Investigation of the nitronate Nazarov cyclization

By

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Abstract

The Nazarov cyclization is a common synthetic tool in the synthesis of cyclopentenone rings. The reaction is characterized by a divinyl ketone starting reagent that undergoes a 4π-electron electrocyclization after addition of a Lewis/Brønsted acid; forming the cyclopentadienyl cation that undergoes cyclization. An extension of this methodology involves using a divinyl imine starting reagent. This cyclization is less favoured due to the electron donating ability of the nitrogen atom, causing the pentadienyl cation to be relatively stable and unwilling to undergo cyclization. To improve this cyclization, the imine is replaced with the electron withdrawing nitronate functionality. It is hypothesized that by doing so the addition of an acid will form the cyclopentadienyl cation that will readily undergo Nazarov cyclization. The synthesis of an aryl vinyl silyl nitronate was optimized and the compound was tested with a number of different acid catalysts to determine if the nitronate Nazarov cyclization is possible.

June 25, 2014

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List of Abbreviations and Symbols

α: alpha

Ac: acetyl

β: beta

Bn: benzyl

Bu: butyl

Cy: cyclohexyl

Et: ethyl

δ: delta

DABCO: 1,4-diazabicyclo[2.2.2]octane

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DMF: *N*,*N*-dimethylformamide

°C: degree Celsius

FMO: frontier molecular orbitals

FT: Fourier transform

h: hour

HOMO: highest occupied molecular orbital

HPLC: High pressure liquid chromatography

HRMS: high resolution mass spectrometry

Hz: hertz

i-Pr: isopropyl

IR: infrared

kcal: kilocalorie

LA: Lewis acid

LUMO: lowest unoccupied molecular orbital

m: multiplet

m-CPBA: *meta*-chloroperoxybenzoic acid

Me: methyl

MHz: megahertz

min: minute

mol: mole

MS: molecular sieves

NMR: nuclear magnetic resonance

NOE: nuclear Overhauser effect

Ph: phenyl

ppm: parts per million

Pr: propyl

rt: room temperature

s: singlet

SOMO: singly occupied molecular orbital

TBDMS: *tert*-butyldimethylsilyl

Tf: triflate

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TIPS: triisopropylsilyl

TLC: thin layer chromatography

TMS: trimethylsilyl

TMS (in NMR discussions):

tetramethylsilane

T.S.: transition state

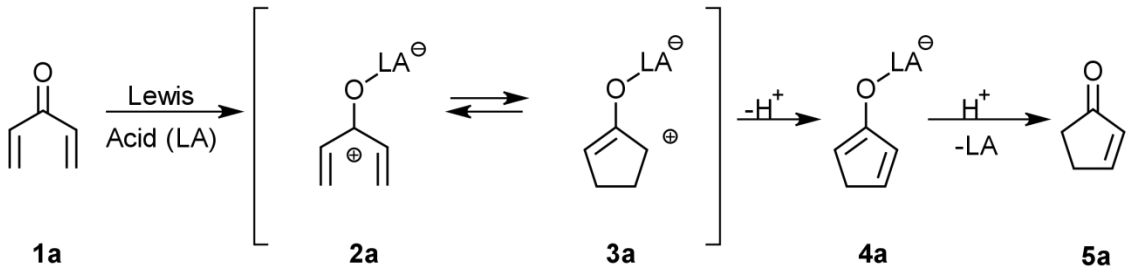
Ts: tosyl

Chapter 1: The nitronate Nazarov cyclization: a new variation to a classic synthetic tool

Electrocyclic reactions are commonly used as synthetic tools for pharmaceutical ingredients and natural products.[1] The Nazarov cyclization is an example of such a reaction and it has been studied extensively by organic chemists to improve yields and product outcomes (see section 1.1). Recently, reports have emerged that describe an imino Nazarov cyclization; however, examples are limited and the cyclization has proven difficult to initiate (see section 1.2). An investigation into a new variation called the nitronate Nazarov cyclization was initiated in an attempt to improve the heteroatom version of the Nazarov cyclization. This report will describe the investigation into the synthesis of an appropriate nitronate Nazarov reagent, and the results of attempted nitronate Nazarov cyclizations.

1.1 The Nazarov cyclization

The Nazarov cyclization is a well-known 5-membered ring forming reaction that is still drawing interest over 60 years after it was first reported.[2-6] It is the 4π-electron electrocyclic reaction of divinyl ketone **1a** to cyclopentenone product **5a** (Scheme 1).



Scheme 1: A general reaction scheme of the Nazarov cyclization

The cyclization occurs when a Lewis or Brønsted-Lowry acid coordinates to the oxygen atom of the ketone **1a** and promotes the formation of pentadienyl cation **2a**, which must be formed if the cyclization is to occur. Once this cation forms a new carbon-carbon bond is made at the terminal end of each double bond and produces cyclopentene cation **3a**. Elimination of a proton affords structure **4a**, which is followed by addition of a proton and the loss of the Lewis acid to yield the final product **5a**. Ever since this cyclization was first described, chemists have studied and developed the stereoselectivity,[7] reagent geometry,[8] and reaction catalysts;[2] to name only a few examples.

1.1.1 Stereochemistry in the Nazarov cyclization

An important aspect of any chemical reaction is the ability to control or predict the stereochemical outcome of the transformation. With electrocyclic reactions this outcome can be predicted by first understanding the ways in which orbitals rotate and form bonds in these reactions.

In 1965, Woodward and Hoffmann reported on the stereochemistry of electrocyclic reactions,[9] and began a study of molecular orbital symmetry. In this report they described electrocyclic reactions as: *the formation of a single bond between the*

termini of a linear system consisting of k π-electrons, and the converse process,[9] where in this definition, k is an even integer. To form a new carbon-carbon bond in an electrocyclic reaction, the p orbitals at the ends of the linear conjugated system must rotate such that the same phase of each orbital meet and overlap. These reactions can be initiated either thermally or photochemically, and either method produces a different stereochemical outcome for a given conjugated system.

The different outcomes are a result of the frontier molecular orbital (FMO) that is involved in the bond forming process. For a thermally induced reaction, the highest occupied molecular orbital (HOMO) of the conjugated system is involved in the cyclization. For example, in the thermal electrocyclic ring closing of butadiene (Figure 1a), the only way that the orbitals can overlap in the same phase is if both orbitals rotate in a clockwise (or counter clockwise) direction. This rotation is said to be conrotatory. If hexatriene (Figure 1b) were the reagent undergoing the cyclization, the orbitals would each have to rotate in different directions to ensure proper same-phase overlap of orbital lobes. This is known as a disrotatory cyclization.

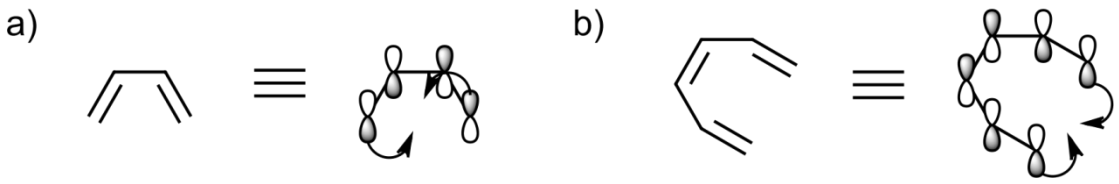


Figure 1: HOMOs of a) butadiene and b) hexatriene

From the observations of many electrocyclic reactions and the determination of the stereochemistry of the products, Woodward and Hoffmann proposed the following

rule: under thermal reaction conditions, conrotatory cyclization occurs when k = 4q; where q is an integer and k is the value described in the definition by Woodward and Hoffman above. Similarly, for hexatriene (6 π-electrons) and other compounds with π-electrons not in multiples of four, the rule was proposed that when k = 4q + 2 the cyclization will be disrotatory if initiated thermally.[9,10]

Another method to initiate reactions is photochemically. If a conjugated system absorbs a photon, an electron is excited from the HOMO to the lowest occupied molecular orbital (LUMO). This molecular orbital then contains one excited electron, and the orbital is called a singly occupied molecular orbital (SOMO). It is then the movement of the orbitals of the SOMO that generates the stereochemical outcome. Again, using butadiene and hexatriene Figure 2 shows that the terminal orbitals of the SOMO must rotate in a disrotatory and conrotatory manner respectively. If the reaction is initiated photochemically, the orbitals rotate in directions opposite from when the cyclization is initiated thermally, and therefore the same compound can make two different stereochemical products depending on how the reaction is initiated.

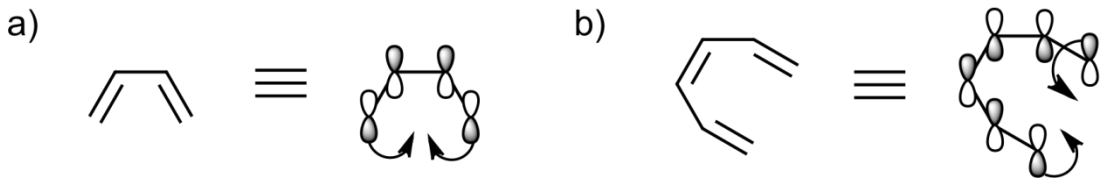
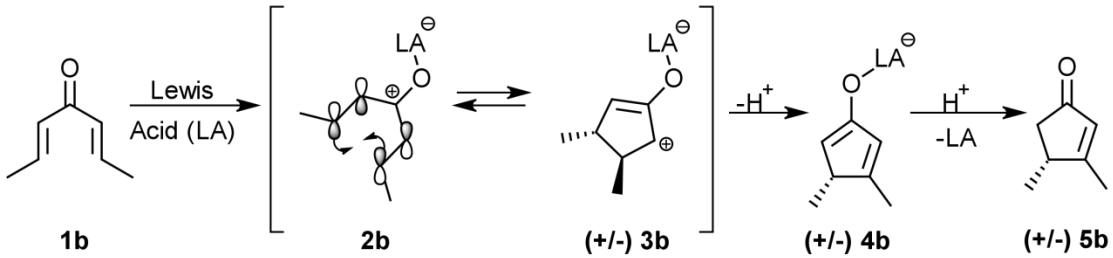


Figure 2: SOMOs of a) butadiene and b) hexatriene

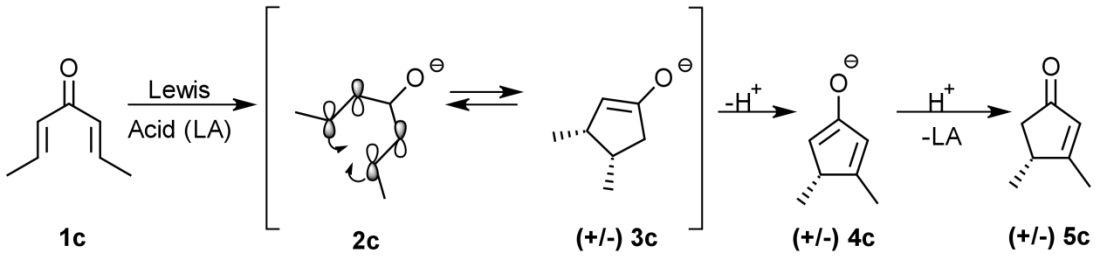
In the Nazarov cyclization, the pentadienyl cation **2** is a linear system that contains 4π-electrons. Therefore, based on Woodward and Hoffmann rules (k = 4q)[9,10] the cyclization is conrotatory under thermal reaction conditions (Scheme 2). With Nazarov

reagents containing substiutents at the ends of the double bonds, orbital rotation will affect the stereochemistry of the product. Once the pentadienyl cation **2b** is formed, cyclization occurs to yield the cyclopentenyl cation **3b** that contains two new stereocentres. Due to the fact that chemists can predict the rotation of the terminal orbitals, and that the geometry of the alkenes in the divinyl ketone can be determined pre-cyclization, it is possible to predict the relative stereochemical outcome for the intermediate compound. As the reaction progresses, one of these stereocentres is lost, but variations of the Nazarov cyclization exist in which these stereocentres are maintained (section 1.1.4).



Scheme 2: Stereochemical result of the thermally initiated Nazarov cyclization

The Nazarov cyclization can also be initiated photochemically and therefore without the need for a Lewis acid catalyst.[11-13] When the Nazarov cyclization is initiated photochemically it is no longer the symmetry of the HOMO of the pentadienyl cation that dictates how the orbitals will rotate, but the SOMO of the divinyl ketone. Therefore, the cyclization occurs in a disrotatory manner (Scheme 3).



Scheme 3: Stereochemical result of the photochemically initiated Nazarov cyclization

Controlling the absolute stereochemistry of the final product of the Nazarov cyclization can occur by the choice of catalyst. There are reported examples of acid catalysts that promote the formation of one stereoisomer,[14] as well as auxiliaries such as oxazolidinone that can transfer chirality to the final product.[15] Tius *et al.* have published an excellent review of the asymmetric Nazarov cyclization, which includes these, and many more examples.[3]

1.1.2 Optimal divinyl ketone geometry

In order for the cyclization event to occur in the Nazarov reaction, the geometry of the divinyl ketone is important. This geometry can adopt three different shapes: (1) s-trans/s-trans (2) s-trans/s-cis (3) s-cis/s-cis (Figure 3). The optimal geometry of the divinyl ketone for cyclization is the s-trans/s-trans conformation.[4] In this geometry the terminal orbitals of each double bond are close enough to overlap upon rotation and form the new carbon-carbon bond. Unfortunately, when the divinyl ketone adopts the s-trans/s-cis or the s-cis/s-cis geometry, the orbitals located at the terminal ends of the double bond cannot overlap to produce the Nazarov outcome. Studies have shown that non-hydrogen substitution on the α-carbon (R_1, R_2, Figure 3) increases reactivity towards the Nazarov cyclization due to the prevalence of the s-trans/s-trans isomer.[16,17] Alkyl and

aryl substituents are large and experience steric interactions that make the s-cis/s-cis conformation highly unstable due to the proximity of the substituents. Therefore, alkyl and aryl substituents promote the s-trans/s-trans geometry required for the Nazarov cyclization. Conversely, when R_1 and R_2 are hydrogen atoms, the prevalent conformer is s-cis/s-cis because steric instability is minimized when these two atoms are close to one another, and the Nazarov cyclization is disfavoured.

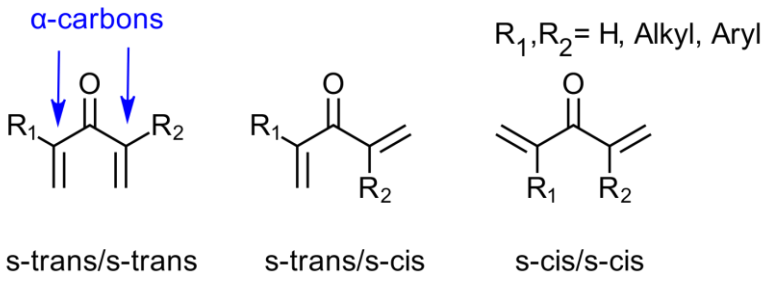


Figure 3: Conformers of divinyl ketones

One method of ensuring that half of the divinyl ketone adopts the proper s-trans geometry is to incorporate an aromatic ring as one of the alkenes, constructing an aryl vinyl ketone (Figure 4), to be discussed in section 2.4.1. This would ensure the proper s-trans/s-trans geometry due to the resonance hybrid of an aromatic ring.

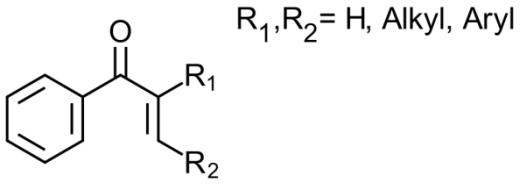


Figure 4: Structure of an aryl vinyl ketone

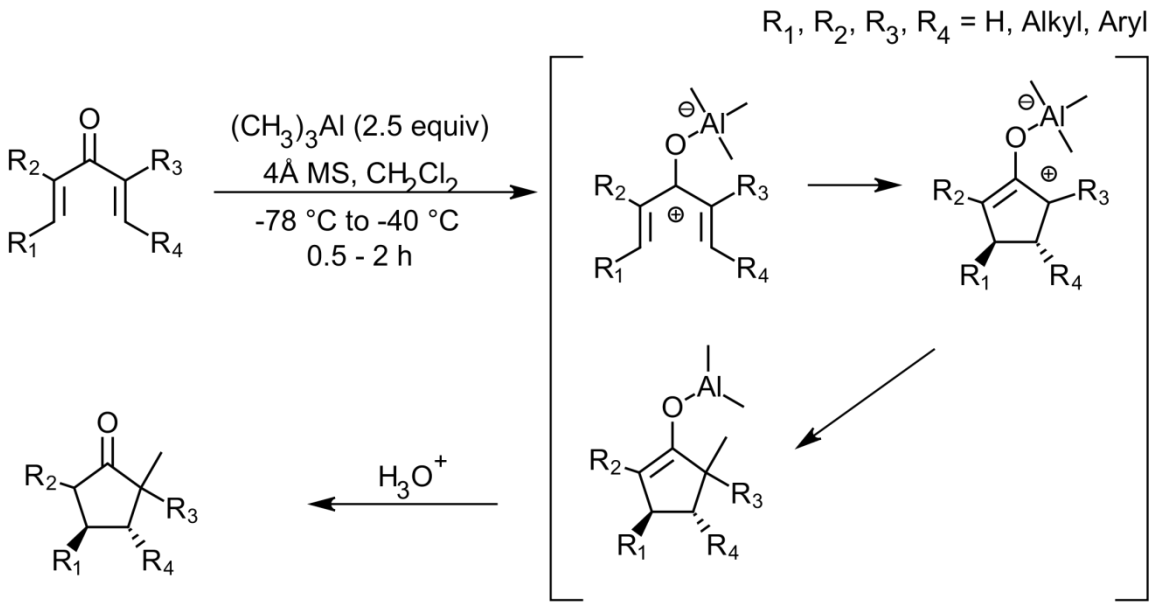
1.1.3 Nazarov catalysts

There are many different catalysts that have been useful in promoting the Nazarov cyclization. The most recent examples are outlined in a review by Frontier *et al.*[2] and include: Brønsted-Lowry acids,[14] organocatalysts,[18] heterogeneous catalysts,[19]

supramolecular hosts,[20] and Lewis acids.[21] The collection of reports described demonstrates one main goal; the use of these compounds in catalytic amounts and under relatively mild reaction conditions to promote the formation of the pentadienyl cation required to undergo the Nazarov cyclization.

1.1.4 The interrupted Nazarov cyclization

An interesting variation of the Nazarov cyclization is known as the interrupted Nazarov cyclization.[17,22] This variation involves adding a nucleophile to the reaction mixture that will stop the reaction before it reaches completion. The nucleophile will add to the cyclopentenyl cation and a third stereocentre is formed. In this variation, elimination does not occur, and the stereochemistry across the carbon-carbon bond formed during the cyclization remains intact. Recently, this methodology was used with an organoaluminum compound that transferred a methyl group to the cyclopentenyl cation (Scheme 4).[23] By using this alternate reaction, chemists can obtain products with multiple chiral centres and predicted stereochemistry; a useful tool in the synthesis of any product.



Scheme 4: Interrupted Nazarov cyclization using a trimethylaluminum catalyst

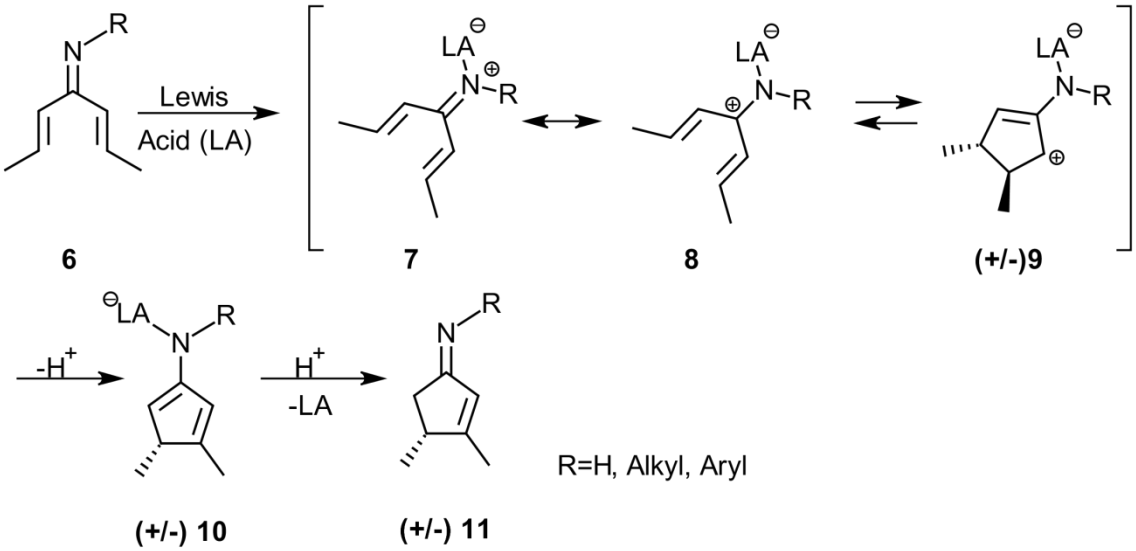
1.1.5 The Nazarov cyclization highlights

The Nazarov cyclization has been optimized over the years to ensure efficient formation and stereochemical control of cyclopentenone products, and this optimization has led to the use of this cyclization in the synthesis of natural products.[24-26] There is; however, a less studied version of the Nazarov cyclization that has yet to reach full synthetic potential. The details of this variation are discussed below.

1.2 The imino Nazarov cyclization

A variation of the Nazarov cyclization involves replacing the oxygen atom of the divinyl ketone with a nitrogen atom, resulting in a divinyl imine Nazarov reagent **6** (Scheme 5). The cyclization proceeds the same way as the Nazarov cyclization once addition of an acid catalyst forms the pentadienyl cation **8**, which cyclizes to form five-membered rings with a nitrogen substituent. In two examples from Section 1.2.2 an

enamine functionality is present in the product, and this is beneficial because enamines can be used in further reactivity.[27] Despite these benefits, this variation of the cyclization is much less studied and more research is needed before it can be used efficiently in organic synthesis.



Scheme 5: A general reaction scheme of the imino Nazarov cyclization

1.2.1 Pentadienyl cation stability and conformation

The lack of interest in this variation is likely due to the increased stability of the pentadienyl cation **8** compared to the pentadienyl cation **2** as described in a computational study by Smith and Ulmer. This study calculated the activation energy, the energy required to reach the transition

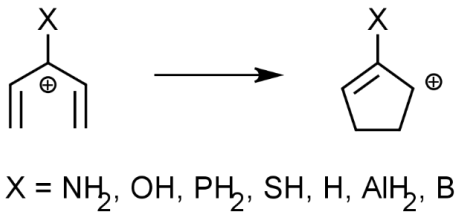
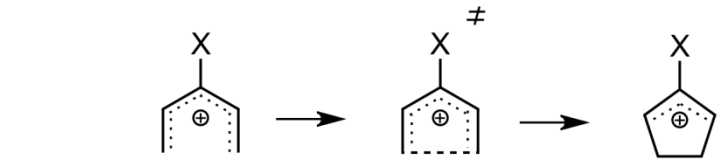


Figure 5: Pentadienyl cations studied in computational study

state between the pentadienyl cation and the cyclopentenyl cation, of a number of simple Nazarov reagents in which the substituent atom at the 3-position of the divinyl pentane skeleton was altered (Figure 5).[28]

These calculations show that of all of the substituents studied, an amine group requires the most energy (21.1 kcal/mol) to reach the transition state,[29] while that of an alcohol substituent takes only 11 kcal/mol (Figure 6). Smith and Ulmer explain that the increased energy is due to the higher electron donating properties of the amine when compared to the oxygen atom. The 2p electrons of the nitrogen atom easily donate into the cationic π-system and make the reactants quite stable due to the delocalization of electrons and more energy is needed to reach the transition state of the cyclization.



NH_2	[0.0]	21.1	-.0
OH	[0.0]	11.	-.0

Figure 6: Energies (kcal/mol) for stationary points in the cyclization of 3-substituted pentadienyl cation[29]

A second calculation performed in this study shows that the most stable geometry for the pentadienyl cation with an amine substituent at the 3-position and no α-substituents is s-trans/s-trans (Figure 7). This is beneficial because it is the required geometry for the

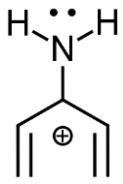


Figure 7: Most stable geometry for the amine substituted pentadienyl cation

Nazarov cyclization.[4]

1.2.2 Examples of the imino Nazarov cyclization

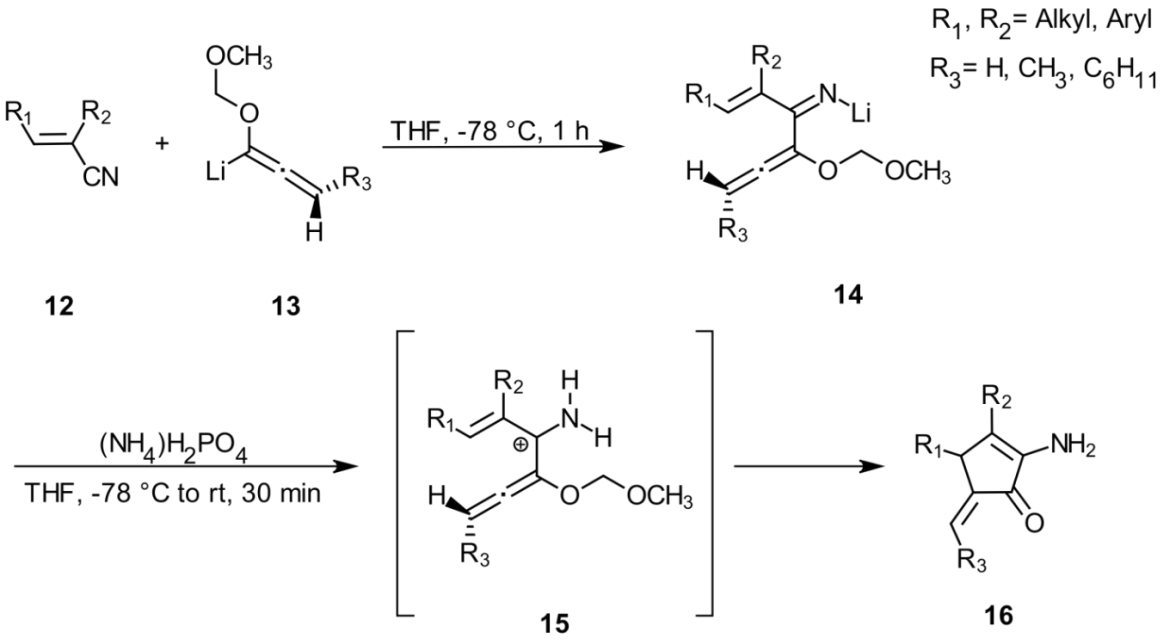
Although Smith and Ulmer show that the imino Nazarov cyclization is less likely to occur than the Nazarov cyclization,[28] to date there are five examples in the literature. These examples use unique methodology to overcome the higher activation energy and the results are impressive for a reaction less likely to occur than the Nazarov cyclization.

1.2.2.1 Cyclization of α,β-unsaturated nitriles and (methoxy)-methoxyallenes

In 2001, Tius *et al.* reported the first example of the imino Nazarov cyclization.[30] By combining various α,β-unsaturated nitriles **12** with three different γ-(methoxy)-methoxy substituted allenes **13** in THF at -78 °C, a number of α-aminocyclopentenone products were obtained (Scheme 6). The γ-(methoxy)-methoxy substituted allene adds to the α,β-unsaturated nitrile to produce an allenylvinyl lithioimine **14**, that forms the pentadienyl cation **15** after the addition of saturated aqueous ammonium dihydrogen phosphate. Yields of these products range from 46-92% and reaction time is 1.5 hours.

Although the thermodynamic issues of this reaction have been presented above, Tius reports that the cyclization can occur due to the irreversible loss of the methoxymethyl cation that results in the formation of the final product. It is this step that stops the reverse reaction pathway and enables only one product to form. Another factor that promotes cyclization is the loss of allene strain from the molecule after cyclization. Relief of this strain helps overcome the unfavourable equilibrium of the imino Nazarov

cyclization. Finally, with substituents on each α-carbon, the geometry of the pentadienyl cation is s-trans/s-trans and the cyclization can occur.

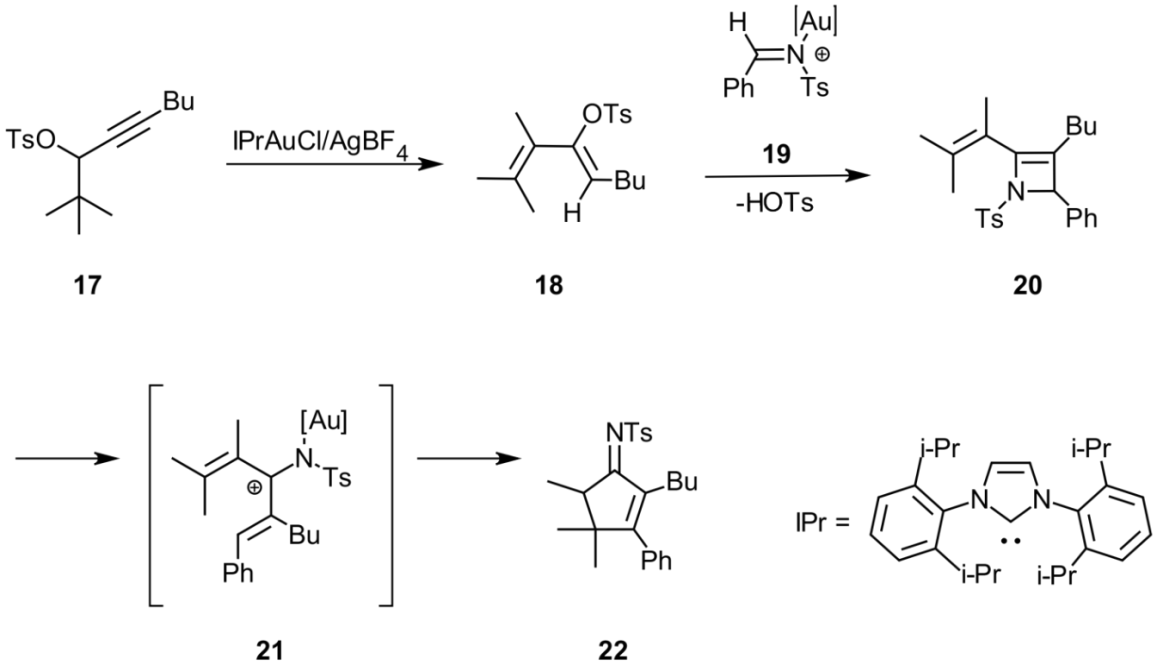


Scheme 6: Imino Nazarov cyclization of α,β-unsaturated nitriles with γ-(methoxy)-methoxy substituted allenes

1.2.2.2 Gold catalyzed imino Nazarov cyclization

The research group of González reported an imino Nazarov cyclization catalyzed by a gold metal complex.[31] The cyclization is unique because the authors propose a series of rearrangement reactions that occur prior to the ring closing step. The reaction involves addition of a gold metal catalyst (IPrAuCl/$AgBF_4$) to a mixture of the propargyl tosylate **17** and *N*-tosylimine **19** (Scheme 7). First, the gold catalyst coordinates to the propargyl tosylate **17** and initiates an isomerization. This leads to a 1,3-diene structure **18** that adds to the activated imine **19**. This step is followed by a cyclization and loss of *p*-toluenesulfonic acid to yield structure **20**. An electrocyclic ring opening process occurs,

followed by coordination of the gold catalyst to afford the pentadienyl cation **21**, which then undergoes imino Nazarov cyclization. The yields of this cyclization are good (47-88%), but the need for specific starting materials limit the scope of this reaction.

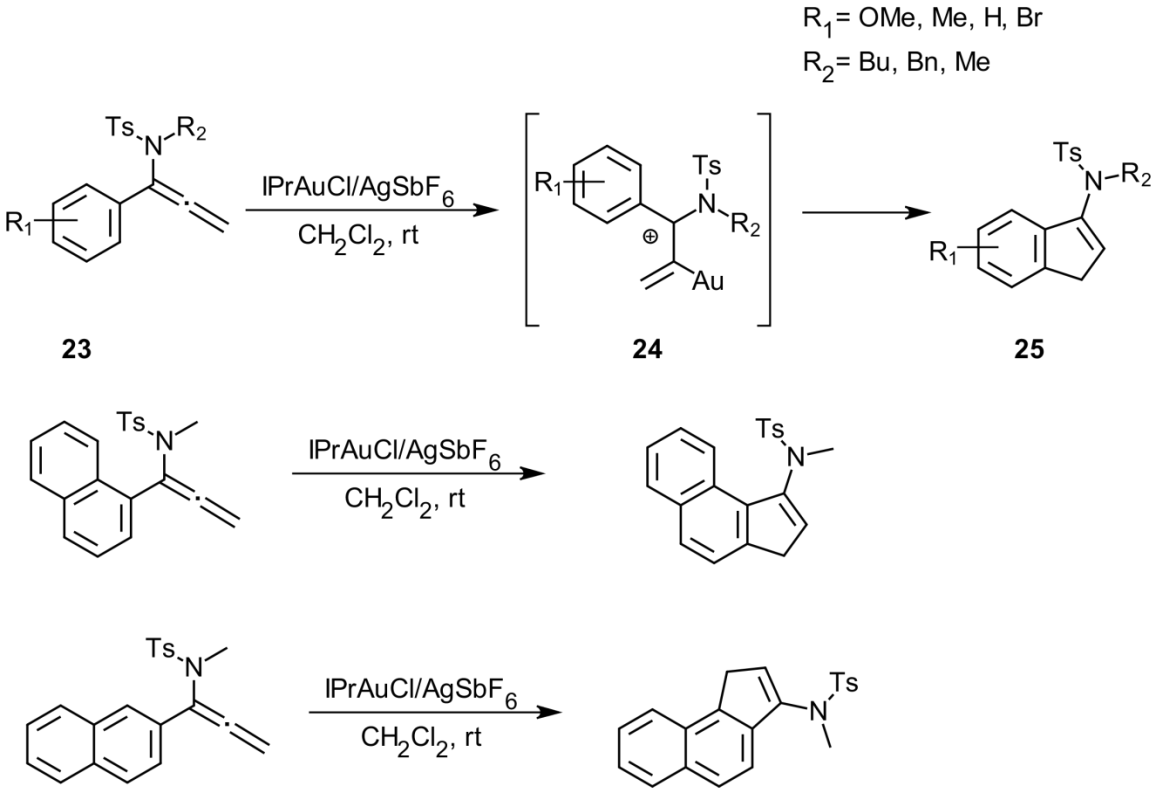


Scheme 7: Gold catalyzed imino Nazarov cyclization between propargyl tosylate **17** and N-tosylimine **19**

Again, this cyclization occurs because the geometry for the pentadienyl cation is in the s-trans/s-trans conformation due to the presence of α-substituents in the structure. Also, Tius has hypothesized that the presence of the tosyl group on the nitrogen atom of the divinyl imine overcomes the unfavorable equilibrium of the imino Nazarov cyclization.[32] The electron withdrawing properties of the tosyl functionality destabilize the pentadienyl cation by preventing the lone pair of electrons on the nitrogen atom from donating into the π-system. This raises the energy of the starting material, and the ring

closing step occurs under the specified reaction conditions. This is a promising result for future study of the imino Nazarov cyclization.

Another example of a cyclization using a similar gold catalyst was reported by Hsung *et al*. A number of α-aryl-substituted allenamides **23** reacted in dichloromethane with a gold metal catalyst to form aromatic ring-fused cyclopentenamides **25** (Scheme 8).[33] Yields for this reaction range from poor to excellent (16-97%) and reaction times from 1-36 hours, making it unreliable.



Scheme 8: Gold catalyzed imino Nazarov cyclization of α-aryl-substituted allenamides

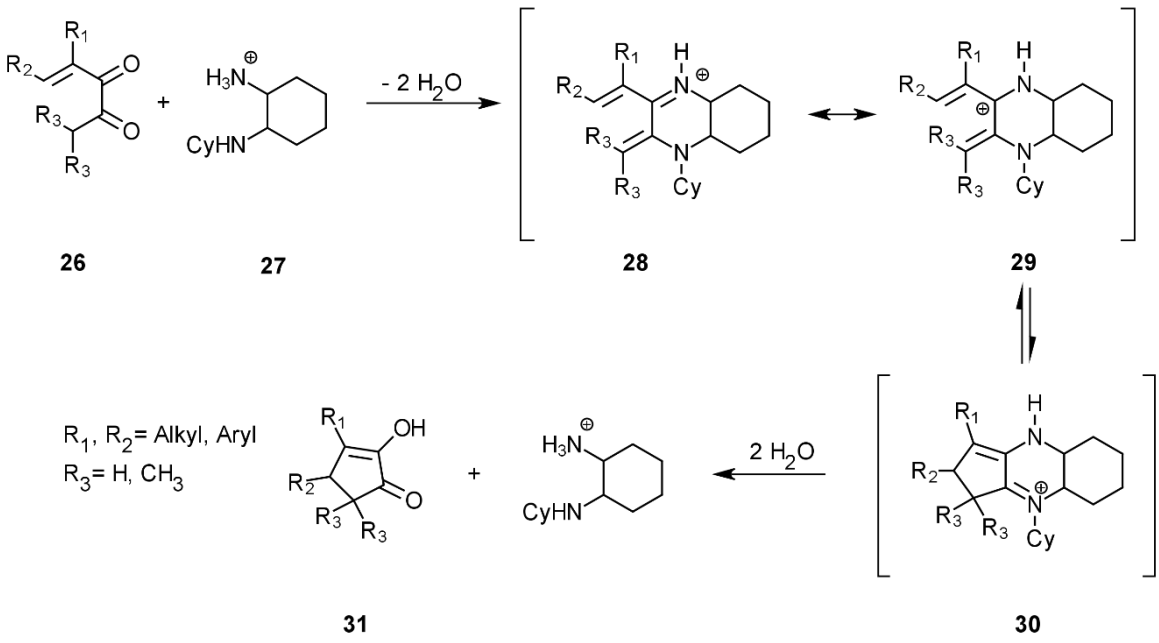
Unfortunately, use of a Brønsted-Lowry acid with these reagents when Ts in Scheme 8 is replaced by an acyl group led to a hydrolysis reaction. When the tosyl group was present, almost all attempts at gold and platinum metal catalysis produced dimerized

products that then underwent the cyclization. It was only IPrAuCl/$AgSbF_6$ that enabled the imino Nazarov cyclization to occur efficiently. In spite of these limitations, the reaction conditions are mild (room temperature), and the gold complex is used in catalytic amounts (5 mol%), providing evidence of the potential usefulness of this cyclization.

As with the previous example, and the authors believe that the key to this reaction is the presence of the tosyl group on the nitrogen atom. Similarly, as in the example by Tius, relief of the allene strain helps overcome any unfavourable equilibrium. Lastly, the α-substituents on the pentadienyl cation after bonding to the metal catalyst promote the s-trans/s-trans conformation and the cyclization occurs.

1.2.2.3 The enamine-iminium ion Nazarov cyclization

The enamine-iminium ion Nazarov cyclization was reported by Tius in 2009.[32] Salts of 1,2-diamines **27** react with α-ketoenones **26** in acetonitrile with 25 mol% water at room temperature to form an enamine-iminium ion **28** which has a resonance structure that is the pentadienyl cation **29** (Scheme 9). The pentadienyl cation then undergoes cyclization to yield another enamine-iminium ion intermediate **30**. Hydrolysis of this intermediate then yields the starting diamine and the α-hydroxycyclopentenone product **31**.



Scheme 9: Enamine-iminium ion Nazarov cyclization involving α-diketones

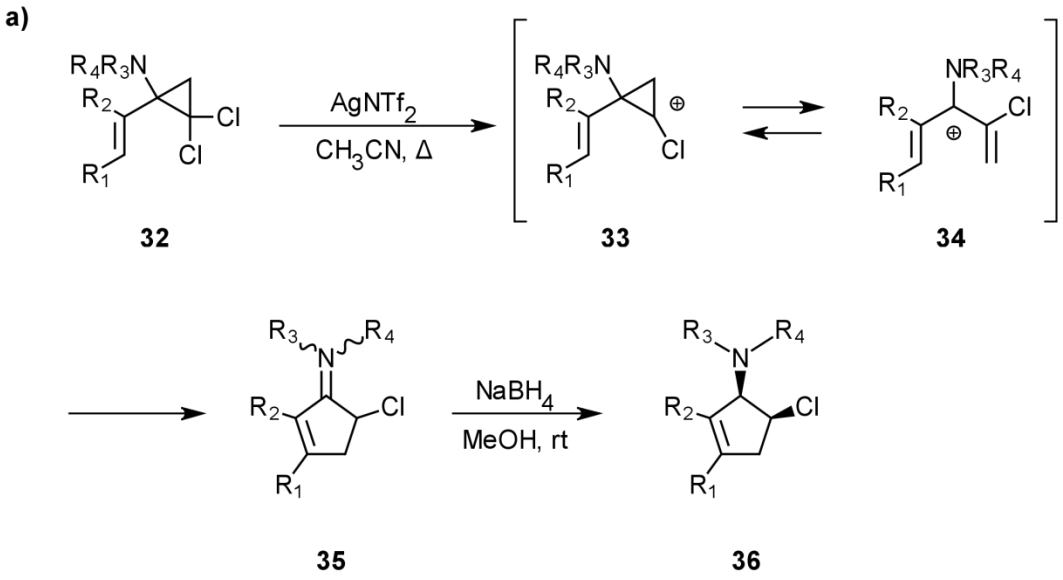
Unfortunately, the reaction is impractical for organic synthesis because it requires approximately 7.5 days to react and it produces low to moderate yields (11-66%). There is; however, one benefit to this reaction. When using chiral diamines, stereochemistry is maintained in the final product, and the enantiomeric ratios are excellent. This is an impressive result, but the other aspects of the reaction must be improved upon before it can be considered synthetically useful. Interestingly, when attempts were made to catalyze this reaction using monoamines in the presence of a Brønsted-Lowry acid, the reaction times were slower and yields were less than 10%. This indicates that the reaction is in fact proceeding through the formation of an enamine-iminium ion.

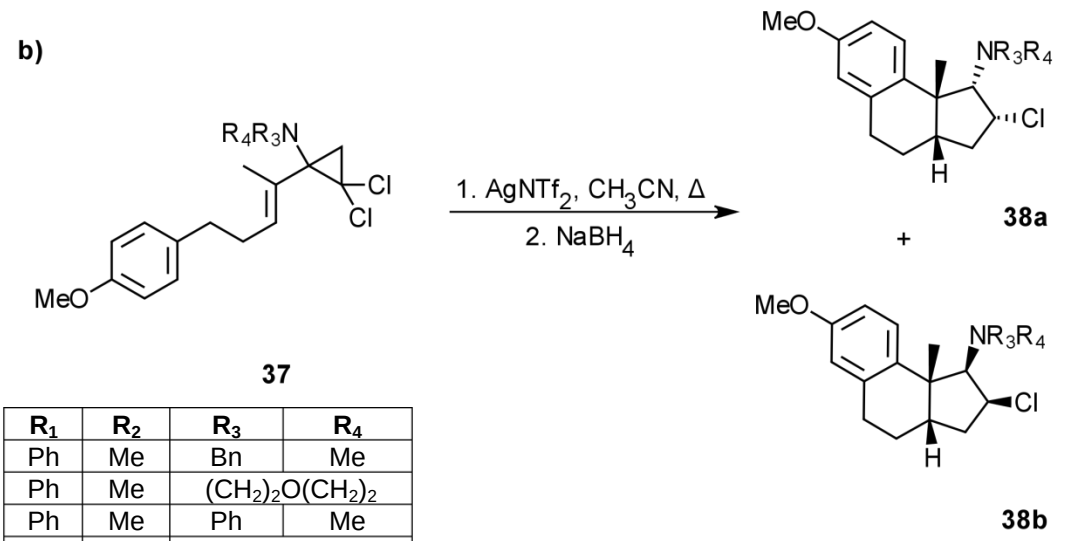
Although this reaction is not ideal, it represents another example of overcoming the thermodynamic issues of the imino Nazarov cyclization. The enamine portion of intermediate **28** is polarized through mesomeric donation, making the alkene electron

rich,[32] which has been shown to react favourably in the Nazarov cyclization.[34] Furthermore, the conversion of the enamine-iminium ion intermediate **29** to another enamine-iminium ion intermediate **30** produces compounds that are both are stabilized by the lone pair of electrons on the nitrogen atom. This stabilization means that it would be unlikely that equilibrium would favour one intermediate over the other.[32] Lastly, the cyclization can occur due to the geometry of the pentadienyl cation as there are α-substituents on both sides of the structure and the s-trans/s-trans conformer is prevalent.

1.2.2.4 The Nazarov cyclization of vinyl cyclopropylamines

The most recent example of the imino Nazarov cyclization also includes examples in which the interrupted Nazarov cyclization occurs.[35] 1-Alkenyl-1-amino-2,2-dichlorocyclopropanes **32** react with a silver catalyst to produce the pentadienyl cation **34** once a ring opening of the cyclopropane ring occurs. The imino Nazarov cyclized iminium products **35** are then formed through cyclization, and are subsequently reduced to yield amino chlorocyclopentenes **36** in 12-50% yields (Scheme 10a). When substrates of the type **37** are used, an interrupted imino Nazarov cyclization occurs to yield amino chlorocyclopentane derivatives **38** (32-65% yield) (Scheme 10b).





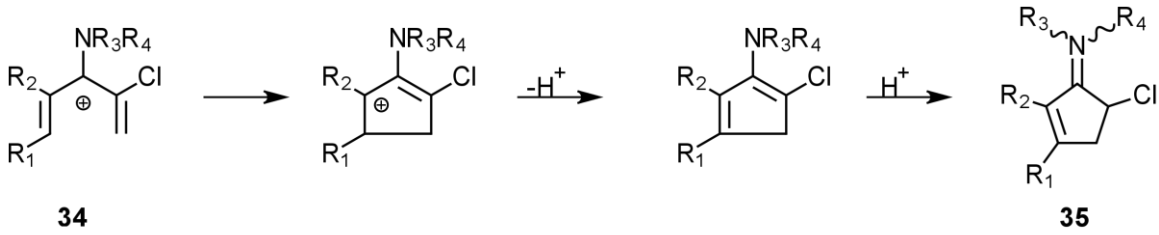
R_1	R_2	R_3	R_4
Ph	Me	Bn	Me
Ph	Me	$(CH_2)_2O(CH_2)_2$	
Ph	Me	Ph	Me
H	Me	$(CH_2)_2O(CH_2)_2$	
$(CH_2)_4$		$(CH_2)_2O(CH_2)_2$	

Scheme 10: Imino Nazarov cyclization of vinyl cyclopropylamines

For this cyclization to occur, the cyclopropane ring must open. This releases 27.9 kcal/mol of energy due to loss of ring strain.[36] This, and the heat added to the reaction mixture provide enough energy for the cyclization to occur. Furthermore, the

divinyl framework contains α-substituents that ensure the geometry is s-trans/s-trans for the cyclization.

Interestingly, the authors report that this cyclization does not occur when there is an electron withdrawing group on the nitrogen atom. In the mechanism forming the iminium product **35**, the lone pair of electrons on the nitrogen atom must be able to donate into the cyclopentene ring system, causing a π bond to break and form a new carbon-hydrogen bond (Scheme 11). With an electron withdrawing group, this reactivity would not occur, and the iminium intermediate would not form.



34 **35**

Scheme 11: Stepwise formation of iminium product **35** from the pentadienyl cation **34**

1.2.3 Imino Nazarov summary

The imino Nazarov cyclization has not been widely studied in the literature, and therefore the reaction has not reached its full potential in organic synthesis. Although computational studies have shown that the cyclization is less favoured energetically than the Nazarov cyclization, chemists have found ways to lower the activation energy by decreasing the stability of the pentadienyl cation by preventing the lone pair of electrons on the nitrogen atom from stabilizing the cation or through other structural variations. By doing so, the cyclization can advance easier than computational studies would suggest. Though the examples are few, each method involves different characteristics that overcome the thermodynamic issue of the cyclization. With more research directed

towards finding a generic reagent that will react easily in this cyclization, organic synthesis could benefit greatly from the opportunities this cyclization provides.

1.3 The nitronate Nazarov cyclization

A hypothesized methodology to overcome the unfavourable thermodynamic problem of the imino Nazarov cyclization involves increasing the electron withdrawing properties of substituents on the nitrogen atom by replacing the imine functionality with a nitronate functionality. After cyclization, the nitro group could be removed or reduced to yield a variety of final products. This section describes the theory behind the nitronate Nazarov cyclization, and presents a hypothesis as to how this reaction could occur.

1.3.1 The electronic argument

Tius has made the hypothesis that the addition of an electron withdrawing group on the nitrogen atom decreases the stability of pentadienyl cation.[32] In two examples of the imino Nazarov cyclization,[31,33] a tosyl group was bonded to the nitrogen involved in the cyclization (Figure 8). It is believed that the electron withdrawing properties of the tosyl functionality withdraw electron density from the nitrogen atom and prevent the lone pair of electrons from donating into the π-system. The energy of the pentadienyl cation then increases when compared to the 3-amino pentadienyl cation and the ring closing step occurs under the specified reaction conditions.

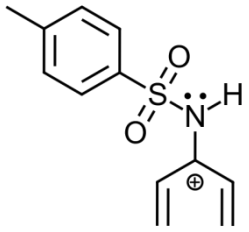


Figure 8: Pentadienyl cation of a divinyl imine with a tosyl substituent

Leading from this hypothesis, replacing the imine functionality with a nitronate functionality would produce results similar to when a tosyl substituent was bonded to the nitrogen atom. This new structure is a divinyl nitronate **39**. When a Lewis acid catalyst coordinates to the anionic oxygen atom, the iminium ion **40** is generated that has a resonance hybrid **41** that is the pentadienyl cation needed for the Nazarov reaction (Figure 9). Coordination of the acid catalyst decreases mesomeric donation by the lone pairs of electrons on the oxygen atoms and they will withdraw electron density away from the nitrogen atom through sigma bonds. With this sigma withdrawing affect, resonance structure **41** will be the dominant resonance hybrid. These two resonance structures have more charge separation than that of the nitronate **39**, and their formation would require the addition of some amount of energy. However, it is hypothesized that based on the nature of Lewis acids pertaining to the empty orbital with which a lone pair of electrons can coordinate and fill, these resonance structures will form.

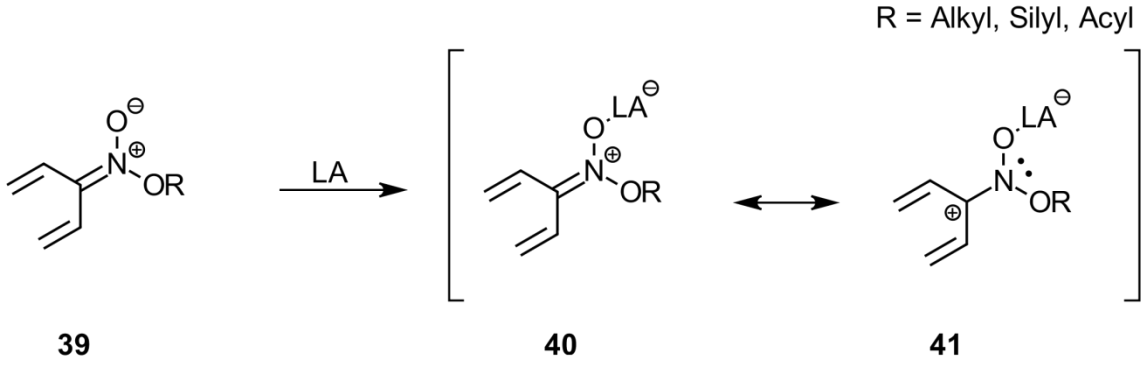


Figure 9: Resonance structures of the pentadienyl cation of a divinyl nitronate

1.3.2 The conformational argument

Another benefit to this reaction is that the pentadienyl cation should predominantly assume the required s-trans/s-trans conformation, regardless of whether there is substitution on the α-carbons or not. This hypothesis is based on the calculations by Smith and Ulmer[28] mentioned above that demonstrate that for divinyl structures with an amino substituent, the favoured conformation is the s-trans/s-trans conformation. Furthermore, calculations regarding diprotonated 1-phenyl-2-propenone (Figure 10) indicate that the lowest energy conformation is also s-trans for this system when using theoretical calculations to determine the energy minima for these hypothetical structures.[37] These studies help form the hypothesis that two substituents on the oxygen or nitrogen atom increase the likelihood that the geometry will be the desired s-trans/s-trans conformation. In this geometry, energy is not required to go into the system to alter the conformation to that which is required for cyclization and less energy will be required for cyclization.

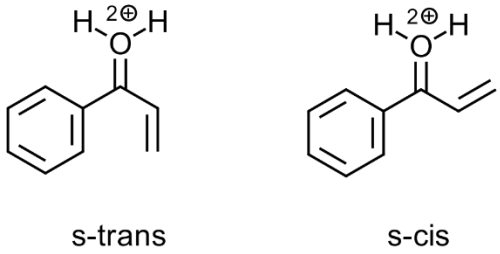


Figure 10: Geometries of diprotonated 1-phenyl-2-propenones

1.3.3 Nitronate Nazarov cyclization hypothesis

Despite the potential benefits of this cyclization, there are currently no reports in the literature. This research would represent the first example of a divinyl nitronate

compound reacting in a Nazarov cyclization. It is hypothesized that upon addition of a Lewis or Bronsted-Lowry acid catalyst to the divinyl nitronate, the pentadienyl cation will form and the reaction will progress in the same manner as the Nazarov cyclization. Similar to the Nazarov cyclization, thermal initiation of the 4π-electron cyclization will involve the terminal orbitals rotating in the same direction (conrotation) to obtain same phase overlap (Figure 11). In this manner the product will have the same stereochemical outcome as the acid catalyzed Nazarov cyclization.

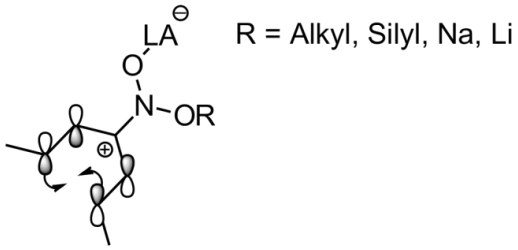
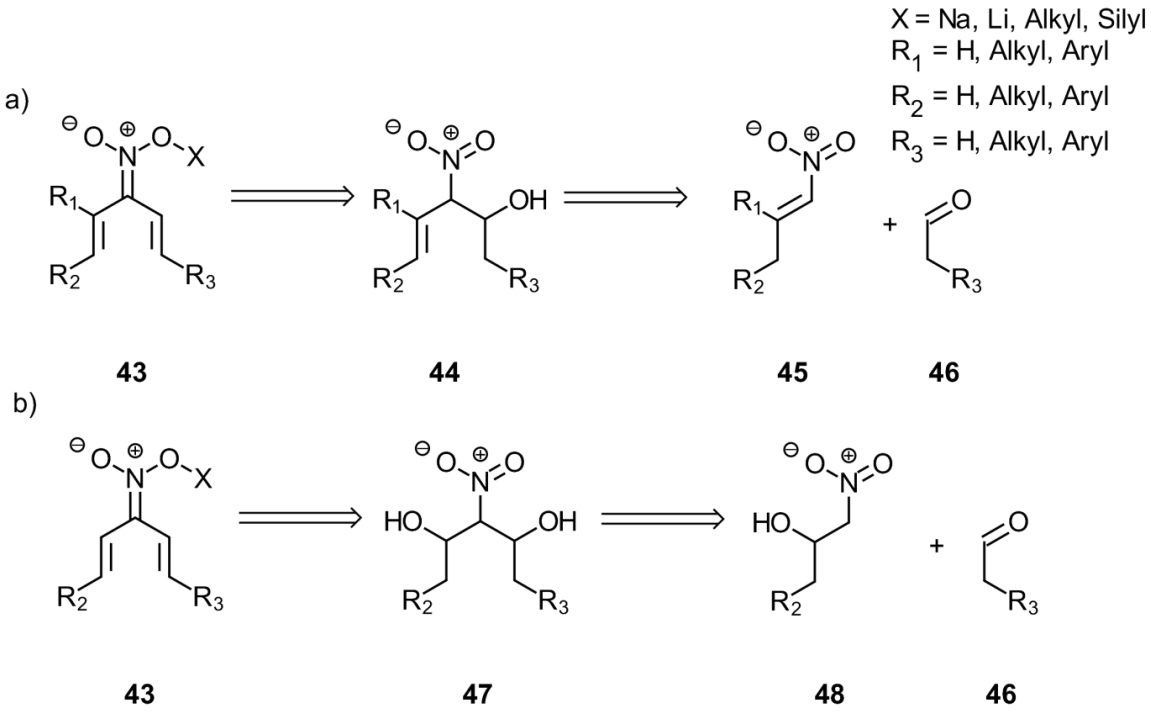


Figure 11: HOMO of the pentadienyl cation of the nitronate Nazarov cyclization

1.3.4 Nitronate Nazarov cyclization research plan

In order to investigate the feasibility of the nitronate Nazarov cyclization, a molecular framework that incorporates a nitronate functionality into the divinyl structure must be synthesized. A retrosynthetic analysis of a divinyl nitronate **43** demonstrates the brief synthesis of a divinyl nitronate using known methods (Scheme 12). The key step in this synthesis involves a reaction between a nitroalkene **45** and an aldehyde **46** to yield a 1,2-nitroalcohol **44** (Scheme 12, retrosynthesis a). This structure will then undergo further reaction to lead to the divinyl nitronate **43**. Another possibility is to react 1,2-nitroalcohols **48** in the Henry reaction with an aldehyde **46** to yield 2-nitro-1,3-diol

compounds **47**. This product could then undergo further reaction to yield the divinyl nitronate **43** (Scheme 12, retrosynthesis b).



Scheme 12: Retrosynthetic analysis of a divinyl nitronate

The following chapter outlines the method of synthesis of two different nitronate Nazarov frameworks, a divinyl and an aryl vinyl nitronate, and investigates the methodology and issues that arose when attempting these syntheses.

Chapter 2: Synthesizing the nitronate Nazarov reagent

The nitronate Nazarov cyclization can only be useful if the synthesis of a divinyl nitronate is readily performed. These structures have not been synthesized in the literature, but there are a number of examples of the synthesis and reactivity of other nitronate frameworks. The synthesis of a divinyl nitronate represents a new extension to the methodology already developed regarding nitronates, and an investigation into their synthesis is described below.

2.1 Nitronates in the literature

There are many different species of nitronates that can be found in the literature and they are all derivatives of the nitronic acid functional group. In solution, the nitro group exists in an equilibrium with a nitronic acid;[38] a tautomer of the nitro group (Figure 12). Nitronic acids are known to be unstable and typically have half-lives ranging from minutes to weeks and generally decompose into oximes.[39] Derivatives of nitronic acids can be more stable, and many different variations have been synthesized and isolated.

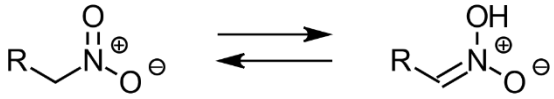


Figure 12: The nitro group tautomerism to a nitronic acid

2.1.1 Synthesis and use of nitronic acid derivatives

Nitronates (Figure 13) are a chemical structure where the OH group of the nitronic acid has been modified to an OX group, where X is an atom other than hydrogen. For example, silyl nitronates ($X=SiR_3$) are derivatives of nitronic acids in which the hydrogen atom is exchanged for a silyl group. They are commonly synthesized by addition of a

base and a silylating agent (ex. TIPSCl) to a nitro compound,[40-42] and can be used in further reactions to form carbon-carbon bonds or heterocyclic rings.[41,43-45] These derivatives are known to be relatively stable and have not decomposed at high temperatures.[46] Nitronic esters (X=Alkyl) are reported to be unstable due to their facile decomposition and their tendency to undergo electrocyclic reactions.[39,47] They are most commonly synthesized from nitronate salts after addition of diazo compounds[48] or oxonium salts.[49] Acyl nitronates ($X=CH_3CO$) are synthesized through formation of the anionic metal nitronate followed by addition of an acyl halide or carboxylic acid anhydrides;[50,51] however, they are reported to readily decompose. Lastly, there are a few reports of boryl nitronates ($X=BR_2$) in the literature.[52-54] They are synthesized by first isolating the nitronate salt, and then reacting it with a halogenated alkylborane species. Boryl nitronates have not been studied in depth because they readily undergo dimerization and rearrangement at room temperature.[52,53]

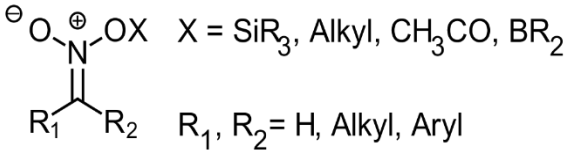


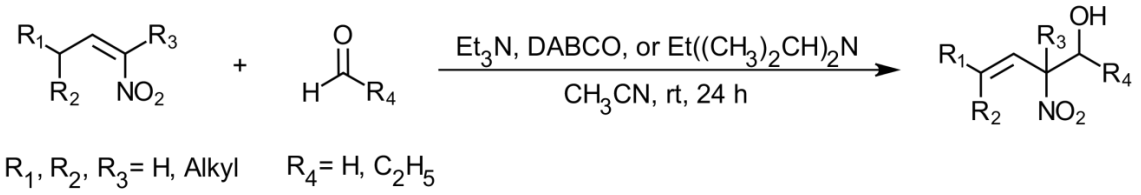
Figure 13: Structure of a nitronate

Though these nitronates are all reported to be unstable, synthesizing secondary nitronates, adding conjugation, or increasing the electron withdrawing properties on the nitronate carbons have been shown to increase their stability.[39] If a carbon framework can be synthesized that increases the stability of these nitronates, they could prove useful as reagents in the nitronate Nazarov cyclization. Despite their instabilities, nitronates have many uses in the field of organic synthesis, and are known to react in an important carbon-carbon bond forming reactions.

2.2 Reactions forming 1,2-nitroalcohol products

2.2.1 Hydroxyalkylation of α,β-unsaturated nitro compounds

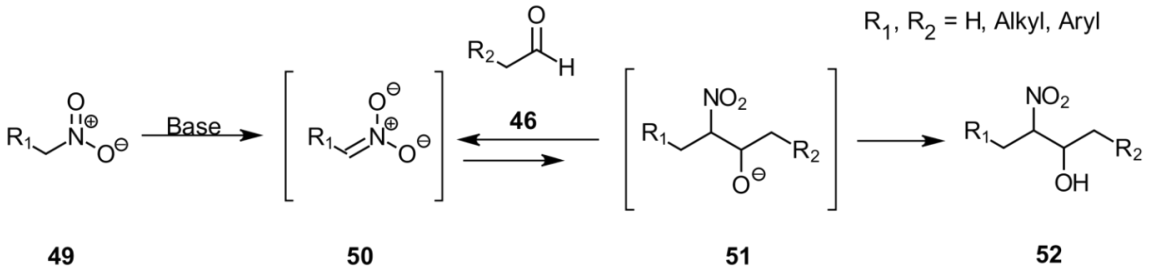
One method to synthesize a divinyl nitronate involves reacting a nitroalkene with an aldehyde (Scheme 12 above). Ono *et al.* performed this reaction with a series of nitroalkenes and formaldehyde or ethanal and produced acceptable yields (55 and 58% for ethanal, 60-94% for formaldehyde) of the 1,2-nitroalcohol (Scheme 13).[55] Unfortunately this reported methodology does not encompass many aldehydes and the scope was quite limited, but this route is intriguing as it would bring the molecular structure close to the required divinyl nitronate.



Scheme 13: Hydroxyalkylation of nitroalkenes

2.2.2 The Henry reaction

The Henry reaction was first described in 1895,[56] and has since been altered and optimized to ensure efficient formation of various 1,2-nitroalcohol products.[57-60] The reaction occurs when a nitroalkane **49** and an aldehyde **46** are combined in a basic reaction environment. The base promotes the formation of a nitronate **50**, which reacts with the aldehyde to form an alkoxide intermediate **51**. Upon quenching the reaction, the alkoxide becomes protonated and the 1,2-nitroalcohol product **52** is formed (Scheme 14).



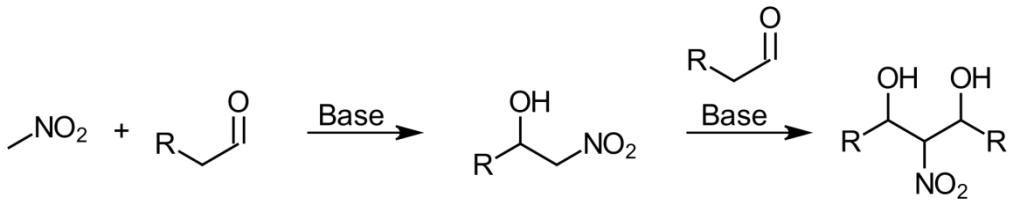
Scheme 14: General reaction scheme for the Henry reaction

The Henry reaction has associated thermodynamic issues which prevent it from reaching its full synthetic potential within the field of organic chemistry. A recent computational study has shown that the change in Gibbs energy between the nitronate **50** and the alkoxide **51** is +11.2 kcal/mol, resulting in an equilibrium that is shifted towards the starting material.[61] To overcome this thermodynamic issue, the nitroalkane is commonly used in 5 molar excess or greater.[62-66] The excess nitroalkane acts as an acid to protonate the alkoxide anion and remove it from the equilibrium under Le Chatelier's principle. Unfortunately, this methodology is only practical when volatile and cheap nitroalkanes are used (i.e. nitromethane, nitroethane), and so reports in which the nitroalkane and aldehyde are used in equimolar amounts are of importance.

2.2.2.1 The Henry reaction with 1,2-nitroalcohols

A 1,2-nitroalcohol can be used as a reactant in the Henry reaction producing a 2-nitro-1,3-diol product (Scheme 15). In the synthesis of a divinyl nitronate, the 2-nitro-1,3-diol could be eliminated to yield a 3-nitro-1,3-diene structure that is the precursor to the desired Nazarov framework. Examples of these Henry reactions include the use of the following bases to promote the reaction: potassium carbonate,[67] basic

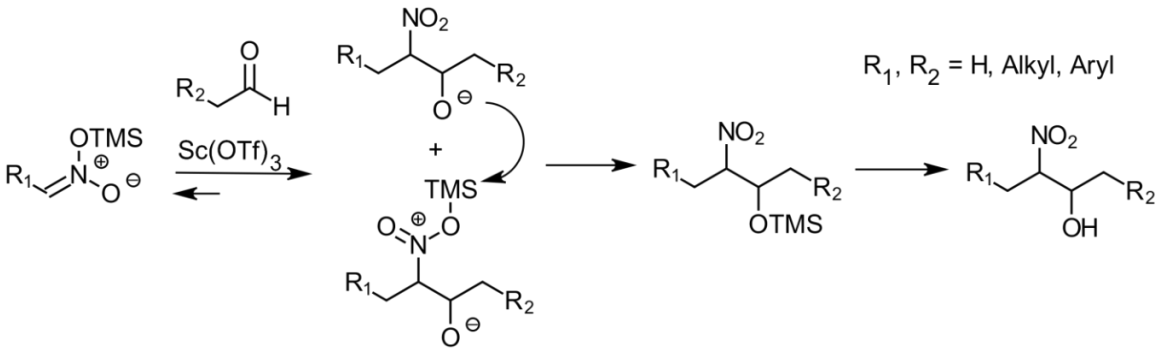
aluminum oxide,[68] or Amberlyst A21.[69] With a number of examples of this reaction in the literature, it represents a viable option as a step in the synthesis of a divinyl nitronate.



Scheme 15: 2-Nitro-1,3-diols from nitromethane and simple aldehydes

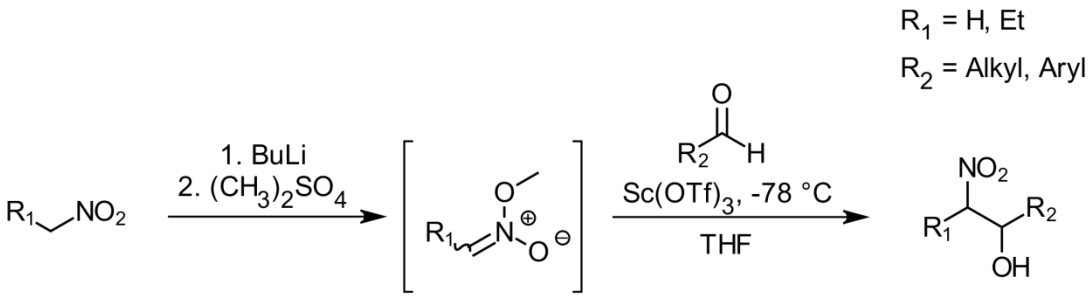
2.2.2.2 The Henry reaction of neutral nitronates

Silyl nitronates have been used in the Henry reaction[46] and represent one variation that has eliminated the need for excess nitroalkane[70-72] because the silyl group acts to trap the alkoxide intermediate and forces the unfavourable equilibrium towards the products. Unfortunately, reaction conditions are basic and can lead to side reactivity of the aldehyde[73,74] and/or elimination of the 1,2-nitroalcohol.[75,76] One report of silyl nitronates in the Henry reaction uses scandium(III) triflate to produce a Lewis acidic environment, and it is hypothesized that the alkoxide is trapped through an intermolecular reaction (Scheme 16).[41] The silyl nitronate is synthesized *in situ* using butyllithium and TMSCl, and an aldehyde is added to the solution. The yields in this report are good to moderate (25-77%), but most importantly, the nitroalkane is used in an almost equimolar amount to the aldehyde.



Scheme 16: The Henry reaction of silyl nitronates

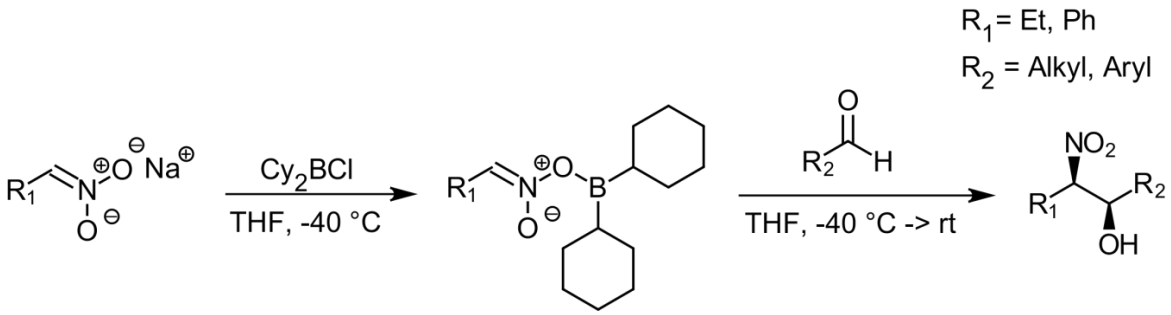
Using nitronic esters as reagents in the Henry reaction is an extension of previous research using silyl nitronates.[41] It was hypothesized that this change would increase the yields of the reaction because a methyl group would trap the alkoxide longer than the labile silyl group. The methodology is similar to that using silyl nitronates in a Lewis acidic environment, and succeeded in producing higher yields of the 1,2-nitroalcohol product (42-91%) using both alkyl and aryl aldehydes (Scheme 17).[77]



Scheme 17: The Henry reaction using nitronic esters

The most interesting and recent variation to nitronates within the Henry reaction is the use of boryl nitronates to produce products with high diastereoselectivity. It has been demonstrated that boryl nitronates can react in a Henry reaction using equimolar amounts to the aldehyde to produce the 1,2-nitroalcohol in poor to moderate yields (20-53%), but in high syn-diastereoselectivity (18:1-50:1) (Scheme 18).[78] The boryl nitronate is

synthesized *in situ* by adding chlorodicyclohexyl borane to the sodium nitronate salt at -40 °C, and the Henry reaction occurs after addition of an aldehyde.

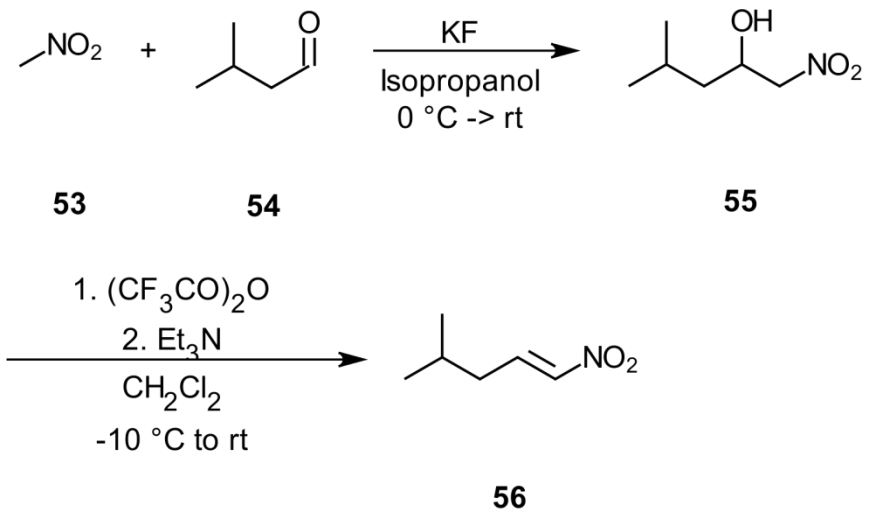


Scheme 18: The Henry reaction using boryl nitronates

2.3 Synthetic attempts of a divinyl nitronate

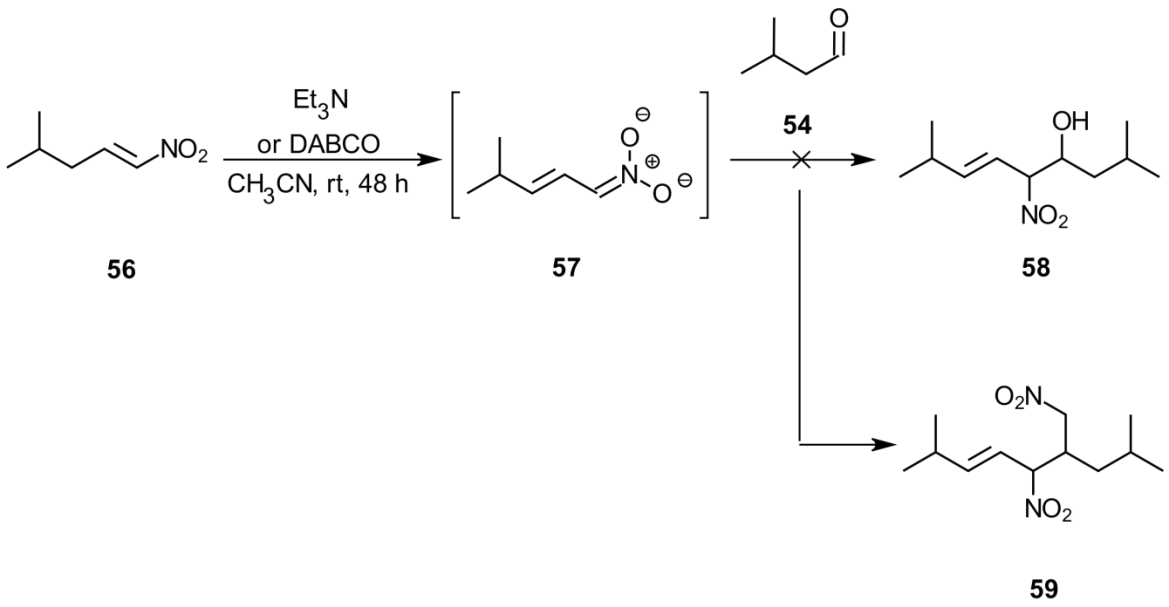
2.3.1 Forming 1,2-nitroalcohol/nitrodiol compounds using nitroalkenes/ 1,2-nitroalcohols

In order to attempt the methodology described by Ono *et al.*,[55] nitroalkene **56** was targeted because the research group has experience producing this type of molecular structure. Using traditional Henry reaction synthetic methods, nitromethane (**53**) was mixed with isovaleraldehyde (**54**) in the presence of catalytic amounts of potassium fluoride to form 4-methyl-1-nitropentan-2-ol (**55**) in a 98% yield. Pure 1,2-nitroalcohol **55** then underwent an elimination reaction by mixing it with trifluoroacetic anhydride followed by triethylamine to produce (*E*)-4-methyl-1-nitropentene (**56**) in a 70% yield (Scheme 19).[79] This methodology produces a majority of the *E*-isomer of the nitroalkene **56**,[79] and comparison of the NMR data to a literature source[80] confirmed the double bond geometry of the isolated nitroalkene.



Scheme 19: Synthesis of (*E*)-4-methyl-1-nitropentene **56**

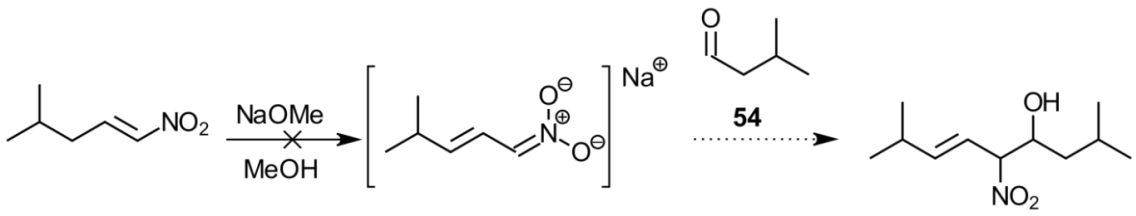
Nitroalkene **56** was then used in a Henry reaction with isovaleraldehyde using the methodology of Ono *et al.* (Scheme 20).[55] The reaction was performed with both triethylamine and DABCO to promote the reaction, but in each case the desired 1,2-nitroalcohol product **58** was not formed. Instead, a Michael addition product was isolated. Nitronate **57** is formed *in situ* from (*E*)-4-methyl-1-nitropentene upon introduction of either base, and adds to an unreacted nitroalkene **56** to yield the Michael product **59**. NMR analysis of the material obtained after column chromatography suggested that this addition reaction was occurring multiple times, something known to happen with nitroalkanes and electron poor alkenes,[81] but unfortunately the exact molecular structures could not be determined.



56 **57** **58** **59**

Scheme 20: Result of the attempted Henry reaction of (*E*)-4-methyl-1-nitropentene **56** with isovaleraldehyde

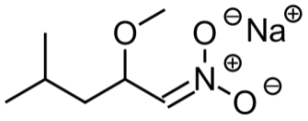
Considering the 1,2-nitroalcohol product **58** was not seen from this reaction, the formation of structure **59** indicated that the Michael reaction was occurring faster than the formation of the 1,2-nitroalcohol. If the sodium salt of the conjugated nitronate **57** was first synthesized and isolated from the reaction conditions, a Michael addition to unreacted nitroalkene could not occur and it was hypothesized that a Henry reaction would. The proposed methodology involved synthesizing **57** from sodium methoxide and the nitroalkene **56** in methanol. The solvent is then removed, and the salt should be isolated without further purification. This salt would then be used in a Henry reaction with isovaleraldehyde to yield the desired product **58** (Scheme 21).



56 **57** **58**

Scheme 21: Proposed Henry reaction of the nitronate of (*E*)-4-methyl-1-nitropentene **56**

Attempts were made to synthesize sodium nitronate salt **57** but they were unsuccessful. The nitronate salt that was isolated was the Michael addition product of the methoxide anion to the nitroalkene to yield sodium 2-methoxy-4-methylpentanenitronate (**60**) (Figure 14).

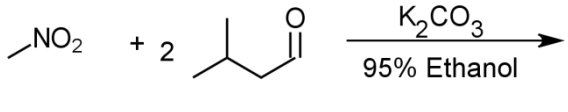
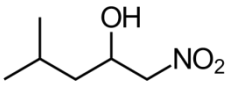
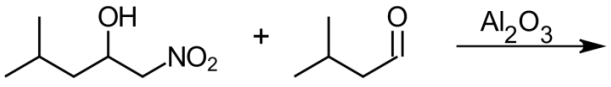
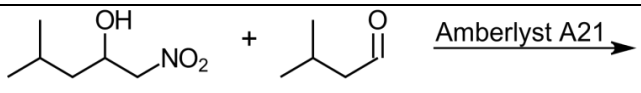
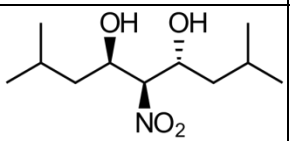


60

Figure 14: Structure of sodium 2-methoxy-4-methylpentanenitronate

After these attempts it was clear that forming a 1,2-nitroalcohol using a nitroalkene was not going to work for this framework without further investigation. Since this was not the focus of the project, the next attempt at synthesizing a divinyl nitronate was to first synthesize a 2-nitro-1,3-diol **61**. Three different reactions from the literature were attempted, with the final experiment yielding the desired nitrodiol **61** in a 56% yield (Table 1).

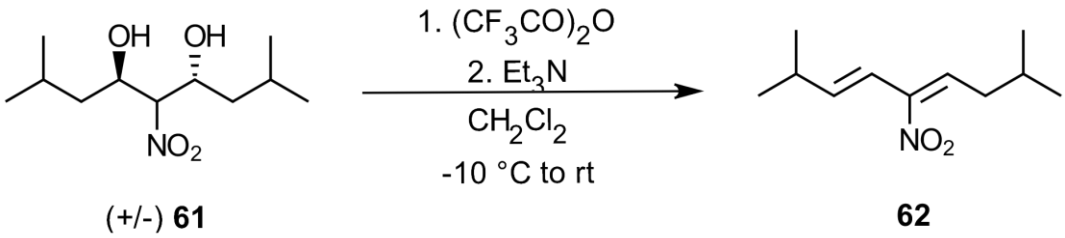
Table 1: Reactions intended to produce 2-nitro-1,3-diol product 61

Entry	Reaction	Product	Yield (%)
1	 **53** **54** Sprang et *al.*[67]	 **55**	87
2	 **55** **54** Rosini et *al.*[68]	NR	NR
3	 **55** **54** Schulz et *al.*[69]	 (+/-) **61**	56

Examining the NMR spectra relating to compound **61** it is evident that it is not the meso compound that is formed in this reaction. In the ^{13}C NMR there are 11 signals indicating a lack of symmetry in the molecule.

2.3.2 Synthesis of a divinyl nitronate

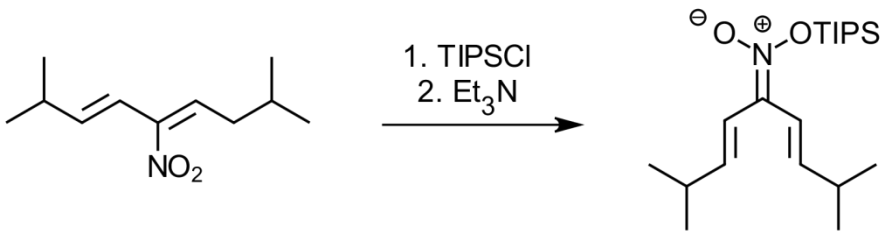
2-Nitro-1,3-diol **61** then underwent an elimination reaction using trifluoroacetic anhydride followed by triethylamine. Two equivalents of trifluoroacetic anhydride and then four equivalents of triethylamine were added to yield 59% of the eliminated product **62** (Scheme 22).



(+/-) **61** **62**

Scheme 22: Synthesis of divinyl nitro compounds

Since the literature contains many examples of formation and isolation of simple silyl nitronates,[82] nitroalkene **62** was then used in attempts to synthesize a divinyl silyl nitronate. Nitroalkene **62** was subjected to triisopropylsilyl (TIPS) chloride and triethylamine in dichloromethane at 0 ^{o}C for 2.5 hours (Scheme 23).



62 **63**

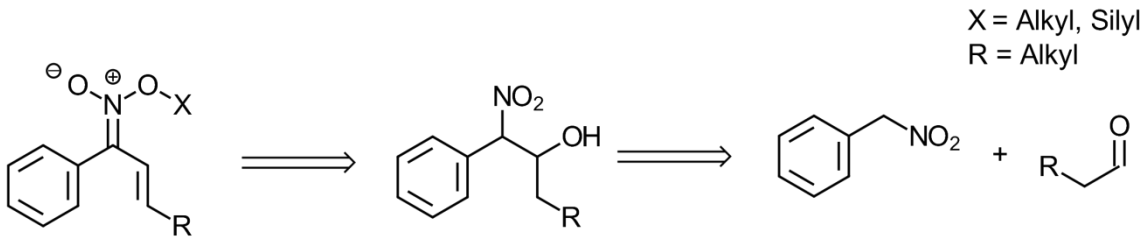
Scheme 23: Synthesis of the divinyl silyl nitronate

TLC analysis revealed that a new compound had formed after these additions; however, after column chromatography this spot had disappeared, indicating that the compound decomposed on the silica gel. ^{1}H NMR analysis of fractions obtained after the separation indicated that a small amount of the nitronate **63** remained after column chromatography (~0.5%). The ^{1}H NMR has a doublet of doublets at 6.90 ppm (J = 15.8, 6.6 Hz, 2H) and a doublet at 6.31 ppm (J = 15.8 Hz, 2H) corresponding to the protons of the alkene portions of the framework. There is also a multiplet ranging from 2.58-2.44 ppm indicative of the CH proton of the isopropyl group (Appendix 2). Unfortunately this compound eluted with TIPSOH and of the collected fractions, only 2% of the mixture was the nitronate. The presence of TIPSOH in the NMR spectrum indicates that the nitronate is readily hydrolysed during purification using silica gel column chromatography.

This work was not successful in isolating a pure divinyl silyl nitronate that could be tested under possible nitronate Nazarov reaction conditions. However, it could be possible for small chain divinyl nitronates to be synthesized react without isolation in a nitronate Nazarov cyclization if reaction conditions were already developed. To possibly increase stability of the divinyl nitronate it was decided to partially embed an aromatic ring into this system. Therefore, the goal was set to synthesize an aryl vinyl silyl nitronate. The results of this attempted synthesis are provided in the following section.

2.4 Synthesis of an aryl vinyl silyl nitronate

The synthesis of a small chain divinyl nitronate was not high yielding in this work, and for this reason, the synthesis of an aryl vinyl nitronate was proposed. Previous research[83] demonstrated that both the silyl nitronate and the nitronic ester of phenylnitromethane could be isolated due to the extended conjugation of the molecule which increased the overall stability. Therefore, it was hypothesized that the isolation of an aryl vinyl silyl nitronate **64** could occur. A retrosynthetic analysis of compound **64** (Scheme 24) shows that it can be synthesized using a Henry reaction, but this time the 1,2-nitroalcohol is replaced with phenylnitromethane (**66**).



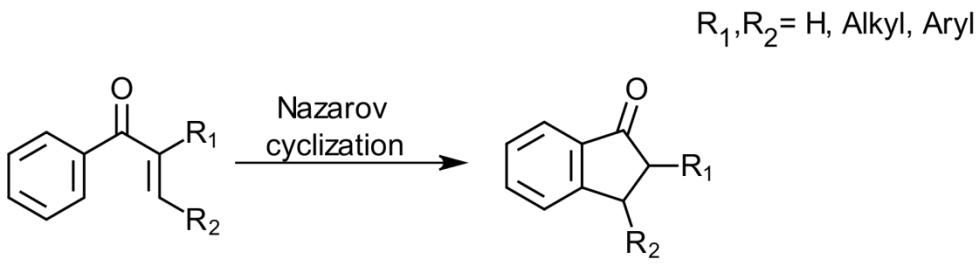
64 **65** **66** **46**

Scheme 24: Proposed synthesis of an aryl vinyl nitronate

2.4.1 Aryl vinyl Nazarov reagents: previous success

Aryl vinyl ketones have been reported sporadically as reagents in the Nazarov cyclization. This is likely due to the fact that in order for Nazarov cyclization to occur, 36 kcal/mol of energy must be added to the reaction to break aromaticity. This, in addition to the energy needed for cyclization is a large amount of energy requirement for the reaction to occur. Typically reaction conditions involve increased temperature and stoichiometric amounts of acid catalyst. These reactions conditions include adding the Nazarov reagent to hot (~120 °C) and/or concentrated acids,[84-86] or subjecting it to microwave conditions (135 °C) to force reactivity.[87]

Recent literature surrounding indanone synthesis using the Nazarov cyclization employs catalytic amounts of initiator,[88-90] or reaction at room temperature.[91,92] However, the products of these cyclizations are important indanone derivatives (Scheme 25); privileged structures (structures that are high affinity ligands for more than one type of biological receptor)[93] that are commonly found in natural products and active pharmaceutical ingredients,[26,86,88,94] and so the efficient synthesis of these compounds is of interest.



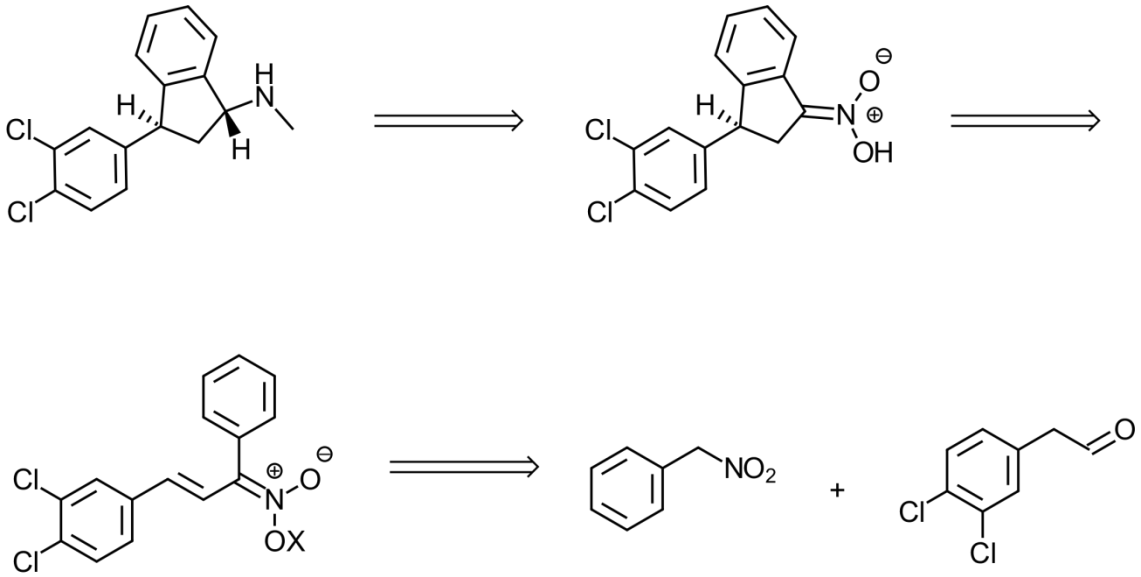
Scheme 25: The Nazarov cyclization of aryl vinyl ketones giving indanone products

In one example of the imino Nazarov cyclization (Scheme 8, Section 1.2.2.2), a series of aryl vinyl imines were used as the reagent undergoing cyclization.[33] This report represents an excellent method to synthesize derivatives of indanamine compounds, without the need for forcing reaction conditions or stoichiometric amounts of catalyst like those used in the majority of syntheses for indanones, and demonstrates that these systems can cyclize efficiently with specific structural variations.

2.4.2 Synthetic potential of aryl vinyl nitronates

Based on the success of aryl vinyl ketones and imines in the Nazarov cyclization, it is possible that indanone or indanamine derivatives could be synthesized using the nitronate Nazarov cyclization of aryl vinyl nitronates. Forcing reaction conditions may not be necessary if the increased reactivity hypothesized for this reaction is correct. If the nitronate Nazarov cyclization can be optimized for many different frameworks, it would represent a viable option for the synthesis of indanones as a Nef reaction can be performed on the product to replace the nitro group for a ketone, or for the synthesis of indanamines by reducing the nitro group to an amine. The nitronate Nazarov cyclization would then be very useful to synthetic chemists when synthesizing natural products or active pharmaceutical ingredients containing these, and other structures of five-membered

rings with a nitrogen substituent. A pharmaceutical ingredient that could be synthesized using the nitronate Nazarov cyclization of aryl vinyl nitronates is (+)-indatraline, a drug targeted to treat depression and psychostimulant abuse.[95-97] A retrosynthetic analysis shows how this compound could be synthesized from phenylnitromethane and 3,4-dichlorophenylacetaldehyde (Scheme 26).



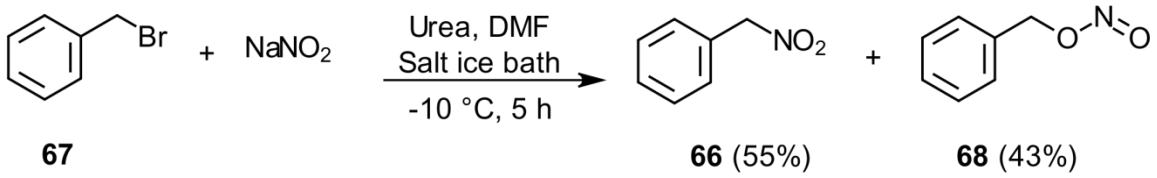
Scheme 26: Retrosynthetic analysis of (+)-indatraline

2.4.3 Synthetic methods of an aryl vinyl silyl nitronate

In the retrosynthesis of the aryl vinyl silyl nitronate (Scheme 24), phenylnitromethane is needed to react in a possible Henry reaction. The 1,2-nitroalcohol obtained from a Henry reaction must then be modified to generate the desired aryl vinyl silyl nitronate. The details of these investigations are described within the following section.

*2.4.3.1 Synthesis of phenylnitromethane **66***

As phenylnitromethane (**66**) is an expensive commercial reagent ($52.50/g from Sigma Aldrich) it was decided to produce this reagent in the lab as significant amounts of phenylnitromethane will be needed for the proposed investigations. The reaction of benzyl bromide with silver nitrite in water to produce phenylnitromethane was attempted,[98] but this reaction was unsuccessful. Another method involving reaction of benzyl bromide (**67**) with sodium nitrite in *N*,*N*-dimethylformamide was then attempted.[99] When the published procedure was repeated, the reaction produced a 50/50 mixture of phenylnitromethane (**66**) and benzyl nitrite (**68**) which was separated using vacuum distillation at 5 mm Hg (Scheme 27).



67 **66** (55%) **68** (43%)

Scheme 27: Literature synthesis of phenylnitromethane **66**

The possibility of forming these two products is due to the fact that the nitrite ion is an ambident nucleophile (Figure 15). This means that there are two atoms on the molecule that are capable of reacting as a nucleophile, and both can add to the electrophilic carbon atom of benzyl bromide.

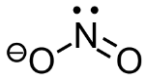
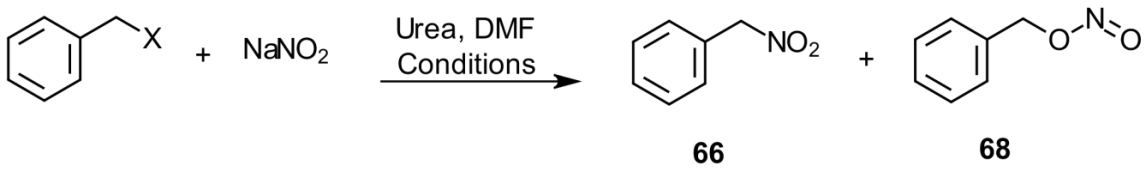


Figure 15: Structure of the nitrite ion

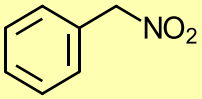
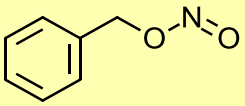
As the literature example did not reveal any kind of investigation to improve this reaction, a brief investigation was initiated in an attempt to obtain larger amounts of phenylnitromethane. A number of different reaction conditions were altered in an attempt

to promote the formation of phenylnitromethane over benzyl nitrite and the results of this investigation are listed in Table 2.

Table 2: Variations to the procedure to synthesize phenylnitromethane 66



66 **68**

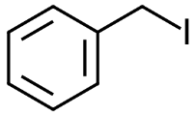
Entry	X	Conditions	Percentage of mixture*	
			 **66**	 **68**
1	Br	-10 °C, 5 h (original procedure)	50%	50%
2	Br	-20 °C, 20 h	50%	50%
3	Br	-40 °C, 20 h	0%	30%
4	Br	-20 °C, 5.5 h	60%	40%
5	I	-20 °C, 5.5 h	50%	50%
6	Cl	-20 °C, 5.5 h	0%	0%
7	Br	Addition of TMSCl, -20 °C, 20 h	0.03%	31%

*based on ^{1}H NMR analysis of crude mixture

First, the reaction was performed in a cooling bath which would maintain the temperature at the desired -10 °C. Even with a constant temperature, the reaction still produced a 50/50 mixture of the two products. The temperature at which the reaction occurred was then altered, excluding room temperature because the original literature report stated that the reaction did not occur when attempted.[99] It was found that if temperatures were too cold (-40 °C), very little reaction occurred and the only product was benzyl nitrite (Entry 3). In this temperature study it was found that by using an electronic cold bath set to a constant -20 °C, the highest ratio of phenylnitromethane to benzyl nitrite (3:2) was obtained (Entry 4). One experiment investigated the effect of time

on the reaction. The reaction was left overnight, and it was discovered that there was no increase in the yield of phenylnitromethane (Entry 2); therefore the time of 5.5 hours was maintained for the remainder of the investigation.

The starting material for the reaction was then altered in attempts to improve the yield of phenylnitromethane. Benzyl iodide (**69**) (Figure 16) was made in a 97% yield by reacting benzyl bromide with sodium iodide in dry acetone.[100] Upon isolation of this compound, ^{1}H and ^{13}C NMR spectra were obtained. The chemical shifts indicative of the CH_2 protons was a singlet at 4.46 ppm, while the carbon atom was at 5.73 ppm, matching the literature data for benzyl iodide.[101] When benzyl iodide was subjected to sodium nitrite and urea in DMF, the reaction produced a 50/50 mixture of the two products (Entry 5). When the halide was altered to chloride, neither reaction product was formed (Entry 6).



69

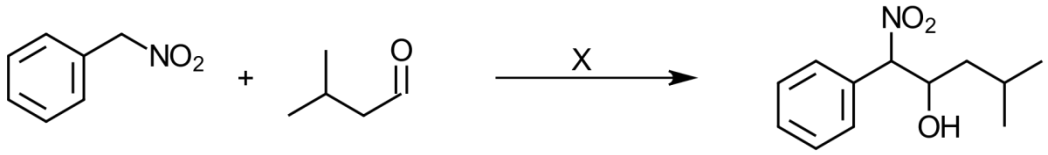
Figure 16: Structure of benzyl iodide

A reaction involving trimethylsilyl (TMS) was performed in an attempt to have TMS add to one of the nucleophilic sites preferentially. If this occurred then a single product could be obtained from this reaction. Since benzyl nitrite was the only product compound isolated from this reaction, at -20 °C (Entry 7), it is apparent that TMS was adding to the nitrogen atom indicating that at this temperature, the nitrogen atom is more nucleophilic towards the TMS group than the anionic oxygen atom. Upon completion of this investigation, it was apparent that the best methodology for synthesizing phenylnitromethane involved a constant temperature of -20 °C and a reaction time of 5.5 hours when benzyl bromide was the starting material.

*2.4.3.2 The Henry reaction with phenylnitromethane (**66**)*

The Henry reaction of α-aryl substituted nitroalkanes has been reported many times in the literature, using catalysts such as copper diamine complexes,[102,103] a guanidine/thiourea organocatalyst,[104] and aluminum oxide,[105] producing good to excellent yields; however, only the aluminum oxide methodology was tested because it was readily available, a catalyst was not required to be synthesized, and a large excess of phenylnitromethane was not needed so isolation of the product from the starting nitroalkane would be significantly less difficult. This reaction produced 33% of the desired 1,2-nitroalcohol **70**; however, considering this is only the second step in the synthesis of an aryl vinyl silyl nitronate, a series of reactions using phenylnitromethane (**66**) and isovaleraldehyde (**54**) were performed to determine if the yield of the 1,2-nitroalcohol **70** could be improved (Table 3).

Table 3: Henry reactions[a] attempted to produce high yield of the 1,2-nitroalcohol



66 **54** **70**

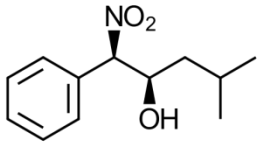
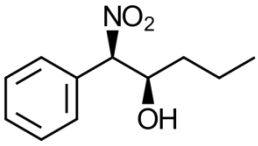
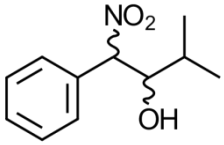
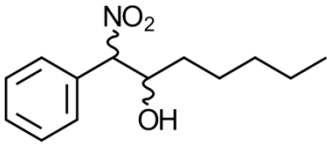
Entry	X	Yield (%)
1	Al_2O_3 (1% H_2O), Neat, 0 °C → rt, 20 h[68]	33
2	5 mol% KF, isopropanol, 0 °C → rt, 20 h[79]	0[b]
3	10 mol % DBU[c], acetonitrile, rt, 24 h[106]	35
4	1. DBU, TIPSCl, -20 °C[d] 2. $Sc(OTf)_3$, rt, 1.5 h	0[b]
5	1. BuLi, $(CH_3O)_2SO_2$[c] 2. $Sc(OTf)_3$, -78 °C → rt, 3 days[77]	0[b]
6	1. NaOMe[d] 2. Cy_2BCl,[c] THF, -40 °C → rt, 3 days[78]	40

[a]ratio of aldehyde to nitroalkane was 1:1 excluding reaction with KF which was 1:2
[b]based on ^1H NMR analysis of crude material
[c]added to phenylnitromethane, followed by addition of aldehyde
[d]nitronate isolated from reaction mixture then added to aldehyde

Unfortunately, the Henry reaction methodology involving potassium fluoride used in the synthesis of a divinyl nitronate was not successful when the nitroalkane became phenylnitromethane. The reaction using DBU produced the 1,2-nitroalcohol in a yield similar to when using aluminum oxide, but this methodology was rejected because phenylnitromethane was not recovered at the end of the process. The methodology developed previously in the laboratory involving silyl nitronates and nitronic esters were both unsuccessful at producing the 1,2-nitroalcohol, even when the nitronate was first isolated and purified, then added to the aldehyde and brought to reflux in THF. The use of boryl nitronates within the Henry reaction was also rejected due to the cost of the boron

reagent and the inability to isolate phenylnitromethane after the reaction. The most practical synthesis of the 1,2-nitroalcohol involves reaction of phenylnitromethane and the aldehyde in a solvent free environment over basic aluminum oxide with 1% water content. The reaction rests, without stirring for 20 hours and the compounds react on the surface of the aluminum oxide powder. This reaction is most practical because after the reaction is complete, phenylnitromethane can be isolated from the mixture (52% recovery when isovaleraldehyde was used) and used again in more reactions. This methodology was then used to synthesize a number of 1,2-nitroalcohol products which were purified using flash chromatography through silica gel (Table 4).

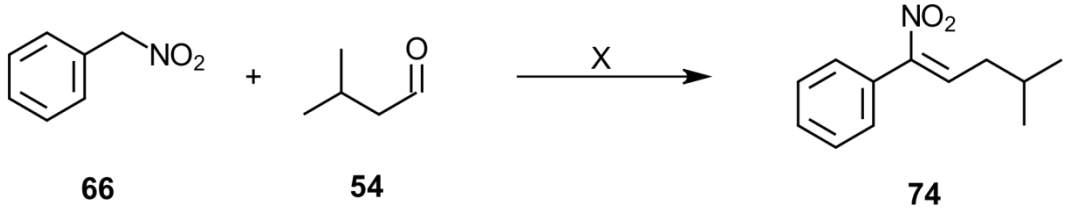
Table 4: Isolated yields of synthesized 1,2-nitroalcohols

Entry	1,2-Nitroalcohol	Yield (%)	Entry	1,2-Nitroalcohol	Yield (%)
1	 (+/-) **70**	33	2	 (+/-) **71**	32
3	 **72**	14	4	 **73**	15

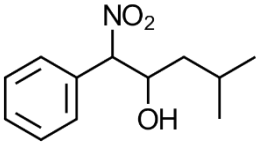
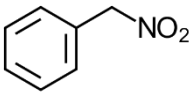
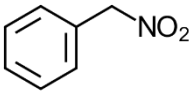
2.4.3.3 Synthesis of nitroalkenes

Another feasible synthetic route to the aryl vinyl silyl nitronate involves forming the nitroalkene directly from phenylnitromethane (**66**) and isovaleraldehyde (**54**) which would decrease the amount of synthetic steps and ideally increase overall yield (Table 5). Unfortunately these attempts to form the nitroalkene **74** using literature reports were not successful.

Table 5: Reactions designed to produce the nitroalkene using direct methods

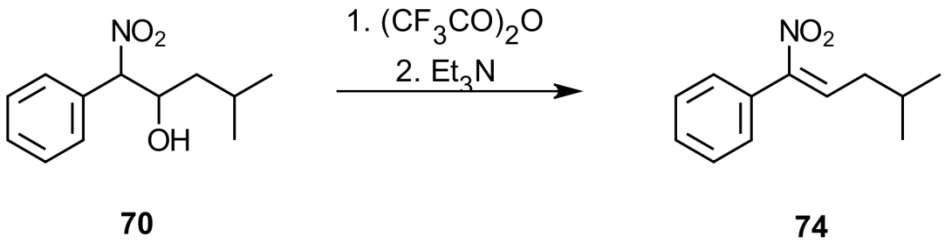


66 **54** **74**

Entry	X	Compound isolated
1	1. Al_2O_3, rt, 24 h 2. CH_2Cl_2, 40 °C[107]	 **70**
2	Piperidine, CH_2Cl_2, reflux[108]	 **66**
3	*tert*-Butylamine[a], acetic acid, rt[109]	 **66**

[a]added to aldehyde and imine was isolated, then added to phenylnitromethane

Since the above methods were unsuccessful, the original synthetic scheme of forming the 1,2-nitroalcohol first was used. A common method of synthesis for nitroalkenes from 1,2-nitroalcohols is an elimination reaction that involves one equivalent of trifluoroacetic anhydride or methanesulfonyl chloride[110] followed by two equivalents of a base.[111] This methodology was performed on the 1,2-nitroalcohol **70** using trifluoroacetic anhydride and triethylamine and was successful in producing the desired nitroalkene **74** in a 79% yield (Scheme 28).[79]



70 **74**

Scheme 28: Synthesis of (*Z*)-4-methyl-1-nitro-1-phenylpentene **74**

With this procedure, the major isomer isolated was always the *Z*-isomer, and the geometry of this compound was determined through NOE experiments. The major isomer has a signature peak in the ^{1}H NMR spectrum at 7.42 ppm corresponding to the proton of the alkene, while the *E*-isomer has this peak at 6.06 ppm. The NOE experiment with the minor isomer indicated that when the protons of the isopropyl group were irradiated, there was an amplification of the signal of the aromatic protons (Figure 17). This was not observed in NOE experiments on the major isomer. It is only in the *E*-geometry that the isopropyl groups would be close in space to the aromatic protons, and cause this signal; therefore, the major isomer was assigned the *Z*-geometry, and the minor was assigned *E*. This methodology was then used to synthesize four nitroalkene products which were purified using flash chromatography on silica gel in good to very good yields (Table 6).

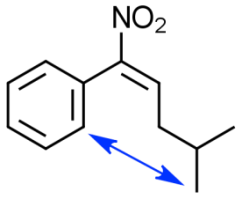
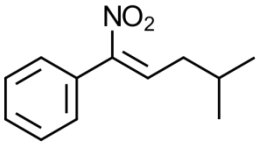
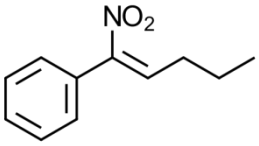
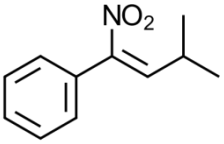
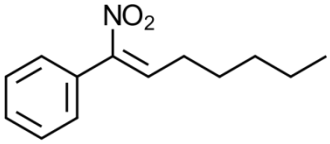


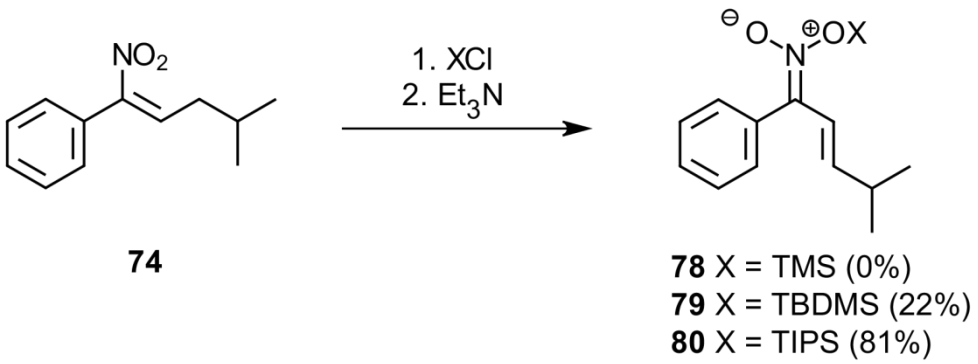
Figure 17: NOE enhancement present in *E*-isomer of the nitroalkene

Table 6: Isolated yields of synthesized nitroalkenes

Entry	Nitroalkene	Yield (%)	Entry	Nitroalkene	Yield (%)
1	 **74**	79	2	 **75**	40
3	 **76**	61	4	 **77**	77

2.4.3.4 Formation of the aryl vinyl silyl nitronate

The final step in the synthesis is the formation of the aryl vinyl silyl nitronate. For this framework, three different silyl groups were used to determine which group would produce the highest yield of the nitronate. The syntheses of the TMS, *tert*-butyldimethylsilyl (TBDMS), and TIPS nitronates were attempted by adding the appropriate silyl chloride and triethylamine to 4-methyl-1-nitro-1-phenylpentene **74** (Scheme 29). When the silyl compound was TMSCl, none of the desired nitronate **78** was isolated. In the synthesis using TBDMSCl, the desired nitronate **79** was isolated in a 22% yield, and when using TIPSCl, triisopropylsilyl 4-methyl-1-phenylpent-2-enenitronate (**80**) is isolated in an 81% yield. These results indicate that a larger, less labile silyl group is required to isolate the aryl vinyl silyl nitronate using a purification procedure.



Scheme 29: Syntheses of aryl vinyl silyl nitronates

A 1D NOE experiment was performed to help determine the geometry of the aryl vinyl silyl nitronate **80**. This experiment suggests that the aryl vinyl silyl nitronate is in the desired s-trans/s-trans geometry due to the presence of an NOE between the β-proton of the alkene and the aromatic protons and a lack of an NOE between the α-proton of the alkene and the aromatic protons (Figure 18). The presence of the NOE suggests that the geometry is correct to perform the Nazarov cyclization. Considering the NOE experiment and the computational studies[28,37] these data suggest that s-trans/s-trans is the most populated geometry. Another 1D NOE experiment was performed to determine which oxygen atom the silyl group was bound to. When the protons of the TIPS group were irradiated, an NOE was not observed between either the aromatic protons or the isopropyl protons of the carbon skeleton. Unfortunately a definitive location for the TIPS group could not be determined through these experiments.

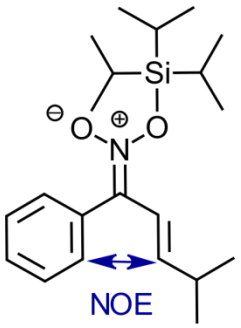
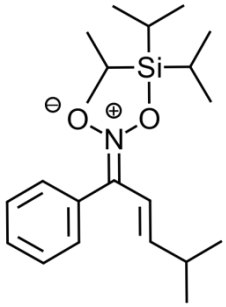
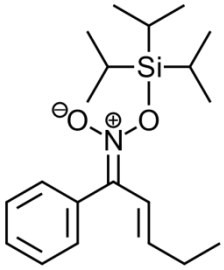
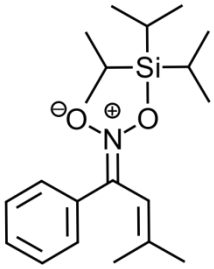
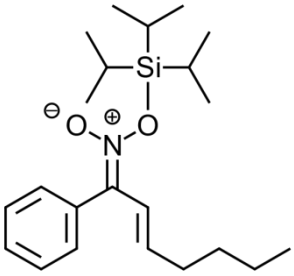


Figure 18: Geometry of the nitronate leading to NOE signal enhancement

With a complete synthesis for a stable silyl nitronate available, the synthesis of four silyl nitronates was completed (Table 7). The only variation was in the synthesis of triisopropylsilyl 3-methyl-1-phenylbut-2-enenitronate (**82**), which used DBU as the base promoting the reaction.

Table 7: Isolated yields of synthesized aryl vinyl silyl nitronates

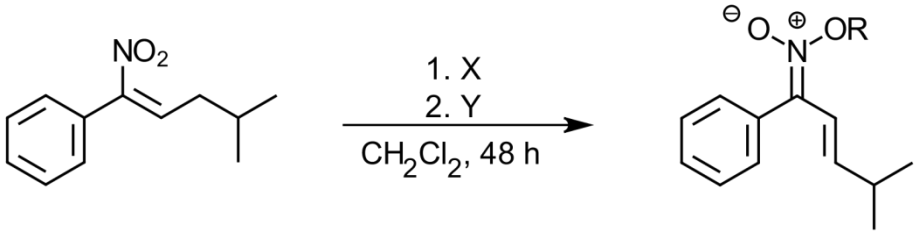
Entry	Aryl vinyl silyl nitronate	Yield (%)	Entry	Aryl vinyl silyl nitronate	Yield (%)
1	 **80**	81	2	 **81**	33
3	 **82**	27	4	 **83**	68

2.4.4 Investigation into the synthesis of other nitronates

The synthesis of an aryl vinyl acyl nitronate was also attempted in order to examine the reactivity of different kinds of aryl vinyl nitronates within the nitronate Nazarov cyclization. Though these species are said to be very unstable, the electron withdrawing properties of the acyl group could potentially increase reactivity even more towards Nazarov cyclization. A number of attempts were made to synthesize an acyl nitronate but during the reaction there was only a small change in the TLC (excluding

reactions with butyllithium), and the acyl nitronate proved difficult to purify (Table 8). The acyl nitronate could not be purified using column chromatography, but it was hypothesized that based on ^{1}H NMR analysis some of the nitronate had formed based on the presence of the following peaks: 7.03 (dd, *J* = 15.5, 6.6 Hz, 1H) and 6.82 (d, *J* = 15.6 Hz, 1H) ppm (Appendix 3). The fractions containing the nitronate structure was less than 10% of the theoretical mass of the acyl nitronate.

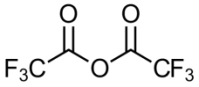
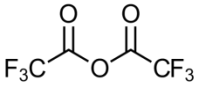
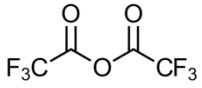
Table 8: Investigation into optimal methodology to yield an acyl nitronate



74

84 R = CH_3CO

85 R = CF_3CO

Entry	X	Y	Success
1		Et_3N	No
2		DBU	Yes[a]
3	BuLi		Yes[a]
4		DBU	0

[a]based on NMR analysis of fractions isolated from column chromatography proposed to contain this compound

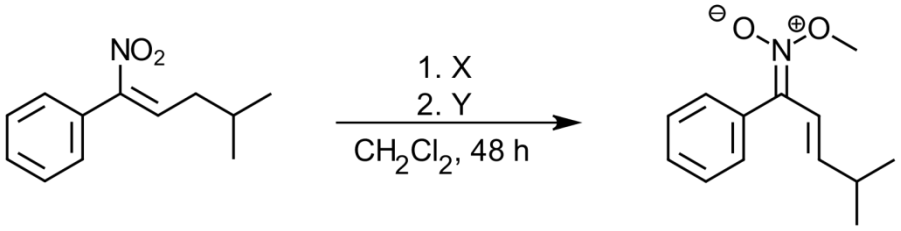
From this table it is clear that an acyl nitronate is more difficult to synthesize than the silyl nitronate. It is possible that the base used to deprotonate the nitroalkene is not strong enough unless a good coordinating group is present in the reaction mixture. Contrary to when a silyl group is used, the acylating agent must not be coordinating as

well to the anionic oxygen atom of the nitro group. Without this coordination, the proton to be removed must not be acidic enough for either triethylamine or DBU to remove it in a high yield.

It is also possible that more energy is required to promote the formation of the acyl nitronate than the silyl nitronate. The temperature of the reaction using trifluoroacetic anhydride and DBU was altered to determine if doing so would yield more of the nitronate. Experiments revealed that refluxing the reaction in dichloromethane or THF did not produce higher yields of the acyl nitronate, and this synthetic product was rejected within this work.

A number of different experiments to synthesize a nitronic ester **86** were also performed, despite reports saying these compounds are unstable. Previous research[83] was able to synthesize and isolate the nitronic ester of phenylnitromethane, so it was thought that the synthesis and isolation of an aryl vinyl nitronic ester could be performed as well. Results from this investigation are shown in Table 9.

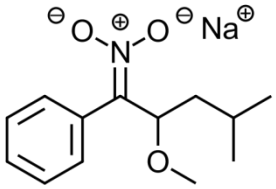
Table 9: Investigation into optimal methodology to yield a nitronic ester



74 **86**

Entry	X	Y	Success
1	Et_3N	CH_3OTf	No
2	BuLi	CH_3OTf	No
3	DBU	$(CH_3O)_2SO_2$	No
4	Et_3N	$(CH_3O)_2SO_2$	No
5	Et_3N	$(CH_3)_3O^+BF_4^-$	No
6	BuLi	$(CH_3)_3O^+BF_4^-$	No
7	$NaN(TMS)_2$	CH_3OTf	Yes

The first attempts used methyl triflate or dimethyl sulfate as the alkylating agent with various bases. Unfortunately these reactions did not produce any nitroic ester. A literature report synthesized a nitronic ester using triethyl oxonium tetrafluoroborate by reacting the nitronate salt with the oxonium salt.[49] The synthesis of a sodium nitronate salt was attempted with 4-methyl-1-nitro-1-phenylpentene **74** using sodium methoxide. As before, the methoxide anion was acting as a nucleophile and added to the nitroalkene forming sodium 2-methoxy-4-methyl-1-phenylpentanenitronate **87** (Figure 19).



87

Figure 19: Sodium 2-methoxy-4-methyl-1-phenylpentanenitronate

When butyllithium was used as the base to promote the formation of both the acyl nitronate and the nitronic ester, it was evident that butyllithium was not reacting exclusively as a base. NMR analysis indicated that a portion of butyllithium was also acting as a nucleophile and was adding to the nitroalkene in a Michael fashion. To eliminate this possibility, a strong base that is non-nucleophilic was used. Using sodium bis(trimethylsilyl)amide, initial experiments indicate that this base was successful in promoting the formation of the nitronic ester. This is likely due to the strength of the base, along with the fact that it is non-nucleophilic, and can only react as a base in this reaction. To synthesize a practical amount of the nitronic ester, optimization of the alkylating agent and reaction conditions must occur. The ^{1}H NMR spectrum of the hypothesized nitronic ester had key signals at 7.49-7.34 (m, 5H), 6.71 (d, J = 16.0 Hz, 1H), 5.68 (dd, J = 16.0, 6.8 Hz, 1H), 3.74 (s, 3H), 2.52-2.36 (m, 1H), and 1.00 (d, 6.5 Hz, 6H) ppm that could indicate the presence of the nitronic ester.

2.5 Future directions

The synthetic method outlined above has been successful in synthesizing the nitronate Nazarov reagent, an aryl vinyl silyl nitronate, in acceptable yields. This reagent will be used in the screening of Lewis and Brønsted-Lowry acid catalysts that will promote the nitronate Nazarov cyclization. The methodology developed can also be used in the synthesis of aryl vinyl silyl nitronates derived from other aldehydes and α-aryl nitroalkanes, and these frameworks can be tested for success in the nitronate Nazarov cyclization.

The syntheses of other aryl vinyl nitronates were attempted, and it was found that a strong, non-nucleophilic base deprotonates the nitroalkene and forms the anionic nitronate. Improvements to this methodology are required before it can be used in nitronate Nazarov cyclizations.

2.6 Experimental methods

General information:

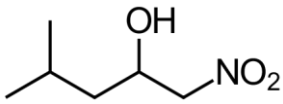
Reagents and solvents were purchased from commercial sources and used without further purification. Exceptions include all aldehydes, which were distilled prior to use, and anhydrous THF and dichloromethane, which were obtained from a PureSolv machine made by Innovation Technology (Newburyport, MA). Ultra high purity argon was purchased from Air Liquide (Halifax, NS). A constant temperature was maintained by placing the flask in a dewar of methanol cooled using a Jubalo FT902 cold finger. Glassware was dried in an oven set at 110 °C for 24 hours and cooled in desiccators containing Drierite prior to use.

Analysis:

Thin layer chromatography was performed on Whatman 250 µm layer Aluminum backed TLC sheets with an F-254 Fluorescent indicator, and plates were developed using potassium permanganate stain. Nuclear Magnetic Resonance (NMR) spectra were recorded at the Nuclear Magnetic Resonance Research Resource (Dalhousie University, Halifax, NS) on a Bruker Avance 500 MHz NMR, or at Saint Mary's University on a Bruker Avance 300 MHz NMR using $CDCl_3$ or $(CD_3)_2SO$ as a solvent with tetramethylsilane as an internal reference. ^1H NMR experiments were performed at 500.1

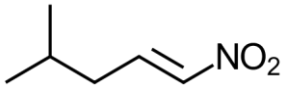
or 300.3 MHz, while ^{13}C NMR experiments were performed at 125.8 or 75.5MHz. Infrared (IR) spectra were recorded neat between sodium chloride plates, or as a KBr pellet on a Nicolet Avatar 330 FT-IR spectrometer. Accurate mass measurements (HRMS) were recorded on a CEC 21-110B spectrometer (Dalhousie University, Halifax, NS).

4-Methyl-1-nitropentan-2-ol (55)



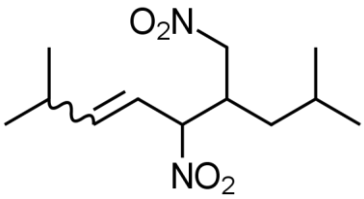
Nitromethane (10.00 mL, 0.19 mol) was added to a solution of isovaleraldehyde (9.87 mL, 92.0 mmol) and potassium fluoride (0.70 g, 12 mmol) in isopropanol (50 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 20 hours. The mixture was diluted with water (50 mL), and extracted with ether (3 x 50 mL). The ether layer was dried over sodium sulfate, gravity filtered, and the compound was isolated after concentration of the organic layer under reduced pressure (12.84 g, 98 %): R_f: 0.30 (20% EtOAc/Hexanes); Clear, colourless liquid; IR (neat): 3415, 2967, 2873, 1556, 1385 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.45-4.38 (m, 3H), 2.64 (br. s, 1H), 1.92-1.84 (m, 1H), 1.58-1.53 (m, 1H), 1.31-1.26 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 81.0, 66.9, 42.4, 24.2, 23.1, 21.7 ppm. This NMR data was consistent with literature values.[80]

(*E*)-4-Methyl-1-nitropentene (56)



To a solution of 4-methyl-1-nitropentan-2-ol (0.65 g, 4.4 mmol) in anhydrous CH_2Cl_2 (10 mL) and under an atmosphere of argon was added trifluoroacetic anhydride (0.61 mL, 4.4 mmol) at 0 °C. This mixture stirred for 15 minutes, after which triethylamine (1.22 mL, 8.8 mmol) was added dropwise. The reaction mixture warmed to room temperature and stirred for 2.5 hours. The mixture was diluted with dichloromethane (20 mL), and the organic layer was washed with water (20 mL), saturated ammonium chloride (20 mL), and brine (20 mL). The organic layer was dried over sodium sulfate, gravity filtered, and the solvent was removed under reduced pressure to give a clear, colourless liquid that was isolated using flash chromatography on silica gel that was 10% deactivated made by adding 10% by mass of distilled water to the silica gel and stirring until homogeneous (5% EtOAc/Hexanes) (2.63 g, 70%): R_f: 0.69 (20% EtOAc/Hexanes); Clear, yellow liquid; IR (neat): 3105, 2960, 2872, 1649, 1525, 1349 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dt, *J* = 13.2, 8.0 Hz, 1H), 6.98 (dt, *J* = 13.1, 1.4 Hz, 1H), 2.20 (ddd, *J* = 8.0, 6.7, 1.4 Hz, 2H), 1.93-1.85 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 141.6, 140.1, 37.2, 27.8, 22.2 ppm. This NMR data was consistent with literature values.[80]

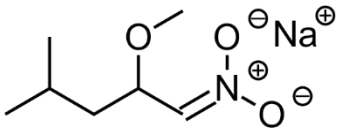
2,8-Dimethyl-5-nitro-6-(nitromethyl)non-3-ene (59)



To a solution of (*E*)-4-methyl-1-nitropentene (0.32 g, 2.5 mmol) and isovaleraldehyde (0.27 mL, 2.5 mmol) in acetonitrile (5 mL) under an inert atmosphere of argon was added DABCO (28 mg, 0.25 mmol). This mixture stirred for 2 days and was diluted with water (12.5 mL) and 1M HCl (2.5 mL). The aqueous phase was extracted with ethyl acetate (3 x 12.5 mL), and the combined organic layer was washed with water (12.5 mL). The organic layer was dried over sodium sulfate, gravity filtered, and the solvent was removed under reduced pressure and the product was isolated using flash chromatography (5% EtOAc/Hexanes) as a mixture of diastereomers (158.4 mg, 29%): R_f: 0.58 (5% EtOAc/Hexanes); Viscous, yellow liquid; IR (neat): 3105, 2960, 2872, 1649, 1525, 1349 cm^{-1}; (Major isomer) ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.77 (t, *J* = 10.4 Hz, 1H), 5.54-5.42 (m, 2H), 4.59 (dd, *J* = 13.7, 5.7 Hz, 1H), 4.46 (dd, *J* = 13.7, 4.5 Hz, 1H) 2.91-2.86 (m, 1H) 2.80-2.73 (m, 1H), 1.73-1.68 (m, 1H), 1.40 (ddd, *J* = 14.2, 9.3, 5.0 Hz, 1H), 1.23 (ddd, *J* = 14.0, 9.3, 4.5 Hz, 1H), 1.06-1.04 (m, 6H), 0.98 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 148.3, 118.0, 85.9, 74.6, 38.7, 36.9, 27.6, 25.1, 23.1, 22.48, 22.46, 21.2 ppm. (Minor isomer) ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.77 (t, *J* = 10.4 Hz, 1H), 5.54-5.42 (m, 2H), 4.55 (dd, *J* = 13.6, 5.8 Hz, 1H), 4.40 (dd, *J* = 13.5, 5.0 Hz, 1H) 2.95-2.91 (m, 1H) 2.69-2.62 (m, 1H), 1.78-1.73 (m, 1H), 1.31-1.29 (m, 1H), 1.29-1.27, (m, 1H), 1.06-1.04 (m, 6H), 0.95 (d, *J* = 6.4 Hz, 6H) ppm; ^{13}C NMR (125.8 MHz,

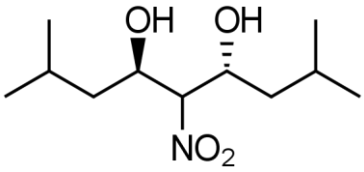
$CDCl_3$): δ = 147.7, 117.7, 84.6, 75.2, 38.8, 36.5, 27.6, 25.0, 22.9, 22.5, 22.4, 21.6 ppm; HRMS: MNa^+: 281.1459, calculated ($C_{12}H_{22}NaN_2O_4$): 281.1477.

Sodium 2-methoxy-4-methylpentanenitronate (60)



HPLC grade methanol (1.00 mL) was added slowly to sodium hydride (400 mg, 10 mmol) cooled in an ice bath. The reaction mixture was stirred for 20 minutes and (*E*)-4-methyl-1-nitropent-1-ene (1.33 mL, 10 mmol) was added. The reaction mixture was stirred for another hour while warming to room temperature. The solvent was removed by distillation at 5 mm Hg, and the salt was further dried at this pressure for 24 hours at room temperature. (1.68 g, 92%): IR (KBr pellet): 2957, 2896, 2870, 1560, 1101 cm^{-1}; ^1H NMR (300.3 MHz, $(CD_3)_2SO$): δ = 5.37 (br. d, *J* = 7.4 Hz, 1H), 4.40 (q, *J* = 7.3 Hz, 1H), 3.15 (s, 3H), 1.68-1.56 (m, 1H), 1.37-1.27 (m, 1H), 1.22-1.12 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 6H) ppm. ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$): δ = 108.0, 74.8, 55.1, 43.1, 24.4, 23.1, 22.5 ppm.

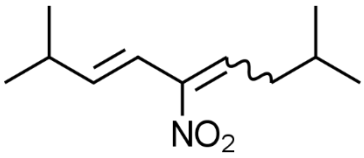
(+/-)-2,8-Dimethyl-5-nitrononane-4,6-diol (61)



(+/-)

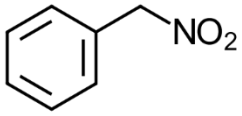
4-Methyl-1-nitropentan-2-ol (0.15 g, 1.0 mmol) was stirred with isovaleraldehyde (0.11 mL, 1.0 mmol), Amberlyst A21 (0.14 g) was added and the mixture stirred for 9 hours. To the mixture was added diethyl ether (2 mL) and this was stirred for three hours. Amberlyst A21 was then removed using gravity filtration, and the solvent was then evaporated and the solid was crystallized from hexanes. (130.6 mg, 56%): R_f: 0.05 (CH_2Cl_2); white solid; melting point$_{(hexanes)}$: 86.0 – 88.0 °C; IR (KBr pellet): 3422, 2959, 2871, 1546, 1367 cm^{-1}; ^1H NMR (300.3 MHz, $CDCl_3$): δ = 4.45-4.29 (m, 2H), 4.29-4.16 (m, 1H), 2.75-2.64 (m, 2H), 1.96-1.76 (m, 2H), 1.67-1.55 (m, 1H), 1.55-1.44 (m, 1H), 1.39-1.26 (m, 1H), 1.26-1.12 (m, 1H), 1.02-0.89 (m, 12H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 94.2, 69.4, 67.6, 42.7, 42.6, 24.5, 24.4, 23.5, 23.0, 21.9, 21.4 ppm: HRMS: MNa^+: 256.1526, calculated ($C_{11}H_{23}NNaO_4$): 256.1517.

2,8-Dimethyl-5-nitro-3,5-nonadiene (62)



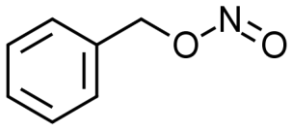
To a solution of 2,8-dimethyl-5-nitrononane-4,6-diol (0.19 g, 0.80 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added trifluoroacetic anhydride (0.22 mL, 1.6 mmol). This mixture stirred for 15 minutes, after which triethylamine (0.46 mL, 3.2 mmol) was added. The reaction mixture stirred for 2.5 hours and was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with saturated ammonium chloride (20 mL), followed by brine (20 mL) and then dried over sodium sulfate. The sodium sulfate was removed by filtration and the solvent was removed under reduced pressure. Flash chromatography (40% CH_2Cl_2/hexanes) was performed to isolate the product. (93.5 mg, 59%): R_f (3*E*,5*Z* isomer - major) 0.41, (3*E*,5*E* isomer - minor): 0.53; (40% CH_2Cl_2/Hexanes); pale yellow liquid; IR (neat): 2962, 2874, 1642, 1556, 1344 cm^{-1}; (3*E*,5*Z* isomer - major) ^1H NMR (300.3 MHz, $CDCl_3$): δ = 7.01 (t, *J* = 7.7 Hz, 1H), 6.12 (d, *J* = 16.0 Hz, 1H), 5.92 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.58-2.40 (m, 1H), 2.22 (t, *J* = 7.3 Hz, 2H), 1.91-1.75 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 6H), 0.98 (d, *J* = 6.5 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.0, 146.9, 134.7, 114.9, 37.2, 31.8, 28.7, 22.5, 21.9 ppm; (3*E*,5*E* isomer - minor) ^1H NMR (300.3 MHz, $CDCl_3$): δ = 5.98 (d, *J* = 15.8 Hz, 1H), 5.74 (dd, *J* = 15.8, 6.5 Hz, 1H), 5.63 (t, *J* = 7.6 Hz, 1H), 2.47-2.33 (m, 1H), 2.11 (t, *J* = 7.2 Hz, 2H), 1.84-1.68 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 6H), 0.94 (d, *J* = 6.5 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.5 (x 2), 125.7, 118.7, 36.7, 31.1, 28.4, 22.3, 21.8 ppm. HRMS: MNa^+: 220.1298, calculated ($C_{11}H_{19}NNaO_2$): 220.1306.

Phenylnitromethane (66)



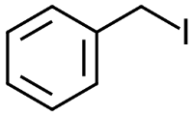
Benzyl bromide (17.8 mL, 0.15 mol) was added to a solution of sodium nitrite (18.0 g, 0.26 mol) and urea (19.0 g) in DMF (270 mL) cooled to -20 °C. The solution stirred at this temperature for 5.5 hours. The mixture was extracted using cold distilled water (300 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (4 x 200 mL) and the combined organic layers were washed with distilled water (4 x 150 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude material was purified using vacuum distillation at 5 mm Hg. Decomposition of phenylnitromethane occurs at 80 °C at 5 mm Hg, so benzyl nitrite was removed (40 °C, 5 mm Hg), and phenylnitromethane remained in the distillation flask. (12.14 g, 59%): R_f: 0.36 (40% CH_2Cl_2/Hexanes); Clear, yellow liquid; IR (neat): 3067, 3036, 2916, 1552, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 500.1 MHz): δ = 7.49-7.43 (m, 5H), 5.47 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 130.0, 129.9, 129.7, 129.1, 80.0 ppm. This NMR data was consistent with literature values.[112]

Benzyl nitrite (68)



Isolated from phenylnitromethane reaction using vacuum distillation at 5 mm Hg (8.84 g, 43%): bp: 43 – 44 °C (5 mm Hg); IR (neat): 3090, 3067, 3035, 2942, 2875, 1651, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 7.49-7.32 (m, 5H), 5.75 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 135.5, 128.7, 128.5, 128.1, 69.9 ppm. The boiling point and NMR data was consistent with literature values.[99]

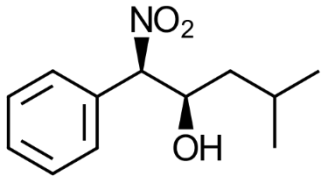
Benzyl iodide (69)



To a solution of benzyl bromide (0.50 mL, 4.2 mmol) in dry acetone (15 mL) was added NaI (694 mg, 4.60 mmol). The mixture then stirred at room temperature for overnight. NaI was filtered off, and the solvent was removed under reduced pressure to yield benzyl iodide (0.89 g, 97%): Yellow liquid; IR (neat): 3061, 3027, 1493, 1453, 1157, 754, 693 cm^{-1} ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 7.41-7.35 (m, 2H), 7.31-7.26 (m, 2H), 7.26-7.21 (m, 1H), 4.46 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 139.3, 128.8, 128.7, 127.9, 5.7 ppm. This NMR data was consistent with literature values.[101]

General method for the synthesis of 1,2-nitroalcohols: To phenylnitromethane (1 equiv) was added the aldehyde (1 equiv) in an ice bath. After five minutes of stirring, basic aluminum oxide (1% water by weight) (1 equiv) was added and the reaction mixture was warmed to room temperature and stirred for a further hour. The mixture then sat for 22 hours. The solid mixture was placed in a Büchner funnel and washed with dichloromethane (5 x 40 mL) using suction filtration techniques. The filtrate was dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure.

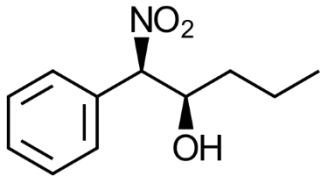
(+/-)-4-Methyl-1-nitro-1-phenylpentan-2-ol (70)



(+/-)

Flash chromatography (dichloromethane) was used to isolate the product (2.76 g, 33%): R_f: 0.24 (CH_2Cl_2); Clear, yellow liquid; IR (neat): 3427, 2958, 2871, 1556, 1362 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.46-7.41 (m, 5H), 5.32 (d, *J* = 9.6 Hz, 1H), 4.66 (td, *J* = 10.1, 2.1 Hz, 1H), 2.47 (br. s, 1H), 1.94-1.86 (m, 1H), 1.39 (ddd, *J* = 14.0, 10.5, 3.7 Hz, 1H), 0.94-0.89 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 132.0, 130.1, 129.1, 128.1, 97.2, 70.8, 41.1, 23.9, 23.5, 20.8 ppm; HRMS MNa^+: 246.1102, calculated ($C_{12}H_{17}NaNO_3$): 246.1106. The *syn* diastereomer was determined using information provided in the following report submited for publication.[78]

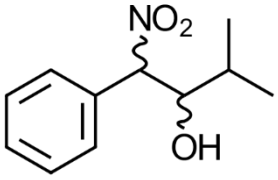
(+/-)-1-Nitro-1-phenylpentan-2-ol (71)



(+/-)

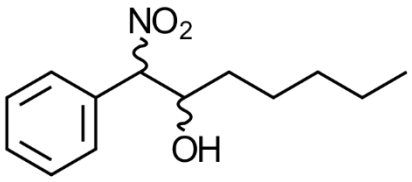
Product was purified by crystallization from hexanes (2.06 g, 32%); R_f: 0.27 (CH_2Cl_2); White solid; melting point$_{(hexanes)}$: 70.0-72.0 °C; IR (KBr pellet): 3371, 2965, 2875, 1551, 1363 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.47-7.40 (m, 5H), 5.36 (d, *J* = 9.8 Hz, 1H), 4.63-4.58 (m, 1H), 2.53-2.49 (m, 1H), 1.63-1.52 (m, 1H), 1.45-1.31 (m, 2H), 1.26-1.19 (m, 1H) 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 132.1, 130.2, 129.2, 128.0, 96.8, 72.3, 34.2, 18.2, 13.6 ppm. This NMR data is consistent with literature values (stereochemistry not determined).[104]

3-Methyl-1-nitro-1-phenylbutan-2-ol (72)



Product was purified by crystallization from hexanes (2.31 g, 14%); R_f: 0.25 (CH_2Cl_2); white solid; melting point$_{(hexanes)}$; 48.0-50.0 °C; IR (KBr pellet): 3459, 2965, 2933, 2876, 1552, 1368 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.8 Hz, 2H), 7.45-7.40 (m, 3H), 5.47 (d, *J* = 10.2 Hz, 1H), 4.53-4.48 (m, 1H), 2.28 (d, *J* = 5.5 Hz, 1H), 1.51-1.43 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 131.9, 130.2, 129.2, 128.1, 95.3, 76.1, 28.4, 20.2, 13.9 ppm. HRMS MNa^+: 232.0934, calculated ($C_{11}H_{15}NaNO_3$): 232.0942.

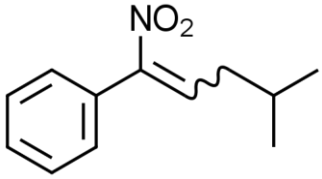
1-Nitro-1-phenylheptan-2-ol (73)



Product was purified by crystallization from hexanes (1.82 g, 15%): R_f: 0.15 (CH_2Cl_2); white solid; melting point$_{(hexanes)}$: 83.0-84.0 °C; IR (KBr pellet): 3358, 2922, 2854, 1548, 1367 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.48-7.39 (m, 5H), 5.33 (d, *J* = 9.8 Hz, 1H), 4.60-4.53 (m, 1H), 2.38 (d, *J* = 5.2 Hz, 2H) 1.54-1.42 (m, 1H), 1.38-1.27 (m, 2H), 1.27-1.11 (m, 5H), 0.84 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 132.1, 130.2, 129.2, 128.0, 96.7, 72.5, 32.1, 31.3, 24.6, 22.4, 13.9 ppm; HRMS MNa^+: 260.1259, calculated ($C_{13}H_{19}NaNO_3$): 260.1263. This NMR data is consistent with literature values (stereochemistry not determined).[105]

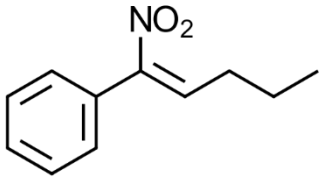
General method for the synthesis of nitroalkenes: To a solution of 1,2-nitroalcohol (1 equiv) in CH_2Cl_2 (10 mL) under an atmosphere of argon at -10 °C was added trifluoroacetic anhydride (1 equiv). This mixture stirred for five minutes, after which triethylamine (2 equiv) was added slowly. The reaction mixture stirred for three hours. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated ammonium chloride (2 x 20 mL), the aqueous layer was back-extracted with CH_2Cl_2 (40 mL), and the combined organic layers were washed with brine (20 mL) and then dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure.

4-Methyl-1-nitro-1-phenylpentene (74)



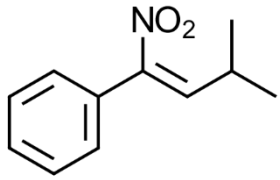
Flash chromatography (40% CH_2Cl_2/Hexanes) was performed to isolate the product (1.52 g, 79%): R_f: 0.33 (40% CH_2Cl_2/Hexanes); Clear, yellow liquid; IR (neat): 3051, 2958, 2931, 2871, 1522, 1334 cm^{-1}; (*Z* isomer-major) = ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.46-7.44 (m, 3H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.28-7.24 (m, 2H), 2.02 (t, *J* = 7.5 Hz, 2H) 1.87-1.77 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 6H) ppm.; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 151.7, 137.7, 130.4, 129.7, 129.5, 128.4, 37.3, 28.3, 22.3 ppm.; (*E* isomer-minor) = ^1H NMR (300.3 MHz, $CDCl_3$): δ = 7.44-7.33 (m, 5H), 6.06 (t, *J* = 7.7 Hz, 1H), 2.26 (t, *J* = 7.2 Hz, 2H) 1.95-1.77 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.9, 131.6, 129.5, 128.8, 127.1, 126.2, 37.1, 28.4, 22.3 ppm.; This NMR data was consistent with literature values.[113] HRMS MNa^+: 228.0987, calculated ($C_{12}H_{15}NaNO_2$): 228.1000.

(*Z*)-1-Phenyl-1-nitropentene (75)



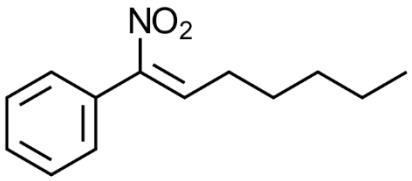
Flash chromatography (40% CH_2Cl_2/Hexanes) was performed to isolate the product (123.3 mg, 40%); R_f: 0.28 (40% CH_2Cl_2/Hexanes); Pale green liquid; IR (neat): 3052, 2926, 2933, 2873, 1660, 1522, 1334 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40-7.37 (m, 3H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.23-7.19 (m, 2H), 2.09 (q, *J* = 7.6 Hz, 2H), 1.56-1.47 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 151.4, 138.5, 130.3, 129.7, 129.5, 128.5, 30.4, 21.8, 13.7 ppm. This NMR data was consistent with literature values.[80]

(*Z*)-3-Methyl-1-nitro-1-phenylbutene (76)



Flash chromatography (40% CH_2Cl_2/Hexanes) was performed to isolate the product (1.13 g, 61%); R_f: 0.57 (40% CH_2Cl_2/Hexanes); Pale yellow solid; Melting point: 43.5-45.0 °C; IR (KBr pellet): 3051, 2966, 2931, 2872, 1522, 1333 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47-7.42 (m, 3H), 7.29-7.24 (m, 2H), 7.18 (d, *J* = 10.9 Hz, 1H), 2.41-2.31 (m, 1H), 1.07 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 149.7, 144.2, 130.2, 129.9, 129.5, 128.5, 28.3, 21.9 ppm; HRMS MNa^+: 214.0838, calculated ($C_{12}H_{15}NaNO_2$): 214.0836.

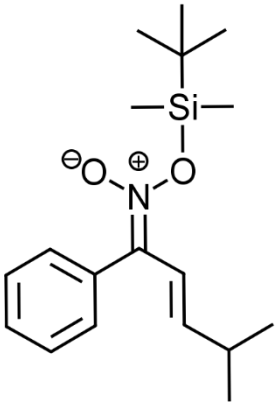
(*Z*)-1-Nitro-1-phenylheptene (77)



Flash chromatography (40% CH_2Cl_2/Hexanes) was performed to isolate the product (1.30 g, 77%); R_f: 0.36 (40% CH_2Cl_2/Hexanes); Pale yellow liquid; IR (neat): 3058, 2957, 2930, 2859, 1522, 1333 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.46-7.43 (m, 3H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.29-7.24 (m, 2H), 2.12 (q, *J* = 7.7 Hz, 2H) 1.52-1.44 (m, 2H), 1.29-1.22 (m, 4H), 0.89-0.84 (m, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 151.2, 138.8, 130.3, 129.7, 129.5, 128.4, 31.3, 28.5, 28.1, 22.2, 13.8 ppm; HRMS MNa^+: 242.1162, calculated ($C_{12}H_{15}NaNO_2$): 242.1157.

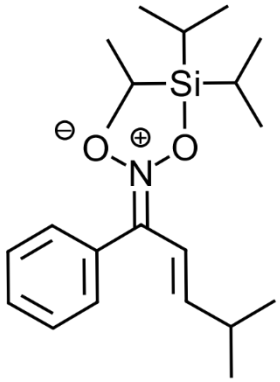
General method for the synthesis of silyl nitronates: To the nitroalkene (1 equiv) in CH_2Cl_2 (10 mL) under an atmosphere of argon at -10 °C was added the given silyl chloride (1 equiv). The mixture was stirred for five minutes, and triethylamine (1 equiv) was added. The mixture was warmed to room temperature and stirred for 2 days. The mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated ammonium chloride (10 mL), the aqueous layer was re-extracted with CH_2Cl_2 (10 mL), the combined organic layers were washed with brine (10 mL) and dried over sodium sulfate, filtered, and the solvent was eliminated under reduced pressure.

(*E*)-*tert*-Butyldimethylsilyl 4-methyl-1-phenylpent-2-enenitronate (79)



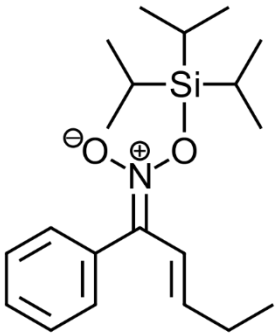
Flash chromatography (dichloromethane) was used to isolate the product (68.2 mg, 22%). R_f: 0.33 (CH_2Cl_2); Clear, pale green liquid; IR (neat): 3024, 2932, 2884, 2872, 1558 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.41-7.30 (m, 5H), 6.78 (d, *J* = 16.0 Hz, 1H), 5.61 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.51-2.36 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 6H), 0.80 (s, 9H), 0.33 (s, 6H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 146.2, 131.6, 129.8, 128.4, 128.0, 127.9, 120.4, 31.8, 25.7, 21.8, 17.6, -4.16 ppm; HRMS MNa^+: 342.1850, calculated ($C_{18}H_{35}NaNO_2Si$): 342.1857.

(*E*)-Triisopropylsilyl 4-methyl-1-phenylpent-2-enenitronate (80)



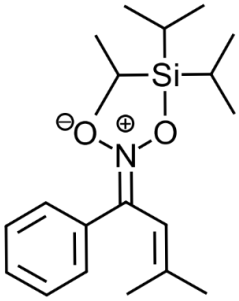
Flash chromatography (40% CH_2Cl_2/Hexanes) was used to isolate the product (2.05 g, 81%). R_f: 0.21 (40% CH_2Cl_2/Hexanes); Clear, viscous, pale green liquid; IR (neat): 3032, 2947, 2893, 2867, 1555 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.43-7.39 (m, 2H), 7.38-7.34 (m, 3H), 6.80 (dd, *J* = 16.1, 1.3 Hz, 1H), 5.59 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.43 (dqd, *J* = 13.5, 6.7, 1.3 Hz, 1H), 1.35-1.25 (m, 3H), 1.06 (d, *J* = 7.5 Hz, 18H), 1.01 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 145.8, 131.7, 129.8, 128.4, 128.1, 127.0, 120.4, 31.8, 21.9, 17.9, 12.6 ppm; HRMS MNa^+: 384.2315, calculated ($C_{21}H_{35}NaNO_2Si$): 384.2327.

(*E*)-Triisopropylsilyl 1-phenylpent-2-enenitronate (81)



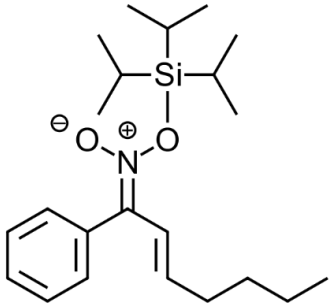
Flash chromatography (40% CH_2Cl_2/hexanes) was used to isolate the product (482.6 mg, 33%); Pale green liquid; R_f: 0.18 (40% CH_2Cl_2/Hexanes); IR (neat): 3033, 2964, 2945, 2892, 2867, 1556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.39 (m, 2H), 7.37-7.35 (m, 3H), 6.83 (br. d, *J* = 16 Hz, 1H), 5.66 (dt, *J* = 15.9, 6.7 Hz, 1H), 2.18 (quin, *J* = 7.5 Hz, 2H), 1.30 (spt, *J* = 7.4 Hz, 3H), 1.06 (d, *J* = 7.5 Hz, 18H), 1.02 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 140.6, 131.7, 129.7, 128.4, 128.1, 126.9, 122.2, 26.4, 18.0, 13.0, 12.6 ppm; HRMS MNa^+: 370.2172, calculated ($C_{20}H_{33}NaNO_2Si$): 370.2170.

Triisopropylsilyl 1-phenylbut-2-enenitronate (82)



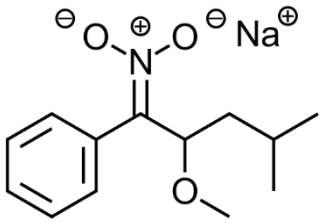
Flash chromatography (40% CH_2Cl_2/Hexanes) was used to isolate the product (93.6 mg, 27%); R_f: 0.16 (40%CH_2Cl_2/Hexanes); Yellow liquid; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ = 7.62-7.56 (m, 2H), 7.40-7.28 (m, 3H), 6.21 (s, 1H), 1.88 (s, 3H), 1.39-1.26 (m, 3H), 1.28 (s, 3H), 1.07 (d, *J* = 7.6 Hz, 18H) ppm. The compound decomposed before characterization could be completed, and the compound has not been synthesized since.

(*E*)-Triisopropylsilyl 1-phenylhept-2-enenitronate (83)



Flash chromatography (40% CH_2Cl_2/Hexanes) was used to isolate the product (571.5 mg, 68%); R_f: 0.16 (40% CH_2Cl_2/Hexanes); Pale yellow liquid: IR (neat): 3041, 2945, 2940, 2883, 2870, 1558 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$) δ = 7.44-7.31 (m, 5H), 6.83 (d, *J* = 15.9 Hz, 1H), 5.68-5.54 (m, 1H), 2.22-2.10 (m, 2H), 1.41-1.21 (m, 7H), 1.05 (d, *J* = 7.2 Hz, 18H), 0.88 (t, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.3, 131.7, 129.8, 128.4, 128.1, 126.9, 123.0, 33.1, 31.0, 22.2, 18.0, 13.9, 12.6 ppm. HRMS MNa^+: 398.2480, calculated ($C_{22}H_{37}NaNO_2Si$): 398.2483.

Sodium 2-methoxy-4-methyl-1-phenylpentanenitronate (87)



HPLC grade methanol (1.00 mL) was added slowly to sodium hydride (400 mg, 10.0 mmol) cooled in an ice bath. The reaction mixture was stirred for 20 minutes and 4-methyl-1-phenylnitropentene (0.21 g, 10.0 mmol) was added. The reaction mixture was stirred for another hour while warming to room temperature. The solvent was removed by distillation at 5 mm Hg, and the solid was further dried at this pressure for 24 hours. (0.20 g, 92%): orange solid; IR (KBr pellet): 3064, 2924, 2854, 1560, 1388, 1143, 984 cm^{-1}; ^{1}H NMR (300.3 MHz, $(CD_3)_2SO$): δ = 7.77 (br. d, *J* = 7.6 Hz, 2H), 7.15 (br. t, *J* = 7.7 Hz, 2H), 6.96 (br. t, *J* = 7.0 Hz, 1H), 5.36 (t, *J* = 7.2 Hz, 1H), 3.19 (s, 3H), 1.62-1.51 (m, 1H), 1.49-1.37 (m, 1H), 1.31-1.19 (m, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$): δ = 141.4, 136.6, 128.3, 126.5, 123.6, 77.5, 55.1, 42.5, 24.8, 23.1, 22.6 ppm.

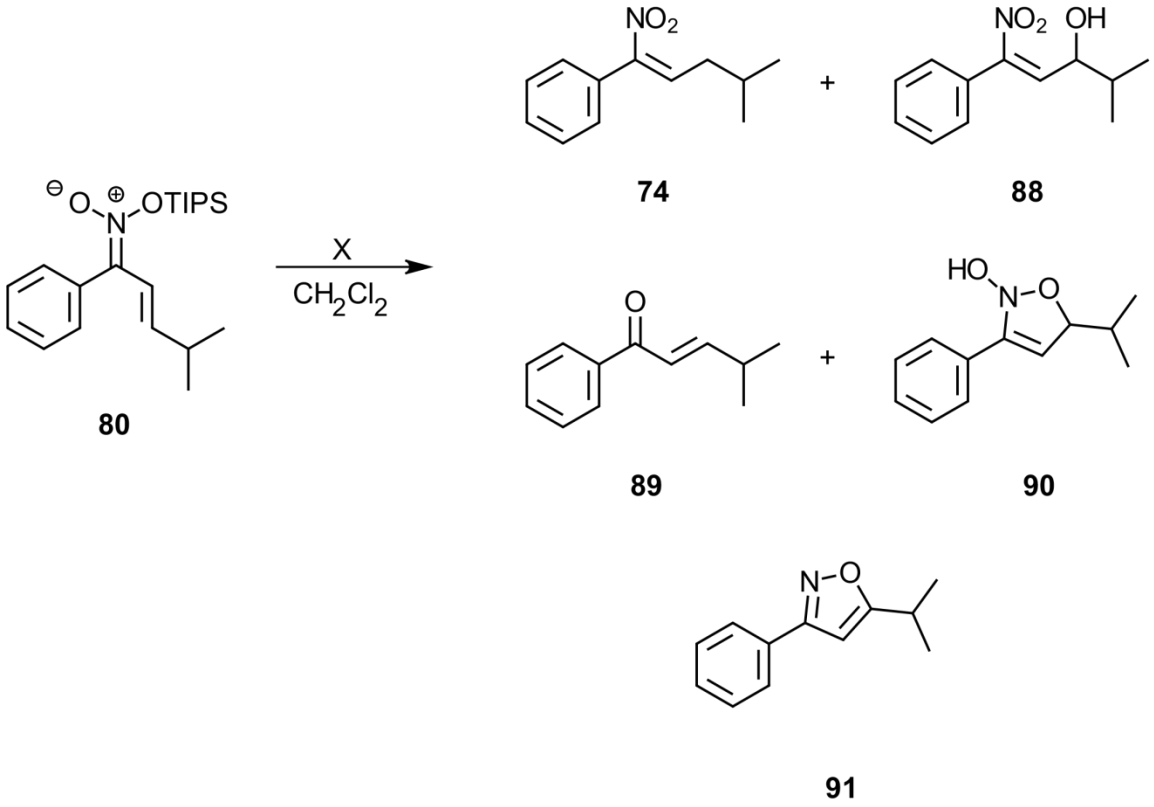
Chapter 3: Investigation of the nitronate Nazarov cyclization

With many aryl vinyl silyl nitronates in hand, it was possible to investigate reaction conditions that would promote the nitronate Nazarov cyclization. This investigation involved a screening of Lewis and Brønsted-Lowry acid catalysts and a study of temperature variance. The results of these investigations are described in this chapter.

3.1 Initial acid screening

The Nazarov cyclization has been initiated using a number of different Lewis or Brønsted-Lowry acid catalysts ranging from simple to complex.[2-6] To begin the investigation of the nitronate Nazarov cyclization a number of simple Lewis and Brønsted-Lowry acid catalysts were added to solutions containing (*E*)-triisopropylsilyl 4-methyl-1-phenylpent-2-enenitronate (**80**) in dichloromethane. The reaction was monitored by TLC analysis for the disappearance of the starting nitronate (Table 10). Each reaction produced a combination of products; some of which were seen in many reaction mixtures.

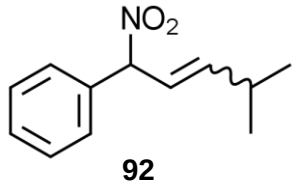
Table 10: Acid catalyst screening for the nitronate Nazarov cyclization



Entry	X	Time (h)	Amount of catalyst	Yield (%)				
				74	**88**	**89**	**90**	**91**
1	$Sc(OTf)_3$	5	5 mol%	24	0	0	0	20
2	$Cu(OTf)_2$	24	5 mol%	40	0	3	0	20
3	$SnCl_2$	24	1 equiv	29	0	7	0	8
4	BF_3 etherate	24	1 equiv	30	0	0	7	0
5	H_2SO_4	24	1 equiv	25	0	0	23	16
6	HBr	24	1 equiv	40	0	0	26	0
7	H_3PO_4	24	1 equiv	36	14	0	0	0
8	HCl	24	1 equiv	38	9	2	0	0
9	HNO_3	24	1 equiv	61	7	10	4	0

In each reaction, the remaining mass that did not constitute products **74** and **88 – 91** was intractable material. A common result of this screening was to isolate the *E*

and *Z* isomer of 4-methyl-1-nitro-1-phenylpentene (**74**) from the reaction mixture, as well as 4-methyl-1-nitro-1-phenylpent-2-ene (**92**) (Figure 20). The presence of these nitroalkene products indicates that under the Brønsted-Lowry acid reaction conditions, a proton was adding to the nitronate and the silyl group was removed. When a Lewis acid catalyst is used and reaction conditions were assumed to be aprotic, it is clear that there was some amount of water present in order to form the nitroalkene **74**. This indicates that in order to optimize reactivity of the aryl vinyl silyl nitronate and prevent the possibility of forming the nitroalkene, the reaction should occur in a glove box to ensure a completely anhydrous atmosphere.



92

Figure 20: 4-methyl-1-nitro-1-phenylpent-2-ene

One of the products isolated from this screening was 4-methyl-1-nitro-1-phenylpenten-3-ol (**88**), the result of the addition of water to the alkene of the aryl vinyl silyl nitronate followed by hydrolysis of the TIPS group. Another example of water reacting with the aryl vinyl nitronate is evident in the formation of the ketone **89**. It is the result of the hydrolysis of the nitronate to form the nitronic acid, which then reacts via a Nef reaction under the acidic conditions to form the aryl vinyl ketone. This reaction requires the presence of water, and indicates that completely anhydrous conditions were not present in the Lewis acid reaction of tin(II) chloride and copper(II) triflate. The formation of products **88** and **89** indicate that reaction conditions must not be wet if the nitronate Nazarov cyclization is to occur. If water is present in the reaction mixture, reaction with water occurs faster than the proposed nitronate Nazarov cyclization at room temperature. Therefore, care must be taken to ensure that conditions are kept anhydrous.

Another product that was isolated in this screening was 5-isopropyl-3-phenyl-2,5-dihydroisoxazol-2-ol (**90**). Though this structure has not previously been reported, a full characterization of the compound was performed (^{1}H NMR, ^{13}C NMR, 2D NMR experiments, IR, HRMS) and all spectra indicate that this compound had been formed. Finally, the major product isolated in most of the reactions is 5-isopropyl-3-phenylisoxazole **91**. This isoxazole is known in the literature, and the characterization data match this report.[114] These two products are a result of a different cyclization, to be discussed in Section 3.3.

3.2 Further attempts at the nitronate Nazarov cyclization

The temperature at which the attempted nitronate Nazarov cyclization was occurring was then altered to determine if this would promote Nazarov reactivity. The reaction chosen was that using scandium(III) triflate because of all the reactions attempted, this catalyst yielded the smallest amount of the aryl vinyl nitronate undergoing hydrolysis to the nitroalkene **74**. A comparison of the temperature of reaction and yield of product is provided in Table 11.

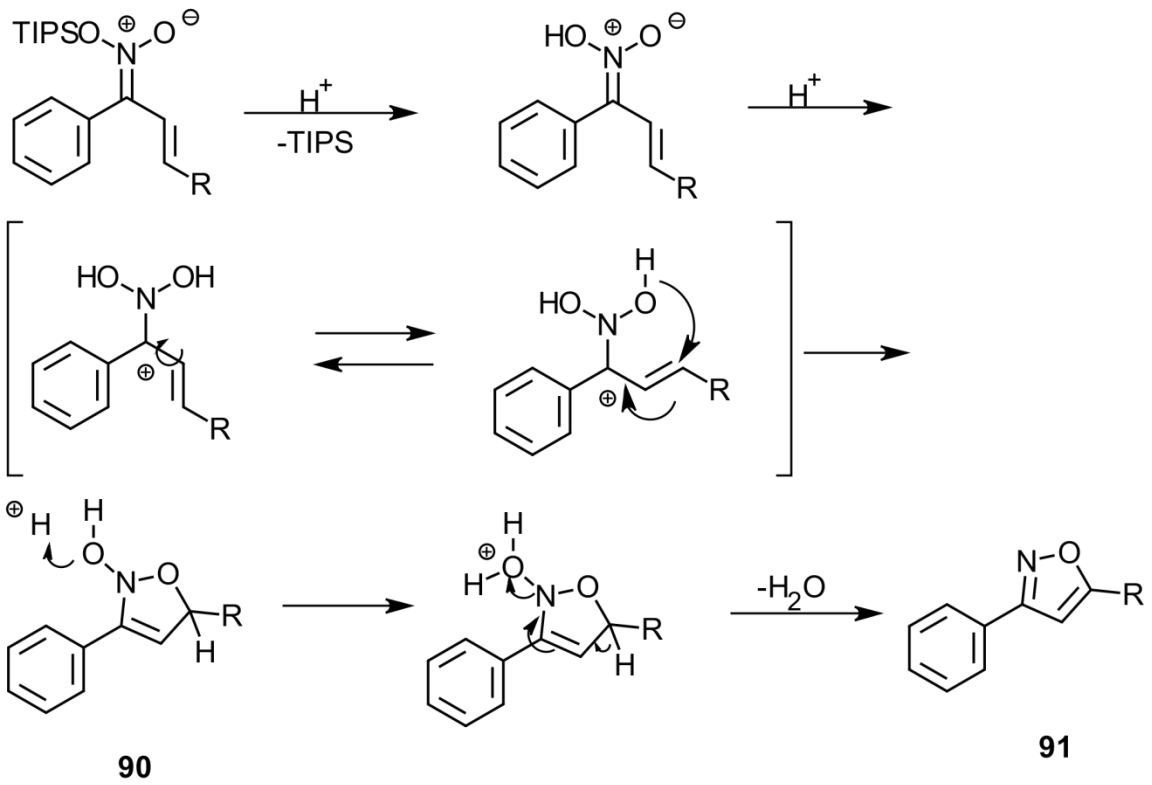
Table 11: Temperature variations of the attempted nitronate Nazarov reactions

Entry	Solvent	Temperature	Product (Yield)
1	CH_2Cl_2	-78 °C →-40 °C →-20 °C	4-methyl-1-nitro-1-phenylpentene **74** (85%)
2	CH_2Cl_2	rt	5-isopropyl-3-phenylisoxazole **91** (20%)
3	THF	66 °C	5-isopropyl-3-phenylisoxazole **91** (27%)
4	Toluene	111 °C	5-isopropyl-3-phenylisoxazole **91** (54%)

It is worth mentioning that upon heating the aryl vinyl silyl nitronate at reflux temperature in toluene the compound did not decompose or react; indicating the stability of this nitronate. It was only upon addition of scandium(III) triflate did the silyl nitronate react and/or decompose. Once scandium(III) triflate was added, the isoxazole product was isolated in higher yields than when the reaction occurred at room temperature. Raising the temperature provided enough energy for the cyclization reaction yielding the isoxazole products. With experiments at temperatures below 0 °C, the reactions were monitored at each temperature using TLC analysis. When no change in TLC occurred over one hour, the temperature was increased until a change was observed and the nitronate spot had disappeared. In this experiment, 4-methyl-1-nitro-1-phenylpentene was isolated in an 85% yield and a very small amount of an unknown product was obtained. This compound eluted with TIPSOH, and was not able to be purified and characterized. The results of this experiment demonstrate the need for heat if any cyclization is to occur.

3.3 Explaining the formation of the isoxazole and dihydroisoxazole

In order to determine why the desired nitronate Nazarov cyclization is not occurring, a small investigation into the mechanism of formation of the isoxazole and dihydroisoxazole products began. The first step in the proposed mechanism is the hydrolysis of the TIPS group of the aryl vinyl silyl nitronate to yield an aryl vinyl nitronic acid. Then, the anionic oxygen atom attacks the β-carbon of the nitronate and forming a five membered ring. It is hypothesized that for the isoxazole, elimination of a proton and loss of water completes the reaction (Scheme 30). When the dihydroisoxazole is formed, this elimination reaction does not occur.



Scheme 30: Proposed Mechanism of formation for the isoxazole and dihydroisoxazole products

This hypothesis was supported using ^{29}Si NMR experiments. If the TIPS group was carried along on the nitronate throughout the reaction pathway then ^{29}Si NMR spectra would yield multiple peaks; indicative of the intermediate compounds in the mechanism. In an NMR tube, H_2SO_4 was added to the silyl nitronate **81** in $CDCl_3$ and in the other NMR tube, $Sc(OTf)_3$ was added. For the experiment containing $Sc(OTf)_3$ (Appendix 5), after two hours of reacting, the ^{1}H NMR spectrum contained peaks relating to the aryl vinyl silyl nitronate **81**, the isoxazole product **91**, and the nitroalkene **74**. The presence of the nitronate indicates that the reaction was still taking place at this time. The ^{1}H-^{29}Si HMBC spectrum only showed peaks relating to TIPSOH (15 ppm), the aryl vinyl silyl nitronate (23 ppm), and TIPSCl (36 ppm), there were no intermediate compounds

found. It is evident that TIPSCl must have been carried through from the formation of the nitronate. The chemical shift was confirmed by comparison to a TIPSCl standard.

When H_2SO_4 was the acid catalyst (Appendix 6), after two hours of reacting the ^{1}H NMR spectrum indicated that some nitronate remained and was reacting to form the dihydroisoxazole and the isoxazole product. The ^{1}H-^{29}Si HMBC spectrum had peaks at 15 ppm (TIPSOH), 25 ppm, 30 ppm, 33 ppm and 36 ppm (TIPSCl). It was first hypothesized that these new peaks were intermediates in the reaction mechanism; however NMR experiments three days after the start of the reaction disproved this. The ^{1}H NMR no longer contained any nitronate, and the isoxazole and dihydroisoxazole products were visualized. Again in the ^{1}H-^{29}Si HMBC spectrum the five peaks were seen (15, 25, 30, 33, 36 ppm). This indicates that the unknown peaks at 25, 30 and 33 ppm are not reaction intermediates, but some other compound containing silicon. In both of these experiments, it is clear that silicon is not present throughout the reaction pathway, and therefore it is believed that the TIPS group is hydrolyzed before cyclization occurs.

The formation of these products indicates that the pentadienyl cation is forming under the given reaction conditions. This can be said because the formation of a five-membered ring using the aryl vinyl silyl nitronate framework represents a 5-*endo-trig* cyclization. Under Baldwin's rules, these cyclizations are disfavoured[115] unless the structure contains a cation.[116] Furthermore, it is clear that in the formation of these products the pentadienyl cation formed does not react

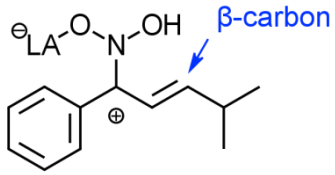
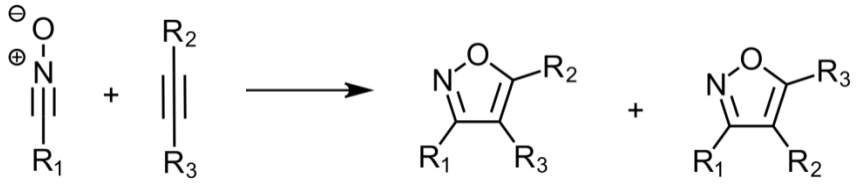


Figure 21: s-trans/s-cis geometry of the aryl vinyl silyl nitronate

in an s-trans conformation, but in an s-cis conformation (Figure 21). In any reaction mixture, there is equilibrium between the geometries of structures. Although the s-trans configuration is hypothesized to be more stable, some of the s-cis conformation is still present, and can therefore react to form the isoxazole product. From experiments that increase the temperature of the reaction, it appears that energy is going into forming more of the s-cis conformation and leading to more isoxazole product.

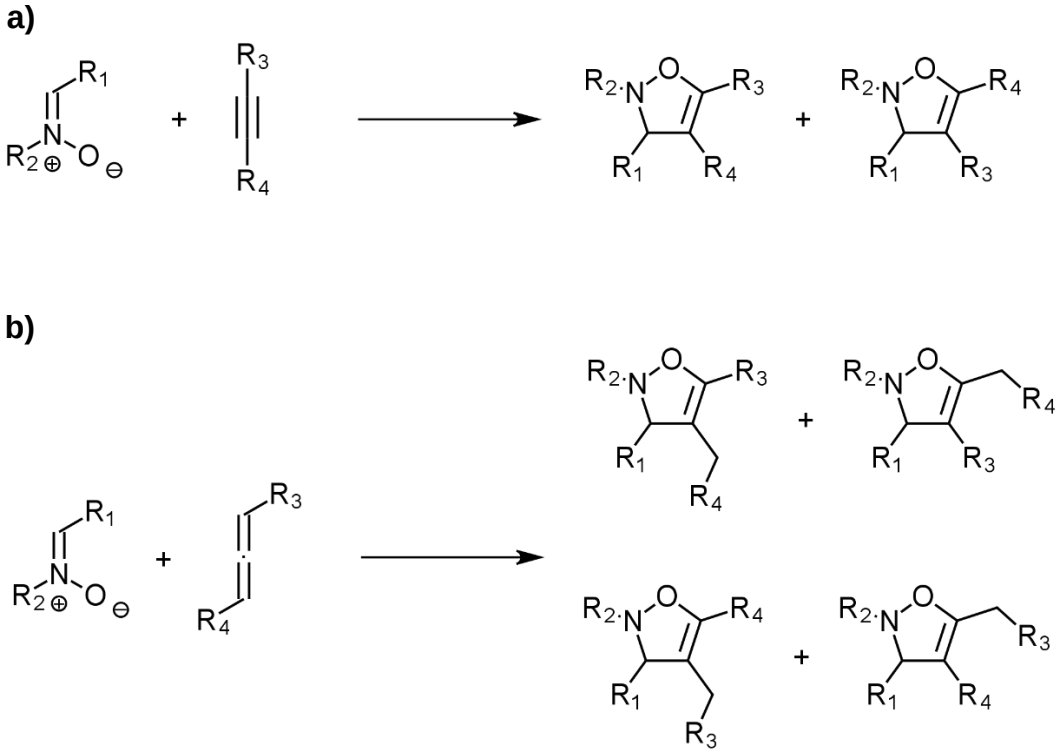
Isoxazoles are useful pharmacophores, and are known to exhibit different biological activities.[117] These structures are most commonly formed by 1,3-dipolar cycloadditions of alkynes with nitrile oxides,[118] but without specific reagents, regioselectivity could be difficult (Scheme 31). If the synthesis of the isoxazole product using an aryl vinyl nitronate could be optimized, it would represent another viable route towards regioselective formation of isoxazoles.



Scheme 31: Synthesis of isoxazoles using a 1,3-dipolar cycloaddition

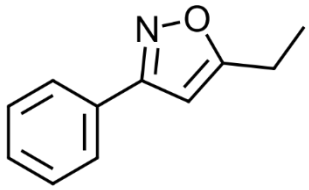
Dihydroisoxazoles are also useful reagents and they undergo further reactivity, producing important chemical structures;[119] therefore, it could prove beneficial to increase the yield and regioselectivity of this compound as well. The synthesis of these compounds is typically achieved through 1,3-dipolar cycloadditions of nitrones and alkynes (Scheme 32a) or allenes (Scheme 32b),[120] but as with the formation of isoxazoles, these reaction can produce a mixture of regioisomers. Again, optimizing the

formation of this product using aryl vinyl nitronates would assist in the regioselective formation of these products.



Scheme 32: Synthesis of dihydroisoxazoles using a 1,3-dipolar cycloaddition

5-Isopropyl-3-phenylisoxazole (**91**) was formed in the highest yield when the acid catalyst was scandium(III) triflate and so this catalyst was used in a reaction with two different aryl vinyl silyl nitronate frameworks at room temperature. The first framework was with triisopropylsilyl 1-phenylpent-2-enenitronate (**81**). Under the Lewis acidic conditions caused by scandium(III) triflate, 5-ethyl-3-phenylisoxazole (**94**) (Figure 22) was isolated in



94

Figure 22: Structure of 5-ethyl-3-phenylisoxazole

a 34% yield. The second framework was *tert*-butyldimethylsilyl 4-methyl-1-phenylpent-2-enenitronate (**79**). When this compound was in the presence of scandium(III) triflate, 5-isopropyl-3-phenylisoxazole (**76**) was isolated in a 27% yield.

3.4 Conclusion

This work has successfully synthesized a series of aryl vinyl silyl nitronates that have not been reported in the literature. These compounds reacted under proposed nitronate Nazarov cyclization conditions to yield isoxazoles and dihydroisoxazoles through a disfavoured 5-*endo*-*tet* cyclization. If this methodology can be optimized, it would represent an efficient, regioselective synthesis towards these products. This method of synthesis eliminates regioselective issues by using an intramolecular reaction, and would represent a better synthesis towards isoxazoles and dihydroisoxazoles than the 1,3-dipolar cycloadditions commonly used now. Lastly, the first steps into the investigation of a successful nitronate Nazarov cyclization have been taken. It has been found that the pentadienyl cation is forming under the tested reaction conditions; however the desired reactivity is not occurring. This is most likely due to the additional energy required to break the aromaticity in these aryl vinyl silyl nitronates, and investigations into this requirement are necessary. Research expanding on the work accomplished in this report will improve upon the current understanding of reactivity of divinyl nitronates and the nitronate Nazarov cyclization.

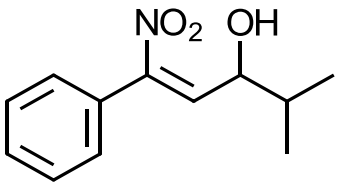
3.5 Experimental methods

See section 2.6 for general and analysis information.

General methods for liquid Lewis/Brønsted-Lowry acid screening: All reactions were performed under an atmosphere of argon and used anhydrous solvents. (*E*)-Triisopropylsilyl 4-methyl-1-phenylpent-2-ene nitronate (0.10 g, 0.28 mmol) was dissolved in dichloromethane (2 mL). At room temperature, the given acid was added dropwise. The reaction was monitored using TLC analysis for the disappearance of the starting material, or the lack of change after 24 hours.

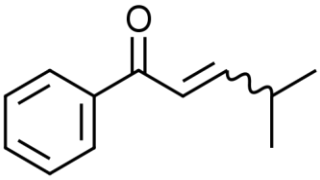
General methods for solid Lewis acid screening: All reactions were performed under an atmosphere of argon and used anhydrous solvents. (*E*)-Triisopropylsilyl 4-methyl-1-phenylpent-2-ene nitronate (0.10 g, 0.28 mmol) was dissolved in dichloromethane (1 mL) and added dropwise to a solution of the given acid dissolved in dichloromethane (1mL) at room temperature. The reaction was monitored using TLC analysis for the disappearance of the starting material, or the lack of change after 24 hours.

(Z)-4-Methyl-1-nitro-1-phenylpenten-3-ol (88)



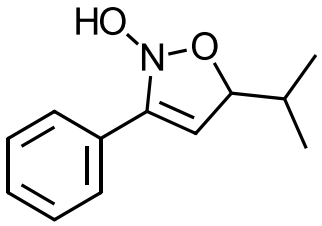
R_f: 0.23 (CH_2Cl_2); Clear, yellow liquid; IR (neat): 3405, 3078, 2963, 1529, 1335 cm^{-1}; ^1H NMR (300.3 MHz, $CDCl_3$): δ = 7.51-7.43 (m, 3H), 7.36-7.29 (m, 2H), 7.25 (d, *J* = 9.8 Hz, 1H), 3.85 (dd, *J* = 9.3, 6.7 Hz, 1H), 1.93-1.75 (m, 1H), 1.69 (br. s, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H) ppm. After deuterium exchange using D_2O, the peak at 1.69 disappeared; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 152.5, 136.4, 130.3, 130.0, 129.1, 128.6, 73.2, 34.2, 18.2, 17.6 ppm; HRMS MNa^+: 244.0941, calculated ($C_{12}H_{14}NaNO_3$): 244.0942.

4-methyl-1-phenylpent-2-enone (89)



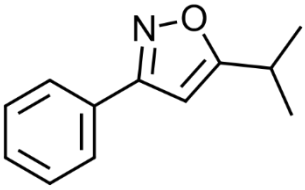
R_f: 0.75 (CH_2Cl_2); Clear, yellow liquid; IR (neat): 3398, 2963, 2859, 2360 1622 cm^{-1}; ^1H NMR (300.3 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.7 Hz, 2H), 7.60-7.52 (m, 1H), 7.52-7.43 (m, 2H), 7.05 (dd, *J* = 15.5, 6.6 Hz, 1H), 6.83 (d, *J* = 15.5 Hz, 1H), 2.68-2.50 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 191.4, 156.1, 138.1, 132.5, 128.5, 123.1, 31.5, 21.4 ppm; APCI MS MH^+: 175.1. This NMR data was consistent with literature values.[121]

5-Isopropyl-3-phenyl-2,5-dihydroisoxazol-2-ol (90)



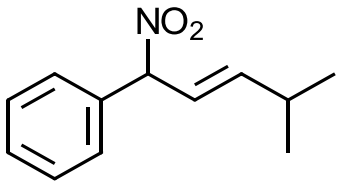
R_f: 0.25 (CH_2Cl_2); White solid; Melting Point: 74.5-75.5 °C; IR (KBr pellet): 3311, 2982, 2962, 2925, 2871, 1079 cm^{-1}; ^1H NMR (300.3 MHz, $CDCl_3$): δ = 7.89-7.78 (m, 2H), 7.46-7.40 (m, 3H), 5.23 (br d, *J* = 3.1 Hz, 1H), 4.26 (dd, *J* = 6.6, 3.8 Hz, 1H), 2.25 (br. s, 1H), 1.99-1.84 (m, 1H), 1.08-0.99 (m, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.3, 130.2, 128.9, 128.2, 126.9, 94.0, 79.5, 30.7, 17.9, 17.8 ppm; HRMS MNa^+: 228.0997, calculated ($C_{12}H_{15}NaNO_2$): 228.0995.

5-Isopropyl-3-phenylisoxazole (91)



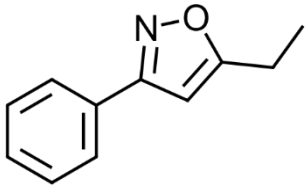
R_f: 0.51 (CH_2Cl_2); Clear, yellow, viscous liquid; IR (neat): 2947, 2893, 2867, 1555 cm^{-1}; ^1H NMR (300.3 MHz, $CDCl_3$): δ = 7.82-7.79 (m, 2H), 7.46-7.43 (m, 3H), 6.27 (s, 1H), 3.14 (spt, *J* = 6.9 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 6H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 179.3, 162.2, 129.7, 129.5, 128.8, 126.7, 97.0, 27.2, 20.9 ppm; HRMS MNa^+: 210.0881, calculated ($C_{12}H_{13}NaNO$): 210.0889. This NMR data was consistent with literature values.[114]

4-Methyl-1-nitro-1-phenylpent-2-ene (92)



R_f: 0.36 (40% CH_2Cl_2/Hexanes); Clear, yellow liquid; IR (neat): 2958, 2931, 2871, 1522, 1334 cm^{-1}; ^1H NMR (300.3 MHz, $CDCl_3$): δ = 7.50-7.38 (m, 5H), 6.07 (dd, *J* = 15.2, 8.6 Hz, 1H), 5.96 (d, *J* = 8.7 Hz, 1H), 5.86 (dd, *J* = 15.2, 6.3 Hz, 1H), 2.50-2.34 (m, 1H), 1.06 (d, *J* = 3.0 Hz, 3H), 1.04 (d, *J* = 2.9 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 145.9, 134.9, 129.6, 129.0, 127.7, 121.2, 92.9, 31.0, 21.7 ppm.

5-Ethyl-3-phenylisoxazole (94)



R_f: 0.50 (CH_2Cl_2); (20.0 mg, 34%); pale yellow liquid; IR (neat): 2962, 2892, 2861, 1548 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82-7.79 (m, 2H), 7.48-7.43 (m, 3H), 6.30 (s, 1H), 2.84 (q, *J* = 7.5 Hz, 1H), 1.36 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.4, 162.3, 129.8, 129.4, 128.8, 126.7, 98.2, 20.3, 11.8 ppm; HRMS MNa^+: 196.0735, calculated ($C_{11}H_{11}NaNO$): 196.0731.

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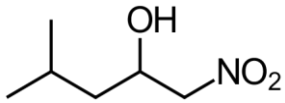
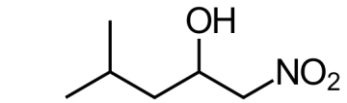
Appendix 1

The following pages contain the ^{1}H NMR and ^{13}C NMR spectra for all compounds isolated and characterized in this work.



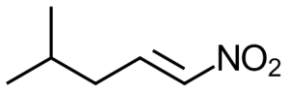
4-methyl-1-nitropentan-2-ol (55)

^{1}H NMR 500.1 MHz, $CDCl_3$



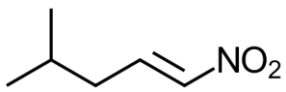
4-methyl-1-nitropentan-2-ol (55)

^{13}C NMR 125.8 MHz, $CDCl_3$



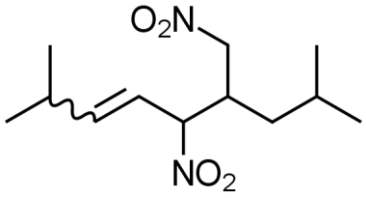
(*E*)-4-methyl-1-nitropent-1-ene (56)

^{1}H NMR 500.1 MHz, $CDCl_3$



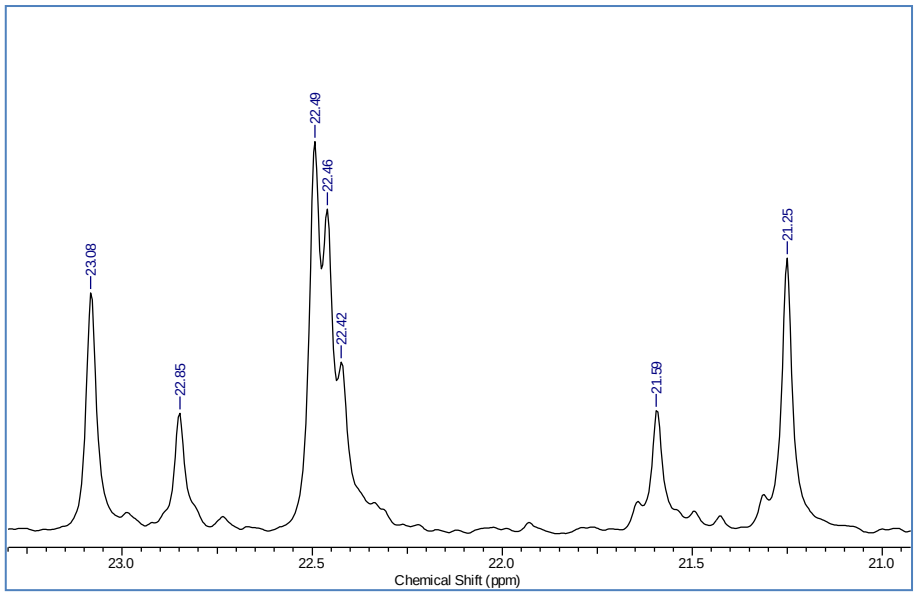
(*E*)-4-methyl-1-nitropent-1-ene (56)

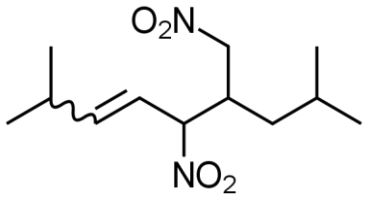
^{13}C NMR 125.8 MHz, $CDCl_3$



2,8-dimethyl-5-nitro-6-(nitromethyl)non-3-ene (59)

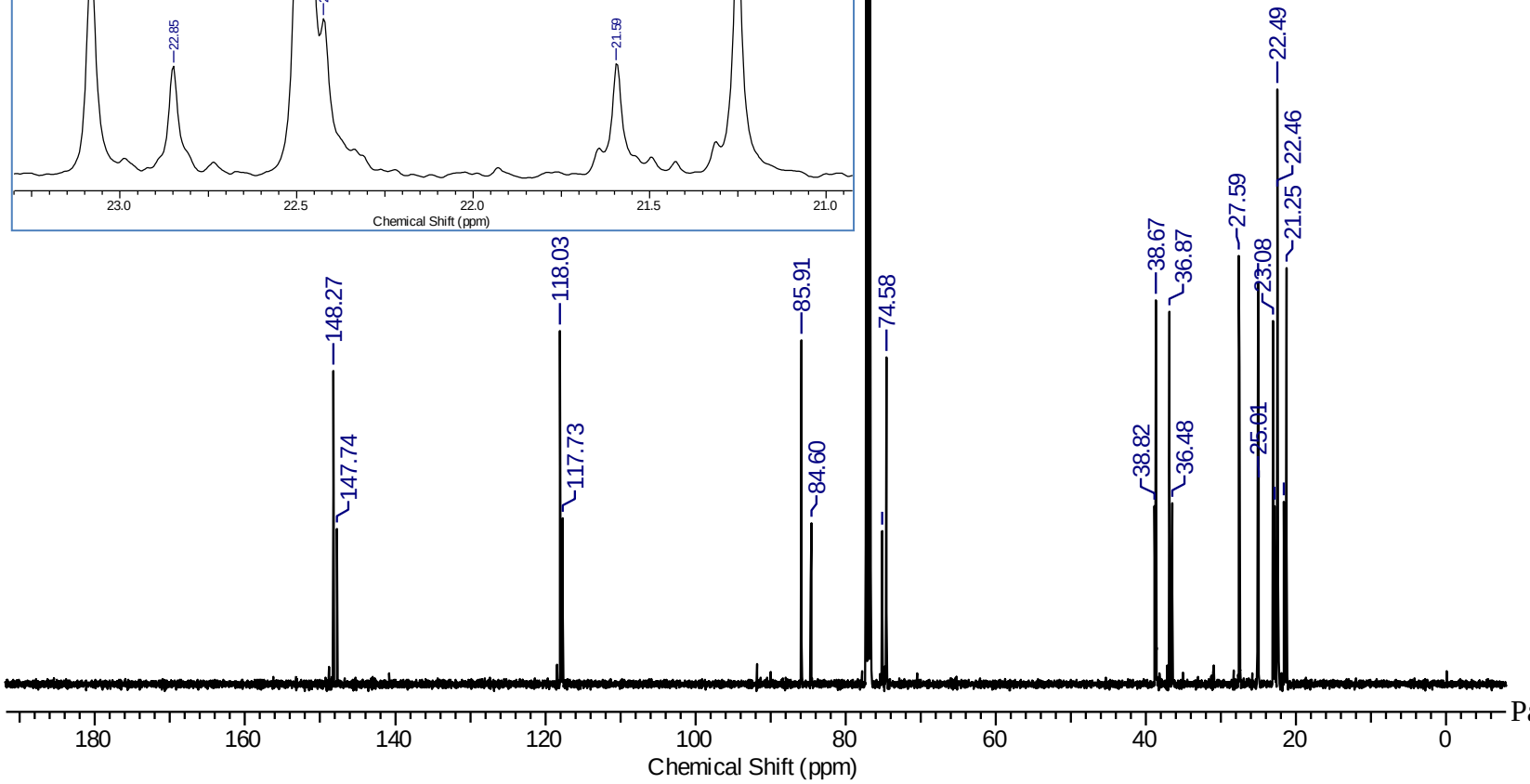
^{1}H NMR 500.1 MHz, $CDCl_3$

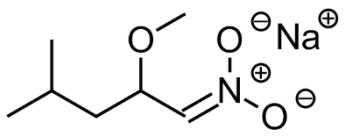




2,8-dimethyl-5-nitro-6-(nitromethyl)non-3-ene (59)

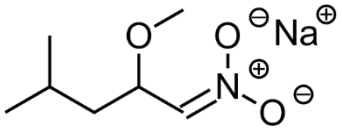
^{13}C NMR 125.8 MHz, $CDCl_3$





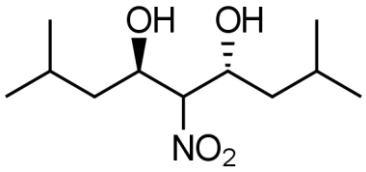
Sodium 2-methoxy-4-methylpentanenitronate (60)

^{1}H NMR 300.3 MHz, $(CD_3)_2SO$



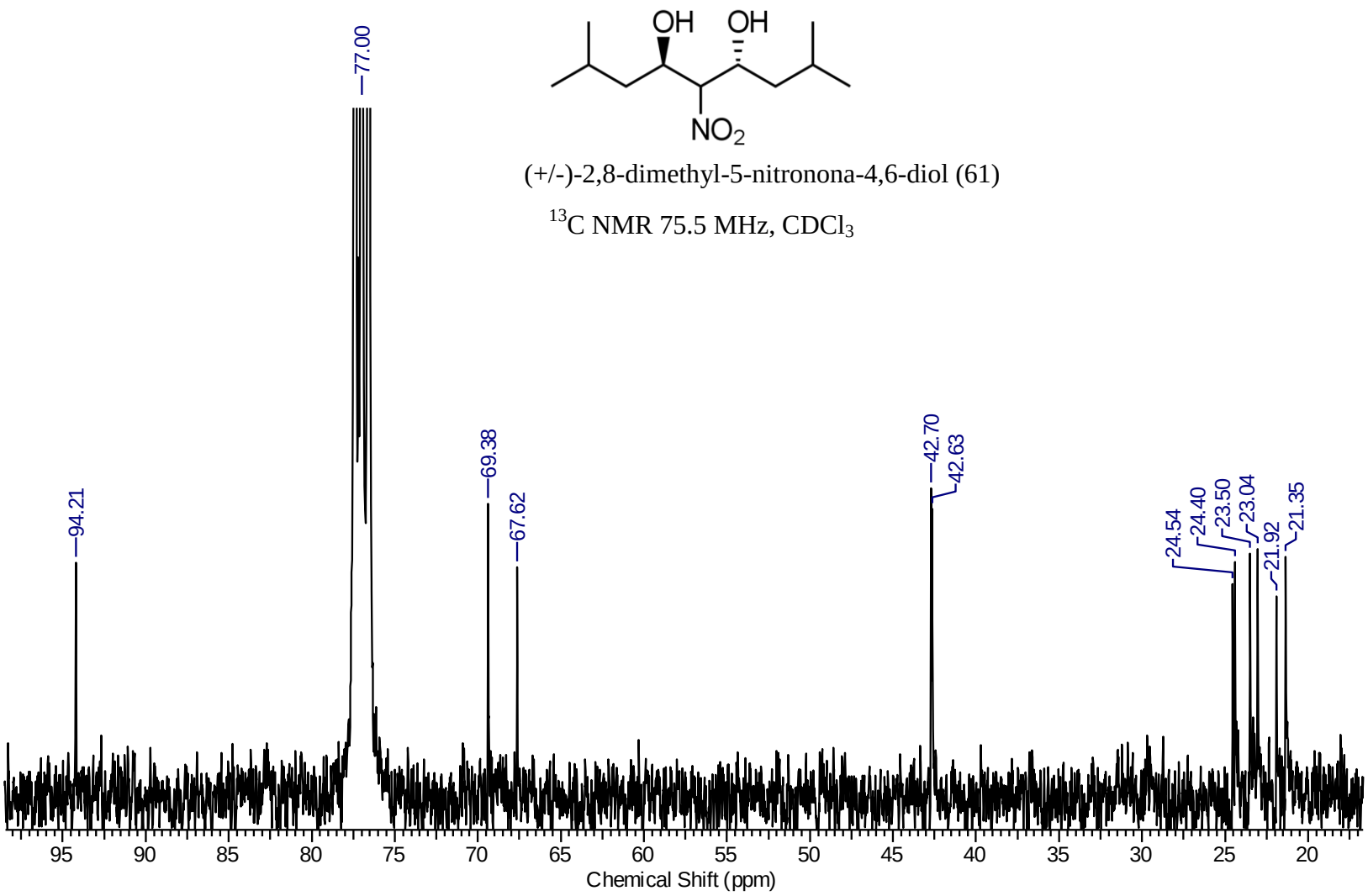
Sodium 2-methoxy-4-methylpentanenitronate (60)

^{13}C NMR 75.5 MHz, $(CD_3)_2SO$



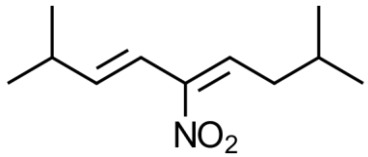
(+/-)-2,8-dimethyl-5-nitronona-4,6-diol (61)

^{1}H NMR 300.3 MHz, $CDCl_3$



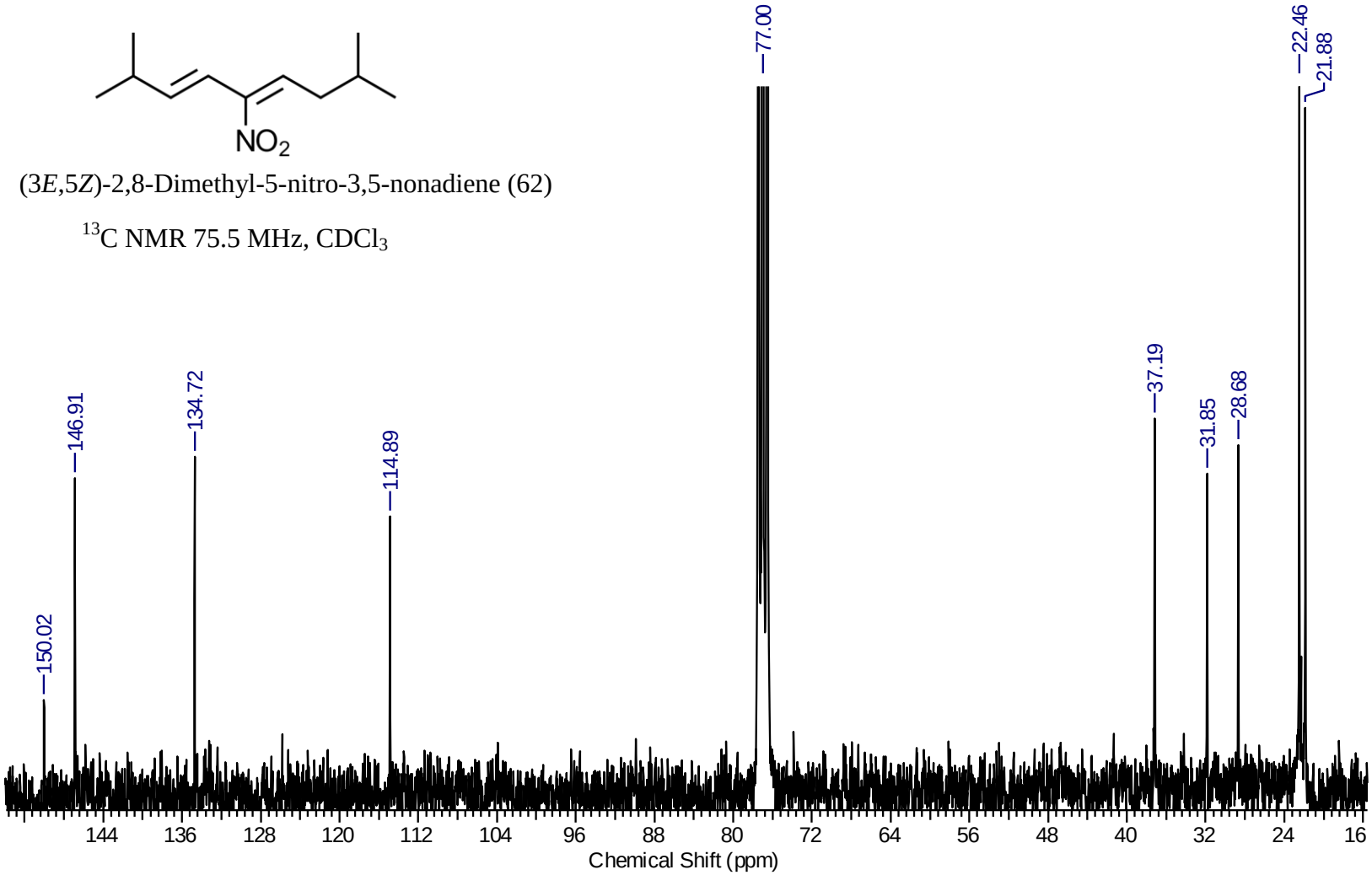
(+/-)-2,8-dimethyl-5-nitronona-4,6-diol (61)

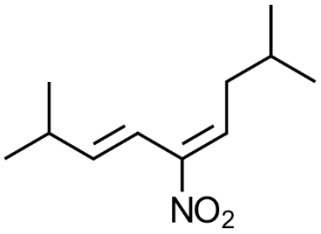
^{13}C NMR 75.5 MHz, $CDCl_3$



(3*E*,5*Z*)-2,8-Dimethyl-5-nitro-3,5-nonadiene (62)

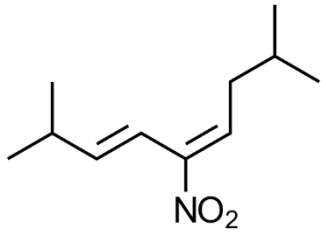
^{1}H NMR 300.3 MHz, $CDCl_3$


NO2
(3E,5Z)-2,8-Dimethyl-5-nitro-3,5-nonadiene (62)
13C NMR 75.5 MHz, CDCl3
150.02
146.91
134.72
114.89
77.00
37.19
31.85
28.68
22.46
21.88
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)



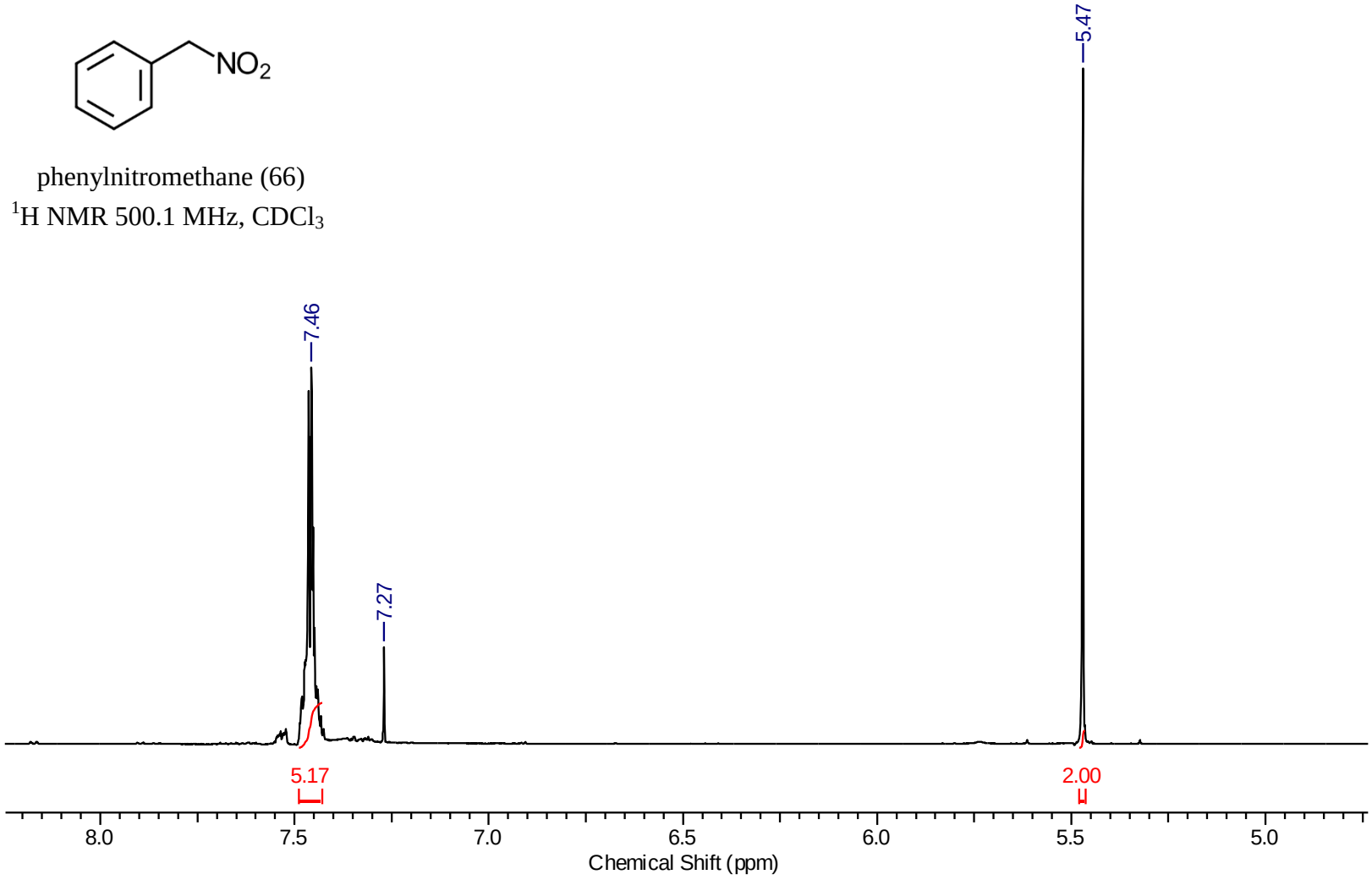
(3*E*,5*E*)-2,8-Dimethyl-5-nitro-3,5-nonadiene (62)

^{1}H NMR 300.3 MHz, $CDCl_3$



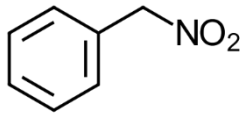
(3*E*,5E)-2,8-Dimethyl-5-nitro-3,5-nonadiene (62)

^{13}C NMR 75.5 MHz, $CDCl_3$



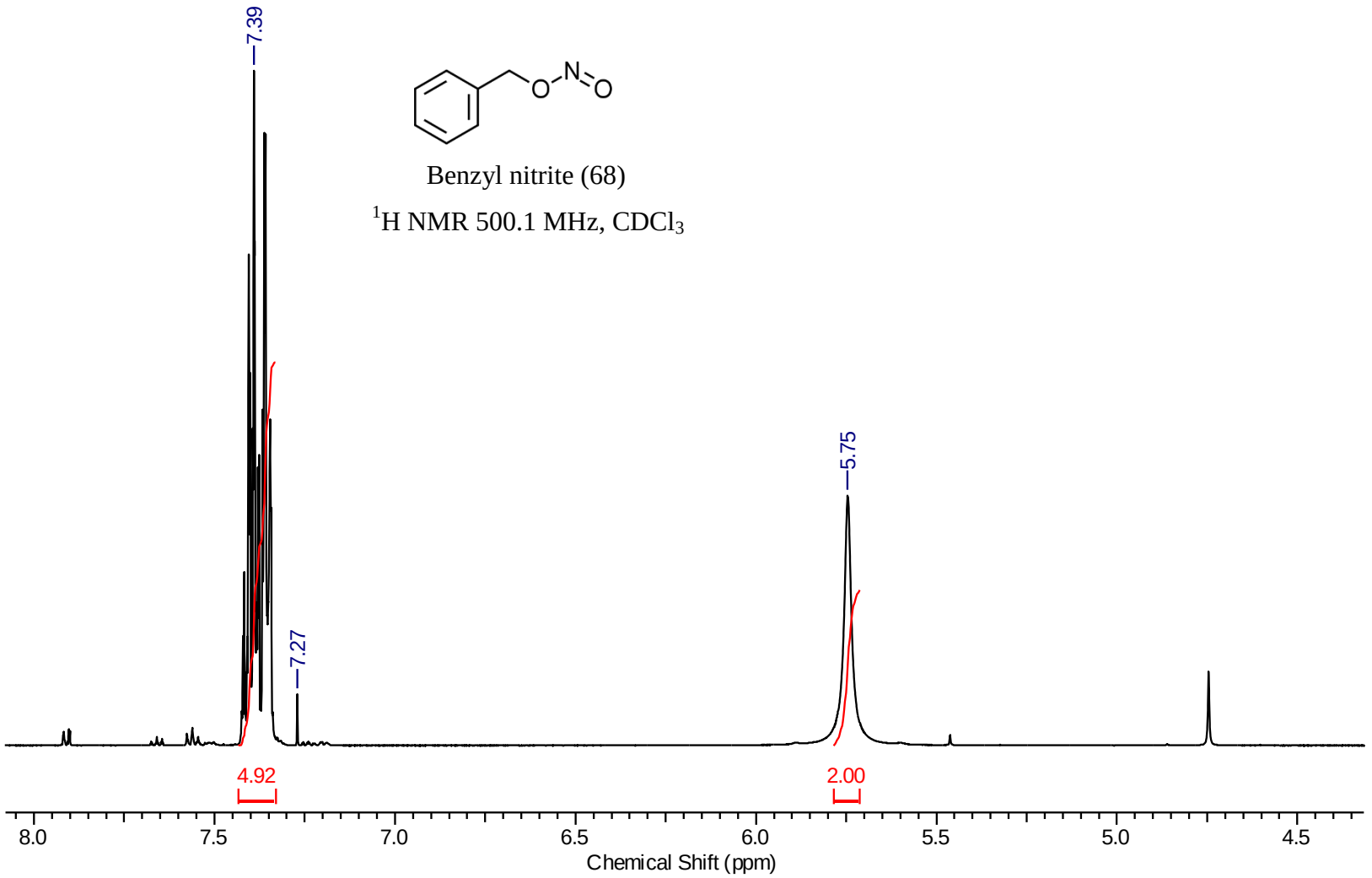
phenylnitromethane (66)

^{1}H NMR 500.1 MHz, $CDCl_3$



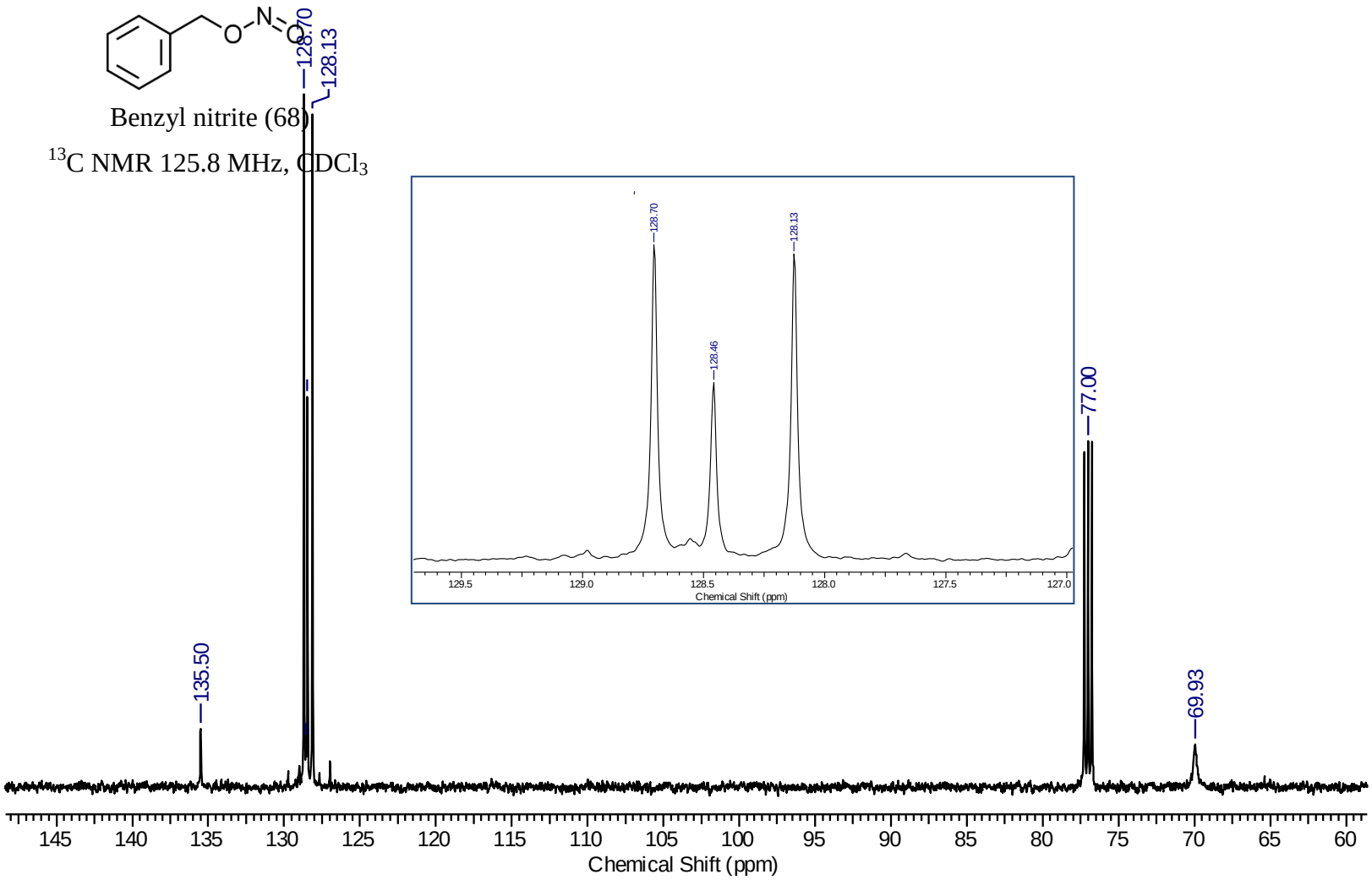
Phenylnitromethane (66)

^{13}C NMR 125.8 MHz, $CDCl_3$



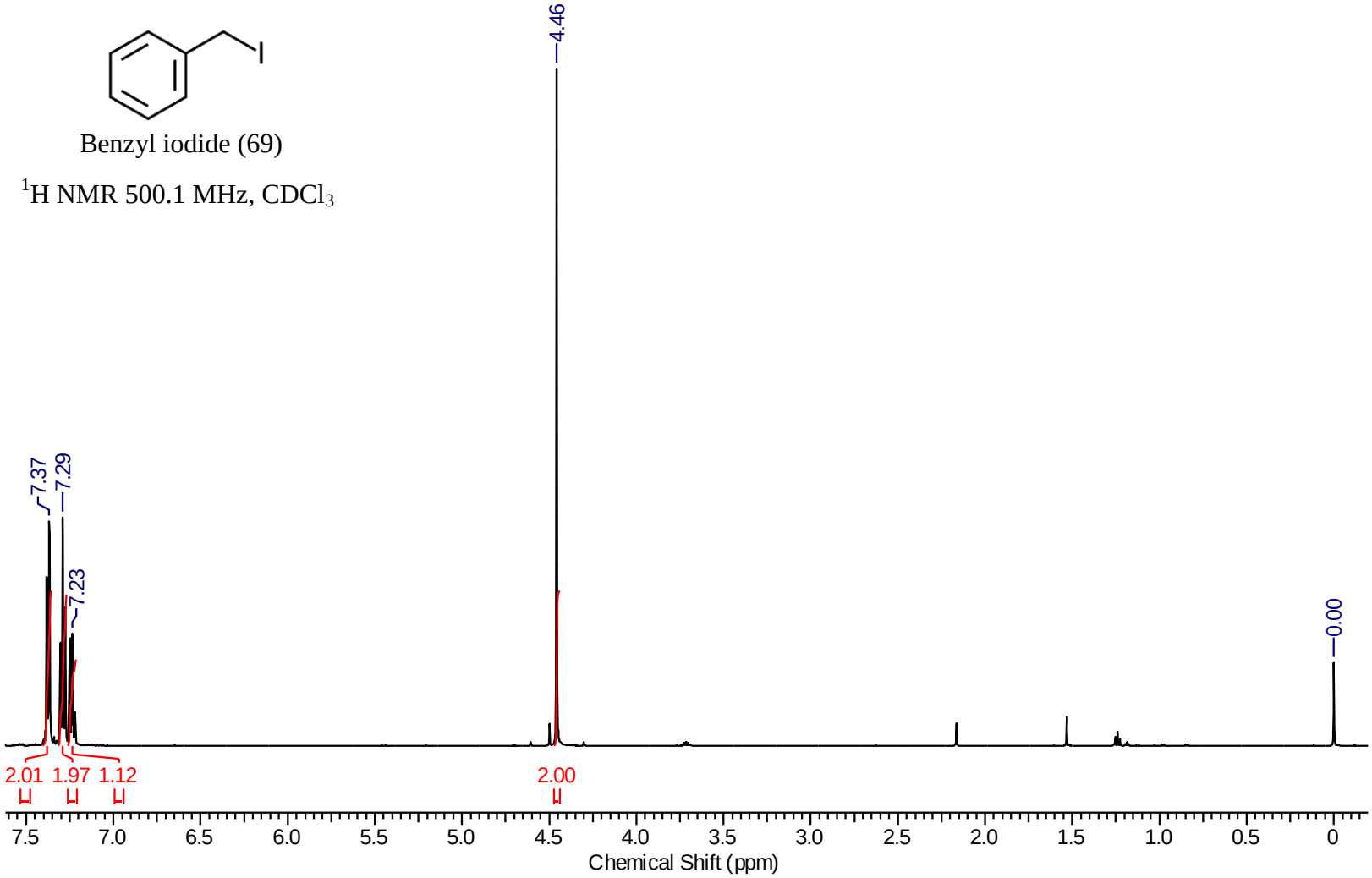
Benzyl nitrite (68)

^{1}H NMR 500.1 MHz, $CDCl_3$



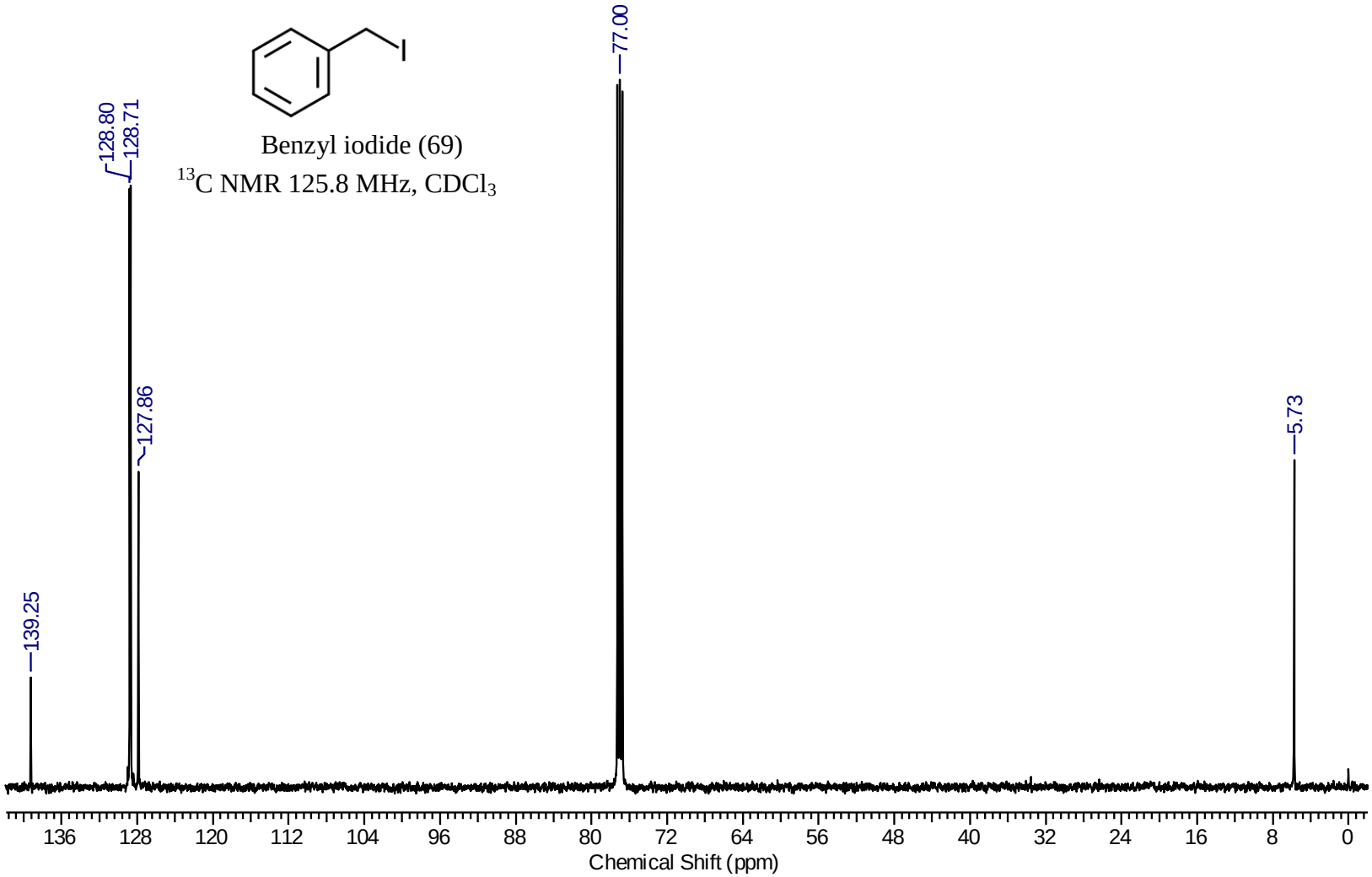
Benzyl nitrite (68)

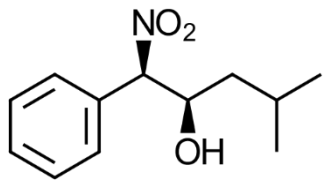
^{13}C NMR 125.8 MHz, $CDCl_3$



Benzyl iodide (69)

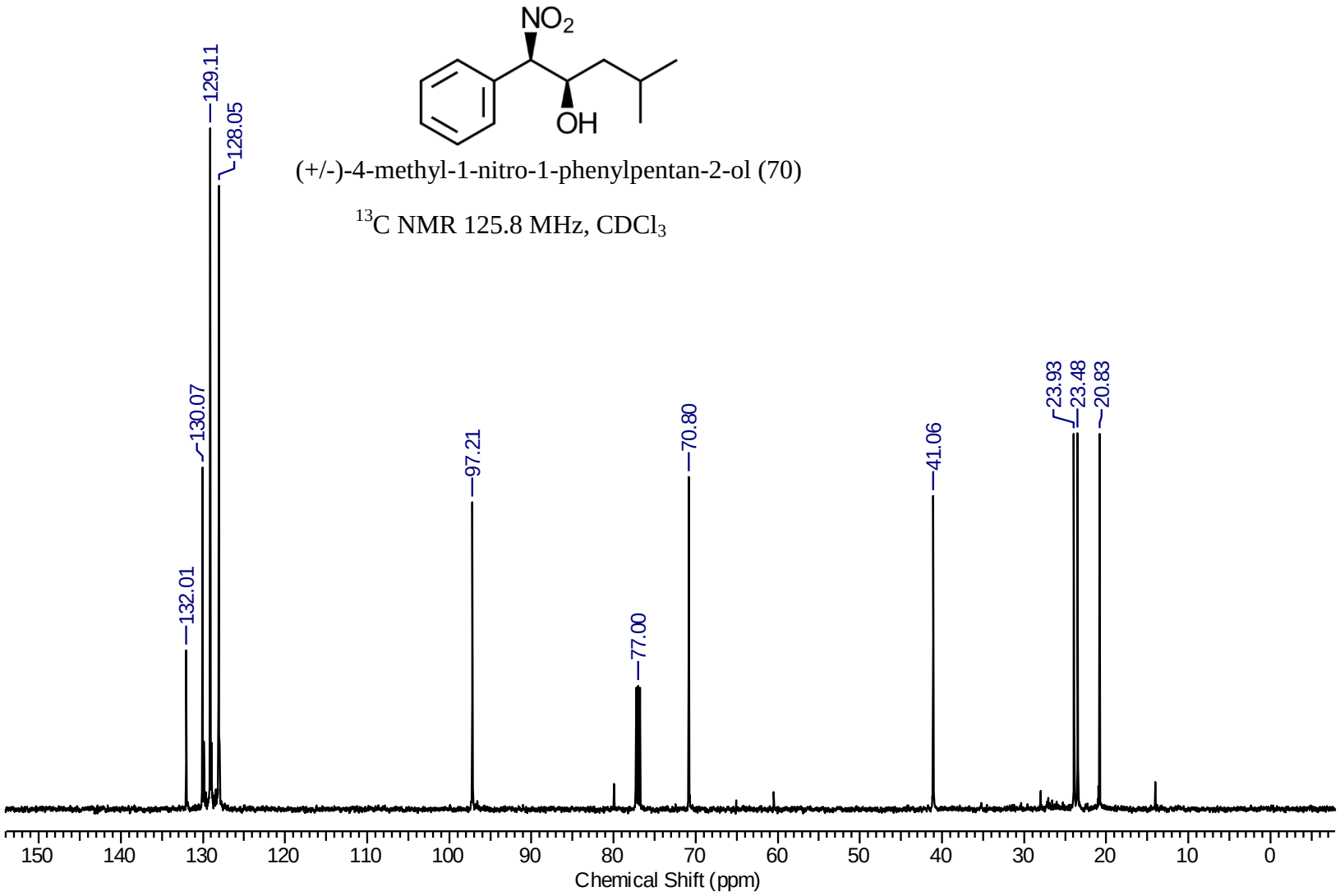
^{1}H NMR 500.1 MHz, $CDCl_3$


Benzyl iodide (69)
^{13}C NMR 125.8 MHz, $CDCl_3$
139.25
128.80
128.71
127.86
77.00
5.73
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)



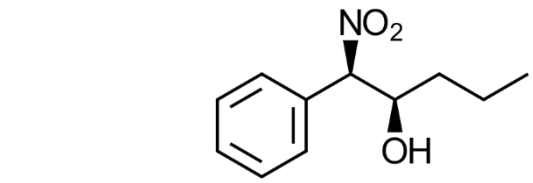
(+/-)-4-methyl-1-nitro-1-phenylpentan-2-ol (70)

^{1}H NMR 500.1 MHz, $CDCl_3$



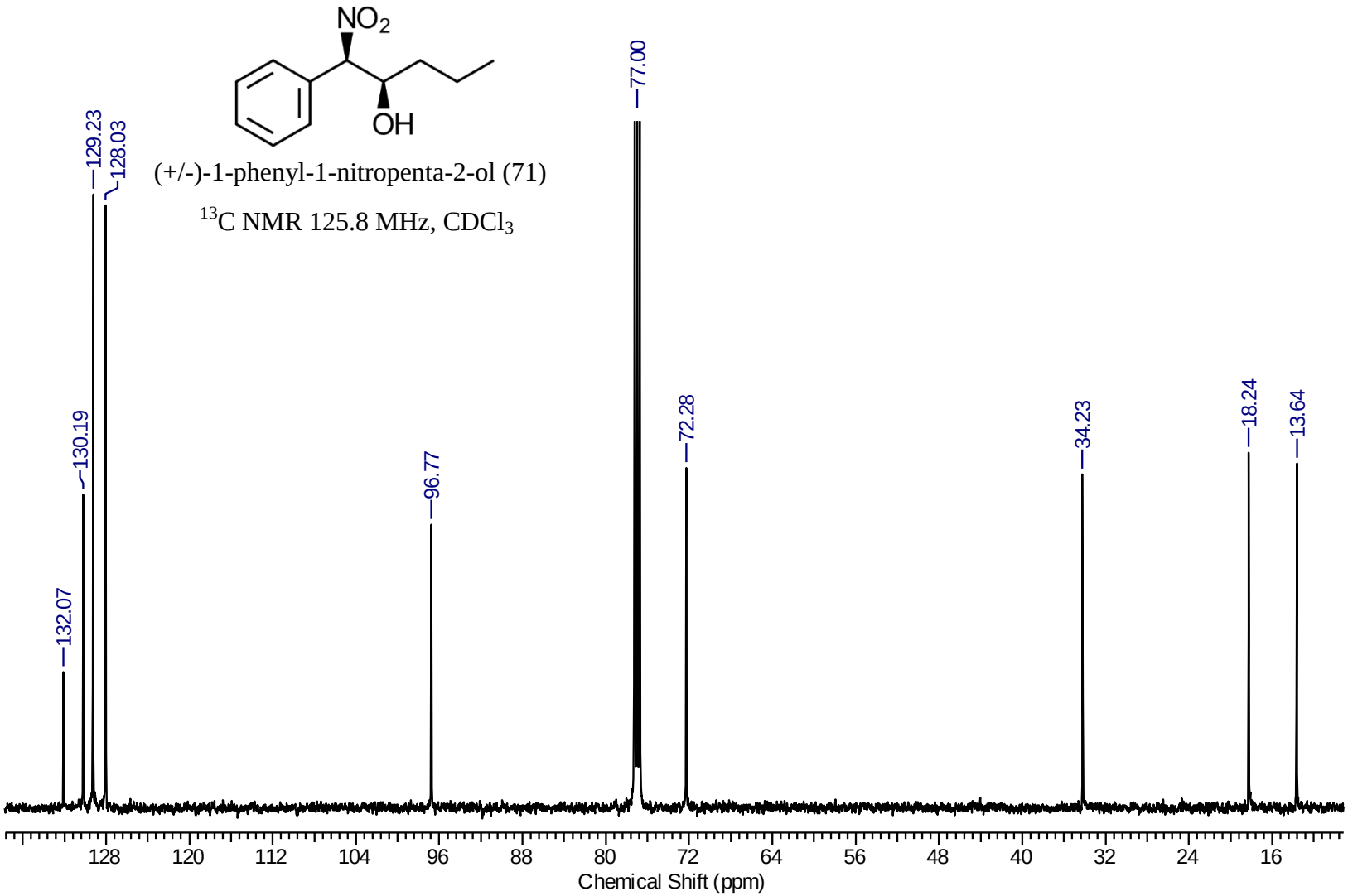
(+/-)-4-methyl-1-nitro-1-phenylpentan-2-ol (70)

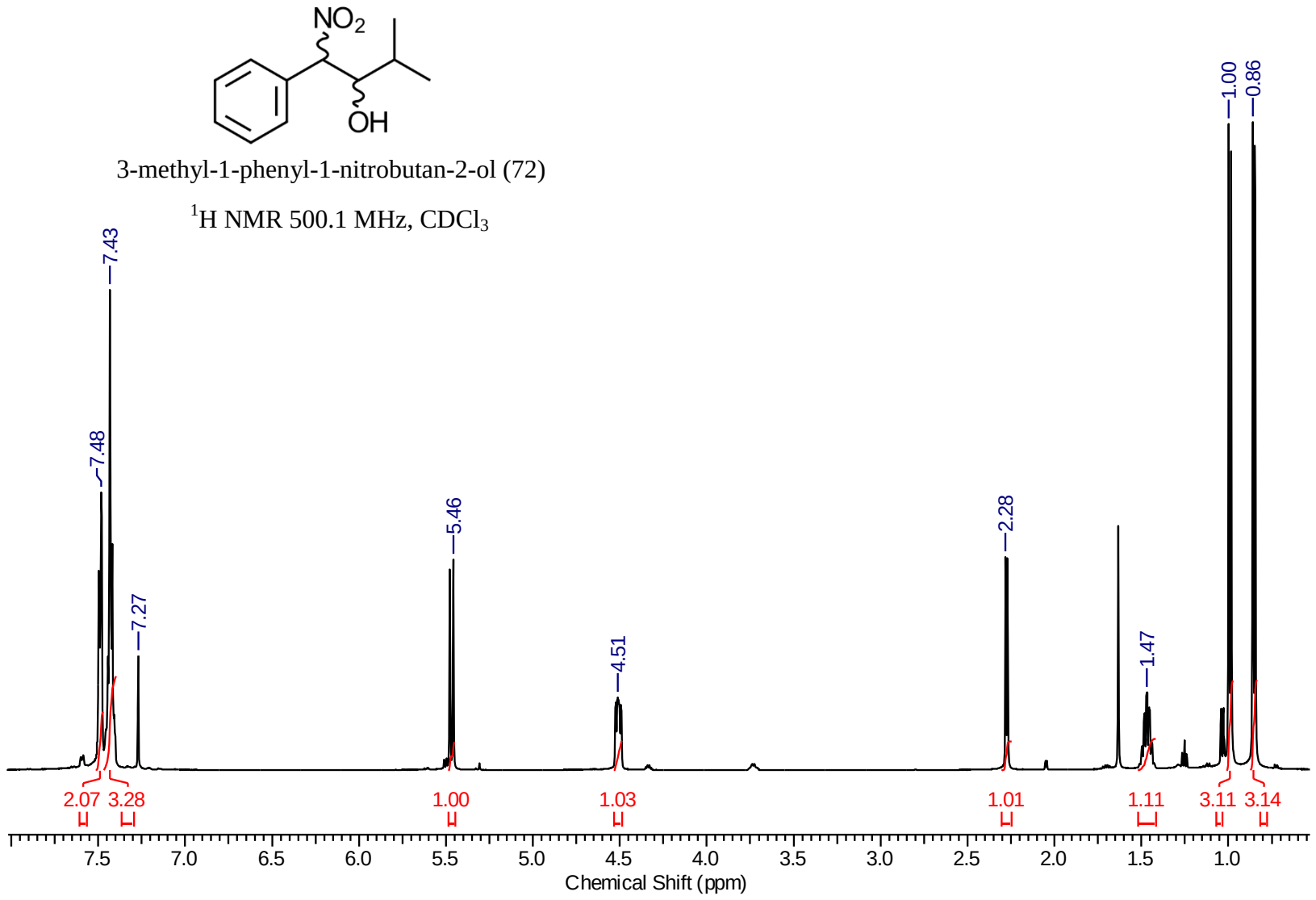
^{13}C NMR 125.8 MHz, $CDCl_3$

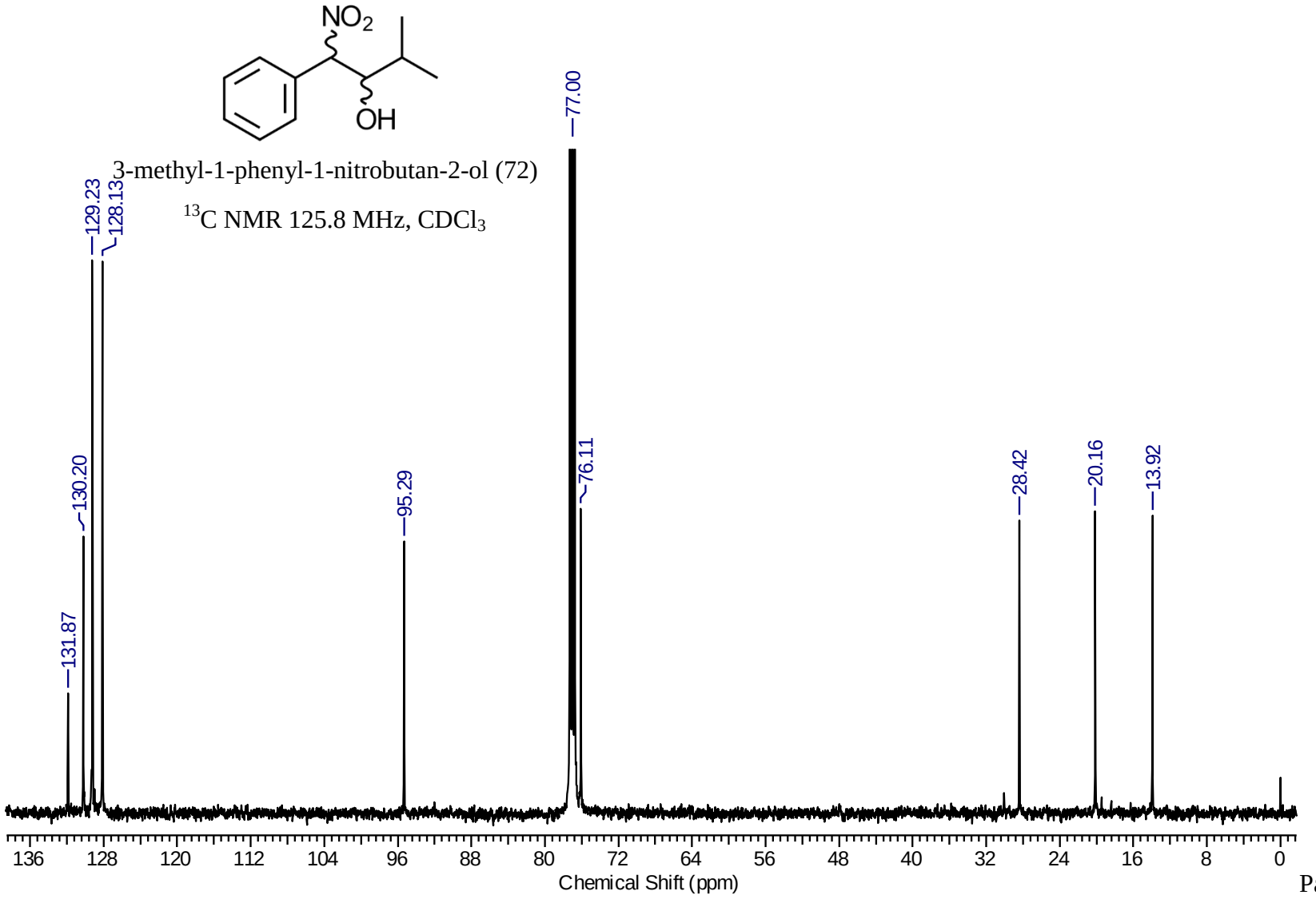


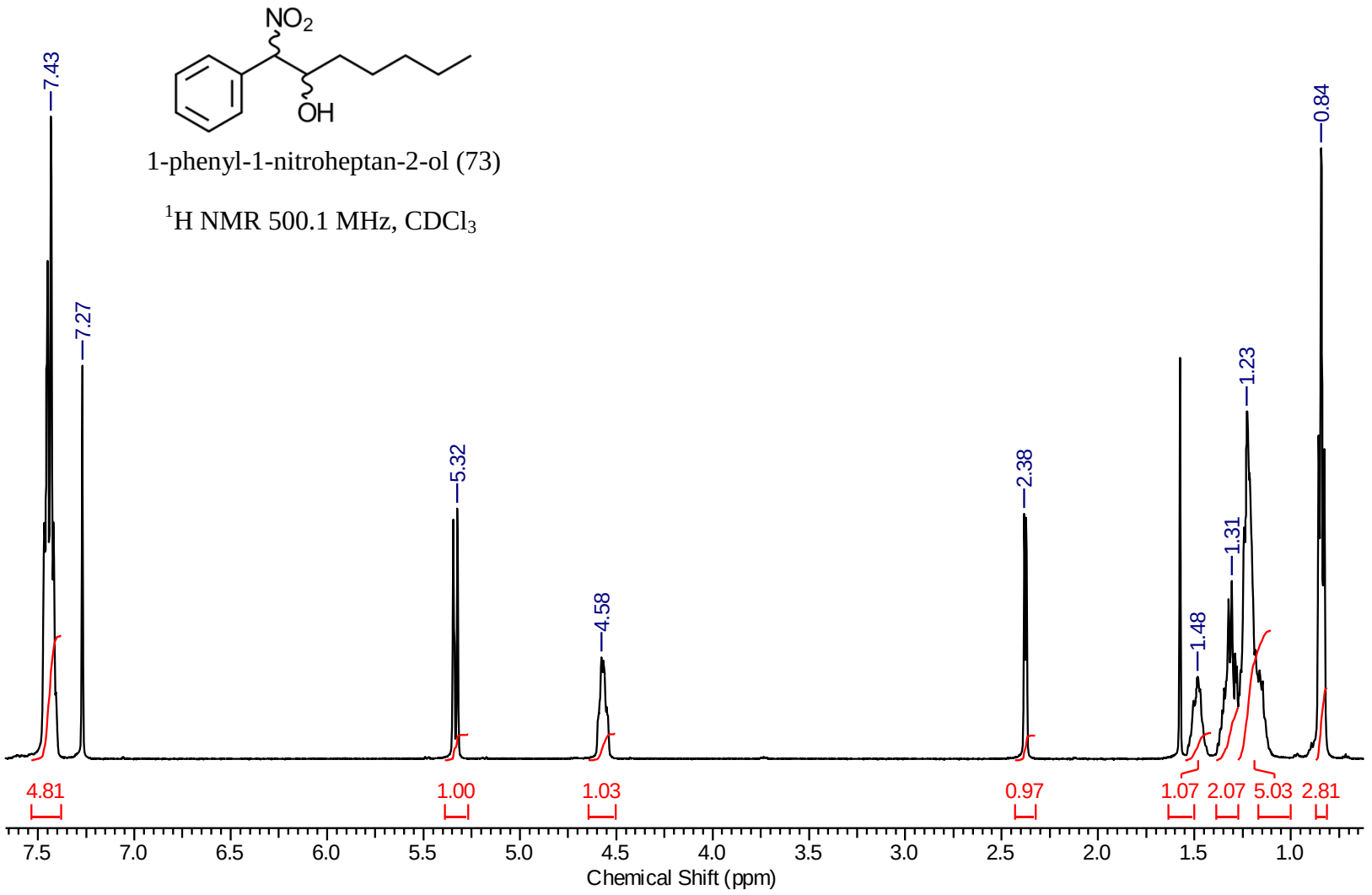
(+/-)-1-phenyl-1-nitropenta-2-ol (71)

^{1}H NMR 500.1 MHz, $CDCl_3$


NO2
OH
(+/-)-1-phenyl-1-nitropenta-2-ol (71)
13C NMR 125.8 MHz, CDCl3
132.07
130.19
129.23
128.03
96.77
77.00
72.28
34.23
18.24
13.64
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

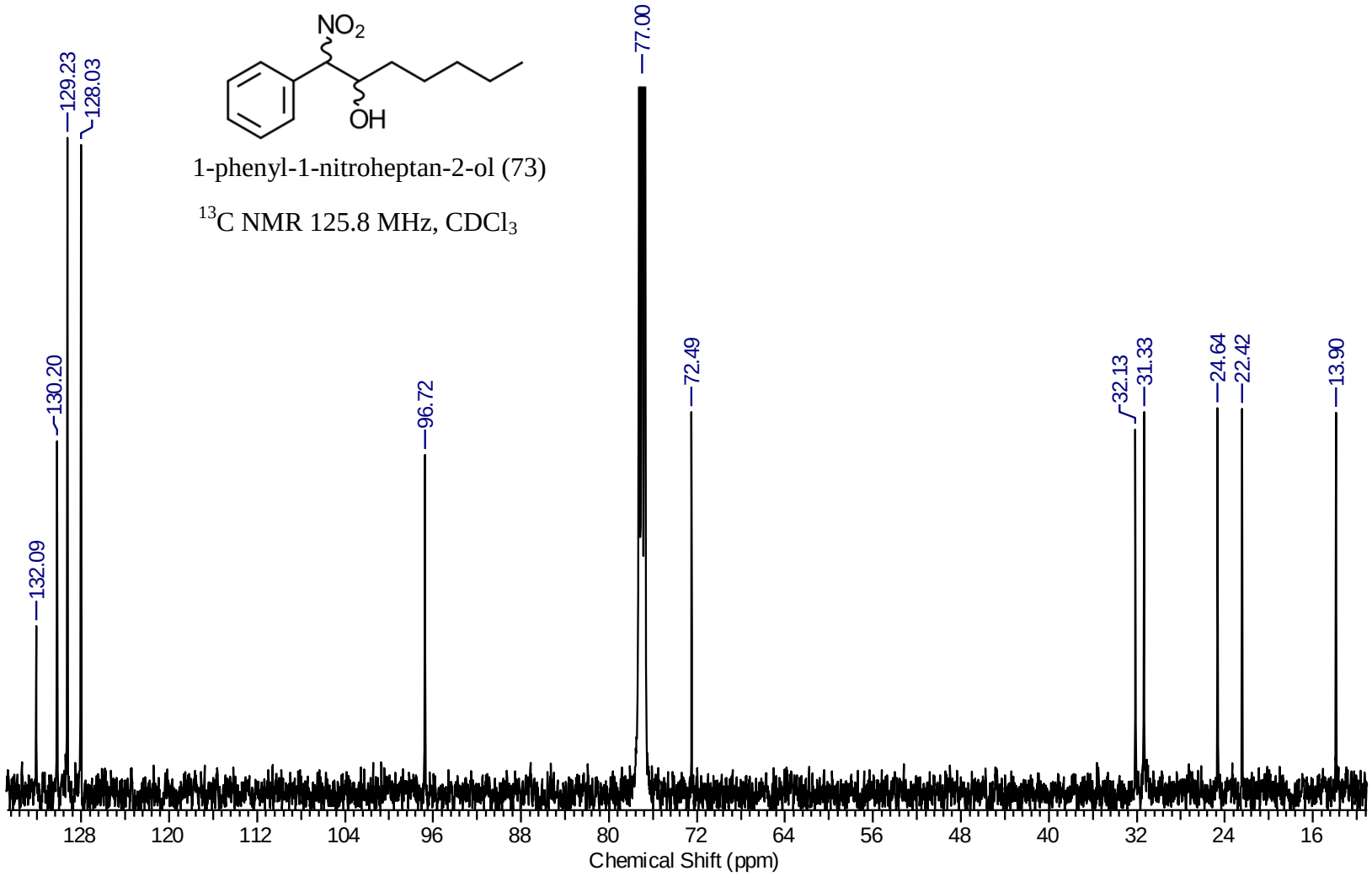

NO2
OH
3-methyl-1-phenyl-1-nitrobutan-2-ol (72)
1H NMR 500.1 MHz, CDCl3
7.43
7.48
7.27
5.46
4.51
2.28
1.47
1.00
0.86
2.07
3.28
1.00
1.03
1.01
1.11
3.11
3.14
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

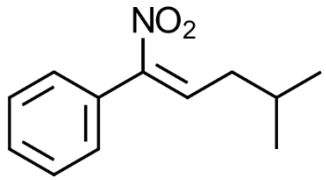

NO2
OH
3-methyl-1-phenyl-1-nitrobutan-2-ol (72)
13C NMR 125.8 MHz, CDCl3
77.00
129.23
128.13
130.20
131.87
95.29
76.11
28.42
20.16
13.92
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)



1-phenyl-1-nitroheptan-2-ol (73)

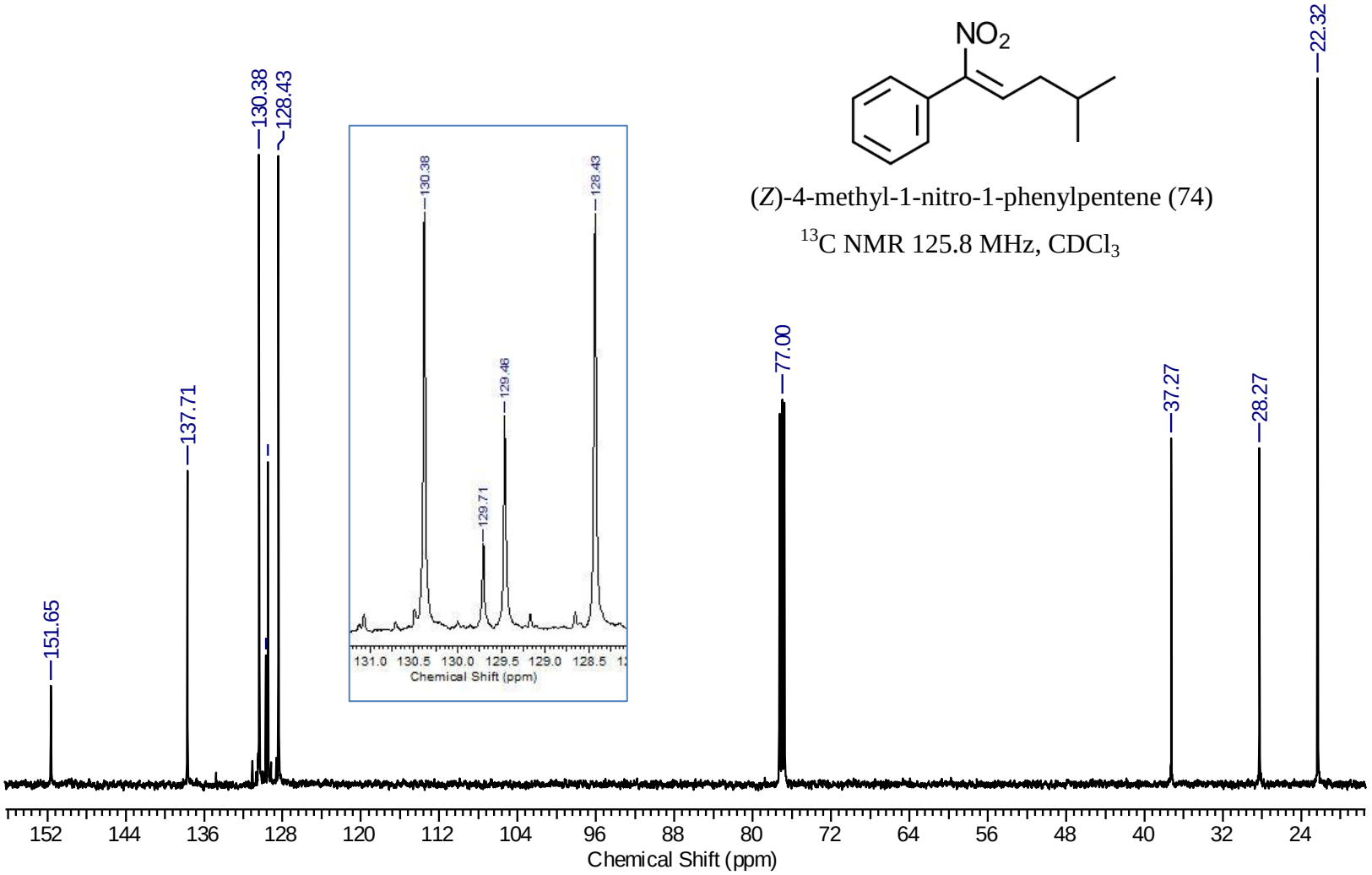
^{1}H NMR 500.1 MHz, $CDCl_3$

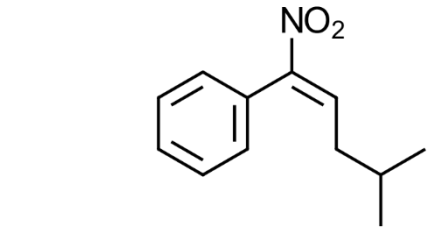

NO2
OH
1-phenyl-1-nitroheptan-2-ol (73)
13C NMR 125.8 MHz, CDCl3
132.09
130.20
129.23
128.03
96.72
77.00
72.49
32.13
31.33
24.64
22.42
13.90
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)



(*Z*)-4-methyl-1-nitro-1-phenylpentene (74)

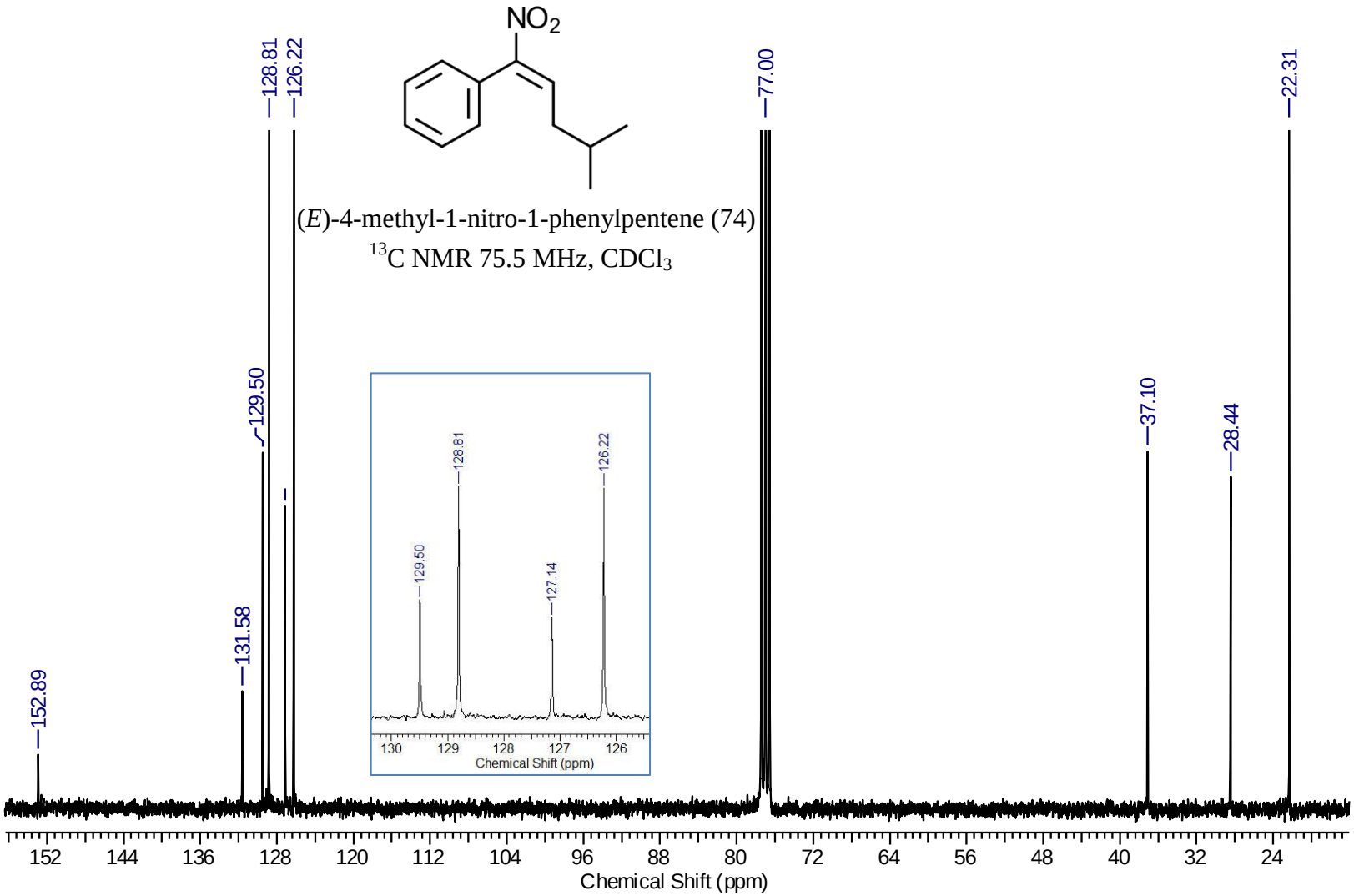
^{1}H NMR 500.1 MHz, $CDCl_3$


NO2
(Z)-4-methyl-1-nitro-1-phenylpentene (74)
13C NMR 125.8 MHz, CDCl3
151.65
137.71
130.38
128.43
129.71
129.46
77.00
37.27
28.27
22.32
Chemical Shift (ppm)



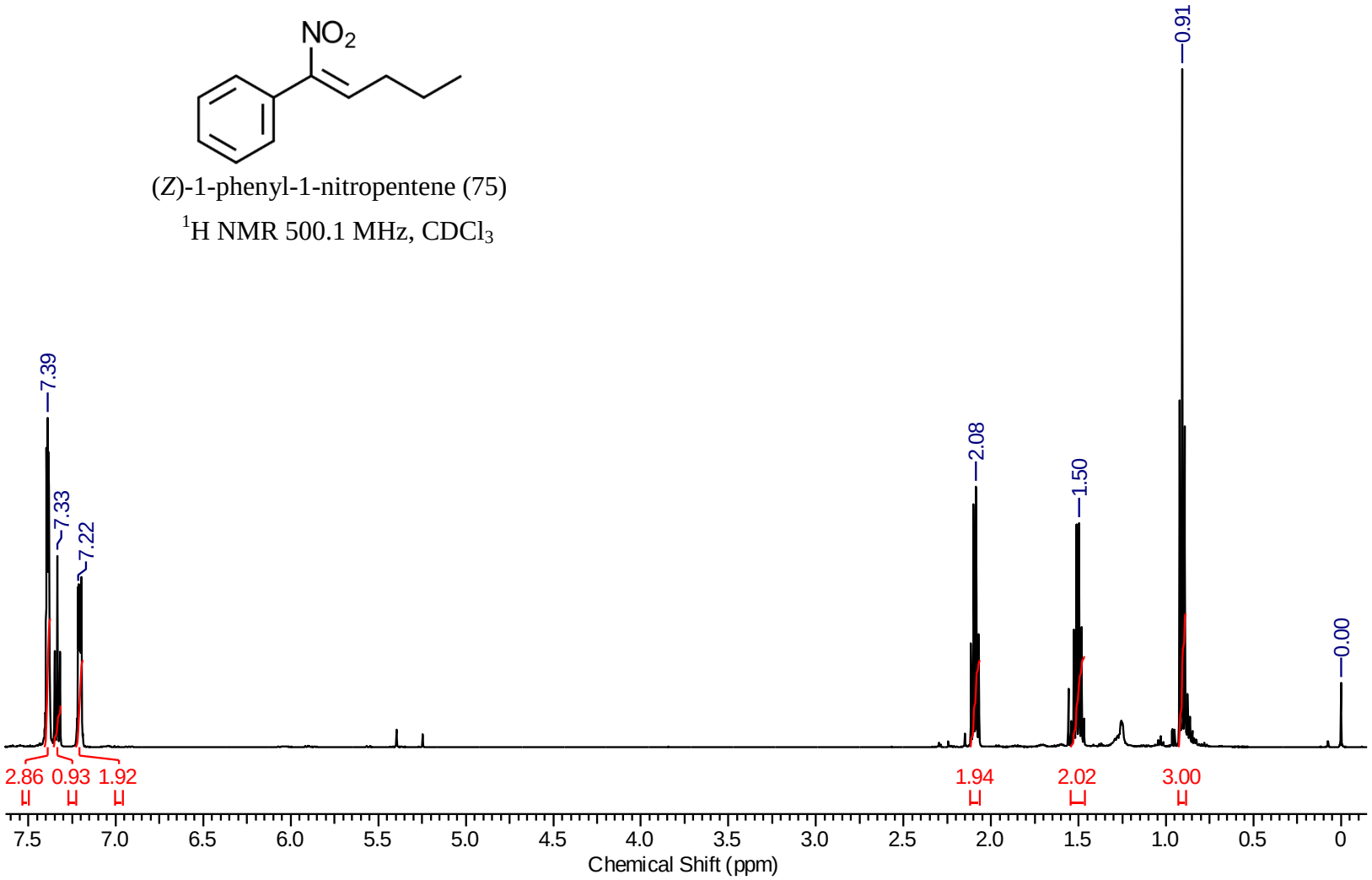
(*E*)-4-methyl-1-nitro-1-phenylpentene (74)

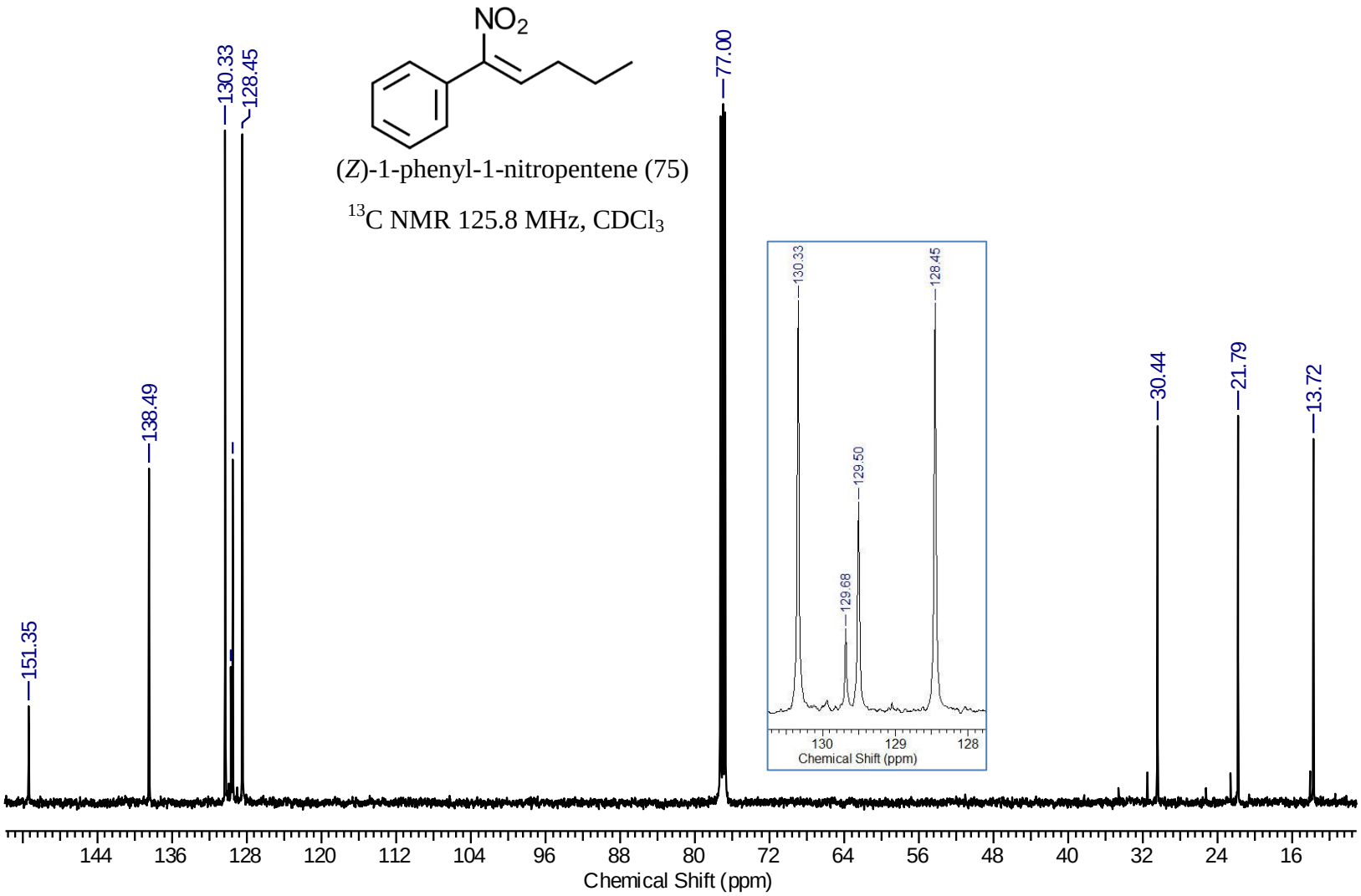
^{1}H NMR 300.3 MHz, $CDCl_3$

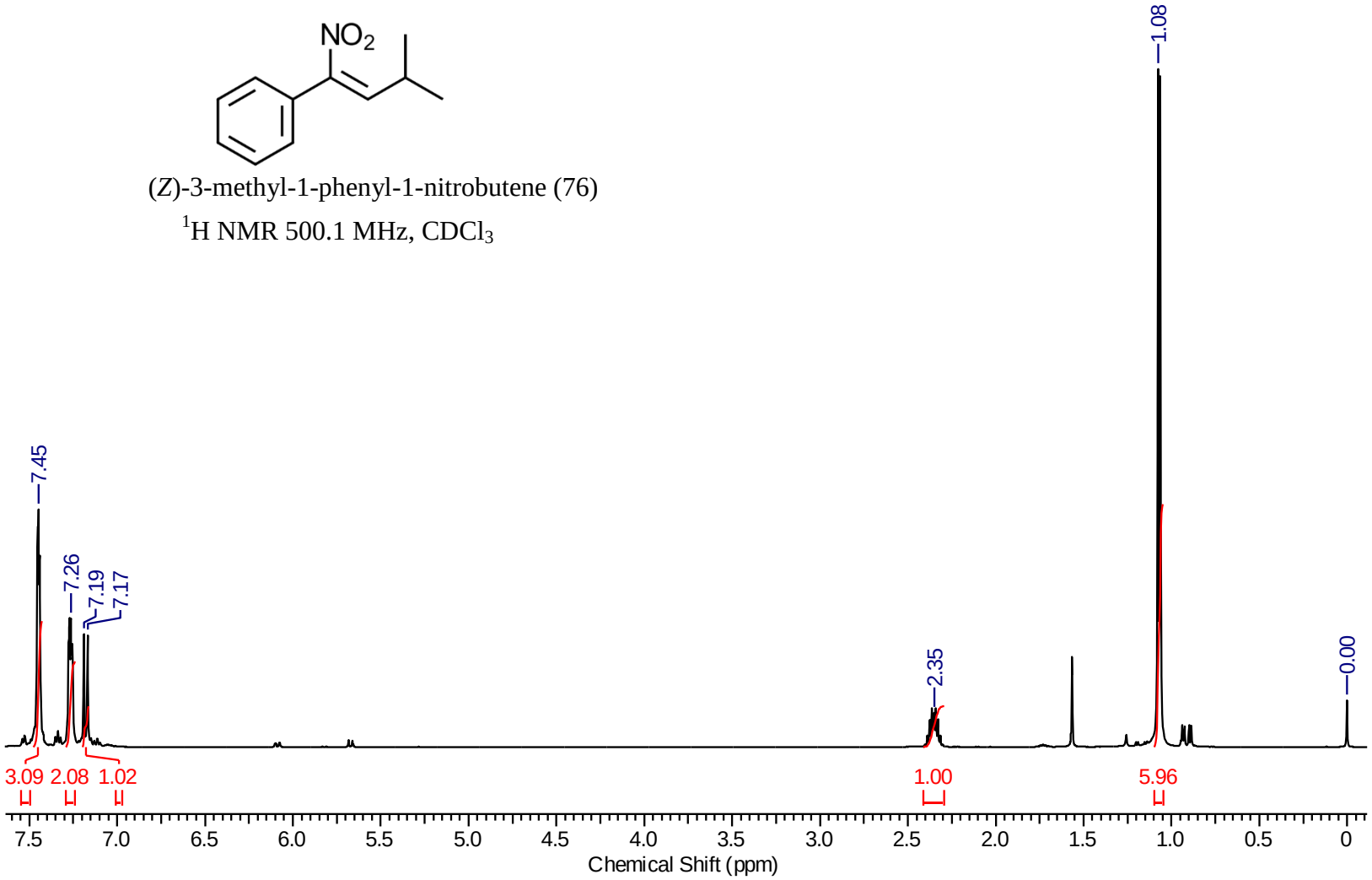


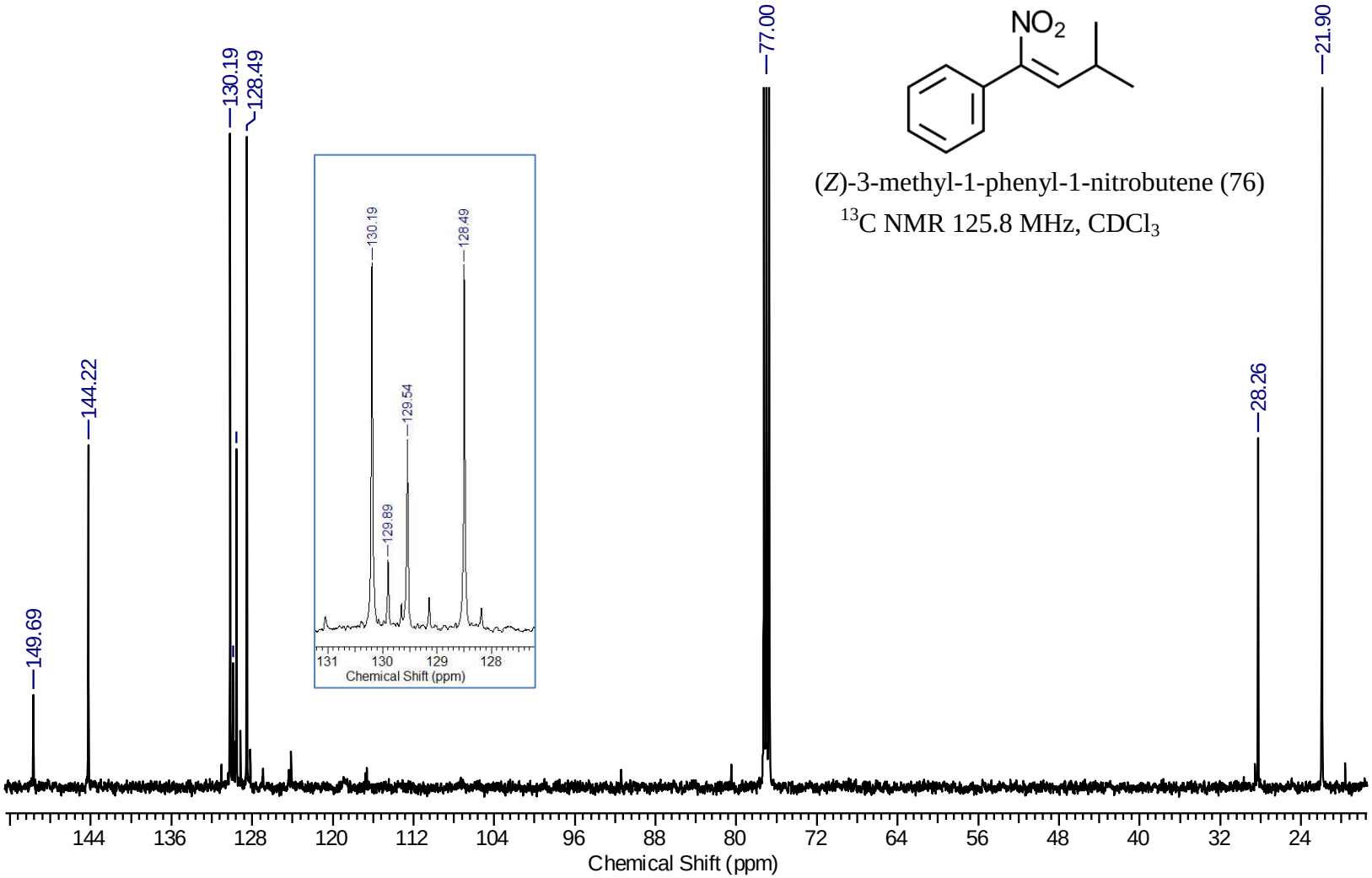
(*E*)-4-methyl-1-nitro-1-phenylpentene (74)

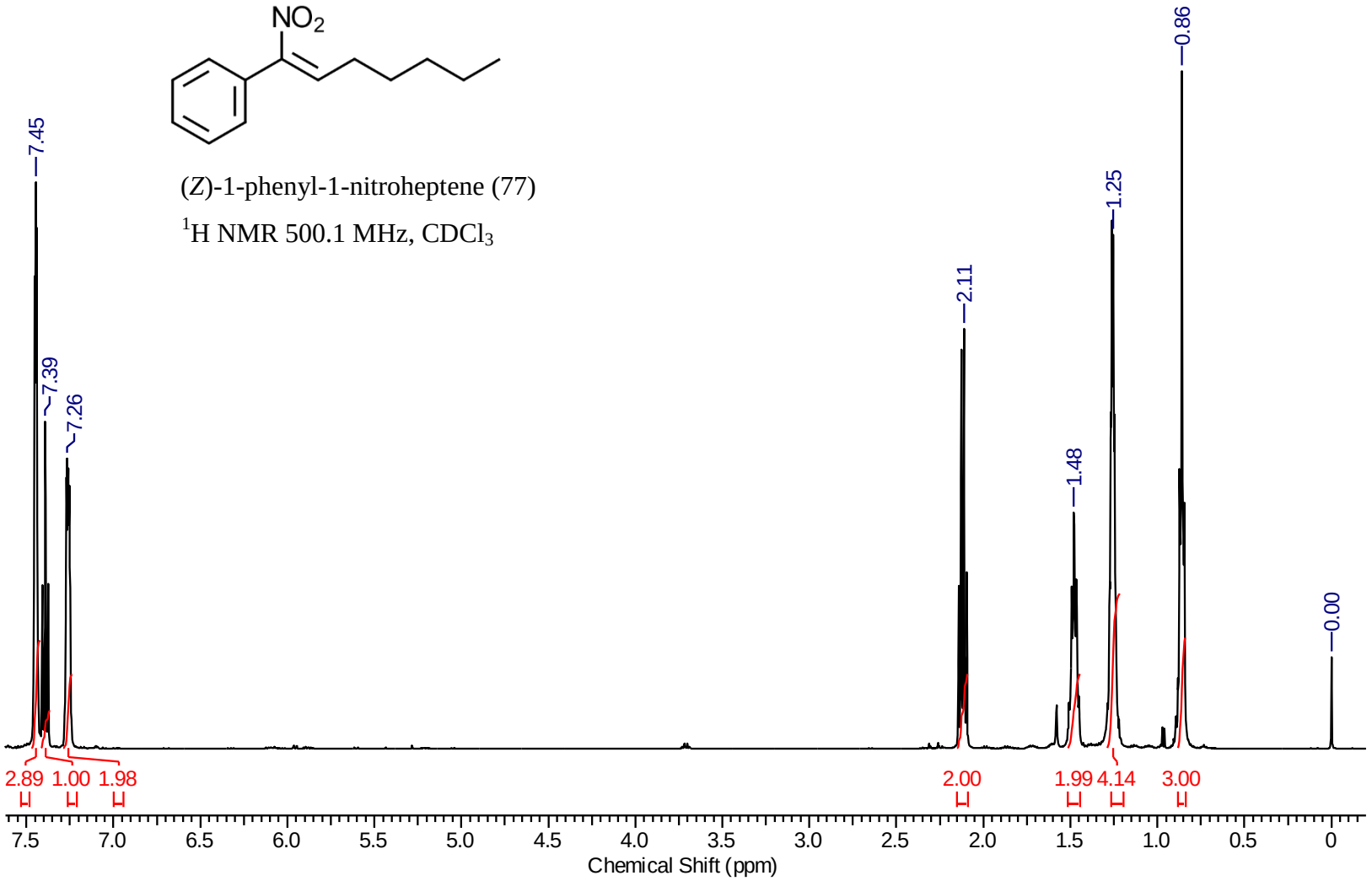
^{13}C NMR 75.5 MHz, $CDCl_3$

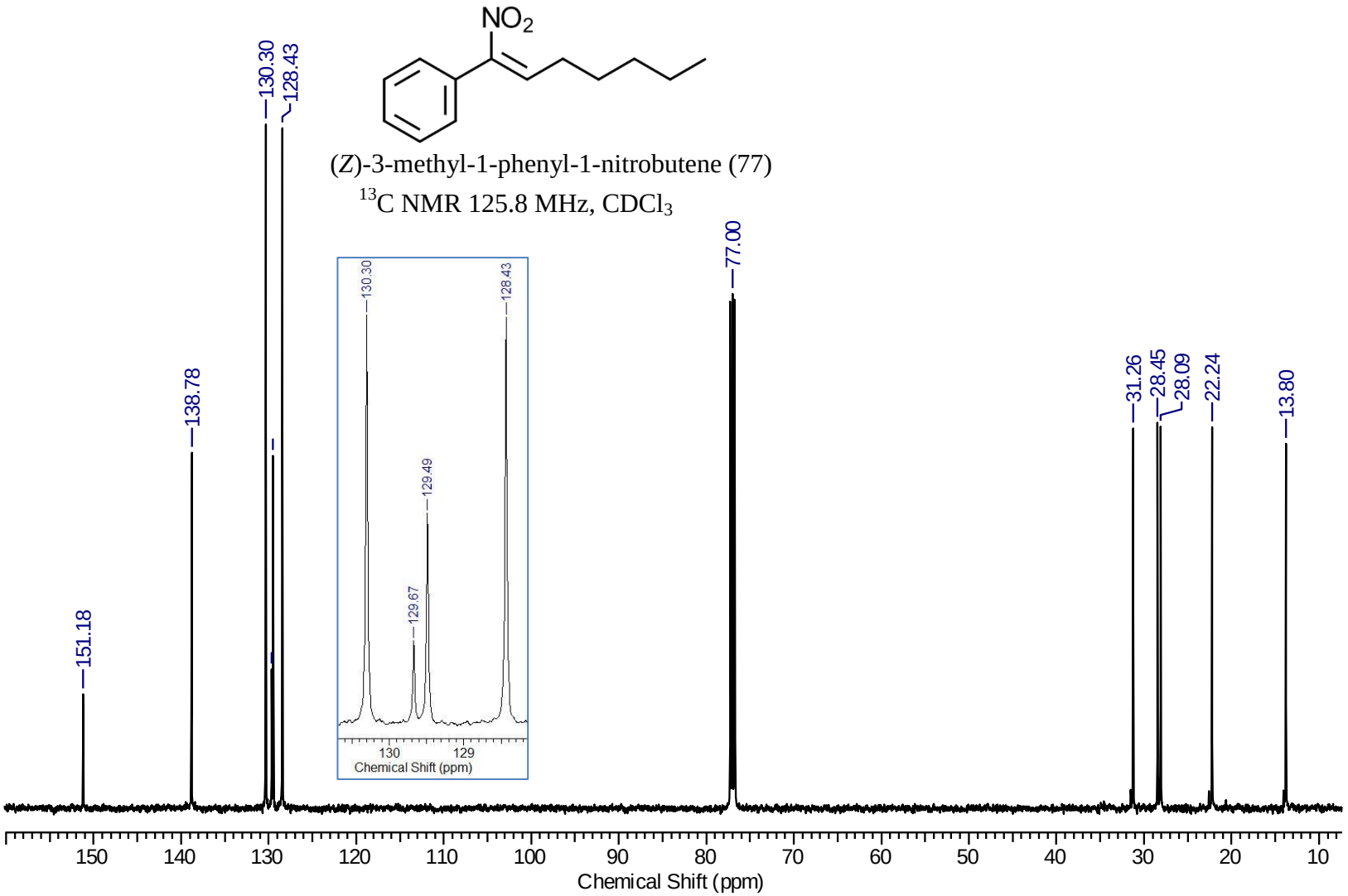

NO2
(Z)-1-phenyl-1-nitropentene (75)
1H NMR 500.1 MHz, CDCl3
7.39
7.33
7.22
2.08
1.50
0.91
0.00
2.86
0.93
1.92
1.94
2.02
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

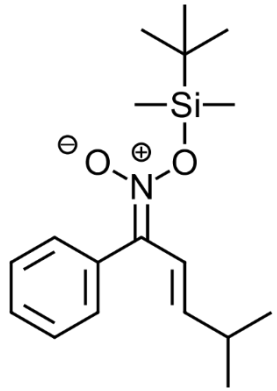

NO2
(Z)-1-phenyl-1-nitropentene (75)
13C NMR 125.8 MHz, CDCl3
151.35
138.49
130.33
128.45
77.00
30.44
21.79
13.72
129.68
129.50
Chemical Shift (ppm)
Chemical Shift (ppm)


NO2
(Z)-3-methyl-1-phenyl-1-nitrobutene (76)
1H NMR 500.1 MHz, CDCl3
7.45
7.26
7.19
7.17
2.35
1.08
0.00
3.09
2.08
1.02
1.00
5.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


NO2
(Z)-3-methyl-1-phenyl-1-nitrobutene (76)
13C NMR 125.8 MHz, CDCl3
149.69
144.22
130.19
128.49
77.00
28.26
21.90
129.89
129.54
Chemical Shift (ppm)
Chemical Shift (ppm)

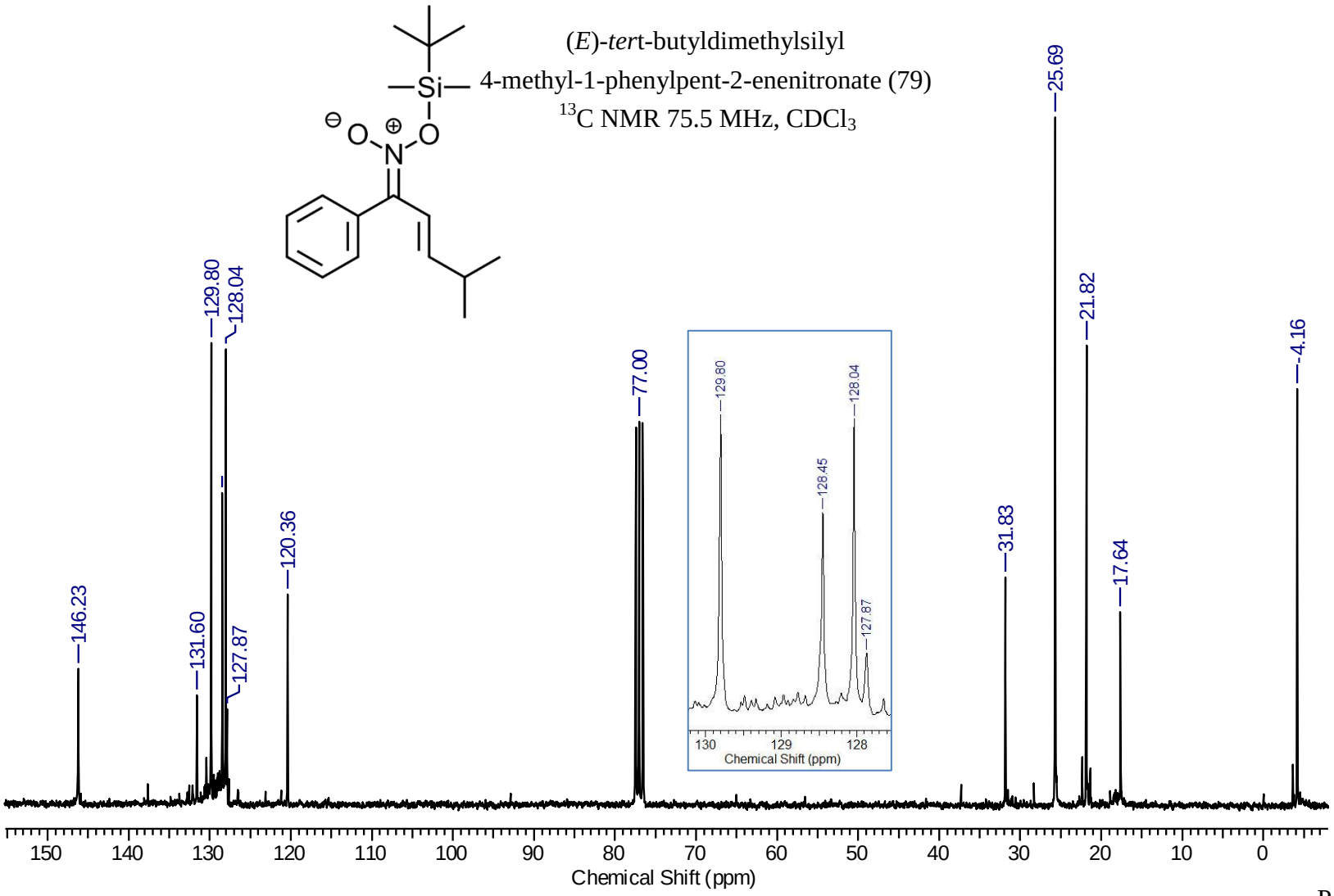

NO2
(Z)-1-phenyl-1-nitroheptene (77)
1H NMR 500.1 MHz, CDCl3
7.45
7.39
7.26
2.11
1.48
1.25
0.86
0.00
2.89
1.00
1.98
2.00
1.99
4.14
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

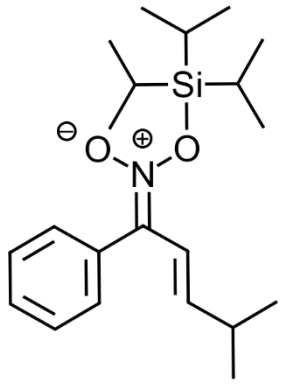

NO2
(Z)-3-methyl-1-phenyl-1-nitrobutene (77)
13C NMR 125.8 MHz, CDCl3
151.18
138.78
130.30
128.43
77.00
31.26
28.45
28.09
22.24
13.80
129.67
129.49
Chemical Shift (ppm)
Chemical Shift (ppm)



(*E*)-*tert*-butyldimethylsilyl 4-methyl-1-phenylpent-2-enenitronate (79)

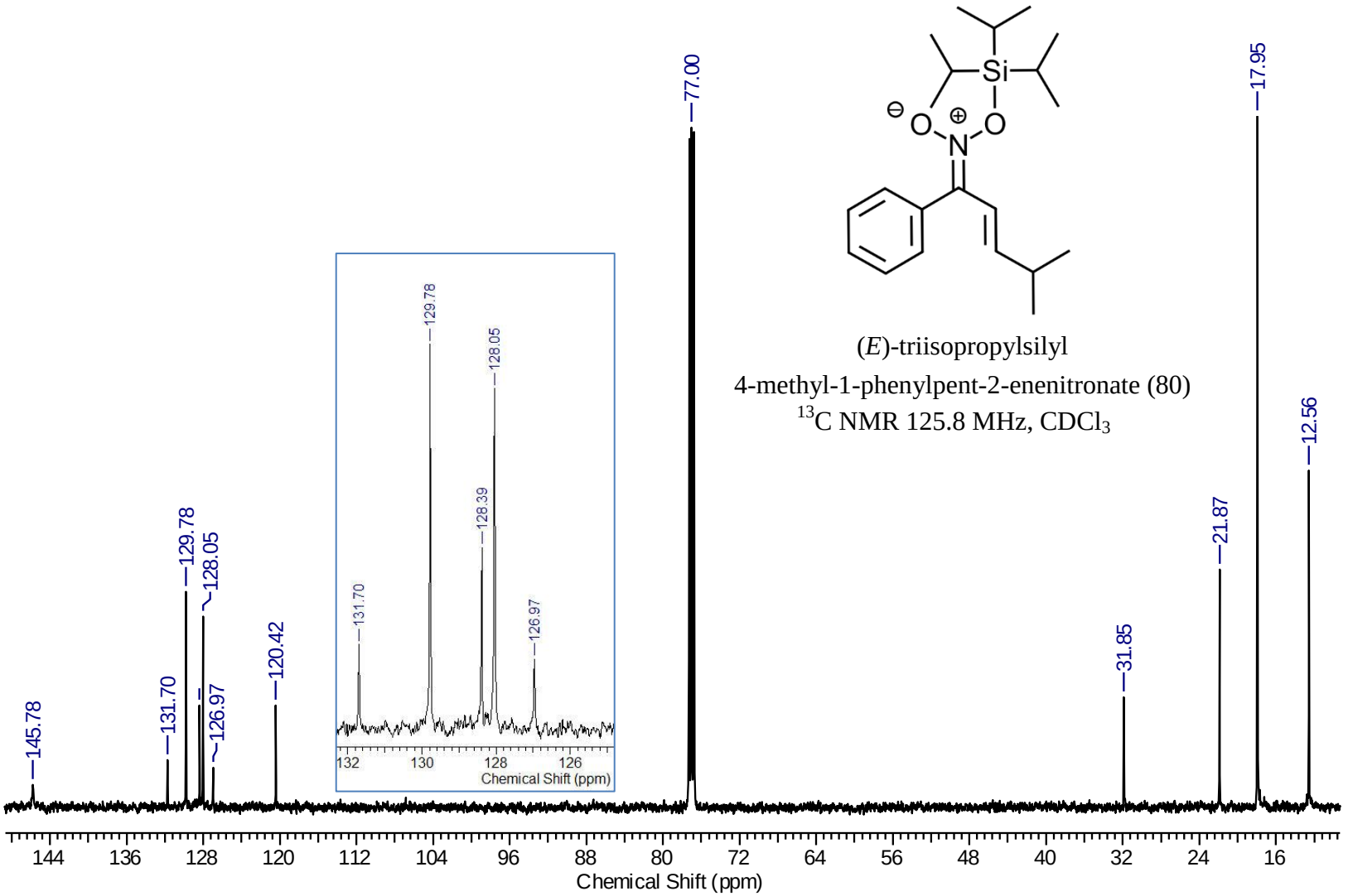
^{1}H NMR 300.3 MHz, $CDCl_3$

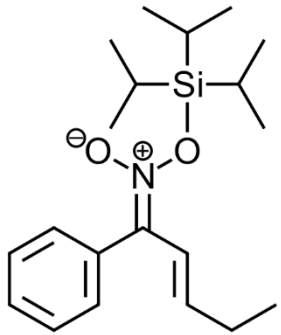

(E)-tert-butyldimethylsilyl
4-methyl-1-phenylpent-2-enenitronate (79)
13C NMR 75.5 MHz, CDCl3
Si
O
N
O
146.23
131.60
129.80
128.04
127.87
120.36
77.00
31.83
25.69
21.82
17.64
4.16
128.45
Chemical Shift (ppm)
Chemical Shift (ppm)



(*E*)-triisopropylsilyl 4-methyl-1-phenylpent-2-enenitronate (80)

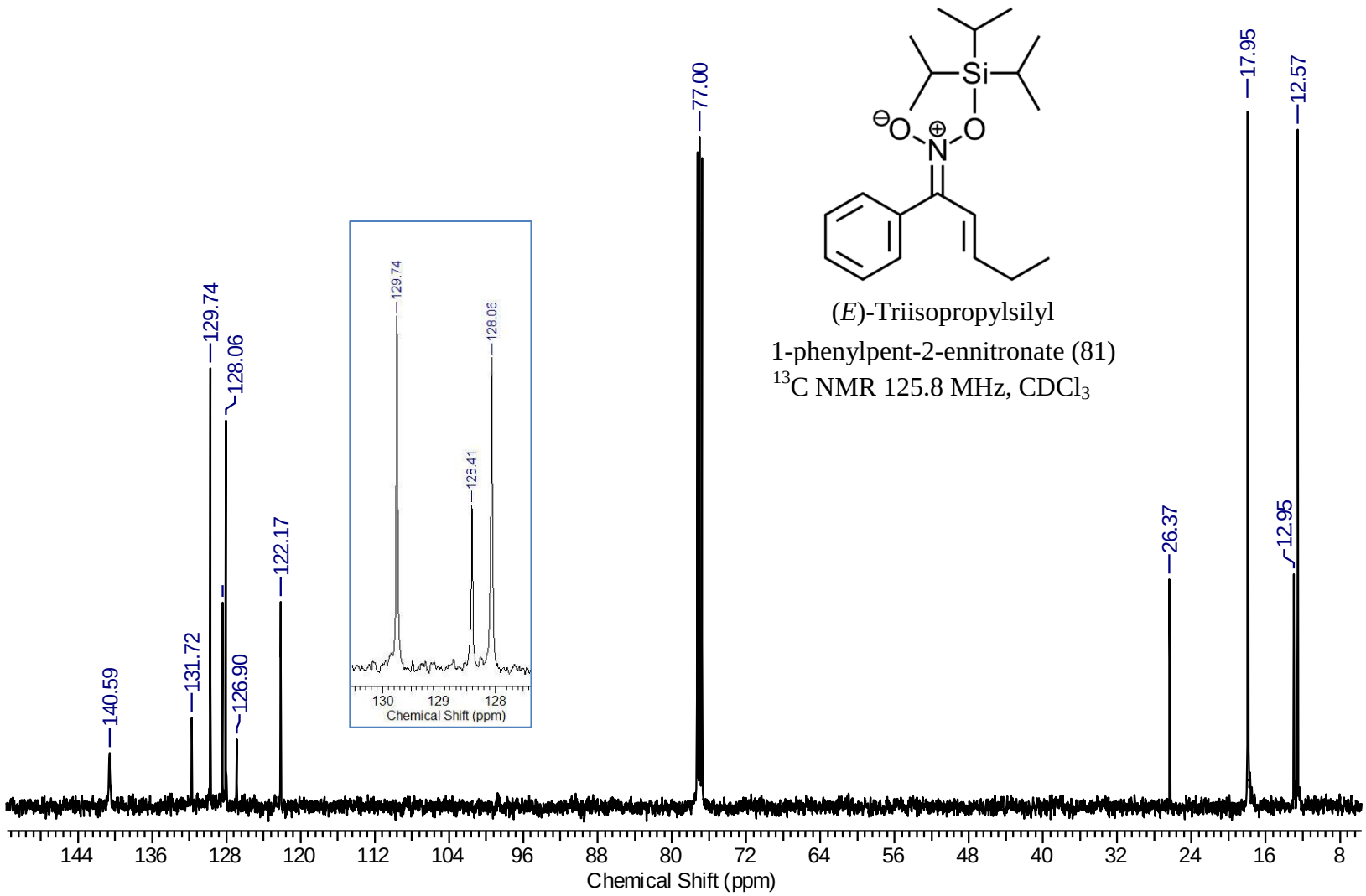
^{1}H NMR 500.1 MHz, $CDCl_3$

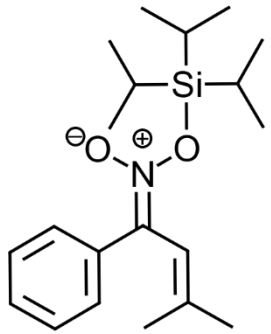

Si
O
N
O
(E)-triisopropylsilyl
4-methyl-1-phenylpent-2-enenitronate (80)
13C NMR 125.8 MHz, CDCl3
145.78
131.70
129.78
128.05
126.97
120.42
77.00
31.85
21.87
17.95
12.56
Chemical Shift (ppm)



(*E*)-Triisopropylsilyl 1-phenylpent-2-ennitronate (81)

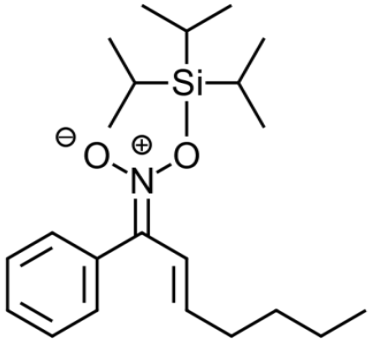
^{1}H NMR 500.1 MHz, $CDCl_3$


Si
O
N
O
(E)-Triisopropylsilyl
1-phenylpent-2-ennitronate (81)
13C NMR 125.8 MHz, CDCl3
140.59
131.72
129.74
128.06
126.90
122.17
77.00
26.37
17.95
12.95
12.57
128.41
Chemical Shift (ppm)
Chemical Shift (ppm)



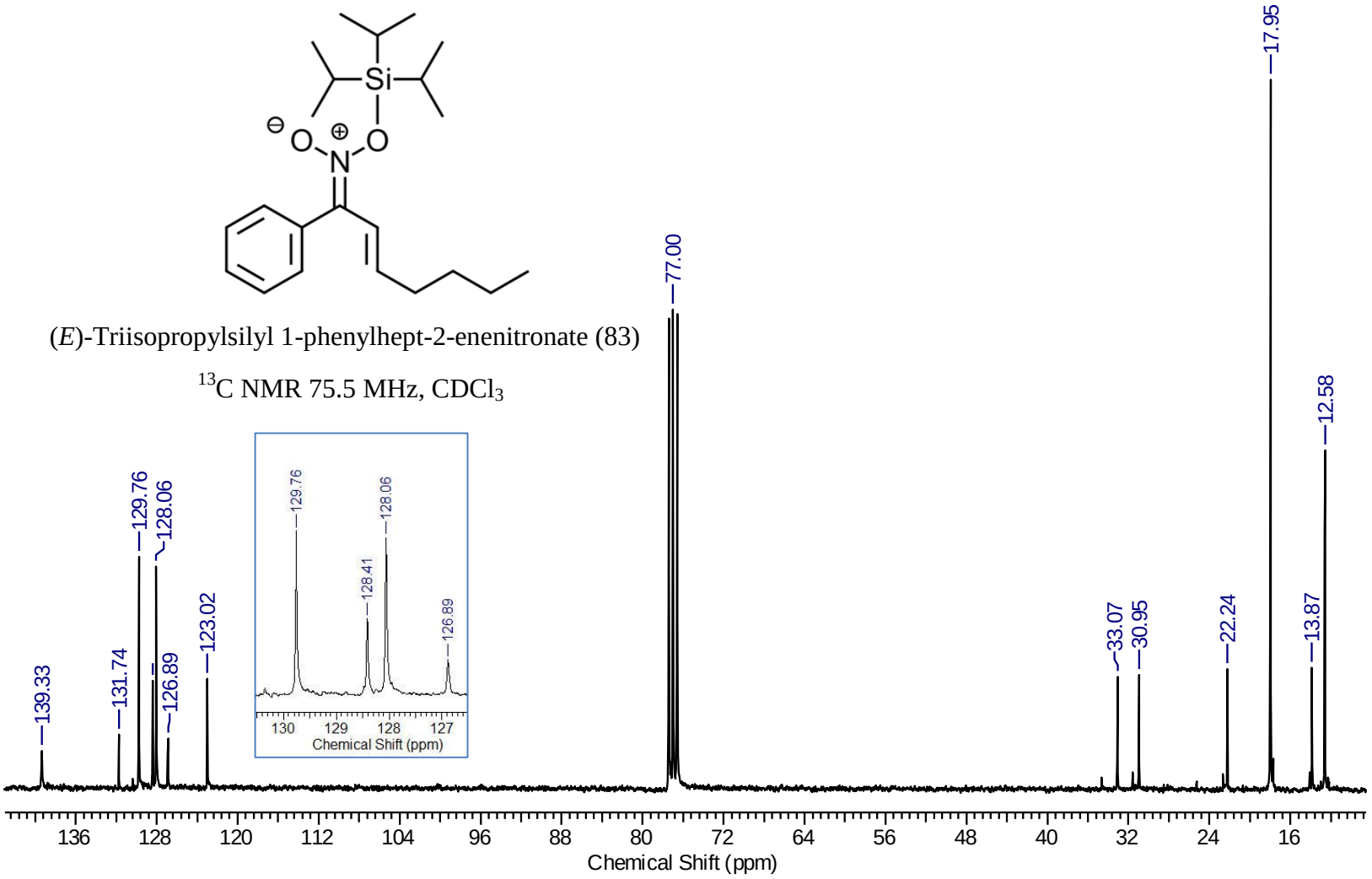
triisopropylsilyl 3-methyl-1-phenylbut-2-enenitronate (82)

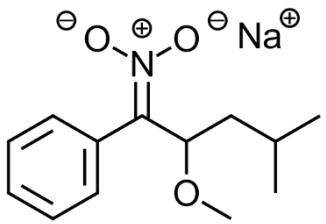
^{1}H NMR 500.1 MHz, $CDCl_3$



(*E*)-Triisopropylsilyl 1-phenylhept-2-enenitronate (83)

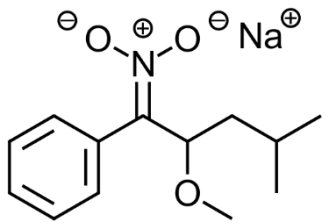
^{1}H NMR 300.3 MHz, $CDCl_3$


Si
O
N
O
(E)-Triisopropylsilyl 1-phenylhept-2-enenitronate (83)
13C NMR 75.5 MHz, CDCl3
139.33
131.74
129.76
128.06
126.89
123.02
77.00
33.07
30.95
22.24
17.95
13.87
12.58
129.76
128.41
128.06
126.89
130
129
128
127
Chemical Shift (ppm)
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)



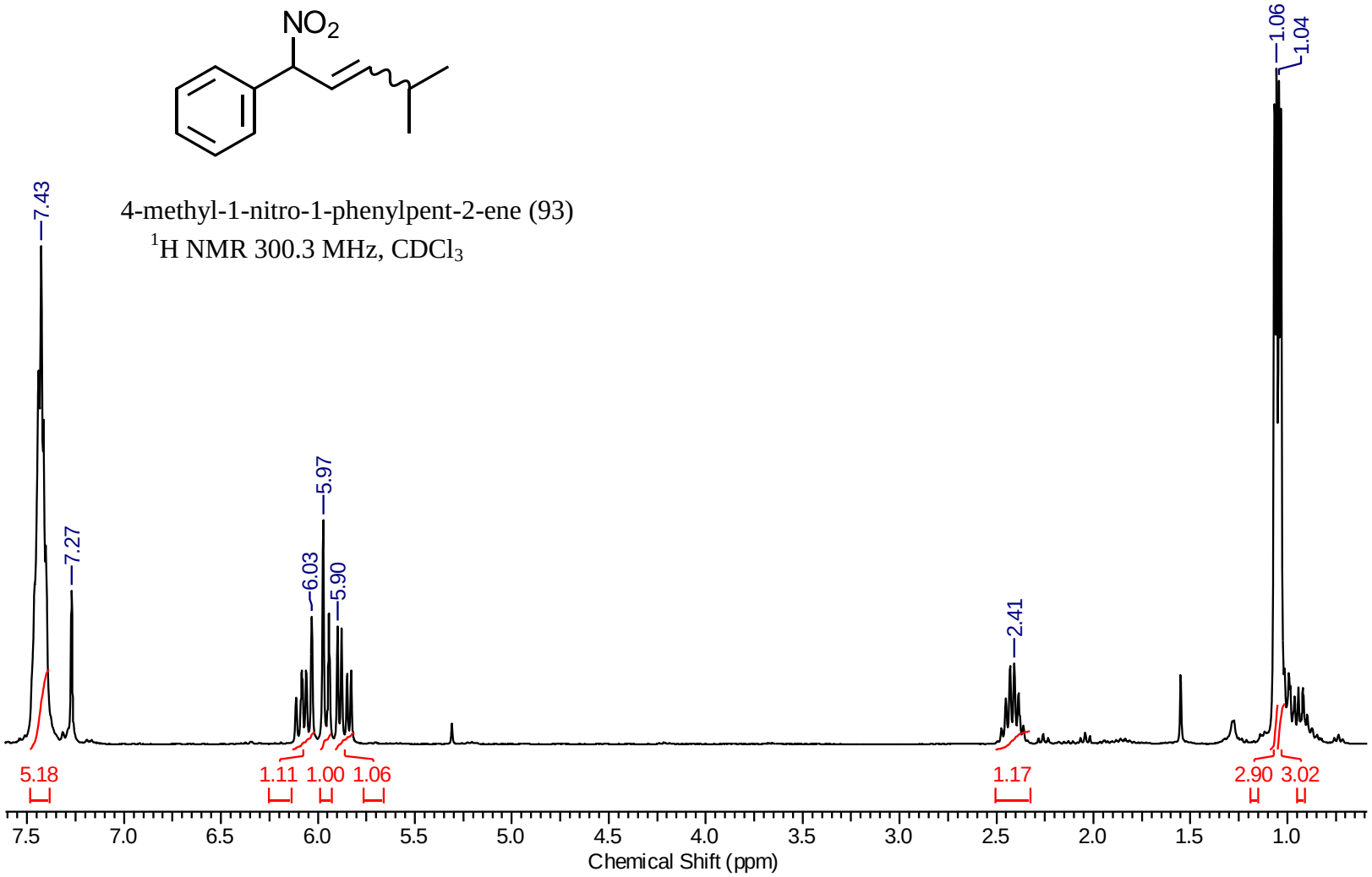
Sodium 2-methoxy-4-methyl-1-phenylpentanenitronate (87)

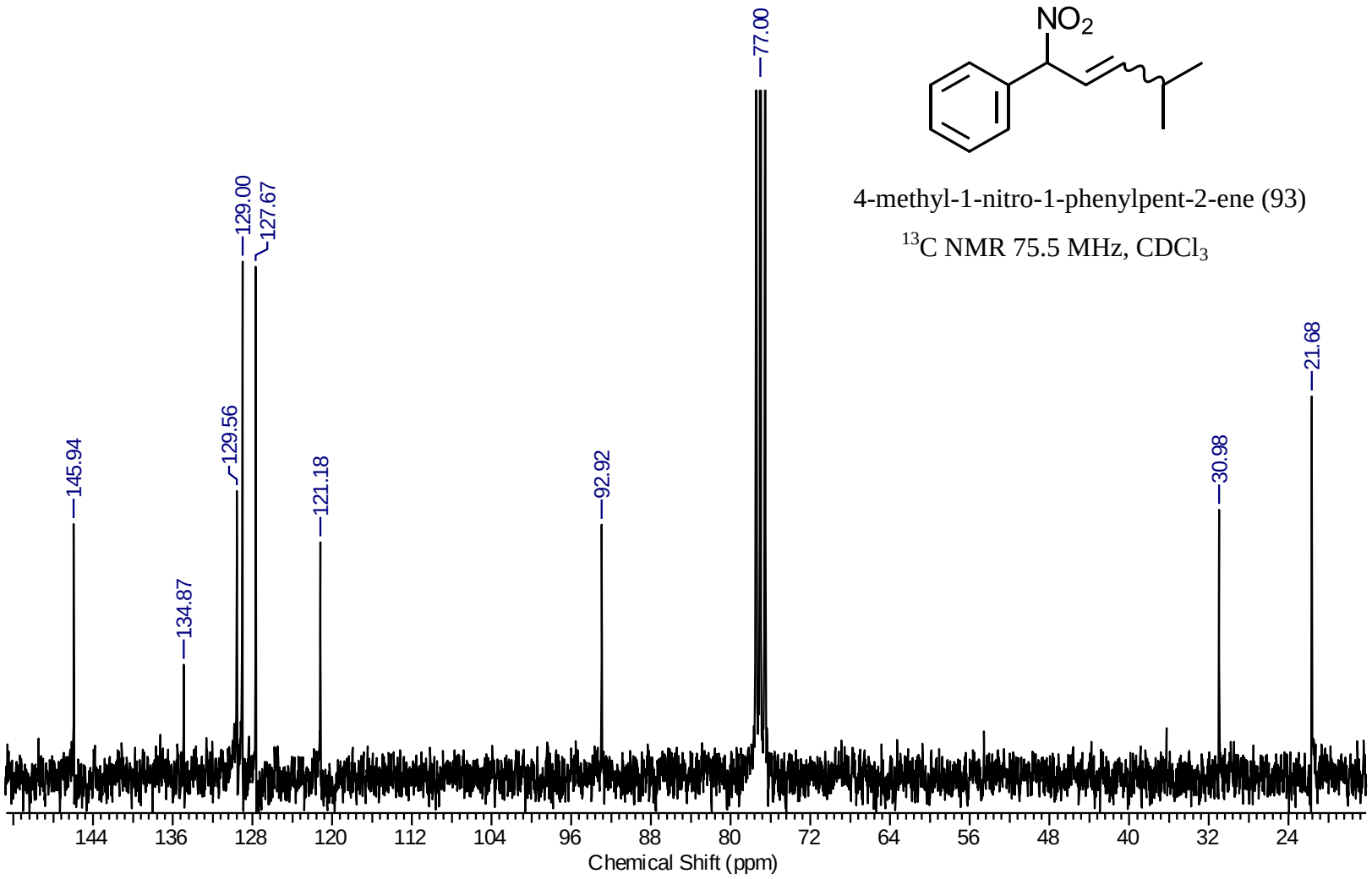
^{1}H NMR 300.3 MHz, $(CD_3)_2SO$



Sodium 2-methoxy-4-methyl-1-phenylpentanenitronate (87)

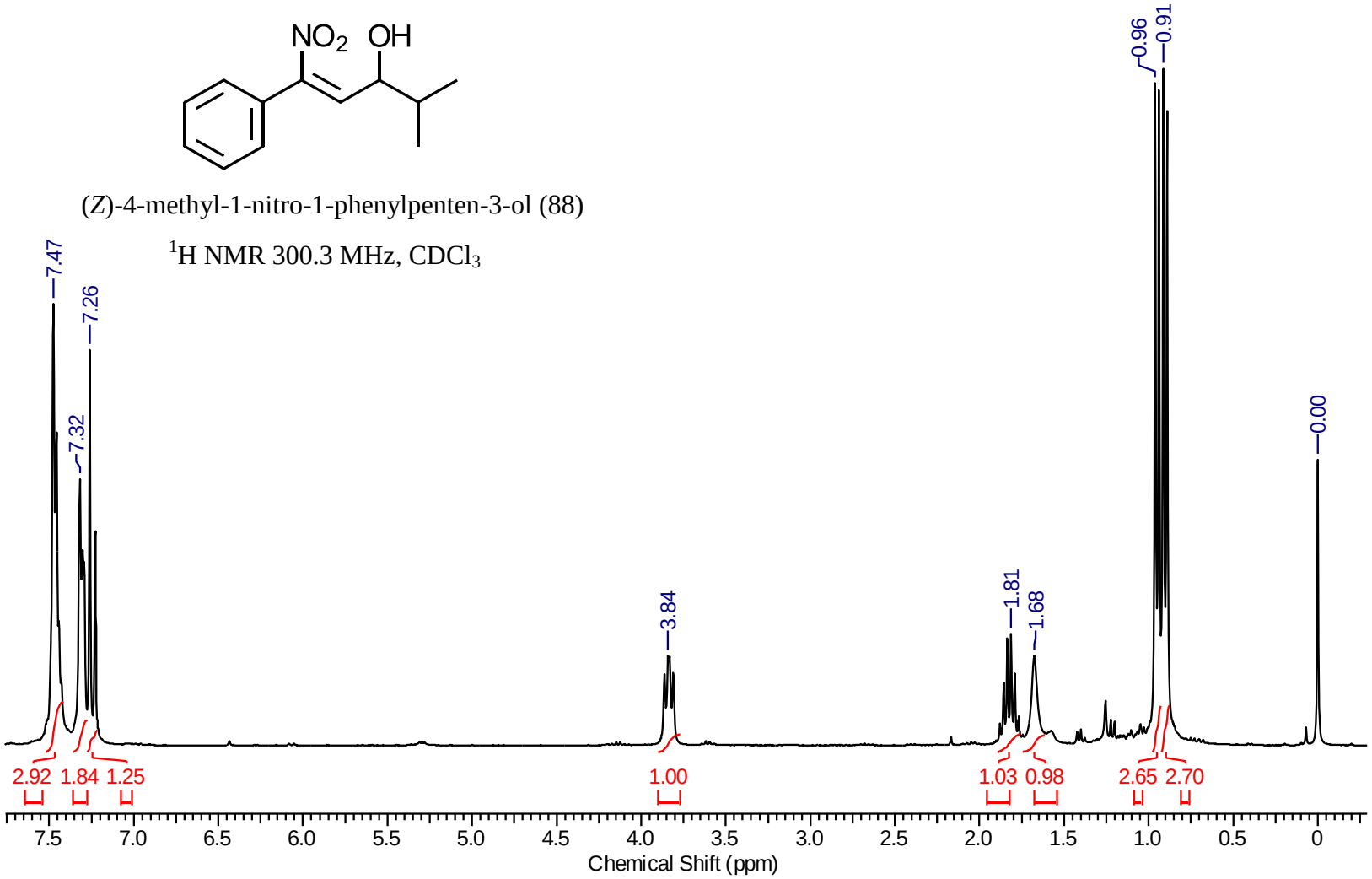
^{13}C NMR 75.5 MHz, $(CD_3)_2SO$

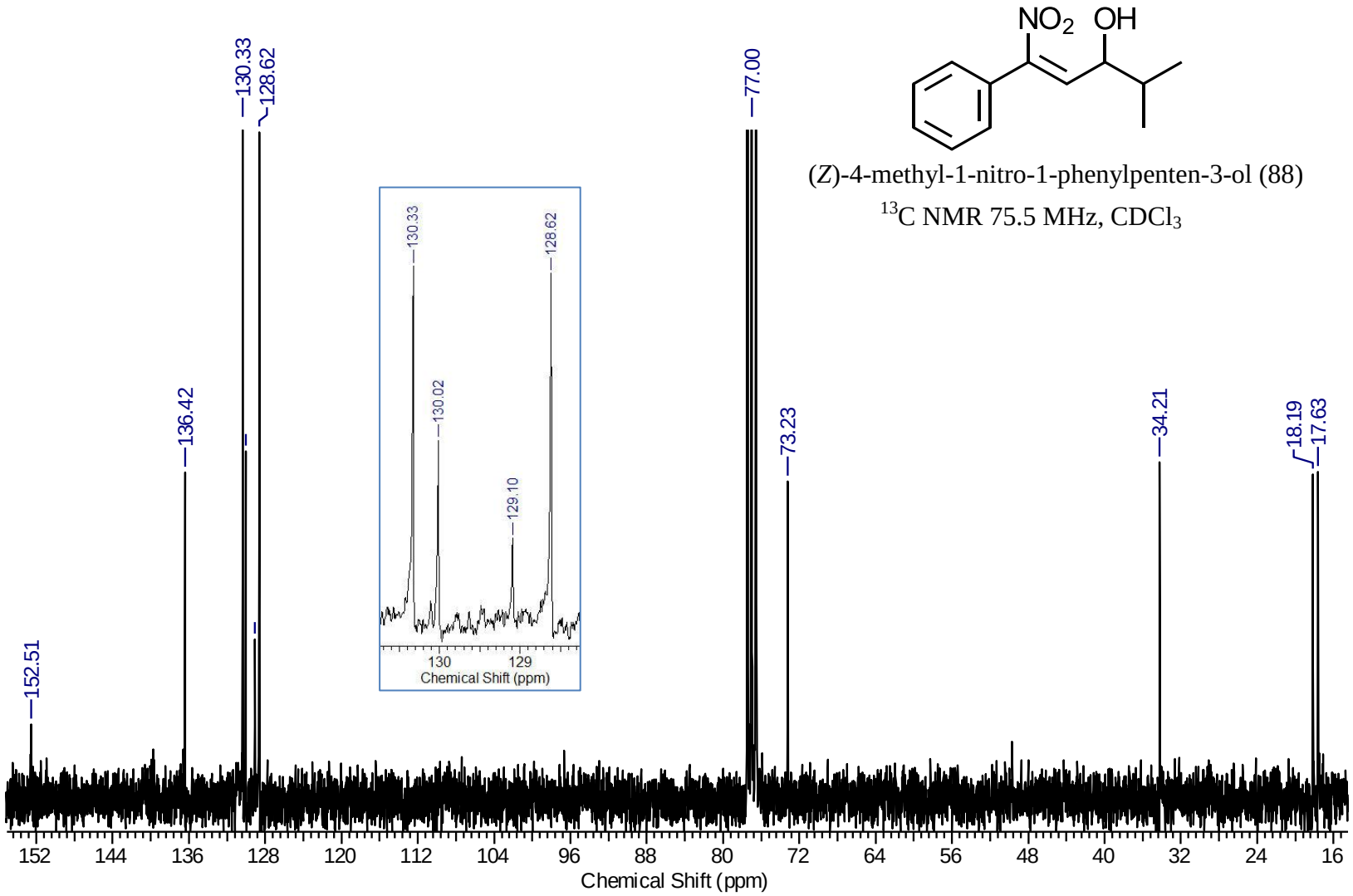

NO2
4-methyl-1-nitro-1-phenylpent-2-ene (93)
1H NMR 300.3 MHz, CDCl3
7.43
7.27
6.03
5.97
5.90
2.41
1.06
1.04
5.18
1.11
1.00
1.06
1.17
2.90
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

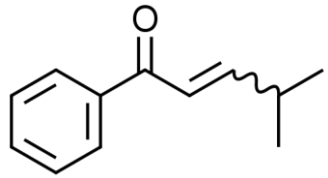


4-methyl-1-nitro-1-phenylpent-2-ene (93)

^{13}C NMR 75.5 MHz, $CDCl_3$

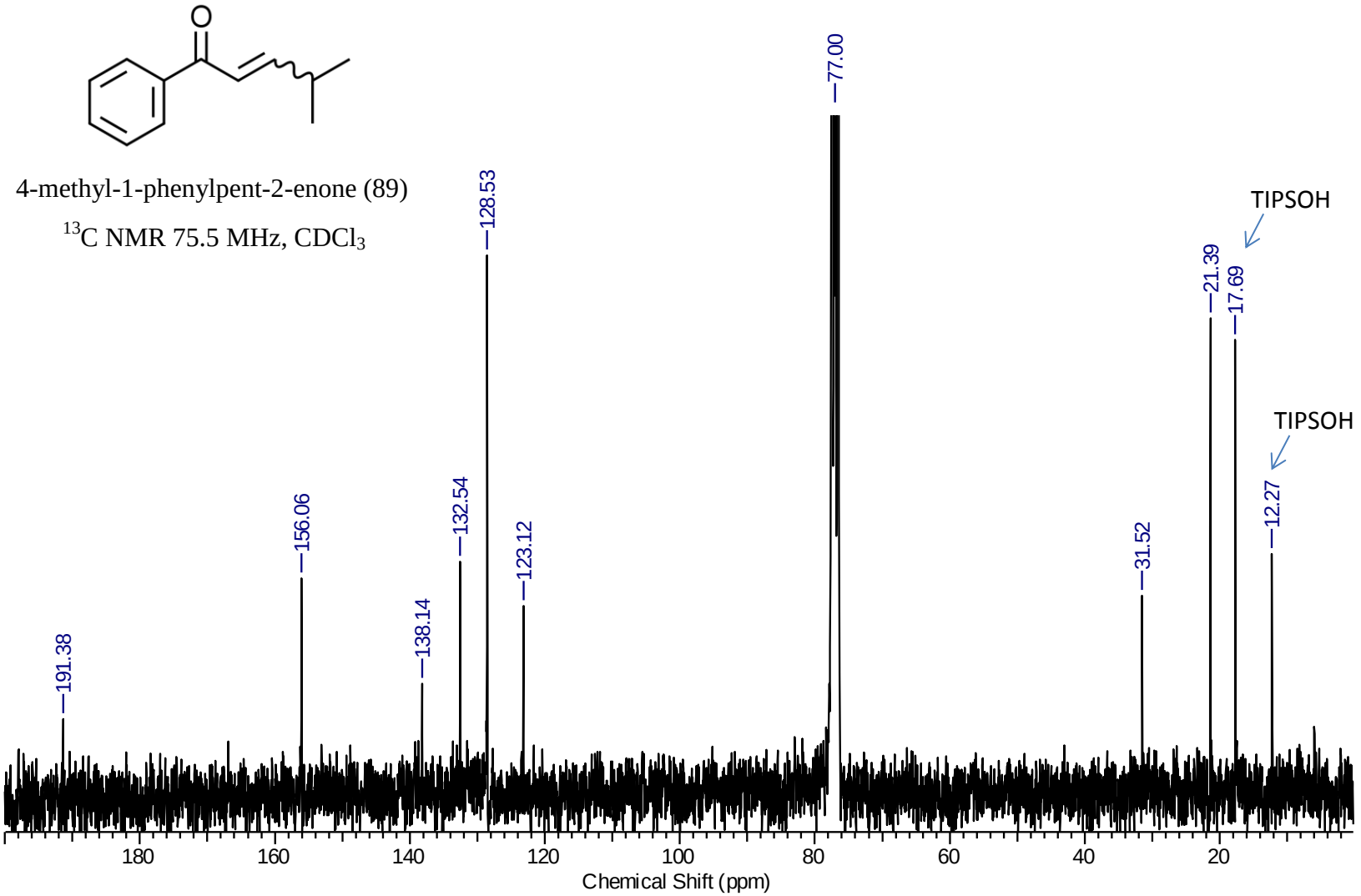

NO2 OH
(Z)-4-methyl-1-nitro-1-phenylpenten-3-ol (88)
1H NMR 300.3 MHz, CDCl3
7.47
7.26
7.32
3.84
1.81
1.68
0.96
0.91
0.00
2.92 1.84 1.25
1.00
1.03 0.98
2.65 2.70
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

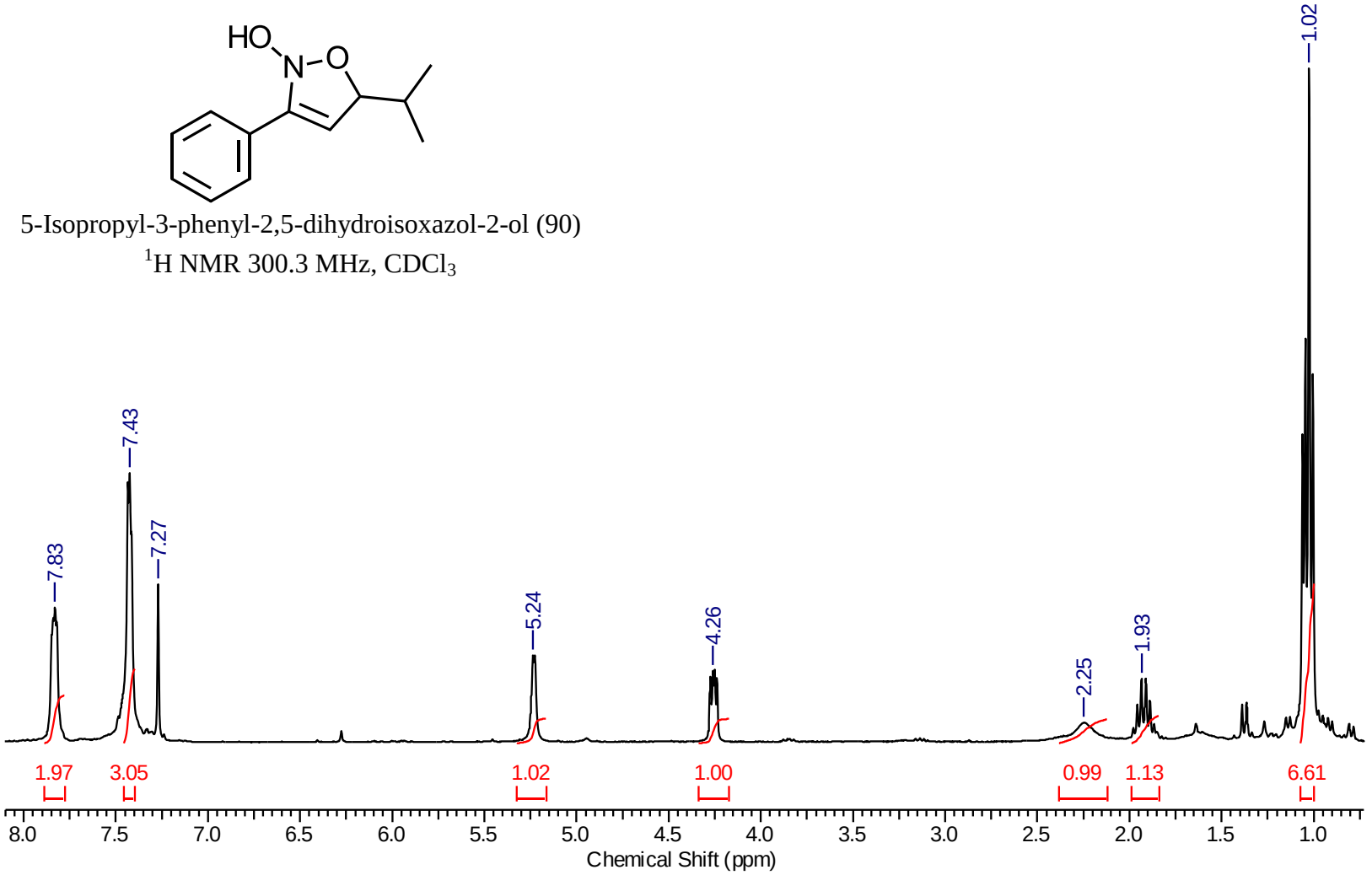

NO2 OH
(Z)-4-methyl-1-nitro-1-phenylpenten-3-ol (88)
13C NMR 75.5 MHz, CDCl3
152.51
136.42
130.33
128.62
77.00
73.23
34.21
18.19
17.63
130.33
130.02
129.10
128.62
130
129
Chemical Shift (ppm)
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)



4-methyl-1-phenylpent-2-enone (89)

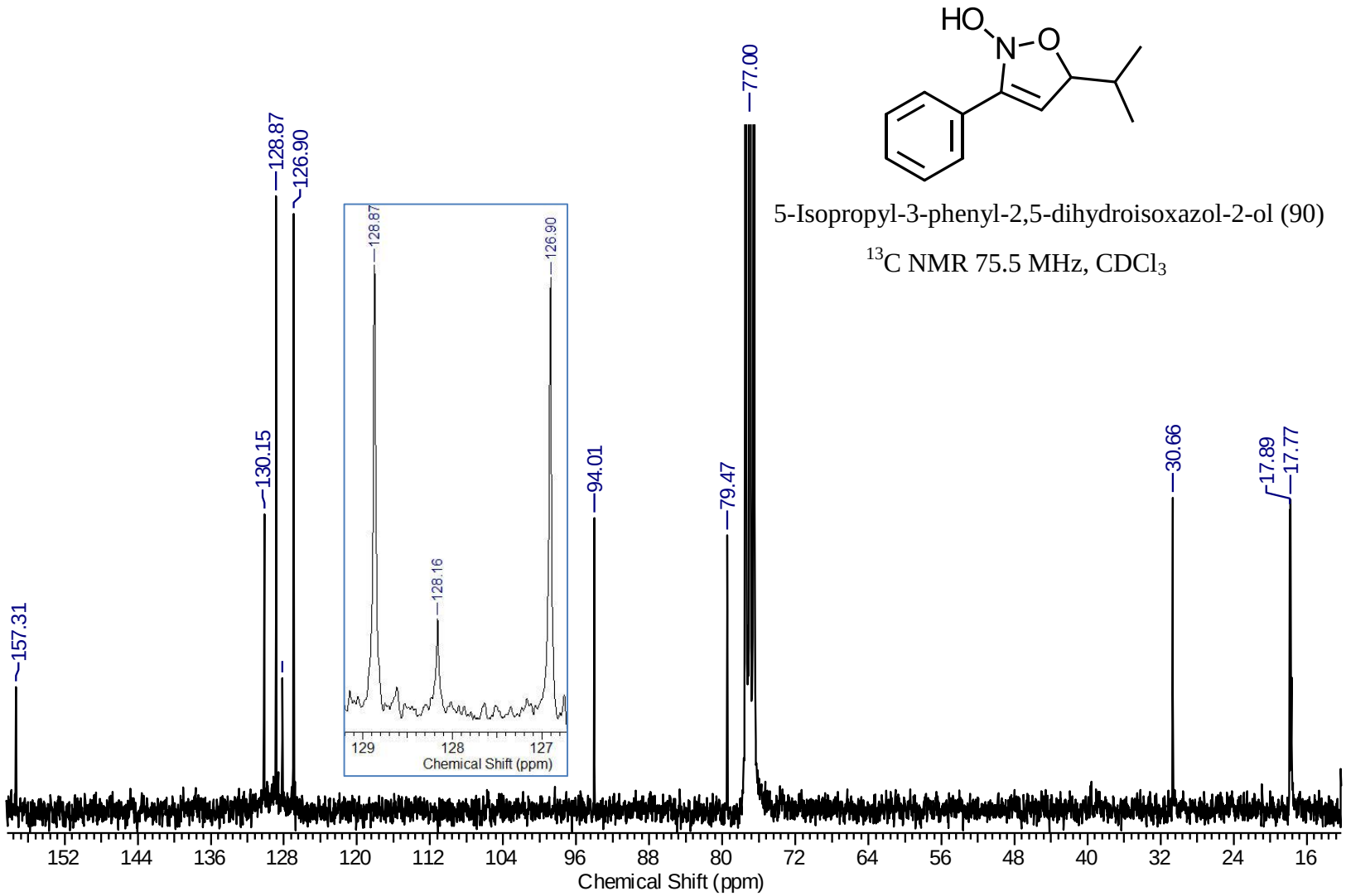
^{1}H NMR 300.3 MHz, $CDCl_3$


4-methyl-1-phenylpent-2-enone (89)
^{13}C NMR 75.5 MHz, $CDCl_3$
191.38
156.06
138.14
132.54
128.53
123.12
77.00
31.52
21.39
17.69
12.27
TIPSOH
TIPSOH
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)



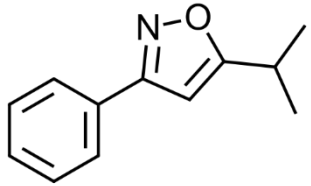
5-Isopropyl-3-phenyl-2,5-dihydroisoxazol-2-ol (90)

^{1}H NMR 300.3 MHz, $CDCl_3$



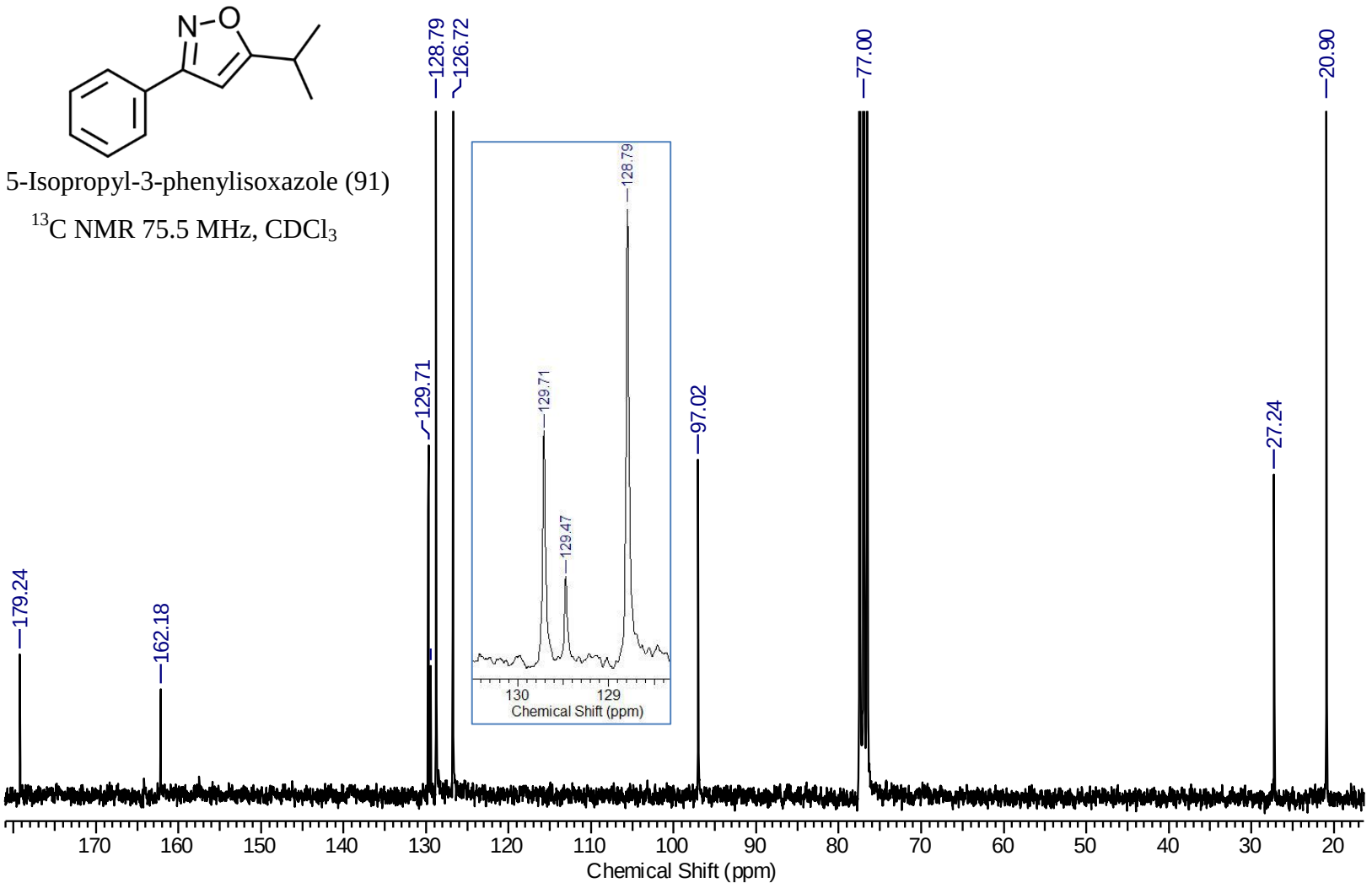
5-Isopropyl-3-phenyl-2,5-dihydroisoxazol-2-ol (90)

^{13}C NMR 75.5 MHz, $CDCl_3$



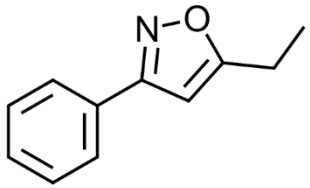
5-Isopropyl-3-phenylisoxazole (91)

^{1}H NMR 300.3 MHz, $CDCl_3$



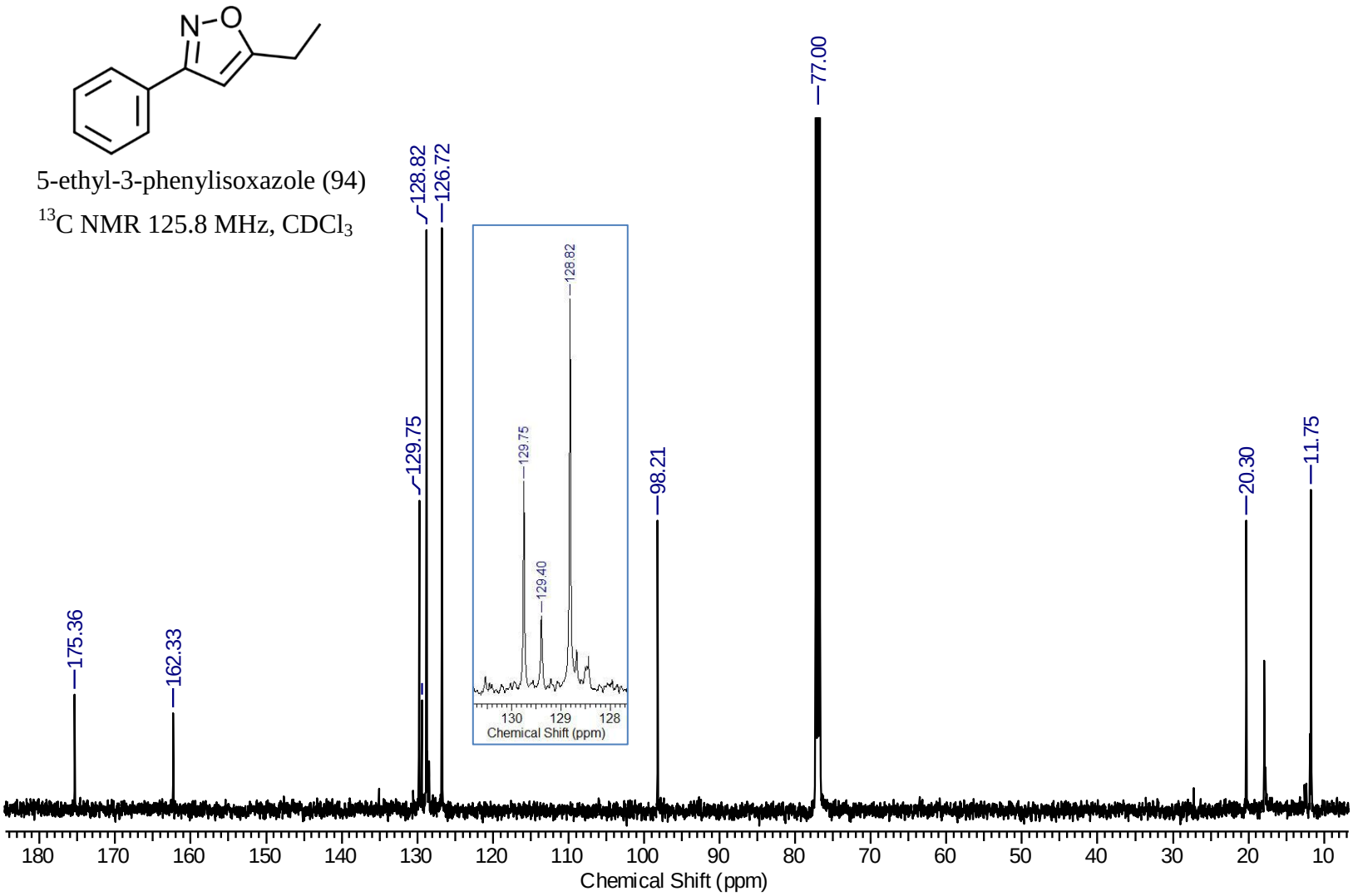
5-Isopropyl-3-phenylisoxazole (91)

^{13}C NMR 75.5 MHz, $CDCl_3$



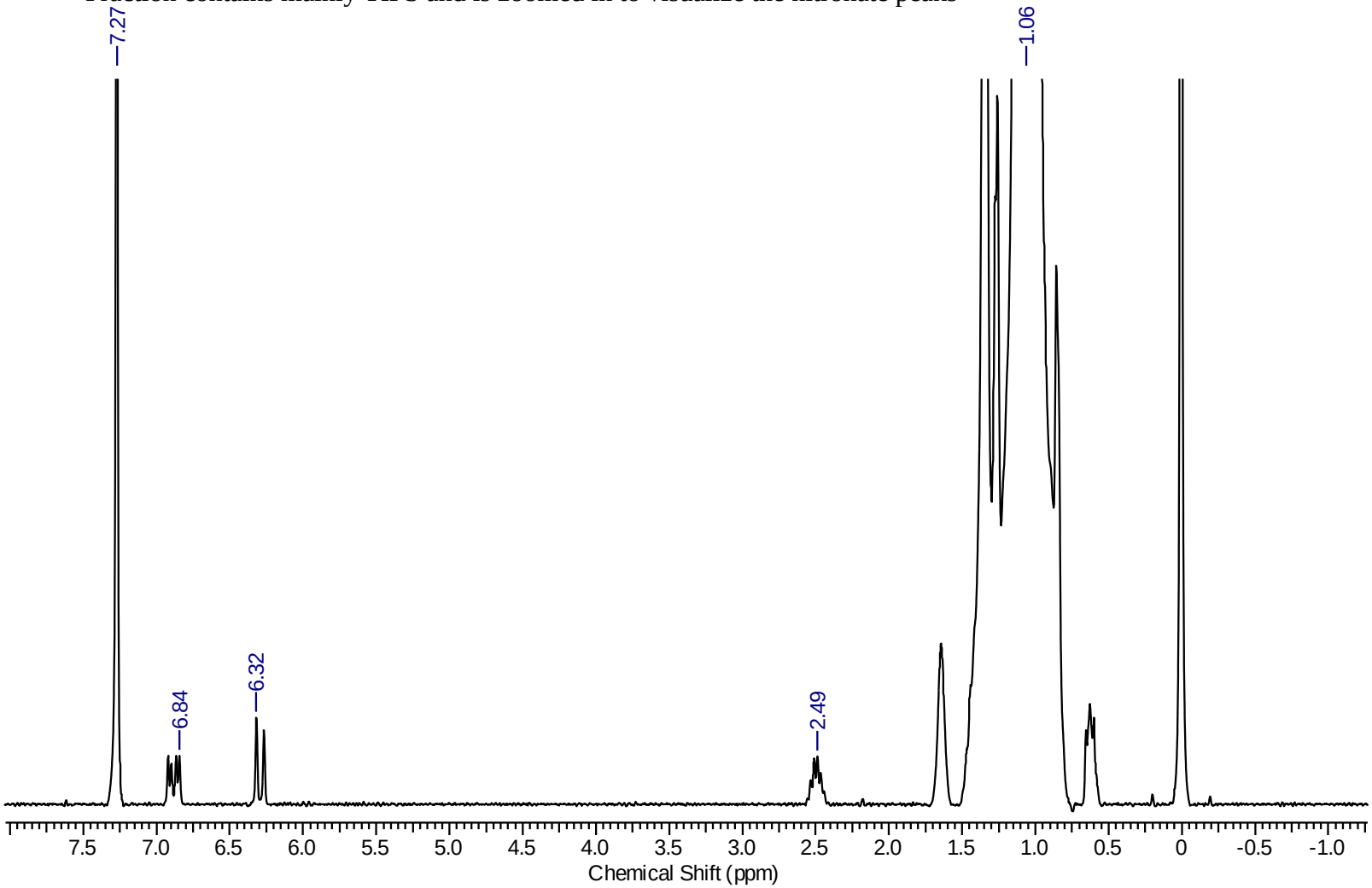
5-ethyl-3-phenylisoxazole (94)

^{1}H NMR 500.1 MHz, $CDCl_3$


N
O
5-ethyl-3-phenylisoxazole (94)
13C NMR 125.8 MHz, CDCl3
175.36
162.33
129.75
128.82
126.72
98.21
77.00
20.30
11.75
129.75
129.40
128.82
130
129
128
Chemical Shift (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

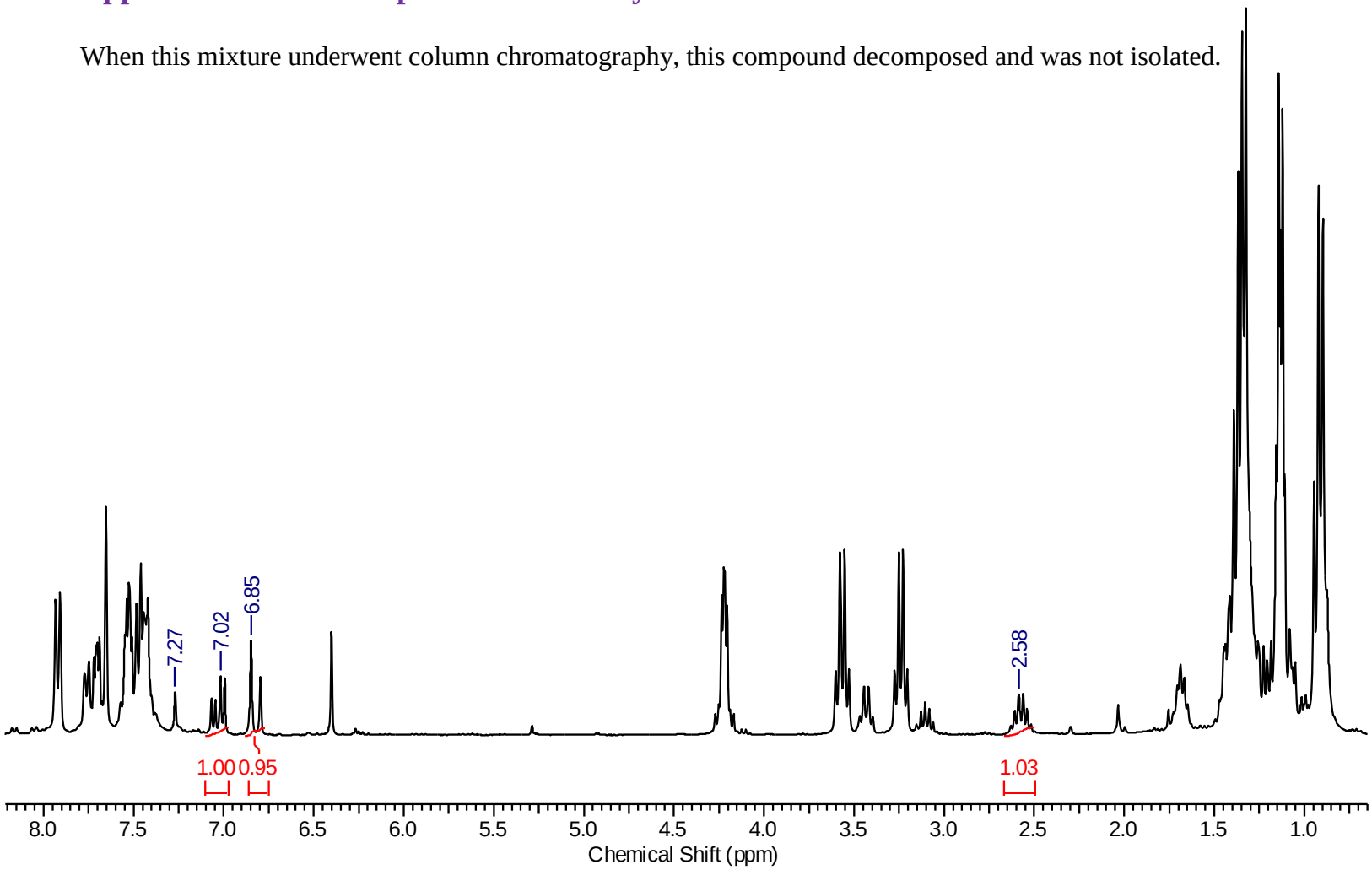
Appendix 2: ^{1}H NMR Spectrum of compound 62

Fraction contains mainly TIPS and is zoomed in to visualize the nitronate peaks

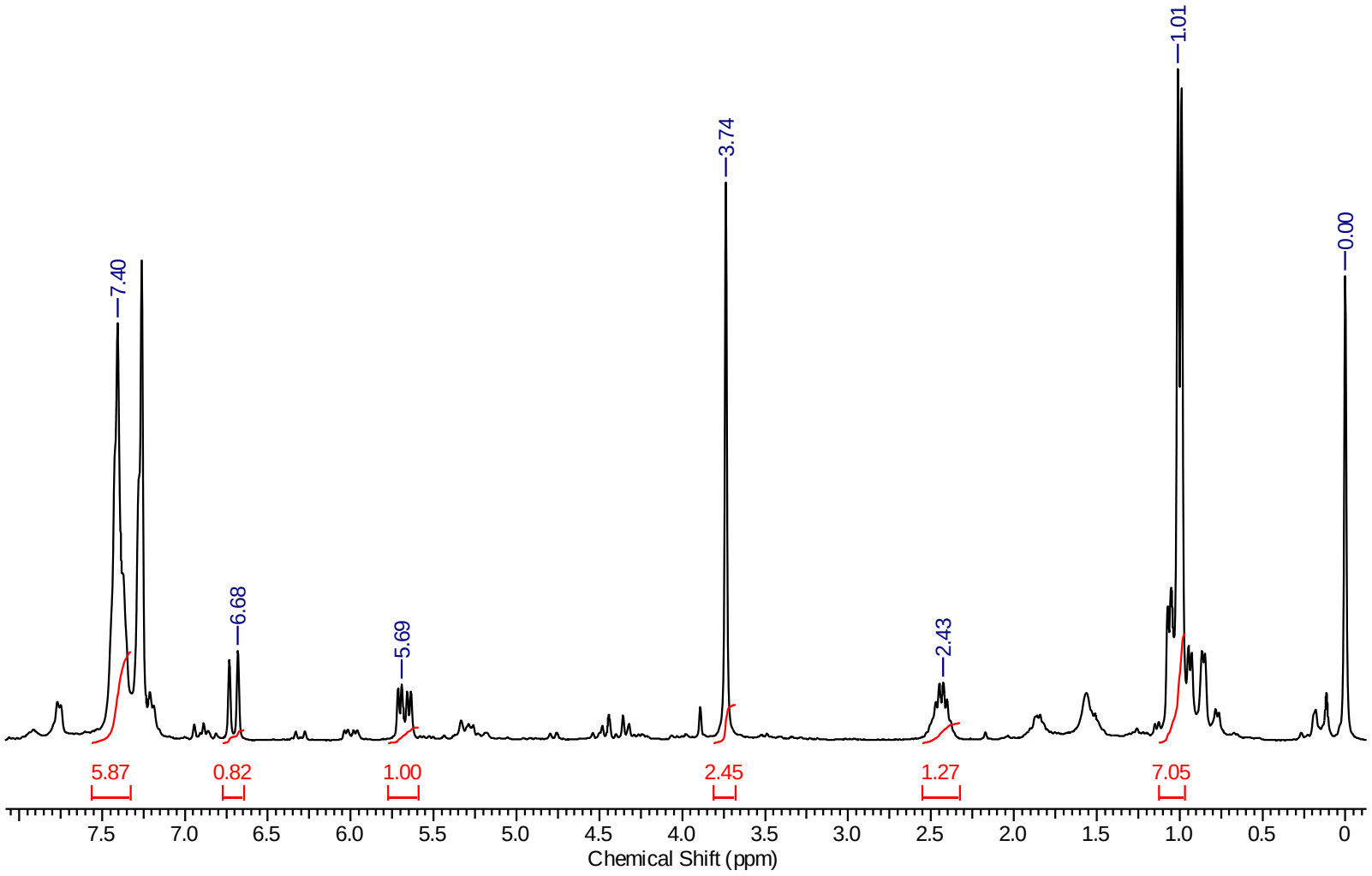


Appendix 3: ^{1}H NMR Spectrum of the acyl nitronate 85

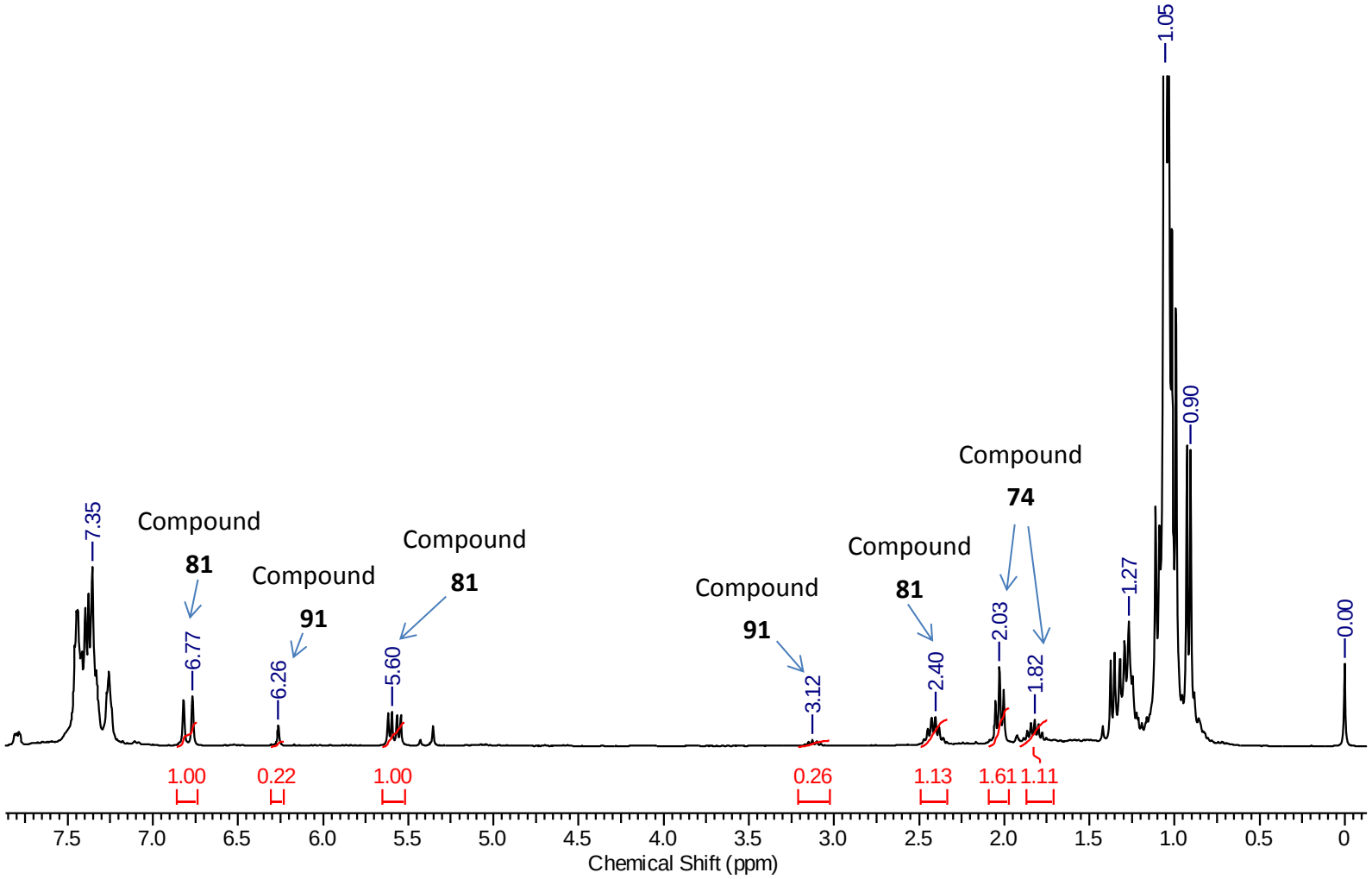
When this mixture underwent column chromatography, this compound decomposed and was not isolated.



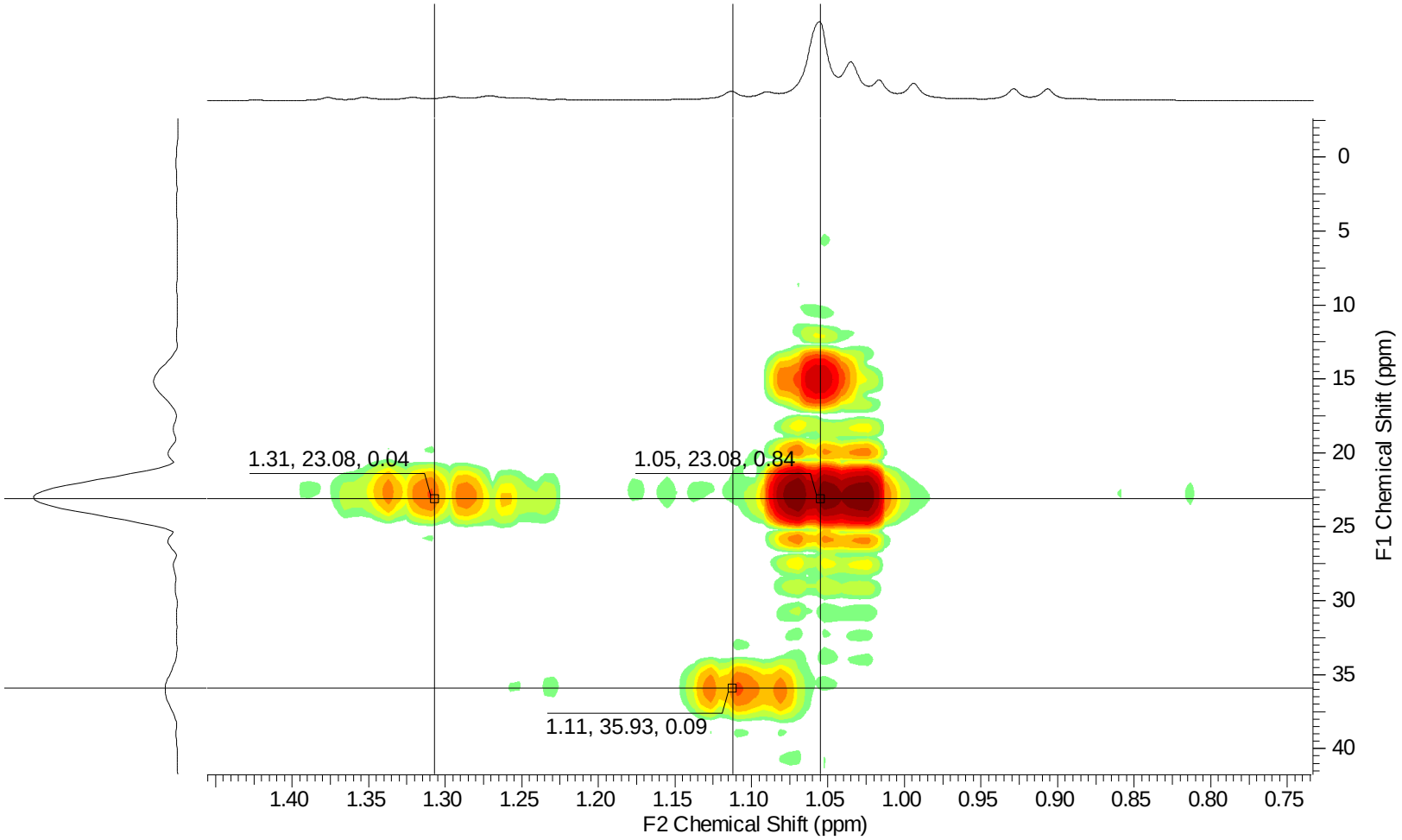
Appendix 4: ^{1}H NMR Spectrum of the nitronic ester 86



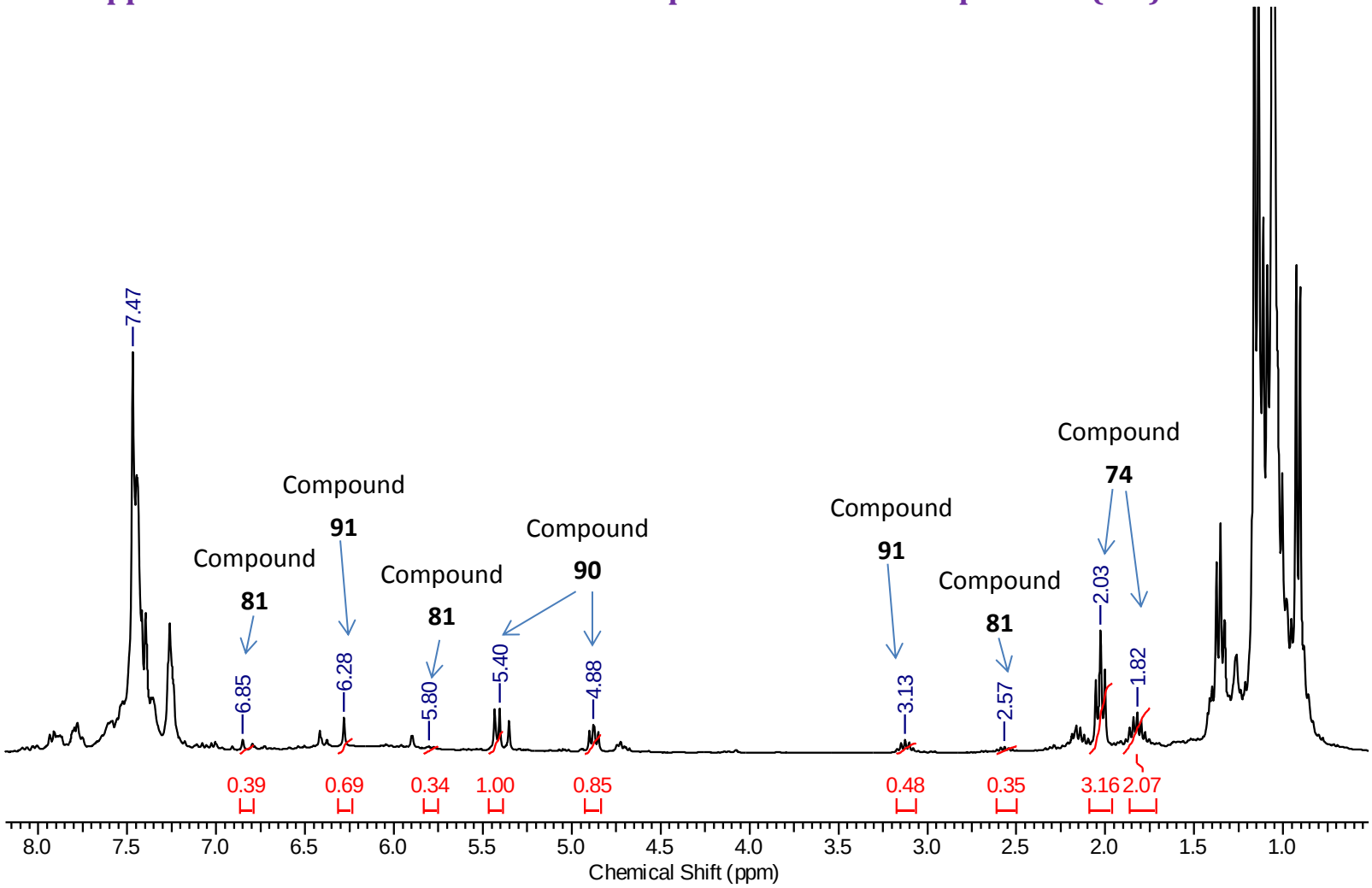
Appendix 5: Reaction of $Sc(OTf)_3$ and compound 81: ^1H NMR Spectrum



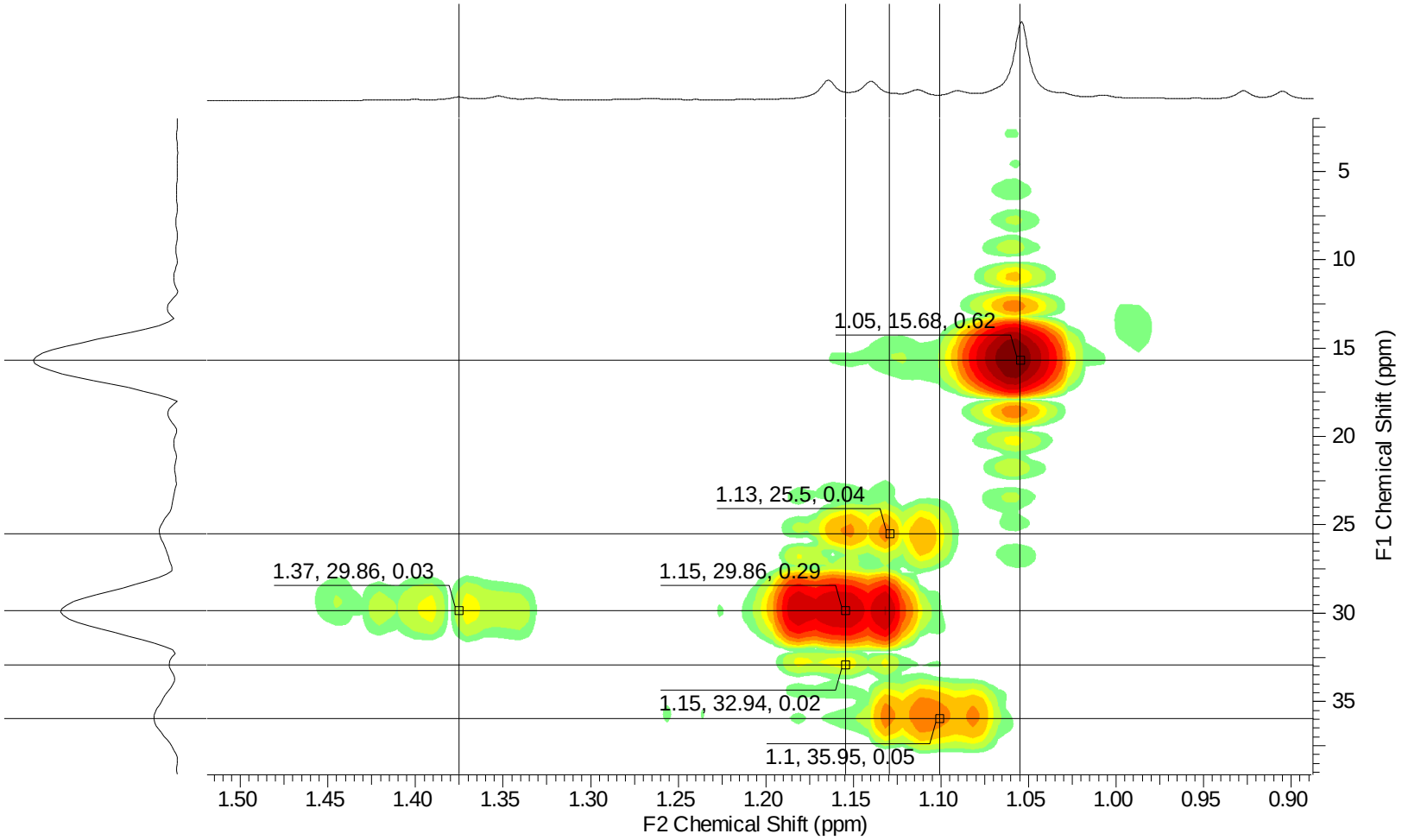
^{1}H-^{29}Si HMBC Spectrum



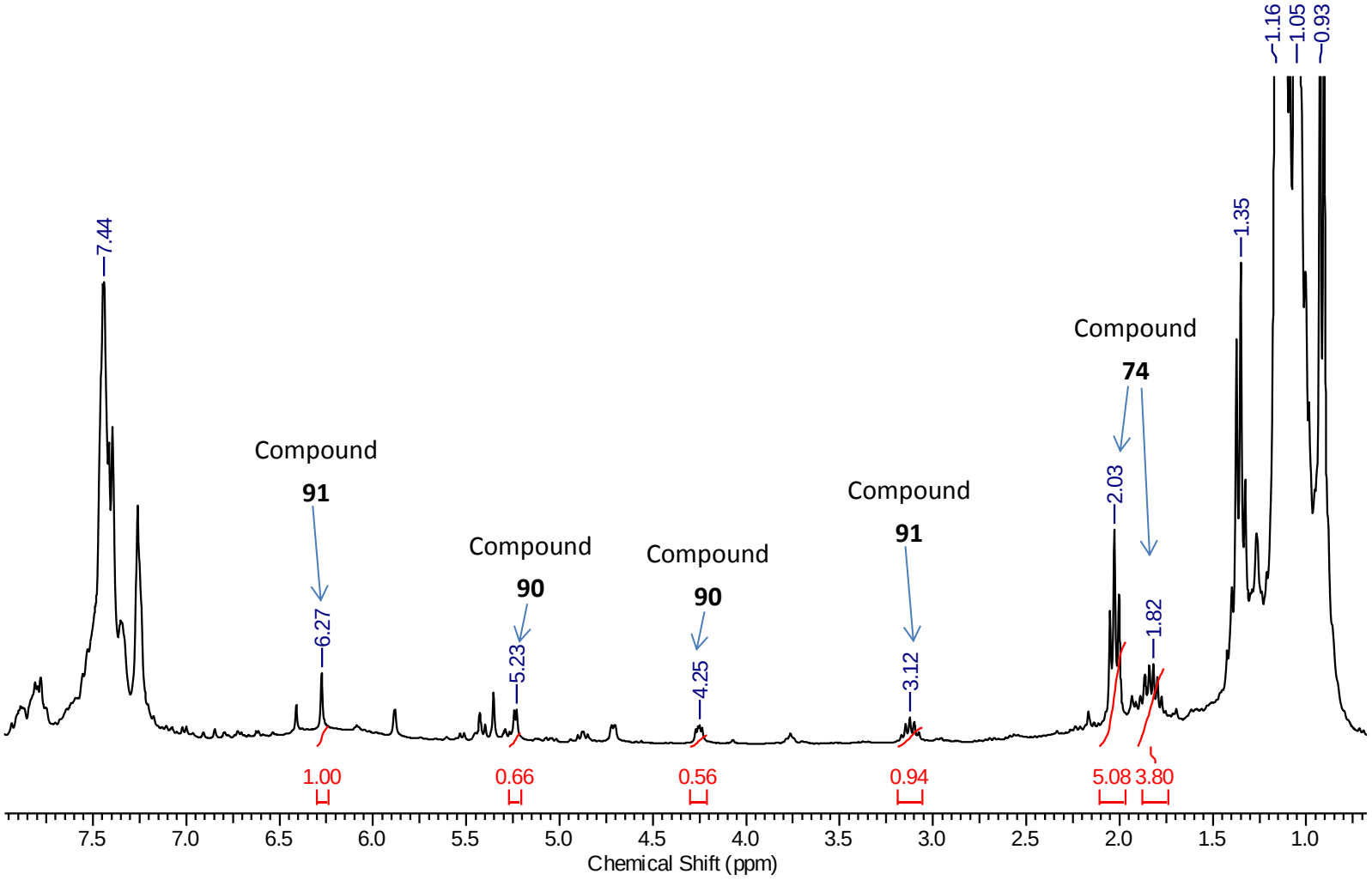
Appendix 6: Reaction of H_2SO_4 with compound 81: ^1H NMR Spectrum (2 h)



^{1}H-^{29}Si HMBC Spectrum (2 h)



^{1}H NMR Spectrum (3 days)



^{1}H-^{29}Si HMBC Spectrum (3 days)