

**AZA-NAZAROV CYCLIZATION REACTIONS
USING
ANION EXCHANGE STRATEGY**

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By
Selin Ezgi DÖNMEZ

July 2019

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ANION EXCHANGE STRATEGY

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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

Yunus Emre TÜRKMEN (Advisor)

Bilge BAYTEKİN

Salih ÖZÇUBUKÇU

Approved for the Graduate School of Engineering and Science:

Ezhan KARAŞAN

Director of the Graduate School

ABSTRACT

AZA-NAZAROV CYCLIZATION REACTIONS USING ANION EXCHANGE STRATEGY

Selin Ezgi Dönmez

M.Sc. in Chemistry

Advisor: Yunus Emre Türkmen

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Although Nazarov reaction is a synthetically useful route for the synthesis of five-membered rings, there are a very limited number of studies on its analogous process producing *N*-heterocycles; aza-Nazarov reaction, and an effective methodology that proceeds under mild conditions has yet to be developed. In consideration of the importance of nitrogen containing heterocyclic compounds in organic and pharmaceutical chemistry, developing a new aza-Nazarov reaction will have the potential to be beneficial in many synthetic applications. In this work, a novel catalytic aza-Nazarov reaction between 3,4-dihydroisoquinolines and α,β -unsaturated acyl chlorides, that can be used for a broad range of substrates, has been developed. By taking advantage of the stabilizing β -silicon effect and the anion exchange strategy, the proposed reaction proceeds under much better conditions with respect to reaction yield, reaction conditions and environmental issues. Our initial efforts focused on the use of achiral anion exchange strategy employing silver trifluoromethanesulfonate (AgOTf) as the anion source to develop a novel aza-Nazarov reaction. To demonstrate that the reaction has a wide substrate scope, the substituents on the starting materials have been changed with electron withdrawing and donating groups. Several attempts have been

made to render the developed reaction enantioselective using chiral catalysts, nevertheless asymmetric aza-Nazarov reactions could not be achieved.

Keywords: Aza-Nazarov reaction, *N*-heterocycles, β -silicon effect, anion exchange strategy.

ÖZET

ANYON DEĞİŞTİRME YÖNTEMİ KULLANILARAK AZA-NAZAROV TEPKİMELERİNİN GELİŞTİRİLMESİ

Selin Ezgi Dönmez

Kimya, Yüksek Lisans

Tez Danışmanı: Yunus Emre Türkmen

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Nazarov tepkimesi beşli halkaların sentezinde kullanışlı bir sentetik yol olmasına rağmen, bu tepkimenin bir türevi olan ve *N*-heterosiklik bileşikler üreten aza-Nazarov tepkimeleri üzerine sınırlı sayıda çalışma bulunmaktadır. Aza-Nazarov tepkimesi için etkili ve ılımlı koşullar altında çalışan bir yöntem henüz geliştirilmemiştir. Azot atomu içeren heterosiklik bileşiklerin organik ve farmasötik kimyada önemi göz önüne alınınca, yeni bir aza-Nazarov tepkimesinin geliştirilmesi birçok sentetik kullanımda yararlı olacaktır. Bu çalışmada, 3,4-dihidroizokinolin ve α,β -doymamış açıl klorür bileşikleri arasında yeni bir katalitik aza-Nazarov tepkimesi geliştirilmiştir. β -silikon kararlılık etkisi ve anyon değiştirme yönteminden faydalanılarak oluşturulan tepkime verim, tepkime koşulları ve çevre sorunları açısından çok daha uygun koşullar altında yürümektedir. İlk aşamada, akiral anyon değiştirme yönteminde anyon kaynağı olarak gümüş triflorometilsülfonat (AgOTf) kullanılmıştır. Tepkimenin geniş bir substrat aralığında çalıştığını göstermek için başlangıç maddelerinin bileşenleri elektron çekici ve verici gruplarla değiştirilerek denenmiştir. İlerleyen aşamalarda tepkimeyi enantioseçici yapmak amacıyla kiral katalizörler ile birçok deneme yapılmasına rağmen sonuçlar tatmin edici olamamıştır.

Anahtar kelimeler: Aza-Nazarov tepkimesi, *N*-heterosiklik bileşikler, β -silikon etkisi, anyon deęiřtirme yöntemi.

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LIST OF ABBREVIATIONS

DCE	1,2-Dichloroethane
DCM	Dichloromethane
ee	Enantiomeric excess
EtOAc	Ethyl acetate
FTIR	Fourier-Transform Infrared
HRMS	High Resolution Mass Spectrometry
HPLC	High Performance Liquid Chromatography
MeCN	Acetonitrile
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
-OTf	Trifluoromethanesulfonate
PMA	Phosphomolybdic acid
PPA	Polyphosphoric Acid
TfOH	Trifluoromethanesulfonic acid
TMS	Trimethylsilyl
UV	Ultraviolet
XRD	X-Ray Diffraction

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1. INTRODUCTION

1.1. Heterocycles in Chemistry

Heterocyclic compounds which are composed of a ring including at least one heteroatom i.e. an atom other than carbon, continue to have a crucial role in organic chemistry since the day they were first classified.¹ Nitrogen heterocycles, simply called *N*-heterocycles, constitute one of the most valuable sub-classes of heterocyclic compounds due to their biological activities. This property leads to the presence of *N*-heterocyclic frameworks in many natural products and pharmaceutical drugs.² Thus, these heterocycles are found as necessary intermediates for organic synthesis.³ The analysis of U.S. FDA approved drugs has shown that 59% of drugs involve a nitrogen heterocycle.⁴ A common method for the production of *N*-heterocycles proceeds through the cyclization of *N*-acyliminium ions due to their reactive nature in the intramolecular C-C bond forming reactions (Figure 1).⁵ The Nazarov reaction and its analogue aza-Nazarov reaction are cyclization reactions that are able to successfully produce specially five-membered carbocycles and *N*-heterocycles, respectively.⁶

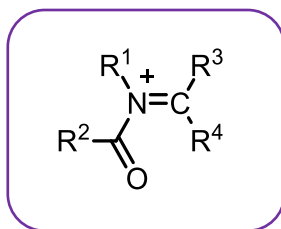
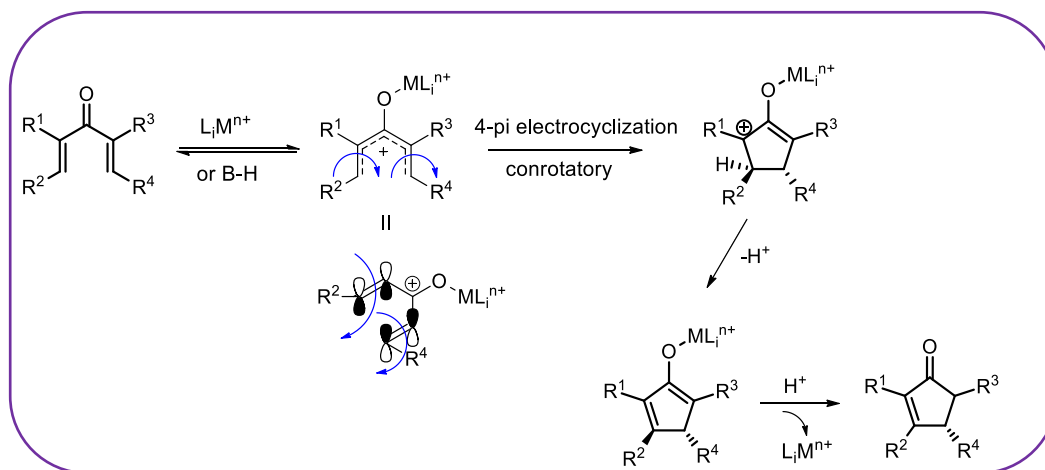


Figure 1. *N*-Acyliminium ion.

1.2. Nazarov Cyclization Reaction

The Nazarov cyclization reaction was discovered by the Russian organic chemist Ivan Nazarov in 1941 while studying on the rearrangement of allyl vinyl ketones.⁷ It is classified as a ring forming reaction where a Lewis or Brønsted acid is used to activate the starting divinyl ketone and produces five membered rings. The reaction mechanism proceeds through a 4π -electrocyclization which generally is the rate determining step. Nazarov reaction is a conrotatory process under thermal conditions determined by the Woodward-Hoffmann rules for pericyclic reactions based on the symmetry of interacting orbitals (Scheme 1).⁸



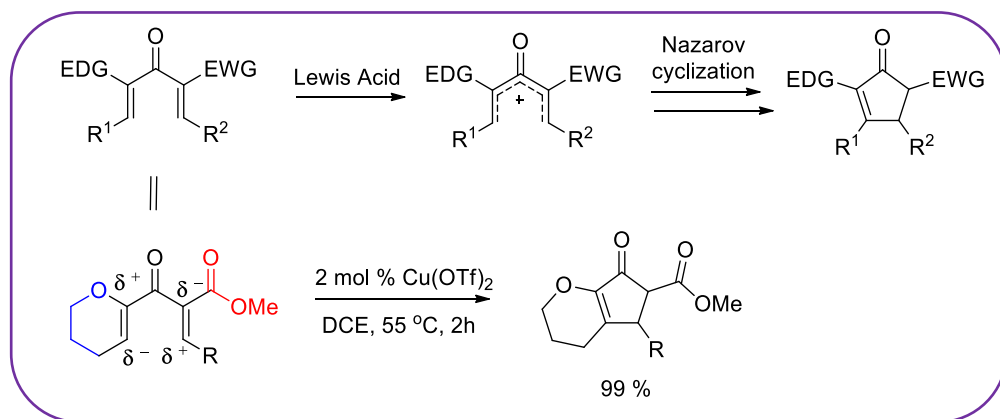
Scheme 1. Nazarov cyclization reaction mechanism.

Due to its mechanism, Nazarov reaction has some shortcomings reducing its potential utility. It requires strong Lewis or Brønsted acid to promote the reaction, the β -elimination step prevents the formation of two new stereocenters and reduces the regioselectivity. Finally, the protonation step of the resulting enolate may not be stereoselective with the used divinyl ketones.

1.3. History of Nazarov Reaction

1.3.1. Advances on Nazarov Reaction

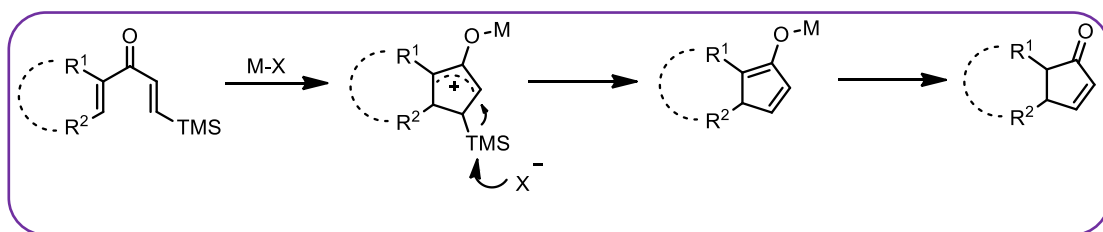
After the mid-1980s, Nazarov reaction has been studied and developed to enable the use of various substrates apart from divinyl ketones by many research groups. Frontier research group has introduced some electron withdrawing and donating groups substituted to the starting divinyl ketones to investigate their effect on the reaction outcome. This way the starting material becomes polarized and could undergo cyclization more easily. This strategy enabled the reaction to be catalytic under mild conditions (Scheme 2).⁹



Scheme 2. Polarized Nazarov reactions.

The work by West and co-workers has disclosed a new concept called interrupted Nazarov reaction.¹⁰ In these variants of the Nazarov cyclization, oxyallyl cation intermediates can be trapped, usually in an intramolecular fashion, by a variety of functionalities leading to the construction of complex carbo- and heterocycles.

For instance, using triethylsilyl hydride in order to trap the oxyallyl cation to remove the elimination step, has increased stereoselectivity. The method developed by the Tius research group, rate acceleration was achieved in the β -hydrogen elimination step by using allenyl vinyl ketones.¹¹ Another study to increase the regioselectivity of the reaction was performed by Denmark and co-workers (Scheme 3).¹² A TMS group, attached on a strategic position, was demonstrated to direct the formation of the double bond on the less substituted bond selectively. This method takes advantage of the presence of silicon controlling the regiochemistry of carbocations also known as the β -silicon effect.

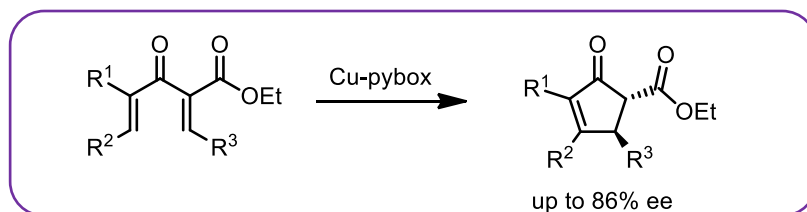


Scheme 3. Nazarov cyclization reaction using β -silicon effect.

The total synthesis of the natural product Silphinene benefits from this methodology.¹³ Using pentadienyl cation as the starting of the Nazarov reaction has been investigated by many research groups.¹⁴ One of the examples employs silver catalysis to allow cationic ring opening for allylic dichloro cyclopropanes.¹⁵ This method is used to synthesize the natural product Rocaglamide.¹⁶

1.3.2. Enantioselective Nazarov Reactions

One of the most important developments on the Nazarov reaction is the generation of efficient enantioselective methods. There are many examples of such methods using different chiral catalysts and reaction designs.¹⁷ Most of the studies are built upon torquoselectivity, favoring only one direction for the two olefin groups to rotate.¹⁴ Aggarwal and co-workers used chiral Cu(II)-bisoxazoline complexes as efficient chiral Lewis acids for the Nazarov reaction (Scheme 4).¹⁸



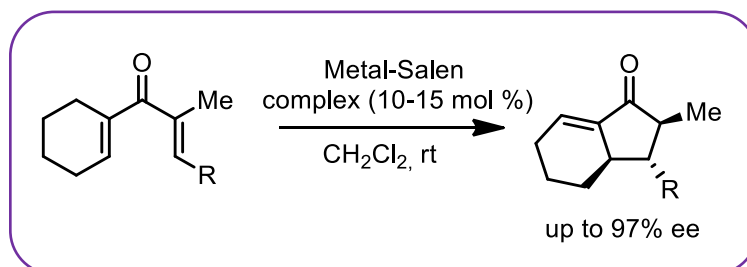
Scheme 4. Asymmetric Nazarov reaction using Pyridine Bis(oxazoline) ligands.

In another work by Trauner and co-workers, 2-alkoxy-1,4-pentadien-3-ones were used as highly reactive substrates in the asymmetric Nazarov cyclizations (Scheme 5).¹⁹ The use of chiral scandium indane-pybox complex as the catalyst has provided a bidentate coordination to the substrate yielding high enantioselectivities through asymmetric protonation. The first alkoxy dienone substrate that was examined had suffered from racemization thus giving low reaction yield and ee value. Exchanging one of the terminal substituents to hydrogen had resulted in high yields and enantioselectivities.



Scheme 5. Asymmetric Nazarov reaction using 2-alkoxy-1,4-pentadien-3-ones.

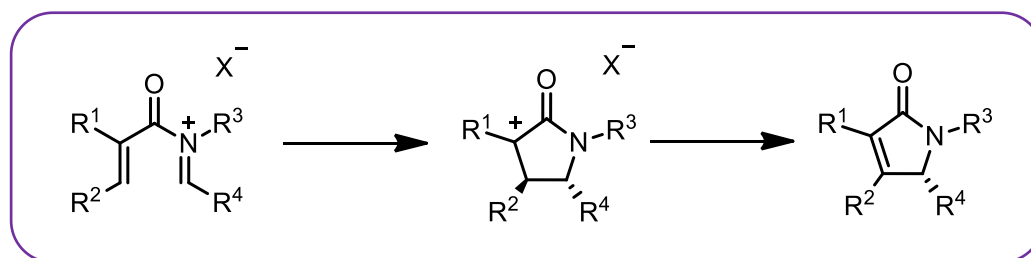
Rueping research group used BINOL-based chiral phosphoramidate derivatives to act as chiral Brønsted acid catalysts.²⁰ This study holds an important place in the advancement of the Nazarov reaction as being not only the first example of using organocatalysts in the asymmetric Nazarov reactions but also being the first example using organocatalysts in enantioselective electrocyclic reactions. Another important asymmetric method was established by Rawal and co-workers where they used unactivated dienones i.e. divinyl ketones containing no electron withdrawing or donating groups, with a metal-salen complex (Scheme 6).²¹



Scheme 6. Asymmetric Nazarov cyclization starting from unactivated dienones.

1.4. Aza-Nazarov Cyclization Reaction

Even though Nazarov reaction has been subject of interest over the years, its analogue, aza-Nazarov reaction which produces *N*-heterocycles has remained mostly unstudied. This reaction allows the synthesis of pyrrolidinone derivatives (Scheme 7).



Scheme 7. Aza-Nazarov cyclization reaction.

In general, the reaction involves an *N*-acyliminium salt. When this iminium is chosen to be cyclic, the reaction can provide the synthesis of indolizidine and pyrrolizidine derivatives, which are both valuable heterocycles in synthetic organic chemistry. These cores are found in the structures of many biologically active alkaloid natural products (Figures 2 and 3).²²

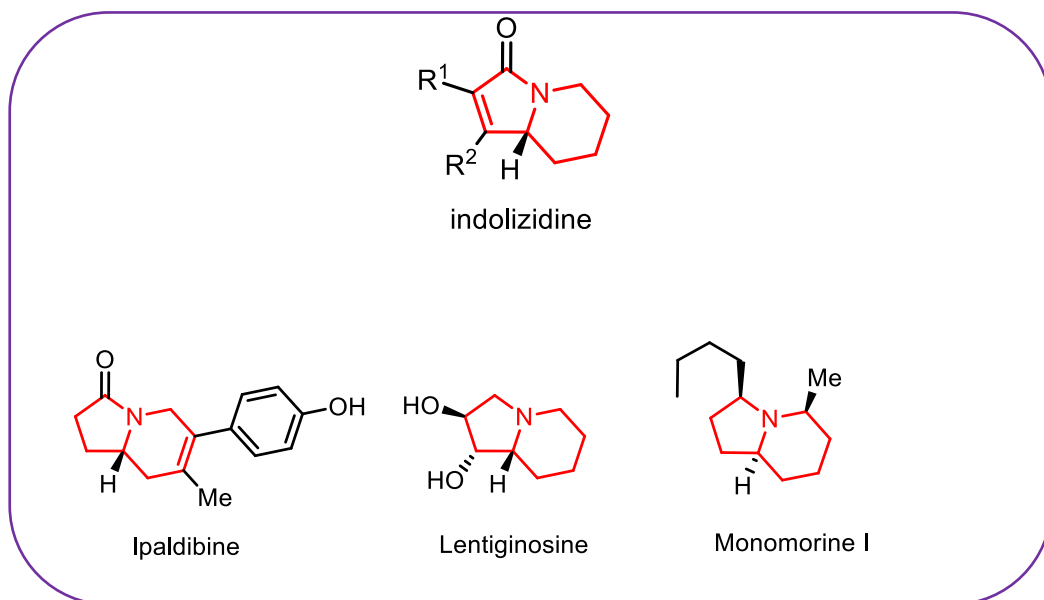


Figure 2. Examples of alkaloids with indolizidine structure.

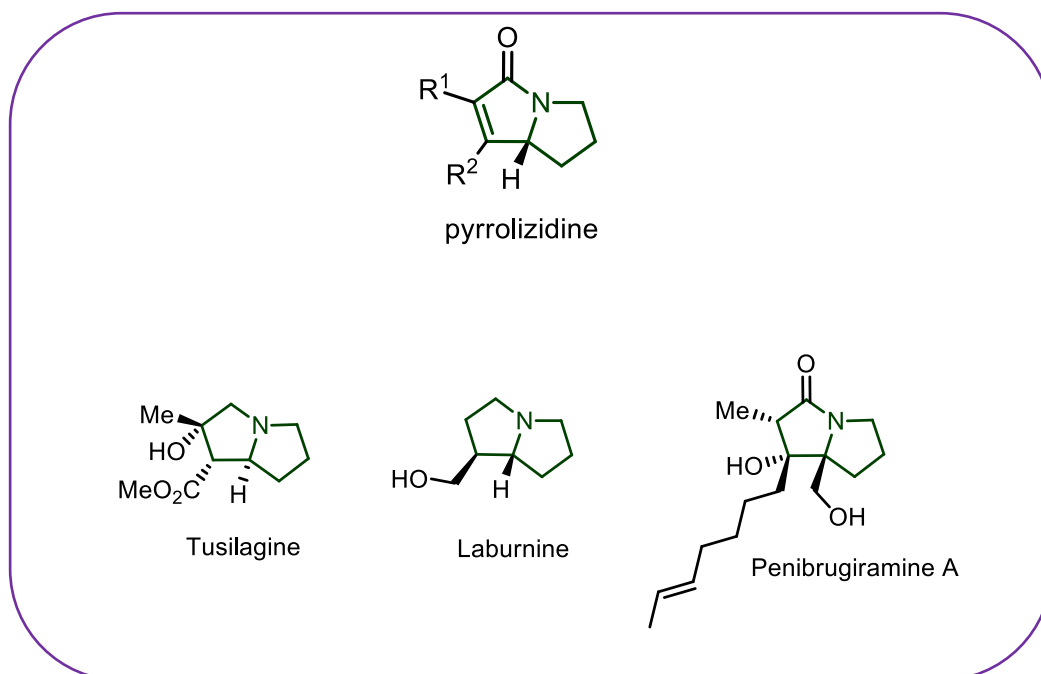
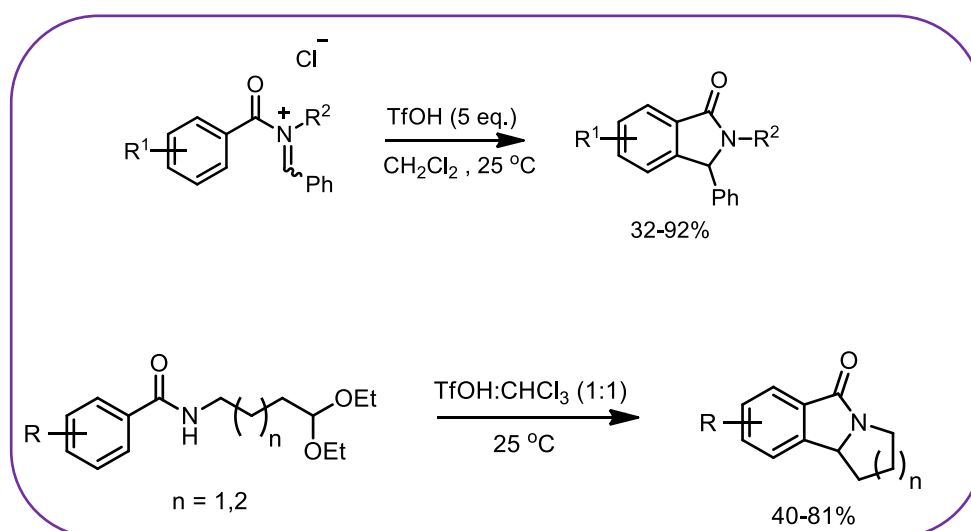


Figure 3. Examples of alkaloids with pyrrolizidine structure.

1.4.1. Recent Advances on Aza-Nazarov Reaction

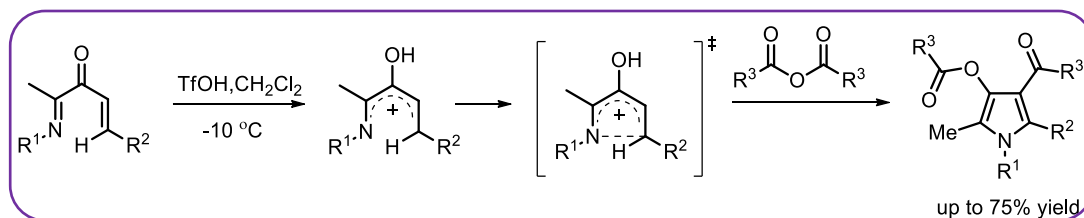
Although it is a promising reaction for synthetic organic chemistry, allowing the synthesis of five membered heterocyclic structural motifs found in many natural products, there are limited number of studies towards the aza-Nazarov reaction. Klumpp research group is one of the few groups working on the development of aza-Nazarov reaction. In 2007, these researchers reported a method using 5 or more equivalents of TfOH (trifluoromethanesulfonic acid) along with the iminium salt to produce aza-Nazarov products (Scheme 8).²³ In 2011, they extended their methodology to produce aza-Nazarov products by using in situ generated iminium ions.²⁴



Scheme 8. Studies on aza-Nazarov reaction by Klumpp and co-workers.

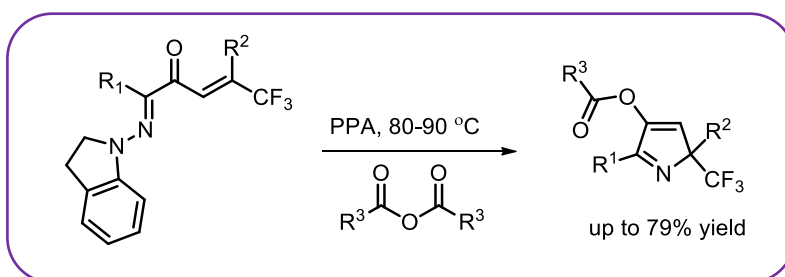
Würthwein and co-workers used starting materials where the nitrogen atom is placed on the β -position to the carbonyl group, in that case synthesis of pyrrole derivatives was achieved with aza-Nazarov reaction using strong Brønsted acids like TfOH or PPA (Scheme 9).²⁵ In this study, unsubstituted or substituted acid anhydrides were used to trap the hydroxyl group on the 3-position which was causing instability of

compounds and in the resulting products it was transformed into the more stable acetoxy group.



Scheme 9. Aza-Nazarov reactions using acid anhydride trapping.

With the same methodology using hydrazine fragments on the substrate, Würthwein research group employed 3*H*-indole as the leaving group in the N-N bond breaking step to obtain aza-Nazarov products (Scheme 10).²⁶

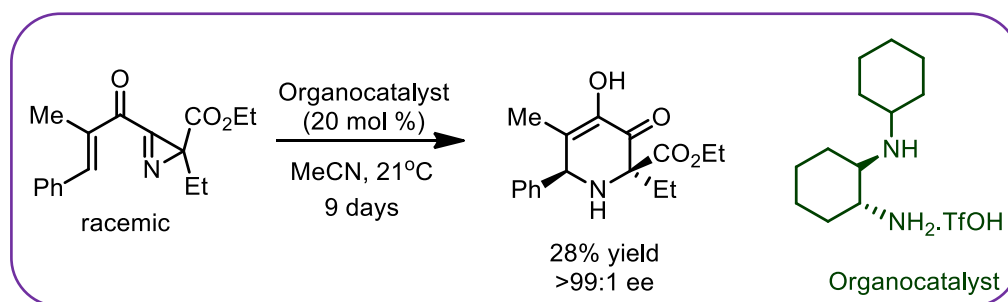


Scheme 10. Aza-Nazarov reactions employing 3*H*-indole as leaving group.

All these existing methodologies suffer from certain drawbacks minimizing the generality of them and decreasing their area of utilization. They require stoichiometric or sometimes super-stoichiometric amounts of corrosive reagents which are hardly environmentally friendly. They have narrow substrate scope, possibly due to the harsh reaction conditions involved, and the reaction precursors need to have specific structures

like having aromatic groups on the iminium. Finally, the use of stoichiometric amount of promoters makes the development of a catalytic and enantioselective reaction practically impossible.

The only reported catalytic aza-Nazarov reaction was achieved by the Tius group in 2010 (Scheme 11).²⁷ The reaction employs a chiral organocatalyst and proceeds through a ring expansion following the aza-Nazarov cyclization. The reaction provides high enantiomeric ratios, but the yields are low. The very narrow substrate scope reported for this reaction is another major drawback of this work.



Scheme 11. The only catalytic aza-Nazarov reaction.

Furthermore, the product of this reaction contains a six-membered ring which discards the possibility of the reaction to be used in the production of alkaloid natural products having pyrrolidine structures. In a recent work, it was proposed that aza-Nazarov reaction can be involved in transition-metal catalyzed reactions. In this work, a gold-catalyzed reaction producing various 2-aminopyrroles was proposed to involve an intermolecular aza-Nazarov cyclization in its mechanism.²⁸

1.5. β -silicon Effect

β -silicon effect is a stabilizing effect mediated through silicon atom on the formation of a positive charge on a carbon atom on the β -position with respect to silicon. The σ bond between C-Si has a potential to donate electron to the anti-bonding orbital of the leaving group bonded to the β -carbon (Figure 4). This is a much more effective type of hyperconjugation in terms of stabilization compared to C-C or C-H hyperconjugation.²⁹ The reason is that silicon is less electronegative than carbon which makes the resulting molecular orbital of their σ bond higher in energy compared to C-C bonding molecular orbital. This makes that molecular orbital a better electron donor and by orbital interaction it can donate electron, favoring the formation of a carbocation. Again through this hyperconjugation, it stabilizes the carbocation by electron donation to the empty p orbital of the carbocation.³⁰

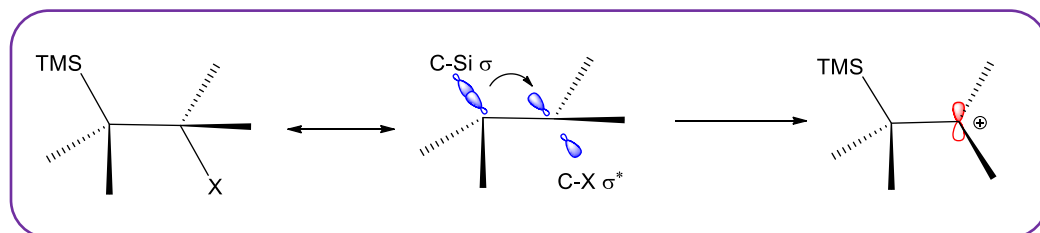
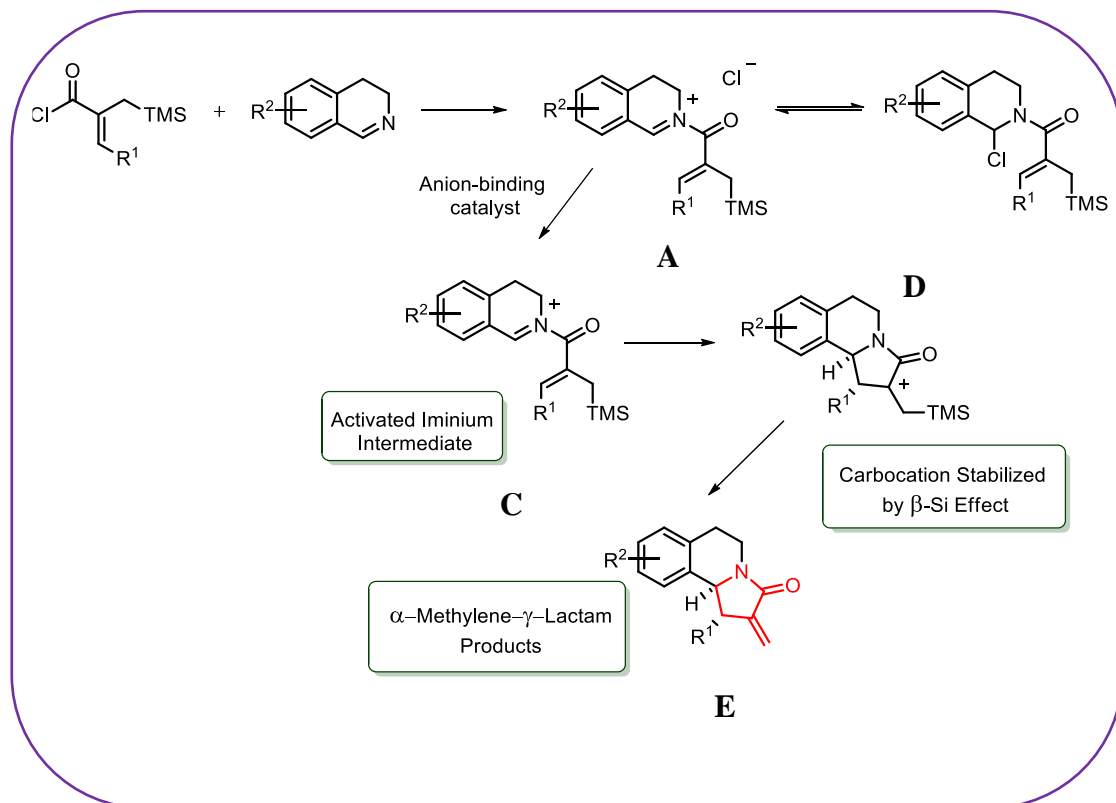


Figure 4. β -silicon stabilization effect.

1.6. Aim of This Project

Considering all these studies and their drawbacks, developing a novel, catalytic aza-Nazarov reaction that proceeds under mild conditions and eventually can be rendered enantioselective is the ultimate aim for the future of the aza-Nazarov reaction. This aim comprises the main goal of this thesis. A catalytic aza-Nazarov reaction is designed to take place with α,β -unsaturated *N*-acyl iminium salts as the reactants, and produce α -methylene- γ -lactam products in high yields. This α -methylene- γ -lactam unit is a motif found in various natural products and biologically active compounds.³¹ The reaction mechanism takes advantage of the β -Si effect to lower the reaction barrier in the cyclization step. With this reaction design, it is desired to overcome the issues of previous studies and to present a general and efficient aza-Nazarov reaction, able to be employed in the synthesis of pyrrolidine, pyrrolizidine and indolizidine compounds.

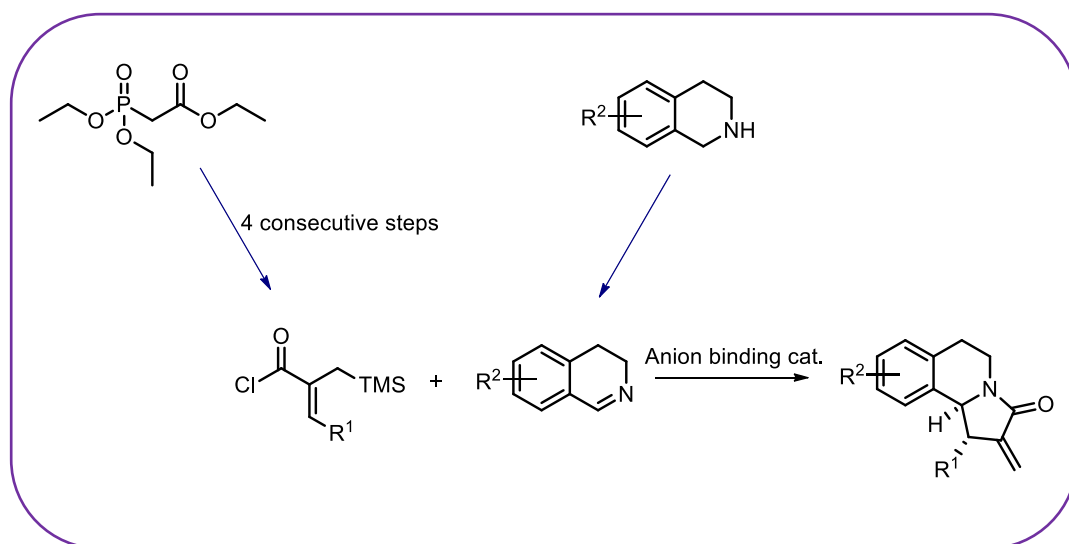
The proposed reaction mechanism starts with the formation of *N*-acyl iminium cation originating from α,β -unsaturated acyl chloride and 3,4-dihydroisoquinoline (Scheme 12). With the addition of an anion binding catalyst, the iminium intermediate will be activated towards aza-Nazarov cyclization and yield the desired products. In that case the regeneration of the active iminium intermediate is expected following the desilylation step.



Scheme 12. Proposed reaction design.

The presence of an equilibrium between ion pair **A** and compound **B** is expected based on literature precedents.³² The catalyst will promote a shift in the equilibrium towards the ion pair and form the activated iminium intermediate **C** through binding with chloride. This will enable aza-Nazarov cyclization due to the non-nucleophilic nature of the new counter anion. After the cyclization step, which will be facilitated with the electron donation of TMS group to the nucleophilic vinyl, the carbocation **D** will be formed. This carbocation is expected to be stabilized through β -silicon effect. The chloride anion in another ion pair will take up the -TMS group on the carbocation, forming the aza-Nazarov product, TMSCl and the activated ion pair once again. In that way, the reaction will proceed catalytically.

In this study, a novel aza-Nazarov reaction that proceeds catalytically under mild conditions has been developed (Scheme 13). The optimal reaction conditions were achieved after investigating a variety of Lewis acids, temperature values and solvents. With the optimized conditions, the substrate scope studies were conducted to ensure that this methodology is applicable to a broad range of substrates unlike the already existing studies. The design starts with the synthesis of α,β -unsaturated acyl chloride starting from the commercially available triethyl phosphonoacetate and of 3,4-dihydroisoquinoline starting from the commercially available tetrahydroisoquinolines, tetrahydroisoquinoline salts or substituted phenethylamines followed by aza-Nazarov cyclization.



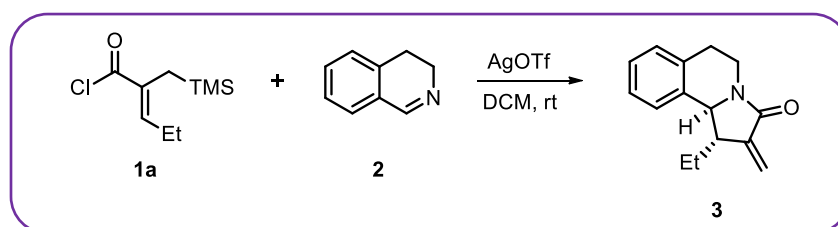
Scheme 13. The steps included in the reaction design.

2. RESULTS AND DISCUSSION

2.1. Optimization Studies of the Aza-Nazarov Cyclization Reaction

The conditions for the aza-Nazarov reaction were initially optimized by screening different solvents, temperature and Lewis acids. The conditions producing the highest yield have been determined by isolation of the products using flash column chromatography. The optimal conditions have generated a new methodology for the aza-Nazarov reaction. For that purpose, the acyl chloride derivatives were synthesized starting with the TMS-alkylation of commercially available triethyl phosphonoacetate, then Horner-Wadsworth-Emmons (HWE) reaction was performed to obtain the corresponding ester followed by hydrolysis and chlorination reactions.³³

The studies were started with ethyl group on the β -position of the acyl chloride, and unsubstituted 3,4-dihydroisoquinoline. First the Lewis acid equivalent is adjusted using DCM as the solvent and AgOTf as the Lewis acid.



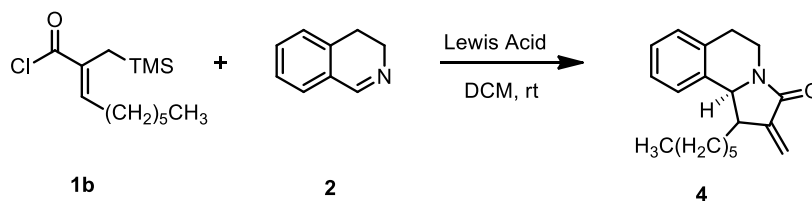
Scheme 14. Optimization studies to adjust the equivalence of Lewis Acid.

The aza-Nazarov product **3** was obtained in 45% yield with the use of stoichiometric amount of AgOTf at room temperature for a day and in 47% yield at 40 °C under the same conditions. When the amount of AgOTf was decreased to 20 mol % based on the

3,4-dihydroisoquinoline amount, the product formation could not be observed. Thereby, it was concluded that to use DCM as the solvent at room temperature, stoichiometric amount of AgOTf is necessary for the reaction to succeed

In order to investigate different Lewis acids, a number of reactions were conducted using *n*-hexyl group this time on the acyl chloride using stoichiometric amount of Lewis acids in DCM at room temperature (Table 1). The use of *n*-hexyl-substituted acyl chloride **1b** in this screening was due to the higher volatility of the ethyl-substituted acyl chloride **1a**.

Table 1. Investigation of different Lewis Acid



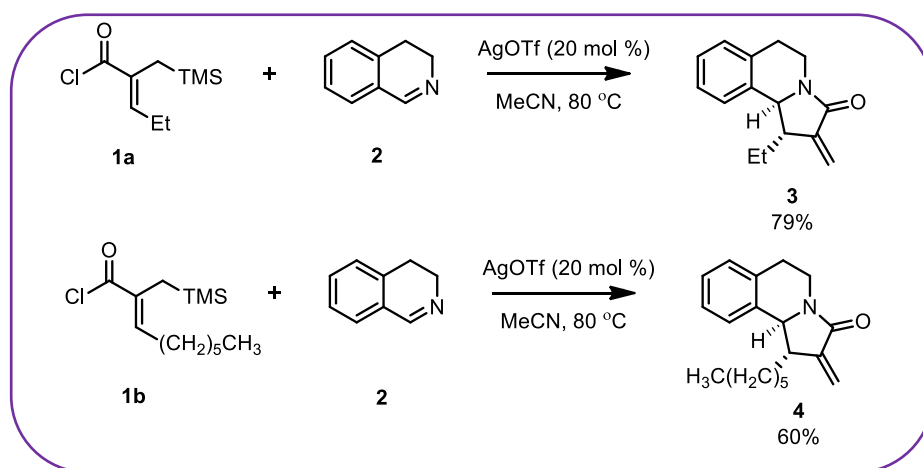
Entry	Lewis Acid ^a	Yield (%)
1	AgOTf	68
2	AgOTf	56 ^b
3	BF ₃ .OEt ₂	8
4	TMSOTf	53
5	Zn(OTf) ₂	59

^a The Lewis acid equivalent is calculated by considering the E/Z isomer ratio of the acyl chloride.

^b In this experiment, 4Å molecular sieves were used.

When AgOTf was used as the Lewis acid the reaction gave 68% yield. To see whether using molecular sieves would increase the yield we have used 4Å molecular sieves, unfortunately it had a disadvantageous effect. TMSOTf and Zn(OTf)₂ were moderately successful Lewis acids giving 53% and 59% yields respectively compared to BF₃.OEt₂ giving only 8% yield. As is seen from Table 1, the Lewis acid yielding the best results was AgOTf. Hence, it was chosen to be used in the latter reactions.

Our later attempts focused on carrying out the reaction in catalytic amount of AgOTf. The temperature of the reaction was increased to 80 °C and the solvent was changed to MeCN for this purpose. Both ethyl and n-hexyl groups on acyl chloride were examined for comparison. The resulting data is shown in Scheme 15.



Scheme 15. Reactions using catalytic amount of AgOTf.

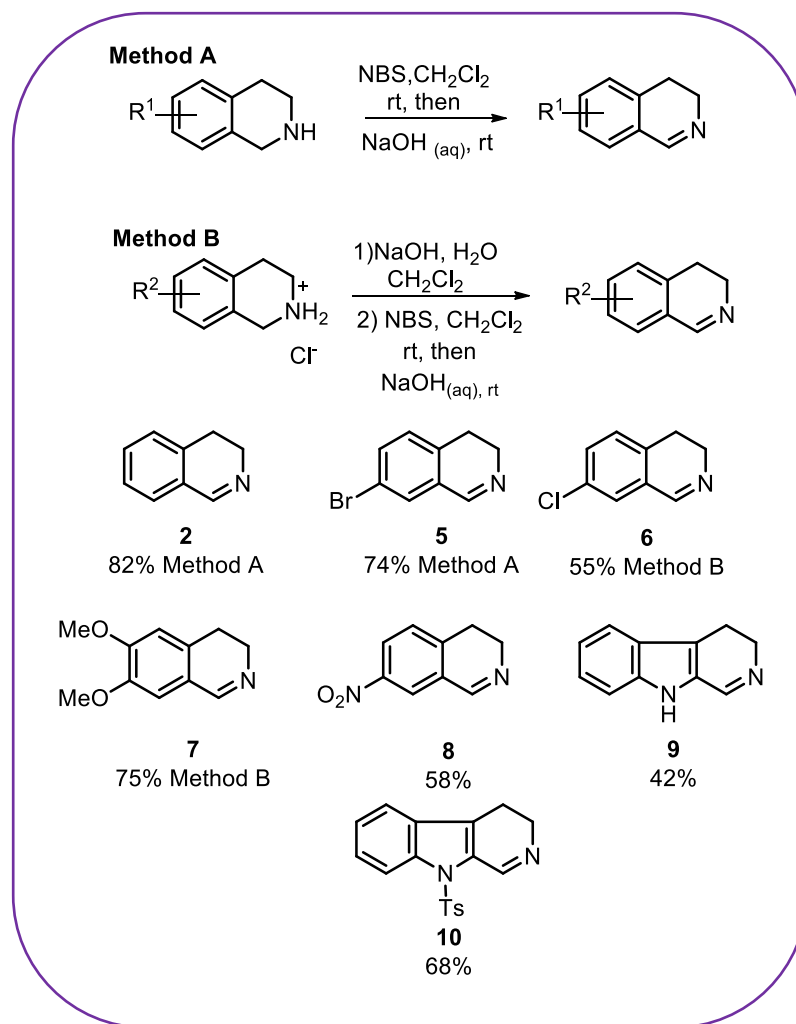
The best yield was achieved with ethyl group on the acyl chloride at 80 °C in MeCN, and therefore the substrate scope studies where 3,4-dihydroisoquinolines substituted with different R groups were conducted using ethyl group.

2.2. Substrate Scope

The substrate scope studies were carried out using the optimized reaction conditions i.e. 20 mol % AgOTf in MeCN at 80 °C. The effect of electron-withdrawing and electron-donating groups attached to 3,4-dihydroisoquinoline on the reaction were investigated. Moreover, besides the n-hexyl and ethyl groups, two different alkyl chains were studied for the substrate scope.

2.2.1. Preparation of 3,4-Dihydroisoquinoline Derivatives

The 3,4-dihydroisoquinoline derivatives were synthesized starting from a convenient commercially available compound bearing different substituents at the 6- or 7-position following different processes (Scheme 16).^{34a,b} The imines **8**^{34c}, **9**^{34d} and **10**^{34e} were synthesized following literature procedures. The yields were reported following purification by flash column chromatography and the resulting products were characterized by ¹H-NMR and ¹³C-NMR spectroscopy, FTIR-ATR and HRMS.



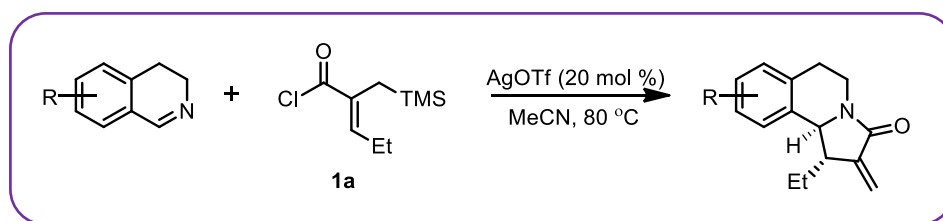
Scheme 16. Synthesis of 3,4-Dihydroisoquinoline derivatives.

Compound **2** was synthesized starting from 1,2,3,4-tetrahydroisoquinoline in 82% isolated yield. Similarly, 3,4-dihydroisoquinoline having bromine at 7-position was prepared starting from its tetrahydroisoquinoline derivative in 74% yield. The 3,4-dihydroisoquinoline derivatives having dimethoxy and chlorine substituents—compounds **6** and **7**, respectively—were synthesized starting from the tetrahydroisoquinoline HCl salts in 55% and 75% yields, respectively. The nitro-substituted 3,4-dihydroisoquinoline was synthesized by the electrophilic aromatic nitration reaction of the unsubstituted 3,4-

dihydroisoquinoline. All these isoquinoline derivatives were synthesized in order to test the effect of electron withdrawing groups on the cyclization reaction and to examine the tolerance of the methodology towards the electron donating groups. Bromine, chlorine and nitro being electron withdrawing groups are expected to facilitate the cyclization by making the iminium electron deficient, thus more electrophilic for the key aza-Nazarov cyclization step. On the other hand, electron donating methoxy groups would make the iminium electron rich, but pleasingly it was observed that the methodology is able to tolerate those electron donating groups in the aza-Nazarov cyclization reaction, and yield the desired products in fairly good yields. Compound **9** was synthesized starting from tryptamine with mildly low 42% yield, and N-tosyl-dihydro- β -carboline (**10**) was synthesized in 68% yield to broaden the substrate scope of the reaction by showing its usefulness for the cyclization of dihydrocarboline.

2.2.2. Screening of 3,4-Dihydroisoquinolines in the Aza-Nazarov Reaction

The synthesized 3,4-dihydroisoquinoline derivatives were reacted with ethyl substituted acyl chloride **1a** in the optimized reaction conditions (Scheme 17).



Scheme 17. Aza-Nazarov reactions of various 3,4-dihydroisoquinoline derivatives.

The final products and obtained yields are given in Figure 5. Reaction with the unsubstituted imine **2** resulted in 79% yield as stated in the optimization studies. The dihydroisoquinolines that possess electron-withdrawing bromine, chlorine and nitro substituents gave good yields of 69%, 64% and 58% respectively. The dimethoxy substituted imine also provided a good yield of 55% showing the success of the reaction at tolerating the presence of two electron-donating groups. Unfortunately the dihydro- β -carboline **9** gave a relatively low yield (25%) and the *N*-Ts substituted dihydro- β -carboline **10** did not give aza-Nazarov cyclization reaction with the acyl chloride, possibly due to the enhanced steric encumbrance around the iminium carbon.

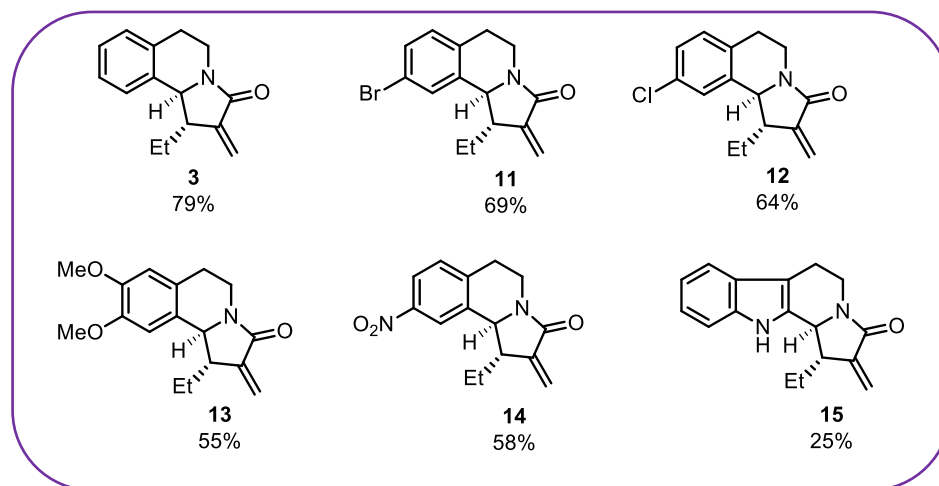


Figure 5. Aza-Nazarov products of various 3,4-dihydroisoquinoline derivatives.

Besides these synthesized imines, several commercially available imines like quinoline, isoquinoline, phthalazine and benzo[*c*]cinnoline were screened in our methodology, however they were all unsuccessful at entering aza-Nazarov cyclization reaction (Figure 6).

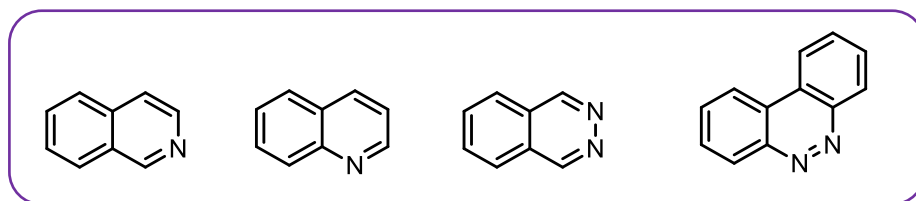
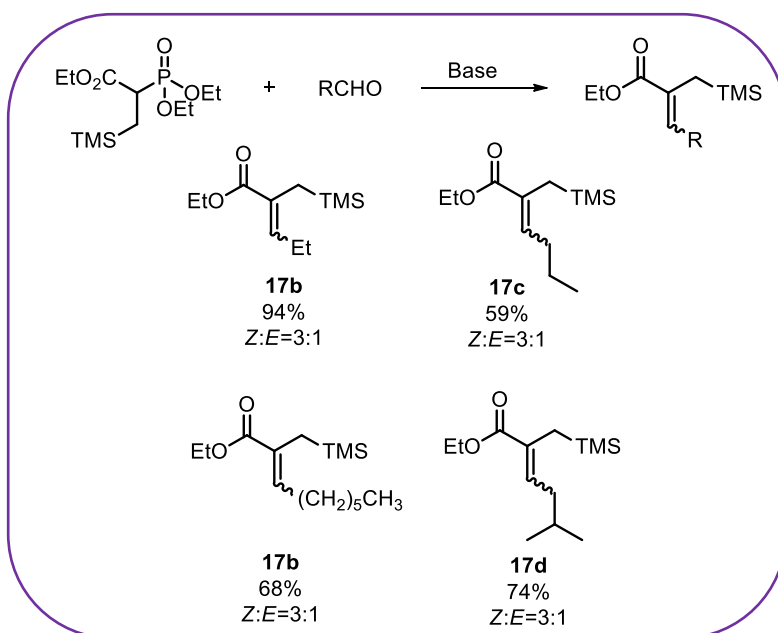


Figure 6. Imines giving no product in the aza-Nazarov reaction.

2.2.3. Preparation of α,β -Unsaturated Acyl Chlorides

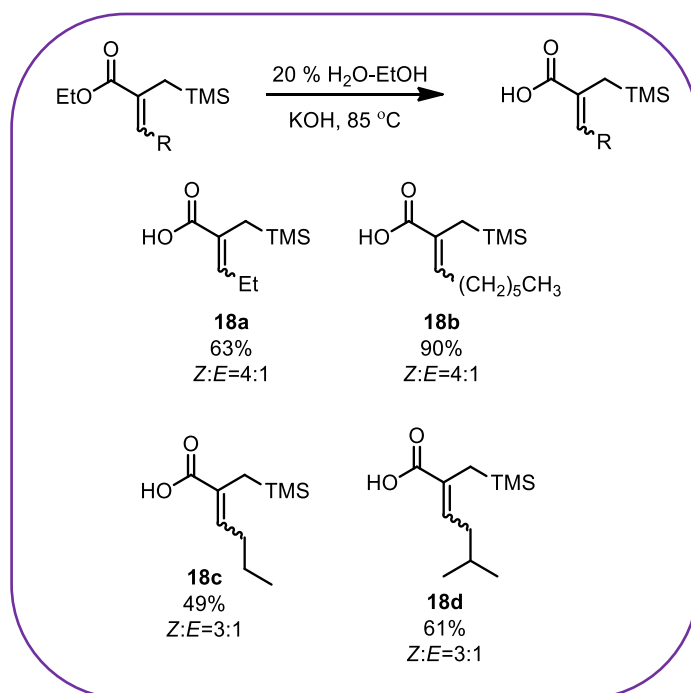
The α,β -unsaturated acyl chlorides employing different alkyl groups on the β -position were synthesized starting from triethyl phosphonoacetate in order to add the alkyl-TMS group based on a known literature procedure.³³ This process is common for all of the acyl chlorides synthesized. After the alkylation, the product enters Horner-Wadsworth-Emmons reaction with the appropriate aldehyde and base.³⁵



Scheme 18. Synthesized esters with HWE reaction.

Esters containing long, short and branched alkyl chains were synthesized for the substrate scope studies (Scheme 18).

To produce the corresponding carboxylic acids, these esters were hydrolyzed by saponification. The reactions were performed using KOH as the base in 20% H₂O-EtOH mixture at 85 °C for 24 hours (Scheme 19). The diastereomeric ratios for the products were approximately the same as the starting esters. The resulting yields were satisfactory although the yield for the n-propyl substituted carboxylic acid was relatively low (Scheme 19).



Scheme 19. Synthesized carboxylic acids through saponification .

The final step involves the conversion of carboxylic acids into acyl chlorides by using oxalyl chloride (Figure 7). Since these acyl chlorides are prone to decomposition and are unstable, they were used immediately. A small portion of each acyl chlorides was analyzed by ¹H-NMR spectroscopy to conclude that the diastereomeric ratios of acyl

chlorides are the same with their carboxylic acid analogues.

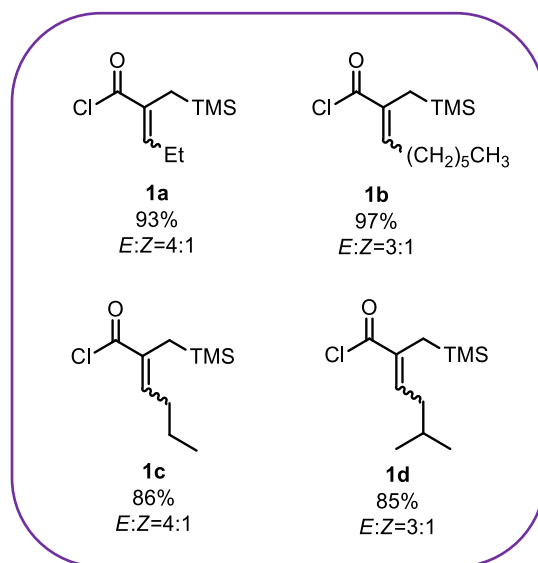


Figure 7. Synthesized acyl chlorides with different alkyl chains.

2.2.4. Screening of Acyl Chlorides in the Aza-Nazarov Reaction

The synthesized acyl chlorides were screened in the aza-Nazarov reaction using unsubstituted 3,4-dihydroisoquinoline in the optimized reaction conditions. The final products and obtained yields are given in Figure 8. (The obtained yields for the ethyl and n-hexyl chains were stated in the optimization studies as 79% and 60% respectively using optimized reaction conditions)

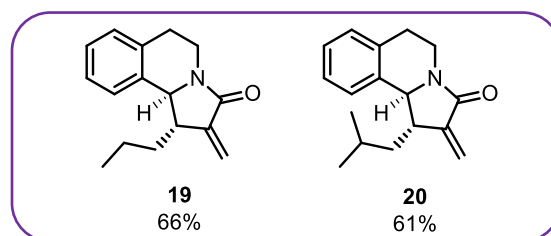
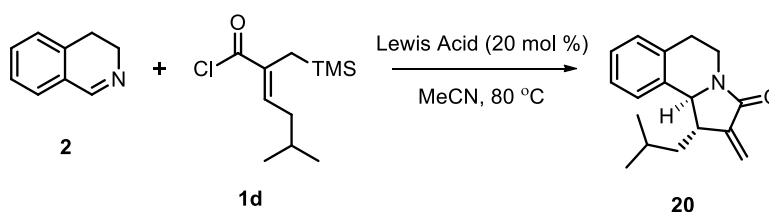


Figure 8. Aza-Nazarov products with *n*-propyl and isobutyl chains.

2.3. Screening of Other Lewis Acids in the Optimized Reaction Conditions

The Lewis acids examined during the optimization studies were screened once more using the optimized reaction conditions to investigate the effectiveness of AgOTf under these conditions. For this purpose, α,β -unsaturated acyl chloride containing isobutyl chain **1d** and the unsubstituted imine **2** were used as the starting substrates (Table 2).

Table 2. Screening of Lewis acids in the optimized reaction conditions



Entry	Lewis Acid	Yield (%)
1	BF ₃ .OEt ₂	62
2	NaBF ₄	54
3	TMSOTf	47
4	Zn(OTf) ₂	36

Considering the 61% yield obtained with these substrates in the same reaction conditions in 1.0 mmol scale using AgOTf, it can be seen that the developed methodology offers the use of various Lewis acids to obtain the desired products in good to moderate yields.

2.4. Relative Stereochemistry of the Aza-Nazarov Products

In all of the reactions described so far, the aza-Nazarov products were always obtained as single diastereomers, which was determined by $^1\text{H-NMR}$ spectroscopy. In order to determine the relative stereochemistry of the two contiguous stereocenters we have conducted 2D-NMR studies. The NOESY analysis of compound **3** justified our initial prediction that the two hydrogens on these stereocenters have *trans*-arrangement with respect to each other (Figure 9).

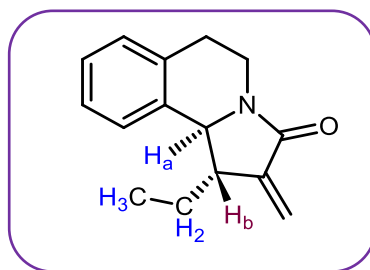


Figure 9. Structure of compound **3**.

The NOE intensity of H_a with the hydrogens of CH_2 and CH_3 in the ethyl group was observed to be higher than the one with H_b indicating that those hydrogens are *trans*- to each other whereas ethyl group and H_a are *cis* to each other. Subsequently, good quality crystals of **13** were obtained by the vapor diffusion of pentane into its solution in CH_2Cl_2 . The single-crystal XRD analysis of these crystals approved our conclusion about the relative stereochemistry of compound **13** (Figure 10).

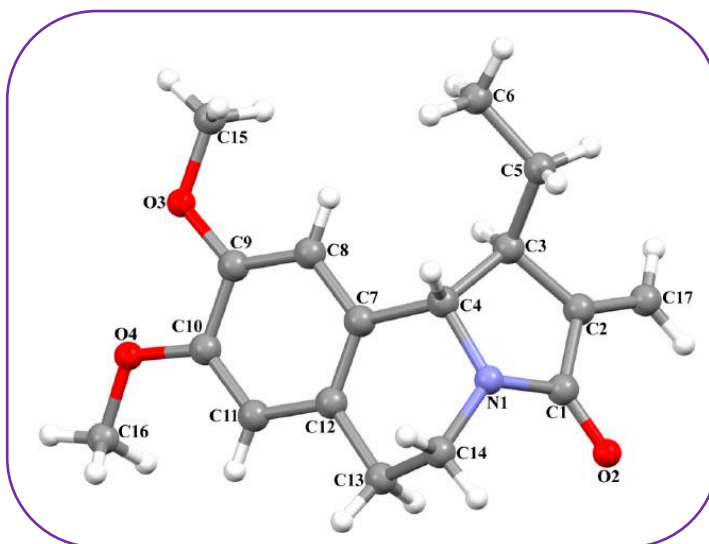


Figure 10. Crystal structure of compound **13**.

2.5. Screening of Acyclic Imines in the Aza-Nazarov Reaction

As our methodology provided successful results with dihydroisoquinoline substrates, we sought to test our reaction design using acyclic imines, which have pleasingly expanded the substrate scope of the reaction. The acyclic imines were synthesized starting from an appropriate aldehyde and amine to produce the imine based on literature procedures.³⁶ After a simple filtration process, the synthesized imine was checked by ¹H-NMR spectroscopy and directly used after evaporation of the solvent. The imine was reacted afterwards with acyl chloride under the optimized conditions to produce pyrrolidinone products subsequent to aza-Nazarov cyclization. The aza-Nazarov products and obtained yields are given in Figure 11. The Results indicate moderate to good yields and the diastereomeric ratios range from 12.5:1 to 5:1. The yields are averagely lower when acyclic imines are used as starting instead of 3,4-dihydroisoquinolines. The reason for this is the higher probability of acyclic imines getting hydrolyzed during the reaction and forming aldehyde which was observed in the crude ¹H-NMR spectroscopy at higher intensities compared to reactions with 3,4-

dihydroisoquinoline derivatives.

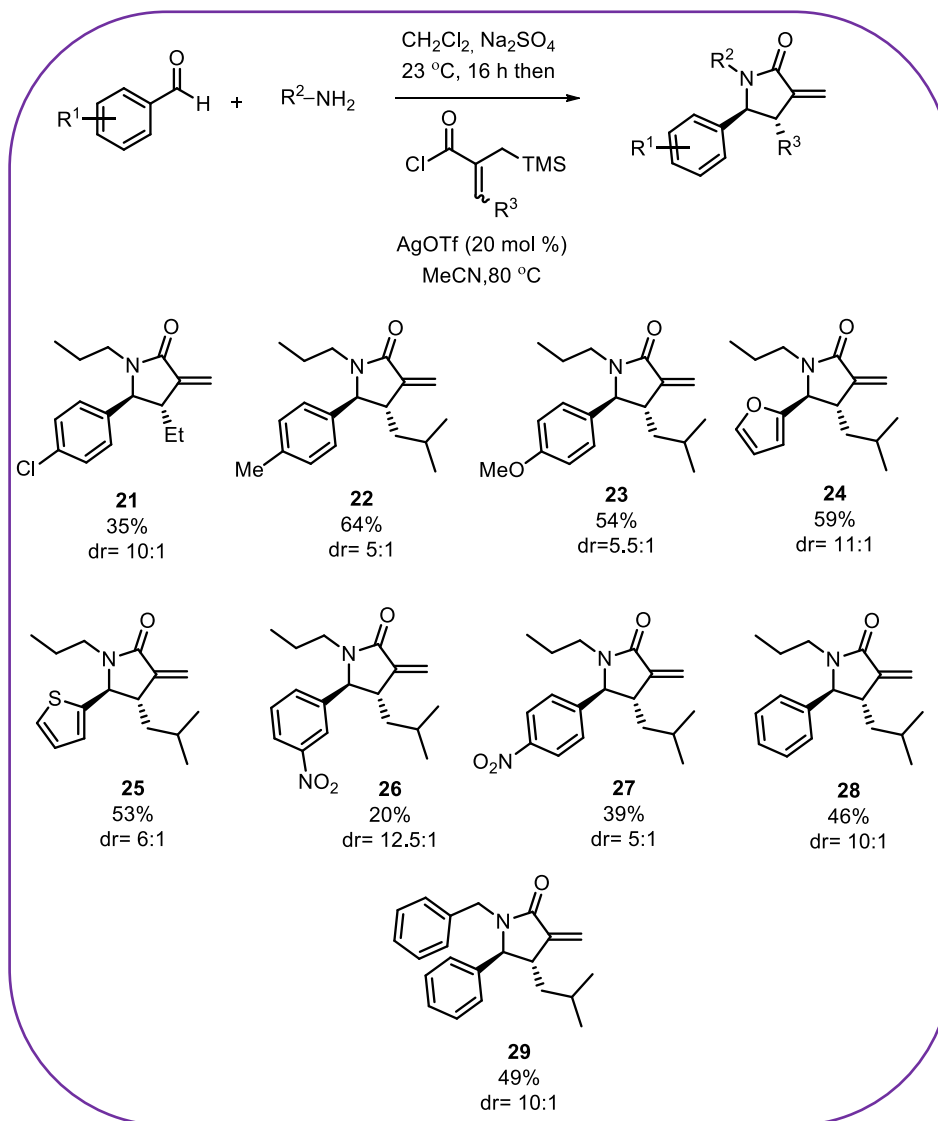
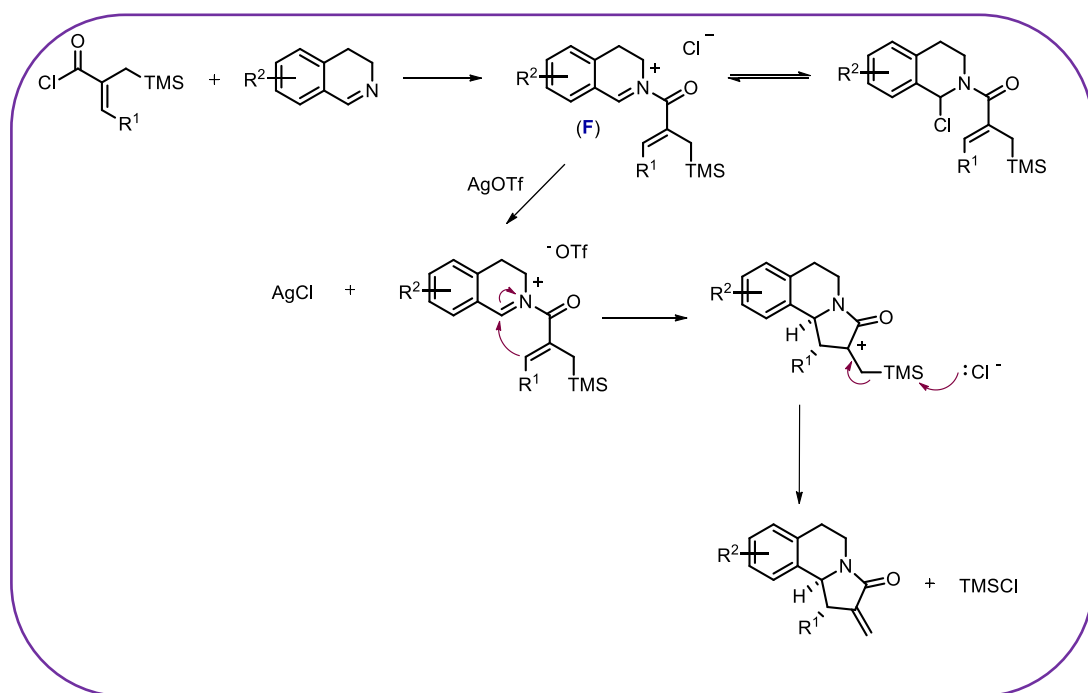


Figure 11. Aza-Nazarov products of acyclic imines.

2.6. Investigation of the Reaction Mechanism

The proposed reaction mechanism is shown in Scheme 20. The reaction starts by mixing the imine with acyl chloride which generates an iminium salt (**F**). This step was investigated by $^1\text{H-NMR}$ experiment without the addition of a Lewis Acid, based on the chemical shift values, all of the imine was consumed to form the iminium salt within 10 minutes. Then AgOTf is added into the reaction medium provoking anion exchange in which $-\text{OTf}$ anion replaces Cl^- . This anion exchange process induces the precipitation of AgCl . The non-coordinating $-\text{OTf}$ anion renders the cyclization easier by making the iminium cation more active towards the cyclization. The produced carbocation is stabilized through β -silicon effect that further favors the cyclization. At the end, the Cl^- ion of another ion pair is proposed to take up the $-\text{TMS}$ moiety to form stable TMSCl , generate another active iminium ion pair, and the aza-Nazarov product.



Scheme 20. Proposed aza-Nazarov reaction mechanism.

Certain control experiments were conducted in order to see the effect of AgOTf and the –TMS group on the reaction outcome. First, a control reaction was run where no AgOTf was added to the acyl chloride-imine mixture at both room temperature in DCM and 80 °C in MeCN. No aza-Nazarov product formation was observed at room temperature. However, aza-Nazarov product **3** was obtained in 13% isolated yield when the background reaction was checked at 80 °C in MeCN in the absence of AgOTf. This result clearly shows that higher temperature allows the reaction to proceed even without the anion exchange process, albeit in a much lower yield. Secondly, control reactions to emphasize the effect of –TMS group on the cyclization reaction were performed using methacryloyl chloride and the unsubstituted 3,4-dihydroisoquinoline. No aza-Nazarov product was formed either at room temperature or 80 °C with and without AgOTf.

In addition to the experimental mechanistic studies mentioned above, computational studies were performed by the Bozkaya research group at Hacettepe University to further validate our reaction design. The reaction barriers for the cyclization step for *N*-acyliminium cations with and without TMS group on the allylic position were determined. As shown in Figure 12, the reaction barrier for the aza-Nazarov cyclization is less for the cation bearing TMS group (14.7 kcal/mol) compared to the cyclization barrier for the cation without TMS group (27.2 kcal/mol). Further, the reaction energies for the cyclization of the cation having TMS group is much lower than the energy of the cation without TMS group. These findings support our argument on β -silicon effect, facilitating the cyclization reaction by providing the formation of a more stable carbocation.

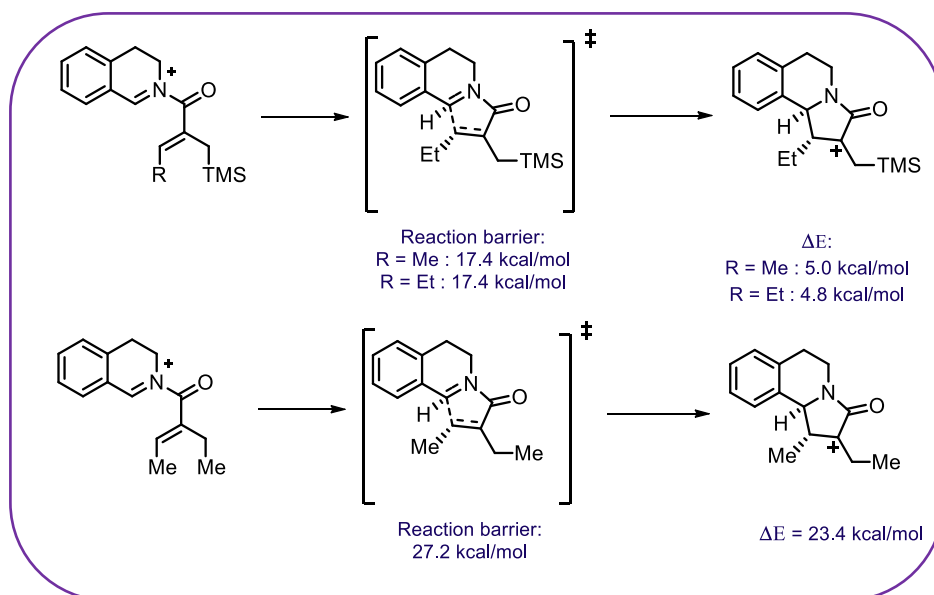


Figure 12. Computational studies on the aza-Nazarov cyclization.

These results justify our hypothesis on the cruciality of the -TMS group for the cyclization to proceed through β -silicon effect. The transition state structures calculated by our collaborators comparing the same cations with and without TMS group are shown in Figure 13. The interatomic distances in the structures give information about the nature of the transition state for both cation structures. The newly forming C-C bond in the transition state has a 2.106 Å distance when we have TMS group and a 1.894 Å distance when there is methyl group instead of TMS. This supports the fact that without TMS group, a higher reaction energy is required to provoke cyclization in accordance with Hammond-Leffler postulate on the late transition states.³⁷ When there is no TMS group in the structure, the transition state resembles the products more than reactants meaning compared to the structure with TMS group indicating a later transition state, thus requiring higher energy for the cyclization reaction.

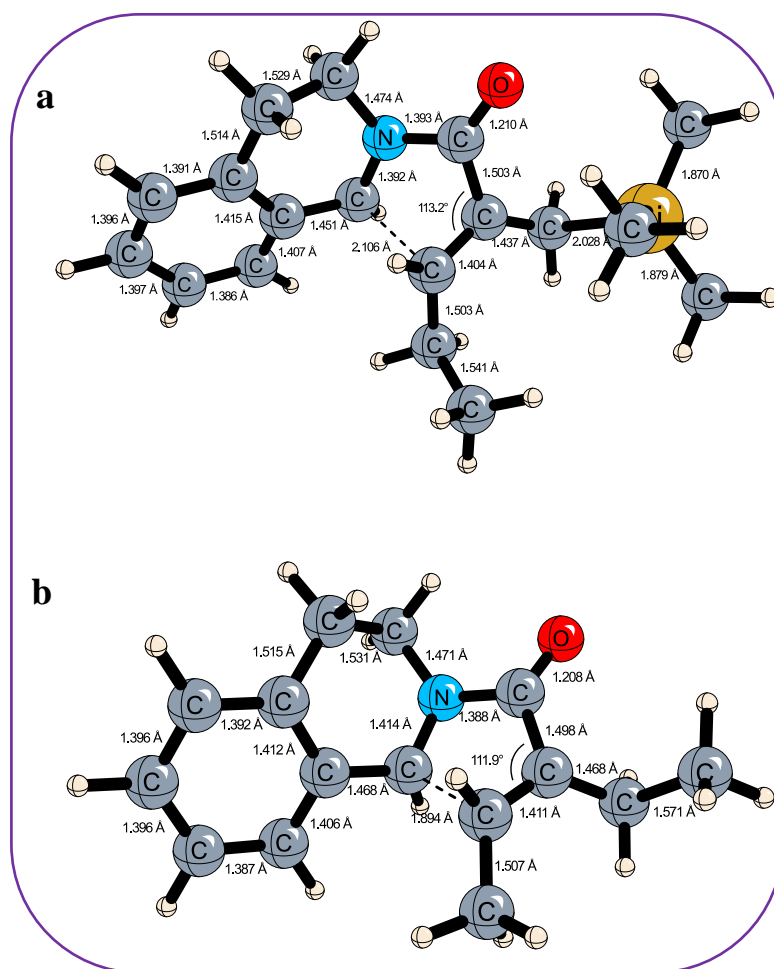
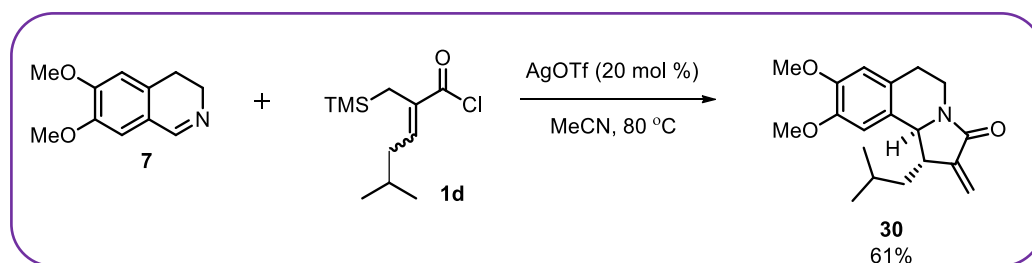


Figure 13. Computationally calculated bond distances.

The bond distances also show the β -Si effect on the carbocation stability. The C-Si bond on the structure **a** has a shorter distance (2.028 Å) compared to a typical C-Si single bond (1.85 Å) indicating the breaking of the C-Si bond (Figure 13). The C-C bond on the other hand is getting shorter (1.437 Å) compared to a C-C single bond (1.54 Å) indicating the formation of a double bond.³⁸

2.7. Scalability of the Aza-Nazarov Reaction

The scalability of the newly developed aza-Nazarov reaction was surveyed under optimized reaction conditions using AgOTf. For this purpose, aza-Nazarov reaction was carried out using dimethoxy-substituted 3,4-dihydroisoquinoline **7** (1.54 g) and isobutyl-substituted acyl chloride **1d** (2.43 g) on 8 mmol scale (Scheme 21). The product **30** was obtained in 61% yield (1.42 g) after purification and it was fully characterized by ¹H-NMR and ¹³C-NMR spectroscopy, HRMS and FTIR-ATR. With this outcome, we can conclude that our methodology can be scaled up for practical synthetic applications.



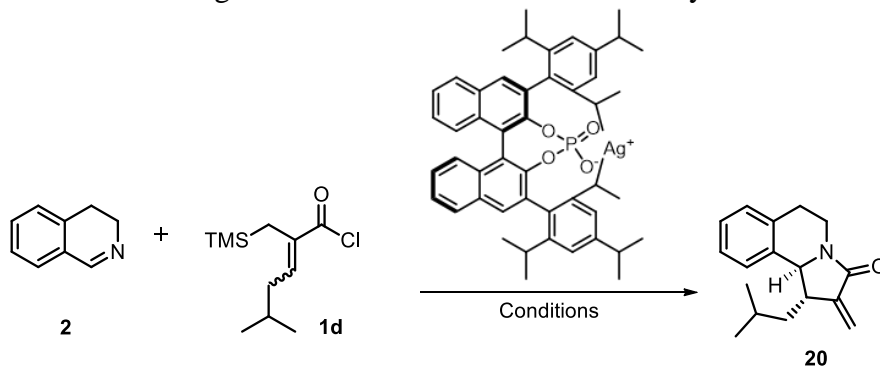
Scheme 21. Aza-Nazarov product obtained in the scale up reaction.

2.8. Attempts on Enantioselective Synthesis

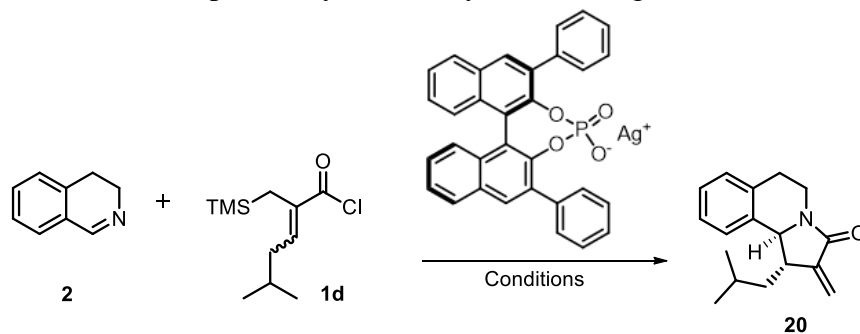
As the ultimate aim of this project, several attempts have been made to render the developed reaction enantioselective with the use of chiral catalysts. The first trial was made with BINOL derived chiral silver phosphate salts for the enantioselective studies.³⁹ BINOL derived silver catalysts would generate AgCl precipitation just like AgOTf but this time the chiral bulky phosphate anion becomes the chiral counter anion of the iminium cation. This anion was expected to block one phase of the substrate during cyclization and make the reaction enantioselective. The yields were obtained for the conditions that were able to produce products and enantiomeric excess values were analyzed by HPLC. Although we

tried many conditions, the desired enantioinduction could not be achieved. The corresponding data are given in Tables 3 and 4.

Table 3. Investigation of BINOL derived chiral catalysts

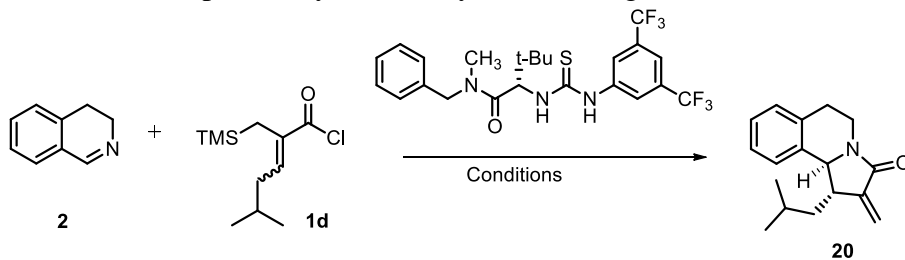


Entry	Catalyst Equiv.	Solvent	Temperature	Yield (%)	ee (%)
1	0.2	MeCN	80 °C	33	0
2	0.2	DCM	rt	No product	---
3	1.0	DCM	rt	No product	---

Table 4. Attempts on asymmetric synthesis using BINOL derived catalyst

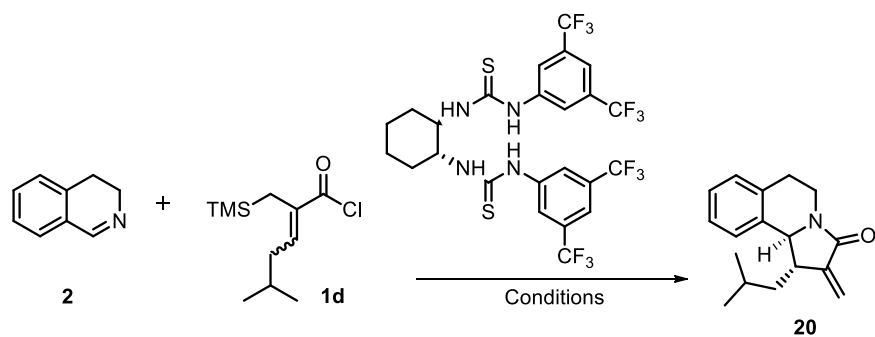
Entry	Catalyst Equiv.	Solvent	Temperature	Yield (%)	ee (%)
1	0.2	MeCN	80 °C	63	0
2	0.2	DCM	rt	No product	---

In consequence of these results, we next investigated thiourea-derived H-bonding catalysts known to bind successfully to chloride anion from past studies.⁴⁰ The reaction was conducted with two different thiourea-derived chiral catalysts in various reaction conditions apart from the optimized conditions. The corresponding data are shown in Tables 5 and 6.

Table 5. Attempts on asymmetric synthesis using thiourea-derived catalysts

Entry	Catalyst Equiv.	Solvent	Temperature	Yield (%)	ee (%)
1	0.2	MeCN	80 °C	82	0
2	0.2	MeCN	60 °C	41	0
3	0.2	DCE	80 °C	20	0
4	0.2	DME	80 °C	No product	---
5	0.2	Toluene	80 °C	No product	---
6	0.2	Trifluorotoluene	80 °C	No product	---

Table 6. Attempts on asymmetric synthesis



Entry	Catalyst Equiv.	Solvent	Temperature	Yield (%)	ee (%)
1	0.2	MeCN	rt	10	0
2	0.2	DCM	rt	No product	---
3	1.4	DCM	rt	No product	---

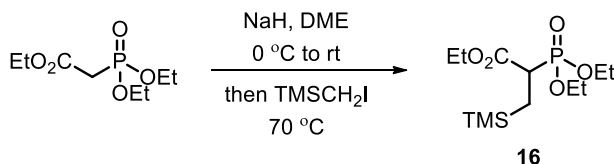
3. EXPERIMENTAL PART

(Certain sections of this part is also described in Selin E. Donmez et al. “Aza-Nazarov Cyclization Reactions via Anion Exchange Catalysis”, *Organic Letters*, 2019, 21, 554-558).⁴¹

All reactions were performed using oven- or flame-dried glassware under an inert atmosphere of nitrogen. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed plates pre-coated with silica gel (Merck, Silica Gel 60 F₂₅₄). UV light and/or KMnO₄ and PMA (phosphomolybdic acid) staining solutions were used for TLC visualization. Flash column chromatography was performed on Silicycle 40-63 μm (230-400 mesh) flash silica gel. NMR spectra were measured on a Bruker spectrometer at 400 MHz for ¹H-NMR spectra and 100 MHz for ¹³C-NMR spectra and calibrated from internal standard (TMS, 0 ppm) or residual solvent signals (chloroform at 7.26 ppm for ¹H spectra, and at 77.16 ppm and for ¹³C spectra). ¹H-NMR data are reported as follows: chemical shift (parts per million, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, br = broad, app = apparent), coupling constant (Hz). Infrared (FTIR) spectra were recorded on a Bruker Alpha-Platinum-ATR spectrometer with only selected peaks reported. Mass spectral analyses were performed on Agilent Technologies 6224 TOF LC/MS at UNAM-National Nanotechnology Research Center and Institute of Materials Science and Nanotechnology, Bilkent University. HPLC analyses were performed on Agilent Technologies 1260 Infinity II instrument using chiral IA column with n-hexane : i-PrOH = 90 : 10 solvent system.

3.1. Synthesis of Acyl Chloride Substrates

3.1.1. Compound 16



The synthesis of **16** was performed following a literature procedure.²⁸ NaH (375 mg, 9.37 mmol, 60% dispersion in mineral oil) was added as a solid to a solution of triethyl phosphonoacetate (2.00 g, 1.78 mL, 8.92 mmol) in anhydrous DME (7.0 mL) at 0 °C under nitrogen. After the reaction mixture was stirred at rt for 30 min, TMSCH₂I (2.29 g, 1.59 mL, 10.7 mmol) was added. The resulting mixture was heated at 70 °C for 125 min, and the progress of the reaction was monitored by TLC. Afterwards, the reaction mixture was cooled down to rt and quenched with saturated NH₄Cl solution. The aqueous phase was extracted three times with CHCl₃. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave pure product **16** as a colorless oil (1.833 g, 66% yield).

R_f = 0.29 (EtOAc:hexanes = 1:1)

Note: During TLC analysis, PMA solution was used for the visualization of the product.

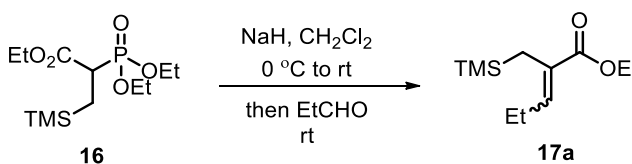
¹H NMR (400 MHz; CDCl₃) δ: 4.21-4.10 (6H, m), 2.94 (1H, ddd, *J* = 22.5, 12.7, 2.5 Hz), 1.32 (6H, dt, *J* = 7.0, 0.4 Hz), 1.28 (3H, t, *J* = 7.1 Hz), 1.29-1.23 (1H, m), 1.04 (1H, ddd, *J* = 15.6, 14.8, 2.5 Hz), 0.00 (9H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 170.1, 62.9 (d, $J_{\text{C-P}} = 6.7$ Hz), 62.8 (d, $J_{\text{C-P}} = 6.6$ Hz), 61.4, 41.2 (d, $J_{\text{C-P}} = 128$ Hz), 16.6 (d, $J_{\text{C-P}} = 5.8$ Hz), 16.5 (d, $J_{\text{C-P}} = 5.9$ Hz), 14.2, 13.3 (d, $J_{\text{C-P}} = 7.2$ Hz), -1.6.

FTIR ν_{max} (ATR, film)/ cm^{-1} : 2982, 2955, 2905, 1733, 1321, 1248, 1022.

HRMS (+ESI) Calcd for $\text{C}_{12}\text{H}_{27}\text{PSiO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 333.1258, found: 333.1269.

3.1.2. Compound 17a



Synthesis of **17a** was performed following a literature procedure.²⁹ To a suspension of NaH (251 mg, 6.28 mmol, 60% dispersion in mineral oil) in 4.0 mL of anhydrous CH_2Cl_2 was added to a solution of **16** (1.30 g, 4.19 mmol) in anhydrous CH_2Cl_2 (4.0 mL) at $0\text{ }^\circ\text{C}$ under nitrogen. After the mixture was stirred at rt for 30 min, propanal (457 μL , 6.28 mmol) was added. The resulting mixture was stirred at rt for an additional 190 min, and then quenched with saturated NH_4Cl solution. The aqueous phase was extracted three times with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Product **17a** was obtained as a pale yellow oil (843 mg, 94% yield, $Z:E = 3:1$). Due to the volatility of this compound, it was directly used in the next step without further purification. The purity of **17a** was checked by ^1H -NMR spectroscopy.

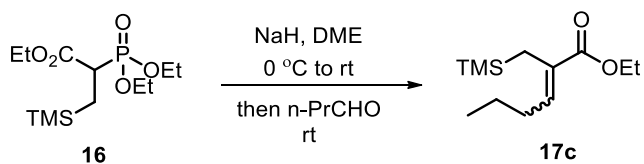
$R_f = 0.44$ (EtOAc:hexanes =1:100)

¹H NMR (400 MHz; CDCl₃) δ; Z- (major) isomer: 6.58 (1H, t, *J* = 7.3 Hz), 4.17 (2H, q, *J* = 7.2 Hz), 2.11 (2H, quint, *J* = 7.5 Hz), 1.80 (2H, s), 1.29 (3H, t, *J* = 7.2 Hz), 1.04 (3H, t, *J* = 7.5 Hz), -0.01 (9H, s).

E- (minor) isomer: 5.65 (1H, t, *J* = 7.5 Hz), 4.17 (2H, q, *J* = 7.2 Hz), 2.40 (2H, quint, *J* = 7.5 Hz), 1.72 (2H, s), 1.30 (3H, t, *J* = 7.2 Hz), 1.00 (3H, t, *J* = 7.5 Hz), -0.02 (9H, s).

FTIR ν_{max} (ATR, film)/cm⁻¹ 2957, 2932, 1709, 1636, 1247, 1160.

3.1.3. Compound 17c



NaH (155 mg, 3.87 mmol, 60% dispersion in mineral oil) was added to a solution of **16** (800 mg, 2.58 mmol) in DME (4.0 mL) at 0 °C under nitrogen. After the mixture was stirred at rt for 30 min, butanal (340 μ L, 3.87 mmol) was added. The resulting mixture was stirred at rt for an additional 55 min, and then quenched with saturated NH₄Cl solution. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:19) gave product **17c** as a colorless oil (346 mg, 59% yield, *Z*:*E* = 3:1).

R_f = 0.58 (EtOAc:hexanes = 1:100)

¹H NMR (400 MHz; CDCl₃) δ: 6.61 (1H, t, *J* = 7.3 Hz), 4.17 (2H, q, *J* = 7.1 Hz), 2.07 (2H, q, 7.4 Hz), 1.81 (2H, s), 1.49-1.32 (2H, m), 1.29 (3H, t, *J* = 7.1 Hz), 0.94 (3H, t, *J* = 7.4 Hz), 0.00 (9H, s).

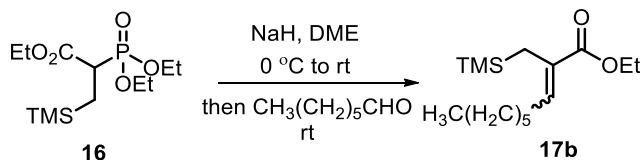
¹³C NMR (100 MHz; CDCl₃) δ: 168.6, 138.5, 130.3, 60.5, 31.3, 22.2, 17.4, 14.4, 14.1, -0.9

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2957, 2930, 2873, 1709, 1637, 1462, 1368, 1248.

HRMS (+APCI) Calcd for C₁₁H₂₁SiO₂ [M-CH₃]⁺ 213.1306, found: 213.1299.

(Despite all our attempts, fragmentation of the -CH₃ group was observed in the HRMS data).

3.1.4. Compound 17b



NaH (139 mg, 5.79 mmol, 60% dispersion in mineral oil) was added to a solution of **16** (1.20 g, 3.87 mmol) in anhydrous DME (8.0 mL) at 0 °C under nitrogen. After the mixture was stirred at rt for 30 min, heptanal (810 μ L, 5.79 mmol) was added. The resulting mixture was stirred at rt for an additional 60 min, and then quenched with saturated NH₄Cl solution. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:100) gave product **17b** as a colorless oil (708 mg, 68% yield, *Z*:*E* = 3:1).

R_f = 0.65 (EtOAc:hexanes = 1:100)

¹H NMR (400 MHz; CDCl₃) δ; Z- (major) isomer: 6.62 (1H, t, *J* = 7.3 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 2.10 (2H, q, *J* = 7.3 Hz), 1.82 (2H, s), 1.46-1.40 (2H, m), 1.33-1.27 (9H, m), 0.91-0.89 (3H, m), 0.01 (9H, s).

***E*- (minor) isomer:** 5.68 (1H, t, *J* = 7.6 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 2.41 (2H, q, *J* = 7.4 Hz), 1.74 (2H, s), 1.46-1.40 (2H, m), 1.33-1.27 (9H, m), 0.91-0.89 (3H, m), 0.00 (9H, s).

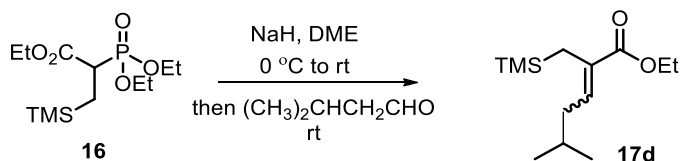
¹³C NMR (100 MHz; CDCl₃) δ: 168.6, 138.8, 130.1, 60.5, 31.9, 29.32, 29.27, 28.9, 22.7, 17.4, 14.4, 14.2, -0.9

FTIR ν_{max} (ATR, film)/cm⁻¹ 2955, 2926, 2857, 1709, 1463, 1248, 1157.

HRMS (+ESI) Calcd for C₁₄H₂₇SiO₂ [M-CH₃]⁺ 255.1775, found: 255.1775.

(Despite all our attempts, fragmentation of the -CH₃ group was observed in the HRMS data).

3.1.5. Compound 17d



NaH (155 mg, 3.87 mmol, 60% dispersion in mineral oil) was added to a solution of **16** (800 mg, 2.58 mmol) in DME (4.0 mL) at 0 °C under nitrogen. After the mixture was stirred at rt for 30 min, isovaleraldehyde (420 μ L, 3.87 mmol) was added. The resulting mixture was stirred at rt for an additional 35 min, and then quenched with saturated NH₄Cl solution. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under

reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:100) gave product **17d** as a yellow oil (464 mg, 74% yield, *Z:E* = 3:1). While this product was used as a diastereomeric mixture in the next step, a small portion was purified to obtain analytically pure *Z*- isomer.

$R_f = 0.59$ (EtOAc:hexanes = 1:100)

$^1\text{H NMR}$ (400 MHz; CDCl_3) δ : 6.64 (1H, t, $J = 7.3$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 1.98 (2H, t, $J = 7.0$ Hz), 1.80 (2H, s), 1.72 (1H, sept, $J = 6.7$ Hz), 1.29 (3H, t, $J = 7.2$ Hz), 0.93 (6H, d, $J = 6.6$ Hz).

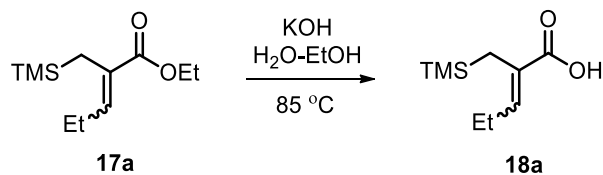
$^{13}\text{C NMR}$ (100 MHz; CDCl_3) δ : 168.6, 137.6, 130.8, 60.5, 38.3, 28.5, 22.7, 17.5, 14.4, -0.9

FTIR ν_{max} (ATR, film)/ cm^{-1} 2956, 2901, 2872, 1709, 1636, 1465, 1283, 1249.

HRMS (+ESI) Calcd for $\text{C}_{12}\text{H}_{23}\text{SiO}_2$ $[\text{M}-\text{CH}_3]^+$ 227.1462, found: 227.1474.

(Despite all our attempts, fragmentation of the $-\text{CH}_3$ group was observed in the HRMS data).

3.1.6. Compound 18a



KOH (1.66 g, 29.6 mmol) was added to a solution of **17a** (2.08 g, 9.70 mmol) in 20% H_2O -EtOH mixture (8 mL) at rt, and the mixture was heated at 85 °C for 24 h. It was then cooled down to rt and quenched with 1.0 M HCl solution, followed by saturated

NH₄Cl solution. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:5) gave product **18a** as a yellow oil (1.145 g, 63% yield, *Z:E* = 4:1).

R_f = 0.33 (EtOAc:hexanes = 1:9)

¹H NMR (400 MHz; CDCl₃) δ; *Z*- (major) isomer: 6.75 (1H, t, *J* = 7.3 Hz), 2.14 (2H, quint, *J* = 7.5 Hz), 1.80 (2H, s), 1.05 (3H, t, *J* = 7.5 Hz), 0.01 (9H, s).

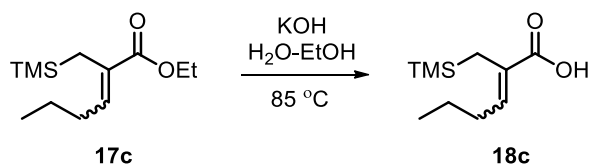
***E*- (minor) isomer:** 5.83 (1H, t, *J* = 7.6 Hz), 2.50 (2H, quint, *J* = 7.5 Hz), 1.74 (2H, s), 1.02 (3H, t, *J* = 7.5 Hz), 0.00 (9H, s)

¹³C NMR (100 MHz; CDCl₃) δ: 174.0, 142.9, 129.0, 23.8, 17.1, 13.2, -1.0

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2956, 2930, 1681, 1630, 1420, 1282, 1248

HRMS (-ESI) Calcd for C₉H₁₇SiO₂ [M-H]⁻ 185.1003, found: 185.1002.

3.1.7. Compound 18c



KOH (214 mg, 3.81 mmol) was added to a solution of **17c** (285 mg, 1.25 mmol) in 20% H₂O-EtOH mixture (4.0 mL) at rt, and the mixture was heated at 85 °C for 24 h. It was then cooled down to rt and quenched with 1.0 M HCl solution, followed by saturated NH₄Cl solution. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under

reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:5) gave product **18c** as a yellow oil (123 mg, 49% yield, *Z:E* = 3:1).

$R_f = 0.57$ (EtOAc:hexanes = 1:19)

^1H NMR (400 MHz; CDCl_3) δ ; *Z*- (major) isomer: 6.78 (1H, t, $J = 7.3$ Hz), 2.11 (2H, q, $J = 7.3$ Hz), 1.80 (2H, s), 1.52-1.43 (2H, m), 0.95 (3H, t, $J = 7.3$ Hz), 0.02 (9H, s).

***E*- (minor) isomer:** 5.84 (1H, t, $J = 7.5$ Hz), 2.47 (2H, q, $J = 7.3$ Hz), 1.75 (2H, s), 1.50-1.41 (2H, m), 0.93 (3H, t, $J = 7.4$ Hz), 0.00 (9H, s).

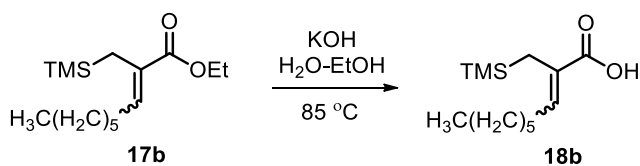
^{13}C NMR (100 MHz; CDCl_3) δ ; *Z*- (major) isomer: 174.0, 141.4, 129.6, 31.5, 22.1, 17.1, 14.1, -0.9

***E*- (minor) isomer:** 174.2, 142.8, 128.6, 32.0, 23.9, 23.1, 14.0, -1.5

FTIR ν_{max} (ATR, film)/ cm^{-1} 2957, 2901, 2874, 1681, 1630, 1421, 1286, 1263, 1248.

HRMS (-ESI) Calcd for $\text{C}_{10}\text{H}_{19}\text{SiO}_2$ [M-H] $^-$ 199.1159, found: 199.1170.

3.1.8. Compound 18b



KOH (448 mg, 7.99 mmol) was added to a solution of **17b** (708 mg, 2.62 mmol) in 20% H_2O -EtOH mixture (8.0 mL) at rt, and the mixture was heated at 85 °C for 6 h. It was then cooled down to rt and quenched with 1.0 M HCl solution, followed by saturated NH_4Cl solution. The aqueous phase was extracted three times with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under

reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:5) gave product **18b** as a pale yellow oil (568 g, 90% yield, *Z:E* = 4:1). While this product was used as a diastereomeric mixture in the next step, a small portion was purified to obtain analytically pure *Z*- isomer.

$R_f = 0.31$ (EtOAc:hexanes = 1:9)

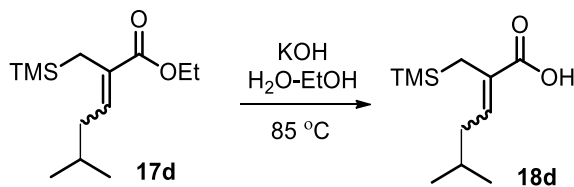
$^1\text{H NMR}$ (400 MHz; CDCl_3) δ : 6.77 (1H, t, $J = 7.3$ Hz), 2.12 (2H, q, $J = 7.3$ Hz), 1.80 (2H, s), 1.47-1.40 (2H, m), 1.35-1.26 (6H, m), 0.89 (3H, t, $J = 6.9$ Hz), 0.01 (9H, s).

$^{13}\text{C NMR}$ (100 MHz; CDCl_3) δ : 173.8, 141.7, 129.4, 31.9, 29.5, 29.3, 28.8, 22.7, 17.1, 14.2, -0.9

FTIR ν_{max} (ATR, film)/ cm^{-1} 2955, 2926, 2857, 1680, 1630, 1459, 1420, 1284, 1248.

HRMS (-ESI) Calcd for $\text{C}_{13}\text{H}_{25}\text{SiO}_2$ $[\text{M}-\text{H}]^-$ 241.1629, found: 241.1644.

3.1.9. Compound 18d



KOH (296 mg, 5.28 mmol) was added to a solution of **17d** (421 mg, 1.73 mmol) in 20% H₂O-EtOH mixture (4.0 mL) at rt, and the mixture was heated at 85 °C for 24 h. It was then cooled down to rt and quenched with 1.0 M HCl solution, followed by saturated NH₄Cl solution. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under

reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:5) gave product **18d** as a yellow oil (225 mg, 61% yield, *Z:E* = 3:1).

$R_f = 0.44$ (EtOAc:hexanes = 1:9)

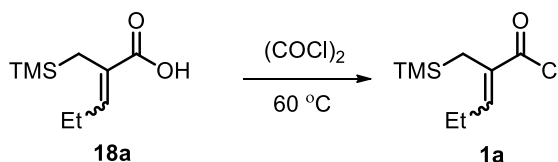
$^1\text{H NMR}$ (400 MHz; CDCl_3) δ : 6.80 (1H, t, $J = 7.3$ Hz), 2.02 (2H, t, $J = 7.1$ Hz), 1.80 (2H, s), 1.78-1.72 (1H, m), 0.94 (6H, d, $J = 6.5$ Hz), 0.02 (9H, s).

$^{13}\text{C NMR}$ (100 MHz; CDCl_3) δ : 173.6, 140.5, 130.1, 38.5, 28.5, 22.7, 17.2, -0.8

$\text{FTIR } \nu_{\text{max}}$ (ATR, film)/ cm^{-1} 2955, 2898, 2871, 1681, 1628, 1421, 1288, 1247

HRMS (-APCI) Calcd for $\text{C}_{11}\text{H}_{21}\text{SiO}_2$ $[\text{M-H}]^-$ 213.1316, found: 213.1315.

3.1.10. Compound 1a



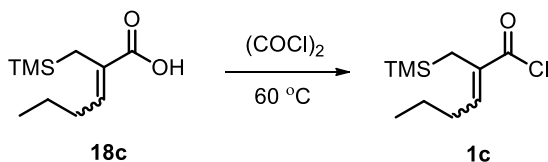
A solution of **18a** (600 mg, 3.22 mmol) in 4.0 mL of $(\text{COCl})_2$ (oxalyl chloride) was stirred at $60\text{ }^\circ\text{C}$ for 2 h. It was then cooled down to rt, and removal of excess $(\text{COCl})_2$ using a rotary evaporator inside a well-ventilated fume hood gave **1a** as an orange oil (613 mg, 93% yield, *dr* = 4:1).

Notes: 1) Care has to be taken during the removal of excess oxalyl chloride *in vacuo* as product **1a** has a certain level of volatility.

2) This product is unstable and prone to decomposition. Therefore, it was used immediately after preparation.

$^1\text{H NMR}$ (400 MHz; CDCl_3) δ : 7.05 (1H, t, $J = 7.3$ Hz), 2.23 (2H, quint, $J = 7.5$ Hz), 1.84 (2H, s), 1.11 (3H, t, $J = 7.5$ Hz), 0.02 (9H, s).

3.1.11. Compound 1c

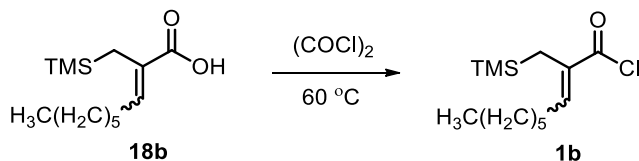


A solution of **18c** (98.6 mg, 0.49 mmol) in 2.0 mL of $(\text{COCl})_2$ (oxalyl chloride) at $60\text{ }^\circ\text{C}$ for 2 h. It was then cooled to rt, and removal of excess $(\text{COCl})_2$ using a rotary evaporator inside a well-ventilated fume hood gave **1c** as an orange oil (105 mg, 97% yield, dr = 3:1).

Note: This product is unstable and prone to decomposition. Therefore, it was used immediately after preparation.

$^1\text{H NMR}$ (400 MHz; CDCl_3) δ : 7.08 (1H, t, $J = 7.3$ Hz), 2.21-2.16 (2H, m), 1.84 (2H, s), 1.58-1.48 (2H, m), 0.98 (3H, t, $J = 7.4$ Hz), 0.01 (9H, s).

3.1.12. Compound 1b



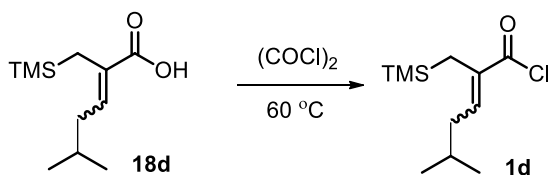
A solution of **18b** (551 mg, 2.28 mmol) in 4.0 mL of $(\text{COCl})_2$ (oxalyl chloride) at $60\text{ }^\circ\text{C}$ for 2 h. It was then cooled to rt, and removal of excess $(\text{COCl})_2$ using a rotary

evaporator inside a well-ventilated fume hood gave **1b** as an orange oil (509 mg, 86% yield, dr = 4:1).

Note: This product is unstable and prone to decomposition. Therefore, it was used immediately after preparation.

¹H NMR (400 MHz; CDCl₃) δ: 7.08 (1H, t, *J* = 7.3 Hz), 2.20 (2H, q, *J* = 7.5 Hz), 1.84 (2H, s), 1.53-1.46 (2H, m), 1.41-1.26 (6H, m), 0.90 (3H, t, *J* = 6.7 Hz), 0.02 (9H, s).

3.1.13. Compound 1d



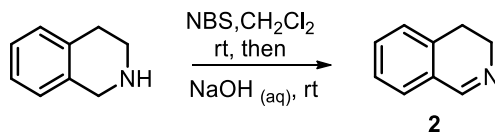
A solution of **18d** (361 mg, 1.68 mmol) in 3.0 mL of (COCl)₂ (oxalyl chloride) at 60 °C for 2 h. It was then cooled to rt, and removal of excess (COCl)₂ using a rotary evaporator inside a well-ventilated fume hood gave **1d** as an orange oil (332 mg, 85% yield, dr = 3:1).

Note: This product is unstable and prone to decomposition. Therefore, it was used immediately after preparation.

¹H NMR (400 MHz; CDCl₃) δ: 7.10 (1H, t, *J* = 7.3 Hz), 2.09 (2H, t, *J* = 7.1 Hz), 1.82 (2H, s), 1.81-1.76 (1H, m), 0.96 (6H, d, *J* = 6.7 Hz), 0.01 (9H, s).

3.2. Synthesis of Imine Substrates

3.2.1. Compound 2



The procedure for the preparation of **2** was modified based on a literature report.³⁰ *N*-Bromosuccinimide (NBS) (1.47 g, 8.30 mmol) was added slowly to a solution of 1,2,3,4-tetrahydroisoquinoline (**S3**) (0.95 mL, 7.51 mmol) in 12 mL of anhydrous CH₂Cl₂ at rt under nitrogen. The reaction mixture was stirred for 1 h. Afterwards, 30% (w/v) aqueous NaOH solution (10 mL) was added, and the resulting mixture was stirred at rt for 1 h. At the end of this time, the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:1 to only EtOAc) gave pure product **2** as an orange oil which solidified upon storing in the refrigerator (812 mg, 82% yield).

$R_f = 0.47$ (EtOH:EtOAc = 1:9)

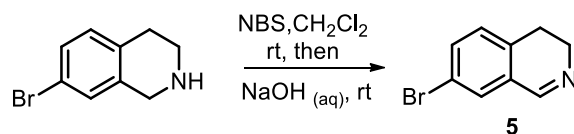
¹H NMR (400 MHz; CDCl₃) δ : 8.32 (1H, s), 7.36-7.24 (2H, m), 7.14 (1H, dd, $J = 6.8, 0.8$ Hz), 3.78-3.74 (2H, m), 2.73 (2H, t, $J = 7.7$ Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 174.7, 161.0, 136.4, 131.9, 128.1, 127.6, 127.3, 46.1, 25.0.

FTIR ν_{\max} (ATR, solid)/cm⁻¹: 3167, 3044, 2938, 2795, 1657, 1563, 1469, 1373, 1275, 1172, 1129, 887.

HRMS (+ESI) Calcd for C₉H₁₀N [M+H]⁺ 132.0808, found: 132.0810.

3.2.2. Compound 5



N-Bromosuccinimide (NBS) (121 mg, 0.68 mmol) was added slowly to a solution of 1,2,3,4-tetrahydroisoquinoline derivative (132 mg, 0.62 mmol) in 4.0 mL of anhydrous CH₂Cl₂ at rt under nitrogen. The reaction mixture was stirred for 1 h. Afterwards, 30% (w/v) NaOH aqueous solution (1.0 mL) was added, and the resulting mixture was stirred at rt for 1 h. At the end of this time, the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:hexanes = 1:1 to only EtOAc) gave pure product **5** as an orange solid (96.4 mg, 74% yield).

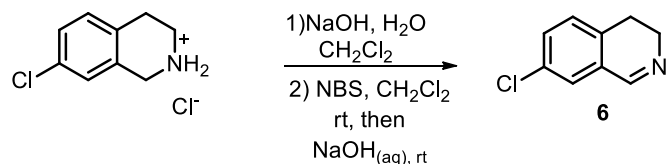
The spectral data are in accordance with the reported values in the literature.³¹

¹H NMR (400 MHz; CDCl₃) δ: 8.28 (1H, s), 7.47 (1H, dd, *J* = 8.0, 1.8 Hz), 7.40 (1H, s), 7.04 (1H, d, *J* = 8.0 Hz), 3.80-3.76 (2H, m), 2.69 (2H, t, *J* = 7.7 Hz).

FTIR ν_{\max} (ATR, solid)/cm⁻¹: 2955, 2928, 1665, 1622, 1426, 1264, 1248.

HRMS (+APCI) Calcd for C₉H₉⁷⁹BrN [M+H]⁺ 209.9913, found: 209.9915.

3.2.3. Compound 6



To a solution of tetrahydroisoquinoline salt derivative (119 mg, 0.58 mmol) in 6 mL of CH₂Cl₂ was added a mixture of NaOH (160 mg, 4.0 mmol), 2.5 mL of H₂O and 2.5 mL of brine. The resulting mixture was stirred at rt for 45 min. Afterwards, the mixture was transferred to a separatory funnel, and the two phases were partitioned. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting oil (56.2 mg, 0.34 mmol) was dissolved in 2.0 mL of anhydrous CH₂Cl₂ at rt under nitrogen, and *N*-Bromosuccinimide (NBS) (67 mg, 0.37 mmol) was added. The reaction mixture was stirred for 1 h. Afterwards, 30% (w/v) NaOH aqueous solution (1.0 mL) was added, and the resulting mixture was stirred at rt for 1 h. At the end of this time, the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (only EtOAc to 10% MeOH in EtOAc) gave pure product **6** as a beige solid (53 mg, 55% yield)

R_f = 0.45 (only EtOAc)

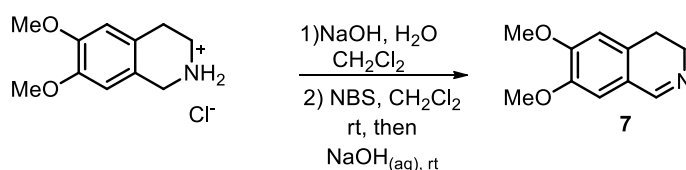
¹H NMR (400 MHz; CDCl₃) δ: 8.28 (1H, app s), 7.31 (1H, dd, J = 8.0, 2.2 Hz), 7.25 (1H, d, J = 2.1 Hz), 7.09 (1H, d, J = 8.0 Hz), 3.79-3.75 (2H, m), 2.71 (2H, t, J = 7.5 Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 159.1, 134.7, 132.8, 131.0, 129.7, 128.9, 127.2, 47.5, 24.5

FTIR ν_{max} (ATR, film)/ cm^{-1} : 2938, 2896, 2852, 1721, 1673, 1627, 1567, 1484, 1427, 1265.

HRMS (+APCI) Calcd for $\text{C}_9\text{H}_9^{35}\text{ClN}$ $[\text{M}+\text{H}]^+$ 166.0419, found: 166.0418.

3.2.4. Compound 7



To a solution of tetrahydroisoquinoline salt derivative (300 mg, 1.31 mmol) in 9 mL of CH_2Cl_2 was added a mixture of NaOH (160 mg, 4.0 mmol), 2.5 mL of H_2O and 2.5 mL of brine. The resulting mixture was stirred at rt for 45 min. Afterwards, the mixture was transferred to a separatory funnel, and the two phases were partitioned. The aqueous phase was extracted three times with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting solid (244 mg, 1.26 mmol) was dissolved in 4.0 mL of anhydrous CH_2Cl_2 at rt under nitrogen, and *N*-Bromosuccinimide (NBS) (247 mg, 1.39 mmol) was added. The reaction mixture was stirred for 1 h. Afterwards, 30% (w/v) NaOH aqueous solution (2.0 mL) was added, and the resulting mixture was stirred at rt for 1 h. At the end of this time, the aqueous phase was extracted with EtOAc (3 \times 5 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% to 15% MeOH in EtOAc) gave pure product **7** as an orange oil (182 mg, 75% yield).

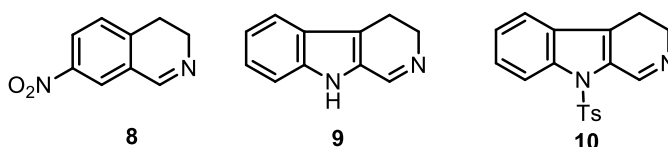
The spectral data are in accordance with the reported values in the literature.³²

¹H NMR (400 MHz; CDCl₃) δ : 8.05 (1H, t, $J = 2.1$ Hz), 6.63 (1H, s), 6.50 (1H, s), 3.73 (3H, s), 3.71 (3H, s), 3.57-3.53 (2H, m), 2.49 (2H, t, $J = 7.9$ Hz)

¹³C NMR (100 MHz; CDCl₃) δ : 159.4, 151.1, 147.7, 129.7, 121.4, 110.32, 110.29, 56.0, 55.8, 47.1, 24.6

FTIR ν_{max} (ATR, film)/cm⁻¹: 3001, 2936, 2835, 1628, 1604, 1573, 1514, 1462, 1349, 1320

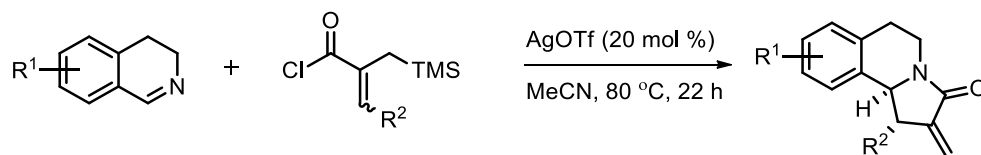
HRMS (+APCI) Calcd for C₁₁H₁₄NO₂ [M+H]⁺ 192.1019, found: 192.1018.



The previously known imine derivatives **8**^{34c}, **9**^{34d} and **10**^{34e} were prepared by following the reported procedures.

3.3. Synthesis of Aza-Nazarov Products

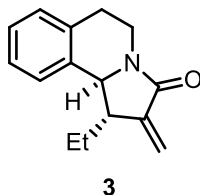
3.3.1. General Procedure I



A 25-mL, flame-dried Schlenk flask was cooled to rt under nitrogen and charged with the imine reactant (0.50 mmol) and 0.5 mL of anhydrous CH₃CN. The solution of acyl

chloride reactant (0.65 mmol) in 0.5 mL anhydrous CH₃CN was added to the reaction mixture, and the resulting clear solution was stirred for 5 min at rt. After the addition of AgOTf (25.7 mg, 0.10 mmol), formation of a cloudy mixture was observed. The reaction mixture was inserted into a preheated oil bath at 80 °C, and stirred at this temperature for 22 h. It was then cooled to rt and quenched with saturated NaHCO₃ solution (3 mL). The aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the product was carried out by flash column chromatography using SiO₂ as the stationary phase.

3.3.2. Compound 3



Product **3** was prepared according to the General Procedure I using dihydroisoquinoline **2** (60.5 mg, 0.46 mmol), acyl chloride **1a** (128 mg, 0.60 mmol; *Z:E* = 4:1), AgOTf (23.7 mg, 0.092 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave pure aza-Nazarov product **3** as an orange oil (82.4 mg, 79% yield).

R_f = 0.51 (EtOAc:hexanes = 1:1)

¹H NMR (400 MHz; CDCl₃) δ: 7.26-7.18 (3H, m), 7.13 (1H, d, *J* = 7.2 Hz), 6.08 (1H, d, *J* = 2.7 Hz), 5.31 (1H, d, *J* = 2.3 Hz), 4.48 (1H, d, *J* = 3.6 Hz), 4.36 (1H, ddd, *J* =

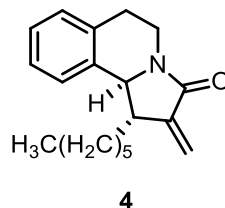
12.9, 6.3, 3.0 Hz), 3.23 (1H, ddd, $J = 12.9, 10.8, 4.8$ Hz), 3.08-2.96 (2H, m), 2.77 (1H, ddd, $J = 16.1, 4.6, 3.1$ Hz), 1.97-1.90 (2H, m), 1.12 (3H, t, $J = 7.4$ Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 166.8, 143.8, 137.9, 134.5, 129.4, 127.2, 126.9, 124.8, 115.9, 59.2, 45.4, 38.2, 28.4, 27.9, 10.6

FTIR ν_{max} (ATR, film)/ cm^{-1} 2961, 2926, 2874, 1685, 1656, 1492, 1456, 1419, 1303, 1157

HRMS (+APCI) Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$ 228.1383, found: 228.1390.

3.3.3. Compound 4



Product **4** was prepared according to the General Procedure I using dihydroisoquinoline **2** (10.1 mg, 0.077 mmol), acyl chloride **1b** (24.1 mg, 0.092 mmol; $Z:E = 9:1$), AgOTf (3.9 mg, 0.015 mmol) and 1.0 mL of anhydrous CH_3CN . Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave pure aza-Nazarov product **4** as an orange oil and single diastereomer (13.1 mg, 60% yield).

$R_f = 0.49$ (EtOAc:hexanes = 1:2)

^1H NMR (400 MHz; CDCl_3) δ : 7.25-7.18 (3H, m), 7.13 (1H, d, $J = 7.9$ Hz), 6.06 (1H, d, $J = 2.7$ Hz), 5.31 (1H, d, $J = 2.2$ Hz), 4.48 (1H, d, $J = 3.4$ Hz), 4.34 (1H, ddd, $J = 12.9, 6.3, 3.0$ Hz), 3.23 (1H, ddd, $J = 12.9, 10.7, 4.9$ Hz), 3.08-2.99 (2H, m), 2.76 (1H,

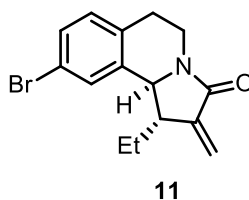
dt, $J = 16.0, 3.4$ Hz), 1.89-1.83 (2H, m), 1.57-1.49 (2H, m), 1.42-1.37 (2H, m), 1.35-1.31 (4H, m), 0.91 (3H, t, $J = 7.0$ Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 166.9, 144.3, 137.9, 134.5, 129.4, 127.2, 126.9, 124.8, 115.8, 59.9, 44.3, 38.2, 35.6, 31.9, 29.7, 28.4, 26.4, 22.8, 14.2

FTIR ν_{max} (ATR, film)/ cm^{-1} 2954, 2927, 2855, 1694, 1657, 1457, 1423

HRMS Calcd for: $\text{C}_{19}\text{H}_{26}\text{NO}$ $[\text{M}+\text{H}]^+$ 284.2009, found: 284.2022.

3.3.4. Compound 11



Product **11** was prepared according to the General Procedure I using dihydroisoquinoline **5** (69.2 mg, 0.33 mmol), acyl chloride **1a** (107 mg, 0.52 mmol; $Z:E = 4:1$), AgOTf (16.9 mg, 0.066 mmol) and 1.0 mL of anhydrous CH_3CN . Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave pure aza-Nazarov product **11** as an orange oil and single diastereomer (69 mg, 69% yield).

$R_f = 0.60$ (only EtOAc)

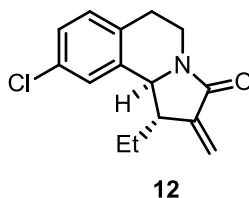
^1H NMR (400 MHz; CDCl_3) δ : 7.31-7.28 (2H, m), 6.98 (1H, d, $J = 8.7$ Hz), 6.07 (1H, d, $J = 2.7$ Hz), 5.31 (1H, d, $J = 2.3$ Hz), 4.42 (1H, d, $J = 3.3$ Hz), 4.35 (1H, ddd, $J = 13.0, 6.4, 2.7$ Hz), 3.17 (1H, ddd, $J = 13.0, 10.9, 4.9$ Hz), 2.98-2.90 (2H, m), 2.70 (1H, dt, $J = 16.3, 2.8$ Hz), 1.91 (2H, quint, $J = 7.4$ Hz), 1.09 (3H, t, $J = 7.4$ Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 166.8, 143.2, 139.9, 133.3, 131.0, 130.3, 127.8, 120.4, 116.3, 58.8, 45.2, 37.9, 27.81, 27.79, 10.4

FTIR ν_{max} (ATR, film)/cm⁻¹ 2961, 2930, 2874, 1686, 1656, 1482, 1425, 1303

HRMS (+APCI) Calcd for C₁₅H₁₇⁷⁹BrNO [M+H]⁺ 306.0488, found: 306.0489.

3.3.5. Compound 12



Product **12** was prepared according to the General Procedure I using dihydroisoquinoline **6** (42.2 mg, 0.25 mmol), acyl chloride **1a** (68 mg, 0.33 mmol; *Z:E* = 4:1), AgOTf (12.8 mg, 0.050 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (only EtOAc) gave pure aza-Nazarov product **12** as a yellow oil and single diastereomer (42.9 mg, 64% yield).

R_f = 0.60 (only EtOAc)

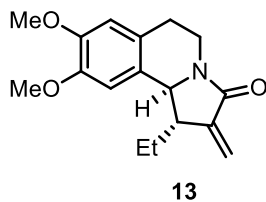
¹H NMR (400 MHz; CDCl₃) δ: 7.17-7.15 (2H, m), 7.04 (1H, d, *J* = 8.8 Hz), 6.09 (1H, d, *J* = 2.7 Hz), 5.33 (1H, d, *J* = 2.3 Hz), 4.43 (1H, d, *J* = 3.5 Hz), 4.37 (1H, ddd, *J* = 13.0, 6.4, 2.7 Hz), 3.18 (1H, ddd, *J* = 13.0, 10.9, 4.8 Hz), 3.02-2.93 (2H, m), 2.73 (1H, dq, *J* = 16.2, 2.8 Hz), 1.92 (2H, quint, *J* = 7.4 Hz), 1.11 (3H, t, *J* = 7.4 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 166.8, 143.3, 139.6, 132.8, 132.5, 130.7, 127.4, 125.0, 116.3, 59.0, 45.3, 38.0, 27.9, 27.8, 10.5

FTIR ν_{max} (ATR, film)/cm⁻¹ 2962, 2929, 2875, 1687, 1657, 1426, 1403, 1303.

HRMS (+APCI) Calcd for C₁₅H₁₇³⁵ClNO [M+H]⁺ 262.0994, found: 262.0982.

3.3.6. Compound 13



Product **13** was prepared according to the General Procedure I using dihydroisoquinoline **7** (78.2 mg, 0.41 mmol), acyl chloride **1a** (107 mg, 0.52 mmol; *Z:E* = 4:1), AgOTf (20.5 mg, 0.079 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:1 to only EtOAc) gave pure aza-Nazarov product **13** as an orange solid and single diastereomer (64.5 mg, 55% yield).

R_f = 0.57 (only EtOAc)

M.P. = 106.8-107.7 °C

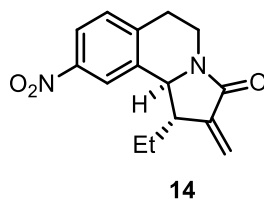
¹H NMR (400 MHz; CDCl₃) δ: 6.67 (1H, s), 6.59 (1H, s), 6.07 (1H, d, *J* = 2.7 Hz), 5.30 (1H, d, *J* = 2.3 Hz), 4.43-4.37 (2H, m), 3.87 (3H, s), 3.85 (3H, s), 3.15 (1H, dt, *J* = 11.4, 4.7 Hz), 3.01-2.89 (2H, m), 2.67-2.62 (1H, m), 1.91 (2H, quint, *J* = 7.1 Hz), 1.13 (3 H, t, *J* = 7.4 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 166.8, 148.3, 148.2, 143.9, 129.7, 126.6, 115.9, 112.1, 108.1, 59.1, 56.3, 56.1, 45.6, 38.3, 28.0, 27.9, 10.7

FTIR *v*_{max} (ATR, solid)/cm⁻¹ 2959, 2931, 2874, 1685, 1656, 1611, 1514, 1429, 1359, 1254, 1221

HRMS (+APCI) Calcd for C₁₇H₂₂NO₃ [M+H]⁺ 288.1594, found: 288.1595.

3.3.7. Compound 14



Product **14** was prepared according to the General Procedure I using dihydroisoquinoline **8** (80 mg, 0.45 mmol), acyl chloride **1a** (120 mg, 0.58 mmol; *Z:E* = 4:1), AgOTf (23.1 mg, 0.090 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:1 to only EtOAc) gave pure aza-Nazarov product **14** as a pale yellow solid and single diastereomer (71 mg, 58% yield).

R_f = 0.55 (only EtOAc)

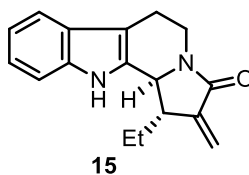
¹H NMR (400 MHz; CDCl₃) δ: 8.07 (1H, d, *J* = 2.2 Hz), 8.04 (1H, dd, *J* = 8.4, 2.3 Hz), 7.29 (1H, d, *J* = 8.4 Hz), 6.10 (1H, d, *J* = 2.7 Hz), 5.36 (1H, d, *J* = 2.3 Hz), 4.51 (1H, d, *J* = 3.3 Hz), 4.42 (1H, ddd, *J* = 13.1, 6.5, 2.7 Hz), 3.23 (1H, ddd, *J* = 13.1, 10.8, 4.8 Hz), 3.08 (1H, ddd, *J* = 13.7, 10.1, 4.6 Hz), 3.04-3.00 (1H, m), 2.89 (1H, ddd, *J* = 16.9, 8.1, 5.6 Hz), 2.01-1.93 (2H, m), 1.14 (3H, t, *J* = 7.4 Hz)

¹³C NMR (100 MHz; CDCl₃) δ: 166.7, 146.9, 142.7, 142.2, 139.4, 130.5, 122.1, 120.2, 116.9, 59.0, 45.4, 37.4, 28.5, 28.0, 10.5

FTIR *v*_{max} (ATR, solid)/cm⁻¹ 2963, 2931, 2876, 1689, 1658, 1520, 1429, 1344, 1308.

HRMS (+APCI) Calcd for C₁₅H₁₇N₂O₃ [M+H]⁺ 273.1234, found: 273.1251.

3.3.8. Compound 15



Aza-Nazarov product **15** was prepared according to the General Procedure I using imine **9** (62.6 mg, 0.38 mmol), acyl chloride **1a** (102.4 mg, 0.50 mmol; *Z:E* = 4:1), AgOTf (20.0 mg, 0.076 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave pure aza-Nazarov product **15** as a dark orange oil and single diastereomer (24.9 mg, 25% yield).

R_f = 0.61 (only EtOAc)

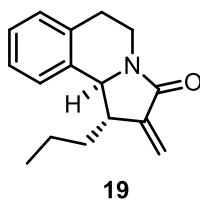
¹H NMR (400 MHz; CDCl₃) δ: 7.91 (1H, br s), 7.48 (1H, d, *J* = 7.7 Hz), 7.36 (1H, d, *J* = 8.0 Hz), 7.21-7.17 (1H, m), 7.15-7.11 (1H, m), 6.12 (1H, d, *J* = 2.9 Hz), 5.34 (1H, d, *J* = 2.4 Hz), 4.69-4.63 (2H, m), 3.15 (1H, ddd, *J* = 12.9, 11.6, 5.1 Hz), 2.99-2.89 (2H, m), 2.80 (1H, dd, *J* = 15.5, 5.2 Hz), 2.01-1.95 (1H, m), 1.93-1.82 (1H, m), 1.23 (3H, t, *J* = 7.4 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 167.0, 143.4, 136.4, 132.9, 127.0, 122.6, 120.2, 118.6, 116.5, 111.2, 109.3, 57.5, 44.2, 38.5, 27.2, 21.0, 11.5

FTIR *v*_{max} (ATR, film)/cm⁻¹ 3268, 2962, 2927, 2852, 1676, 1654, 1432, 1324.

HRMS (+APCI) Calcd for C₁₇H₁₉N₂O [M+H]⁺ 267.1492, found: 267.1487.

3.3.9. Compound 19



Product **19** was prepared according to the General Procedure I using dihydroisoquinoline **2** (46 mg, 0.35 mmol), acyl chloride **1c** (98 mg, 0.45 mmol; *Z:E* = 3:1), AgOTf (18.0 mg, 0.074 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave pure aza-Nazarov product **19** as an orange oil and single diastereomer (55.7 mg, 66% yield).

R_f = 0.56 (EtOAc:hexanes = 1:1)

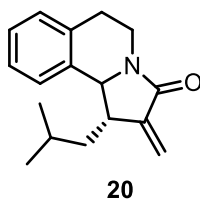
¹H NMR (400 MHz; CDCl₃) δ: 7.24-7.17 (3H, m), 7.12 (1H, d, *J* = 7.2 Hz), 6.05 (1H, d, *J* = 2.7 Hz), 5.30 (1H, d, *J* = 2.2 Hz), 4.47 (1H, d, *J* = 3.5 Hz), 4.34 (1H, ddd, *J* = 12.9, 6.4, 3.1 Hz), 3.23 (1H, ddd, *J* = 12.9, 10.7, 4.9 Hz), 3.07-2.99 (2H, m), 2.76 (1H, dt, *J* = 16.1, 3.2 Hz), 1.87-1.82 (2H, m), 1.62-1.52 (2H, m), 1.04 (3H, t, 7.3 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 166.8, 144.2, 137.8, 134.4, 129.3, 127.2, 126.9, 124.7, 115.8, 59.9, 44.1, 38.2, 37.9, 28.3, 19.8, 14.4

FTIR *v*_{max} (ATR, film)/cm⁻¹ 2956, 2929, 2871, 1686, 1656, 1456, 1420, 1358, 1302

HRMS (+APCI) Calcd for C₁₆H₂₀NO [M+H]⁺ 242.1540, found: 242.1554.

3.3.10. Compound 20



Aza-Nazarov product **20** was prepared according to the General Procedure I using dihydroisoquinoline **2** (131 mg, 1.0 mmol), acyl chloride **1d** (310 mg, 1.33 mmol; *Z:E* = 3:1), AgOTf (51.4 mg, 0.20 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave pure aza-Nazarov product **20** as an orange solid and single diastereomer (156 mg, 61% yield).

R_f = 0.57 (EtOAc:hexanes = 1:2)

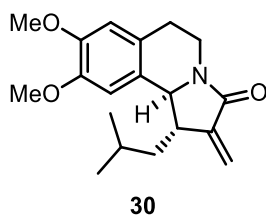
¹H NMR (400 MHz; CDCl₃) δ: 7.25-7.16 (3H, m), 7.10 (1H, d, *J* = 7.2 Hz), 6.02 (1H, d, *J* = 2.5 Hz), 5.30 (1H, d, *J* = 2.2 Hz), 4.40 (1H, d, *J* = 2.6 Hz), 4.32 (1H, ddd, *J* = 12.8, 6.3, 2.9 Hz), 3.21 (1H, ddd, *J* = 12.8, 10.7, 4.9 Hz), 3.06-2.98 (2H, m), 2.76-2.70 (1H, m), 2.00-1.87 (1H, m), 1.73 (1H, dt, *J* = 13.9, 7.0 Hz), 1.65 (1H, dt, *J* = 14.0, 7.2 Hz), 1.08 (3H, d, *J* = 6.5 Hz), 1.04 (3H, d, *J* = 6.6 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 166.9, 144.8, 137.7, 134.5, 129.4, 127.3, 126.9, 124.6, 116.1, 61.3, 46.5, 42.2, 38.3, 28.3, 25.7, 23.1, 22.9

FTIR *v*_{max} (ATR, film)/cm⁻¹ 2954, 2927, 2869, 1688, 1656, 1456, 1419, 1302

HRMS (+APCI) Calcd for C₁₇H₂₂NO [M+H]⁺ 256.1696, found: 256.1696.

3.3.11. Compound 30



Product **30** was prepared according to the General Procedure I using 6,7-Dimethoxy-3,4-dihydroisoquinoline **7** (1.54 g, 8.04 mmol), acyl chloride **1d** (2.43 g, 10.5 mmol; *Z:E* = 4:1), AgOTf (413.7 mg, 1.61 mmol) and 9.8 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:1 to only EtOAc) gave pure aza-Nazarov product **30** as an orange solid and single diastereomer (1.42 g, 61 % yield).

R_f = 0.50 (only EtOAc)

¹H NMR (400 MHz; CDCl₃) δ: 6.64 (1H, s), 6.57 (1H, s), 6.01 (1H, d, *J* = 2.5 Hz), 5.29 (1H, d, *J* = 1.9 Hz), 4.39-4.34 (2H, m), 3.84 (3H, s), 3.83 (3H, s), 3.13 (1H, ddd, *J* = 12.7, 11.3, 4.7 Hz), 3.03-2.92 (2H, m), 2.64-2.59 (1H, m), 2.02-1.92 (1H, m), 1.75-1.59 (2H, m), 1.09 (3H, d, *J* = 6.5 Hz), 1.05 (3H, d, *J* = 6.6 Hz).

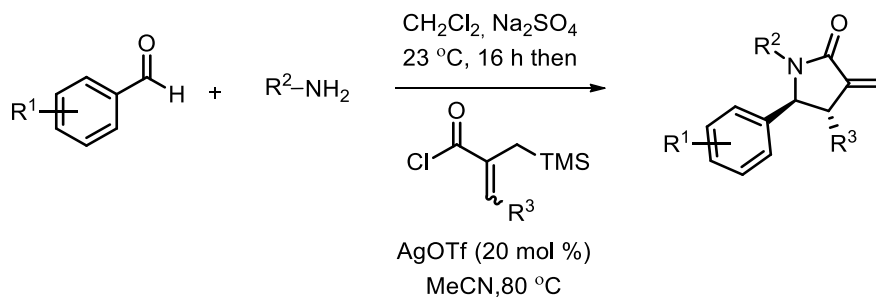
¹³C NMR (100 MHz; CDCl₃) δ: 166.8, 148.2, 148.0, 145.0, 129.5, 126.5, 116.0, 112.0, 107.8, 61.0, 56.0, 46.6, 42.5, 38.3, 27.8, 26.0, 23.1, 22.8

FTIR *v*_{max} (ATR, film)/cm⁻¹ 2953, 2930, 2868, 1687, 1655, 1513, 1463, 1452.

HRMS (+APCI) Calcd for C₁₉H₂₆NO₃ [M+H]⁺ 316.1908, found: 316.1911.

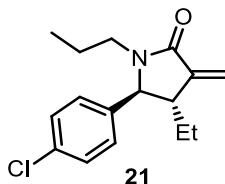
3.4. Synthesis of Acyclic Aza-Nazarov Products

3.4.1. General Procedure II



The corresponding amine was added to a mixture of corresponding aldehyde on anhydrous Na₂SO₄ in 5.0 mL of anhydrous CH₂Cl₂. The reaction mixture was stirred at rt for 16 h and filtered to give the imine intermediate, which was observed to be pure by ¹H-NMR spectroscopy. A 25-mL, flame-dried Schlenk flask was cooled to rt under nitrogen and charged with the imine reactant and 0.5 mL of anhydrous CH₃CN. The solution of acyl chloride reactant in 0.5 mL anhydrous CH₃CN was added to the reaction mixture, and the resulting clear solution was stirred for 5 min at rt. Then AgOTf was added. The reaction mixture was inserted into a preheated oil bath at 80 °C, and stirred at this temperature for 22 h. It was then cooled to rt and quenched with saturated NaHCO₃ solution (3 mL). The aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the product was carried out by flash column chromatography using SiO₂ as the stationary phase.

3.4.2. Compound 21



Product **21** was prepared according to the General Procedure II using imine reactant (47.2 mg, 0.26 mmol), acyl chloride **1a** (70 mg, 0.34 mmol), AgOTf (13.4 mg, 0.052 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:2) gave pure aza-Nazarov product **21** as a pale yellow oil (25.3 mg, 35% yield) in 10:1 dr.

R_f = 0.60 (EtOAc:hexanes = 1:2)

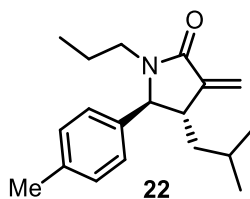
¹H NMR (400 MHz; CDCl₃) δ : 7.33-7.29 (2H, m), 7.11-7.07 (2H, m), 6.12 (1H, d, J = 2.3 Hz), 5.32 (1H, d, J = 2.0 Hz), 4.21 (1H, d, J = 2.9 Hz), 3.68 (1H, ddd, J = 16.1, 13.7, 7.6 Hz), 2.62-2.55 (2H, m), 1.66 (2H, quint, J = 7.3 Hz), 1.51-1.37 (2H, m), 0.96 (3H, t, J = 7.4 Hz), 0.83 (3H, t, J = 7.4 Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 168.1, 143.1, 139.8, 134.0, 129.3, 128.0, 116.5, 64.8, 48.0, 42.7, 28.1, 20.3, 11.4, 10.8

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2964, 2931, 2875, 1687, 1658, 1491, 1410, 1209, 1090.

HRMS (+APCI) Calcd for C₁₆H₂₁³⁵ClNO [M+H]⁺ 278.1307, found: 278.1323.

3.4.3. Compound 22



Product **31** was prepared according to the General Procedure II using imine reactant (64.5 mg, 0.40 mmol), acyl chloride **1d** (130 mg, 0.56 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:2) gave pure aza-Nazarov product **22** as an orange oil (72.8 mg, 64% yield) in 5:1 dr.

$R_f = 0.61$ (EtOAc:hexanes = 1:2)

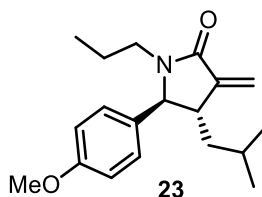
¹H NMR (400 MHz; CDCl₃) δ : 7.13 (2H, d, $J = 7.8$ Hz), 7.03 (2H, d, $J = 8.1$ Hz), 6.07 (1H, dd, $J = 2.3, 0.5$ Hz), 5.27 (1H, dd, $J = 2.0, 0.6$ Hz), 4.15 (1H, d, $J = 2.8$ Hz), 3.70-3.61 (1H, m), 2.78-2.72 (1H, m), 2.58 (1H, ddd, $J = 13.5, 8.3, 5.2$ Hz), 2.32 (3H, s), 1.82-1.72 (1H, m), 1.55-1.38 (4H, m), 0.88 (3H, d, $J = 6.6$ Hz), 0.82 (3H, t, $J = 7.4$ Hz), 0.75 (3H, d, $J = 6.6$ Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 168.0, 144.5, 137.93, 137.89, 129.7, 126.6, 115.7, 66.1, 45.6, 44.5, 42.6, 25.1, 23.0, 22.1, 20.3, 11.4.

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2958, 2929, 2870, 1687, 1657, 1514, 1443, 1416, 1265.

HRMS (+APCI) Calcd for C₁₉H₂₈NO [M+H]⁺ 286.2166, found: 286.2158.

3.4.4. Compound 23



Product **23** was prepared according to the General Procedure II using imine reactant (70.9 mg, 0.40 mmol), acyl chloride **1d** (130 mg, 0.56 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:2) gave pure aza-Nazarov product **23** as an orange oil (64.5 mg, 54% yield) in 5.5:1 dr.

$R_f = 0.57$ (EtOAc:hexanes = 1:2)

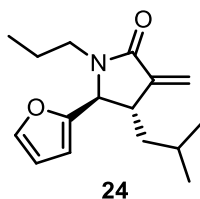
¹H NMR (400 MHz; CDCl₃) δ : 7.06 (2H, d, $J = 8.6$ Hz), 6.85 (2H, d, $J = 8.7$ Hz), 6.06 (1H, d, $J = 2.4$ Hz), 5.27 (1H, d, $J = 2.0$ Hz), 4.13 (1H, d, $J = 3.0$ Hz), 3.78 (3H, s), 3.66-3.58 (1H, m), 2.77-2.72 (1H, m), 2.58 (1H, ddd, $J = 13.6, 8.4, 5.2$ Hz), 1.80-1.70 (1H, m), 1.54-1.35 (4H, m), 0.88 (3H, d, $J = 6.6$ Hz), 0.81 (3H, t, $J = 7.4$ Hz), 0.74 (3H, d, $J = 6.5$ Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 167.9, 159.5, 144.6, 132.9, 127.9, 115.6, 114.4, 65.8, 55.3, 45.4, 44.5, 42.5, 25.2, 23.1, 22.0, 20.3, 11.4

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2958, 2931, 2871, 2839, 1686, 1657, 1512, 1442, 1416, 1274.

HRMS (+APCI) Calcd for C₁₉H₂₈NO₂ [M+H]⁺ 302.2115, found: 302.2107.

3.4.5. Compound 24



Product **24** was prepared according to the General Procedure II using imine reactant (54.9 mg, 0.40 mmol), acyl chloride **1d** (130 mg, 0.56 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:2) gave pure aza-Nazarov product **24** as an orange oil (61.7 mg, 59 % yield) in 11:1 dr.

$R_f = 0.68$ (EtOAc:hexanes = 1:2)

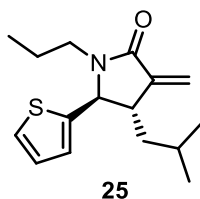
¹H NMR (400 MHz; CDCl₃) δ : 7.35 (1H, dd, $J = 1.8, 0.8$ Hz), 6.30 (1H, dd, $J = 3.2, 1.8$ Hz), 6.22 (1H, dd, $J = 3.3, 0.6$ Hz), 6.03 (1H, d, $J = 2.5$ Hz), 5.27 (1H, d, $J = 2.1$ Hz), 4.25 (1H, d, $J = 3.7$ Hz), 3.51 (1H, ddd, $J = 13.7, 8.6, 7.1$ Hz), 3.05-2.99 (1H, m), 2.78 (1H, ddd, $J = 13.7, 8.6, 5.3$ Hz), 1.74-1.64 (2H, m), 1.58-1.50 (1H, m), 1.43-1.27 (3H, m), 0.88 (3H, d, $J = 6.4$ Hz), 0.81 (3H, t, $J = 7.4$ Hz), 0.76 (3H, d, $J = 6.5$ Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 167.6, 152.7, 144.1, 142.8, 115.4, 110.5, 108.2, 59.7, 44.7, 42.9, 40.7, 25.2, 23.2, 21.8, 20.4, 11.3

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2958, 2931, 2871, 1689, 1658, 1530, 1505, 1418.

HRMS (+APCI) Calcd for C₁₆H₂₄NO₂ [M+H]⁺ 262.1802, found: 262.1804.

3.4.6. Compound 25



Product **25** was prepared according to the General Procedure II using imine reactant (61.3 mg, 0.40 mmol), acyl chloride **1d** (130 mg, 0.56 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:9 to EtOAc:hexanes = 1:1) gave pure aza-Nazarov product **25** as an orange oil (58.9 mg, 53 % yield) in 6:1 dr.

$R_f = 0.59$ (EtOAc:hexanes = 1:2)

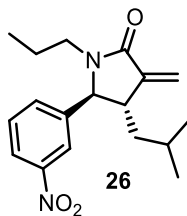
¹H NMR (400 MHz; CDCl₃) δ: 7.28-7.26 (1H, m), 6.97-6.94 (2H, m), 6.10 (1H, d, $J = 2.3$ Hz), 5.33 (1H, d, $J = 2.1, 0.5$ Hz), 4.50 (1H, d, $J = 3.2$ Hz), 3.66 (1H, ddd, $J = 13.7, 8.6, 7.4$ Hz), 2.96-2.90 (1H, m), 2.75 (1H, ddd, $J = 13.7, 8.5, 5.1$ Hz), 1.82-1.75 (1H, m), 1.60-1.45 (4H, m), 0.92 (3H, d, $J = 6.5$ Hz), 0.86 (3H, t, $J = 7.4$ Hz), 0.82 (3H, d, $J = 6.5$ Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 167.4, 144.9, 143.8, 126.9, 125.7, 125.6, 116.1, 61.8, 45.2, 45.1, 42.6, 25.3, 23.1, 22.1, 20.4, 11.4

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2957, 2928, 2870, 1688, 1658, 1532, 1417.

HRMS (+APCI) Calcd for C₁₆H₂₄NOS [M+H]⁺ 278.1574, found: 278.1579.

3.4.7. Compound 26



Product **26** was prepared according to the General Procedure II using imine reactant (76.9 mg, 0.40 mmol), acyl chloride **1d** (111.8 mg, 0.48 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:2) gave pure aza-Nazarov product **26** as a yellow oil (25.2 mg, 20 % yield) in 12.5:1 dr.

R_f = 0.60 (EtOAc:hexanes = 1:2)

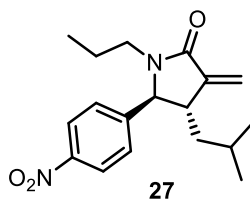
¹H NMR (400 MHz; CDCl₃) δ : 8.18 (1H, ddd, J = 8.0, 2.3, 1.2 Hz), 8.04 (1H, t, J = 2.0 Hz), 7.56 (1H, t, J = 7.9 Hz), 7.49 (1H, dt, J = 7.7, 1.4 Hz), 6.14 (1H, d, J = 2.2 Hz), 5.35 (1H, d, J = 2.0 Hz), 4.32 (1H, d, J = 2.6 Hz), 3.71 (1H, ddd, J = 13.8, 8.5, 7.5 Hz), 2.78-2.73 (1H, m), 2.58 (1H, ddd, 13.7, 8.5, 5.1 Hz), 1.83-1.73 (1H, m), 1.61-1.41 (4H, m), 0.92 (3H, d, J = 6.6 Hz), 0.85 (3H, t, J = 7.4 Hz), 0.79 (3H, d, J = 6.6 Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 168.0, 148.9, 143.6, 143.2, 132.4, 130.4, 123.4, 121.8, 117.1, 65.7, 45.6, 44.6, 42.9, 25.2, 22.9, 22.1, 20.4, 11.4

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2960, 2931, 2872, 1692, 1659, 1532, 1420.

HRMS (+APCI) Calcd for C₁₈H₂₅N₂O₃ [M+H]⁺ 317.1860, found: 317.1878.

3.4.8. Compound 27



Product **27** was prepared according to the General Procedure II using imine reactant (76.9 mg, 0.40 mmol), acyl chloride **1d** (121.1 mg, 0.52 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:2) gave pure aza-Nazarov product **27** as an orange oil (48.9 mg, 39 % yield) in 5:1 dr.

R_f = 0.57 (EtOAc:hexanes = 1:2)

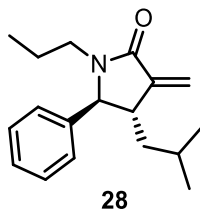
¹H NMR (400 MHz; CDCl₃) δ : 8.22-8.18 (2H, m), 7.35-7.31 (2H, m), 6.11 (1H, d, J = 2.1 Hz), 5.33 (1H, d, J = 1.8 Hz), 4.32 (1H, d, J = 2.6 Hz), 3.70 (1H, ddd, J = 13.9, 8.4, 7.5 Hz), 2.75-2.70 (1H, m), 2.57 (1H, ddd, 13.7, 8.5, 5.2 Hz), 1.80-1.70 (1H, m), 1.59-1.39 (4H, m), 0.90 (3H, d, J = 6.6 Hz), 0.84 (3H, t, J = 7.4 Hz), 0.78 (3H, d, J = 6.6 Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 168.0, 148.6, 143.1, 127.4, 124.5, 117.1, 65.6, 45.6, 44.5, 43.0, 25.2, 22.9, 22.1, 20.4, 11.4

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2959, 2932, 2872, 1690, 1659, 1522, 1345.

HRMS (+APCI) Calcd for C₁₈H₂₅N₂O₃ [M+H]⁺ 317.1860, found: 317.1862.

3.4.9. Compound 28



Product **28** was prepared according to the General Procedure II using imine reactant (58.9 mg, 0.40 mmol), acyl chloride **1d** (121.1 mg, 0.52 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:5) gave pure aza-Nazarov product **28** as a yellow oil (50.1 mg, 46 % yield) in 10:1 dr.

$R_f = 0.56$ (EtOAc:hexanes = 1:2)

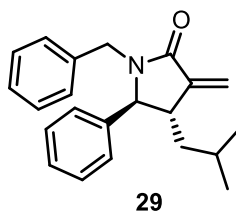
¹H NMR (400 MHz; CDCl₃) δ : 7.34-7.28 (3H, m), 7.16-7.13 (2H, m), 6.08 (1H, dd, $J = 2.3, 0.4$ Hz), 5.29 (1H, dd, $J = 2.0, 0.6$ Hz), 4.19 (1H, d, $J = 2.8$ Hz), 3.67 (1H, ddd, $J = 13.6, 8.4, 7.6$ Hz), 2.80-2.75 (1H, m), 2.59 (1H, ddd, $J = 13.6, 8.4, 5.1$ Hz), 1.83-1.73 (1H, m), 1.58-1.40 (4H, m), 0.90 (3H, d, $J = 6.7$ Hz), 0.83 (3H, t, $J = 7.4$ Hz), 0.76 (3H, d, $J = 6.6$ Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 168.1, 144.4, 141.1, 129.1, 128.2, 126.7, 115.9, 66.3, 45.6, 44.5, 42.7, 25.2, 23.1, 22.1, 20.3, 11.4

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2959, 2932, 2871, 1691, 1658, 1457, 1421.

HRMS (+APCI) Calcd for C₁₈H₂₆NO [M+H]⁺ 272.2009, found: 272.2023.

3.4.10. Compound 29



Product **29** was prepared according to the General Procedure II using imine reactant (78.1 mg, 0.40 mmol), acyl chloride **1d** (121.1 mg, 0.52 mmol), AgOTf (20.6 mg, 0.080 mmol) and 1.0 mL of anhydrous CH₃CN. Purification by flash column chromatography (EtOAc:hexanes = 1:5) gave pure aza-Nazarov product **29** as a white solid (41.2 mg, 49 % yield) in 10:1 dr.

R_f = 0.65 (EtOAc:hexanes = 1:2)

¹H NMR (400 MHz; CDCl₃) δ: 7.37-7.26 (6H, m), 7.12-7.09 (4H, m), 6.17 (1H, d, J = 2.3 Hz), 5.36 (1H, d, J = 2.0 Hz), 5.18 (1H, d, J = 14.7 Hz), 3.97 (1H, d, J = 3.0 Hz), 3.50 (1H, d, J = 14.7 Hz), 2.83-2.78 (1H, m), 1.68-1.61 (1H, m), 1.42-1.36 (2H, m), 0.82 (3H, d, J = 6.6 Hz), 0.69 (3H, d, J = 6.6 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 168.0, 144.3, 140.6, 136.3, 129.1, 128.7, 128.6, 128.3, 127.7, 127.0, 116.4, 65.3, 45.2, 44.7, 44.3, 25.1, 23.0, 22.0

FTIR ν_{\max} (ATR, film)/cm⁻¹ 2955, 2927, 2869, 1693, 1659, 1419.

HRMS (+APCI) Calcd for C₂₂H₂₆NO [M+H]⁺ 320.2009, found: 320.2009.

4. CONCLUSION

This thesis outlines the development of a novel aza-Nazarov cyclization reaction between 3,4-dihydroisoquinolines and α,β -unsaturated acyl chlorides that proceeds using catalytic amount of an anion exchange reagent. The developed reaction provides high yields and produces α -methylene- γ -lactam products as single diastereomers. The mechanism benefits from the stabilizing β -Si effect that is afforded by TMS group on the allylic position of the acyl chloride. The optimization studies revealed 20 mol % of AgOTf in MeCN at 80 °C as the ideal reaction conditions. The substrate scope studies were performed according to these conditions and the results fortunately demonstrated that this methodology is useful for various dihydroisoquinoline and acyl chloride derivatives.

To broaden the scope of the reaction, acyclic imines were used to produce pyrrolidinone products with many different substituents using optimized reaction conditions. The proposed reaction mechanism was studied with computational methods which proved the effect of TMS group in the reduction of the reaction barrier and in the regeneration of the active iminium ion to provide catalytic reaction conditions. With the use of chiral catalysts, studies were conducted to render the reaction enantioselective. Although many reaction conditions and catalysts were tried, the resulting products were racemic mixtures. Nevertheless, the final results show that this novel aza-Nazarov reaction is a useful method to synthesize a broad range of *N*-heterocycles under mild reaction conditions.

5. BIBLIOGRAPHY

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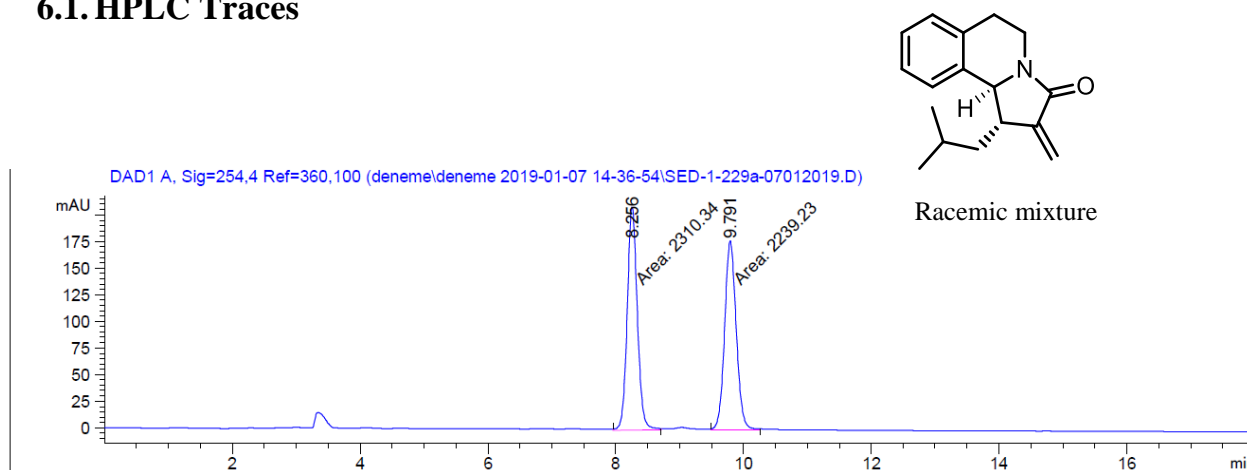
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6. APPENDIX

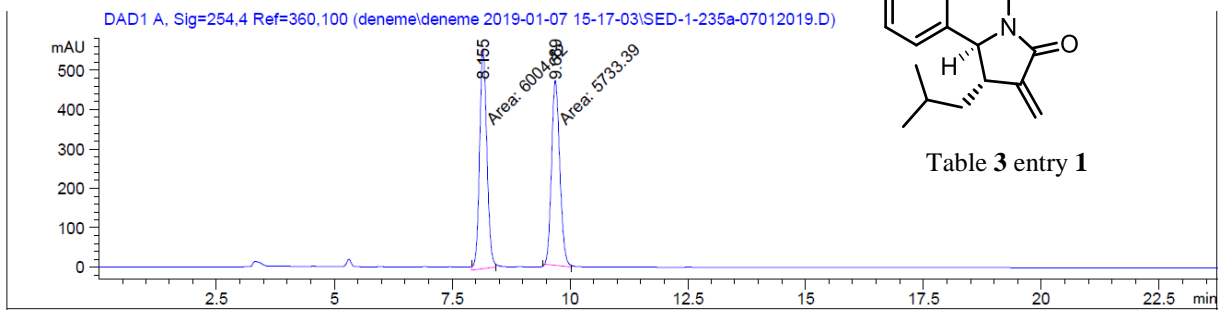
6.1. HPLC Traces



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.256	MM	0.1835	2310.34448	209.79546	50.7816
2	9.791	MM	0.2104	2239.22632	177.39836	49.2184

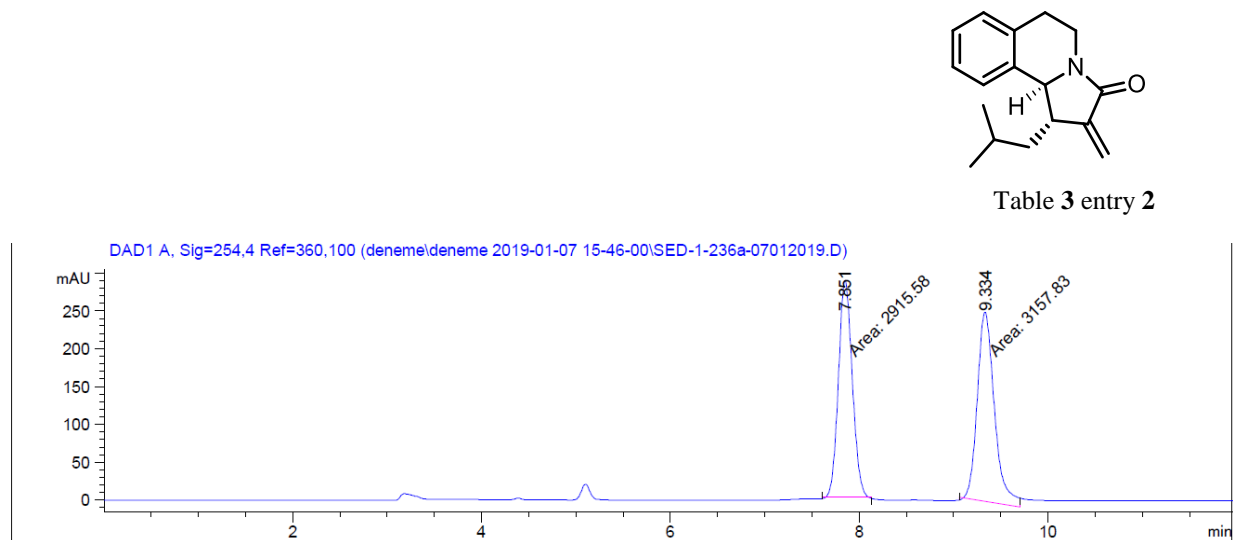
Totals : 4549.57080 387.19382



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.155	MM	0.1796	6004.41943	557.20288	51.1545
2	9.689	MM	0.2037	5733.39355	469.06714	48.8455

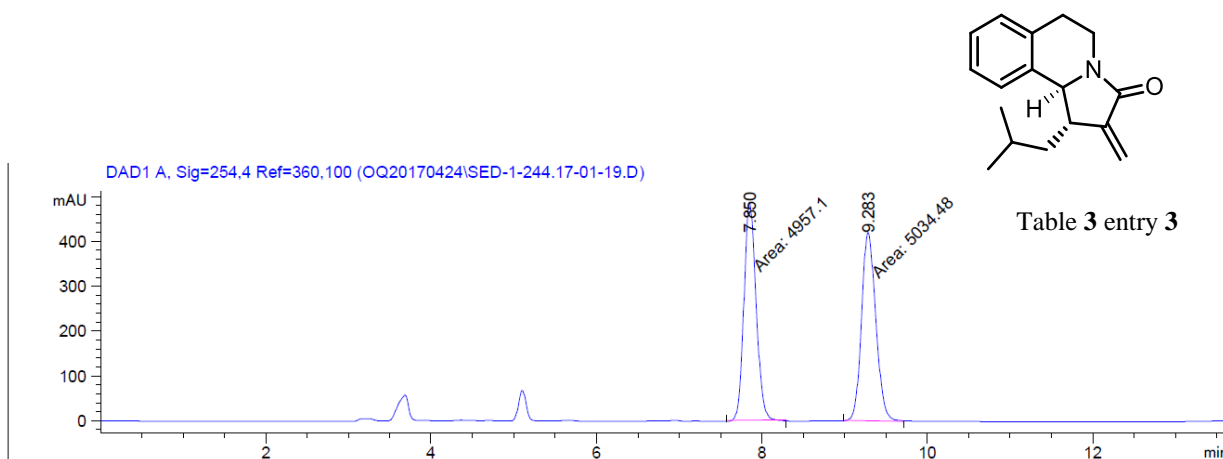
Totals : 1.17378e4 1026.27002



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.851	MM	0.1693	2915.58423	286.95441	48.0057
2	9.334	MM	0.2105	3157.82642	249.99527	51.9943

Totals : 6073.41064 536.94968



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.850	MM	0.1698	4957.10107	486.58832	49.6128
2	9.283	MM	0.1996	5034.48389	420.28677	50.3872

Totals : 9991.58496 906.87509

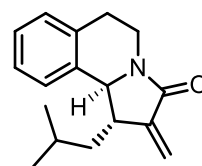
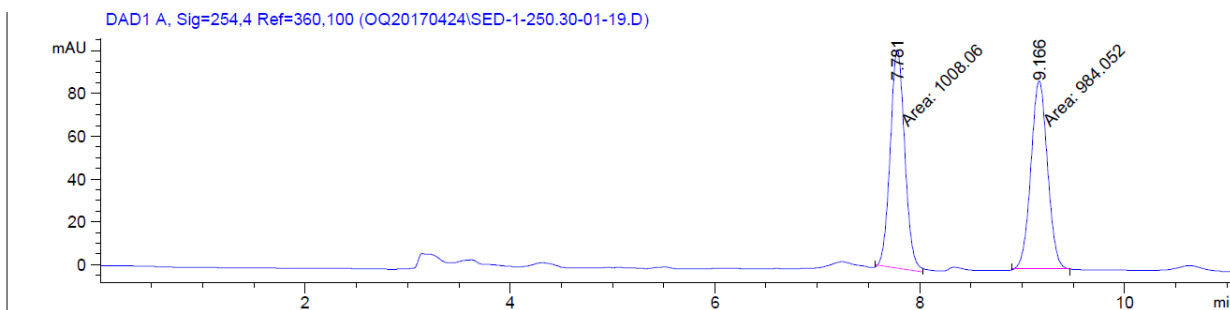


Table 4 entry 1



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.781	MM	0.1644	1008.06116	102.20744	50.6026
2	9.166	MM	0.1869	984.05182	87.74907	49.3974

Totals : 1992.11298 189.95650

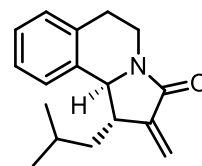
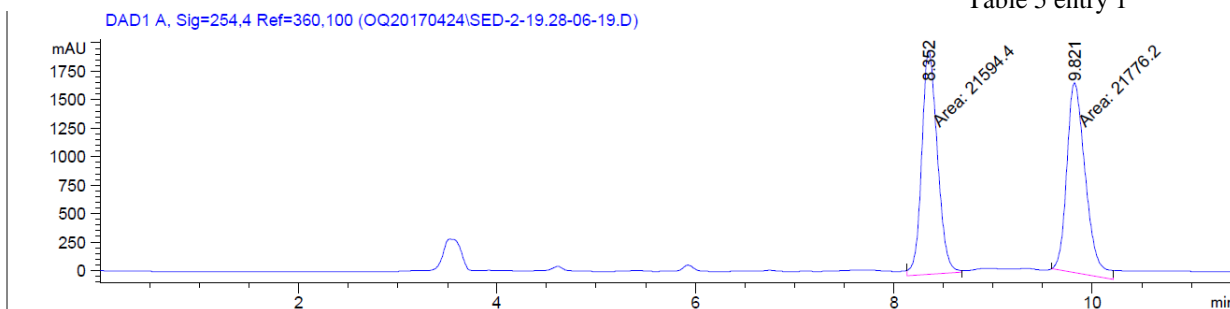


Table 5 entry 1



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.352	MM	0.1829	2.15944e4	1967.32898	49.7904
2	9.821	MM	0.2178	2.17762e4	1666.07263	50.2096

Totals : 4.33706e4 3633.40161

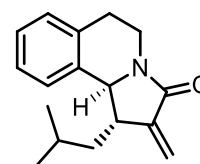
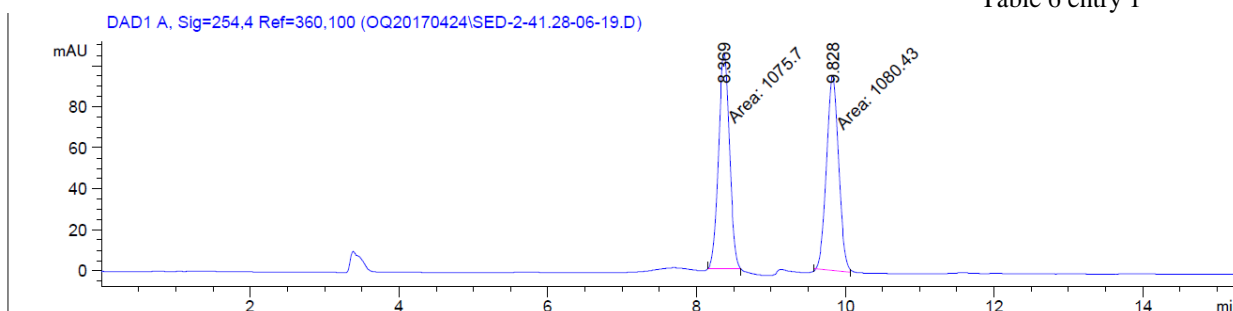


Table 6 entry 1



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.369	MM	0.1701	1075.70325	105.39672	49.8905
2	9.828	MM	0.1893	1080.42615	95.10109	50.1095

Totals : 2156.12939 200.49781

6.2. NMR Spectra

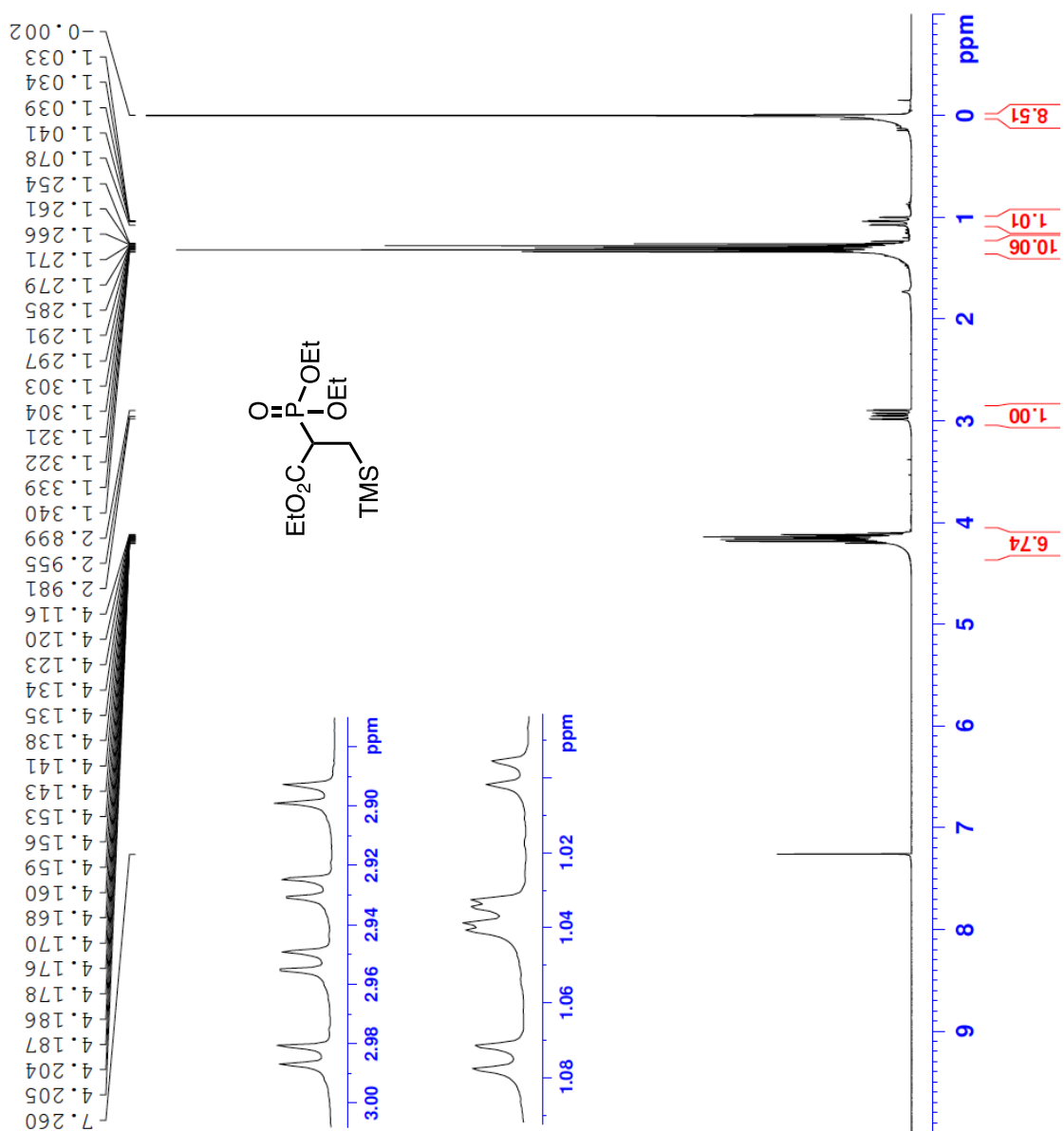


Figure 14. $^1\text{H-NMR}$ spectrum of compound 16.

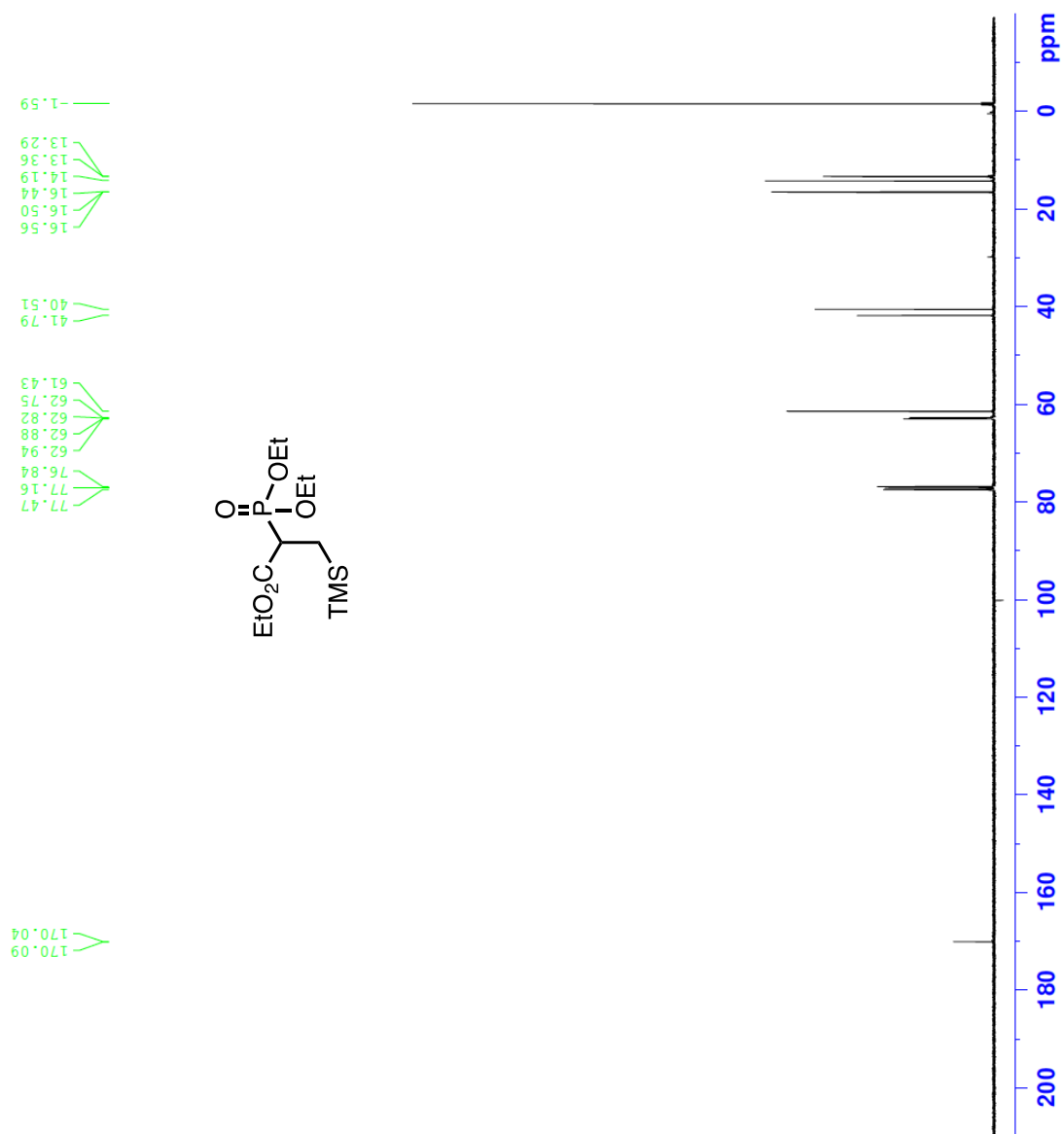


Figure 15. ¹³C-NMR spectrum of compound 16.

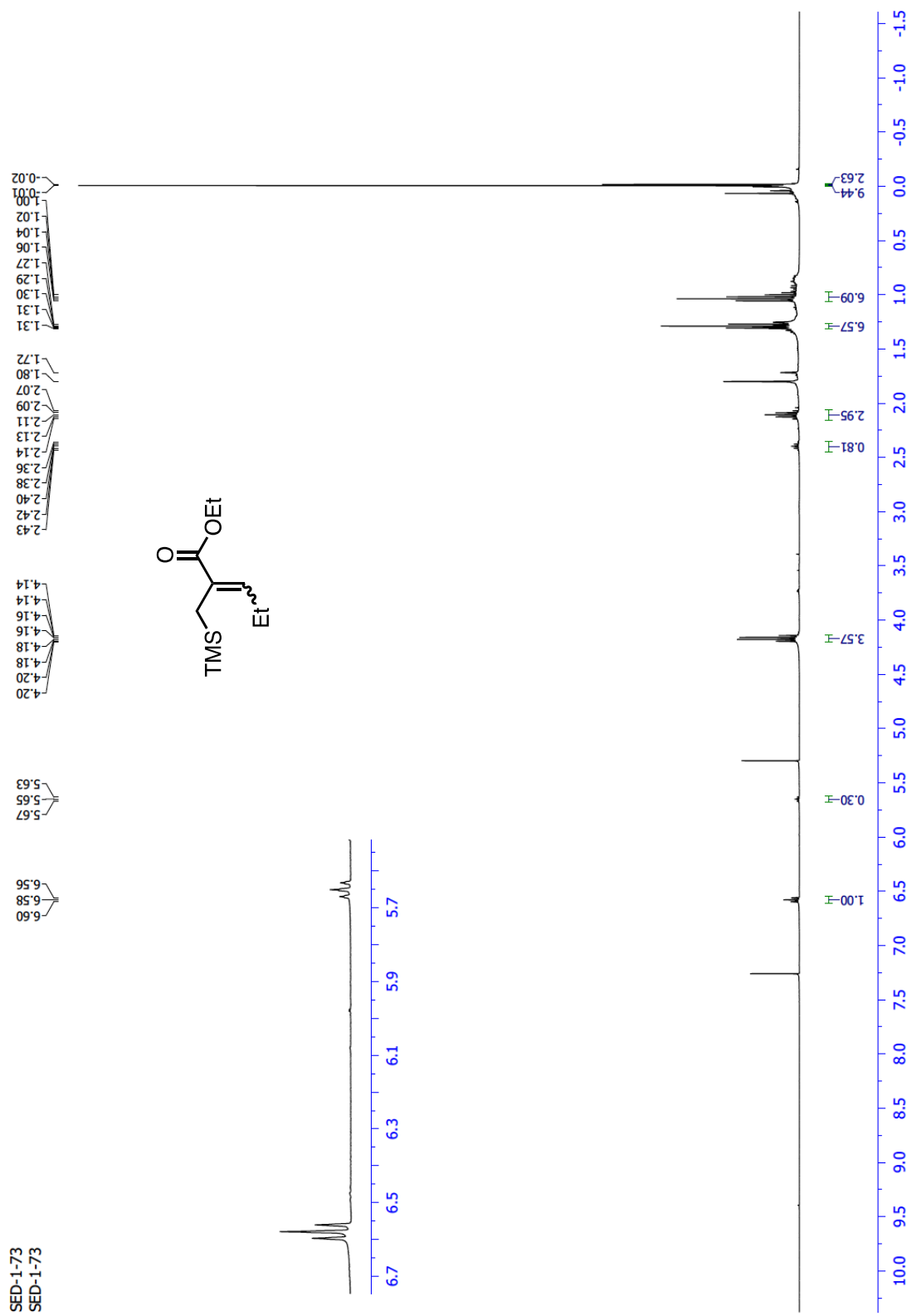


Figure 16. $^1\text{H-NMR}$ spectrum of compound 17a.

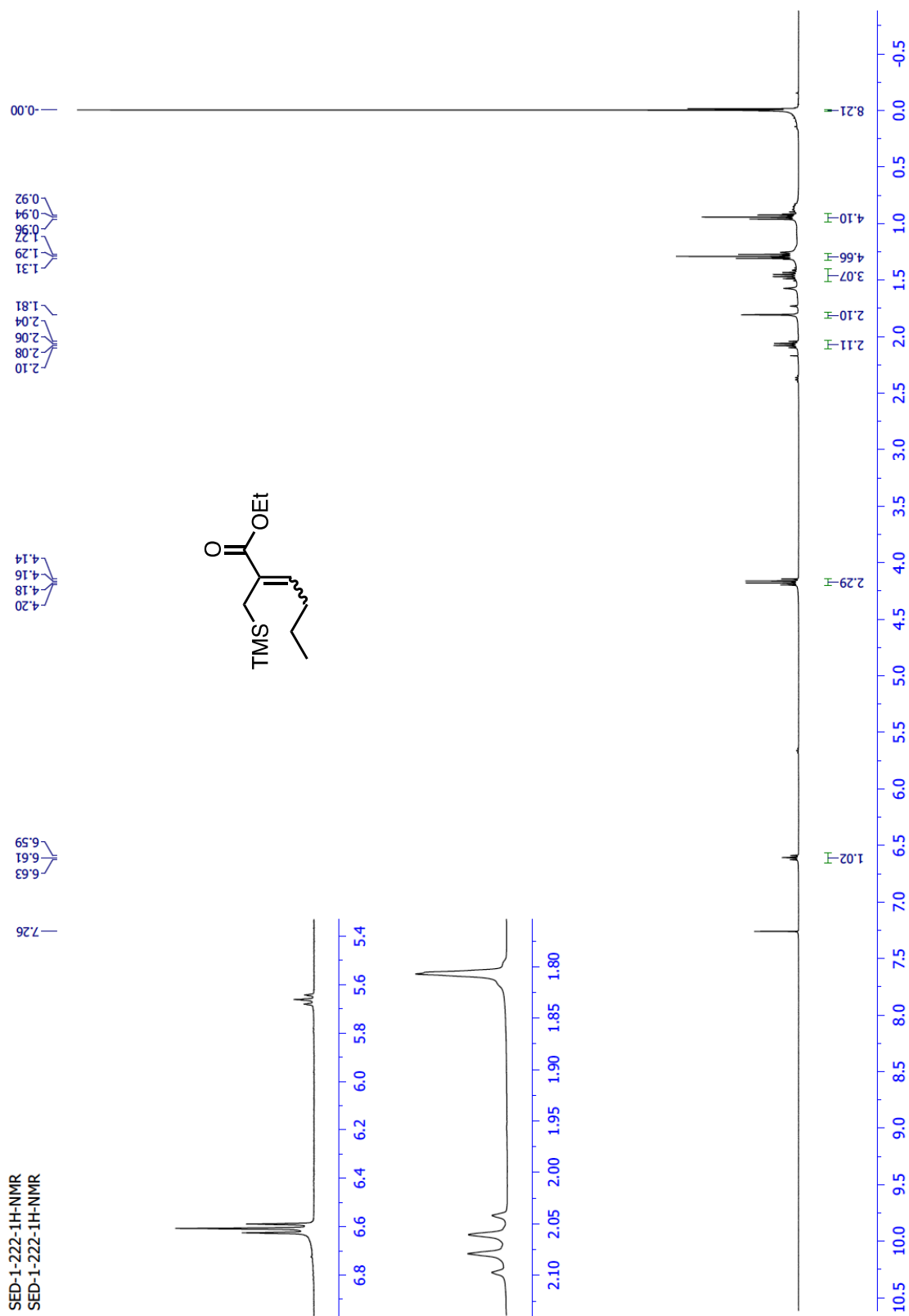


Figure 17. ¹H-NMR spectrum of compound 17c.

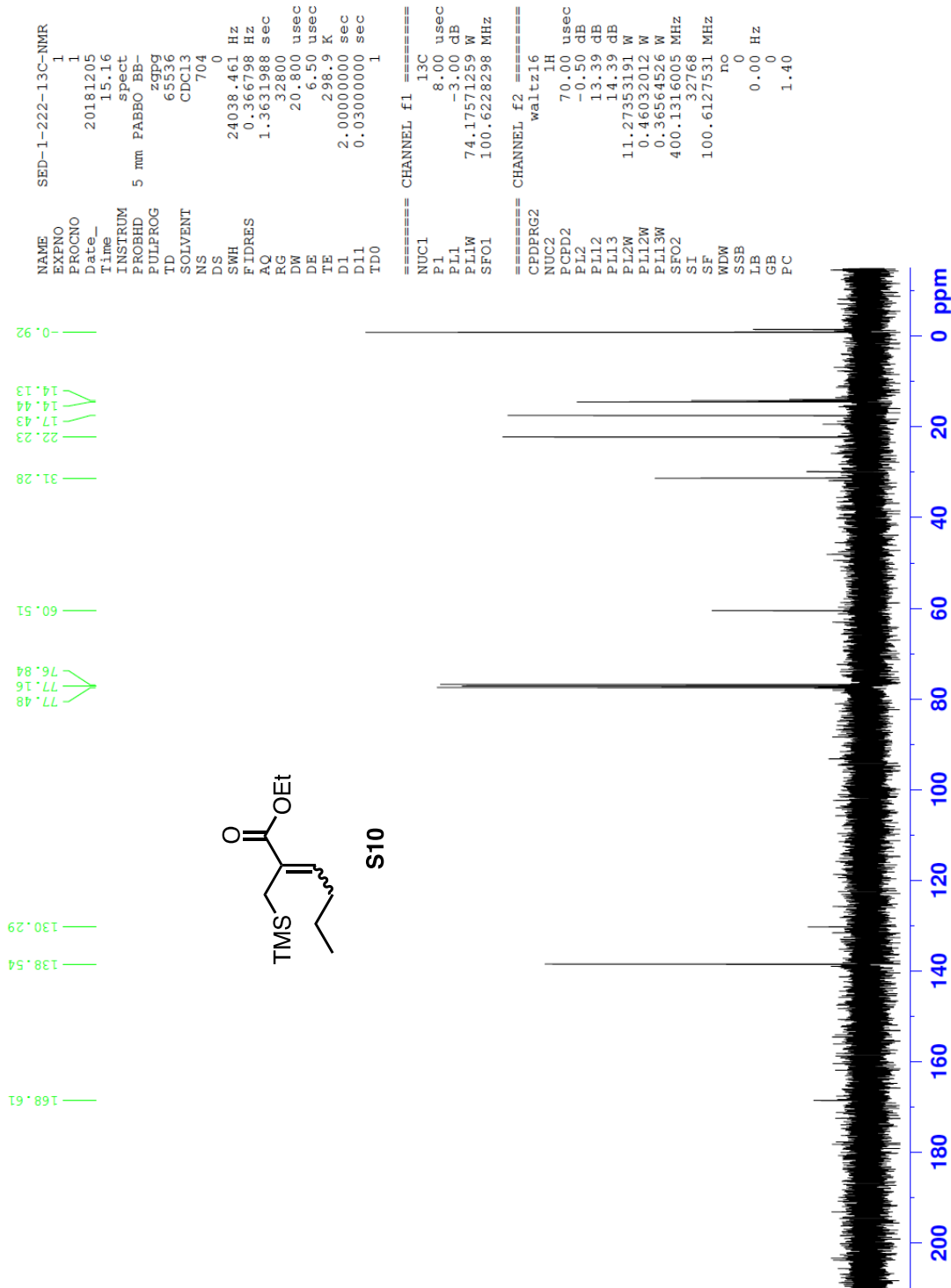


Figure 18. ^{13}C -NMR spectrum of compound 17c.

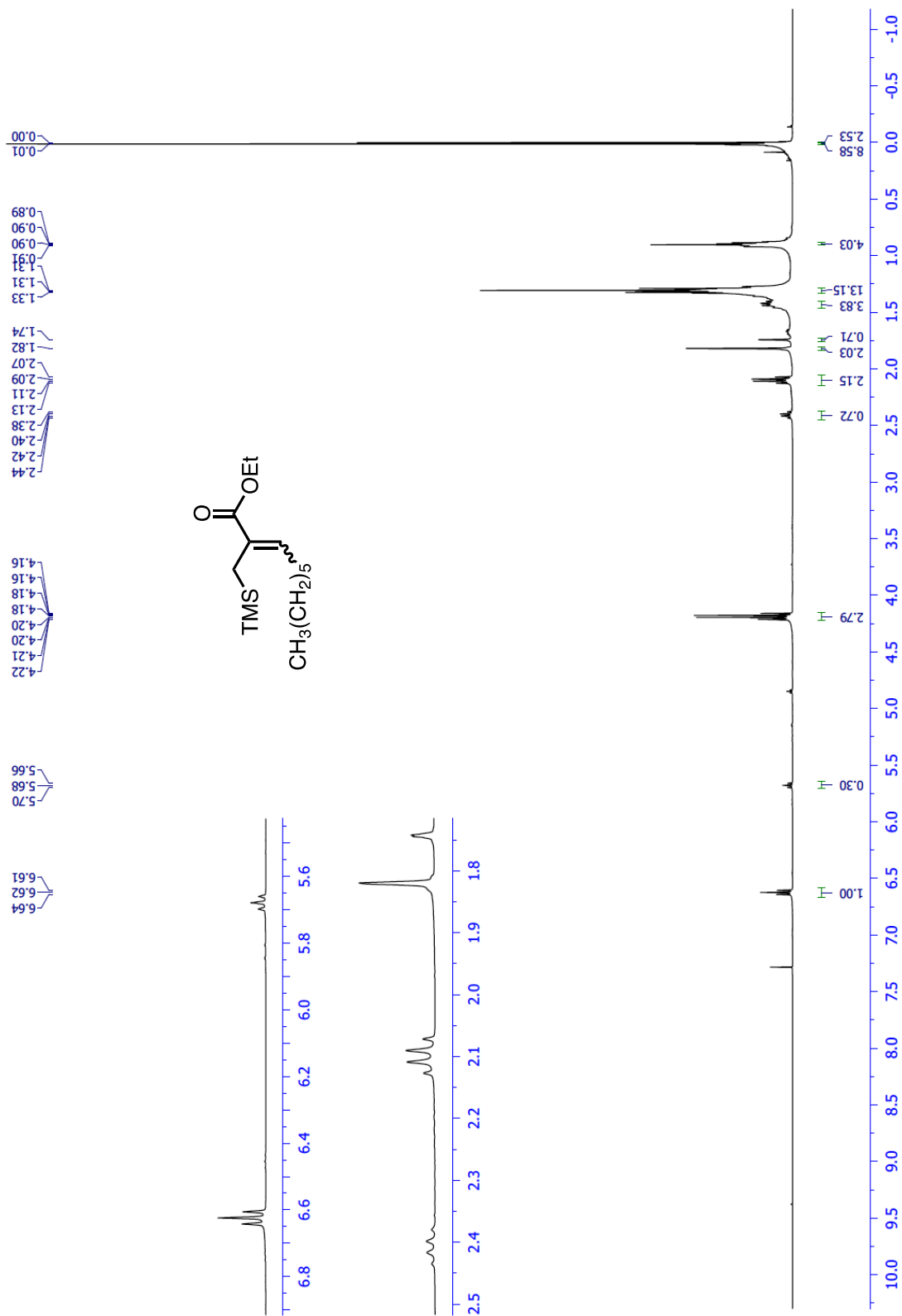


Figure 19. ¹H-NMR spectrum of compound 17b.

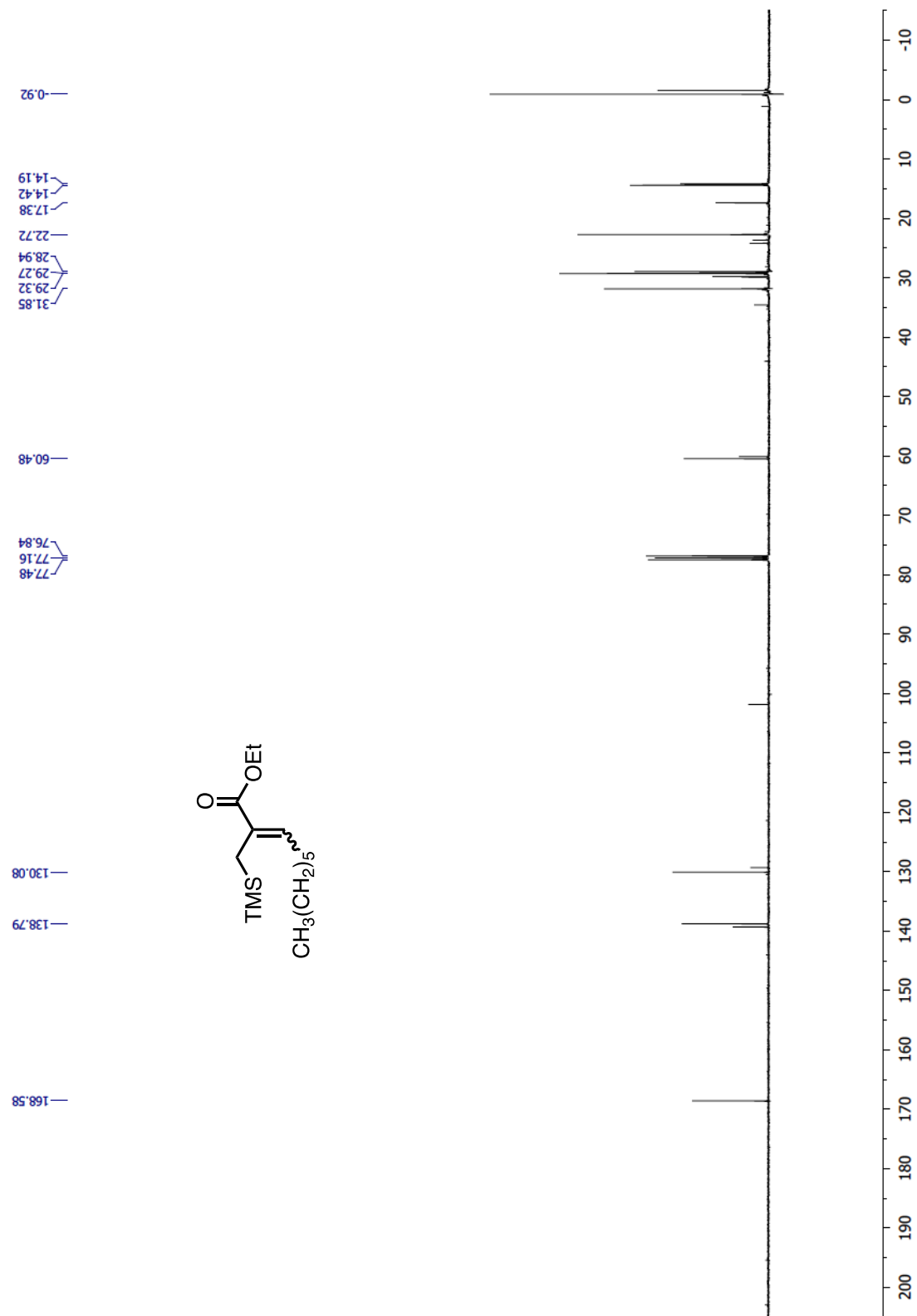


Figure 20. ^{13}C -NMR spectrum of compound 17b.

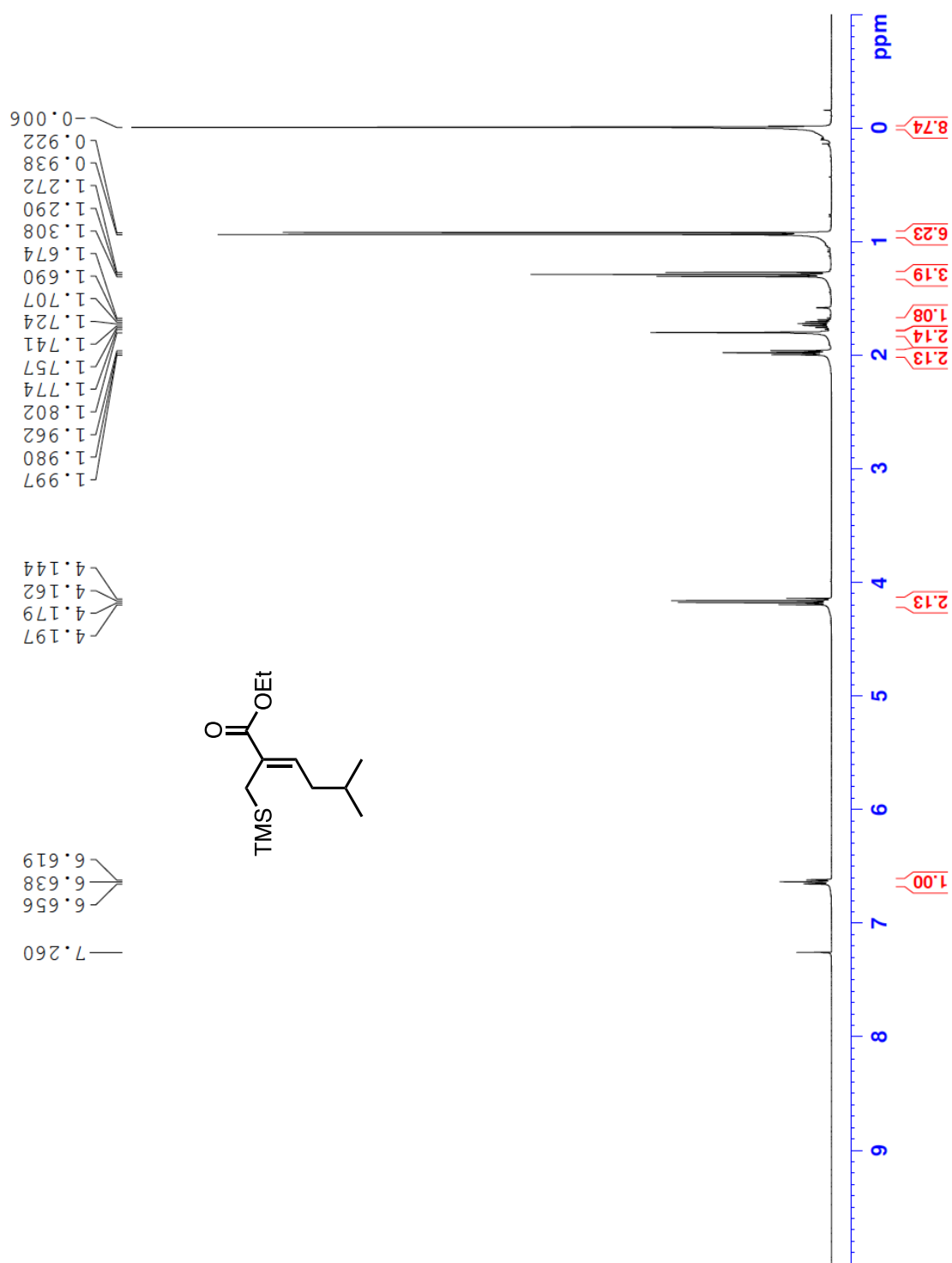


Figure 21. ¹H-NMR spectrum of compound **17d**.

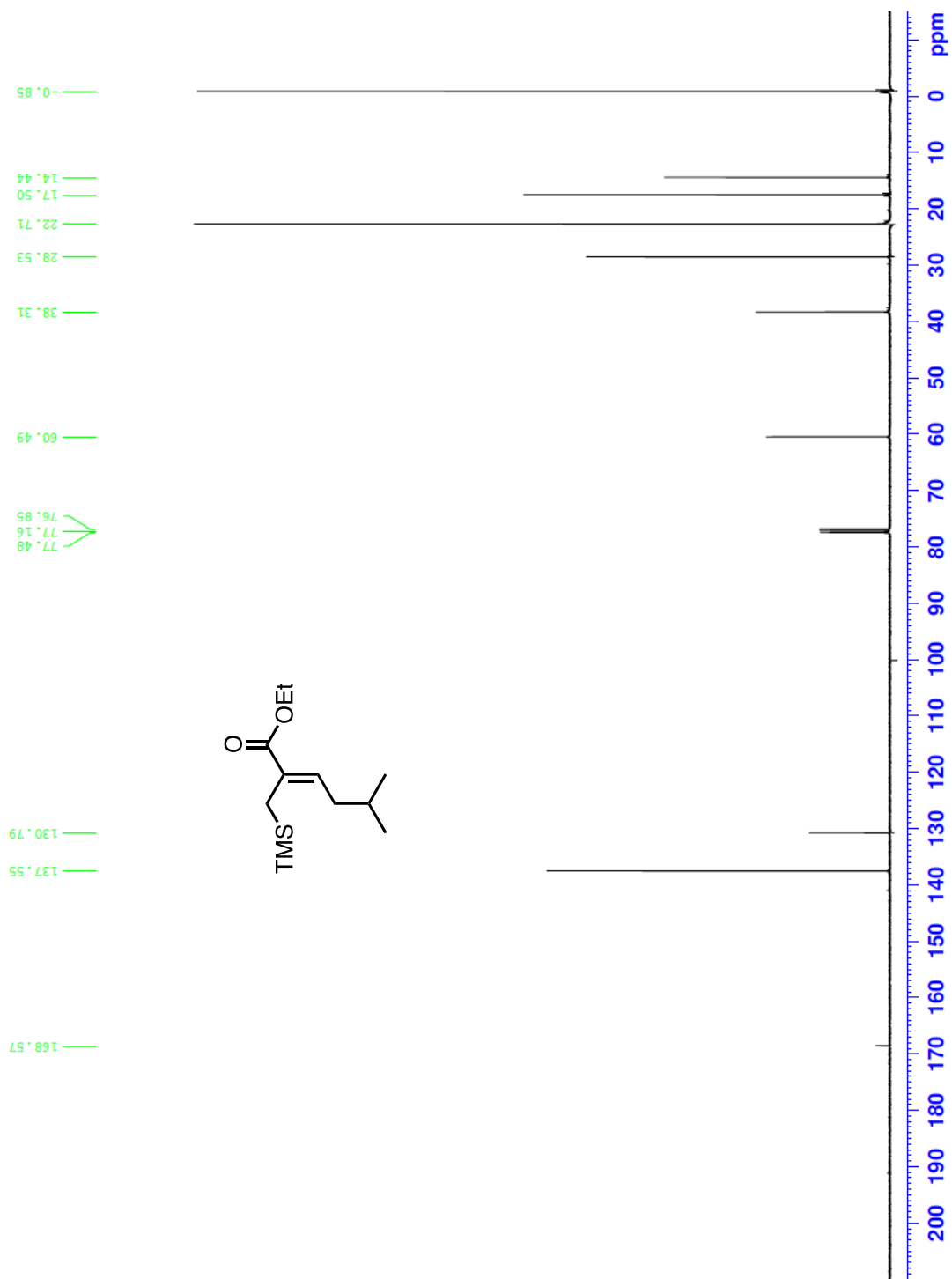


Figure 22. $^{13}\text{C-NMR}$ spectrum of compound 17d.

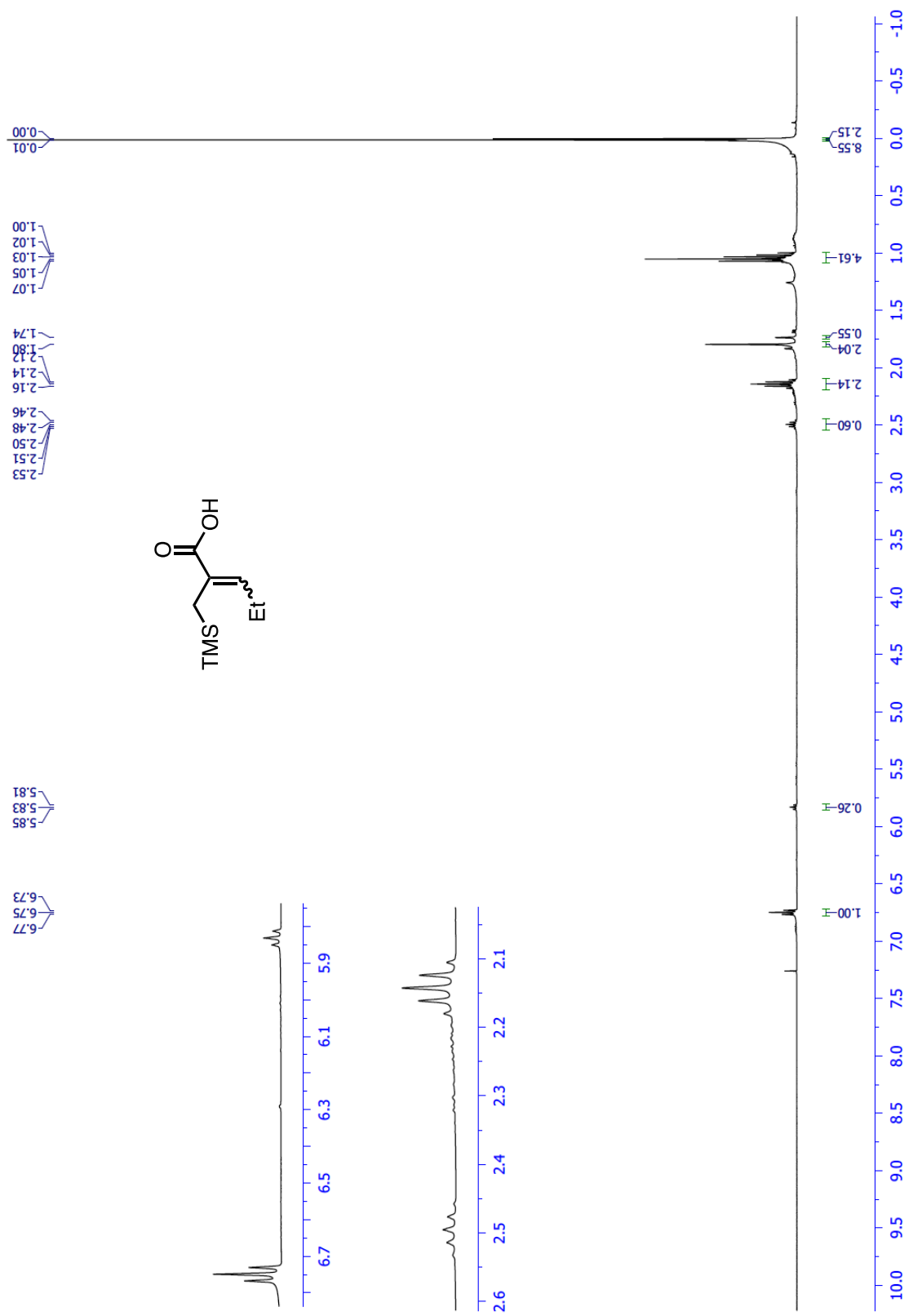


Figure 23. $^1\text{H-NMR}$ spectrum of compound **18a**.

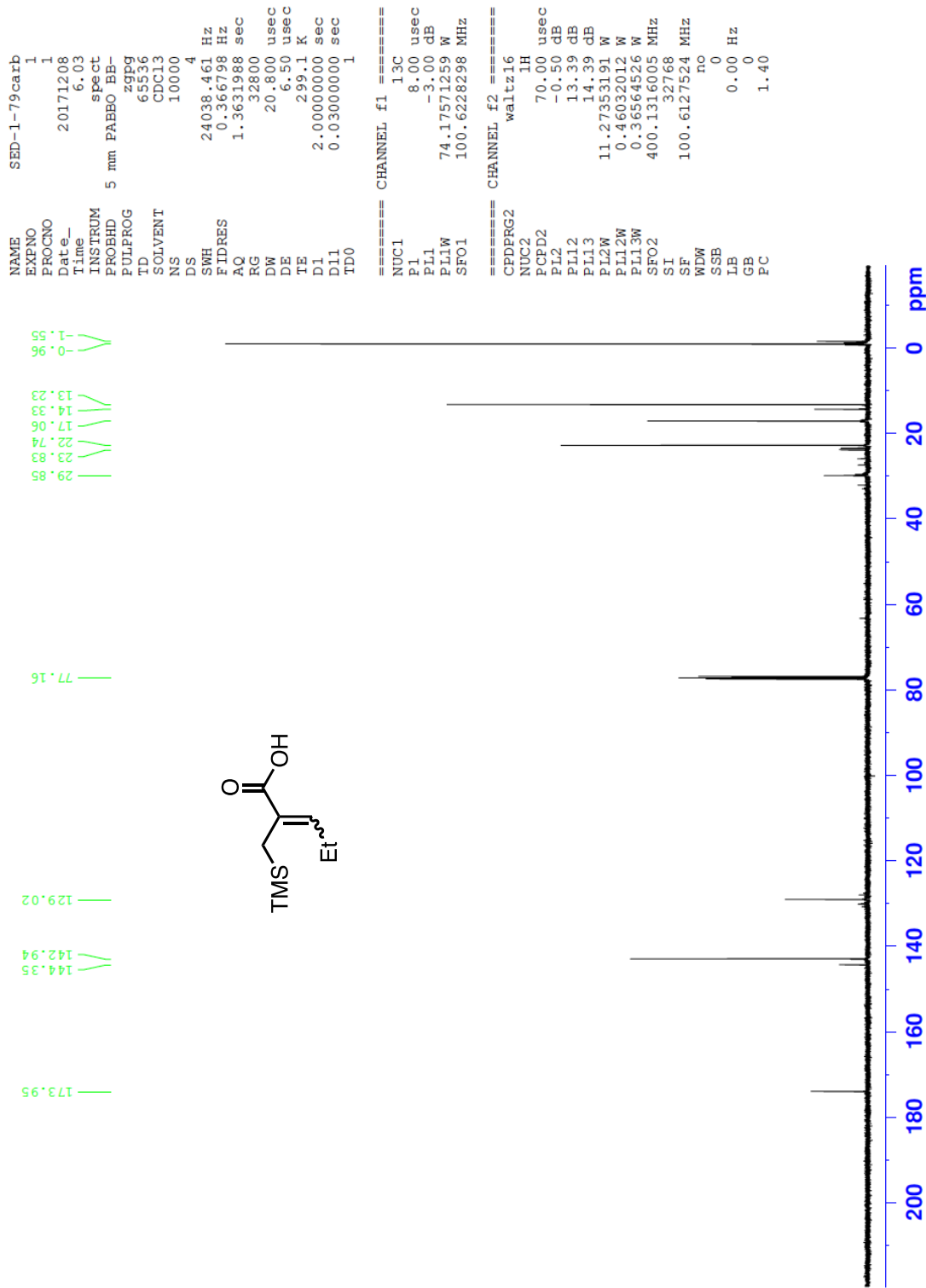


Figure 24. ¹³C-NMR spectrum of compound 18a.

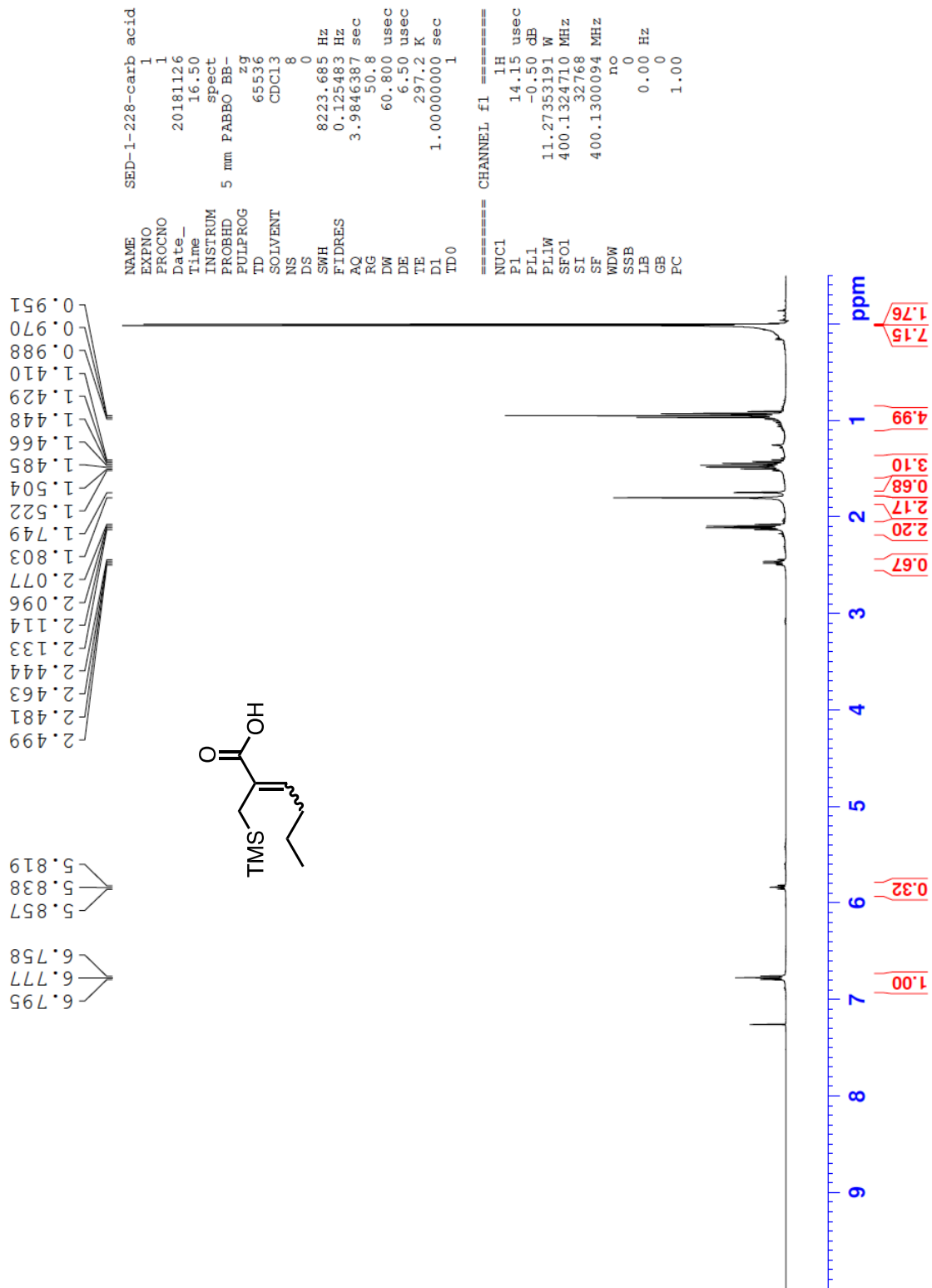


Figure 25. $^1\text{H-NMR}$ spectrum of compound 18c.

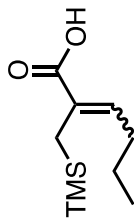
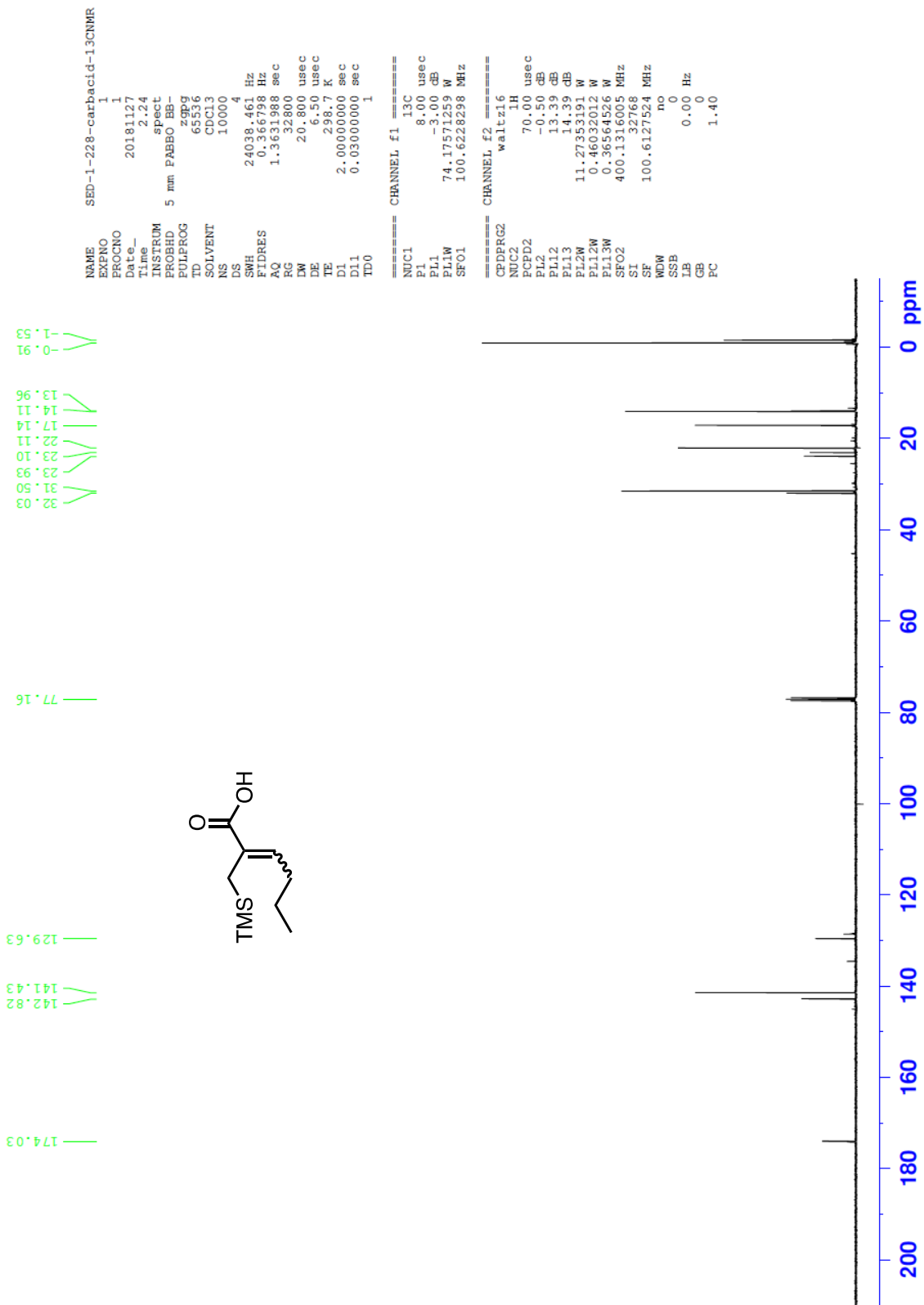


Figure 26. ¹³C-NMR spectrum of compound 18c.



Figure 27. ¹H-NMR spectrum of compound 18b.

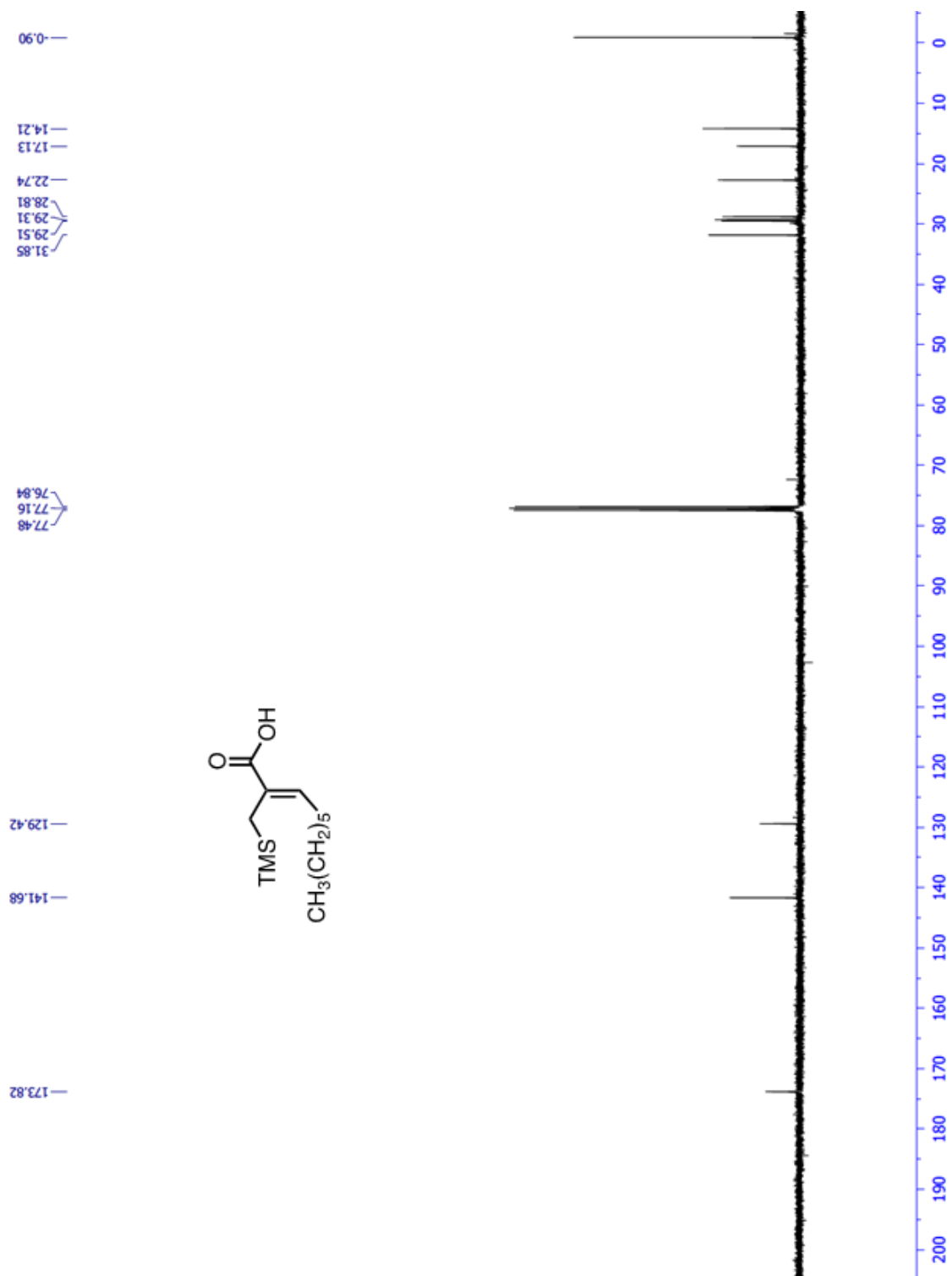


Figure 28. ¹³C-NMR spectrum of compound 18b.

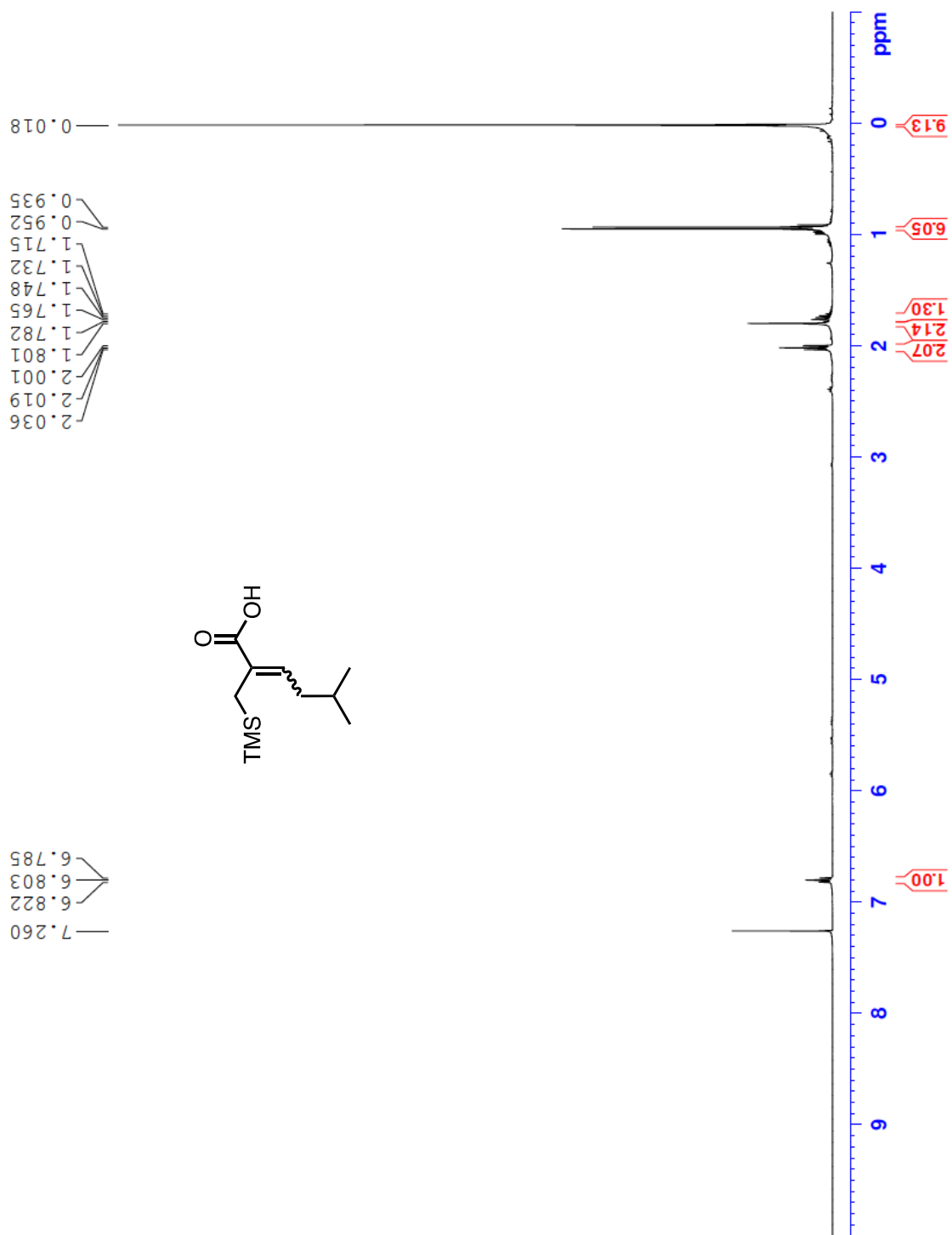


Figure 29. ¹H-NMR spectrum of compound **18d**.

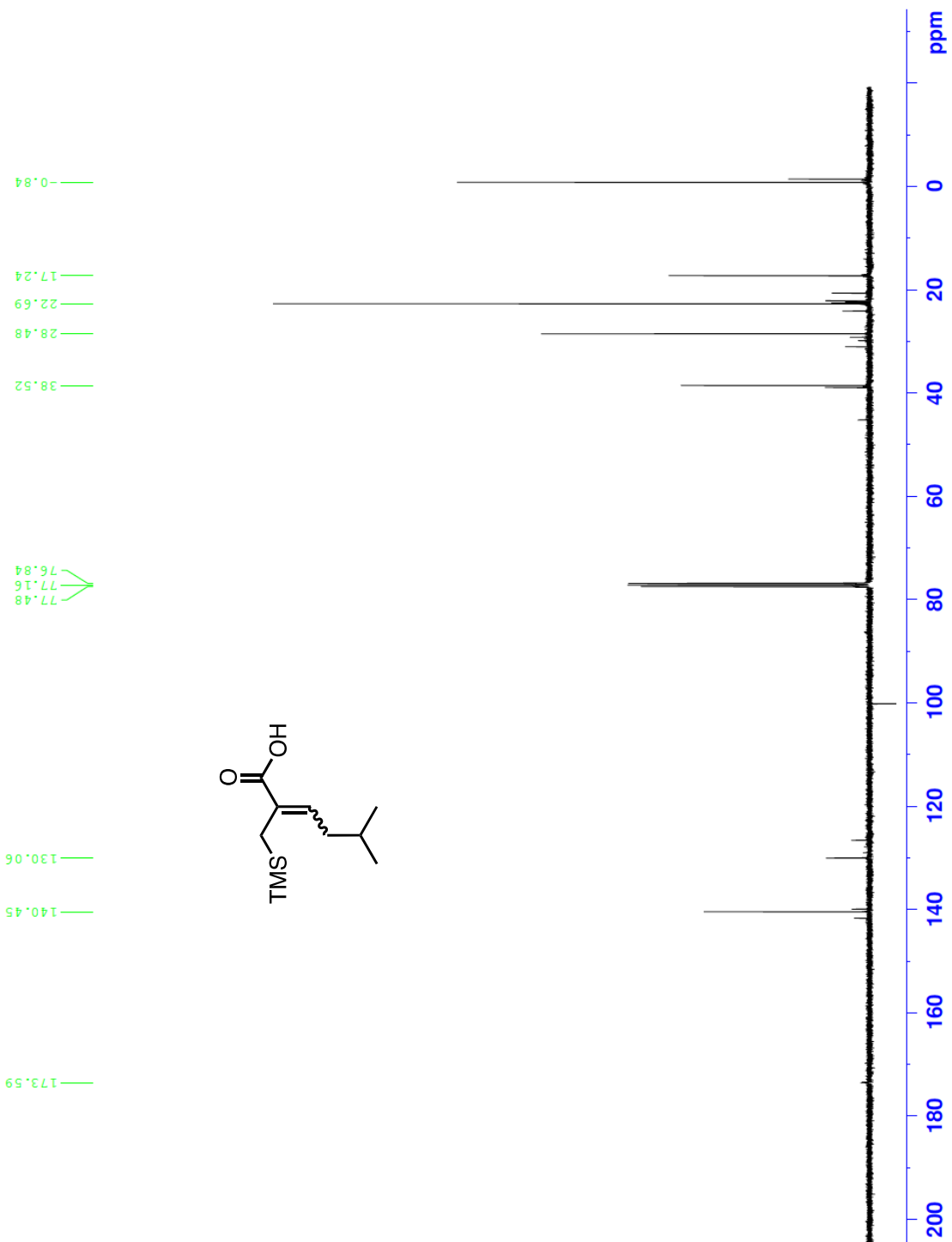


Figure 30. ^{13}C -NMR spectrum of compound 18d.

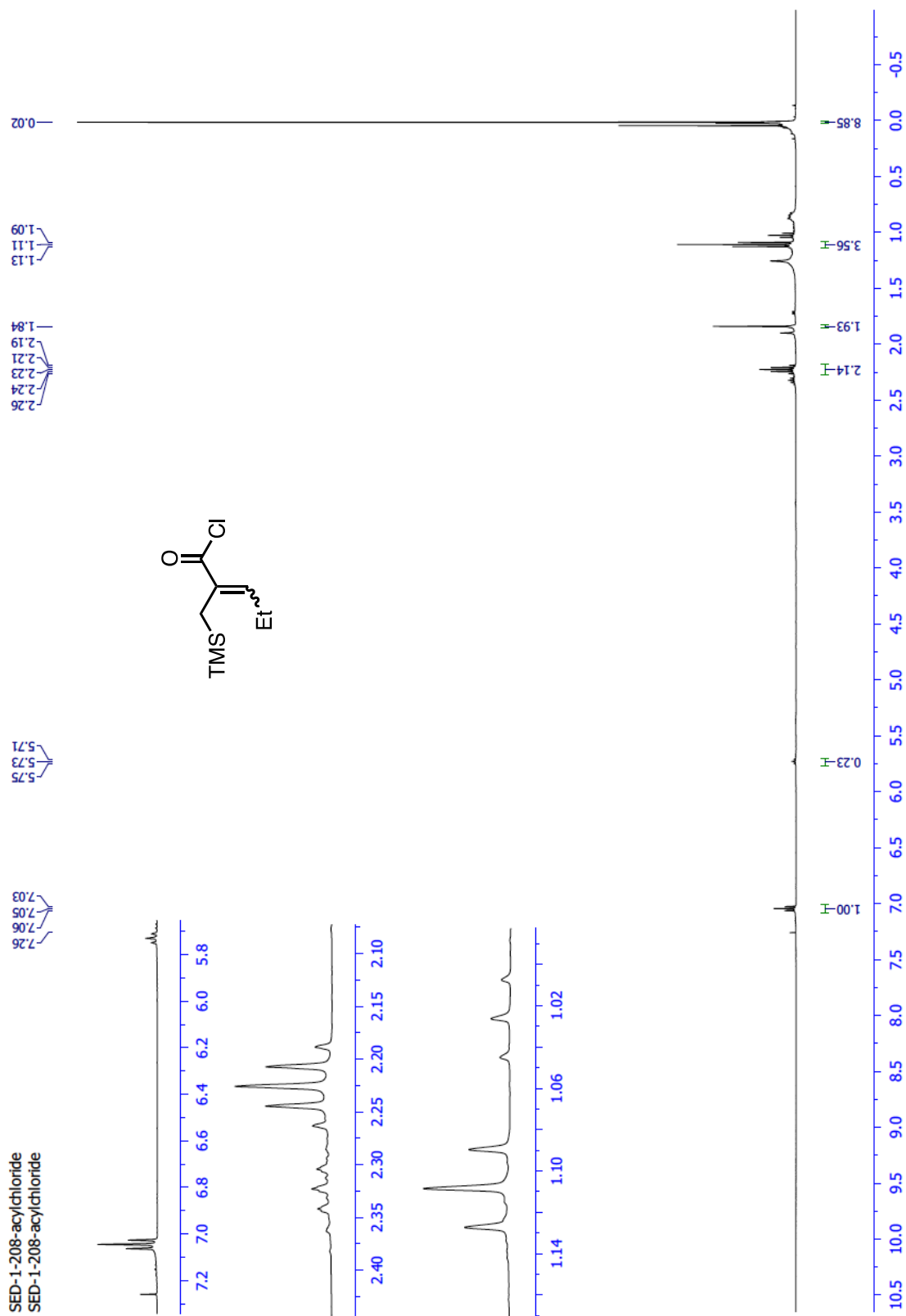


Figure 31. ¹H-NMR spectrum of compound **1a**.

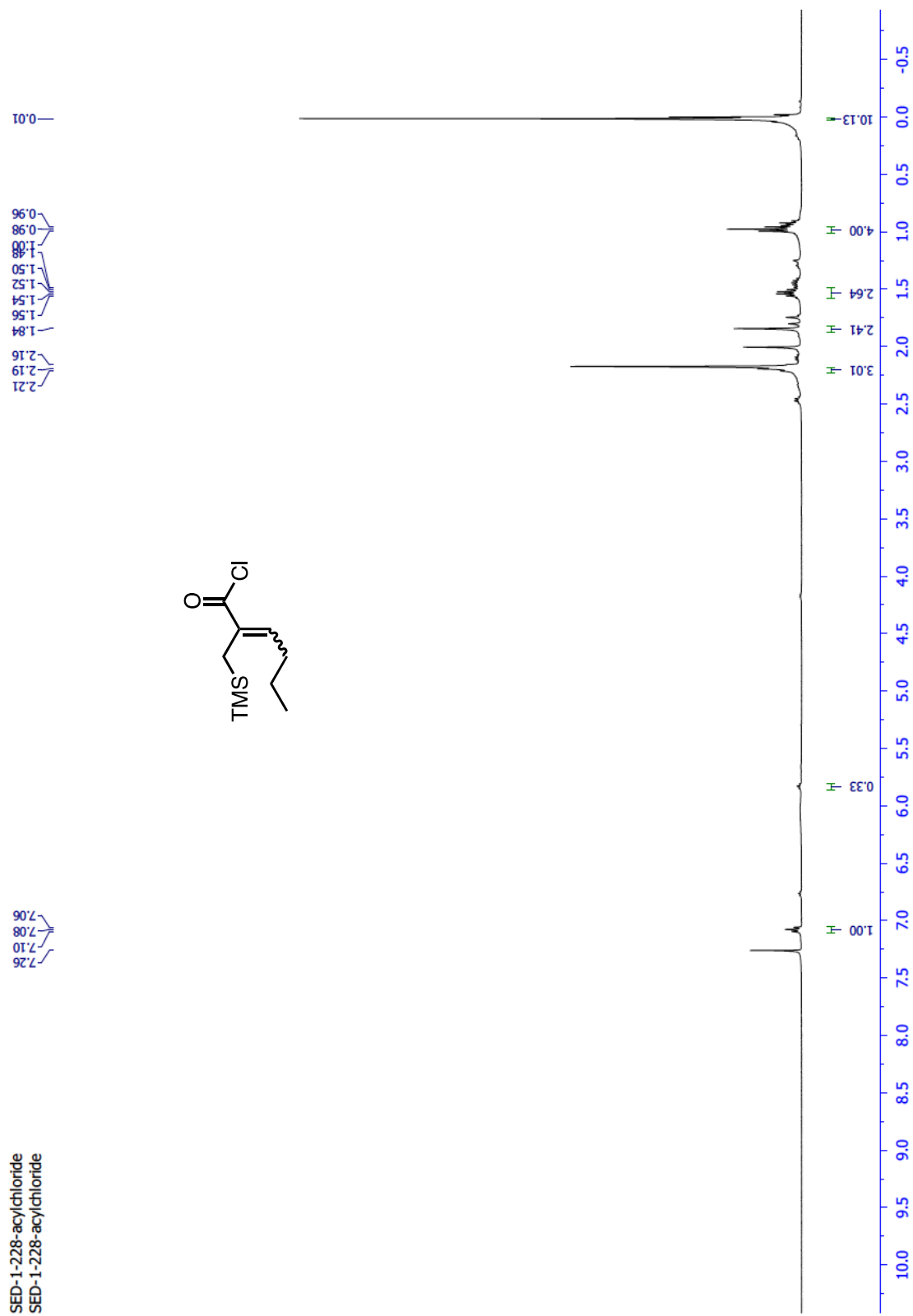


Figure 32. ¹H-NMR spectrum of compound 1c.

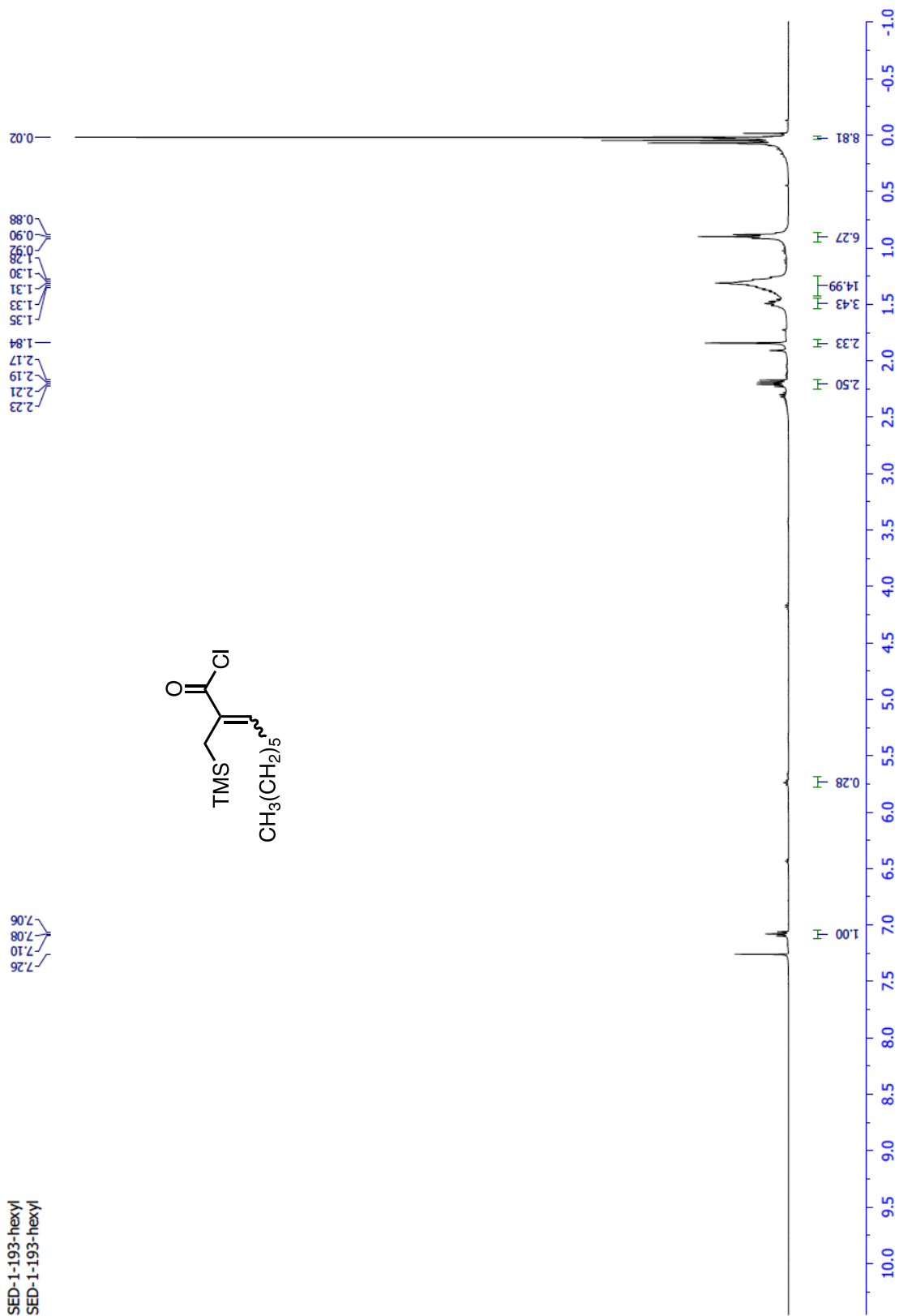


Figure 33. $^1\text{H-NMR}$ spectrum of compound **1b**.

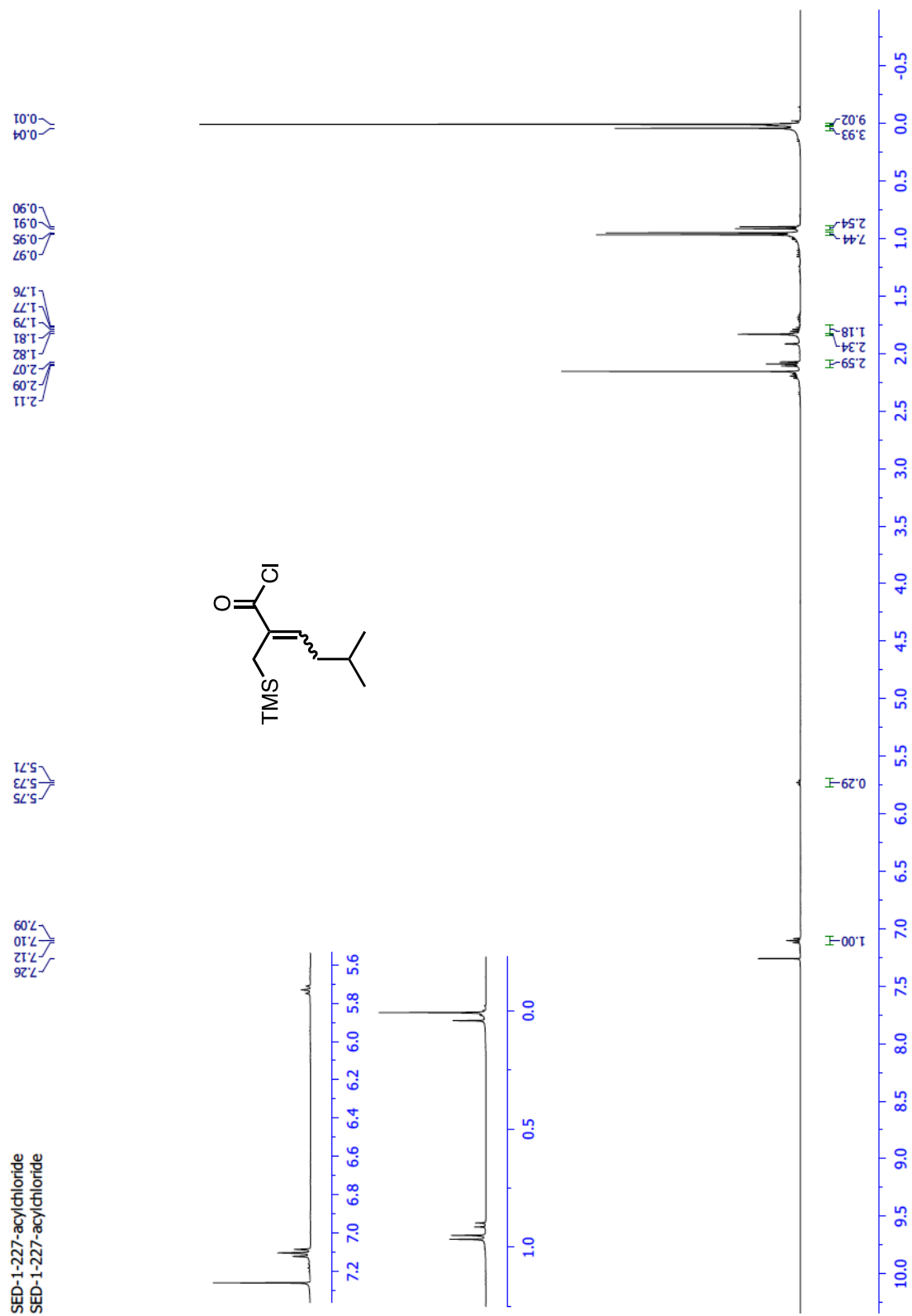


Figure 34. ^1H -NMR spectrum of compound **1d**.

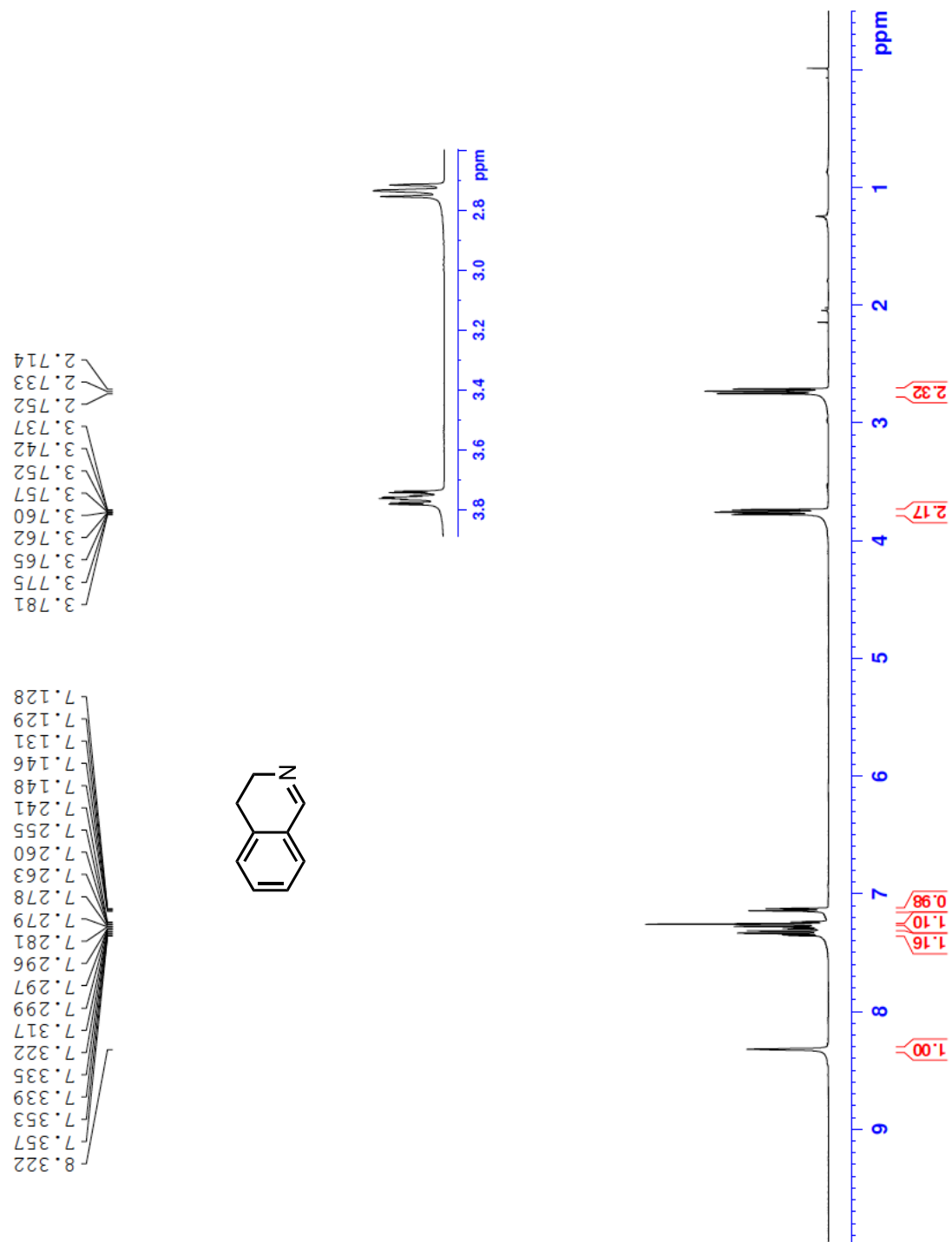


Figure 35. ¹H-NMR spectrum of compound 2.

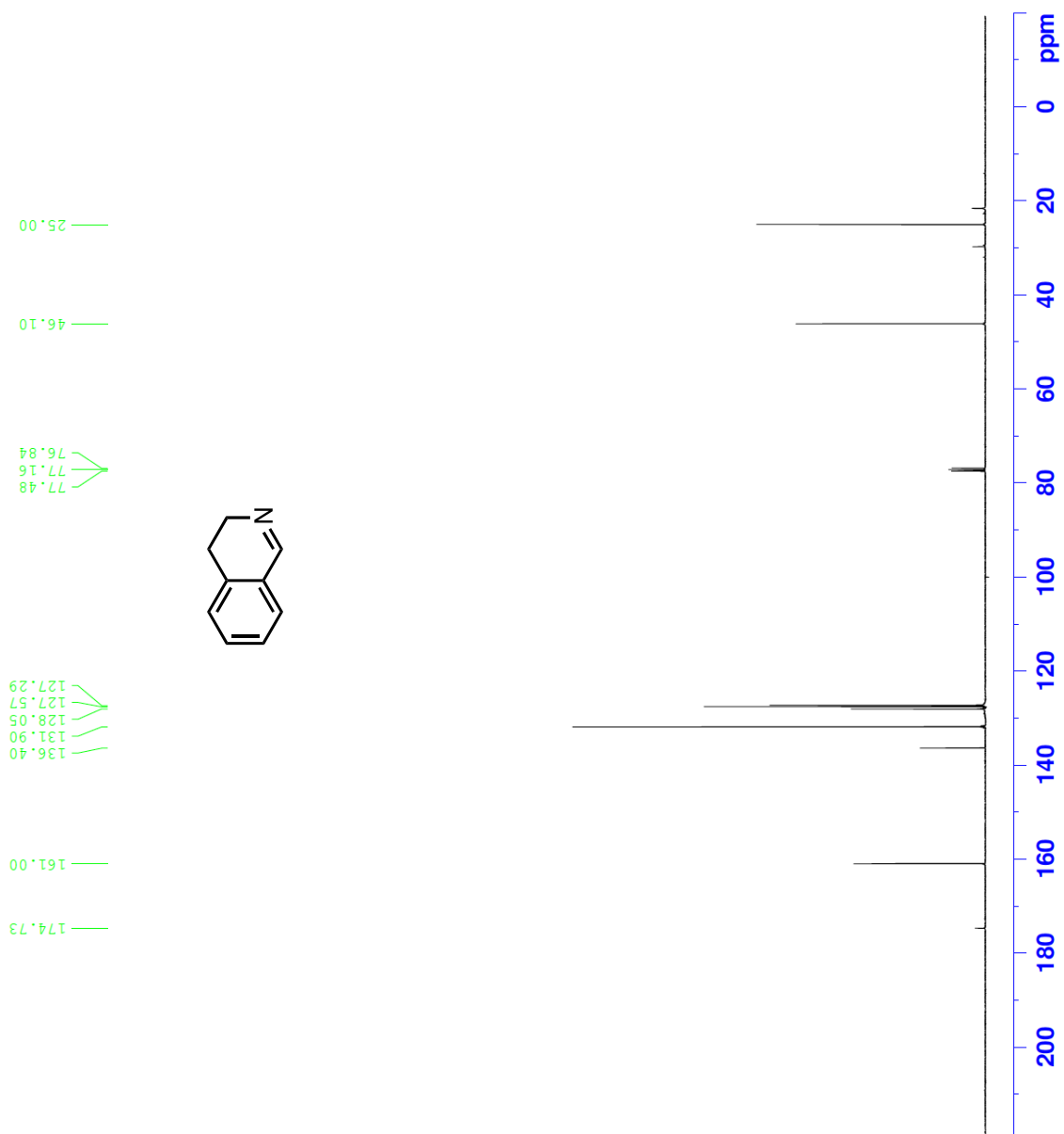


Figure 36. ^{13}C -NMR spectrum of compound 2.

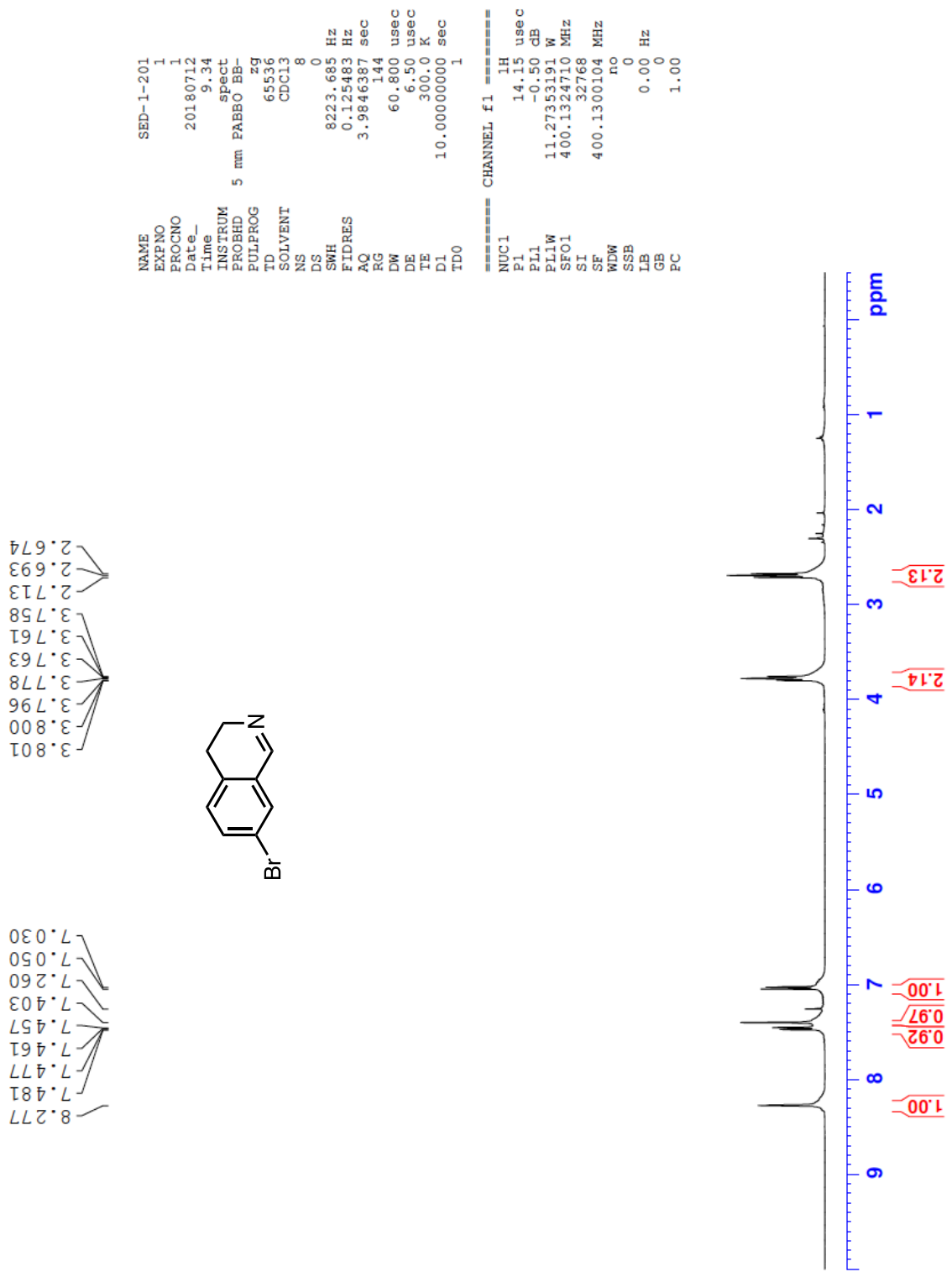


Figure 37. ¹H-NMR spectrum of compound 5.

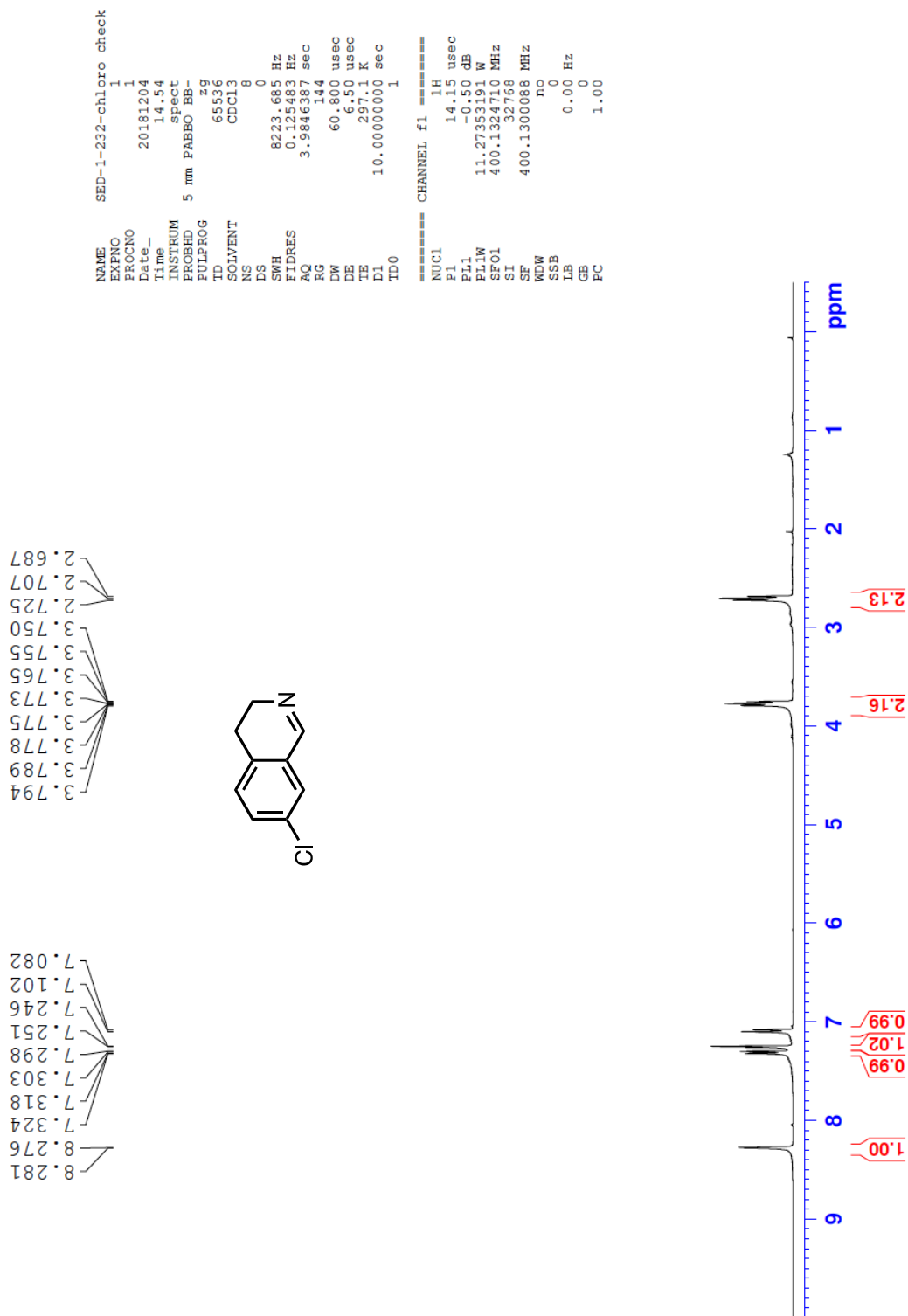


Figure 38. $^1\text{H-NMR}$ spectrum of compound 6.

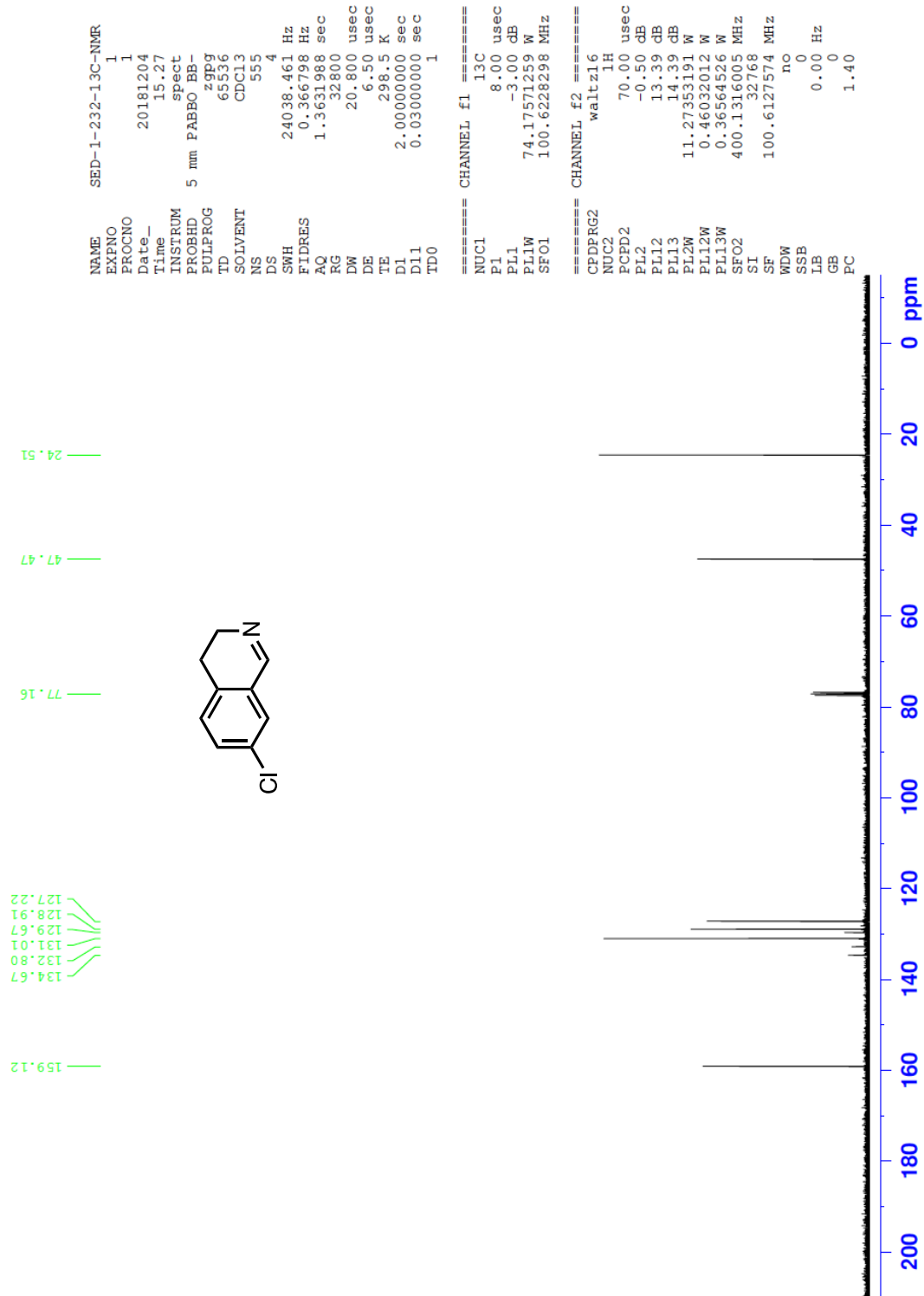


Figure 39. ^{13}C -NMR spectrum of compound 6.

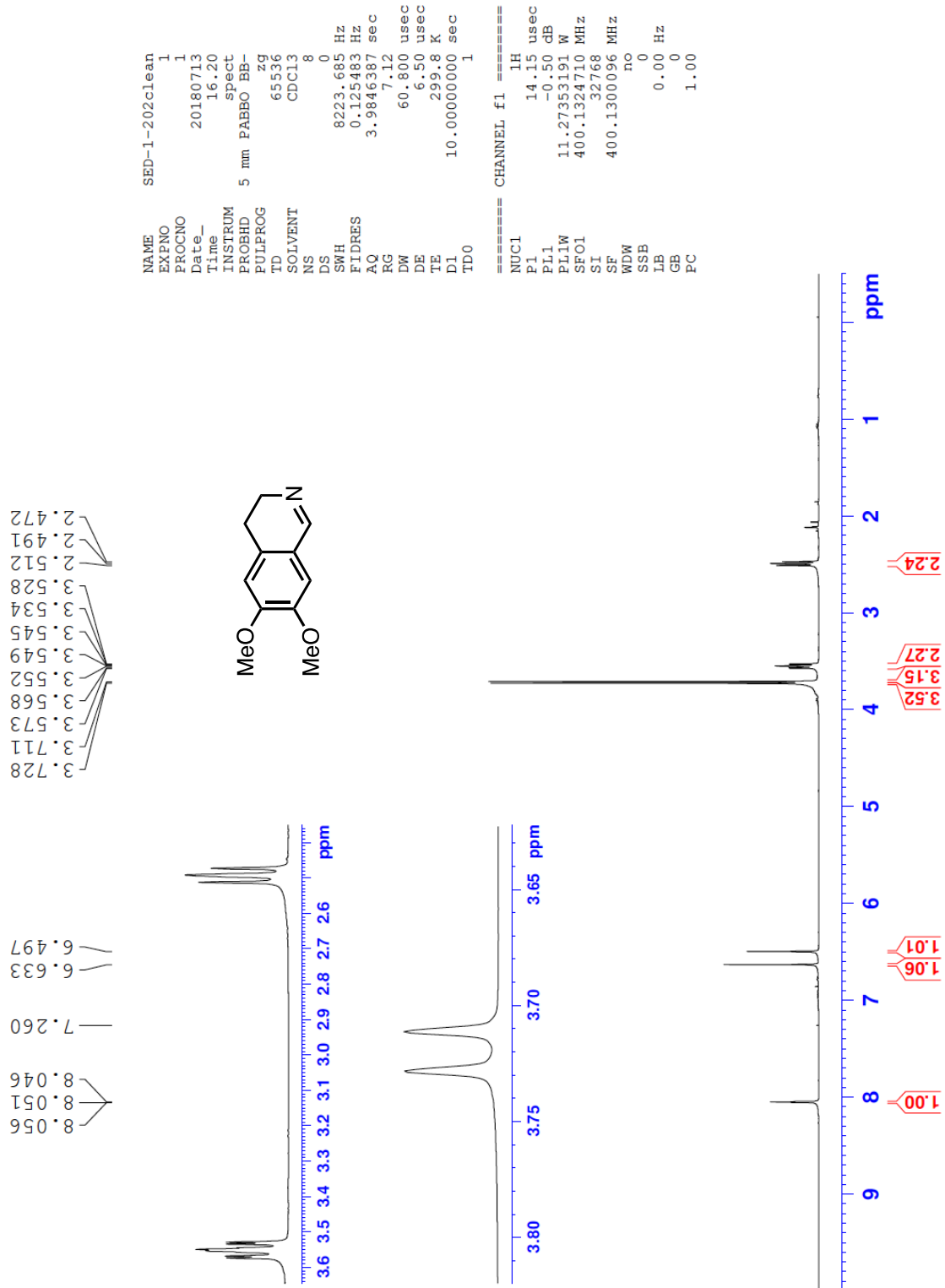


Figure 40. $^1\text{H-NMR}$ spectrum of compound **7**.

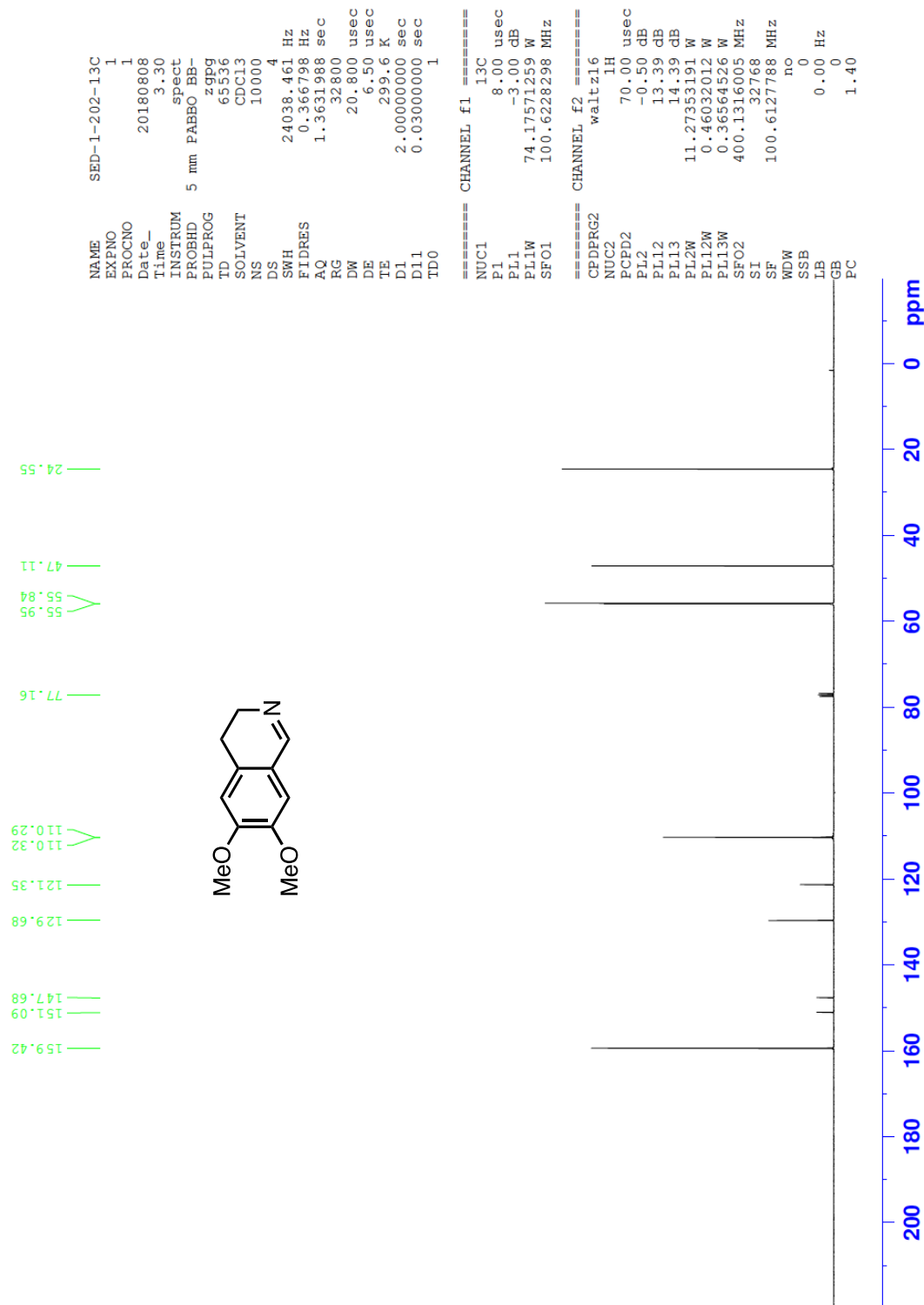


Figure 41. ¹³C-NMR spectrum of compound 7.

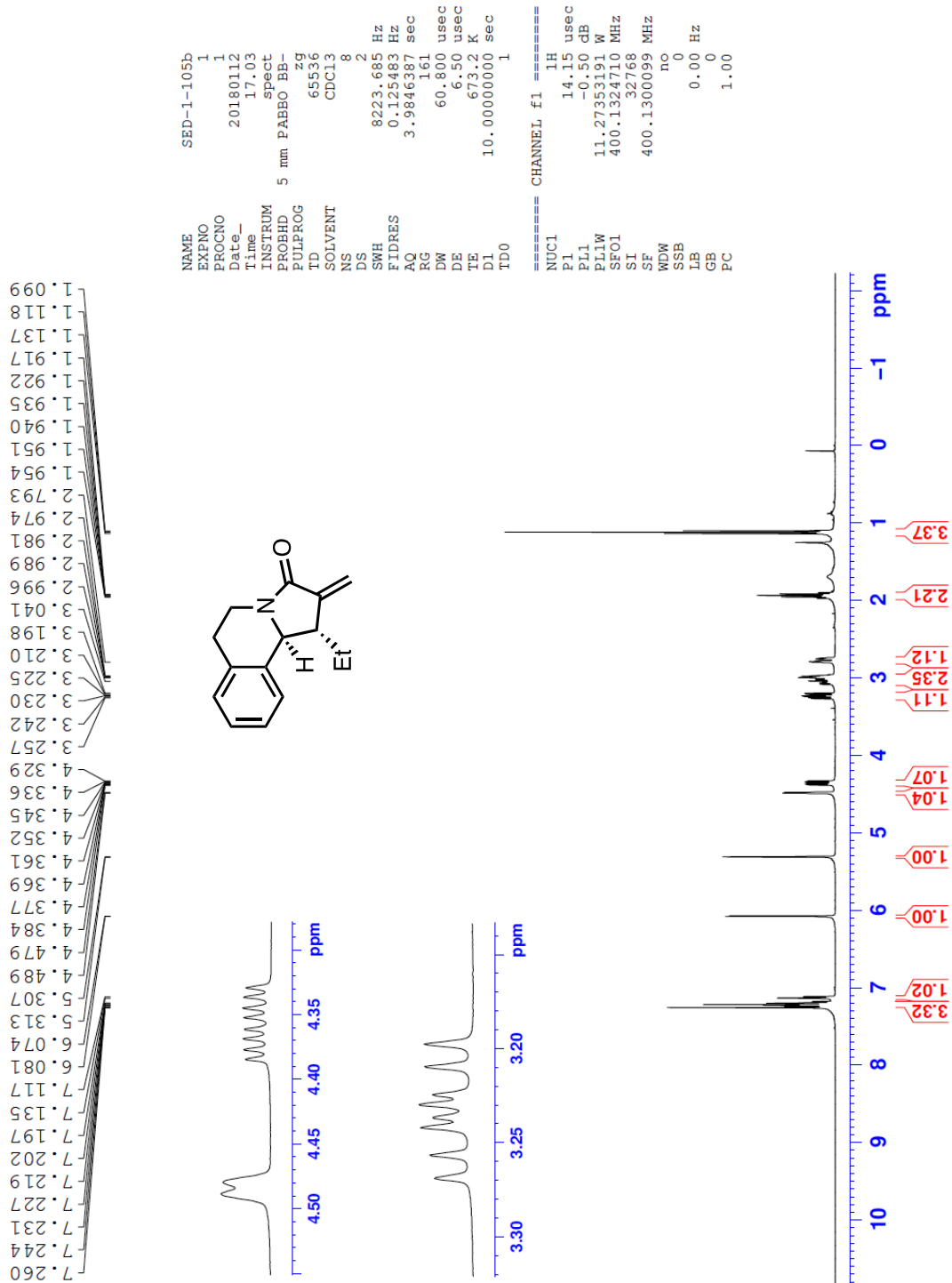


Figure 42. $^1\text{H-NMR}$ spectrum of compound 3.

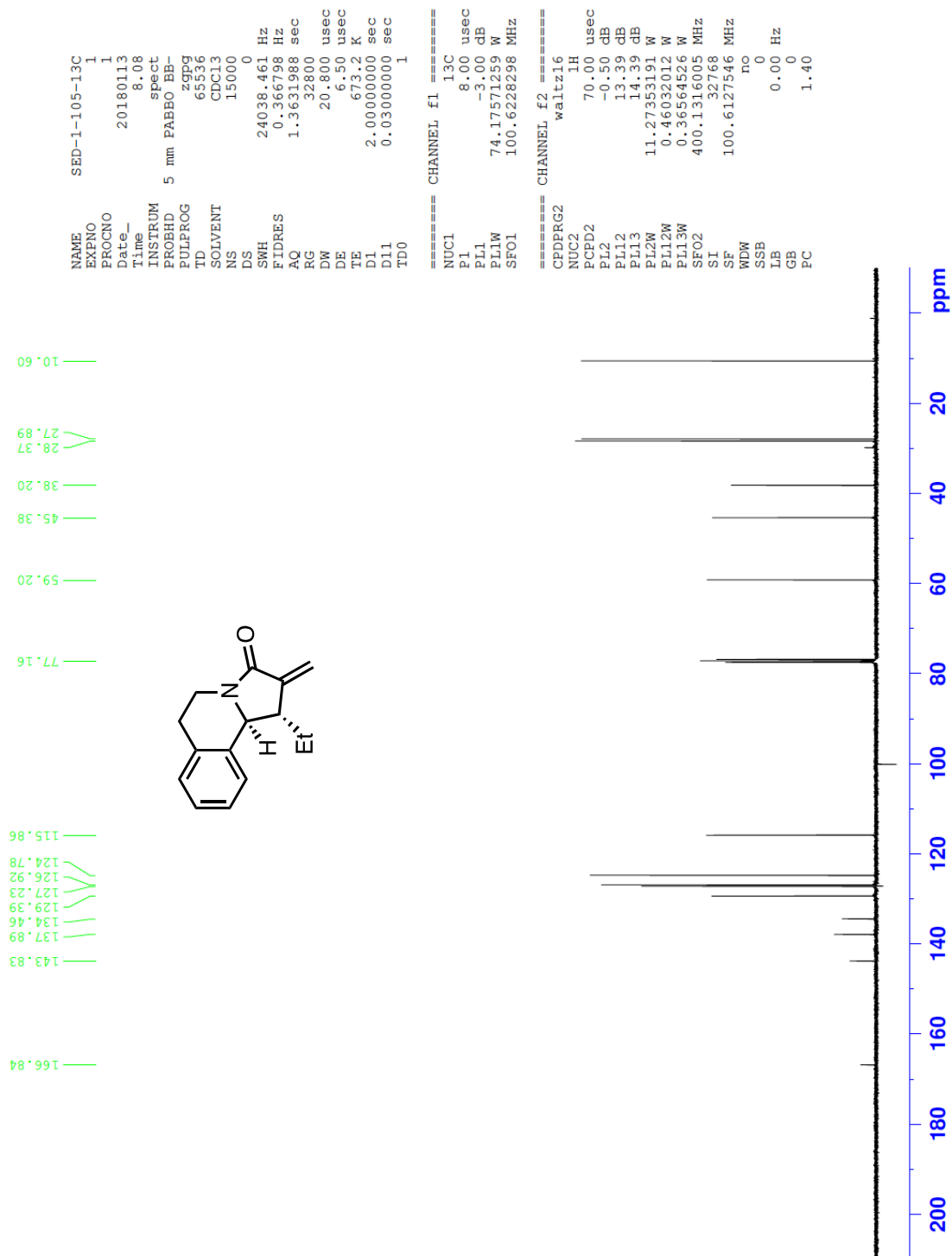


Figure 43. ^{13}C -NMR spectrum of compound **3**.

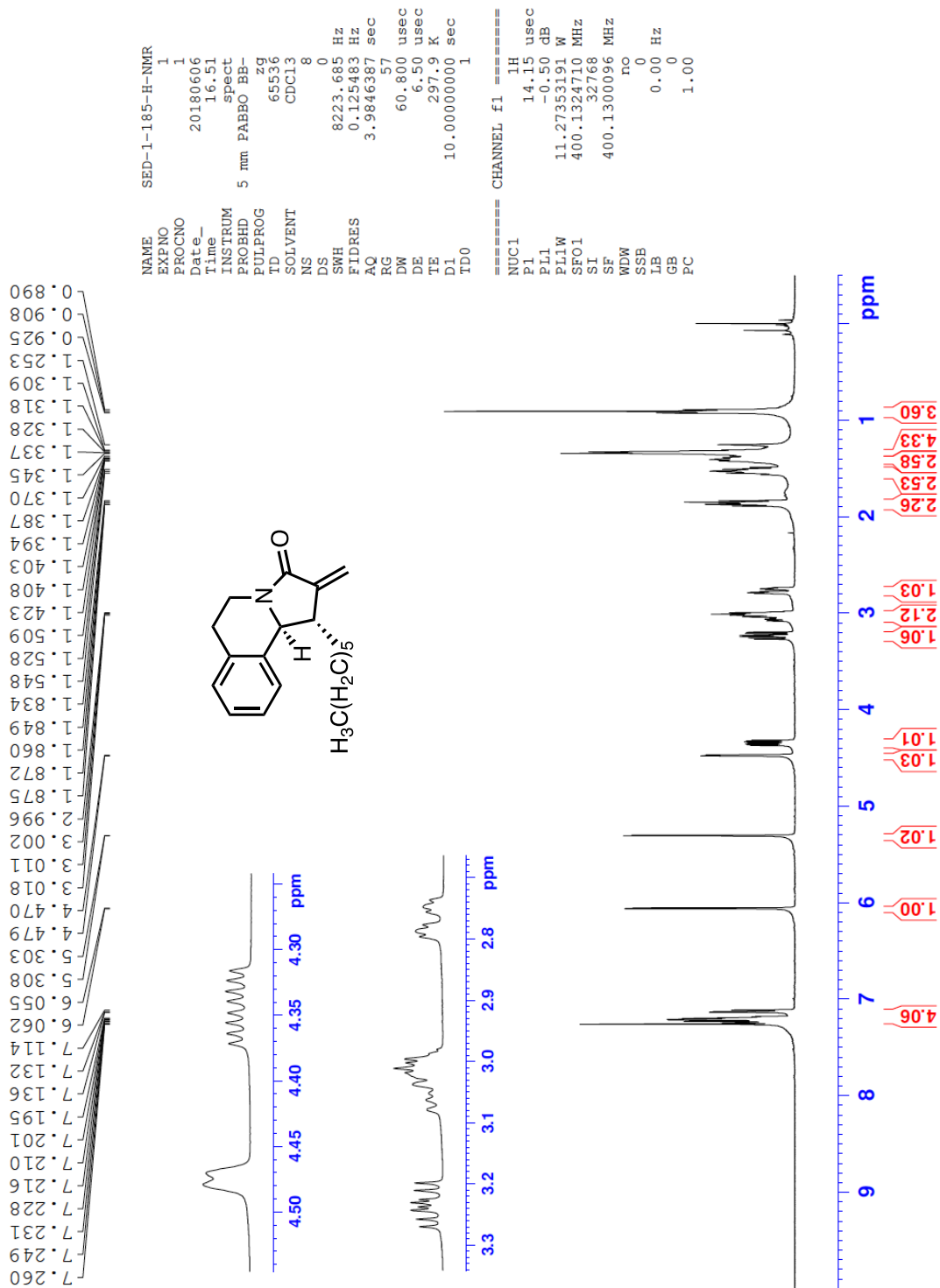


Figure 44. 1H -NMR spectrum of compound 4.

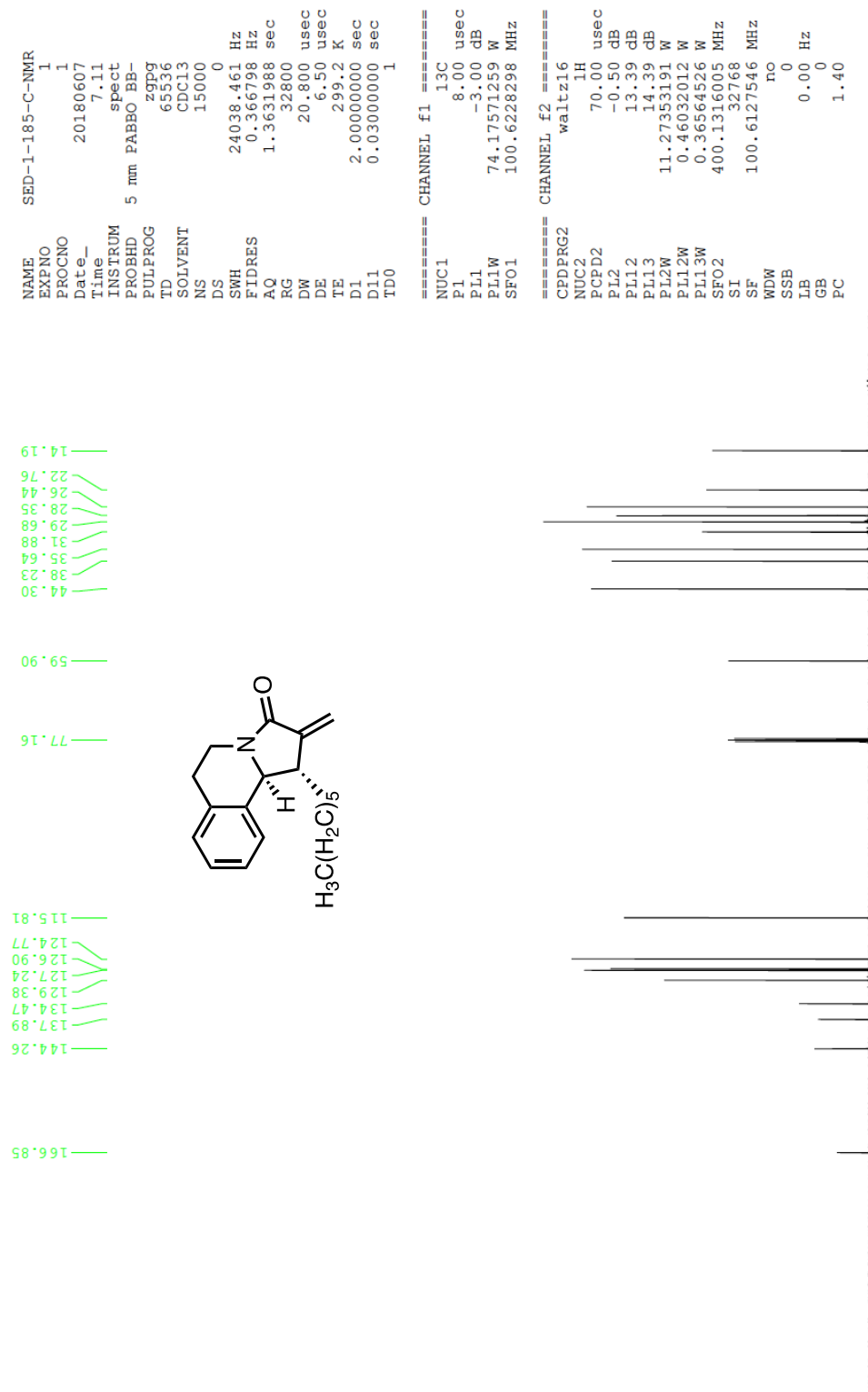


Figure 45. ^{13}C -NMR spectrum of compound 4.

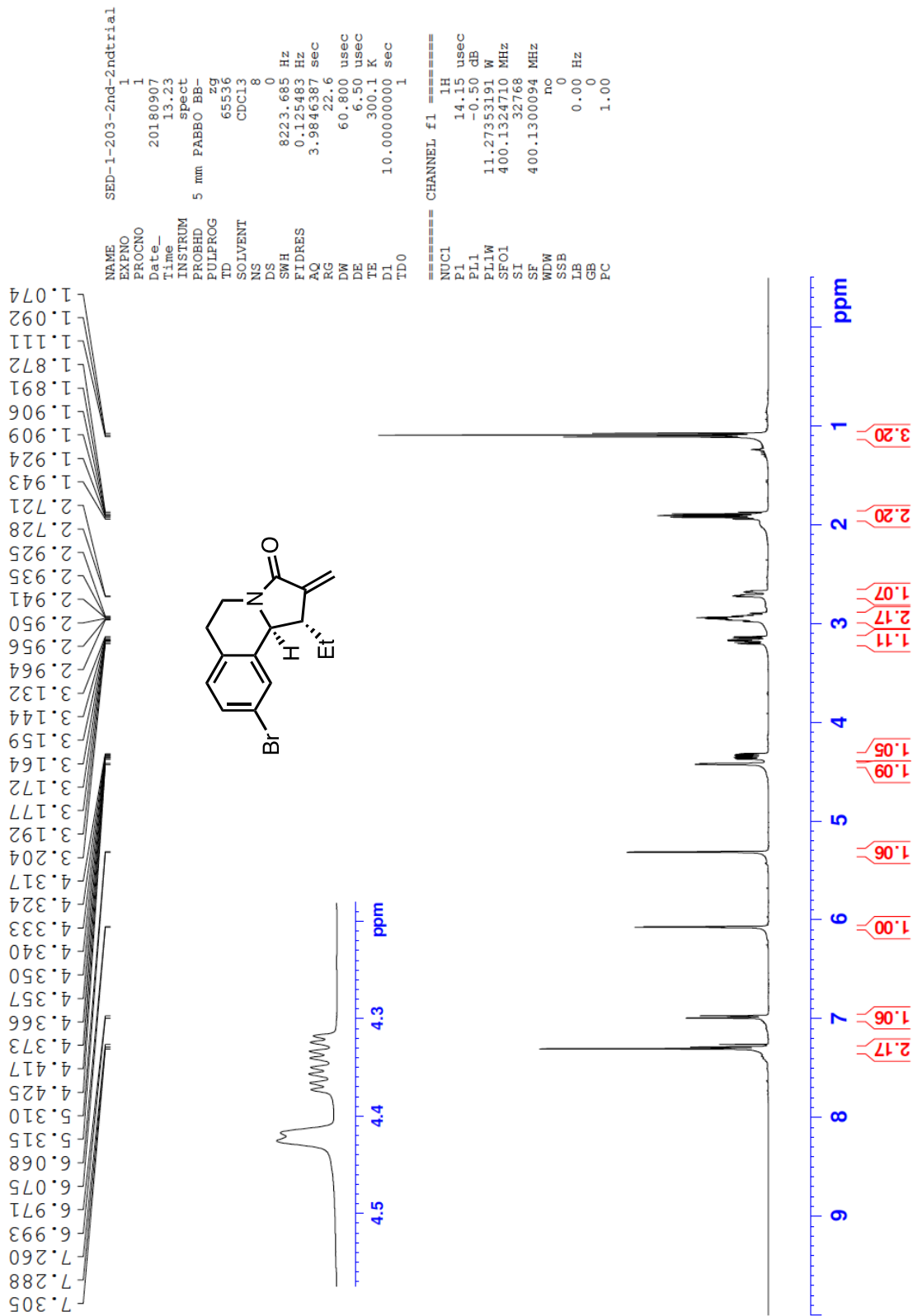


Figure 46. ^1H -NMR spectrum of compound 11.

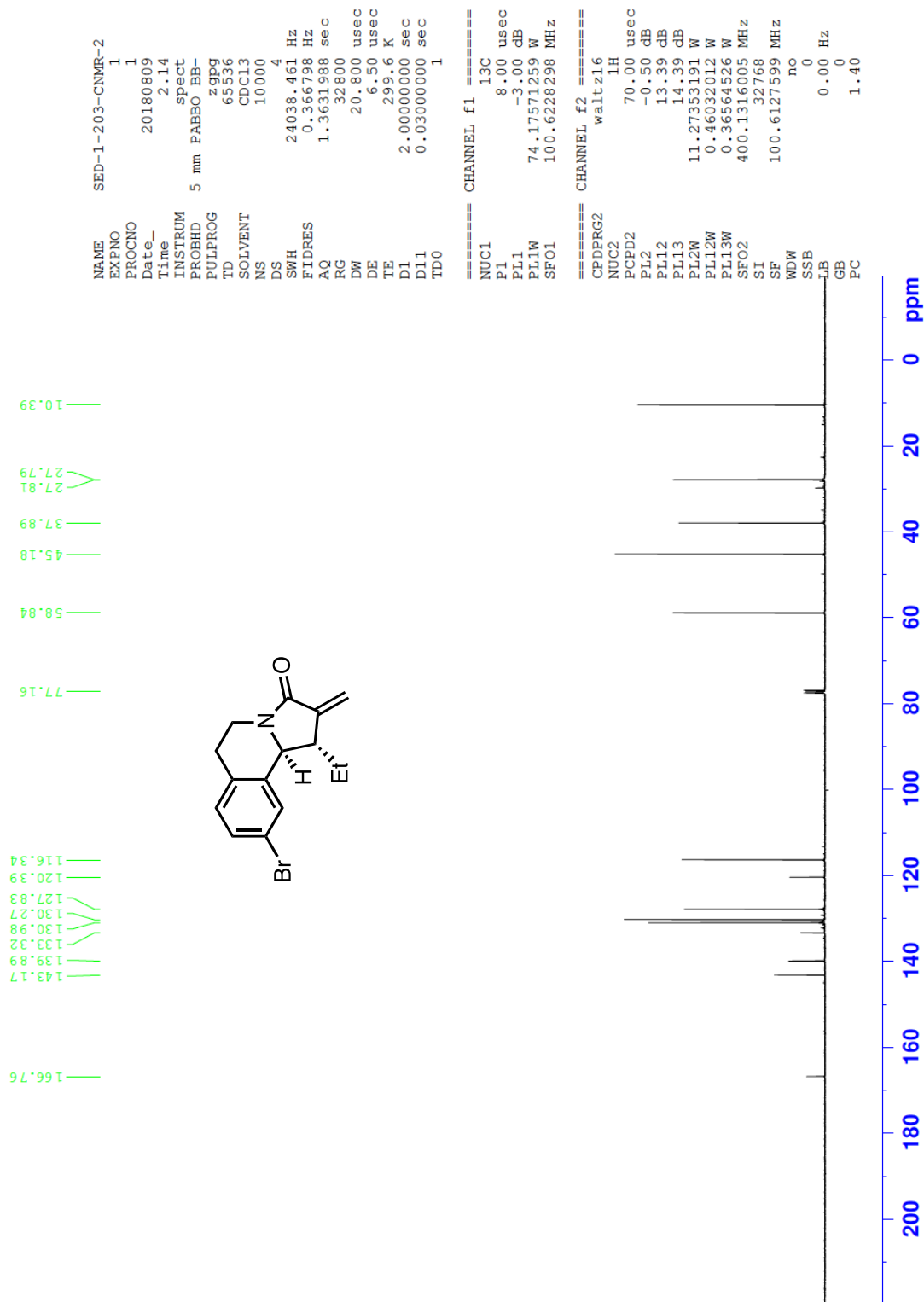


Figure 47. ^{13}C -NMR spectrum of compound 11.

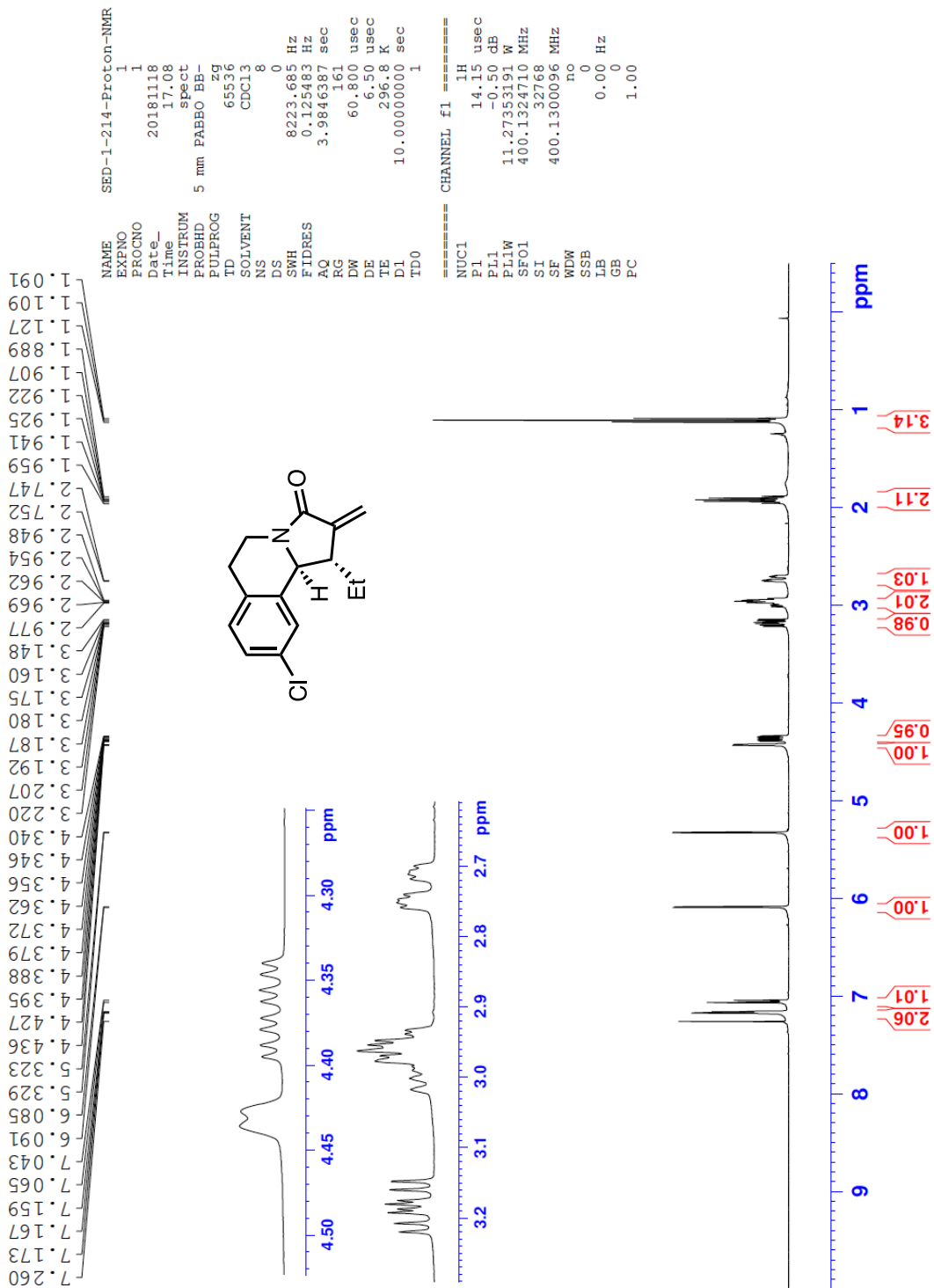


Figure 48. ^1H -NMR spectrum of compound 12.

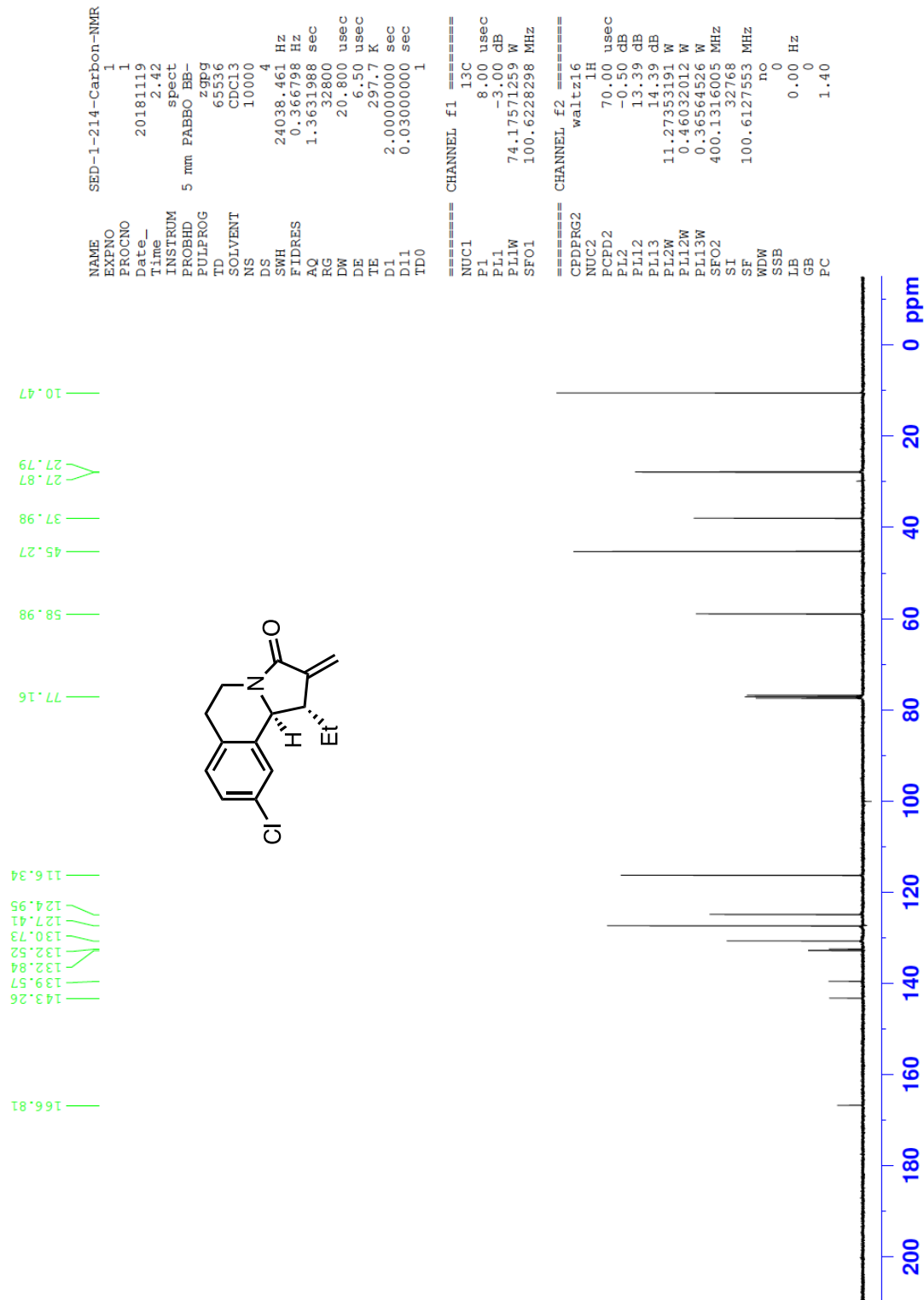


Figure 49. ¹³C-NMR spectrum of compound 12.

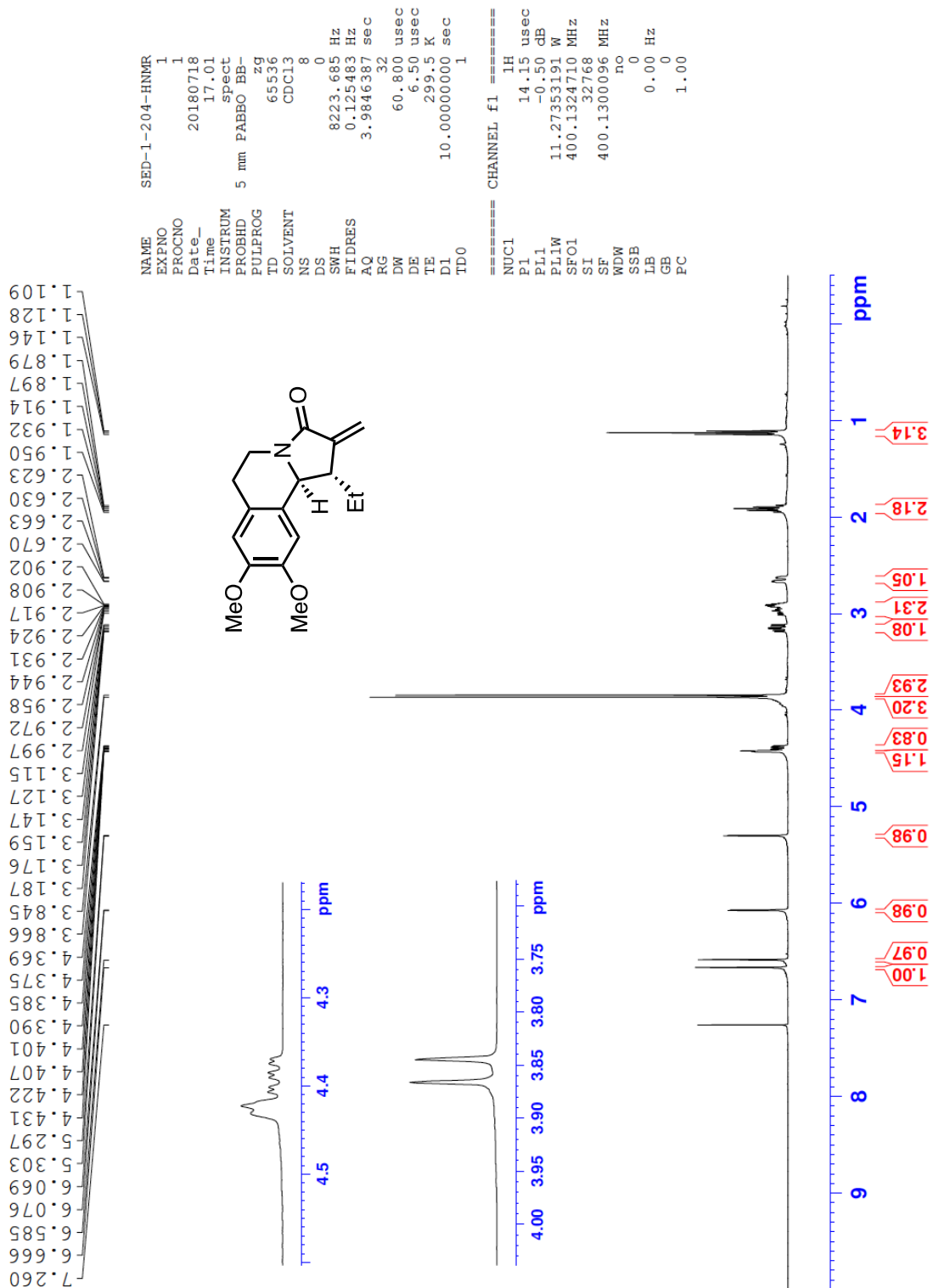


Figure 50. $^1\text{H-NMR}$ spectrum of compound 13.

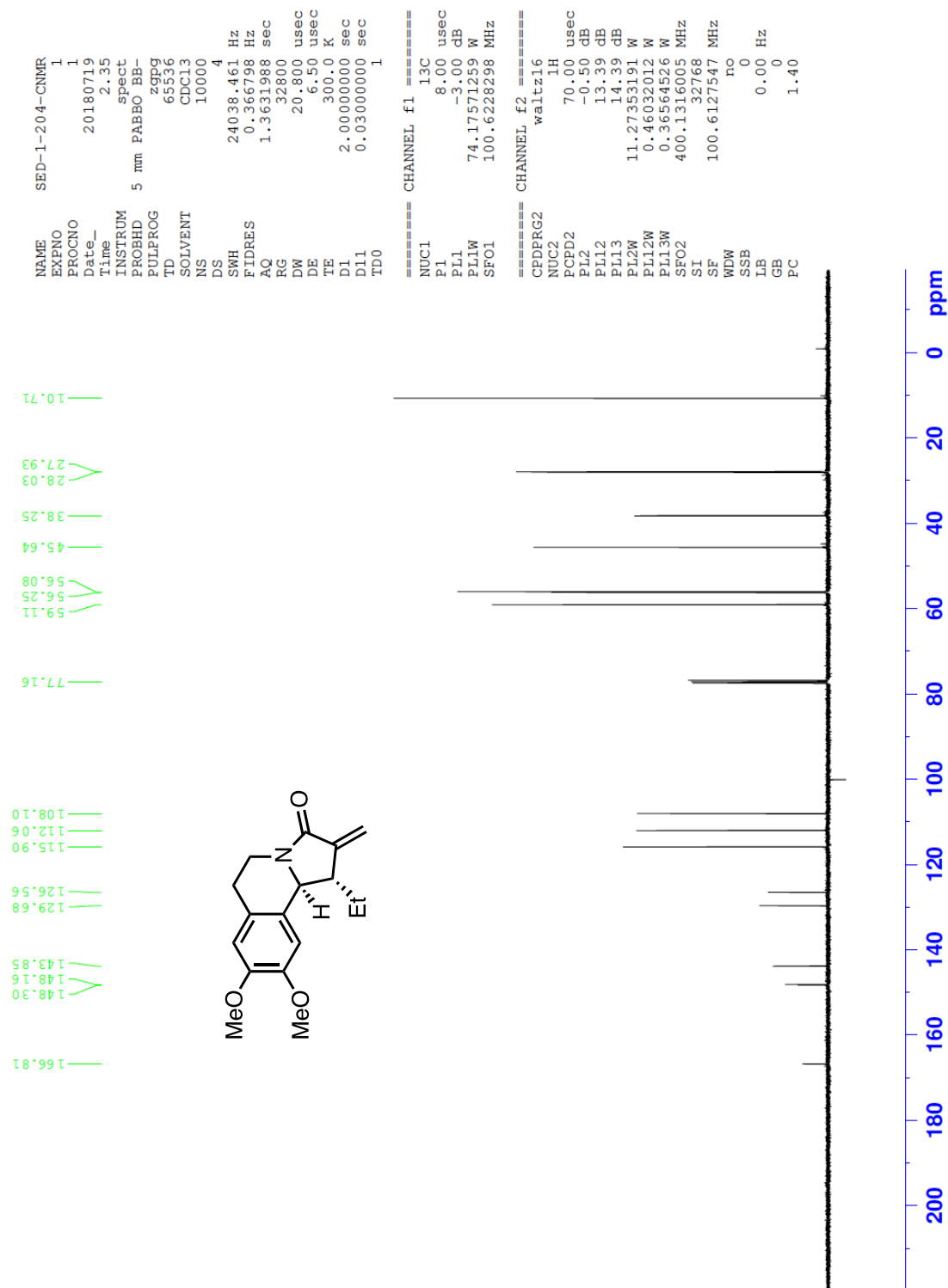


Figure 51. ^{13}C -NMR spectrum of compound 13.

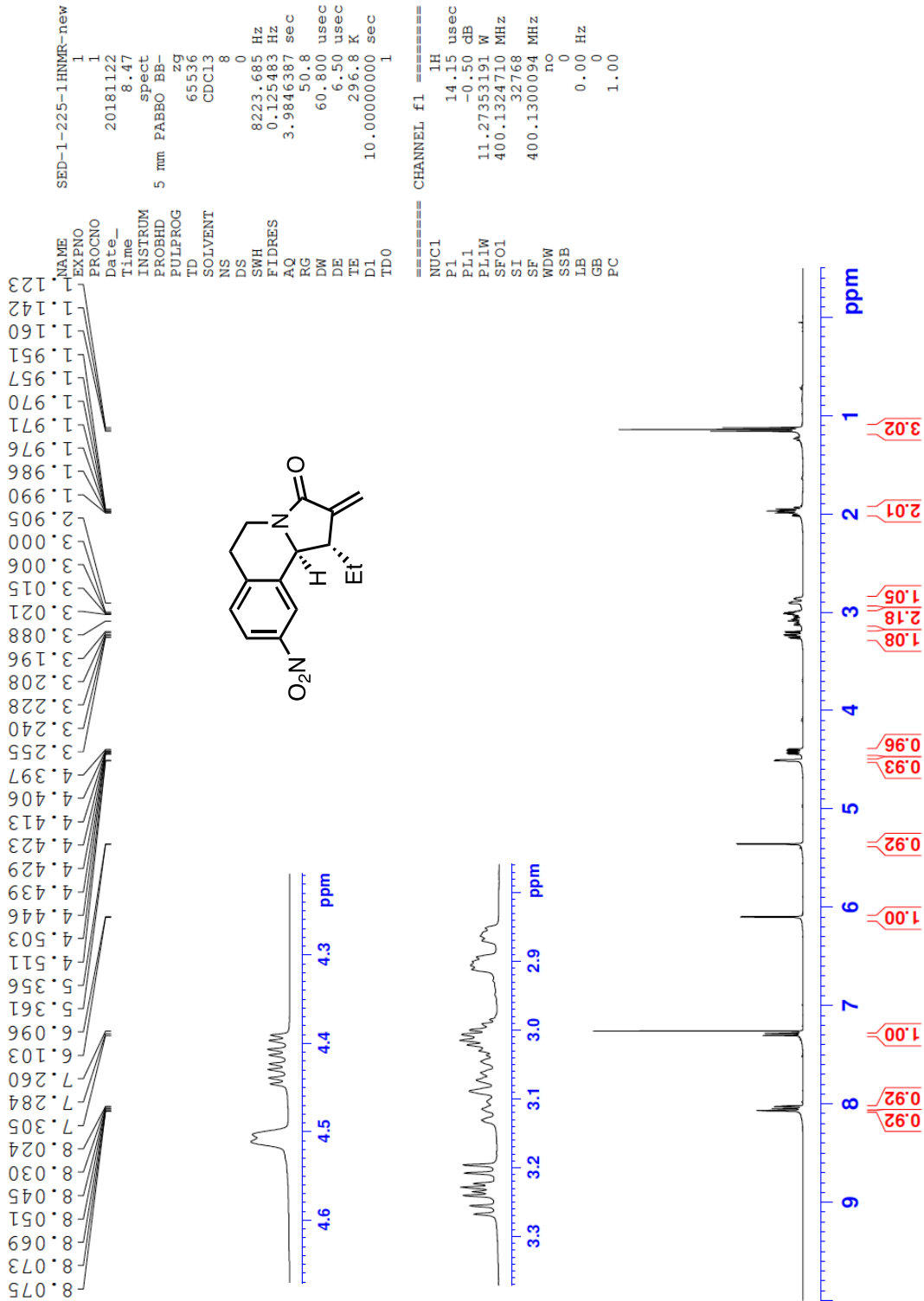


Figure 52. ¹H-NMR spectrum of compound 14.

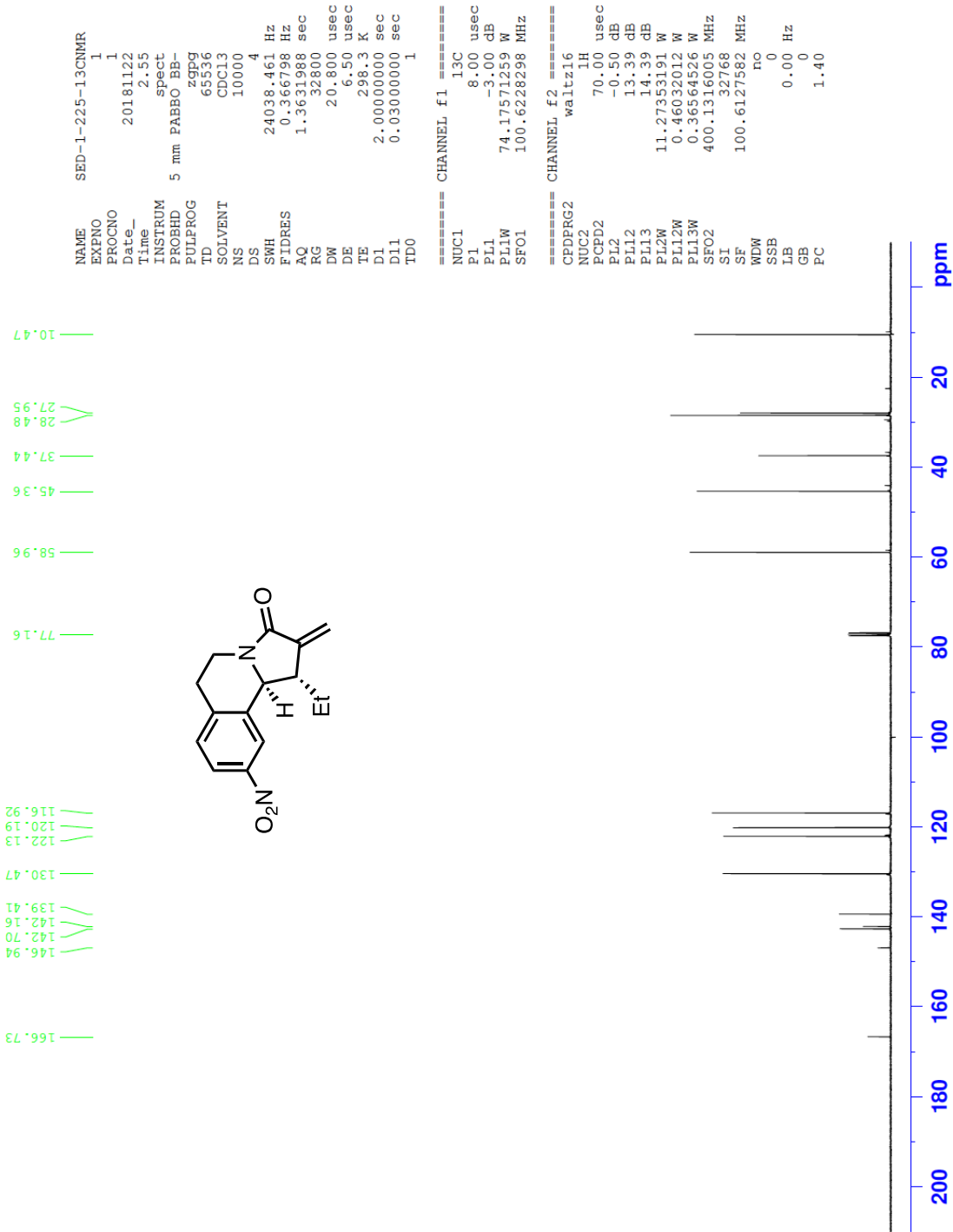


Figure 53. ^{13}C -NMR spectrum of compound **14**.

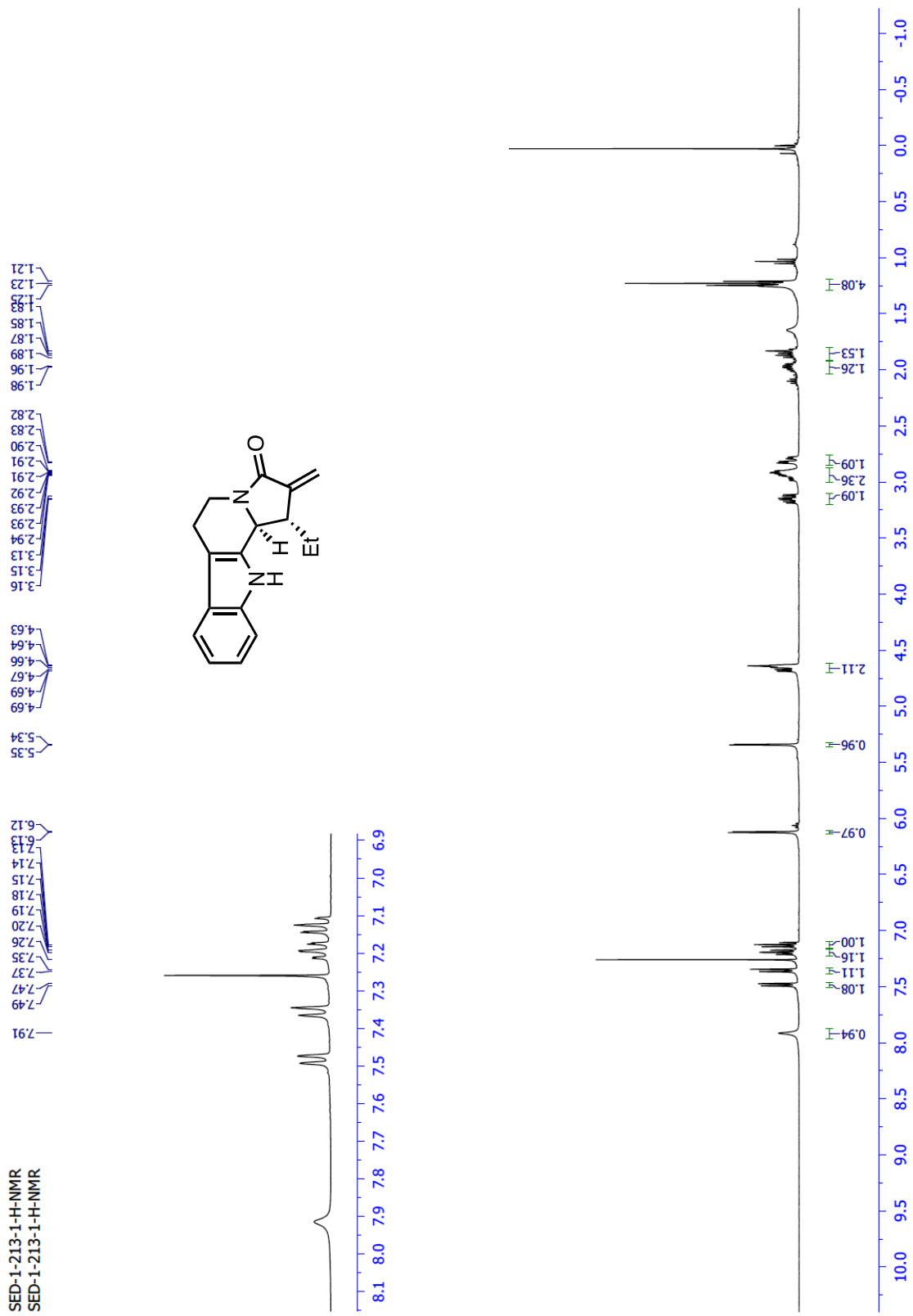


Figure 54. ¹H-NMR spectrum of compound 15.

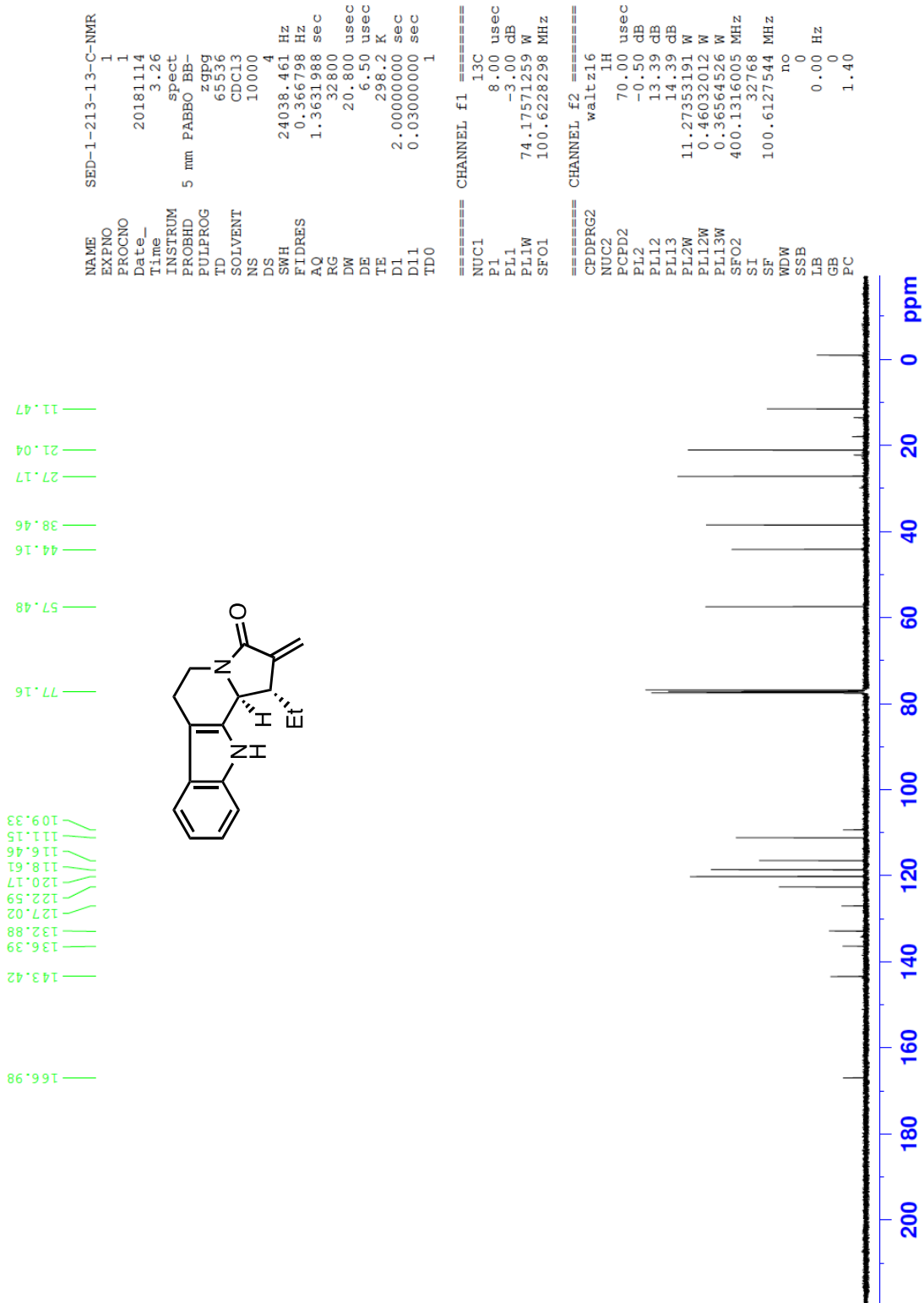


Figure 55. ¹³C-NMR spectrum of compound 15.

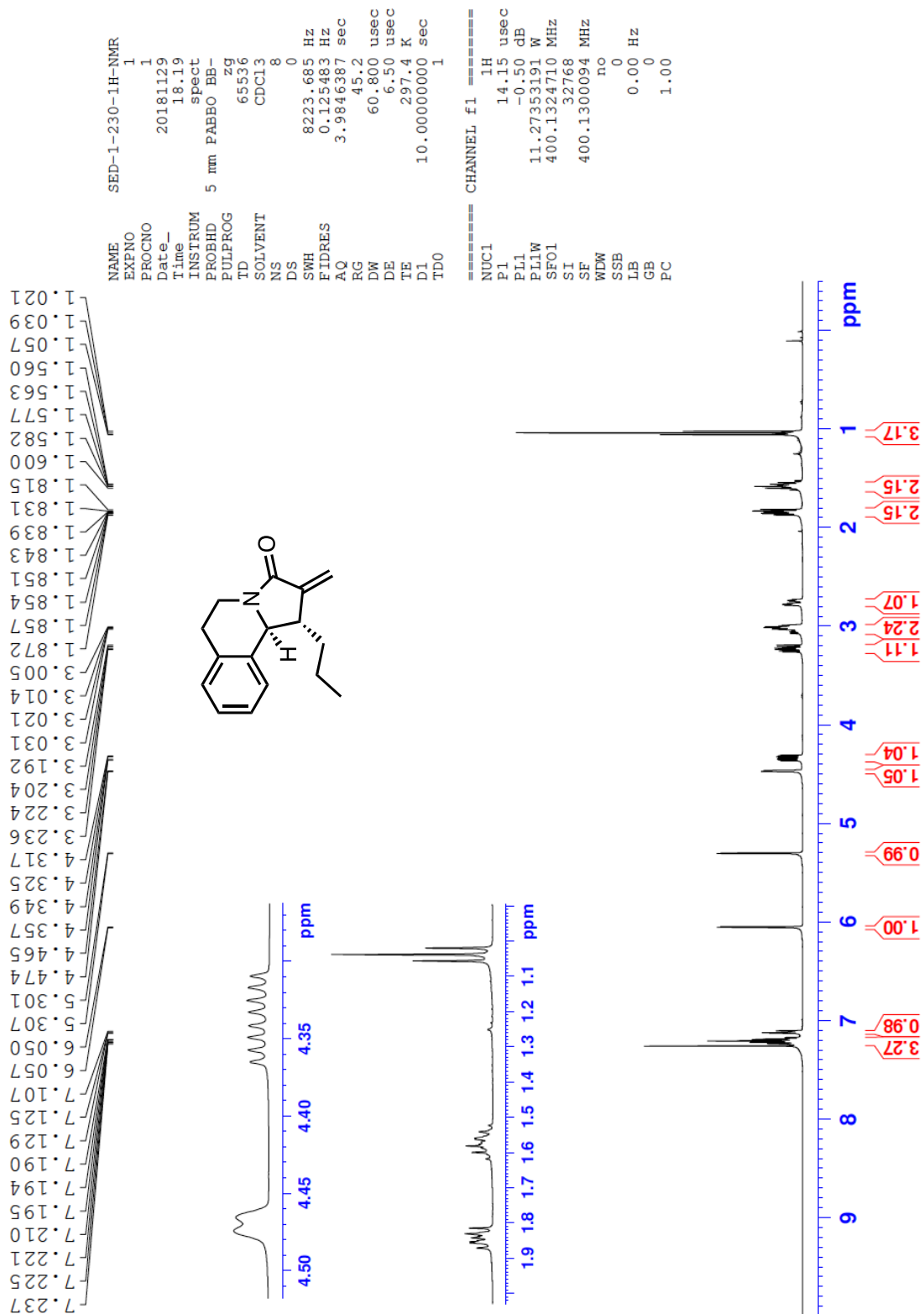


Figure 56. ^1H -NMR spectrum of compound 19.

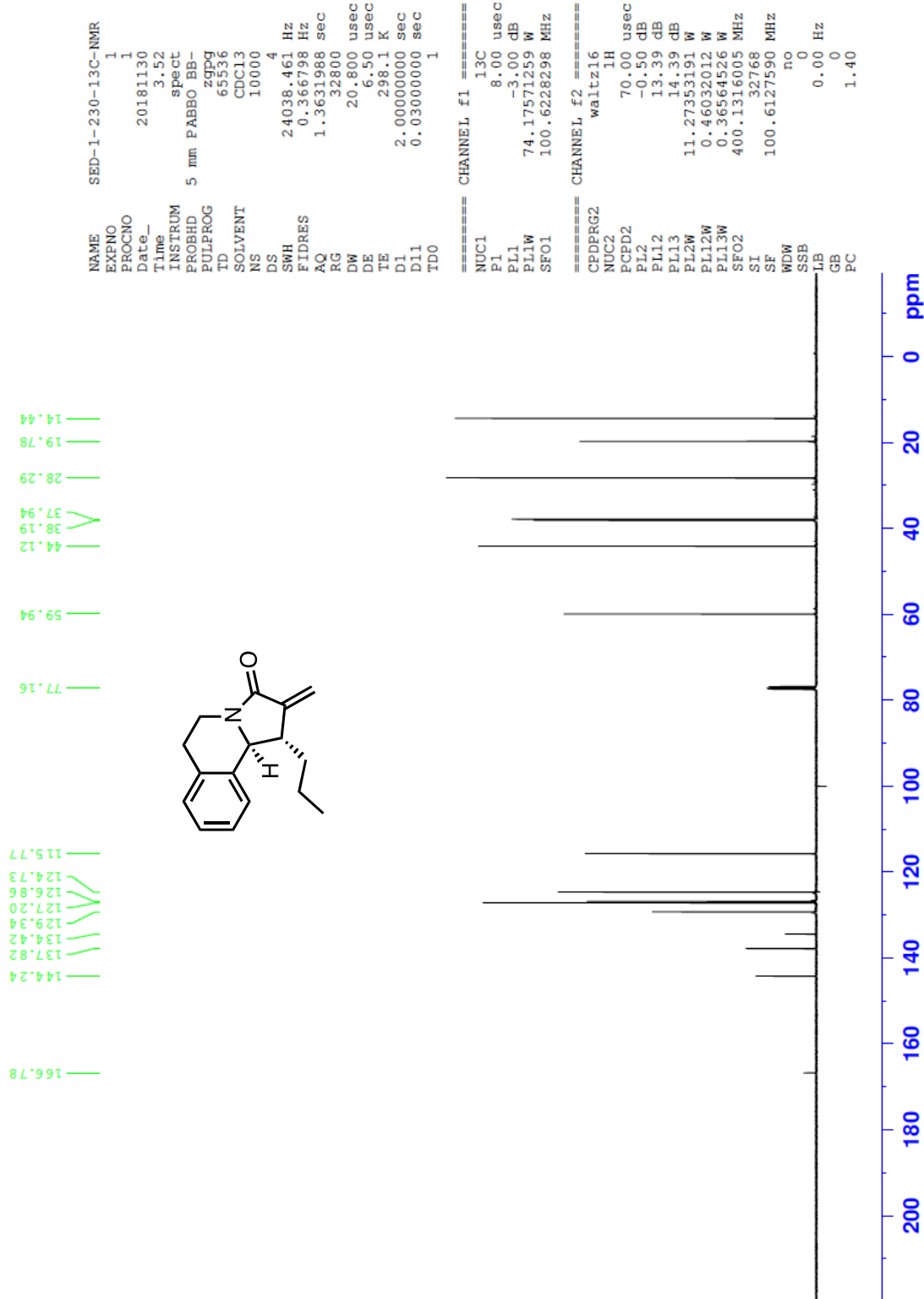


Figure 57. ^{13}C -NMR spectrum of compound **19**.

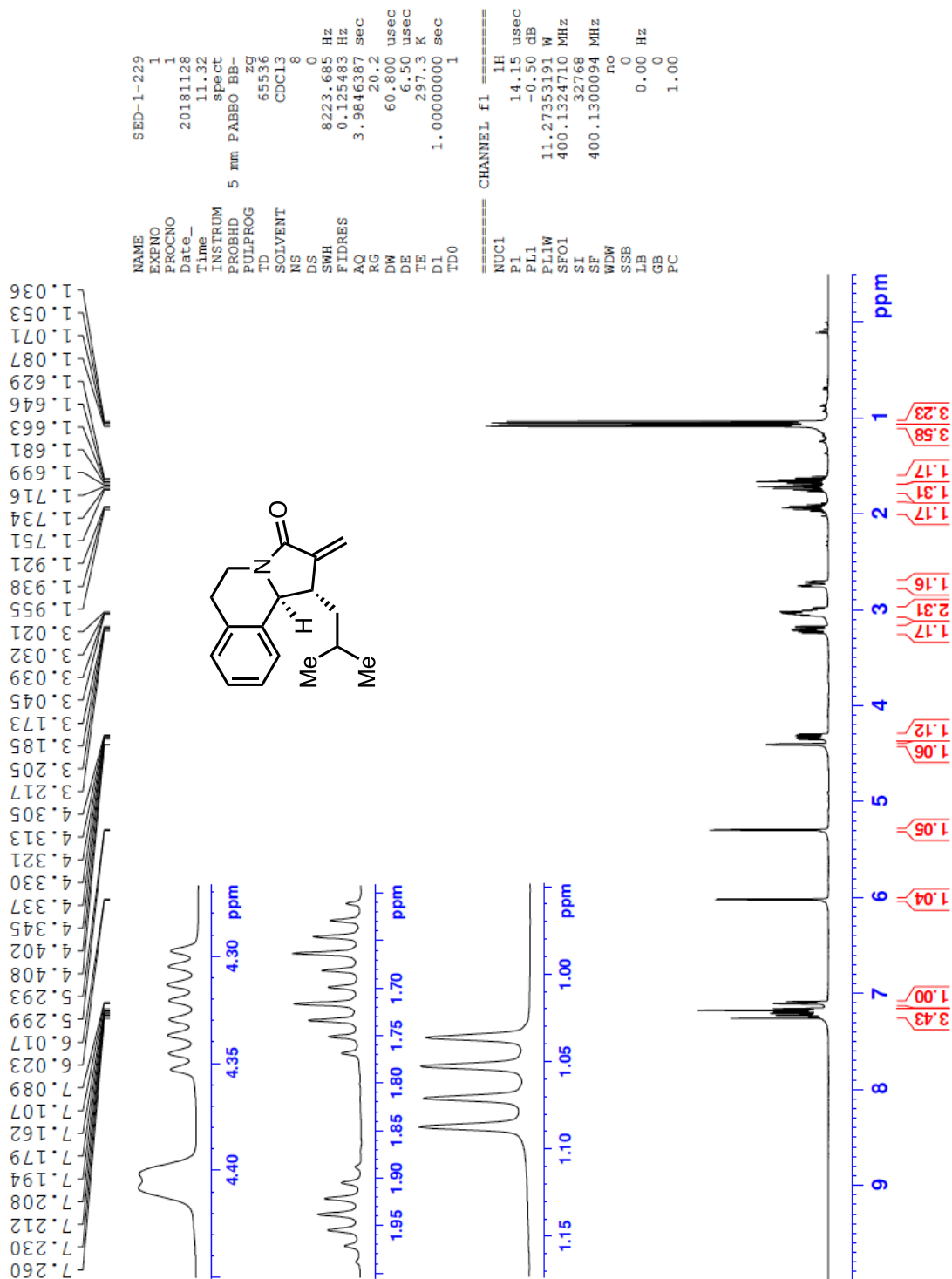


Figure 58. ^1H -NMR spectrum of compound 20.

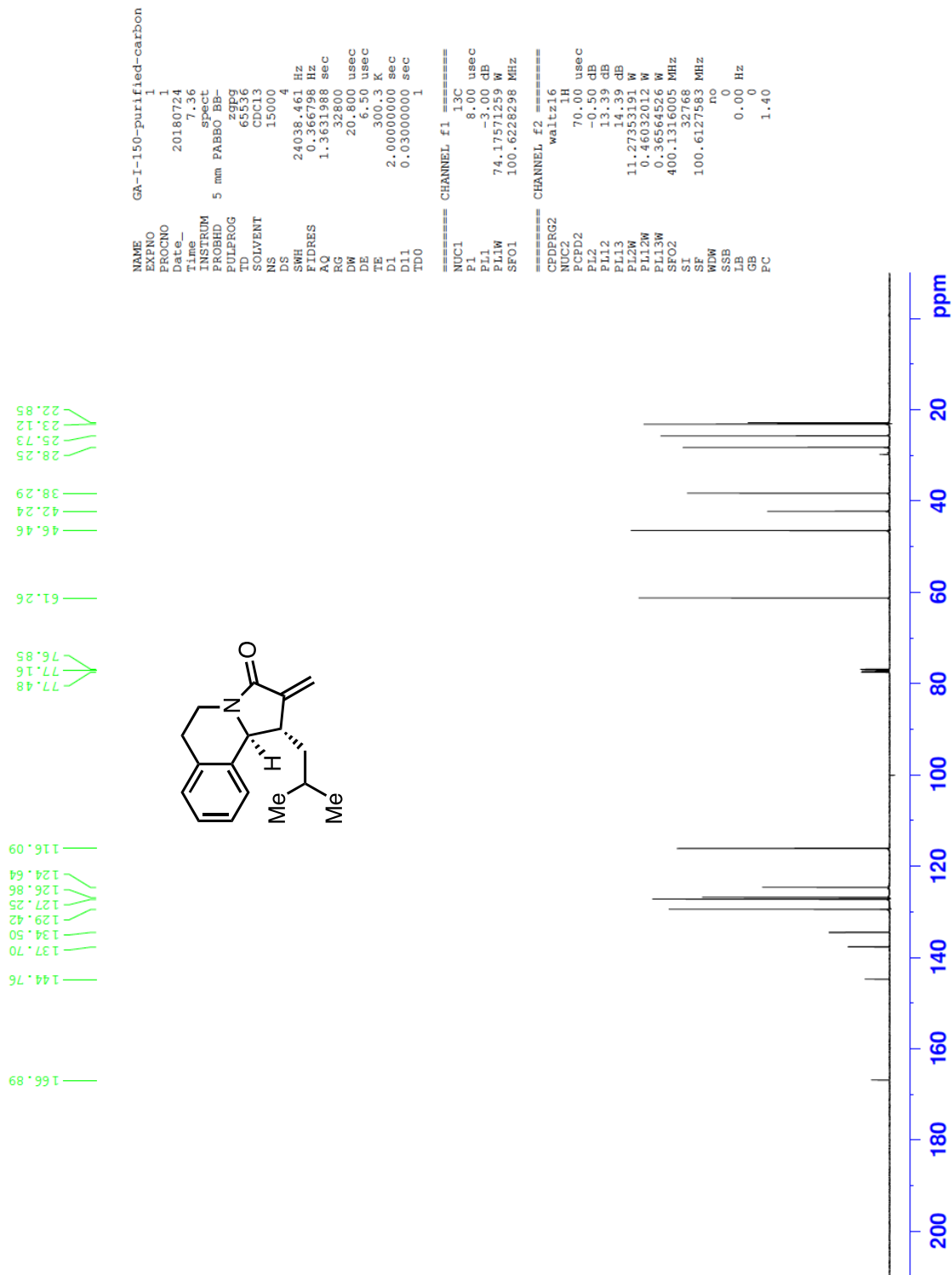


Figure 59. ^{13}C -NMR spectrum of compound 20.

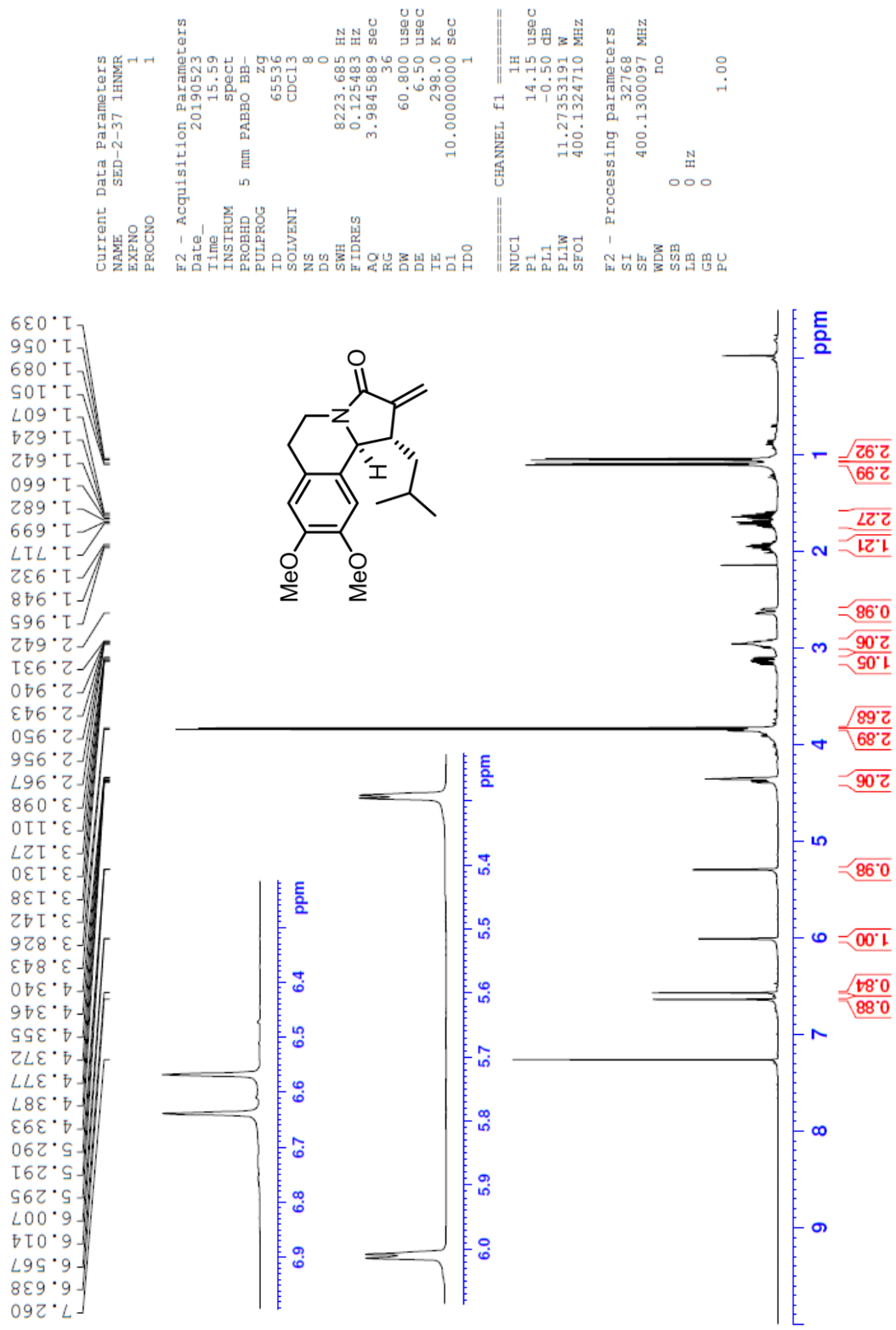


Figure 60. ¹H-NMR spectrum of compound 30.

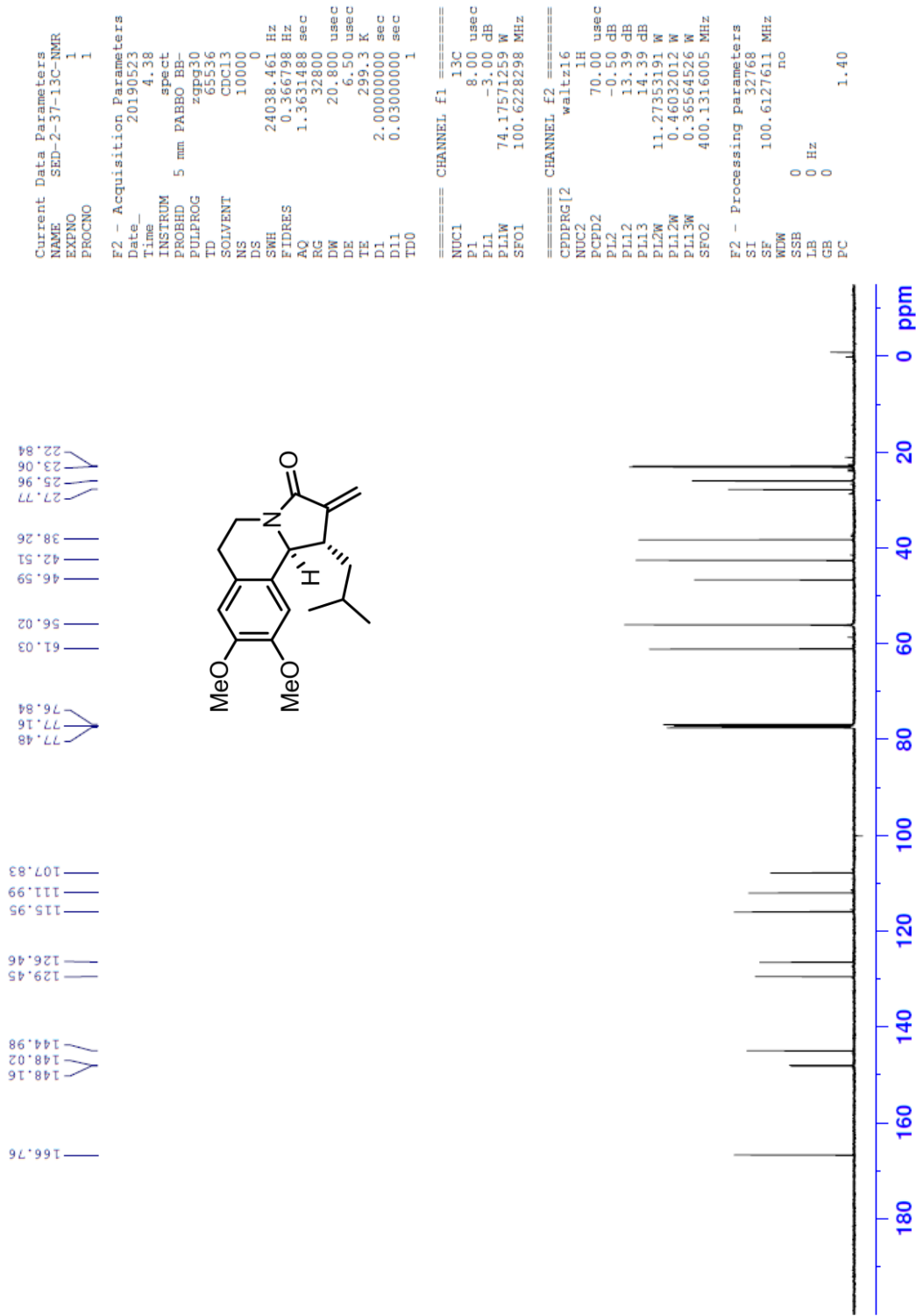


Figure 61. ¹³C-NMR spectrum of compound 30.

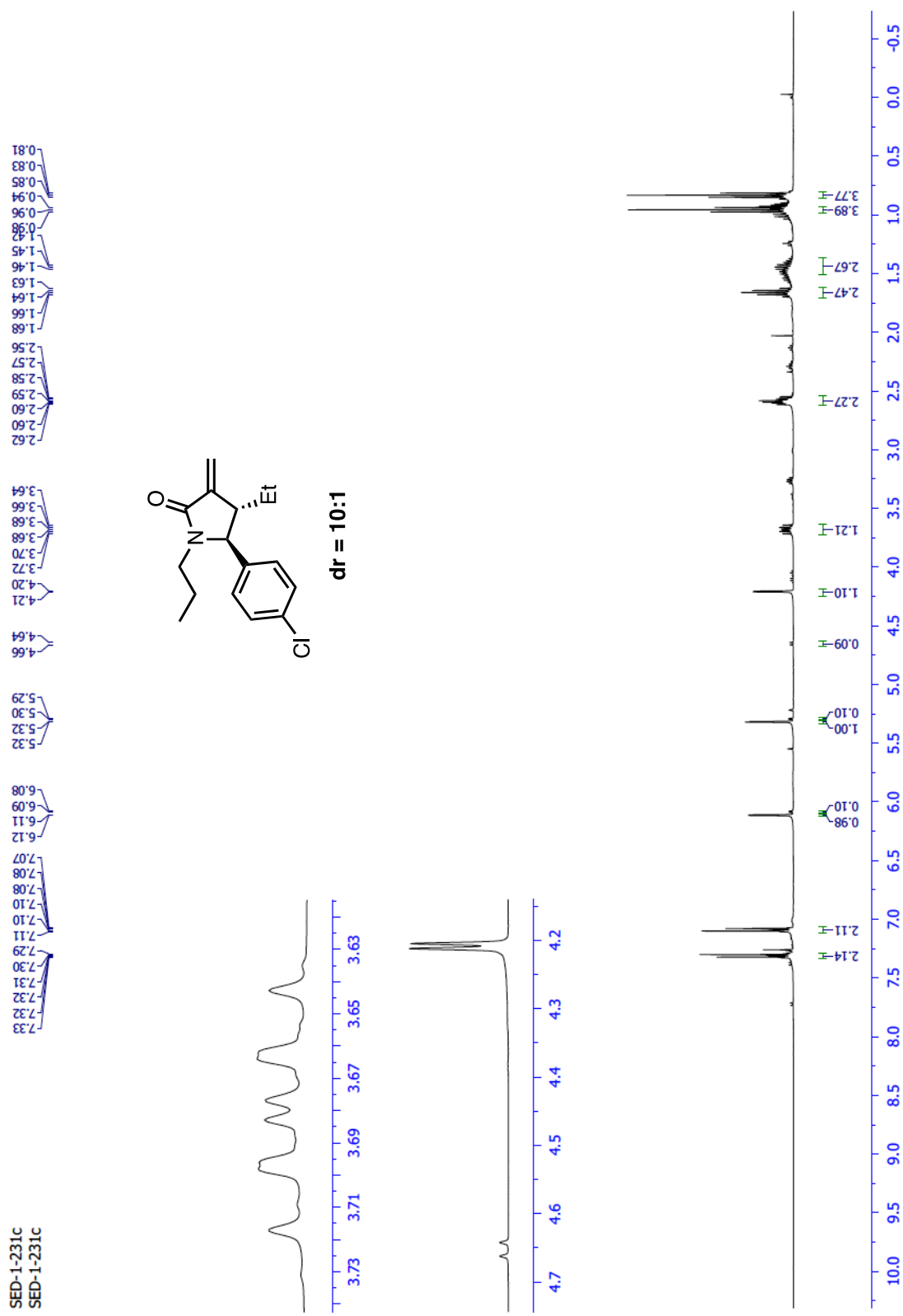


Figure 62. $^1\text{H-NMR}$ spectrum of compound 21.

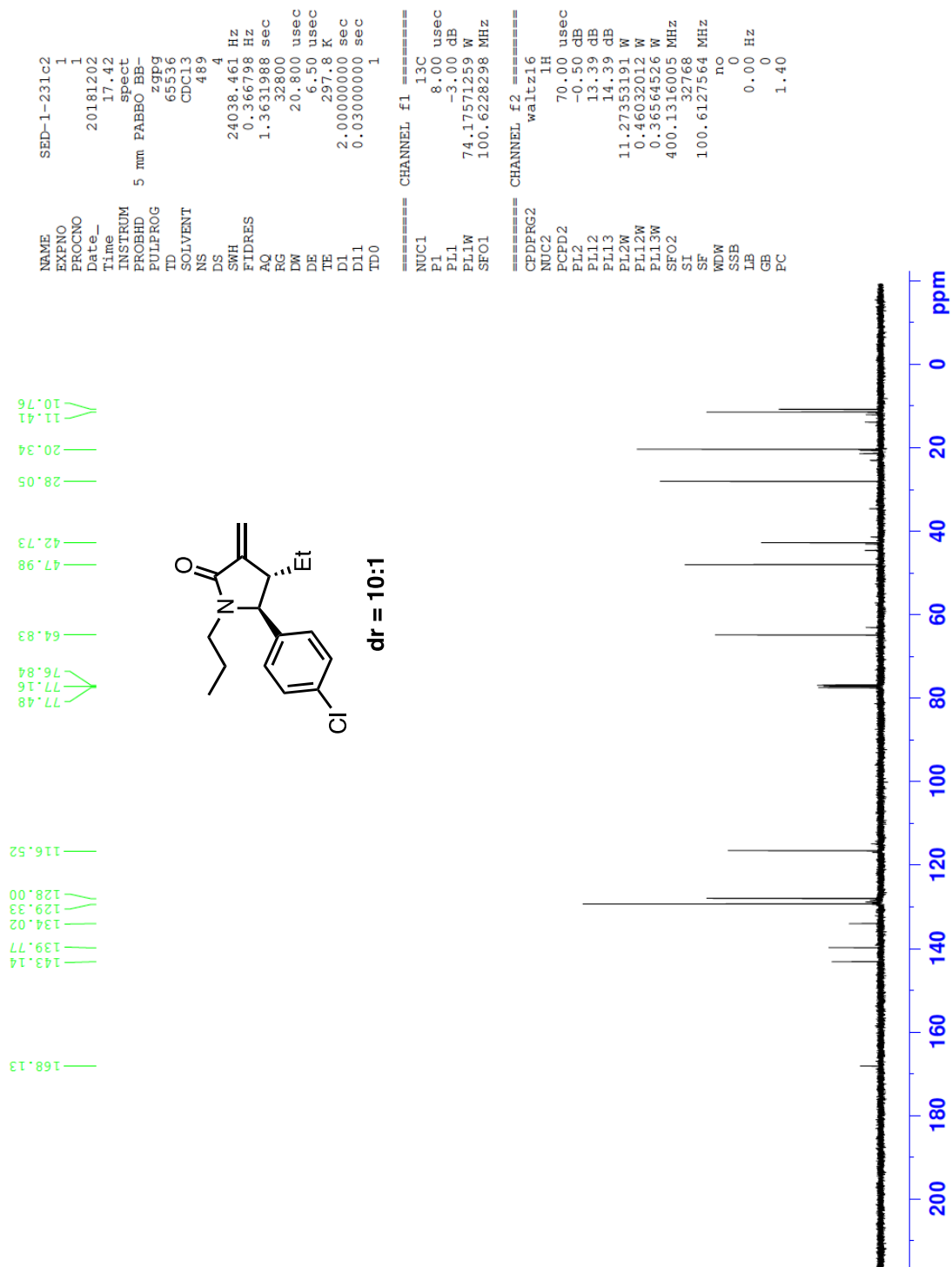


Figure 63. ^{13}C -NMR spectrum of compound 21.

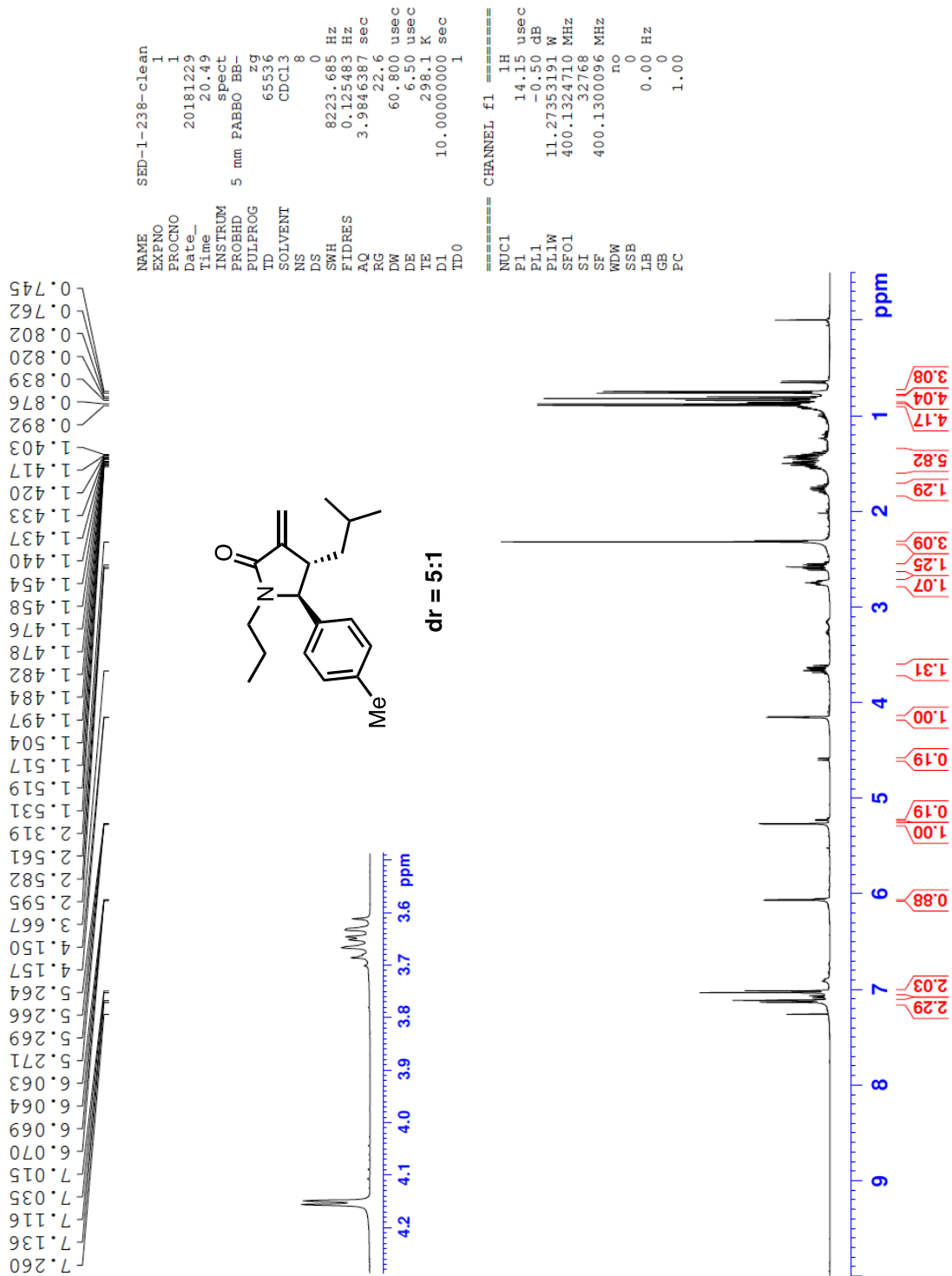


Figure 64. 1H -NMR spectrum of compound 22.

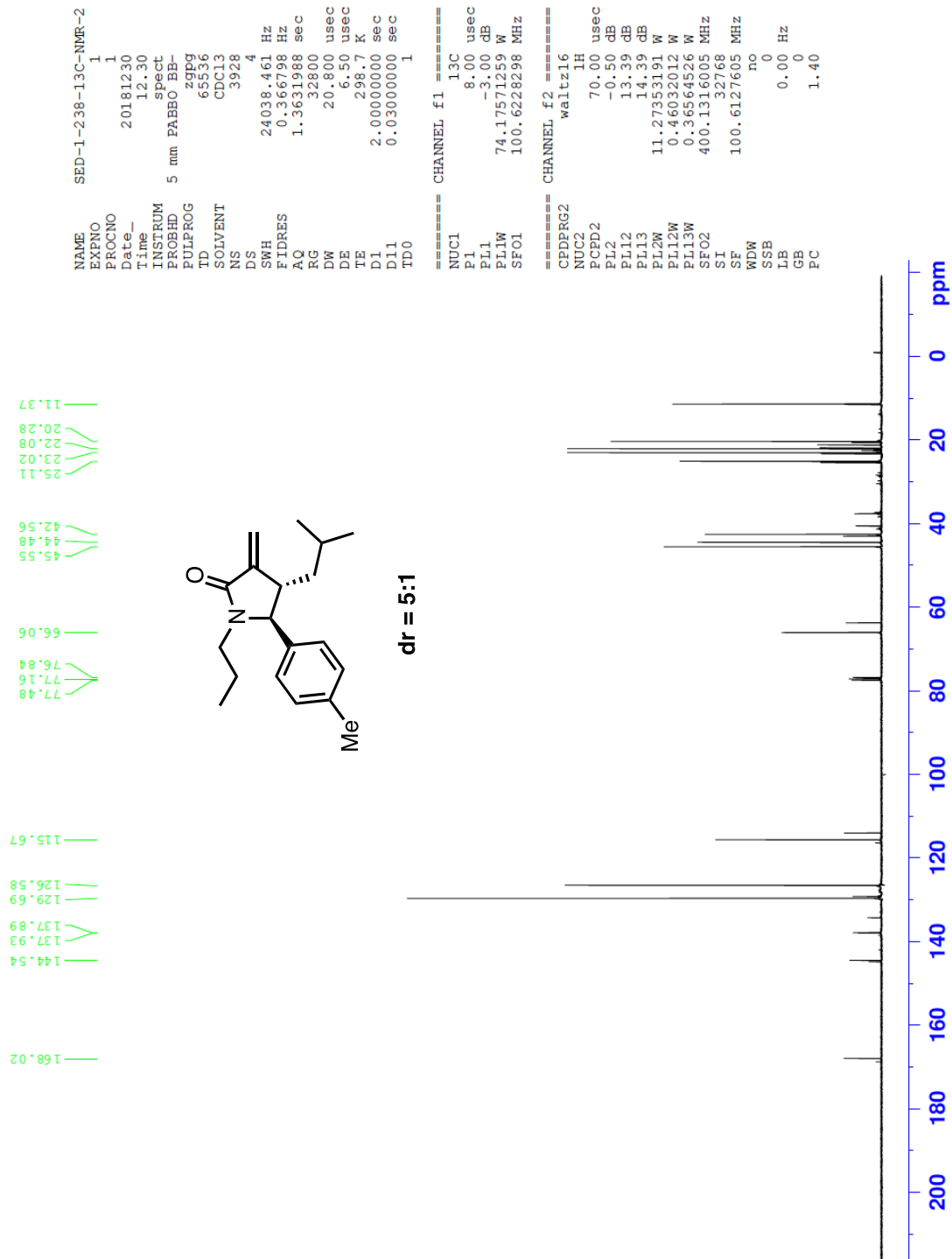


Figure 65. ^{13}C -NMR spectrum of compound 22.

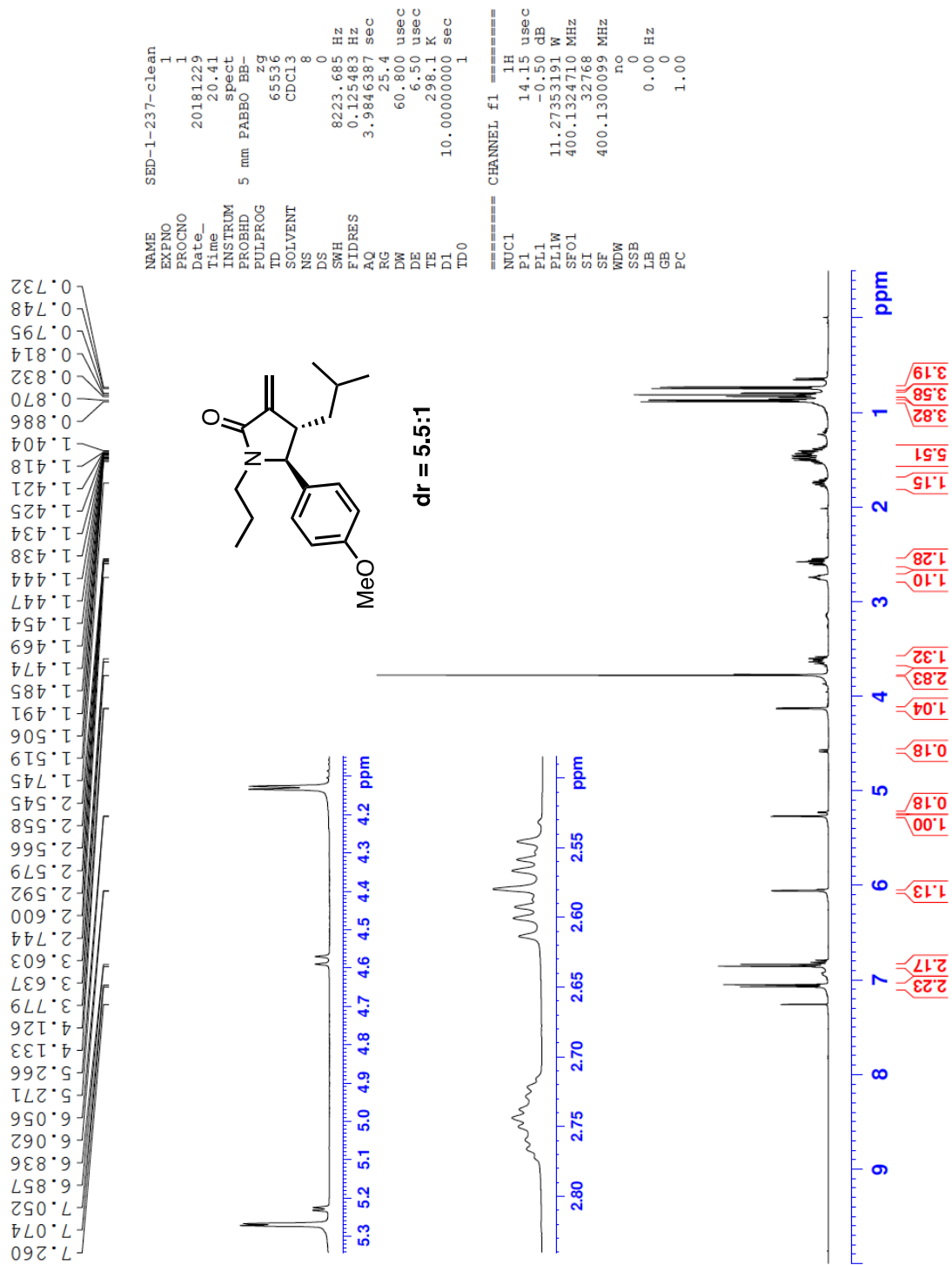


Figure 66. ¹H-NMR spectrum of compound 23.

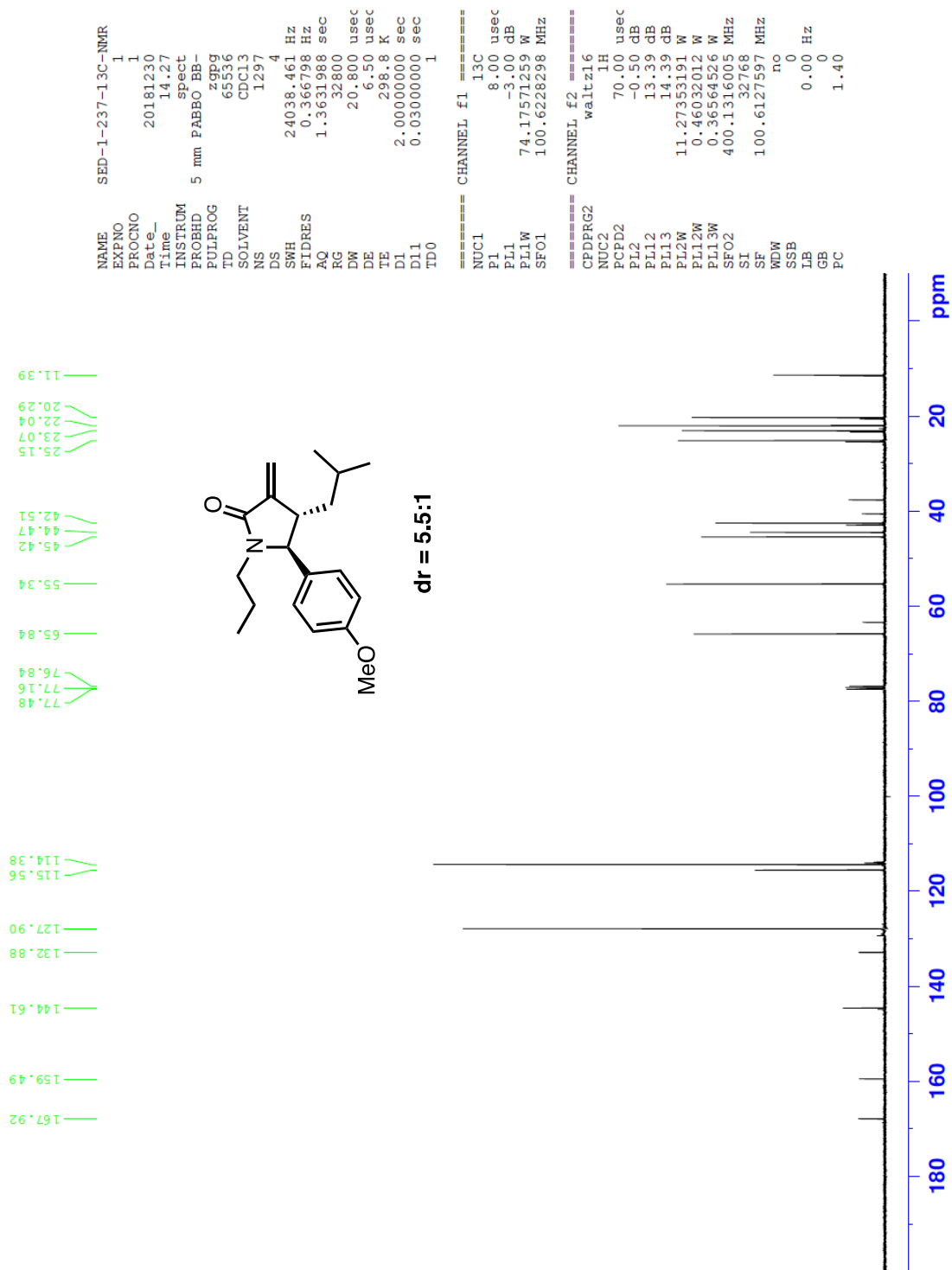


Figure 67. ^{13}C -NMR spectrum of compound 23.

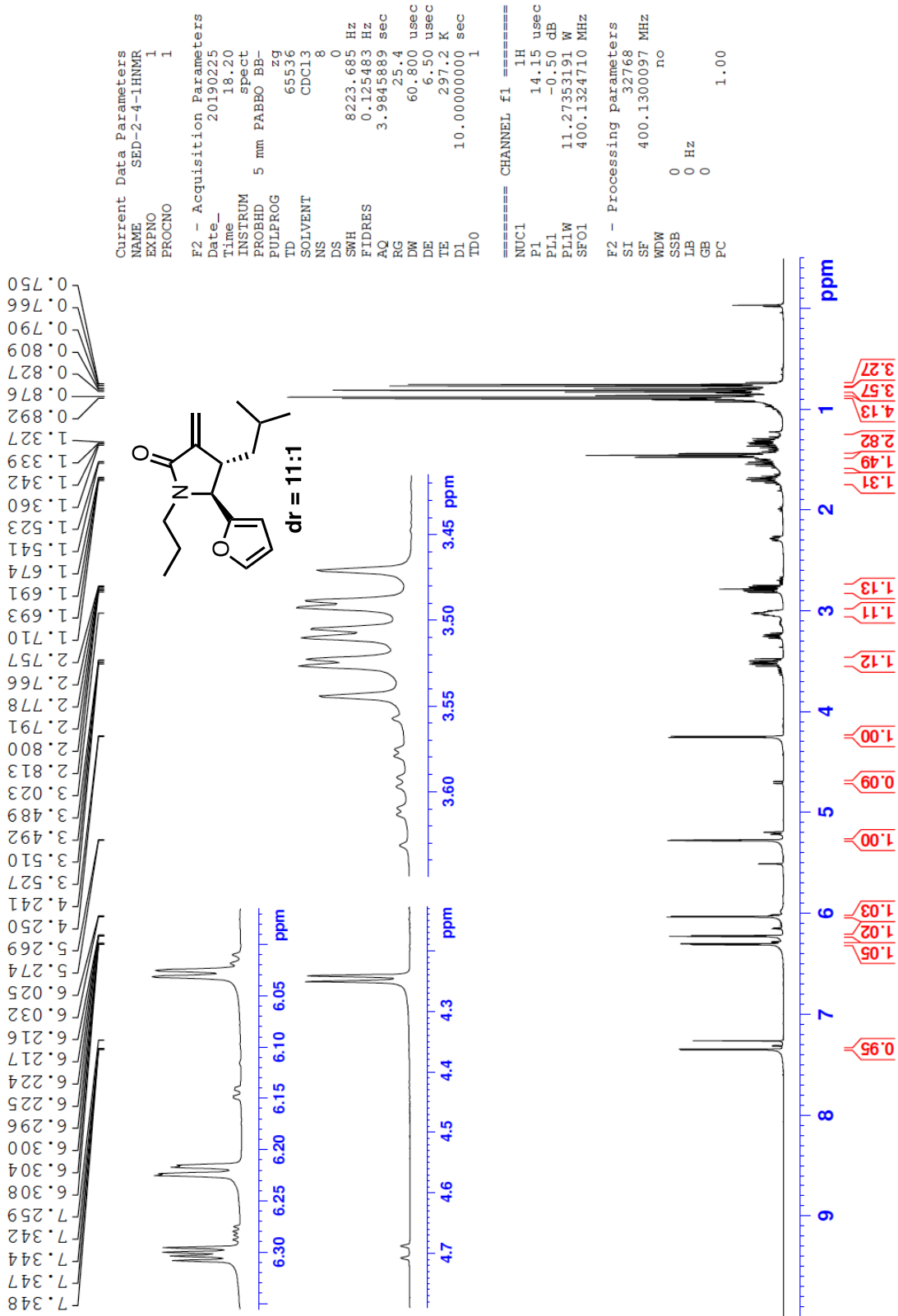


Figure 68. ¹H-NMR spectrum of compound 24.

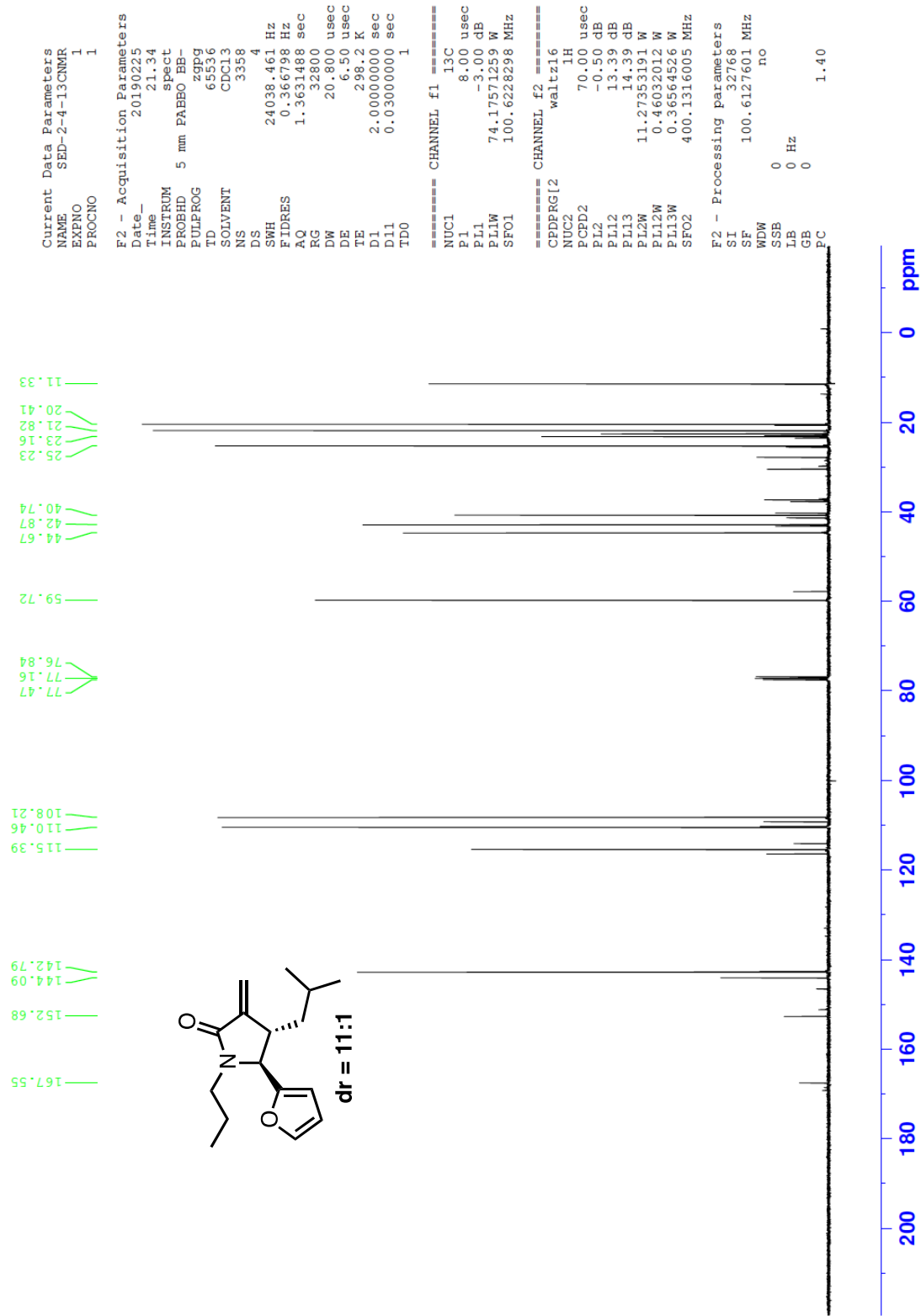


Figure 69. ¹³C-NMR spectrum of compound 24.

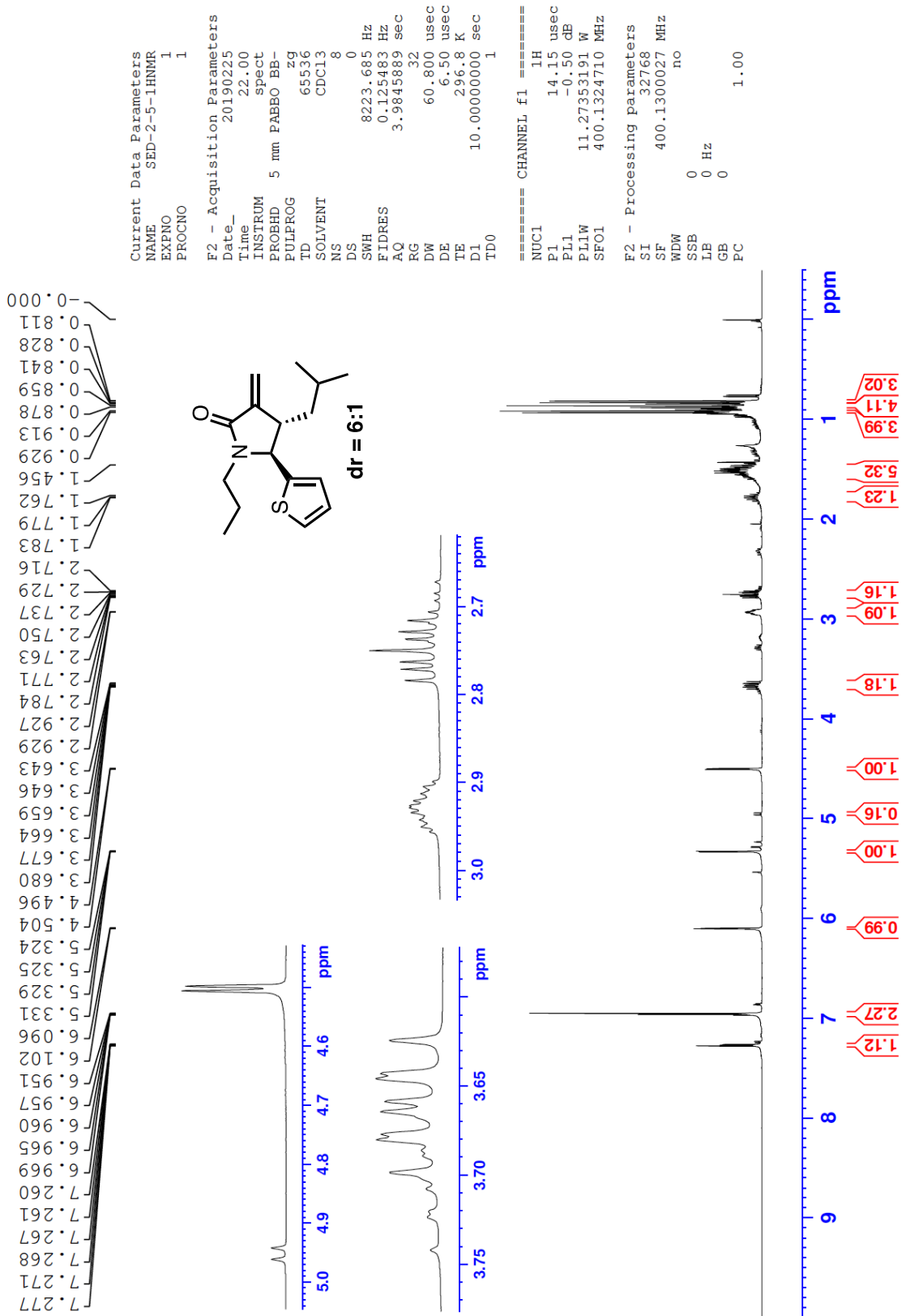


Figure 70. ¹H-NMR spectrum of compound 25.

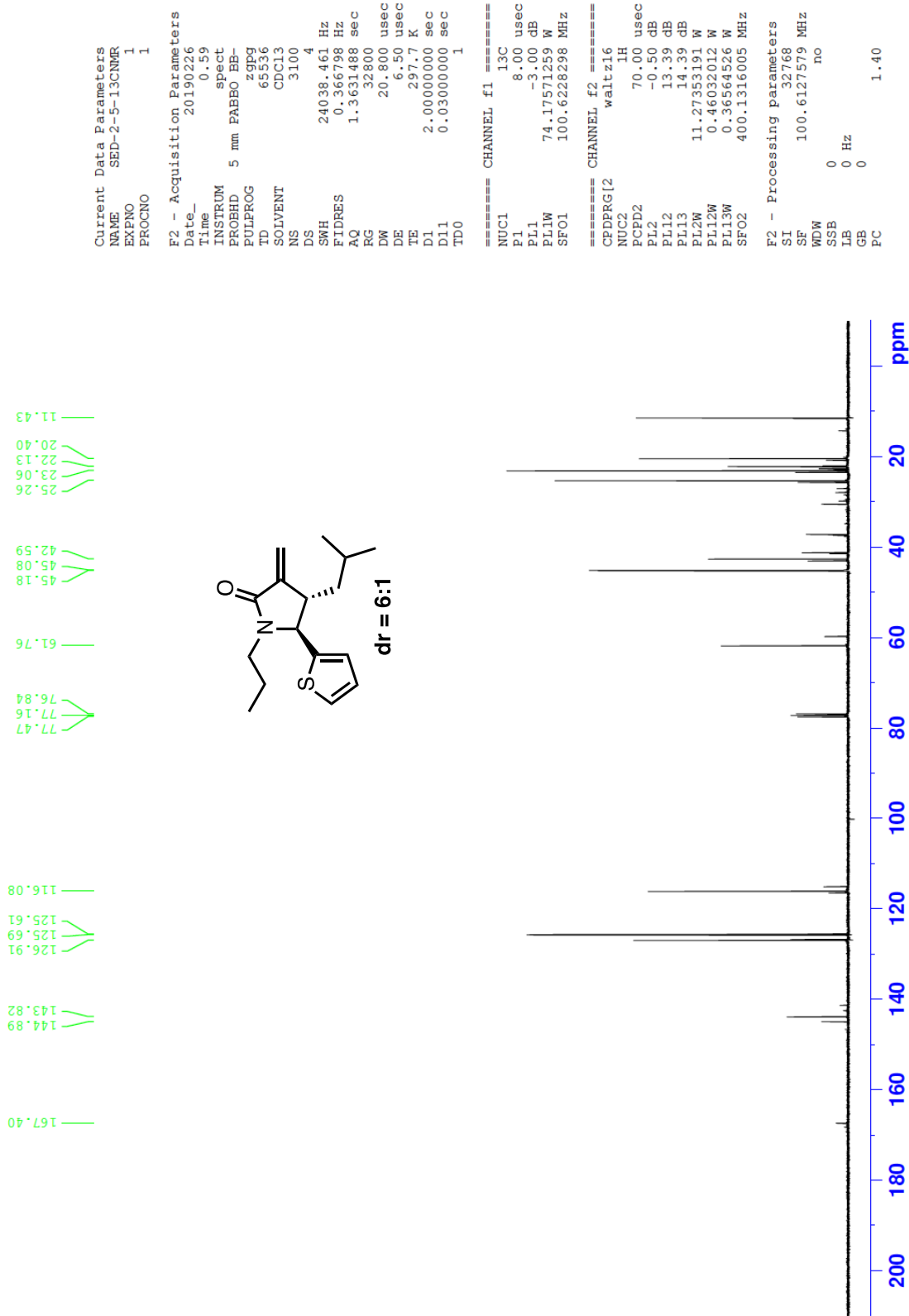


Figure 71. ¹³C-NMR spectrum of compound 25.

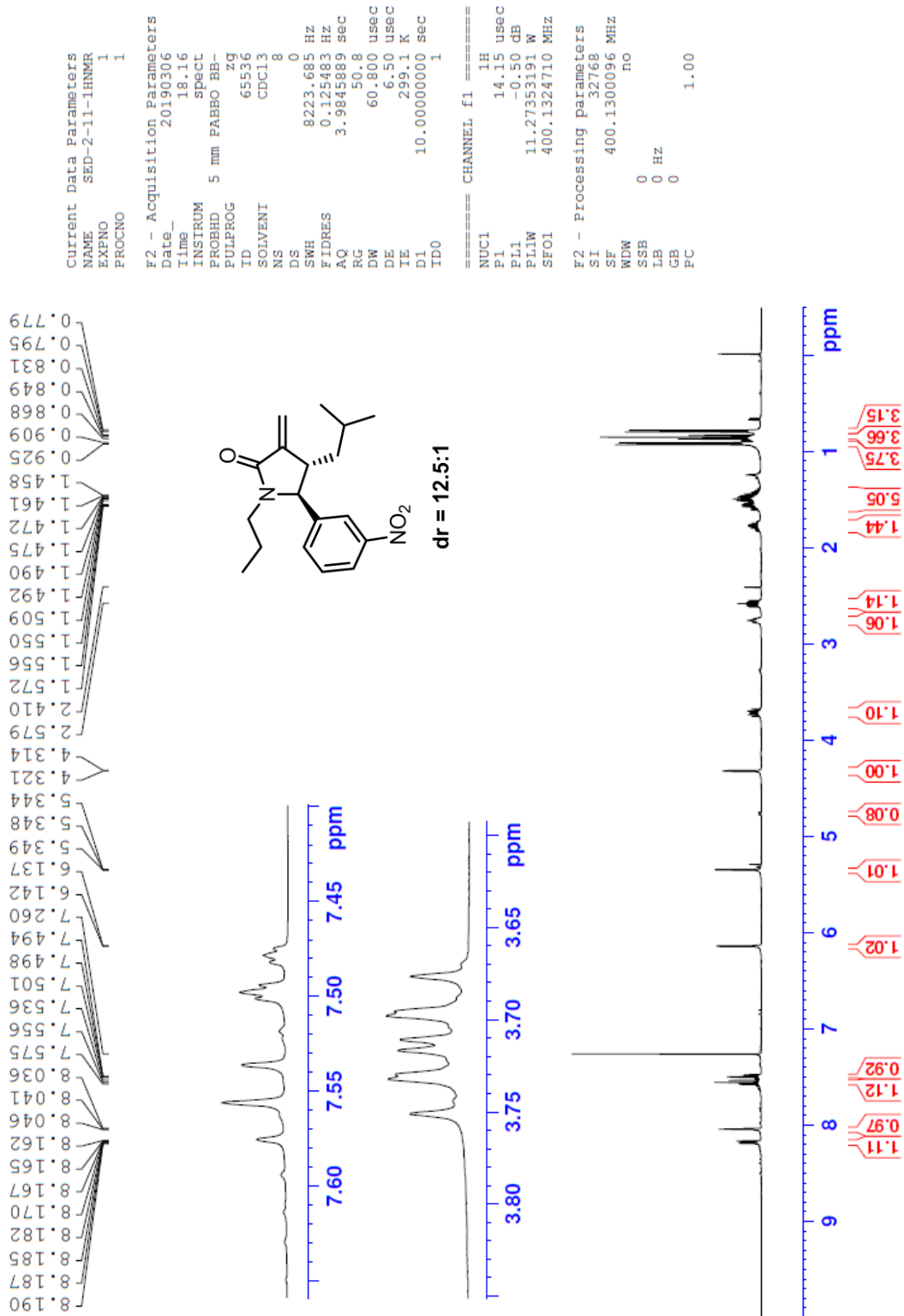


Figure 72. ¹H-NMR spectrum of compound 26.

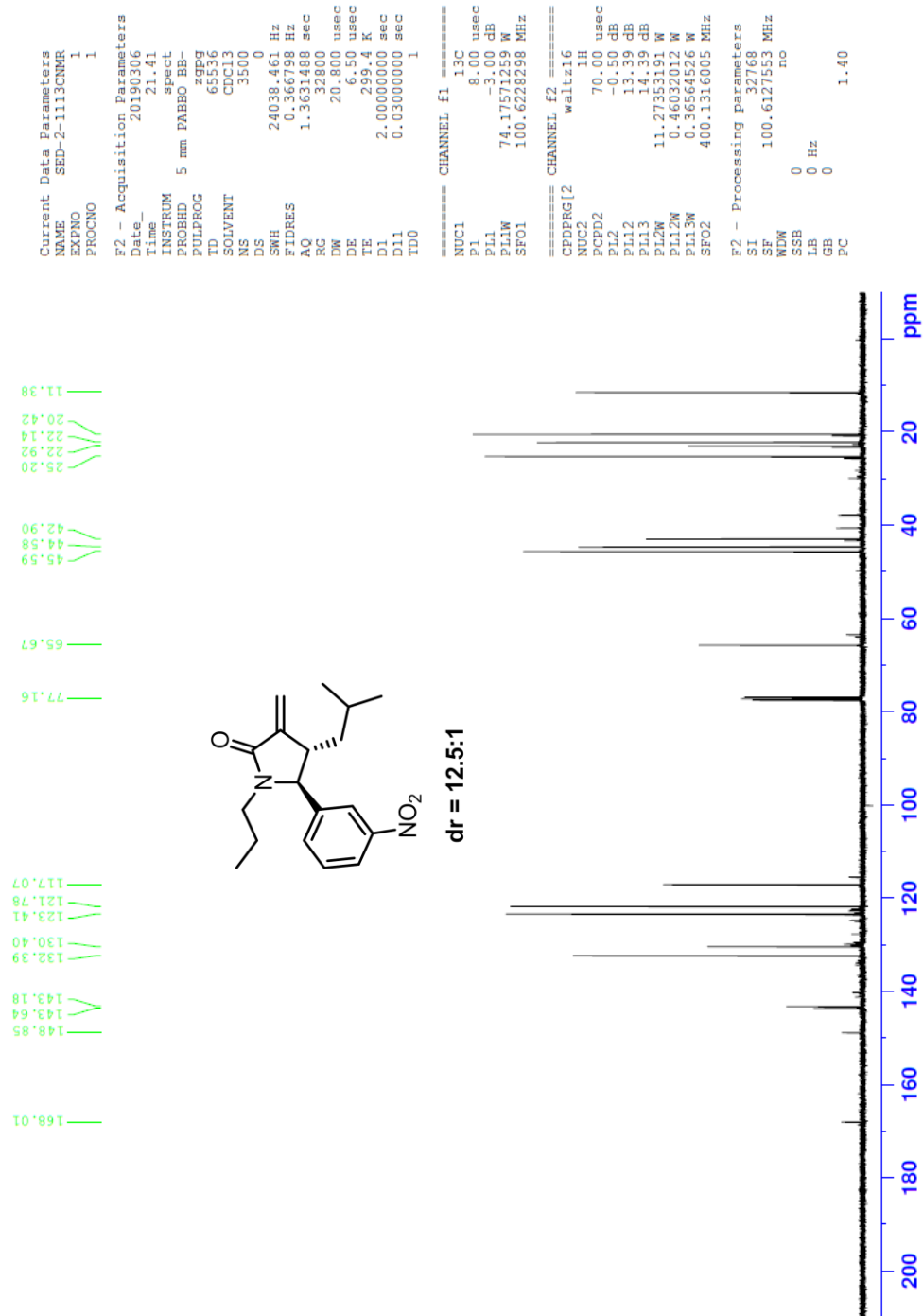


Figure 73. ^{13}C -NMR spectrum of compound 26.

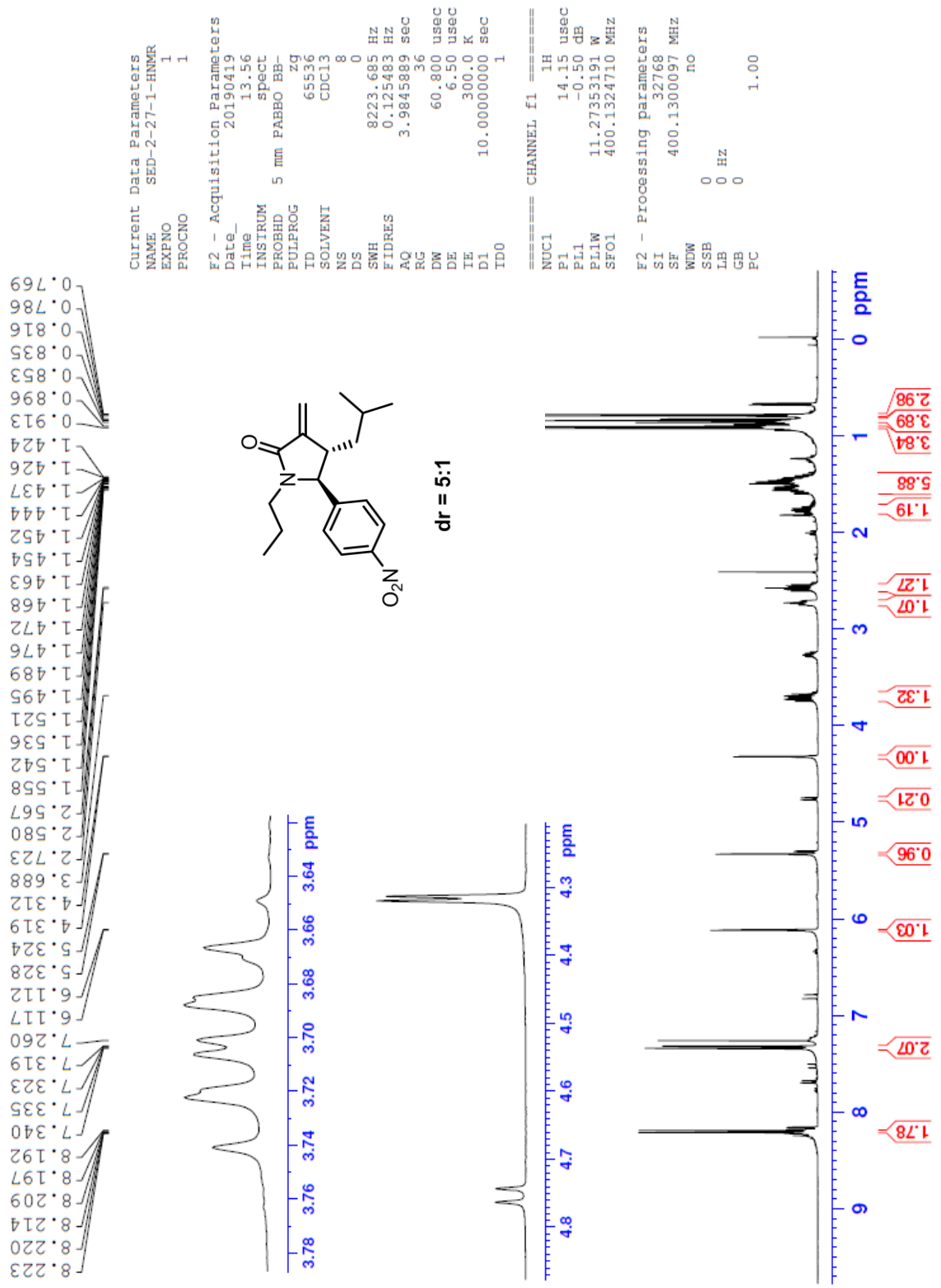


Figure 74. ¹H-NMR spectrum of compound 27.

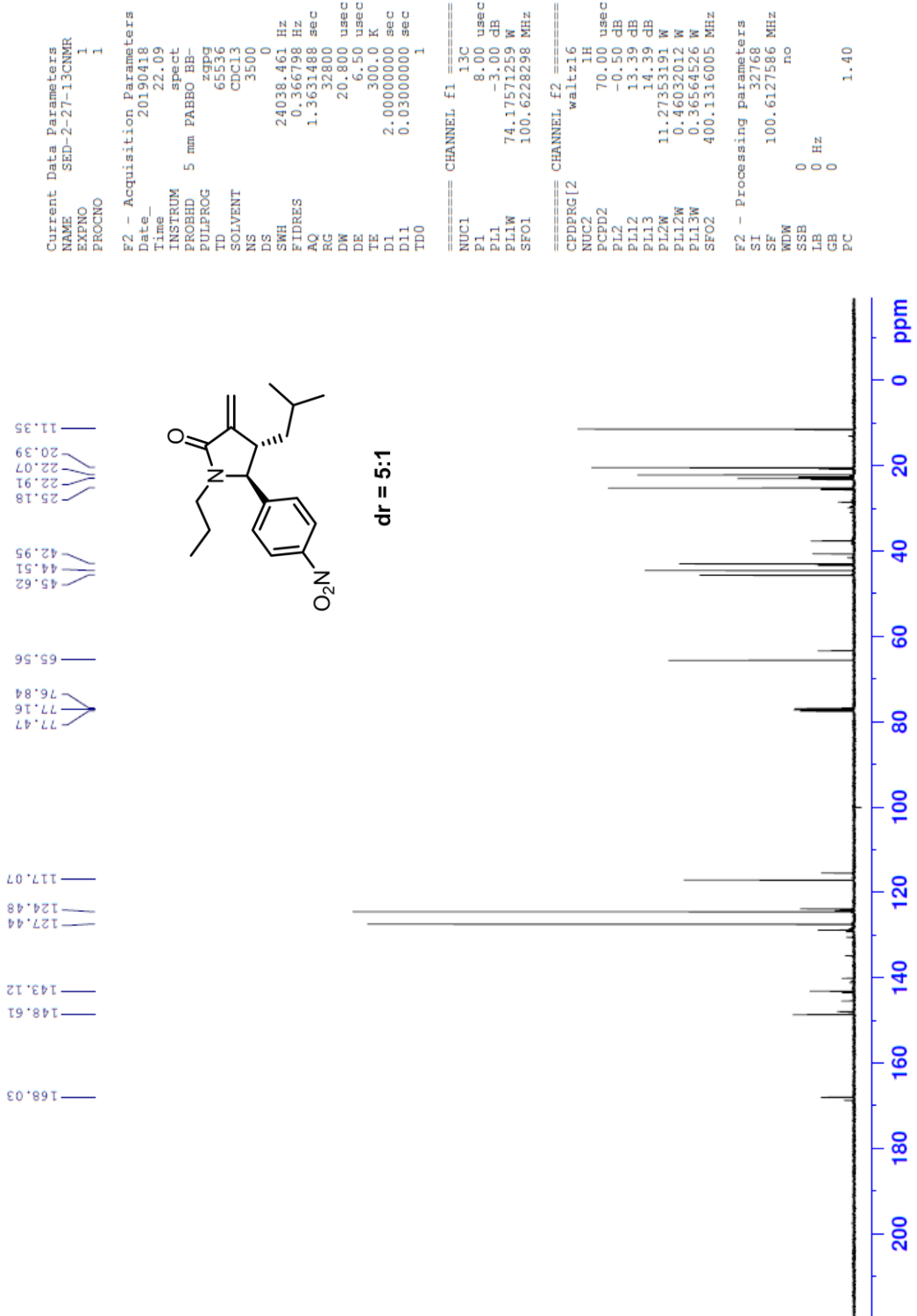


Figure 75. ^{13}C -NMR spectrum of compound **27**.

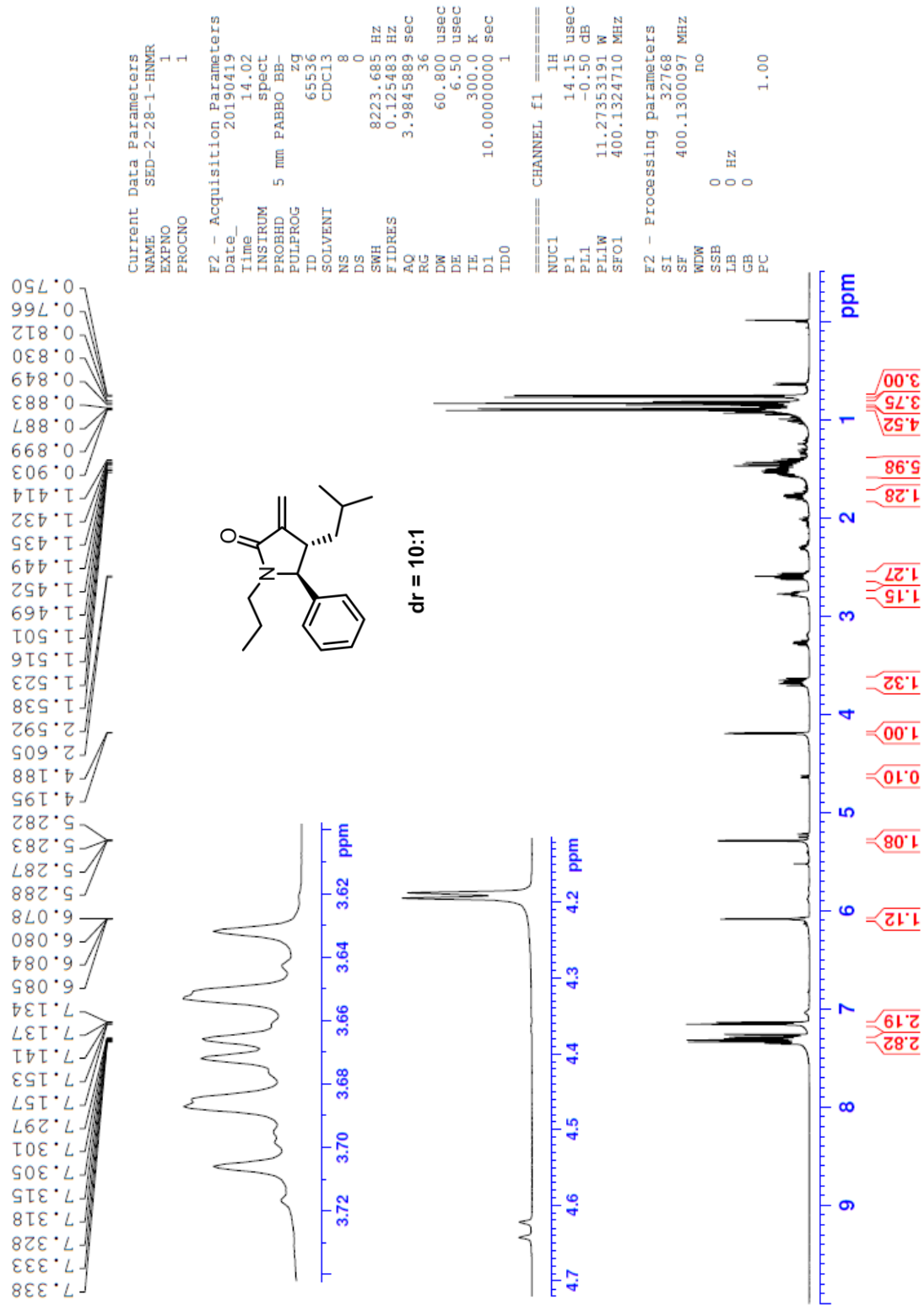


Figure 76. ¹H-NMR spectrum of compound 28.

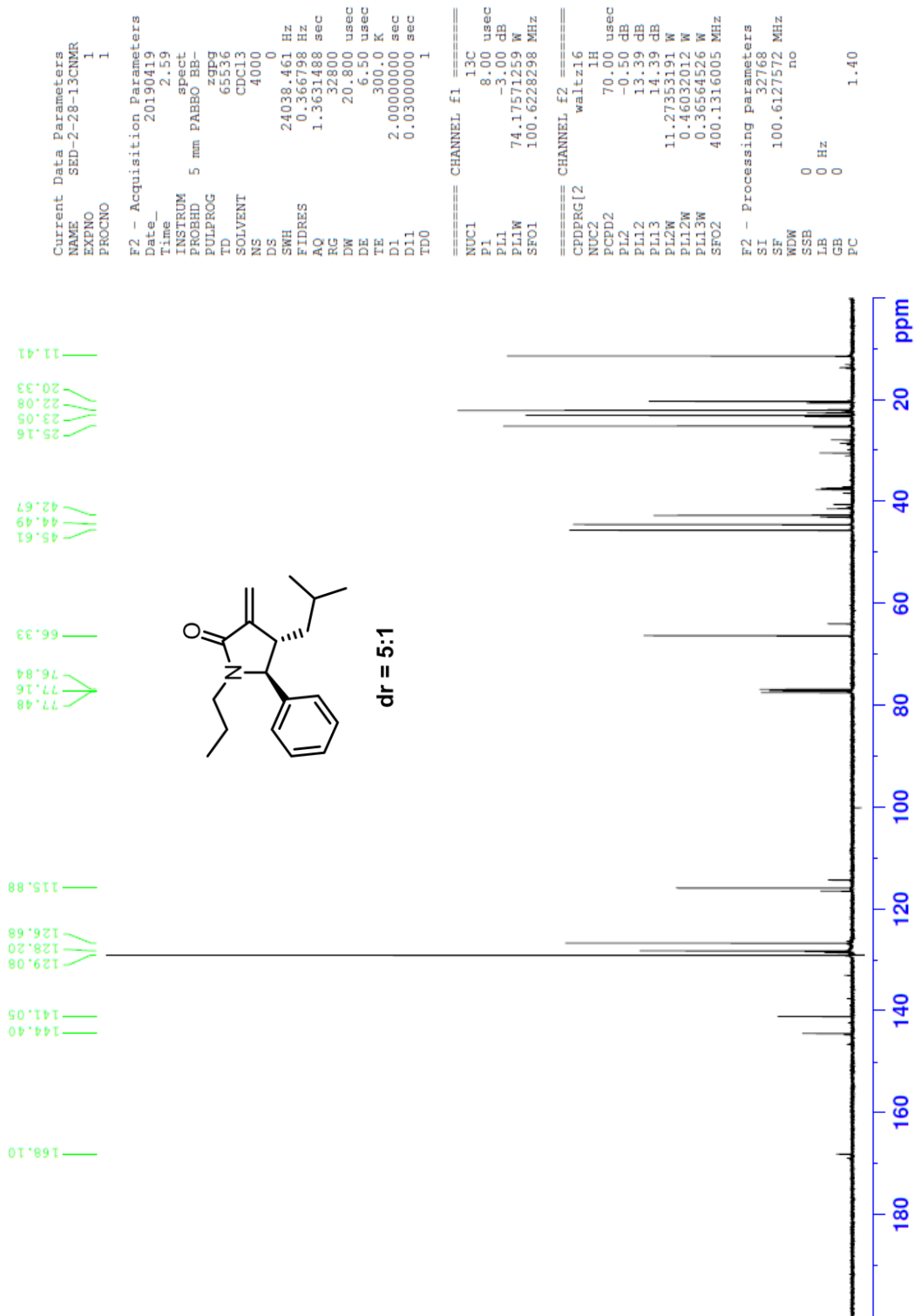


Figure 77. ¹³C-NMR spectrum of compound 28.

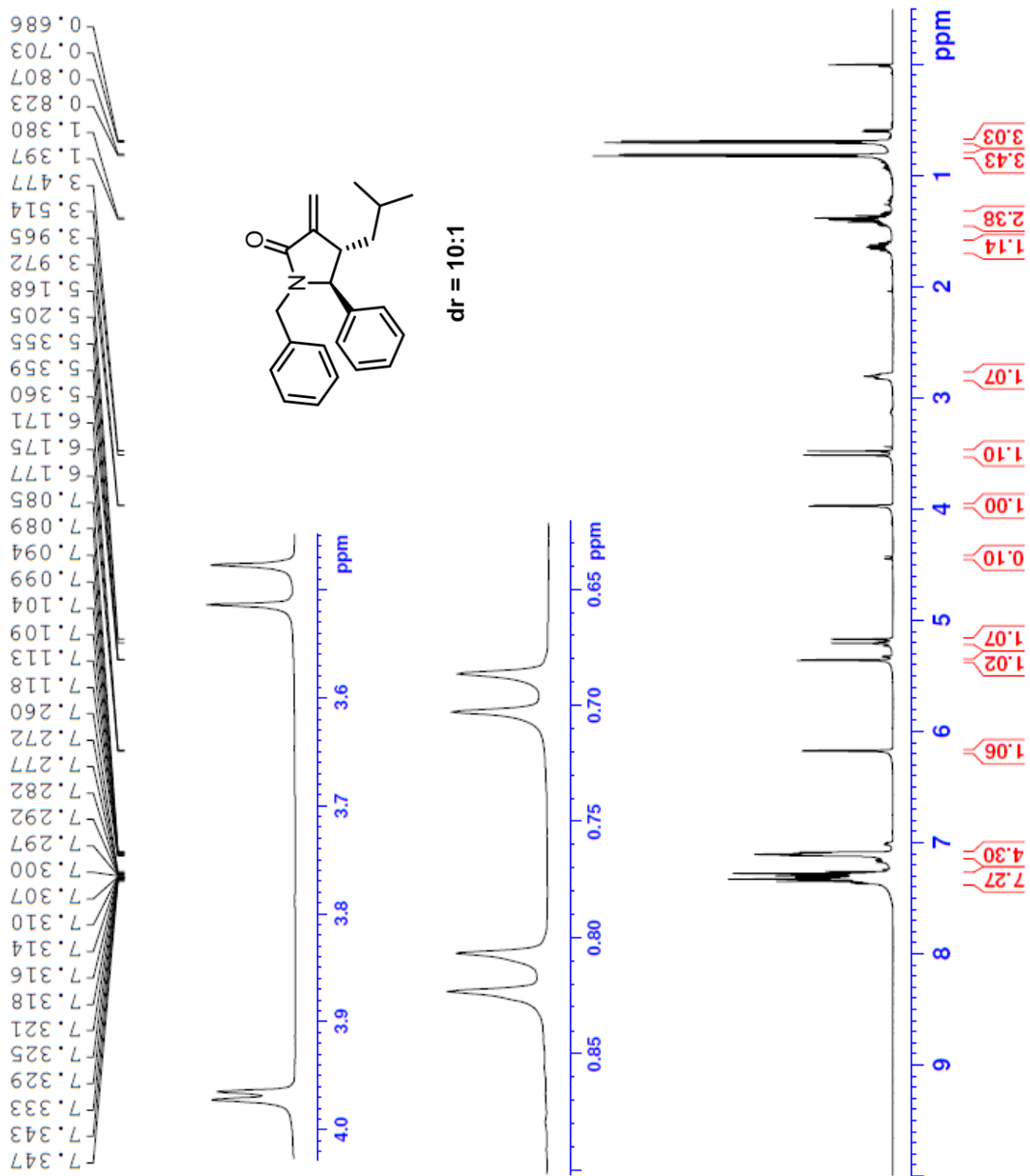


Figure 78. ¹H-NMR spectrum of compound 29.

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Current Data Parameters
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EXPNO 1
PROCNO 1

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Time_ 22.30
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TD 65536
SOLVENT CDCl3
NS 4000
DS 0
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3831488 sec
RG 32800
DW 20.800 usec
DE 6.50 usec
TE 299.0 K
D1 2.0000000 sec
D11 0.0300000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 13C
P1 8.00 usec
PL1 -3.00 dB
PL1W 74.17571259 W
SFO1 100.6228298 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PL2 -0.50 dB
PL12 13.59 dB
PL13 14.39 dB
PL12W 11.27353191 W
PL12W 0.46032012 W
PL13W 0.36564526 W
SFO2 400.1316005 MHz

F2 - Processing Parameters
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SSB 0
LB 0 Hz
GB 0
PC 1.40

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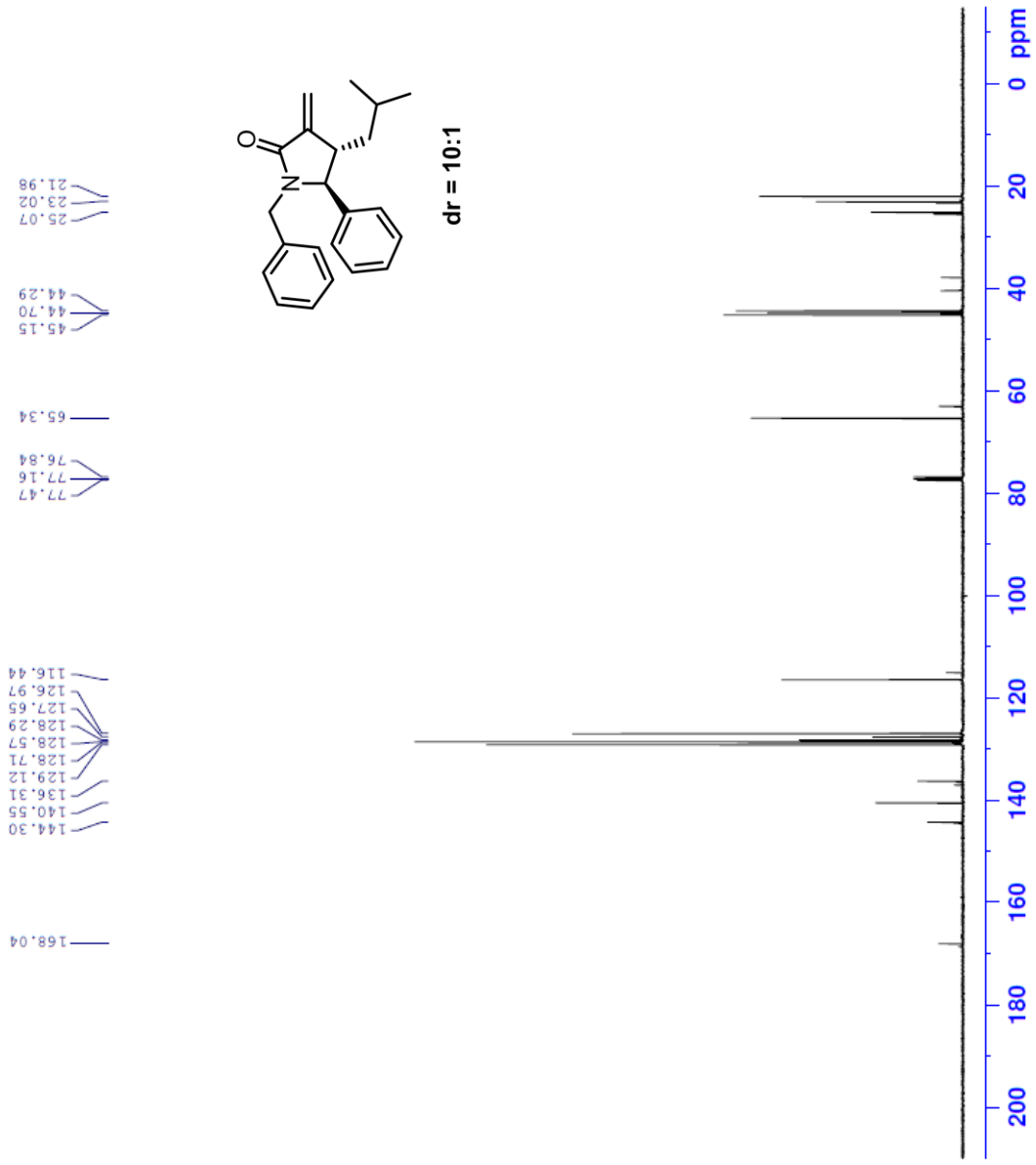


Figure 79. ¹³C-NMR spectrum of compound 29.

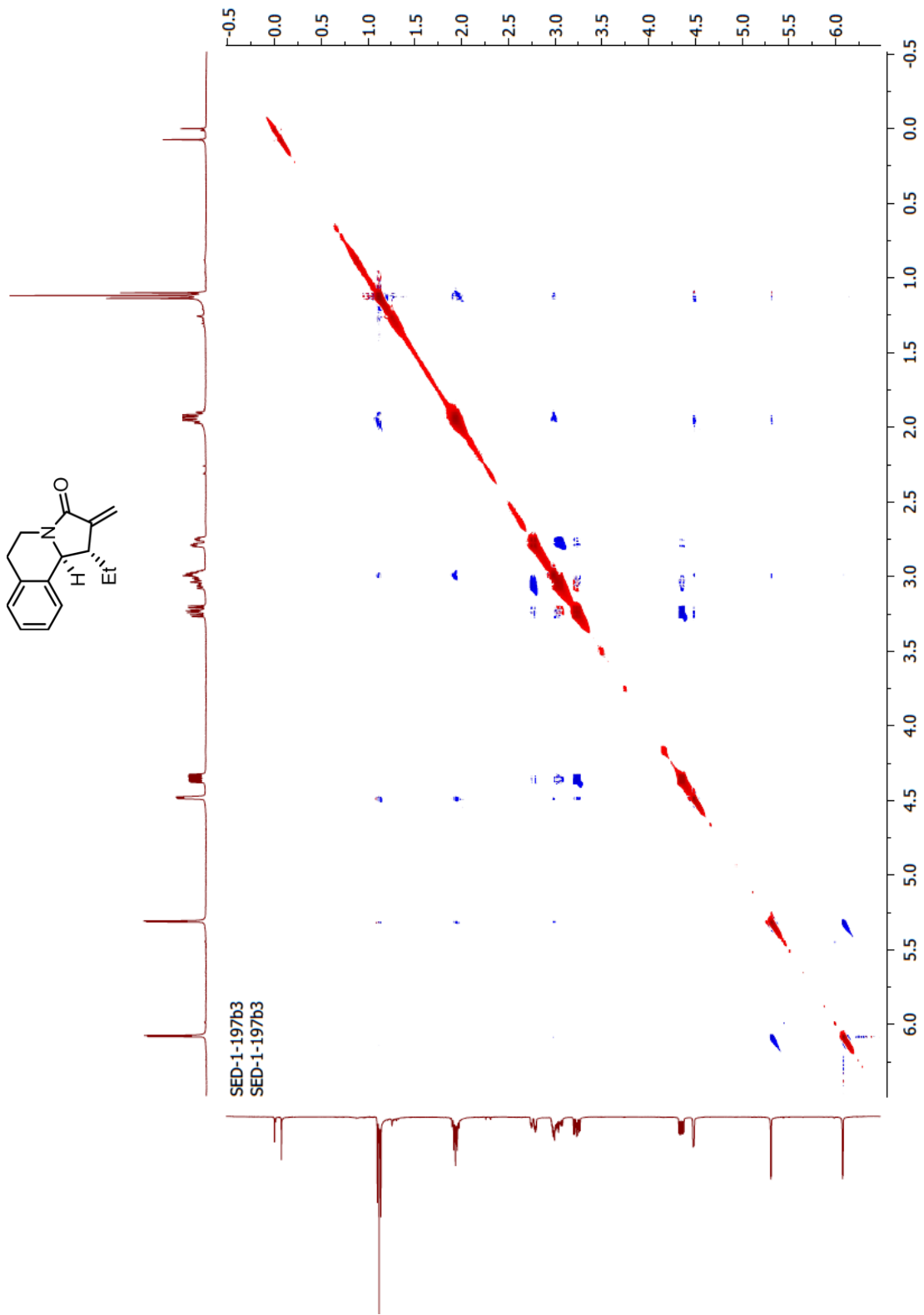


Figure 80. NOESY spectrum of compound **3**.