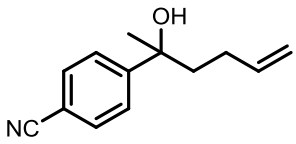
Ketone **1-33** (5.13 g, 22 mmol, 1 eq) was taken up in ether (125 mL) in a flask equipped with a condenser. Methylmagnesium bromide (3M in ether, 9 mL, 27 mmol, 1.2 eq) was introduced dropwise at room temperature. After 2 h excess Grignard reagent was quenched by addition of half-saturated NH_4Cl (30 mL). The layers were separated and the aqueous extracted with ether (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (1% EtOAc/Hexanes - 3% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (3.42 g, 63%). R_f 0.73 (30% EtOAC/Hexanes); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.84 (dddd *J* = 16.8, 10.2, 6.6, 6.6 Hz, 1 H), 5.00-5.05 (m, 1 H), 4.92-4.96 (m, 1 H), 3.43 (d, *J* = 9.8 Hz, 1 H), 3.38 (d, *J* = 9.4 Hz, 1H), 2.33 (s, 1 H), 2.06-2.20 (m, 2 H), 1.47-1.63 (m, 2 H), 1.12 (s, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.06, 114.17, 72.16, 70.10, 37.64, 28.17, 25.86, 23.06, 18.28, -5.46; HRMS *m/z* 245.1930 (calc for $C_{13}H_{28}O_2Si+H^+$, 245.1931).

Compound 1-34



Manually ground magnesium turnings (0.43 g, 18 mmol, 1.8 eq) and an I_2 crystal were combined in a round bottom flask equipped with a condenser. Ether (100 mL) was introduced and the resulting suspension brought to reflux. 4-bromo-1-butene (1.3 mL, 13 mmol, 1.3 eq) was introduced through the condenser and the condenser rinsed with ether (1 mL). After 1 h the resulting homoallyl magnesium bromide was allowed to cool to room temperature. 4-cyanobenzaldehyde (1.31 g, 10 mmol, 1 eq) in Ether (10 mL) and THF (3.5 mL) was introduced through the condenser and the reaction monitored for completion by TLC. On completion excess Grignard reagent was quenched with half-saturated NH_4Cl (30 mL). The layers were separated and the aqueous extracted with ether (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue (1.69 g, 9 mmol, 1 eq) was taken up in CH_2Cl_2 (90 mL). *i*Pr_2NEt (11 mL, 63 mmol, 7 eq) and DMSO (3.2 mL, 45 mmol, 5 eq) were introduced and the solution cooled to 0 °C. SO_3•Pyr complex (4.30 g, 27 mmol, 3 eq) was then introduced. The cooling bath was removed. After 1 h half-saturated $NaHCO_3$ (30 mL) was introduced. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (15% EtOAc/Hexanes) to afford the title compound (1.074 g, 58% over 2 steps) as a clear colourless oil. ^{1}H NMR (600MHz, $CDCl_3$) δ 8.04-8.05 (m, 2 H), 7.76-7.78 (m, 2 H), 5.85-5.92 (m, 1H), 5.07-5.11 (m, 1 H), 5.02-5.04 (m, 1 H), 3.09 (t, *J* = 7.6 Hz, 2 H), 2.50 (dt, *J* = 14.1, 7.0 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 139.8, 136.6, 132.5, 128.4, 117.9, 116.3, 115.7, 38.0, 27.8; HRMS *m/z* 185.0833 (calcd for $C_{12}H_{11}NO$, 185.0841).

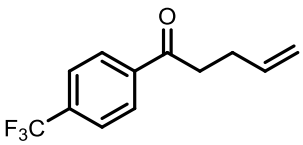
Compound 1-30



Ketone **1-34** (1.02 g, 5.5 mmol, 1 eq), was taken up in THF (50 mL) and methylmagnesium bromide (3 M, 3.6 mL, 11 mmol, 2 eq) was introduced dropwise at room temperature. After 1.5 h excess Grignard reagent was quenched by the addition of half-saturated NH_4Cl (30 mL). The layers were separated and the aqueous extracted with ether (3 x 30 mL). The combined organic layers were

washed with brine, dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (10% EtOAc/Hexanes) to afford the title compound as a clear orange oil (0.97 g, 87%). R_f 0.43 (30% EtOAc/Hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 5.77 (dddd, *J* = 17.0, 10.5, 6.4, 6.4 Hz, 1 H), 4.93-4.98 (m, 2 H), 2.03 – 2.08 (m, 1 H), 1.85-1.95 (m, 3 H), 1.57 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.04, 138.09, 132.06, 125.72, 118.91, 115.09, 110.47, 74.71, 42.82, 30.46, 28.28; HRMS *m/z* 201.1153 (calcd for $C_{13}H_{15}NO$, 201.1154).

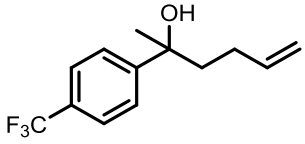
Compound 1-35



Manually ground magnesium turnings (0.64 g, 27 mmol, 1.8 eq) and an I_2 crystal were combined in a round bottom flask equipped with a condenser. Ether (100 mL) was introduced and the resulting suspension brought to reflux. 4-bromo-1-butene (2.0 mL, 19.5 mmol, 1.3 eq) was introduced through the condenser and the condenser rinsed with ether (1 mL). After 1 h the resulting homoallyl magnesium bromide was allowed to cool to room temperature. 4-trifluoromethylbenzaldehyde (2 mL, 15 mmol, 1 eq) in Ether (10 mL) was introduced through the condenser and the reaction monitored for completion by TLC. On completion excess Grignard reagent was quenched with half-saturated NH_4Cl (30 mL). The layers were separated and the aqueous extracted with ether (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue (3.07 g, 13.3 mmol, 1 eq) was taken up in CH_2Cl_2 (100 mL). *i*Pr_2NEt (16 mL, 93 mmol, 7 eq) and DMSO (4.7 mL, 66.5 mmol, 5 eq) were introduced and the solution cooled to 0 °C. SO_3•Pyr complex (6.35 g, 40 mmol, 3 eq) was then introduced. The cooling bath was removed. After 1.5 h half-saturated $NaHCO_3$ (30 mL) was introduced. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (1.68 g, 49% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 8.2 Hz, 2 H), 5.90 (dddd, *J* = 16.8, 10.2, 6.6, 6.6 Hz, 1 H), 5.07-5.12 (m, 1 H), 5.01-5.05 (m, 1 H), 3.10 (t, *J* = 7.4 Hz, 2 H), 2.49-2.45 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 139.5, 136.8, 134.2 (q, *J* = 32.2 Hz), 128.3, 125.6 (q,

J = 3.8 Hz), 123.6 (q, *J* = 273.0 Hz), 115.6, 38.0, 27.9; HRMS *m/z* 228.0772 (calcd for $C_{12}H_{11}F_3O$, 228.0762).

Compound 1-31

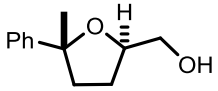


Ketone **1-35** (1.64 g, 7.2 mmol, 1 eq), was taken up in ether (100 mL) and methylmagnesium bromide (3 M in ether, 6 mL, 18 mmol, 2.5 eq) was introduced dropwise at room temperature. After 1 h excess Grignard reagent was quenched by the addition of half-saturated NH_4Cl (30 mL). The layers were separated and the aqueous extracted with ether (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (10% EtOAc/Hexanes – 20% EtOAc/Hexanes) to afford the title compound as a clear yellow oil (1.21 g, 69%). R_f 0.58 (30% EtOAc/Hexanes); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 5.75-5.82 (m, 1 H), 4.95-4.99 (m, 2 H), 4.93-4.95 (m, 2H), 2.04-2.09 (m, 1 H), 1.88-1.97 (m, 3 H), 1.58 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.63, 138.30, 128.81 (q, *J* = 32.2 Hz), 152.22, 125.09 (q, *J* = 3.83 Hz), 124.38 (q, *J* = 272.21 Hz), 114.85, 74.68, 42.89, 30.34, 28.30; HRMS *m/z* 244.1071 (calcd for $C_{13}H_{15}F_3O$, 244.1075).

1.84 Cyclized Products

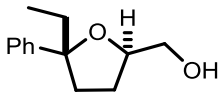
Compounds **1-20a**, **1-21a**, and **1-23a** were prepared by Cory Palmer and Andrew Stevens. Compounds **1-18a**, **1-19a**, **1-22a**, **1-24a**, and **1-25a** were previously reported by Cory Palmer but these experiments were re-run in order to confirm results or acquire additional data for full characterization.

Compound 1-18a



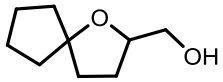
The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.066, 63%) as a 7:1 mixture of diastereomers. R_f 0.23 (20% EtOAc/Hexanes); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.43 – 7.49 (m, 2 H), 7.32-7.34 (m, 2 H), 7.21-7.24 (m, 1 H), [minor 4.30-4.34 (m, 1H), major 4.15-4.19 (dddd, *J* = 6.5, 6.5, 6.5, 3.5 Hz, 1 H)], [major 3.76-3.78 (m, 1 H), minor 3.76-3.78 (m, 1 H)], 3.57-3.59 (m, 1 H), 2.25-2.30 (m, 1 H), 2.04-2.08 (m, 2 H), 1.82-1.85 (m, 2 H), [major 1.55 (s, 3 H), minor 1.52 (s, 3 H)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 128.2, 126.5, 124.6, 85.3, 78.9, 65.4, 39.5, 30.5, 27.3. HRMS *m*/*z* 193.1223 (calcd for $C_{12}H_{16}O_2$+H^+, 193.1229).

Compound 1-19a



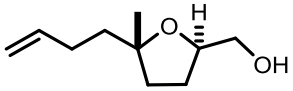
The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.081 g, 42%) as a 5:1 mixture of diastereomers. R_f 0.39 (40% EtOAc/Hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.38 (m, 4 H), 7.21-7.23 (m, 1 H), [minor 4.24-4.28 (m, 1 H), major 4.11-4.15 (m, 1 H)], [major 3.76 (dd, *J* = 11.1, 3.5 Hz, 1 H), minor 3.69 (dd, *J* = 11.1, 3.5 Hz, 1 H), major 3.55 (dd, *J* = 11.7, 5.9 Hz, 1 H), minor 3.50 (dd, *J* = 11.1, 5.9 Hz, 1 H)], 2.14-2.25 (m, 1 H), 2.04-2.10 (m, 1 H), 1.75-1.89 (m, 5 H), 1.54 (brs, 1 H), [major 0.78 (t, *J* = 7.6 Hz, 3 H), minor 0.75 (t, *J* = 7.6 Hz, 3 H)]; ^{13}C NMR ($CDCl_3$, 101 MHz) δ 146.7, 146.2, 127.9, 126.3, 125.2, 125.1, 88.0, 87.8, 79.6, 78.5, 65.6, 65.4, 37.4, 37.3, 35.7, 35.0, 27.3, 27.1, 8.7, 8.67; HRMS *m*/*z* 207.1389 (calcd for $C_{13}H_{18}O_2$+H^+, 207.1380).

Compound 1-22a



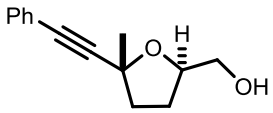
The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.035 g, 44%). R_f 0.15 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.04 - 4.08 (m, 1 H), 3.67 (ddd, *J* = 11.2, 5.9, 2.9 Hz, 1 H), 3.48 (ddd, *J* = 11.7, 5.9, 5.9 Hz, 1 H), 1.93-1.98 (m, 2 H), 1.83-1.87 (m, 3 H), 1.73-1.82 (m, 5 H), 1.51-1.64 (m, 4 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 91.9, 78.3, 65.4, 38.9, 38.1, 36.6, 27.6, 24.0; HRMS *m*/*z* 156.1149 (calcd for $C_9H_{16}O_2$, 156.1150).

Compound 1-24a



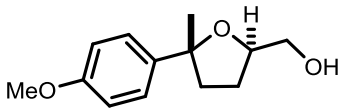
The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.064 g, 38%) as a As a 2:1 mixture of diastereomers. R_f 0.17 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 13.5, 10.6, 7.0, 7.0 Hz, 1 H), 5.00-5.02 (m, 1 H), 4.92-4.93 (m, 1 H), [minor 4.07-4.11 (m, 1 H), major 4.02-4.06 (m, 1 H)], [major 3.67 (dd, *J* = 11.7, 3.5 Hz, 1 H), minor 3.64 (d, *J* = 3.5 Hz, 1 H)], [major 3.47 (dd, *J* = 11.1, 5.3 Hz, 1 H)], 2.04-2.15 (m, 3 H), 1.89-1.98 (m, 1 H), 1.75-1.84 (m, 2 H), 1.65-1.75 (m, 2 H), 1.53-1.65 (m, 3 H), [major 1.21 (s, 3 H), minor 1.20 (s, 3 H)]; ^{13}C NMR ($CDCl_3$, 101 MHz) δ 138.9, 114.2, 114.2, 114.1, 83.5, 83.4, 79.2, 78.4, 65.3, 65.1, 40.9, 40.1, 37.0, 36.6, 29.0, 28.9, 27.5, 27.1, 26.7, 25.6; HRMS *m/z* 171.1385 (calcd for $C_{10}H_{18}O_2$+H^+, 171.1380).

Compound 1-25a



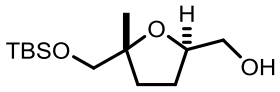
The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.046 g, 19%) as a As a 5:1 mixture of diastereomers. R_f 0.21 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl3) δ 7.36-7.39 (m, 2 H), 7.22-7.25 (m, 3 H), [major 4.26-4.32 (m, 1 H), minor 4.20-4.26 (m, 1 H)], [major 3.72-3.76 (m, 1 H), minor 3.59-3.65 (m, 1 H)], 3.48-3.54 (m, 1 H), 2.25-2.35 (m, 1 H), 2.12-2.23 (m, 1 H), 1.77-1.90 (m, 3 H), [major 1.61 (s, 3 H), minor 1.61 (s, 3 H)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.7, 131.6, 128.2, 91.9, 83.0, 80.7, 79.2, 64.9, 41.0, 40.3, 28.0, 27.1; HRMS *m*/*z* 216.1155 (calcd for $C_{14}H_{16}O_2$, 216.1150).

Compound 1-26a



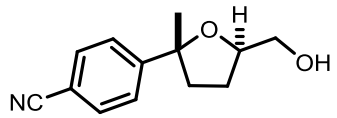
The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.0468 g, 44%) as a 2:1 mixture of diastereomers. R_f 0.27 (40% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.33 (m, 2 H), 6.84-6.88 (m, 2 H), [minor 4.27 (m, 1 H), major 4.11-4.18 (m, 1 H)], [major 3.80 (s, 3 H)], [major (ddd, *J* = 11.3, 6.3, 3.5 Hz, 1 H)], 3.53-3.59 (m, 1 H), 2.21-2.28 (m, 1 H), 1.98-2.05 (m, 2 H), 1.80-1.85 (m, 2 H), [major 1.52 (s, 3 H), minor 1.50 (s, 3 H)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 139.8, 125.8, 125.7, 113.5, 85.0, 84.7, 79.3, 78.9, 65.7, 65.5, 55.3, 39.4, 39.3, 30.6, 27.6, 27.4; HRMS *m*/*z* 222.1256 (calcd for $C_{13}H_{18}O_3$, 222.1251).

Compound 1-27a



The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.117 g, 45%) as a As a 2:1 mixture of diastereomers. R_f 0.46 (40% EtOAc/Hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ [minor 4.17-4.20 (m, 1 H), major 4.09-4.13 (m, 1 H)], [minor 3.76 (dt, *J* = 11.2, 3.5 Hz, 1 H), major 3.66-3.70 (m, 1 H)], [minor 3.59-3.61 (d, *J* = 10.6 Hz 1 H)], 3.42-3.49 (m, 5 H), 2.15-2.20 (m, 1 H), 1.99-2.06 (m, 2 H), 1.92-1.98 (m, 2 H), 1.88-1.91 (m, 1 H), 1.76-1.82 (m, 1 H), 1.56-1.65 (m, 2 H), [major 1.20 (s, 3 H), minor 1.15 (s, 3 H)], [minor 0.91 (s, 9 H), major 0.90 (s, 9 H)], [minor 0.08 (s, 6 H), major 0.05 (s, 6 H)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.0, 83.9, 80.0, 79.4, 69.4, 69.3, 65.6, 65.1, 33.9, 33.4, 27.9, 27.5, 25.94, 25.90, 24.6, 24.2, 18.5, 18.3, –5.4, –5.46, –5.54; HRMS *m*/*z* 261.1886 (calcd for $C_{13}H_{28}O_3Si+H^+$, 261.1880).

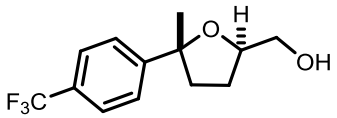
Compound 1-30a



The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (0.076 g, 35%) as a As a 4:1 mixture of diastereomers. R_f 0.16 (40% EtOAc/Hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ [minor 7.68-7.69 (m, 1 H), major 7.62 (d, *J* = 8.2 Hz, 2 H)], [minor 7.54-7.55 (m, 3 H), major 7.50 (d, *J* = 8.8 Hz, 2 H**)]**, [minor 4.33 (dddd, *J* = 7.0, 7.0, 7.0, 3.5 Hz, 1 H), major 4.15 (dddd, *J* = 7.0, 7.0, 7.0, 3.5 Hz, 1 H)], [major 3.78 (ddd, *J* = 11.7, 6.4, 3.5 Hz, 1 H), minor 3.72 (ddd, *J* = 11.1, 7.0, 3.5 Hz, 1 H)], 3.55-3.61 (m, 1 H),

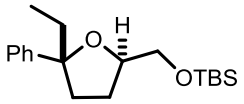
2.10-2.24 (m, 3 H), 1.80-1.94 (m, 3 H), [major 1.54 (s, 3 H), minor 1.51 (s, 3 H)];); ^{13}CNMR (101 MHz, $CDCl_3$) δ 153.4, 132.2, 132.1, 125.5, 118.9, 110.4, 84.9, 84.6, 79.6, 79.4, 65.5, 65.2, 39.4, 39.3, 30.2, 27.4, 27.3; HRMS *m/z* 218.1189 (calcd for $C_{13}H_{15}NO_2$, 217.1103).

Compound 1-31a



The title compound was prepared according to the general cyclization procedure to afford a clear colourless oil (.129 g, 49%) as a As a 4:1 mixture of diastereomers. R_f 0.31 (40% EtOAc/Hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2 H), [minor 7.54 (d, J = 8.2 Hz, 2 H), major 7.51 (d, J = 8.2 Hz, 2 H)], [minor 4.33 (dddd, *J* = 7.0, 7.0, 7.0, 3.5 Hz, 1 H), major 4.16 (dddd, *J* = 7.0, 7.0, 7.0, 3.5 Hz, 1 H)], [major, 3.78 (dd, *J* = 11.1, 2.9 Hz, 1 H), minor 3.71 (dd, *J* = 11.1, 3.5 Hz, 1 H)], [major 3.59 (dd, *J* = 11.1, 5.3 Hz, 1 H), minor 3.56 (dd, *J* = 11.7, 6.4 Hz, 1 H)], 2.16-2.27 (m, 1 H), 2.04-2.13 (m, 1 H), 1.65-1.90 (m, 3 H), [major 1.55 (s, 3 H), minor 1.52 (s, 3 H)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 151.9, 128.8 (q, J = 32.2 Hz), 125.2 (q, J = 3.8 Hz), 125.0, 124.2 (q, J = 272.2 Hz), 85.0, 84.7, 79.6, 79.3, 65.6, 65.3, 39.4, 39.3, 30.3, 29.7, 29.4, 27.5, 27.3; HRMS m/z 261.1110 (calcd for $C_{13}H_{15}F_3O_2$+H^+, 261.1097).

Compound 1-32



TBSCl (0.181 g, 1.2 mmol, 1.2 eq) and imidazole (0.204 g, 3 mmol, 3 eq) were combined in CH_2Cl_2 (20 mL). Crude THF **1-19a** (0.211 g, 1 mmol, 1 eq) was introduced. After one hour half-saturated $NaHCO_3$ (10 mL) was introduced. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (8% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.108 g, 34% over 2 steps) as a 3:1 mixture of diasteriomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.40 (m, 1 H), 7.38 – 7.36 (m, 2 H), 7.33 – 7.28 (m, 2 H), 7.22 – 7.20 (m, 1 H), [minor 4.20 – 4.16 (m, 1 H), major 4.10 – 4.06 (m, 1 H)], 3.76 – 3.72 (m, 1 H), [major 3.66 – 3.64, minor 3.57 – 3.54 (m, 1 H)], 2.17 – 2.13 (m, 1 H), 2.09 – 2.04 (m, 1 H), 1.88 – 1.75 (m, 5 H), [major 0.93 (s, 9 H), minor 0.88 (s, 9 H)], [major 0.78 (t, *J* = 7.63 Hz, 3 H), minor 0.76 (t, *J* = 7.63 Hz, 3 H)], [major 0.10 (s, 6 H), minor 0.06 (s, 3 H), 0.04 (s, 3 H)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 146.8, 127.9, 127.6, 126.1, 126.0, 125.4, 125.3,

87.7, 87.4, 79.9, 78.9, 65.93, 65.86, 37.7, 36.9, 35.6, 34.9, 28.3, 27.6, 25.93, 25.89, 18.3, 8.8, 8.7, -5.27, -5.30. HRMS *m/z* 261.1886 (calcd for $C_{13}H_{28}O_3Si+H^+$, 261.1880).

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[14] For catalyst synthesis see supporting information: Palmer, C.; Morra, N.A.; Stevens, A.C.; Bajtos, B.; Machin, B.P.; Pagenkopf, B.L. *Org. Lett.* **2009**, *11*, 5614-5617.

Chapter Two: Synthesis of β-Carboline Alkaloids

2.0 Introduction

The development of the modified Mukaiyama cyclization procedure for tri-substituted bishomoallylic alcohols presented an opportunity to apply $Co(nmp)_2$ catalyzed oxidative cyclizations towards the synthesis of a natural product. Such a synthesis would continue to test the versatility of $Co(nmp)_2$ and demonstrate its potential to access unique target molecules. Chrysotricine **2-1** (Figure 2.1) was chosen as a synthetic target due to the occurrence of the 2,5,5-substituted THF ring. The alkaloid is derived from the Chinese herb medicine *Hedyotis chrysotricha* and was first reported in 1997 as a trace alkaloid (0.0001%) isolated from the plant.[1] Chrysotricine was again isolated in 1998 from *H. capitellata* along with several other notable β-Carboline alkaloids including (-)-isocyclocapitelline **2-4**, (+)-cyclocapitelline **2-3** and isochrysotricine **2-2** (Figure 2.0).[2] Chrysotricine was shown to inhibit the growth of HL-60 cells *in vitro* adding to its value as a synthetic target.

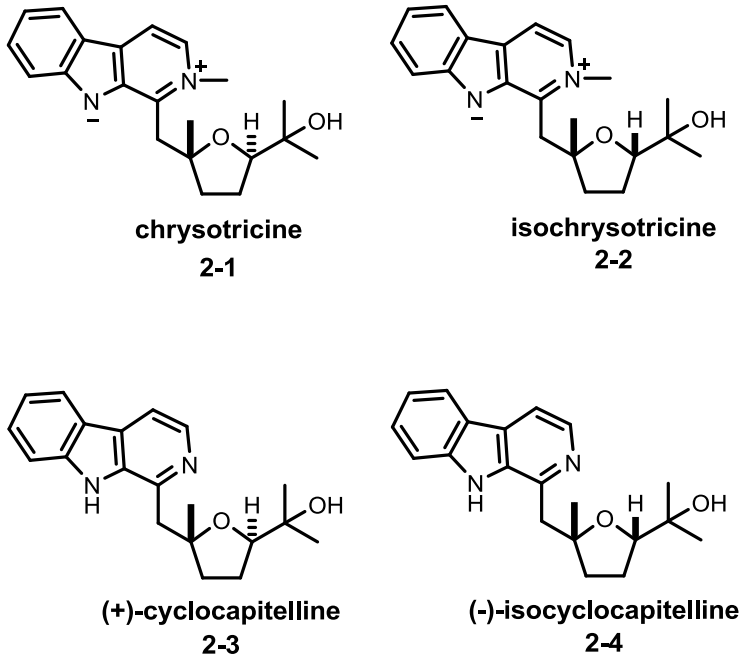
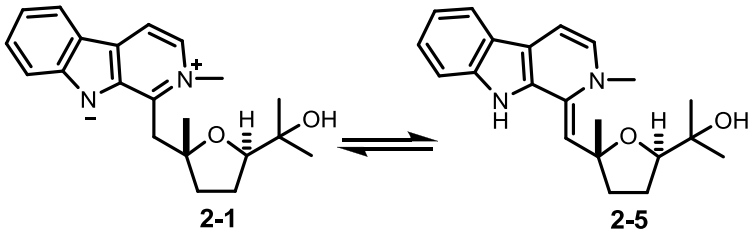


Figure 2.0. β-Carboline alkaloids.

Chrysotricine features a 2,5,5-*trans*-THF core along with a tertiary alcohol at the 2 position and a methylated β-Carboline at the 5 position. The natural product possesses an interesting zwitterionic structure with a positively charged quaternary nitrogen and negatively charged nitrogen derived from the indole nitrogen of the β-carboline. Isolation studies of the compound revealed that chrysotricine tautomerizes in methanol forming an equilibrium between **2-1** and **2-2** (Scheme 2.1).[2]

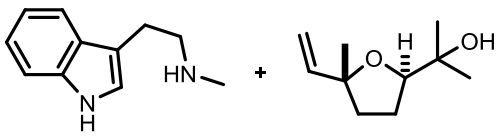
Scheme 2.1. Tautomeric equilibrium of chrysotricine.



2-1 **2-5**

Biosynthetically, chrysotricine is thought be derived through the combination of a methyl tyrptamine derivative and *trans* linayl oxide **2-7**, a natural product commonly found in many plant systems (Scheme 2.2). [2]

Scheme 2.2. Proposed biosynthetic precursors to chrysotricine



2-6 **2-7**

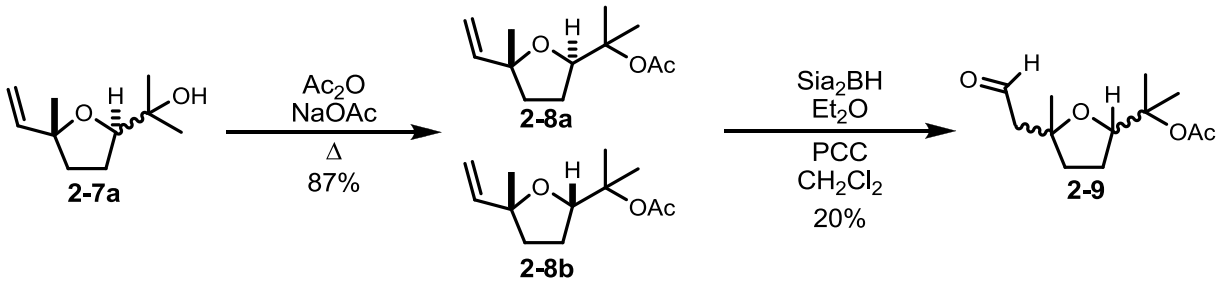
Since isolation in 1997 there have been two syntheses of Chrysotricine reported in the literature. The first total synthesis was conducted racemically by Schollmeyer and coworkers and

took advantage of the proposed biosynthetic generation of Chrysotricine.[3] Within the same year Liang and coworkers reported the first total synthesis of enantioenriched Chrysotricine.[4] Examination of these syntheses provides insight into possible strategies and pitfalls to avoid.

2.1 Schollmeyer's Synthesis of Chrysotricine

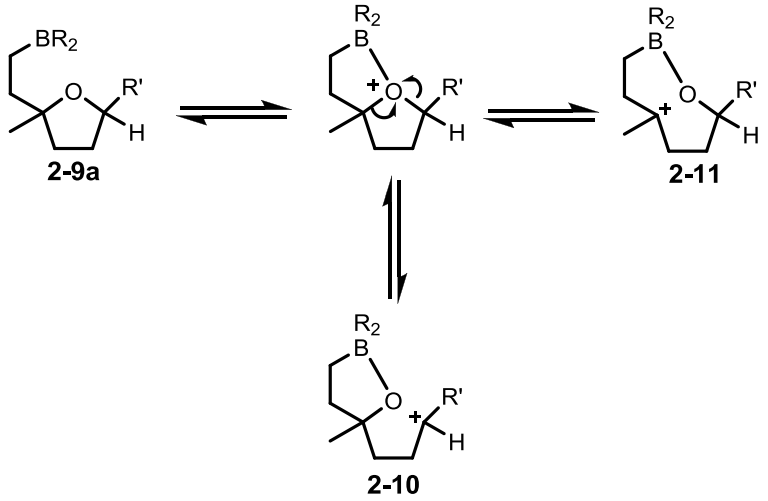
Schollmeyer and coworkers began their synthetic efforts towards chrysotricine through the acetylation of a commercially available diastereomeric mixture of linalyl oxides **2-7a**. This was required in order to separate the diastereomers of the commercial mixture (Scheme 2.3). The separated enantiomerically pure diastereomers **2-8a** and **2-8b** were then converted separately into aldehydes **2-9** through a sequential hydroboration, oxidation of the of the pendant alkene. Unfortunately they found that the hydroboration/oxidation sequence caused a scrambling of stereochemistry resulting in a mixture of diastereomers for each of the respective products. These products were also found to be racemates.

Scheme 2.3 Schollmeyer's preparation of the Pictet-Spengler precursor.



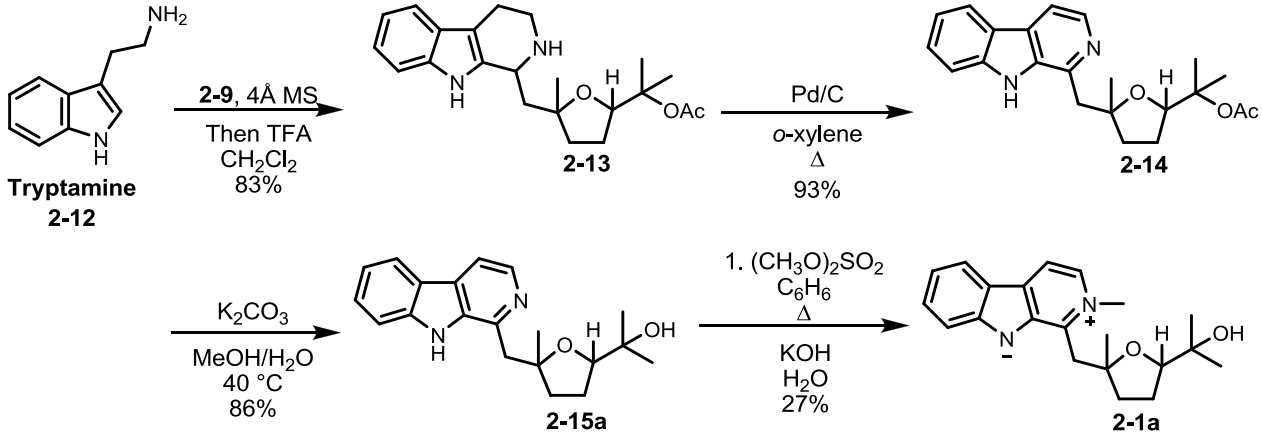
Schollmeyer speculated that boroxolane **2-9a** formed during the hydroboration reaction would destabilize the THF at the 2 and 5 position leading to ring opening forming secondary carbocation **2-10** or tertiary carbocation **2-11** (Scheme 2.4), thus allowing scrambling of the previously set stereocenters.

Scheme 2.4. Erosion of stereochemistry via a boroxolane intermediate.



The diastereomeric mixture of **2-9** was combined and subjected to a Pictet-Spengler reaction with tryptamine without isolation of the intermediate imine (Scheme 2.5). The resulting 1-substituted-1,2,3,4-tetrahydro-β-carbolines **2-13** were acquired as a mixture of four diastereomeric racemates. The tetrahydro-β-carbolines were then dehydrogenated with Pd/C in hot *o*-xylene to afford β-carbolines **2-14**. Removal of the acyl group was accomplished with K_2CO_3 in methanol/water to reveal the tertiary alcohol **2-15a**. Finally quaternization of the β-carboline nitrogen was accomplished with dimethyl sulfate followed by deprotonation with 2M KOH to afford the final product **2-1a** as a mixture of enantiomers following separation.

Scheme 2.5. Completion of Schollmeyer's synthesis of chrysotricine.

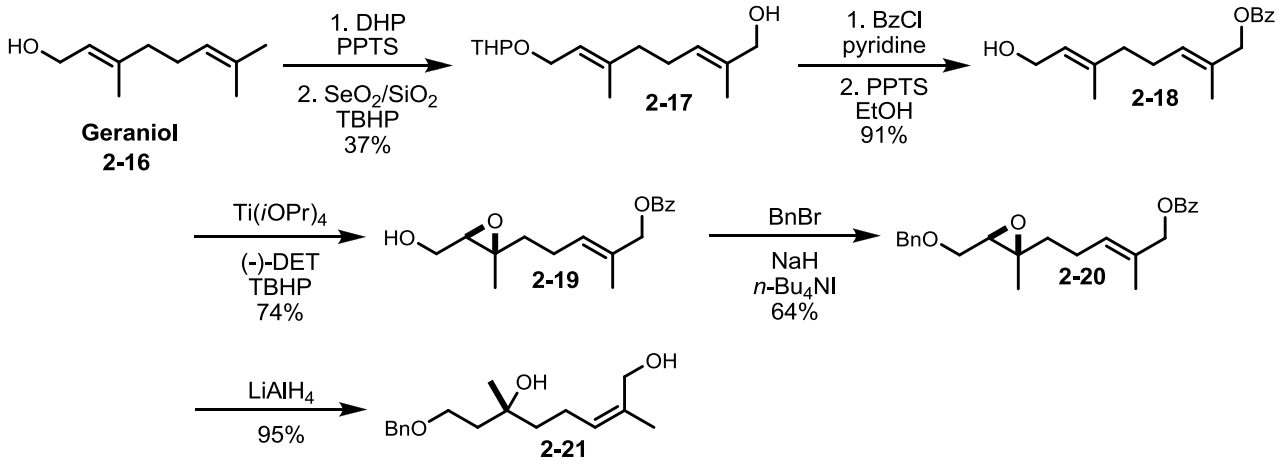


Schollmeyer's synthesis produced racemic product starting from enantiomerically pure starting materials. The loss of stereochemistry during the hydroboration oxidation sequence of acylated linayl oxide was a critical problem with the synthesis. It served as an important precedent demonstrating the challenges to forming the natural product using a biosynthetic approach.

2.2 Liang's Synthesis of chrysotricine.

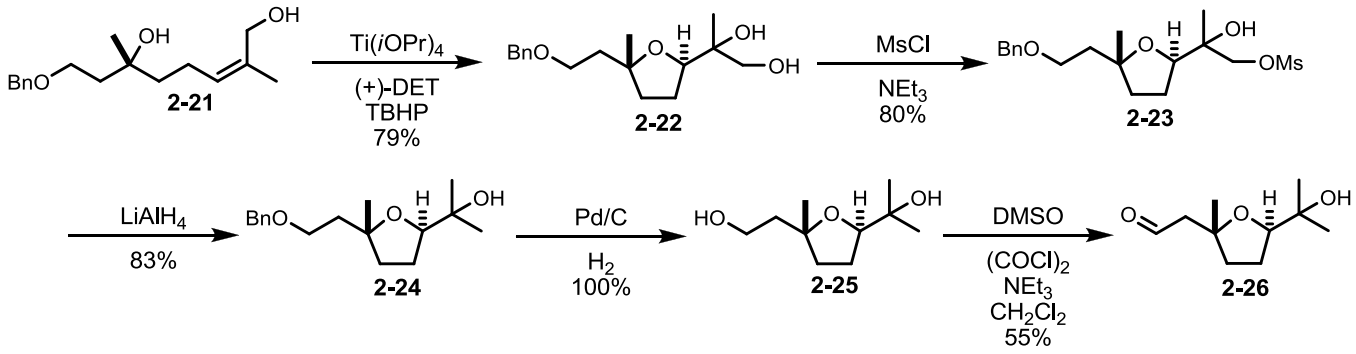
Liang and coworkers chose to stay away from a biosynthetically inspired route to chrysotricine, instead starting with prochiral starting material. The synthesis began with the THP ether protection of commercially available geraniol (Scheme 2.6). Allylic oxidation of the tri-substituted alkene then afforded primary alcohol **2-17**.[5] Protection of the newly formed alcohol was accomplished with benzoyl chloride followed by removal of the THP ether with PPTS to yield **2-18**. Sharpless epoxidation of allylic alcohol **2-18** afforded epoxide **2-19** in 90% ee. Protection of the primary alcohol was then accomplished with benzyl bromide to afford **2-20** followed by one pot epoxide opening and benzoyl deprotection with $LiAlH_4$ to afford diol **2-21**.

Scheme 2.6. Synthesis of the THF precursor.



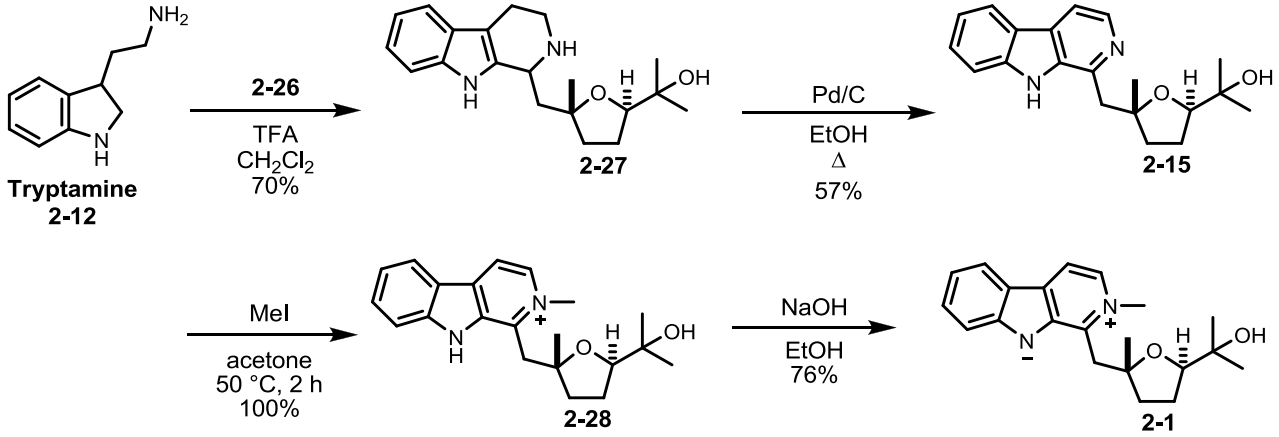
A second Sharpless epoxidation of the now revealed allylic alcohol followed by ring closure was accomplished in one step forming the THF core of chrysotricine **2-22** with 82% de (scheme 2.7). Mesylation of the primary alcohol of **2-22** followed by treatment with $LiAlH_4$ afforded the tertiary alcohol of chrysotricine **2-24**. Hydrogen gas with Pd/C was then employed to remove the benzyl protecting group to reveal primary alcohol **2-25**. Swern oxidation of the primary alcohol afforded THF aldehyde **2-26** in moderate yield.

Scheme 2.7. Liang's formation of the chrysotricine THF core.



Aldehyde **2-26** converged with Schollmeyer's racemic synthesis of chrysotricine. From the aldehyde Liang forms β-carboline **2-15** through a Pictet-Spengler and dehydrogenation sequence similar to Schollmeyer (Scheme 2.8). To complete the natural product Liang methylated the β-carboline nitrogen with methyl iodide followed by deprotonation with NaOH. Overall Liang's synthesis provides access to chrysotricine in 16 steps (1.1% overall yield). The synthesis is lengthier than Schollmeyer's and requires a number of protecting group manipulations but it does provide access to enantioenriched product.

Scheme 2.8. Completion of Liang's synthesis of chrysotricine.



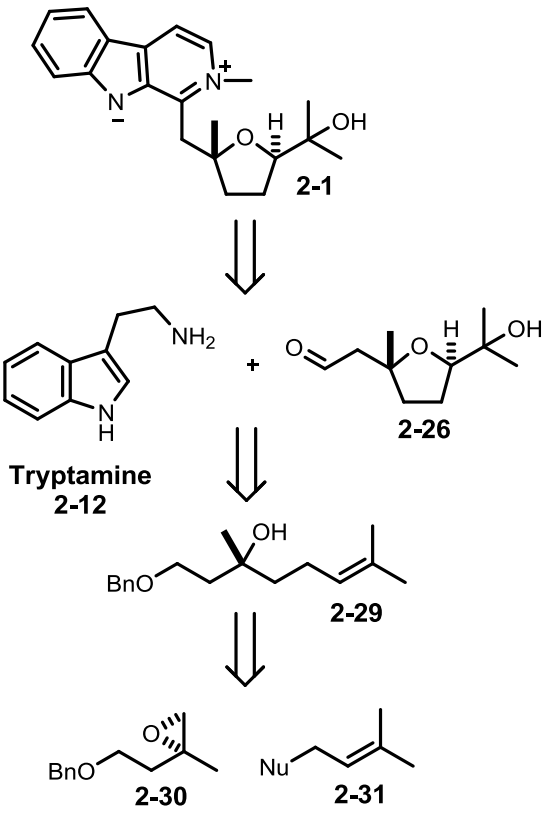
2.3 Progress Towards Chrysotricine: Synthetic Route One

The method developed for the oxidative cyclization of tertiary bishomoallylic alcohols to 2,5,5-*trans*-THFs produced THFs containing a methanol subunit at the 2 position in the resulting products. Chrysotricine however, has an isopropanol at the 2 position. If the THF core of Chrysotricine and the isopropanol unit could be formed simultaneously through a Mukaiyama cyclization it would provide access to an advanced Chrysotricine intermediate in very short order. Such a transformation would require cyclization of a bishomoallylic alcohol containing a tri-substituted alkene. Cyclizations with this class of tertiary pentenol had not yet been attempted with the Mukaiyama cyclization protocol and thus it was advantageous to try to extend the methodology further to this class of tertiary bishomoallylic alcohols.

Retrosynthetically, chrysotricine could be arrived at through a Pictet-Spengler reaction between tryptamine and THF aldehyde **2-26** (Scheme 2.9) in a similar manner to that described by Schollmeyer and Liang. This would be followed by oxidation of the resulting tetrahydro-β-carboline, methylation of the carboline nitrogen and finally deprotonation of the indole nitrogen to give the zwitterionic natural product. The THF aldehyde **2-26** would be arrived at through an oxidative cyclization of protected pentenol **2-29** followed by deprotection and oxidation of the

primary alcohol. Ultimately the pentenol would come from the opening of enantioenriched epoxide **2-30** with the appropriate prenyl nucleophile **2-31**.

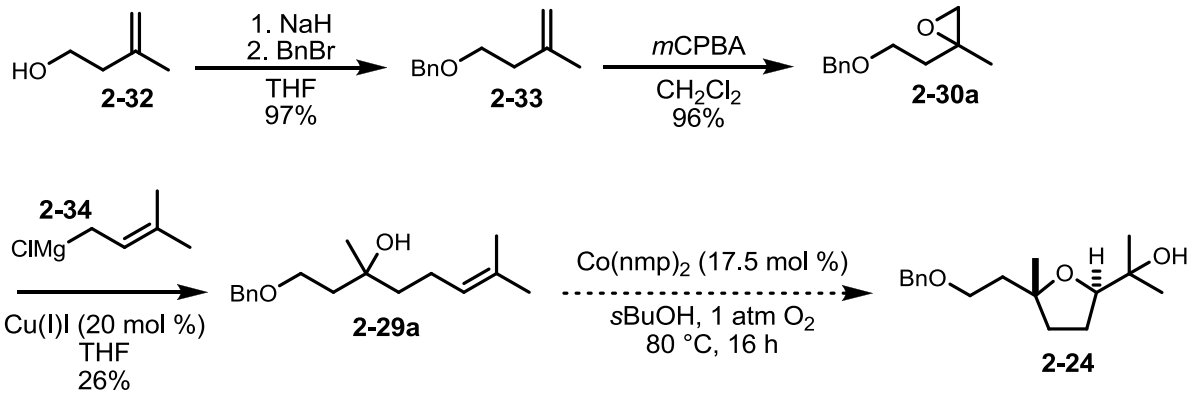
Scheme 2.9. Retrosynthetic analysis of Chrysotricine.



Forward synthetic efforts towards Chrysotricine began with protection of Methyl-3-buten-1-ol as benzyl protected alcohol **2-33** in excellent yield (Scheme 2.10).[6] Epoxidation of **2-33** was readily carried out with *m*CPBA to give racemic epoxide **2-30a**. With the epoxide in hand the next step was to conduct and epoxide opening in order to access substituted pentenol **2-29a** for use in the key core forming cyclization step. When epoxide **2-30a** was introduced to prenyl cuprate **2-34** formation of tertiary pentenol **2-29a** was accomplished in 26% yield with 54% recovery of starting material.[7] Subsequent attempts to modify the reactions conditions of this addition were unsuccessful in increasing the yield. Monitoring of the reaction mixtures by

TLC indicated that the reaction failed to go to completion, leaving significant quantities of epoxide unreacted. Increasing the amount of copper(I)iodide in an attempt to force the reaction to completion resulted in unwanted byproducts and the use of prenyl magnesium chloride alone was ineffective. The epoxide was prone to opening by chloride at elevated temperatures making reproducibility of the method challenging.

Scheme 2.10. Route one forward synthetic efforts.



Having obtained pentenol **2-29a** in modest amount, an attempt was made at cyclizing the substrate in order to form the core of chrysotricine. Unfortunately the conditions established for the cyclization of tertiary pentenols onto mono-substituted alkenes were unsuccessful when applied to tri-substituted alkene **2-29a** yielding only recovered starting material.

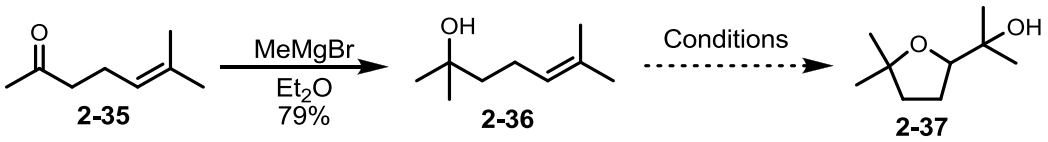
2.4 Development of a Model System

After determining that alkenol **2-29a** could not be cyclized under the Mukaiyama cyclization procedure, we chose to develop a simpler model substrate in order to test the overall viability of cyclizing tertiary alkenols bearing tri-substituted alkenes with the $Co(nmp)_2$ catalyst. 2,6-dimethylhept-5-en-2-ol **2-36** was chosen as it represents the simplest such substrate.

Synthesis of the pentenol was carried out by addition of methyl magnesium bromide to commercially available 6-methylhept-5-en-2-one **2-35** in 79% yield.

With the cyclization substrate in hand efforts were made to cyclize the compound under modified Mukaiyama conditions (Table 2.0). Following the short reaction screening it became clear that simple modifications of the reaction conditions would not permit the formation of the product. Increasing the temperature (entry 1), changing the solvent and altering the catalyst loading (entries 2 and 3) and the use of high pressure (entry 4) did not yield any product. Further experimentation is needed to establish conditions suitable for the cyclization, however it may be that the $Co(nmp)_2$ catalyst is simply not suited to such substrates.

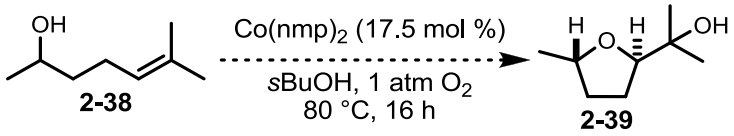
Table 2.0. Cyclization of a model substrate.



Entry	Cat	Solvent	Temp	Product
1	17.5	*s*BuOH	100	N/A
2	10	EtOH	75	N/A
3	20	EtOH	75	N/A
4	17.5	CH_2Cl_2	rt 150,000 psi	N/A

Hartung has demonstrated the potential for secondary alcohols bearing tri-substituted alkenes to cyclize using a bis[3-trifluoroacetylcampherato(−1)]cobalt(II) complex however with low yield, poor selectivity and considerable byproduct formation.[8] When $Co(nmp)_2$ was applied to a secondary pentenol, 6-methylhept-5-en-2-ol however, the reaction failed to yield any cyclized product (Scheme 2.11.)

Scheme 2.11. Attempted cyclization of 6-methylhept-5-en-2-ol.

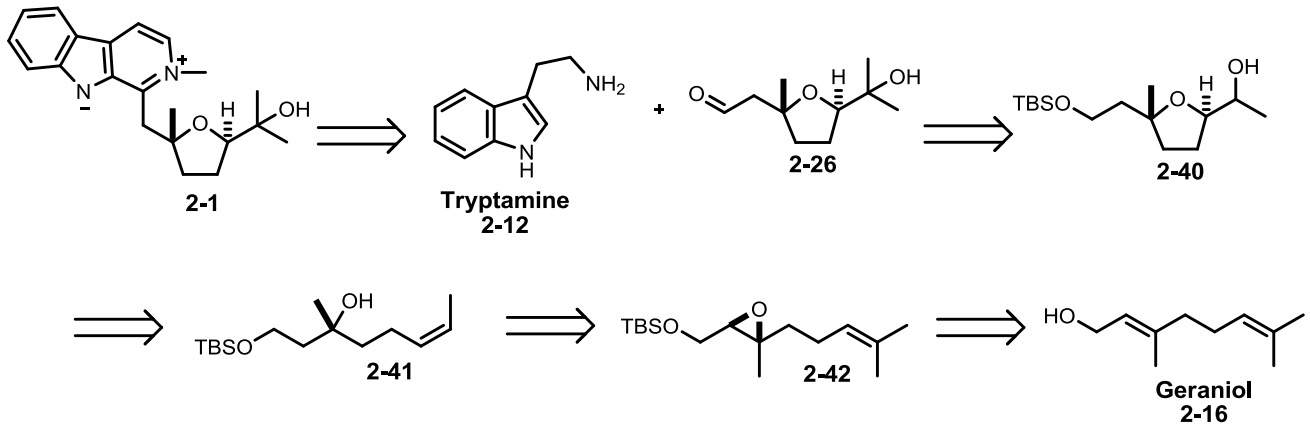


While it is still unclear why this class of substrate is as yet incompatible with the $Co(nmp)_2$ catalyst it may be speculated that both steric and electronic factors are limiting the ability of $Co(nmp)_2$ to successfully catalyze the cyclization.

2.5 Revised Synthetic Route to Chrysotricine: Route Two

After having determined that cyclizations of tertiary pentenols bearing tri-substituted alkenes was not achievable under our established cyclization conditions we chose to revise our synthetic route to chrysotricine. Retrosynthetically, (scheme 2.12), THF aldehyde **2-26** would arise from THF alcohol **2-40** through an oxidation of the secondary alcohol followed by addition of a methyl nucleophile. Deprotection of the primary alcohol and oxidation would then afford the aldehyde.

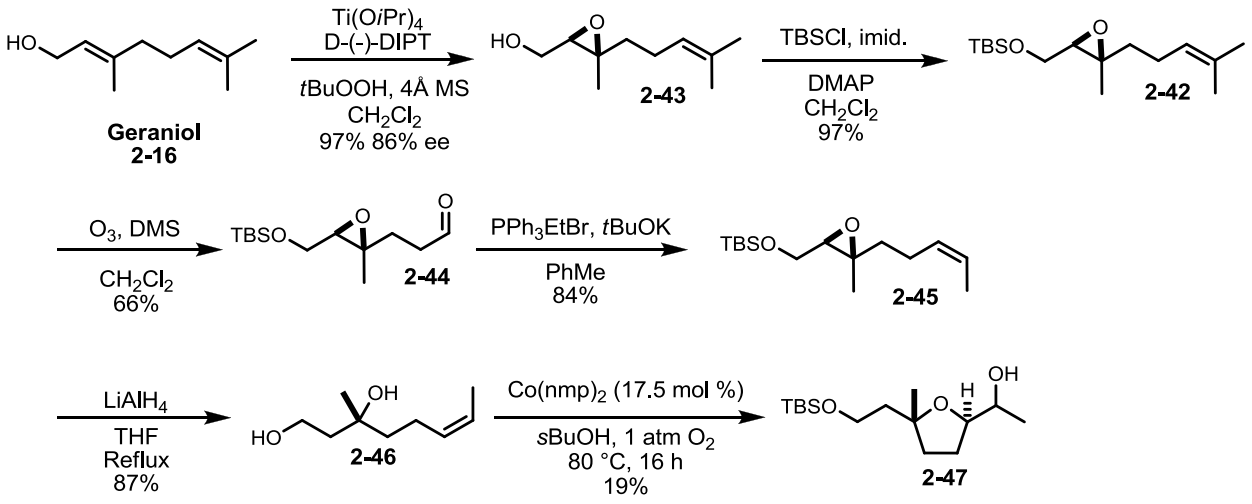
Scheme 2.12. Revised retrosynthesis.



THF alcohol **2-40** would come from cyclization of pentenol **2-41** which in turn would arise from epoxide **2-42** following cleavage of the alkene bond through ozonolysis, Wittig olefination and epoxide opening. The protected epoxide **2-42** would be arrived at through the elaboration of commercially available geraniol via a Sharpless asymmetric epoxidation and protection of the primary alcohol.

This synthetic route would employ yet another untested Mukaiyama cyclization substrate, a bishomoallylic tertiary alcohol possessing a di-substituted alkene. Such a cyclization would again be advantageous to extend the previously developed methodology to a new class of substrates. In addition the ability to conduct a Sharpless asymmetric epoxidation on geraniol would simplify the production of enantiomerically enriched material at an early stage.

Scheme 2.13. Route two forward synthetic efforts.



Sharpless epoxidation of geraniol was carried out readily to yield enantioenriched epoxide **2-43** in 97% yield and 86% ee as determined through Mosher's ester analysis (Scheme 2.13).[9] Protection of epoxide **2-43** as the TBS ether was accomplished in 97% yield. After acquiring the primary alcohol protected epoxy geraniol **2-42** the tri-substituted olefin was cleaved via ozonolysis followed by a reductive workup with dimethyl sulfide to yield epoxy aldehyde **2-44**. Wittig olefination of the aldehyde then provided access to alkene **2-45**. With

alkene **2-45** in hand an epoxide opening was all that remained in order to access key cyclization precursor **2-41**. Epoxide opening was carried out with $LiAlH_4$ in refluxing THF. The opened product was acquired however the opening occurred along with loss of the TBS protecting group providing diol **2-46**. The loss of the TBS group at this stage was inconsequential as it could be selectively re-protected at a later stage.

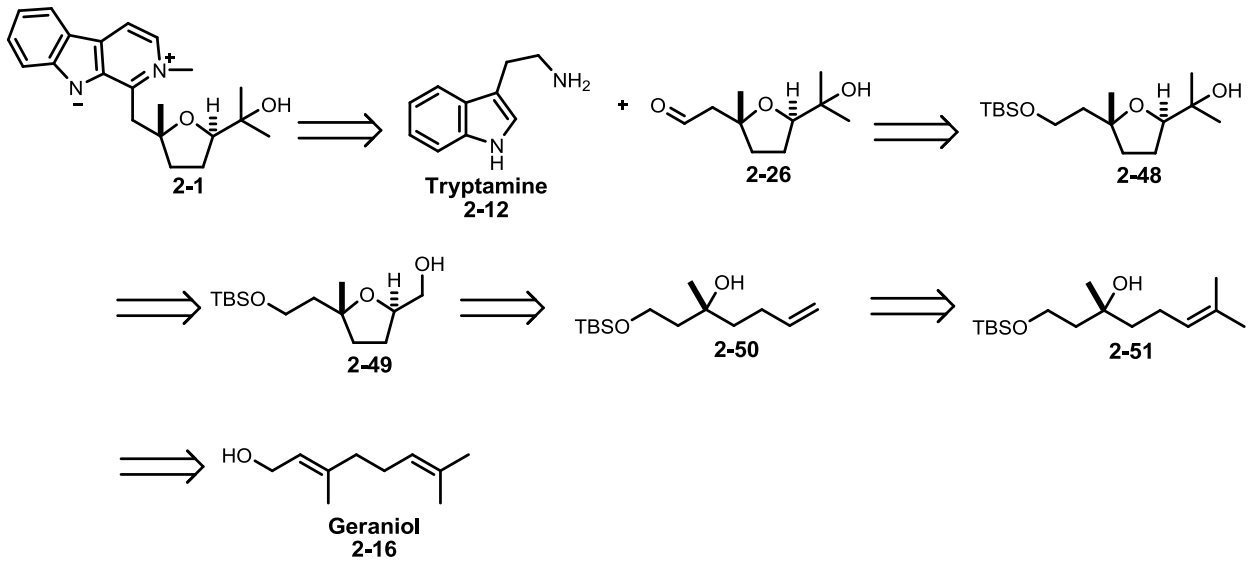
Pentenol **2-46** was then subjected to the standard oxidative cyclization conditions. Gratifyingly, the cyclization was successful producing THF **2-47** in 19% yield as a complex mixture of diastereomers.

The formation of THF **2-47** presents a new substrate class for this type of Mukaiyama cyclization with the $Co(nmp)_2$ catalyst however further optimization is required for the method to be effective within the synthetic route to chrysotricine. Given the low yield of the cyclization product this synthetic route was abandoned in favor of higher yielding alternatives.

2.6 Synthetic Route Three

The Mukaiyama cyclization of tertiary pentenols bearing di and tri substituted alkenes proved to be an ineffective strategy towards the synthesis of chrysotricine. As a result a third synthetic strategy towards chrysotricine was developed (Scheme 2.14). Similarly to route two, route three would see THF aldehyde **2-26** arising from tertiary alcohol **2-48** following deprotection of the primary alcohol and oxidation.

Scheme 2.14. Route three retrosynthetic analysis.

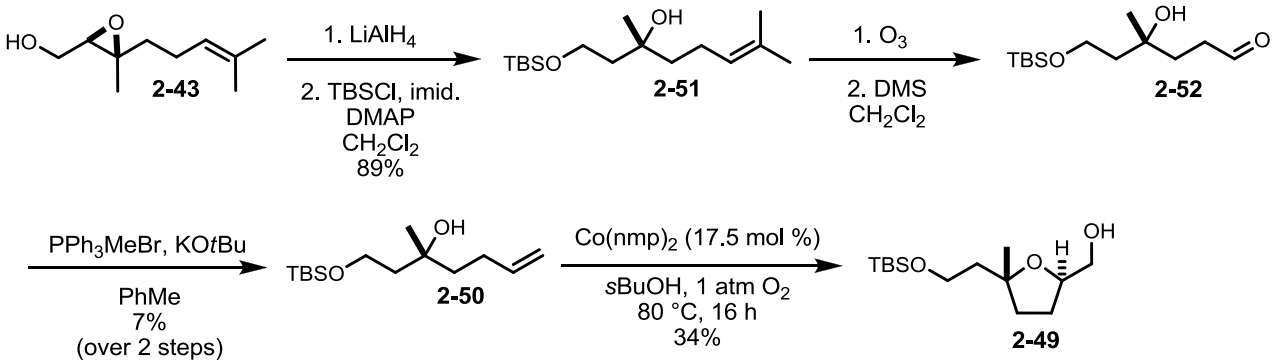


The tertiary alcohol would arise from THF methanol **2-49** via a stepwise oxidation of the free alcohol and double methyl nucleophile addition. THF methanol **2-49** would arise from a Mukaiyama oxidative cyclization of key cyclization substrate **2-50**, a tertiary pentenol bearing a monosubstituted alkene. As cyclizations of these substrates had previously been established it was thought that use of the monosubstituted alkene would provide for greater yields and a more effective synthetic strategy. The pentenol would come from protected hydroxy alkene **2-51** following ozonolysis of the alkene and Wittig olefination of the resulting aldehyde. Hydroxy alkene **2-51** would arise from an opening of 2,3-epoxy-geraniol followed by selective protection of the primary alcohol.

Forward synthetic progress began again with previously synthesized 2,3-epoxy geraniol **2-43** (Scheme 2.15). Opening of 2,3-epoxy-geraniol followed by selective TBS protection of the primary alcohol was accomplished in 89% yield over two steps. Epoxide opening was conducted at an earlier stage in this synthetic route in order to avoid loss of the silyl protecting group as previously observed. Ozonolysis of **2-51** followed by reductive workup provided a complex product mixture most likely due to formation of a hemiacetal through addition of the tertiary

alcohol to the newly formed aldehyde. Purification of this material proved challenging and thus crude material was transferred directly onward to the next step. Wittig olefination of the crude mixture yielded pentenol **2-50** in a low 7% yield over two steps.

Scheme 2.15. Route three forward synthetic efforts.



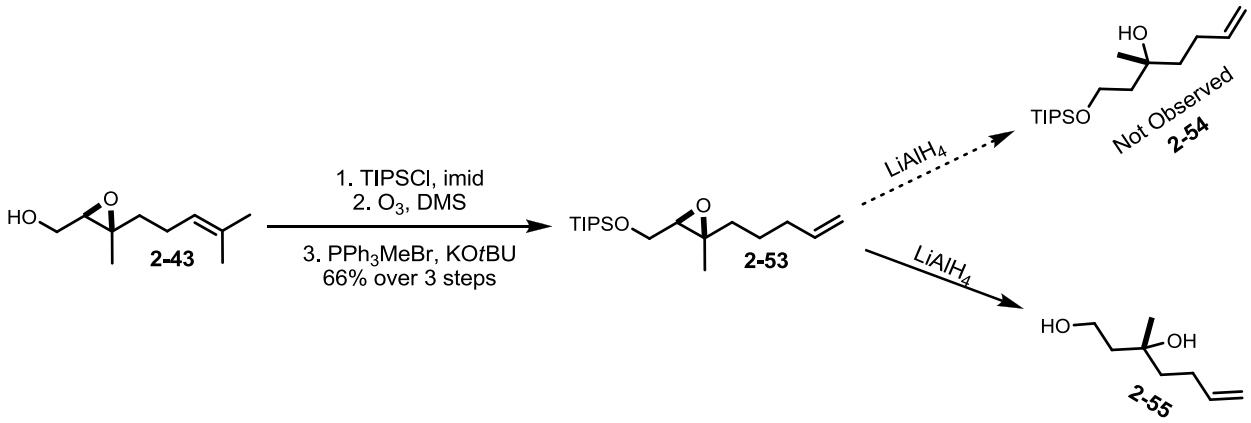
Key cyclization substrate **2-50** was subjected to oxidative cyclization under the modified Mukaiyama procedure. Gratifyingly after exposing the pentenol to pre-oxidized $Co(nmp)_2$ (17.5%) for 16 hours in *sec*-butanol at 80 °C, THF methanol was acquired in 34% yield (39% BRSM) as a 3:1 mixture of diastereomers. The yield of this product was along the lines of other THFs prepared via this method. We hoped that further optimization of this reaction would enable us to increase the yield slightly.

Having exhausted a significant amount of material in efforts to obtain THF methanol **2-49** production of larger quantities of starting materials was required. A significant loss of material had occurred during the ozonolysis and Wittig reaction sequence. At this stage we chose to return to a previous strategy of late stage epoxide opening in order to avoid the complex mixture seen following ozonolysis of tertiary alcohol **2-51**. This strategy would be more effective but only if loss of protecting groups could be avoided during epoxide opening.

To circumvent this problem, the more robust triisopropylsilyl (TIPS) protecting group was chosen to mask the primary alcohol of geraniol. Epoxide **2-53** was acquired in a three step TIPS protection, ozonolysis and Wittig methylation sequence in 66% overall yield.

Unfortunately treatment of the epoxide with $LiAlH_4$ did not produce opened product with retention of the silyl protecting group as desired. Monitoring of the reaction mixture by TLC revealed slow and incomplete conversion to diol **2-55** with loss of the TIPS protecting group (Scheme 2.16).

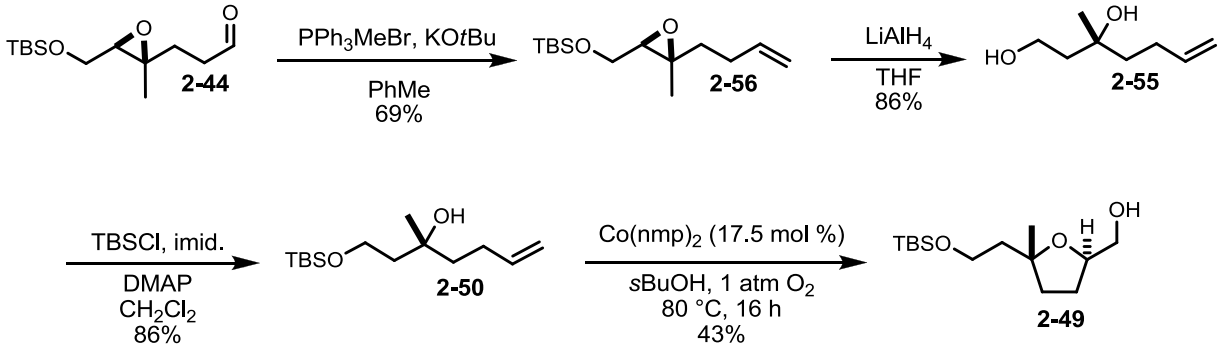
Scheme 2.16. Attempted opening of TIPS protected 2,3-epoxy-geraniol.



2.7 Synthetic Route Four

Undeterred by the setbacks of the previous synthetic efforts, we compiled all of the successful steps from the previous synthetic routes in order to develop a route with the most effective steps as possible. Towards that end, a fourth synthetic route to chrysotricine was established. In this approach late stage epoxide opening along with loss of silyl protecting group would be followed by selective re-protection of the primary alcohol of **2-55** (Scheme 2.17).

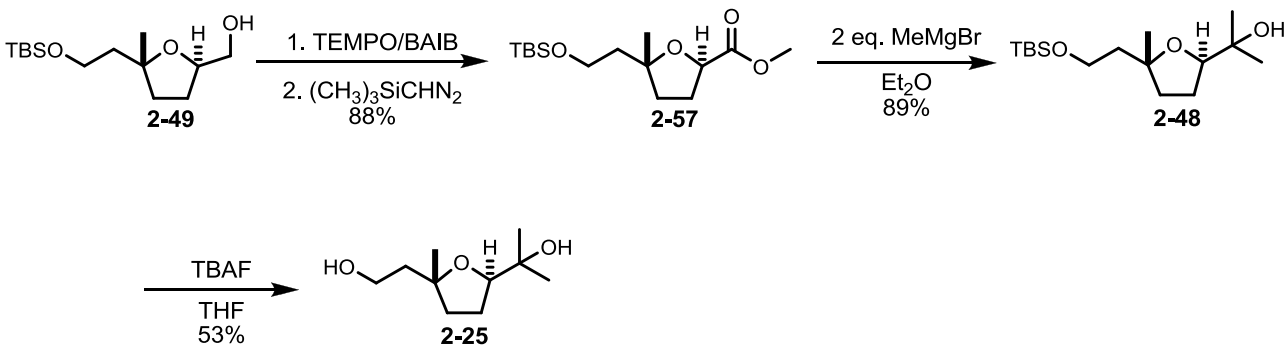
Scheme 2.17. Chrysotricine synthetic route four.



Starting from aldehyde **2-44**, Wittig olefination with the ylide of methytriphenylphosphonium bromide yielded alkene **2-56**. Opening with $LiAlH_4$ in refluxing THF provided diol **2-55** in 86% yield. The primary alcohol was then selectively re-protected as the TBS ether in 86% yield providing cyclization substrate **2-50**. With the cyclization substrate once again in hand cyclization was carried out to provide protected THF methanol **2-49** this time in 43% yield (52% BRSM) as a 3:1 mixture of diastereomers and improved yield over the previous cyclization.

Protected THF methanol **2-49** was carried forward by oxidation of the primary alcohol to its corresponding carboxylic acid with a TEMPO/BAIB oxidation system (Scheme 2.18).[10] Methylation of the resulting crude carboxylic acid was accomplished with trimethylsilyldiazomethane to provide ester **2-57** over two steps in 88% yield.[11] Tertiary alcohol **2-48** was then acquired through a sequential double methyl Grignard addition and overall yield of 89%. Finally, removal of the TBS protecting group was accomplished using TBAF to provide THF alcohol **2-25** in 53% yield. THF alcohol **2-25**, constitutes a formal synthesis of chrysotricine based on the total synthesis of Liang and coworkers.

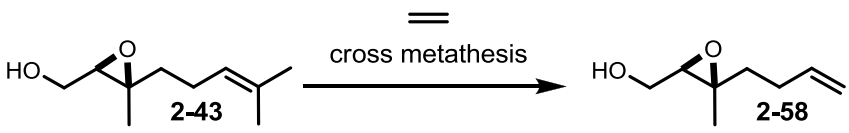
Scheme 2.18. Completion of formal synthesis.



With THF diol **2-25** in hand only five synthetic steps remained to the completion of chrysotricine. Before embarking on the remaining forward synthetic steps however we chose to go back and optimize the route thus far in order to create a more effective synthesis to carry through large quantities of material. Despite having formed the formal synthetic product, several of the steps in getting to the product had been low yielding; for example the Wittig olefination was challenging on large scale in terms of purification given the difficulty in removal of the significant quantity of phosphine oxide byproduct formed. Additionally, ozonolysis products were difficult to reproduce with consistent yield.

Our optimization efforts began with the ozonolysis/Wittig olefination sequence with the goal of replacing the two steps with a one-step conversion of protected 2,3-epoxy geraniol **2-43** directly to alkene **2-58**. The most direct method for such a transformation would be a cross metathesis of **2-43** with ethylene gas to effectively convert the tri-substituted alkene of geraniol to the desired mono-substituted alkene (Scheme 2.19).

Scheme 2.19. Direct conversion of **2-43** to **2-58**.



Olefin cross metathesis has seen a significant increase in use for synthetic transformations since the development of more active catalyst systems such as the Grubb's and Hoveyda-Grubb's type catalysts (Figure 2.1). Despite this its application is still less common than other olefin metathesis methods such as ring opening metathesis polymerization (ROMP) and ring closing metathesis (RCM).[12] This can be attributed to several factors such as lower catalyst activity towards cross metathesis as compared to ROMP or RCM, lower product selectivity for the cross metathesis product (loss of yields due to homodimerization and secondary metathesis products), and poorer selectivity for stereochemistry in the newly formed olefin.

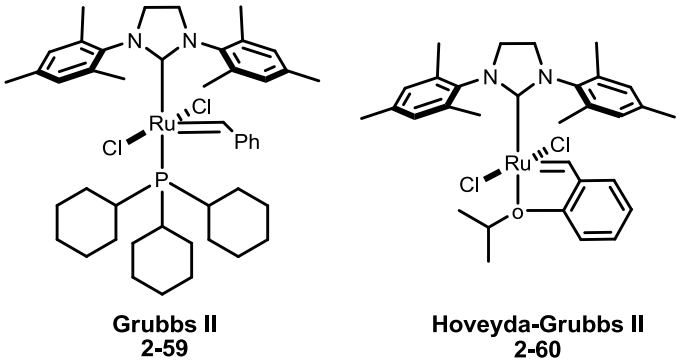


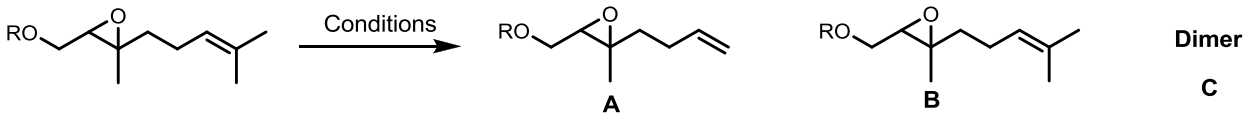
Figure 2.1. Cross metathesis catalysts.

With respect to cross metathesis of substrate **2-43** only one alkene is present for metathesis and the stereochemistry of the resulting product is not an issue. The anticipated difficulty with the transformation was with the activity of the catalyst towards the hindered tri-substituted alkene and the possible de-activation of the catalyst by the ethylene gas reagent.

Our work towards this transformation began with alkene **2-43** as the cross metathesis partner with ethylene gas (Table 2.1). Several metathesis conditions were probed including the use of a high pressure Parr reactor, however all attempts failed to produce all but trace amounts of product leaving starting material mostly untouched (entries 1-2). Undeterred we switched unprotected alcohol **2-43** for protected alcohol **2-42**.

Gratifyingly after bubbling ethylene gas through a solution of alkene **2-42** with a 5% catalyst loading of Grubbs second generation catalyst and heating the solution to reflux the desired cross metathesis product was acquired. The reaction however, failed to go to completion and a complex mixture of dimer product was also present. Separation of the dimer was possible via column chromatography; however the starting material and product were acquired as an inseparable mixture.

Table 2.1. Optimization of cross metathesis.



Entry	R	Catalyst	Reaction Time (h)	Catalyst Loading (%)	Concentration [mmol][a]	Product Ratio **A:B:C**
1	H	Grubbs II	24	5	0.33[b]	1:>16:0
2	H	Grubbs II	24	5	0.06[c]	1:>10:0
3	TBS	Grubbs II	24	5	0.14	1:1:0.4
4	TBS	Grubbs II	2	5	0.05	1:1:1.5
5	TBS	Grubbs II	50 min	5	0.016	1:1:0.1
6	TBS	Grubbs II	1.5	5	0.008	2:1:0
7	TBS	Grubbs II	3	5	0.008	3:1:0
8	TBS	Grubbs I	24	5	0.008	-
9	TBS	Grubbs II	3	1	0.008	1:1:0
10	TBS	Grubbs II	24	2	0.008	2:1:0
11	TBS	Grubbs II	24	2	0.008[c]	1:13:0
12	TBS	Hoveyda-Grubbs II	24	3	0.008	2:1:0.3
13	TBS	Grubbs II	24	3	0.008	2:1:0
14	TBS	Grubbs II	24	3	0.014[d]	5:1:0.2
15	TBS	Grubbs II	24	3	0.014[d]	3:1:0

[a] All reactions run at 0.5 mmol unless otherwise noted.
[b] 1 mmol scale
[c] Parr reactor, 80 psi ethylene gas
[d] 3.5 mmol scale

With the initial success of the cross metathesis reaction we looked for new conditions that would suppress dimer formation and yet force the reaction to completion. Increasing the dilution to 0.008M was effective at suppressing formation of the dimer product (entries 3-7). Lowering the catalyst loading to 1% and 2% yielded lower levels of conversion (entries 9-10). A 3% catalyst loading proved to be the most effective in terms of conversion and economy producing consistent and scalable result (entries 13-15). Use of the high pressure Parr reactor produced only a minor amount of product (entry 11). The Hoveyda-Grubbs second generation catalyst provided product albeit with a greater percentage of dimer side product (entry 12). Grubb's first generation catalyst failed to catalyze the reaction at all providing only starting material (entry 8). The failure of Grubb's I to catalyze the reaction was disappointing although not unexpected. The catalyst is less active than its second generation counterparts however from an operational standpoint its ineffectiveness was a setback as it is notably cheaper.

Having optimized the conditions for cross metathesis of **2-42** the issue of purification of the crude material became the next synthetic obstacle due to the starting material and product being completely inseparable through column chromatography. An alternative method had to be developed for their separation. We overcame this obstacle via an oxidative work up with *m*CPBA. In the presence of a mixture of alkenes with differing substitutions, *m*CPBA will selectively epoxidize the more electron rich alkenes first. In the case of the crude epoxide mixture, tri-substituted alkene starting material **2-42** and mono substituted alkene product **2-56**, the more electron rich **2-42** would be epoxidized first.

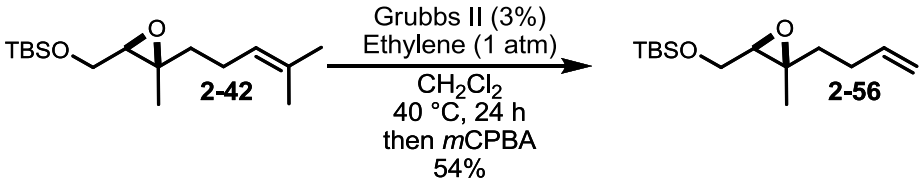
We believed that selective epoxidation of **2-42** within the crude reaction mixture would allow for it to be separated from the desired mono-substituted alkene product via column chromatography. Gratifyingly, when the crude reaction mixture was treated with *m*CPBA the desired alkene product was found to be separable from the epoxidized starting material allowing for isolation of **2-56** through column chromatography.

It should be noted that an attempt was made to carry the inseparable cross metathesis product/starting material mixture through an epoxide opening and oxidative cyclization sequence. Opening of the epoxide was possible but separation of the two opened products was still not attainable. Cyclization of the opened mixture produced substantially reduced yields of

THF product **2-49** most likely due to interference of the tri-substituted alkene contaminant with the $Co(nmp)_2$ catalyst.

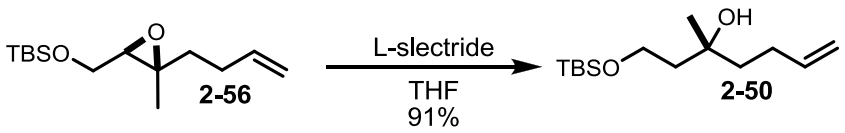
Overall, employing a 3% catalyst loading of Grubbs second generation catalyst in with alkene **2-42** and ethylene gas in CH_2Cl_2 followed by workup with *m*CPBA gave access to the cross metathesis product **2-56** in 54% yield (Scheme 2.20). This approach shows a significant improvement over the previous ozonolysis/Wittig olefination sequence. The cross metathesis procedure produced yields comparable to the two step sequence, was easier to employ, and provided quicker and more direct access to the desired product.

Scheme 2.20. Cross metathesis of **2-42** with ethylene gas.



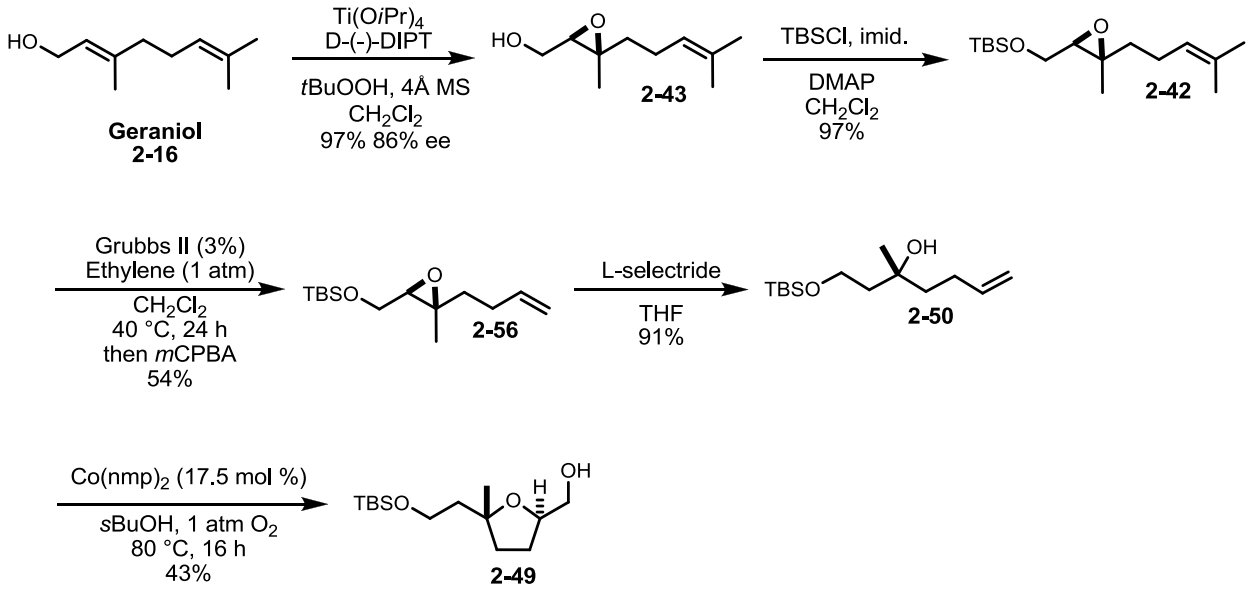
Having obtained a direct route to epoxide **2-56** we now focused our attention on the issue of epoxide opening and concurrent loss of silyl protecting group. Thankfully, with a short reactant screening it was discovered that Lithium tri-sec-butylborohydride (L-selectride) was able to open the epoxide without loss of the silyl protecting group and with higher overall yields (Scheme 2.21).

Scheme 2.21. Epoxide opening with L-selectride.



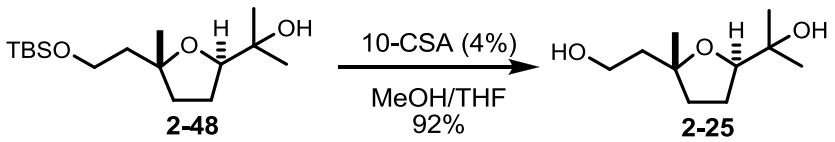
The optimization of several of the synthetic steps towards chrysotricine constituted an overall optimized route towards the natural product (Scheme 2.22). From geraniol, Sharpless epoxidation provided access to epoxide **2-43**. TBS protection was carried out in excellent yield affording protected epoxy geraniol **2-42**. Cross metathesis of **2-42** yielded alkene **2-56** in 54% yield in one step compared to a yield of 67% when the two step ozonolysis/Wittig sequence was employed. Opening of **2-56** was accomplished in 91% yield with L-selectride with retention of the silyl protecting group as compared to a yield of 86% over two steps when **2-56** was opened with $LiAlH_4$ with loss of the protecting group and then re-protected. Finally, oxidative cyclization of **2-50** provided THF methanol **2-49** in 43% yield and 3:1 dr. Overall the optimized route has five steps to key cyclization product **2-49** as compared to seven steps in the previous synthetic route.

Scheme 2.22. Optimized synthetic route.



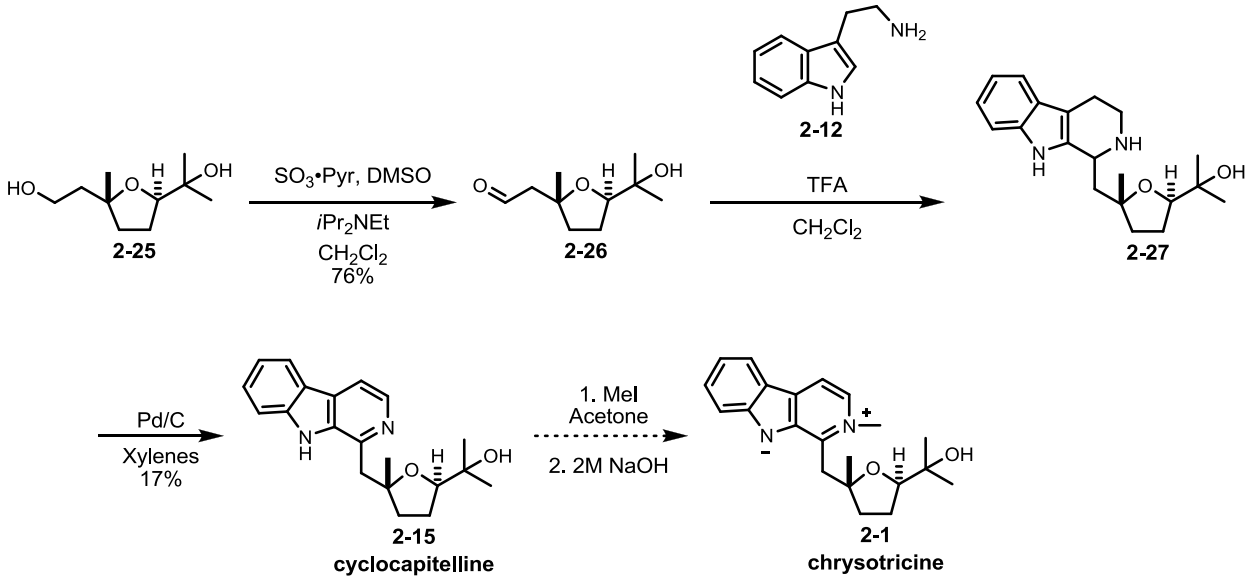
Further optimization was carried out when it was discovered that removal of the TBS protecting group of **2-48** could be accomplished in higher yield (92% vs 53%) when camphor sulfonic acid was employed in a catalytic amount in methanol/THF (Scheme 2.23).

Scheme 2.23. TBS deprotection with 10-CSA.



To complete the total synthesis of chrysotricine, the primary alcohol of **2-25** was oxidized under Parikh-Doering conditions to afford THF aldehyde **2-26** in 76% yield (Scheme 2.24).[13] When TFA was introduced to a mixture of tryptamine and THF aldehyde **2-26** tetrahydro-β-carboline **2-27** was acquired as a complex mixture of diastereomers along with a significant amount of byproducts. Separation of the Pictet-Spengler product followed by dehydrogenation with Pd/C afforded the β-carboline product **2-15** in 17% yield over two steps as a 1.5:1 mixture of diastereomers.[14]

Scheme 2.24. Completion of cyclocapitelline.



The synthesis of β-carboline product **2-15** constitutes a total synthesis of the natural product cyclocapitelline **2-3**. When comparing the NMR spectra of the 1.5:1 mixture of diastereomers to the reported spectra of cyclocapitelline it became evident that one set of diastereomeric peaks corresponded to cyclocapitelline with its *trans* stereochemistry at the 2 and 5 positions of the THF.[2] The peaks from the other diastereomer were found to correspond to isocyclocapitelline the *cis* diastereomer of cyclocapitelline. This spectroscopic evidence confirms that both *cis* and *trans* 2,5,5-THFs were formed during the oxidative cyclization reaction which formed the molecules THF core **2-49**. The major diastereomer corresponded to the *trans* diastereomer, cyclocapitelline, which confirms the oxidative cyclizations propensity for the formation of *trans* stereochemistry at the 2 and 5 positions of the THF products.

Following the procedure of Liang, an attempt was made to methylate the nitrogen of the β-carboline with methyl iodide followed by deprotonation to form chrysotricine. Analysis of the crude material after the deprotonation step indicated that chrysotricine may have been present however no product could be isolated through flash chromatography. Unmethylated starting material was recovered, but interestingly the dr had been eroded from 1.5:1 to 1:1. This may indicate that during the methylation reaction one diastereomer (the *trans*) is preferentially methylated over the other. Due to a lack of advanced material and lack of time synthetic efforts were ceased at this point.

2.8 Conclusion and Future Work

This chapter has outlined the synthetic work conducted towards the synthesis of β-carboline alkaloids cyclocapitelline and chrysotricine. A total synthesis of cyclocapitelline was completed providing the product as a 1.5:1 mixture of diastereomers. The formal synthesis of chrysotricine was also completed based on the total synthesis of Liang and coworkers.

The THF core of the natural products was formed through a Mukaiyama aerobic oxidative cyclization of a tertiary bishomoallylic alcohol with the $Co(nmp)_2$ catalyst. The formation of the core demonstrates the potential for $Co(nmp)_2$ to be employed in the synthesis of complex natural products.

Future work would see the completion of chrysotricine through a final methylation and deprotonation sequence.

2.9 Experimental

2.9.1 General Experimental Details

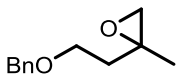
All reactions were conducted under Argon atmosphere unless otherwise indicated. All glassware was oven dried and cooled in a desiccator prior to use. Solvents and reagents were purified using standard methods.[15] All reactions were stirred with a magnetic stir bar. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by passing solvents through activated alumina columns. Isopropyl alcohol was used as obtained from Caledon Laboratory Chemicals. All other chemicals were reagent grade and used as obtained from commercial sources unless otherwise noted. The progress of reactions were monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by staining with potassium permanganate or ceric ammonium molybdate (CAM). Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[16]

^{1}H and ^{13}C NMR were acquired on 400 and 600 MHz spectrometers in deuterated chloroform. ^{1}H NMR were referenced to residual chloroform at δ 7.26 ppm and the center peak of the triplet at δ 77(t) ppm for ^{13}C NMR. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. EI mass spectra were obtained on a Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV.

2.9.2 Experimental Details

Compound **2-33** and **2-43** were prepared according to a literature procedures.[6,9]

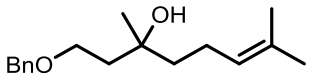
Compound 2-30a



To a flask containing Benzyl protected alcohol **2-33** (0.52 g, 3 mmol, 1.0 equiv) in 10 mL CH_2Cl_2 was added *m*CPBA (70%, 0.81 g, 3.3 mmol, 1.1 equiv) resulting in a pale yellow solution. The reaction mixture was allowed to stir for 2.5 hr. The resulting opaque white solution was quenched with saturated K_2CO_3 (20 mL). The layers were

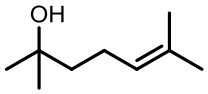
separated and aqueous extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with $NaHCO_3$, brine, dried over $MgSO_4$, filtered through Celite then concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (15% EtOAc/hexanes) to yield the title compound as a clear colourless oil (96%, 0.5540 g). R_f 0.5 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5 H), 4.50 (s, 2 H), 3.82 – 3.52 (m, 2 H), 2.70 (d, *J* = 4.7 Hz, 1 H), 2.59 (d, *J* = 5.1 Hz, 1 H), 1.98 – 1.91 (m, 2 H), 1.34 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 128.4, 127.6, 73.0, 66.6, 55.5, 54.0, 36.6, 21.5. HRMS *m/z* 192.1158 (calcd for $C_{12}H_{16}O_2$, 192.1150).

Compound 2-29a



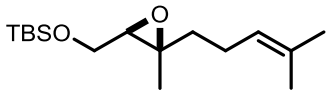
Prenyl chloride (0.23 mL, 2 mmol, 2 eq) was introduced to a suspension of Mg (0.05g, 2.05 mmol, 2.05 eq) in THF (2 mL). After 30 min the resulting Grignard reagent was transferred to a suspension of CuI (0.038g, 0.2 mmol, 0.2 eq) in THF (3 mL) at -78 °C. The solution was stirred for 20 minutes before introducing benzyl protected epoxide **2-30a** (0.19 g, 1 mmol, 1 eq) in THF (0.7 mL). The resulting solution was stirred for 10 min at -78 °C following which the cooling bath was removed. After 1 h excess cuprate was quenched with the addition of saturated NH_4Cl (10 mL). The resulting solution was filtered through Celite and the layers separated. The aqueous was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (10 % EtOAc/hexanes) to yield the title compound as a clear colourless oil (0.068 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5 H), 5.13 – 5.09 (m, 1 H), 4.52 (s, 2 H), 3.74 – 3.70 (m, 2 H), 2.09 – 1.98 (m, 2 H), 1.89 – 1.72 (m, 2 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.56 – 1.43 (m, 2 H), 1.19 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 128.4, 127.7, 124.5, 73.4, 72.3, 67.5, 42.3, 39.8, 26.6, 25.7, 22.7, 17.6. HRMS *m/z* 263.2001 (calcd for $C_{17}H_{26}O_2+H^+$, 263.2006).

Compound 2-36



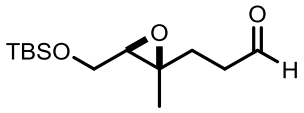
To a solution of 2,6-dimethylhept-5-en-2-ol (1.89 g, 15 mmol, 1 eq) in ether (50 mL) was added dropwise over 10 min, 3M methylmagnesium bromide (7.5 mL, 22.5 mmol, 1.5 eq). After 45 min excess Grignard reagent was quenched through addition of half-saturated NH_4Cl (20 mL). The layers were separated and the aqueous extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (10% EtOAc/Hexanes) to afford the title compound as a volatile clear colourless oil with a strong fruity fragrance (1.69 g, 79 %). R_f 0.36 (20% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 5.12-5.15 (m, 1 H), 2.06 (dddd, *J* = 7.0, 7.0, 7.0, 7.0 Hz, 2 H), 1.69 (s, 3 H), 1.63 (s, 3 H), 1.51 (ddd, *J* = 5.9, 8.8 Hz, 2 H), 1.30 (s, 1 H), 1.22 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 124.4, 71.0, 43.6, 29.2, 25.7, 23.1, 17.6; HRMS *m/z* 143.1437 (calcd for $C_9H_{18}O+H^+$, 143.1430).

Compound 2-42



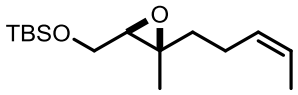
Epoxide **2-43** (4.0 g, 23 mmol, 1 eq) was taken up in CH_2Cl_2 (100 mL). To the resulting solution were added imidazole (3.4 g, 50 mmol, 2.2 eq), TBSCl (3.5 g, 23 mmol, 1 eq), and DMAP (0.28 g, 2.3 mmol, 0.1 eq). The reaction was monitored by TLC for completion. On depletion of the starting material half-saturated $NaHCO_3$ (50 mL) was added. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (2% EtOAc/Hexanes-10% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (6.32 g, 97%). R_f 0.69 (10% EtOAc/Hexanes); ^{1}H NMR **(**400 MHz, $CDCl_3$) δ 5.07-5.12 (m, 1 H), 3.69-3.77 (m, 2 H), 2.90 (t, *J* = 5.3 Hz, 1 H), 2.04-2.11 (m, 2 H), 1.63-1.70 (m, 1 H), 1.68 (d, *J* = 1.2 Hz, 3 H), 1.60 (s, 3 H), 1.41-1.49 (m, 1 H), 1.26 (s, 3 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 123.5, 63.2, 62.3, 60.5, 38.6, 25.9, 25.7, 23.8, 18.3, 17.6, 16.7, -5.2, -5.3; HRMS *m/z* 285.2243 (calcd for $C_{16}H_{32}O_2Si+H^+$, 285.2244).

Compound 2-44



Protected epoxide **2-42** (0.285 g, 1 mmol, 1 eq) was taken up in CH_2Cl_2 (20 mL) and cooled to -78 °C. Ozone was bubbled through the solution (open to atmosphere) until excess blue ozone could be seen. The reaction was then placed under Argon (balloon) and dimethyl sulfide (0.22 mL, 3 mmol, 3 eq) was introduced. The resulting solution was allowed to warm to room temperature following which it was poured into water (30 mL). The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (5% EtOAc/Hexanes-10% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.696 g, 66 %). R_f 0.39 (20% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 9.78 (s, 1 H), 3.73 (d, *J* = 5.3 Hz, 2 H), 2.91 (t, *J* = 5.3 Hz, 1 H), 2.52-2.54 (m, 2 H), 1.86-1.97 (m, 2 H), 1.28 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 62.8, 62.0, 59.5, 39.1, 30.1, 25.9, 18.3, 17.0, -5.2, -5.4; HRMS *m/z* 259.1729 (calcd for $C_{13}H_{26}O_3Si+H^+$, 259.1724).

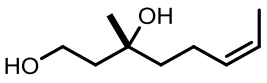
Compound 2-45



Ethyltriphenylphosphonium bromide (1.86 g, 5 mmol, 5 eq) was dissolved in toluene (30 mL) and cooled to 0 °C. To the resulting solution was added KO*t*Bu (0.56 g, 5 mmol, 5 eq). The resulting ylide was allowed to stir for 30 min before cooling to -78 °C. Aldehyde **2-44** in 10 mL toluene was then introduced and the reaction monitored by TLC for completion. Following depletion of the starting material water (30 mL) was introduced. The layers were separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (5% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.228 g, 84%). R_f 0.73 (20% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 5.43-5.49 (m, 1 H), 5.35-5.39 (m, 1 H), .37 (dd, *J* = 5.3, 2.4 Hz, 2 H), 2.91 (t, *J* = 5.3 Hz, 1 H), 2.10-2.20 (m, 2 H), 1.70 (ddd, *J* = 14.1, 8.8, 6.5 Hz, 1 H), 1.61-1.62 (m, 3 H), 1.48 (ddd, *J* = 13.5, 9.4, 6.5 Hz, 1 H), 1.28 (s, 3 H), 0.91 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100

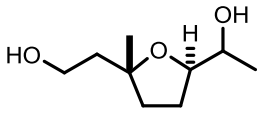
MHz, $CDCl_3$) δ 129.4, 124.4, 63.2, 62.2, 60.4, 38.3, 25.9, 22.6, 18.3, 16.7, 12.7, -5.4; HRMS *m/z* 271.2090 (calcd for $C_{15}H_{30}O_2Si+H^+$, 271.2088).

Compound 2-46



A suspension of $LiAlH_4$ (0.045 g, 1.2 mmol, 1.5 eq) in THF (5 mL) was cooled to 0 °C. To the suspension was added Alkene **2-45** (0.214 g, 0.8 mmol, 1 eq) in 6 mL THF. The ice bath was then removed and the reaction heated to reflux and left to stir overnight. The reaction mixture was allowed to cool to room temperature and then excess $LiAlH_4$ was quenched by slow addition of water (10 mL). The layers were separated and the aqueous extracted with ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (70 % EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.110 g, 87%). R_f 0.26 (70% EtOAc/Hexanes); ^{1}H NMR **(**400 MHz, $CDCl_3$) δ 5.37-5.51 (m, 2 H), 3.84-3.95 (m, 2 H), 2.62 (m, 1 H), 2.31 (m, 1 H), 2.08-2.16 (m, 2 H), 1.82 (ddd, *J* = 14.5, 7.4, 4.3 Hz, 1 H), 1.65-1.72 (m, 1 H), 1.63 (d, *J* = 7.4 Hz, 3 H), 1.56-1.60 (m, 2 H), 1.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.2, 124.3, 73.9, 59.9, 42.1, 41.6, 26.7, 21.6, 12.7; HRMS *m/z* 159.1386 (calcd for $C_9H_{18}O_2+H^+$, 159.1380).

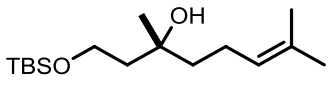
Compound 2-47



A flask containing previously prepared $Co(nmp)_2$ (0.062 g, 0.11 mmol, 0.175 eq) was evacuated and refilled with oxygen. [17] *i*PrOH (3 mL) was introduced followed by *t*BuOOH (4 M in toluene, 0.03 mL, 0.11 mmol, 0.175 eq) and the resulting solution was heated to 50 °C. [18] After 1 h the solvent removed under reduced pressure to afford oxidized $Co(nmp)_2$ as green crystals. The flask containing the oxidized catalyst was then evacuated and refilled with oxygen. Pentenol **2-46** (0.104 g, 0.65 mmol, 1 eq) in 2 mL *s*BuOH was then introduced and the resulting solution heated to 80 °C. After 16 h solvent was removed under reduced pressure and the residue passed through a plug of silica on Celite with excess EtOAc (50 mL). Solvent was then removed under reduced pressure and the residue purified by flash chromatography (80% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.019 g, 17 %) as a complex mixture of diastereomers. ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 5.12-5.14 (m, 1 H), 3.86-3.95 (m, 3 H), 3.73-3.82 (m, 1 H), 3.18-3.20

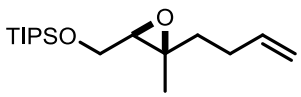
(m, 1 H), 1.68-1.95 (m, 6 H), 1.29 (s, 3 H), 1.11-1.88 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.2, 84.1, 83.4, 70.7, 67.6, 67.3, 59.8, 59.7, 58.4, 41.8, 41.7, 41.6, 38.3, 38.2, 37.7, 29.7, 27.8, 26.7, 26.3, 25.7, 24.2, 24.1, 19.2, 18.4, 17.9; HRMS *m/z* 175.1339 (calcd for $C_9H_{18}O_3$+H^+, 175.1329).

Compound 2-51



Epoxy alkene **2-43** (1.0g, 5.87 mmol, 1 eq) in THF (10 mL) was added to a suspension of $LiAlH_4$ (0.334 g, 8.81 mmol, 1.5 eq) in THF (10 mL) at 0 °C. The resulting solution was allowed to warm to room temperature. After 5 h the reaction was cooled to 0 °C and diluted with ether (10 mL). Excess $LiAlH_4$ was then quenched by the addition of water (10 mL). The layers were separated and the aqueous extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue (1.021 g) was then taken up in CH_2Cl_2 (50 mL). To the resulting solution were added imidazole (0.885 g, 13 mmol, 2.2 eq), TBSCl (0.889 g, 5.9 mmol, 1 eq), and DMAP (0.072 g, 0.59 mmol, 0.1 eq). After 2 h the reaction mixture was poured into half-saturated NH_4Cl (100 mL). The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. The residue was purified by flash chromatography to afford the title compound as a clear colourless oil (1.50 g, 89% over 2 steps). R_f 0.8 (40% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 5.12-5.14 (m, 1 H), 3.87-3.93 (m, 2 H), 3.71 (s, 1 H), 1.98-2.10 (m, 2 H), 1.73-1.78 (m, 1 H), 1.69 (s, 3 H), 1.63-1.68 (m, 1 H), 1.62 (s, 3 H), 1.45-1.56 (m, 2 H), 1.21 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 124.7, 72.6, 60.7, 42.3, 41.3, 26.4, 25.8, 25.7, 22.7, 18.1, 17.6, -5.6; HRMS *m/z* 287.2406 (calcd for $C_{16}H_{34}O_2Si$+H^+, 287.2401).

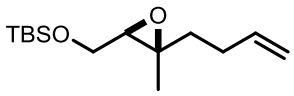
Compound 2-53



To a solution of epoxy alkene **2-43** (0.50 g, 2.9 mmol, 1 eq) in 25 mL CH_2Cl_2 was added imidazole (0.592 g, 8.7 mmol, 3 eq). TIPSCl (0.9 mL, 4.4 mmol, 1.5 eq) was then introduced and the resulting solution stirred for 2 h. The reaction mixture was then diluted with ether (25 mL) and the layers separated. The organic layer was washed with brine, water, dried over $MgSO_4$, filtered through Celite and concentrated under

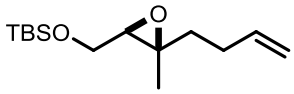
reduced pressure. The resulting crude material was then ozonized following the synthesis of **2-44** and then subjected to Wittig olefination as carried out for **2-56** to afford after purification of the Wittig product by flash chromatography (5% EtOAc/Hexanes) the title compound as a clear colourless oil (0.866 g, 66% over 3 steps). R_f 0.75 (20% EtOAc/Hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (dddd, *J* = 17.0, 10.0, 6.5, 6.5 Hz, 1 H), 5.02-5.05 (m, 1 H), 4.95-4.98 (m, 1 H), 3.81 (dd, *J* = 7.6, 5.3 Hz, 2 H), 2.94 (t, *J* = 5.2 Hz, 1 H), 2.12-2.22 (m, 2 H), 1.75 (ddd, *J* = 14.1, 9.4, 5.9 Hz, 1 H), 1.53 (ddd, *J* = 14.7, 10.0, 7.0 Hz, 1 H), 1.28 (s, 3 H), 1.06-1.12 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 114.9, 63.3, 62.4, 60.2, 37.8, 29.4, 17.9, 16.7, 11.9; HRMS *m/z* 299.2407 (calcd for $C_{17}H_{34}O_2Si+H^+$, 299.2401).

Compund 2-56



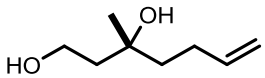
KO*t*Bu (3.37 g, 30 mmol, 2 eq) in 50 mL of toluene was cooled to 0 °C. To the resulting suspension was added methyltriphenylphosphonium bromide (10.72 g, 30 mmol, 2 eq) and the resulting yellow ylide solution stirred for 30 min. The ylide was cooled to – 78 °C and aldehyde **2-44** (3.87 g, 14.9 mmol, 1 eq) in 40 mL toluene was introduced. The resulting solution was stirred for 25 min at – 78 °C then allowed to warm to 0 °C. After 1 h the reaction mixture was poured into water (50 mL). The layers were separated and the aqueous extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (2% EtOAc/Hexanes-5%EtOAc/Hexanes) to afford the title compound as a clear colourless oil (2.62 g, 69%). R_f 0.58 (10% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 16.4, 10.0, 6.5, 6.5 Hz, 1 H), 5.01-5.05 (m, 1 H), 4.95-4.98 (m, 1 H), 3.73 (dd, *J* = 5.3, 1.8 Hz, 2 H), 2.90 (t, *J* = 5.3 Hz, 1 H), 2.11-2.21 (m, 2 H), 1.73 (ddd, *J* = 14.1, 9.4, 5.9 Hz, 1 H), 1.53 (ddd, *J* = 13.5, 10.0, 6.5 Hz, 1 H), 1.27 (s, 3 H), 0.91 (s, 9 H), 0.09 (s. 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 114.9, 63.2, 62.2, 60.3, 37.8, 29.4, 25.9, 18.3, 16.7, -5.2, -5.4; HRMS *m/z* 257.1942 (calcd for $C_{14}H_{28}O_2Si+H^+$, 257.1931).

Compound 2-56



Cross Metathesis Procedure: Grubb's second generation catalyst (0.089 g, 0.11 mmol, 0.03 eq) was placed in a three neck flask equipped with a reflux condenser. The flask was evacuated and then re-filled with argon. CH_2Cl_2 (248 mL) was then introduced. Alkene **2-42** (1.0 g, 3.5 mmol, 1 eq) was introduced neat with a syringe and the syringe rinsed with CH_2Cl_2 (2 mL). The reaction vessel was cooled to –78 °C and ethylene was bubbled through the solution for 5 min. The reaction was placed under an atmosphere of ethylene (balloon) and then heated a 40 °C. After 24 h the flask was then allowed to cool to room temperature following which solvent was removed under reduced pressure. The residue was filtered through a plug of silica on Celite with EtOAc then concentrated under reduced pressure. The crude product containing (0.303 g, 1.06 mmol, 1 eq) of cross metathesis starting material as determined by NMR analysis of the crude reaction mixture was then taken up in CH_2Cl_2 (50 mL) and cooled to °C. *m*CPBA (70%, 0.523 g, 2.12 mmol, 2 eq) was then introduced. After 30 min, half-saturated $NaHCO_3$ (20 mL) was introduced. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (3% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.484 g, 54%).

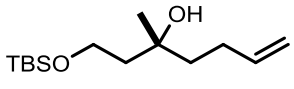
Compound 2-55



To a suspension of $LiAlH_4$ 0.114 g, 3 mmol, 1.5 eq) in 20 mL THF was added epoxy alkene **2-56** (0.513 g, 2 mmol, 1 eq) in 10 mL THF and the resulting solution heated to reflux. After 12 h the reaction was allowed to cool to room temperature and excess $LiAlH_4$ was quenched through the slow addition of water (20 mL). The layers were separated and the aqueous extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (70% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.247g, 86%). R_f 0.16 (40% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 16.8, 10.2, 6.6, 6.6 Hz, 1 H), 5.03-5.09 (m, 1 H), 4.96-4.99 (m, 1 H), 3.84-3.96 (m, 2 H), 2.46 (t, *J* = 5.1 Hz, 1 H), 2.26 (s,

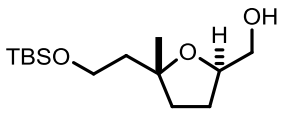
1 H), 2.11-2.18 (m, 2 H), 1.81 (ddd, *J* = 14.8, 7.8, 4.7 Hz, 1 H), 1.60-1.72 (m, 3 H), 1.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 114.6, 73.8, 59.8, 41.5, 28.4, 26.72, 26.65; HRMS *m/z* 145.1225 (calcd for $C_8H_{16}O_2+H^+$, 145.1223).

Compound 2-50



Alkene **2-56** (0.5 g, 1.9 mmol, 1 eq) and THF (15 mL) were combined in a flask equipped with a condenser. L-selectride (1M in THF, 3.8 mL, 3.8 mmol, 2 eq) was introduced through the condenser and the resulting solution heated to 60 °C. After 20.5 h the reaction mixture was allowed to cool to room temperature. Water (10 mL) was introduced dropwise through the condenser. The layers were separated and the aqueous extracted with ether (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (8% EtOAc/Hexanes) to afford the title compound as clear colourless oil (0.446 g, 91%). R_f 0.55 (20% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.0, 10.0, 6.5, 6.5 Hz, 1 H), 5.02-5.05 (m, 1 H), 4.93-4.95 (m, 1 H), 3.90 (ddd, *J* = 11.7, 7.6, 4.1 Hz, 2 H), 3.77 (s, 1 H), 2.07-2.20 (m, 2 H), 1.76 (ddd, *J* = 14.7, 8.2, 4.7 Hz, 1 H), 1.53-1.66 (m, 3 H), 1.21 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 114.1, 72.5, 60.7, 41.5, 41.3, 28.4, 26.3, 25.8, 18.1, -5.63; HRMS *m/z* 259.2088 (calcd for $C_{14}H_{30}O_2Si+H^+$, 259.2088).

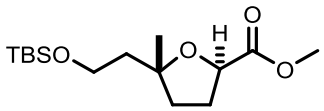
Compound 2-49



A flask containing previously prepared $Co(nmp)_2$ (0.170g, 0.3 mmol, 0.175 eq) was evacuated and refilled with oxygen. *i*PrOH (3 mL) was introduced followed by *t*BuOOH (4 M in toluene, 0.08 mL, 0.3 mmol, 0.175 eq) and the resulting solution was heated to 50 °C. After 1 h the solvent removed under reduced pressure to afford oxidized $Co(nmp)_2$ as green crystals. The flask containing the oxidized catalyst was then evacuated and refilled with oxygen. Pentenol **2-56** (0.462 g, 1 mmol, 1 eq) in 2 mL *s*BuOH was then introduced and the resulting solution heated to 80 °C. After 16 h solvent was removed under reduced pressure and the residue passed through a plug of silica on Celite with excess EtOAc (50 mL). Solvent was then removed under reduced pressure and the resulting crude material purified by flash chromatography (20% EtOAc/Hexanes-40% EtOAc/Hexanes) to afford the title

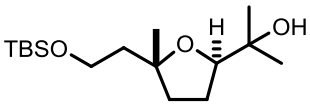
compound as a clear colourless oil (0.198 g, 43 %) as a 3:1 mixture of diastereomers. R_f 0.35 (40% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ [minor 4.09-4.13 (m, 1.0 H), 4.06 (dddd, *J* = 11.7, 5.9, 3.5, 3.5 Hz, 1 H), 3.67-3.81 (m, 5 H), [major 3.48 (dd, *J* = 11.2, 5.3 Hz, 1 H), minor 3.45 (dd, *J* = 11.2, 4.7 Hz, 1 H),] 1.88-1.97 (m, 4 H), 1.67-1.86 (m, 7 H), [major 1.23 (s, 3 H), minor 1.22 (s, 1 H)], [minor 0.9 (s, 4 H), major 0.89 (s, 9 H)], [minor 0.06 (s, 2 H), major 0.05 (s, 6 H)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7, 82.6,79.0, 78.6, 65.2, 64.9, 60.0, 59.8, 44.0, 43.5, 37.59, 37.55, 27.4, 27.2, 27.1, 26.2, 26.0, 25.9, 25.8, 18.34, 18.25, -5.3, -5.4; HRMS *m/z* 275.2044 (calcd for $C_{14}H_{30}O_3Si+H^+$, 275.2037).

Compound 2-57



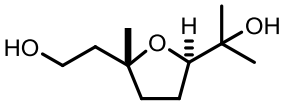
THF methanol **2-20** (.208 g, 0.76 mmol, 1 eq) was taken up in acetonitrile (3.8 mL) and water (3.8 mL). TEMPO (0.154 g, 1.0 mmol, 1.3 eq) and BAIB (0.857 g, 2.66 mmol, 3.5 eq) were then introduced sequentially. After 1.5 h the reaction mixture was diluted with EtOAc (5 mL) and water (5 mL). The layers were separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue (0.58 g, 2.01 mmol, 1 eq) was dissolved in toluene (16.1 mL) and freshly distilled MeOH (4.0 mL) and cooled to 0 °C. Trimethylsilyldiazomethane (2M in Hexane, 1.2 mL, 2.4 mmol, 1.2 eq) was introduced and the cooling bath removed. After 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.203 g, 88%) as a 3:1 mixture of diastereomers. R_f 0.23 (10% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ [minor 4.50 (d, *J* = 6.5 Hz, 0.14 H), major 4.48 (dd, *J* = 7.6, 6.5 Hz, 1 H)], 3.75-3.81 (m, 1 H), [major 3.74 (s, 3 H), minor 3.73 (s, 3 H)], 3.69-3.73 (m, 1 H), 2.27-2.33 (m, 1 H), 2.09-2.14 (m, 1 H), 1.93-1.98 (m, 1 H), 1.87-1.89 (m, 1 H), 1.69-1.83 (m, 4 H), [major 1.32 (s, 3 H), minor 1.24 (s, 3 H)], [minor 0.89 (s, 9 H), major 0.88 (s, 9 H)], [major 0.05 (s, 6 H), major 0.04 (s, 6 H)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 84.63,84.58,76.8, 76.4, 59.8, 59.7, 52.00, 51.95, 43.7, 43.5, 36.7, 36.5, 30.3, 30.2, 26.3, 26.0, 25.9**,** 18.2, -5.39; HRMS *m/z* 303.1989 (calcd for $C_{15}H_{30}O_4Si+H^+$, 303.1986).

Compound 2-48



Methylmagnesium bromide (3 M in ether, 0.48 mL, 1.45 mmol, 2.2 eq) was introduced to a solution ester **2-57** (0.202 g, 0.66 mmol, 1 eq) in ether (13 mL) at 0 °C. The cooling bath was removed and the reaction allowed to stir 1.5 h. Excess Grignard reagent was then quenched through the slow addition of half-saturated NH_4Cl (10 mL). The layers were separated and the aqueous extracted with ether (3 x 30 mL). The combine organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (10% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.177 g, 89%) as a 3:1 mixture of diastereomers. R_f 0.53 (30% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 3.71-3.81 (m, 4 H), 2.13 (s, 1 H), 1.91-1.74 (m, 7 H), 1.66-1.70 (m, 1 H), [minor 1.21 (s, 6 H), major 1.20 (s, 6 H)], [major 1.12 (s, 3 H), minor 1.11 (s, 3 H)], [minor 0.90 (s, 9 H), major 0.89 (s, 9 H)],[minor 0.064 (s, 3 H), minor 0.061 (s, 3 H), major 0.056 (s, 6 H)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.5, 84.9, 82.2, 82.1, 70.9, 70.7, 60.0, 59.9, 43.9, 43.8, 37.9, 37.8, 27.64, 27.57, 26.9, 26.4, 26.3, 26.1, 26.0, 25.9, 24.3, 24.1, 18.4, 18.3, -5.32; HRMS *m/z* 303.2358 (calcd for $C_{16}H_{34}O_3Si+H^+$, 303.2350).

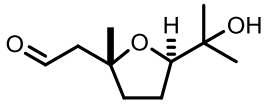
Compound 2-25



10-CSA (0.005 g, 0.022 mmol, 0.04 eq) was introduced to THF alcohol **2-48** (0.167 g, 0.55 mmol, 1 eq) in wet MeOH (7.1 mL) and THF (1.8 mL) and the reaction monitored for completion by TLC. On depletion of the starting material the reaction mixture was poured into half-saturated $NaHCO_3$ (10 mL). The layers were separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (80% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.095 g, 92%) as a 3:1 mixture of diastereomers. R_f 0.1 (50% EtOAc/Hexanes); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 3.92-3.95 (m, 0.2 H), 3.88-3.91 (m, 1 H), 3.82 (dd, *J* = 9.4, 5.3 Hz, 1 H), 3.75-3.79 (m, 1 H), 3.22 (brs, 1 H), 1.76-2.00 (m, 6 H), 1.70-1.74 (m, 1 H), 1.285 (s, 3 H), 1.28 (s, 1 H), 1.25 (s, 1 H), 1.23 (s. 1 H), 1.22 (s, 3 H), 1.125 (s, 3 H), 1.20 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.3, 85.7, 84.4, 83.9, 70.9, 70.3, 59.9, 41.9,

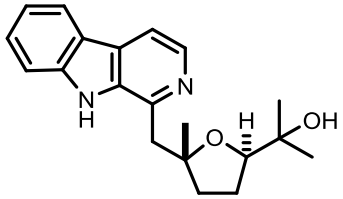
41.7, 38.6, 38.2, 27.7, 26.4, 25.9, 25.7, 25.4, 25.0, 24.4; HRMS *m/z* 189.1481 (calcd for $C_{10}H_{20}O_3+H^+$, 189.1485).

Compound 2-26



THF diol **2-25** (0.059 g, 0.31 mmol, 1 eq), *i*Pr_2NEt (0.36 mL, 2.1 mmol, 7 eq), and DMSO (0.1 mL, 1.5 mmol, 5 eq) were combined in CH_2Cl_2 (6 mL) at 0 °C. SO_3•Pyr complex (0.148 g, 0.93 mmol, 3 eq) was then added in one portion and the cooling bath removed. After one hour the half-saturated $NaHCO_3$ (10 mL) was introduced. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The residue was then purified by flash chromatography (50% EtOAc/Hexanes) to afford the title compound as a clear colourless oil (0.044g, 76%); R_f 0.27 (50% EtOAc/Hexanes) ^{1}H NMR **(**600 MHz, $CDCl_3$) δ [minor 9.85 (t, *J* = 3.1 Hz, 1 H), major 9.82 (t, *J* = 2.3 Hz, 1 H)], 3.80-3.85 (m, 1 H), 3.56-3.65 (m, 2 H), 2.00 (brs, 1 H), 1.80-1.95 (m, 4 H), [minor 1.38 (s, 3 H), major 1.34 (s, 3 H), [minor 1.225 (s, 3 H), major 1.22 (s, 3 H)], [major 1.13 (s, 3 H), 1.11 (s, 3 H)]; H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 202.1, 86.1, 85.7, 81.2, 81.1, 71.0, 70.7, 54.2, 54.1, 38.1, 38.0, 27.6, 27.4, 27.3, 26.2, 26.0, 24.4, 24.1; HRMS *m/z* 185.1172 (calcd for $C_{10}H_{18}O_3- H^+$, 185.1172).

Compound 2-15



A Solution of THF Aldehyde **2-26** (0.052 g, 0.28 mmol, 1 eq) and tryptamine (0.045 g, 0.28 mmol, 1 eq) in CH_2Cl_2 (8 mL) was cooled to – 78 °C. TFA (0.04 mL, 0.56 mmol, 2 eq) was introduced and the solution allowed to warm to room temperature over 2 h. Saturated $NaHCO_3$ (6 mL) was introduced and the layers separated. The aqueous was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (10% MeOH/CH_2Cl_2) to afford tetrahydro-β-carboline **2-27** as an inseparable mixture of diastereomers (0.027 g). **2-27** (0.027 g, 0.08 mmol, 1 eq) was taken up in xylenes (2 mL) and Pd/C (0.008 g) was introduced and the solution heated to reflux. After 1 h, the reaction mixture was allowed to cool to room temperature then filtered through Celite and concentrated

under reduced pressure. The residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford the title compound as an orange wax (0.016 g, 17% over 2 steps) as a 1.5:1 mixture of diastereomers. R_f 0.61 (20% MeOH/CH_2Cl_2); ^{1}H NMR **(**600 MHz, $CDCl_3$) δ 10.19 (brs 0.5 H), 9.79 (s, 1 H), [major 8.37 (d, *J* = 5.3 Hz, 1 H), minor 8.32 (m, 1 H)], [major 8.12 (d, *J* = 8.2 Hz, 1 H), minor 8.08 (d, *J* = 8.2 Hz, 1 H)], [major, 7.86 (d, *J* = 5.3 Hz, 1 H), minor 7.81 (d, *J* = 4.7 Hz, 1 H)], 7.50-7.54 (m, 2 H), 7.44 (d, *J* = 8.2 Hz, 1 H), 7.23-7.28 (m, 1 H), [minor 3.92 (dd, *J* = 76, 5.9 Hz, 1 H), major 3.58 (dd, *J* = 10.0, 5.3 Hz, 1 H)], [major 3.53 (d, *J* = 14.7 Hz, 1 H), minor 3.49 (s, 2 H), major 3.42 (d, *J* = 14.7 Hz, 1 H)], 2.14 (brs, 1 H), 1.91-2.04 (m, 5 H), 1.71-1.75 (m, 1 H), [Minor 1.31 (s, 3 H), major 1.32 (s, 3 H)], [major 1.28 (s, 3 H), minor 1.26 (m, 3 H), minor 1.22 (s, 3 H), major 1.11 (s, 3 H)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.9, 140.6, 138.3, 135.87, 135.78, 129.0, 128.9, 128.21, 128.7, 122.0, 121.8, 121.7, 121.6, 119.8, 119.6, 113.5, 113.2, 111.9, 111.7, 86.9, 86.4, 85.2, 84.1, 71.4, 70.3, 48.4, 39.0, 36.8, 28.2, 27.8, 27.6, 26.18, 26.15, 25.9, 24.1; HRMS *m/z* 324.1836 (calcd for $C_{20}H_{24}N_2O_2$, 324.1838).

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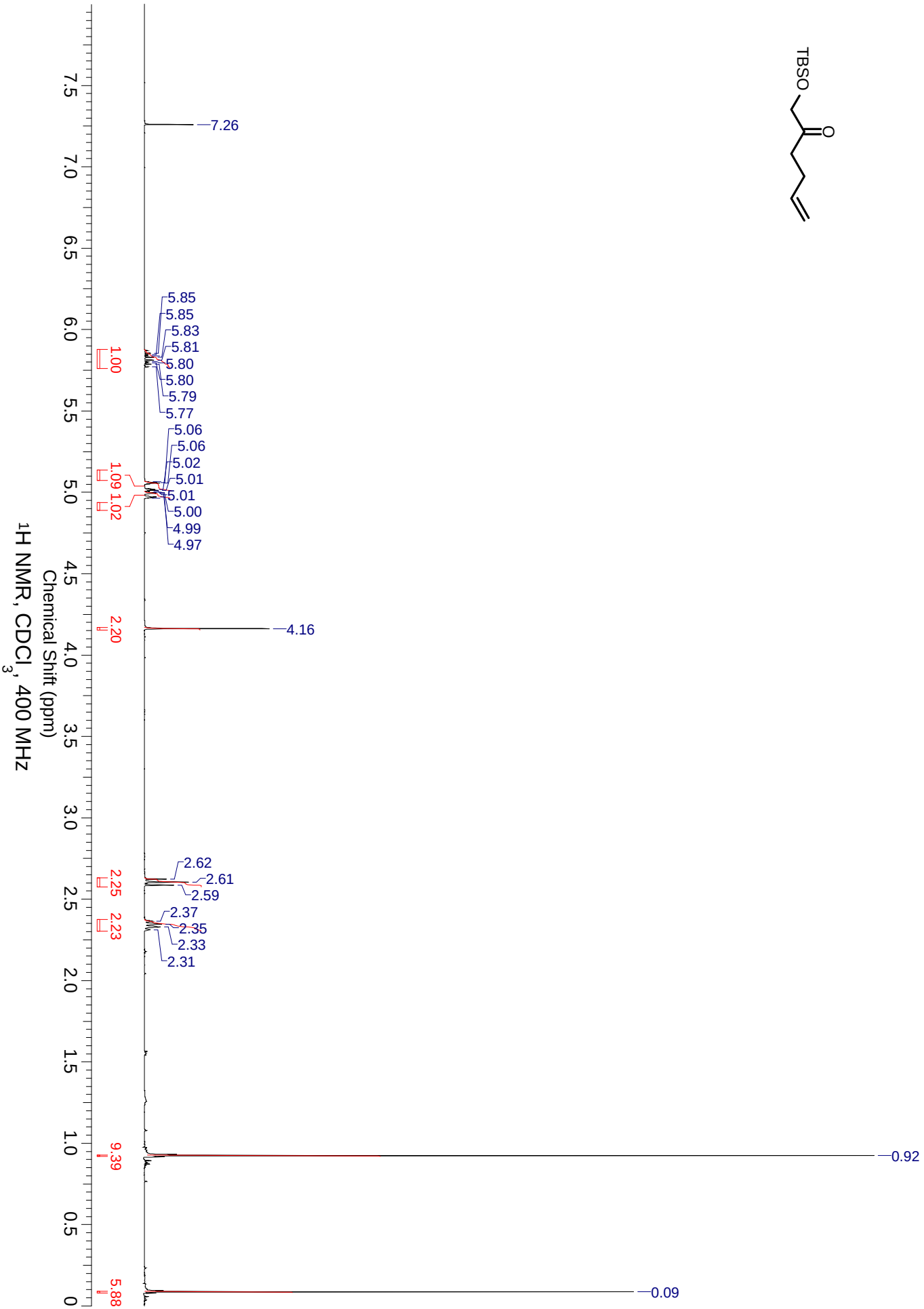
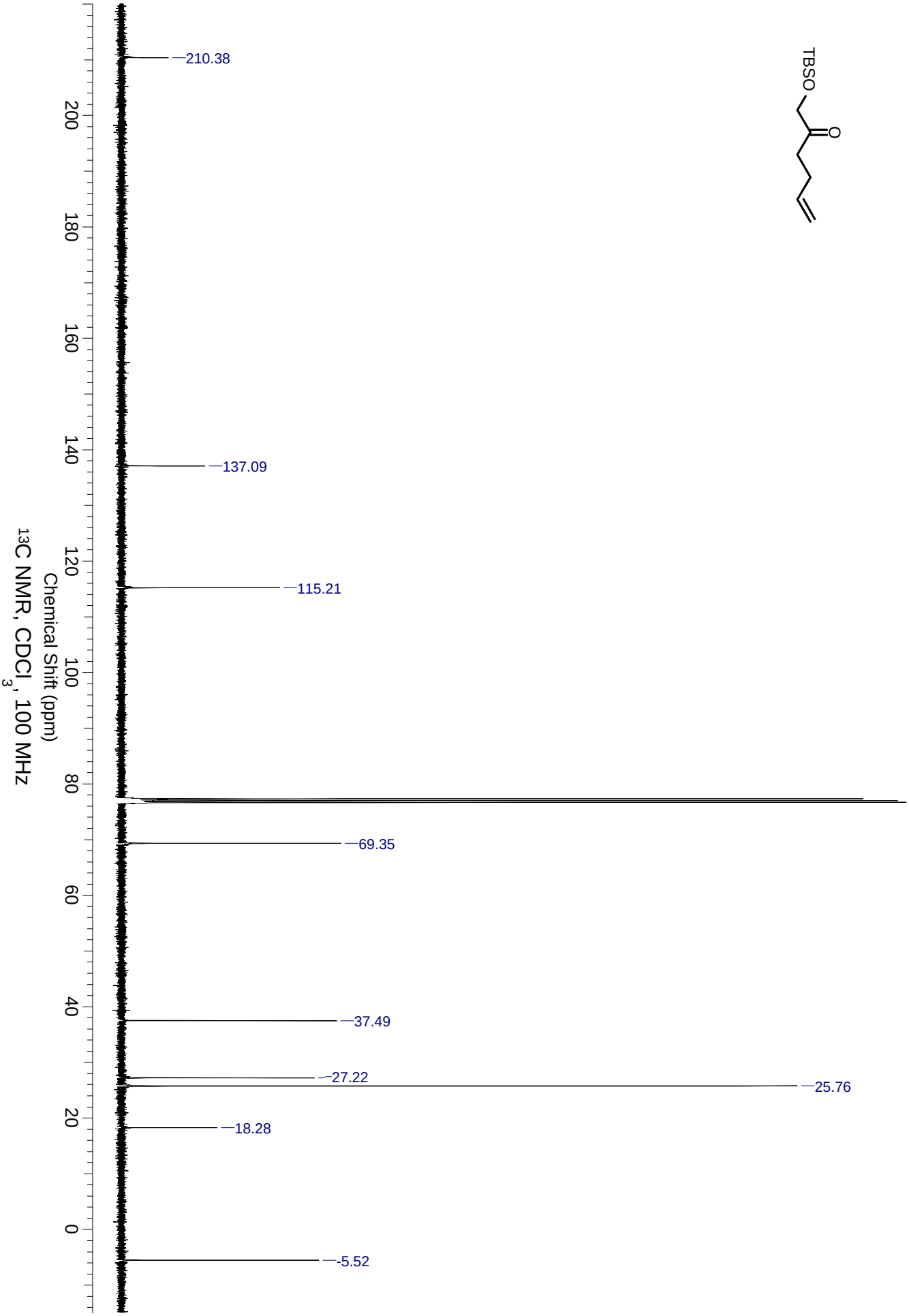
Appendix 1 – NMR Spectral Data for Chapter 1



Compound 1-33



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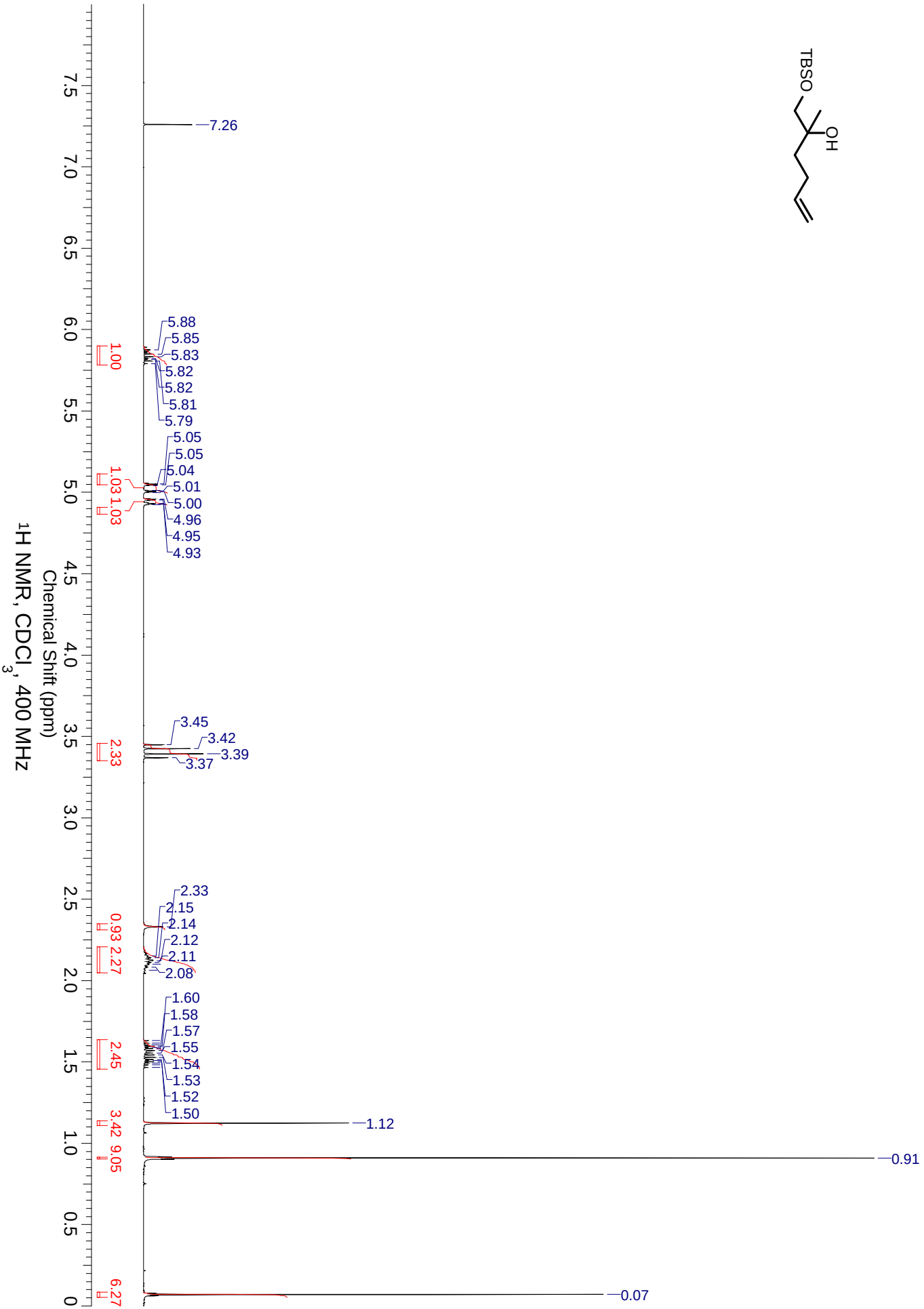
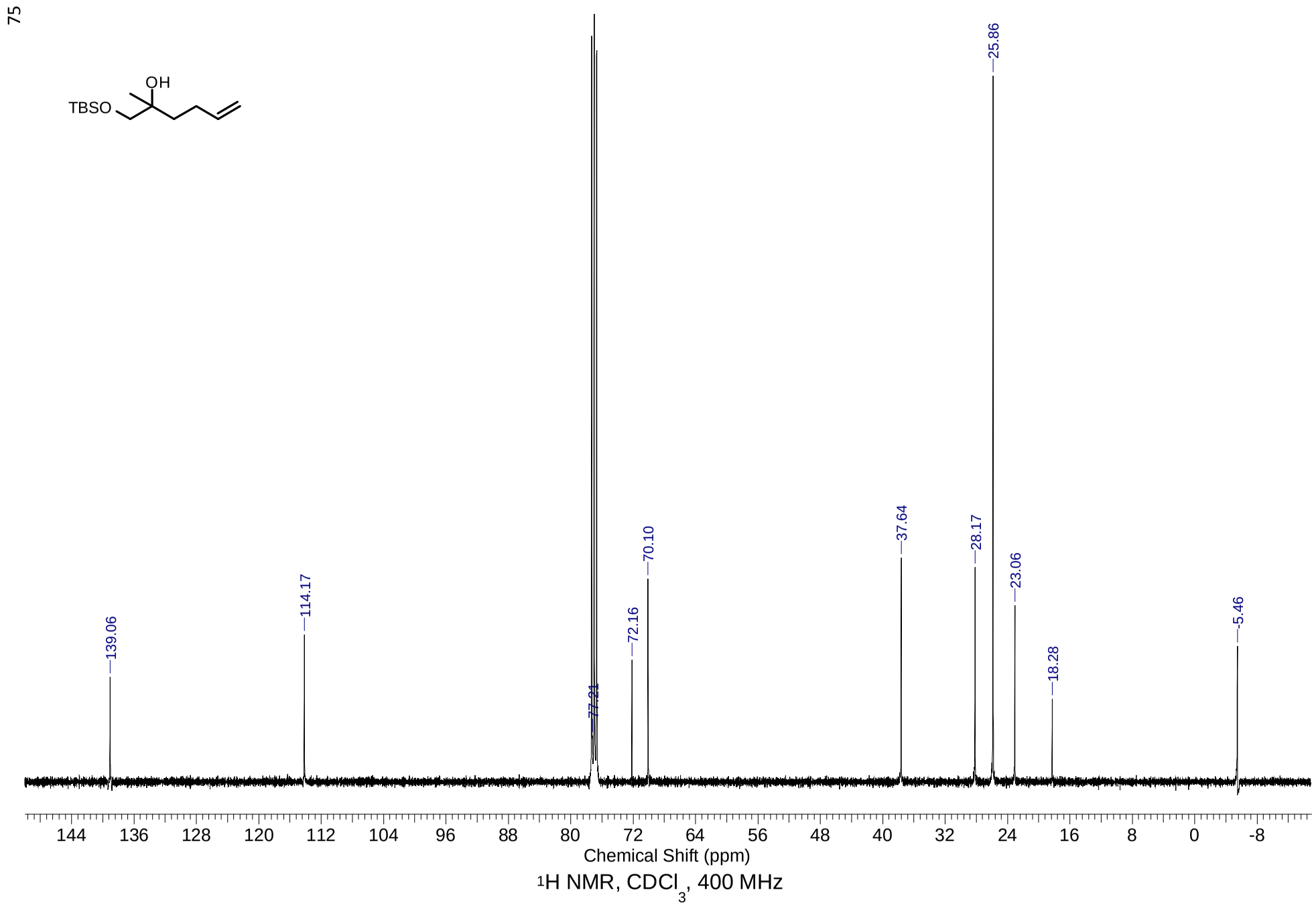
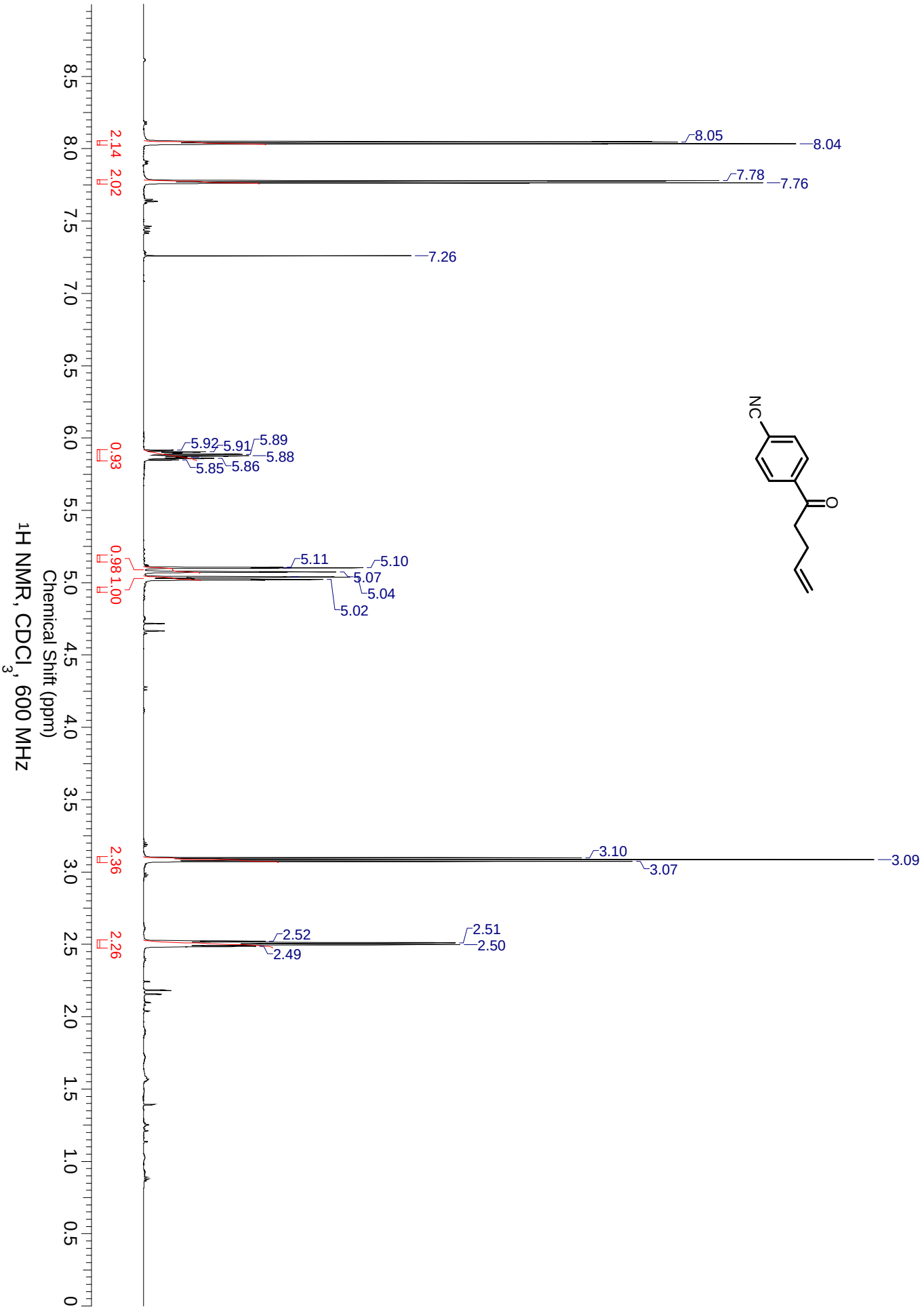


Compound 1-27

Compound 1-27





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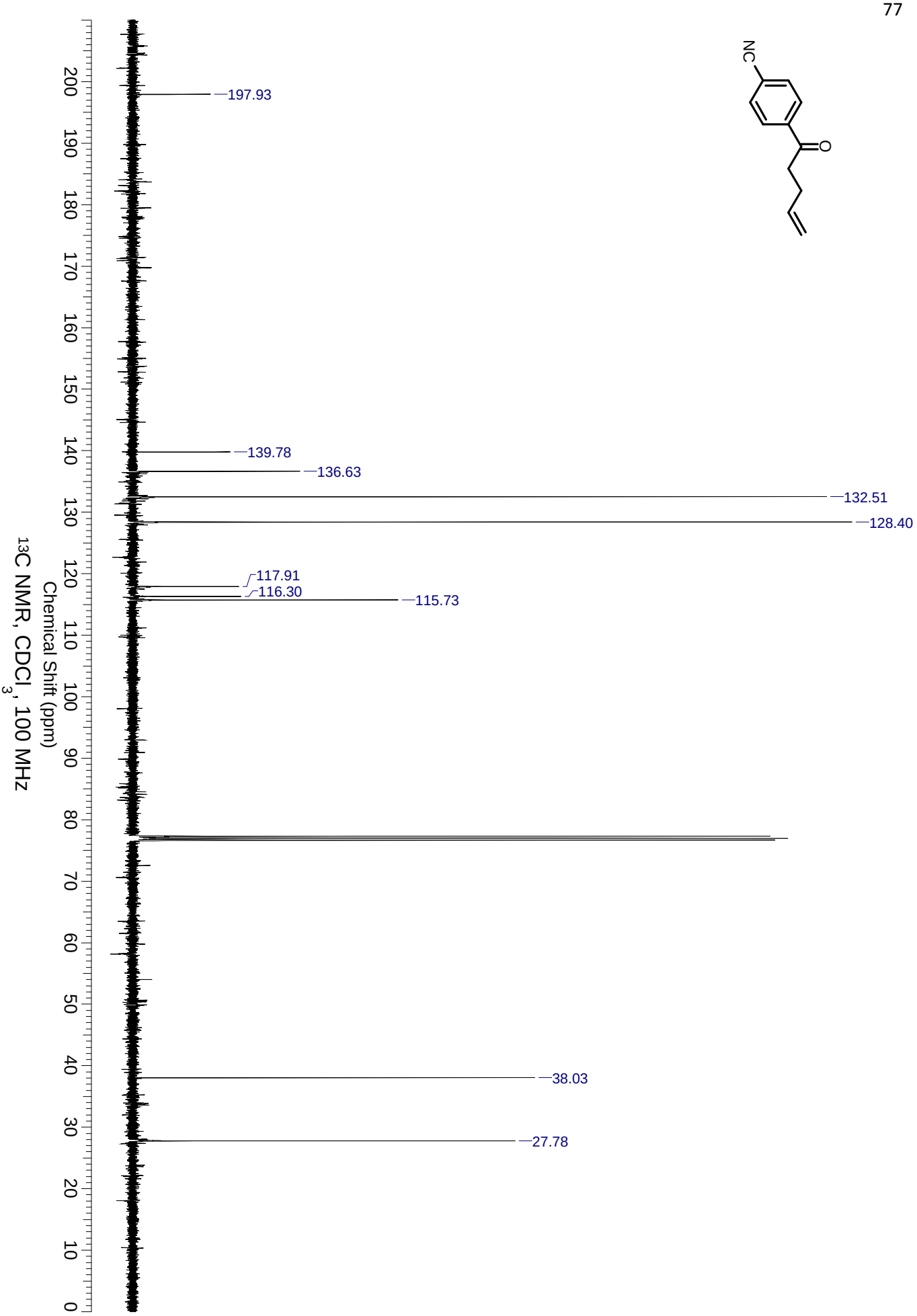

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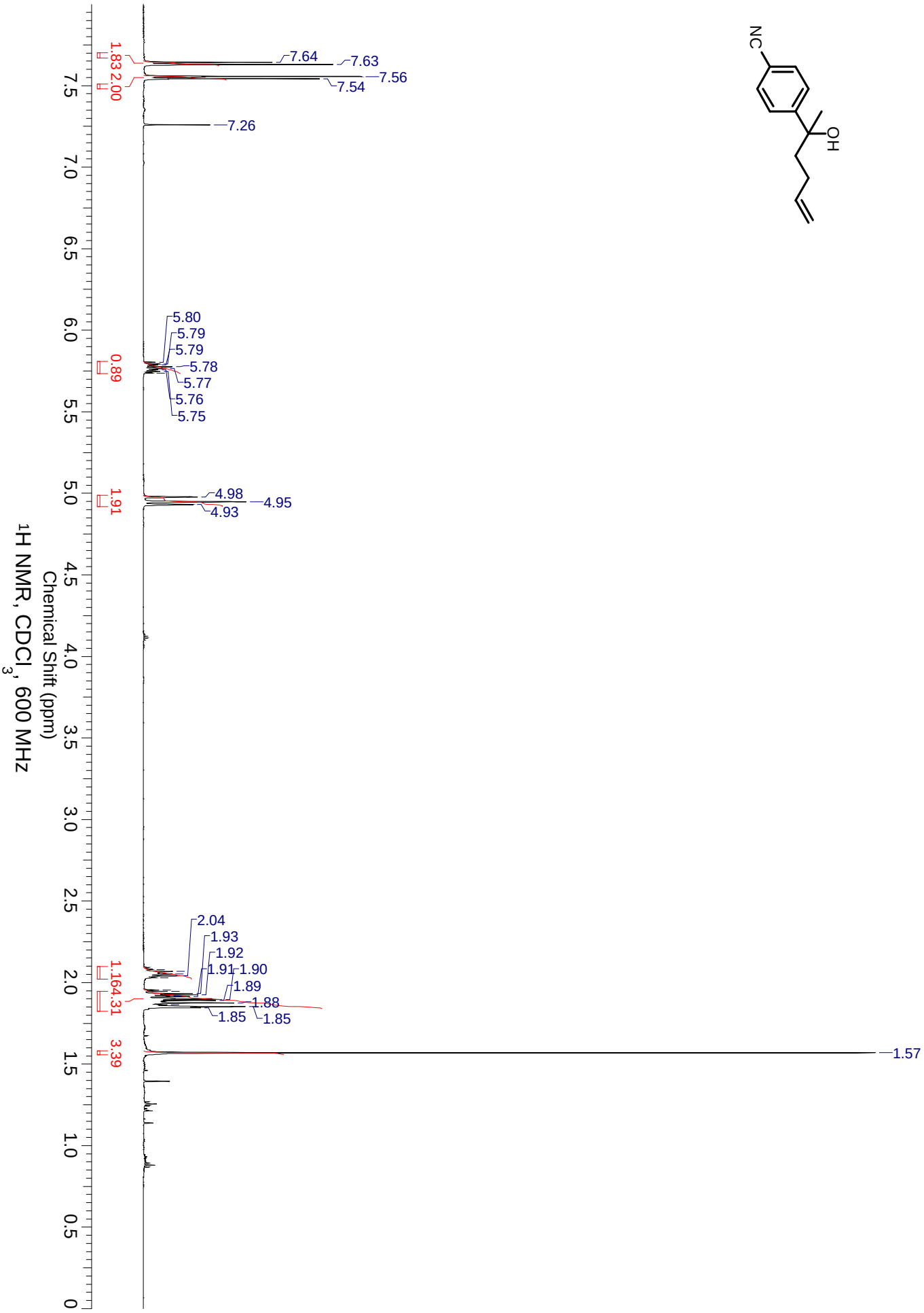
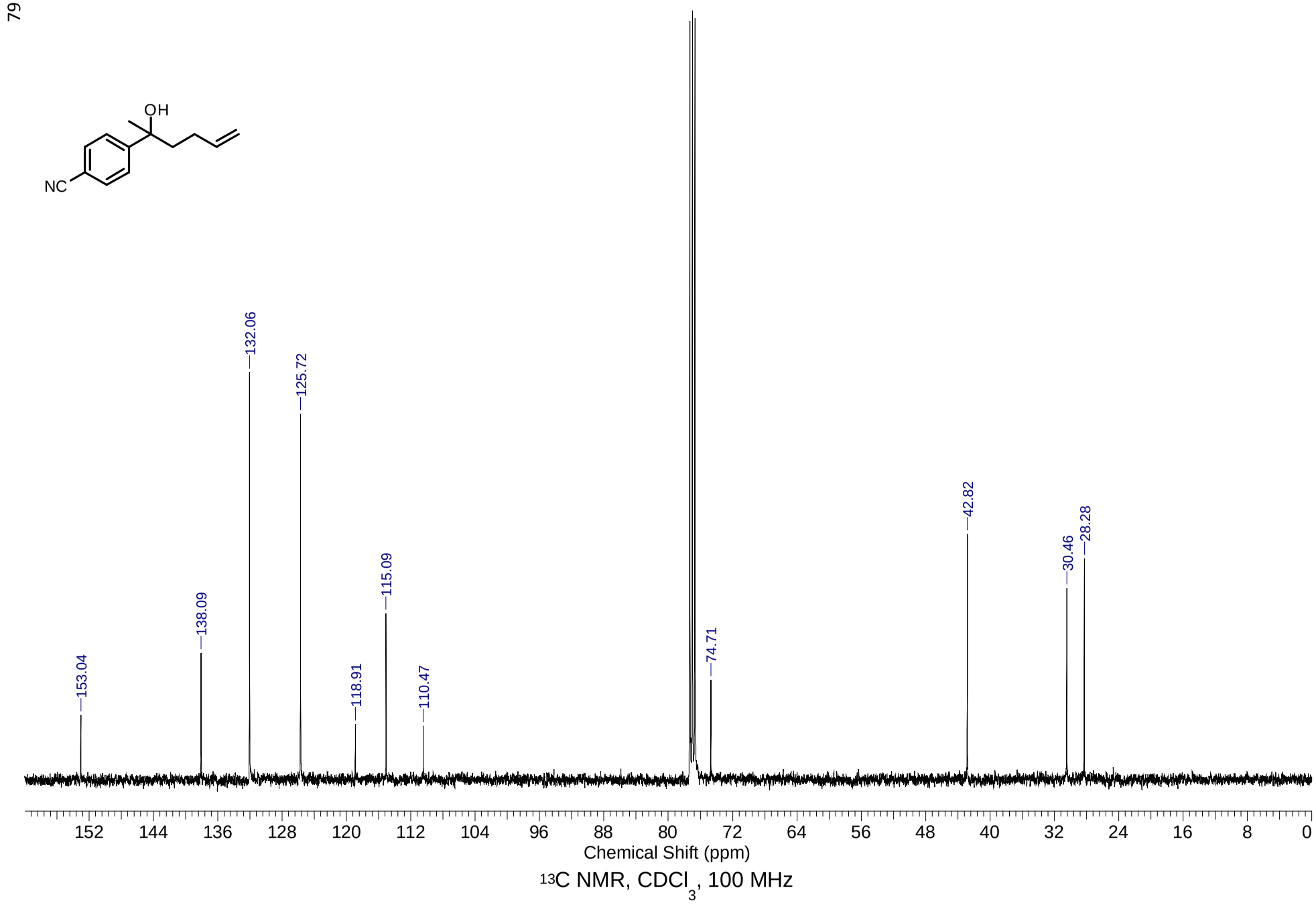
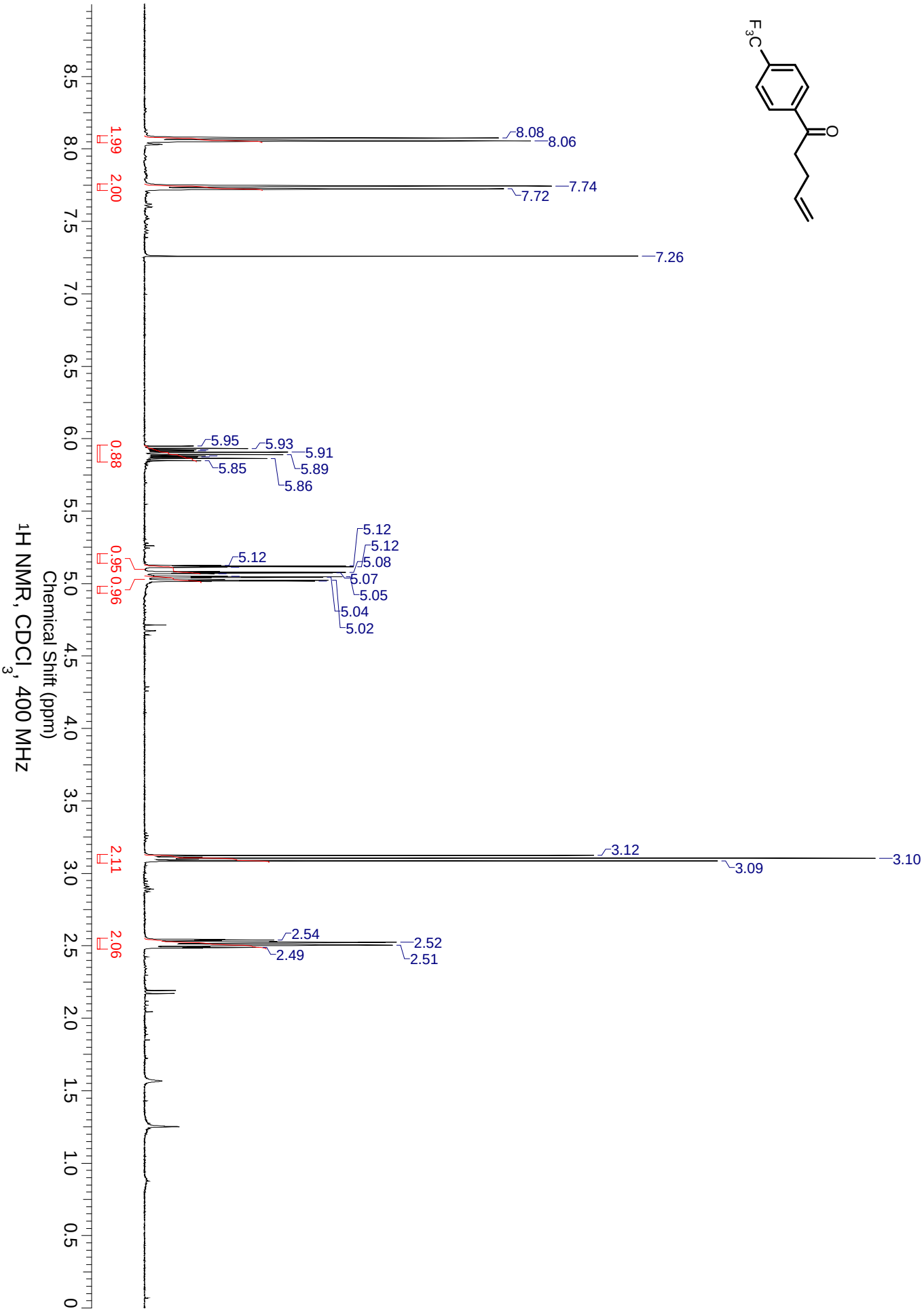


Compound 1-30

Compound 1-30





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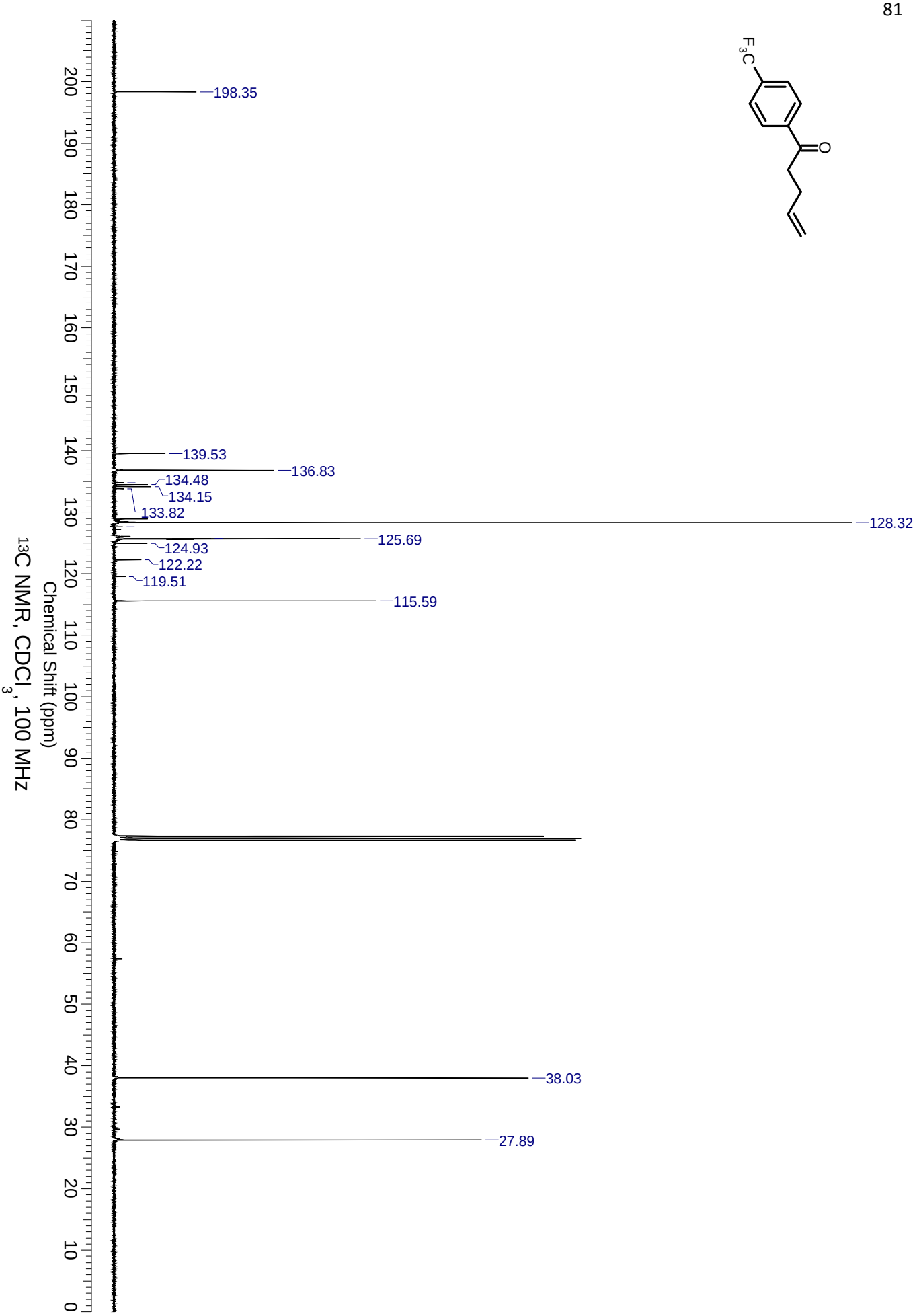

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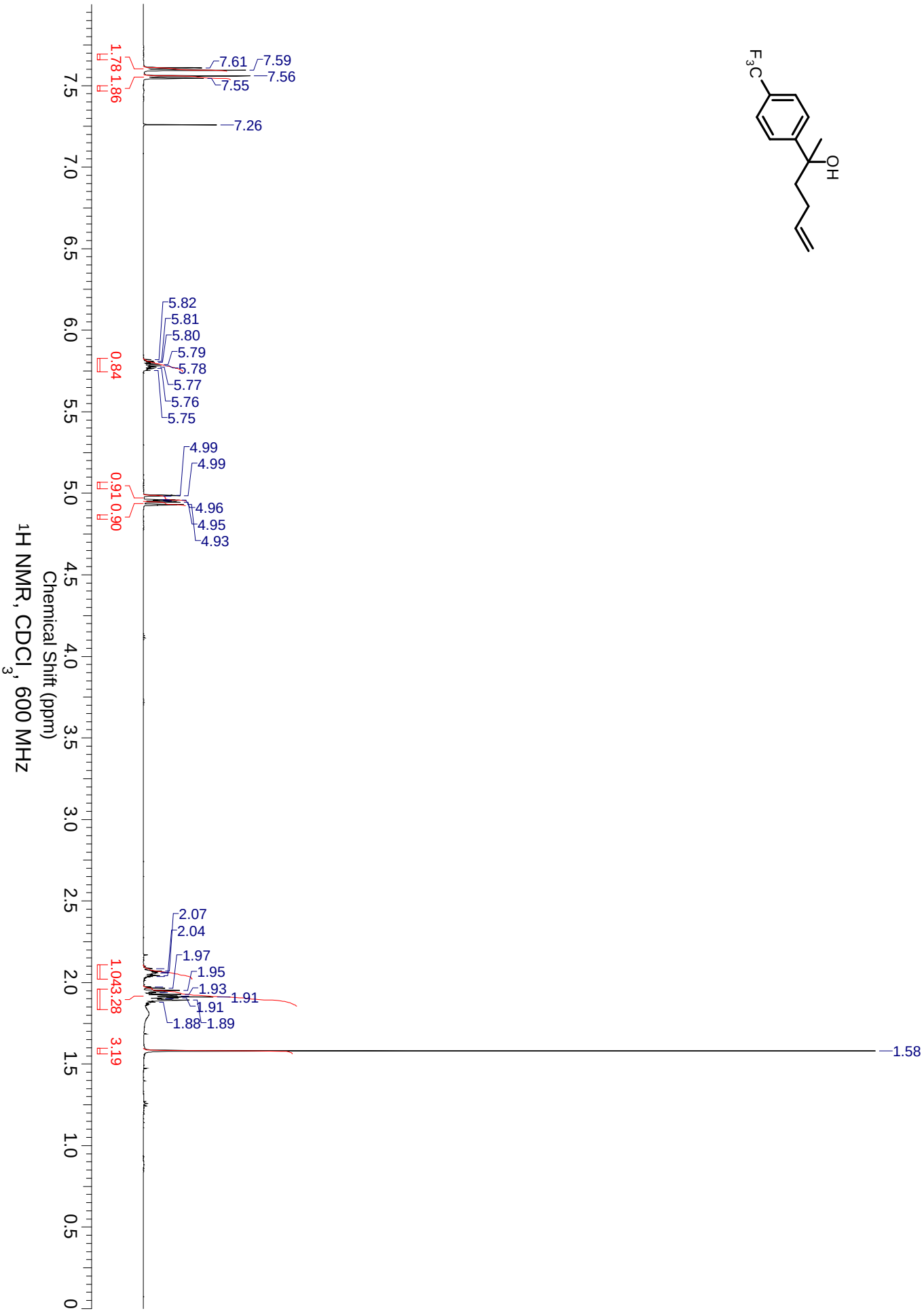
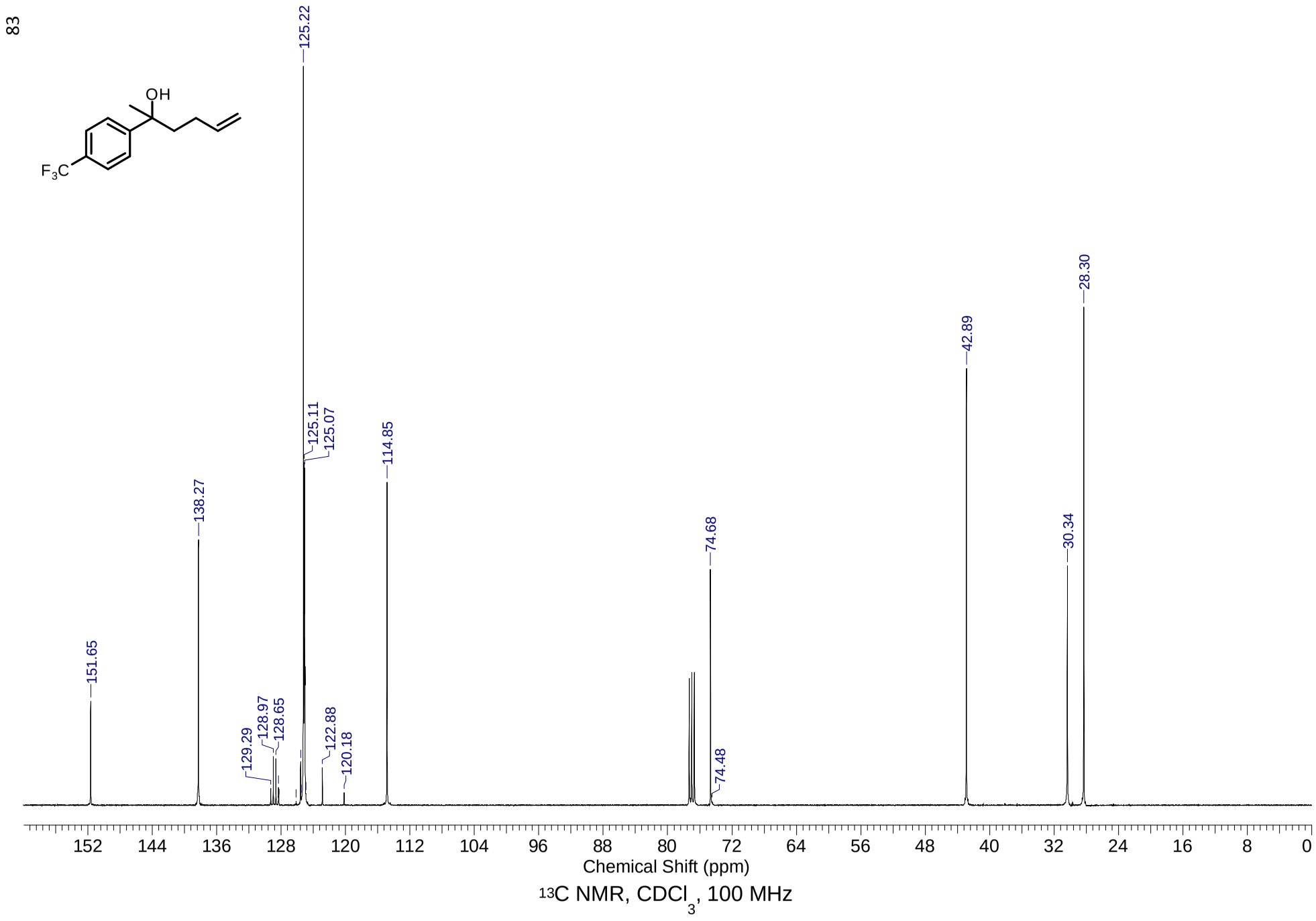


Compound 1-31

Compound 1-31



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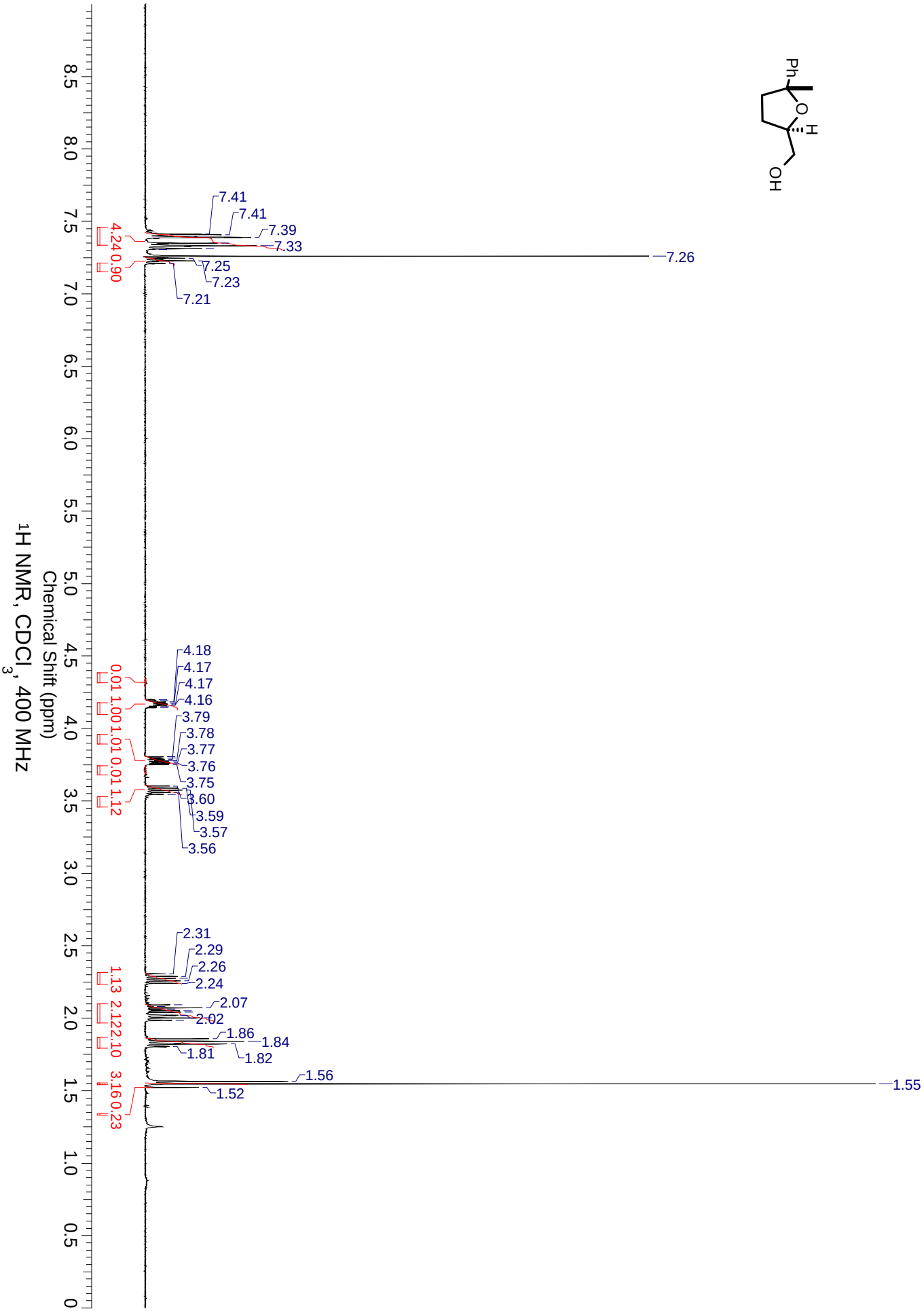
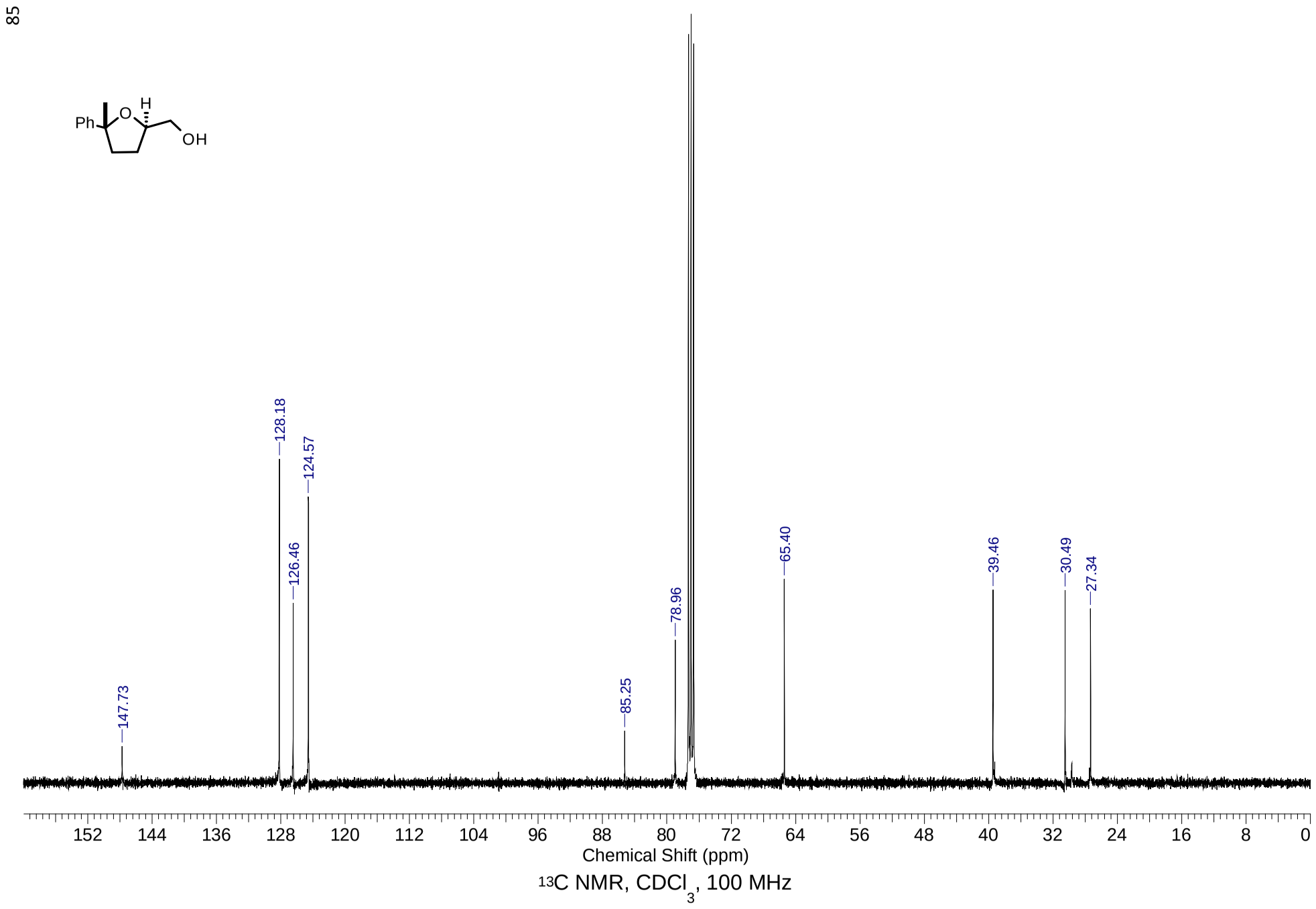
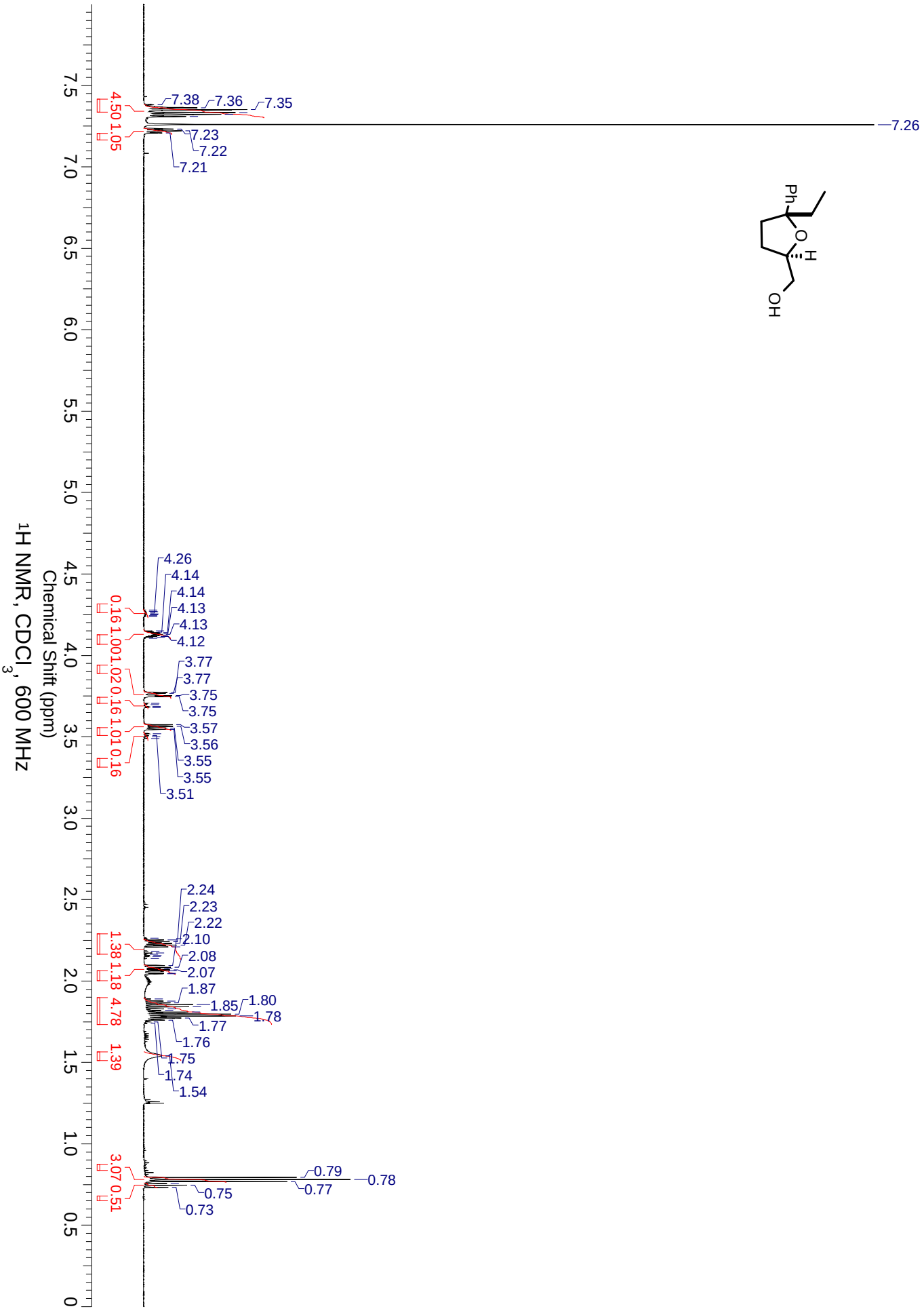


Compound 1-18a





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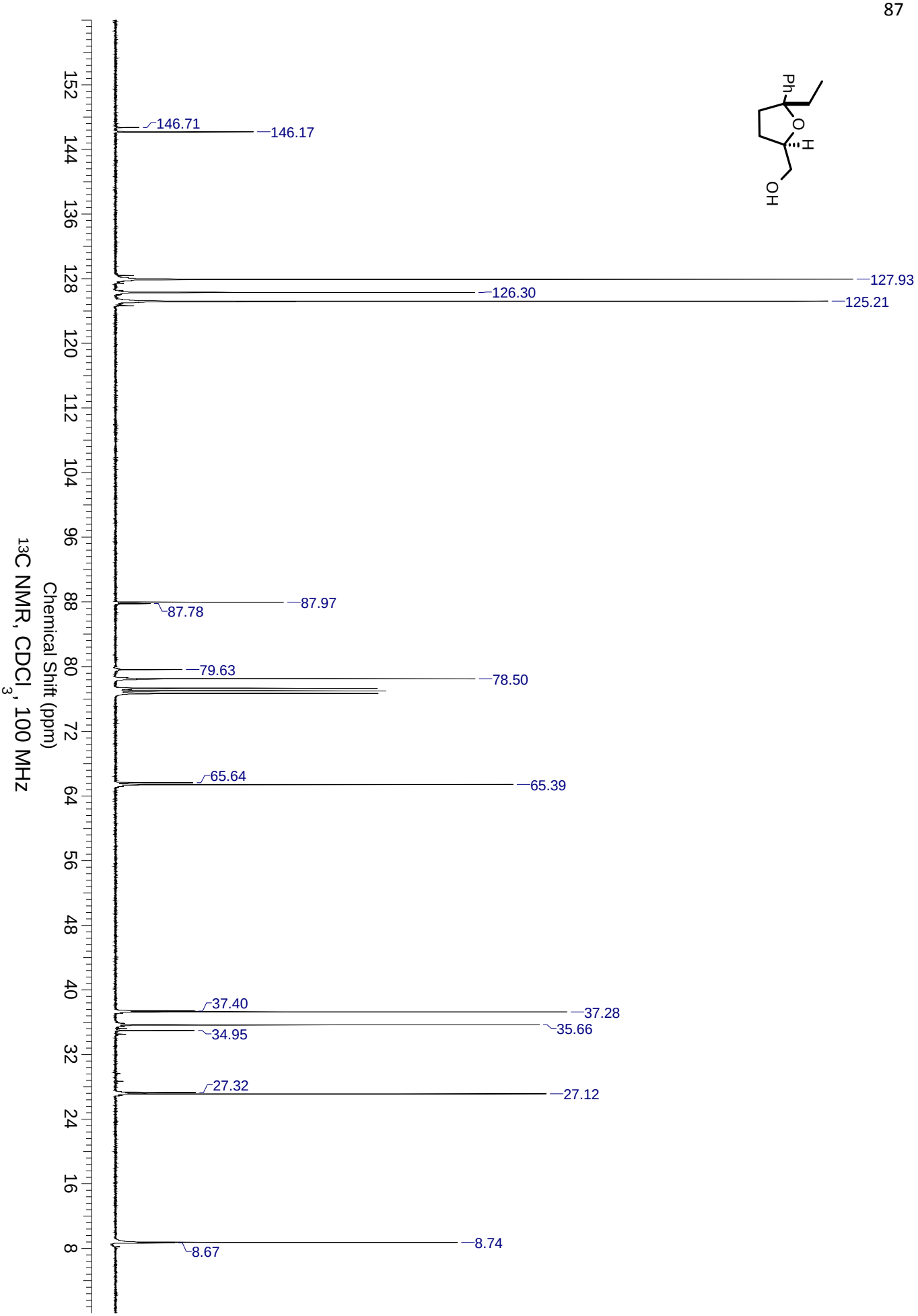
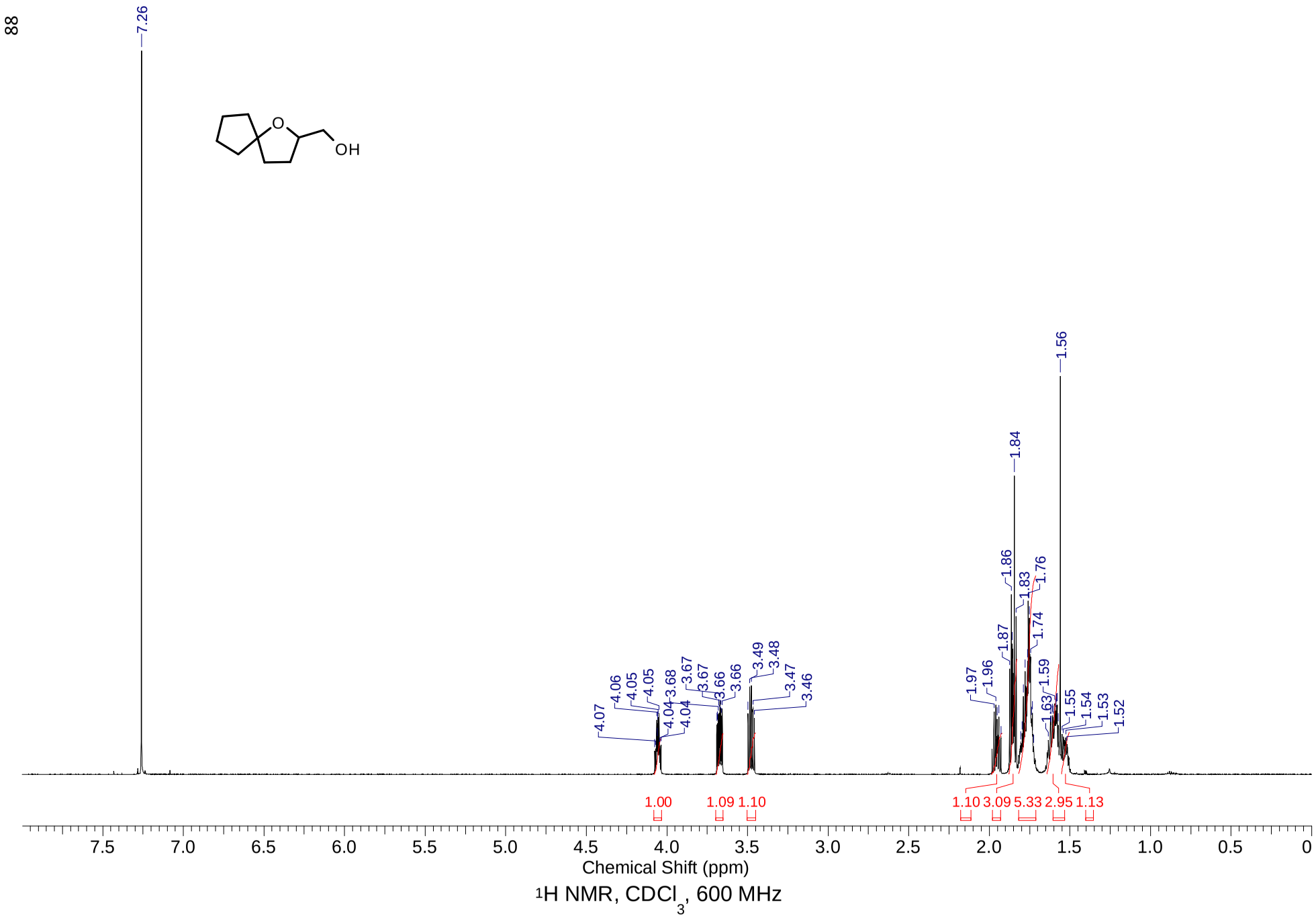
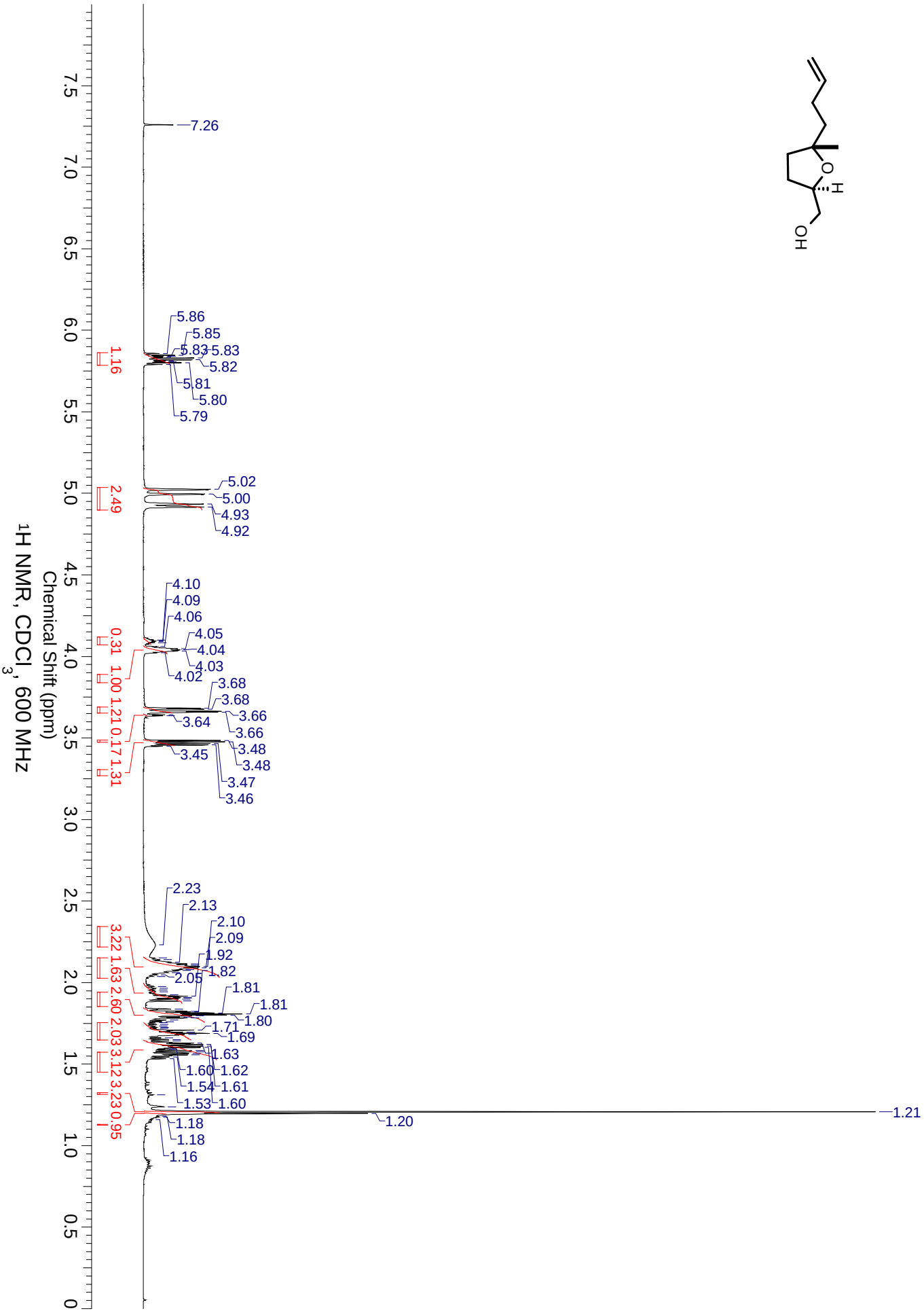


Compound 1-19a

Compound 1-22a

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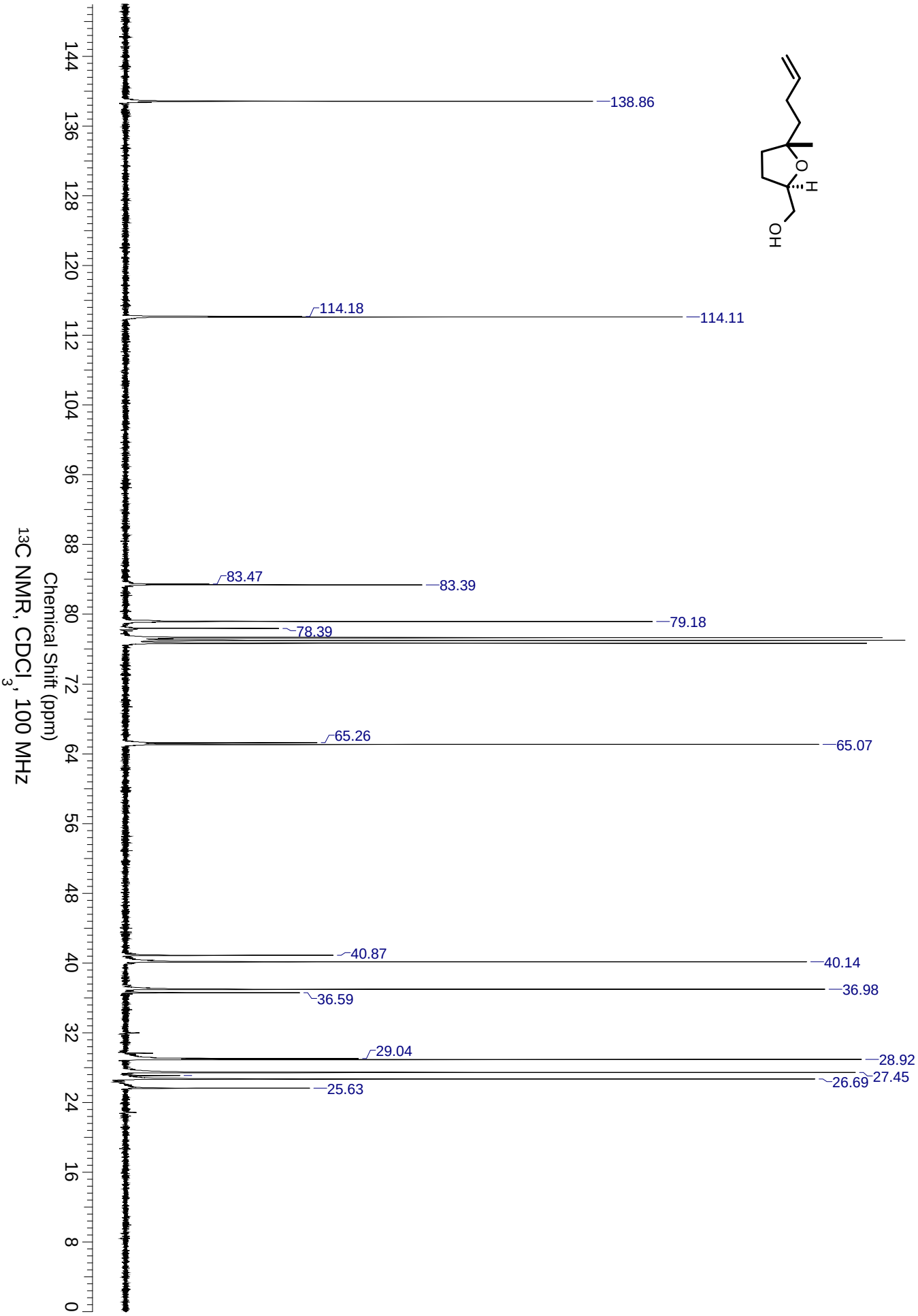
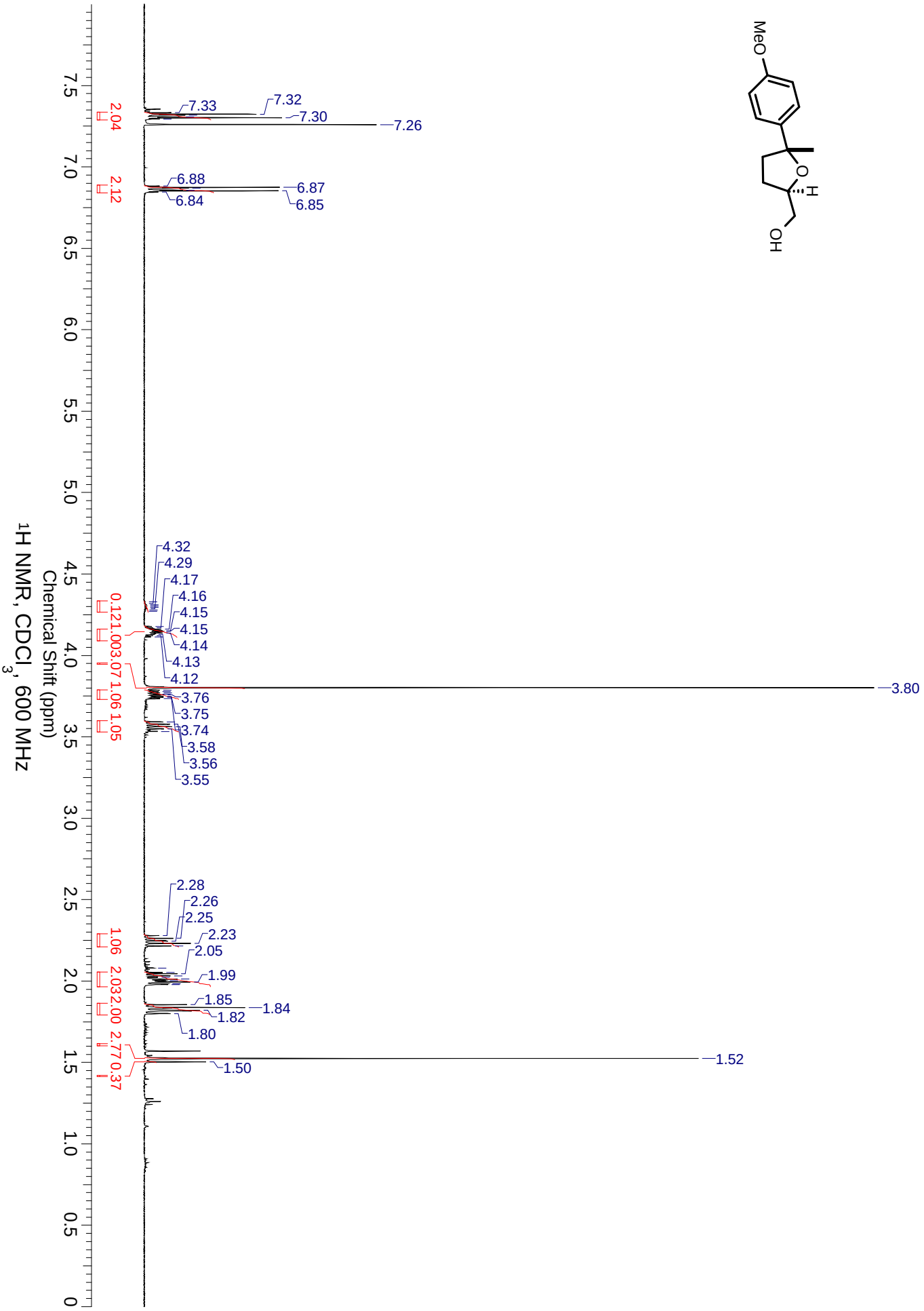
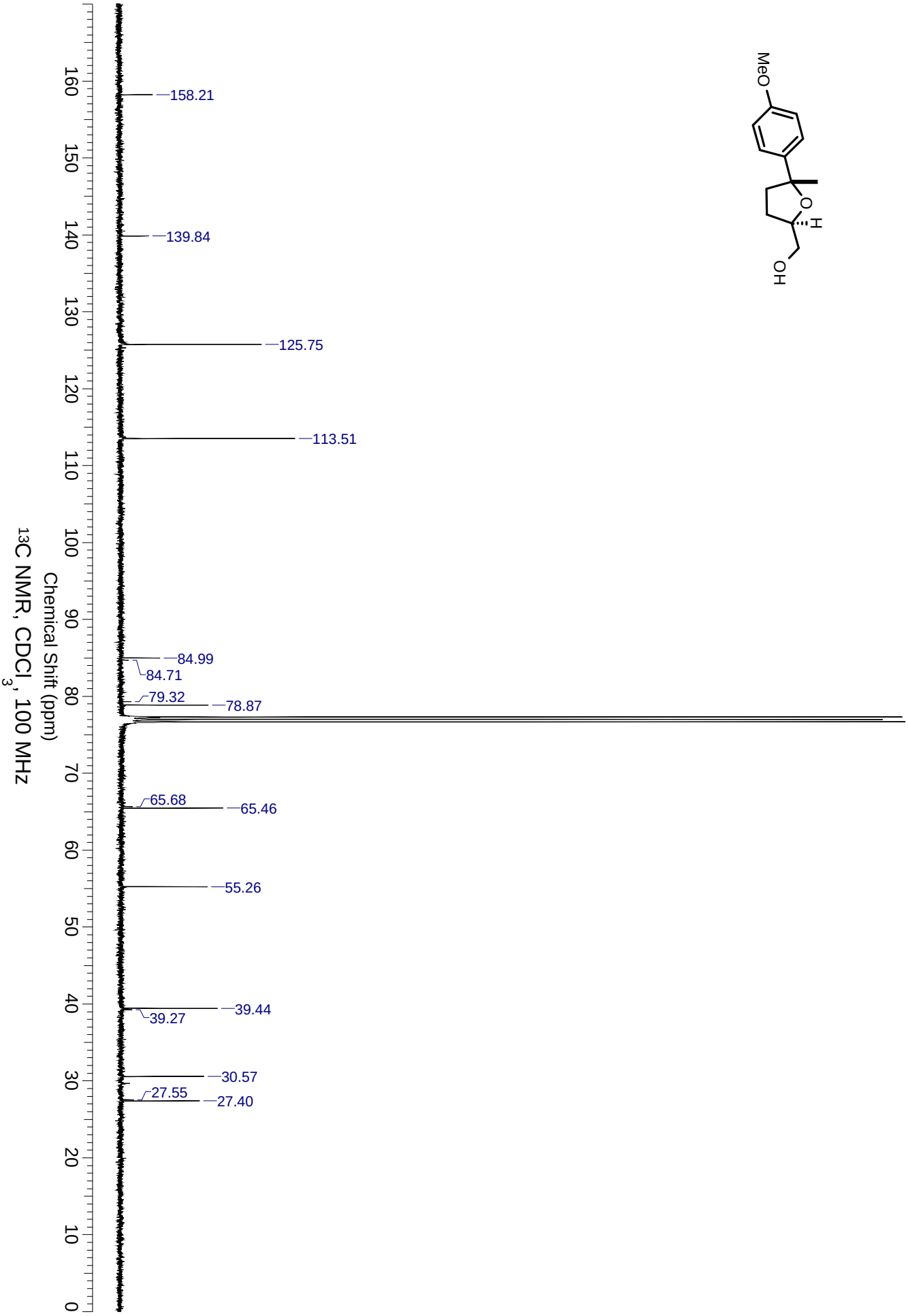


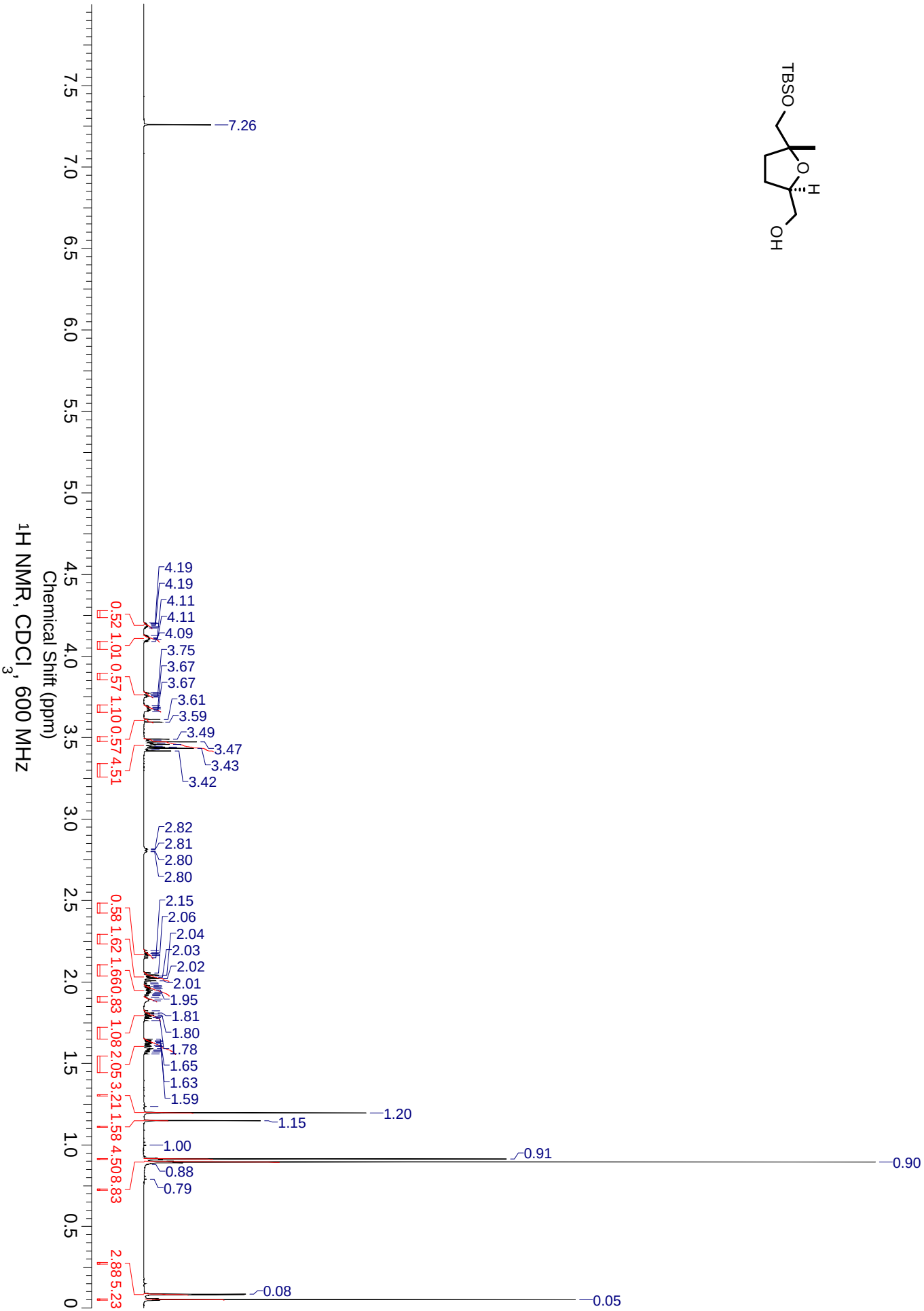
Compound 1-24a



Compound 1-26a

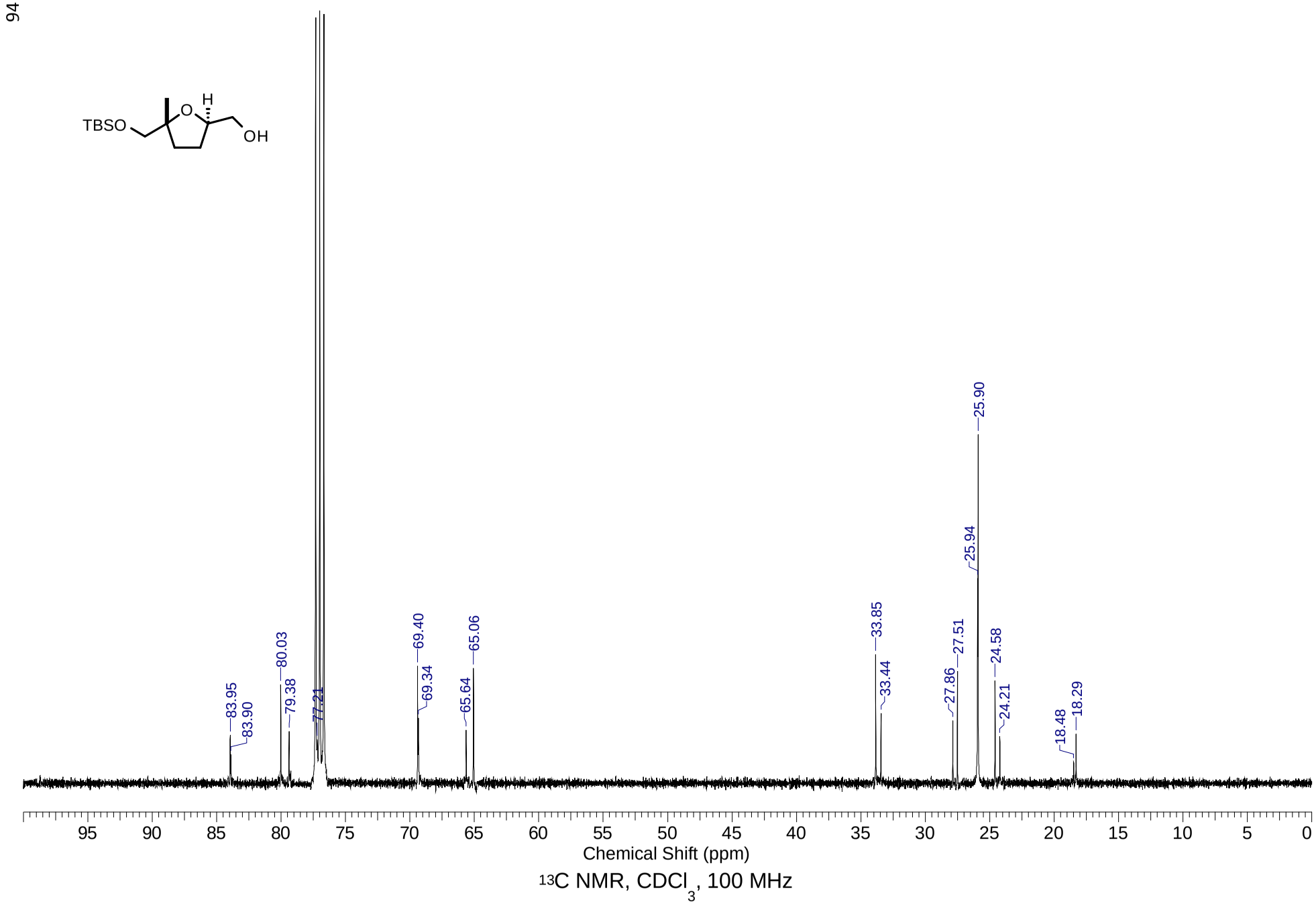


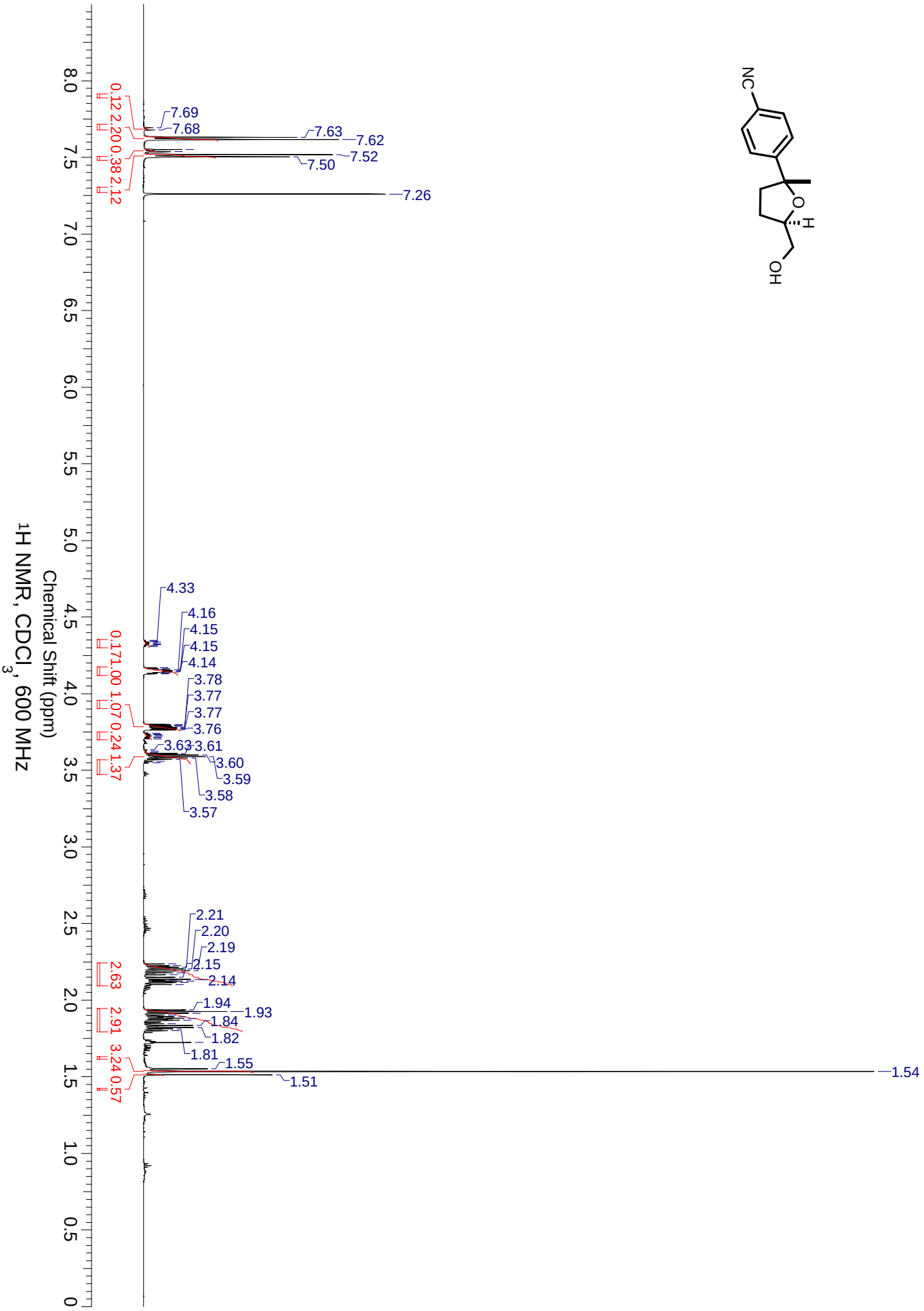
Compound 1-26a



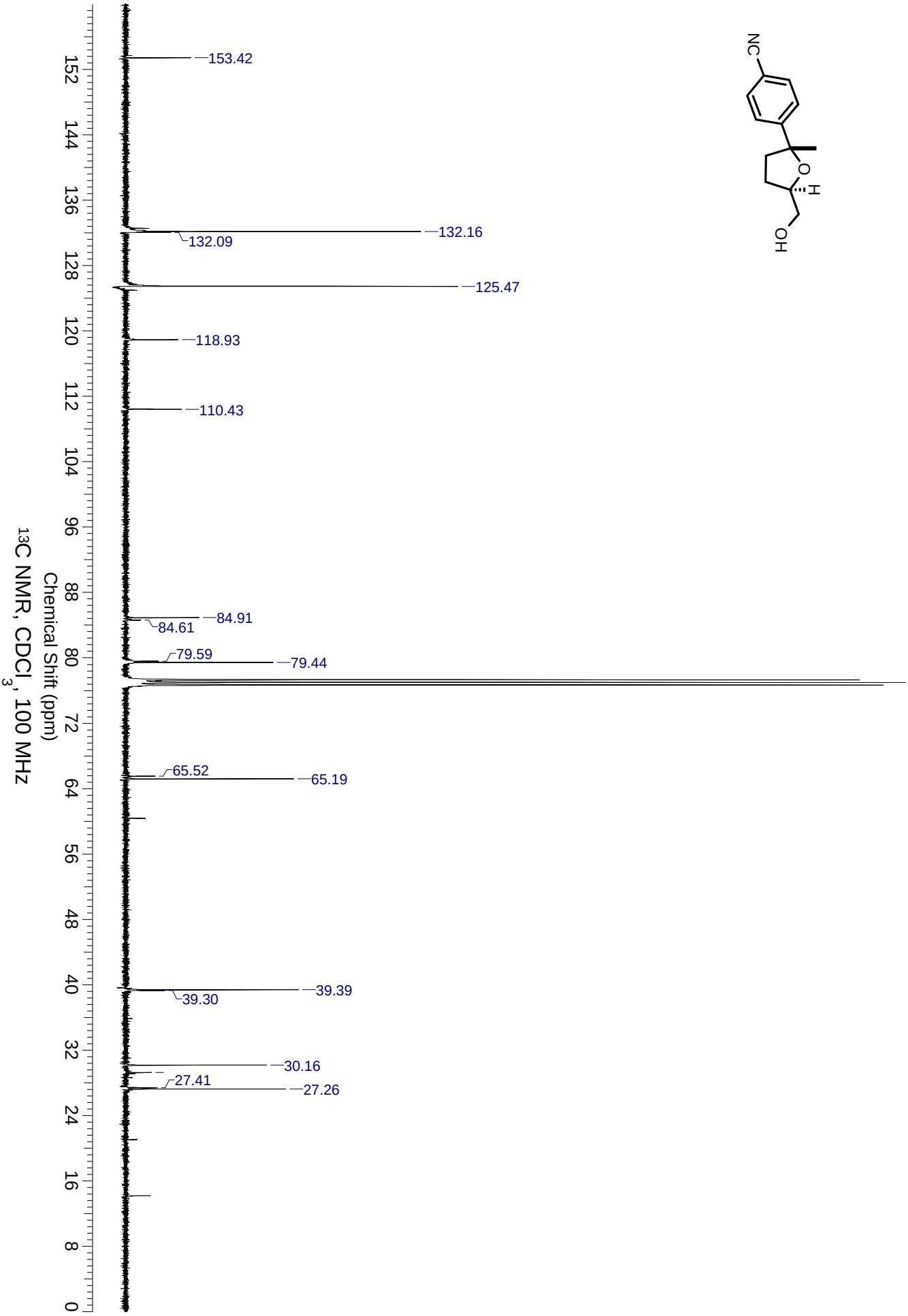
Compound 1-27a

Compound 1-27a





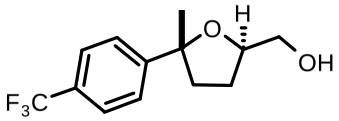
Compound 1-30a



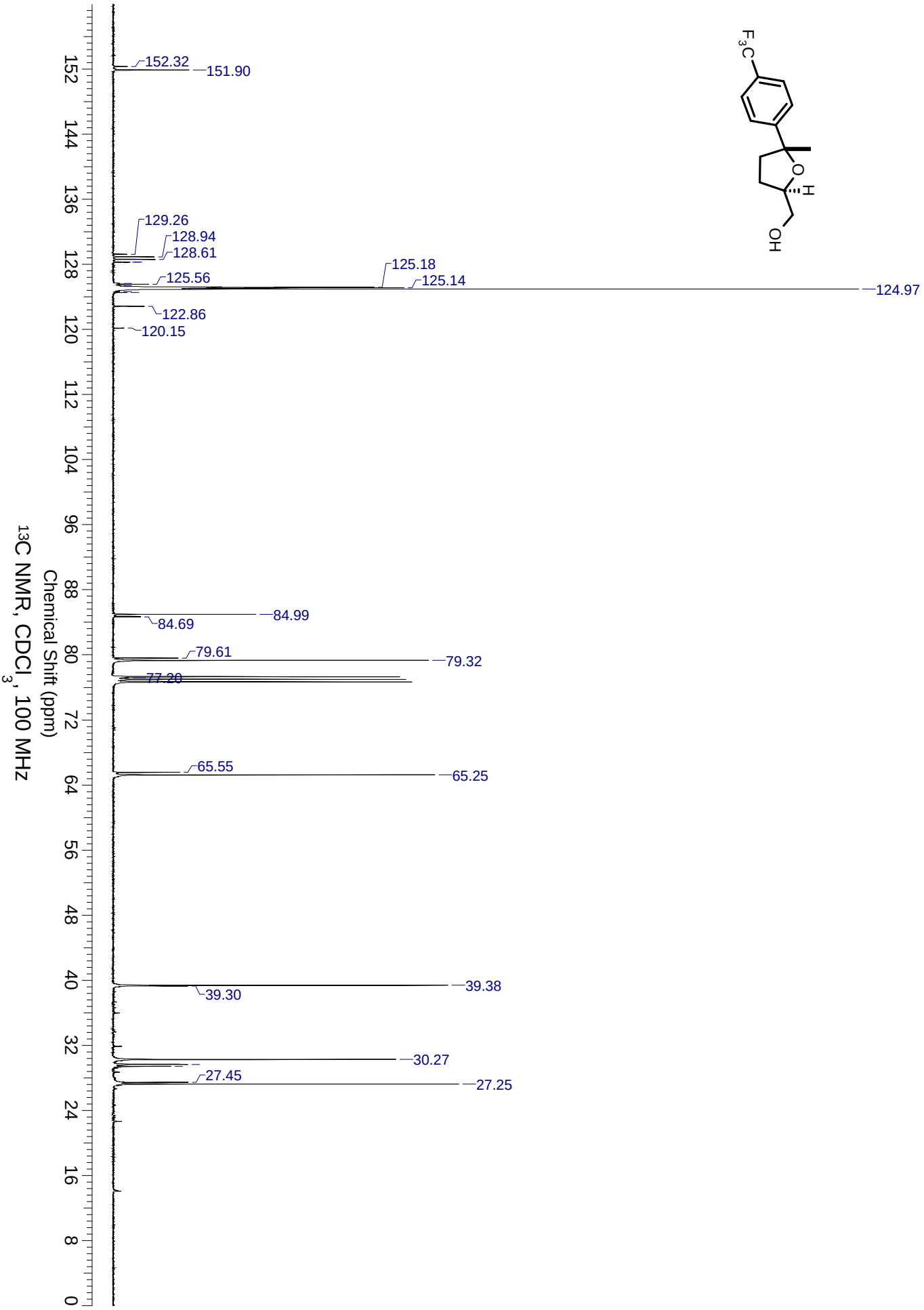
Compound 1-30a

Compound 1-31a

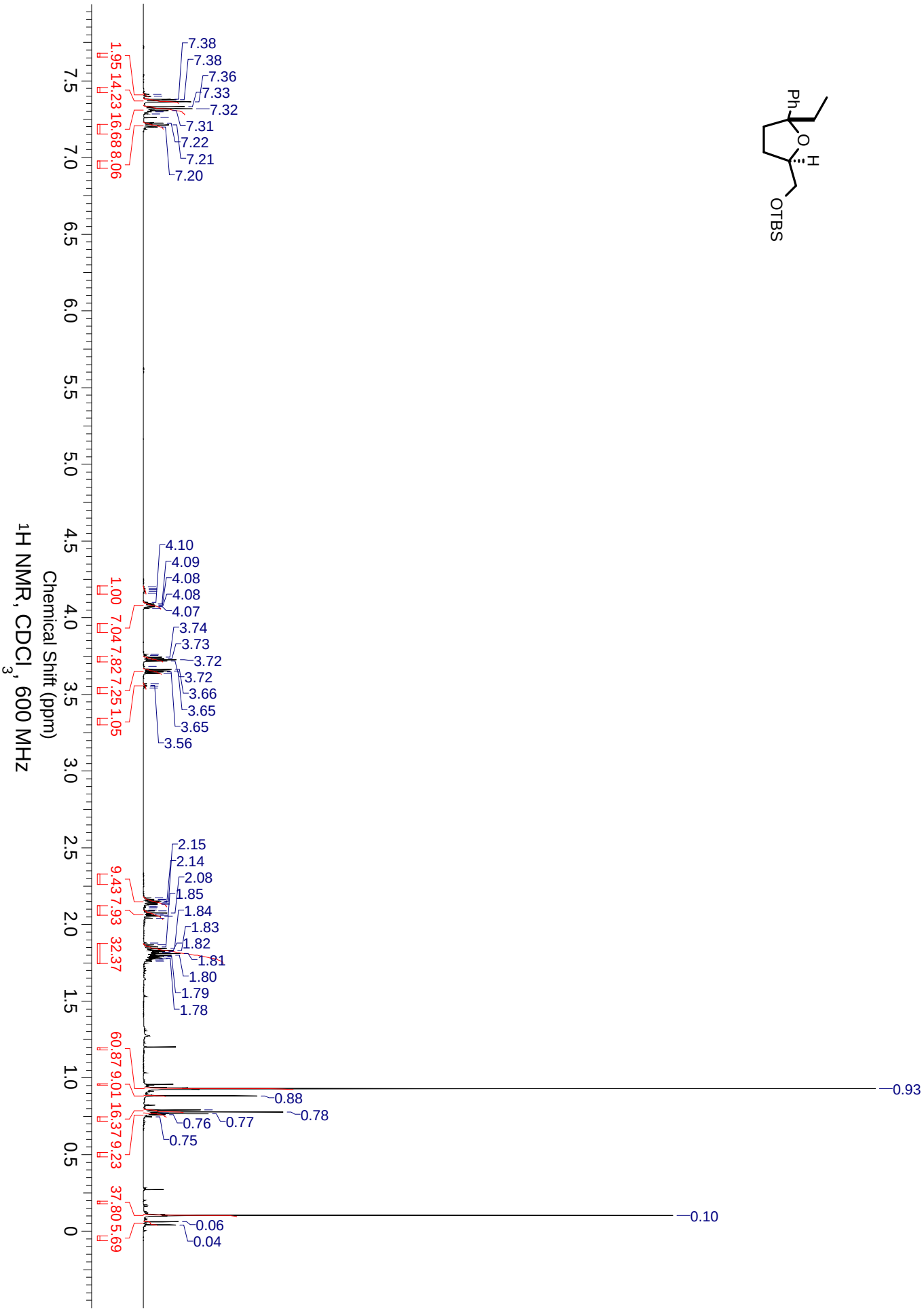
97



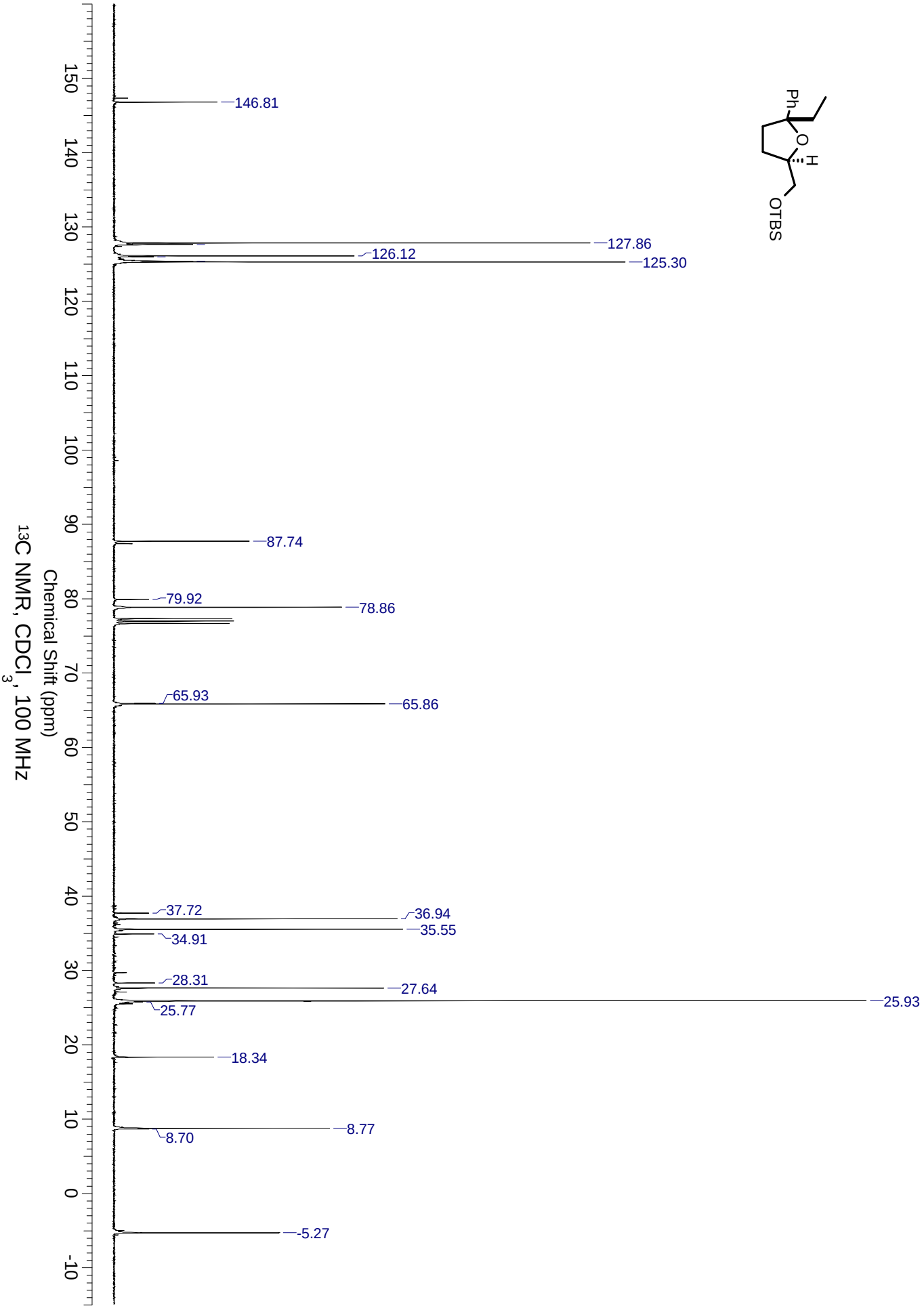
^{1}H NMR, $CDCl_3$, 600 MHz



Compound 1-31a

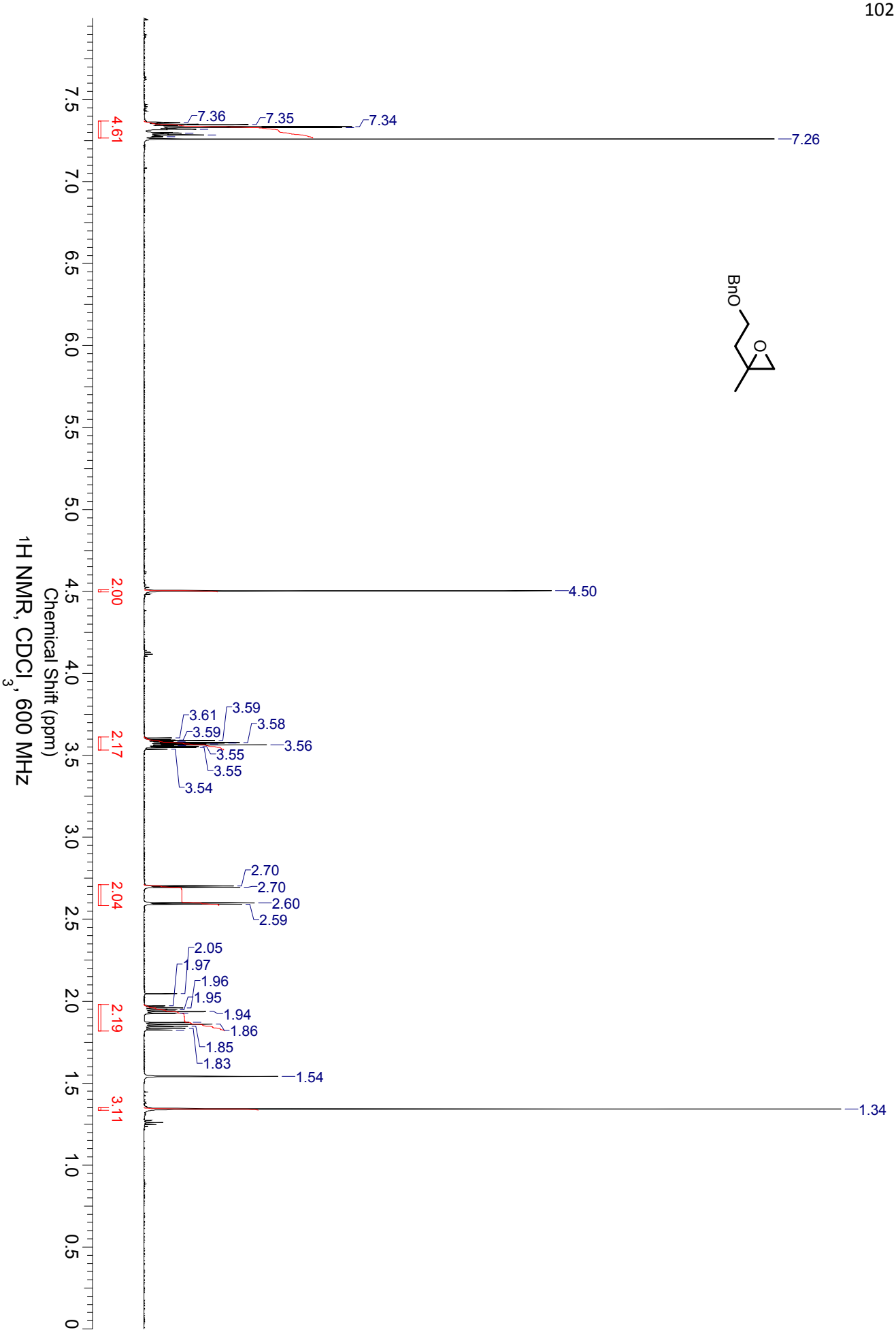


Compound 1-32



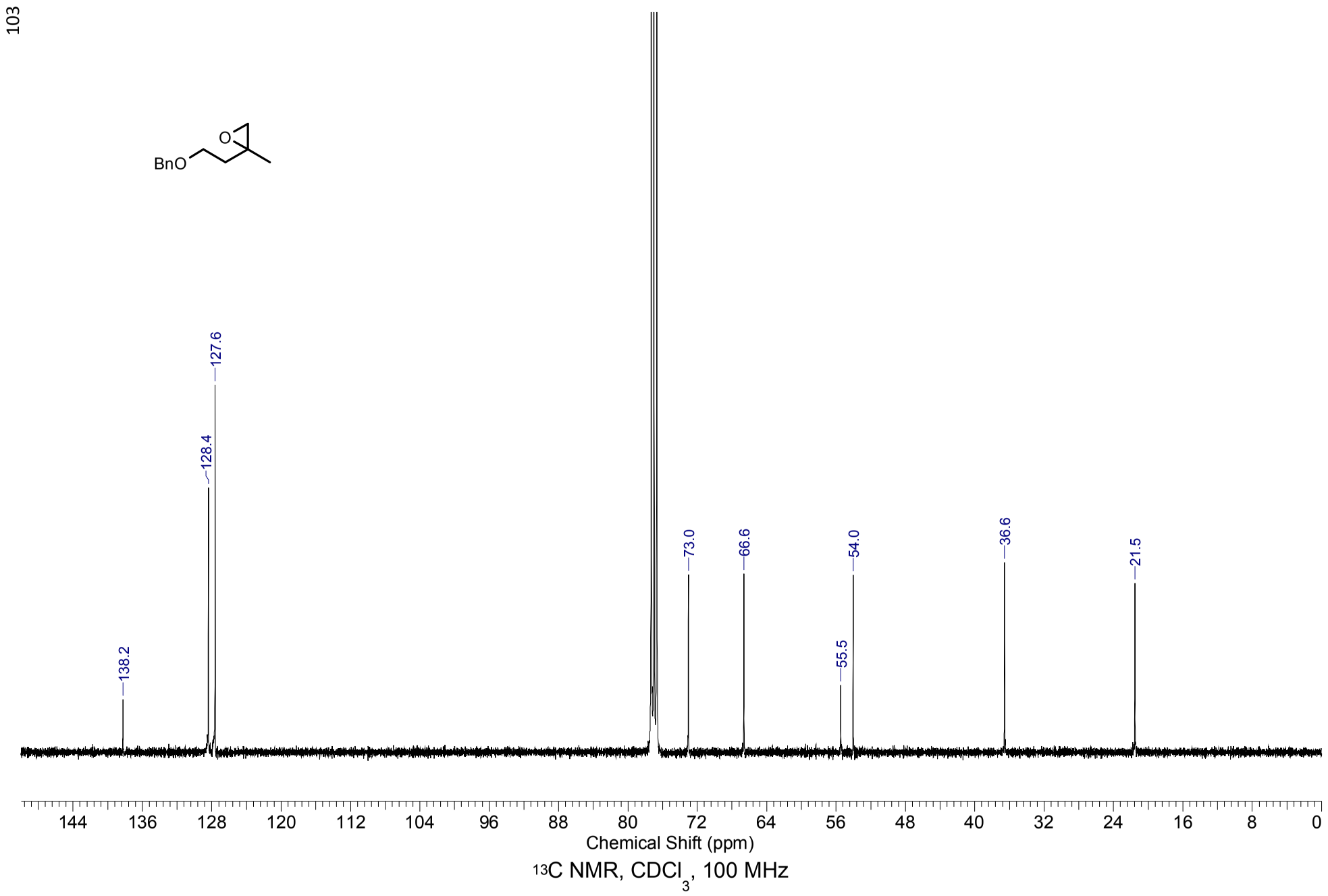
Compound 1-32

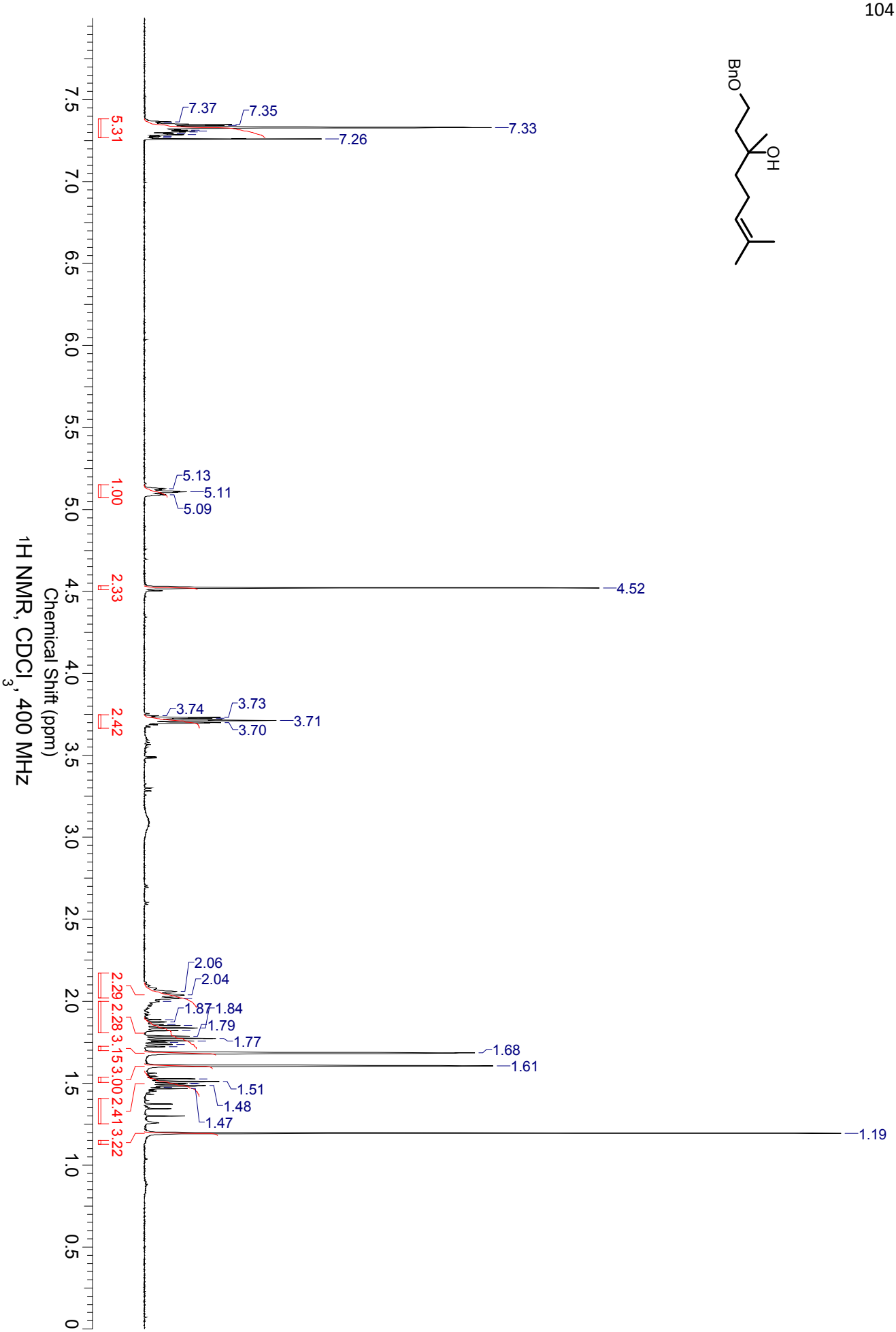
Appendix 2 – NMR Spectral Data for Chapter 2



Compound 2-30a

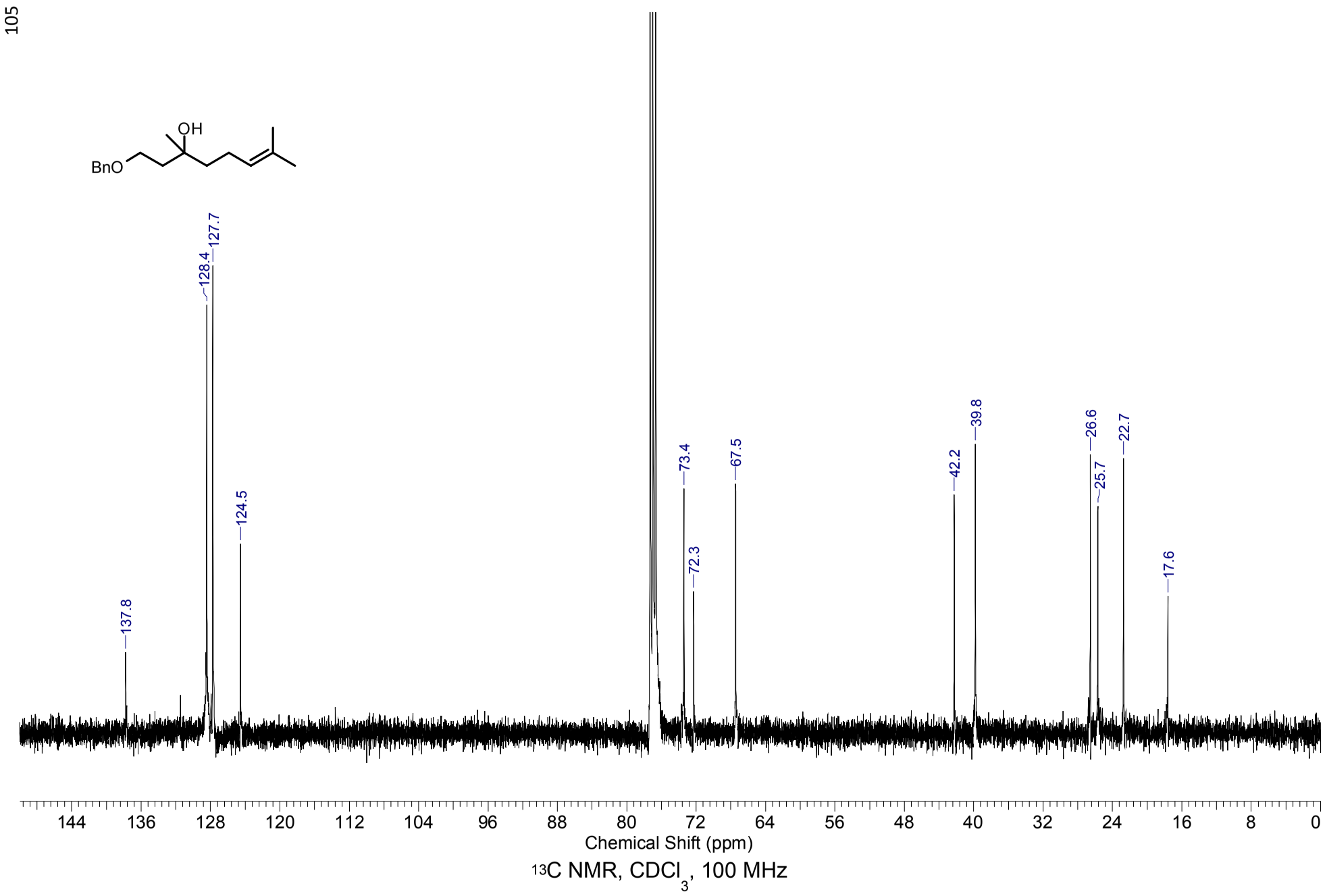
Compound 2-30a

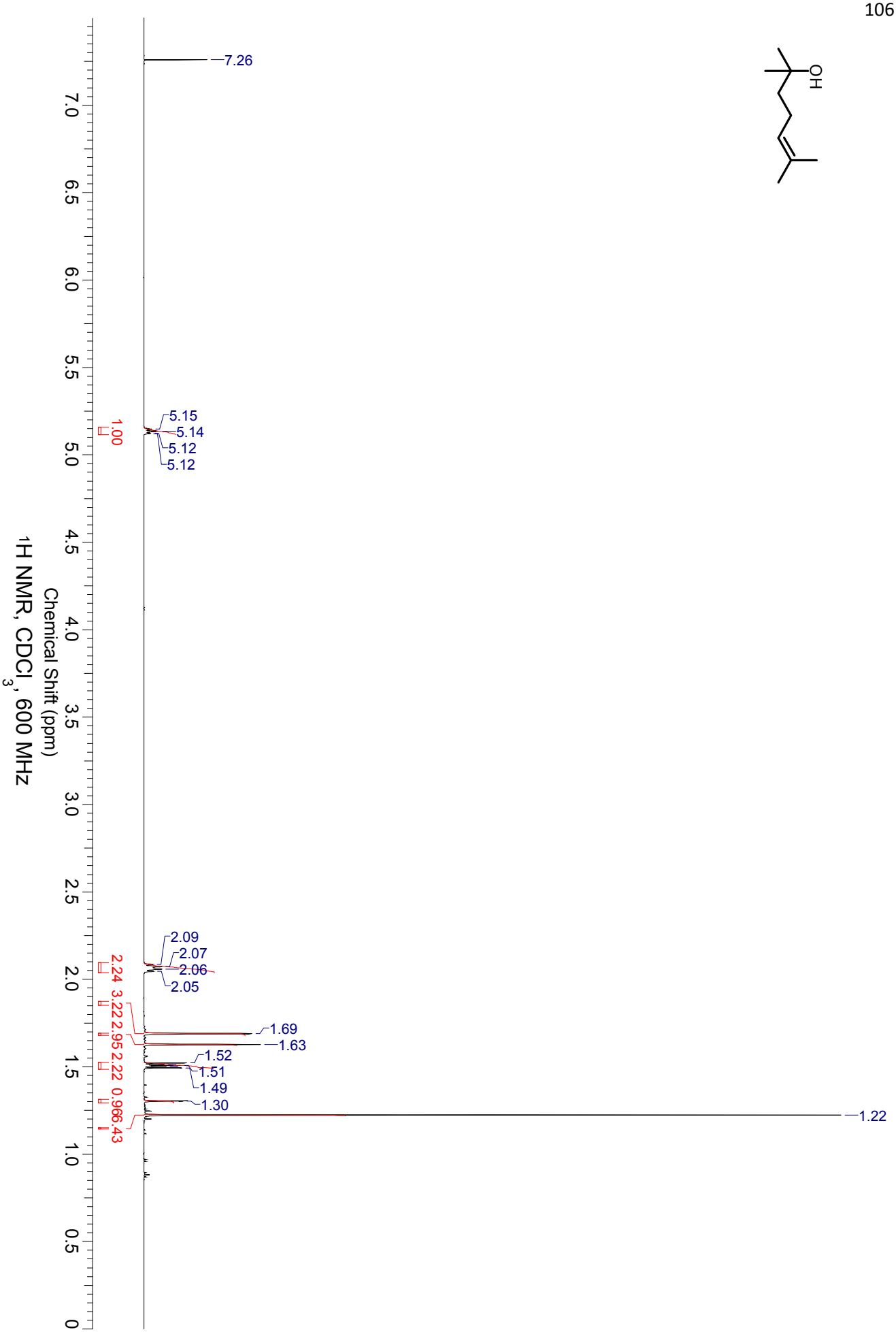




Compound 2-29a

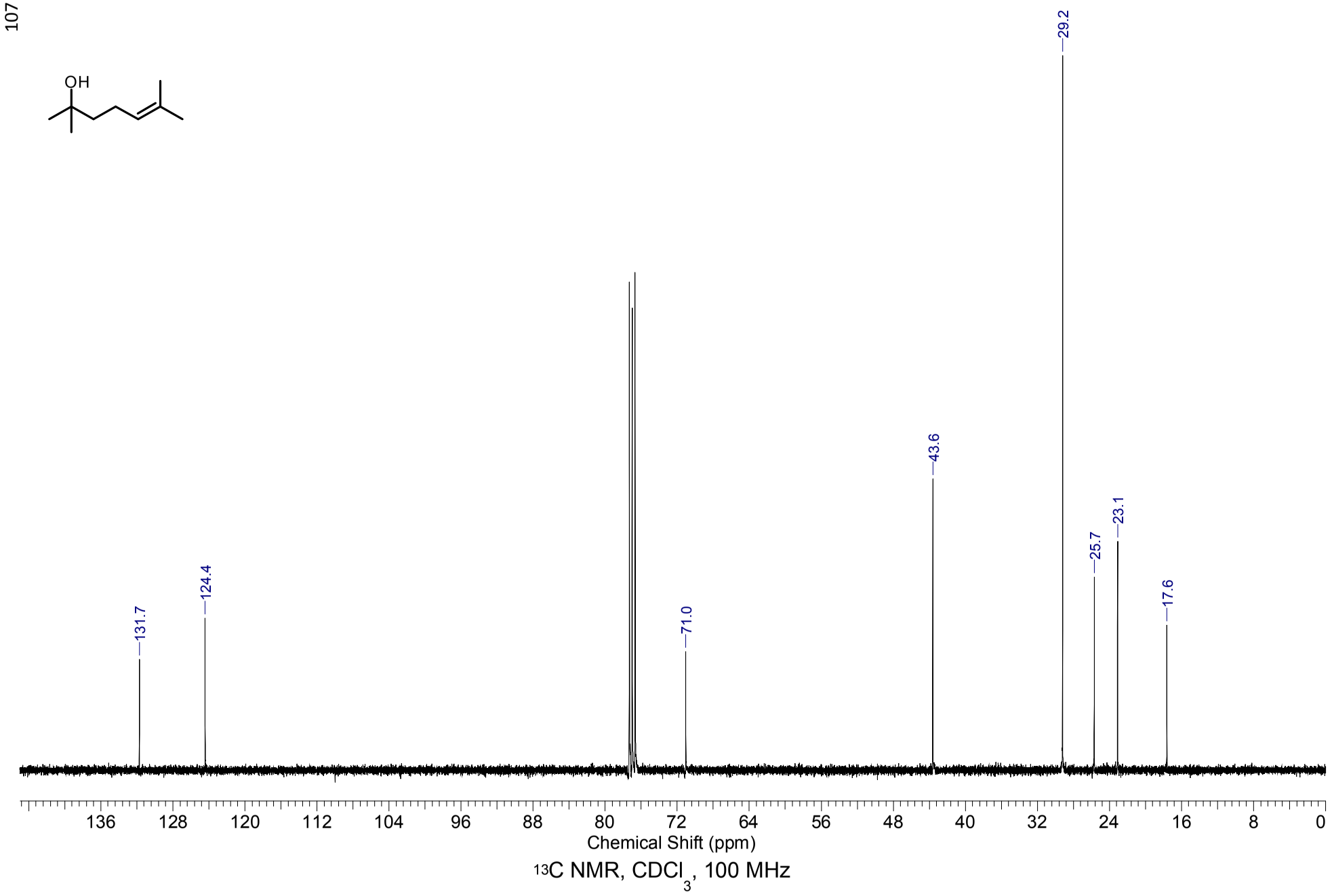
Compound 2-29a

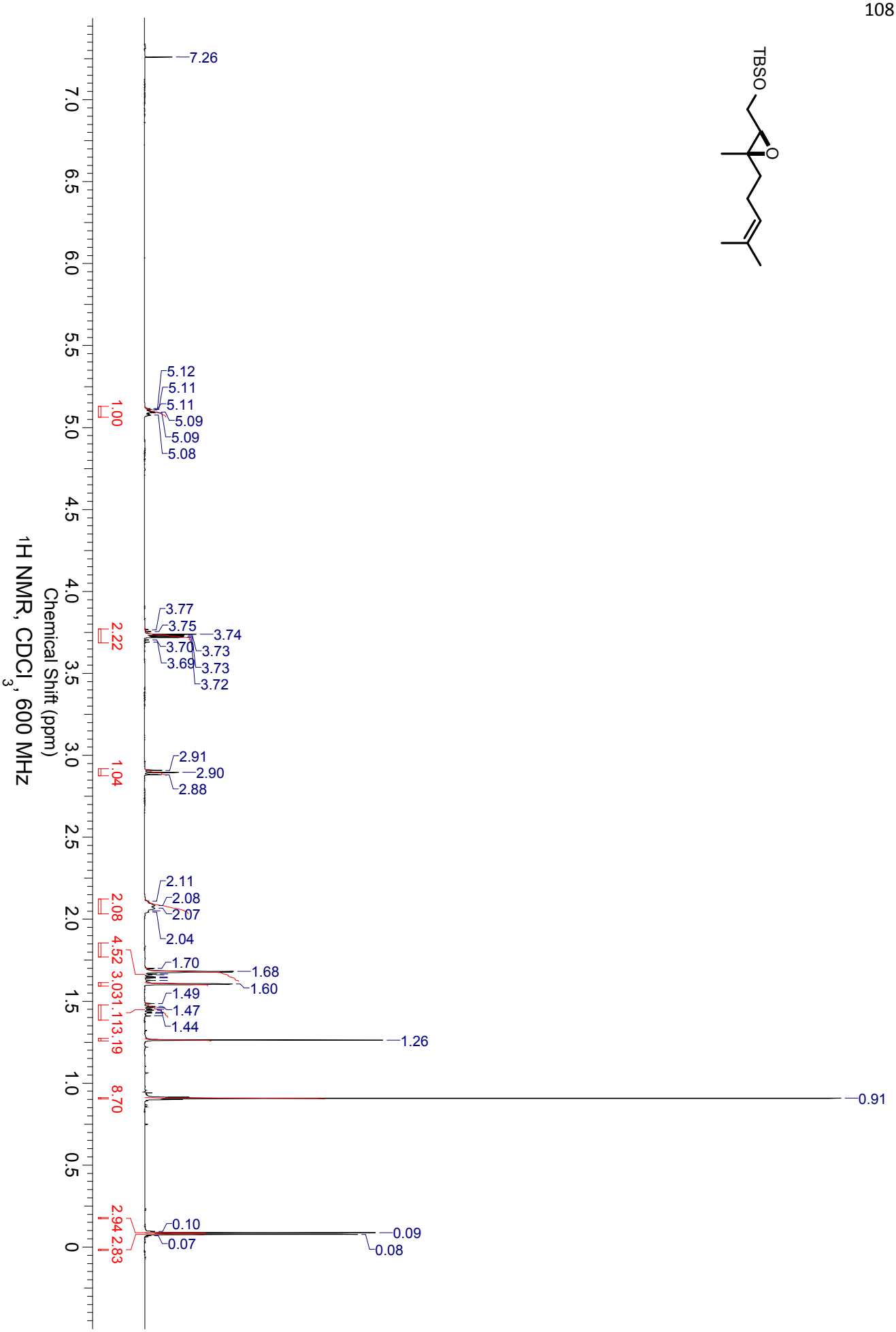




Compound 2-36

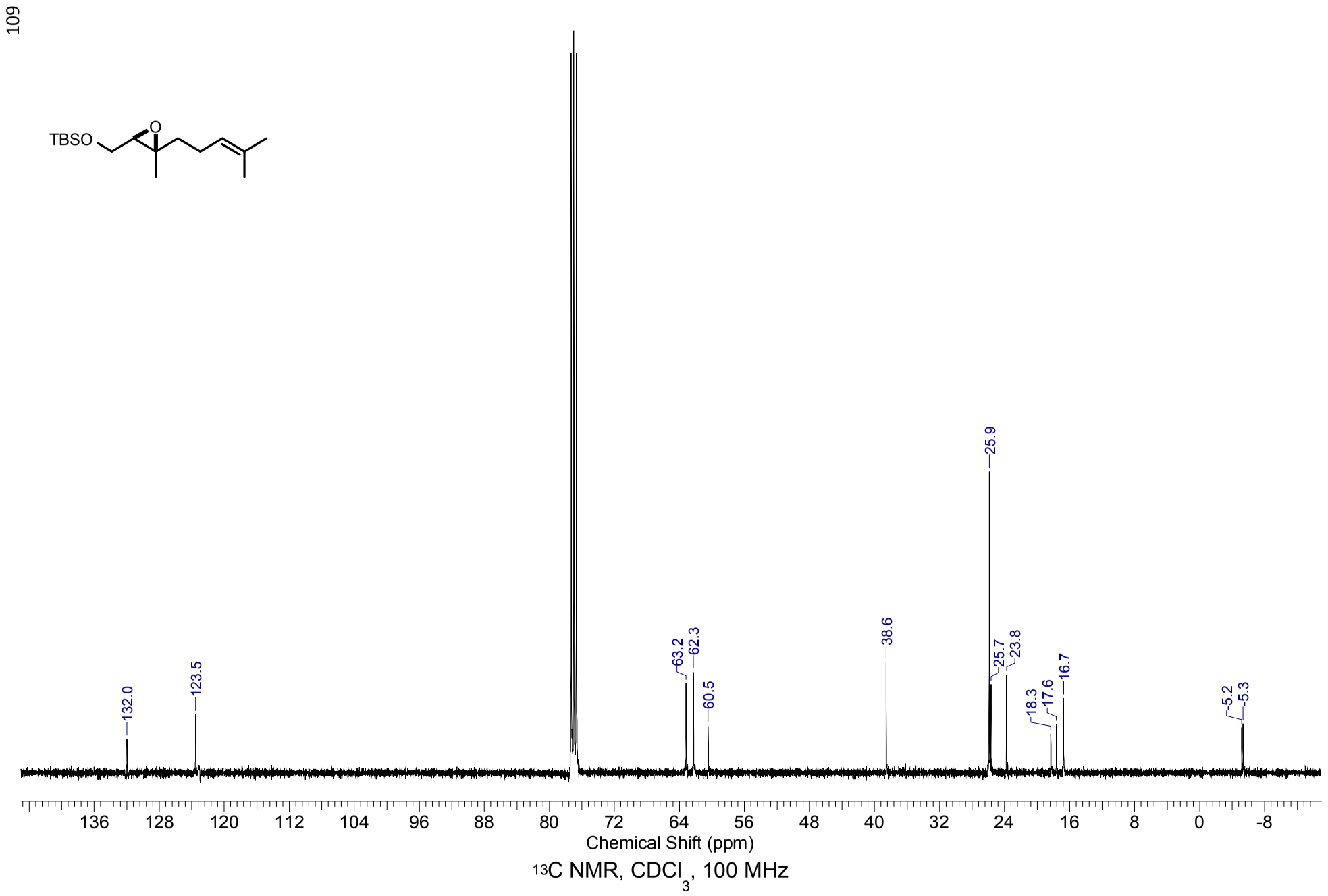
Compound 2-36

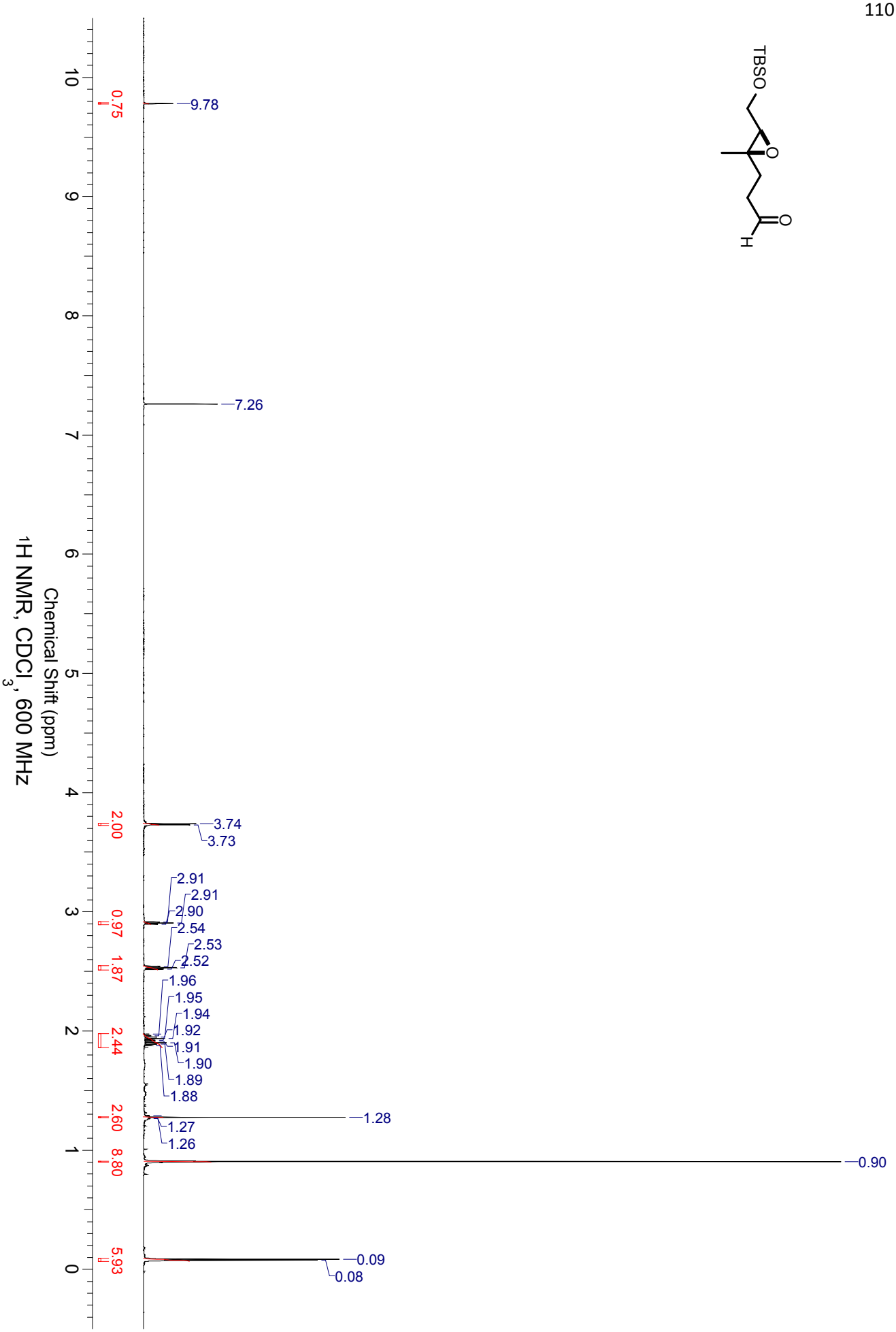




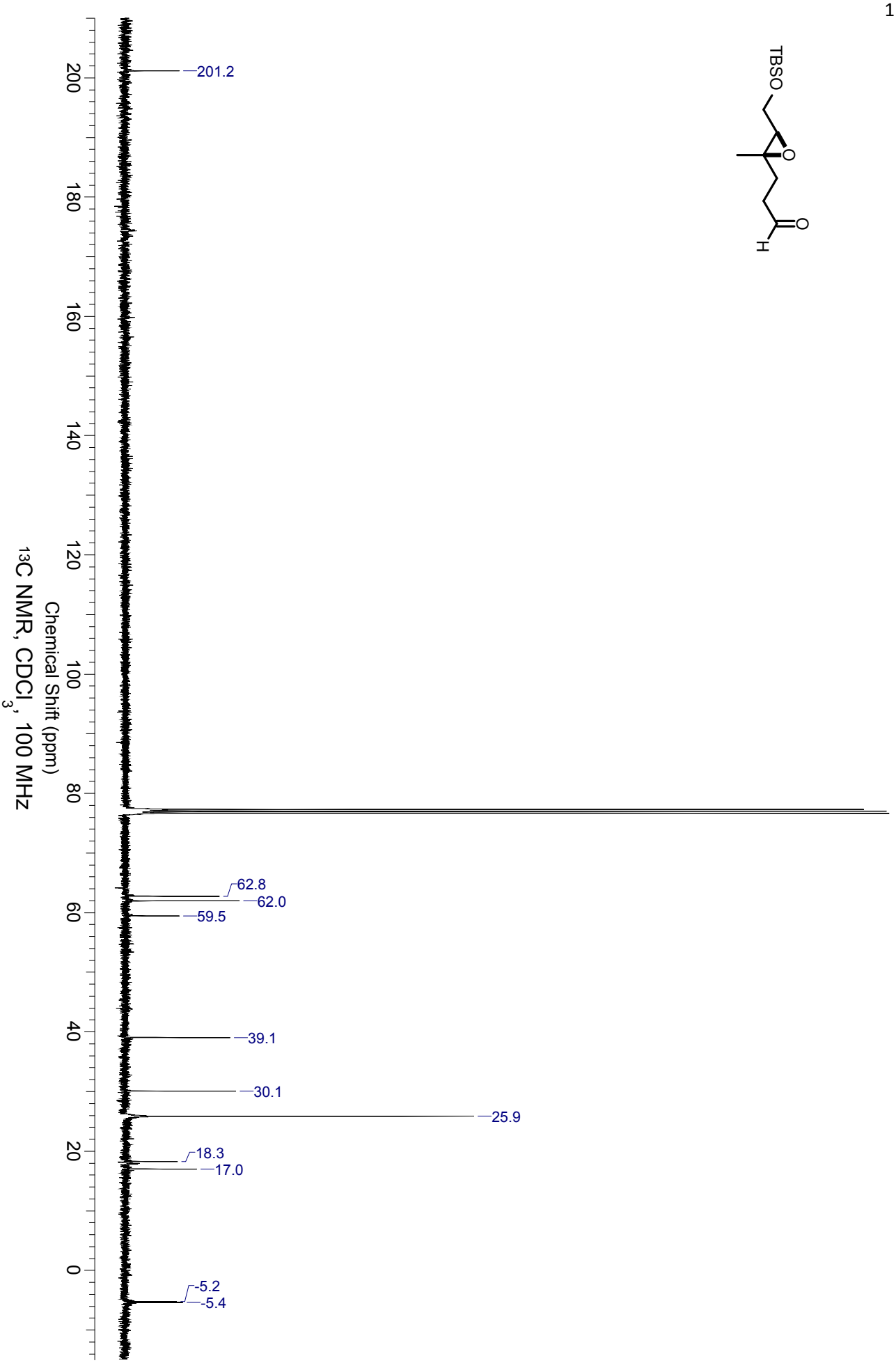
Compound 2-42

Compound 2-42

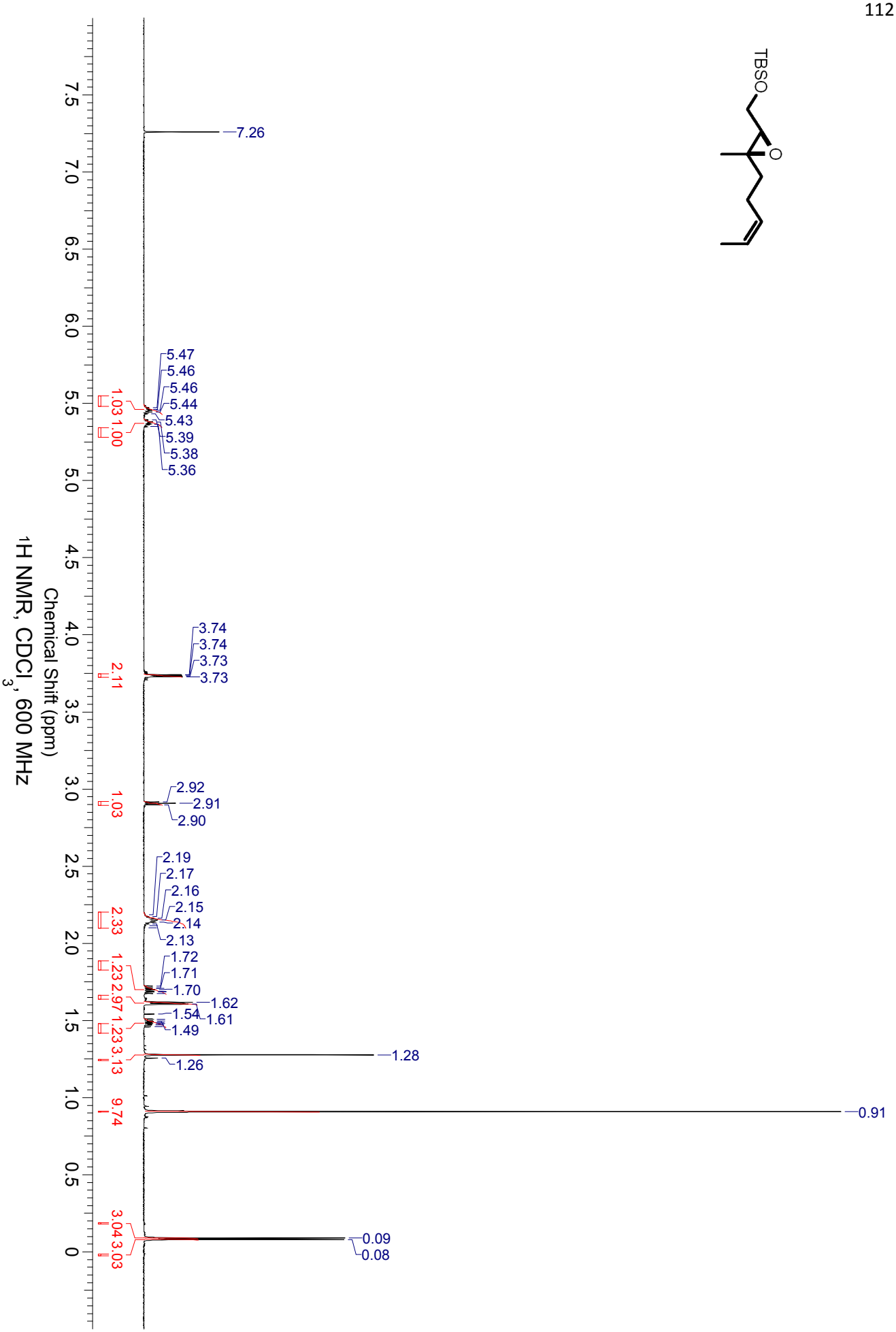




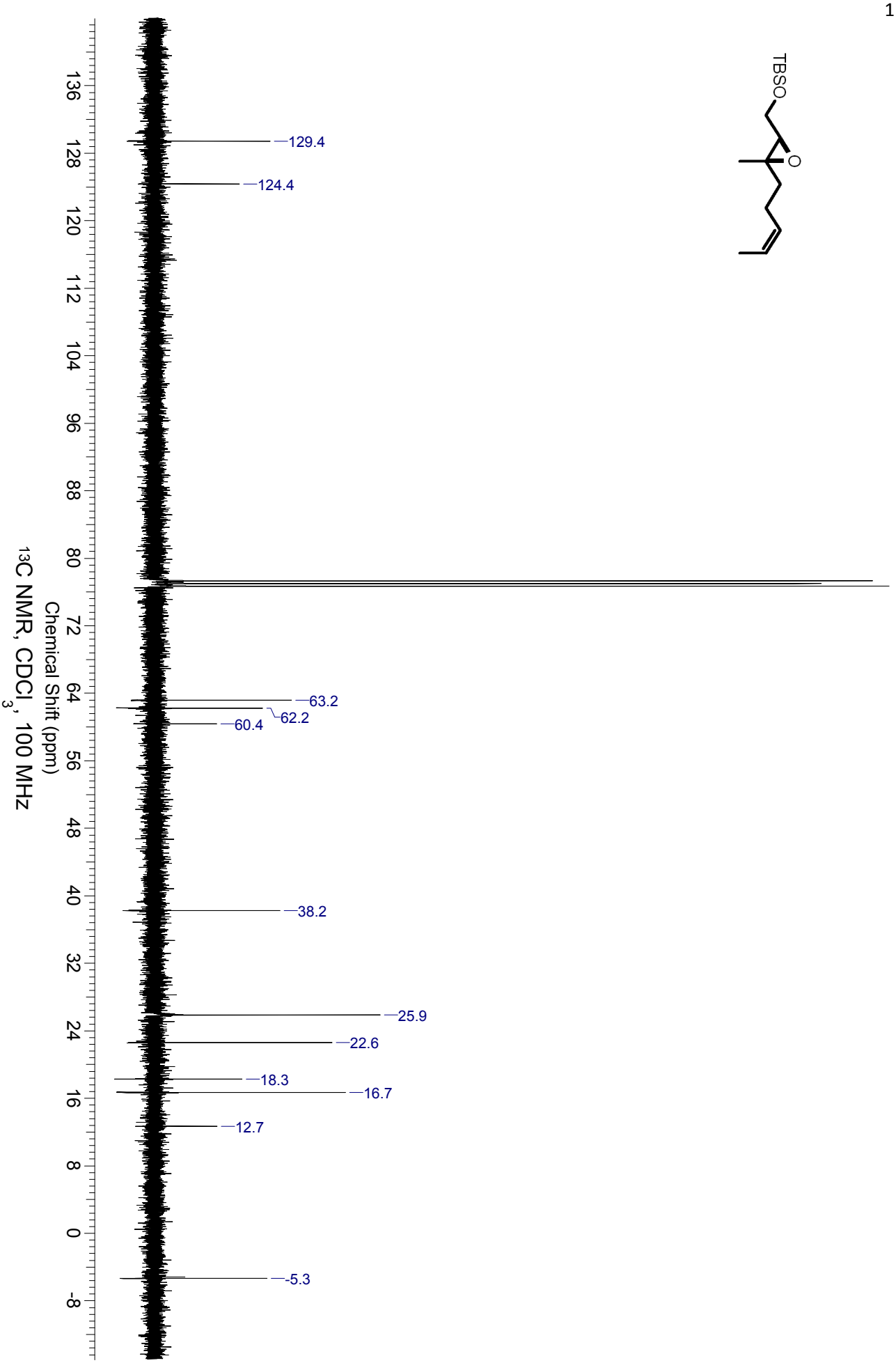
Compound 2-44



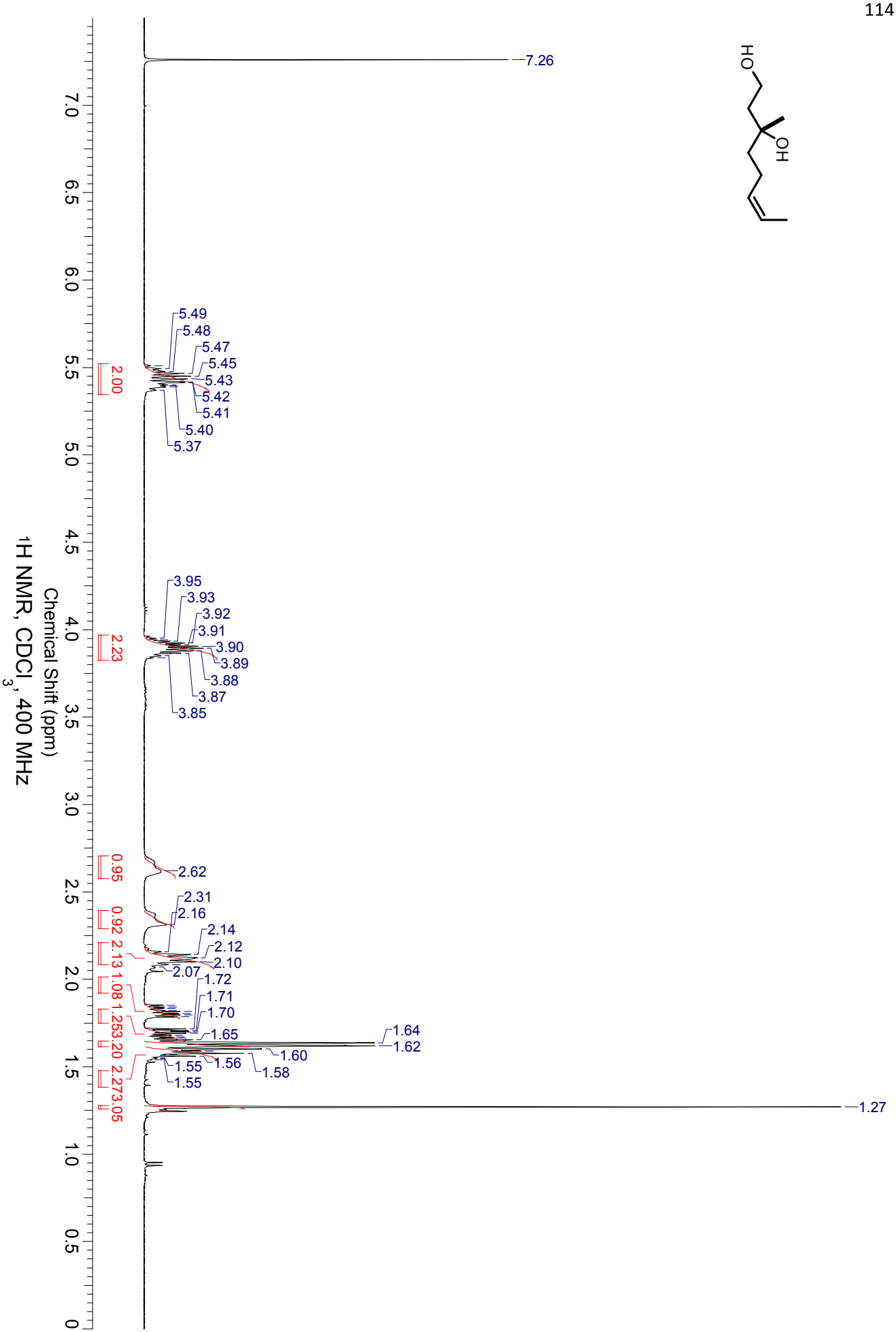
Compound 2-44



Compound 2-45

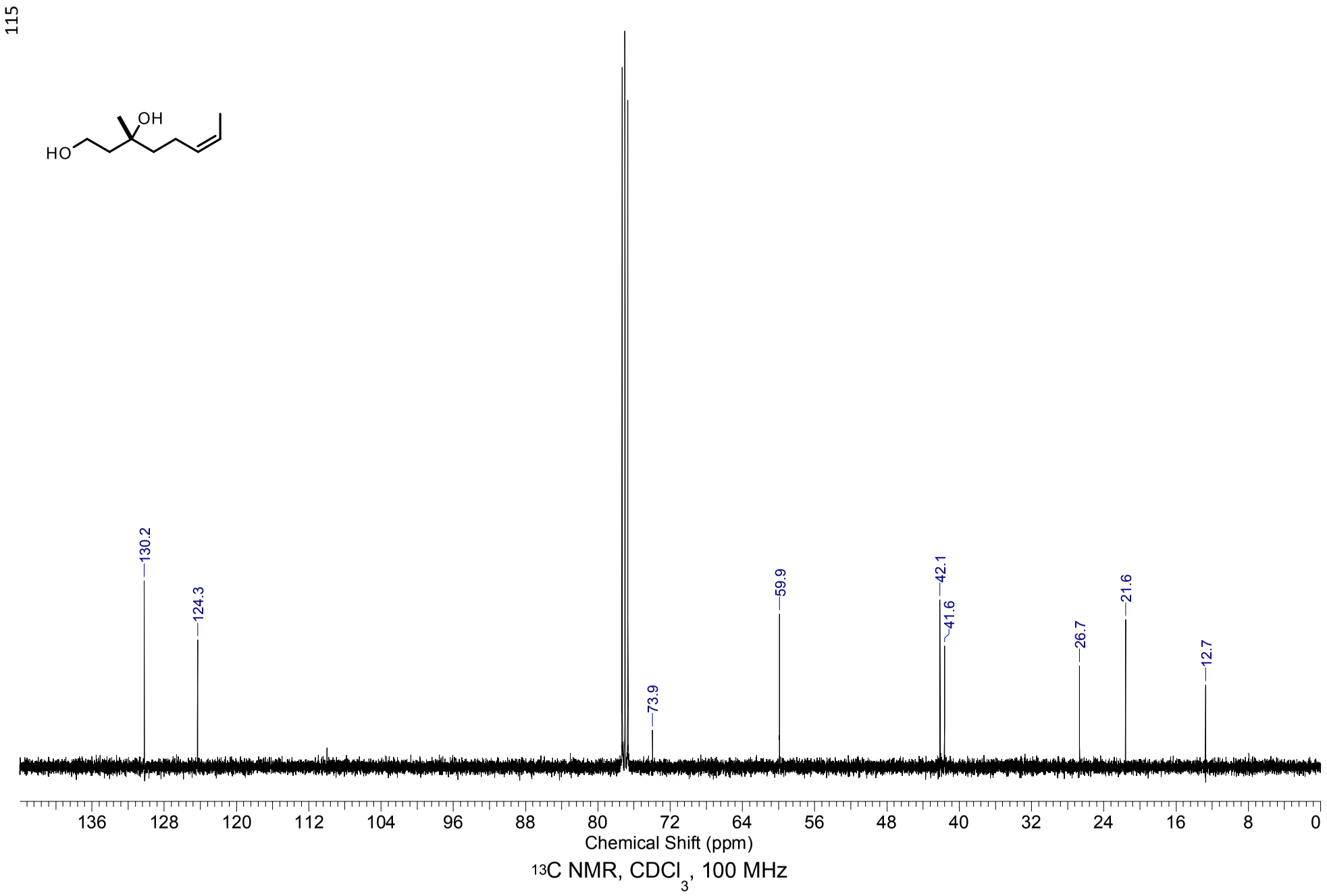


Compound 2-45

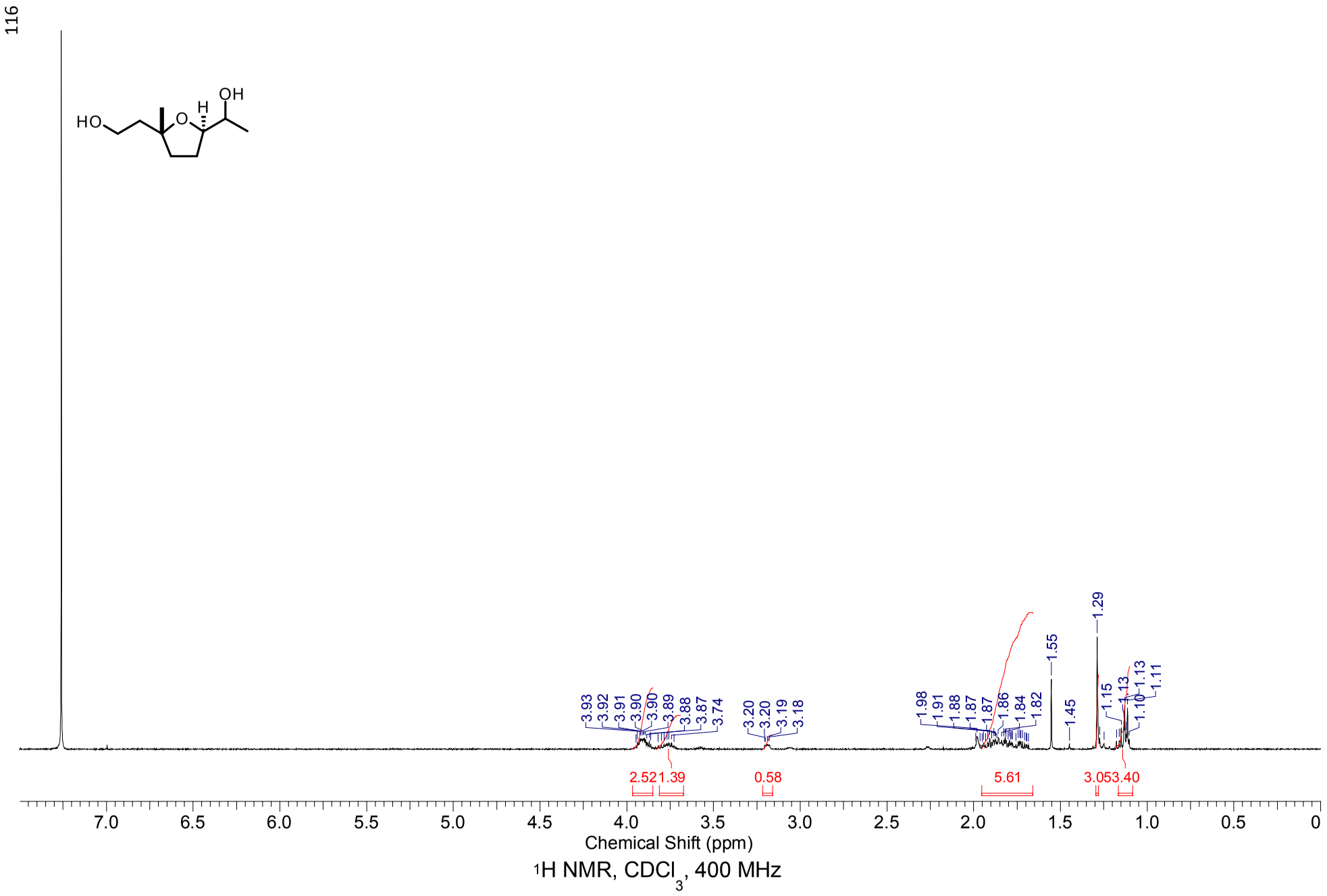


Compound 2-46

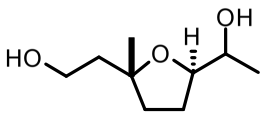
Compound 2-46



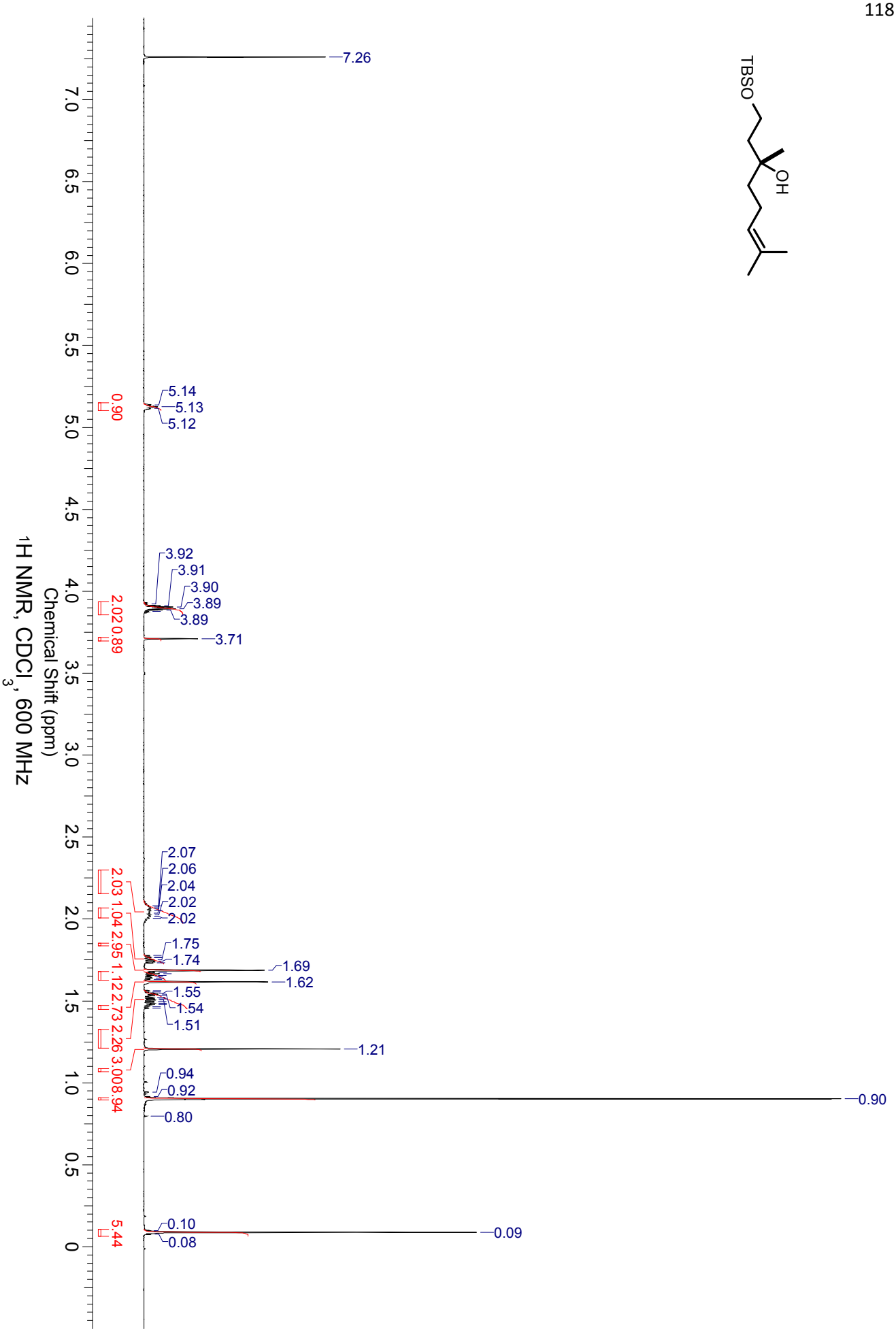
Compound 2-47



Compound 2-47

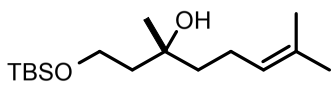


^{13}C NMR, $CDCl_3$, 100 MHz

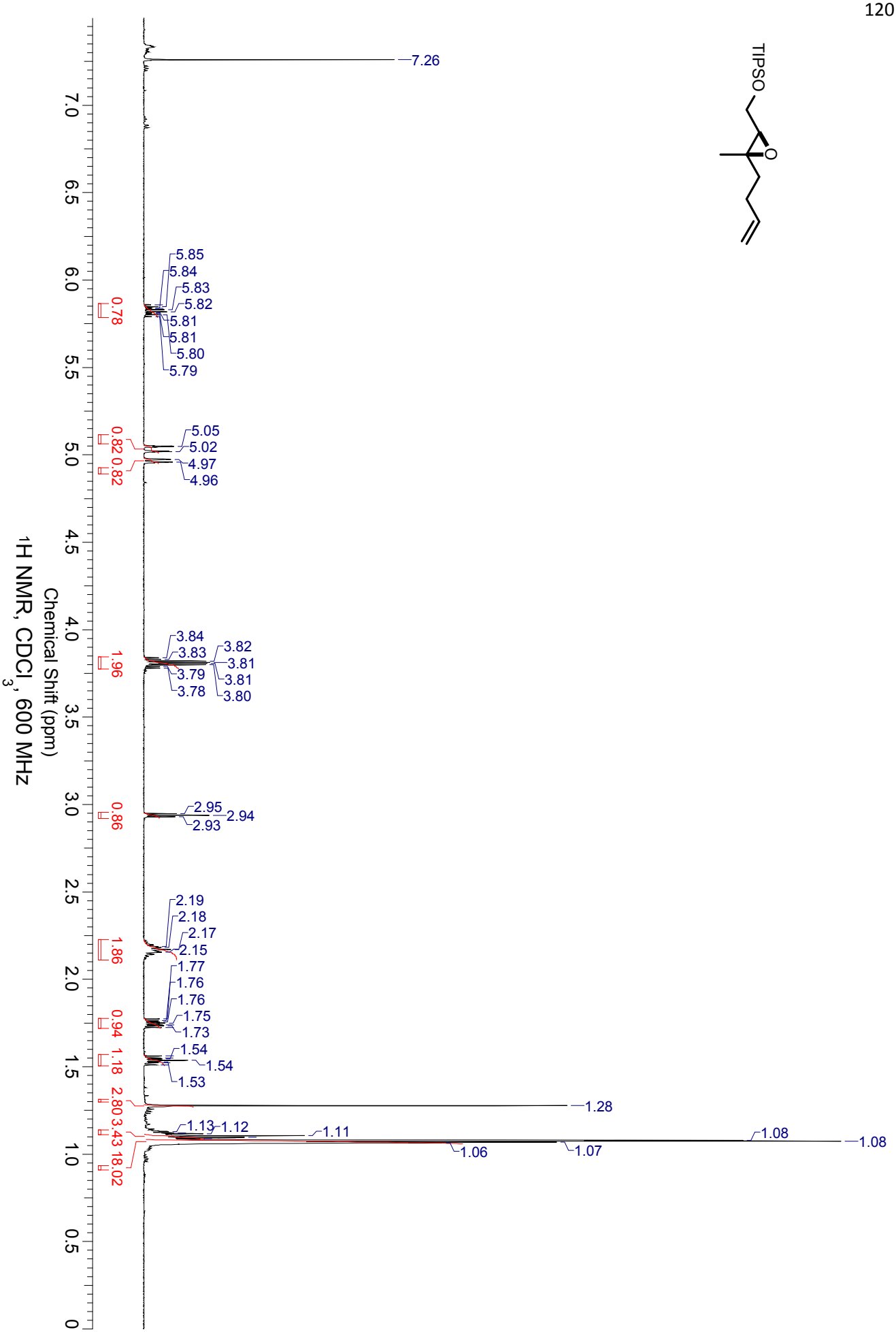


Compound 2-51

Compound 2-51

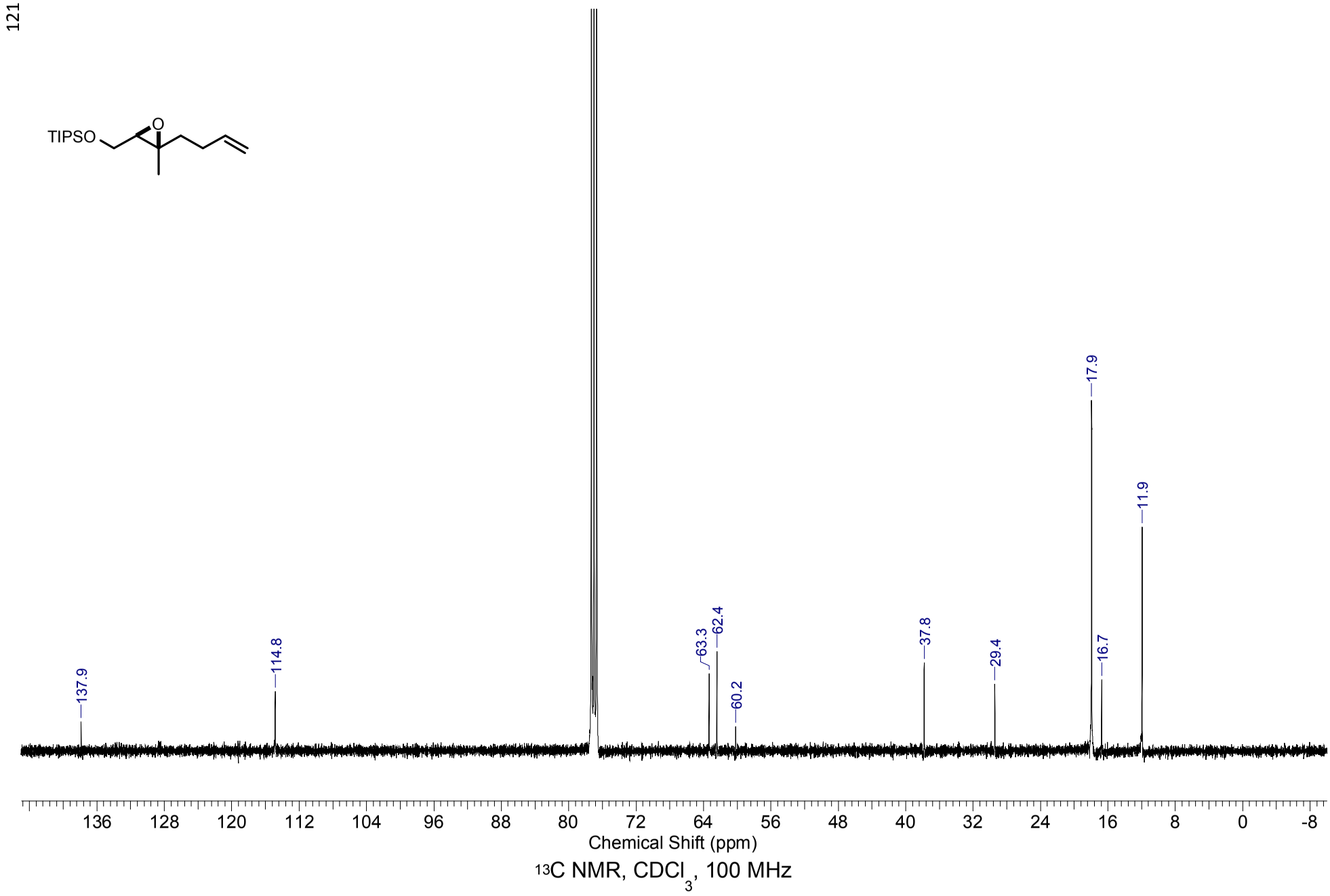


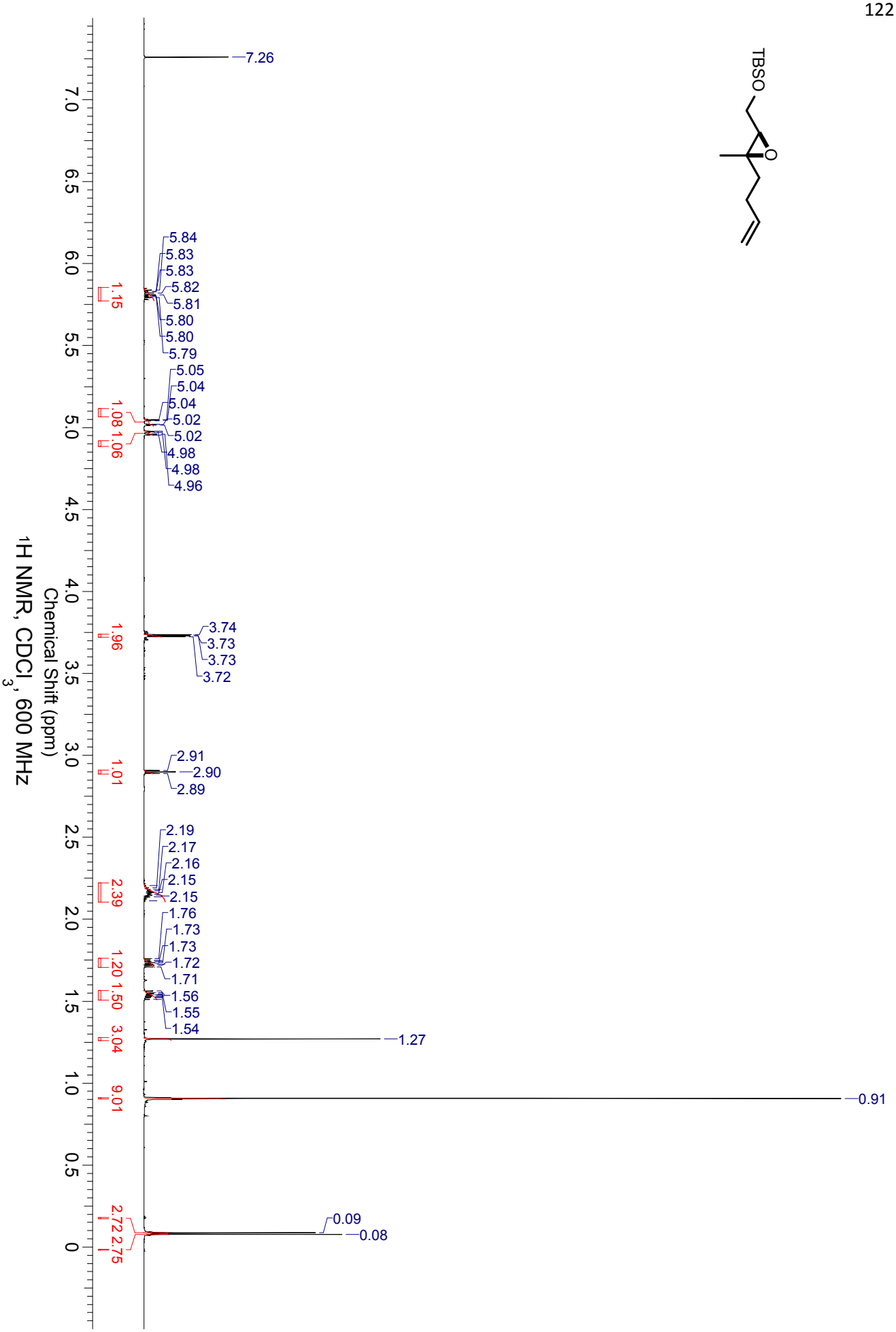
^{13}C NMR, $CDCl_3$, 100 MHz



Compound 2-53

Compound 2-53



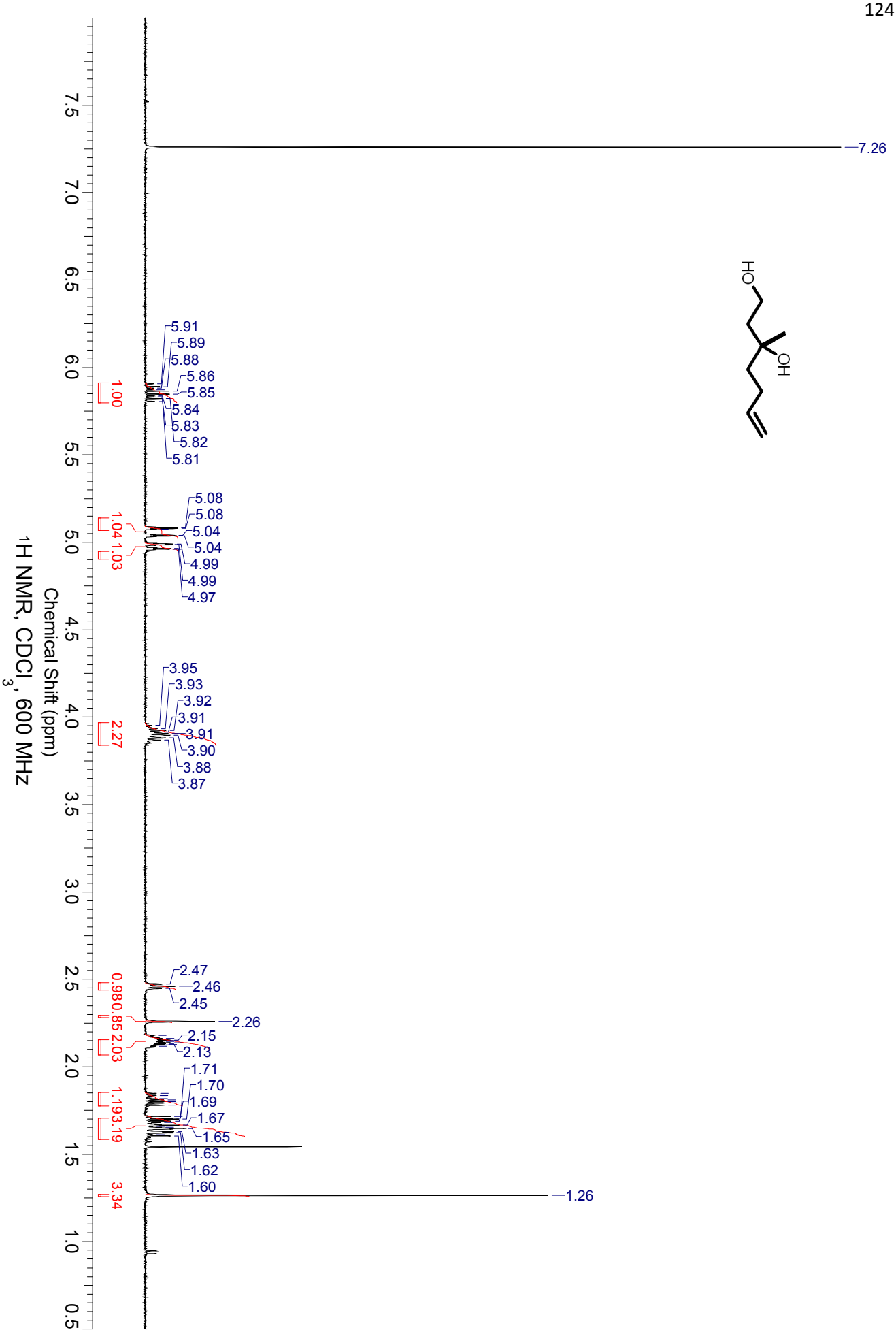


Compound 2-56

Compound 2-56

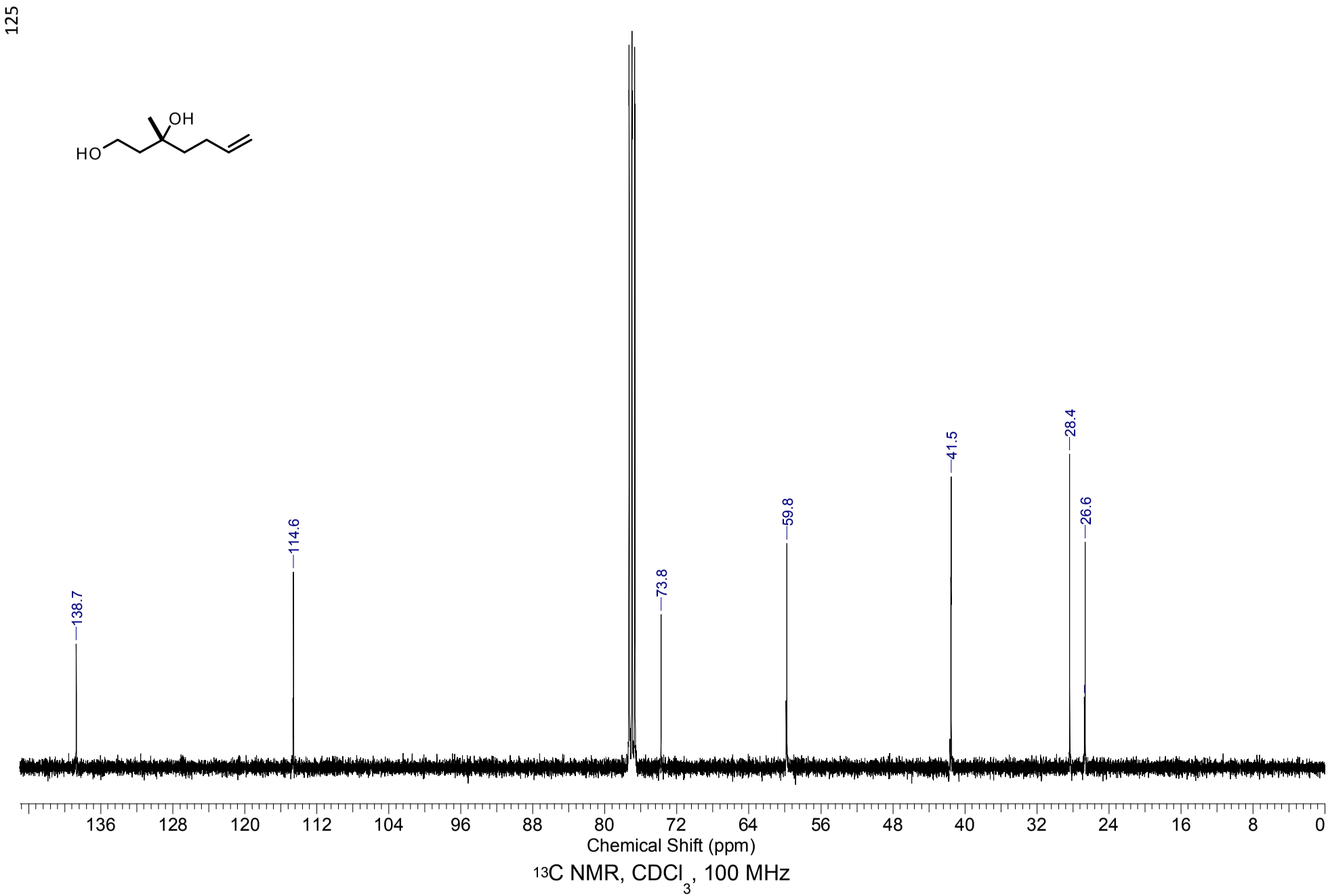
123

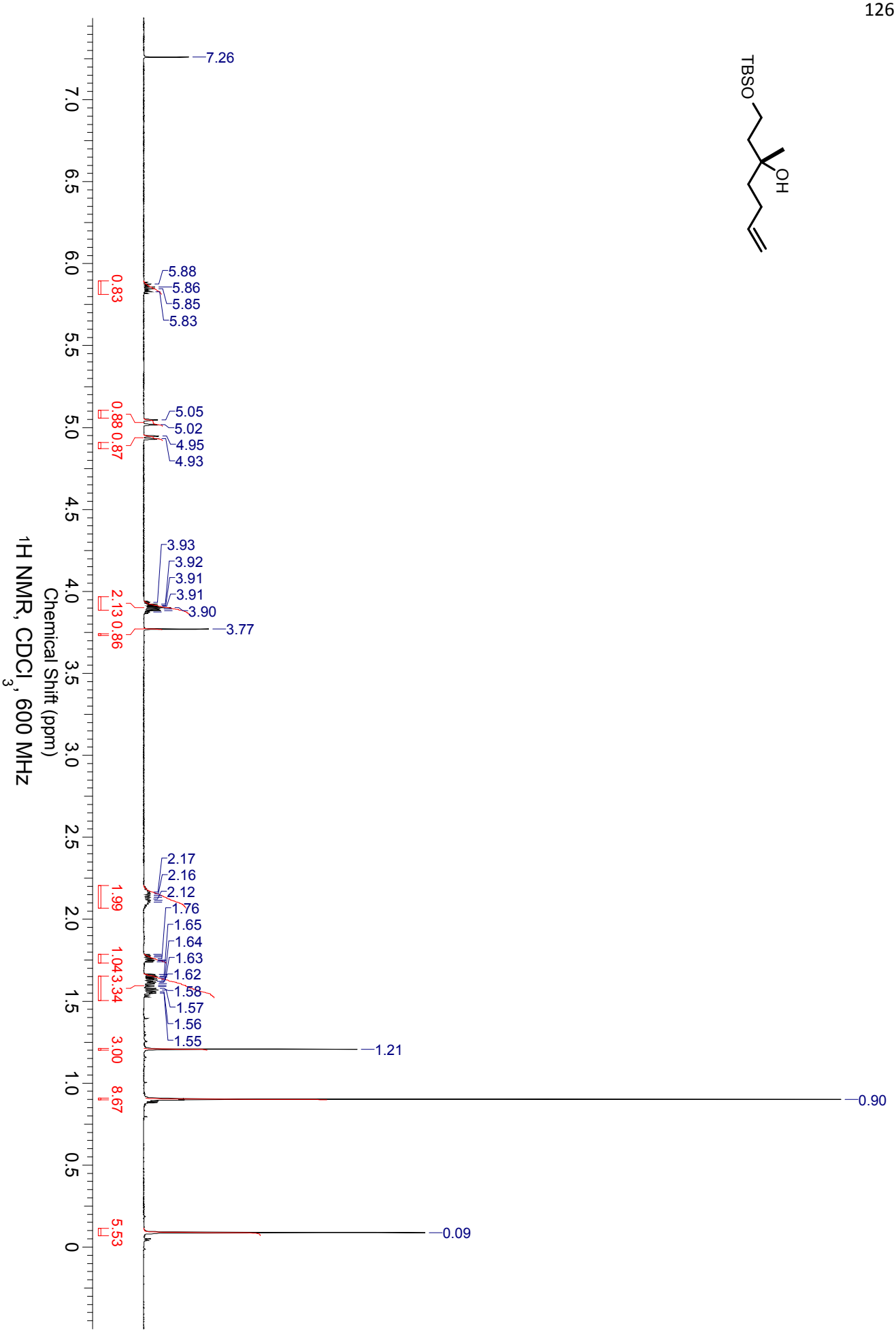
^{13}C NMR, $CDCl_3$, 100 MHz



Compound 2-55

Compound 2-55





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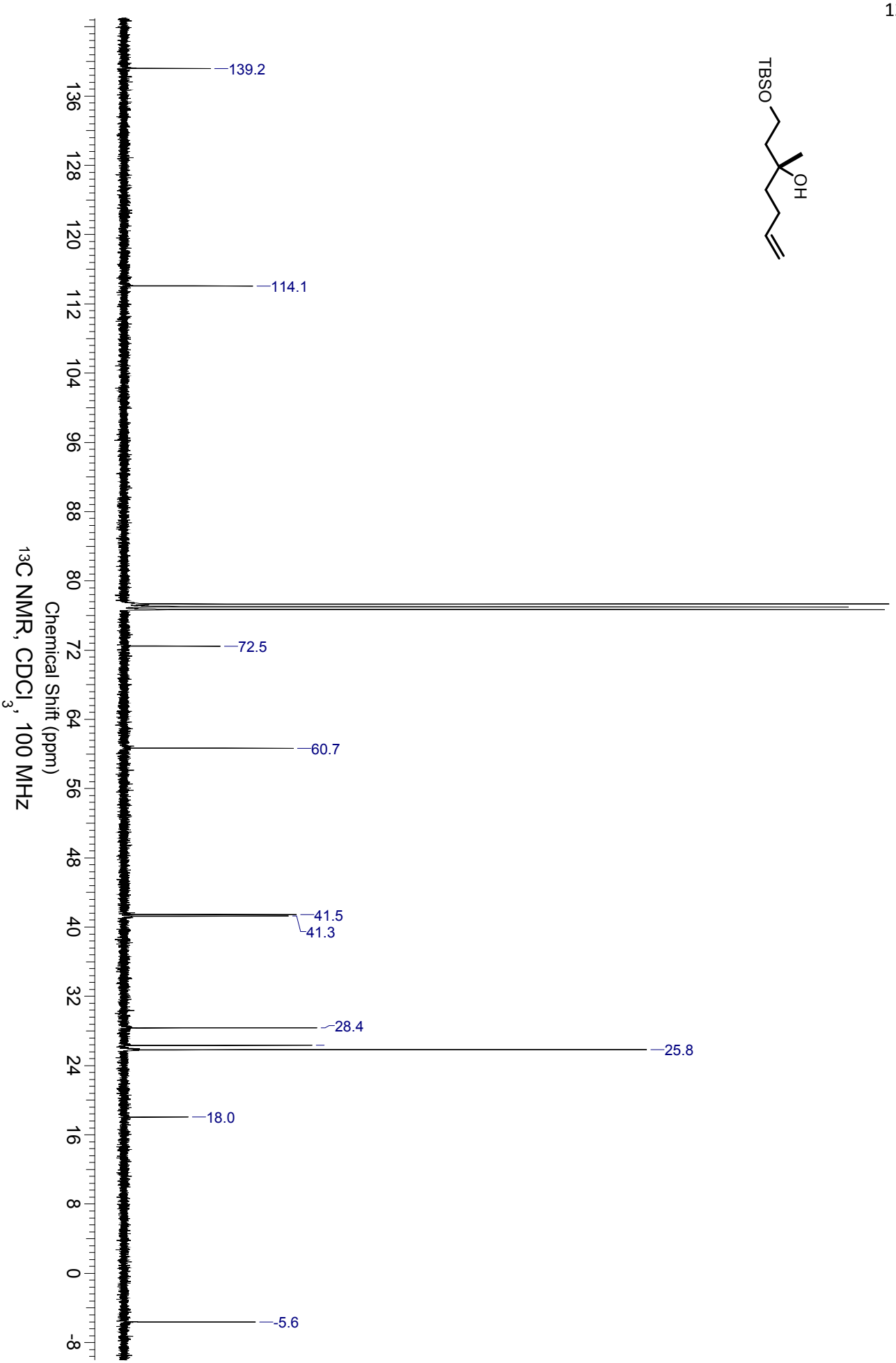
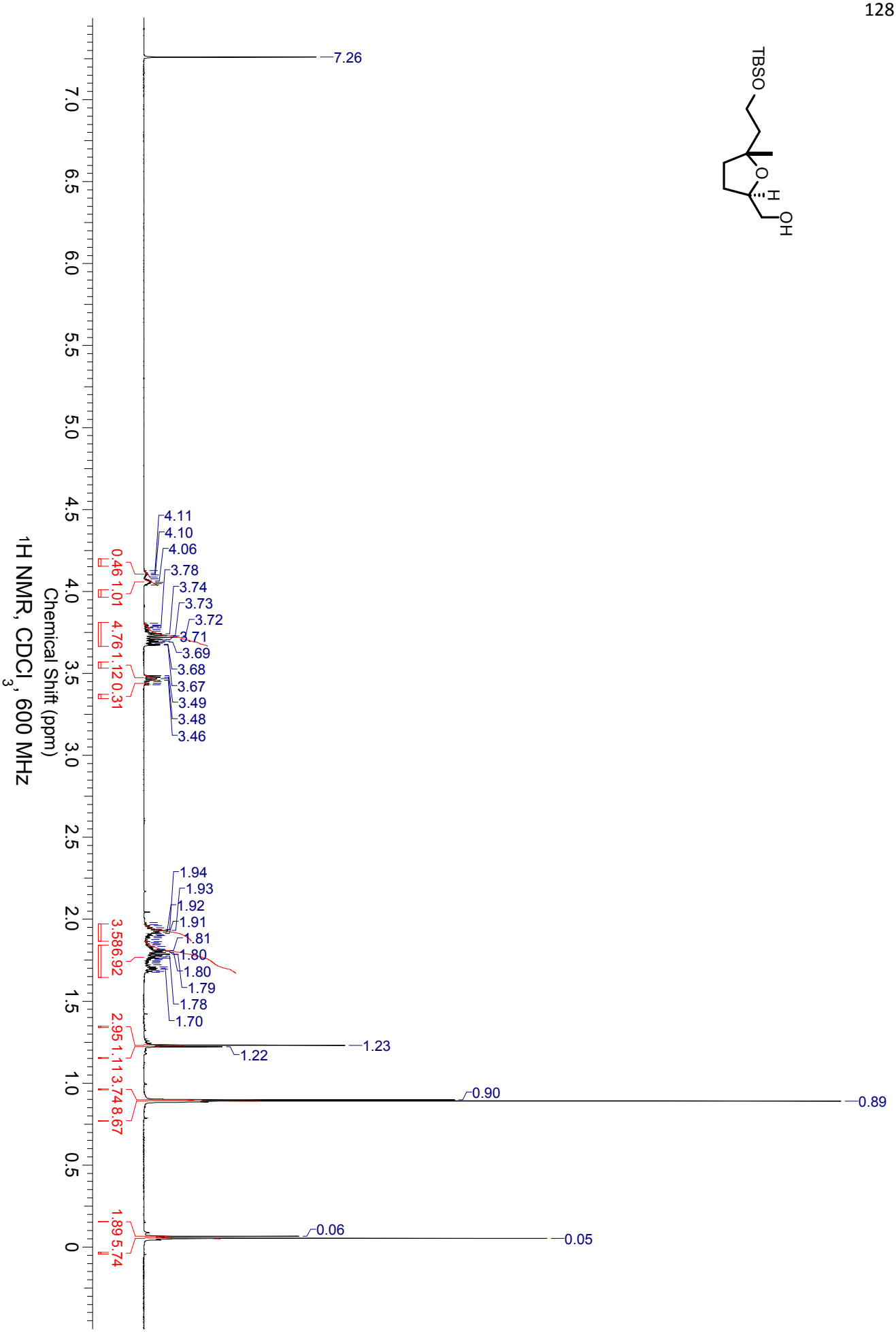
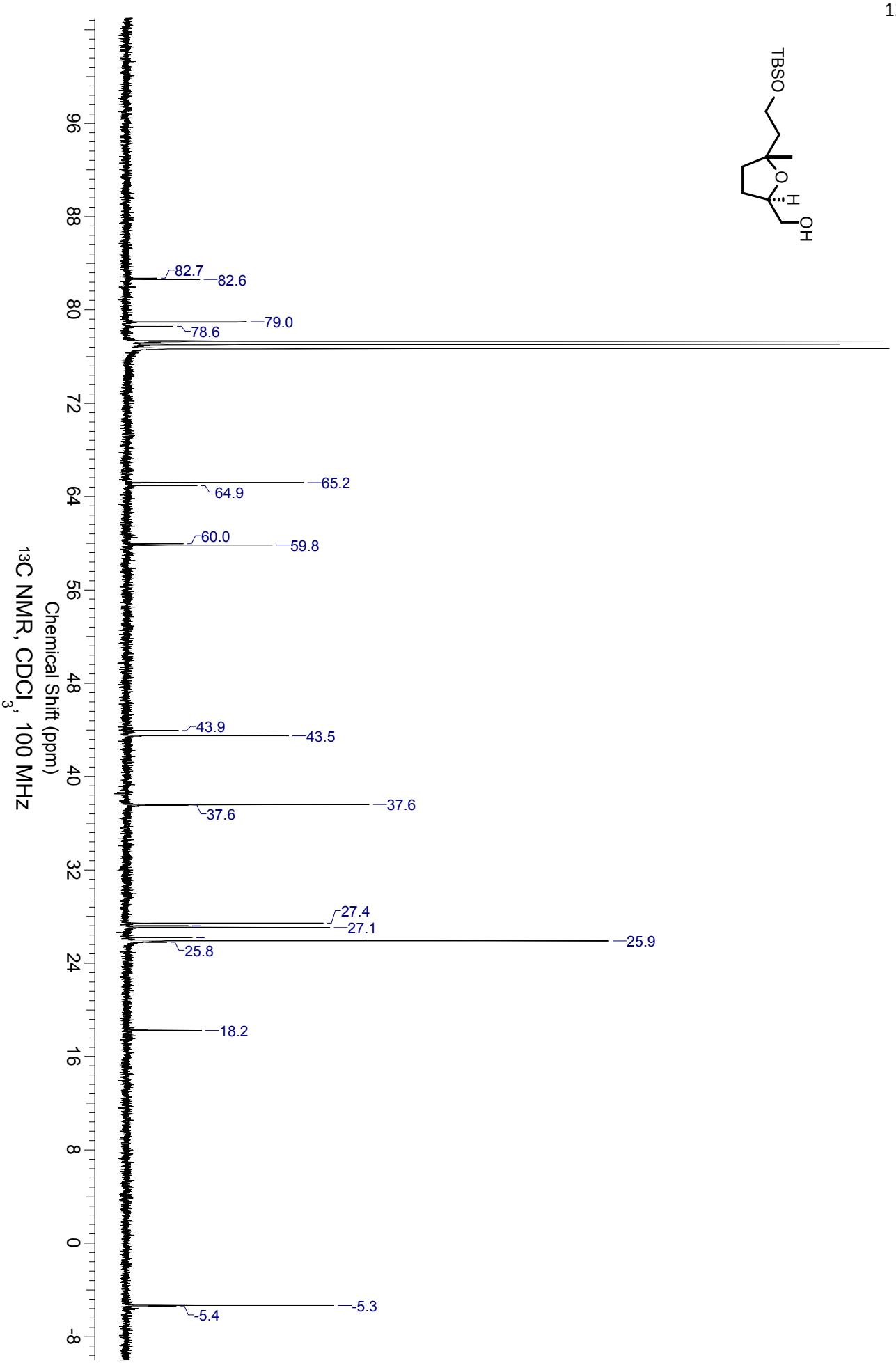


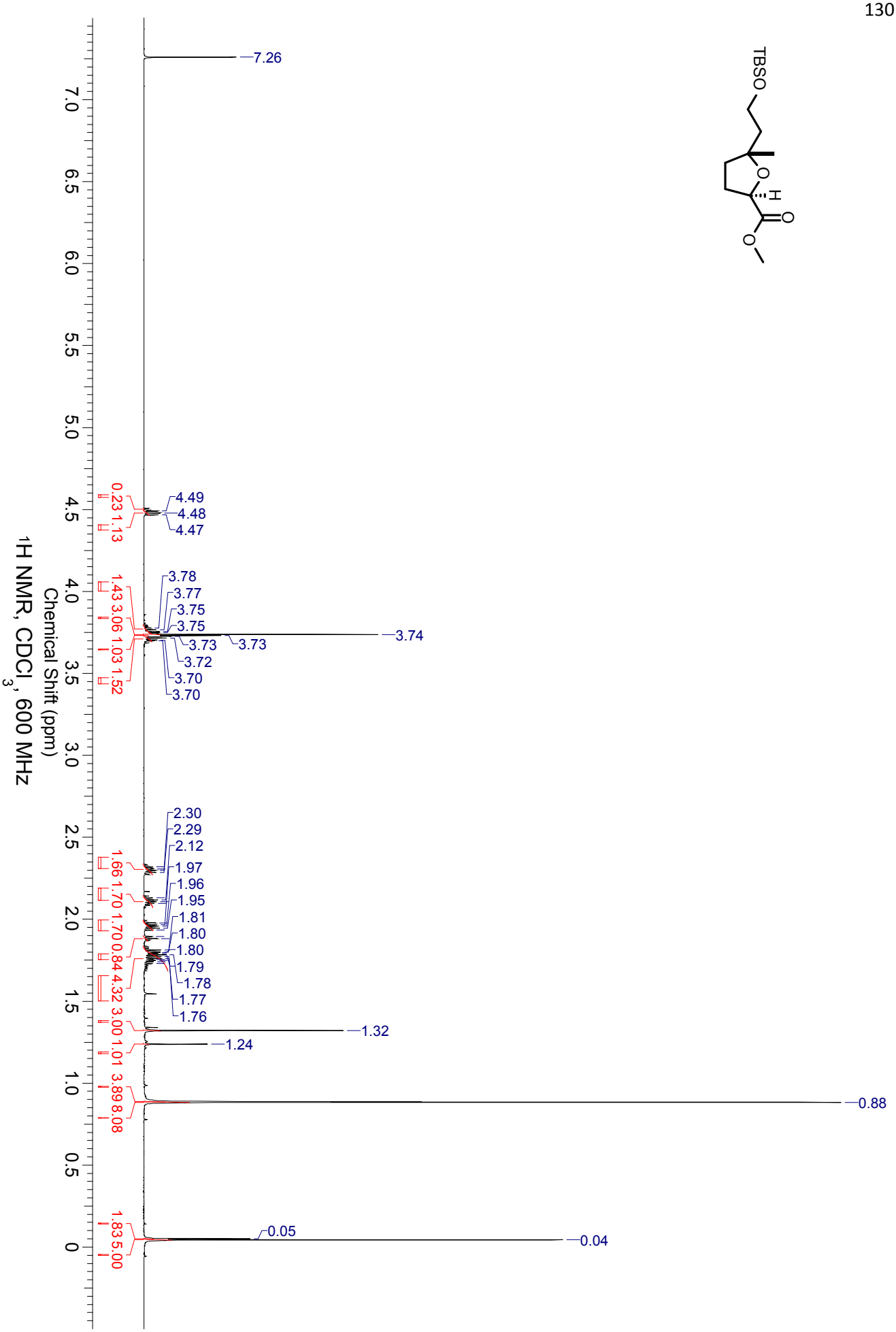
Compound 2-50



Compound 2-49

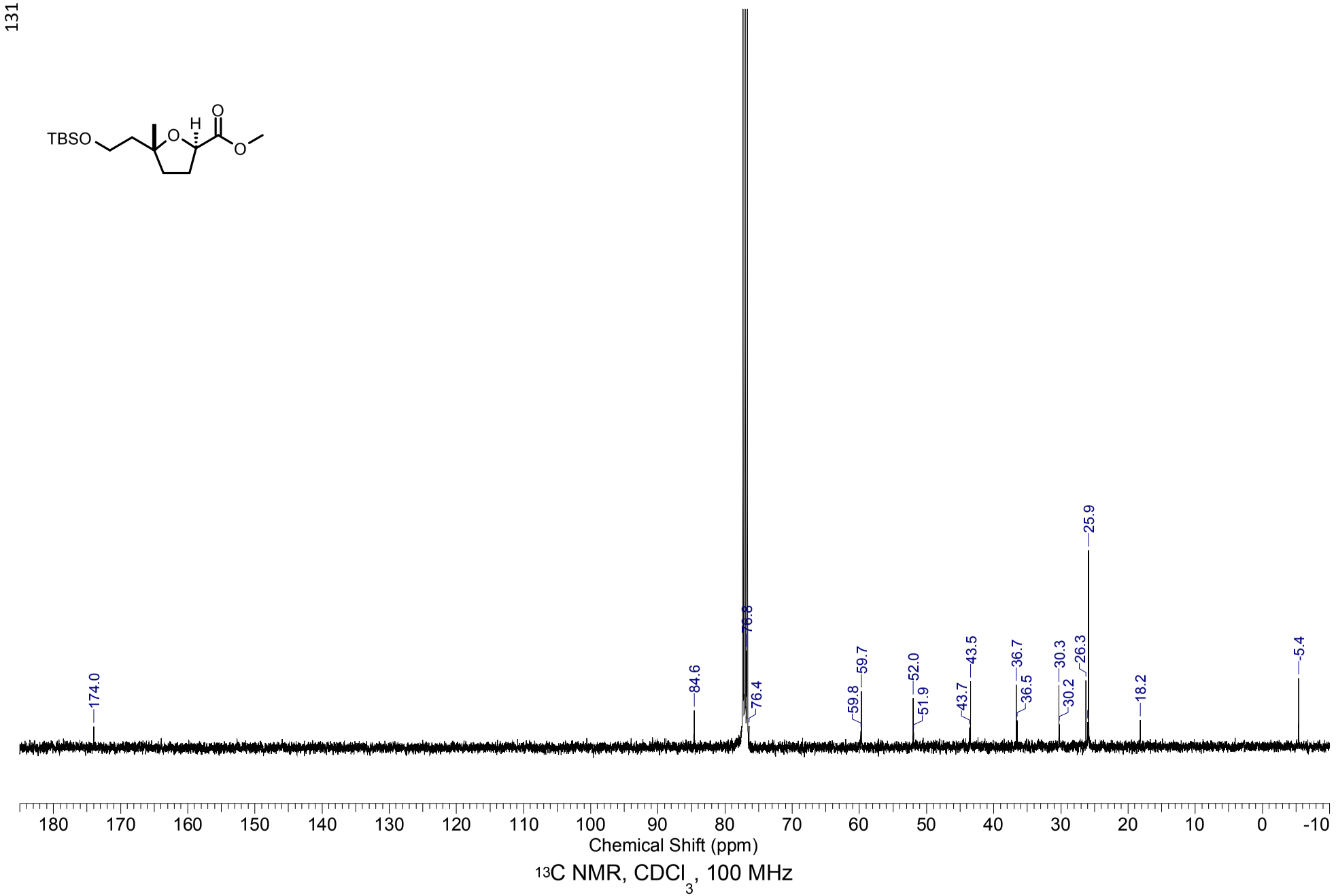


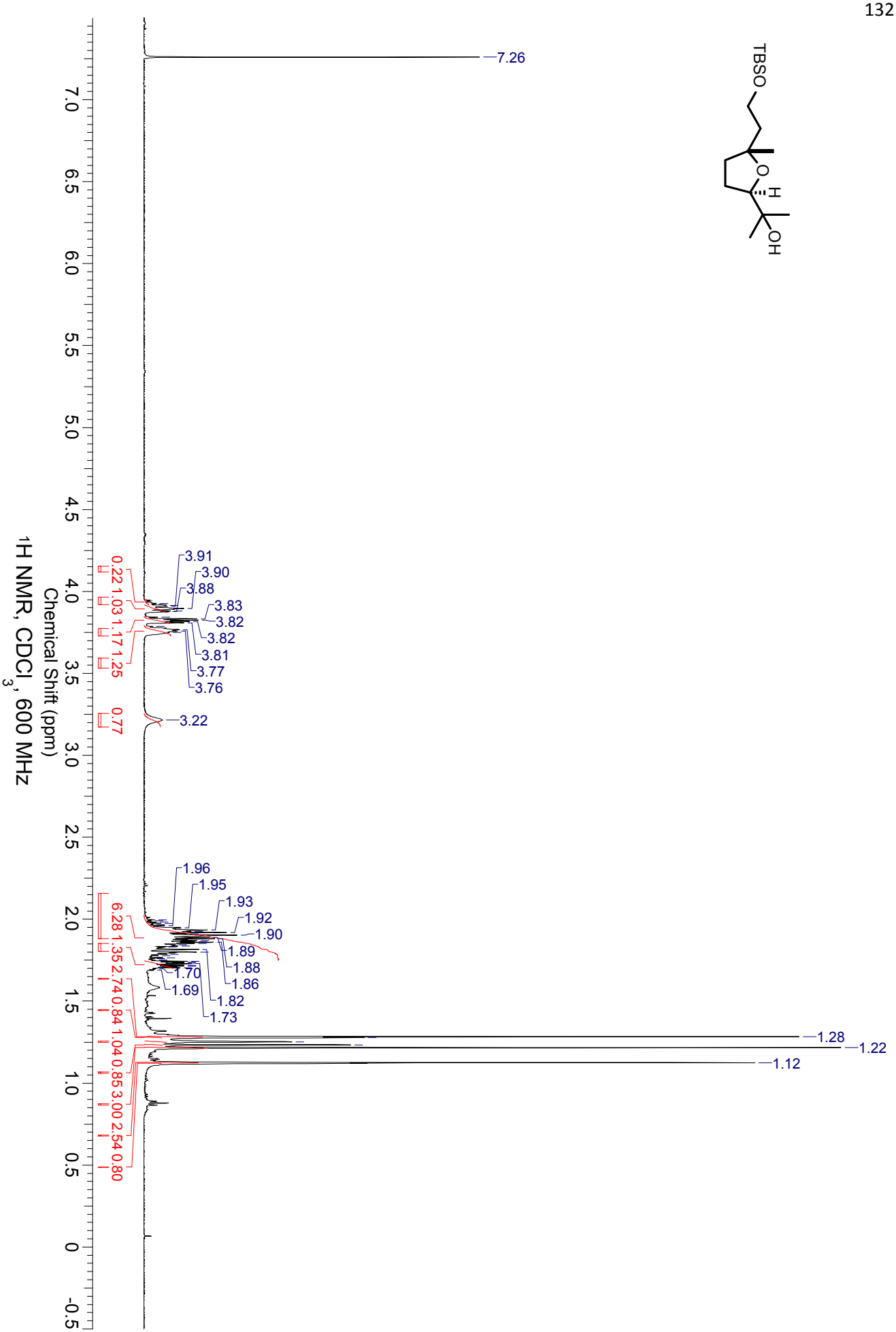
Compound 2-49



Compound 2-57

Compound 2-57

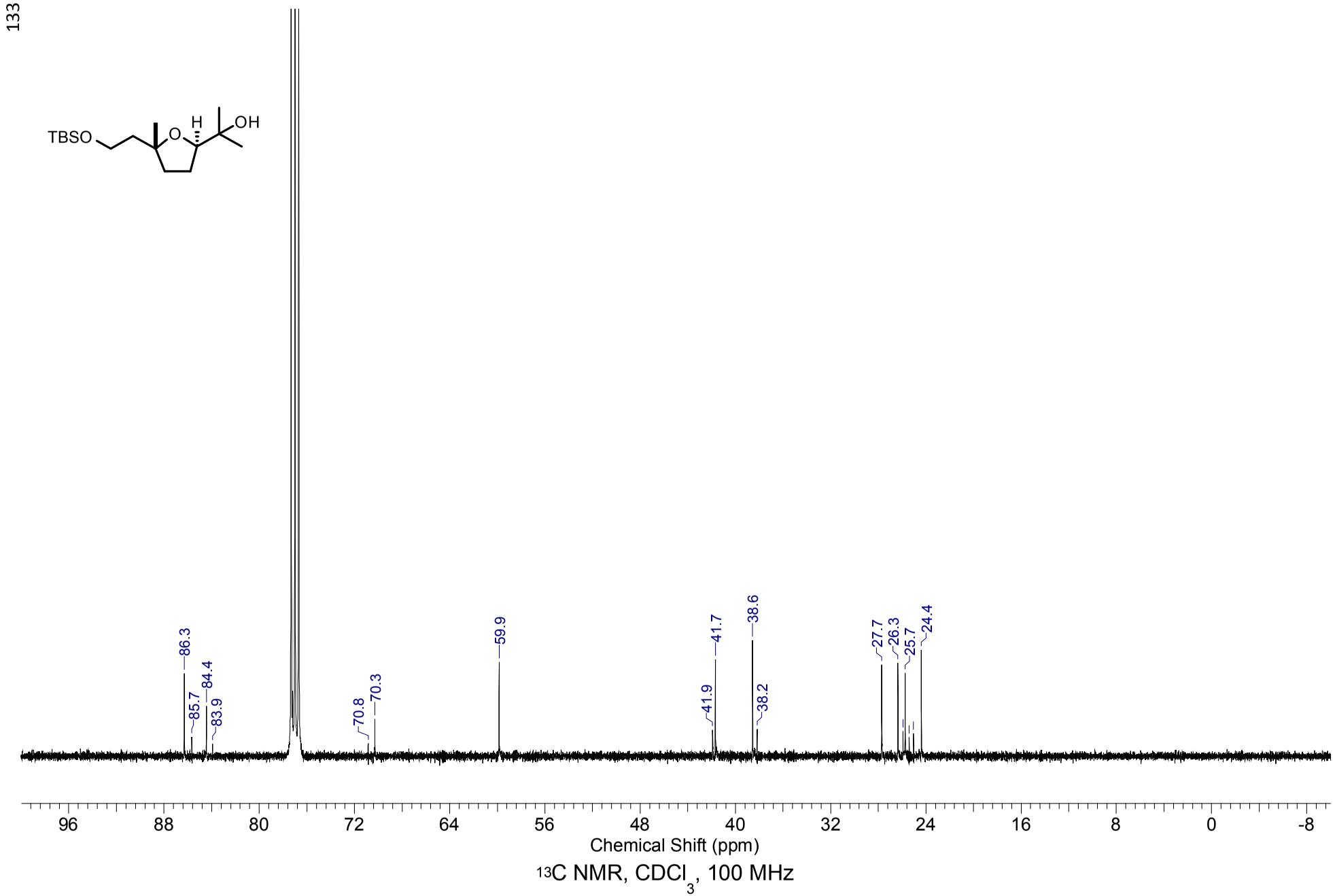


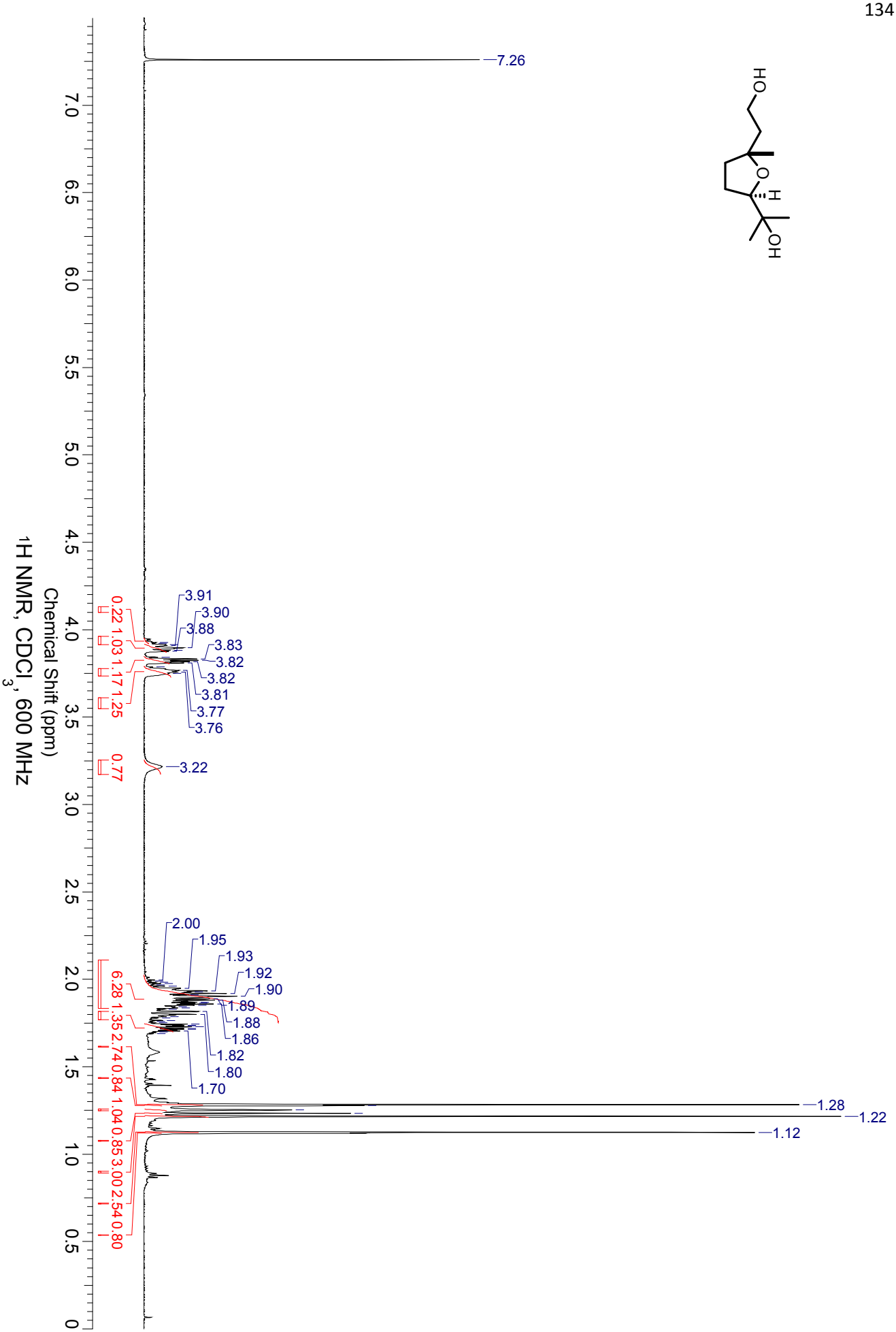


^{1}H NMR, $CDCl_3$, 600 MHz

Compound 2-48

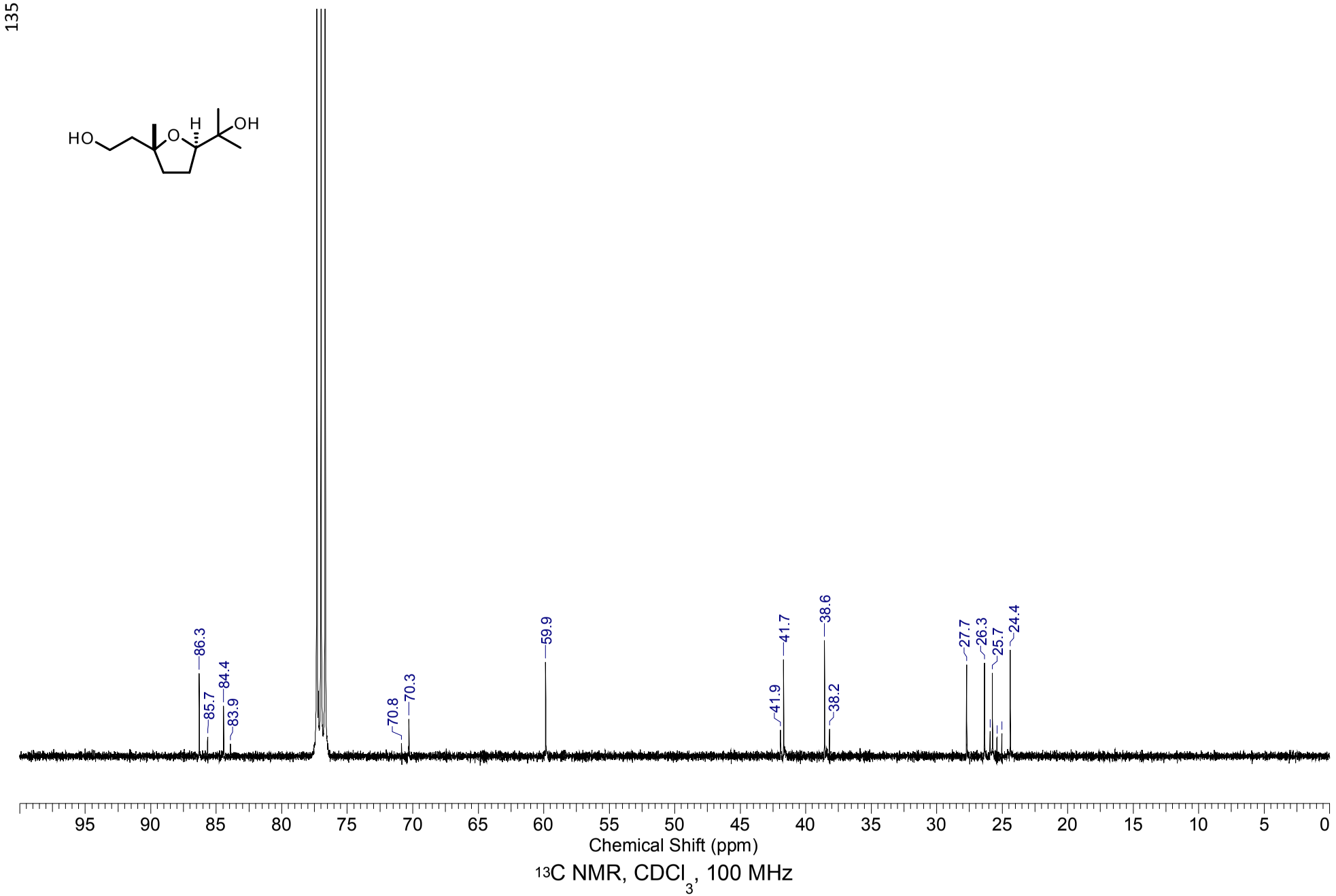
Compound 2-48

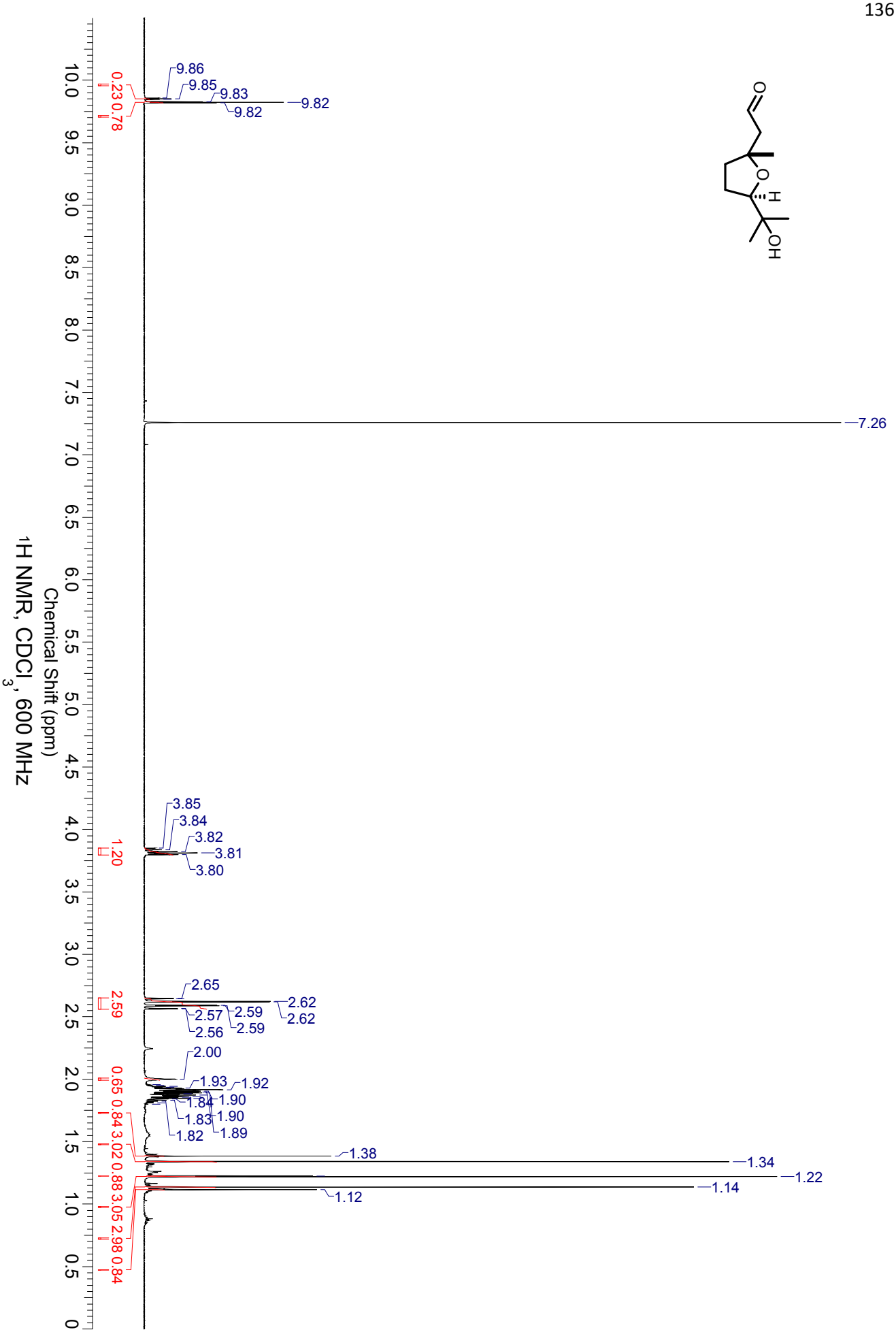




Compound 2-25

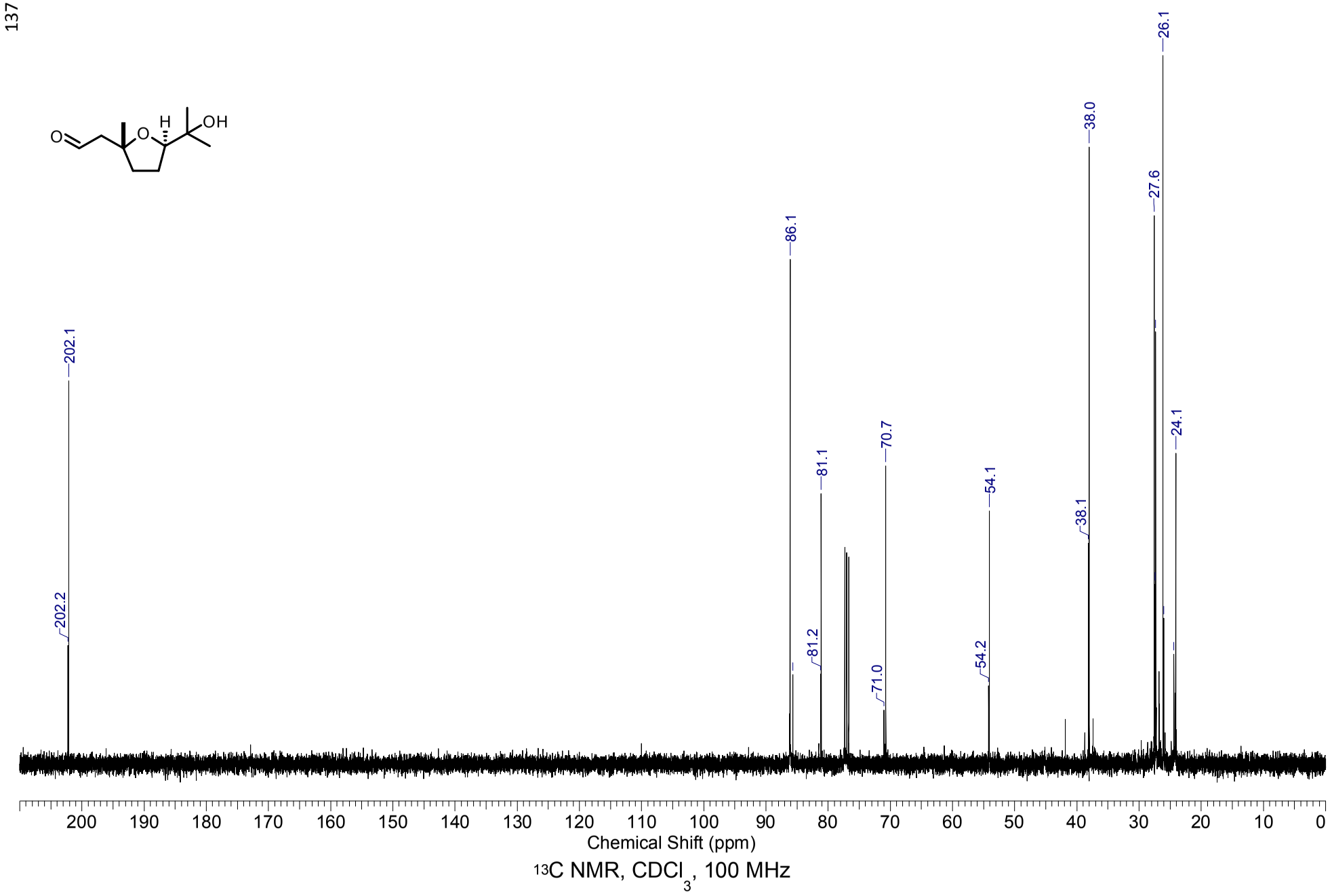
Compound 2-25

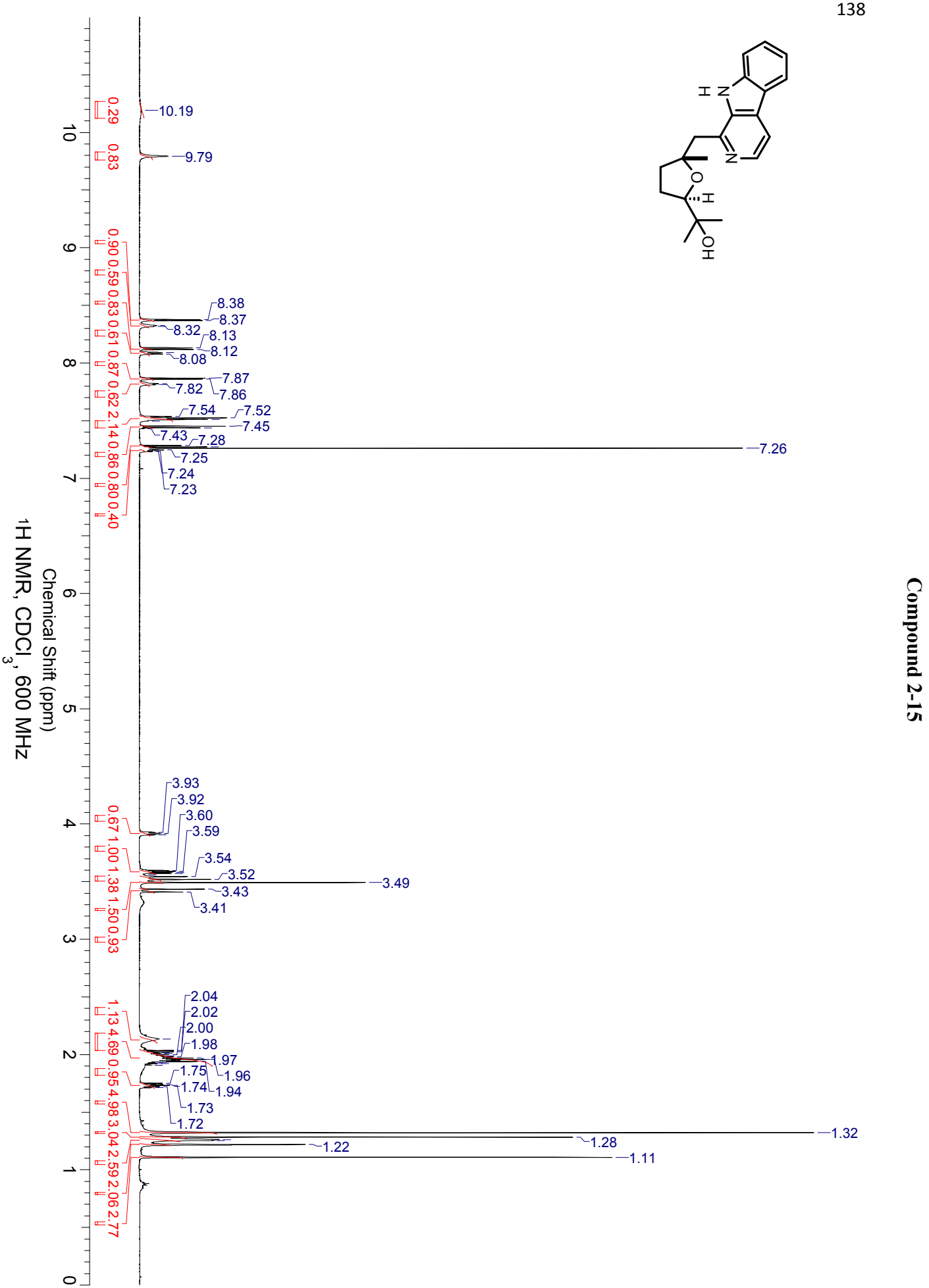




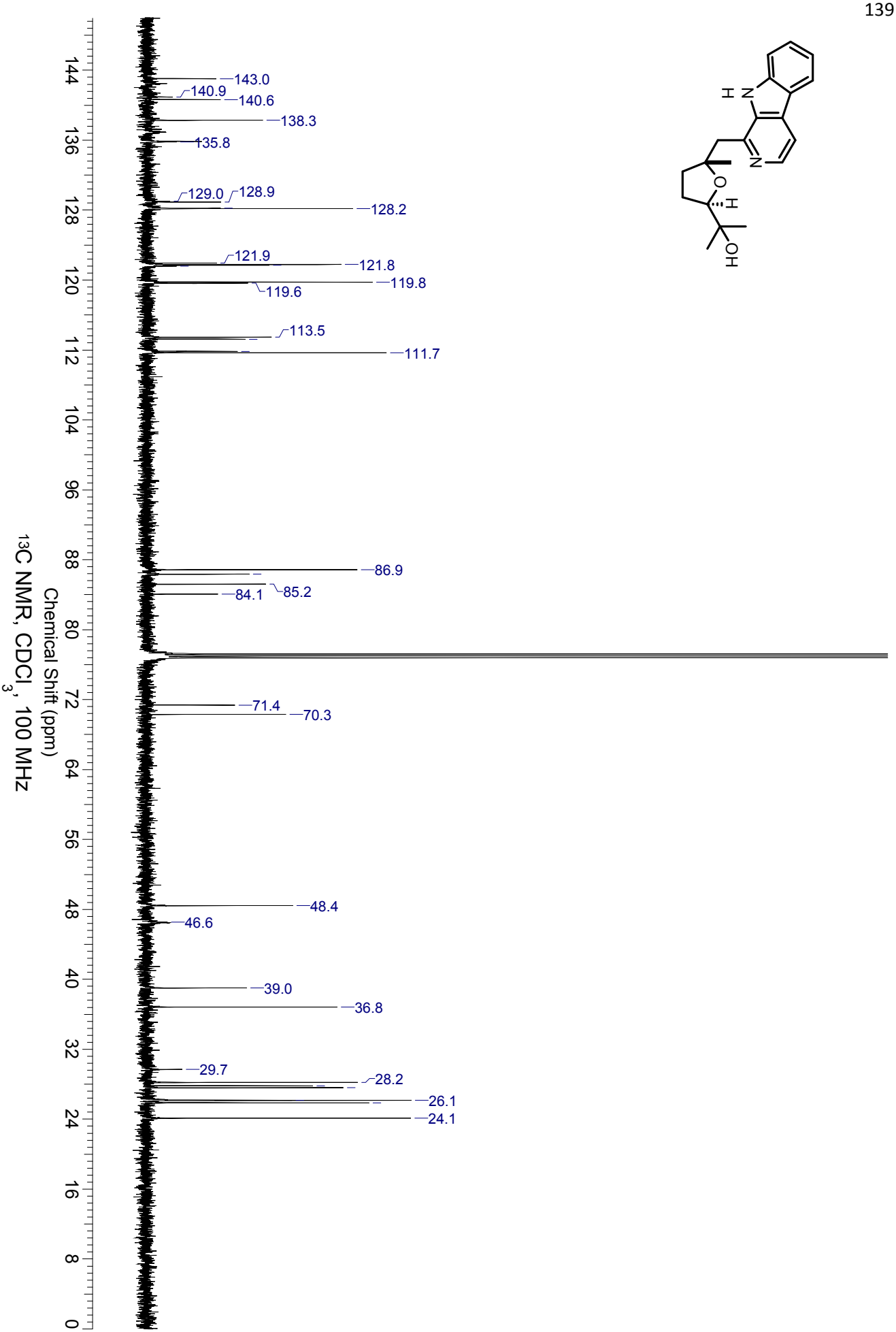
Compound 2-26

Compound 2-26





Compound 2-15



Compound 2-15

Curriculum Vitae
Geoffrey Phillips

Education

Master of Science Candidate (2014)
Organic Chemisry
Supervisor: Professor Brian L. Pagenkopf
The University *of* Western Ontario, London, Ontario

Bachelor of Science (2012)
Honours Specialization in Chemistry
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Research Experience

Graduate Student Researcher September 2012 - August 2014
The University *of* Western Ontario, London, Ontario
Supervisor: Professor Brian L. Pagenkopf

Teaching Assistant September 2012 – August 2014
The University *of* Western Ontario, London, Ontario

Undergraduate Thesis Student September 2011 – April 2012
The Univeristy *of* Western Ontario, London, Ontario

Awards

2008 – 2012 Dean's Honour List (*The* Univeristy *of* Western Ontario)