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The Synthesis of Polycyclic Fused-Ring Systems *via* Rh(I)-Catalyzed Higher Order Cycloaddition Reactions with Carbon Monoxide

A Dissertation Presented

by

Alexandra A. Athan

to

The Graduate School

in Partial Fulfillment of the

Requirements

for the Degree of

Doctor of Philosophy

in

Chemistry

Stony Brook University

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Stony Brook University

The Graduate School

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Abstract of the Dissertation

The Synthesis of Polycyclic Fused-Ring Systems *via* Rh(I)-Catalyzed Higher Order Cycloaddition Reactions with Carbon Monoxide

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The seven-membered ring is a common motif in various bioactive natural products. Many examples of natural product cores possessing fused-ring systems are also prevalent. Therefore, it is useful to provide methods that allow access to these cores rapidly and efficiently. We have previously reported the successful construction of fused-ring skeletons containing seven-membered rings *via* Rh-catalyzed carbocyclization and cycloaddition reactions. As part of our continuing study on higher order metal-catalyzed reactions, novel dienynes, enediynes and triynes have been subjected to the Rh-catalyzed [2+2+2+1] cycloaddition reaction.

In the presence of Rh under CO, cycloheptene-diynes were converted to the corresponding 5-7-7-5 tetracyclic products. Variable amounts of [2+2+2] byproducts were also observed. We would like to further extend this methodology to synthesize new classes of colchicine and allocolchicine derivatives. Novel triyne substrates have been synthesized and subjected to our previously developed Rh(I)-catalyzed cycloaddition reactions. The 6-7-6-7 tetracyclics have been obtained in good yields in the presence of [Rh(cod)Cl2]2 and DPPP in TFE using microwave irradiation. The 6-7-7-6 carbonylated tetracyclics have also been obtained under ambient CO pressures in toluene. The scope and the mechanism of these novel processes will be discussed.

Dedicated to my grandparents, parents, sisters, the Resch family, and Daniel Resch.

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Chapter 1

Introduction to Carbocyclization Reactions and Higher Order Cycloaddition Reactions

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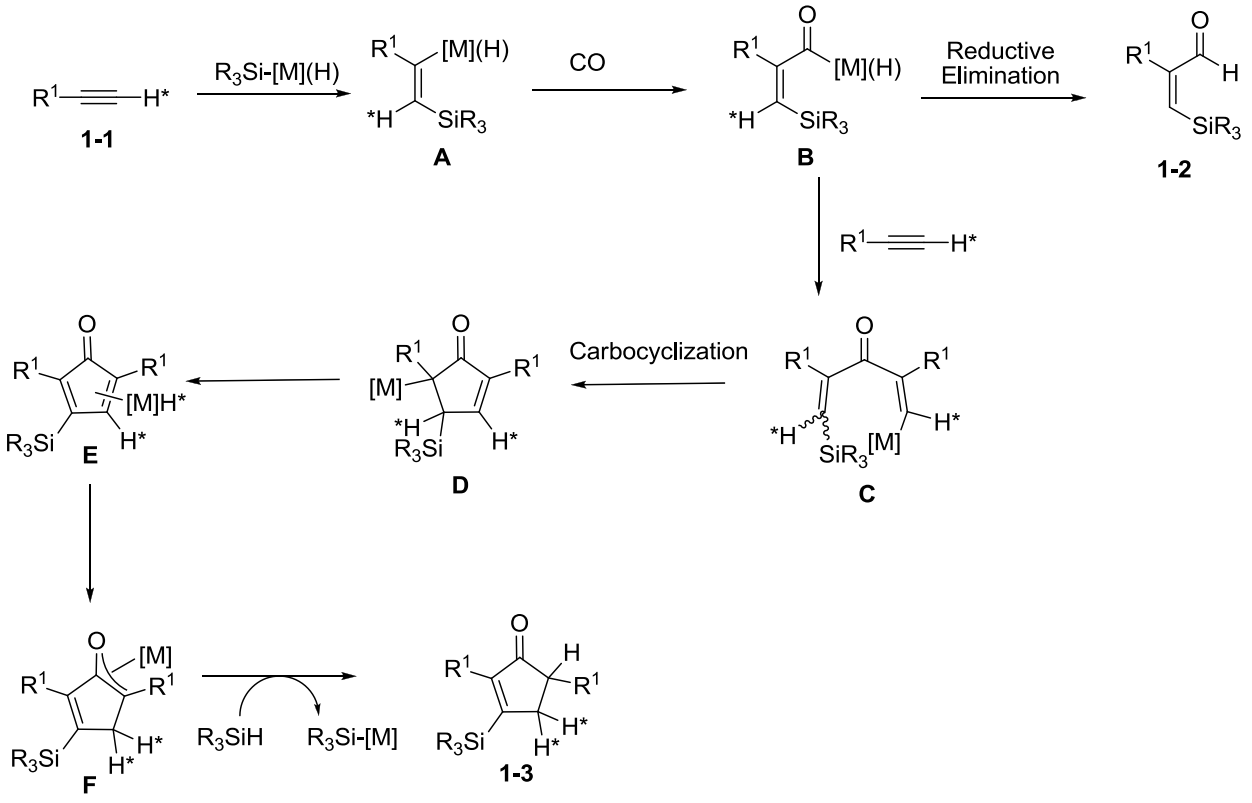
1.1 Introduction

Complex fused ring systems are commonly found in various bioactive natural and unnatural products.[1] The development of novel methods to efficiently synthesize complex polycyclic moieties is an ongoing effort, and it is worthwhile to discover processes that allow facile access to these polycyclic cores.[2] In the past, chemists have relied on ring-forming methods that utilize multicomponent reactions (MCRs) such as higher order cycloaddition reactions and cascade reactions.[3] These reactions are useful to furnish complex polycyclic molecules from simple, linear starting materials. Cycloadditions are an example of a common and convenient MCR. Furthermore, cycloaddition reactions which may normally be symmetry forbidden do proceed in the presence of rhodium and other transition metals,[4] and the field of transition metal catalyzed higher-order cycloadditions is widely studied.[5] A promising method utilizing this methodology is the silicon-initiated, Rh-catalyzed intramolecular carbocyclization[6] developed by the Ojima laboratory. The versatile Rh-catalyzed, silicon-initiated carbocyclization is the basis for intramolecular carbocyclization reactions such as silylcarbocyclization (SiCaC),[7] carbonylative silylcarbocyclization (CO-SiCaC),[7b, 8] silylcarbobicyclization (SiCaB),[9] and silylcarbotricyclization (SiCaT) reactions.[10] The in-depth study of these processes later led the Ojima group to discover the Rh(I)-catazlyzed [2+2+2+1] cycloaddition reaction.[2, 11] These processes allow multiple new C-C bonds to be formed in one step, which is useful when applied to the synthesis of complex, polycyclic natural products.[2] An in-depth discussion of these processes and their mechanisms is presented herein.

1.2 Silicon-Initiated Carbocyclization Reactions

During studies on the silylformylation of 1-hexyne, the Ojima group discovered a novel carbometalation-cyclization process that yielded silylcyclopentenones.[8] The reaction was

catalyzed by novel Rh-Co complexes in the presence of hydrosilanes under a CO atmosphere. Deuterium-labeling studies were carried out in order to confirm the mechanism illustrated in **Scheme 1-1**.[12]

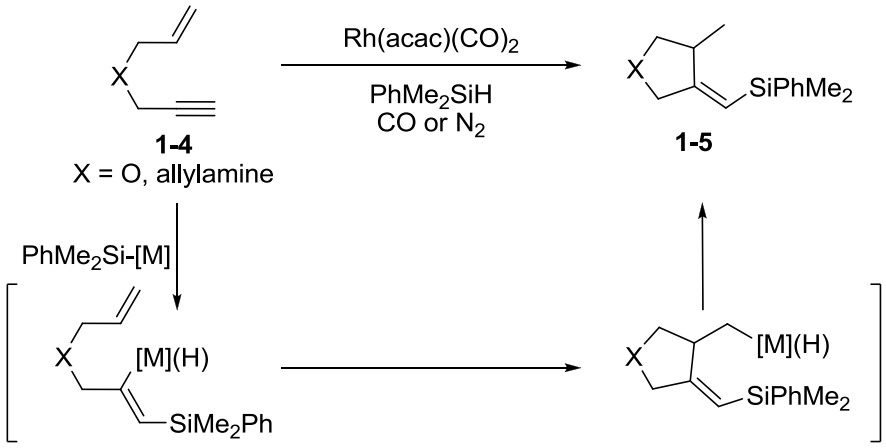


Scheme 1-1: Mechanism of the carbometalation-cyclization of alkynes

The alkyne **1-1** first inserts into the Si-[M] active species in a highly regioselective manner to form β-silylethenyl-metal complex **A**. Carbon monoxide insertion gives β-silylcryloyl-metal complex **B**. At this stage, intermediate **B** can either undergo a reductive elimination to yield silylformylated product **1-2** or the β-silylacryloyl-metal species can be trapped by another molecule of alkyne. The pathway when intermediate **B** is trapped by a molecule of alkyne was observed in the presence of trialkylsilanes while the formation of **1-3**

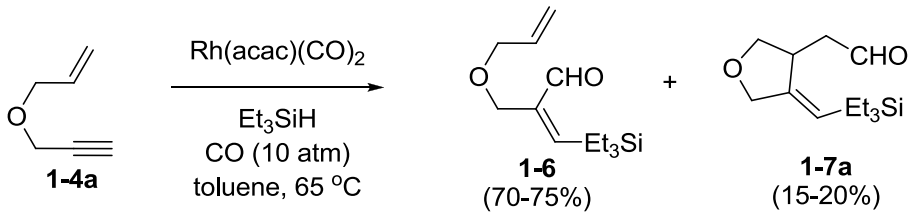
was observed in the presence of phenylsilanes. The trapping of intermediate **B** is followed by a carbocyclization and subsequent β-hydride elimination to form complex **E**. A highly regioselective reduction at the less sterically hindered site and the regeneration of the silyl-[M] active species gives the final product **1-3**. Under optimized conditions (ie. triethylsilane/(*t*-BuNC)$_4$RhCo-(CO)$_4$ at 60 ^{o}C), the final product was obtained in 54% yield.[12] Thus, the intermolecular novel carbonylative silylcarbocyclization (CO-SiCaC) reaction of alkynes was established.

During optimization of reaction conditions, a novel intramolecular silylcarbocyclization (SiCaC) of enynes was also discovered.[12-13] The SiCaC reaction of allyl propargyl ether or diallylpropargylamine proceeded smoothly. It was hypothesized that the reaction should also proceed in the absence of CO. As predicted, the product was obtained in 85% yield when allyl propargyl ether was subjected to the reaction catalyzed by Rh(acac)(CO)$_2$ in the presence of PhMe$_2$SiH under a nitrogen atmosphere. These results indicated that the product was formed *via* trapping of the β-silylethenyl[M] intermediate with the alkene moiety followed by a hydride shift from the metal (**Scheme 1-2**).[13]



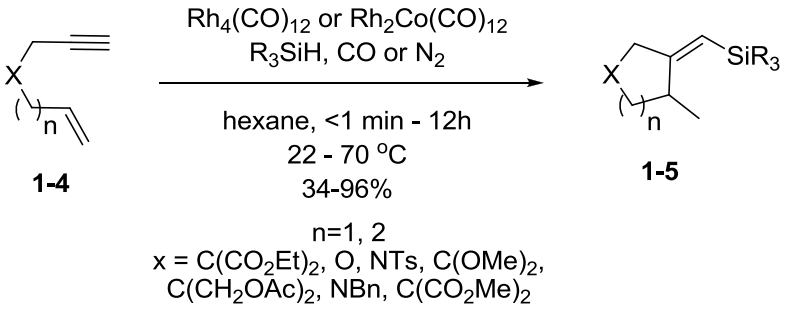
Scheme 1-2: Mechanism of the SiCaC of enynes

During these studies, a cyclized carbonylated side product was also observed when allyl propargyl ether **1-4a** was subjected to the reaction in the presence of Et_3SiH under higher pressures of CO (10 atm). The major silylformylated product **1-6** was observed in up to 75% yield along with the minor CO-SiCaC product **1-7a** (**Scheme 1-3**).[13]



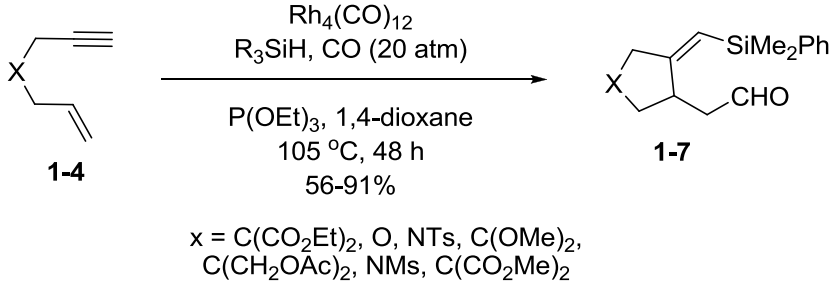
Scheme 1-3: Silylformylation of **1-4a** and minor CO-SiCaC product

The Rh(I)-catalyzed intramolecular SiCaC and CO-SiCaC reactions of 1,6- and 1,7-enynes were shown to have good functional group tolerance when various substrates were subjected to the reaction conditions.[7b] Functionalized 5- and 6-membered rings could be obtained by these processes. Excellent results were obtained for the SiCaC process when Rh and Rh-Co clusters such as Rh_4-$(CO)_{12}$ and $Rh_2Co_2(CO)_{12}$ were used. In most cases, the reaction proceeded in less than one minute at ambient temperature with high selectivity towards the desired SiCaC product. The reaction was also shown to proceed in the presence of various hydrosilanes with aryl groups as well as alkoxy hydrosilanes (**Scheme 1-4**).



Scheme 1-4: SiCaC reaction of 1,6- and 1,7-enynes

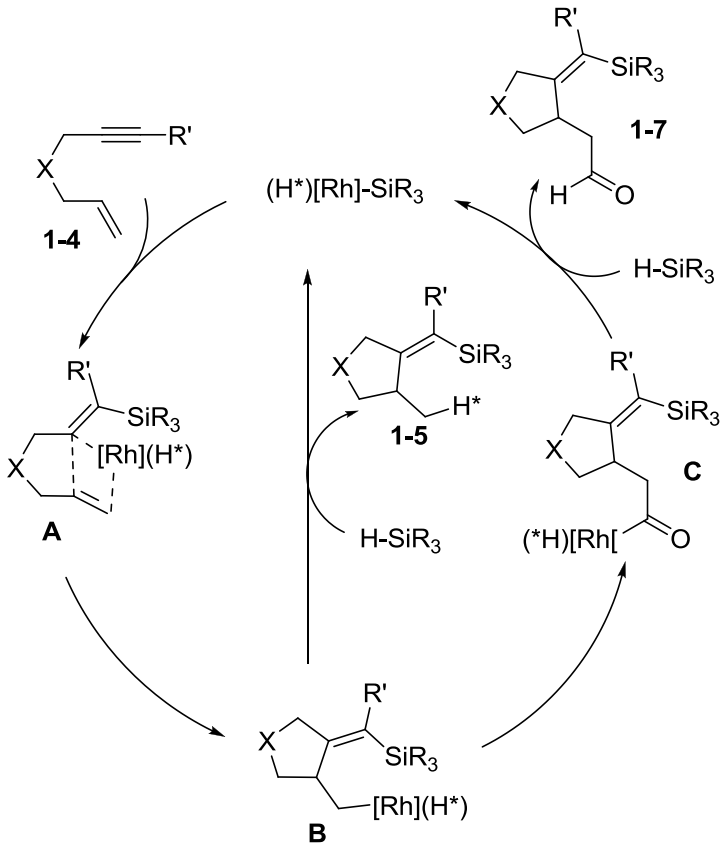
The CO-SiCaC reaction of 1,6-enynes was also optimized.[7b] Matsuda and coworkers have reported a similar process.[14] The best results were obtained (up to 91% yield) using $Rh_4(CO)_{12}$ as the catalyst in the presence of Me_2PhSiH and $P(OEt)_3$ as a ligand in dioxane under 20 atm of CO at 105 ^oC (**Scheme 1-5**). The reaction was further improved by optimizing it to proceed at higher concentrations using the "freeze and CO" protocol.[7b]



Scheme 1-5: CO-SiCaC of 1,6-enynes

The mechanism for the SiCaC and CO-SiCaC reactions of 1,6-enynes is illustrated in **Scheme 1-6**.[7b] The reaction begins with the insertion of the alkyne into the Si-[Rh] active species. This is followed by coordination of the alkene moiety and an intramolecular carbometalation to give intermediate **A**. A subsequent hydrosilane-promoted reductive

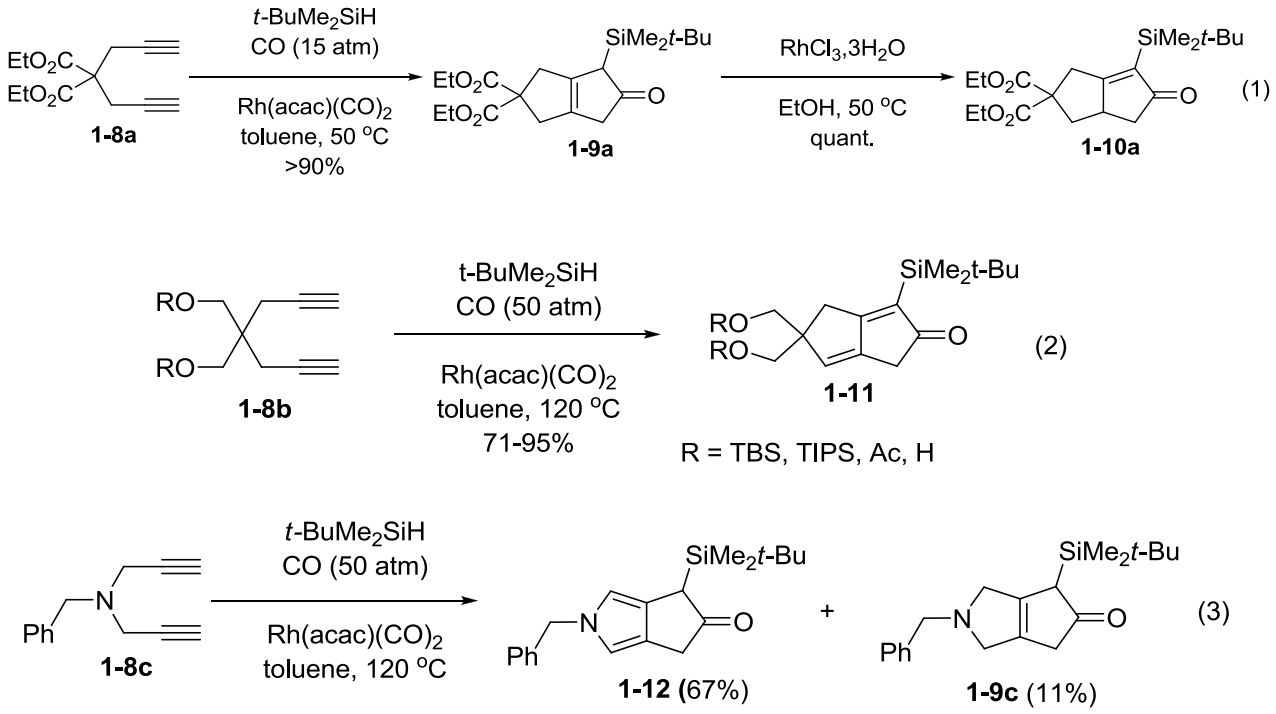
elimination (hydride shift) occurs to yield the SiCaC product **1-5** in the absence of CO or at very low CO concentration. Under high CO pressure, the carbocyclization is followed by migratory insertion of CO into the acyl-[Rh] bond of species **B** followed by a reductive elimination to yield the CO-SiCaC product **1-7**. It is important to note that although a CO atmosphere is not necessary for the formation of the SiCaC product, the presence of CO does stabilize the active [Rh] catalyst species in this reaction.[7b]



Scheme 1-6: Mechanism of the SiCaC and CO-SiCaC of 1,6-enynes

This methodology was further expanded to accomplish the silylcarbobicyclization (SiCaB) of 1,6-diynes.[9] The Ojima group reported the first "truly catalytic" bicyclization of alkynes incorporating CO. This method allowed convenient access to bicyclo[3.3.0]octenones

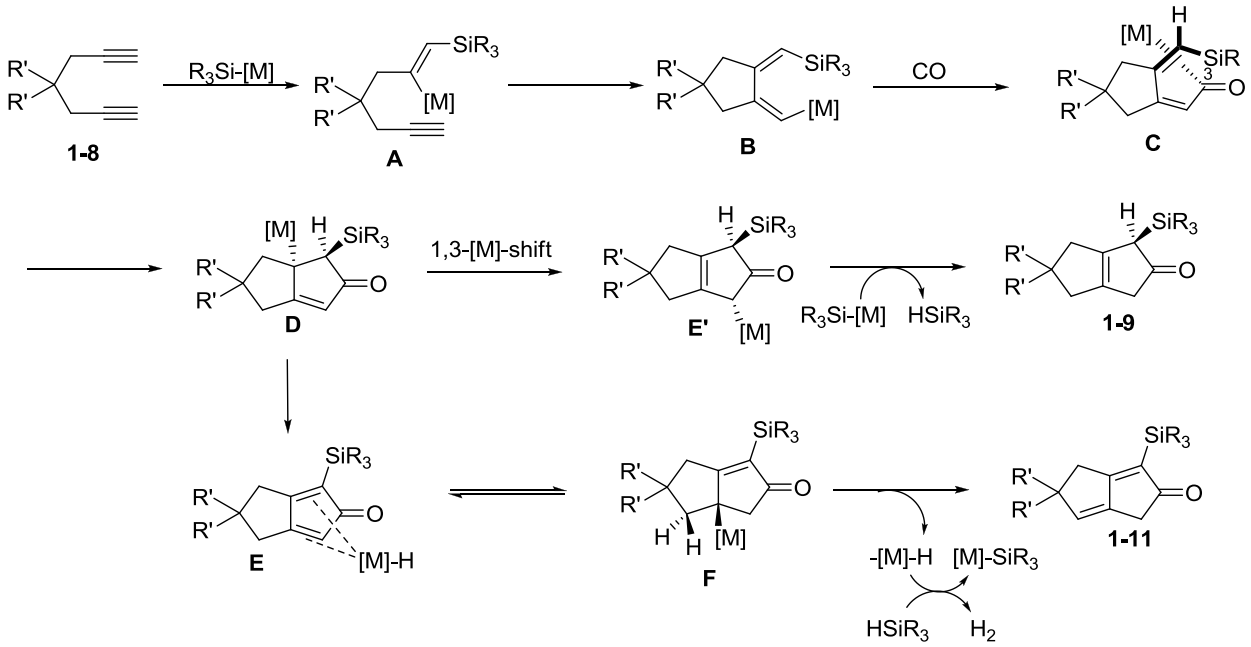
and bicyclo[3.3.0]octa-1,5-dien-3-ones (**Scheme 1-7**). Bicyclo[3.3.0]octenone **1-9a** was easily isomerized to the corresponding 2-silylbicyclo[3.3.0]oct-l-en-3-one **1-10** in the presence of $RhCl_3 \cdot H_2O$ in EtOH at 50 ^oC. The observed products and distribution of products was found to be highly dependent on the substituent at the C4 position of the 1,6-diynes.[9a] For example, when the tether was a benzylamino moiety, the bicyclic pyrole **1-12** was the major product observed. The formation of **1-12** is most likely driven by the aromatization energy of the pyrole.



Scheme 1-7: SiCaB of 1,6-diynes

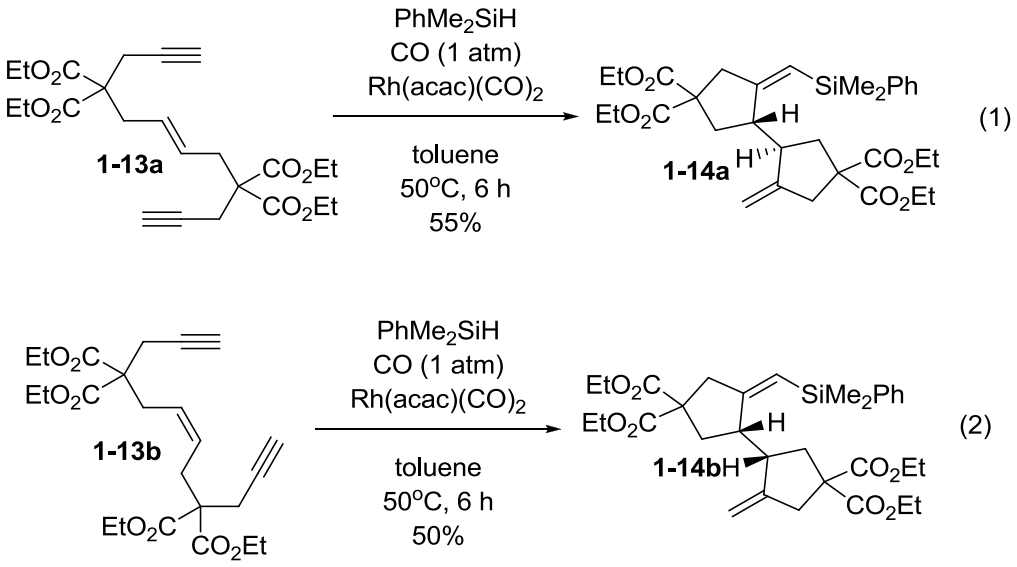
The mechanism that accounts for the formation of SiCaB products **1-9** and **1-11** is illustrated in **Scheme 1-8**. The mechanism starts with insertion of one of the alkyne moieties into the Si-[M] active species and a subsequent carbocyclization to form intermediate **B**. Then, CO insertion occurs to give intermediate **C** followed by the second carbocyclization to give **D**. At this point, the reaction can follow two different pathways. The formation of **1-9** is accomplished

by the transformation of **D** to **E'** *via* a 1,3-[M] shift followed by a reductive elimination in the presence of another molecule of hydrosilane. Alternatively, **D** may be converted to **E** *via* hydrometalation of the less hindered double bond followed by a β-hydride elimination to give **1-11**.



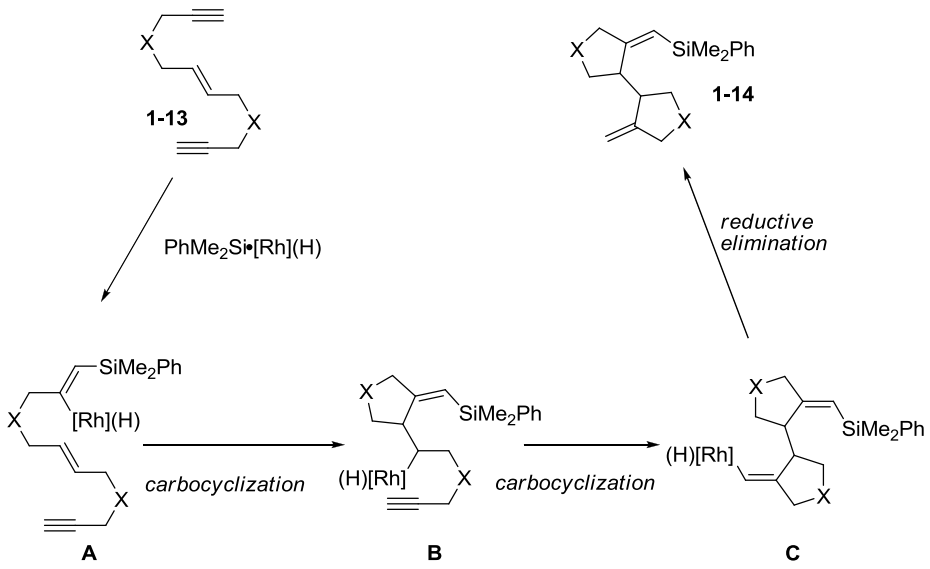
Scheme 1-8. Mechanism of the SiCaB of 1,6-diynes

The SiCaC reaction was then extended to enediynes to test whether the alkyl-[Rh](H) intermediate formed after the second carbocyclization could be trapped by an additional, strategically placed alkene or alkyne moiety. The reaction occurred smoothly in the presence of $Rh(acac)(CO)_2$, PhMeSiH, and CO (1 atm) in toluene (**Scheme 1-9**).[7a]



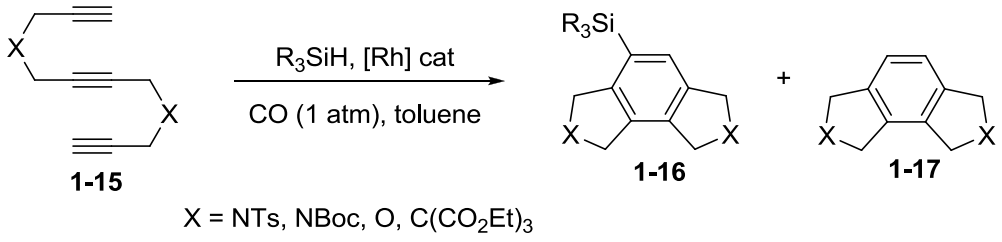
Scheme 1-9: SiCaC of enediynes

It is important to note that this cascade carbocyclization occurred stereospecifically, and the mechanism for the SiCaC reaction of enediynes is illustrated in **Scheme 1-10**. The reaction is initiated by the formation of the Rh-silicon active species. The Rh-Si species selectively reacts with the triple bond, and this insertion is followed by two successive carbocyclizations. The final product is formed *via* a reductive elimination.[7a]



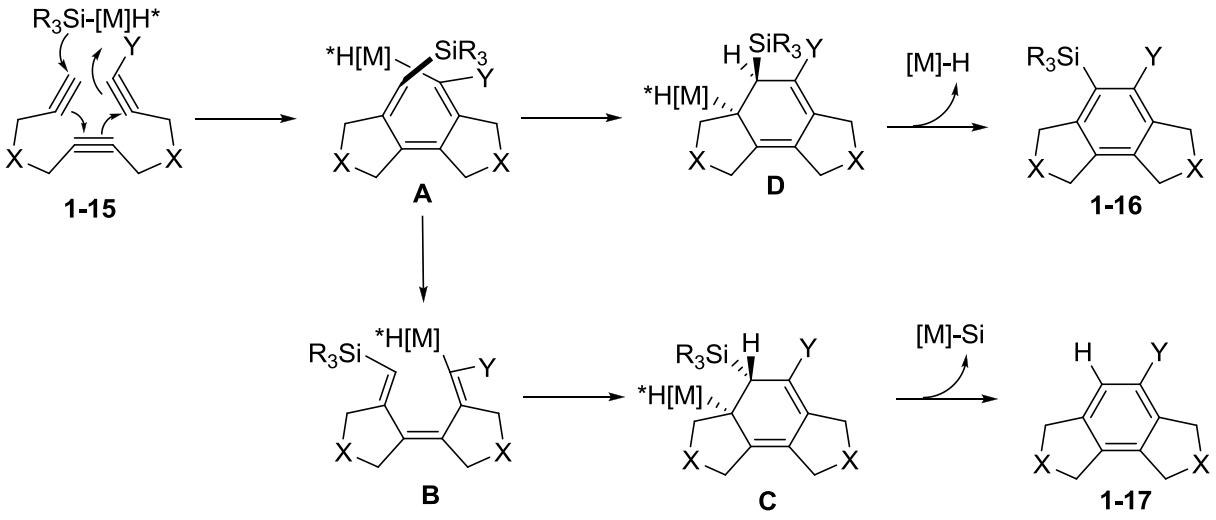
Scheme 1-10. Mechanism of the SiCaC of enediynes

Due to the rotational freedom about the bond connecting the two cyclopentyl units, a third carbocyclization did not occur for enediyne substrates. Theoretically, if the bond could be locked as an alkene, then a third carbocyclization should occur and tricyclic products could be obtained. As predicted, the silylcarbotricyclization (SiCaT) reaction of dodec-1,6,11-triynes, tridec-1,6,12-triyne, and tetradec-1,7-13-triyne was accomplished.[10] The reaction was catalyzed by Rh or Rh-Co complexes in the presence of a variety of hydrosilanes to give 5-6-5 tricyclic benzene derivatives (**Scheme 1-11**). The product selectivity for **1-16** or **1-17** could be controlled based on reaction conditions and was also substrate dependent.



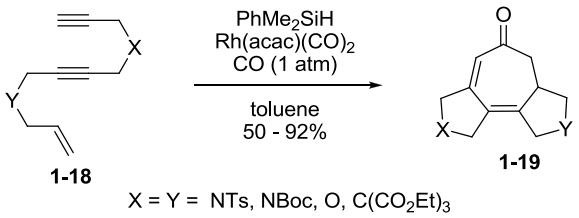
Scheme 1-11: SiCaT of triynes

The mechanism for the SiCaT reaction of triynes is illustrated in **Scheme 2-12**. After the formation of the [Rh]-Si active species, a silicon-initiated cascade carbometalation occurs to form intermediate **A**. Intermediate **A** can then undergo a subsequent carbocyclization to give intermediate **D** which then undergoes β-hydride elimination to form the expected SiCaT product **1-16**. If intermediate **A** undergoes *Z-E* isomerization to give intermediate **B** which then undergoes a subsequent carbocyclization followed by a β-silyl elimination to yield tricyclic product **1-17**. The formation of nonsilylated **1-17** was observed at high reaction temperatures and in the presence of heteroatoms tethers of **1-15**.[10]



Scheme 1-12: Mechanism of the SiCaT of triynes

An extension of the silicon-initiated metal-catalyzed cascade reactions is the carbonylative carbotricyclization (CO-SiCaT) of enediynes (**Scheme 1-13**).[2 15] The optimization studies showed that the desired product was formed exclusively under dilute conditions and in the presence of substoichiometric amounts of hydrosilane.[2] These findings also provided insight into the mechanism of the CO-SiCaT reaction (**Scheme 1-14**).[2]



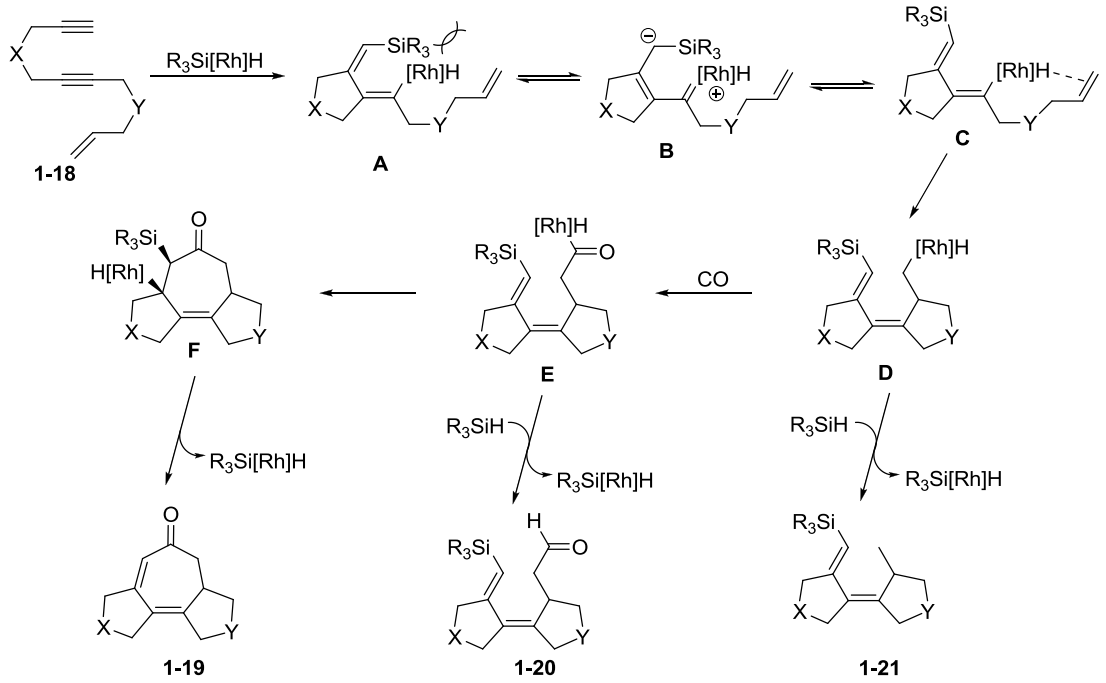
Scheme 1-13: CO-SiCaT of enediynes

The reaction starts by the insertion of the terminal alkyne into the Si-[Rh] bond. This is followed by a carbocyclization which gives the *Z*-alkenyl intermediate **A**. The steric hindrance between the Si and [Rh] promotes *Z*→*E* isomerization to intermediate **C** *via* the "Ojima-Crabtree mechanism".[2] Another carbocyclization leads to intermediate **D**. This is followed by CO insertion to lead to the acyl-[Rh](H) intermediate **E**. A subsequent carbocyclization gives the tricyclic intermediate **F** where the Si and [Rh] groups are *syn*, and the final product **1-19** is formed via a β-silyl elimination, with regeneration of the catalytic species.[2]

The mechanism illustrated in **Scheme 1-14** accounts for the formation of observed products **1-19, 1-20**, and **1-21**. The mechanism was rationalized based on the extent of dilution, substrate concentration, and catalyst concentration. It was reported that the CO-SiCaT product formed in more dilute solutions (0.015 M vs 0.15 M). In more dilute solutions, more CO is able to dissolve, thus aiding its insertion into the substrate.[2]

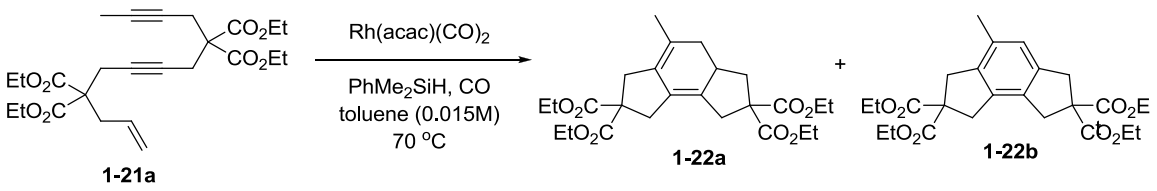
In addition, these studies provided insight into the role of the hydrosilane. First of all, no reaction occurred in the absence of hydrosilane. At substoichiometric equivalents of hydrosilane (0.5 eq vs 2.0 eq), the desired product **1-19** was readily formed. In contrast, when using stoichiometric amounts of silane, side products **1-20** and **1-21** were observed. These observations suggest that the active Si-Rh species is formed *via* an intramolecular, unimolecular process

during the β-silyl elimination step which leads to product **1-19**. In contrast, the active Si-Rh species is regenerated *via* an intermolecular, bimolecular process when **1-20** and **1-21** were observed.



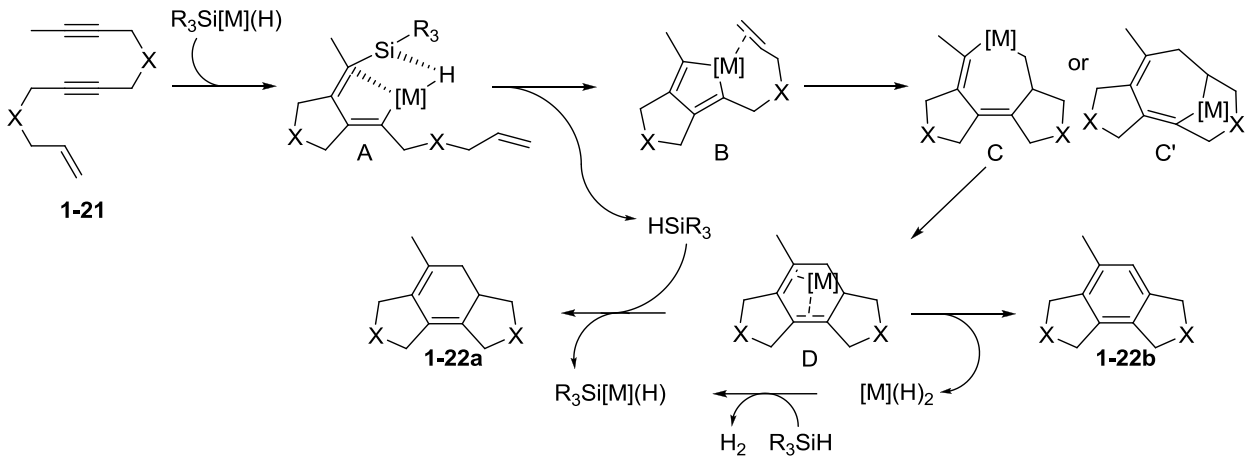
Scheme 1-14: Mechanism of the CO-SiCaT of enediynes

Although this CO-SiCaT reaction afforded high yields and high selectivity for substrates similar to the one shown in **Scheme 1-14**, certain substrates did not yield the predicted CO-SiCaT products. For example, the predicted tricyclic products which incorporates CO is not obtained when the terminal propargyl is replaced with a 2-butynyl in the enediyne (**Scheme 1-15**).[2]



Scheme 1-15: Substrate limitations for the CO-SiCaT of enediynes

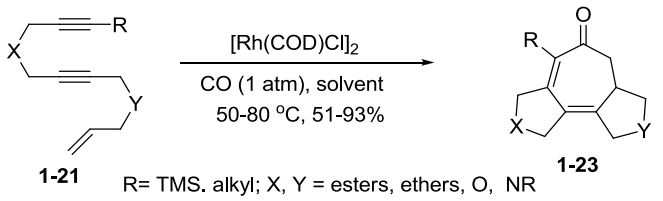
The mechanism which accounts for the formation of the tricyclic products **1-22a** and **1-22b** is illustrated in **Scheme 1-16.** There are a few differences between the SiCaT reaction mechanism in **Scheme 1-16** and the CO-SiCaT mechanism in **Scheme 1-14** which explain why enediynes with internal alkynes are not transformed to the carbonylated product in the presence of hydrosilane. For the 2-butynyl substrate **1-21a**, no *Z*→*E* isomerization occurs. In intermediate **A, t**he silyl and Rh groups are close enough to undergo a σ-bond metathesis where hydrosilane is liberated. In intermediate **B**, the terminal alkene may insert into the [M]-C bond in two different orientations leading to intermediates **C** and/or **C'**. It was reported that intermediate **C** should be able to undergo CO insertion. Since no CO insertion is observed in the presence of hydrosilane, the reaction in **Scheme 1-16** probably proceeds via intermediate **C'**. Product **1-22a** is formed as the hydrosilane in the system reacts with intermediate **D**. Aromatization *via* dehydrogenation gives product **1-22b** along with a dihydro-[M] species. The $[M](H)_2$ species reacts with hydrosilane, liberates molecular hydrogen, and regenerates the [M]-Si active species.[2]



Scheme 1-16: Mechanism for the formation of 5-6-5 tricyclic products

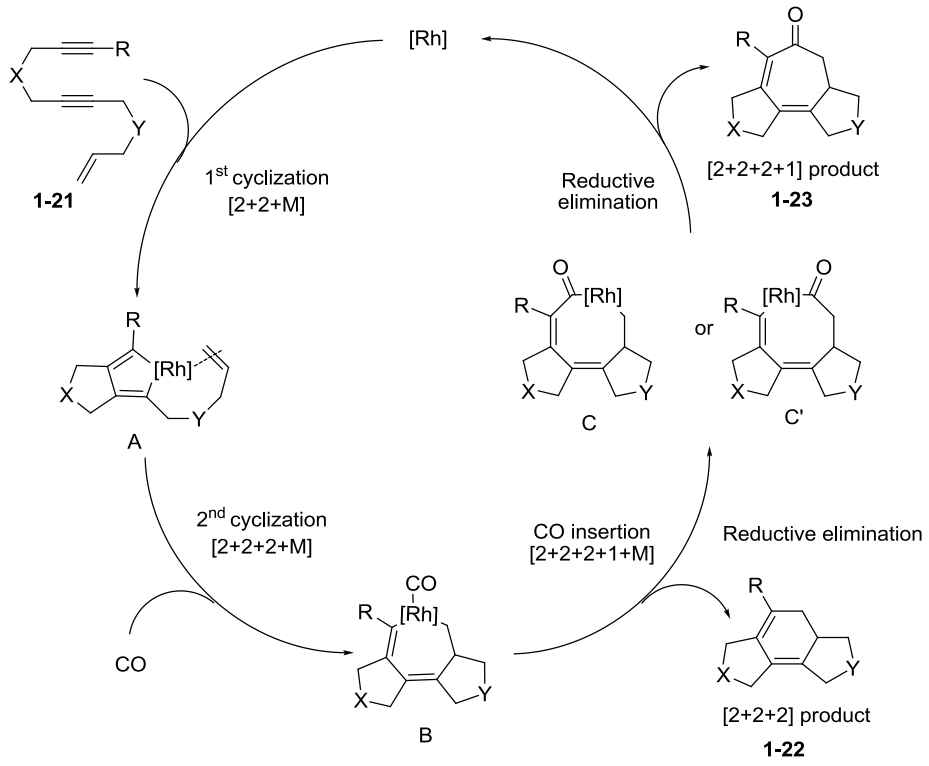
1.3 Rh(I)-Catalyzed [2+2+2+1] Cycloaddition Reactions with Carbon Monoxide

During optimization of the CO-SiCaT reaction of enediynes it was found that carbonylated tricyclic products could be obtained in the absence of hydrosilane. It was reported that the reaction proceeds *via* a cycloaddition rather than a carbocyclization.[2, 11a] The cycloaddition proceeds *via* a series of metallacycles, while the carbocyclization mechanism is defined as a series of carbometalations. This was the first example of the intermolecular [2+2+2+1] cycloaddition of enediynes (**Scheme 1-17**).



Scheme 1-17: Formation of 5-7-5 tricyclics *via* the Rh(I)-catalyzed [2+2+2+1] cycloaddition of enediynes

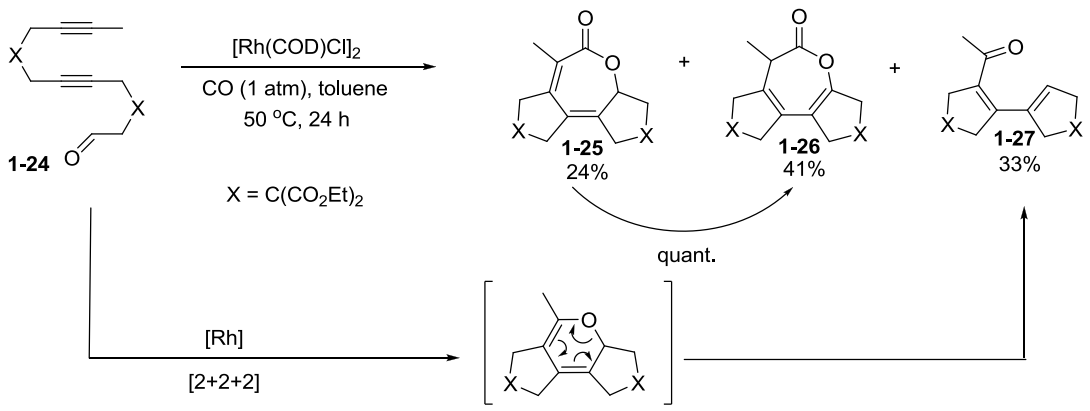
The mechanism for the formation of these products is illustrated in **Scheme 1-18**. The cycloaddition starts with the coordination of the diyne moiety to the [Rh] catalyst ([2+2+M]). This is followed by olefin insertion into the Rh-C bond ([2+2+2+M]). Next, CO coordinates to [Rh], and this is followed by a migratory insertion of CO into the Rh-C bond ([2+2+2+1+M]). The final product **1-23** is formed *via* a reductive elimination. The active Rh-catalyst species is also regenerated. It is also important to note that, during optimization, the amount of the [2+2+2] side product **1-22** was decreased to trace amounts.[2, 11a]



Scheme 1-18: Mechanism of the Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of enediynes

The functional group tolerance of this reaction was further examined by changing the ene component to an aldehyde. The formation of 5-7-5 lactone products was observed as a mixture of isomers. The acetylbis(cyclopentenyl) product was also observed.[2] Upon monitoring the

reaction, it was observed that **1-25** was formed early on in the reaction suggesting that it is the kinetic isomer. The complete conversion of **1-25** to **1-26** was observed after leaving the NMR sample of the mixture of 5-7-5 isomers in chloroform at ambient temperature for two weeks. This confirms that **1-26** is the thermodynamically favorable isomer. The formation of **1-27** occurs from the formation of the [2+2+2] intermediate which then undergoes an electrocyclic ring opening (**Scheme 1-8**).



Scheme 1-19: Isomerization of 5-7-5 lactones

The Rh(I)-catalyzed CO-SiCaT and [2+2+2+1] cycloaddition have been applied to a wide range of substrates. A variety of tricyclic products have been obtained by both methods. These results suggest that these reactions could be applied to enediynes with different substitution patterns and functional groups. For example, if the ene component exists as part of a ring, then, theoretically, tetracyclic products could be obtained. Tetracyclic products could also be obtained by tethering the linear unsaturated components to a ring. Furthermore, the hard-to-access tropolone ring could be obtained by subjecting tryines to the reaction conditions. The functional group tolerance and substrate scope of this process is discussed and reported in the following chapters.

1.4 References

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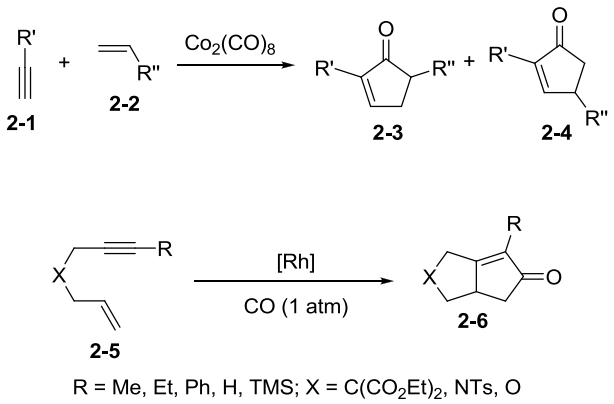
Chapter 2

The Synthesis of Polycyclics from Linear Dienynes or Enediynes via Rh(I)-Catalyzed [2+2+1] and [2+2+2+1] Cycloaddition Reactions

Table of Contents

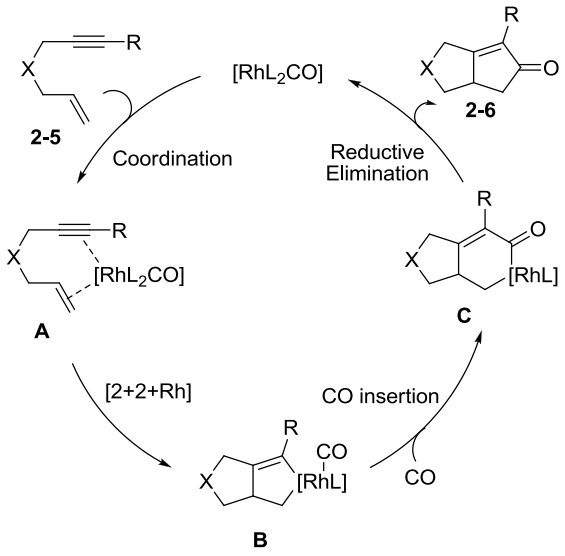
2.1 Introduction to the [2+2+1] (Pauson-Khand) Reaction

The Pauson-Khand reaction (PKR) is a [2+2+1] cycloaddition reaction catalyzed by Co, Rh, Ti, Zr, Ir, and Ru complexes.[1] The PKR has been applied to a variety of enyne and allenyne substrates in the presence of a CO source in both inter- and intramolecular reactions (**Scheme 2-1**). In each case, the products contain a cyclopentenone ring. The intermolecular reaction involving an alkyne, alkene, and CO was reported in 1973. However, the regioselectivity of the reaction was poor. [2] The intramolecular version reported later[3] with the bicyclic products being useful intermediates in natural product synthesis.[4]



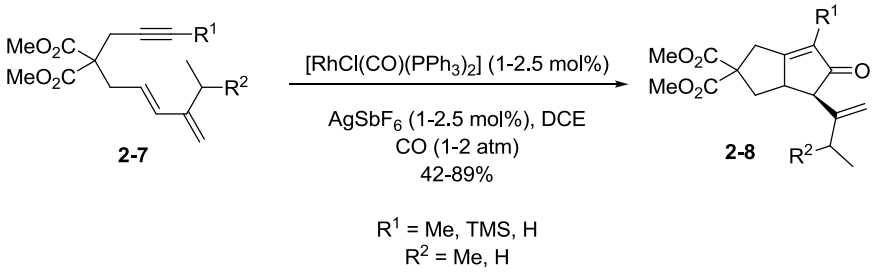
Scheme 2-1: Inter- and intramolecular PKR

The mechanism for the PKR is illustrated in **Scheme 2-2**. The mechanism starts by coordination of the active Rh catalyst to the enyne system followed by insertion of the metal. A subsequent CO coordination and migratory insertion occurs to give intermediate **C** and a reductive elimination yields the final product **2-6**.



Scheme 2-2: Rh(I)-catalyzed PKR mechanism [5]

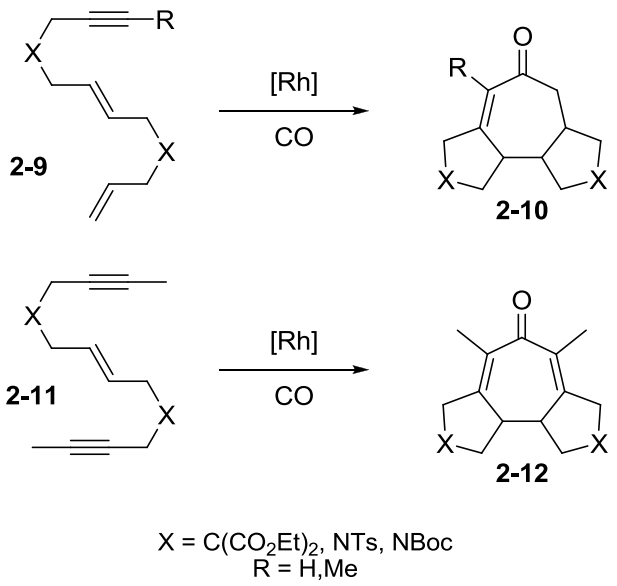
Dieneynes have also been successfully subjected to PKR conditions. A wide range of substrates and functional groups are tolerated in this reaction (**Scheme 2-3**). Higher yields were observed when the reaction was applied to dieneynes with internal alkynes versus terminal alkynes. The best results were obtained using $[RhCl(CO)(PPh_3)_2]$ as the catalyst and $AgSbF_6$ as an additive in dichloroethane under CO (1-2 atm).[6]



Scheme 2-3: PKR of dieneynes

Even though the [2+2+1] PKR has been studied extensively, the methodology has not been further expanded to the [2+2+2+1] cycloaddition of dieneynes. Theoretically, the formation

of tricyclic products can be accomplished *via* a [2+2+2+1] cycloaddition of enediynes with the ene at the 7-position. It should also be possible to form 5-7-5 tricyclics by subjecting dieneynes to the [2+2+2+1] cycloaddition reaction conditions (**Scheme 2-4**). The attempts to optimize these processes for the formation of polycyclics are presented in this section.



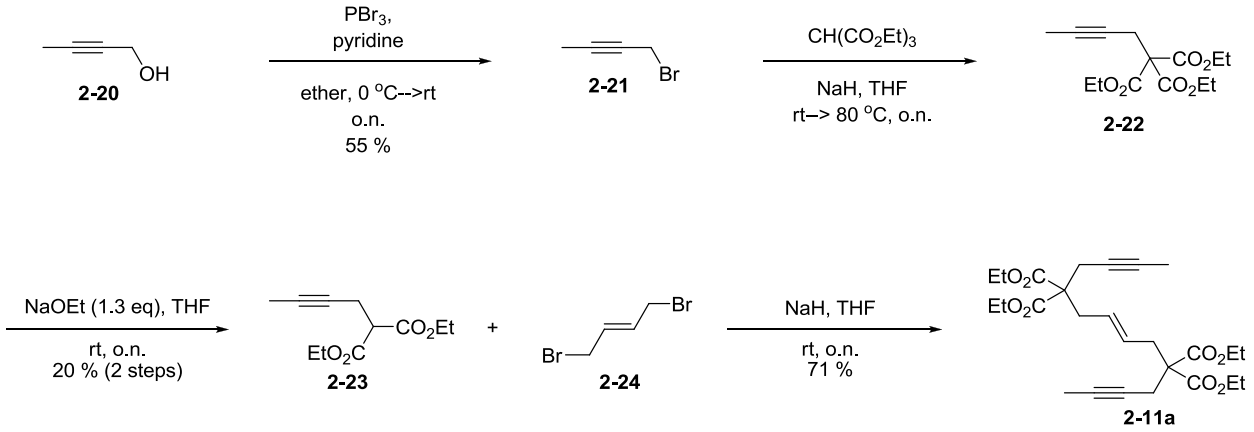
Scheme 2-4: Possible formation of 5-7-5 tricyclics via the Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction

2.2 Results and Discussion

2.2.1 Substrate Synthesis

In order to expand the substrate scope of our previously developed higher order cycloaddition reactions, enediyne **2-11a** was synthesized from commercially available starting materials in good yields. First, 2-butynol (**2-20**) was converted to the corresponding bromide **2-21** in the presence of PBr_3 and pyridine in 55% yield. The bromide **2-21** was converted to the corresponding malonate **2-23** over 2 steps in 20% yield. Malonate **2-23** was coupled with 2,4-

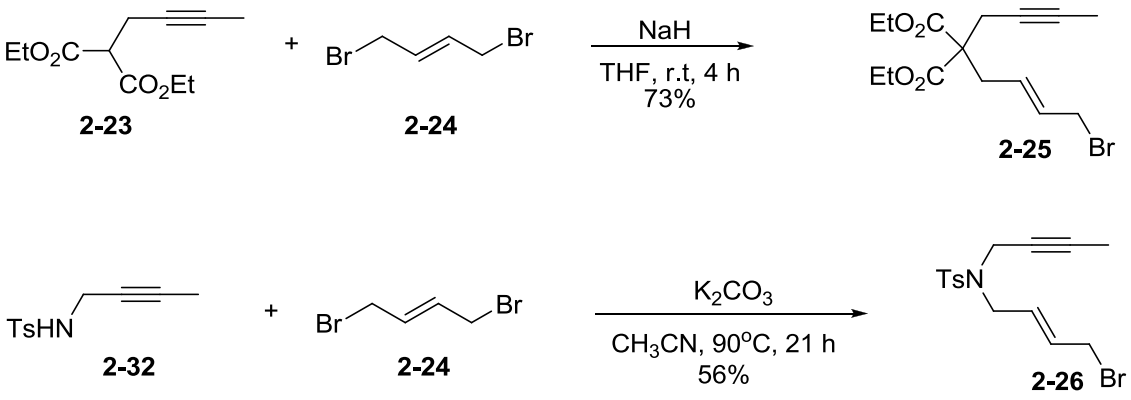
dibromobutene (**2-24**) in the presence of sodium hydride to give the enediyne substrate **2-11a** in 71% yield (**Scheme 2-5**).



2-20 **2-21** **2-22** **2-23** **2-24** **2-11a**

Scheme 2-5: Synthesis of substrate **2-11a**

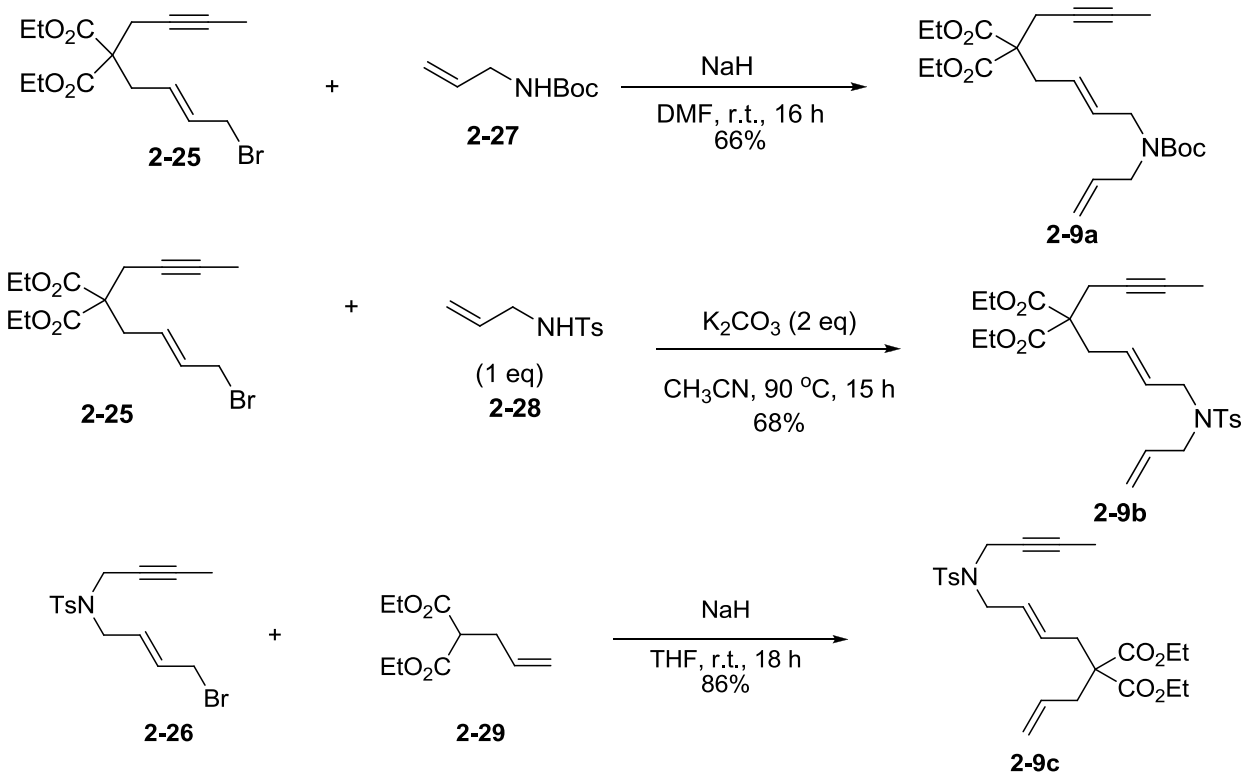
The syntheses of the enyne bromide components are outlined in **Scheme 2-6**. Coupling of malonate **2-23** and dibromide **2-24** in the presence of NaH in THF gave **2-25** in 73% yield. Compound **2-26** was obtained in 56% yield in a similar coupling reaction using K_2CO_3 as the base.



2-23 **2-24** **2-25** **2-32** **2-24** **2-26**

Scheme 2-6: Synthesis of **2-25** and **2-26**

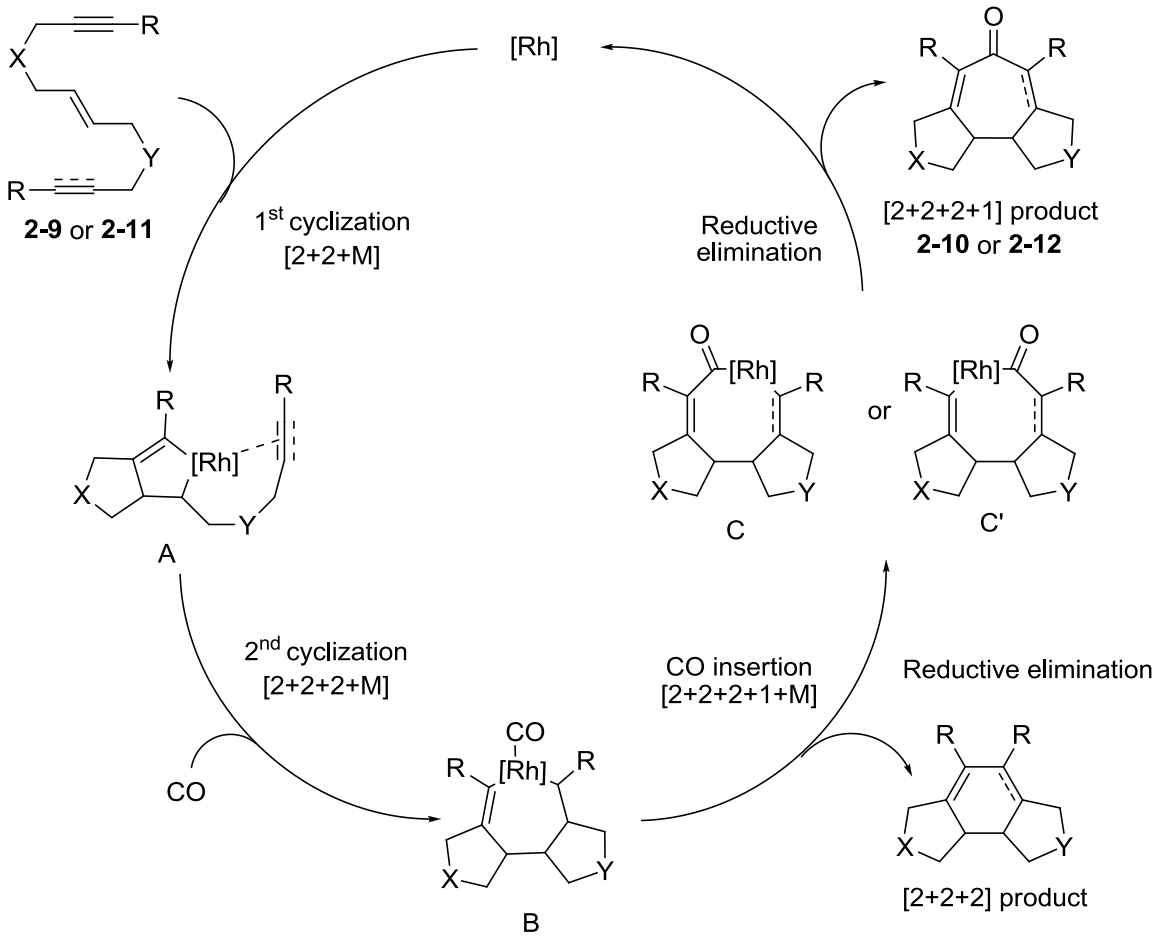
With the enyne bromides in hand, the alkene components were installed via a substitution reaction using either NaH or K_2CO_3 as the base. Dienyne **2-9a** was obtained in 66% yield. Dienyne **2-9b** with a NTs tether between the alkene was prepared in 68% yield, and dienyne **2-9c** with a malonate tether between the alkenes was obtained in 86% yield.



Scheme 2-7: Synthesis of dienynes **2-9a**, **2-9b**, and **2-9c**

2.2.2 Reaction Condition Optimization

Enediyne substrate **2-11a** was subjected to the [2+2+2+1] cycloaddition under various conditions. The mechanism for the formation of the 5-7-5 tricyclic is illustrated in **Scheme 2-8**.

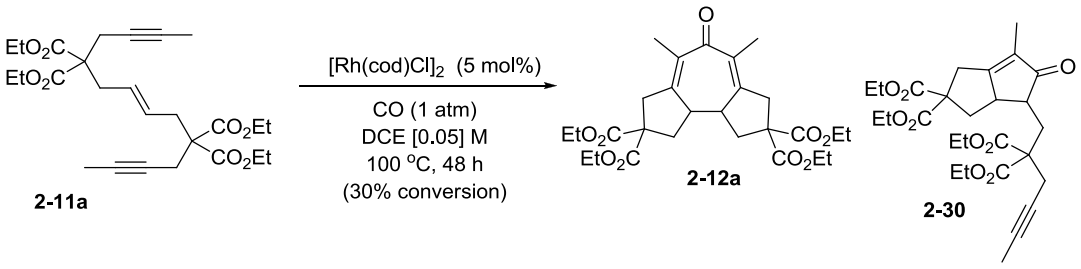


Scheme 2-8. Proposed **m**echanism for the formation of 5-7-5 tricyclics *via* the [2+2+2+1] cycloaddition

The cycloaddition reaction is initiated by the coordination of the enyne moiety to the [Rh] catalyst ([2+2+M]). Next, CO coordinates to [Rh], and this is followed by a migratory insertion of CO into the Rh-C bond ([2+2+1+M]). It is possible that a reductive elimination could preclude the CO insertion and result in the formation of the [2+2+2] product. The carbonylated product is formed via a reductive elimination of intermediate species C or C'.

An initial optimization attempt is shown in **Scheme 2-9.** The reaction was run using DCE as the solvent at 100 ^{o}C in the presence of $[Rh(cod)Cl]_2$ for 48 h. After purifying the reaction

mixture *via* column chromatography, three different fractions were isolated and characterized by ^{1}H NMR and ^{13}C NMR. The purity of each fraction was determined *via* HPLC. The HPLC trace in **Figure 2-1** corresponds to the starting material. The reaction proceeded with only 30% conversion based on the recovered starting material. The [2+2+2] product was not observed. The HPLC trace in **Figure 2-2** corresponds to the [2+2+2+1] cycloaddition product. The HPLC trace in **Figure 2-3** corresponds to the Pauson-Khand adduct.



Scheme 2-9: [2+2+2+1] and [2+2+1] cycloaddition reactions of enediyne **2-11a**

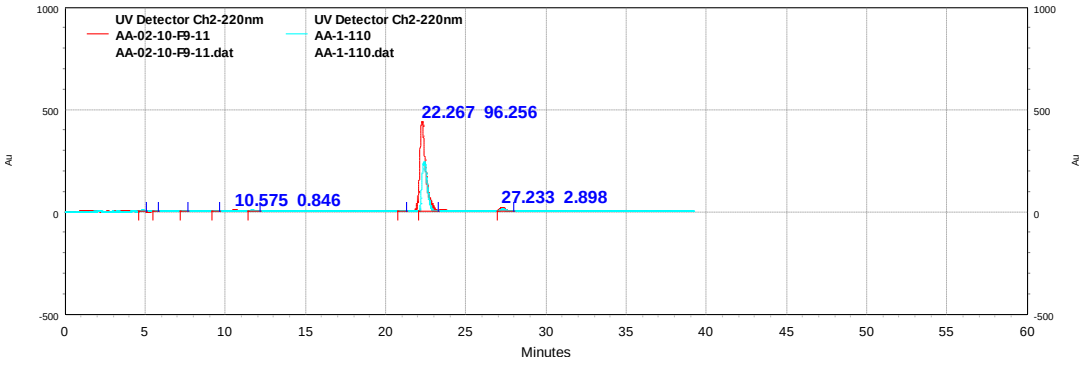


Figure 2-1: HPLC trace for **2-11a** isolated after reaction

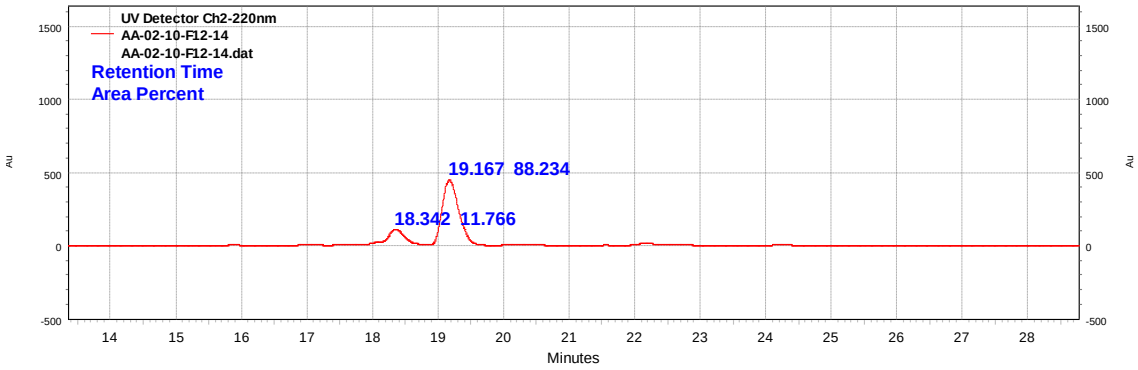


Figure 2-2: HPLC trace for **2-12a** isolated after reaction

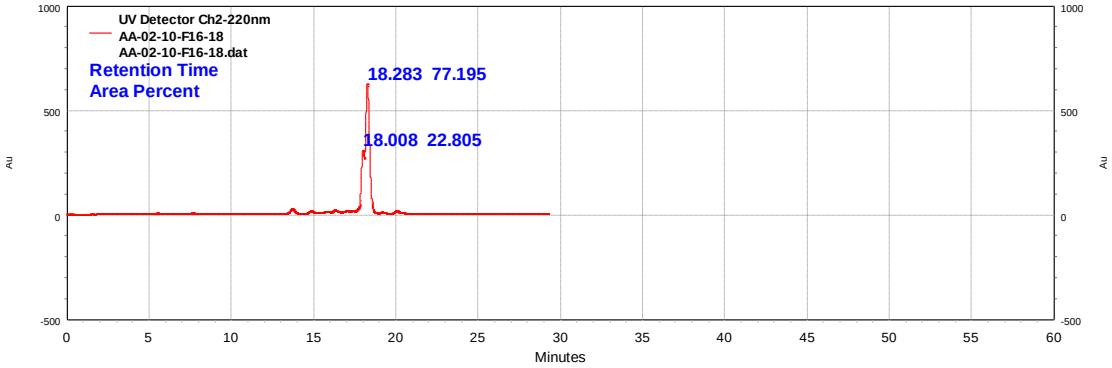
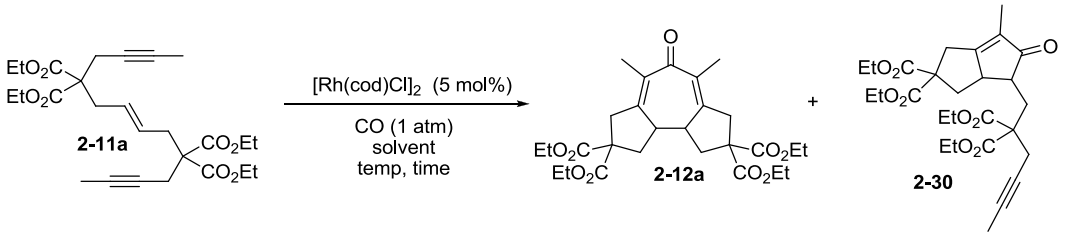


Figure 2-3: HPLC trace for **2-30** isolated after reaction

Subsequent attempts to optimize reaction conditions are summarized in **Table 2-1**. The effect of solvent, temperature, time and concentration were probed. All reactions were performed under 1 atm of CO and in the presence of $[Rh(cod)Cl]_2$ as the catalyst. In TFE at 100 ^{o}C at 0.1 M, the reaction failed to reach completion and favored formation of the [2+2+1] adduct over the [2+2+2+1] adduct (**Table 2-1, Entry 1**). Varying the concentration of the reaction in DCE or a mixture of toluene and TFE (10:1) at 100, 110, or 120 ^{o}C had no effect on the product distribution (**Table 2-1**, **Entries 2-6**).

Table 2-1. Optimization of reaction conditions

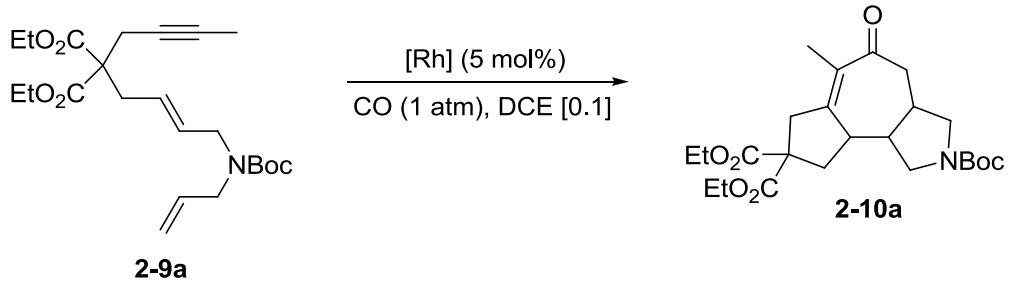


Entry	Solvent	Temperature (^{o}C)	Concentration (M)	Time (h)	Conversion (%)	Product Ratio **2-12a:2-30**
1	TFE	100	0.1	45	75	1:5
2	DCE	110	0.1	48	67	1:1
3	toluene:TFE (10:1)	100	0.025	25	67	1:1
4	DCE	100	0.025	21	67	1:1
5	toluene:TFE (10:1)	100	0.1	48	67	1:1
6	toluene:TFE (10:1)	120	0.1	48	67	1:1

Ratios determined *via* reverse phase HPLC (Jupiter Proteo column, eluent: H_2O/MeCN=1:1 with 40/45 mL/min increase of MeCN, flow rate: 1mL/min

In order to expand the substrate scope, dienyne **2-9a** was subjected to various conditions of the Ojima lab's already developed Rh-catalyzed [2+2+2+1] cycloaddition reaction.[7] The results of initial reaction optimization attempts are shown in **Table 2-2**. At 50 ^{o}C in DCE [0.1], in the presence of three different Rh catalysts, only starting material was observed. At 80 ^{o}C, using the same concentration of DCE, in the presence of the $[Rh(CO)_2Cl]_2$ catalyst, mass spectrometry showed the presence of a carbonylated product. Despite the results of mass spectrometry, TLC analysis showed a significant amount of the unreacted starting material.

Table 2-2: Catalyst and temperature screening



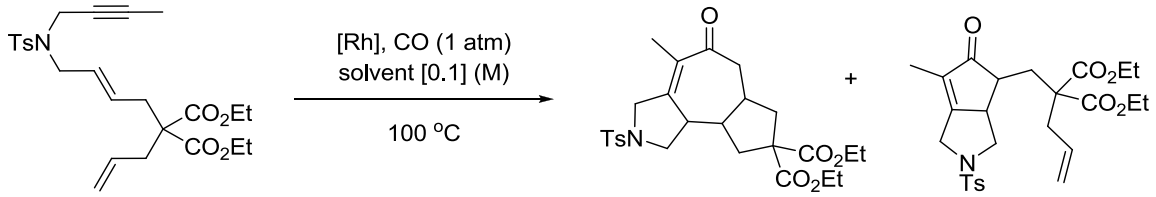
2-9a **2-10a**

Entry	Catalyst (5 mol%)	Temperature (^{o}C)	Time (hours)	Result*
1	$[Rh(CO)_2Cl]_2$	50	23	No reaction
2	$[Rh(cod)_2]OTf$	50	24	No reaction
3	$[RhCl(CO)(PPh_3)_2]/AgSbF_6$	50	21	No reaction
4	$[Rh(CO)_2Cl]_2$	80	24	MS showed carbonylated product

(DCE=dichloroethane, cod=1,5-cyclooctadiene, MS=mass spectrometry)
*Conversion was determined qualitatively by TLC

In an attempt to increase the overall conversion for the [2+2+2+1] cycloaddition of dienynes, substrate **2-9c** was subjected to the conditions reported by Wender et al. for similar substrates[6]. In addition to the desired [2+2+2+1] product, however, the [2+2+1] adduct was observed under various reaction conditions. The results for various attempts to bias the [2+2+2+1] product over the [2+2+1] adduct are shown in **Table 2-3**.

Table 2-3: Solvent and catalyst screening



2-9c **2-10c** **2-31a**

Entry	Catalyst (5 mol%)	Solvent [0.1]	Time (h)	Conversion (%)[2]	Product Ratio[1] 2-10c:2-31a
1	$[Rh(CO)_2Cl]_2$	toluene	24	84	7:1
2	$[Rh(CO)_2Cl]_2$	toluene:TFE (10:1)	24	>95	2.5:1
3	$[Rh(cod)_2]OTf$	toluene:TFE (10:1)	30	>95	1:5
4	$[Rh(CO)_2Cl]_2$ PPh_3 (10 mol%)	toluene:TFE (10:1)	24	94	1:2
5	$[Rh(cod)_2]OTf$ PPh_3 (5 mol%)	toluene:TFE (10:1)	24	>95	0:1

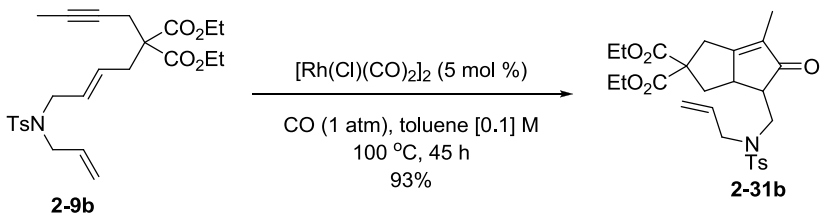
[1]Ratios determined *via* reverse phase HPLC (Jupiter Proteo column, eluent: H_2O/MeCN=1:1 with 40/45 mL/min increase of MeCN, flow rate: 1mL/min, t_1=16 min, t_2=17 min, t_3=21 min) [2]Conversion based on comparing peak areas determined by HPLC
(TFE = 2,2,2-trifluorethanol, PPh_3 = triphenylphosphine)

When the reaction was performed using toluene as the solvent, HPLC indicated a product ratio of 7:1 (**Table 2-3**, Entry 1), and the reaction conversion was 84% after 24 hours. The reaction was then performed using a 10:1 ratio of toluene:TFE (**Table 2-3**, Entry 2). According to HPLC analysis, the TFE additive did improve the overall conversion for this reaction. The mixture was purified by column chromatography, and HPLC analysis suggested the presence of two compounds with a 2.5:1 ratio. ^{13}C NMR analysis of the fraction containing the two products confirmed the presence of two carbonylated products with carbonyl chemical shifts at 201 ppm and 208 ppm. The two ^{13}C chemical shifts at 201 ppm and 208 ppm correspond with two

different carbonyl carbons. These shifts were assigned to the [2+2+2+1] and [2+2+1] cycloaddition products, respectively based on the literature reported values of similar products[7b]. The carbonylation reaction was also run using an ionic catalyst (**Table 2-3**, Entry 3). According to ^{13}C NMR and ^{1}H NMR, the [2+2+1] product is favored under these reaction conditions. According to HPLC analysis, there was a trace amount of the starting material, and the ratio of [2+2+2+1] to Pauson-Khand product was 1:5.

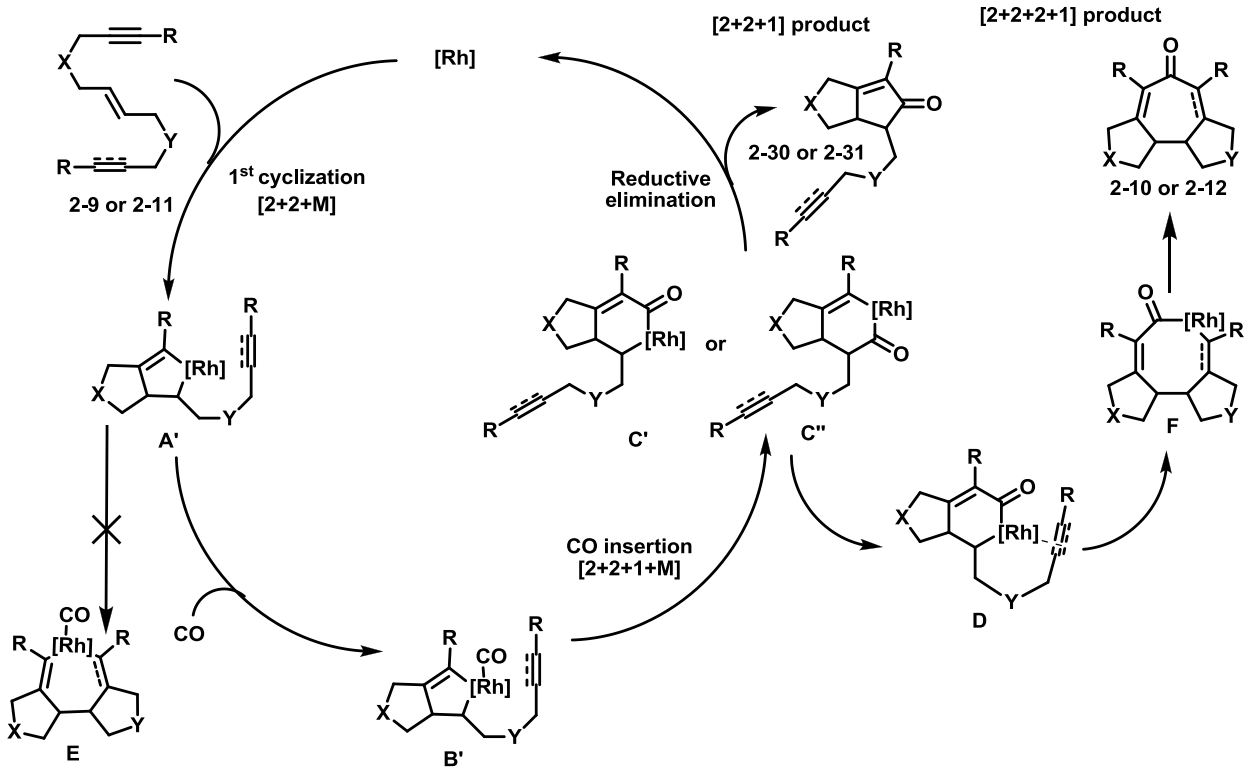
In an attempt to prevent the early CO insertion which leads to the Pauson-Khand product, PPh_3 was added[8] to the reaction mixture (**Table 2-3**, Entries 4 and 5). According to HPLC analysis, the addition of PPh_3 to the two reaction mixtures catalyzed by $[Rh(CO)_2Cl]_2$ and $[Rh(cod)_2]OTf$, respectively, did not bias the [2+2+2+1] product over the [2+2+1] adduct. For the $[Rh(CO)_2Cl]_2$ catalyst (**Table 2-3**, Entry 4), there was a 1:2:1 ratio of [2+2+2+1] adduct to Pauson-Khand product to the starting material. For the $[Rh(cod)_2]OTf$ catalyst (Table 2, Entry 5), there was a trace amount of the starting material, and only the Pauson-Khand product was observed.

Dienyne **2-9b** was then subjected to the reaction conditions which gave the highest selectivity towards the [2+2+2+1] product on a larger scale. However, only the [2+2+1] product was observed and was isolated in 93% yield (**Scheme 2-10**). The reductive elimination to form this PK product occurred more readily than coordination of the second alkene to the Rh and subsequent cyclizations.



Scheme 2-10: PKR of substrate **2-9b**

The mechanism for the formation of the [2+2+1] product from enediynes and dienynes is shown in **Scheme 2-11**.



Scheme 2-11: Proposed mechanism for the formation of the PK product and [2+2+2+1] product

The PKR is initiated by the coordination of the enyne moiety to the [Rh] catalyst ([2+2+M]). Next, CO coordinates to [Rh], and this is followed by a migratory insertion of CO into the Rh-C bond ([2+2+1+M]). Based on the results for the dienyne substrates, the migratory

insertion happens faster than a subsequent coordination of the second alkene. For enediynes, the coordination of the second alkyne happens at the same rate as CO insertion and [2+2+1+M] The final product is formed *via* a reductive elimination of C' or C''.

Since the [2+2+2] product was not observed for dienyne or enediynes substrates, an alternate route towards the formation of **2-10** or **2-12** has been proposed. The [2+2+2] product would be formed *via* a reductive elimination of intermediate **E**. Since this product was not observed for the enediyne or dienyne substrates, it is likely that coordination of the second alkene or alkyne occurs giving intermediate **D**. This is followed by a third cyclizations to give intermediate **F** which undergoes a reductive elimination to give the [2+2+2+1] product. For the case of enediynes, the two carbonylated products were observed in a 1:1 ratio which suggests that the coordination and subsequent cyclizations are equally likely to occur. For the case of the dienynes, the coordination of the second alkene does not occur as readily due to the decreased nucelophilicity of an alkene versus an alkyne.

2.3 Conclusion

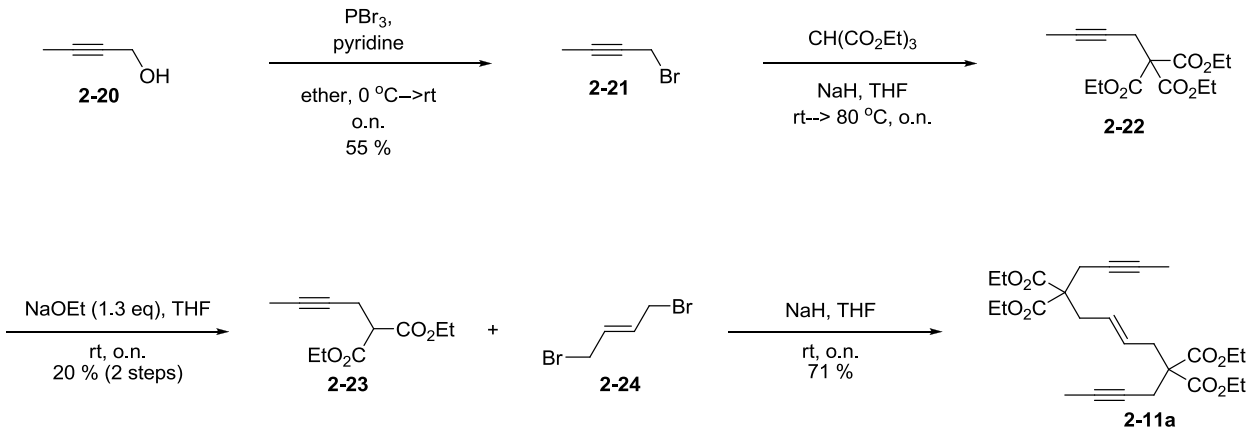
A study of carbonylative higher order cycloaddition reactions has been accomplished for novel diene and enediyne substrates. In the case of enediyne substrates, low conversion was observed, and both the [2+2+2+1] and [2+2+1] products were observed in equal ratios when DCE, toluene, and toluene/TFE were used as the solvents. An increase in selectivity towards the [2+2+1] product was observed when TFE was used as the solvent, but the overall conversion was poor. It is also worthy to note that the [2+2+2] product was not observed. These results may suggest that the product is being formed *via* the PK reaction pathway.

Two different dienyne substrates have been shown to undergo the Rh(I)-catalyzed [2+2+2+1] and [2+2+1] cycloaddition reactions. Different solvents and temperatures were explored in order to improve the selectivity for this reaction. Neutral catalysts, cationic catalysts, and the cases when PPh_3 was used as an additive gave mainly the Pauson-Khand product. When the reaction was run under 1 atm of CO using $[Rh(CO)_2Cl]_2$ as the catalyst in toluene, the PK product was obtained in excellent yield. In addition, the [2+2+2] product was not observed for either case. This further the supports the formation of the bicyclic product *via* the PK reaction pathway outlined above.

2.4 Experimental Section

General Methods: All chemicals were obtained from either Sigma-Aldrich or Acros Organics and used as received unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Solvents were dried under nitrogen using the PURESOLV system (Inovatative Technologies, Newport, MA). All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents and using Fisher silica gel (particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C NMR spectra were obtained using either a 300 MHz Varian Gemni 2300 (75 MHz ^{13}C) spectrometer or a 400 MHz Varian INOVA 400 (100 MHz ^{13}C) spectrometer in $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm and standardized with a solvent as an internal standard based on literature reported values. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Low-resolution mass spectrometry was performed on an Agilent 6890GC/5973 Mass Selective Detector.

4,4,10,10-bis(ethoxycarbonyl)-trideca-7-ene-2,12-diyne (2-11a):



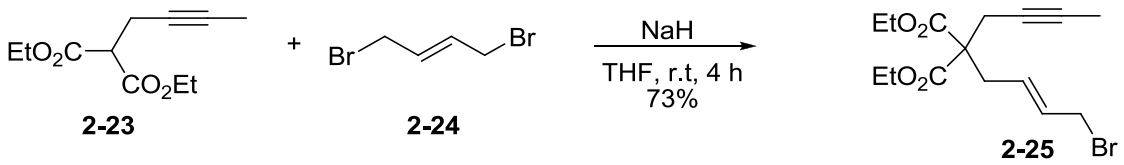
Phosphorus tribromide (36.17 g, 133.5 mmol) in ether (30 mL) was added dropwise over 10 minutes to a solution of 2-buty-1-ol (**2-20**, 23.3 g, 334 mmol) and pyridine (2.64 g, 33.4 mmol) in ether (40 mL) at 0 ^{o}C. The reaction was allowed to come to rt overnight. The reaction mixture was washed with water and extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was purified by distillation at ambient pressure at 120 ^{o}C to yield 1-bromobut-2-yne **2-21** (24.37 g, 55 % yield) as a clear, colorless liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.89 (t, 3H, *J* = 3 Hz), 3.92 (q, 2H, *J* = 3 Hz). Values are consistent with previously reported data.[9]

Triethyl methanetricarboxylate (10.0 g, 41.0 mmol) in THF (50 mL) was added to a suspension of NaH (60 % in mineral oil, 1.97 g, 49.2 mmol) in THF (70 mL) at rt. The mixture was allowed to stir for 10 min. Bromobut-2-yne **2-21**, 6.5 g, 49.2 mmol) was added to the suspension all at once, and the reaction mixture was refluxed overnight. The reaction mixture was quenched with water (100 mL) and extracted with ether (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and the solvent was removed *via*

rotary evaporation. The crude reaction mixture in THF (30 mL) was added to a suspension of sodium ethoxide (3.63 g, 53.3 mmol) in THF (30 mL) at rt. The reaction mixture was allowed to stir overnight. The reaction mixture was acidified to pH 1 with 6N HCl and extracted with ether (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over $MgSO_4$, and the solvent was removed *via* rotary evaporation. The crude product was distilled at 140 ^oC under reduced pressure to yield diethyl 2-(but-2-ynyl)malonate **2-23** (2.4 g, 28 % yield) as a clear, colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 6H, *J* = 7.2 Hz), 1.75 (t, 3H, *J* = 2.4 Hz), 2.73 (m, 2H), 3.52 (t, 1H, *J* = 7.8 Hz), 4.25 (q, 4H, *J* = 7.2 Hz). Values are consistent with previously reported data.[7a]

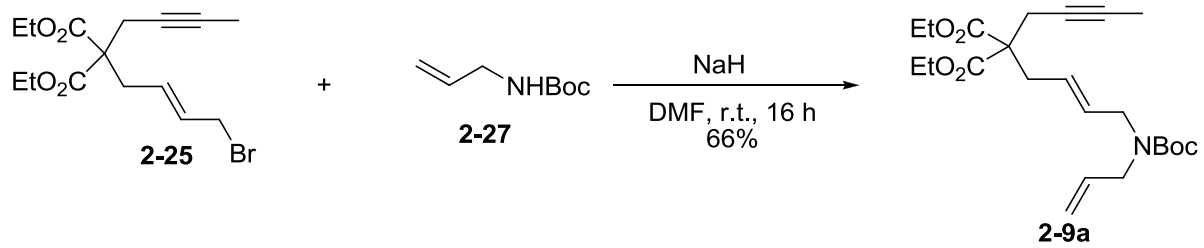
A solution of diethyl 2-(but-2-ynyl)malonate **2-23** (1.1 g, 5.18 mmol) in dry THF (12 mL) was added dropwise to a suspension of NaH (60 % in mineral oil, 0.185 g, 6.22 mmol) in dry THF (4 mL) under N_2. Dibromo-2-butene **2-24** (0.353 g, 1.65 mmol) was then added all at once to the solution. The reaction mixture was allowed to stir overnight. The reaction mixture was quenched with H_2O and washed with ether. The organic layer was then washed with brine, dried over $MgSO_4$, and filtered. Solvent was removed via rotary evaporation, and the product was purified via flash chromatography on silica gel using 10% ethyl acetate in hexanes as the eluent to yield the enediyne **2-11a** (0.592 g, 71%) as a clear, colorless viscous oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (m, 12H), 1.75 (t, 6H, *J* = 2.7 Hz), 2.72 (m, 8H), 4.22 (q, 8H, *J* = 6.9 Hz), 5.39 (m, 2H); HRMS (ES) m/z calcd for $C_{26}H_{36}O_8$ $(M + H)^+$: 477.2483, found 477.2489 (Δ 0.89 ppm).

(*E*)-Diethyl 2-(4-bromobut-2-enyl)-2-(but-2-ynyl)malonate (2-25):[10]



A solution of diethyl 2-(but-2-ynyl)malonate **2-23** (**25**, 1.5 g, 7.07 mmol) in dry THF (10 mL) was added dropwise to a suspension of NaH (0.34 g, 8.47 mmol) in dry THF (10 mL) under N_2. Dibromo-but-Z-ene **2-24** (**26**, 2.27 g, 10.6 mmol) in THF (10 mL) was then added all at once to the solution under N_2. The reaction mixture, which started as a white milky color, was allowed to stir for 4 h. The reaction mixture was quenched with H_2O and washed with ether. The organic layer was then washed with brine, dried over $MgSO_4$, and filtered. Solvent was removed via rotary evaporation, and the product was purified via flash chromatography on silica gel using 8% ethyl acetate in hexanes as the eluent to give the enyne bromide **2-25** (1.83 g, 73% yield) as a pale yellow, clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, 6H, *J* = 6Hz), 1.76 (t, 3H, *J* = 3Hz), 2.72 (q, 2H, *J* = 3Hz), 2.79 (d, 2H, *J* = 6Hz), 3.91 (d, 2H, 6Hz), 4.23 (q, 4H, *J* = 6Hz), 5.65 (m, 1H), 5.82 (m, 1H). Values are consistent with previously reported data.[10]

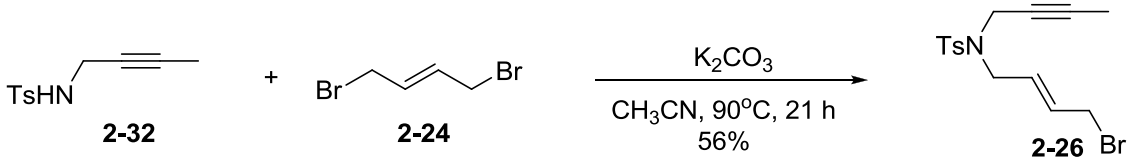
4-*tert*-Butoxycarbonyl-9,9-bis(ethoxycarbonyl)-4-azatrideca-1,6-diene-11-yne (2-9a):



To a suspension of sodium hydride (0.082 g, 2.04 mmol) in dry DMF (5 mL) under N_2, **2-25** (**27**, 0.267 g, 1.70 mmol) in DMF (5 mL) was added dropwise. (*E*)-diethyl 2-(4-bromobut-

2-enyl)-2-(but-2-ynyl)malonate (**2-25**, 0.587 g, 1.70 mmol) in DMF (5 mL) was added to the suspension all at once. The reaction mixture was stirred under N_2 at r.t. overnight for 16 h. The reaction mixture was a clear, orange/brown brown solution which was washed with distilled H_2O (400 mL) to remove DMF, and extracted with ether (3x100mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and solvent was removed under reduced pressure. The crude product was purified *via* flash chromatography on silica gel using 10% ethyl acetate in hexanes as the eluent to give the dieneyne **2-9a** (0.472 g, 66% yield) as a clear, viscous, pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 6H, *J* = 7.2 Hz), 1.45 (s, 9H), 1.76 (t, 3H, *J* = 2.7 Hz), 2.71 (q, 2H, J = 2.7 Hz), 2.79 (d, 2H, J = 2.7), 3.74 (t, 4H, J = 6.0 Hz), 4.22 (q, 4H, J = 7.2 Hz), 5.07-5.12 (m, 2H), 5.32-5.40 (m, 1H), 5.48-5.56 (m, 1H), 5.68-5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.44, 14.07, 22.92, 28.37, 34.85, 47.74, 48.37, 57.09, 61.44, 73.33, 78.81, 79.57, 115.30, 125.0, 130.68, 133.94, 155.32, 169.98. HRMS (ES) m/z calcd for $C_{23}H_{35}NO_6$ $(M + H)^+$: 422.2537, found 422.2544 (Δ 1.7 ppm).

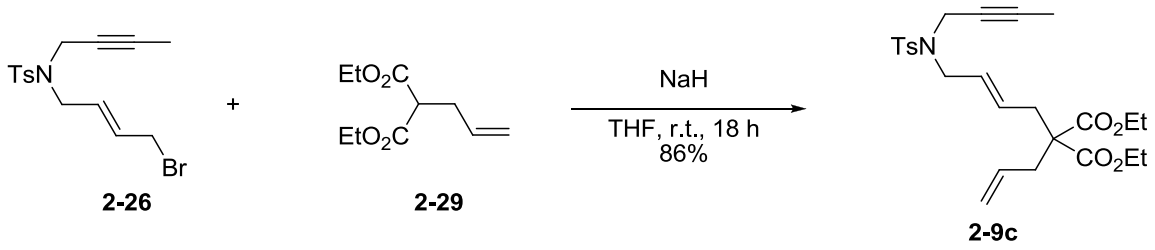
(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-(but-2-ynyl)-4-methylbenzenesulfonamide (2-26):



N-(but-2-ynyl)-4-methylbenzenesulfonamide (**2-32**, 2.00 g, 8.96 mmol) and potassium carbonate (2.50 g, 17.91 mmol) were dissolved in acetonitrile (50 mL) with stirring at 90°C. After stirring for 15 minutes, 1,4-dibromo-2(*Z*)-butene (**2-24**, 3.83 g, 17.91 mmol) in acetonitrile (10 mL) was added. After 21 h, the resulting solution was filtered through celite, and solvent was removed via rotary evaporation. The crude mixture was purified via flash chromatography on

silica gel using 10% ethyl acetate in hexanes as the eluent to give enyne bromide **2-26** (1.80 g, 56% yield) as a light yellow, viscous oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (t, 3H, *J* = 3 Hz), 2.48 (s, 3H), 3.88 (d, 2H, *J* = 6 Hz), 3.99 (d, 2H, *J* = 9 Hz), 4.06 (q, 2H, *J* = 3 Hz), 5.79 (m, 1H), 6.03 (m, 1H), 7.38 (d, 2H, *J* = 3 Hz), 7.94 (d, 2H, *J* = 3 Hz); MS (FIA) m/z calcd for $C_{15}H_{18}BrNO_2S$ $(M + H)^+$: 356.0, found 356.1.

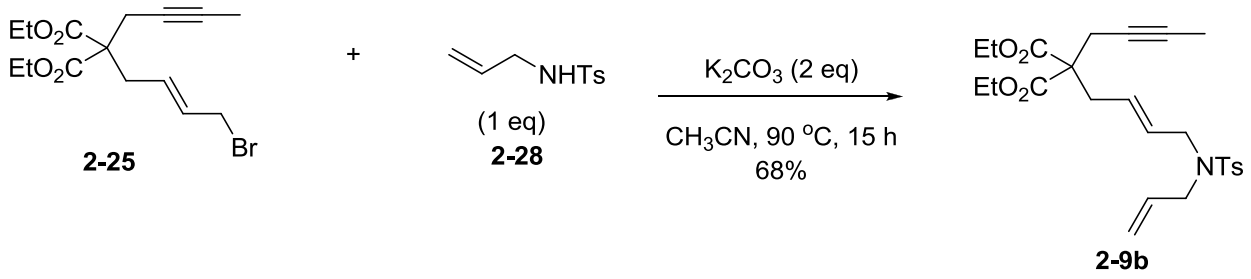
9-(4-Methylbenzenesulfonyl)-4,4-bis(ethoxycarbonyl)-9-azatrideca-1,6-diene-11-yne (2-9c):



To a suspension of sodium hydride (0.105 g, 4.38 mmol) in dry THF (15 mL) under N_2, diethyl 2-allylmalonate (**2-26**, 0.438 g, 2.19 mmol) was added dropwise. After stirring for 20 min, the reaction mixture turned from cloudy white to clear yellow, and enyne bromide (**2-29**, 0.780 g, 2.19 mmol) in THF (10 mL) was added all at once. After 18 h, the reaction mixture was washed with distilled H_2O, and extracted with ether (2x200mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and solvent was removed under reduced pressure. The product was purified via flash chromatography on silica gel to give the dieneyne **2-9c** (0.900 g, 86% yield) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, 6H, *J* = 9 Hz), 1.52 (t, 3H *J* = 3 Hz), 2.41 (s, 3H), 2.61 (m, 4H), 3.72 (d, 2H, *J* = 6 Hz), 3.96 (d, 2H, *J* = 3 Hz), 4.17 (q, 4H, *J* = 9 Hz), 5.10 (m, 2H), 5.56 (m, 3H), 7.29 (d, 2H, *J* = 9 Hz), 7.71 (d, 2H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.19, 14.08, 21.47, 35.09, 36.14, 36.79, 48.09, 57.32,

61.30, 71.59, 81.51, 119.22, 127.85, 128.39, 129.21, 129.82, 132.15, 136.12, 143.19, 170.56; HRMS (ES) m/z calcd for $C_{25}H_{33}NO_6S$ $(M + H)^+$: 476.2102, found 476.2106 (Δ 0.89 ppm).

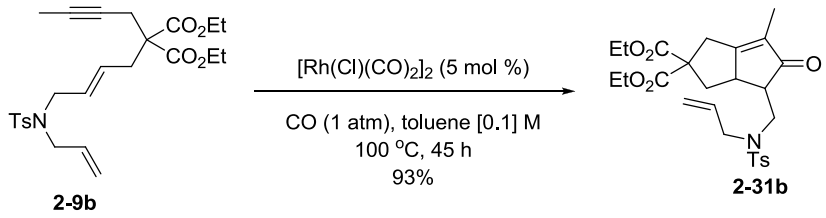
4-(4-methylbenzenesulfonyl)-9,9-Bis(ethoxycarbonyl)-4-azatrideca-1,6-diene-11-yne (2-9b):



Enyne bromide **2-25** (0.900 g, 2.61 mmol) was added dropwise to a suspension of K_2CO_3 (0.748 g, 5.41 mmol) and *N*-allyl-4-methylbenzenesulfonamide **2-28** (0.551 g, 2.61 mmol) in acetonitrile (10 mL) under N_2 at reflux. The reaction mixture was allowed to stir overnight. The reaction mixture was diluted with acetonitrile and filtered over celite. Solvent was removed via rotary evaporation, and the product was purified via flash chromatography on silica gel using 10% ethyl acetate in hexanes as the eluent to yield dieneyne **2-9b** (1.21 g, 56%) as a clear colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (6H, t, *J* = 7.2 Hz), 1.75 (3H, t, *J* = 2.7 Hz), 2.43 (3H, s), 2.64 - 2.66 (2H, m), 2.69 – 2.71 (2H, m), 3.73 – 3.77 (4H, m), 4.11 – 4.71 (4H, m), 5.11 – 5.18 (2H, m), 5.36 – 5.40 (2H, m), 7.30 (2H, d, *J* = 8.4), 7.70 (2H, d, *J* = 8.4). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.23, 21.64, 35.22, 35.70, 36.95, 48.20, 57.45, 61.45, 73.85, 76.61, 119.38, 127.85, 128.16, 129.58, 130.44, 132.26, 136.08, 143.65, 170.65; HRMS (ES) m/z calcd for $C_{25}H_{33}NO_6S$ $(M + H)^+$: 476.2102, found 476.2101 (Δ 0.16 ppm).

[2+2+1] Cycloaddition:

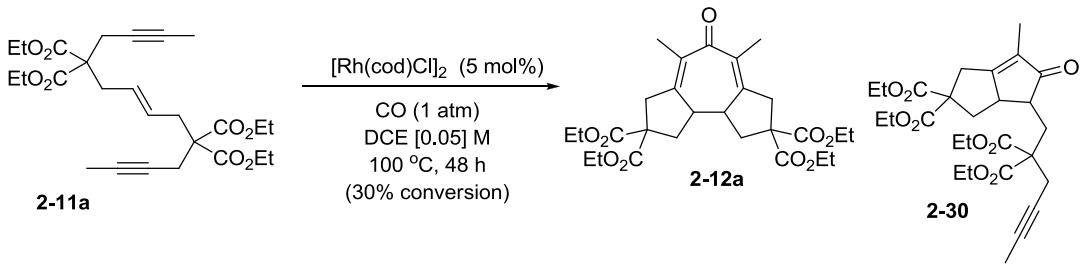
2,2-diethyl 6-methyl-5-oxo-4-{[N-(prop-2-en-1-yl)4-methylbenzenesulfonamido]methyl}-1,2,3,3a,4,5-hexahydropentalene-2,2-dicarboxylate (2-31b):



2-9b **2-31b**

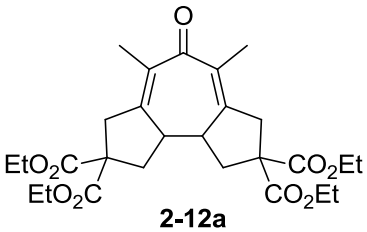
Dienyne **2-9b**, $[Rh(Cl)(CO)_2]_2$ (0.0026 g, 0.0067 mmol), and toluene (1.35 mL) were combined in a reaction flask. The flask was transferred to an autoclave and purged with CO and released (4x). **Caution: Purging with CO must be done in a well ventilated fume hood.** The autoclave was then purged to 1 atm of CO. The autoclave was immersed in an oil bath at 100 ^{o}C for 45 h, and then cooled to room temperature. The gas was released carefully from the autoclave in a well ventilated fume hood, and the reaction flask was taken out. The mixture was purified *via* column chromatography to yield **2-31b** as a clear, colorless oil (0.063 g, 93%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 – 1.34 (6H, m), 1.69 (3H, s), 2.43 (3H, s), 2.94 – 3.14 (3H, m), 2.56 – 3.40 (3H, m), 3.74 – 3.80 (4H, m), 4.20 – 4.31 (4H, m), 5.11 – 5.15 (1H, m), 5.19 (1H, d, *J* = 1.2), 5.61 (1H, m), 7.34 (2H, d, *J* = 8.1), 7.69 (2H, d, *J* = 8.1). ^{13}C NMR ($CDCl_3$, 500 MHz) δ8.59, 14.0, 21.5, 25.6, 34.1, 38.8, 47.7, 48.4, 54.1, 61.4, 61.9, 62.2, 68.0, 119.6, 127.3, 129.8, 131.7, 133.0, 136.2, 143.4, 171.1, 171.4, 177.0, 208.4; HRMS (ES) m/z calcd for $C_{26}H_{33}NO_7S$ $(M + H)^+$: 504.2051, found 504.2048 (Δ 0.55 ppm).

[2+2+2+1] Cycloaddition:



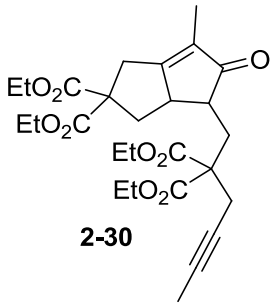
Typical procedure for [2+2+2+1] Cycloaddition of Dieneyne 2-11a: A round-bottomed flask was charged with dienyne **2-11a** (101.3 mg, 0.213 mmol), DCE (4.25 mL), $[Rh(cod)Cl]_2$ (5.20 mg, 0.0106 mmol), and stir bar. The flask was transferred to an autoclave and purged with CO and released (4x). **Caution: Purging with CO must be done in a well ventilated fume hood.** The autoclave was then purged to 1 atm of CO. The autoclave was immersed in an oil bath at 100 ^{o}C for 48 h, and then cooled to room temperature. The gas was released carefully from the autoclave in a well ventilated fume hood, and the reaction flask was taken out. The mixture was concentrated and purified using flash column chromatography. The reaction conversion was determined to be only 30% based on recovered starting material.

tetraethyl 4,6-dimethyl-5-oxo-9,9a-dihydro-1H-cyclopenta[e]azulene-2,2,8,8 (3H,5H,7H,9bH)-tetracarboxylate (2-12a):



Clear, colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) 1.23-1.29 (m, 12H), 1.85 (s, 6H), 1.99 (t, 2H, *J* = 15.0 Hz), 2.66 (dd, 2H, *J* = 5.0 Hz), 2.84-2.87 (m, 1H), 3.13-3.14 (m, 3H), 3.76 (t, 2H, *J* = 10.0 Hz), 4.16-4.24 (m, 8H). ^{13}C NMR ($CDCl_3$, 500 MHz) 14.0, 16.6, 39.6, 41.4, 46.2, 58.1, 61.8, 61.9, 131.9, 153.9, 170.9, 189.8; HRMS (ES) m/z calcd for $C_{27}H_{36}O_9$ $(M + H)^+$: 505.2432, found 505.2433 (Δ 0.24 ppm).

diethyl 4-(2,2-bis(ethoxycarbonyl)hex-4-ynyl)-6-methyl-5-oxo-3,3a,4,5-tetrahydropenta-lene-2,2(1H)-dicarboxylate (2-30):



2-30

Clear, colorless oil:^{1}H NMR (CDCl3, 300 MHz) 1.19-1.31 (m, 12H), 1.58 (s, 1H), 1.65-1.76 (m, 4H), 1.83-1.87 (m, 2H), 2.04-2.07 (m, 1H), 2.70-2.83 (m, 3H), 2.98-3.18 (m, 3H), 3.72-3.77 (m, 2H), 4.10-4.29 (m, 8H) ^{13}C NMR ($CDCl_3$, 500 MHz) δ 3.47, 8.75, 14.0, 23.7, 25.6, 32.2, 33.9, 34.0, 39.5, 40.0, 40.3, 49.7, 52.5, 56.5, 60.8, 61.9, 62.1, 68.0, 73.0, 79.5, 131.7, 170.3, 170.4, 171.0, 171.5, 175.7, 209.3; HRMS (ES) m/z calcd for $C_{27}H_{36}O_9$ $(M + H)^+$: 505.2432, found 505.2429 (Δ 0.55 ppm).

2.5 References

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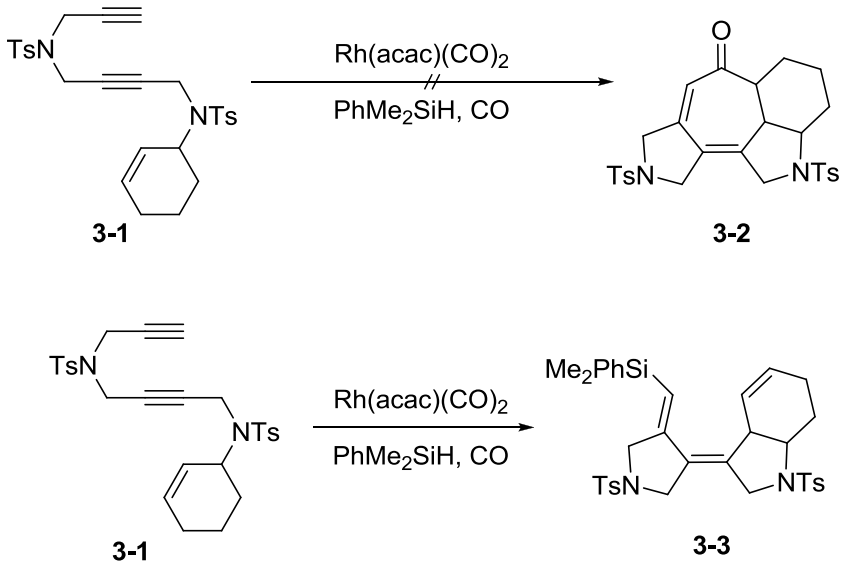
Chapter 3

The Synthesis of Cycloheptene-diynes and their Applications to Rh(I)-Catalyzed [2+2+2] and [2+2+2+1] Cycloaddition Reactions

Table of Contents

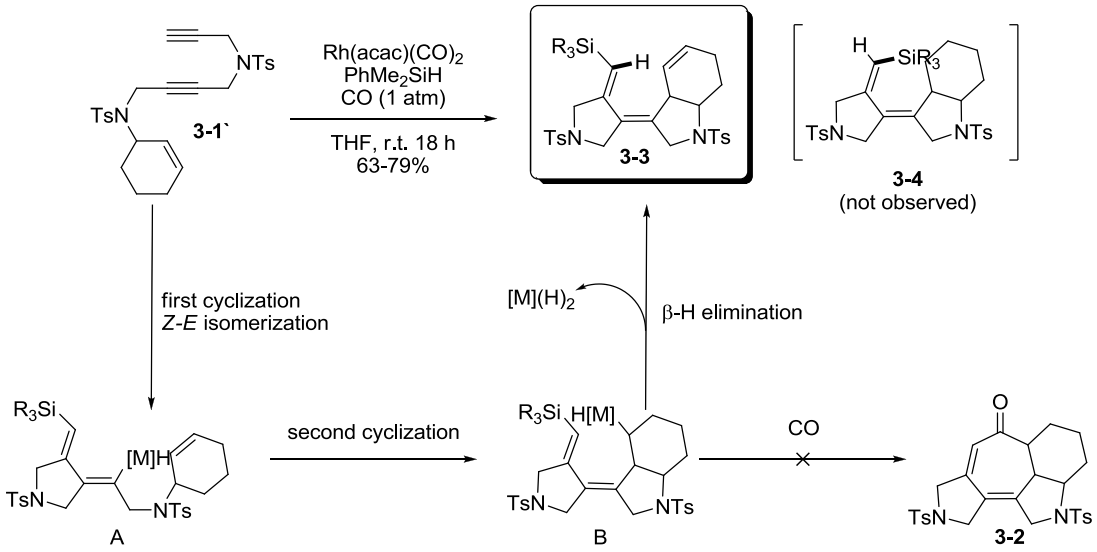
3.1 Introduction to the Rh(I)-Catalyzed [2+2+2+1] Cycloaddition Reaction of Cyclohexene-diynes

During optimization of the CO-SiCaT reaction of enediynes, it was found that desired tetracyclic product **3-2** was not obtained when the ene moiety was part of a ring. Only the tricyclic product **3-3** was obtained (**Scheme 3-1**).



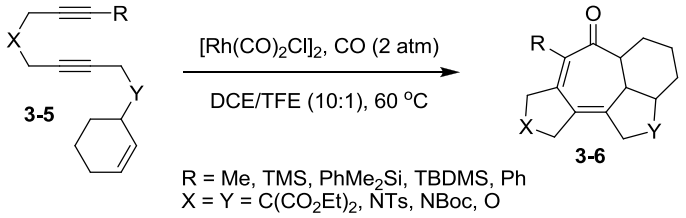
Scheme 3-1: CO-SiCaT of cyclohexene-diyne **3-1**

The mechanism for the formation of this product is illustrated in **Scheme 3-2**. The mechanism shown in **Scheme 3-2** begins with the insertion of the Rh-Si active species, followed by the first cyclization and *Z*→*E* isomerization (Intermediate **A**). A second cyclization leads to intermediate **B**. The carbonylated product **3-2** was not observed because the β-hydride elimination to form tricyclic product **3-3** proceeds faster than the cyclization. The silane was incorporated into product **3-3** with an *E* double bond configuration. The product with the silane incorporated in the *Z* double bond (**3-4**) was not observed.[1]

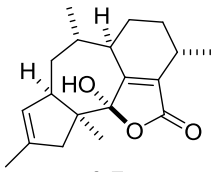


Scheme 3-2: Formation of tricyclic product **3-3**

It was later found that the 5-7-6-5 tetracyclic products could be obtained *via* a cycloaddition reaction in the absence of hydrosilane.[2] The Ojima lab successfully optimized the conditions for the [2+2+2+1] cycloaddition of a variety cyclohexene-diynes (**Scheme 3-3**). The results were particularly promising because the 5-7-6-5 adduct which was formed comprises the core of natural product, Caribenol A. Caribenol A possesses significant inhibitory activity against *Mycobacterium tuberculosis* (**Figure 3-1**).[3]



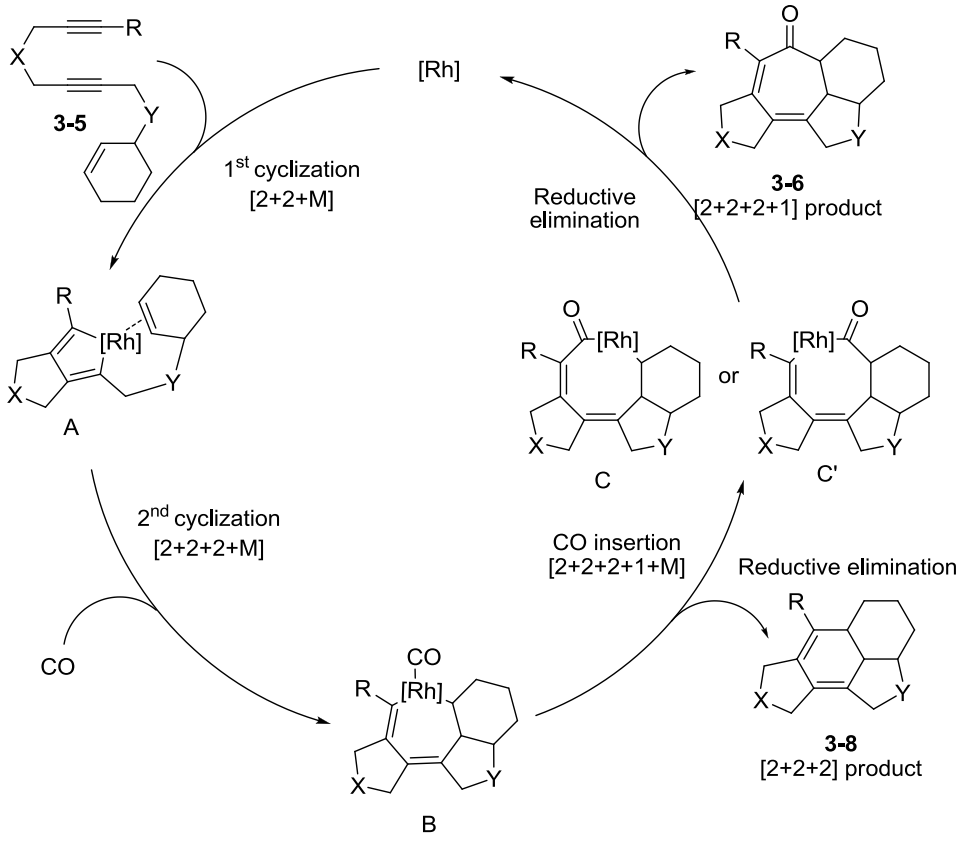
Scheme 3-3: [2+2+2+1] Cycloaddition of cyclohexene-diynes



3-7
Caribenol A

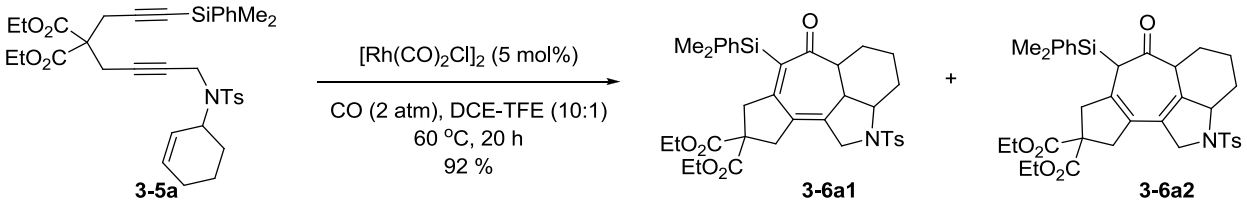
Figure 3-1: Natural product Caribenol A

The mechanism for the formation of these tetracyclics is shown in **Scheme 3-4**. The cycloaddition starts with the coordination of the diyne moiety to the [Rh] catalyst ([2+2+M]). This is followed by olefin insertion into the Rh-C bond ([2+2+2+M]). Next, CO coordinates to [Rh], and this is followed by a migratory insertion of CO into the Rh-C bond ([2+2+2+1+M]). The final product is formed via a reductive elimination. The active Rh-catalyst species is also regenerated. It is also important to note that, during optimization, the amount of the [2+2+2] side product was decreased to trace amounts.



Scheme 3-4: Mechanism for the [2+2+2+1] cycloaddition of cyclohexene-diynes

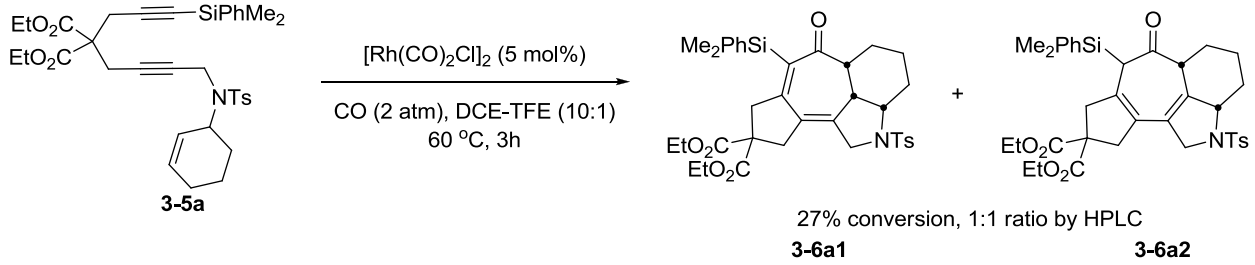
When the optimized reaction conditions were applied towards cyclohexene-diynes, unexpected, isomerized carbonylated products were formed (**Scheme 3-5**).[4]



Scheme 3-5: Isomerized carbonylated products **3-6a1** and **3-6a2**

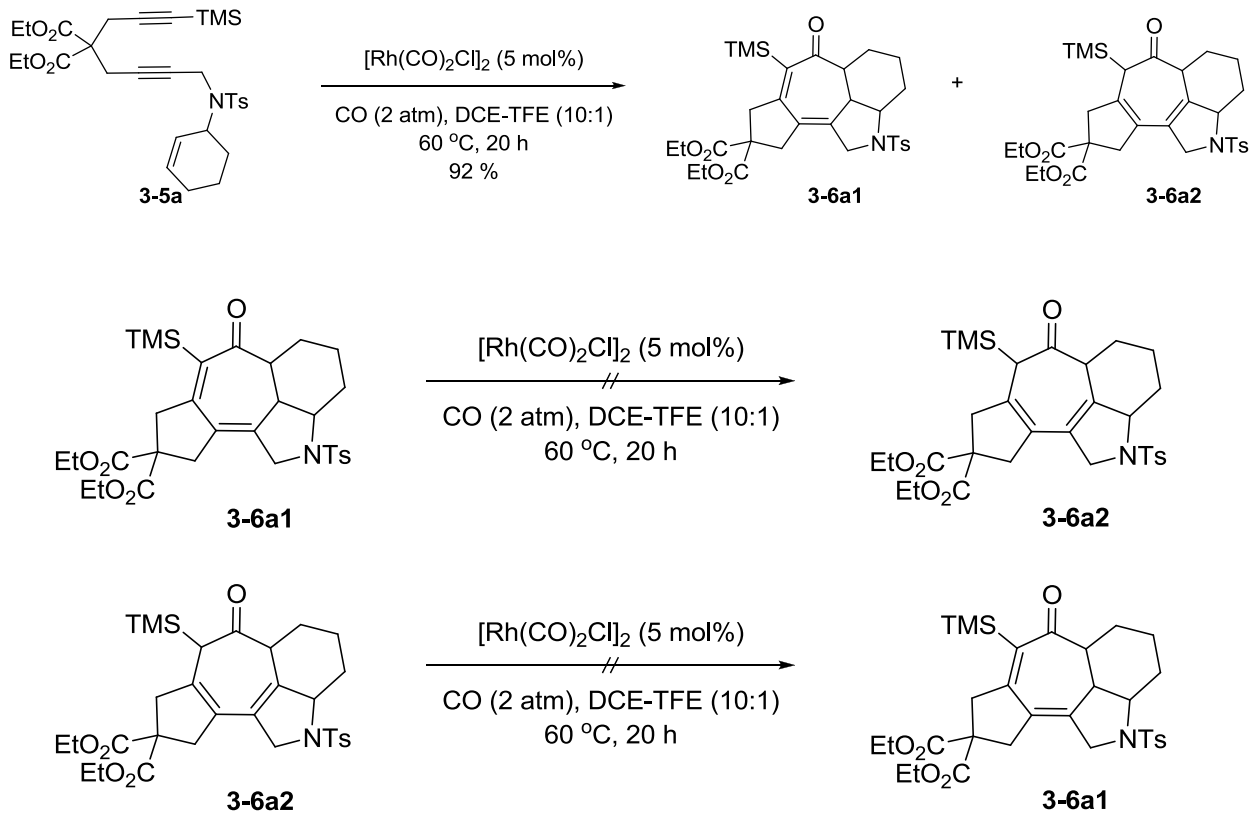
The diene-shifted isomers **3-6a1** and **3-6a2** were obtained as a *ca.* 1:1 mixture for various silyl-capped substrates. In order to investigate the mechanism for the observed isomerization

various experiments were conducted. The reaction of **3-5a** was carried out for a shortened reaction time of 3 hours. HPLC analysis showed 27% conversion and a 1:1 mixture of the two products. This result indicates that the product distribution is set early in the reaction, and the ratio remains constant during the course of the reaction (**Scheme 3-6**).[4]



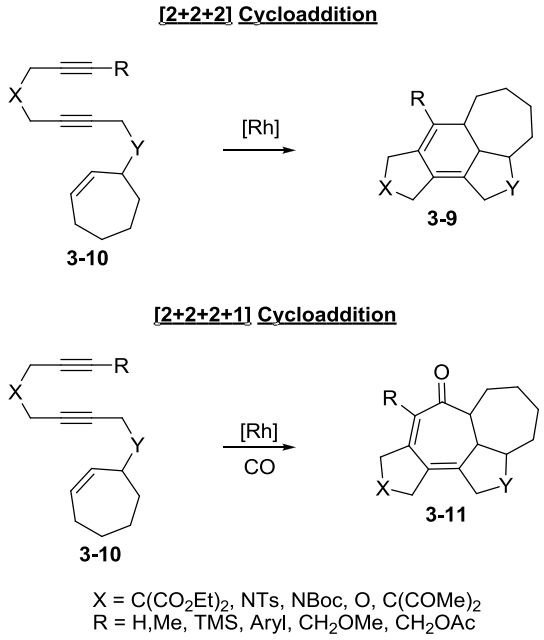
Scheme 3-6: [2+2+2+1] cycloaddition of cyclohexene-diyne **3-5**a with CO

If the isomers are not formed directly from the starting material during the course of the reaction, perhaps a [Rh]-catalyzed isomerization of the products occurs. In order to test this possibility, each isomer (**3-6a1** and **3-6a2)** was isolated and separately subjected to the reaction conditions. However, HPLC analysis showed no conversion of either isomer (**Scheme 3-7**).[4] It is also important to note that isomerization of the [2+2+2] product was not observed. Based on this observation along with the isomerization studies mentioned above, the isomerization most likely occurs during or directly before the final reductive elimination.



Scheme 3-7: Attempted isomerization of 5-7-6-5 tetracyclics **3-6a1** and **3-6a2**

In order to expand the substrate scope, novel cycloheptene-diyne substrates were synthesized and subjected to the reaction. The formation of 5-6-7-5 and 5-7-7-5 ring cores may be obtained from the cycloheptene-diyne precursors in one step (**Scheme 3-8**). The results are discussed herein.

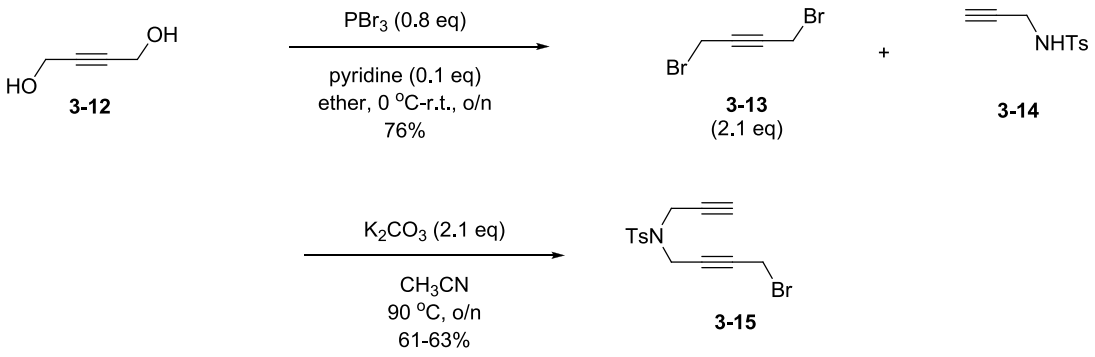


Scheme 3-8: Novel substrates to undergo Rh(I)-catalyzed [2+2+2] and [2+2+2+1] cycloaddition reactions

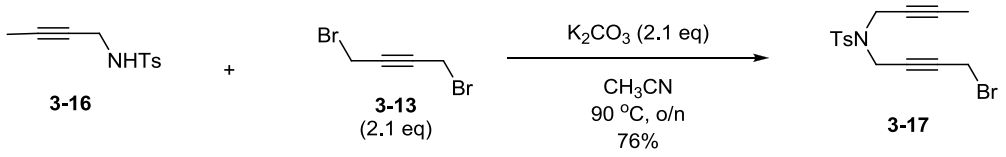
3.2 Results and Discussion

3.2.1 Substrate Synthesis

Diyne bromides with various tethers were synthesized from readily available starting materials. But-2-yne-1,4-diol (**3-12**) was converted to the corresponding dibromide **3-13** in the presence of PBr_3 and pyridine in 76% yield. The dibromide **3-13** was then coupled with **3-14** in the presence of K_2CO_3 at reflux in acetonitrile to afford the corresponding diyne bromide **3-15** in 61-63% yield (**Scheme 3-9**). The methyl-capped diyne bromide was synthesized in a similar fashion (**Scheme 3-10**).

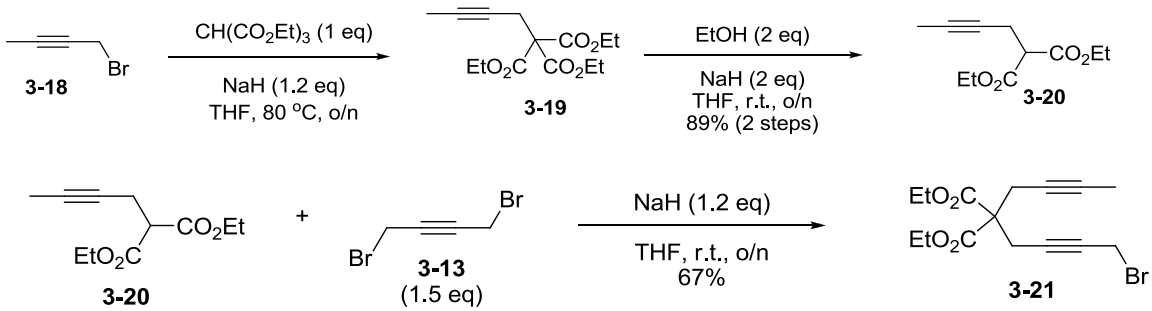


Scheme 3-9: Synthesis of diyne bromide **3-15**



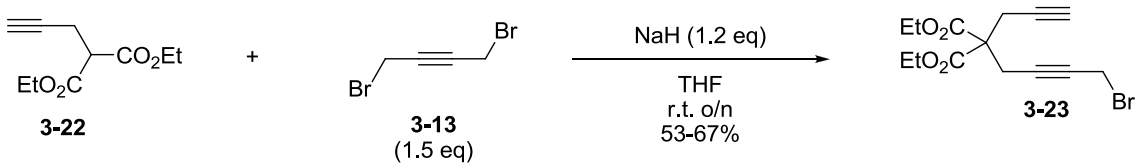
Scheme 3-10: Synthesis of diyne bromide **3-17**

The diyne bromide with a methyl-capped alkyne was synthesized by reacting 2-butynyl bromide with the triethyl methanetricarboxylate in the presence of NaH. The crude **3-19** was treated with NaOEt, generated in situ, to yield **3-20** in 89% yield over 2 steps. The malonate was then coupled with 1,2-dibromo-2-butyne in the presence of NaH to yield the **3-21** in 67% yield (**Scheme 3-11**).



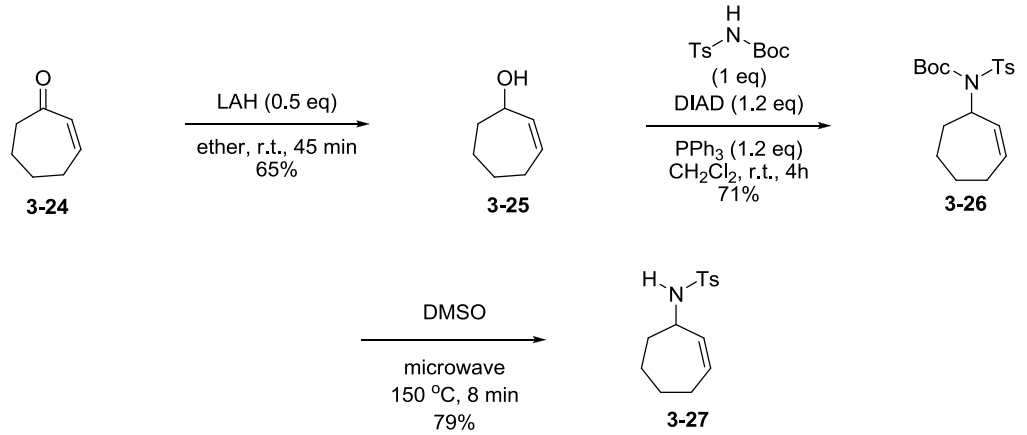
Scheme 3-11: Synthesis of diyne bromide **3-21**

Diyne bromide **3-23** with a malonate tether bearing a terminal alkyne was also synthesized. Dibromide **3-13** was coupled with propargyl malonate **3-22** in the presence of sodium hydride to afford **3-23** in up to 67% yield (**Scheme 3-12**).



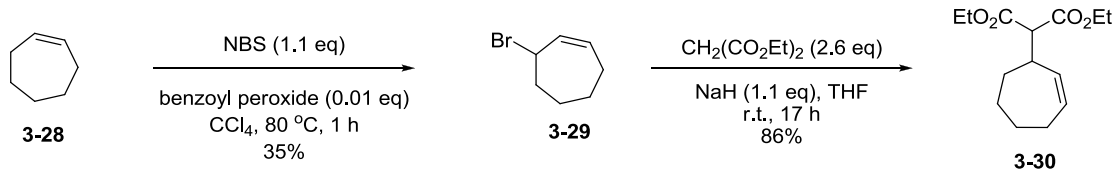
Scheme 3-12: Synthesis of diyne bromide **3-16**

The cycloheptene component with *N*-tosyl tether was synthesized as outlined in **Scheme 3-13.** In the presence of lithium aluminum hydride, cyclohept-2-enone (**3-24**) was reduced to the corresponding alcohol (**3-25**) in 65% yield. The subsequent alcohol was subjected to a Mitsunobu reaction with Boc-protected tosylamide, which was then deprotected to give *N*-(cyclohept-2-enyl)-4-methylbenzenesulfonamide (**3-27**) in 79% yield.



Scheme 3-13: Synthesis of *N*-(cyclohept-2-enyl)-4-methylbenzenesulfonamide (**3-27**)

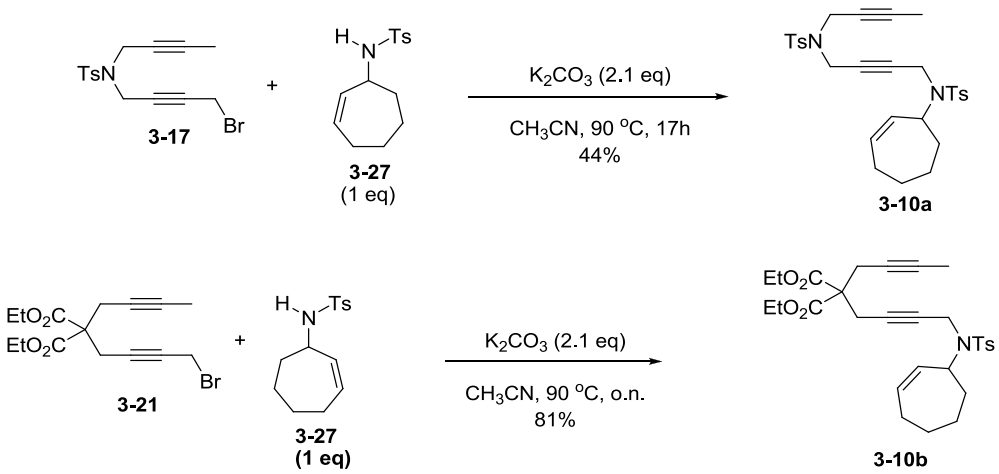
In order to obtain the cycloheptyl moiety with a malonate tether, cycloheptene (**3-28**) was brominated in the presence of NBS[5] to yield **3-29** in 35% yield. The cycloheptenebromide was then coupled with diethyl malonate to yield diethyl 2-(cyclohept-2-enyl)malonate (**3-30**) in 86% yield (**Scheme 3-10**).



3-28 **3-29** **3-30**

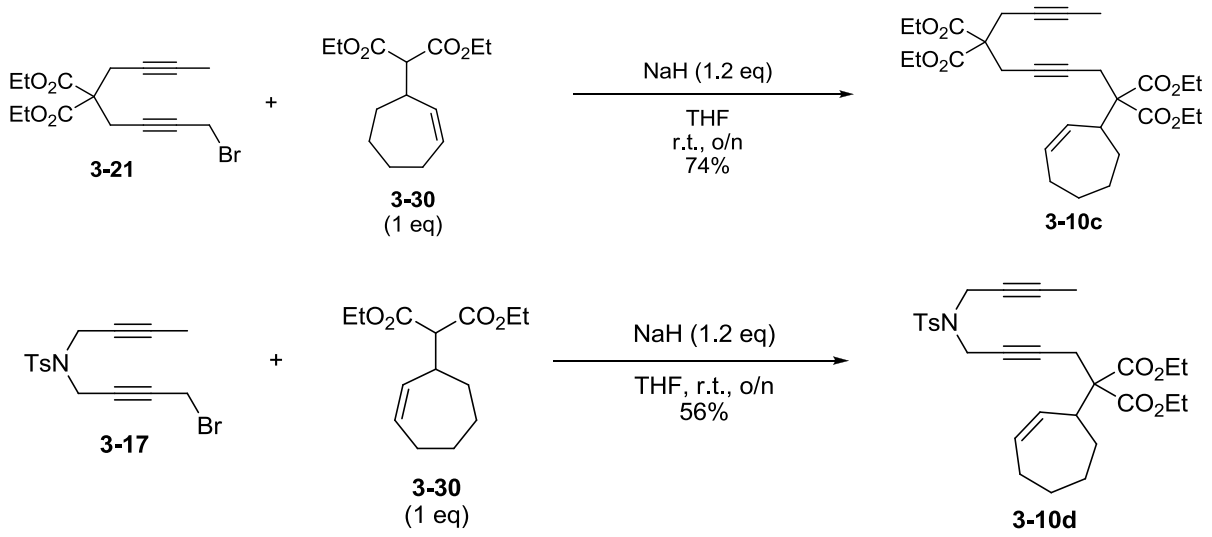
Scheme 3-14: Synthesis of diethyl 2-(cyclohept-2-enyl)malonate (**3-30**)

With the diyne bromides and cycloheptenyl components in hand, the final cycloheptene-diyne substrates were synthesized. Diyne bromide **3-17** was coupled with sulfonamide **3-27** in the presence of potassium carbonate in acetonitrile at reflux to yield the bis-NTs-tethered substrate **3-10a** in 44% yield. The cycloheptene substrate bearing a malonate and sulfonamide tether (**3-10b**) was synthesized in the same fashion (**Scheme 3-15**).



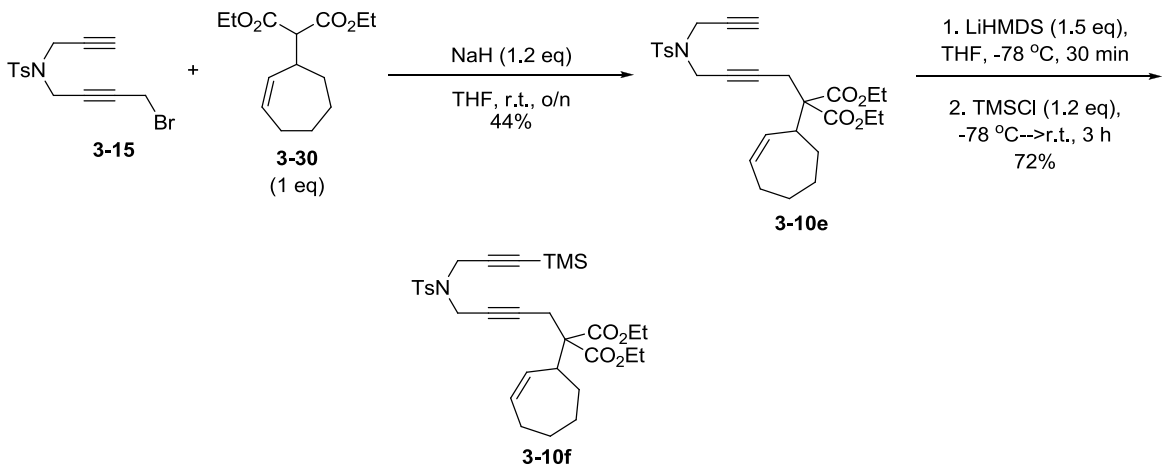
Scheme 3-15: Synthesis of cycloheptene-diyne substrates **3-10a** and **3-10b**

In order to functionalize cycloheptenylmalonate **3-30** with diyne bromide **3-21**, the two components were coupled in the presence of NaH, and the final product **3-10c** was obtained in 74% yield. Substrate **3-10d** was synthesized in a similar fashion (**Scheme 3-16**).

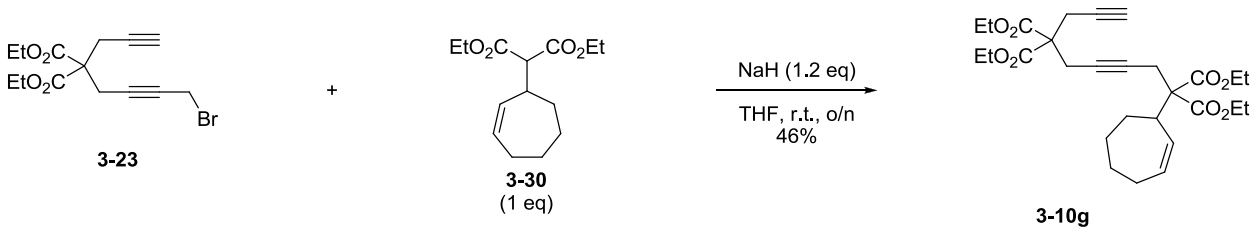


Scheme 3-16: Synthesis of cycloheptene-diyne substrates **3-10c** and **3-10d**

The TMS-capped cycloheptene-diyne **3-10f** was also synthesized. In the presence of sodium hydride, the cycloheptenylmalonate **3-30** was coupled with a diyne bromide **3-15** to afford the enediyne with a terminal alkyne **3-10e** in 44% yield. The lithium acetylide was then formed in the presence of LiHMDS, followed by a coupling with TMSCl to yield the desired substrate **3-10f** in 72% yield (**Scheme 3-17**). Cycloheptene-diyne **3-10g** was synthesized in a similar fashion (**Scheme3-18**).



Scheme 3-17: Synthesis of cycloheptene-diyne substrate **3-10f**

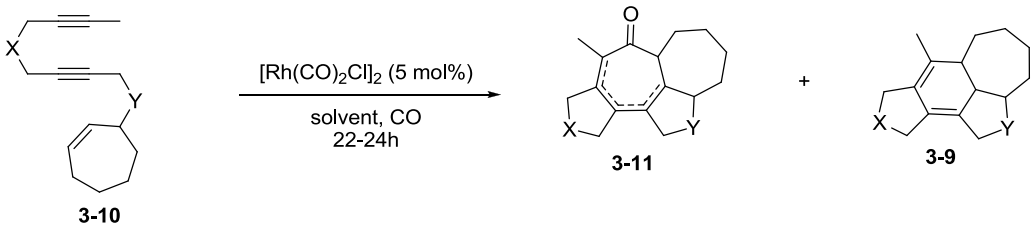


Scheme 3-18: Synthesis of cycloheptene-diyne **3-10g**

3.2.2 Optimization of the [2+2+2+1] Cycloaddition Reaction of Cycloheptene-diynes

The enediyne substrates were then subjected to the [2+2+2+1] cycloaddition under various conditions. Initial optimization attempts for these novel substrates are shown in **Table 3-1.**

Table 3-1: Optimimization of the [2+2+2+1] cycloaddition reaction of **3-10**



3-10 **3-11** **3-9**

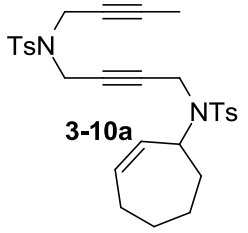
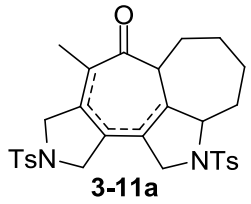
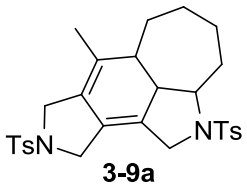
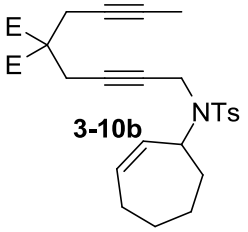
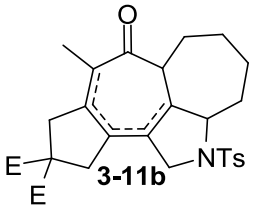
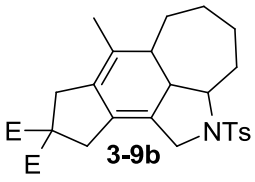
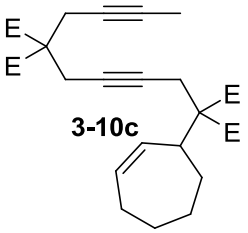
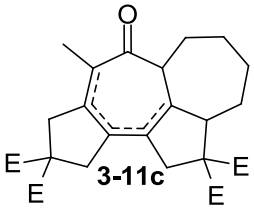
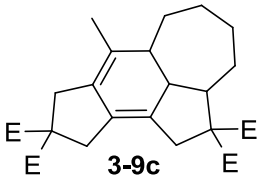
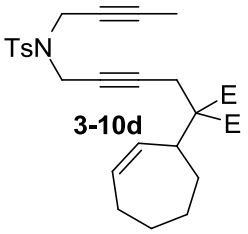
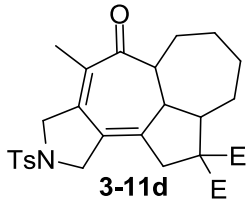
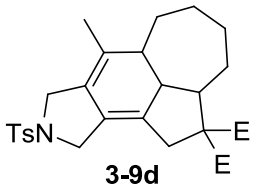
Entry[1]	X	Y	Temp. (°C)	CO (atm)	Solvent	Conc. (M)	Conversion (%)	Product Ratio[a] **3-11:3:9**
1	$C(CO_2Et)_2$	$C(CO_2Et)_2$	50	1	DCE	0.05	>95	45:55
2	$C(CO_2Et)_2$	$C(CO_2Et)_2$	50	2	DCE	0.05	>95	49:51
3	NTs	NTs	50	1	DCE	0.025	90	87:13*
4	NTs	NTs	60	1	DCE	0.025	>95	82:18
5	NTs	NTs	50	2	DCE	0.05	>95	87:13
6	NTs	$C(CO_2Et)_2$	50	1	DCE	0.05	>95	51:49
7	$C(CO_2Et)_2$	NTs	60	2	TFE	0.025	>95	0:100
8	$C(CO_2Et)_2$	NTs	60	1	DCE	0.05	>95	97:3

DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol. [1]All reactions were performed in an autoclave. [a]Determined by reverse phase HPLC analysis (MeOH:H_2O, Phenomenex, Jupitor 10 Proteo 90A) for 20-24 h reaction. *90% conversion according to HPLC

The substrates were screened in different mixtures and concentrations of DCE and TFE. The cycloaddition reactions were also run at various temperatures. For the bis-malonate tethered cycloheptene-diyne, running the reaction under either 1 or 2 atm in DCE, the product distribution was essentially 1:1 (**Table 3-1,** Entries 1 and 2). When the cycloheptene-diyne with bis-sulfonamide tethers was subjected to the reaction conditions it showed the best selectivity towards the carbonylated product when run in DCE at 50 °C under 2 atm CO (Entry 5). When the substrate with mixed tethers was run in TFE, only the [2+2+2] product was observed even under a CO atmosphere (Entry 7). This substrate also showed excellent selectivity towards the

carbonylated product when run in DCE at 60 ^{o}C under 1 atm of CO (Entry 8). The reaction was then scaled up for 4 different substrates, and the results are summarized in **Table 3-2**.

Table 3-2: Isolation of [2+2+2+1] and [2+2+2] products

Entry	Substrate	(yield %)[a]		(yield %)[a]	
1[1]	 **3-10a**	 **3-11a**	(55)	 **3-9a**	(12)
2[1]	 **3-10b**	 **3-11b**	(68)	 **3-9b**	(7)
3[2]	 **3-10c**	 **3-11c**	(50)	 **3-9c**	(39)
4[1]	 **3-10d**	 **3-11d**	(51)	 **3-9d**	(41)

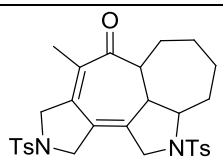
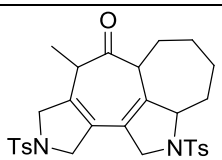
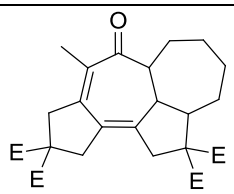
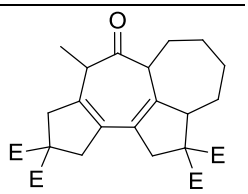
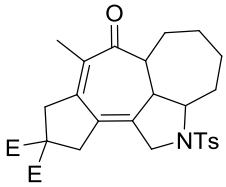
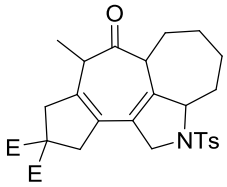
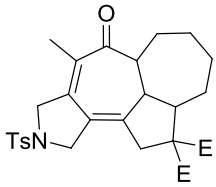
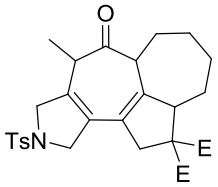
[a]Isolated yield of products based on one run using 80 mg of substrate
[1]5 mol% $[Rh(CO)_2Cl]_2$, CO (1 atm) in DCE at [0.05] at 60 ^{o}C for 21-24h at 60 ^{o}C
[2]5 mol% $[Rh(CO)_2Cl]_2$, CO (2 atm) in DCE at [0.05] at 50 ^{o}C for 24h at 60 ^{o}C
E = CO_2Et_2

When four different substrates were subjected to the reaction, various product distributions were observed. The best selectivity (9:1) was observed for substrate **3-10b** (**Table 3-2**, Entry 2). The products were obtained in a 75% combined isolated yield The next best selectivity (4.5:1) was observed for substrate **3-10a** (**Table 3-2**, Entry 1) and the products were obtained in a combined yield of 67%. When substrate **3-10c** was subjected to the reaction (**Table 3-2**, entry 3), the products were obtained with a selectivity of 1.3:1 and in 89% combined isolated yield. For these three cases, two carbonylated products were observed by LCMS and ^{13}C NMR. The masses were identical according to LCMS, thus the products were determined to be isomers. In addition, the isomers have different chemical shifts for the ketone carbon. This result is not completely unexpected since isomerization was observed for the silyl-capped cyclohexene-diyne substrates.[2] However, it is the first case isomerization has been observed for methyl-capped substrates. When **3-10d** was subjected to the cycloaddition reaction conditions, only one isomer was obtained (**Table 3-2**, entry 4). The carbonylated and noncarbonylated products were obtained in a ratio of 1.2:1 in 92% combined isolated yield.

3.2.3 Mechanism of isomerization

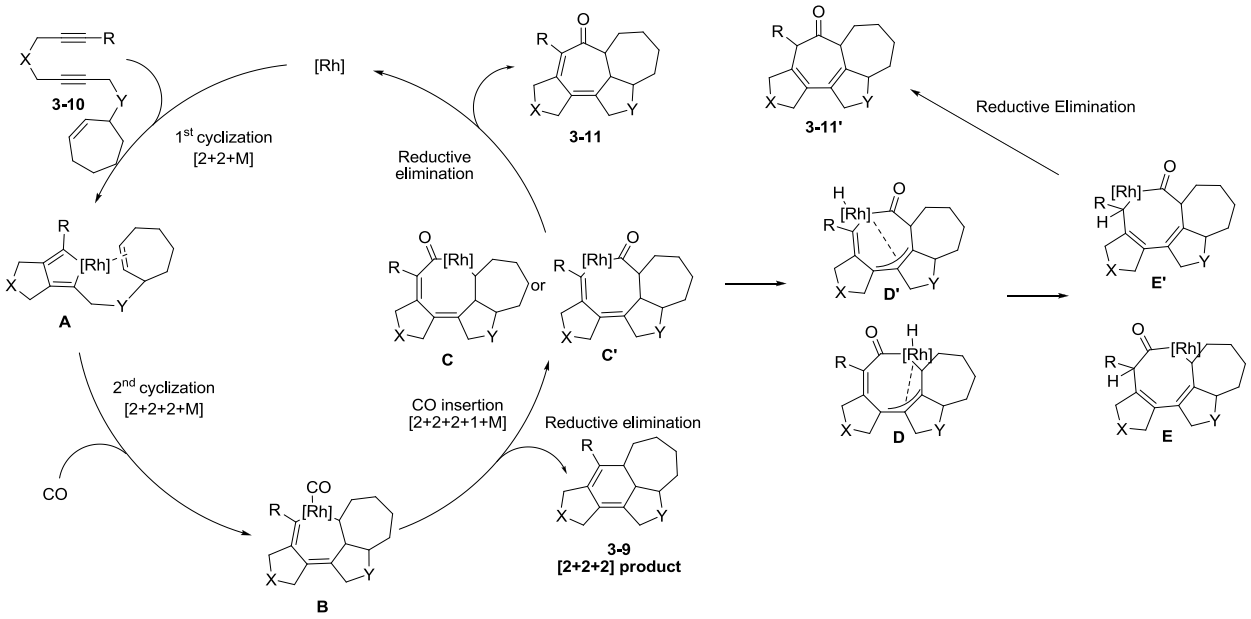
In order to gain insight into the mechanism of isomerization, molecular modeling calculations (MMFF, PM3, and AM1; Wavefunction Inc. Spartan 08, Irvine, CA, 2008) were carried out for the products (**Table 3-3**).

Table 3-3: Molecular modeling calculations for isomerized carbonylated products

					
MMFF	55.0	0	MMFF	66.1	0
AM1	0	33.4	AM1	0	27.2
PM3	0	9.8	PM3	0	19.8
					
MMFF	0	14.8	MMFF	49.7	0
AM1	0	24.6	AM1	1.0	0
PM3	0	8.9	PM3	0	3.0

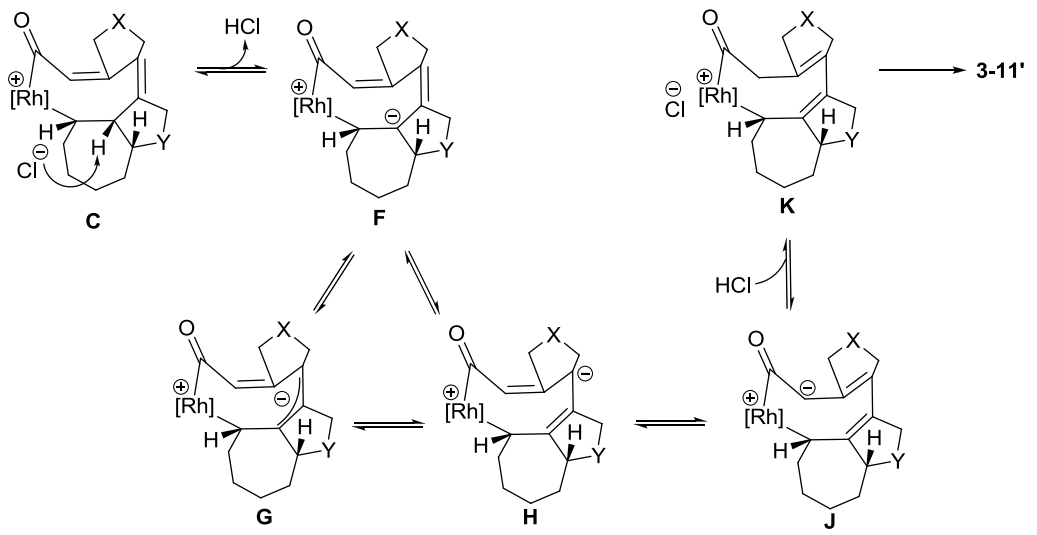
Relative energies (kJ/mol) are reported for each set of isomers

In some cases, the unexpected diene-shifted isomer was lower in energy, but in other cases the expected product was lower in energy. This suggests that the formation of the diene-shifted isomer is not thermodynamic, and the isomerization occurs before the final product is formed. This data is consistent with previous attempts to isomerize cyclohexene-diynes from one isomer to the other.[4] Furthermore, only one [2+2+2] product was observed in all cases. Thus, the isomerization must occur after the formation of intermediate **B**. A mechanism that accounts for the formation of the diene-shifted isomer is illustrated in **Scheme 2-19**. It is possible that Rh-promoted allylic C-H activation of **C** or **C'** could occur to facilitate a 1,5-hydride shift.[6] Isomerization could then occur to form intermediate **E** or **E'**, followed by a reductive elimination to yield the isomerized product **3-11'**.



Scheme 3-19: Proposed mechanism of isomerization *via* C-H activation

Another possible route towards the formation of **3-11'** is the deprotonation of a proton by chloride ion as shown in **Scheme 2-20**. Intermediate **F** can then isomerize to give **G** or **H**. Isomerization of intermediate **H** to **J** can then occur, and a subsequent protonation leads to the formation of intermediate **K**. Intermediate **K** can then undergo a final reductive elimination to yield the isomerized carbonylated product **3-11'**. In this pathway, isomerization occurs from intermediate **C**, while **C'** does not isomerizes in this pathway. If **C** and **C'** are formed in a 1:1 ratio, then this explains the 1:1 product distribution of the two carbonylated isomers.

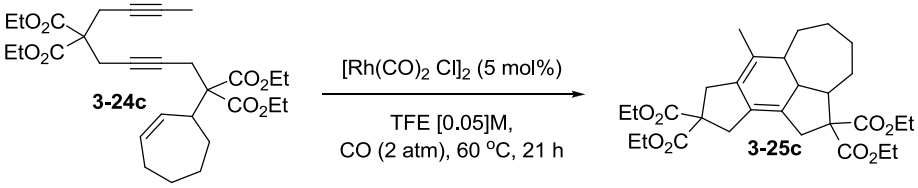
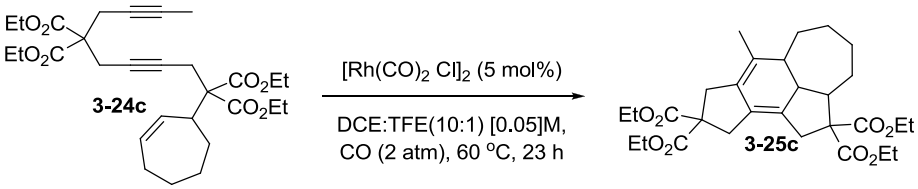
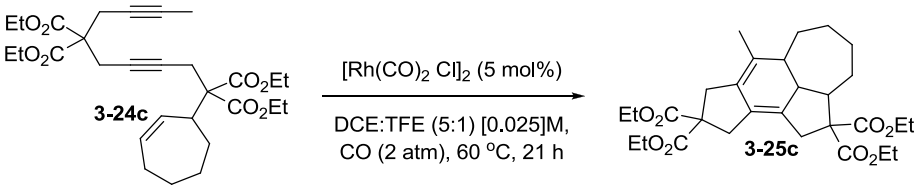


Scheme 3-20: Proposed mechanism of isomerization *via* deprotonation

3.2.4 Optimization of the [2+2+2] Cycloaddition Reaction of Cycloheptene-diynes

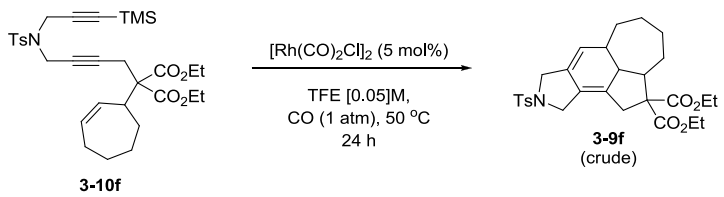
Since excellent selectivity for the [2+2+2] product was observed when the reaction was run in TFE, solvent mixtures of TFE with DCE were studied and the results are summarized in **Table 3-4**. The product was obtained in the highest yield (89%) when a 5:1 mixture of DCE:TFE was used (Entry 3).

Table 3-4: [2+2+2] Cycloaddition of **3-10c**

Entry		Yield (%)
(1)		50
(2)		80
(3)		89

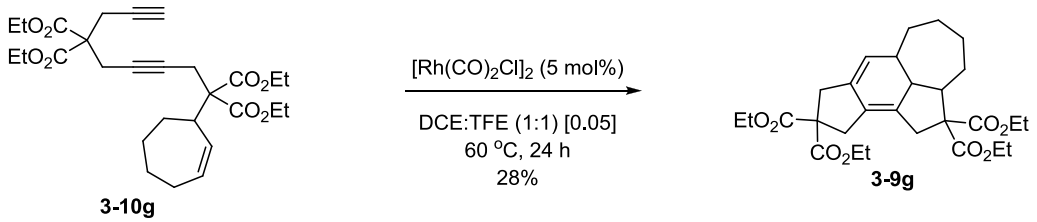
All reactions were run on a 0.07-0.09 mmol scale.

In order to further probe the substrate scope for our cycloaddition reaction, novel silyl-capped enediyne **3-10f** was subjected to the reaction (**Scheme 3-21**). When the reaction was run in pure TFE [0.05]M at 50 ^{o}C under ambient pressure of CO, only the desilylated [2+2+2] product **3-9f** was observed according mass spectroscopy and crude ^{1}H NMR. An explanation for the formation of this product is that the terminal acetylene was deprotected in the presence of TFE, and then the [2+2+2] cycloaddition occurred. Although these conditions did not yield any carbonylated product, this was a promising start for subsequent [2+2+2] studies on similar substrates.



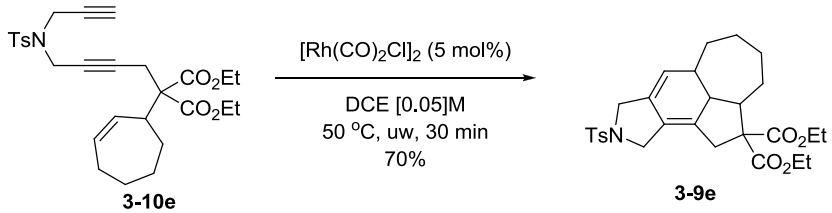
Scheme 2-21: Desilylation and [2+2+2] cycloaddition of **3-10f**

Cycloheptene-diyne **3-10g** bearing a terminal alkyne was subjected to the Rh(I)-catalyzed (2+2+2) reaction under conventional heating in the absence of CO using a mixture of DCE:TFE (1:1), but the 2+2+2 product was obtained in poor yield (28%) (**Scheme 3-22**).



Scheme 3-22: [2+2+2] Cycloaddition of **3-10g**

Higher yield was obtained when the reaction was run in the microwave in DCE at 50 °C. The cyclized product **3-9e** was obtained in 70% yield after 30 min (**Scheme 3-23**).



Scheme 2-23: [2+2+2] Cycloaddition of **3-10e**

3.3 Conclusion

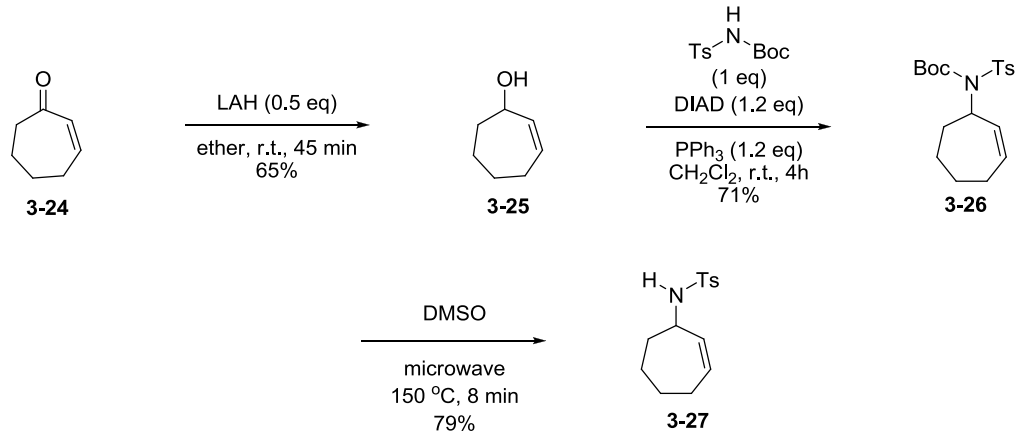
Novel cycloheptene-diyne substrates possessing terminal alkynes, internal alkynes, and silyl caps have been synthesized. The 5-6-7-5 products were obtained *via* the [2+2+2] cycloaddition of cycloheptene-diynes using microwave irradiation in the presence of $[Rh(CO)_2Cl]_2$. Various 5-7-7-5 tetracyclics were also obtained using conventional heating in the presence of the same catalyst and under a CO atmosphere. Isomers of the carbonylated products were obtained. Molecular modeling suggested that the isomerization was not driven by thermodynamics, and occurs at some point before the final products are formed. It is possible that the acyl-[Rh] intermediates are undergoing a 1,5-hydride shift which then allows isomerization to occur. Alternatively, one of the acyl-Rhodium intermediates may be deprotonated by a chloride ion thus allowing isomerization to occur.

3.4 Experimental Section

General Methods: All chemicals were obtained from either Sigma-Aldrich or Acros Organics and used as received unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Solvents were dried under nitrogen using the PURESOLV system (Inovatative Technologies, Newport, MA). All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents and using Fisher silica gel (particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C NMR spectra were obtained using either a 300 MHz Varian Gemini 2300 (75 MHz ^{13}C) spectrometer or a 400 MHz Varian INOVA 400 (100 MHz ^{13}C) spectrometer in $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm and standardized with a solvent as an internal standard based on literature reported values. Melting points were measured with a

Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Shimadzu FTIR-84005 spectrophotometer. Low-resolution mass spectrometry was performed on an Agilent 6890GC/5973 Mass Selective Detector.

***N*-(Cyclohept-2-enyl)-4-methylbenzenesulfonamide (3-27):** [7]



3-24 **3-25** **3-26** **3-27**

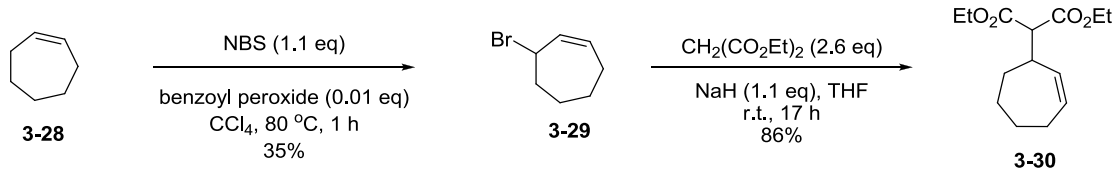
2-cycloheptenone (**3-24**, 3.00 g, 27.2 mmol) in ether (10 mL) was slowly added to a suspension of lithium aluminum hydride (534 mg, 13.6 mmol) in ether (40 mL). The reaction mixture was allowed to stir at room temperature for 45 min. The reaction mixture was quenched with water (5 mL), and neutralized with $MgSO_4$. The reaction mixture was filtered over celite, concentrated over reduced pressure, and purified *via* distillation. The final product **3-25** was obtained (1.98 g, 65% yield) as a clear, colorless liquid; bp 48-50 ^oC at 2 torr; ^1H NMR ($CDCl_3$, 500 MHz) δ1.34-1.37 (m, 1H), 1.56-1.68 (m, 4H), 1.84-1.87 (m, 1H), 1.90-1.84 (m, 1H), 2.02-2.05 (m, 1H), 2.15-2.19 (m, 1H), 4.40 (d, 1H, J = 8.5 Hz), 5.70-5.75 (m, 2H). These values are in agreement with the values reported in the literature.[8]

DIAD (4.5 mL, 21.24 mmol) was added dropwise to a solution of PPh_3 (5.6 g, 21.24 mmol) and Boc-protected sulfonamide (4.79 g, 17.7 mmol) in CH_2Cl_2 (50 mL). The resulting

yellow solution was stirred for 30 min. 2-cycloheptenol (**3-25**, 1.98 g, 17.7 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was allowed to stir at room temperature for 4 hours. The crude reaction mixture was concentrated under reduced pressure and purified *via* column chromatography. The Boc-protected tosylamide **3-26** was obtained (4.6 g, 71% yield) as an off white solid; mp 91-94 ^oC.

The final product **3-27** was obtained *via* a subsequent microwave Boc-deprotection of **3-26** in DMSO (12 mL) as a white solid (2.6 g, 79% yield); mp=84-85 ^oC; NMR ($CDCl_3$, 300 MHz) δ1.34-1.40 (m, 1H), 1.52-1.65 (m, 4H), 1.73-1.85 (m, 2H), 2.02-2.17 (m, 2H), 2.42 (s, 3H), 3.97 (broad s, 1H), 4.51 (d, 1H, *J* = 7.5 Hz), 5.37-5.42 (m, 1H), 5.66-5.75 (m, 1H), 7.31 (d, 2H, *J* = 7.8 Hz), 7.77 (d, 2H, *J* = 8.4 Hz). These values are in agreement with the values reported in the literature.[7]

Diethyl 2-(cyclohept-2-enyl)malonate (3-30):[9]



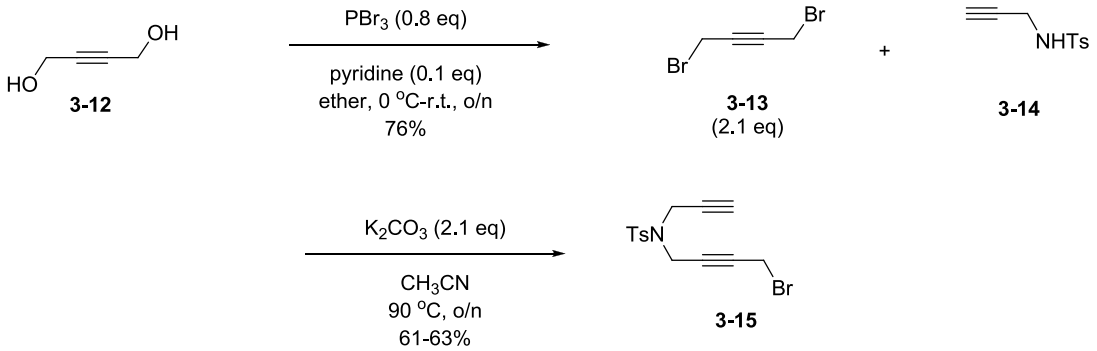
3-28 **3-29** **3-30**

Cycloheptene (**3-28**, 2.43 mL, 18.72 mmol), freshly recrystallized NBS (3.7 g, 20.8 mmol), and benzoyl peroxide (0.050 g, 0.208 mmol) were dissolved in CCl_4 (10 mL) at 80 ^oC. The reaction was allowed to stir for 1 hour, and then brought to 0 ^oC. The reaction mixture was filtered over celite, washing with CH_2Cl_2. The crude mixture was washed with 5% $NaHCO_3$ (aq). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified *via* distillation, and pure bromide **3-29** (1.15 g, 35% yield) was obtained as a clear, colorless liquid[5]; bp 44 ^oC at 2 torr (Lit. bp 42 ^oC (1.7 mmHg); ^1H

NMR ($CDCl_3$, 300 MHz) δ 1.45-1.55 (m, 1H), 1.78-1.90 (m, 2H), 1.95-2.14 (m, 2H), 2.15-2.27 (m, 3H), 4.92-4.97 (m, 1H), 5.81-5.96 (m, 2H). These values are in agreement with the values reported in the literature.[5]

To a suspension of NaH (0.279 g, 6.91 mmol) in THF (10 mL) was added diethyl malonate (2.48 mL, 16.34 mmol) dropwise at 0 ^oC. The suspension was allowed to stir for 15 minutes. 2-cycloheptenebromide (**3-29**, 1.1 g, 6.28 mmol) was added to the mixture all at once. The reaction mixture was allowed to stir over night, and then quenched with water and extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The excess diethyl malonate was distilled off at 45-50 ^oC at 2 torr. The residue was purified *via* column chromatography using 5% ethyl acetate in hexanes as the eluent to yield the final product **3-30** (1.35 g, 86% yield) as a clear, colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz) δ1.23-1.41 (m, 8H), 1.60-1.68 (m, 3H), 1.92-1.94 (m, 1H), 2.11-2.17 (m, 2H), 3.04 (broad s, 1H), 3.43 (d, 1H, J = 8.7 Hz), 4.15-4.24 (m, 4H), 5.64 (dd, 1H, J_1 = 4.8 Hz, J_2 = 4.5 Hz), 5.80-5.84 (m, 1H). These values are in agreement with the values reported in the literature.[9]

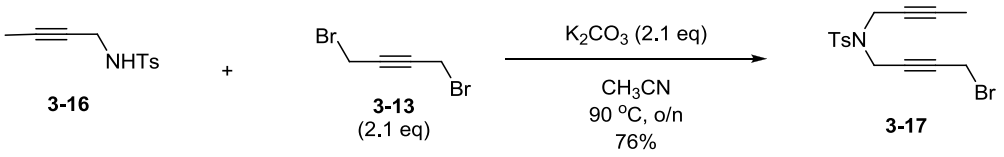
***N*-(4-Bromobut-2-ynyl)-*N*-(prop-2-ynyl)-4-methylbenzenesulfonamide (3-15):[1, 10]**



To a solution of but-2-yne-1,4-diol (**3-12**, 10.0 g, 116.2 mmol), pyridine (0.75 mL, 9.29 mmol), and ether (60 mL) at 0 ^{o}C was added PBr_3 (8.7 mL, 92.9 mmol). The reaction was allowed to warm to room temperature over 21 h. The reaction mixture was quenched with water (100 mL) and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 1,4-dibromobut-2-yne (**3-13**, 18.6 g, 76% yield) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.96 (s, 4H). The product was used without further purification.

To a suspension of K_2CO_3 (4.18 g, 30.21 mmol) and CH_3CN (50 mL) was added *N*-(Prop-2-ynyl)-4-methylbenzenesulfonamide (**3-14**, 3.01 g, 14.38 mmol) at reflux temperature. After the solution was allowed to stir for 15 minutes, 1,4-dibromobut-2-yne (**3-13**, 6.40 g, 30.21 mmol) was added. The reaction was stirred at reflux for 17 h and then filtered over celite and concentrated. The reaction was purified by column chromatography using 10 % ethyl acetate in hexanes as the eluent. The product **3-15** was obtained (3.00 g, 61% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (t, *J* = 2.4 Hz, 1H), 2.43 (s, 3H), 3.71 (t, *J* = 2.4 Hz, 2H), 4.12 (d, *J* = 2.4 Hz, 2H), 4.23 (t, *J* = 1.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz), 2H), 7.73 (d, *J* = 8.4 Hz, 2H). All data are in agreement with those reported in the literature.[1, 10]

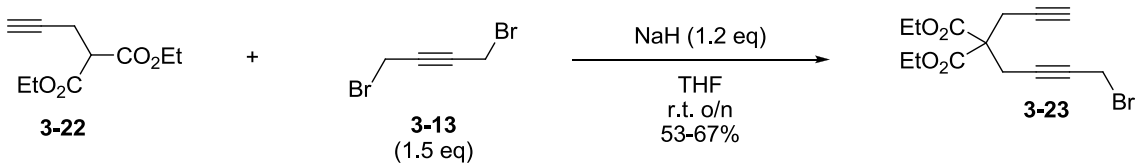
***N*-(4-Bromobut-2-ynyl)-*N*-(but-2-ynyl)-4-Methylbenzenesulfonamide** (**3-17**):[1, 10]



To a suspension of K_2CO_3 (3.61 g, 26.2 mmol) and CH_3CN (75 mL) was added *N*-(But-2-ynyl)-4-methylbenzenesulfonamide (**3-16**, 2.78 g, 12.5 mmol) at reflux temperature. After the solution was allowed to stir for 15 minutes, 1,4-dibromobut-2-yne (**3-13**, 5.29 g, 24.9 mmol) was

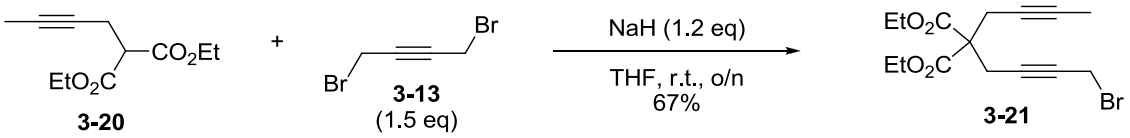
added. The reaction was stirred at reflux for 15 h and then filtered over celite and concentrated. The reaction was purified by column chromatography using 10 % ethyl acetate in hexanes as the eluent. The product **3-17** was obtained (2.30 g, 52% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.67 (t, 3H, *J* = 2.4 Hz), 2.43 (s, 3H), 3.71 (t, 2H, *J* = 2.1 Hz), 4.06 (q, 2H, *J* = 2.1 Hz), 4.20 (t, 2H, *J* = 2.1 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.1 Hz). All data are in agreement with those reported in the literature.[1, 10]

Diethyl 2-(4-bromobut-2-ynyl)-2-(prop-2-ynyl) malonate (3-23):[1, 10]



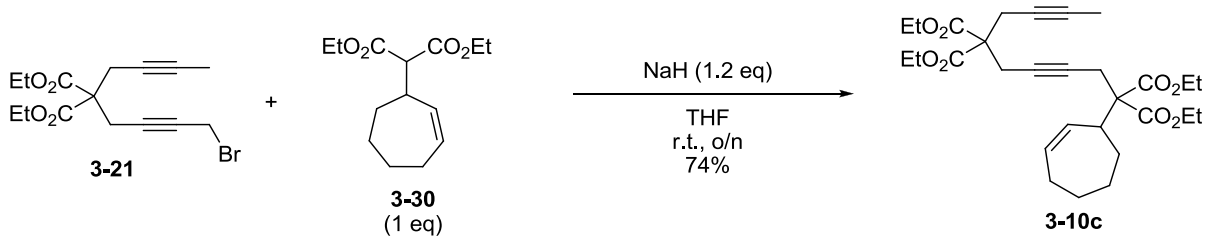
To a suspension of NaH (60% dispersion in mineral oil, 1.21 g, 30.2 mmol) in THF (50 mL) was added diethyl 2-(prop-2-ynyl) malonate (**3-22**, 5.00 g, 25.2 mmol) dropwise. After stirring for 15 minutes, dibromobut-2-yne (**3-13**, 8.02 g, 27.8 mmol) was added all at once. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then quenched with water and extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using 10% ethyl acetate in hexanes as the eluent. The final product **3-23** was obtained as a white solid (3.73 g, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 6 H, *J* = 7.2 Hz), 2.03 (t, 1 H, *J* = 2.4 Hz), 2.96 (d, 2H, *J* = 2.7 Hz), 3.04 (t, 2 H, *J* = 2.7 Hz), 3.86 (t, 2 H, *J* = 2.4 Hz), 4.24 (q, 4 H, *J* = 6.9 Hz). All data are in agreement with those reported in the literature.[1, 10]

Diethyl 2-(4-Bromobut-2-ynyl)-2-(but-2-ynyl)malonate (**3-21**):[1, 10]



To a suspension of NaH (60% dispersion in mineral oil, 0.641 g, 16.0 mmol) in THF (35 mL) was added diethyl 2-(but-2-ynyl)malonate[11] (**3-20**, 2.83 g, 13.4 mmol) dropwise. After stirring for 15 minutes, dibromobut-2-yne (**3-13**, 5.94 g, 28.0 mmol) was added all at once. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then quenched with water and extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using 16% ethyl acetate in hexanes as the eluent. The final product **3-21** was obtained as a colorless viscous oil (3.37 g, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, 6H, *J* = 7.2 Hz), 1.74 (t, 3H, *J* = 1.8 Hz), 2.89 (q, 2H, *J* = 1.8 Hz), 3.01 (t, 2H, *J* = 2.0 Hz), 3.86 (t, 2H, *J* = 2.5 Hz), 4.24 (q, 4H, *J* = 7.2 Hz). All data are in agreement with those reported in the literature.[12]

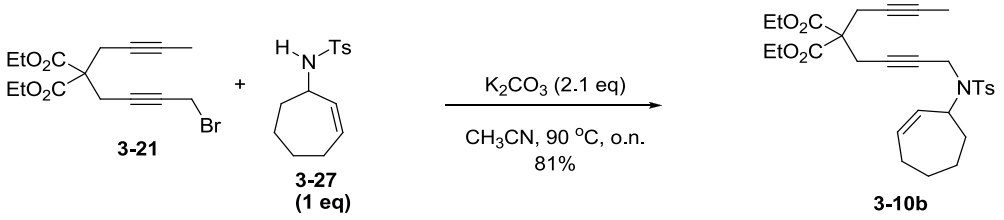
1-(Cyclohept-2-en-1-yl)-1,1,6,6-tetracarbethoxydeca-3,8-diyne (3-10c):



Cycloheptenylmalonate (**3-30**, 0.519 g, 2.04 mmol) in THF (3 mL) was added to a suspension of NaH (60% in mineral oil) (0.098 g, 2.45 mmol) in THF (10 mL). The solution was allowed to stir for 15 min. The diyne bromide (**3-21**, 0.700 g, 2.04 mmol) in THF (3 mL) was

added, and the reaction was allowed to stir over night. The reaction mixture was quenched with water and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified *via* column chromatography, and the final product **3-10c** was obtained (0.780 g, 74% yield) as a clear, colorless, viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.21-1.29 (m, 12H), 1.64-1.73 (m, 5H),1.83-1.86 (m, 1H), 1.99-2.03 (m, 1H), 2.09-2.16 (m, 1H), 2.20-2.26 (m, 1H), 2.78-2.80 (m, 2H), 2.86-2.90 (m, 4H), 3.14-3.18 (m, 1H), 4.15-4.21 (m, 8H), 5.67-5.71 (m, 1H), 5.77-5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 3.41, 13.98, 22.76, 23.45, 26.12, 27.74, 29.77, 31.38, 42.46, 56.69, 60.29, 61.24, 61.64, 73.33, 77.32, 78.47, 78.66, 131.71, 132.93, 169.0, 169.9. HRMS (ES) m/z calcd for $C_{29}H_{40}O_8$ $(M + H)^+$: 517.2796, found 517.2794 (Δ 0.3 ppm).

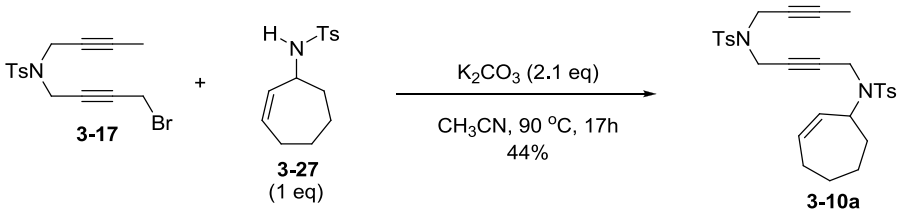
1-Aza-1-(cyclohept-2-en-1-yl)-6,6-dicarbethoxy-1-(4-methylbenzenesulfonyl)nona-3,8-diyne (3-10b):



To a suspension of sulfonamide (**3-27**, 0.541 g, 2.04 mmol) and K_2CO_3 (0.607 g, 4.40 mmol) in acetonitrile (10 mL) at reflux was added diyne bromide (**3-21**, 0.725 g, 2.04 mmol) in acetonitrile (10 mL) after suspension had stirred for 15 minutes. The reaction was allowed to go over night. The crude reaction mixture was filtered over celite, concentrated, and purified *via* column chromatography. The final product **3-10b** was obtained (0.869 g, 81% yield) as a clear, slightly yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.23-1.27 (m, 6H), 1.31-1.33 (m, 1H), 1.45-1.48 (m, 1H), 1.57 (m, 1H), 1.68-1.75 (m, 6H), 1.85-1.88 (m, 1H), 2.04 (m, 1H), 2.17-2.19 (m,

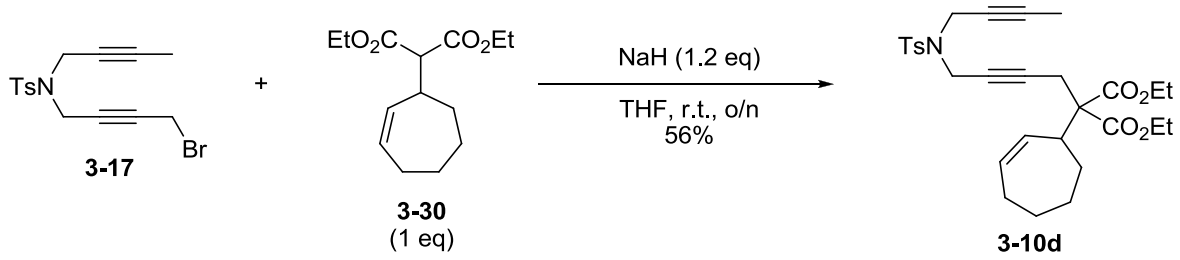
1H), 2.42 (s, 3H), 2.79 (t, 2H, *J* = 2.0 Hz), 2.86 (s, 2H), 3.97-4.15 (m, 2H), 4.16-4.21 (m, 4H), 4.51 (s, 1H), 5.50 (d, 1H, *J* = 11.0 Hz), 5.72-5.76 (m, 1H), 7.30 (d, 2H *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 500 MHz) δ3.452, 14.00, 21.51, 22.80, 22.95, 26.29, 27.54, 28.22, 33.12, 33.54, 56.60, 59.52, 61.75, 73.11, 78.80, 78.86, 79.41, 127.0,127.4, 129.4, 129.6, 132.4, 133.3, 143.0, 169.0. HRMS (ES) m/z calcd for $C_{29}H_{37}NO_6S$ $(M + H)^+$: 528.2408, found 528.2415 (Δ 1.3 ppm).

1-Aza-1-(cyclohept-2-en-1-yl)-4,6-methylbenzenesulfonyl-nona-3,8-diyne (3-10a):



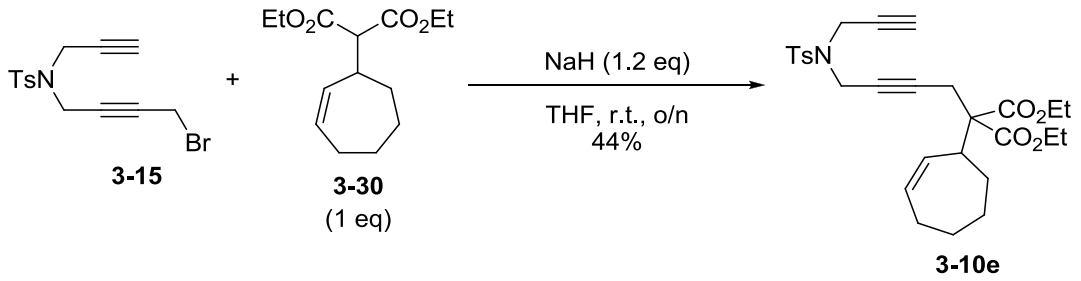
To a suspension of sulfonamide (**3-27**, 0.524 g, 1.98 mmol) and K_2CO_3 (0.575 g, 4.16 mmol) in acetonitrile (10 mL) at reflux was added diyne bromide (**3-17**, 0.700 g, 1.98 mmol) in acetonitrile (5 mL) after suspension had stirred for 15 minutes. The reaction was allowed to proceed at room temperature over night. The crude reaction mixture was filtered over celite, concentrated, and purified *via* column chromatography. The final product **3-10a** was obtained (0.469 g, 44% yield) as a thick, orange oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24-1.31 (m, 1H), 1.43-1.47 (m, 1H), 1.59-1.61 (m, 4H), 1.65-1.69 (m, 2H), 1.81-2.03 (m, 1H), 2.16-2.17 (m, 1H), 2.41 (s, 6H), 3.91-4.00 (m, 6H), 4.52 (d, 1H, *J* = 12.5 Hz), 5.42 (d, 1H, *J* = 14.5 Hz), 5.70-5.74 (m, 1H), 7.27-7.30 (m, 4H), 7.66-7.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 3.300, 21.46, 21.47, 26.20, 27.40, 28.14, 33.05, 33.24, 36.36, 36.64, 59.44, 71.24, 77.32, 81.68, 81.77, 127.2, 127.9, 129.3, 129.5, 132.6, 133.0, 135.3, 137.7, 143.3, 143.6. HRMS (ES) m/z calcd for $C_{29}H_{34}N_2O_4S_2$ $(M + NH_4)^+$: 556.2298, found 556.2296 (Δ 0.4 ppm).

6-Aza-1-(cyclohept-2-en-1-yl)-,1,1-dicarbethoxy-6-(4-methylbenzenesulfonyl)deca-3,8-diyne (3-10d):



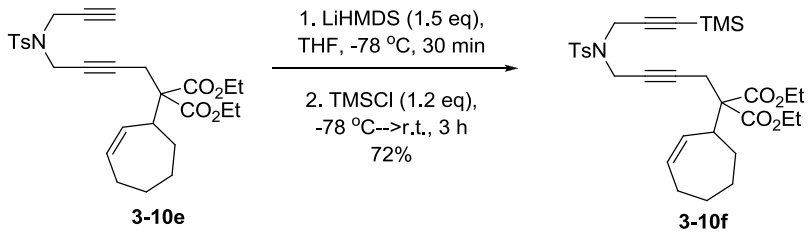
Cycloheptenylmalonate (**3-30**, 0.359 g, 1.41 mmol) in THF (3 mL) was added to a suspension of NaH (60% in mineral oil, 0.0680 g, 2.82 mmol) in THF (7 mL). The solution was allowed to stir for 15 min. The diyne bromide (**3-17**, 0.449 g, 1.27 mmol) was added, and the reaction was allowed to stir over night. The reaction mixture was quenched with water and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified *via* column chromatography, and the final product **3-10d** was obtained (0.628 g, 56% yield) as a clear, yellow, viscous oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.23 (t, 6H, *J* = 9.0 Hz), 1.60 (s, 3H), 1.63-1.64 (m, 3H), 2.12-2.17 (m, 2H), 2.42 (s, 3H), 2.80 (t, 2H, *J* = 2.1 Hz), 3.09-3.14 (m, 1H), 4.15 (d, 2H, *J* = 2.1 Hz), 4.1 (d, 2H, *J* = 1.8 Hz), 4.20 (d, 2H, *J* = 2.1 Hz), 5.63-5.67 (m, 1H), 5.77-5.85 (m, 1H), 7.30 (d, 2H, *J* = 7.8 Hz), 7.70 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 3.495, 14.19. 14.21, 21.65, 23.52, 26.21, 28.02, 29.96, 31.62, 36.65, 36.73, 42.97, 60.42, 61.56, 61.58, 71.66, 75.76, 81.61, 81.81, 128.1, 129.4, 129.5, 132.1, 132.8, 135.7, 143.6, 169.9, 170.0; HRMS (ES) m/z calcd for $C_{29}H_{37}NO_6S$ $(M + H)^+$: 528.2415, found 528.2413 (Δ 0.3 ppm).

1,1-dicarbethoxy-1-(cyclohept-2-en-1-yl)-6-methylbenzenesulfonyl-l-octa-3,8-diyne (3-10e):



To a suspension of sodium hydride (60 % in mineral oil, 0.229 g, 5.72 mmol) in THF (15 mL) was added cycloheptenylmalonate (**3-30**, 1.32 g, 5.20 mmol) in THF (10 mL). After the suspension had stirred for 15 minutes, diyne bromide (**3-15**, 1.77 g, 5.20 mmol) in THF (10 mL) was added all at once. The reaction was allowed to stir at room temperature overnight. The reaction mixture was quenched with water and extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified *via* column chromatography using 10% ethyl acetate in hexanes as the eluent to obtain the pure product **3-10e** (1.18 g, 44% yield) as a yellow liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21–1.27 (m, 6H), 1.59-1.79 (m, 5H), 1.96-2.02 (m, 1H), 2.07-2.17 (m, 3H), 2.42 (s, 3H), 2.71 (t, 2H, *J* = 2.4 Hz), 3.11-3.13 (m, 1H), 4.08 (t, 2H, *J* = 2.1 Hz), 4.14-4.22 (m, 6H), 5.61-5.66 (m, 1H), 5.77-5.83 (m, 1H), 7.31 (d, 2H, *J* = 8.7 Hz), 7.70 (d, 2H, *J* = 8.4 Hz). HRMS (ES) m/z calcd for $C_{28}H_{35}NO_6S$ $(M + H)^+$: 514.2264, found 514.2258 (Δ 1.2 ppm).

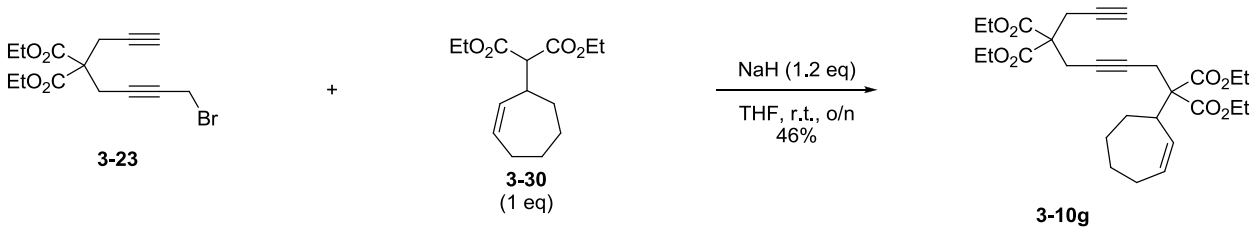
1,1-dicarbethoxy-1-(cyclohept-2-en-1-yl)-6-methylbenzenesulfonyl-9-trimethylsilyl-nona-3,8-diyne (3-10f):



3-10e 3-10f

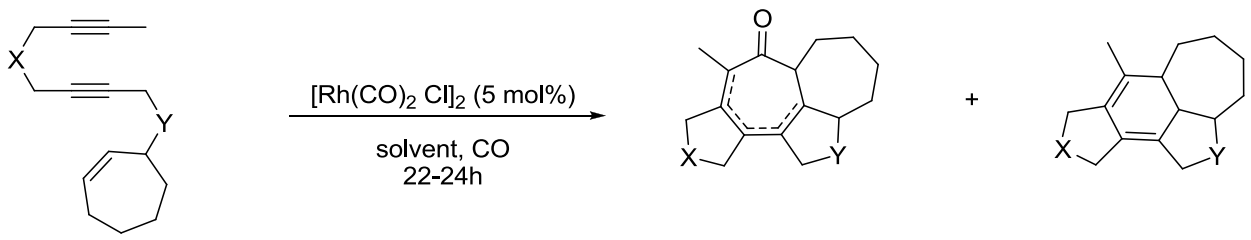
To a solution of cycloheptene-diyne **3-10e** in THF (25 mL) at -78 ^{o}C was added LiHMDS (1.65 mL, 1.65 mmol), and the solution stirred for 30 minutes. TMSCl (0.169 mL, 1.32 mmol) was added, and the reaction stirred an additional 60 min at -78 ^{o}C. The reaction flask was allowed to warm to r.t. and stir for 3 additional hours. The reaction mixture was quenched with solid NH_4Cl and extracted with ether (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by column chromatography using 10% ethyl acetate in hexanes as the eluent to obtain the product **3-10f** (464.0 mg, 72% yield) as a light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ0.017 (s, 9H), 1.12-1.26 (m, 7H), 1.59-1.80 (m, 3H), 1.96-2.16 (m, 3H), 2.40 (s, 1H), 2.72 (t, 2H, *J* = 2.4 Hz), 3.09-3.13 (m, 1H), 4.03-4.04 (m, 2H), 4.14-4.16 (m, 6H), 5.61-5.66 (m, 1H), 5.77-5.83 (m, 1H), 7.29 (d, 2H, *J* = 8.1 Hz), 7.68 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ0.434, 14.04, 21.47, 23.30, 26.00, 27.88, 29.77, 31.46, 36.54, 36.87, 42.83, 60.22, 61.40, 75.41, 81.51, 90.89, 97.53, 127.8, 129.5, 132.0, 132.6, 135.5, 143.5, 169.7, 169.8. HRMS (ES) m/z calcd for $C_{31}H_{43}NO_6SSi$ $(M + H)^+$: 586.2653, found 586.2649 (Δ 0.6 ppm).

1,1-dicarbethoxy-1-(cyclohept-2-en-1-yl)-6,6- dicarbethoxy-nona-3,8-diyne (3-10g):



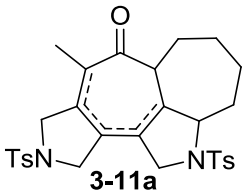
To a suspension of NaH (60% dispersion in mineral oil, 0.242 g, 5.65 mmol) in THF (12 mL) was added diethyl 2-(cyclohept-2-enyl) malonate (**3-30**, 1.40 g, 5.49 mmol) dropwise. After stirring for 15 minutes, diethyl 2-(4-bromobut-2-ynyl)-2-(prop-2-ynyl) malonate (**3-23**, 1.86 g, 5.65 mmol) was added all at once. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then quenched with water and extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel. The final product **3-10g** was obtained as a colorless oil (1.33 g, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ1.13-1.26 (m, 15 H), 1.66-1.73 (m, 2 H), 1.82-1.86 (m, 1 H), 1.98 (t, 1 H, *J* = 2.7 Hz), 2.00-2.20 (m, 2 H), 2.80 (d, 2 H, *J* = 1.5 Hz), 2.92-2.93 (m, 2 H), 2.97 (d, 2 H, *J* = 3.0 Hz), 3.15-3.17 (m, 1 H), 4.16-4.25 (m, 8 H), 5.67-5.73 (m, 1 H), 5.78-5.85 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ14.0, 22.4, 22.8, 23.5, 26.1, 27.8, 29.8, 31.4, 42.5, 56.4, 60.3, 61.3, 71.3, 77.3, 78.8, 78.9, 131.8, 132.9, 168.7, 169.9. HRMS (ES) m/z calcd for $C_{28}H_{38}O_8$ $(M + H)^+$: 503.2640, found 503.2638 (Δ 0.4 ppm).

[2+2+2+1] Cycloaddition:



Typical procedure for [2+2+2+1] Cycloaddition: Substrate in a desired solvent and a rhodium catalyst were combined in a reaction flask. The flask was transferred to an autoclave and purged with CO and released (4x). **Caution: Purging with CO must be done in a well ventilated fume hood.** The autoclave was then purged to the desired pressure of CO. The autoclave was immersed in an oil bath at the desired temperature for 20-49 h, and then cooled to room temperature. The gas was released carefully from the autoclave in a well ventilated fume hood, and the reaction flask was taken out. The mixture was concentrated and analyzed *via* HPLC and NMR. The crude reaction mixture was purified *via* column chromatography.

7-Methyl-4,15-bis(4-methylbenzenesulfonyl)-4,15-diazatetracyclo[7.7.1.0^{1,6}.0^{14,17}]hepta-deca-1,6-dien-8-one and 7-methyl-4,15-bis(4-methylbenzenesulfonyl)-4,15-diazatetracyclo [7.7.1.0^{2,6}.0^{14,17}]heptadeca-1(17),2(6)-dien-8-one (3-11a):

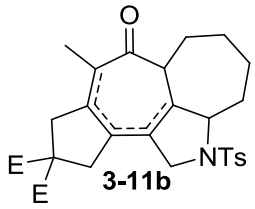


3-11a

Clear colorless oil, (37.9 mg, 55%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.924 (t, 1H, *J* = 4.0 Hz), 1.14 (d, 2H, *J* = 7.2 Hz), 1.25 (s, 1H), 1.34-1.47 (m, 4H), 1.56-1.63 (m, 2H), 1.68 (s, 2H), 1.73-1.89

(m, 5H), 2.03 (s, 1H), 2.18 (s, 2H), 2.42 (s, 6H), 2.48 (s, 2H), 2.79-2.81 (m, 1H), 2.87-2.88 (m, 1H), 2.97-2.99 (m, 1H), 3.16-3.23 (m, 1H), 3.33-3.34 (m, 1H), 3.42-3.47 (m, 1H), 3.61-3.73 (m, 2H), 3.80-3.89 (m, 2H), 4.04-4.14 (m, 5H), 4.58-4.59 (m, 1H), 6.94 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 3H, *J* = 8.0 Hz), 7.43 (t, 2H, *J* = 7.6 Hz), 7.67-7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ11.79, 16.53, 19.24, 21.34, 21.60, 21.63, 21.68, 21.71, 22.64, 24.58, 28.22, 28.25, 29.76, 34.20, 35.48, 38.86, 47.11, 50.87, 51.34, 51.83, 52.07, 52.14, 52.47, 55.05, 55.13, 55.43, 61.35, 64.49, 69.24, 125.6, 125.8, 126.7, 127.2, 127.2, 127.5, 127,7, 128.1, 129.8, 130.0, 130.1, 130.2, 132.1, 132.2, 133.4, 133.9, 134.1, 134.3, 134.6, 135.1, 141.0, 143.6, 143.9, 144.0, 144.5, 202.4, 205.8. HRMS (ES) m/z calcd for $C_{30}H_{34}N_2O_5S_2$ $(M + NH_4)^+$: 584.2247, found 584.2235 (Δ 2.1 ppm).

4,4-Diethyl 7-methyl-15-(4-methylbenzenesulfonyl)-8-oxo-15-azatetracyclo[7.7.1.0^{2,6}.0^{14,17}] heptadeca-1,6-diene-4,4-dicarboxylate and 4,4-diethyl 7-methyl-15-(4-methylbenzenesulfonyl)-8-oxo-15-azatetracyclo[7.7.1.0^{2,6}.0^{14,17}]heptadeca-1(17),2(6)-diene-4,4-dicarboxylate (3-11b):

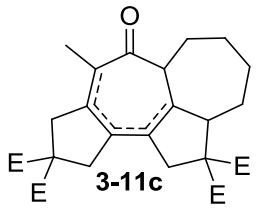


3-11b

Clear colorless oil, (35.5 mg, 68%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.927 (t, 1H, *J* = 6.0 Hz), 1.13- 1.19 (m, 2H), 1.25 (s, 3H), 1.34-1.61 (m, 6H), 1.68 (s, 2H), 1.75-1.89 (m, 6H), 2.04 (s, 1H), 2.18 (s, 2H), 2.38-2.48 (m, 10H), 2.79-2.88 (m, 1H), 3.19-3.21 (m, 1H), 3.35-3.45 (m, 2H), 3.62-3.73 (m, 2H), 3.80-3.86 (m, 2H), 4.04-4.14 (m, 3H), 6.95 (d, 1H, *J* = 6.0 Hz), 7.31-7.35 (m, 4H), 7.43 (t, 2H, *J* = 7.6 Hz), 7.67-7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ12.04, 14.11,

14.15, 14.17, 16.51, 21.54, 21.66, 22.50, 23.47, 24.05, 24.69, 24.81, 28.33, 28.38, 29.27, 30.21, 30.77, 34.39, 35.95, 36.77, 39.15, 39.21, 40.57, 41.07, 41.23, 48.21, 51.56, 51.66, 52.12, 52.36, 55.91, 57.20, 58.14, 61.87, 61.99, 62.02, 62.04, 62.05, 67.83, 69.31, 127.5, 127.8, 128.1, 128.8, 129.8, 130.0, 132.7, 134.6, 134.8, 135.3, 137.0, 139.5, 143.5, 143.8, 170.7, 171.1, 171.4, 171.7, 203.8, 206.9; HRMS (ES) m/z calcd for $C_{30}H_{37}NO_7S$ $(M + H)^+$: 556.2364, found 556.2354 (Δ 1.76 ppm).

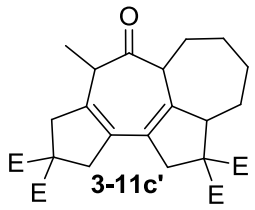
4,4,15,15-Tetraethyl 7-methyl-8-oxotetracyclo[7.7.1.$0^{2,6}$.$0^{14,17}$]heptadeca-1,6-diene-4,4,15,15-tetracarboxylate and 4,4,15,15-tetraethyl 7-methyl-8-oxotetracyclo[7.7.1.$0^{2,6}$.$0^{14,17}$]heptadeca-1(17),2(6)-diene-4,4,15,15-tetracarboxylate (3-11c):



3-11c

Light yellow oil, (41.8 mg, 50%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.21-1.27 (m, 14 H), 1.73-1.76 (m, 2H), 1.92-2.01 (m, 2H), 2.14 (s, 1H), 2.23-2.30 (m, 1H), 2.51-2.67 (m, 1H), 2.92-2.99 (M, 1H), 3.09-3.21 (m, 1H), 3.46-3.51 (m, 1H), 4.13-4.23 (m, 8H) ; ^{13}C NMR ($CDCl_3$, 500 MHz) δ13.72, 13.86, 13.91, 13.99, 14.03, 14.08, 14.09, 14.14, 14.17, 16.14, 17.40, 26.49, 27.74, 28.38, 29.70, 30.29, 36.91, 39.28, 47.05, 48.23, 48.46, 49.84, 55.93, 59.75, 61.23, 61.35, 61.38, 61.52, 61.54, 61.59, 61.63, 61.68, 61.76, 61.83, 61.88, 61.97, 62.02, 62.05, 62.09, 62.15, 62.17, 62.25, 62.27, 62.32, 70.65, 71.40, 128.3, 130.4, 130.7, 134.3, 136.6, 138.6, 138.9, 149.0, 149.5, 170.1, 170.6, 170.8, 170.9, 171.1, 171.4, 199.5, 205.2; HRMS (ES) m/z calcd for $C_{30}H_{40}O_9$ (M - H): 543.2599, found 543.2590 (Δ 1.70 ppm).

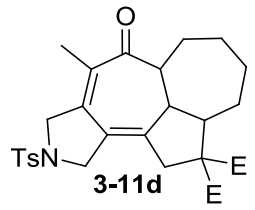
4,4,15,15-Tetraethyl 7-methyl-8-oxotetracyclo[7.7.1.$0^{2,6}$.$0^{14,17}$]heptadeca-1(17),2(6)-diene-4,4,15,15-tetracarboxylate (3-11c'):



3-11c'

Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.23-1.27 (m, 13H), 1.33-1.46 (m, 3H), 1.60-1.65 (m, 1H), 1.88 (s, 3H), 2.05-2.06 (m, 1H), 2.25-2.31 (m, 1H) 2.58-2.63 (m, 1H), 2.80-2.85 (m, 1H), 2.90-2.96 (m, 2H), 3.06 (s, 1H), 3.13-3.17 (m, 1H), 4.15-4.22 (m, 8H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ14.10, 14.16, 14.28, 17.69, 25.33, 26.67, 29.97, 30.66, 39.83, 39.96, 41.08, 47.25, 51.65, 54.47, 57.30, 60.22, 61.62, 61.64, 61.92, 127.3, 129.9, 138.4, 142.2, 170.7, 171.0, 171.3, 204.2; HRMS (ES) m/z calcd for $C_{30}H_{40}O_9$ (M - H): 543.2599, found 543.2590 (Δ 1.70 ppm).

15,15-Diethyl 7-methyl-4-(4-methylbenzenesulfonyl)-8-oxo-4-azatetracyclo[7.7.1.$0^{2,6}$.$0^{14,17}$] heptadeca-1,6-diene-15,15-dicarboxylate (3-11d):

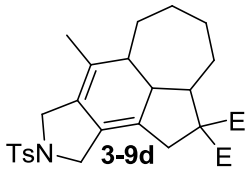


3-11d

Yellow oil, (34.4 mg, 51%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.22-1.30 (m, 10H), 1.78 (s, 3H), 1.87-1.94 (m, 2H), 2.04-2.09 (m, 1H), 2.14-2.20 (m, 1H), 2.44 (s, 3H), 2.75 (t, 1H, *J* = 9.2 Hz),

2.85-2.89 (m, 1H), 3.07-3.12 (m, 1H), 3.72-3.77 (m, 1H), 3.88-3.92 (m, 1H), 4.08-4.08 (m, 1H), 4.17-4.23 (m, 4H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ14.21, 14.26, 17.18, 21.67, 25.10, 26.26, 29.90, 30.88, 39.37, 47.05, 51.70, 52.46, 53.54, 53.90, 60.02, 61.84, 124.0, 127.9, 129.4, 130.1, 132.8, 138.3, 139.1, 144.2, 170.5, 171.2, 202.9; HRMS (ES) m/z calcd for $C_{30}H_{37}NO_7S$ $(M + H)^+$: 556.2364, found 556.2358 (Δ 1.0 ppm).

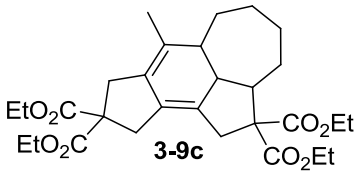
3,3-Diethyl 10-methyl-13-(4-methylbenzenesulfonyl)-13-azatetracyclo[7.6.1.0^{4,16}.0^{11,15}] hexadeca-1(15),10-diene-3,3-dicarboxylate (3-9d):



3-9d

Clear colorless oil, (19.1 mg, 41%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.19-1.27 (m, 11H), 1.31-1.47 (m, 4H), 1.63 (s, 3H), 1.71-1.84 (m, 2H), 1.97-2.02 (m, 1H), 2.17-2.29 (m, 3H), 2.41 (s, 1H), 2.43 (s, 3H), 2.80-3.18 (m, 3H), 3.77-3.96 (m, 4H), 4.14-4.24 (m, 4H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ14.03, 18.05, 21.49, 27.17, 29.79, 32.22, 43.72, 45.99, 51.46, 60.19, 61.26, 122.7, 124.9, 125.2, 126.7, 127.7, 129.7, 133.1, 143.5, 170.9, 171.7; HRMS (ES) m/z calcd for $C_{29}H_{37}NO_6S$ $(M + H)^+$: 528.2415, found 528.2412 (Δ 0.52 ppm).

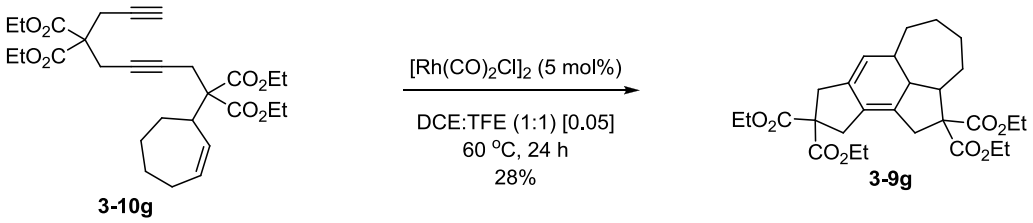
3,3,13,13-Tetraethyl 10-methyltetracyclo[7.6.1.0^{4,16}.0^{11,15}]hexadeca-1(15),10-diene-3,3,13,13-tetracarboxylate (3-9c):



Clear colorless oil, (37.1 mg, 89%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.07-1.19 (m, 1H), 1.20-1.29 (m, 14H), 1.43-1.54 (m, 1H), 1.68 (s, 3H), 1.70-1.74 (m, 1H), 1.78-1.81 (m, 2H), 2.03-2.16 (m, 2H), 2.33-2.39 (m, 2H), 2.60-2.65 (m, 1H), 2.71-2.88 (m, 2H), 2.99-3.10 (m, 3H), 4.11-4.22 (m, 8H). ^{1}H NMR ($CDCl_3$, 500 MHz) δ14.0, 14.1, 25.2, 27.4, 31.3, 31.8, 37.8, 40.9, 41.7, 47.1, 53.7, 58.2, 60.9, 61.1, 61.4, 61.5, 121.7, 130.8, 131.2, 133.5, 171.9, 172.1, 172.3; HRMS (ES) m/z calcd for $C_{29}H_{40}O_8$ $(M - H)^+$: 515.2650, found 515.2623 (Δ 5.3 ppm).

[2+2+2] Cycloaddition:

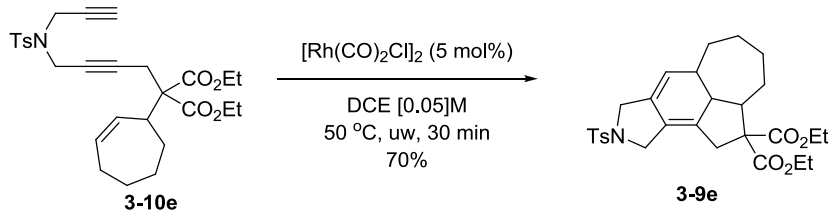
3,3,13,13-Tetraethyl tetracyclo[7.6.1.0^{4,16}.0^{11,15}]hexadeca-1(15),10-diene-3,3,13,13-tetracarboxylate (3-9g):



A round-bottomed flask was charged with substrate **3-10g** (83.0 mg, 0.165 mmol), DCE:TFE (1:1) (3.4 mL), and $[Rh(CO)_2Cl]_2$ (3.19 mg, 0.00820 mmol). The reaction mixture was heated at 60 ^{o}C for 24 h. The mixture was concentrated purified *via* preparatory reverse phase HPLC to yield the product **3-9g** as a colorless oil (23.0 mg, 28% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.21-1.33 (m, 16H), 1.74 (q, 1H, *J* = 13.0 Hz), 1.88 (d, 1H, *J* = 13.0 Hz), 1.93 – 2.00 (m, 1H), 2.06 – 2.10 (m, 1H), 2.67-2.71 (m, 1H), 2.76-2.78 (m, 1H), 3.25 (d, 1H, *J* = 17.0 Hz), 3.47-

3.58 (m, 4H), 3.75 (d, 1H, *J* = 17.0 Hz), 4.11 (d, 1H, *J* = 11.5 Hz), 4.15-4.28 (m, 8H), 6.79 (s, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ13.99, 14.09, 28.06, 30.16, 31.27, 36.03, 38.75, 38.85, 40.34, 51.76, 60.50, 61.28, 61.53, 61.64, 64.26, 123.0, 132.8, 134.6, 138.9, 139.0, 142.8, 170.8, 171.8, 172.2; HRMS (ES) m/z calcd for $C_{28}H_{38}O_8$ $(M - H)^+$: 501.2494, found 501.2481 (Δ 2.6 ppm).

3,3-Diethyl 13-(4-methylbenzenesulfonyl)-13-azatetracyclo[7.6.1.0^{4,16}.0^{11,15}]hexadeca-1(15),10-diene-3,3-dicarboxylate (3-9e):



3-10e **3-9e**

A microwave reaction vial was charged with substrate **3-10e** (31.4 mg, 0.0611 mmol), DCE (1.2 mL), and $[Rh(CO)_2Cl]_2$ (1.10 mg, 0.00290 mmol). The reaction mixture was heated at 50 °C for 30 min. The mixture was concentrated purified *via* column chromatography on silica gel to yield the product **3-9e** as a colorless oil (20.4 mg, 70% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.22-1.28 (m, 6H), 1.81-1.85 (m, 1H), 1.96-2.00 (m, 1H), 2.04 (s, 1H), 2.17-2.23 (m, 2H), 2.40-2.43 (m, 4H), 2.84-3.03 (m, 2H), 3.83-3.99 (m, 4H), 4.16-4.22 (m, 4H), 5.09 (s, 1H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.70 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) δ14.2, 21.5, 30.1, 32.0, 36.1, 37.8, 44.9, 49.6, 51.1, 51.4, 59.8, 61.3, 61.4, 122.7, 127.4, 127.8, 129.7, 130.7, 132.9, 143.6, 171.1, 171.7. HRMS (ES) m/z calcd for $C_{28}H_{35}NO_6S$ $(M + H)^+$: 514.2258, found 514.2256 (Δ 0.3 ppm).

3.5 References

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Chapter 4

Synthesis of Colchicinoids and Allocolchicinoids *via* Rh(I)-Catalyzed [2+2+2+1] and [2+2+2] Cycloaddition Reactions

Table of Contents

4.1 Introduction to the Synthesis of Colchicinoids and Allocolchicinoids

Colchicine is an alkaloid natural product isolated from the meadow saffron (*Colchicum autumnale* L.). It has been used to treat acute gout and familial Mediterranean fever.[1] Colchicine also binds to tubilin and acts as an antimitotic agent by inducing microtubial depolymerization. Allocolchicine is a derivative of colchicine not found in nature that possesses a benzene ring instead of a tropolone moiety (**Figure 4-1**).[2] Allocolchicine derivatives have shown promising anticancer activity, and the benzene moiety is less reactive than the tropolone moiety.[2] These anticancer properties make colchicine and its derivatives attractive synthetic targets.

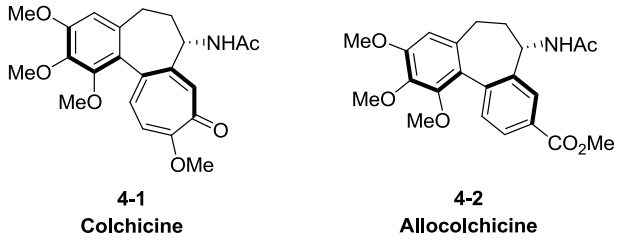


Figure 4-1: Colchicine and Allocolchicine

A number of syntheses towards colchicines and its derivatives have been reported. The unusual 6-7-7-membered ring system possessing a tropolone moiety is one of the main challenges in the synthesis of colchicines.[1] Examples of colchicine core syntheses are illustrated in **Figure 4-2**.

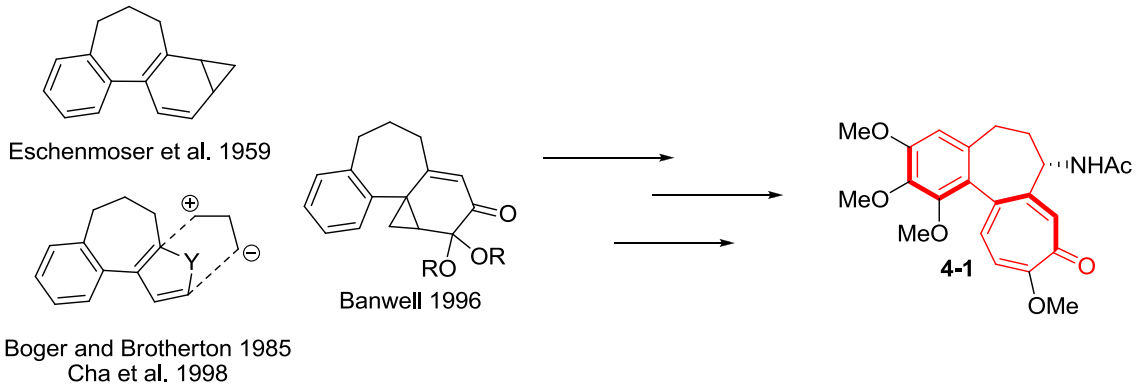
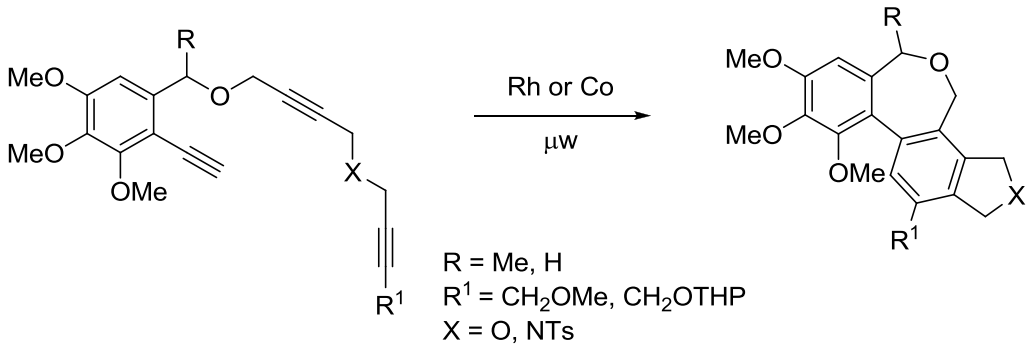


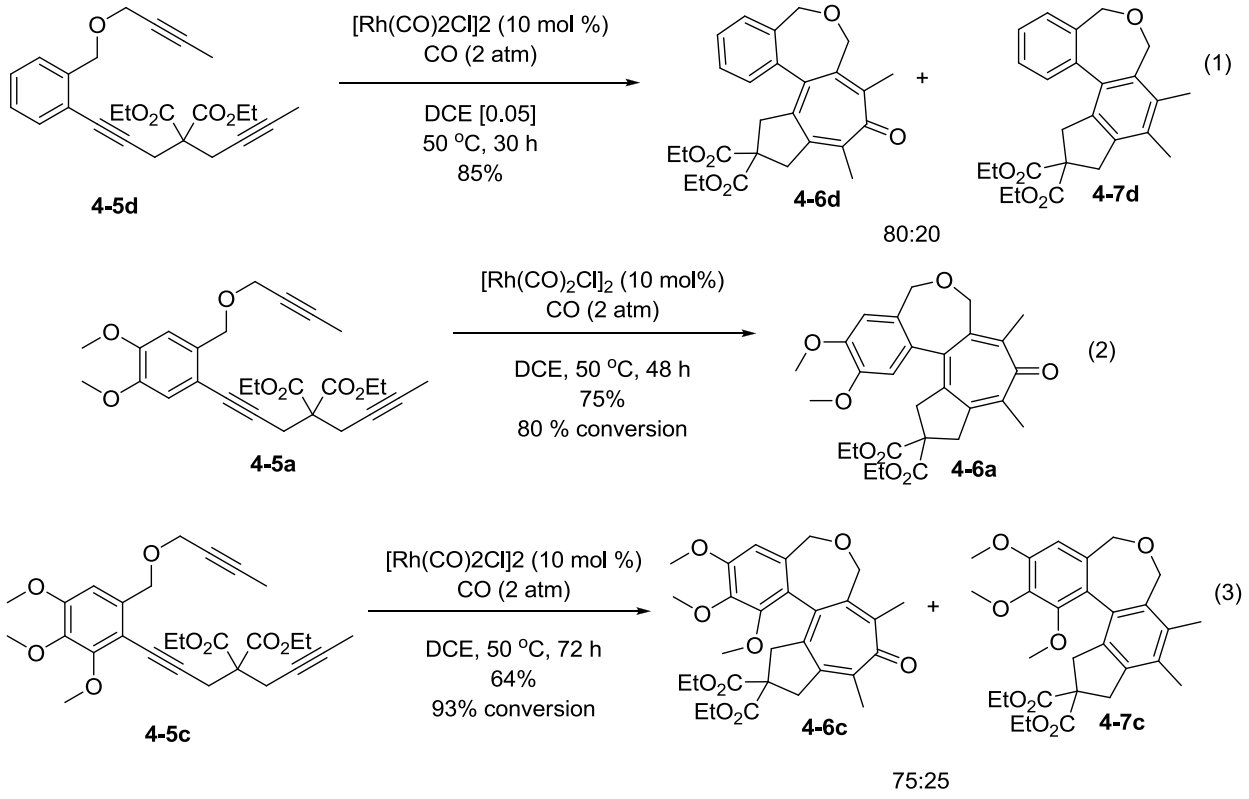
Figure 4-2. Colchicine core syntheses

Recently, Nicolaus *et al.* reported a straightforward approach towards the synthesis of allocolchicine derivatives bearing a 6-7-6-5 tetracyclic core.[2] Their approach involves the [2+2+2] Co- or Rh-catalyzed intramolecular cycloaddition reaction. The transformation was completed using microwave irradiation with up to 90% yield of the final tetracyclic product (**Scheme 4-1**).



Scheme 4-1: Microwave-promoted [2+2+2] cycloaddition of triynes to form novel tetracyclics

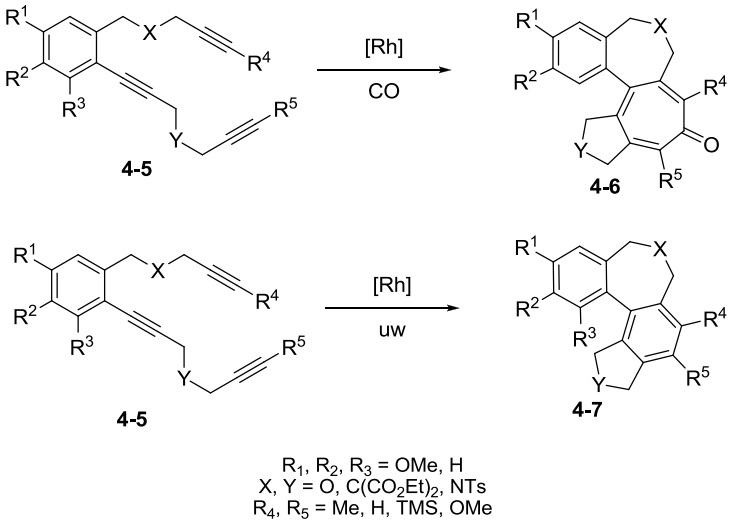
Inspired by this report, we would like to synthesize new classes of colchicine and allocolchicine derivatives. We have previously synthesized 6-7-7-5 and 6-7-6-5 tetracyclics can *via* our previously developed Rh(I)-catalyzed [2+2+2+1] and [2+2+2] cycloaddition reactions, respectively. A novel class of triynes was developed in our laboratory, and the pioneering results are shown in **Scheme 4-2.**[3]



Scheme 4-2: Previous studies on the [2+2+2+1] and [2+2+2] cycloadditions of triynes[3]

Triyne substrates were synthesized with different numbers of methoxy groups on the benzene ring. For triyne **4-5d** bearing no methoxy groups (**Scheme 4-2**, Eq.1), the two tetracyclic products were obtained in a combined yield of 85% and an isolated ratio of 80:20. For the dimethoxy tiryne **4-5a**, the carbonylated product was obtained exclusively in 75% yield, and 80% conversion was achieved after 48 hours. For the trimethoxy substrate **4-5c**, the products were obtained in 64% isolated yield in a 75:25 isolated ratio, and 93% conversion was achieved after 72 hours.[3]

Further cycloaddition reaction condition optimization as well as expansion of the substrate scope are reported herein (**Scheme 4-3**).

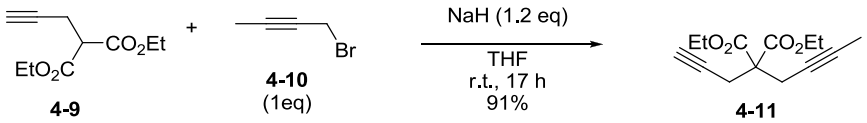


Scheme 4-3: Formation of novel 6-7-7-5 and 6-7-6-5 tetracyclics

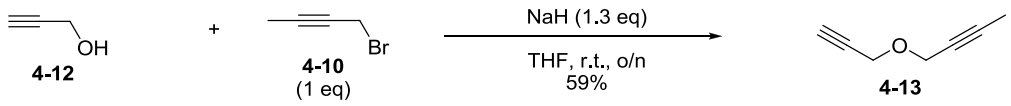
4.2 Results and Discussion

4.2.1 Substrate Synthesis

Two triynes were synthesized to be subjected to the Rh(I)-catalyzed [2+2+2+1] and [2+2+2] cycloaddition reactions. The diyne portion with the malonate tether (**4-11**) was synthesized *via* a sodium hydride-mediated coupling of propargyl malonate **4-9** and 2-butynl bromide (**4-10**) in 91% yield (**Scheme 4-4**). The ether diyne **4-13** was synthesized *via* a similar coupling of propargyl alcohol (**4-12**) and 2-butynyl bromide (**4-10**) (**Scheme 4-5**).

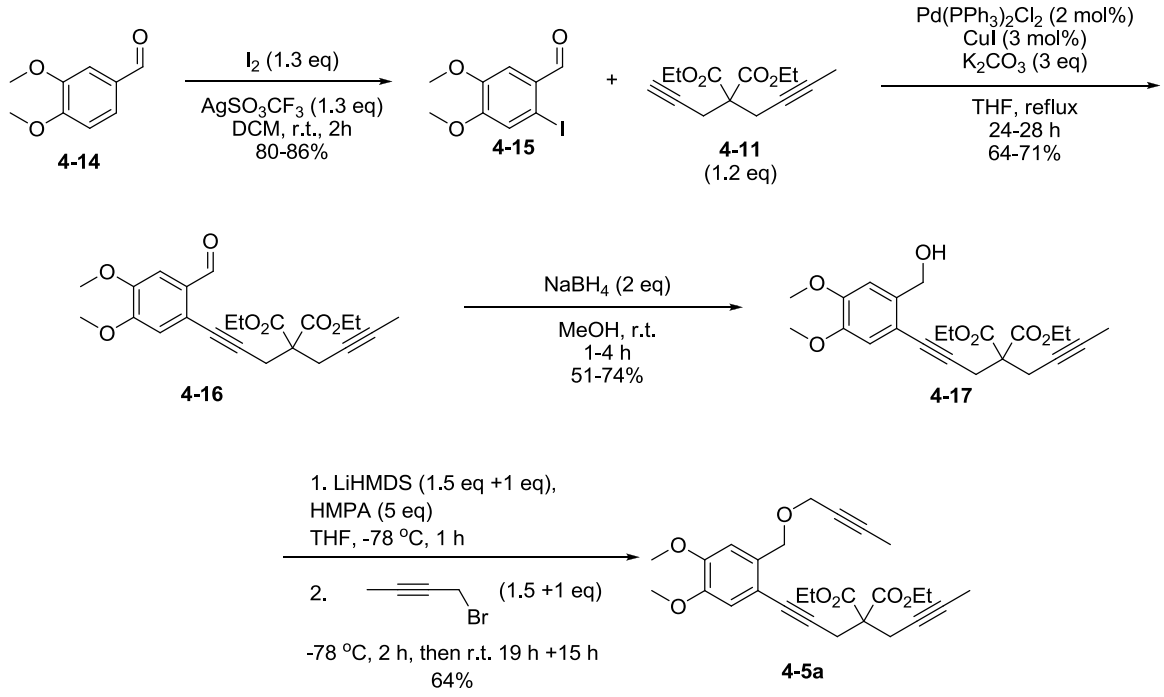


Scheme 4-4: Synthesis of diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate **4-11**

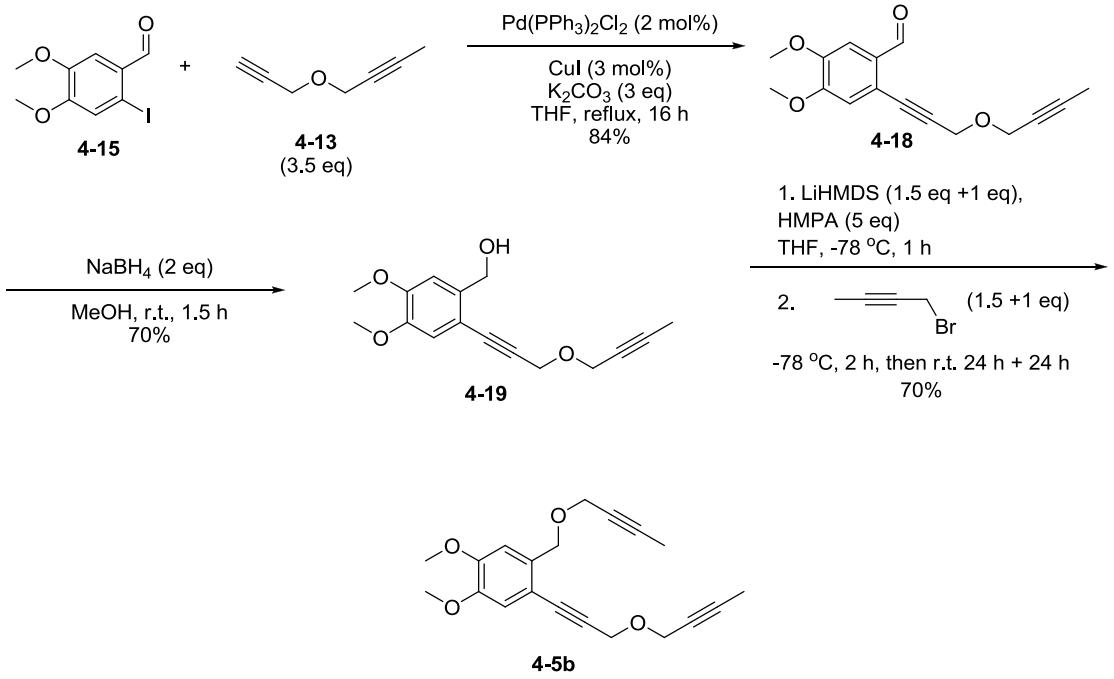


Scheme 4-5: Synthesis of 1-(prop-2-ynyloxy)but-2-yne **4-13**

In order to complete the triyne synthesis, 3,4-dimethoxybenzaldehyde (**4-14**) was treated with iodine and silver trifluoromethanesulfonate in DCM at room temperature for 2 h to form 2-iodo-4,5-dimethoxybenzaldehyde (**4-15**) in good yield. The iodide **4-15** was subjected to the Sonogashira reaction with diyne **4-11** in the presence of $Pd(PPh_3)_2Cl_2$, copper(I) iodide, and potassium carbonate in THF at reflux temperature to form diyne **4-16** in moderate yield. The aldehyde **3-16** was then reduced in the presence of sodium borohydride to afford the corresponding alcohol **4-17** in up to 74% yield. The alcohol **4-17** was coupled with 2-butynyl bromide in the presence of LiHMDS, and the final substrate **4-5a** was obtained (**Scheme 4-6**). Triyne **4-10b** was obtained *via* similar procedures (**Scheme 4-7**).



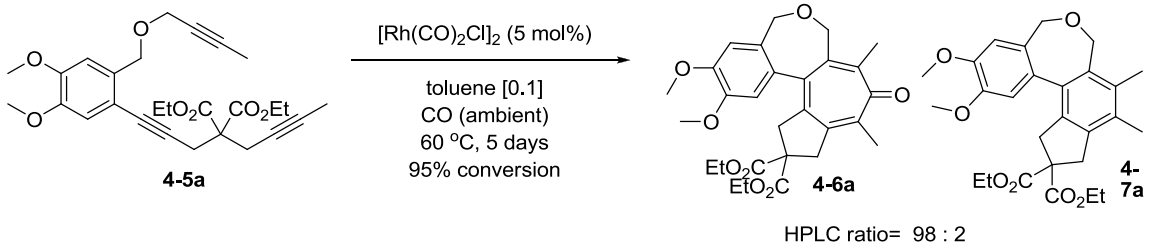
Scheme 4-6: Synthesis of triyne **4-5a**



Scheme 4-7: Synthesis of triyne **4-5b**

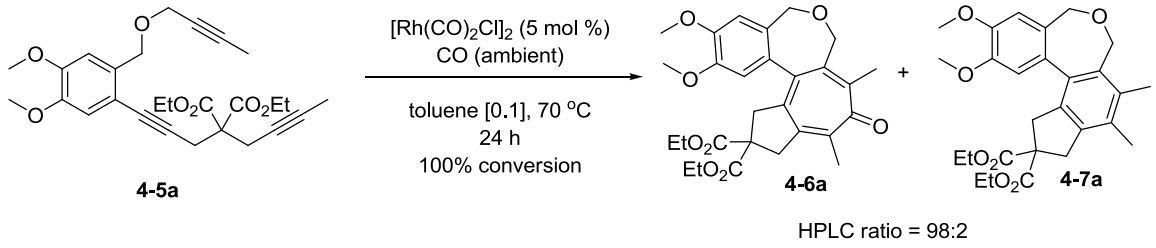
4.2.2 Optimization of the [2+2+2+1] Cycloaddition of Triynes

Triyne **4-5a** was then subjected to the Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. The reaction was run under ambient pressure of CO in toluene at 60 ^{o}C. After 5 days, complete conversion was not achieved. However, excellent selectivity towards the carbonylated product was observed according to HPLC (**Scheme 4-8**).



Scheme 4-8: Rh(I)-catalyzed [2+2+2+1] cycloaddition of triyne **4-5a**

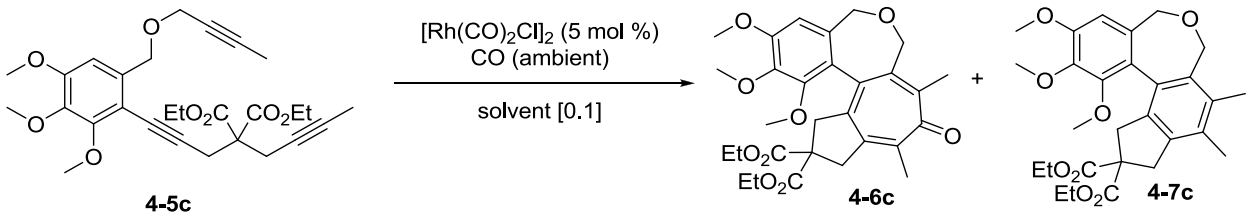
In order to improve the conversion of this reaction, the temperature was raised from 60 ^{o}C to 70 ^{o}C. Complete conversion was achieved after 24 h, and the excellent selectivity was retained (**Scheme 4-9**).



Scheme 4-9: Further optimization of Rh(I)-catalyzed [2+2+2+1] cycloaddition of triyne **4-5a**

For substrates bearing 3 methoxy groups on the benzene ring, it was shown that using K10 as an additive sped up the rate of the reaction without sacrificing the product selectivity. The reaction time also decreased at lower temperatures compared with when no K10 was used. (**Table 4-1**).

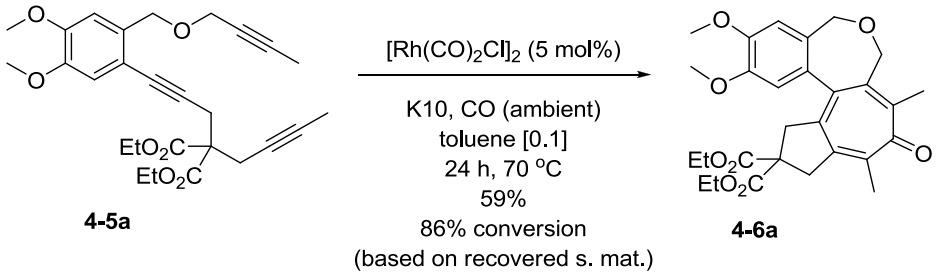
Table 4-1: Optimization of [2+2+2+1] cycloaddition of **4-5c***



Entry	Solvent, Additive	Temperature (^{o}C)	Time (h)	Conversion (%)	Product Selectivity (**4:6c:4:7c**)
1	toluene, none	60	120	60	68:32
2	toluene, none	80	60	100	66:34
3	toluene, Montmorillonite K10	80	24	100	69:31
4	toluene, Montmorillonite K10	60	32	100	70:30

* Studies done by Chih-Wei Chien – unpublished results.

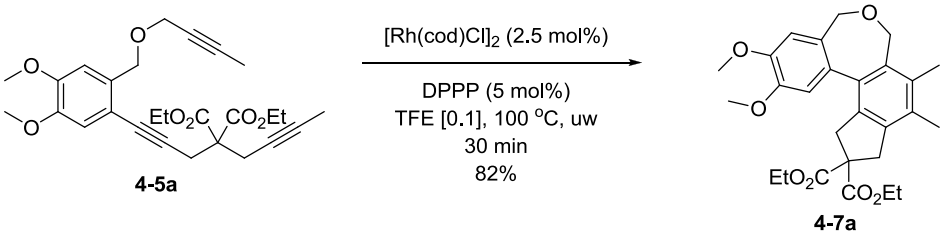
When the reaction of **4-5a** was scaled up, K10 was used as an additive to aid in complete conversion of the larger amount of material. The carbonylated product was obtained exclusively in 59% yield, but incomplete conversion was observed (**Scheme 4-10**). The reaction time or temperature will have to be increased to achieve complete conversion.



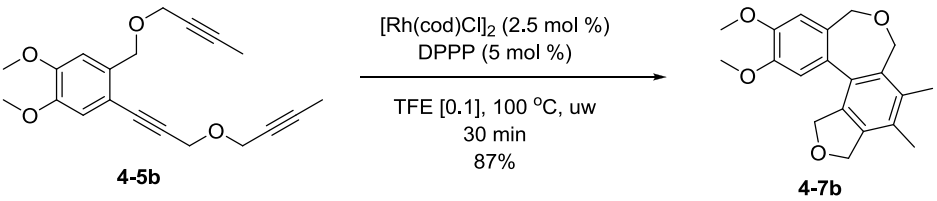
Scheme 4-10: [2+2+2+1] Cycloaddition of **4-5a**

4.2.3 Optimization of the [2+2+2] Cycloaddition of Triynes

The triynes were then subjected to the Rh(I)-catalyzed [2+2+2] cycloaddition under microwave irradiation at 100 ^{o}C in TFE for 30 min. Novel 6-7-6-5 tetracyclics were obtained in good yields (**Scheme 4-11** and **Scheme 4-12**).

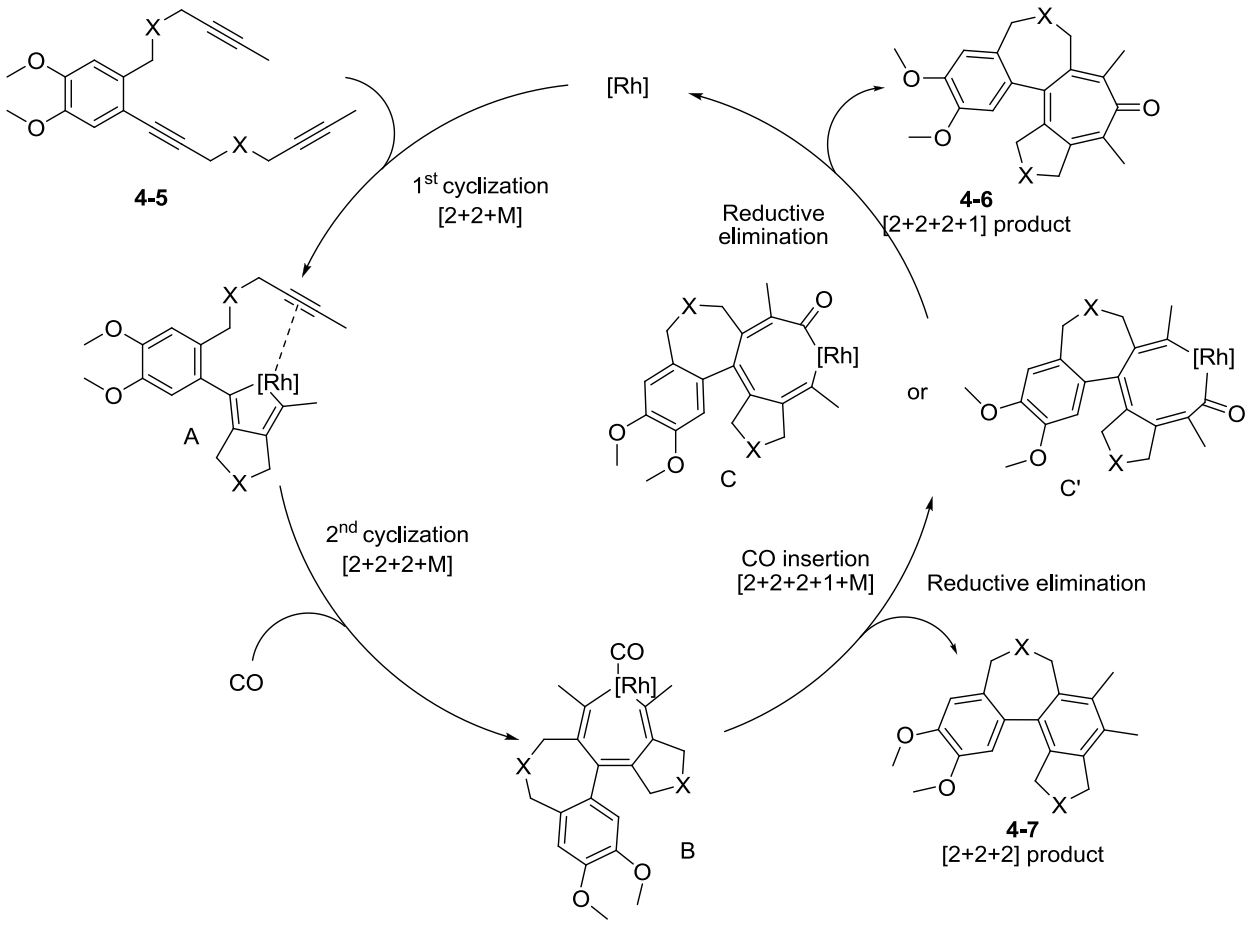


Scheme 4-11: Rh(I)-catalyzed [2+2+2] cycloaddition of triyne **4-5a**



Scheme 4-12: Rh(I)-catalyzed [2+2+2] cycloaddition of triyne **4-5b**

The mechanism that accounts for the formation of 6-7-6-5 and 6-7-7-6 tetracyclics is illustrated in **Scheme 4-13**. The cycloaddition starts with the coordination of the diyne moiety to the [Rh] catalyst ([2+2+M]). This is followed by insertion of the third alkyne into the Rh-C bond ([2+2+2+M]). Next, CO coordinates to [Rh], and this is followed by a migratory insertion of CO into the Rh-C bond ([2+2+2+1+M]). The final product is formed via a reductive elimination. The active Rh-catalyst species is also regenerated. The [2+2+2] product is formed when a reductive elimination occurs instead of migratory insertion of CO.



Scheme 4-13: Mechanism of the [2+2+2+1] and [2+2+2] cycloadditions of **4-5**

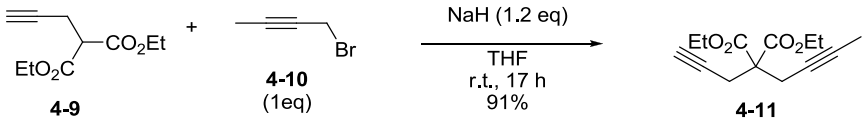
4.3 Conclusion

Novel triyne substrates have been synthesized and subjected to our previously developed Rh(I)-catalyzed cycloaddition reactions. The 6-7-6-5 tetracyclics have been obtained in good yields the presence of $[Rh(cod)Cl_2]_2$ and DPPP in TFE using microwave irradiation. The exclusive formation of 6-7-7-5 carbonylated tetracyclics has also been accomplished under ambient CO pressure in toluene.

4.4 Experimental Section

General Methods: All chemicals were obtained from either Sigma-Aldrich or Acros Organics and used as received unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Solvents were dried under nitrogen using the PURESOLV system (Inovatative Technologies, Newport, MA). All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents and using Fisher silica gel (particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C NMR spectra were obtained using either a 300 MHz Varian Gemini 2300 (75 MHz ^{13}C) spectrometer or a 400 MHz Varian INOVA 400 (100 MHz ^{13}C) spectrometer in $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm and standardized with a solvent as an internal standard based on literature reported values. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Shimadzu FTIR-84005 spectrophotometer. Low-resolution mass spectrometry was performed on an Agilent 6890GC/5973 Mass Selective Detector.

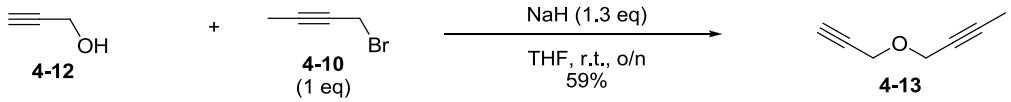
Diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (4-11):[3]



To a suspension of NaH (60% dispersion in mineral oil, 0.576 g, 14.4 mmol) in THF (20 mL) at 0 ^{o}C was added diethyl propargyl malonate (**4-9**, 2.38 g, 12.0 mmol) in THF (10 mL) dropwise. After the solution stirred for 15 min, 2-butynyl bromide (**4-10**) was added in THF (10 mL) all at once and the solution was allowed to stir at rt for 17 h. The reaction was quenched with water and extracted with ether (3 x 100 mL). The combined organic layer was washed with

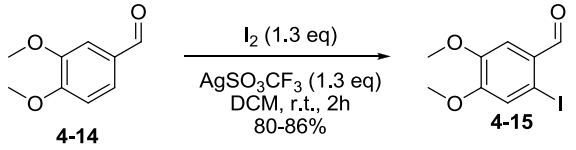
brine, collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/Hexanes = 0% → 17%) and the final product diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (**4-11**) was obtained as a clear, colorless liquid (2.74 g, 91% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.25 (t, 6H, *J* = 7.0 Hz), 1.75 (t, 3H, *J* = 3.0 Hz), 2.00 (t, H, *J* = 2.5 Hz), 2.92 (d, 2H, *J* = 2.5 Hz), 2.97 (d, 2H, *J* = 3.0 Hz), 4.24 (q, 4H, *J* = 7.0 Hz). These results are in agreement with previously reported values.[3]

1-(Prop-2-ynyloxy)but-2-yne (4-13): [4]



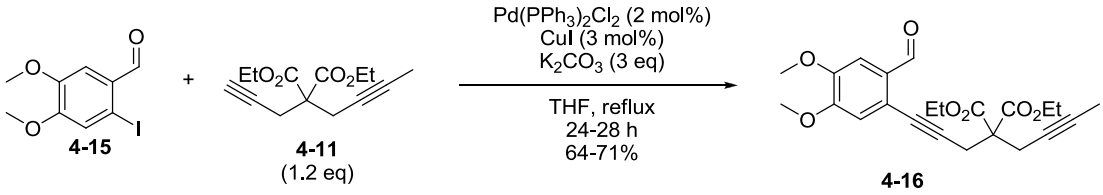
To a suspension of NaH (60% dispersion in mineral oil, 1.97 g, 49.3 mmol) in THF (100 mL) at 0 ^{o}C was added propargyl alcohol (**4-12**, 2.11 g, 37.6 mmol) in THF (10 mL) dropwise. After the solution stirred for 15 min, 2-butynyl bromide (**4-10**) was added in THF (15 mL) all at once and the solution was allowed to stir at rt for 23 h. The reaction was quenched with water and extracted with ether (3 x 100 mL). The combined organic layer was washed with brine, collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/Hexanes = 0% → 10%) and the final product 1-(prop-2-ynyloxy)but-2-yne (**4-13**) was obtained as a clear, colorless liquid (2.39 g, 59% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.87 (t, 3H, *J* = 2.1 Hz), 2.44 (t, 1H, *J* = 2.4 Hz), 4.23 (d, 2H, *J* = 2.1 Hz), 4.25 (d, 2H, *J* = 2.4 Hz). All data are in agreement with those reported in the literature. [4]

2-Iodo-4,5-dimethoxybenzaldehyde (4-15): [5]



To a solution of 3,4-dimethoxybenzaldehyde (**4-14**, 2.0 g, 12.1 mmol) in DCM (160 mL) was added $AgSO_3CF_3$ (4.02 g, 15.7 mmol) and crushed iodine (3.97 g, 15.7 mmol). The dark purple solution was allowed to stir at rt for 2 h after which the solution turned dark red. The reaction mixture was filtered over celite and the solution was washed with sat. Na_2SO_3. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated over reduced pressure. The crude solid was purified by triturating with cold ether to obtain 2-iodo-4,5-dimethoxybenzaldehyde (**4-15**) as an off-white solid (3.03 g, 86% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.92 (s, 3H), 3.96 (s, 3H), 7.31 (s, 1H), 7.42 (s, 1H), 9.78 (s, 1H). All data are in agreement with those reported in the literature.[5]

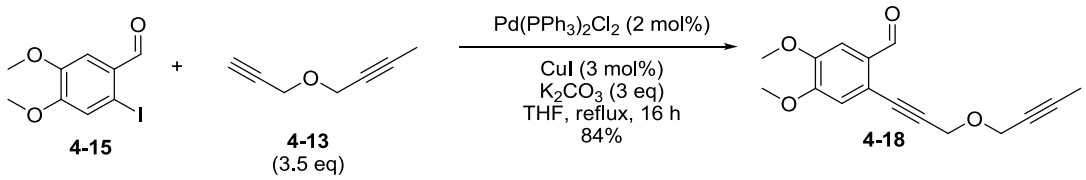
Diethyl 2-(but-2-ynyl)-2-(3-(2-formyl-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (4-16):[3]



2-Iodo-4,5-dimethoxybenzaldehyde (**4-15**, 0.200 g, 0.685 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (9.60 mg, 0.0137 nmmol), CuI (3.90 mg, 0.0206 mmol), and K_2CO_3 (0.284 g, 2.06 mmol) in THF (5 mL). A solution of diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (**4-11**, 0.216 g, 0.824 mmol) in THF (2 mL) was added and the mixture was heated at reflux for 24 h. The crude mixture was filtered over celite, concentrated under reduced pressure, and purified by

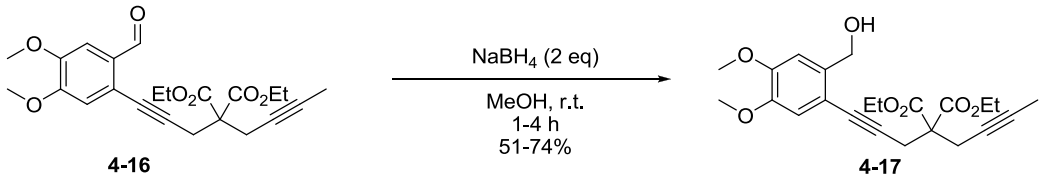
column chromatography on silica gel (EtOAc/Hexanes = 0% → 33%) and the final product diethyl 2-(but-2-ynyl)-2-(3-(2-formyl-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (**4-16**) was obtained as a yellow oil (0.201 g, 71% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.29 (t, 6H, *J* = 7.2 Hz), 1.78 (t, 3H, *J* = 2.4 Hz), 2.97 (q, 2H, *J* = 2.4 Hz), 3.25 (s, 2H), 3.93 (s, 3H), 3.94 (s, 1H), 4.28 (q, 4H, 6.9 Hz), 6.90 (s, 1H), 7.36 (s, 1H), 10.3 (s, 1H). These results are in agreement with previously reported values.[3]

2-(3-(But-2-yn-1-yloxy)prop-1-ynyl)-4,5-dimethoxybenzaldehyde (4-18):



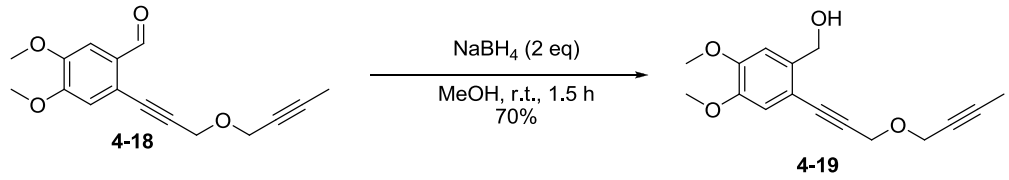
2-Iodo-4,5-dimethoxybenzaldehyde (**4-15**, 0.500 g, 1.71 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (24.0 mg, 0.0342 mmol), CuI (9.80 mg, 0.0513 mmol), and K_2CO_3 (0.709 g, 5.13 mmol) in THF (10 mL). A solution of 1-(prop-2-ynyloxy)but-2-yne (**4-13**, 0.648 g, 5.99 mmol) in THF (7 mL) was added and the mixture was heated at reflux for 16 h. The crude mixture was filtered over celite, concentrated under reduced pressure, and purified by column chromatography on silica gel (EtOAc/Hexanes = 0% → 33%) and the final product **4-18** was obtained as a yellow viscous liquid (0.201 g, 71% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.89 (t, 3H, *J* = 2.1 Hz), 3.94 (s, 3H), 3.95 (s, 3H), 4.28 (q, 2H, *J* = 2.1 Hz), 4.51 (s, 2H), 6.98 (s, 1H), 7.38 (s, 1H), 10.4 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 3.81, 56.3, 56.5, 57.2, 57.7, 74.3, 82.1, 83.7, 90.5, 108.3, 114.8, 120.8, 130.6, 150.0, 153.7; MS (FIA) m/z calcd for $C_{16}H_{16}O_4$ $(M + H)^+$: 273.1, found 273.2.

Diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (4-17):[3]



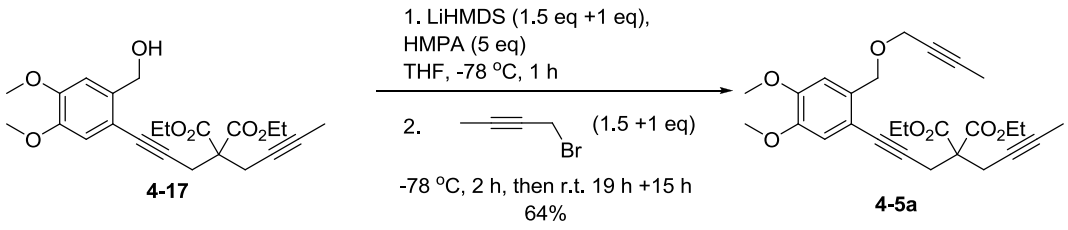
$NaBH_4$ (0.110 g, 2.91 mmol) was added to a solution of diethyl 2-(but-2-ynyl)-2-(3-(2-formyl-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (**4-16**, 0.603 g, 1.45 mmol) in MeOH (36 mL). The reaction was allowed to stir for 2 h at rt. The mixture was then quenched with 2M HCl (aq) and the MeOH was removed under reduced pressure. The crude mixture was extracted with ether, and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/Hexanes = 20% → 40%) to yield diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (**4-17**) as an off-white solid (0.447 g, 74% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.29 (t, 6H, *J* = 7.2 Hz), 1.78 (t, 3H, *J* = 2.7 Hz), 2.97 (d, 2H, *J* = 2.4 Hz), 3.20 (s, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 4.28 (q, 4H, *J* = 6.0 Hz), 4.68 (d, 2H, *J* = 5.7 Hz), 6.89 (s, 1H), 6.90 (s, 1H). These results are in agreement with previously reported values.[3]

2-(3-(but-2-yn-1-yloxy)prop-1-yn-1-yl-4,5-dimethoxyphenyl)methanol (4-19):



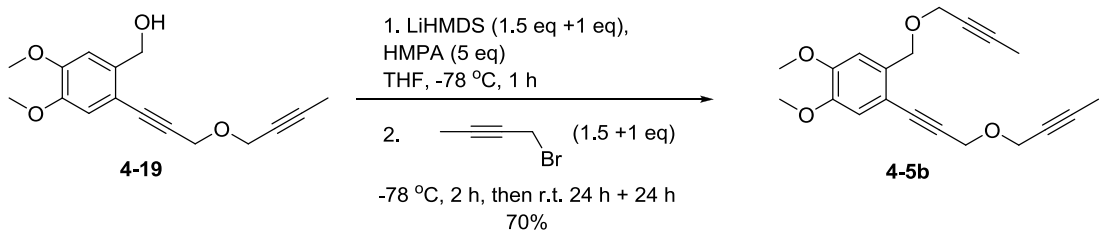
$NaBH_4$ (0.103 g, 2.72 mmol) was added to a solution of diethyl 2-(3-(but-2-yn-1-yloxy)prop-1-ynyl)-4,5-dimethoxybenzaldehyde (**4-18**, 0.370 g, 2.72 mmol) in MeOH (34 mL). The reaction was allowed to stir for 1.5 h at rt. The mixture was then quenched with 2M HCl (aq) and the MeOH was removed under reduced pressure. The crude mixture was extracted with ether, and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/Hexanes = 20% → 40%) to yield **4-19** as a yellow oil (0.260 g, 70% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.89 (t, 3H, *J* = 2.4 Hz), 3.87 (s, 1H), 3.91 (s, 1H), 4.28 (q, 2H, *J* = 2.4 Hz), 4.48 (s, 1H), 4.78 (d, 2H, *J* = 4.2 Hz), 6.94 (s, 1H), 6.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 3.80, 13.4, 56.1, 56.2, 57.3, 57.5, 58.0, 63.8, 65.1, 74.5, 83.5, 87.9, 110.7, 115.0, 126.2, 129.2, 136.5, 136.6, 148.1, 149.8; MS (FIA) m/z calcd for $C_{16}H_{16}O_4$ $(M + H)^+$: 275.1, found 275.0.

Diethyl 2-(but-2-ynyl)-2-[3-(2-(but-2-ynyloxy)methyl)]-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (4-5a):[3]



1 M LiHMDS (0.720 mL) and HMPA (0.420 mL, 2.40 mmol) were added to a solution of diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (**4-17**, 0.200 g, 0.480 mmol) in THF (5 mL) at -78 °C. After stirring for 1 h, 2-butynyl bromide (0.0960 g, 0.720 mmol) was added and the solution was stirred for an additional 2 h at -78 °C. The solution was then brought to room temperature and allowed to stir for 19 h. The solution was then cooled back down to -78 °C and 1 M LiHMDS (0.480 mL) was added, and the solution was allowed to stir for 1 h. Then, 2-butynl bromide (0.0640 g, 0.480 mmol) was added and the solution was brought to room temperature after stirring for 2 h at -78 °C. After 15 h, the reaction was quenched with sat. NH_4Cl (aq) and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexanes/EtOAc as the eluent. The final product **4-5a** was obtained as a colorless oil (0.143 g, 64% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.29 (t, 6H, *J* = 7.1 Hz), 1.78 (t, 3H, *J* = 2.7 Hz), 1.88 (t, 3H, *J* = 2.4 Hz), 2.99 (d, 2H, *J* = 2.4 Hz), 3.21 (s, 1H), 3.85 (s, 3H), 3.89 (s, 3H), 4.19 (d, 2H, *J* = 2.1 Hz), 4.25 (q, 6H, *J* = 7.2 Hz), 4.62 (s, 2H), 6.84 (s, 1H), 6.95 (s, 1H). These results are in agreement with the previously reported values.[3]

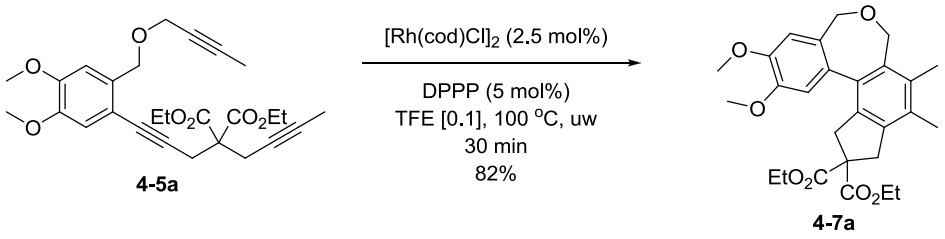
1-[3-(But-2-yn-1-yloxy)prop-1-yn-1-yl]-4,5-dimethoxy-2-[2-(prop-1-yn-1-yloxy)ethyl] benzene (4-5b):



1 M LiHMDS (1.42 mL) and HMPA (0.822 mL, 4.73 mmol) were added to a solution of 2-(3-(but-2-yn-1-yloxy)prop-1-yn-1-yl-4,5-dimethoxyphenyl)methanol (**4-19**, 0.260 g, 0.948 mmol) in THF (10 mL) at -78 ^{o}C. After stirring for 1 h, 2-butynyl bromide (0.189 g, 1.42 mmol) was added and the solution was stirred for an additional 2 h at -78 ^{o}C. The solution was then brought to room temperature and allowed to stir for 24 h. The solution was then cooled back down to -78 ^{o}C and 1 M LiHMDS (0.950 mL) was added, and the solution was allowed to stir for 1 h. Then, 2-butynl bromide (0.126 g, 0.950 mmol) was added and the solution was brought to room temperature after stirring for 2 h at -78 ^{o}C. After 24 h, the reaction was quenched with sat. NH_4Cl (aq) and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/Hexanes = 0% → 60%). The final product **4-5b** was obtained as a yellow oil (0.215 g, 70% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.89 (t, 6H, *J* = 1.8 Hz), 3.86 (s, 3H), 3.91 (s, 3H), 4.18 (d, 2H, *J* = 2.4 Hz), 4.29 (d, 2H, *J* = 2.4 Hz), 4.49 (s, 2H), 4.68 (s, 2H), 6.93 (s, 1H), 6.97 (s, 1H). HRMS (ES) m/z calcd for $C_{20}H_{22}O_4$ $(M + H)^+$: 327.1591, found 327.1590 (Δ 0.2 ppm).

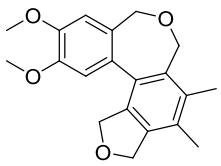
[2+2+2] Cycloaddition of triynes:

Diethyl 2,3-dimethoxy-8,9-dimethyl-10,12-dihydro-5H-benzo[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (4-7a):



Typical procedure is described for the reaction of triyne **4-5a**: A 10 mL microwave reactor tube charged with **4-5a** (60.0 mg, 0.128 mmol), $[Rh(cod)Cl]_2$ (1.60 mg, 0.00320 mmol), DPPP (26.4 mg, 0.00640 mmol), TFE (1.28 mL) and stir bar was placed in a microwave reactor and heated to 100 ^{o}C for 30 min. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc/Hexanes = 0% → 60%) to yield the pure product **4-7a** as a white solid (49.0 mg, 82% yield): NMR ($CDCl_3$, 400 MHz) δ1.20 (t, 3H, *J* = 7.1 Hz), 1.30 (t, 3H, *J* = 7.1 Hz), 2.28 (s, 3H), 2.37 (s, 3H), 3.36 (d, 1H, *J* = 16.4 Hz), 3.59 (d, 1H, *J* = 16.5 Hz), 3.73 (d, 1H, *J* = 16.5 Hz), 3.82 (d, 1H, *J* = 11.9 Hz), 3.95 (s, 6H), 3.99-4.15 (m, 5H), 4.24-4.27 (m, 1H), 4.40 (d, 1H, *J* = 11.2 Hz), 4.83 (d, 1H, *J* = 11.8 Hz), 6.94 (s, 1H), 7.08 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 13.89, 14.02, 15.52, 16.82, 40.24, 40.57, 55.93, 56.06, 59.86, 61.63, 61.71, 62.67, 67.01, 111.2, 112.3, 128.0, 132.0, 132.5, 133.8, 134.1, 134.7, 139.7, 148.3, 171.5, 171.8. HRMS (ES) m/z calcd for $C_{27}H_{32}O_7$ $(M + H)^+$: 469.2221, found 469.2222 (Δ 0.3 ppm).

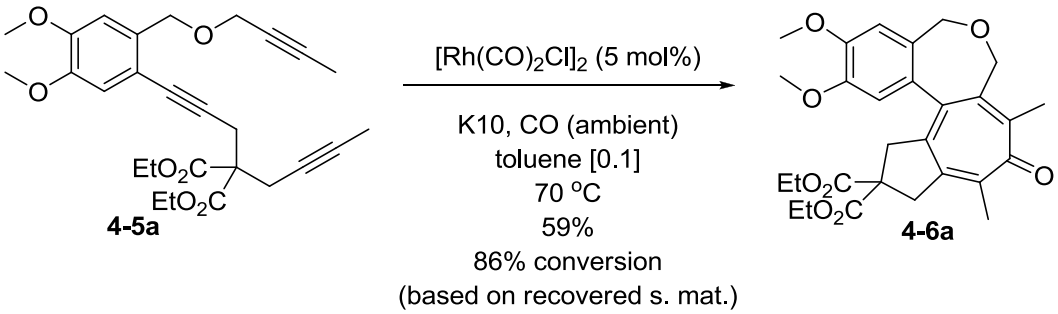
10,11-Dimethoxy-4,5-dimethyl-1,3,6,8-tetrahydrobenzo[e]isobenzofuro[5,4-c]oxepine (4-7b):



4-7b

Yellow oil (52.0 mg, 87% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (d, 1H, *J* = 5.96 Hz), 2.34 (s, 3H), 2.40 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.01 (d, 1H, *J* = 8.00 Hz), 4.43 (d, 1H, *J* = 8.52 Hz), 4.87 (d, 1H, *J* =8.96 Hz), 4.87 (d, 1H, *J* = 8.96 Hz), 4.96 (d, 1H, *J* = 8.96 Hz), 5.19 (d, 2H, *J* = 12.6 Hz), 5.58 (d, 1H, *J* = 8.80 Hz), 6.89 (s, 1H), 6.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 15.19, 16.88, 55.92, 55.97, 62.53, 67.05, 73.80, 74.17, 109.9, 112.6, 128.0, 129.4, 132.1, 132.8, 132.9, 133.1, 134.7, 139.0, 148.5, 148.6; HRMS (ES) m/z calcd for $C_{20}H_{22}O_4$ $(M + H)^+$: 327.1591, found 327.1587 (Δ 1.2 ppm).

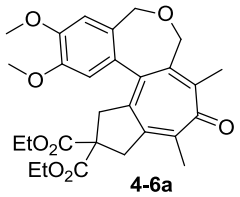
[2+2+2+1] Cycloaddition of triynes:



Typical procedure is described for the reaction of triyne **4-5a**: A 5 mL two-necked round-bottomed flask was charged with a stir bar, triyne (**4-5a**, 80.0 mg, 0.171 mmol), K10 (80.0 mg), and $[Rh(CO)_2Cl]_2$ (3.30 mg, 0.00860 mmol). The flask was attached to a condenser and was vacuumed and purged with CO (5x). **Caution: Purging with CO must be done in a well**

ventilated fume hood. Toluene (1.71 mL) was added, and the solution was heated to 70 ^{o}C for 24h. The crude mixture was concentrated under reduced pressure and purified by flash column chromatography on silca gel.

Diethyl11,12-dimethoxy-4,6-dimethyl-5-oxo-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**4-6a**):



4-6a

Yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) d 1.18-1.24 (m, 6H), 2.25 (s, 3H), 2.37 (s, 3H), 3.50 (s, 2H), 3.86 (s, 3H), 3.94 (s, 3H), 4.05-4.15 (m, 4H), 4.48 (s, 2H), 6.67 (s, 1H), 6.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 13.96, 18.43, 19.72, 42.27, 44.74, 56.04, 56.19, 57.74, 61.94, 65.19, 67.76, 111.7, 112.0, 125.2, 134.1, 138.3, 140.0, 140.9, 142.1, 145.5, 148.7, 149.1, 170.6, 190.4. HRMS (ES) m/z calcd for $C_{28}H_{32}O_8$ $(M + H)^+$: 497.2170, found 497.2170 (Δ 0.0 ppm).

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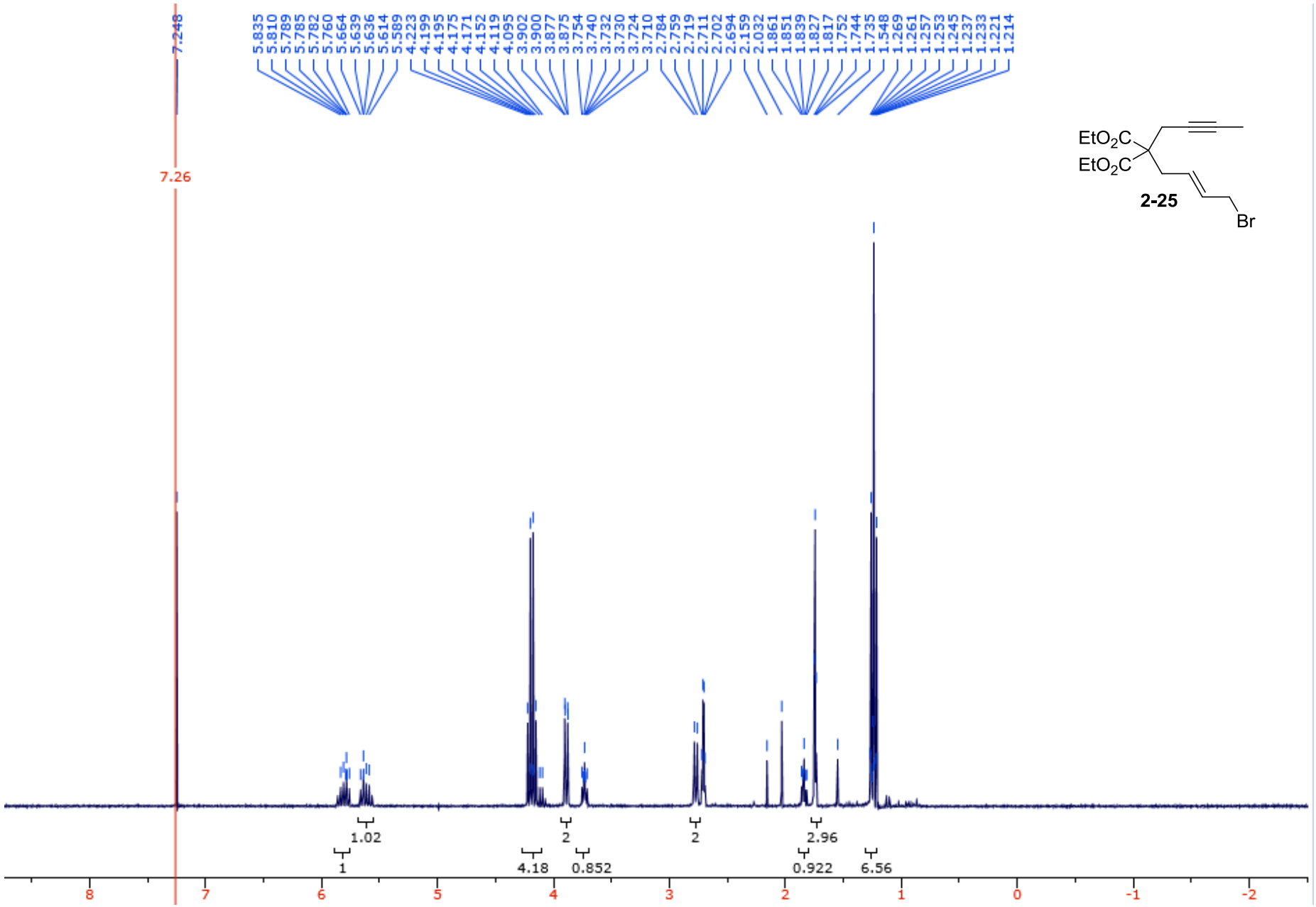
Appendix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EtO2C
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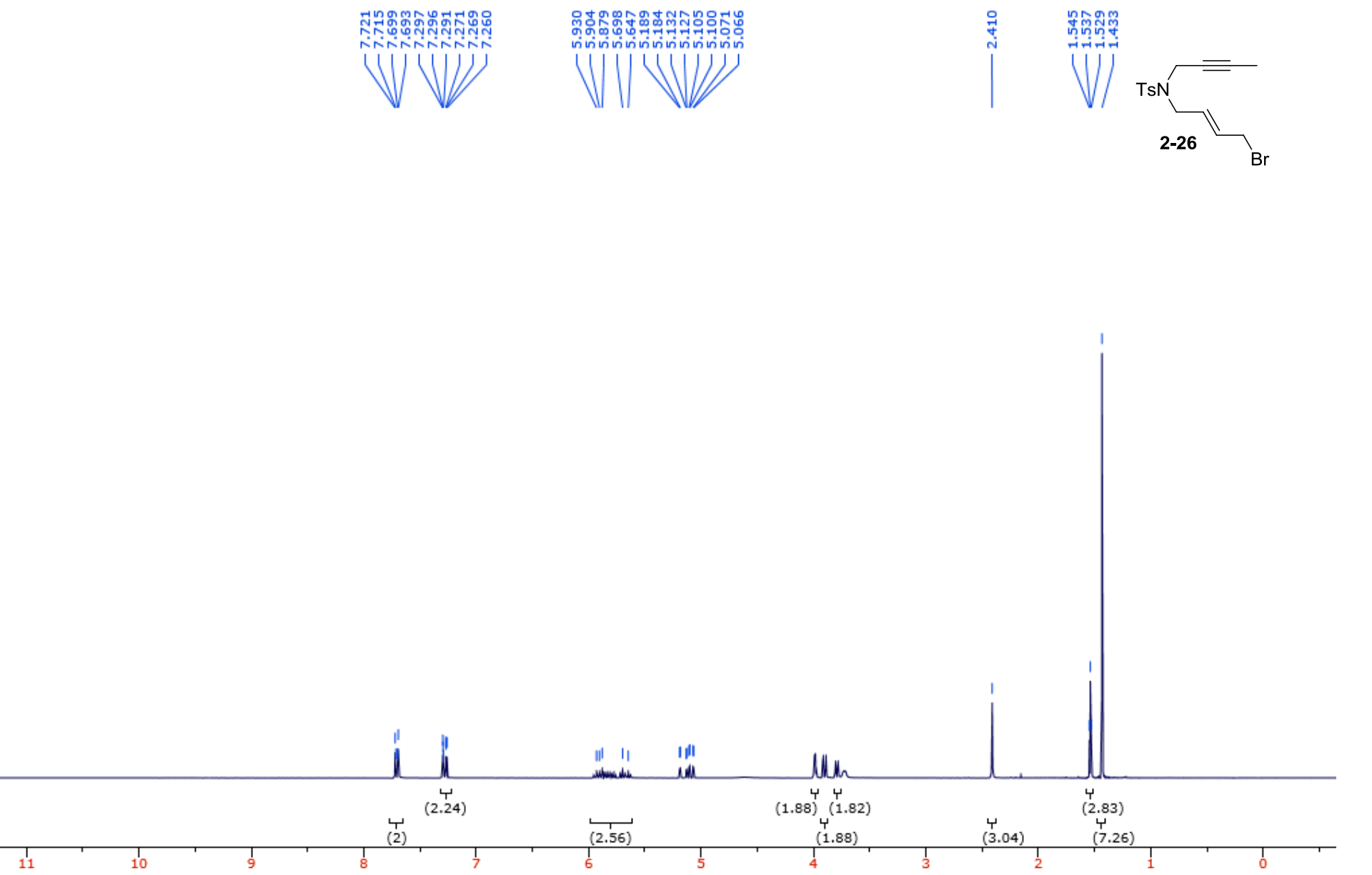
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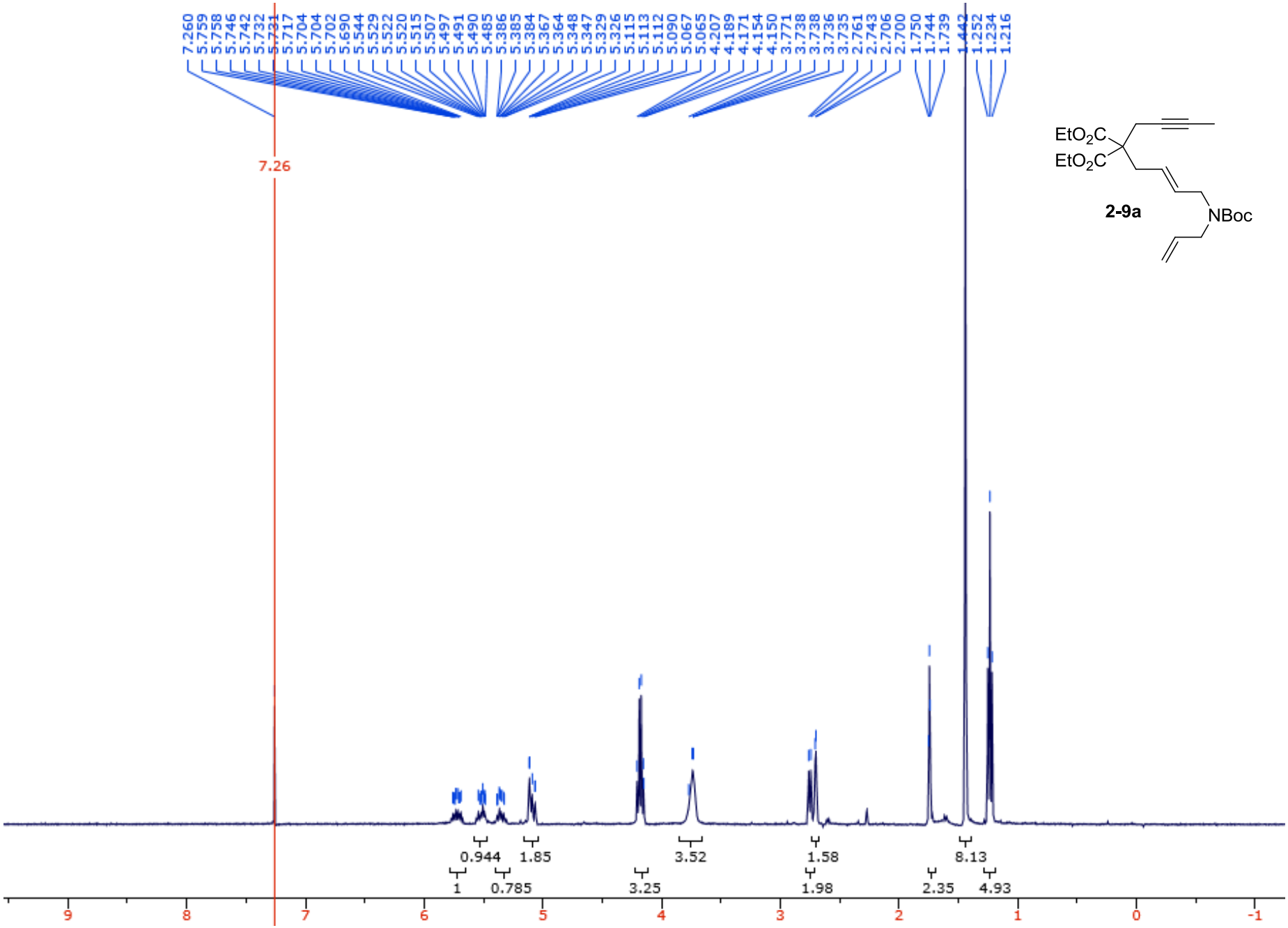
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4.150
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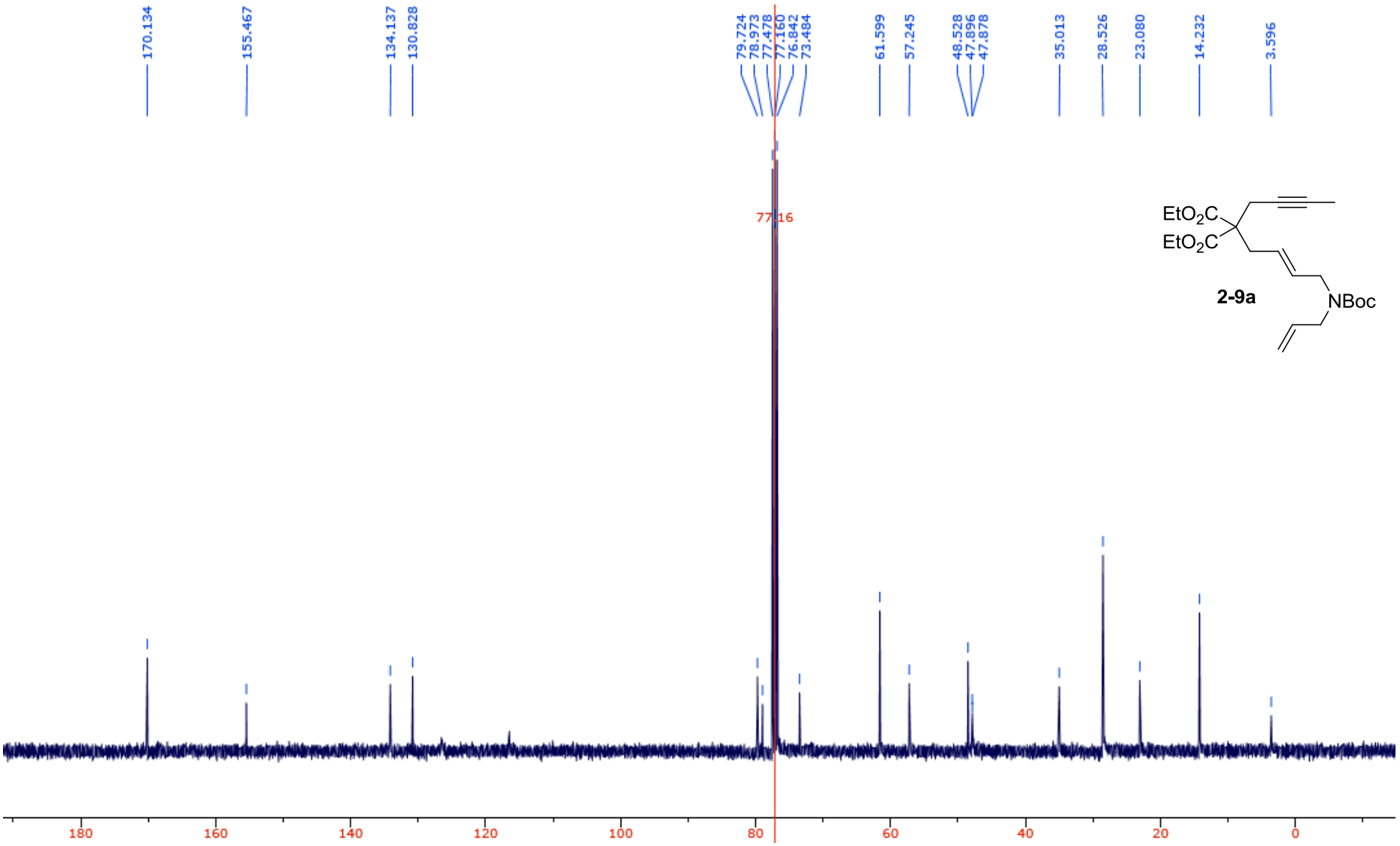
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EtO2C
NBoc
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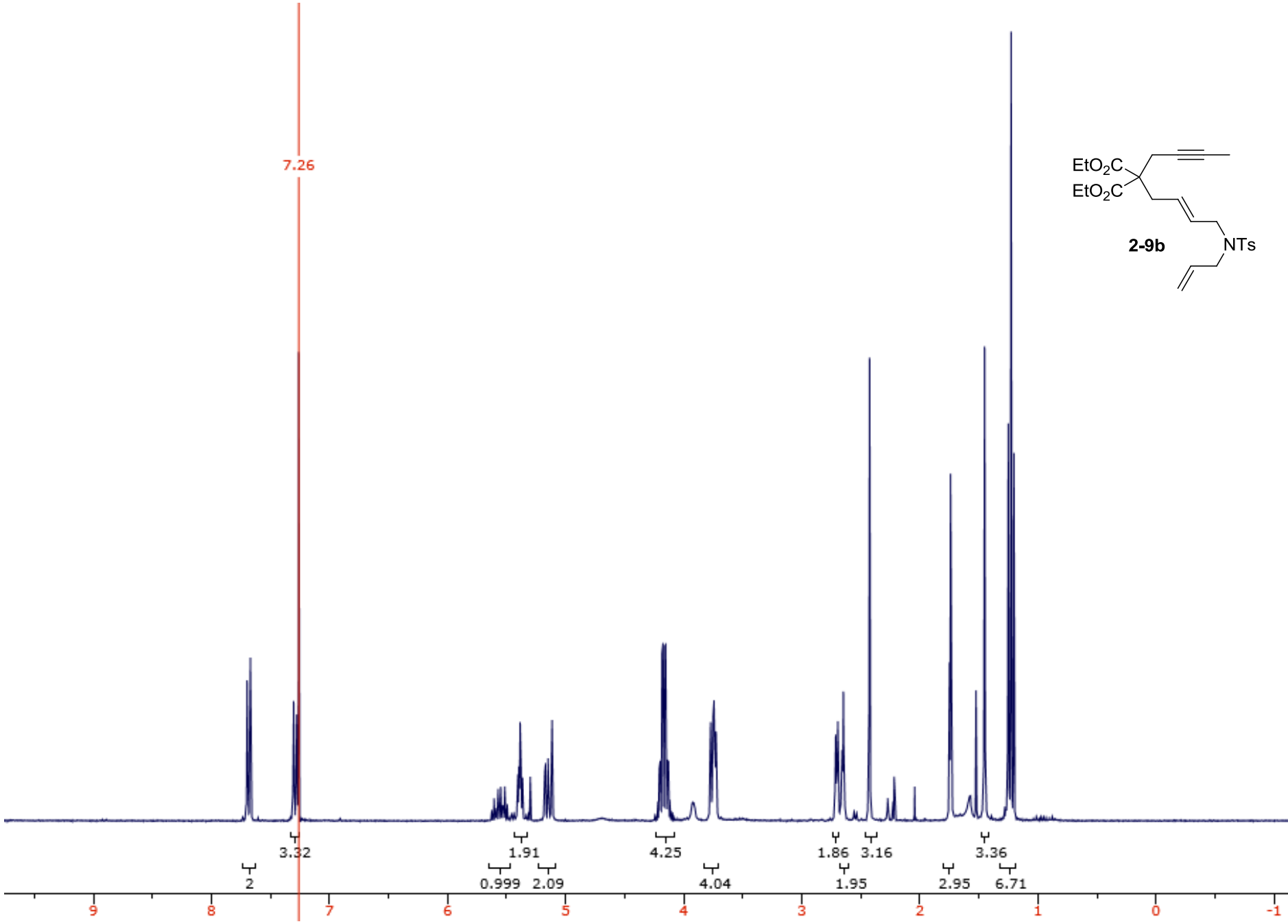
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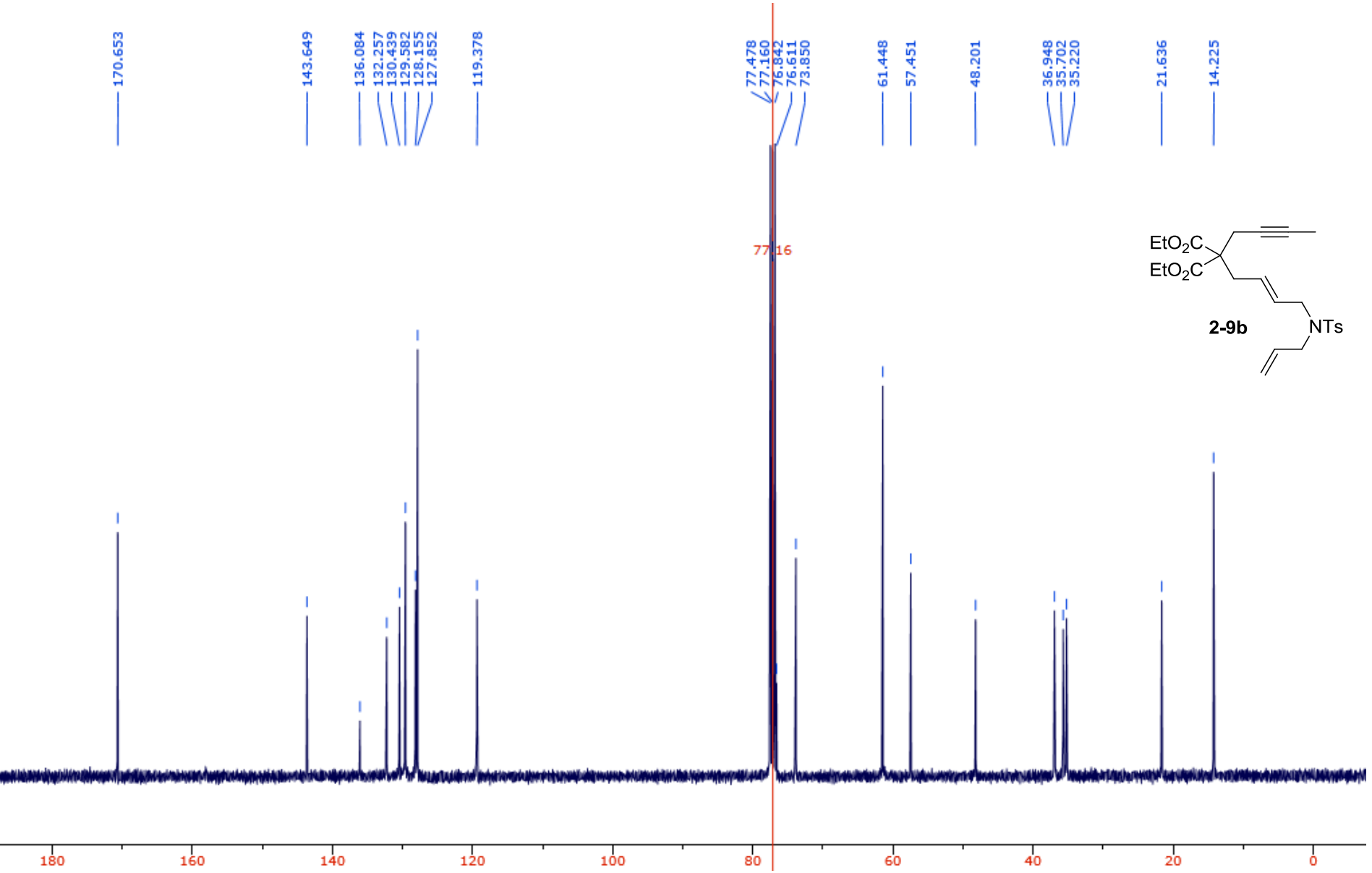
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EtO2C
NTs
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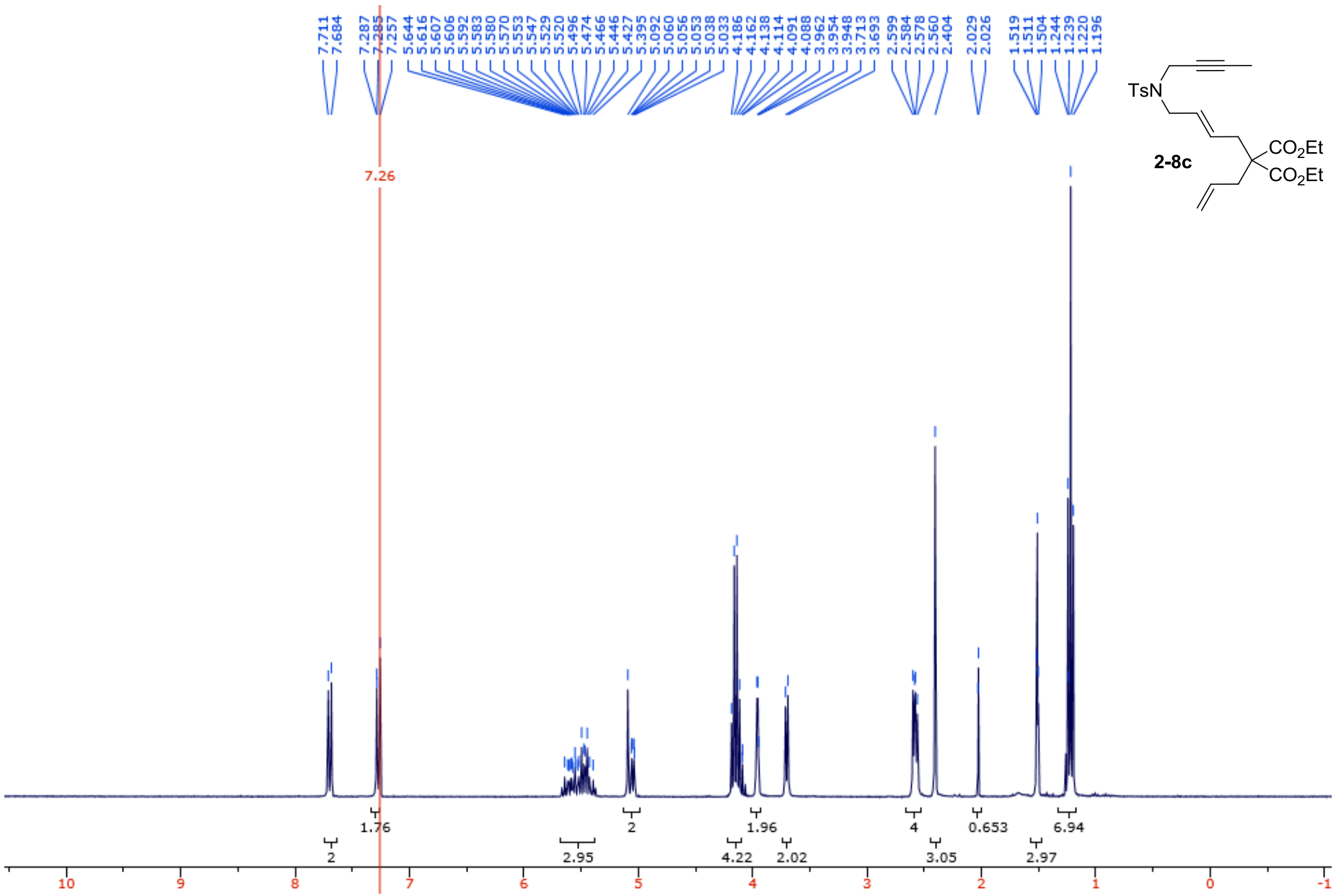
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CO2Et
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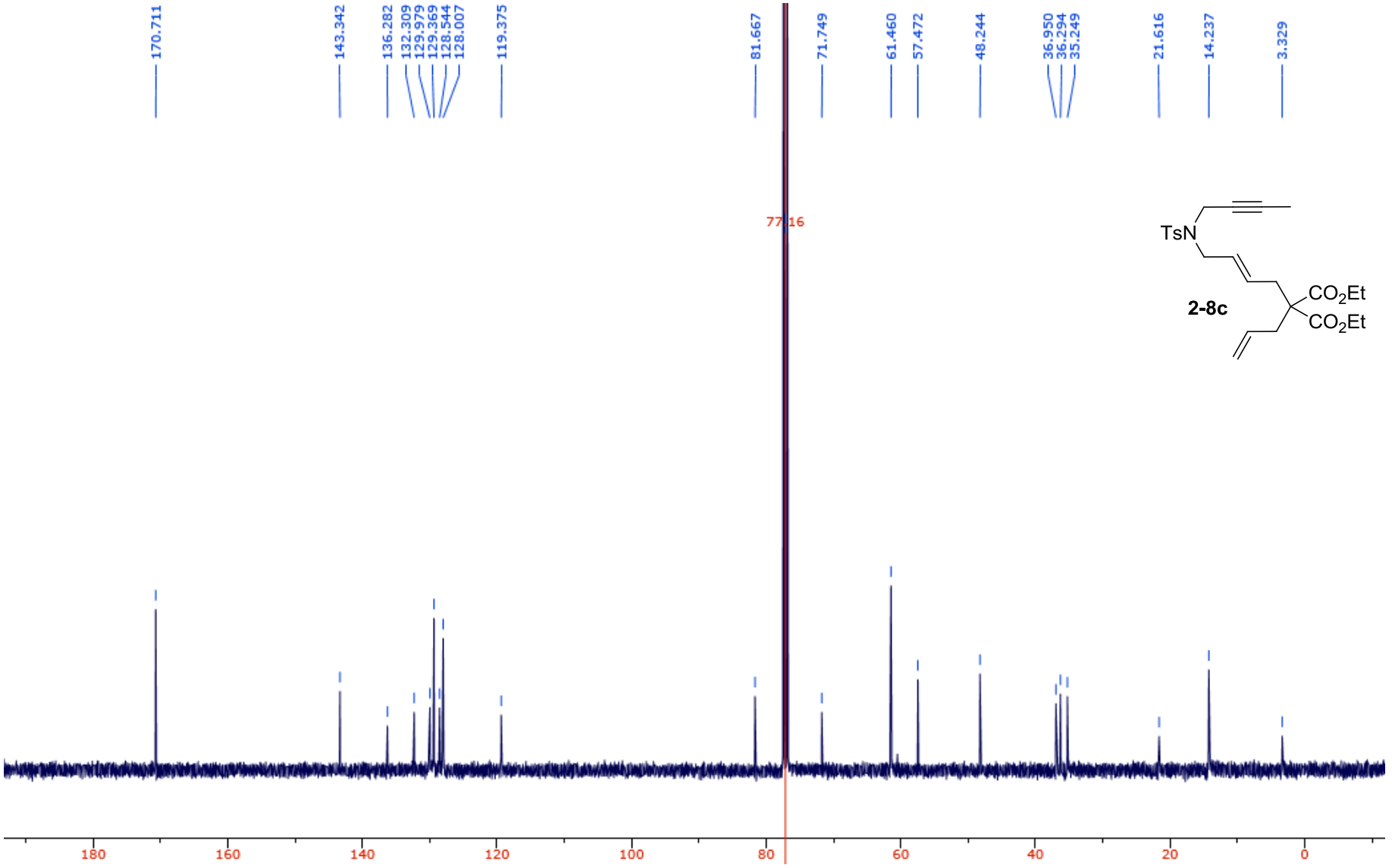
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CO2Et
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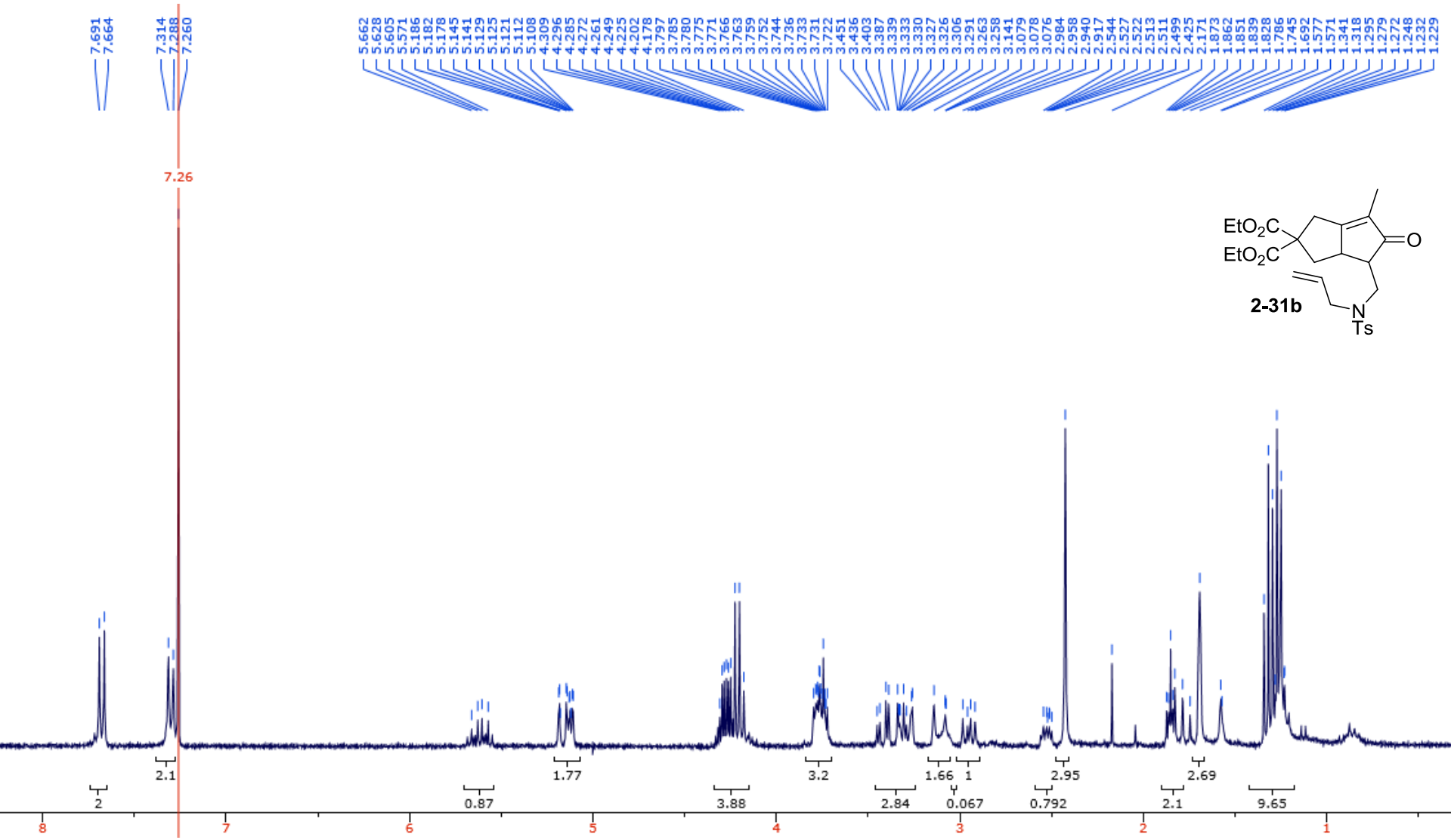
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EtO2C
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N
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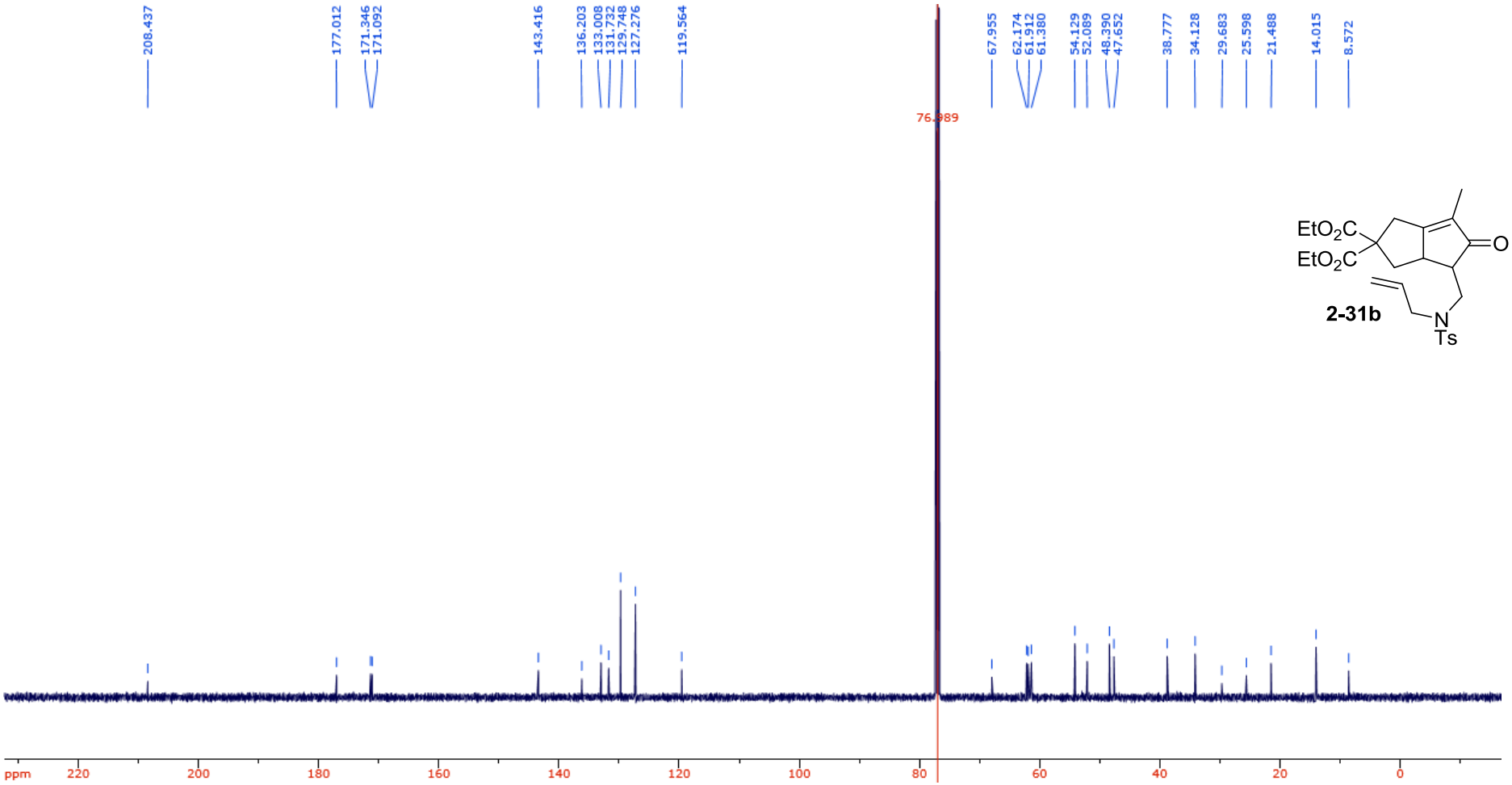
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EtO2C
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Ts
2-31b
ppm
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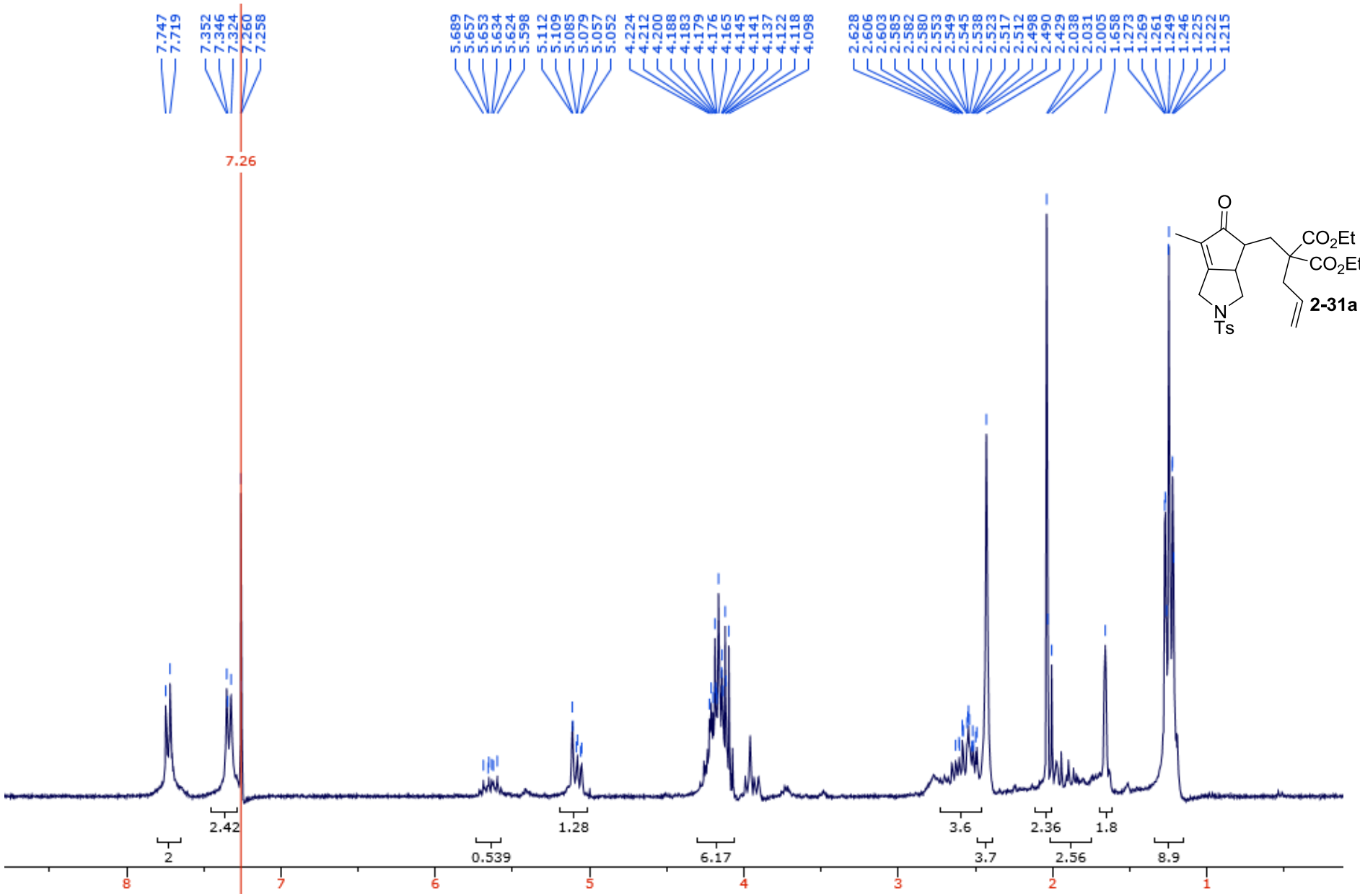
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1.249
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CO2Et
N
Ts
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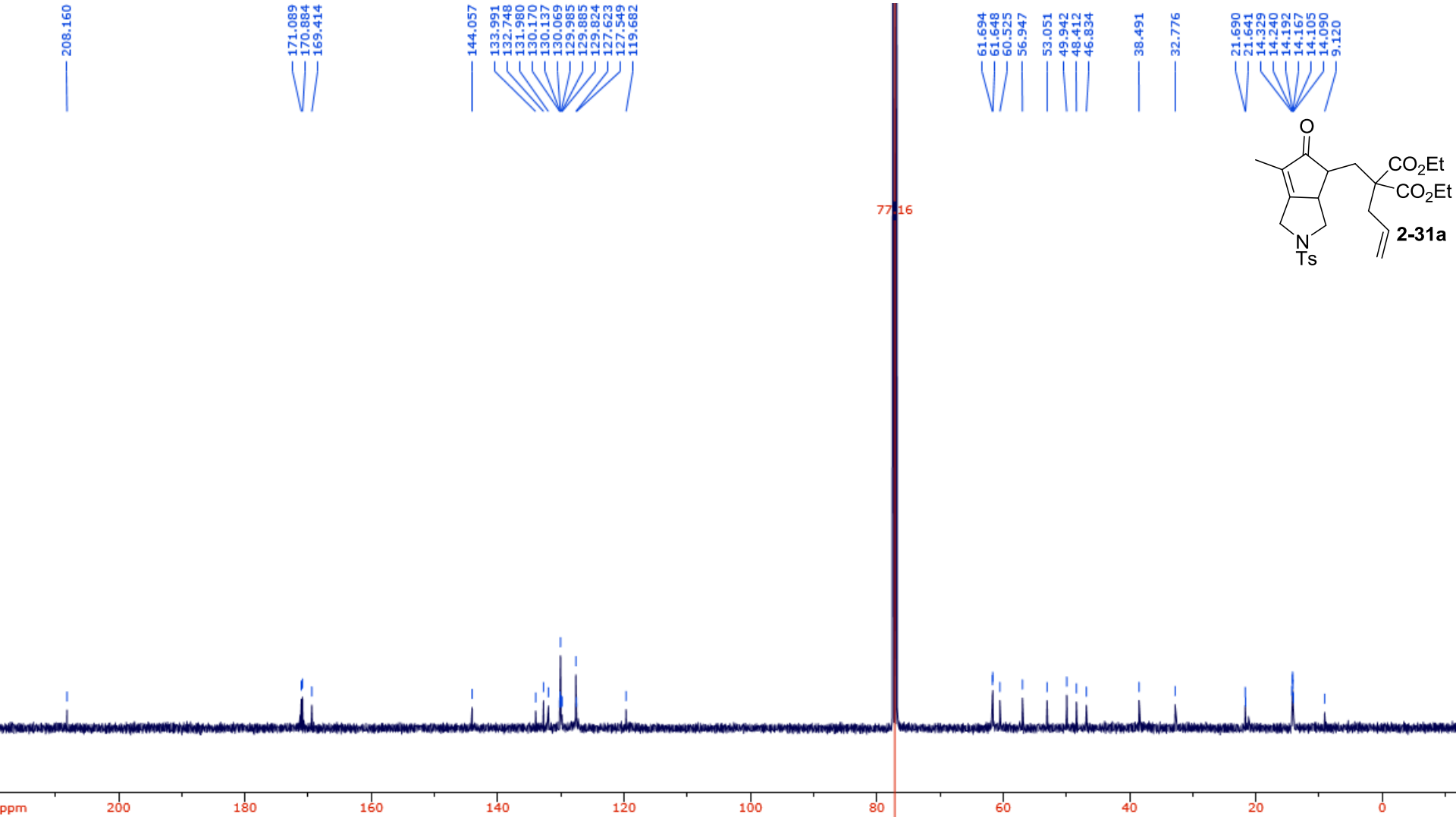
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N
Ts
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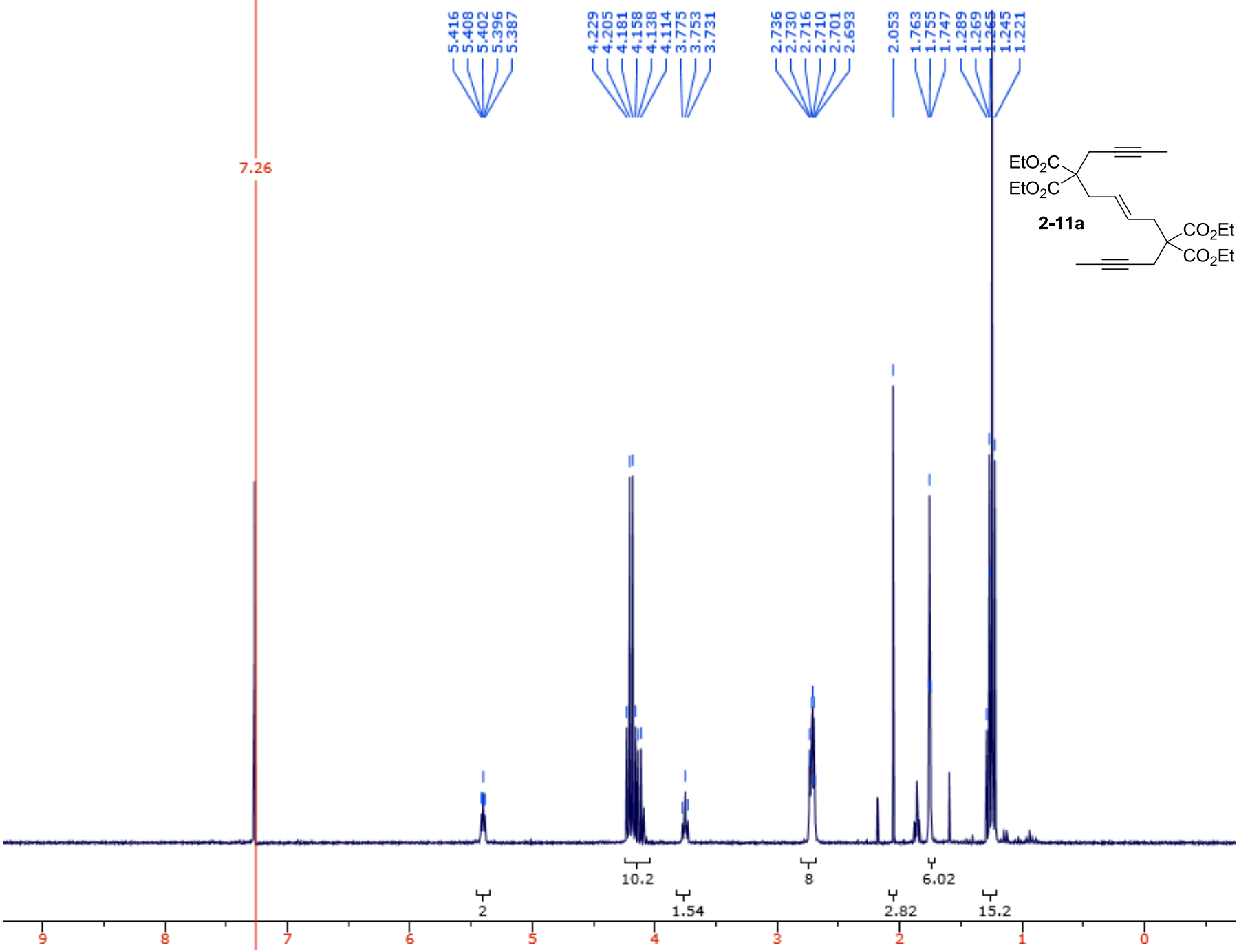
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EtO2C
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CO2Et
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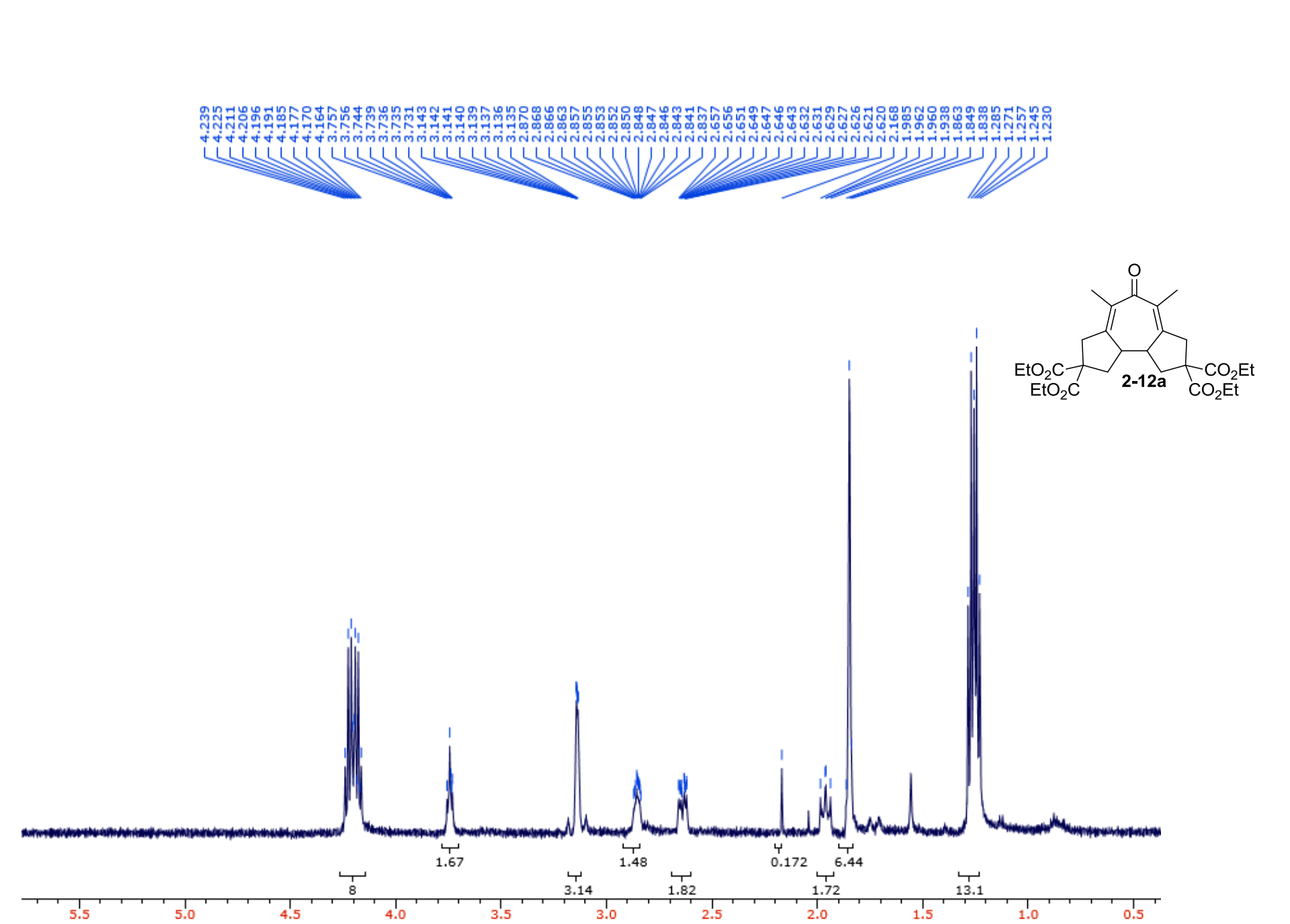
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EtO2C
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CO2Et
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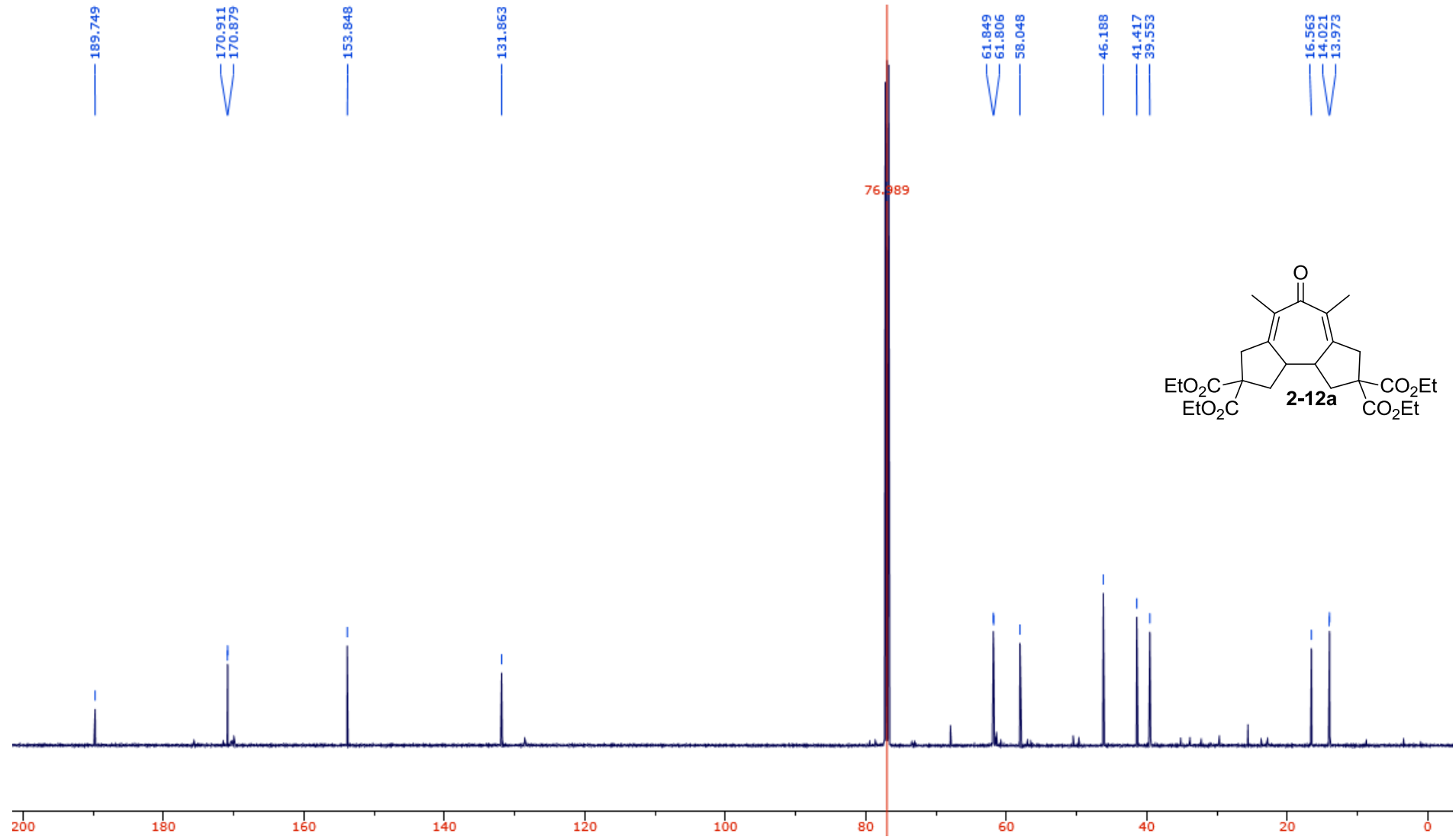
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CO2Et
CO2Et
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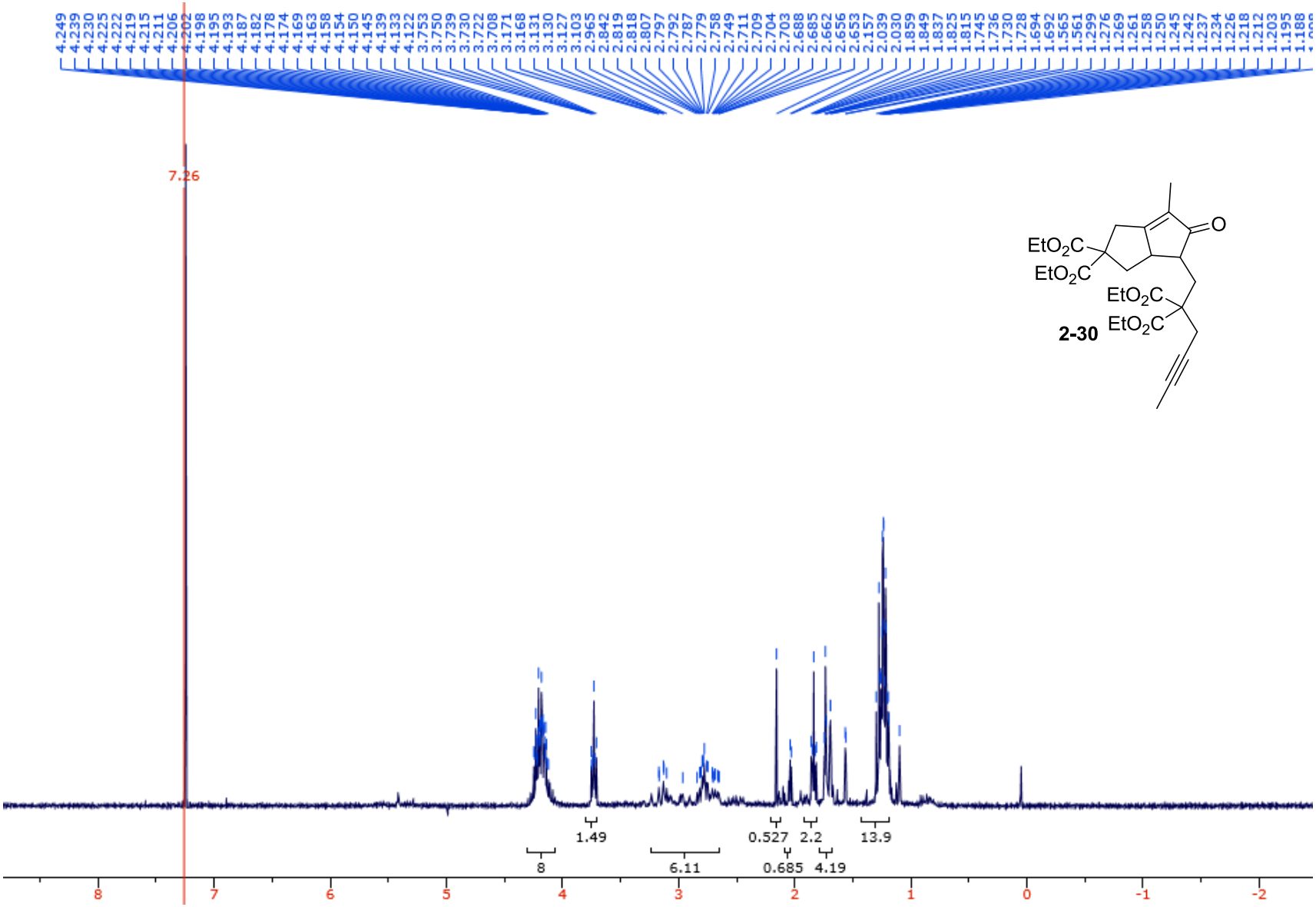
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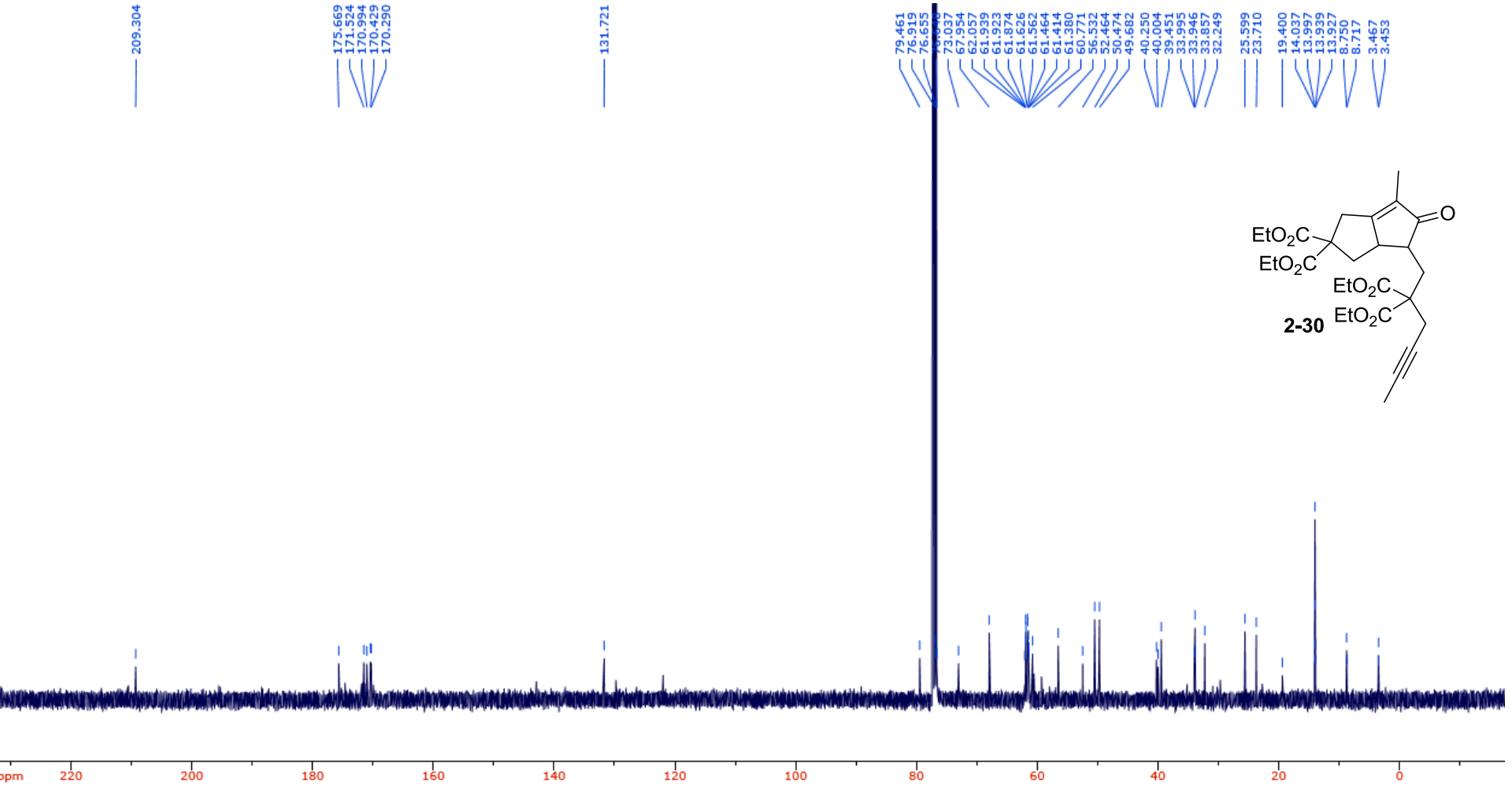
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O
EtO2C
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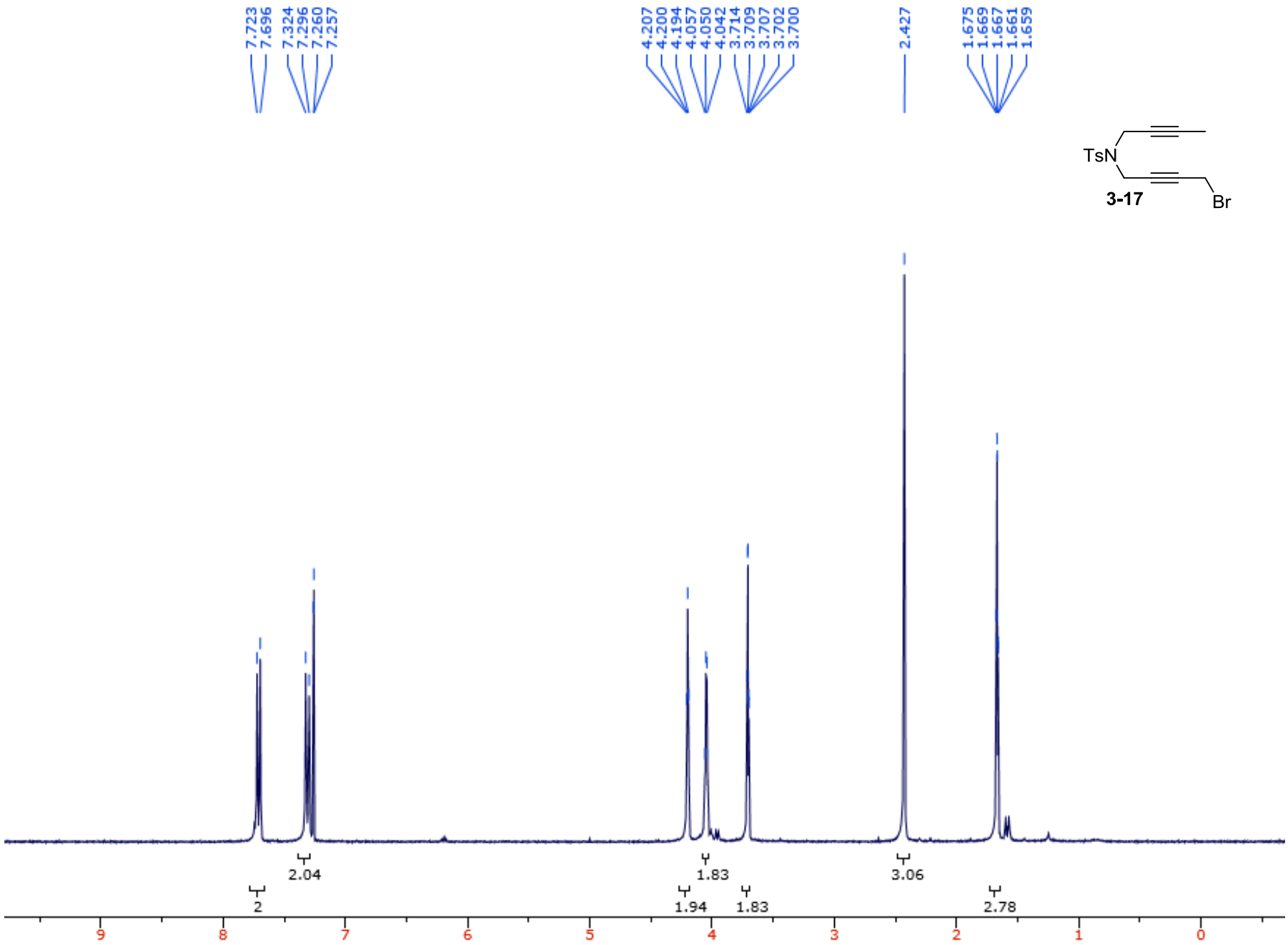
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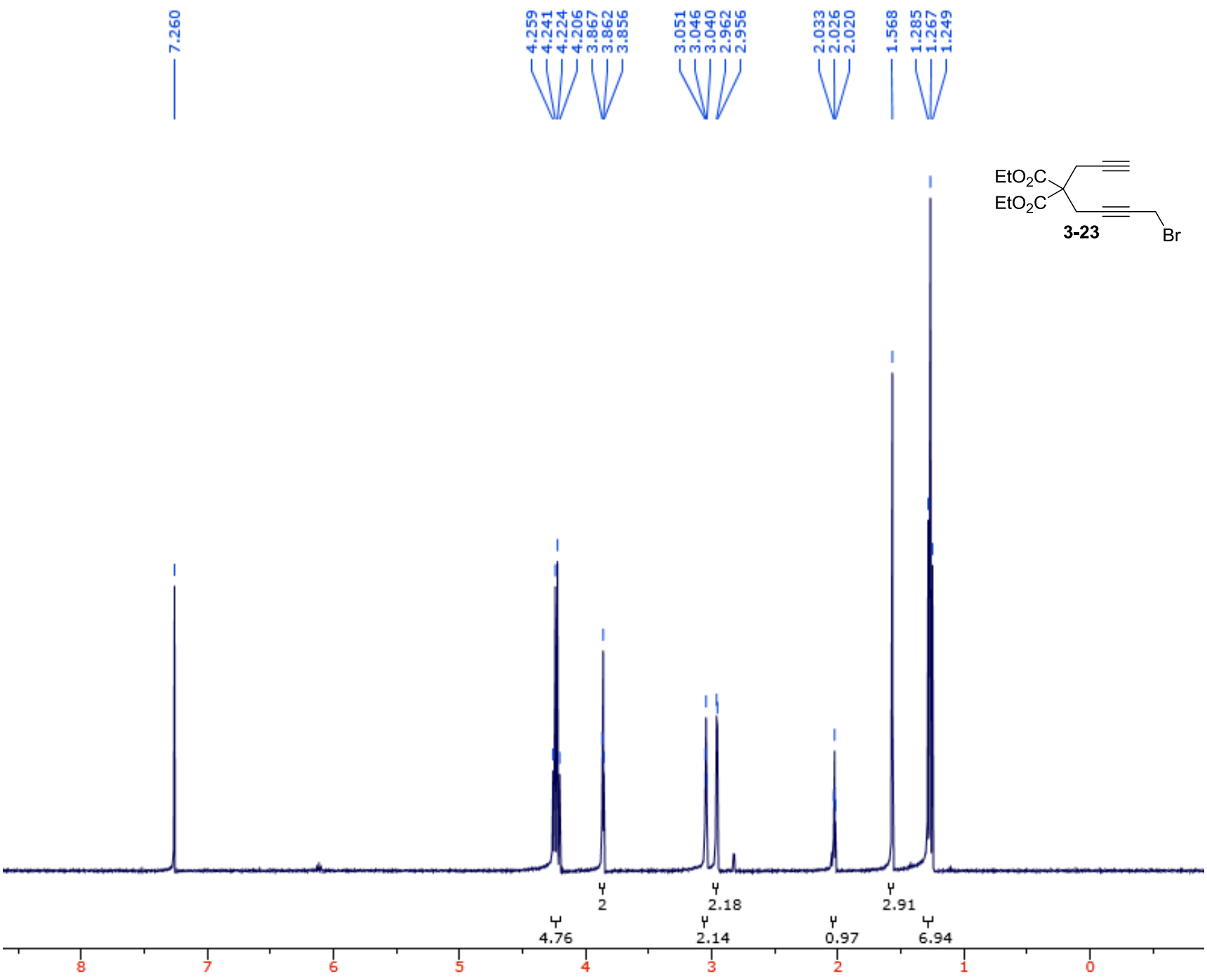
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EtO2C
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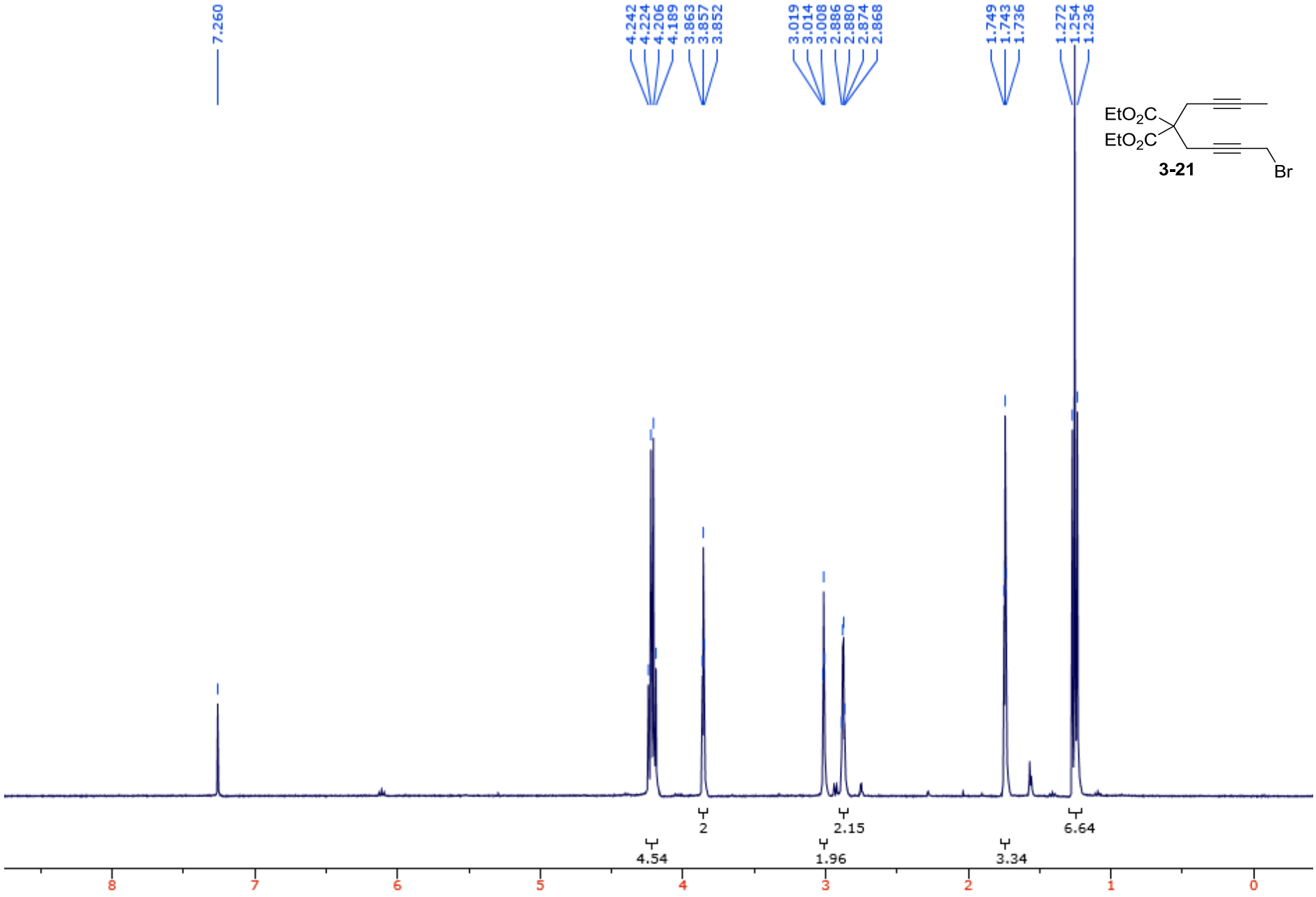
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EtO2C
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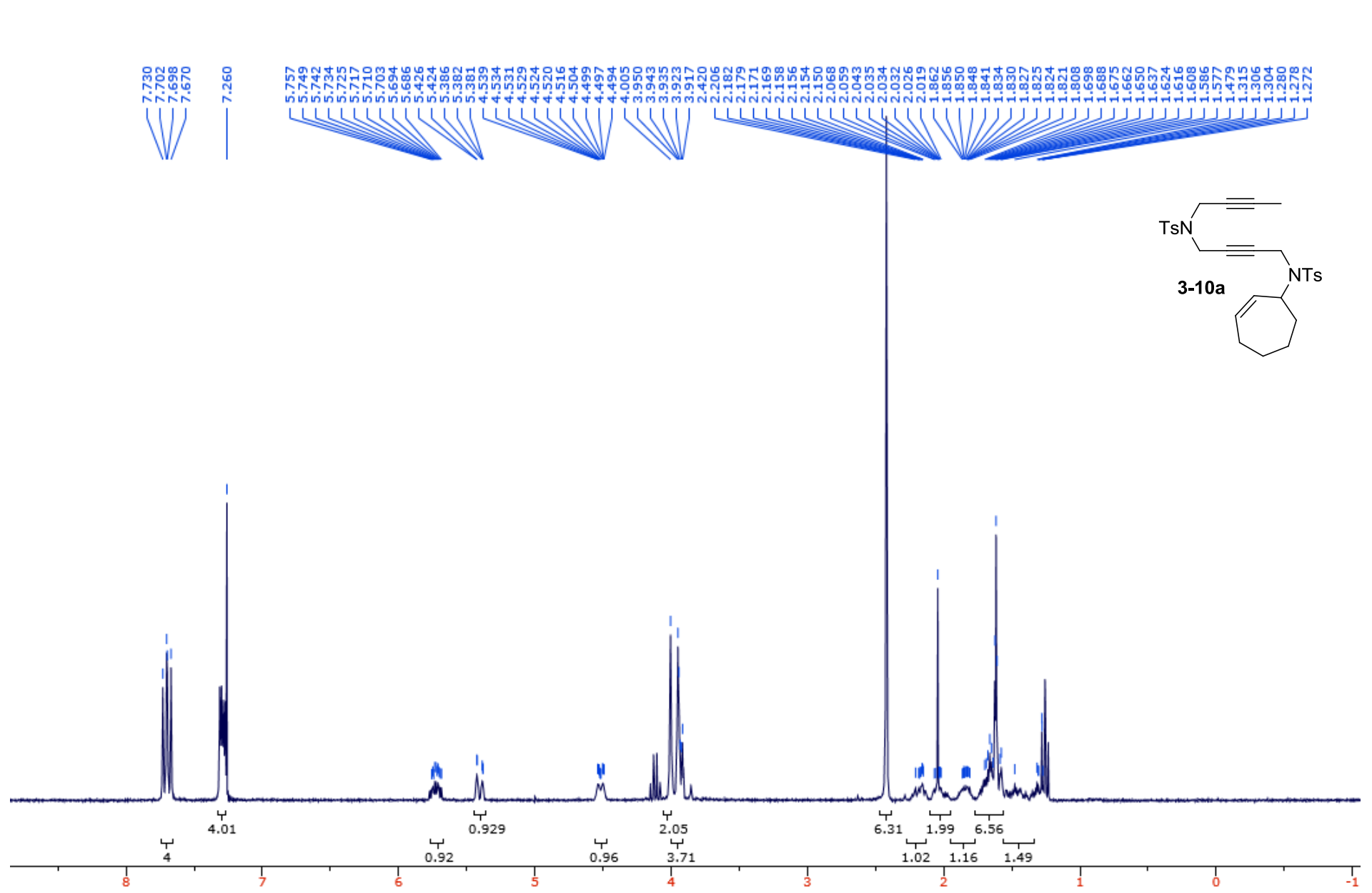
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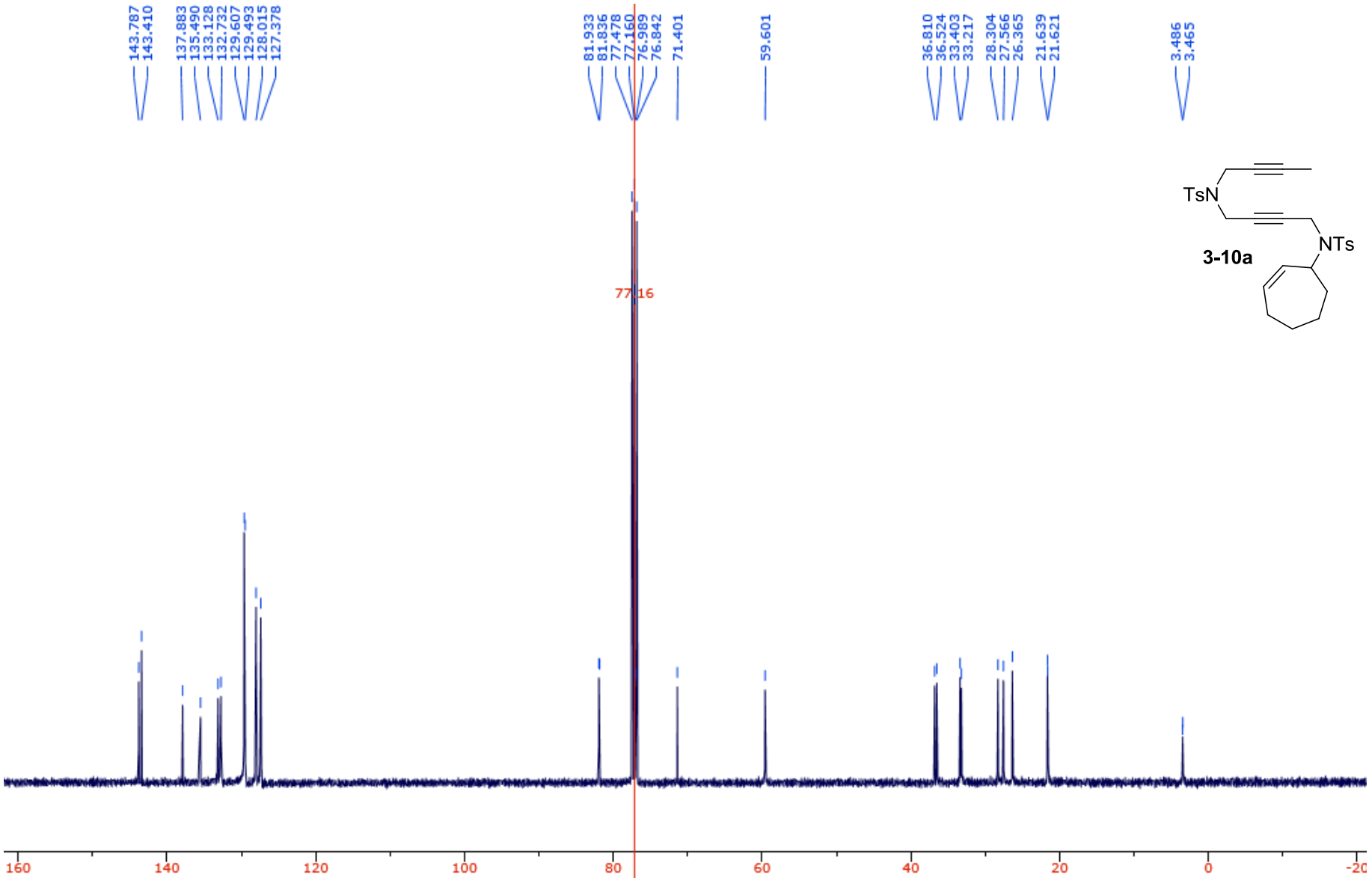
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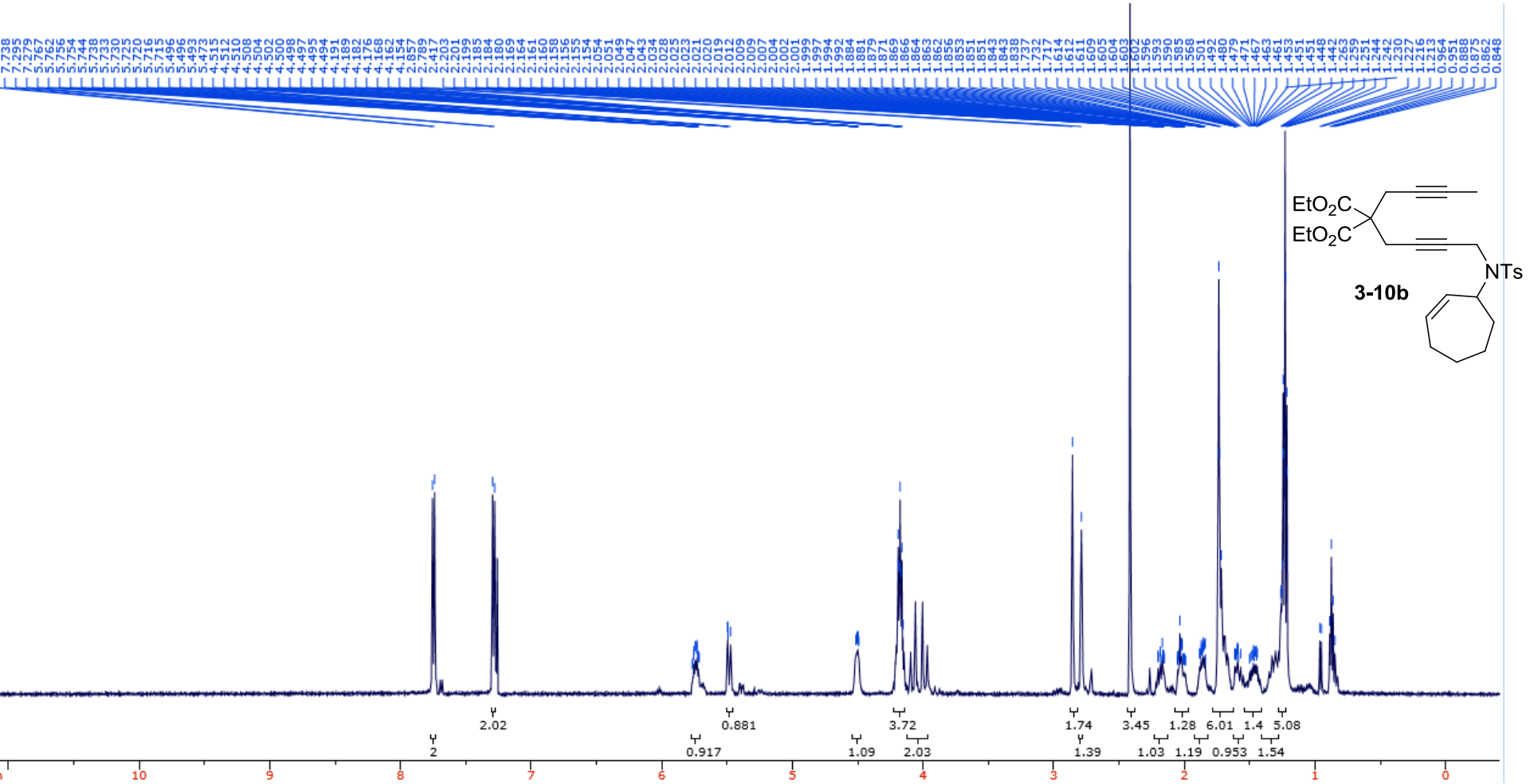
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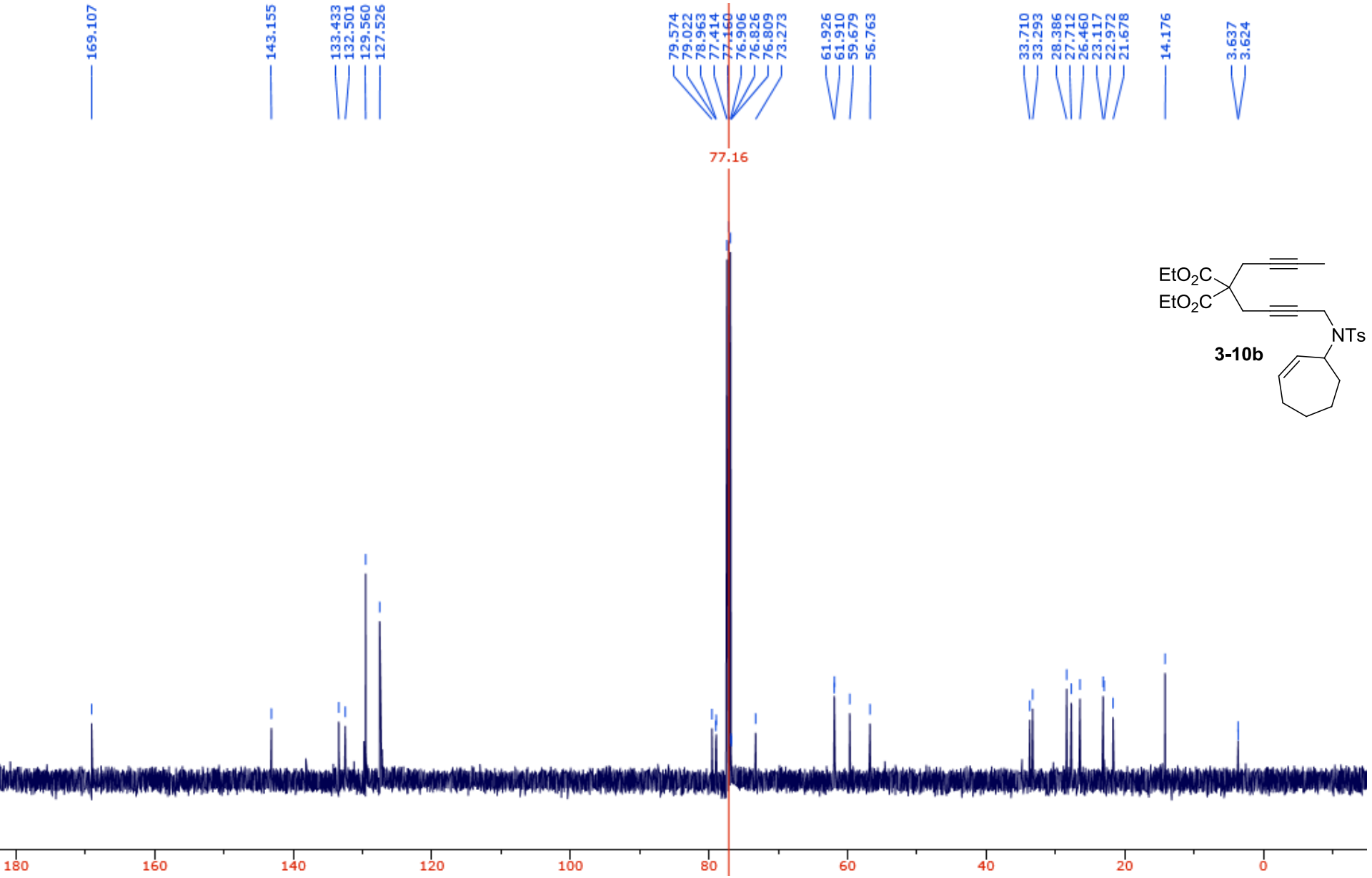
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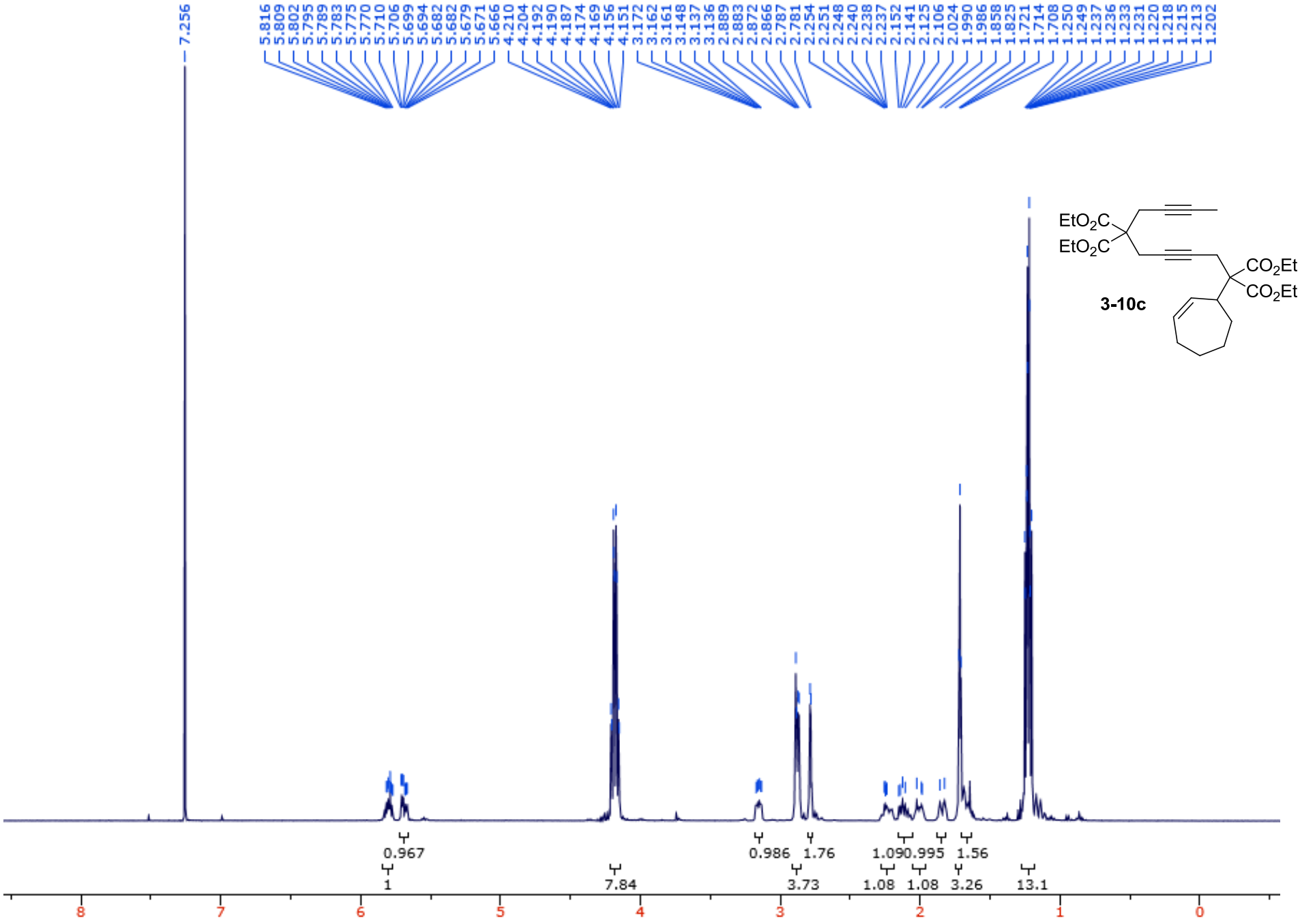
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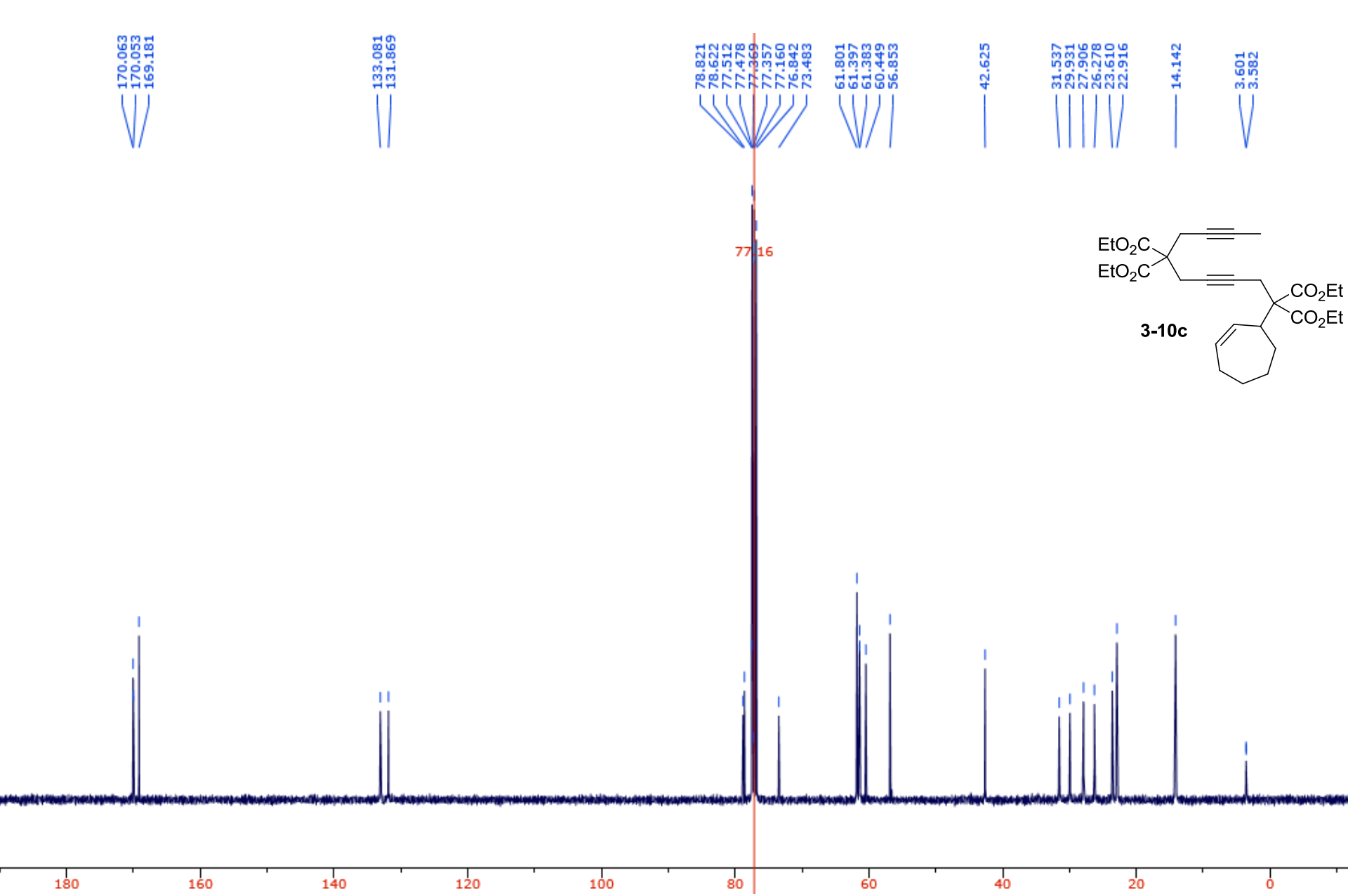
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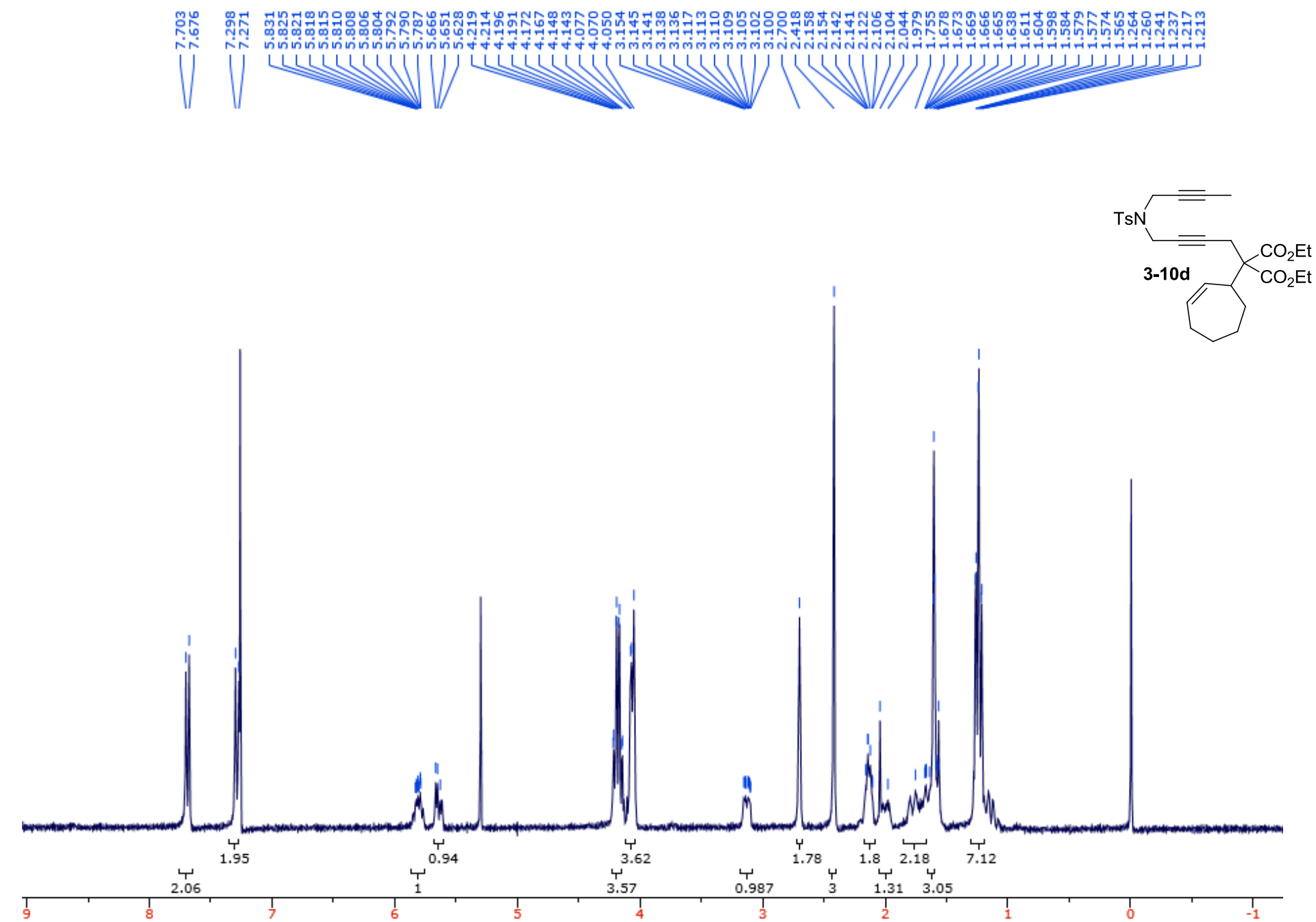
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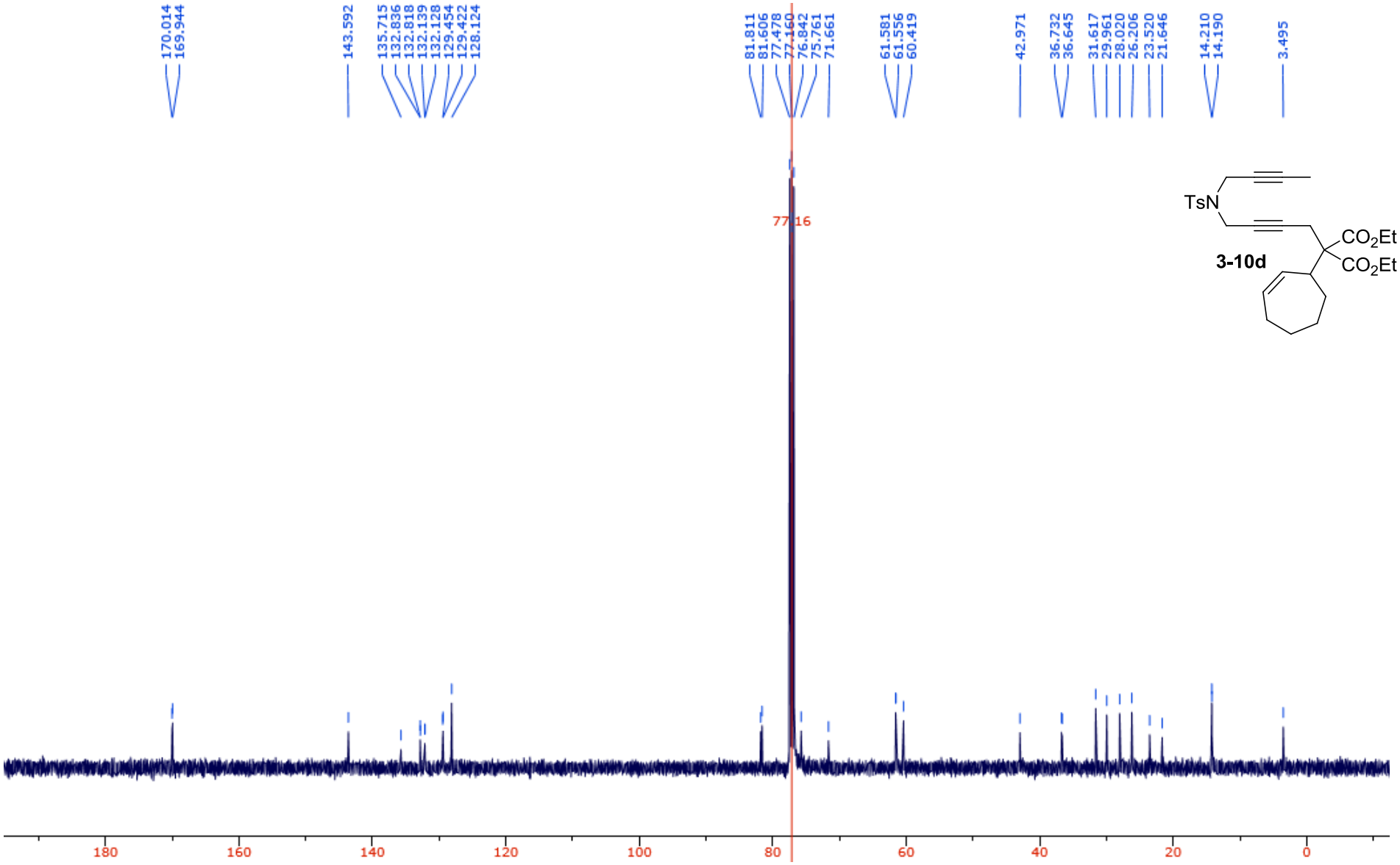
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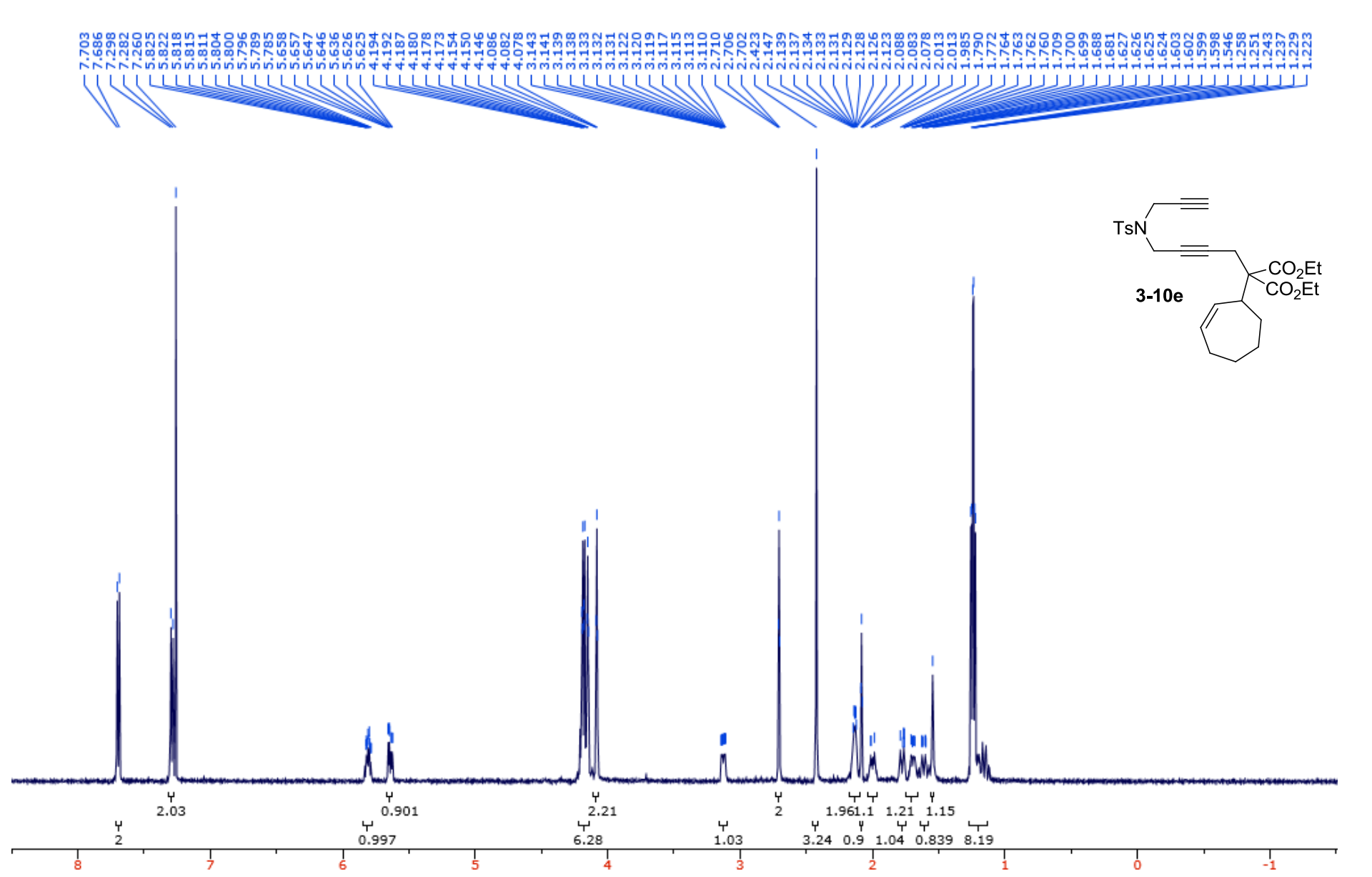
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CO2Et
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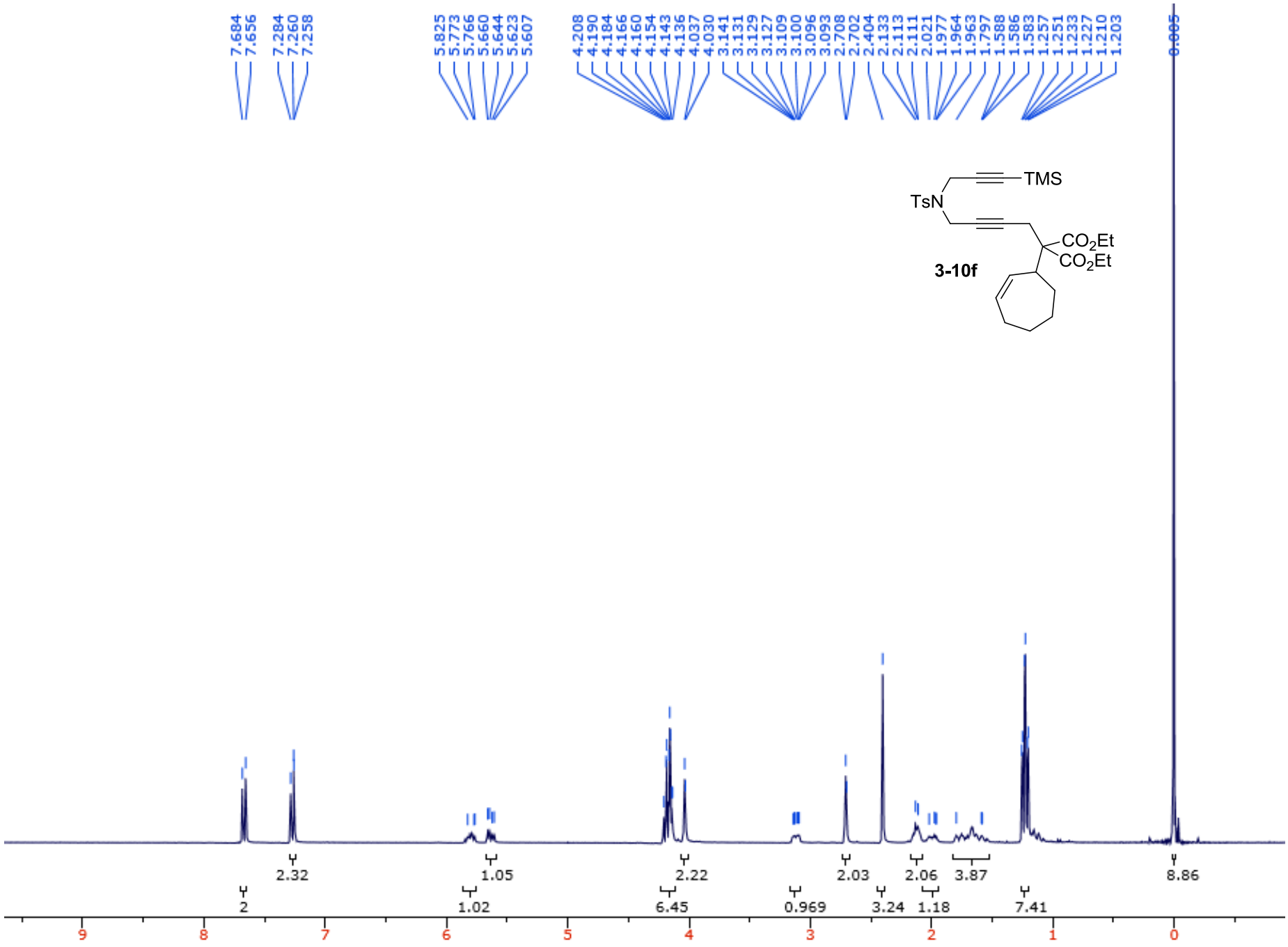
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CO2Et
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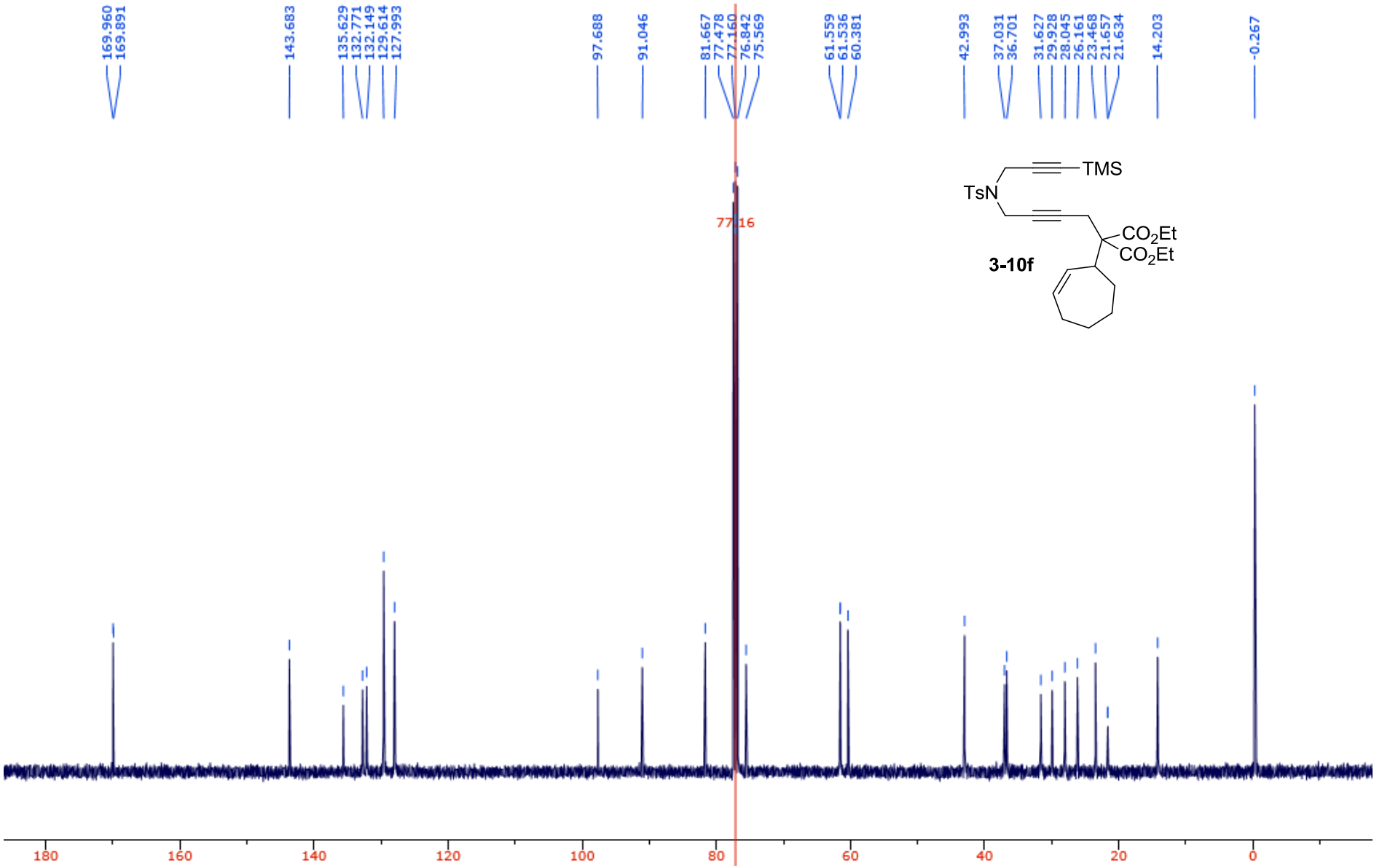
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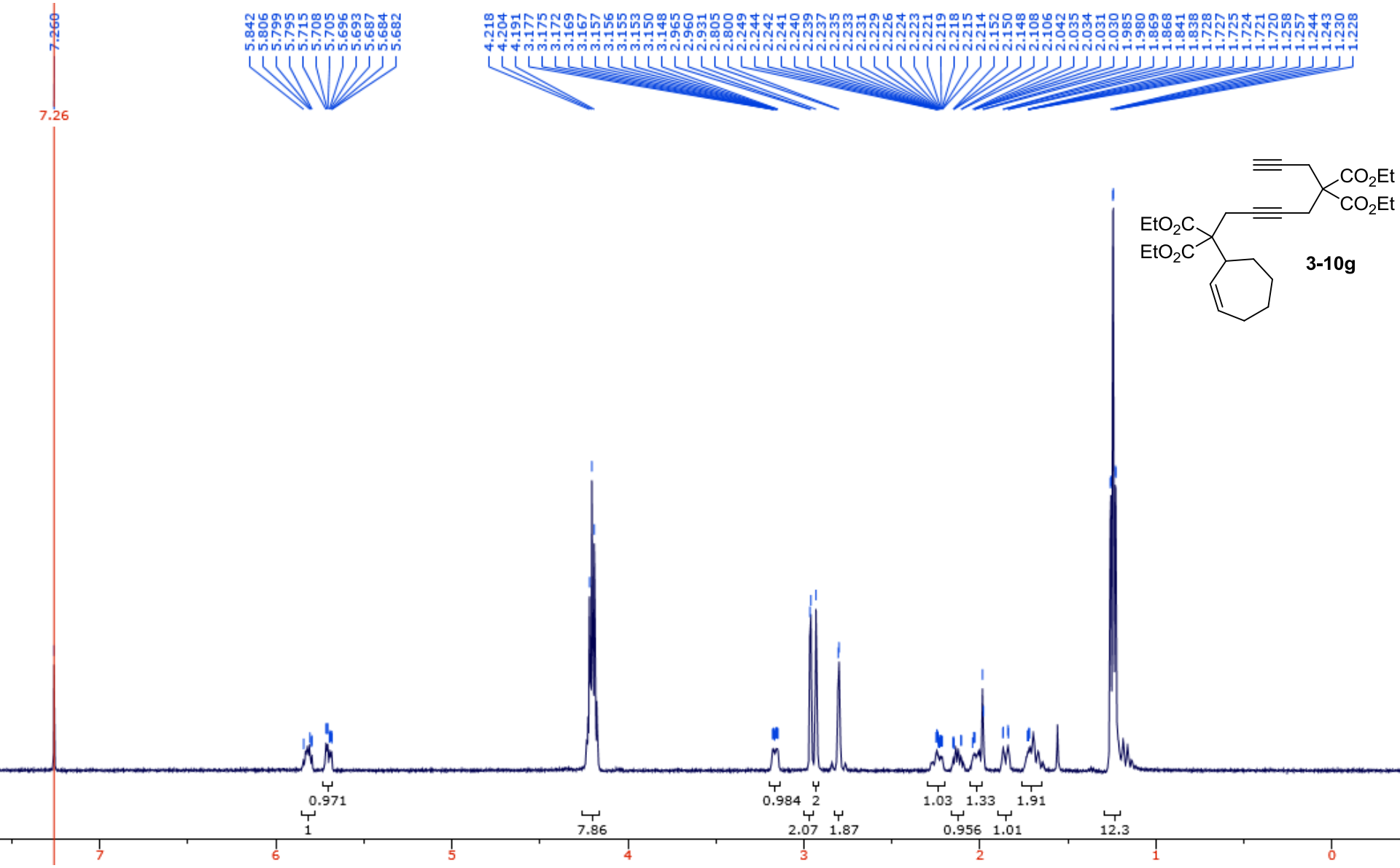
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CO2Et
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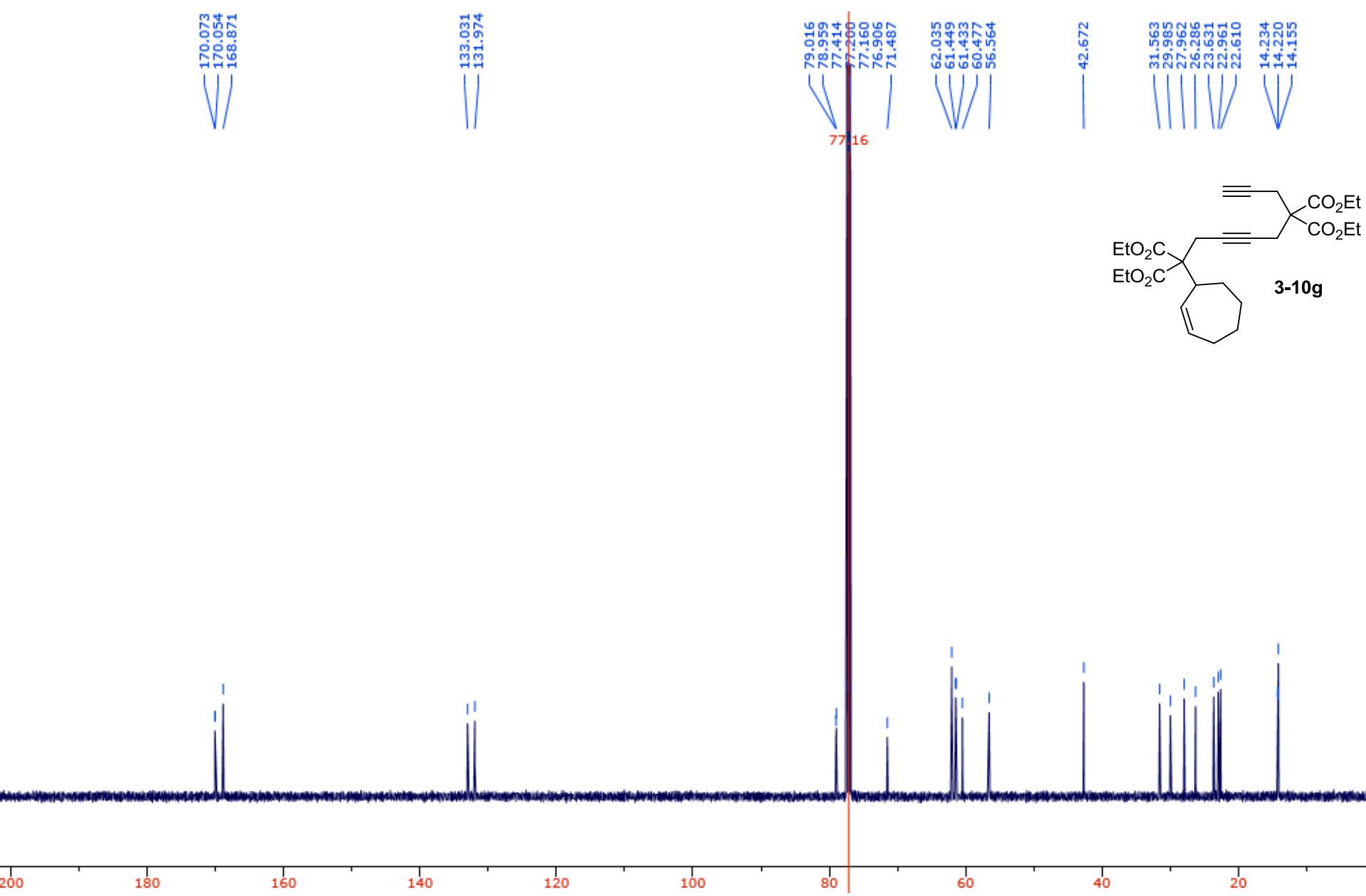
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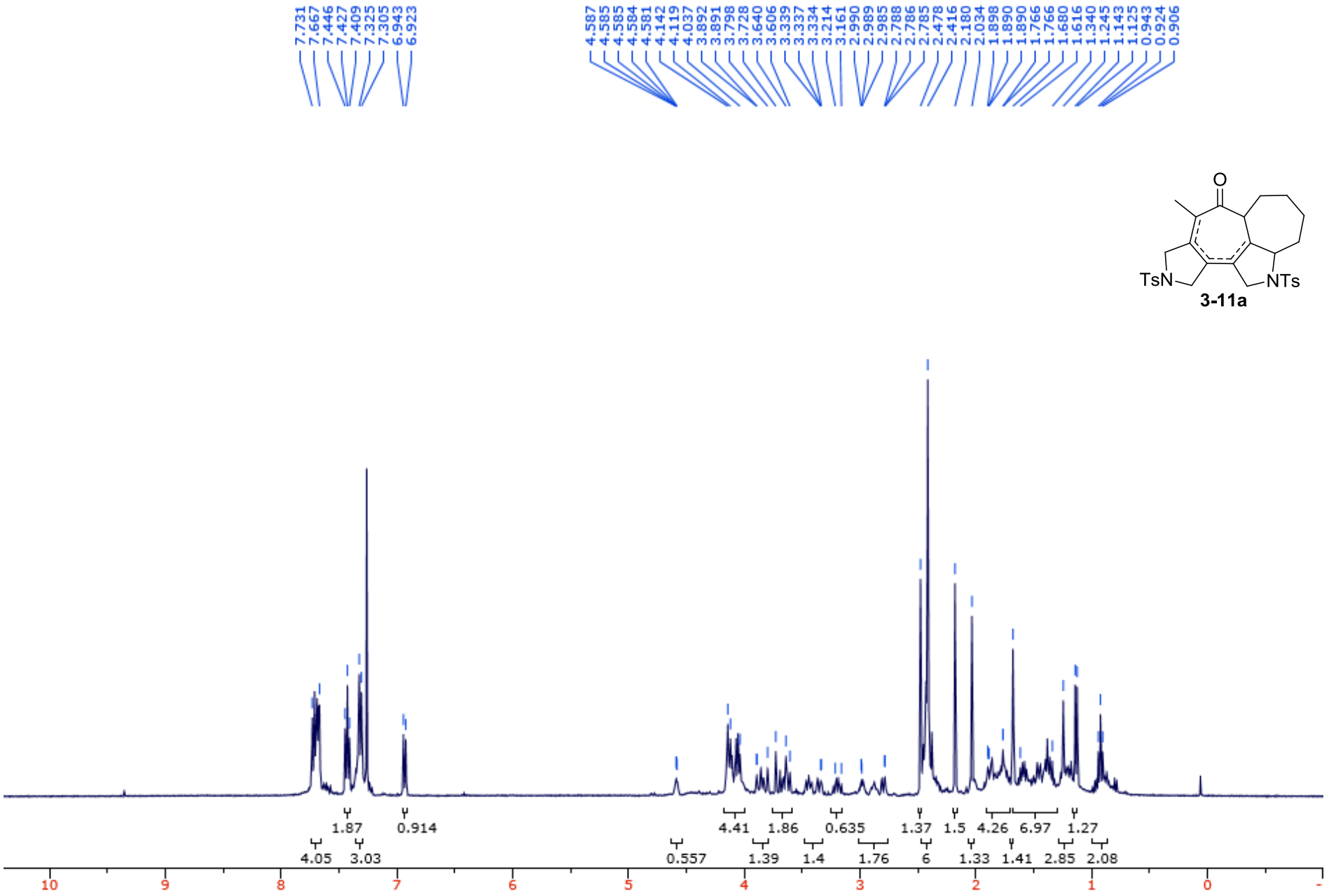
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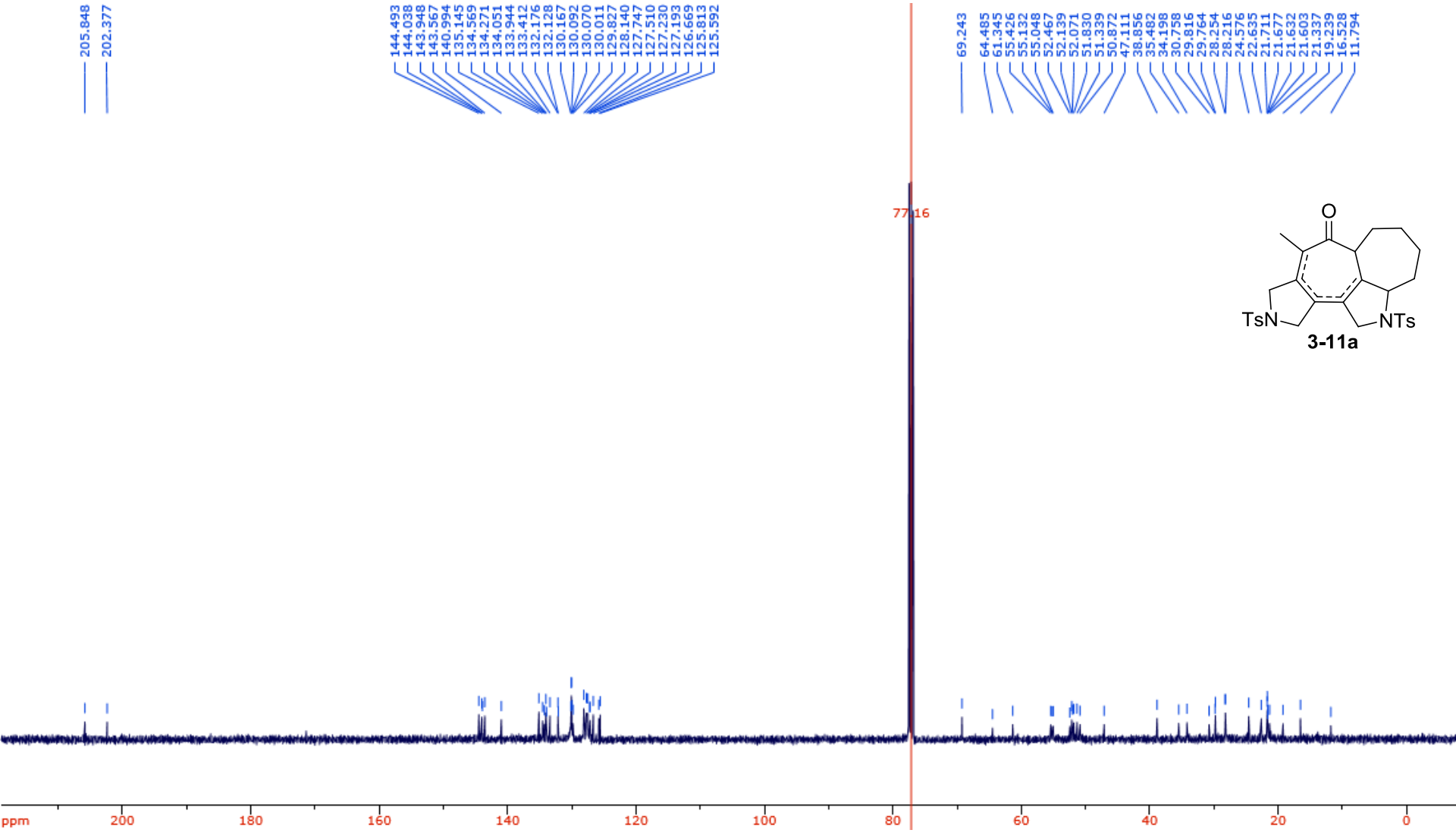
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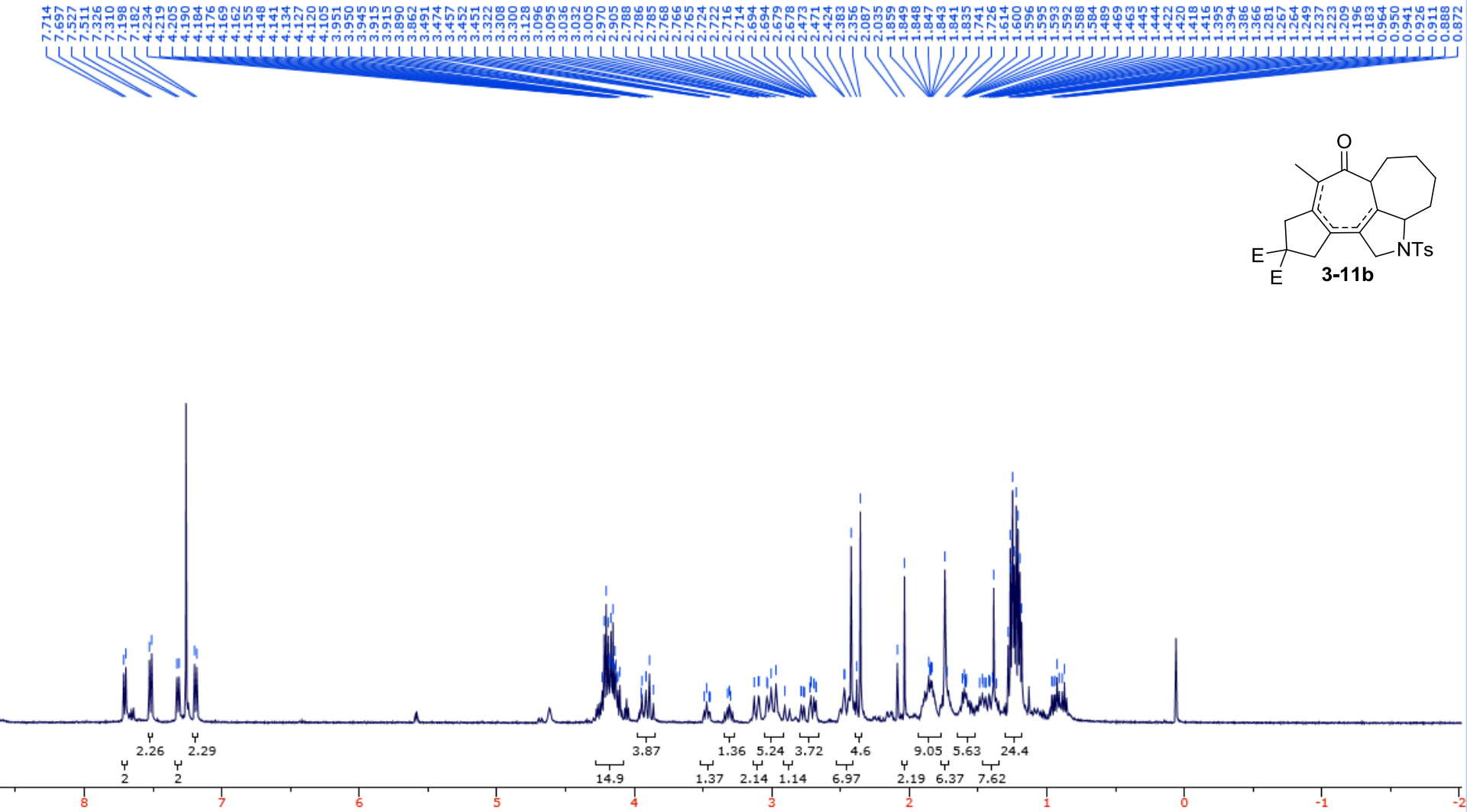
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NTs
E
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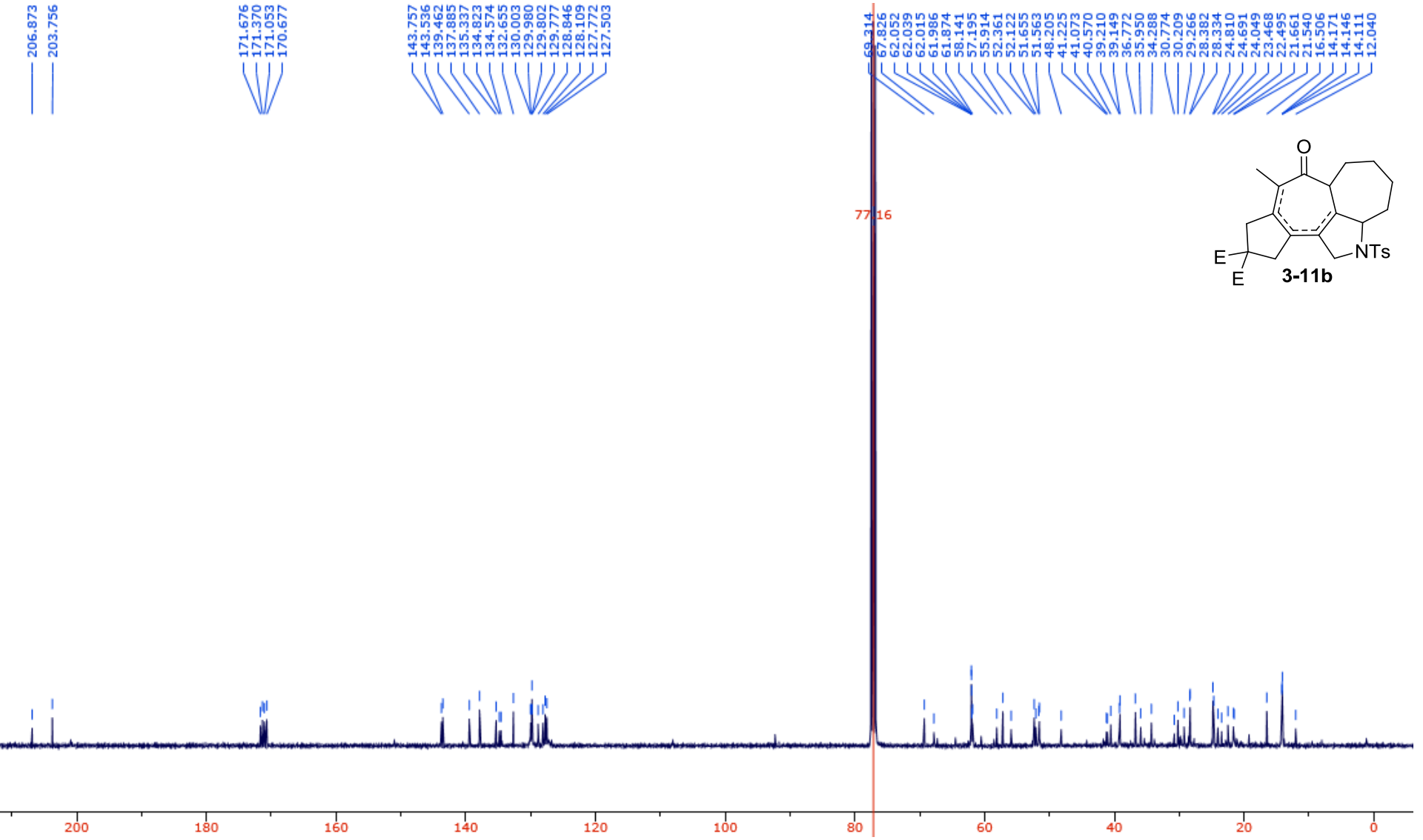
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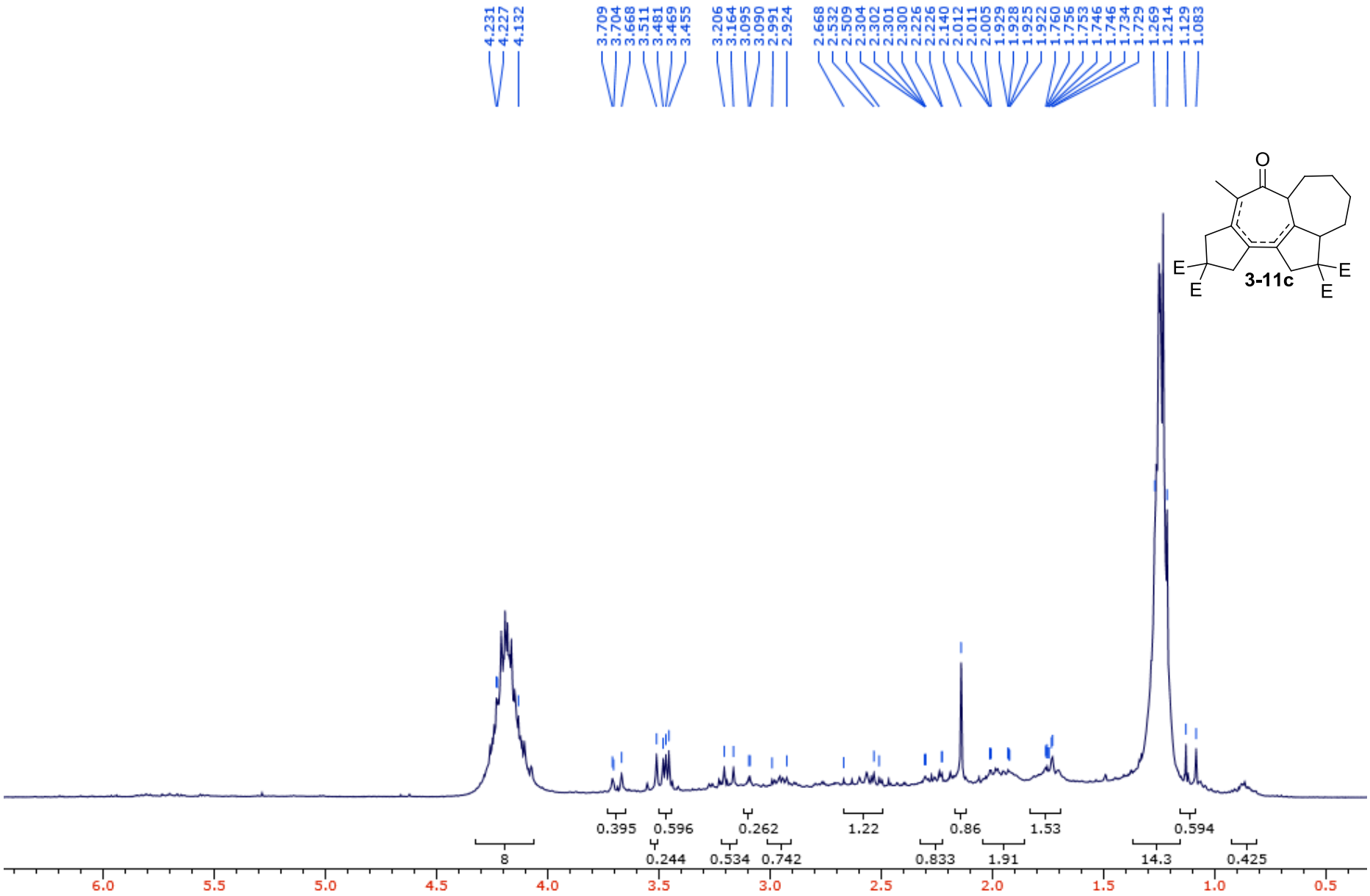
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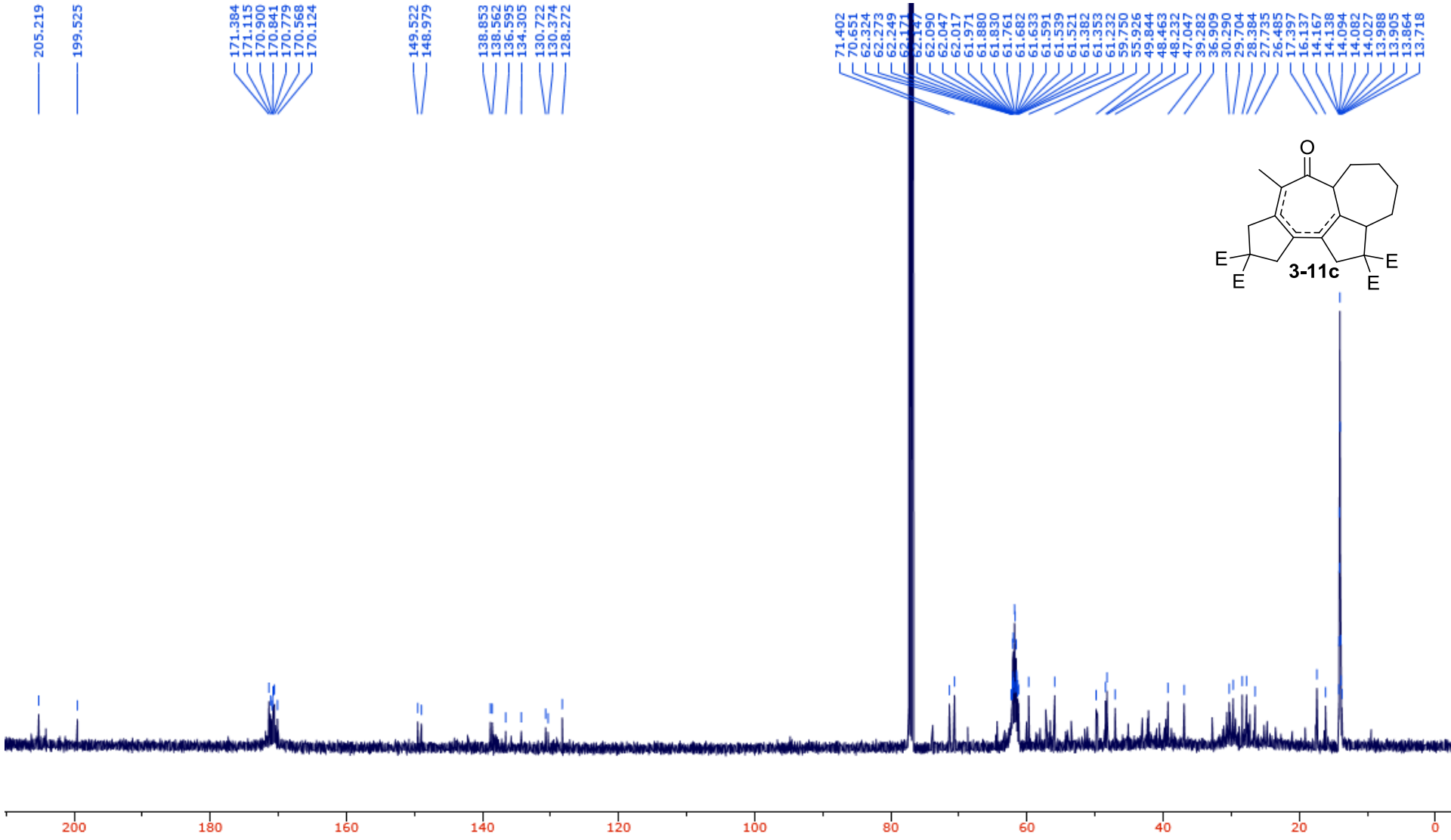
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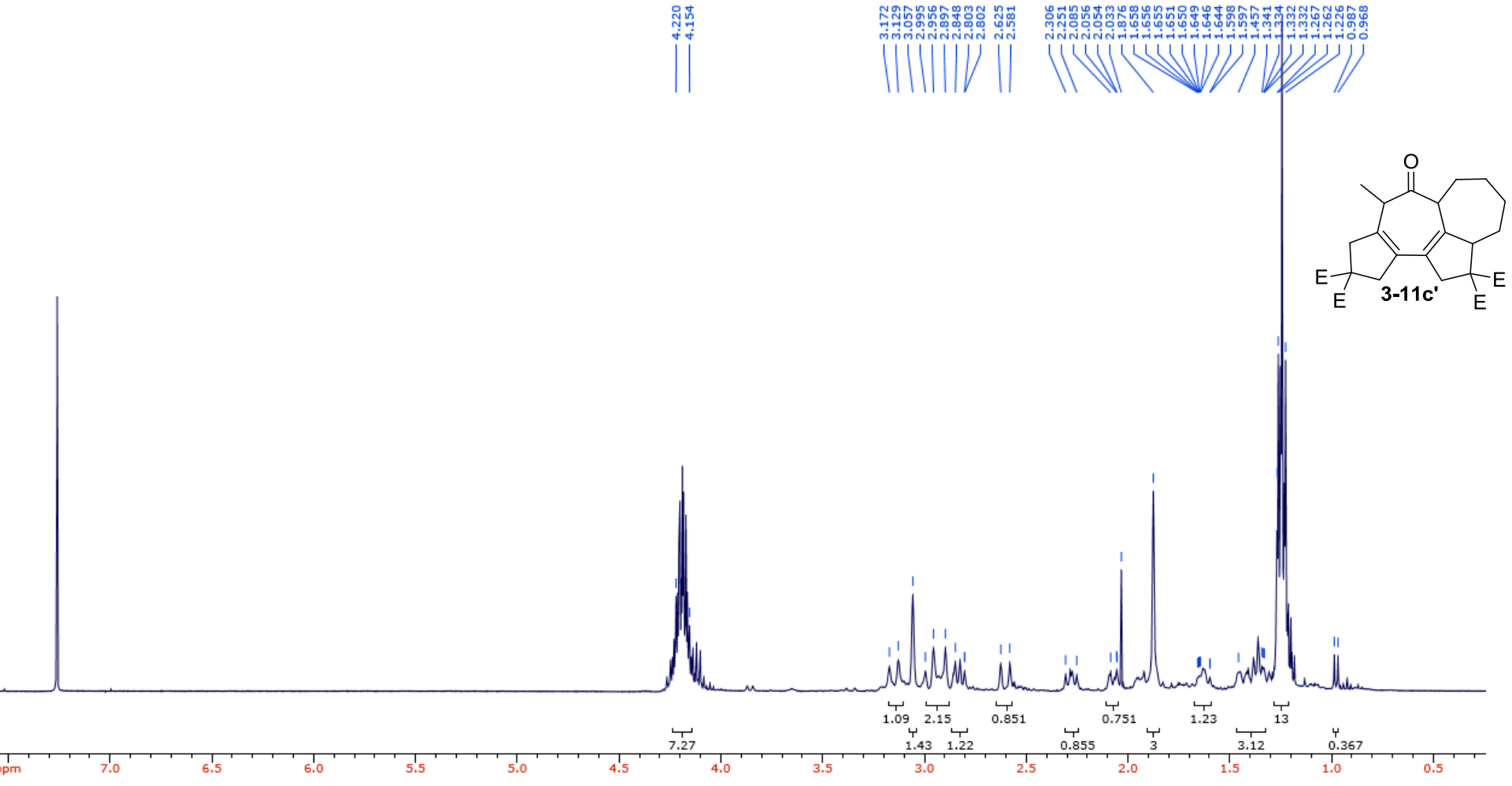
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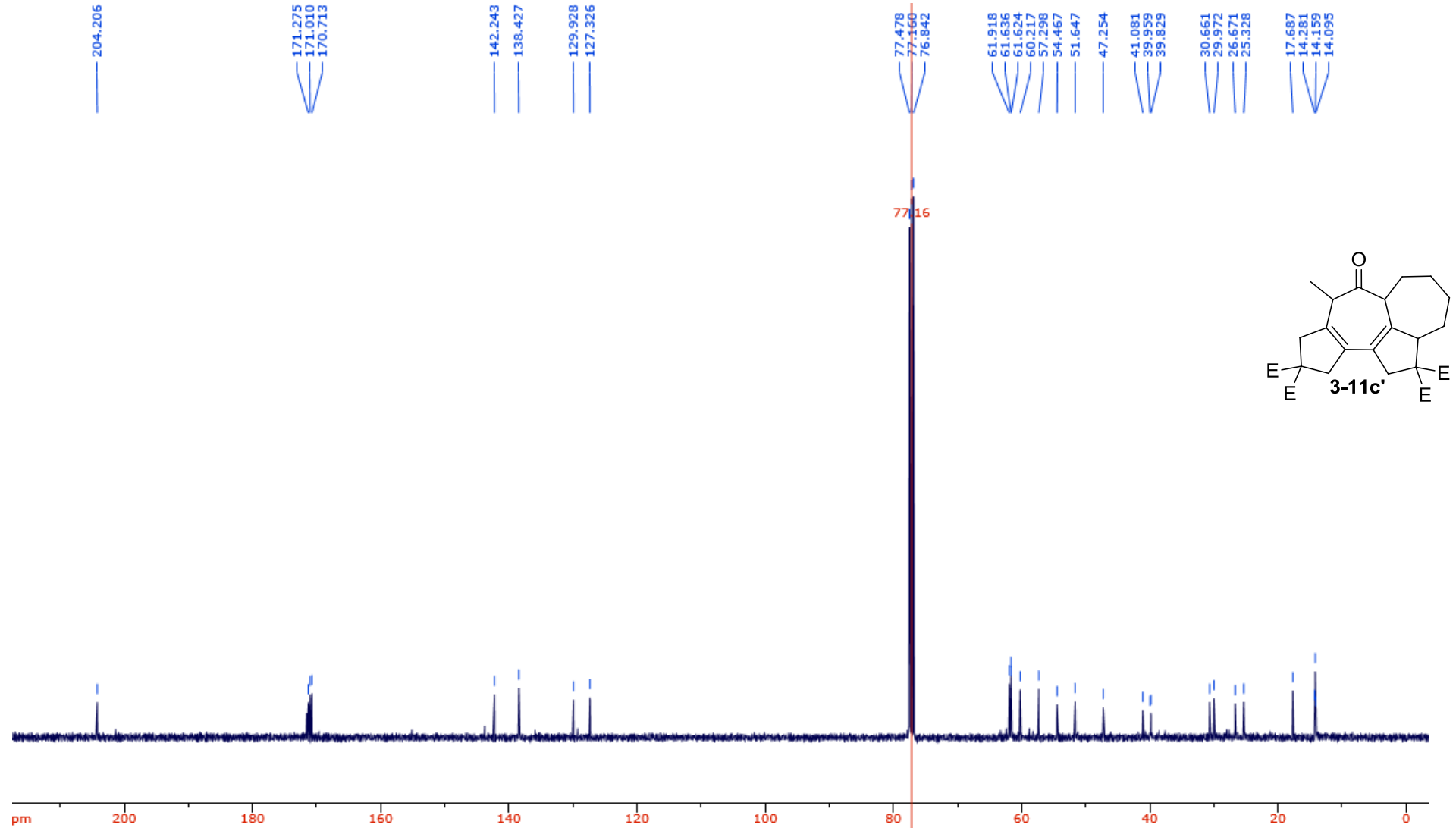
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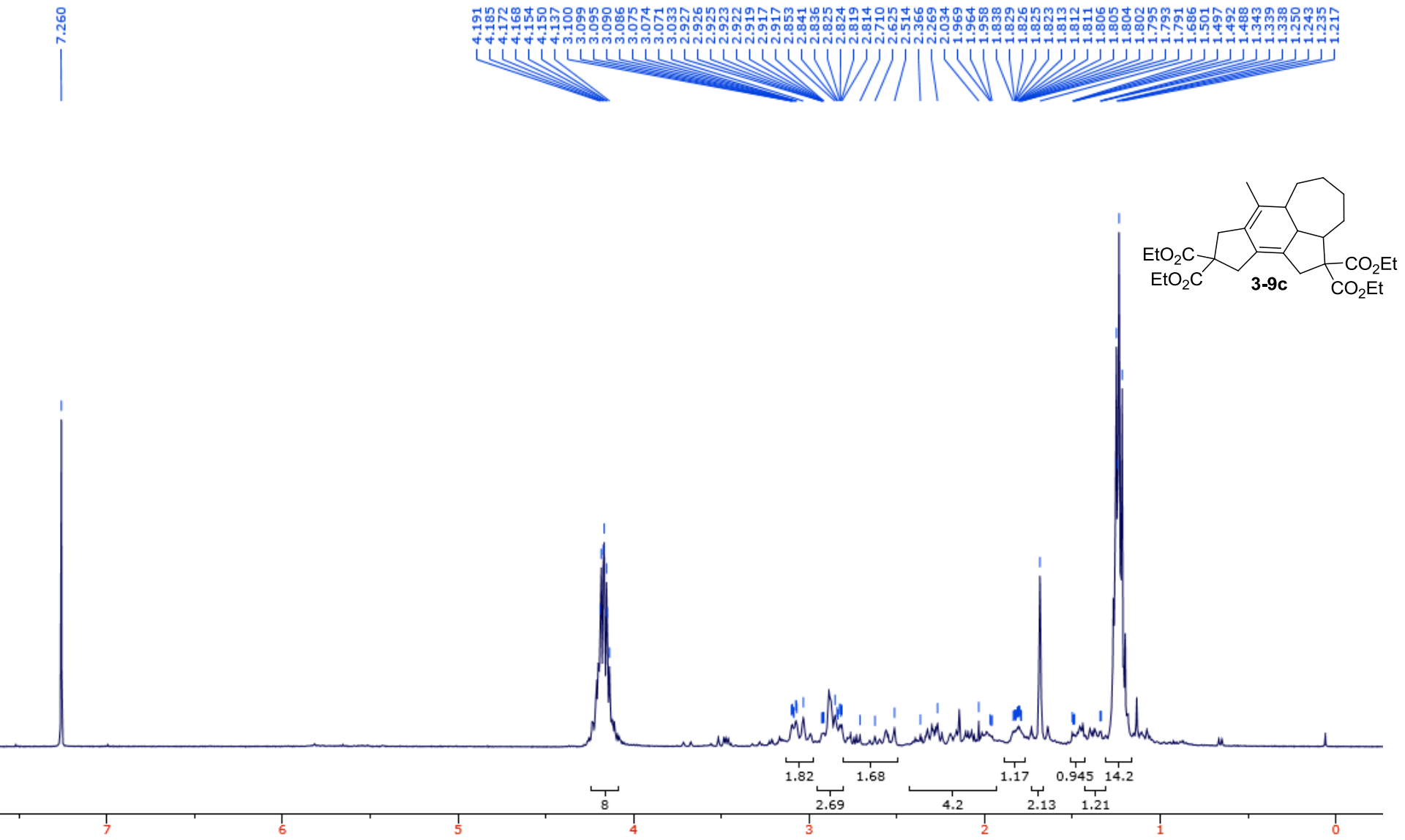
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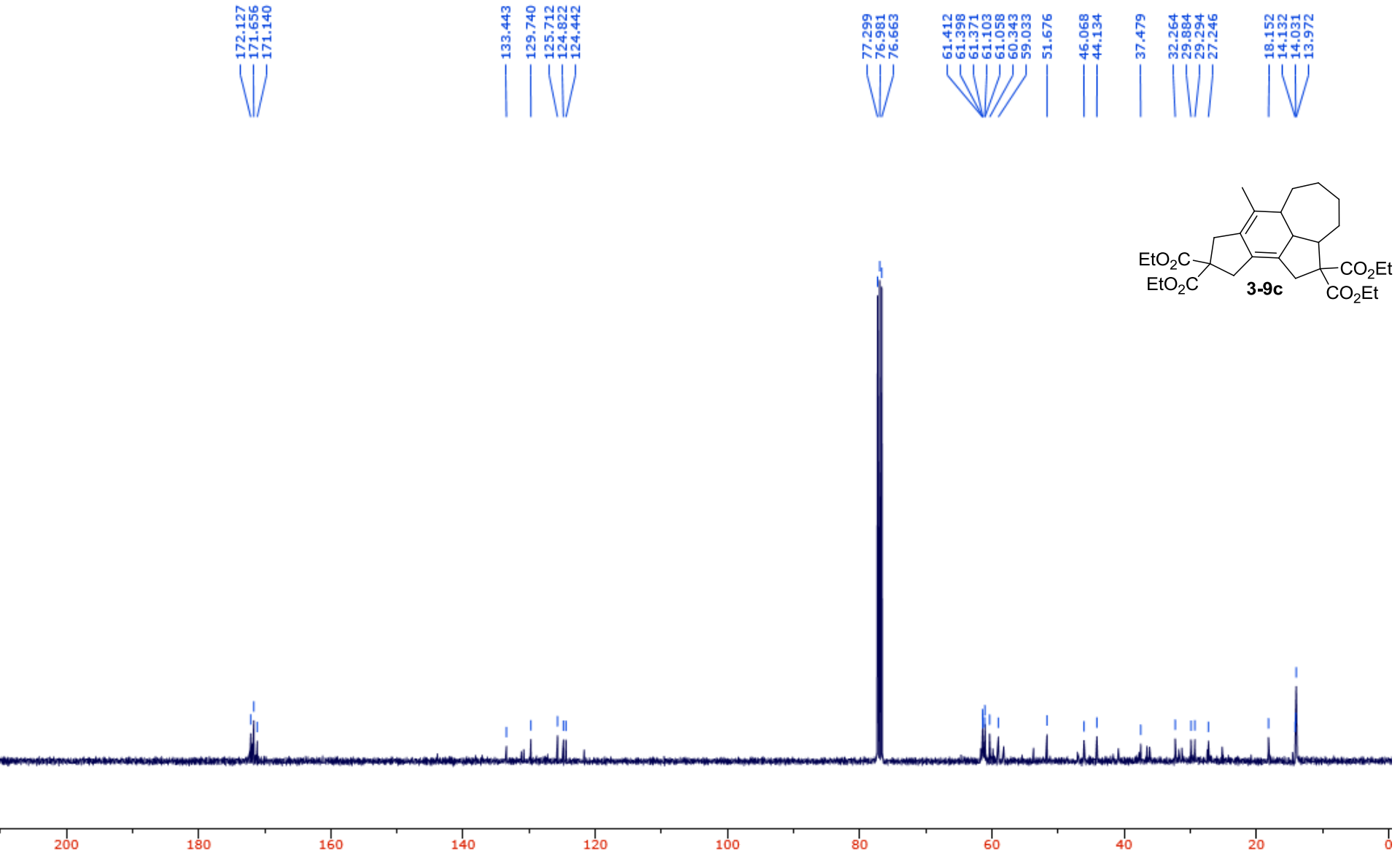
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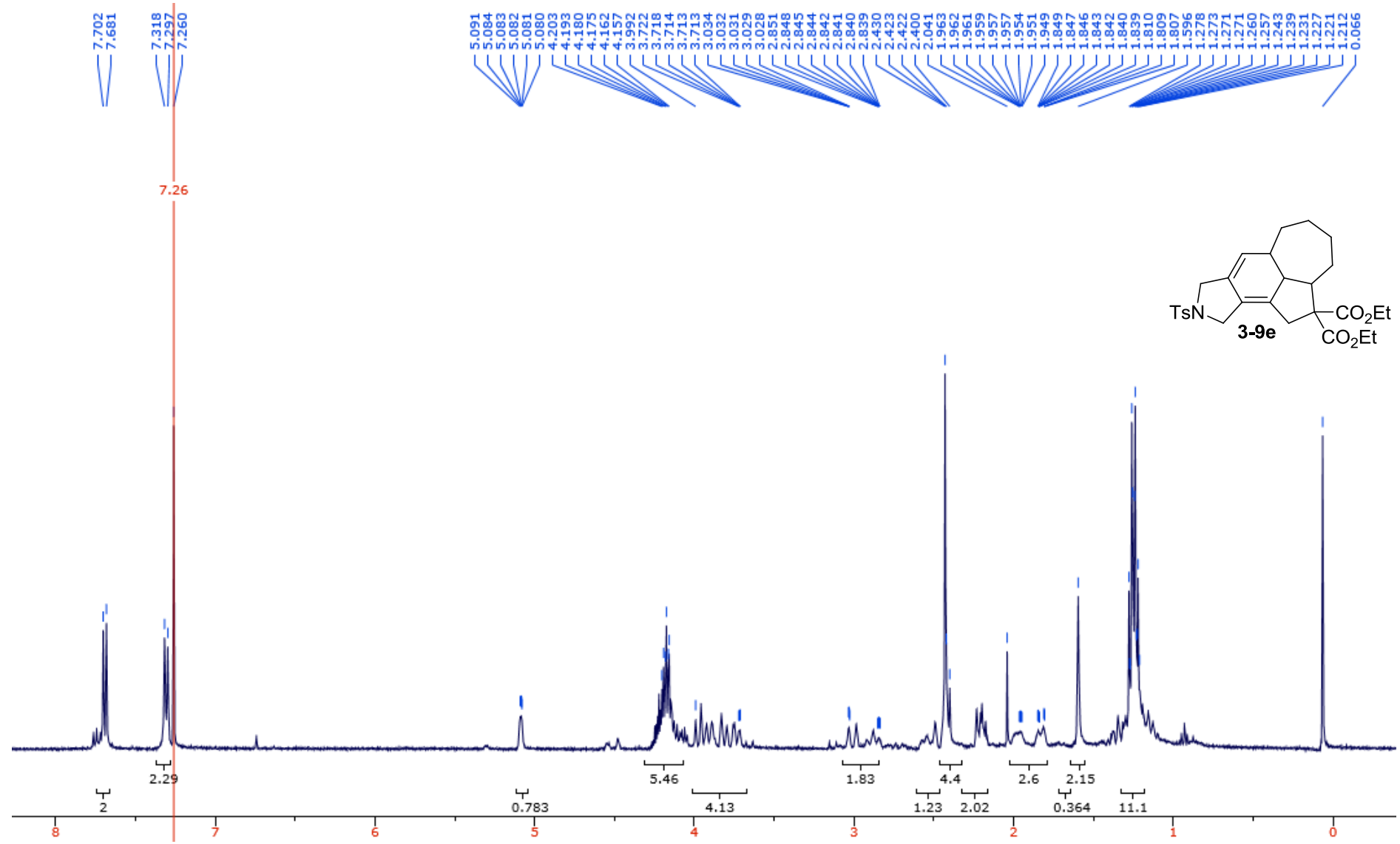
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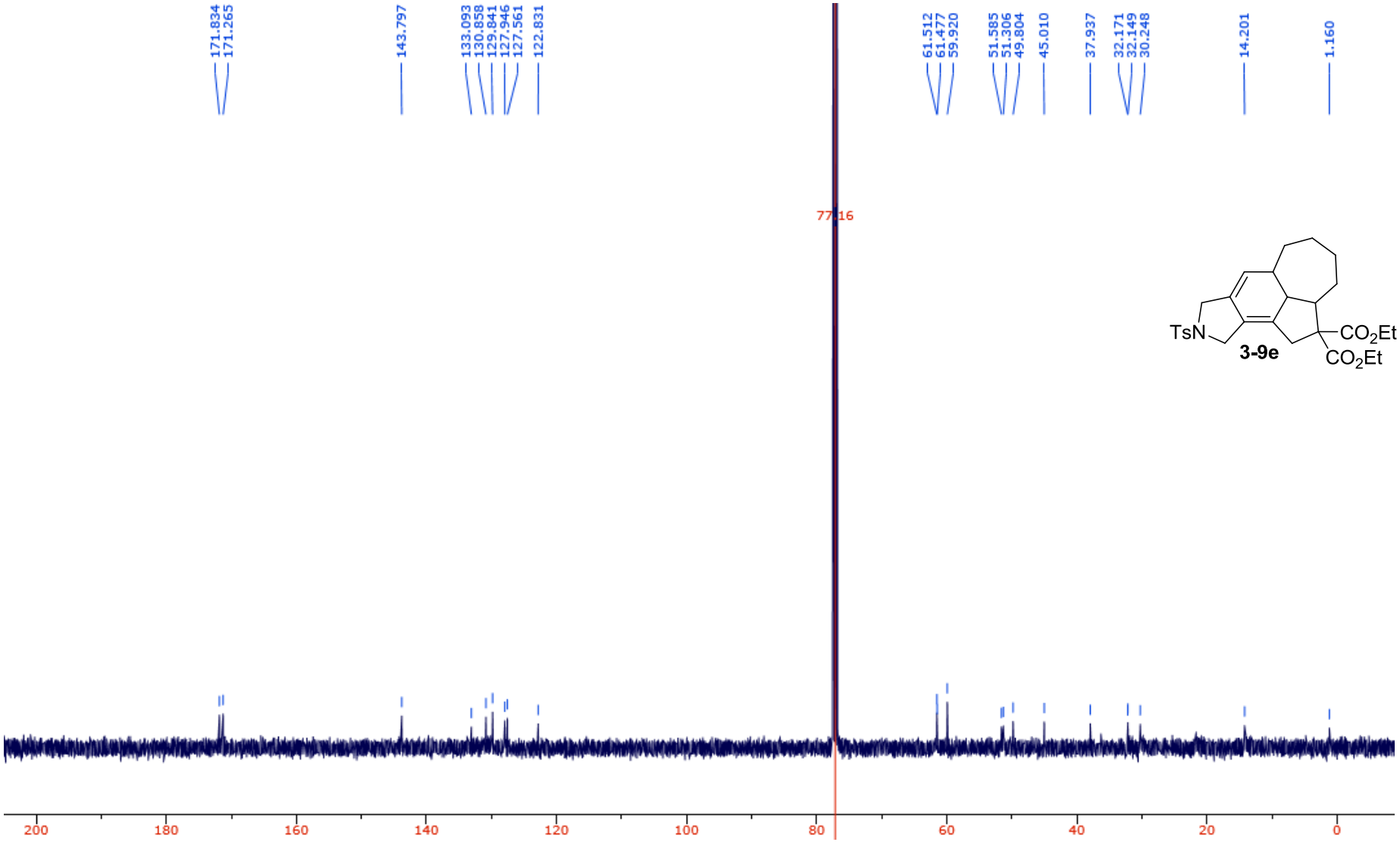
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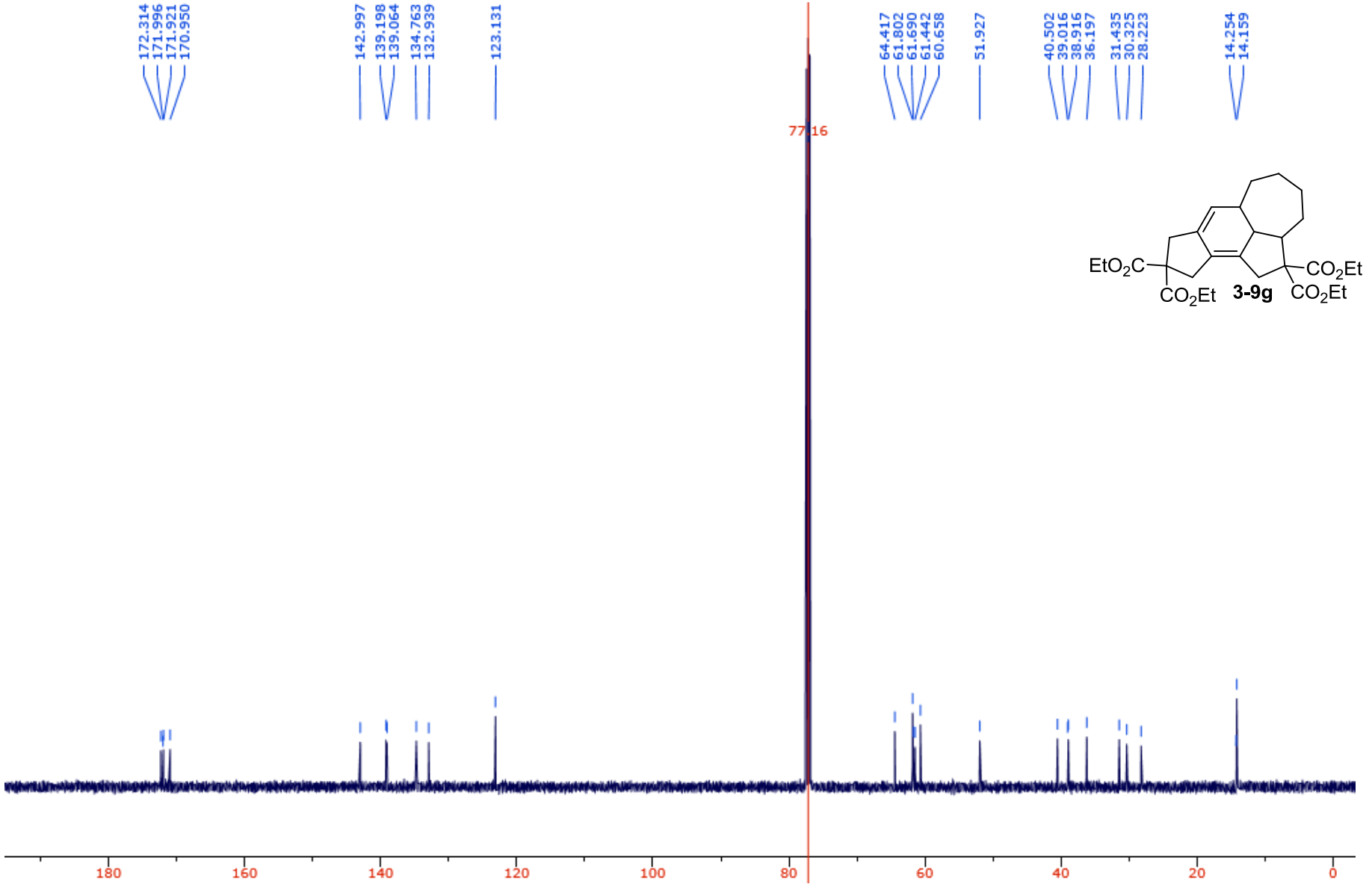
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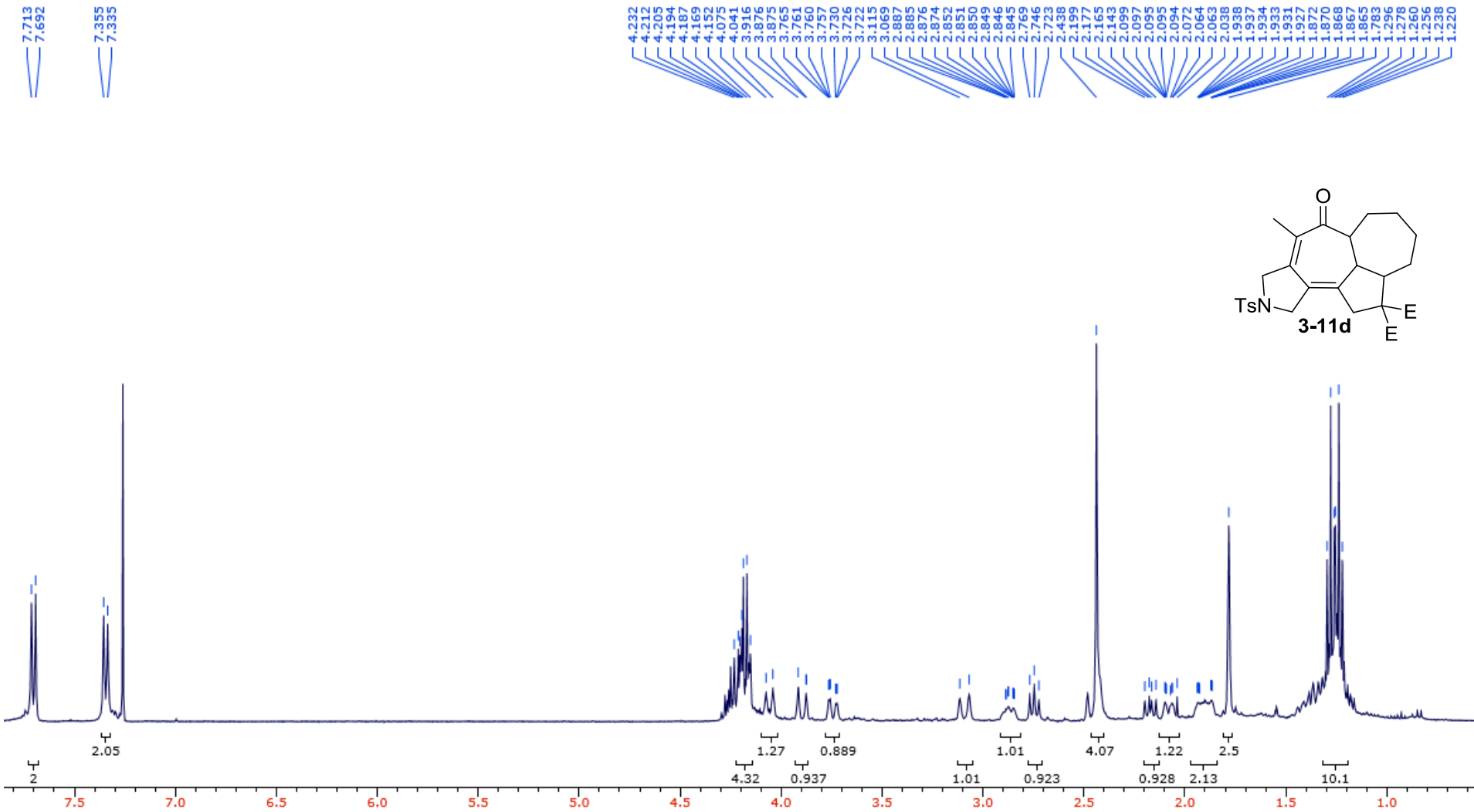
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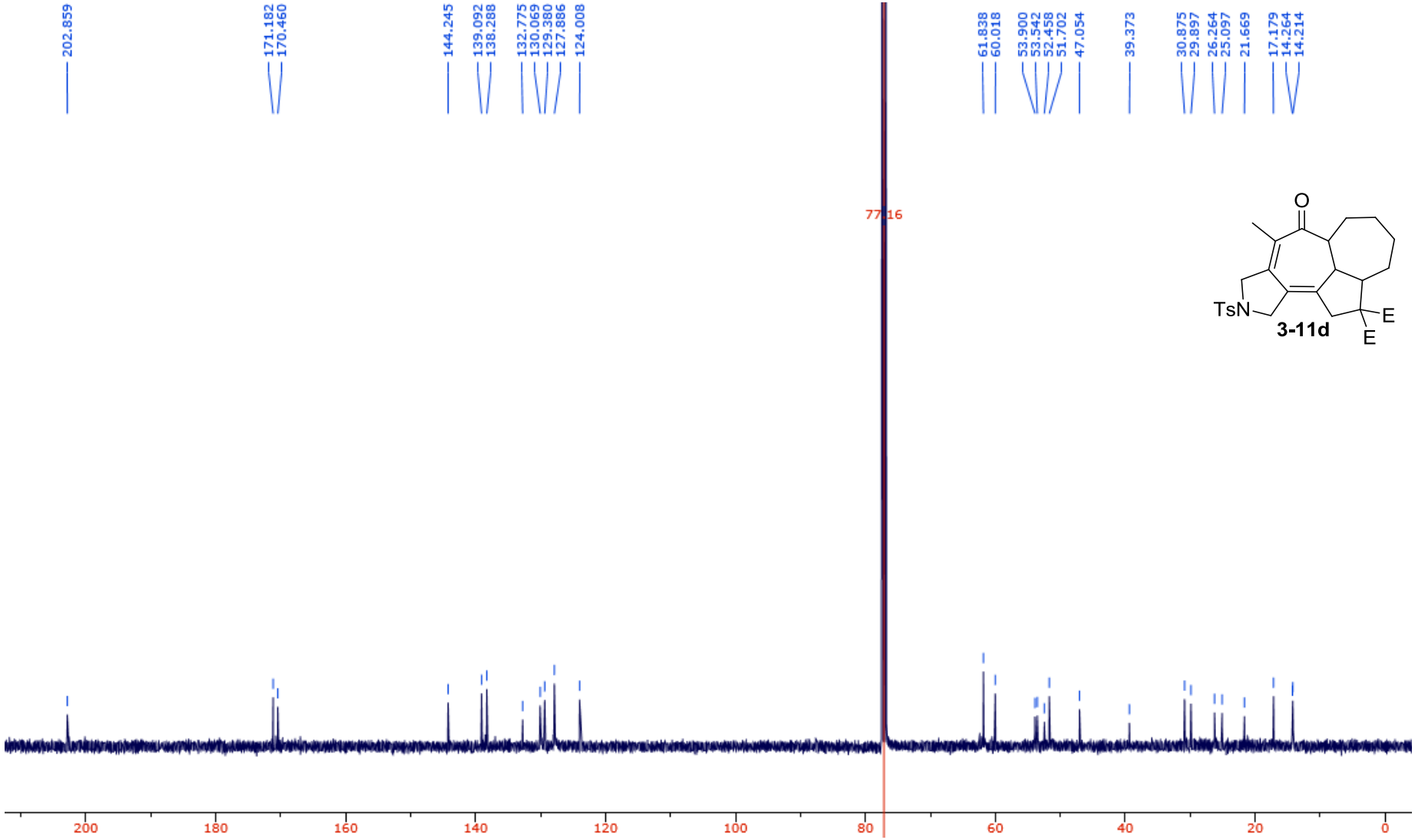
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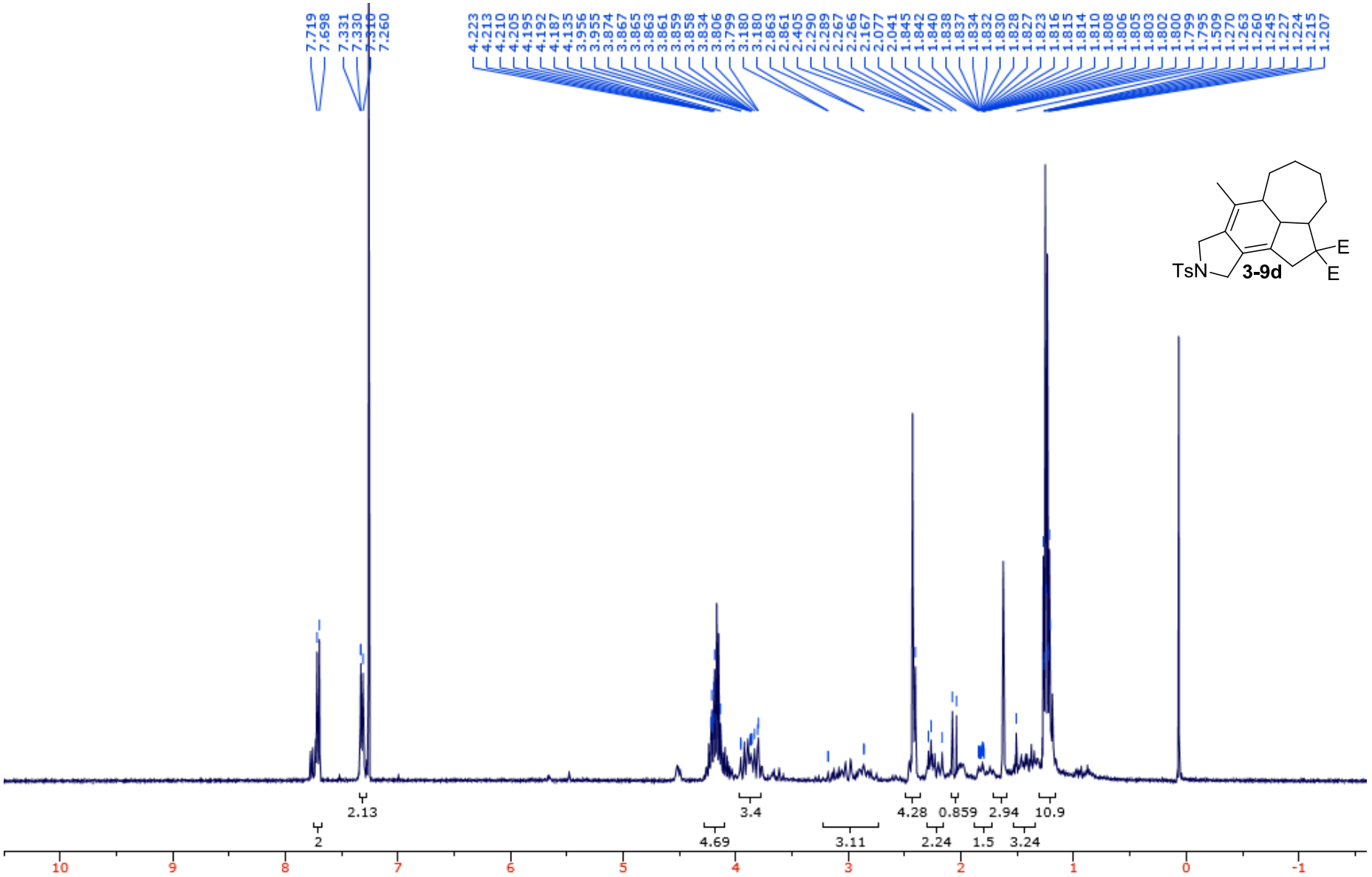
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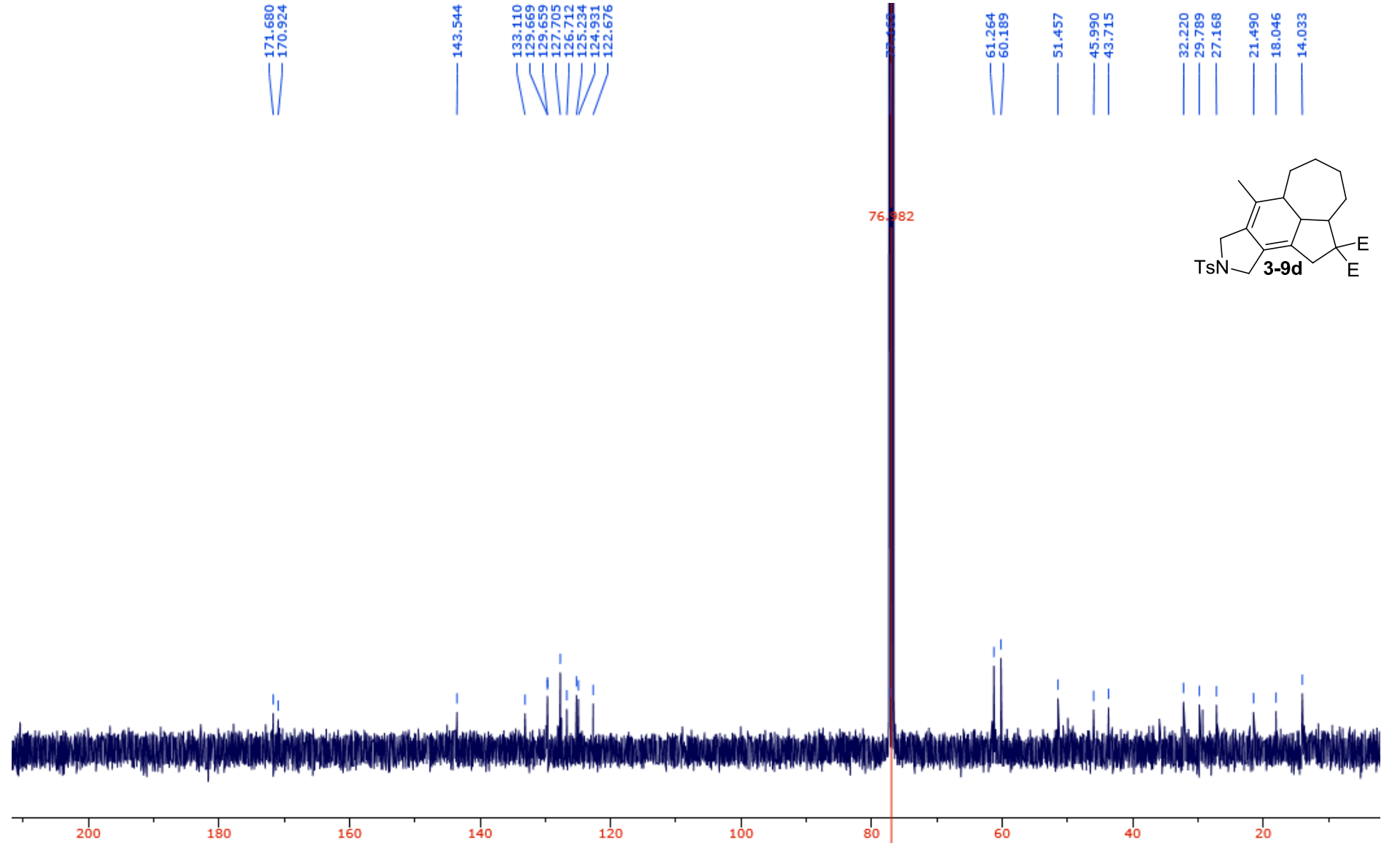
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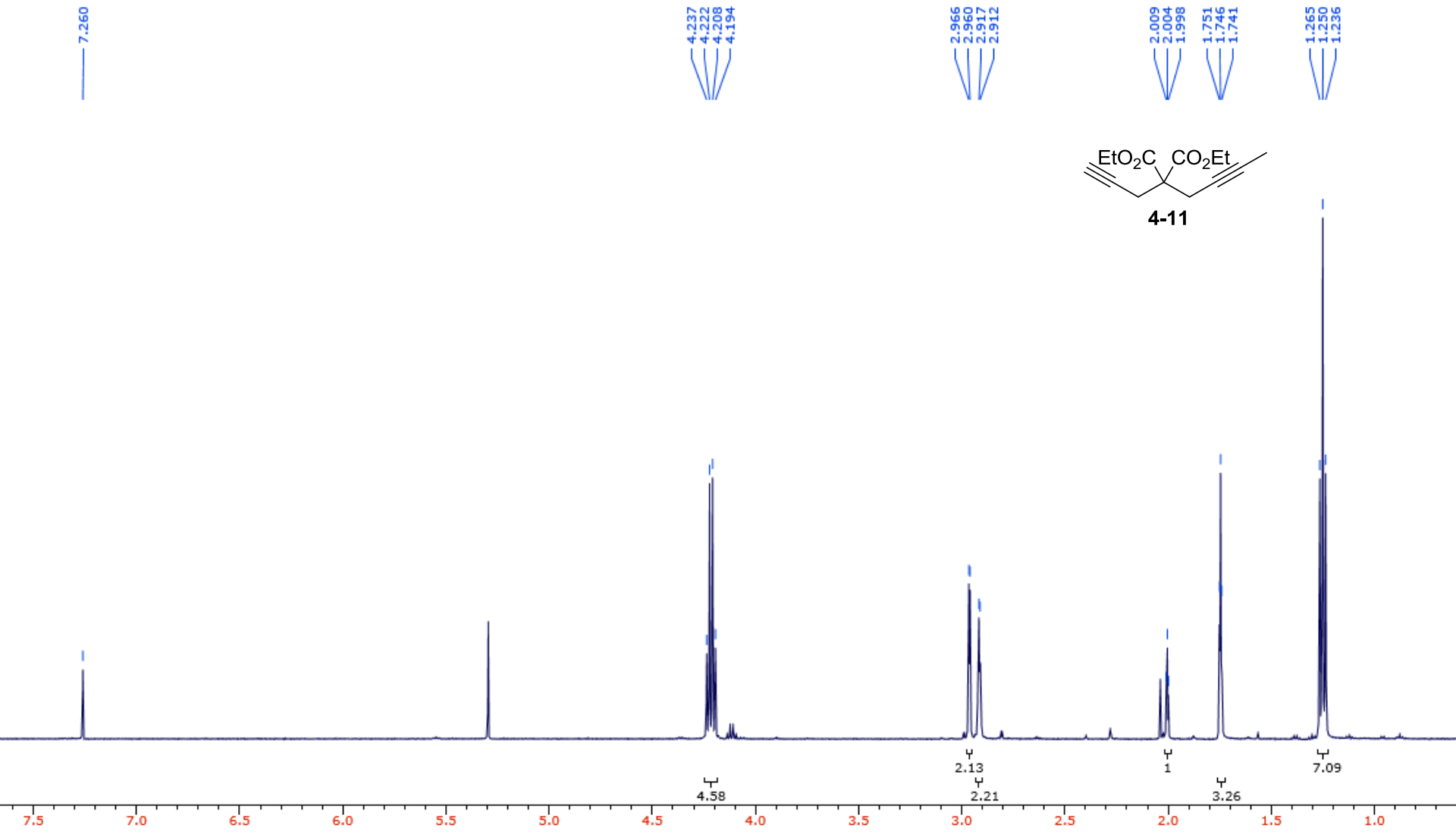
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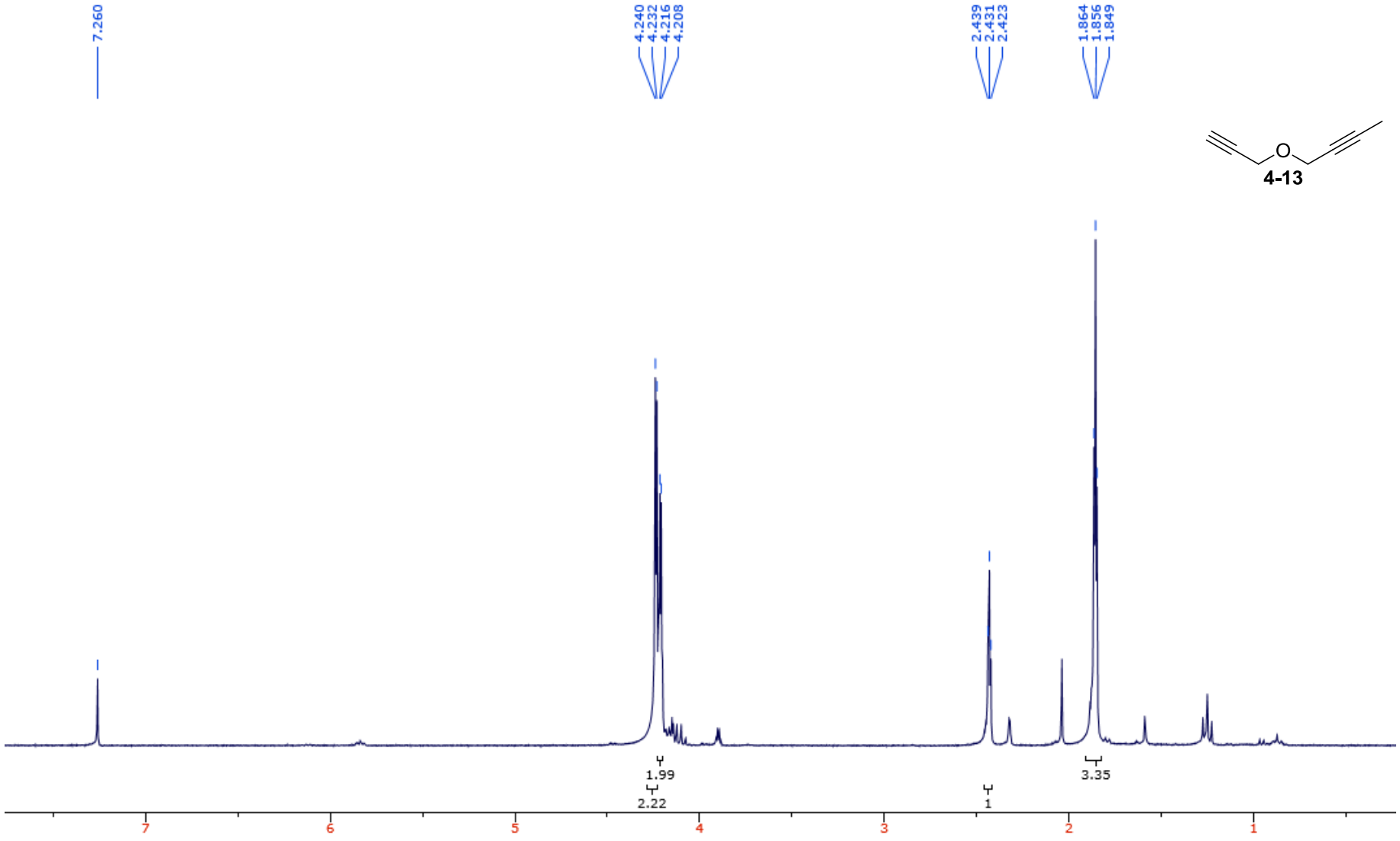
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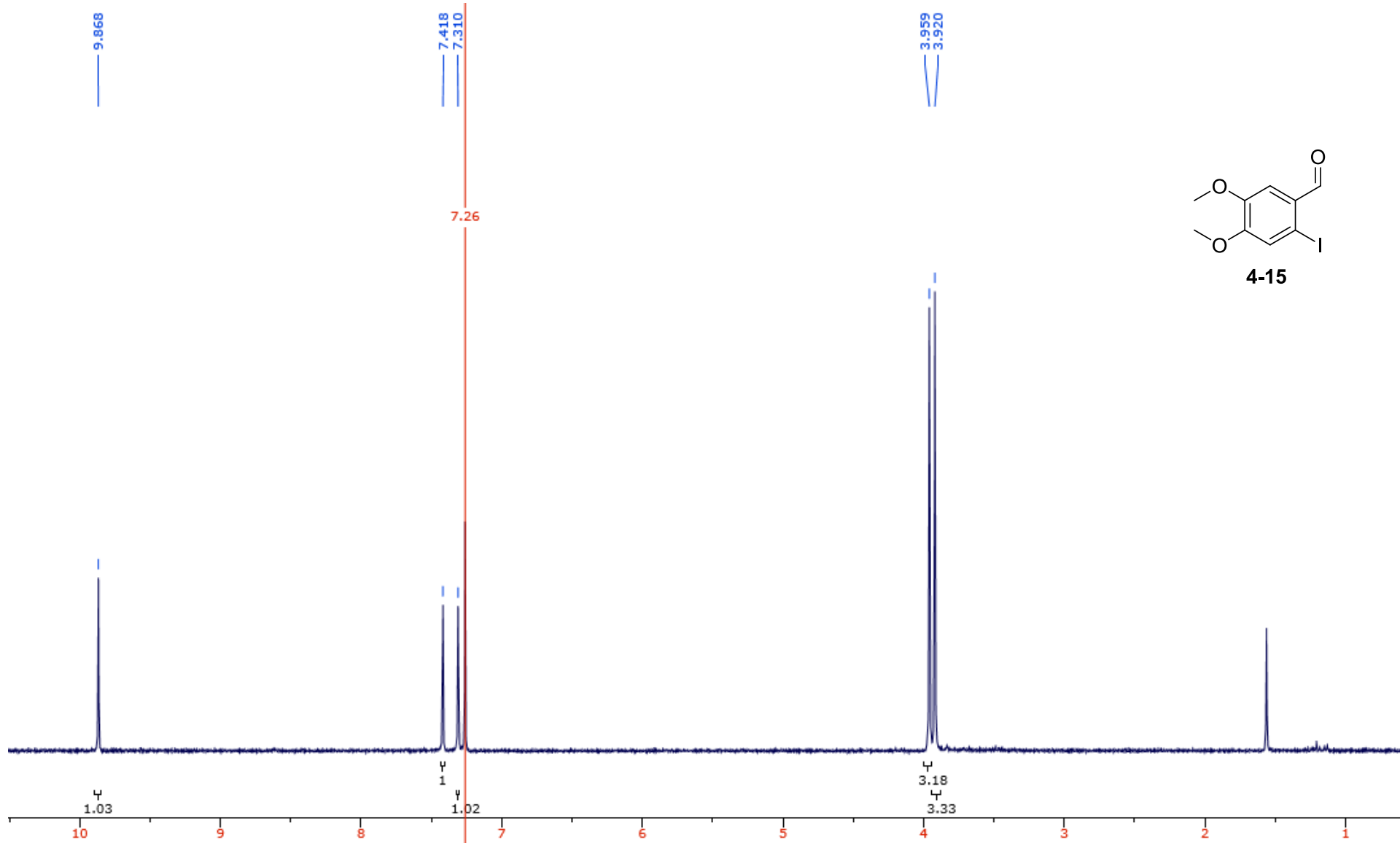
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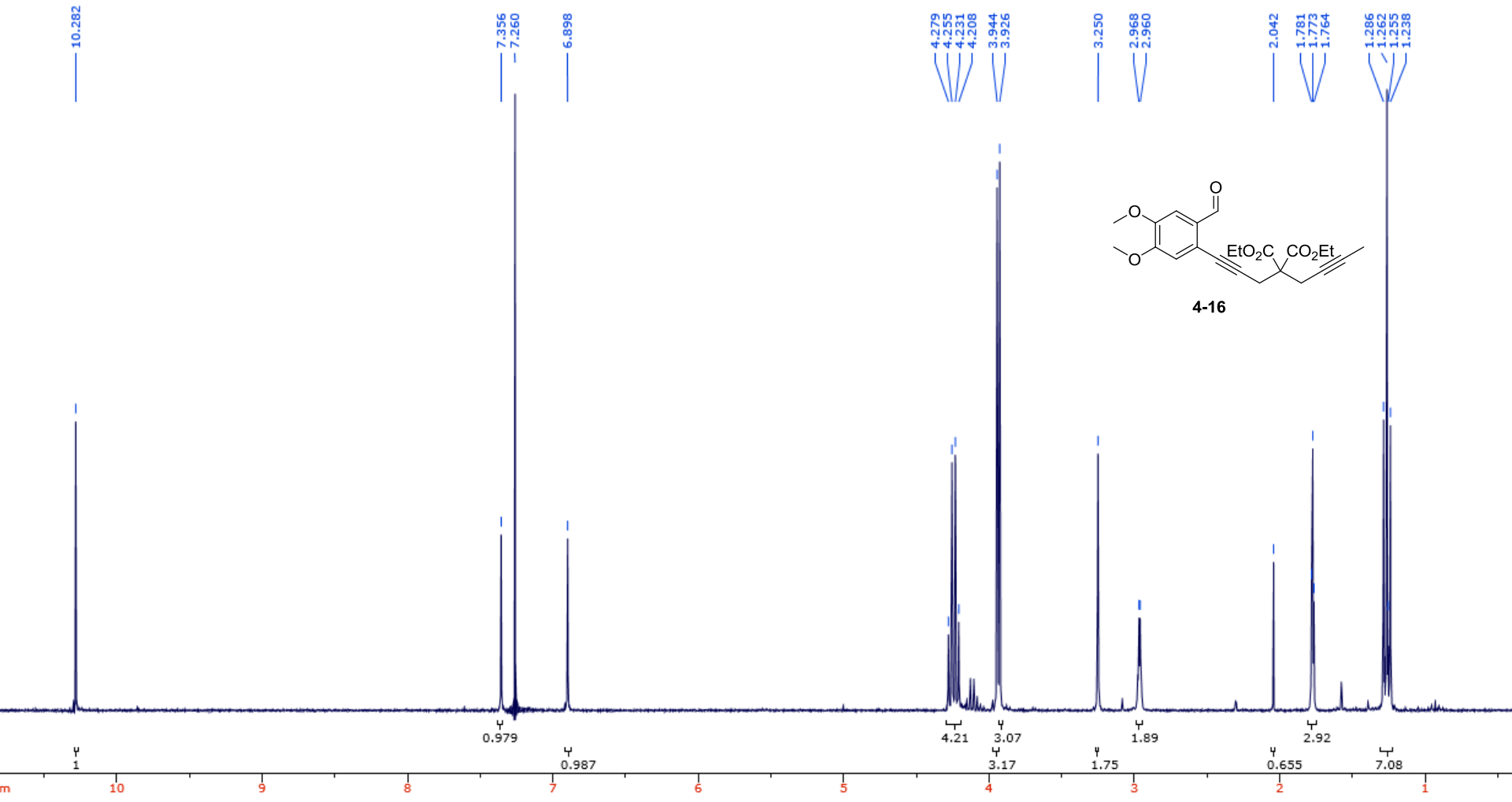
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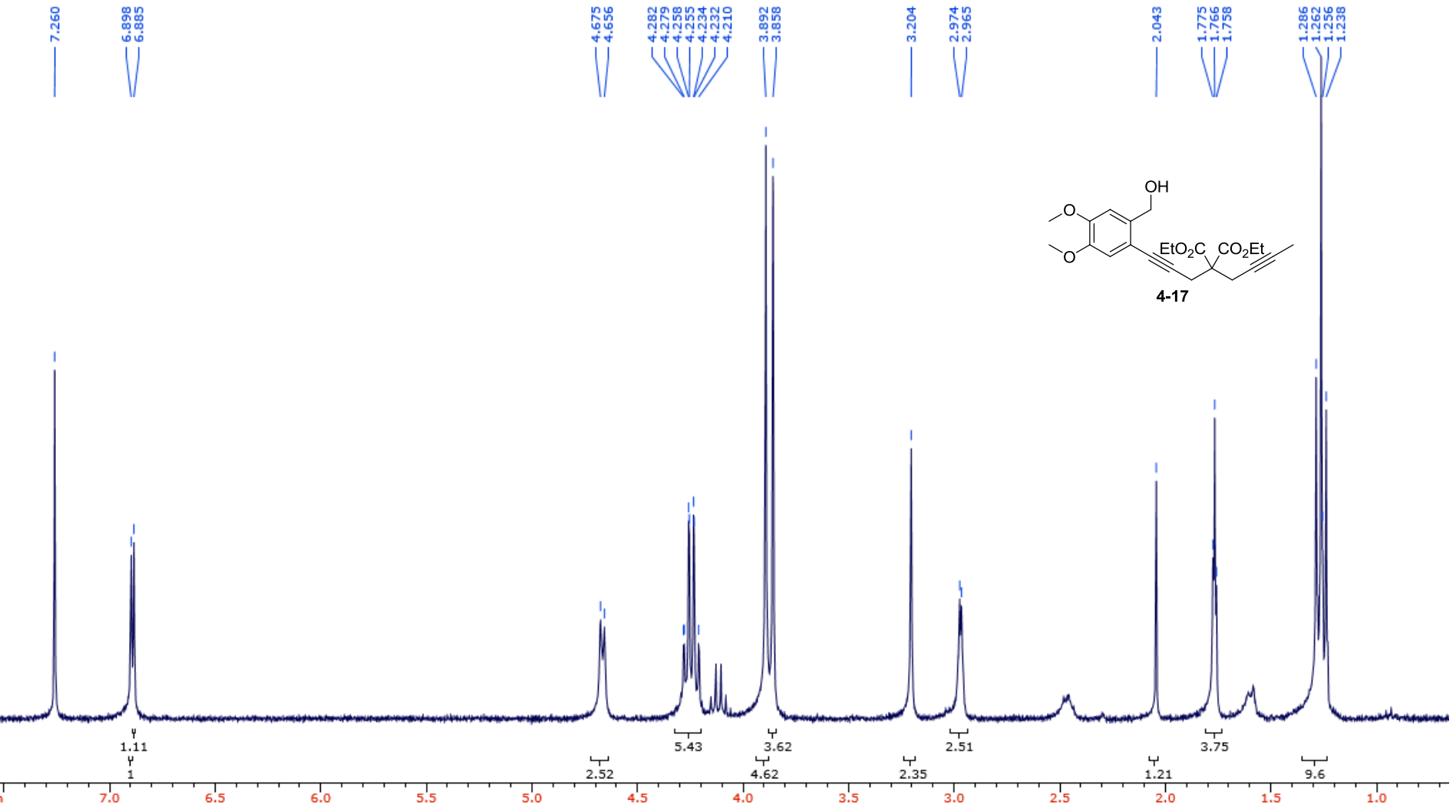
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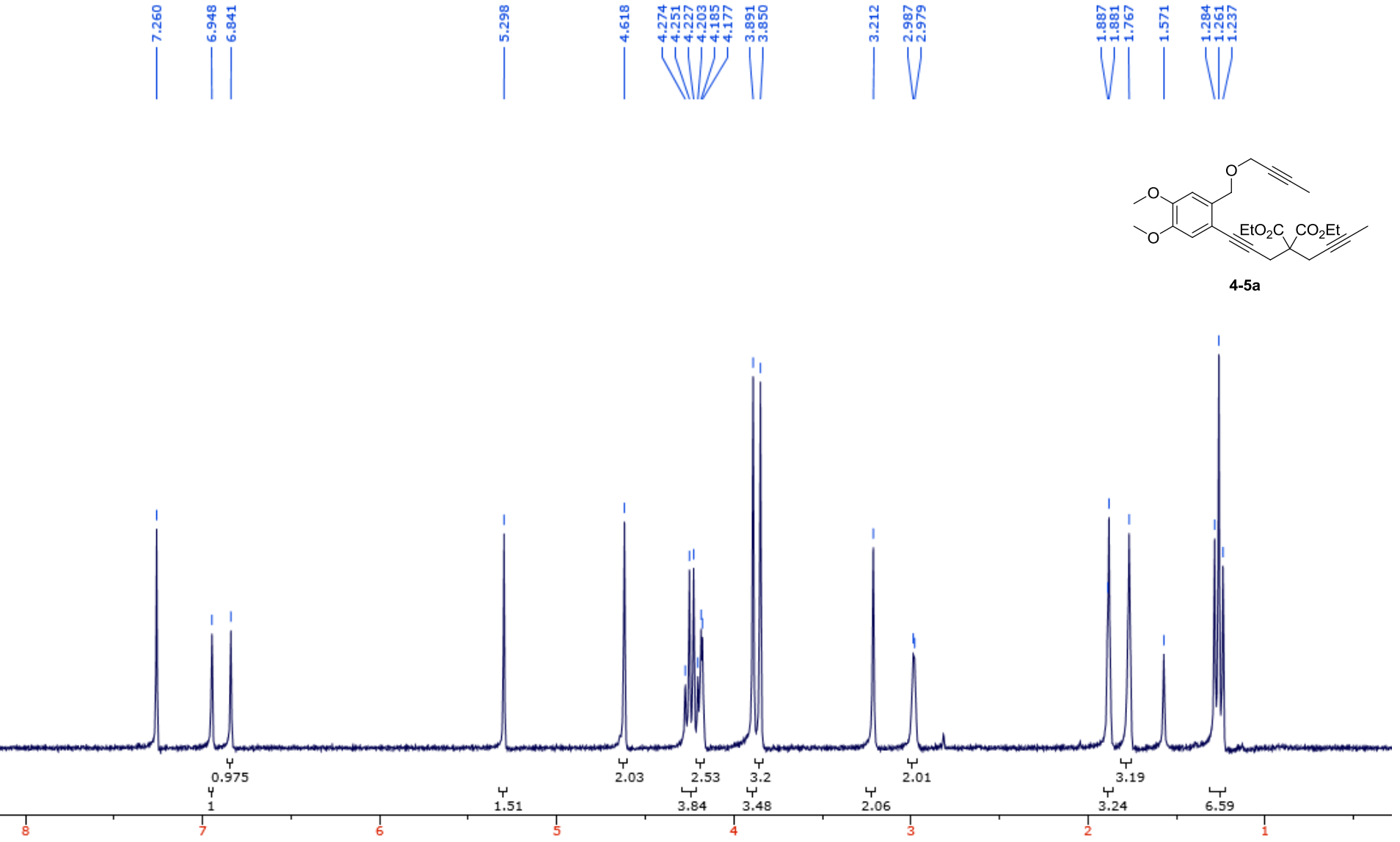
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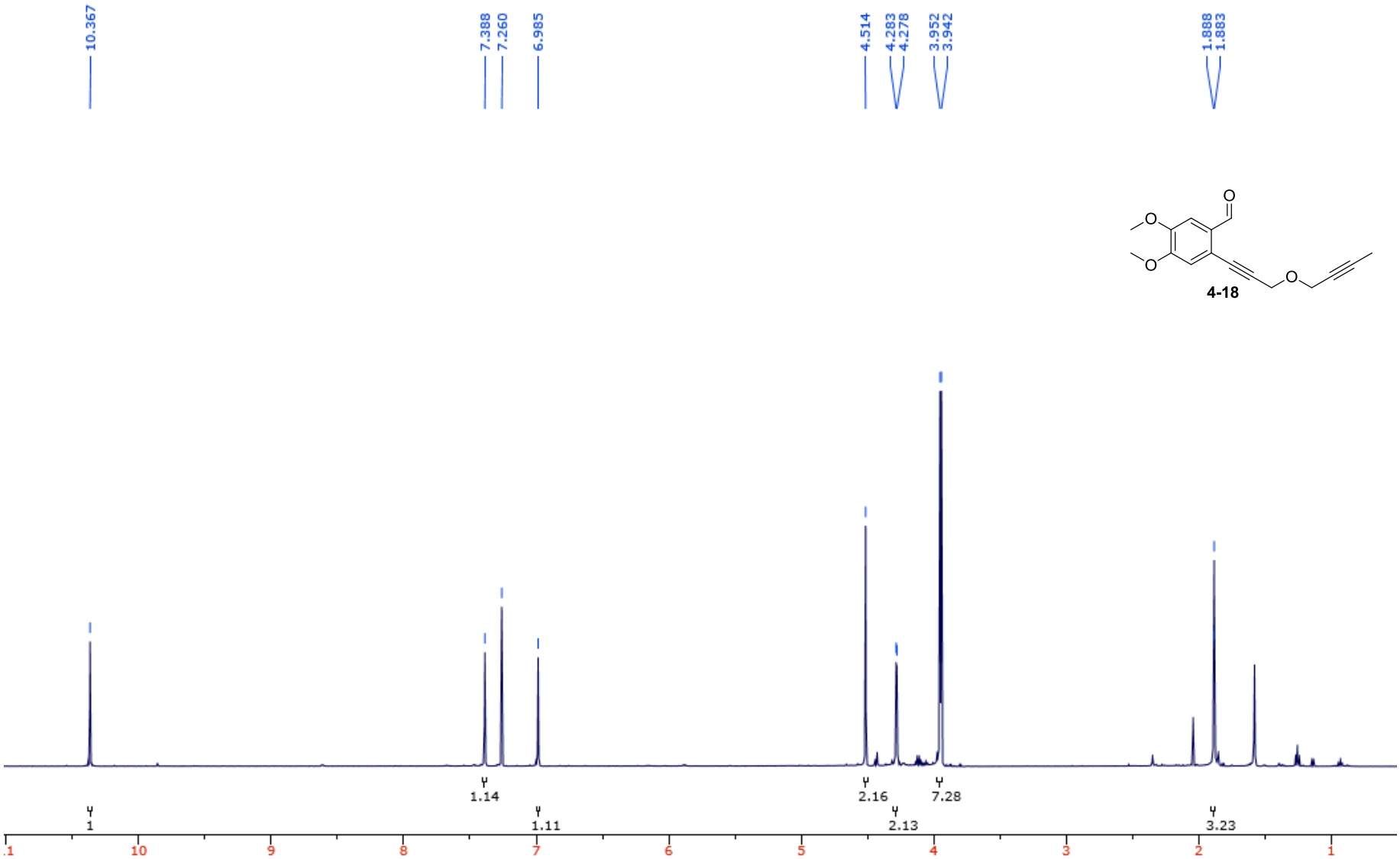
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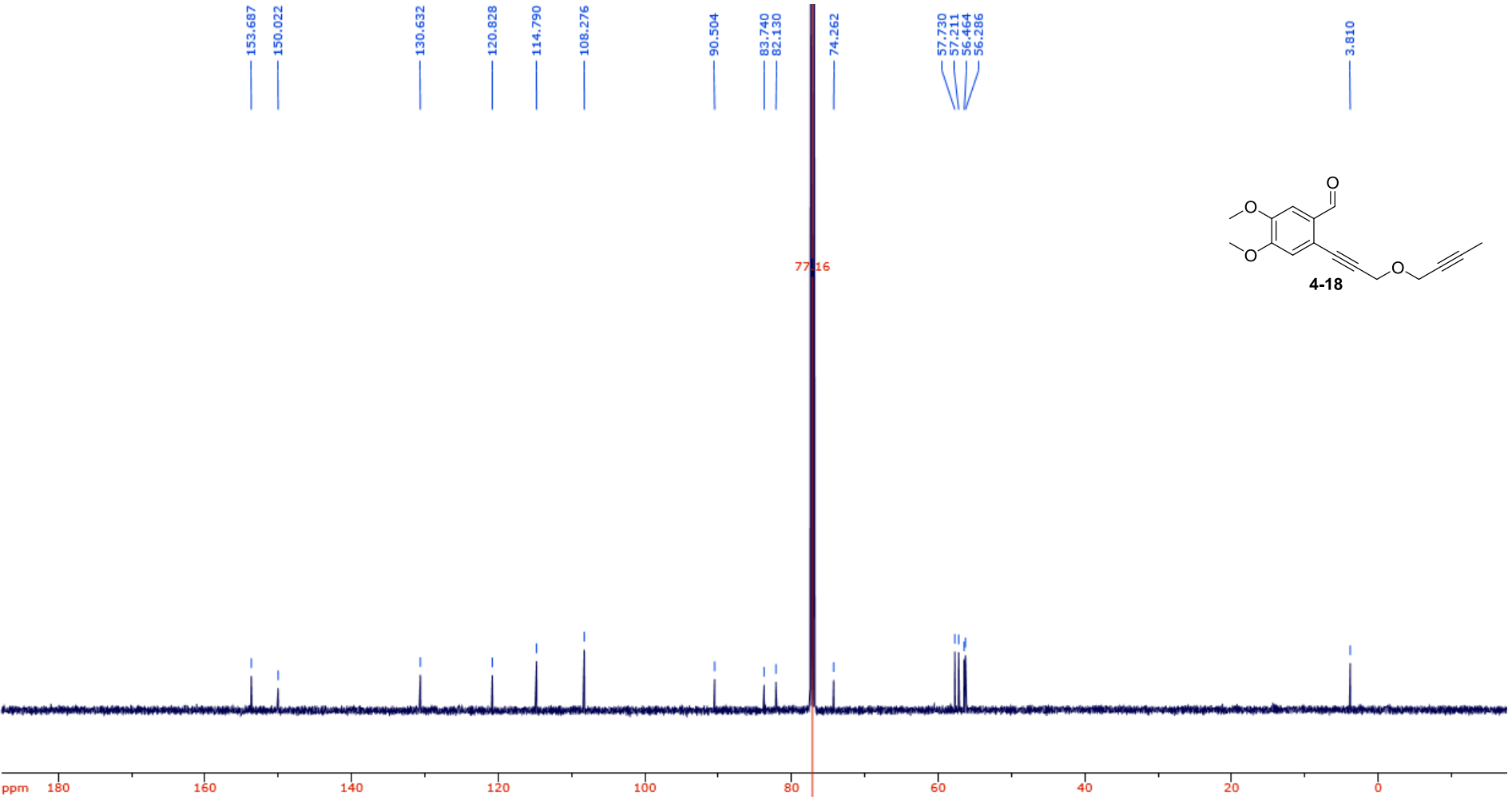
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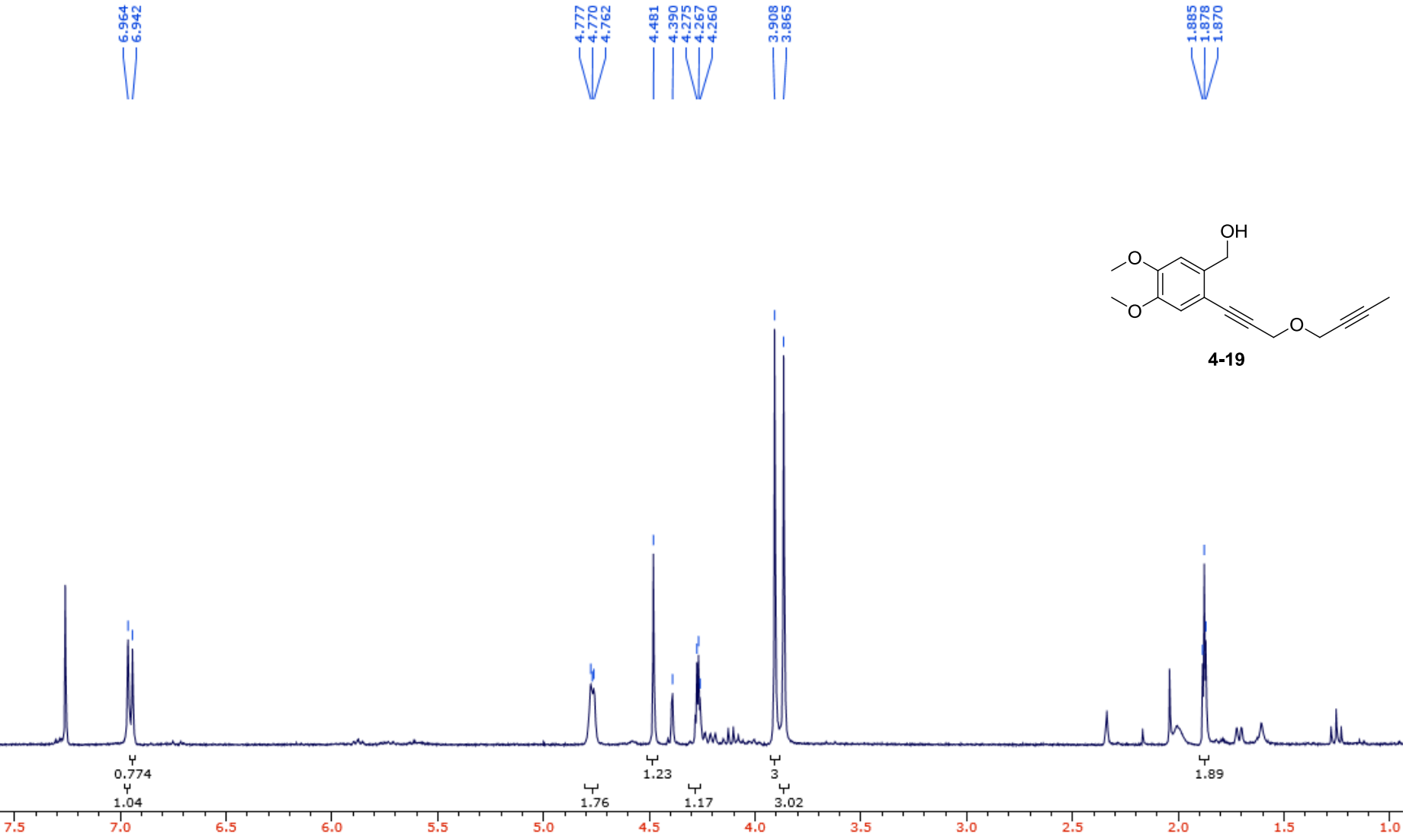
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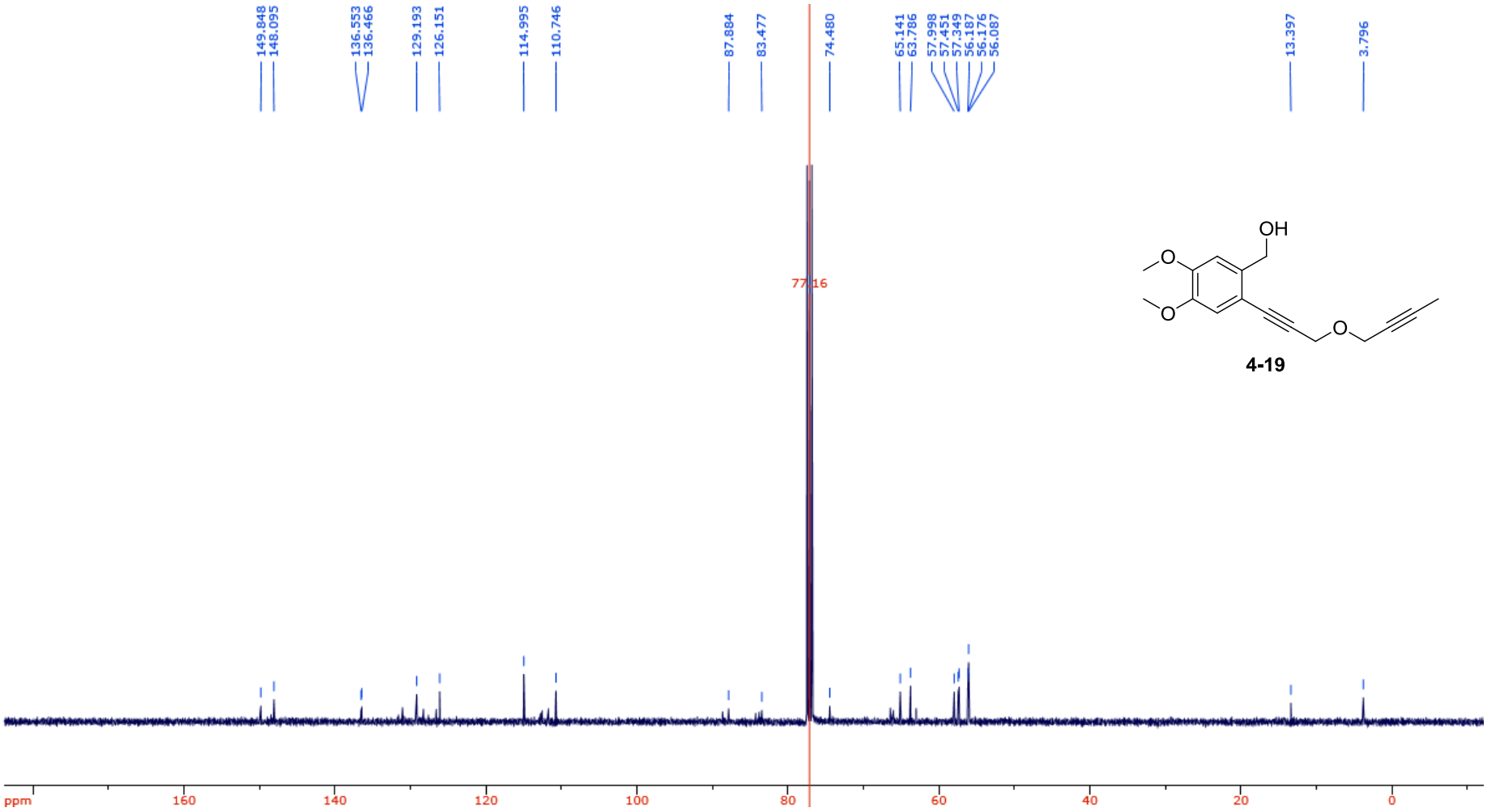
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74.480
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57.998
57.451
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56.176
56.087
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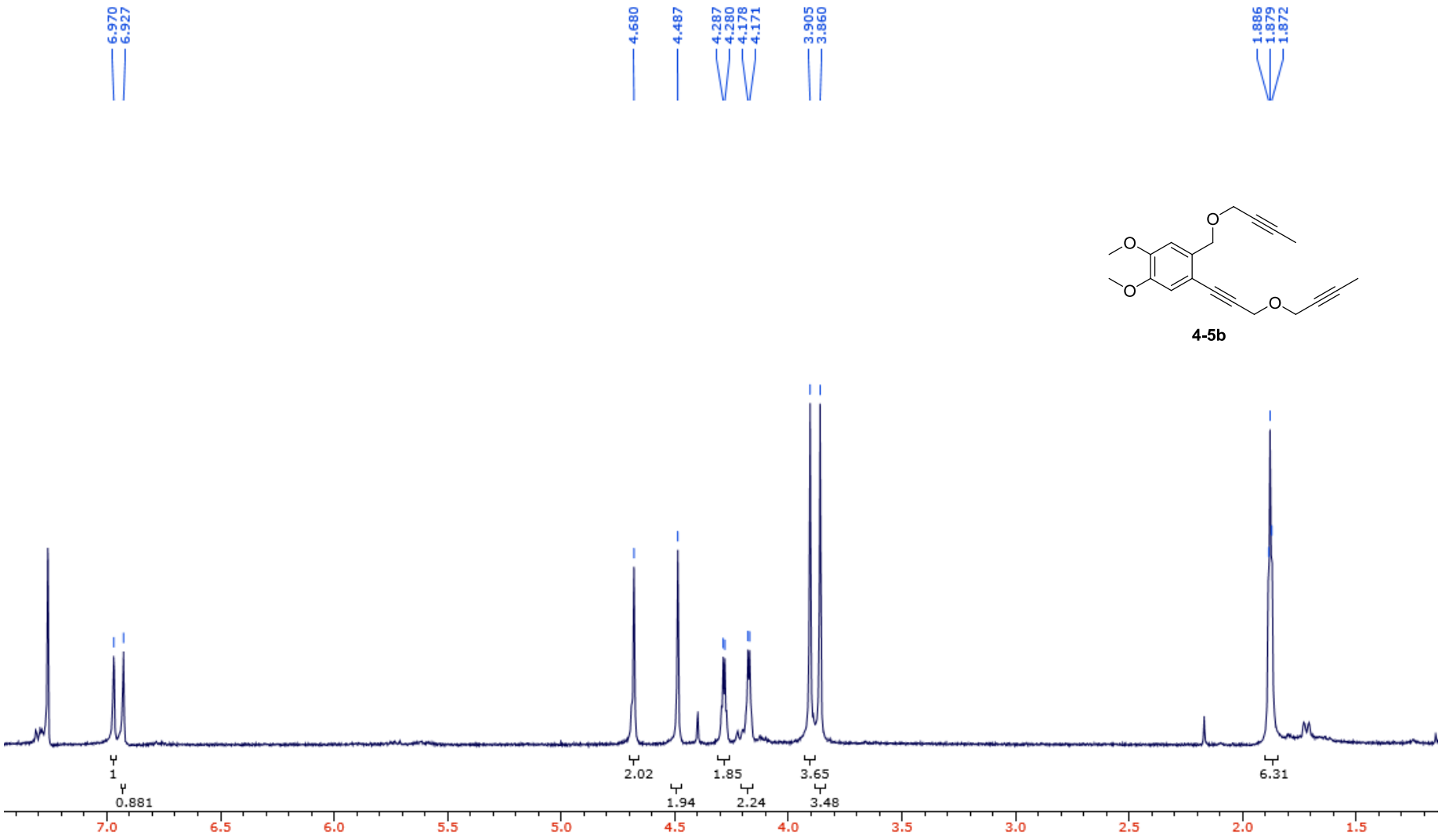
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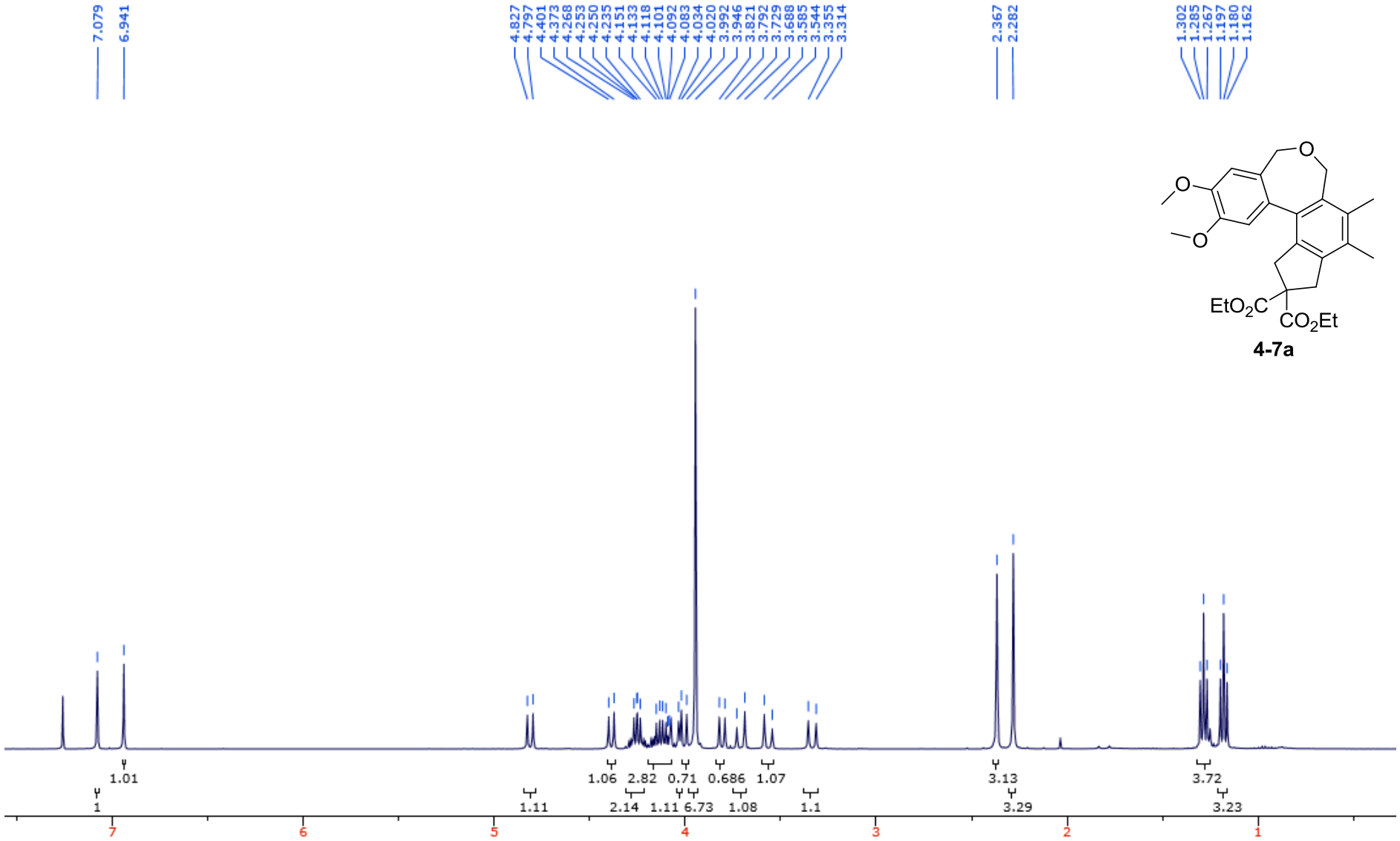
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3.992
3.946
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3.688
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3.544
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1.180
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CO2Et
4-7a
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1.06
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0.686
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3.13
3.72
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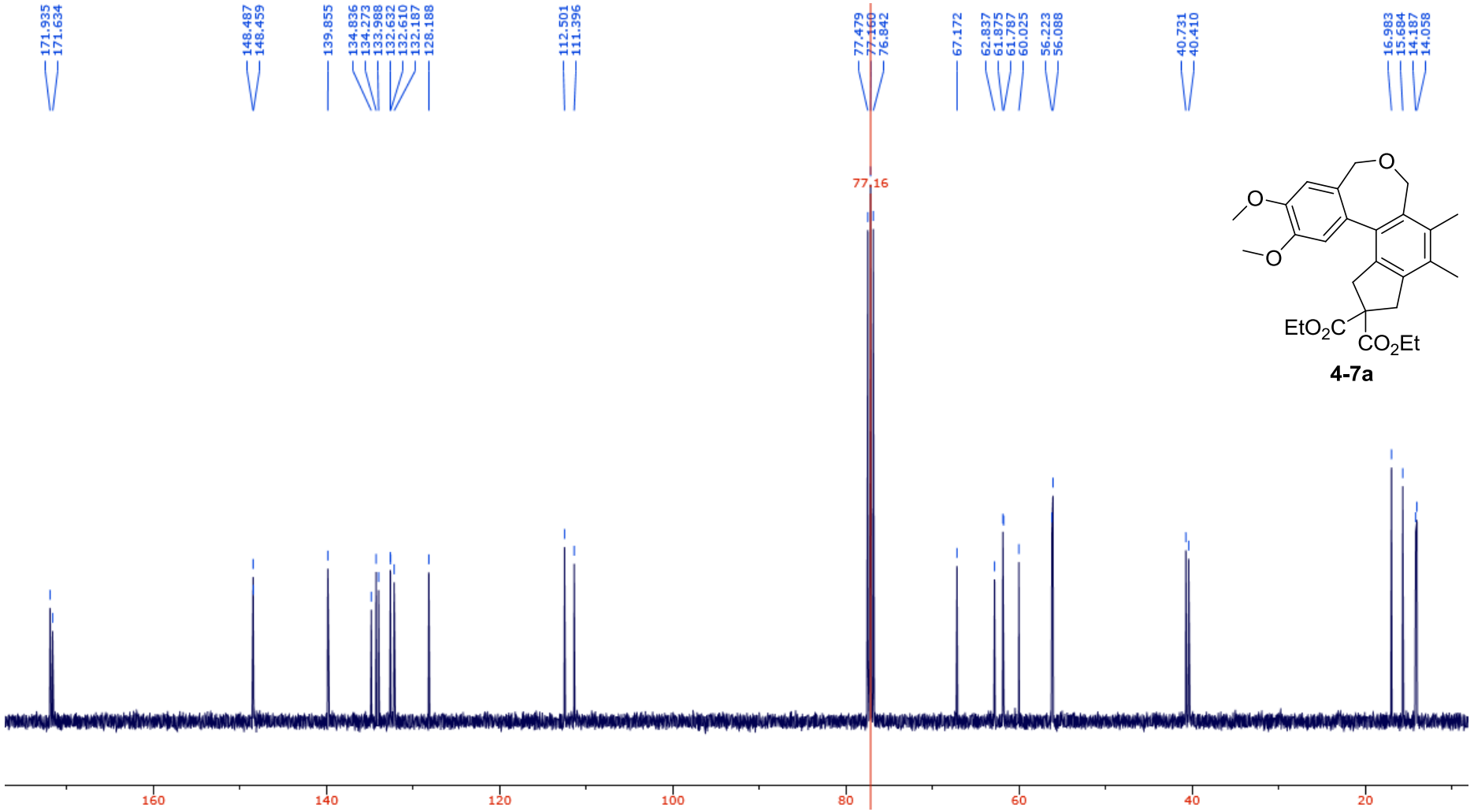
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CO2Et
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80
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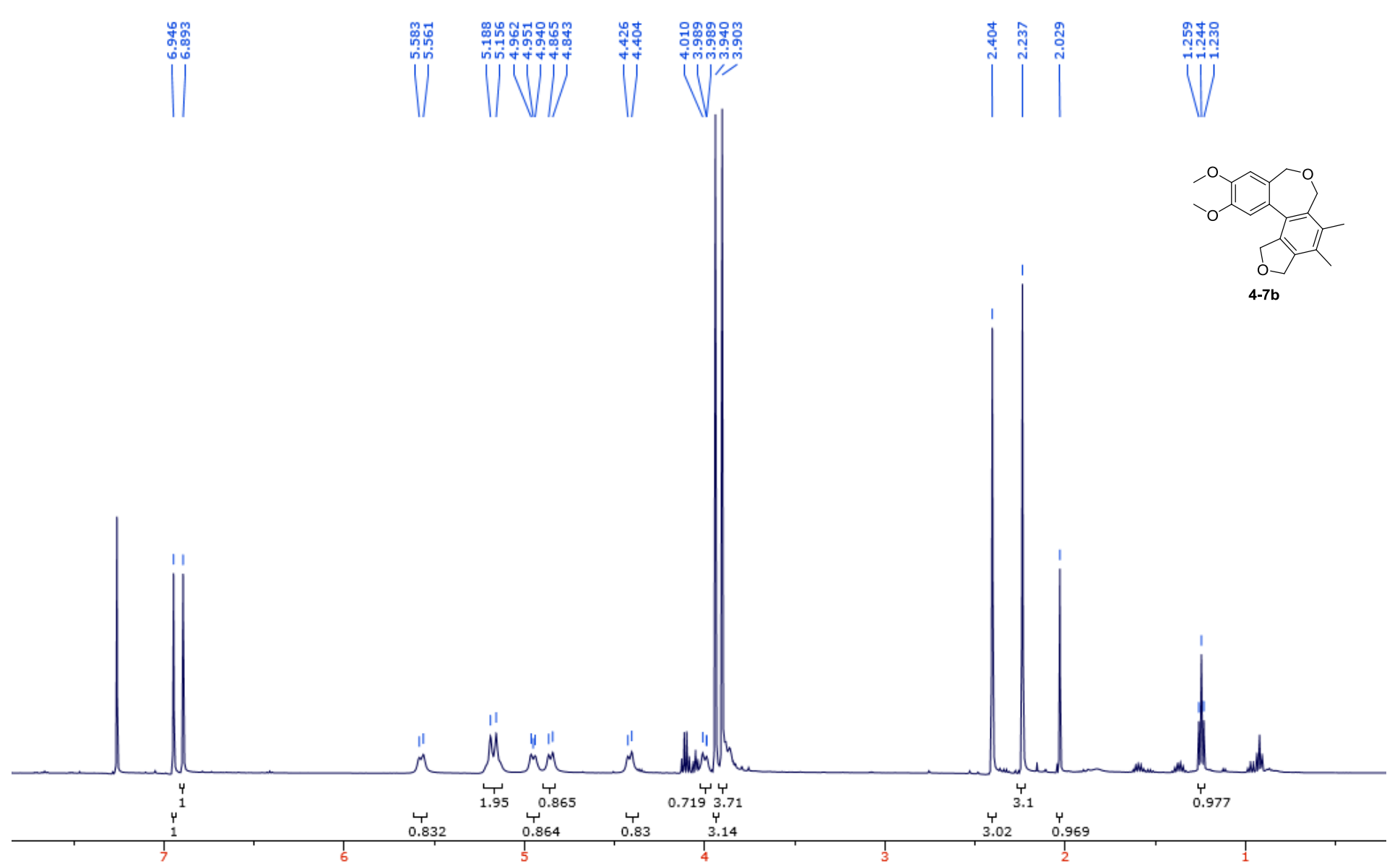
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4-7b
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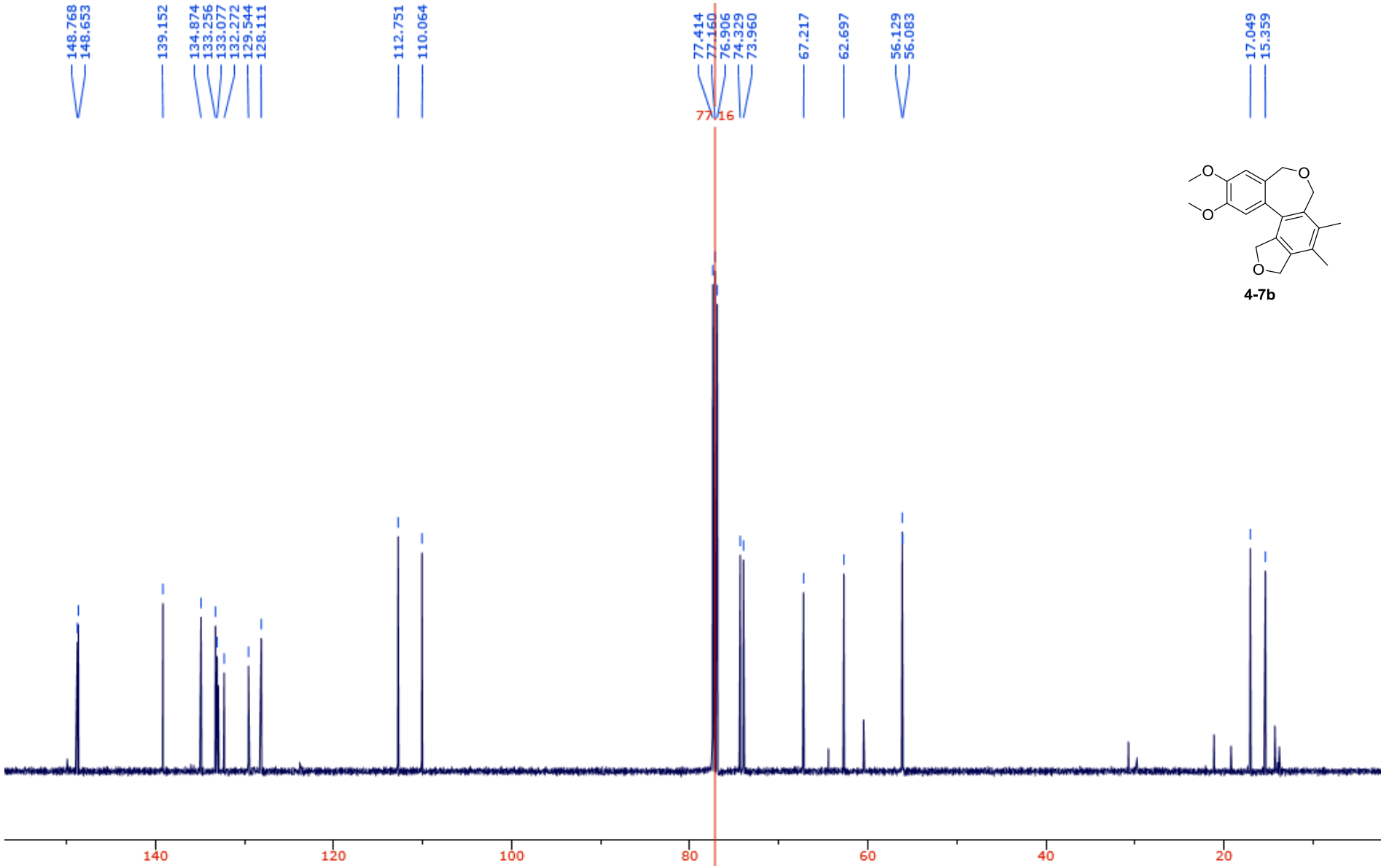
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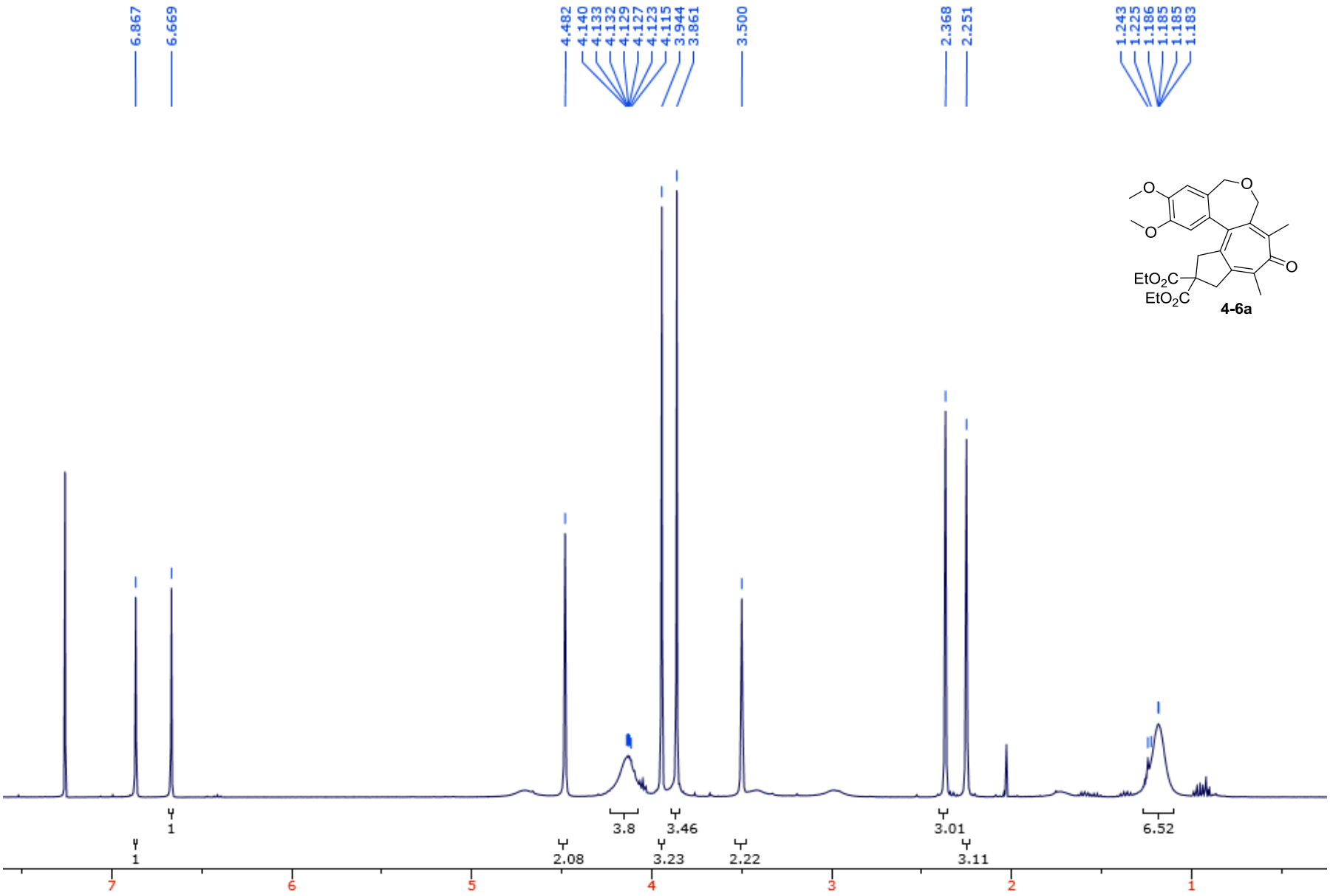
40
20

4-7b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2.251
1.243
1.225
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1.185
1.185
1.183
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O
O
O
EtO2C
EtO2C
4-6a
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1
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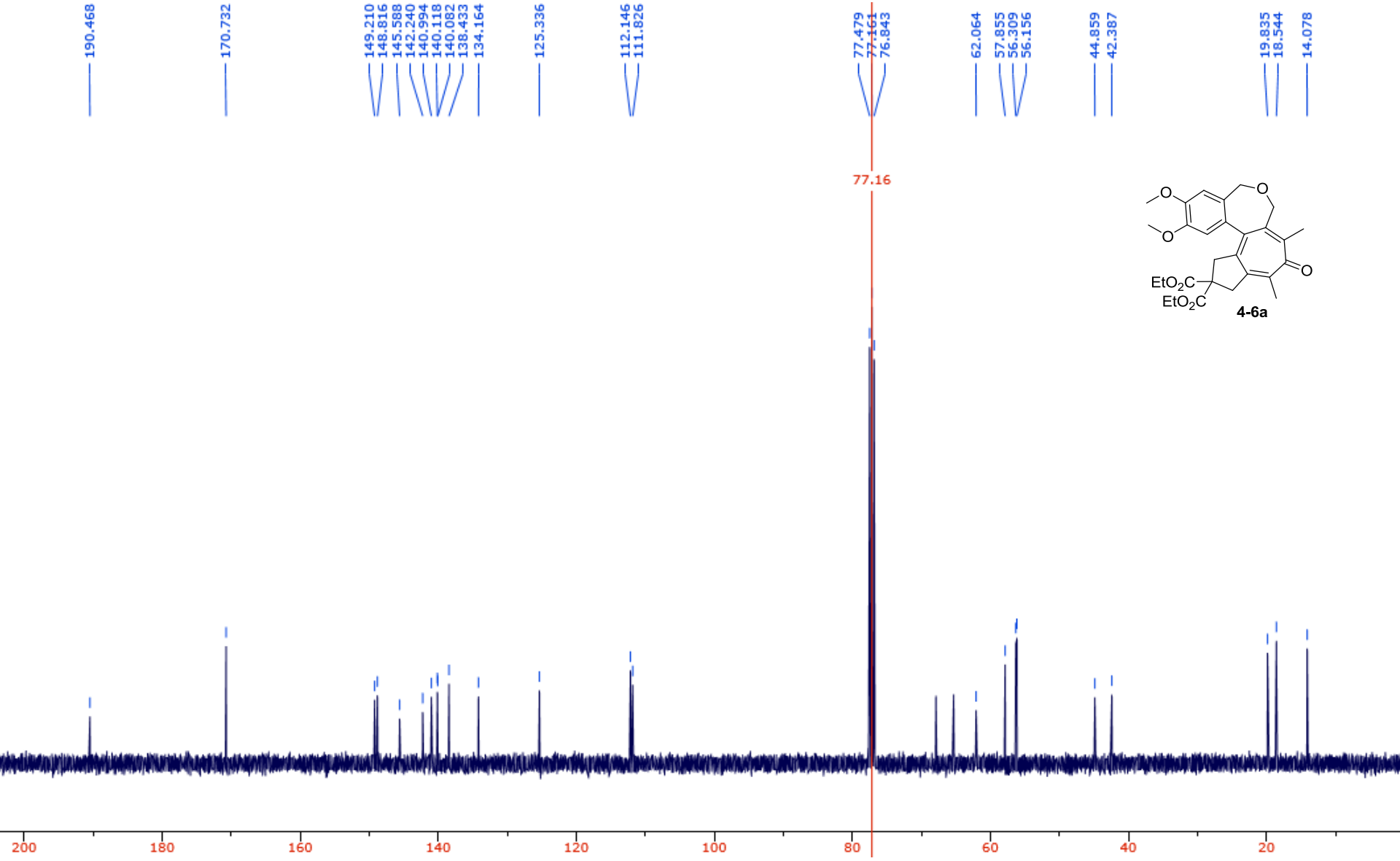
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56.309
56.156
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42.387
19.835
18.544
14.078
77.16
O
O
O
O
EtO2C
EtO2C
4-6a
200
180
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140
120
100
80
60
40
20