

Avenues Towards Fused Pyrroles and Thiophenes by
Exploiting the Reactivity of Heteroarylium Cycloadducts

By

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Abstract

Dipolar (3+2) cycloadditions are extensively utilized by synthetic chemists for accessing important 5-membered heterocyclic structures. After the pioneering work by Rolf Huisgen in the early 1960s, the field greatly matured and found applications in a variety of fields of chemistry. Worthy of mention, the discovery by Meldal, Sharpless, and Folkin of copper-catalyzed azide alkyne cycloadditions (CuAAC), also referred to as a “Click” reaction, was awarded the Nobel Prize in 2022. The finding of this ideal CuAAC reaction originated from the reliability of dipolar (3+2) cycloaddition reactions, whose transformation was rendered extremely kinetically favorable and stereospecific with the use of copper-catalysis. It is therefore of high importance to continue finding novel (3+2) cycloadditions, despite the apparent maturity of the field. The research described in this thesis presents the efforts towards the synthesis of fused pyrroles and thiophenes by means of (3+2) cycloaddition cascades using ynamides and alkynyl sulfides as isoelectronic species to 1,3-dipoles.

In Chapter 2, the exploration of different strategies to bridge the *in-situ* synthesis of alkyne tethered ynamide and our group’s previously described thermally induced (3+2) cycloaddition cascade was investigated. Many challenges were faced when attempting to design *one-pot* procedures including the unprecedented degradation of yne-ynamides under metal-containing reaction conditions. This impeded the use of copper-catalyzed cross-coupling reactions as a general retrosynthetic disconnection for the *in-situ* formation of the ynamide functionality. Even an attempt to functionalize an ynamide precursor containing a tethered terminal alkyne by a Sonogashira cross-coupling was unsuccessful. With the aim to find an efficient way of synthesizing these diynes while limiting the use of stoichiometric reagents, the

use of a previously unreported ynamide substituted propynal building block was explored. These aldehyde synthons were easily synthesized from accessible ynamide substituted propargyl alcohols using Dess-Martin Periodinane as the oxidant. Upon mixing these propynal derivatives with primary propargyl amines, a rapid condensation reaction takes place as long as the removal of water is done. These *in-situ* formed yne-ynamides then undergo (3+2) cycloaddition cascades towards fully substituted fused pyrroles at temperatures ranging from 60 to 100 °C. While the method was found to be limited to [3.3.0] fused pyrroles and moderate yields were observed (22-55% yields, 8 examples), this *one-pot* method permitted an extremely rapid growth of molecular complexity. Collectively, the work described in this chapter further accentuates the utility of ynamides as building blocks for densely functionalized pyrrole heterocycles.

In Chapter 3, the reactivity of analogous alkyne tethered alkynyl sulfides (thioalkynes) was investigated. Alkynyl sulfides are an important class of heteroatom-substituted alkynes, whose alkynyl carbons are weakly polarized in contrast to ynamines (*N*-alkynyl amines) derivatives. While thioalkynes display superior stability in contrast to ynamides, both X-alkynyl species share similar reactivities. Upon heating of *S*-ester substituted yne-alkynyl sulfides, fully substituted thiophenes were obtained indicating that the reactivity observed with ynamides (as 4π cycloaddition partner) was transferable to thioalkynes. When *S*-alkyl substituted yne-thioalkynes are used, 5-unsubstituted thiophenes are formed instead. The use of *S*-tert-butyl substituted alkynyl sulfides enabled a broad scope of 5-unsubstituted fused thiophenes to be obtained via an intramolecular (3+2) cycloaddition and dealkylation cascade. The transient thiophenium ylide cycloadducts formed as a result of (3+2) cyclization were also efficiently trapped with electrophiles generating complex functionalized thiophenes. The use of *S*-n-propyl substituted

yne-alkynyl sulfide was necessary in this case to provide control over product selectivity and to permit the electrophilic trapping to occur before dealkylation. Collectively, the reactivity cascades of thermally formed thiophenium ylides cycloadducts were studied in detail revealing a modifiable and controllable reactivity by judicious choice of alkynyl sulfide substitution and reaction condition.

In Chapter 4 the use of coinage metals for catalyzing the (3+2) cycloaddition of yne-alkynyl sulfides at room temperature was presented. Our group established that metal-induced low-energy pathways are accessible when alkynyl sulfides are tethered with terminal alkynes. Application of the new set of reaction conditions to an *S*-phenyl substituted yne-thioalkyne substrate revealed the formation of a thiophenium cycloadduct intermediate. The screening of alternative reaction conditions enabled the successful isolation of this *S*-phenyl thiophenium cycloadduct by precipitation from the reaction crude enabling structure confirmation by NMR and X-ray crystallography. The reactivity of this previously undescribed *S*-phenyl thiophenium salt was also evaluated under thermolysis and (metallo)photoredox conditions. The synthesis of *S*-(hetero)aryl yne-thioalkynes derivatives was first tackled revealing an incompatibility of the current methods described in the literature for a broad range of (hetero)aryl substituted alkynyl sulfides. Despite the numerous challenges encountered, the synthesis of *para*-substituted electron-poor and rich phenyl derivatives was successfully achieved using sulfur umpolung methods. A *one-pot* strategy was applied to these *S*-phenyl derivatives involving the *in-situ* formation of thiophenium cycloadducts which readily underwent a [1,5]-sigmatropic rearrangement and aromatization upon mild heating (70 °C) towards 2-aryl substituted fused thiophenes. Lastly, the compatibility of the *S*-phenyl thiophenium cycloadduct in

(metallo)photoredox transformations for new C_{Ph}-C bond formation was evaluated. In contrast to electrophilic *S*-aryl sulfonium reagents commonly employed, this first generation of thiophenium salt was not efficient in providing high yields for the desired cross-coupled products. It was postulated that undesired HAT side reactivity was detrimental to the reaction efficacy. These preliminary studies allowed us to gain crucial insight into the inherent reactivity of an *S*-phenyl thiophenium salt with the hope to guide the next generation of potentially useful electrophilic reagents.

Acknowledgments

I started my journey in the Gagosz lab in May 2020, in the middle of the Covid-19 lockdown. Luckily, Fabien provided me with the opportunity to learn about and perform density functional theory calculations from home. I also got to virtually meet the group as well as the members of the Barriault lab, whom we shared weekly group meetings with. I started working at the bench in June and I quickly knew I was going to enjoy my time as an undergraduate intern. That first summer will always be memorable, I still remember coming back from the lab and telling my mom how much fun I was having all day! I would like to thank Fabien for making the lab environment welcoming and for teaching me so many things throughout the years. You were always present to guide me and discuss chemistry which was very helpful. You always had confidence in me and believed I could achieve anything even when I doubted myself.

I would like to specifically thank Dominic for being an amazing project partner. I always felt very lucky to be able to learn from you and collaborate on these very fun and rewarding projects together. I enjoyed the years we spent working beside each other, I will always remember the times when we would get excited about our results which was very motivating. You always had great ideas which were very helpful for moving past the many challenges I faced. Ali, thank you for being the best of friend through my graduate studies. I enjoyed the good conversations, the laughs, and the rants but most of all thanks for always being there for me. Karim, you always had the craziest stories to share which always ended up making everyone laugh. Mila, thank you for being so brave tackling some of the most unexpectedly challenging syntheses. You are a very talented undergraduate student and I wish you the best of luck with your studies!

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Statement of Contributions

The projects presented in this thesis were primarily done in collaboration with PhD candidate Dominic Campeau. Undergraduate students Stéphane Lauzon-Brisson and Mila Gorodnichy also participated in a few studies in Chapters 3 and 4 respectively. Their work is accredited throughout the thesis in the text and experiments performed by them will be labeled in the Figures and Tables. In Chapter 2, I joined Dominic Campeau when he was approaching the end of his project on the thermal (3+2) cycloaddition cascades of yne-ynamides. His investigations were at the core of our ideas for the development of *one-pot* procedures for the expedited synthesis of fused pyrroles. All the experiments and results obtained from this study were done by myself, with close supervision and guidance from Dominic and my supervisor. The work presented in Chapter 2 was performed during my Honours Project and published at the beginning of my graduate studies. It was included in the thesis for discussion purposes.

In Chapter 3, Dominic Campeau and I worked on investigating the reactivity of analogous yne-alkynyl sulfide system. The initial investigation and reaction optimization of *S*-alkyl yne-thioalkynes was performed by myself. Stéphane Lauzon-Brisson participated in evaluating the reactivity of an *S*-benzyl derivative and he established the formation of (*Z*)-stilbene as a by-product. The isolation of model thiophene and obtention of crystals was done by myself while the acquiring of X-ray crystallography was done by Dominic Campeau. Dominic Campeau and I then evaluated the reactivity of *S*-ester and *S*-phenyl derivatives for which we independently synthesized the substrates and isolated the thiophene products, if possible. The reaction scope of fused thiophenes obtained when modifying the alkyne substitution and linker structure was performed in collaboration with Dominic and Stéphane. The screening of *S*-alkyl substitution for

evaluating the electrophilic interception of the intermediate ylide with methyl chloroformate was performed by myself. Dominic then joined the scope investigation of electrophiles. DFT calculations and the deuteration studies on the *S*-tert-butyl and *S*-n-propyl derivatives were performed by Dominic Campeau. The synthesis of probe substrate **3.1n** and the initial observation and isolation of 2*H*-thiopyran product **3.4** was done by me. It was then repurposed by Dominic Campeau for refining the dealkylation mechanism of *S*-alkyl thiophenium ylides.

In Chapter 4, the work towards the access and reactivity investigations of isolable thiophenium cycloadduct was made possible by a collaboration between Dominic Campeau, Mila Gorodnichy, and myself. The initial observation that reaction conditions promoting a Sonogashira cross-coupling induced the cyclization of a yne-alkynyl sulfide substrate at room temperature was made by myself. The preliminary screenings discussed in the thesis used to gain an understanding of the important parameters of the low-energy pathway were performed by Dominic and myself. The major milestones of reaction optimization utilizing a *S*-tert-butyl derivative, done by Dominic Campeau, were presented as they were fundamental for the understanding of the reaction mechanism. Additionally, the findings by Dominic Campeau were crucial as the use of his reaction conditions enabled the observation of a *S*-phenyl thiophenium cycloadduct. The observation, structure confirmation, and evaluation of the reactivity of this *S*-phenyl thiophenium cycloadduct were done by myself. The synthesis of *S*-aryl yne-alkynyl sulfides derivatives and their rearrangement towards 2-aryl substituted thiophenes were performed by Mila Gorodnichy and myself. The results obtained by Mila Gorodnichy and Dominic Campeau for a *S*-thiophenyl and *S*-alkynyl derivative respectively were also presented as 2-functionalized thiophenes were also observed.

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Abbreviations

[M] – generic metal
°C – degrees Celsius
 δ – chemical shift in parts per million
 Δ – thermolysis
1,10-phen – 1,10-phenanthroline
Å – angstrom
Ac – acetyl
AcOH – acetic acid
APCI – atmospheric pressure chemical ionization
atm – atmosphere
B3LYP – Becke-3-Lee-Yang-Parr
BHT – butylated hydroxy toluene (2,6-di-*t*-butyl-4-methylphenol)
Bn – benzyl
Boc – *tert*-butyloxycarbonyl
bpy – bipyridine
C – carbon
CDCl₃ – deuterated chloroform
CHCl₃ – chloroform
conv. – conversion
COSY – homonuclear correlation spectroscopy
DBE – dibromoethane
DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene
DBT⁺ – dibenzothiophenium
DCE – dichloroethane
DPS⁺ – diphenylsulfoium
DIPEA – *N,N*-Diisopropylethylamine
DCM – dichloromethane
DFT – density functional theory
DIAD – diisopropyl azodicarboxylate
dtbbpy – 4,4'-Di-*tert*-butyl-2,2'-dipyridyl
DMP – Dess-Martin Periodinane
DMSO – dimethyl sulfoxide
EBX – ethynylbenziodoxolone
EDA – electron-donor acceptor
 E_{red} – reduction potential
Et – ethyl
E – generic electrophile
E – entgegen (opposite, trans)
EI – electronic impact
ESI – electrospray ionization
EDG – electron donating group

equiv. – stoichiometric equivalent
EWG – electron-withdrawing group
Et₃N – triethylamine
EtOH – ethanol
EtOAc – ethyl acetate
FG – functional group
g – gram
HetAr – generic heteroatomic
HRMS – high-resolution mass spectrometry
HFIP – hexafluoroisopropanol
Hex – hexanes
HAT – hydrogen atom-abstraction
HMBC – heteronuclear multiple bond correlation
HSQC – heteronuclear single quantum coherence
h – hour
Hz – hertz
i-Pr – isopropyl
J – coupling constant
JohnPhos – 2-(Di-*tert*-butylphosphino)biphenyl
LG – leaving group
MeCN – acetonitrile
Ms – metanesulfonyl
NMR – nuclear magnetic resonance
Me – methyl
MS – molecular sieves
MHz – megahertz
mg – milligram
M – molar
MeOH – methanol
mmol – millimole
min – minute
n-Bu – *n*-butyl
NTf₂ – bistriflimide
NBS – N-bromosuccinimide
n-Oct – *n*-octyl
N – nitrogen
Na-Asc – sodium ascorbate
Nuc – nucleophile
NOESY – nuclear overhauser effect spectroscopy
OTf – trifluoromethanesulfonate
OAc – acetoxy
p – para
Ph – phenyl
pyr – pyridine

P.T. – proton transfer
PPh₃ – triphenylphosphine
p-Tol – *para*-toluene
PTSA – *p*-toluenesulfonic acid
PPTS – pyridinium *p*-toluenesulfonate
PTH – 10-phenylphenothiazine
PA – *para*-anisaldehyde
ppm – parts per million
r.t. – room temperature
R – generic group
RDS – rate-determining step
R_f – retention factor
S or S – sulfur
S_EAr – electrophilic aromatic substitution
SCE – saturated calomel electrode
t-Bu – *tert*-butyl
TMS – trimethylsilyl
TS – transition state
temp. – temperature
THP – tetrahydropyran
TMG – tetramethylguanidine
TBD – 1,5,7-triazobicyclo[4.4.0]dec-5-ene
TIPS – triisopropylsilane
TT⁺ – thianthrenium
TLC- thin-layer chromatography
TBAI – tetra-*n*-butylammonium iodide
Tf₂O – triflic anhydride
TFE – 2,2,2-trifluoroethanol
Ts – *para*-toluenesulfonyl
Tf – trifluoromethanesulfonyl
TFA – trifluoroacetic acid
THF – tetrahydrofuran
t-BuOH – *tert*-butanol
UV – ultraviolet
yne – alkyne
Z – zusammen (same side, cis)

1 Chapter 1 : Introduction

1.1 A review on dipolar (3+2) cycloaddition reactions

Cycloaddition reactions are recognized as an indispensable tool in organic chemistry and represent a major synthetic method for accessing cyclic structures. Out of the many of this type, dipolar (3+2) cycloaddition reactions became a staple tool in heterocyclic chemistry after the pioneering work by Rolf Huisgen in the 1960s.^{1, 2} The term dipolar comes from the usage of 1,3-dipoles as 4π component in the $[4\pi + 2\pi]$ cycloaddition process toward 5-membered cycloadducts (Figure 1). The potential of 1,3-dipolar cycloadditions (1,3-DA) was recognized after Huisgen systemically categorized C,N,O based 1,3-dipoles in two main classes known today as the allyl (sp_2 -centered) and the propargyl-allenyl type (sp -centered) (Figure 1, A). The allyl-type present a bent geometry with four electrons being shared by all three “abc” atoms via three parallel p_z orbitals while the propargyl-allenyl type display a linear geometry due to an additional π orbital within their structure.

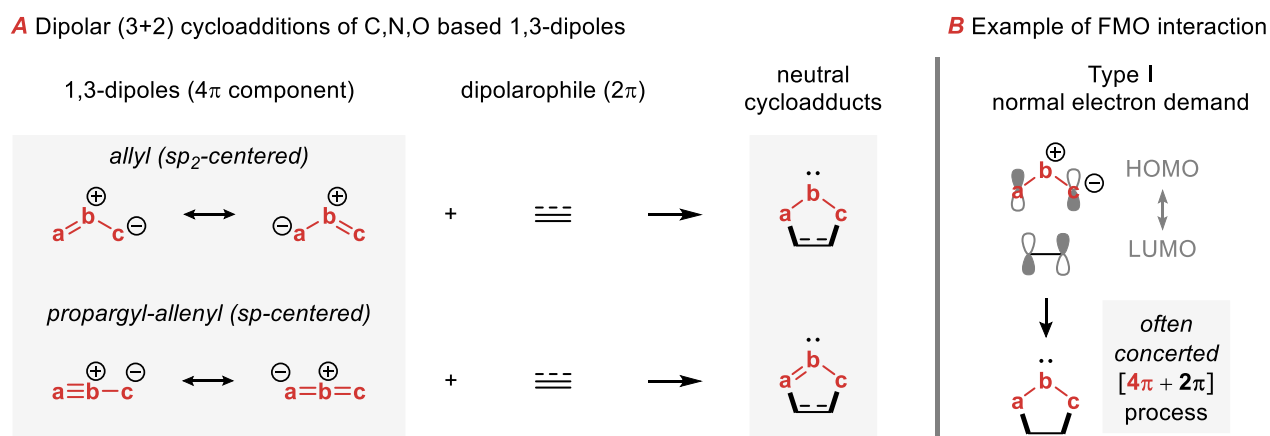


Figure 1 1,3-dipolar cycloaddition reactions. A) two classes of C,N,O based 1,3-dipoles. B) Example of frontier molecular orbital interactions for HOMO-controlled cyclization.

Understanding of the reactivity differences between these C,N,O based synthons appeared shortly after by Sustmann who classified 1,3-DA based on frontier molecular orbital (FMO) interaction between the 1,3-dipoles and dipolarophiles.³ For instance, type I is controlled by the interaction between the HOMO of the 1,3-dipole and the LUMO of the dipolarophile, also termed normal electron demand (Figure 1, B). This followed extensive mechanistic studies making 1,3-DA one of the most well-studied transformations often proceeding by a concerted process.^{4, 5}

Of utmost importance, all 1,3-dipoles are capable of delocalizing a minimum of 4π electrons over three-atoms. This is the fundamental feature that all 1,3-dipoles share which gives them the ability to participate in (3+2) cycloadditions with dipolarophiles. This class of reagents is generally called three-atom components (TACs), i.e. an overall neutral specie composed of three-atoms sharing an electron density of at least 8 electrons.⁴ 1,3-Dipoles will be interchangeably called *charged-TACs*, the term “charged” referring to the formal charges present in their Lewis structure. The ability to use 1,3-dipoles as synthons for 5-membered heterocycles has created a common retrosynthetic disconnection that has spread in a variety of fields of chemistry.⁶ This ranges from the use of 1,3-dipoles in stereoselective synthesis⁷ and natural product formation⁸ to material science⁹ and biorthogonal chemistry.^{10, 11} The latter field in particular was greatly impacted after the discoveries of “click” reactions between azides and alkynes,¹² a variation of 1,3-DA which was honored the Nobel prize in 2022 (Figure 2).

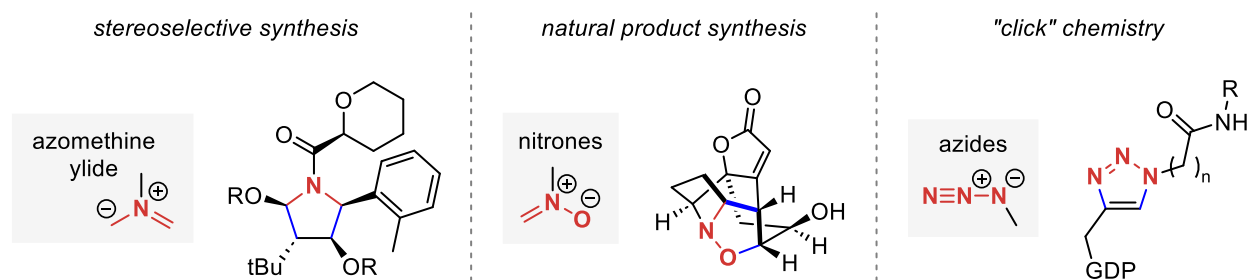


Figure 2 Dipolar (3+2) cycloadditions as a common retrosynthetic disconnection.

1.2 Towards the finding of analogous reactions to classical 1,3-dipolar cycloadditions

Despite the maturity in the field of dipolar (3+2) cycloadditions, the heterocyclic structures that can be accessed are inherently limited by the structural arrangements available on these *charged*-TACs (1,3-dipoles). For instance, the central atom for all C,N,O-based 1,3-dipoles is restricted to nitrogen or oxygen as it must accommodate a lone pair of electrons upon cycloaddition with a dipolarophile.² While the use of these reactive 1,3-dipoles is useful from a synthetic standpoint as they directly lead to the formation of neutral and often stable cycloadduct (*vide-supra*), the heterocyclic structures that are routinely accessed by means of (3+2) cycloadditions may be expanded by exploring the use of unconventional C,N,O based isoelectronic species, such as *neutral*-TACs instead. The term “neutral” in this case is utilized to describe overall neutral species that do not possess charges within their Lewis structures (Figure 3). The terms “charged” or “neutral”-TACs are not used to describe the type of cycloadducts obtained (Figure 4, B) but rather to differentiate the classical 1,3-dipoles from the less explored species discussed in this thesis.

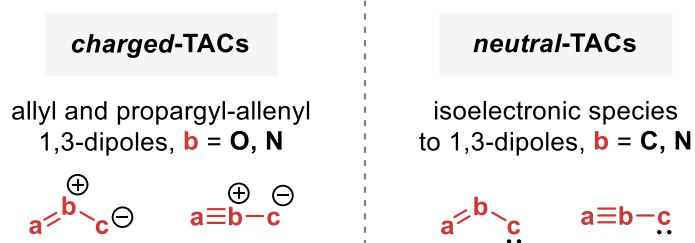


Figure 3 Terms utilized in this thesis to differentiate 1,3-dipoles (*charged-TACs*) from the underexplored isoelectronic TAC species (*neutral-TACs*).

This concept of finding a new chemical space from well-established reactivities is not novel and has been applied to other pericyclic reactions. For instance, dehydropericyclic variants of the well-known Diels-Alder (DA) reaction are scattered in the literature (Figure 4, A). The classical-DA cyclization is a highly exothermic reaction between a diene and an alkene dienophile towards the formation of isolable cyclohexene derivatives by means of C-C bond formation and breakage (eq. 1). In contrast, dehydro-DA variants use more oxidized systems by replacing one (or multiple) double bonds by a triple bond. Examples of such reactions range from didehydro-DA (eq. 2) to the highest oxidized case of hexadehydro-DA (eq. 3) depending on the isoelectronic diene and/or dienophile used.¹³

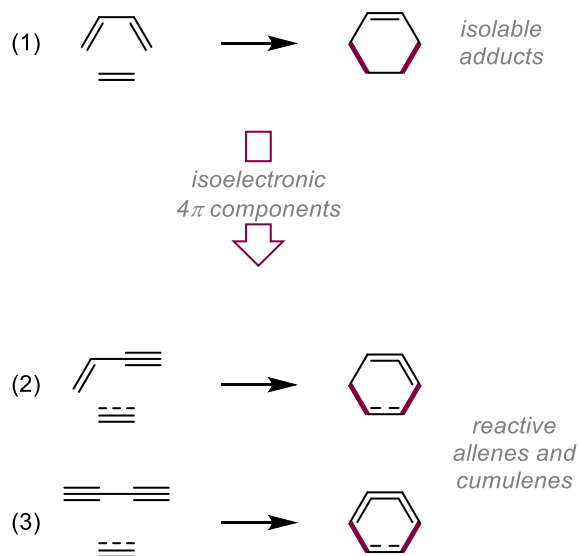
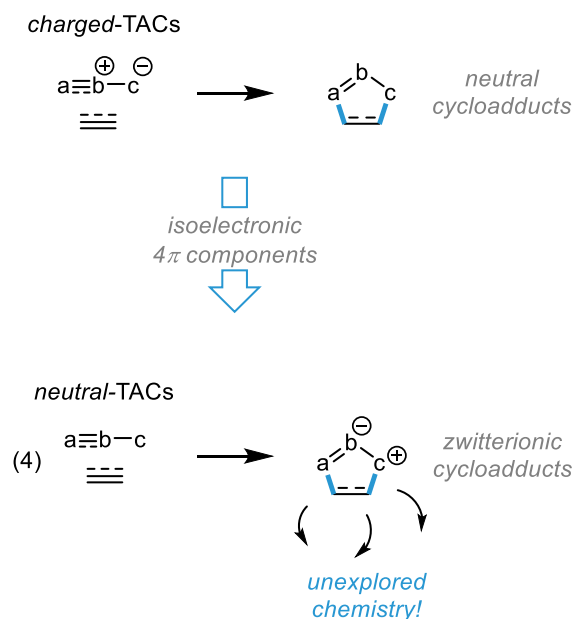
A (Dehydro)-Diels-Alder reactions**B** Possible (3+2) cycloadditions

Figure 4 Contrasting classical and unconventional [4+2] cycloaddition reactions. A) Cycloadducts formed in (Dehydro)-Diels-Alder reactions. B) Transferring the concept to (3+2) cycloaddition reactions.

As stated by Johnson et al., “the dehydropericyclic concept not only provides a straightforward approach for fitting known processes into a broader framework but also facilitates the invention of new chemical reactions and routes to reactive intermediates”. In the context of dehydro-Diels-Alder reactions, the intermediates formed upon cycloaddition are highly strained cyclic allenes and cumulenes. These cycloaddition reactions have an activation barrier that is slightly higher than the parent DA system (around 5-6 kcal/mol higher per triple bond) and surprisingly most of the cyclizations shown (eq. 2 and 3) are exothermic.^{14, 15} A variety of (4+2) cycloaddition cascades utilizing dehydro-isoelectronic 4π partners have been described and the intermediacy of these strained intermediates is well established.^{16, 17}

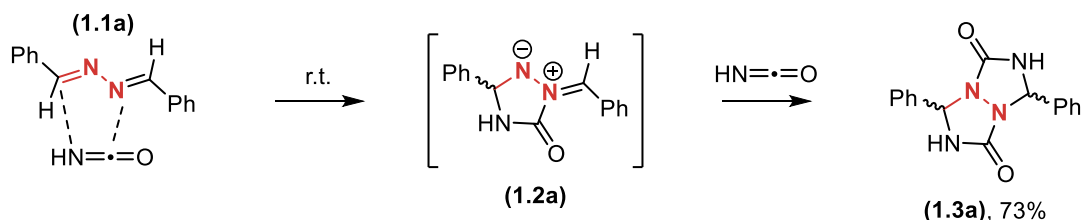
Variations of dipolar (3+2) cycloaddition reactions, that is using *neutral*-TACs instead of *charged*-TACs (1,3-dipoles), is largely unexplored in the literature which is likely due to the presumably unfavorable thermodynamic profile which leads to reactive zwitterionic cycloadducts (Figure 4, B). The finding of novel *neutral*-TAC species would offer however a great opportunity for diversifying the 5-membered heterocyclic structures that can be obtained as 1) very little overlap in atom sequence is seen between the C,N,O based *charged* and *neutral*-TACs;¹⁸ 2) the resulting cycloadduct is zwitterionic and can further react complexifying the transformation outcome. The next sections will present an overview of the *neutral*-TACs (*n*TACs) species that have been reported to undergo (3+2) cycloaddition reactions. While both sp_2 (bent) and sp (linear) centered *n*TACs will be discussed, more details will be provided for the sp centered *n*TACs as they are of greater importance for the research discussed in this thesis.

1.3 Sp_2 centered *neutral*-TACs as isoelectronic species to 1,3-dipoles

Interestingly, instances of (3+2) cycloadditions involving unconventional TAC species were briefly highlighted in Huisgen's review on 1,3-dipolar cycloadditions.² In particular, Huisgen described the discovery made by Bailey and coworkers in 1917 involving a thermodynamically unfavorable cycloaddition.¹⁹ The reaction in question showed that benzalazines **1.1a** (sp_2 centered *neutral*-TACs) are capable of undergoing two-fold (3+2) cycloaddition reactions with cyanic acid, also known as a criss-cross cycloaddition (CCC) (Figure 5, A). Huisgen proposed that two consecutive cycloaddition reactions take place by the intermediacy of a zwitterionic cycloadduct **1.1a** which contains an azomethine imine 1,3-dipole motif. This mechanism was later validated when Burger et al. isolated a stable cycloadduct **1.2b** (85% yield) resulting from a (3+2) cycloaddition between an electron-poor azine **1.1b** and 2-methylpropene as the dipolarophile

(Figure 5, B).²⁰ These isolable adducts can then undergo further cyclization with various dipolarophiles towards bicyclic compounds containing two bridgehead nitrogen atoms **1.3**.²¹ The use of azines in criss-cross cycloadditions for generating complex heterocyclic systems has recently been reviewed and represents great examples of structure complexification by using isoelectronic 1,3-dipolar species (*neutral-TACs*).²²

A Bailey and coworkers (1917)



B Isolation of a zwitterionic cycloadduct for *mixed* criss-cross cycloadditions

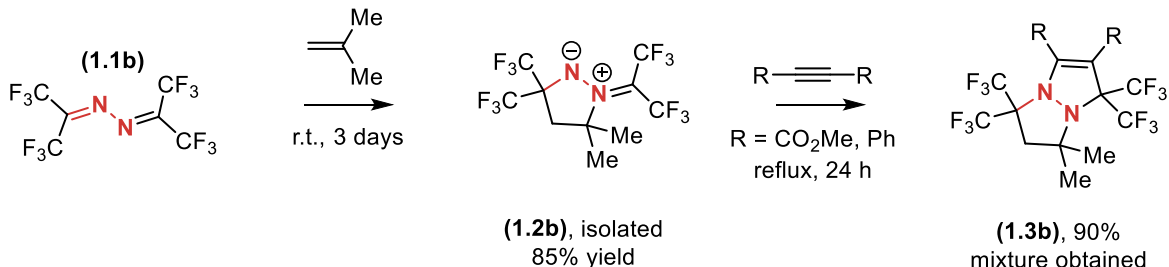


Figure 5 Criss-cross cycloaddition reactions with azines. A) Proposed (3+2) cycloaddition reactivity between benzalazines and cyanic acid. B) Isolation of a stable zwitterionic cycloadduct containing an azomethine imine motif.

The use of other *sp*₂-centered *neutral-TACs* started making appearances after Easton and Leaver reported the cycloaddition reactions of trithiocarbonate derivatives in 1965 (Figure 6, top).²³ They describe that ethylene trithiocarbonate **1.4** can thermally react with dimethyl acetylene dicarboxylate to give isotrithione adduct **1.6** in almost quantitative yield. Although the formation of zwitterionic cycloadduct **1.5** was not proposed at the time, it can be imagined that this intermediate may irreversibly collapse to give the observed product upon loss of ethylene. This mechanism was later proposed by Cava et al. in 1976 as a selenium analogue **1.7** gave a

mixture of isomers which was explained by the formation of a zwitterionic adduct which can readily undergo cycloreversion.²⁴ Reports of cycloaddition cascades with oxo and aza-analogues were also reported during this time (Figure 6, bottom left).²⁵ Nakayama and coworkers confirmed the formation of a zwitterionic adduct in 1996 by isolating an intermediate sulfonium **1.9** in an excellent 85% yield by trapping with HCl. This was made possible by utilizing reactive *in-situ* generated benzyne as dipolarophiles which allowed for the cycloaddition with benzotrithione derivative **1.8** to occur at lower temperatures (Figure 6, bottom right).²⁶ More recently, the use of dithiocarbamates²⁷ and electron poor thioamides²⁸ as *neutral*-TACs has remerged in the literature involving (3+2) cycloaddition cascades with benzyne as dipolarophile.

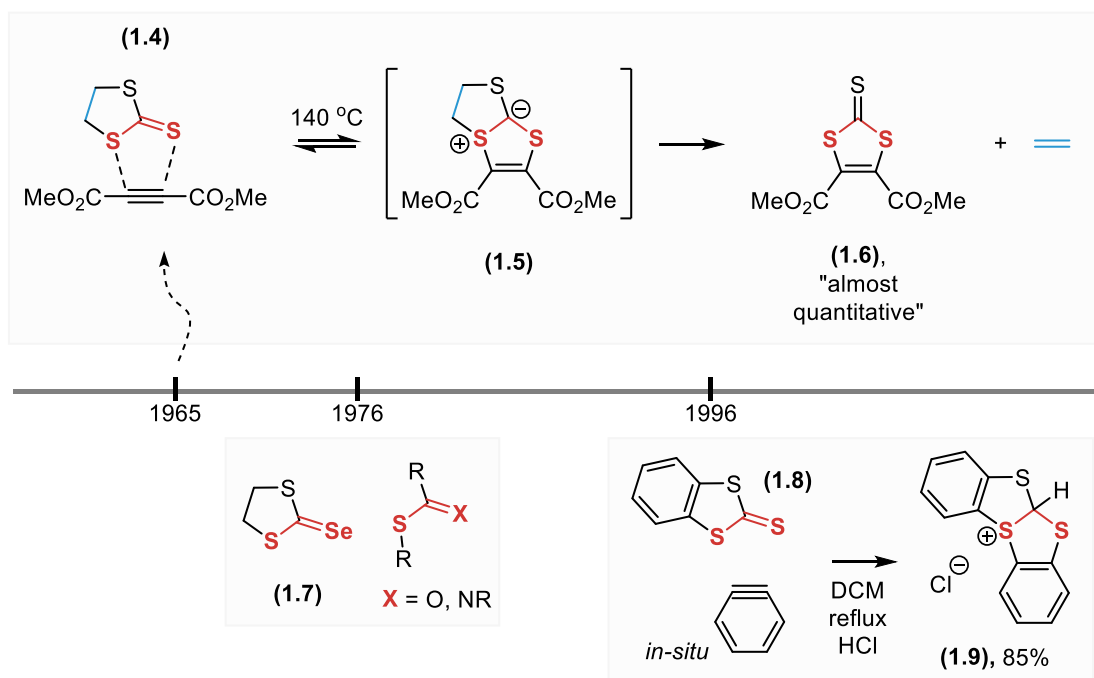
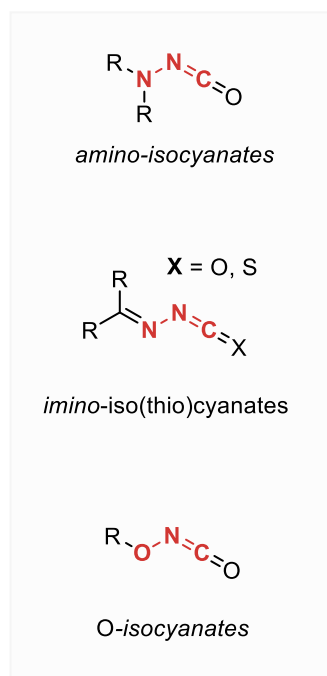


Figure 6 Early examples of thio-derived *sp*²-centered *neutral*-TACs.

The last class of bent-type *neutral*-TACs are isocyanates derivatives (Figure 7, A). The ability of amino- and imino-isocyanates to undergo (3+2) cycloaddition reactions was first discovered by Lwowski²⁹ and Jones.³⁰ It wasn't until the Beauchemin group exploited and

expanded their reactivity as isoelectronic 1,3-dipoles species (*n*TACs) that their potential for accessing nitrogen-containing heterocycles was made evident. For example, *in-situ* generated amino-isocyanates can react with tethered alkenes directly leading to the formation of β -aminocarbonyl products (pyrazolidinones) (Figure 7, B).^{31, 32} This amino-carbonylation reaction was shown to proceed *via* a highly reversible (3+2) cycloaddition reaction towards aminimides intermediates which undergo irreversible proton transfer and/or 1,2-shift.³³

A Isocyanates as *n*TACs



B Amino-isocyanates as synthons for *aza*-proline heterocycles

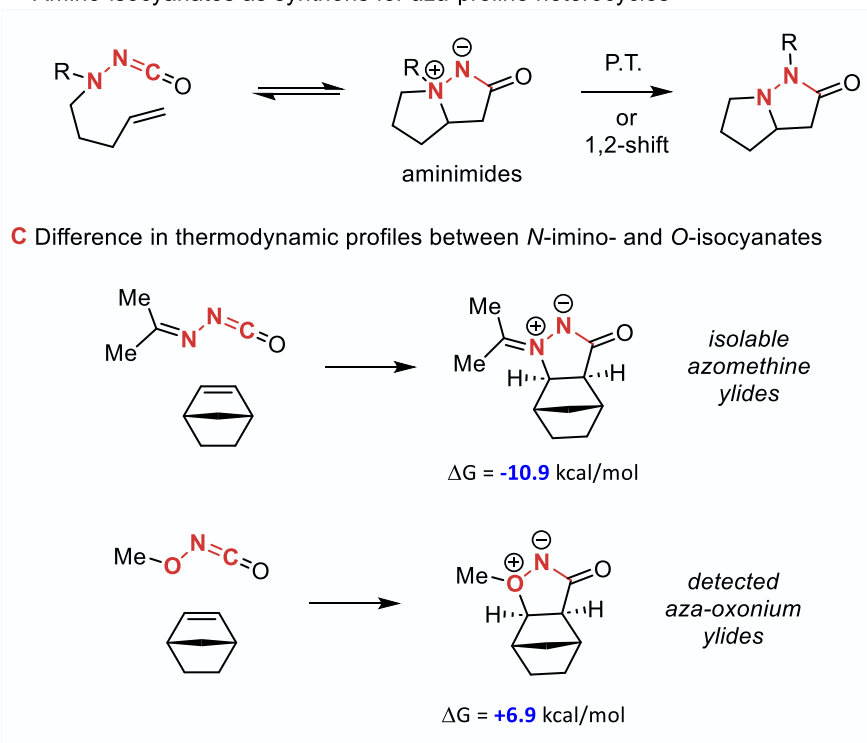


Figure 7 Isocyanates as reactive species capable of (3+2) reactivity. A) Classes of isocyanates described to react as *neutral*-TACs. B) (3+2) cycloaddition cascades of *amino*-isocyanates by the intermediacy of aminimides adducts. C) Comparing the cycloaddition between *imino*-isocyanates and *O*-isocyanates with norbornene as a dipolarophile.

In addition to *N*-iso(thio)cyanates,^{31, 34} the group recently described that *O*-isocyanates³⁵ exhibit favored reactivity as *neutral*-TACs rather than participating in (2+2) cycloaddition pathways. Computational investigations suggest that similarly to *amino*-isocyanates, both *imino*-

and *O*-isocyanates undergo concerted and asynchronous cycloaddition towards azomethine and aza-oxonium ylides respectively (Figure 7, C).³⁶ Interestingly, the cycloaddition between *imino*-isocyanate with norbornene as dipolarophile was found to be exothermic while when *O*-isocyanates are employed, an endothermic cyclization is seen instead. This correlated well with experimental observations as azomethine ylides were readily isolable while the aza-oxonium ylides underwent further reactivity *in-situ*. Despite the apparent instability of these previously unknown aza-oxonium ylides, the divergent reactivity from this common intermediate enabled for the synthesis of isoxazolidinone and lactam products of interest. Overall, the use of *N*- and *O*-isocyanates as *neutral*-TACs enabled the synthesis of useful molecules containing X-N-C=O (X=N, O) motifs which would be hard to access by means of classical 1,3-dipolar cycloaddition reactions.

While the use of these sp_2 -centered *n*TACs variants (azine, thiones, isocyanates, etc.) provides access to a complementary set of heterocycles, the reactions often require the need to use highly reactive aryne or strained dipolarophile partners limiting the scope of the reactions. Additionally, while isocyanates are highly reactive species which enabled for intermolecular cycloaddition cascades to be devised, these amphoteric reagents must be formed *in-situ* as they are prone to dimerization. It is therefore of interest to find novel *neutral*-TACs which are easy to synthesize and handle.

1.4 Heteroatom-substituted alkynes : possibility to react as sp -centered *neutral*-TACs

For instance, when thinking about finding isoelectronic species to the linear (sp -centered) propargyl-allenyl 1,3-dipoles, one can imagine that α heteroatom-substituted alkynes (X-alkynyl species) may react similarly as they fit the criteria of TAC species (*vide supra*). This subclass of alkynes is exceptionally electron-rich due to the electron-donating effect of the heteroatom

(Figure 8, A). In consequence, the triple bond of these X-alkynyl species is polarized, giving it an ambivalent character that is exploited by organic chemists for achieving highly regioselective transformations.^{37, 38}

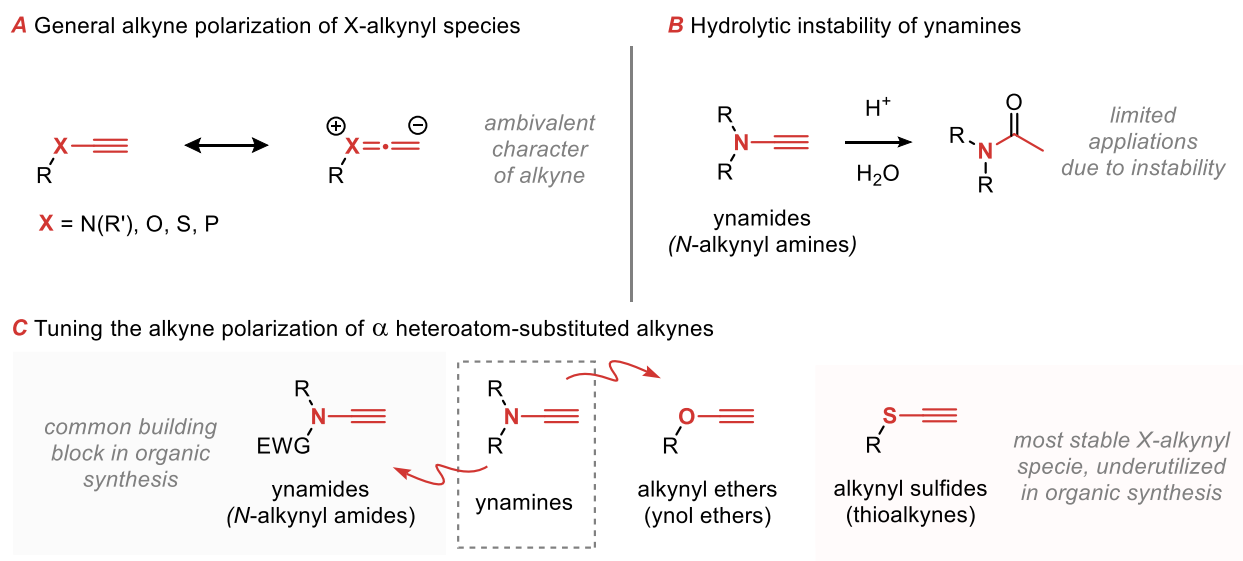


Figure 8 General introduction to α heteroatom-substituted alkynes. A) Resonance structure showing the polarization of the alkyne induced by the heteroatom. B) Amide formation upon hydrolysis of ynamines under acidic aqueous conditions. C) More stable X-alkynyl species utilized in organic synthesis.

In particular, ynamine derivatives are the most reactive (and polarized) however they are notoriously associated with being unstable and difficult to manipulate as they are prone to hydrolysis (Figure 8, B).³⁹ On the other hand, electron-poor ynamide derivatives display a superior stability conferred by the electron-pulling effect of the electron-withdrawing group (EWG). While they are less reactive than the parent ynamine, the alkynyl carbons remain highly polarized, a feature that was at the origin of their increased popularity as building blocks in organic synthesis. Ynol ethers and alkynyl sulfides are also characterized by a weaker alkyne polarization (as compared to ynamines) due to a decrease in electron donation by the heteroatom. The use of these derivatives in synthesis is however far less common. In the case of ynol ethers, this may be

due to their instability to thermal conditions as decomposition towards reactive ketenes is often observed. In contrast, alkynyl sulfides display enhanced stability which enables complementary reactivity to be observed.³⁸

In fact, an increase in the number of publications regarding methodologies for the synthesis of alkynyl sulfides is seen in the past years.⁴⁰ These reports further exemplify the ease of access and stability of this class of heteroatom-substituted alkynes with the aim to encourage their utility in organic synthesis. Furthermore, a recent review by Wan and Chen briefly highlights the similarities and differences in reactivity seen between (thio)ynol ethers and ynamides.⁴¹ To provide one example, both ynamides and alkynyl sulfides were found to participate in ruthenium-catalyzed azide-alkyne cycloaddition reactions (RuAAC) giving rise to a single 1,5-triazole regioisomer (Figure 9).^{42, 43} In the case of ynamides, an interaction between the R group (CO₂Me or Ph) of the alkyne and the metal center was proposed to provide regiocontrol over the transformation. On the other hand, when employing alkynyl sulfides, exclusive formation of the 1,5-adduct was ascribed to a favorable interaction between the sulfur atom with the ruthenium center. The scope of triazole products was therefore expanded to alkyl and non-coordinating groups by making use of thioalkynes instead.

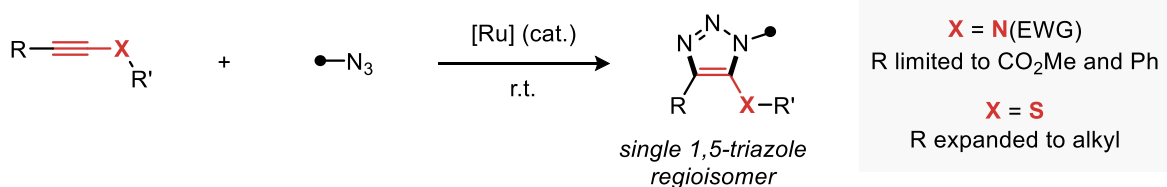
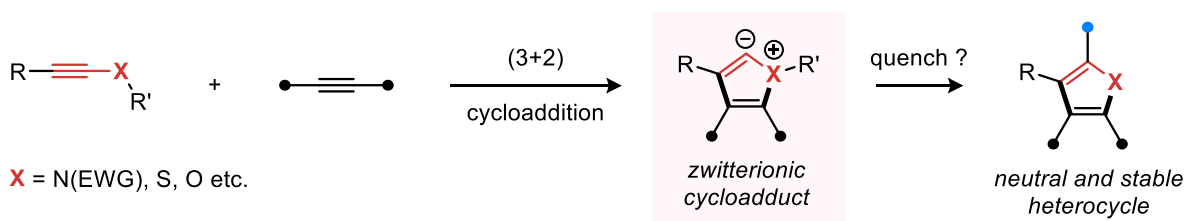


Figure 9 Ynamides and alkynyl sulfides as 2 π components in RuAAC.

This represents an example of reactivity differences between heteroatom-substituted alkynes, and how exploring the use of less common alkynyl sulfides may be beneficial. This

concept is likely to be more prevalent when the heteroatom is directly participating in new bond formations, for instance when reacting as an isoelectronic 1,3-dipole equivalent (Figure 10, A). It is possible that the reactivity of these species as *neutral*-TACs may be discovered given their structural overlap with classical propargyl-allenyl type 1,3-dipoles (Figure 10, B) and the precedent in the literature with sp_2 -centered *n*TACs (*vide-supra*). While this hypothetical reaction would give rise to a presumably unstable zwitterionic cycloadduct, the quenching of these intermediates may result in the formation of neutral and stable heterocycles.

A Heterosubstituted alkynes (X-alkynyl species) as *neutral*-TACs



B From charged to neutral sp -centered TACs for new heteroarylium ylides

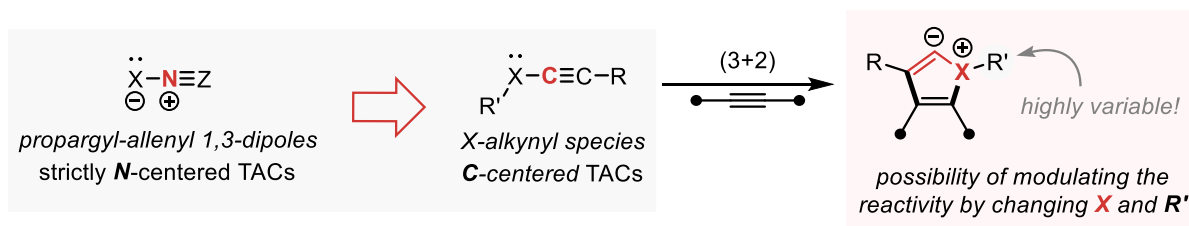


Figure 10 X-alkynyl species : from polarized alkynes to *neutral*-TACs. B) Hypothesis that X-alkynyl species may form 5-membered heterocycles upon (3+2) cycloaddition. C) X-alkynyl species as isoelectronic species to 1,3-dipoles for the formation of modurable heteroarylium ylides.

Furthermore, while ynamides were described to have set the “gold standard for balancing reactivity and stability” when it comes to functionalization of the triple-bond,³⁹ alkynyl sulfides and ynol ethers do not require substitution by an electron-withdrawing group and can handle more substitution variations, especially alkynyl sulfides. This feature may be exploited in order to modulate the reactivity and stability of these heteroarylium ylides towards isolable

intermediates and/or by providing predictable neutralization sequences. From a synthetic point of view, the finding of these reactions would be highly desirable as the linear type 1,3-dipoles are strictly *N*-centered,⁶ while *X*-alkynyl species would provide *C*-centered TAC analogues. Unlocking this mode of reactivity would provide access to a complementary set of heterocyclic structures that are inaccessible by classical 1,3-dipolar cycloaddition reactions.

1.5 Previous reactivity of (thio)ynol ethers as *neutral*-TACs in intermolecular reactions

Surprisingly, the observation that alkynyl sulfides can participate in (3+2) cycloaddition reactions was first made by Boonstra and Arens in 1960 where neat heating of *S*-ethyl alkynyl sulfide **1.10** produced thiophene **1.11** in 40% yield alongside gas formation which mainly consisted of ethylene (Figure 11, A).⁴⁴ A similar observation was made almost 40 years later by Markovsky and coworkers where dimerization of a *S*-alkyl alkynyl sulfide **1.12** is seen upon heating in toluene (Figure 11, B).⁴⁵ The authors reported the formation of a different 5-unsubstituted thiophene regioisomer **1.13** in a 30% yield alongside 1-butene as a by-product. A two-step mechanism involving the thermolysis of thioacetylene **1.12** followed by a (3+2) cycloaddition cascade was proposed at the time (Figure 11, C). It is clear from these early examples that the intermolecular (3+2) cycloaddition of alkynyl sulfides is very energetically demanding. This may be better explained by a cycloaddition event directly from the alkyl-substituted thioalkyne instead giving rise to a presumably unstable zwitterionic cycloadduct (endergonic process!).

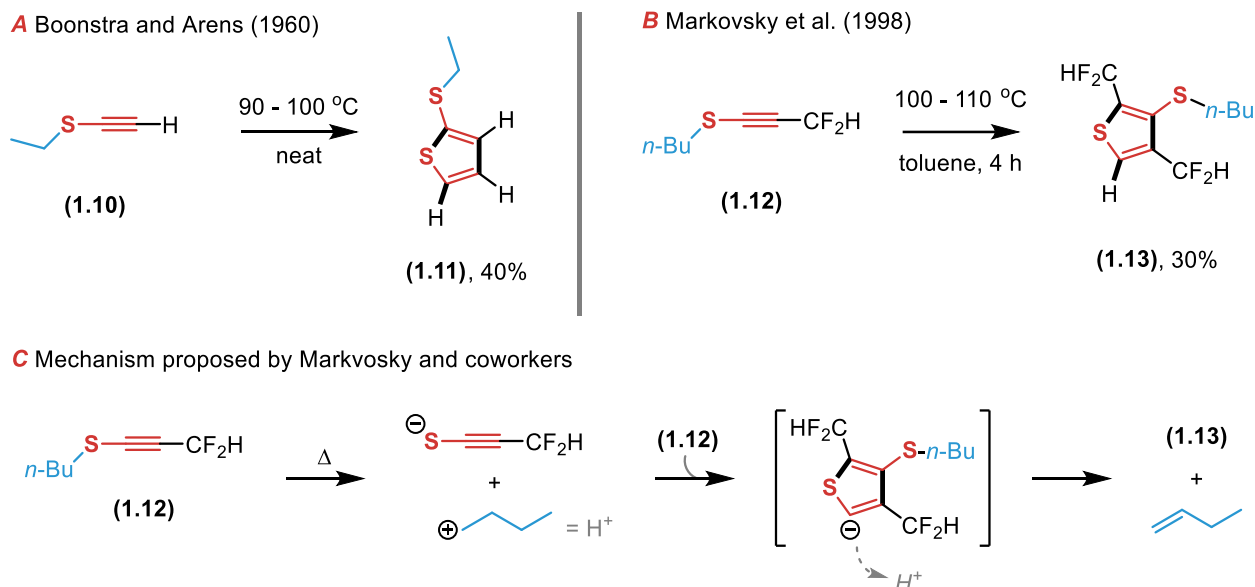
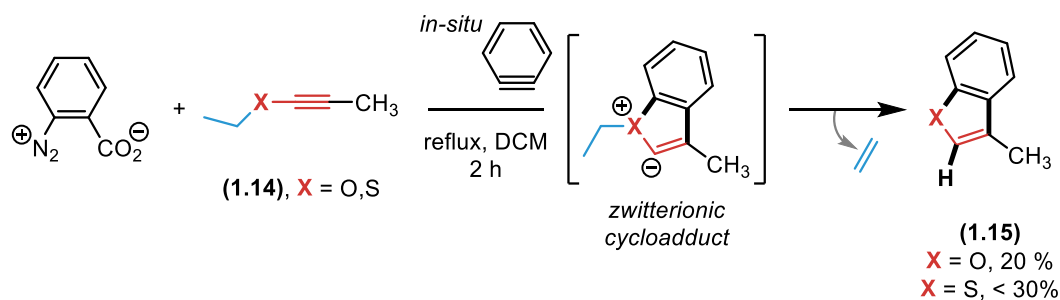


Figure 11 Early observations of alkynyl sulfide dimerization towards substituted thiophenes. A) Observations made by Boonstra and Arens upon neat heating of S-ethyl alkynyl sulfide. B) Formation of a highly substituted thiophene upon heating of electron-poor alkynyl sulfide. C) Proposed mechanism for the formation of thiophene **1.13** and alkene by-product.

Such charged cycloadducts were even proposed by Wasserman and Fernandez in 1968 when the reaction between (thio)ynol ethers with benzyne was evaluated (Figure 12, A).⁴⁶ Once again the energy required for the cycloaddition process was attenuated by the use of highly reactive aryne dipolarophiles. It was reported that mild heating of benzenediazonium-2-carboxylate, a benzyne precursor, in the presence of X-alkynyl species **1.14** resulted in the formation of benzofuran (X = O) or benzothiophene (X = S) **1.15** as the major product observed. The authors propose that upon the formation of a zwitterionic cycloadduct, loss of a β -hydrogen from the ethyl chain occurs in order to generate the neutral product. The observation that both X-alkynyl species reacted similarly hinted that a common mechanism may be at play, which can easily be explained when considering their reactivity as three-atom components.

A Wasserman and Fernandez (1968)



B Yoshida et al. (2020)

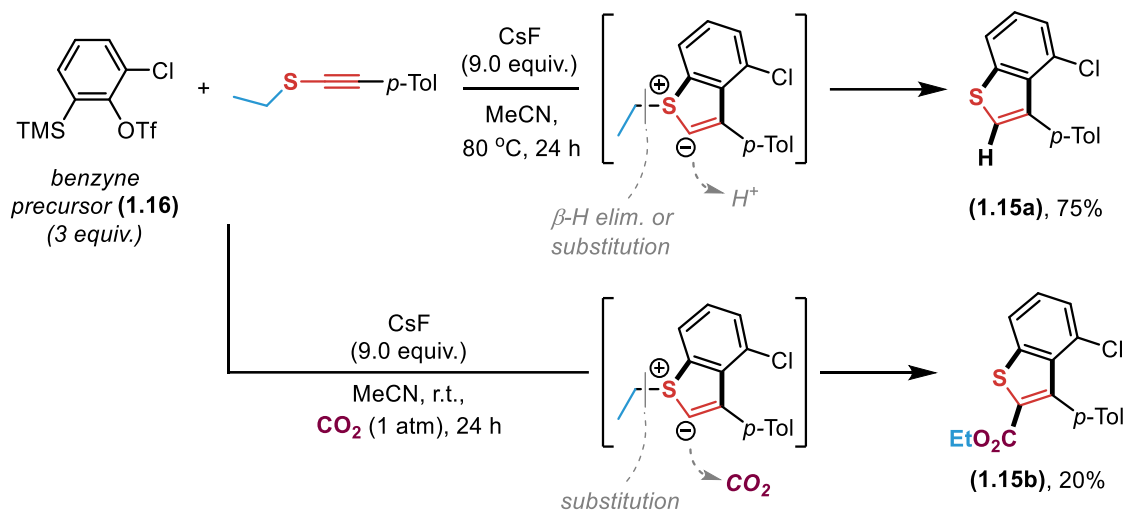


Figure 12 (3+2) cycloaddition of (thio)ynol ethers with benzyne. A) Early observations of benzo-fused heterocycles via a cycloaddition cascade. B) Controlling the cycloaddition of alkynyl sulfides with more stable benzyne precursors.

More recently, the group of Yoshida greatly expanded the scope of benzothiophene products by utilizing more stable benzyne precursors such as **1.16** (Figure 12, B).⁴⁷ The group proposes that a stepwise (3+2) cycloaddition takes place giving rise to the same zwitterionic benzo-fused cycloadduct which is then quenched by a sequence of protonation and dealkylation (either β -hydrogen elimination or substitution) towards 5-unsubstituted benzothiophene **1.15a** (75% yield). Interestingly, a 2-carboxylate ester product **1.15b** was obtained instead when the reaction is performed at room temperature in an atmosphere of carbon dioxide (20% yield). The

functionalization of the benzothiophene product was proposed to occur by trapping of the zwitterionic cycloadduct with CO₂ generating a carboxylate nucleophile that then substitutes the ethyl chain. The obtention of this trapped product provides further evidence for the proposed charged cycloadduct as the carbon-centered anion can either function as a base or nucleophile depending on the reaction condition.

The report by Yoshida represents the first instance where high yields for the neutral heterocycles are obtained which provides hope that despite the presumable instability of the zwitterionic cycloadducts, their fate can be controlled. Additionally, the possibility to intercept the charged cycloadduct by an electrophile shows the power of using *neutral*-TACs as it provides an additional handle to functionalize heterocycles. Although the strategy of using highly reactive benzyne species makes these difficult cyclizations possible at room temperature, this limits the scope to benzo-fused heterocycles.

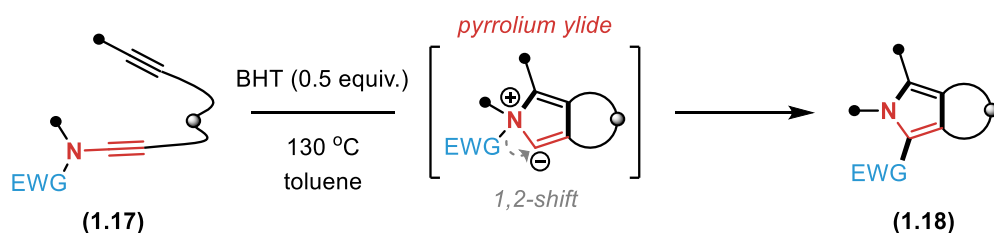
1.6 Ynamides as *n*TACs in intramolecular (3+2) cycloaddition cascades

Our group's entry into the field came from our interest in utilizing ynamides, nitrogen-substituted alkynyl species, in metal-induced cyclization cascades. It was surprising to us that a TAC reactivity of ynamide has not been described yet despite its popular use in organic synthesis.^{39, 48, 49} In fact ynamides reactivity is centered around the ability of the nitrogen to polarize alkynes enabling regioselective bond forming events at their alkynyl portion,^{37, 50, 51} with a few exceptions seen with transition metal-catalyzed cyclization cascades.⁵²⁻⁵⁶ Even the reactivity between dialkylaminoalkynes (i.e. ynamines) and benzyne showed a preference for a (2+2) cycloaddition.⁵⁷ We imagined however that this may be unique to ynamine derivatives and/or when reacting with highly reactive aryne partners. One can suppose that the

intermolecular (3+2) cycloaddition between ynamides and alkynes, if possible, is likely highly energetically demanding as seen with analogous (thio)ynol ethers (*vide-supra*). We hypothesized however that the cyclization may be facilitated by tethering the two partners with an appropriate linker, allowing for a (3+2) reactivity to be discovered. Gratifyingly, the novel reactivity of ynamides as *neutral*-TACs was disclosed by our group in 2021 by making use of this intramolecular linkage strategy.⁵⁸

It was demonstrated that a variety of alkyne tethered ynamides **1.17** cleanly underwent a thermally induced (3+2) cycloaddition cascade towards highly substituted pyrroles **1.18** (Figure 13, A). In contrast to the protonation and/or electrophilic interception quenching events observed with alkyl (thio)ynol ethers TACs (Figure 11 and Figure 12), the pyrrolium ylides formed undergo electron-withdrawing group (EWG) migration instead. Furthermore, computational evidence for the formation of these reactive ylides was provided for the first time. The cyclization towards the intermediate ylide was calculated to be endergonic and rate limiting, which is in accordance with the experimental observations. This is not surprising considering that the ylide formed bears an unstable carbon-centered anion which is, in this case, quenched by the EWG migration event. Density functional theory (DFT) calculations suggest that the (3+2) event occurs either by a concerted asynchronous pathway (closed shell) or *via* a stepwise diradical mechanism (open shell) (Figure 13, B). A transition state for the 1,2-shift event was also easily located computationally and a cross-over experiment was performed hinting that the migration occurs intramolecularly *via* a [1,5]-sigmatropic rearrangement.

A Gagosz et al. (2021) :



B Proposed mechanism :

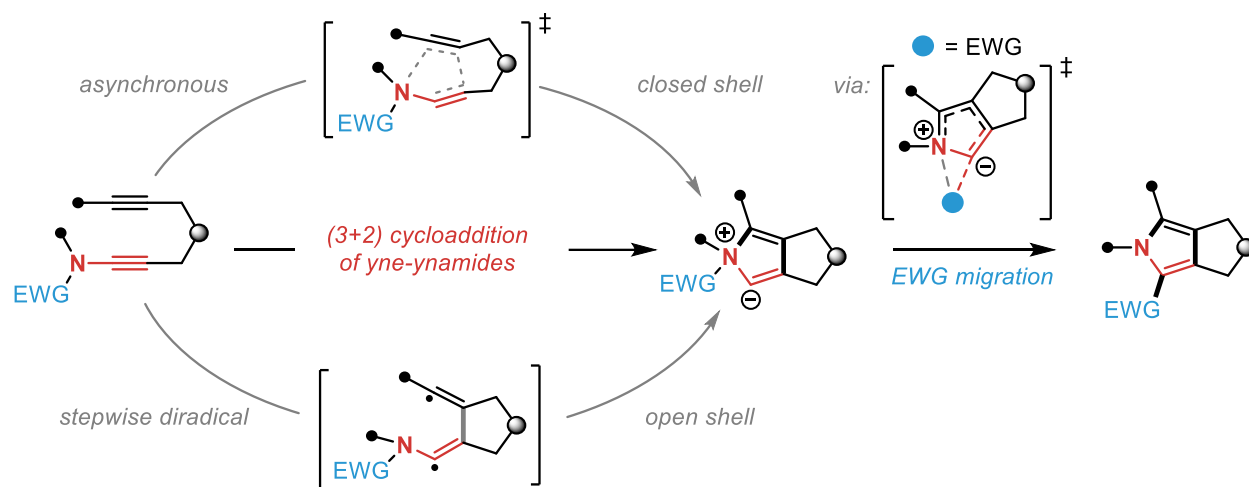
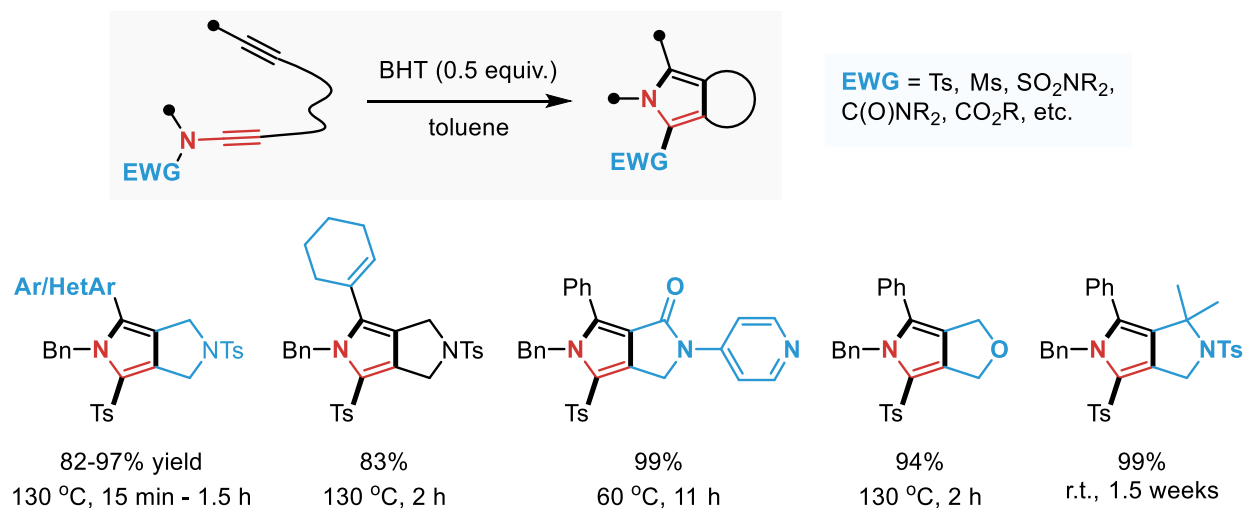


Figure 13 Ynamides as *neutral-TACs* in (3+2) cycloaddition cascades with tethered alkynes. A) General reactivity observed with yne-ynamides. B) Proposed mechanism for the (3+2) cycloaddition cascade.

The addition of BHT proved to be beneficial and enabled high yields for the fused pyrroles to be obtained. This effect was explained by its ability to intercept radicals formed upon heating at elevated temperatures. Gratifyingly, the 1,2-shift of a variety of electron-withdrawing groups proceeded smoothly which was attributed to the high migratory aptitude of these groups (Figure 14, A). In general, yne-ynamides that are linked by three-membered tethers efficiently cyclize at temperatures lower than or of 130 °C. Substitution at the alkyne terminus was also found to be important in obtaining high yields for the pyrrole products. For instance, (hetero)aryl substituted alkynes as well as those substituted with an alkenyl derivative were high yielding for the

corresponding fully substituted pyrroles. On the contrary, alkynyl, alkyl, as well as unsubstituted alkynes are not well tolerated as a complex mixture was obtained upon heating and the desired pyrroles products were detected in low yields (Figure 14, B). Scope limitations were also observed with the linker size as the need to use higher temperatures for longer four-membered tethers often resulted in substrate degradation and/or a low yield for the 3,4-fused pyrrole was obtained.

A General scope for the intramolecular cyclization of yne-ynamides



B Limitations in linker size and alkyne substitution

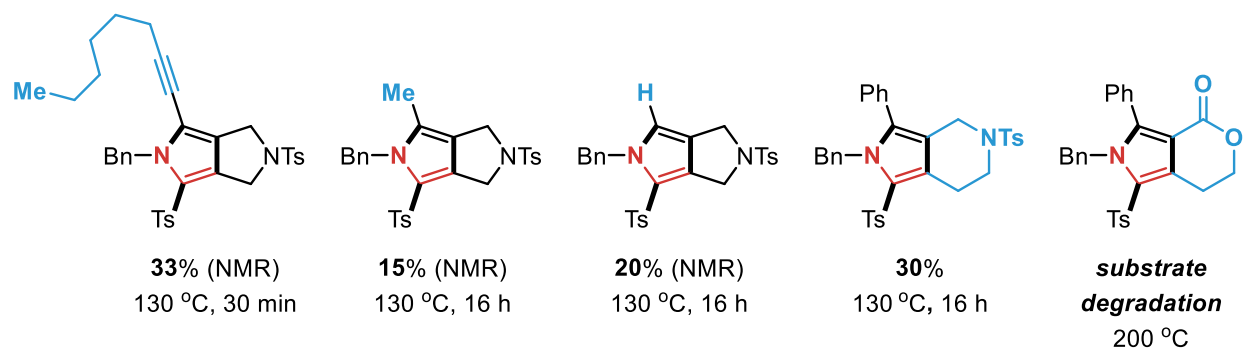
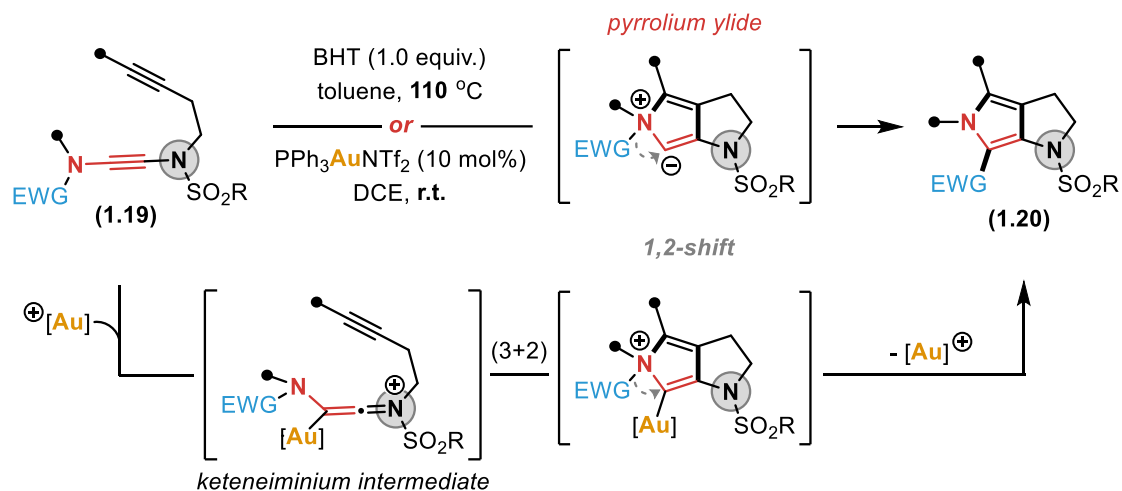


Figure 14 Selected examples of fused pyrroles obtained by the thermally induced intramolecular cycloaddition of yne-ynamides. A) General functional group tolerance and the effect of linker size on the rate of cyclization. B) Structural limitations associated with the thermal cycloaddition.

Despite these limitations, the simple reaction conditions are attractive in providing access to fully substituted fused pyrroles products. Most importantly, the thermodynamically

unfavorable (3+2) cycloaddition step can be overcome by the irreversible EWG shifting event providing a sink to the reaction. Additionally, this provided further proof of concept that X-alkynyl species can be regarded as *neutral*-TACs rather than polarized alkynes. Following our paper on the cyclization of yne-ynamides, the group of Anderson reported that diyne substrates bearing electron rich ynediamides **1.19** also cyclize efficiently upon heating yielding amidopyrrole products **1.20** (Figure 15, A).⁵⁹ Interestingly, the group also described that a low-energy cyclization pathway can in some instances be achieved under gold(I) catalyzed conditions. This room temperature pathway was proposed to occur by the formation of a reactive keteneiminium intermediate upon π -activation of the ynediamide. Cyclization give rise to a cyclic pyrrolium intermediate which is stabilized by the gold center. Since the same 2-EWG containing amidopyrroles **1.20** are obtained, a 1,2-migration and protodemetalation event was proposed as the last step of the mechanism.

A Anderson et al. (2021) :



B Complementary scope between the thermal and gold(I) catalyzed processes :

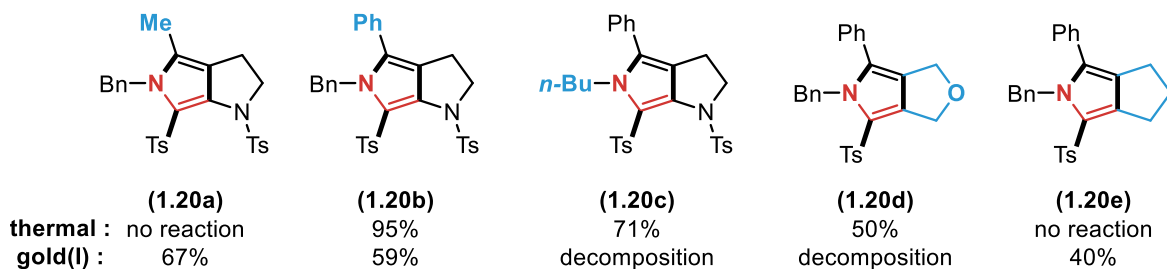


Figure 15 Ynediamides in thermally induced and/or gold catalyzed cycloaddition cascades with tethered alkynes. A) Reaction intermediates proposed by Anderson and coworkers. B) Complementary fused pyrrole products obtained utilizing both reaction conditions.

This alternative catalyzed pathway was found useful for obtaining alkyl substituted amidopyrrole **1.20a** which showed no reactivity under the thermal conditions while it was obtained in a 67% yield under the gold(I) procedure (Figure 15, B). Despite the capability to dramatically decrease the energy barrier for the transformations, the yields obtained under the catalyzed conditions were often lower (**1.20b**) or decomposition was seen instead (**1.20c,d**). In addition, this reduced energy barrier was only achieved when electron rich ynediamides are used limiting the method to the synthesis of amidopyrroles. The authors found an exception where an all-methylene linked yne-ynamide underwent cyclization at room temperature under the same

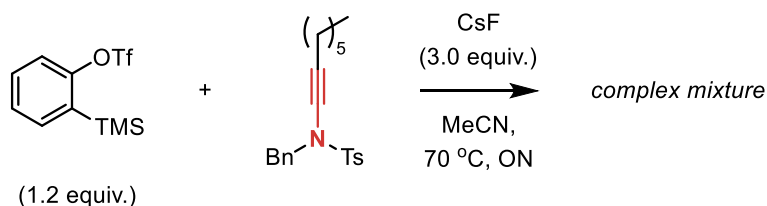
metal-catalyzed conditions (**1.20e**). Despite the reoccurring instances of decomposition, the use of this alternative set of conditions was at times found fruitful when thermal cyclization is difficult. Unfortunately, an attempt to tackle the limitation associated with the linker size previously described by our group (Figure 14) was not explored and only [3.3.0] bicyclic pyrroles were synthesized. The finding of metal-catalyzed conditions able to catalyze the (3+2) cycloaddition of X-alkynyl species remains unexplored despite its potential in enabling otherwise difficult cyclization.

As described previously, the intermolecular reaction of alkynyl sulfides and/or enol ethers with benzyne represents one of the first examples of the reactivity of these species as *neutral*-TACs. Despite it being expanded by Yoshida et al. in 2020, the reaction was only described for alkynyl sulfide derivatives. Our group's findings that ynamides are also capable of acting as isoelectronic species to 1,3-dipoles prompted us to attempt to react ynamides with benzyne with the hope to obtain indole products. When utilizing similar conditions to those described by Yoshida and coworkers however the resulting crude mixture was overly complex, and the outcome of the reaction could not be properly determined at the time (Figure 16, A).

Very recently, the group of Takikawa and Takasu unraveled the previously unreported (3+2) cycloaddition between benzyne and ynamide.⁶⁰ They determined that the intermolecular variant (Figure 16, B) give rise to indole product **1.21** in a low 9% yield however that this indole product overreacts with benzyne generating a structurally undetermined by-product **1.22** consisting of indole **1.21** and two molecules of benzyne (12%). In fact, 2-unsubstituted indole product of type **1.21** was previously hypothesized to be formed by our group due to the observation of the characteristic 2-H indole signal which lies around 6.8-6.9 ppm. The

comprehensive study done by Takikawa et al. confirmed that in contrary to the literature precedent using (thio)ynol ethers as cycloaddition partners, the (3+2) cycloaddition between ynamides and benzyne is not as straightforward. In fact, they computed that the (2+2) cyclization is energetically favored which explains the low yield obtained for the (3+2) derived indole.

A Previously attempted reaction by our group (unpublished 2020)



B Takikawa and Takasu (2023)

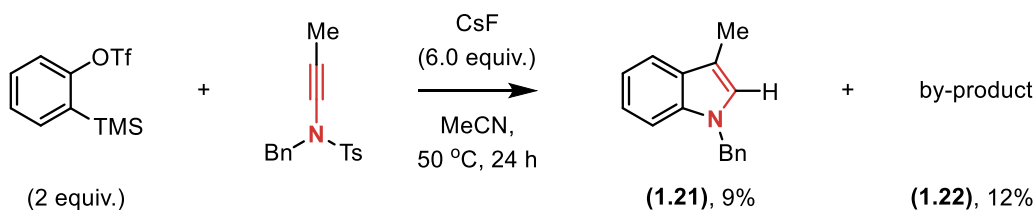


Figure 16 Reacting ynamides with in-situ formed benzyne species. A) Attempted intermolecular reaction between a simple ynamide with benzyne utilizing Yoshida et al. conditions. B) Isolation of a (3+2) derived indole product and rationalization of reaction outcome by Takikawa et al.

A specially designed Si-O tether (**1.23**) was found to be important in ensuring selectivity over the (2+2) pathway and high yield for indole products (Figure 17). The use of Cs_2CO_3 and 18-crown-6 allowed for the formation of the benzyne moiety at room temperature while leaving the tether intact. Surprisingly, no indole product derived from electron-withdrawing group migration upon formation of the indolium ylide was observed across all the EWGs evaluated. Rather, protonation of the ylide followed by substitution of the electron-withdrawing group was observed towards 2-unsubstituted indoles **1.24** (62-79%). This was an unprecedented result as

the cyclization of alkyne tethered ynamides led to the retention of the EWG group (Figure 13). The authors suggest that the proton source originates from using highly hygroscopic Cs_2CO_3 and/or 18-crown-6 and that the resulting hydroxide readily substituted the EWG group on the nitrogen center.

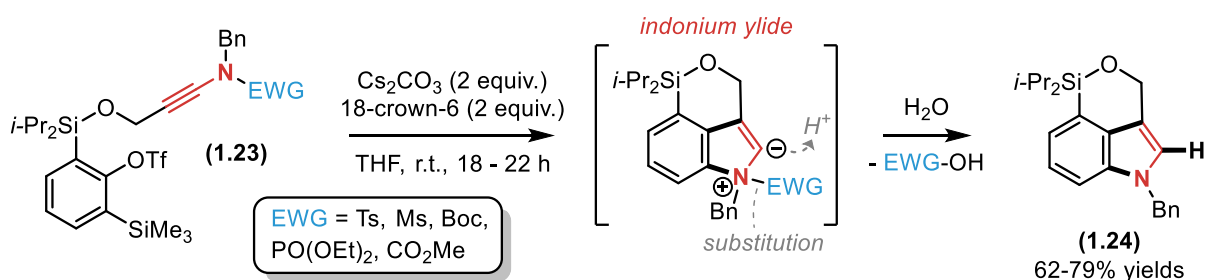
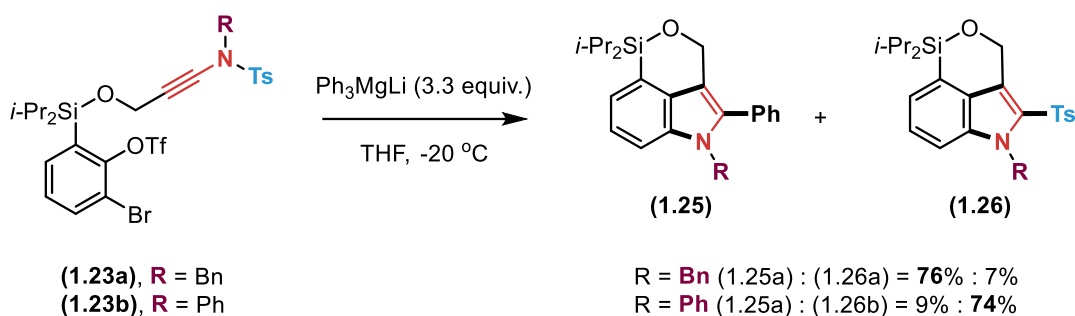


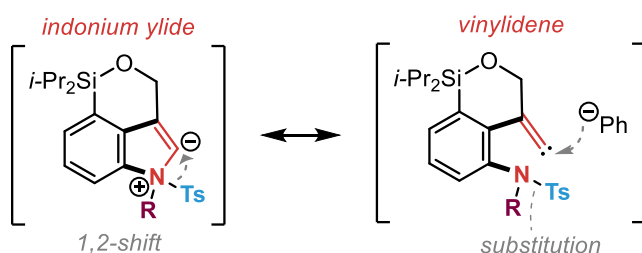
Figure 17 The use of a specially designed linker for the intramolecular (3+2) cycloaddition between ynamide and benzyne.

Interestingly, a carbene-like reactivity of the indonium ylide was also observed (Figure 18, A). The generation of benzyne from a *o*-bromoaryl tosylate benzyne precursor (**1.23a**) upon treatment with Ph_3MgLi led to the unprecedented formation of phenyl substituted indole (**1.25a**) in 76% yield alongside a 1,2-EWG shift derived product **1.26a** in a low 7% yield. Changing of the *N*-tosylamide moiety (**1.23b**) led to a complete change in selectivity with formation of the EWG containing product **1.26b** in a high 74% yield instead. The drastic change in selectivity between the tethered ynamides was not rationalized however it is interesting that the 2-H indole product **1.24** is not observed in this case.

A Unprecedented carbene-like reactivity of indonium ylides



B Vinylidene resonance structure



C Scope limitation

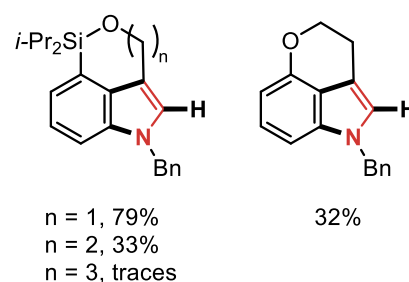


Figure 18 A carbene reactivity observed with indonium ylides and reaction scope limitation. A) Drastic change in product selectivity between benzyl and aryl substituted ynamides. B) Ylide and vinylidene resonance structures of the cycloadduct and the ambivalent reactivity observed. C) Linker size and structure limitations seen with the (3+2) pathway.

The authors suggest that the vinylidene resonance structure explains the electrophilic nature of this C2 position where a nucleophilic addition by the Grignard reagent was possible followed by intramolecular displacement at the nitrogen center (Figure 18, B). This carbene-like character highlights another reactivity of these fleeting ylides and the utility for the synthesis of multi-functionalized heterocycles. While the reaction between ynamide and benzyne is now devised, the success of the cyclization cascade was found to be highly dependent on the linker (Figure 18, C). For instance, increasing the length of the model Si-O linker or changing it to an O-C linker instead was detrimental and lower yields for the 2-unsubstituted indole products were obtained.

1.7 Research goals

While the use of ynamides as isoelectronic 1,3-dipole species is as of now limited to intramolecular variants, these preliminary reports show that finding novel TACs opens the door to the formation of complementary heterocyclic structures. For instance, the synthesis of pyrrole heterocycles by means of 1,3-dipolar cycloaddition reactions was historically done by using nitrile ylides or Münchnones 1,3-dipoles.⁶ Now, fused pyrroles can be easily obtained by exploiting the novel reactivity of ynamides as *neutral*-TACs.⁵⁸ Additionally, our group has shown that the pyrrole products can be easily derivatized by means of redox chemistry towards highly functionalized γ -lactam which are privileged motifs in bioactive compounds (Figure 19, middle).⁶¹ Furthermore, access to these pyrrolo-pyrrole cores is highly valuable as the fully reduced structure is that of diazabicycloalkenes, a class of medicinally relevant structures (right).⁶² This motivated our continued investigation on the development of *one-pot* procedures for the expedited synthesis of structurally diverse fused pyrroles (left). To this end, Chapter 2 discusses the utility of a novel building block for bridging the *in-situ* yne-ynamide synthesis and cyclization event.

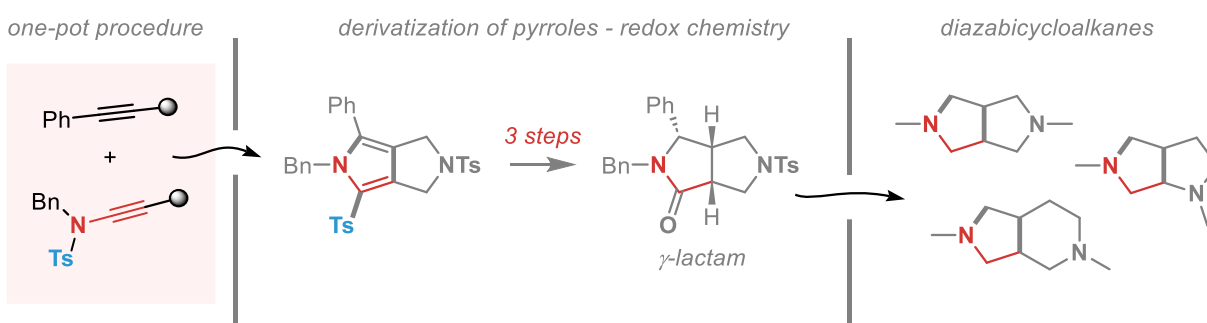


Figure 19 Motivation for the finding of one-pot procedures for the expedited synthesis of fused pyrroles.

Although using ynamides as TAC enabled important nitrogen-containing heterocycles to be formed, the pyrrolium and indolium ylides studied so far exhibit a nucleophilic character that is tied to an EWG migration or protonation quenching event.^a While the EWG migration event could in theory be avoided by using *N*-alkynyl amines instead, ynamine species are very sensitive to hydrolysis. This structural restriction inherently limits the variation of nitrogen-containing ylides that can be studied. In contrast, alkynyl sulfides exhibit higher stability under acidic, basic, and thermal conditions (*vide supra*). Furthermore, alkynyl sulfides are easily synthesized and can handle diverse structural modifications.⁴⁰ These are all desirable properties that were found to be essential in our continued studies on heteroarylium cycloadducts (Figure 20).

In Chapter 3, the reactivity of novel thiophenium ylides and their synthetic potential for the synthesis of polysubstituted thiophenes will be discussed. The factors influencing the quenching pathways of these reactive ylides will be explained in detail. In Chapter 4, the discovery of a low-energy pathway for the intramolecular cyclization of a special class of yne-alkynyl sulfide using a transition metal-catalyzed cycloaddition is presented. The finding of milder reaction conditions enabled the synthesis of a complementary library of fused thiophenes to be obtained by the intermediacy of thiophenium salts. Collectively, the work described in this thesis is focused on providing an understanding of the reactivity of thiophenium cycloadducts ranging from intramolecular rearrangements to photoredox applications.

^a Attempt to trap the indolium ylides with electrophiles was found to be unsuccessful (Takikawa et al.)

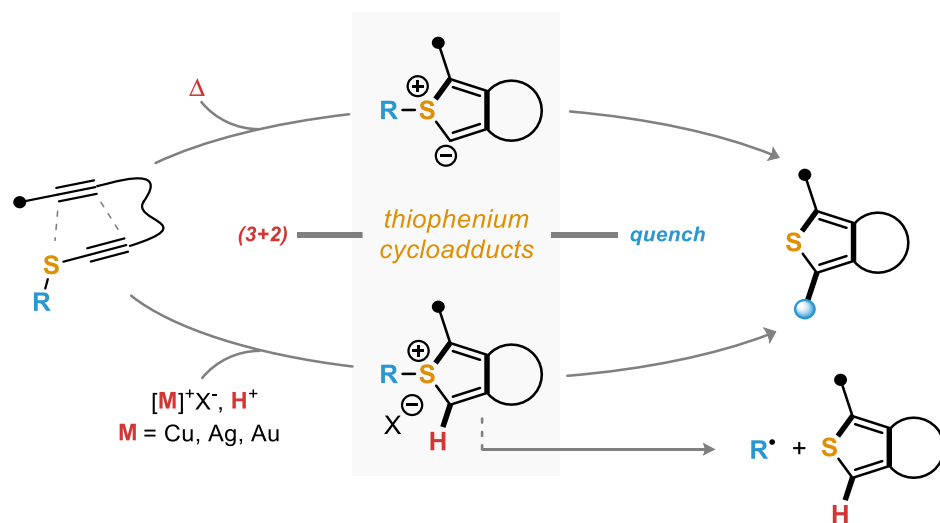


Figure 20 Avenues towards and general reactivity of the thiophenium cycloadducts studied in this thesis.

2 Chapter 2 : Towards the expedited synthesis of fused pyrroles

2.1 Background on the thermally induced (3+2) cycloaddition of yne-ynamides

Our group's findings that ynamides can be regarded as isoelectronic species to propargyl-type 1,3-dipoles highlighted a novel reactivity of these commonly employed functional groups.⁵⁸ When tethered with appropriate linkers, yne-ynamides undergo a thermally induced (3+2) cycloaddition cascade towards fused pyrroles. As mentioned previously, a broad range of structural modifications at the alkyne and ynamide terminus were tolerated however scope limitations were observed with linker size. Specifically, high yields for [3.4.0] fused pyrroles were only obtained when using geometrically constricted linkers (Figure 21).

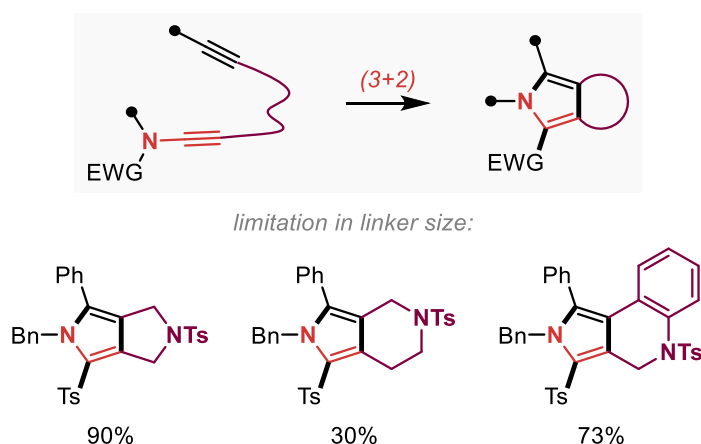
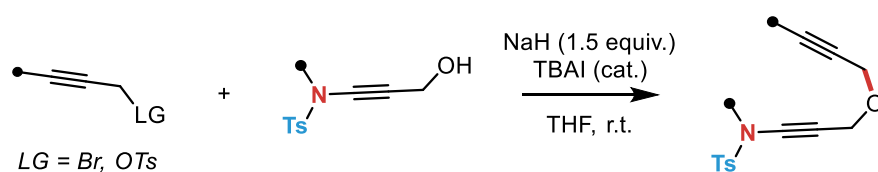


Figure 21 Limitation in linker size with the thermally induced cyclization of yne-ynamides.

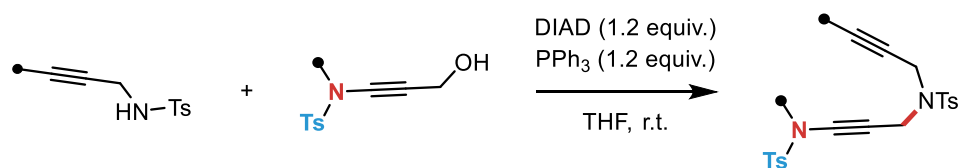
The in-depth study on the structural parameters influencing the cyclization of yne-ynamides done by Dominic Campeau enabled to obtain the fundamental knowledge necessary for the development of *one-pot* procedures. Knowing that the synthesis of [3.3.0] pyrrole bicycles was efficient with a variety of linkers, this structural motif was chosen as an initial target. As the overall yield for the final fused pyrrole products will be greatly impacted by the synthesis efficacy of the reactive substrates, the use of robust and high-yielding reactions is desired. A good starting

point for choosing retrosynthetic disconnections is by looking at the methods employed for the synthesis of these tethered ynamide substrates. For instance, Dominic Campeau utilized substitution and Mitsunobu reactions to synthesize many yne-ynamides however these two methods require the synthesis of distinct precursors making them less attractive in *one-pot* and/or two step procedures (Figure 22, A-B). Additionally, these reaction types inherently limit the scope to heteroatom containing linkers which is not optimal for product diversity.

A Substitution using propargyl bromides or tosylates



B Mitsunobu coupling between propargyl alcohols and tosylamides



C Coupling between tosylamides and bromoalkynes according to Hsung et al.

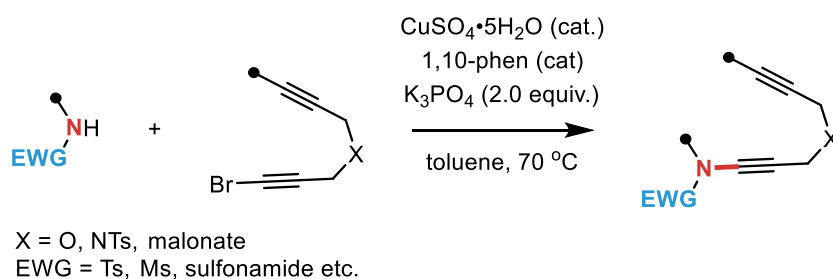


Figure 22 Main synthetic disconnections for yne-ynamides that afforded [3.3.0] fused pyrroles. A) Formation of the linker by substitution reactions. B) Formation of a tosylamide containing tether by a Mitsunobu coupling. C) Ynamide synthesis according to Hsung.

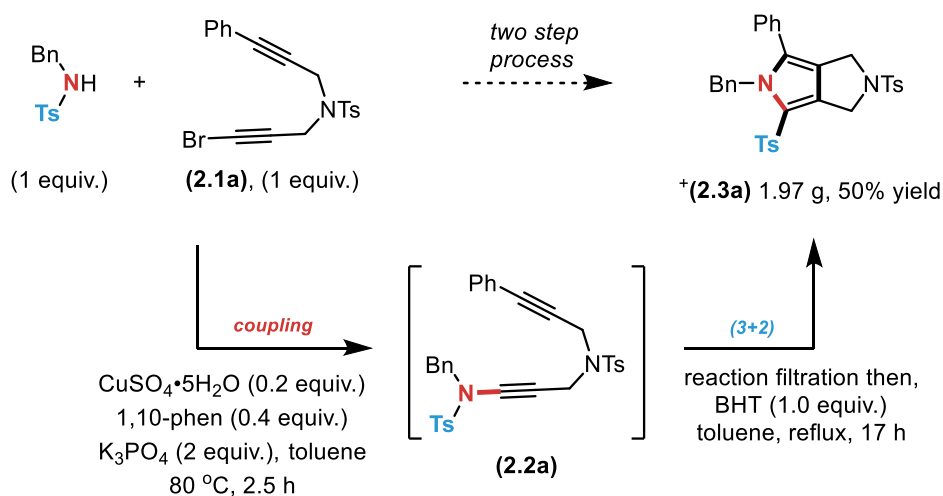
In contrast to the poor atom economy seen with the Mitsunobu substitution, catalytic reactions greatly limit the use of stoichiometric reagents. It was found that the coupling between

bromoalkynes and tosylamides described by Hsung and coworkers,⁶³ was a practical route towards yne-ynamides with various electron-withdrawing groups (EWG) and linkers (Figure 22, C). This approach is desirable as it has the potential to increase product diversity and functional group tolerance. Furthermore, Dominic Campeau determined that a two-step procedure starting from bromoalkyne **2.1a** involving this copper catalyzed coupling afforded the expected fused pyrrole **2.3a** in a 50% yield over 2 steps (Figure 23, A). This preliminary result prompted us to use this disconnection first for the development of *one-pot* procedures.

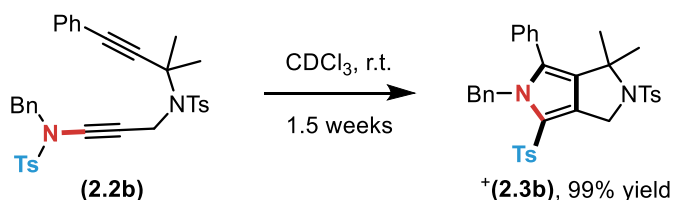
2.2 Efforts towards the *in-situ* synthesis of yne-ynamides *via* coupling reactions

It was previously shown that the introduction of a dimethyl group in the tosylamide linker accelerated the rate of cyclization by a Thorpe Ingold effect (Figure 23, B). Additionally, the addition of BHT was not necessary as pyrrole **2.3b** was obtained in an excellent 99% yield upon rearrangement of yne-ynamide **2.2b** at room temperature. Although this ynamide possessing a dimethylmethylene unit in the linker was previously made by a Mitsunobu coupling (Figure 22, B), the results obtained from the two-step procedure (Figure 23, A) prompted the use of this synthesis strategy instead. For these reasons, the *in-situ* formation of this modified tethered ynamide **2.2b** instead of **2.2a** was attempted in the coupling and cyclization *one-pot* sequence utilizing the conditions described by Hsung (Figure 23, C).

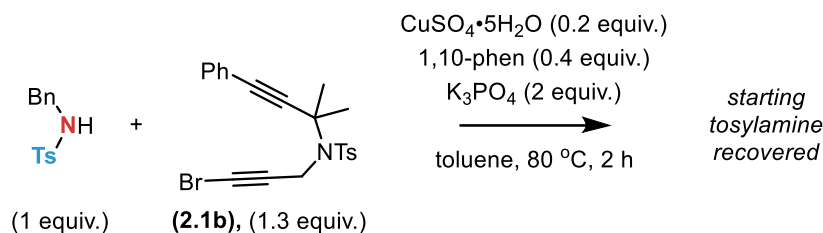
A Two step process for pyrrole **2.3a**



B Room-temperature (3+2) cyclization of yne-ynamides



C One-pot attempt starting from bromoalkyne **2.1b**



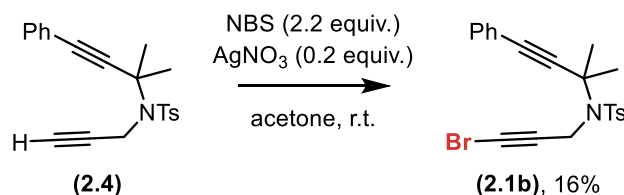
[†]Results by Dominic Campeau

Figure 23 First attempt towards a *one-pot* procedure. A) Two step process previously reported by our group. B) Dimethyl-induced Thorpe-Ingold effect. C) Attempt to use the coupling described by Hsung and coworkers for a one-pot coupling and cyclization sequence.

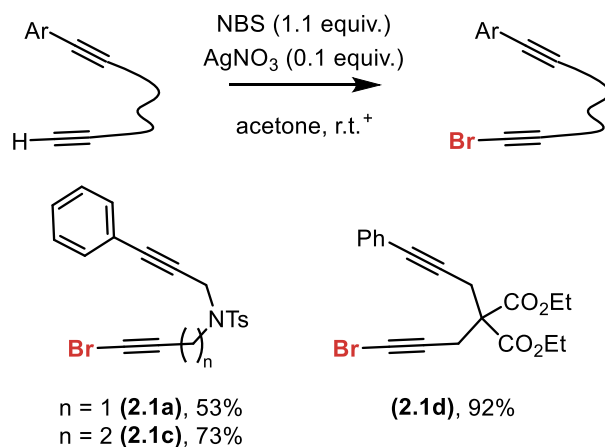
Analysis of the result by crude NMR indicated however that no desired pyrrole product **2.3b** was formed. Instead, recovery of the N -benzyl- p -toluenesulfonamide starting material was observed. Interestingly, the starting bromoalkyne was consumed despite it being used in excess (1.3 equiv.) therefore we suspected that the bromoalkyne was degrading under the reaction

conditions. Additionally, the synthesis of this bromoalkyne precursor **2.1b** from terminal alkyne **2.4** was low yielding (16%) which was not expected as similar precursors were previously synthesized by our group in moderate to excellent yields (53-92%) (Figure 24).⁵⁸ Interestingly, when comparing the yield obtained across the bromoalkynes precursors (**2.1a,c,d**) synthesized by Dominic Campeau, the efficiency for this simple bromination transformation varies dramatically depending on the nature of the tethers (Figure 24, B). To avoid using bromoalkyne precursor **2.1b**, an alternative coupling approach using terminal alkyne **2.4** as the substrate was tested next (Figure 25).

A Synthesis of precursor **2.1b**



B Gagosz et al. (2021)

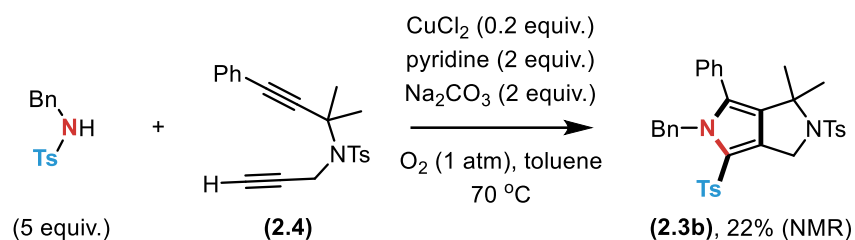


⁺Results by Dominic Campeau.

Figure 24 Synthesis of bromoalkyne precursors. A) Synthesis of precursor **2.1b** from terminal alkyne **2.4**. B) Previously synthesized bromoalkynes by our group.

Similarly to the method found by Hsung, Stahl et al. developed a copper (II) mediated oxidative amidation of terminal alkynes for the synthesis of ynamides.⁶⁴ Employing this strategy from alkyne precursor **2.4** in a *one-pot* coupling and cyclization sequence led to the formation of the desired pyrrole product **2.3b** in a 22% NMR yield (Figure 25, A). Consumption of the alkyne precursor **2.4** was however seen by NMR with no detection of the ynamide intermediate. In order to verify the experimental manipulations, a coupling using a simpler terminal alkyne was performed and the expected ynamide product **2.5** was observed in a high 72% NMR yield (Figure 25, B). This experiment suggests that the coupling from diyne **2.4** was likely less efficient as a low yield for the desired (3+2) cycloadduct was observed. The possibility that the reaction conditions employed are not compatible with the cyclization of tethered ynamide **2.2b** cannot be excluded, however. Additionally, it is possible that the tethered ynamide formed *in-situ* degraded under the reaction conditions. The high temperature required for the cross-coupling renders it difficult to determine if the formation of the tethered ynamide is efficient. For these reasons, an alternative *one-pot* approach was considered.

A One-pot procedure using Stahl's coupling



B Using a simple terminal alkyne as coupling partner

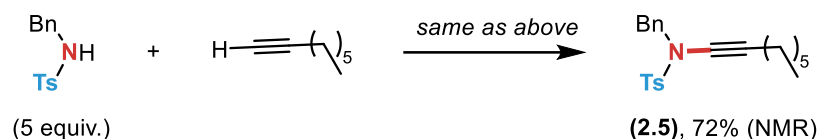
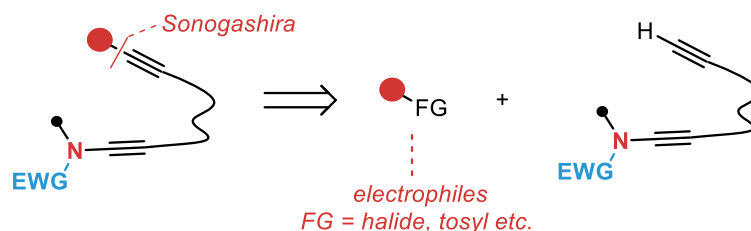


Figure 25 Using terminal alkynes as coupling partners for the formation of ynamides. A) Testing a *one-pot* approach from alkyne **2.4** B) Verifying experimental manipulations using a simpler alkyne.

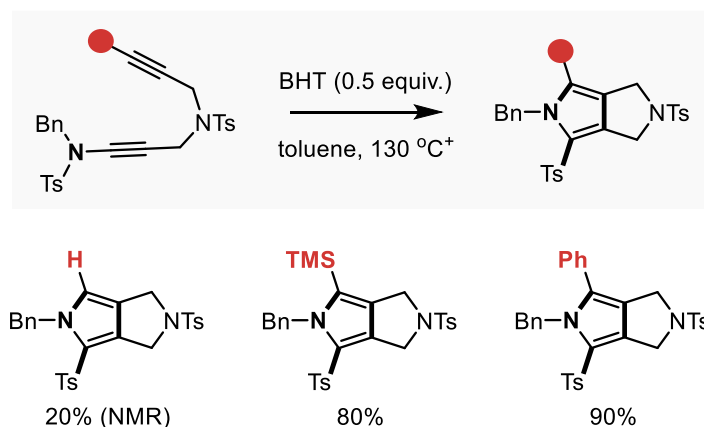
2.3 Attempt to use a Sonogashira cross-coupling as an alternative *one-pot* approach

Since the *one-pot* procedures involving the *in-situ* formation of the ynamide functionality were found unexpectedly challenging, an alternative approach starting from a pre-installed ynamide precursor was envisaged. It was hypothesized that ynamide precursors that are linked to a terminal alkyne could be rapidly functionalized utilizing a Sonogashira cross-coupling reaction (Figure 26, A). Our group previously observed that ynamides that are tethered by a terminal alkyne do not lead to a selective rearrangement (many side products observed) as compared to those that are substituted (Figure 26, B). As many electrophiles commonly used in Sonogashira cross-coupling reactions are commercially available, the implementation of this coupling strategy in *one-pot* procedures has the potential to rapidly generate a wide variety of substituted pyrrole products.

A Alternative retrosynthetic disconnection



B Gagosz et al. (2021)



⁺Results by Dominic Campeau

Figure 26 Alkyne functionalization as an alternative *one-pot* approach. A) Sonogashira disconnection for the formation of different tethered ynamides. B) The effect of alkyne substitution on the cyclization of yne-ynamides.

The implementation of this approach using diyne **2.6** was however unsuccessful as it led to a complex mixture of products with no clear evidence for the formation of the desired cyclized pyrrole product (Figure 27). Surprisingly, no Sonogashira product **2.2c** could be detected by TLC at room temperature and heating of the mixture only led to degradation of the starting yne-ynamide. The recurring event of starting material degradation in the presence of metal containing reaction conditions hinted that unwanted side reactions and polymerization were occurring. To avoid this issue, metal catalyzed reactions were put on the side and the synthesis of tethered ynamides was reinvestigated.

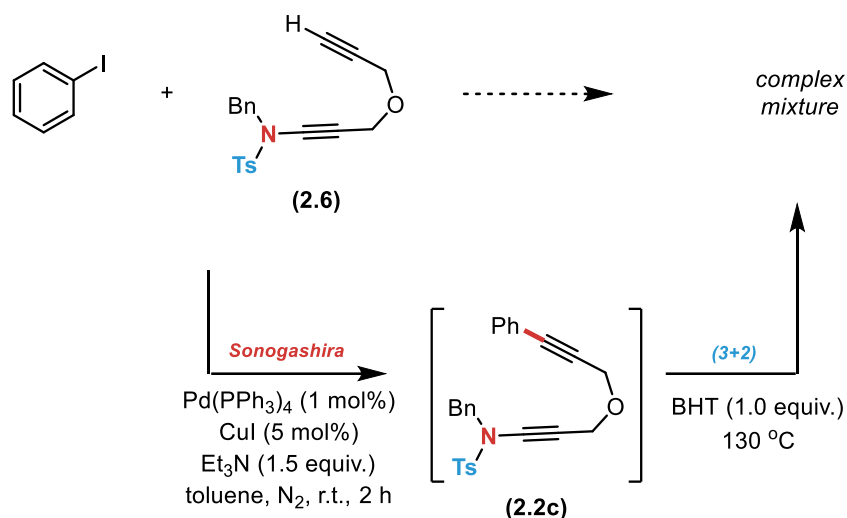


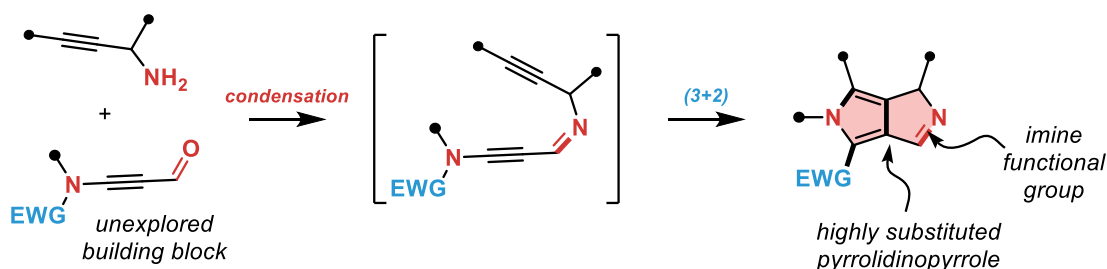
Figure 27 Attempt for a one-pot Sonogashira coupling followed by cyclization procedure.

2.4 Unexplored ynamide building blocks for the *in-situ* synthesis of yne-ynamides

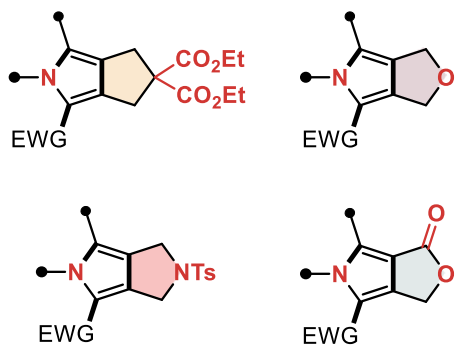
With our desire to use mild reaction conditions, it was postulated that a condensation reaction between propargyl amines and an unexplored ynamide carboxaldehyde building block would fit this criterion (Figure 28, A). This way an imine-containing linker could be generated *in-situ* without the need to use stoichiometric reagents. Intramolecular cyclization of this tethered ynamide would then afford densely functionalized bicyclic pyrroles with an imine containing linker that is subject to further functionalization. Additionally, this approach would permit structural diversification in pyrrole products from those previously obtained by our group (Figure 28, B).⁵⁸ The presence of the imine functionality of the final product would also open the door to further synthetic manipulation for instance pyrrolidine ring opening, reduction, and nucleophilic additions. The synthesis of propargyl amine precursors **2.7** was performed in a single step from commercially available materials by using a Sonogashira cross-coupling reaction (Figure 28, C). The propynal derivative **2.8** was obtained by oxidation of the corresponding propargyl alcohol using Dess-Martin Periodinane (DMP). The propargyl alcohol starting material was easily

obtained by the coupling described by Hsung (See Supporting Information section 7.3.7 for more details).⁶³

A Condensation strategy



B Gagosz et al (2021)



C Synthesis of precursors

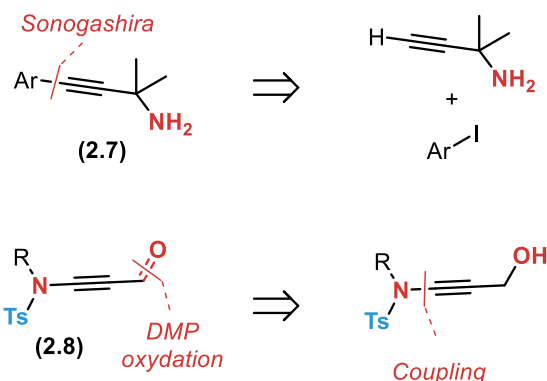


Figure 28 A condensation strategy for the synthesis of imine containing [3.3.0] pyrrole products. A) A new approach for the *in-situ* formation of yne-ynamides. B) Fused pyrroles previously obtained by our group. C) Retrosynthetic disconnections for the synthesis of the precursors.

Gratifyingly, the consumption of propargyl amine **2.7a** and propynal derivative **2.8a** was seen after just 1 h of stirring in toluene in the presence of molecular sieves (Figure 29). Alongside their consumption, the formation of a new product was observed by TLC and tentatively attributed to the desired yne-ynamide **2.2d**. Mild heating of the reaction mixture at 60 °C led to the cyclization into bicyclic pyrrole **2.9a** which was ultimately isolated in a 55 % yield. Motivated by this positive result, the synthesis of additional propargyl amines and propynal derivatives was done in order to mix and match them under the same reaction conditions (Figure 30).

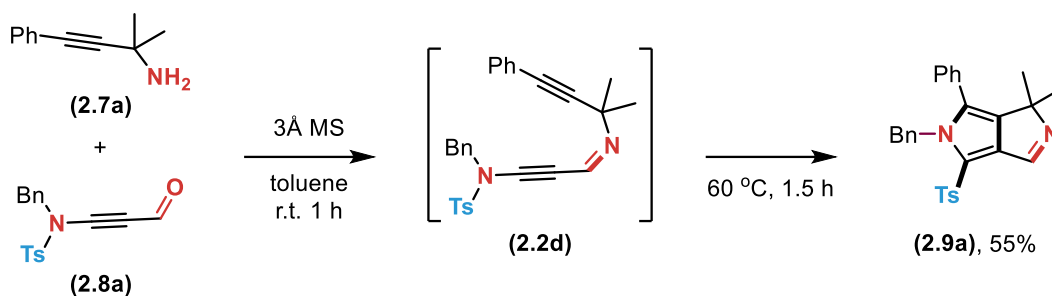
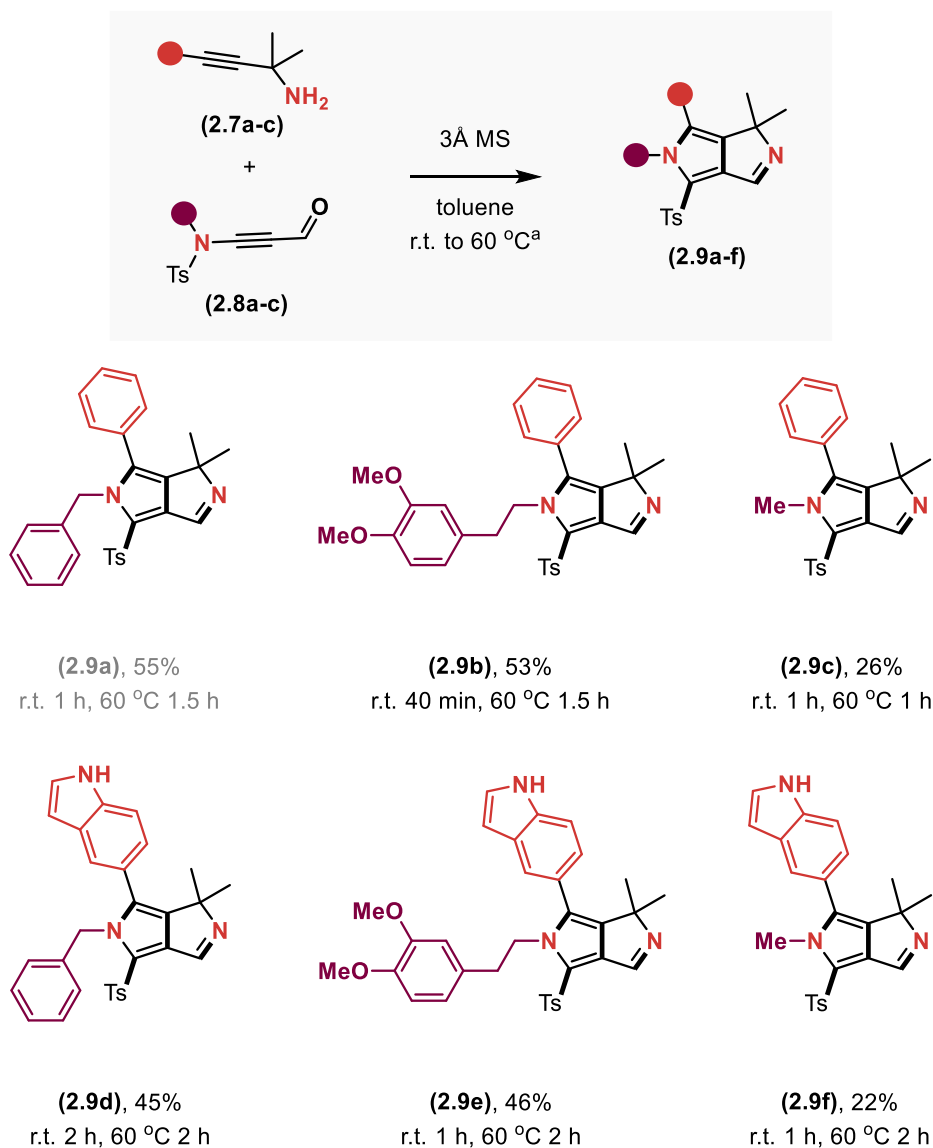


Figure 29 Hit obtained for a one-pot condensation and cyclization procedure.

The matching between benzyl **(2.8a)** and homoveratryl derivative **(2.8b)** with the substituted propargyl amines **(2.7a,b)** gave consistent moderate yields for the desired pyrroles **(2.9a-b,d-e)** (45-55%). Utilizing the methyl substituted precursor **2.8c** was however less efficient as the bicyclic pyrroles **(2.9c,f)** were obtained in lower yields (22-26%) (Figure 30). Seeing that these aromatic substituted pyrroles were easily obtained, the synthesis of additional propargyl amines was done in order to evaluate the scope of the procedure (Figure 31). Knowing that ynamide tethered with an unsubstituted alkyne do not cyclize efficiently (Figure 14), the *one-pot* condensation and cyclization of a TMS variant was done first. Due to a higher temperature needed for the cyclization to occur, 0.5 equivalents of BHT were added to the reaction mixture prior to heating to 100 °C. Gratifyingly, the mixing of the TMS substituted propargyl amine **2.7d** with aldehyde **2.8a** afforded the substituted pyrrole **2.9g** in a 51% yield. Variation of the aldehyde was however found to be detrimental as a lower yield of 27% was obtained for the homoveratryl substituted pyrrole **2.9h** and utilizing the methyl substituted propynal derivative **2.8c** only resulted in a complex mixture.

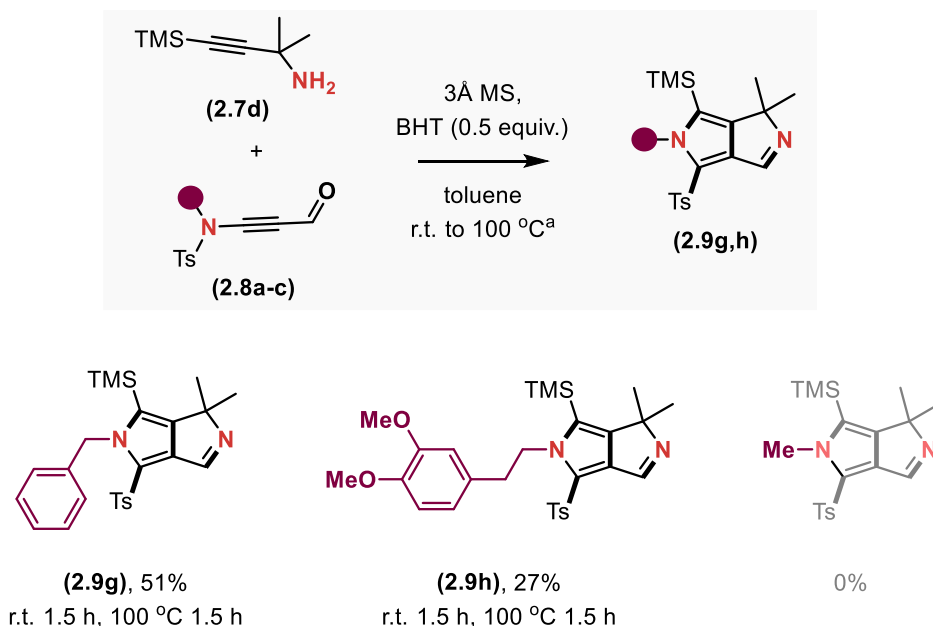


^aThe reactions were performed in sealed reaction tubes at the 0.1 mmol scale in toluene (0.1 M).
Figure 30 Small library of pyrroles obtained from mixing and matching condensation precursors.

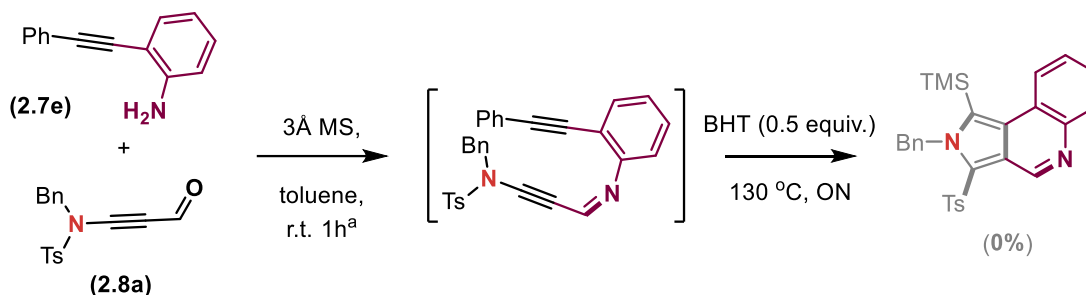
Finally, it was attempted to broaden the scope of this *one*-pot procedure to the formation of [3.4.0] bicyclic pyrrole (Figure 31, B). Although the usage of a benzene-fixed linker was previously found to be beneficial for the synthesis of similar [3.4.0] pyrrole (Figure 21), mixing of aniline derivative **2.7e** with propynal derivative **2.8a** did not result in the formation of the desired cycloadduct even upon heating at 130 °C overnight. It is likely that the conformation needed for

the cyclization cannot be accessed easily when utilizing this imine containing linker therefore degradation of the tethered ynamide was seen instead.

A Cyclization of a TMS substituted tethered-ynamide



B Formation of a 4-membered linker



^aThe reactions were performed in sealed reaction tubes at the 0.1 mmol scale in toluene (0.1 M). **Figure 31** Attempt to expand the scope of fused pyrroles obtained by changing the amine precursor. A) Utilizing a TMS-substituted propargyl amine as the coupling partner. B) Cyclization of a benzene fixed tether.

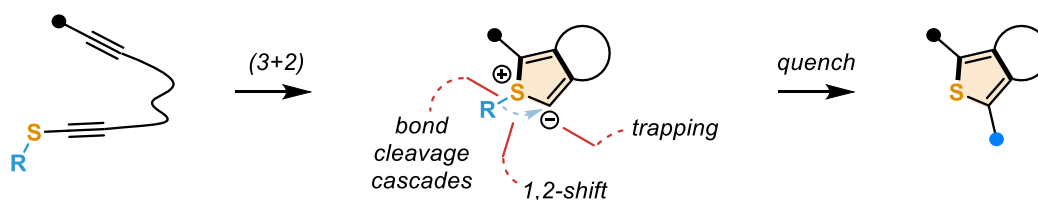
Despite the challenges associated with the implementation of *one-pot* variants to the (3+2) cycloaddition cascade of tethered ynamides, the investigation of different strategies allowed for the discovery of a previously unreported class of ynamides **2.8**. These propynal

building blocks were condensed with propargyl amines generating tethered ynamides capable of rapid cyclization upon mild heating. The small library of fused pyrroles obtained by making use of this simple procedure contained an imine functionality that may be further derivatized. Additionally, the pyrrole core may be reduced by means of redox chemistry towards privileged motif, as shown previously by our group.⁵⁸ This short study further accentuates the importance of finding novel *n*TACs as they may serve as useful synthons for heterocyclic motifs. While the studied yne-ynamides showed an unprecedented sensitivity to metal-containing reaction conditions, the observations made were at the origin of our increasing interest in finding metal-catalyzed cycloaddition reactions (see Chapter 4).

3 Chapter 3 : Exploring the moduable reactivity of thiophenium ylides

In this chapter, the reactivity of postulated thiophenium ylides generated upon (3+2) cycloaddition of yne-alkynyl sulfides will be presented (Figure 32, A). While thioalkynes have been previously found to act as a three-atom component in (3+2) cycloaddition reactions, the use of highly reactive aryne partners was employed as a strategy to overcome the energy demand. Furthermore, the reactivity of the benzo-fused zwitterionic cycloadducts was not explored in depth (Figure 12). Additionally, our group's previous observations that intramolecular linkage between ynamides and alkynes enables efficient (3+2) cycloaddition cascades to be devised motivated our continued study on the use of X-alkynyl species as *n*TACs.

A General reactivity of fleeting thiophenium ylides



B Generic structures of important 3,4-fused thiophene cores

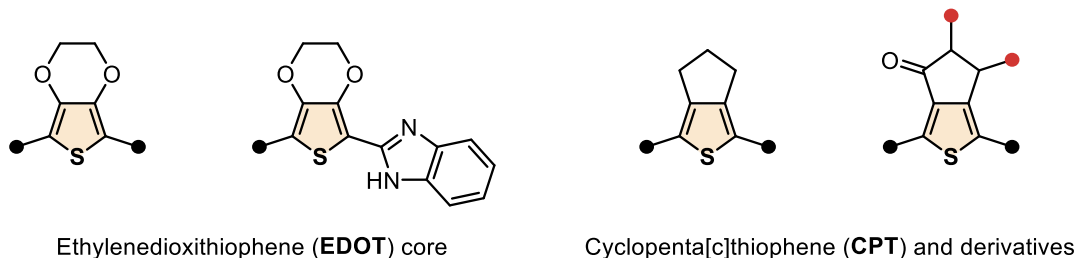


Figure 32 From yne-thioalkynes to densely functionalized thiophenes. A) Using the intramolecular tethering strategy to access fused thiophenes *via* (3+2) cycloaddition cascades. B) Important 3,4-fused thiophenes cores found in material and medicinal chemistry.

Alkynyl sulfides were chosen as the heteroatom-substituted alkyne to study next due to their stability in acidic, basic, and thermal conditions.³⁸ Furthermore, many methods for the synthesis of various S-substituted thioalkynes are described and have been recently reviewed.⁴⁰

In contrast to ynamides which are substituted by an EWG, alkynyl sulfides can tolerate more substitution variation. These properties were found to be crucial for an in-depth study of the faith and synthetic potential of the sulfur-containing heteroarylium ylides discussed in this thesis. The modulation of their reactivity enabled a broad scope of fused thiophenes to be obtained by means of bond cleavage cascades, intramolecular rearrangements as well as electrophilic trapping.

Fused thiophenes are recognized as important scaffolds in the fields of material science and medicinal chemistry.⁶⁵⁻⁷⁰ For instance, the 3,4-ethylenedioxithiophene (EDOT) and cyclopenta[*c*]thiophenes (CPT) cores are important building blocks for conjugated polymers.^{65, 66} When substituted with benzimidazole, fused thiophenes containing the EDOT core have been shown to display antimicrobial effects. On the other hand, thiophenes with derivatized CPT core display anticancer activity. (Figure 32, B).⁶⁸

3.1 Synthesis of alkynyl sulfides

The synthesis of alkynyl sulfides was historically performed by dehydrohalogenation strategies^{71, 72} (Figure 33, eq. 1) however this method shows limited functional group compatibility and often requires an additional step for the functionalization of the alkyne terminus. A modified version of a procedure developed by the Anderson group for the synthesis of yndiamides⁵⁹ was applied to the synthesis of thioynamide substrate **3.1a** (eq. 2).

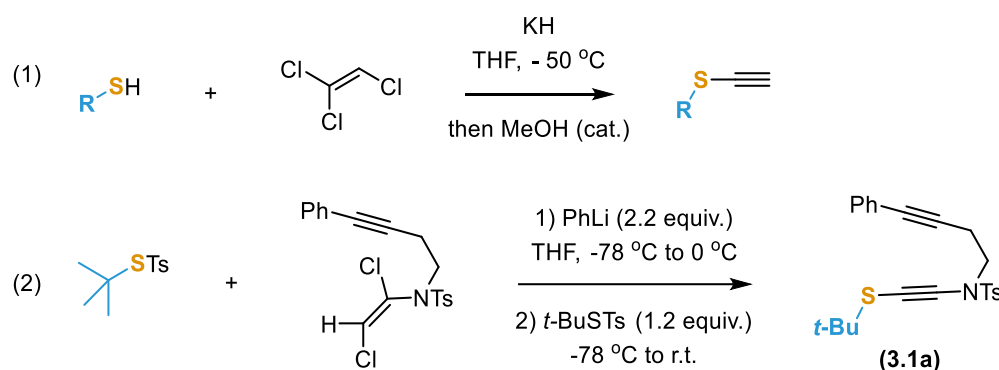
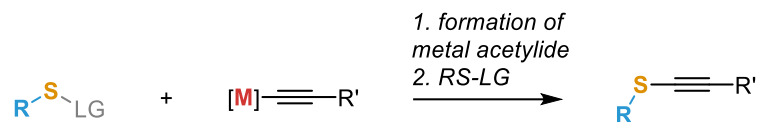


Figure 33 Using chloroethylene derivatives in dehydrohalogenation reactions for the synthesis of alkynyl sulfides.

In contrast to dehydrohalogenation strategies, a direct approach for the synthesis of alkynyl sulfides is by the formation of the key $C_{sp}-S$ bond (Figure 34, A). Many approaches utilizing this disconnection have been developed and were categorized as either sulfur or alkyne umpolung strategies. First developed by the groups of Arens in 1961⁷³ and later revised by MaGee et Kabanyane in 1992⁷⁴ the sulfur umpolung methods utilize electrophilic sulfur sources and a nucleophilic acetylide formed *in-situ*. The simplicity of this approach was found useful as it allowed for the rapid synthesis of alkyl (**3.1b-g**) and aryl (**3.1h,i**) substituted alkynyl sulfide substrates. This sulfur umpolung strategy was however not applicable to all yne-tethered alkynyl sulfides such as substrates **3.1j,k** for which the use of milder reaction conditions was required.⁷⁵

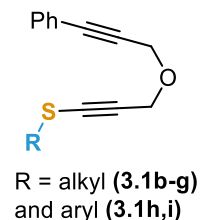
A C_{sp}-S bond formation

Sulfur Umpolung

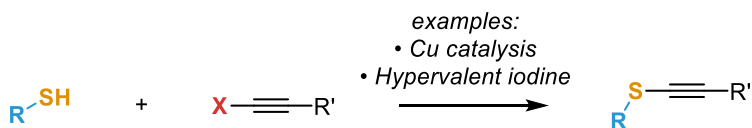


LG = SR, SO₂R, SO₃Na, halide etc.

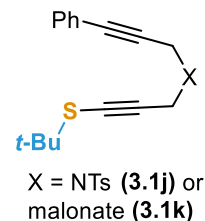
M = Li, Mg, Zn



Alkyne Umpolung



X = halide, EBX



B Thiol alkynylation

Nucleophilic thiol alkynylation

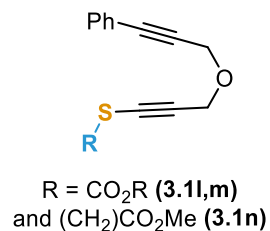
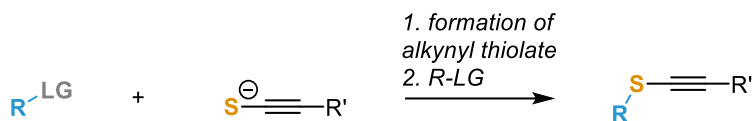


Figure 34 Direct approaches for the synthesis of alkynyl sulfides. A) Sulfur and alkyne umpolung methods. B) Nucleophilic thiol alkynylation from *in-situ* generated alkynyl thiolates.

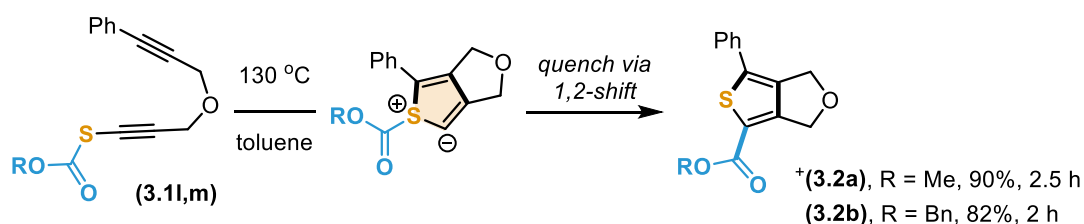
A reverse umpolung strategy was utilized in this case where the alkyne is now rendered electrophilic by utilizing copper catalysis. Another notable example of such umpolung strategy was developed by the Waser group^{76,77} utilizing hypervalent iodine based reagents (EBX alkynes). This strategy enabled an impressive scope of alkynyl sulfides to be synthesized but is not atom economical. The simplicity found with Collins⁷⁵ copper catalyzed cross-coupling between bromoalkynes and thiols prompted us to choose this alkyne umpolung method over others.⁴⁰

A third disconnection utilizes thiol alkynylation strategies first reported by Arens et al.⁷⁸ In this class of reactions, the nucleophilic thiol alkynylation strategy developed by Hu and

coworkers⁷⁹ was found useful for the synthesis of yne-alkynyl sulfides **3.1l-n** (Figure 34, B). This approach uses *in-situ* formed alkynyl thiolates produced by functionalizing an organometallic acetylide with sulfur powder. The intermediate alkynyl thiolate can then act as a nucleophile in substitution or acylation reactions to generate stable alkynyl sulfide products. Despite the need to employ these approaches in combination, a rapid and straightforward synthesis of various alkynyl sulfides could be achieved (see Supporting Information section 7.4.3 for more details).

3.2 Reactivity differences between S-ester and S-alkyl substituted yne-alkynyl sulfides

Our study on the possibility to generate and react thiophenium ylide intermediates began with the synthesis of ester substituted alkynyl sulfides **3.1l,m**. We were pleased to observe the formation of thiophenes **3.2a,b** in excellent yields upon their simple heating in toluene (82-90%) (Figure 35). This outcome can be explained by an efficient intramolecular rearrangement that takes place from the zwitterionic intermediate due to the labile S-ester bond. This result indicated that the reactivity previously observed with pyrrolium ylides could be transferred to thiophenium ylides.⁵⁸



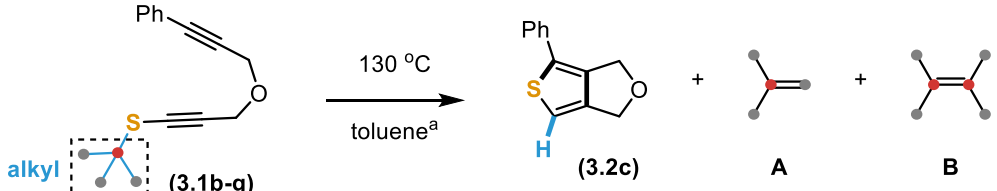
[†]Example by Dominic Campeau.

Figure 35 1,2-shift observed for ester substituted thiophenium ylides.

Although these S-ester derivatives were easily accessed, the synthesis of alkyl substituted alkynyl sulfides remains more common and would allow for a variety of S-alkyl yne-alkynyl sulfides to be studied (**3.1b-g**) (Table 1). Upon submission of these alkyl derivatives to thermal

conditions, we observed a clear trend in reactivity. All these *S*-alkyl derivatives form the same 5-unsubstituted thiophene **3.2c** for which the structure has been confirmed by NMR analyses and single-crystal X-ray diffraction studies (see Supporting Information section 7.4.12).

Table 1 Optimization of *S*-alkyl substitution for 5-unsubstituted thiophene **3.2c**.



(3.1b-g)	alkyl	Time (h)	(3.2c), yield (%) ^b	A , yield (%) ^b	B , yield (%) ^b
(3.1b)	Me	1	38	-	ethylene, traces
(3.2c)	<i>n</i> -Pr	1	46	propene, 17	-
(3.2d)	<i>n</i> -Oct	0.75	40	1-octene, 25	-
(3.2e)	<i>i</i> -Pr	0.75	73	propene, 53	-
(3.2f)	<i>t</i> -Bu	1	91 (85) ^c	isobutene, 60	-
(3.2g) ^d	Bn	1	90	-	(<i>Z</i>)-stilbene, 12

^aAll reactions were performed in sealed NMR tubes at the 0.05 mmol scale in toluene-*d*₈ (0.1 M) with 2.0 μL of mesitylene as internal NMR standard. ^bYields were assessed by ¹H-NMR analysis after the indicated time. ^cIsolated yield. ^dSynthesis of **3.2g** and entry done by Stéphane Lauzon-Brisson.

Interestingly appreciable amounts of alkene by-products (**A** or **B**) were observed by NMR for each alkyl derivatives. All alkyl derivatives possessing a β-hydrogen (**3.1c-f**) underwent elimination exclusively, forming the corresponding elimination by-product **A**. This observation suggests that the α-hydrogen of the thiophene product could originate from the alkyl group initially present on the S atom. It was observed that the use of primary alkyl chains (**3.1b-d**) provided lower yields for thiophene **3.2c** while increasing the substitution (**3.1e,f**) led to an improvement in efficiency. Since easily cleavable alkyl chains (ex: *tert*-butyl and benzyl groups) favor the formation of thiophene **3.2c**, a link between the trend in selectivity and efficiency was

easily rationalized by comparing the weakness of the C-S bond (see Section Deuteration studies for an understanding of the reactivity differences between *S*-alkyl substituted ylides^{3.8} for further discussion). Notably, the *tert*-butyl derivative **3.1f** gave an excellent isolated yield of 85%. In addition, this substrate allowed for efficient scalability as a gram-scale reaction afforded 0.85 g (80% yield) of thiophene **3.2c** (Table 2).

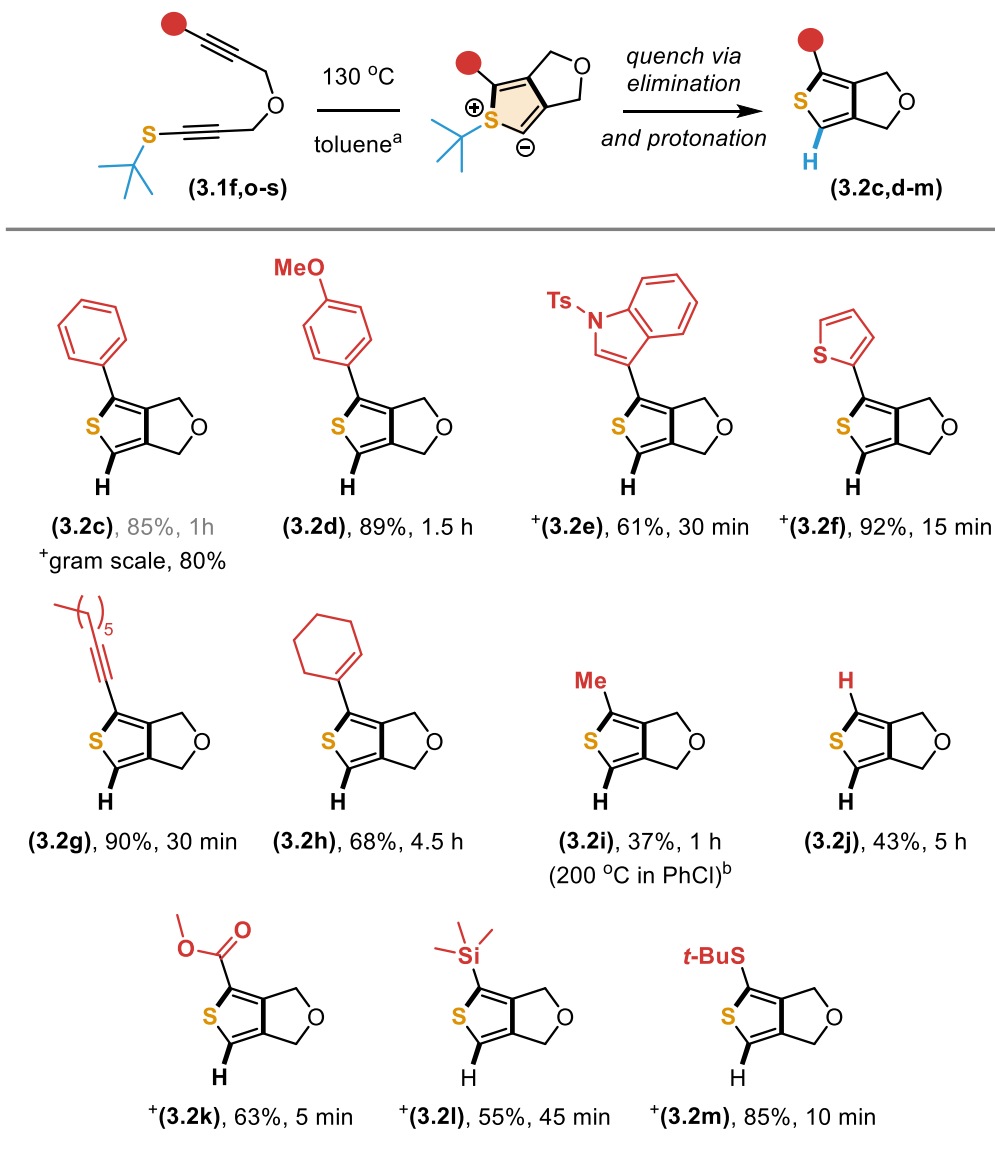
In contrast, substrates **3.1b** and **3.2g**, both lacking a β -hydrogen to S, gave small amounts of dimerization by-product **B** instead. The trends in yields observed for thiophene **3.2c** and formation of these alkene by-products are further discussed in sections 3.8-3.9. Although both the *tert*-butyl (**3.2f**) and benzyl (**3.2g**) substituted alkynyl sulfides gave high yields for the trisubstituted thiophene product **3.2c**, the *t*-Bu derivative was chosen as the substituent of choice for evaluating the reaction scope.

3.3 Investigation of the factors influencing the rate and efficiency of the cycloaddition

In collaboration with Dominic Campeau, an investigation of the structural motifs achievable with this methodology was undertaken, first by varying the alkyne substituent (Table 2). Changing the electronics of the phenyl group with a *p*-OMe group provided a high yield for thiophene **3.2d** (89%), albeit in a slightly longer reaction time. Heteroaromatic groups were also well tolerated and considerably shortened the reaction times while proving good yields for thiophenes **3.2e,f** (61-92%). Alkynyl and alkenyl derivatives also provided good to excellent yields for trisubstituted thiophenes **3.2g,h** (68-90%). The alkenyl derivative required however a much longer reaction time. Alkyl and unsubstituted alkyne also required higher temperatures or longer reaction times for full conversion of the substrate to be seen. The corresponding substituted thiophenes **3.2i,j** were efficiently isolated with moderate yield (37%-43%) despite their low

molecular weight and volatility. Lastly, acyl, silyl, and sulfide derivatives all participated well giving access to functionalized thiophenes **3.2k,l,m** in moderate to excellent yields (55-85%) in short reaction times. Notably, the acyl derivative **3.2k** rearranges slowly at room temperature! Overall, a broad range of functional groups was well tolerated at the alkyne terminus.

Table 2 Effect of alkyne substitution on the (3+2) cycloaddition of yne-alkynyl sulfides.



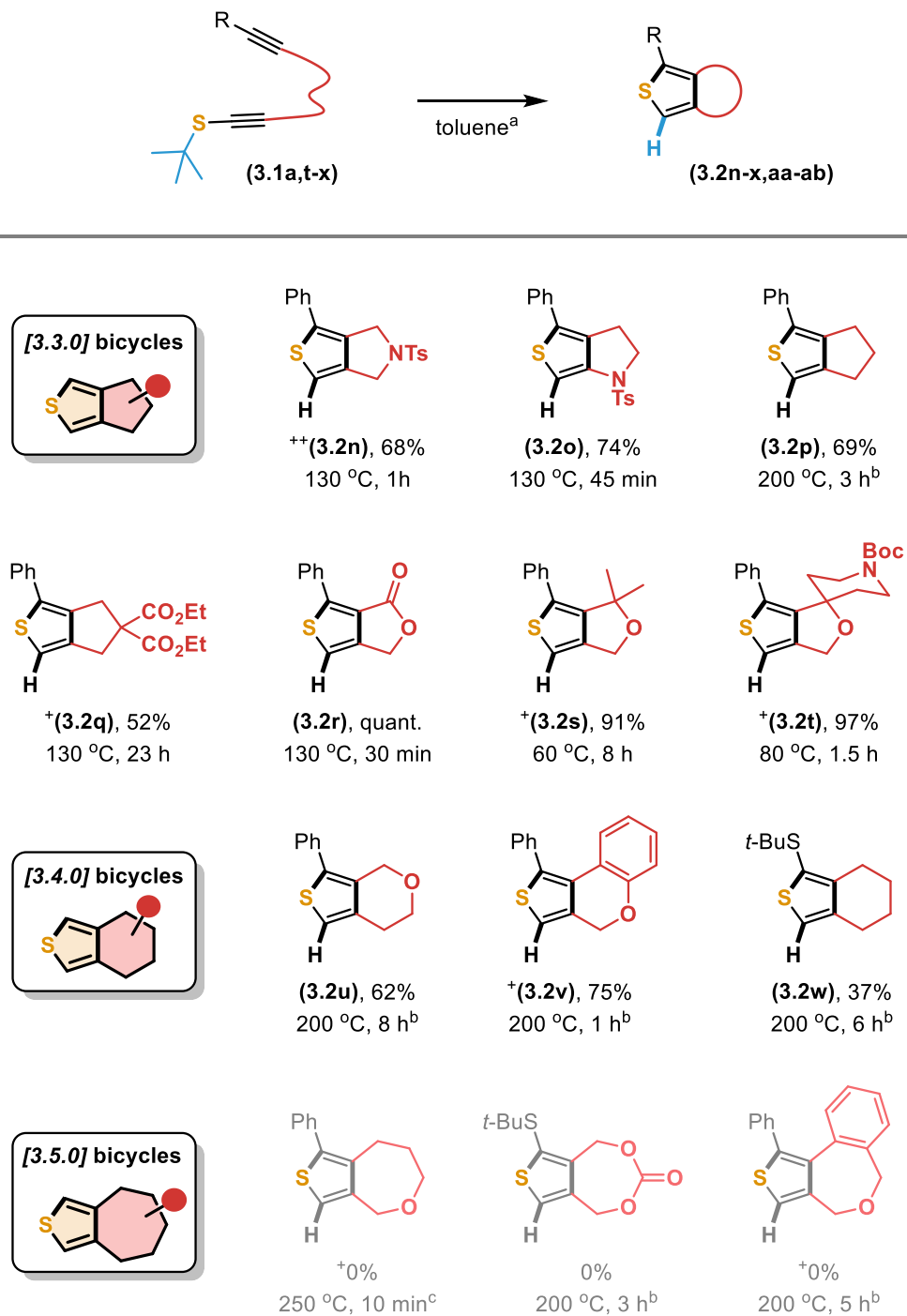
^aUnless otherwise specified, the reactions were performed in sealed reaction tubes at the 0.1 mmol scale in toluene (0.1 M). ^bDone using a microwave reactor. *Examples by Dominic Campeau.

As the intramolecular (3+2) cycloaddition between alkynyl sulfides and alkynes proceeds at 130 °C with a three-membered ether linker, we suspected that change in the linker would have an important impact on the rate of cyclization. Despite the high-energy profile of this reaction, a

variety of three and four membered tethers efficiently promoted the (3+2) cycloaddition at temperatures ranging between 60 – 200 °C (Table 3). Changing the model ether linker by a sulfonamide linker led to a moderate 68% yield of thiophene **3.2n** with no effect on the rate of the reaction. Changing the position of the sulfonamide group did not affect the efficiency of the cycloaddition as thiophene **3.2o** was produced in a 74% yield. Even an all-methylene 3-membered linker efficiently cyclized at a higher temperature furnishing the corresponding thiophene **3.2p** in a good yield (69%). An analogous all-carbon linker containing a malonate substituent was found less reactive than the heteroatom containing linkers. The Thorpe-Ingold effect of the malonate substituent allowed cyclization to occur slowly at 130 °C to moderately yield the corresponding thiophene **3.2q** (52%).

The rate enhancement seen with heteroatom containing linkers can be explained by the inductive effect conferred by the heteroatom as well as a shorter carbon-heteroatom bond bringing the two reacting units in closer proximity. Similar observations were made by Hoyer et al. when they examined the effect of a variety of linkers on the reaction rate of an intramolecular hexadehydro-Diels-Alder (HDDA) reaction.⁸⁰ In line with their observations, the addition of a carbonyl group greatly enhances the rate of the (3+2) cycloaddition as the ester containing linker efficiently cyclized forming the corresponding lactone-fused thiophene **3.2r** in a quantitative yield. The energy required to perform this cycloaddition could be further decreased by substituting the model ether linker. In these cases, the cycloaddition occurred at lower temperatures (60-80 °C) and an increased in yields for the fused thiophenes **3.2s,t** was observed (91-97%).

Table 3 Effect of the nature of the linker on the (3+2) cycloaddition of yne-thioalkynes.



^aUnless otherwise specified, the reactions were performed at the indicated temperature in sealed reaction tubes at the 0.1 mmol scale in toluene (0.1 M). ^bDone in chlorobenzene using a

microwave reactor. ^cDone in dichlorobenzene using a microwave reactor. ⁺Examples by Dominic Campeau. ⁺⁺Example by Stéphane Lauzon-Brisson.

When increasing the linker size by one carbon, the energy demand for cyclization increases, and, as a result, heating the reaction mixture at 200 °C was necessary for the (3+2) cycloaddition to occur in a relatively short reaction time. For instance, adding a methylene unit to the model 3-membered ether linker required heating at higher temperatures for the formation of thiophene **3.2u** (62% yield). The reaction rate and yield could be improved when geometrically constraining the linker as can be seen with derivative **3.2v** (75% yield). Even the all-methylene 4-membered linker cyclized to the corresponding substituted thiophene **3.2w** in a moderate 37% yield. Although a variety of [3.3.0] and [3.4.0] fused thiophenes were synthesized, limitations were seen with the synthesis of [3.5.0] bicyclic structures. All the five-membered linker substrates synthesized led to degradation over time with no detectable product formation. At this stage, the high-energy profile of this thermal intramolecular (3+2) cycloaddition reaction imposes limitations on the bicyclic thiophene products obtained.

3.4 Evaluating the interception of postulated S-alkyl thiophenium ylides

With the aim to further explore the synthetic potential of the *in-situ* generated cycloadduct, we began investigating the possibility of trapping the thiophenium ylide with electrophiles to form fully functionalized thiophene (Figure 36, path a). Such a transformation appeared challenging as two other pathways might be in competition : 1) protonation of the ylide (path b) towards 5-unsubstituted thiophene 2) intramolecular rearrangement (path c). A careful choice of the R group was found to be the key for limiting or eliminating these undesired pathways.

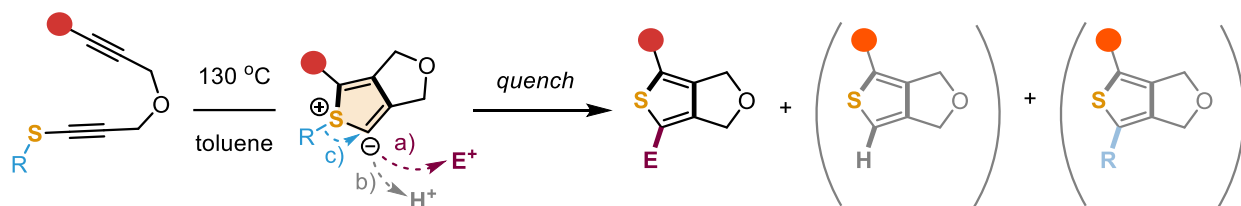


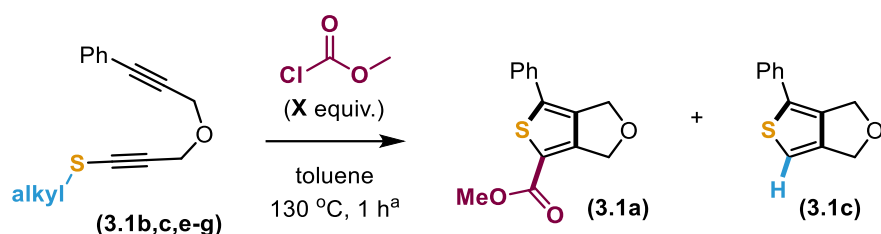
Figure 36 Competing pathways to electrophilic trapping of the thiophenium ylides.

The difference in reactivity seen between ester and alkyl substituted alkynyl sulfide substrates prompted us to look at *S*-alkyl derivatives first as the latter are not prone to intramolecular rearrangement. Additionally, it was hypothesized that stronger *S*-alkyl bonds (i.e. difficult to cleave) may result in longer lived ylide intermediates enabling intermolecular trapping with electrophiles. We reacted five structurally different *S*-alkyl derivatives (**3.1b,c,e-g**) under thermal conditions in the presence of methyl chloroformate as the electrophile (Table 4). Gratifyingly, trapping of the electrophile was observed in all cases and a mixture of functionalized thiophene **3.1a** and 5-unsubstituted thiophene **3.1c** was observed (entry 1-5). Interestingly, yne-alkynyl substrates **3.1b,c,e** provided the highest yields for the desired trapped product as compared to the *tert*-butyl and benzyl derivatives that yielded almost exclusively the 5-unsubstituted thiophene **3.1c**. The *n*-Pr substrate provided the best ratio for the desired product (entry 2) therefore it was chosen for subsequent optimization.

When increasing the equivalents of methyl chloroformate used (entry 6-8), the yield and ratio for the desired trapped product also improved. When 10 equivalents of methyl chloroformate were used, the desired functionalized thiophene **3.1a** was obtained in a 91% yield while the 5-unsubstituted thiophene **3.2c** was only observed in small quantities (8%), thus giving a 11 : 1 ratio in favor of the trapped product. The two products were separated by column chromatography and the desired functionalized thiophene **3.1a** was isolated in 85% yield. A

control experiment was performed by Dominic Campeau to ensure that the functionalization with methyl chloroformate occurred upon formation of the thiophenium ylide rather than after the protonation and elimination events (Figure 37).

Table 4 Effect of *S*-alkyl substitution on trapping efficacy.



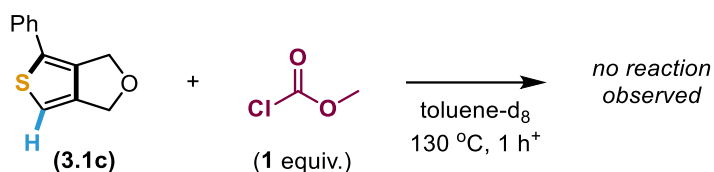
Entry	(3.1)	alkyl	X	(3.1a), yield (%) ^b	(3.1c), yield (%) ^b	(3.1a) : (3.1c) ratio
1	(3.1b)	Me	1	59	35	1.7 : 1
2	(3.1c)	<i>n</i> -Pr	1	48	20	2.4 : 1
3	(3.1e)	<i>i</i> -Pr	1	59	27	2.2 : 1
4	(3.1f)	<i>t</i> -Bu	1	4	82	1 : 20
5	(3.1g)	Bn	1	7	70	1 : 10
6	(3.1c)	<i>n</i> -Pr	2	57	16	3.4 : 1
7	(3.1c)	<i>n</i> -Pr	4	61	13	4.9 : 1
8	(3.1c)	<i>n</i> -Pr	10	91 (85) ^c	8	11 : 1

^aAll reactions were performed in sealed reaction tubes at the 0.05 mmol scale in toluene (0.1 M).

^bYields assessed by ¹H-NMR analysis with 2.0 μL of 1,2-DBE as NMR standard. ^cIsolated yield.

The results obtained from the optimization study showed that the nature of the *S*-alkyl substituent drastically affects the yield obtained for the functionalized product as well as the ratio between the trapped and unfunctionalized product. As initially considered, the trend observed suggests that *S*-alkyl substituents that do not cleave easily upon formation of the thiophenium ylide (**3.1b,c,e**) allow for efficient trapping by methyl chloroformate. Further

discussion about the distribution of the product obtained from these *S*-alkyl derivatives is found in section 3.8.



⁺Performed by Dominic Campeau.

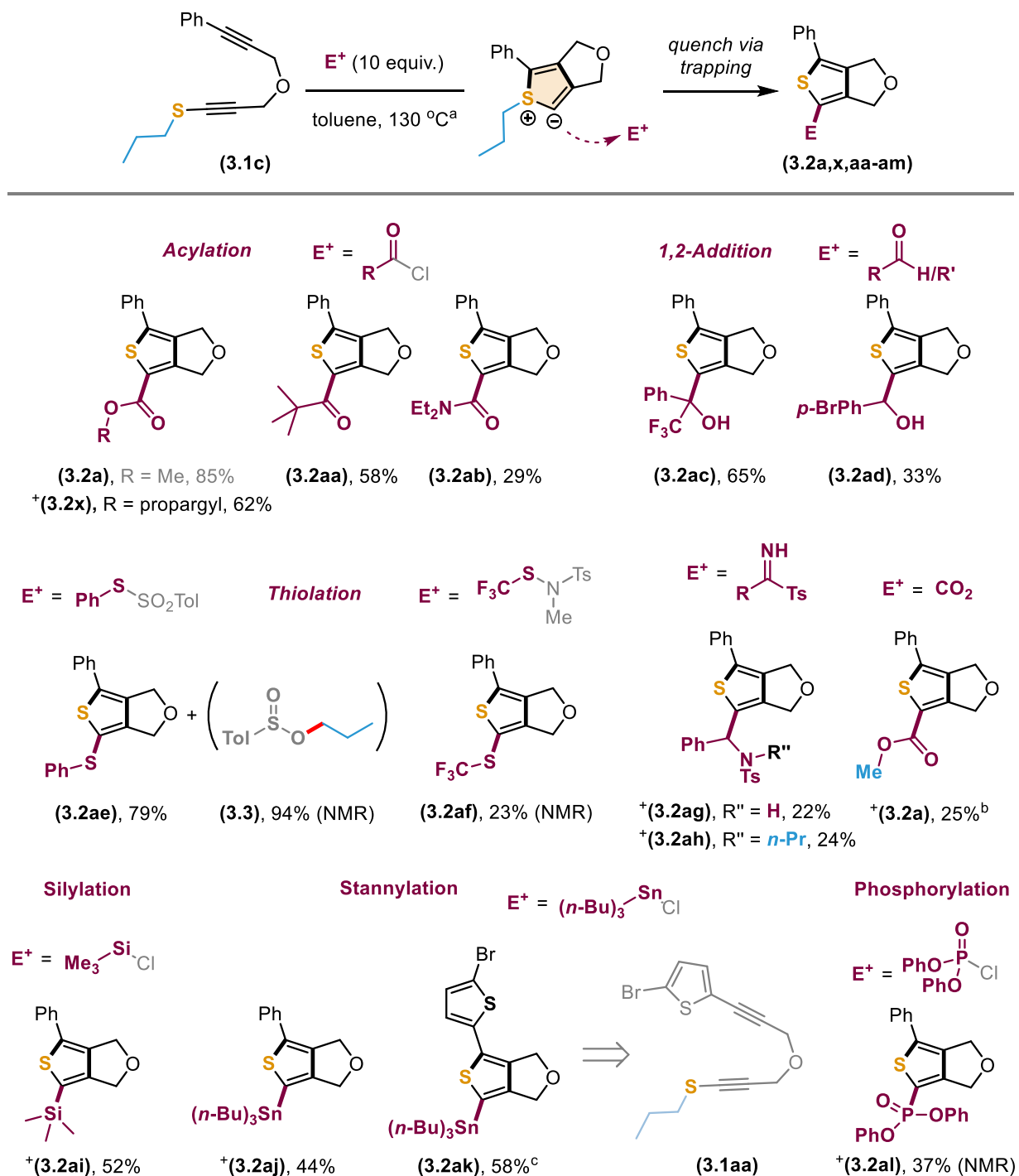
Figure 37 Control experiment showing that **3.1c** is not acylated by methyl chloroformate.

3.5 Exploiting the nucleophilicity of thiophenium ylides for heterocycle functionalization

With these optimized conditions in hand, Dominic Campeau and I began screening trapping agents with varying electrophilic strength (Table 5). Propargyl chloroformate and pivaloyl chloride were found to be good electrophiles affording carbonyl derivatives **3.2x** and **3.2aa** in moderate yields (58-62%). When the electrophilicity of the reaction partner was decreased, a lower yield for the functionalized product was observed as attested by the result obtained when diethylcarbamoyl chloride was used (**3.2ab**, 29% yield). In addition to acyl chlorides and chloroformates, ketones, and aldehydes were found to be good trapping agents affording the corresponding alcohol derivatives **3.2a(c,d)** in moderate yields (33-65%). Interestingly, when an *N*-sulfonylimide electrophile was used, two products were observed in a 1 : 1 ratio. The expected product **3.2ag** was obtained in a 22% yield along with a *N*-alkylated sulfonamide derivative **3.2ah** (24%) whose formation could be explained by the transfer of the *n*-Pr chain from a *S*⁺-alkyl electrophilic site. Similarly, when *S*-methyl alkynyl sulfide substrate **3.1b** was heated in the presence of CO₂ as the electrophile, the model ester substituted thiophene product was obtained as the sole product **3.2a** (25%). The formation of the two alkylated

products **3.2ag** and **3.2ah** suggest that substitution onto an electrophilic S^+ -alkyl chain occurs upon formation of a carboxylate or sulfonate nucleophile.

Table 5 Scope of electrophiles that trapped the *in-situ* generated thiophenium ylide.

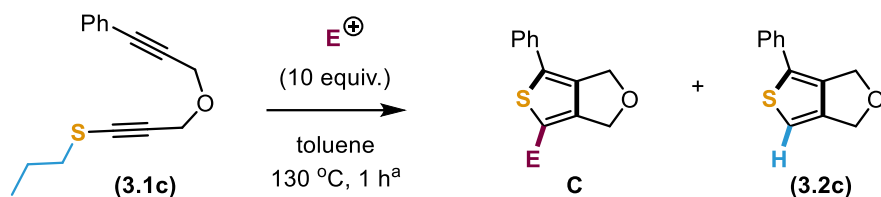


^aThe reactions were performed in sealed reaction tubes at the 0.1 mmol scale with 10 equivalents of an electrophile in toluene (0.1 M). ^bStarting from substrate **3.1b** ^cStarting from substrate **3.1aa**. [†]Examples by Dominic Campeau.

Additionally, when a thiosulfonate was used as an electrophile the corresponding functionalized product **3.2ae** was obtained in an excellent 79% yield alongside with *n*-propyl *p*-toluenesulfinate **3.3** formed as a by-product (94% yield by NMR). The formation of this by-product supports the hypothesis that functionalization should occur upon formation of the thiophenium ylide from which a dealkylation event would afford a neutral thiophene product (see Supporting Information section 7.4.8). A thiophene **3.2af** possessing a trifluoromethylsulfide group at position C2 could be produced in a low 23% yield. Silyl, stannyl, and phosphoryl based electrophiles were also efficiently reacted affording functionalized products **3.2a(i-l)** in moderate yields (37-58%). The utility of this strategy is exemplified by the formation of the nonsymmetrical bis-thiophene product **3.2ak** (58%) which contains two synthetically useful handles (bromine and tin). The regioselectivity was insured by installing the stannyl moiety by reacting *in-situ* the generated thiophenium ylide intermediate with tributyltin chloride.

Overall, quenching of this postulated intermediate allowed for the synthesis of a broad scope of 5-functionalized thiophenes from simple *S*-propyl alkynyl sulfide. Accessing these functionalized thiophenes would otherwise require the synthesis of more complex substrates such as derivatives **3.1l,m**. Additionally, exploiting the nucleophilic character of the proposed thiophenium ylide provides access to fully functionalized thiophenes which would otherwise be difficult to obtain *via* intramolecular rearrangements. Due to the propensity of these *S*-alkyl thiophenium ylides to undergo dealkylation, this intermolecular quenching is however limited to relatively strong electrophiles, as the formation of 5-unsubstituted thiophene **3.2c** was exclusively seen otherwise. A list of electrophiles tested but found unsuccessful in trapping the thiophenium ylide is shown in Table 6.

Table 6 List of other electrophiles tested.

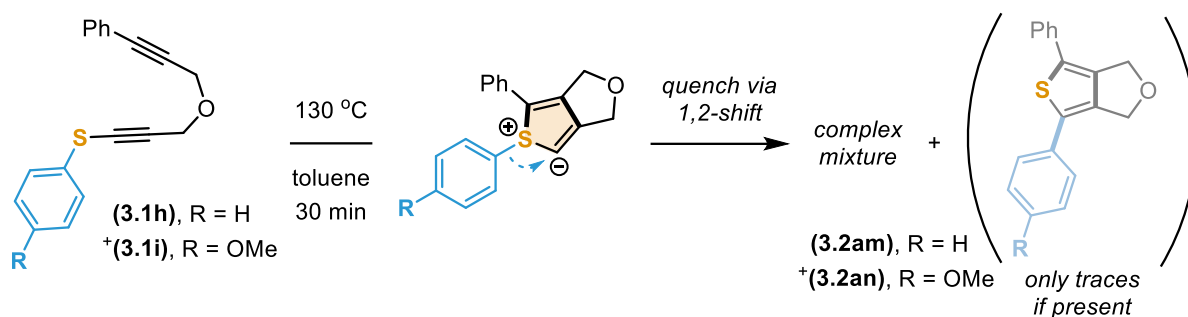


Electrophile	C, yield (%) ^b	(3.2c), yield (%) ^b	Electrophile	C, yield (%) ^b	(3.2c), yield (%) ^b
MeI	< 5	48	S ₈	0	5
BnBr	0	50	⁺ (MeS) ₂ ^c	8	26
TMSOTf	0	0	Ac ₂ O ^c	0	43
B(OMe) ₃	0	60	⁺ Paraformaldehyde	0	29
TsCl	0	34	CS ₂	0	64

^aAll reactions were performed in sealed reaction tubes at the 0.1 mmol scale in toluene (0.1 M) with 10 equivalents of electrophile unless otherwise noted. ^bYields were assessed by ¹H-NMR analysis with 2.0 μ L of 1,2-DBE as NMR standard. ^c1 equivalent of electrophile used. ⁺Performed by Alice Pommainville.

3.6 Degradation observed upon heating of S-Aryl yne-alkynyl sulfide derivatives

Another class of accessible alkynyl sulfides are S-Aryl derivatives. Although a variety of aryl-substituted thiophenes were accessed by functionalizing the alkyne terminus (Table 2), we envisaged that utilizing S-Aryl derivatives instead could lead to the formation of 2,5-diaryl thiophenes **3.2a(m,n)** if the *in-situ* generated S⁺-Aryl thiophenium ylide undergoes intramolecular rearrangement (Figure 38). Unfortunately, heating of electron-neutral or rich aryl derivatives only led to a complex mixture with no clear evidence for the formation of the desired bis-aryl thiophene products. In contrast to S-ester derivatives (**3.1l,m**) studied previously, it was hypothesized that the formation of S-Aryl thiophenium ylides likely occurs however degradation is observed under the employed reaction conditions. Expansion of this methodology to S-Aryl alkynyl sulfides derivatives requires the use of an alternative pathway which is later discussed in Chapter 4.



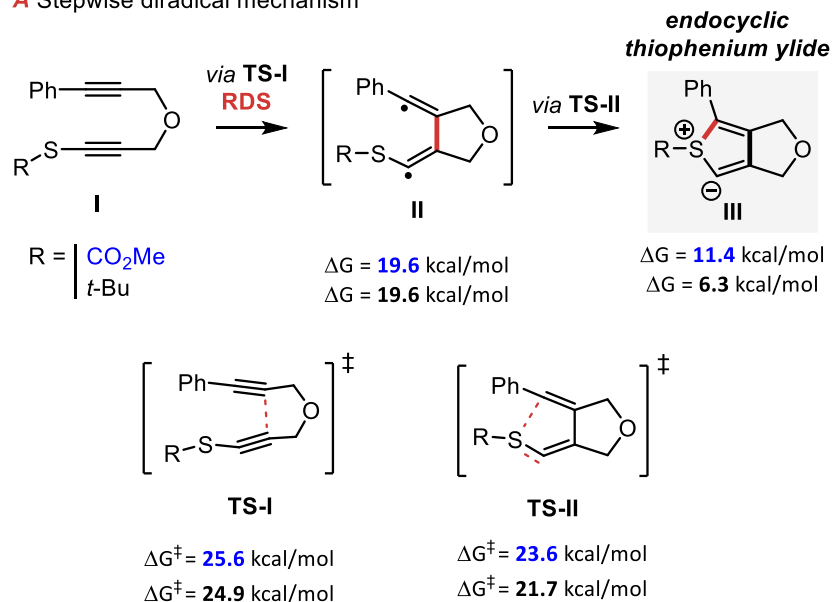
*Example by Dominic Campeau.

Figure 38 Thermal (3+2) cyclization of S-(Aryl) alkynyl sulfides.

3.7 Computational study on the cycloaddition cascades of yne-alkynyl sulfides

The formation of multi substituted thiophenes by heating of simple yne-alkynyl sulfide substrates was reasonably explained by a (3+2) cycloaddition giving rise to unstable thiophenium ylides. In addition, these fleeting ylides explain the occurrence of diverse quenching pathways that lead to the various thiophene products observed. Since these ylide intermediates could never be directly observed, density functional theory (DFT) calculations done by Dominic Campeau (performed at the B3LYP/6-31 + G(d) level of theory) provided computational evidence for the formation of these reactive cycloadducts.⁸¹

A Stepwise diradical mechanism



B Concerted mechanism

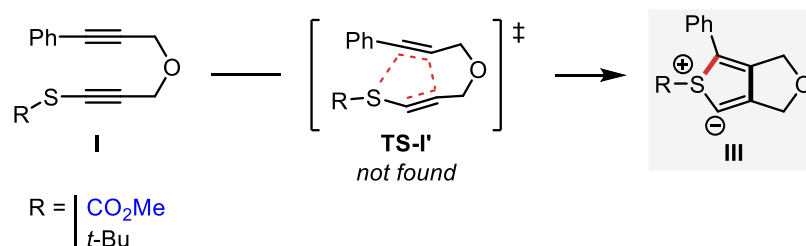


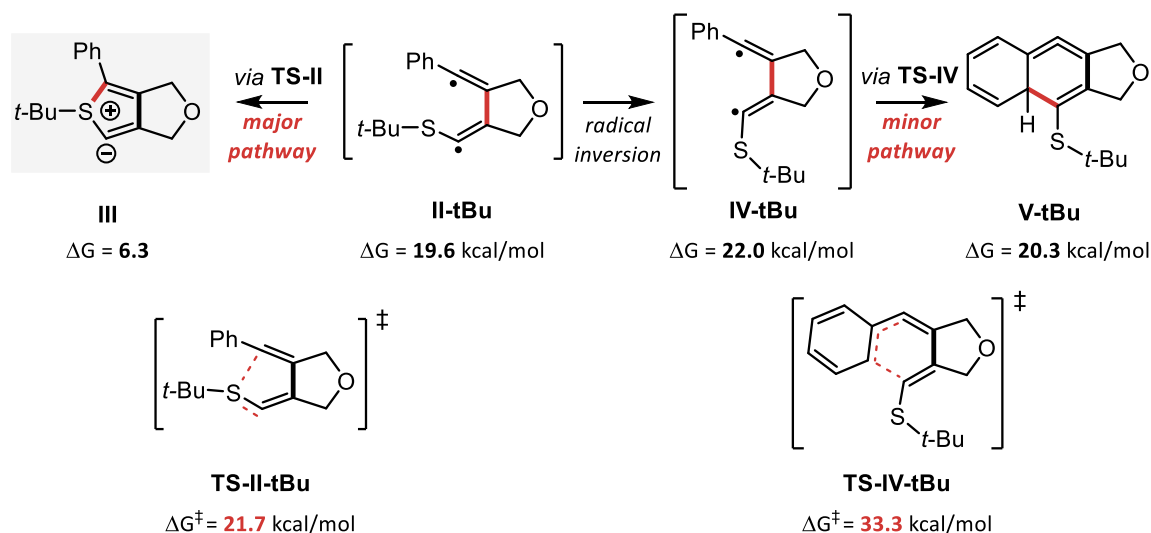
Figure 39 DFT studies on the (3+2) cyclization step towards endocyclic ylide **III**.

Two case studies were performed providing evidence for the formation of these endocyclic thiophenium ylides upon (3+2) cycloaddition with energies of 11.4 kcal mol⁻¹ (**III**, R = CO₂Me) and 6.3 kcal mol⁻¹ (**III**, R = *t*-Bu) (Figure 39, A). Although both a stepwise radical mechanism and a concerted mechanism can explain the formation of this ylide intermediate, no stable closed shell transition state could be located for either case study (Figure 39, B). On the other hand, a stepwise diradical pathway was located for both substrates studied where the rate-limiting step was found to be the formation of the initial C-C bond with barrier energies of 25.6

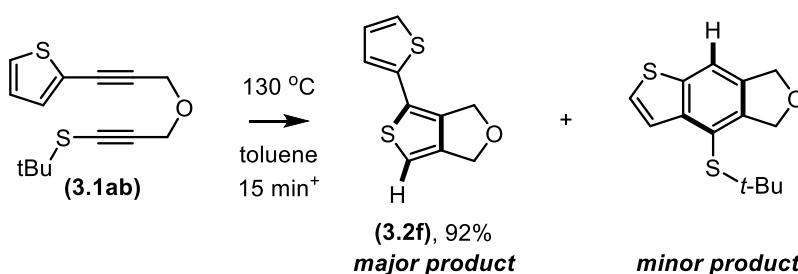
kcal mol⁻¹ (**TS-I**, R = CO₂Me) and 24.9 kcal mol⁻¹ (**TS-I**, R = *t*-Bu). A less energy demanding C-S bond formation from intermediate **II** then leads to the proposed zwitterionic ylide **III**.

Interestingly, intermediate **II** found in the stepwise (3+2) pathway also provides an explanation for a non-competitive divergent (4+2) pathway (Figure 40, A). This E-diradical intermediate **II** is a proposed intermediate for the tetrahydro Diels-Alder (TDDA) reaction⁸² however the barrier for this alternate (4+2) cyclization is much higher at 33.3 kcal mol⁻¹ (**TS-IV-tBu**) for the *t*-Bu case study as compared to 21.7 kcal mol⁻¹ (**TS-II-tBu**) for the S-C bond formation towards zwitterionic intermediate **III**. This computational result explains why the (3+2) is almost exclusively observed for these yne-alkynyl sulfide substrates. Experimental evidence also supports this where for a few substrates, TDDA derived products were observed as minor products. For instance, heteroatom substituted yne-alkynyl sulfide **3.1ab** gives the (3+2) derived thiophene product **3.2f** as a major product along with trace amount of a (4+2) derived benzothiophene product (Figure 40, B).

A (3+2) and (4+2) pathways divergence



B Experimental observation



⁺Results obtained by Dominic Campeau.

Figure 40 Competing (4+2) cyclization from II. A) DFT studies on the diverging pathways. B) Experimental evidence for a preferred (3+2) cyclization.

Experimentally, S-ester and S-alkyl yne-alkynyl sulfide yield different thiophene products and this can be explained by considering the reactivity of the thiophenium ylide generated (Figure 41, A). Although the 1,2-migration from the reactive zwitterionic cycloadduct is possible for both S-alkyl and S-ester ylides **III**, DFT studies done by Dominic Campeau show that the barriers for this 1,2-migration are considerably different for both species. The barrier for 1,2-migration of the ester group is found to be 17.2 kcal mol⁻¹ (**TS-III**, R = CO₂Me) while it is much higher for the *tert*-butyl group at 27.3 kcal mol⁻¹ (**TS-III**, R = *t*-Bu) (Figure 41, B). This energy difference explains why 1,2-migration was not seen with S-alkyl thiophenium ylides but rather elimination of the alkyl

group prevails. A transition state for a concerted protonation-elimination pathway for *S*-*tert*-butyl thiophenium ylide **III** towards the experimentally observed 5-unsubstituted thiophene **VI'** was however not located by DFT (Figure 41, C).

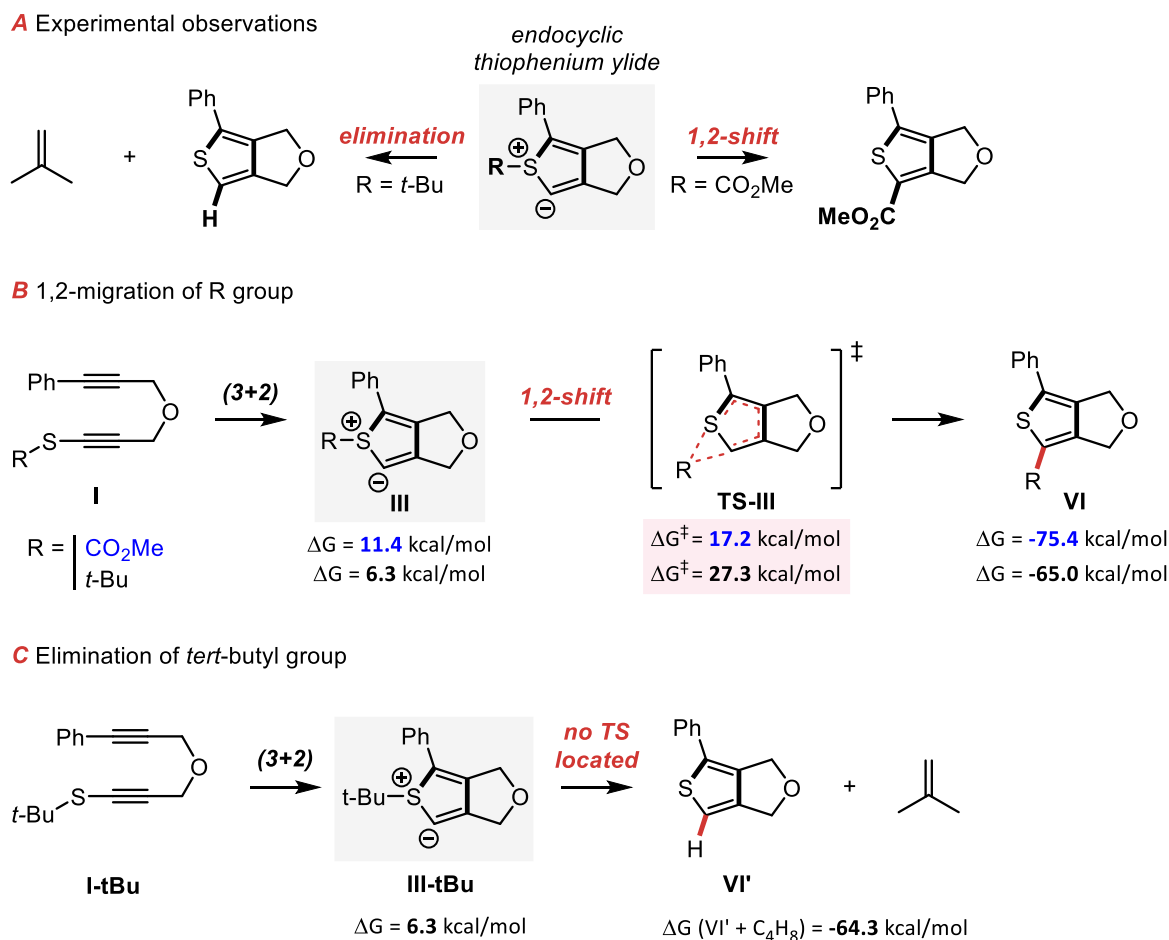


Figure 41 Quenching pathways of the thiophenium ylides. A) Experimental evidence for divergent pathway depending on substitution. B) DFT calculation on intramolecular 1,2-shift. C) Unsuccessful DFT calculations on a concerted protonation-elimination pathway.

An alternative mechanism for *S*-alkyl derivatives could be envisaged, that is, the formation of a reactive thiokene (**I'**) upon heating of *S*-*tert*-Butyl alkynyl sulfide (**I**). The formation of thioketene intermediates upon heating of *S*-alkyl alkynyl sulfides has been proposed by E. Schaumann⁸³ however this is unlikely as Dominic Campeau found that substrates such as **3.1ac** and **3.1ad** undergo rearrangement towards 5-unsubstituted thiophenes at room temperature!

Since the reaction rates and yields of these cyclization cascades of yne-alkynyl sulfides are highly dependent upon substrate substitution at the alkyne terminus and on the tether (see Table 2 and Table 3) a (3+2) cycloaddition and elimination pathway is likely operating instead.

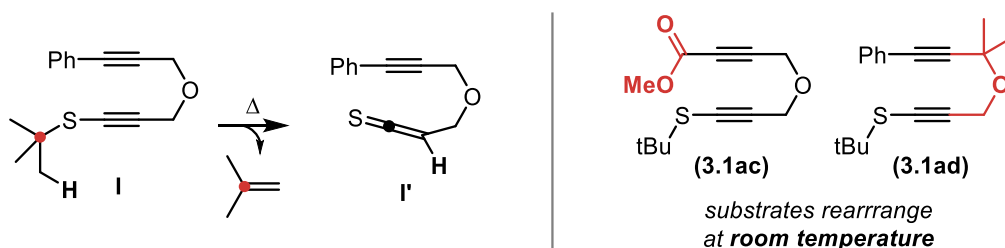


Figure 42 Thioketene formation by thermal decomposition of *S*-*t*-Bu alkynyl sulfides : an unlikely mechanism proposal.

3.8 Deuteration studies for an understanding of the reactivity differences between *S*-alkyl substituted ylides

Since the faith of *S*-alkyl thiophenium ylides could not be fully rationalized by DFT, we turned our attention to experimental observations and deuteration studies. It is clear that endocyclic thiophenium ylides of type **A** can be trapped by various electrophiles presumably generating thiophenium **B'** as an intermediate (Figure 43, path B). In section 3.4 it was discussed that when evaluating the effect of *S*-alkyl substituents and the ability of the corresponding thiophenium ylides to be trapped by methyl chloroformate, very different product ratios were obtained for 5-functionalized and unfunctionalized thiophene products. The trend observed was rationalized by considering the strength of the *S*⁺-alkyl bond of ylide **A** where weaker bonds (*S*⁺-*tert*-butyl and *S*⁺-benzyl) will cleave easily and therefore favor path **A** as they provide a source of proton towards thiophenium **B**. In contrast, stronger *S*⁺-alkyl bonds (*S*⁺-Me, *S*⁺-*n*-Pr, and *S*⁺-*i*-Pr) are presumably longer lived and allow for path **B** to occur to a greater extent (Figure 43).

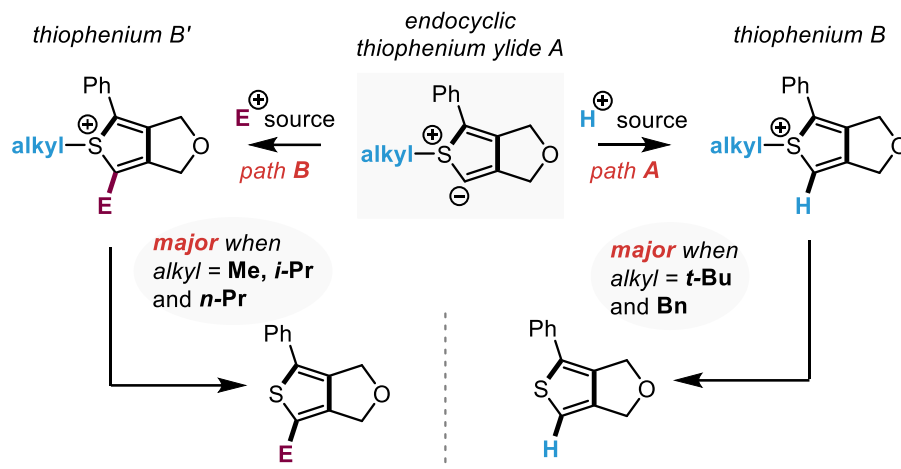


Figure 43 Trend observed on the effect of S-alkyl substitution on the trapping of ylide A.

Differences between these S-alkyl yne-alkynyl sulfides derivatives (**3.1b-g**) were also seen when evaluating their efficiency for the formation of 5-unsubstituted thiophene **3.2c** upon heating at 130 °C in toluene (Table 1). Deuteration studies were performed by Dominic Campeau with *tert*-butyl and *n*-propyl yne-alkynyl sulfides to further understand the difference in reactivity seen between these S-alkyl derivatives (Table 7). Three deuterated additives (AcOH-d₄, MeOH-d₄ and MeCN-d₃) were tested and the percentage of deuteration at position C(5) of the thiophene product **3.2c** was determined.

Table 7 Deuteration study on *tert*-butyl and *n*-propyl S-alkyl derivatives.

% Yield (% D)				
R	No additive	AcOH-d ₄	MeOH-d ₄	MeCN-d ₃
<i>t</i> -Bu	91(--)	79(51)	75(37)	75(<5)
<i>n</i> -Pr	46(--)	85(79)	35(23)	38(<5)
Co-solv : 29(96)				

For both substrates, the percentage of deuteration follows the acidity of the additive, with AcOH-d₄ providing the most deuteration at position C(5) of the thiophene product **3.2c**. In addition, when the quantity of deuterium source was increased, as can be seen when MeOH-d₄ is used as a co-solvent, the C(5) position of the thiophene was almost exclusively deuterated (96%). These results are consistent with our hypothesis that endocyclic thiophenium ylide **A** can act either as a base or nucleophile (Figure 43). Protonation of the *in-situ* generated ylide **A** by a proton source therefore generates an S⁺-alkyl thiophenium **B** which is prone to dealkylation (path A). A control study was performed by Dominic Campeau which suggests that deuteration occurs along the way toward thiophene **3.2c** rather than after the product is formed (Figure 44).

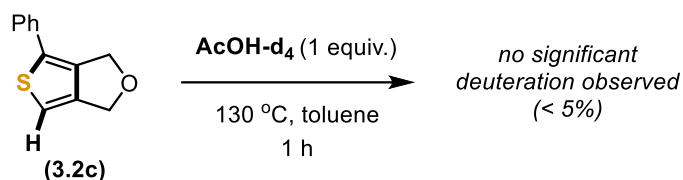


Figure 44 Control experiment showing that **3.2c** is not deuterated by AcOH-d₄.

Continuing on the results obtained from the deuteration study, when AcOH-d₄ was present as an additive, the yield for thiophene **3.2c** was greatly increased in the case of the *n*-propyl alkynyl sulfide with a boost in yield from 46% to 85% (Table 7)! The yield for thiophene **3.2c** was however not increased when MeOH-d₄ was used, even when employed as a co-solvent. On the opposite, the *tert*-butyl alkynyl sulfide derivative was high yielding for the thiophene product **3.2c** regardless of, if and which additive was used. Since the (3+2) cycloaddition occurs without the presence of any additive, and that similar percentage of deuteration was seen with both substrates across the additives used, the divergence seen likely derives from unproductive pathways occurring from thiophenium of type **B** (Figure 45).

Although the *tert*-butyl derived thiophenium **B** generates a weaker C-S⁺ bond as compared to the *n*-propyl derivative, this alone doesn't entirely explain the low yield obtained for the 5-unsubstituted thiophene **3.2c**. The *tert*-butyl derivative also differs from the *n*-propyl by the absence of a α -hydrogen therefore elimination from the β -hydrogen is the only dealkylation pathway possible (Figure 45, path C). In the *n*-propyl case α -deprotonation might occur generating exocyclic thiophenium ylide **A'** which may be causing degradation and therefore proving low yield for the 5-unsubstituted thiophene **3.2c** (path D).

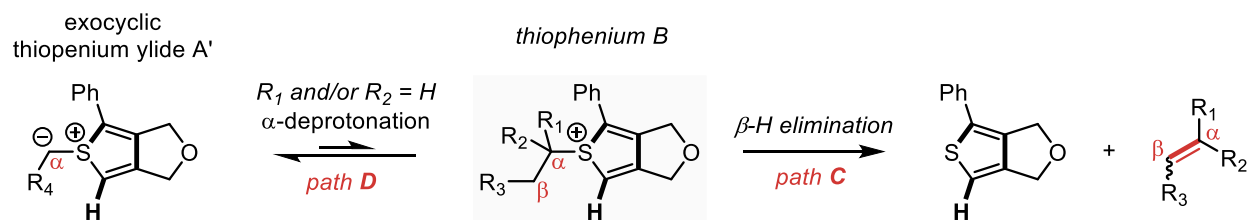


Figure 45 Hypothesis that unproductive α protonation leads to exocyclic ylide **A'**.

3.9 Evaluating the reactivity of a probe substrate for refining the dealkylation mechanism of S-alkyl thiophenium ylides

To test whether the formation of an exocyclic thiophenium ylide **A'** correlates with a low yield for the thiophene product, a probe substrate **3.1n** was designed where upon (3+2) cycloaddition, a proton transfer mediated equilibrium would favor the formation of a stabilized ylide **A'** (Figure 46). According to precedent literature,⁸⁴⁻⁸⁶ the formation of this exocyclic ylide **A'** would lead to formation of 2*H*-thiopyrans product **3.4** via a [1,2]-alkenyl shift. Additionally, since no β -hydrogen was present the formation of 5-unsubstituted thiophene via a β -H elimination cannot occur (path C).

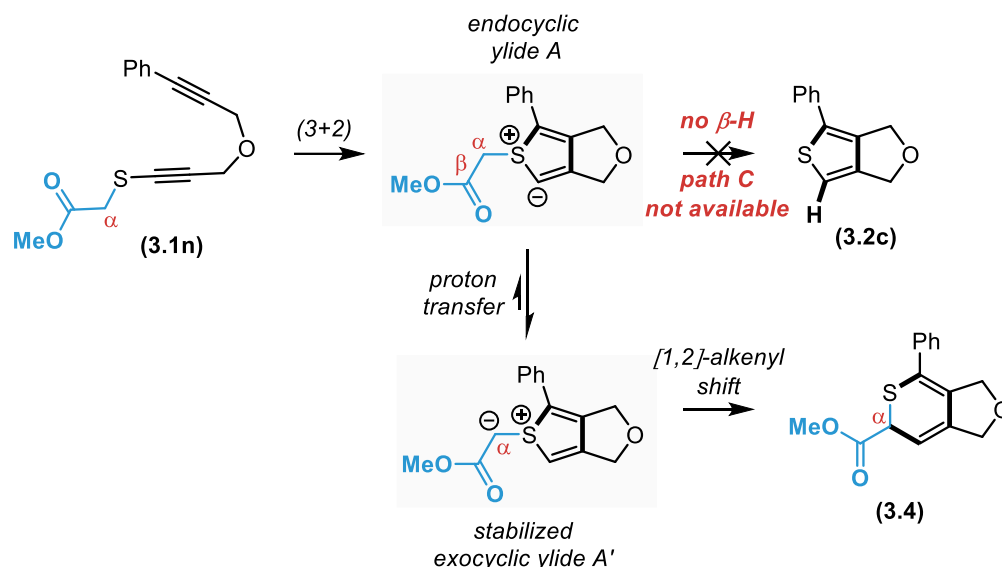
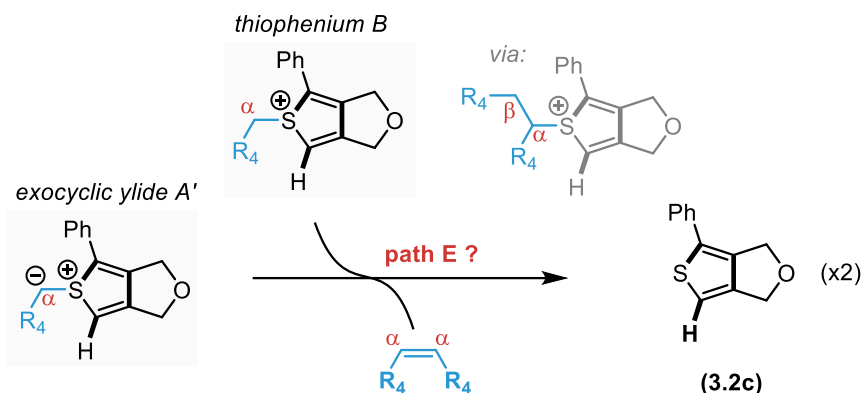
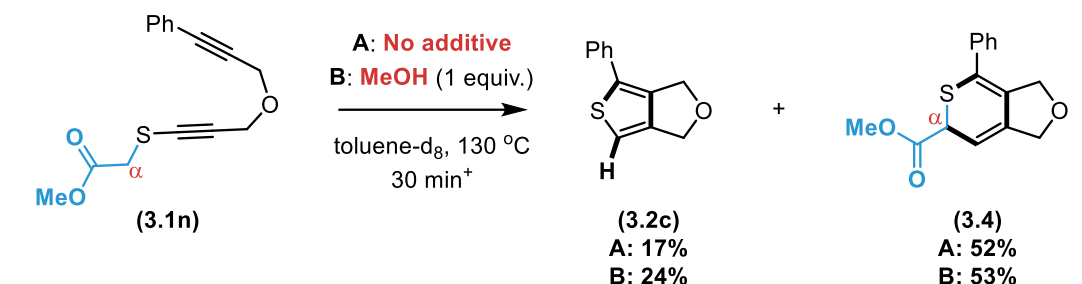


Figure 46 Hypothesis that probe **3.2n** would lead to the formation of exocyclic ylide **A'**.

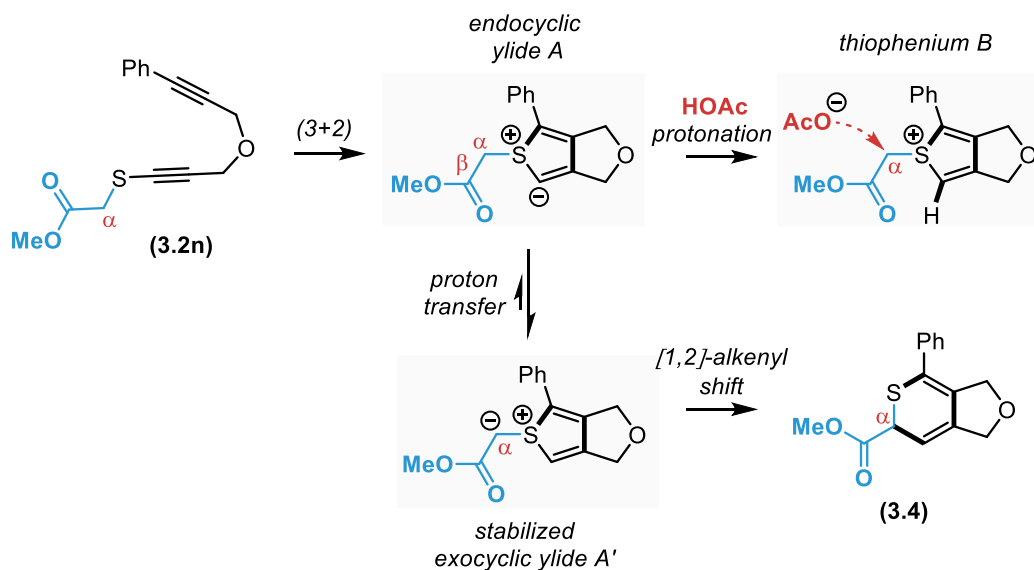
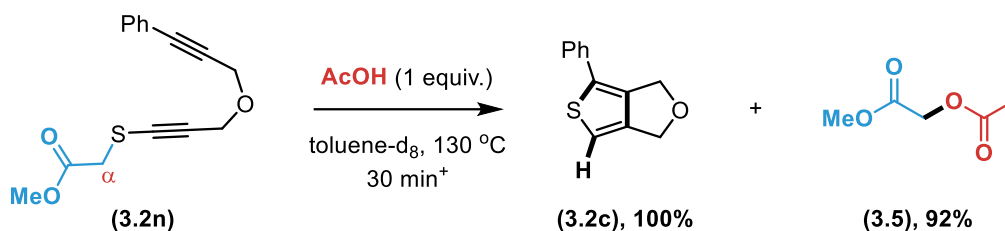
Experiments done by Dominic Campeau (Figure 47 and Figure 48) enabled this hypothesis to be tested. Heating of probe **3.1n** in toluene- d_8 with or without MeOH as an additive gives a mixture of the expected *2H*-thiopyran product **3.4** (52-53%) along with formation of 5-unsubstituted thiophene product **3.2c** as a minor product (17-24%) (Figure 47). These results suggest that β -hydrogen elimination is not the only pathway leading to thiophene **3.2c** and that an alternative pathway from the exocyclic ylide **A'** is likely occurring (path E). It is possible that thiophenium **B** reacts with the exocyclic ylide **A'** forming two units of 5-unsubstituted thiophene along with a symmetrical alkene by-product deriving from the alkyl chain. This alternative pathway would explain why the *S*-methyl and *S*-benzyl yne-alkynyl sulfides substrates (**3.1b** and **3.1g**) gave large amounts of the 5-unsubstituted thiophene (38 and 90%) although they lack a β -hydrogen (Table 1).



⁺Synthesis of **3.1n** and characterization of **3.4** done by Alice Pommainville. Reactions shown done by Dominic Campeau.

Figure 47 Alternative pathway towards thiophene **3.2c** involving exocyclic ylide **A'**.

A change in product selectivity was however seen when AcOH was used as an additive (Figure 48). Now, the 5-unsubstituted thiophene was observed as the sole product in a quantitative yield alongside a substitution by-product **3.5**. The results obtained can be explained by protonation of the exocyclic ylide **A** by acetic acid, followed by nucleophilic substitution onto thiophenium **B**. In contrary to when MeOH was used as an additive (Figure 47), formation of ylide **A'** seems to be inhibited as no 2*H*-thiopyran product **3.4** was observed. This result also explains why the yield for the 5-unsubstituted thiophene product **3.1c** greatly improved (85%) when the *n*-Pr substrate was heated in the presence of AcOH- d_4 as an additive (Table 7).



[†]Result by Dominic Campeau

Figure 48 Change in reaction outcome of probe **3.1n** when AcOH is present.

Overall, the results obtained from the deuteration study and on the reactivity of probe **3.1n** done by Dominic Campeau provide a clearer picture of the dealkylation mechanism for *S*-alkyl thiophenium ylides. The presence of α -hydrogens on these fleeting thiophenium ylides allows for proton transfer to occur towards a more stable exocyclic ylide **A'**. When this exocyclic ylide is further stabilized (such as with probe **3.1n**), a ring expansion can occur leading to the formation of *2H*-thiopyran product **3.4** as the major product. The selectivity can be completely inverted by addition of acetic acid to form the simple thiophene **3.2c** as the sole product.

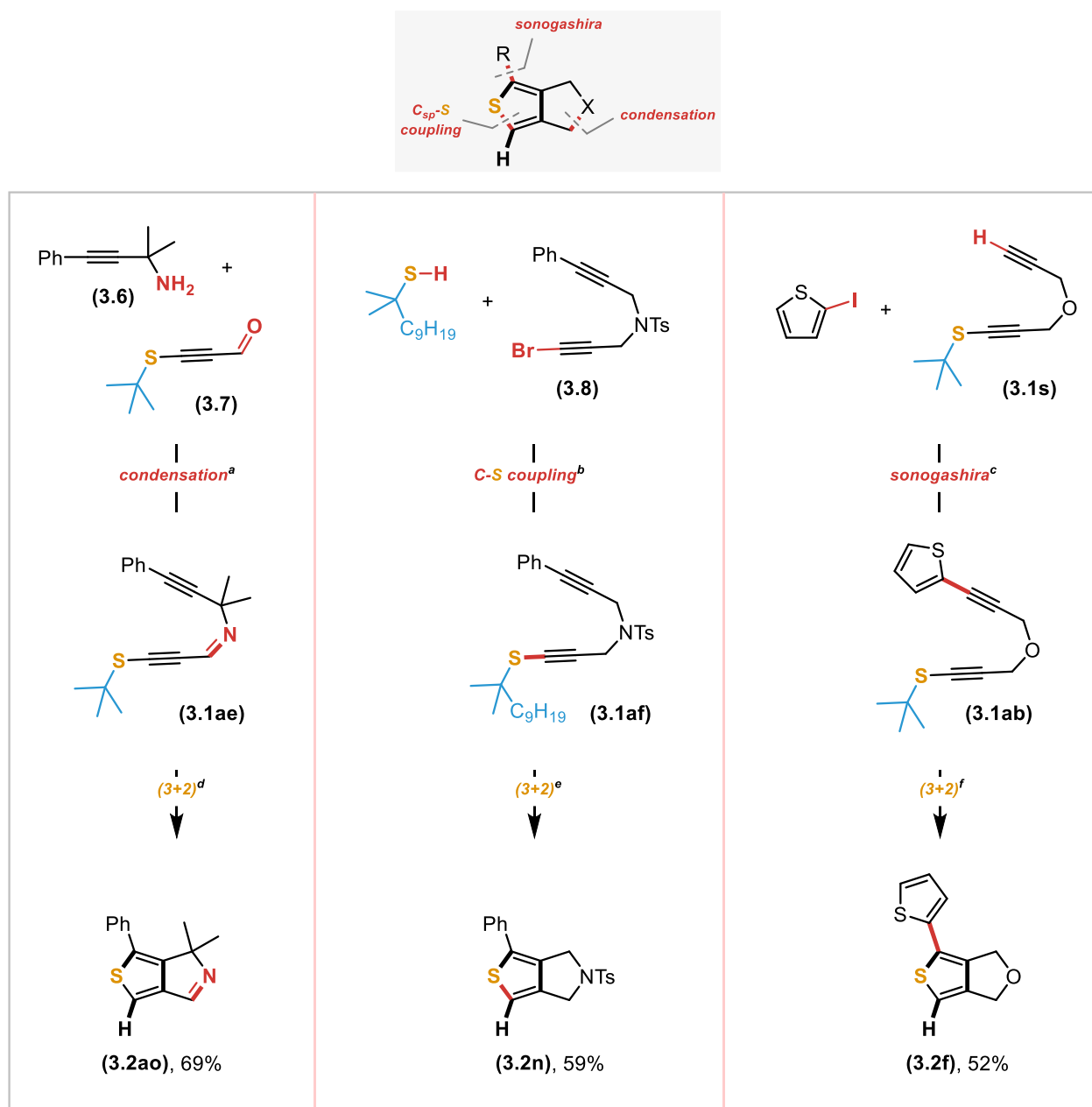
3.10 Facile implementation of two-step procedures and rapid access to polythiophenes

The synthesis of fused thiophenes *via* this method can be expedited by using *one-pot*/two step procedures. In Chapter 2 the utility of *one-pot* procedures to rapidly generate a small library of structures *via* multiple bond formation was discussed. The use of *one-pot* procedures and/or two-step procedures is very attractive if the goal is to obtain the final product of a transformation as the isolation of the reactive substrate can be skipped. This is only possible if the reaction conditions used to generate the substrate and those needed for the formation of the final product are compatible with each other. As discussed in Chapter 2, many retrosynthetic disconnections were envisaged and tested, and it was found that for yne-ynamides, formation of the reactive substrate *via* a condensation reaction was the most efficient route. An analogous reaction afforded a reactive yne-alkynyl sulfide substrate **3.1ae** by condensation of propargyl amine **3.6** and aldehyde **3.7** (Table 8). This *in-situ* generated substrate was found to undergo cyclization at a temperature as low as 60 °C and afforded the desired imine containing thiophene adduct **3.2ao** in a 69% yield.

Pleased with the good yield obtained, we then looked at other disconnections such as formation of substrate **3.1af** by a C_{sp}-S coupling⁷⁵ between grapefruit-scented *tert*-dodecyl mercaptan and yne-bromoalkyne **3.8**. This rapidly provided the reactive yne-alkynyl sulfide substrate at room temperature which was directly heated at 130 °C to deliver the trisubstituted thiophene **3.2n** in a 59% yield. The compatibility of the Cu mediated coupling with the (3+2) cycloaddition prompted us to the obtention of substrate **3.1ab** *via* a Sonogashira cross-coupling reaction between 2-iodothiophene and yne-alkynyl sulfide **3.1s**. Gratifyingly, a smooth cross-coupling event followed by directly heating the mixture to 130 °C for 15 minutes provided the

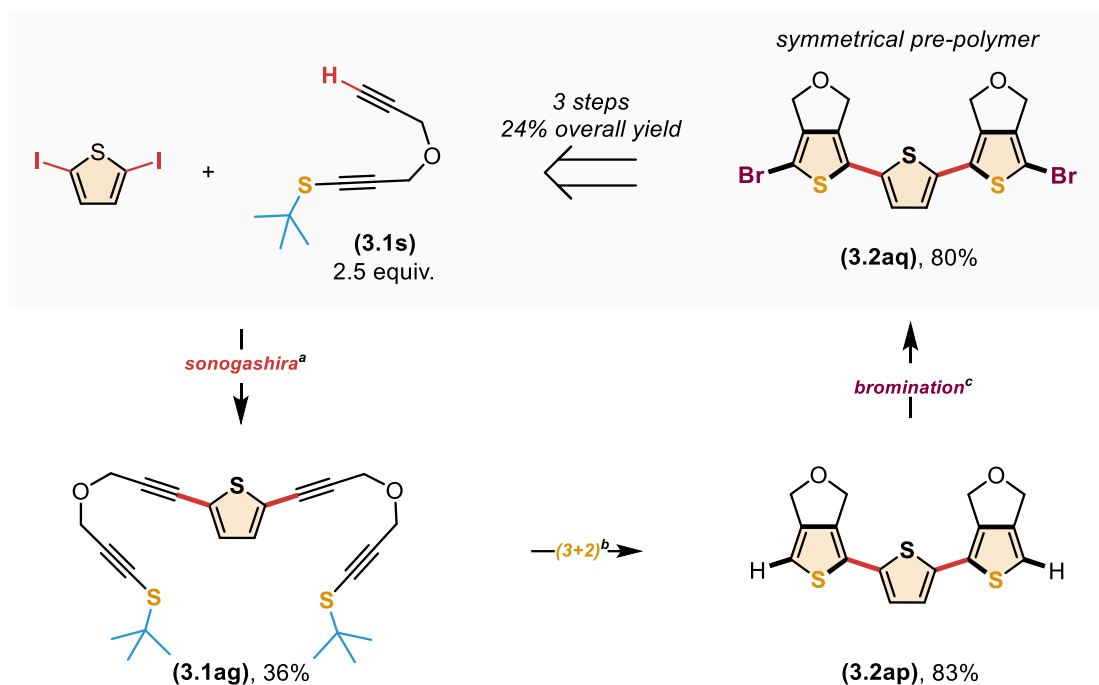
expected bis-thiophene product **3.2f** in a moderate 52% yield. In contrast to ynamides, alkynyl sulfides were found to be more tolerant to metal-based reaction conditions. Overall, three procedures were found to be effective for the rapid synthesis of trisubstituted thiophene products starting from commercially available and/or easily synthesized precursors.

Table 8 Two step procedures for the rapid synthesis of fused thiophenes.



^aDCM/hexanes, r.t., 1 h. ^bCu(MeCN)₄PF₆ (10 mol%), dtbbpy (20 mol%), 2,6-lutidine (2 equiv.), toluene, r.t., 1h. ^cPd(PPh₃)₂Cl₂ (5 mol%), CuI (10 mol%), Et₃N (2 equiv.), toluene, r.t., 1h. ^dDiluted with toluene then, evaporation of volatiles followed by heating at 60 °C for 45 min. ^eHeating at 130 °C for 1.5 h. ^fHeating at 130 °C for 15 min. (see Supporting Information section 7.4.9).

Encouraged by the compatibility of alkynyl sulfides with the Sonogashira experimental reaction conditions and the importance of polythiophenes in material science,⁶⁵ we envisaged that a symmetrical polythiophene pre-polymer **3.2aq** could be accessed in a three-step sequence starting from 2,5-di-iodothiophene and yne-alkynyl sulfide precursor **3.1s** (Figure 49 Three step synthesis towards a polythiophene building block. Figure 49). First, Sonogashira cross-coupling gave the symmetrical thiophene substrate **3.1ag** containing two reactive yne-alkynyl sulfides capable of undergoing (3+2) cycloaddition upon heating. An excellent 83% yield for polythiophene **3.2ap** was obtained upon (3+2) cycloaddition and elimination of the two *tert*-butyl units. In addition, this symmetrical tris-thiophene product **3.2ap** was easily brominated, generating a pre-polymer containing two new synthetic handles that could be used for further functionalization. The synthesis of fused thiophenes via (3+2) cycloaddition cascades, might provide an original and rather rapid access to useful symmetrical (or asymmetrical, see Table 5 example **3.2ak**) oligothiophene building blocks whose synthesis would be harder *via* more classical routes.



^aPd(PPh₃)₂Cl₂ (2.5 mol%), CuI (5 mol%), Et₃N (4 equiv.), dry THF, 50 °C, 2 h. ^bHeating at 130 °C for 30 min. ^cNBS (2.05 equiv.), CHCl₃, r.t., 1 h. (see Supporting Information section 7.4.10 for more details).

Figure 49 Three step synthesis towards a polythiophene building block.

3.11 Summary of the reactivities observed with thiophenium ylides

In contrary to dipolar (3+2) cycloadditions, employing alkynyl sulfides as three-atom components (*n*TAC) generate a non-aromatic thiophenium ylide intermediate which opens the door to subsequent reactivity (Figure 50). In this chapter it was presented that the thermally induced (3+2) cycloaddition cascades of yne-alkynyl sulfides are controlled by both the substrate substitution pattern and the reaction condition, thus allowing for structural rearrangements or trapping of the ylide to occur as wished. In contrast to the pyrrolium ylides previously studied,⁵⁸ the *in-situ* formation of thiophenium ylides enabled for a more in-depth exploration of the synthetic potential of these heteroarylium ylides.

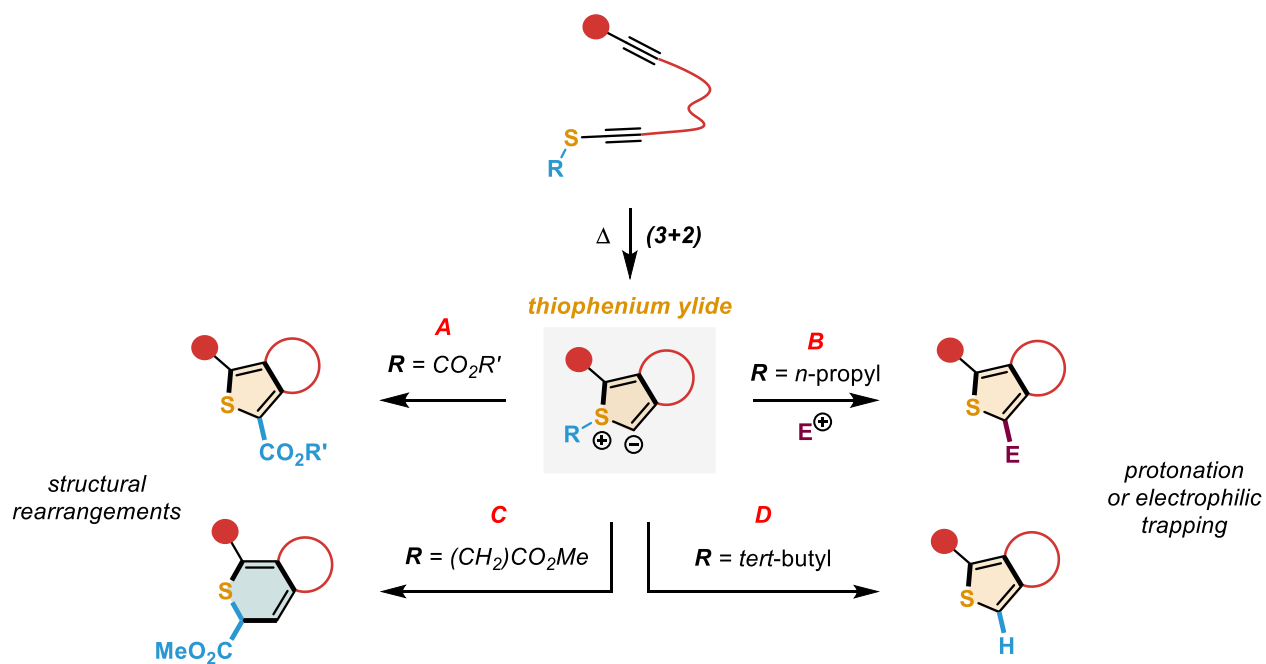


Figure 50 Reactivity pathways observed from the thermally formed thiophenium ylide.

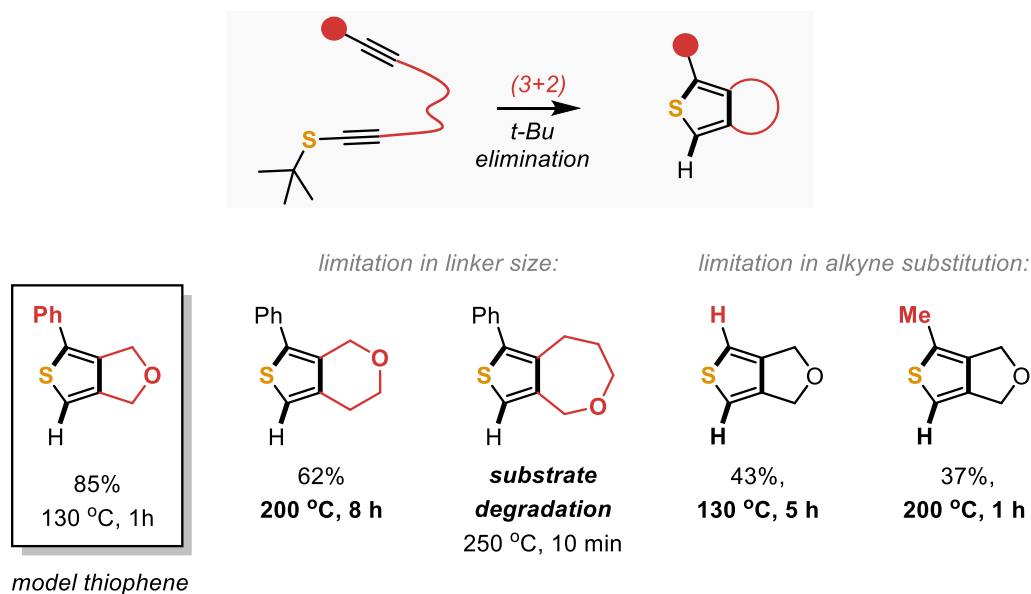
4 Chapter 4 : Access and reactivity investigations of isolable thiophenium cycloadducts

4.1 Summary of the limitations associated with the thermally induced pathway

The chemistry of alkynyl sulfides as *neutral*-TACs in (3+2) cycloaddition reactions is as of now limited to the use highly reactive alkyne (benzyne) species⁴⁷ or to intramolecular tethering.⁸¹ Our group's detailed investigation on the thermally induced cyclization of tethered alkynyl sulfides enabled a broad scope of 3,4-fused thiophenes to be synthesized utilizing simple reaction conditions (heating only!). It was established that the cyclization success is dependent on 1) the tether structure; 2) the alkyne substitution; and 3) the type of alkynyl sulfide utilized. This inherently imposes scope limitations. The use of *tert*-butyl substituted alkynyl sulfides allowed for high yields of 5-unsubstituted thiophenes to be obtained as long as an appropriate tether and alkyne substitution is utilized.

For instance, the model [3.3.0] fused thiophene was obtained in an 85% yield when the corresponding yne-alkynyl sulfide precursor was heated at 130 °C for 1 hour (Figure 51, A). Modification of the model tether to a larger 4-membered ether link required heating at 200 °C for 8 hours for the [3.4.0] fused thiophene to be obtained with a 62% yield. The limit was seen when it was attempted to synthesize a [3.5.0] fused thiophene which could not be accessed due to degradation of the starting yne-alkynyl sulfide at 250 °C. The high-energy profile associated with the thermally induced cyclization of yne-alkynyl sulfide limits the scope to small-fused thiophene cycles. Additionally, utilizing unsubstituted or alkyl substituted alkynes renders the cyclization difficult as can be seen by the higher temperature and/or longer reaction times needed for consumption of these yne-thioalkynes.

A Difficult yne-alkynyl sulfide cyclizations



B Limitation seen with alkynyl sulfide substitution

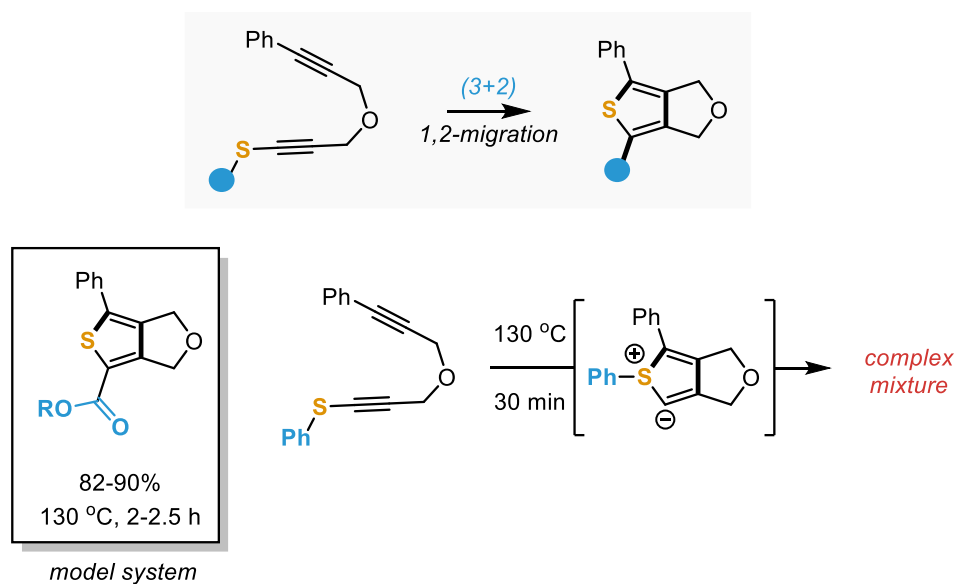


Figure 51 Limitations observed with the thermally induced cyclization of yne-alkynyl sulfides. A) Difficult to access fused thiophenes due to an increase in energetic demand. B) Decomposition and/or complex mixture observed with S-Ph derivatives.

In addition to easily cleavable alkyl groups, the use of carbonate substituted alkynyl sulfides allows for a different cycloaddition cascade to occur towards fully substituted

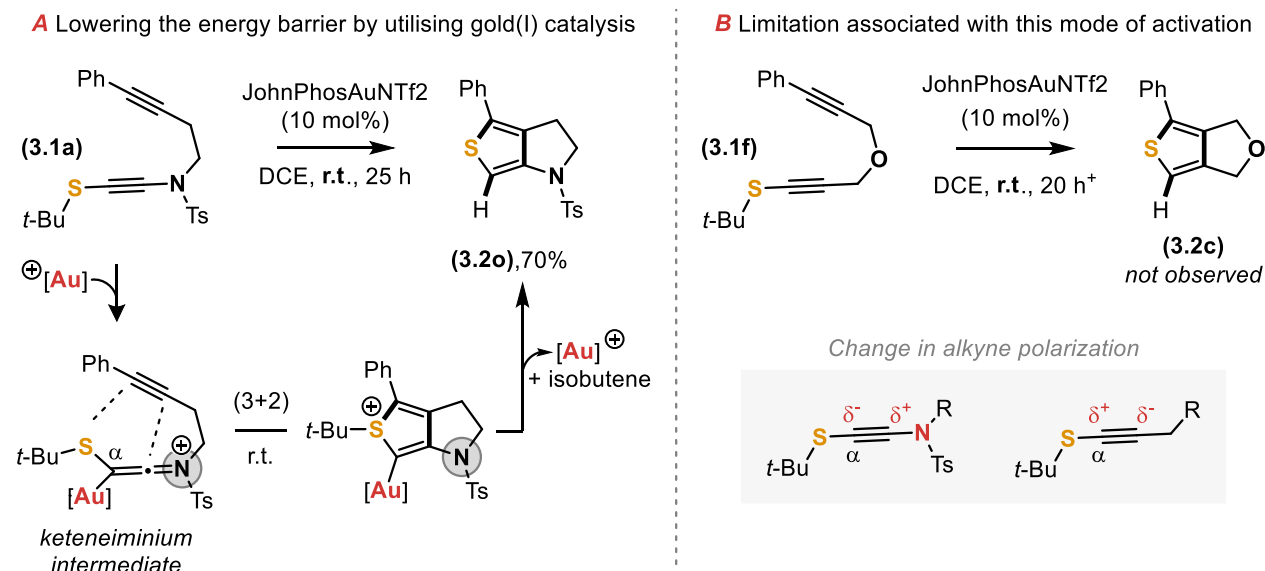
thiophenes. Due to the high-migratory aptitude of these carbonate substituents, ester substituted thiophenes were obtained in high yields by a cyclization and intramolecular rearrangement sequence (82-90%) (Figure 51, B). Attempting to utilize phenyl-substituted alkynyl sulfide instead led to a complex mixture. This result indicated that if the same ylide intermediate is formed upon (3+2) cycloaddition, then it does not undergo clean migration under the thermal conditions (130 °C).

4.2 Initial hit for a general low-energy pathway

The finding of alternative milder cyclization condition may enable the scope of fused thiophenes to be expanded or even for intermolecular variant to become accessible. For instance, the use of gold(I) catalyzed condition established by the Anderson group enabled for a specially tethered thioynamide substrate **3.1a** to rearrange at room temperature towards fused amido-thiophene **3.2o** (70% yield) (Figure 52, A).⁵⁹ This transformation was previously found to require high temperature under the thermally induced condition (Table 3). In line with the mechanism proposed by Anderson, the cyclization is likely induced by the electrophilic π -activation of the thioynamide alkyne which leads to the formation of a reactive keteneiminium intermediate. This cationic specie is then prone to cyclization which upon protodemetalation and cleavage of the *tert*-butyl group affords the neutral product.

This lower energy pathway was however only achieved when using electron-rich thioalkynes as the cyclization of yne-alkynyl sulfide **3.1f** does not occur under the same reaction condition (Figure 52, B). In the case of thioynamide **3.1a**, the development of an incipient negative charge alpha to the sulfur atom enables the (3+2) reactivity to be favored. On the contrary, the alpha carbon to sulfur on alkynyl sulfide **3.1f** is electrophilic due to a change in the

alkyne polarization. The finding of a different low-energy pathway that do not rely on the use of electron rich thioalkynes is likely the key to expanding the scope of fused-thiophenes obtained.

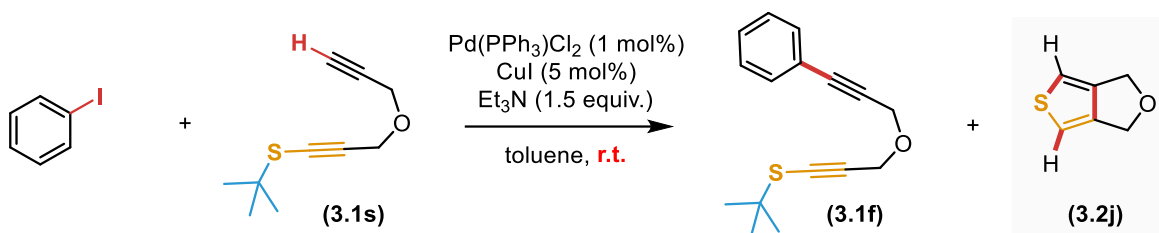


*Example by Dominic Campeau, 23% conversion of **3.1f** is seen.

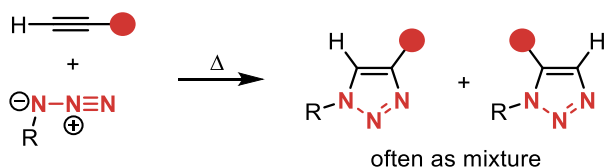
Figure 52 Attempt to catalyze the (3+2) cycloaddition of yne-alkynyl sulfides with gold catalysis. A) Successful implementation of Anderson's gold(I) catalyzed condition for the cyclization of electron rich yne-thioalkynes B) No reactivity observed with **3.1f** due to a change in alkyne polarization.

When attempting to perform a Sonogashira reaction between yne-alkynyl sulfide **3.1s** and iodobenzene the formation of a mixture of products was obtained two of which were easily detected by NMR, that is the expected cross-coupled product **3.1f** and thiophene **3.2j** (Figure 53, A). This was an impressive result as the cyclization of yne-alkynyl sulfide **3.1s** towards 2,5-unsubstituted thiophene **3.2j** previously required heating at 130 °C (Table 2). This result was reminiscent to the discovery by Nobel prize winners Meldal and Sharpless of mild reaction conditions enabling the cycloaddition between azides and terminal alkynes at room temperature (also known as "Click" chemistry).

A Initial hit : cyclization of yne-alkynyl sulfide **3.1s** at room temperature



B Azides in 1,3-dipolar cycloaddition reaction



C Copper-catalyzed azide-alkyne cycloaddition

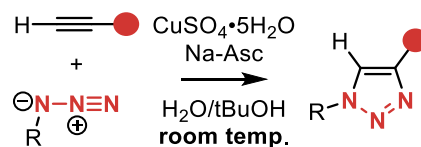


Figure 53 First hit of a low energy pathway for the cyclization of yne-alkynyl sulfide. A) Formation of thiophene **3.2j** at room temperature utilizing Sonogashira reaction conditions. B) The thermally induced 1,3-dipolar cycloaddition reaction between azides and terminal alkynes. C) Discovery of CuAAC for the formation of a single triazole isomer.

1,3-Dipolar cycloadditions between azides and alkynes was first reported by Huisgen however it required high temperatures and often resulted in the mixture of 1,4 and 1,5-substituted triazole products (Figure 53, B).⁸⁷ In 2002, the groups of Meldal⁸⁸ as well as of Fokin and Sharpless⁸⁹ described the finding of alternative copper-catalyzed conditions for the (3+2) cycloaddition between azides and alkynes, also termed CuAAC. This revolutionized the use of azides in (3+2) cycloaddition reactions as they are now characterized as mild, high yielding reactions providing a single triazole isomer. Many reaction conditions are used in CuAAC, such as the well-known Sharpless-Fokin conditions utilizing copper(II) sulfate pentahydrate as a cost-efficient salt that is *in-situ* reduced to catalytically active copper(I) by sodium ascorbate (Figure 53, C). Although these staple conditions are often utilized, the direct use of copper(I) salts (ex: CuI , CuOTf , etc.) in combination with a nitrogen base (ex: 2,6-lutidine, Et_3N , DIPIEA, etc.) was also established as suitable conditions for CuAAC, however, by-products formation was often

observed.⁸⁹ This exciting initial hit for the cyclization of yne-alkynyl sulfide **3.1s** at room temperature appeared to be a good starting point for the next chapter of investigations with the hope that limitations associated with the thermally induced process are lifted.

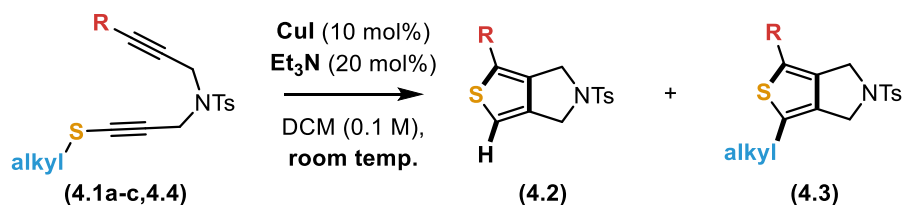
4.3 Establishing the key elements enabling the room temperature cyclization of yne-alkynyl sulfide

To avoid working with volatile 2,5-unsubstituted thiophene **3.2j**, subsequent investigations were performed utilizing sulfonamide containing yne-alkynyl sulfides instead (Table 9). Suspecting that copper iodide and triethyl amine were likely responsible for the unexpected cyclization event during the Sonogashira coupling, the addition of Pd(II) was omitted. Gratifyingly, when *tert*-butyl substituted yne-alkynyl sulfide **4.1a** was subjected to these new reaction condition, the formation of two thiophene products was obtained, one having lost the *tert*-butyl group (**4.2**, 22%) while the other had retained it (**4.3**, 11%) (*entry 1*). Since alkynyl sulfide substitution was previously shown to be an important factor influencing the success of the cyclization of alkyl-substituted alkynyl sulfide (Table 1) the screening of alkyl groups was similarly done here.

Changing the alkynyl sulfide substitution by a benzyl (**4.1b**) or *n*-propyl (**4.1c**) substituent was however detrimental as significantly lower yields for the thiophene products were observed (*entry 2-3*). In the case of the *n*-propyl substituted alkynyl sulfide **4.1c**, no alkyl containing thiophene derivative was seen by NMR (*entry 3*). It is interesting that the benzyl derivative was not high yielding for 5-unsubstituted thiophene **4.2** under these catalyzed condition, while it proved to be an appropriate substituent in the thermally induced process (Table 1). The observation that easily cleavable tertiary alkyl group (*t*-Bu) was higher yielding for **4.2** than when

a primary *n*-propyl alkyl chain was employed, suggests however that the strength and nature of the S-alkyl group are of importance.

Table 9 Effect of alkynyl sulfide and alkyne substitution.



Entry	(4.1/4.4)	alkyl	R	Time (h)	Conv., (%)	(4.2), yield (%)	(4.3), yield (%)
1	(4.1a) ⁺	<i>t</i> -Bu	H	1	61	22	11
2	(4.1b)	Bn	H	1	56	6	4
3	(4.1c)	<i>n</i> -Pr	H	1	76	2	0
4 ⁺	(4.4)	<i>t</i> -Bu	Ph	21	0	0	0

⁺Synthesis of **4.1a** and entry 4 done by Dominic Campeau.

Dominic Campeau found that when the tethered alkyne is substituted (**4.4**) no reactivity is observed after 24 h and full recovery of the starting material was seen (entry 4). While this result indicates the strict need to use terminal alkynes, the cyclization of **4.1** towards fused thiophene **4.2** was previously shown to be an efficient thermal process, a statement that was not true for thioalkynes linked with terminal alkynes (Table 2). The formation of alkyl substituted thiophene **4.3** was quite interesting as these adducts were not observed using our thermally induced conditions.⁸¹ Our efforts were however shifted towards optimizing the formation of 2,5-unsubstituted thiophene **4.2** (R = H) as it appeared to be the major product under these simple reaction conditions. The *tert*-butyl substituted yne-alkynyl sulfide **4.1a** was chosen as the model substrate for subsequent optimization as it provided the highest yield for thiophene **4.2** (22%).

The results obtained in Table 9 further hinted that the cycloaddition of yne-alkynyl sulfides may engender reactivity overlap with the well-known CuAAC. More specifically, the lack of reactivity seen with phenyl substituted yne-alkynyl sulfide **4.4** suggest the initial formation of a copper-acetylide, a known first intermediate in CuAAC processes.⁹⁰ Additionally, our group has extensively demonstrated that alkynyl sulfides should be regarded as *neutral* three-atom components capable of undergoing (3+2) cycloaddition reactions. It is therefore reasonable to imagine that a similar mechanism to that proposed for the copper-catalyzed azide-alkyne (3+2) cycloaddition may be at play (Figure 54). There is evidence in the literature for the involvement of two copper(I) ions in the stepwise CuAAC pathway, a statement that has been backed up by kinetic experiments and DFT studies.⁹¹ The generally proposed mechanism for CuAAC is a stepwise mechanism where two equivalents of copper(I) centers are involved in the rate-determining C-N bond formation (**I** $\rightarrow$ **II**) resulting in the formation of a six-membered metallacycle. A ring closing event then occurs towards the formation of triazolide complex (**III**).⁹¹⁻⁹³

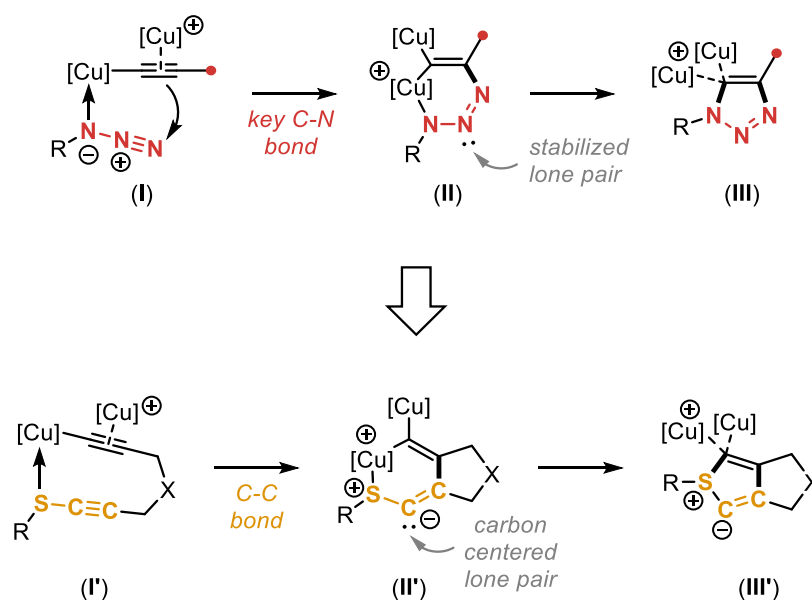
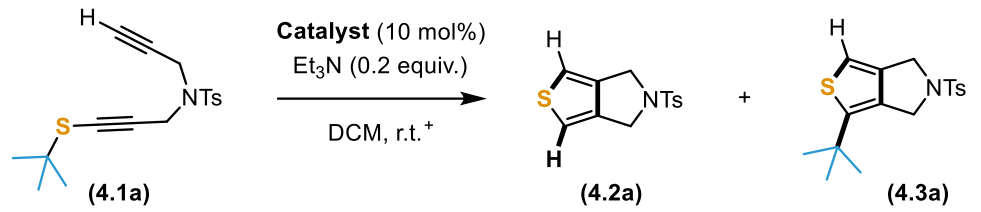


Figure 54 Transposing the mechanistic proposal for CuAAC onto the yne-alkynyl sulfide system.

When transposing this pathway onto our yne-alkynyl sulfide system, it is possible to draw a mechanism where the alkynyl sulfide now acts as the cycloaddition partner. An important key difference can be rapidly seen which is imparted by the uncharged structure of alkynyl sulfide (**I'**) as opposed to azides which are charged species (**I**). Due to this structural difference, the resulting 6-membered metallacycle now bears an unstabilized carbon-centered lone pair (**II'**). Finally, a similar ring-closing event by the formation of the S-C bond (**III'**) would generate the fused thiophene core that was observed experimentally. This difference in charge stabilization found within intermediates **II** and **II'** may partially explain why the copper-catalyzed cyclization of thioalkynes still requires the need for intramolecular linkage, while azides react intermolecularly at room temperature. Despite the need to use tethered alkynes, the impressive decrease in energy demand (130 °C to r.t.!) supported our hypothesis that the use of metal catalysis is likely the key to lifting the limitations associated with the thermally induced process.

Interestingly, this strategy was previously found to be unsuccessful when employing yne-ynamides instead. When Dominic Campeau attempted to promote the cyclization of alkyne tethered ynamide **4.5** utilizing copper(I) as the catalyst and triethylamine as a base, no (3+2) derived product was observed even upon heating at 60 °C (Figure 55). The observation that a copper-induced cyclization was rendered possible when utilizing alkynyl sulfides instead, as can be seen by the preliminary results (Table 9), suggests that the presence of the sulfur atom plays an important role in the success of the reaction (see section 4.5).

Table 10 Optimization of the catalyst for the formation of thiophene **4.2a**.

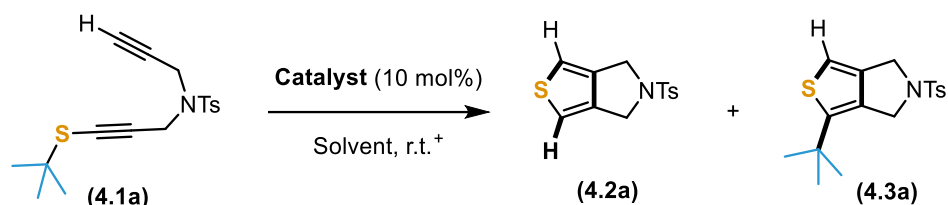


Entry	Catalyst	Time	Conv. (4.1a), (%)	(4.2a), yield (%)	(4.3a), yield (%)
1	AgOTf	1 h	>95	>95	2
2	CuOTf ^a	1 h	93	47	8
3	(DMS)AuCl	13 h	47	13	5

^aas the [(CuOTf)₂·benzene] complex. ⁺Results obtained by Dominic Campeau.

Upon screening different coinage metals, Dominic Campeau determined that AgOTf proved to be the best catalyst as an almost quantitative yield of **4.2a** was obtained within 1 hour (>95% yield) (entry 1). Knowing that the AgOTf/Et₃N system provides an excellent yield for thiophene **4.2a**, Dominic Campeau undertook the screening of ligands and solvents to accelerate the rate of the reaction and simplify the reaction conditions (Table 11). In CuAAC and related copper-catalyzed (3+2) cycloaddition reactions, copper(I) acetate is an effective catalyst in additive-free reaction conditions where the acetate counter anion acts both as a bidentate ligand and a base necessary for the formation of the initial copper-acetylide.^{100, 101} When employing AgOAc instead of the AgOTf/Et₃N system, thiophene **4.2a** was obtained in a moderate 61% yield after 4 h (entry 1). In contrast, it was observed that the use of AgOTf alone does not efficiently catalyze the cycloaddition (entry 2). It was therefore concluded that the use of mildly basic X-type ligand is needed if additive-free reaction conditions are desired. This result also supported the hypothesis that the formation of a metal acetylide is required for the (3+2) cyclization to occur.

Table 11 Simplifying the reaction conditions and solvent acceleration effect.



Entry	Catalyst	Solvent	Time	Conv. (4.1a) , (%)	(4.2a) , yield (%)	(4.2b) , yield (%)
1	AgOAc	DCM	4 h	84	61	15
2	AgOTf	DCM	1 h	44	1	0
3	AgOAc	EtOH	4 h	>95	>95	2
4	AgOAc	AcOH	5 min	>95	>95	0
5	CuOAc ^a	AcOH	10 min	>95	89	7

^a1 equiv. of Na-Asc was added. ⁺Results by Dominic Campeau.

While the use of AgOAc required a longer reaction time and is less selective for the targeted 5-unsubstituted thiophene **4.2a** in comparison to the AgOTf/Et₃N system, Dominic Campeau observed that changing the nature of the solvent increased product selectivity and shortened the reaction times (entry 3-4). In particular, when AcOH was employed as the solvent, a dramatic increase in the rate of the reaction was observed and full conversion of the substrate was seen after just 5 minutes with exclusive formation of 5-unsubstituted thiophene **4.2a**. Interestingly, rate enhancement of copper-catalyzed azide-alkyne cycloadditions processes when using carboxylic acid additives have been reported by the groups of Straub¹⁰² and Hu.^{100, 103, 104} While silver was previously established to be the best coinage metal for the cyclization of yne-alkynyl sulfide **4.1a** in aprotic solvents (Table 10), it was found that copper is capable of providing high yields for thiophene **4.2a** in protic and mildly acidic solvent (i.e. AcOH) (Table 11, entry 5).

4.5 Preliminary mechanistic proposal for the copper-catalyzed cyclization of yne-alkynyl sulfide 4.1a

The effect of acetic acid as well as related carboxylic acids in the various steps of the CuAAC mechanism has been investigated primarily by the group of Hu (Figure 56).¹⁰³ They suggest that the presence of AcOH, released upon formation of the copper-acetylide, plays two roles in the mechanism. First, it is proposed that AcOH displaces the equilibrium between the *in-situ* generated copper-acetylide dimers/polymers towards the formation of a catalytically active di-nuclear copper(I)-alkyne complex (**X**). Secondly, upon (3+2) cycloaddition with the azide, acetic acid enables for a rapid protodemetalation of triazolide complex of type **Y** affording triazole **Z**. While the triazolide complex **Y** may be protonated by another unit of terminal alkyne instead, Straub reported that the protodemetalation step is way faster when HOAc is present.¹⁰²

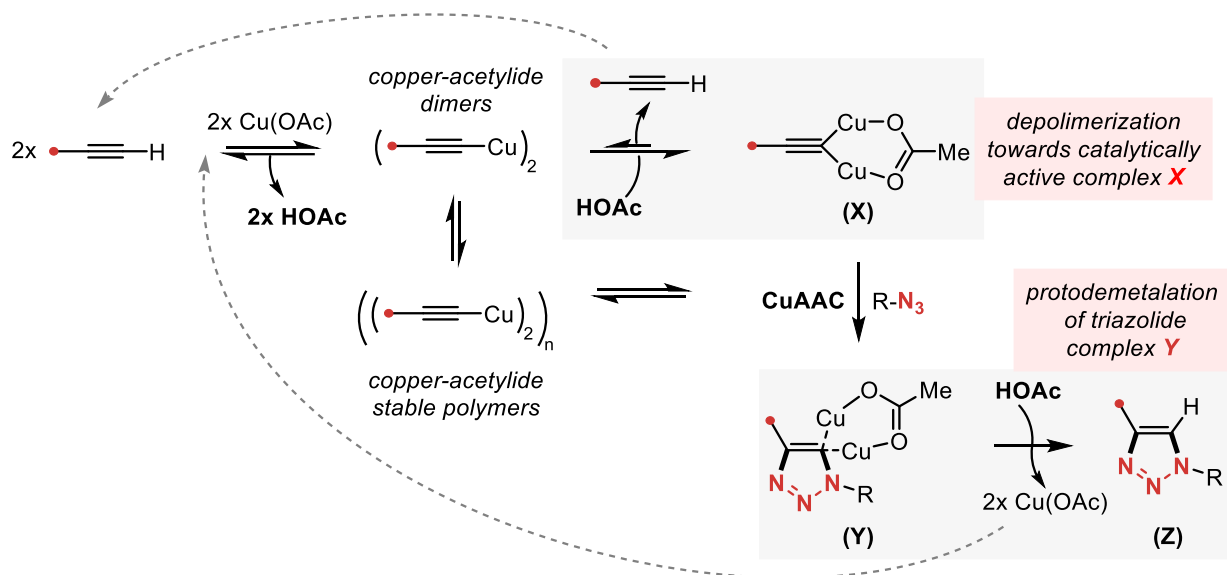


Figure 56 Carboxylic acid promoted copper(I) catalyzed azide-alkyne cycloaddition.

The rationalization of the optimization results obtained by Dominic Campeau led to the mechanistic proposals shown in Figure 57. For simplification, the mechanism shown is representative of when CuOAc is used as a catalyst. The rate enhancement observed when acetic

was employed as the solvent was quite indicative that a di-nuclear copper(I)-alkyne complex of type **X'** was likely the catalytically active specie, as suggested by literature precedent for CuAAC variants (*vide-supra*). Additionally, the sulfur atom is likely complexing with the metal center, as no catalysis is seen when employing ynamides instead (Figure 55).

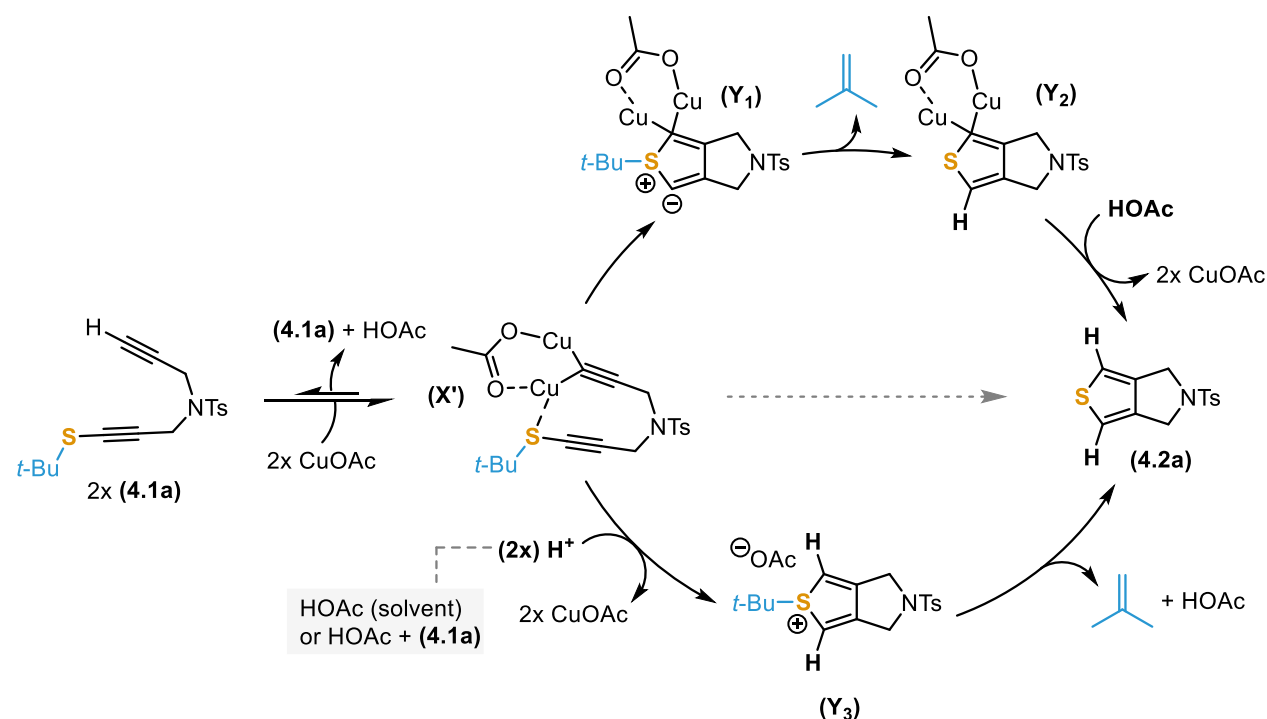


Figure 57 Mechanistic proposals for the copper-catalyzed cycloaddition of yne-alkynyl sulfides.

Following the (3+2) cycloaddition, two intermediates may be formed, that is either ylide **Y₁** or thiophenium salt **Y₃**. In the presence of AcOH, especially when employed as solvent, intermediate **Y₃** is likely formed directly upon (3+2) cyclization and protonation. Alternatively, if the ylide **Y₁** is formed, cleavage of the weak S⁺-t-Bu bond may occur at this stage giving rise to intermediate **Y₂** instead. This cationic specie would then afford the observed thiophene **4.2a** upon protodemetalation. Mechanistic studies are currently underway by Dominic Campeau to establish the plausibility of the proposed intermediates and to gain a better understanding of the rate acceleration effects observed experimentally.

4.6 The first observation of a reaction intermediate using a *S*-phenyl yne-thioalkyne

Although the formation of thiophenium salt of type **Y₃** was never observed experimentally, presumably because the *tert*-butyl group is easily cleaved by β -hydrogen elimination, analogous intermediates containing a stronger and/or difficult to cleave S^+-R bond may be longer lived. For instance, the cleavage of an S^+ -aryl bond would presumably be more energy-demanding which may allow for thiophenium salt of type **Y₃** to be observed if formed under the reaction conditions. Based on this hypothesis, phenyl-substituted yne-alkynyl sulfide **4.6a** was introduced to the condition previously optimized and the reaction was followed by NMR in deuterated acetic acid (Figure 58). The use of AgOAc as catalyst was opted instead of CuOAc as it proved to be more selective for 5-unsubstituted thiophene **4.2a** (*vide-supra*).

After just 10 minutes full conversion of the starting material was seen and a previously unobserved product was detected by NMR (Figure 59). The AB system observed was quite indicative of thiophenium salt **4.7-OAc-d_(3/5)** as the sulfur atom adopts a pyramidal geometry making the hydrogens of the ether linker diastereotopic. Furthermore, if the formation of this thiophenium salt occurs by the mechanism proposed, then one may expect the hydrogens at the 2 and 5 positions of the thiophenium core to be deuterated when deuterium-enriched acetic acid is employed as the solvent. In fact, the aromatic region only showed a total of 5H which was attributed to the phenyl group.

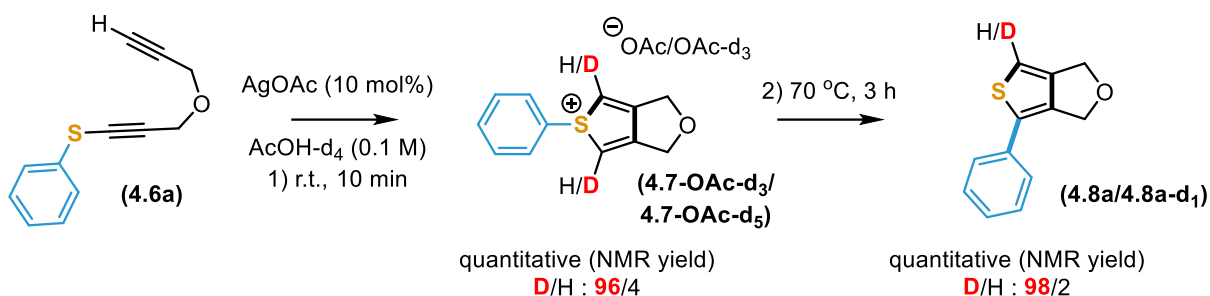


Figure 58 On the search for a reaction intermediate utilizing a *S*-phenyl derivative.

An isolable version of this thiophenium salt possessing a triflate counteranion (**4.7-OTf**) was synthesized later on (see section 4.13) which allowed us to determine where the 2,5-H of the thiophenium core would reside. In the case of thiophenium salt **4.7-OAc-d₃**, they appear as a triplet at 7.50 ppm (in AcOH-d_4), and as can be seen in Figure 59, those positions are almost completely deuterated (D/H : 96/4). Interestingly, when comparing the NMRs of this first reaction (**4.6a** to **4.7-OAc-d_(3/5)**) it is possible to observe an appreciable increase in the AcOH signal, which is consistent with the hypothesis that a metal acetylide is formed as the first step (see Supporting Information section 7.5.10 for more details). Overall, the observation of this thiophenium salt indicated that these thiophenium intermediates are likely formed in the metal-catalyzed cyclization of yne-alkynyl sulfides.

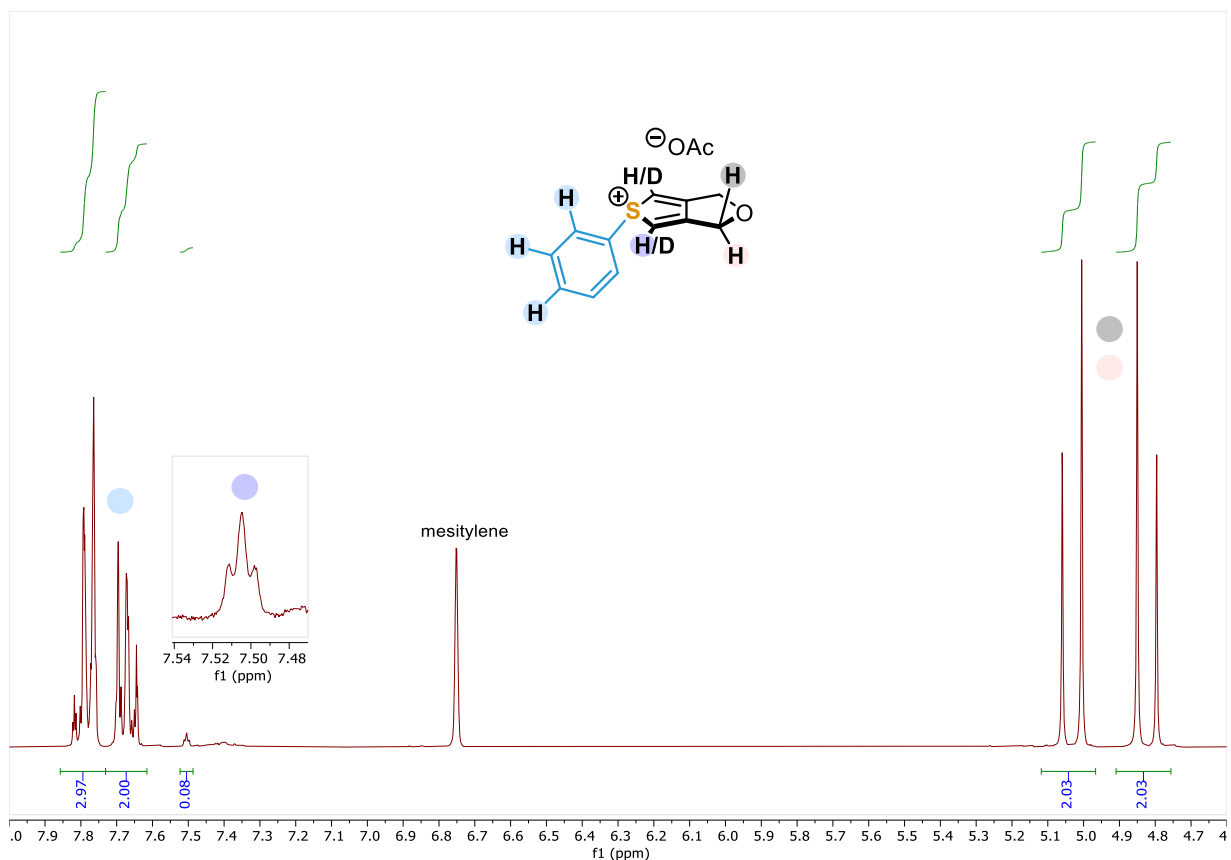


Figure 59 NMR obtained when *S*-phenyl derivative **4.6a** is subjected to the optimized conditions.

Unexpectedly, this *in-situ* formed thiophenium salt appeared to be slowly getting consumed at room temperature therefore the reaction mixture was heated to gain more knowledge on its reactivity. Gratifyingly, this thiophenium intermediate cleanly underwent rearrangement affording thiophene **4.8a/4.8a-d₁** upon heating at 70 °C for 3 h (Figure 58). The observation of a clean rearrangement of thiophenium salt **4.7-OAc-d_(3/5)** was quite impressive as it was previously shown that direct heating of *S*-phenyl yne-alkynyl sulfide **3.1h** only led to a complex mixture (Figure 60).

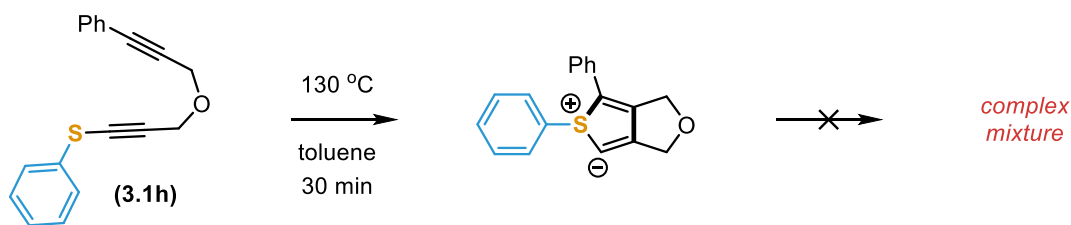


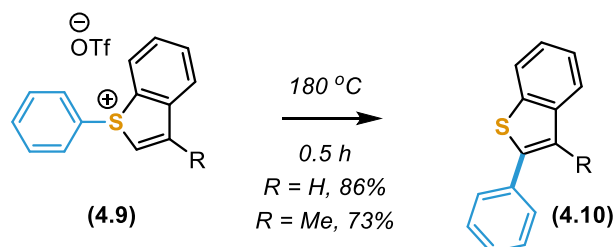
Figure 60 Unsuccessful cyclization of yne-alkynyl sulfide **3.1h** under the thermal condition.

4.7 The thermal rearrangements of *S*-Aryl (benzo)thiophenium salts

To our knowledge, *S*-phenyl thiophenium salts have never been reported before. Only *S*-alkyl thiophenium salts have been synthesized but very limited reactivity of these salts is known due to their high electrophilicity.¹⁰⁵⁻¹⁰⁷ *S*-Aryl thiophenium salts are presumably more stable due to a stronger *S*-aryl bond. Kitamura et al. reported the synthesis of structurally related 1-phenyl benzo[*b*]thiophenium salts which allowed further study on the reactivity of these thiophenium derivatives.¹⁰⁸ Similarly to the rearrangement that we observed for **4.7-OAc-d**_(3/5), Kitamura et al. have shown that *S*-aryl benzo[*b*]thiophenium salts also underwent the same thermal rearrangement giving aryl substituted benzothiophenes (Figure 61).¹⁰⁹

They have shown that *S*-phenylbenzo[*b*]thiophenium salts of type **4.9** undergo selective phenyl migration at the 2-position giving 2,3-substituted benzothiophene **4.10** (Figure 61, A). They propose that this migration occurs via a [1,5] sigmatropic rearrangement of the phenyl group followed by aromatization (loss of H⁺). They provide evidence for this mechanism by neatly heating 2-tolyl substituted benzo[*b*]thiophenium salt **4.11** which resulted in a 3 : 1 mixture of constitutional isomers (Figure 61, B). The non-specific migration of the phenyl group was explained by two subsequent [1,5] sigmatropic rearrangements, the first one giving intermediate **4.12** which was then prone to either Ph-migration or Tol-migration to give **4.13a** and **4.13b** respectively after aromatization.

A The thermal rearrangement of S-aryl benzo[b]thiophenium salts



B Evidence for a [1,5]-sigmatropic rearrangement mechanism

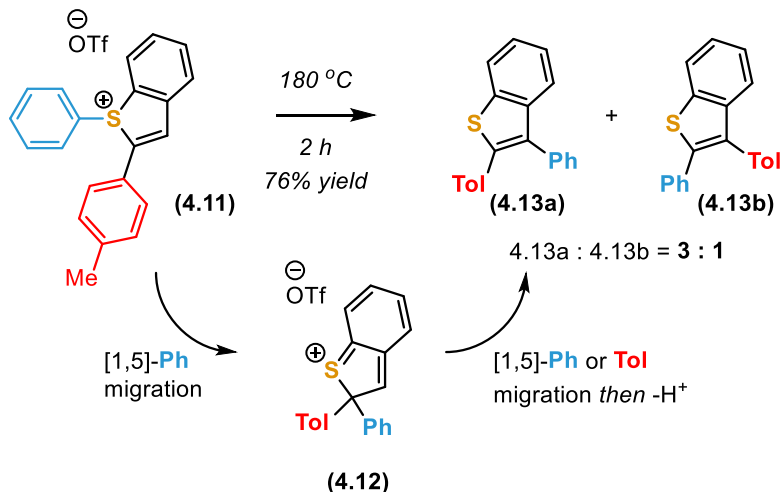
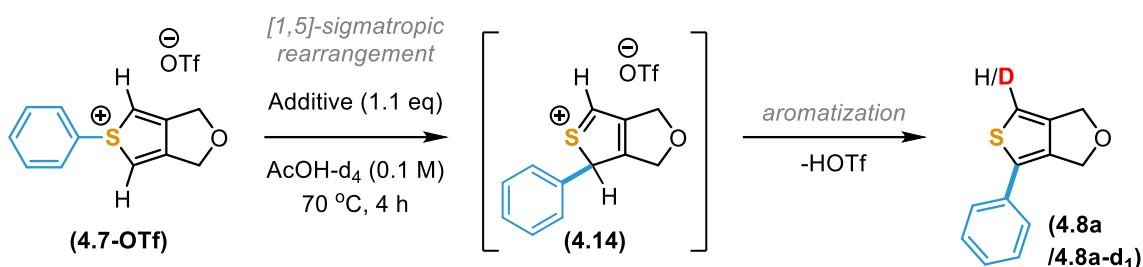


Figure 61 The thermal rearrangement of S-aryl benzo[b]thiophenium salts. A) Selective migration of the phenyl group at the 2-position. B) Unselective migration when employing 2-tolyl substituted benzo[b]thiophenium salts suggesting a [1,5]-sigmatropic rearrangement mechanism.

In contrast to the benzo[b]thiophenium species studied by Kitamura whose rearrangement proceeds by dearomatization of the benzene ring, the rearrangement of S-phenyl thiophenium salt of type **4.7-OAc-d_(3/5)** do not, which explains the lower temperature required (70 °C). A similar mechanism is likely at play with the simpler S-phenyl thiophenium salt, that is a [1,5] sigmatropic rearrangement followed by aromatization of the thiophene core. Furthermore, selective migration at the 2-position is in line with the expected reactivity of this species. To establish if the rearrangement observed with thiophenium salt **4.7-OAc** is heat-induced and does not require the presence of silver, a control experiment was performed utilizing an isolable

version of the thiophenium salt possessing a triflate counteranion (see section 4.13 for more details).^b Indeed the thiophenium triflate salt **4.7-OTf** cleanly underwent rearrangement in AcOH-d₄ providing the expected thiophene **4.8a/4.8a-d₁** product in a quantitative yield after 4 h of heating at 70 °C (Table 12).

Table 12 The thermal rearrangement of thiophenium triflate salt **4.7-OTf**.



Entry	Additive	Yield (%)	Deuteration (%)
1	-	Quantitative	96
2	Pyridine	Quantitative	11

When no basic additives are present the thiophene α -hydrogen was almost exclusively deuterated (entry 1). It was hypothesized that the deuteration was caused by formation of triflic acid upon aromatization of intermediate **4.14**. This is in line with the acid-catalyzed hydrogen exchange seen with substituted thiophenes¹¹⁰ and as can be expected, the addition of pyridine as an additive decreased the deuteration to 11% (entry 2). Furthermore, a control study on thiophene **4.8a** indicates that deuteration of the α -hydrogen in AcOH-d₄ occurs at room temperature in the presence of triflic acid (Figure 62).

^b The thiophenium triflate salt (**4.7-OTf**) was isolated by precipitation with a mixture of acetone and ether (1:1) therefore traces of silver might still be present.

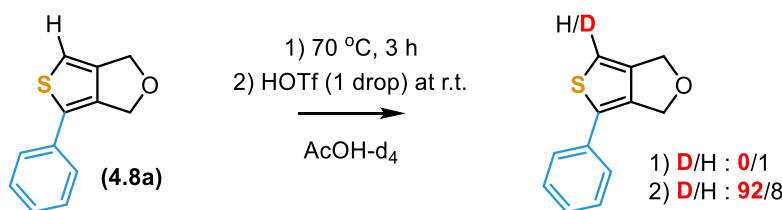


Figure 62 Triflic acid-induced deuteration of thiophene **4.8a** in AcOH-d_4 .

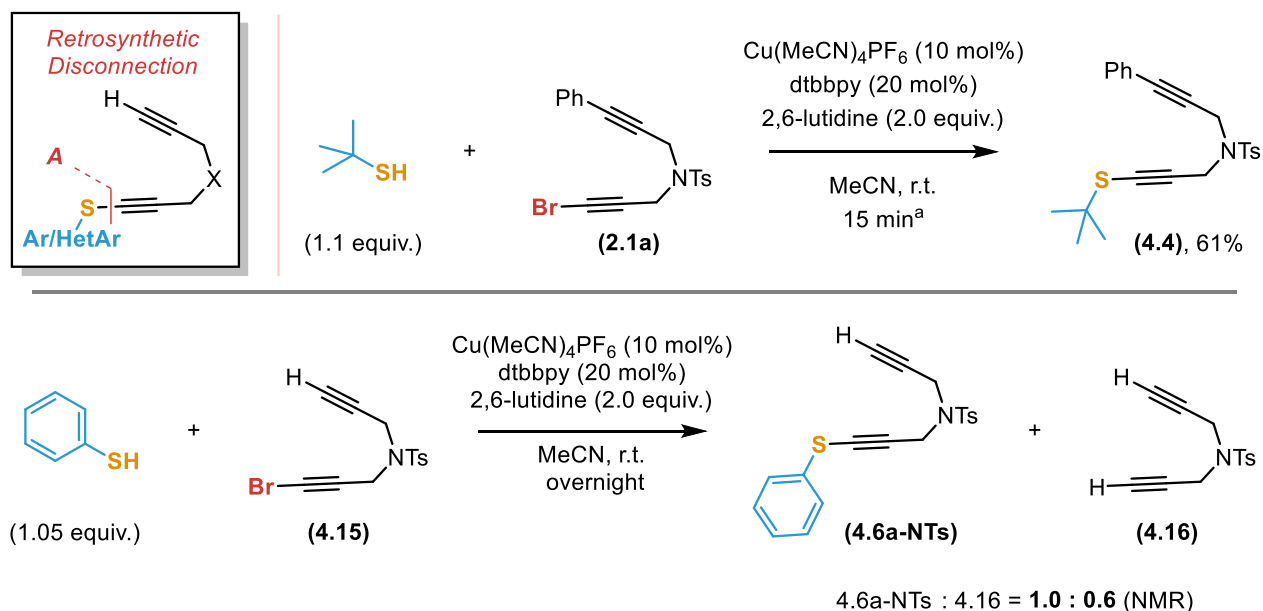
Overall, these experiments suggest that the rearrangement of thiophenium salts of type **4.7** is heat-induced and likely occurs by the mechanism proposed. Additionally, these control studies suggest that the deuteration observed at the α -hydrogen of thiophene **4.8a/4.8a-d₁** occurs along the reaction pathway (see Figure 58). This is true unless the presence of silver salts causes deuteration of the α -hydrogen of thiophene **4.8a**.

4.8 Challenges associated with the synthesis of *S*-aryl derivatives

With the limited literature on the [1,5]-sigmatropic rearrangement of *S*-Aryl benzo[*b*]thiophenium salts (aryl only Ph and *p*-Tol),¹⁰⁹ an investigation of the reaction scope utilizing *in-situ* formed *S*-Aryl thiophenium salts of type **4.7** was undertaken. First, the synthesis of *S*-Aryl substituted yne-alkynyl sulfides was tackled. The synthesis of yne-alkynyl sulfides was briefly covered in section 3.1 and as discussed, it varied depending on the targeted substrates. Since the interest had shifted towards evaluating the reactivity of aryl and/or heteroaryl substituted alkynyl sulfides, the first strategy investigated was to form the key $\text{C}_{\text{sp}}\text{-S}$ bond as it would provide a way to rapidly modify the *S*-Aryl unit (Figure 63).

Collins et al's method,⁷⁵ was previously used by our group to synthesize *S*-*tert*-butyl substituted yne-alkynyl sulfides.⁸¹ For instance, bromoalkyne precursor **2.1a** was coupled in just 15 minutes with *tert*-butyl thiol under Cu(I) catalysis yielding yne-alkynyl sulfide **4.4** in 61% yield. Additionally, the group of Collins demonstrated that the method was tolerant to the use of

thiophenol as well as *p*-methoxy and *p*-fluorobenzene thiols. Although only a limited number of examples were provided by Collins et al, the simplicity of the reaction conditions prompted the use of this method. When attempting to perform an analogous reaction utilizing a previously synthesized precursor **4.15** with thiophenol as the nucleophile, a mixture of two products was observed by NMR which were associated with the desired yne-alkynyl sulfide **4.6a-NTs** as well as by-product **4.16** who was present in significant amount (1.0 : 0.6 ratio) (See Supporting Information section 7.5.7 for more details). The two being similar in *R_f*, isolation of yne-alkynyl sulfide **4.6a-NTs** was difficult and therefore an alternative approach had to be envisaged (Figure 64).



^aSubstrate synthesized during our study on the thermal rearrangement of yne-alkynyl sulfides.⁸¹
Figure 63 Initial synthetic approach for the synthesis of *S*-phenyl yne-alkynyl sulfide bearing a terminal alkyne.

We hypothesized that if a polar intermediate propargyl alcohol **4.18a** was made instead from the coupling of thiophenol with bromo-propargyl alcohol **4.17** then the purification would be easier as any by-products formed would be either volatile (ex: propargyl alcohol) or apolar

(phenyl disulfide).^c Gratifyingly, this strategy enabled for the multi-gram synthesis of model substrate **4.6a** with a combined two-step yield of 46% (2.80 g obtained). With this procedure in hand, the copper-catalyzed coupling with electron poor phenyl thiols was investigated next (Figure 65).

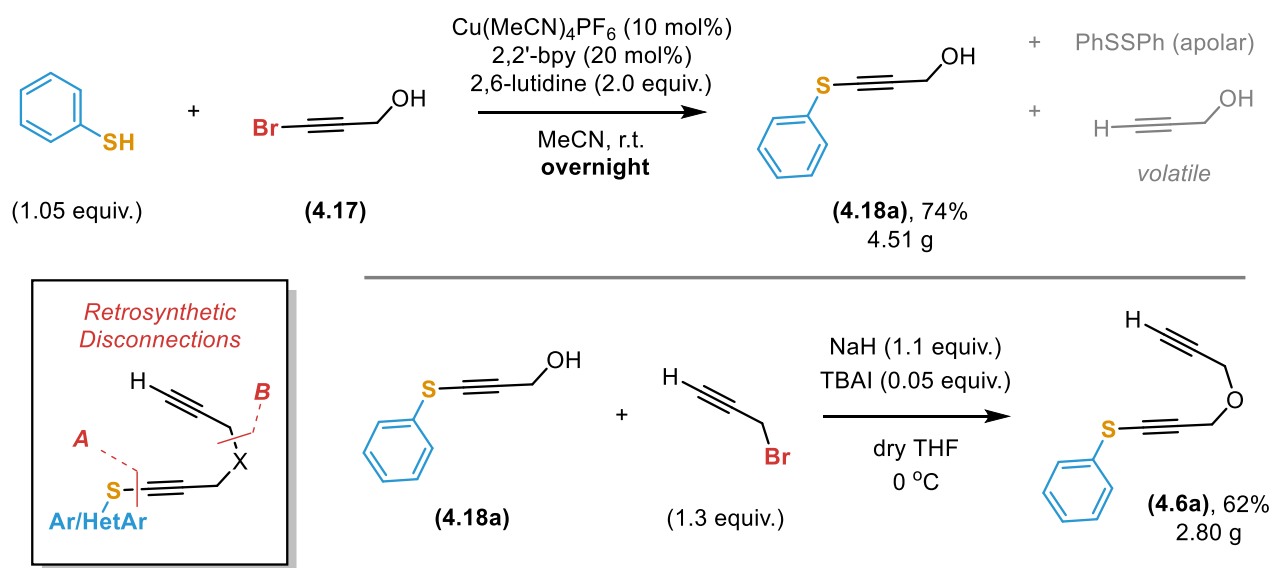
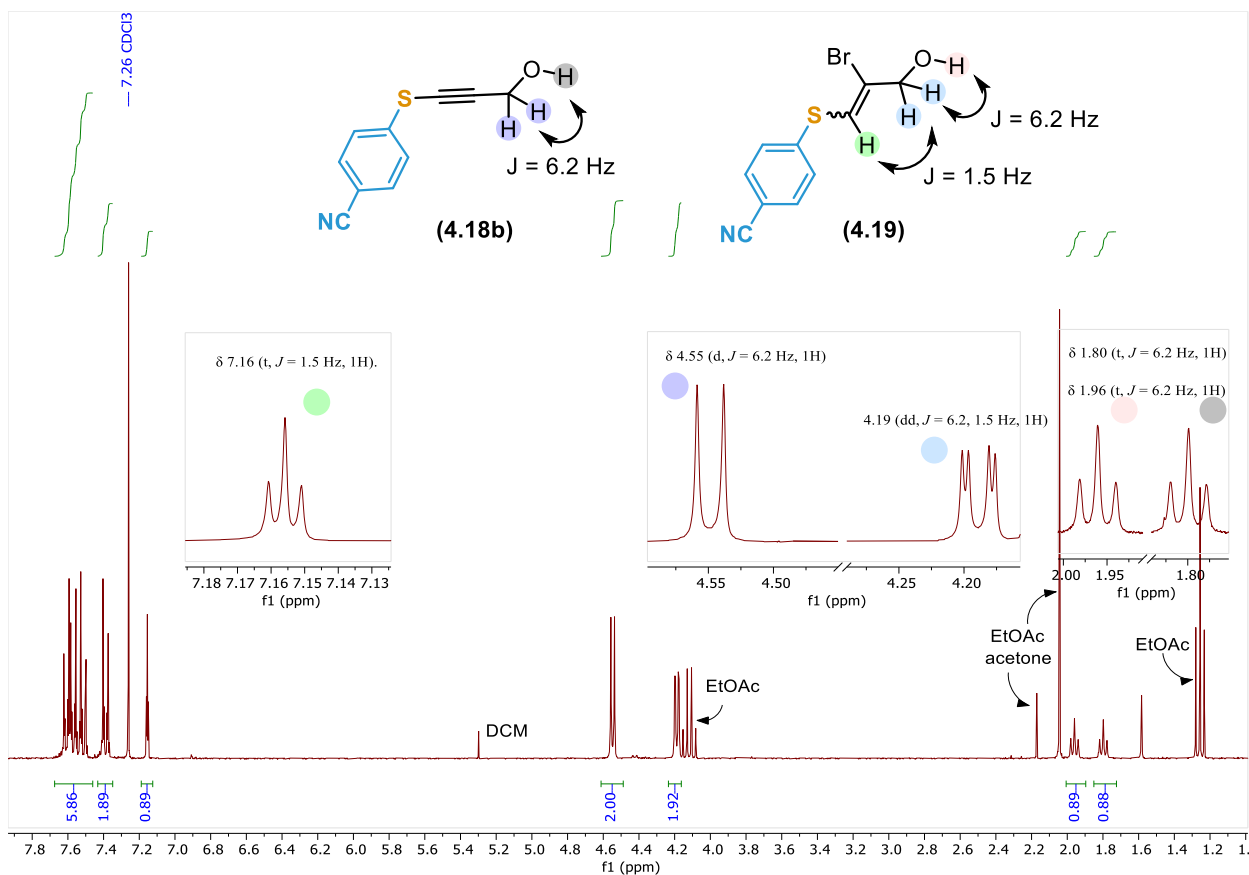
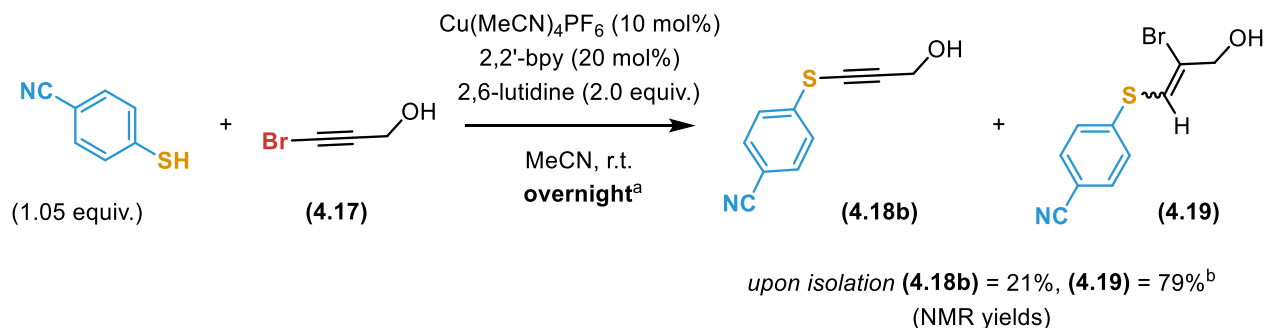


Figure 64 A stepwise approach : Collins's coupling followed by a substitution reaction.

Unfortunately, when 4-cyanobenzenethiol was used, the desired propargyl alcohol **4.18b** was obtained as a minor product alongside a vinyl-sulfide **4.19** as the major product. The presence of bromine was quickly determined by LR-MS (APCI) and the regioisomer shown is proposed due to the coupling constants observed by NMR (Figure 65). As can be expected, separating the two species was not possible by flash chromatography as all the fractions collected contained a mixture of the two products. Interestingly, only one stereoisomer is observed. The allylic coupling constant found of 1.5 Hz suggests that a *cis* configuration is more probable (*J*_{trans} for allylic alcohols around 1.25 Hz). The rationalization for the formation of this by-product was

^c The formation of disulfides is often observed as a by-product in these coupling reactions.

not further investigated and it was concluded that the coupling method developed by the group of Collins is not compatible with electron-poor aromatic thiols.



^aThe reaction was performed at the 8.00 mmol scale and purified by flash chromatography using hexanes:EtOAc = 7:3. ^bAll the fractions collected resulted in a mixture of **4.18** and **4.19** with ratios varying from 0.13 : 1 to 1 : 1 respectively. The approximate yield were determined by NMR analysis of the fractions.

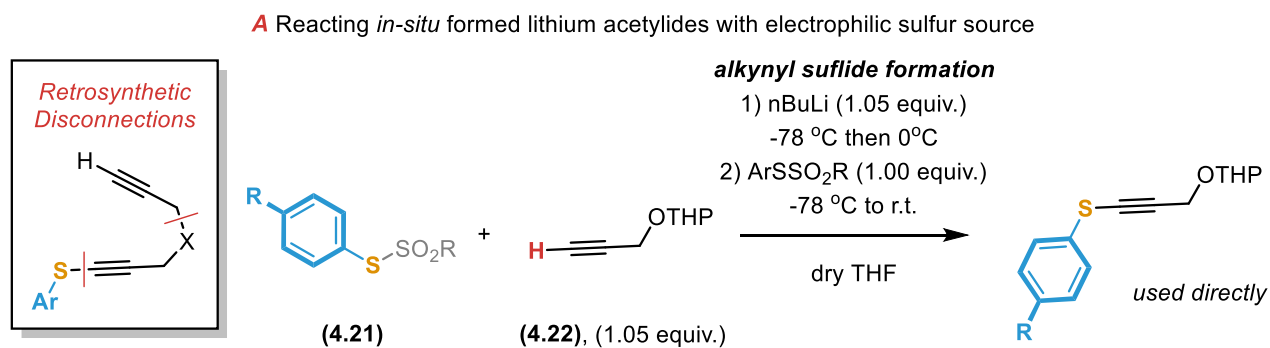
Figure 65 Formation of a vinyl-sulfide by-product when utilizing 4-cyanobenzenethiol as the coupling partner.

4.9 Accessing *para*-substituted aryl derivatives utilizing a sulfur umpolung strategy

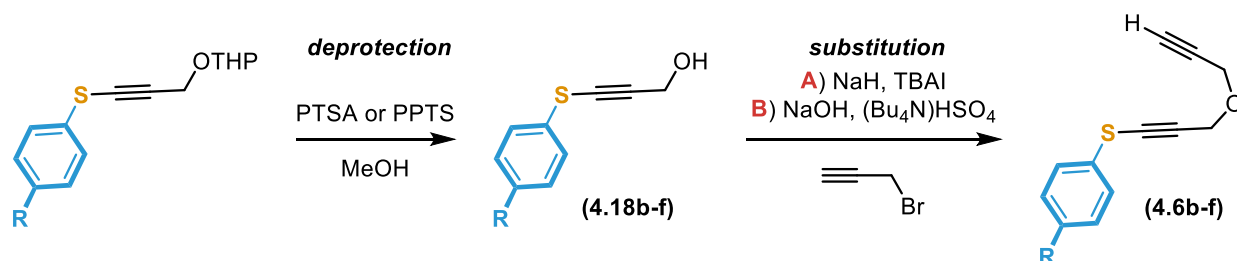
This unprecedented result led to revisiting our synthesis approach and we soon realized that there is no general method for the synthesis of a broad scope of *S*-Aryl and/or *S*-Heteroaryl substituted alkynyl sulfides. Although a variety of methods have been described for the synthesis of alkynyl sulfides,⁴⁰ the synthesis of *S*-Aryl alkynyl sulfides is often limited to electron-rich phenyl derivatives^{75, 111, 112} and examples of heteroaryl-substituted alkynyl sulfides are even more rare.⁷⁶ Due to this lack of scope investigation for these aryl derivatives, it was decided that a safer approach would be to use the classical sulfur umpolung approach utilizing electrophilic sulfur sources (Figure 66). Mila Gorodnichy and I utilized this retrosynthetic strategy to synthesize both electron-rich and poor *S*-phenyl substituted alkynyl sulfides.

Essentially, the strategy was the same as previously, except instead of generating the alkynyl sulfide bond by a copper-catalyzed coupling, this key bond was synthesized by reacting an *in-situ* generated lithium acetylide onto electrophilic sulfur sources (thiosulfonates or disulfides). A THP-protected alcohol **4.22** was therefore synthesized as well as various *S*-(aryl) thiosulfonates reagents **4.21** (Figure 66, A). All of them reacted well producing *S*-aryl substituted alkynyl sulfides **4.18b-f** upon deprotection of the THP group (Figure 66, B). Although the yields were quite different across the thiosulfonates used (47%-88%) this sulfur umpolung method was found to be tolerated by a variety of electron-poor and rich phenyl derivatives (Figure 66, C). The yne-alkynyl sulfides **4.6b-f** were then made by substitution onto propargyl bromide. Although the *p*-OMe derivative provided a high yield for the corresponding yne-alkynyl sulfide (79%) utilizing conditions **A** (NaH as base), the *p*-NO₂ derivative didn't and a low yield for the corresponding yne-alkynyl sulfide was obtained (12%). For this reason, conditions **B** (NaOH as base) were later used

instead providing moderate to good yields (37-80%) for the rest of the yne-alkynyl sulfides synthesized (Figure 66, C).



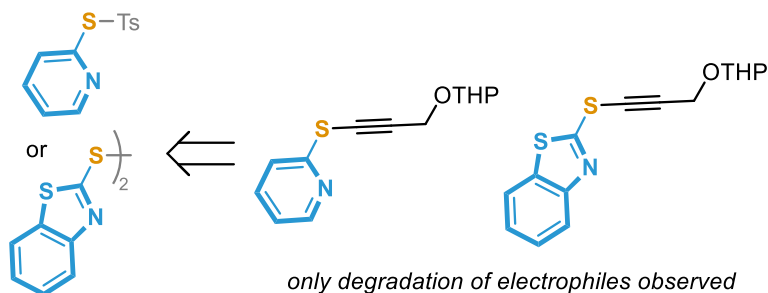
B Formation of yne-alkynyl sulfides **4.6b-f** by a deprotection and substitution sequence



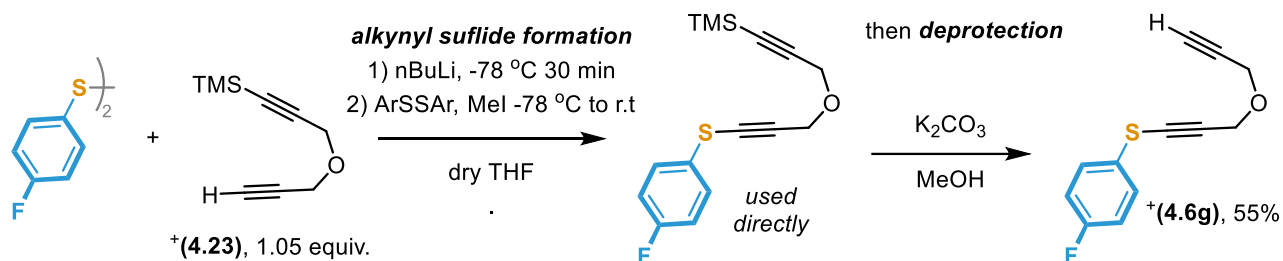
C Yields obtained

(4.18b-f)	(4.6b-f)
R	R
OMe, 55%	OMe, 79% -A
Me, 78%	NO ₂ , 12% -A
CF ₃ , 88%	Me, 80% -B
+CN, 47%	CF ₃ , 46% -B
NO ₂ , 85%	+CN, 37% -B

D Attempt to synthesize S-Heteroaryl substituted alkynyl sulfides



E Alternative two-step approach utilizing a TMS-substituted diyne **4.23**



See Supporting Information section 7.5.5 for more details. *Synthesis done by Mila Gorodnichy.

Figure 66 Using electrophilic sulfur sources for the synthesis of electron-poor and rich phenyl substituted alkynyl sulfides. A) Using the classical sulfur umpolung approach for para-substituted S-phenyl substituted alkynyl sulfides. B) Deprotection and propargylation procedures for yne-alkynyl sulfides **4.6b-f**. C) Yields obtained for the THP-protected alcohols and the final yne-

thioalkynes substrates. D) Attempt to expand the method to heteroaryl-substituted alkynyl sulfides. E) Using a TMS substituted diyne as an alternative precursor for yne-alkynyl sulfides.

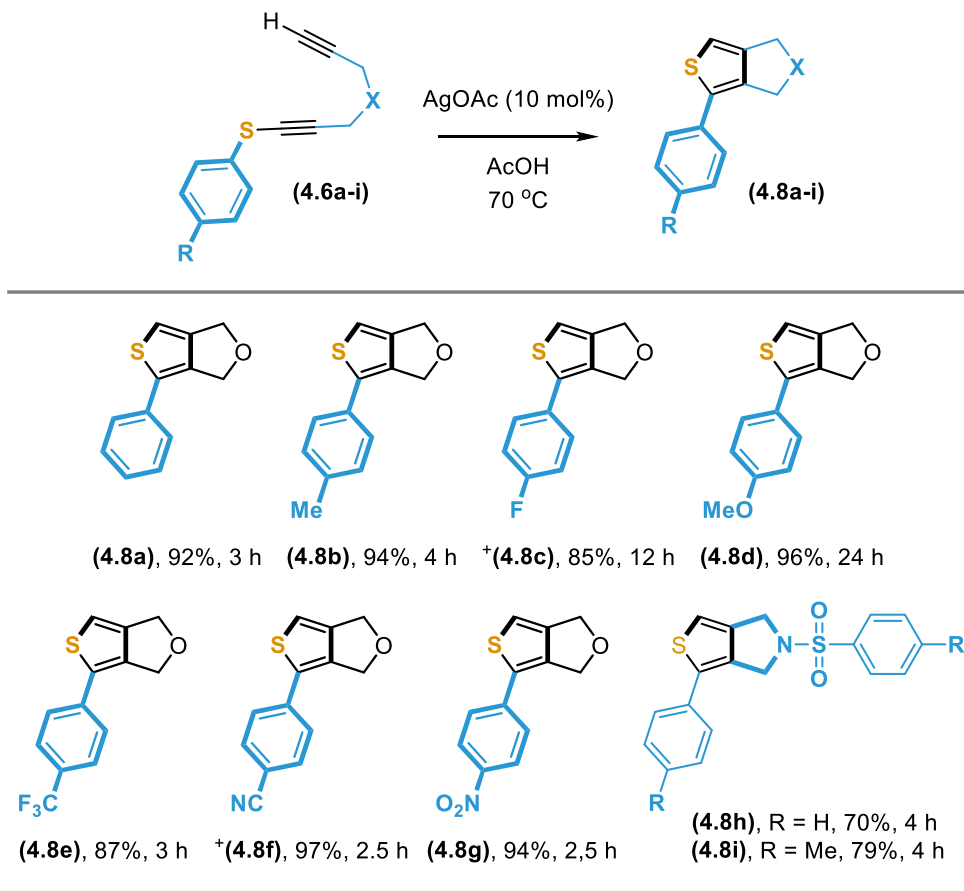
Although this method was found to be extremely useful for the synthesis of both electron-rich and electron poor phenyl derivatives, attempt to synthesize *S*-heteroaromatic alkynyl sulfides only led to degradation of the electrophilic sulfur sources (Figure 66, D). Finally, to avoid the often low-yielding substitution reactions, the terminal alkyne can be pre-installed by utilizing a TMS-substituted alkyne **4.23** instead of the THP-protected alcohol **4.22** (Figure 66, E).

4.10 Synthesis of 2-Aryl substituted thiophenes *via* thiophenium intermediates

Since we were interested in the rearrangement of *in-situ* formed thiophenium salts of type **4.7**, these *S*-(Aryl) yne-alkynyl sulfides (**4.6a-i**) were directly heated at 70 °C in AcOH in the presence of catalytic AgOAc (Table 13). These results were performed by Mila Gorodnichy and myself. To our delight, model substrate **4.6a** gave an excellent isolated yield of thiophene **4.8a** (92%) following this simplified procedure. *S*-Phenyl derivatives containing electron-donating groups also provided the desired 2-aryl substituted thiophenes **4.8b-d** (42-95%). The methoxy and fluoro derivatives required however significantly longer reaction times.^d Electron-poor aryls were also well tolerated as excellent yields for thiophenes **4.8e-g** were observed (87-97%). Changing the model ether linker by a sulfonamide linker resulted in the formation of thiophenes **4.8h,i** in good yields (75-79%) without affecting the rate of the reaction.

^dWhen following the reaction for the methoxy derivative, consumption of the intermediate thiophenium salt was not observed after 6 h therefore it was left to run overnight. The reaction seemed however almost to completion at the 6 h mark, so the reaction time is likely closer to 6 h than 24 h.

Table 13 Synthesis of 2-aryl substituted thiophenes by the rearrangement of *in-situ* formed thiophenium intermediates.



⁺Examples by Mila Gorodnichy.

To confirm the intramolecular nature of the rearrangement, a cross-over experiment was carried out between an equimolar amount of structurally comparable yne-alkynyl sulfides **4.6h** and **4.6i** (Figure 67). Since both substrates react at the same rate (*vide-supra*), they are suitable candidates for the experiment as the *in-situ* formed thiophenium salts will be heated together in the same pot. NMR and HRMS analysis shows the formation of a mixture of thiophenes **4.8h** and **4.8i** with no evidence for the formation of cross-over products **4.8j,k** therefore an intermolecular pathway can be ruled out. The cross-over products have the same mass which was not detected by HRMS of the reaction crude. Additionally, NMR analysis showed a 1 : 1 mixture of thiophenes **4.8h** and **4.8i** with no additional peaks suggesting the formation of any of other thiophene

products. NMR overlap with cross-product **4.8j** which was previously synthesized by our group⁸¹ showed that it was not formed which supports the HRMS analysis done (see Supporting Information section 7.5.18 for more details).

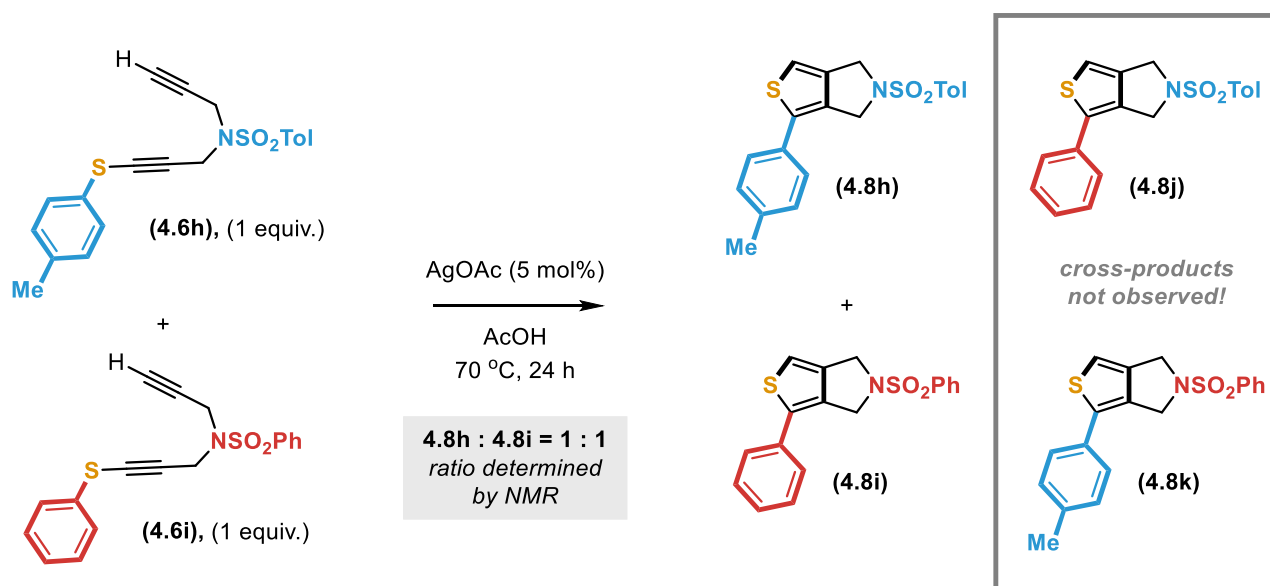
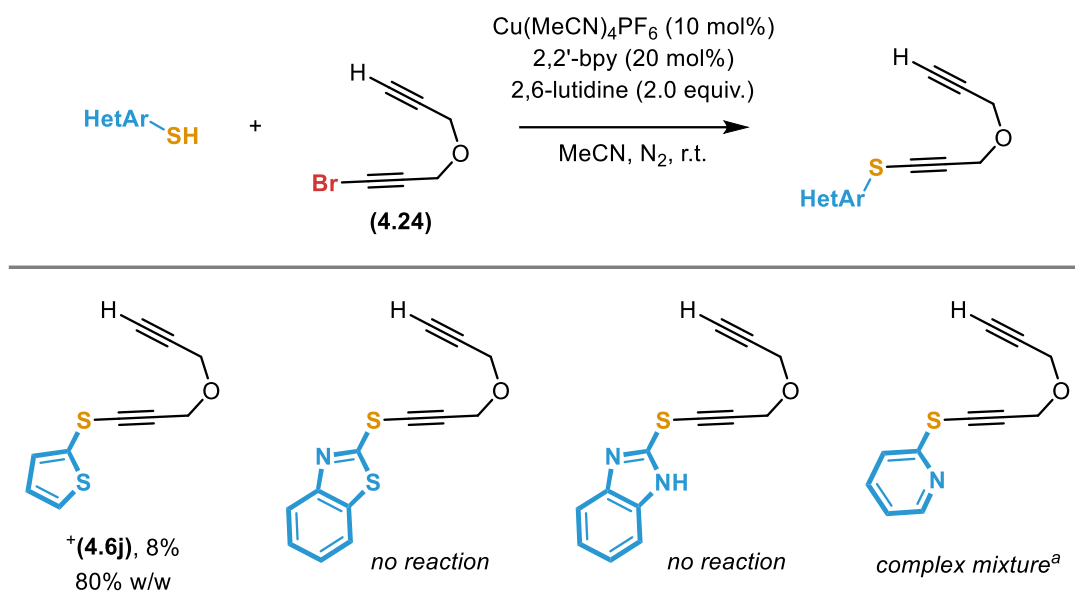


Figure 67 Cross-over experiment for the rearrangement of *S*-(Aryl) thiophenium salts.

4.11 Efforts toward the synthesis of *S*-(Heteroaryl) derivatives

Seeing that both electron-rich and poor *S*-(phenyl) derivatives provided the corresponding 2-aryl substituted thiophenes by the intermediacy of thiophenium salts we wondered if this method could be extended to heterocycles. Although Collins et al. method was not suitable for the synthesis of electron-poor *S*-(phenyl) alkynyl sulfides, we hoped that thiols bearing electron-rich heterocycles may be suitable cross-coupling partners (Figure 68). Mila Gorodnichy found that the 2-mercaptothiophene substrate underwent coupling with bromoalkyne **4.24** however a low yield for thiophene-substituted yne-alkynyl sulfide **4.6j** was obtained (8%). Additionally, the coupling reaction generated many by-products making purification difficult. As a result, a purity of 80% (w/w) was estimated for yne-alkynyl sulfide **4.6j**. Benzothiazole and benzimidazole

derivatives were however not accessed using this method as no reaction was taking place when the corresponding heteroaromatic thiols are used. On the contrary, using electron-deficient mercaptopyridine only resulted in a complex mixture (See Supporting Information section 7.5.9 for more details).



⁺Result by Mila Gorodnichy. ^aDMF was used instead of MeCN.

Figure 68 Using heteroaromatic substituted thiols in S-C_{sp} cross-coupling reactions.

These results are not surprising as very few examples of S-(heteroaryl) substituted alkynyl sulfides are reported in the literature. A method described by Waser et al. utilizing ethynyl benziiodoxolone (EBX) reagents as electrophilic reagents represents one notable exception. EBX substituted alkynes efficiently couple with thiols in the presence of tetramethylguanidine (TMG) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a base (Figure 69).^{76, 77} Their first report utilizing TIPS-EBX substituted alkynes was found to be tolerant to many aromatic thiols including electron-rich heterocycles. For instance, heteroaromatic benzimidazole product **4.25** was obtained with a 94% yield. No examples of electron-poor heterocycles were mentioned, however.⁷⁶ Their second

report expanded their scope of EBX reagents, to aliphatic alkynes such as **4.26** and **4.27** however the use of heteroaromatic thiols as coupling partners was not evaluated.⁷⁷ Although using Waser's method may have enabled for more *S*-(heteroaryl) yne-alkynyl sulfides to be synthesized, there is no certainty of reaction success. Overall, there is no general method for the synthesis of a broad scope of *S*-((het)aryl) alkynyl sulfides which renders it difficult to study their reactivity.

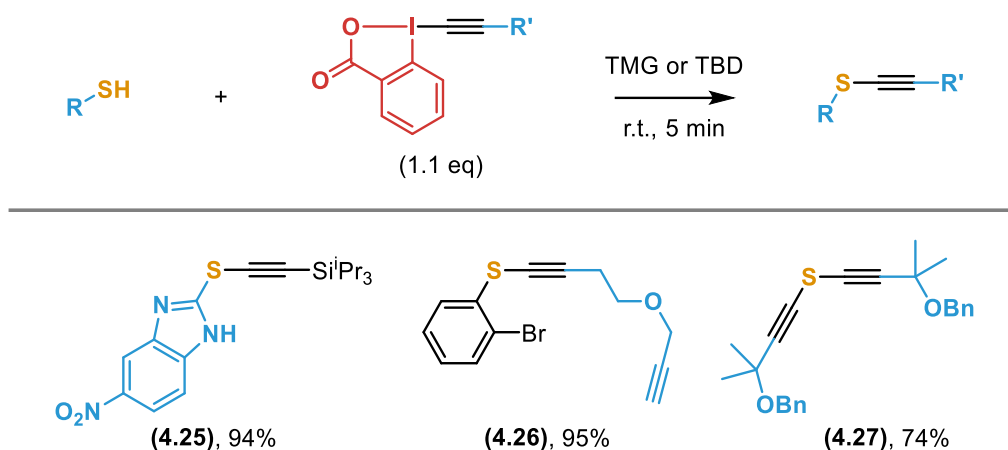


Figure 69 EBX-reagents for the formation of alkynyl sulfides.

Nevertheless, Mila Gorodnichy found that thiophenyl derivative **4.6j** efficiently cyclized under the optimized reaction conditions towards bis-thiophene **4.8l** ($\approx 73\%$ yield) (Figure 70).

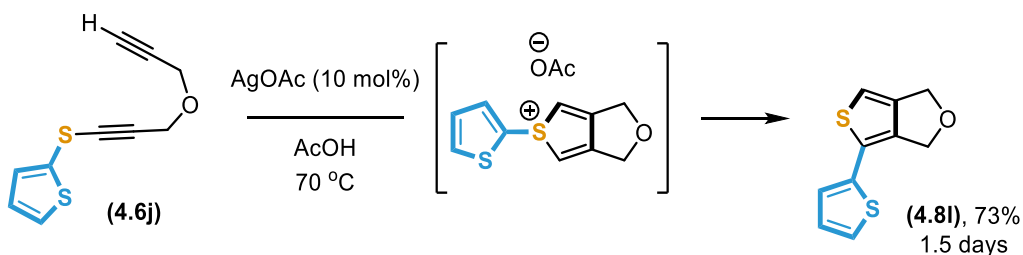


Figure 70 The cyclization and rearrangement of *S*-(thiophenyl) substituted alkynyl sulfide.

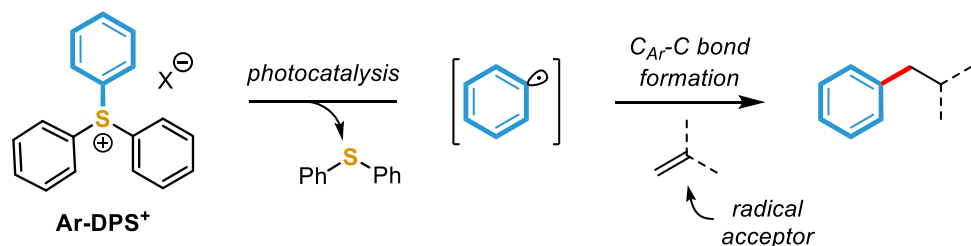
4.12 Current limitations associated with the synthesis of *S*-(Aryl) sulfonium salts

The intramolecular rearrangement of anti-aromatic *S*-(phenyl) thiophenium and benzothiophenium salts are, in part, driven by the cleavage of a weaker $C_{Ar}-S^+$ bond and formation of a stronger $C-C_{Ar}$ bond. Additionally, the resulting products are stable aromatic substituted (benzo)thiophenes. The chemistry seen with related sulfonium salts however goes far beyond sigmatropic rearrangements. The utility of *S*-(Aryl) sulfonium salts in organic synthesis have been rediscovered in the realm of cross-coupling reactions and photoredox catalysis.¹¹³⁻¹¹⁵ Additionally, their reactivity as acceptors in EDA complexes has recently been reviewed.¹¹⁶ Despite the transformation, *S*-(Aryl) organo-sulfur^(IV) compounds act as linchpins for the formation of new $C_{Ar}-C$ and $C_{Ar}-X$ bonds by cleavage of their weak $C_{Ar}-S^+$ bond.

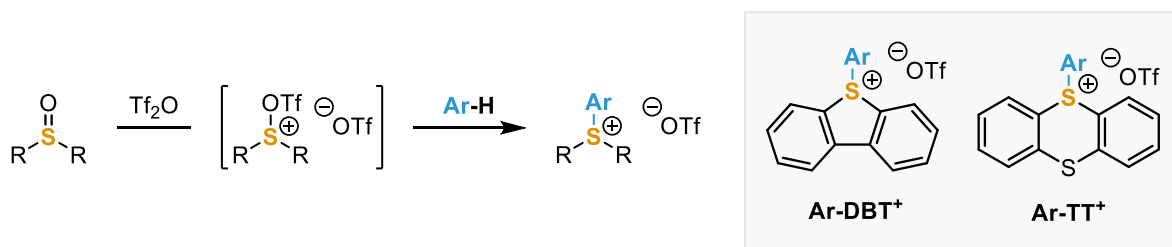
Although the use of sulfonium salts in photoredox reactions represents one of the earliest reports of photoredox catalysis,^{117, 118} the ability of *S*-(Aryl) sulfonium salts to cleanly form new $C_{Ar}-C$ bond by photoinduced processes appeared in 2013 when Fensterbank, Goddard, Olliver et al. utilized diphenylsulfonium salts (**DPS**⁺) as precursors for aryl radicals (Figure 71, A).¹¹⁹ Modern *S*-(Aryl) sulfonium reagents are dibenzothiophenium (**DBT**⁺) and thianthrenium (**TT**⁺) salts who can be easily synthesized from their corresponding sulfoxides. Activation of the sulfoxides by an acid anhydride (such as Tf_2O) generates a reactive $S^{(IV)}$ intermediate which undergoes electrophilic aromatic substitution (S_EAr) with arenes (Figure 71, B).¹²⁰⁻¹²² Although impressive selectivity for C-H functionalization is seen, especially with thianthrenium derivatives,¹²³ the scope of aromatic compounds that can undergo this C-H functionalization reaction is limited by their ability to react via electrophilic aromatic substitution (S_EAr) (Figure 71, C). This means that the sulfonium salts generated are generally limited to electron-rich (hetero)aromatics. Electron-

poor arenes such as trifluoromethylbenzene are too electron-poor to react¹²² while benzofuran represents the upper limit of nucleophilicity. For example, electron-rich indole derivatives cannot be accessed using this strategy as reduction of the sulfoxide is observed instead.¹²¹

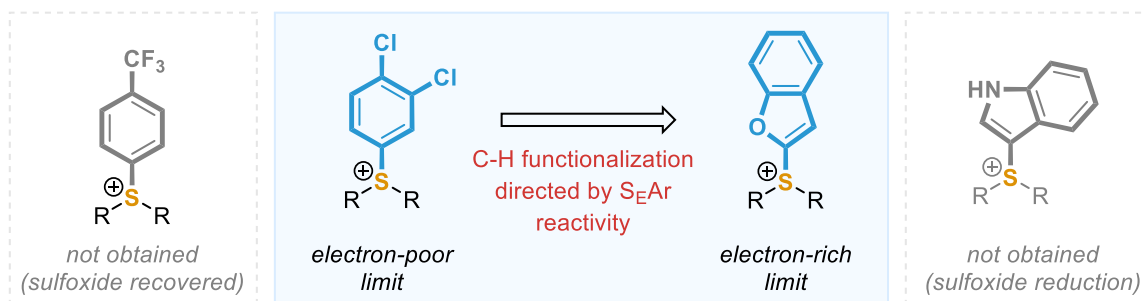
A Diphenyl sulfonium salts (DPS⁺) as radical precursors



B The synthesis of most commonly utilized S-(aryl)-sulfonium salts



C Limitations associated with the C-H functionalization strategy



D A novel approach for the synthesis of S-(aryl)-sulfonium salts

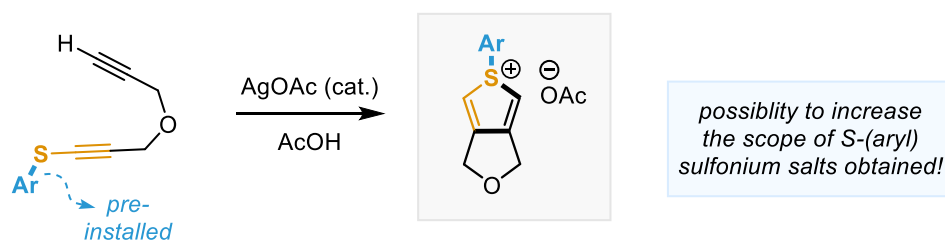


Figure 71 Triarylsulfonium salts as radical precursors and the limitations associated with the synthesis of modern S-(Aryl) sulfonium salts. A) S-phenyl substituted diphenylsulfonium salts as radical precursors for new C-C bond formation. B) Commonly employed method for the synthesis of modern sulfonium salts. C) Scope limitations observed with the C-H functionalization strategy. D) Novel route towards the synthesis of S-(Aryl) sulfonium salts.

On the other hand, the synthesis of *S*-(Aryl)-sulfonium salts via a silver-catalyzed (3+2) cycloaddition of yne-alkynyl sulfides would provide a completely novel route toward potentially useful electrophilic reagents (Figure 71, D). The pre-installation of the arene ring may enable for a broad range of *S*-(Aryl)-sulfonium salts to be synthesized as their access would no longer rely on S_EAr reactivity. Excited by this possibility, we turned our attention toward the isolation of the thiophenium specie.

4.13 The isolation of a previously unreported *S*-(phenyl) thiophenium salt **4.7-OTf**

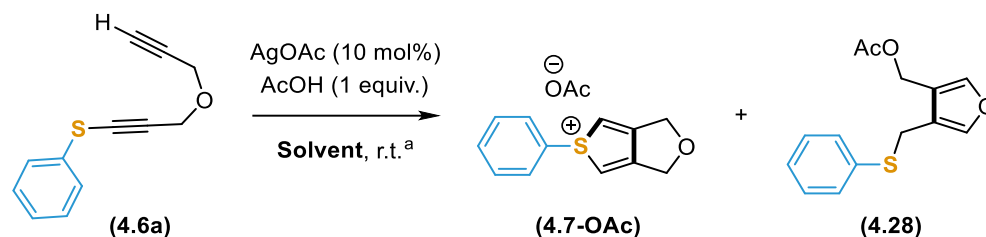
Challenges associated with isolation of the model *S*-(phenyl) thiophenium acetate salt **4.7-OAc** were however faced. Precipitation of the salt from acetic acid was difficult due to its high solubility and although removal of the acetic acid by rotatory evaporation can be done easily, it required prolonged heating which prompted the rearrangement of the thiophenium to occur. Its high polarity and solubility in water rendered isolation by column chromatography and/or liquid-liquid extraction less attractive and attempts to do so were not successful. For these reasons, an investigation of new reaction conditions was conducted and is presented herein.

As shown previously, using acetic acid as the solvent dramatically increased the reaction rate for the metal-catalyzed (3+2) of *S*-(alkyl) alkynyl sulfides (Table 14). This reaction speed was found to be of high importance for the isolation of the thiophenium salt as prolonged reaction time results in rearrangement (aryl migration) over time. The goal was therefore to find reaction conditions with a similar rate while limiting or completely avoiding using acetic acid as it rendered precipitation difficult. For instance, the use of an alcohol solvent with a lower boiling point may facilitate isolation of the thiophenium salt as it can be easily removed by rotatory evaporation at room temperature. Additionally, Dominic Campeau previously found that the use of protic

solvents such as ethanol, instead of aprotic ones such as DCM, increased the rate of the reaction (Table 11). We therefore hypothesized that using acidic trifluorinated alcohol solvents would increase the reaction rate even more.

A new set of reaction conditions was therefore tested utilizing now 1 equivalent of AcOH as the stoichiometric proton source and 2,2,2-trifluoroethanol (TFE) as the solvent. Gratifyingly, these modified reaction conditions resulted in complete consumption of the model substrate in just 4 hours, and a high yield for thiophenium **4.7-OAc** was obtained (89%) (entry 1). Similarly, using hexafluoroisopropanol (HFIP) instead further increased the rate of the reaction (2 h) however a furan by-product **4.28** was obtained in traces amount (5%) (entry 2). On the contrary, when the reaction is performed in aprotic solvents slow conversion of yne-alkynyl sulfide is seen and only traces of thiophenium salt **4.7-OAc** is observed by NMR (entry 3-5). Surprisingly, the formation of 2-aryl substituted thiophene **4.8a** was never observed, instead, **4.28** is detected within the complicated crude NMRs (See Supporting Information section 7.5.11 for more details).

Table 14 Finding alternative reaction conditions while limiting the use of acetic acid.



Entry	Solvent	Time	Conv. (4.6a) , (%) ^c	(4.7-OAc) , yield (%) ^c	(4.28) , yield (%) ^c
1	TFE	4 h	100	89	0
2	HFIP	2 h	100	83	5
3 ^b	CHCl ₃	ON	78	traces	11
4 ^b	EtOAc	3 days	45	traces	35
5 ^b	Acetone	3 days	73	traces	48

^aAll reactions were performed in amber vials at the 0.25 mmol scale in the indicated solvent (1 M) unless otherwise indicated. ^bReactions are performed at the 0.12 mmol scale instead. ^cConversion and yields assessed by ¹H-NMR analysis with 2.0 μ L of 1,2-DBE as NMR standard.

This furan by-product (**4.28**) may be derived from the ring-opening of thiophenium salt **4.7-OAc** by the acetate counteranion followed by isomerization to the aromatic furan cycle. Interestingly, Yoshimatsu et al. reported the formation of furan products when yne-alkynyl sulfides (as well as selenides) reacted with various nucleophiles.^{124, 125} For instance, when yne-alkynyl sulfide **4.6-a'** was stirred at room temperature with excess ammonium acetate and DBU as a base, an analogous furan product (**4.28'**) was formed in 64% yield. They propose that cyclization occurs from allene intermediates such as **4.29** formed upon isomerization at the propargylic positions.

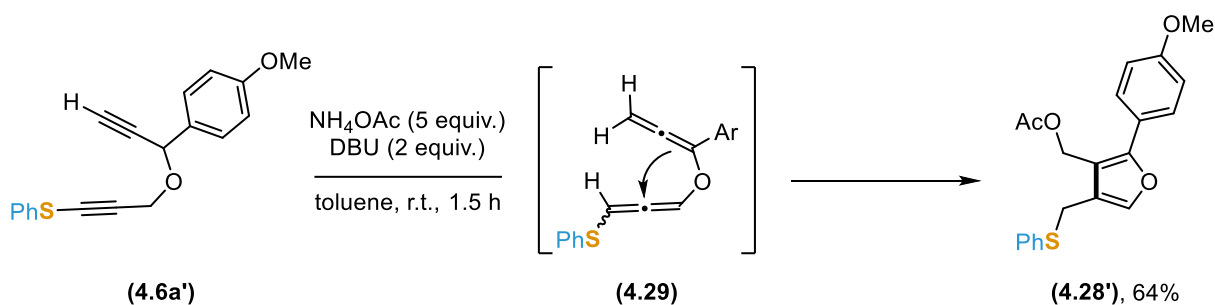


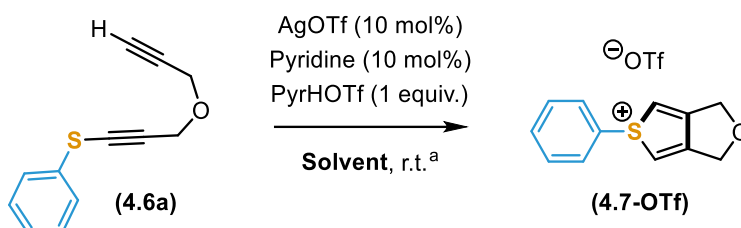
Figure 72 Base-induced cyclo-isomerization of yne-alkynyl sulfide **4.6a'** towards highly substituted furan product.

Although using acidic alcohol solvents provided a high yield for thiophenium **4.7-OAc** while limiting the formation of the furan by-product, non-nucleophilic counteranions will prevent any undesired ring opening of the thiophenium core. To completely avoid the formation of acetate, both the catalyst (AgOAc) and the protic source (AcOH) should be replaced. According to the previous optimization done with the *S*-(*tert*-butyl) derivative, AgOAc can be replaced by AgOTf as long as an exogenous base is added as well (Table 11). Additionally, it was hypothesized that pyridinium triflate (PyrHOTf) can be used as the stoichiometric proton source instead of AcOH due to their similar pK_a .

To assess the impact of these modifications, 2,2,2-trifluoroethanol (TFE, $\text{pK}_a \approx 12$) was used as solvent first as full conversion of the model substrate towards thiophenium **4.7-OAc** was seen when using the AgOAc/AcOH system. After 4 h, analysis of the crude NMR shows the formation of thiophenium **4.7-OTf** in a good 67% yield (Table 15, entry 1). It was however observed that the reaction mixture was non-homogeneous, which we believed could be detrimental to the reaction speed and yield. Although using dichloromethane (DCM) led to a completely homogenous reaction mixture, the reaction was slow and low-yielding (entry 2). Similarly, when employing acetonitrile (MeCN) as a solvent, no productive reactivity was

observed (entry 3). This observation might be related to the Lewis basicity of this solvent which favors complexation to electrophilic metallic species and might consequently reduce or quench the activity of the Ag⁺ salt in the process.

Table 15 Optimization of reaction condition for the isolation of thiophenium triflate **4.7-OTf**.



Entry	Solvent	Time	Conv. (4.6a) , (%) ^b	(4.7-OTf) , yield (%) ^b
1	TFE	4 h	89	67
2	DCM	4 h	29	6
3	MeCN	4 h	18	0
4	TFE : DCM (10 : 1)	4 h	100	89
5	MeOH : DCM (10 : 1)	4 h	44	29
6	MeOH : DCM (10 : 1)	24 h	92	52
7	TFE : DCM (10 : 1)	4 h	100	86 ^c

^a All reactions were performed in sealed reaction tubes at the 0.06 mmol scale in the indicated solvent (0.1 M). ^b Yields and consumptions were assessed by ¹H-NMR analysis after the indicated time with 2.0 μL of mesitylene as NMR standard. ^c Isolated yield, 3.50 mmol scale.

Using a mixture of TFE : DCM (10:1) was found to allow complete solubility throughout the reaction and full consumption of the substrate within 4 hours (entry 4). Attempt to replace TFE with the less acidic and nucleophilic methanol (MeOH) was found to dramatically decrease the rate of the reaction (entry 5). Running the reaction for 24 h did not lead to complete conversion of the substrate and the yield was dramatically affected (entry 6). Overall, these results strongly suggest that the acidity of the solvent is an important factor in ensuring rapid and

clean formation of the thiophenium triflate salt **4.7-OTf**. Gratifyingly, the thiophenium salt was easily precipitated from the concentrated reaction crude utilizing a mixture of acetone and diethyl ether (1:1). It could be isolated in 86% yield under the optimal conditions (entry 7). The structure of **4.7-OTf** was confirmed by NMR analysis (see Supporting Information section 7.5.12).

Monocrystals of **4.7-OTf** could be grown thus allowing single crystal X-ray diffraction studies (see Supporting Information section 7.5.13) (Figure 73, A). Similarly to previously reported *S*-(Aryl) dibenzothiophenium (DBT⁺),^{122, 126} the x-ray structure of **4.7-OTf** shows a central S atom that adopts a pyramidal geometry. The phenyl group lies perpendicular to the thiophenium core and an interaction between the S atom with the triflate counteranion is observed. Similar interatomic distances and angles are found between thiophenium triflate **4.7-OTf** and that of *S*-phenyl dibenzothiophenium triflate **Ph-DBT⁺** previously reported by Bolotin et al. (Figure 73, B).¹²⁶ For the two crystal sets of thiophenium triflate **4.7-OTf**, the average S₁-C_{Ar} bond length is 1.783 Å while that of **Ph-DBT⁺** is 1.786 Å (Figure 73, A-B). The average bond angle between the C_{Ar}-S₁-C_{cent.} (C_{cent.} is a centroid atom between the C₃ and C₄ carbons of the thiophenium core) is 117.9° which is slightly wider than that of **Ph-DBT⁺** (116.1°). Furthermore, the reduction potential of thiophenium triflate **4.7-OTf** was found to be -0.82 V (vs SCE) which is significantly more positive than that for dibenzothiophenium and thianthrene salts (Figure 73, C) (See Supporting Information section 7.5.14 for more details).^{120, 127}

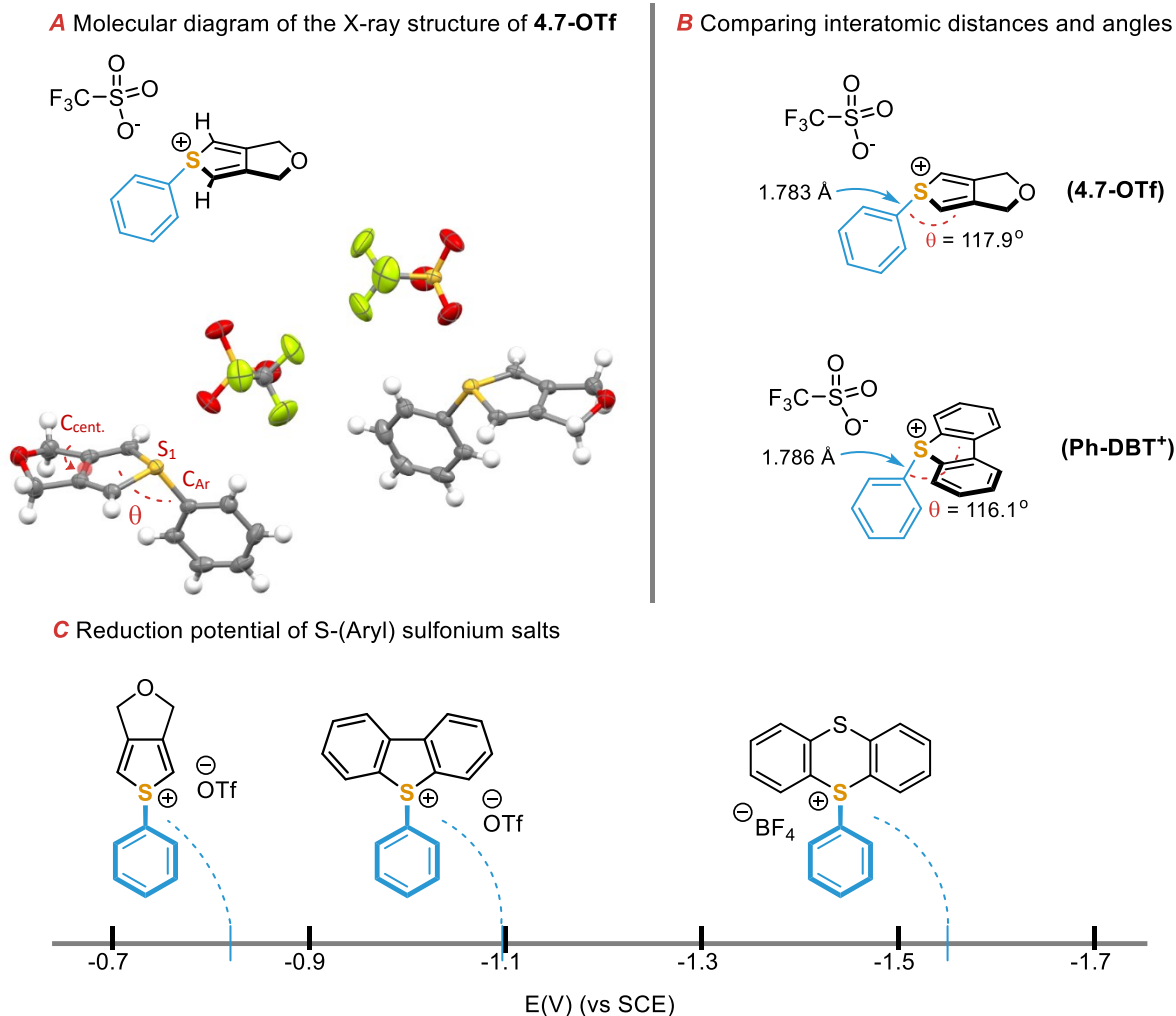


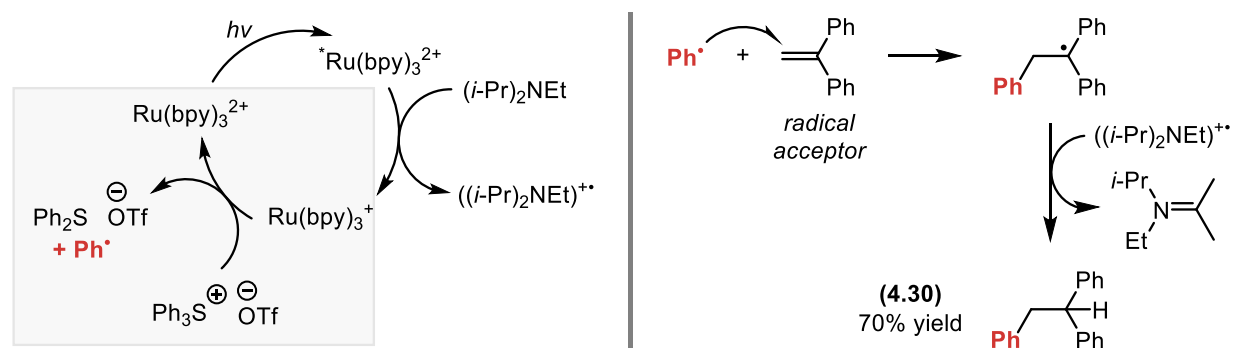
Figure 73 The geometry and reduction potential of S-(Aryl) sulfonium salts. A) Molecular structure of thiophenium triflate **4.7-OTf** as shown by X-ray. B) Comparing the interatomic distances and angles with previously reported S-(phenyl) dibenzothiophenium salt **Ph-DBT⁺**. C) The finding of a more positive reduction potential for thiophenium **4.7-OTf** as compared to the commonly employed sulfonium salts.

4.14 The compatibility of thiophenium triflate **4.7-OTf** in photoredox conditions

Excited to have obtained this bench-stable thiophenium triflate salt **4.7-OTf**, we were eager to test it for its ability to act as a mild electrophile in photoredox reactions. We first attempted to employ the reaction conditions described by Fensterbank et al. which allowed for the homolytic reduction of triarylsulfonium salt (-1.2 V vs. MSE) using $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ as a photocatalyst (Figure 74, A).¹¹⁹ The proposed mechanism for this transformation is that the

photoexcited Ru(II) catalyst undergoes reductive quench from the sacrificial electron donor (the amine). The resulting Ru(I) specie (-1.33 V vs. SCE) then reduces the triphenyl sulfonium salt which gives an aryl radical alongside diphenyl sulfide as a by-product. The phenyl radical can then be trapped by a radical acceptor (for instance 1,1-diphenylethylene) generating a stabilized radical. Subsequent hydrogen atom-abstraction (HAT) from the amine radical cation previously generated provides the final product **4.30** in 70% yield. Since the reduction potential of thiophenium salt **4.7-OTf** was found to be *ca.* -0.82V (vs. SCE), we hypothesized that reduction from the Ru(I) specie should be possible.

A Using triaryl sulfonium salts as radical precursors



B Testing the thiophenium salt **4.7-OTf** in photoredox conditions

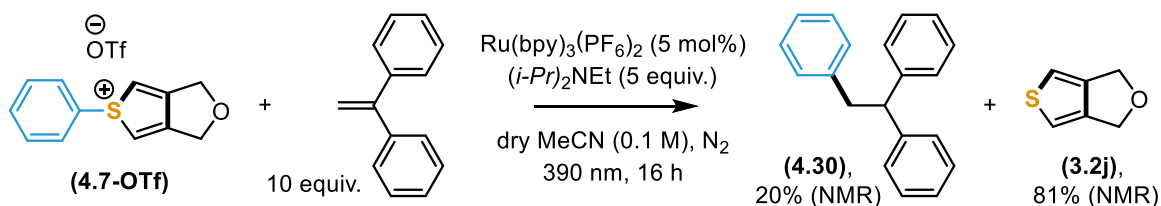
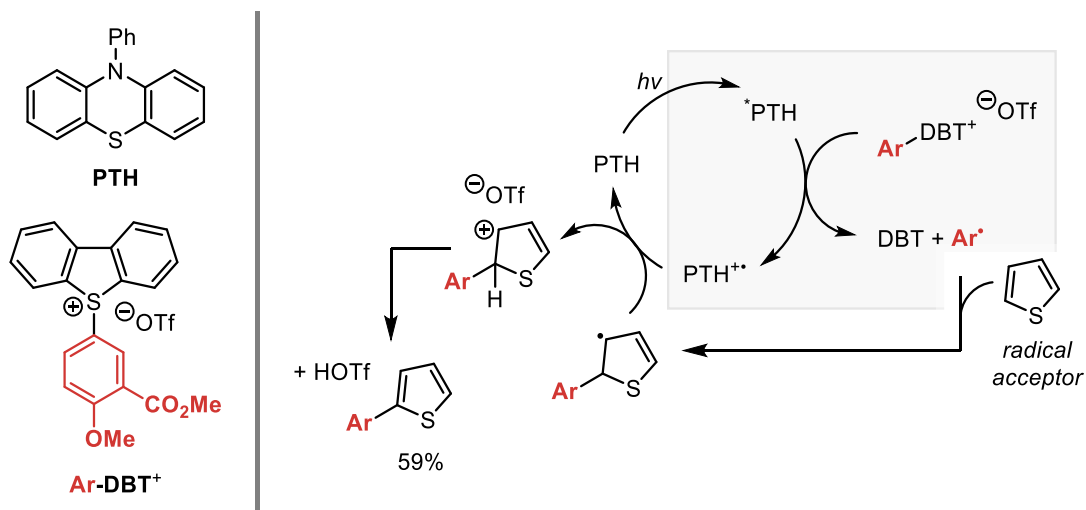


Figure 74 The reduction of sulfonium salts by metallophotoredox. A) Mechanism proposed by Fensterbank et al. B) Attempt to use the isolated thiophenium triflate salt **4.7-OTf** as aryl radical precursor instead.

When attempting to perform a similar reaction utilizing now the isolated thiophenium triflate salt **4.7-OTf** in the presence of a catalytic amount of $[\text{Ru}(\text{bpy})_3]\text{PF}_6$ led to a complex

mixture by NMR (Figure 74, B). In this mixture, the desired product **4.30** was observed in a 20% yield (NMR) alongside the 2,5-unsubstituted thiophene **3.2j** (80%) resulting from the cleavage of the S⁺-Ph bond of the thiophenium specie. Since a high yield for **3.2j** is obtained, the reduction of the thiophenium specie was likely efficient under these reaction conditions. To better understand the fate of the aryl radical generated, we turned our attention to photo redox reactions utilizing structurally similar dibenzothiophenium salts (DBT⁺) instead.

A Dibenzothiophenium salts in photoredox induced C_{Ar}-C bond formation



B Testing the use of thiophenium triflate **4.7-OTf**

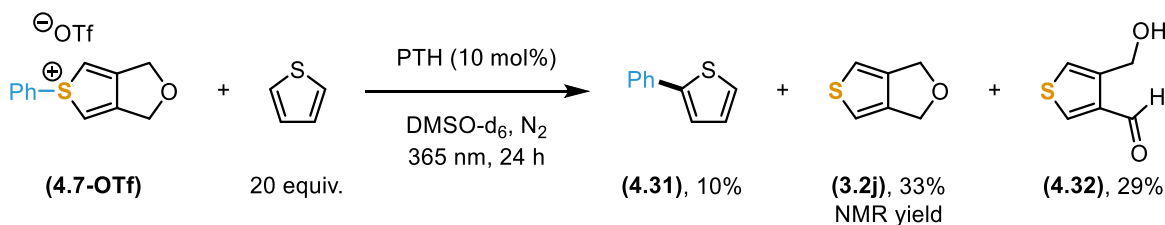


Figure 75 10-phenylphenothiazine as an organic photocatalyst for the single electron reduction of sulfonium salts. A) The use of a phenothiazine photocatalyst for the reduction of S-aryl dibenzothiophenium salts as described by Procter et al. B) Attempt to perform the radical cross-coupling reaction using thiophenium triflate **4.7-OTf** and isolation of by-product **4.32**.

The Procter group has recently reported that aryl-dibenzothiophenium salts (Ar-DBT⁺) can also be used as precursors for the formation of aryl radicals (Figure 75, A). They found that the

use of an organic photocatalyst 10-phenylphenothiazine (PTH) which has a reduction potential of -2.1V vs. SCE efficiently mediated the radical cross-coupling reaction with heteroaromatics as radical acceptors.¹²⁰ In contrast to the mechanism proposed by Fensterbank et al. which is mediated first by a reductive quench of the excited Ru²⁺ catalyst with a basic amine additive, Procter et al. propose that dibenzothiophenium salts can directly quench the excited PTH catalyst. They then propose that the resulting aryl radical generated undergoes radical addition onto the radical acceptor (ex: thiophene) generating a stabilized radical. Catalyst turnover then occurs by reductive quench from the newly formed radical intermediate and aromatization delivers the desired cross-coupled product. When thiophene was used as radical acceptor a good yield of 59% is reported by Procter and coworkers.

When performing a similar reaction using the isolated thiophenium triflate salt **4.7-OTf** we observed a complex mixture by NMR in which the 2,5-unsubstituted thiophene **3.2j** was observed in a 33% yield (NMR) (Figure 75, B). Purification of the reaction crude by column chromatography allowed to determine that the desired product **4.31** was made in a poor 10% yield. Interestingly, by-product **4.32** was isolated in a 29% yield which suggests that the ether linker was not inert under the reaction conditions. HAT between the *in-situ* generated phenyl radical and the methylene C-H bond of the linker might be competitive to addition onto the heterocyclic radical acceptor. The low yield of the bis-aryl product **4.31** obtained was therefore likely due to uncontrolled processes from the reactive aryl radicals generated. The synthesis of a thiophenium salt containing a different linker will likely be key in optimizing such photo redox reactions.

Another challenge associated with the use of thiophenium salts of type **4.7-OTf** in photoredox and/or cross-coupling reactions is that they are prone to aryl migration upon heating. Although *S*-(Aryl) sulfonium salts are excellent mild-electrophiles, the reactions that are described in the literature often require heating and/or long reaction times.^{113, 114, 121} This would evidently not be suitable with thiophenium salts **4.7-OTf** as intramolecular rearrangement would be highly competitive. The third challenge associated with the study of these thiophenium salts has to do with incompatibility with nucleophiles as the 2 and 5 positions of the thiophenium core is electrophilic making the system prone to ring-opening.

As mentioned previously, sulfonium salts are also used as electron acceptors in electron-donor (EDA) complexes. Many electron donors have been reported to form EDA complexes with sulfonium salts.¹¹⁶ For instance, the Molander group has recently described that sulfinate salts are capable of forming molecular aggregates with *S*-(Aryl) thianthrenium salts (**Ar-TT⁺**) (Figure 76, A).¹²⁸ In the ground state, the complex formed is activated by visible light and a single electron transfer between the donor and acceptor molecule occurs without the use of an exogenous photocatalyst. This SET event generates a radical ion pair which triggers irreversible fragmentation of the thianthrenium moiety generating an aryl radical upon loss of the thianthrene (TT) leaving group. The resulting radicals generated (aryl radical and sulfonyl radical) recombine affording the sulfone product **4.33** (78% yield). Although mixing of the thiophenium triflate salt **4.7-OTf** with sodium *p*-toluenesulfinate in DMSO-*d*₆ resulted in the formation of a slightly yellow solution suggesting that an EDA complex is formed, ring opening of the thiophenium is observed right away giving **4.34** (Figure 76, B).

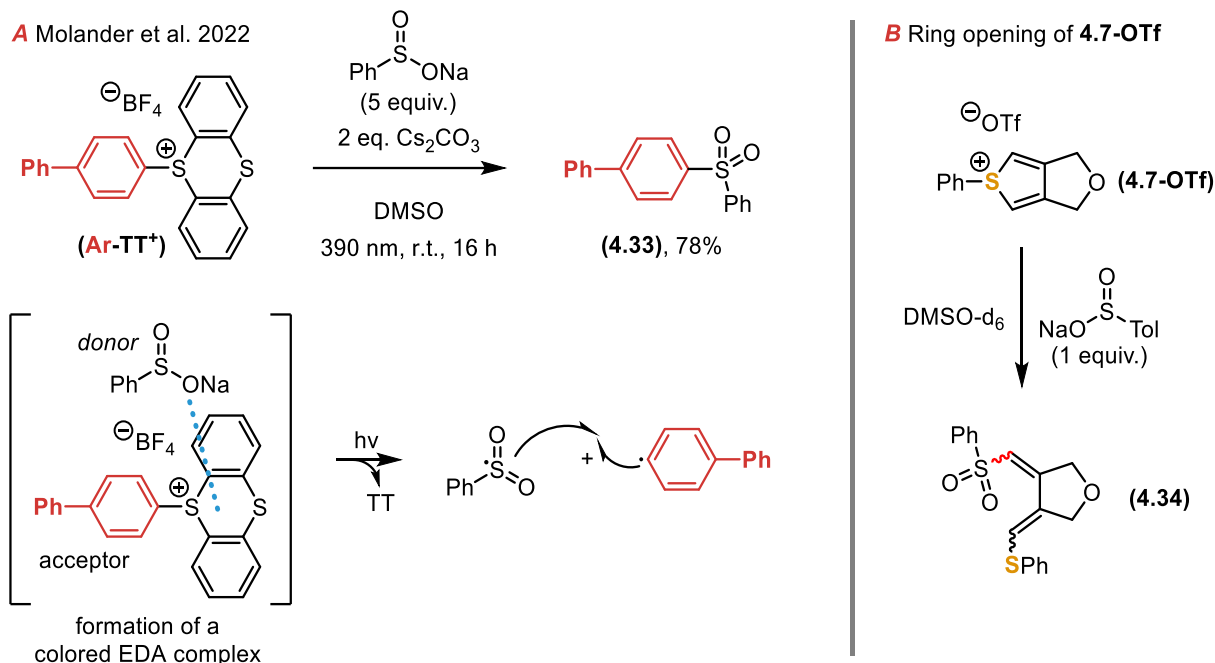


Figure 76 Sulfonium salts in EDA complexes. A) *S*-(aryl) thianthrenium salts as electron acceptors in EDA complexes for the formation of aryl substituted sulfones. B) Rapid ring opening of thiophenium triflate **4.7-OTf** upon mixing with sodium *p*-toluenesulfinate.

4.15 Ideas for the next generation of thiophenium salts

Although the chemistry of the commonly employed *S*-(Aryl) sulfonium salts could not be directly transferred to the simpler thiophenium **4.7-OTf** system, the observations that were made serve as guidance for the synthesis of the next generation *S*-(aryl)-thiophenium salts (Figure 77). Changing of the model ether linker to a more inert unsaturated system will eliminate the possibility of side reactivity with radicals in photoredox/metallophotoredox chemistry. Additionally, since the 2 and 5 positions of the thiophenium core are prone to nucleophilic attack, substitution may help in preventing this undesired reactivity. Furthermore, if those positions are blocked the migration of the aryl group can no longer occur by the [1,5]-rearrangement and aromatization sequence previously described. Although addition of all these modifications will render the system less atom economical as compared to the commonly employed

dibenzothiophenium and thianthrenium salts, these previously unreported *S*-(Aryl) thiophenium salts hold many synthetic advantages.

First, since the exogenous *S*-aryl bond is pre-installed, the resulting sulfonium salts can in theory be substituted by any (hetero)aromatics groups. This is a major advantage as the commonly used sulfonium salts are generally restricted to electron-rich (hetero)aromatics and regioselectivity is governed by S_EAr (Figure 76). Furthermore, the more positive reduction potential of the model thiophenium salt **4.7-OTf** as compared to the DBT⁺ and TT⁺ may open doors to milder photoredox and/or metallophotoredox conditions. The big difference in reduction potential is not surprising as it is known that changing the sulfur-containing moiety has a significant impact on the reduction potential (Figure 76), while electronic modifications on the exogenous aryl group do not.^{116, 127} It will therefore be important to assess the effect of structural modifications of the fused thiophenium core on the reduction potential of the species.

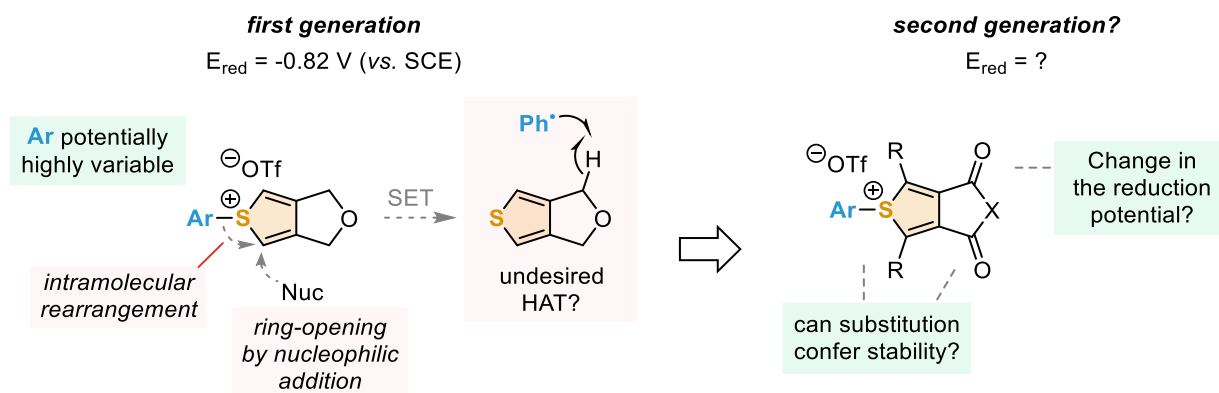


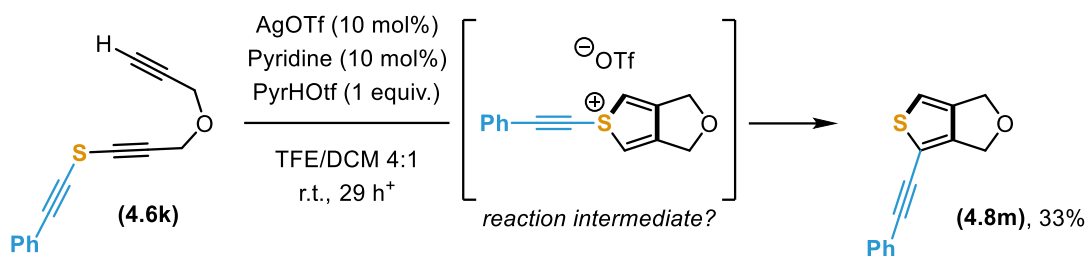
Figure 77 Tuning the structure of model thiophenium triflate **4.7-OTf**.

Although we are still at an early stage with using *S*-(Aryl) thiophenium salts as linchpins for the formation of new C_{Ar}-C and C_{Ar}-X bonds, we believe that the advantages described above are worthwhile as they may lift the limitations associated with the current methodologies around

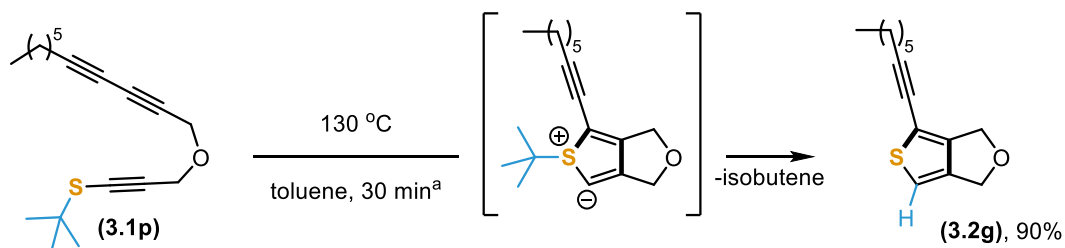
S-(Aryl) sulfonium salts. The question remains, where do we go from now? The first challenge that needs to be addressed is the synthesis of S-(Aryl) alkynyl-sulfides as no general method is present in the literature which tolerates both electron-rich and poor (hetero)aromatics substituents. Then, there will be a need to establish if isolation of thiophenium salts containing both electron-poor and rich exogenous S⁺-Ar bonds is possible utilizing the metal-catalyzed cycloaddition of yne-alkynyl sulfides. Kinetic experiments will be useful in investigating the electronic effects of the (hetero)aryl moiety on the rate of the (3+2) cycloaddition step. In the same line, can the metal-induced cyclization be coupled with functionalization at the 2 and 5 positions of the thiophenium core towards more stable variants? This may be particularly useful for impeding the intramolecular rearrangement of thiophenium salts containing electron-poor S⁺-Ar exogenous bonds which are rapid as compared to electron-rich variants (see Table 13 Synthesis of 2-aryl substituted thiophenes by the rearrangement of *in-situ* formed thiophenium intermediates and Figure 70).

Interestingly, Dominic Campeau has shown that S-(Alkynyl) substituted alkynyl sulfide **4.6k** also undergoes rearrangement to the corresponding 2-alkynyl substituted thiophene **4.8m** under the silver-catalyzed conditions (Figure 78, A). In contrary to aryl groups, migration of the alkyne is rapid and consumption of the yne-alkynyl sulfide is observed after 29 h at room temperature. Although a low 33% yield was obtained, the synthesis of a similar 2-alkynyl substituted thiophene **3.2g** previously required heating of yne-alkynyl sulfide **3.1p** at 130 °C (Figure 78, B). The use of metal-catalyzed reaction conditions for lifting the limitations with the linker size observed previously (see Figure 51) is currently being investigated by Dominic Campeau and will be reported in an upcoming manuscript.

A Migration of an alkynyl group observed



B Previous method for accessing 2-alkynyl substituted thiophene



⁺Reaction performed by Dominic Campeau. ^aResult obtained during our study on the thermal rearrangement of yne-alkynyl sulfides.⁸¹

Figure 78 Two routes towards the synthesis of 2-alkynyl substituted fused thiophenes.

5 Conclusion

Overall, the work presented in this thesis highlights the underutilized facet of α heteroatom-substituted alkynes, specifically ynamides and alkynyl sulfides, as isoelectronic species to 1,3-dipoles. The scarcity of using *neutral*-TACs as 4π components in (3+2) cycloaddition cascades is undoubtedly due to their association with being highly reversible processes with uncontrolled reactivity of the resulting zwitterionic cycloadducts. Strategies to overcome these unfavorable reaction features have included the use of highly reactive *neutral*-TACs and/or 2π cycloaddition partners or by structural stabilization of the resulting cycloadducts. More recently, the control over the reactivity of highly energetic zwitterionic cycloadducts has employed intramolecular and/or intermolecular quenching techniques. For instance, our group has extensively shown that pyrrolium ylides formed upon a thermally induced cyclization of yne-ynamides undergo selective 1,2-shift towards stable fully substituted pyrroles. In Chapter 2, the investigations of different strategies for the expedited synthesis of fused pyrroles from *in-situ* formed yne-ynamides were presented. The finding of a previously unexplored ynamide substituted propynal building block enabled a small library of fused pyrroles to be obtained using a condensation and cyclization strategy. The development of general *one-pot* procedures towards highly substituted pyrroles remains however to be devised. This challenge may be overcome by taking a closer look at the sensitivity of the studied yne-ynamides towards metal-containing reaction conditions.

In Chapter 3, an in-depth study on the reactivity cascades of thermally formed thiophenium ylides was presented. The use of thioalkynes as *n*TACs in thermally induced intramolecular cycloaddition reactions with alkynes enabled a continued exploration of the

synthetic potential of heteroarylium ylides. Due to the variability available with alkynyl sulfides synthons, the reactivity of *in-situ* formed thiophenium ylides could be further modulated and controlled. Additionally, the increased stability of thioalkynes towards thermal and metal-containing reaction conditions enabled a broad scope of highly substituted fused thiophenes to be obtained. Limitations associated with the thermally induced process were however seen due to the high-energy reaction profile. In particular, the cyclization of yne-alkynyl sulfides could not be expanded to the synthesis of [3.5.0]-fused thiophenes due to substrate degradation observed at elevated temperatures (250 °C). Additionally, the cyclization was found to be inefficient when utilizing unsubstituted alkynes or when the *S*-aryl substituted alkynyl sulfides were employed.

In Chapter 4, the lifting of the latter limitations using mild coinage metal-catalyzed cycloaddition pathways was discussed. For the first time, an S^+ -phenyl substituted thiophenium cycloadduct was observed experimentally and efficiently isolated. The heat-induced rearrangement of these *in-situ* formed S^+ -aryl thiophenium salts derivatives provided access to 2-aryl substituted fused thiophenes without the need to use specially substituted thioalkynes and/or elevated temperatures. Furthermore, exploration of the use of this previously undescribed *S*-phenyl thiophenium salt as linchpin in (metallo)photoredox transformations revealed contrasting properties with the commonly employed sulfonium salts. These preliminary studies should serve as guidance for the synthesis of the next generation of *S*-aryl thiophenium salts toward potentially useful electrophilic reagents.

In general, the research discussed in this thesis exemplifies that the discovery of new (3+2) cycloaddition reactions is possible by using underexplored *neutral*-TAC species. Despite the unfavorable thermodynamic profile associated with the formation of zwitterionic cycloadducts,

the heteroarylium ylides generated underwent various controlled quenching avenues towards important fused pyrrole and thiophene heterocycles. Lastly, the work presented in this thesis illustrate the power of reaction optimization and the use of transition-metal catalysis for achieving difficult cyclizations. We hope that these findings will inspire continued efforts in this area of research and that new routes towards relevant heterocyclic motifs become unlocked.

6 Publications and presentations of work discussed in this thesis

Published articles (⁺⁺Co-first authors, contributed equally ; *Corresponding authors) :

Campeau, D.*, **Pommainville, A.**, Gagosz, F.* Ynamides as Three-Atom Components in Cycloadditions: An Unexplored Chemical Reaction Space. *Journal of the American Chemical Society* **2021**, 143 (25), 9601-9611.

Pommainville, A.⁺⁺, Campeau, D.⁺⁺, Gagosz, F.* The Synthetic Potential of Thiophenium Ylide Cycloadducts. *Angewandte Chemie International Edition* **2022**, 61 (32), e202205963. [Selected as Hot Paper]

Selected presentations (presenting authors in bold) :

Campeau, D., **Pommainville, A.**, Gorodnichy, M., Gagosz, F. New Cycloaddition Reactions with Special Alkynes : High Heat to Mild Catalysis. *Centre For Catalysis Research and Innovation (CCRI)* seminar, oral presentation. December 2022, Ottawa, ON.

Pommainville, A., Campeau, D., Gagosz, F. Ynamides as Springboards for New (3+2) Cycloaddition Cascades. *CCCE*, oral presentation. June 2022, Calgary, AB.

Pommainville, A., Campeau, D., Gorodnichy, M., Gagosz, F. A Coinage Metal Catalyzed (3+2) Cycloaddition Using a Neutral Three-Atom Component. *Ottawa-Carleton Chemistry Institute (OCCI)* day, oral presentation. June 2022, Ottawa, ON.

Pommainville, A., Campeau, D., Gagosz, F. Expanding the Use of Neutral Three-Atom Components in (3+2) Cycloaddition Cascades with Alkynyl Sulfides. *QOMSB*, virtual poster presentation. December 2021, Ottawa, ON.

Pommainville, A., Campeau, D., Gagosz, F. Bridging the Gap Between an Unexplored Class of Ynamides and New (3+2) Cycloaddition Cascades. *SOUSCC*, virtual oral presentation. May 2021, Ottawa, ON.

7 Supporting Information

7.1 General Information

All NMR spectra were recorded at room temperature on a Bruker Avance II400, Bruker Avance II300, Bruker Avance 300, Bruker Avance III500, or Bruker Avance III 600 instrument operating at the indicated frequency. Chemical shifts (δ) are given in parts per million (ppm) using a deuterated solvent as reference (CHCl_3 at 7.26 ppm, C_6H_6 at 7.16 ppm, acetone- d_6 at 2.05 ppm, DMSO- d_6 at 2.50 ppm or AcOH- d_4 at 2.04 ppm for ^1H NMR and CDCl_3 at 77.2 ppm, C_6D_6 at 128.1 ppm, acetone- d_6 at 29.8 ppm, DMSO- d_6 at 39.5 ppm for ^{13}C NMR). Signal multiplicities are reported as : s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sex = sextuplet, sept = septuplet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, tt = triplet of triplet, dq = doublet of quartet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, bs = broad singlet. Integration and coupling constant(s) in Hz.

High-resolution mass spectrometry by electron impact (HRMS-EI) was performed on a JEOL JMC GCmate II mass spectrometer, and high-resolution mass spectrometry by electrospray ionization (HRMS-ESI) was performed on a Micromass Q-TOF II Mass Spectrometer. Low resolution mass spectra were obtained on an Advion Expression CMS spectrometer using an APCI or ESI probe, as indicated. Molecular ion and/or fragment signals were given in mass per charge number (m/z). Due to the highly fragmenting nature of yne-alkynyl sulfides substrates leading to low molecular ion $[\text{M}^+]$ intensities, either of the consistently observed $[\text{M}-\text{H}]^+$, $[\text{M}-\text{CH}_3]^+$ and $[\text{M}-\text{C}_4\text{H}_9]^+$ fragments were used as characteristic HRMS-EI signals for these substrates when necessary.

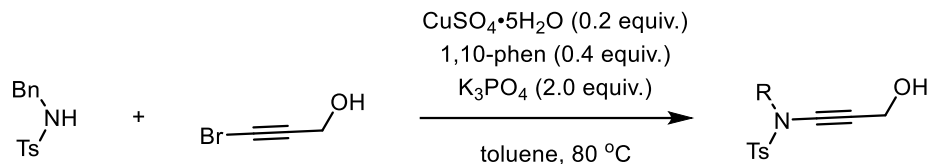
Building blocks used in this Supporting Information have been characterized by ^1H NMR and ^{13}C NMR, unless otherwise specified with N/A. All yne-ynamides and yne-alkynyl sulfides as well the corresponding pyrroles and thiophene/thiophenium products have been characterized by ^1H NMR and ^{13}C NMR and HRMS.

7.2 Materials

All commercially available materials were purchased from Sigma-Aldrich, Alfa-Aesar, Oakwood Chemicals, TCI America, Fluorochem Chemical, Combi-Blocks or Ambeed suppliers and were used as delivered without further purification. Reactions carried out under inert atmosphere were performed under nitrogen gas. Purifications were performed by flash column chromatography with silica gel using a forced flow of eluents. Thin layer chromatography (TLC) was performed on TLC Silicagel 60 F254 plates. Visualization was done with UV light and staining was routinely performed using a para-anisaldehyde solution (PA).

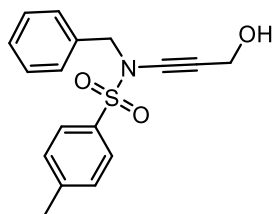
7.3 Supporting Information for Chapter 2

7.3.1 Synthesis of propargyl alcohol precursors **S1-3**



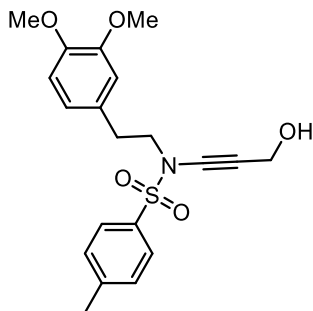
Following a modified procedure to that described by Hsung and coworkers.⁶³ : In a flame dried round bottom flask, *N*-benzyl-4-methylbenzenesulfonamide (1.0 equiv.), CuSO₄·5H₂O (0.2 equiv.), 1,10-phenanthroline (0.4 equiv.) and K₃PO₄ (2.0 equiv.) were added. Three cycles of vacuum/purging with nitrogen were done to render the flask inert. A solution of 3-bromoprop-2-yn-1-ol previously prepared by our group⁵⁸ (1.0 equiv.) in dry toluene (0.3 M) was then added via a syringe. The reaction mixture is stirred at 80°C for the indicated reaction time. The mixture was then filtered through celite using EtOAc as the eluent and the resulting mixture is concentrated under reduced pressure to produce a crude mixture which is purified by silica gel chromatography using the indicated solvent system.

(S1)



Propargyl alcohol **S1** was prepared and described by our group⁵⁸ using the method described above.

(S1)

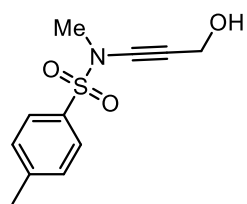


Using 2.78 mmol of *N*-benzyl-4-methylbenzenesulfonamide. Reaction time = 2 h. Eluent system = Hexanes/EtOAc gradient of 1:1 to 2:3. Produced 717 mg (66% yield) of a yellow solid.

¹H NMR (400MHz, CDCl₃) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.69 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 4.41 (d, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.60 – 3.50 (m, 2H), 2.93 – 2.81 (m, 2H), 2.43 (s, 3H), 1.63 (t, *J* = 6.1 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 149.1, 148.0, 144.8, 134.8, 130.0, 129.9, 127.6, 121.0, 112.3, 111.4, 79.2, 70.5, 56.0 (x2), 52.9, 51.4, 34.2, 21.8.

(S3)

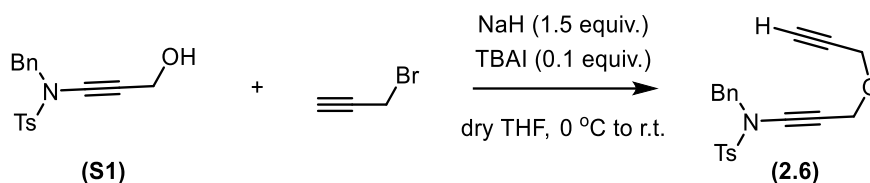


Using 3.30 mmol of *N*-benzyl-4-methylbenzenesulfonamide. Reaction time = 1 h. Eluent system = Hexanes/EtOAc gradient 3:2. Produced 350 mg (44% yield) of a beige solid.

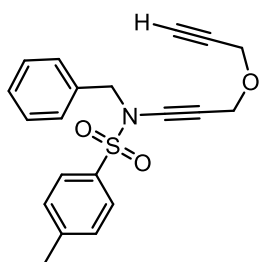
^1H NMR (400MHz, CDCl_3) δ 7.79 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.37 (d, J = 6.1 Hz, 2H), 3.07 (s, 3H), 2.46 (s, 3H), 1.65 (t, J = 6.1 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 145.0, 133.5, 130.0, 127.9, 80.9, 68.2, 51.3, 39.2, 21.8.

7.3.2 Synthesis of diynes **2.1b**, **2.4** and **2.6**

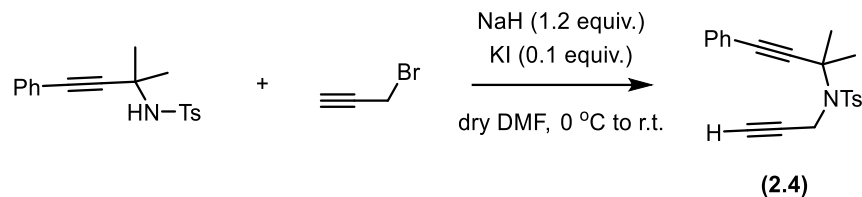


In a flame-dried round bottom flask cooled to 0 °C a solution of alcohol **S1** (1.0 equiv.), propargyl bromide and tetrabutylammonium iodide (0.1 equiv.) in dry THF (0.1 M). To the cooled solution was added NaH (1.5 equiv., 60 % w/w). The mixture is stirred at 0 °C until the evolution of H_2 gas had passed, the reaction mixture was brought to rt and stirred for 2 hours. The mixture was then quenched with NH_4Cl sat. aq. solution and diluted with EtOAc. The organic phase was washed once with water, then once with brine. The organic phase was dried using MgSO_4 , filtered, and concentration under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using Hexanes/EtOAc/ Et_3N 85:14:1 as the eluent system to yield 176mg (73% yield) of diyne **2.6**.

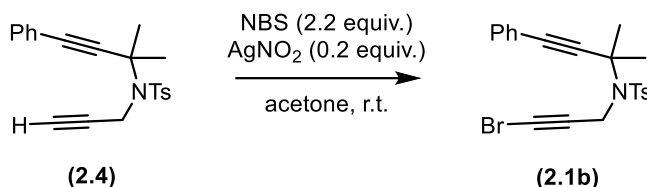
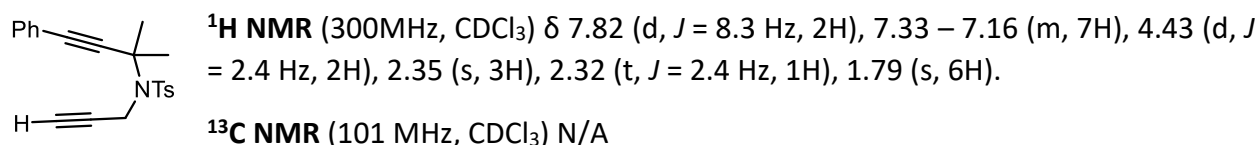


^1H NMR (300MHz, CDCl_3) δ 7.75 (d, J = 8.3 Hz, 2H), 7.35 – 7.26 (m, 7H), 4.51 (s, 2H), 4.30 (s, 2H), 3.99 (d, J = 2.4 Hz, 2H), 2.45 (s, 3H), 2.41 (t, J = 2.4 Hz, 1H).

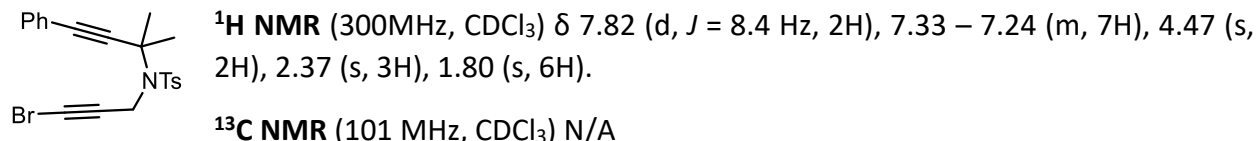
^{13}C NMR (101 MHz, CDCl_3) δ 144.9, 134.8, 134.5, 129.9, 128.9, 128.7, 128.5, 127.8, 80.7, 79.2, 74.8, 67.3, 56.9, 55.7, 55.6, 21.8.



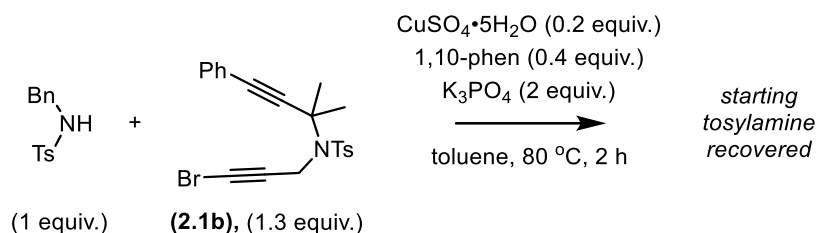
In a flame dried round bottom flask was added 4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (3.96 mmol, 1.0 equiv.), propargyl bromide (3.93 mmol, 1.5 equiv.) and KI (0.396 mmol, 0.1 equiv.). Three rounds of vacuum/purging with nitrogen were done. Dry DMF was then added to the flask via a syringe and the mixture is cooled to 0°C before the quick addition of NaH (4.75 mmol, 1.2 equiv.). The reaction mixture is then warmed to room temperature and stirred for an additional hour. The mixture is then quenched with water and Et₂O is added as the organic solvent for extractions with water three times and brine once. The organic phases are dried with MgSO₄, filtered, and concentrated under reduced pressure to yield a crude mixture. The crude is then purified by silica gel chromatography using Hexanes/EtOAc 9:1 as the eluent system to yield 445 mg (60% yield) of diene **2.4**.



In a round bottom flask a solution of diene **2.4** (1.26 mmol, 1.0 equiv.), *N*-bromosuccinimide (2.77 mmol, 2.2 equiv.) and AgNO₃ (0.25 mmol, 0.2 equiv.) in acetone (0.3 M) is stirred at room temperature for 3 h. The reaction mixture is then concentrated under reduced pressure, redissolved in Et₂O and washed four times with an aqueous solution of NaOH (5% w/w) followed by brine. The organic phase was dried with MgSO₄, filtered, and concentrated under reduced pressure to produce a crude mixture. The crude is purified by silica gel chromatography using Hexanes/EtOAc 9:1 as the eluent system to yield 88 mg (16% yield) of bromoalkyne **2.1b**.

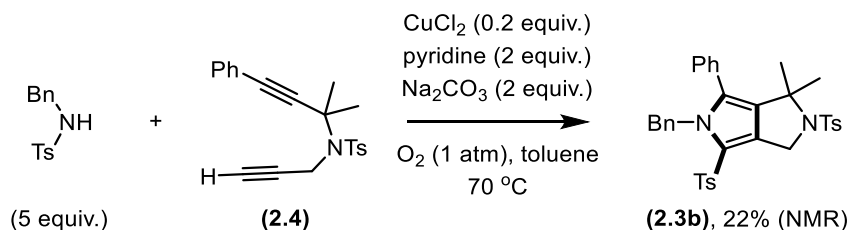


7.3.3 Procedure for the attempted *one-pot* reaction starting from bromoalkyne **2.1b**

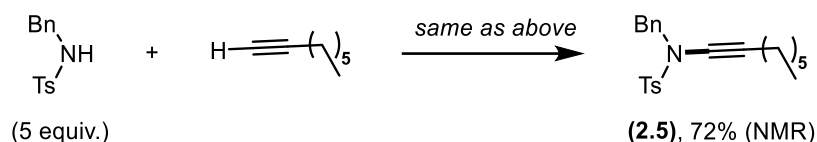


Following a modified procedure to that described by Hsung and coworkers.⁶³ In a reaction vial taken from the oven was added *N*-benzyl-4-methylbenzenesulfonamide (0.16 mmol, 1.0 equiv.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.032 mmol, 0.2 equiv.), 1,10-phenanthroline (0.064 mmol, 0.4 equiv.) and K_3PO_4 (0.32 mmol, 2.0 equiv.). Three cycles of vacuum/purging with nitrogen were done to render the flask inert. A solution of bromoalkyne **2.1b** (0.21 mmol, 1.3 equiv.) in dry toluene (2 mL, 0.1 M) was then added via a syringe. The reaction mixture is stirred at 80°C for 2 h. The mixture was then filtered through celite using EtOAc as the eluent and the resulting mixture is concentrated under reduced pressure to produce a crude mixture. Analysis of the crude by NMR only shows recovery of the starting tosylamide and degradation of bromoalkyne **2.1b**.

7.3.4 Procedure for the attempted *one-pot* reaction starting from alkyne **2.4**

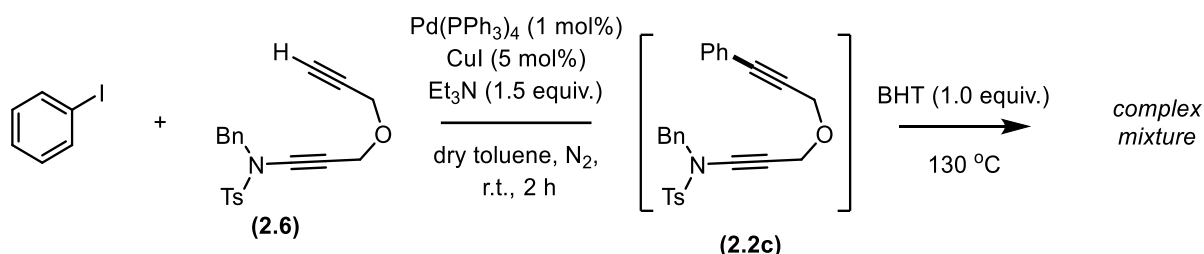


Following a modified procedure to that described by Stahl and coworkers.⁶⁴ In a reaction vial taken from the oven was added CuCl_2 (0.02 mmol, 0.2 eq.), *N*-benzyl-4-methylbenzenesulfonamide (0.5 mmol, 5.0 eq.) and Na_2CO_3 (0.2 mmol, 2.0 eq.). The flask was purged three times with oxygen then a source of oxygen (1 atm) is introduced constantly (an oxygen balloon was used in this case). Dry pyridine (0.2 mmol, 2.0 eq.) in dry toluene (0.5 mL) is then added to the round bottom flask followed by heating to 70°C in an oil bath. Terminal alkyne **2.4** in dry toluene (0.5 mL) is then introduced by a syringe pump over a period of 4 hour. The reaction mixture is run overnight and was cooled down to room temperature the next morning since consumption of alkyne **2.4** was seen by TLC analysis. The reaction mixture is directly filtered through celite with DCM as the eluent and the resulting filtrate is concentrated by reduced pressure. The resulting crude showed formation of desired product **2.3b** in a 22% NMR yield (1,2-DBE was added as the internal standard).



This control experiment was set up the same way as described above using 0.1 mmol of commercially available 1-octyne. The desired ynamide **2.5** was detected by NMR in a 72% yield.

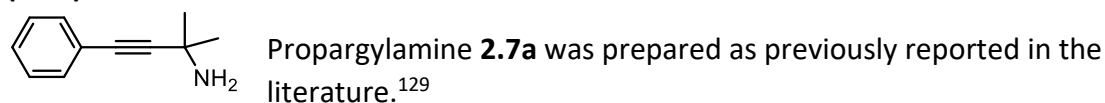
7.3.5 Procedure for the attempted *one-pot* Sonogashira and cyclization from ynamide **2.6**



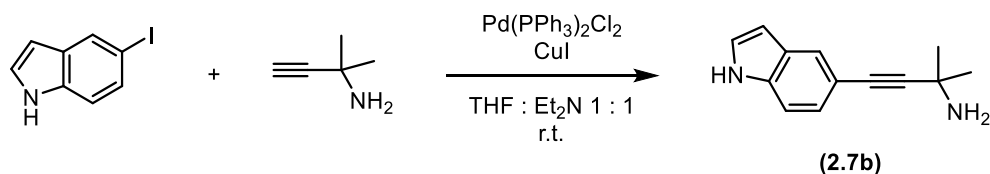
In a reaction vial taken from the oven was added iodobenzene (0.057 mmol, 1.0 equiv.), Pd(PPh₃)₂Cl₂ (0.01 equiv.) and CuI (0.05 equiv.). Three cycles of vacuum/purging with N₂ were done to render the flask inert. A solution of alkyne **2.6** (1.0 mmol, 1.0 equiv.) in dry toluene (1mL, 0.06 M) was added via syringe. Triethylamine (0.085 mmol, 1.5 equiv.) was then added to the mixture. The reaction mixture was stirred for 2 hours at room temperature. Although no Sonogashira cross-coupled product **2.2c** was detected by TLC, BHT (0.057 mmol, 1.0 equiv.) added, and the flask is heated to 130 °C overnight. The reaction mixture was then concentrated under reduced pressure however a complex mixture was obtained upon analysis by NMR.

7.3.6 Synthesis and characterization of propargylamines precursors **2.7**

(2.7a)

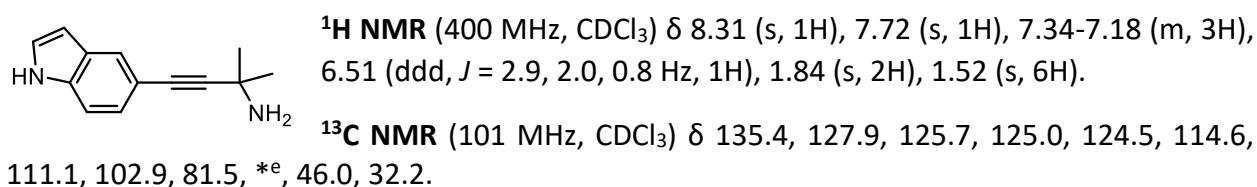


(2.7b)



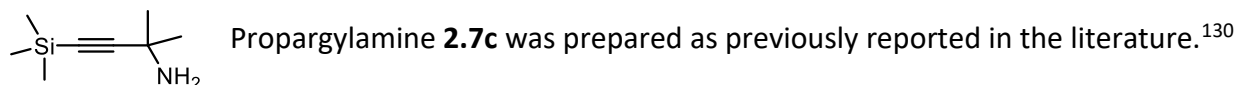
In a flame dried round bottom flask was added 5-iodoindole (1.00 mmol, 1.0 equiv.), Pd(PPh₃)₂Cl₂ (0.025 mmol, 0.025 equiv.) and CuI (0.05 mmol, 0.05 equiv.). Three cycles of vacuum/purging

with N₂ were done to render the flask inert. A solution of 1,1-dimethylprop-3-ynylamine (1.0 mmol, 1.0 equiv.) in dry THF : Et₃N (1 : 1, 10 mL, 0.1 M) was added via syringe. The reaction mixture was stirred for 45 minutes at room temperature. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc, then washed twice with water and once with brine. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude mixture. The crude was then purified via flash chromatography using a MeOH/DCM 1 : 9 system as the eluent. The collected fractions were concentrated and washed with water (to remove traces of silica) then dried with MgSO₄ and concentrated to yield the corresponding propargylamine **2.7b** as a beige solid (100 mg, 50% yield).

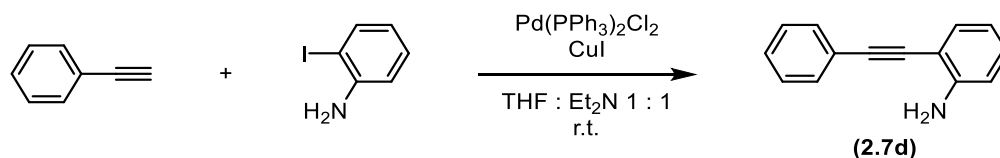


MS-APCI (*m/z*) : 167.5 (15%), 182.5% (20%, [M-NH₂]⁺), 380.1 (100%, [2M-NH₂]⁺).

(2.7c)



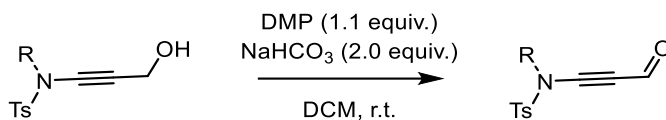
(2.7d)



In a flame dried round bottom flask was added phenylacetylene (1.03 mmol, 1.0 equiv.), Pd(PPh₃)₂Cl₂ (0.025 mmol, 0.025 equiv.) and CuI (0.05 mmol, 0.05 equiv.). Three cycles of vacuum/purging with N₂ were done to render the flask inert. A solution of 2-iodophenylamine (1.03 mmol, 1.0 equiv.) in dry THF : Et₃N (1 : 1, 10 mL, 0.1 M) was added via syringe. The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc, then washed twice with water and once with brine. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude mixture. The crude was then purified via flash chromatography using EtOAc/Et₃N/Hexanes 8:2:90 to yield amine **2.7d** as an orange solid (108 mg, 50% yield). The NMR obtained were consistent with those previously described in the literature.¹³¹

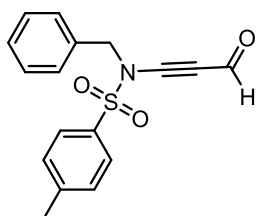
^e Peak is hidden behind the solvent peak.

7.3.7 Synthesis and characterization of aldehyde precursors 2.8



In a round bottom flask was added a solution of propargyl alcohol (1.00 equiv.) in DCM (10 mL, 0.1 M) and NaHCO₃ (2.0 equiv.). Dess-Martin periodinane (1.10 equiv.) was then added to the flask. The reaction mixture was stirred at room temperature for 5 minutes, then filtered through a short pad of silica gel using DCM as the eluent. The filtrate was then concentrated under reduced pressure to yield the desired aldehyde.

(2.8a)



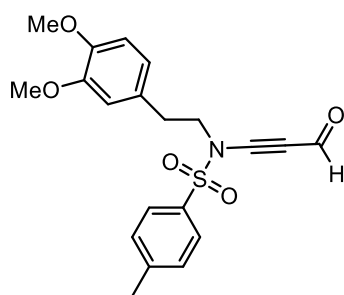
Using 0.640 mmol of propargyl alcohol **S-1**. Produced 110 mg (71% yield) of a yellow oil.

¹H NMR (400MHz, CDCl₃) δ 9.14 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.20 (m, 7H), 4.63 (s, 2H), 2.43 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 174.7, 146.0, 134.3, 133.4, 130.23, 129.0, 129.0, 128.8, 128.0, 93.7, 79.1, 56.0, 21.9.

MS-APCI (*m/z*) : 91.1 (100%, [C₇H₇]⁺), 155.6 (35%, [Ts]⁺), 314.1 (61%, [M+H]⁺), 384.0 (21%), 473.1 (14%).

(2.8b)



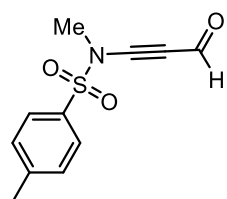
Using 0.485 mmol of propargyl alcohol **S-2**. Produced 149 mg (79% yield) of an orange oil.

¹H NMR (400MHz, CDCl₃) δ 9.25 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.67 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.74 – 3.66 (m, 2H), 2.94 – 2.87 (m, 2H), 2.45 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 174.8, 149.2, 148.3, 146.0, 134.1, 130.2, 129.1, 127.8, 121.1, 112.1, 111.5, 93.4, 79.6, 56.0, 55.9, 53.1, 34.2, 21.9.

MS-APCI (*m/z*) : 233.4 (11%, [M+H-Ts]⁺), 360.0 (17%), 388.0 (100%, [M+H]⁺).

(2.8c)



Using 0.811 mmol of propargyl alcohol **S-3**. Produced 154 mg (80% yield) of a yellow oil.

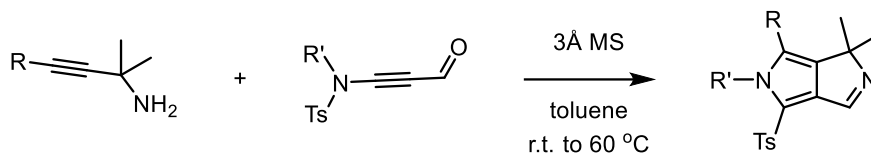
¹H NMR (400MHz, CDCl₃) δ 9.24 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 3.21 (s, 3H), 2.48 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 174.9, 146.2, 133.2, 130.4, 128.0, 94.6, 76.9, 39.1, 21.9.

MS-APCI (m/z) : 155.6 (55%, [Ts]⁺), 238.3 (33%, [M+H]⁺), 255.3 (17%), 308.0 (16%), 372.9 (16%), 392.1 (19%), 405.0 (100%), 447.1 (24%), 475.1 (28%, [2M+H]⁺).

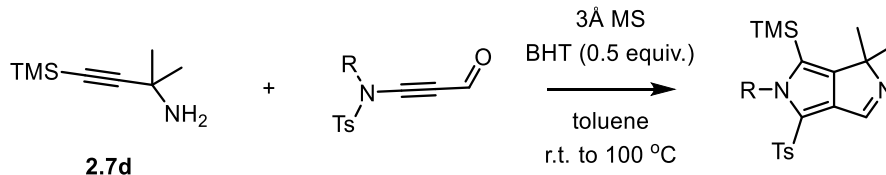
7.3.8 Synthesis of fused pyrroles **2.9** by the condensation and cyclization strategy

Standard procedure 2-A : for pyrroles **2.9a-f**



In a reaction vial under vacuum was flame-dried molecular sieves (3Å). To the room temperature-cooled flask was added a solution of propargyl amine (0.100 mmol, 1.0 equiv.) and aldehyde (0.100 mmol, 1.0 equiv.) in toluene (1.00 mL, 0.1 M)^f. The tube was lightly shaken, and the condensation reaction was followed by TLC at room temperature. Once the condensation step completed, the tube was heated to 60 °C in an oil bath until full consumption of the condensate is seen. The mixture was evaporated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired pyrrole.

Standard procedure 2-B : for pyrroles **2.9g-h**

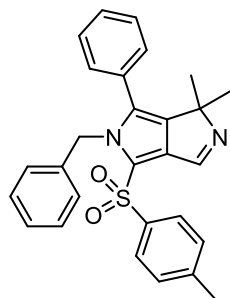


In a reaction vial under vacuum was flame-dried molecular sieves (3Å). To the room temperature-cooled flask was added a solution of propargyl amine **2.7d** (0.100 mmol, 1.0 equiv.) and aldehyde (0.100 mmol, 1.0 equiv.) in toluene (1.00 mL, 0.1 M). The tube was lightly shaken, and the condensation reaction was followed by TLC at room temperature. Once the condensation step completed, BHT was added (0.0500 mmol, 0.5 equiv.) and the tube was heated to 100 °C in an oil bath until full consumption of the condensate is seen. The mixture was evaporated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired pyrrole.

^f A 1 : 1 mixture of toluene:DCM was used instead when employing propargylamine **2.7b** due to its poor solubility in toluene.

7.3.9 Characterization of thiophene products **2.9a-h**

(2.9a)



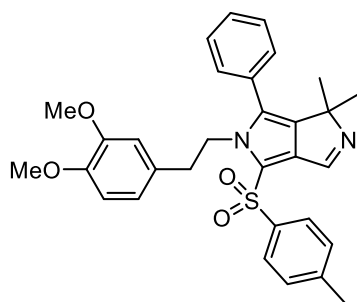
Using standard procedure **2-A** with 0.100 mmol of propargylamine **2.7a** and 0.100 mmol of aldehyde **2.8a**. Condensation time = 1 h, rearrangement time = for 1 h 30. Solvent system = Hexanes/Acetone/Et₃N 75:22:3. Produced 24.8 mg (55% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 8.44 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.23 (m, 3H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.07 – 6.99 (m, 3H), 6.99 – 6.91 (m, 2H), 6.43 (d, *J* = 7.3 Hz, 2H), 5.32 (s, 2H), 2.31 (s, 3H), 1.35 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 153.7, 143.9, 142.8, 138.3, 137.1, 136.0, 131.9, 130.3, 130.0, 129.7, 129.2, 128.6, 128.3, 127.5, 126.8, 125.7, 118.1, 72.4, 48.8, 25.8, 21.6.

HRMS-EI : Calculated for C₂₈H₂₆N₂O₂S [M]⁺: 454.1710; found: 454.1729.

(2.9b)



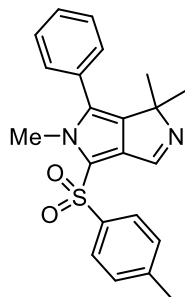
Using standard procedure **2-A** with 0.100 mmol of propargylamine **2.7a** and 0.100 mmol of aldehyde **2.8b**. Condensation time = 40min, rearrangement time = 60 °C for 1 h 30. Solvent system = Hexanes/Acetone/Et₃N 75:22:3. Produced 28.0 mg (53% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 8.22 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.41 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.15 (m, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.25 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.14 (d, *J* = 1.9 Hz, 1H), 4.19 – 4.10 (m, 2H), 3.81 (s, 3H), 3.68 (s, 3H), 2.65 – 2.56 (m, 2H), 2.43 (s, 3H), 1.30 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 153.4, 149.0, 147.9, 144.6, 142.8, 139.2, 135.8, 131.3, 130.4, 130.3, 130.2, 130.2, 129.1, 128.7, 127.7, 120.7, 117.1, 111.8, 111.3, 72.3, 56.0, 55.8, 47.9, 37.3, 25.8, 21.8.

HRMS-EI : Calculated for C₃₁H₃₂N₂O₄S [M]⁺: 528.2077; found: 528.2072.

(2.9c)



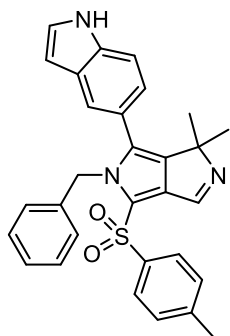
Using standard procedure **2-A** with 0.100 mmol of propargylamine **2.7a** and 0.100 mmol of aldehyde **2.8c**. Condensation time = 1 h, rearrangement time = 1 h. Solvent system = Hexanes/EtOAc gradient of 1:1 to 2:3. Produced 9.9 mg (26% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 8.25 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.50 – 7.40 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.24 (m, 2H), 3.56 (s, 3H), 2.44 (s, 3H), 1.33 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 153.4, 144.6, 142.4, 138.8, 135.4, 131.5, 130.3, 130.2, 130.1, 129.2, 128.8, 127.8, 117.8, 72.4, 33.3, 25.8, 21.8.

HRMS-EI : Calculated for C₂₂H₂₂N₂O₂S [M]⁺: 378.1397; found: 378.1404.

(2.9d)



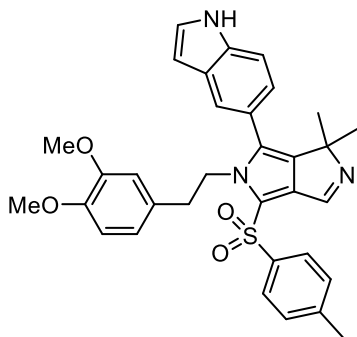
Using standard procedure **2-A** with 0.100 mmol of propargylamine **2.7b** and 0.100 mmol of aldehyde **2.8a**. Condensation time = 2 h, rearrangement time = 2 h. Solvent system = Hexanes/EtOAc gradient of 1:1 to 2:3. Produced 22 mg (45% yield) of a white solid.

¹H NMR (300MHz, CDCl₃) δ 8.49 (s, 1H), 8.45 (s, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 1.4 Hz, 1H), 7.35 – 7.21 (m, 2H), 7.06 – 6.88 (m, 6H), 6.52 – 6.41 (m, 3H), 5.35 (s, 2H), 2.31 (s, 3H), 1.37 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 153.8, 143.6, 142.8, 138.5, 137.5, 136.1, 136.0, 133.6, 129.6, 128.2, 127.8, 127.4, 126.6, 125.7, 125.4, 124.1, 123.0, 121.0, 117.2, 111.2, 103.0, 72.5, 48.7, 25.8, 21.6.

HRMS-EI : Calculated for C₃₀H₂₇N₃O₂S [M]⁺: 493.1818; found: 493.1815.

(2.9e)



Using standard procedure **2-A** with 0.100 mmol of propargylamine **2.7b** and 0.100 mmol of aldehyde **2.8b**. Condensation time = 1 h, rearrangement time = 2 h. Solvent system = Hexanes/EtOAc 3:7. Produced 26.1 mg (46% yield) of a white solid.

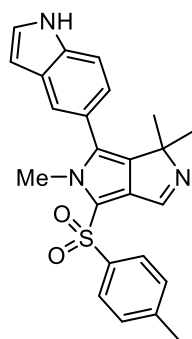
¹H NMR (400MHz, CDCl₃) δ 8.71 (s, 1H), 8.31 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.52 – 7.41 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.33 – 7.28 (m, 1H), 7.00 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 6.59 – 6.55 (m, 1H), 6.28 (dd, *J* = 8.1, 1.7 Hz, 1H), 5.94 (d, *J* = 1.7 Hz, 1H), 4.28 – 4.00 (m, 2H), 3.79 (s, 3H), 3.41 (s, 3H), 2.77 – 2.53 (m, 2H), 2.44 (s,

3H), 1.34 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 153.8, 148.9, 147.8, 144.5, 142.6, 139.4, 136.0, 135.4, 132.9, 130.4, 130.2, 128.0, 127.7, 125.6, 124.2, 123.0, 121.3, 120.6, 116.6, 111.6, 111.4, 111.1, 103.2, 72.3, 56.0, 55.4, 47.9, 37.4, 25.7, 21.8.

HRMS-EI : Calculated for C₃₃H₃₃N₃O₄S [M]⁺: 567.2186; found: 567.2182.

(2.9f)



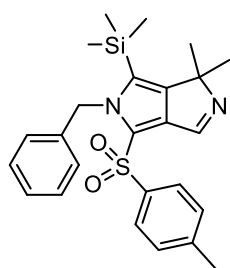
Using standard procedure **2-A** with 0.100 mmol of propargylamine **2.7b** and 0.100mmol of aldehyde **2.8c**. Condensation time = 1 h, rearrangement time = 2 h. Solvent system = Hexanes/EtOAc 3:7. Produced 9.0 mg (22% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 8.49 (s, 1H), 8.35 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.53 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 2.8 Hz, 1H), 7.06 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.59 (m, 1H), 3.58 (s, 3H), 2.45 (s, 3H), 1.38 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 153.6, 144.4, 144.2, 142.3, 139.1, 136.0, 135.3, 133.1, 130.2, 128.0, 127.8, 125.6, 124.1, 122.9, 121.4, 111.4, 103.1, 72.4, 33.2, 25.8, 21.8.

HRMS-EI : Calculated for C₂₄H₂₃N₃O₂S [M]⁺: 417.1505; found: 417.1491.

(2.9g)



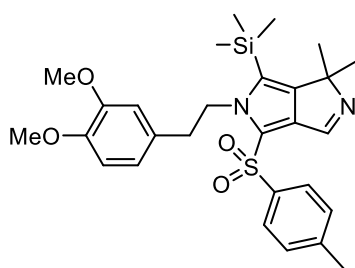
Using standard procedure **2-B** with 0.100 mmol of propargylamine **2.7c** and 0.100 mmol of aldehyde **2.8a**. Condensation time = 1.5 h, rearrangement time = 1.5 h. Solvent system = Hexanes/Acetone/Et₃N 75:22:3. Produced 23.1 mg (51% yield) of a white solid.

¹H NMR (300MHz, CDCl₃) δ 8.48 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.10 – 6.90 (m, 5H), 6.38 (d, *J* = 7.1 Hz, 2H), 5.62 (s, 2H), 2.27 (s, 3H), 1.58 (s, 6H), 0.18 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 153.7, 153.3, 143.8, 137.8, 137.6, 137.2, 132.5, 129.5, 128.4, 127.6, 126.7, 125.1, 122.6, 73.3, 51.0, 25.9, 21.6, 1.4.

HRMS-EI : N/A

(2.9h)



Using standard procedure **2-B** with 0.100 mmol of propargylamine **2.7c** and 0.100 mmol of aldehyde **2.8a**. Condensation time = 1.5 h, rearrangement time = 2.5 h. Solvent system = Hexanes/EtOAc 2:3. Produced 14.3 mg (27% yield) of a yellow oil.

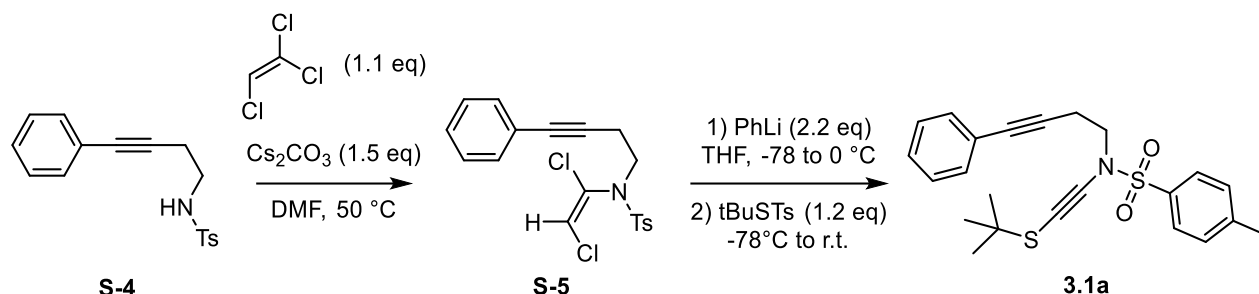
¹H NMR (300MHz, CDCl₃) δ 8.07 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.28 (m, 2H), 6.95 – 6.91 (m, 1H), 6.83 (d, *J* = 1.5 Hz, 2H), 4.40 – 4.24 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.10 – 2.97 (m, 2H), 2.41 (s, 3H), 1.49 (s, 6H), 0.44 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 153.6, 152.9, 149.3, 148.2, 144.7, 139.0, 137.1, 131.4, 130.3, 130.2, 127.5, 121.2, 120.7, 112.2, 111.6, 73.3, 56.1, 56.0, 50.5, 38.5, 25.8, 21.8, 1.9.

HRMS-EI : N/A

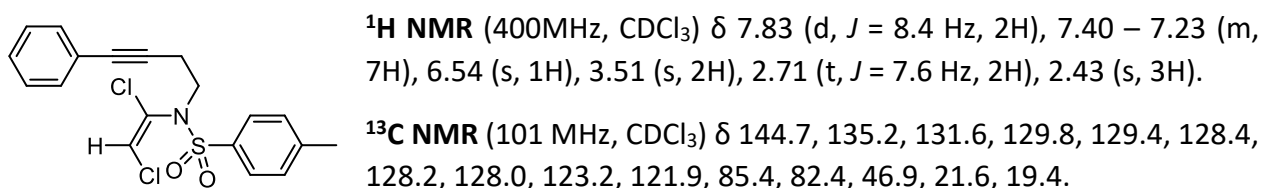
7.4 Supporting Information for Chapter 3

7.4.1 Preparation of substrate **3.1a** based on the procedure reported by Anderson *et al*



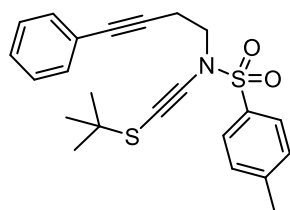
(*E*)-*N*-(1,2-dichlorovinyl)-4-methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (**S-5**)

Following a modified procedure to that described by Anderson *et al.*¹³² : To a suspension of 4-methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide **S-4** prepared as previously reported by Wang *et al.*¹³³ (0.634 mmol, 1.0 equiv.) and powdered Cs_2CO_3 (0.951 mmol, 1.5 equiv.) in DMF (1.3 mL, 0.5M) heated to 50 °C was added trichloroethylene (62.5 μL , 0.597 mmol, 1.1 equiv.) dropwise over 10 minutes. The mixture was stirred at 50 °C for 1 hour. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed four times with water, then once with brine. The organic phase was dried using MgSO_4 , filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using Hexanes:Et₂O 95:5 as the eluent system to yield 192 mg (77% yield) of dichloroenamide **S-5** white solid.



N-((*tert*-butylthio)ethynyl)-4-methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (**3.1a**)

In a flame-dried round bottom flask under N_2 atmosphere was cooled a stirred solution of dichloroenamide **S-5** (188 mg, 0.478 mmol, 1.0 equiv.) in dry THF (4.8 mL, 0.1M) to -78 °C. PhLi (0.55 mL, 1.9 M in dibutyl ether, 1.05 mmol, 2.2 equiv.) was added dropwise over 10 minutes. The solution was then stirred at -78 °C for 1 h then for 10 minutes at 0 °C. The solution is cooled back to -78 °C then alkyl thiosulfonate **S-6** (140 mg, 0.574 mmol, 1.2 equiv.) was added and the reaction mixture was stirred and slowly warmed to room temperature for 1.5 h. The mixture was then quenched with water then extracted with EtOAc. The organic phase was dried using MgSO_4 , filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using hexanes/acetone 97:3 as the eluent system to yield 154 mg (78% yield) of the desired substrate **3.1a** as a yellow oil.

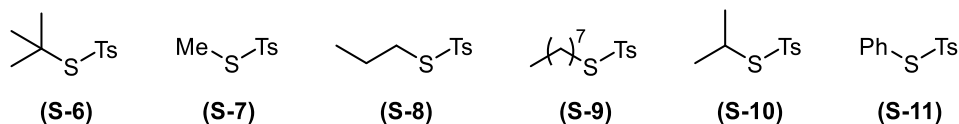


¹H NMR (400MHz, CDCl₃) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.24 (m, 7H), 3.69 (t, *J* = 7.5 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 1.31 (s, 9H).

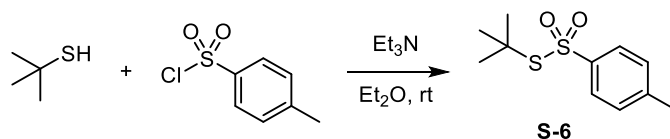
¹³C NMR (101 MHz, CDCl₃) δ 144.8, 134.8, 131.8, 129.9, 128.3, 128.1, 127.9, 123.3, 89.8, 85.4, 82.7, 65.6, 50.5, 47.9, 30.0, 21.8, 19.5.

HRMS-EI : Calculated for C₁₉H₁₆NO₂S₂ [M-C₄H₉]⁺: 354.0622; found: 354.0617.

7.4.2 Synthesis of precursors **S6-17** utilized for the synthesis of yne-alkynyl sulfides



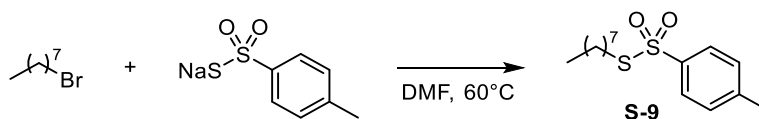
(S-6)



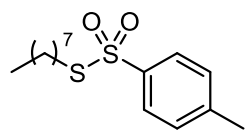
In a round bottom flask was added *tert*-butyl thiol (4.61 mL, 40.9 mmol, 1.0 equiv.) in Et₂O (27 mL, 1.5 M) then Et₃N (6.84 mL, 49.1 mmol, 1.2 equiv.) was added to the solution. *p*-Toluenesulfonyl chloride (9.36 g, 49.1 mmol, 1.2 equiv.) was added to the stirring solution over 10 min. The reaction mixture was then stirred at room temperature overnight (18 h). The mixture was concentrated under reduced pressure to produce a crude which was purified by silica gel chromatography (dry load) using hexanes/Et₂O 9:1 as the eluent system to yield 8.39 g (84% yield) of **S-6** as a white solid. Characterization of **S-6** matches that described in the literature.¹³⁴

(S-7) and (S-8) are synthesized as described in : *Eur. J. Med. Chem.* **2012**, 50, 236-254.

(S-9)



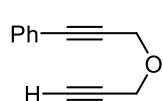
In a round bottom flask was added sodium *p*-toluenethiosulfonate (355 mg, 1.69 mmol, 1.3 equiv.) and 1-bromooctane (0.22 mL, 1.30 mmol, 1.0 equiv.) in dry DMF (13 mL, 0.1M). The solution was stirred at 60°C for 3 hours. The mixture was then diluted with NaHCO₃ sat. aq. solution and Et₂O. The organic phase was washed once with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The crude was purified by silica gel chromatography using hexanes/acetone 95:5 as the eluent system to yield 200 mg (quant. yield) of **S-9** as a white solid.



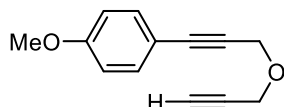
¹H NMR (400MHz, CDCl₃) δ 7.81 (d, *J* = 8.3 Hz, 2H), δ 7.36 – 7.31 (m, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.45 (s, 3H), 1.63 – 1.53 (m, 2H), 1.36 – 1.13 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 144.7, 142.3, 129.9, 127.2, 36.2, 31.8, 29.1, 29.0, 28.7, 28.6, 22.7, 21.8, 14.2.

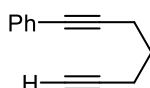
(S-10), (S-11) are synthesized as described in : *Synthesis* **2002**, 3, 343-348.



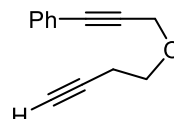
(S-12)
Org. Lett. **2007**,
9, 505-508



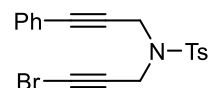
(S-13)
JACS **2007**,
129, 4939-4947



(S-14)
J. Org. Chem. **2007**,
72, 6200-6205

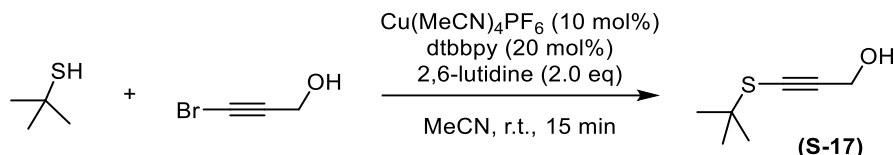


(S-15)
J. Org. Chem. **2020**,
85, 2543-2559



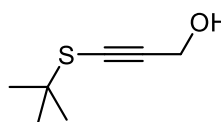
(S-16)
JACS **2021**,
143, 9601-9611

(S-17)



Derived from the coupling method developed by Collins *et al.* ⁷⁵:

In a flame-dried round bottom flask was added 4,4'-di-tert-butyl-2,2'-bipyridine (4.10 mmol, 0.2 equiv.). Three vacuum/N₂ purge cycles were performed to refill the flask with N₂ atmosphere. *Tert*-butyl thiol (22.5 mmol, 1.1 equiv.), the bromoprop-2-yn-1-ol (20.5 mmol, 1.0 equiv.), 2,6-lutidine (41.0 mmol, 2.0 equiv.) and dry, degassed MeCN (22 mL, 1 M) were all added to the flask via syringe. A sonicated suspension of Cu(MeCN)₄PF₆ (2.05 mmol, 0.1 equiv.) in a minimal amount of dry, degassed MeCN (1 mL) was then added to the reaction solution, which immediately took a brownish-red colour. Upon reaction completion (about 15 min, followed by TLC), the reaction took a pale greenish colour. The reaction mixture was then quenched with water and diluted with Et₂O. The organic phase was washed three times with 2.5% HCl aq. solution, three times with 10% NH₃ aq. solution, then once with brine. The organic phase was then dried over MgSO₄ and filtered. The obtained solution was boiled (bath at 60 °C) to dryness in an open flask (to remove residual *tert*-butyl thiol in the fumehood) to produce a crude. The crude was then purified by silica gel chromatography using Hexanes/Et₂O 19:1 → 9:1 as the eluent system to yield 1.18 g (40% yield) of **S-17** as a pale yellow oil.

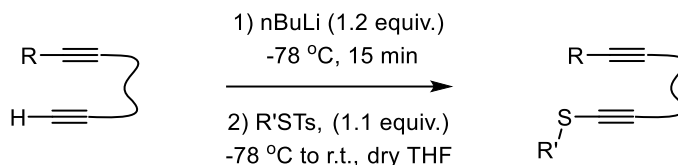


¹H NMR (400MHz, CDCl₃) δ 4.43 (d, *J* = 6.1 Hz, 2H), 1.59 (t, *J* = 6.2 Hz, 1H), 1.41 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 95.7, 76.2, 52.2, 47.9, 30.4.

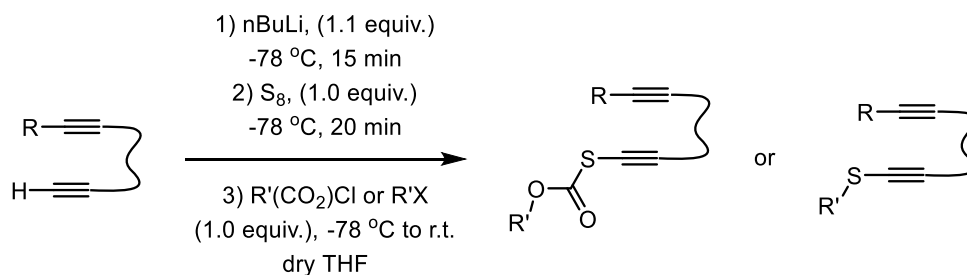
7.4.3 Procedures for the synthesis of yne-alkynyl sulfides **3.1b-f,h,m-x**

Standard procedure 3-A : Using a sulfur umpolung method to access yne-alkynyl sulfides **3.1b-f,h,o,t,v,w**.



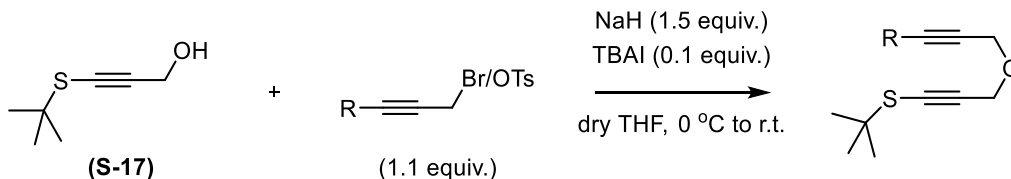
In a flame-dried round bottom flask under N₂ atmosphere was added the alkyne (1.0 equiv.) and dry THF (0.1 M) via syringe. The solution was cooled to -78 °C then nBuLi (2.5 M in hexanes, 1.2 equiv.) was added dropwise to the stirring solution. The solution was then stirred at -78 °C for another 15 min. The alkyl thiosulfonate (R'STs) (1.1 equiv.) was added at once and the reaction mixture was slowly warmed to room temperature. Upon reaction completion (30 min to 1 h), the mixture was quenched with NH₄Cl aq. solution and diluted with diethyl ether. The mixture was washed once with water, then brine. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The resulting crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired alkynyl sulfide.

Standard procedure 3-B : Using a thiol alkynylation method to access yne-alkynyl sulfides **3.1m,n**.



In a flame-dried round bottom flask under N₂ atmosphere was added the alkyne (1.0 equiv.) and dry THF (0.1 M) via syringe. The solution was cooled to -78 °C then nBuLi (2.5 M in hexanes, 1.1 equiv.) was added dropwise to the stirring solution. The solution was then stirred at -78 °C for another 15 min. Sublimation-grade sulfur (1.0 equiv.) was added at once at -78 °C and the reaction mixture was stirred at -78 °C for another 20 min, developing a bright orange colour. The chloroformate or alkyl halide (1.0 equiv.) was then added at once, and the reaction mixture is warmed to room temperature. After 30 min, the mixture was quenched with NH₄Cl aq. solution and diluted with diethyl ether. The mixture was washed once with water, then brine. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The resulting crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired alkynyl sulfide.

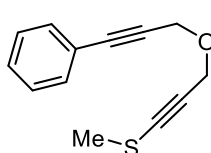
Standard procedure 3-C : Nucleophilic substitution using NaH as base for yne-alkynyl sulfides **3.1q-s**.



In a flame-dried round bottom flask was cooled to 0 °C a solution of alcohol **S-17** (1.0 equiv.), propargyl bromide or tosylate derivative (1.1 equiv.) and tetrabutylammonium iodide (0.1 equiv.) in dry THF (0.5 M). To the cooled solution was added NaH (1.5 equiv., 60 % w/w). The mixture is stirred at 0 °C until the evolution of H₂ gas had passed, the reaction mixture was brought to rt and stirred until full consumption of the substrate was observed by TLC analysis. The mixture was then quenched with NH₄Cl sat. aq. solution and diluted with Et₂O. The organic phase was washed once with water, then once with brine. The organic phase was dried using MgSO₄, filtered, and concentration under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired yne-alkynyl sulfide.

7.4.4 Characterization of yne-alkynyl sulfides **3.1b-f,h,m-x**

methyl(3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)sulfane (3.1b)



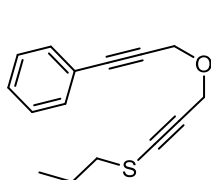
Using standard procedure **3-A** with 0.693 mmol of alkyne **S-12** and thiosulfonate **S-7**. Solvent system = Hexanes/Et₂O 95:5. Produced 105 mg (70% yield) of a pale yellow oil.

¹H NMR (400MHz, CDCl₃) δ 7.50 – 7.40 (m, 2H), 7.38 – 7.26 (m, 3H), 4.47 (s, 2H), 4.41 (s, 2H), 2.40 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 132.0, 128.7, 128.4, 122.7, 88.7, 86.9, 84.5, 79.6, 57.8, 57.3, 19.2.

HRMS-EI Calculated for $C_{13}H_{12}OS$ $[M]^+$: 216.0609; found: 216.0585.

(3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)(*n*-propyl)sulfane (3.1c)



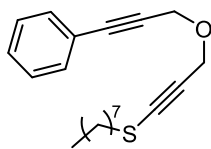
Using standard procedure **3-A** with 2.94 mmol of alkyne **S-12** and thiosulfonate **S-8**. Solvent system = Hexanes/Et₂O 95:5. Produced 608 mg (85% yield) of a pale yellow oil.

 ¹H NMR (400MHz, CDCl₃) δ 7.49 – 7.41 (m, 2H), 7.36 – 7.27 (m, 3H), 4.47 (s, 2H), 4.42 (s, 2H), 2.70 (t, *J* = 7.1 Hz, 2H), 1.78 (h, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 131.9, 128.7, 128.4, 122.7, 89.5, 86.8, 84.5, 78.2, 57.9, 57.2, 37.6, 22.8, 13.0.

HRMS-EI Calculated for C₁₅H₁₆OS [M]⁺: 244.0922; found: 244.0935.

***n*-octyl(3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)sulfane (3.1d)**



Using standard procedure **3-A** with 0.477 mmol of alkyne **S-12** and thiosulfonate **S-9**. Solvent system = Hexanes/Et₂O 95:5. Produced 112 mg (75% yield) of a pale yellow oil.

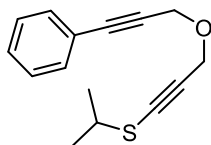
¹H NMR (400MHz, CDCl₃) δ 7.49 – 7.40 (m, 2H), 7.38 – 7.27 (m, 3H), 4.47 (s, 2H), 4.42 (s, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.73 (p, *J* = 7.3 Hz, 2H), 1.49 – 1.18 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 132.0, 128.7, 128.4, 122.7, 89.5, 86.8, 84.5, 78.3, 57.9, 57.2, 35.7, 31.9, 29.4, 29.3, 29.2, 28.4, 22.8, 14.2.

HRMS-EI : Calculated for C₂₀H₂₆OS [M]⁺: 314.1704; found: 314.1700.

isopropyl(3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)sulfane (3.1e)

Using standard procedure **3-A** with 0.627 mmol of alkyne **S-12** and thiosulfonate **S-10**. Solvent system = Hexanes/acetone 95:5. Produced 92.0 mg (66% yield) of a pale yellow oil.

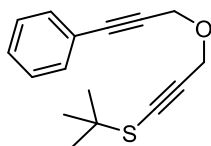


¹H NMR (400MHz, CDCl₃) δ 7.48 – 7.41 (m, 2H), 7.36 – 7.27 (m, 3H), 4.49 (s, 2H), 4.46 (s, 2H), 3.18 (hept, *J* = 6.7 Hz, 1H), 1.38 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 132.0, 128.7, 128.4, 122.7, 91.5, 86.8, 84.5, 77.2, 57.9, 57.2, 39.6, 23.0.

HRMS-EI : Calculated for C₁₅H₁₆OS [M]⁺: 244.0922; found: 244.0926.

***tert*-butyl(3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)sulfane (3.1f)**



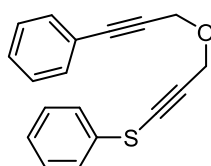
Using standard procedure **3-A** with 0.774 mmol of alkyne **S-12** and thiosulfonate **S-6**. Solvent system = Hexanes/Et₂O 95:5. Produced 116 mg (69% yield) of a pale yellow oil.

¹H NMR (400MHz, CDCl₃) δ 7.49 – 7.41 (m, 2H), 7.36 – 7.28 (m, 3H), 4.50 (s, 2H), 4.49 (s, 2H), 1.43 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 132.0, 128.7, 128.4, 122.7, 92.8, 86.8, 84.5, 77.6, 57.9, 57.1, 48.0, 30.4.

HRMS-EI : Calculated for C₁₅H₁₅OS [M-CH₃]⁺: 243.0844; found: 243.0839.

phenyl(3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)sulfane (3.1h)



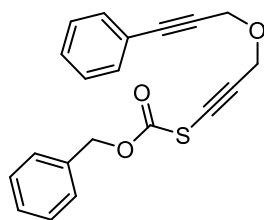
Using standard procedure **3-A** with 0.717 mmol of alkyne **S-12** and thiosulfonate **S-11**. Solvent system = Hexanes/Et₂O 98:2. Produced 126 mg (63% yield) of a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.49 – 7.42 (m, 4H), 7.37 – 7.29 (m, 5H), 7.26 – 7.20 (m, 1H), 4.57 (s, 2H), 4.53 (s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 132.4, 132.0, 129.4, 128.7, 128.5, 126.8, 126.5, 122.6, 94.9, 87.1, 84.3, 74.5, 57.8, 57.4.

HRMS-EI : Calculated for C₁₈H₁₄OS [M]⁺: 278.0765; found: 278.0739.

O-benzyl S-(3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl) carbonothioate (3.1m)



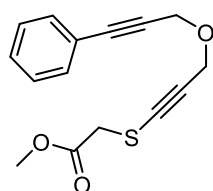
Using standard procedure **3-B** with 0.594 mmol of alkyne **S-12** and benzyl chloroformate. Solvent system = Hexanes/Et₂O 95:5. Produced 79.2 mg (24% yield) of a pale yellow oil.

¹H NMR (400MHz, CDCl₃) δ 7.48 – 7.42 (m, 2H), 7.42 – 7.28 (m, 8H), 5.30 (s, 2H), 4.51 (s, 2H), 4.48 (s, 2H).^g

¹³C NMR (101 MHz, CDCl₃) δ 166.5, 134.3, 132.0, 129.1, 128.9, 128.8, 128.7, 128.4, 122.5, 97.6, 87.1, 84.2, 71.1, 69.1, 57.6, 57.6.

HRMS-EI : Calculated for C₂₀H₁₆O₃S [M]⁺: 336.0820; found: 336.0808.

methyl 2-((3-((3-phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)thio)acetate (3.1n)



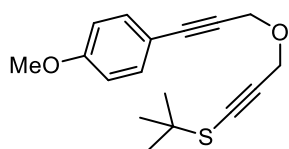
Using standard procedure **3-B** with 0.547 mmol of alkyne **S-12** and methyl bromoacetate. Solvent system = Hexanes/EtOAc 85:15. Produced 50.0 mg (33% yield) of a yellow oil.

¹H NMR (400MHz, CDCl₃) δ 7.50 – 7.40 (m, 2H), 7.37 – 7.27 (m, 3H), 4.47 (s, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.52 (s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 168.8, 131.9, 128.7, 128.4, 122.6, 91.5, 86.9, 84.3, 76.0, 57.7, 57.3, 53.0, 37.4.

HRMS-EI : Calculated for C₁₅H₁₄O₃S [M]⁺: 274.0664; found: 274.0680.

tert-butyl(3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)prop-1-yn-1-yl)sulfane (3.1o)



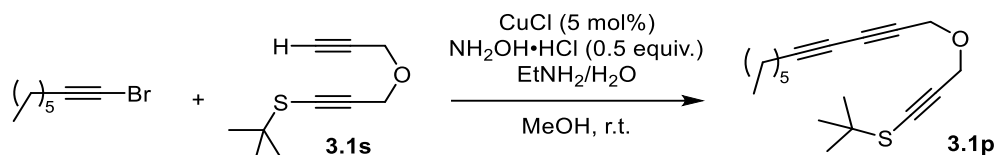
Using standard procedure **3-A** with 0.520 mmol of alkyne **S-13** and thiosulfonate **S-6**. Solvent system = Hexanes/Et₂O 95:5. Produced 91.0 mg (60% yield) of a yellow oil.

¹H NMR (400MHz, CDCl₃) δ 7.39 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.48 (s, 2H), 4.48 (s, 2H), 3.81 (s, 3H), 1.43 (s, 9H).

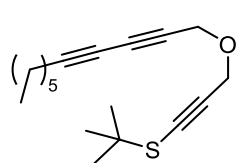
¹³C NMR (101 MHz, CDCl₃) δ 159.9, 133.4, 114.7, 114.1, 92.9, 86.8, 83.1, 77.4, 57.8, 57.2, 55.4, 48.0, 30.4.

HRMS-EI : Calculated for C₁₇H₂₀O₂S [M-CH₃]⁺: 273.0949; found: 273.0933.

^g Inseparable by-product observed by ¹H NMR spectrum. Internal NMR standard shows the purified sample is ~91% w/w desired product.

tert-butyl(3-(undeca-2,4-diyn-1-yloxy)prop-1-yn-1-yl)sulfane (3.1p)

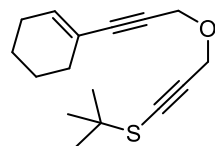
In a round bottom flask was added a solution of 1-bromo-1-octyne prepared as described by Fujihara, T. et al.¹³⁵ (84.7 mg, 0.448 mmol, 1.0 equiv.), alkyne **3.1s** (81.7 mg, 0.448 mmol, 1.0 equiv.), and ethylamine (70% aqueous solution, 0.3 mL) in methanol (9 mL, 0.05 M). Three vacuum/N₂ purge cycles were performed to refill the flask with N₂ atmosphere then CuCl (2.2 mg, 0.0224 mmol, 0.05 equiv.) was added to the mixture. NH₂OH-HCl (15.6 mg, 0.224 mmol, 0.5 equiv.) was then added and the reaction mixture was stirred at room temperature for 24 h. The solution was filtered through celite using MeOH followed by evaporation of volatiles under reduced pressure. The concentrate was dissolved in EtOAc, washed with water, then once with brine. The organic phase was then dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using Hexanes/Et₂O 98:2 as the eluent system to yield 78.2 mg (60% yield) of the desired substrate **9n** as a pale yellow oil.



¹H NMR (400MHz, CDCl₃) δ 4.41 (s, 2H), 4.32 (t, *J* = 1.1 Hz, 2H), 2.27 (tt, *J* = 7.1, 1.0 Hz, 2H), 1.41 (s, 9H), 1.59 – 1.20 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 92.6, 81.6, 77.8, 71.9, 71.1, 64.6, 57.9, 56.8, 48.0, 31.4, 30.4, 28.6, 28.2, 22.6, 19.4, 14.2.

HRMS-EI : Calculated for C₁₄H₁₈OS [M-CH₃]⁺: 275.1470; found: 275.1447.

tert-butyl(3-((3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)oxy)prop-1-yn-1-yl)sulfane (3.1q)

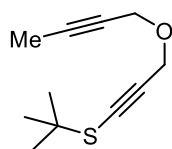
Using standard procedure **3-C** with 0.572 mmol of alcohol **S-17** and 1.0 equivalents of 1-tosyl-3-cyclohexenyl-2-propyne prepared as described in the literature.¹³⁶ Solvent system = Hexanes/Et₂O 98:2. Produced 81.0 mg (54% yield) of a yellow oil.

¹H NMR (400MHz, CDCl₃) δ 6.13 (tt, *J* = 3.8, 1.7 Hz, 1H), 4.42 (s, 2H), 4.37 (s, 2H), 2.18 – 2.02 (m, 4H), 1.69 – 1.51 (m, 4H), 1.42 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 135.8, 120.2, 93.0, 88.7, 81.6, 77.2, 57.6, 57.1, 48.0, 30.4, 29.2, 25.8, 22.4, 21.6.

HRMS-EI : Calculated for C₁₆H₁₂OS [M]⁺: 262.1391; found: 262.1374.

(3-(but-2-yn-1-yloxy)prop-1-yn-1-yl)(tert-butyl)sulfane (3.1r)



Using standard procedure **3-C** with 0.564 mmol of alcohol **S-17** and 1.0 equivalents of but-2-yn-1-yl *p*-tosylate prepared as described in the literature.¹³⁶

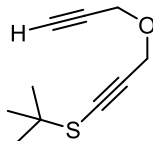
Solvent system = Hexanes/Et₂O 98:2. Produced 84.0 mg (56% yield) of a pale yellow oil.

¹H NMR (400MHz, CDCl₃) δ 4.40 (s, 2H), 4.22 (q, *J* = 2.3 Hz, 2H), 1.86 (t, *J* = 2.3 Hz, 3H), 1.41 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 93.0, 83.1, 77.1, 74.6, 57.7, 56.9, 48.0, 30.4, 3.8.

HRMS-EI : Calculated for C₁₁H₁₅OS [M-H]⁺: 195.0844; found: 195.0833.

tert-butyl(3-(prop-2-yn-1-yloxy)prop-1-yn-1-yl)sulfane (3.1s)



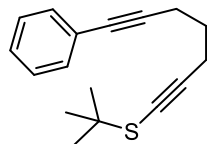
Using standard procedure **3-C** with 3.05 mmol of alcohol **S-17** and propargyl bromide. Solvent system = Hexanes/Et₂O 98:2. Produced 461 mg (83% yield) of a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 4.43 (s, 2H), 4.27 (d, *J* = 2.4 Hz, 2H), 2.44 (t, *J* = 2.4 Hz, 1H), 1.42 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 92.6, 79.2, 77.7, 75.0, 57.8, 56.2, 48.0, 30.4.

HRMS-EI : Calculated for C₁₀H₁₄OS [M]⁺: 182.0765; found: 182.0755.

tert-butyl(7-phenylhepta-1,6-diyn-1-yl)sulfane (3.1t)



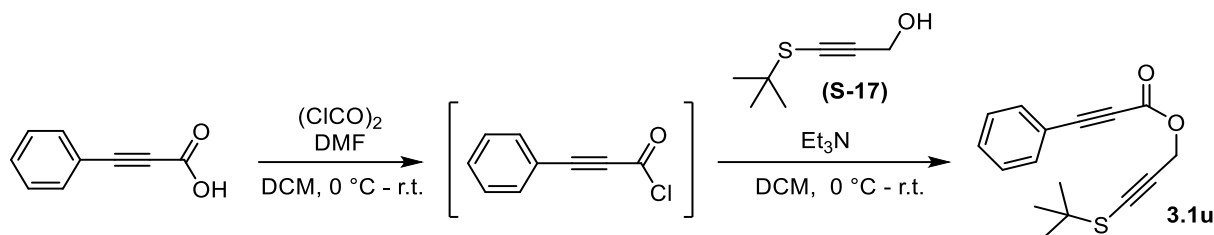
Using standard procedure **3-A** with 0.477 mmol of alkyne **S-14** and thiosulfonate **S-6**. Solvent system = Hexanes/Et₂O 99:1. Produced 103 mg (84% yield) of a yellow oil.

¹H NMR (400MHz, CDCl₃) δ 7.43 – 7.36 (m, 2H), 7.32 – 7.25 (m, 3H), 2.55 (td, *J* = 7.0, 1.4 Hz, 4H), 1.85 (p, *J* = 7.0 Hz, 2H), 1.41 (s, 9H).

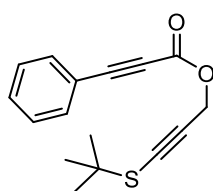
¹³C NMR (101 MHz, CDCl₃) δ 131.7, 128.3, 127.8, 123.9, 96.4, 89.2, 81.4, 68.8, 47.2, 30.4, 28.2, 19.6, 18.8.

HRMS-EI : Calculated for C₁₆H₁₇S [M-CH₃]⁺: 241.1051; found: 241.1031.

3-(*tert*-butylthio)prop-2-yn-1-yl 3-phenylpropiolate (**3.1u**)



In a round bottom flask was added 3-phenylpropionic acid (107 mg, 0.735 mmol, 1.0 equiv.), dry DCM (3.7 mL, 0.2 M) and a drop of DMF. The stirred solution was cooled to 0 °C and oxalyl chloride (0.13 mL, 1.46 mmol, 2.0 equiv.) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. Then, volatiles were evaporated under reduced pressure to give the intermediate acyl chloride as a yellow solid. The crude acyl chloride was redissolved in dry DCM (3.7 mL, 0.2 M) and the mixture was cooled to 0 °C. Et₃N (0.26 mL, 1.84 mmol, 2.5 equiv.) was added to the flask followed by alcohol **S-17**. The mixture was brought to room temperature and stirred for 50 minutes. The reaction mixture was washed with water, then brine. The organic phase was dried with MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using Hexanes/Et₂O 98:2 as the eluent system to yield 71.0 mg (36% yield) of the desired substrate **3.1u** as a yellow oil.

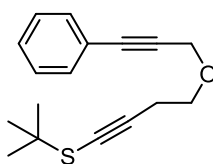


¹H NMR (400MHz, CDCl₃) δ 7.60 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.50 – 7.35 (m, 3H), 4.99 (s, 2H), 1.43 (s, 9H).^h

¹³C NMR (76 MHz, CDCl₃) δ 153.5, 133.2, 131.0, 128.7, 119.5, 90.7, 87.4, 80.2, 79.1, 54.8, 48.4, 30.4.

HRMS-EI : Calculated for C₁₆H₁₆O₂S [M]⁺: 272.0871; found: 272.0843.

tert-butyl(4-((3-phenylprop-2-yn-1-yl)oxy)but-1-yn-1-yl)sulfane (**3.1v**)



Using standard procedure **3-A** with 0.350 mmol of alkyne **S-15** and thiosulfonate **S-6**. Solvent system = Hexanes/Et₂O 19:1. Produced 46.7 mg (49% yield) of a colourless oil.

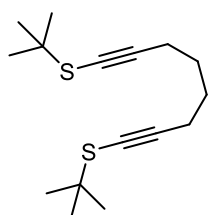
¹H NMR (400 MHz, CDCl₃) δ 7.50 – 7.41 (m, 2H), 7.37 – 7.27 (m, 3H), 4.41 (s, 2H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 7.1 Hz, 2H), 1.40 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 131.9, 128.6, 128.4, 122.7, 93.6, 86.5, 85.0, 69.6, 68.5, 59.0, 47.3, 30.3, 21.6.

HRMS-EI : Calculated for C₁₆H₁₇OS [M-CH₃]⁺: 257.0995; found: 257.1025.

^h Inseparable by-product observed by ¹H NMR spectrum. Internal NMR standard shows the purified sample is 82% w/w desired product. Peaks in the ¹³C NMR were assigned after isolating the by-product upon reacting the mixture using procedure 3-D.

1,8-bis(*tert*-butylthio)octa-1,7-diyne (**3.1w**)



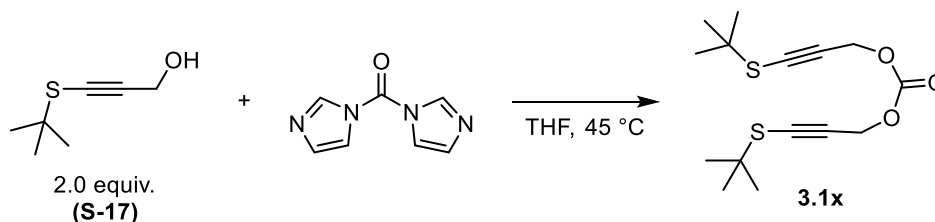
Using standard procedure **3-A** with 0.708 mmol of 1,7-octadiyne, 2.2 equivalents of thiosulfonate **S-6** and 2.4 equivalents of *n*BuLi. Solvent system = Hexanes/Et₂O 99:1. Produced 176 mg (88% yield) of a pale yellow oil.

¹H NMR (400MHz, CDCl₃) δ 2.45 – 2.34 (m, 4H), 1.73 – 1.61 (m, 4H), 1.39 (s, 18H).

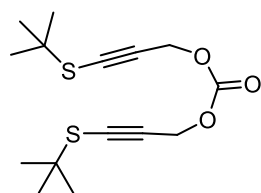
¹³C NMR (101 MHz, CDCl₃) δ 96.9, 68.3, 47.1, 30.3, 28.1, 19.9.

HRMS-ESI : Calculated for C₁₂H₁₇S₂ [M-C₄H₉]⁺: 225.0772; found: 225.0759.

bis(3-(*tert*-butylthio)prop-2-yn-1-yl) carbonate (**3.1x**)



In a round bottom flask was added alcohol **S-17** (110 mg, 0.764 mmol, 2.0 equiv.) in dry THF (7.6 mL, 0.05 M). Carbonyldiimidazole (61.9 mg, 0.382 mmol, 1.0 equiv.) was then added, and the mixture was left to stir at 45 °C for 3 h. The reaction mixture was diluted with water and Et₂O. The organic phase was then dried over MgSO₄ and filtered to produce a crude. The crude was then purified by silica gel chromatography using Hexanes/EtOAc 95:5 as the eluent system to yield 19.4 mg (16% yield) of the desired substrate **3.1x** as a white solid.ⁱ

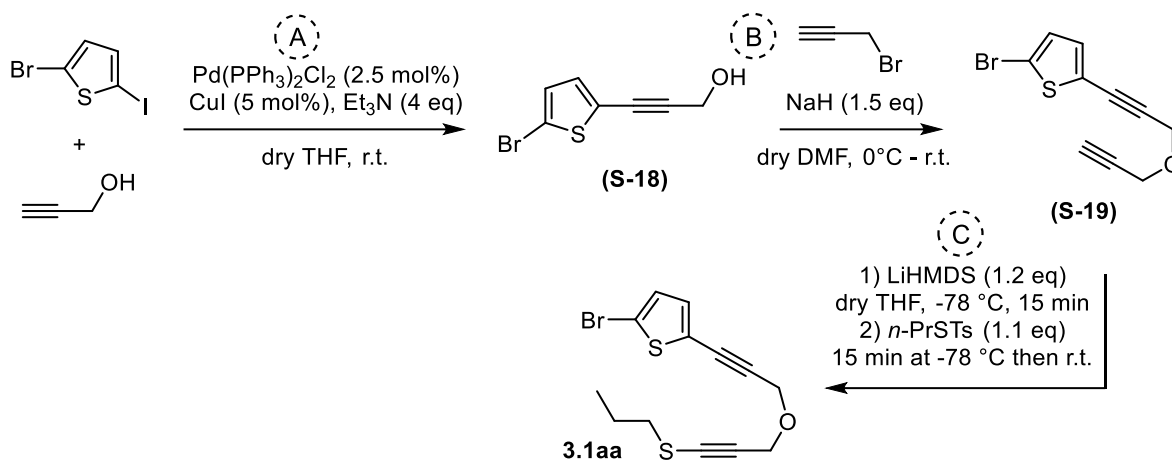


¹H NMR (400MHz, CDCl₃) δ 4.91 (s, 4H), 1.41 (s, 18H).

¹³C NMR (101 MHz, CDCl₃) δ 154.3, 90.8, 79.3, 57.1, 48.4, 30.4.

ⁱ MS data could not be obtained with the following techniques: APCI, ESI and EI.

7.4.5 Synthesis and characterization of yne-alkynyl sulfide **3.1aa**



(A) In a flame-dried round bottom flask under N_2 atmosphere was added propargyl alcohol (1.05 mmol, 1.05 equiv.), 2-bromo-5-iodothiophene (1.00 mmol, 1.00 equiv.), triethylamine (0.28 mL, 2.00 mmol, 2.0 equiv.) and dry THF (10 mL, 0.1 M). The stirred solution was purged with N_2 gas over about 5 min. To the stirred solution was added at once both $\text{Pd(PPh}_3)_2\text{Cl}_2$ (9.9 mg, 0.0141 mmol, 0.025 equiv.) and copper(I) iodide (5.4 mg, 0.0281 mmol, 0.05 equiv.). The stirred reaction mixture was purged with further N_2 gas over another 5 min, and then stirred at room temperature overnight (16 hours). Et_2O and 2.5% HCl aq. solution were then added to the reaction mixture. The organic phase was washed three times with 2.5% HCl aq. solution and once with brine. The organic phase was dried with MgSO_4 , filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using hexanes/ EtOAc 70:30 as the eluent system to yield 193 mg (89% yield) of the desired propargyl alcohol **S-18** as a brown solid.

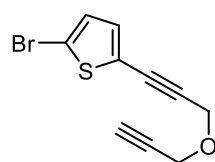
3-(5-bromothiophen-2-yl)prop-2-yn-1-ol (**S-18**)

^1H NMR (400MHz, CDCl_3) δ 6.96 (d, $J = 3.9$ Hz, 1H), 6.92 (d, $J = 3.9$ Hz, 1H), 4.49 (s, 2H), 1.68 (s, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 132.9, 130.1, 124.3, 113.5, 92.3, 78.3, 51.8.

(B) In a round bottom flask was cooled to 0°C a solution of alcohol **S-18** (181 mg, 0.832 mmol, 1.0 equiv.) in dry DMF (1.7 mL, 0.5 M). To the cooled solution was added NaH (40 mg, 60% w/w, 0.998 equiv.). When most of the evolution of H_2 gas had passed, propargyl bromide (0.14 mL, 80% w/w solution in toluene, 1.249 mmol, 1.5 equiv.) was added then the solution was brought to room temperature and stirred for 1 h. The mixture was quenched with NH_4Cl sat. aq. solution and diluted with Et_2O . The organic phase was washed once with water, then with brine. The organic phase was dried using MgSO_4 , and then concentrated under reduced pressure to produce a crude. The crude was then purified via flash chromatography using hexanes/ Et_2O 98:2 as the eluent system to yield 97 mg (46% yield) of the desired alkyne **S-19** as a pale yellow liquid.

2-bromo-5-(3-(prop-2-yn-1-yloxy)prop-1-yn-1-yl)thiophene (**S-19**)

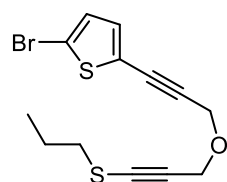


¹H NMR (400MHz, CDCl₃) δ 6.98 (d, *J* = 3.8 Hz, 1H), 6.93 (d, *J* = 3.9 Hz, 1H), 4.48 (s, 2H), 4.29 (d, *J* = 2.4 Hz, 2H), 2.48 (t, *J* = 2.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 133.2, 130.1, 124.2, 113.6, 89.4, 79.3, 78.9, 75.4, 57.4, 56.9.

 In a flame-dried round bottom flask N₂ atmosphere was added the alkyne **S-19** (0.392 mmol, 1.0 equiv.) and dry THF (3 mL, 0.13 M) via syringe. The solution was cooled to -78 °C. To the stirred solution was added LiHMDS (0.47 mL, 0.1 M in THF, 0.470 mmol, 1.2 equiv.) dropwise over 5 minutes. The solution was then stirred at -78 °C for another 15 min. A prepared solution of thiosulfonate **S-8** (0.431 mmol, 1.1 equiv.) in dry THF (1 mL) was then added dropwise to the reaction mixture via syringe, then the solution was stirred for an additional 15 min at -78 °C before slowly warming to room temperature. The solution was stirred at room temperature for 45 minutes before it was quenched with NH₄Cl aq. solution. The reaction mixture was then extracted with Et₂O, washed once with water, then brine. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using hexanes/Et₂O 95:5 as the eluent system to yield 113 mg (84% yield) of the desired alkynyl sulfide **3.1aa** as a dark yellow oil.

2-bromo-5-(3-((3-(propylthio)prop-2-yn-1-yl)oxy)prop-1-yn-1-yl)thiophene (**3.1aa**)



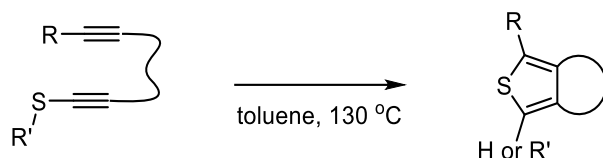
¹H NMR (400MHz, CDCl₃) δ 6.97 (d, *J* = 3.9 Hz, 1H), 6.92 (d, *J* = 3.9 Hz, 1H), 4.46 (s, 2H), 4.38 (s, 2H), 2.70 (dd, *J* = 7.4, 6.9 Hz, 2H), 1.77 (h, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 133.1, 130.1, 124.2, 113.6, 89.7, 89.2, 79.1, 78.5, 58.0, 57.2, 37.6, 22.8, 13.0.

HRMS-EI : Calculated for C₁₃H₁₃OS₂ [M]⁺: 327.9591; found: 327.9586.

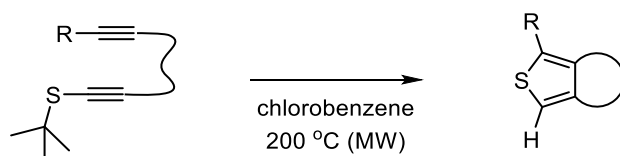
7.4.6 Procedures for the thermal (3+2) cycloaddition cascades

Standard procedure 3-D : for thiophenes **3.2b-d,g,h,j,o,r**.



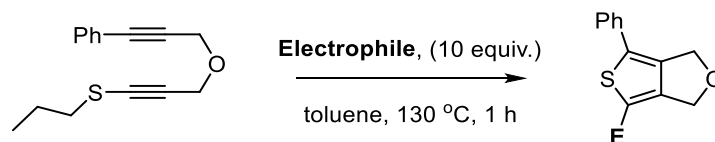
In a sealed reaction vial was added a solution of yne-alkynyl sulfide (0.100 mmol, 1.0 equiv.) in dry toluene (1.0 mL, 0.1 M). The solution was heated in an oil bath at 130 °C for the indicated time. Upon completion (determined by TLC), the mixture was evaporated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired thiophene.

Standard procedure 3-E : for thiophenes **3.2i,p,u,w**.



In a microwave vial was added a solution of yne-alkynyl sulfide (0.100 mmol, 1.0 equiv.) in chlorobenzene (1.0 mL, 0.1 M). The solution was heated at 200 °C in an Anton Paar Monowave 400 microwave reaction for the indicated time. Upon completion (determined by TLC), the mixture was evaporated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired thiophene.

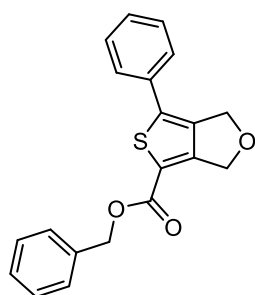
Standard procedure 3-F : for thiophenes **3.2a**, **3.2a(a-f)** and **3.2ak**.



In a sealed reaction vial was added a solution of yne-alkynyl sulfide **3.2c** (0.100 mmol, 1.0 equiv.), the electrophile (1.00 mmol, 10.0 equiv.) in dry toluene (1.0 mL, 0.1 M). The solution was heated in an oil bath at 130 °C for 1 h. The mixture was evaporated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired thiophene.

7.4.7 Characterization of thiophene products 3.2

benzyl 6-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-4-carboxylate (3.2b)



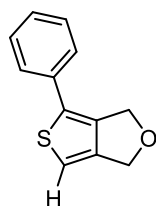
Using standard procedure **3-D** with 0.0536 mmol of substrate **3.1m**. Reaction time = 2 h. Solvent system = Hexanes/EtOAc 98:2. Produced 14.8 mg (82% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 7.46 – 7.30 (m, 10H), 5.32 (s, 2H), 5.05 (s, 2H), 5.03 (s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8, 153.8, 141.8, 139.0, 135.9, 132.8, 129.4, 128.8, 128.8, 128.5, 128.2, 126.5, 119.1, 69.7, 69.2, 67.0.

HRMS-EI : Calculated for C₂₀H₁₆O₃S [M]⁺: 336.0820; found: 336.0836.

4-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan (3.2c)



Using standard procedure **3-D** with 0.100 mmol of substrate **3.1f**. Reaction time = 1 h. Solvent system = Hexanes/Et₂O 9:1. Produced 17.2 mg (85% yield) of a white solid.

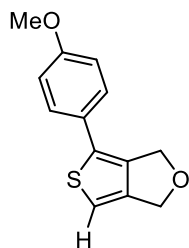
¹H NMR (400MHz, CDCl₃) δ 7.41 – 7.35 (m, 4H), 7.31 – 7.23 (m, 1H), 6.79 (t, *J* = 1.3 Hz, 1H), 5.05 (s, 2H), 4.85 (q, *J* = 1.1 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 146.7, 141.2, 133.8, 132.2, 129.2, 127.4, 126.0, 111.6, 69.1, 68.1.

HRMS-EI : Calculated for C₁₂H₁₀OS [M]⁺: 202.0452; found: 202.0442.

Supplementary ¹H, ¹³C, COSY, HSQC, HMBC and NOESY data for **3.2c** in C₆D₆ section 9.1.

4-(4-methoxyphenyl)-1*H*,3*H*-thieno[3,4-*c*]furan (3.2d)



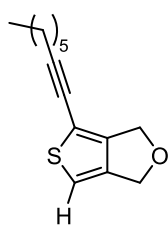
Using standard procedure **3-D** with 0.100 mmol of substrate **3.1o** Reaction time = 1.5 h. Solvent system = Hexanes/Et₂O 9:1. Produced 20.6 mg (89% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H), 5.01 (s, 2H), 4.84 (s, 2H), 3.83 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 159.0, 146.6, 140.1, 132.1, 127.3, 126.6, 114.6, 110.5, 68.9, 68.1, 55.5.

HRMS-EI : Calculated for C₁₃H₁₂O₂S [M]⁺: 232.0558; found: 232.0548.

4-(oct-1-yn-1-yl)-1*H*,3*H*-thieno[3,4-*c*]furan (3.2g)



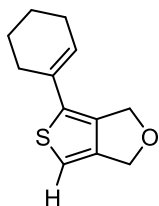
Using standard procedure **3-D** with 0.100 mmol of substrate **3.1p**. Reaction time = 0.5 h. Solvent system = Hexanes/EtOAc 98:2. Produced 21.0 mg (90% yield) of a yellow oil.

¹H NMR (400MHz, CDCl₃) δ 6.65 (t, *J* = 1.3 Hz, 1H), 4.83 (s, 2H), 4.79 (q, *J* = 1.1 Hz, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 1.62 – 1.22 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 148.3, 145.0, 113.0, 112.7, 96.9, 72.2, 68.7, 68.4, 31.4, 28.7, 28.6, 22.7, 19.9, 14.2.

HRMS-EI : Calculated for $\text{C}_{14}\text{H}_{18}\text{OS}$ $[\text{M}]^+$: 234.1078; found: 234.11075.

4-(cyclohex-1-en-1-yl)-1*H*,3*H*-thieno[3,4-*c*]furan (3.2h)



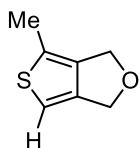
Using standard procedure **3-D** with 0.100 mmol of substrate **3.1q**. Reaction time = 4.5 h. Solvent system = Hexanes/ Et_2O 95:5. Produced 14.1 mg (68% yield) of a yellow oil.

^1H NMR (400MHz, CDCl_3) δ 6.62 (t, J = 1.4 Hz, 1H), 5.89 (tt, J = 4.0, 1.7 Hz, 1H), 4.90 (s, 2H), 4.77 (q, J = 1.1 Hz, 2H), 2.35 – 2.26 (m, 2H), 2.23 – 2.14 (m, 2H), 1.82 – 1.69 (m, 2H), 1.69 – 1.55 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 146.0, 139.3, 135.0, 130.9, 125.1, 109.5, 69.3, 67.8, 28.0, 25.8, 22.8, 21.9.

HRMS-EI : Calculated for $\text{C}_{12}\text{H}_{14}\text{OS}$ $[\text{M}]^+$: 206.0765; found: 206.0750.

4-methyl-1*H*,3*H*-thieno[3,4-*c*]furan (3.2i)



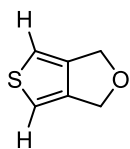
Using standard procedure **3-E** with 0.100 mmol of substrate **3.1r**. Reaction time = 1 h. Solvent system = Hexanes/ EtOAc 98:2. Produced 5.2 mg (37% yield)^j of a yellow oil.

^1H NMR (400MHz, CDCl_3) δ 6.58 (t, J = 1.2 Hz, 1H), 4.78 (s, 2H), 4.75 (q, J = 1.0 Hz, 2H), 2.33 (t, J = 1.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 145.3, 142.3, 127.0, 109.8, 68.6, 67.6, 13.6.

HRMS-EI : Calculated for $\text{C}_7\text{H}_9\text{OS}$ $[\text{M}]^+$: 140.0296; found: 140.0278.

1*H*,3*H*-thieno[3,4-*c*]furan (3.2j)



Using standard procedure **3-D** with 0.300 mmol of substrate **3.1s**. Reaction time = 5 h. Solvent system = Hexanes/ EtOAc 95:5. Produced 16.1 mg (43% yield)^j of a yellow solid.

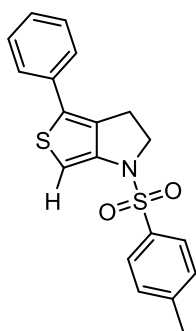
^1H NMR (400MHz, CDCl_3) δ 6.85 (t, J = 0.9 Hz, 2H), 4.84 (d, J = 0.8 Hz, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 145.8, 112.9, 68.2.

HRMS-EI : Calculated for $\text{C}_{13}\text{H}_{12}\text{S}$ $[\text{M}]^+$: 126.0139; found: 200.0642.

^j Product was shown to be volatile upon concentrating with a vacuum line.

4-phenyl-1-tosyl-2,3-dihydro-1*H*-thieno[3,4-*b*]pyrrole (3.2o)



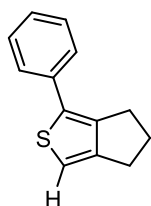
Using standard procedure **3-D** with 0.0490 mmol of substrate **3.1a**. Reaction time = 45 min. Solvent system = Hexanes/EtOAc gradient of 9:1 → 5:1 Produced 12.8 mg (74% yield) of a yellow solid.

¹H NMR (400MHz, CDCl₃) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.21 (m, 7H), 6.77 (s, 1H), 4.16 (t, *J* = 7.8 Hz, 2H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.40 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 144.5, 144.1, 133.9, 133.7, 133.4, 132.6, 129.9, 129.0, 127.7, 127.6, 126.0, 100.8, 55.7, 25.8, 21.7.

HRMS-EI : Calculated for C₁₉H₁₇NO₂S₂ [M]⁺: 355.0701; found: 355.0676.

1-phenyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene (3.2p)



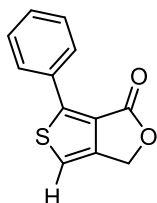
Using standard procedure **3-E** with 0.100 mmol of substrate **3.1t**. Reaction time = 3 h. Solvent system = Hexanes. Produced 13.7 mg (69% yield) of a pale yellow oil.

¹H NMR (400MHz, CDCl₃) δ 7.56 (dt, *J* = 8.2, 1.6 Hz, 2H), 7.43 – 7.33 (m, 2H), 7.29 – 7.20 (m, 1H), 6.74 (t, *J* = 1.4 Hz, 1H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.70 (td, *J* = 7.2, 1.1 Hz, 2H), 2.48 – 2.40 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 150.6, 145.1, 135.1, 132.6, 128.8, 126.7, 126.4, 113.0, 31.5, 28.7, 27.5.

HRMS-EI : Calculated for C₁₃H₁₂S [M]⁺: 200.0660; found: 200.0642.

6-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-1-one (3.2r)



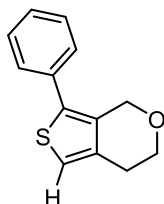
Using standard procedure **3-D** with 0.0833 mmol of substrate **3.1u**. Reaction time = 0.5 h. Solvent system = Hexanes/EtOAc gradient of 98:2 → 85:15. Produced 18.7 mg (quantitative yield) of a yellow solid.

¹H NMR (400MHz, CDCl₃) δ 8.07 – 8.02 (m, 2H), 7.49 – 7.36 (m, 3H), 6.98 (t, *J* = 1.4 Hz, 1H), 5.20 (d, *J* = 1.3 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 164.2, 148.8, 148.1, 131.3, 129.7, 129.1, 128.1, 126.2, 112.8, 66.7.

HRMS-EI : Calculated for C₁₂H₈O₂S [M]⁺: 216.1245; found: 216.0250.

3-phenyl-6,7-dihydro-4*H*-thieno[3,4-*c*]pyran (3.2u)



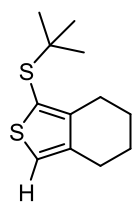
Using standard procedure **3-E** with 0.0740 mmol of substrate **3.1v**. Reaction time = 8 h. Solvent system = Hexanes:EtOAc 95:5. Produced 10.0 mg (62% yield)

¹H NMR (400MHz, CDCl₃) δ 7.44 – 7.28 (m, 5H), 6.97 (t, *J* = 1.3 Hz, 1H), 4.91 (s, 2H), 3.92 (t, *J* = 5.9 Hz, 2H), 2.89 (td, *J* = 5.9, 1.3 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 136.2, 135.6, 134.2, 131.7, 128.9, 128.0, 127.4, 119.1, 67.8, 65.3, 27.0.

HRMS-EI : Calculated for C₁₃H₁₂OS [M]⁺: 216.0609; found: 216.0630.

1-(*tert*-butylthio)-4,5,6,7-tetrahydrobenzo[*c*]thiophene (3.2w)



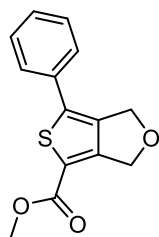
Using standard procedure **3-E** with 0.100 mmol of substrate **3.1w**. Reaction time = 6 h. Solvent system = Hexanes. Produced 8.3 mg (37% yield) of a colorless oil.

¹H NMR (400MHz, CDCl₃) δ 6.98 (t, *J* = 1.3 Hz, 1H), 2.77 – 2.65 (m, 4H), 1.77 – 1.68 (m, 4H), 1.32 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 145.6, 139.1, 125.0, 123.7, 48.2, 31.0, 26.7, 26.5, 23.4, 23.3.

HRMS-EI : Calculated for C₁₂H₁₈S₂ [M]⁺: 226.0850; found: 226.08219.

methyl 6-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-4-carboxylate (3.2a)



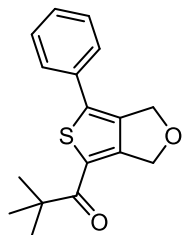
Using standard procedure **3-F** with 0.100 mmol of substrate **3.1c** and methyl chloroformate. Solvent system = Hexanes/EtOAc gradient of 9:1 → 17:3. Produced 20.8 mg (85% yield) of a yellow solid.

¹H NMR (400MHz, CDCl₃) δ 7.47 – 7.29 (m, 5H), 5.05 (s, 2H), 5.03 (s, 2H), 3.87 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 162.4, 153.6, 141.7, 138.7, 132.8, 129.4, 128.8, 126.4, 119.0, 69.7, 69.2, 52.4.

HRMS Calculated for C₁₄H₁₂O₃S [M]⁺: 260.0507; found: 260.0519.

2,2-dimethyl-1-(6-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-4-yl)propan-1-one (3.2aa)



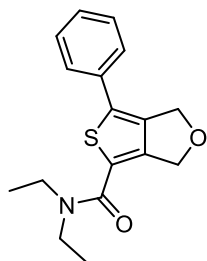
Using standard procedure **3-F** with 0.100 mmol of substrate **3.1c** and trimethyl acetyl chloride. Solvent system = Hexanes/EtOAc gradient of 96:4 → 94:6. Produced 16.7 mg (58% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 7.51 – 7.30 (m, 5H), 5.09 (s, 2H), 5.06 (s, 2H), 1.41 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 198.5, 157.0, 141.0, 137.5, 132.8, 129.4, 128.8, 126.5, 123.7, 71.1, 68.6, 43.8, 27.9.

HRMS-EI : Calculated for C₁₇H₁₈O₂S [M]⁺: 286.1028; found: 286.0999.

N,N-diethyl-6-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-4-carboxamide (3.2ab)



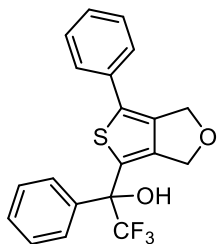
Using standard procedure **3-F** with 0.100 mmol of substrate **3.1c** and diethylcarbonyl chloride. Solvent system = Hexanes/EtOAc 8:2. Produced 8.8 mg (29% yield) of a yellow solid.

¹H NMR (400MHz, CDCl₃) δ 7.45 – 7.37 (m, 4H), 7.36 – 7.29 (m, 1H), 5.05 (s, 4H), 3.60 (q, *J* = 7.0 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) 162.4, 153.2, 140.7, 134.4, 132.9, 129.2, 128.1, 126.2, 121.0, 69.9, 68.7, 42.4, 13.9.

HRMS-EI : Calculated for C₁₇H₁₉NO₂S [M]⁺: 301.1136; found: 301.1121.

2,2,2-trifluoro-1-phenyl-1-(6-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-4-yl)ethan-1-ol (3.2ac)



Using standard procedure **3-F** with 0.100 mmol of substrate **3.1c** and 2,2,2-trifluoroacetophenone. Solvent system = Hexanes/EtOAc 10:1. Produced 24.4 mg (65% yield) of white solid.

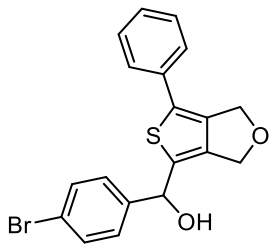
¹H NMR (400MHz, CDCl₃) δ 7.68 – 7.60 (m, 2H), 7.46 – 7.37 (m, 3H), 7.38 – 7.22 (m, 5H), 4.90 (s, 2H), 4.44 (d, *J* = 13.0 Hz, 1H), 4.32 (d, *J* = 13.1 Hz, 1H), 3.49 (br. s, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 146.0, 141.2, 137.5, 133.0, 132.8, 129.5, 129.2, 128.7, 128.2, 127.8, 127.0 (q, *J* = 1.8Hz), 126.1, 125.0 (q, *J* = 286.2 Hz)^k, 77.8 (q, 30.4 Hz)¹⁵, 68.5, 68.3 (q, *J* = 2.2 Hz).

¹⁹F NMR (377 MHz, CDCl₃) δ -75.9.

HRMS-EI : Calculated for C₂₀H₁₅F₃O₂S [M]⁺: 376.0745; found: 376.0721.

(4-bromophenyl)(6-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-4-yl)methanol (3.2ad)



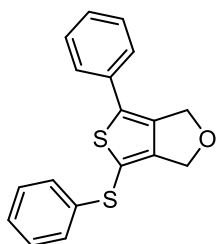
Using standard procedure **3-F** with 0.100 mmol of substrate **3.1c** and 4-bromobenzaldehyde. Solvent system = Hexanes/EtOAc gradient of 9:1 → 8:2. Produced 12.7 mg (33% yield) of a white solid.

¹H NMR (600 MHz, acetone-d₆) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.35 (m, 4H), 7.27 (t, *J* = 7.0 Hz, 1H), 5.98 – 5.94 (m, 1H), 5.42 (d, *J* = 4.4 Hz, 1H), 4.90 (s, 2H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.45 (d, *J* = 12.4 Hz, 1H).^l

¹³C NMR (151 MHz, acetone-d₆) δ 144.4 (x2), 144.0 (x2), 142.5, 135.6 (2x), 134.7, 132.4, 131.0, 130.1, 129.5, 128.1, 126.5, 122.0, 71.1 (x2), 68.8, 67.9.^m

HRMS-EI : Calculated for C₁₉H₁₅BrO₂S [M]⁺: 385.9976; found: 385.9956.

4-phenyl-6-(phenylthio)-1*H*,3*H*-thieno[3,4-*c*]furan (3.2ae)



Using standard procedure **3-F** with 0.100 mmol of substrate **3.1c** and thiosulfonate **S-11**. Solvent system = Hexanes/EtOAc 95:5. Produced 24.6 mg (79% yield) of a white solid.

¹H NMR (400MHz, CDCl₃) δ 7.43 – 7.25 (m, 9H), 7.23 – 7.17 (m, 1H), 5.09 (s, 2H), 4.78 (s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 153.1, 141.6, 137.3, 136.9, 133.3, 129.3, 129.3, 128.0, 127.6, 126.6, 126.0, 117.7, 69.8, 68.2.

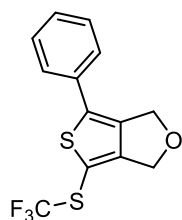
HRMS-EI : Calculated for C₁₈H₁₄OS₂ [M]⁺: 310.0486; found: 310.0506.

^k It was not possible to locate all the peaks of the quadruplet due to low intensity and/or overlapping with other peaks.

^l Acetone-d₆ is used as the solvent as the compound rapidly degrades in chloroform.

^m Splitting of four carbons peaks is seen when the spectra is taken with acetone-d₆.

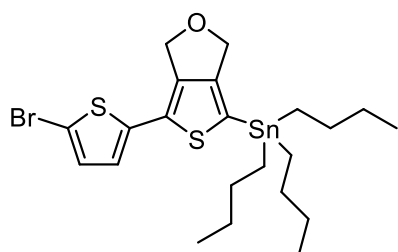
4-phenyl-6-((trifluoromethyl)thio)-1*H*,3*H*-thieno[3,4-*c*]furan (**3.2af**)



Using standard procedure **3-F** with 0.100 mmol of substrate **3.1c** and *N*-Methyl-*N*-[(trifluoromethyl)thio]-*p*-toluenesulfonamide. Due to difficulty in isolating **3.2af** from the complex mixture by silica gel chromatography, the yield for **3.2af** was determined by NMR using 2.0 μ L of 1,2-DBE as external standard. NMR Yield = 23%

(6-(5-bromothiophen-2-yl)-1*H*,3*H*-thieno[3,4-*c*]furan-4-yl)tributylstannane (**3.2ak**)

Using a slightly modified version of standard procedure **3-F** with 0.075 mmol of substrate **3.1aa** and tributyltin chloride. Crude concentrate was first filtered through silica pad with hexanes/ Et_3N 97:3 eluent to remove the majority of excess (*n*-Bu) $_3$ SnCl before proceeding with flash chromatography. Solvent system = Hexanes/ Et_2O 98:2. Produced 25.0 mg (58% yield) of a pale yellow oil.



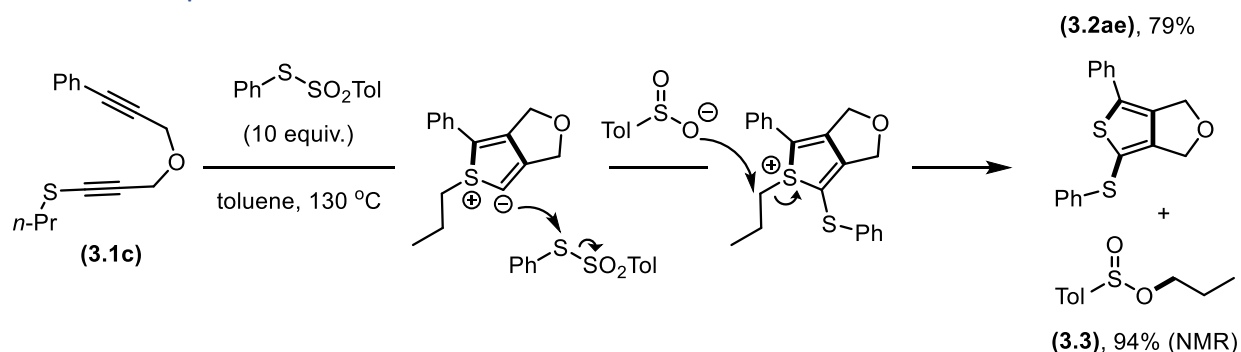
^1H NMR (400MHz, CDCl_3) δ 6.96 (d, J = 3.8 Hz, 1H), 6.77 (d, J = 3.9 Hz, 1H), 4.93 (t, J = 1.1 Hz, 2H), 4.80 – 4.76 (m, 2H), 1.67 – 1.44 (m, 6H), 1.34 (dq, J = 14.4, 7.3 Hz, 6H), 1.21 – 0.99 (m, 6H), 0.91 (t, J = 7.3 Hz, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 154.9, 142.4, 138.4, 130.8, 130.3, 123.9, 123.6, 111.2, 69.1, 68.6, 29.1, 27.4, 13.8, 10.9.

HRMS-EI : Calculated for $\text{C}_{22}\text{H}_{33}\text{BrOS}_2\text{Sn}$ [M] $^+$: 578.1058; found:

578.0154.ⁿ

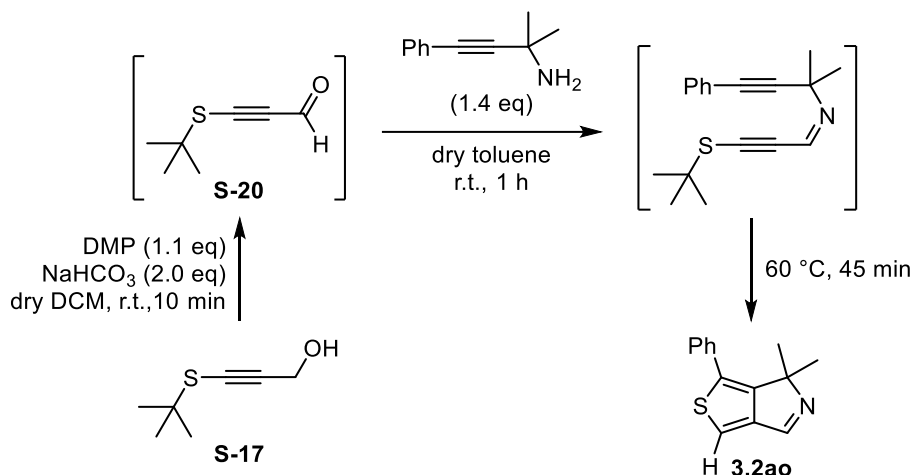
7.4.8 Proposed mechanism for the formation of **3.3**



Using standard procedure **4-F**, the crude was analyzed by NMR before purification by silica gel chromatography. By-product **3.3** was observed by NMR in a 94% yield when 2.0 μ L of 1,2-DBE was used as external NMR standard.

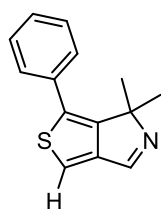
ⁿ [M] $^+$ reported for the abundant ^{81}Br / ^{120}Sn isotopologue.

7.4.9 Two-step procedures for the expedited synthesis of **3.2ao** and **3.2n,f**



In a reaction vial was added a solution of alcohol **S-17** (22.6 mg, 0.157 mmol, 1.0 equiv.) in dry DCM (0.5 mL, 0.3 M). NaHCO_3 (26.4 mg, 0.314 mmol, 2.0 equiv.) is then added, followed by Dess-Martin periodinane (73.4 mg, 0.173 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 10 minutes, then filtered through a short pad of silica gel using hexanes/DCM 1:1 (around 2 mL) as the eluent to afford a solution of aldehyde **S-20**.^o 2-methyl-4-phenylbut-3-yn-2-amine prepared as described in the literature¹²⁹ (29.9 mg, 0.188 mmol, 1.4 equiv.) was added to the filtrate and the mixture is stirred at room temperature for 1 hour to obtain the imine condensate intermediate. Dry toluene (2 mL, 0.08 M) was then added to the mixture, and the hexanes and DCM are evaporated under reduced pressure at 40 °C. The resulting solution is stirred at 60 °C for 45 minutes in a reaction vial, then the mixture is concentrated under reduced pressure to produce a crude mixture. The crude mixture was then purified via flash chromatography using hexanes/acetone 3:1 as the eluent system to yield 24.6 mg (69% yield) of the desired product **3.2ao** as a pale yellow solid.

4,4-dimethyl-3-phenyl-4H-thieno[3,4-c]pyrrole (**3.2ao**)

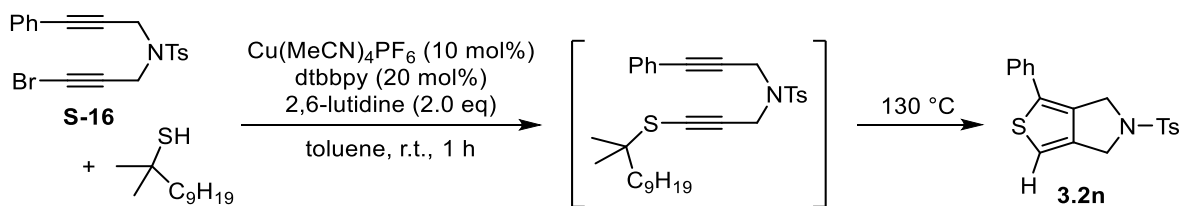


¹H NMR (500MHz, CDCl_3) δ 8.05 (s, 1H), 7.54 (dd, J = 8.2, 1.3 Hz, 2H), 7.45 – 7.34 (m, 3H), 7.12 (s, 1H), 1.49 (s, 6H).

¹³C NMR (126 MHz, CDCl_3) δ 154.4, 153.9, 148.8, 133.5, 133.3, 129.0, 128.7, 128.1, 114.1, 71.0, 25.9.

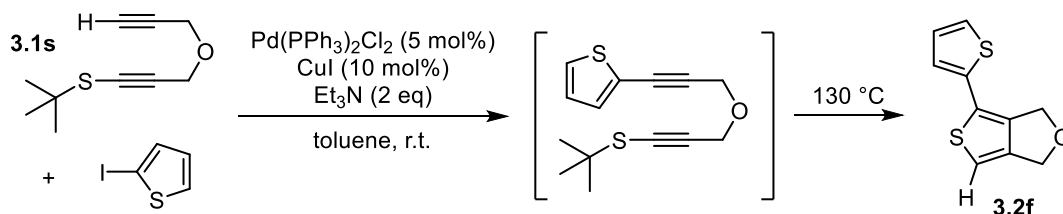
HRMS-EI : Calculated for $\text{C}_{14}\text{H}_{13}\text{NS}$ $[\text{M}]^+$: 227.0769; found: 227.0776.

^o The aldehyde is used in solution as it degrades upon concentration.



Derived from the coupling method developed by Collins *et al.*⁷⁵:

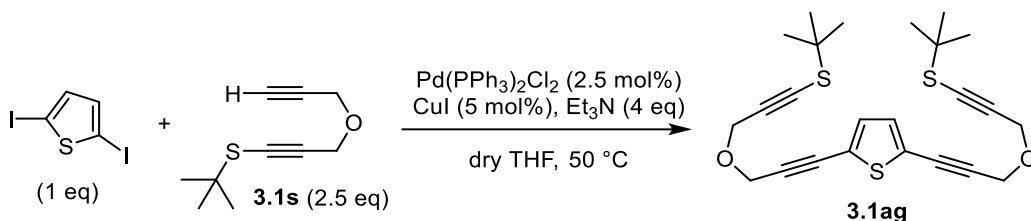
In a flame-dried reaction vial was added 4,4'-di-*tert*-butyl-2,2'-bipyridine (2.7 mg, 0.01 mmol, 0.2 equiv.) and bromoalkyne **S-16** (20.1 mg, 0.05 mmol, 1.0 equiv.). Three vacuum/N₂ purge cycles were performed to refill the flask with N₂ atmosphere. *Tert*-dodecyl thiol (13.0 μ L, 0.055 mmol, 1.1 equiv.), 2,6-lutidine (11.6 μ L, 0.1 mmol, 2.0 equiv.) and dry toluene (0.5 mL, 0.1M) were all added to the vial via syringe. The solution was degassed with N₂ for 2 minutes, then Cu(MeCN)₄PF₆ (1.9 mg, 0.003 mmol, 0.1 equiv.) was added quickly. The reaction vial was sealed then stirred at room temperature for one hour (until completion of the C-S coupling, followed by TLC) then at 130°C for 1.5 hours. The resulting mixture was concentrated under reduced pressure then purified by silica gel chromatography using a gradient of hexanes/EtOAc 19:1 $\rightarrow$ 9:1 as the eluent system to yield 8.6 mg (48% yield) of the desired product **3.2n** as a yellow solid. **3.2n** was previously characterized in section 7.4.9.



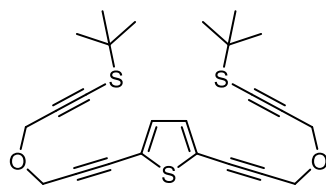
In a flame-dried reaction vial was added yne-alkynyl sulfide **3.1s** (18.2 mg, 0.100 mmol, 1.0 equiv.), 2-iodothiophene (11.6 μ L, 0.105 mmol, 1.05 equiv.), triethylamine (27.9 μ L, 0.200 mmol, 2.0 equiv.) and dry toluene (1 mL, 0.1 M). The stirred solution was purged with N₂ gas over one minute. To the stirred solution was added at once both Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 0.05 equiv.) and copper(I) iodide (1.9 mg, 0.01 mmol, 0.1 equiv.). The stirred reaction mixture was purged with further N₂ gas over another minute and then stirred at room temperature for 1 hour (until completion of the Sonogashira coupling, followed by TLC) then at 130 °C for 15 minutes. The resulting mixture was then filtered through a short pad of celite using DCM as the eluent, then evaporated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using hexanes/Et₂O 95:5 as the eluent system to yield 10.8 mg (52% yield) of the desired product **3.2f** as a white solid. **3.2f** was previously characterized in section 7.4.9.

7.4.10 Synthesis of **3.1ag** and three-step procedure towards polythiophenes **3.2a(p,q)**

2,5-bis(3-((3-(*tert*-butylthio)prop-2-yn-1-yl)oxy)prop-1-yn-1-yl)thiophene (**3.1ag**)



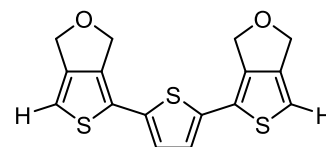
In a flame-dried round bottom flask under N₂ atmosphere was added yne-alkynyl sulfide **3.1s** (1.406 mmol, 2.5 equiv.), 2,5-diiodothiophene (0.562 mmol, 1.0 equiv.), triethylamine (0.31 mL, 2.248 mmol, 4.0 equiv.) and dry THF (6.0 mL, 0.1M). The stirred solution was purged with N₂ gas over 5 min. To the stirred solution was added at once both Pd(PPh₃)₂Cl₂ (9.9 mg, 0.0141 mmol, 0.025 equiv.) and copper(I) iodide (5.4 mg, 0.0281 mmol, 0.05 equiv.). The stirred reaction mixture was purged with further N₂ gas over another 5 min, and then stirred at 50 °C for 2 hours until completion. Et₂O and 2.5% HCl aq. solution were then added to the reaction mixture. The organic phase was washed three times with 2.5% HCl aq. solution and once with brine. The organic phase was dried with MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using Hexanes/Et₂O 95:5 as the eluent system to yield 89 mg (36% yield) of the desired bis alkynyl sulfide **3.1ag** as a yellow oil.^p



¹H NMR (400MHz, CDCl₃) δ 7.06 (s, 2H), 4.49 (s, 4H), 4.46 (s, 4H), 1.43 (s, 18H).

¹³C NMR (101 MHz, CDCl₃) δ 132.4, 124.1, 92.6, 89.6, 79.4, 77.9, 58.1, 57.0, 48.1, 30.4.

2,5-bis(1*H*,3*H*-thieno[3,4-*c*]furan-4-yl)thiophene (**3.2ap**)



Using standard procedure **3-D** with 0.177 mmol of substrate **3.1ag**. Reaction time = 0.5 h. Solvent system = EtOAc. Produced 48.9 mg (83% yield) of a white solid.

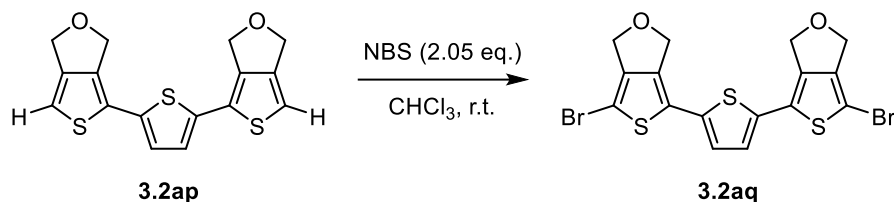
¹H NMR (400MHz, CDCl₃) δ 6.92 (s, 2H), 6.72 (s, 2H), 4.96 (s, 4H), 4.84 (s, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 146.4, 141.8, 135.8, 125.1, 124.7, 111.4, 68.7, 68.3.

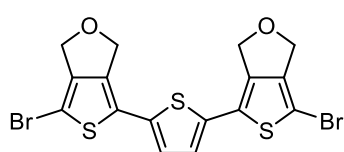
HRMS-EI : Calculated for C₁₆H₁₂O₂S₃ [M]⁺: 331.9999; found: 331.9992.

^p Despite testing a variety of conditions and temperatures, **3.1ag** seems to fragment too readily during MS analysis. Characteristic molecular peaks could not be obtained with either of EI, APCI or ESI.

2,5-bis(6-bromo-1*H*,3*H*-thieno[3,4-*c*]furan-4-yl)thiophene (**3.2aq**)



In a small reaction vial was added a solution of **3.2ap** (16.8 mg, 0.0505 mmol, 1.0 equiv.) in CHCl_3 (0.1 M) then *N*-bromosuccinimide (18.4 mg, 0.104 mmol, 2.05 equiv.) was added in small portions. The mixture was stirred at room temperature for one hour before it was quenched with H_2O , and extracted with chloroform. The collected organic phases were then washed with brine. The organic phase was dried with MgSO_4 , filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography (dry load) using Hexanes:EtOAc 8:2 as the eluent system to yield 19.9 mg (80% yield) of the desired product **3.2aq** as a yellow solid.



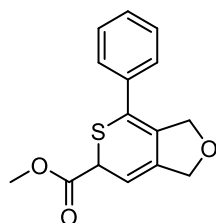
^1H NMR (500MHz, CDCl_3) δ 6.85 (s, 2H), 4.96 (s, 4H), 4.74 (s, 4H).

^{13}C NMR (126 MHz, CDCl_3) δ 146.8, 141.6, 135.2, 126.1, 124.9, 98.6, 69.6, 68.6.

HRMS-ESI : Calculated for $\text{C}_{16}\text{H}_{10}\text{Br}_2\text{O}_2\text{S}_3$ $[\text{M}]^+$: 487.8210; found: 487.8218.

7.4.11 Characterization of 2*H*-thiopyran product **3.4**

methyl 4-phenyl-1,6-dihydro-3*H*-thiopyrano[3,4-*c*]furan-6-carboxylate (**3.4**)



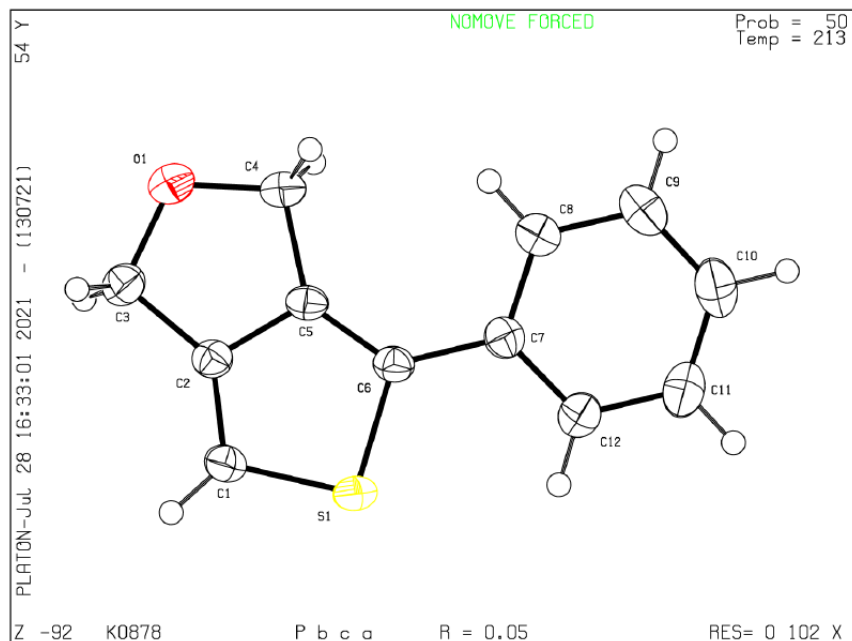
^1H NMR (400MHz, CDCl_3) δ 7.44 – 7.27 (m, 5H), 5.48 (dt, J = 6.2, 1.9 Hz, 1H), 4.67 (d, J = 12.7 Hz, 1H), 4.61 (d, J = 12.7 Hz, 1H), 4.61 – 4.58 (m, 2H), 4.50 (dt, J = 6.2, 1.5 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 170.9, 140.8, 136.8, 128.7, 128.6, 127.9, 127.4, 124.8, 103.0, 71.6, 71.6, 53.0, 42.8.

HRMS-ESI : Calculated for $\text{C}_{15}\text{H}_{14}\text{O}_3\text{S}$ $[\text{M}]^+$: 274.0664; found: 274.0664.

Supplementary COSY, HSQC, HMBC and NOESY data for **3.4** provided in section 9.1.

7.4.12 X-ray of **3.2c**, CCDC deposition number : 2149613



Bond precision: C-C = 0.0018 Å

Wavelength=0.71073

Cell: a=7.6271(3) b=7.0371(2) c=37.2366(13)
 alpha=90 beta=90 gamma=90

Temperature: 213 K

	Calculated	Reported
Volume	1998.59(12)	1998.59(12)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C12 H10 O S	C12 H10 O S
Sum formula	C12 H10 O S	C12 H10 O S
Mr	202.26	202.26
Dx, g cm ⁻³	1.344	1.344
Z	8	8
Mu (mm ⁻¹)	0.284	0.284
F000	848.0	848.0
F000'	849.31	
h,k,lmax	12,11,62	12,11,62
Nref	4909	4901
Tmin,Tmax	0.892,0.944	0.670,0.747
Tmin'	0.878	

Correction method= # Reported T Limits: Tmin=0.670 Tmax=0.747
 AbsCorr = MULTI-SCAN

Data completeness= 0.998

Theta(max)= 36.530

R(reflections)= 0.0514(3566)

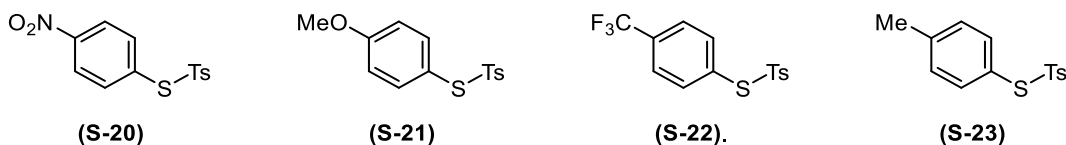
wR2(reflections)= 0.1393(4901)

S = 1.062

Npar= 127

7.5 Supporting Information for Chapter 4

7.5.1 Aryl thiosulfonates **S-20** to **S-23** used for the synthesis of *S*-(Aryl) yne-alkynyl sulfides

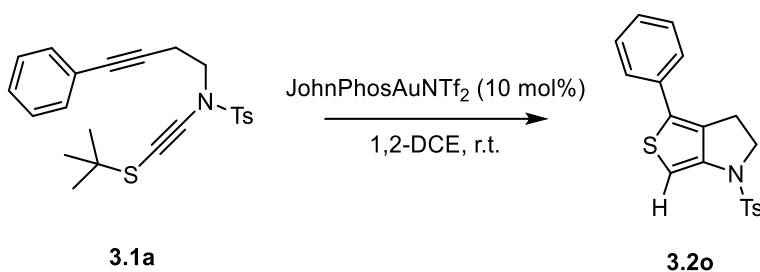


(S-20) synthesized as described in : *Chem. Eur. J.* **2019**, *25*, 8225.

(S-21) and **(S-22)** synthesized as described in : *Synthesis* **2002**, *3*, 0343-0348.

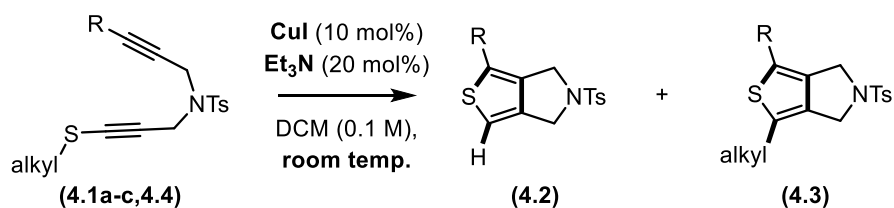
(S-23) synthesized as described *Asian J. Org. Chem.* **2017**, *6*, 677.

7.5.2 Gold-catalyzed (3+2) cycloaddition of **3.1a**



To a small reaction vial was added the yne-alkynyl sulfide substrate **3.1a** (20.6 mg, 0.0500 mmol, 1.0 equiv.) in 1,2-DCE (0.5 mL, 0.1 M). JohnPhosAuNTf₂ (3.9 mg, 0.005 mmol, 0.1 equiv.) was then added and the mixture was stirred at room temperature for 25 hours. Volatiles were then evaporated under reduced pressure to yield a crude mixture. The crude was purified by silica gel chromatography using hexanes:EtOAc gradient 9:1 → 8:2 as the eluent system to yield 12.4 mg (70% yield) of **3.2o** as a yellow solid. **3.2o** was previously characterized in section 7.4.7.

7.5.3 Standard procedure for the results discussed in section 4.3



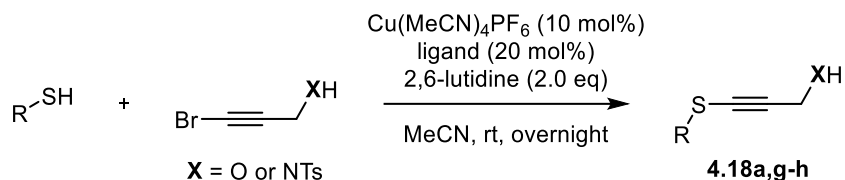
Entry	(4.1/4.4)	alkyl	R	Time (h)	Conv., (%) ^b	(4.2), yield (%) ^b	(4.3), yield (%) ^b
1	(4.1a)	<i>t</i> -Bu	H	1	61	22	11
2	(4.1b)	Bn	H	1	56	6	4
3	(4.1c)	<i>n</i> -Pr	H	1	76	2	0
4	(4.4)	<i>t</i> -Bu	Ph	21	0	0	0

In a sealed reaction tubes were added alkynyl sulfide **4.1a-c** or **4.4** (0.0500 mmol, 1.0 equiv.), Et₃N (0.0100 mmol, 0.2 equiv.) and DCM (0.5 mL, 0.1 M). The solution was stirred at room

temperature for 1 hour then filtration through a short silica pad with EtOAc was done. The mixture was then evaporated under reduced pressure to produce a crude which is directly analyzed by ^1H NMR analysis using 2.0 μL of 1,2-DBE as NMR standard. Synthesis of **4.1a** and entry 4 were done by Dominic Campeau.

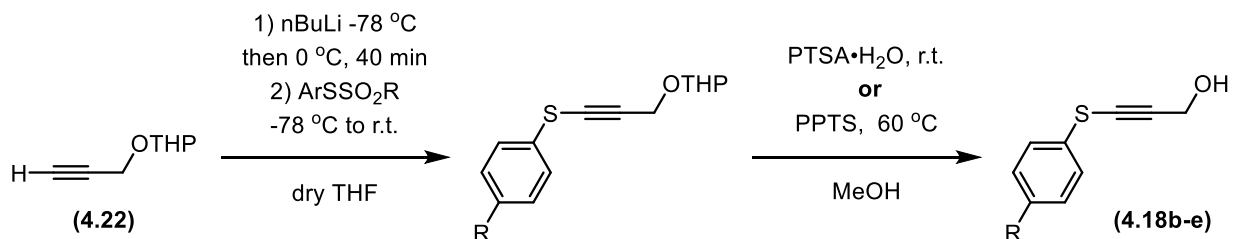
7.5.4 Synthesis and characterization of propargyl alcohol/tosylamide precursors 4.18a-e,g-h

Standard procedure 4-A : preparation of propargyl alcohols **4.18a,g-h** using a modified procedure from that described by Collins et al.⁷⁵



In a flame-dried round bottom flask was added 4,4'-di-tert-butyl-2,2'-bipyridine or 2,2'-bipyridine^q (0.20 equiv.). Three vacuum/ N_2 purge cycles were performed to refill the flask with N_2 atmosphere. The thiol (1.05 – 1.10 equiv.), the bromoalkyne (1.00 equiv.), 2,6-lutidine (2.00 equiv.), and MeCN (0.1 – 0.5 M) were all added to the flask via syringe. The mixture is then degassed with N_2 , then $\text{Cu(MeCN)}_4\text{PF}_6$ (0.10 equiv.) was added quickly. The mixture is stirred overnight at room temperature then quenched with water and diluted with ethyl acetate. The organic phase was washed three times with 2.5% HCl aq. solution, three times with 10% NH_3 aq. solution, then once with brine. The organic phase was then dried over MgSO_4 , filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired alkynyl sulfide.

Standard procedure 4-B : using a sulfur umpolung method to access propargyl alcohols **4.18b-e**.



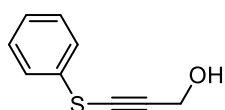
In a flame-dried round bottom flask under N_2 atmosphere was added alkyne **4.22** synthesized as previously described in the literature¹³⁷ (1.05 equiv.) and dry THF (0.5 M) via syringe. The solution was cooled to -78°C then nBuLi (1.05 equiv.) was added dropwise to the stirring solution. The solution was then warmed to 0°C and stirred for an additional 40 minutes. The solution is cooled back to -78°C then the aryl thiosulfonate (1.00 equiv.) was added at once and the reaction is slowly warmed to room temperature. Upon reaction completion, the mixture was quenched with

^q 2,2'-bipyridine was used instead of 4,4'-di-tert-butyl-2,2'-bipyridine for the large scale synthesis of alkynyl sulfide **4.18a** as it is less expensive, and we have found that the same yield is obtained using either ligand.

NH₄Cl aq. solution and diluted with ethyl acetate. The mixture was washed once with water, then brine. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The resulting crude is used without purification in the next step.

The crude was redissolved in methanol (0.5 M). To the solution was added PTSA-H₂O (0.10 equiv.) then the mixture is stirred at room temperature until completion by TLC. OR was added PPTS (0.10 equiv.) instead then the mixture is heated at 60 °C until completion by TLC. The mixture is then quenched with NaHCO₃ aq. solution and diluted with ethyl acetate. The organic phase was washed once with water, then brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired alkynyl sulfide.

(4.18a)

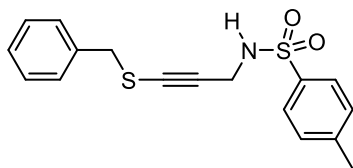


Using standard procedure [4-A](#) with 37.0 mmol of 3-bromoprop-2-yn-1-ol (0.5 M) and 38.8 mmol (1.05 equiv.) of thiophenol. Solvent system = Hexanes/EtOAc 8:2. Produced 4.51 g (74% yield) of a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 4.51 (s, 2H), 1.71 (s, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 132.4, 129.4, 126.9, 126.6, 97.4, 73.4, 52.2.

(4.18g)

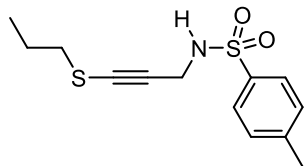


Using standard procedure [4-A](#) with 0.767 mmol (0.1 M) of 4-methyl-N-(3-bromoprop-2-yn-1-yl)benzenesulfonamide prepared as previously described in the literature¹³⁸ and 0.844 mmol (1.10 equiv.) of benzyl mercaptan. Solvent system = Hexanes/EtOAc 8:2. Produced 230 mg (97% w/w, 96% yield) of a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.18 (m, 7H), 4.62 (t, *J* = 6.1 Hz, 1H), 3.90 (d, *J* = 6.0 Hz, 2H), 3.75 (s, 2H), 2.41 (s, 3H).^r

¹³C NMR (101 MHz, CDCl₃) δ 143.9, 136.7, 136.4, 129.8, 129.1, 128.7, 128.0, 127.5, 89.5, 75.5, 39.9, 34.4, 21.7.

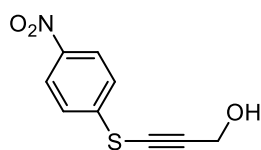
^r Inseparable by-products observed in ¹H NMR spectrum, internal NMR standard shows the purified sample is ~97%w/w desired product.

(4.18h)

Using standard procedure **4-A** with 1.235 mmol (0.1 M) of 4-methyl-N-(3-bromoprop-2-yn-1-yl)benzenesulfonamide and 1.235 mmol (1.05 equiv.) of propane thiol. Solvent system = Hexanes/EtOAc gradient of 9:1 → 8:2. Produced 285 mg (81% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.29 (m, 2H), 4.52 (t, *J* = 5.9 Hz, 1H), 3.95 (d, *J* = 6.0 Hz, 2H), 2.53 – 2.48 (m, 2H), 2.43 (s, 3H), 1.61 (h, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

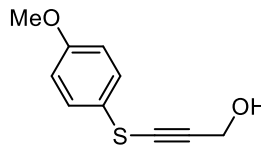
¹³C NMR (101 MHz, CDCl₃) δ 143.9, 136.8, 129.8, 127.5, 87.6, 75.9, 37.3, 34.5, 22.7, 21.7, 13.0.

(4.18b)

Using standard procedure **4-B** with 4.33 mmol of thiosulfonate **S-20**. Deprotection using PTSA and DCM (1.0 M) was added to help with solubility. Reaction times ; thiolation = 35 min, deprotection = 4 h. Solvent system = Hexanes/EtOAc 7:3. Produced 773 mg (85% yield) of a orange solid.

¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 9.1 Hz, 2H), 7.56 (d, *J* = 9.1 Hz, 2H), 4.57 (s, 2H), 1.80 (s, 1H).

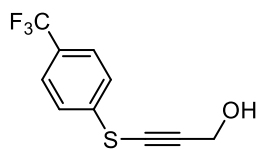
¹³C NMR (151 MHz, CDCl₃) : δ 146.5, 142.3, 126.0, 124.4, 100.3, 70.5, 52.1.

(4.18c)

Using standard procedure **4-B** with 7.50 mmol of thiosulfonate **S-21**. Deprotection using PTSA, done at 0.75 M instead. Reaction times ; thiolation = 45 min, deprotection = 2 h. Solvent system = Hexanes/EtOAc gradient of 4:1 → 6:4. Produced 799 mg (55% yield) of a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.46 (d, *J* = 5.2 Hz, 2H), 3.80 (s, 3H), 1.67 (t, *J* = 5.7 Hz, 1H).

¹³C NMR (76 MHz, CDCl₃) : δ 159.4, 129.6, 122.5, 115.2, 95.6, 75.0, 55.6, 52.2.

(4.18d)

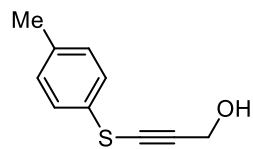
Using standard procedure **4-B** with 4.22 mmol of thiosulfonate **S-22**, done at 0.3 M instead. Deprotection using PPTS. Reaction times ; thiolation = 1 h, deprotection = 4 h. Solvent system = Hexanes/EtOAc 5:1. Produced 857 mg (88% yield) of a light yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.63 – 7.48 (m, 4H), 4.54 (s, 2H), 1.72 (s, 1H).

¹³C NMR (76 MHz, CDCl₃) δ 137.8, 129.0 (q, J = 32.7 Hz), 126.21 (q, J = 3.9 Hz), 126.1, 124.1 (q, J = 272.1 Hz), 99.1, 71.6, 52.1.^s

¹⁹F NMR (283 MHz, CDCl₃) δ -62.5.

(4.18e)

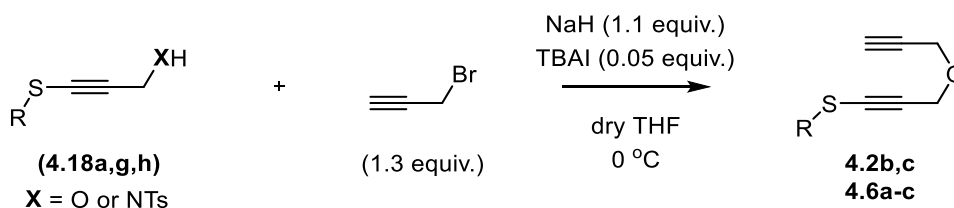


Using standard procedure **4-B** with 7.24 mmol of thiosulfonate **S-23**. Deprotection using PPTS. Reaction times ; thiolation = 1.5 h, deprotection = 6 h. Solvent system = Hexanes/EtOAc 5:1. Produced 1.01 g (78% yield) of a light yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.33 (d, J = 8.3 Hz, 2H), 7.19 – 7.12 (m, 2H), 4.49 (s, 2H), 2.34 (s, 3H), 1.73 (s, 1H).

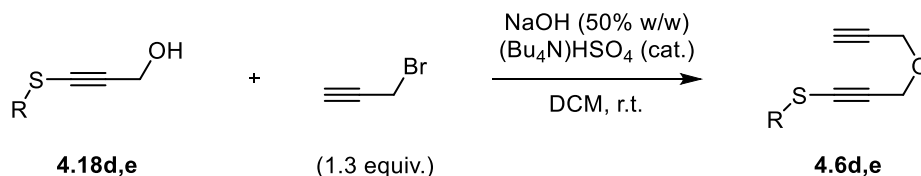
¹³C NMR (76 MHz, CDCl₃) δ 137.1, 130.2, 128.6, 127.0, 96.7, 74.0, 52.2, 21.1.

7.5.5 Procedures for the synthesis of yne-alkynyl sulfides 4.2b,c and 4.6a-e,h-i
Standard procedure 4-C : Nucleophilic substitution using NaH as base for **4.2b,c** and **4.6a-c**



In a flame-dried round bottom flask was cooled to 0 °C a solution of alkynyl sulfide (1.0 equiv.), propargyl bromide (1.3 equiv.) and tetrabutylammonium iodide (0.05 equiv.) in dry THF (0.25 – 0.35 M). To the cooled solution was added NaH (1.1 equiv., 60 % w/w). The mixture is stirred at **0 °C** until completion by TLC^t. The mixture was then quenched with NH₄Cl sat. aq. solution and diluted with Et₂O. The organic phase was washed once with water, then once with brine. The organic phase was dried using MgSO₄, filtered, and concentration under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system to yield the desired yne-alkynyl sulfide.

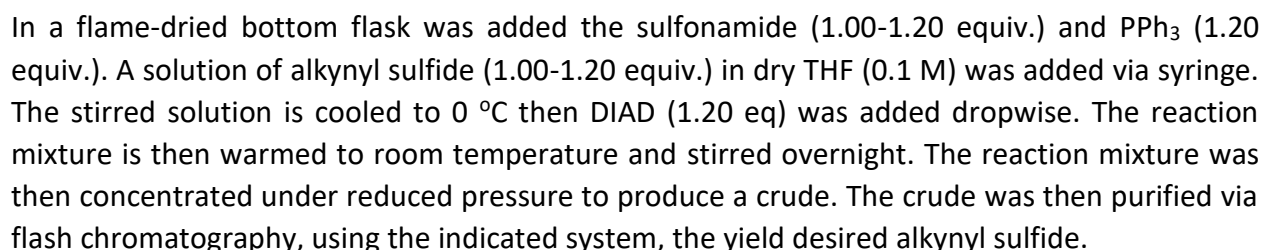
Standard procedure 4-D : Nucleophilic substitution using NaOH as base for **4.6d,e**.



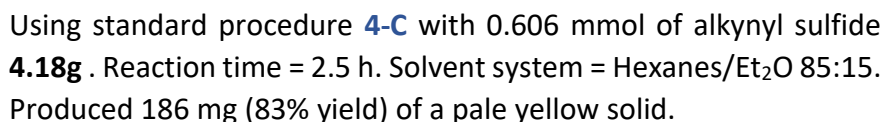
^s It was not possible to locate all the peaks of the quadruplets due to low intensity and/or overlapping with other peaks.

^t Running the reaction at 0 °C was found to be important in ensuring high yields for the yne-alkynyl sulfides.

Standard procedure 4-E : Mitsunobu coupling for accessing **4.6h,i**.



(4.2b)

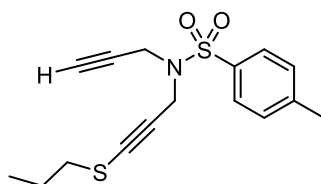


¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.21 (m, 7H), 4.23 (s, 2H), 3.94 (d, *J* = 2.5, 2H), 3.78 (s, 2H), 2.41 (s, 3H), 2.14 (t, *J* = 2.5 Hz, 1H).^u

¹³C NMR (101 MHz, CDCl₃) δ 144.0, 136.5, 135.2, 129.7, 129.1, 128.8, 128.0, 128.0, 87.9, 76.6, 76.4, 74.0, 39.9, 37.7, 36.3, 21.7.

HRMS-EI Calculated for $C_{12}H_{18}NO_2S_2$ $[M-H]^+$: 368.0778; found: 368.0778.

177

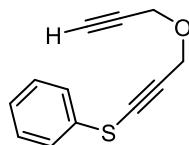
(4.2c)

Using standard procedure **4-C** with 0.988 mmol of alkynyl sulfide **4.18h**. Dry DMF was used as solvent instead (0.2 M). Reaction time = 21 h. Solvent system = Hexanes/Et₂O 85:15. Produced 312 mg (98% yield) of a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.27 (s, 2H), 4.13 (d, *J* = 2.4 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 2.14 (t, *J* = 2.5 Hz, 1H), 1.64 (h, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 144.0, 135.4, 129.7, 128.0, 85.9, 76.9, 76.5, 74.0, 37.8, 37.3, 36.4, 22.7, 21.7, 12.9.

HRMS-EI Calculated for C₁₆H₁₉NO₂S₂ [M]⁺: 321.0857; found: 321.0856.

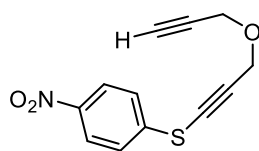
(4.6a)

Using standard procedure **4-C** with 22.2 mmol of alkynyl sulfide **4.18a**. Reaction time = 2 h. Solvent system = Hexanes/Et₂O 98:2. Produced 2.80 g (62% yield) of a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.41 (m, 2H), 7.38 – 7.31 (m, 2H), 7.27 – 7.21 (m, 1H), 4.51 (s, 2H), 4.31 (d, *J* = 2.4 Hz, 2H), 2.48 (t, *J* = 2.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 132.3, 129.4, 126.9, 126.6, 94.6, 79.0, 75.3, 74.6, 57.7, 56.5.

HRMS-EI Calculated for C₁₂H₁₀OS [M-H]⁺: 201.0374; found: 201.0368.

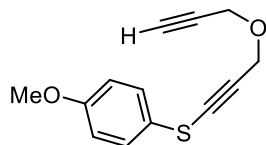
(4.6b)

Using standard procedure **4-C** with 3.65 mmol of alkynyl sulfide **4.18b**. Reaction time = 45 min. Solvent system = Hexanes/Et₂O 95:5. Produced 108 mg (12% yield) of a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 9.2 Hz, 2H), 7.56 (d, *J* = 9.1 Hz, 2H), 4.56 (s, 2H), 4.32 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H).

¹³C NMR (76 MHz, CDCl₃) δ 146.4, 142.1, 125.9, 124.3, 97.4, 78.5, 75.5, 71.6, 57.4, 56.7.

HRMS-EI Calculated for C₁₂H₉NO₃S [M-H]⁺: 246.0225 ; found: 246.0208.

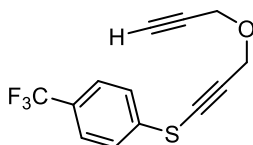
(4.6c)

Using standard procedure **4-C** with 4.08 mmol of alkynyl sulfide **4.18c**.
Reaction time = 2 h. Solvent system = Hexanes/Et₂O 95:5. Produced 748 mg (79% yield) of a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.46 (s, 2H), 4.28 (d, *J* = 2.4 Hz, 2H), 3.80 (s, 3H), 2.46 (t, *J* = 2.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 159.3, 129.4, 122.4, 115.2, 92.7, 79.0, 76.2, 75.2, 57.7, 56.4, 55.6.

HRMS-EI Calculated for C₁₃H₁₂O₂S [M]⁺: 232.0558 ; found: 232.0554 and C₁₃H₁₁O₂S [M-H]⁺: 231.0480 ; found: 231.0477.

(4.6d)

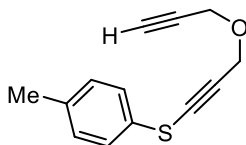
Using standard procedure **4-D** with 2.78 mmol of alkynyl sulfide **4.18d**.
Reaction time = 15 min. Solvent system = Hexanes/Et₂O 97:3. Produced 345 mg (46% yield) of a light yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.62 – 7.56 (m, 2H), 7.56 – 7.49 (m, 2H), 4.54 (s, 2H), 4.31 (d, *J* = 2.4 Hz, 2H), 2.49 (t, *J* = 2.4 Hz, 1H).

¹³C NMR (76 MHz, CDCl₃) δ 137.7, 129.0 (q, *J* = 32.8 Hz), 126.2 (q, *J* = 3.9 Hz), 126.1, 124.0 (q, *J* = 271.9 Hz), 96.2, 78.6, 75.4, 72.7, 57.5, 56.5.^v

¹⁹F NMR (283 MHz, CDCl₃) δ -62.5.

MS-APCI+ : 170.9 (14%), 196.9 (11%), 214.9 (20%), 216.9 (20%), 240.9 (14%), 242.9 (19%), 244.9 (11%), 270.9 ([M+H]⁺, 35%), 309.0 (12%), 429.0 ([2M+H-2C₃H₄OH]⁺, 100%), 430.0 (25%), 431.0 (13%), 485.1 ([2M+H-C₃H₄OH]⁺, 15%).

(4.6e)

Using standard procedure **4-D** with 3.47 mmol of alkynyl sulfide **4.18e**.
Reaction time = 15 min. Solvent system = Hexanes/Et₂O 97:3. Produced 599 mg (80% yield) of a light yellow oil.

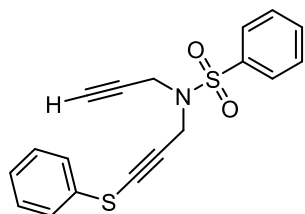
¹H NMR (300 MHz, CDCl₃) δ 7.33 (d, *J* = 8.5 Hz, 2H), 7.19 – 7.12 (m, 2H), 4.49 (s, 2H), 4.30 (d, *J* = 2.4 Hz, 2H), 2.47 (t, *J* = 2.4 Hz, 1H), 2.34 (s, 3H).

¹³C NMR (76 MHz, CDCl₃) δ 137.0, 130.2, 128.6, 127.0, 93.8, 79.0, 75.3, 75.2, 57.7, 56.4, 21.1.

HRMS-EI Calculated for C₁₃H₁₂OS [M]⁺: 216.0609 ; found: 216.0589 and C₁₃H₁₁OS [M-H]⁺: 215.0531; found: 215.0550.

^v It was not possible to locate all the peaks of the quadruplets due to low intensity.

(4.6h)



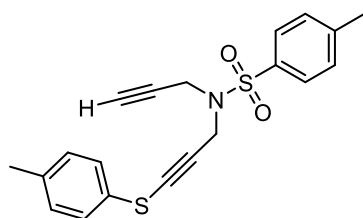
Using standard procedure [4-E](#) with 0.700 mmol (1.20 equiv.) of *N*-(prop-2-yn-1-yl)benzenesulfonamide and 0.580 mmol (1.00 equiv.) of alcohol **4.18a**. Two subsequent purifications were needed with Hexanes/Acetone 5:1 then Hexanes/DCM gradient of 2:3 → 1:4. Produced 150 mg (75% yield) of a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.90 – 7.80 (m, 2H), 7.59 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 7.39 – 7.16 (m, 5H), 4.45 (s, 2H), 4.18 (d, *J* = 2.5 Hz, 2H), 2.18 (t, *J* = 2.5 Hz, 1H).

¹³C NMR (76 MHz, CDCl₃) δ 138.0, 133.2, 131.9, 129.3, 129.0, 127.8, 126.8, 126.4, 91.1, 76.2, 74.2, 73.4, 37.9, 36.6.

HRMS-EI Calculated for C₁₈H₁₄NO₂S₂ [M-H]⁺: 340.0466 ; found: 340.0442.

(4.6i)



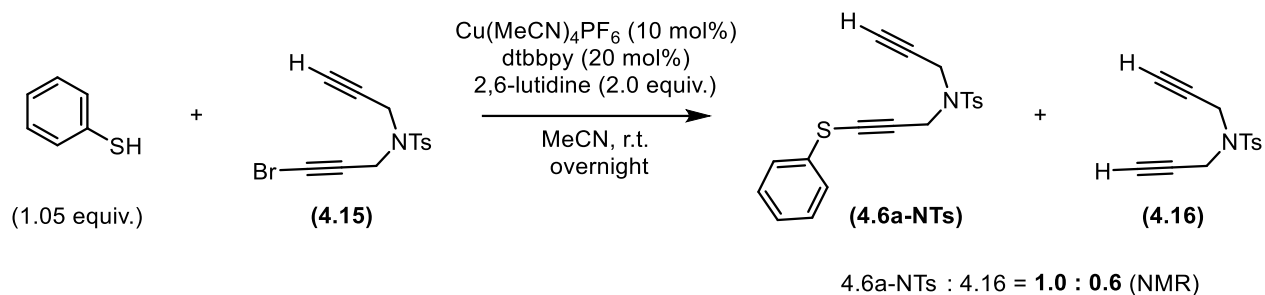
Using standard procedure [4-E](#) with 0.500 mmol (1.00 equiv.) of amide 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide and 0.600 mmol (1.20 equiv.) of alcohol **4.18e**. Two subsequent purifications were needed with Hexanes/Acetone 5:1 then Hexanes/DCM gradient of 2:3 → 1:4. Produced 85.5 mg (46% yield) of a light yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.09 (m, 6H), 4.41 (s, 2H), 4.15 (d, *J* = 2.5 Hz, 2H), 2.36 (s, 3H), 2.33 (s, 3H), 2.19 (t, *J* = 2.5 Hz, 1H).

¹³C NMR (76 MHz, CDCl₃) δ 144.2, 137.0, 135.1, 130.2, 129.8, 128.3, 128.0, 126.8, 90.7, 76.5, 74.2, 73.8, 37.9, 36.6, 21.7, 21.1.

HRMS-EI Calculated for C₂₀H₁₈NO₂S₂ [M-H]⁺: 368.0779 ; found: 368.0766.

7.5.7 Challenges with the synthesis of **4.6a-NTs** when using Collins et al. method



The attempted synthesis of **4.6-NTs** was done using standard procedure **4-A** with 0.317 mmol of bromoalkyne **4.15** synthesized as previously described by our group⁵⁸ (0.1 M), 0.333 mmol (1.05 equiv.) of thiophenol and dtbbpy as ligand. Crude NMR showed formation of **4.6a-NTs** as well as **4.16** in an approximate 1.0 to 0.6 molar ratio respectively. Signals for **4.16** are in accordance with what is described in the literature.¹³⁹

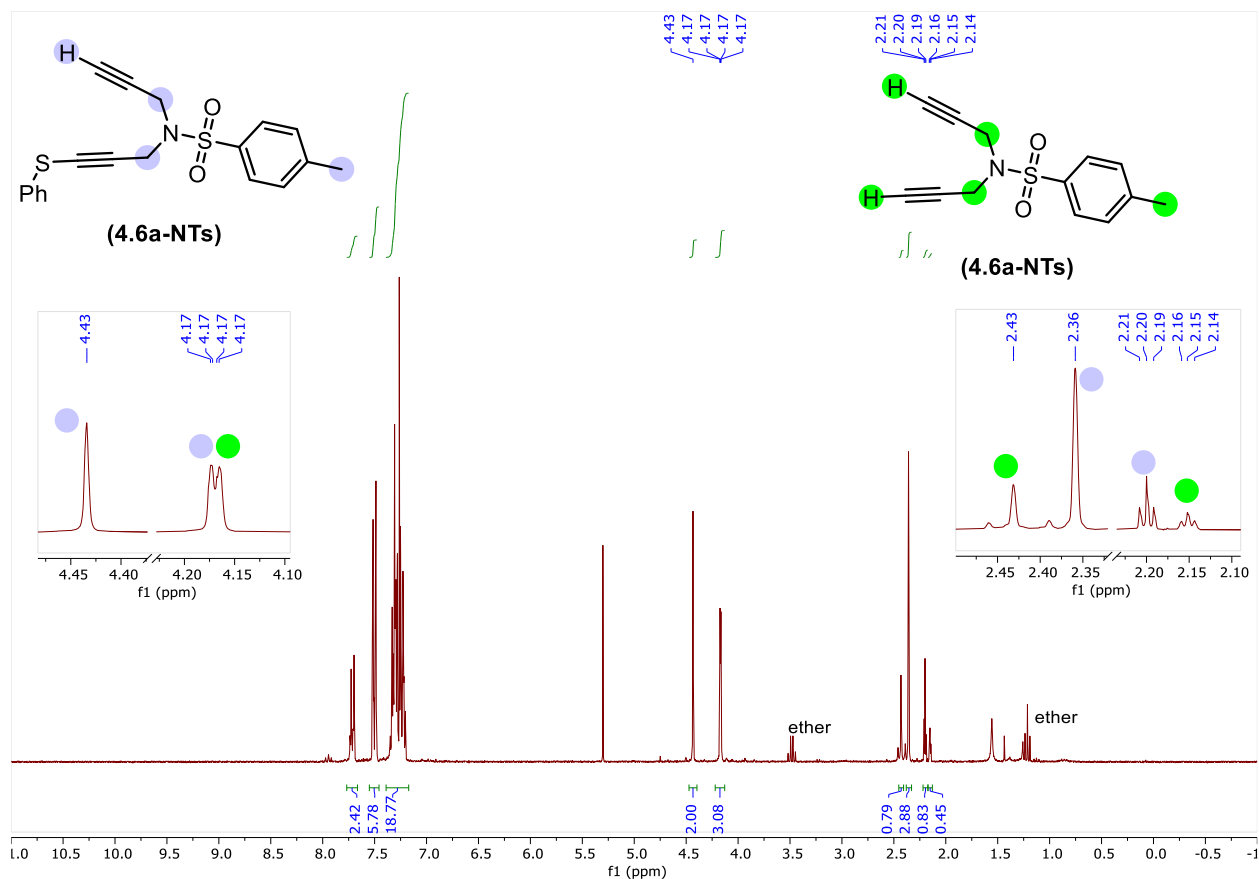
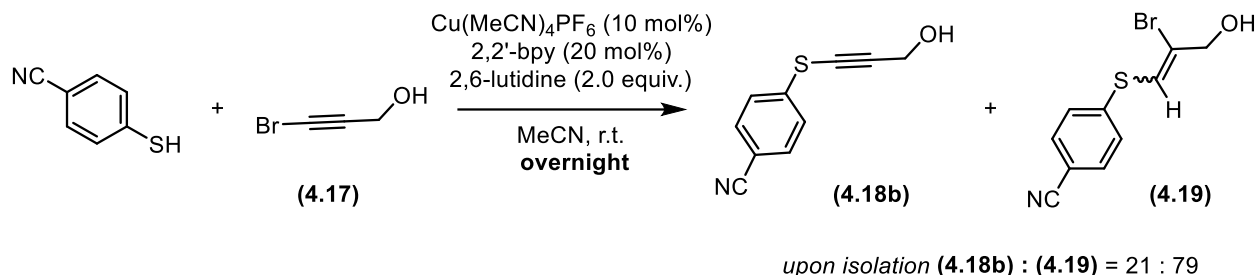


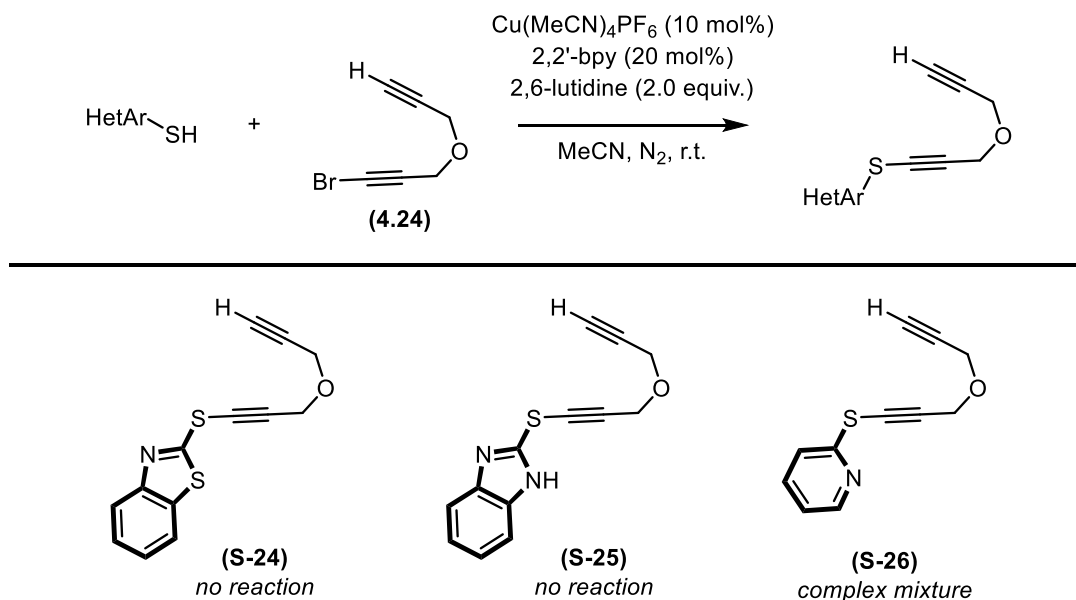
Figure 79 Crude NMR obtained when attempting to form **4.6a-NTs** using a cross-coupling reaction.

7.5.8 Challenges with the synthesis of **4.18b** when using Collins et al. method



The attempted synthesis of **4.18b** was done using standard procedure **4-A** with 8.00 mmol of bromoalkyne **4.17** (0.1 M), 8.40 mmol (1.05 equiv.) of 4-cyanobenzenethiol and 2,2'-bpy as ligand. Solvent system = Hexanes/EtOAc 7:3. All the fractions obtained contained a mixture of **4.18b** and **4.19** with respective ratios varying from 0.13 : 1 to 1 : 1 therefore **4.18b** could not be efficiently isolated. NMR and mass analysis of all the fractions resulted suggested a quantitative conversion of **4.17** with formation of **4.18b** in a 21% yield and **4.19** in a 79% yield. The NMR analysis was shown in section 4.8.

7.5.9 Additional comments on the attempted synthesis of hetaryl derivatives



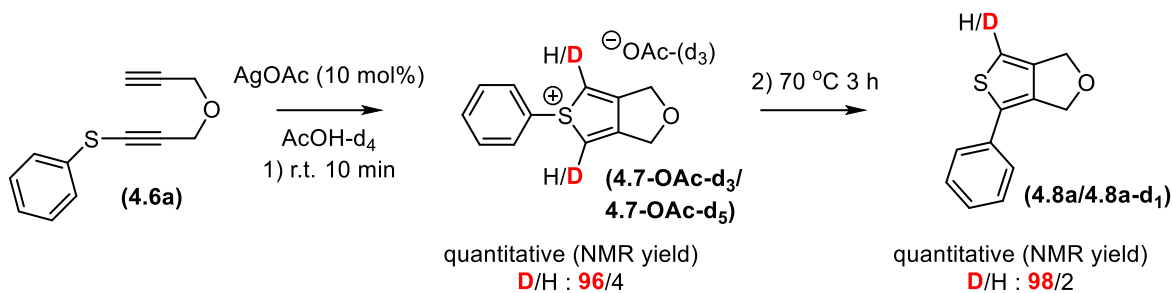
The attempted synthesis of **S-24**, **S-25** and **S-26** was done using standard procedure **4-A** with bromoalkyne **4.24** synthesized as previously described in the literature¹⁴⁰ and the corresponding thiols. In the case of **S-24** and **S-25** the reaction was followed by TLC-MS (APCI) and TLC. For **S-26** the reaction was performed in DMF to help solubility of the pyridine thiol and was quenched with water and extracted only with EtOAc.

Comments for **S-26**, reaction scale 0.250 mmol : the ¹H-NMR of the reaction crude was very complicated and showed many terminal alkyne signals suggesting that the reaction was not selective.

Comments for **S-25**, reaction scale 0.100 mmol : upon addition of the copper(I) catalyst, the reaction turns dark red which is a typical sign that the catalysis has begun. After 10 minutes, the reaction turns green and then brown which typically signify that the reaction has completed ($\text{Cu(I)} \rightarrow \text{Cu(II)}$). However upon analysis by TLC and APCI, no formation of **S-25** can be detected. Only the starting benzimidazole thiol is seen by APCI and a lot of bromoalkyne **4.24** is seen by TLC. Seeing that this thiol is not very soluble in MeCN, DMF was added until solubility was seen (0.1 mL) then the reaction mixture is resubjected to N_2 and copper (I) however this did not help. Our conclusion was that the benzimidazole thiol is likely quenching the copper(I) specie and a rapid reduction to copper(II) is seen without cross-coupling.

Comments for **S-24**, reaction scale 0.500 mmol : with the hope that changing the thiol to a less coordinating benzothiazole led similar observations than those described for **S-25**. When adding the copper(I) however, the reaction mixture remained dark red for a long time which seemed promising at first. No reactivity was however seen at room temperature and even heating of the reaction mixture did not lead to any change in reaction profile.

7.5.10 Detection of thiophenium **4.7-OAc** by NMR and thermal rearrangement to **4.8a**



In a sealed NMR tube was added the yne-alkynyl sulfide substrate **4.6a** (10.3 mg, 0.0509 mmol, 1.0 equiv.) and deuterated acetic acid (0.5 mL, 0.1 M). 2.0 μL of mesitylene was added as internal NMR standard. AgOAc (0.8 mg, 5.09×10^{-3} mmol, 0.1 equiv.) was then added to the NMR tube. The solution was analyzed by ^1H NMR experiment before addition of the catalyst (0 min), after 10 min at room temperature, and followed while heating at 70°C until consumption of the thiophenium intermediate (**4.7-OAc**) is seen (3 h) (Figure 80).

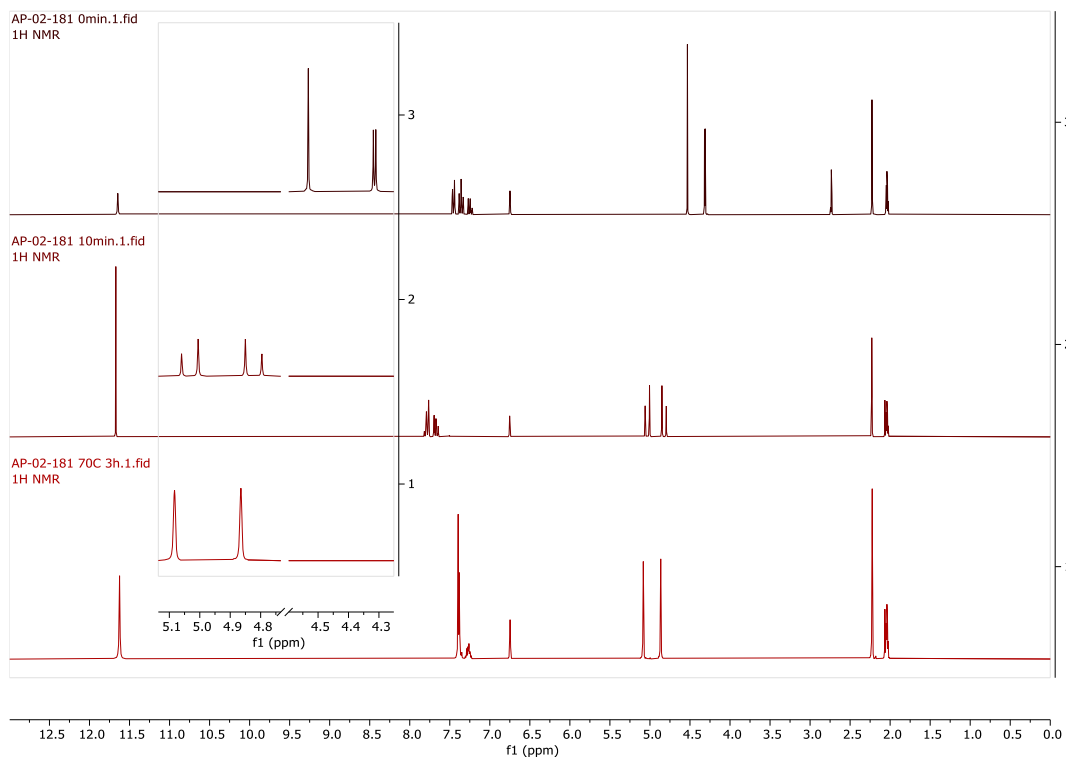


Figure 80 NMR spectra overlap taken at time 0 min (top), after 10 min at room temperature (middle) and after 3 h of heating at 70°C (bottom).^w

^w Increase in the signal for AcOH is seen by NMR after formation of the thiophenium intermediate **4.7-OAc** (middle spectra) which is consistent with the initial formation of a silver-acetylide.

The ratio of ^1H NMR signal integration between the thiophenium α -hydrogens and either of the CH_2 groups in a pure sample of thiophenium triflate salt **4.7-OTf** is 1.94 : 2.00. The ratio of ^1H NMR signal integration between the thiophene α -hydrogen and either of the CH_2 groups in a pure sample of thiophene **4.8a** is 0.92 : 2.00. Obtained integrations in each spectrum are set against these respective ratios in order to determine the percentage of deuteration. Spectra of **4.7-OTf** and **4.8a** were taken in AcOH-d_4 and overlapped with those from Figure 80 to determine where the α -hydrogen(s) reside in AcOH-d_4 (Figure 81 and Figure 82).

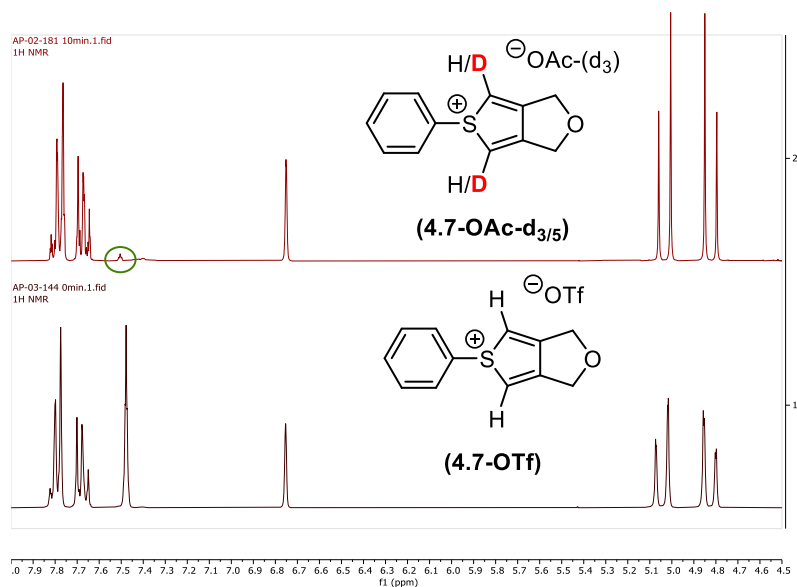


Figure 81 NMR spectra overlap for thiophenium **4.7-OAc-(d_{3/5})** (top) observed during the NMR experiment and that of **4.7-OTf** (bottom).

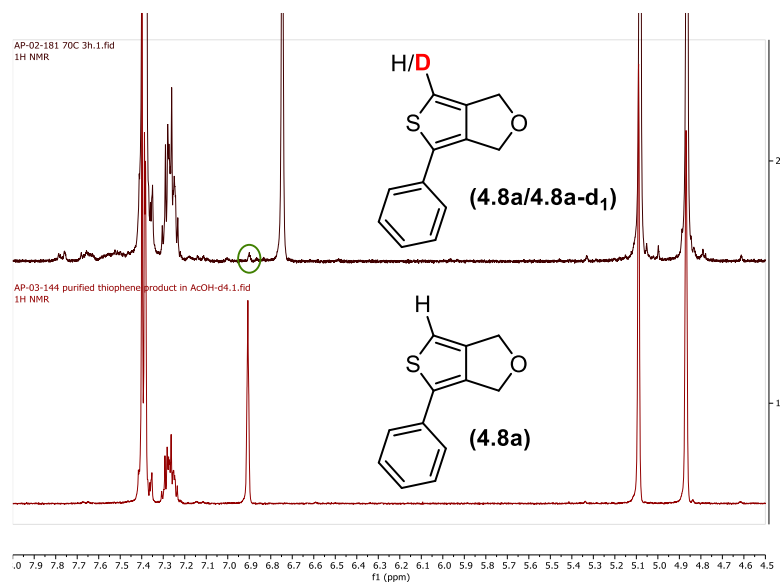
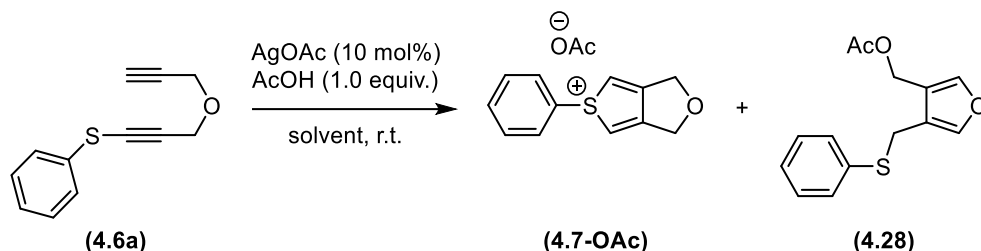


Figure 82 NMR spectra overlap for thiophene **4.8a/4.8a-d₁** (top) observed during the NMR experiment and **4.8a** (bottom).

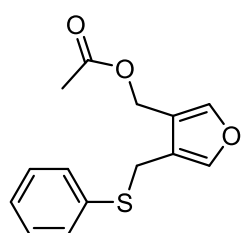
7.5.11 First round of optimization for **4.7-OAc** and observation of by-product **4.28**



Entry	Solvent	Time	Conv. (4.6a), (%)	(4.7-OAc), yield (%)	(4.28), yield (%)
1	TFE	4 h	100	89	0
2	HFIP	2 h	100	83	5
3	CHCl ₃	ON	78	traces	11
4	EtOAc	3 days	45	traces	35
5	Acetone	3 days	73	traces	48

Procedure for entry 1-2: Alkynyl sulfide **4.6a** (50.0 mg, 0.247 mmol, 1.0 equiv.) is dissolved in the reaction solvent (0.25 mL, 1 M) and transferred to an amber vial. AcOH (14.1 μ L, 0.247 mmol, 1.0 equiv.) is then added to the mixture followed by AgOAc (4.1 mg, 2.47×10^{-2} mmol, 0.1 equiv.). The reaction is stirred for the indicated reaction time then the mixture is filtered through a filter using DCM and evaporated at room temperature under reduced pressure. The crude is then analyzed by ¹H NMR in CDCl₃ and the yields are assessed with 2.0 μ L of 1,2-DBE.

Procedure for entry 3-5: The reactions were set up the same but the reaction scales were of 0.123 mmol instead. The reaction mixtures were evaporated under reduced pressure at room temperature then filtered through cotton with CDCl₃ before analysis by NMR as described above.

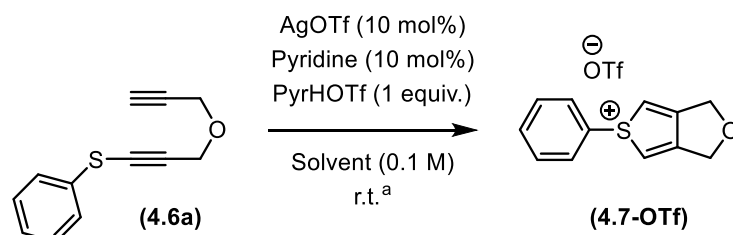


¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.39 (m, 1H), 7.37 – 7.24 (m, 5H), 7.24 – 7.18 (m, 2H), 5.05 (s, 2H), 3.95 (s, 2H), 2.07 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 171.0, 143.0, 141.8, 135.8, 130.6, 129.0, 126.9, 120.7, 120.0, 56.7, 28.0, 21.1.

NMR matches that of similar furan by-products obtained by the group of Yoshimatsu et al.¹²⁴

7.5.12 Second optimization and gram scale synthesis of thiophenium salt **4.7-OTf**

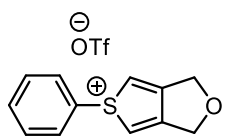


Entry	Solvent	Time	Conv. (%)	Yield (%)
1	DCM	4 h	29	6
2	MeCN	4 h	18	0
3	TFE	4 h	89	67
4	TFE : DCM (10 : 1)	4 h	100	89
5	MeOH : DCM (10 : 1)	4 h	44	29
6	MeOH : DCM (10 : 1)	24 h	92	52
7	TFE : DCM (10 : 1)	4 h	100	86 ^c

Full procedure for entry 1-6 : Alkynyl sulfide **4.6a** (12.1 mg, 0.0600 mmol, 1.0 equiv.) is dissolved in the reaction solvent (0.6 mL, 0.1 M) and transferred to an amber vial. Pyridine (0.5 μL , 6.00×10^{-3} mmol, 0.1 equiv.) and PyrHOTf (13.8 mg, 0.0600 mmol, 1.0 equiv.) are then added to the mixture followed by AgOTf (1.5 mg, 6.00×10^{-3} mmol, 0.1 equiv.). The reaction is stirred for 4 h (or 24 h for entry 6). MeOH (1 mL) is then added to the mixture and NaCl (s) is added in excess to quench the reaction. Filtration through a celite pad with MeOH affords a crude upon evaporation under reduced pressure. The crude is analyzed by ^1H NMR in DMSO- d_6 and the yields are assessed with 2.0 μL of mesitylene.

Procedure for entry 7 : In a round bottom flask was added a solution of yne-alkynyl sulfide substrate **4.6a** (708 mg, 3.50 mmol, 1.0 equiv.) in trifluoroethanol : dichloromethane (10 : 1) (35.0 mL, 0.1 M). Pyridinium triflate (802 mg, 3.50 mmol, 1.0 equiv.) and pyridine (28.0 μL , 0.350 mmol, 0.1 equiv.) were then added to the solution. AgOTf (90.0 mg, 0.350 mmol, 0.1 equiv.) is then quickly added to the reaction mixture. The mixture is stirred at room temperature for 4 hours covered with aluminum foil. The reaction mixture is then concentrated under reduced pressure at room temperature to produce a crude. The crude is then diluted with acetone (approx. 10 mL) then diethyl ether is added to precipitate the thiophenium that is in solution. Diethyl ether is added until precipitation of the thiophenium stops (approx. 10 mL). The solution then decanted using a glass pipette and the salt is washed with diethyl ether a few times. The

resulting precipitate is dried under vacuum yielding 1.06 g (86% yield) of thiophenium **4.7-OTf** as a pale yellow solid.



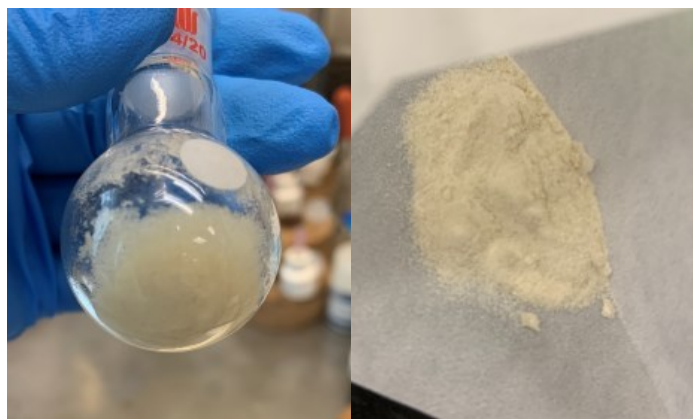
¹H NMR (600 MHz, DMSO) δ 7.80 – 7.75 (m, 3H), 7.72 – 7.66 (m, 2H), 7.56 (q, J = 1.7 Hz, 2H), 4.89 (dd, J = 16.2, 1.4 Hz, 2H), 4.72 (dd, J = 16.2, 1.7 Hz, 2H).

¹³C NMR (151 MHz, DMSO) δ 161.8, 134.4, 131.0, 130.6, 120.7 (q, 322.3 Hz), 121.6, 118.1, 66.5.

¹⁹F NMR (282 MHz, DMSO) δ -77.8.

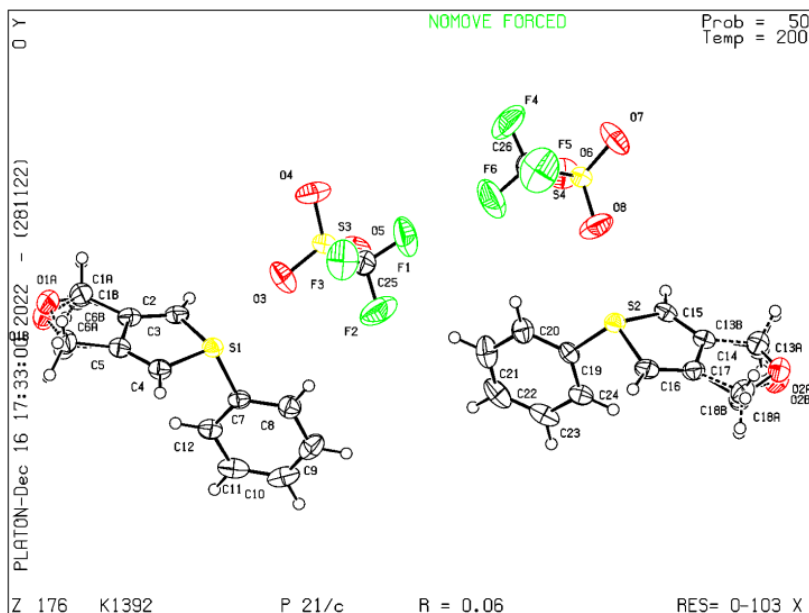
HRMS-ESI Calculated for $C_{12}H_{11}OS^+ [M-OTf]^+$: 203.0525 ; found: 203.0507.

Supplementary COSY, HSQC, HMBC and NOESY data for **4.7-OTf** provided in section 9.1.



Precipitate of thiophenium **4.7-OTf** obtained (1.06g).

7.5.13 X-ray of thiophenium **4.7-OTf**, CCDC deposition number : 2260026



Bond precision: C-C = 0.0050 Å

Wavelength=0.71073

Cell: a=21.7698 (6)

b=9.3822 (3)

c=14.9942 (4)

alpha=90

beta=108.814 (1)

gamma=90

Temperature: 200 K

	Calculated	Reported
Volume	2898.91 (15)	2898.91 (15)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C12 H11 O S, C F3 O3 S	C12 H11 O S, C F3 O3 S
Sum formula	C13 H11 F3 O4 S2	C13 H11 F3 O4 S2
Mr	352.34	352.34
Dx, g cm ⁻³	1.615	1.615
Z	8	8
Mu (mm ⁻¹)	0.415	0.415
F000	1440.0	1440.0
F000'	1442.96	
h, k, lmax	28, 12, 19	28, 12, 19
Nref	6920	6907
Tmin, Tmax	0.884, 0.975	0.596, 0.746
Tmin'	0.872	

Correction method= # Reported T Limits: Tmin=0.596 Tmax=0.746

AbsCorr = MULTI-SCAN

Data completeness= 0.998

Theta(max)= 27.877

R(reflections)= 0.0575 (4378)

wR2(reflections)=
0.1357 (6907)

S = 1.025

Npar= 453

7.5.14 Cyclic voltammetry on thiophenium **4.7-OTf**

The cyclic voltammetry experiments were carried out in a single compartment cell of approximately 50 mL volume under an atmosphere of argon or dinitrogen. The samples were prepared in open-air, sealed, then connected to a Shlenk line, and purged with a nitrogen or argon atmosphere. Measurements were carried out using a VersaSTAT (Princeton Applied Research). A conventional three electrode system was employed consisting of a glassy carbon electrode (diameter = 0.4 cm) used as the working electrode, a platinum wire as the counter electrode, and an Ag/AgCl electrode as a reference. 5 mM solutions (15 mL) of thiophenium **4.7-OTf** were prepared in dry DMSO or DMF along with 0.1 M of tetrabutylammonium hexafluorophosphate as electrolyte. The scan rate of 0.1 V/s was used. The irreversible reduction potential values found are given versus the saturated calomel electrode (SCE). The most positive potential was assigned to the reduction of thiophenium **4.7-OTf** and not the more negative potential as similar cyclic voltammogram (two onsets) were obtained with analogous dibenzo¹²⁰- and thianthrene¹²⁷ sulfonium salts.

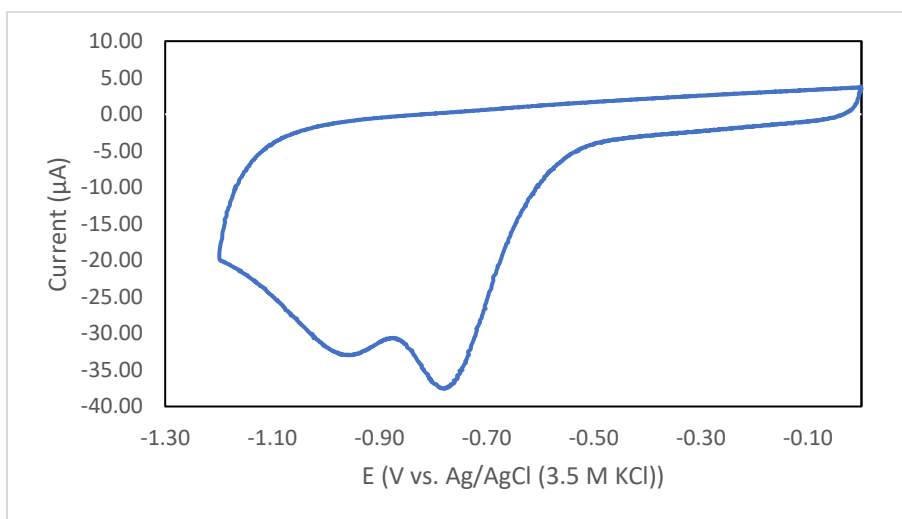


Figure 83 Cyclic voltammogram of **4.7-OTf** in DMF under argon atmosphere.
Reduction at -0.82(V) vs. SCE

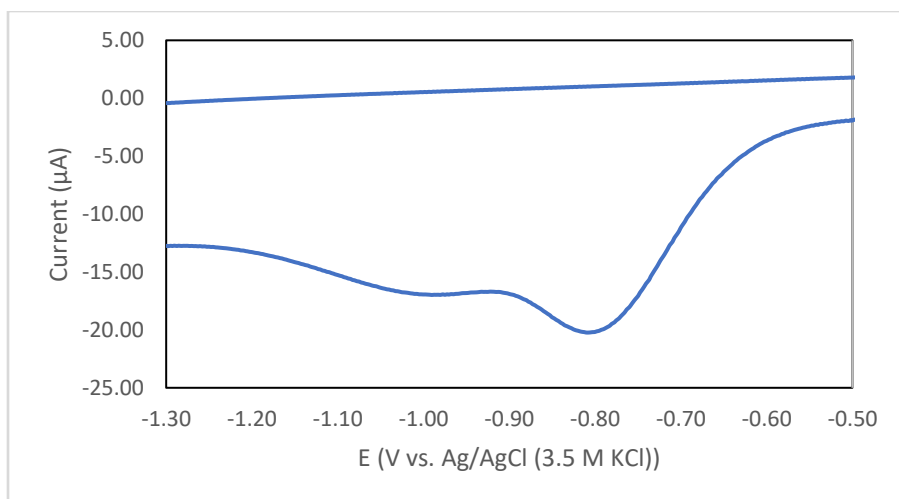
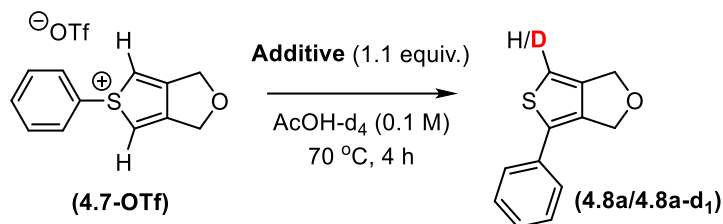


Figure 84 Cyclic voltammogram of **4.7-OTf** in DMSO under dinitrogen atmosphere.
Reduction at -0.85(V) vs. SCE

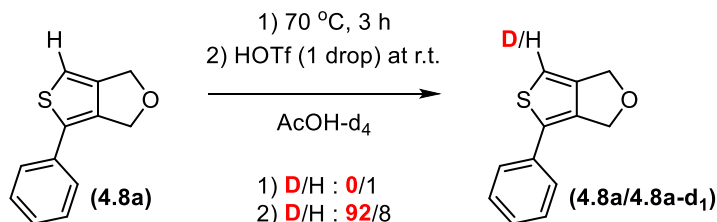
7.5.15 Control experiments on thiophenium **4.7-OTf** and thiophene **4.8a**



Entry	Additive	Yield (%)	Deuteration (%)
1	-	Quantitative	96
2	Pyridine	Quantitative	11

In a sealed NMR tube was added the thiophene triflate salt **4.7-OTf** (17.8 mg, 0.0505 mmol, 1.0 equiv.), deuterated acetic acid (0.5 mL, 0.1 M), 1 drop of DMSO-d₆ to help with solubility of the thiophenium salt and the indicated additive (0.0556 mmol, 1.1 equiv.). 2.0 μL of mesitylene was added as internal NMR standard. The solution was analyzed by ¹H NMR experiment before heating and followed while heating at 70 °C until consumption of the thiophenium is seen (4 h).

The ratio of ¹H NMR signal integration between the thiophene α-hydrogen and either of the CH₂ groups in a pure sample of **4.7-OTf** is 0.92 : 2.00. Obtained ratios in each experiment are set against this ratio in order to determine the percentage of deuteration.

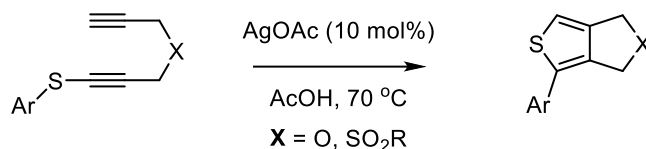


An arbitrary amount of thiophene **4.8a** was dissolved in AcOH-d₄ and it was heated at 70 °C for 3 h then 1 drop of triflic acid was added once the mixture was cooled to room temperature and the level of deuteration was assessed after 5 minutes. The percentage of deuteration is determined as described above.

7.5.16 Silver-catalyzed cycloaddition of S-(Aryl) derivatives towards thiophenes

4.8a-e,g-i

Standard procedure **4-F** : *one-pot* cyclization and rearrangement towards thiophenes **4.8a-e,g-i**.



In a sealed reaction vial was added a solution of yne-alkynyl sulfide (0.0500 – 0.200 mmol, 1.0 equiv.) in acetic acid (0.1 – 0.2 M). AgOAc (0.1 equiv.) was then added to the mixture. The solution was heated in an oil bath at 70 °C for the indicated time. Upon completion (determined by TLC – see below), the mixture is evaporated under reduced pressure to produce a crude. The crude was then purified by silica gel chromatography using the indicated eluent system (unless otherwise noted) to yield the desired 2-substituted thiophene.

Following the reaction by TLC, representative example for derivative **4.6c** (Figure 85).

The TLC are stained with a para-anisaldehyde (PA) solution where both the thiophenium intermediate (**4.7'-OAc**) and the neutral 2-substituted thiophene **4.8d** usually stain as bright blue/purple color. The reaction is determined to be completed when thiophenium **4.7'-OAc** is consumed. Note that some thiophene derivatives, such as **4.8e** and **4.8g**, stain dark black when using the PA solution.

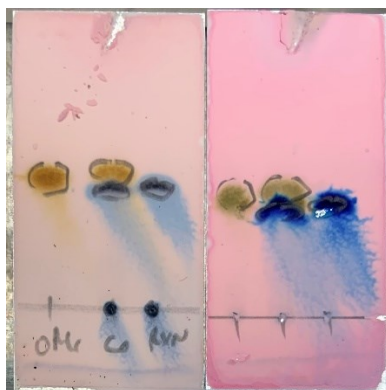
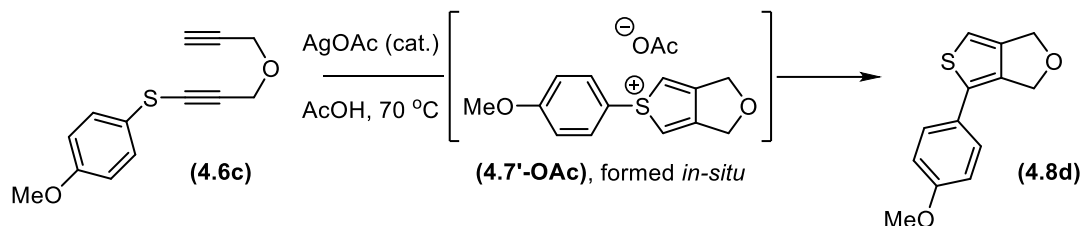
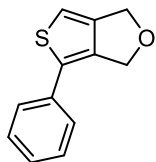


Figure 85 Following the reaction by NMR.

left : during the reaction, right : at the end of the reaction.

7.5.17 Characterization of 2-(Aryl) thiophenes 4.8a-e,g-i

(4.8a)



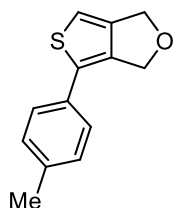
Using standard procedure **4-F** with 0.205 mmol of alkynyl sulfide **4.6a** in AcOH (1.0 mL, 0.2 M). Reaction time = 3h. Solvent system = Hexanes/Et₂O 95:5. Produced 38.2 mg (92% yield) of a white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.44 – 7.34 (m, 2H), 7.32 – 7.22 (m, 2H), 6.79 (t, *J* = 1.4 Hz, 1H), 5.05 (s, 2H), 4.84 – 4.87 (m, 2H).

¹³C NMR (76 MHz, CDCl₃) : δ 146.7, 141.4, 133.8, 132.2, 129.2, 127.4, 126.0, 111.6, 69.1, 68.1.

*Data matches that as previously reported by our group.*⁸¹

(4.8b)



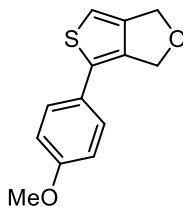
Using standard procedure **4-F** with 0.204 mmol of alkynyl sulfide **4.6e** in AcOH (1.0 mL, 0.2 M). Reaction time = 4 h. Solvent system = Hexanes/Et₂O 95:5. Produced 41.6 mg (94% yield) of a white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, *J* = 8.6 Hz, 2H), 7.22 – 7.16 (m, 2H), 6.75 (t, *J* = 1.4 Hz, 1H), 5.03 (s, 2H), 4.86 – 4.83 (m, 2H), 2.36 (s, 3H).

¹³C NMR (76 MHz, CDCl₃) δ 146.6, 140.8, 137.3, 132.3, 131.0, 129.8, 126.0, 111.0, 69.0, 68.1, 21.3.

HRMS Calculated for C₁₃H₁₂OS [M]⁺: 216.0609; found: 216.0579.

(4.8d)



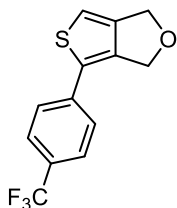
Using standard procedure **4-F** with 0.201 mmol of alkynyl sulfide **4.6c** in AcOH (1.0 mL, 0.2 M). Reaction time = 24 h. Solvent system = Hexanes/Et₂O 9:1. Produced 45.2 mg (96% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃) : ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.72 (t, *J* = 1.3 Hz, 1H), 5.01 (s, 2H), 4.86 – 4.81 (m, 2H), 3.83 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) : δ 159.0, 146.6, 140.2, 132.1, 127.4, 126.6, 114.6, 110.5, 69.0, 68.1, 55.5.

*Data matches that as previously reported by our group.*⁸¹

(4.8e)



Using standard procedure **4-F** with 0.201 mmol of alkynyl sulfide **4.6d** in AcOH (1.0 mL, 0.2 M). Reaction time = 3 h. Solvent system = Hexanes/Et₂O 95:5. Produced 47.1 mg (87% yield) of a white solid.

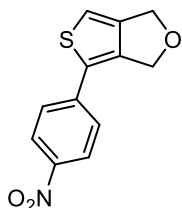
¹H NMR (600 MHz, CDCl₃) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 1.4 Hz, 1H), 5.06 (s, 2H), 4.87 – 4.86 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 147.1, 143.0, 137.19 (q, *J* = 1.5 Hz), 130.5, 129.1 (q, *J* = 32.7 Hz), 124.2 (q, *J* = 271.9 Hz), 126.2 (q, *J* = 3.8 Hz), 126.1, 113.1, 69.0, 68.1.

¹⁹F NMR (283 MHz, CDCl₃) δ -62.57.

HRMS Calculated for C₁₃H₉F₃OS [M]⁺: 270.0326; found: 270.0313.

(4.8g)



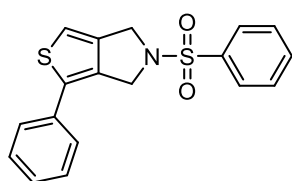
Using standard procedure **4-F** with 0.0501 mmol of alkynyl sulfide **4.6b** in AcOH (0.5 mL, 0.1 M). Reaction time = 2h30. Recrystallized from acetone/hexanes. Produced 11.7 mg (94% yield) of a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 9.0 Hz, 2H), 7.47 (d, *J* = 9.0 Hz, 2H), 6.96 (t, *J* = 1.4 Hz, 1H), 5.08 (s, 2H), 4.89 – 4.86 (m, 2H).

¹³C NMR (76 MHz, CDCl₃) : δ 147.5, 146.4, 144.4, 140.0, 129.7, 126.2, 124.7, 114.7, 69.1, 68.1.

HRMS Calculated for C₁₂H₉NO₃S [M]⁺: 247.0303; found: 247.0322.

(4.8h)



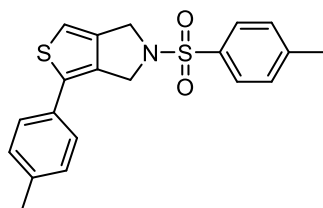
Using standard procedure **4-F** with 0.0990 mmol of alkynyl sulfide **4.6h** in AcOH (1.0 mL, 0.1 M). Reaction time = 4 h. Solvent system = Hexanes/DCM gradient of 2:3 → 1:4. Produced 23.8 mg (70% yield) of a white solid.

¹H NMR (600 MHz, CDCl₃) δ 7.91 (d, *J* = 7.1 Hz, 2H), 7.62 – 7.57 (m, 1H), 7.57 – 7.52 (m, 2H), 7.39 (d, *J* = 4.4 Hz, 4H), 7.32 – 7.27 (m, 1H), 6.82 (s, 1H), 4.62 (s, 2H), 4.42 (s, 4H).

¹³C NMR (151 MHz, CDCl₃) δ 141.0, 137.0, 135.6, 134.6, 133.2, 133.1, 129.4, 129.2, 127.8, 127.6, 126.2, 114.1, 50.0, 48.9.

HRMS Calculated for C₁₈H₁₅NO₂S₂ [M]⁺: 341.0544; found: 341.0537.

(4.8i)



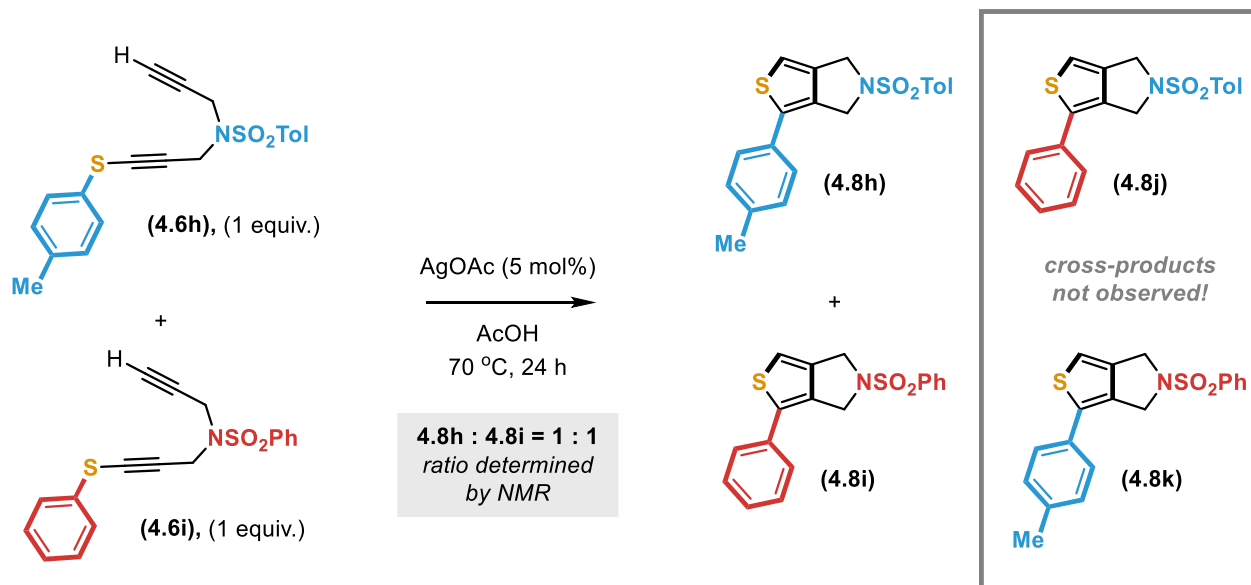
Using standard procedure **4-F** with 0.0994 mmol of alkynyl sulfide **4.6i** in AcOH (1.0 mL, 0.1 M). Reaction time = 4 h. Solvent system = Hexanes/DCM gradient of 2:3 → 1:4. Produced 28.9 mg (79% yield) of a white solid.

¹H NMR (600 MHz, CDCl₃) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.77 (s, 1H), 4.57 (s, 2H), 4.39 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 143.9, 141.1, 137.8, 135.1, 134.6, 134.0, 130.5, 130.0, 129.9, 127.7, 126.1, 113.4, 50.0, 48.9, 21.7, 21.3.

HRMS Calculated for C₂₀H₁₉NO₂S₂ [M]⁺: 369.0857; found: 369.0844.

7.5.18 Cross-over experiment using yne-alkynyl sulfides **4.6h** and **4.6i**



Full procedure: In a sealed NMR tube was added the yne-alkynyl sulfide substrate **4.6h** (15.4 mg, 0.0417 mmol, 1.0 equiv.) and **4.6i** (14.2 mg, 0.0417 mmol, 1.0 equiv.) and acetic acid (0.8 mL). AgOAc (0.7 mg, 4.17×10^{-3} mmol) was then added to the NMR tube. The mixture was heated in an oil bath set to 70 °C for 24 h. The reaction mixture is then concentrated under reduced pressure to produce a crude and a portion of it is dissolved in CDCl₃ for ¹H NMR analysis (Figure 86). After NMR analysis, CDCl₃ is evaporated, and the combined crudes are diluted with MeOH (1 mL) and NaCl (s) is added in excess. After stirring for 5 minutes, filtration through a celite pad with MeOH affords a crude upon evaporation under reduced pressure. The resulting crude is then analyzed by HRMS-El.

Thiophene **4.8j**, which was previously synthesized by our group,⁸¹ was evidently not formed as suggested by NMR spectra overlaps (Figure 87). Furthermore, no molecular ion peak corresponding to the cross-products (**4.8j** and **4.8k**) was observed by HRMS of the reaction crude (Figure 88 - Figure 91).

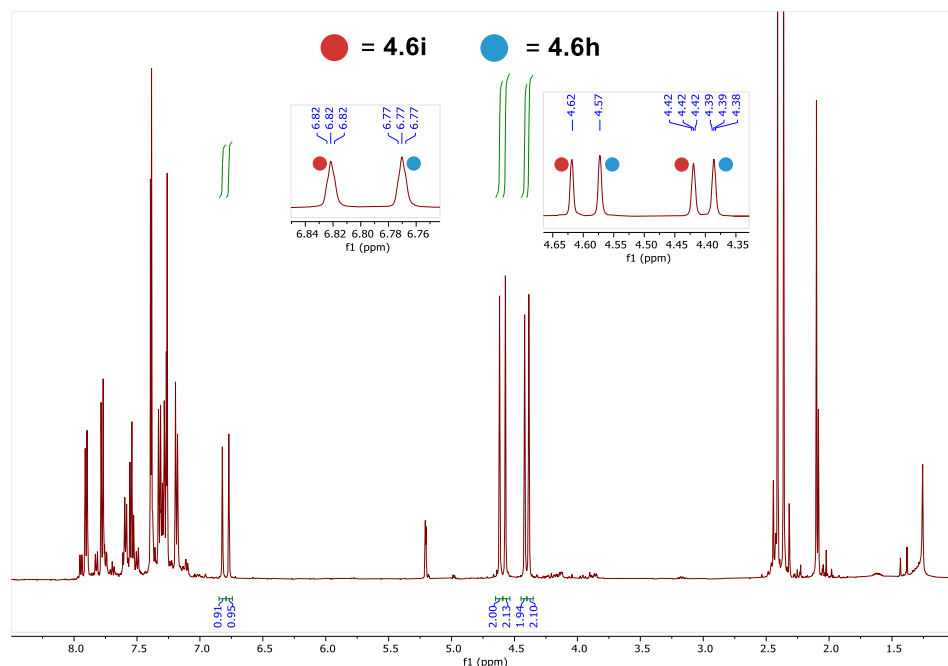


Figure 86 Crude aliquot analyzed by NMR. Integration suggest formation of **4.6h** and **4.6i** in a 1:1 ratio.

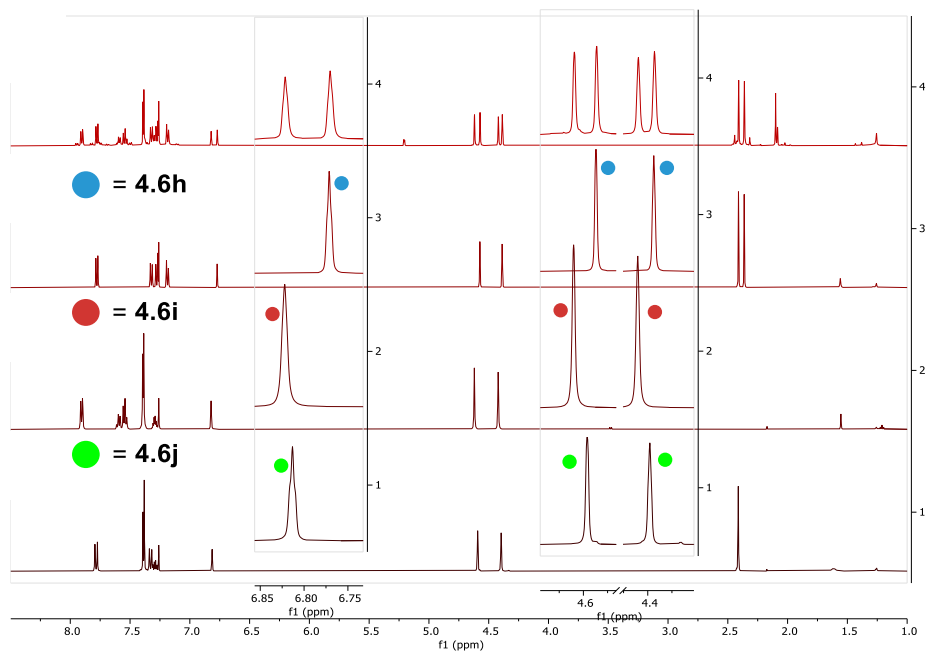


Figure 87 NMR spectra overlap confirming the formation of products **4.6h** and **4.6i** and no formation of cross-over product **4.8j** A) Cross-over experiment reaction crude analyzed by ^1H NMR; B) Isolated product **4.6h**; C) Isolated product **4.6i**; D) NMR of cross-over product **4.8j** in CDCl_3 .

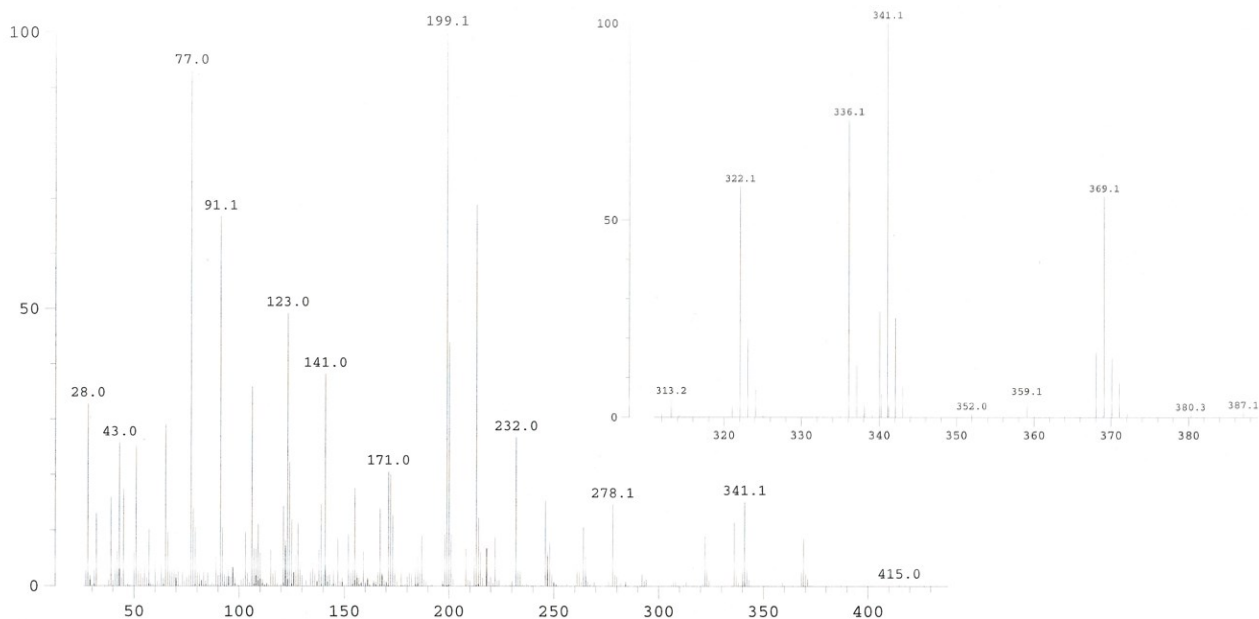


Figure 88 HRMS-EI spectra of the cross-over experiment showing formation of products **4.8i** (341.1 m/z) and **4.8h** (369.1 m/z).

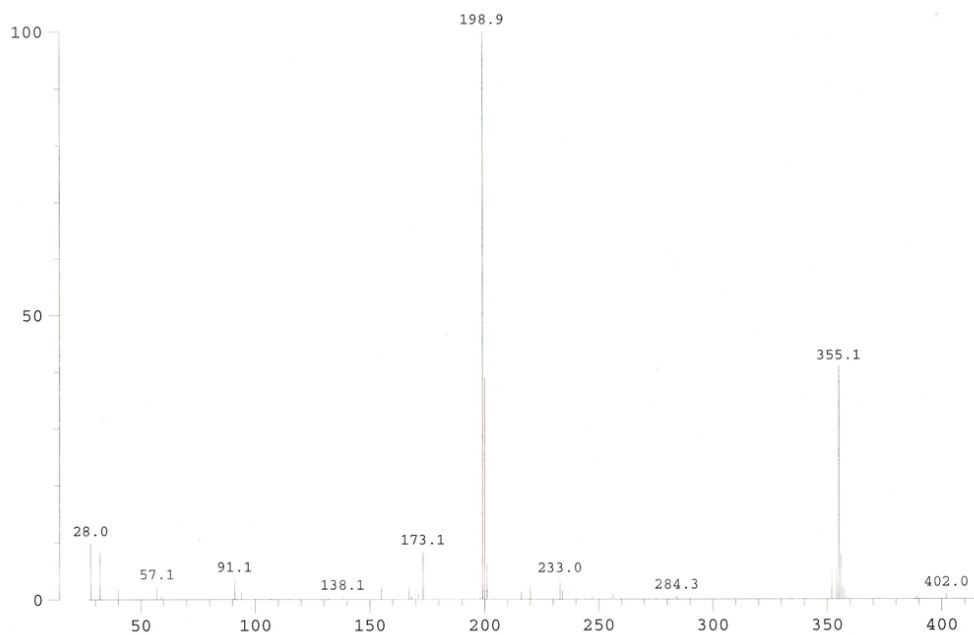


Figure 89 HRMS-EI spectra of theoretical cross-product **4.8j*** (355.1 m/z). This peak is not present in **Figure 88** suggesting that no cross-product is obtained.

^x Both cross-over products (**4.8j** and **4.8k**) have the same mass (355.1) which is not present in the HRMS-EI spectra for the cross-over experiment reaction crude.

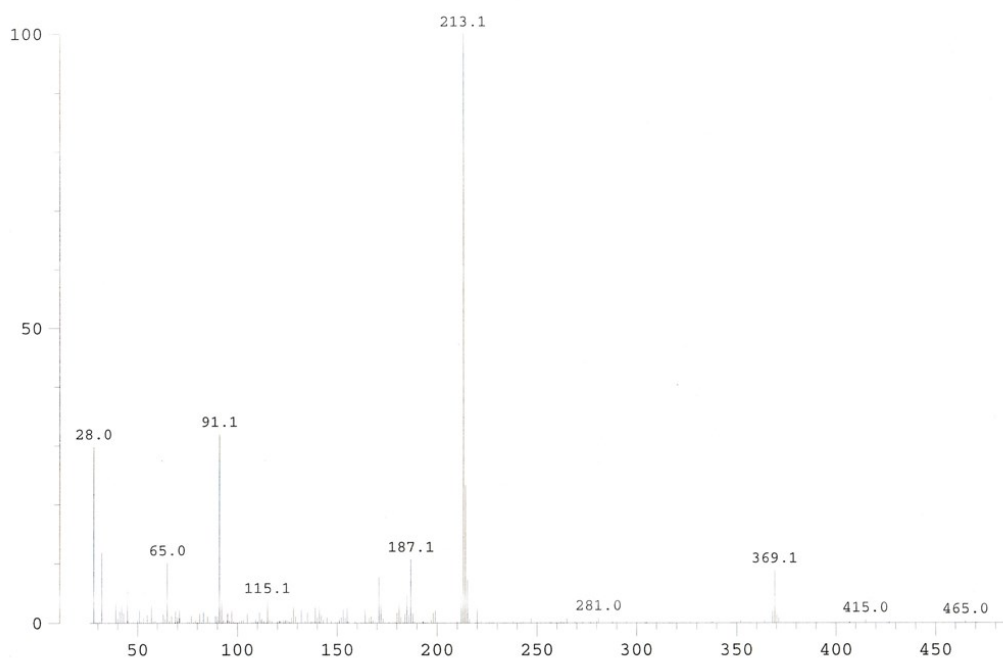


Figure 90 HRMS-El spectra of isolated product **4.8h** (369.1 m/z).

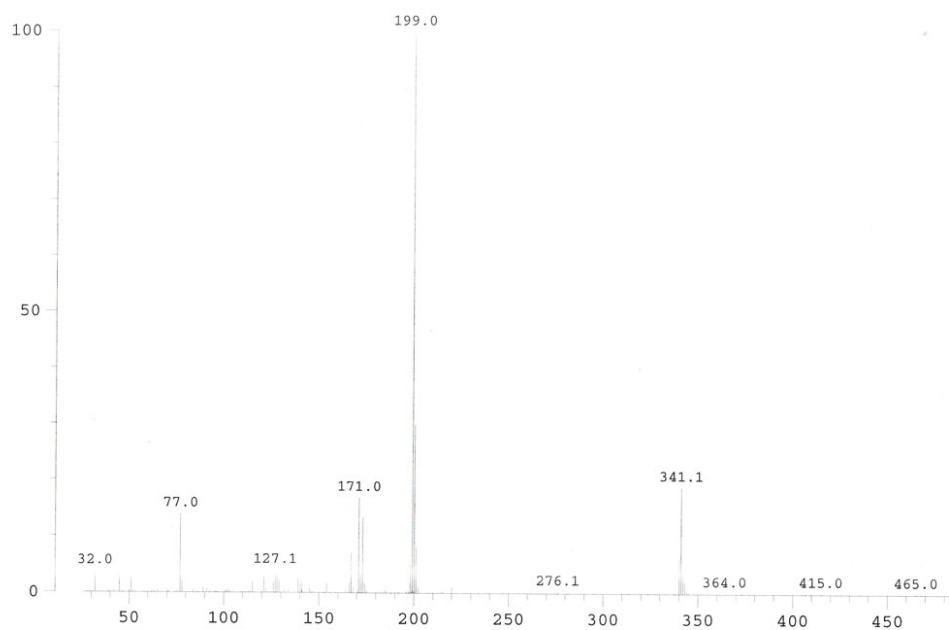
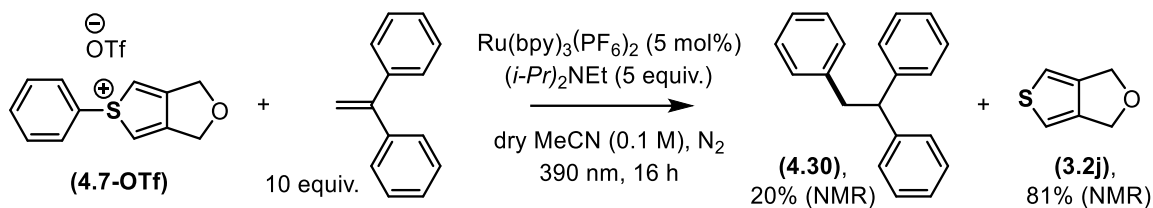


Figure 91 HRMS-El spectra of isolated product **4.8i** (341.1 m/z).

7.5.19 Thiophenium triflate **4.7-OTf** in photoredox procedures



Following a modified procedure reported by Fensterbank et al.¹¹⁹ : In Pyrex glass reaction vial was added a solution of thiophenium triflate salt **4.7-OTf** (35.2 mg, 0.100 mmol, 1.0 equiv.) in dry MeCN (1.0 mL, 0.1 M), *N,N*-diisopropylethylamine (0.09 mL, 0.500 mmol, 5.0 equiv.) and 1,1-diphenylethylene (0.180 mL, 1.00 mmol, 10.0 equiv.). The mixture is then degassed with N₂ for 1 minute then Ru(bpy)₃(PF₆)₂ is added quickly. The reaction vial is sealed and irradiated with a Kessil LED bulb (390 nm) for 16 h. The reaction mixture was then concentrated under reduced pressure to give a crude which is analyzed by ¹H NMR using 2.0 μL of mesitylene as external standard. The desired product **4.30** and 2,5-unsubstituted thiophene **3.2j** were obtained in 20% and 81% NMR yields respectively. The crude is then diluted with EtOAc and extracted with 2.5 % HCl aq. solution twice, then once with brine. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The obtained crude was then purified by silica gel chromatography using Hexanes:Et₂O 9:1 as the eluent system. Fractions containing **4.30** and **3.2j** as well as other by-products was obtained with a total mass of 30.3 mg (**Figure 92**). The signals observed are in accordance with what is described for **4.30**¹¹⁹ and **3.2j**.⁸¹

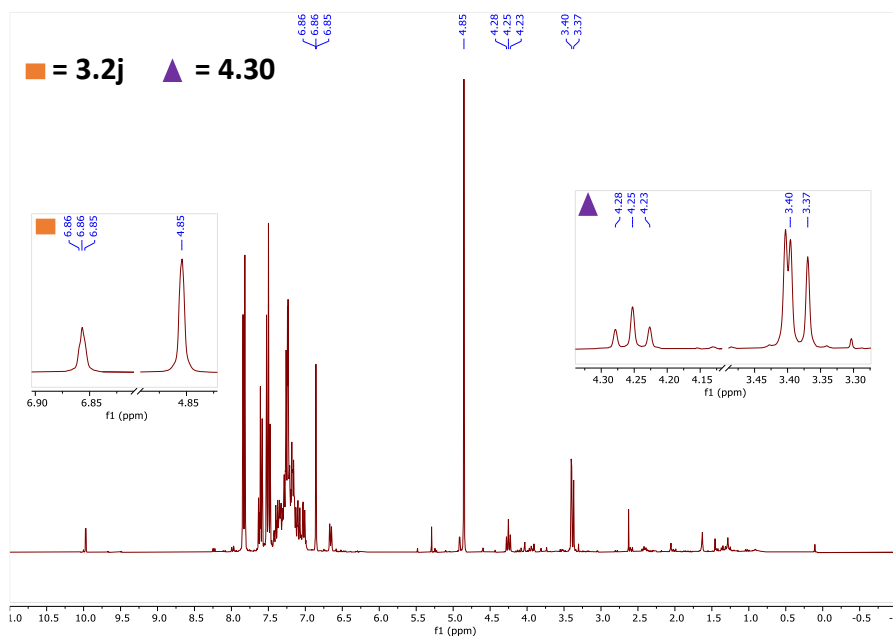
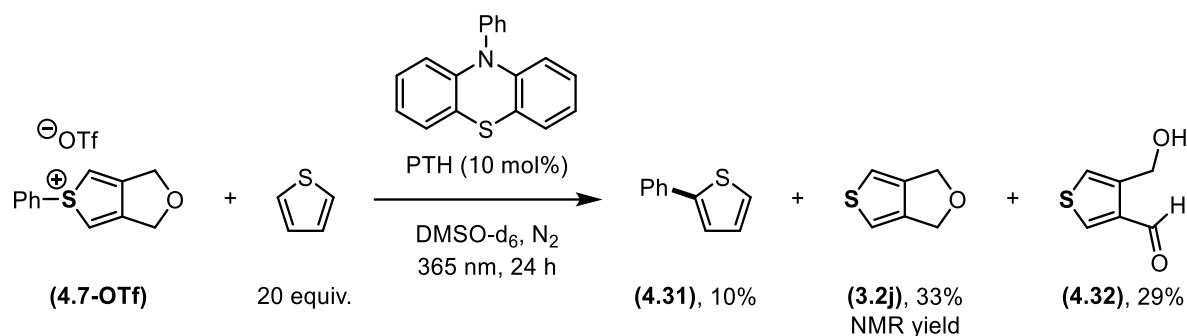
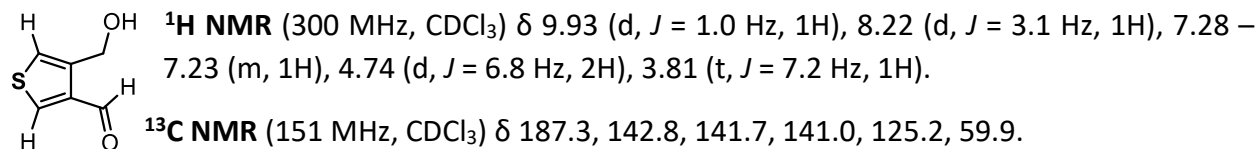


Figure 92 NMR obtained upon purification of the reaction crude by column-chromatography.



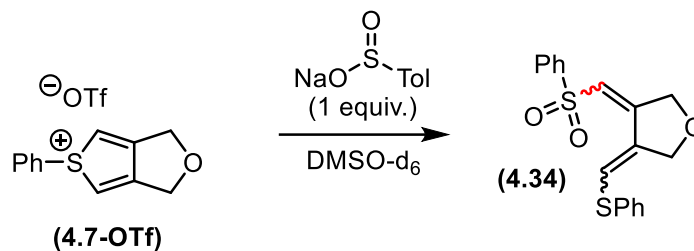
Following a modified procedure reported by Procter et al.¹²⁰: In a Pyrex glass reaction vial was added thiophenium triflate salt **4.7-OTf** (35.2 mg, 0.100 mmol, 1.0 equiv.) and PTH (2.8 mg, 0.020 mmol, 0.1 equiv.) were dissolved in DMSO- d_6 (0.5 mL, 0.2 M). Then, thiophene (0.16 mL, 2.00 mmol, 20.0 equiv.) was added. The solution was then degassed with N_2 for 2 minutes. The reaction mixture was then irradiated with a UVA LED (365 nm) overnight under N_2 atmosphere. After irradiation the solution was quenched with $NaHCO_3$ and EtOAc was added. The organic phase obtained was then washed with brine once. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A crude NMR was taken in $CDCl_3$ with 2.0 μL of 1,2-DBE as an external standard and a yield of 33% for **3.2j** was determined. The NMR sample was concentrated under reduced pressure then it was purified by silica gel chromatography using a gradient of hexanes/EtOAc 100:0 $\rightarrow$ 95:5 to obtain 1.6 mg of **4.31** (10% yield) then increased to a ratio of 50:50 to obtain 4.0 mg of **4.32** (29% yield). Spectra obtained for **4.31** was in accordance with the literature.¹²⁰

(4.32)



Supplementary HSQC data for **4.32** provided in section 9.1.

7.5.20 Ring opening of thiophenium **4.7-OTf** when mixing with sodium *p*-toluenesulfinate



In a sealed NMR tube was added the thiophene triflate salt **4.7-OTf** (3.5 mg, 0.011 mmol, 1.0 equiv.), DMSO- d_6 (0.5 mL) and *p*-toluenesulfonic acid sodium salt (2.0 mg, 0.011 mmol, 1.0 equiv.). An NMR was taken right away (5 min) showing already 50% conversion of thiophene triflate **4.7-OTf** (Figure 93). The peaks were unambiguously assigned after following the reaction by NMR. The signals observed for **4.34** are in accordance with vinyl sulfones from the literature.¹⁴¹

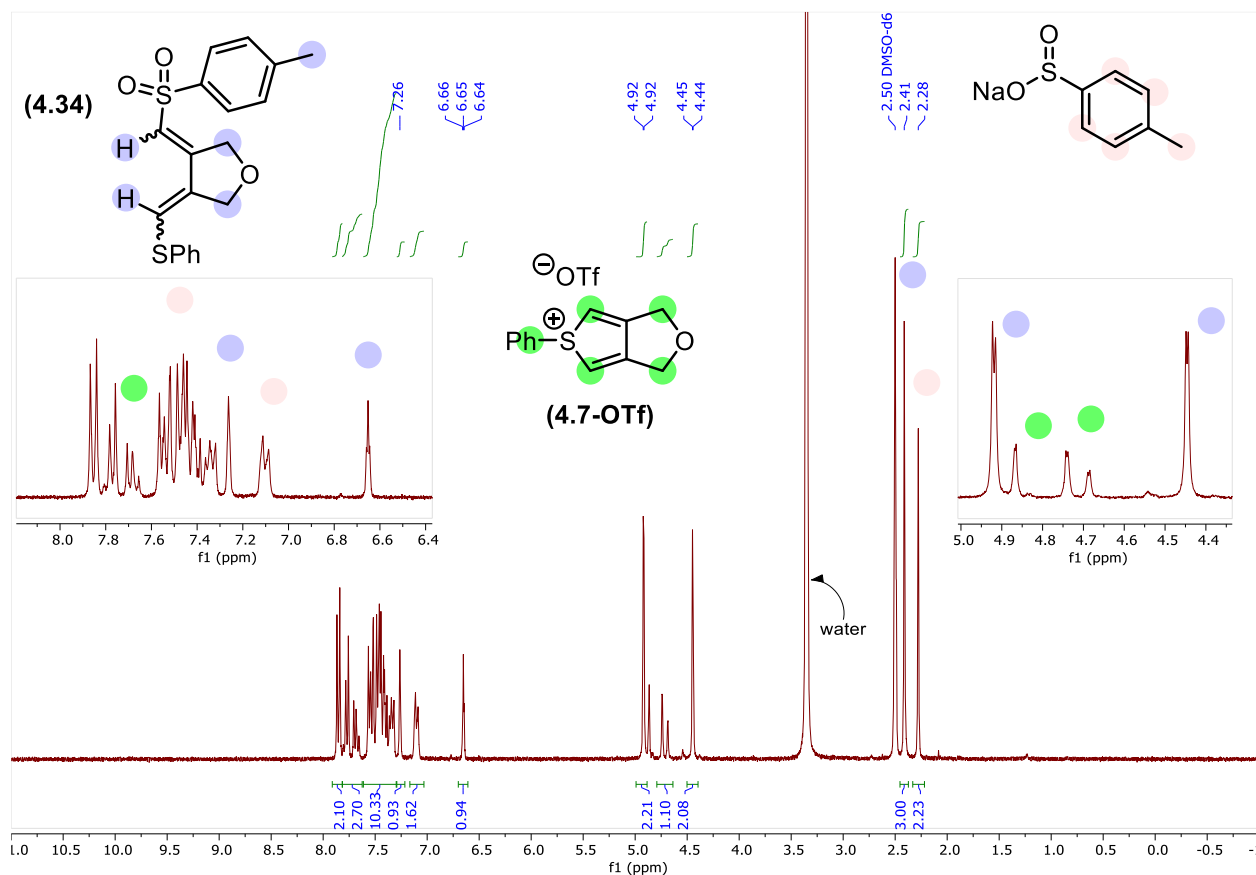


Figure 93 First NMR obtained upon mixing of **4.7-OTf** with sodium *p*-toluenesulfinate.

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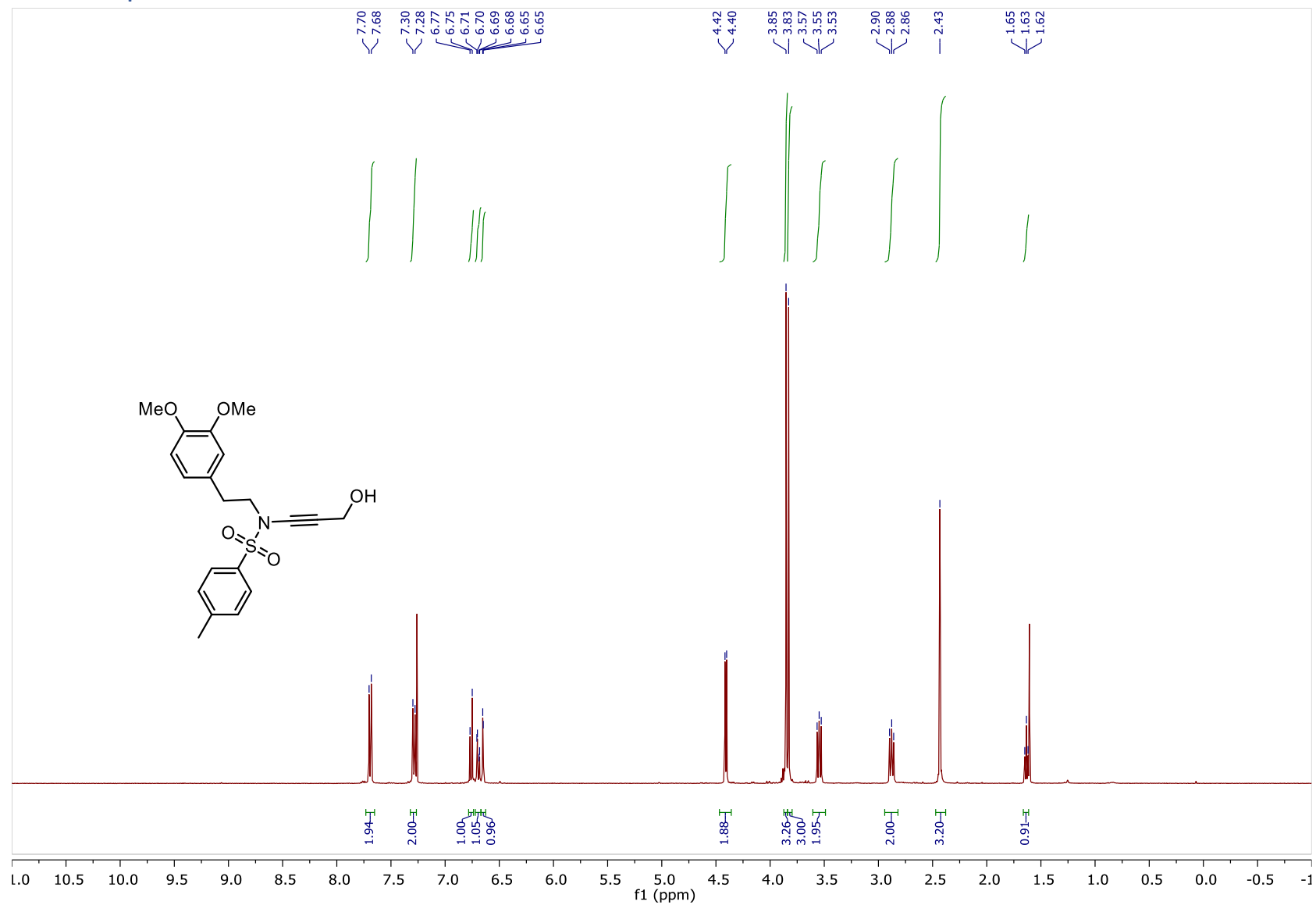
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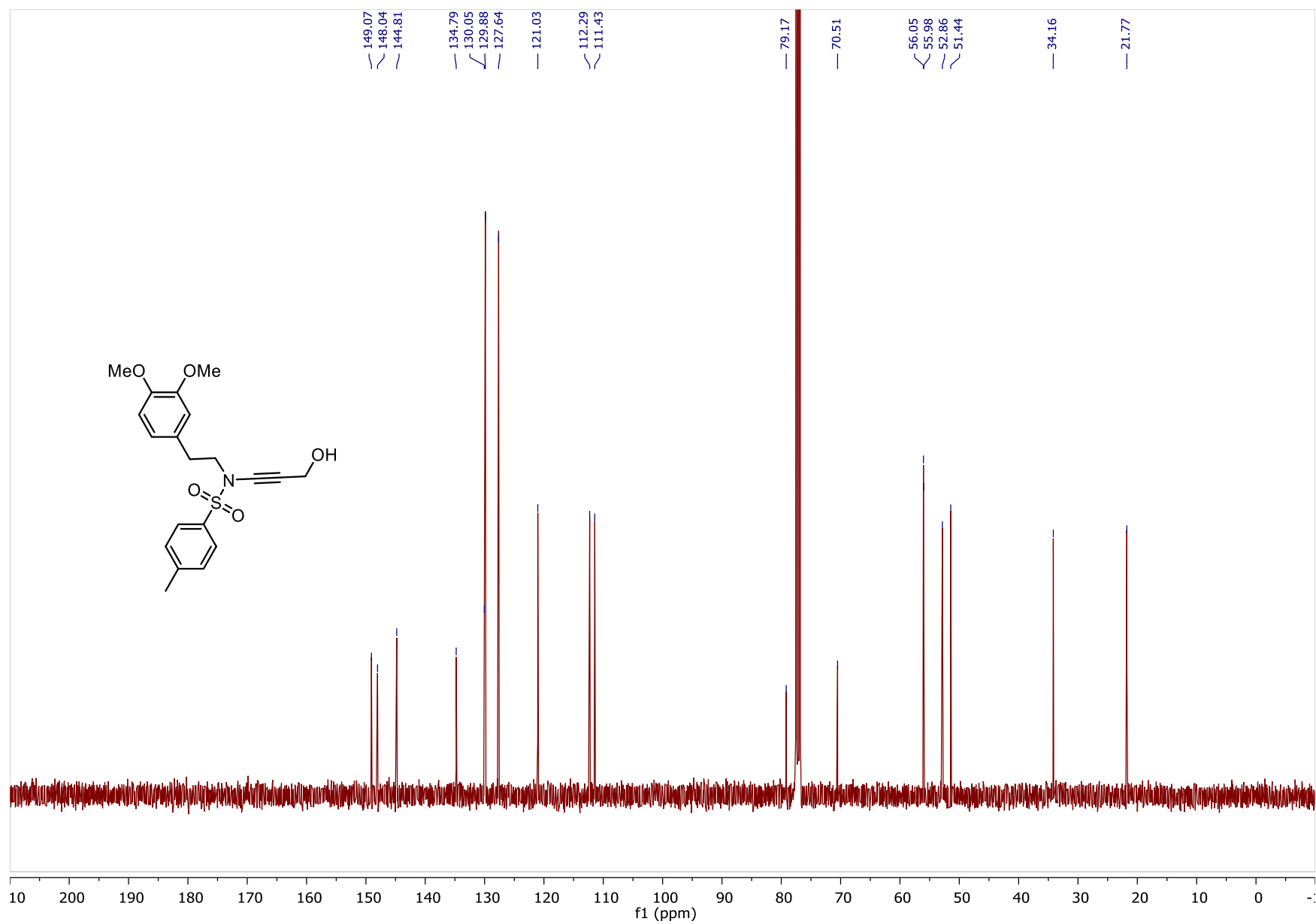
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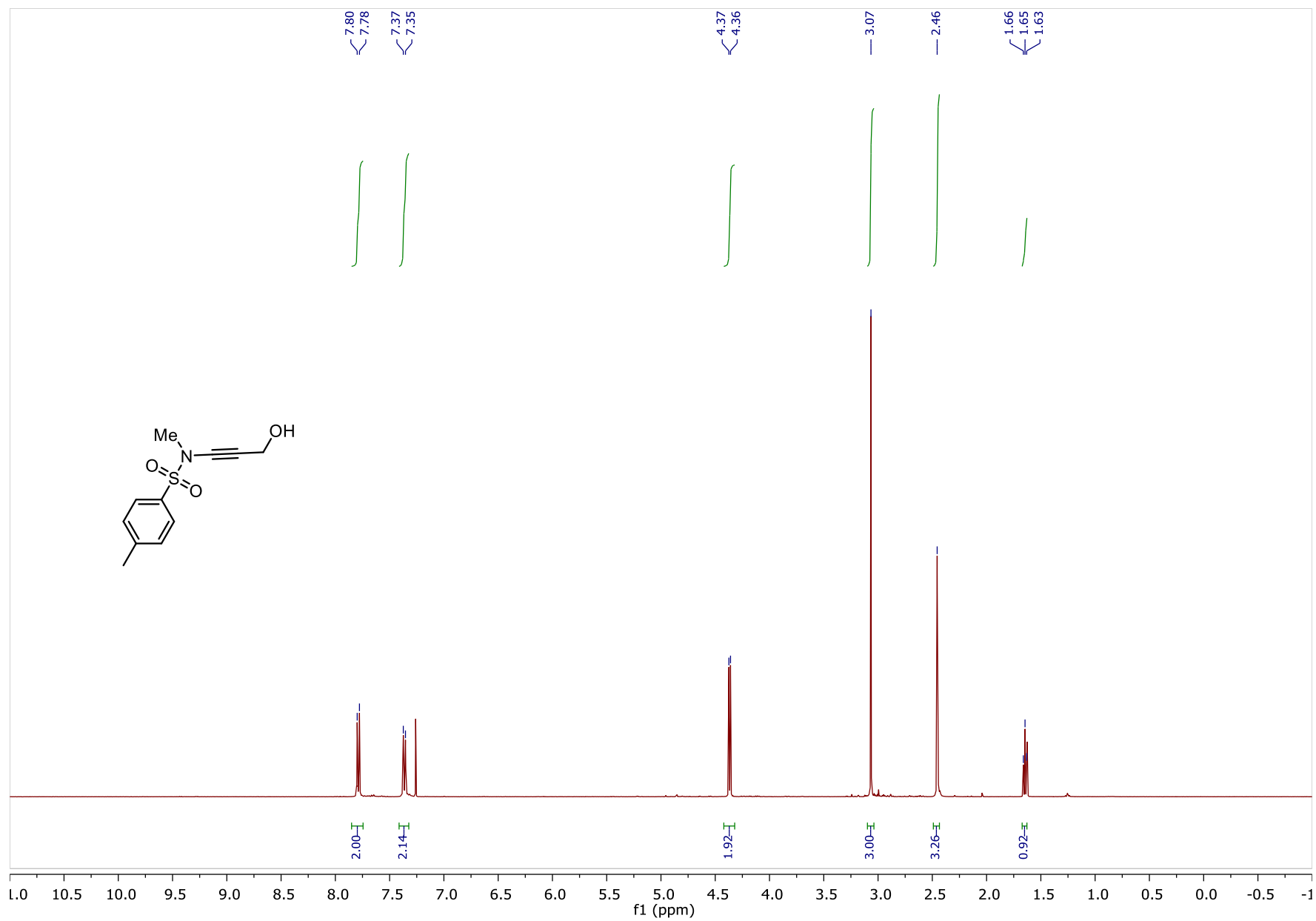
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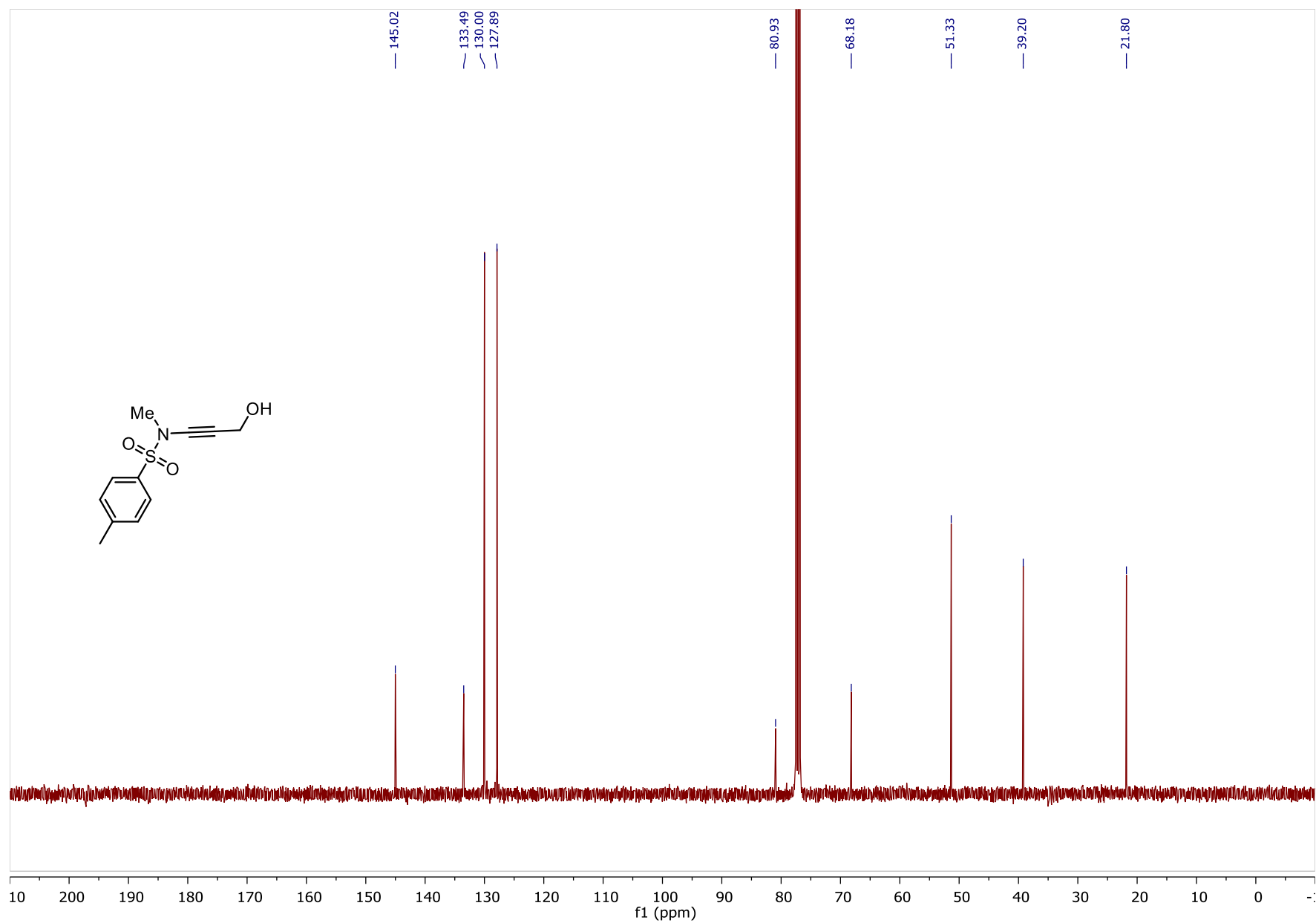
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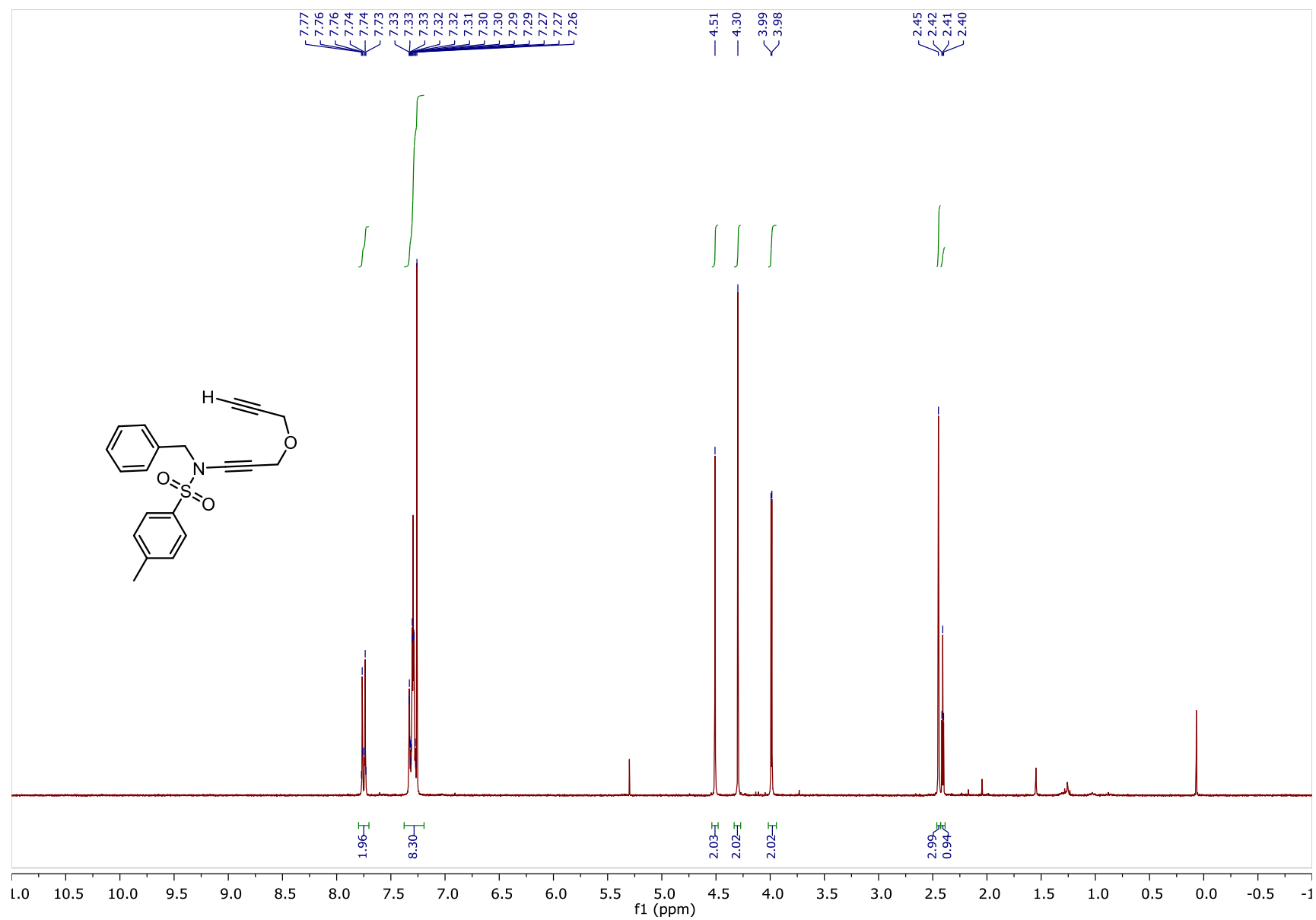
9 NMR spectra

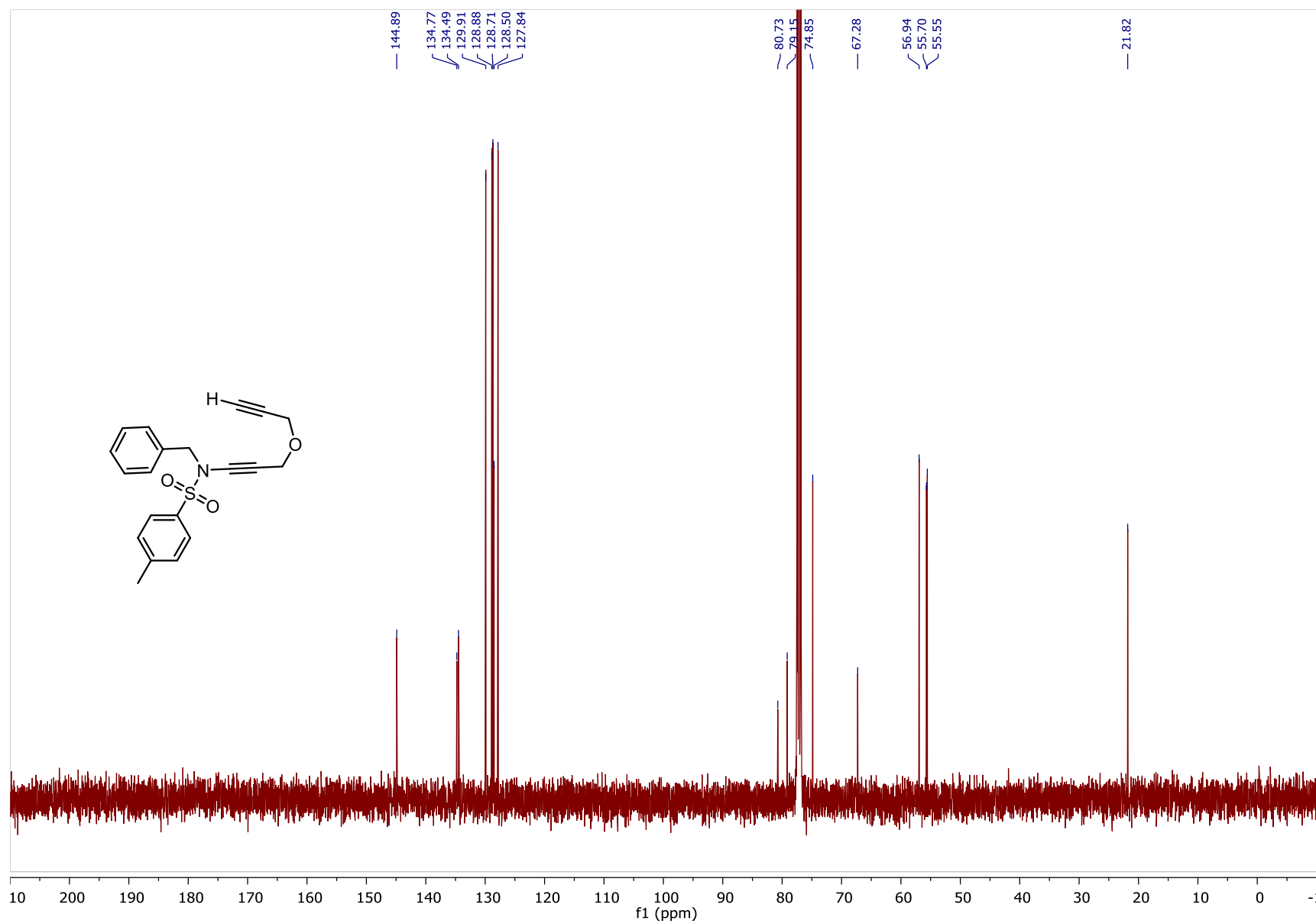


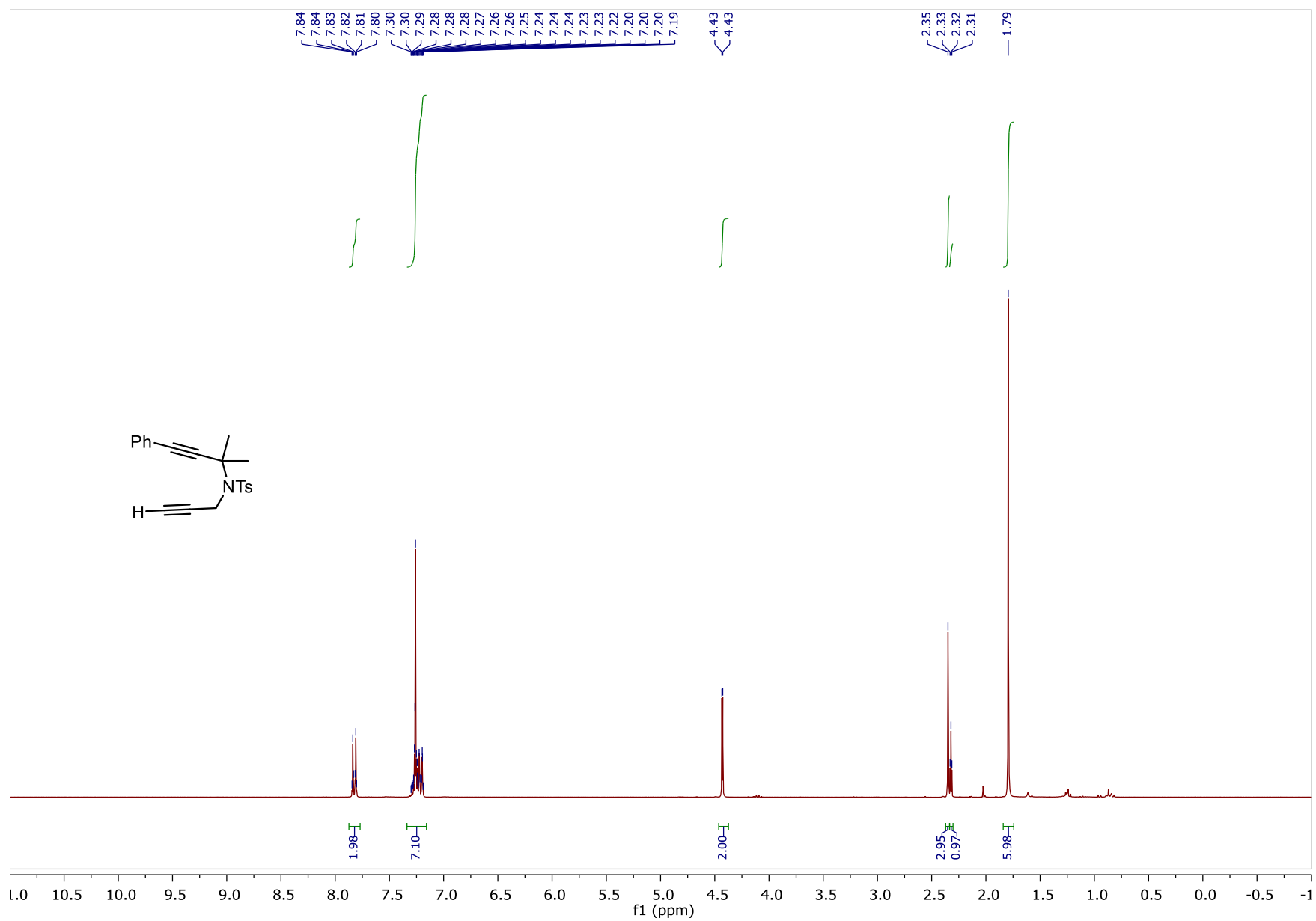


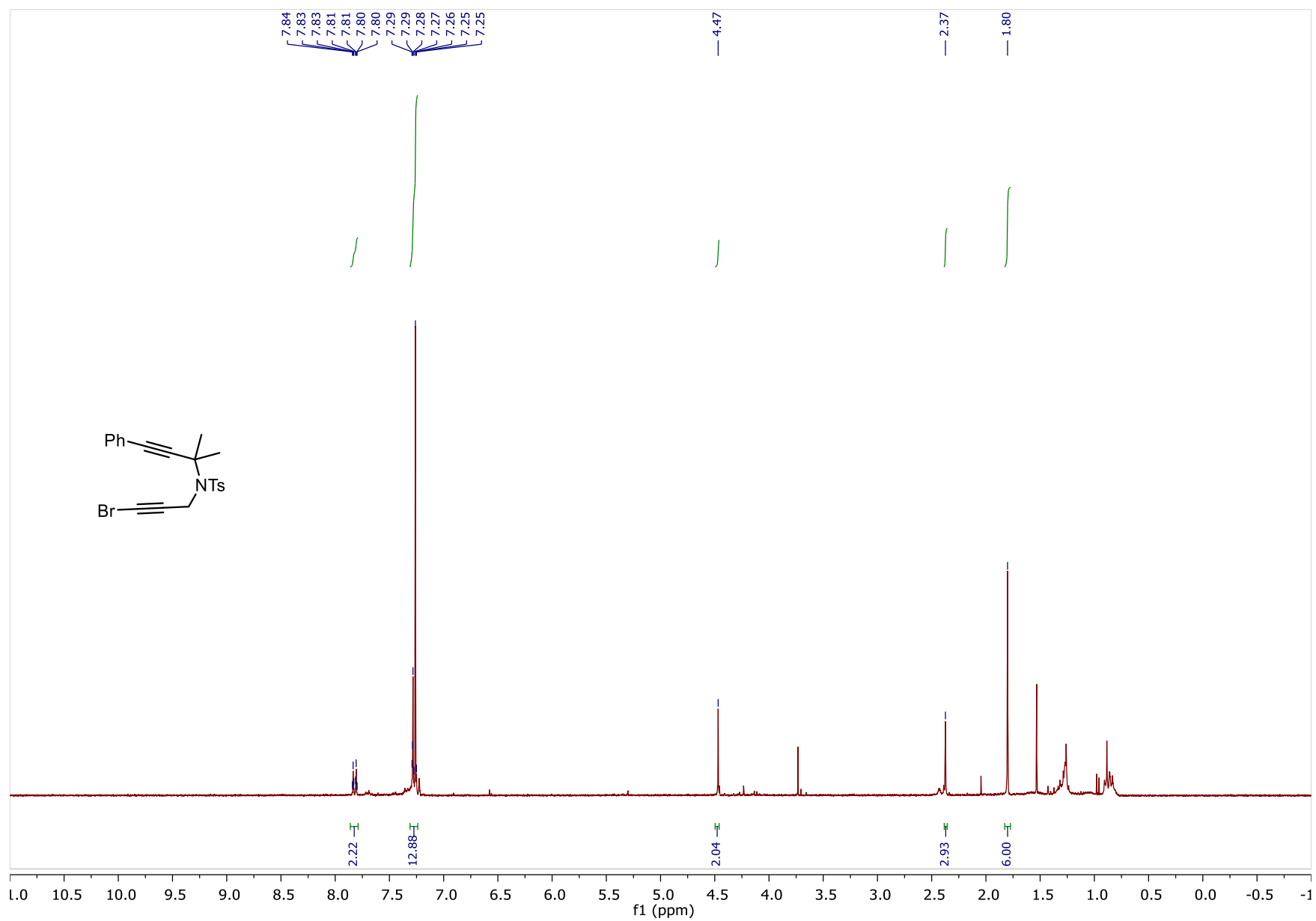


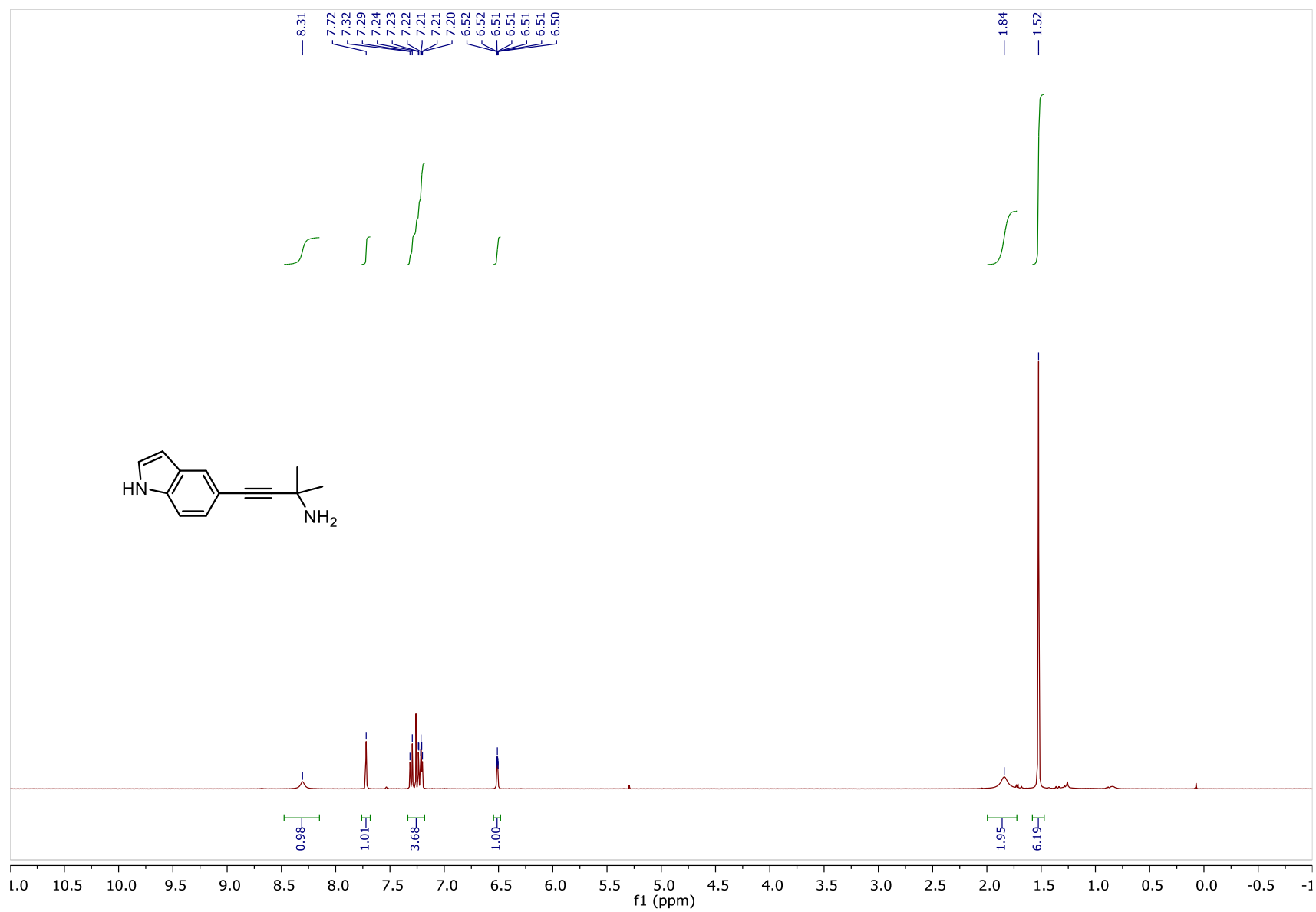


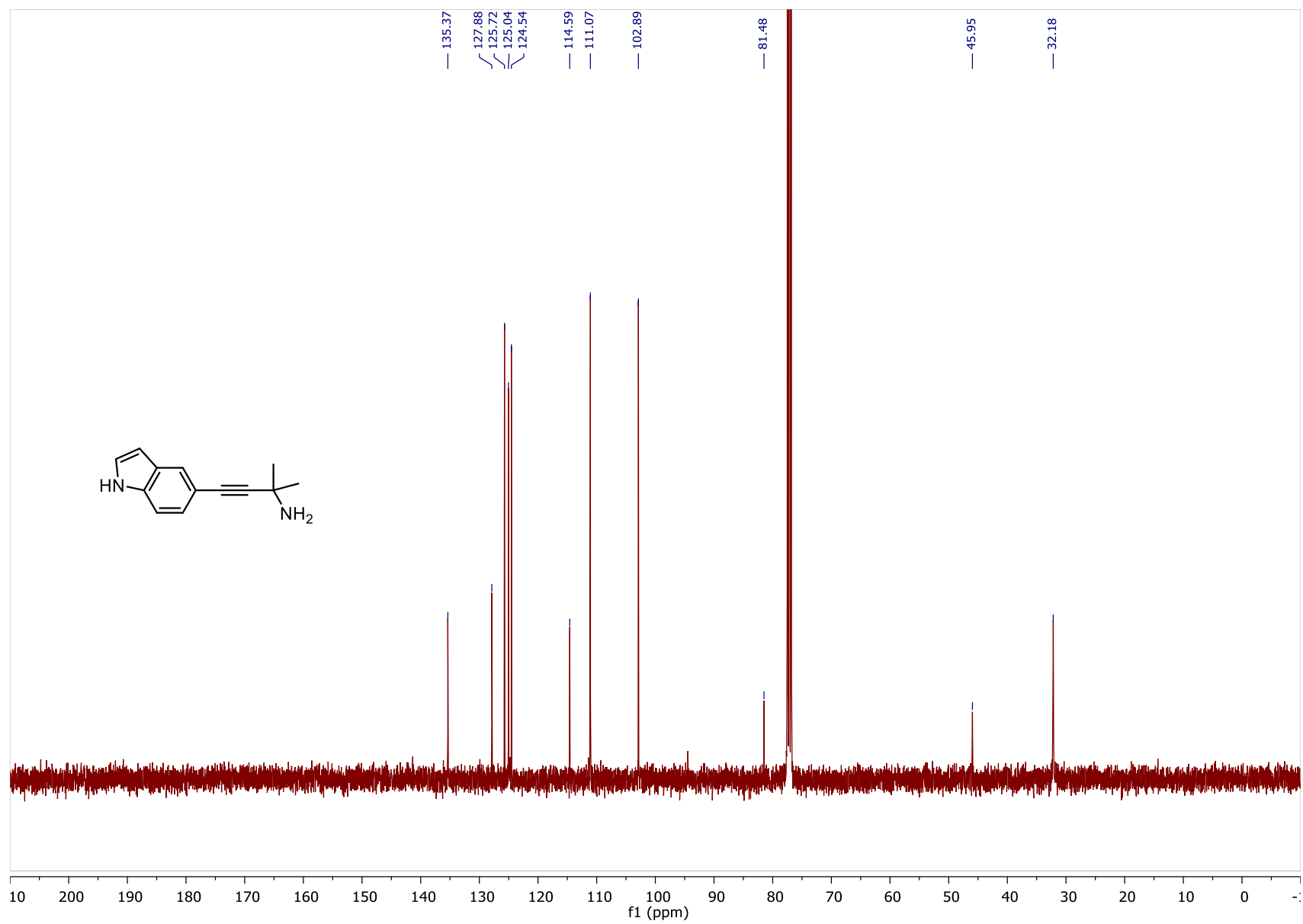


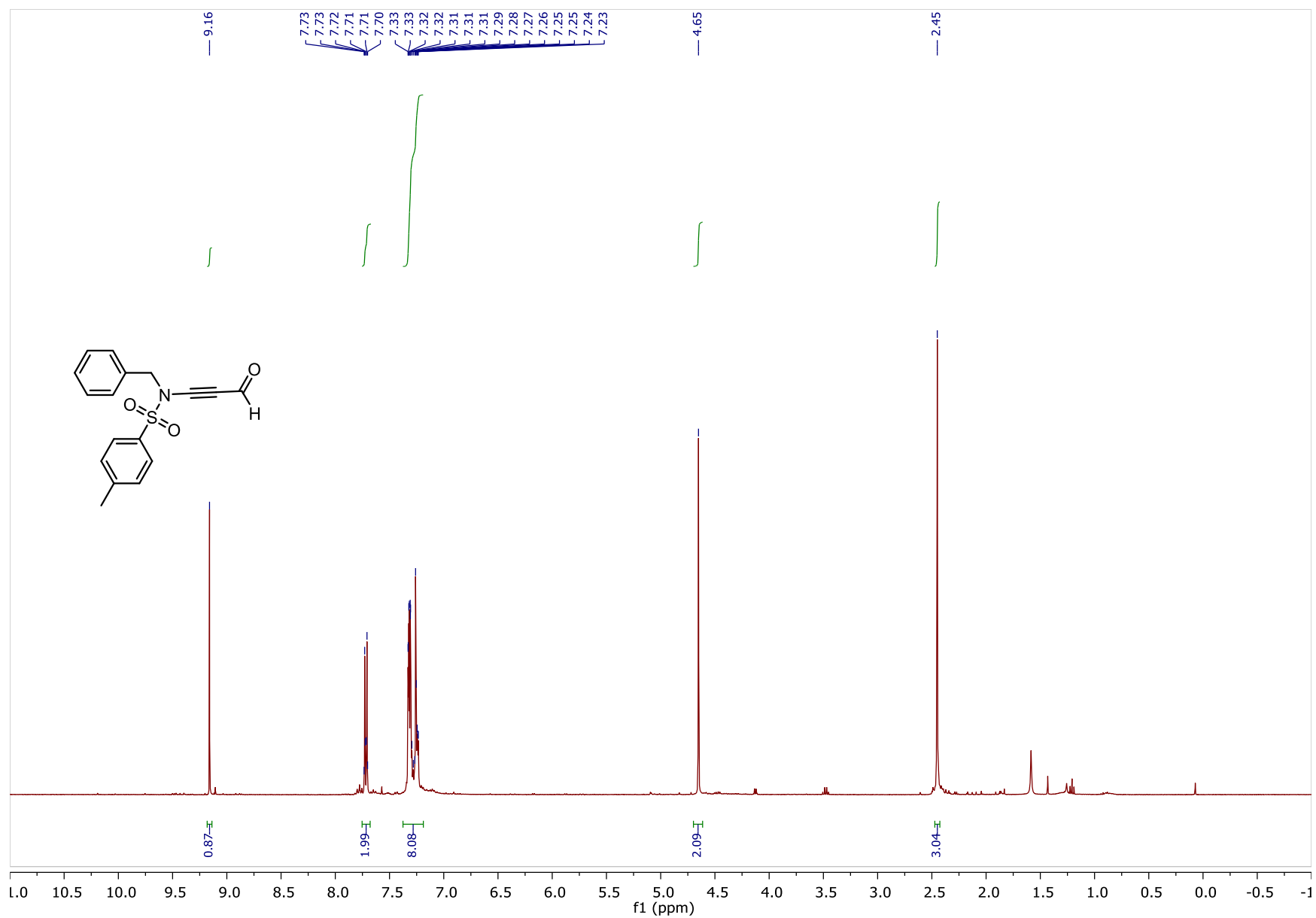


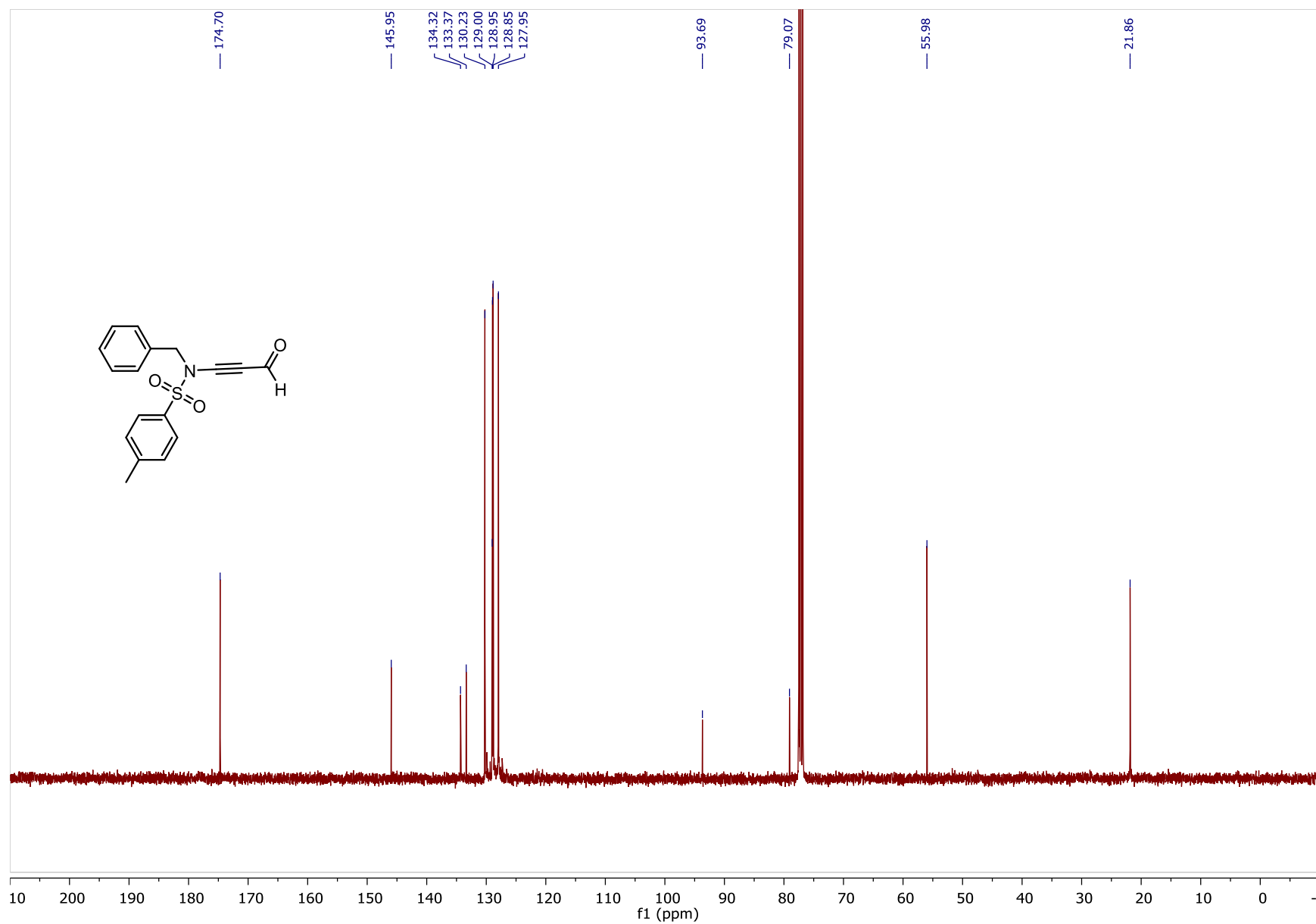


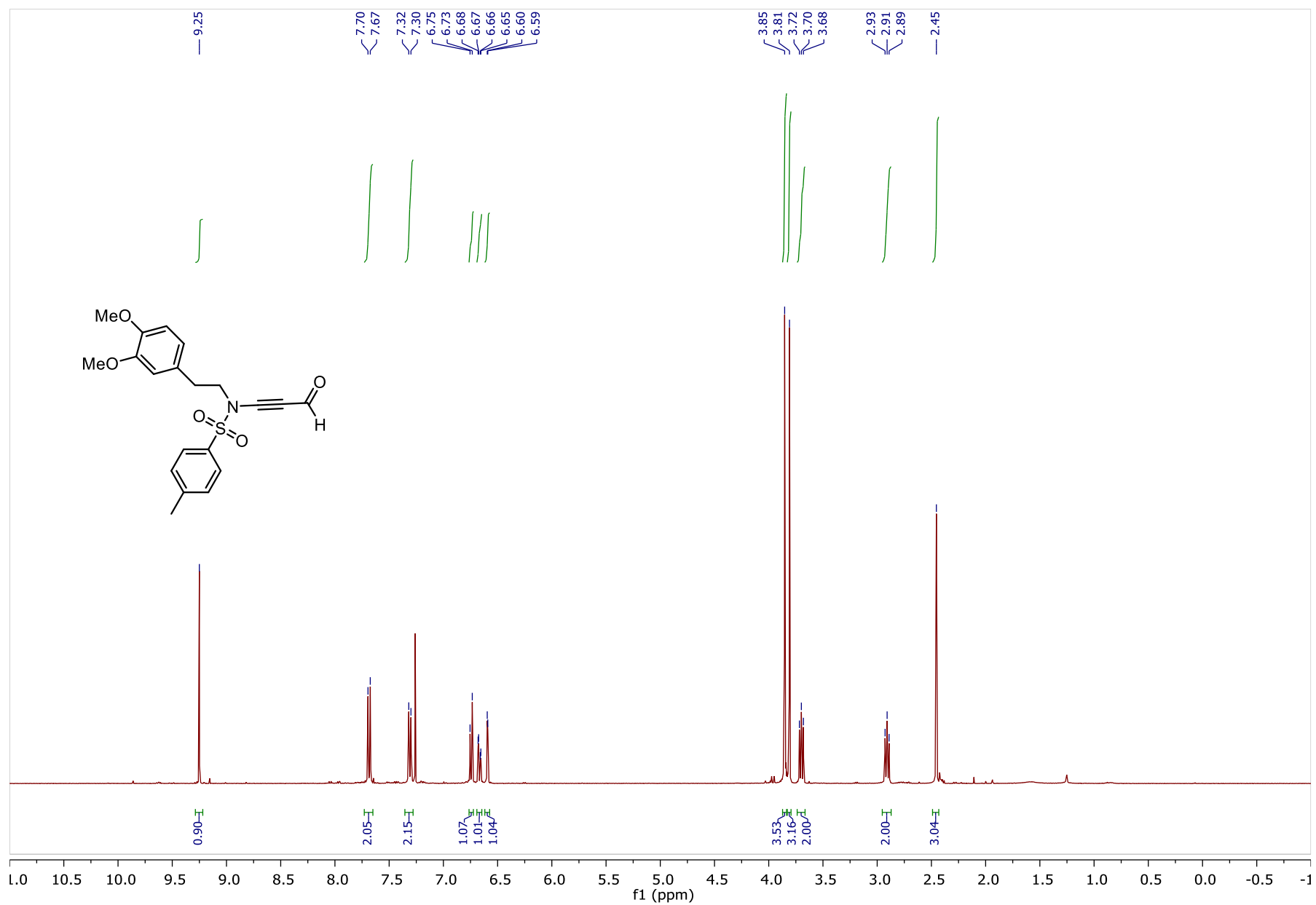


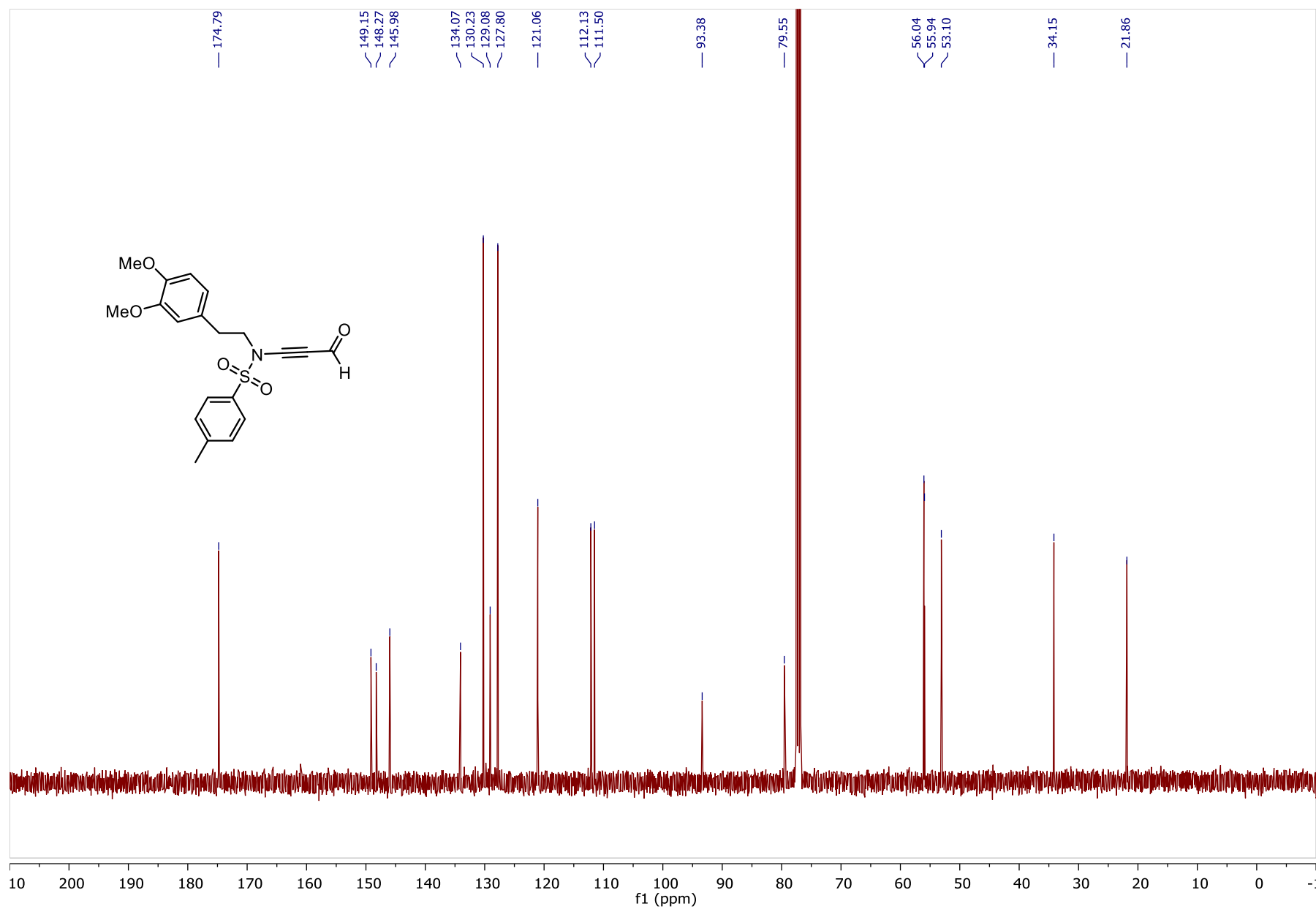


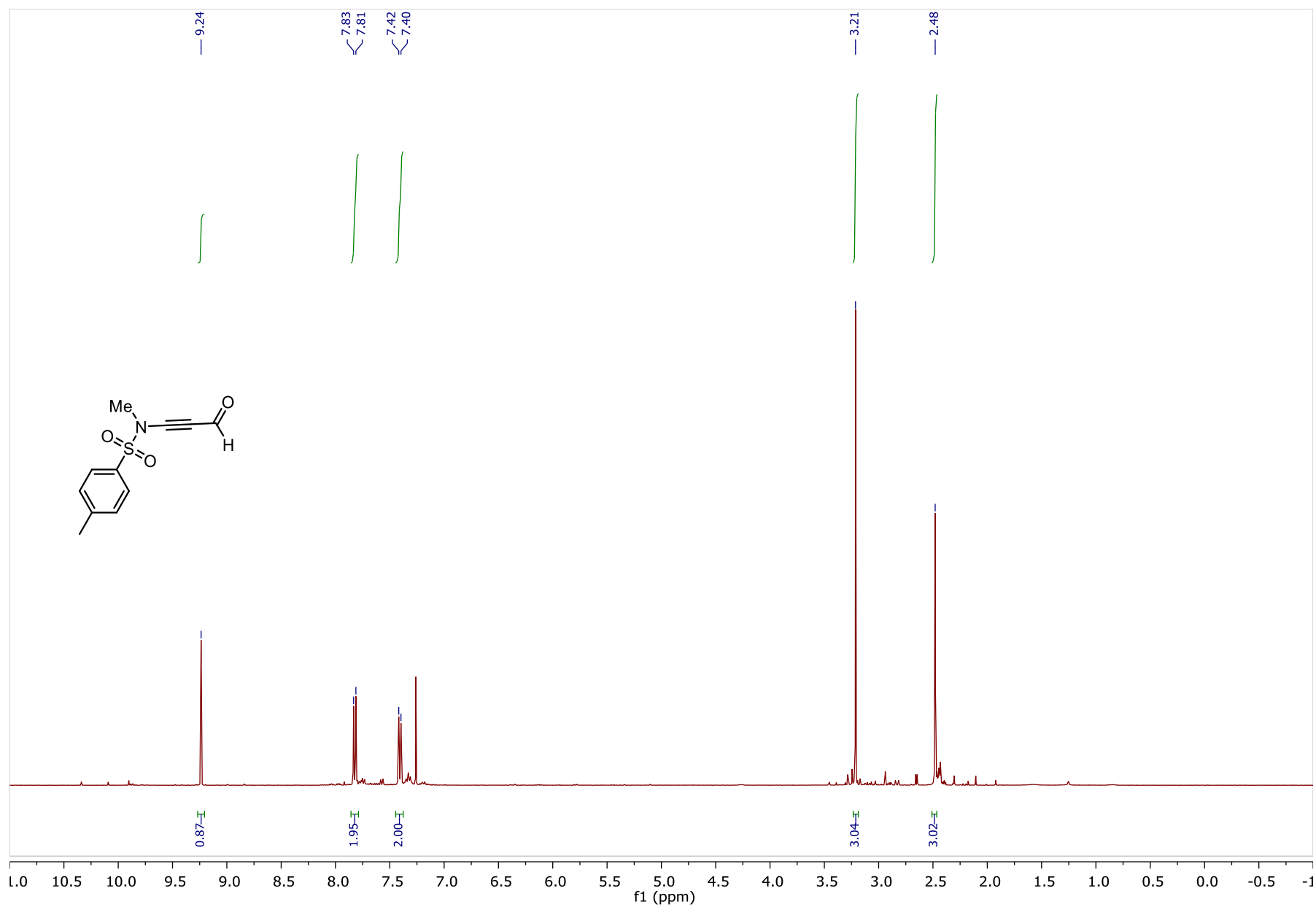


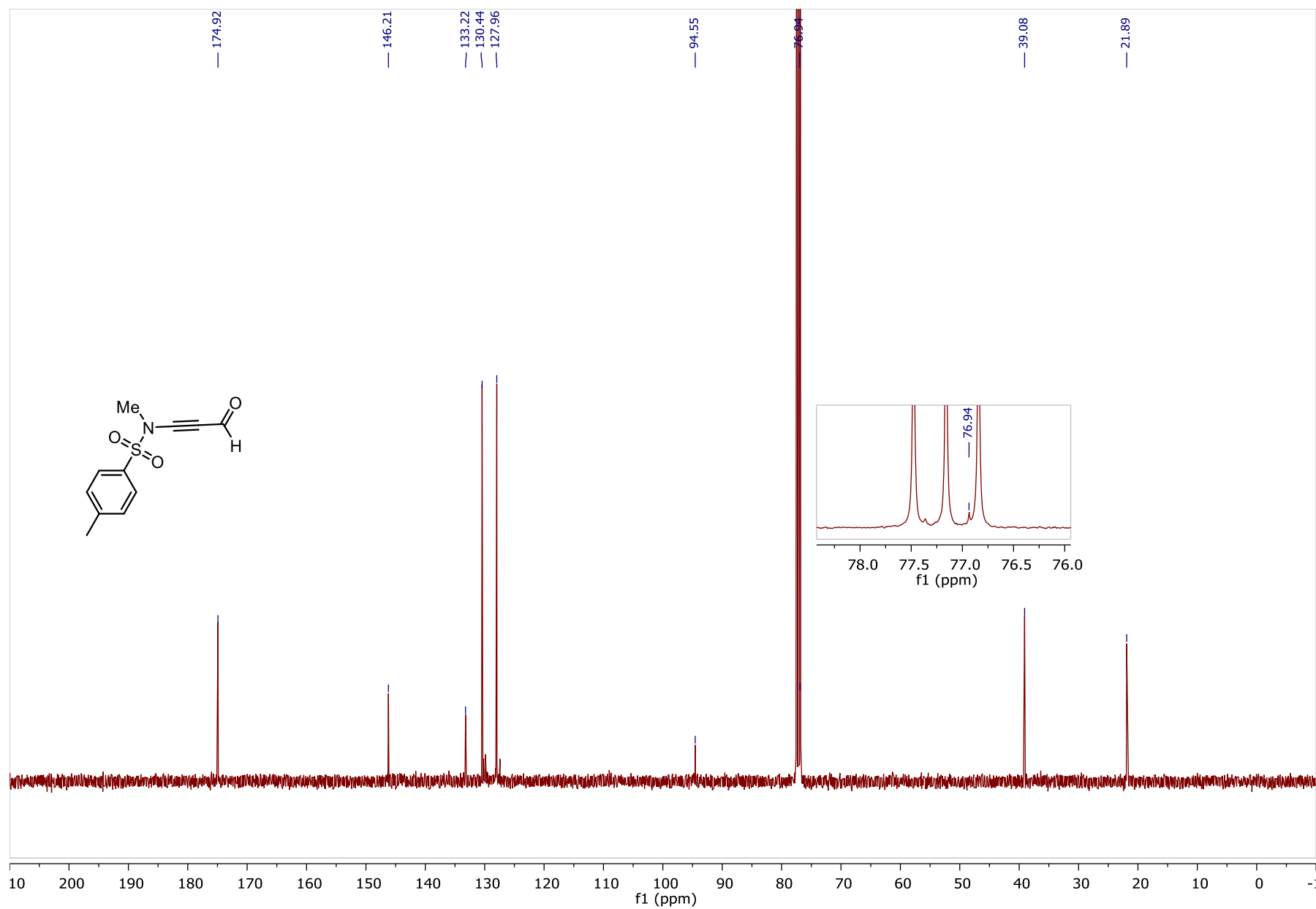


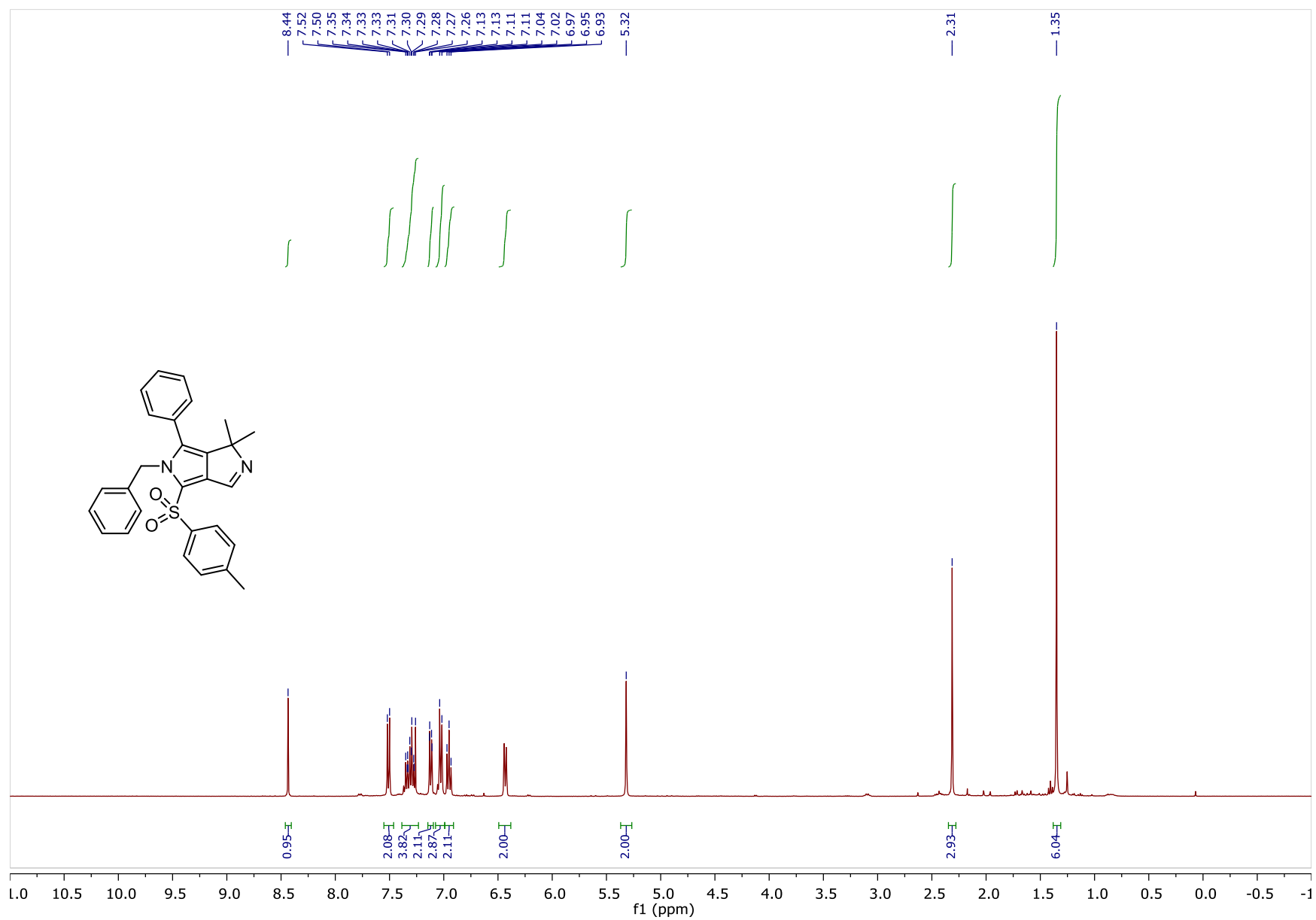


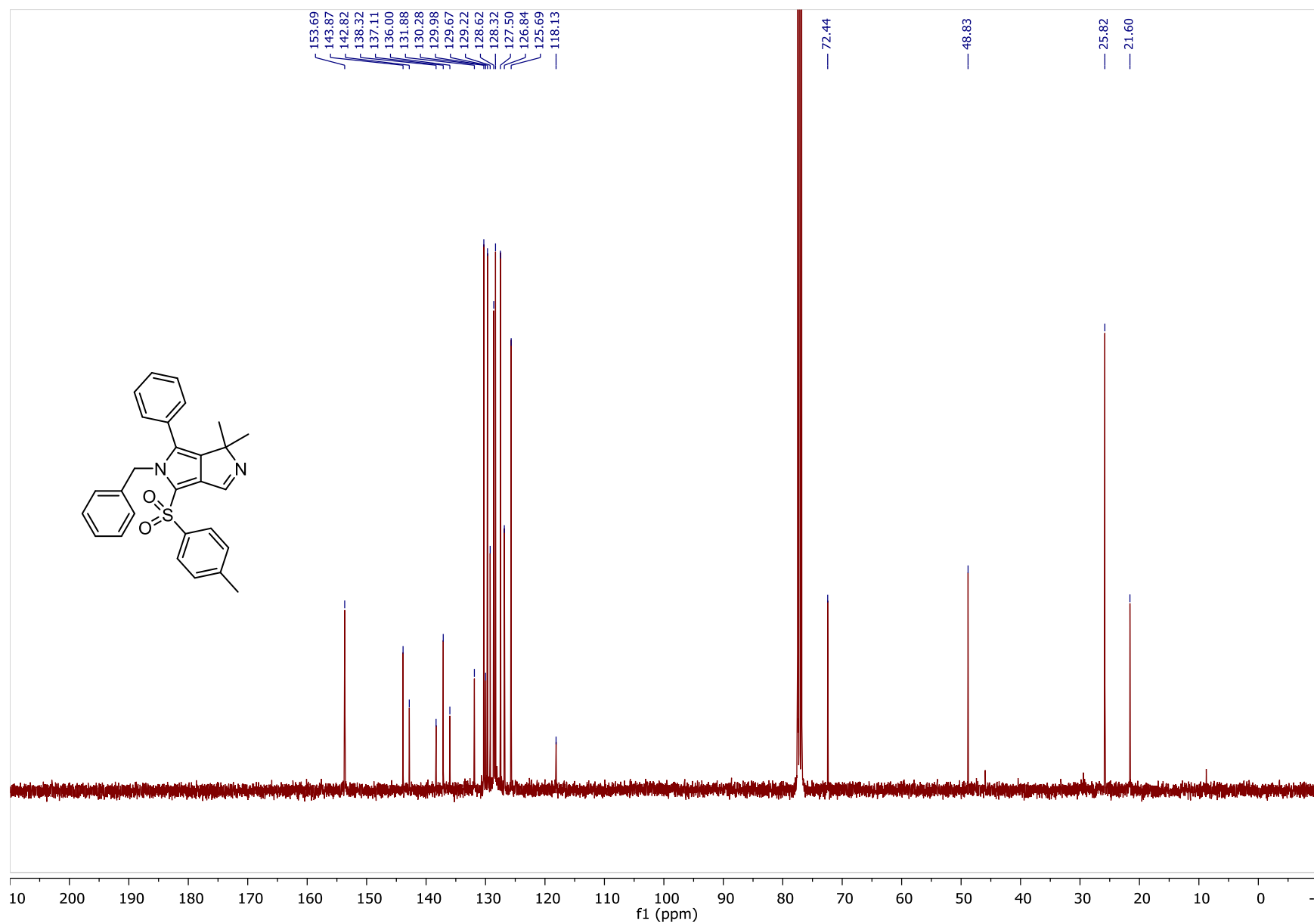


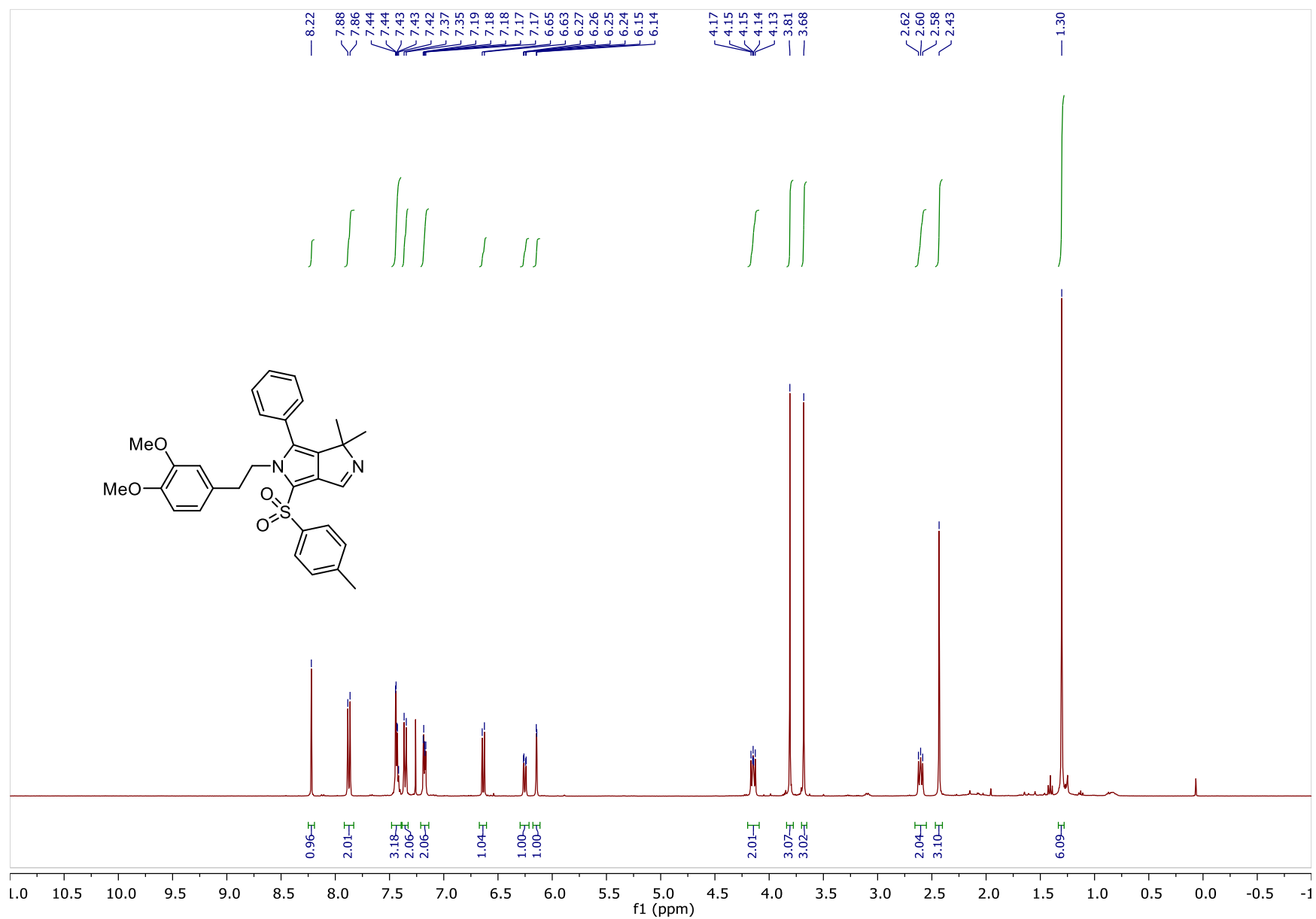


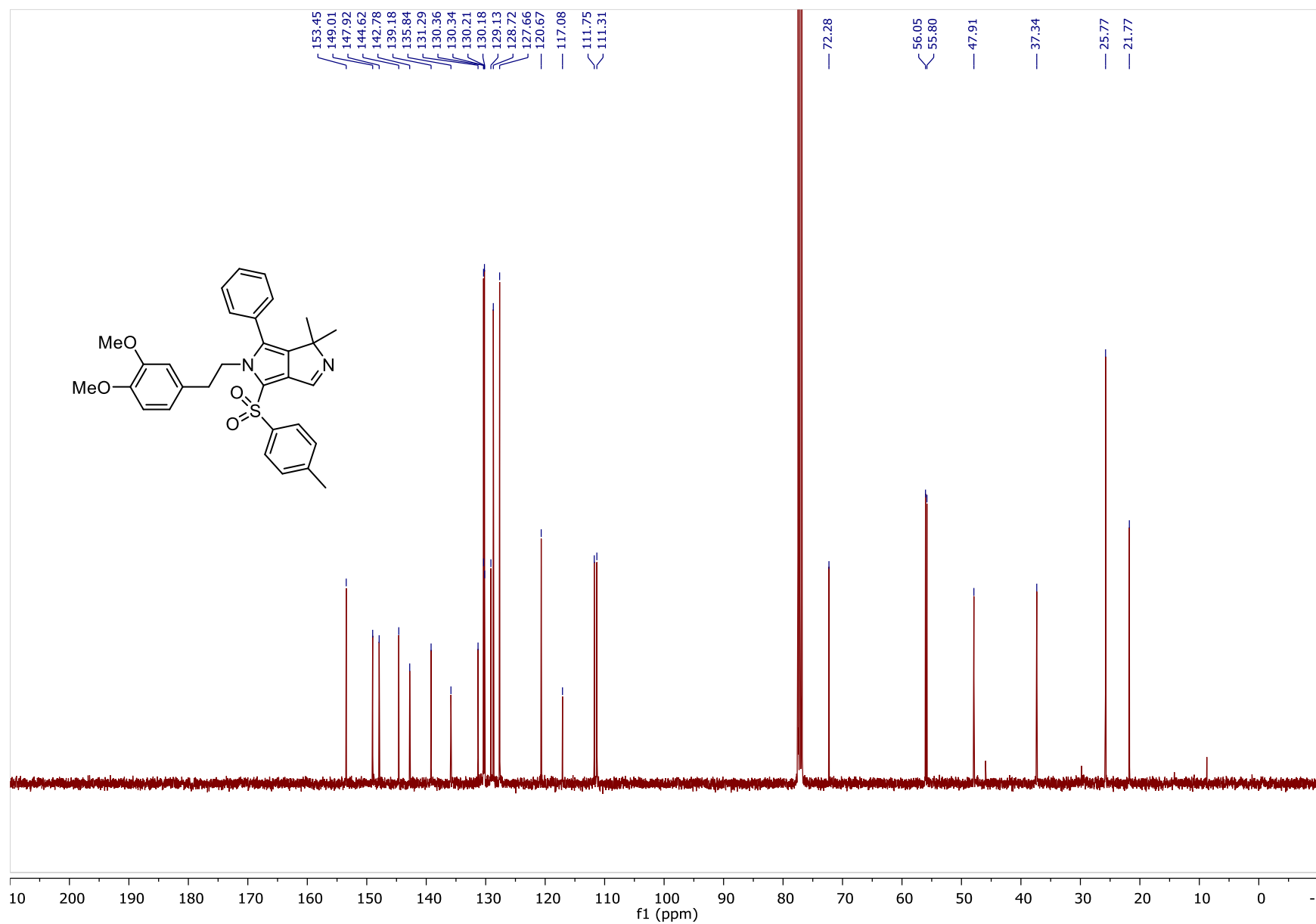


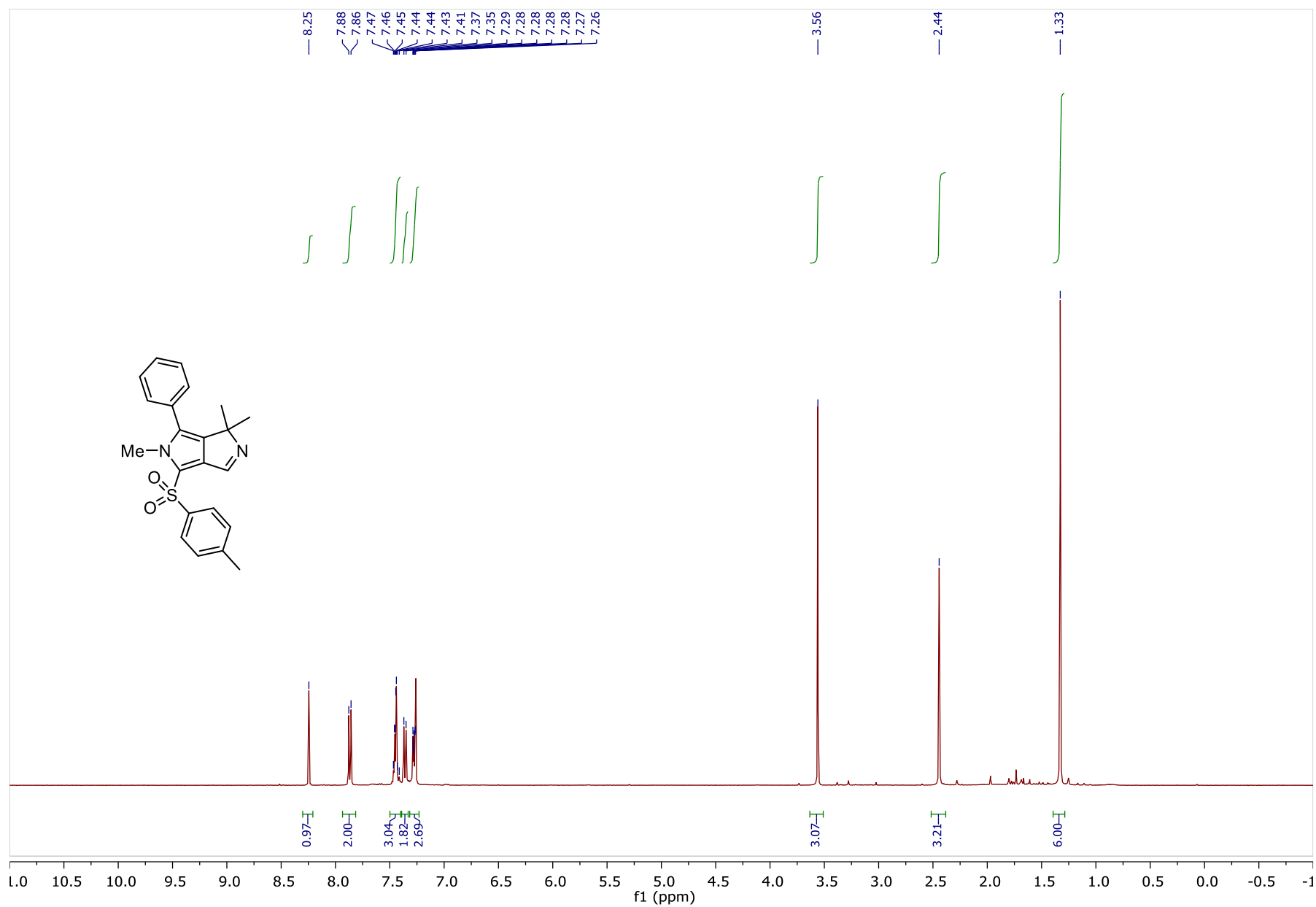


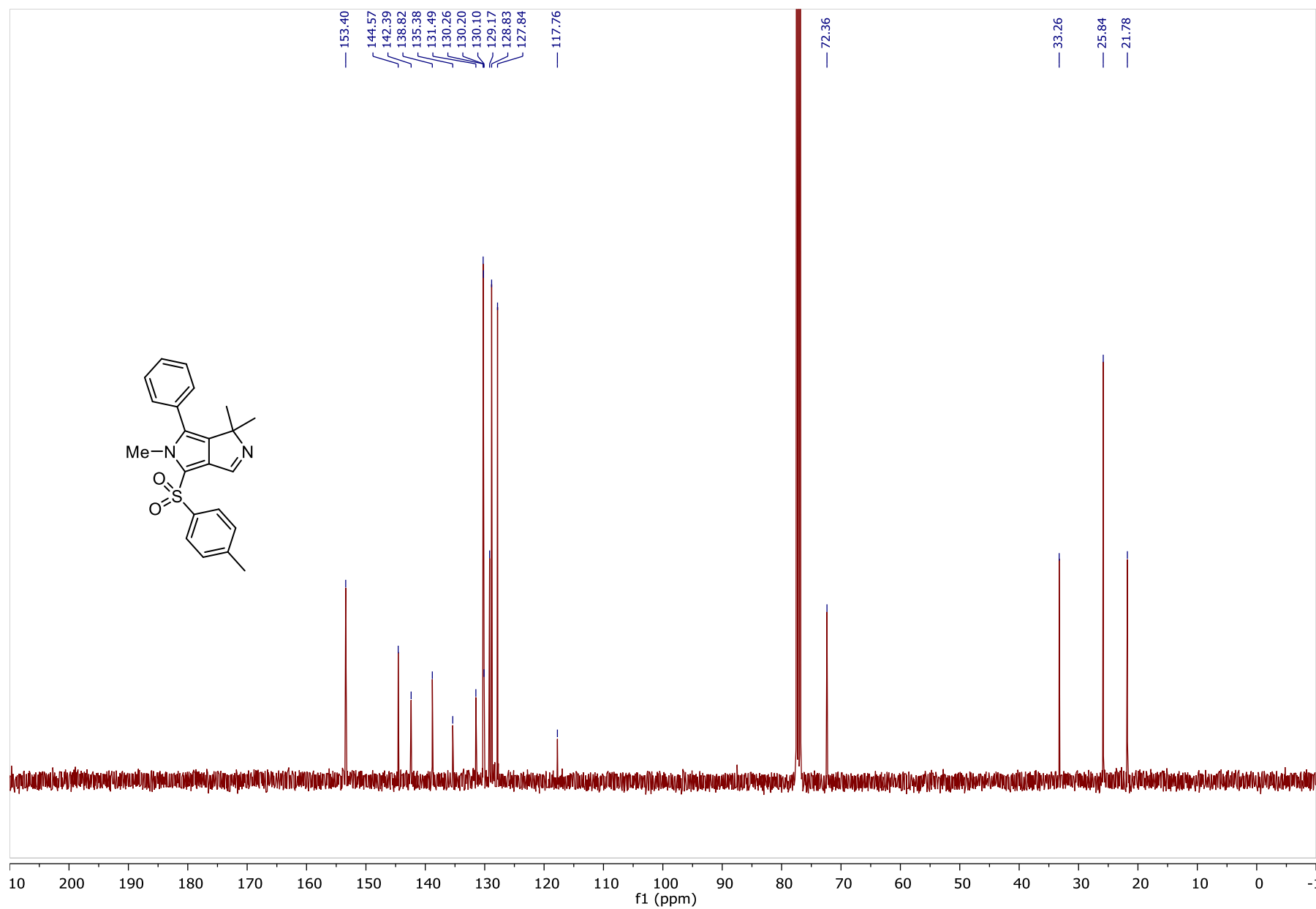


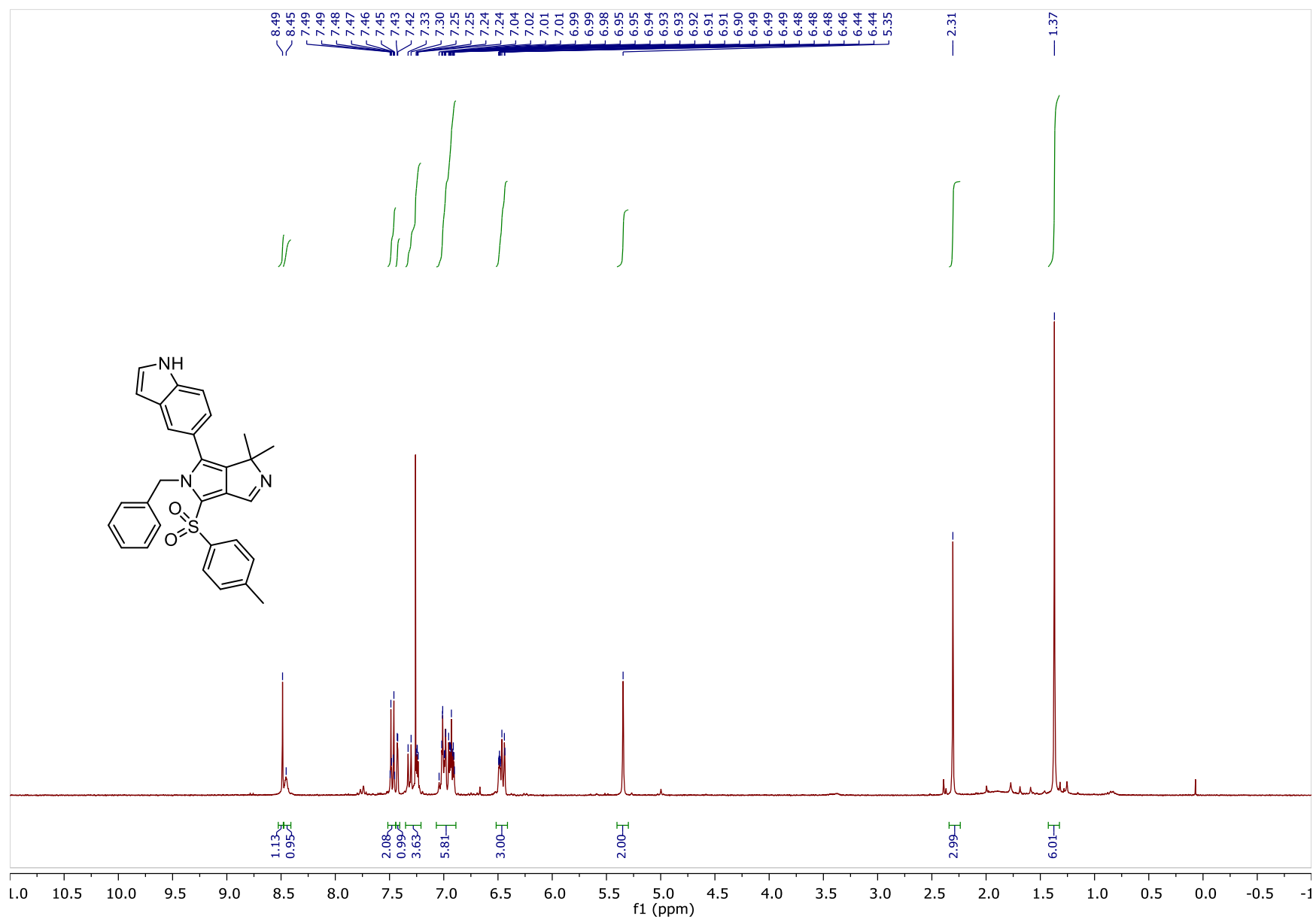


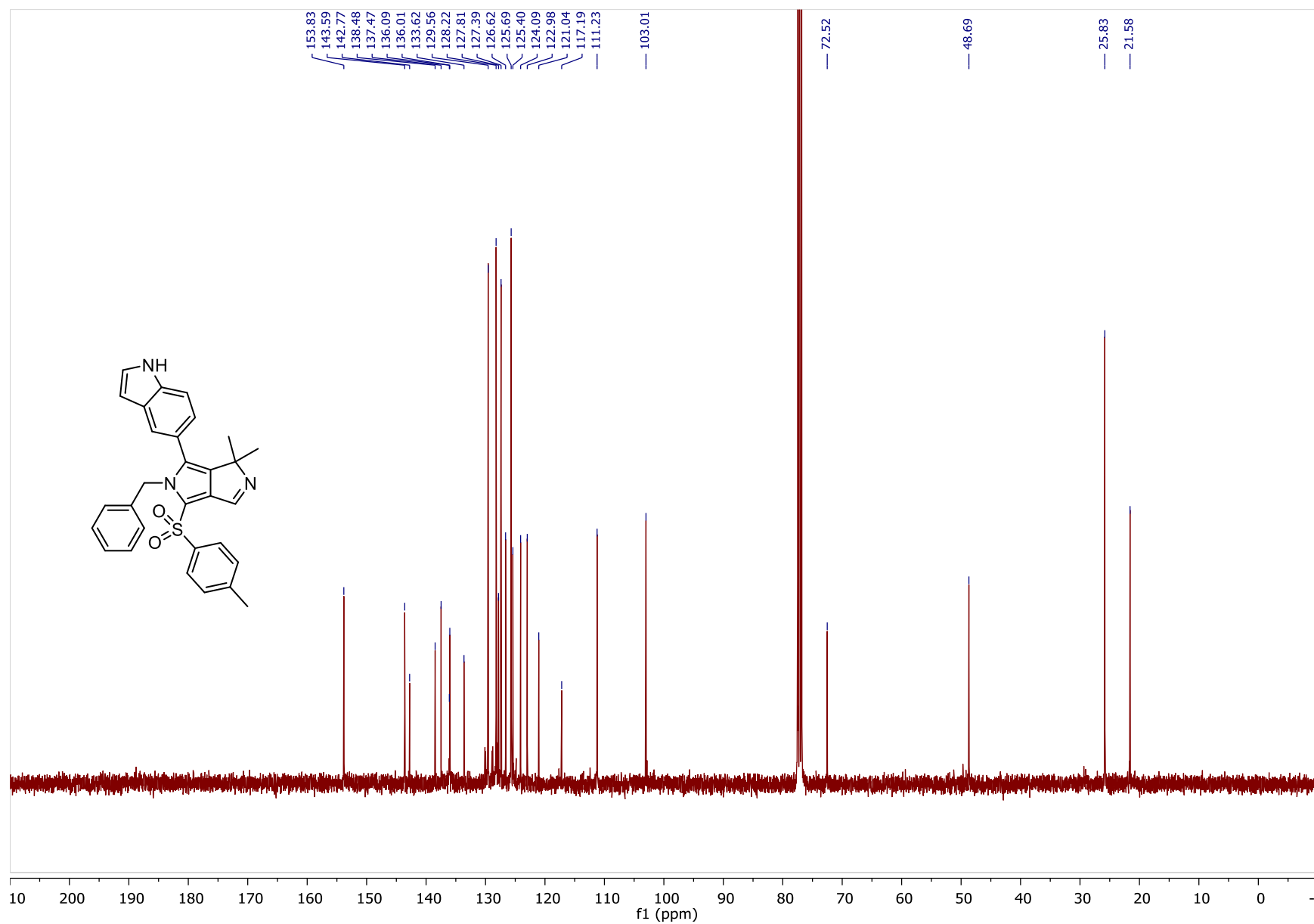


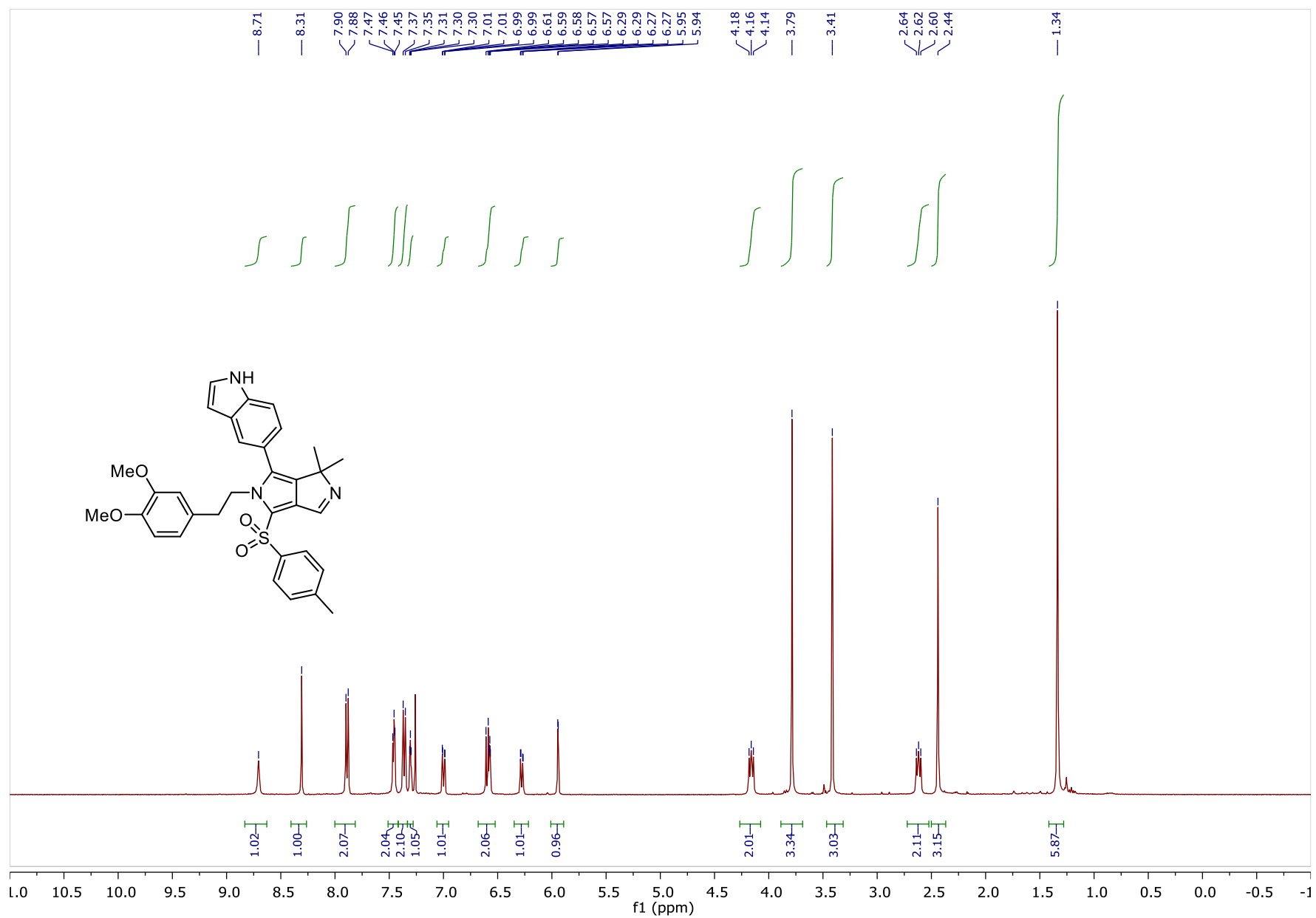


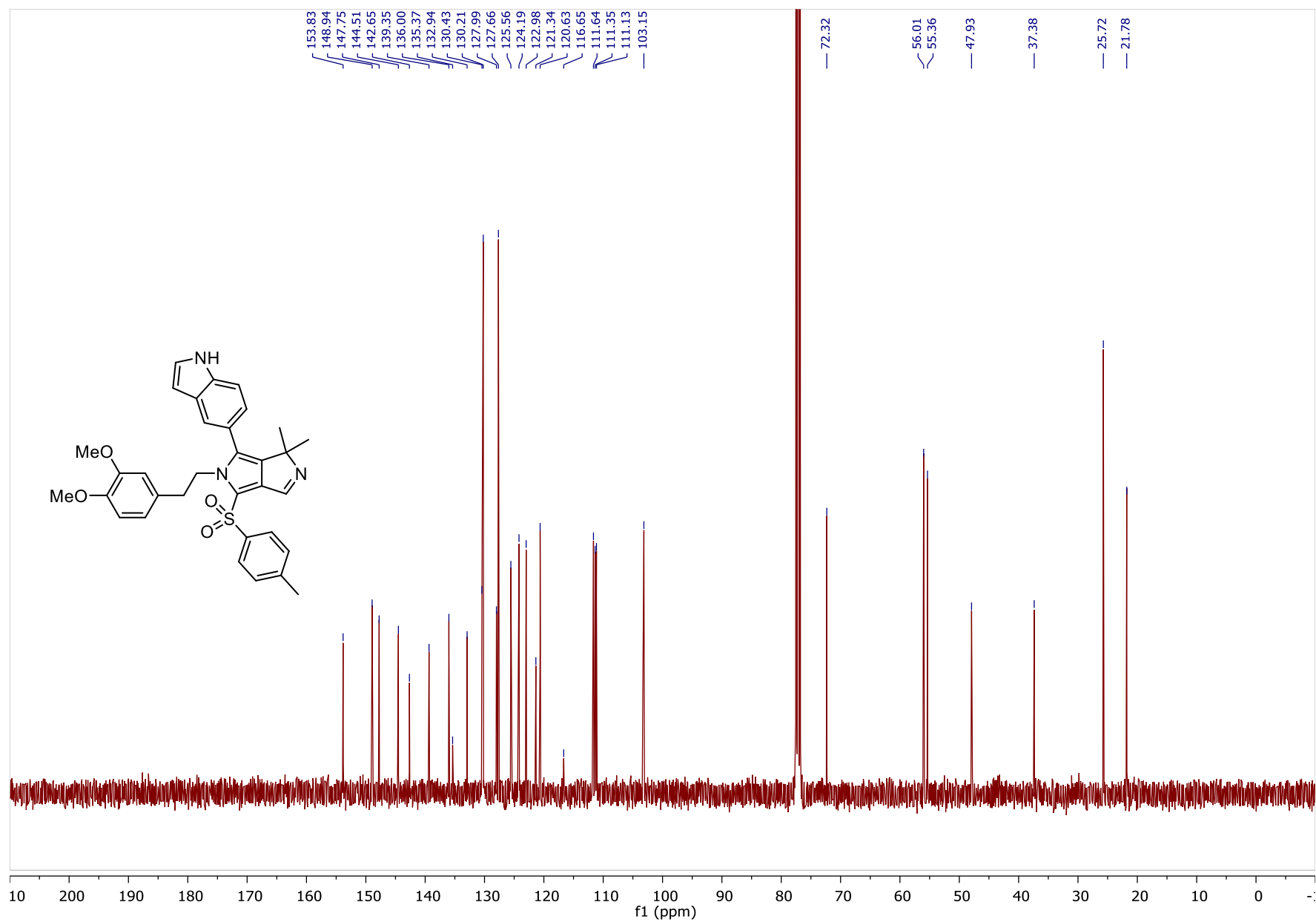


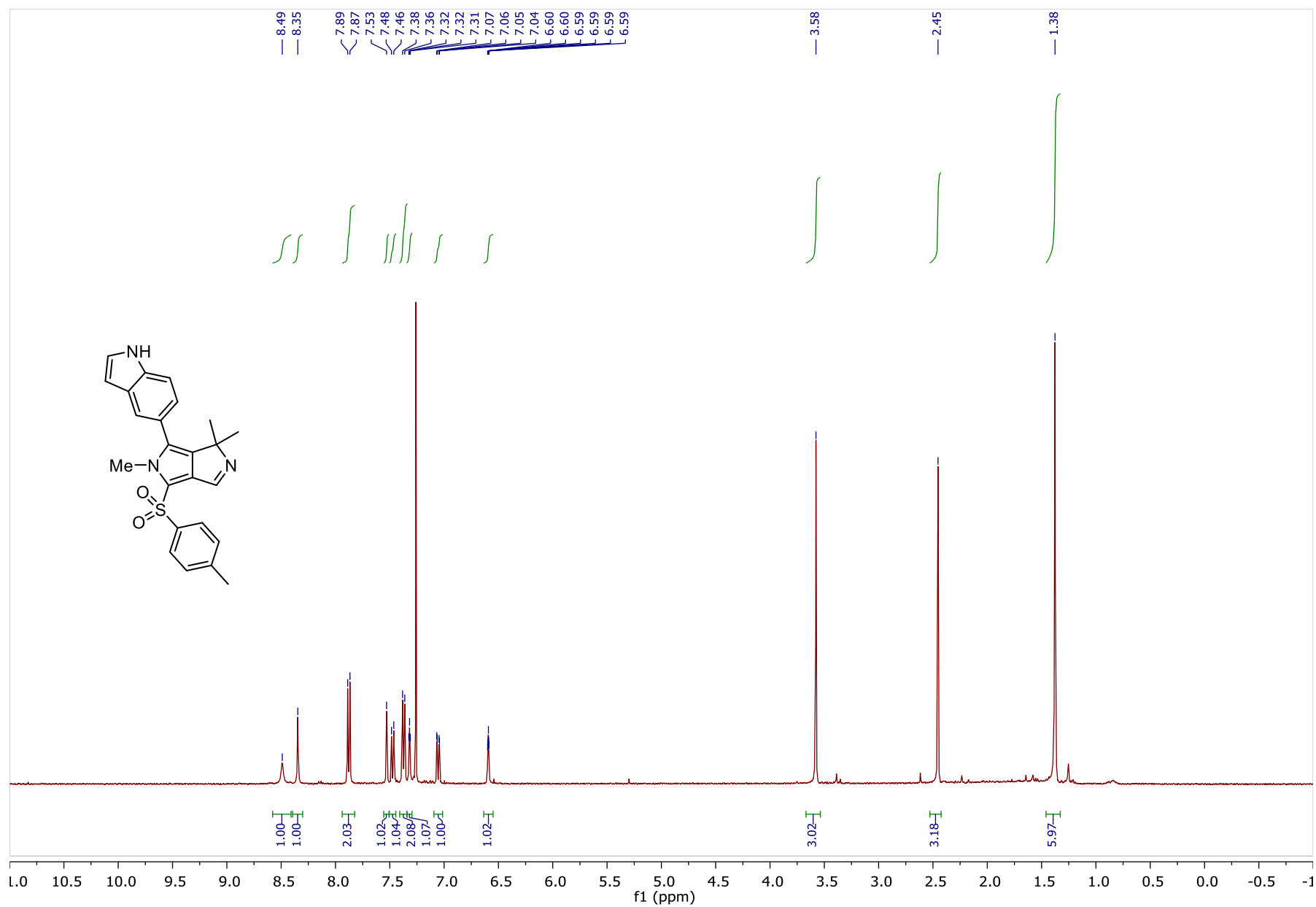


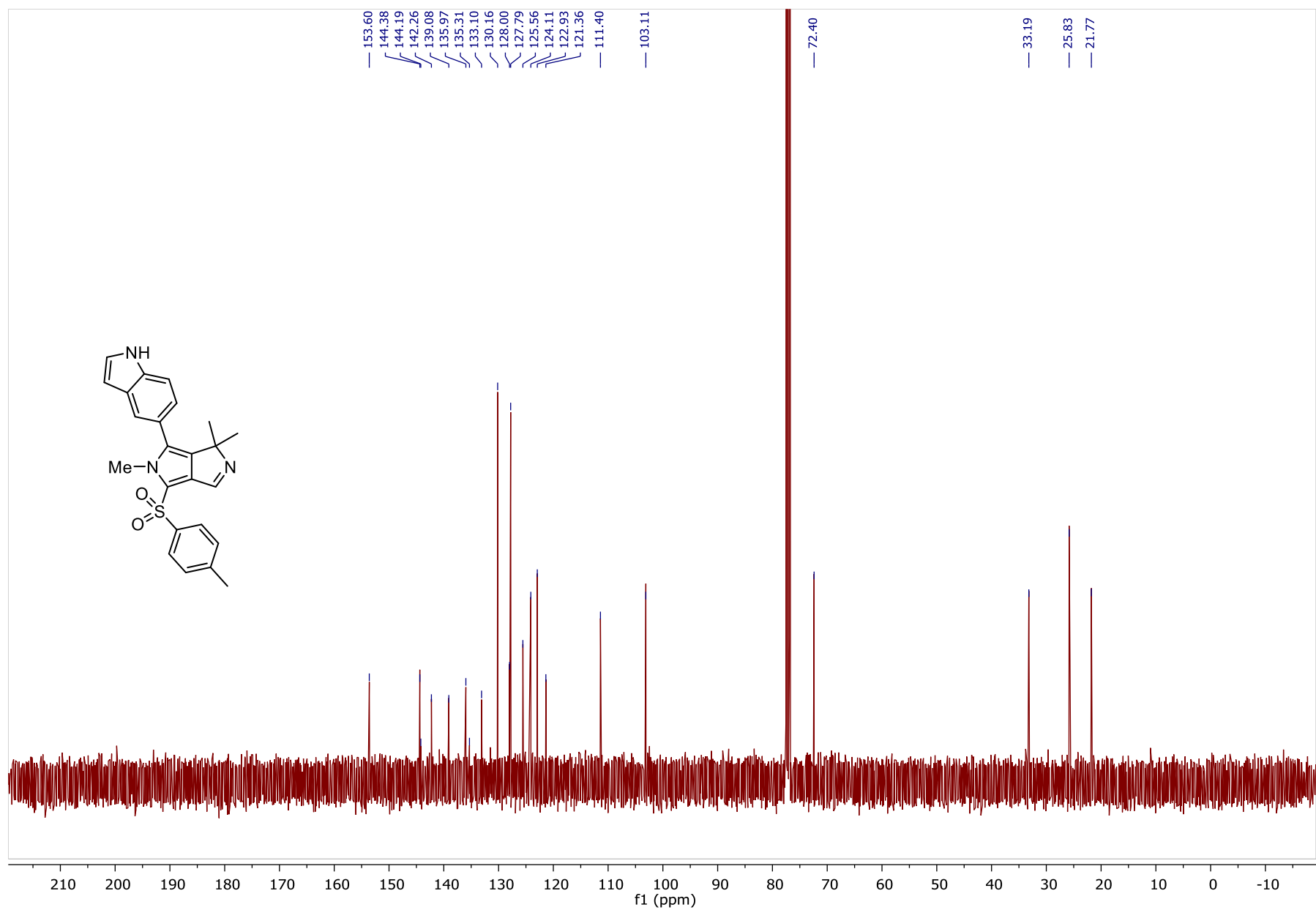


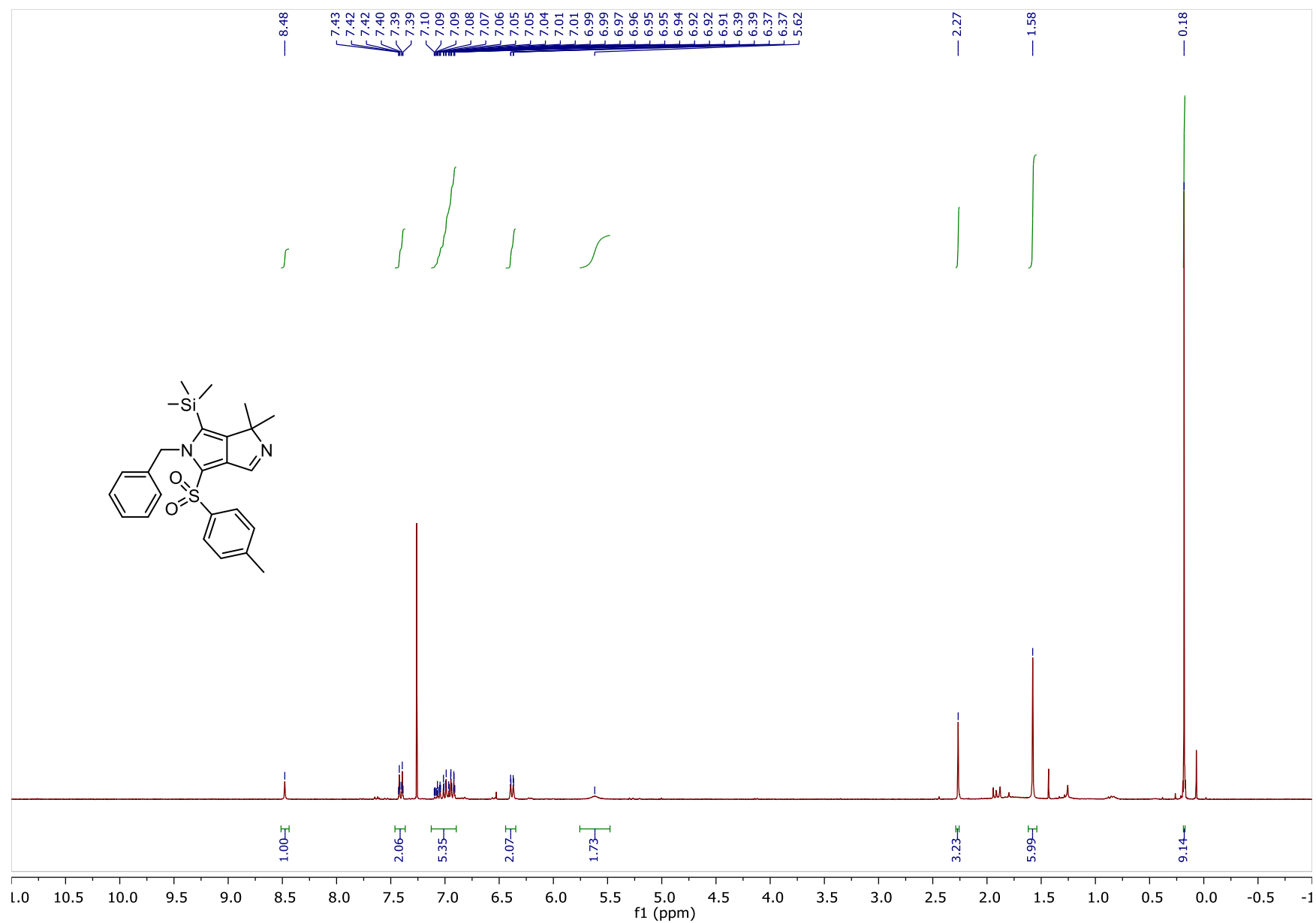


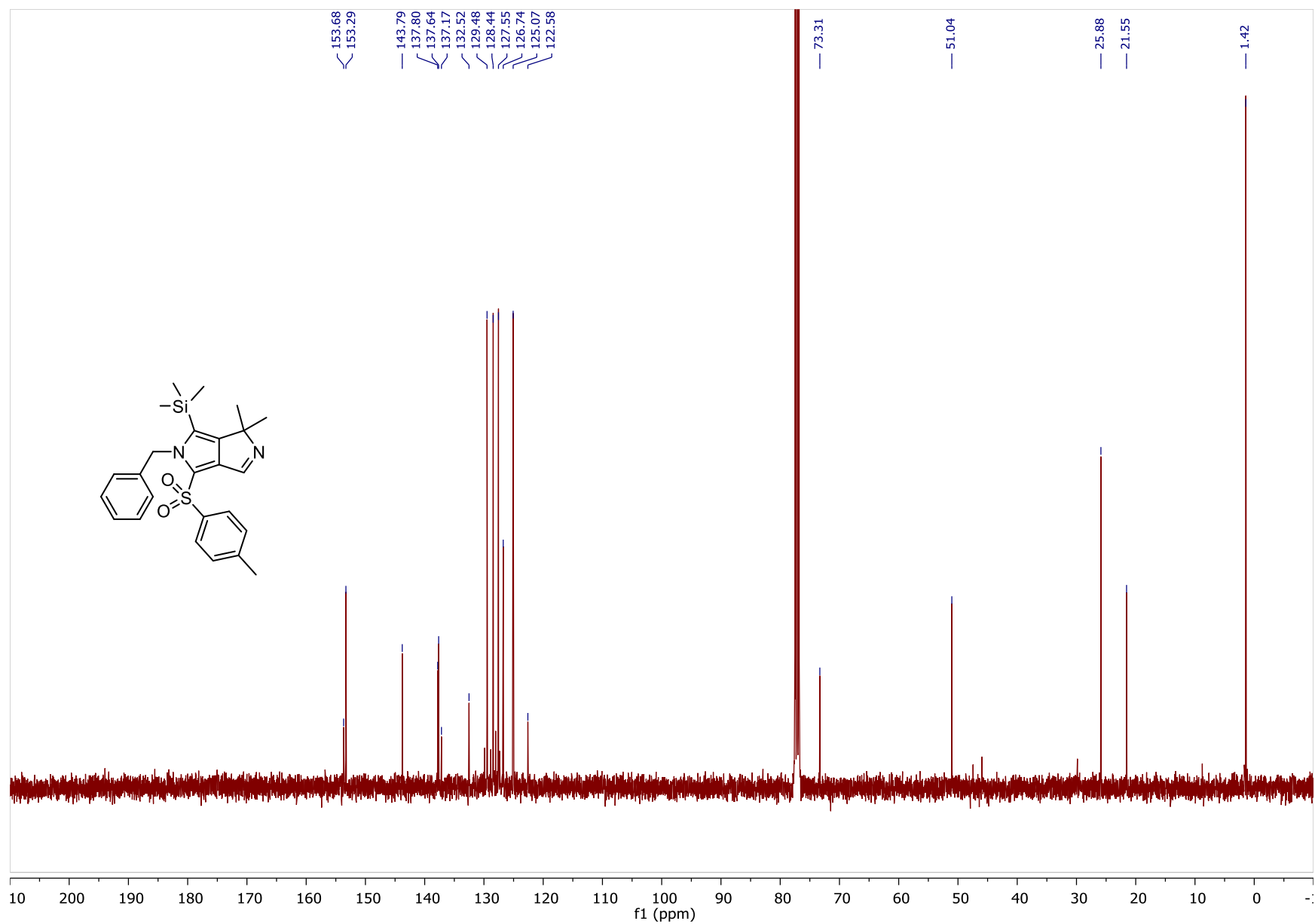


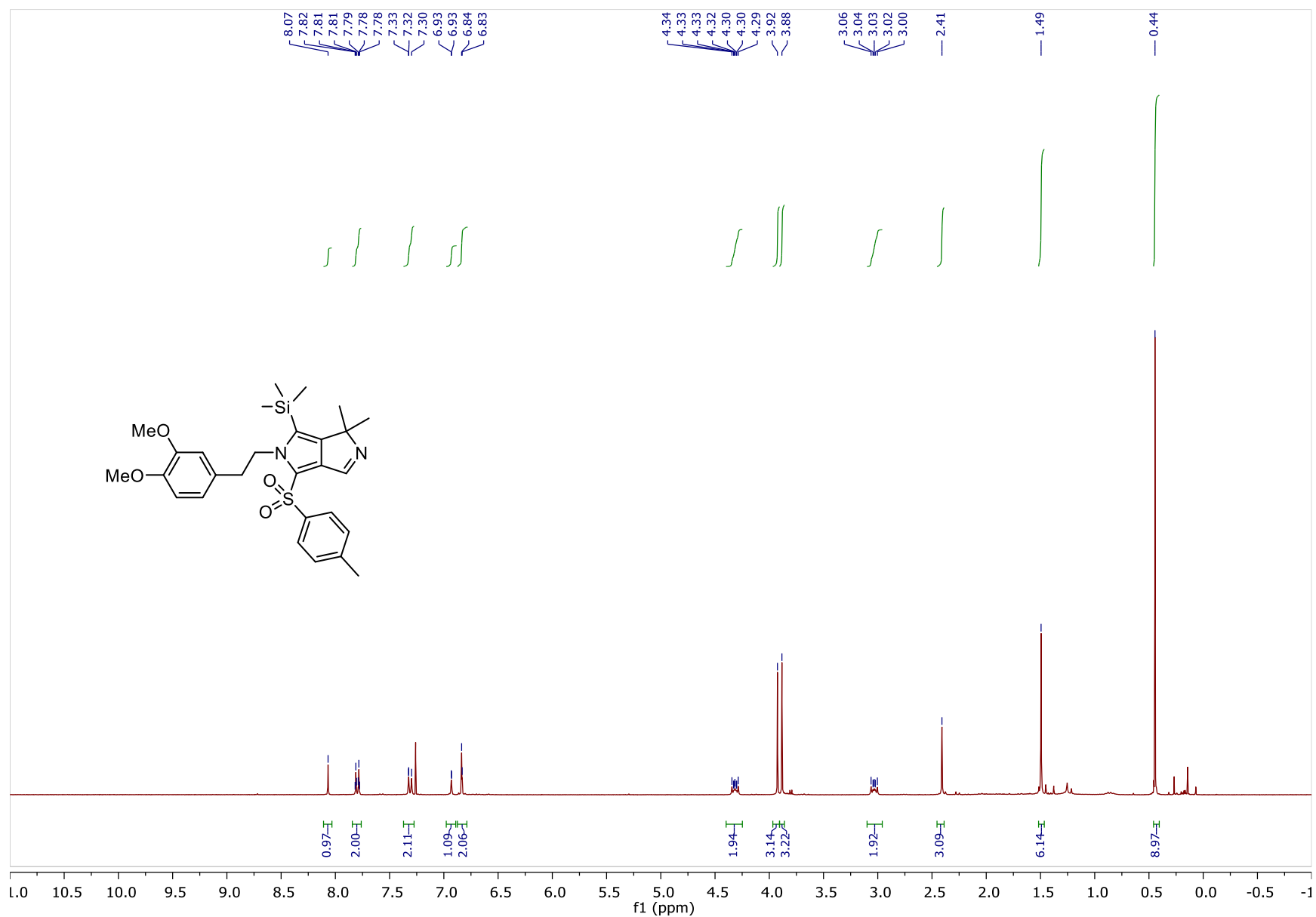


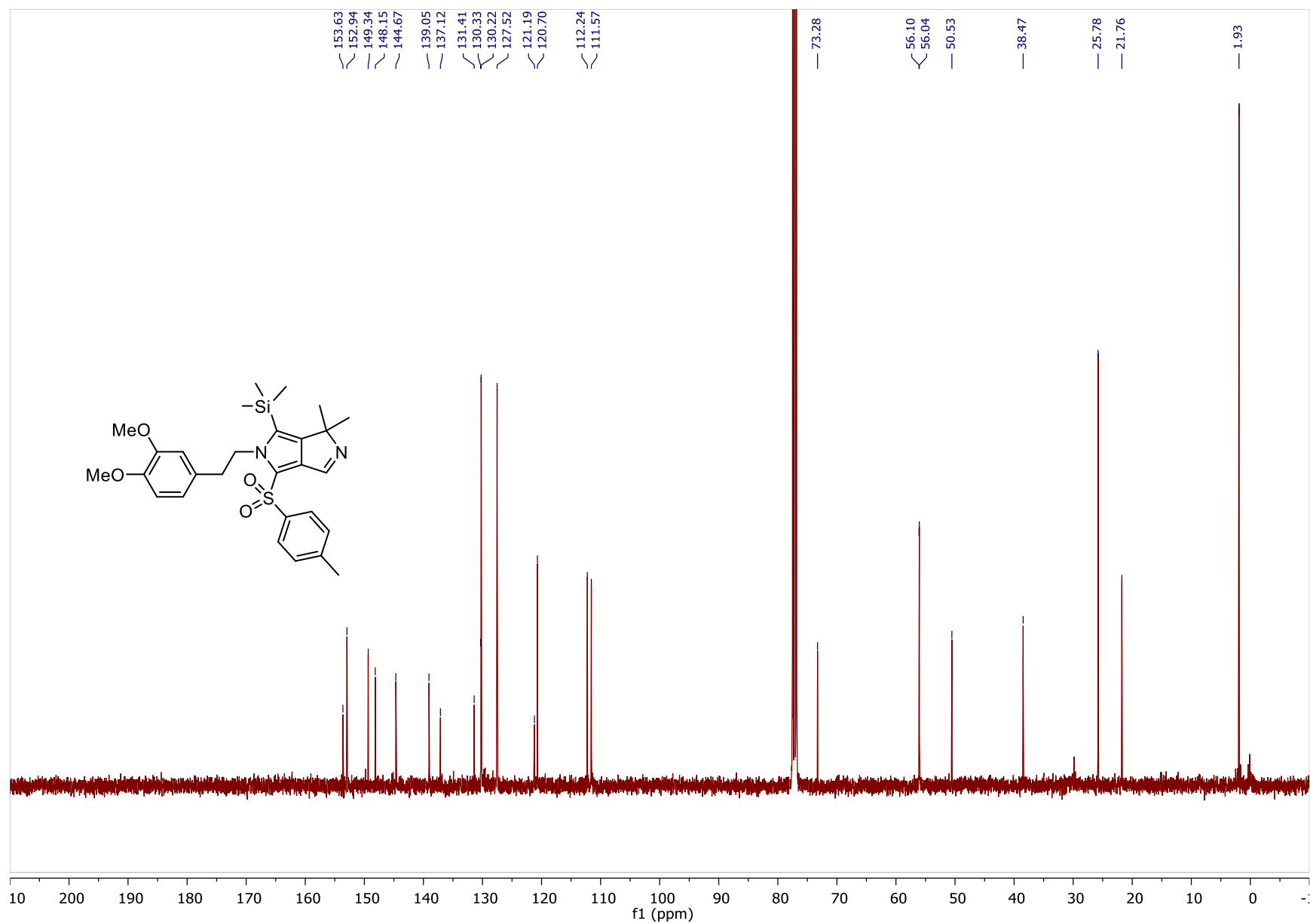


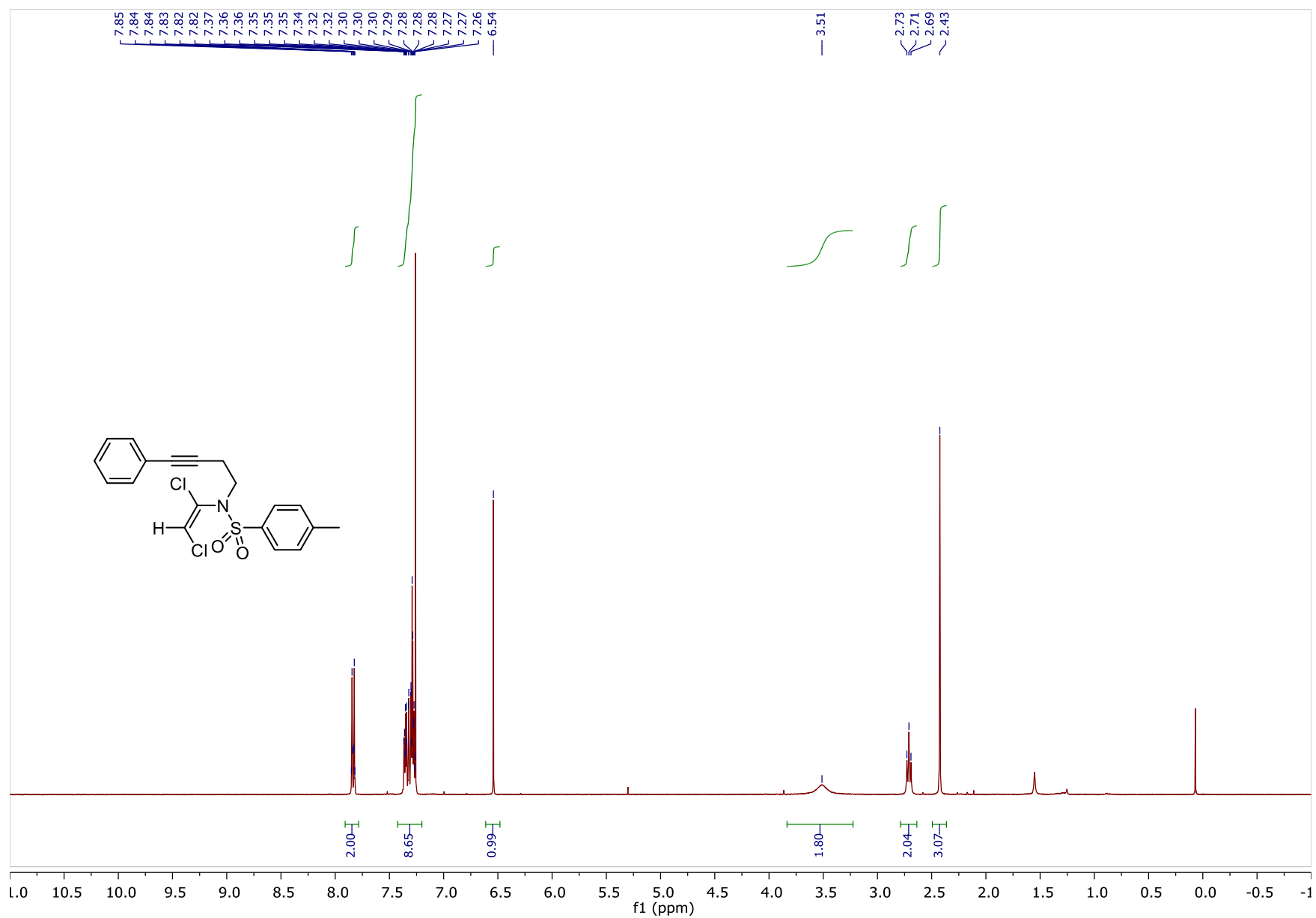


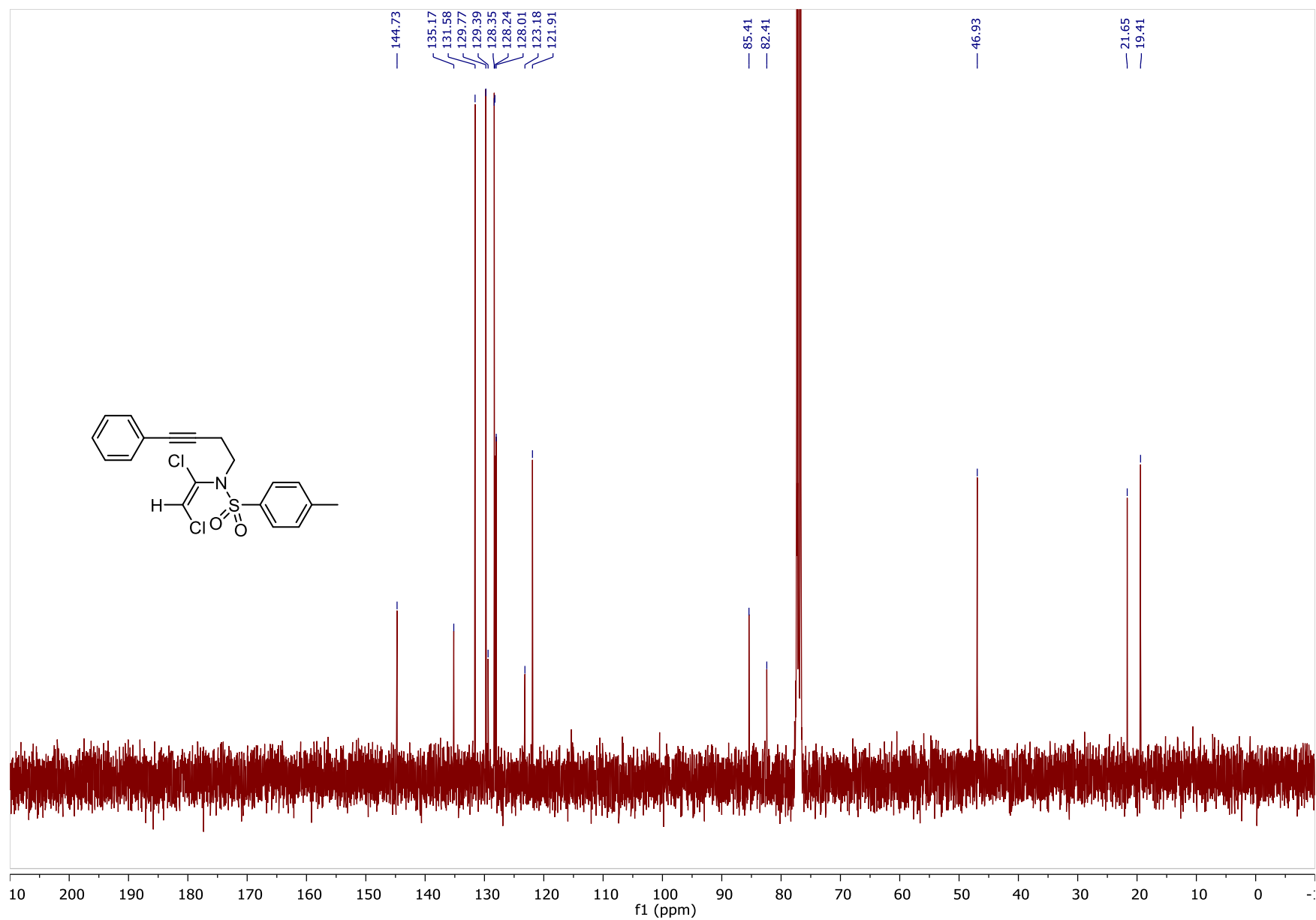


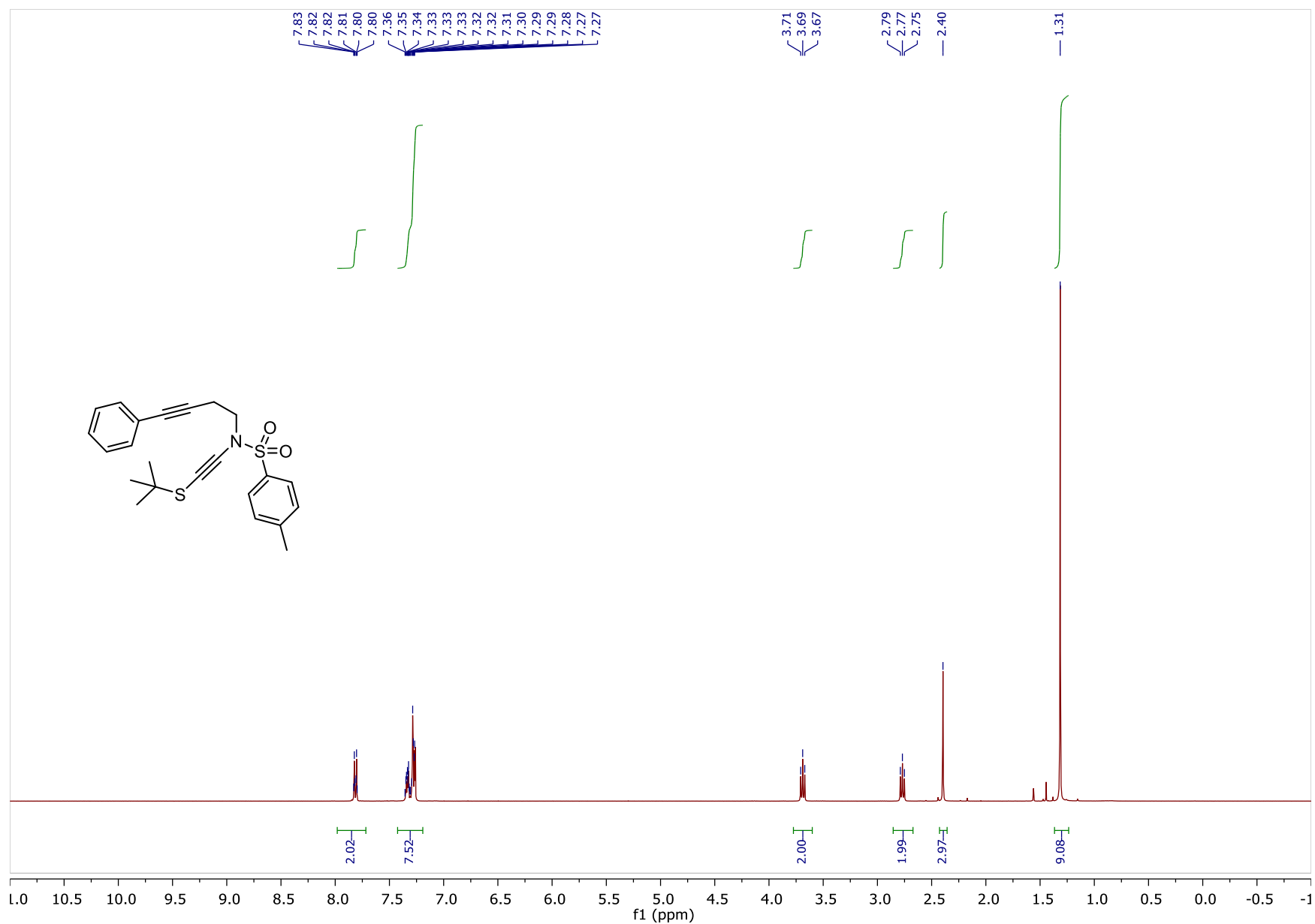


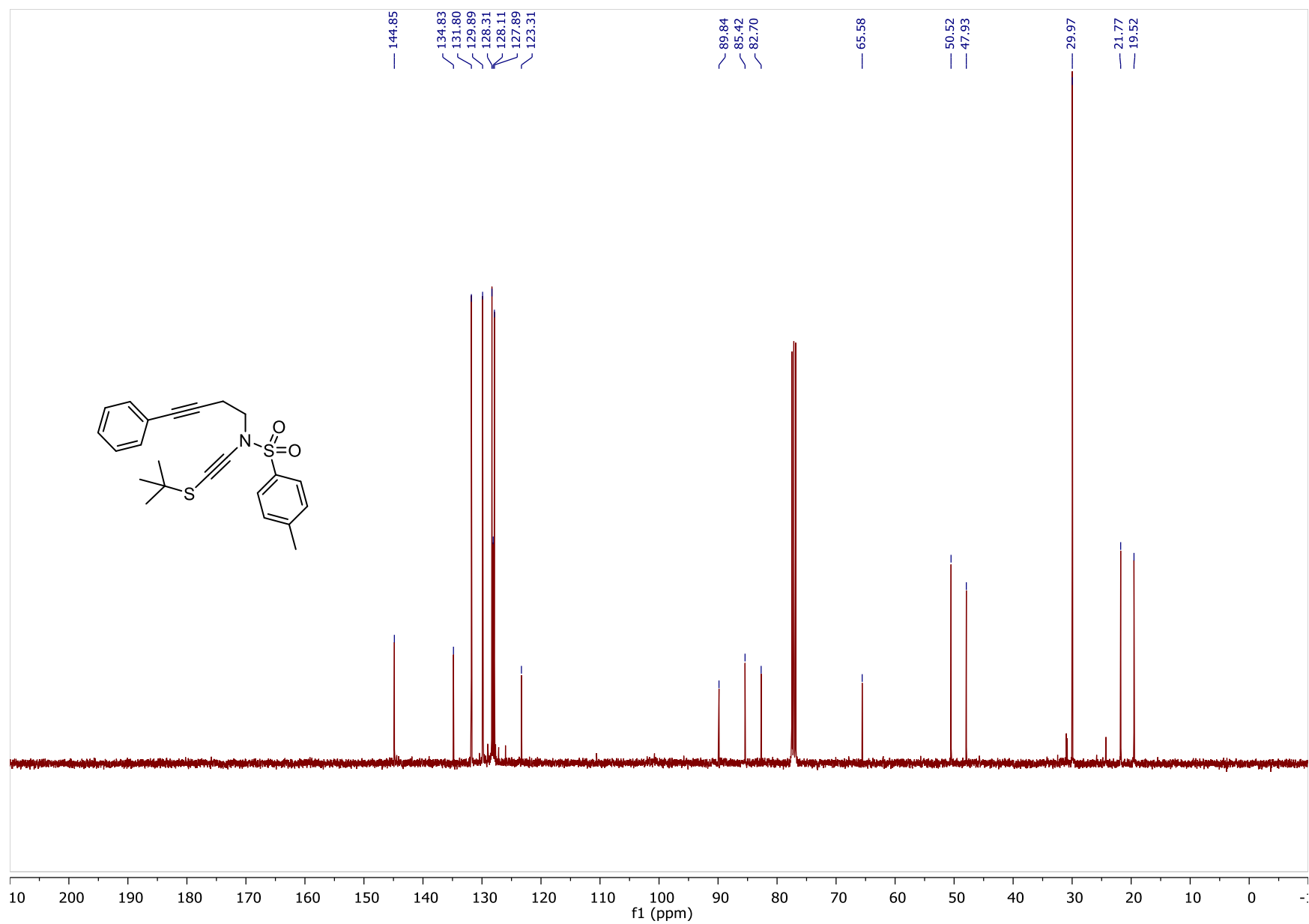


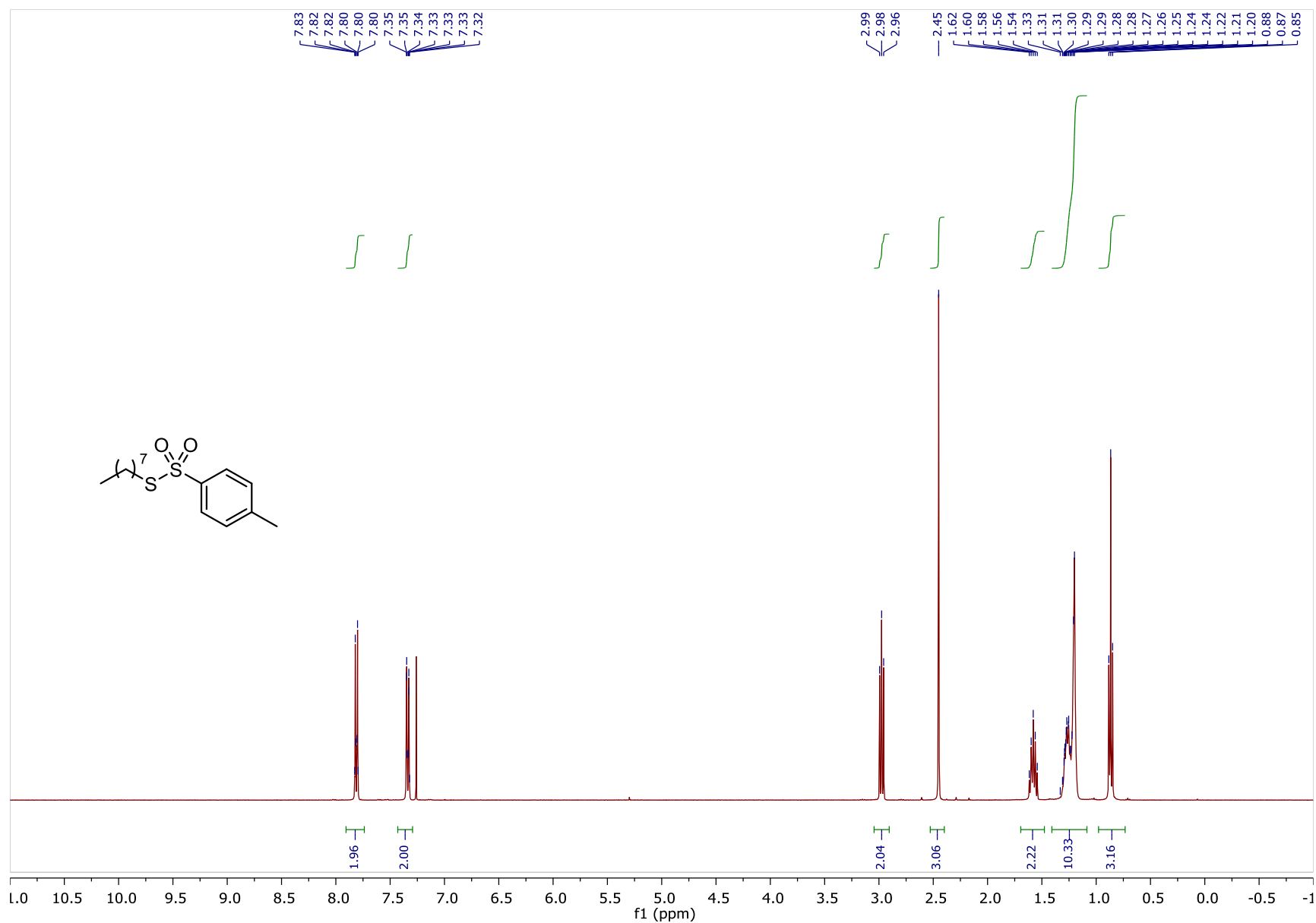


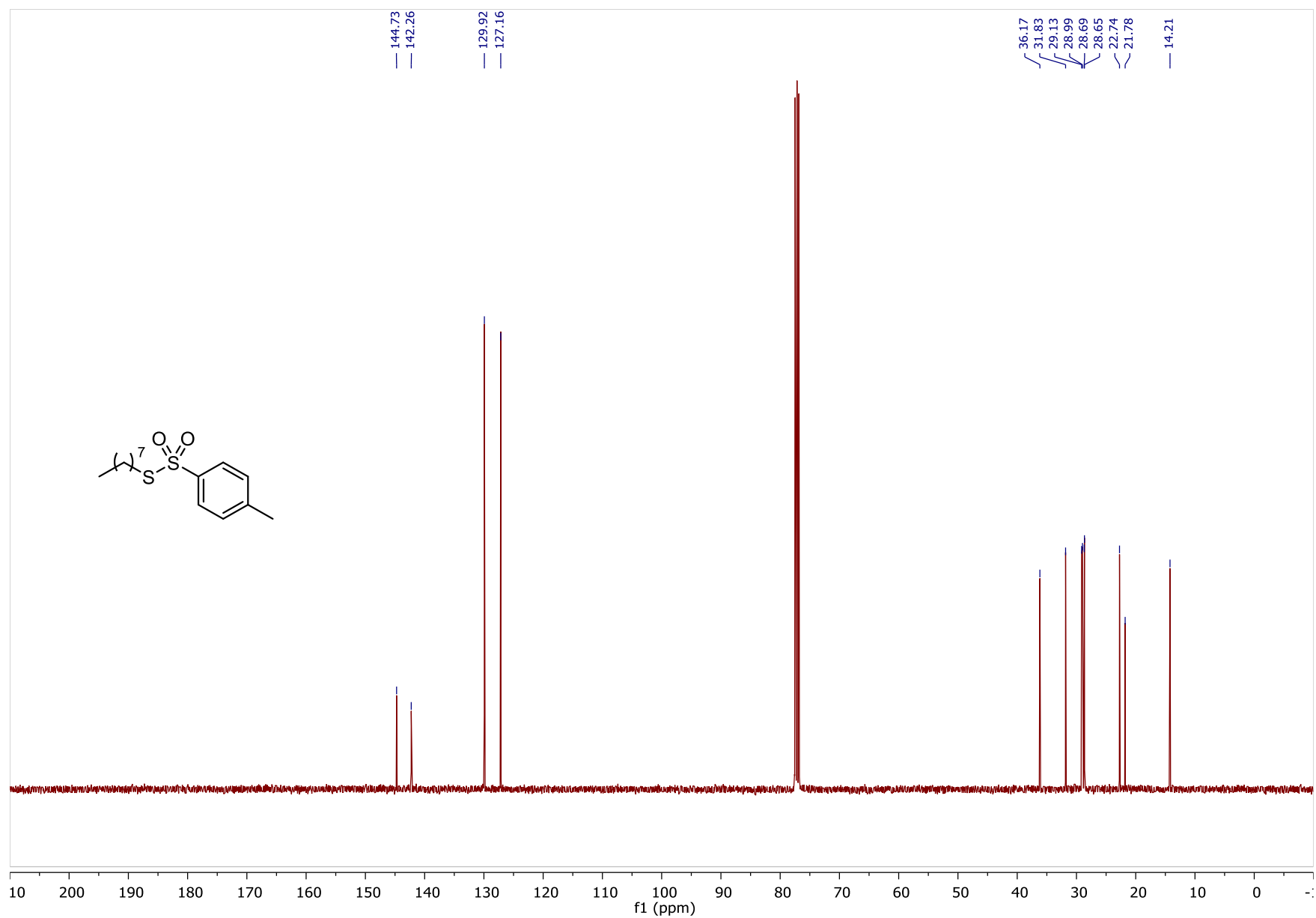


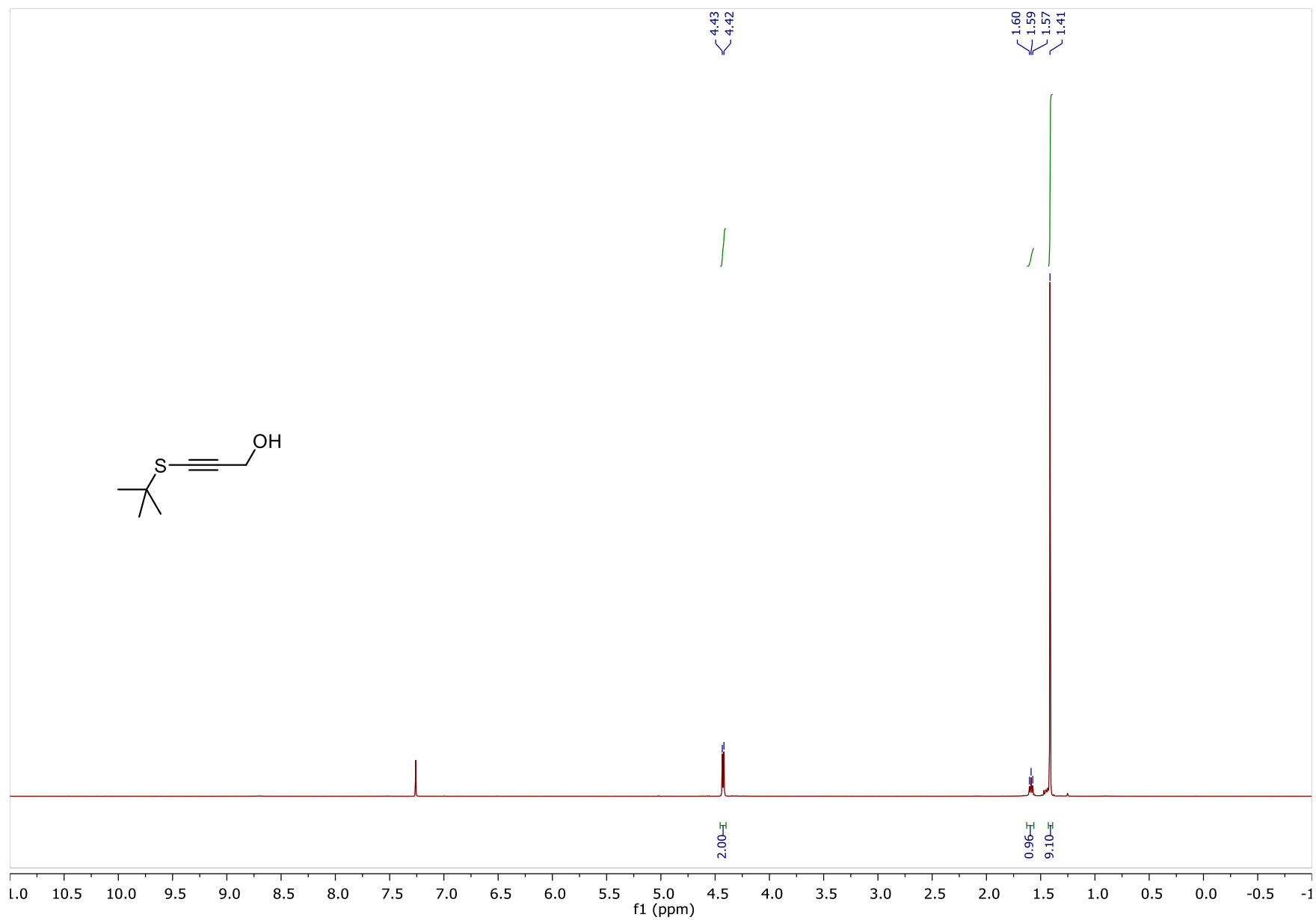
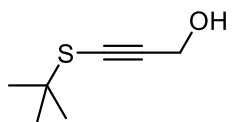


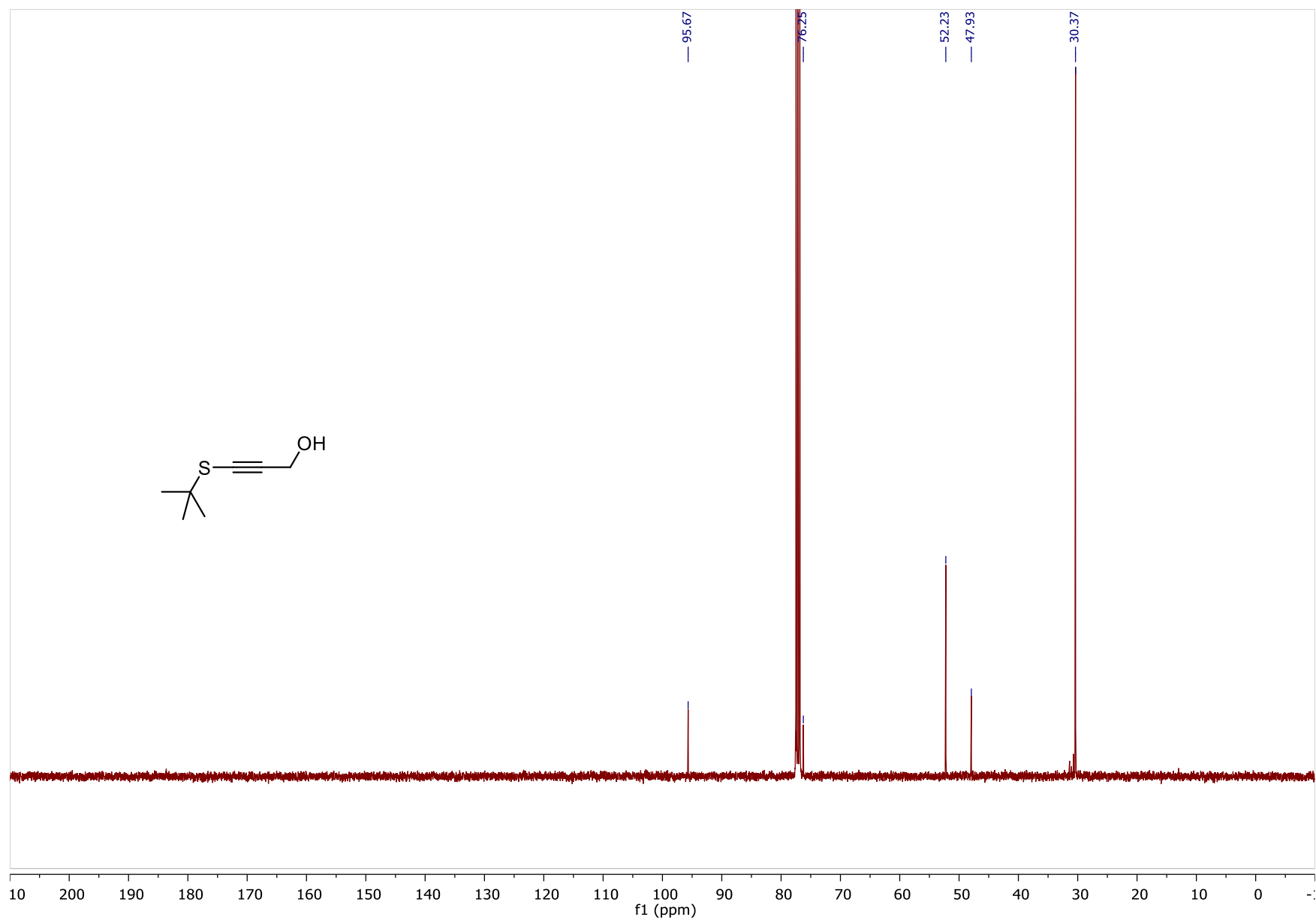


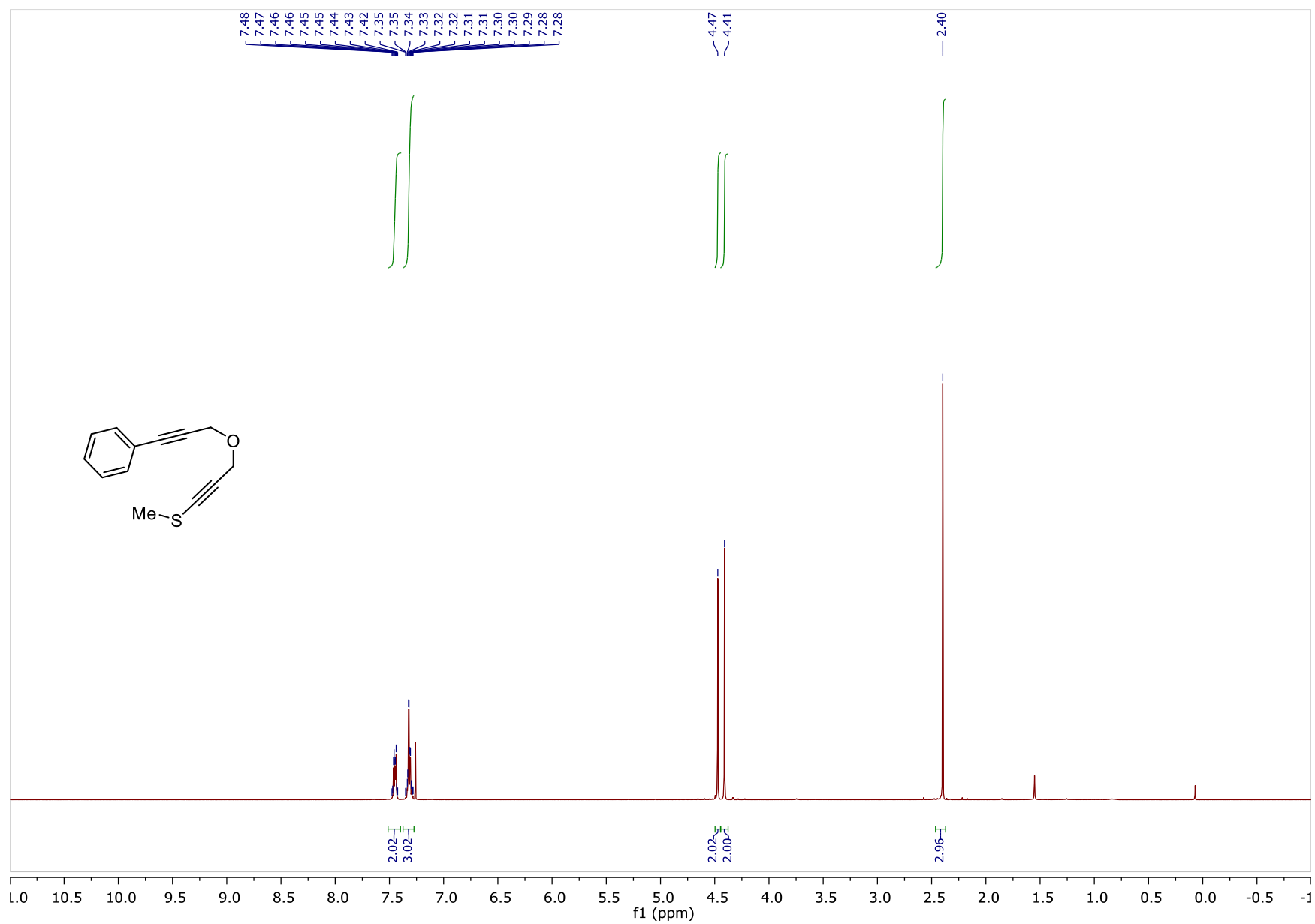


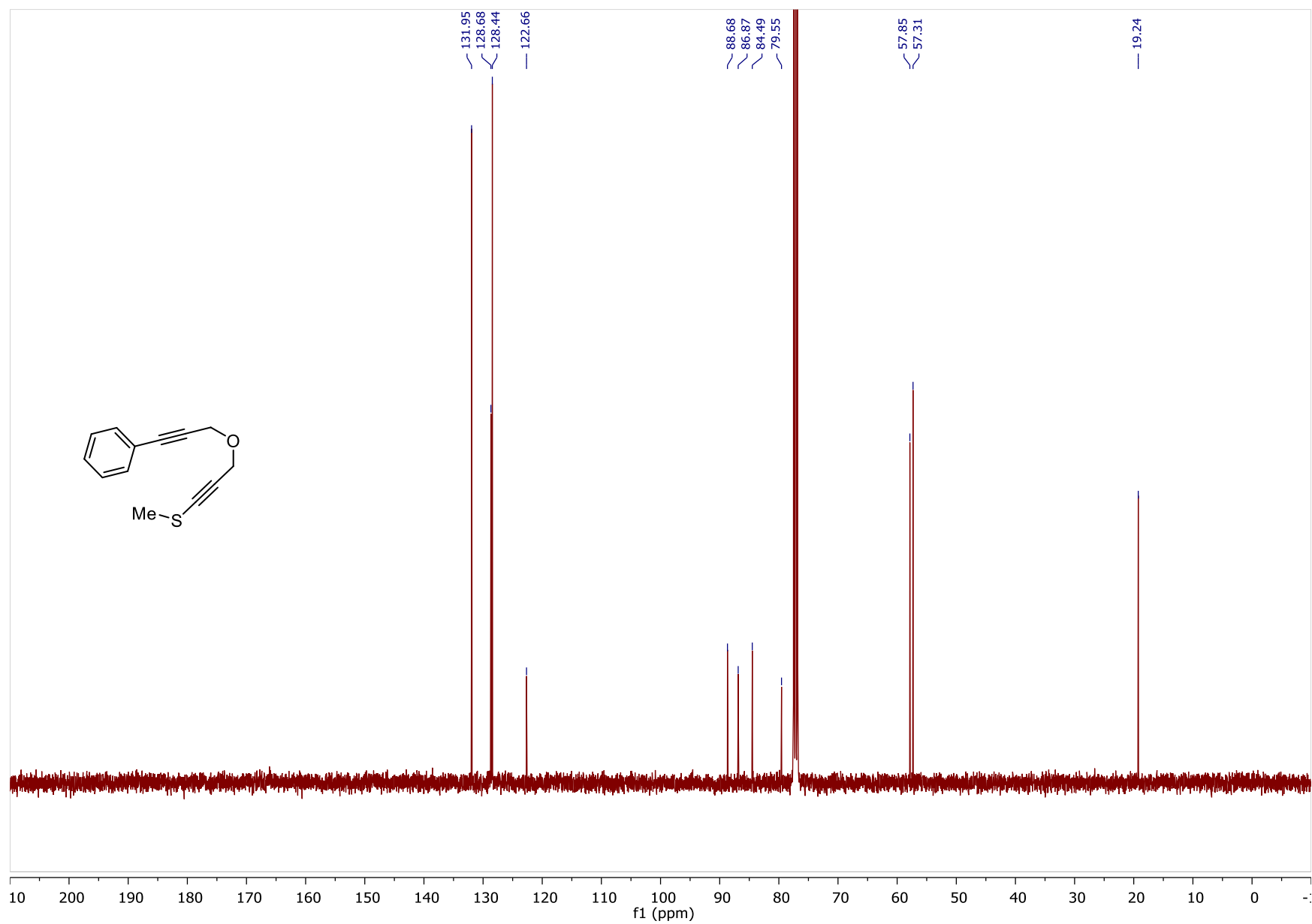


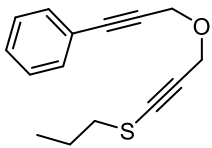


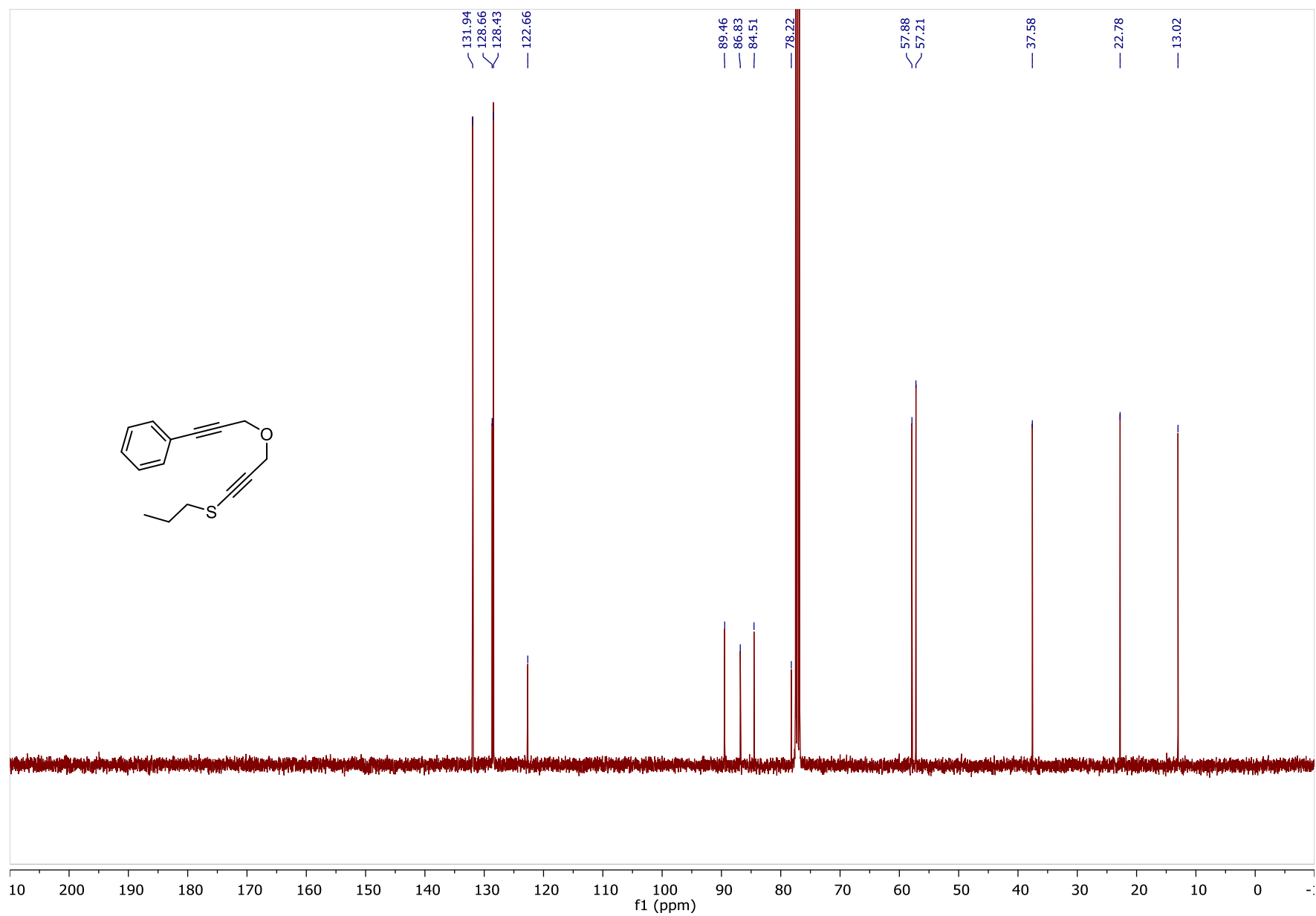


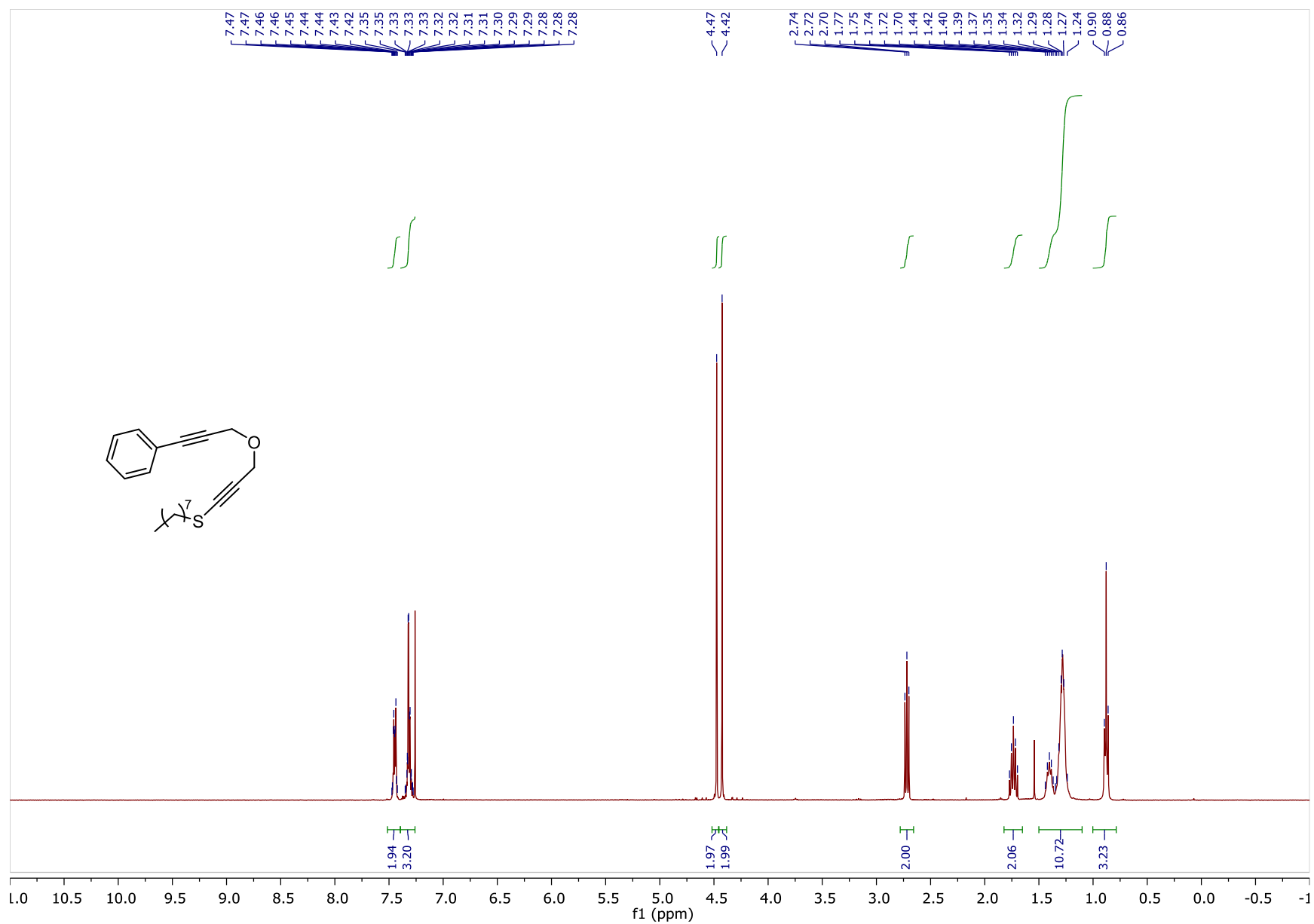


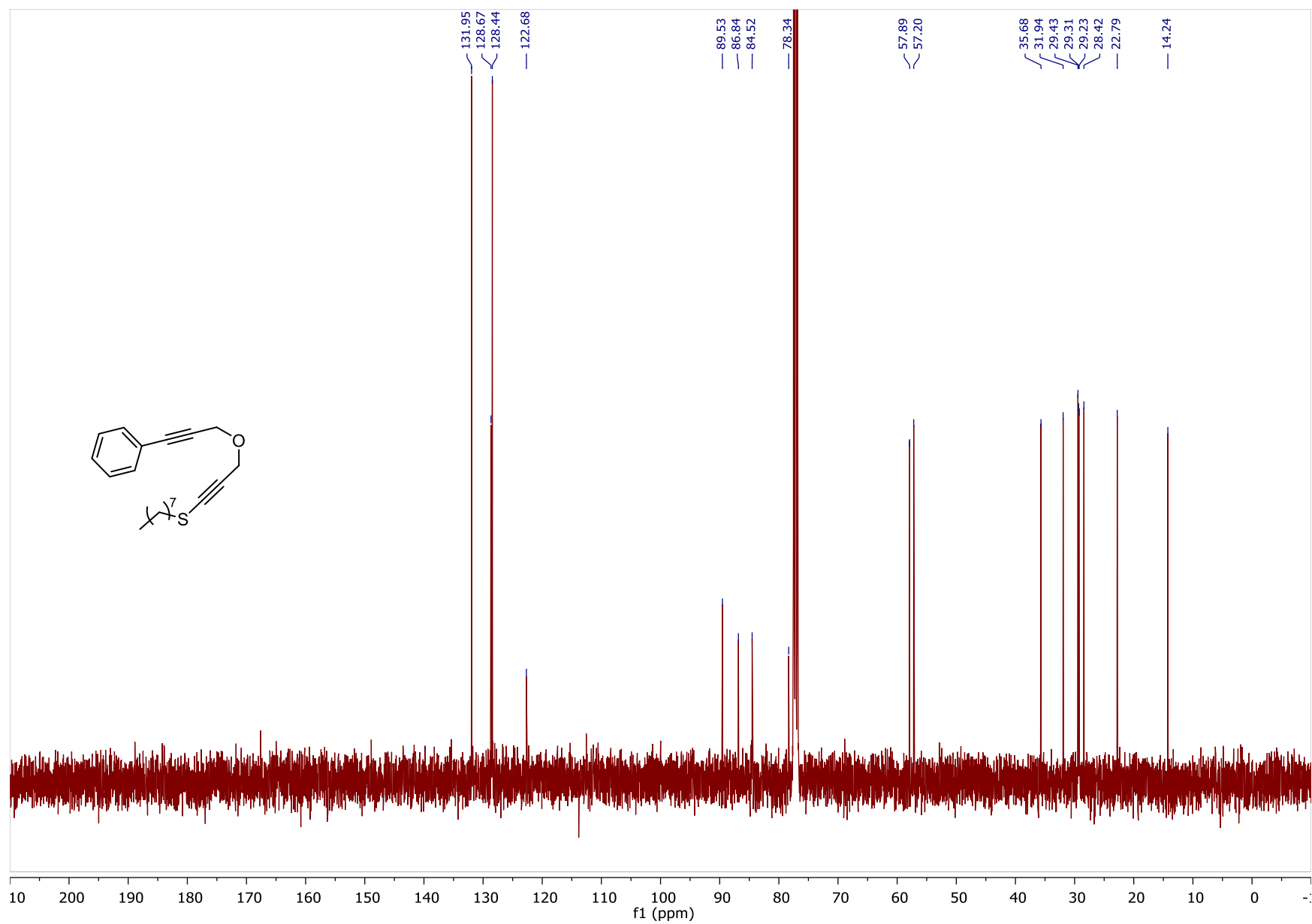


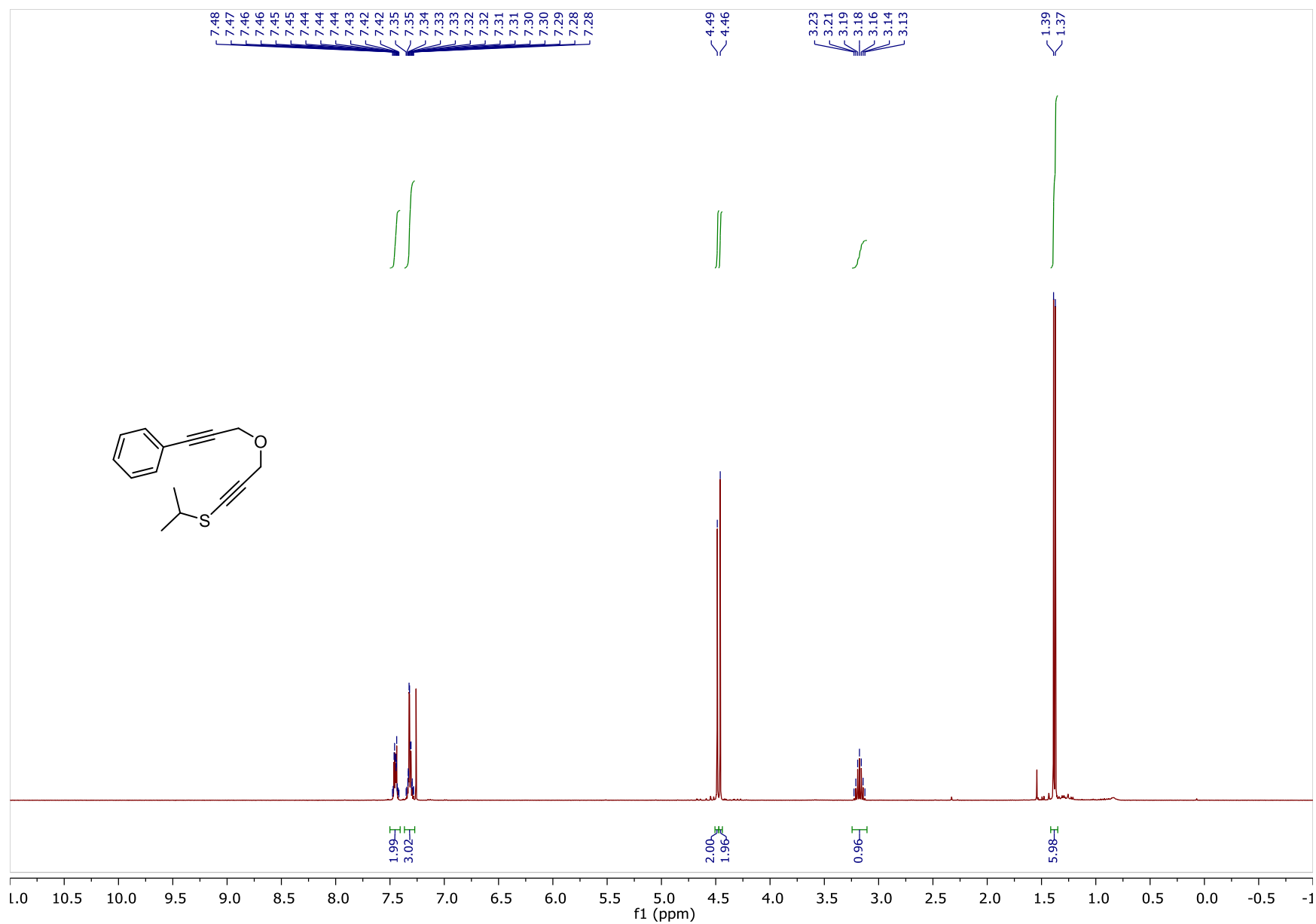


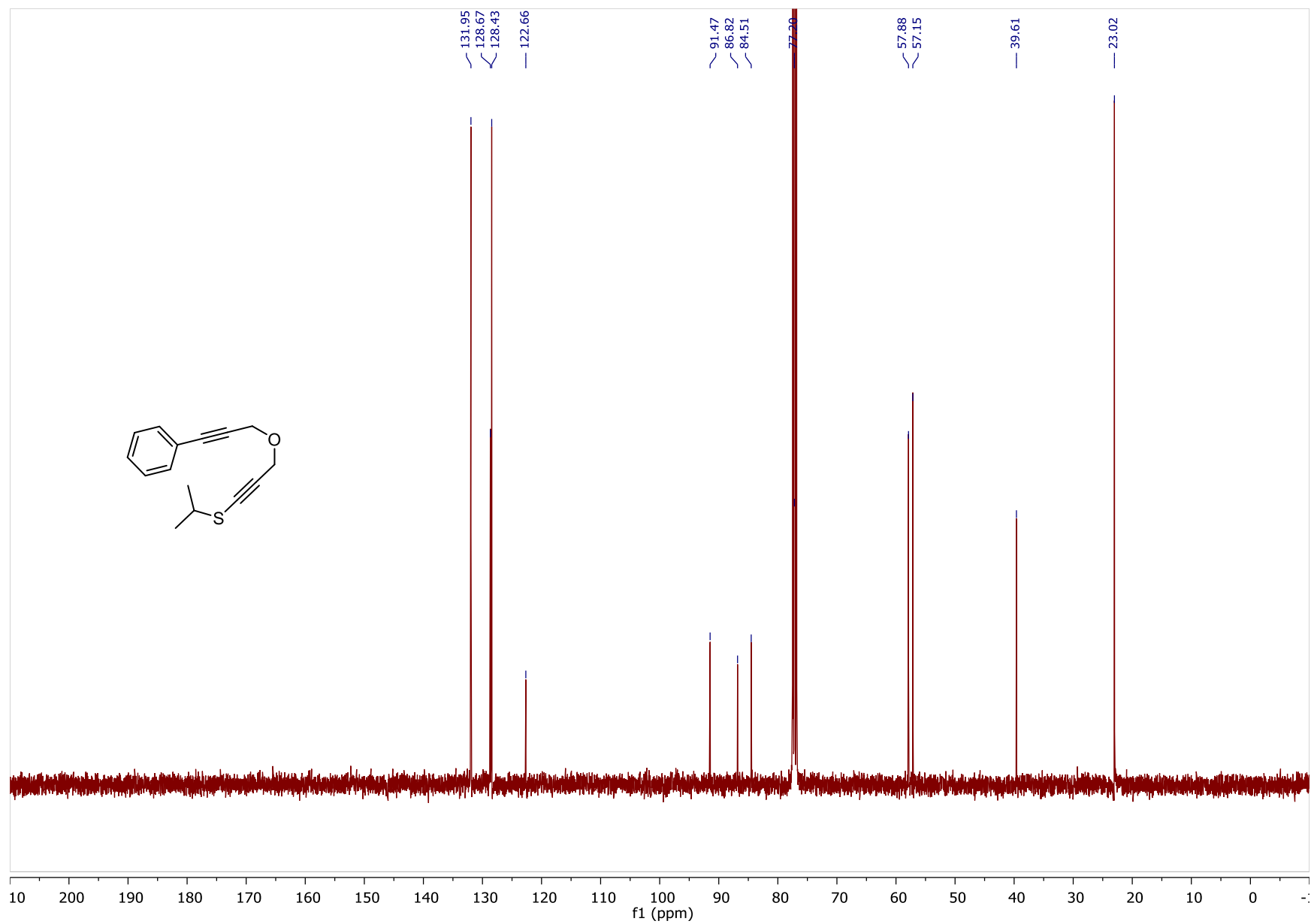


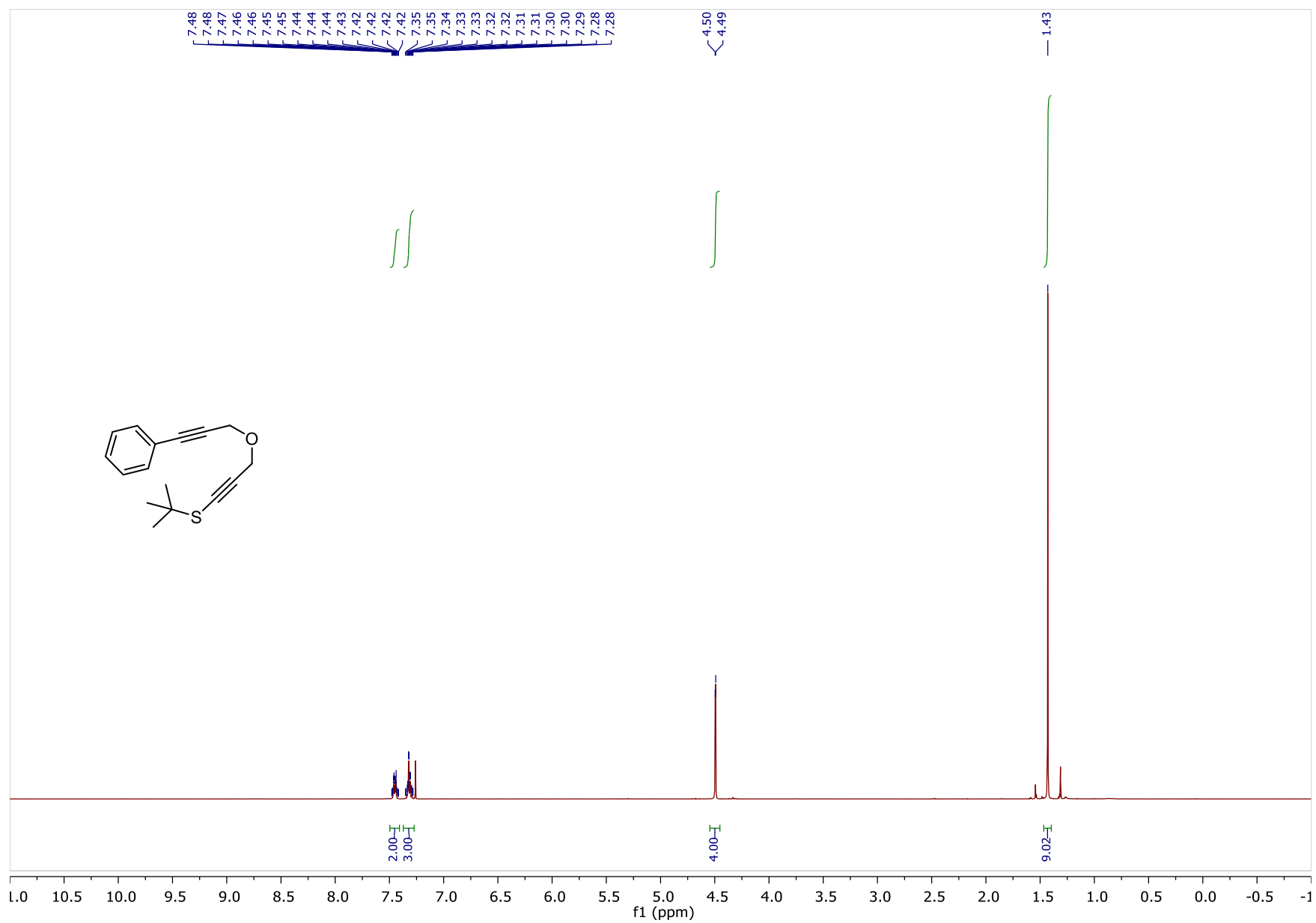


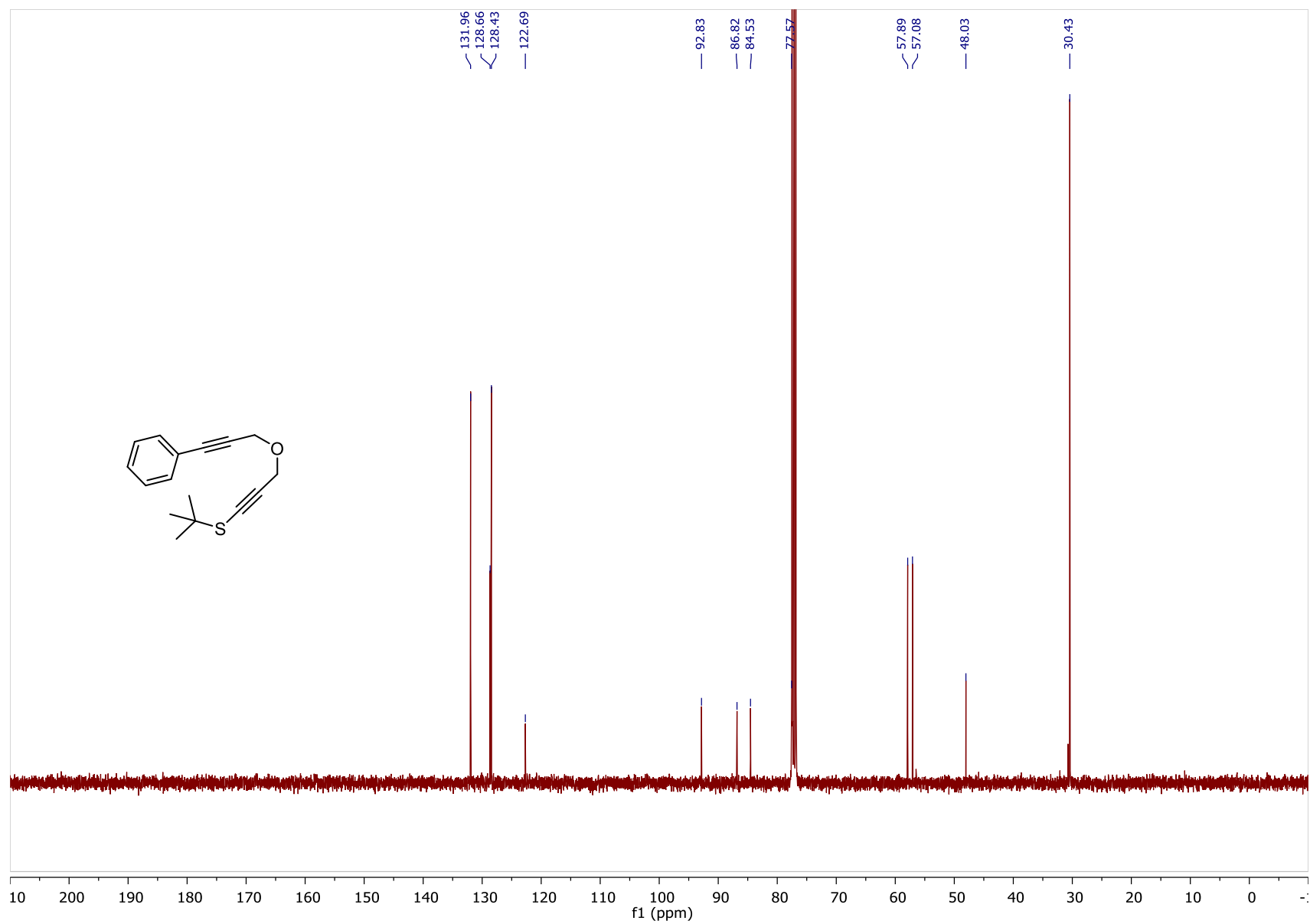


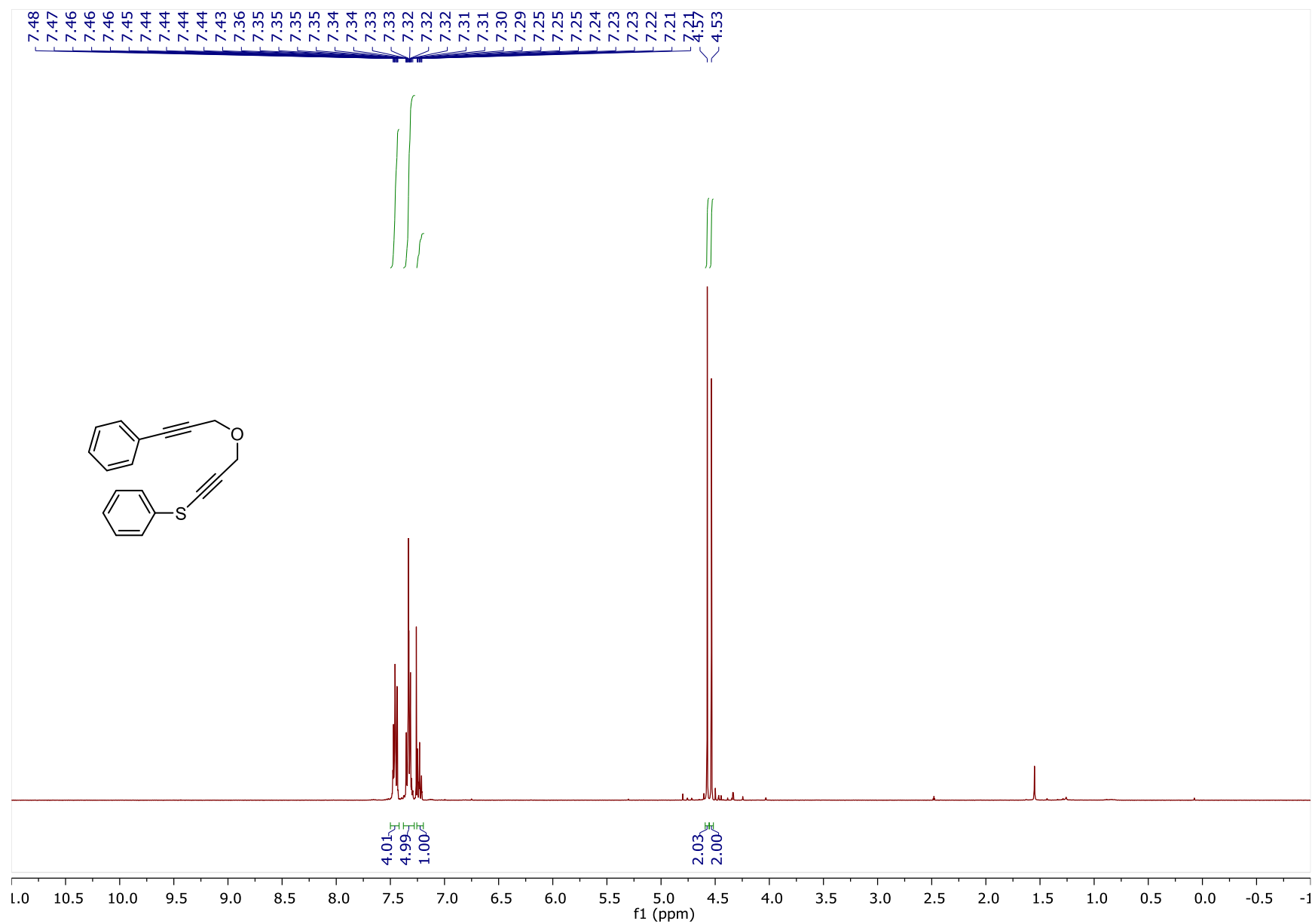


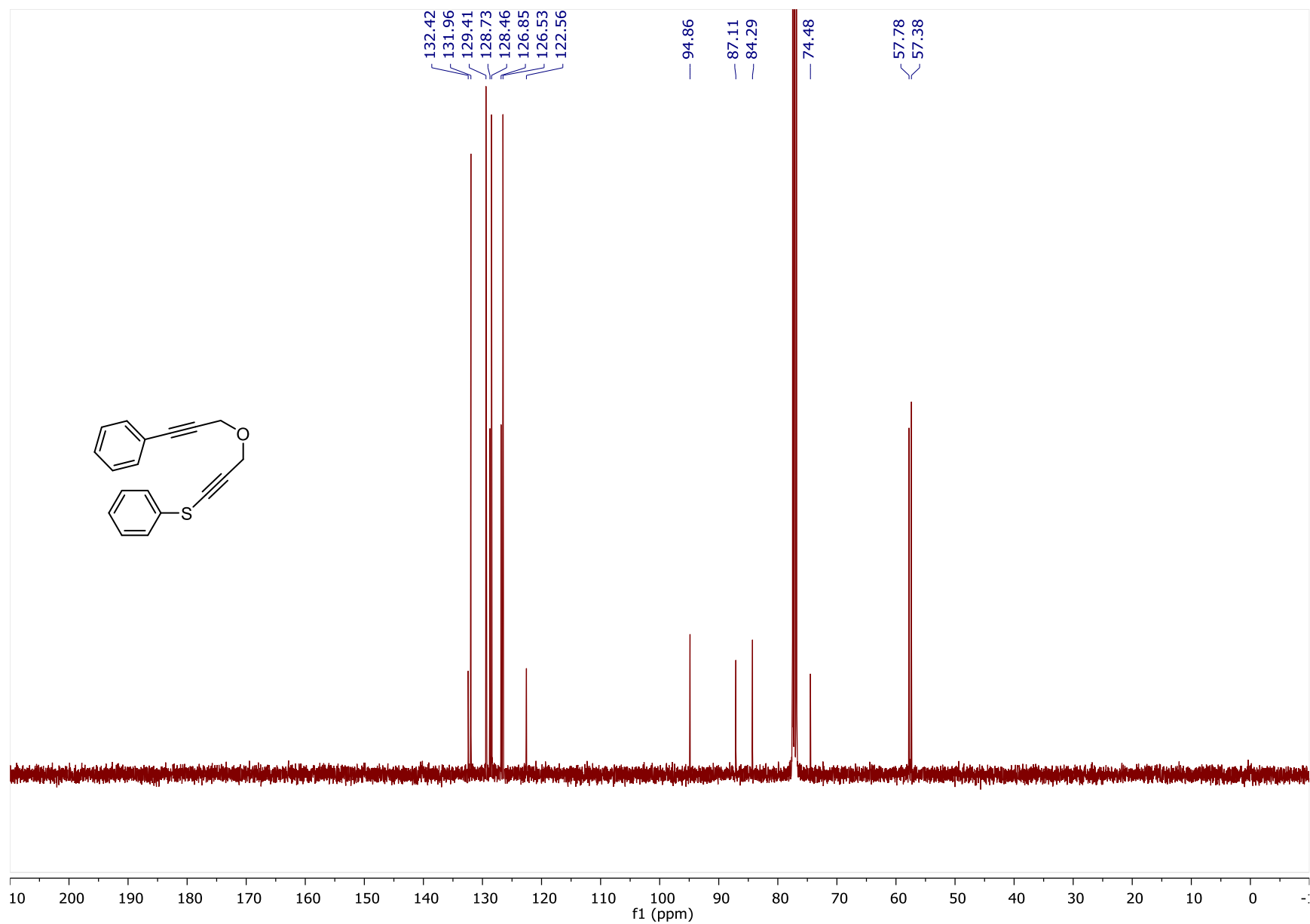


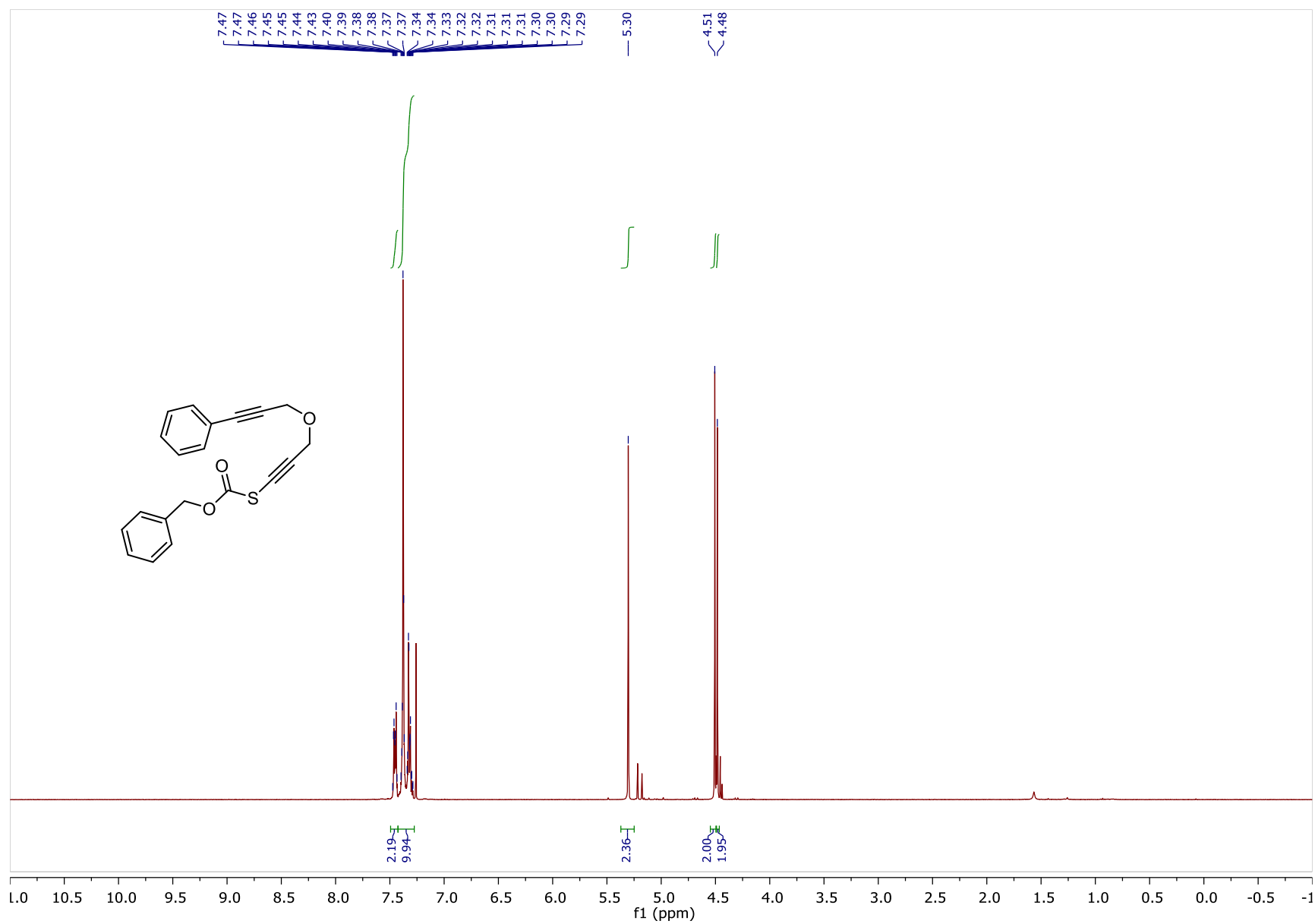


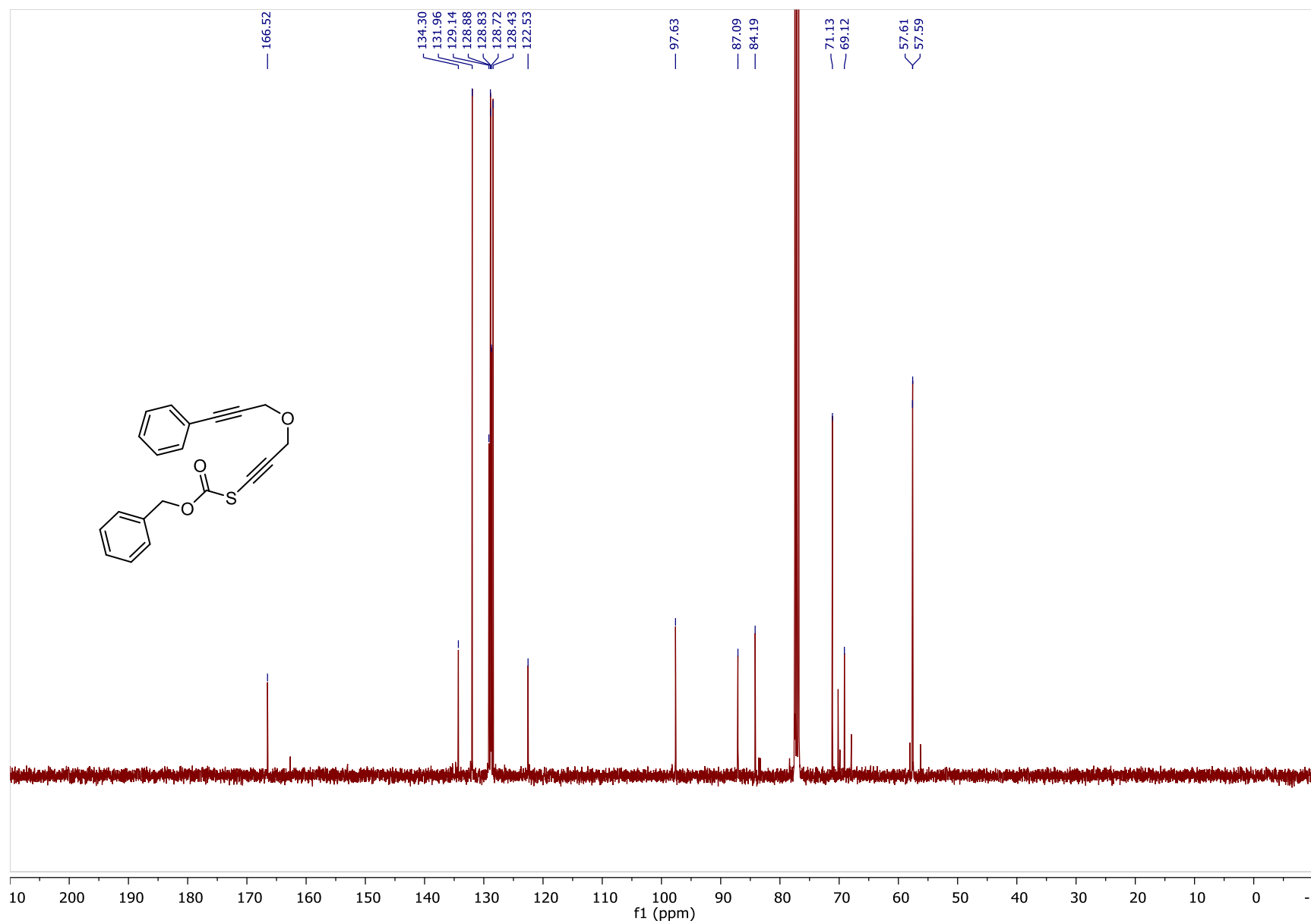


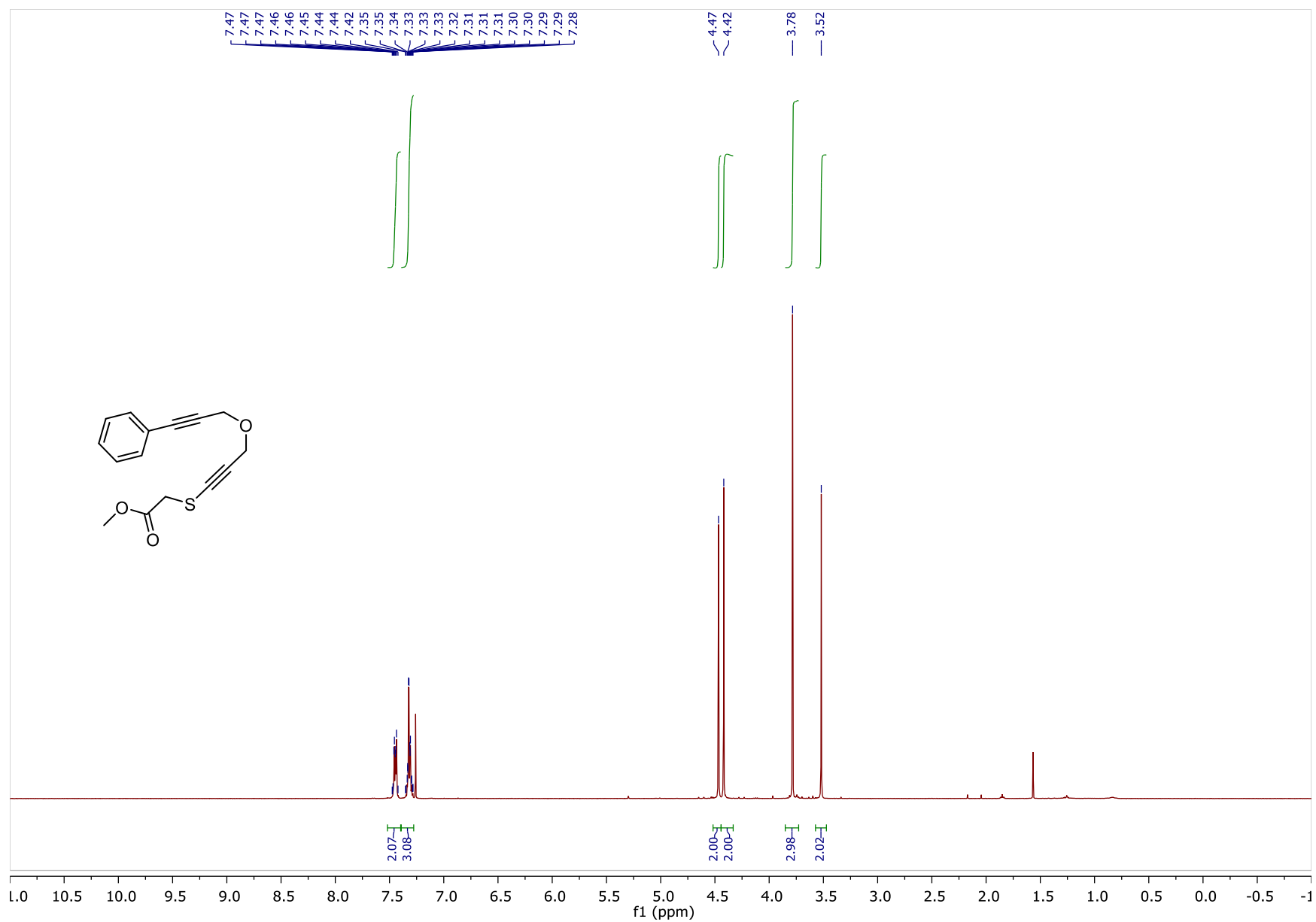


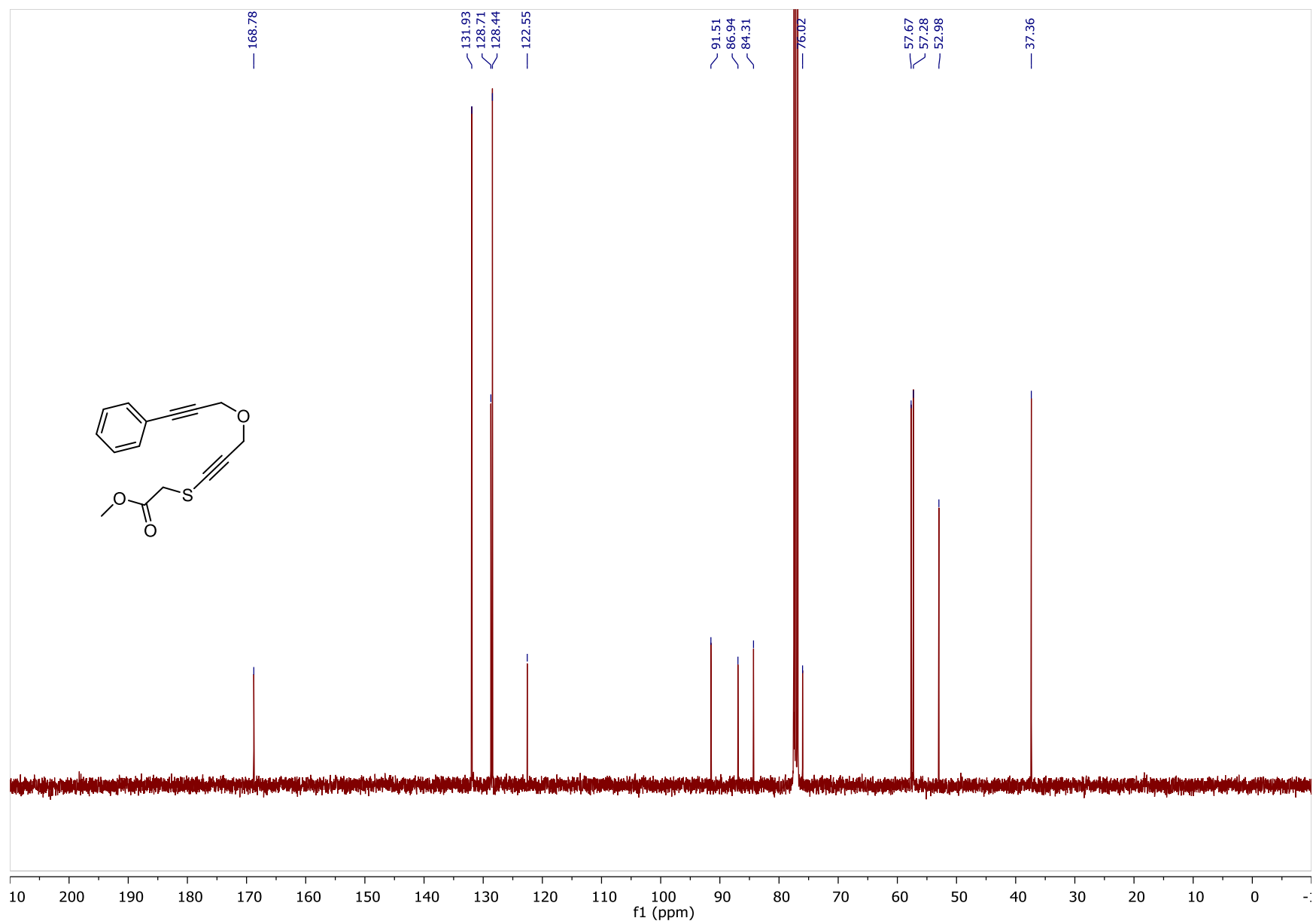


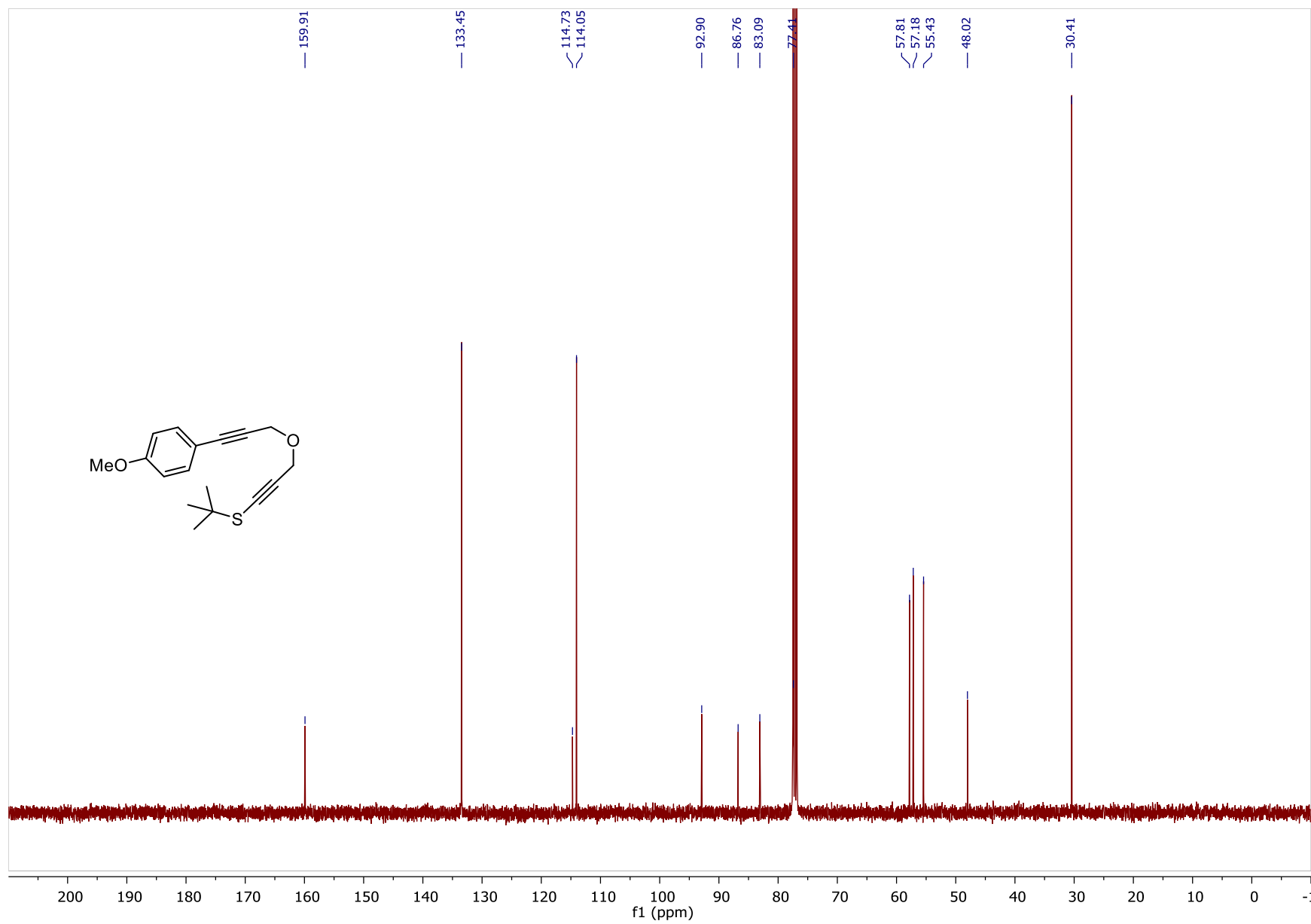


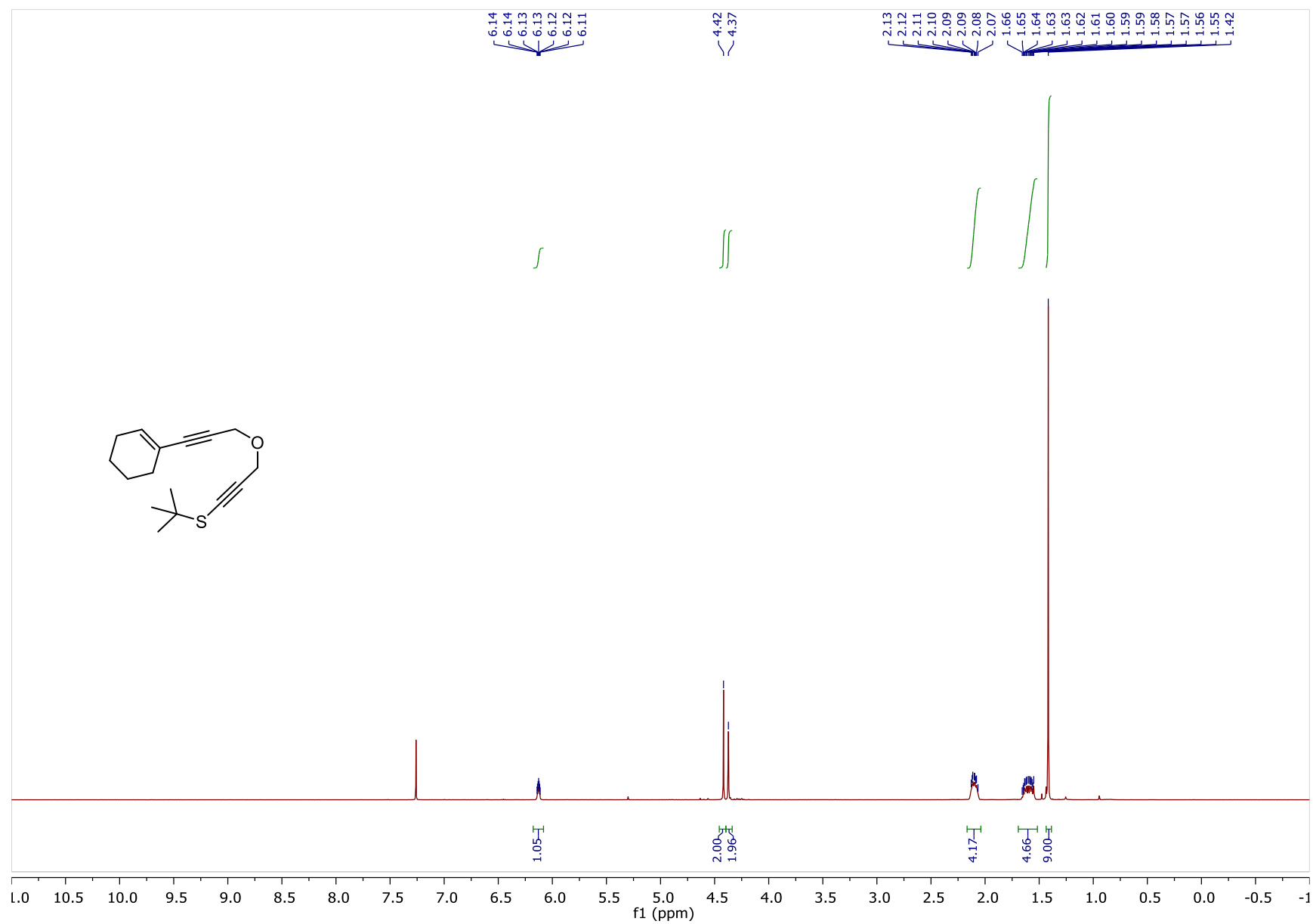


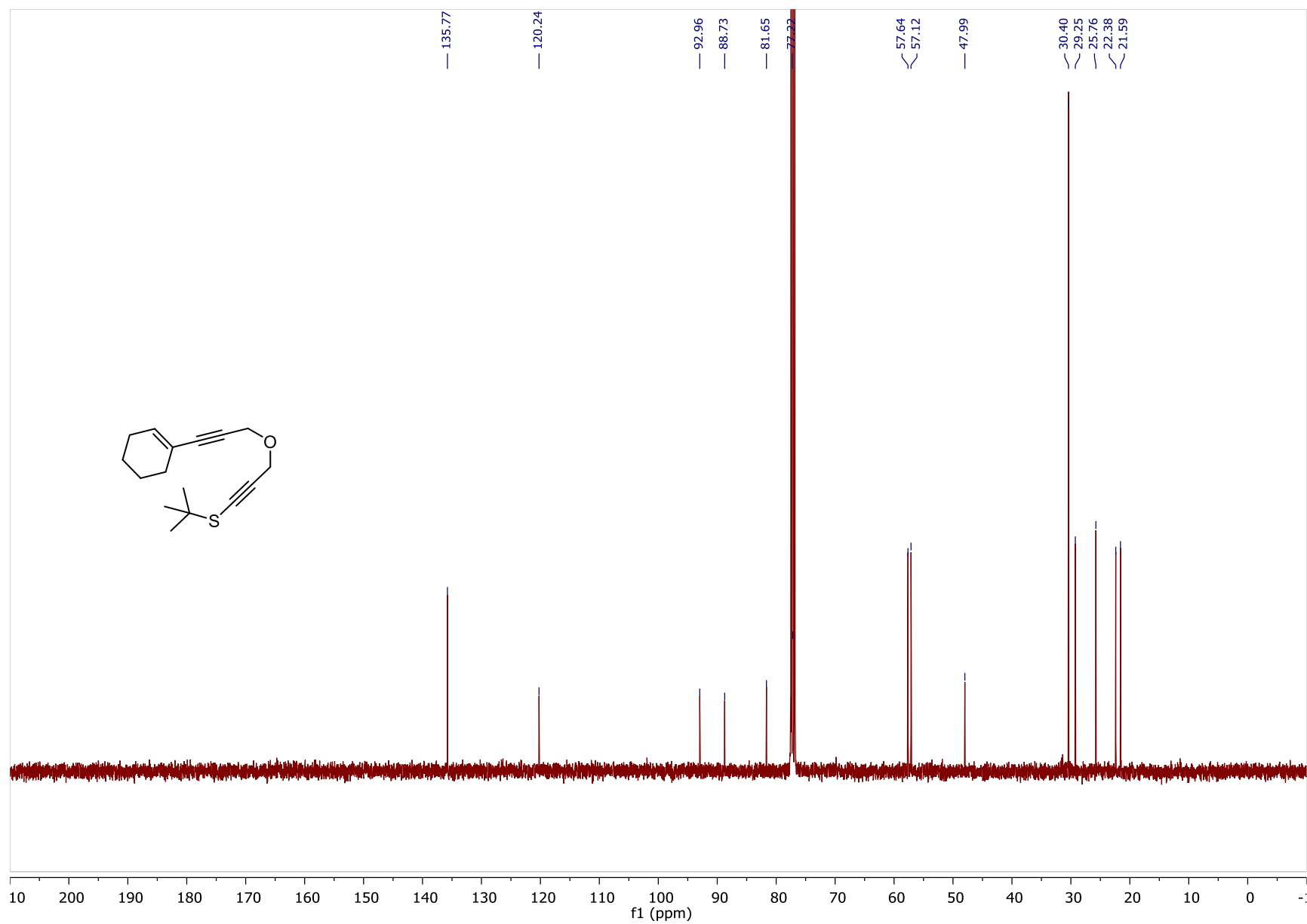


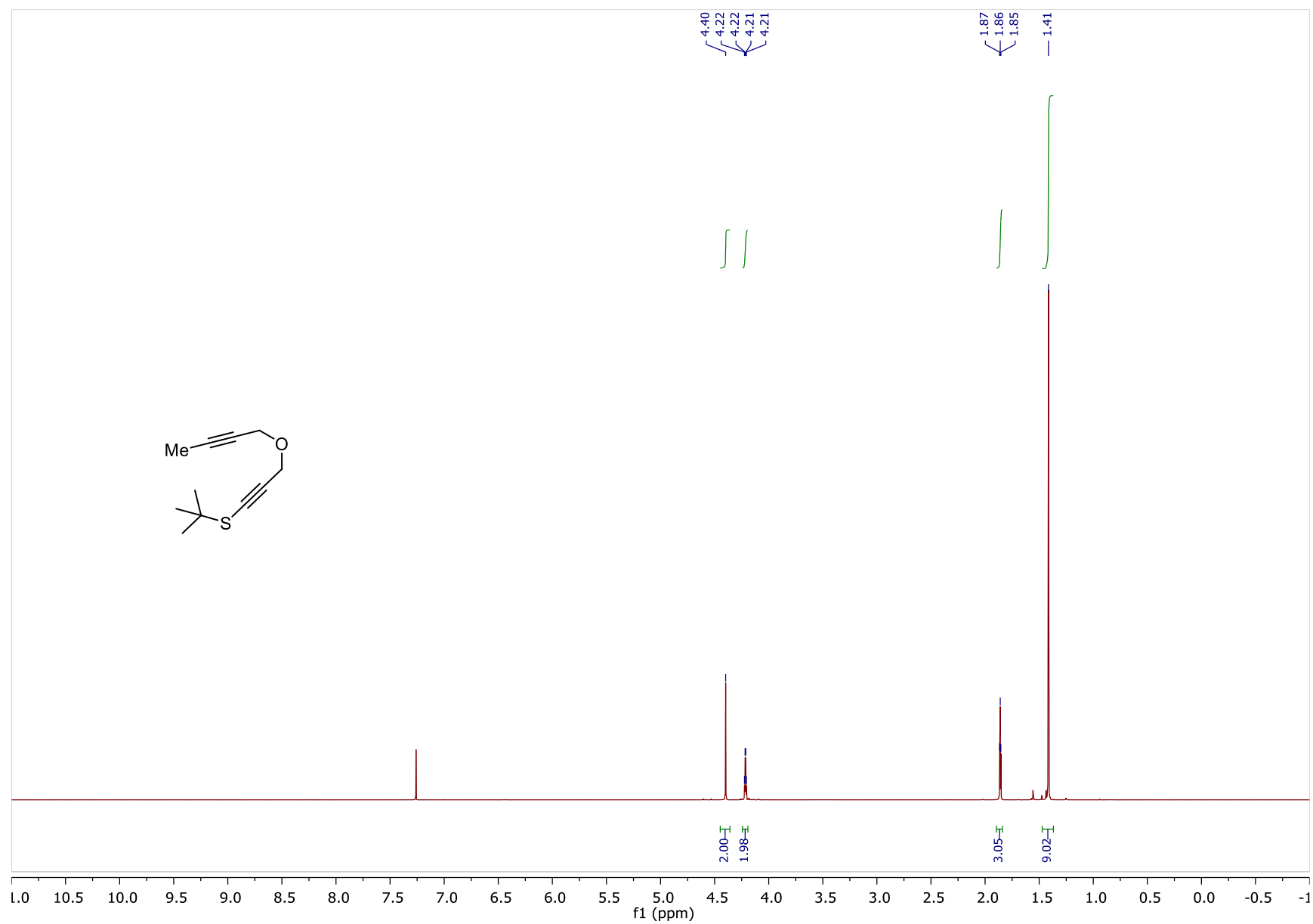


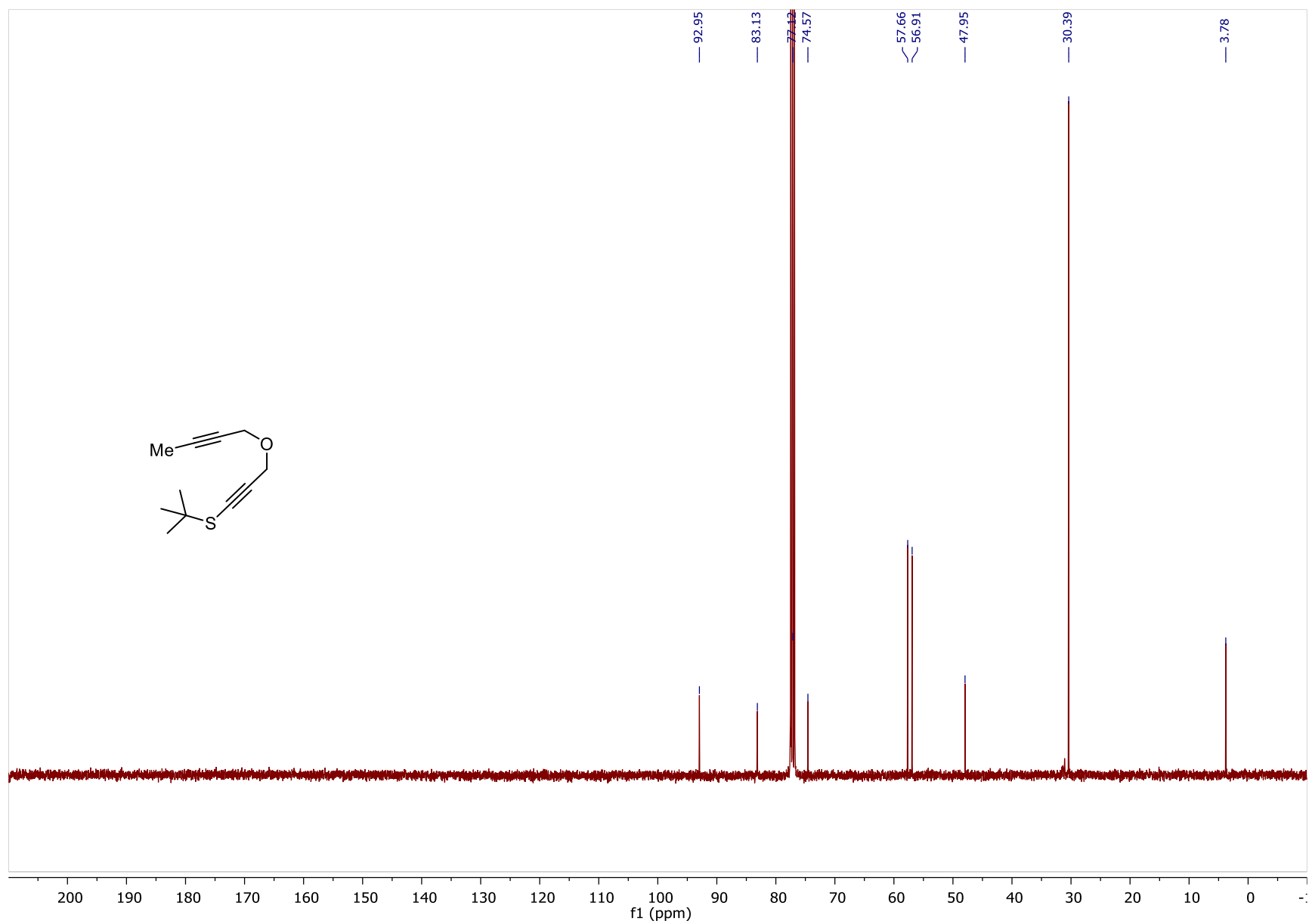


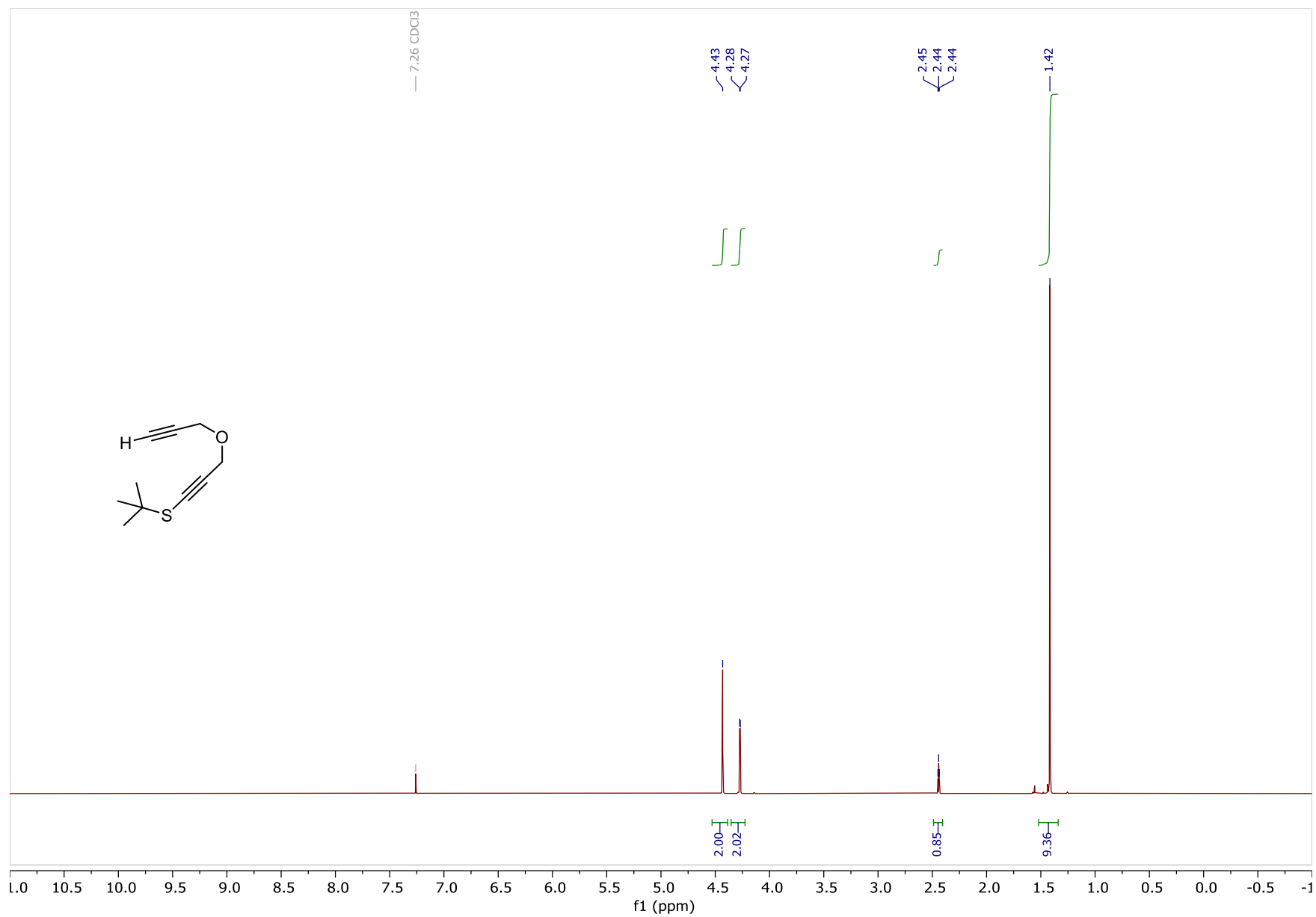


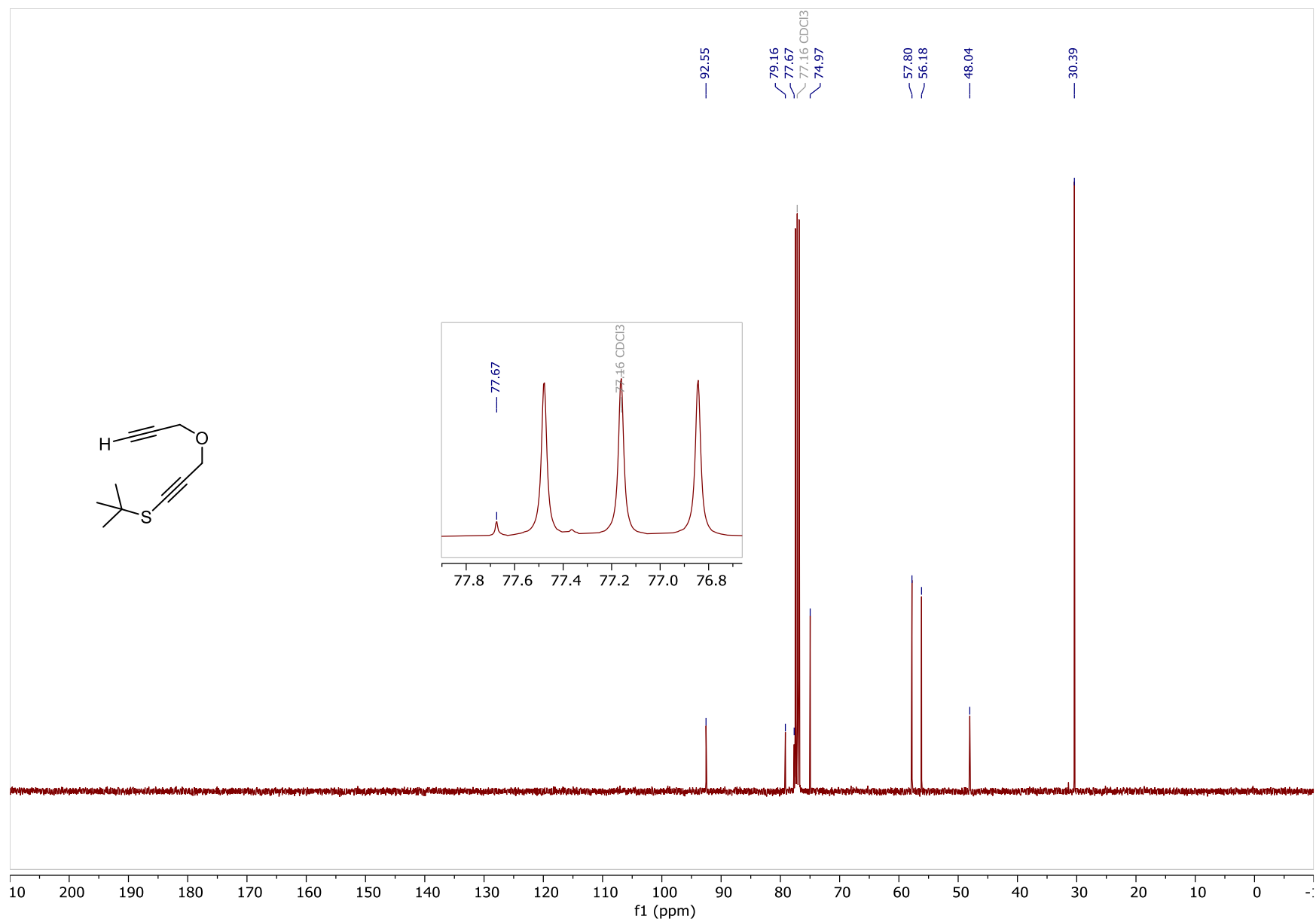


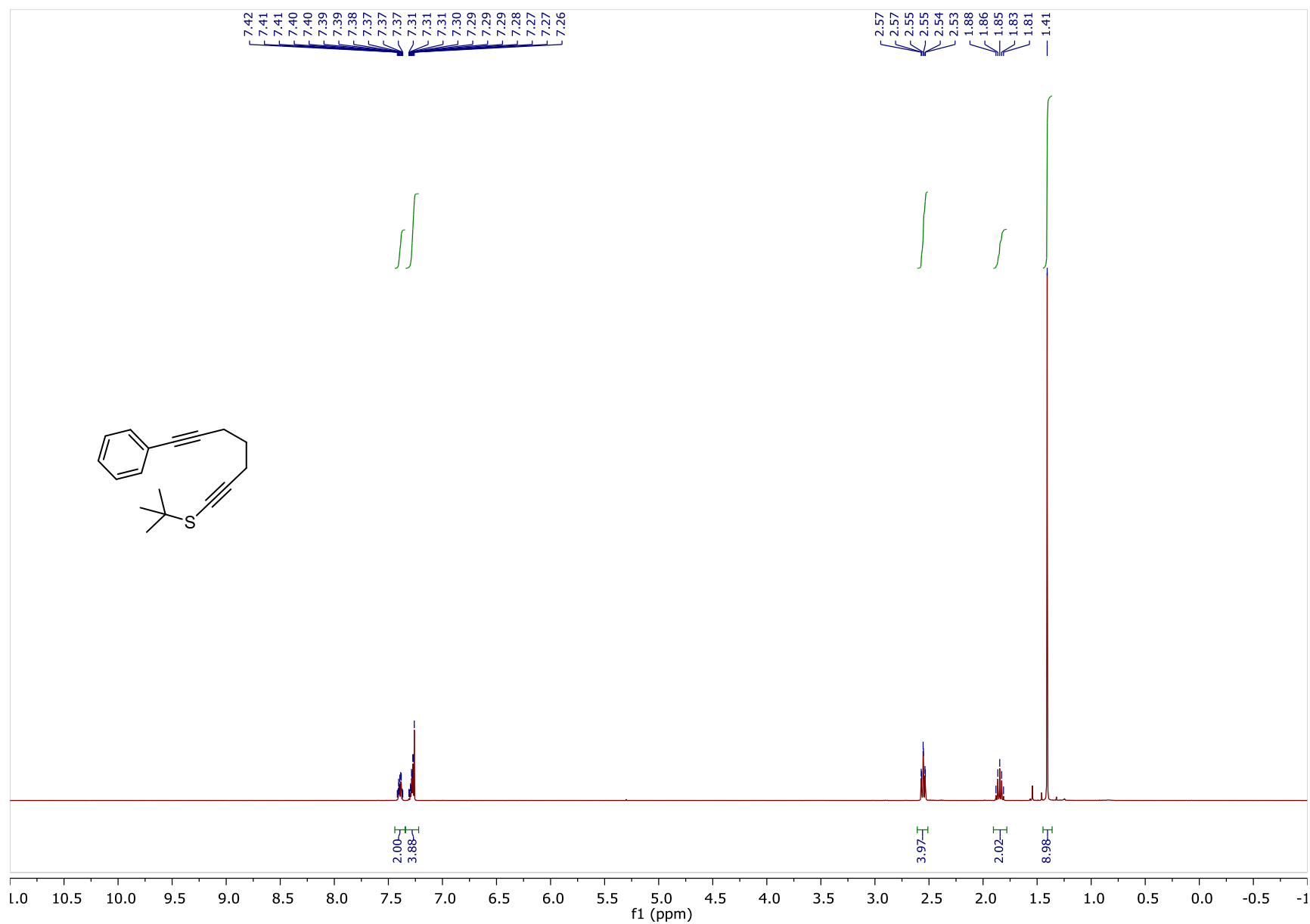


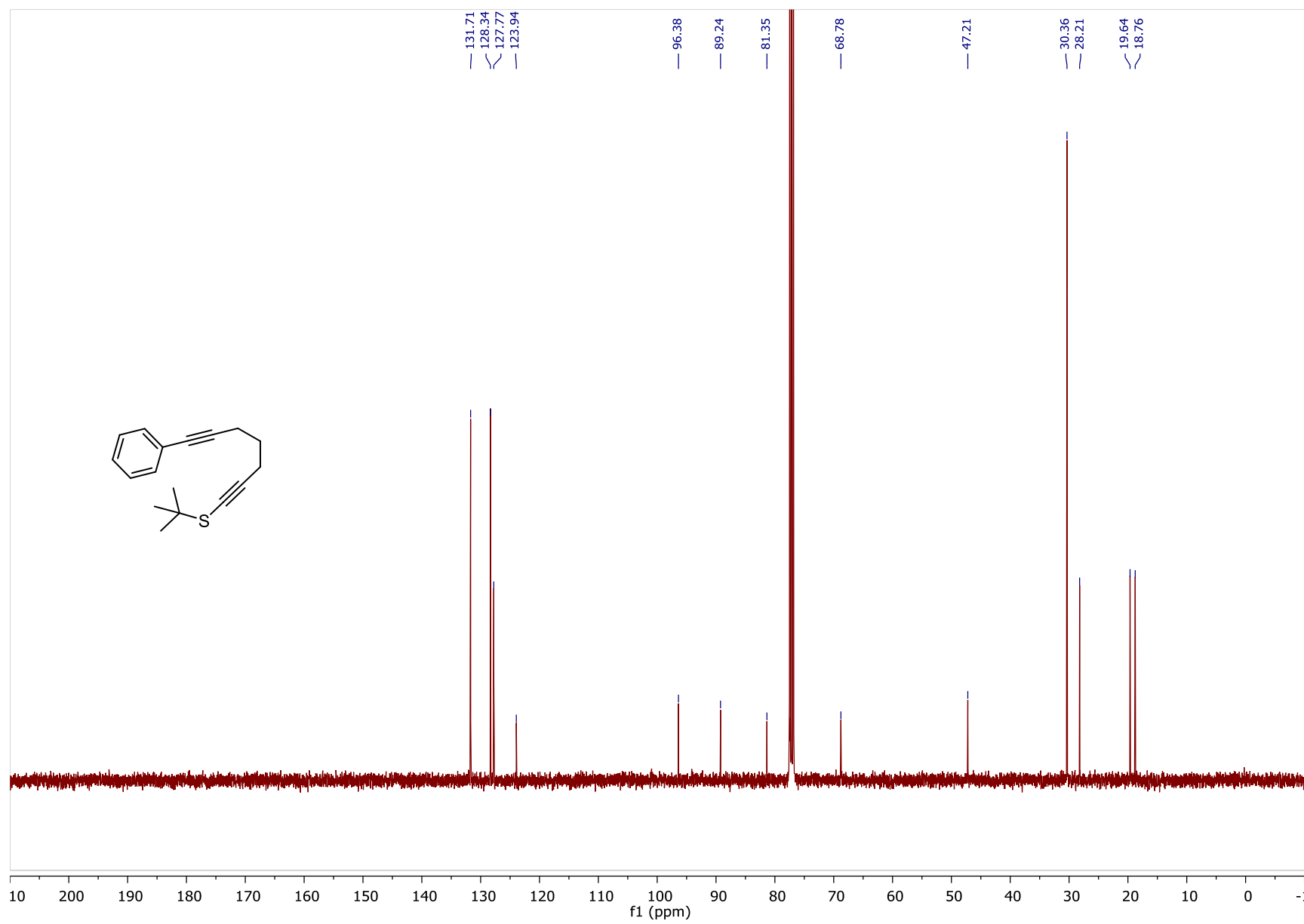


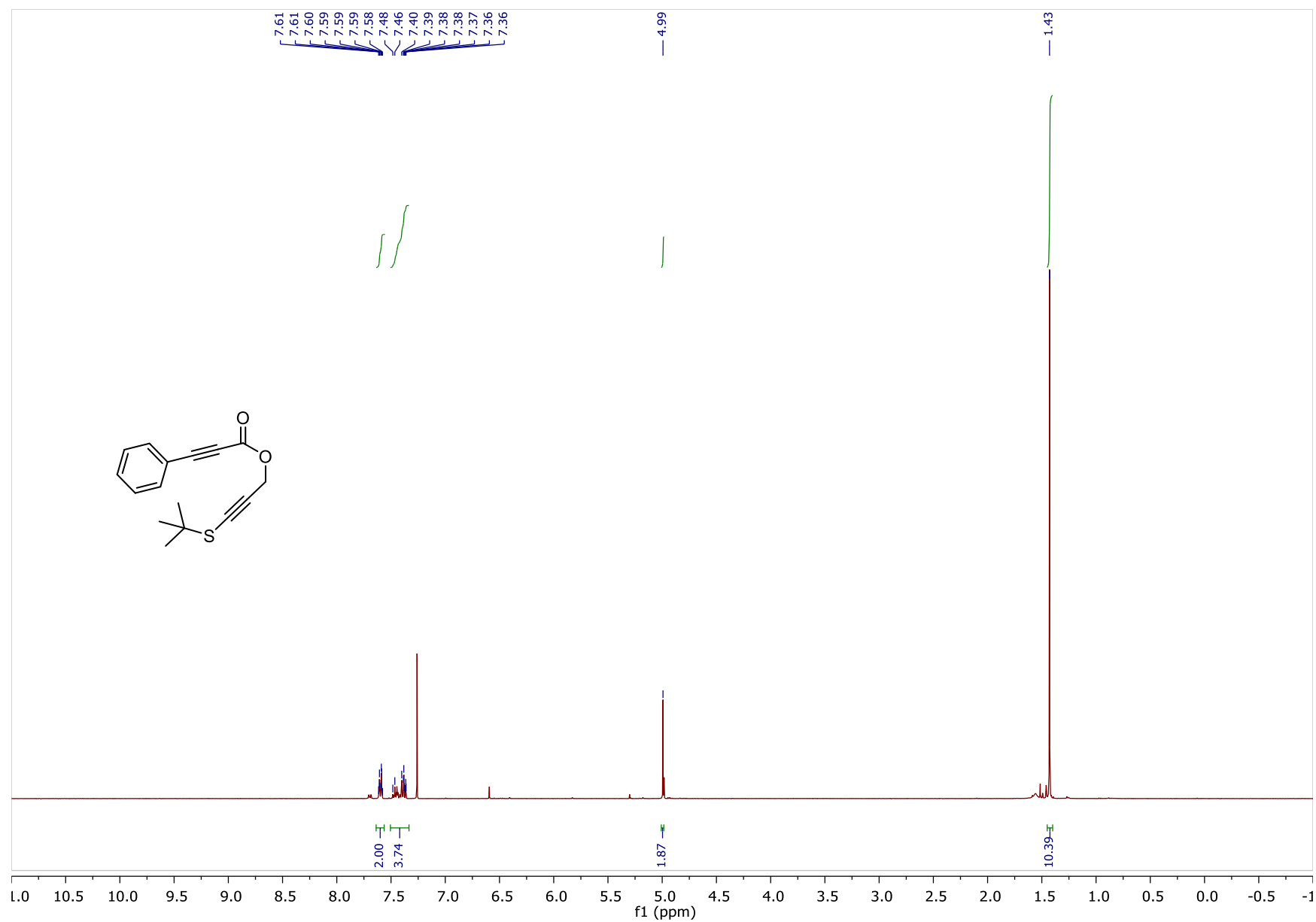


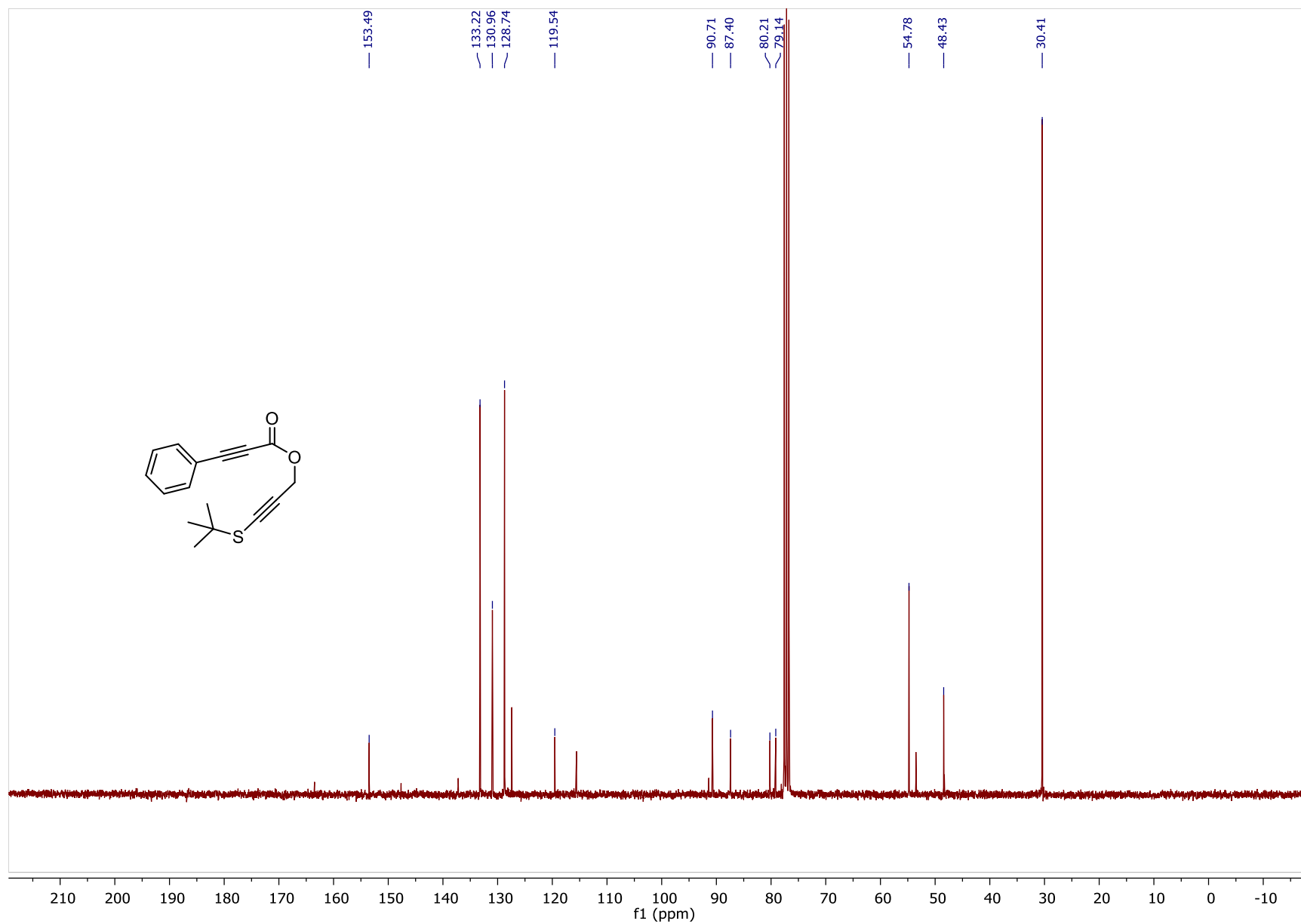


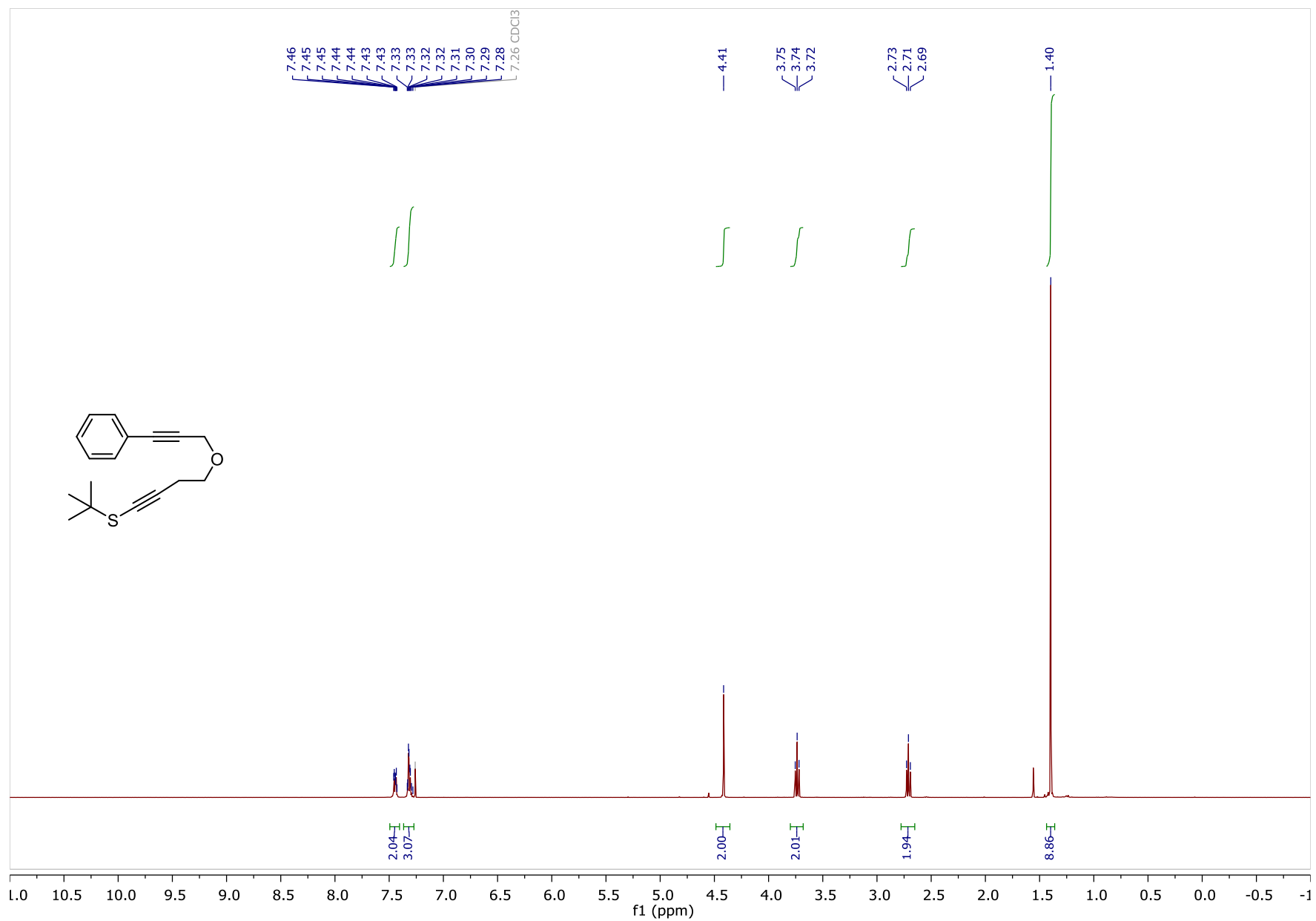


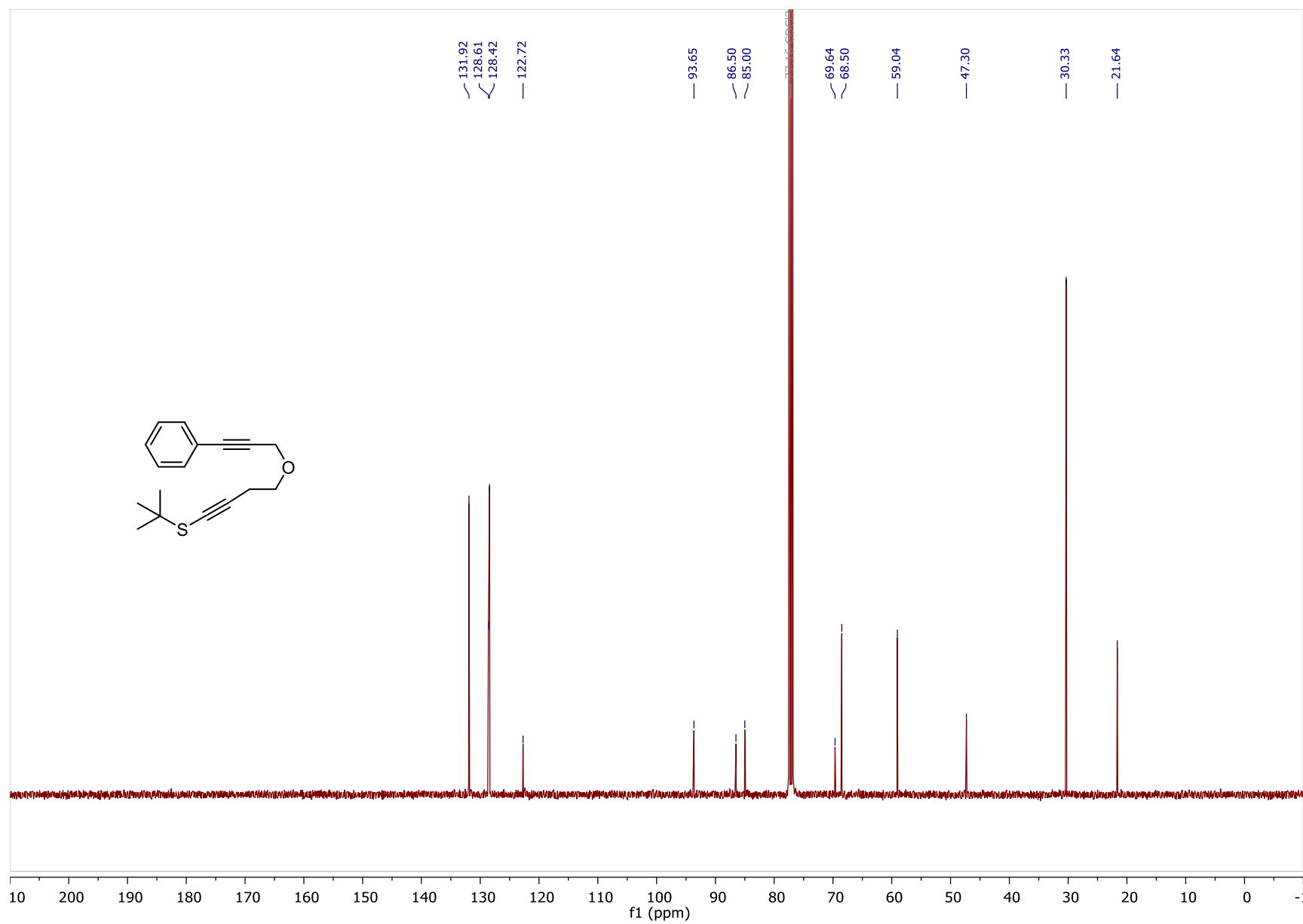


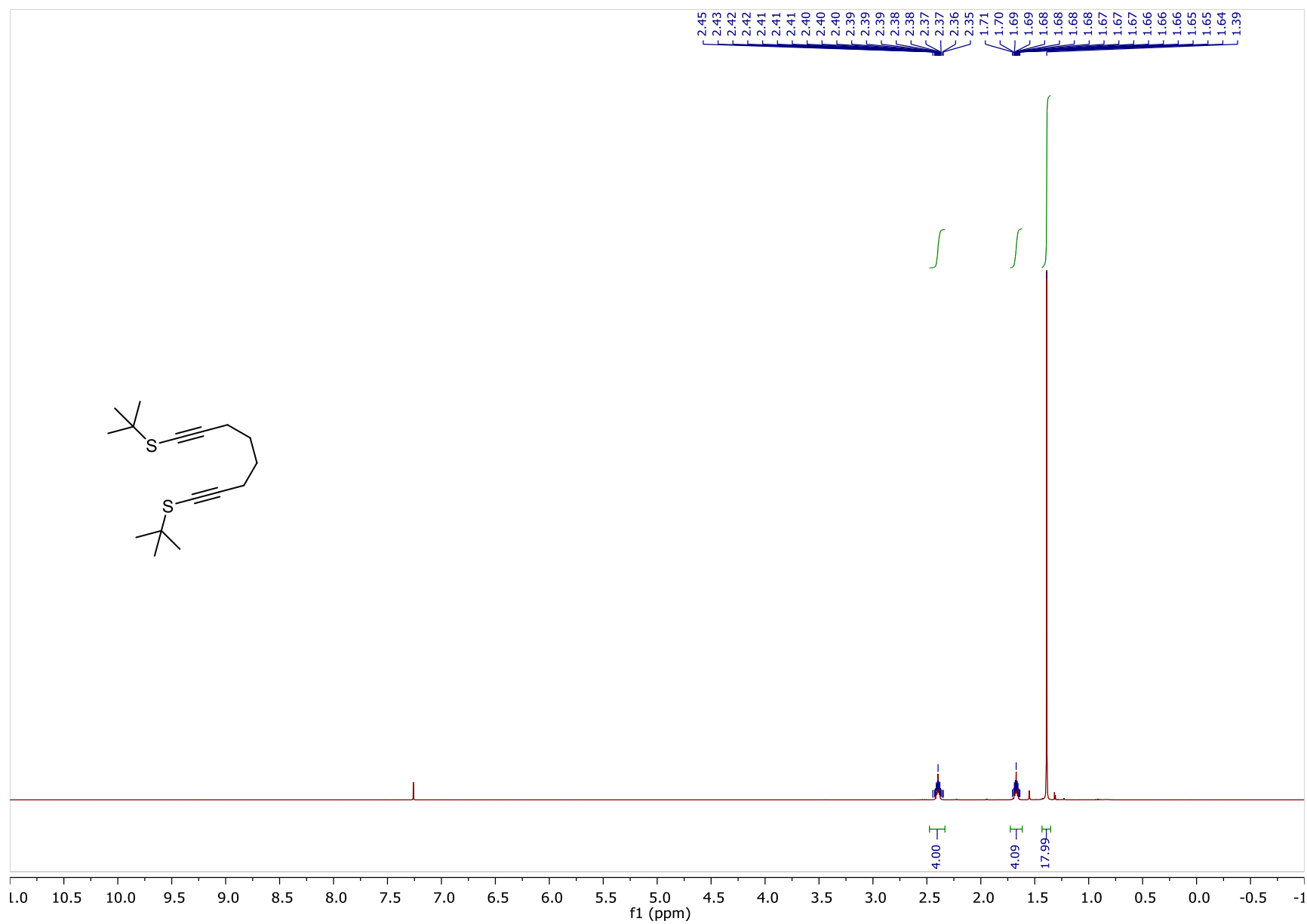


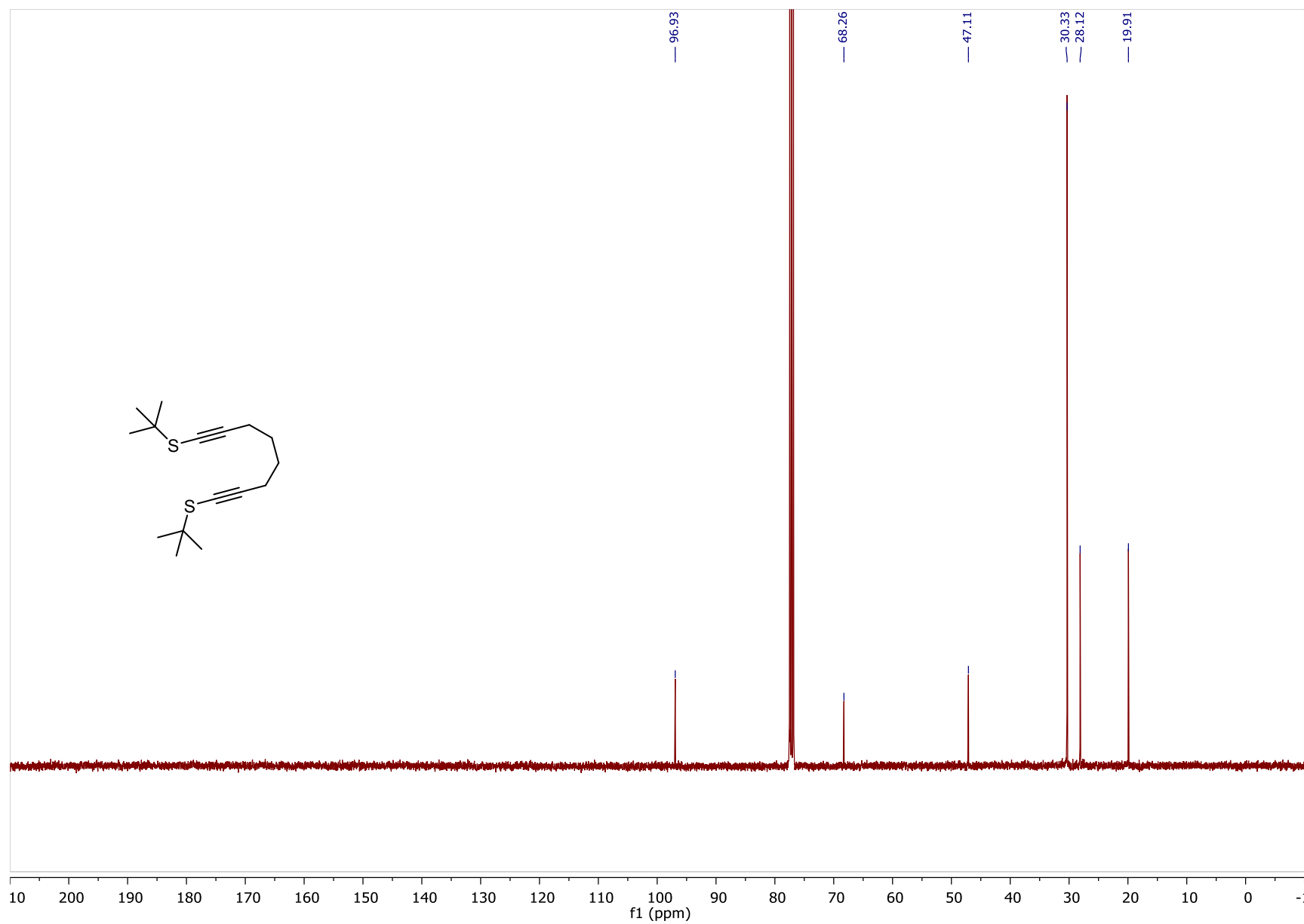




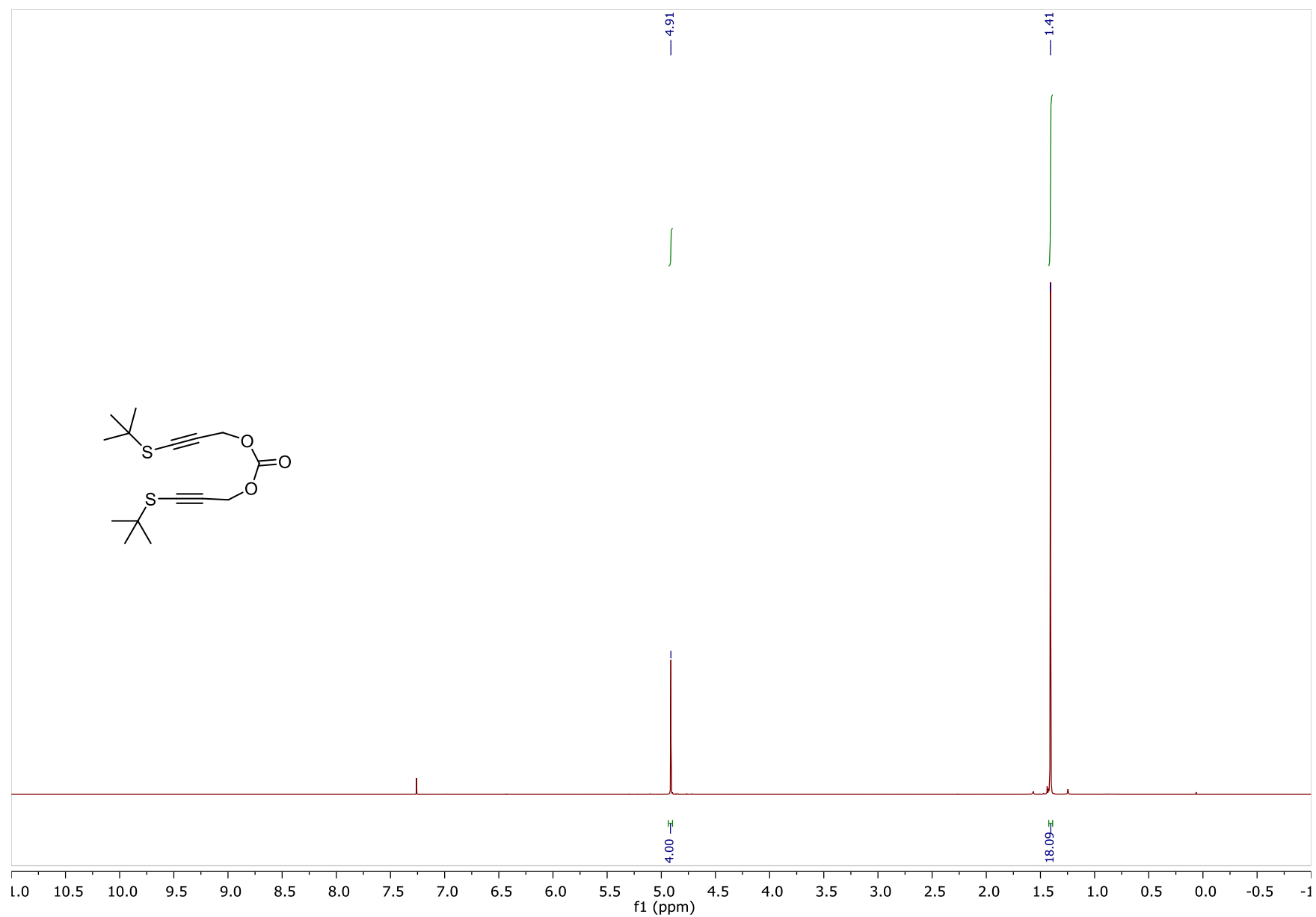




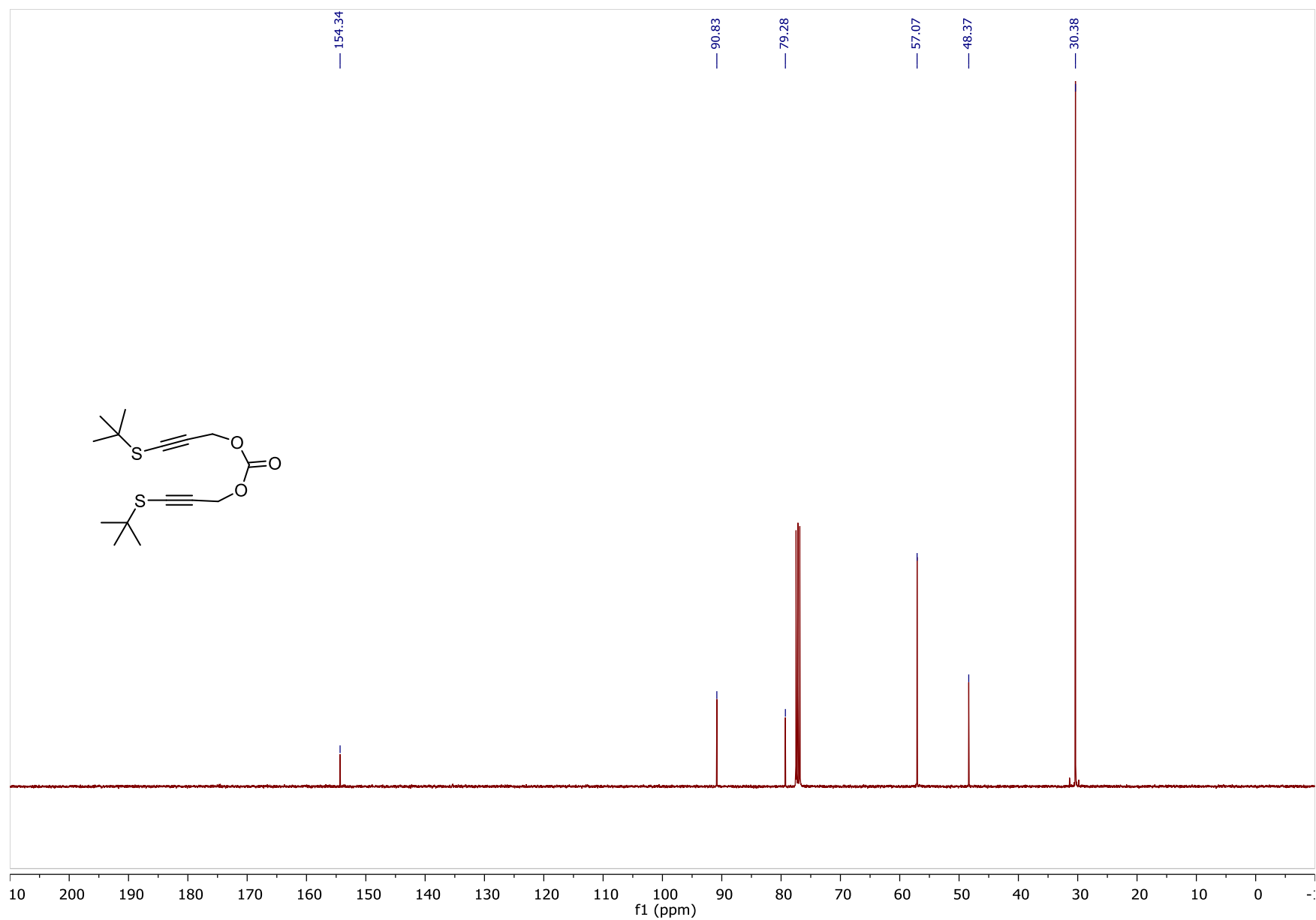


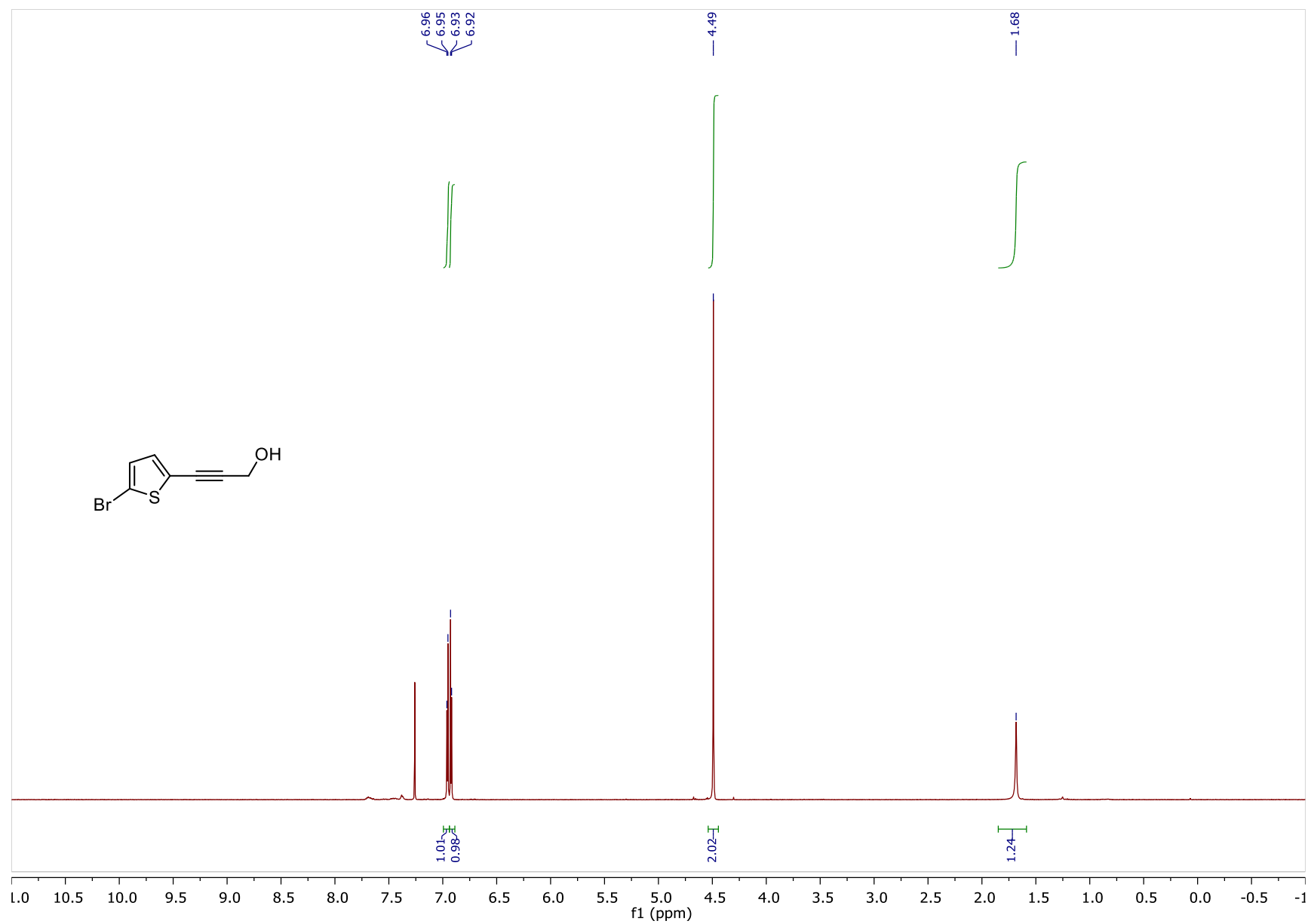


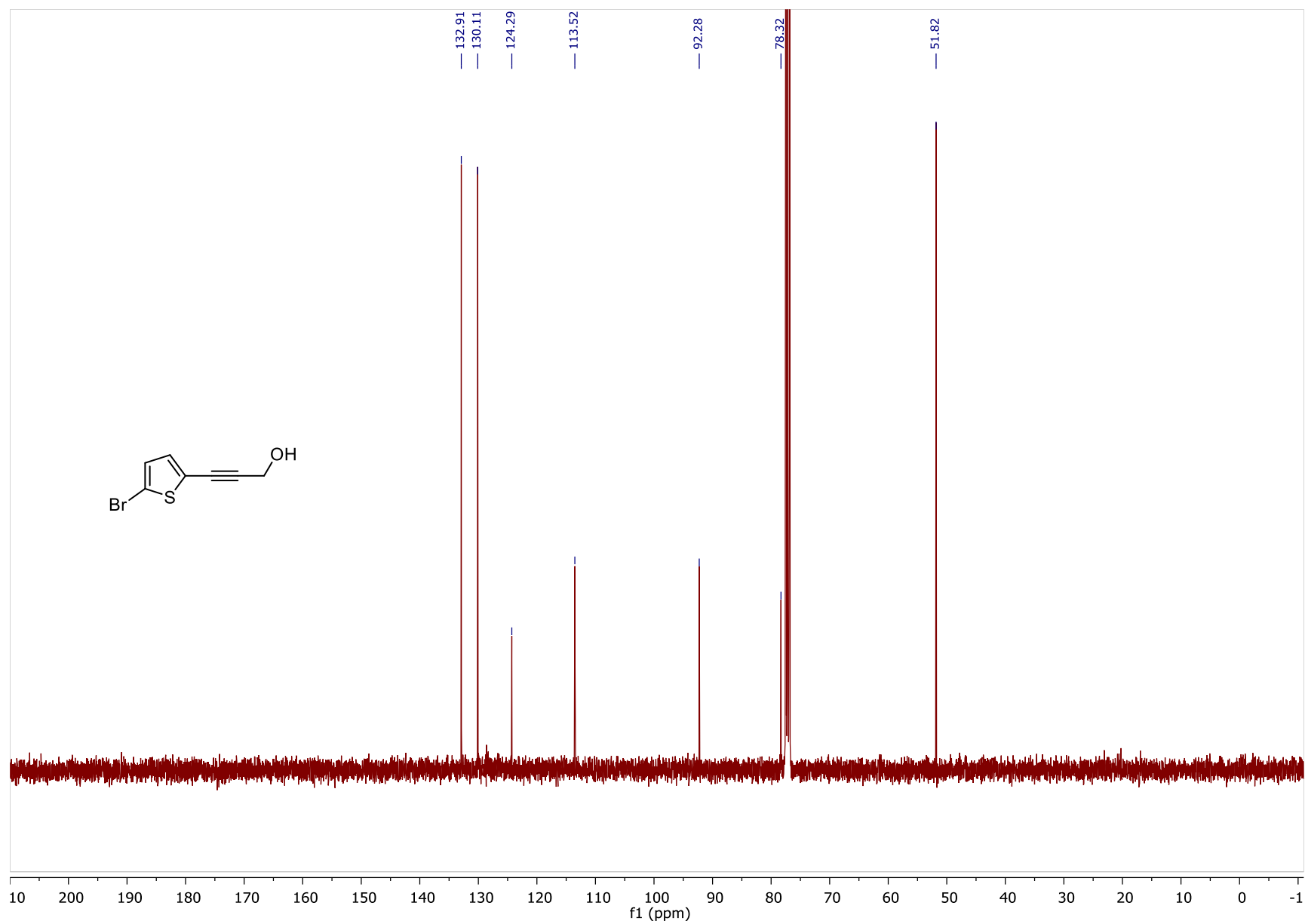
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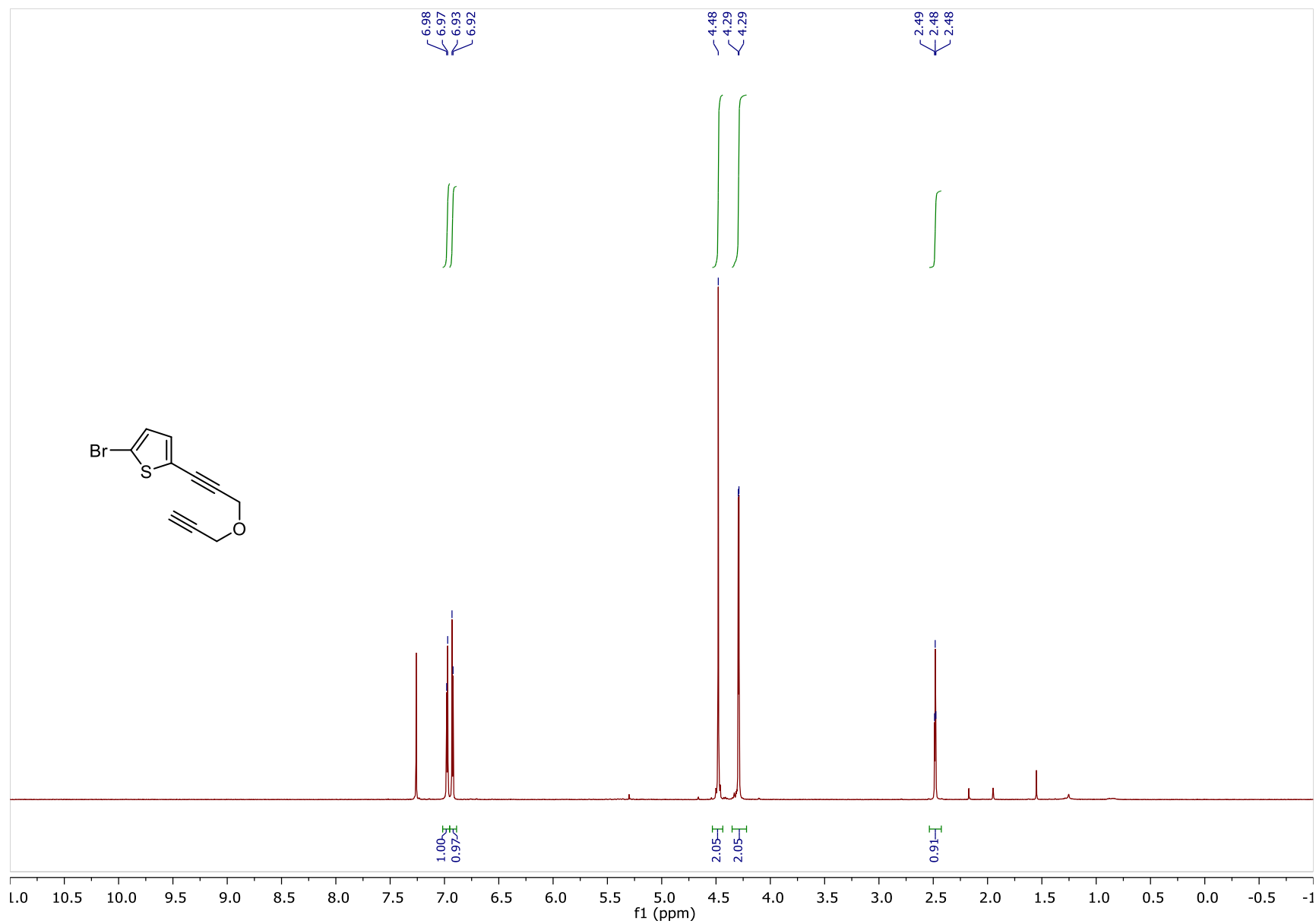


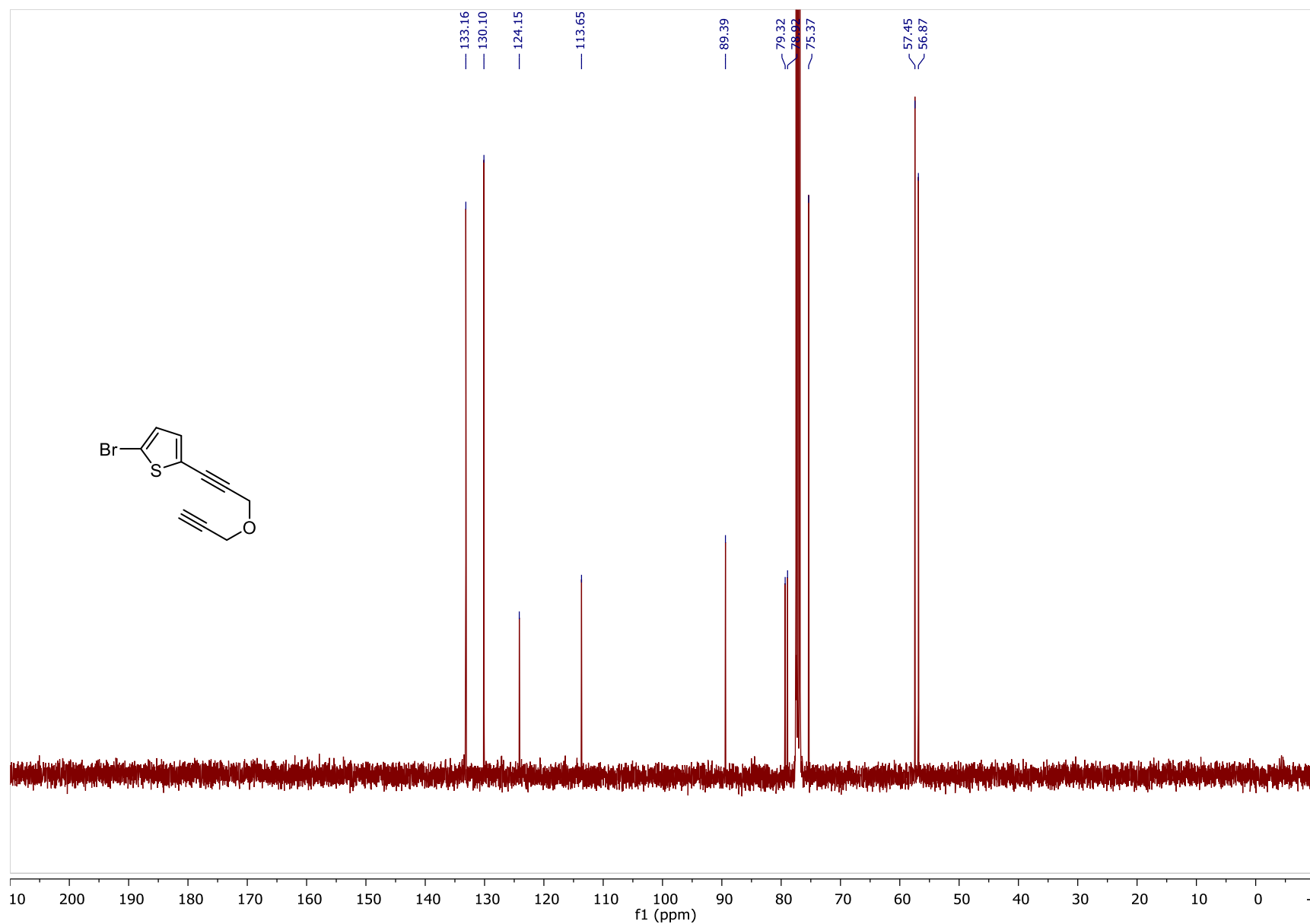
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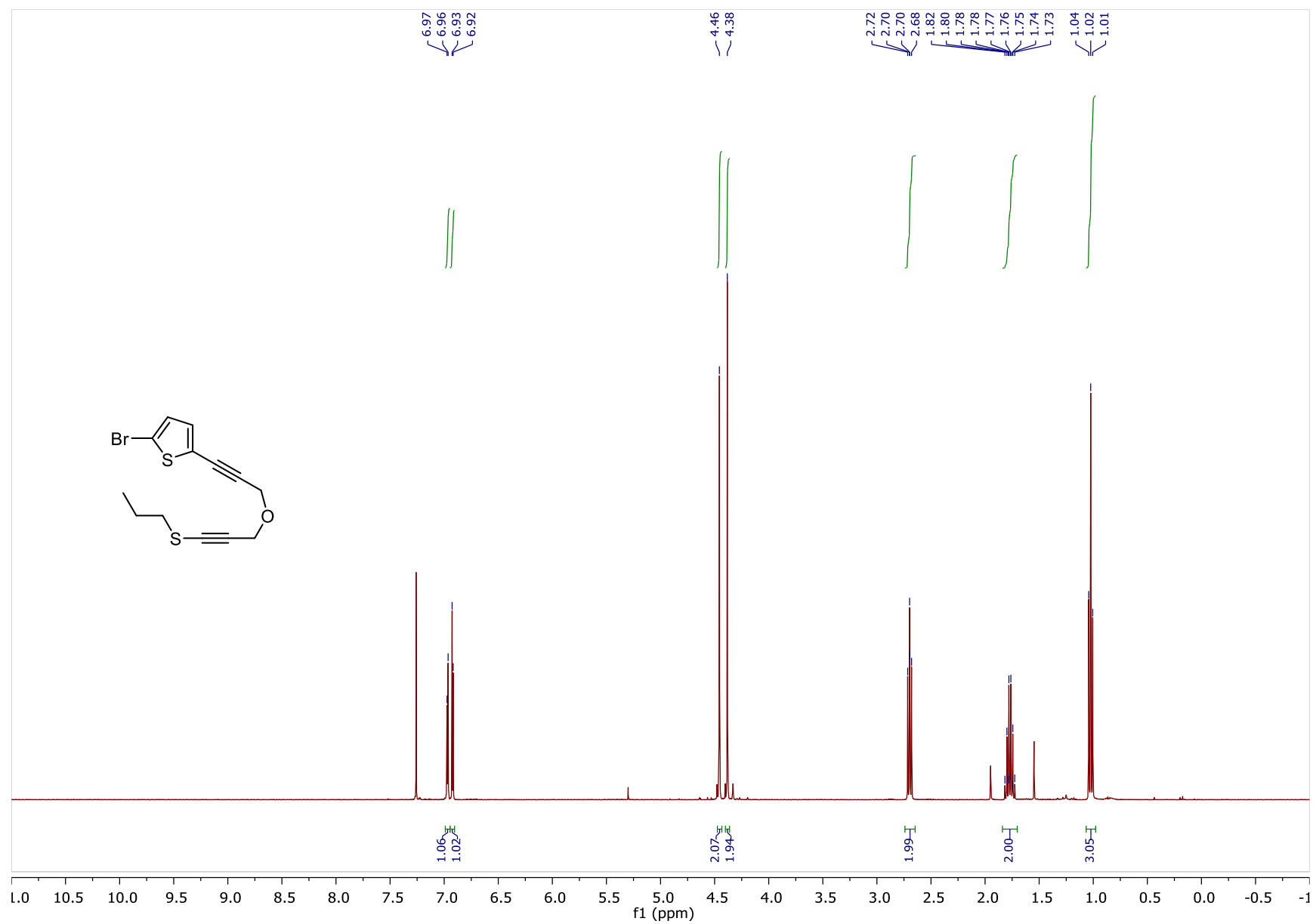


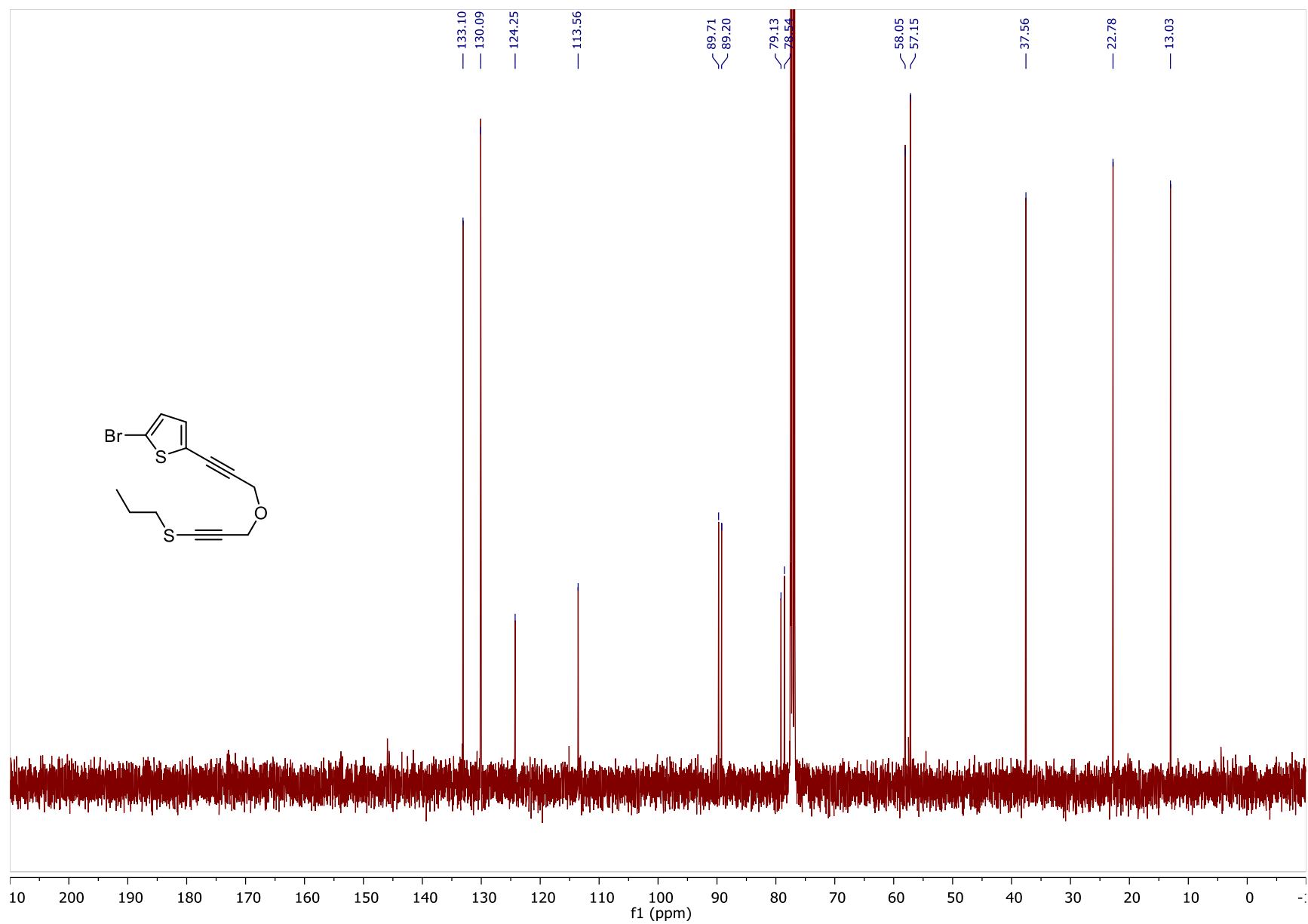


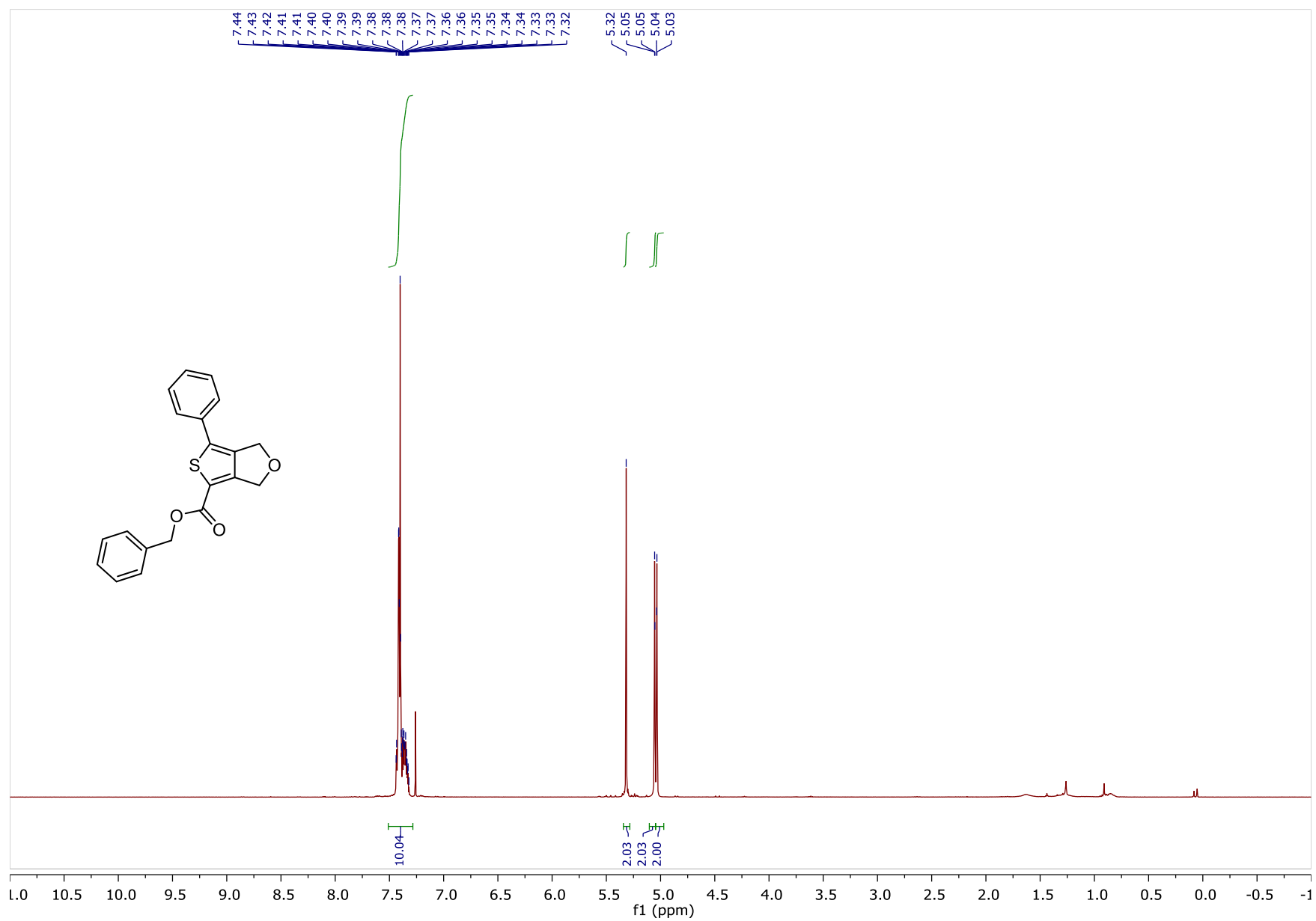


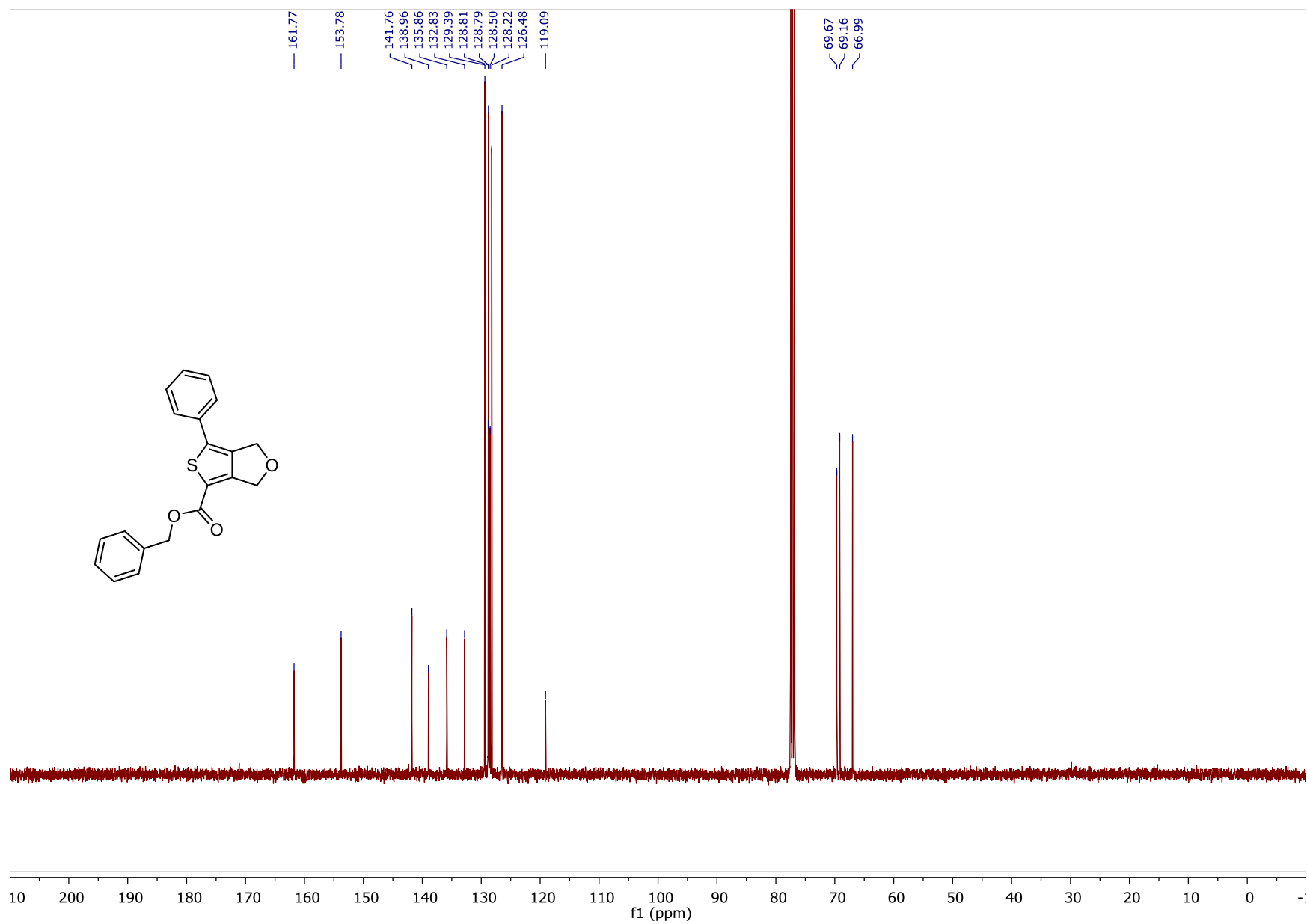


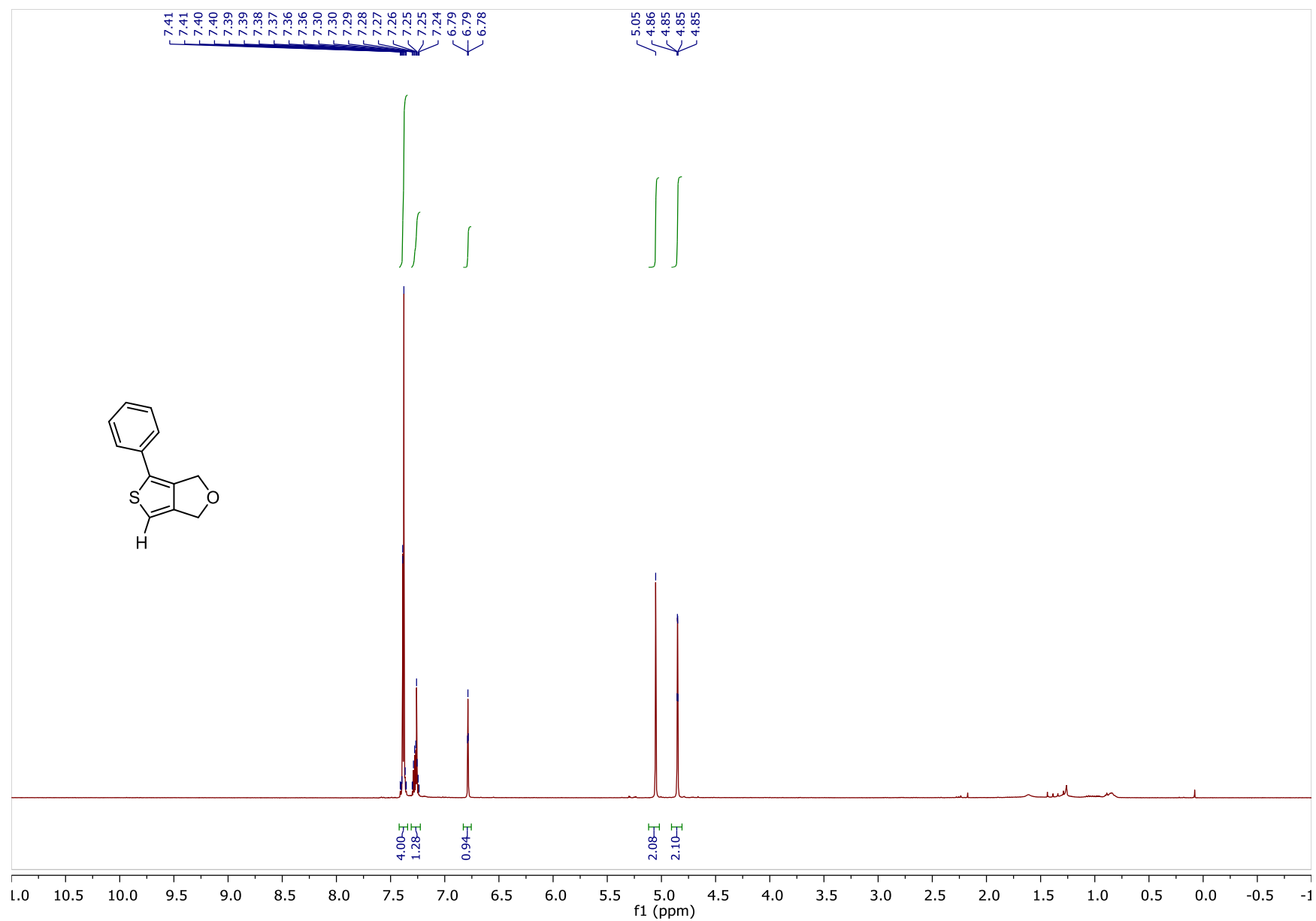


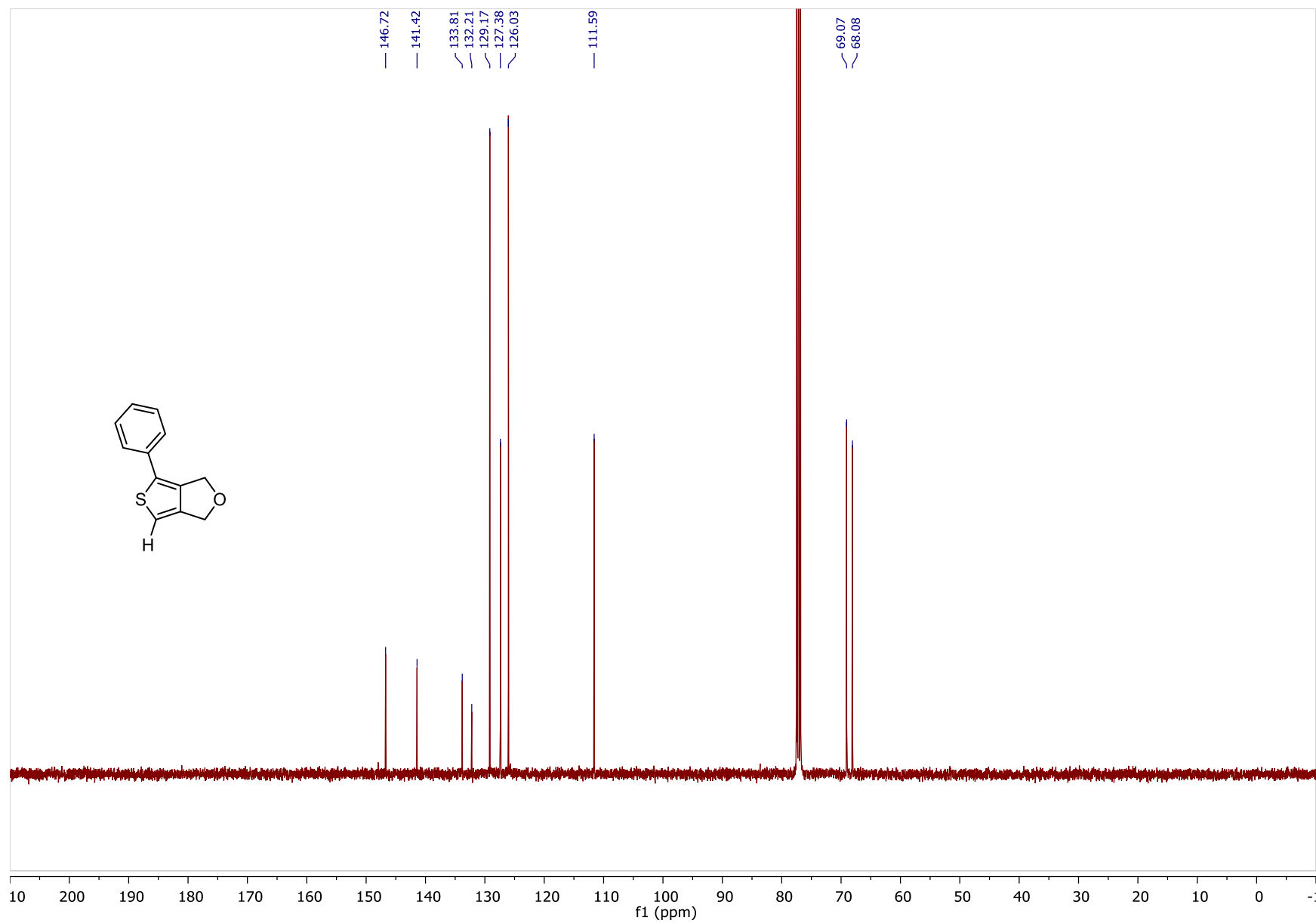


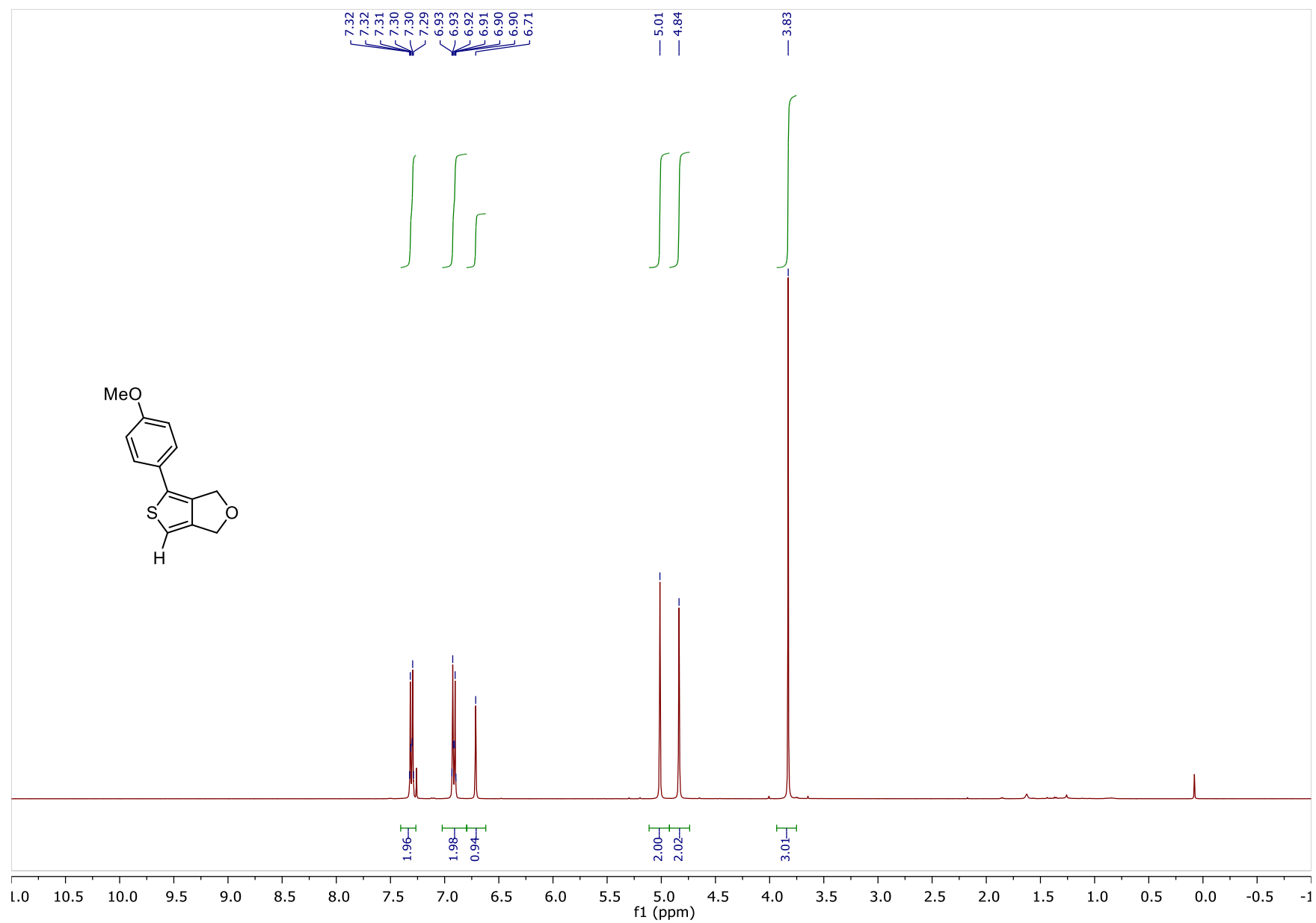


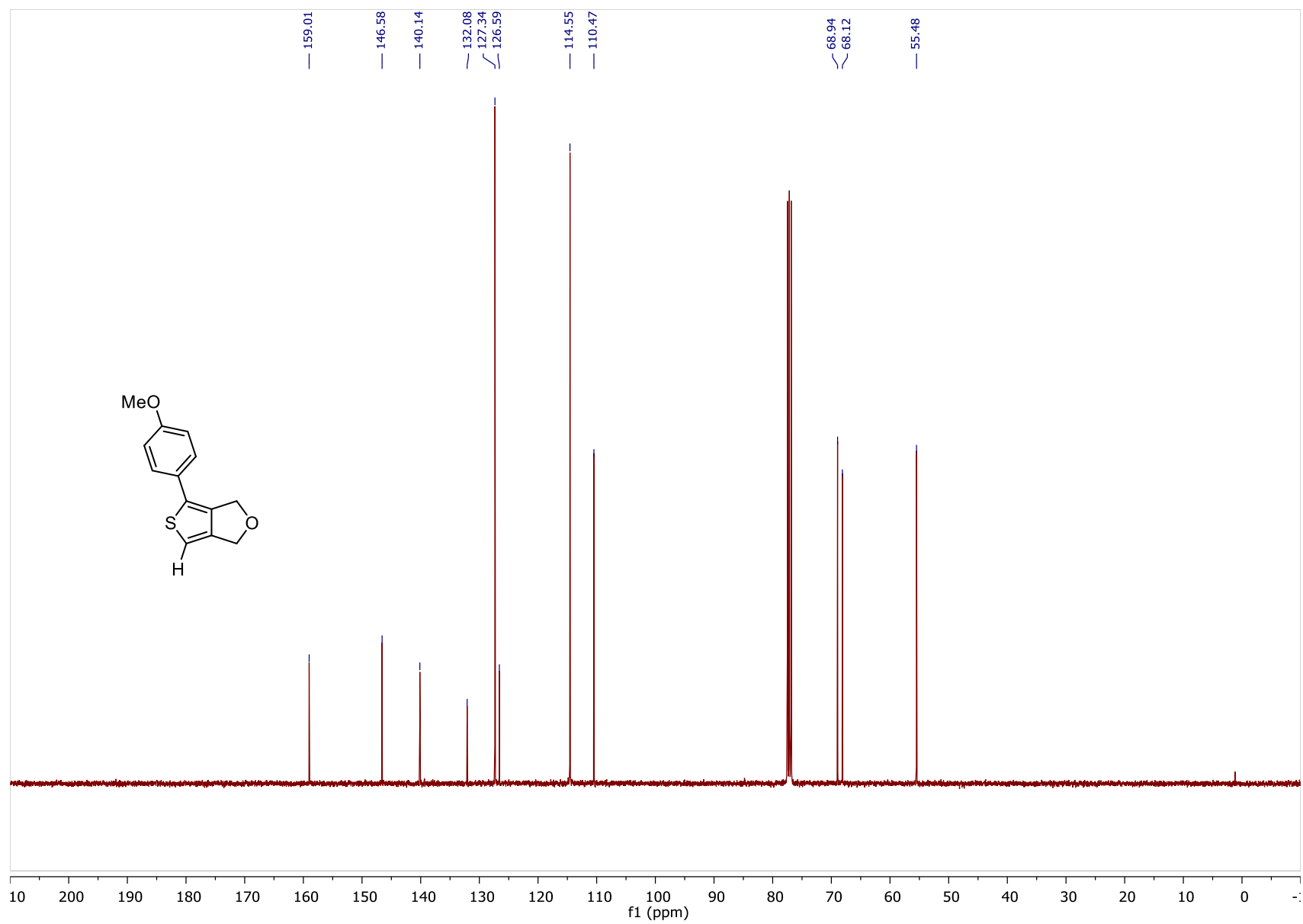


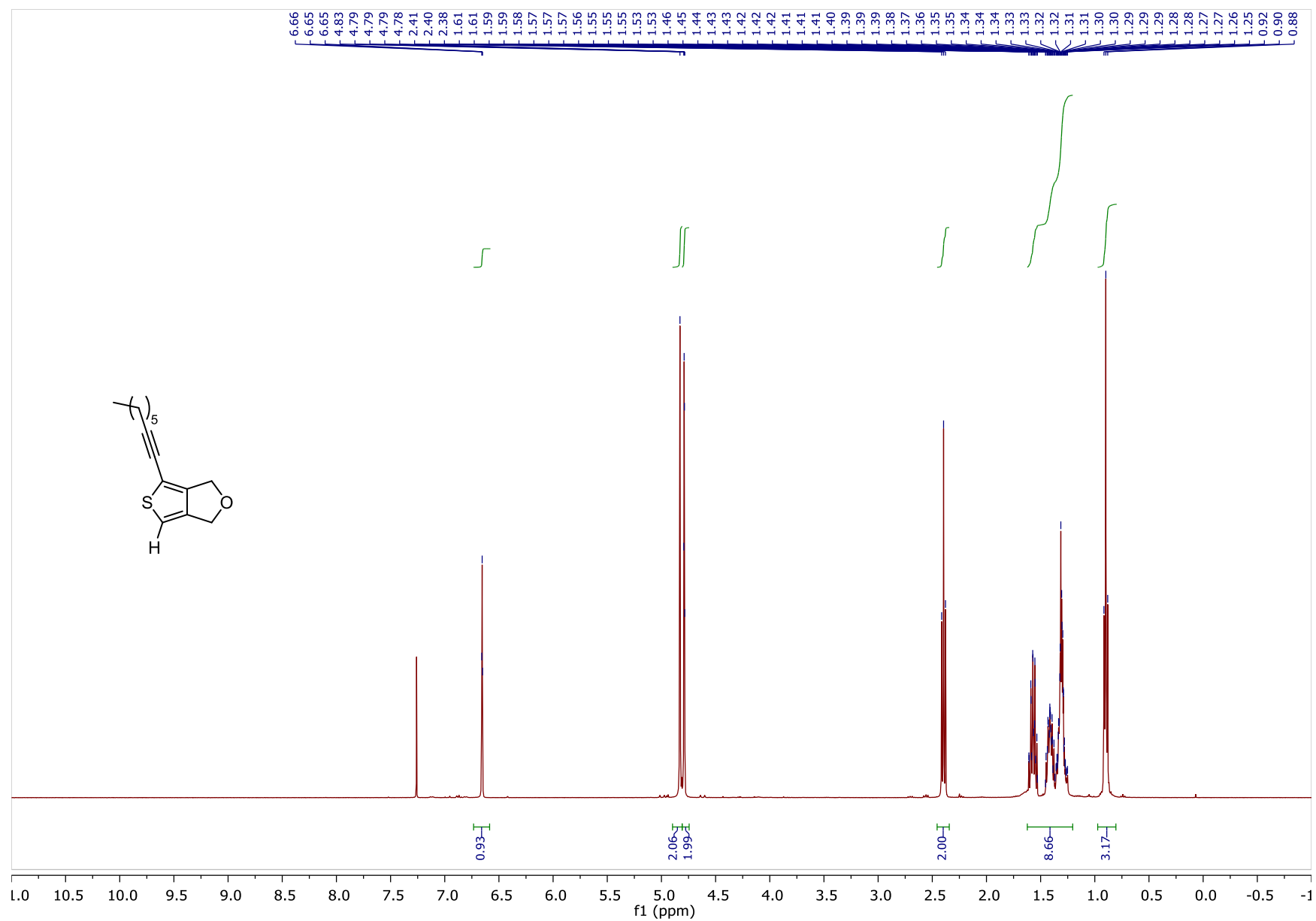


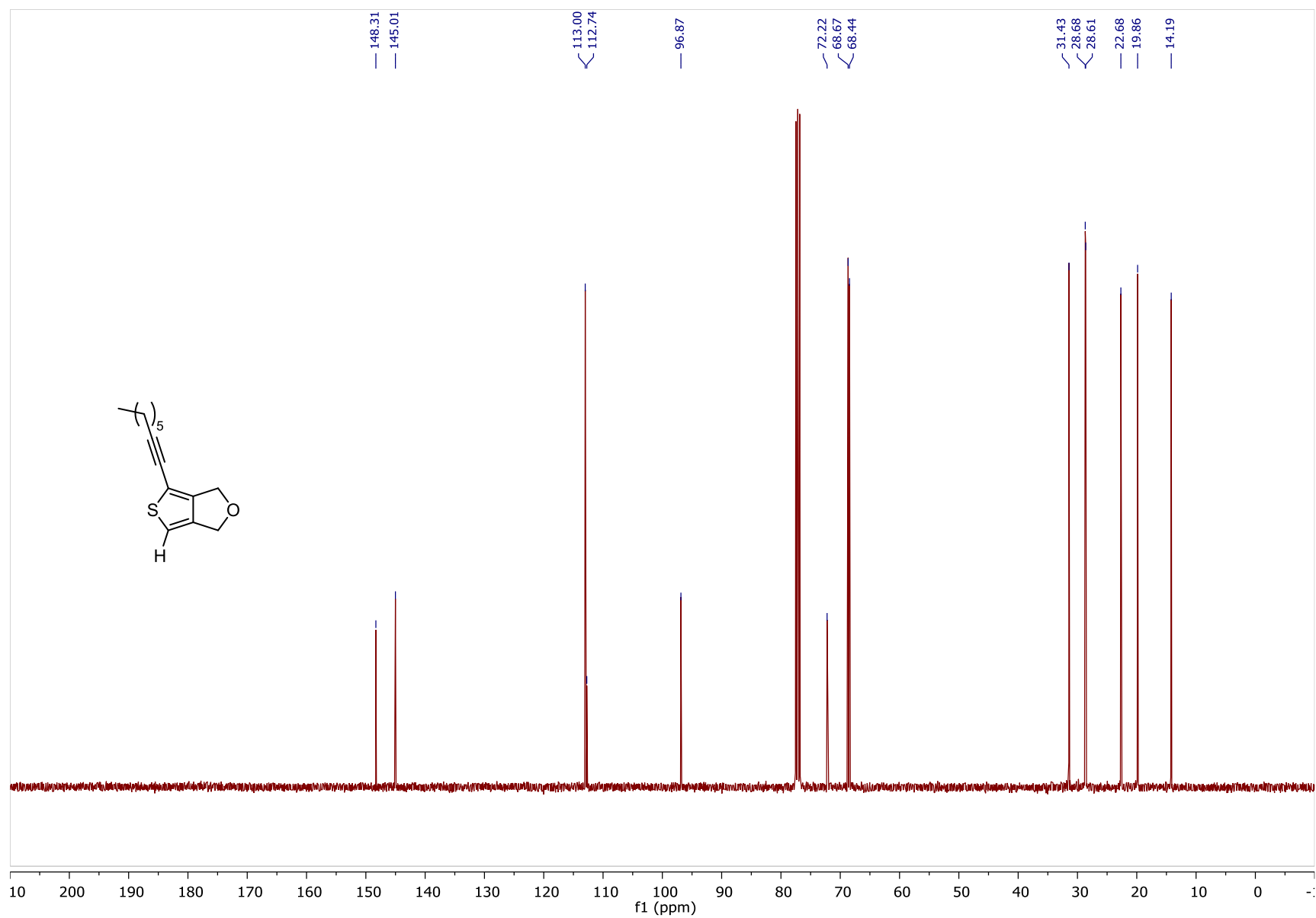


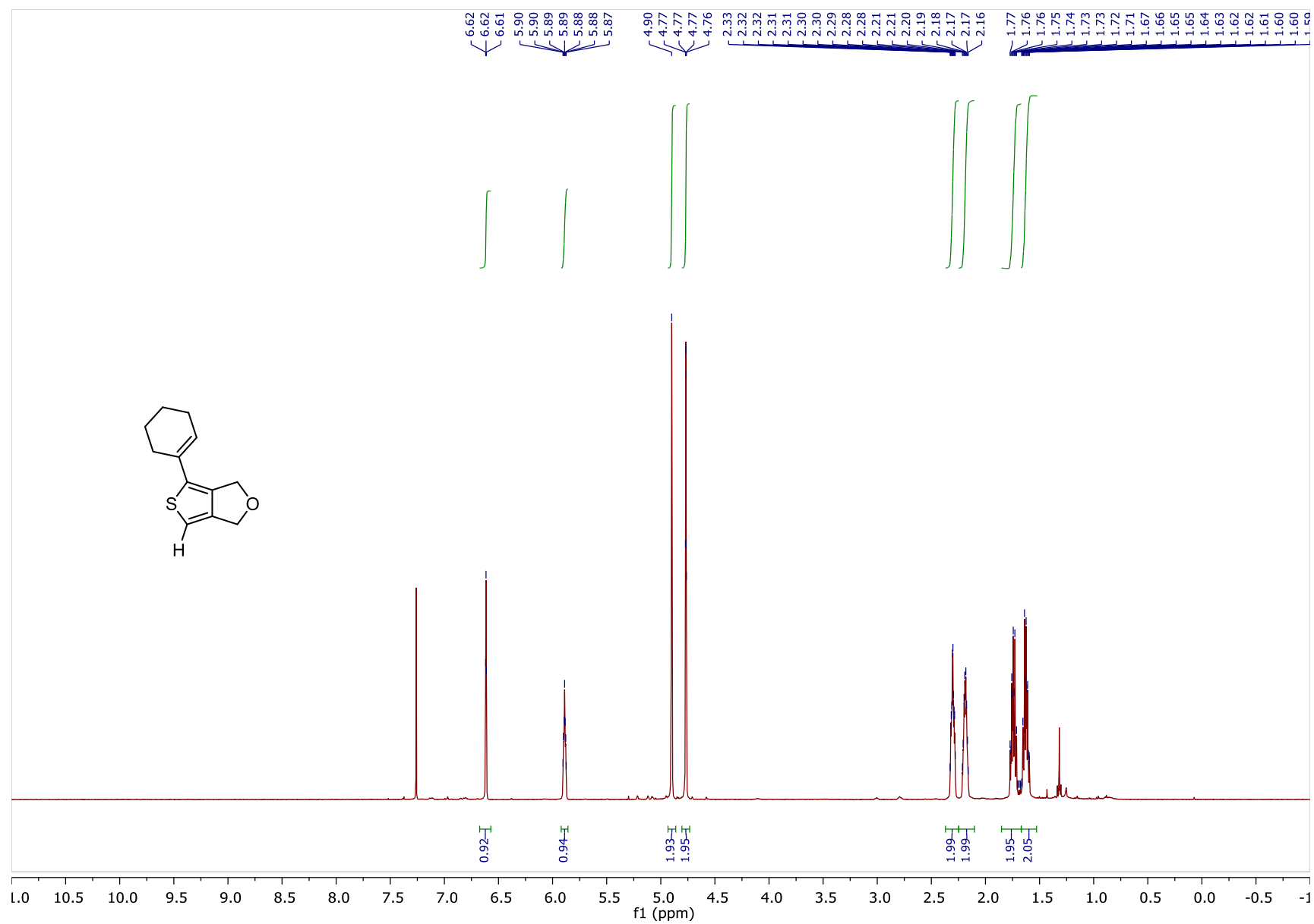


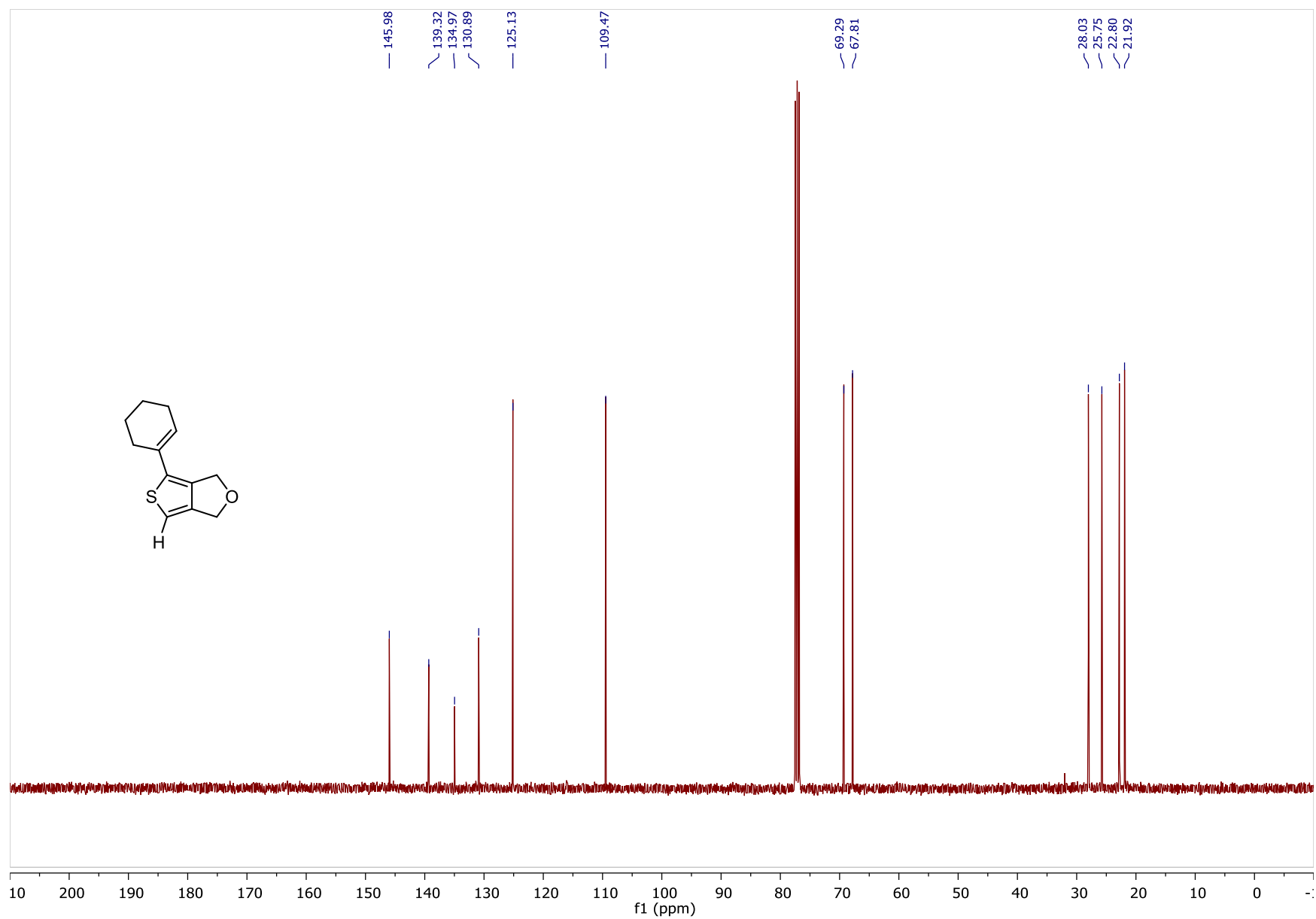


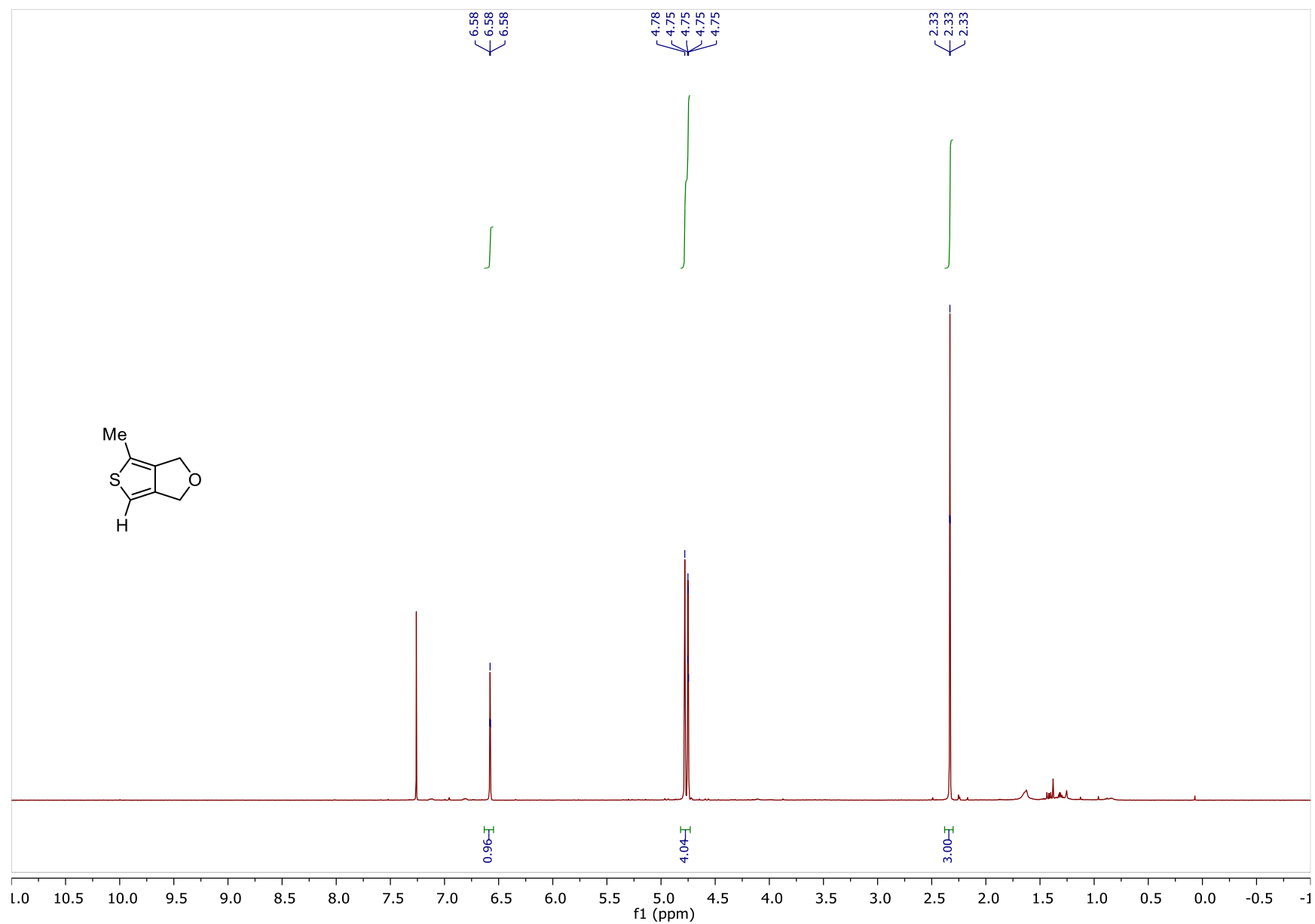


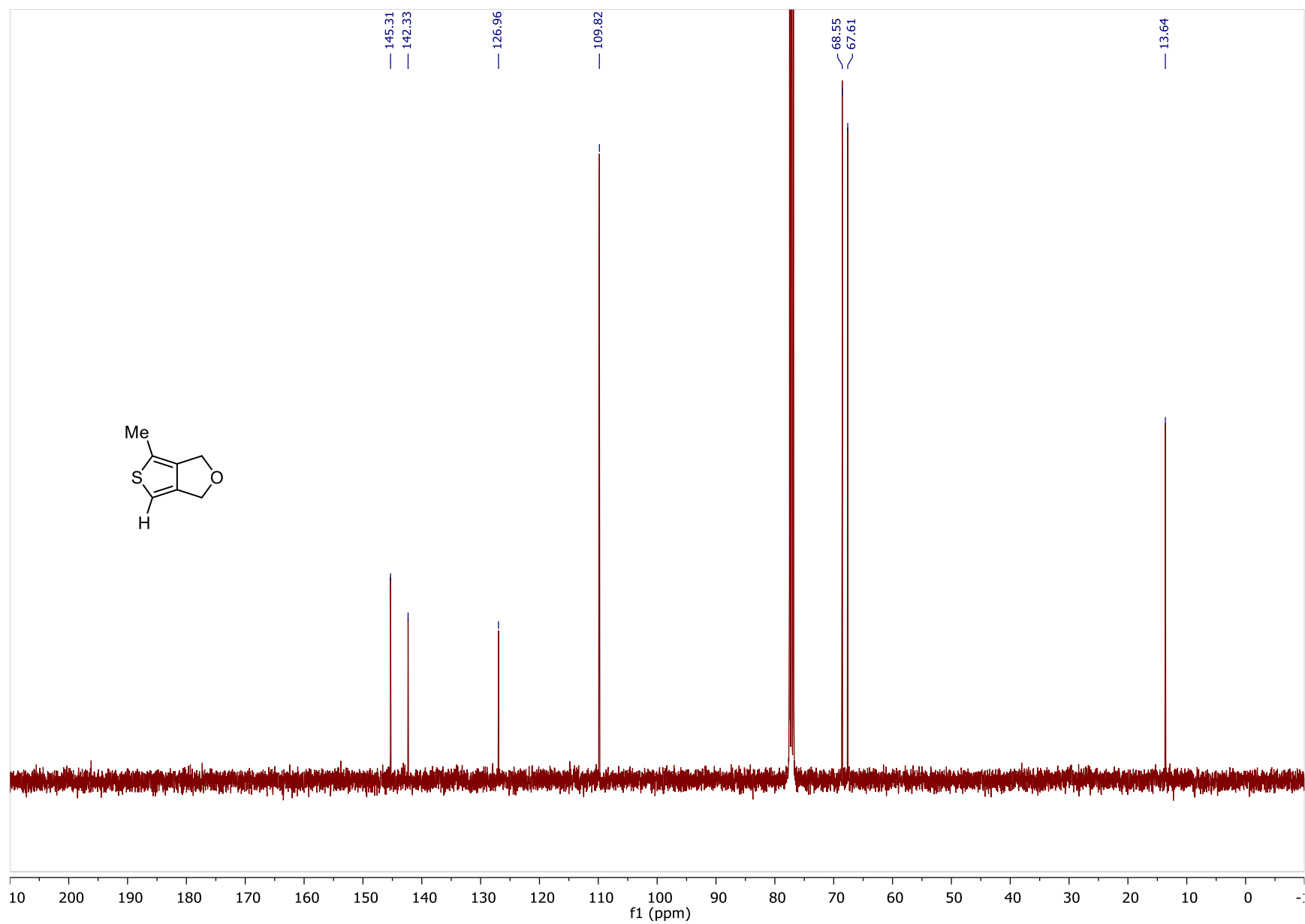


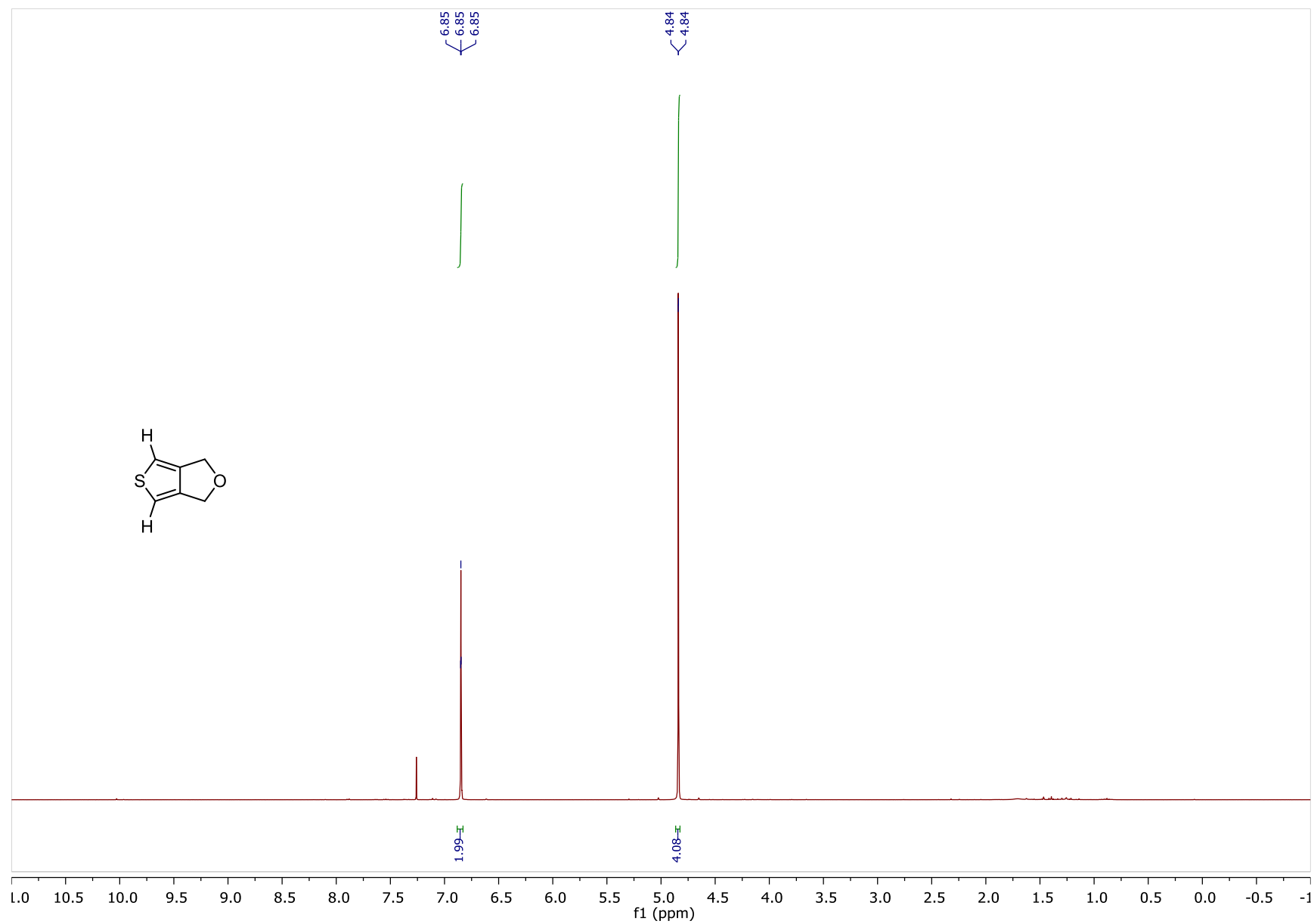


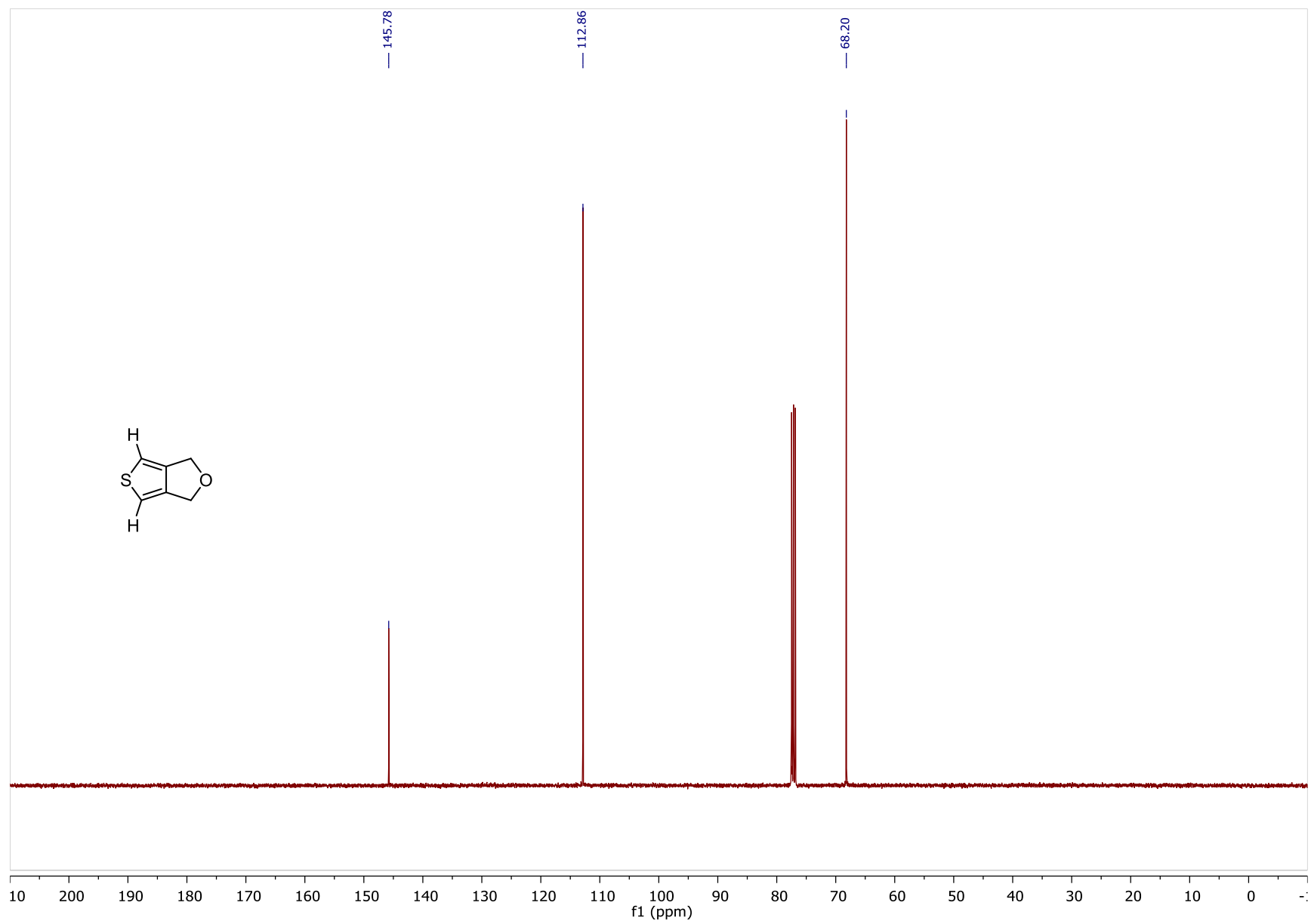


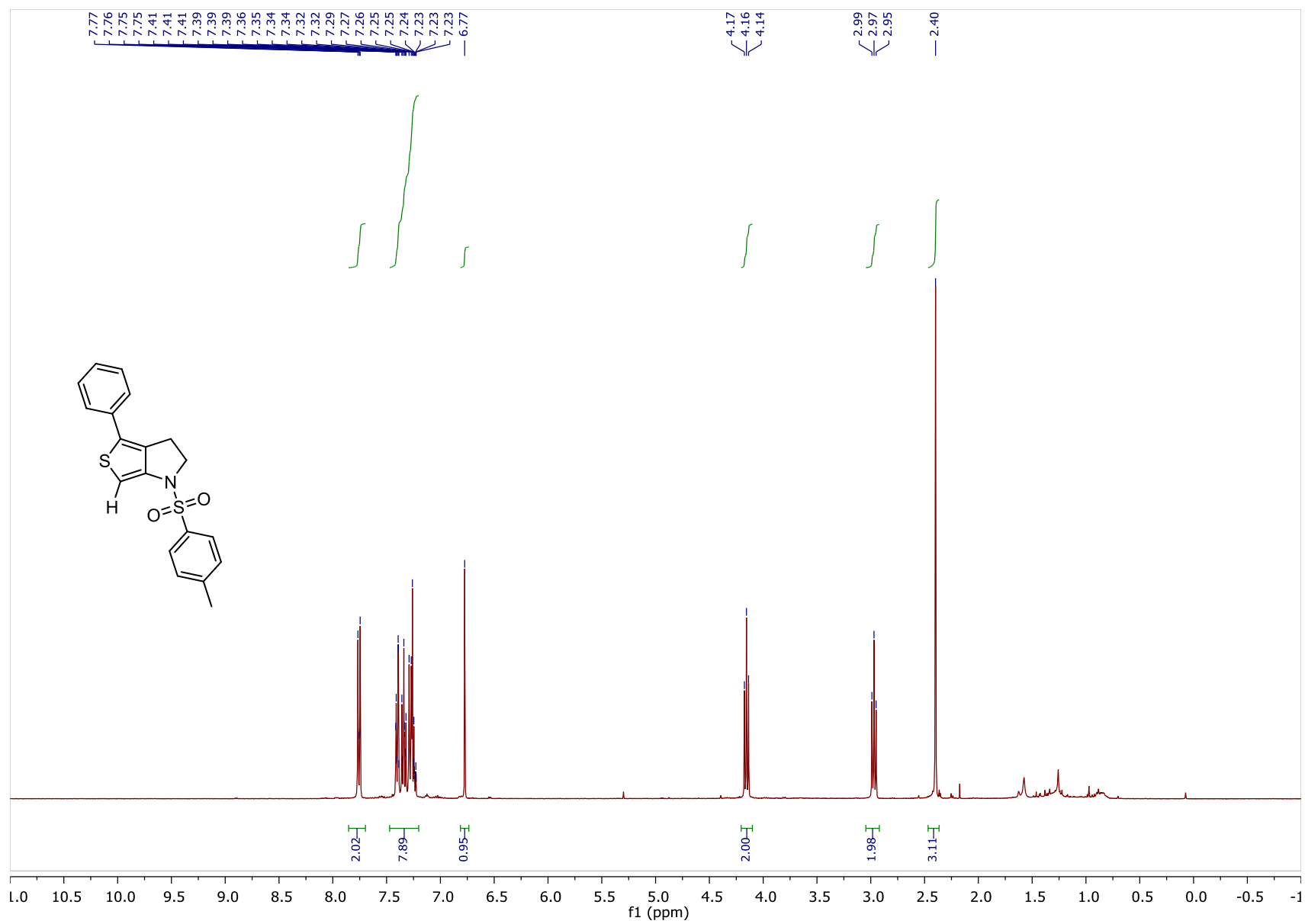


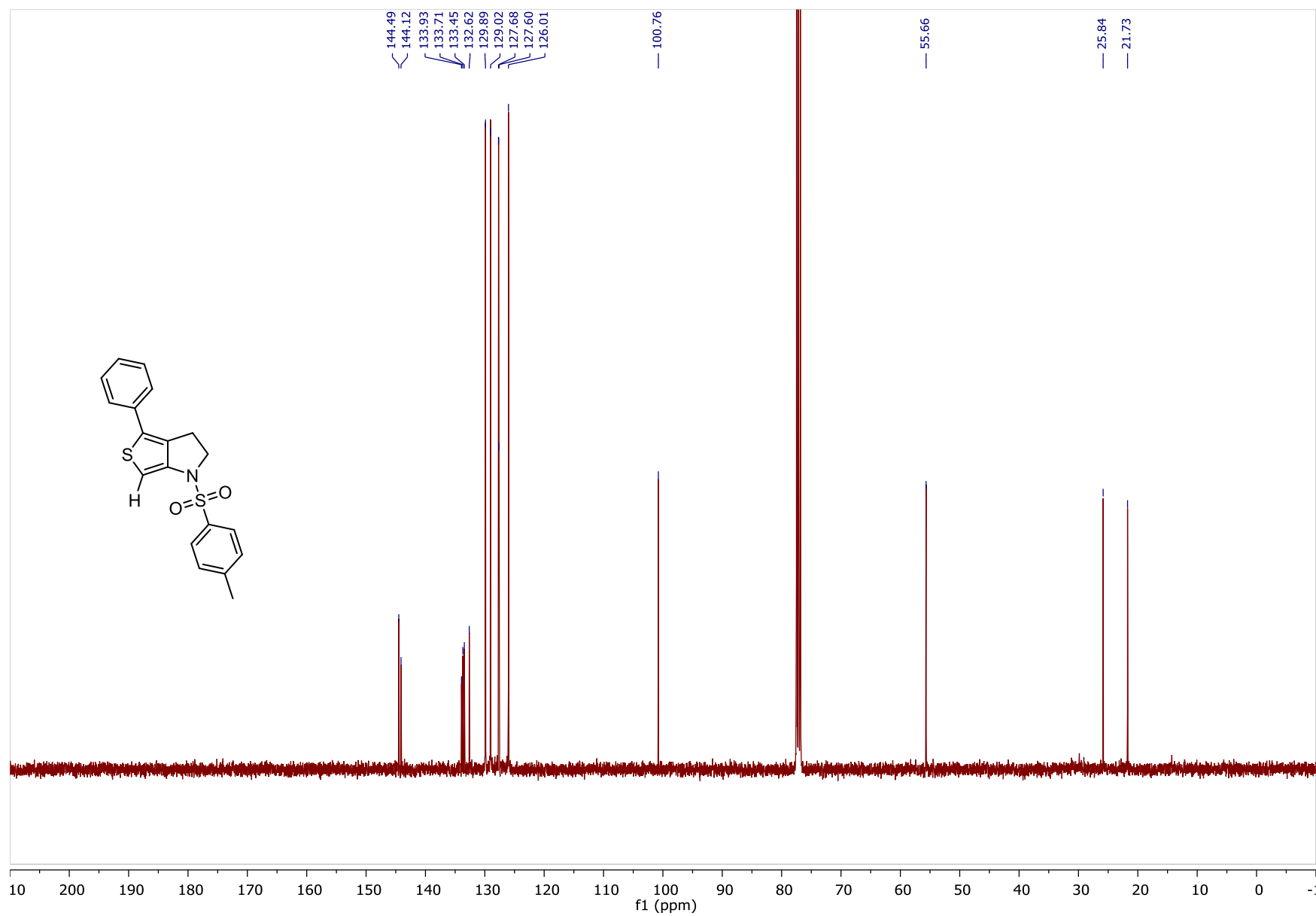


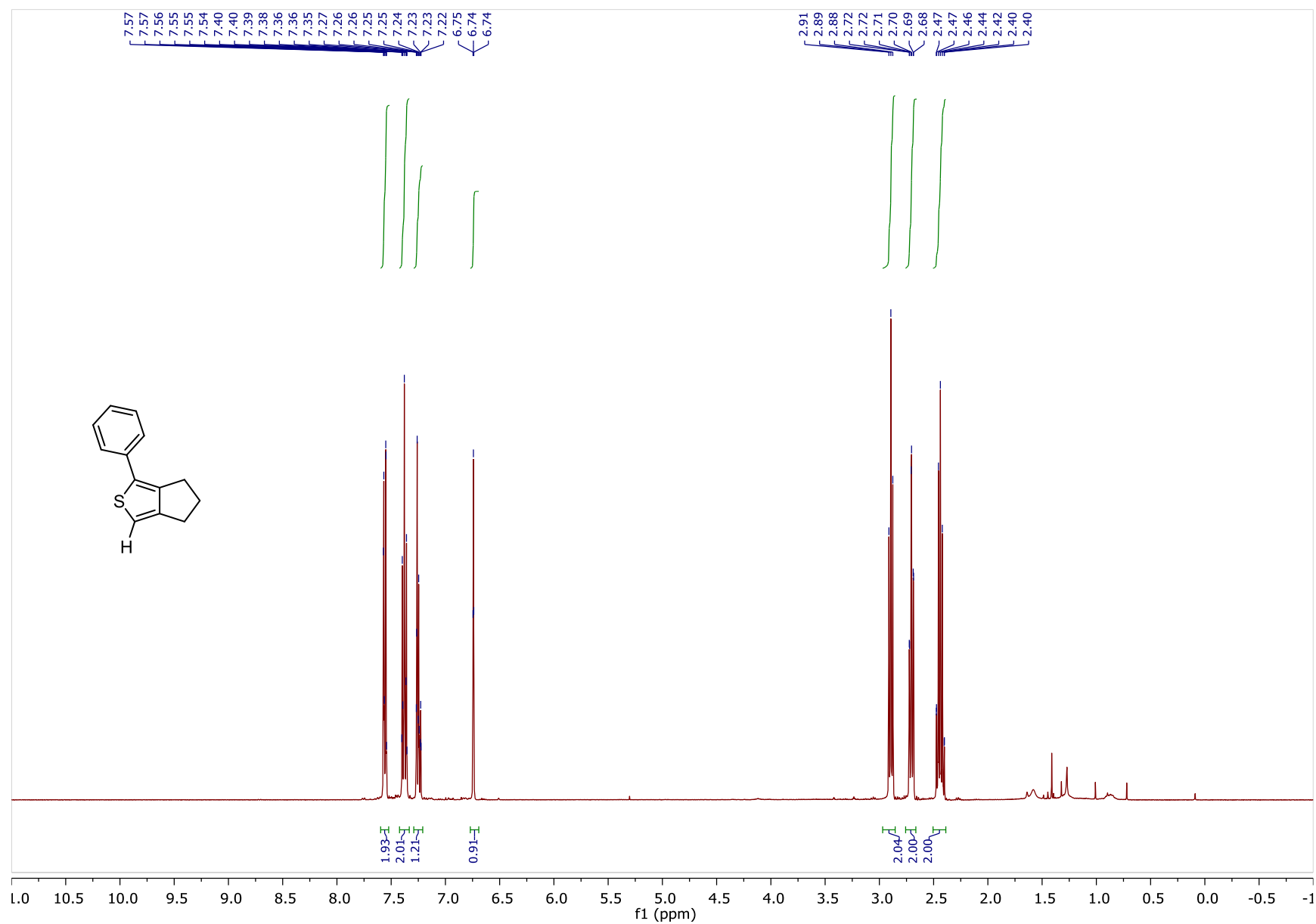


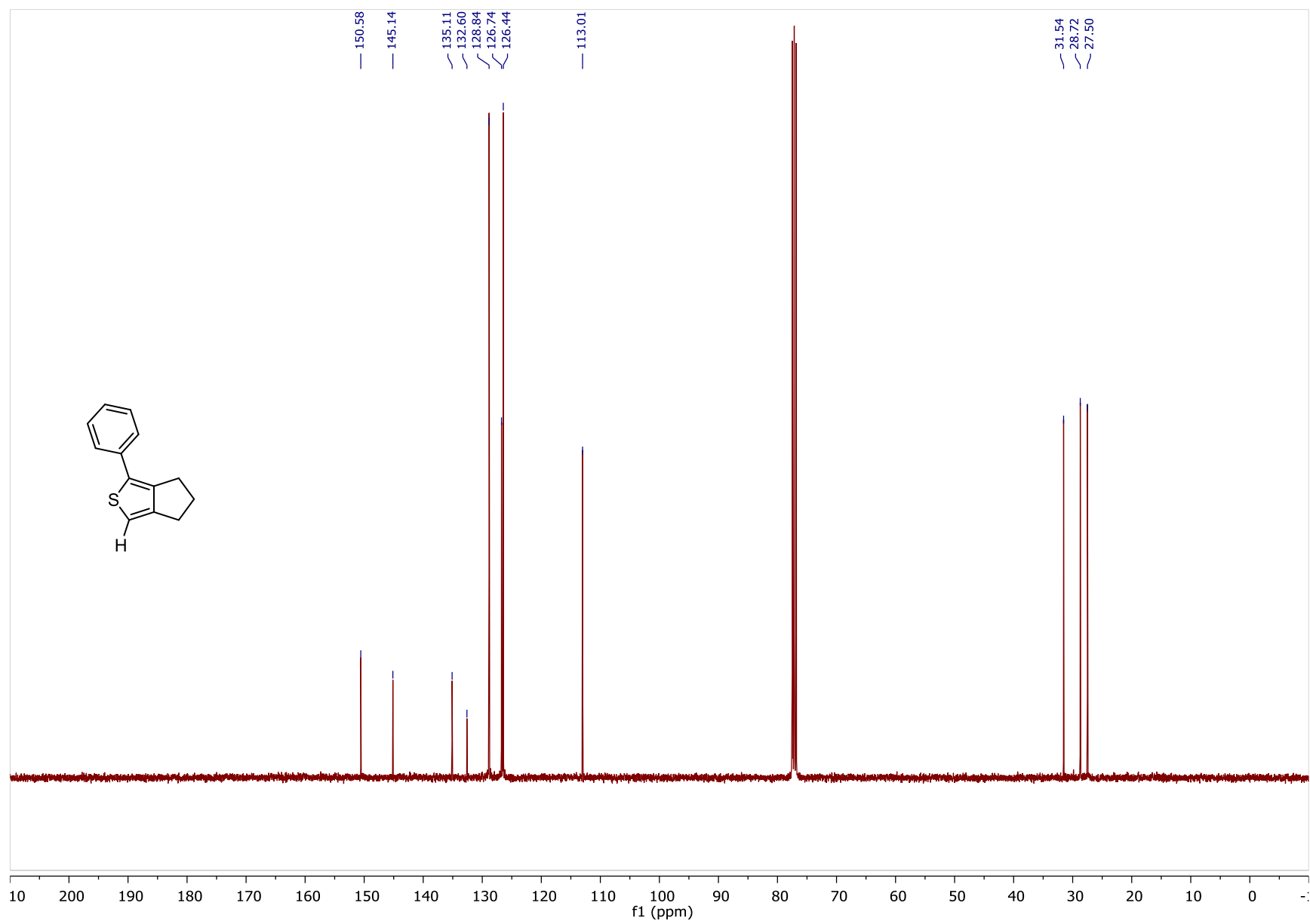


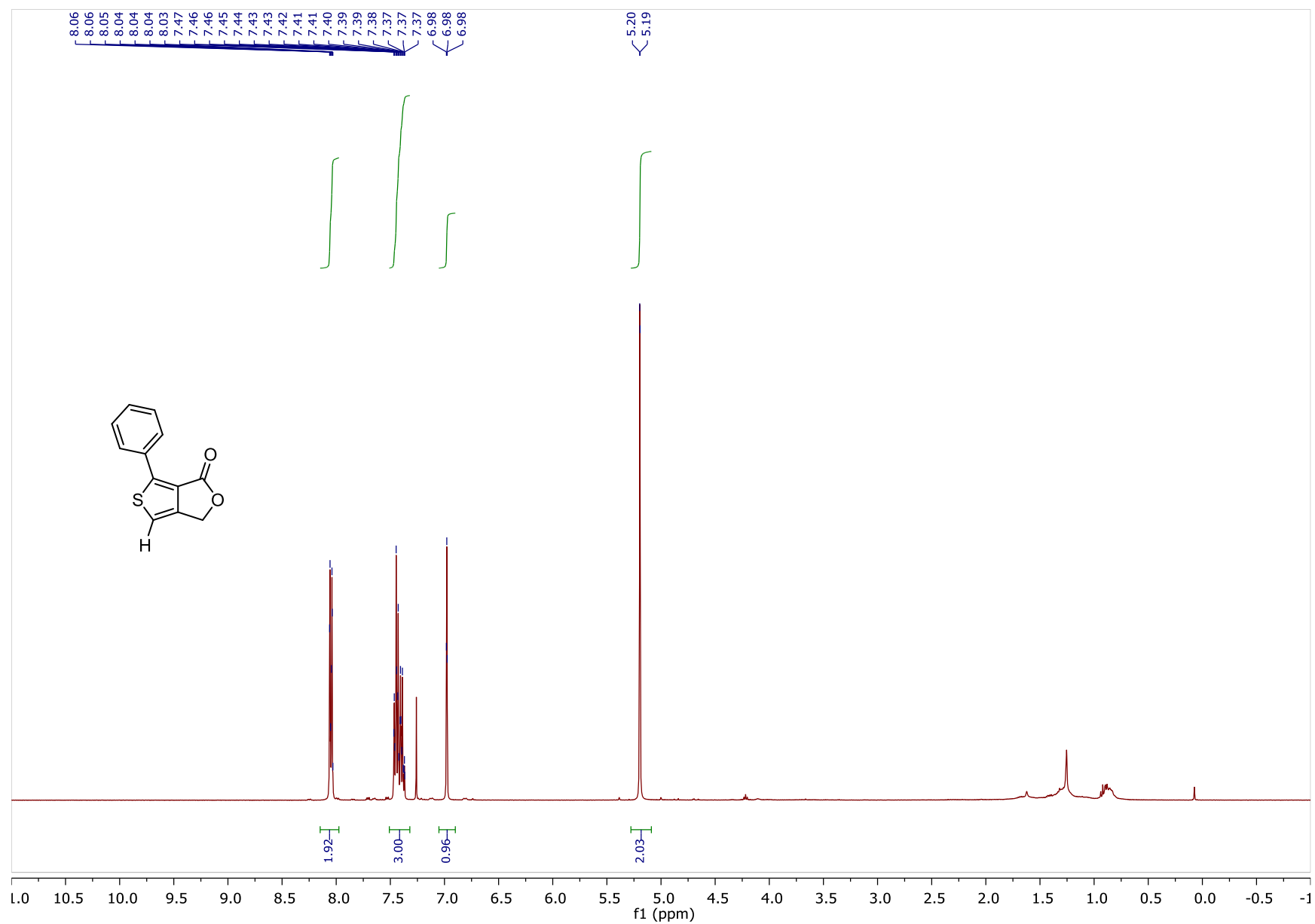


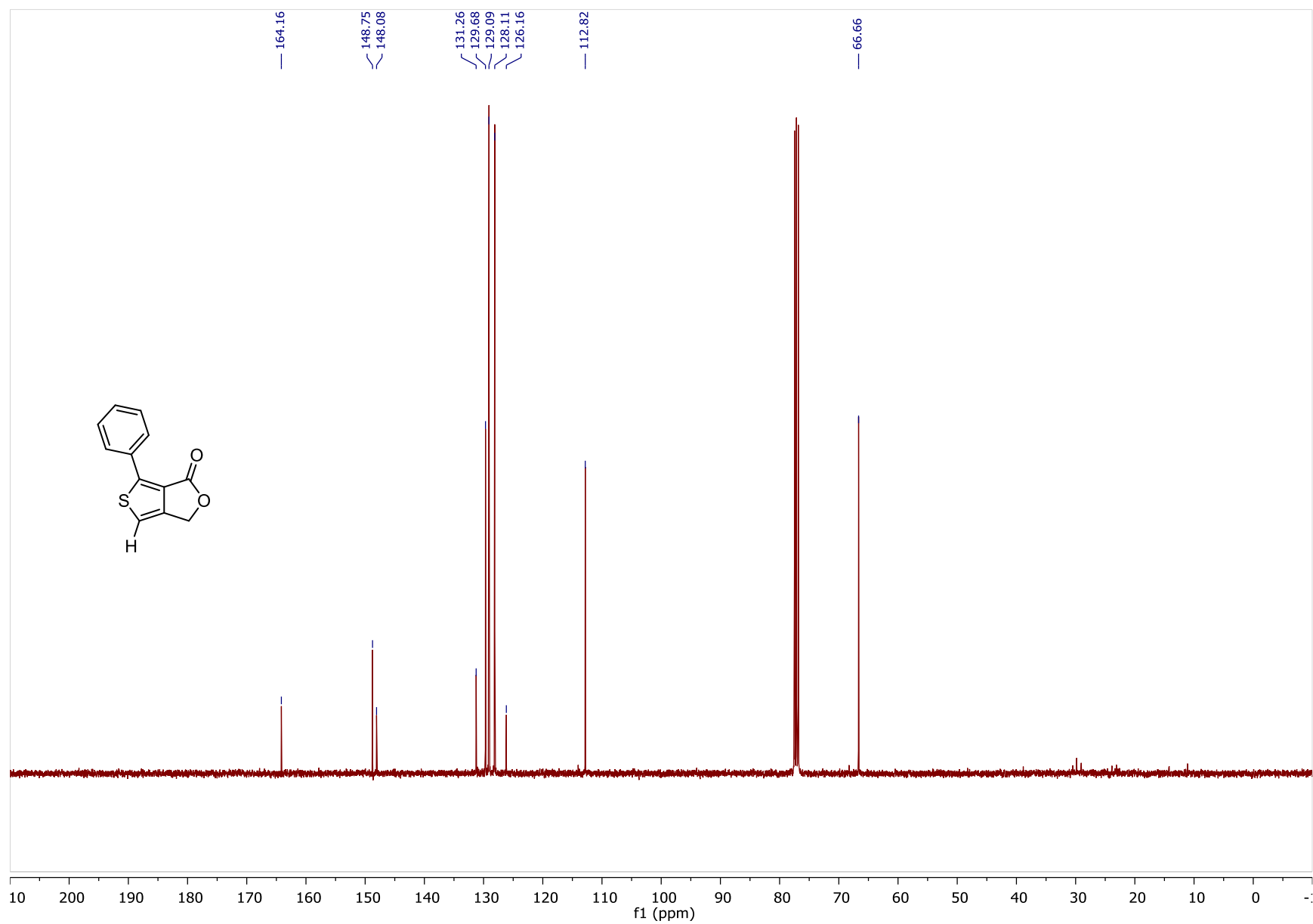


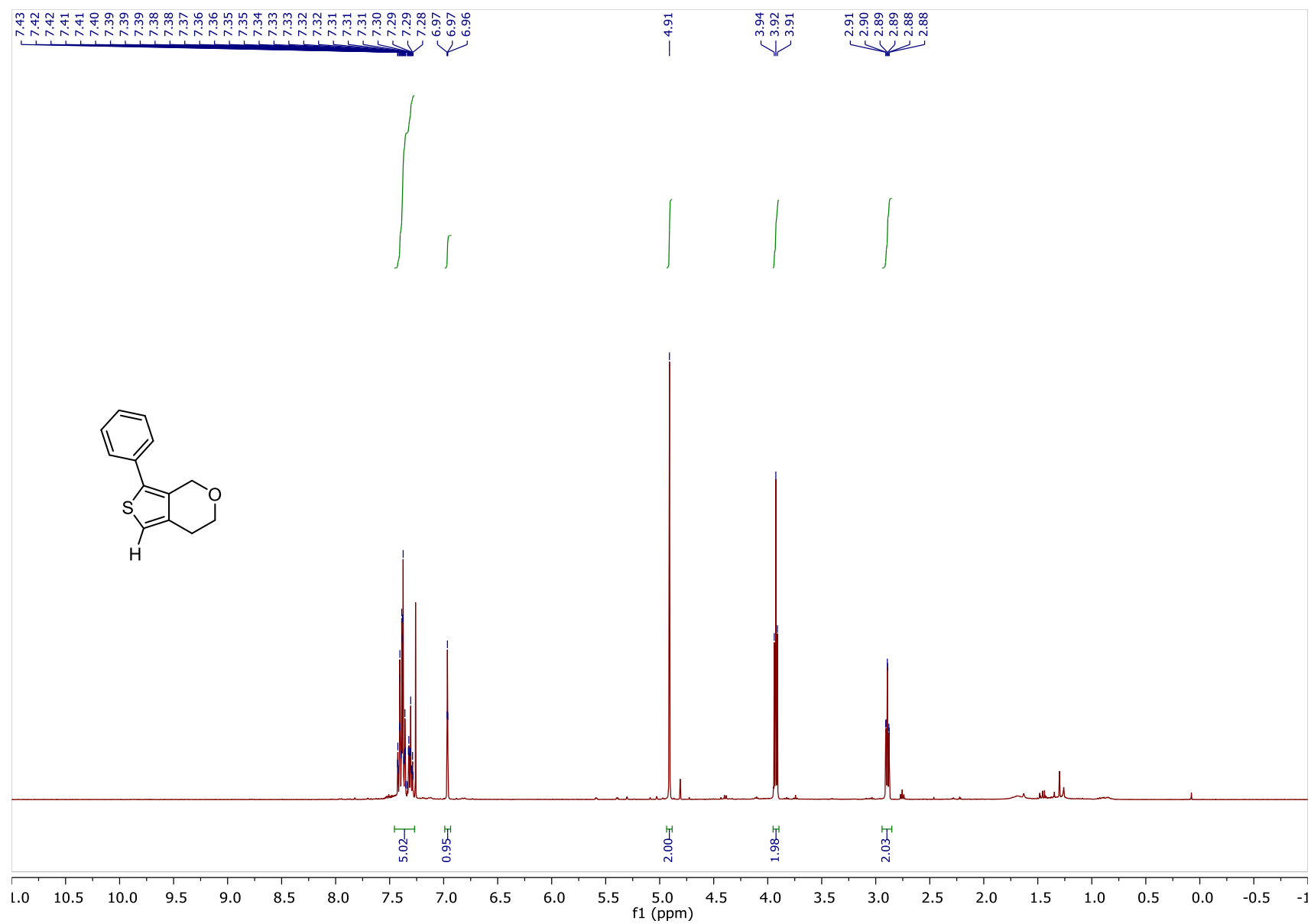


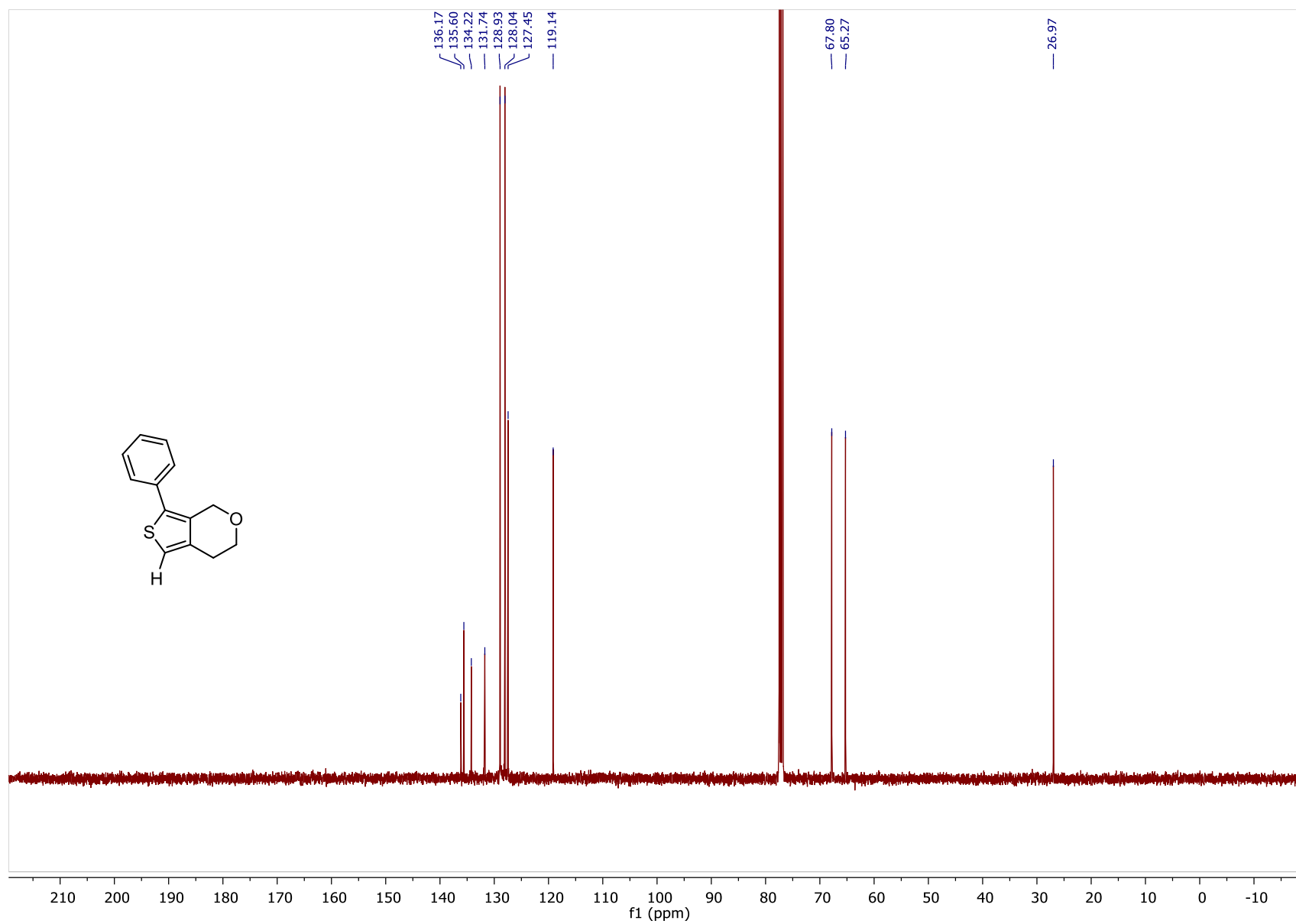


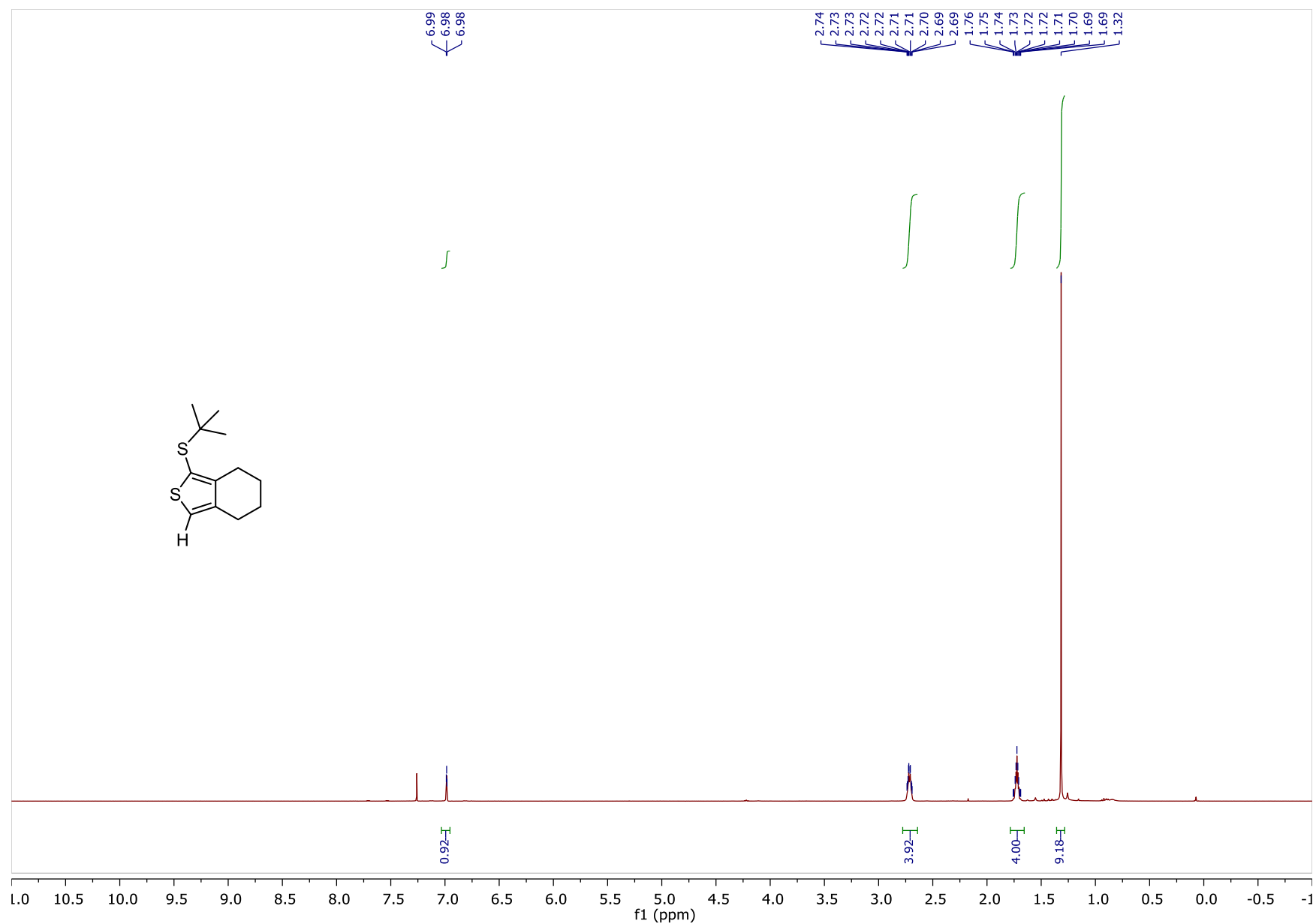


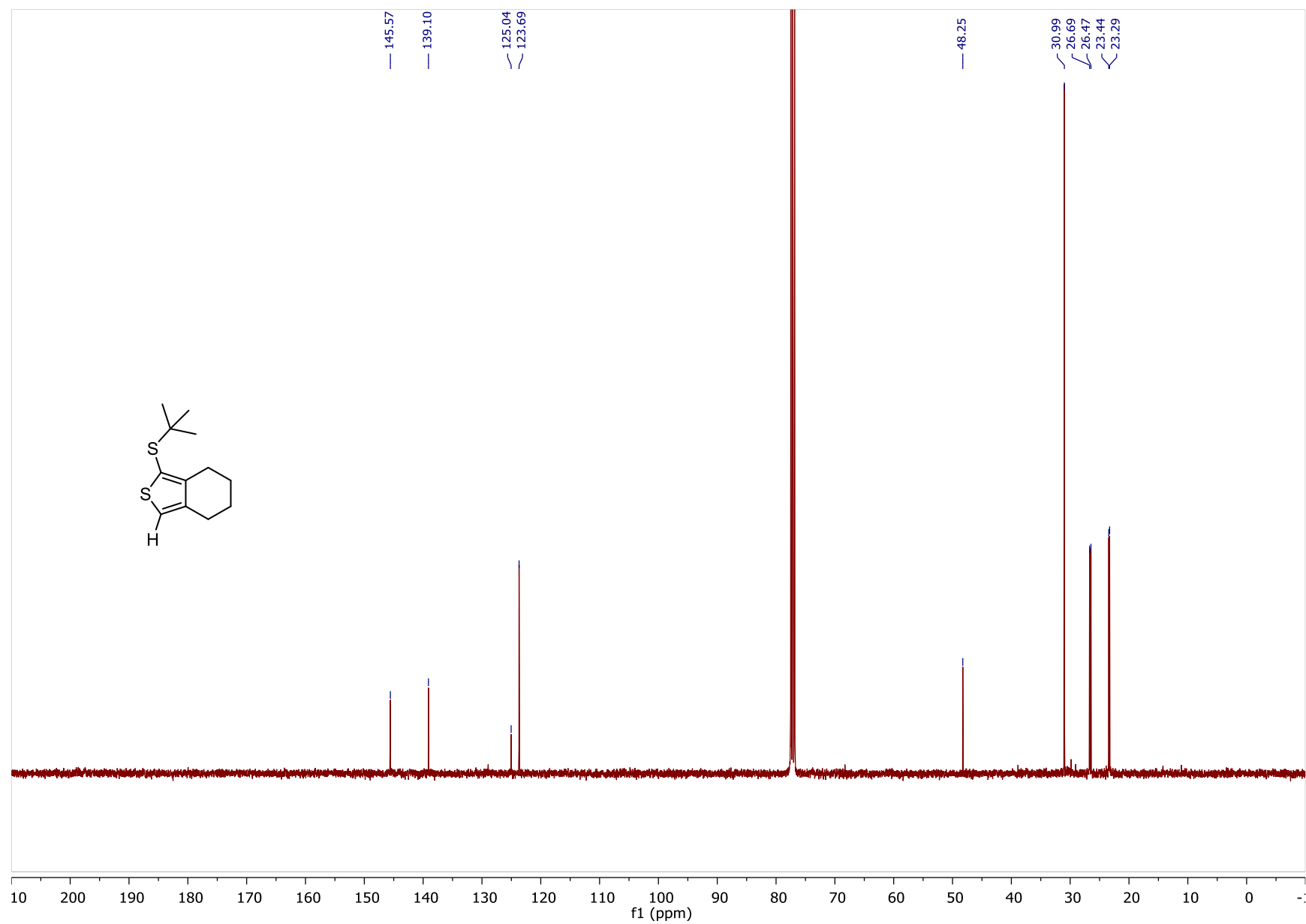


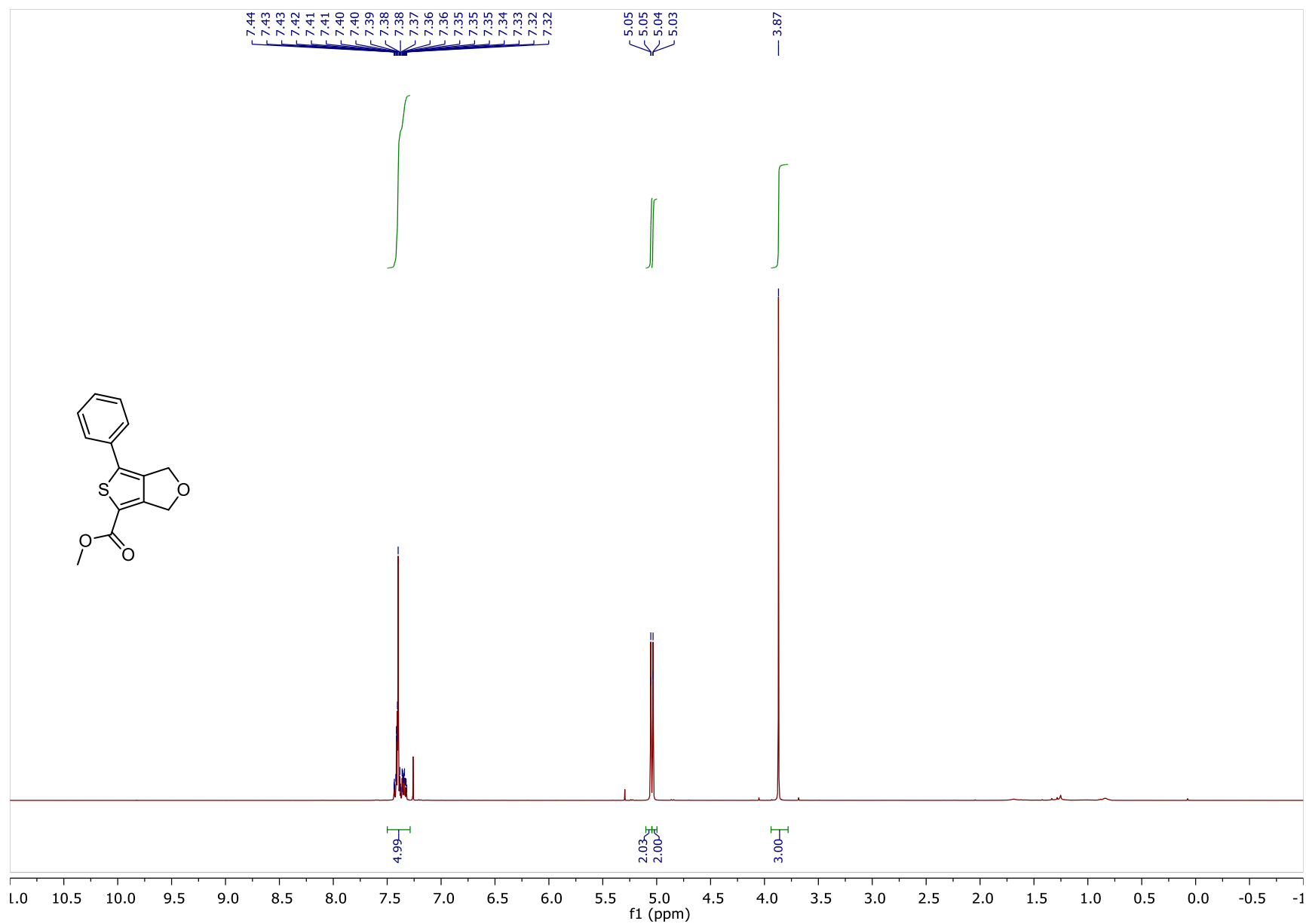


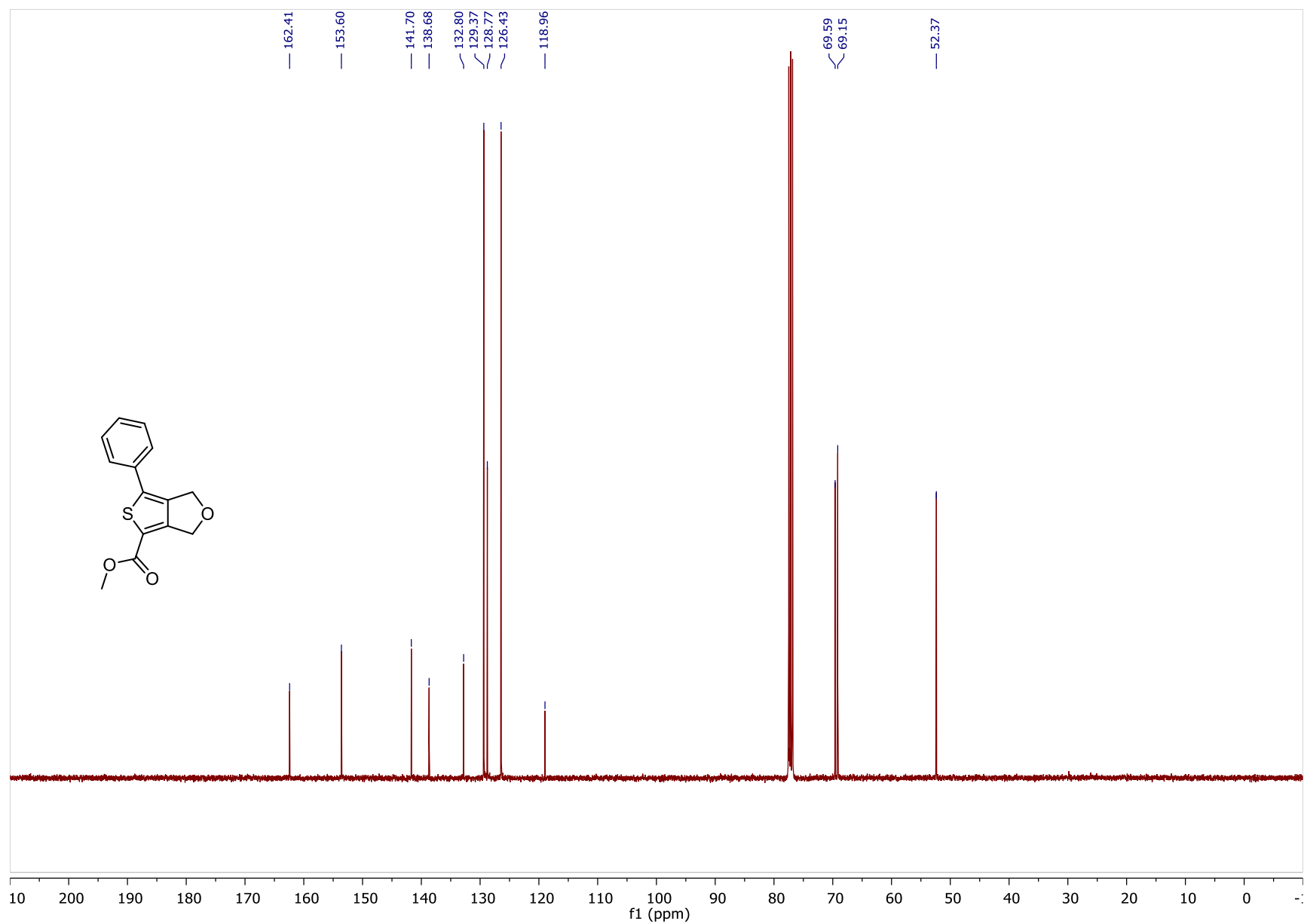


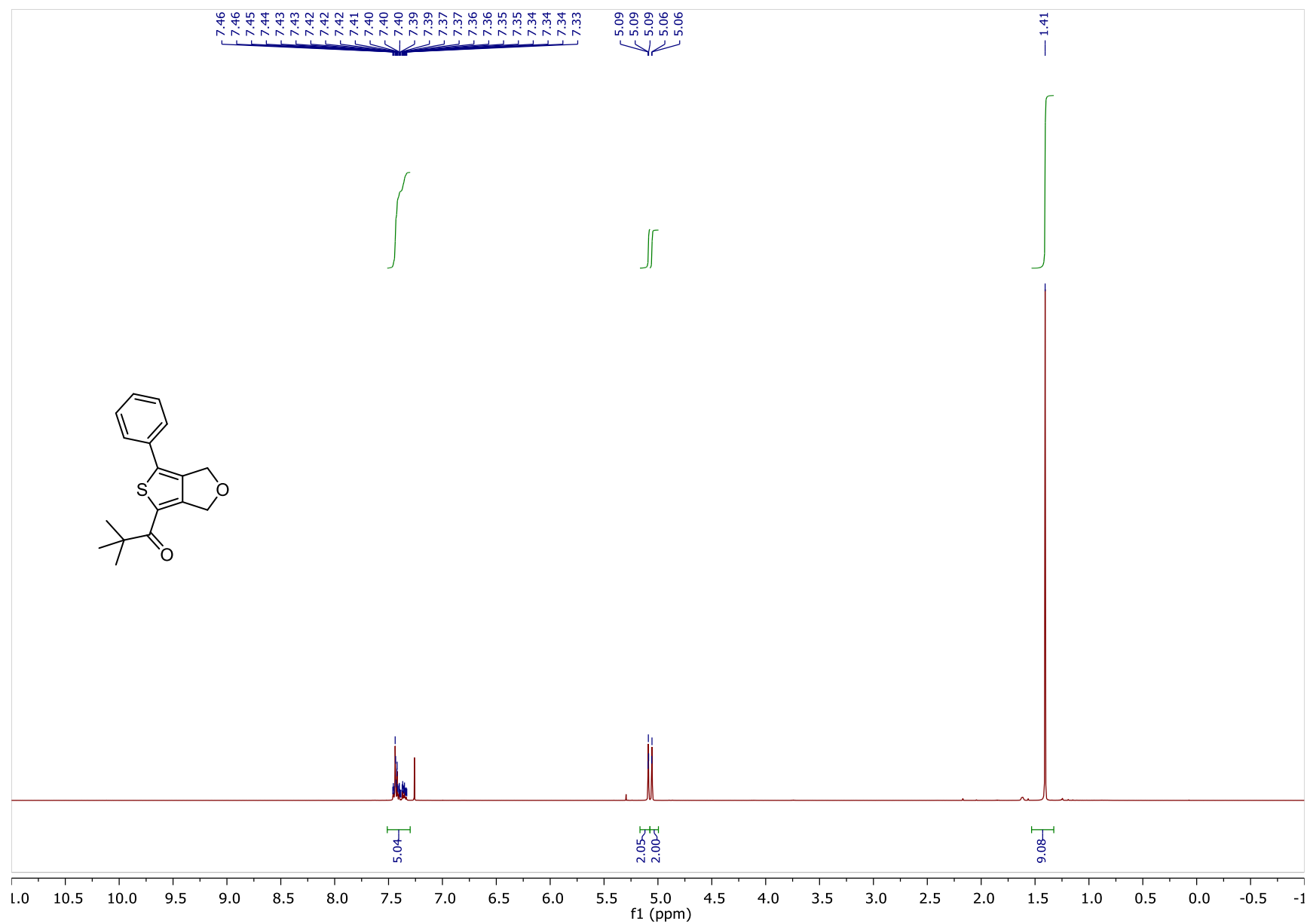


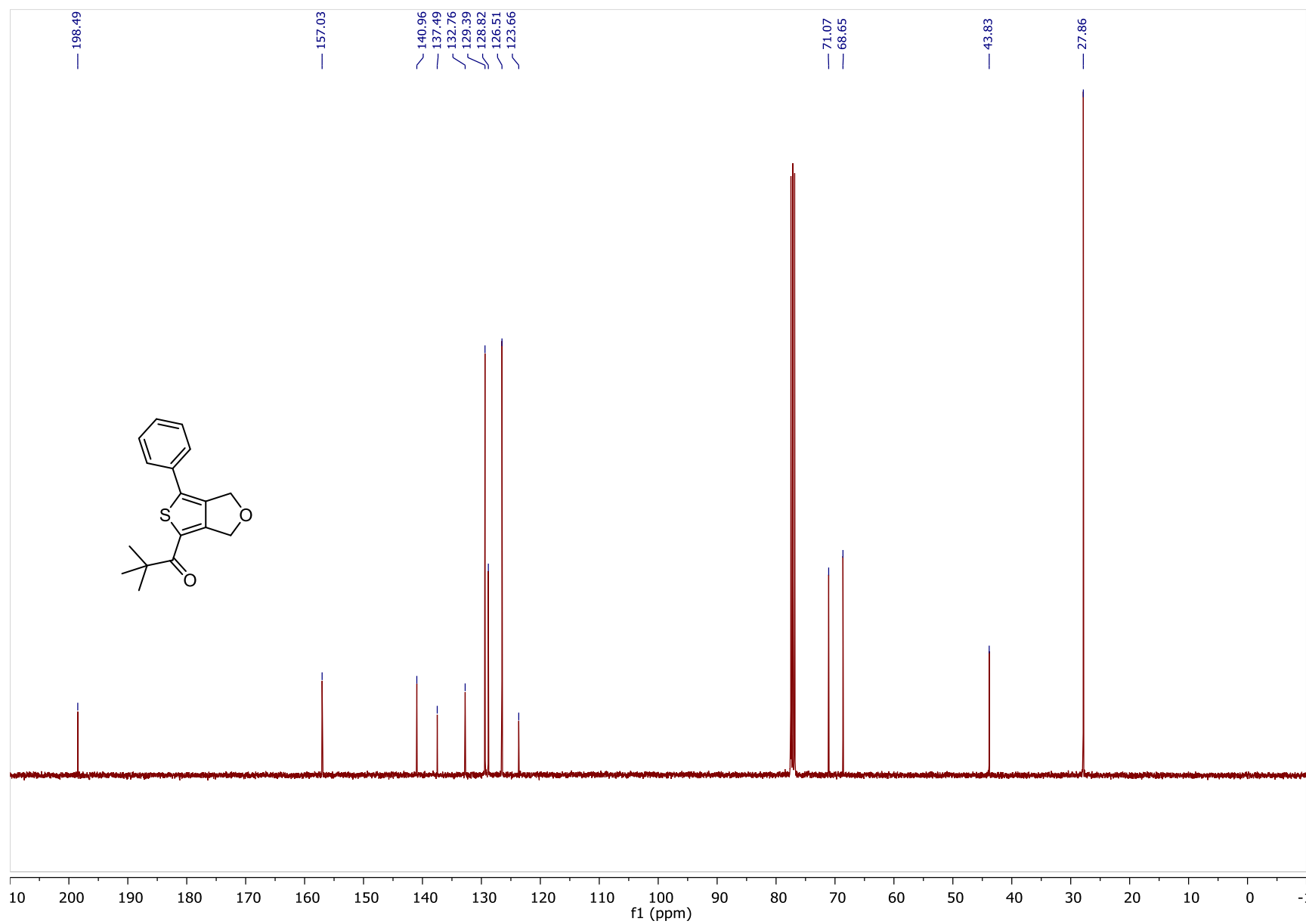


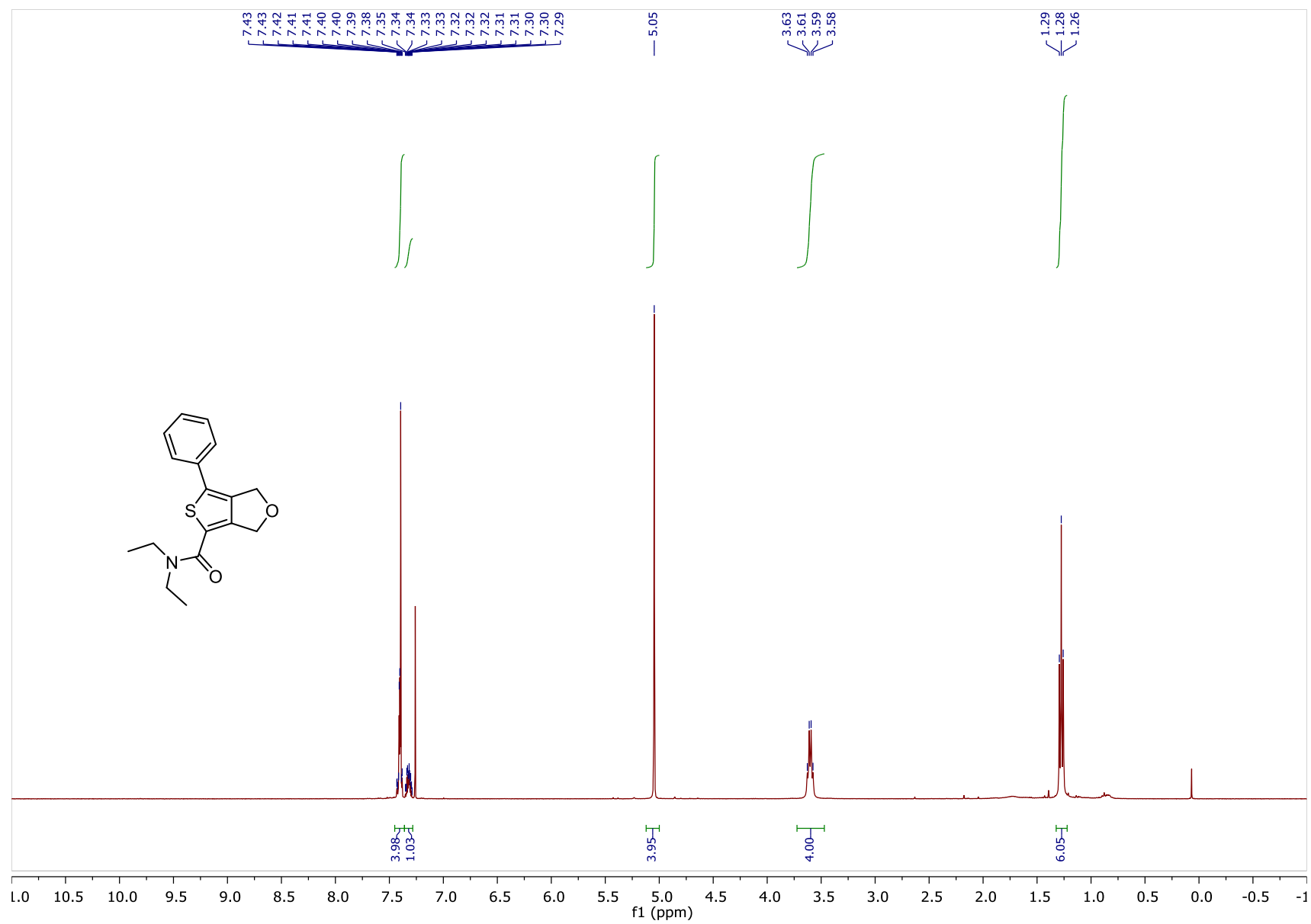


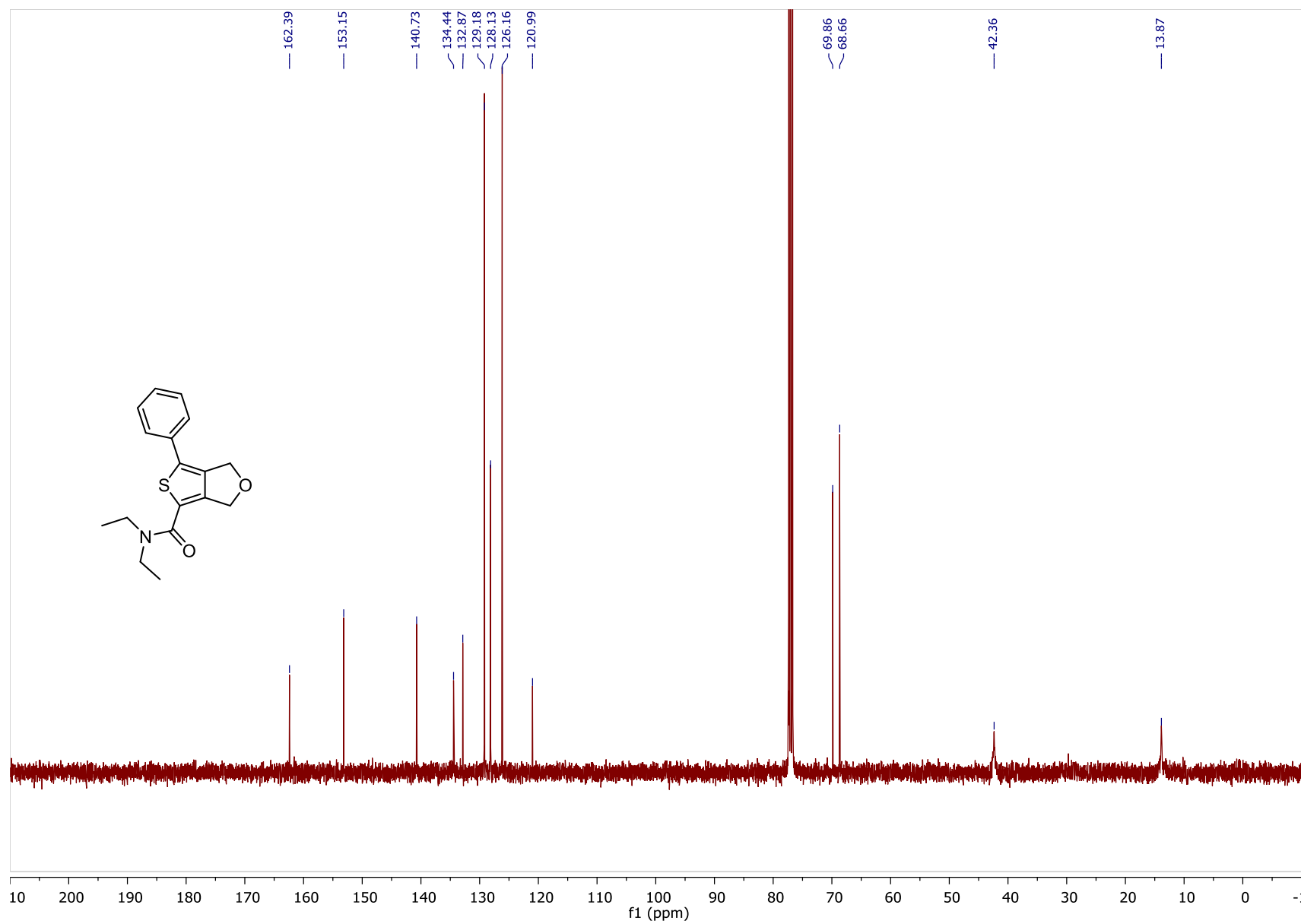


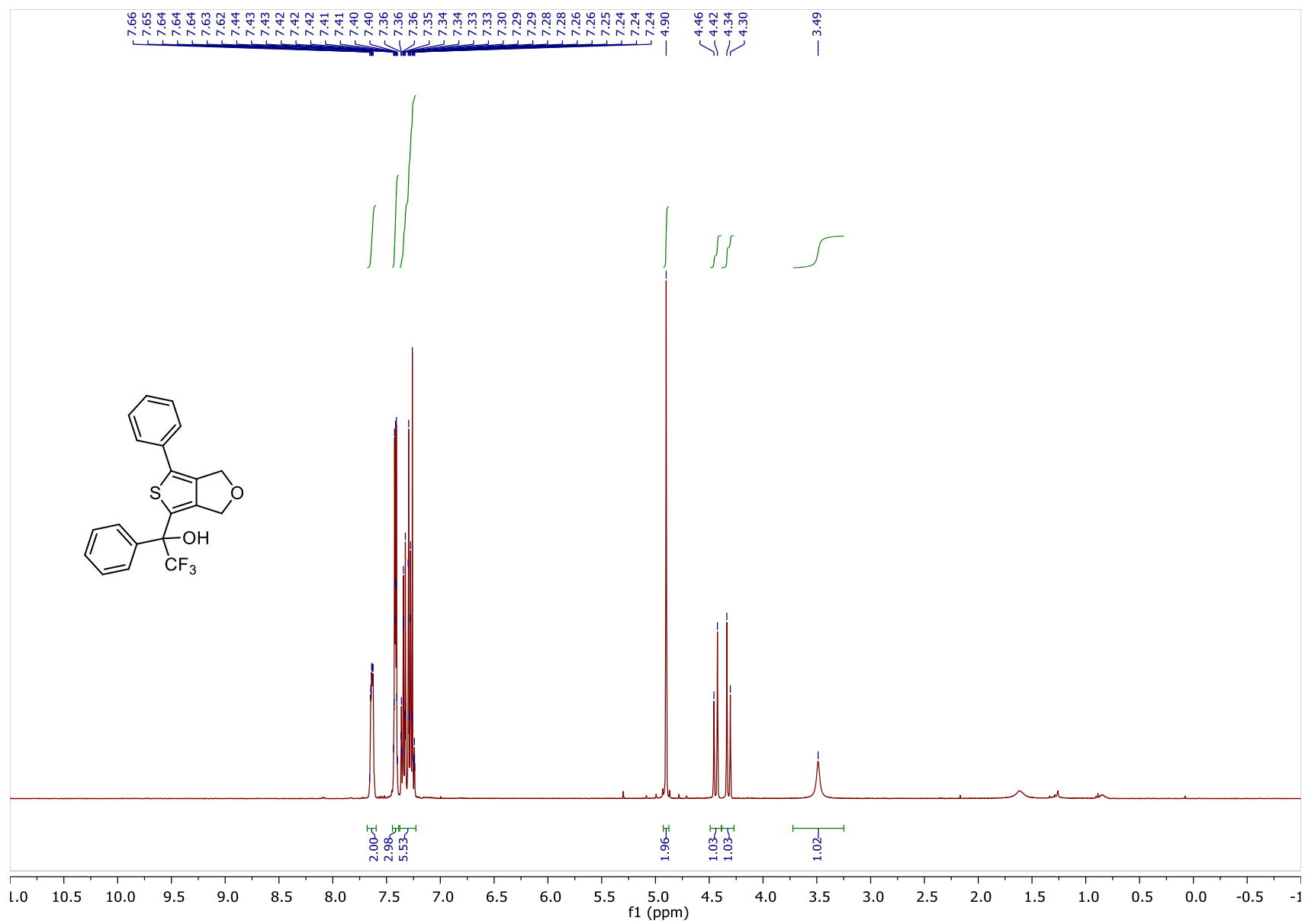


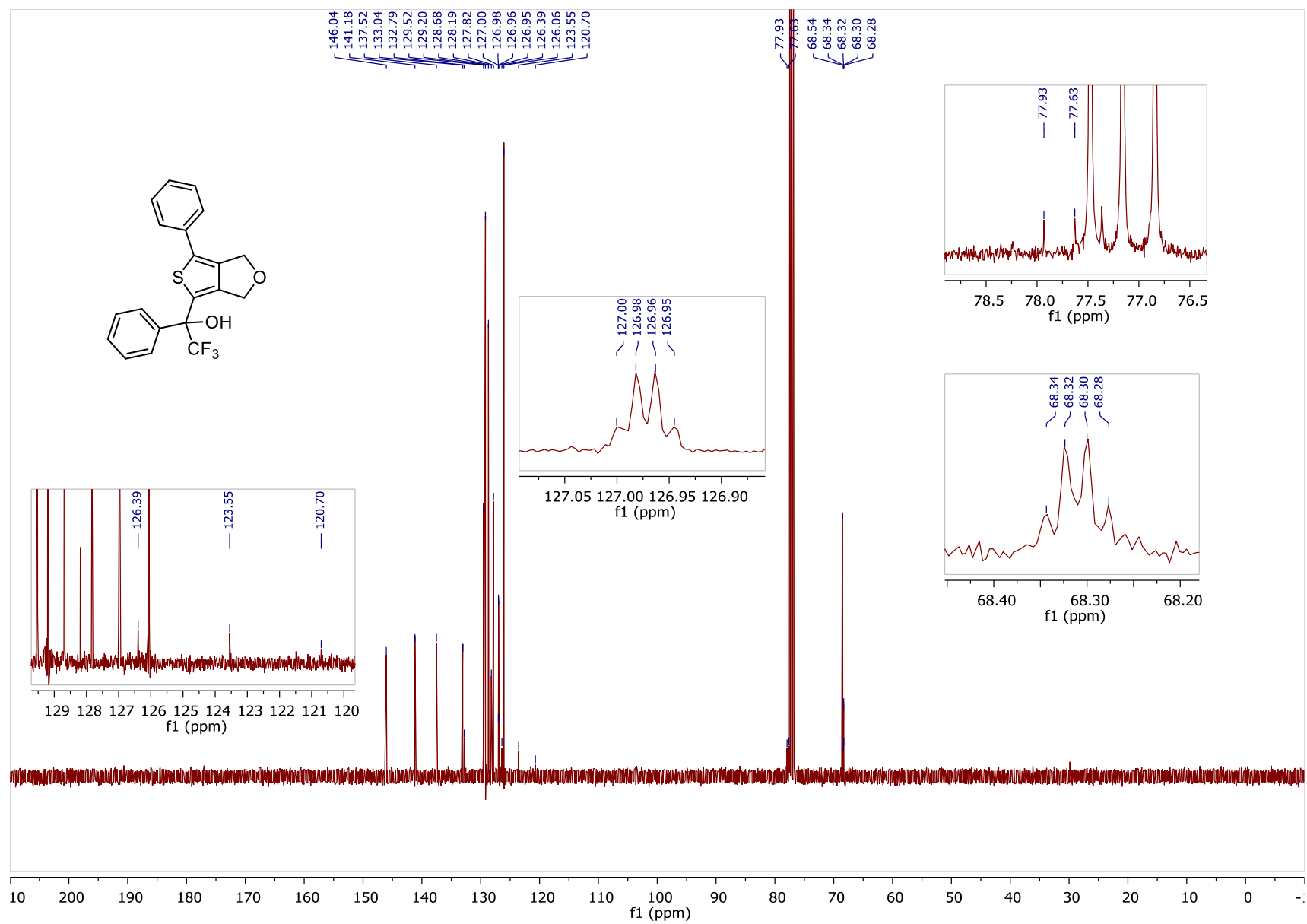


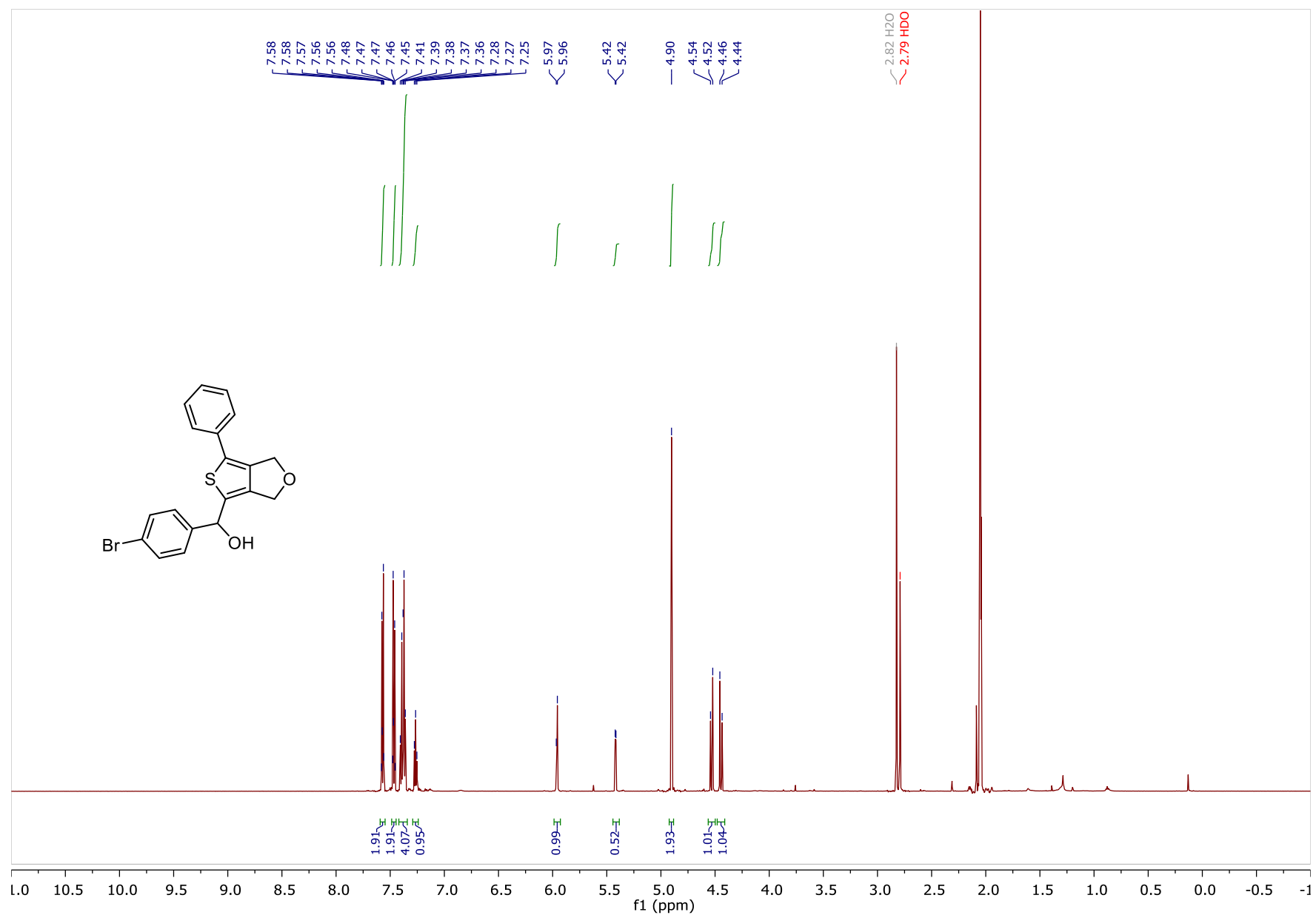


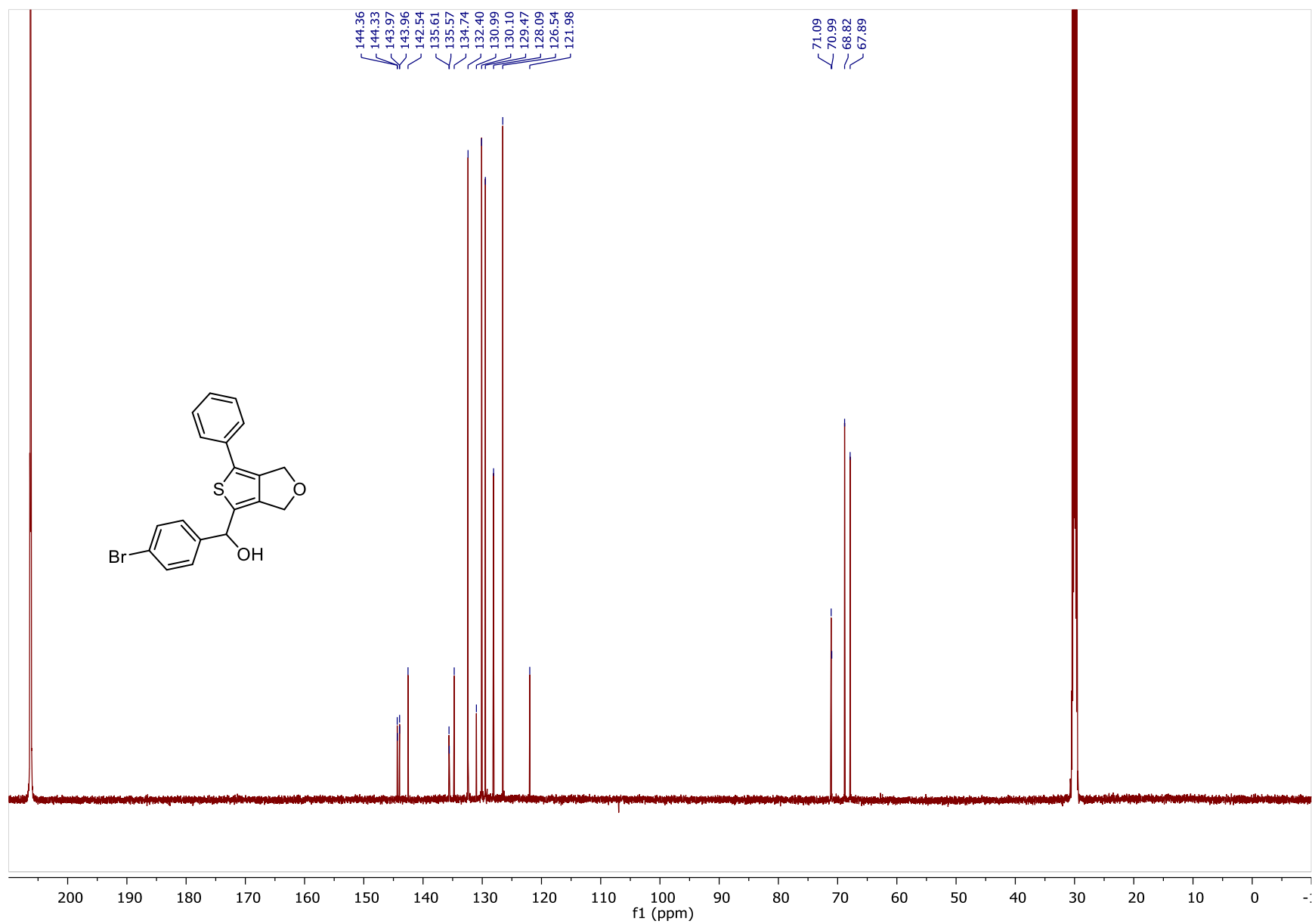


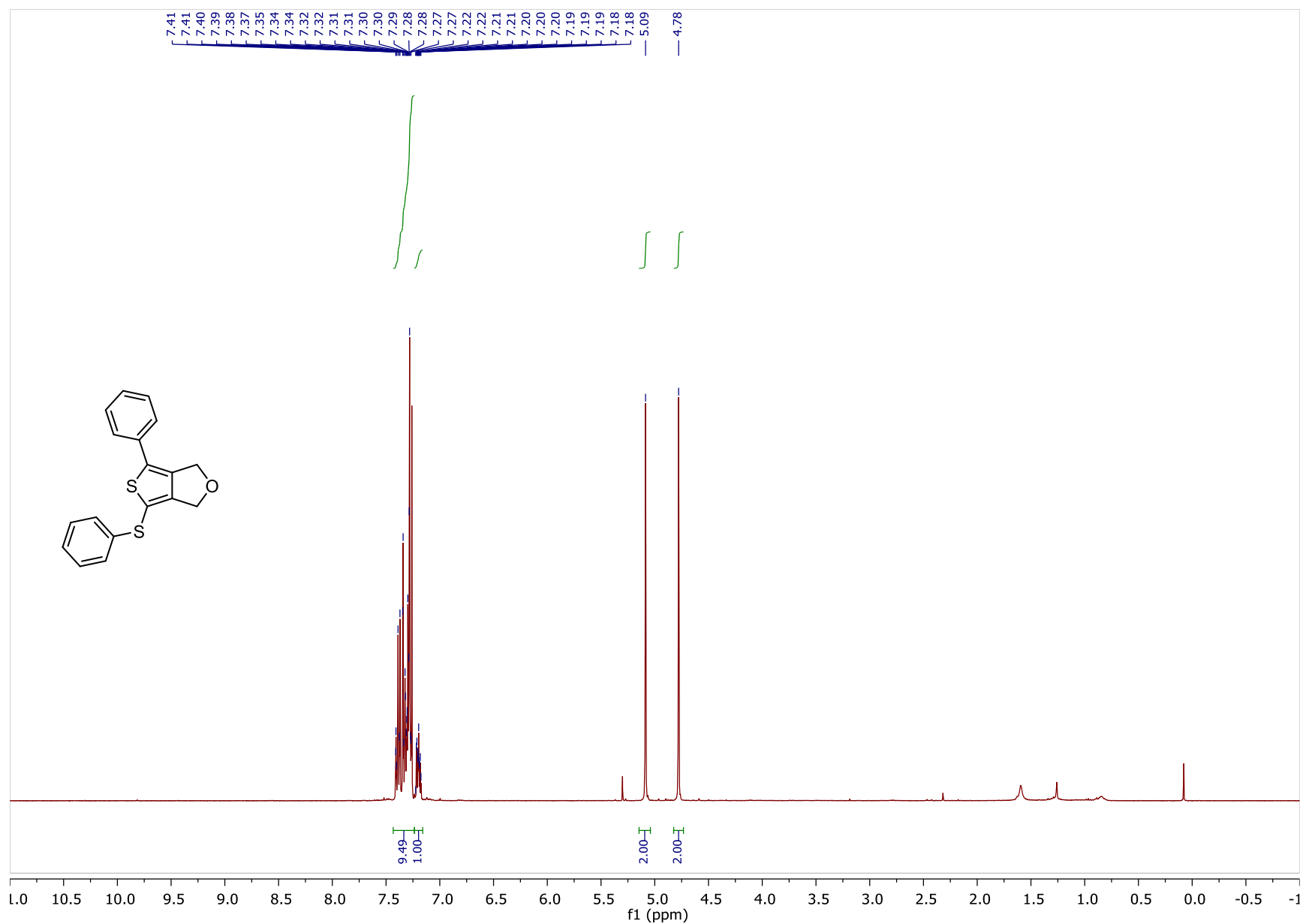


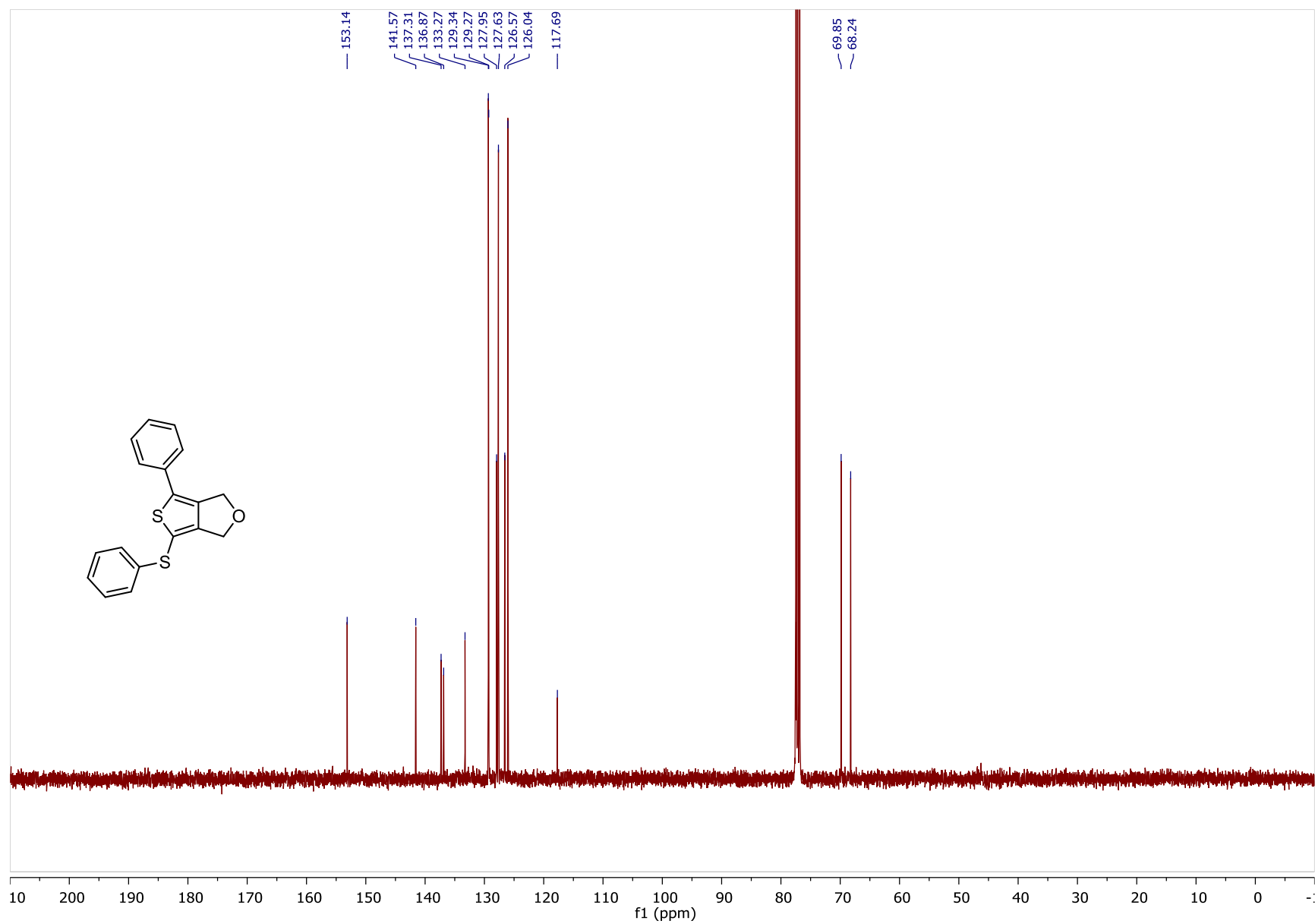


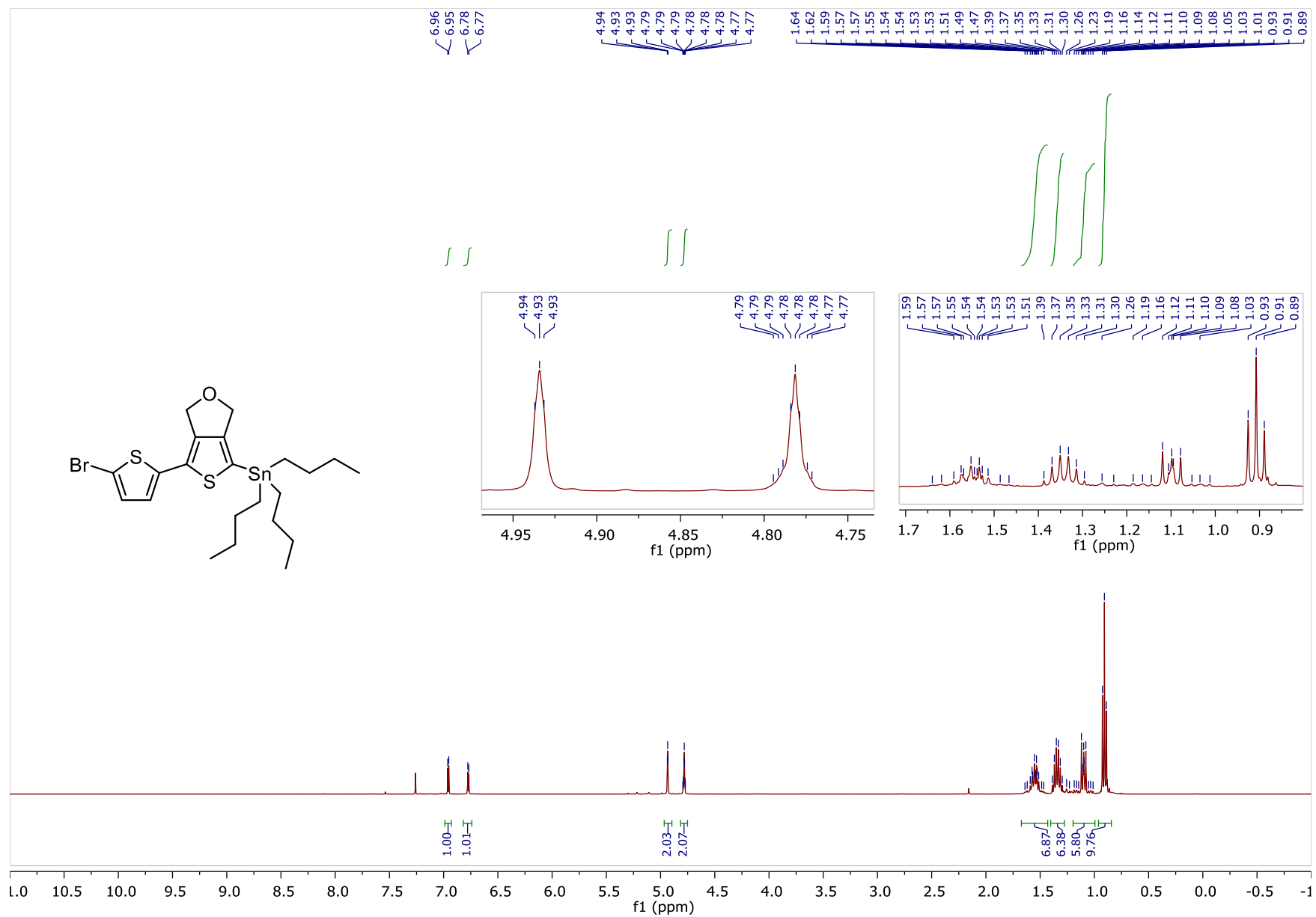


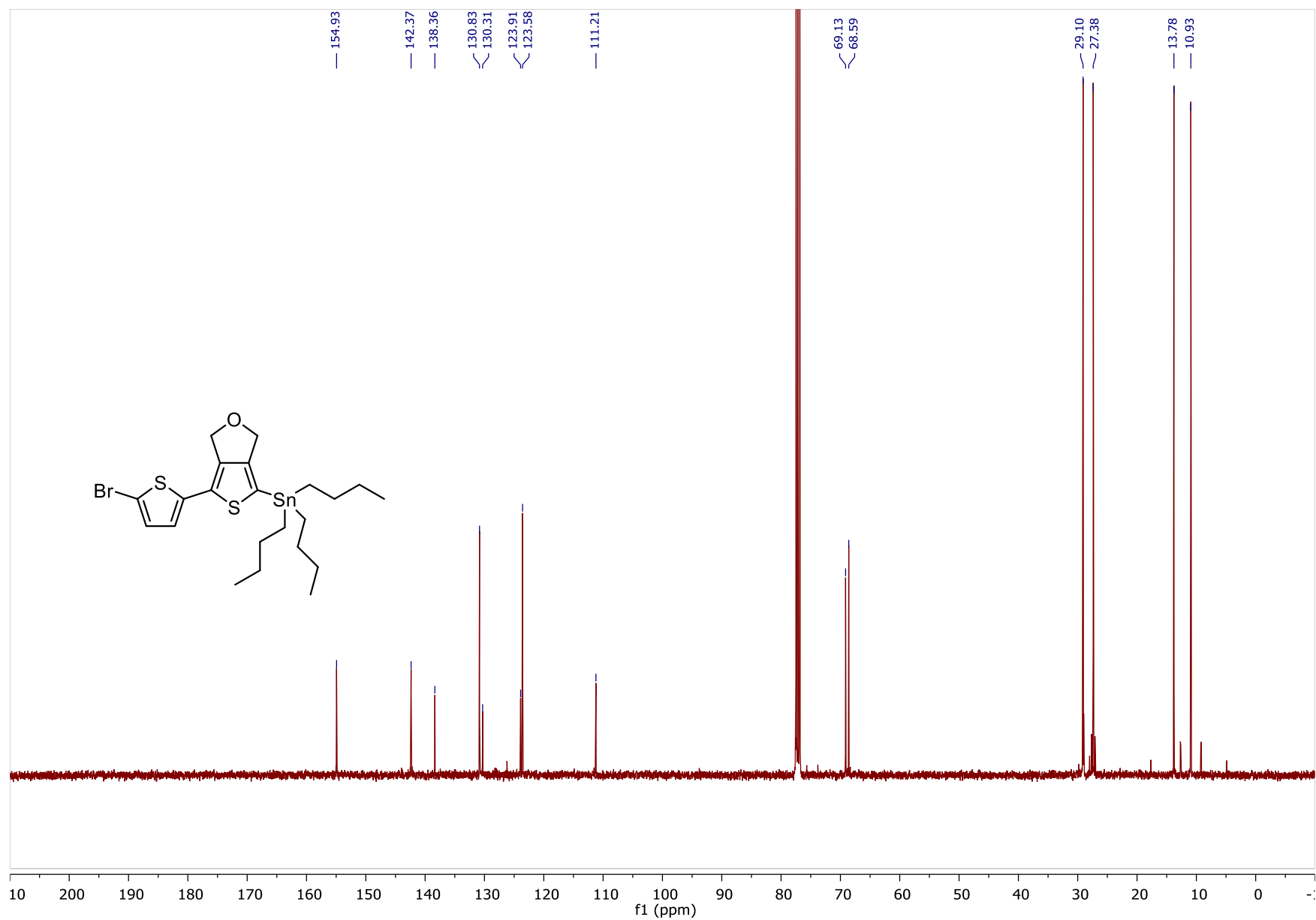


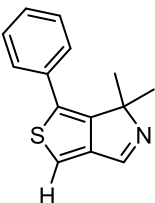


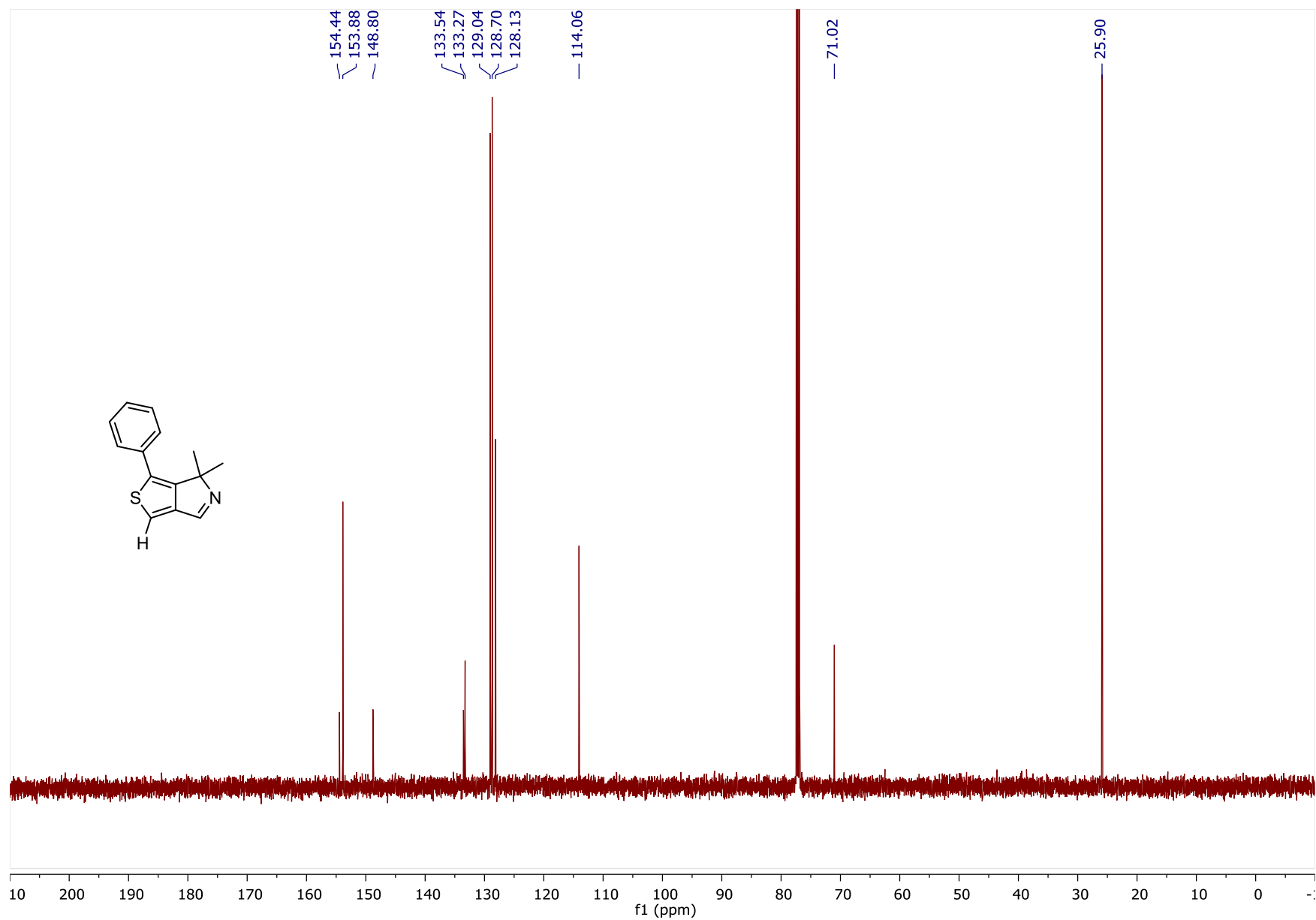


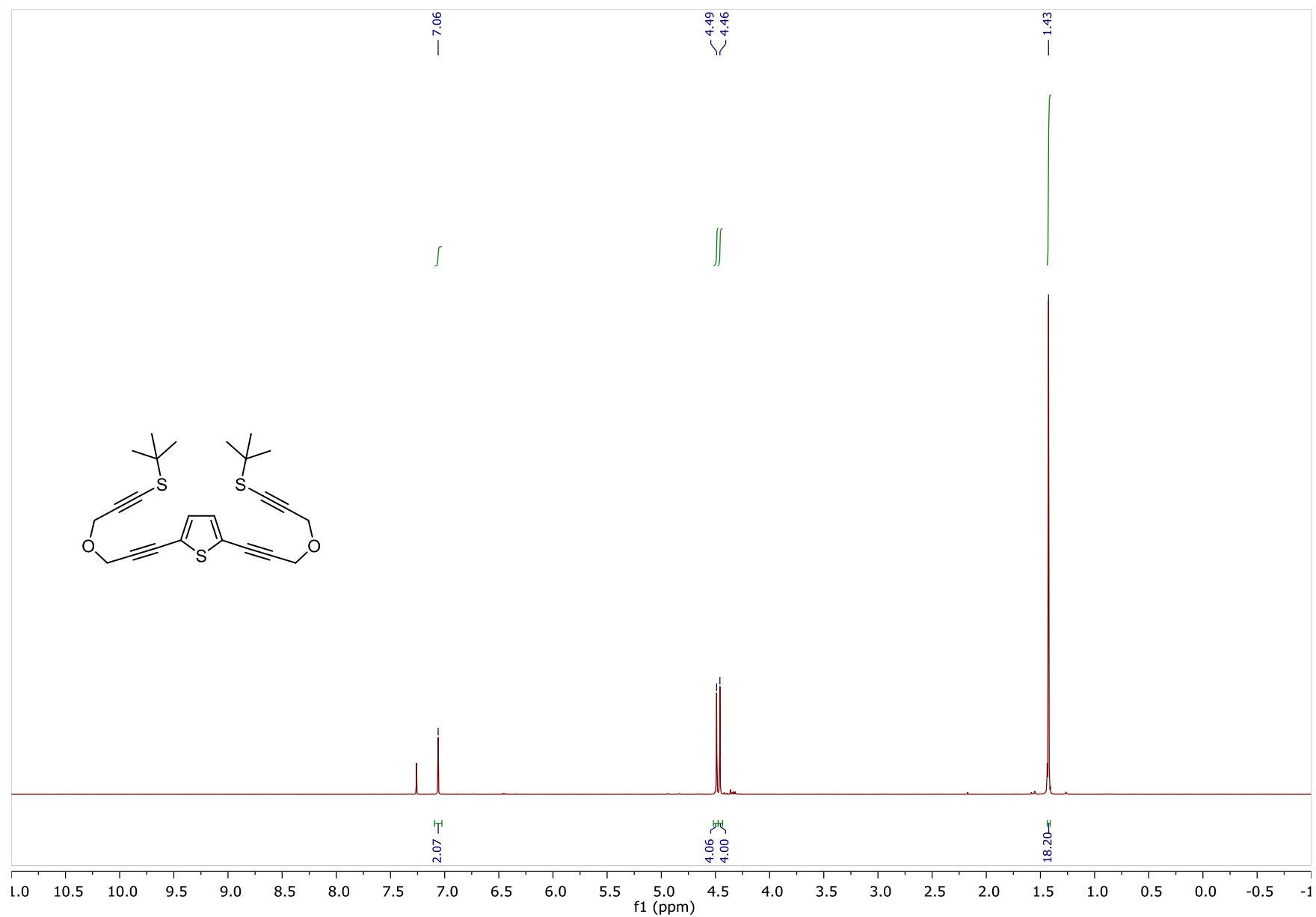


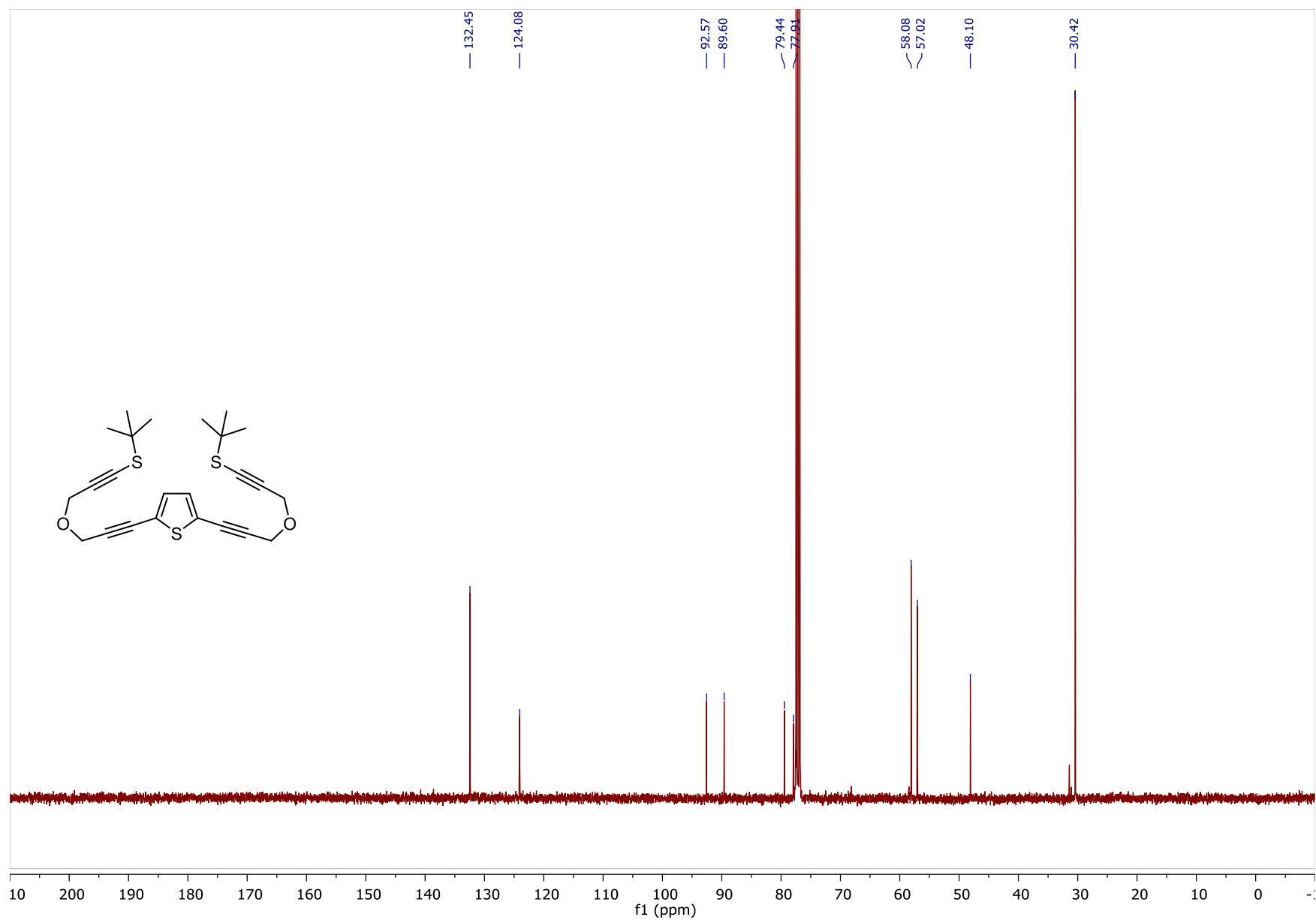


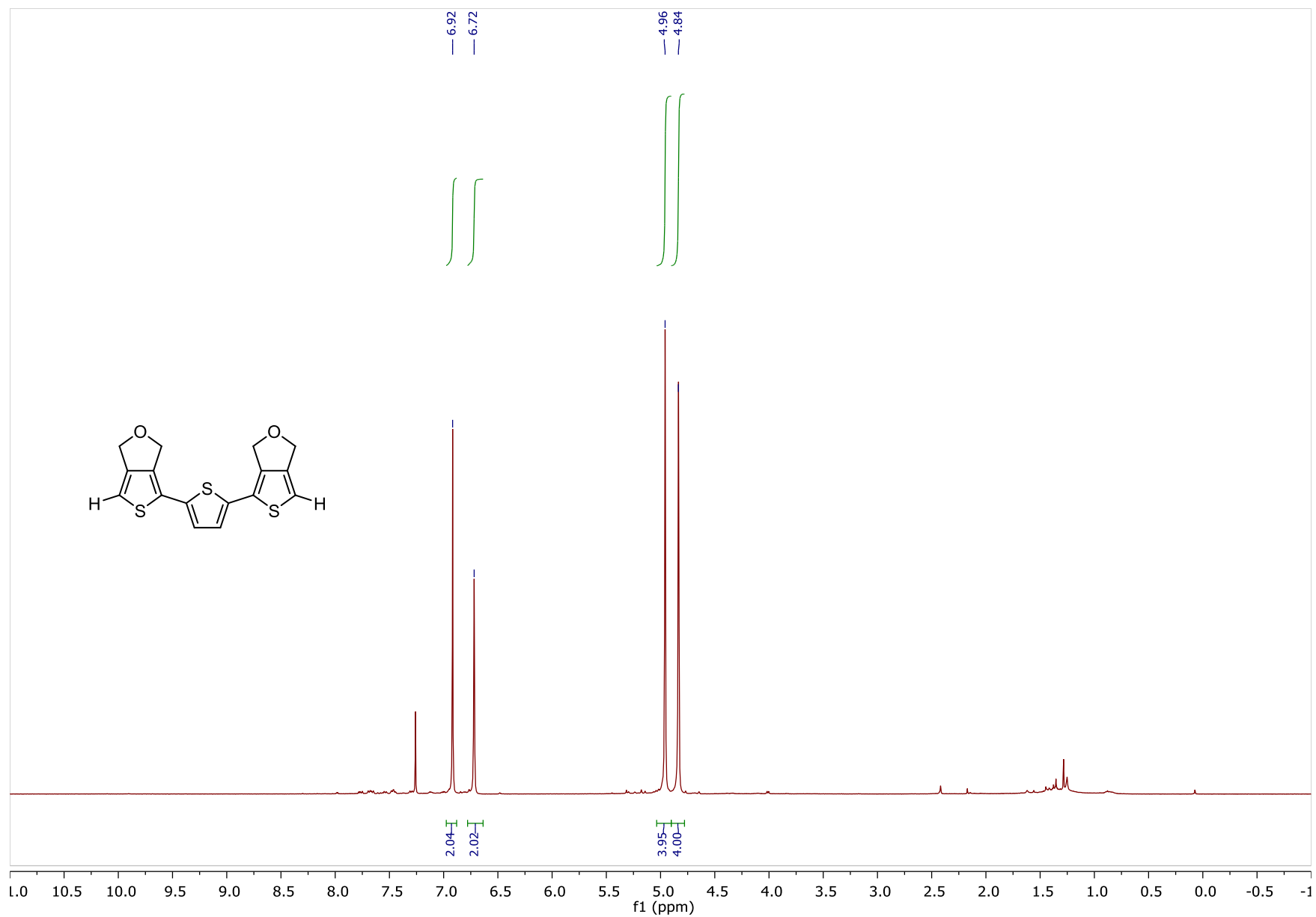


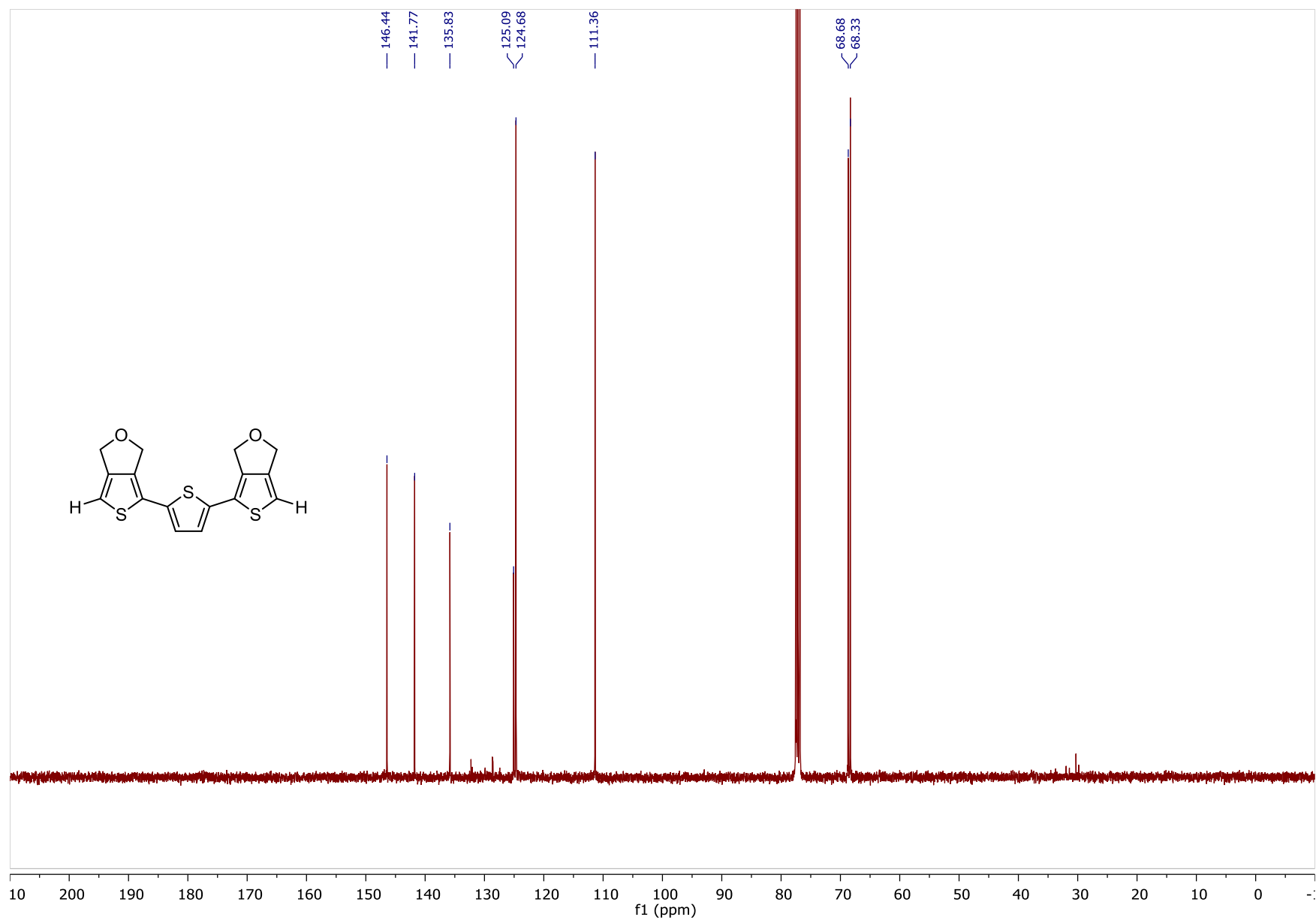


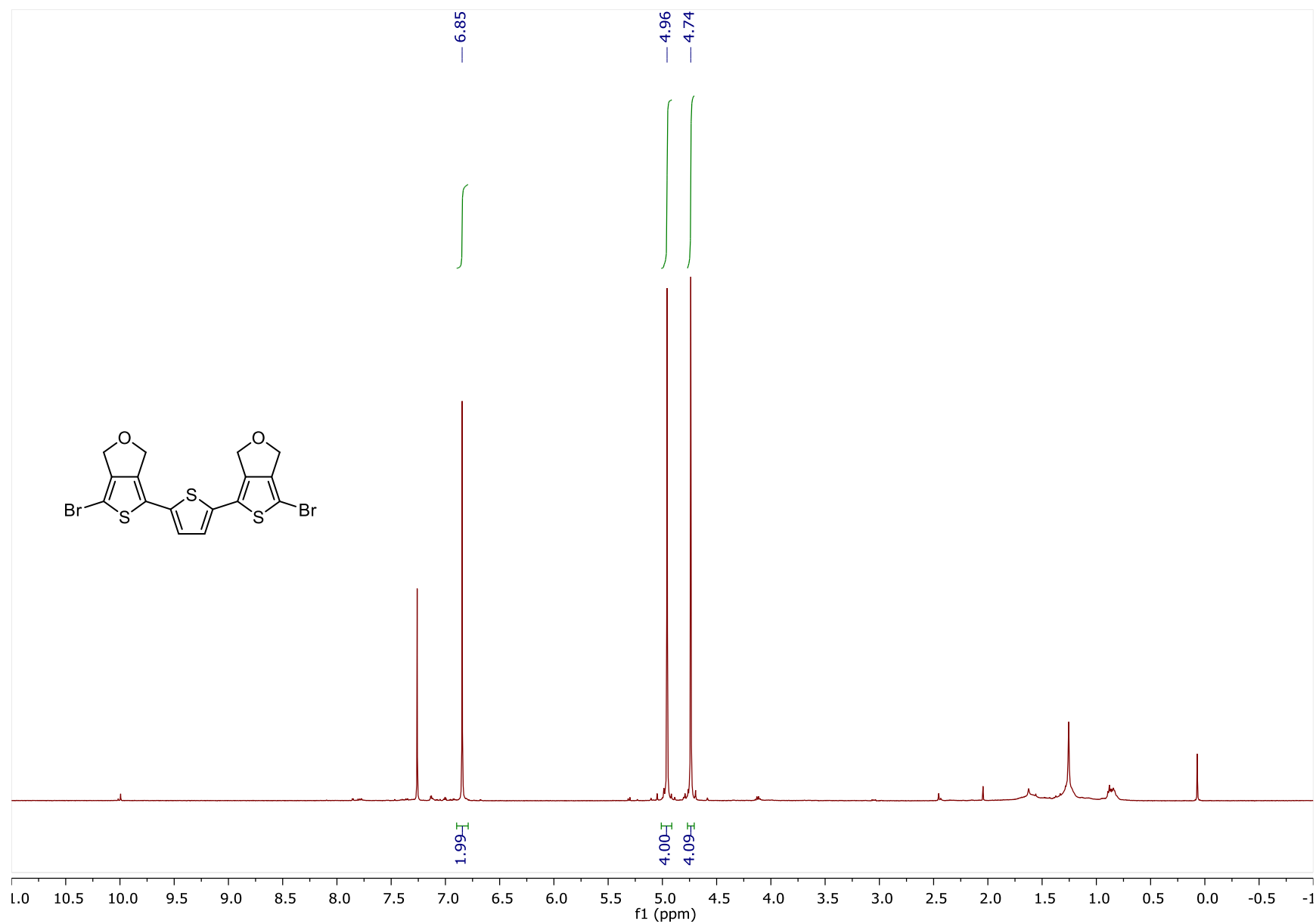


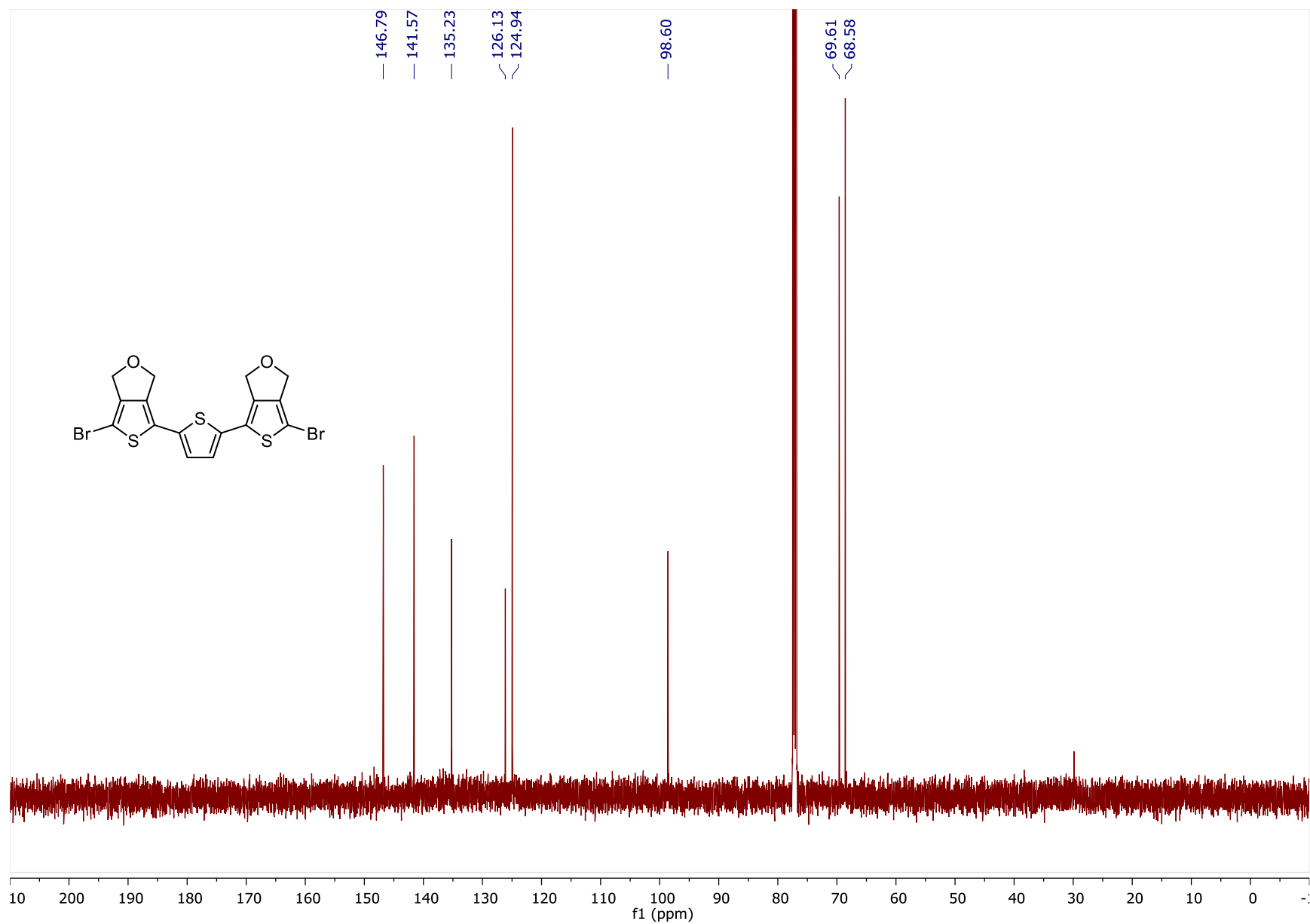


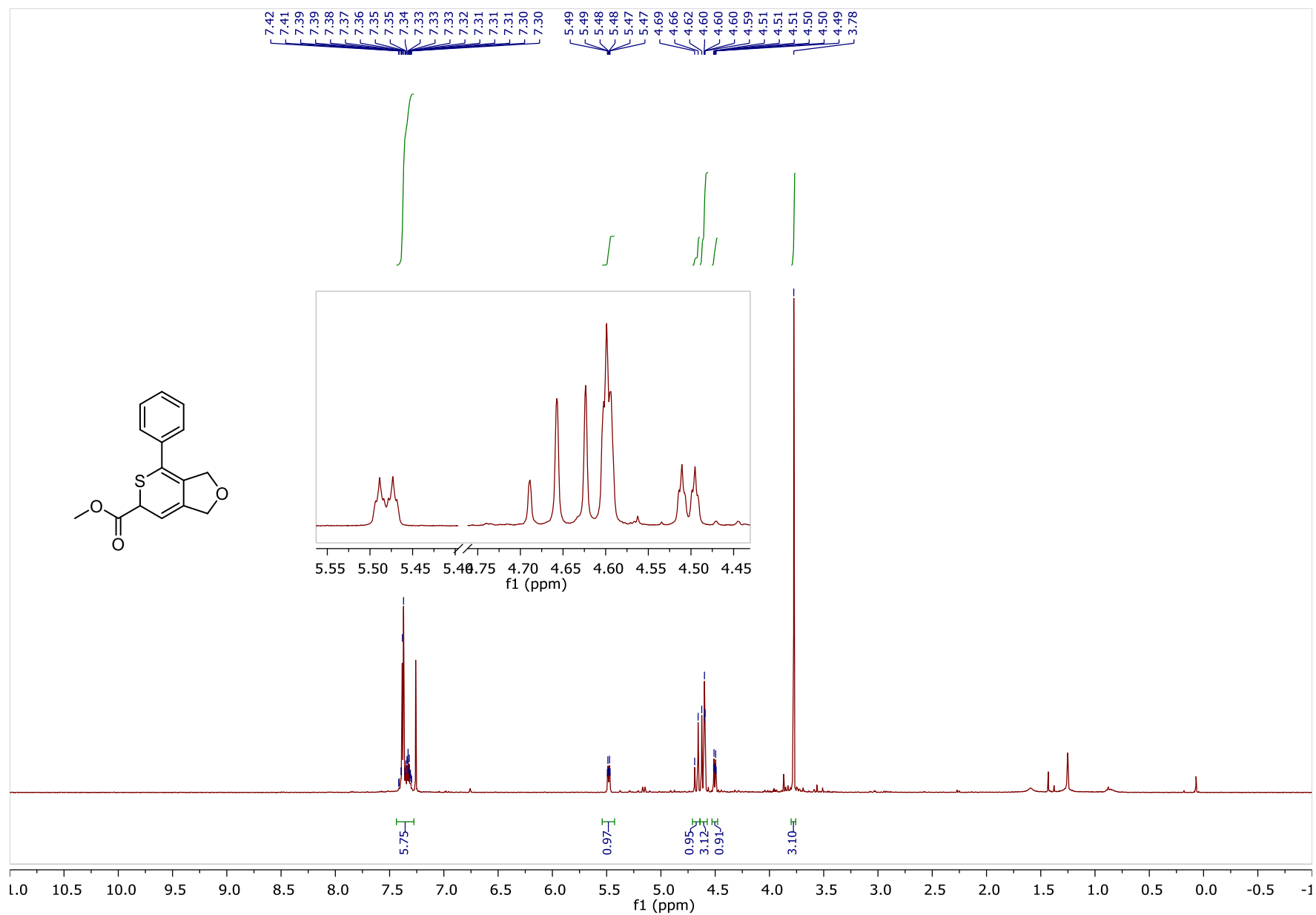


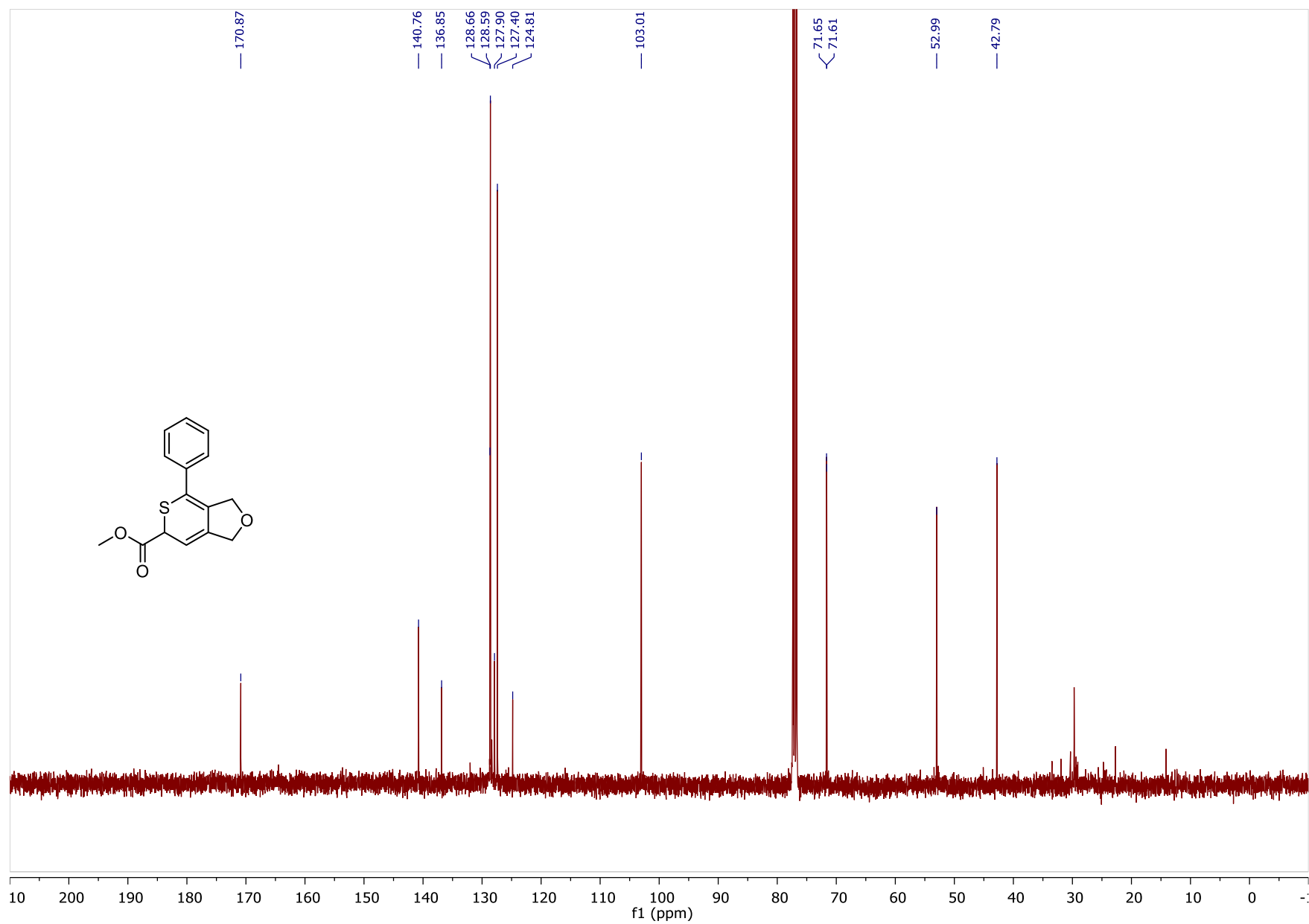


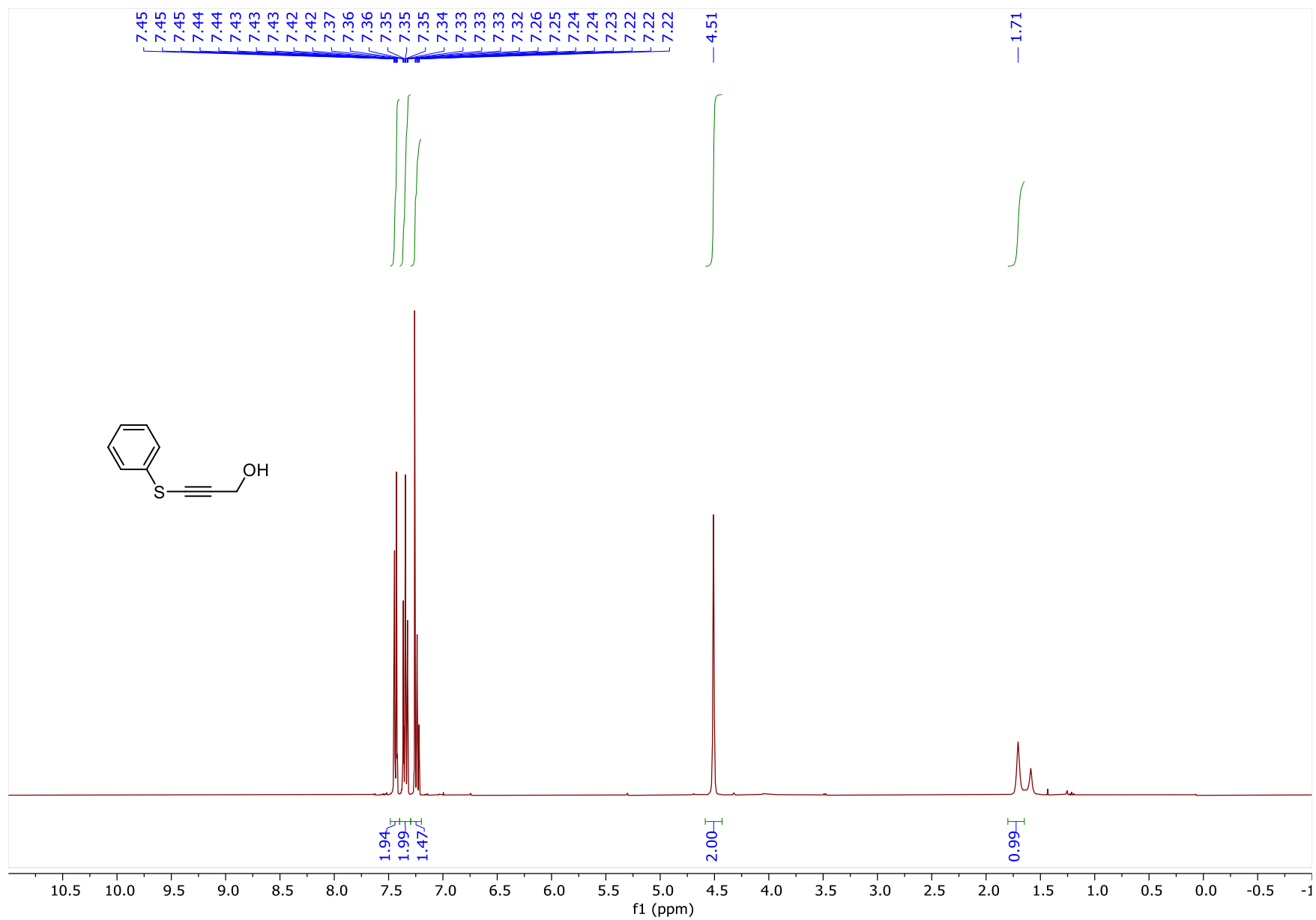


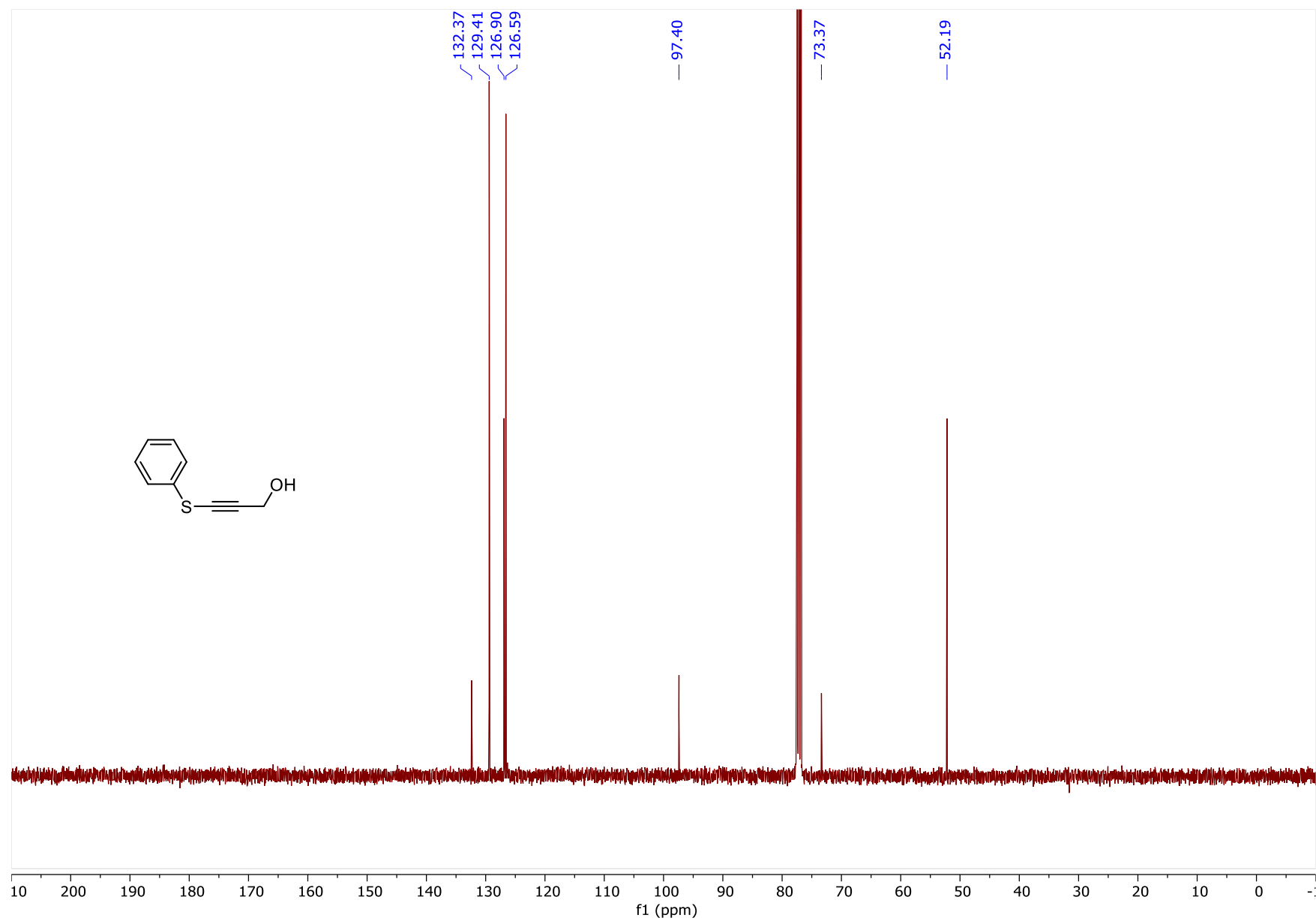


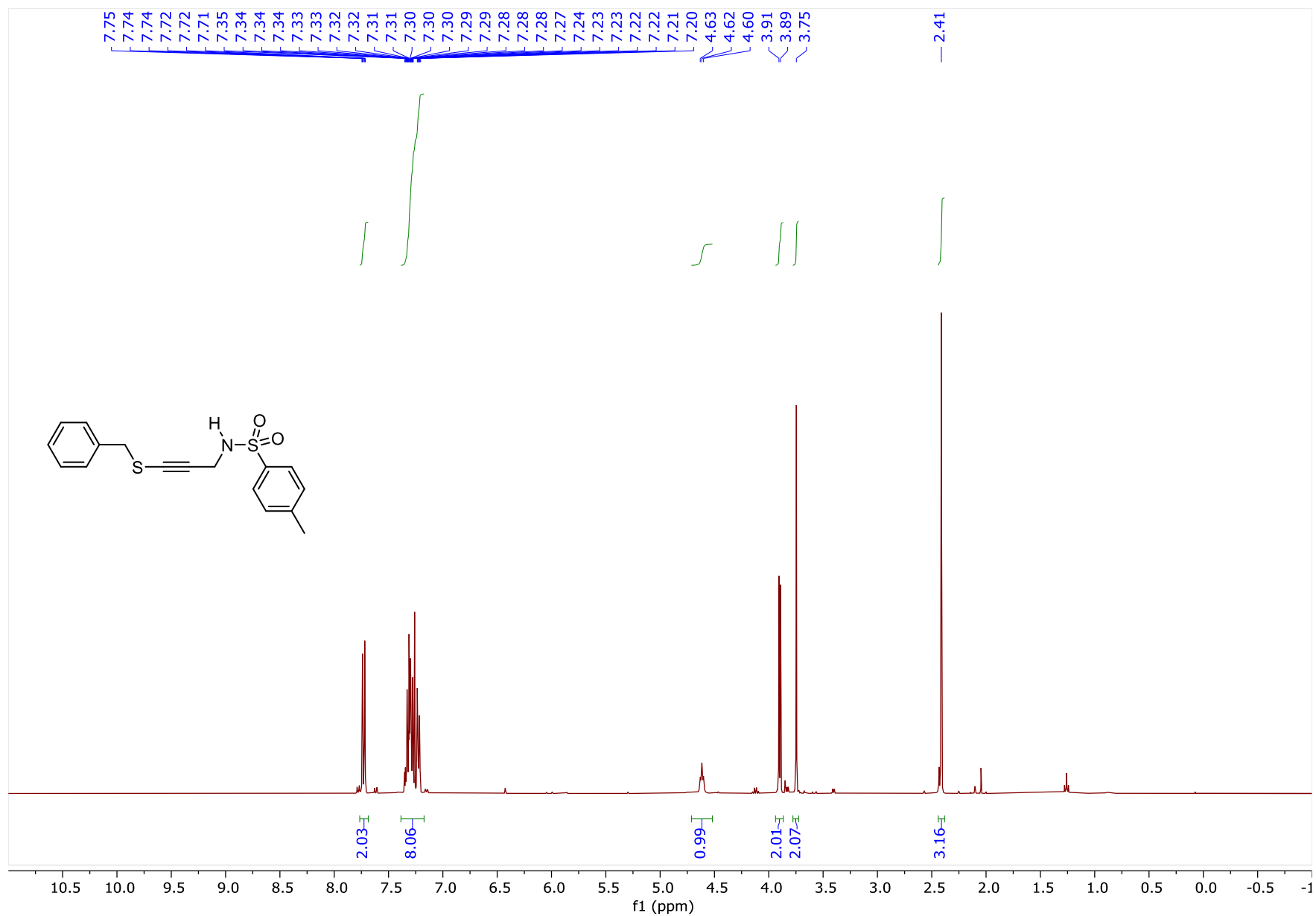


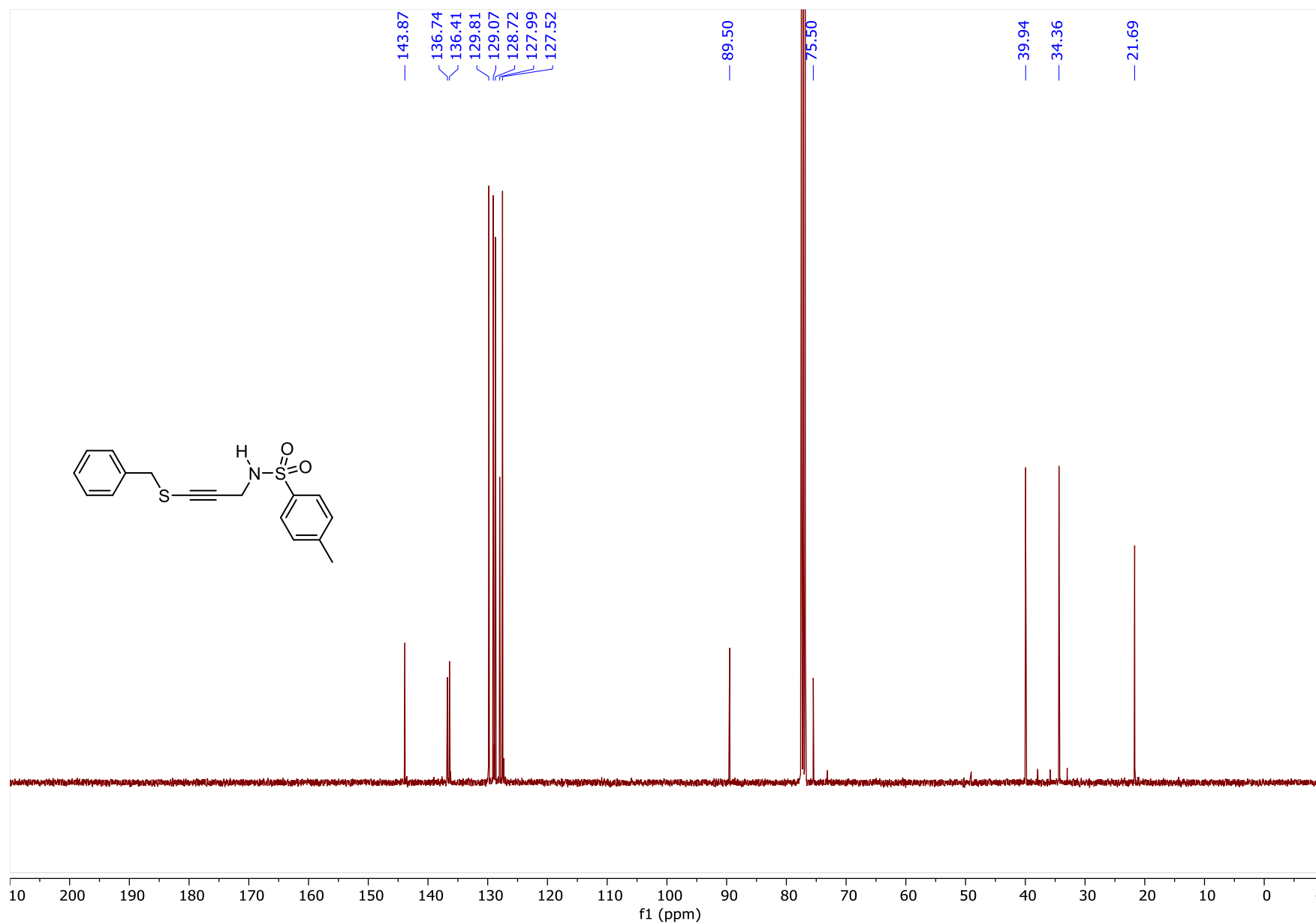


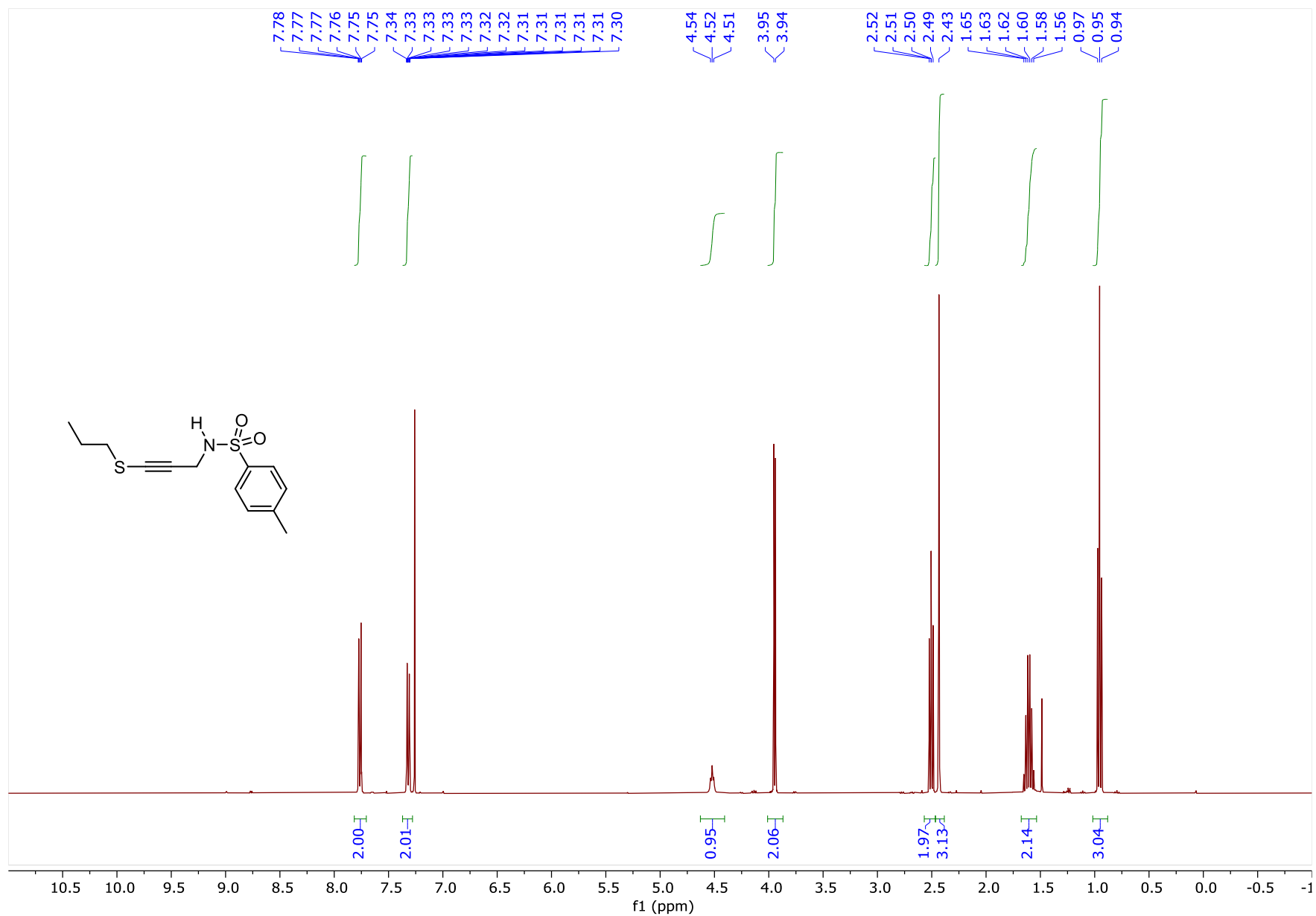


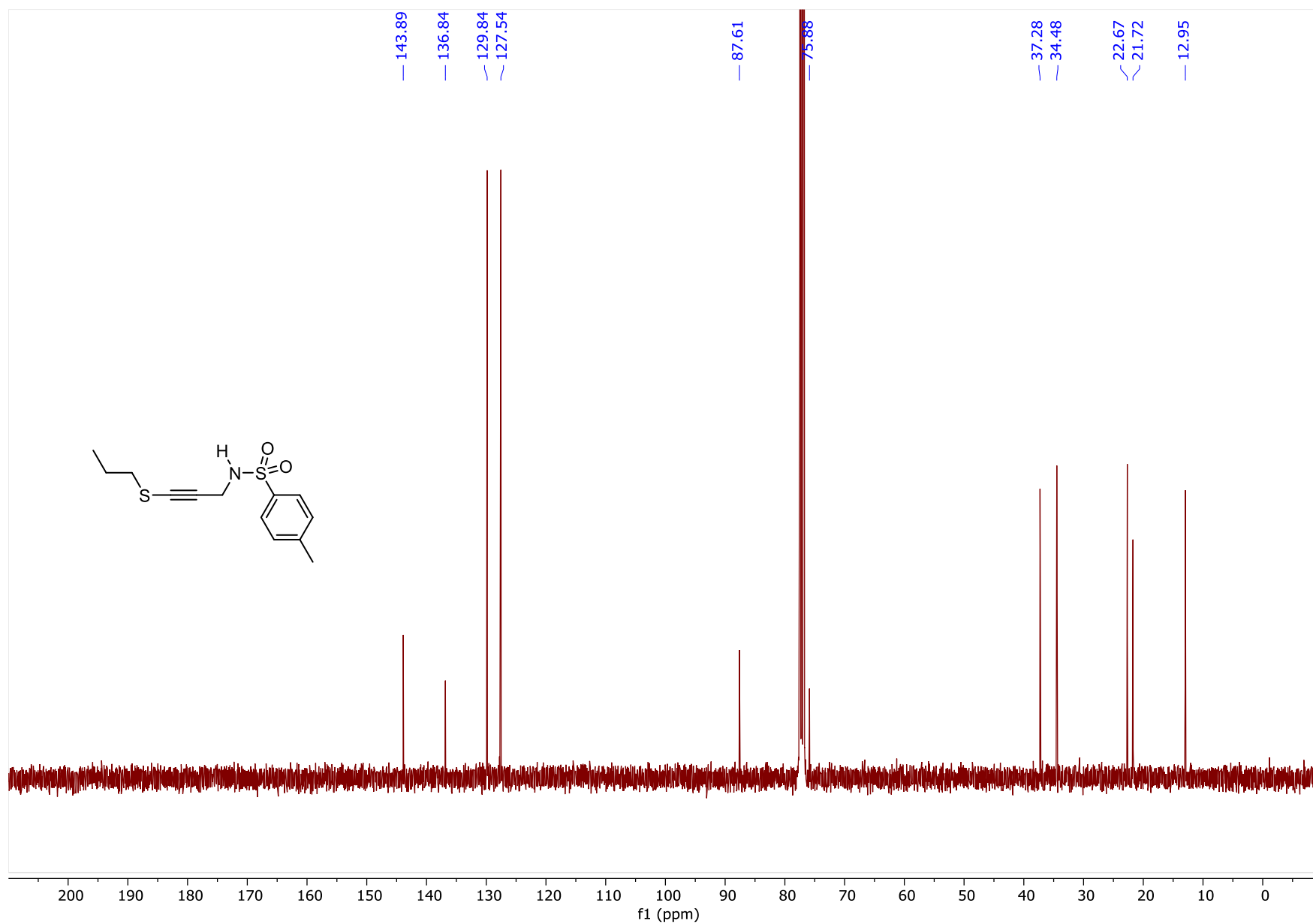


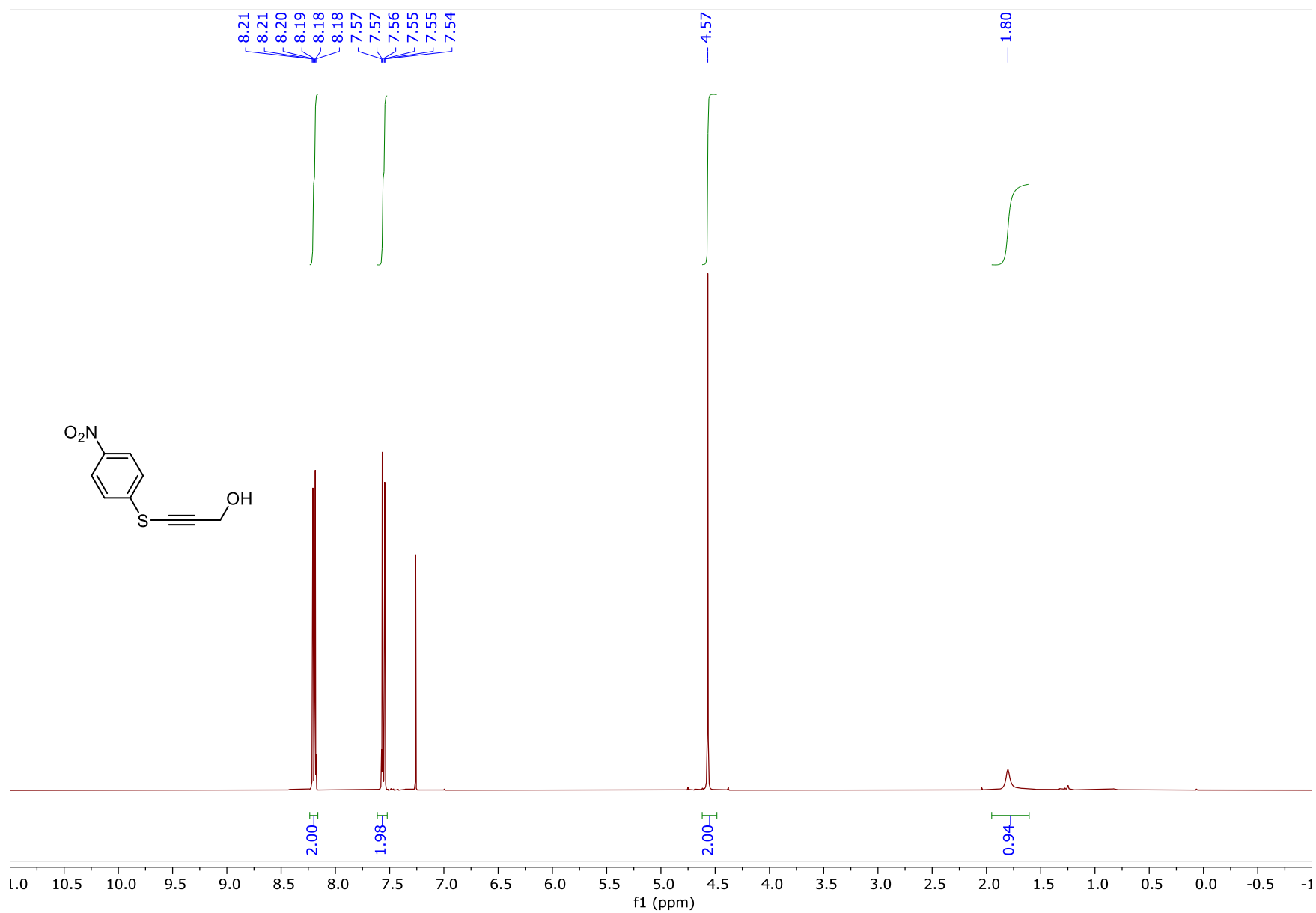


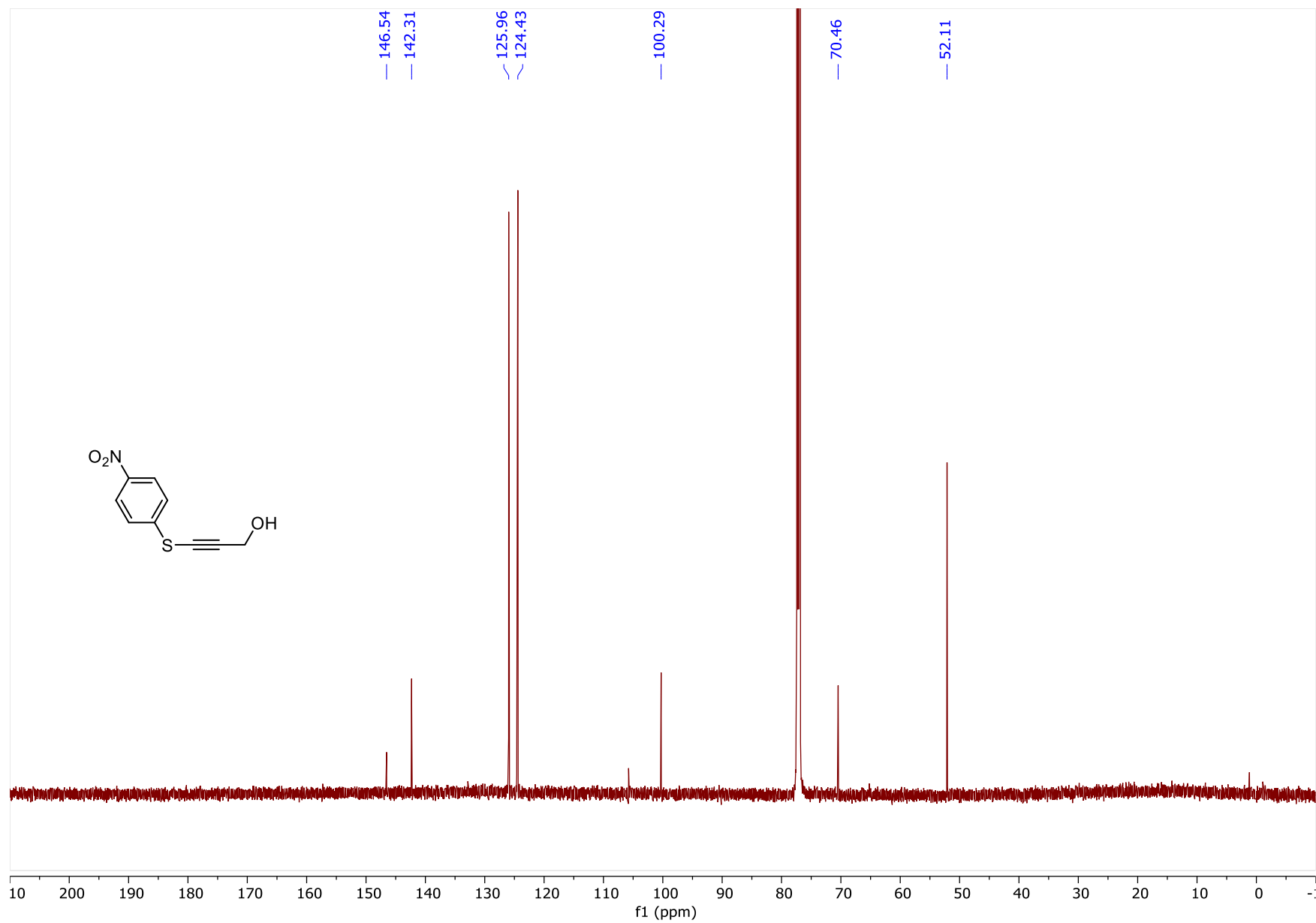


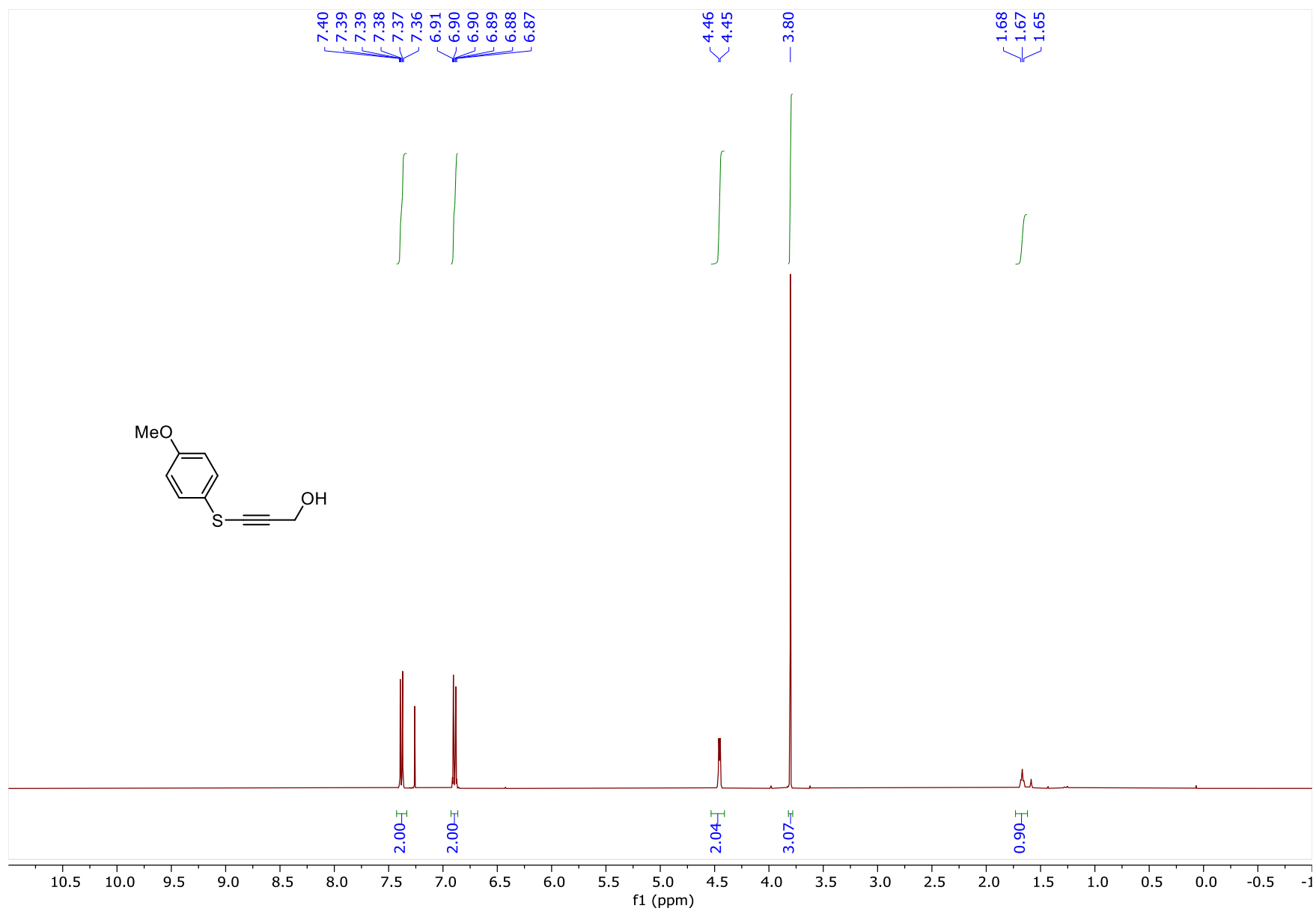


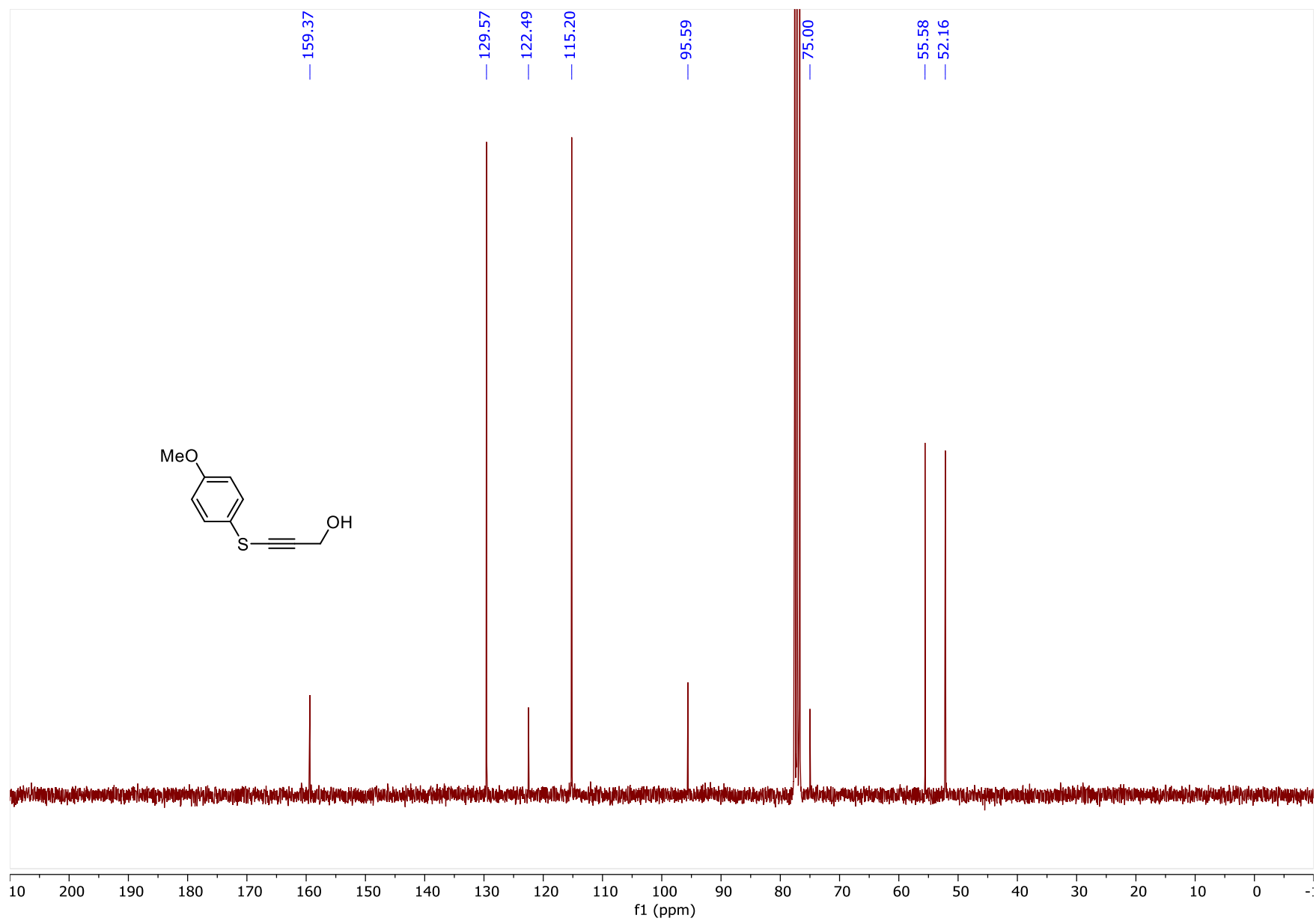




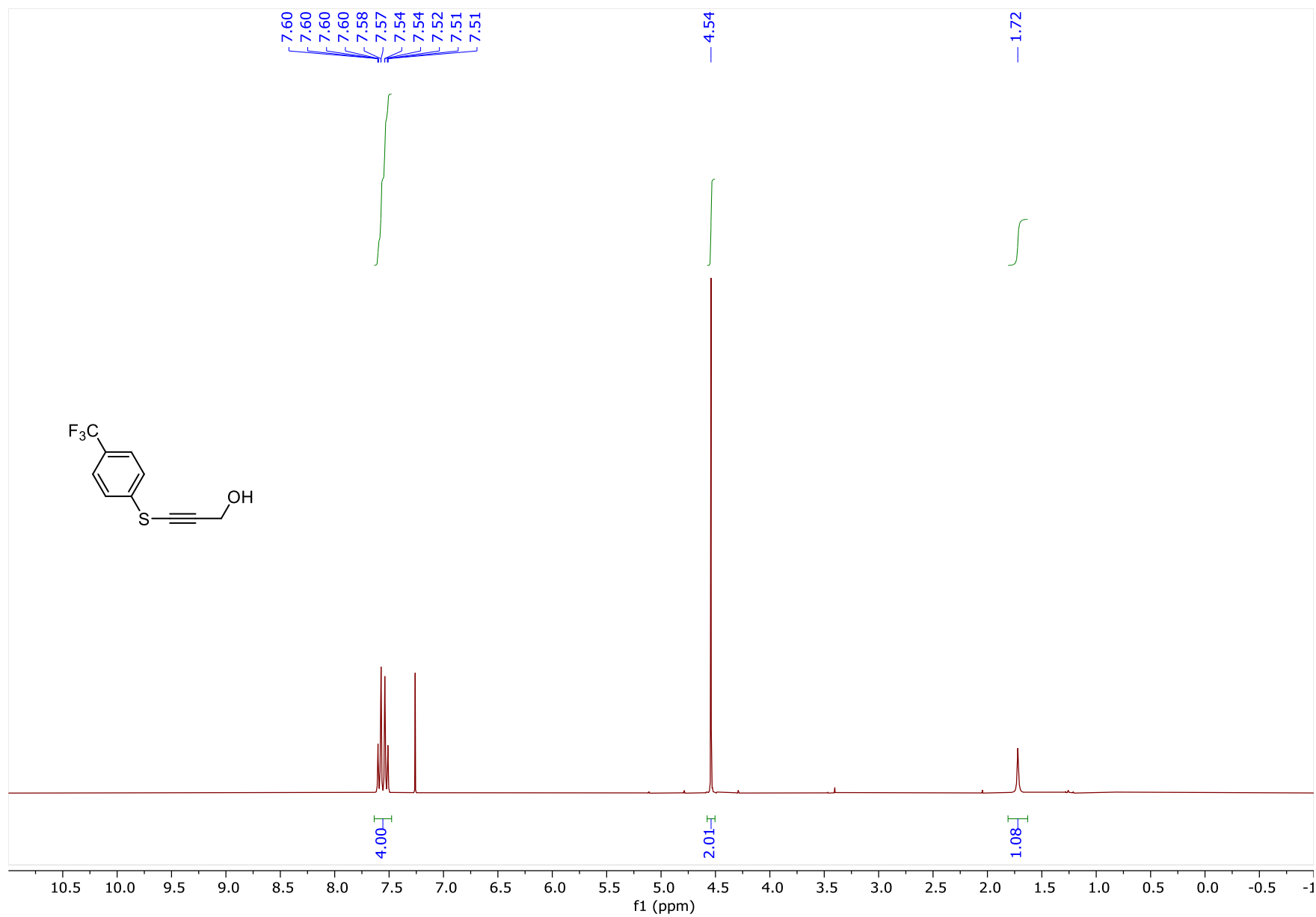


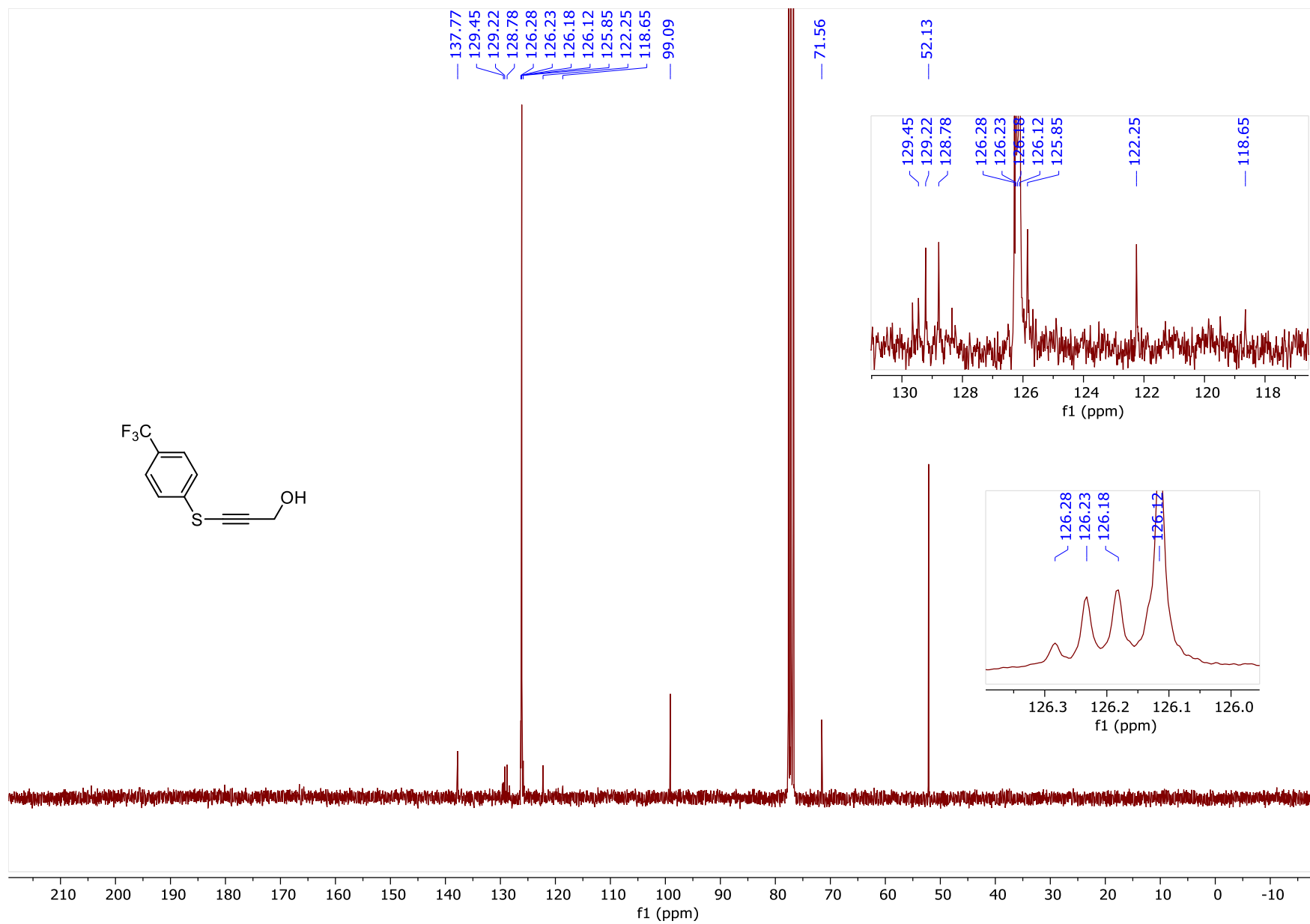


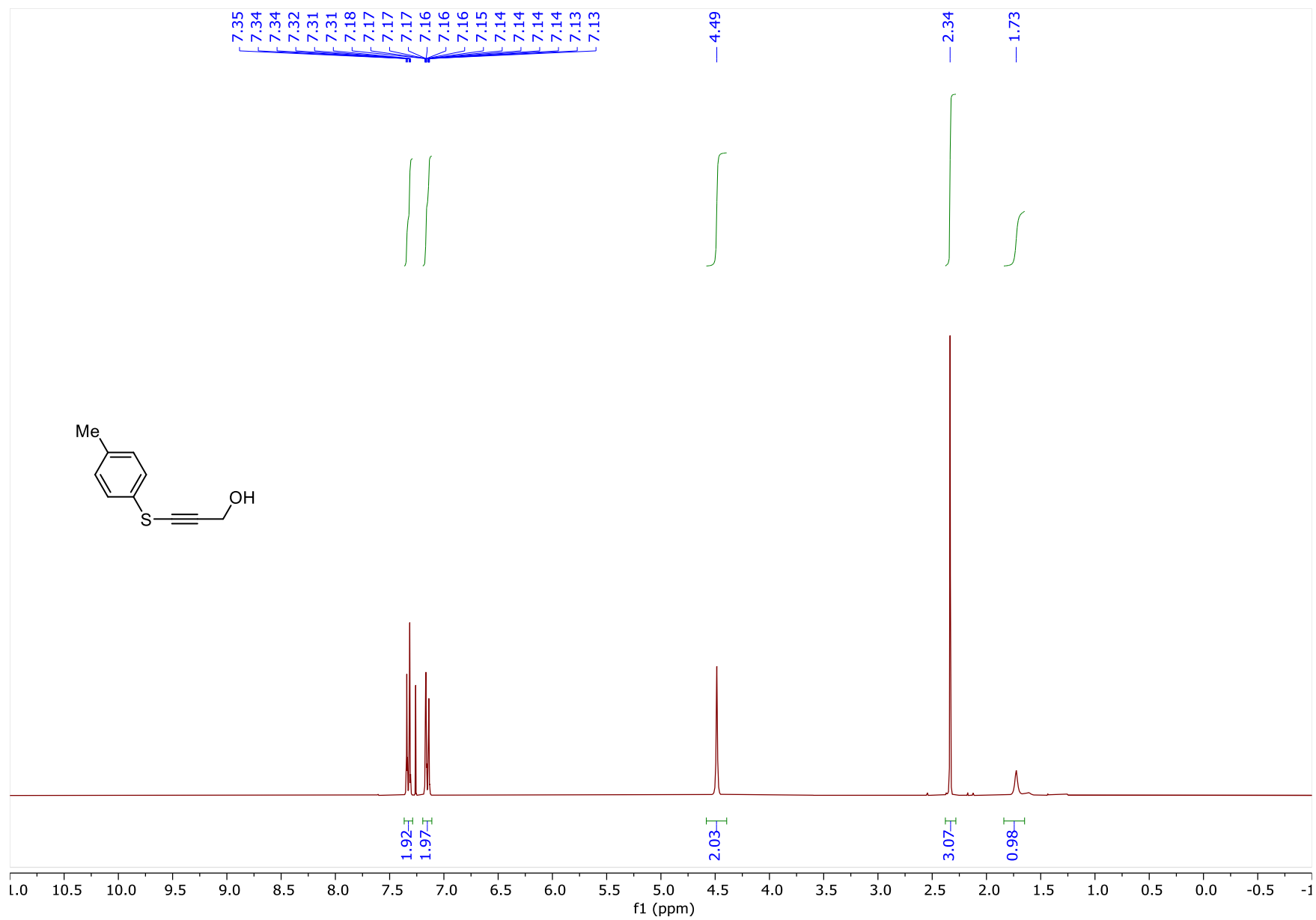


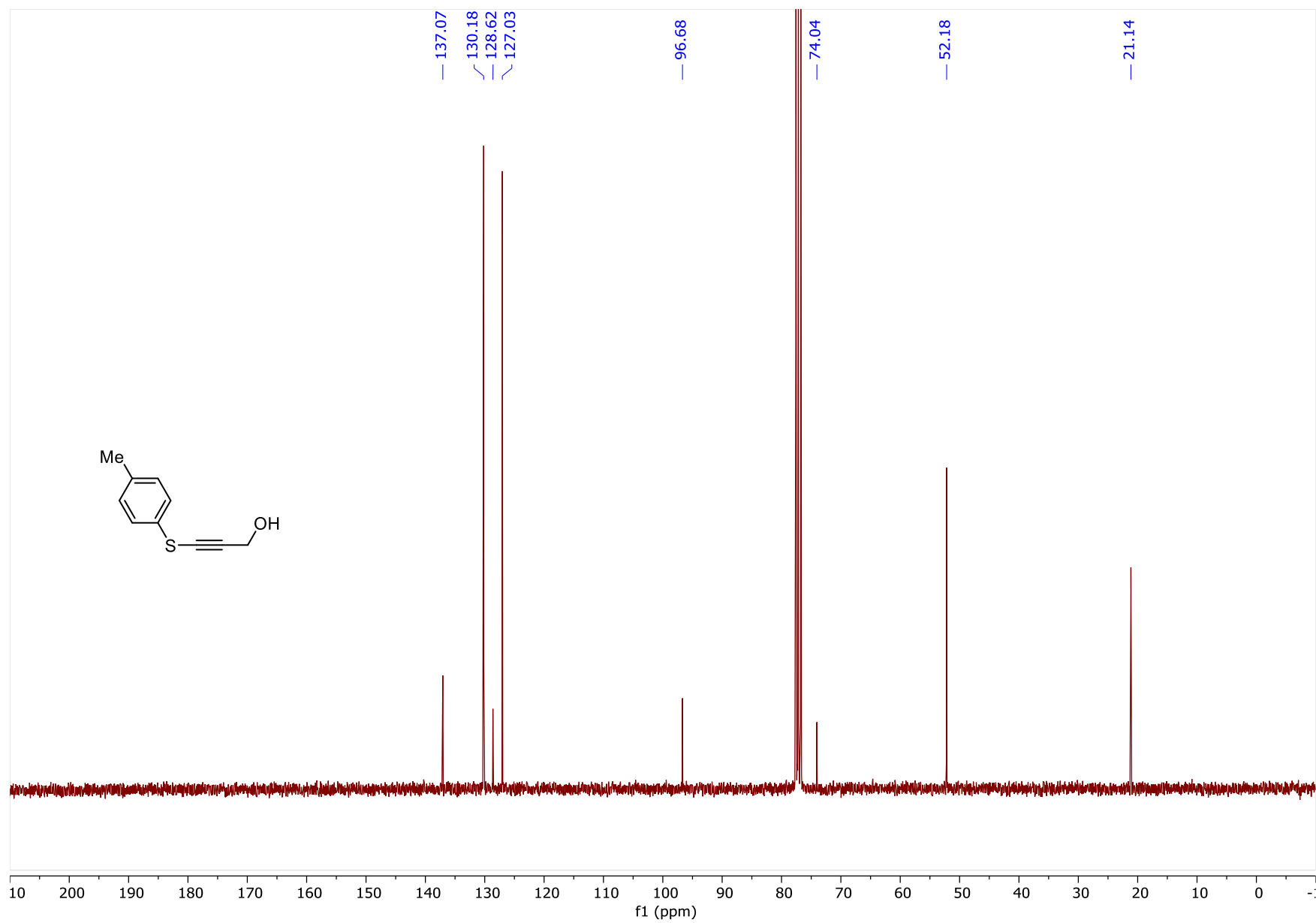


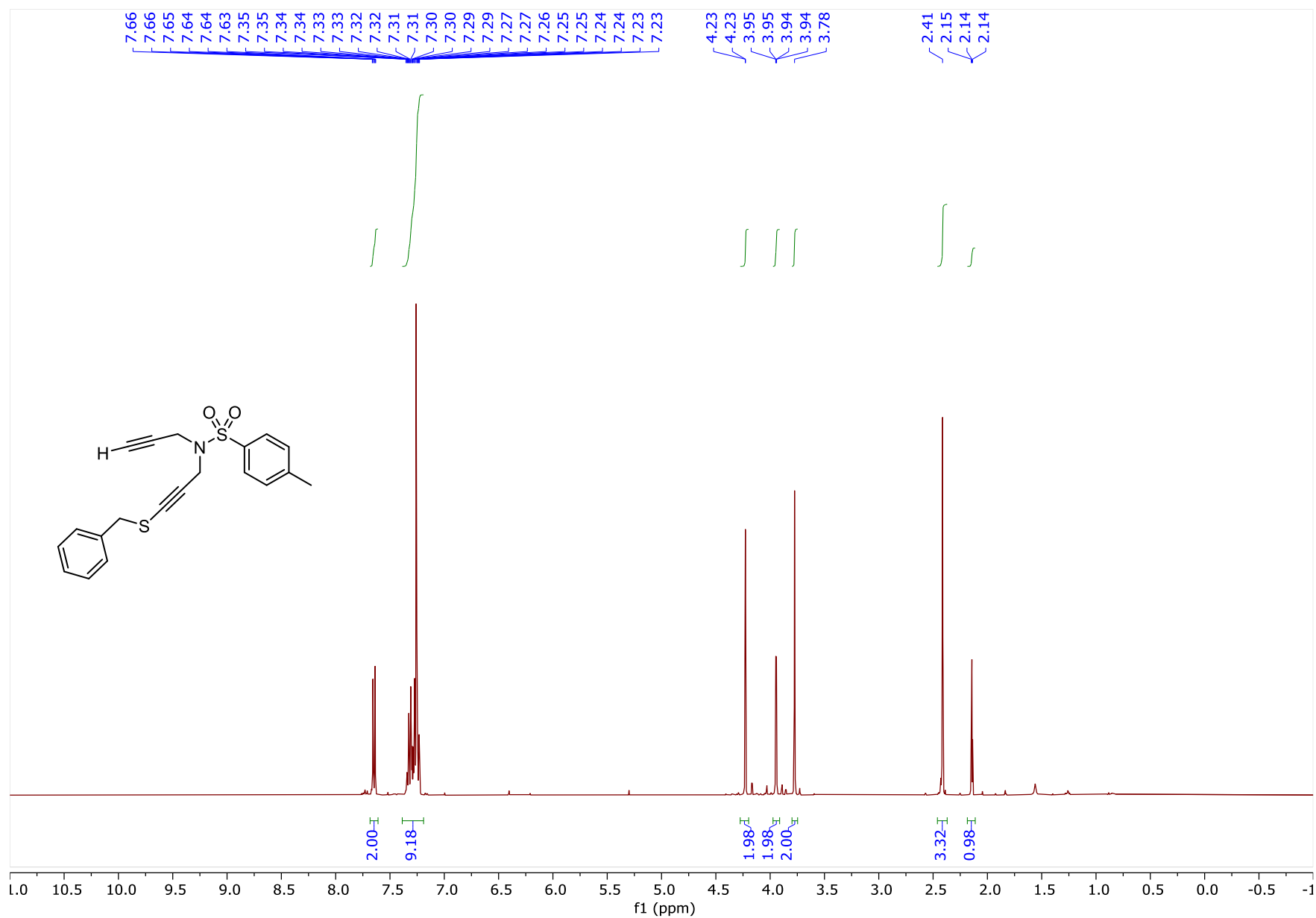
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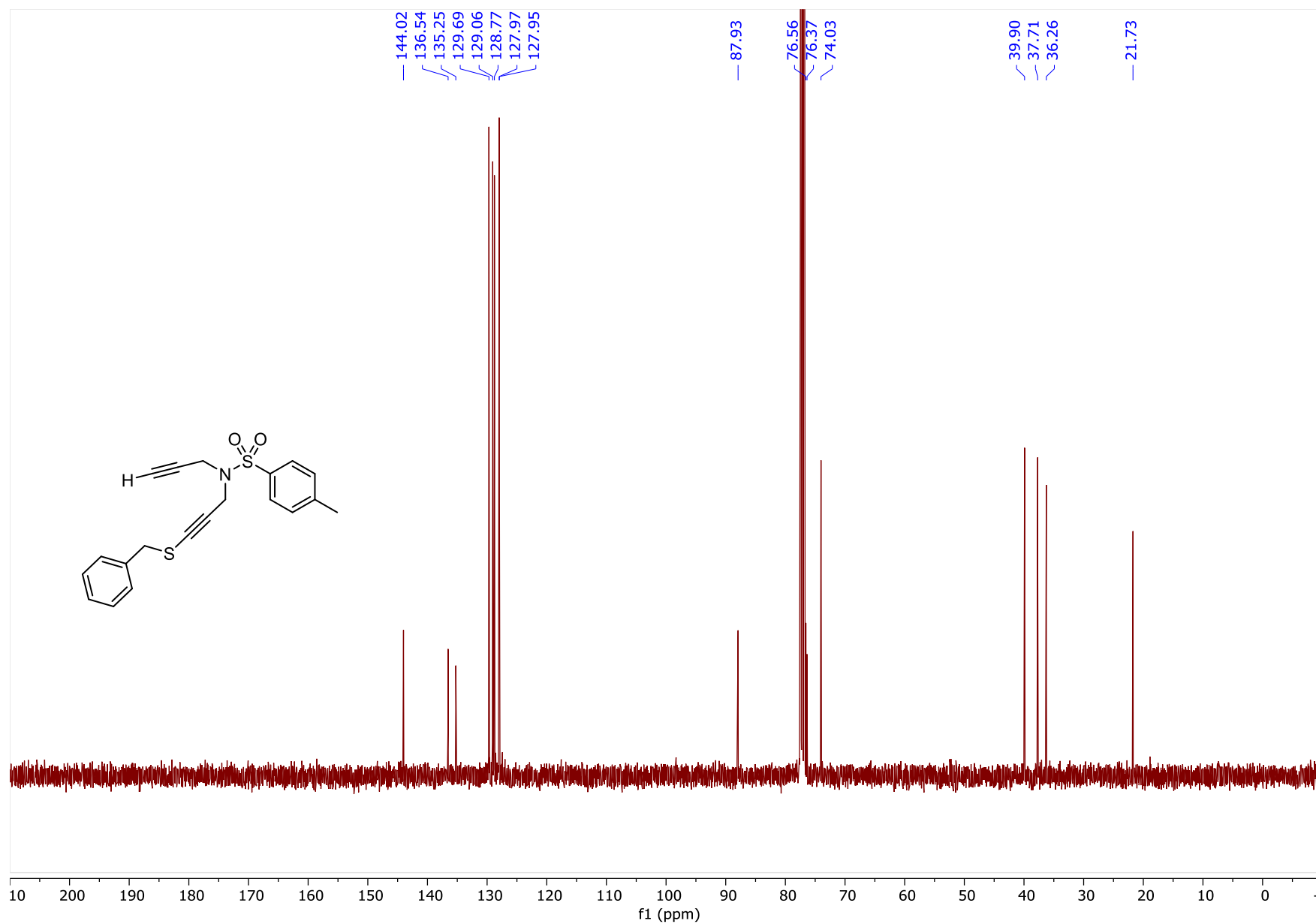


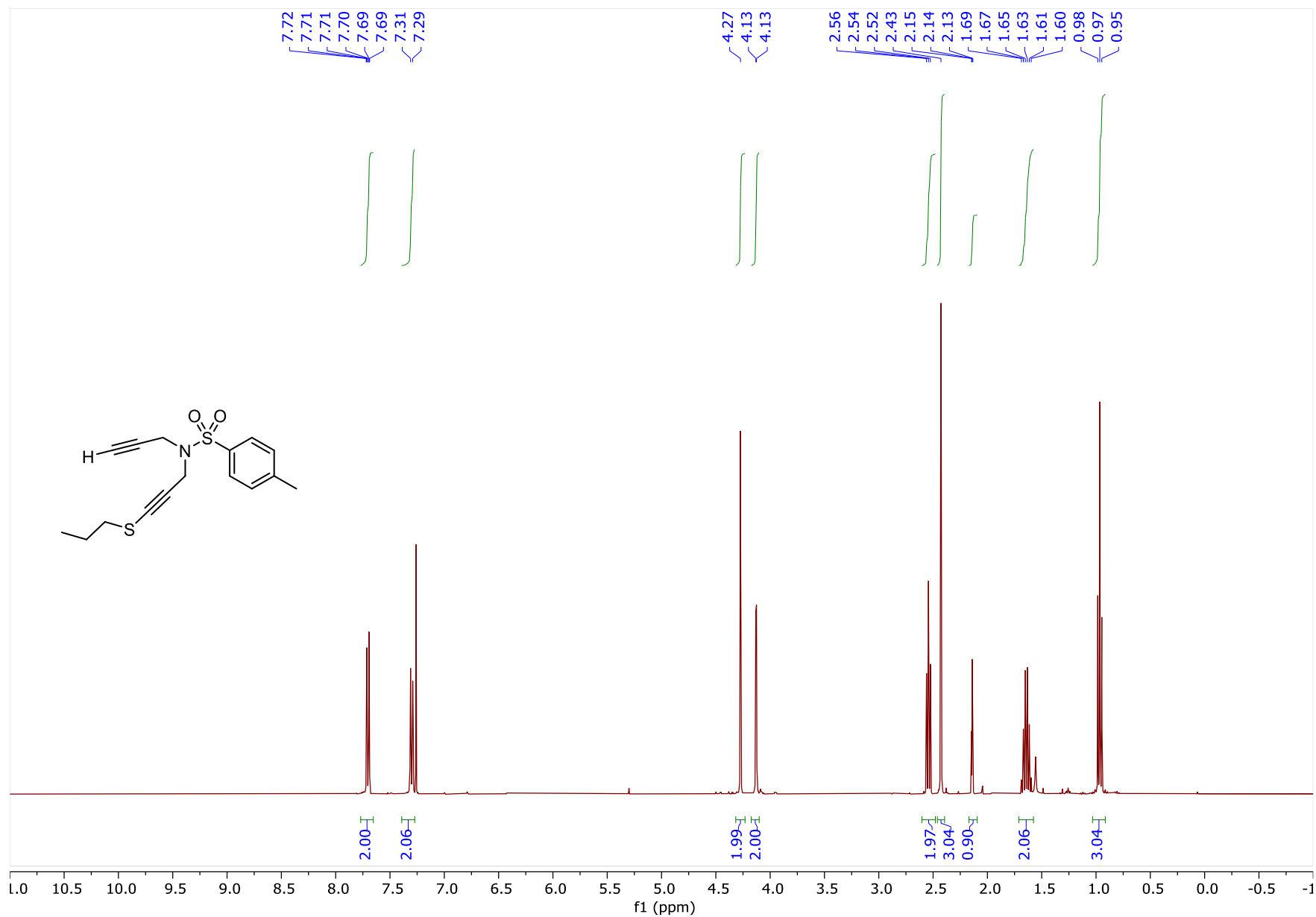


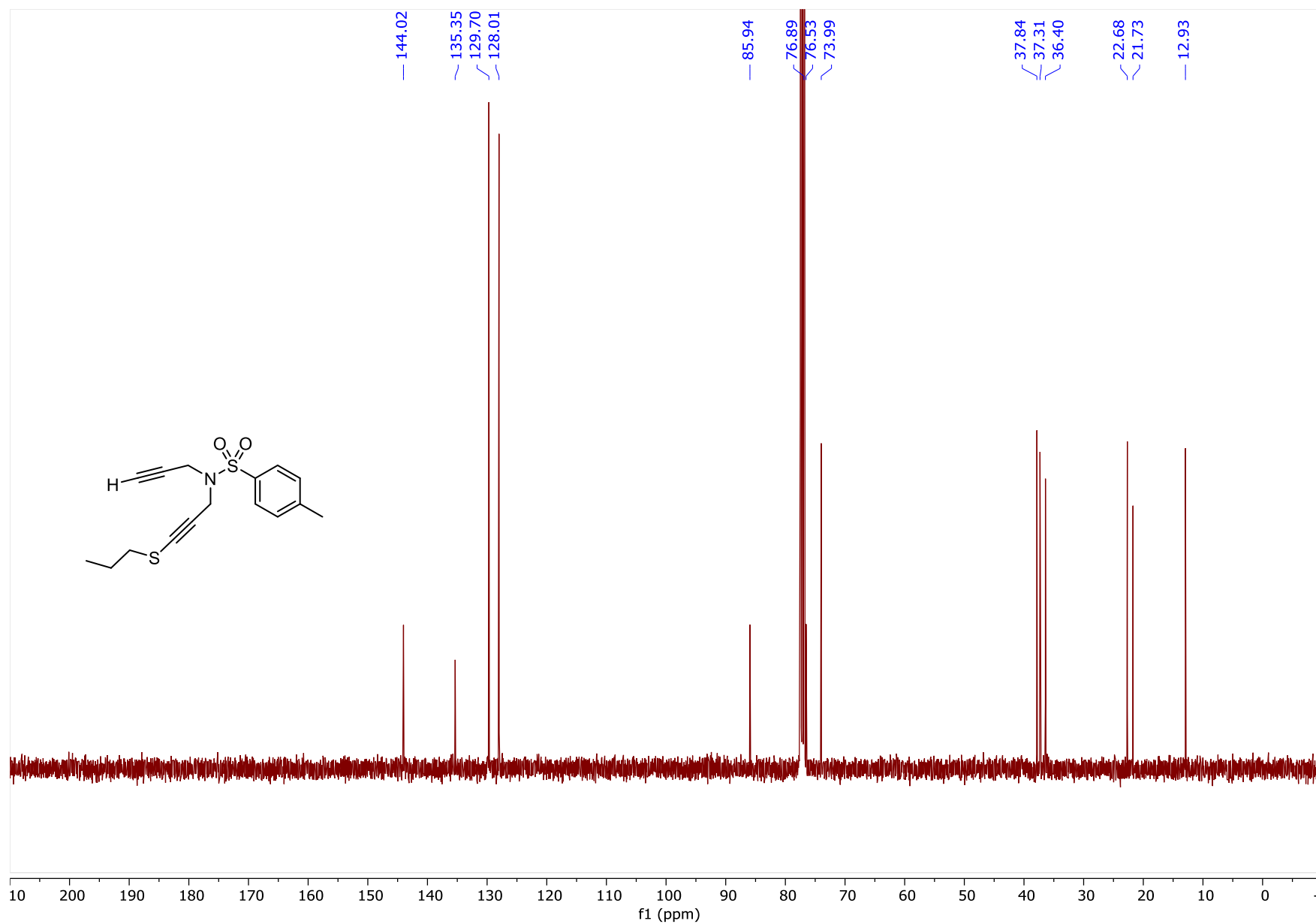


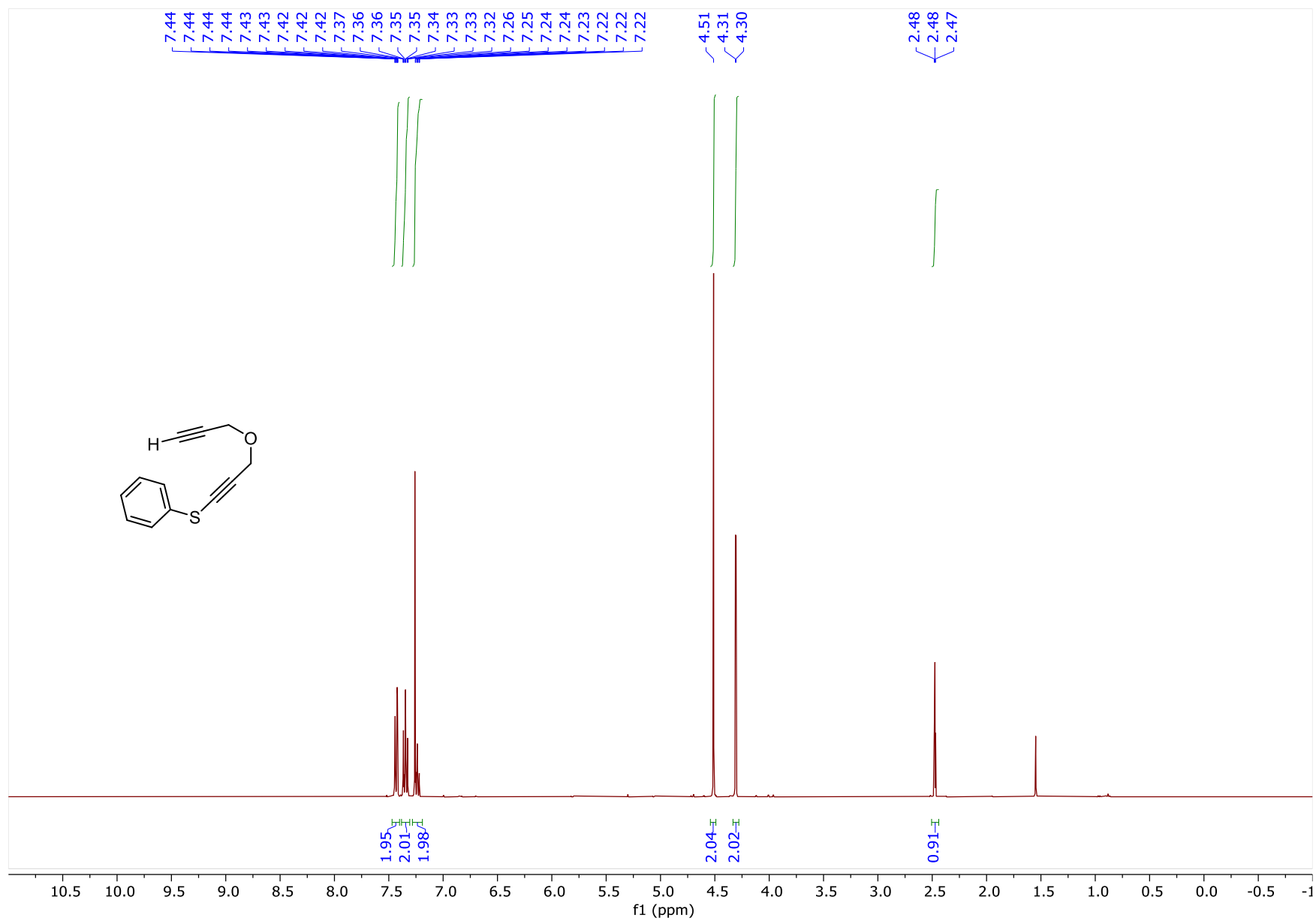


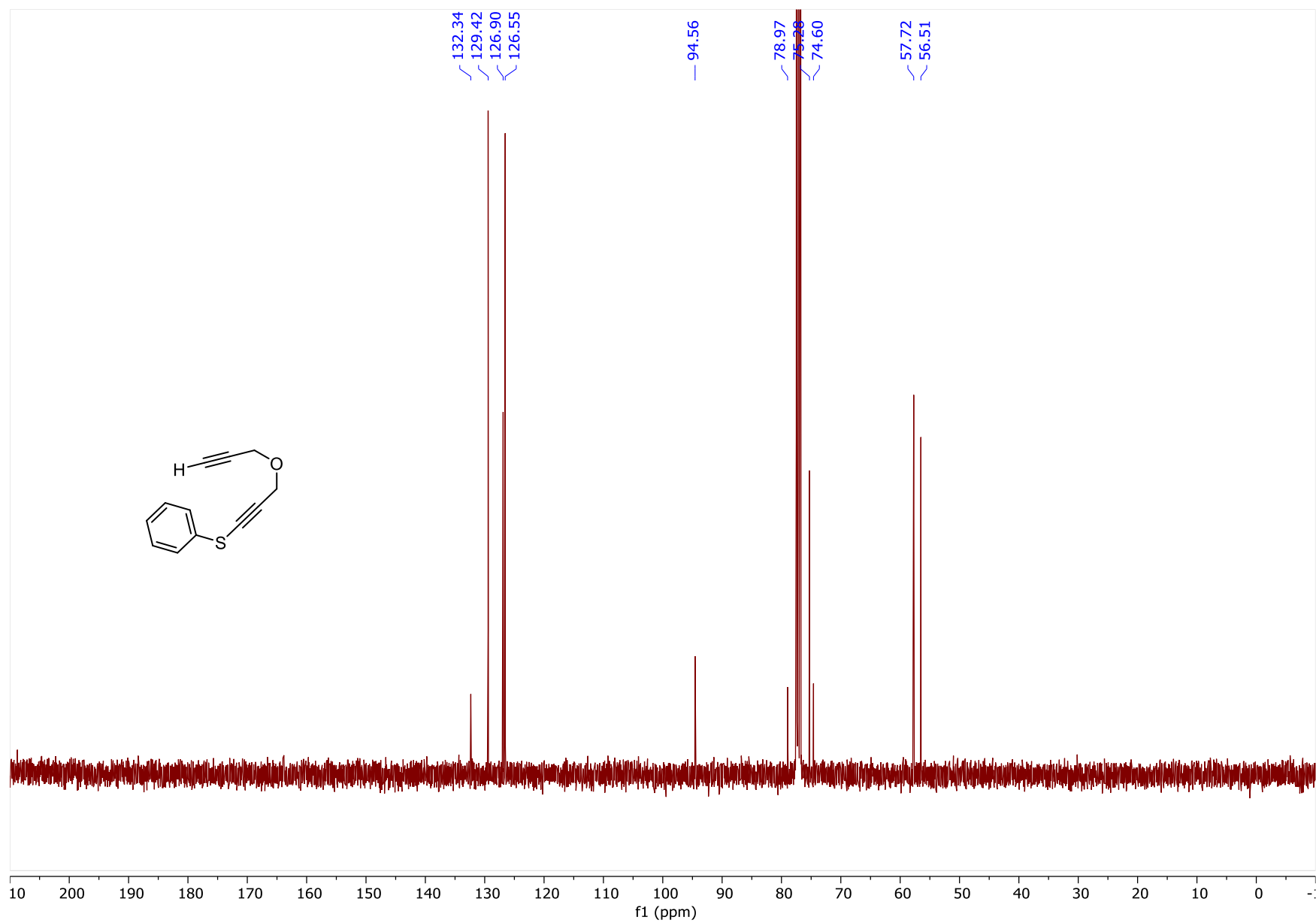




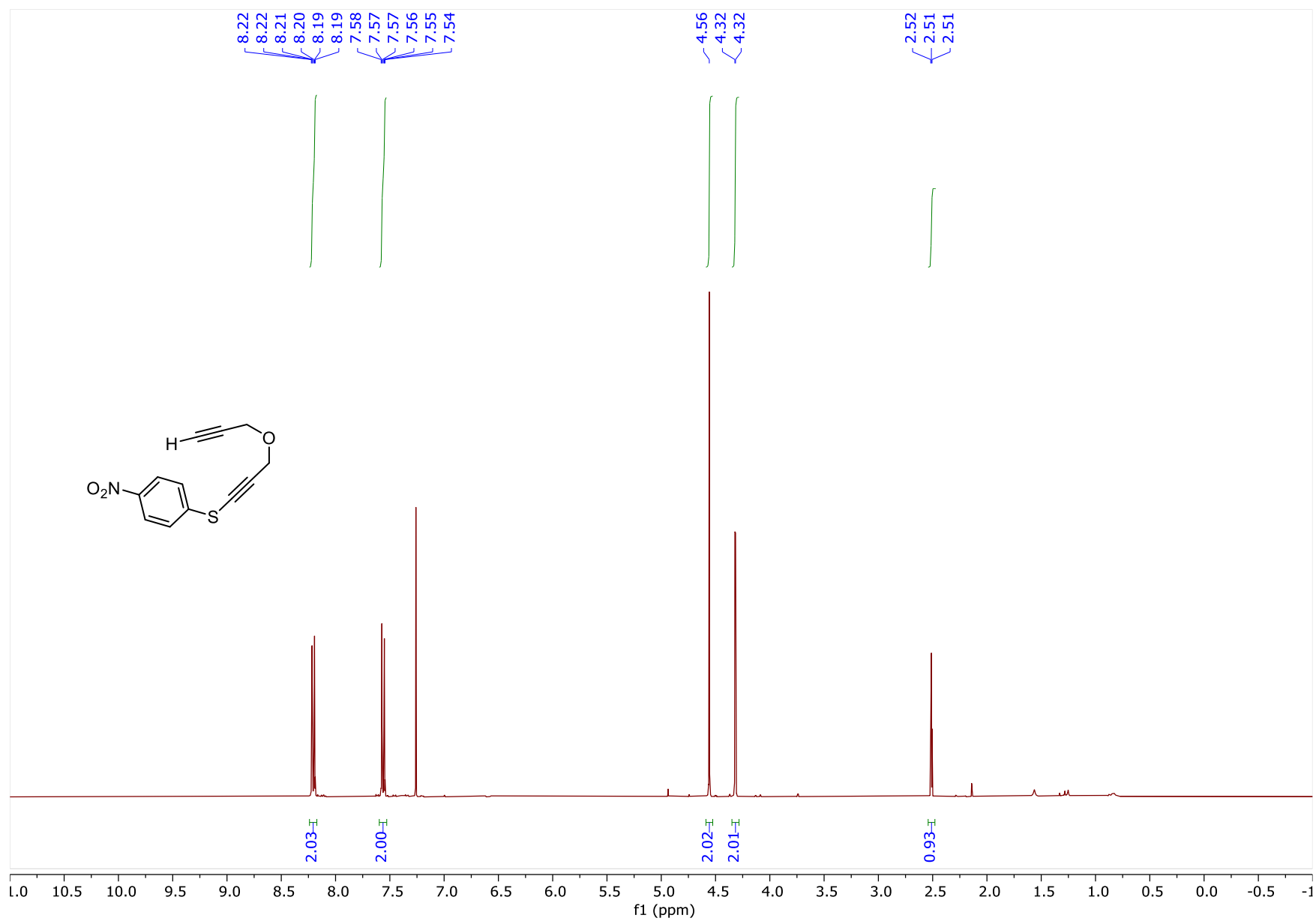


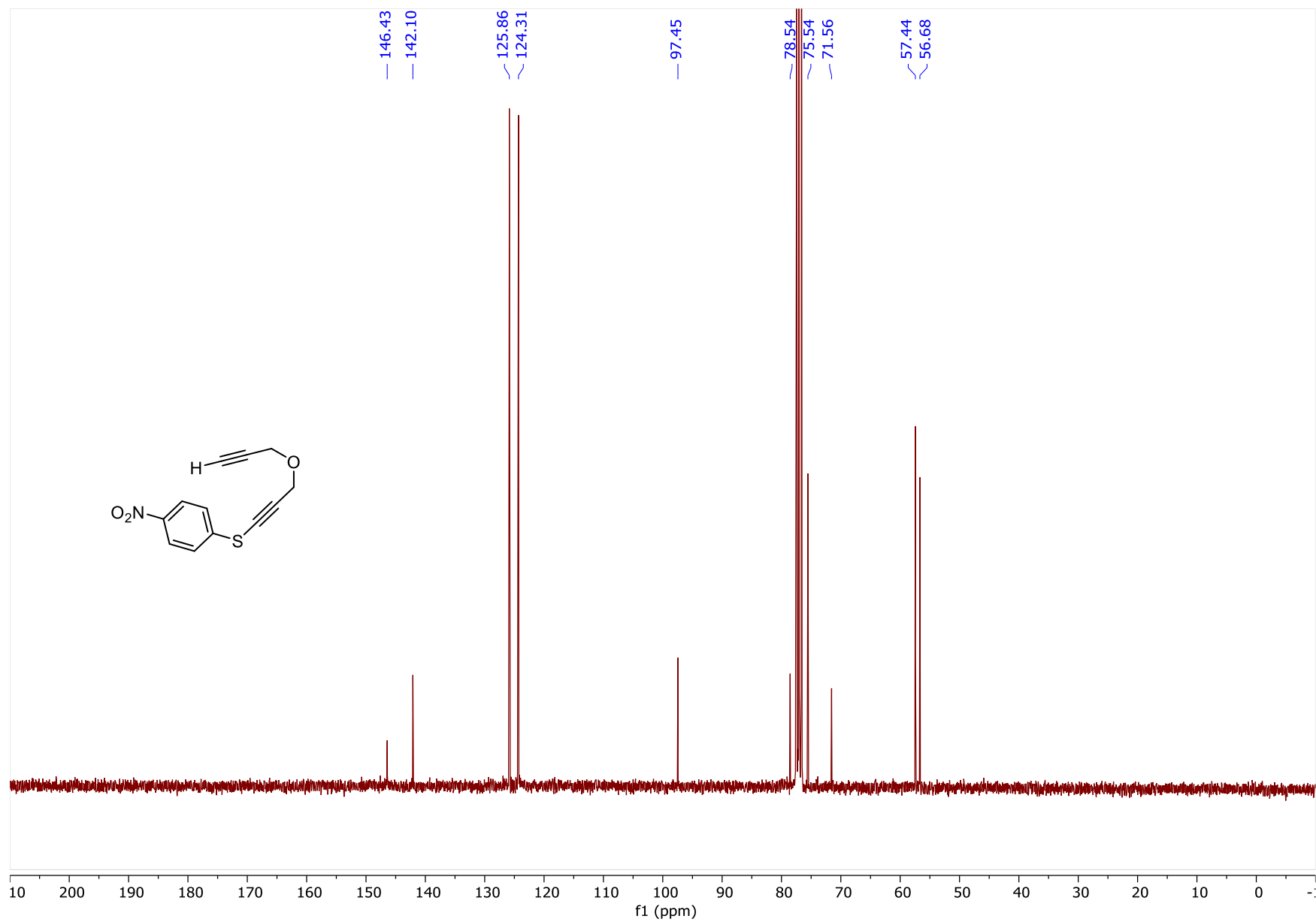


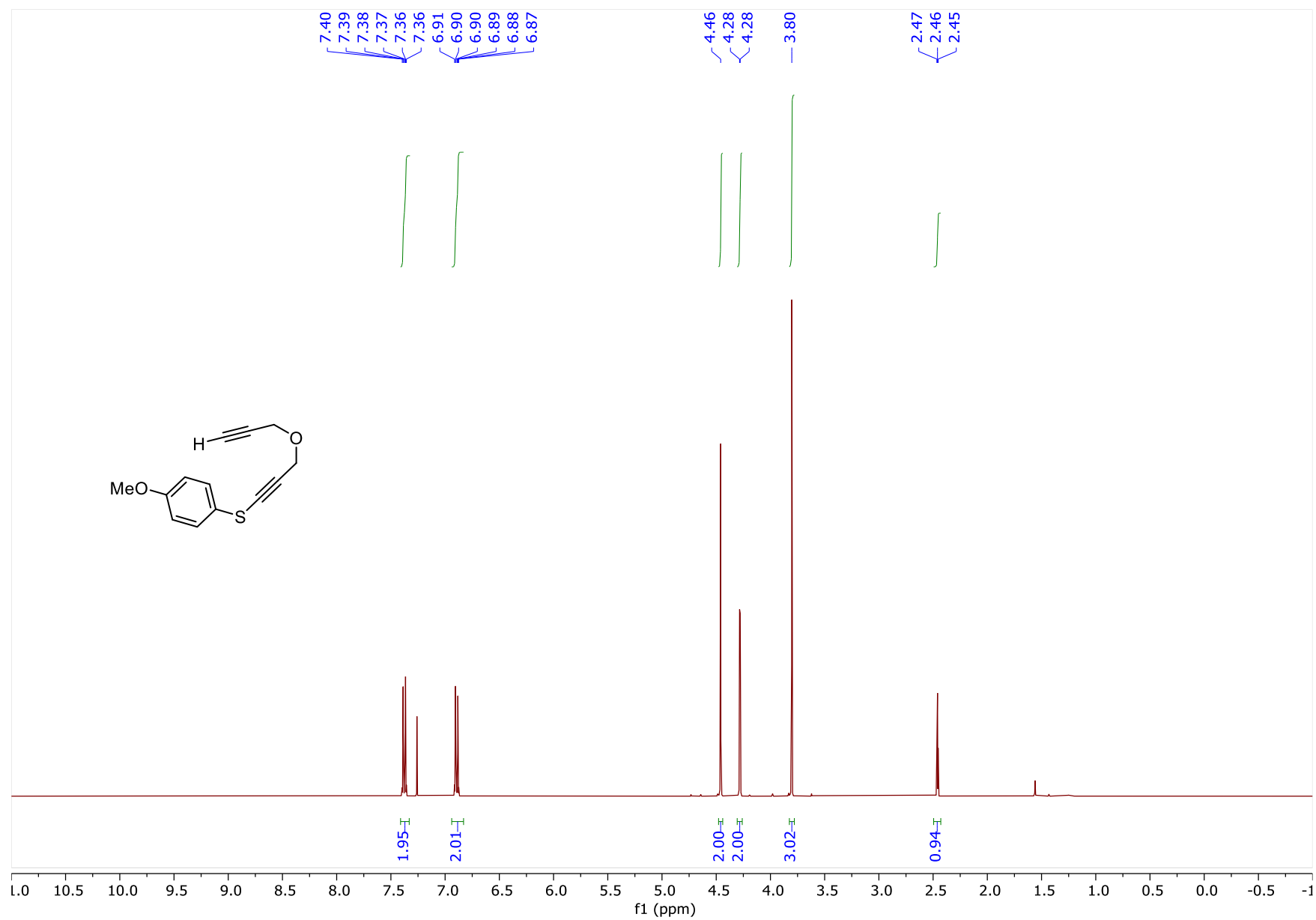


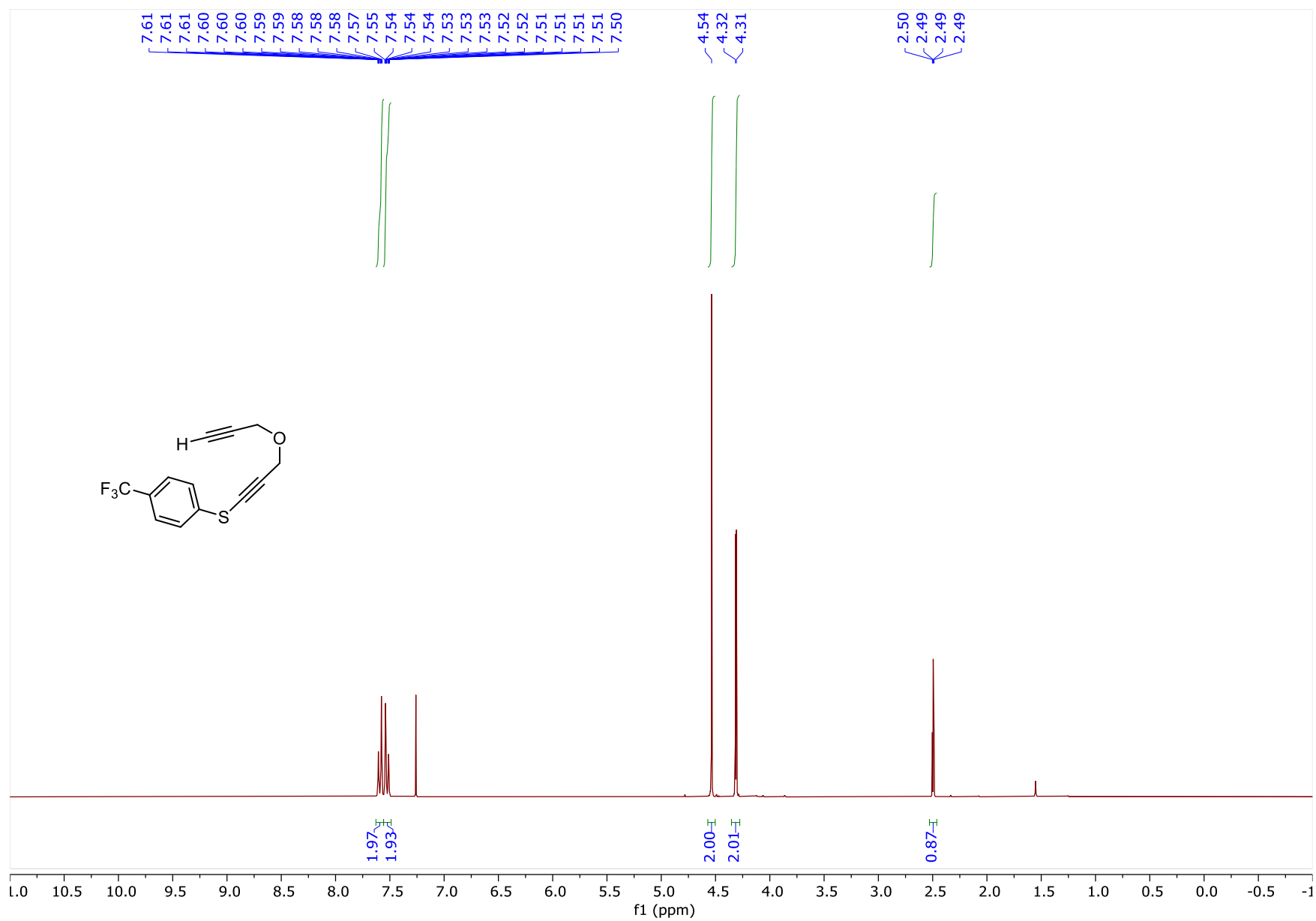


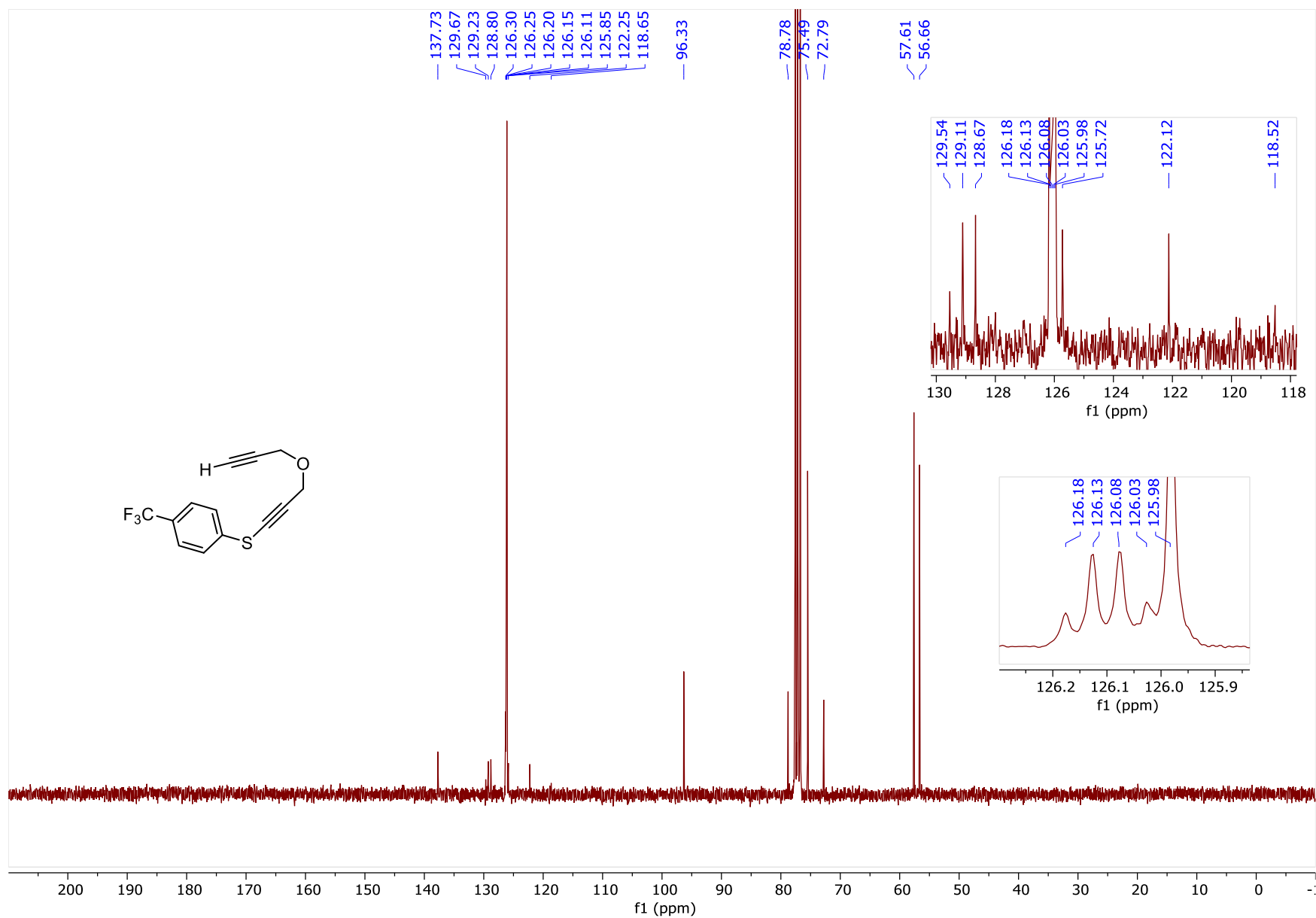
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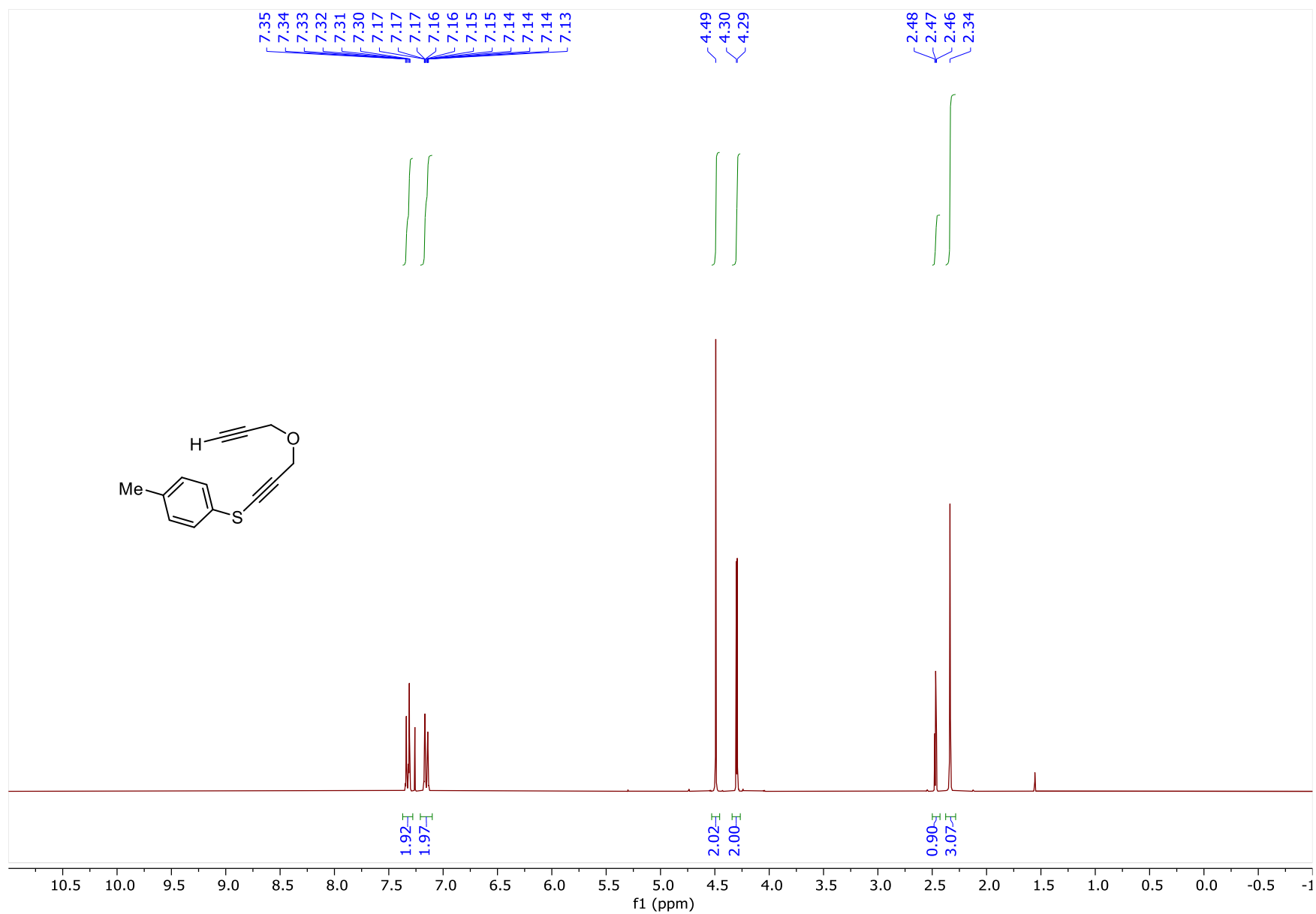


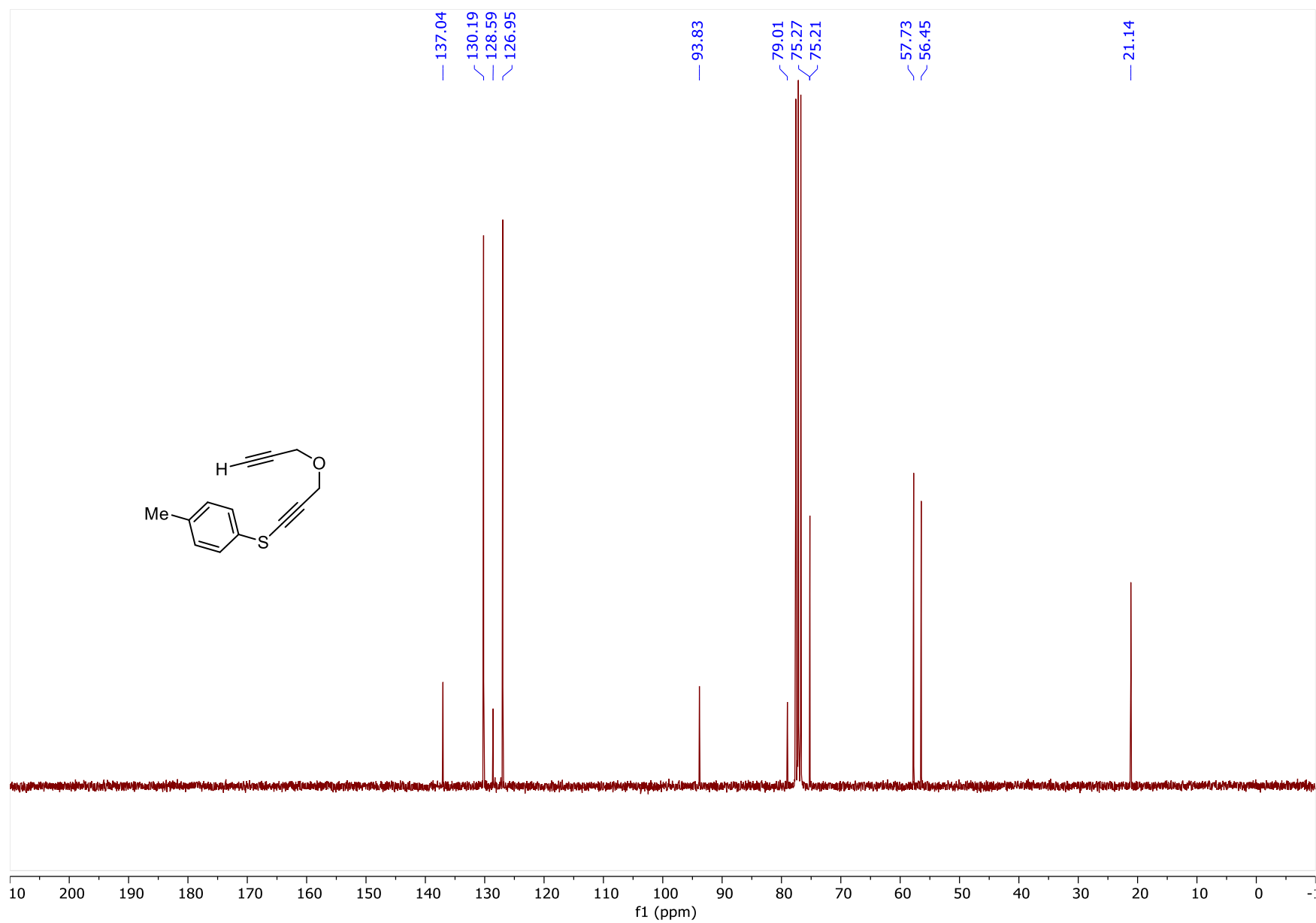


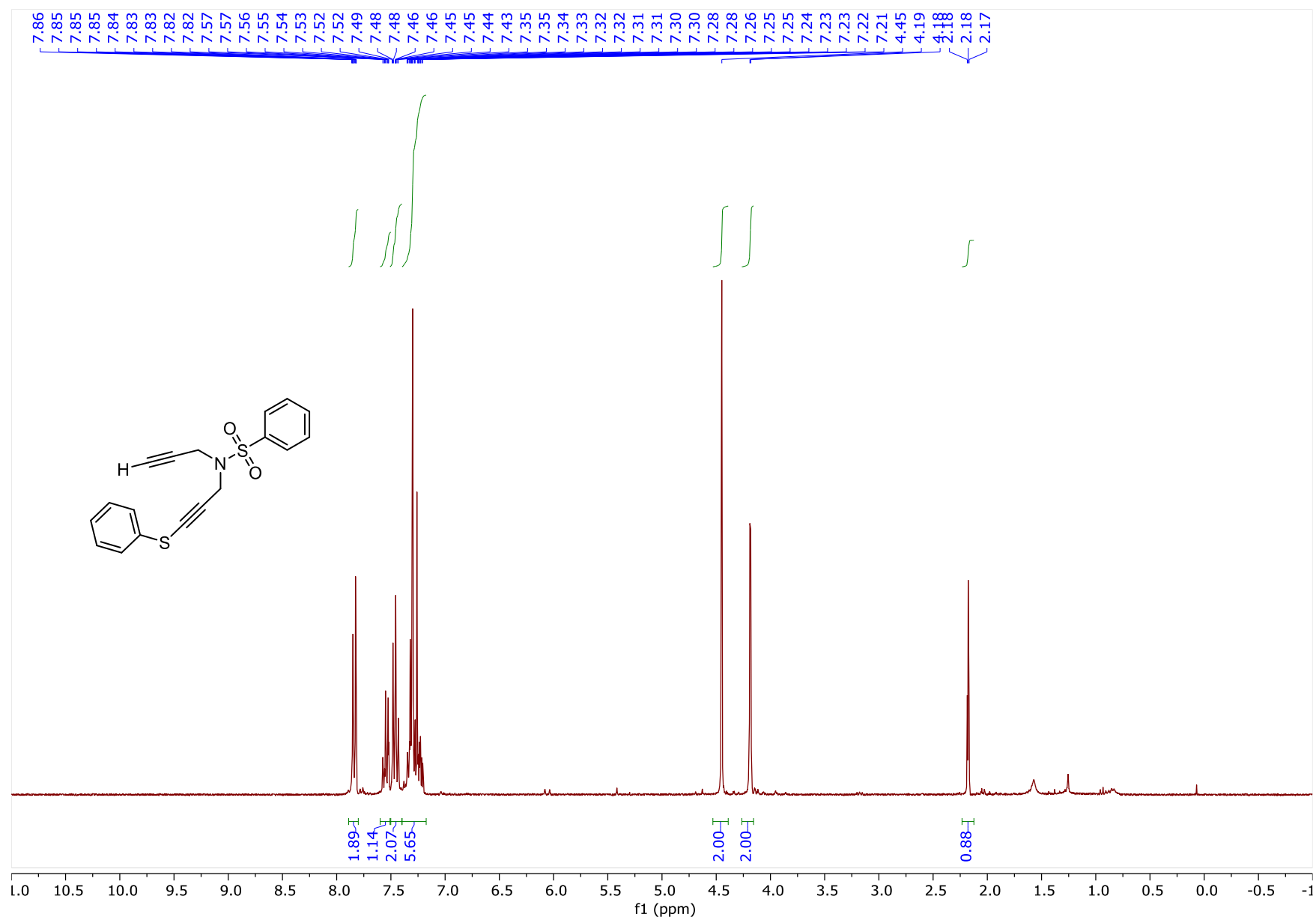


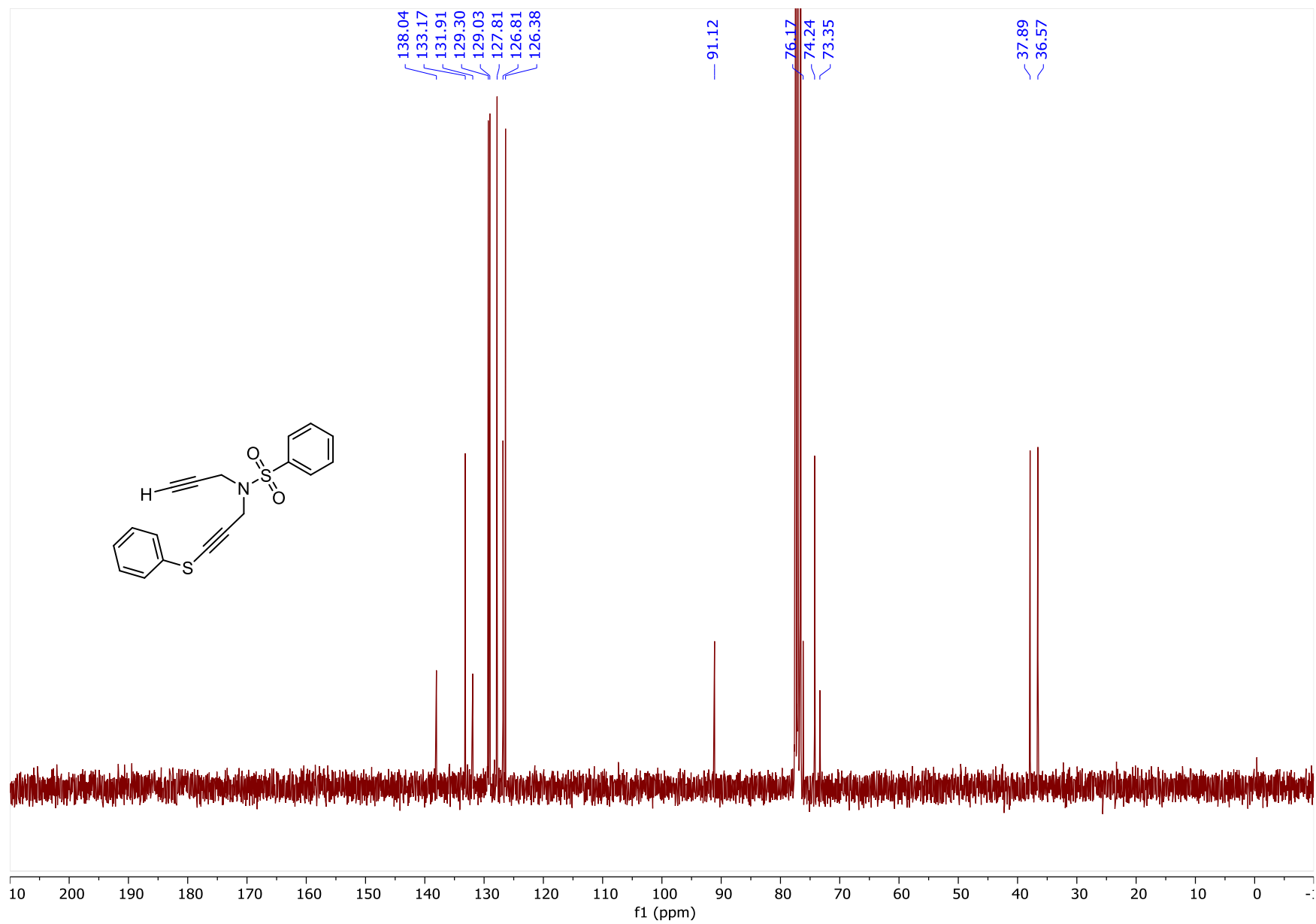




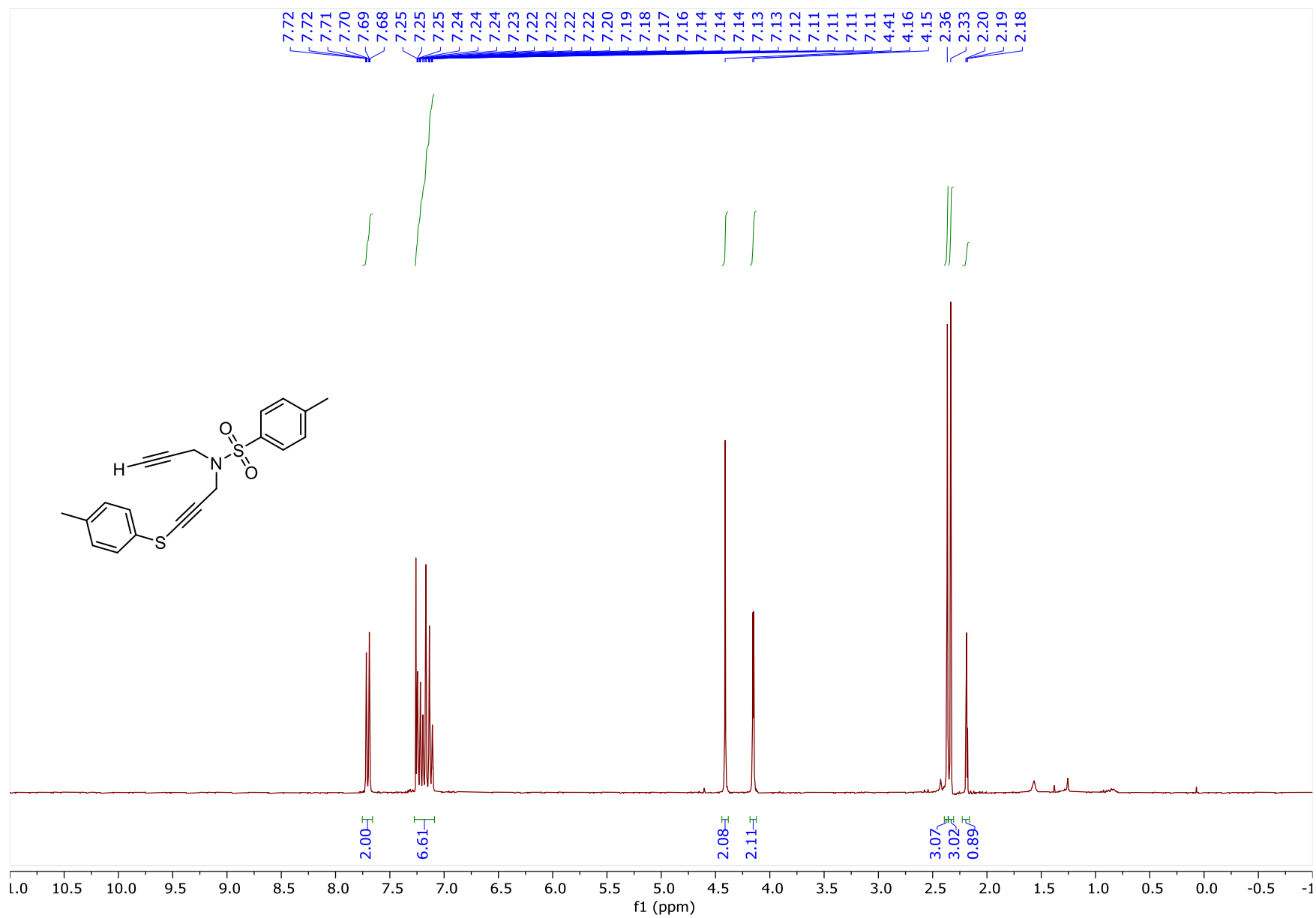


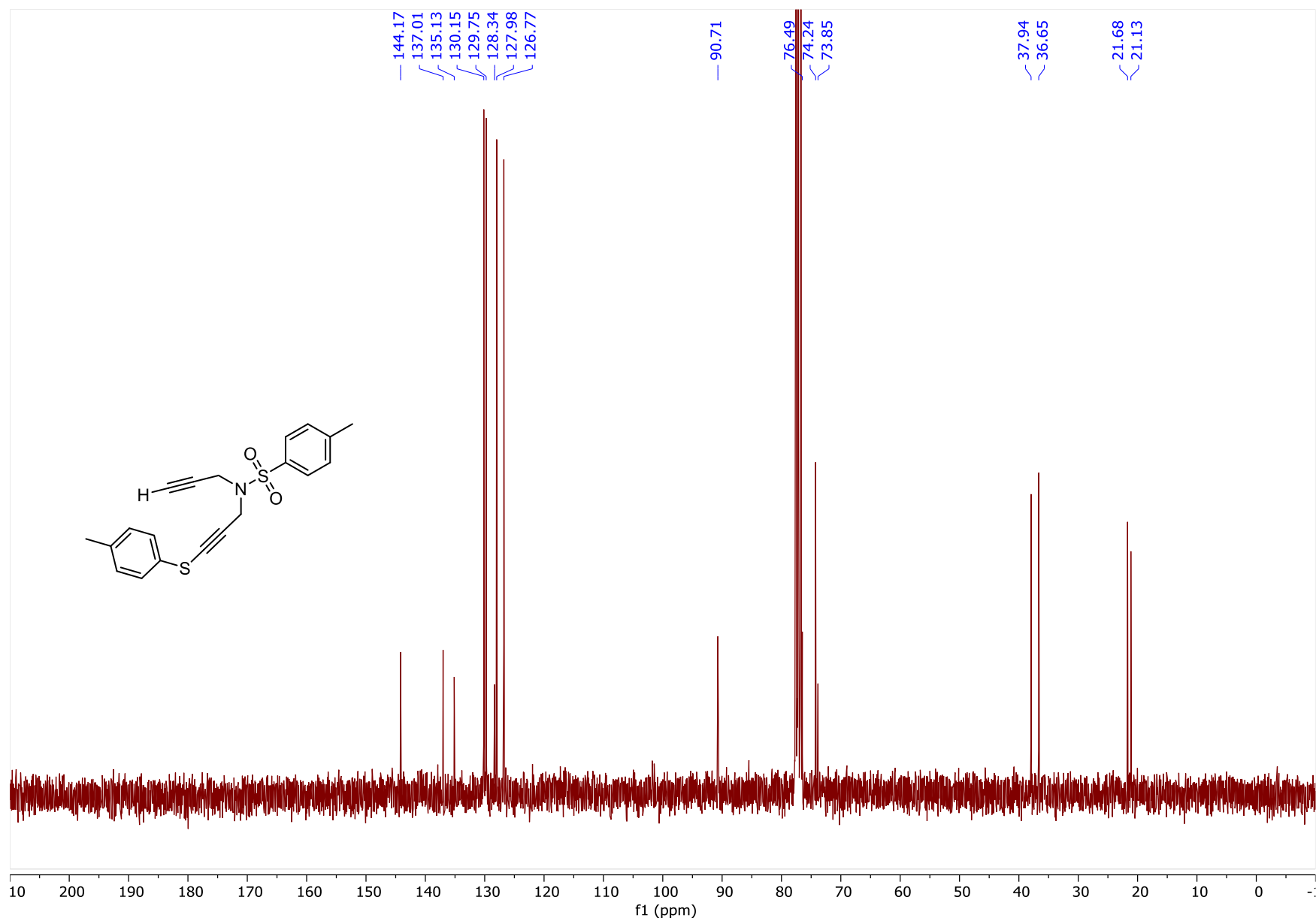


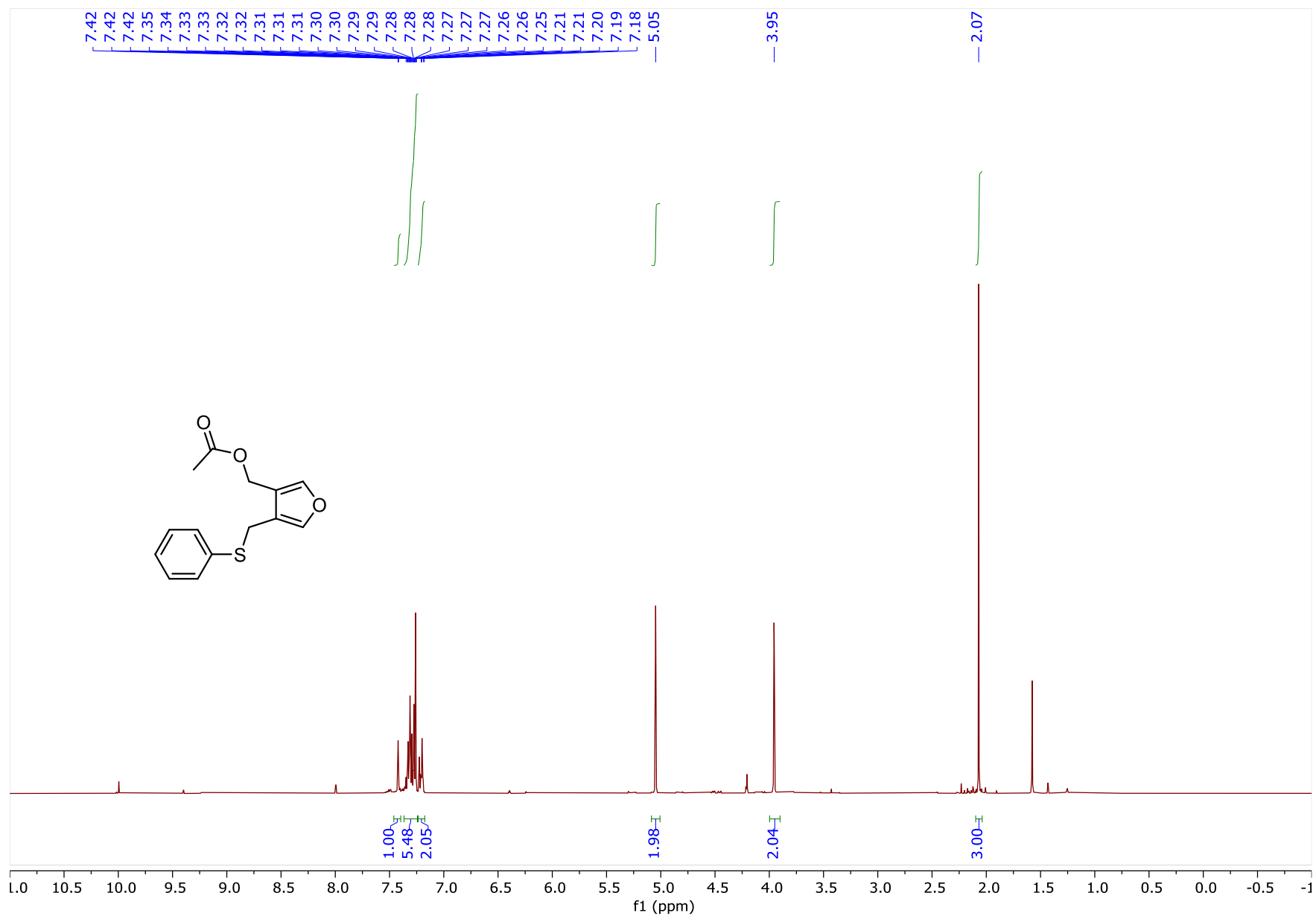


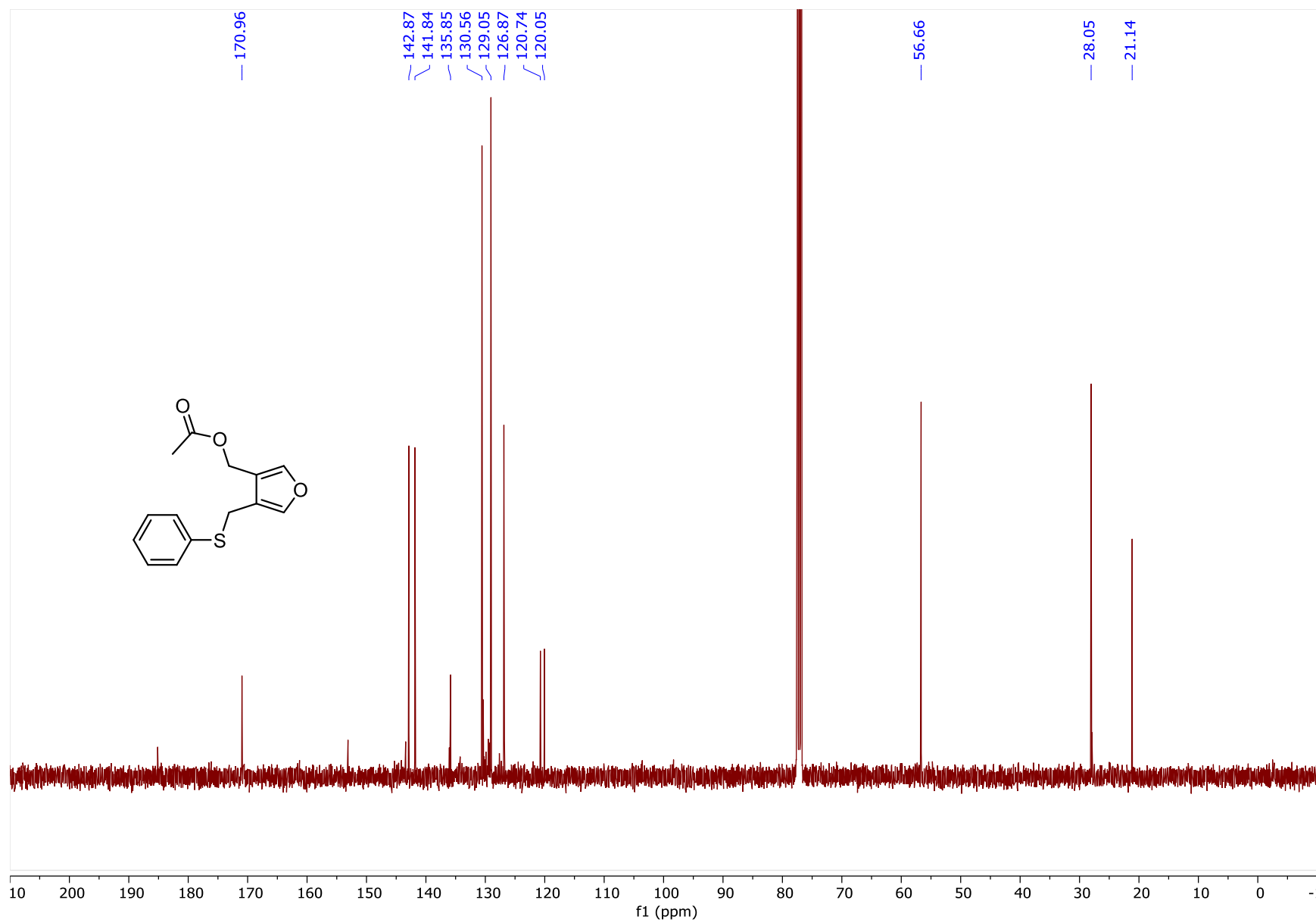


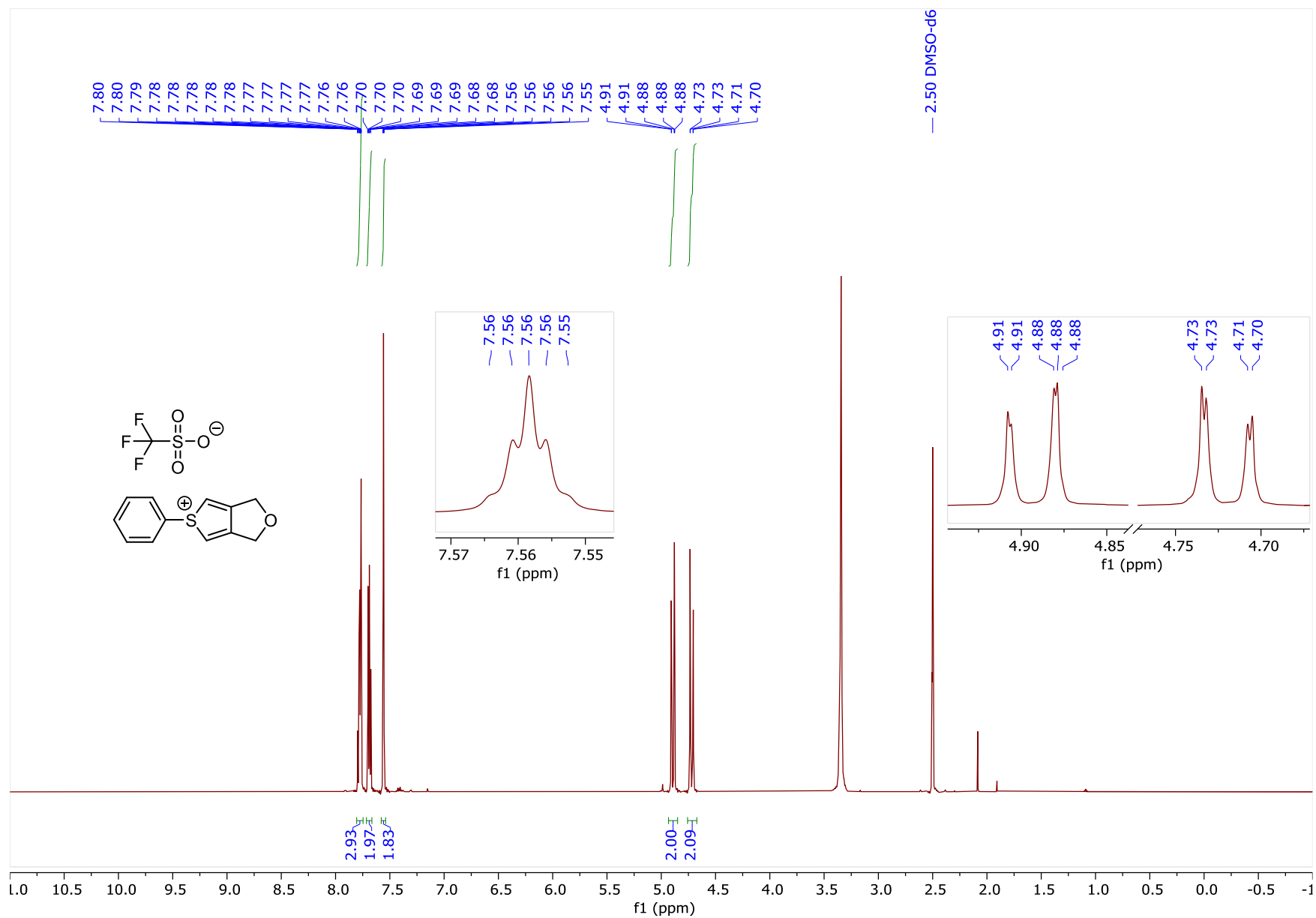
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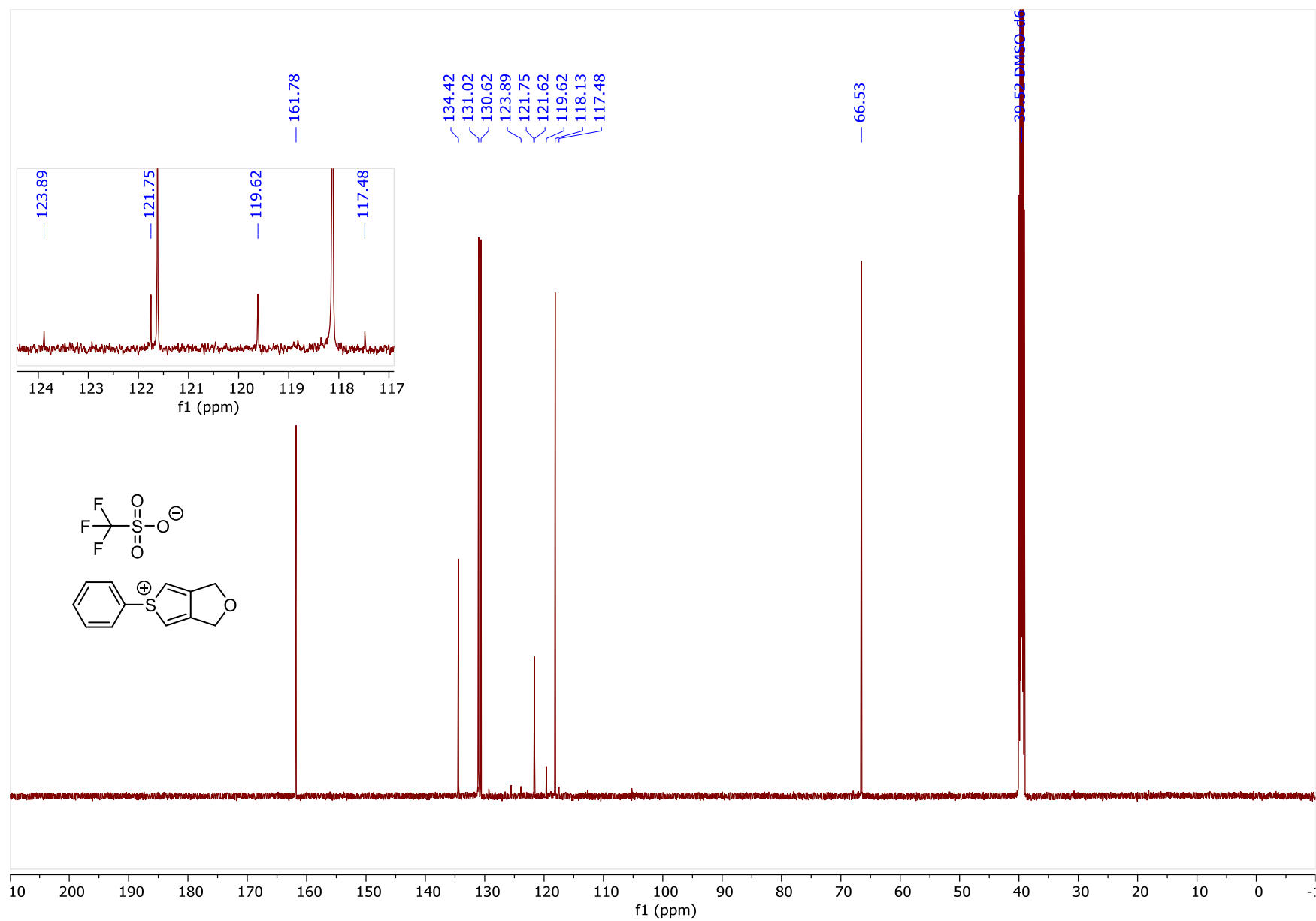


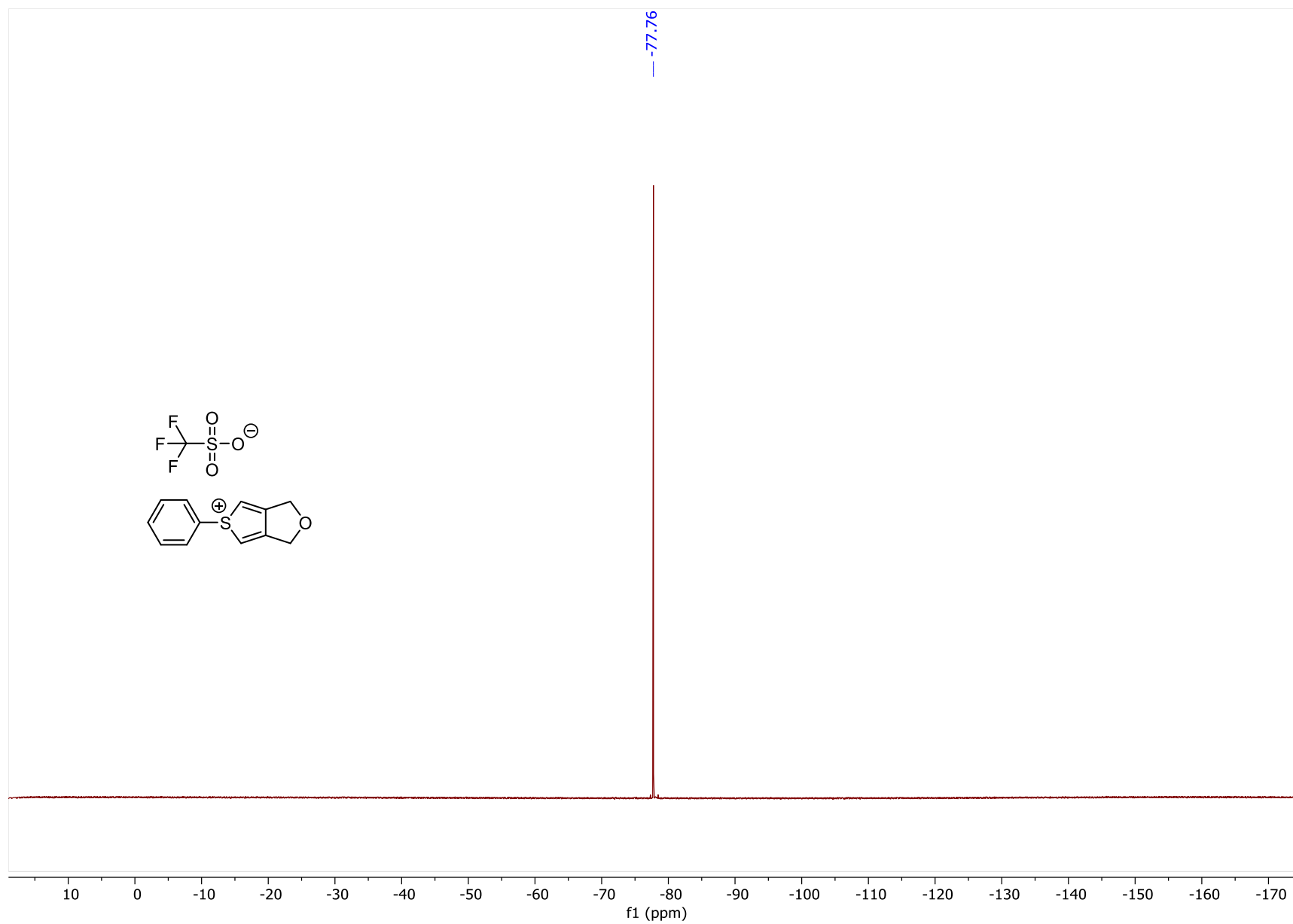
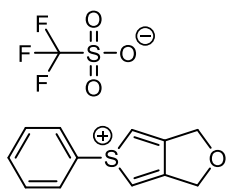


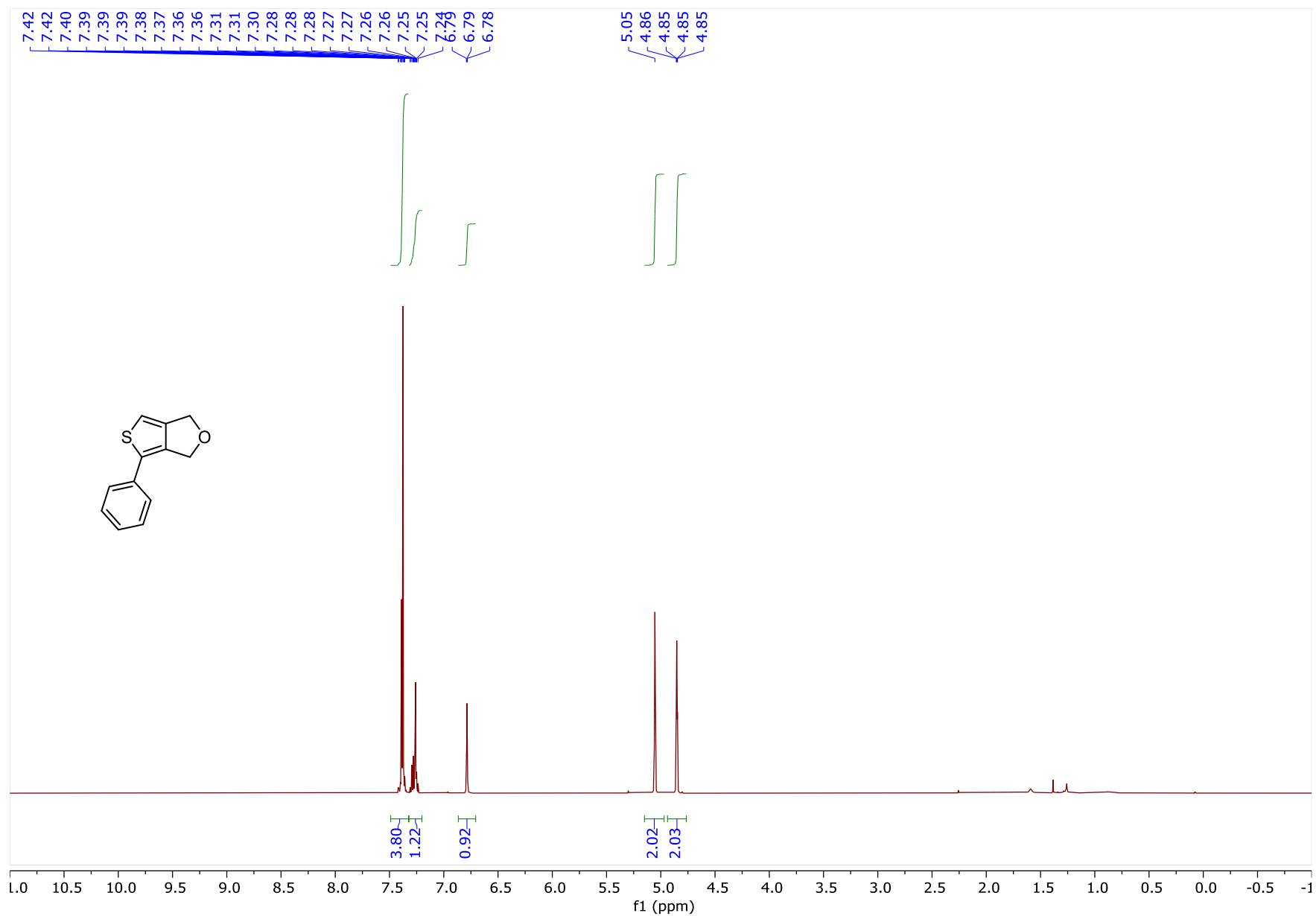




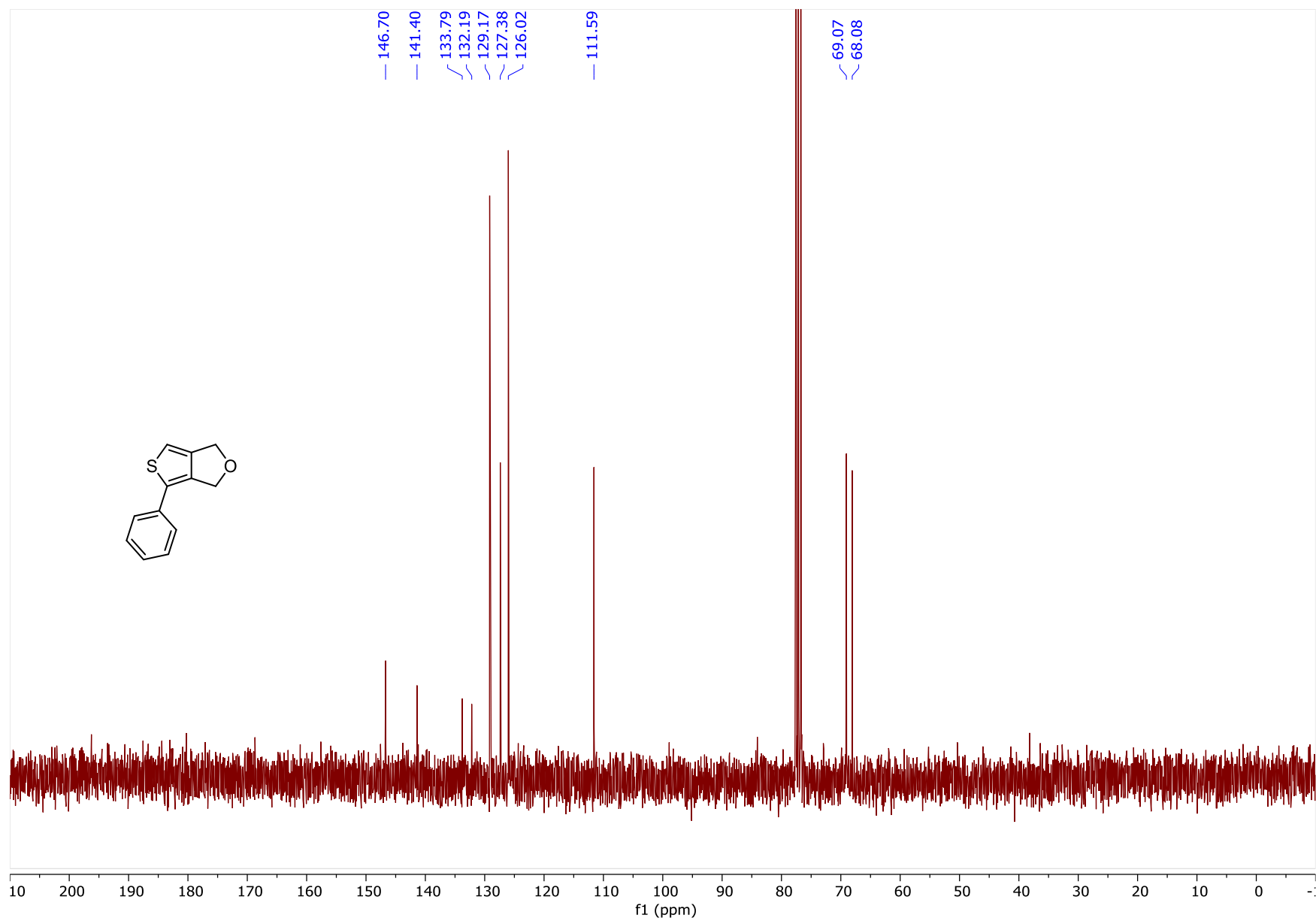


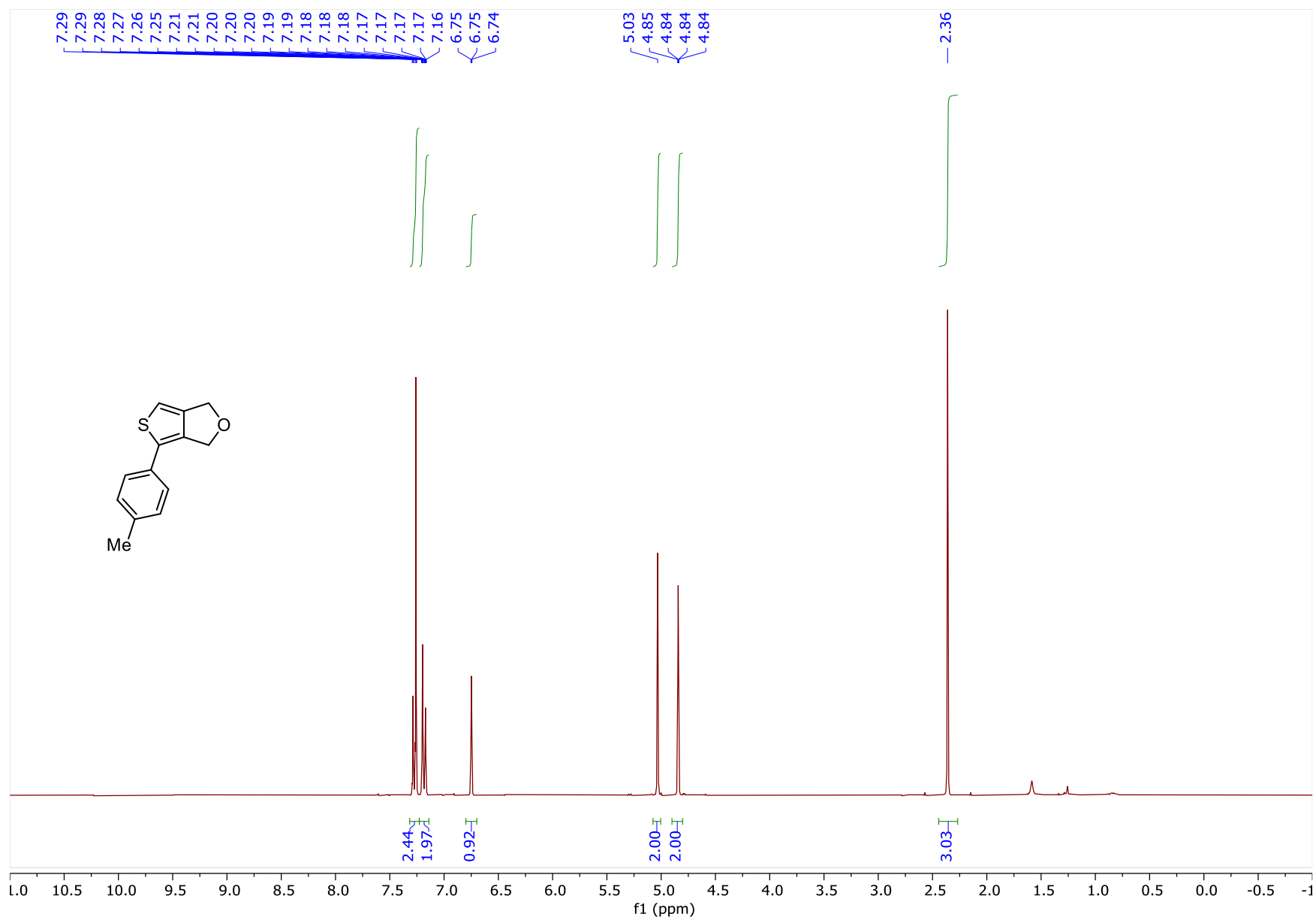


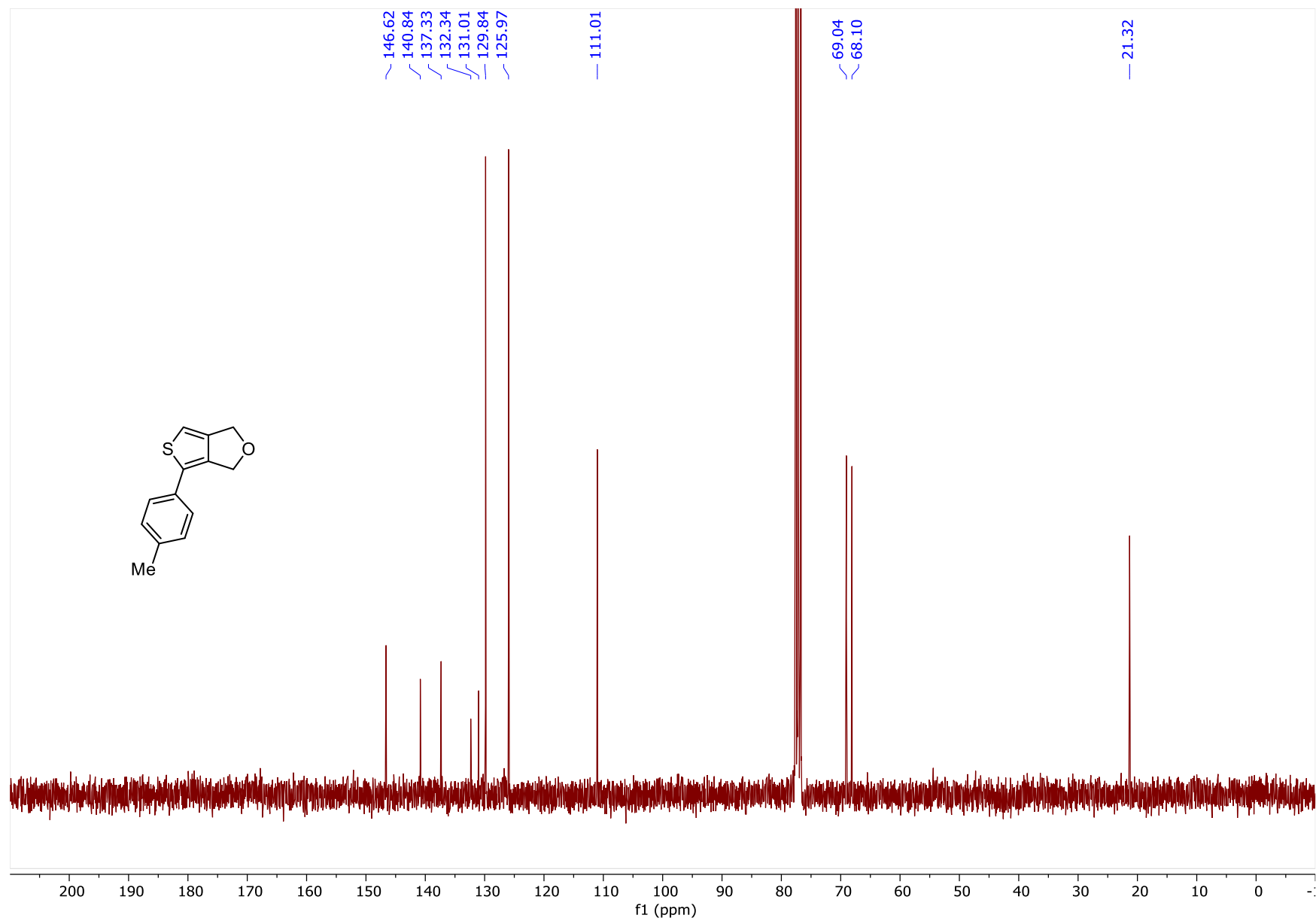
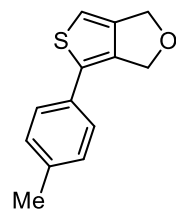


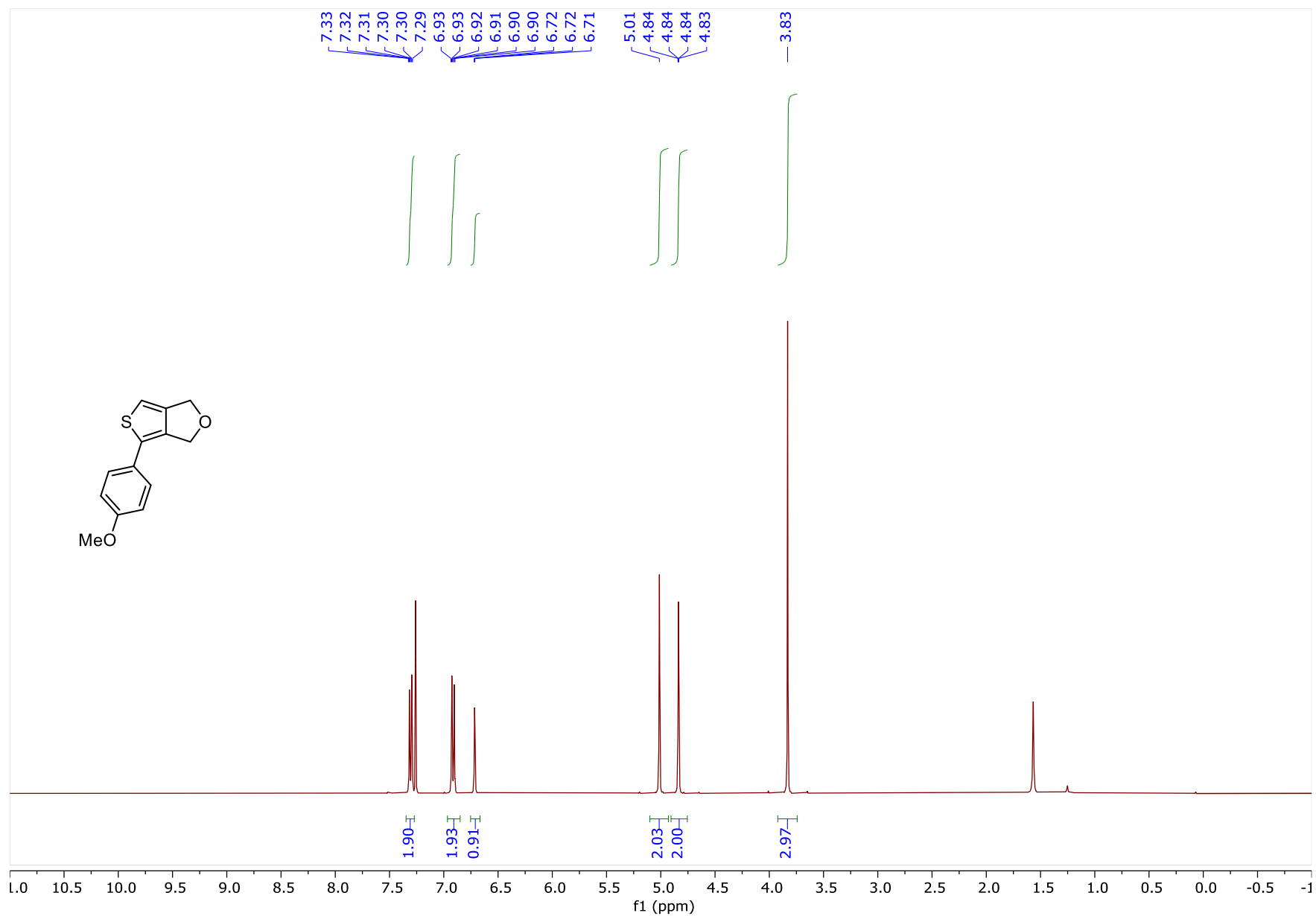


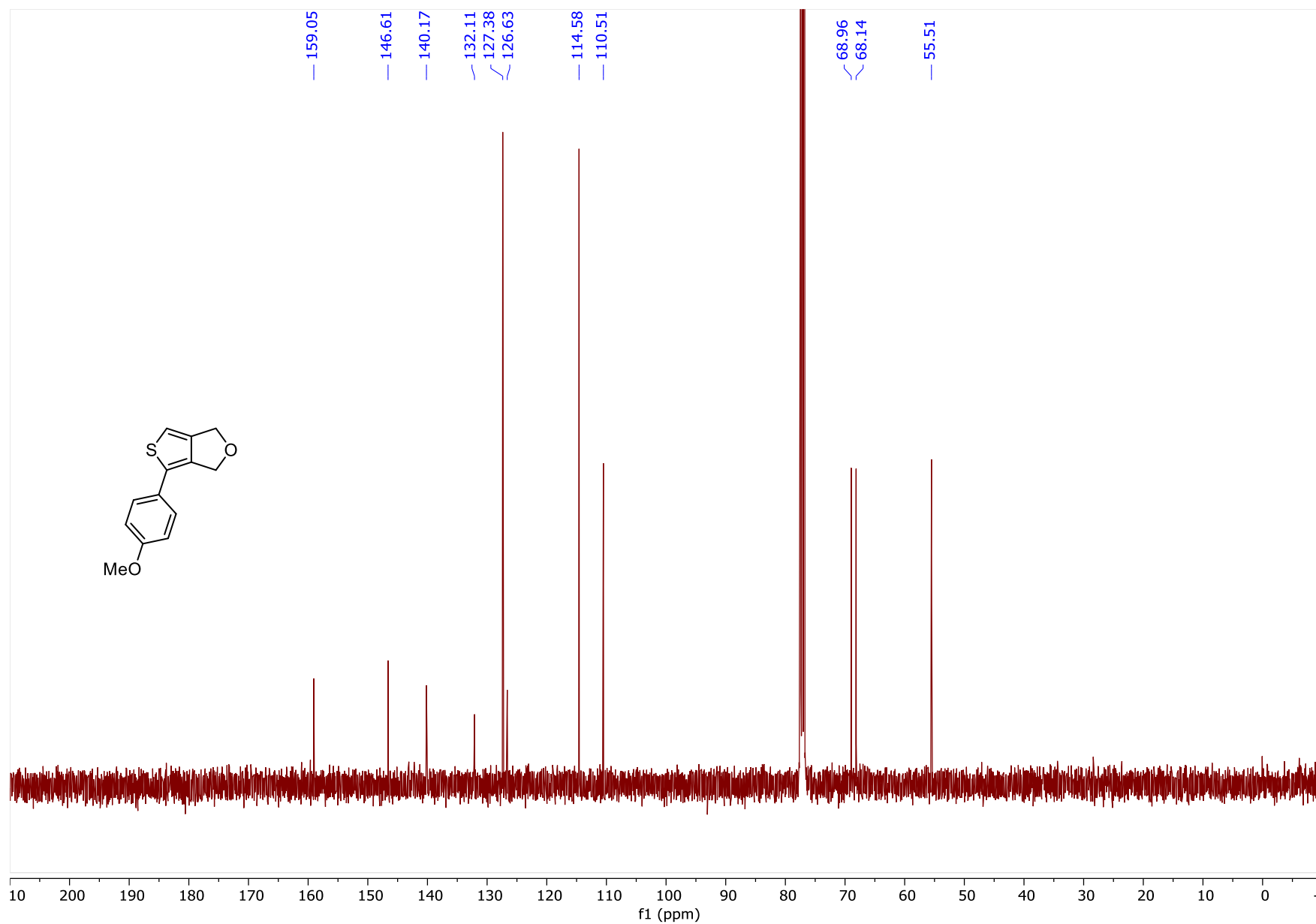
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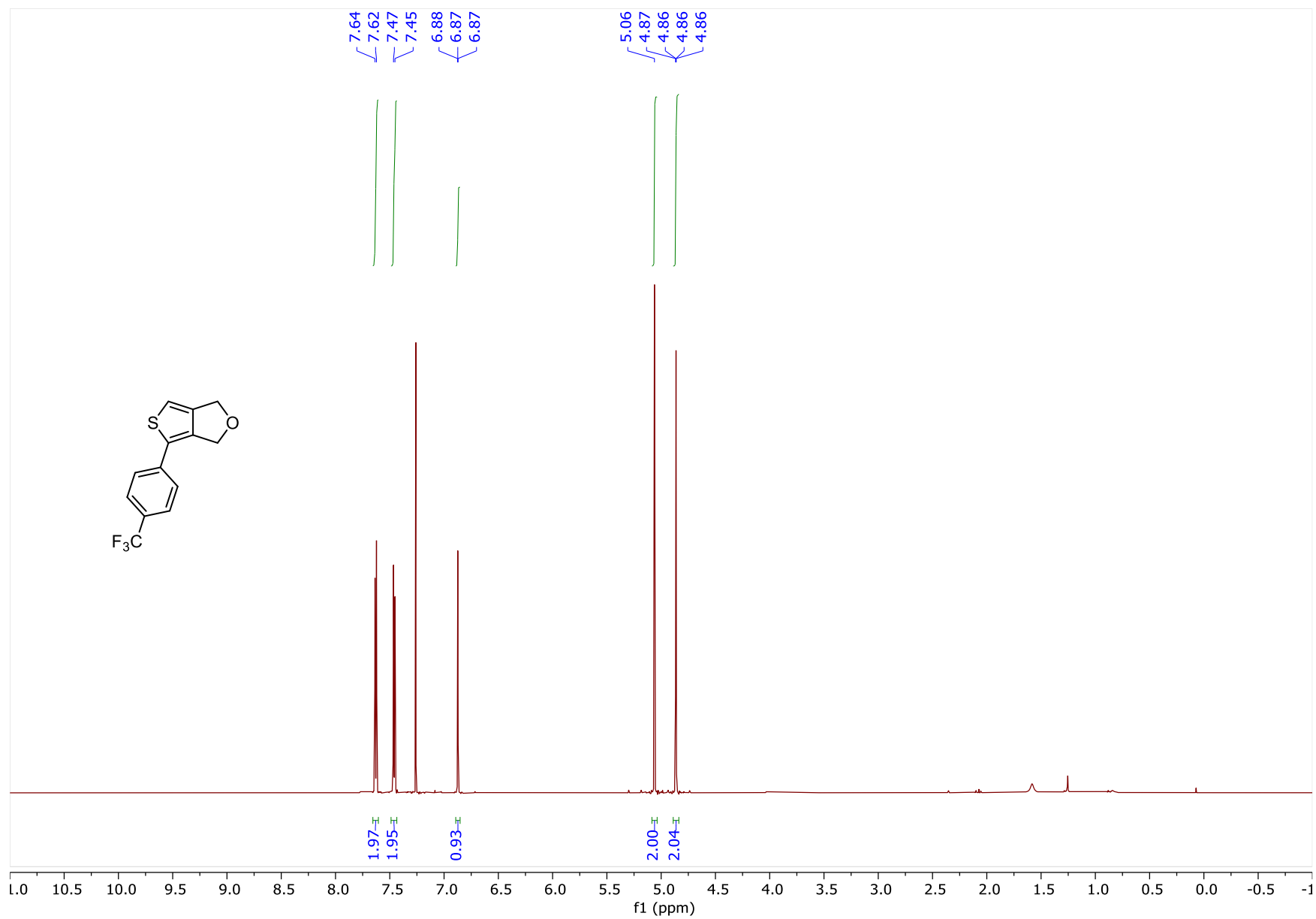


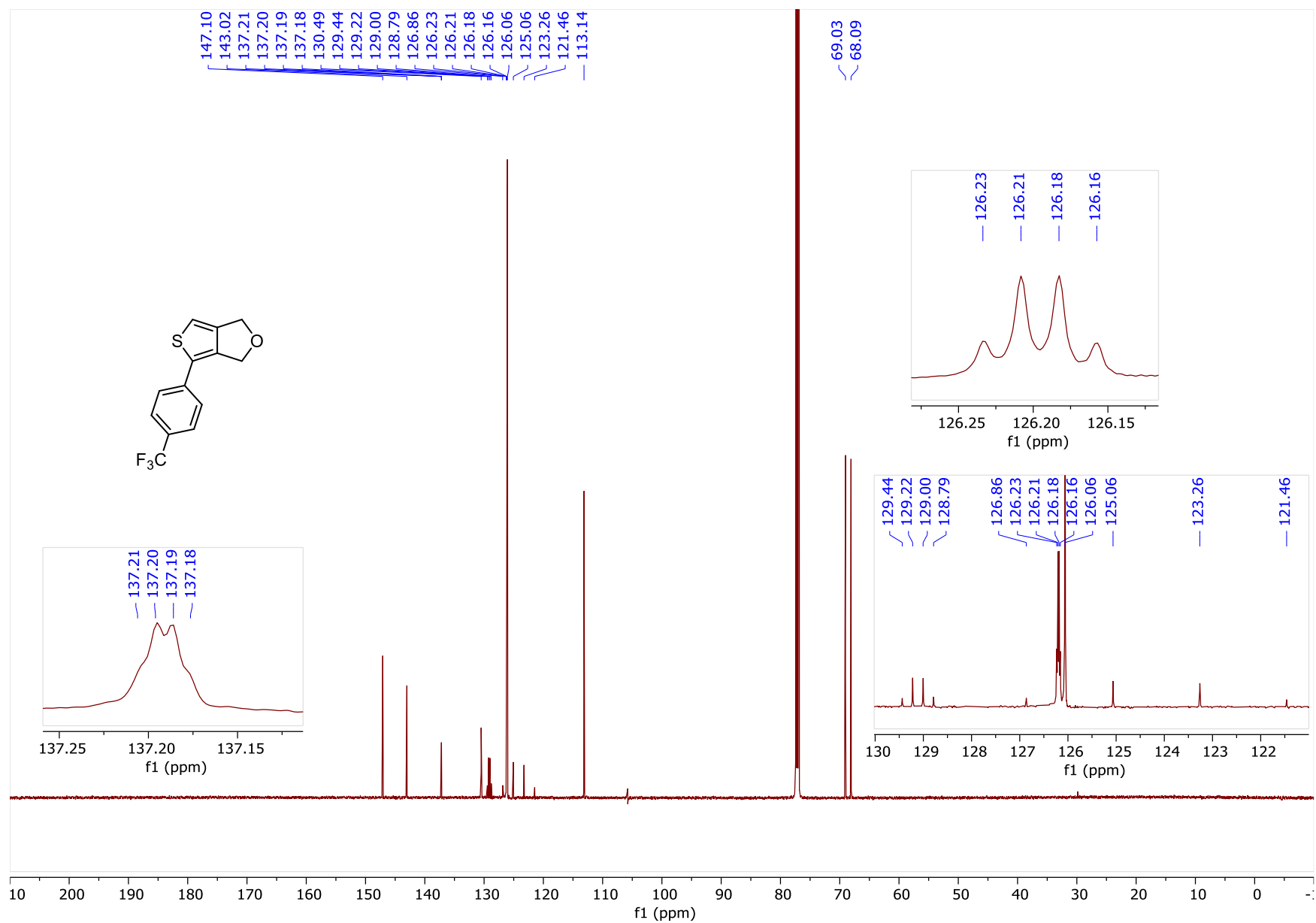


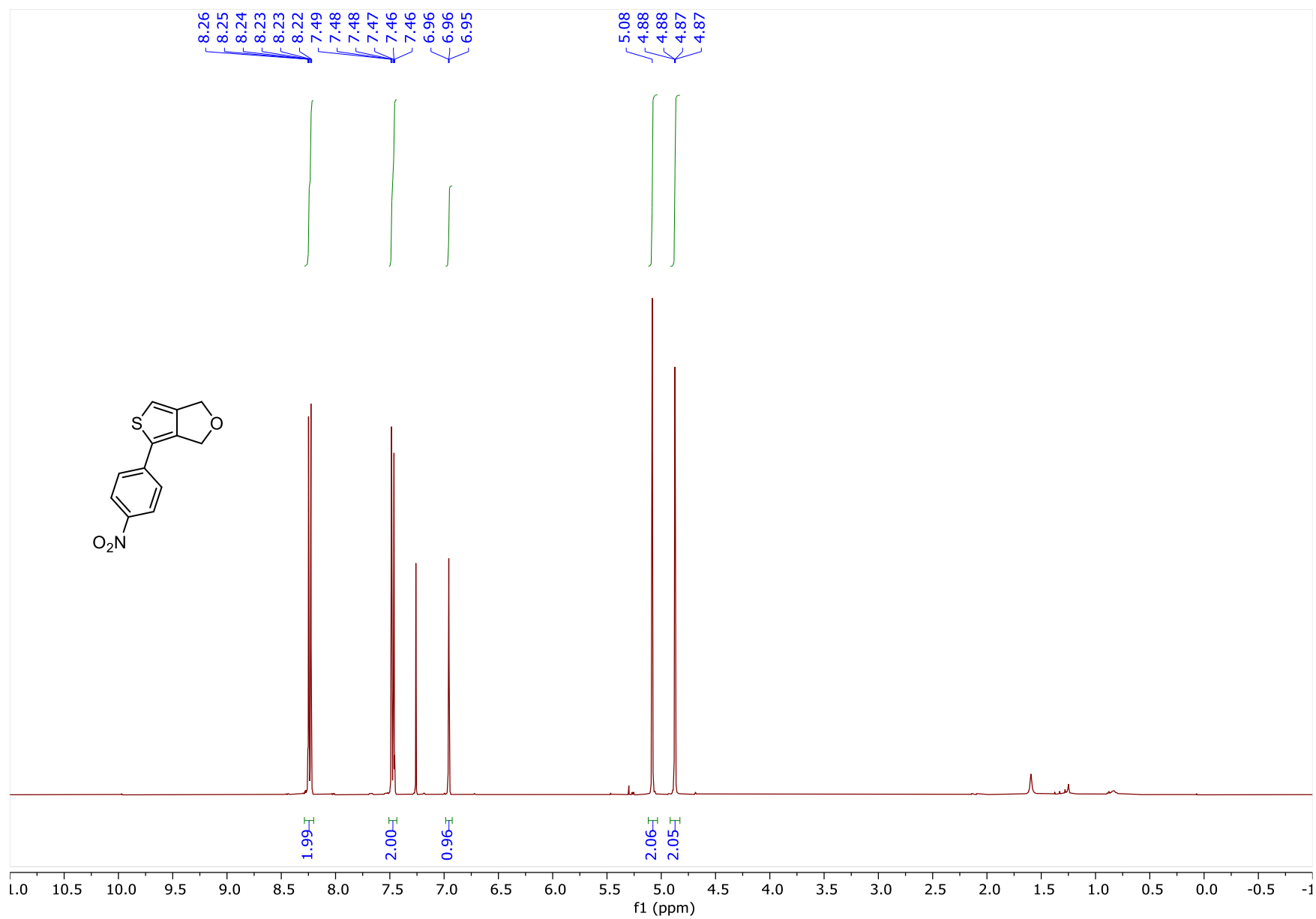


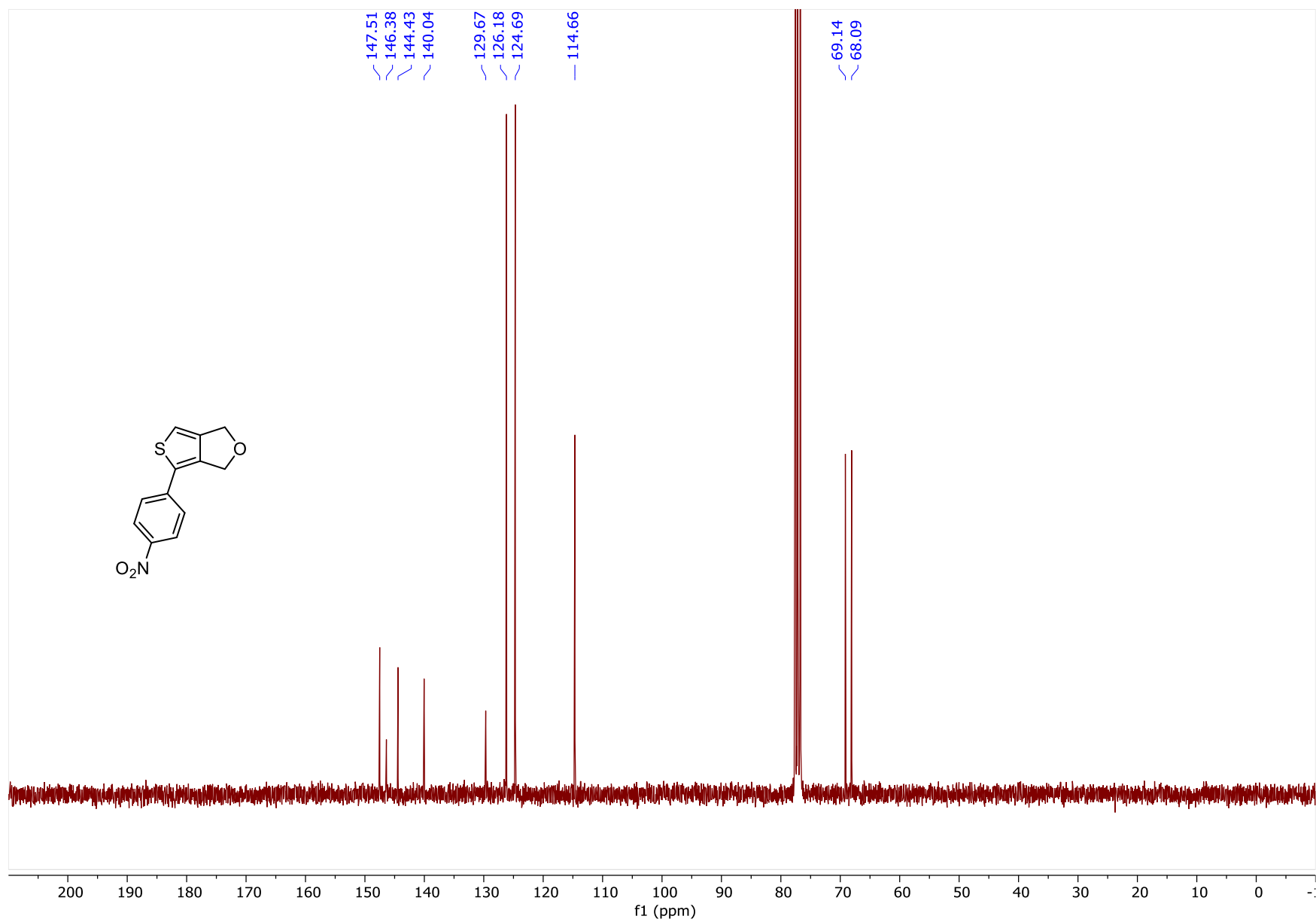


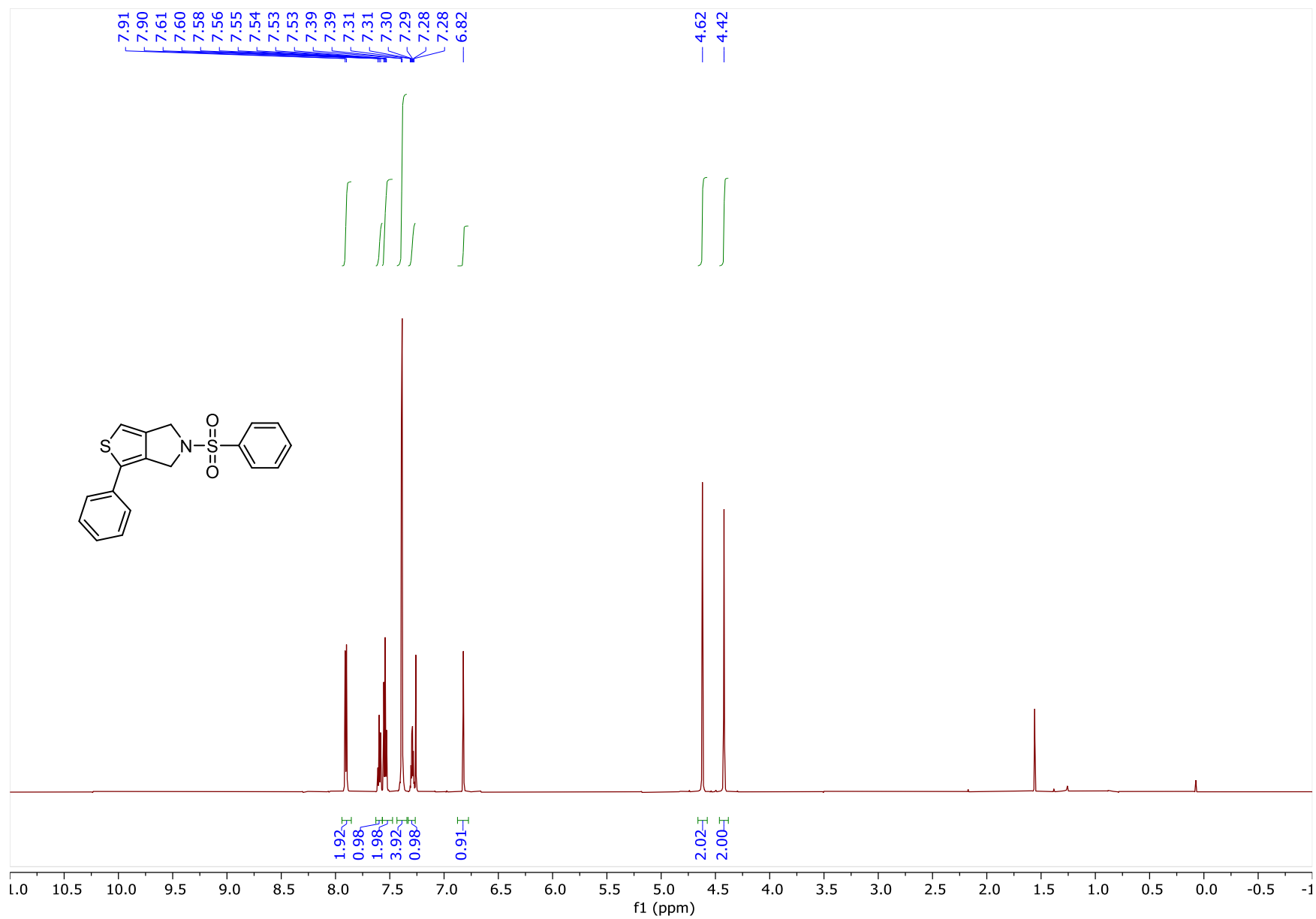


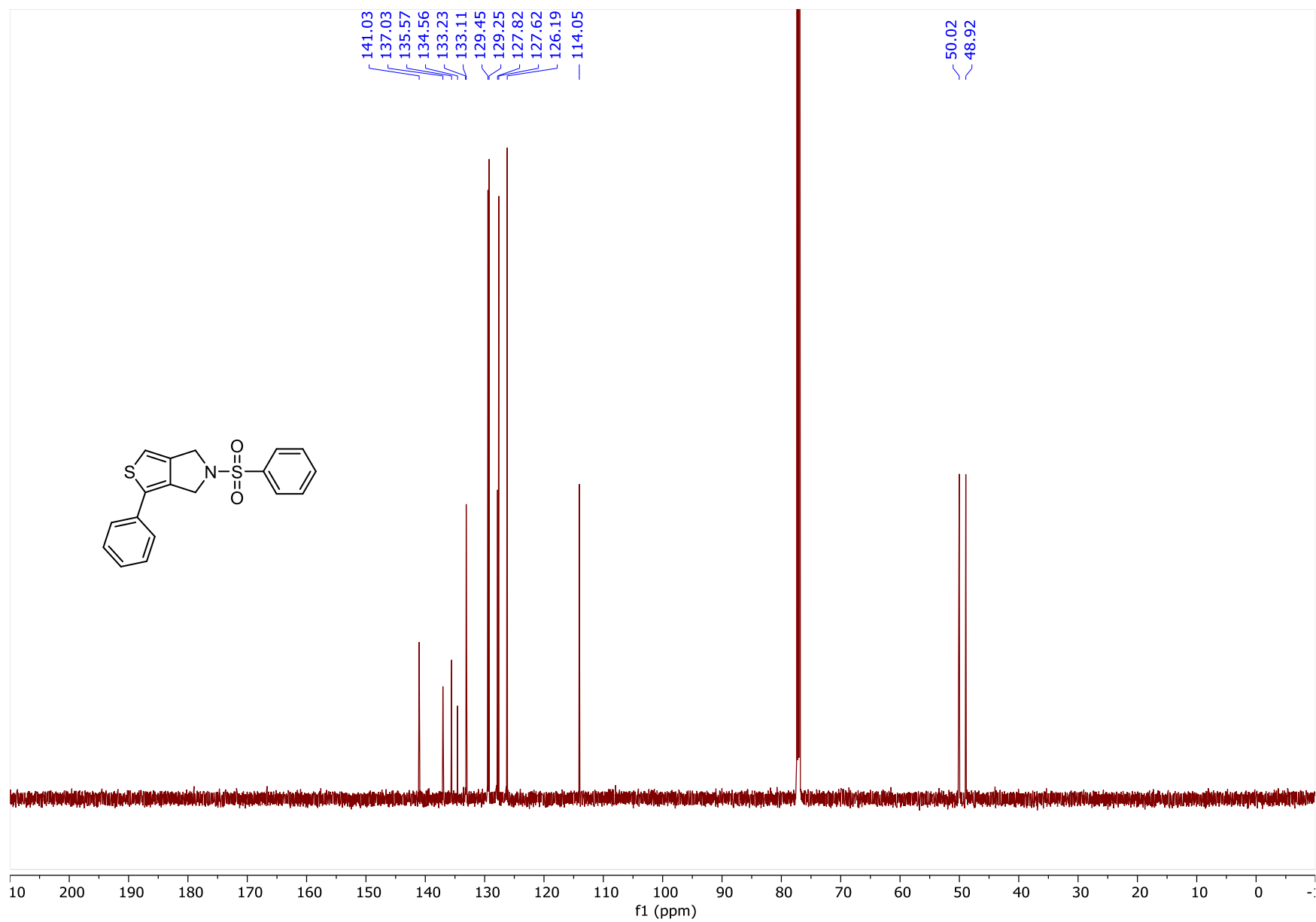


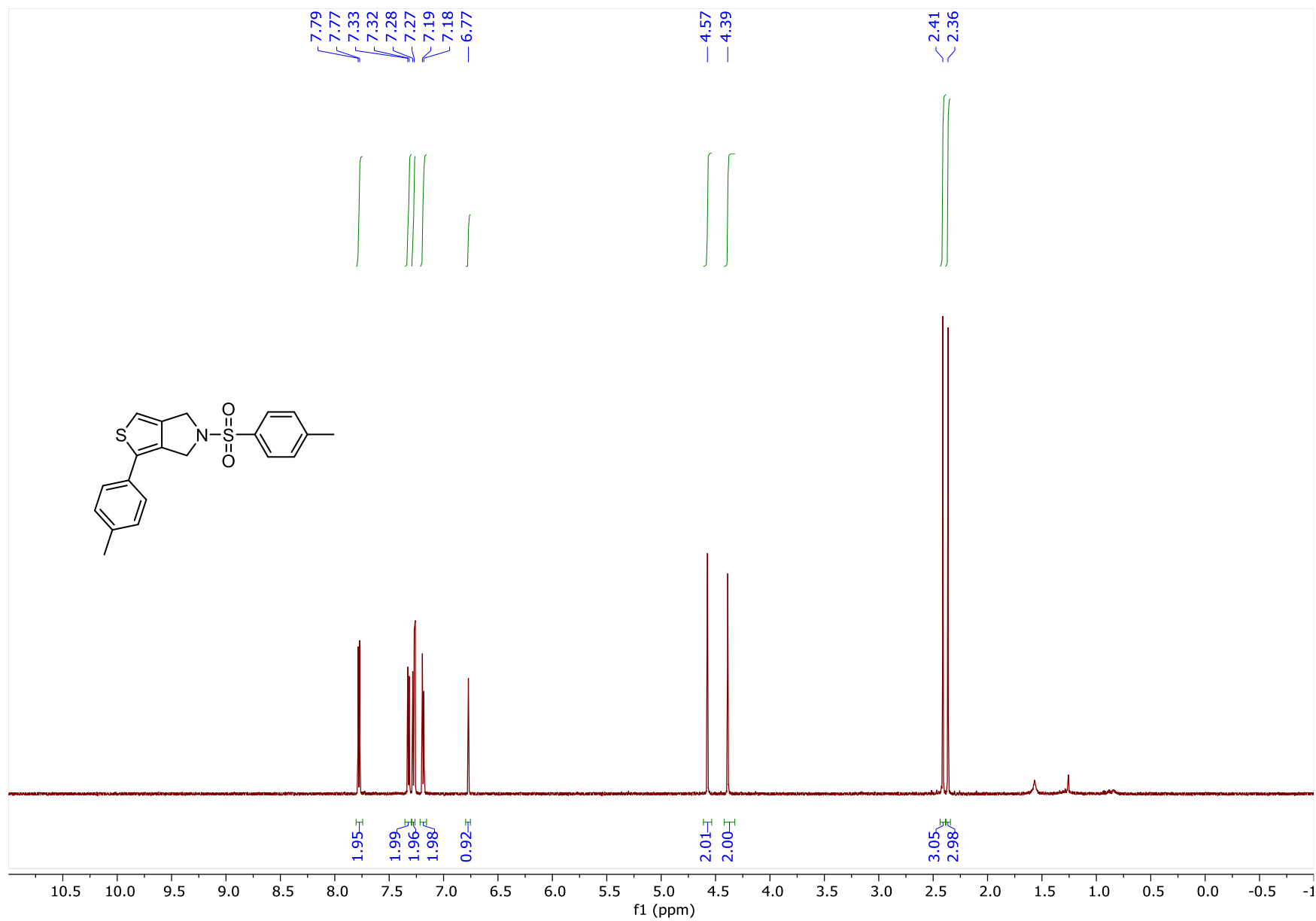


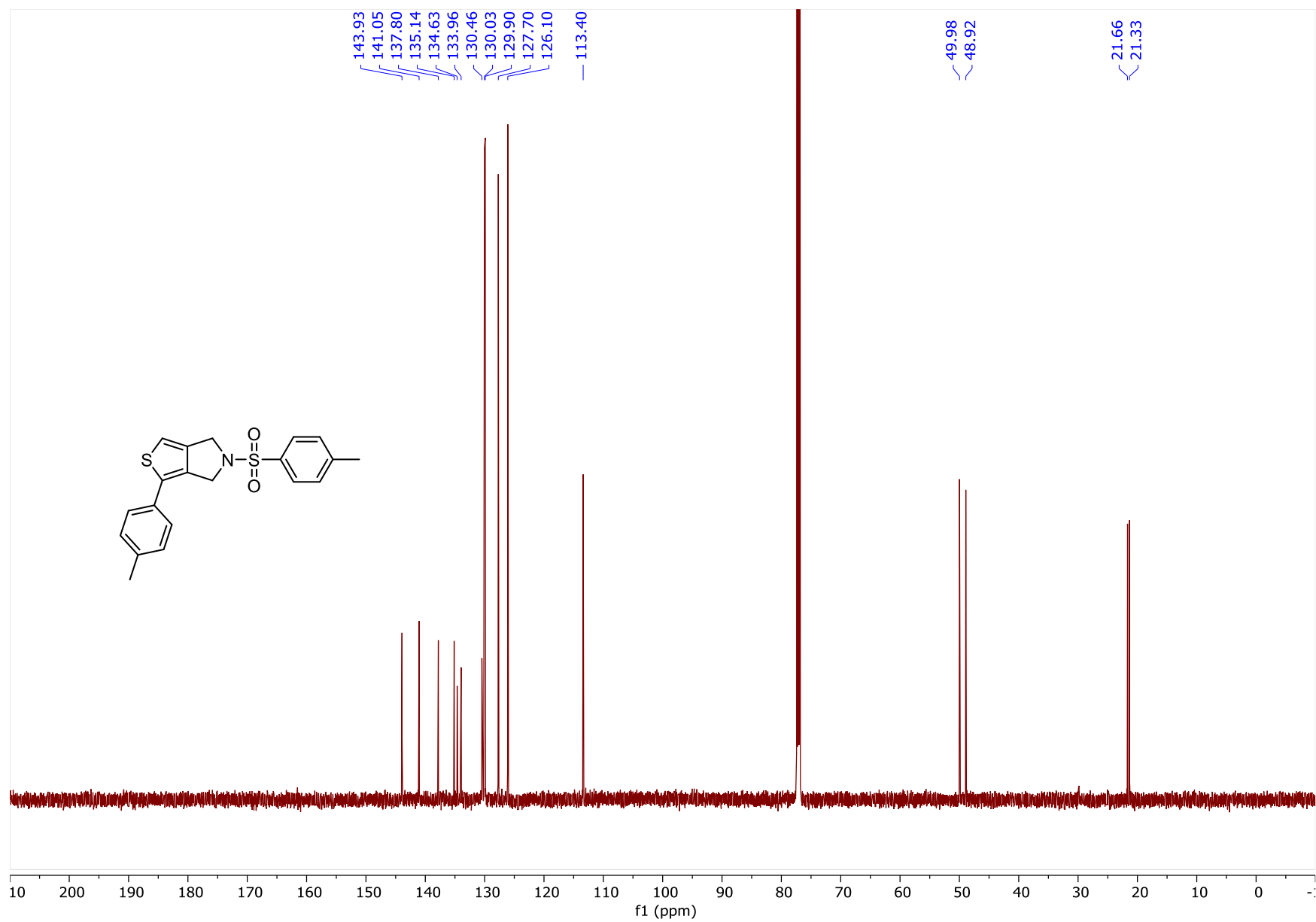


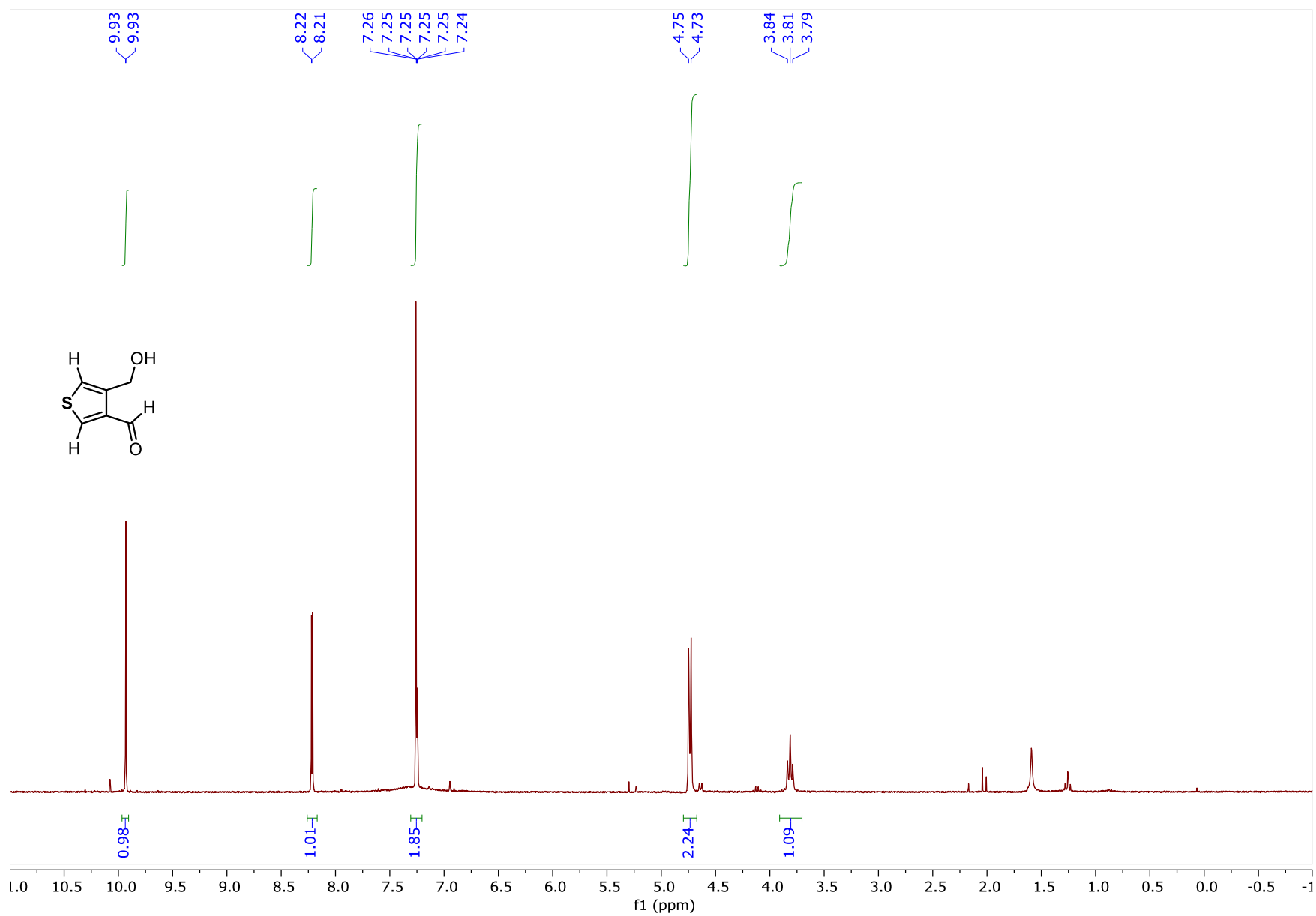


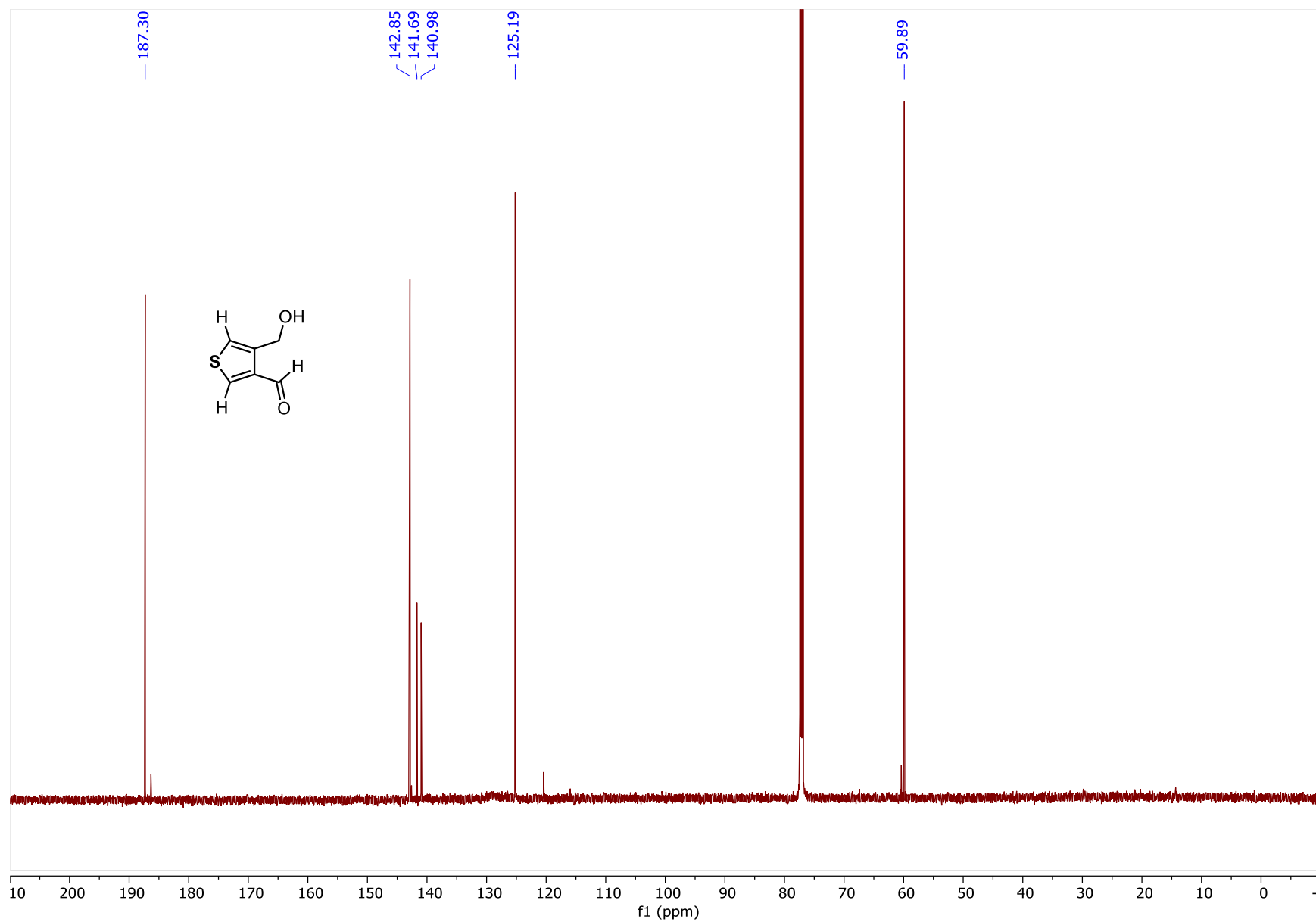




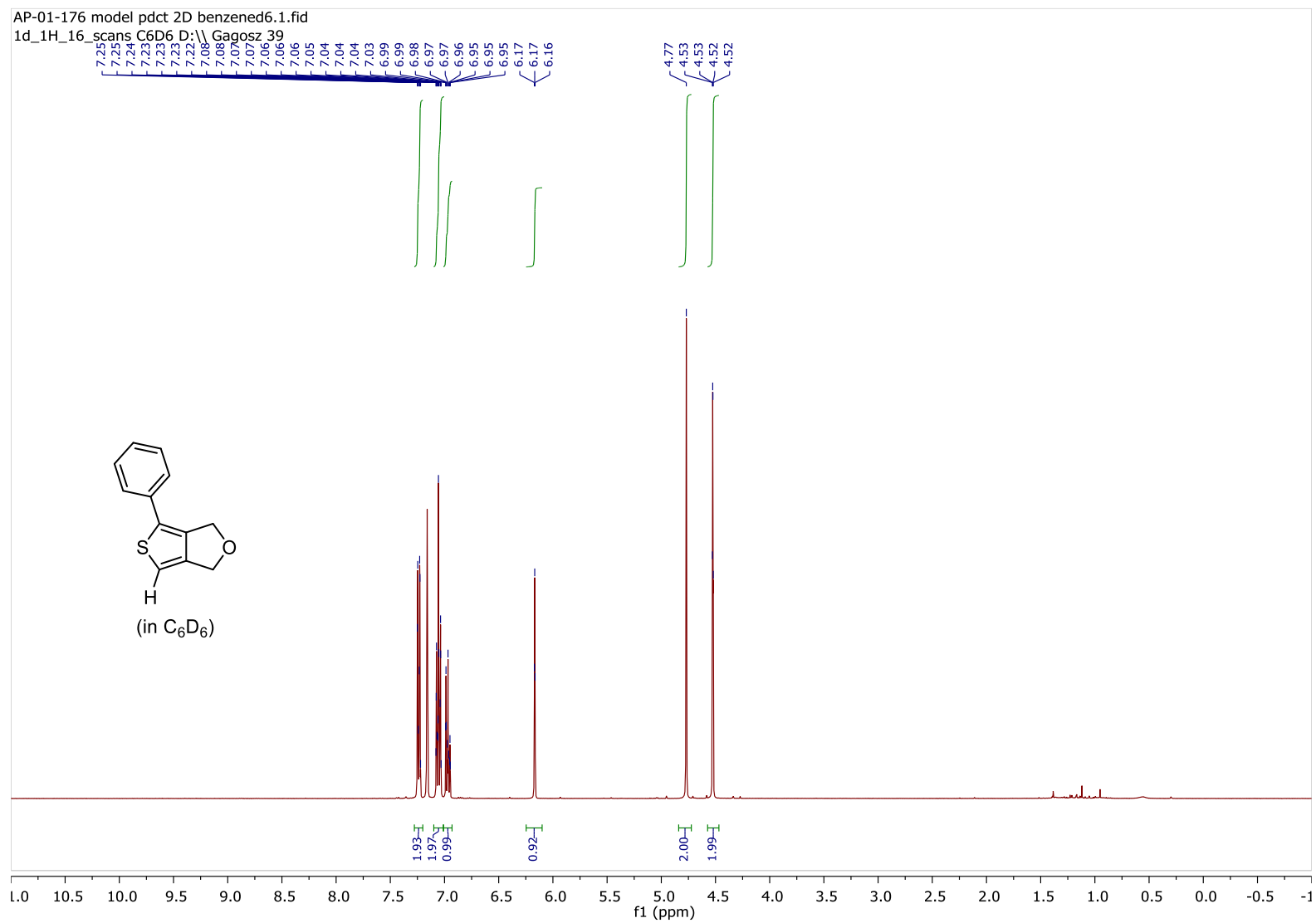




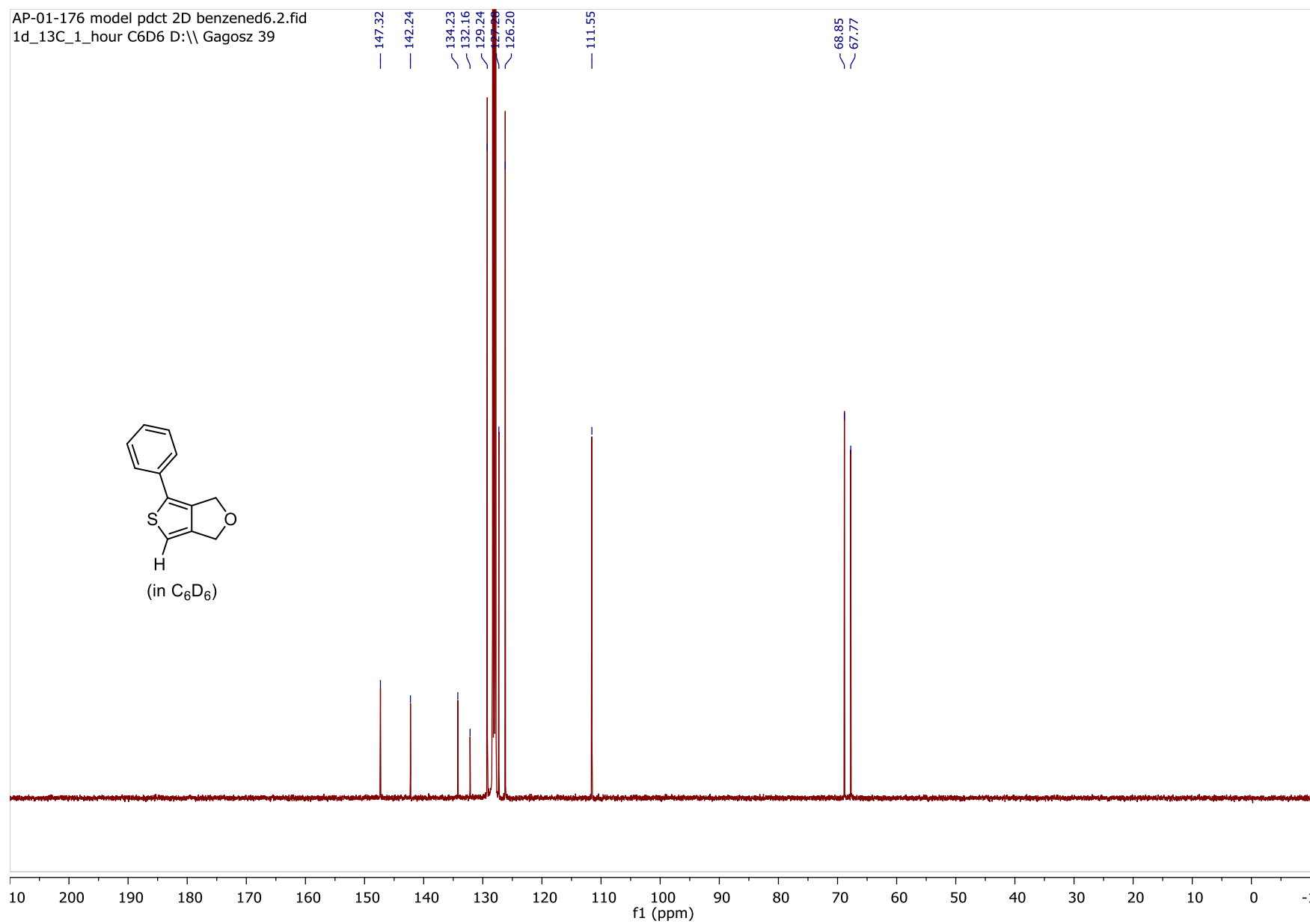


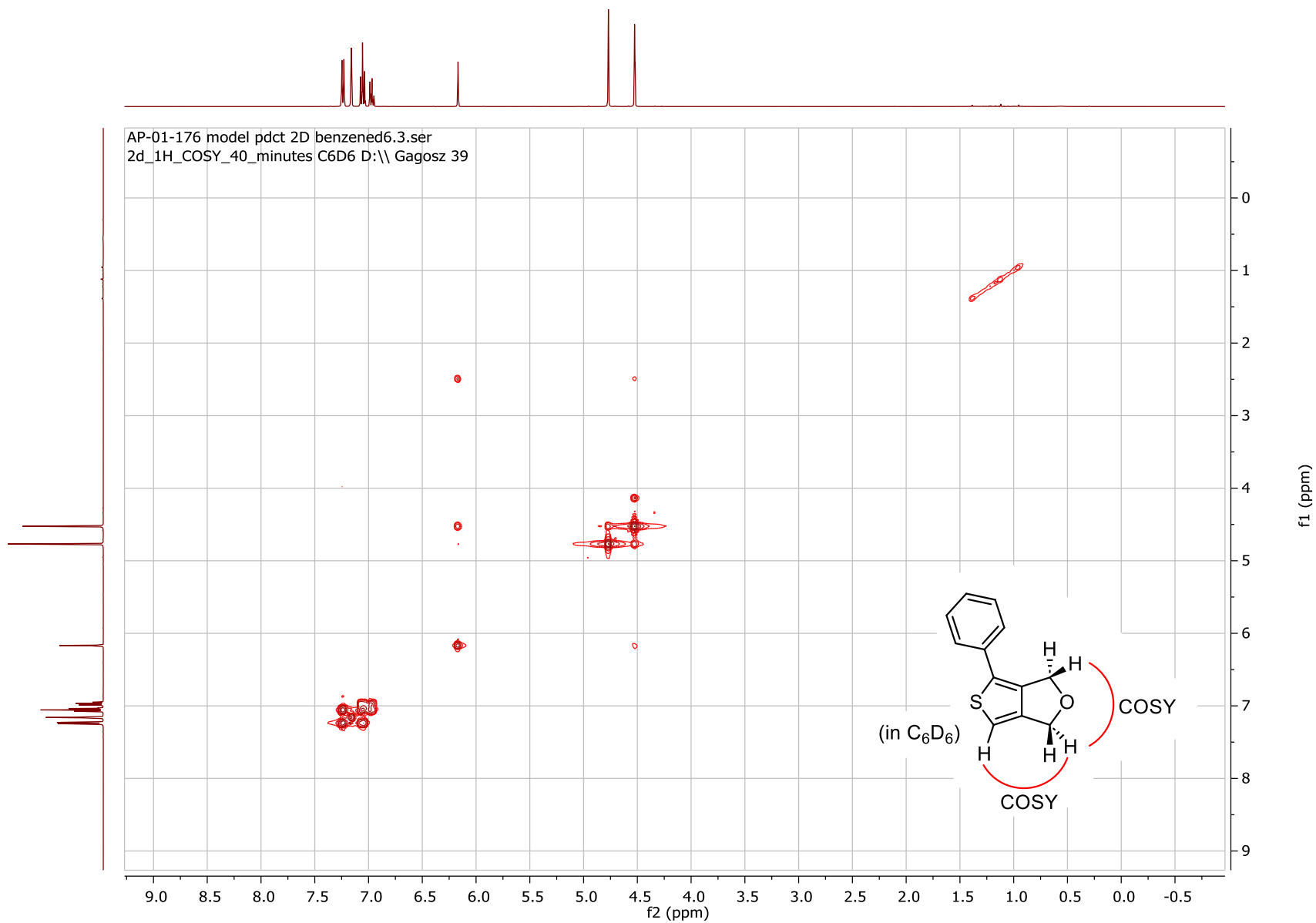


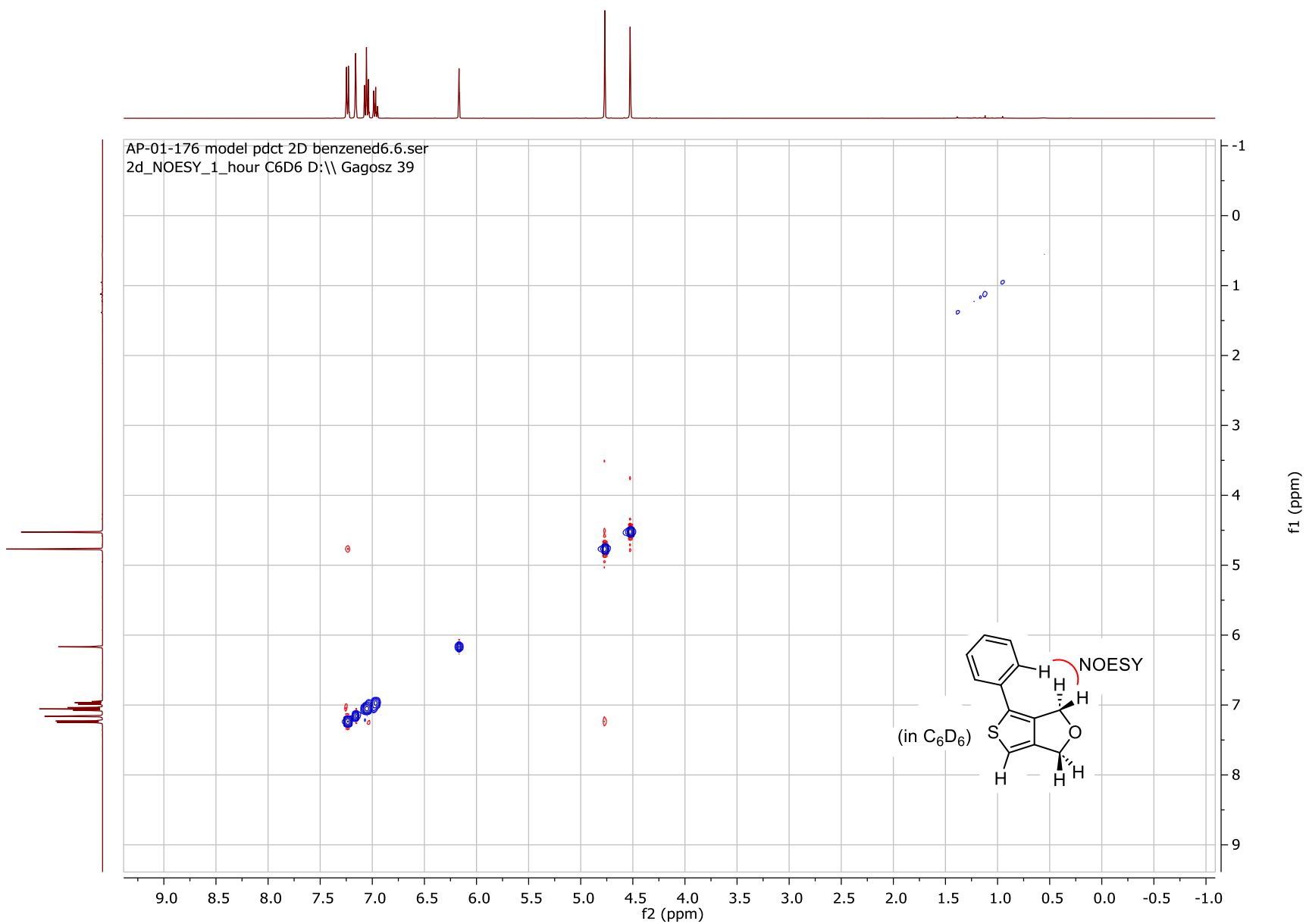
9.1 Additional spectra for 3.2c, 3.4, 4.7-OTf and 4.32

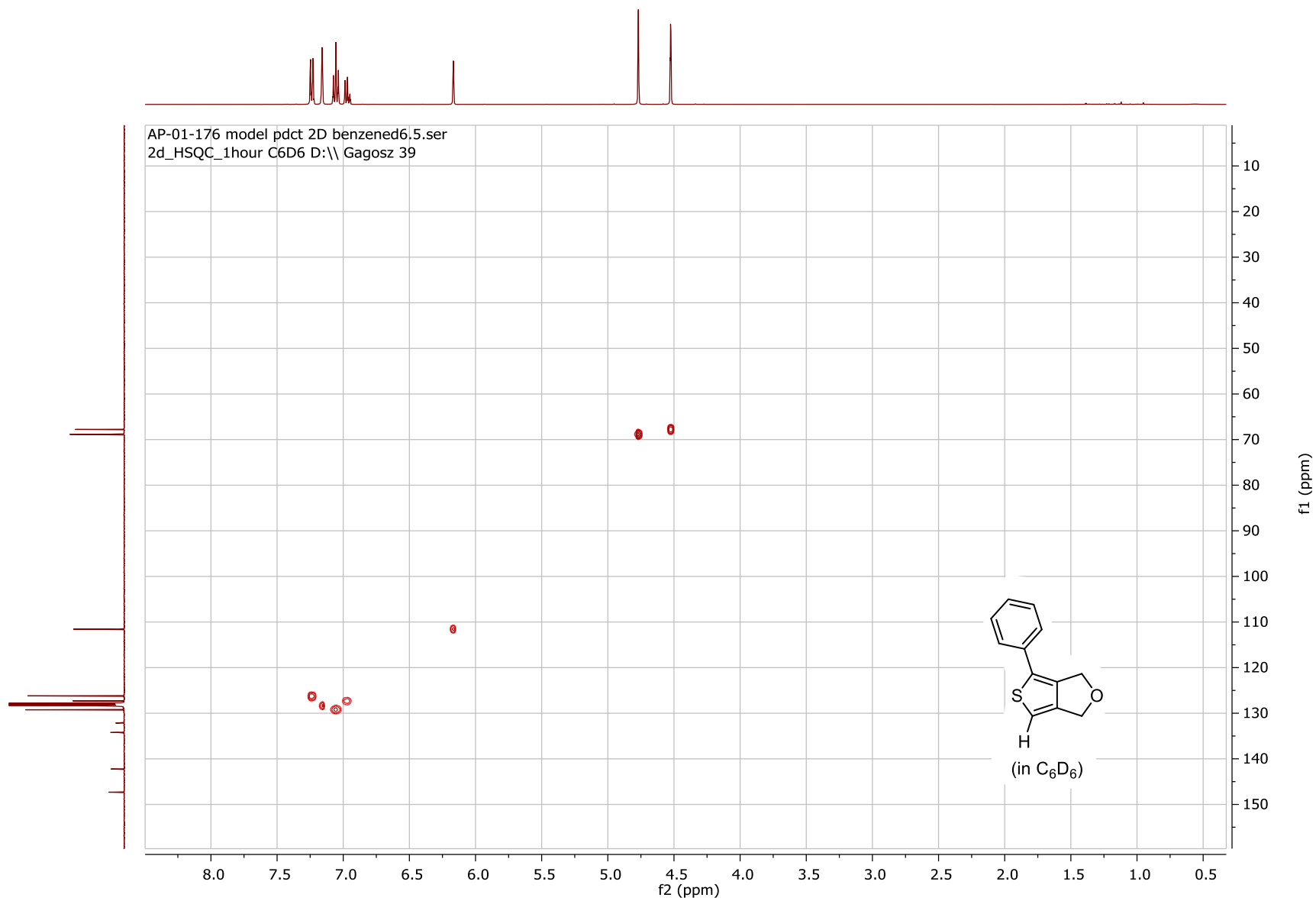


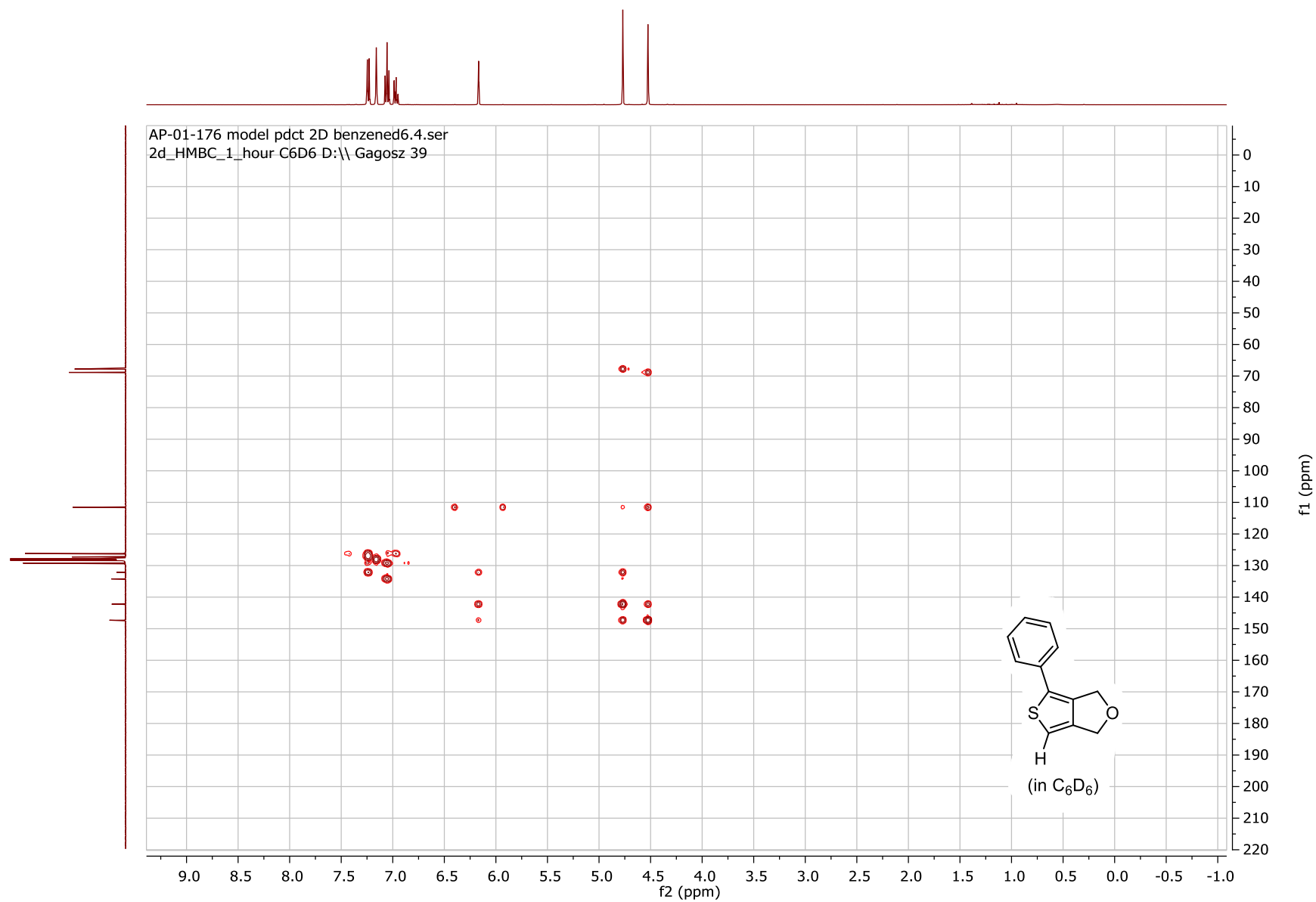
AP-01-176 model pdct 2D benzened6.2.fid
1d_13C_1_hour C6D6 D:\\ Gagosz 39

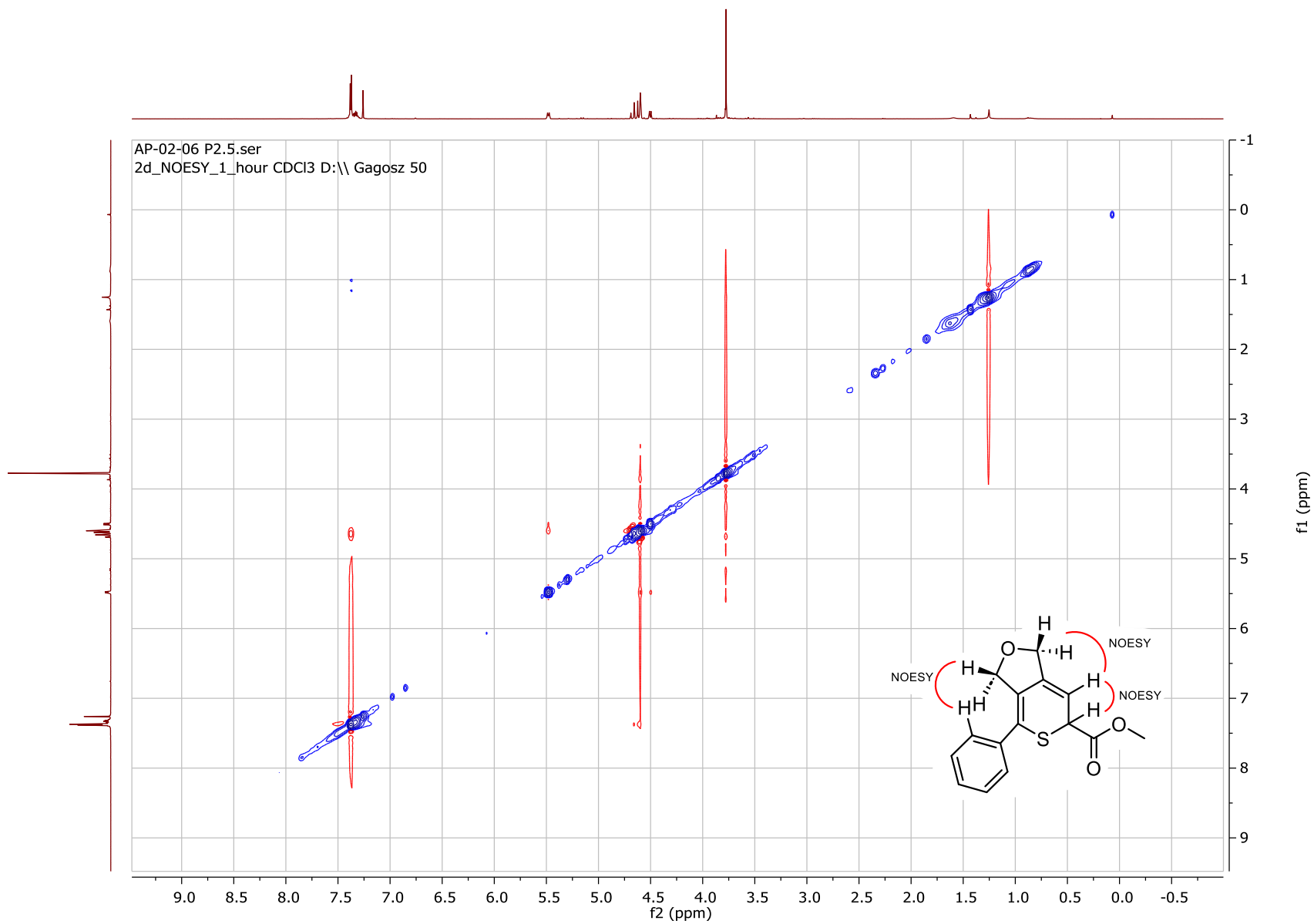


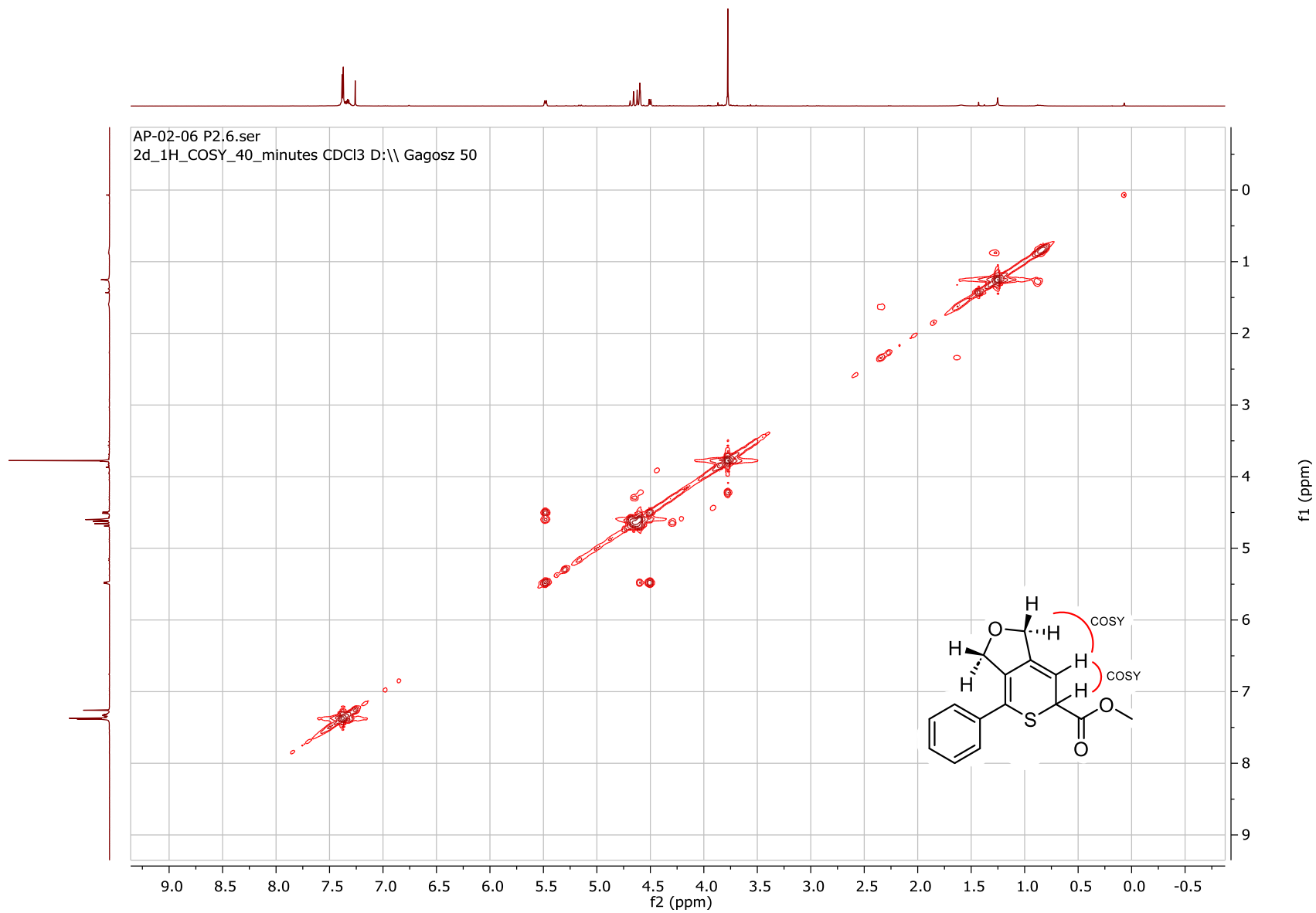


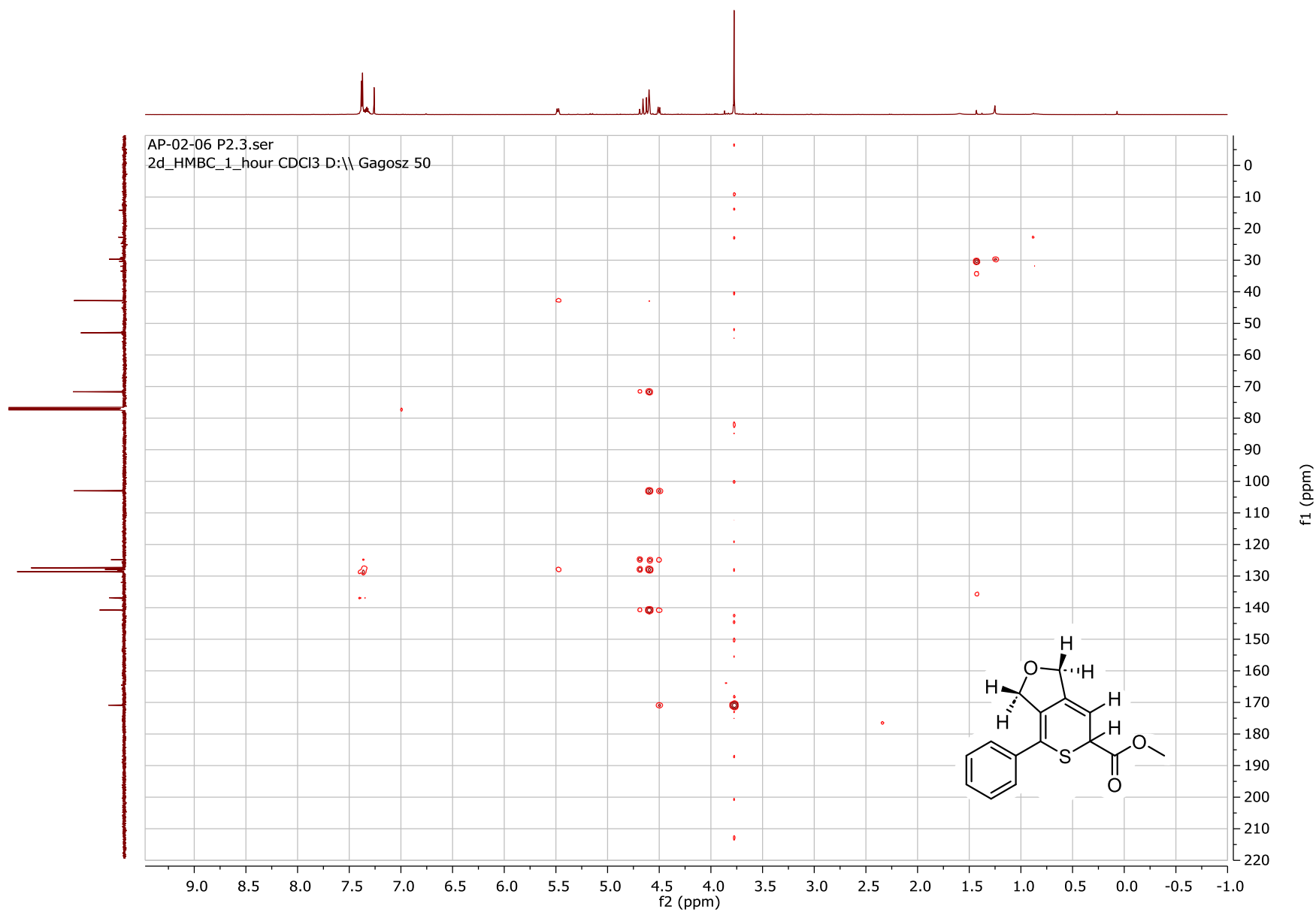


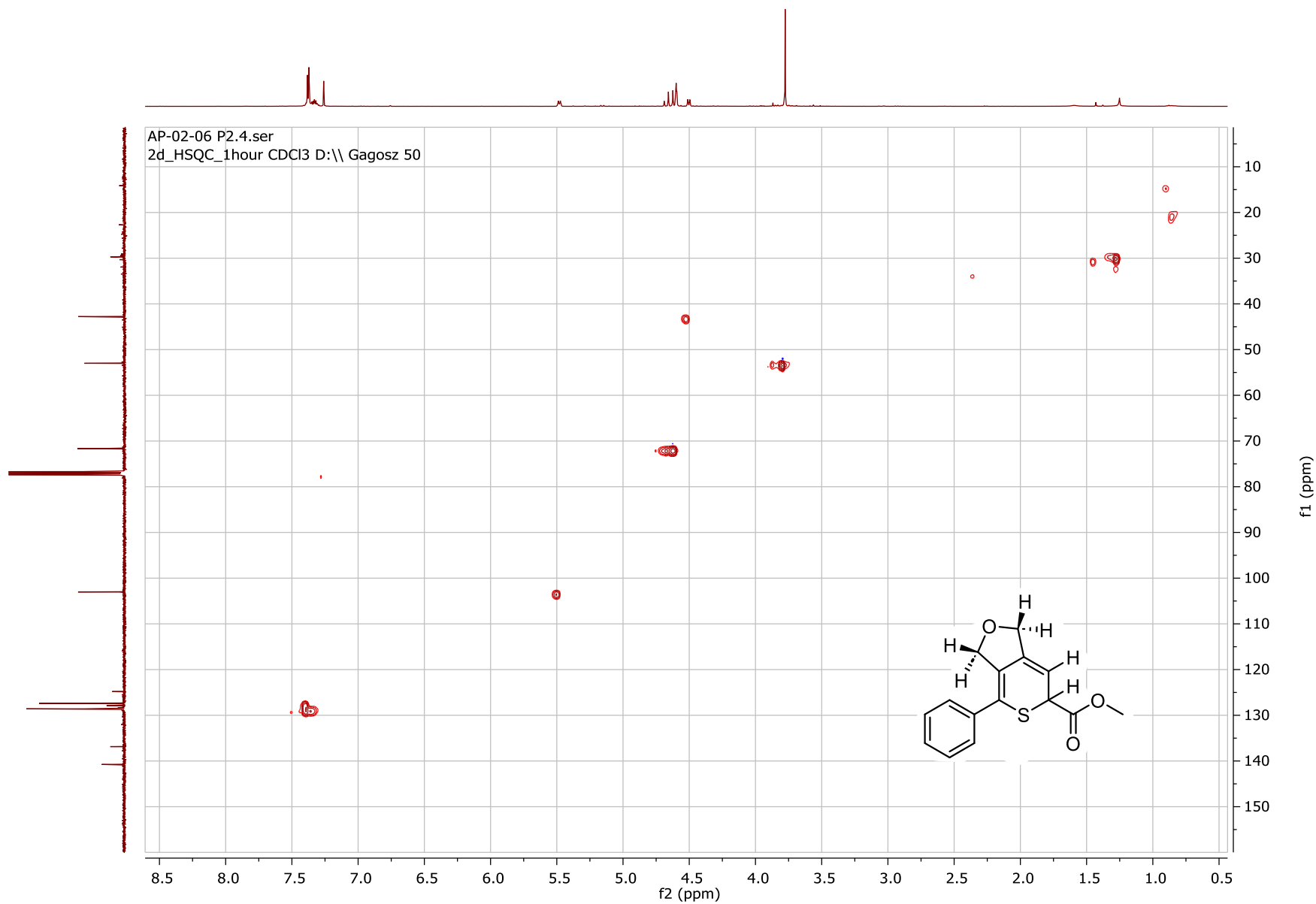


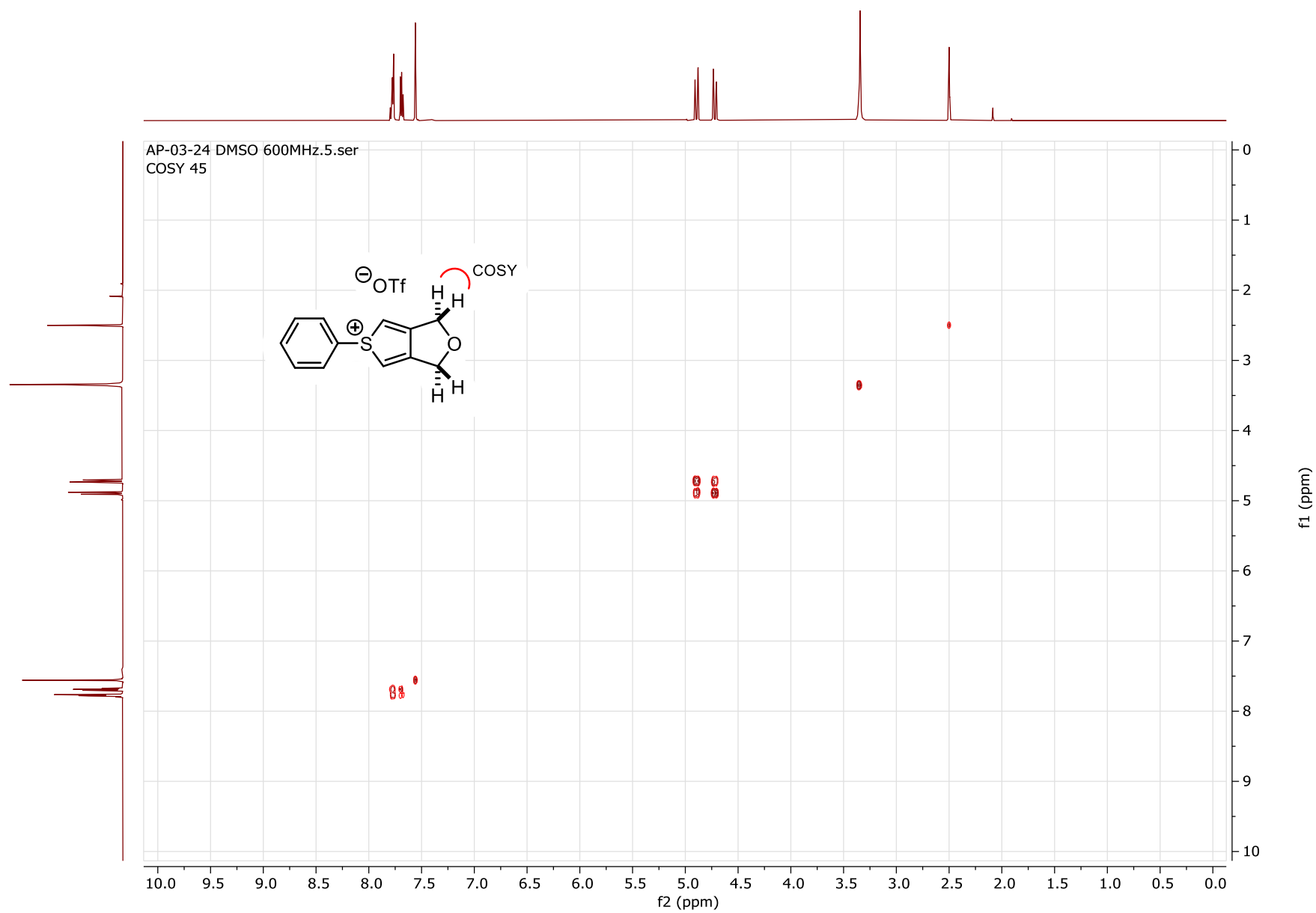


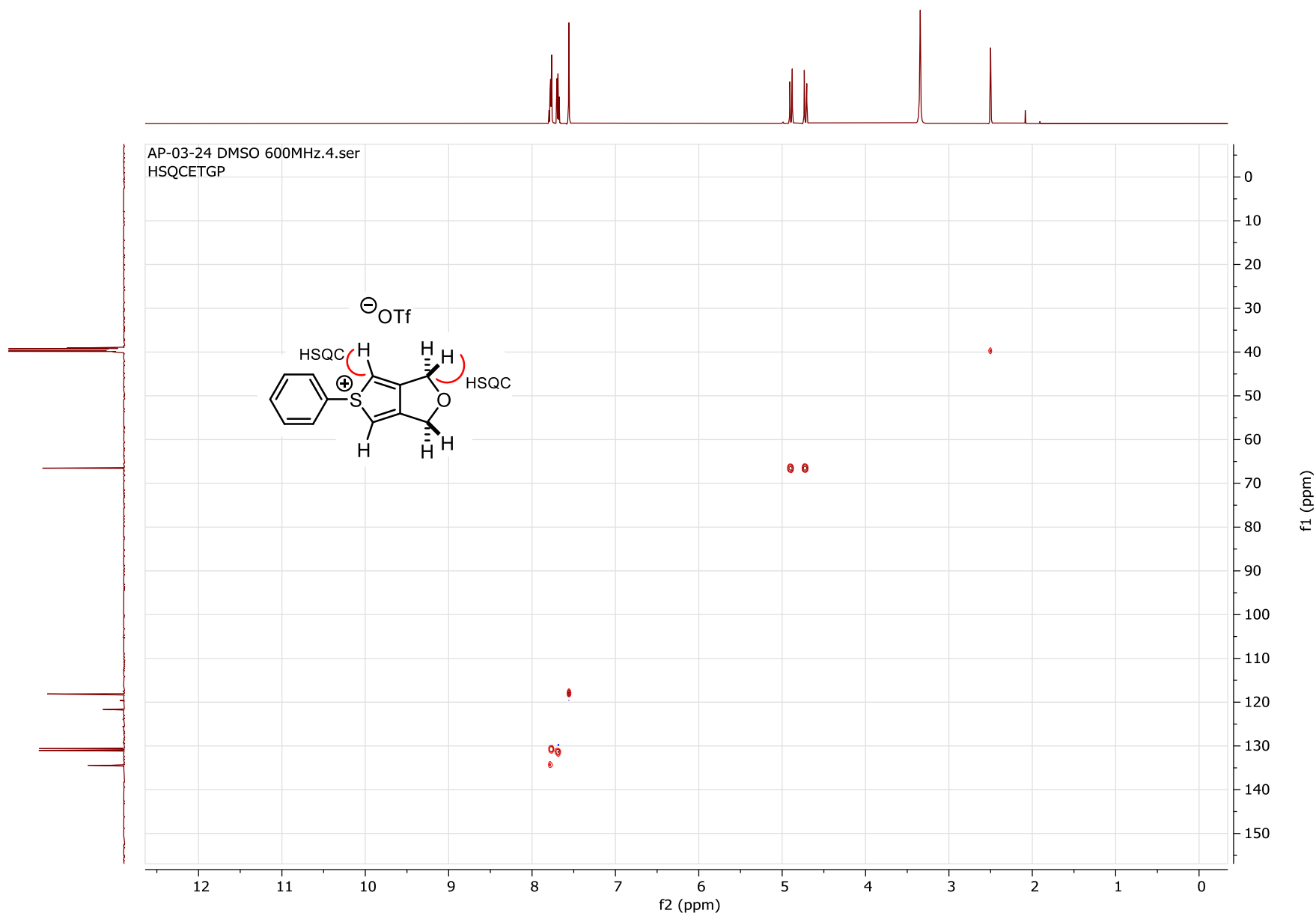


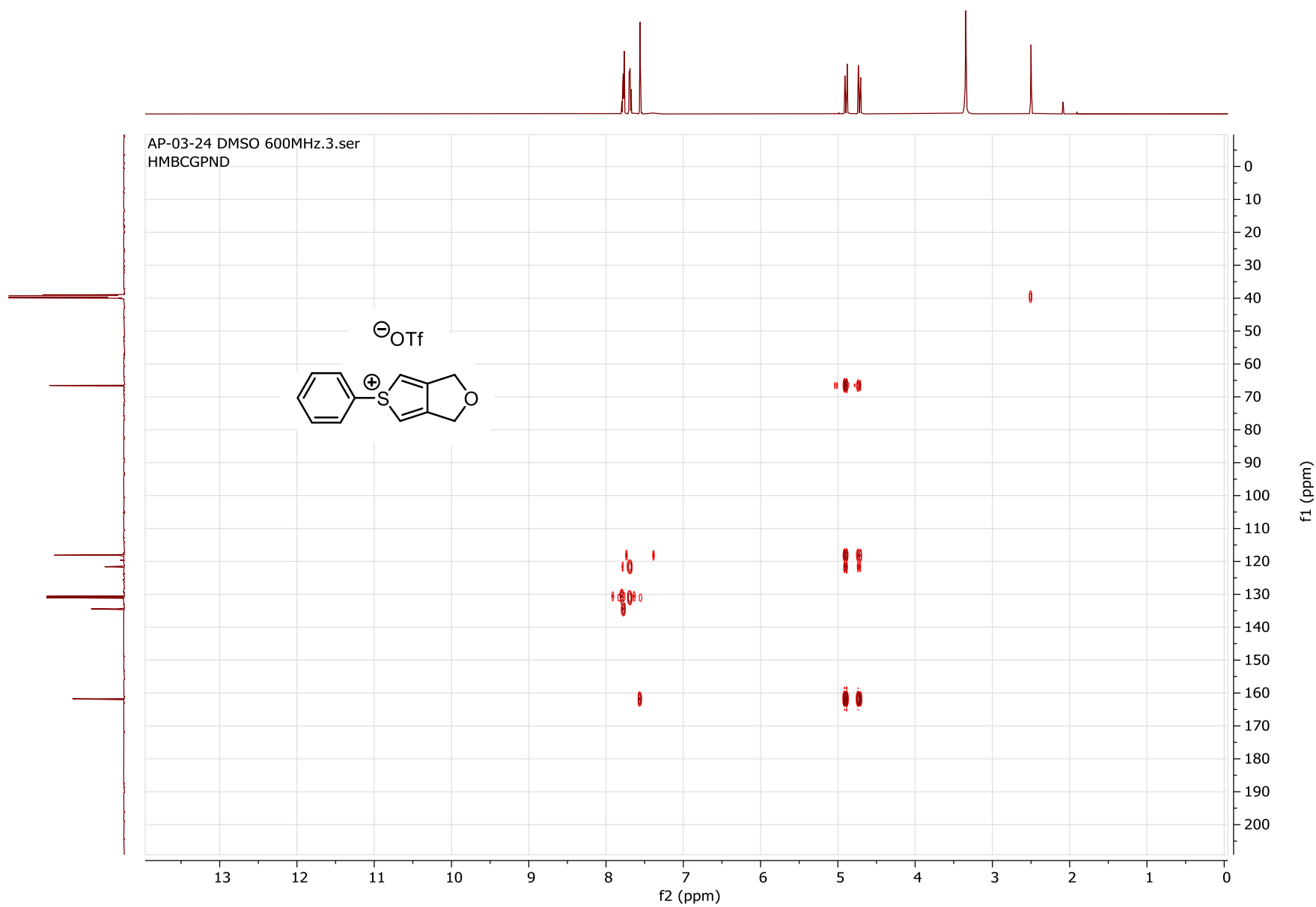


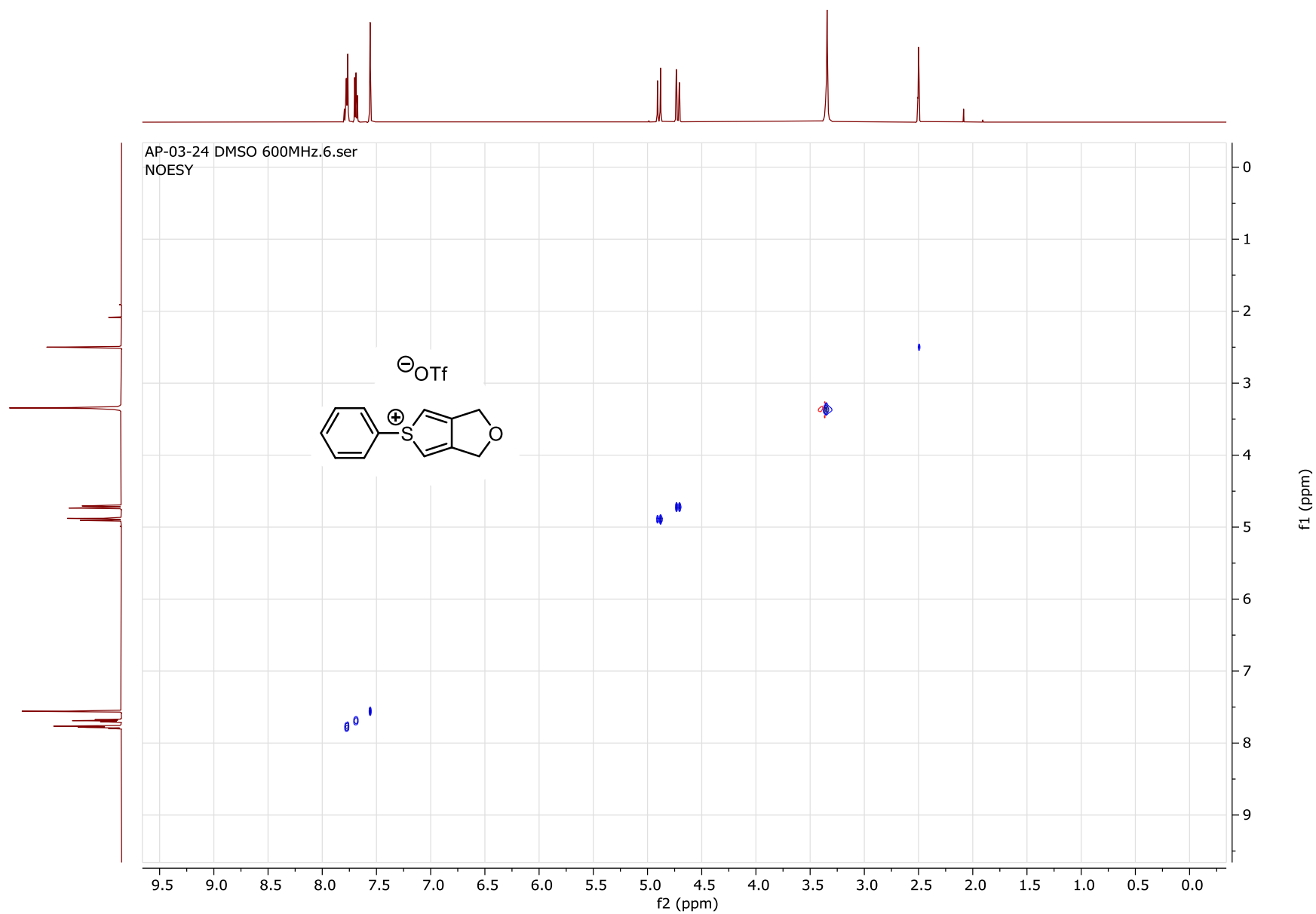












No correlation is seen by NOESY.

