REGIOSELECTIVE HYDROLYSIS OF ALKYNES VIA ORGANOSULFUR INTERMEDIATES

By PAUL SALIBA, B.Sc.

A thesis submitted to the Department of Chemistry and Chemical Biology in partial fulfilment of the requirements for the degree of Master of Science

MASTER OF SCIENCE (2020), McMaster University, Hamilton, Ontario

(Chemistry and Chemical Biology)

TITLE: Regioselective Hydrolysis of Alkynes via Organosulfur Intermediates

AUTHOR: Paul Saliba, B.Sc. (University of Toronto)

SUPERVISOR: Prof. Jakob Magolan

NUMBER OF PAGES: x, 157

Abstract

Many known synthetic methods enable the hydrolysis of alkynes with Markovnikov regioselectivity. In contrast, the synthetic chemist's toolbox lacks broadly effective processes for the hydrolysis of alkynes with anti-Markovnikov regioselectivity. This thesis describes the development of new synthetic method that will help address this deficiency.

This document begins with a review of the concepts of Markovnikov and anti-Markovnikov regioselectivity and an explanation of the broad extension of this terminology that is applied throughout the remainder of this thesis to encompass all alkyne substrates. Next, a review of the published methods of alkyne hydrolysis is presented, with emphasis on the internal alkyne substrates.

The remainder, and bulk, of this thesis details the development of a new synthetic methodology that leverages regioselective radical thiolation chemistry to achieve anti-Markovnikov hydrolysis of alkynes. Internal alkynes are first converted to oxathiolanes or vinyl sulfides with anti-Markovnikov regioselectivity followed by hydrolysis of these moieties to the corresponding anti-Markovnikov ketones. In the case of aryl-alkyl alkyne substrates, complete anti-Markovnikov selectivity is demonstrated with a broad range of examples. Aryl-aryl alkyne substrates offer a mixture of regioisomers favoring anti-Markovnikov products.

Finally, the utility of this methodology is demonstrated with its application to the successful first total synthesis of the bioactive natural product isomeranzin.

Table of Contents

List of Schemes

List of Figures

List of Tables

List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Sia_2BH	disiamylborane
M	Markovnikov
AM	anti-Markovnikov
AIBN	azobisisobutyronitrile
BEt_3	triethylborane
VS	vinyl sulfide
BPO	benzoyl peroxide
TLC	thin-layer chromatography
DCE	dichloroethane
THF	tetrahydrofuran
EDG	electron-donating group
EWG	electron-withdrawing group
α	alpha
NMR	nuclear magnetic resonance
DEPTQ	distortionless enhancement by polarization transfer
HSQC	heteronuclear single quantum coherence
HMBC	heteronuclear multiple bond correlation

Declaration of Academic Achievement

1) **P. Saliba,** J. Magolan. Regioselective Hydrolysis of Alkynes via Organosulfur Intermediates *Manuscript in preparation for submission in 2020; all experimental work was done by Paul Saliba*

2) P. F. Lebeau, J. H. Byun, K. Platko, **P. Saliba**, G. Pare, G. R. Steinberg, L. J. Janssen, S. R. W. Chen, N. G. Seidah, J. Magolan and R. C. Austin. Caffeine Blocks SREBP2-induced Hepatic PCSK9 Expression to Enhance LDLR-Mediated Cholesterol Clearance. *Manuscript in revision following review by Nature Communications; all synthetic chemistry work was done by Paul Saliba, biological studies were done by our collaborators; Paul Saliba will also be a co-inventor on a Provisional Patent Application now in preparation that includes this work.*

3) M. Sguazzin, **P. Saliba,** J. Magolan. Copper-Catalyzed Arylation of Sulfamates. *Manuscript in preparation for submission in 2021; a synthetic chemistry contribution to this work was made by Paul Saliba.*

4) **P. Saliba**, S. Banskota, W. Khan, J. Magolan. Structure-Activity Relationship Studies of the Indole-3-propionic Acid Derivatives with Anti-Inflammatory Activity. *Manuscript in preparation for submission in 2021; all synthetic chemistry work was done by Paul Saliba, biological studies were done by our collaborators.*

1.0 Introduction

1.1 Markovnikov and Anti-Markovnikov Terminology in the Context of this Thesis

Vladimir Markovnikov (1838–1904) was a Russian organic chemist whose name has become associated with the regiochemical outcomes of addition reactions to unsymmetrical olefins. A common version of "Markovnikov's rule" is as follows: when an unsymmetric alkene reacts with a hydrogen halide to give an alkyl halide, the hydrogen adds to the carbon of the alkene that has a greater number of hydrogen substituents, and the halogen to the carbon of the alkene with the fewer number of hydrogen substituents''[1]. This rule was based on the observation that addition of hydrobromic acid (HBr) to alkenes (**1**) results in formation of bromoalkanes **3** and not bromoalkanes **5** (**Figure 1A**). The mechanistic explanation for this regioselectivity is as follows: the olefin (**1**) is protonated to yield one of two possible carbocations, **2** or **4**, one of which is more stable than the other. The more stable carbocation (**2**) dictates the site of bromination and thus regiochemical outcome of this reaction. Product **3**, resulting in bromination of **2,** is the observed product and thus the halogen atom has added to "the carbon of the alkene with the fewer number of hydrogen substituents".

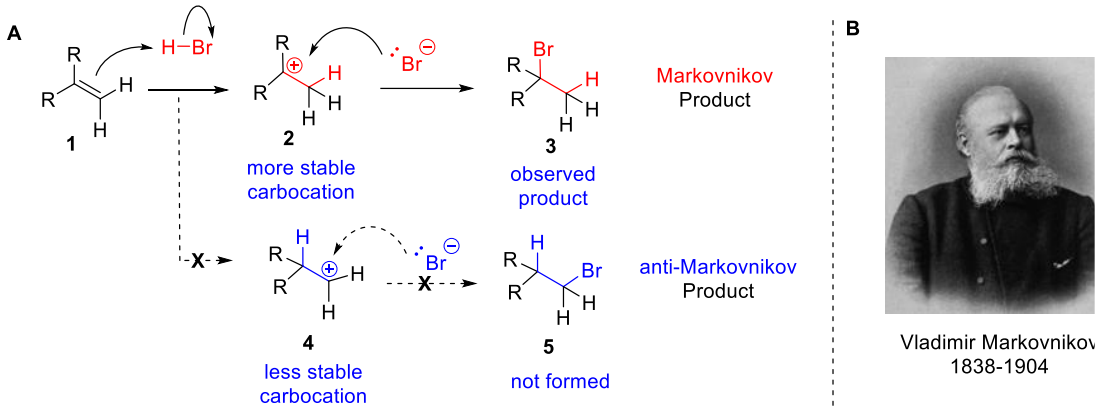
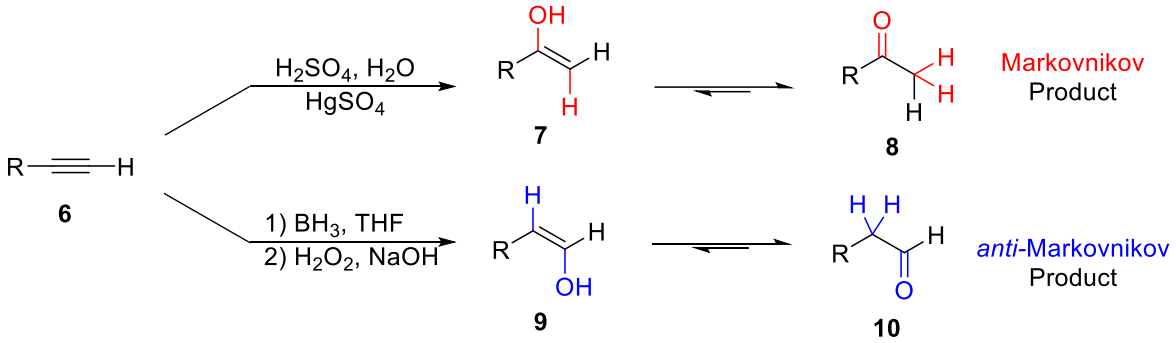


Figure 1. A. Markovnikov and anti-Markovnikov products of alkene hydrohalogenation; B. Picture Vladimir Markovnikov (source: Wikipedia)

Bromoalkane **3** is referred to as the "Markovnikov" product and the regioisomeric bromoalkane (**5**, not formed under these reaction conditions) is called the "anti-Markovnikov" product. Anti-Markovnikov addition to alkenes requires alternative reaction conditions such as radical bromination with HBr in the presence of a radical initiator[2].

The Markovnikov terminology has also been routinely extended to describe regioselectivity in the hydrolysis of terminal alkynes (**Scheme 1**). In this case, one can envision that addition of a water molecule across one of the π bonds of an alkyne (**6**) results in two potential regioisomeric enols (**7** & **9**) which would exist as their corresponding carbonyl tautomers (**8** & **10**). Accordingly, when a terminal alkyne is hydrolyzed the Markovnikov product is a methyl ketone (**8**) and the anti-Markovnikov product is an aldehyde (**10**).



Scheme 1. Regioselective hydrolysis of terminal alkynes to ketones and aldehydes[3-5]

Classical Markovnikov-selective alkyne hydrolysis procedures use strong acids like sulfuric acid (H_2SO_4) paired with mercury salts (**Scheme 1**)[3-5]. The rate of reaction is enhanced in the presence of salts like $HgSO_4$ due to alkyne activation through the formation of a mercurinium ion which is followed by nucleophilic attack of water on the more substituted carbon atom[3]. Such hydrolysis conditions are no longer commonly used due to low functional group compatibility and toxicity of mercury salts[6]. Instead, many alternative Markovnikov hydrolysis methods for terminal alkynes have been reported that rely on transition metals. Gold catalysis appears to be the modern

standard for this transformation[7-9], but many examples are also reported with other metals including cobalt[6], platinum[10-12], indium[13], hafnium[13], rhodium[14], iron[15], and silver[16].

Anti-Markovnikov hydrolysis of terminal alkynes to aldehydes is traditionally accomplished via a two-step hydroboration oxidation procedure (Scheme 1).[3-5] For the hydroboration reaction, typically 9-borabicyclo[3.3.1]nonane (9-BBN) or disiamylborane (Sia_2BH) are employed but other organoboron complexes have also been used[17, 18]. The reaction proceeds through a concerted process in which borane adds to the terminal carbon of the alkyne, due to a steric preference for the less substituted site, to yield a vinylic borane. Bulky borane compounds like 9-BBN are used to enhance the steric effect[3]. The vinylic borane can then be oxidized, commonly with hydrogen peroxide (H_2O_2) in the presence of sodium hydroxide (NaOH), to yield an enol (**9**) which undergoes tautomerization to yield aldehyde (**10**) which is the anti-Markovnikov hydrolysis product (**Scheme 1**)[3-5]. More recently, ruthenium catalysis has also been shown to accomplish the hydrolysis of terminal alkynes with high anti-Markovnikov regioselectivity[19-21].

At the core of the "Markovnikov" and "anti-Markovnikov" terminology lies the concept of stabilization of positive charge density in a cationic intermediate generated under acid catalyzed hydrolysis conditions (**Figure 2**).

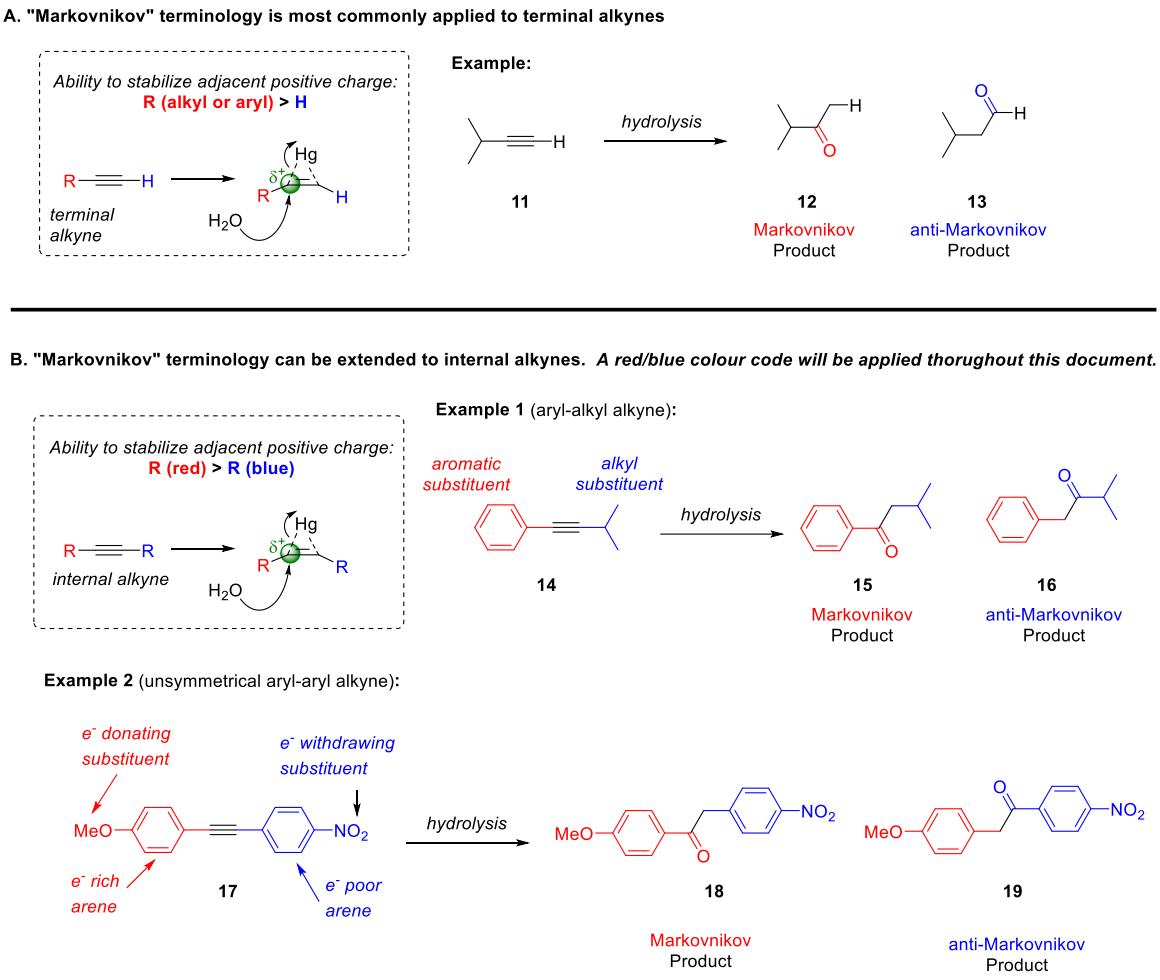


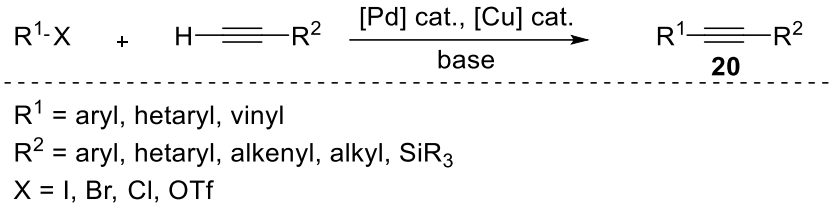
Figure 2. Illustration of how Markovnikov terminology will be used in this thesis

Relative to hydrogen atoms, alkyl substituents stabilize carbocations inductively, via more donation of σ bond electrons into the empty p orbital of a cation[3-5]. With respect to acidic hydrolysis of terminal (monosubstituted) alkynes (**Figure 2A**), the Markovnikov product is rationalized by invoking this same principle: partial positive charge at the more substituted carbon atom of the alkyne is more stabilized than partial positive charge at the terminal (unsubstituted) position. Therefore, the Markovnikov product of acidic hydrolysis of alkyne **11** is the methyl ketone **12**, and not aldehyde **13**.

The work described in this thesis concerns the regioselective hydrolysis of internal (or di-substituted) alkynes (**Figure 2B**). Just like terminal alkynes, Markovnikov and anti-Markovnikov terminology can be extended to internal alkynes, as has been done by other authors, by using the same general principle of positive-charge stabilization. For each internal alkyne substrate, the relative ability of its two substituents to stabilize positive charge density will determine which of the two possible product ketones is referred to as Markovnikov and which is anti-Markovnikov. Throughout this thesis, a red and blue colour scheme will be used to differentiate these substituents as illustrated in **Figure 2**. For example, in the case of phenyl isopropyl alkyne **14**, the Markovnikov hydrolysis product is the benzylic ketone (**15**) because the π system of the benzene ring (red) is better able to stabilize positive charge density on an adjacent atom than the isopropyl substituent (blue). The logic can be applied to unsymmetrical aryl-aryl alkynes. In the case of substrate **15**, the Markovnikov hydrolysis product is ketone **18** which has the carbonyl on the carbon nearest to the more electron rich arene (red) while the anti-Markovnikov product is ketone **19** in which the carbonyl is on the more electron-deficient arene (blue).

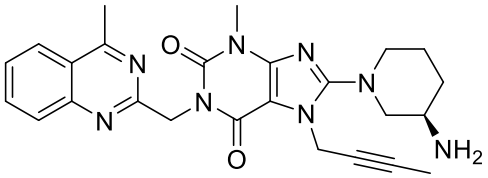
1.1.2. Preparation of Alkynes via Cross-Coupling

The alkyne is a fundamentally important functional group in organic molecules suitable for a wide range of reactions including cycloadditions, oxidative cleavage, carbon–carbon (C–C) couplings, electrophilic additions, hydrolysis to carbonyls, and Sonogashira cross-coupling reactions[3]. A diverse range of alkynes can now be prepared easily via versatile palladium-catalyzed cross-coupling chemistry, as demonstrated by Dieck[22], Cassar[23], Sonogashira[24] and others. This reliable alkyne synthesis technology has enabled access to a vast scope of alkynes. This work is illustrated in **Scheme 2**, which shows the palladium-catalyzed couplings of aryl or alkenyl halides or triflates with terminal alkynes in the presence of a copper(I) cocatalyst[25].

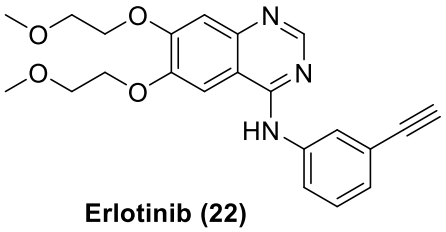


Scheme 2. Alkyne synthesis via palladium catalyzed cross-coupling[25]

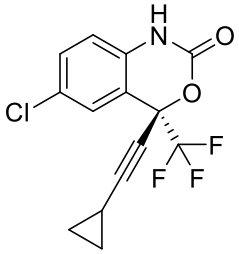
This method is very effective at forming carbon–carbon bonds and has become the most important method to prepare arylalkynes and enynes, which are precursors for natural products and pharmaceuticals[25]. Some examples of pharmaceutical compounds containing this functional group are illustrated in **Figure 3**.



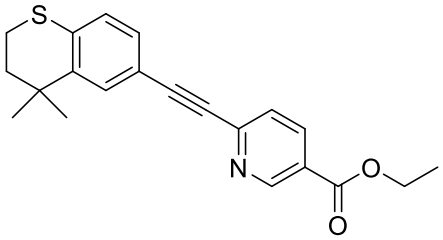
Linaglipti (21)
diabetes mellitus type 2



Erlotinib (22)
Lung/pancreatic cancer



Efavirenz (23)
antiretroviral: HIV/AIDS



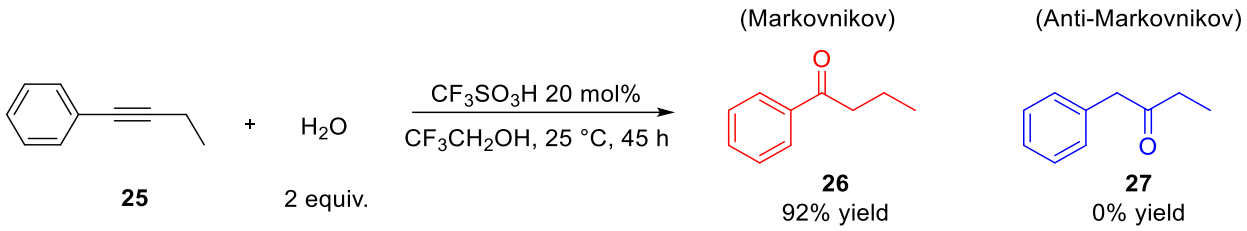
Tazarotene (24)
psoriasis/acne

Figure 3. Pharmaceutical compounds containing an alkyne functional group

Notably, preparation of alkynes encompassed under palladium-catalyzed couplings was acknowledged as a significant contribution to the field of synthetic organic chemistry and was thus awarded a Nobel Prize[26]. With this powerful methodology now available to the synthetic community, a wide range of alkynes are available for use as substrates for subsequent reactions. Accordingly, the development of useful reactions of alkynes continues to thrive in the organic synthetic methods community.

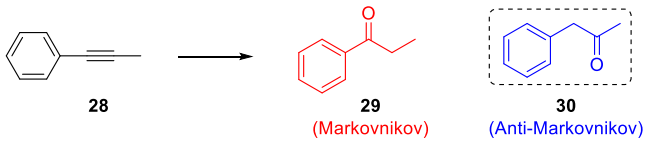
1.1.3. Known Methods for Markovnikov Hydrolysis of Internal Alkynes

Classical Markovnikov-selective alkyne hydrolysis conditions employ strong acids like sulfuric acid, together with mercury salt catalysts like mercury (II) sulfate. When such conditions are applied to internal alkynes, poor selectivity is often observed, with a mixture of the Markovnikov and anti-Markovnikov ketone regioisomers generated[3-5,27]. However, several authors have demonstrated reactions with high selectivity for Markovnikov products. For example, a report by Liu, W, et al. demonstrates the use of trifluoromethanesulfonic acid (TfOH) in trifluoroethanol as an efficient system to achieve Markovnikov-selective hydrolysis of internal alkynes (**Scheme 3**)[28].



Scheme 3. Markovnikov hydrolysis of an internal alkyne using TfOH and trifluoroethanol[28]

In recent years, a powerful new class of transition metal-catalyzed alkyne hydrolysis reactions has emerged that has enabled the hydrolysis of aryl-alkyl alkynes with complete Markovnikov selectivity. A range of transition metals have been utilized including iron[29,30], copper[31], gold[32, 33], hafnium[13], indium[34], and silver[35] (**Scheme 4**).



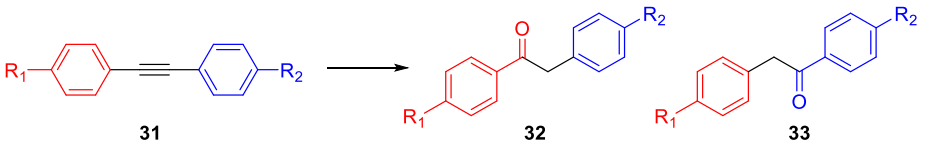
28 **29** (Markovnikov) **30** (Anti-Markovnikov)

Reference	Conditions	Markovnikov	Anti-Markovnikov
Antonino-Cabrero, J. 2013 *ref. 29*	$[Fe(NTf_2)_3]$ dioxane/H_2O 80 °C, 20 h	98%	0%
Park, J. 2013 *ref. 30*	$FeCl_2 \cdot 4H_2O$ $MeSO_3H$ DCE, 60 °C, 18 h	91%	0%
Hassam, M. 2015 *ref. 31*	$Cu(OTf)_2$ EtOAc/H_2O 100 °C, 24 h	94%	0%
Wu, G. 2015 *ref. 32*	WangPhosAuCl MeOH/H_2O 25 °C, 8 h	93%	0%
Rostamizadeh, S. 2014 *ref. 33*	(a-Fe_2O_3)-MCM-41-SH-Au H_2O, 80 °C, 1.5 h	93%	0%
Suta, K. 2018 *ref. 13*	$Hf(OTf)_4$ H_2O/SO_2 70 °C, 16-18 h	82%	0%
Gao, Q. 2013 *ref. 34*	$In(OTf)_3$/PTSA DCE/H_2O 85 °C, 12 h	83%	0%
Chen, Z. 2013 *ref. 35*	$AgBF_4$ AcOH/H_2O 110 °C, 10 h	84%	0%

Scheme 4. Metal-catalyzed Markovnikov hydrolysis of internal alkynes[13,29-35]

Numerous methods are now available to achieve this transformation in high yields with complete regioselectivity. Notable among these methods are the recent techniques that use inexpensive catalysts like copper (II) triflate and iron (II) chloride tetrahydrate to accomplish this transformation in 94% and 91% yield, respectively.

In addition to the effective methods listed above (**Scheme 4**) that achieve Markovnikov hydrolysis of aryl-alkyl alkynes, additional studies have exhibited selective Markovnikov hydrolysis of bis-aryl alkyne systems (**Scheme 5**)[12, 36-39].



31 **32** (Markovnikov) **33** (Anti-Markovnikov)

Reference	Substituents	Conditions	Markovnikov	Anti-Markovnikov	Selectivity
Mei, Q. 2017 *ref. 36*	R_1 = OMe R_2 = Et	CuBr, H_2O p-fluoroaniline 120 °C, 16 h	63(55%)	35%*	1.7:1
Weerasiri, K. 2016 *ref. 37*	R_1 = H R_2 = $C(=O)CH_3$	(NHC)Au(I) dioxane/H_2O 80 °C, 18 h	82%*	18%*	4.5:1
Hsin-Ping, L. 2018 *ref. 12*	R_1 = OH R_2 = H	PtO_2/PTSA MeOH/H_2O 130 °C, 5 h	90%	0%	>9:1
Le Bras, G. 2006 *ref. 38*	R_1 = OMe R_2 = Me	PTSA Ethanol, 120 °C (MW) 30 mins	97%	0%	>30:1
Jacubert, M. 2010 *ref. 39*	R_1 = OMe R_2 = Me	PTSA Ethanol, 120 °C (MW) 30 mins	87%*	10%*	9:1

NOTE: *An asterisk* Indicates a crude NMR yield. Isolated yields may be indicated in parantheses.*

Scheme 5. Markovnikov hydrolysis of bis-aryl alkynes[12, 36-39]

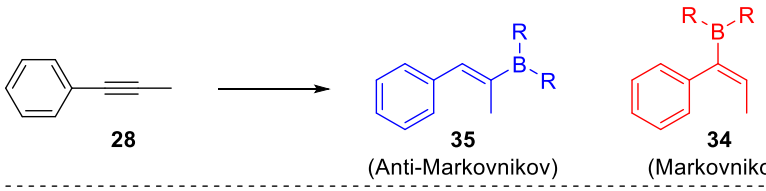
With the techniques summarized above in **Schemes 4** and **5,** obtaining Markovnikov hydrolysis of various internal alkynes can be easily achieved. Therefore, additional methods aimed at achieving Markovnikov selective hydrolysis of internal alkynes are unnecessary.

1.1.4. Known Methods for anti-Markovnikov Hydrolysis of Internal Alkynes

The established strategies for the hydrolysis of alkynes with anti-Markovnikov selectivity are outlined in the following three sub sections: 1) hydroboration, 2) gold catalysis, and 3) hydroamination.

1.1.4.1. Anti-Markovnikov Hydrolysis via Hydroboration

Examples of hydroboration of internal alkynes have been investigated in the literature. While there are several literature reports that obtain a mixture of hydroboration regioisomers under their conditions[40-45], notable are reports that demonstrate complete regioselective anti-Markovnikov hydroboration of internal alkynes (**Scheme 6**)[46-50].

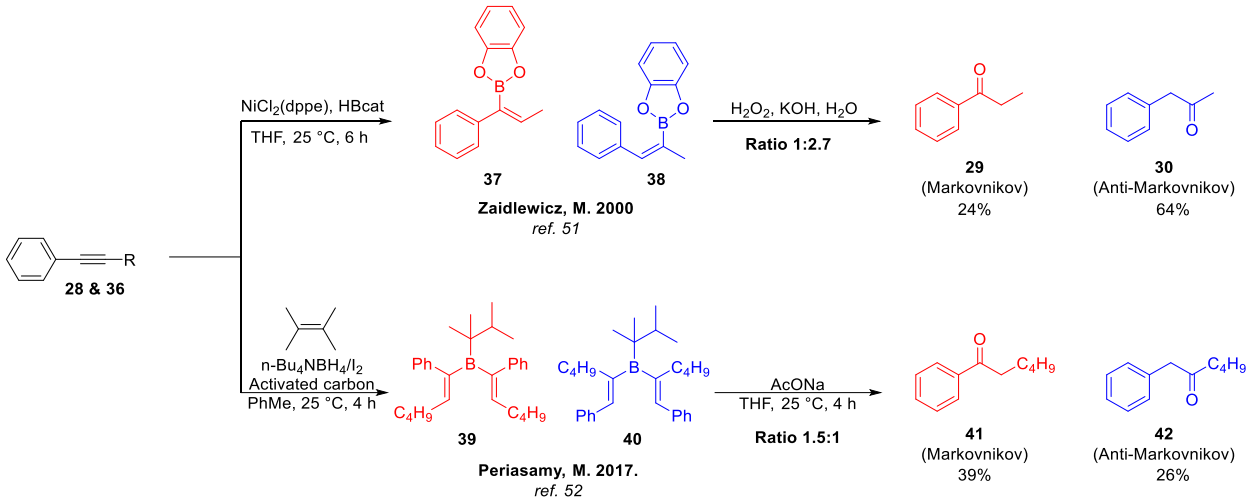


Reference	Conditions	Anti-Markovnikov	Markovnikov	Selectivity
Yan, Q. 2020 *ref. 46*	$CuCl$, PPh_3, B_2Pin_2, NaO^tBu THF, 25 °C, 30 min 2) MeOH, THF, 25 °C, 4 h	81%	0%	>99%
Lawson, J. 2017 *ref. 47*	2,4,6-$BAr^F{}_9$/HBPin DCM, 60 °C, 18 h	96%	0%	>99%
Li, JJ. 2020 *ref. 48*	B_2Pin_2, Cu NaOMe, EtOH, 25 °C, 24 h	61%	0%	>99%
Shimoi, M. 2018 *ref. 49*	NHC-borane, DTBP Benzene, 120 °C, 5 h	70%	0%	>99%
Wen,K. 2013* *ref. 50*	B_2Pin_2, DBU, MeOH, 70 °C, 24 h	84%	0%	99:1

NOTE: *An asterisk* Indicates the alkyne contains an ethyl substituent instead of a methyl*

Scheme 6. Regioselective anti-Markovnikov hydroboration of internal alkynes[46-50]

Remarkably, with these findings reported in literature, hydroboration as a general method to achieve alkyne hydrolysis remains very scarce and examples are rare (**Scheme 7**)[51, 52].



Scheme 7. The use of hydroboration-oxidation to achieve internal alkyne hydrolysis[51, 52]

Of the examples documented in literature (**Scheme 7**), the conditions presented in these papers tend to generate both regioisomers (**37-40**). Notably, one of the two reports suggests a preference toward the Markovnikov product as the main isomer (**39**, **41**). With such limited examples, perhaps the use of hydroboration as a general method to achieve anti-Markovnikov hydrolysis of alkynes has been overlooked. Some possibilities for the lack of research conducted in this area could pertain to use of metal catalysts needed for the reaction as seen in several cases[40-43, 45, 46, 48, 51]. While the latter is not likely the cause, a more plausible explanation could relate to the use of the borane compounds. These compounds are required in non-catalytic amounts (at least 1 equiv.) and are usually air and water sensitive, which could hinder reproducibility. Additionally, these borane compounds are generally sterically hindered, resulting in the formation of regioisomers on larger and more complex alkyne substrates as seen in **Scheme 7**.

In addition to hydroboration as a method to achieve anti-Markovnikov hydrolysis of alkynes, two other methods may be used to achieve this transformation. These methods employ

either a metal-catalyzed hydroamination reaction or a gold-catalyzed hydrolysis technique. The latter of the two techniques should be excluded and the reasons will be provided below.

1.1.4.2. Anti-Markovnikov Hydrolysis via Gold Catalysis

Hydrolysis of terminal alkynes is mainly accomplished using gold catalysis. While this technique generally produces Markovnikov products, there are substrates that generate the anti-Markovnikov product as the preferred isomer. An example of this is seen in a report by Marion et al[9] (**Figure 4**). The authors, who focus on Markovnikov hydrolysis of terminal alkynes, observe the anti-Markovnikov product when an internal alkyne is employed (**26**/**27**).

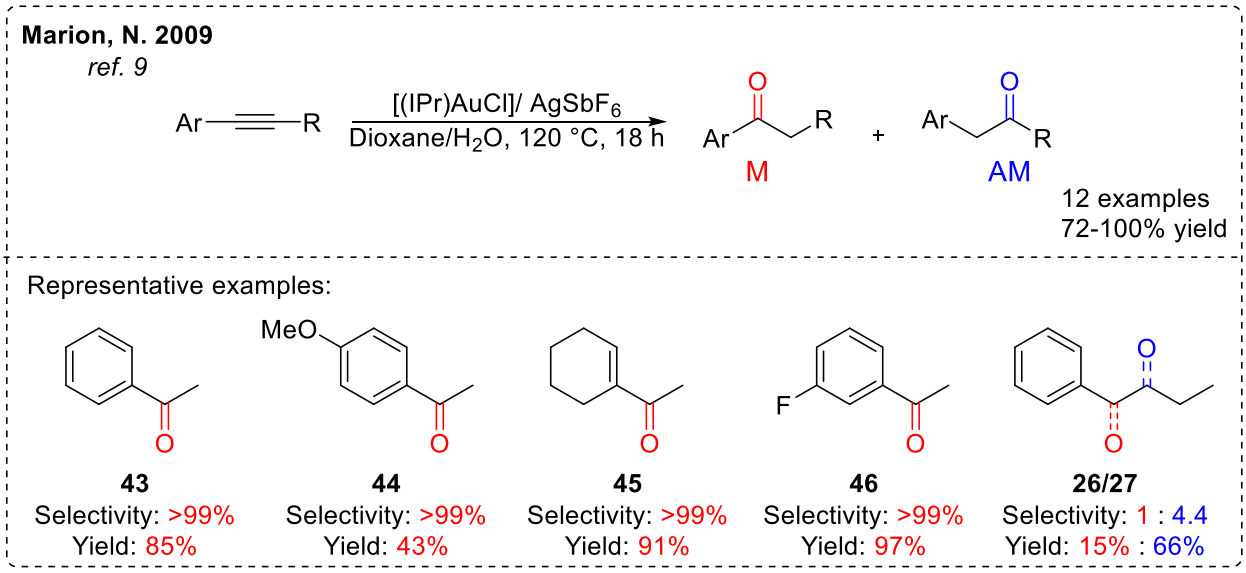


Figure 4. Gold/silver-catalyzed hydrolysis of alkynes[9]

Although this observation is present in their report, this procedure should not be relied on as a general method to achieve anti-Markovnikov hydrolysis of internal alkynes. This observation is indicative of a method that is inconsistent and highly substrate-dependent and using conditions tuned for Markovnikov hydrolysis to achieve anti-Markovnikov hydrolysis would be counterintuitive.

In addition, a report by Rühling et al[53] shows a similar finding (**Figure 5**). Employing a gold catalyst like the one above allowed them to achieve Markovnikov selective hydrolysis of terminal and internal bis-aryl alkynes. However, in one example using an aryl-alkyl alkyne, the selectivity switches to favor the anti-Markovnikov product (**49**/**50**). Though this is observed, this should not provide reason to use this strategy as this technique is not designed to achieve anti-Markovnikov hydrolysis products.

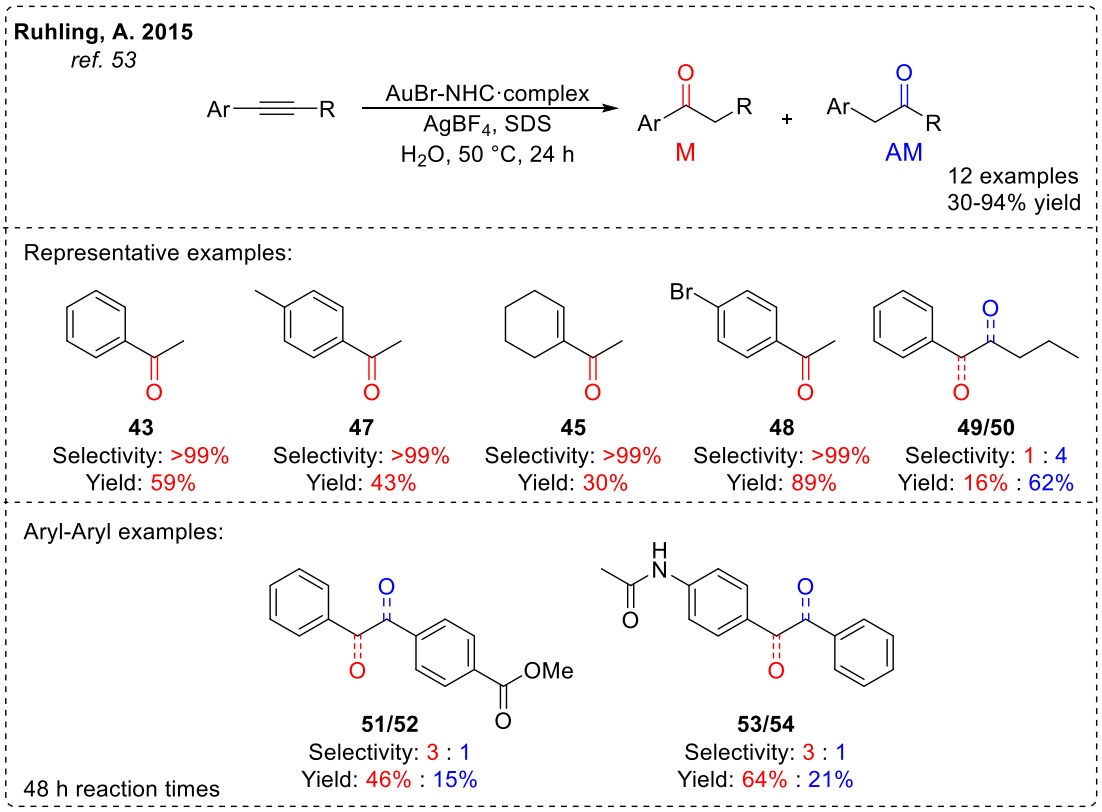


Figure 5. Gold-catalyzed hydrolysis of alkynes[53]

Likewise, there are a several reports that have a similar outcome when an internal alkyne is used, that is it favors the anti-Markovnikov product[37, 54-57]. However, these techniques lack data that would suggest a broader application of this transformation to other internal alkyne substrates.

Nevertheless, an exception to the use of gold catalysts as a technique to favor anti-Markovnikov selectivity has been reported by Endo et al[58]. Endo et al developed a strategy that

utilizes a large gold catalyst to achieve some examples of selective anti-Markovnikov hydrolysis of alkynes (**Figure 6**). While successful at accomplishing this transformation, there are several drawbacks to this approach. For one, the gold catalyst reported in this study is not commercially available. If available however (through synthesis), the use of this large gold cavity to catalyze the reaction comes with disadvantages. For instance, this procedure is very substrate dependent, indicated by the lack of reaction obtained with terminal and bis-aryl alkyne systems (**43**/**55**, **56**/**57**, **58**/**59**, **60**/**61**).

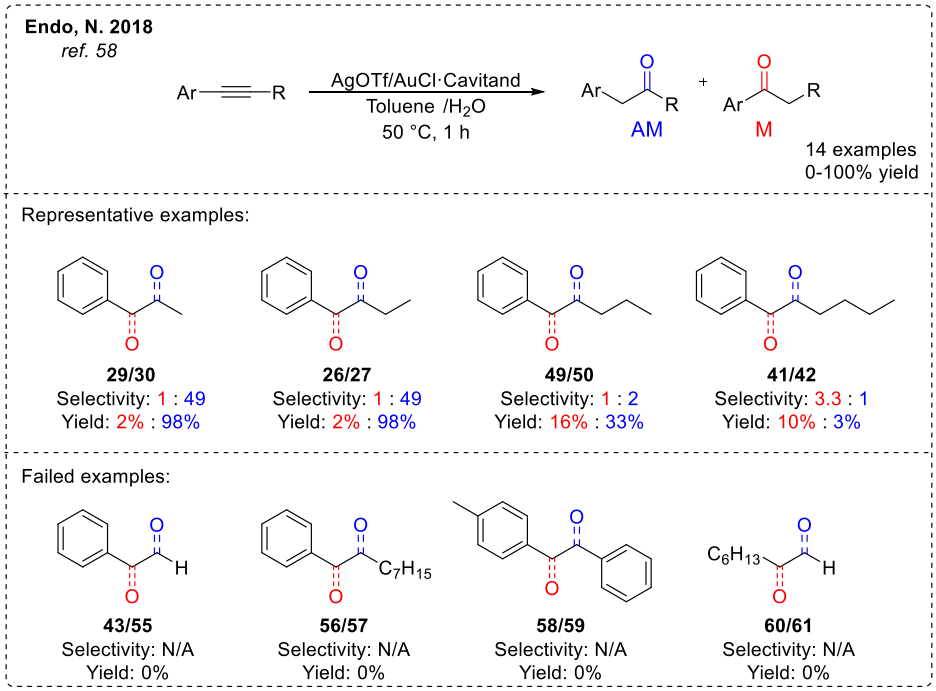


Figure 6. Gold catalyzed hydrolysis of alkynes[58]

Though the yields and selectivity may be good for certain aryl-alkyl alkynes, increasing the alkyl chain length has severe effects on the yield and selectivity which diminish rapidly, as seen in two of the four representative examples (**49**/**50**, **41**/**42**). Notably, as the alkyl chains grow in length, the selectivity switches to favor the Markovnikov product (**41**/**42**) and as the chain length exceeds four carbons (butyl group) the yields drop to 0% (**56**/**57**).

With the several drawbacks listed above, the use of this technique as a general method to achieve anti-Markovnikov hydrolysis of alkynes is unlikely. Therefore, the use of gold catalysts to achieve selective anti-Markovnikov hydrolysis of alkynes should be avoided as studies utilizing these catalysts have tuned their conditions to do the opposite. In the odd case of the literature reported by Endo et al[58], there are several disadvantages that come with this technique and other methods should therefore be used.

1.1.4.3. Anti-Markovnikov Hydrolysis via Hydroamination

Metal-catalyzed hydroamination of internal alkynes has been reported in the literature as a method to achieve selective anti-Markovnikov hydrolysis. Several literature reports have illustrated this technique as an effective method. However, like with many techniques, numerous inconsistencies and disadvantages are apparent.

A report by Haak and colleagues were able to demonstrate three examples of anti-Markovnikov selective hydrolysis of alkynes. This was accomplished through their procedure in which they utilize dimethyltitanocene as their catalyst (**Figure 7**)[59].

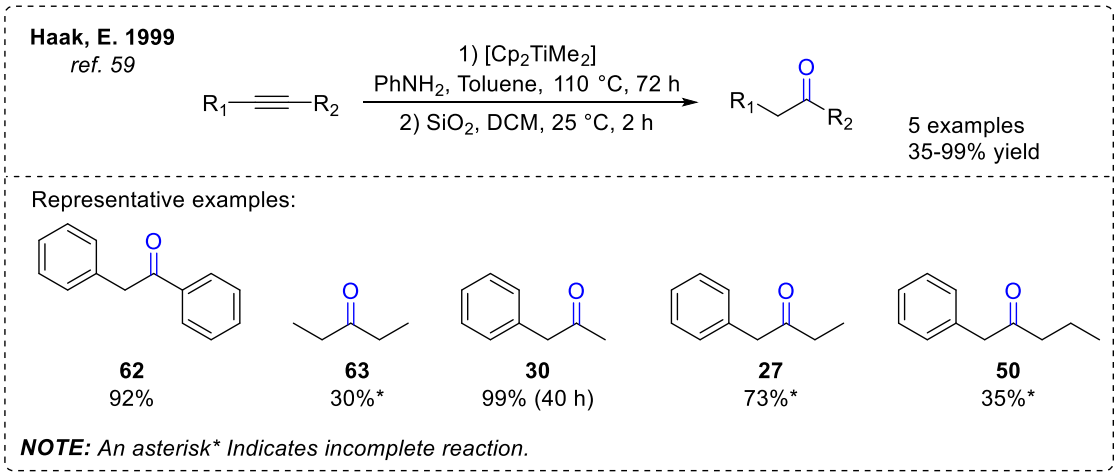


Figure 7. Dimethyltitanocene catalyzed hydroamination/hydrolysis of alkynes[59]

While able to achieve their desired transformation, they lack an in-depth substrate scope. Nevertheless, of the examples provided, we observe several shortcomings with this procedure. For one, we observe a sharp decrease in product yield as the authors increase the alkyl chain length from methyl, to ethyl, to propyl (**30**, **27**, **50**). As well, the reaction times increase with increasing chain length (**27**, **50**). However, even with the increase in reaction time, two of three internal alkynes do not produce a complete reaction (**27**, **50**). While this methodology has potential to become a general method to achieve anti-Markovnikov hydrolysis, the lack of experimental work and an in-depth substrate scope weaken confidence in this procedure.

A hydroamination procedure developed by Mei et al[36] uses copper bromide as a catalyst (**Figure 8**). The authors illustrate several examples of anti-Markovnikov hydroamination and hydrolysis of alkynes with high yields and regioselectivity.

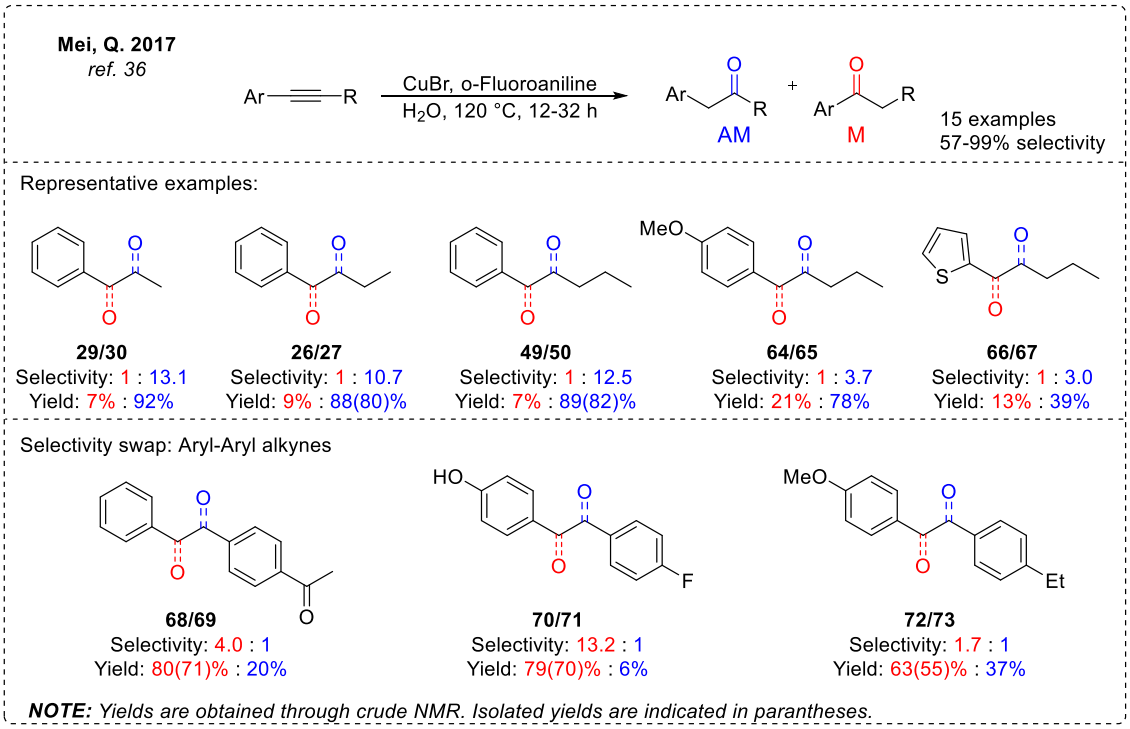


Figure 8. Copper bromide catalyzed hydroamination/hydrolysis of alkynes[36]

Though several alkynes produce high yields and regioselectivity, a significant reduction in regioselectivity is observed in more complex alkynes like those containing a methoxy group (**64**/**65**) or a thiophene (**66**/**67**). This is accompanied by a considerable drop in product yield observed for the thiophene alkyne (**66**/**67**). Furthermore, when attempted on bis-aryl alkyne systems, we observe a complete reversal of regioselectivity in favor of the Markovnikov hydrolysis product (**68**/**69**, **70**/**71**, **72**/**73**).

While this method is useful, is it evident that this technique comes with limitations. To summarize, this technique produces high yields and good regioselectivity for simple aryl-alkyl alkynes. Yet, it is apparent that this procedure is not entirely regioselective and this observation is more noticeable in complex alkynes that show a reduction in selectivity towards the anti-Markovnikov product. Likewise, the reaction is substrate dependent and this is further demonstrated through bis-aryl alkyne systems as they prefer the Markovnikov product.

Lastly, a report by Ackermann, L et al[60] brilliantly strengthens the use of a titanium catalyzed hydroamination reaction to achieve regioselective anti-Markovnikov hydrolysis of internal alkynes. **Figure 9** illustrates this technique as both high-yielding and highly regioselective.

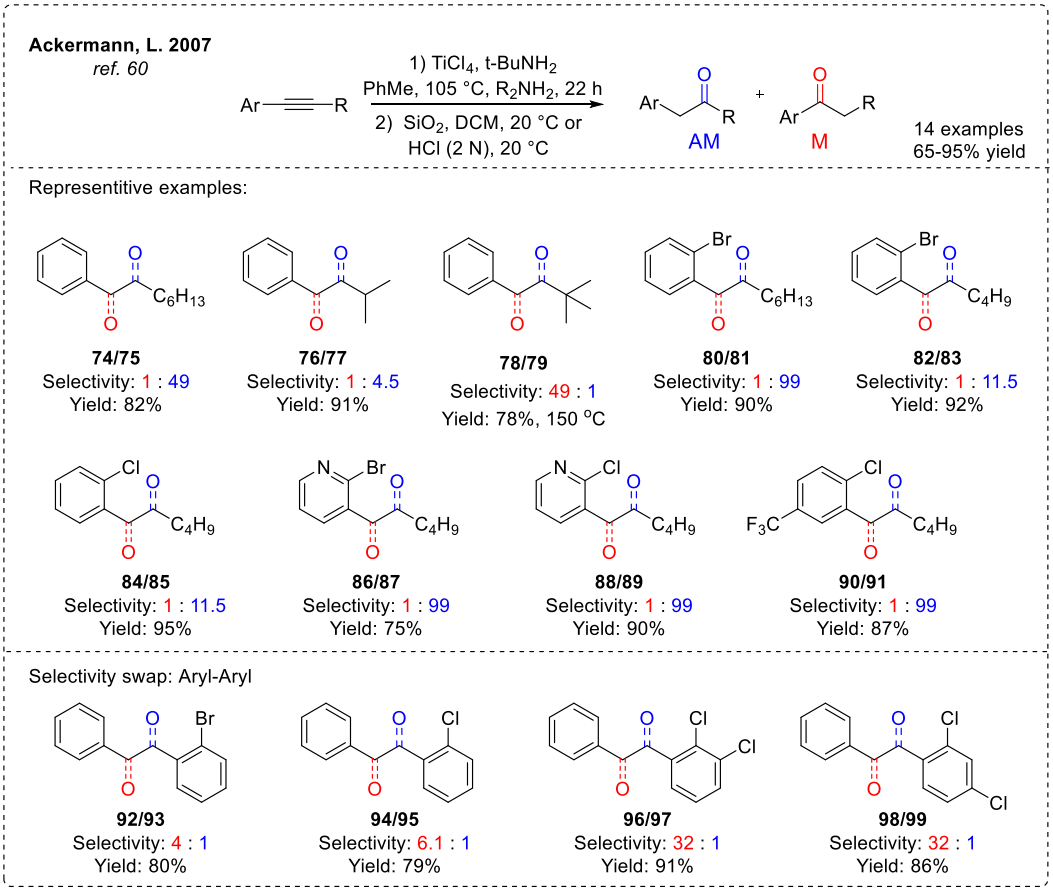


Figure 9. Titanium tetrachloride-catalyzed hydroamination/hydrolysis of alkynes[60]

While remarkable, there are some alkynes that are problematic. For instance, when varying the alkyl chain to an isopropyl group (**76**/**77**), a significant decrease in regioselectivity is observed when compared to other examples. Likewise varying the alkyl chain to a tert-butyl group causes the selectivity to change in favor of the Markovnikov product (**78**/**79**). Nevertheless, the selectivity and product yield observed for most aryl-alkyl alkynes is impressive overall.

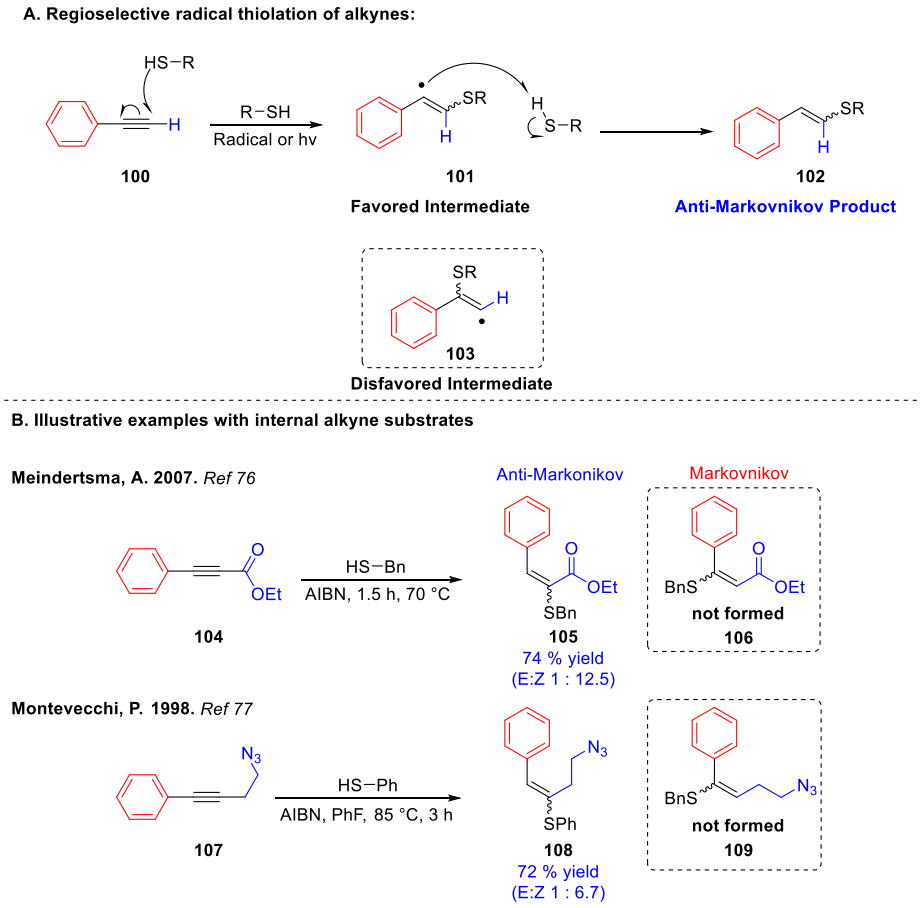
Furthermore, the Markovnikov product is preferred when bis aryl alkynes are subjected to these reaction conditions (**92-99**). This finding is comparable to the findings seen in the Mei et al paper above. Thus, while useful for aryl-alkyl alkyne systems, their conditions become inconsistent when aryl-aryl alkynes are used. Other disadvantages include the use of mostly *ortho*-substituted phenyl systems, which could be one reason for their high selectivity, though there are

a few examples without this substitution pattern. Lastly, they require the use of a harsh Lewis acid ($TiCl_4$) which is both air- and water-sensitive.

1.1.5. A Methodology Gap and our Proposed Contribution

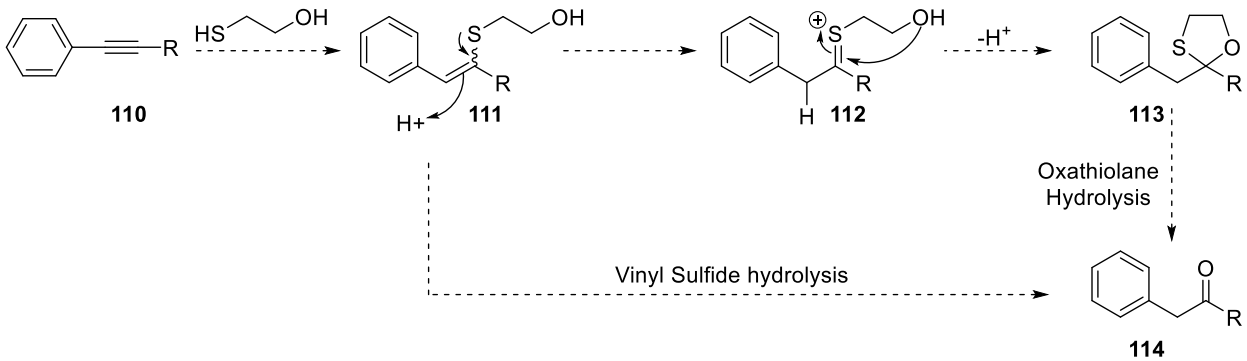
A comprehensive review of alkyne hydrolysis literature indicates that while a wealth of options exist for Markovnikov-selective hydrolysis of alkynes, the synthetic chemist's toolbox still lacks a reliable general methodology for the anti-Markovnikov hydrolysis of alkynes that works for a diverse range of substrates. In this light, we recognized an opportunity to leverage our expertise in organosulfur chemistry to develop a new methodology that achieves regioselective alkyne hydrolysis through organosulfur intermediates generated by regioselective hydrothiolation.

A wealth of synthetic chemistry literature is available concerning the regioselective thiolation of alkynes. Thiolation with Markovnikov selectivity has been accomplished with metal catalysts like rhodium[61-63], iridium[61], thorium and uranium[64], palladium[65], and nickel[65]. Similarly, anti-Markovnikov thiolation can be done with transition metal catalysis using rhodium[66], palladium[67], gold[68], nickel[69], and other metals,[65] but is also readily achieved using simple radical initiators like triethylborane (BEt_3)[70] and azobisisobutyronitrile (AIBN)[71-75]. While radical thiolation of alkynes is most commonly observed with terminal alkyne substrates, some examples also show general applicability to internal alkynes (**Scheme 8**)[75-77].



Scheme 8. Radical induced thiolation of internal alkynes[75-77]

Cognizant of this literature, we wondered whether hydrothiolation of alkynes (**110**) with 2-mercaptoethanol would result in the formation of vinyl sulfides (**111**) or oxathiolanes (**113**) which could also potentially form under the reaction conditions as shown in **Scheme 9**.



Scheme 9. Proposed alkyne hydrolysis via vinyl sulfide or oxathiolane intermediates

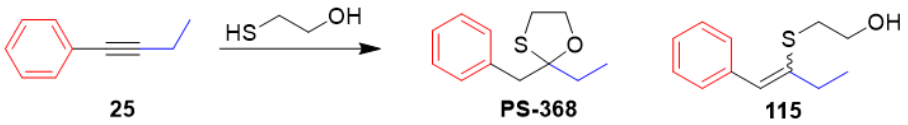
In either case, hydrolysis to the corresponding ketone (**114**) would be possible and would constitute a convenient new strategy for the overall transformation: an anti-Markovnikov alkyne hydrolysis.

2.0 Results and Discussion

2.1 Radical Thiolation of Alkynes with 2-Mercaptoethanol

We began this work by investigating the reaction of alkyne **25** with 2-mercaptoethanol in the presence of varying reaction conditions (**Table 1**).

Table 1. Optimization of radical thiolation of alkynes with 2-mercaptoethanol



25 **PS-368** **115**

Entry	Thiol (eq.)	Radical Initiator	Solvent	Temp. (°C)	Time (h)	Conversion (%) of 25	NMR Yield (%) PS-368	NMR Yield (%) 115
1	4	AIBN 10%	Toluene	Rt	16	<1	-	-
2	4	BEt_3 10%	Toluene	Rt	16	70	32	8
3	4	BPO 10%	Toluene	Rt	16	<1	-	-
4	4	AIBN 10%	Toluene	110	5	>99	76(72)	-
5	4	BEt_3 10%	Toluene	110	5	>90	68	-
6	4	BPO 10%	Toluene	110	5	58	32	-
7	4	AIBN 10%	Benzene	80	5	>99	76	-
8	4	AIBN 10%	DCE	85	5	68	50	-
9	1	AIBN 10%	Toluene	110	5	80	51	-
10	2	AIBN 10%	Toluene	110	5	90	68	-
11	8	AIBN 10%	Toluene	110	5	>99	75	-

We initiated our preliminary tests with toluene, a commonly used solvent for this chemistry, four equivalents of 2-mercaptopethanol, and 10 mol% of our radical initiator. Initially, we tested three radical initiators and the results are depicted in entries 1-3 of **Table 1**. When attempting this reaction at room temperature with AIBN and benzoyl peroxide (BPO) no reaction was detected by thin-layer chromatography (TLC), an observation that was not surprising. As anticipated AIBN and BPO would require higher temperatures to initiate radical decomposition. However, we were pleased to see that at room temperature the use of triethylborane generated the oxathiolane (**PS-368**) as the main product. While we observe a low yield and an incomplete reaction, the formation of oxathiolane (**PS-368**) over vinyl sulfide (**115**) was validated.

We repeated the reaction with the same radical initiators as above but at an increased temperature (110 °C, toluene, reflux) to initiate swift radical decomposition to produce a reaction. These results are summarized in **table 1** (entries 4-6). We were delighted to obtain a complete reaction in a short time (5 hours) when using AIBN (entry 4). Crude ^{1}H NMR analysis of entry 4 with dibromomethane as the internal standard resulted in the following observations: complete anti-Markovnikov selectivity favoring oxathiolane (**PS-368**) formation over vinyl sulfide (**115**), and a good reaction yield (**Figure 10**). However, we observed an incomplete reaction when employing triethylborane and BPO (entry 5-6).

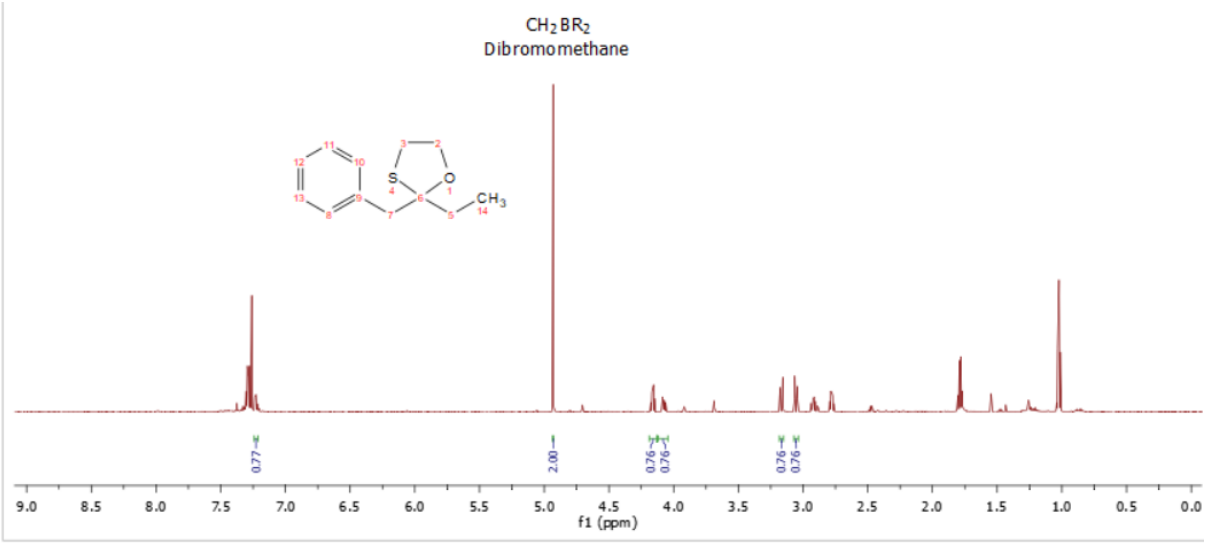


Figure 10. ^{1}H NMR depicting the crude spectra of entry 4 with the standard dibromomethane

We continued forward with AIBN as our initiator of choice. In attempts to further enhance the product yield, a solvent screen was initiated. Entries 7 and 8 illustrate these results. When switching to benzene (entry 7) as the solvent, we observe comparable results to when toluene was employed (entry 4). This result is not surprising due to the structural similarities and non-polar nature of both solvents. On the other hand, when using a polar solvent like DCE, we observe a decrease in the product yield. Consequently, this solvent was insufficient in producing a complete

reaction after 5 hours. From this information, we opted to continue with toluene over benzene due to benzene being categorized as a carcinogen.

Lastly, we varied the equivalents of 2-mercaptoethanol (entry 9-11). We found that using one or two equivalence was insufficient in producing a complete reaction after 5 hours. Moreover, using eight equivalence of 2-mercaptoethanol proved to be adequate in obtaining a complete reaction (entry 11). Using eight equivalence of thiol had comparable results to when four equivalence of thiol was used. Therefore, with the data summarized in **Table 1**, we chose entry 4 as our optimal conditions. This granted us access to oxathiolane **PS-368** in 72% yield (isolated yield).

2.2 A Comparisons of Oxathiolanes with Dioxolanes and Dithiolanes

To our knowledge, this transformation of alkynes to oxathiolanes has not been reported in literature to date. Having a new way to access this functional group prompted us to investigate the relationship of this group with respect to other carbonyl protecting groups. A review by Derek et al[78] categorized this functional group with a stability that lies between an acetal and a dithioacetal (**Figure 11**).

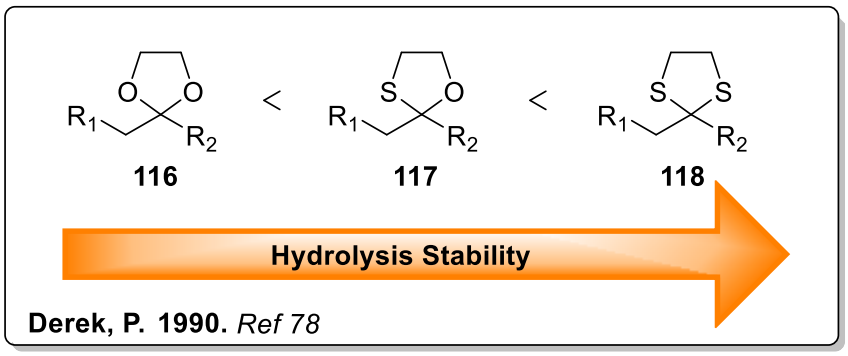
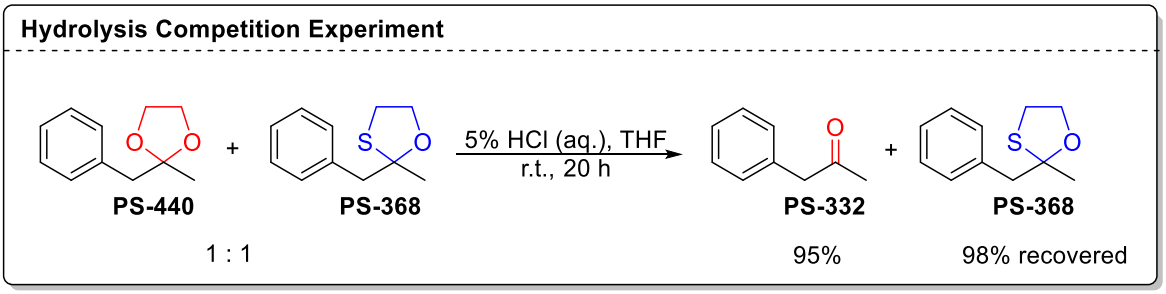


Figure 11. Relative hydrolytic stability of acetals, thioacetals, and dithioacetals

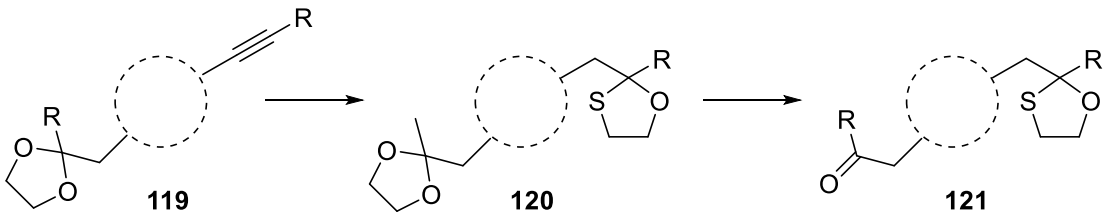
Recognizing the hydrolysis stability of this functional group with respect to other carbonyl protecting groups remains important. For instance, the benefits of this functional group with

respect to an acetal is clear, *O*,*O*-acetals (**116**) are not stable and can be hydrolyzed easily under mild conditions[79]. On the other hand, dithioacetals (**118**) are very stable and require harsh hydrolysis conditions[79]. That said, *S*,*O*-acetals (**117**) make the ideal protecting group as they are not too stable or unstable and consequently require moderate hydrolysis conditions. This finding led us to design a competition experiment to determine whether selective hydrolysis of 1,3-dioxolanes in the presence of 1,3-oxathiolanes could be achieved (**Scheme 10**).



Scheme 10. Competition experiment illustrating selective hydrolysis of a dioxolane

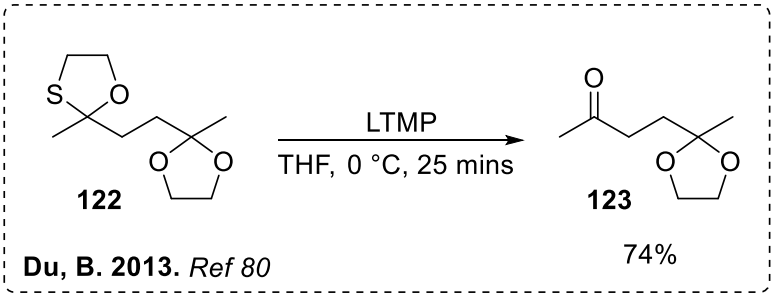
We placed equimolar amounts of both **PS-440** and **PS-368** into one reaction flask and subjected them to mild hydrolysis conditions. After 20 hours at room temperature using a 5% aqueous HCl solution, we were successful in selectively cleaving a 1,3-dioxolane (giving **PS-332**) in the presence of a 1,3-oxathiolane (**PS-368**). Not only does this support the finding of Derek et al[78], it facilitates the possibility of having multiple distinct acetals present on a single molecule and being able to selectively cleave one over the other (**Scheme 11**).



Scheme 11. Selective hydrolysis of a dioxolane in the presence of an oxathiolane

This technique is extremely valuable, enabling the chemist the option of selective acetal cleavage granting access to carbonyl counterparts when desired. For instance, selective cleavage of **120** delivers molecule **121** generating a free carbonyl group capable of undergoing reactions like a Wittig or Grignard that will not impact the oxathiolane.

This technique can also be expanded to incorporate cleavage of oxathiolanes over dioxolanes as examples of this have been reported by Du et al[80]. **Scheme 12** demonstrates base-assisted deprotection of a 1,3-oxathiolane in the presence of a 1,3-dioxolane (**122**).



Scheme 12. Base catalyzed deprotection of a 1,3-oxathiolane over a 1,3-dioxolane

Using lithium tetramethylpiperidine in THF at 0 °C for 25 minutes was sufficient to cleave a 1,3-oxathiolane (**122**) in the presence of a 1,3-dioxolane (**123**). Furthermore, if desired, global deprotection of both 1,3-dioxolanes and a 1,3-oxathiolanes is achievable[79]. Thus, with access to a new method to convert alkynes into 1,3-oxathiolanes, we may see an increase in exploiting the strategies outlined in **Schemes 10** and **11**.

2.3 Synthesis of a Library of Oxathiolanes

We began to synthesize a variety of alkynes that would be used to generate oxathiolanes. These alkynes contained various alkyl chains, phenyl substitution patterns including EDGs and EWGs, and several heterocyclic and heteroaromatic groups. The synthesis of fourteen internal alkynes was accomplished utilizing the Sonogashira cross-coupling reaction (**Figure 12**).

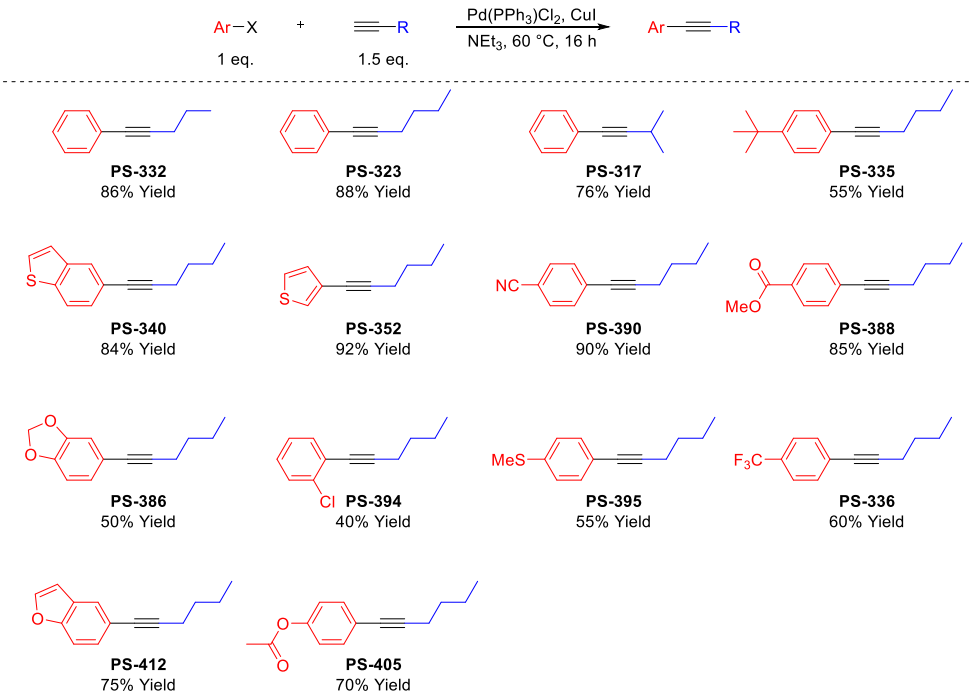


Figure 12. Synthesis of internal alkynes via palladium catalyzed cross-coupling

These alkynes were synthesized in moderate to high yields and information regarding these compounds can be found in the experimental section. A few other commercially available internal alkynes were likewise used in this study (refer to experimental section). Moreover, subjecting these internal alkynes to our optimized thiolation conditions provided us with 15 different oxathiolane products (**Figure 13**). These were obtained in moderate to high yields while maintaining complete regioselectivity.

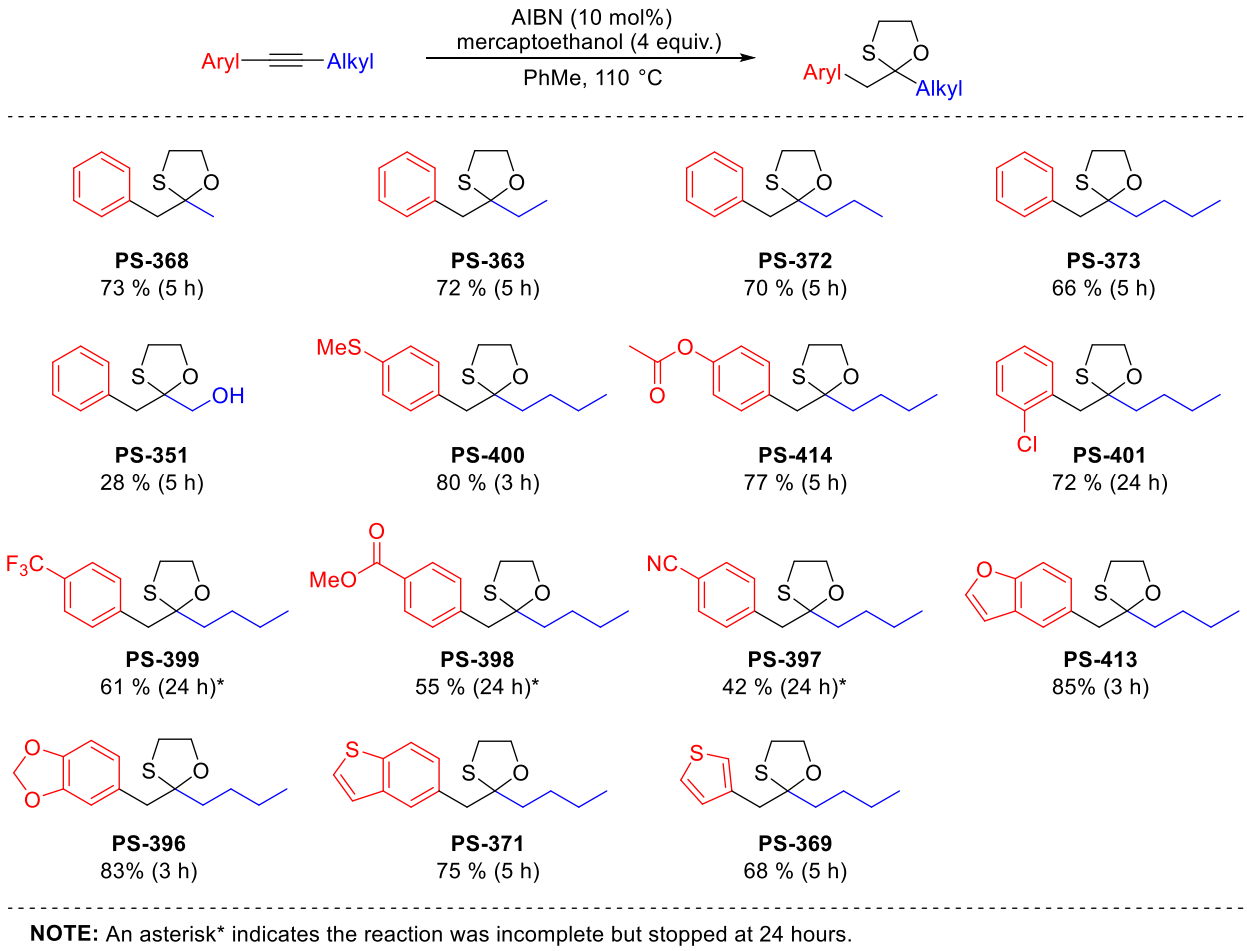


Figure 13. Substrate scope of oxathiolanes from internal alkynes

Thiolation of internal alkynes was compatible with a variety of substrates. For example, alkynes with differing alkyl chain lengths which include methyl, ethyl, propyl, and butyl groups were tolerated well and delivered good yields (**368**, **363**, **372**, **373**). When attempted with a propargyl alcohol derivative the yield was significantly lower (**351**). However, the presence of an α-alcohol under high temperatures and radical conditions could promote side reactions (i.e. elimination) which would impact the yield. Moving forward, two alkynes containing *para*-electron donating groups (EDGs) were subject to our thiolation conditions (**395**, **405**). These examples afforded good yields, providing 80% for the *para*-methyl sulfide and 77% for the *para*-acetate (**400**, **414**). This includes a decrease in reaction time from 5 hours to 3 hours as witnessed with the

methyl sulfide alkyne (**400**). Additional substrates were tested which included alkynes containing electron withdrawing groups (EWG). For example, oxathiolane formation was achieved in good yield when an alkyne containing an *ortho*-chlorine (**394**) was employed. Though compatible, a reaction time of 24 hours was required (**401**). Furthermore, additional alkynes containing EWG's like a *para*-trifluoro, *para*-ester, and *para*-nitrile group were tested (**336**, **388**, **390**). These alkynes were tolerated but with varying degree that indicated the *para*-trifluoro (**399**) with the best yield followed by the *para*-ester (**398**) and lastly the *para*-nitrile alkyne (**397**). However, in all three examples the reaction did not go to completion but was halted after 24 hours as the reaction frequently becomes stagnant after this period. Therefore, it appears that thiolation of alkynes bearing EWG's require longer reaction times and may produce lower product yields in comparison to alkynes that contain EDG's or unsubstituted phenyls. This is not surprising as electron-withdrawing groups could destabilize the radical intermediate that is generated during the reaction (refer to **Scheme 8**)[75-77]. Nonetheless, these alkyne systems were demonstrated to be compatible with this chemistry (**401**, **399**, **398**, **397**).

Lastly, four heterocyclic and heteroaromatic alkyne systems containing a benzofuran, a benzo-dioxolane, a benzothiophene, and a thiophene (**412**, **386**, **340**, **352**) were tested. These alkyne systems proved to be compatible with our chemistry and exhibited good to high oxathiolane yields (**413**, **396**, **371**, **369**). Alkynes bearing a benzofuran or a benzo-dioxolane produced the highest yields, 85% and 83% respectively, while requiring a shortened reaction time (**413**, **396**). Alkynes containing a benzothiophene or a thiophene delivered good yields but required the standard 5 hours to complete (**371**, **369**).

Having generated 15 distinct oxathiolane products from alkynes, we demonstrate the feasibility of this approach and illustrate that a range of substrates are compatible with this procedure. This includes substrates with various alkyl chain lengths, varying phenyl substitution patterns including EDG's and EWG's, and several heterocyclic and heteroaromatic alkynes. Lastly, this approach establishes a way to generate oxathiolanes in a completely regioselective manner paving the way toward a 2-step alkyne hydrolysis procedure that surpasses the selectivity witnessed in other existing methods (section 1.1.2).

2.4 Anti-Markovnikov Hydrolysis via Oxathiolanes

As was anticipated, hydrolysis of the oxathiolanes synthesized above yields ketones that correspond to the anti-Markovnikov hydrolysis products of the parent alkynes. After briefly evaluating hydrolysis conditions, we found that treatment of oxathiolanes with toluene sulfonic acid in refluxing dichloroethane for two hours offered the corresponding ketones in good yields. Hydrolysis to the corresponding ketone was achieved in two steps through hydrolysis of the crude oxathiolane. Through this technique we constructed a substrate scope that encompasses 10 various ketones. These ketones were generated from alkynes previously synthesized above (**Figure 14**).

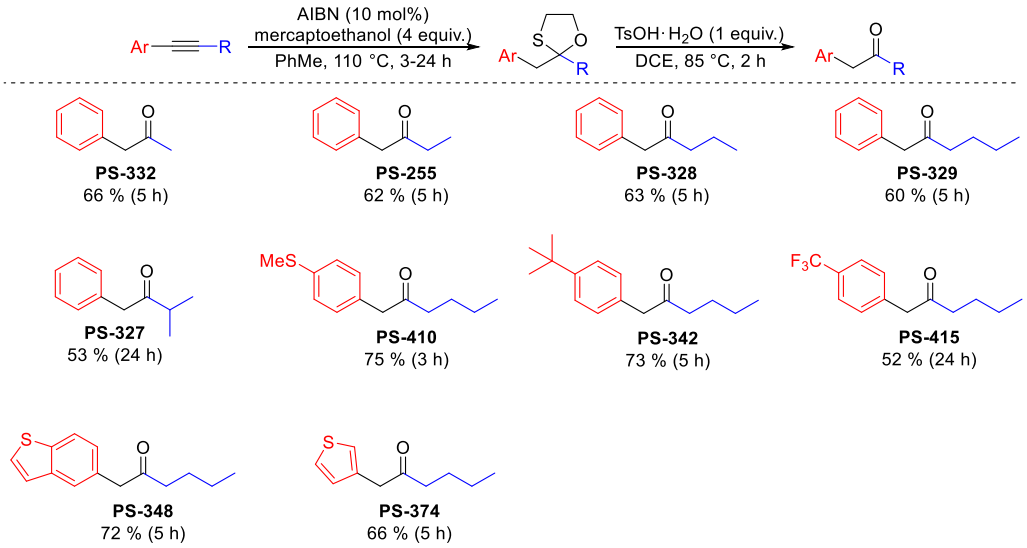
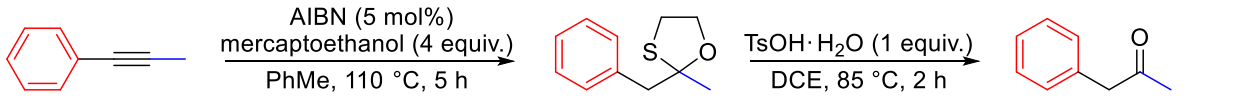


Figure 14. Substrate scope relating to anti-Markovnikov hydrolysis of internal alkynes

We began our study on alkynes containing different alkyl chains ranging from methyl to isopropyl (**28**, **332**, **323**, **317**). When tested, these alkynes were well tolerated and delivered good ketone yields (**332**, **255**, **328**, **329**, **327**). Even when a bulky isopropyl group is present, the yield was only slightly lower compared to other alkyl groups. However, an increase in reaction time (24 hours) was required to achieve **327**. Moreover, three *para*-substituted phenyl ketones were added to the substrate scope in good to moderate yields (**410**, **342**, **415**). The alkyne containing a *para*-methyl sulfide produced the best yield in the shortest reaction time (**410**), followed by the *para*-tert-butyl alkyne (**342**), and lastly the electron-withdrawing *para*-trifluoro alkyne (**415**). Finally, two heteroaromatic alkynes were taken forward and subjected to our conditions to produce the corresponding ketone products (**348**, **374**). Both a benzothiophene and a thiophene were tolerated well with this chemistry and produced good yields.

2.5 A Gram-Scale Alkyne Hydrolysis

With several examples illustrated above showing regioselective anti-Markovnikov hydrolysis of internal alkynes, we initiated a large-scale reaction to demonstrate the efficiency of this method. **Scheme 13** reveals a multi-gram reaction that generates the corresponding oxathiolane (**PS-368**) from alkyne **28** in good yield. This was accomplished using 5 mol% of AIBN instead of 10 mol%.



28
(2.00g 17.2 mmol)

PS-368
Crude (74 % NMR)

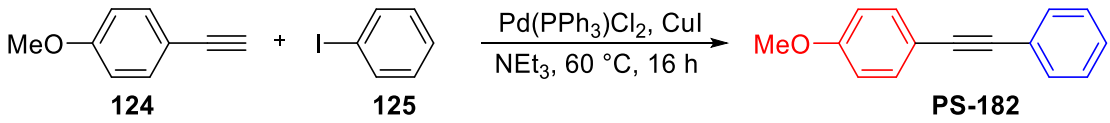
PS-332
(1.57g, 11.7 mmol, 68 %)

Scheme 13. Gram scale reaction of the two-step anti-Markovnikov hydrolysis of alkynes

After achieving the corresponding oxathiolane, we subjected the crude product (after work-up) to our hydrolysis conditions (**Scheme 13**). This generated the corresponding anti-Markovnikov ketone in good yield using *p*-toluenesulfonic acid and DCE (**332**).

2.6 Hydrolysis of Aryl-Aryl Alkynes

We then shifted our focus toward bis-aryl alkyne systems and whether our chemistry would be suitable on these substrates. We learnt from previous literature (section 1.1.2) how difficult it is to achieve selective anti-Markovnikov hydrolysis of bis-aryl alkyne systems. When attempted by the methods described in section 1.1.2, we observe a selectivity that favors the Markovnikov product. This observation drew us toward accomplishing this feat. Therefore, we initiated our investigation by synthesizing an internal bis-aryl alkyne (**Scheme 14**).

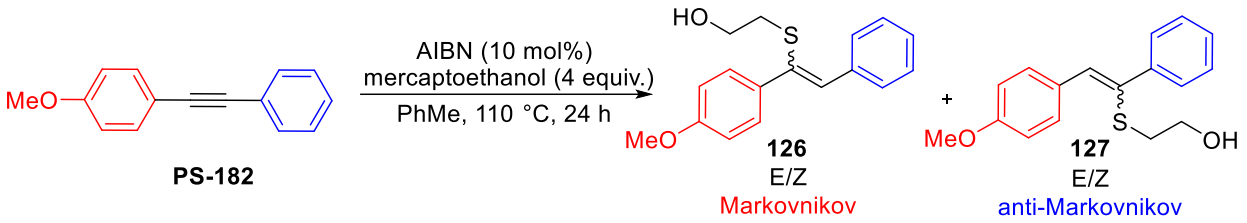


124 **125** **PS-182**

Scheme 14. Bis-aryl alkyne synthesis via palladium catalyzed cross-coupling

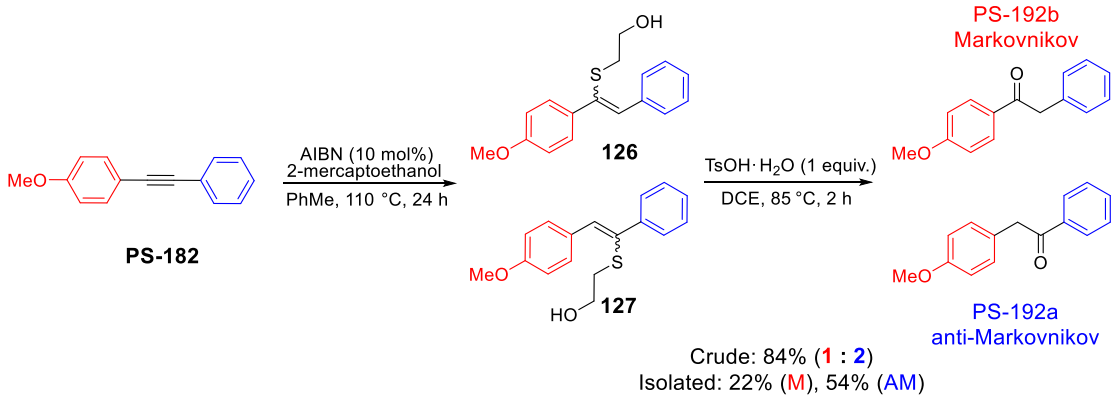
We started by synthesizing a bis-aryl alkyne system that contains a *para*-methoxy group on one phenyl ring while leaving the other unsubstituted (**PS-182**). We anticipated that when subjecting this alkyne system to our 2-step hydrolysis procedure the anti-Markovnikov ketone would be the major product. This approach was rationalized by acknowledging that electron-donating groups increase the electron-density around the corresponding arene system which enhances stability of the radical intermediate that is formed on the adjacent carbon center (**Scheme 8**). Therefore, the radical would be placed on the carbon center adjacent to the electron-rich arene and the thiol would add to the carbon adjacent to the unsubstituted arene.

Following the synthesis of **PS-182**, bis-aryl alkyne thiolation was attempted. TLC analysis indicated a complete reaction after 24 hours. Subsequent work-up and crude ^{1}H NMR analysis revealed the presence of vinyl sulfide regio and stereoisomers (**Scheme 15**).



Scheme 15. Radical thiolation of bis-aryl alkyne yielding regio and stereoisomers

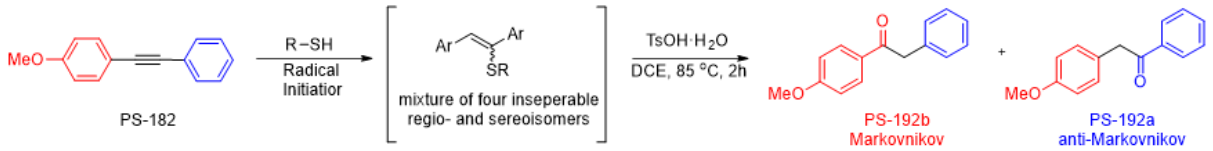
While one side of **PS-182** contains an EDG that enhances radical stabilization, unsubstituted phenyl rings are strong radical stabilizers as well. Therefore, we believe that radical stabilization occurred on both sides of the bis-aryl alkyne producing regioisomers (**126**, **127**). Though, both Markovnikov and anti-Markovnikov vinyl sulfide products were synthesized accompanied by their stereoisomers, it was difficult to designate the major product. Consequently, we determined that it would be simpler to take the crude mixture and subject it to hydrolysis. Hydrolysis was accomplished using *p*-toluenesulfonic acid and DCE to yield a mixture of ketones favoring the anti-Markovnikov product by 2:1 (**Scheme 16**). The use of HSQC and HMBC NMR experiments facilitated the assignment of regioisomers.

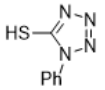
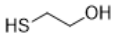
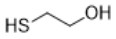
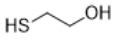
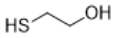
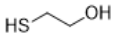
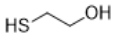
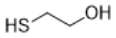
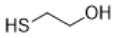


Scheme 16. Bis-aryl alkyne thiolation and vinyl sulfide hydrolysis yielding ketones

Though the selectivity is low in comparison to the selectivity seen with aryl-alkyl alkynes, we were pleased to discover consistency for both aryl-alkyl and bis-aryl alkyne systems. This cannot be said about the methods discussed in section 1.1.2 as the selectivity favors the Markovnikov product for bis-aryl alkyne systems. With this information, we attempted to increase the selectivity toward the anti-Markovnikov product by modifying our reaction conditions. This is summarized in **Table 2**.

Table 2. Optimization of radical thiolation and hydrolysis of bis-aryl alkynes



Entry	Thiol (eq.)	Thiol	Radical Initiator	Solvent	Temp. (°C)	Time (h)	Conversion (%) of 1a	2 step NMR Yield (%)	Ratio of M:AM
1	4	$HS-C_{12}H_{25}$	AIBN 10%	Toluene	110	24	50%	-	-
2	4		AIBN 10%	Toluene	110	48	<1%	-	-
3	4		AIBN 10%	Toluene	110	24	>99%	84	1:2
4	4		BEt_3 10%	Toluene	110	24	50%	-	-
5	4		BPO 10%	Toluene	110	24	<5%	-	-
6	4		AIBN 10%	CyHex	85	72	<5%	-	-
7	4		AIBN 10%	Benzene	85	24	>95%	78	1:2
8	4		AIBN 10%	Xylene	110	24	>99%	84	1:1.9
9	4		AIBN 10%	Toluene	110	72	>99%	69	1:1.88
10	4		AIBN 10%	Toluene	65	24	<10%	-	-

After trying various thiols (entry 1-2), radical initiators (entry 4-5), and solvents (entry 6-8), our initial conditions remained superior, delivering the highest yield and selectivity (entry 3). Therefore, we were satisfied with the results which led us to synthesize more bis-aryl alkynes. These were produced using the Sonogashira cross-coupling procedure (**Figure 15**).

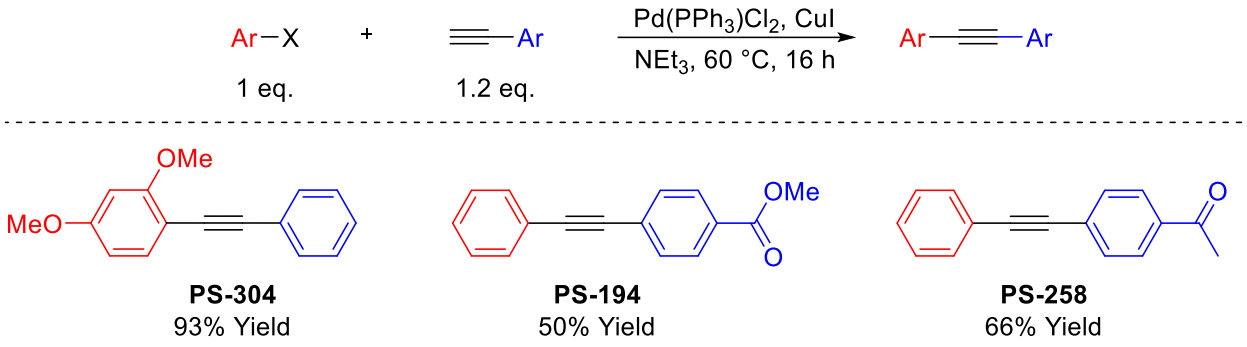
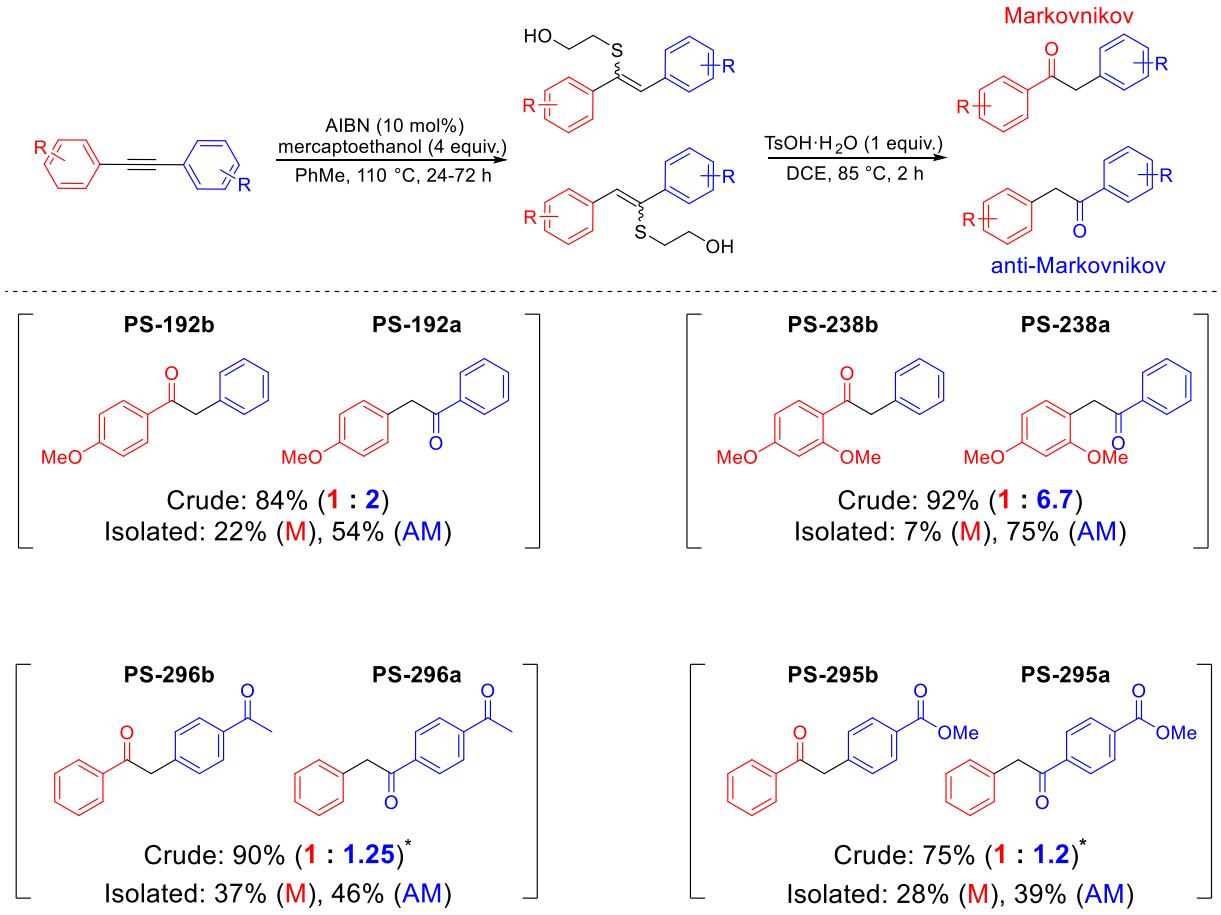


Figure 15. Synthesis of additional bis-aryl alkynes via palladium catalyzed cross-coupling

These bis-aryl alkyne substrates were synthesized in good yields and were subsequently used to generate the corresponding ketones via our two-step hydrolysis procedure (**Figure 16**).



Note: *An asterisk* indicates the reaction took 72 h to complete.*

Figure 16. Substrate scope relating to anti-Markovnikov hydrolysis of bis-aryl alkynes

We were pleased to observe that all three examples remained consistent and afforded the anti-Markovnikov ketone as the major product (with varying selectivity). We noticed that by adding two electron-donating methoxy groups on one phenyl ring (**PS-304**), we were able to improve the selectivity to favor the anti-Markovnikov product by 6.7:1 (**PS-238a**, **PS-238b**) while maintaining a high yield. However, when an EWG is present on one side of the alkyne system (**PS-194**, **PS-258**), we observe a decrease in selectivity toward the anti-Markovnikov product and an increase in reaction time (**PS-296a/b**, **PS-295a/b**). We anticipated the opposite effect would occur for EWGs than for EDGs; that is the side that contains the EWG would decrease the electron-density around the corresponding arene and would thus destabilize the radical intermediate formed on the adjacent carbon. This would force the radical to be placed on the carbon adjacent to the unsubstituted arene as it has more electron-density relative to the other arene. This would predictably favor the anti-Markovnikov product as the thiol would add to the carbon center adjacent to the electron-deficient arene system. This is in fact what we observed, but in a less drastic degree in comparison to when an EDG was utilized. This result suggests that introducing an EWG may prevent the reaction from occurring due to destabilization of the radical species at the adjacent carbon. Nonetheless, these four examples demonstrate that selective anti-Markovnikov thiolation and subsequent hydrolysis of bis-aryl alkynes can be achieved. This hydrolysis method remains consistent for both aryl-alkyl and bis-aryl alkyne systems, unlike those seen in section 1.1.2.

2.7 Total Synthesis of Isomeranzin

To further solidify this as a general and effective method to achieve regioselective hydrolysis of alkynes, we decided to synthesize the coumarin natural product isomeranzin. Isomeranzin has previously been isolated from numerous members of the Rutaceae family including the small tree *Murraya panculata*[81-83], the fruit *Citrus grandis*[84-86] (pomelo fruit), and from the small shrub *Clausena anisata*[87] (**Figure 17**).

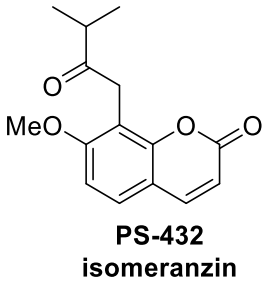
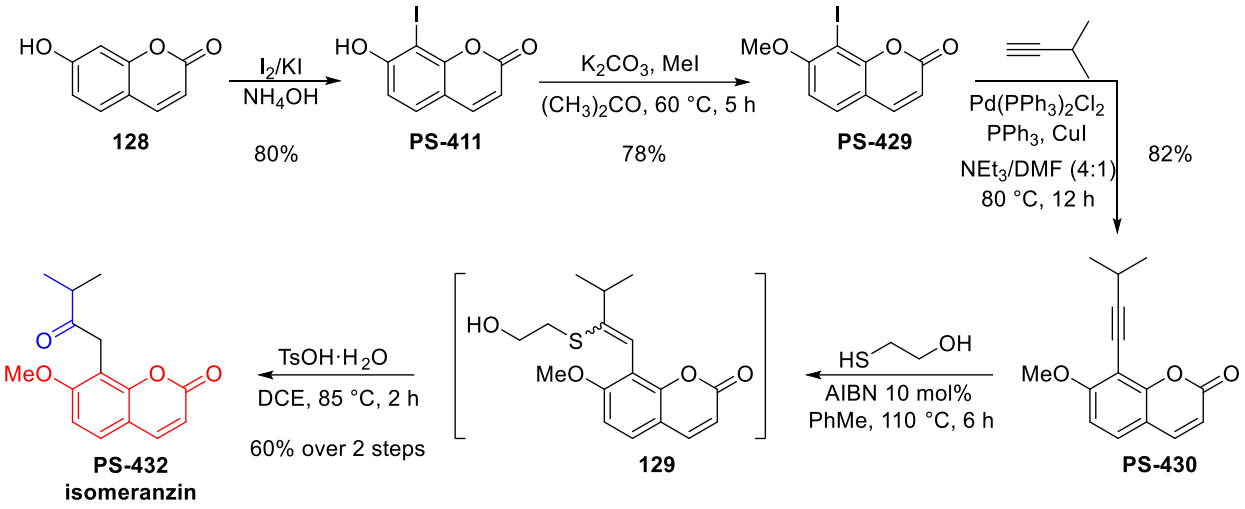


Figure 17. Structure of the coumarin natural product isomeranzin

Like many natural products, the bioactivity of isomeranzin and coumarins in general has been evaluated. Studies establish isomeranzin along with other coumarin natural products as harnessing anti-inflammatory[81, 85,87] and neuroprotective[87] activity, hepatoprotective[84] activity, and anti-fungal[88] activity. Encompassing a variety of bioactive properties and discovering the absence of a chemical synthesis, isomeranzin arose as a suitable target to attempt our chemistry on.

Starting from the commercially available coumarin umbelliferone (**128**), selective iodination was achieved using the procedure outlined by Devji et al[89] (**Scheme 17**).



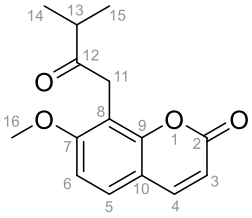
Scheme 17. Total synthesis of the coumarin natural product Isomeranzin

Utilizing iodine, potassium iodide, and ammonium hydroxide afforded 8-iodoumbelliferone (**PS-411**) in 80% yield. Furthermore, the procedure of Gillmore et al[90] was followed to achieve alkylation of the free hydroxyl group. Employing methyl iodide and potassium carbonate in acetone afforded the methylated product 8-iodo-7-methoxychromen-2-one (**PS-429**) in 78% yield. Next, the procedure of Guthertz et al[91] was used to attain an isopropyl alkyne. Subjecting 8-iodo-7-methoxychromen-2-one (**PS-429**) to bis(triphenylphosphine)palladium(II) dichloride, copper(I) iodide, triphenylphosphine, and 3-methyl-1-butyne in triethylamine and dimethylformamide provided the corresponding alkyne 7-methoxy-8-(3-methylbut-1-yn-1-yl)-2H-chromen-2-one (**PS-430**) in 82%. This is the first literature report of this product.

With **PS-430** in hand, we were eager to attempt our 2-step hydrolysis procedure. We started by subjecting 7-methoxy-8-(3-methylbut-1-yn-1-yl)-2H-chromen-2-one (**PS-430**) to our thiolation conditions. We were thrilled to observe the disappearance of **PS-430** by TLC after 6 hours. Interestingly, based on crude ^{1}H NMR analysis the vinyl sulfide product (**129**) was preferred over formation of oxathiolane. Next, we took the crude material forward and treated it with our hydrolysis conditions. After 2 hours, vinyl sulfide hydrolysis was accomplished using *p*-

toluenesulfonic acid and DCE. Generally, vinyl sulfide hydrolysis is achieved using toxic and harsh Lewis acids like mercury(II) chloride ($HgCl_2$)[92, 93] and titanium tetrachloride ($TiCl_4$)[94]. Thus, *p*-toluenesulfonic acid and DCE remains sufficient in hydrolyzing both oxathiolanes and vinyl sulfides. This procedure granted us access to a fast 2-step anti-Markovnikov hydrolysis of **PS-430** in 60% (**PS-432**). Consequently, we were able to accomplish the first reported total synthesis of isomeranzin (**PS-432**) in just 5 steps with an overall yield of 31%. Synthetic isomeranzin was then compared to ^{1}H and ^{13}C NMR spectra of naturally isolated samples and is consistent with these literature reports (**Table 3**)[82, 87].

Table 3. Table comparing ^{1}H and ^{13}C spectra between synthetic and natural isomeranzin



	Synthetic isomeranzin		Natural isomeranzin[80,85]	
Position	^{1}H ppm	^{13}C ppm	^{1}H ppm[80]	^{13}C ppm[85]
2	-	161.12	-	161.20
3	6.23, d (J = 9.4 Hz, 1H)	113.24	6.23, d (J = 9.5 Hz, 1H)	113.00
4	7.63, d (J = 9.5 Hz, 1H)	143.88	7.63, d (J = 9.5 Hz, 1H)	143.50
5	7.38, d (J = 8.6 Hz, 1H)	127.62	7.38, d (J = 8.5 Hz, 1H)	127.30
6	6.85, d (J = 8.6 Hz, 1H)	107.36	6.85, d (J = 8.5 Hz, 1H)	106.80
7	-	160.59	-	160.30
8	-	112.16	-	111.30
9	-	153.37	-	154.10
10	-	113.07	-	112.90
11	4.01, s (2H)	34.83	4.01, s (2H)	34.90
12	-	210.89	-	211.00
13	2.83, h (J = 6.9 Hz, 1H)	41.05	2.83, h (J = 6.8 Hz, 1H),	40.70
14/15	1.21, d (J = 6.9 Hz, 6H)	18.56	1.21, d (J = 6.8 Hz, 6H)	18.50
16	3.86, s (3H)	56.26	3.86, s (3H)	56.10

2.8 Summary

This thesis has described our development of an operationally simple procedure that employs radical induced thiol-yne chemistry to obtain regioselective hydrolysis of both aryl-alkyl and bis-aryl alkyne systems (**Figure 18**).

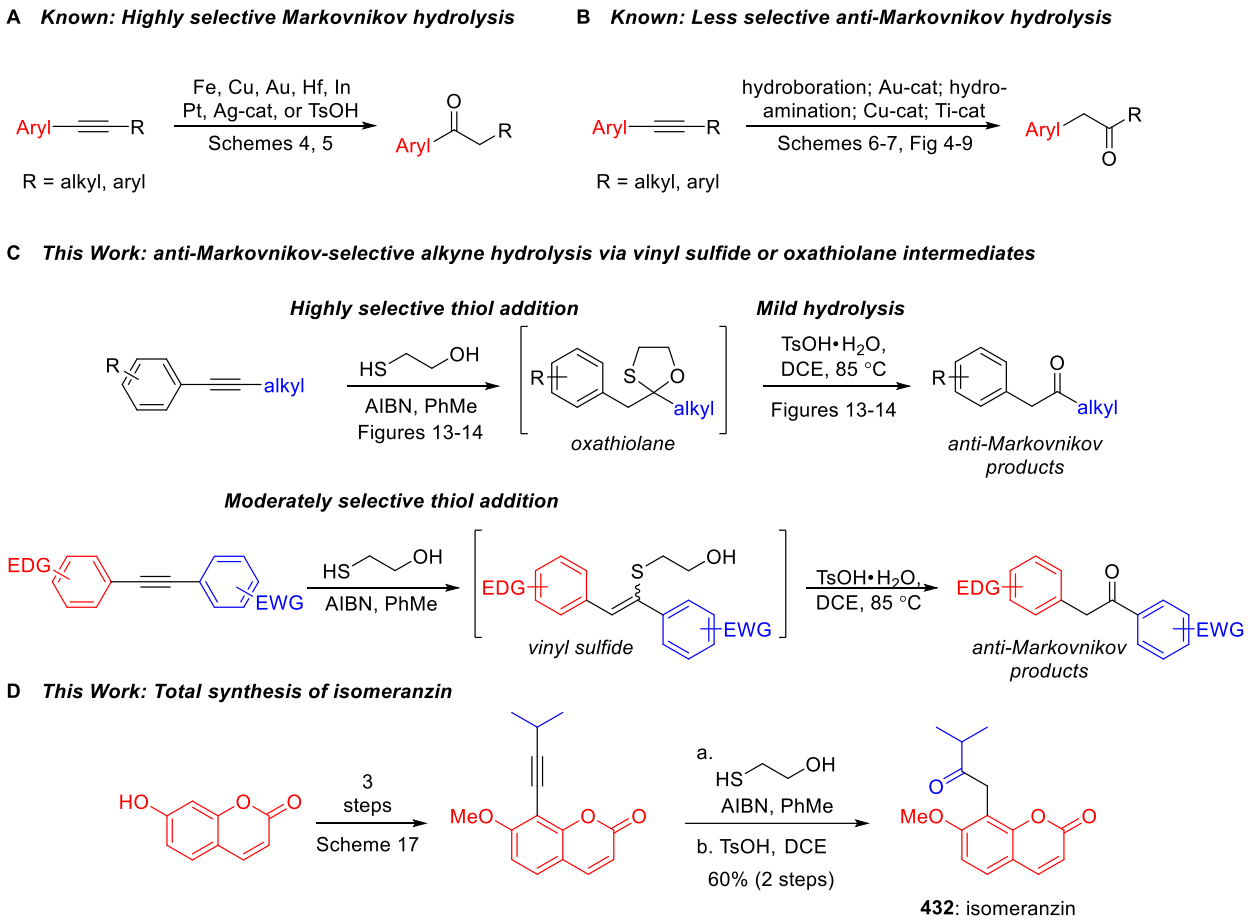


Figure 18. Summary of our work in the context of existing literature

This procedure converts aryl-alkyl alkynes to oxathiolanes in a completely regioselective manner (15 examples) and is the first ever report to do so. This transformation is high yielding and hydrolysis to the corresponding ketone is achieved easily and in good yields (10 examples). This method facilitated the only total synthesis of isomeranzin, a coumarin natural product with several bioactive properties. The synthesis of isomeranzin was accomplished in five steps with an overall

yield of 31%. Additionally, unsymmetrical bis-aryl alkynes, which form vinyl sulfides, are hydrolyzed to ketones to give an unprecedented degree of anti-Markovnikov regioselectivity (up to 6.7:1, 4 examples).

3.0 Experimental Section

[*General Information*]

Substrates, solvents, and reagents were purchased from commercial suppliers. Reaction progress was monitored by analytical thin-layer chromatography, which was precoated with aluminum-backed plates (silica gel F254; SiliCycle Inc.) and visualized under UV light. Purification of reaction products was carried out on Teledyne CombiFlash® Rf 200 automated flash chromatography systems on silica gel cartridges (Teledyne, Inc. or SiliCycle Inc.). ^{1}H NMR and ^{13}C NMR spectra were acquired at 700 MHz with a default digital resolution (Brüker parameter: FIDRES) of 0.18 and 0.15 Hz/point, respectively. Coupling constants reported herein therefore have uncertainties of ±0.4 Hz and ±0.3 Hz, respectively. All assignments of protons and carbons relied on data from 2-dimensional NMR experiments including HSQC and HMBC. Chemical shifts pertaining to ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) with respect to tetramethylsilane (TMS), with calibration of the residual solvent peaks according to values reported by Gottlieb et al ($CDCl_3$: δ_H 7.26, δ_C 77.16, MeOH-d_4: δ_H 3.31, δ_C 49.00)[95]. The ^{13}C NMR (DEPTQ) spectra provided herein show CH and CH_3 carbon signals below the baseline and C and CH_2 carbons above the baseline. Peak multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublets of doublets; qpp, quartet of doublets of doublets; m, multiplet. Melting points (mp) were obtained using the Stuart SMP30 melting point apparatus. Melting points (mp) are uncorrected. High resolution mass analysis (HRMS) was performed on quadruple-time of flight (Q-Tof) mass spectrometer (Micromass, USA) using electrospray ionization (ESI) in positive mode.

[*Solvents*]

Hexanes was purchased from Fisher chemical, catalogue # 188434.

Dichloromethane (DCM) was purchased from Fisher chemical, catalogue # 192705.

Ethyl acetate (EtOAc) was purchased from Fisher chemical, catalogue # 174768.

$CDCl_3$ was purchased from Fisher chemical, catalogue # AC166251000.

MeOH-d_4 was purchased from Fisher chemical, catalogue # AC320750075.

Acetone was purchased from Fisher chemical, catalogue # 190175.

Diethyl ether was purchased from Fisher chemical, catalogue # 189548.

Toluene was purchased from Anachemia, catalogue # 92368540.

Dimethylformamide (DMF) was purchased from Fisher chemical, catalogue # D119-1

Triethylamine (NEt_3) was purchased from Fisher chemical, catalogue # O4884500

Dichloroethane (DCE) was purchased from Fisher chemical, catalogue # AA39121K7

[*Reagents*]

Anhydrous sodium sulfate (Na_2SO_4) was purchased from Fisher Scientific.

2,2'-Azobis(2-methylpropionitrile) (AIBN) was purchased from Sigma-Aldrich.

2-Mercaptoethanol was purchased from Sigma-Aldrich.

***p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$)** was purchased from Oakwood chemicals.

Ammonium Chloride (NH_4Cl) was purchased from Fisher Scientific

Potassium Iodide (KI) was purchased from Fisher Scientific

Iodine (I_2) was purchased from Sigma-Aldrich.

Sulfuric acid (H_2SO_4) was purchased from Sigma-Aldrich.

Iodomethane (MeI) was purchased from Sigma-Aldrich.

Umbelliferone was purchased from AKScientific.

Potassium carbonate (K_2CO_3) was purchased from Sigma-Aldrich.

Hydrochloric acid (HCl) was purchased from Sigma-Aldrich.

Sodium Hydroxide (NaOH) was purchased from Fisher Scientific

Ammonium Hydroxide (NH_4OH) was purchased from Sigma-Aldrich.

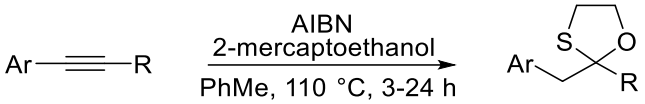
Copper(I) Iodide (CuI) was purchased from Sigma-Aldrich.

Bis(triphenylphosphine)palladium(0) Chloride ($Pd(PPh_3)_2Cl_2$) was purchased from Sigma-Aldrich.

Triphenylphosphine (PPh_3) was purchased from Sigma-Aldrich.

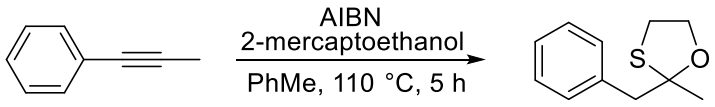
[*General Procedure and Characterization Data*]

General procedure for the synthesis of oxathiolanes from alkynes



General Procedure 1: To a solution of alkyne (0.60 mmol) in toluene (10 mL) was added azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.) followed by 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol) in one portion. The reaction flask was equipped with a reflux condenser and heated at 110 °C until disappearance of the alkyne was observed by thin-layer chromatography (TLC, 3-24 hours). The mixture was then diluted with diethyl ether (Et_2O) and washed with NaOH (2M, approximately 20 mL) twice, to remove excess 2-mercaptoethanol. The organic layer was washed once with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered the corresponding oxathiolane.

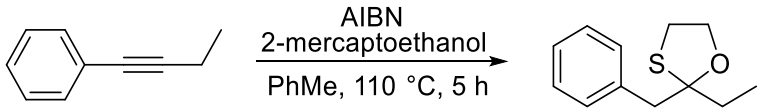
PS-368 (2-benzyl-2-methyl-1,3-oxathiolane)



General Procedure 1 was followed using **1-phenyl-1-propyne** (70 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-368** (**1-phenyl-1-propyne**, 85 mg, 0.44 mmol, 73% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.30, m (4H), 7.25, m (1H), 4.18, dt (*J* = 9.2, 5.6 Hz, 1H), 4.16, ddd (*J* = 9.2, 6.5, 5.7 Hz, 1H), 3.17, d (*J* = 13.7 Hz, 1H), 3.08, d (*J* = 13.7 Hz, 1H), 3.06, dt (*J* = 10.2, 6.1 Hz, 1H), 2.91, dt (*J* = 10.1, 6.2 Hz, 1H), 1.56, s (3H). ^{13}C NMR DEPTQ

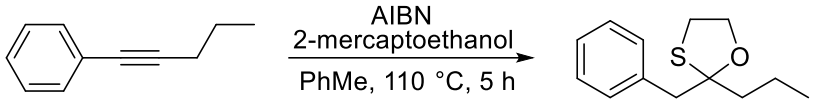
(176 MHz, CDCl3): δ (ppm) 137.46, 130.75, 128.02, 126.71, 95.07, 70.75, 49.39, 34.24, 29.04. LCMS (ESI) *m/z* 195.08381 calculated for $C_{11}H_{15}OS^+$ ($[M + H]^+$); 195.08324 observed.

PS-363 (2-benzyl-2-ethyl-1,3-oxathiolane)



General procedure 1 was followed using **1-phenyl-1-butyne** (78 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-363** (**2-benzyl-2-ethyl-1,3-oxathiolane**, 90 mg, 0.43 mmol, 72% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.29, d (*J* = 6.8 Hz, 2H), 7.28, t (*J* = 7.5 Hz, 1H), 7.23, t (*J* = 7.1 Hz, 1H), 4.17, dt (*J* = 9.0, 5.6 Hz, 1H), 4.08, ddd (*J* = 9.0, 6.5, 5.5 Hz, 1H), 3.17, d (*J* = 13.9 Hz, 1H), 3.06, d (*J* = 13.9 Hz, 1H), 2.93, m (1H), 2.79, m (1H), 1.80, q (*J* = 7.3 Hz, 2H), 1.03, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 137.39, 130.85, 127.94, 126.58, 99.16, 71.29, 47.02, 34.05, 33.68, 9.50. LCMS (ESI) *m/z*: 209.09946 calculated for $C_{12}H_{17}OS^+$ ($[M + H]^+$); 209.09830 observed.

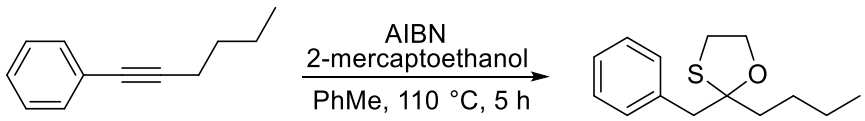
PS-372 (2-benzyl-2-propyl-1,3-oxathiolane)



General procedure 1 was followed using **1-phenyl-1-pentyne** (87 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-372** (**2-benzyl-2-propyl-1,3-oxathiolane**, 93 mg, 0.42 mmol, 70% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.28, m (4H), 7.23, m (1H), 4.15, dt (*J*

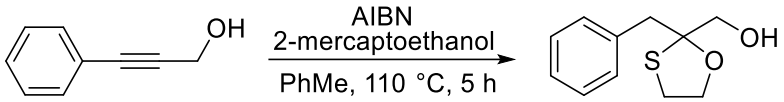
= 9.0, 5.6 Hz, 1H), 4.08, ddd (*J* = 9.1, 6.4, 5.5 Hz, 1H), 3.15, d (*J* = 13.9 Hz, 1H), 3.05, d (*J* = 13.9 Hz, 1H), 2.92, m (1H), 2.77, m (1H), 1.74, m (2H), 1.57, m (1H), 1.47, m (1H), 0.91, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 137.41, 130.88, 127.95, 126.59, 98.56, 71.22, 47.37, 43.30, 34.07, 18.57, 14.36. LCMS (ESI) *m/z*: 223.11511 calculated for $C_{13}H_{19}OS^+$ ($[M + H]^+$); 223.11480 observed.

PS-373 (2-benzyl-2-butyl-1,3-oxathiolane)



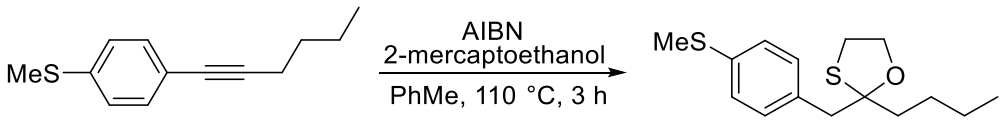
General procedure 1 was followed using **1-phenyl-1-hexyne** (95 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-373** (**2-benyl-2-butyl-1,3-oxathiolane**, 94 mg, 0.40 mmol, 66% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.28, m (4H), 7.23, t (*J* = 6.9 Hz, 1H), 4.15, dt (*J* = 9.0, 5.7 Hz, 1H), 4.08, ddd (*J* = 9.0, 6.3, 5.6 Hz, 1H), 3.16, d (*J* = 13.9 Hz, 1H), 3.05, d (*J* = 13.9 Hz, 1H), 2.93, dt (*J* = 10.1, 6.0 Hz, 1H), 2.76, dt (*J* = 10.2, 5.6 Hz, 1H), 1.76, qdd (*J* = 13.8, 11.3, 4.9 Hz, 2H), 1.52, m (1H), 1.43, m (1H), 1.31, m (2H), 0.90, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 137.40, 130.89, 127.94, 126.58, 98.63, 71.20, 47.31, 40.84, 34.05, 27.47, 23.02, 14.22. LCMS (ESI) *m/z*: 237.13076 calculated for $C_{14}H_{21}OS^+$ ($[M + H]^+$); 237.12994 observed.

PS-351 (2-benzyl-1,3-oxathiolan-2-yl)methanol



General procedure 1 was followed using **3-phenylprop-2-yn-1-ol** (79 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-351** (**2-benzyl-1,3-oxathiolan-2-yl)methanol**, 35 mg, 0.17 mmol, 28% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.34, d (*J* = 7.1 Hz, 2H), 7.29, t (*J* = 7.4 Hz, 2H), 7.24 (*J* = 7.3 Hz, 1H), 4.16, dt (*J* = 9.1, 5.8 Hz, 1H), 4.09, dt (*J* = 9.1, 5.8 Hz, 1H), 3.64, d (*J* = 11.9 Hz, 1H), 3.55, d (*J* = 11.9 Hz, 1H), 3.24, d (*J* = 13.7 Hz, 1H), 3.13, d (*J* = 13.7 Hz, 1H), 2.96, dt (*J* = 11.4, 5.8 Hz, 1H), 2.84, dt (*J* = 11.4, 5.6 Hz, 1H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 136.47, 130.95, 128.12, 126.87, 71.65, 67.16, 43.88, 33.87. LCMS (ESI) *m/z*: 211.07873 calculated for $C_{11}H_{15}O_2S^+$ ($[M + H]^+$); 211.07750 observed.

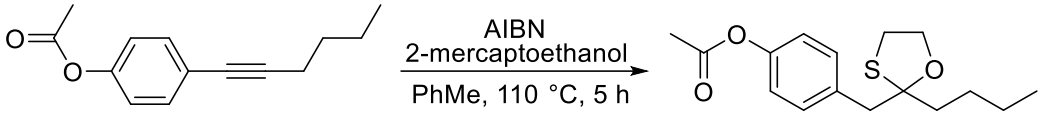
PS-400 (2-butyl-2-(4-(methylthio)benzyl)-1,3-oxathiolane)



General procedure 1 was followed using **1-(hex-1-yn-1-yl)-4-(methylsulfanyl)benzene** (123 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 3 hours. Workup and purification offered **PS-400** (**2-butyl-2-(4-(methylthio)benzyl)-1,3-oxathiolane**, 136 mg, 0.48 mmol, 80% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.22, d (*J* = 8.3 Hz, 2H), 7.18, d (*J* = 8.4 Hz, 2H), 4.14, dt (*J* = 9.1, 5.7 Hz, 1H), 4.07, ddd (*J* = 9.0, 6.1, 5.6, Hz, 1H), 3.09, d (*J* = 14.0 Hz, 1H), 3.01, d (*J* = 14.0 Hz, 1H), 2.92, dt (*J* = 10.2, 5.9 Hz, 1H), 2.75,

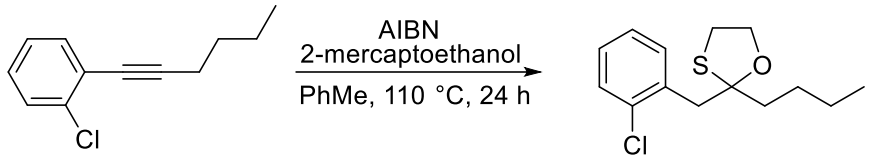
dt (*J* = 10.2, 5.7 Hz, 1H), 2.47, s (3H), 1.74, qdd (*J* = 13.7, 11.3, 4.9 Hz, 2H), 1.51, m (1H), 1.42, m (1H), 1.31, m (1H), 0.90, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 136.31, 134.36, 131.37, 126.35, 98.59, 71.24, 46.72, 40.91, 34.08, 27.45, 23.01, 16.14, 14.23. LCMS (ESI) *m/z*: 283.11848 calculated for $C_{15}H_{23}OS_2^+$ ([M + H]$^+$); 283.11791 observed.

PS-414 (4-((2-butyl-1,3-oxathiolan-2-yl)methyl)phenyl acetate)



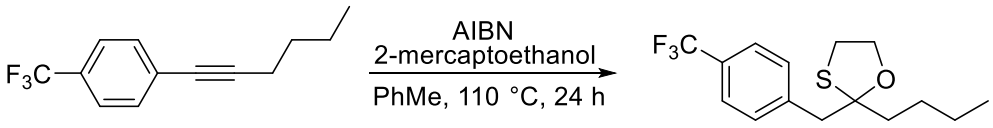
General procedure 1 was followed using **4-(hex-1-yn-1-yl)phenyl acetate** (130 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-414** (**4-((2-butyl-1,3-oxathiolan-2-yl)methyl)phenyl acetate**, 136 mg, 0.46 mmol, 77% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.30, d (*J* = 8.5 Hz, 2H), 7.00, d (*J* = 8.5, 2H), 4.13, dt (*J* = 9.0, 5.7 Hz, 1H), 4.05, dt (*J* = 9.0, 5.7 Hz, 1H), 3.11, d (*J* = 14.0 Hz, 1H), 3.04, d (*J* = 14.0 Hz, 1H), 2.91, dt (*J* = 10.2, 5.8 Hz, 1H), 2.72, dt (*J* = 10.2, 5.7 Hz, 1H), 2.28, s (3H), 1.76, qdd (*J* = 13.6, 11.2, 5.1 Hz, 2H), 1.51, m (1H), 1.42, m (1H), 1.31, m (2H), 0.90, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 169.65, 149.49, 134.96, 131.86, 120.92, 98.46, 71.29, 46.63, 41.00, 34.08, 27.45, 23.00, 21.30, 14.22. LCMS (ESI) *m/z*: 295.13624 calculated for $C_{16}H_{23}O_3S^+$ ([M + H]$^+$); *m/z*: 235.13287 calculated for ketone $C_{14}H_{19}O_3^+$ ([M + H]$^+$). 235.13156 observed.

PS-401 (2-butyl-2-(2-chlorobenzyl)-1,3-oxathiolane)



General procedure 1 was followed using **1-(2-Chlorophenyl)-1-hexyne** (116 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. Workup and purification offered **PS-401** (**2-butyl-2-(2-chlorobenzyl)-1,3-oxathiolane**, 117 mg, 0.43 mmol, 72% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.44, dd (*J* = 7.2, 2.2 Hz, 1H), 7.35, dd (*J* = 7.4, 1.8 Hz, 1H), 7.17, pd (*J* = 7.3, 1.9 Hz, 2H), 4.14, dt (*J* = 9.0, 5.6 Hz, 1H), 4.07, ddd (*J* = 9.0, 6.3, 5.5 Hz, 1H), 3.35, d (*J* = 14.3 Hz, 1H), 3.26, d (*J* =14.3 Hz, 1H), 2.91, dt (*J* = 10.3, 5.8 Hz, 1H), 2.73, dt (*J* = 10.3, 5.6 Hz, 1H), 1.83, qdd, (*J* =13.9, 11.6, 4.7 Hz, 2H), 1.55, m (1H), 1.43, m (1H), 1.32, m (2H), 0.90, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 135.53, 135.43, 132.82, 129.48, 127.95, 126.20, 98.77, 71.35, 43.44, 41.29, 34.24, 27.27, 23.03, 14.22. LCMS (ESI) *m/z*: 271.09179 calculated for $C_{14}H_{20}ClOS^{+}$ ([M + H]$^{+}$); 271.09190 observed.

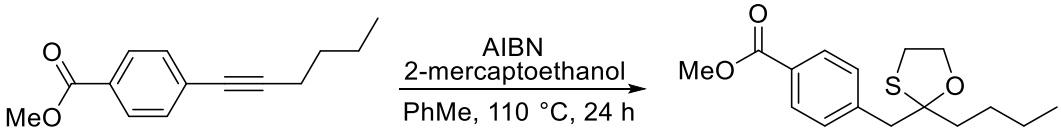
PS-399 (2-butyl-2-(4-(trifluoromethyl)benzyl)-1,3-oxathiolane)



General procedure 1 was followed using **1-(hex-1-yn-1-yl)-4-(trifluoromethyl)benzene** (136 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. Workup and purification offered **PS-399** (**2-butyl-2-(4-(trifluoromethyl)benzyl)-1,3-**

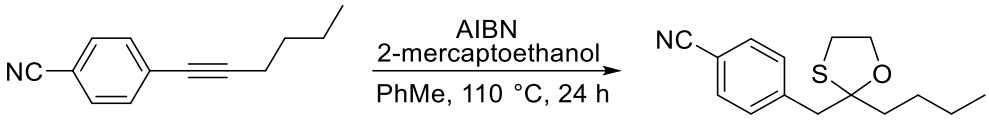
oxathiolane, 112 mg, 0.37 mmol, 61% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.53, d (*J* = 8.0 Hz, 2H), 7.41, d (*J* = 8.0 Hz, 2H), 4.12, ddd (*J* = 9.1, 6.2, 5.5 Hz, 1H), 4.06, dt (*J* = 9.1, 5.7 Hz, 1H), 3.17, d (*J* = 13.8 Hz, 1H), 3.11, d (*J* = 13.9 Hz, 1H), 2.91, dt (*J* = 10.4, 5.6 Hz, 1H), 2.67, dt (*J* = 10.2, 5.9 Hz, 1H), 1.76, qdd (*J* = 13.6, 11.2, 5.1 Hz, 2H), 1.51, m (1H), 1.43, m (1H), 1.32, m (2H), 0.90, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 141.47, 131.29, 129.14-128.59, (q, *J* = 32.4 Hz), 126.85-122.22, (q, *J* = 271.9 Hz), 124.78-124.72, (q, *J* = 3.7 Hz), 98.11, 71.38, 46.98, 41.31, 34.15, 27.46, 23.00, 14.22. LCMS (ESI) *m/z*: 305.11815 calculated for $C_{15}H_{20}F_3OS^+$ ($[M + H]^+$); 305.11961 observed.

PS-398 (Methyl 4-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzoate)



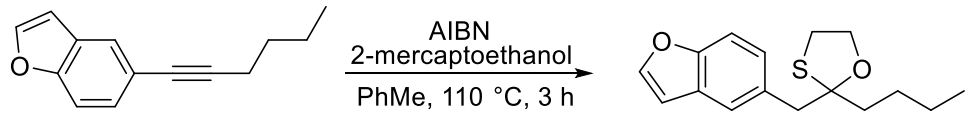
General procedure 1 was followed using **Methyl 4-(hex-1-yn-1-yl)benzoate** (130 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. Workup and purification offered **PS-398** (**methyl 4-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzoate**, 97 mg, 0.33 mmol, 55% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.95, d (*J* = 8.3 Hz, 2H), 7.37, d (*J* = 8.3 Hz, 2H), 4.12, dt (*J* = 9.1, 5.7 Hz, 1H), 4.05, dt (*J* = 9.1, 5.7 Hz, 1H), 3.90, s (3H), 3.17, d (*J* = 13.8 Hz, 1H), 3.11, d (*J* = 13.8 Hz, 1H), 2.90, dt (*J* = 10.3, 5.7 Hz, 1H), 2.67, dt (*J* = 10.2, 5.8 Hz, 1H), 1.75, qdd (*J* = 13.7, 11.3, 5.0 Hz, 2H), 1.51, m (1H), 1.42, m (1H), 1.30, m (2H), 0.89, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 167.36, 142.85, 131.03, 129.15, 128.48, 98.23, 71.35, 52.16, 47.23, 41.31, 34.11, 27.44, 22.98, 14.19. LCMS (ESI) *m/z*: 295.13624 calculated for $C_{16}H_{23}O_3S^+$ ($[M + H]^+$); 295.13620 observed.

PS-397 (4-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzonitrile)



General procedure 1 was followed using **4-(hex-1-yn-1-yl)benzonitrile** (110 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. Workup and purification offered **PS-397** (**4-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzonitrile**, 66 mg, 0.25 mmol, 42% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.57, d (*J* = 8.3 Hz, 2H), 7.41, d (*J* = 8.3 Hz, 2H), 4.09, ddd (*J* = 9.1, 6.5, 5.4 Hz, 1H), 4.03, dt (*J* = 9.1, 5.6 Hz, 1H), 3.14, d (*J* = 13.8 Hz, 1H), 3.11, d (*J* = 13.8 Hz, 1H), 2.90, dt (*J* = 10.7, 5.5 Hz, 1H), 2.62, ddd (*J* = 10.3, 6.4, 5.7 Hz, 1H), 1.76, qdd (*J* = 13.8, 11.4, 4.8 Hz, 2H), 1.49, m (1H), 1.41, m (1H), 1.31, m (2H), 0.90, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 142.99, 131.81, 131.59, 119.25, 110.46, 97.91, 71.42, 47.16, 41.55, 34.17, 27.42, 22.97, 14.19. LCMS (ESI) *m/z*: 262.12601 calculated for $C_{15}H_{20}NOS^+$ ($[M + H]^+$); 262.12531 observed.

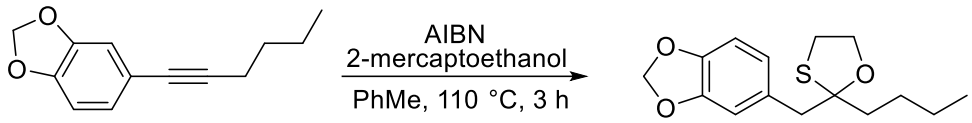
PS-413 (5-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzofuran)



General procedure 1 was followed using **5-(hex-1-yn-1-yl)benzofuran** (119 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 3 hours. Workup and purification offered **PS-413** (**5-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzofuran**, 141 mg, 0.51 mmol, 85% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.59, d (*J* = 2.2 Hz, 1H), 7.52, d (*J* = 1.4 Hz, 1H), 7.41, d (*J* = 8.4 Hz, 1H), 7.24, dd (*J* = 8.4, 1.7 Hz, 1H), 6.74,

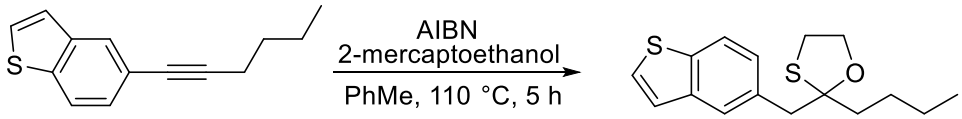
dd (*J* = 2.1, 0.9 Hz, 1H), 4.16, dt (*J* = 9.0, 5.6 Hz, 1H), 4.08, ddd (*J* = 9.0, 6.4, 5.6 Hz, 1H), 3.25, d (*J* = 14.1 Hz, 1H), 3.15, (*J* = 14.1 Hz, 1H), 2.93, dt (*J* = 10.4, 5.7 Hz, 1H), 2.76, dt (*J* = 10.2, 5.6 Hz, 1H), 1.77, qdd (*J* = 13.5, 11.1, 5.0 Hz, 2H), 1.54, m (1H), 1.44, m (1H), 1.31, m (2H), 0.90, t (*J* = 7.4 Hz, 3H).^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 154.11, 145.07, 131.81, 127.29, 127.23, 123.17, 110.61, 106.72, 98.86, 71.21, 47.13, 40.78, 34.07, 27.47, 23.03, 14.24. LCMS (ESI) *m/z*: 277.12568 calculated for $C_{16}H_{21}O_2S^+$ ([M + H]$^+$); 277.12557 observed.

PS-396 (5-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzo[d][1,3]dioxole)



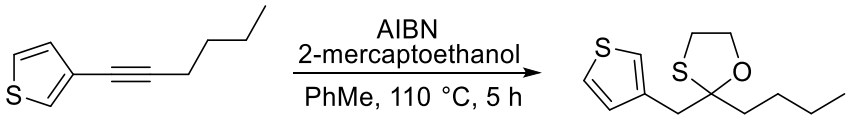
General procedure 1 was followed using **5-(hex-1-yn-1-yl)benzo[d][1,3]dioxole** (121 mg, 0.60 mmol),), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 3 hours. Workup and purification offered **PS-396** (**5-((2-butyl-1,3-oxathiolan-2-yl)methyl)benzo[d][1,3]dioxole**, 140 mg, 0.50 mmol, 83% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 6.82, s (1H), 6.72, m (2H), 5.93, d (*J* = 1.5 Hz, 1H), 5.92, d (*J* = 1.5 Hz, 1H), 4.15, dt (*J* = 9.1, 5.7 Hz, 1H), 4.08, ddd, (*J* = 9.1, 6.3, 5.6 Hz, 1H), 3.07, d (*J* = 14.1 Hz, 1H), 2.96, d (*J* = 14.1 Hz, 1H), 2.94, dt (*J* = 10.2, 5.9 Hz, 1H), 2.82, dt (*J* = 10.3, 5.6 Hz, 1H), 1.74, qdd (*J* = 13.8, 11.4, 4.9 Hz, 2H), 1.50, m (1H), 1.40, m (1H), 1.30, m (2H), 0.90, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 147.22, 146.28, 131.14, 123.86, 111.22, 107.82, 100.90, 98.69, 71.16, 46.92, 40.66, 34.07, 27.45, 23.03, 14.23. LCMS (ESI) *m/z*: 281.12059 calculated for $C_{15}H_{21}O_3S^+$ ([M + H]$^+$); 281.11970 observed.

PS-371 (2-(benzo[*b*]thiophen-5-ylmethyl)-2-butyl-1,3-oxathiolane)



General procedure 1 was followed using **5-(hex-1-ynyl)benzo[b]thiophene** (129 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-371** (**2-(benzo[*b*]thiophen-5-ylmethyl)-2-butyl-1,3-oxathiolane**, 132 mg, 0.45 mmol, 75% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.79, d (*J* = 8.2 Hz, 1H), 7.74, s (1H), 7.41, d (*J* = 5.4 Hz, 1H), 7.32, d (*J* = 5.0 Hz, 1H), 7.30, s (1H), 4.17, dt (*J* = 9.0, 5.6 Hz, 1H), 4.09, dt (*J* = 9.0, 5.6 Hz, 1H), 3.27, d (*J* = 14.0 Hz, 1H), 3.17, d (*J* = 14.0 Hz, 1H), 2.93, dt (*J* = 10.2, 6.0 Hz, 1H), 2.76, dt (*J* = 10.1, 6.2 Hz, 1H), 1.79, qdd (*J* = 13.8, 11.3, 5.0 Hz, 2H), 1.55, m (1H), 1.45, m (1H), 1.31, m (1H), 0.90, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 139.66, 138.13, 133.47, 127.52, 126.36, 125.70, 123.99, 121.78, 98.77, 71.25, 47.20, 40.90, 34.11, 27.47, 23.02, 14.24. LCMS (ESI) *m/z*: 293.10283 calculated for $C_{16}H_{21}OS_2^+$ ($[M + H]^+$); *m/z*: 233.09946 calculated for ketone $C_{14}H_{17}OS^+$ ($[M + H]^+$). 233.10069 observed.

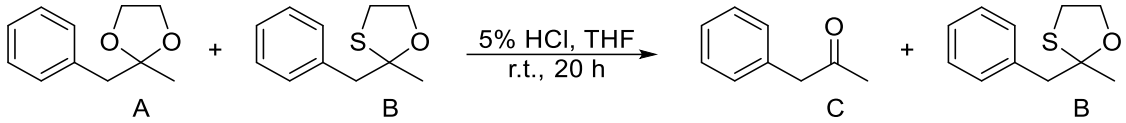
PS-369 2-butyl-2-(thiophen-3-ylmethyl)-1,3-oxathiolane



General procedure 1 was followed using **3-(hex-1-yn-1-yl)thiophene** (99 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. Workup and purification offered **PS-369** (**2-butyl-2-(thiophen-3-ylmethyl)-1,3-oxathiolane**, 99 mg, 0.41

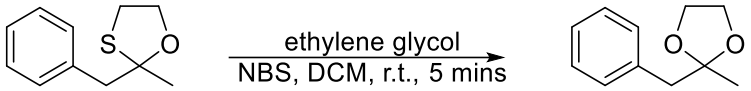
mmol, 68% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.22, dd (*J* = 4.9, 3.0 Hz, 1H), 7.10, d (*J* = 2.5 Hz, 1H), 7.06, dd (*J* = 4.9, 1.0 Hz, 1H), 4.16, dt (*J* = 9.1, 5.7 Hz, 1H), 4.10, dt (*J* = 9.1, 5.9 Hz, 1H), 3.17, d (*J* = 14.4 Hz, 1H), 3.10, d (*J* = 14.4 Hz, 1H), 2.96, dt (*J* = 10.2, 5.9 Hz, 1H), 2.84, dt (*J* = 10.1, 6.0 Hz, 1H), 1.75, qdd (*J* = 13.8, 11.4, 4.9 Hz, 2H), 1.49, m (1H), 1.41, m (1H), 1.30, m (1H), 0.89, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 137.59, 130.07, 124.55, 123.33, 98.37, 71.17, 41.84, 40.71, 34.04, 27.49, 23.02, 14.21. LCMS (ESI) *m/z*: 243.08718 calculated for $C_{12}H_{19}OS_2^+$ ($[M + H]^+$); 243.08737 observed.

Hydrolysis Competition Experiment



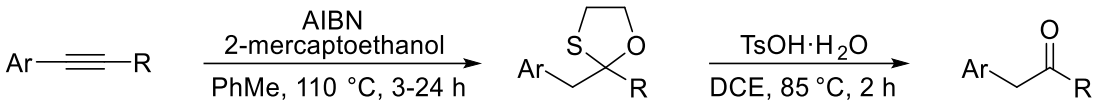
A modified procedure of Grieco et al was employed[96]. To a solution of **PS-440** (**2-benzyl-2-methyl-1,3-oxathiolane**) (58 mg, 0.30 mmol) and **PS-368** (**2-benzyl-2-methyl-1,3-dioxolane**) (54 mg, 0.30 mmol) in THF (3 mL) was added 5% HCl (750 µL). The reaction was stirred at room temperature until disappearance of **2-benzyl-2-methyl-1,3-dioxolane** was observed by thin-layer chromatography (TLC, 20 hours). The mixture was then diluted with diethyl ether (Et_2O) and washed with NaOH (1M) once. The organic layer was washed once with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude products. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered **PS-332** (**1-phenylpropan-2-one**, 38 mg, 0.29 mmol, 95% yield) as a clear oil and **PS-368** (**1-phenyl-1-propyne**, 56 mg, 0.29 mmol, 96% yield) as a light-yellow oil (NMR data previously presented).

PS-440 (2-benzyl-2-methyl-1,3-dioxolane)



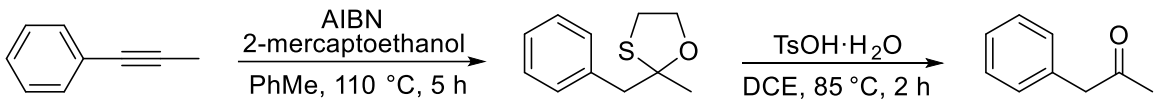
The Procedure of Karimi et al was followed[97]. To a stirred solution of **PS-368** (**2-benzyl-2-methyl-1,3-dioxolane**) (389 mg, 2.00 mmol) and ethylene glycol (372 mg, 336 µL, 6 mmol, 3 equiv.) in dry DCM (15 mL) was added N-bromosuccinimide (NBS, 427 mg, 2.4 mmol, 1.2 equiv.). The resulting mixture was stirred at room temperature until disappearance of **2-benzyl-2-methyl-1,3-dioxolane** was observed by thin-layer chromatography (TLC, 5 mins). After completion of the reaction, the mixture was diluted with NaOH and extracted with DCM (3x). The combined organic layers were washed once with 10% NaOH, once with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered **PS-440** (**2-benzyl-2-methyl-1,3-dioxolane**, 285 mg, 1.6 mmol, 80% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.28, m (4H), 7.23, m (1H), 3.91, m (2H), 3.76, m (2H), 2.93, s (2H), 1.31, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 137.07, 130.61, 128.09, 126.50, 64.97, 45.48, 24.47. This spectral data is consistent with a previous literature report[98].

General procedure for the synthesis of aryl-alkyl ketones:



General Procedure 2: To a solution of alkyne (0.60 mmol) in toluene (10 mL) was added azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.) followed by 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol) in one portion. The reaction flask was equipped with a reflux condenser and heated at 110 °C until disappearance of the alkyne was observed by thin-layer chromatography (TLC, 3-24 hours). The mixture was then diluted with diethyl ether (Et_2O) and washed with NaOH (2M, approximately 20 mL) twice, to remove excess 2-mercaptoethanol. The organic layer was washed once with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude product. Without any further purification, this crude product was diluted with dichloroethane (DCE, 10 mL) followed by addition of *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol, 1.0 equiv.). The reaction flask was then equipped with a reflux condenser and heated at 85 °C for 2 hours. The reaction mixture was then diluted with dichloromethane (DCM) and washed twice with NaOH (2M). The organic layer was washed once with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered the corresponding ketone.

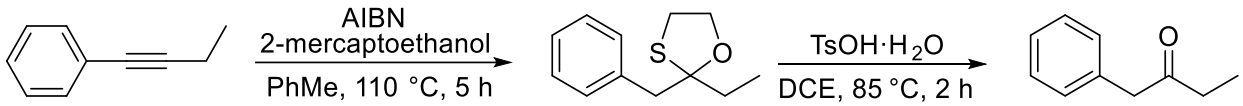
PS-332 1-phenylpropan-2-one



General procedure 2 was followed using **1-phenyl-1-propyne** (70 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. The reaction mixture

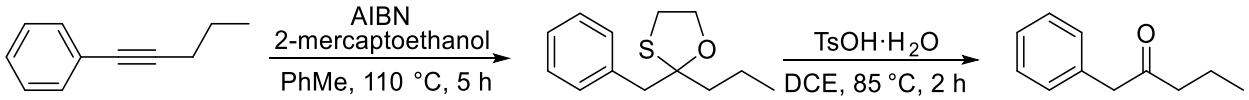
was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-332** (**1-phenylpropan-2-one**, 53 mg, 0.40 mmol, 66% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.34, t (*J* = 7.3 Hz, 2H), 7.27, t (*J* = 7.3 Hz, 1H), 7.21, d (*J* = 7.4 Hz, 2H), 3.70, s (2H), 2.15, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 206.57, 134.40, 129.54, 128.92, 127.22, 51.20, 29.41. This spectral data is consistent with a previous literature report[99].

PS-255 1-phenylbutan-2-one



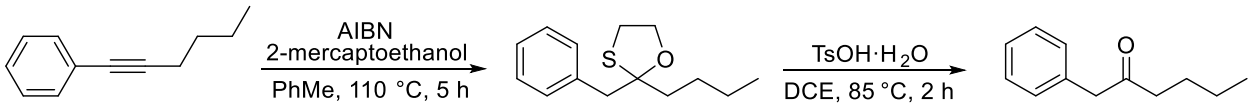
General procedure 2 was followed using **1-phenyl-1-butyne** (78 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-255** (**1-phenylbutan-2-one**, 55 mg, 0.37 mmol, 62% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.33, t (*J* = 7.3 Hz, 2H), 7.26, t (*J* = 7.3 Hz, 1H), 7.21, d (*J* = 7.5 Hz, 2H), 3.69, s (2H), 2.47, q (*J* = 7.3 Hz, 2H), 1.03, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 209.12, 134.62, 129.51, 128.83, 127.08, 49.97, 35.34, 7.90. This spectral data is consistent with a previous literature report[100].

PS-328 1-phenylpentan-2-one



General procedure 2 was followed using **1-phenyl-1-pentyne** (87 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-328** (**1-phenylpentan-2-one**, 61 mg, 0.38 mmol, 63% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.33, t (*J* = 7.5 Hz, 2H), 7.26, t (*J* = 7.4 Hz, 1H), 7.21, d (*J* = 7.0 Hz, 2H), 3.68, s (2H), 2.43, t (*J* = 7.3 Hz, 2H), 1.59, h (*J* = 7.4 Hz, 3H), 0.87, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 208.61, 134.52, 129.54, 128.83, 127.08, 50.31, 44.03, 17.31, 13.77. This spectral data is consistent with a previous literature report[101].

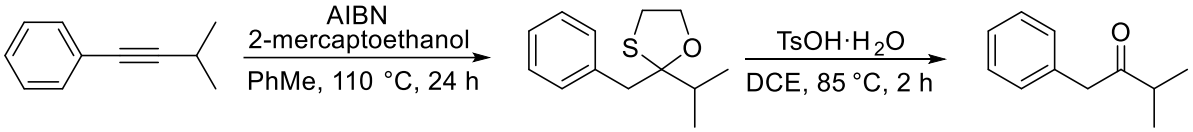
PS-329 1-phenylhexan-2-one



General procedure 2 was followed using **1-phenyl-1-hexyne** (95 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered

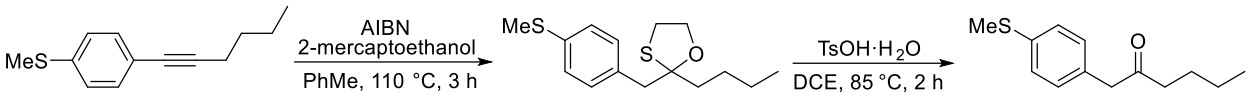
PS-329 (**1-phenylhexan-2-one**, 63 mg, 0.36 mmol, 60% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.33, t (*J* = 7.5 Hz, 2H), 7.26, t (*J* = 7.4 Hz, 1H), 7.21, d (*J* = 7.5 Hz, 2H), 3.68, s (2H), 2.44, t (*J* = 7.4 Hz, 2H), 1.54, dt (*J* = 14.8, 7.4 Hz, 2H), 1.27, dt (*J* = 14.9, 7.5 Hz, 2H), 0.86, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 208.74, 134.55, 129.54, 128.83, 127.08, 50.28, 41.85, 25.97, 22.37, 13.95. This spectral data is consistent with a previous literature report[102].

PS-327 3-methyl-1-phenylbutan-2-one



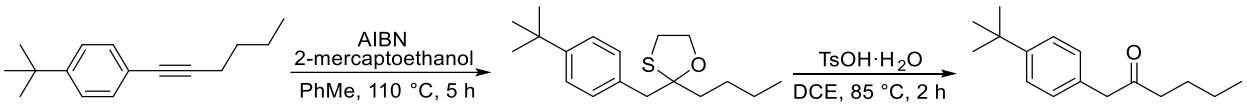
General procedure 2 was followed using **1-phenyl-3-methyl-1-butyne** (87 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-327** (**3-methyl-1-phenylbutan-2-one**, 52 mg, 0.32 mmol, 53% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.32, t (*J* = 7.5 Hz, 2H), 7.25, t (*J* = 7.4 Hz, 1H), 7.20, d (*J* = 7.0 Hz, 2H), 3.74, s (2H), 2.73, h (*J* = 6.9 Hz, 1H), 1.11, d (*J* = 6.9 Hz, 2H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 212.10, 134.59, 129.59, 128.75, 127.00, 47.84, 40.23, 18.47. This spectral data is consistent with a previous literature report[103].

PS-410 1-(4-(methylthio)phenyl)hexan-2-one)



General procedure 2 was followed using **1-(hex-1-yn-1-yl)-4-(methylsulfanyl)benzene** (123 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 3 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate (TsOH·H_2O, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-401** (**1-(4-(methylthio)phenyl)hexan-2-one**, 100 mg, 0.45 mmol, 75% yield) as a light yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.15, d (*J* = 8.3 Hz, 2H), 7.05, d (*J* = 8.3 Hz, 2H), 3.56, s (2H), 2.40, s (3H), 2.36, t (*J* = 7.4 Hz, 2H), 1.46, dt (*J* = 15.1, 7.5 Hz, 2H), 1.20, m (2H), 0.80, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 208.59, 137.15, 131.34, 129.99, 127.13, 49.60, 41.87, 25.95, 22.36, 16.08, 13.95. LCMS (ESI) *m/z*: 223.11511 calculated for $C_{13}H_{19}OS^+$ ($[M + H]^+$); 223.11431 observed.

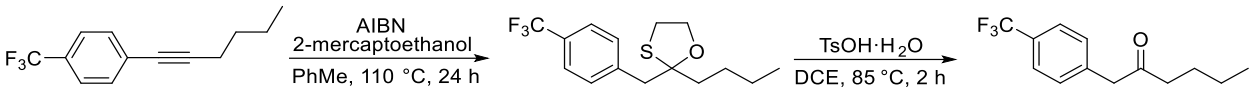
PS-342 1-(4-(*tert*-butyl)phenyl)hexan-2-one



General procedure 2 was followed using **1-tert-butyl-4-(hex-1-ynyl)benzene** (129 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate (TsOH·H_2O, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and

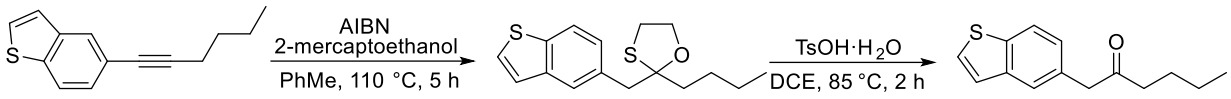
purification offered **PS-342** (**1-(4-(*tert*-butyl)phenyl)hexan-2-one**, 102 mg, 0.44 mmol, 73% yield) as a light yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.35, d (*J* = 8.2 Hz, 2H), 7.14, d (*J* = 8.0 Hz, 2H), 3.65, s (2H), 2.45, t (*J* = 7.4 Hz, 2H), 1.54, dt (*J* = 15.0, 7.6 Hz, 2H), 1.27, dt (*J* = 14.8, 7.5 Hz, 2H), 1.31, s (9H), 0.86, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 209.10, 149.94, 131.46, 129.19, 125.76, 49.74, 41.87, 31.48, 31.25, 26.01, 22.39, 13.97. LCMS (ESI) *m/z*: 233.18999 calculated for $C_{16}H_{25}O^+$ ($[M + H]^+$); 233.18916 observed.

PS-415 1-(4-(trifluoromethyl)phenyl)hexan-2-one



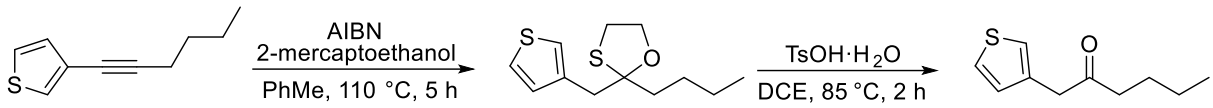
General procedure 2 was followed using **1-(hex-1-yn-1-yl)-4-(trifluoromethyl)benzene** (136 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-415** (**1-(4-(trifluoromethyl)phenyl)hexan-2-one**, 76 mg, 0.31 mmol, 52% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.59, d (*J* = 8.0 Hz, 2H), 7.32, d (*J* = 8.0 Hz, 2H), 3.75, s (2H), 2.48, t (*J* = 7.4 Hz, 2H), 1.56, dt (*J* = 14.9, 7.6 Hz, 2H), 1.29, m (2H), 0.88, t (*J* = 7.4 Hz, 3H).^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 207.49, 138.41, 129.96, 129.96-129.19, q (*J* = 32.6 Hz), 126.61-121.98, q (*J* = 271.9 Hz), 125.73-125.67, q (*J* = 3.7 Hz), 49.63, 42.37, 25.93, 22.37, 13.95. LCMS (ESI) *m/z*: 245.11478 calculated for $C_{13}H_{16}F_3O^+$ ($[M + H]^+$); 245.11544 observed. This spectral data is consistent with a previous literature report[104].

PS-348 1-(benzo[*b*]thiophen-5-yl)hexan-2-one



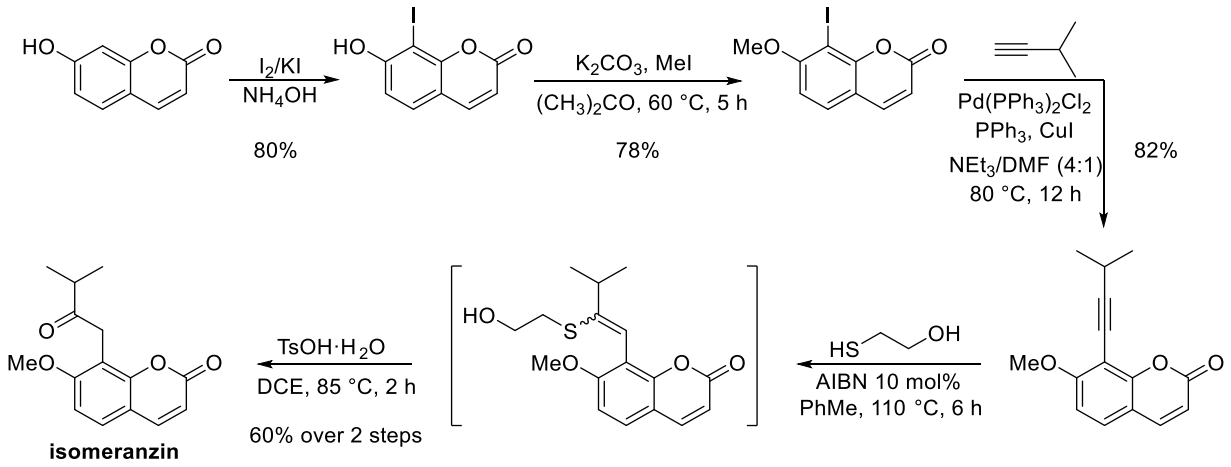
General procedure 2 was followed using **5-(hex-1-ynyl)benzo[b]thiophene** (129 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-348** (**1-(benzo[*b*]thiophen-5-yl)hexan-2-one**, 100 mg, 0.43 mmol, 72% yield) as a light yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.84, d (*J* = 8.2 Hz, 1H), 7.66, d (*J* = 0.9 Hz, 1H), 7.45, d (*J* = 5.4 Hz, 1H), 7.30, dd (*J* = 5.4, 1.0 Hz, 1H), 7.19, dd (*J* = 8.2, 1.2 Hz, 1H), 3.79, s (2H), 2.47, t (*J* = 7.4 Hz, 2H), 1.55, dt (*J* = 15.1, 7.5 Hz, 2H), 1.27, dt (*J* = 14.8, 7.4 Hz, 2H), 0.86, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 208.92, 140.21, 138.59, 130.63, 127.11, 125.90, 124.39, 123.79, 122.81, 50.15, 41.87, 26.00, 23.39, 13.97. LCMS (ESI) *m/z*: 233.09946 calculated for $C_{14}H_{17}OS^+$ ($[M + H]^+$); 233.10016 observed.

PS-374 1-(thiophen-3-yl)hexan-2-one

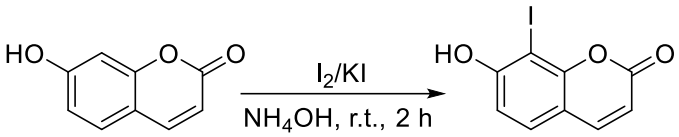


General procedure 2 was followed using **3-(hex-1-yn-1-yl)thiophene** (99 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 5 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-374** (**1-(thiophen-3-yl)hexan-2-one**, 72 mg, 0.40 mmol, 66% yield) as a light yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.30, dd (*J* = 4.9, 3.0 Hz, 1H), 7.09, dd (*J* = 2.8, 1.0 Hz, 1H), 6.97, dd (*J* = 4.9, 1.2 Hz, 1H), 3.71, s (2H), 2.45, t (*J* = 7.4 Hz, 2H), 1.54, dt (*J* = 15.1, 7.5 Hz, 2H), 1.28, dt (*J* = 14.8, 7.4 Hz, 2H), 0.87, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 208.29, 134.24, 128.70, 126.03, 122.94, 44.49, 41.84, 25.98, 22.38, 13.96. LCMS (ESI) *m/z*: 183.08381 calculated for $C_{10}H_{15}OS^+$ ($[M + H]^+$); 183.08316 observed.

Synthesis of isomeranzin

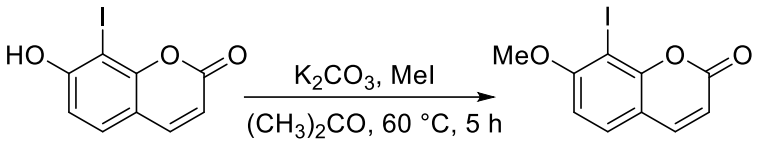


PS-426 (8-iodoumbelliferone)



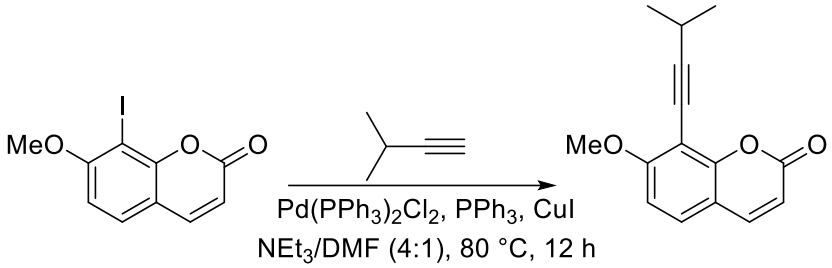
The procedure of Devji et al was followed[89]. **Umbelliferone** (400 mg, 2.46 mmol) was dissolved in a 20% NH_4OH solution (10 mL) to which a solution of iodine (I_2, 626 mg, 2.46 mmol) dissolved in aqueous potassium iodide (KI, 5%, 20 mL) was added slowly. After 2 hours, the reaction was quenched with H_2SO_4 (2.5 M) until acidic and precipitation occurred. The solid was filtered and purified using chromatography over silica gel using gradient elution with EtOAc and DCM to offer **PS-411** (**8-iodoumbelliferone**, 567 mg, 1.97 mmol, 80% yield) as a yellow solid. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.81, d (*J* = 9.4 Hz, 1H), 7.47, d (*J* = 8.5 Hz, 1H), 6.87, d (*J* = 8.4 Hz, 1H), 6.22, d (*J* = 9.4 Hz, 1H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 163.10, 162.88, 156.80, 145.82, 130.49, 113.84, 112.92, 112.86, 74.15. This spectral data is consistent with a previous literature report[89].

PS-429 (8-iodo-7-methoxychromen-2-one)



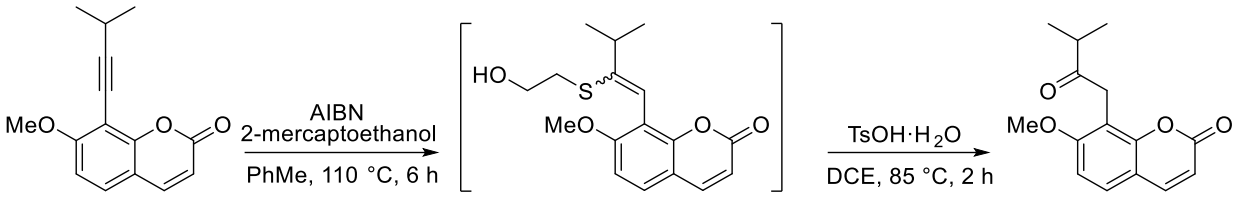
The procedure of Gillmore et al was followed[90]. A mixture of **8-iodoumbelliferone** (547 mg, 1.9 mmol), methyl iodide (539 mg, 237 μL, 3.8 mmol, 2 equiv.), and anhydrous potassium carbonate (525 mg, 3.8 mmol, 2 equiv.) in anhydrous acetone (20 mL) was refluxed for 5 hours. The mixture was then diluted with aqueous HCl (1 M) and extracted with DCM (3x). The combined organic extracts were washed with brine (1x), dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered **PS-429** (**8-iodo-7-methoxychromen-2-one**, 448 mg, 1.48 mmol, 78% yield) as a light-yellow solid. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.58, d (*J* = 9.5 Hz, 1H), 7.44, d (*J* = 8.5 Hz, 1H), 6.81, d (*J* = 8.6 Hz, 1H), 6.27, d (*J* = 9.4 Hz, 1H), 3.99, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 161.83, 160.66, 155.20, 143.21, 129.20, 114.09, 113.88, 107.54, 76.20 57.15. This spectral data is consistent with a previous literature report[90, 105].

PS-430 (7-methoxy-8-(3-methylbut-1-yn-1-yl)-2H-chromen-2-one)



The procedure of Guthertz et al was followed[91]. To a dry two neck flask was added bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$, 19.7 mg, 0.028 mmol, 2 mol%), copper(I) iodide (CuI, 5.3 mg, 0.028 mmol, 2 mol%), triphenylphosphine (PPh_3, 14.7 mg, 0.056 mmol, 4 mol%), **8-iodo-7-methoxychromen-2-one** (423 mg, 1.40 mmol, 1 equiv.) and 3-methyl-1-butyne (114 mg, 171 μL 1.68 mmol, 1.2 equiv.) in triethylamine (NEt_3, 10 mL) and dimethylformamide (DMF, 2.5 mL). The mixture was vacuumed and flushed with Argon for 15 minutes. The mixture was then stirred at 80 ^oC for 12 hours. The reaction was quenched with saturated ammonium chloride and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered **PS-430** (**7-methoxy-8-(3-methylbut-1-yn-1-yl)-2H-chromen-2-one**, 278 mg, 1.15 mmol, 82% yield) as a white solid. Mp: 136.5-138^oC. ^1H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.59, d (*J* = 9.5 Hz, 1H), 7.33, d (*J* = 8.6 Hz, 1H), 6.82, d (*J* = 8.7 Hz, 1H), 6.27, d (*J* = 9.5 Hz, 1H), 3.96, s (3H), 2.93, h (*J* = 6.9 Hz, 1H), 1.35, d (*J* = 6.9 Hz, 6H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 163.02, 160.83, 155.73, 143.27, 127.60, 113.86, 113.02, 107.65, 107.28, 102.51, 69.05, 56.66, 23.07, 21.92. LCMS (ESI) *m/z* 243.10157 calculated for $C_{15}H_{15}O_3^+$ ($[M + H]^+$); 243.10103 observed.

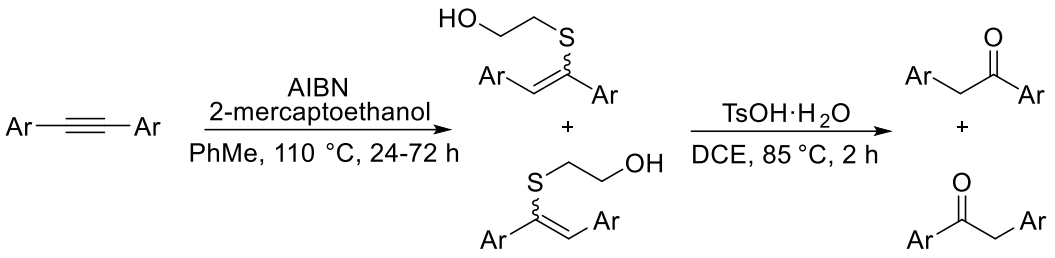
PS-432 (isomeranzin)



General procedure 2 was followed using **7-methoxy-8-(3-methylbut-1-yn-1-yl)-2H-chromen-2-one** (145 mg, 0.6 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 6 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-432 (Isomeranzin**, 94 mg, 0.36 mmol, 60% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.63, d (*J* = 9.5 Hz, 1H), 7.37, d (*J* = 8.6 Hz, 1H), 6.85, d (*J* = 8.6 Hz, 1H), 6.23, d (*J* = 9.4 Hz, 1H), 4.01, s (2H), 3.86, s (3H), 2.82, h (*J* = 6.9 Hz, 1H), 1.21, d (*J* = 6.9 Hz, 6H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 210.89, 161.12, 160.59, 153.37, 143.88, 127.62, 113.24, 113.07, 112.16, 107.36, 56.26, 41.05, 34.83, 18.56. LCMS (ESI) *m/z* 261.11214 calculated for $C_{15}H_{17}O_4^+$ ($[M + H]^+$); 261.11175 observed. This spectral data is consistent with a previous literature report[82, 87].

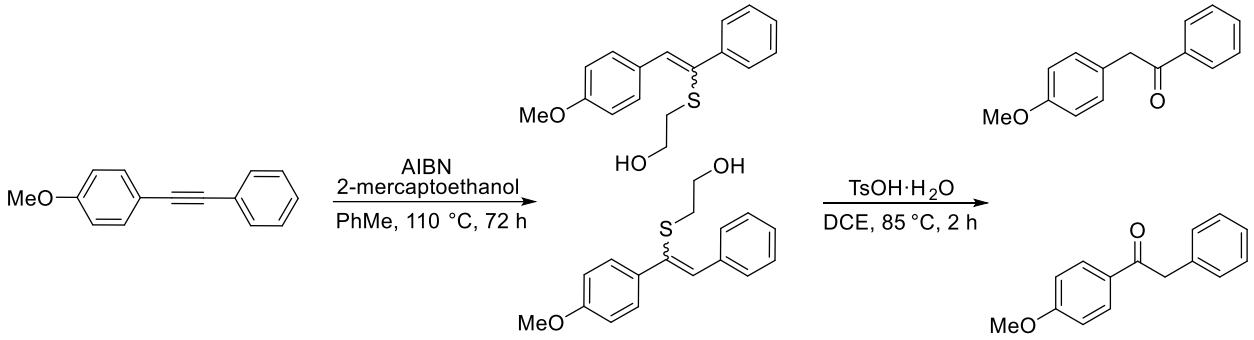
Synthesis of Aryl-Aryl Ketones

General procedure for the synthesis of aryl-aryl ketones:

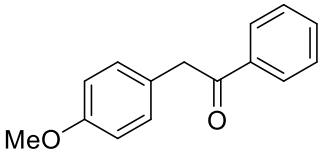


General Procedure 3: To a solution of alkyne (0.60 mmol) in toluene (10 mL) was added azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.) followed by 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol) in one portion. The reaction flask was equipped with a reflux condenser and heated at 110 °C until disappearance of the alkyne was observed by thin-layer chromatography (TLC, 24-72 hours). The mixture was then diluted with diethyl ether (Et_2O) and washed with NaOH (2M) twice, to remove excess 2-mercaptoethanol. The organic layer was washed once with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude product. Without any further purification, this crude product was diluted with dichloroethane (DCE, 10 mL) followed by addition of *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$, 115 mg, 0.6 mmol, 1.0 equiv.). The reaction flask was then equipped with a reflux condenser and heated at 85 °C for 2 hours. The reaction mixture was then diluted with dichloromethane (DCM) and washed twice with NaOH (2M). The organic layer was washed once with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered the corresponding ketone.

PS-192a/b (2-(4-Methoxyphenyl)acetophenone & 4'-Methoxy-2-phenylacetophenone)



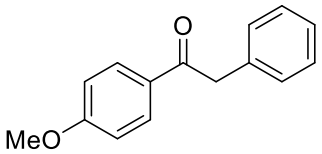
General procedure 3 was followed using **1-methoxy-4-(phenylethynyl)benzene** (125 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-192a** (**2-(4-Methoxyphenyl)acetophenone**, 73 mg, 0.32 mmol, 54% yield) as a beige solid and **PS-192b** (**4'-Methoxy-2-phenylacetophenone**, 30 mg, 0.13 mmol, 22% yield) as a beige solid.



PS-192a (2-(4-Methoxyphenyl)acetophenone)

PS-192a (**2-(4-Methoxyphenyl)acetophenone**, 73 mg, 0.32 mmol, 54% yield) as a beige solid. Mp: 91-92 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 8.02 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.23 (s, CH2, 2H), 3.79 (s, CH3, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 198.02, 158.64, 136.72, 133.20,

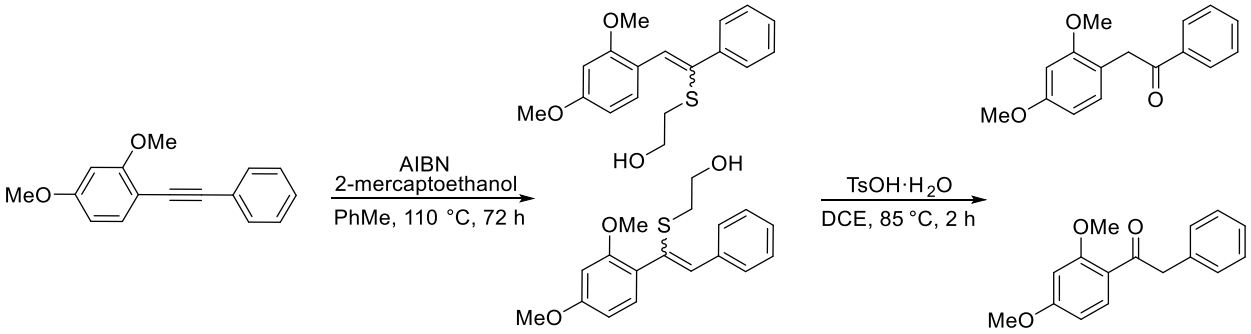
130.57, 128.72, 128.69, 126.60, 114.25, 55.35, 44.73. This spectral data is consistent with a previous literature report[106].



PS-192b (4'-Methoxy-2-phenylacetophenone)

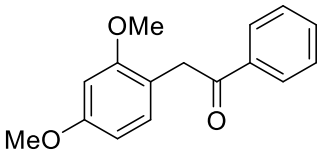
PS-192b (**4'-Methoxy-2-phenylacetophenone**, 30 mg, 0.13 mmol, 22% yield) as a beige solid. Mp: 67-70 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 8.00 (d, *J* = 8.8 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.23 (s, CH2, 2H), 3.86 (s, CH3, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 196.39, 163.66, 135.11, 131.09, 129.78, 129.52, 128.78, 126.62, 113.93, 55.61, 45.51. This spectral data is consistent with a previous literature report[107].

PS-238 2-(2,4-dimethoxyphenyl)-1-phenylethanone & 1-(2,4-dimethoxyphenyl)-2-phenylethanone



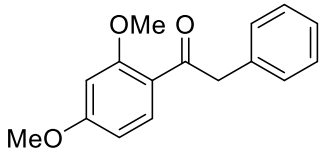
General procedure 3 was followed using **1,3-dimethoxy-5-(2-phenylethynyl)benzene** (143 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 24 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$, 115 mg, 0.6 mmol). The reaction

flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-238a** (**2-(2,4-dimethoxyphenyl)-1-phenylethanone**, 112 mg, 0.44 mmol, 73% yield) as a beige solid and **PS-238b** (**1-(2,4-dimethoxyphenyl)-2-phenylethanone,** 11 mg, 0.04 mmol, 7% yield) as a beige solid.



PS-238a (2-(2,4-dimethoxyphenyl)-1-phenylethanone)

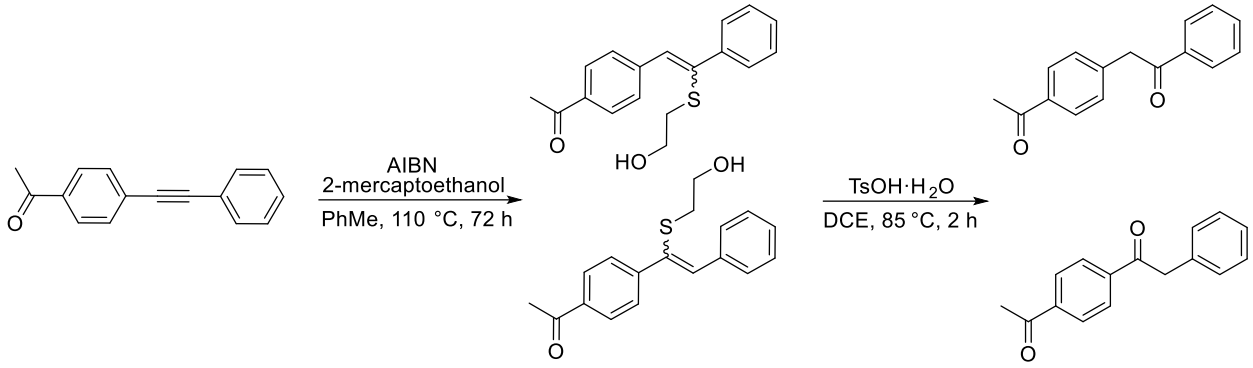
PS-238a (**2-(2,4-dimethoxyphenyl)-1-phenylethanone**, 112 mg, 0.44 mmol, 73% yield) as a beige solid. Mp: 96-97 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 8.04, d (*J* = 7.7 Hz, 2H), 7.54, t (*J* = 7.4 Hz, 1H), 7.45, t (*J* = 7.7 Hz, 2H), 7.08, d (*J* = 8.1 Hz, 1H), 6.48, s (1H), 6.47, d (*J* = 8.2 Hz, 1H), 4.12, s (3H), 3.80, s (3H), 3.77, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 198.42, 160.23, 158.22, 137.15, 132.96, 131.37, 128.61, 128.55, 116.15, 104.43, 98.88, 55.55, 55.50, 39.45. This spectral data is consistent with a previous literature report[108].



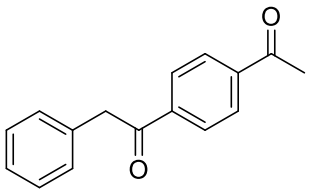
PS-238b (1-(2,4-dimethoxyphenyl)-2-phenylethanone)

PS-238b (**1-(2,4-dimethoxyphenyl)-2-phenylethanone,** 11 mg, 0.04 mmol, 7% yield) as a beige solid. Mp: 40-42 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.81, d (*J* = 8.7 Hz, 2H), 7.29, t (*J* = 7.6 Hz, 1H), 7.22, t (*J* = 7.5 Hz, 3H), 6.52, dd (*J* = 8.7, 2.1 Hz, 1H), 6.45, d (*J* = 1.9 Hz, 1H), 4.28, s (2H), 3.89, s (3H), 3.85, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 197.93, 164.65, 160.79, 135.89, 133.30, 129.76, 128.42, 126.55, 121.06, 105.35, 98.50, 55.67, 55.54, 50.13. This spectral data is consistent with a previous literature report[109].

PS-296 1-(4-acetylphenyl)-2-phenylethanone & 2-(4-acetylphenyl)-1-phenylethanone



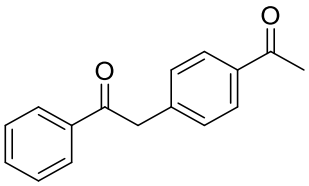
General procedure 3 was followed using **4-(Phenylethynyl)acetophenone** (132 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 72 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 115 mg, 0.6 mmol). The reaction flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-296a** (**1-(4-acetylphenyl)-2-phenylethanone**, 61.5 mg, 0.26 mmol, 43% yield) as a yellow solid and **PS-296b** (**2-(4-acetylphenyl)-1-phenylethanone,** 48.6 mg, 0.20 mmol, 34% yield) as a white solid.



PS-296a (1-(4-acetylphenyl)-2-phenylethanone)

PS-296a (**1-(4-acetylphenyl)-2-phenylethanone**, 62 mg, 0.26 mmol, 43% yield) as a yellow solid. Mp: 106-108 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 8.08-8.07, d (*J* = 8.1 Hz, 2H), 8.02, d (*J* = 8.1 Hz, 2H), 7.33, t (*J* = 7.5 Hz, 2H), 7.26, t (*J* = 7.5 Hz, 3H), 4.31, s (2H), 2.63, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm). 197.56, 197.23, 140.29, 139.86, 134.08, 129.56,

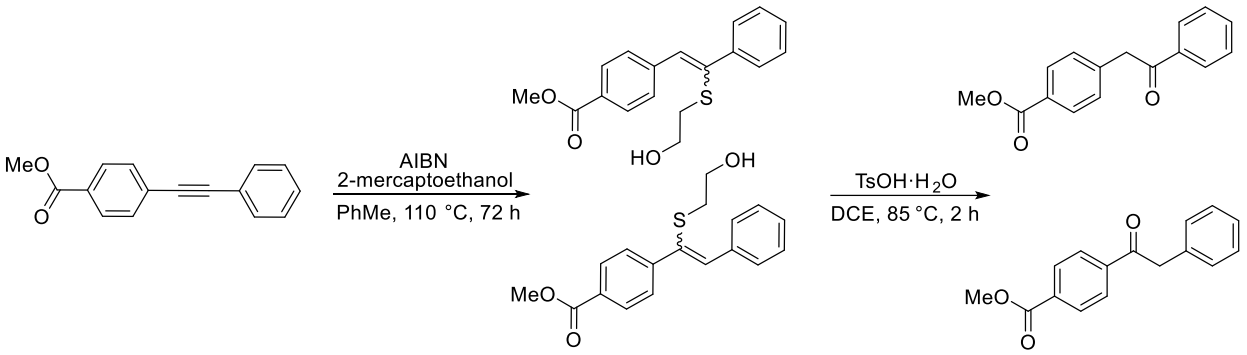
128.95, 128.66, 127.25, 46.04, 27.02. This spectral data is consistent with a previous literature report[110].



PS-296b (2-(4-acetylphenyl)-1-phenylethanone)

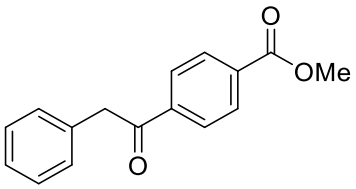
PS-296b (**2-(4-acetylphenyl)-1-phenylethanone,** 49 mg, 0.20 mmol, 34% yield) as a white solid**.** Mp: 158-159 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 8.01, d (*J* = 7.6 Hz, 2H), 7.94, d (*J* = 8.0 Hz, 2H), 7.58, t (*J* = 7.3 Hz, 1H), 7.48, t (*J* = 7.7 Hz, 2H), 7.37, d, (*J* = 8.0 Hz, 2H) 4.36, s (2H), 2.59, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm). 197.87, 196.88, 140.17, 136.52, 136.03, 133.61, 129.98, 128.91, 128.85, 128.68, 45.49, 26.75. This spectral data is consistent with a previous literature report[111].

PS-295 Methyl 4-(2-phenylacetyl)benzoate & Methyl 4-(2-oxo-2-phenylethyl)benzoate



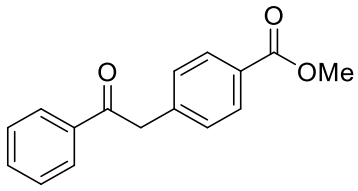
General procedure 3 was followed using **methyl 4-(phenylethynyl)benzoate** (142 mg, 0.60 mmol), toluene (10 mL), azobisisobutyronitrile (AIBN, 10 mg, 0.060 mmol, 0.10 equiv.), and 2-mercaptoethanol (187.5 mg/170µL, 2.40 mmol). The reaction was heated at 110 °C for 72 hours. The reaction mixture was worked up, and to the crude mixture was added dichloroethane (DCE, 10 mL) and *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$, 115 mg, 0.6 mmol). The reaction

flask was then equipped with a reflux condenser and heated to 85 °C for 2 hours. Workup and purification offered **PS-295a** (**Methyl 4-(2-phenylacetyl)benzoate**, 60 mg, 0.23 mmol, 39% yield) as a yellow solid and **PS-295b (Methyl 4-(2-oxo-2-phenylethyl)benzoate**, 41 mg, 0.16 mmol, 27% yield) as a yellow solid.



PS-295a (methyl 4-(2-phenylacetyl)benzoate)

PS-295a (**Methyl 4-(2-phenylacetyl)benzoate**, 60 mg, 0.23 mmol, 39% yield) as a yellow solid. Mp: 104-106 °C ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 8.12, d (*J* = 8.2 Hz, 2H), 8.05, d (*J* = 8.2 Hz, 2H), 7.33, t (*J* = 7.6 Hz, 2H), 7.26, m (3H), 4.31, s (2H), 3.94, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 197.28, 166.32, 139.94, 134.11, 134.06, 130.01, 129.59, 128.93, 128.65, 127.24, 52.62, 46.00. This spectral data is consistent with a previous literature report[12].

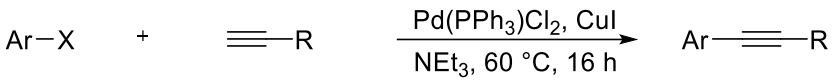


PS-295b (methyl 4-(2-oxo-2-phenylethyl)benzoate)

PS-295b (Methyl 4-(2-oxo-2-phenylethyl)benzoate, 41 mg, 0.16 mmol, 27% yield) as a yellow solid. Mp: 130-131 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 8.01, d (*J* = 7.6 Hz, 4H), 7.58, t (*J* = 7.4 Hz, 1H), 7.47, t (*J* = 7.6 Hz, 2H), 7.35, d (*J* = 7.8 Hz, 2H), 4.35, s (2H), 3.90, s (3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 196.94, 167.05, 139.94, 136.55, 133.57, 130.08, 129.76, 129.02, 128.90, 128.69, 52.23, 45.54. This spectral data is consistent with a previous literature report[12].

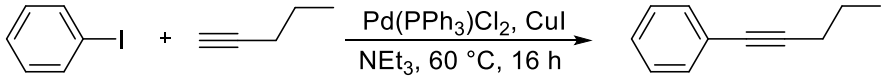
Synthesis of Aryl-Alkyl Alkynes

General procedure for the synthesis of aryl-alkyl alkynes:



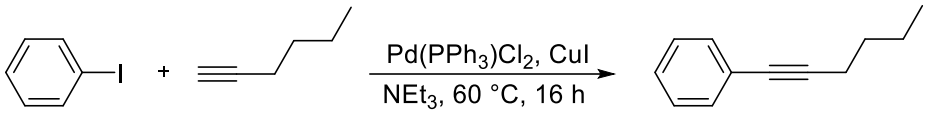
General Procedure 4: To a dry two neck flask was added aryl halide (2.50 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$, 88.0 mg, 0.125 mmol, 5 mol%), copper(I) iodide (CuI, 48.0 mg, 0.25 mmol, 10 mol%), and triethylamine (NEt_3, 20 mL). The mixture was vacuumed and flushed with Argon for 15 minutes. Corresponding alkyne (3.00 mmol, 1.2 equiv.) substrate was then added slowly. The mixture was stirred at 60 °C for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated ammonium chloride (2x) and brine (1x), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered the corresponding alkyne.

PS-322 1-Phenyl-1-pentyne



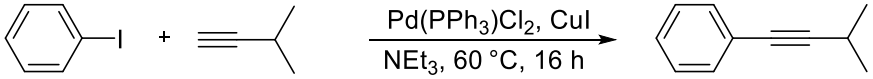
General procedure 4 was followed using **iodobenzene** (510 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-pentyne (204 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-322** (**1-Phenyl-1-pentyne**, 310 mg, 2.15 mmol, 86% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.40, dd (*J* = 7.40, 1.7 Hz, 2H), 7.28, m (3H), 2.39, t (*J* = 7.1 Hz, 2H), 1.64, h (*J* = 7.2 Hz, 2H), 1.05, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 131.69, 128.32, 127.61, 124.24, 90.40, 80.85, 22.37, 21.54, 13.70. This spectral data is consistent with a previous literature report[112].

PS-323 1-Phenyl-1-hexyne



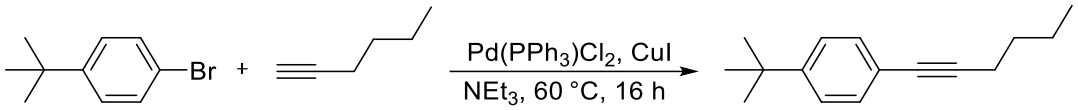
General procedure 4 was followed using **iodobenzene** (510 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-322** (**1-Phenyl-1-hexyne**, 348 mg, 2.20 mmol, 88% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.39, dd (*J* = 7.9, 1.7 Hz, 2H), 7.27, m (3H), 2.41, t (*J* = 7.1 Hz, 2H), 1.59, dt (*J* = 14.8, 7.2 Hz, 2H), 1.49, dq (*J* = 14.5, 7.3 Hz, 2H), 0.95, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 131.69, 128.32, 127.59, 124.26, 90.56, 80.69, 31.01, 22.17, 19.25, 13.80. This spectral data is consistent with a previous literature report[113].

PS-317 1-Phenyl-3-methyl-1-butyne



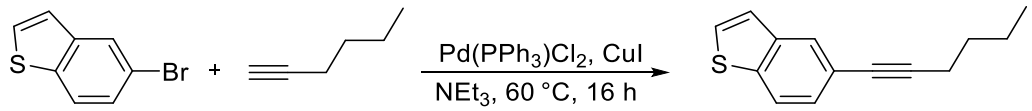
General procedure 4 was followed using **iodobenzene** (510 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 3-methyl-1-butyne (204 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-317** (**1-Phenyl-3-methyl-1-butyne**, 274 mg, 1.90 mmol, 76% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.39, dd (*J* = 7.9, 1.6 Hz, 2H), 7.27, m (3H), 2.79, h (*J* = 6.9 Hz, 1H), 1.27, d (*J* = 6.9 Hz, 6H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 131.70, 128.29, 127.60, 124.16, 95.92, 79.85, 23.18, 21.27. This spectral data is consistent with a previous literature report[114].

PS-335 1-Tert-butyl-4-(hex-1-ynyl)benzene



General procedure 4 was followed using **1-bromo-4-tert-butylbenzene** (533 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-335** (**1-tert-butyl-4-(hex-1-ynyl)benzene**, 295 mg, 1.40 mmol, 55% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.34, d (*J* = 8.5 Hz, 2H), 7.30, d (*J* = 8.6 Hz, 2H), 2.40, t (*J* = 7.1 Hz, 2H), 1.59, dt (*J* = 14.6, 7.3 Hz, 2H), 1.49, dq (*J* = 14.5, 7.4 Hz, 2H), 1.30, s (9H), 0.95, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 150.71, 131.36, 125.29, 121.23, 89.74, 80.66, 34.79, 31.34, 31.07, 22.14, 19.26, 13.79. This spectral data is consistent with a previous literature report[115].

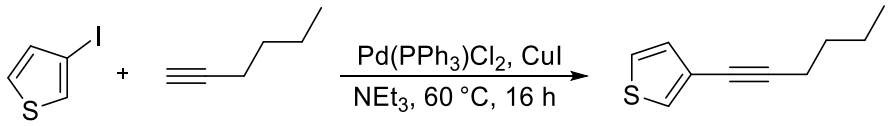
PS-340 5-(hex-1-ynyl)benzo[*b*]thiophene



General procedure 4 was followed using **5-bromo-1-benzo[*b*]thiophene** (533 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-340** (**5-(hex-1-ynyl)benzo[*b*]thiophene**, 451 mg, 2.10 mmol, 84% yield) as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.87, s (1H), 7.78, d (*J* = 8.3 Hz, 1H), 7.44, d (*J* = 5.4 Hz, 1H), 7.36, dd (*J* = 8.3, 1.4 Hz, 1H), 7.28, d (*J* = 5.4 Hz, 1H), 2.44, t (*J* = 7.1 Hz, 2H), 1.62, dt (*J* = 14.6, 7.2 Hz, 2H), 1.51, dq (*J* = 14.5, 7.3 Hz, 2H), 0.97, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 139.68, 139.00, 127.63, 127.19, 126.86,

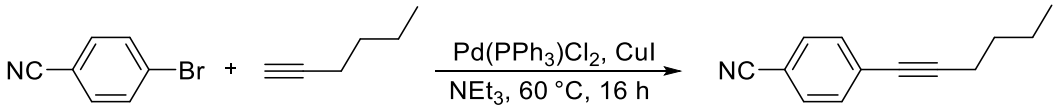
123.76, 122.37, 120.17, 90.01, 80.81, 31.04, 22.19, 19.30, 13.81. LCMS (ESI) *m/z*: 215.08890 for $C_{14}H_{15}S^+$ ($[M + H]^+$); 215.08751 observed.

PS-352 3-(hex-1-yn-1-yl)thiophene



General procedure 4 was followed using **3-iodothiophene** (525 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-352** (**3-(hex-1-yn-1-yl)thiophene**, 378 mg, 2.30 mmol, 92% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.34, dd (*J* = 3.0, 1.0 Hz, 1H), 7.23, dd (*J* = 5.0, 3.0 Hz, 1H), 7.07, dd (*J* = 5.1, 1.1 Hz, 1H), 2.39, t (*J* = 7.1 Hz, 2H), 1.58, ddd (*J* = 12.6, 8.4, 6.3 Hz, 2H), 1.47, m (2H), 0.95, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 130.16, 127.60, 125.08, 123.17, 90.03, 75.65, 30.96, 22.17, 19.21, 13.78. This spectral data is consistent with a previous literature report[116].

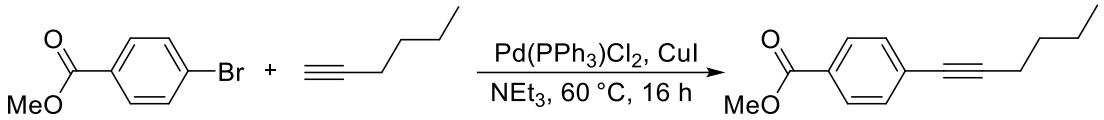
PS-390 4-(hex-1-yn-1-yl)benzonitrile



General procedure 4 was followed using **4-bromobenzonitrile** (455 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-390** (**4-(hex-1-yn-1-yl)benzonitrile**, 412 mg, 2.25 mmol, 90% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.56, d (*J* = 8.5 Hz, 2H), 7.46, d (*J* = 8.4 Hz, 2H), 2.43, t (*J* = 7.1 Hz, 2H), 1.60, dt (*J* = 14.8, 7.2 Hz, 2H), 1.48, m (2H),

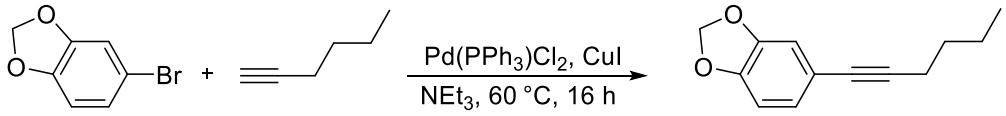
0.95, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 132.23, 132.05, 129.31, 118.81, 110.91, 95.81, 79.56, 30.64, 22.15, 19.33, 13.73. This spectral data is consistent with a previous literature report[117].

PS-388 methyl 4-(hex-1-yn-1-yl)benzoate



General procedure 4 was followed using **methyl 4-bromobenzoate** (538 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-388** (**methyl 4-(hex-1-yn-1-yl)benzoate**, 460 mg, 2.13 mmol, 85% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.95, d (*J* = 8.5 Hz, 2H), 7.44, d (*J* = 8.4 Hz, 2H), 3.91, s (3H), 2.43, t (*J* = 7.1 Hz, 2H), 1.60, m (2H), 1.49, m (2H), 0.95, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 166.84, 131.61, 129.53, 129.10, 128.94, 94.11, 80.23, 52.29, 30.79, 22.16, 19.34, 13.76. This spectral data is consistent with a previous literature report[118].

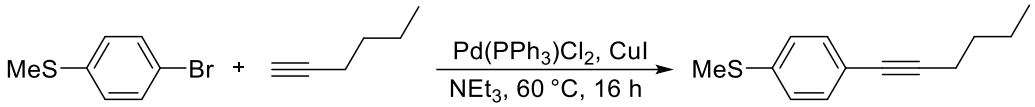
PS-386 5-(hex-1-yn-1-yl)benzo[d][1,3]dioxole



General procedure 4 was followed using **5-bromo-1,3-benzodioxole** (503 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-386** (**5-(hex-1-yn-1-yl)benzo[d][1,3]dioxole**, 253 mg, 1.25 mmol, 50% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 6.91, dd (*J* =

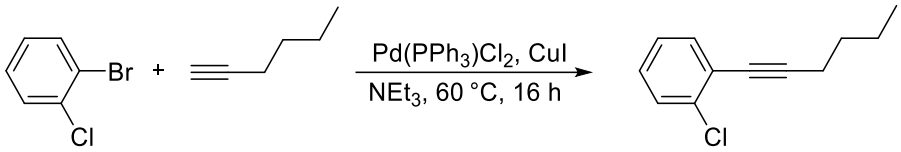
8.0. 1.6 Hz, 1H), 6.85, d (*J* = 1.5 Hz, 1H), 6.72, d (*J* = 8.0 Hz, 1H), 5.94, s (2H), 2.37, t (*J* = 7.1 Hz, 2H), 1.57, m (2H), 1.47, m (2H), 0.94, t (*J* = 7.3 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 147.42, 147.33, 125.96, 117.56, 111.80, 108.43, 101.26, 88.75, 80.39, 31.03, 22.17, 19.20, 13.79. LCMS (ESI) *m/z*: 203.10666 calculated for $C_{13}H_{15}O_2^+$ ([M + H]$^+$); 203.10629 observed. This spectral data is consistent with a previous literature report[117].

PS-395 1-(hex-1-yn-1-yl)-4-(methylsulfanyl)benzene



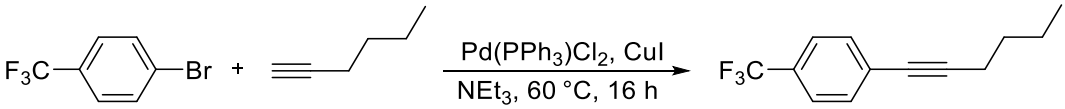
General procedure 4 was followed using **4-bromothioanisole** (508 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-395** (**1-(hex-1-yn-1-yl)-4-(methylsulfanyl)benzene**, 281 mg, 1.38 mmol, 55% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.30, d (*J* = 8.4 Hz, 2H), 7.15, d (*J* = 8.5 Hz, 2H), 2.47, s (3H), 2.40, t (*J* = 7.1 Hz, 2H), 1.58, dt (*J* = 14.8, 7.2 Hz, 2H), 1.48, m (2H), 0.95, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 138.19, 131.99, 126.18, 120.74, 90.63, 80.34, 31.00, 22.17, 19.29, 15.75, 13.79. LCMS (ESI) *m/z*: 205.10455 calculated for $C_{13}H_{17}S^+$ ([M + H]$^+$); 205.10538 observed.

PS-394 1-(2-Chlorophenyl)-1-hexyne



General procedure 4 was followed using **1-bromo-2-chlorobenzene** (479 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-394** (**1-(2-Chlorophenyl)-1-hexyne**, 193 mg, 1.00 mmol, 40% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.43, dd (*J* = 7.3, 2.0 Hz, 1H), 7.37, dd (*J* = 7.5, 1.8 Hz, 1H), 7.18, pd (*J* = 7.4, 1.7 Hz, 2H), 2.48, t (*J* = 7.1 Hz, 2H), 1.63, dt (*J* = 14.7, 7.2 Hz, 2H), 1.52, m (2H), 0.96, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 135.87, 133.43, 129.25, 128.60, 126.43, 124.04, 96.30, 77.64, 30.82, 22.11, 19.43, 13.77. This spectral data is consistent with a previous literature report[119].

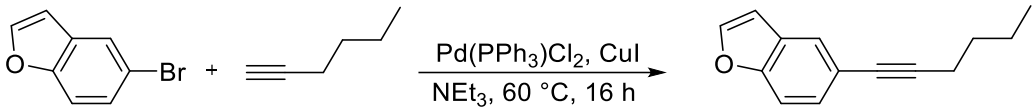
PS-336 1-(hex-1-yn-1-yl)-4-(trifluoromethyl)benzene



General procedure 4 was followed using **1-bromo-4-(trifluoromethyl)benzene** (563 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-336** (**1-(hex-1-yn-1-yl)-4-(trifluoromethyl)benzene**, 339 mg, 1.50 mmol, 60% yield) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.53, d (*J* = 8.2 Hz, 2H), 7.47, d (*J* = 8.1 Hz, 2H), 2.43, t (*J* = 7.1 Hz, 2H), 1.60, dt (*J* = 14.8, 7.2 Hz, 2H), 1.48, m (2H), 0.96, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 131.90, 129.64-129.09, (q, *J* = 32.7 Hz), 128.13, 126.50-123.41, (q, *J* = 271.1

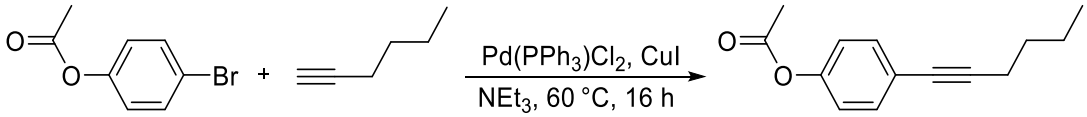
Hz), 125.28-125.22, q (*J* = 3.4 Hz), 93.46, 79.64, 30.77, 22.17, 19.26, 13.76. This spectral data is consistent with a previous literature report[120].

PS-412 5-(hex-1-yn-1-yl)benzofuran



General procedure 4 was followed using **5-bromobenzofuran** (493 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-412** (**5-(hex-1-yn-1-yl)benzofuran**, 372 mg, 1.88 mmol, 75% yield) as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.65, d (*J* = 1.3 Hz, 1H), 7.61, d (*J* = 2.2 Hz, 1H), 7.41, d (*J* = 8.5 Hz, 1H), 7.34, dd (*J* = 8.5, 1.6 Hz, 1H), 6.72, dd (*J* = 2.2, 0.9 Hz, 1H), 2.42, t (*J* = 7.1 Hz, 2H), 1.61, dt (*J* = 14.8, 7.2 Hz, 2H), 1.51, m (2H), 0.96, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 154.31, 145.75, 128.15, 127.58, 124.62, 118.77, 111.44, 106.57, 88.92, 80.80, 31.09, 22.20, 19.25, 13.82. LCMS (ESI) *m/z*: 199.11174 calculated for $C_{14}H_{15}O^+$ ($[M + H]^+$); 199.11128 observed.

PS-405 4-(hex-1-yn-1-yl)phenyl acetate

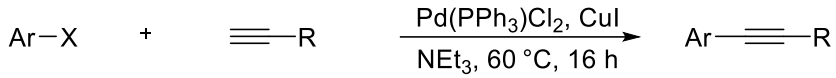


General procedure 4 was followed using **4-bromophenyl acetate** (538 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 1-hexyne (246 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-405** (**4-(hex-1-yn-1-yl)phenyl acetate**, 378 mg, 1.75 mmol, 70% yield) as a light-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.39, d (*J* = 8.7 Hz, 2H),

7.01, d (*J* = 8.7 Hz, 2H), 2.40, t (*J* = 7.1 Hz, 2H), 2.29, s (3H), 1.58, dt (*J* = 14.7, 7.2 Hz, 2H), 1.48, m (2H), 0.95, t (*J* = 7.4 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 169.36, 149.99, 132.77, 121.99, 121.61, 90.66, 79.88, 30.93, 22.15, 21.27, 19.21, 13.78. LCMS (ESI) *m/z*: 217.12231 calculated for $C_{14}H_{17}O_2^+$ ($[M + H]^+$); 217.12134 observed. This spectral data is consistent with a previous literature report[121].

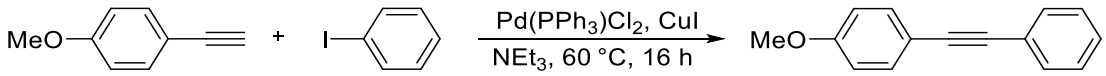
Synthesis of Aryl-Aryl Alkynes

General procedure for the synthesis of aryl-aryl alkynes:



General Procedure 5: To a dry two neck flask was added aryl halide (2.50 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$, 88.0 mg, 0.125 mmol, 5 mol%), copper(I) iodide (CuI, 48.0 mg, 0.25 mmol, 10 mol%), and triethylamine (NEt_3, 20 mL). The mixture was vacuumed and flushed with Argon for 15 minutes. Corresponding alkyne (3.00 mmol, 1.2 equiv.) substrate was then added slowly. The mixture was stirred at 60 °C for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated ammonium chloride (2x) and brine (1x), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude product. Chromatography over silica gel using gradient elution with EtOAc and hexanes offered the corresponding alkyne.

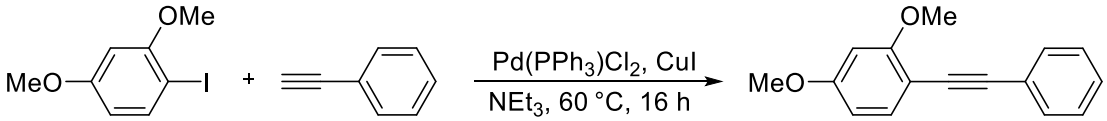
PS-182 1-methoxy-4-(phenylethynyl)benzene



General procedure 5 was followed using **iodobenzene** (510 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and 4-methoxyphenylacetylene (396 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-182** (**1-methoxy-4-(phenylethynyl)benzene**, 375 mg, 1.80 mmol, 72% yield) as a white solid. Mp: 56-57.5 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) 7.53 (d, *J* = 7.1 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.33 (m, 3H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.83 (s, CH_3, 3H). ^{13}C NMR DEPTQ (176 MHz, CDCl3): δ (ppm) 159.75,

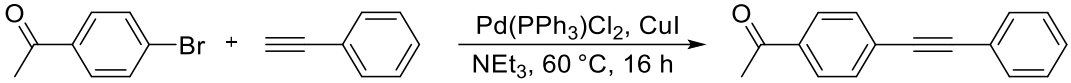
133.19, 131.58, 128.44, 128.06, 123.73, 115.52, 114.13, 89.50, 88.20, 55.44. This spectral data is consistent with a previous literature report[112].

PS-304 1,3-dimethoxy-5-(2-phenylethynyl)benzene



General procedure 5 was followed using **2,4-dimethoxyiodobenzene** (660 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and phenylacetylene (306 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-304** (**1,3-dimethoxy-5-(2-phenylethynyl)benzene**, 554 mg, 2.33 mmol, 93% yield) as a brown oil. ^{1}H NMR (700 MHz, CDCl3 (7.26 ppm)): 7.56, d (*J* = 8.0 Hz, 2H), 7.44, d (*J* = 8.3 Hz, 1H), 7.33, t (*J* = 7.5 Hz, 2H), 7.30, t (*J* = 7.2 Hz, 1H), 6.49, d (*J* = 8.4 Hz, 1H), 6.47, s (1H), 3.89, s (3H), 3.82, s (3H). ^{13}C NMR (700 MHz, CDCl3 (77.16 ppm)): 161.31, 161.24, 134.38, 131.57, 128.28, 127.85, 123.97, 105.07, 104.95, 98.54, 92.10, 85.91, 60.44, 55.89, 55.47. This spectral data is consistent with a previous literature report[122].

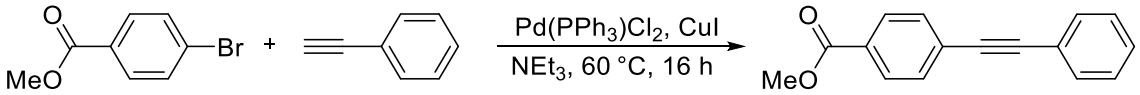
PS-194 4-(phenylethynyl)acetophenone



General procedure 5 was followed using **4'-bromoacetophenone** (498 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and phenylacetylene (306 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-194** (**4-(Phenylethynyl)acetophenone**, 363 mg, 1.65 mmol, 66% yield) as a beige solid. Mp: 96-97 °C. ^{1}H NMR (700 MHz, CDCl3 (7.26 ppm)): 7.95, d (*J* = 8.5 Hz, 2H), 7.62, d (*J* = 8.5 Hz, 2H), 7.56, m (2H), 7.38, m (3H), 2.62, s (3H). ^{13}C NMR

(700 MHz, CDCl3 (77.16 ppm)): 197.48, 136.35, 131.90, 131.85, 128.97, 128.60, 128.43, 128.36, 122.80, 92.86, 88.75, 26.78. This spectral data is consistent with a previous literature report[119].

PS-258 Methyl 4-(phenylethynyl)benzoate



General procedure 5 was followed using **methyl 4-bromobenzoate** (538 mg, 2.50 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.125 mmol, 5 mol%), CuI (48.0 mg, 0.25 mmol, 10 mol%), NEt_3 (20 mL), and phenylacetylene (306 mg, 3.0 mmol, 1.2 equiv.). The mixture was stirred at 60 °C for 16 hours. Workup and purification offered **PS-258** (**methyl 4-(phenylethynyl)benzoate**, 295 mg, 1.25 mmol, 50% yield) as a beige solid. Mp: 118-119 °C. ^{1}H NMR (700 MHz, CDCl3 (7.26 ppm)): 8.03, d (*J* = 8.3 Hz, 2H), 7.60, d (*J* = 8.3 Hz, 2H), 7.55, dd (*J* = 6.5, 2.9 Hz, 2H), 7.37, m (3H), 3.93, s (3H). ^{13}C NMR (700 MHz, CDCl3 (77.16 ppm)): 166.72, 131.89, 131.66, 129.67, 129.62, 128.91, 128.59, 128.16, 122.85, 92.50, 88.77, 52.38. This spectral data is consistent with a previous literature report[119].

4.0 References

1. Markownikoff, W., I. Ueber die Abhängigkeit der verschiedenen Vertretbarkeit des Radicalwasserstoffs in den isomeren Buttersäuren. *Justus Liebigs Annalen der Chemie* **1870,** *153* (2), 228-259.

2. Galli, M.; Fletcher, C. J.; del Pozo, M.; Goldup, S. M., Scalable anti-Markovnikov hydrobromination of aliphatic and aromatic olefins. *Organic & Biomolecular Chemistry* **2016,** *14* (24), 5622-5626.

3. Klein, D., *Organic Chemistry 3rd edition*. Wiley: Johns Hopkins University. Baltimore., 2017.

4. McMurry, J., *Organic Chemistry 5th edition*. Brooks Cole: Cornell University. New York., 2000.

5. Clayden, J.; Greeves, N.; Warren, S., *Organic Chemistry 2nd edition*. Oxford University Press: England, 2012.

6. Hou, S.; Yang, H.; Cheng, B.; Zhai, H.; Li, Y., Cobaloxime-catalyzed hydration of terminal alkynes without acidic promoters. *Chemical Communications* **2017,** *53* (51), 6926-6929.

7. Das, A.; Park, S.; Muthaiah, S., Ligand- and Acid-Free Gold(I) Chloride Catalyzed Hydration of Terminal Alkynes. *Synlett* **2015,** *26* (18), 2517-2520.

8. Fernández, G. A.; Dorn, V.; Chopa, A. B.; Silbestri, G. F., Steric hindrance and electronic effects of sulfonatepropyl chain on gold center. An experimental and DFT study. *Journal of Organometallic Chemistry* **2017,** *852*, 20-26.

9. Marion, N.; Ramón, R. S.; Nolan, S. P., [(NHC)AuI]-Catalyzed Acid-Free Alkyne Hydration at Part-per-Million Catalyst Loadings. *Journal of the American Chemical Society* **2009,** *131* (2), 448-449.

10. Nguyen, V. H.; Dang, T. T.; Nguyen, H. H.; Huynh, H. V., Platinum(II) 1,2,4-Triazolin-5-ylidene Complexes: Stereoelectronic Influences on Their Catalytic Activity in Hydroelementation Reactions. *Organometallics* **2020,** *39* (12), 2309-2319.

11. Trentin, F.; Chapman, A. M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G.; Wass, D. F., Platinum(II) Diphosphinamine Complexes for the Efficient Hydration of Alkynes in Micellar Media. *Advanced Synthesis & Catalysis* **2012,** *354* (6), 1095-1104.

12. Lin, H.-P.; Ibrahim, N.; Provot, O.; Alami, M.; Hamze, A., PtO2/PTSA system catalyzed regioselective hydration of internal arylalkynes bearing electron withdrawing groups. *RSC Advances* **2018,** *8* (21), 11536-11542.

13. Suta, K.; Turks, M. r., In(III) and Hf(IV) Triflate-Catalyzed Hydration and Catalyst-free Hydrohalogenation of Aryl Acetylenes in Liquid Sulfur Dioxide. *ACS Omega* **2018,** *3* (12), 18065-18077.

14. Baidossi, W.; Goren, N.; Blum, J.; Schumann, H.; Hemling, H., Homogeneous and biphasic oligomerization of terminal alkynes by some water soluble rhodium catalysts. *Journal of Molecular Catalysis* **1993,** *85* (2), 153-162.

15. Bassetti, M.; Ciceri, S.; Lancia, F.; Pasquini, C., Hydration of aromatic terminal alkynes catalyzed by iron(III) sulfate hydrate under chlorine-free conditions. *Tetrahedron Letters* **2014,** *55* (9), 1608-1612.

16. Das, R.; Chakraborty, D., AgOTf catalyzed hydration of terminal alkynes. *Applied Organometallic Chemistry* **2012,** *26* (12), 722-726.

17. Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K., Dialkylborane-Catalyzed Hydroboration of Alkynes with 1,3,2-Benzodioxaborole in Tetrahydrofuran. *Synthetic Communications* **1995,** *25* (13), 1957-1962.

18. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M., Sodium perborate: a mild and convenient reagent for efficiently oxidizing organoboranes. *The Journal of Organic Chemistry* **1989,** *54* (25), 5930-5933.

19. Grotjahn, D. B.; Lev, D. A., A General Bifunctional Catalyst for the Anti-Markovnikov Hydration of Terminal Alkynes to Aldehydes Gives Enzyme-Like Rate and Selectivity Enhancements. *Journal of the American Chemical Society* **2004,** *126* (39), 12232-12233.

20. Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L., Combined Effects of Metal and Ligand Capable of Accepting a Proton or Hydrogen Bond Catalyze Anti-Markovnikov Hydration of Terminal Alkynes. *Angewandte Chemie International Edition* **2001,** *40* (20), 3884-3887.

21. Chevallier, F.; Breit, B., Self-Assembled Bidentate Ligands for Ru-Catalyzed anti-Markovnikov Hydration of Terminal Alkynes. *Angewandte Chemie International Edition* **2006,** *45* (10), 1599-1602.

22. Dieck, H. A.; Heck, F. R., Palladium catalyzed synthesis of aryl, heterocyclic and vinylic acetylene derivatives. *Journal of Organometallic Chemistry* **1975,** *93* (2), 259-263.
23. Cassar, L., Synthesis of aryl- and vinyl-substituted acetylene derivatives by the use of nickel and palladium complexes. *Journal of Organometallic Chemistry* **1975,** *93* (2), 253-257.

24. Sonogashira, K.; Tohda, Y.; Hagihara, N., A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Letters* **1975,** *16* (50), 4467-4470.

25. Chinchilla, R.; Nájera, C., The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chemical Reviews* **2007,** *107* (3), 874-922.

26. Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V., Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angewandte Chemie International Edition* **2012,** *51* (21), 5062-5085.

27. Mello, R.; Alcalde-Aragonés, A.; González-Núñez, M. E., Silica-supported HgSO4/H2SO4: a convenient reagent for the hydration of alkynes under mild conditions. *Tetrahedron Letters* **2010,** *51* (32), 4281-4283.

28. Liu, W.; Wang, H.; Li, C.-J., Metal-Free Markovnikov-Type Alkyne Hydration under Mild Conditions. *Organic Letters* **2016,** *18* (9), 2184-2187.

29. Cabrero-Antonino, J. R.; Leyva-Pérez, A.; Corma, A., Iron(III) Triflimide as a Catalytic Substitute for Gold(I) in Hydroaddition Reactions to Unsaturated Carbon–Carbon Bonds. *Chemistry – A European Journal* **2013,** *19* (26), 8627-8633.

30. Park, J.; Yeon, J.; Lee, P. H.; Lee, K., Iron-catalyzed indirect hydration of alkynes in presence of methanesulfonic acid. *Tetrahedron Letters* **2013,** *54* (33), 4414-4417.

31. Hassam, M.; Li, W.-S., Copper-catalyzed Markovnikov hydration of alkynes. *Tetrahedron* **2015,** *71* (18), 2719-2723.

32. Wu, G.; Wang, X.; Zhang, L.; Jiang, T., Au(I) complexes as the efficient catalyst for hydration of alkynes at room temperature. **2015,** *36*, 2461-2467.

33. Rostamizadeh, S.; Estiri, H.; Azad, M., Au anchored to (α-Fe2O3)-MCM-41-HS as a novel magnetic nanocatalyst for water-medium and solvent-free alkyne hydration. *Catalysis Communications* **2014,** *57*, 29-35.

34. Gao, Q.; Li, S.; Pan, Y.; Xu, Y.; Wang, H., The indium-catalysed hydration of alkynes using substoichiometric amounts of PTSA as additive. *Tetrahedron* **2013,** *69* (19), 3775-3781.

35. Chen, Z.-W.; Ye, D.-N.; Qian, Y.-P.; Ye, M.; Liu, L.-X., Highly efficient AgBF4-catalyzed synthesis of methyl ketones from terminal alkynes. *Tetrahedron* **2013,** *69* (30), 6116-6120.

36. Mei, Q.; Liu, H.; Hou, M.; Liu, H.; Han, B., Selective hydration of asymmetric internal aryl alkynes without directing groups to α-aryl ketones over Cu-based catalyst. *New Journal of Chemistry* **2017,** *41* (14), 6290-6295.

37. Weerasiri, K. C.; Chen, D.; Wozniak, D. I.; Dobereiner, G. E., Internal Alkyne Regio- and Chemoselectivity using a Zwitterionic N-Heterocyclic Carbene Gold Catalyst in a Silver-Free Alkyne Hydration Reaction. *Advanced Synthesis & Catalysis* **2016,** *358* (24), 4106-4113.

38. Le Bras, G.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D., Rapid microwave assisted hydration of internal arylalkynes in the presence of PTSA: an efficient regioselective access to carbonyl compounds. *Tetrahedron Letters* **2006,** *47* (31), 5497-5501.

39. Jacubert, M.; Provot, O.; Peyrat, J.-F.; Hamze, A.; Brion, J.-D.; Alami, M., p-Toluenesulfonic acid-promoted selective functionalization of unsymmetrical arylalkynes: a regioselective access to various arylketones and heterocycles. *Tetrahedron* **2010,** *66* (21), 3775-3787.

40. Rami, F.; Bächtle, F.; Plietker, B., Hydroboration of internal alkynes catalyzed by FeH(CO)(NO)(PPh3)2: a case of boron-source controlled regioselectivity. *Catalysis Science & Technology* **2020,** *10* (5), 1492-1497.

41. Mandal, S.; Mandal, S.; Geetharani, K., Zinc-Catalysed Hydroboration of Terminal and Internal Alkynes. *Chemistry – An Asian Journal* **2019,** *14* (24), 4553-4556.

42. Bisai, M. K.; Yadav, S.; Das, T.; Vanka, K.; Sen, S. S., Lithium compounds as single site catalysts for hydroboration of alkenes and alkynes. *Chemical Communications* **2019,** *55* (78), 11711-11714.

43. Magre, M.; Maity, B.; Falconnet, A.; Cavallo, L.; Rueping, M., Magnesium-Catalyzed Hydroboration of Terminal and Internal Alkynes. *Angewandte Chemie International Edition* **2019,** *58* (21), 7025-7029.

44. Carden, J. L.; Gierlichs, L. J.; Wass, D. F.; Browne, D. L.; Melen, R. L., Unlocking the catalytic potential of tris(3,4,5-trifluorophenyl)borane with microwave irradiation. *Chemical Communications* **2019,** *55* (3), 318-321.

45. Hall, J. W.; Unson, D. M. L.; Brunel, P.; Collins, L. R.; Cybulski, M. K.; Mahon, M. F.; Whittlesey, M. K., Copper-NHC-Mediated Semihydrogenation and Hydroboration of Alkynes: Enhanced Catalytic Activity Using Ring-Expanded Carbenes. *Organometallics* **2018,** *37* (18), 3102-3110.

46. Yan, Q.; Shen, X.; Zi, G.; Hou, G., Rh-Catalyzed Asymmetric Hydrogenation of α,β- and β,β-Disubstituted Unsaturated Boronate Esters. *Chemistry – A European Journal* **2020,** *26* (27), 5961-5964.

47. Lawson, J. R.; Wilkins, L. C.; Melen, R. L., Tris(2,4,6-trifluorophenyl)borane: An Efficient Hydroboration Catalyst. *Chemistry – A European Journal* **2017,** *23* (46), 10997-11000.

48. Li, J.-J.; Wang, C.-G.; Yu, J.-F.; Wang, P.; Yu, J.-Q., Cu-Catalyzed C–H Alkenylation of Benzoic Acid and Acrylic Acid Derivatives with Vinyl Boronates. *Organic Letters* **2020,** *22* (12), 4692-4696.

49. Shimoi, M.; Watanabe, T.; Maeda, K.; Curran, D. P.; Taniguchi, T., Radical trans-Hydroboration of Alkynes with N-Heterocyclic Carbene Boranes. *Angewandte Chemie International Edition* **2018,** *57* (30), 9485-9490.

50. Wen, K.; Chen, J.; Gao, F.; Bhadury, P. S.; Fan, E.; Sun, Z., Metal free catalytic hydroboration of multiple bonds in methanol using N-heterocyclic carbenes under open atmosphere. *Organic & Biomolecular Chemistry* **2013,** *11* (37), 6350-6356.

51. Zaidlewicz, M.; Melier, J., MONOHYDROBORATION OF CONJUGATED DIENES, ALKYNES AND FUNCTIONALIZED ALKYNES WITH CATECHOLBORANE CATALYZED BY NICKEL(II) CHLORIDE AND COBALT(II) CHLORIDE COMPLEXES WITH PHOSPHINES. *Main Group Metal Chemistry* **2000,** *23* (12), 765-772.

52. Periasamy, M.; Reddy, P. O.; Shanmugaraja, M., Organoboranes Oxidation and Lewis Base Borane Complexes Preparation Using Oxygen Adsorbed Carbon Materials. *ChemistrySelect* **2017,** *2* (25), 7615-7619.

53. Rühling, A.; Galla, H. J.; Glorius, F., A Remarkably Simple Hybrid Surfactant–NHC Ligand, Its Gold-Complex, and Application in Micellar Catalysis. *Chemistry – A European Journal* **2015,** *21* (35), 12291-12294.

54. Nun, P.; Ramón, R. S.; Gaillard, S.; Nolan, S. P., Efficient silver-free gold(I)-catalyzed hydration of alkynes at low catalyst loading. *Journal of Organometallic Chemistry* **2011,** *696* (1), 7-11.

55. Arai, H.; Yoshida, T.; Nagashima, E.; Hatayama, A.; Horie, S.; Matsunaga, S.; Nomiya, K., Silver- and Acid-Free Catalysis by Polyoxometalate-Assisted Phosphanegold(I) Species for Hydration of Diphenylacetylene. *Organometallics* **2016,** *35* (11), 1658-1666.

56. Nomiya, K.; Murara, Y.; Iwasaki, Y.; Arai, H.; Yoshida, T.; Chikaraishi Kasuga, N.; Matsubara, T., Highly active, homogeneous catalysis by polyoxometalate-assisted N-heterocyclic carbene gold(I) complexes for hydration of diphenylacetylene. *Molecular Catalysis* **2019,** *469*, 144-154.

57. Fang, W.; Presset, M.; Guérinot, A.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V., Silver-Free Two-Component Approach in Gold Catalysis: Activation of [LAuCl] Complexes with Derivatives of Copper, Zinc, Indium, Bismuth, and Other Lewis Acids. *Chemistry – A European Journal* **2014,** *20* (18), 5439-5446.

58. Endo, N.; Inoue, M.; Iwasawa, T., Rational Design of a Metallocatalytic Cavitand for Regioselective Hydration of Specific Alkynes. *European Journal of Organic Chemistry* **2018,** *2018* (9), 1136-1140.

59. Haak, E.; Bytschkov, I.; Doye, S., Intermolecular Hydroamination of Alkynes Catalyzed by Dimethyltitanocene. *Angewandte Chemie International Edition* **1999,** *38* (22), 3389-3391.

60. Ackermann, L.; Kaspar, L. T., TiCl4-Catalyzed Indirect Anti-Markovnikov Hydration of Alkynes: Application to the Synthesis of Benzo[b]furans. *The Journal of Organic Chemistry* **2007,** *72* (16), 6149-6153.

61. Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P., Rhodium(I) and iridium(I) complexes containing bidentate phosphine-imidazolyl donor ligands as catalysts for the hydroamination and hydrothiolation of alkynes. *Dalton Transactions* **2009,** (18), 3599-3614.

62. Yang, J.; Sabarre, A.; Fraser, L. R.; Patrick, B. O.; Love, J. A., Synthesis of 1,1-Disubstituted Alkyl Vinyl Sulfides via Rhodium-Catalyzed Alkyne Hydrothiolation: Scope and Limitations. *The Journal of Organic Chemistry* **2009,** *74* (1), 182-187.

63. Sabarre, A.; Love, J., Synthesis of 1,1-Disubstituted Olefins via Catalytic Alkyne Hydrothiolation/Kumada Cross-Coupling. *Organic Letters* **2008,** *10* (18), 3941-3944.

64. Weiss, C. J.; Wobser, S. D.; Marks, T. J., Organoactinide-Mediated Hydrothiolation of Terminal Alkynes with Aliphatic, Aromatic, and Benzylic Thiols. *Journal of the American Chemical Society* **2009,** *131* (6), 2062-2063.

65. Orlov, N. V., Metal Catalysis in Thiolation and Selenation Reactions of Alkynes Leading to Chalcogen-Substituted Alkenes and Dienes. *ChemistryOpen* **2015,** *4* (6), 682-697.

66. Shoai, S.; Bichler, P.; Kang, B.; Buckley, H.; Love, J. A., Catalytic Alkyne Hydrothiolation with Alkanethiols using Wilkinson's Catalyst. *Organometallics* **2007,** *26* (24), 5778-5781.

67. Gerber, R.; Frech, C. M., Alkyne Hydrothiolation Catalyzed by a Dichlorobis(aminophosphine) Complex of Palladium: Selective Formation of cis-Configured Vinyl Thioethers. *Chemistry – A European Journal* **2012,** *18* (29), 8901-8905.

68. Corma, A.; González-Arellano, C.; Iglesias, M.; Sánchez, F., Efficient synthesis of vinyl and alkyl sulfides via hydrothiolation of alkynes and electron-deficient olefins using soluble and heterogenized gold complexes catalysts. *Applied Catalysis A: General* **2010,** *375* (1), 49-54.

69. Zhang, Y.; Xu, X.; Zhu, S., Nickel-catalysed selective migratory hydrothiolation of alkenes and alkynes with thiols. *Nature Communications* **2019,** *10* (1), 1752.

70. Nozaki, K.; Oshima, K.; Uchimoto, K., Et3B-induced radical addition of R3SnH to acetylenes and its application to cyclization reaction. *Journal of the American Chemical Society* **1987,** *109* (8), 2547-2549.

71. Bader, H.; Cross, L. C.; Heilbron, I.; Jones, E. R. H., 132. Researches on acetylenic compounds. Part XVIII. The addition of thiolacetic acid to acetylenic hydrocarbons. The conversion of monosubstituted acetylenes into aldehydes and 1 : 2-dithiols. *Journal of the Chemical Society (Resumed)* **1949,** (0), 619-623.

72. Greengrass, C. W.; Hughman, J. A.; Parsons, P. J., New routes to tetracycline analogues: an intramolecular Diels–Alder approach. *Journal of the Chemical Society, Chemical Communications* **1985,** (13), 889-890.

73. Beauchemin, A.; Gareau, Y., STUDIES OF TRIPHENYLSILANETHIOL ADDITION TO ALKYNES: PREPARATION OF VINYL SULFIDES. *Phosphorus, Sulfur, and Silicon and the Related Elements* **1998,** *139* (1), 187-192.

74. Montevecchi, P. C.; Navacchia, M. L., THIOL MEDIATED 5-(π-ENDO)ORTHO VINYL RADICAL CYCLIZATIONS. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2000,** *166* (1), 201-219.

75. Zalesskiy, S. S.; Shlapakov, N. S.; Ananikov, V. P., Visible light mediated metal-free thiol–yne click reaction. *Chemical Science* **2016,** *7* (11), 6740-6745.

76. Meindertsma, A. F.; Pollard, M. M.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J., Asymmetric hydrogenation of alkyl(vinyl)thioethers: a promising approach to α-chiral thioethers. *Tetrahedron: Asymmetry* **2007,** *18* (24), 2849-2858.

77. Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P., A Study of Vinyl Radical Cyclization onto the Azido Group by Addition of Sulfanyl, Stannyl, and Silyl Radicals to Alkynyl Azides☆. *European Journal of Organic Chemistry* **1998,** *1998* (6), 1219-1226.

78. Satchell, D. P. N.; Satchell, R. S., Mechanisms of hydrolysis of thioacetals. *Chemical Society Reviews* **1990,** *19* (1), 55-81.

79. Greene, T. W., P., *Greene's Protective Groups in Organic Synthesis*. 4th ed.; John Wiley & Sons: 2007; p 1-1082.

80. Du, B.; Yuan, C.; Zhang, L.; Yang, L.; Liu, B., Deprotection of 1,3-oxathiolanes to ketones promoted by base. *Tetrahedron Letters* **2013,** *54* (18), 2217-2220.

81. Xu, G.; Feng, L.; Song, P.; Xu, F.; Li, A.; Wang, Y.; Shen, Y.; Wu, X.; Luo, Q.; Wu, X.; Sun, Y.; Wu, X.; Xu, Q., Isomeranzin suppresses inflammation by inhibiting M1 macrophage polarization through the NF-κB and ERK pathway. *International Immunopharmacology* **2016,** *38*, 175-185.

82. Imai, F.; Kinoshita, T.; Sankawa, U., Constituents of the Leaves of Murraya paniculata Collected in Taiwan. *CHEMICAL & PHARMACEUTICAL BULLETIN* **1989,** *37* (2), 358-362.

83. Wang, X.; Liang, H.; Zeng, K.; Zhao, M.; Tu, P.; Li, J.; Jiang, Y., Panitins A-G: Coumarin derivatives from Murraya paniculata from Guangxi Province, China show variable NO inhibitory activity. *Phytochemistry* **2019,** *162*, 224-231.

84. Tian, D.; Wang, F.; Duan, M.; Cao, L.; Zhang, Y.; Yao, X.; Tang, J., Coumarin Analogues from the Citrus grandis (L.) Osbeck and Their Hepatoprotective Activity. *Journal of Agricultural and Food Chemistry* **2019,** *67* (7), 1937-1947.

85. Zhao, Y.-L.; Yang, X.-W.; Wu, B.-F.; Shang, J.-H.; Liu, Y.-P.; Zhi, D.; Luo, X.-D., Anti-inflammatory Effect of Pomelo Peel and Its Bioactive Coumarins. *Journal of Agricultural and Food Chemistry* **2019,** *67* (32), 8810-8818.

86. Kuo, P.-C. L., Y.-R.; Hung, H.-Y.; Chuang, C.-W.; Hwang, T.-L.; Huang, S.-C.; Shiao, Y.-J.; Kuo, D.-H.; Wu, T.-S, Anti-Inflammatory and Neuroprotective Constituents from the Peels of Citrus grandis. *Molecules* **2017,** *22*, 967.

87. Cao, N.; Zhu, S.; Li, J.; Tu, P.; Jiang, Y., Coumarins from the stems and leaves of Clausena dunniana H. Lév. *Biochemical Systematics and Ecology* **2020,** *90*, 104048.

88. Song, P.-P.; Zhao, J.; Liu, Z.-L.; Duan, Y.-B.; Hou, Y.-P.; Zhao, C.-Q.; Wu, M.; Wei, M.; Wang, N.-H.; Lv, Y.; Han, Z.-J., Evaluation of antifungal activities and structure–activity relationships of coumarin derivatives. *Pest Management Science* **2017,** *73* (1), 94-101.

89. Devji, T.; Reddy, C.; Woo, C.; Awale, S.; Kadota, S.; Carrico-Moniz, D., Pancreatic anticancer activity of a novel geranylgeranylated coumarin derivative. *Bioorganic & Medicinal Chemistry Letters* **2011,** *21* (19), 5770-5773.

90. Gillmore, A.; Lauret, C.; Roberts, S. M., A route to the structure proposed for puetuberosanol and approaches to the natural products marshrin and phebalosin. *Tetrahedron* **2003,** *59* (24), 4363-4375.

91. Guthertz, A.; Leutzsch, M.; Wolf, L. M.; Gupta, P.; Rummelt, S. M.; Goddard, R.; Farès, C.; Thiel, W.; Fürstner, A., Half-Sandwich Ruthenium Carbene Complexes Link trans-Hydrogenation and gem-Hydrogenation of Internal Alkynes. *Journal of the American Chemical Society* **2018,** *140* (8), 3156-3169.

92. Corey, E. J.; Shulman, J. I., Application of lithium reagents from (1-methylthio) alkylphosphonate esters to the synthesis of ketones. *The Journal of Organic Chemistry* **1970,** *35* (3), 777-780.

93. Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H., New synthesis of ketones using 1-(alkylthio)vinyllithium. *Journal of the American Chemical Society* **1973,** *95* (8), 2694-2695.

94. Mura, A. J.; Majetich, G.; Grieco, P. A.; Cohen, T., Methods for the conversion of vinyl sulfides to aldehydes. *Tetrahedron Letters* **1975,** *16* (50), 4437-4440.

95. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A., NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *The Journal of Organic Chemistry* **1997,** *62* (21), 7512-7515.

96. Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N., Sesquiterpene lactones: total synthesis of (.+-.)-vernolepin and (.+-.)-vernomenin. *Journal of the American Chemical Society* **1977,** *99* (17), 5773-5780.

97. Karimi, B.; Seradj, H.; Maleki, J., Highly efficient and chemoselective interchange of 1,3-oxathioacetals and dithioacetals to acetals promoted by N-halosuccinimide. *Tetrahedron* **2002,** *58* (22), 4513-4516.

98. Chakraborty, N.; Santra, S.; Kundu, S. K.; Hajra, A.; Zyryanov, G. V.; Majee, A., Combination of NH2OH·HCl and NaIO4: an effective reagent for molecular iodine-free regioselective 1,2-difunctionalization of olefins and easy access of terminal acetals. *RSC Advances* **2015,** *5* (70), 56780-56788.

99. Li, P.; Lü, B.; Fu, C.; Ma, S., Zheda-Phos for General α-Monoarylation of Acetone with Aryl Chlorides. *Advanced Synthesis & Catalysis* **2013,** *355* (7), 1255-1259.

100. Zhang, G.; Hu, X.; Chiang, C.-W.; Yi, H.; Pei, P.; Singh, A. K.; Lei, A., Anti-Markovnikov Oxidation of β-Alkyl Styrenes with H2O as the Terminal Oxidant. *Journal of the American Chemical Society* **2016,** *138* (37), 12037-12040.

101. Andersen, T. L.; Donslund, A. S.; Neumann, K. T.; Skrydstrup, T., Carbonylative Coupling of Alkyl Zinc Reagents with Benzyl Bromides Catalyzed by a Nickel/NN2 Pincer Ligand Complex. *Angewandte Chemie International Edition* **2018,** *57* (3), 800-804.

102. Genna, D. T.; Posner, G. H., Cyanocuprates Convert Carboxylic Acids Directly into Ketones. *Organic Letters* **2011,** *13* (19), 5358-5361.

103. Gudla, V.; Balamurugan, R., AuCl3/AgSbF6-catalyzed rapid epoxide to carbonyl rearrangement. *Tetrahedron Letters* **2012,** *53* (39), 5243-5247.

104. Shimada, T.; Yamamoto, Y., Palladium-Catalyzed Intermolecular Hydroamination of Alkynes: A Dramatic Rate-Enhancement Effect of o-Aminophenol. *Journal of the American Chemical Society* **2002,** *124* (43), 12670-12671.

105. Yin, Q.; Yan, H.; Zhang, Y.; Wang, Y.; Zhang, G.; He, Y.; Zhang, W., Palladium-catalyzed synthesis of 8-allyl or 8-prenylcoumarins by using organotin reagents as multicoupling nucleophiles. *Applied Organometallic Chemistry* **2013,** *27* (2), 85-88.

106. Chen, X.; Chen, Z.; So, C. M., Exploration of Aryl Phosphates in Palladium-Catalyzed Mono-α-arylation of Aryl and Heteroaryl Ketones. *The Journal of Organic Chemistry* **2019,** *84* (10), 6337-6346.

107. Landers, B.; Berini, C.; Wang, C.; Navarro, O., (N-Heterocyclic Carbene)-Pd-Catalyzed Anaerobic Oxidation of Secondary Alcohols and Domino Oxidation−Arylation Reactions. *The Journal of Organic Chemistry* **2011,** *76* (5), 1390-1397.

108. Pandey, G.; Tiwari, S. K.; Budakoti, A.; Sahani, P. K., Transition-metal-free photoredox intermolecular α-arylation of ketones. *Organic Chemistry Frontiers* **2018,** *5* (17), 2610-2614.

109. Fillion, E.; Fishlock, D., Scandium triflate-catalyzed intramolecular Friedel–Crafts acylation with Meldrum's acids: insight into the mechanism. *Tetrahedron* **2009,** *65* (33), 6682-6695.

110. Liu, M.; Hyder, Z.; Sun, Y.; Tang, W.; Xu, L.; Xiao, J., Efficient synthesis of alkyl aryl ketones & ketals via palladium-catalyzed regioselective arylation of vinyl ethers. *Organic & Biomolecular Chemistry* **2010,** *8* (9), 2012-2015.

111. Gao, K.; Yorimitsu, H.; Osuka, A., α-Arylation of Ketimines with Aryl Sulfides at a Low Palladium Catalyst Loading. *Angewandte Chemie International Edition* **2016,** *55* (14), 4573-4576.

112. Chu, Y.-T.; Chanda, K.; Lin, P.-H.; Huang, M. H., Aqueous Phase Synthesis of Palladium Tripod Nanostructures for Sonogashira Coupling Reactions. *Langmuir* **2012,** *28* (30), 11258-11264.

113. Pfeifer, L.; Gouverneur, V., Controlled Single and Double Iodofluorination of Alkynes with DIH- and HF-Based Reagents. *Organic Letters* **2018,** *20* (6), 1576-1579.

114. Egi, M.; Kawai, T.; Umemura, M.; Akai, S., Heteropolyacid-Catalyzed Direct Deoxygenation of Propargyl and Allyl Alcohols. *The Journal of Organic Chemistry* **2012,** *77* (16), 7092-7097.

115. Qrareya, H.; Protti, S.; Fagnoni, M., Aryl Imidazylates and Aryl Sulfates As Electrophiles in Metal-Free ArSN1 Reactions. *The Journal of Organic Chemistry* **2014,** *79* (23), 11527-11533.

116. Saleh, S.; Picquet, M.; Meunier, P.; Hierso, J.-C., A straightforward copper-free palladium methodology for the selective alkynylation of a wide variety of S-, O-, and N-based mono- and diheterocyclic bromides and chlorides. *Tetrahedron* **2009,** *65* (34), 7146-7150.

117. Molander, G. A.; Katona, B. W.; Machrouhi, F., Development of the Suzuki−Miyaura Cross-Coupling Reaction: Use of Air-Stable Potassium Alkynyltrifluoroborates in Aryl Alkynylations. *The Journal of Organic Chemistry* **2002,** *67* (24), 8416-8423.

118. Hao, W.; Xi, Z.; Cai, M., A Practical Synthesis of Biaryls and Aromatic Acetylenes by Stille Coupling in Room-Temperature Ionic Liquids. *Synthetic Communications* **2012,** *42* (16), 2396-2406.

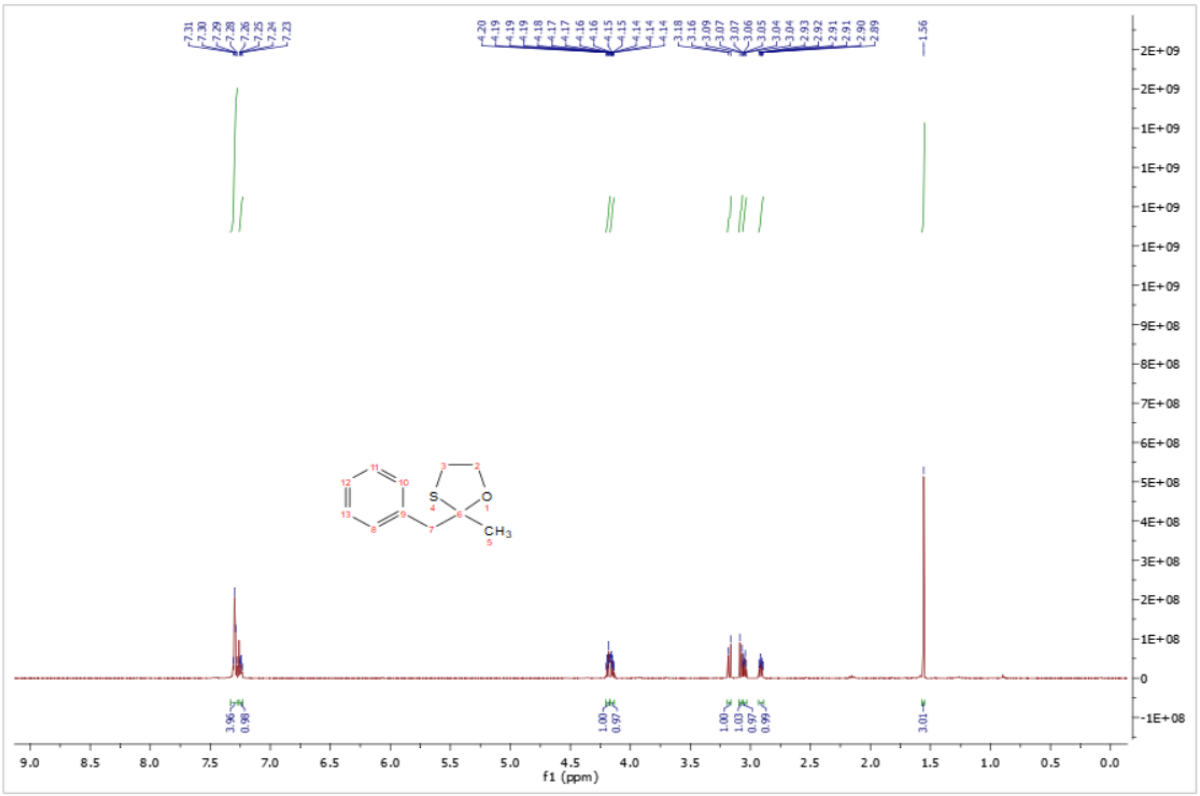
119. Gregori, B. J.; Schwarzhuber, F.; Pöllath, S.; Zweck, J.; Fritsch, L.; Schoch, R.; Bauer, M.; Jacobi von Wangelin, A., Stereoselective Alkyne Hydrogenation by using a Simple Iron Catalyst. *ChemSusChem* **2019,** *12* (16), 3864-3870.

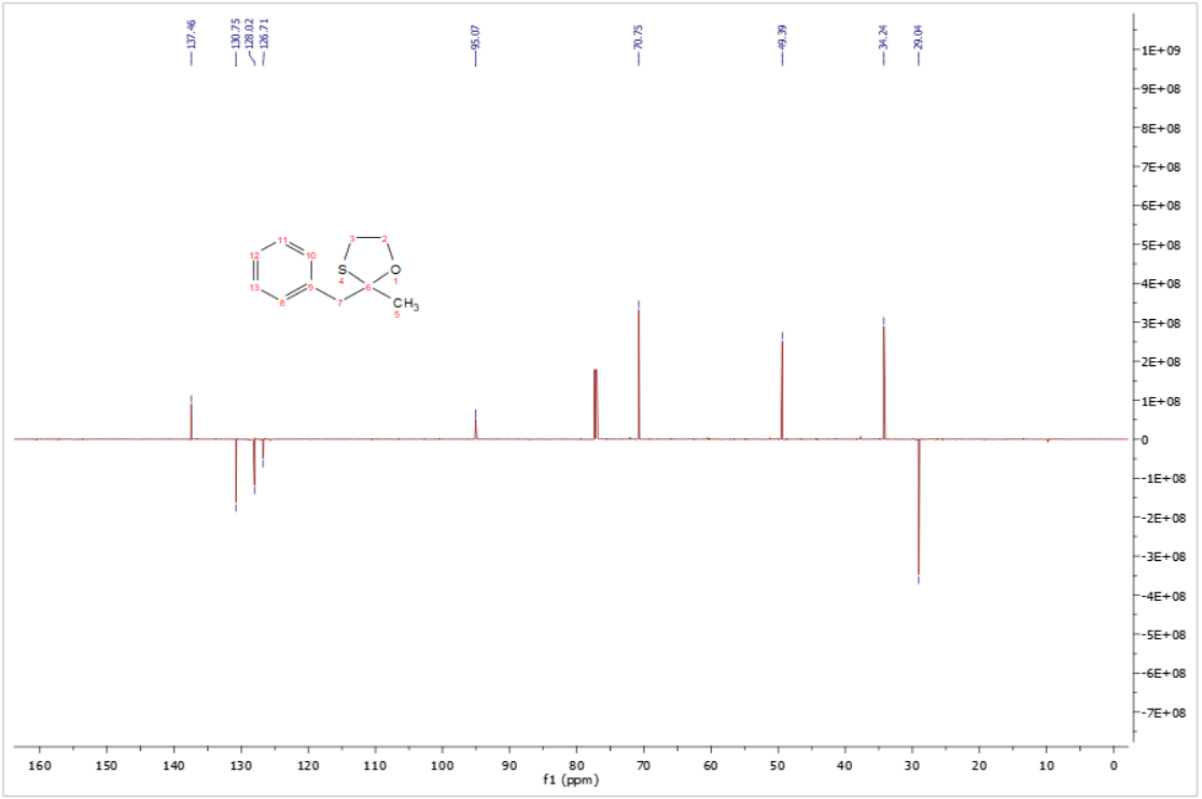
120. Guo, W.-H.; Zhao, H.-Y.; Luo, Z.-J.; Zhang, S.; Zhang, X., Fluoroalkylation–Borylation of Alkynes: An Efficient Method To Obtain (Z)-Tri- and Tetrasubstituted Fluoroalkylated Alkenylboronates. *ACS Catalysis* **2019,** *9* (1), 38-43.

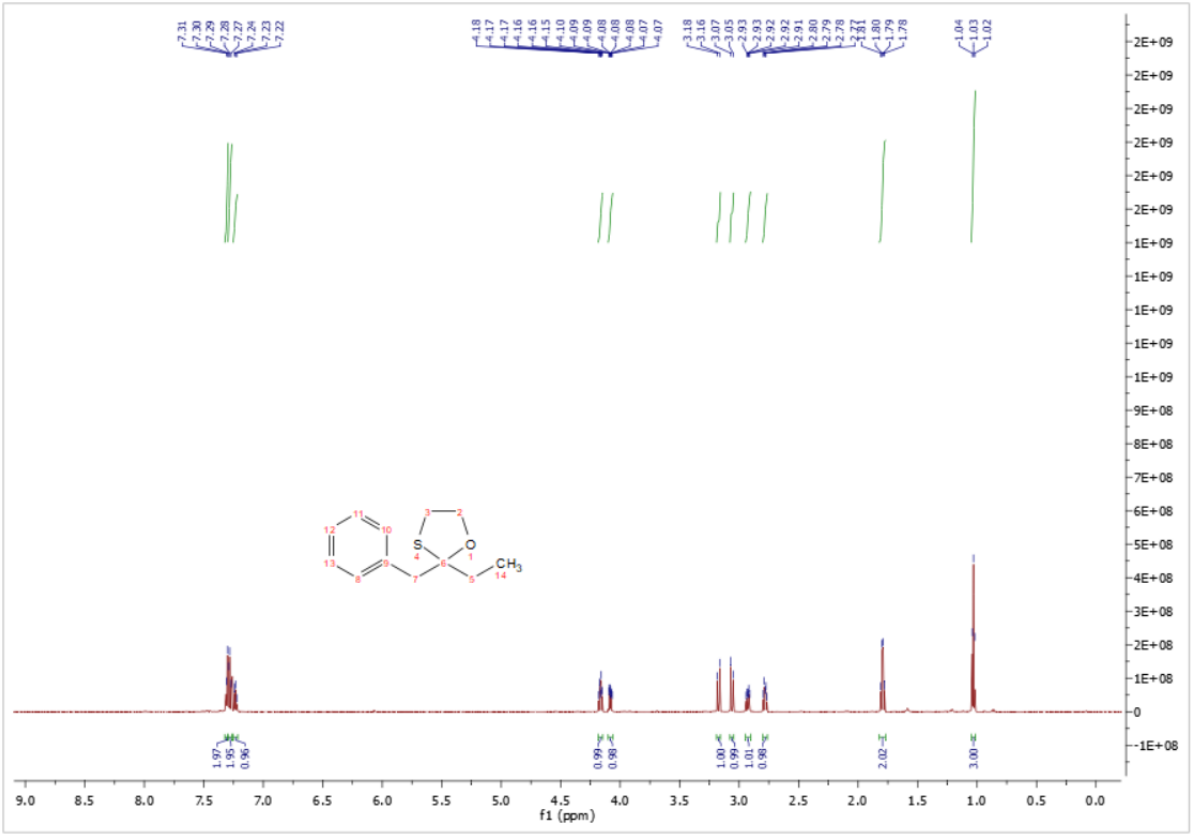
121. Ackermann, L.; Lygin, A. V., Cationic Ruthenium(II) Catalysts for Oxidative C–H/N–H Bond Functionalizations of Anilines with Removable Directing Group: Synthesis of Indoles in Water. *Organic Letters* **2012,** *14* (3), 764-767.

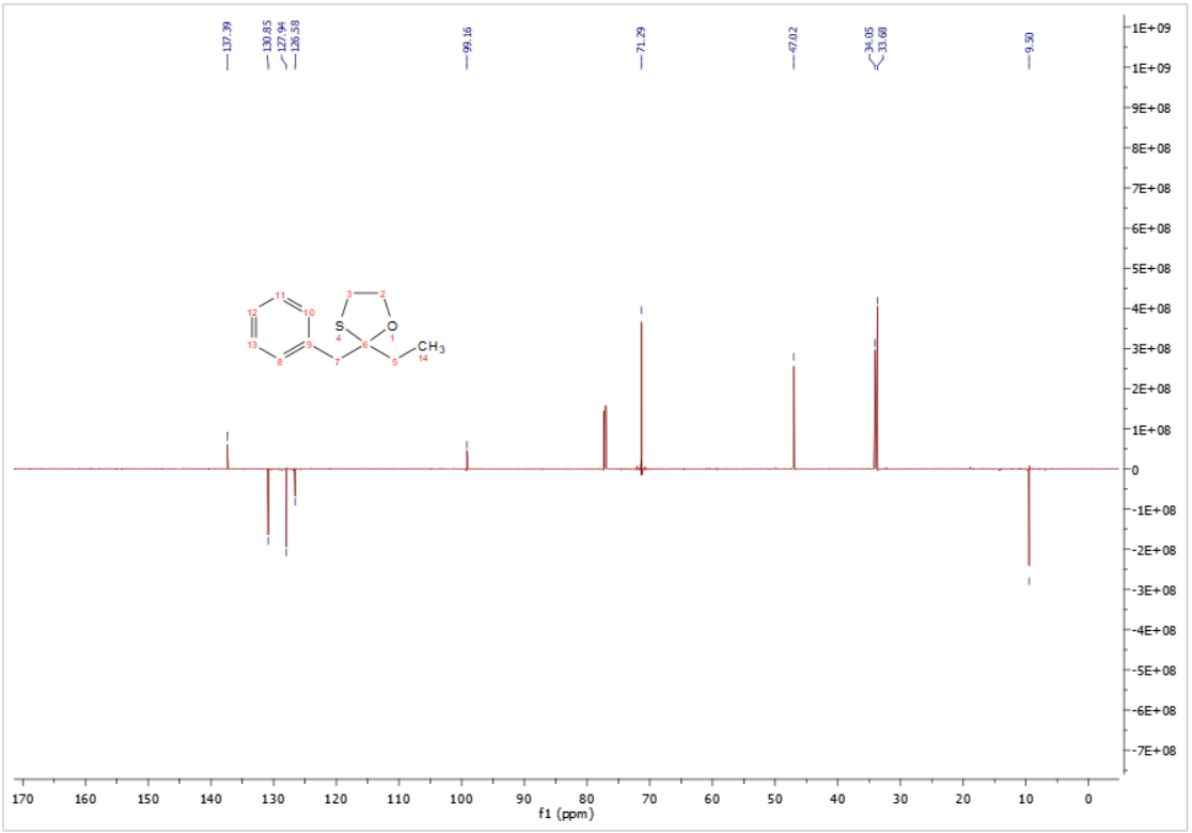
122. Jung, Y.; Kim, I., Chemoselective reduction of quinols as an alternative to Sonogashira coupling: synthesis of polysubstituted benzofurans. *Organic & Biomolecular Chemistry* **2016,** *14* (44), 10454-10472.

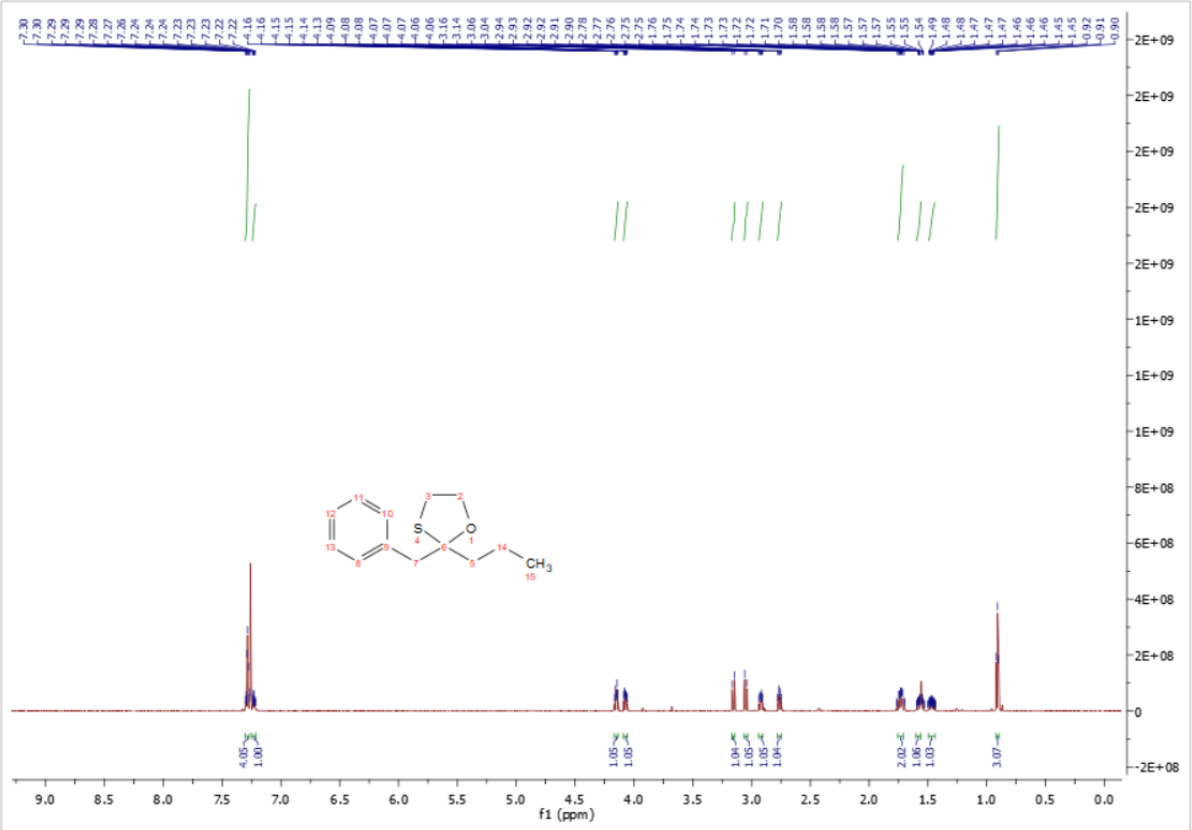
5.0 Appendix: ^{1}H and ^{13}C NMR Spectra

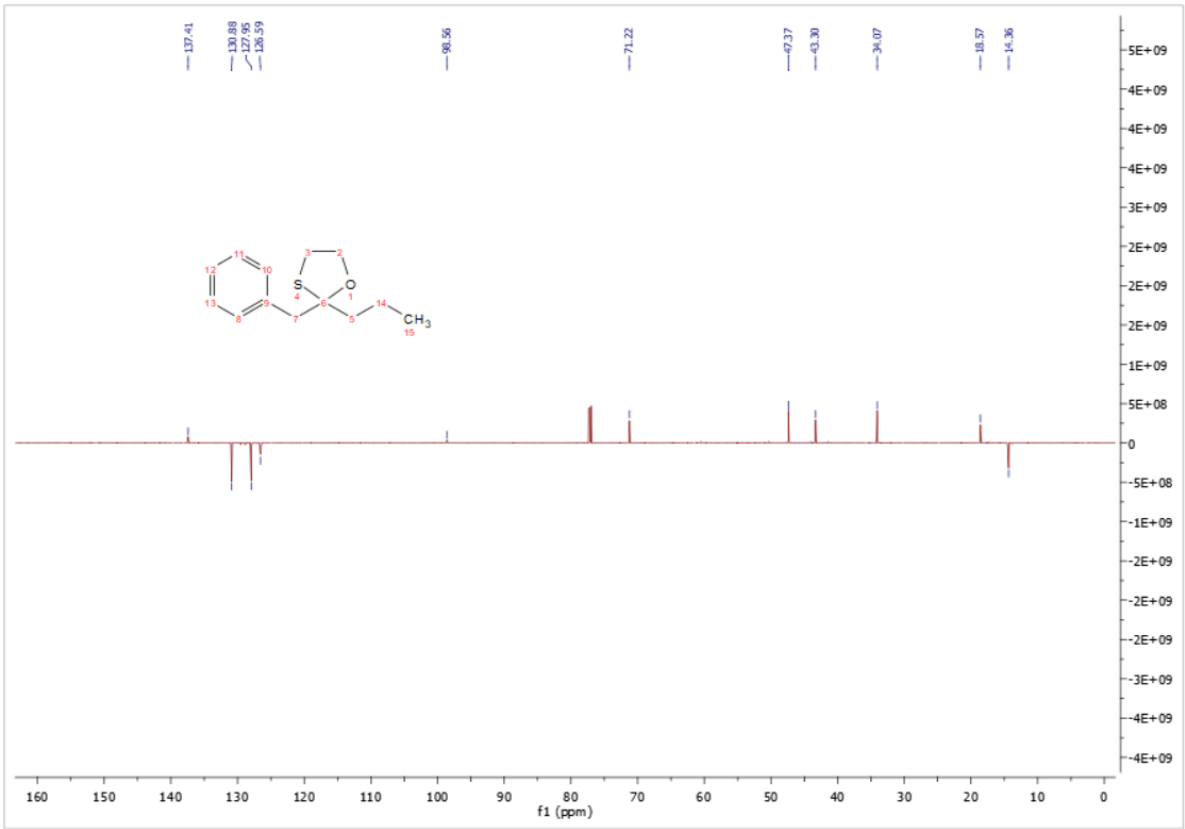


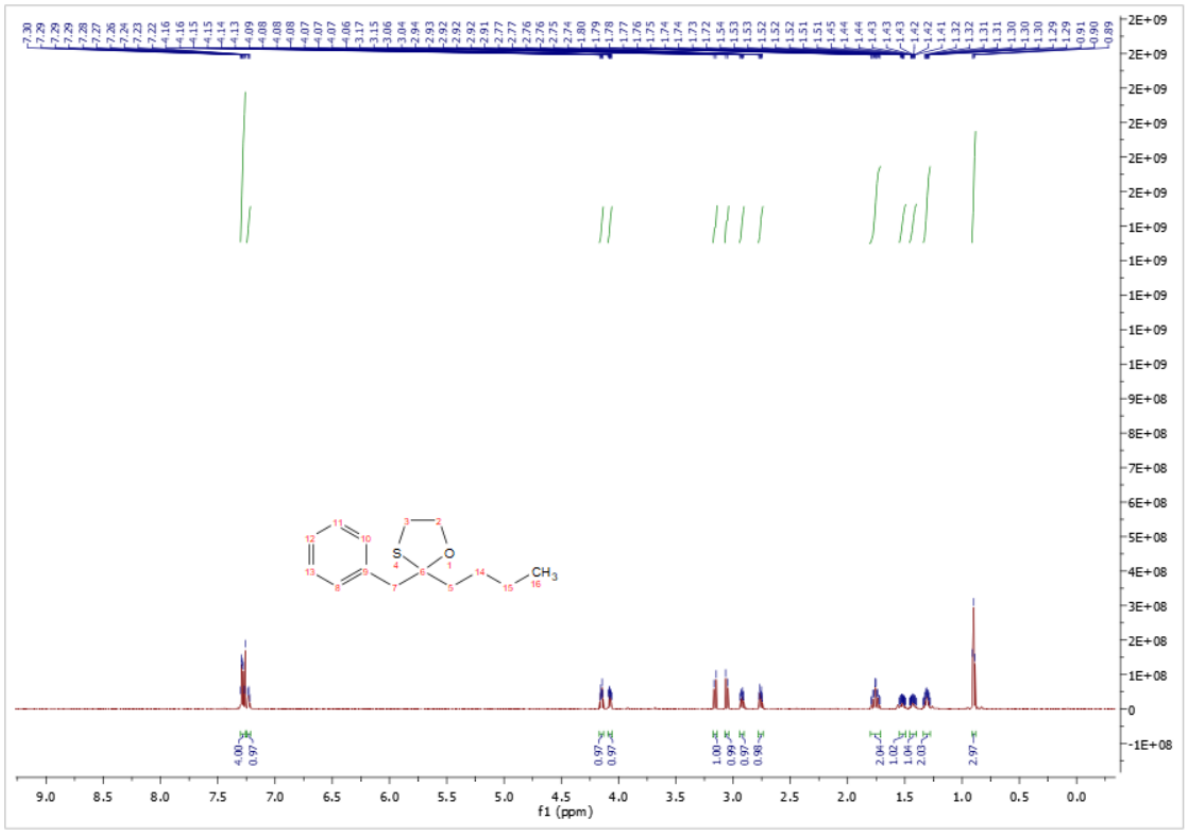


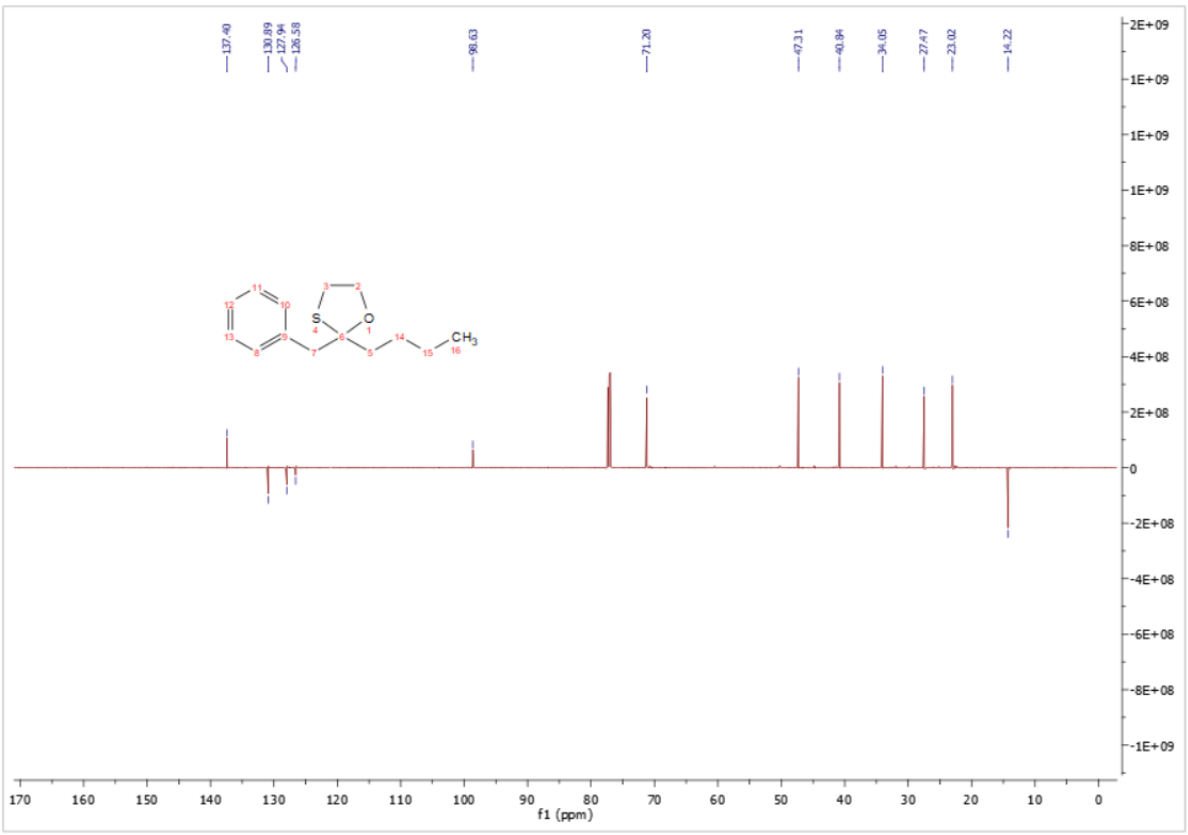

f1 (ppm)

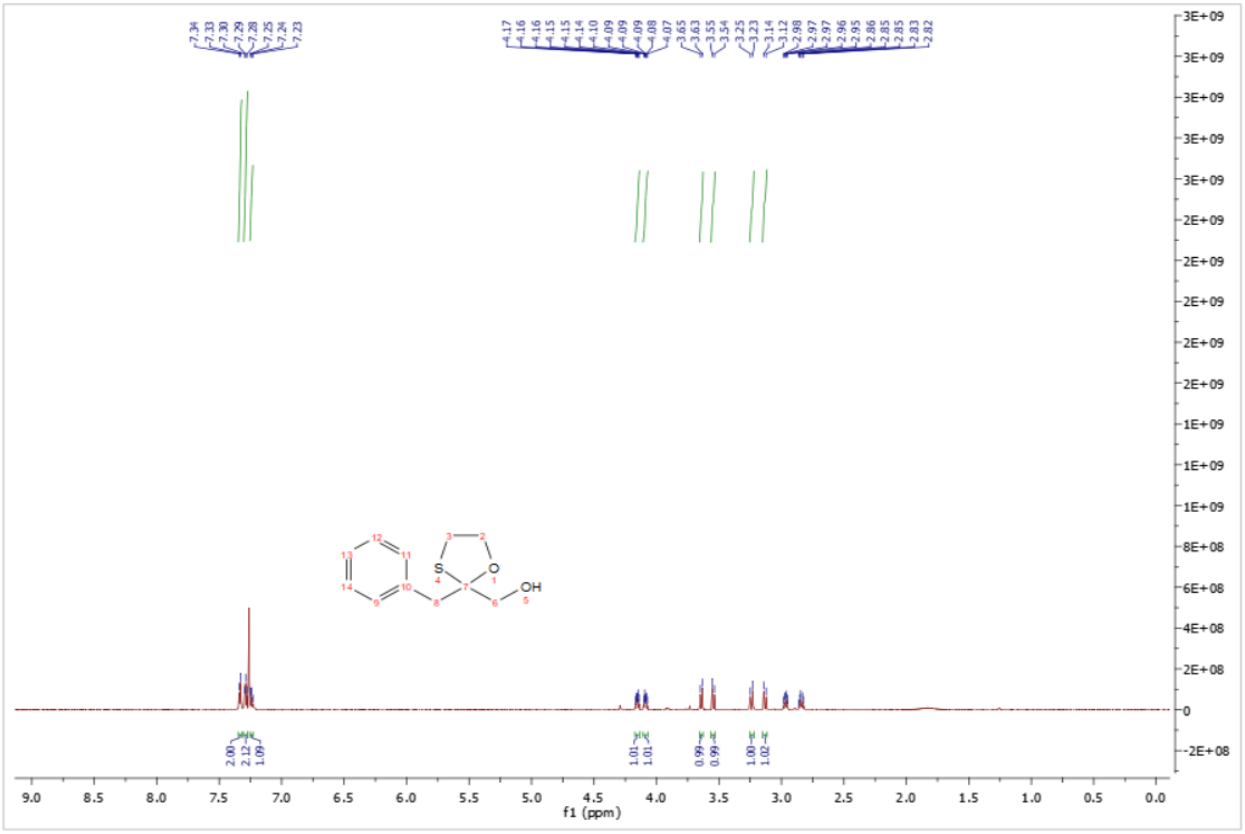

f1 (ppm)

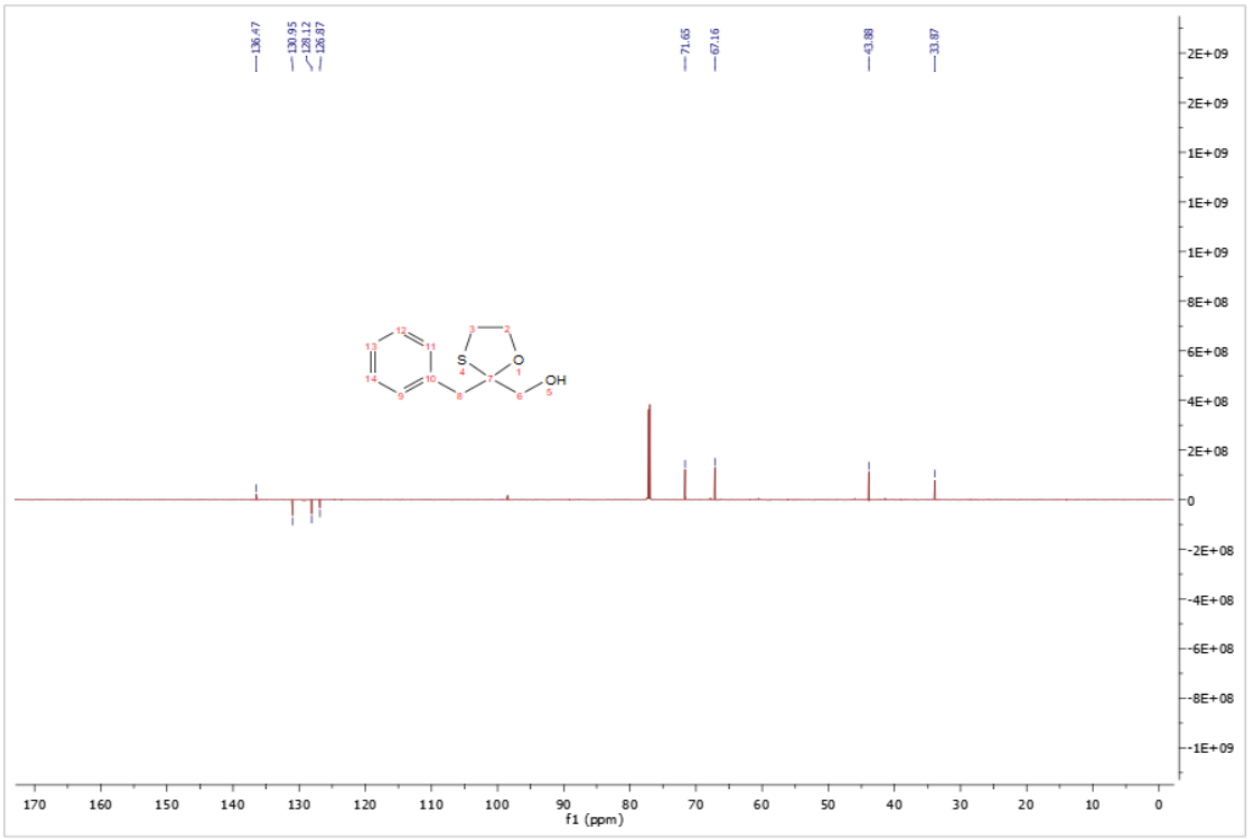

f1 (ppm)

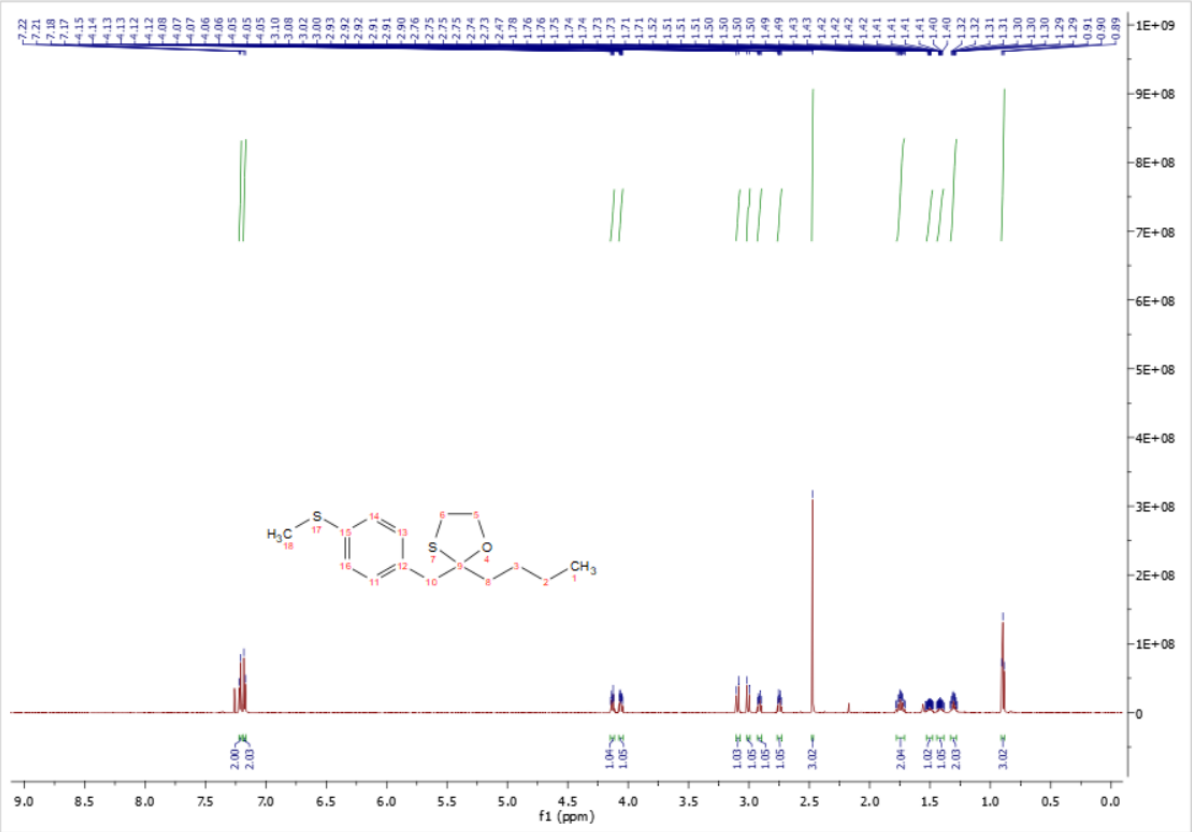

137.41
130.88
127.95
126.59
98.56
71.22
47.17
43.30
34.07
18.57
14.36
f1 (ppm)

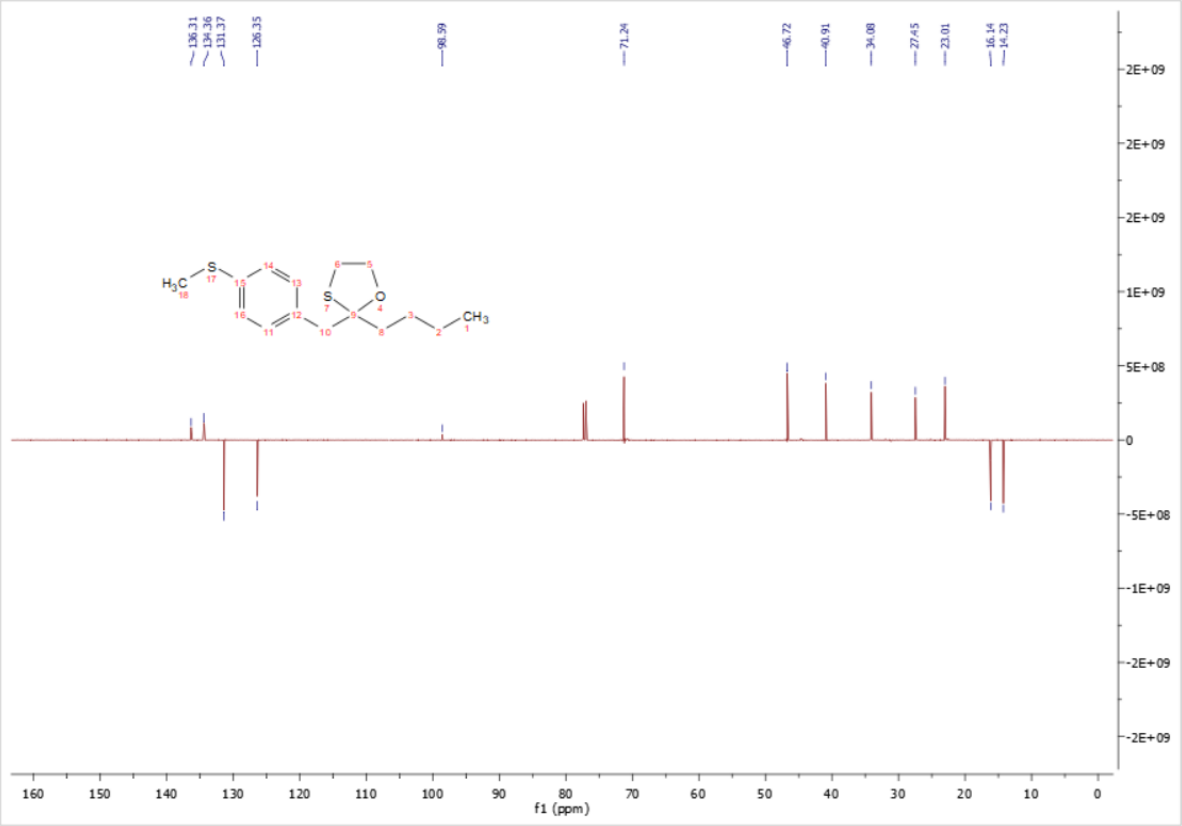

f1 (ppm)

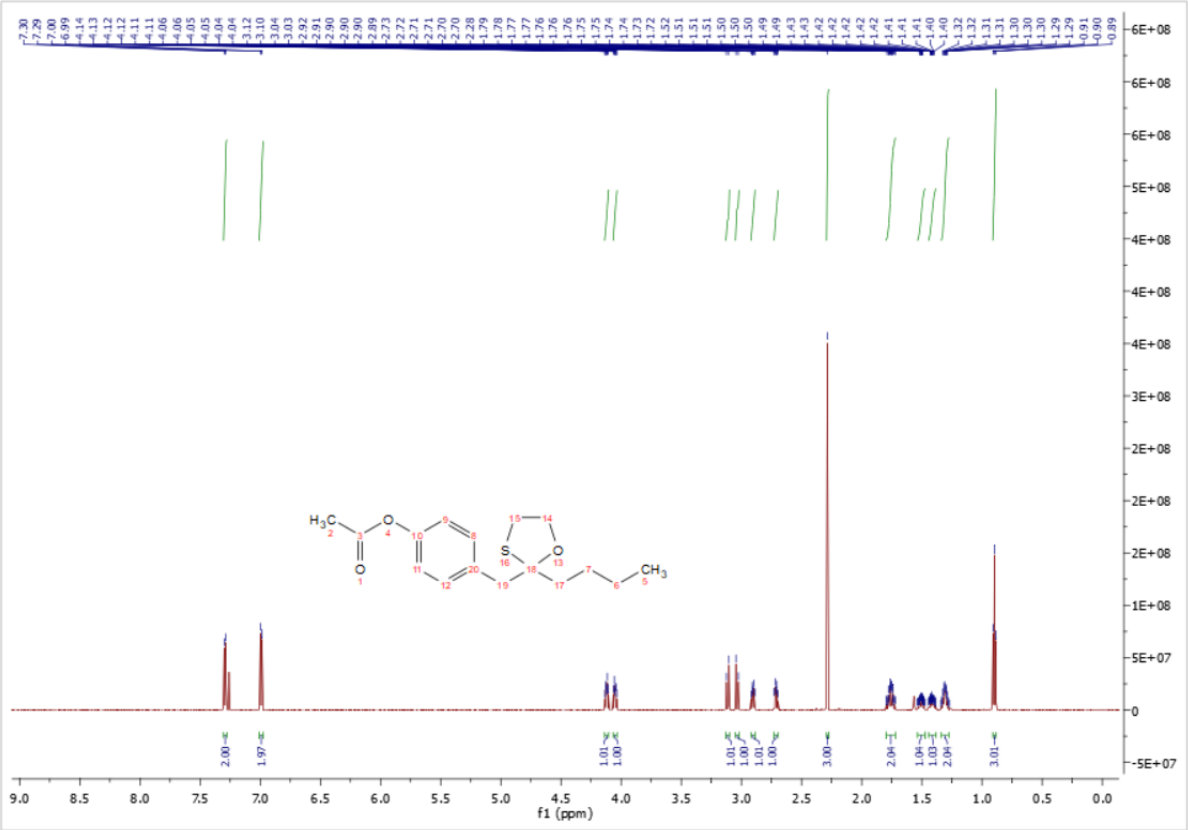

f1 (ppm)

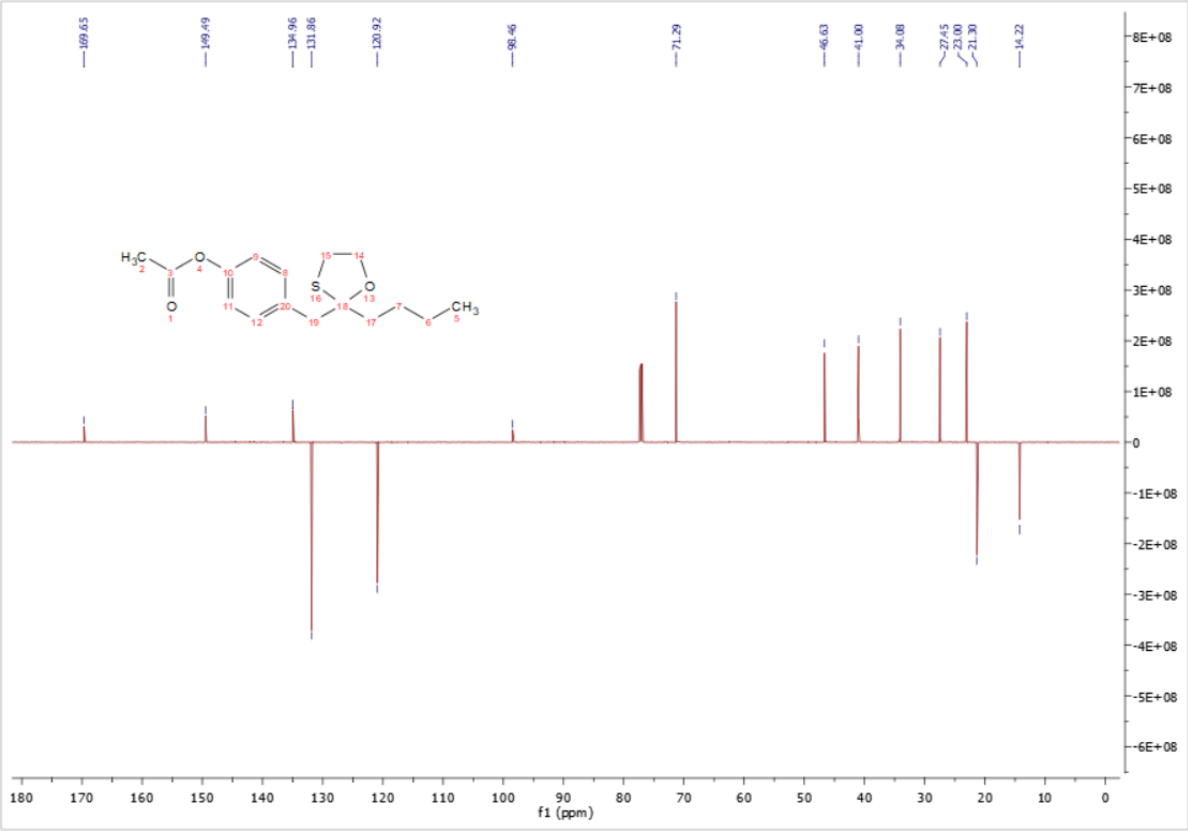

f1 (ppm)

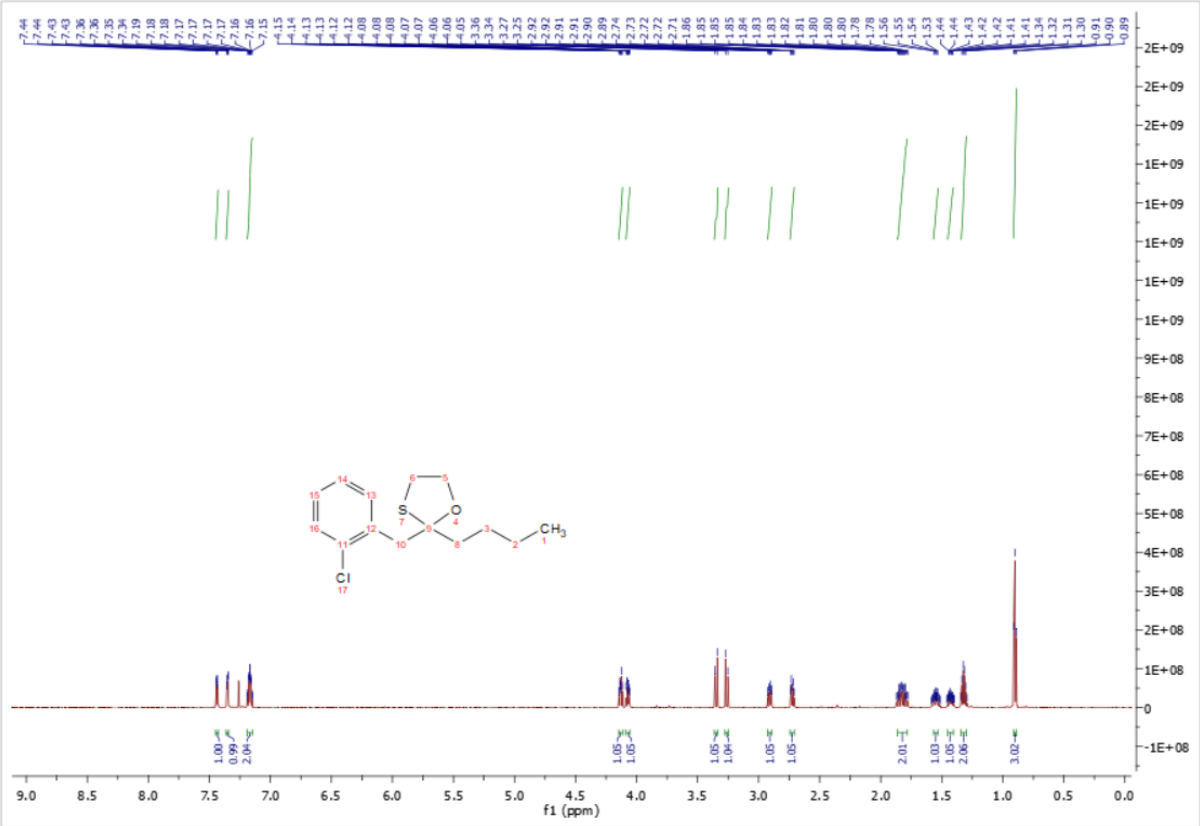

f1 (ppm)

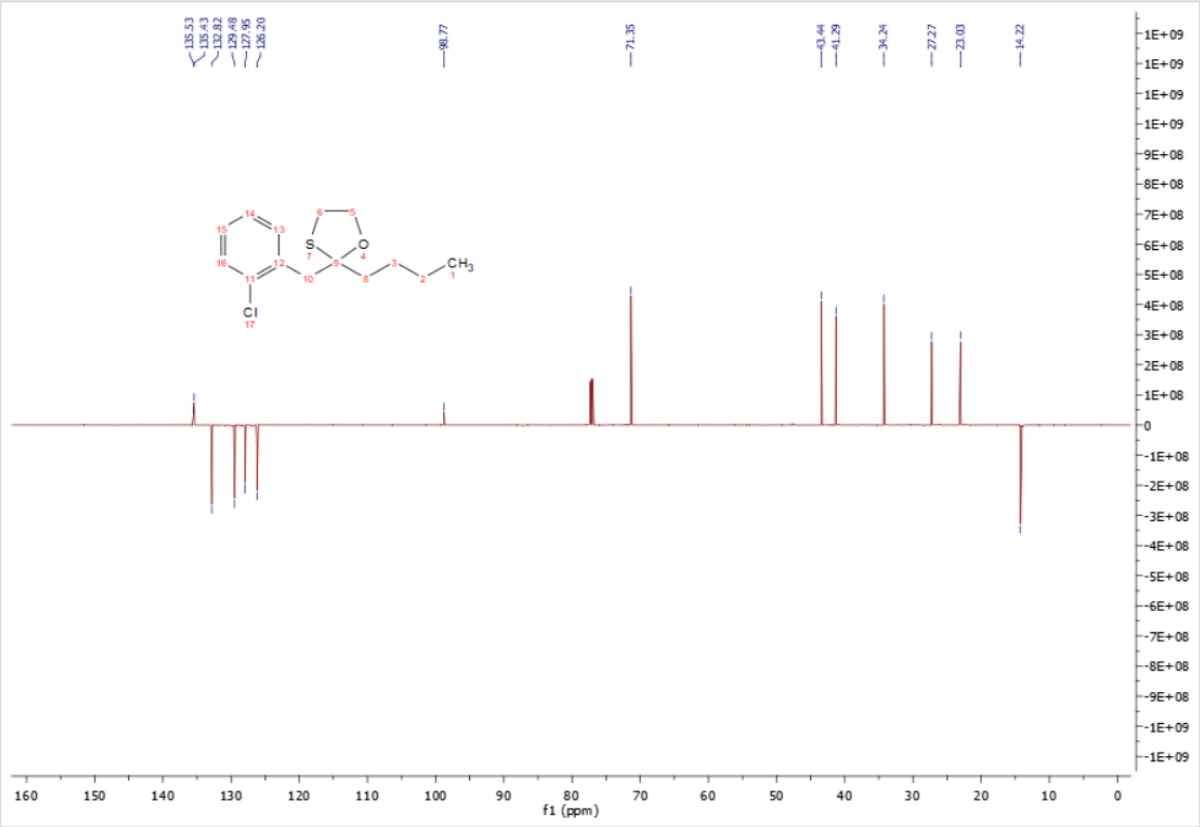

f1 (ppm)

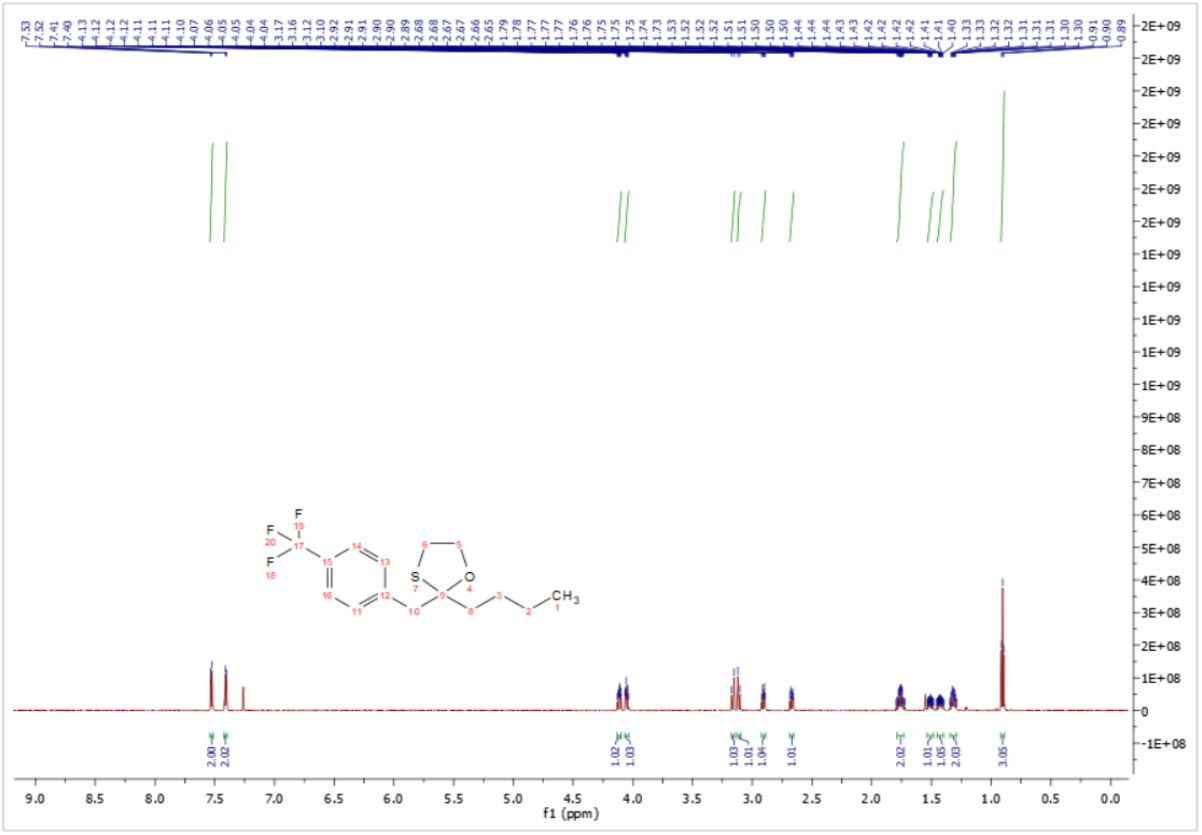

f1 (ppm)

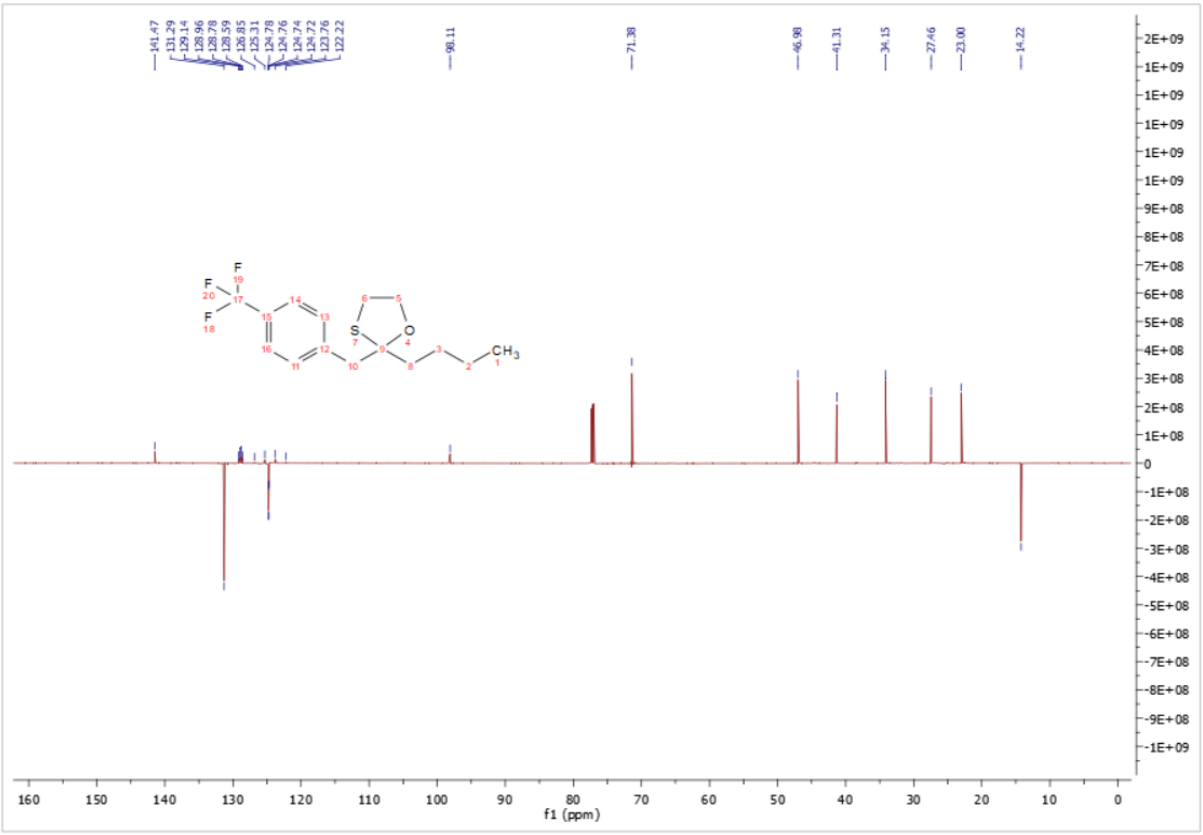

f1 (ppm)

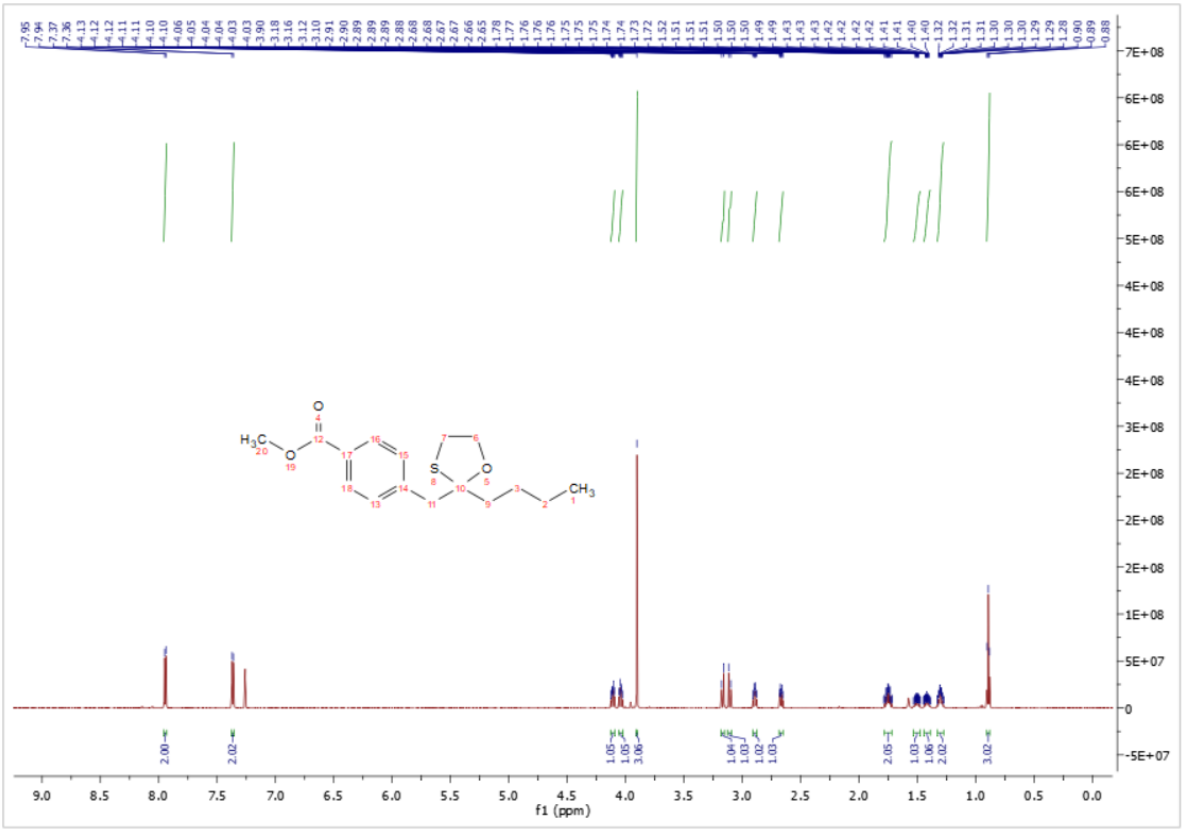

f1 (ppm)

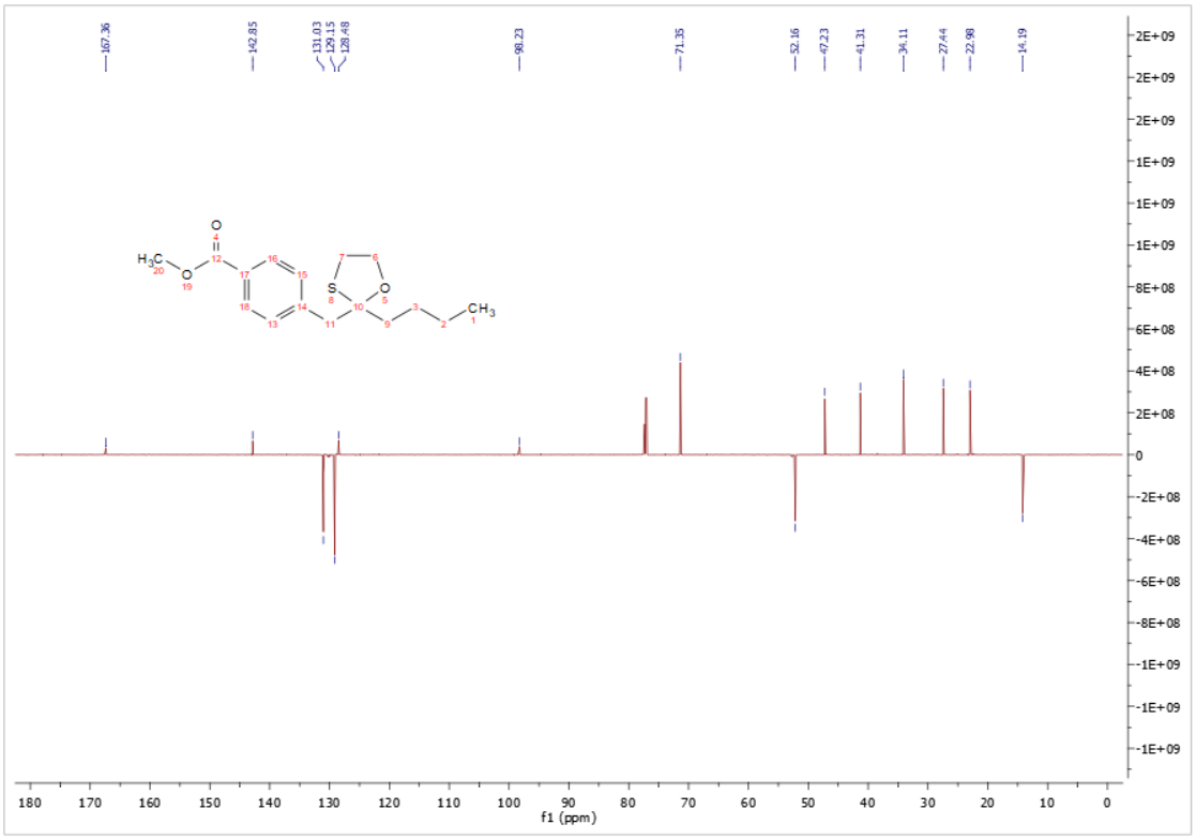

f1 (ppm)
CH3
Cl
S
O

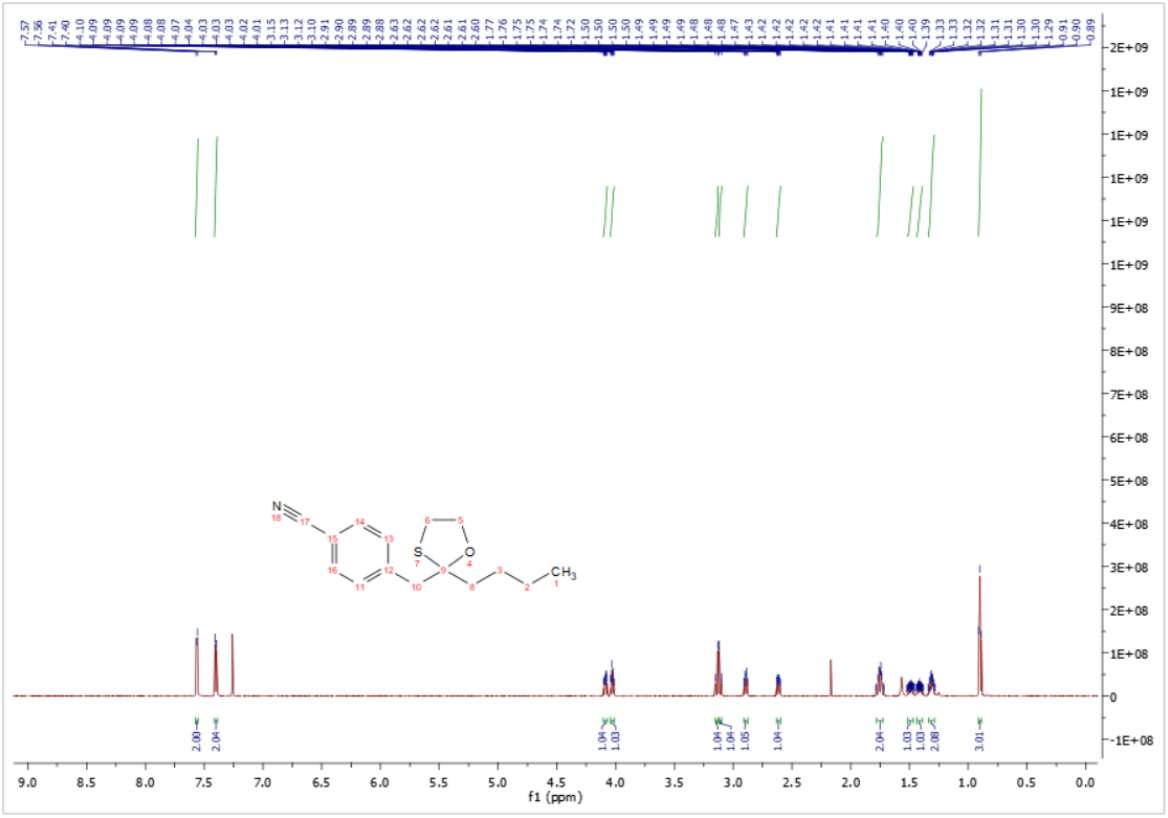

135.53
135.43
132.82
129.48
127.95
126.20
98.77
71.35
63.44
41.29
34.24
27.27
23.03
14.22
f1 (ppm)
CH3
Cl
S
O

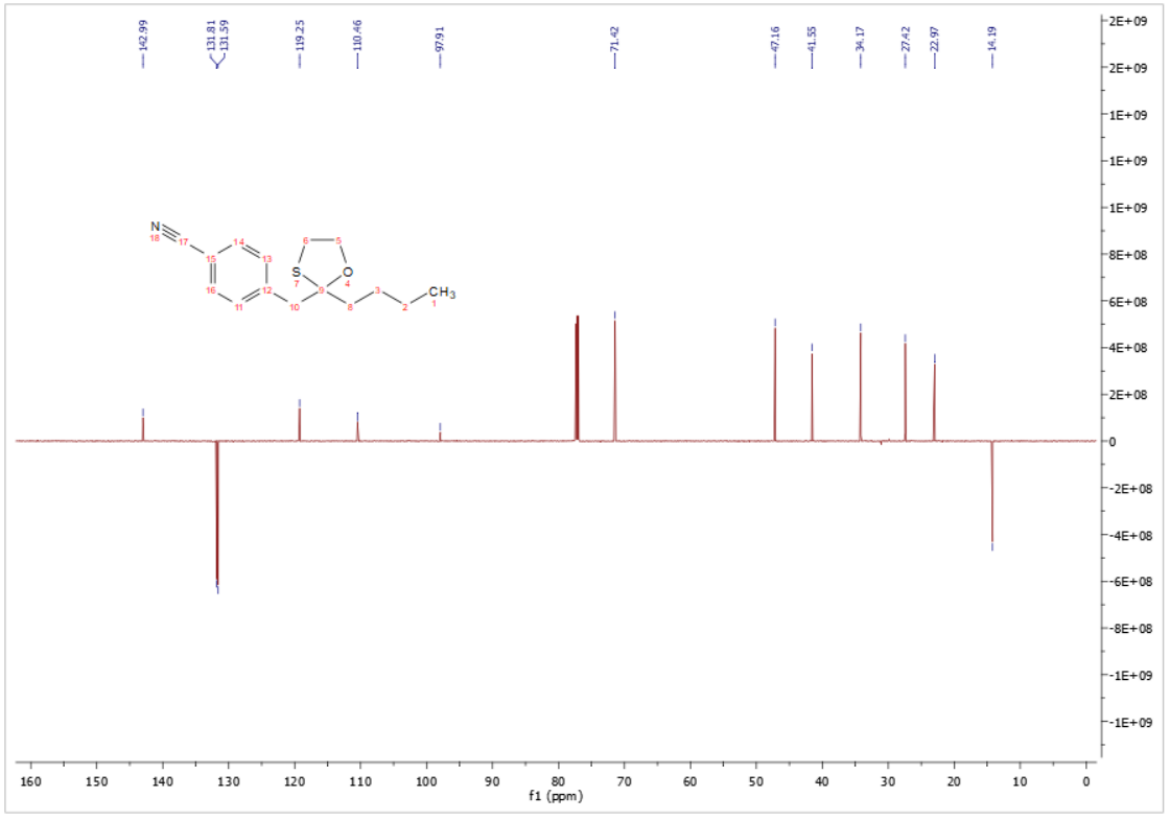

f1 (ppm)

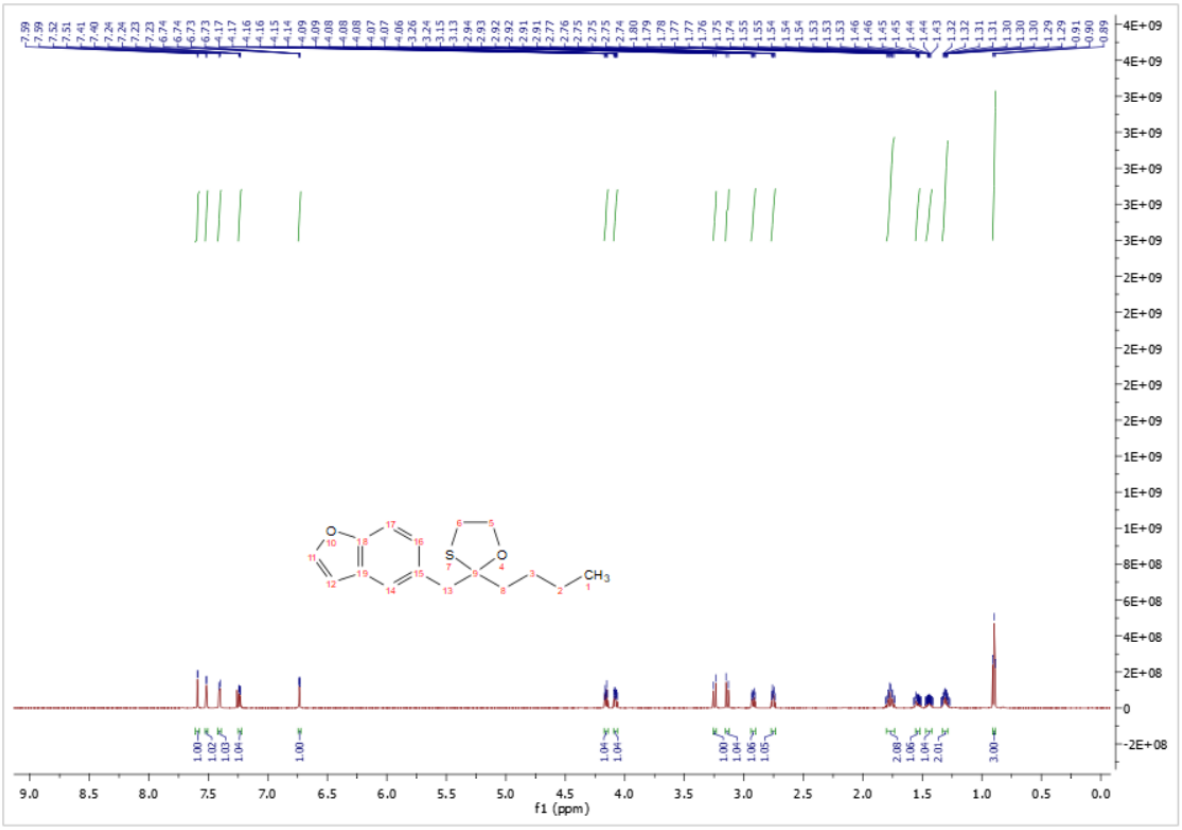

f1 (ppm)

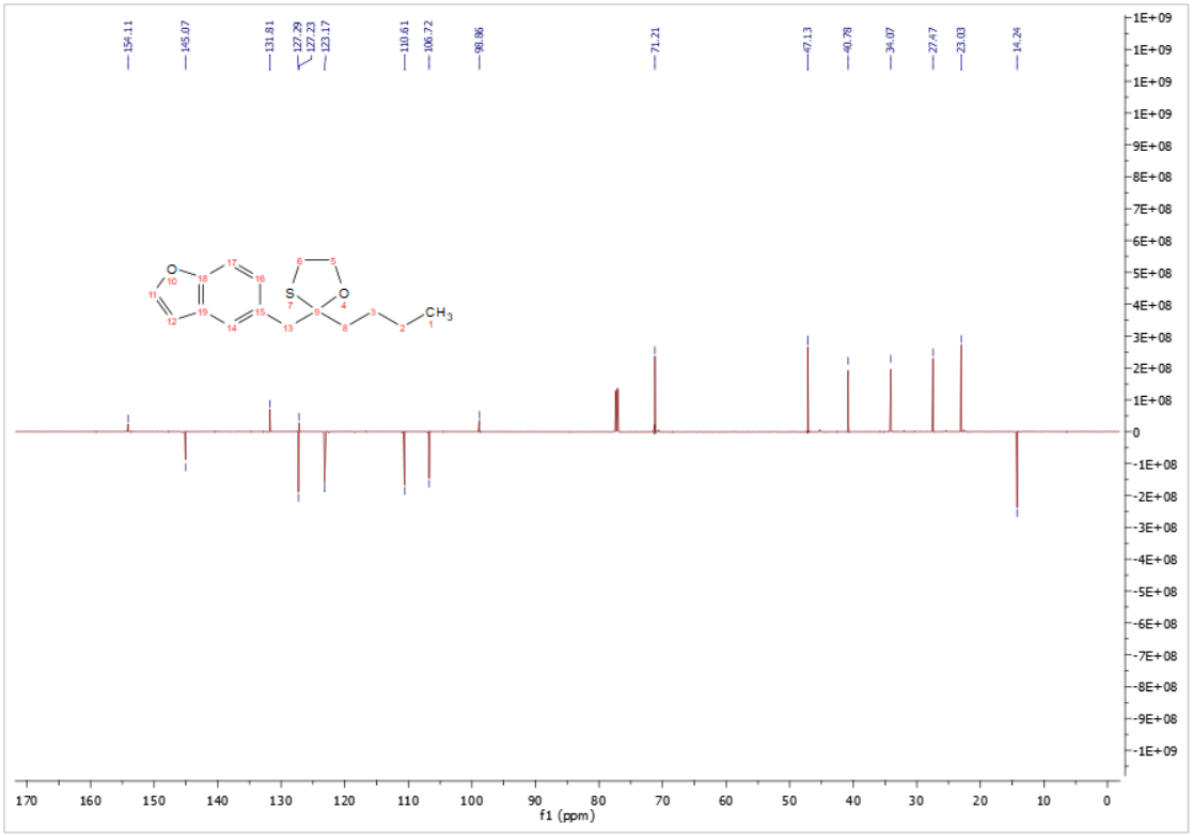

f1 (ppm)

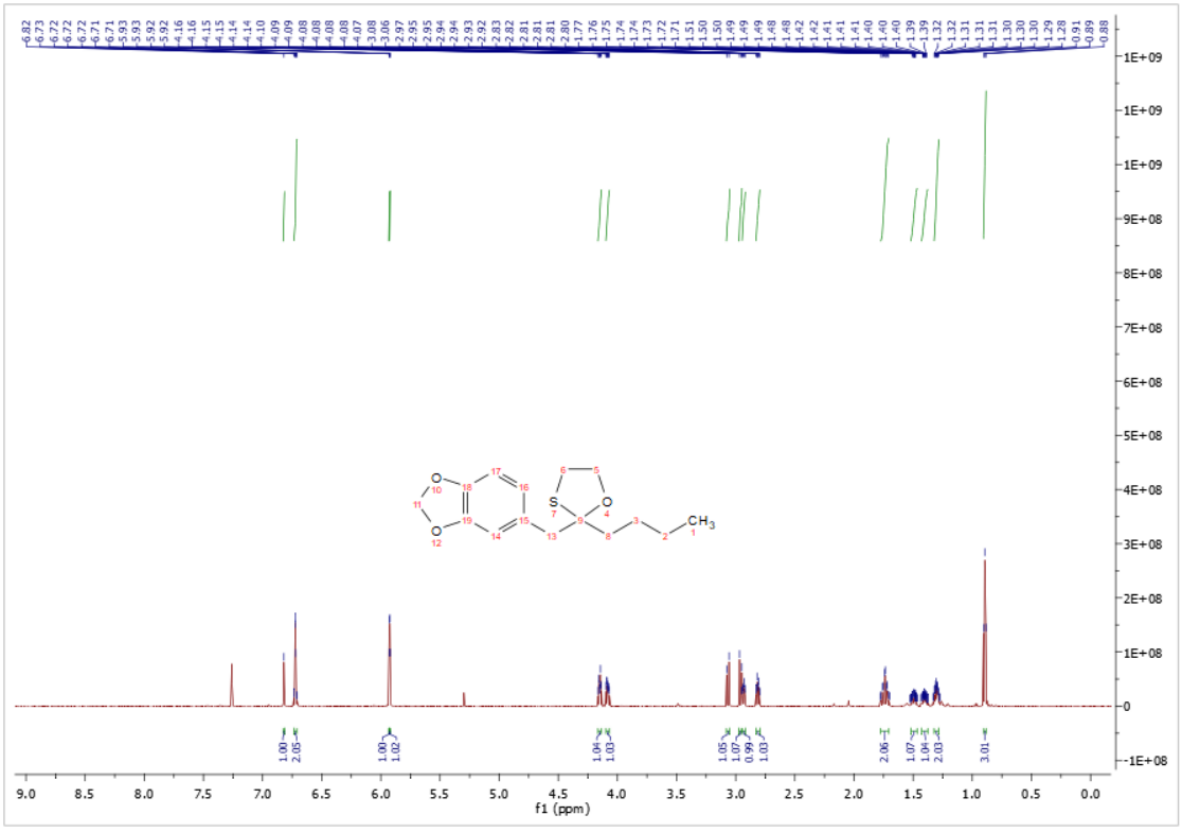

f1 (ppm)

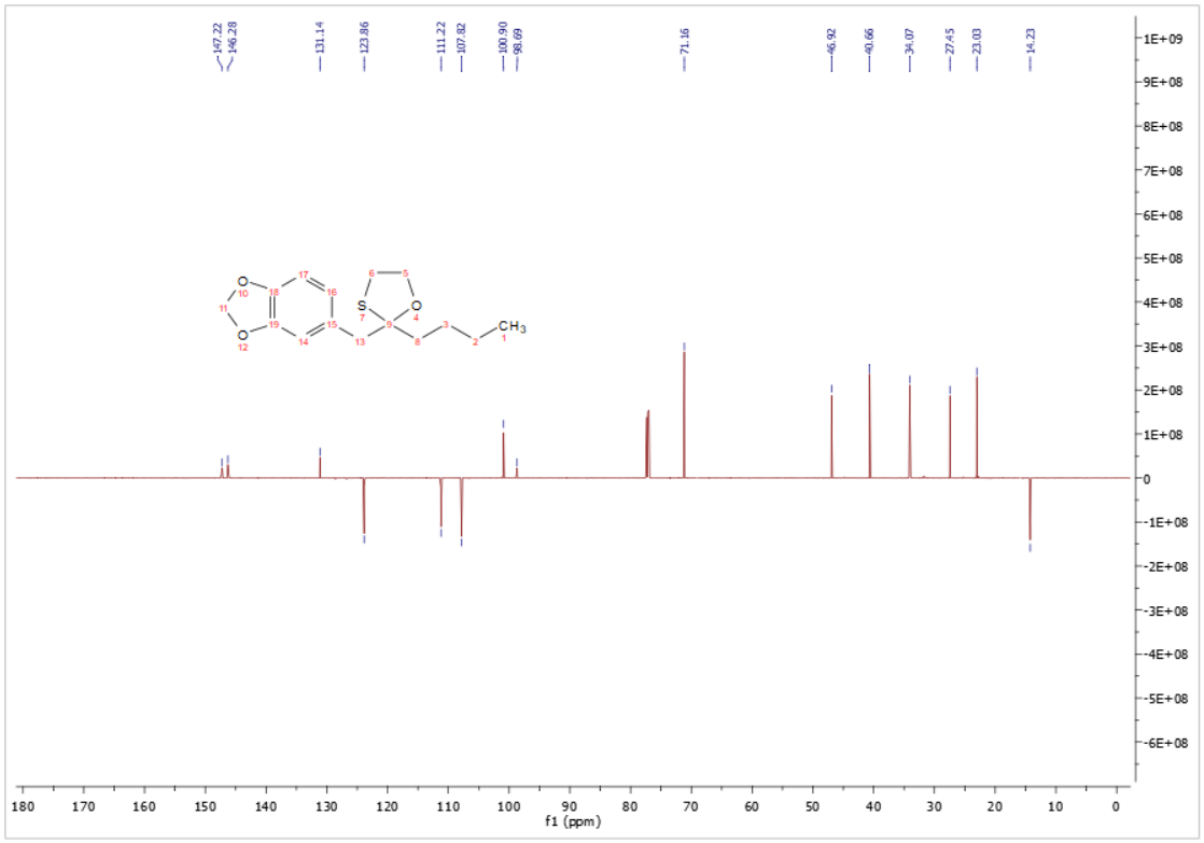

f1 (ppm)

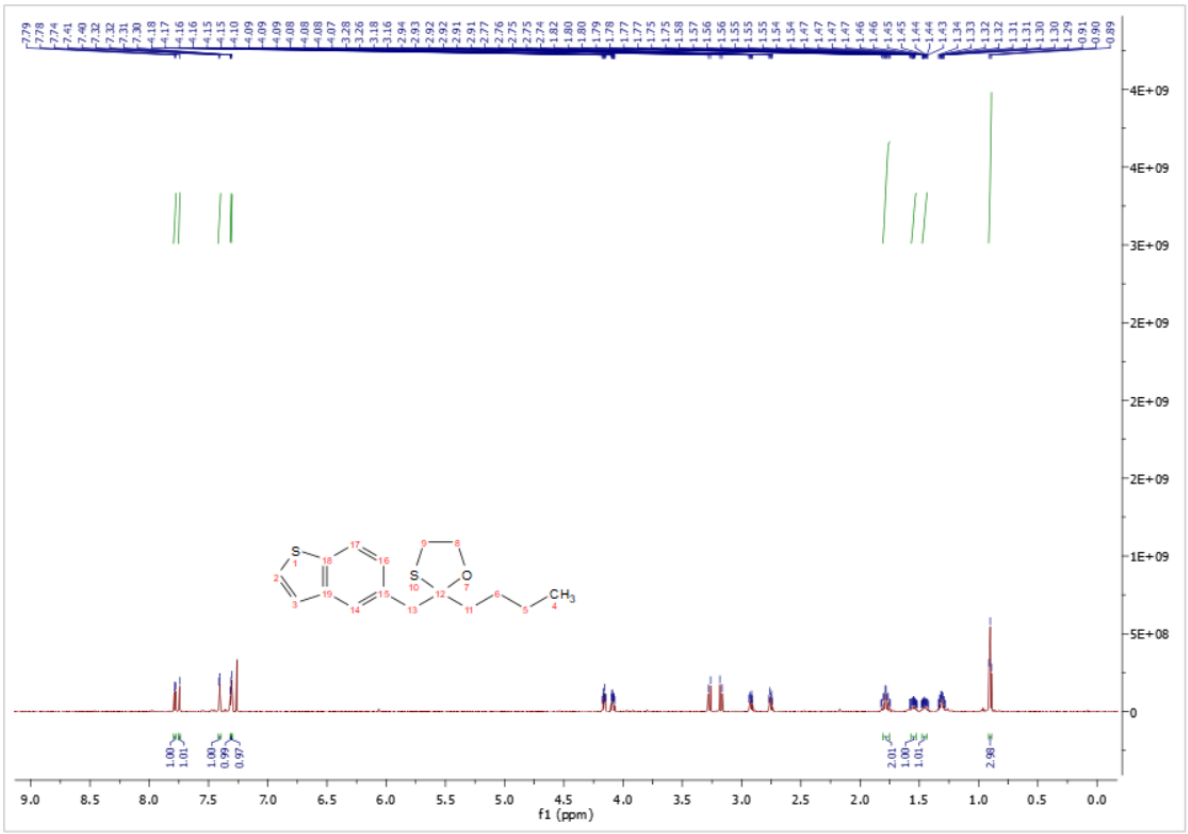

142.99
131.81
131.59
119.25
110.46
97.91
71.42
47.16
41.55
34.17
27.42
22.97
14.19
f1 (ppm)

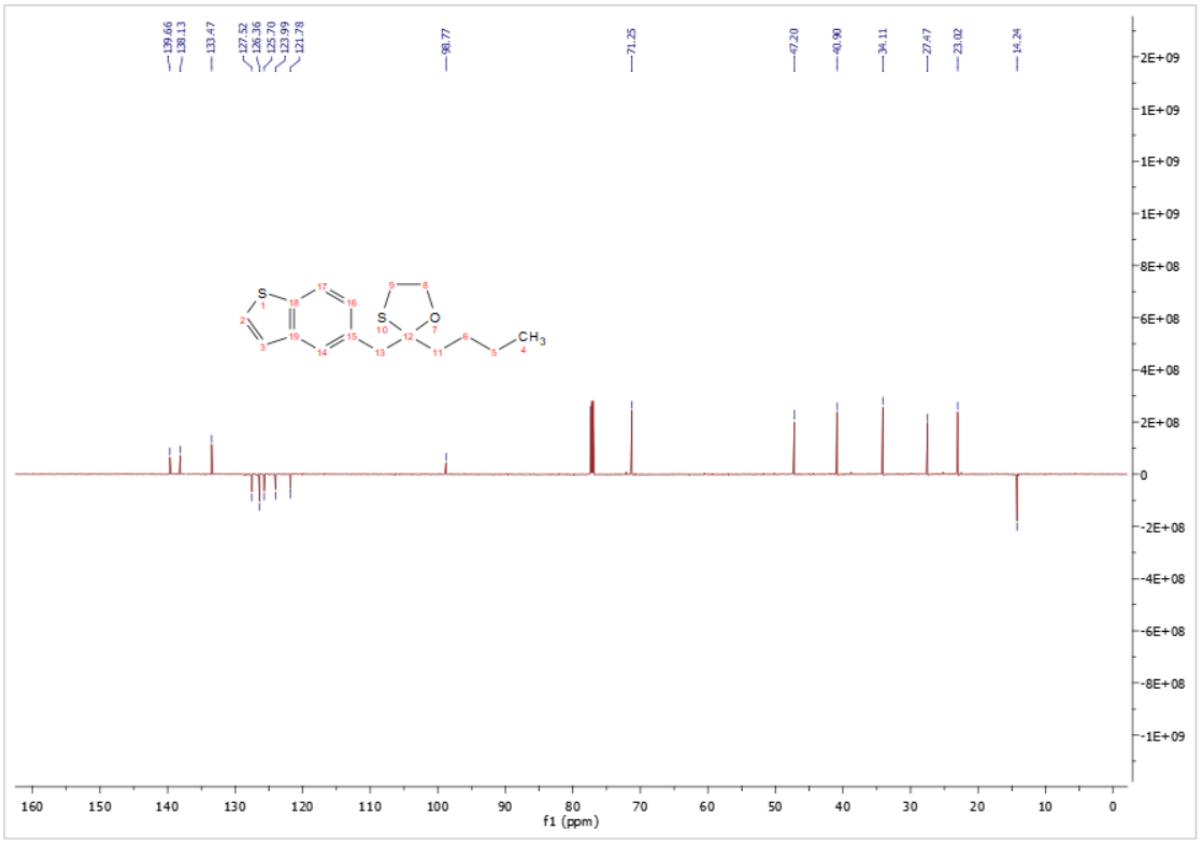

f1 (ppm)

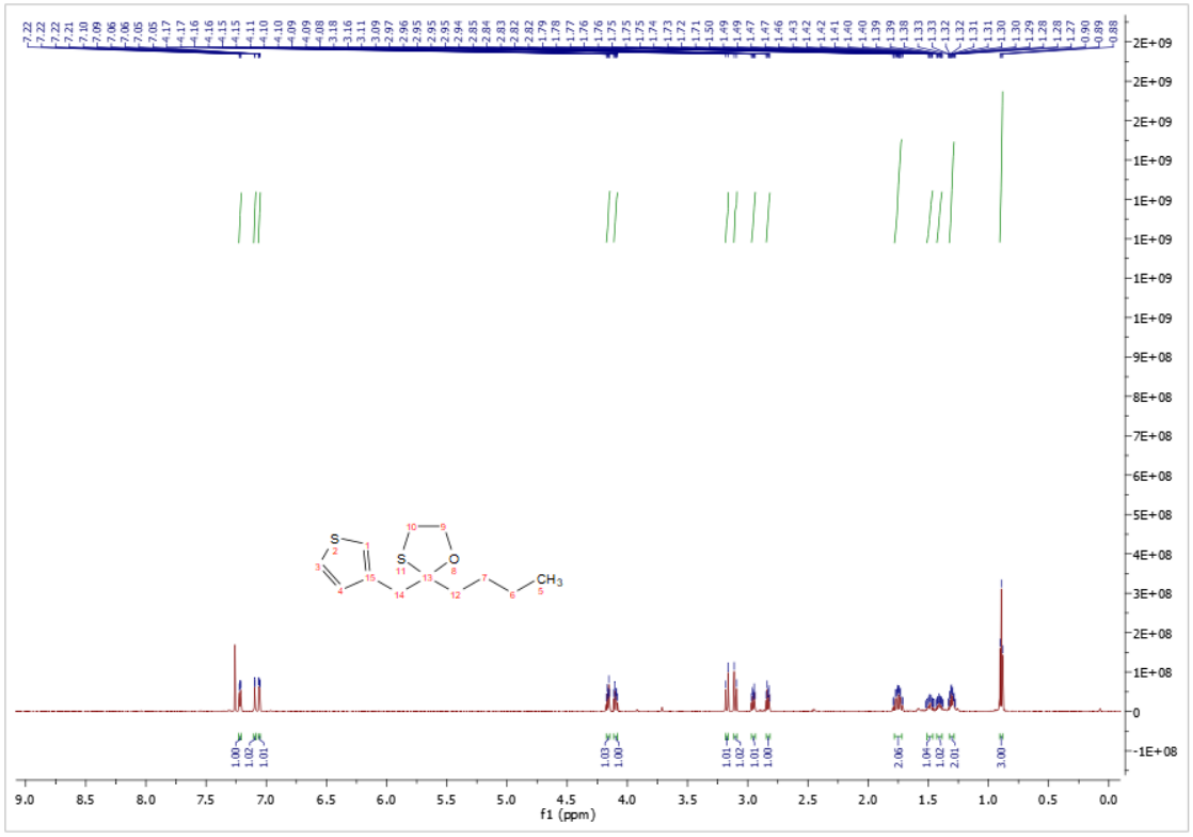

154.11
145.07
131.81
127.29
127.23
123.17
110.61
106.72
98.86
71.21
67.13
60.78
34.07
27.47
23.03
14.24
f1 (ppm)

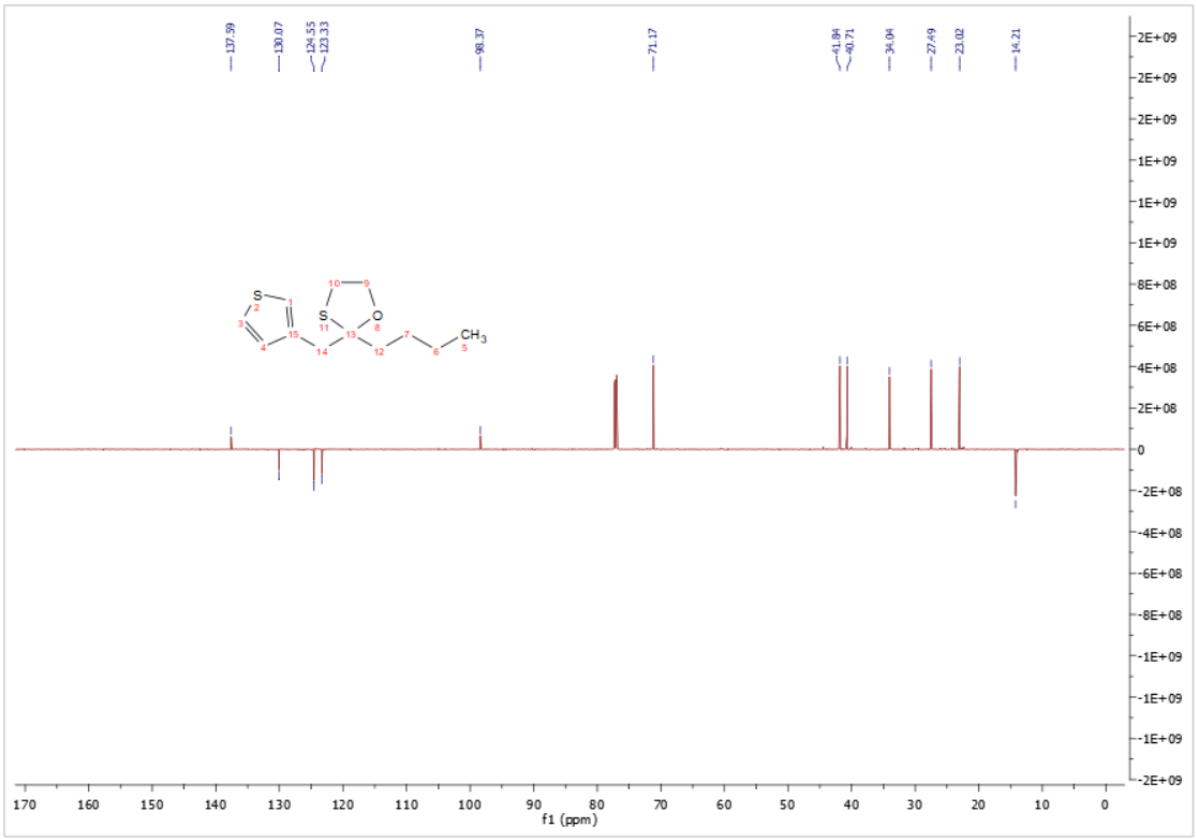

f1 (ppm)

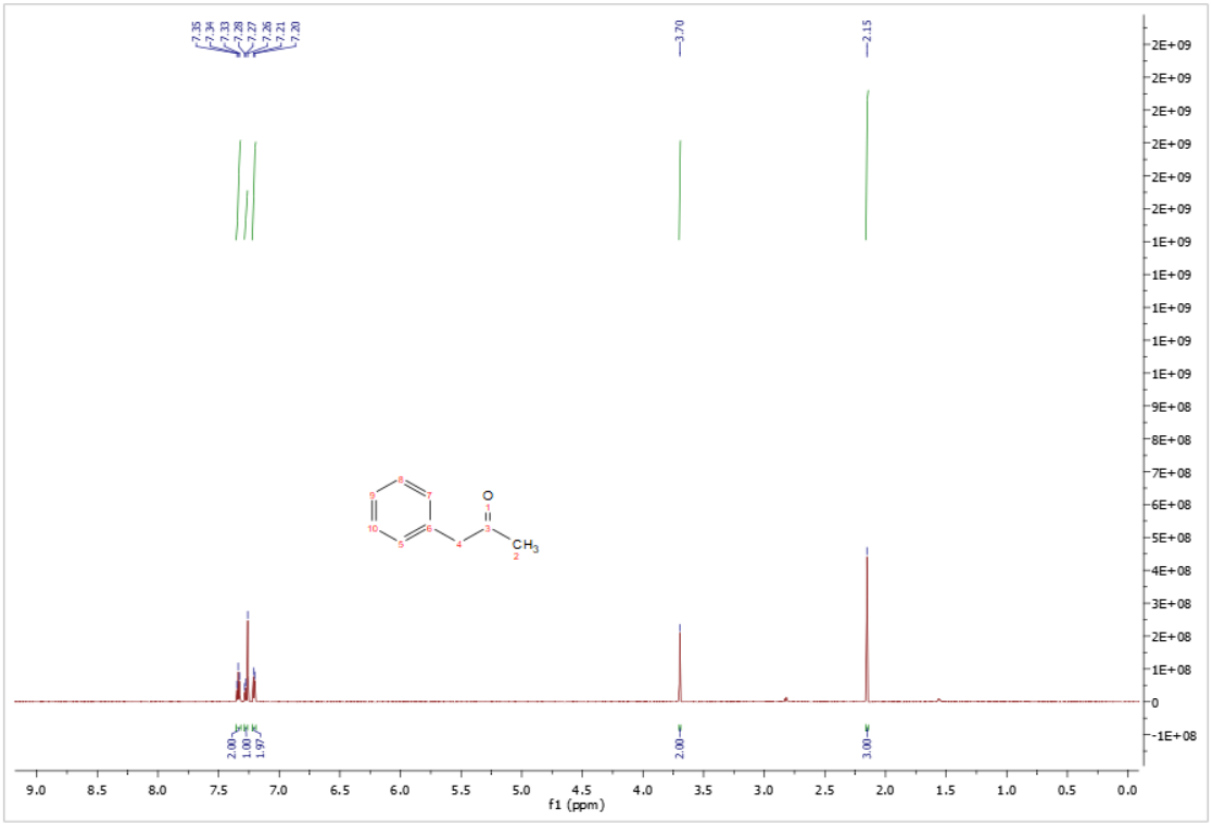

f1 (ppm)


f1 (ppm)

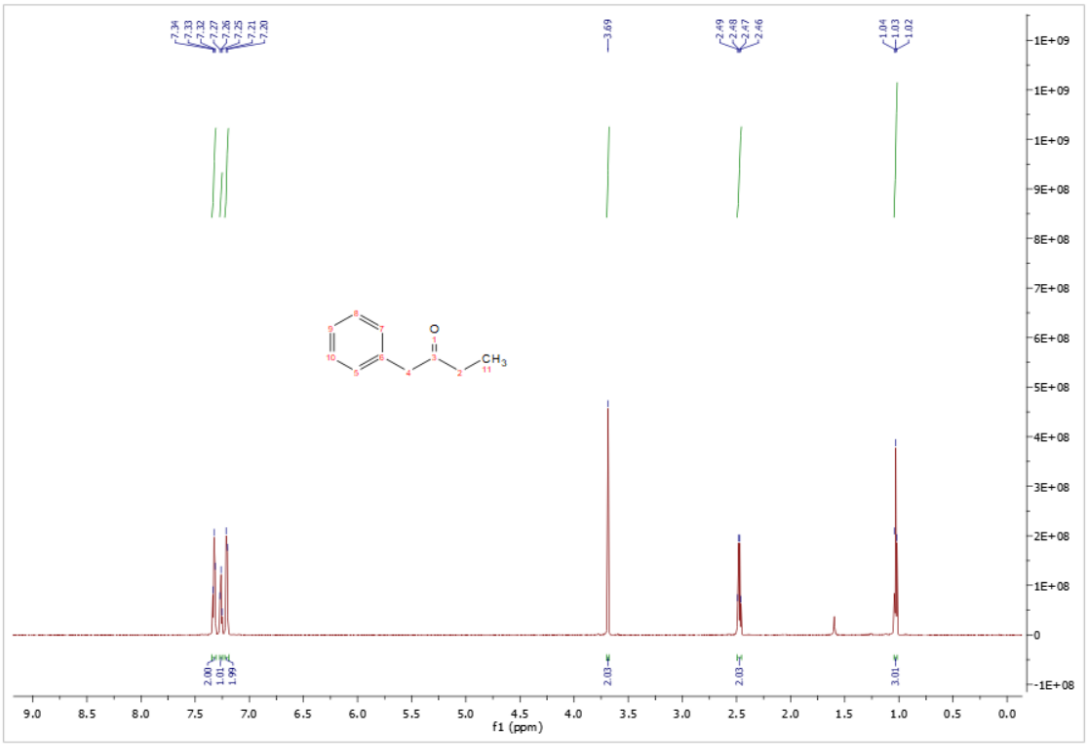

f1 (ppm)

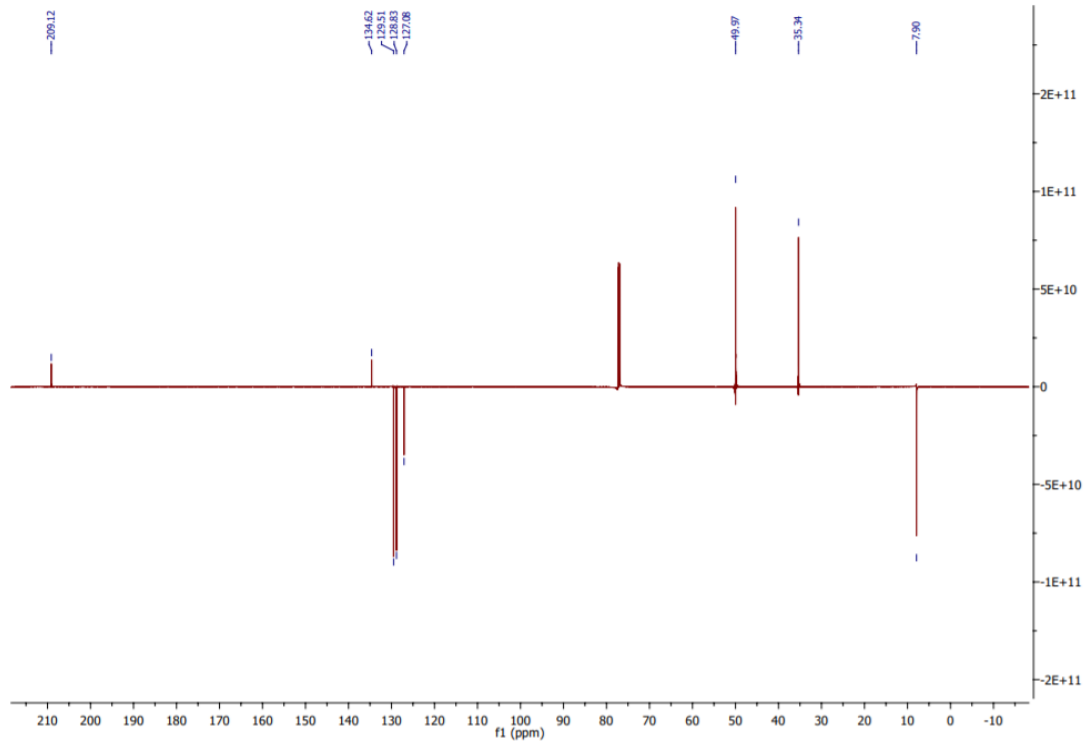

f1 (ppm)

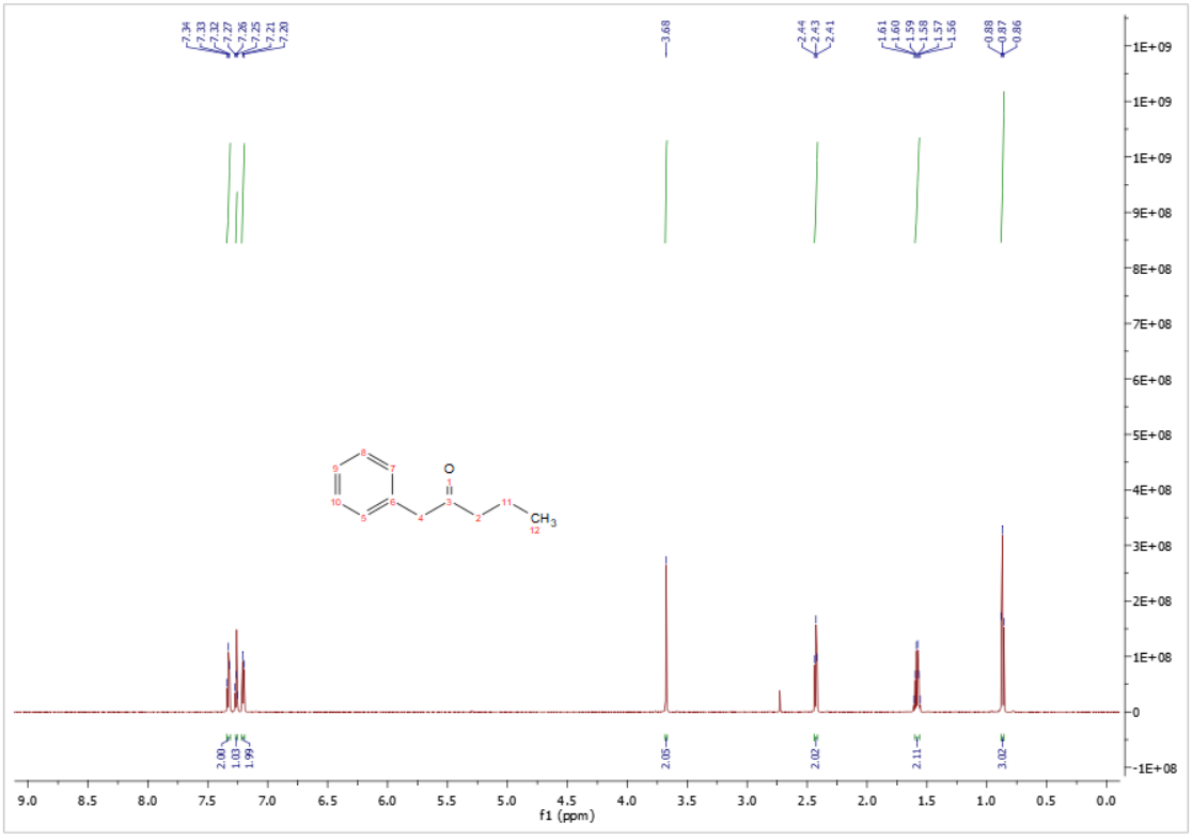

f1 (ppm)

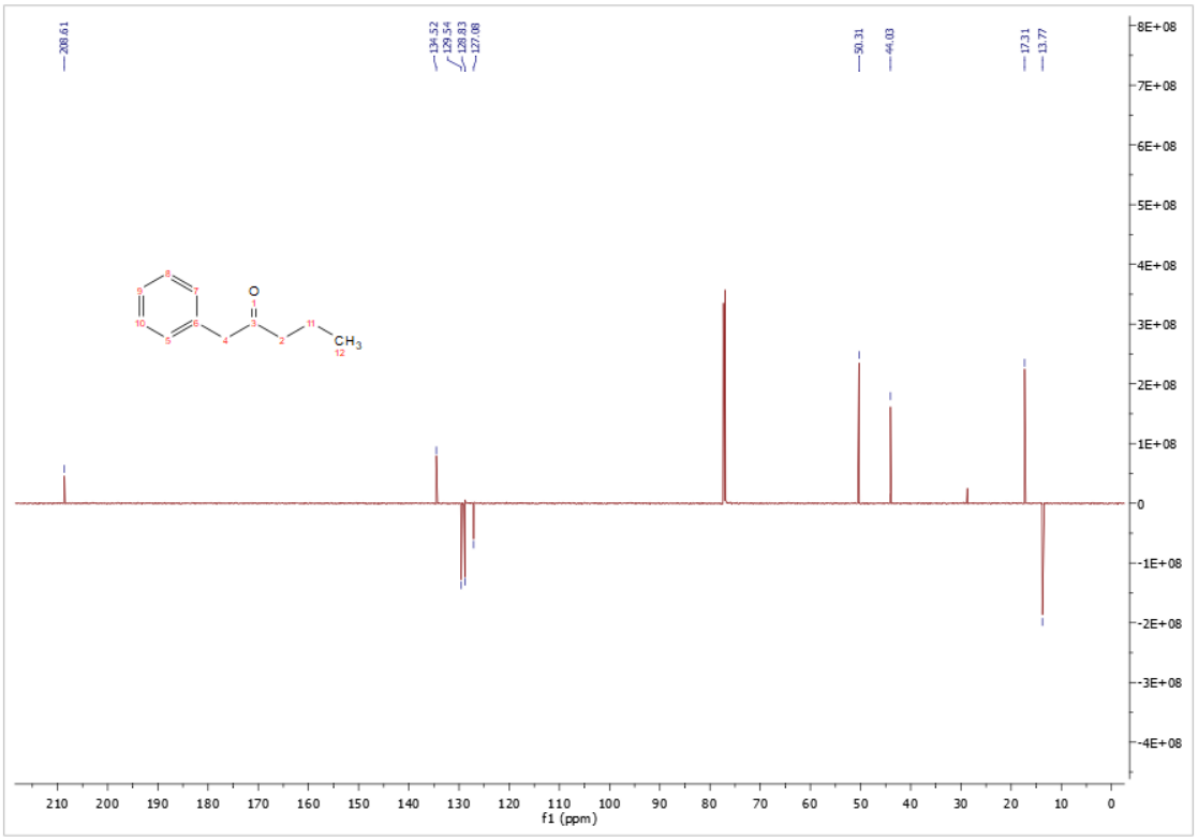

7.35
7.34
7.33
7.28
7.27
7.26
7.21
7.20
3.70
2.15
O
CH3
2.00
1.00
1.97
2.00
3.00
f1 (ppm)

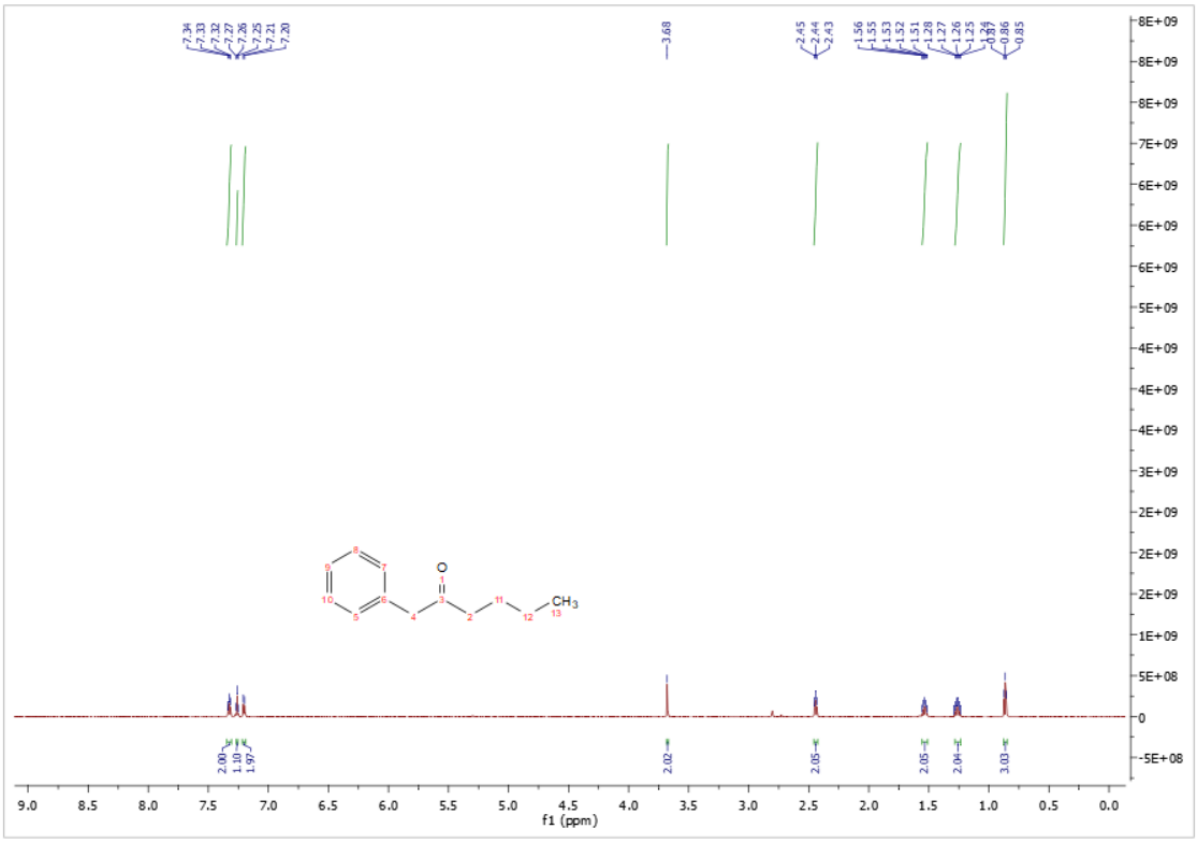

206.57
134.40
129.54
128.92
127.22
51.20
29.41
O
CH3
f1 (ppm)

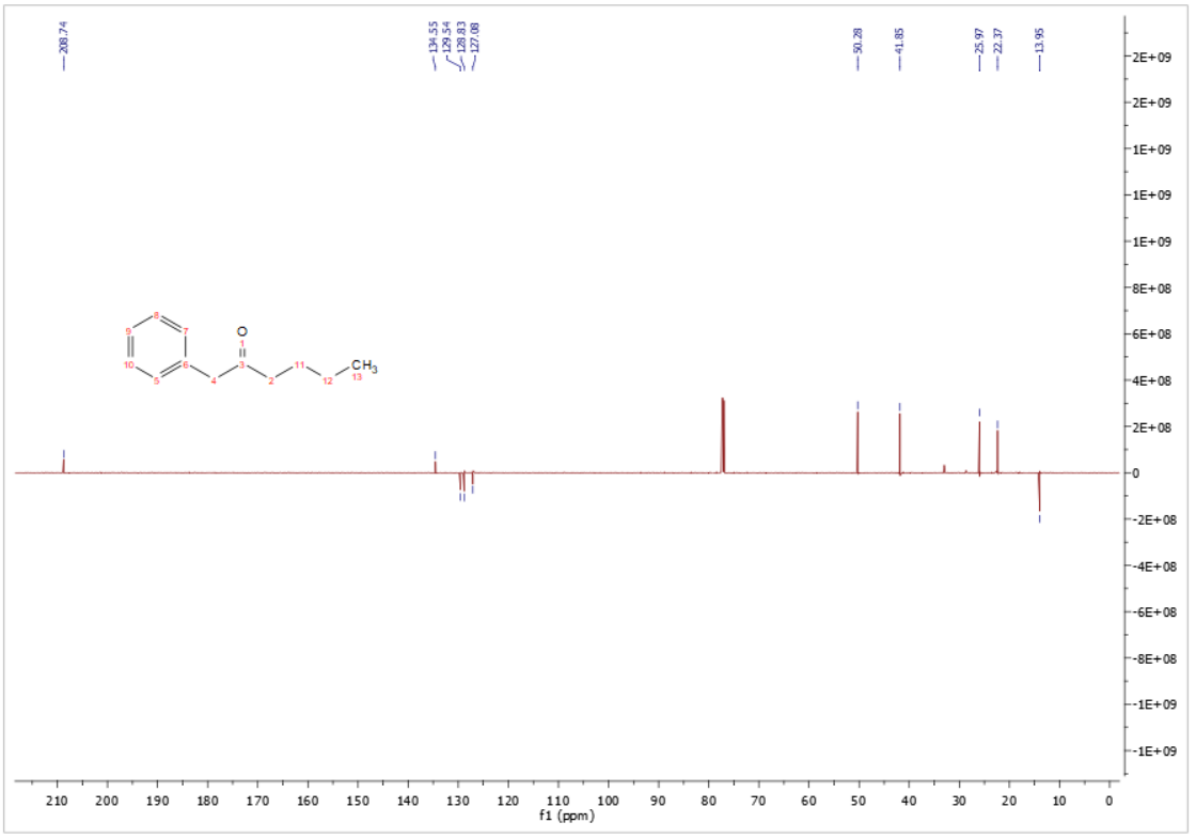

7.34
7.33
7.32
7.27
7.26
7.25
7.21
7.20
3.69
2.49
2.48
2.47
2.46
1.04
1.03
1.02
O
CH3
2.00
1.01
1.99
2.03
2.03
3.01
f1 (ppm)

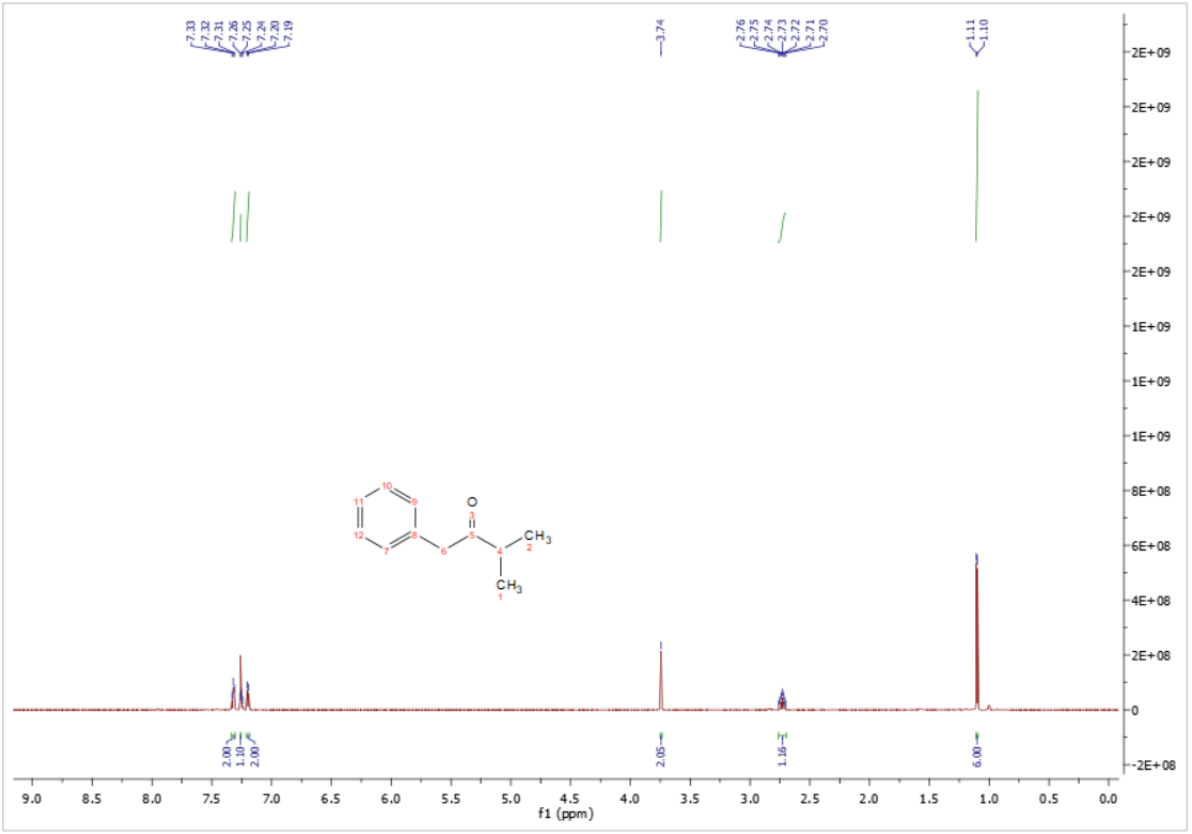

209.12
134.62
129.51
128.83
127.08
49.97
35.34
7.90
f1 (ppm)

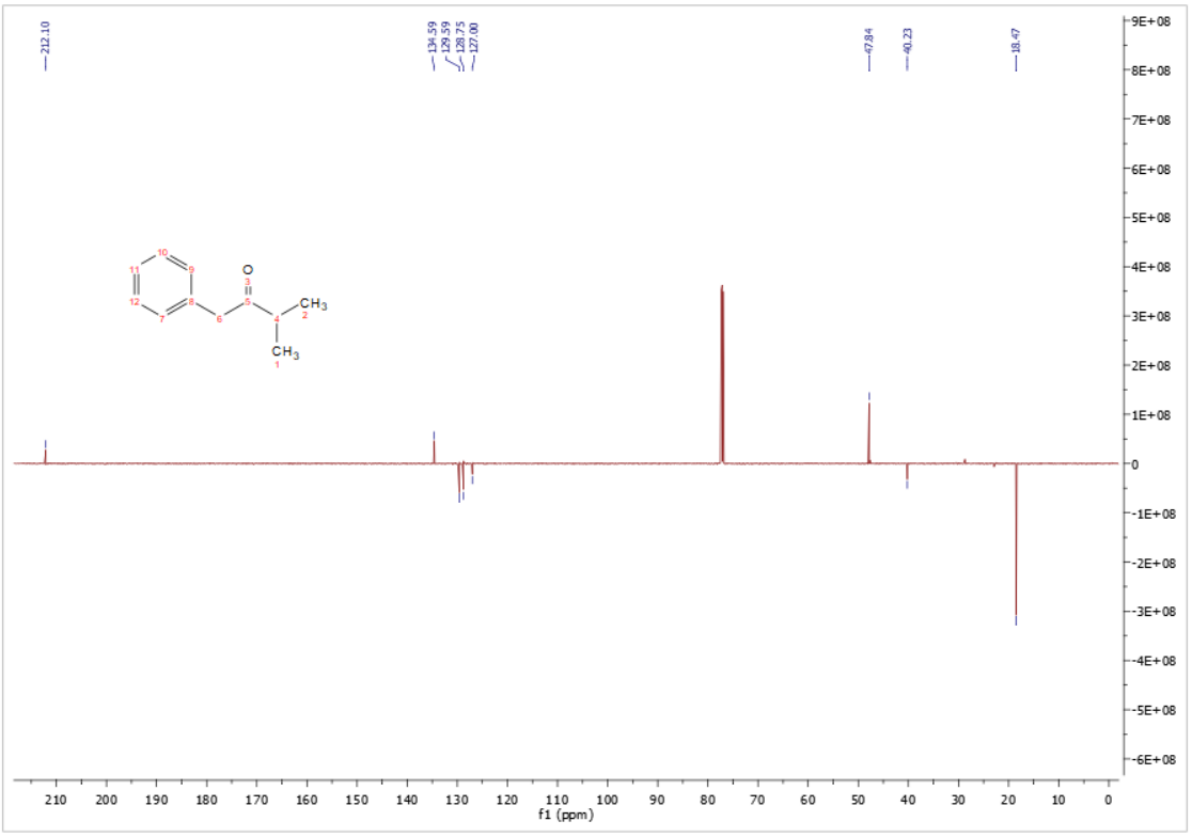

7.34
7.33
7.32
7.27
7.26
7.25
7.21
7.20
3.68
2.44
2.43
2.41
1.61
1.60
1.59
1.58
1.57
1.56
0.88
0.87
0.86
O
CH3
2.00
1.03
1.99
2.05
2.02
2.11
3.02
f1 (ppm)

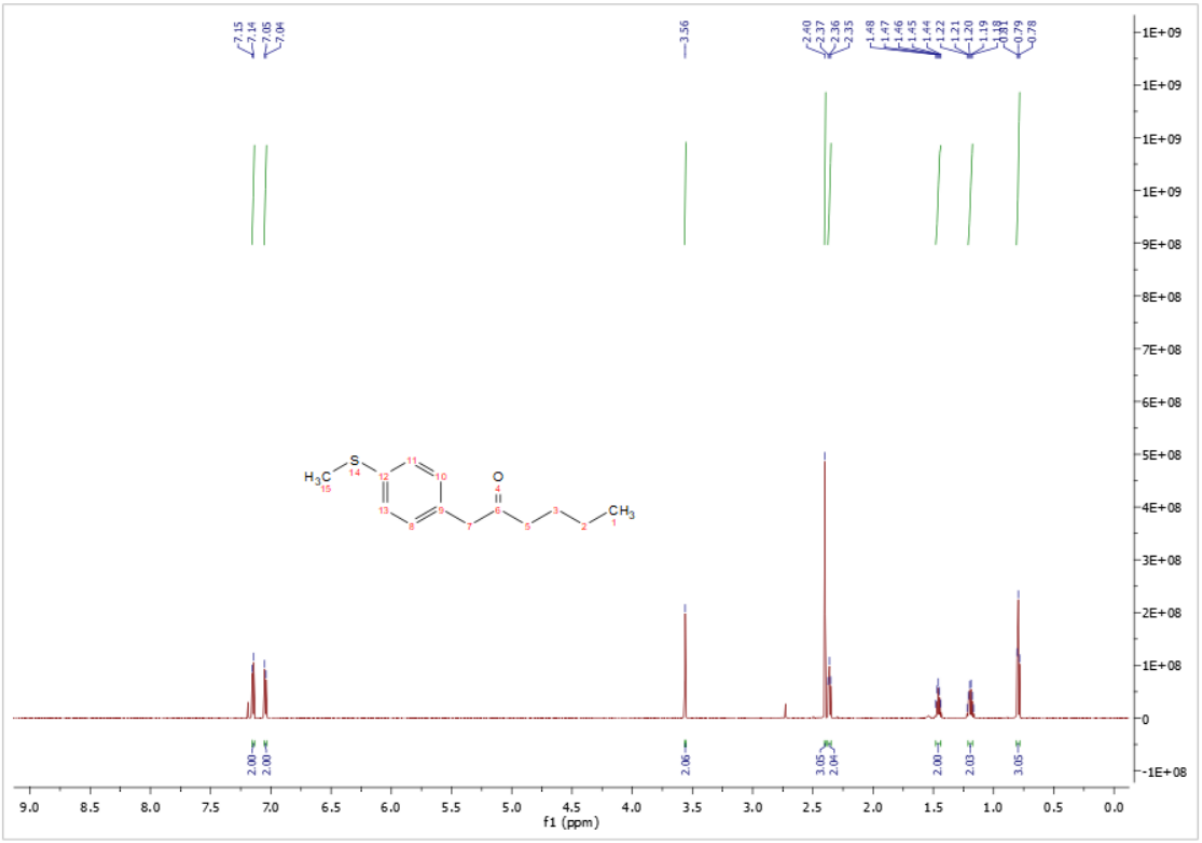

208.61
134.52
129.54
128.83
127.08
50.31
44.03
17.31
13.77
O
CH3
f1 (ppm)

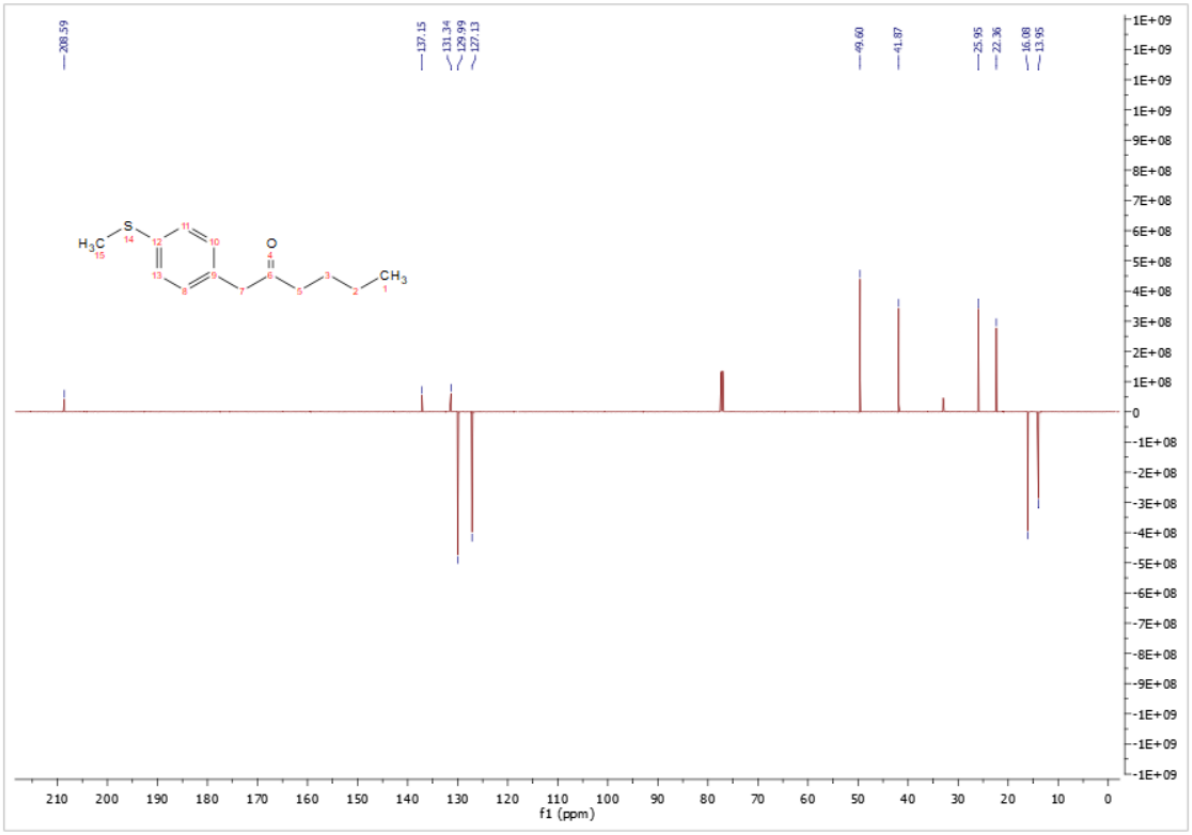

7.34
7.33
7.32
7.27
7.26
7.25
7.21
7.20
3.68
2.45
2.44
2.43
1.56
1.55
1.53
1.52
1.51
1.28
1.27
1.26
1.25
0.87
0.86
0.85
O
CH3
2.00
1.10
1.97
2.02
2.05
2.05
2.04
3.03
f1 (ppm)

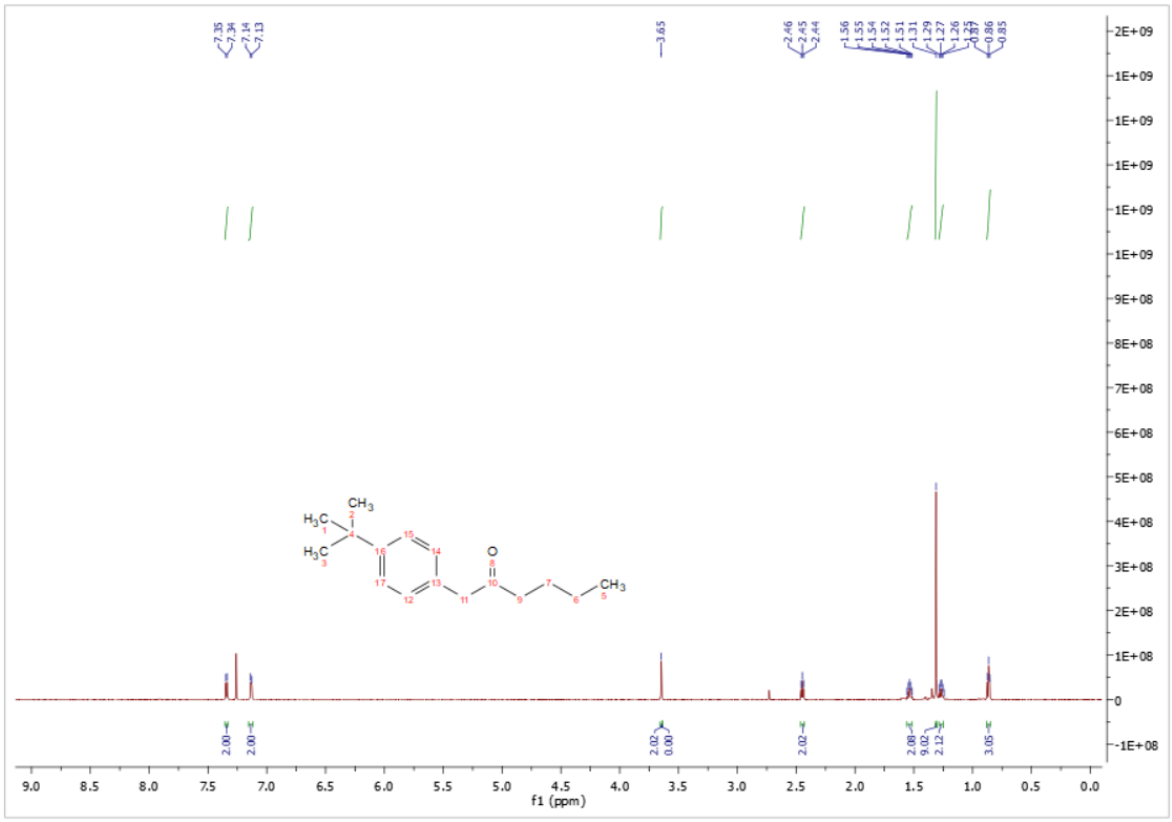

208.74
134.55
129.54
128.83
127.08
50.28
41.85
25.97
22.37
13.95
O
CH3
f1 (ppm)

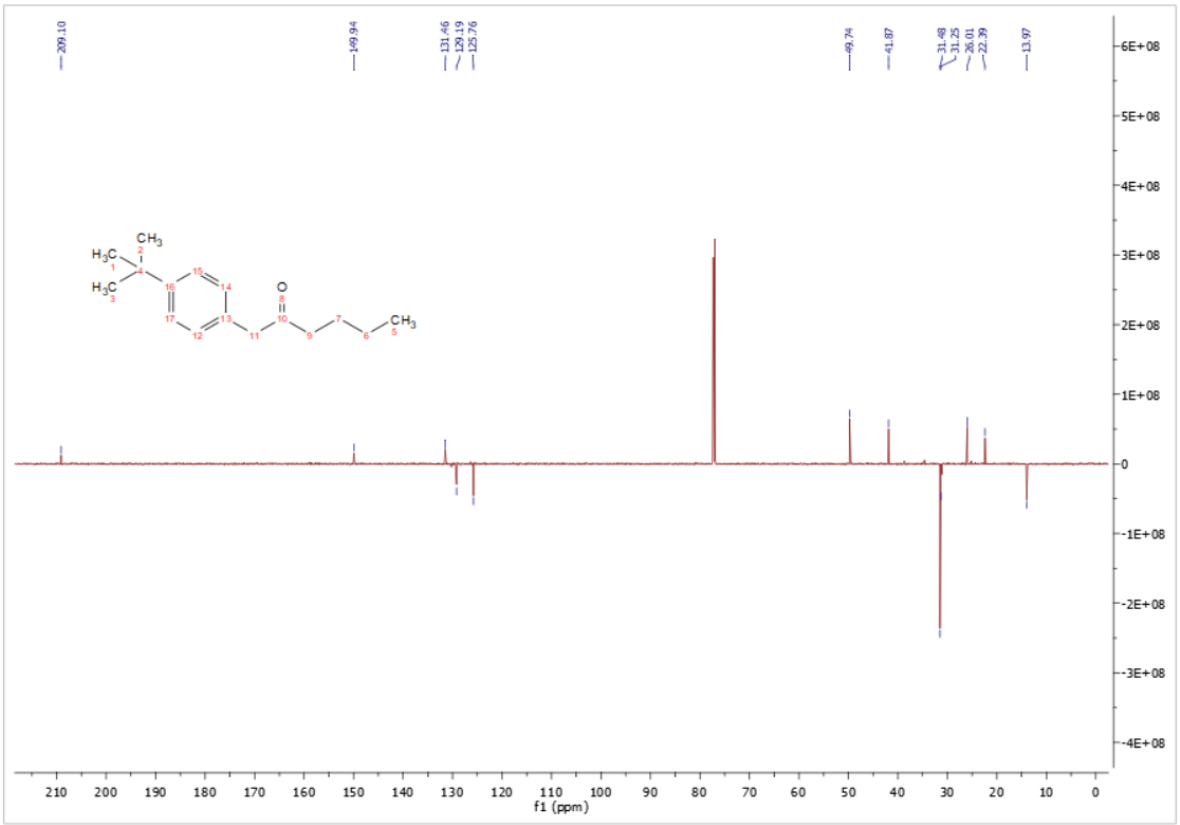

7.33
7.32
7.31
7.26
7.25
7.24
7.20
7.19
3.74
2.76
2.75
2.74
2.73
2.72
2.71
2.70
1.11
1.10
O
CH3
CH3
2.00
1.10
2.00
2.05
1.16
6.00
f1 (ppm)

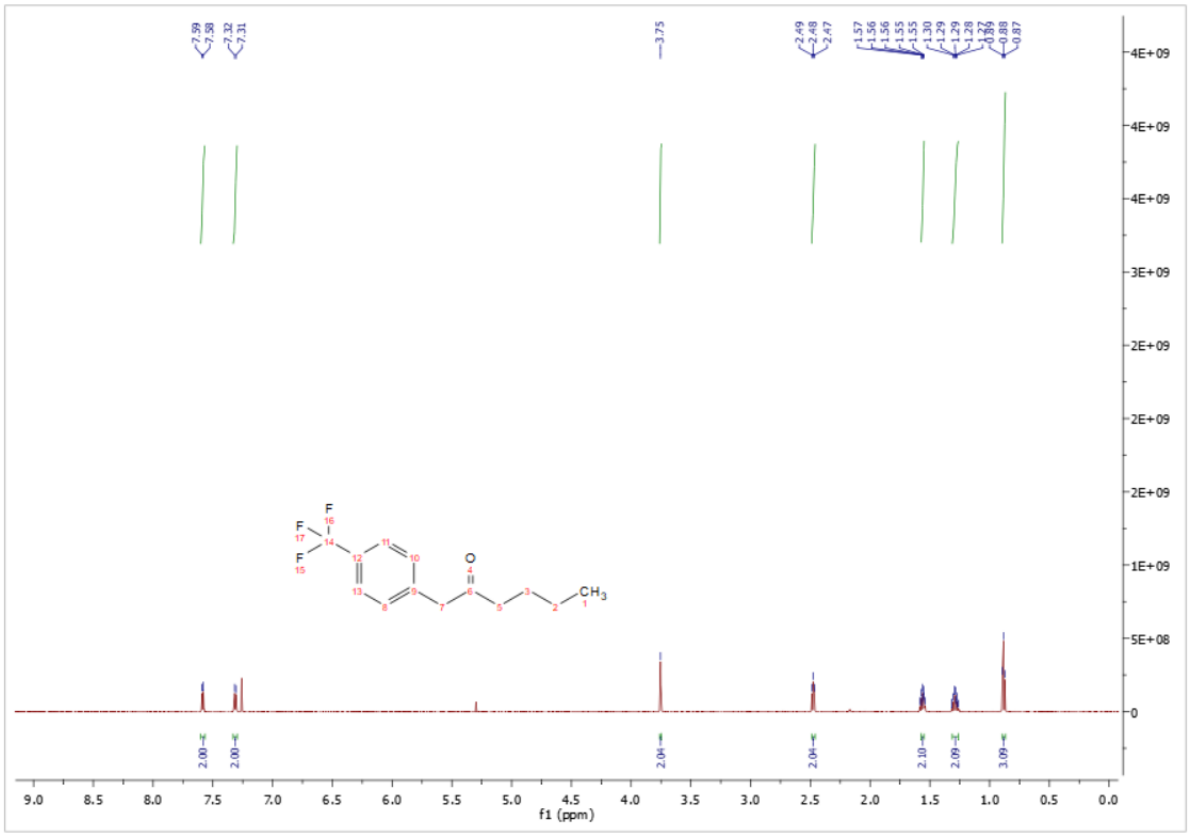

212.10
134.59
129.59
128.75
127.00
47.84
40.23
18.47
O
CH3
CH3
f1 (ppm)

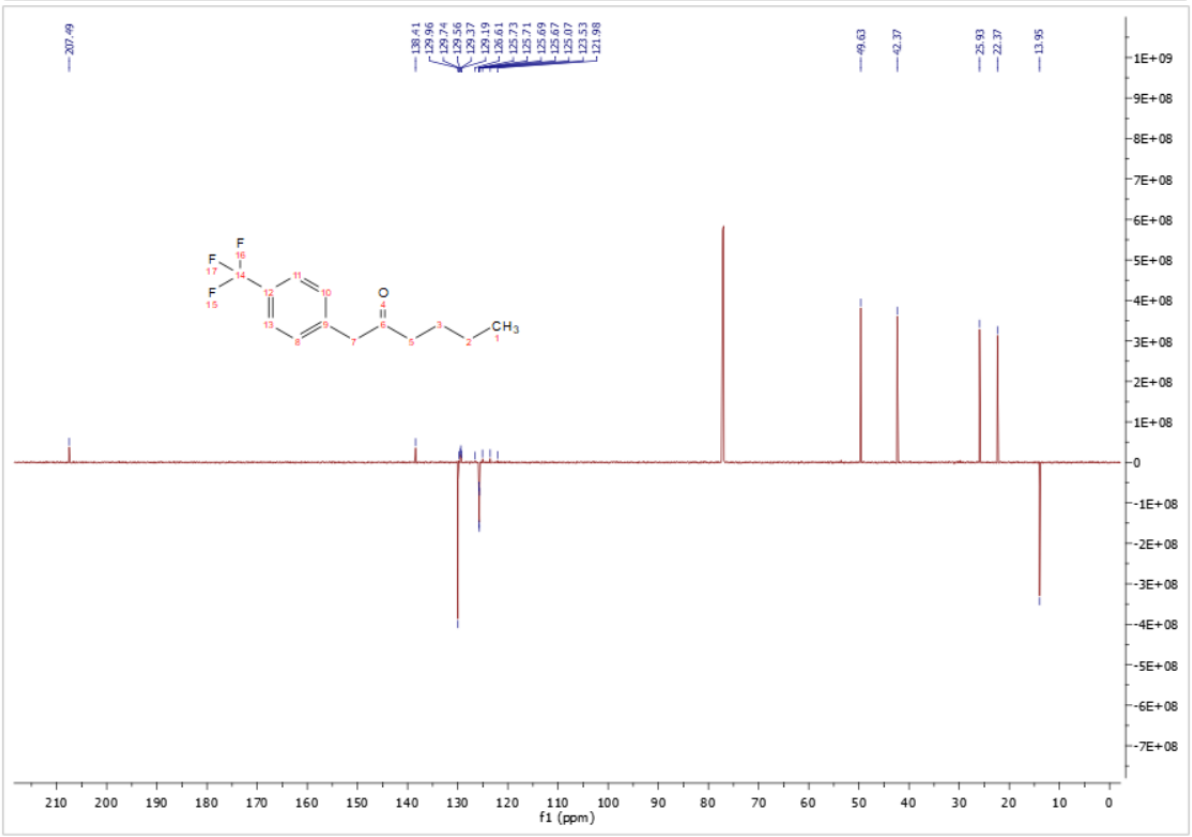

7.15
7.14
7.05
7.04
3.56
2.40
2.37
2.36
2.35
1.48
1.47
1.46
1.45
1.44
1.22
1.21
1.20
1.19
0.81
0.79
0.78
2.00
2.00
2.06
3.05
2.04
2.00
2.03
3.05
f1 (ppm)

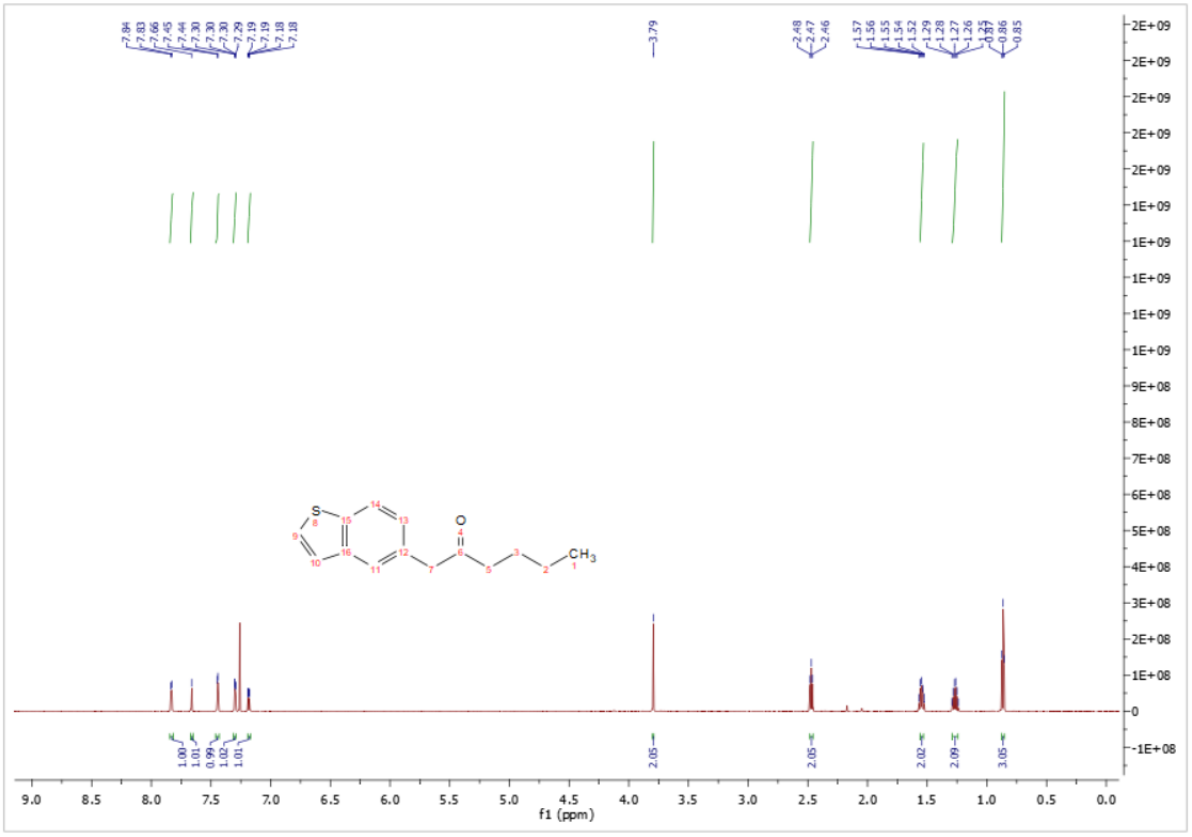

208.59
137.15
131.34
129.99
127.13
49.60
41.87
25.95
22.36
16.08
13.95
f1 (ppm)

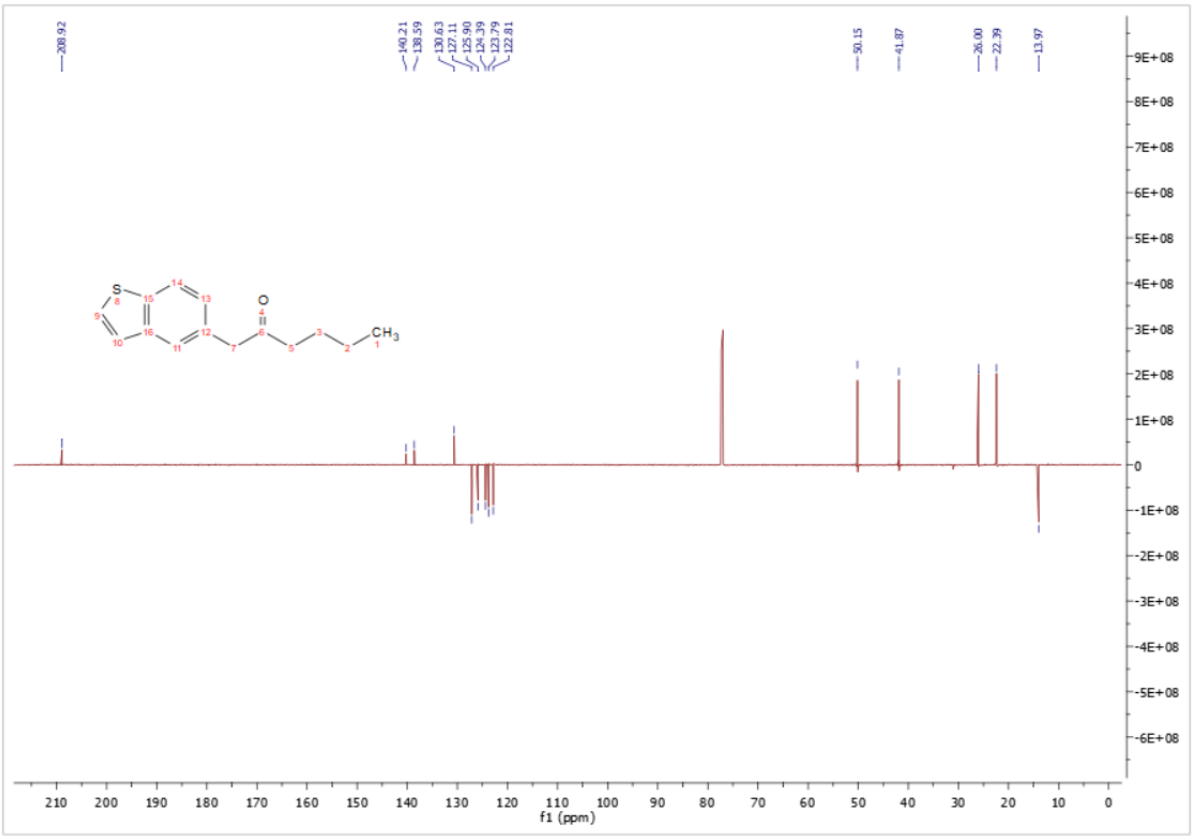

7.35
7.34
7.14
7.13
3.65
2.46
2.45
2.44
1.56
1.55
1.54
1.52
1.51
1.31
1.29
1.27
1.26
0.86
0.85
CH3
H3C
H3C
O
CH3
2.00
2.00
2.02
0.00
2.02
2.08
9.02
2.12
3.05
f1 (ppm)

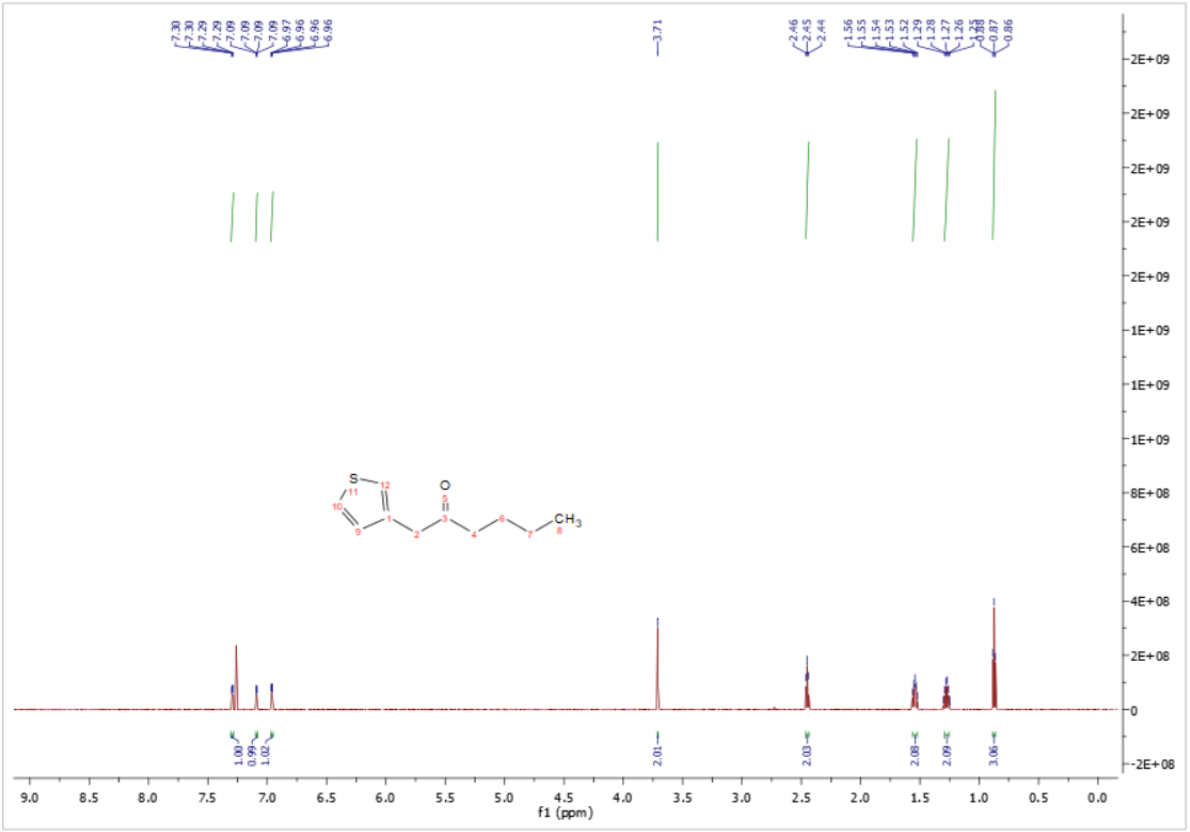

209.10
149.94
131.46
129.19
125.76
49.74
41.87
31.48
31.25
26.01
22.39
13.97
CH3
H3C
H3C
O
CH3
f1 (ppm)

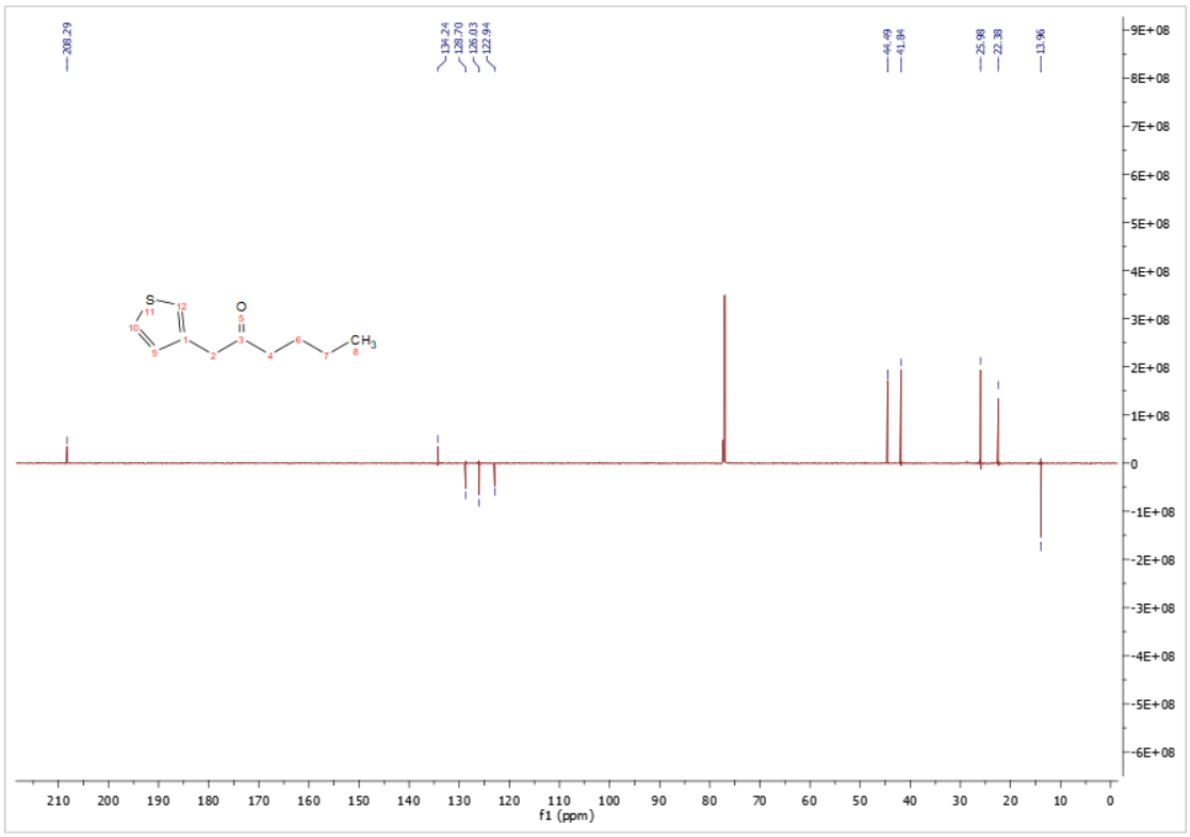

7.59
7.58
7.32
7.31
3.75
2.49
2.48
2.47
1.57
1.56
1.56
1.55
1.55
1.30
1.29
1.29
1.28
0.89
0.88
0.87
F
F
F
O
CH3
2.00
2.00
2.04
2.04
2.10
2.09
3.09
f1 (ppm)

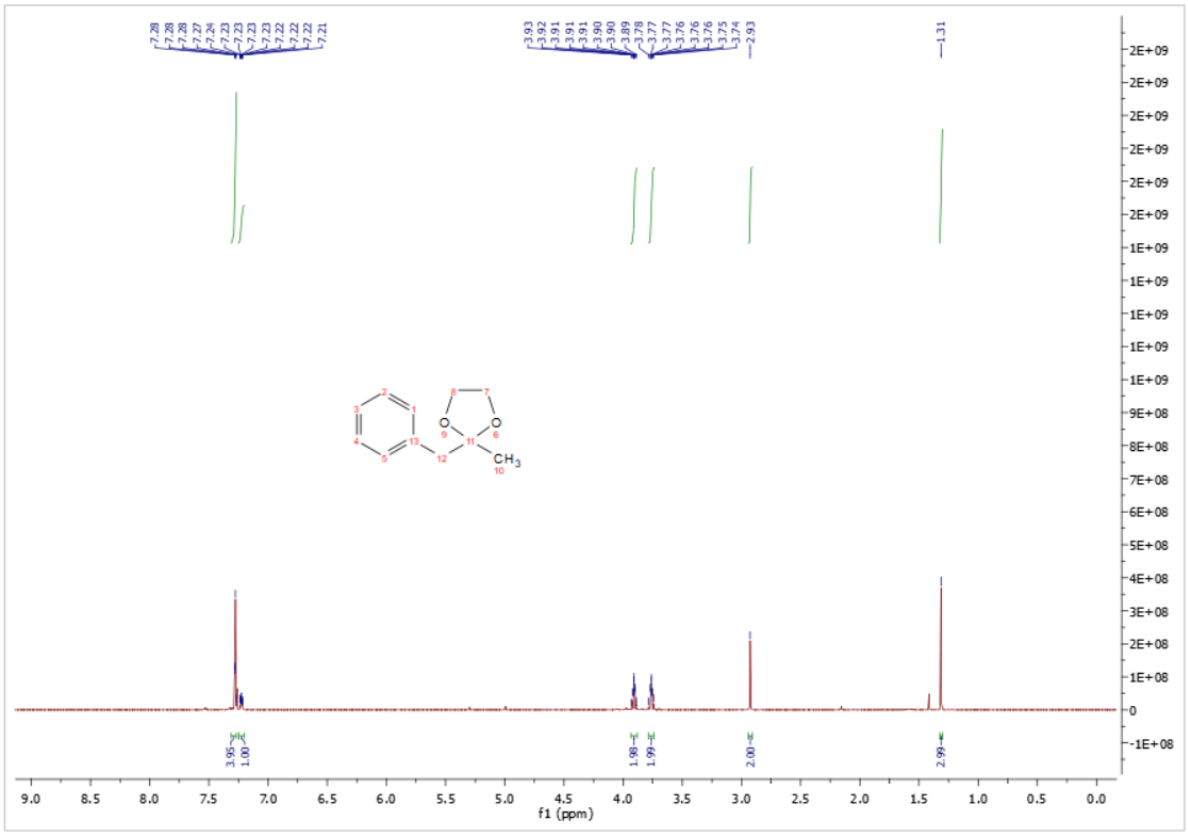

207.49
138.41
129.96
129.74
129.56
129.37
129.19
126.61
125.73
125.71
125.69
125.67
125.07
123.53
121.98
49.63
42.37
25.93
22.37
13.95
F
F
F
O
CH3
f1 (ppm)

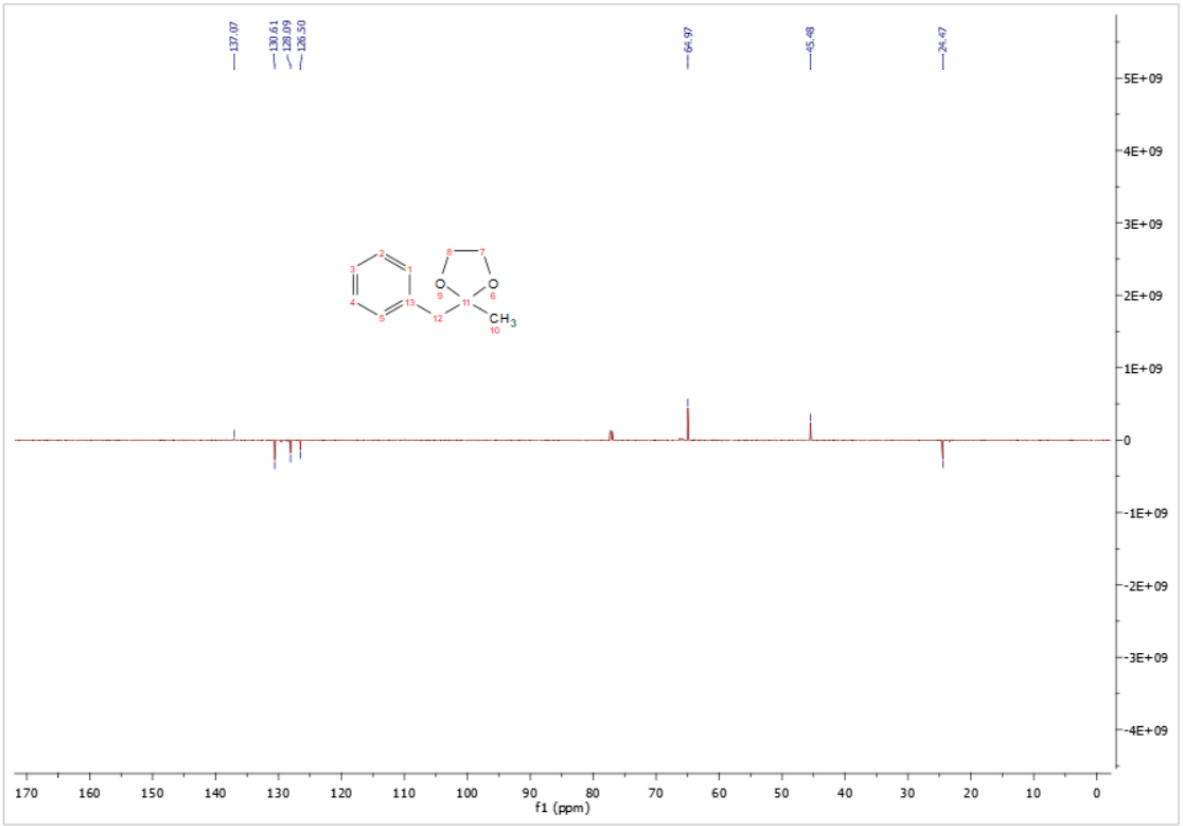

7.94
7.83
7.66
7.45
7.44
7.30
7.30
7.30
7.29
7.19
7.19
7.18
7.18
3.79
2.48
2.47
2.46
1.57
1.56
1.55
1.54
1.52
1.29
1.28
1.27
1.26
0.87
0.86
0.85
S
O
CH3
1.00
1.01
0.99
1.02
1.01
2.05
2.05
2.02
2.09
3.05
f1 (ppm)

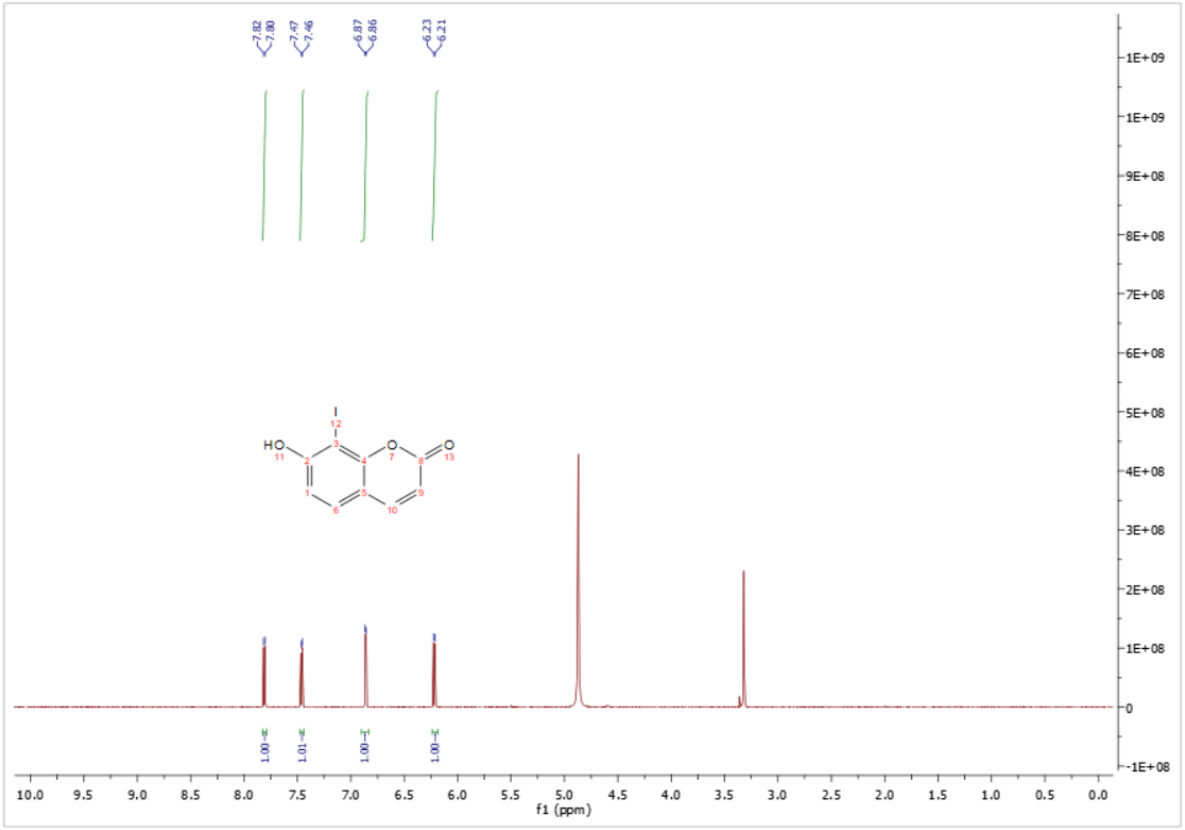

208.92
140.21
138.59
130.63
127.11
125.90
124.39
123.79
122.81
50.15
41.87
26.00
22.39
13.97
S
O
CH3
f1 (ppm)

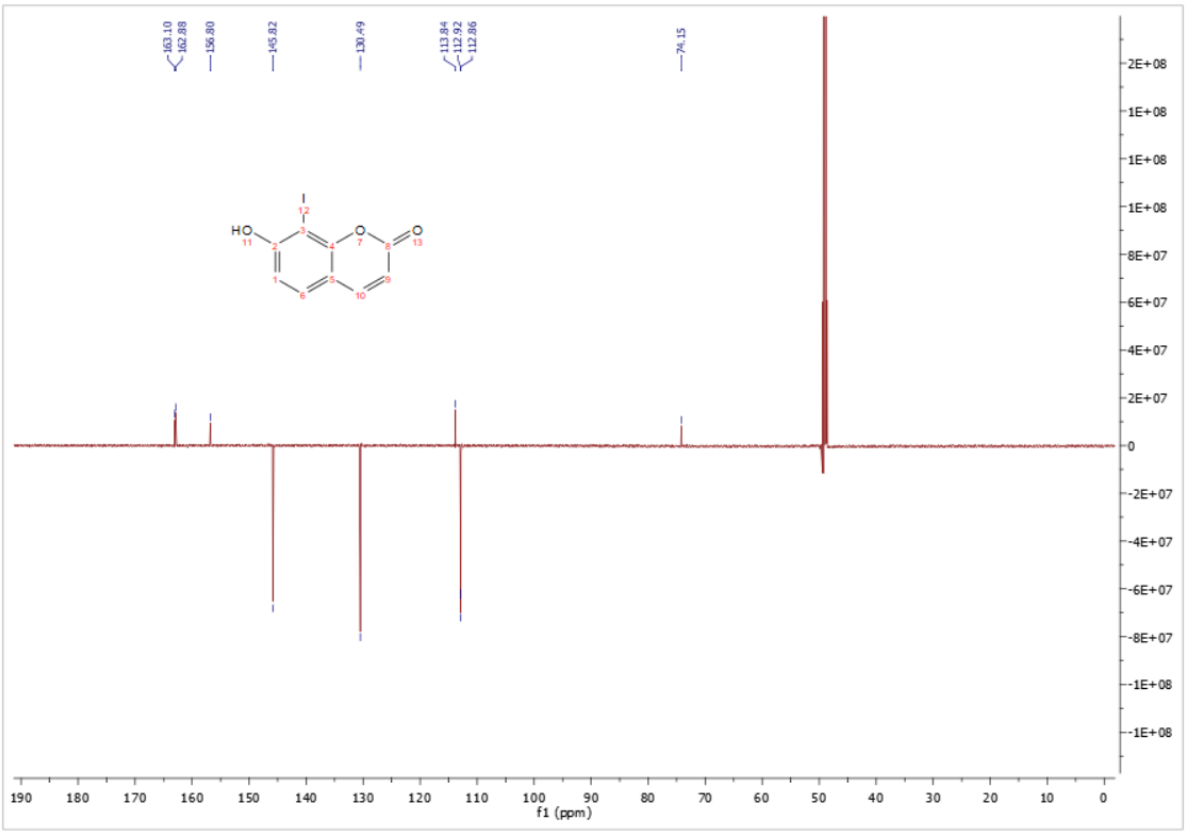

f1 (ppm)

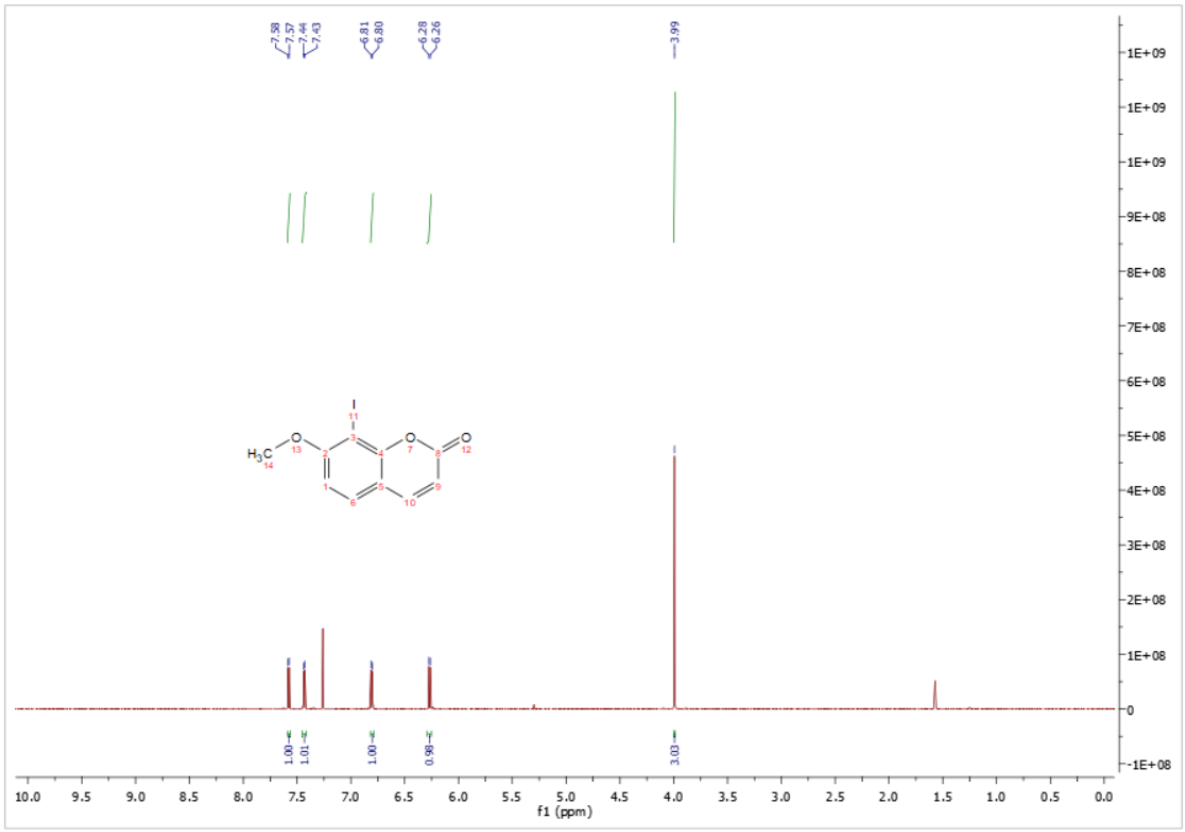

f1 (ppm)

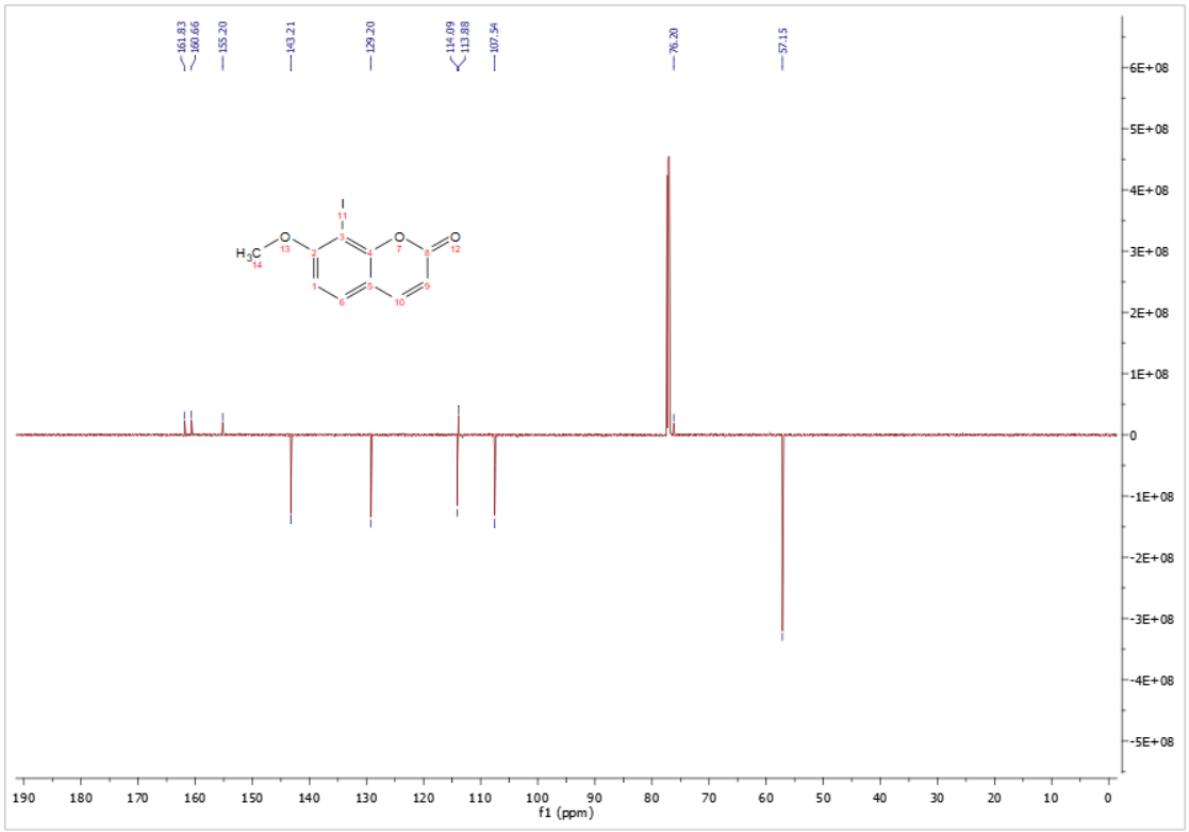

7.28
7.28
7.28
7.27
7.24
7.23
7.23
7.23
7.23
7.22
7.22
7.22
7.21
3.93
3.92
3.91
3.91
3.91
3.90
3.90
3.89
3.78
3.77
3.77
3.76
3.76
3.76
3.75
3.74
2.93
1.31
CH3
3.95
1.00
1.98
1.99
2.00
2.99
f1 (ppm)

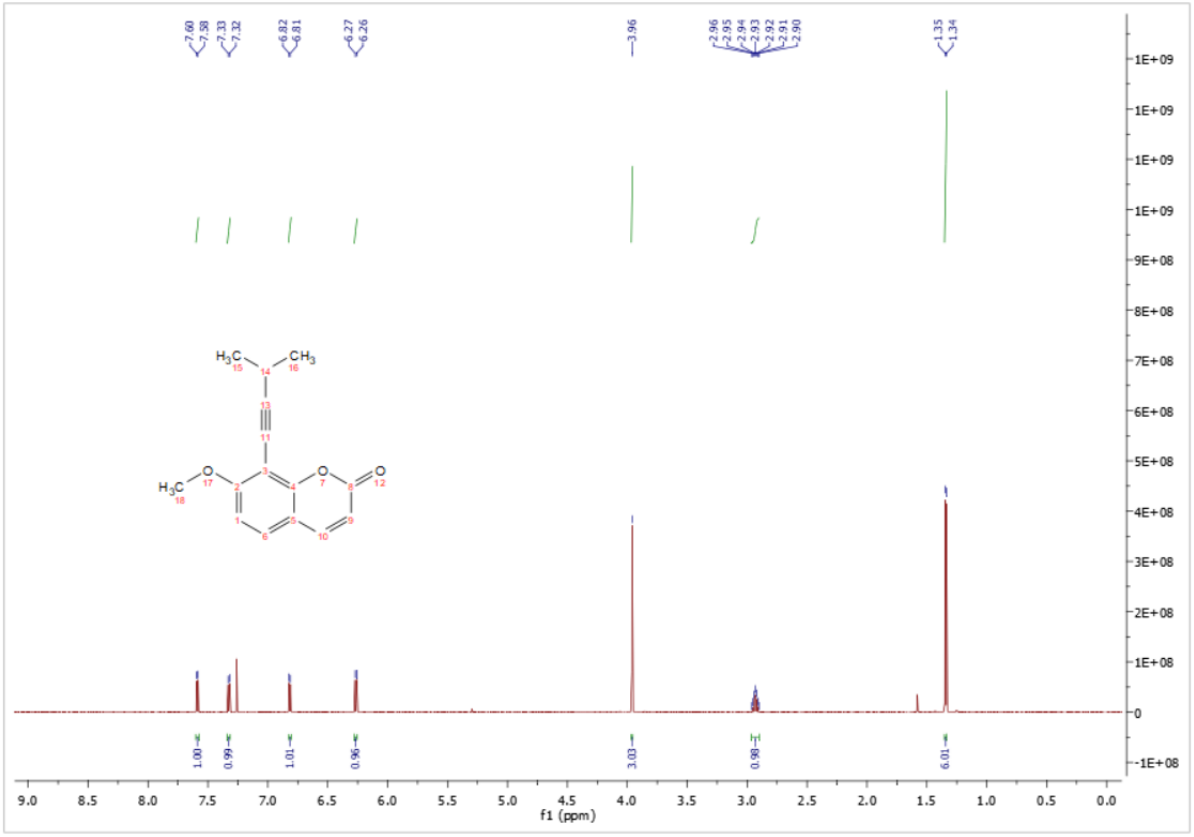

137.07
130.61
128.09
126.50
64.97
45.48
24.47
CH3
f1 (ppm)

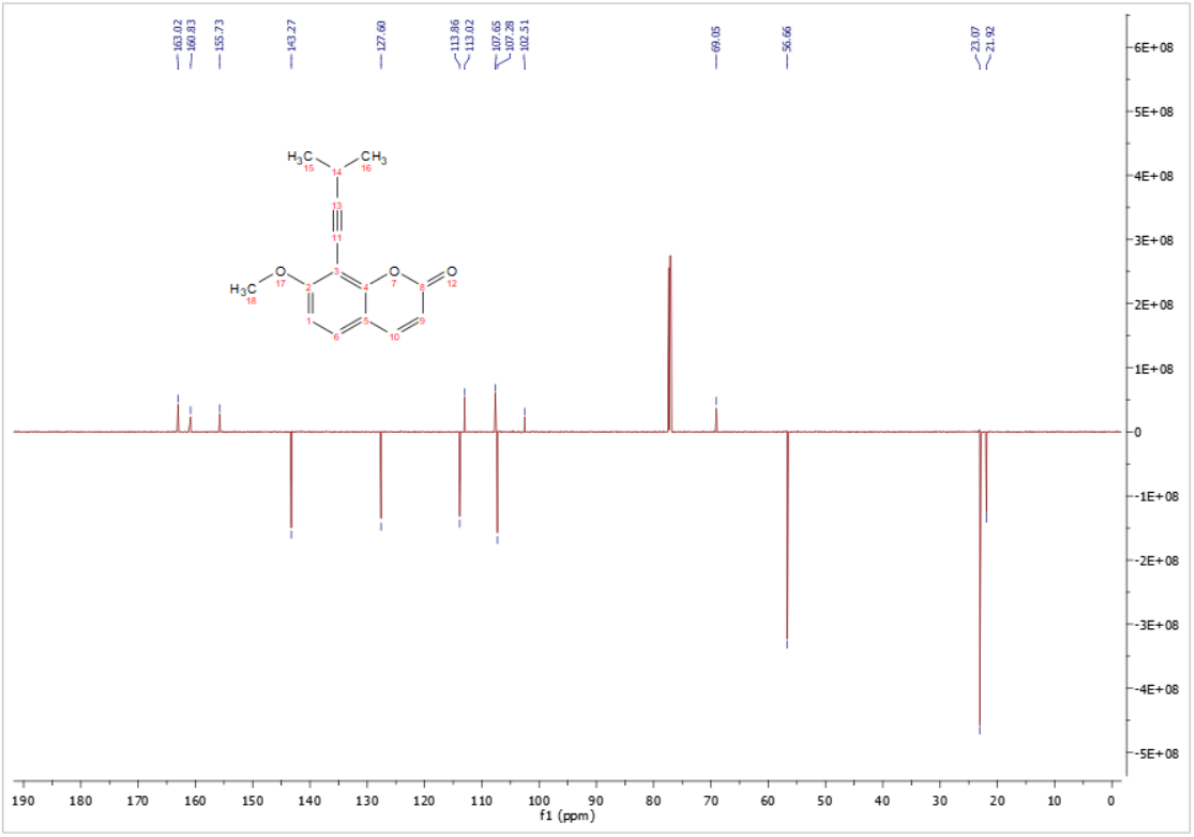

7.82
7.80
7.47
7.46
6.87
6.86
6.23
6.21
1.00
1.01
1.00
1.00
f1 (ppm)

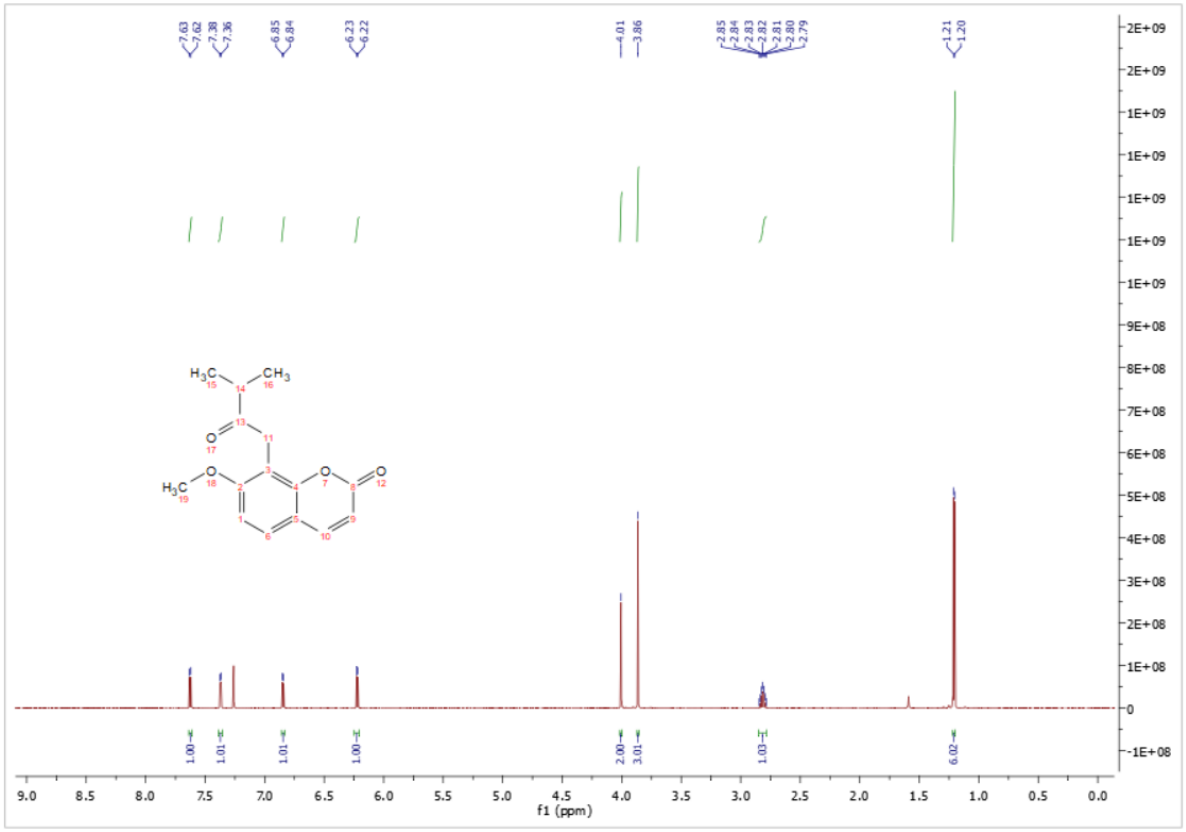

163.10
162.88
156.80
145.82
130.49
113.84
112.92
112.86
74.15
f1 (ppm)

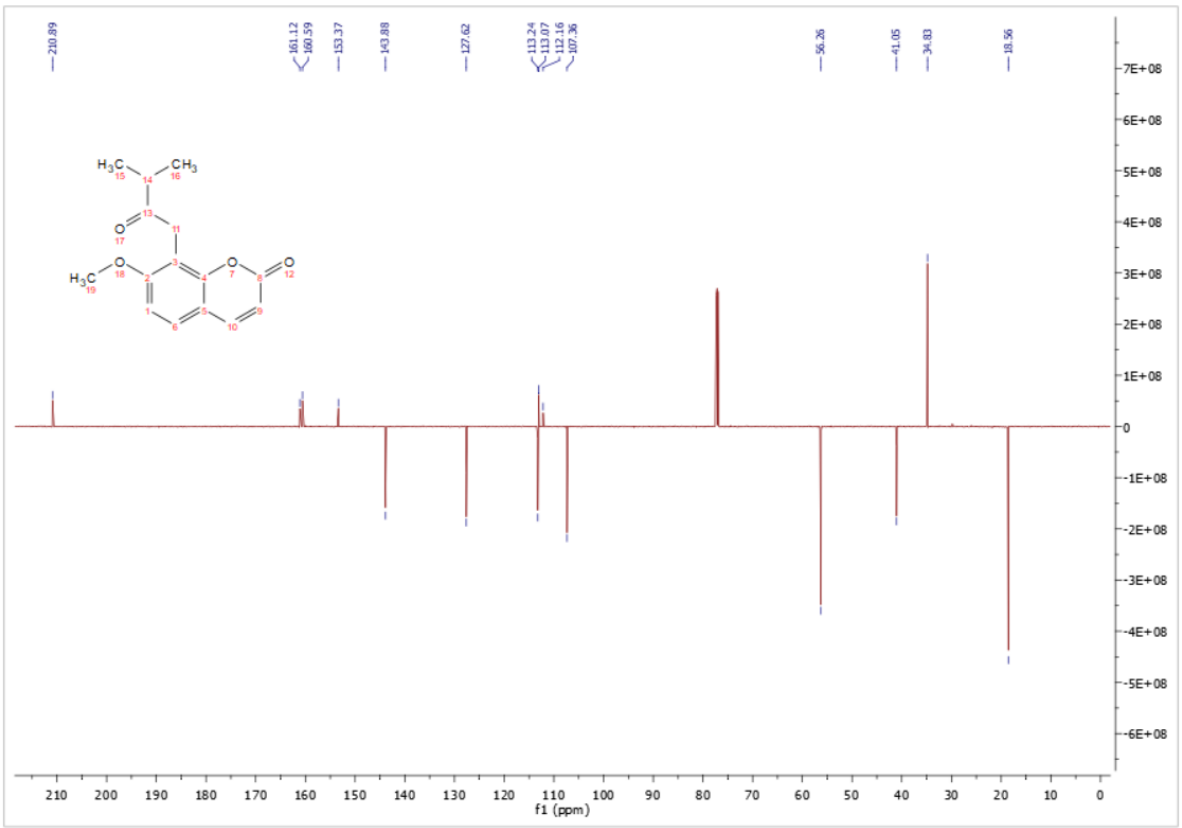

7.58
7.57
7.44
7.43
6.81
6.80
6.28
6.26
3.99
1.00
1.01
1.00
0.98
3.03
f1 (ppm)

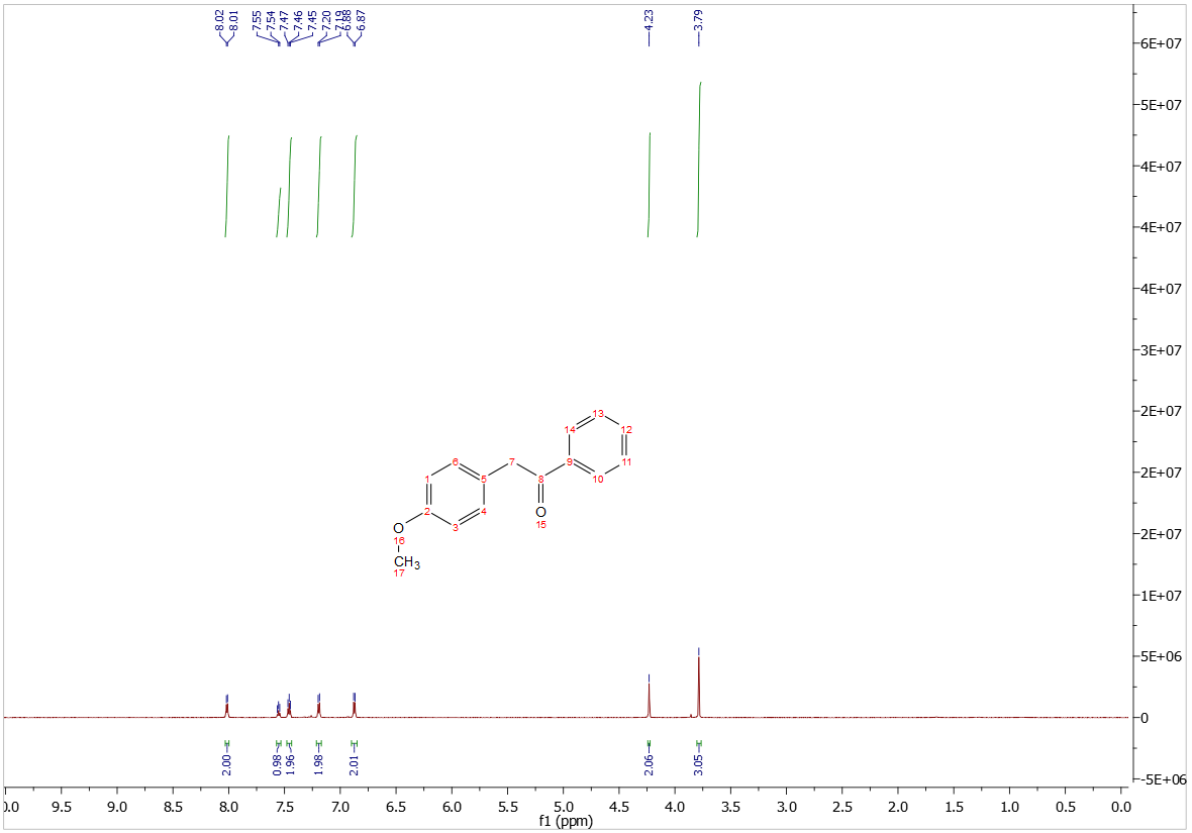

161.83
160.66
155.20
143.21
129.20
114.09
113.88
107.54
76.20
57.15
f1 (ppm)

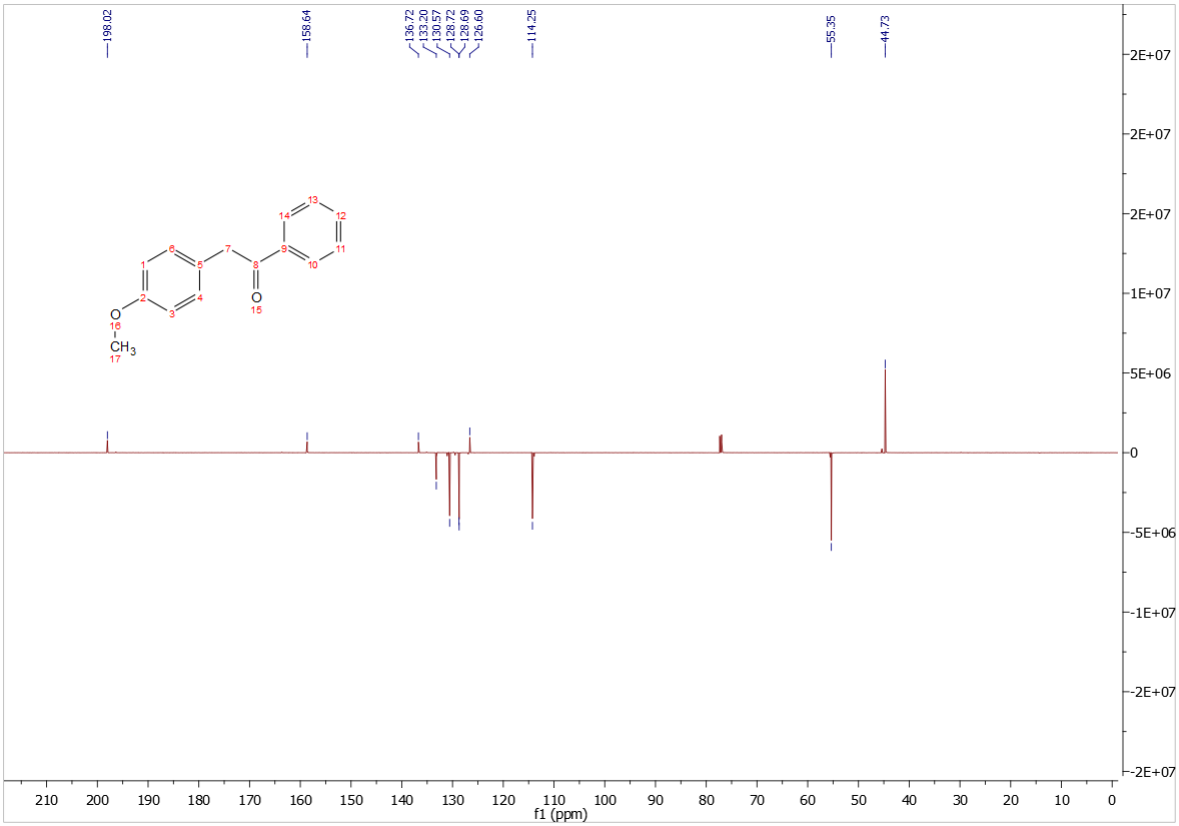

7.60
7.58
7.33
7.32
6.82
6.81
6.27
6.26
3.96
2.96
2.95
2.94
2.93
2.92
2.91
2.90
1.35
1.34
1.00
0.99
1.01
0.96
3.03
0.98
6.01
f1 (ppm)

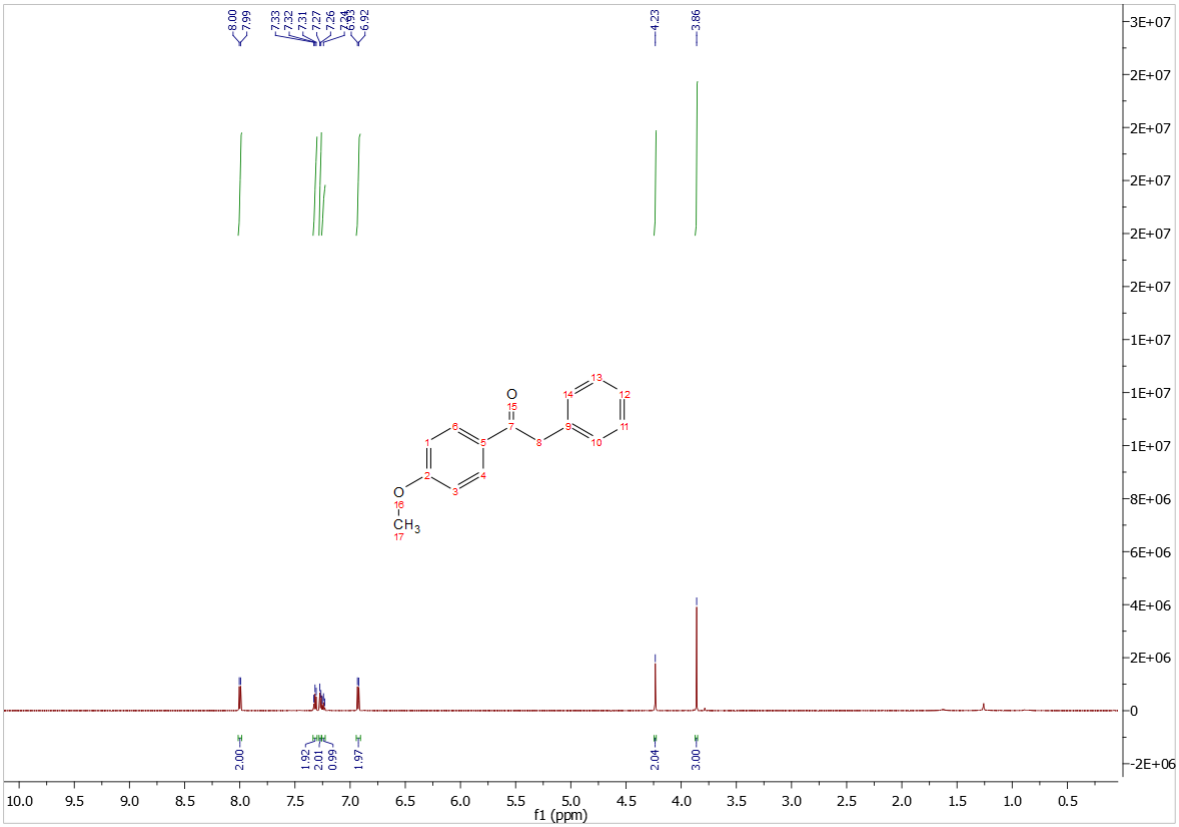

163.02
160.83
155.73
143.27
127.60
113.86
113.02
107.65
107.28
102.51
69.05
56.66
23.07
21.92
f1 (ppm)

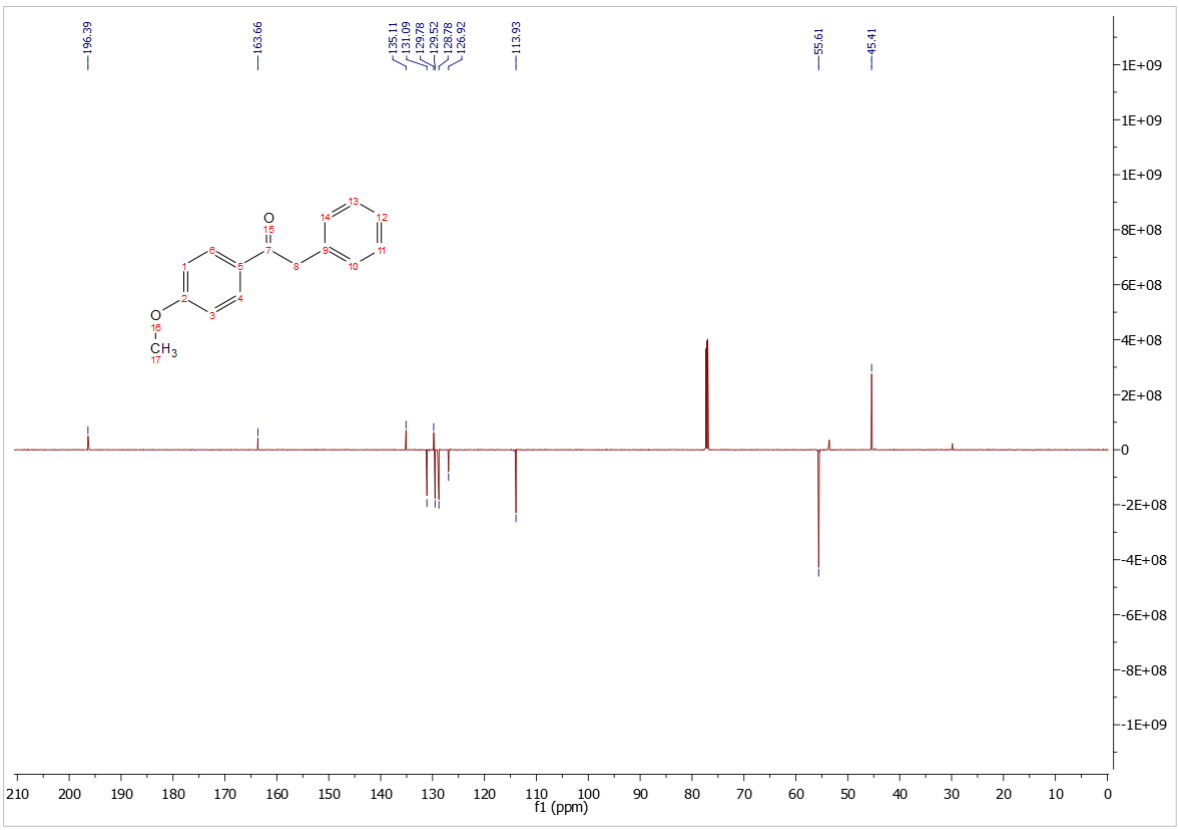

7.63
7.62
7.38
7.36
6.85
6.84
6.23
6.22
4.01
3.86
2.85
2.84
2.83
2.82
2.81
2.80
2.79
1.21
1.20
1.00
1.01
1.01
1.00
2.00
3.01
1.03
6.02
f1 (ppm)

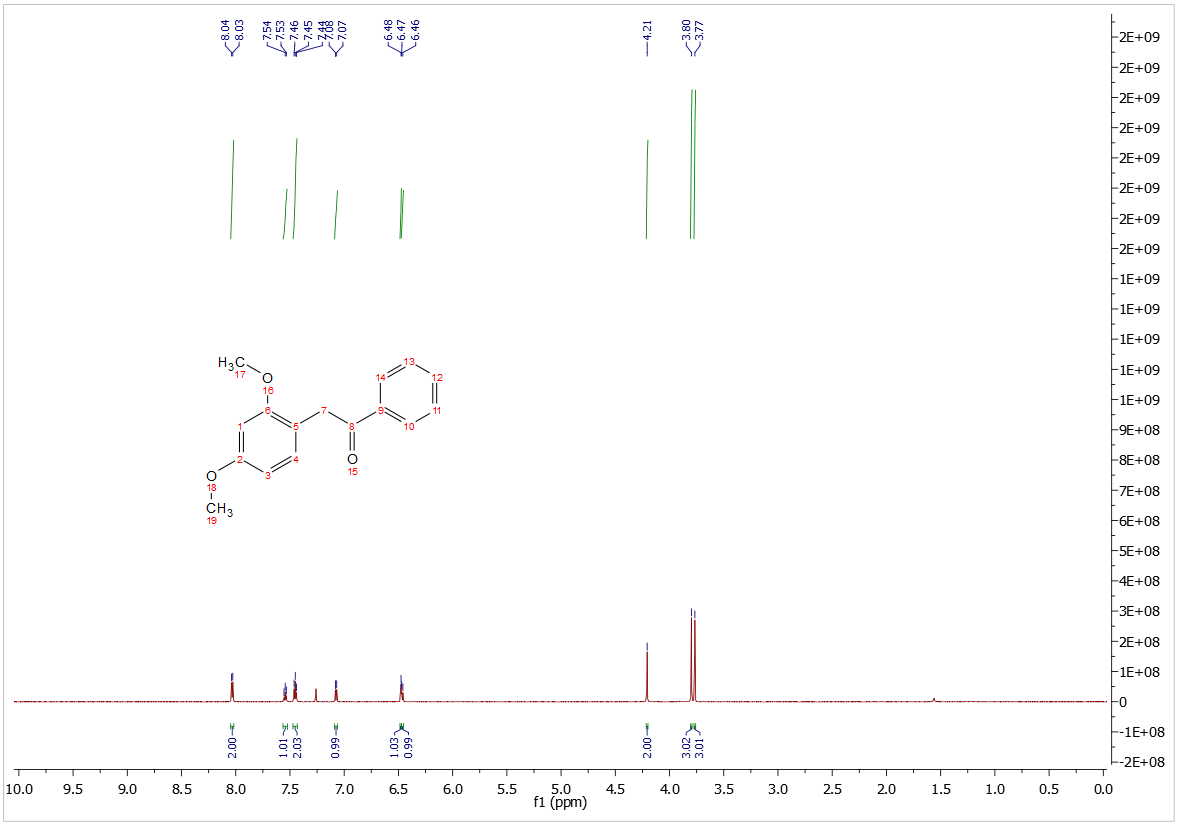

210.89
161.12
160.59
153.37
143.88
127.62
113.24
113.07
112.16
107.36
56.26
41.05
34.83
18.56
f1 (ppm)

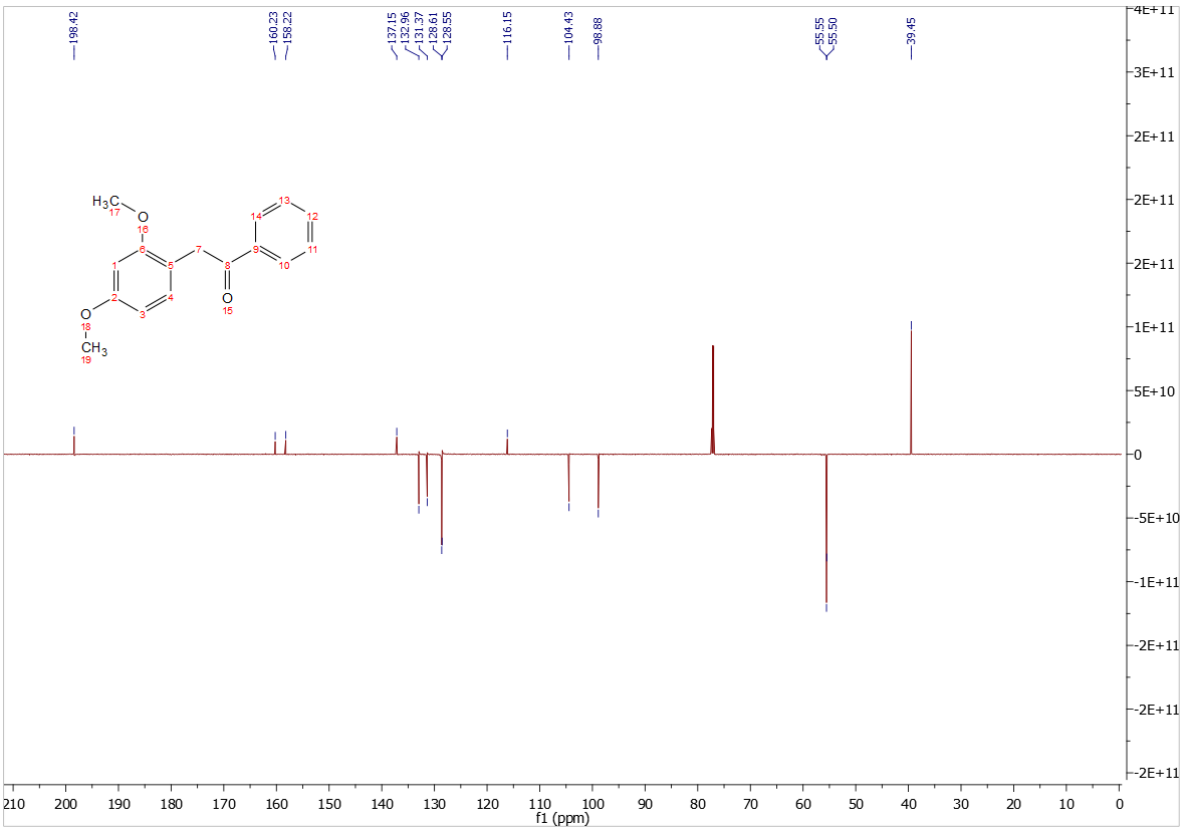

8.02
8.01
7.55
7.54
7.47
7.46
7.45
7.20
7.19
6.88
6.87
4.23
3.79
2.00
0.98
1.96
1.98
2.01
2.06
3.05
f1 (ppm)

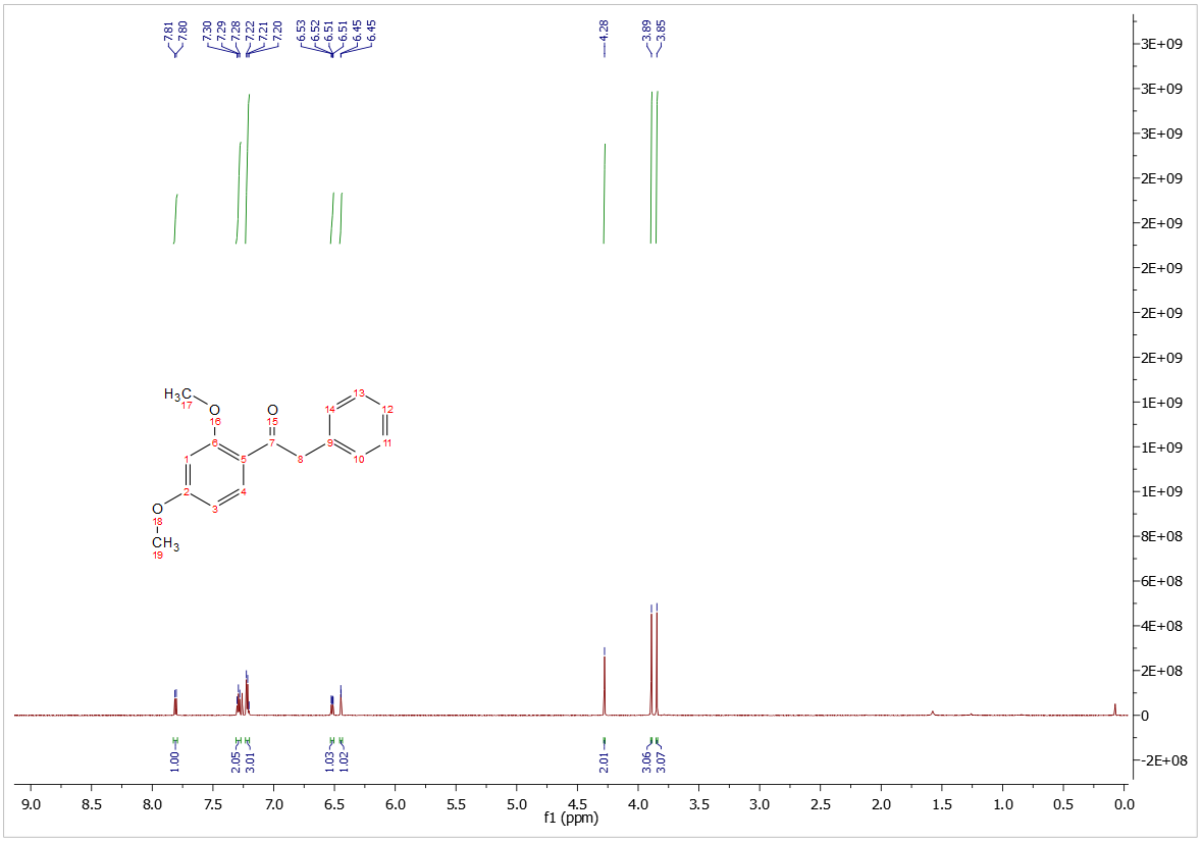

198.02
158.64
136.72
133.20
130.57
128.72
128.69
126.60
114.25
55.35
44.73
f1 (ppm)

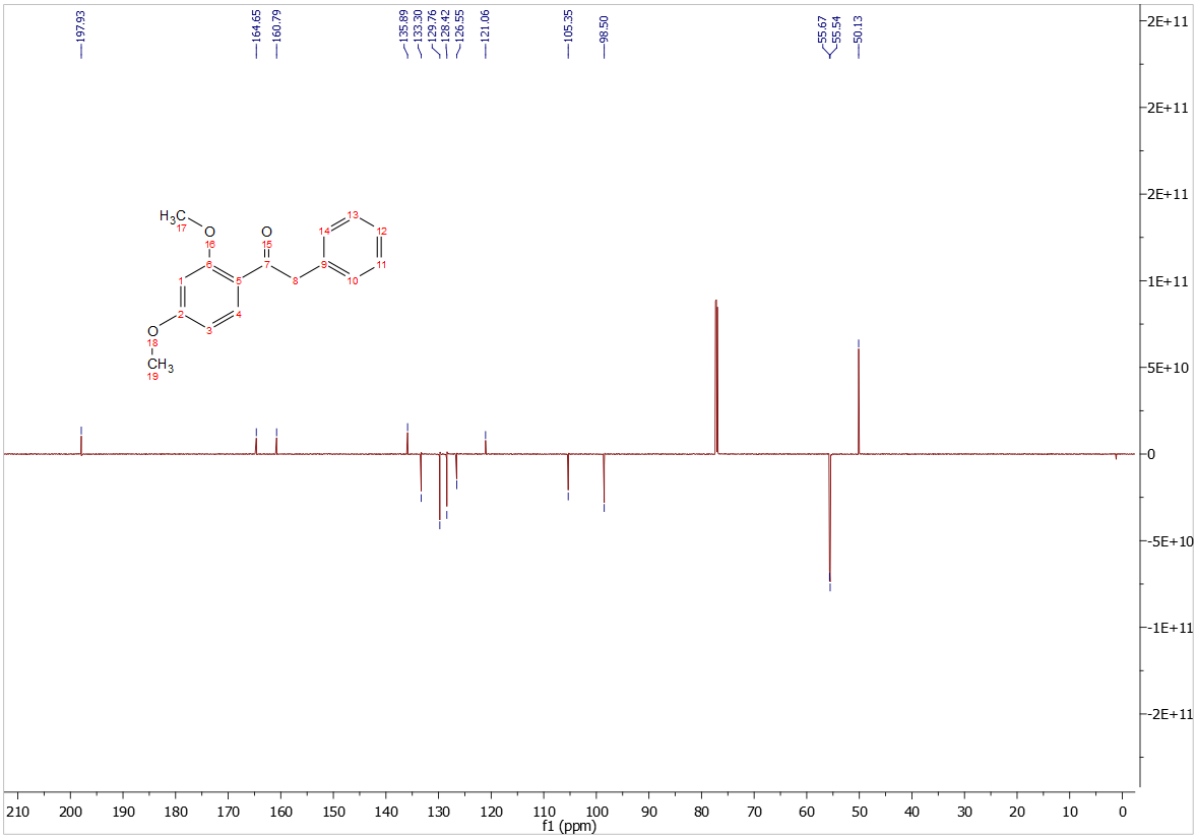

8.00
7.99
7.33
7.32
7.31
7.27
7.26
6.93
6.92
4.23
3.86
2.00
1.92
2.01
0.99
1.97
2.04
3.00
f1 (ppm)

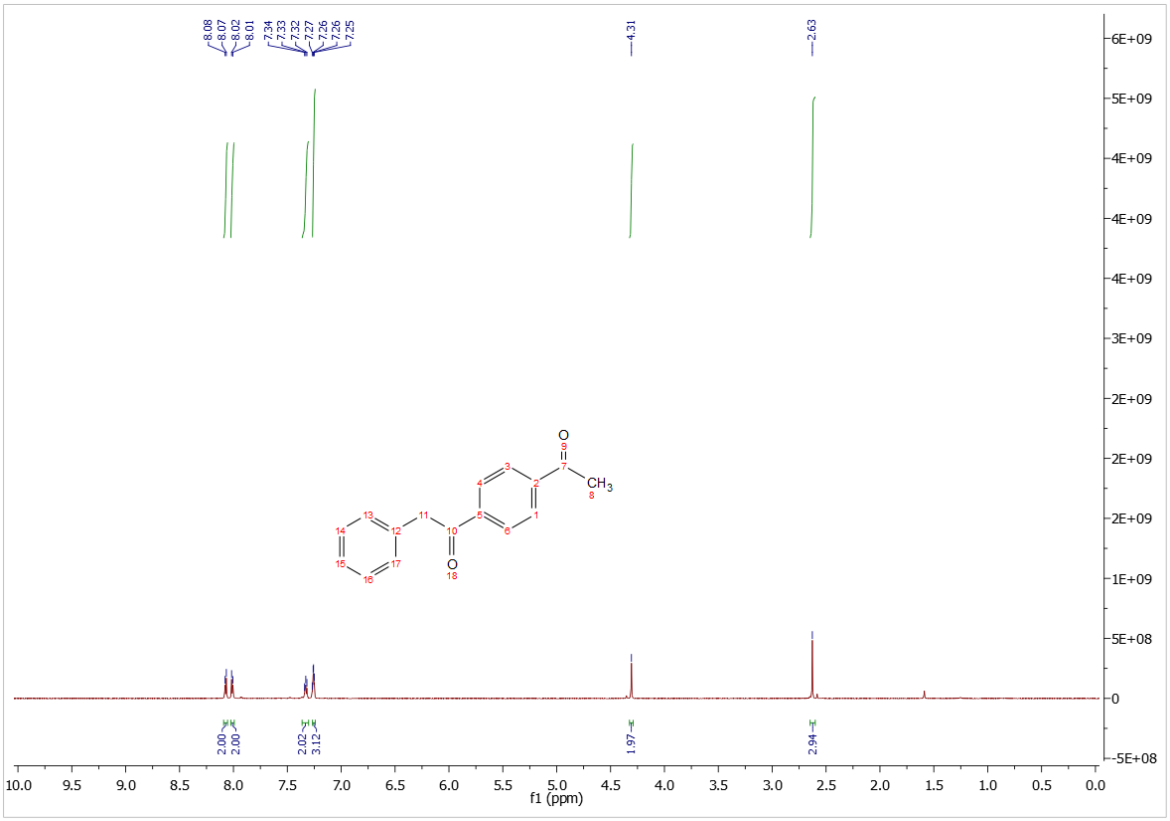

196.39
163.66
135.11
131.09
129.78
129.52
128.78
126.92
113.93
55.61
45.41
f1 (ppm)

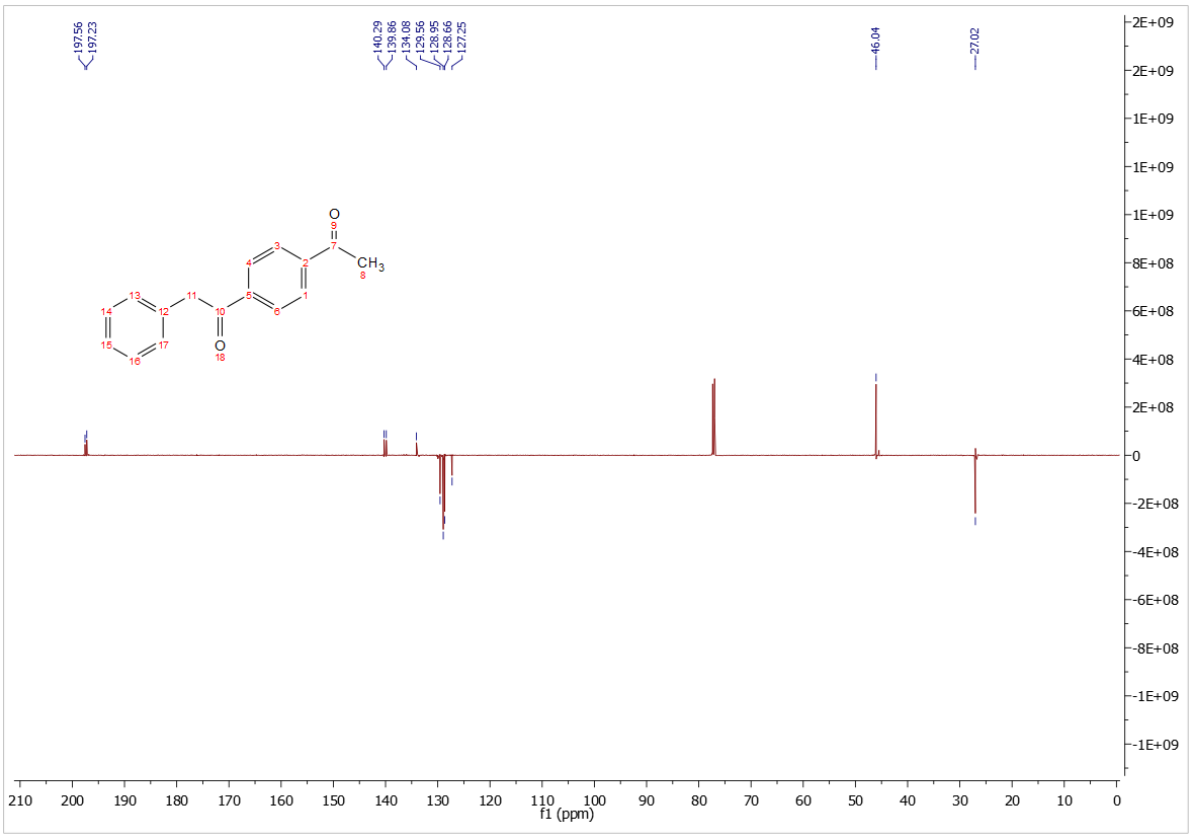

8.04
8.03
7.54
7.53
7.46
7.45
7.44
7.08
7.07
6.48
6.47
6.46
4.21
3.80
3.77
2.00
1.01
2.03
0.99
1.03
0.99
2.00
3.02
3.01
f1 (ppm)

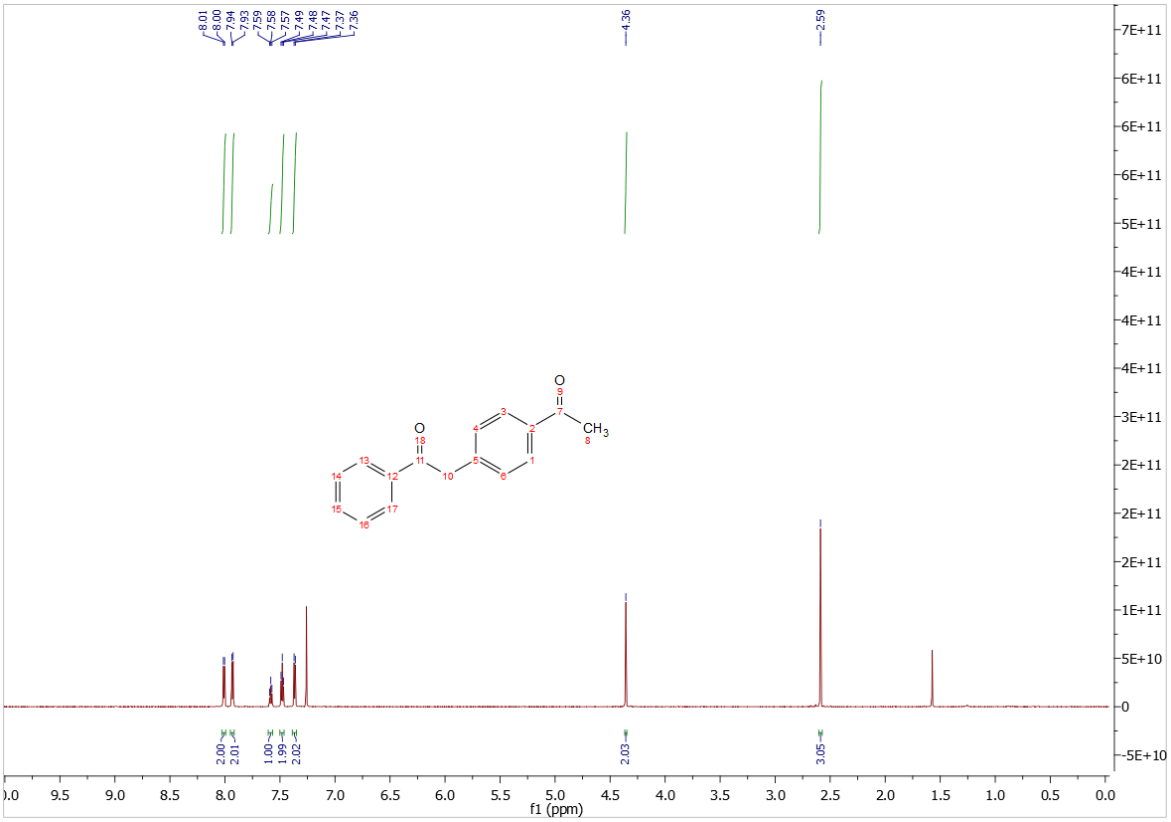

198.42
160.23
158.22
137.15
132.96
131.37
128.61
128.55
116.15
104.43
98.88
55.55
55.50
39.45
f1 (ppm)

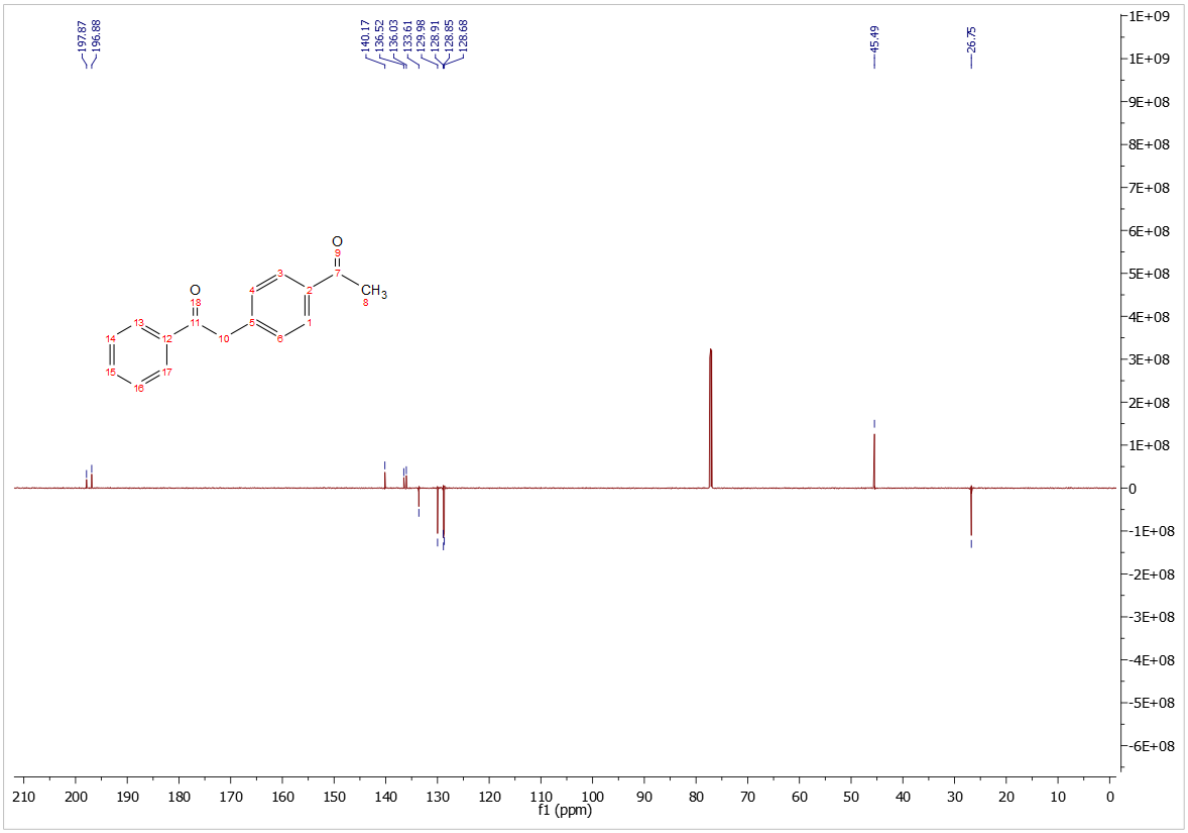

7.81
7.80
7.30
7.29
7.28
7.22
7.21
7.20
6.53
6.52
6.51
6.51
6.45
6.45
4.28
3.89
3.85
1.00
2.05
3.01
1.03
1.02
2.01
3.06
3.07
f1 (ppm)

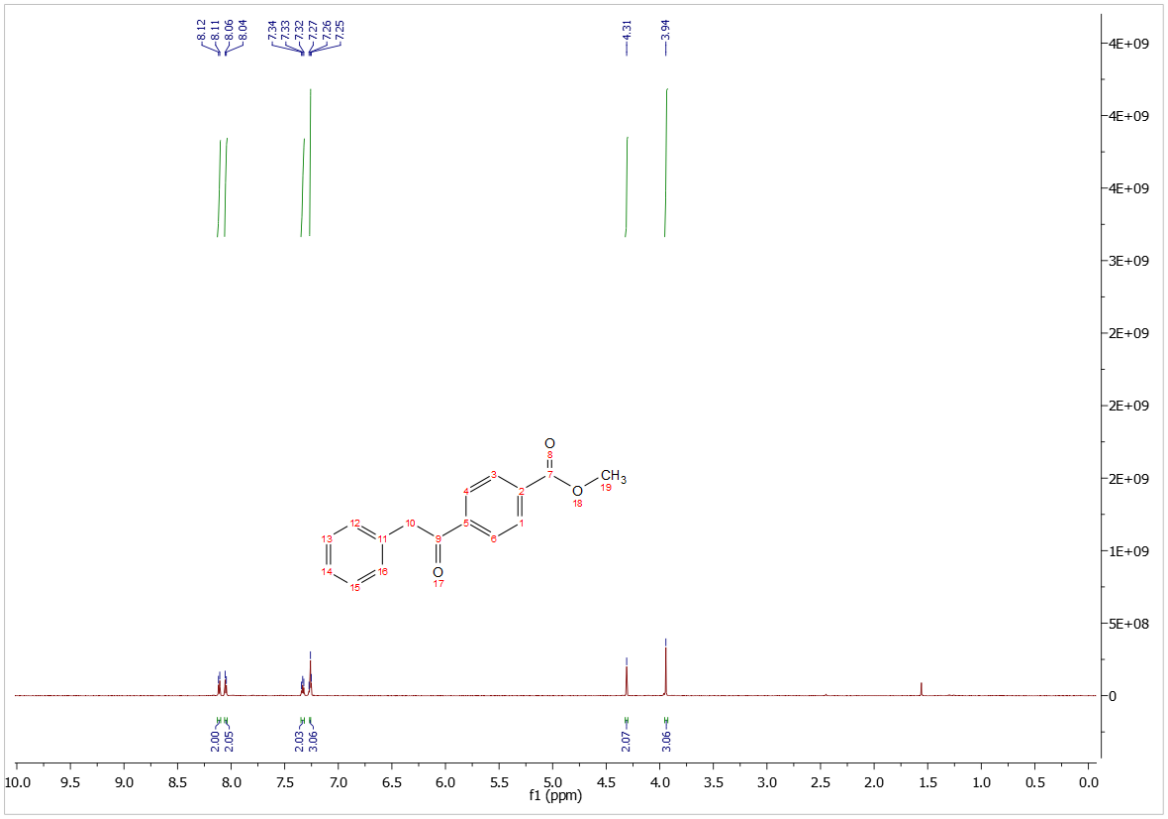

197.93
164.65
160.79
135.89
133.30
129.76
128.42
126.55
121.06
105.35
98.50
55.67
55.54
50.13
f1 (ppm)

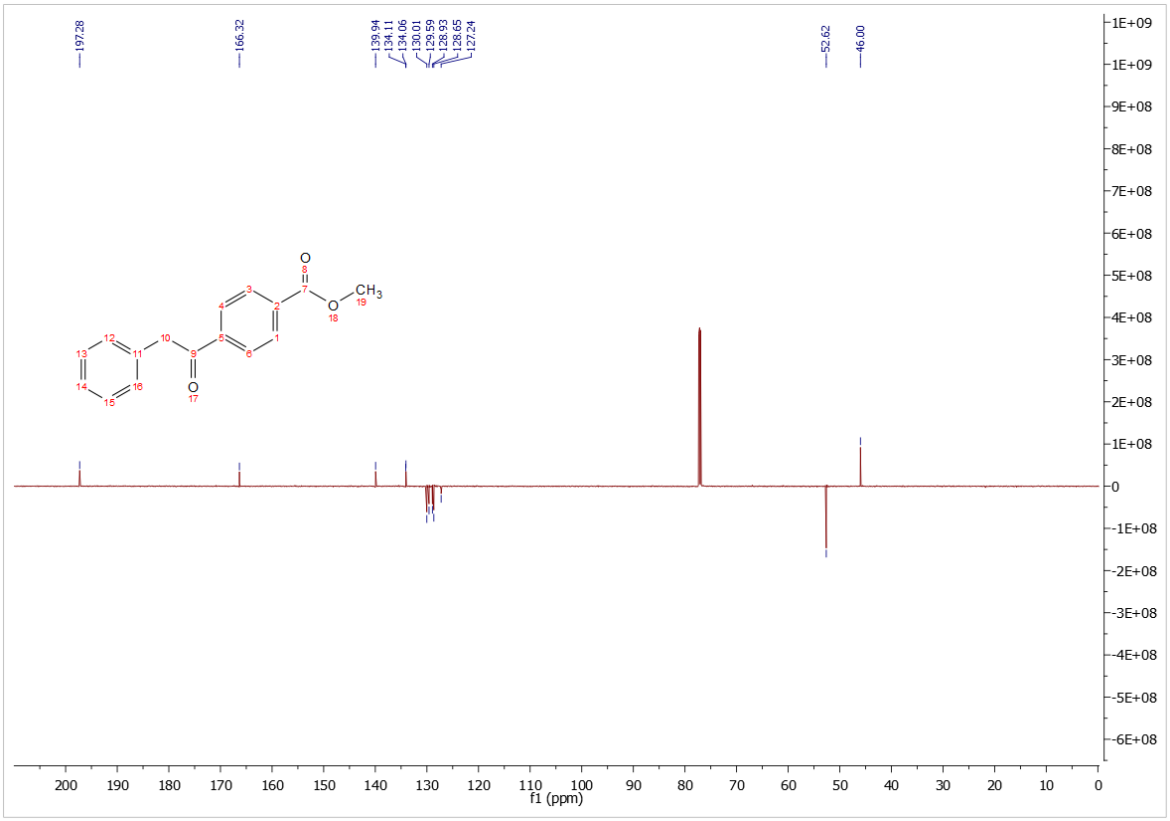

8.08
8.07
8.02
8.01
7.34
7.33
7.32
7.27
7.26
7.26
7.25
4.31
2.63
2.00
2.00
2.02
3.12
1.97
2.94
f1 (ppm)

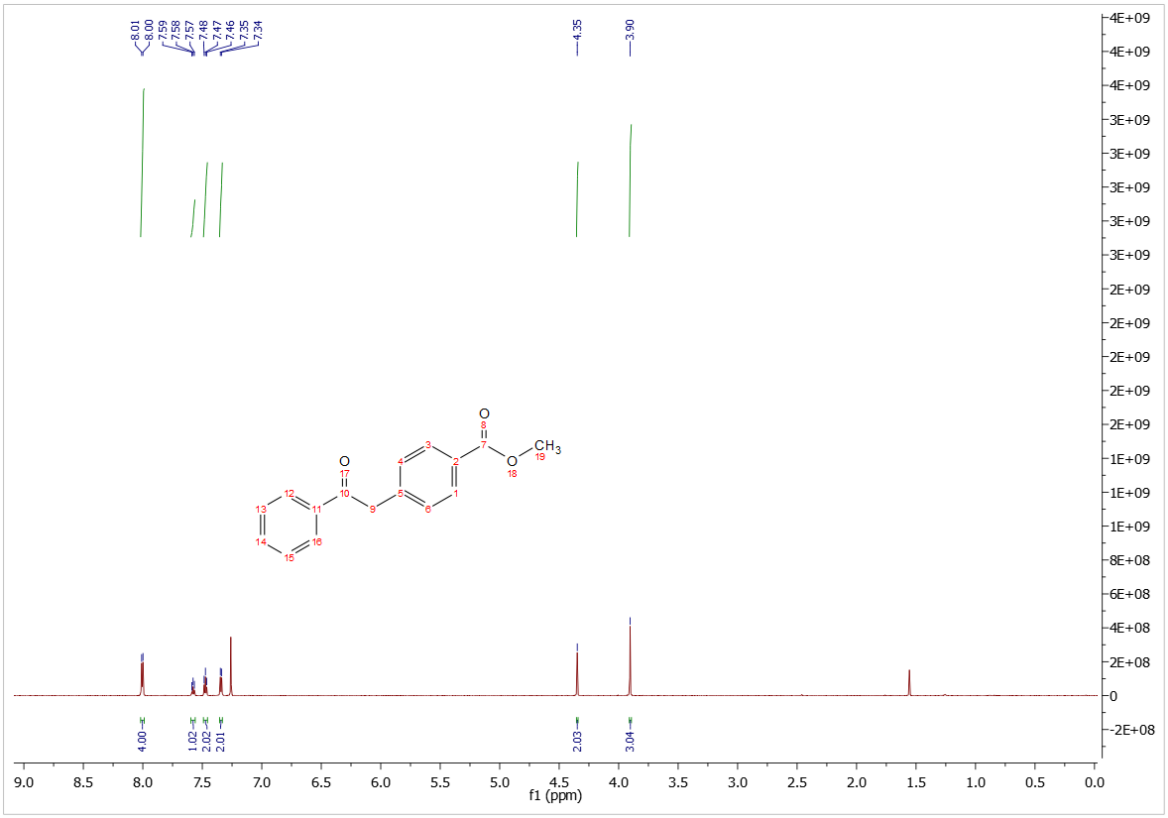

197.56
197.23
140.29
139.86
134.08
129.56
128.95
128.66
127.25
46.04
27.02
f1 (ppm)

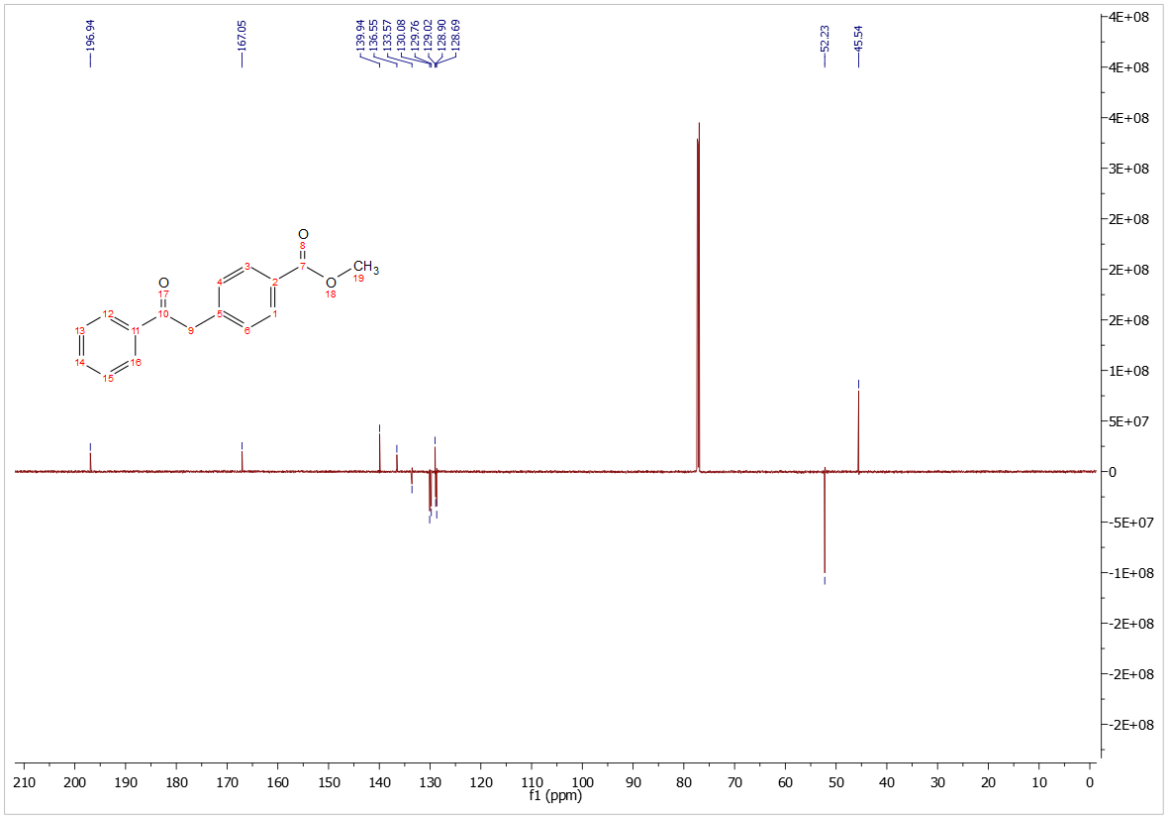

8.01
8.00
7.94
7.93
7.59
7.58
7.57
7.49
7.48
7.47
7.37
7.36
4.36
2.59
2.00
2.01
1.00
1.99
2.02
2.03
3.05
f1 (ppm)

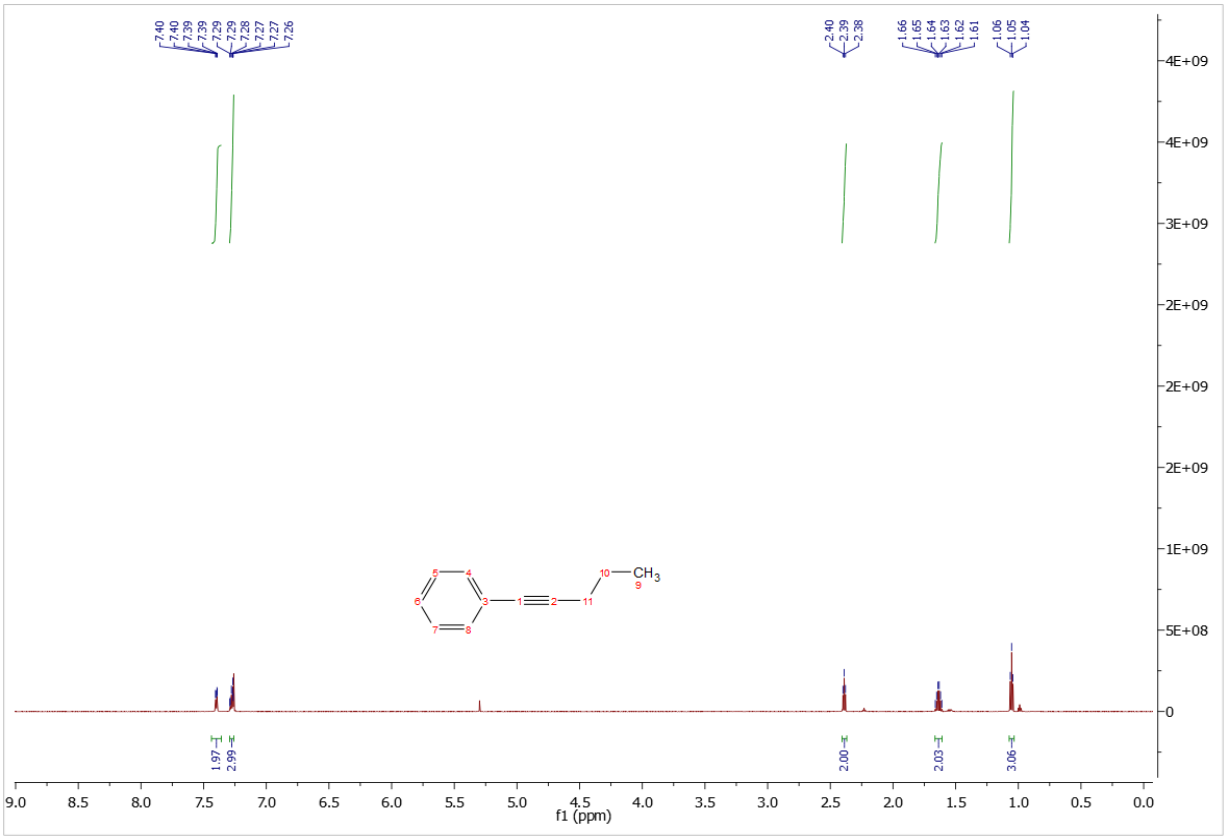

197.87
196.88
140.17
136.52
136.03
133.61
129.98
128.91
128.85
128.68
45.49
26.75
f1 (ppm)

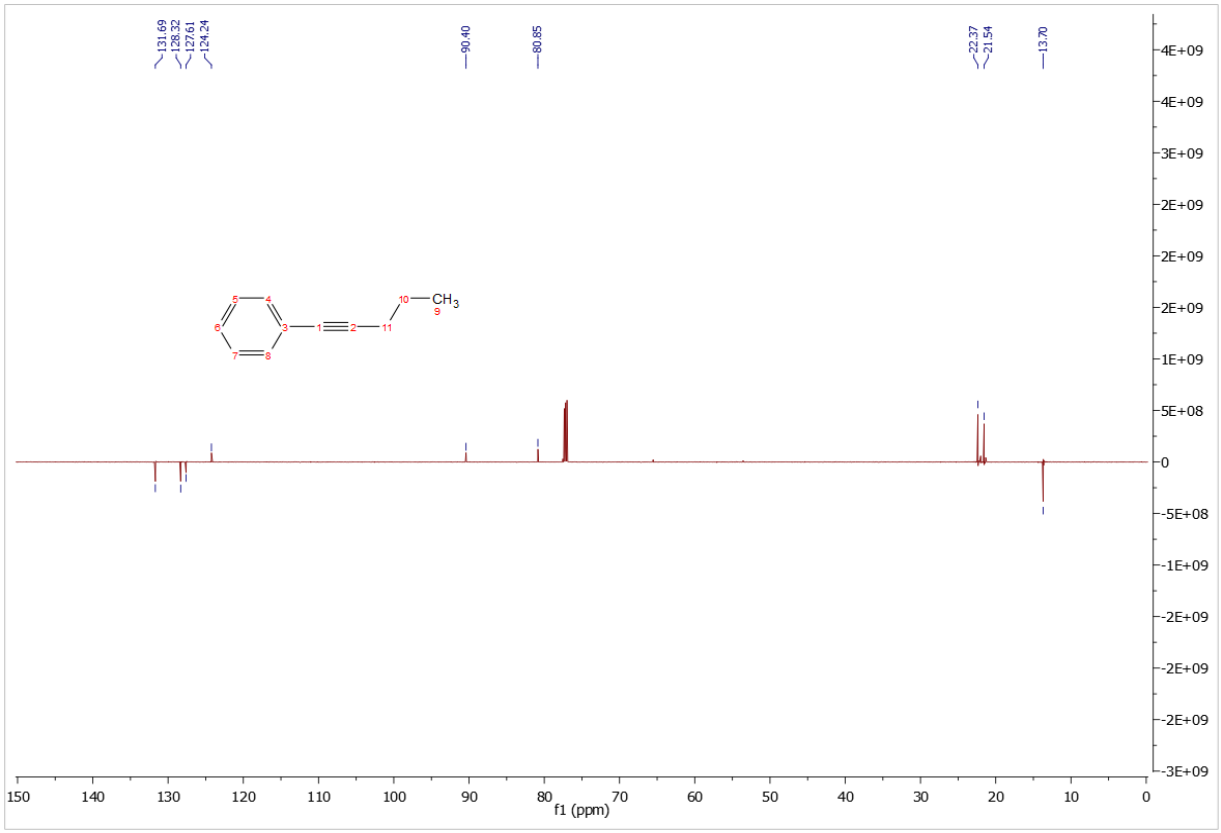

8.12
8.11
8.06
8.04
7.34
7.33
7.32
7.27
7.26
7.25
4.31
3.94
2.00
2.05
2.03
3.06
2.07
3.06
f1 (ppm)

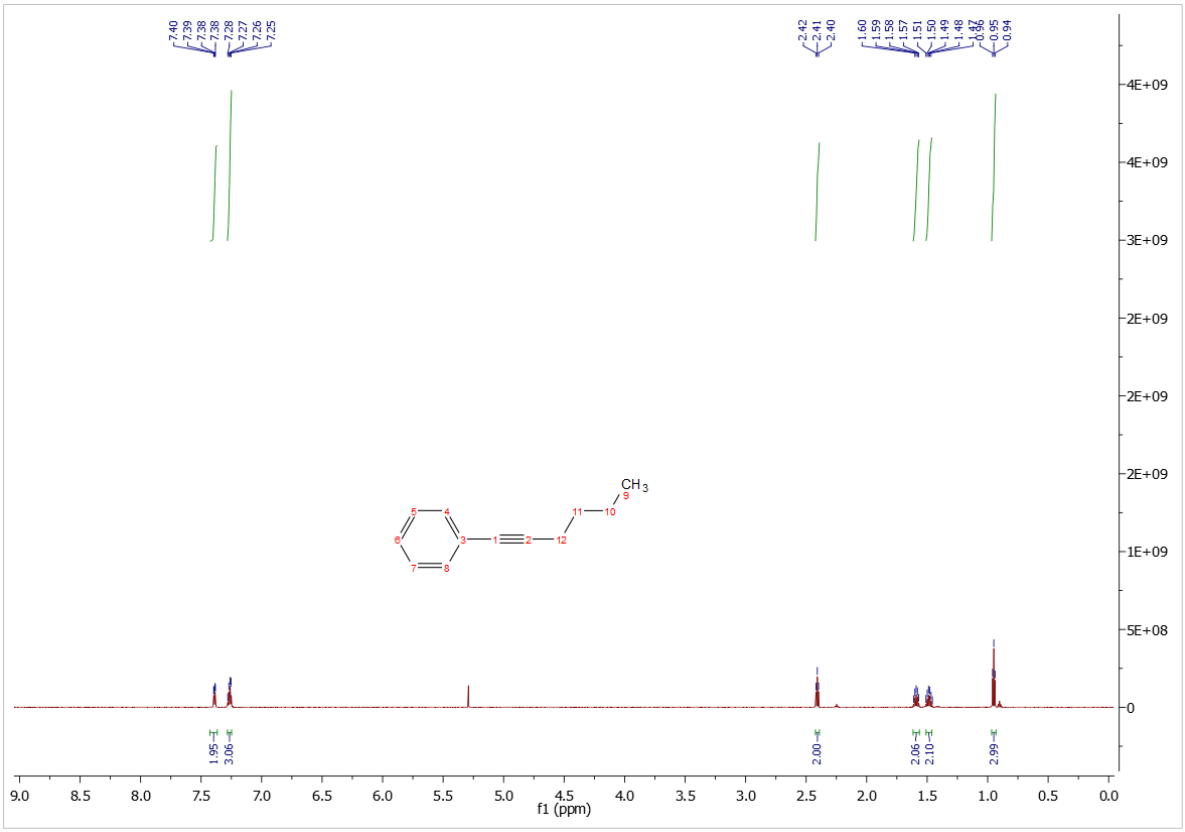

197.28
166.32
139.94
134.11
134.06
130.01
129.59
128.93
128.65
127.24
52.62
46.00
f1 (ppm)

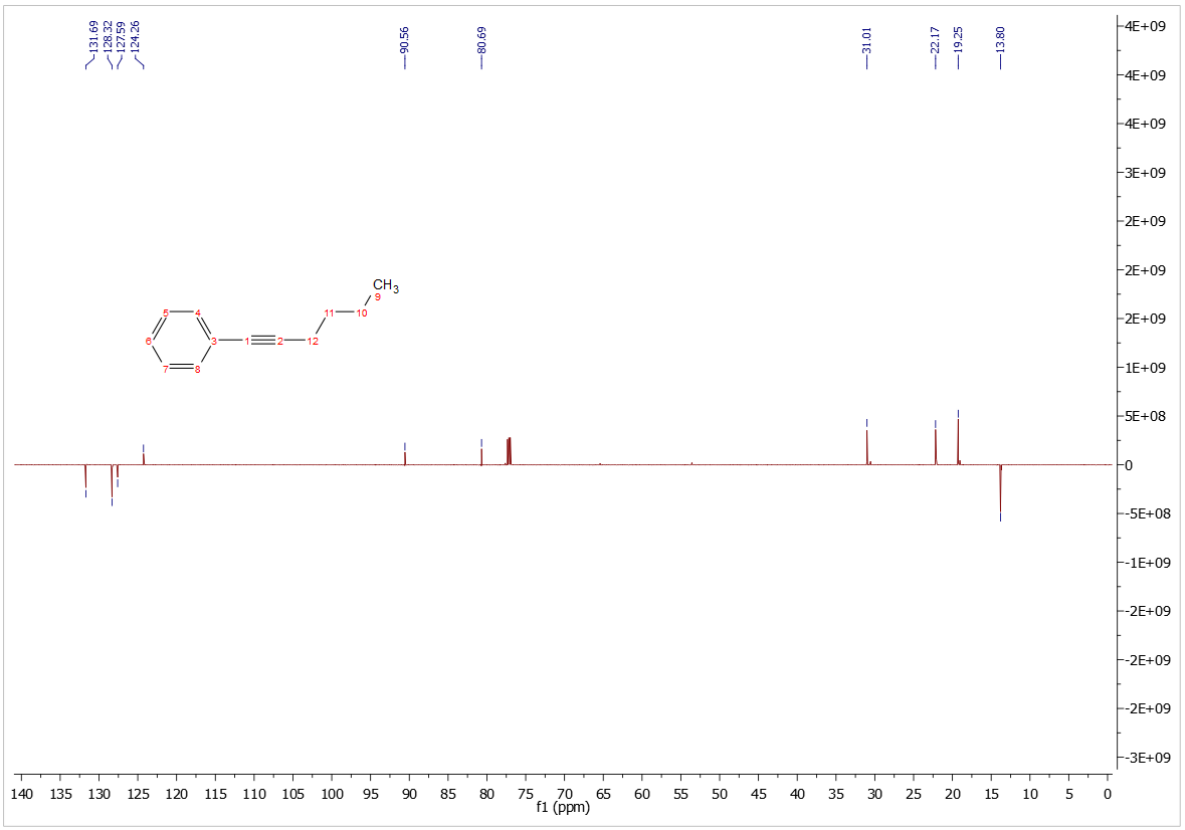

8.01
8.00
7.59
7.58
7.57
7.48
7.47
7.46
7.35
7.34
4.35
3.90
4.00
1.02
2.02
2.01
2.03
3.04
f1 (ppm)

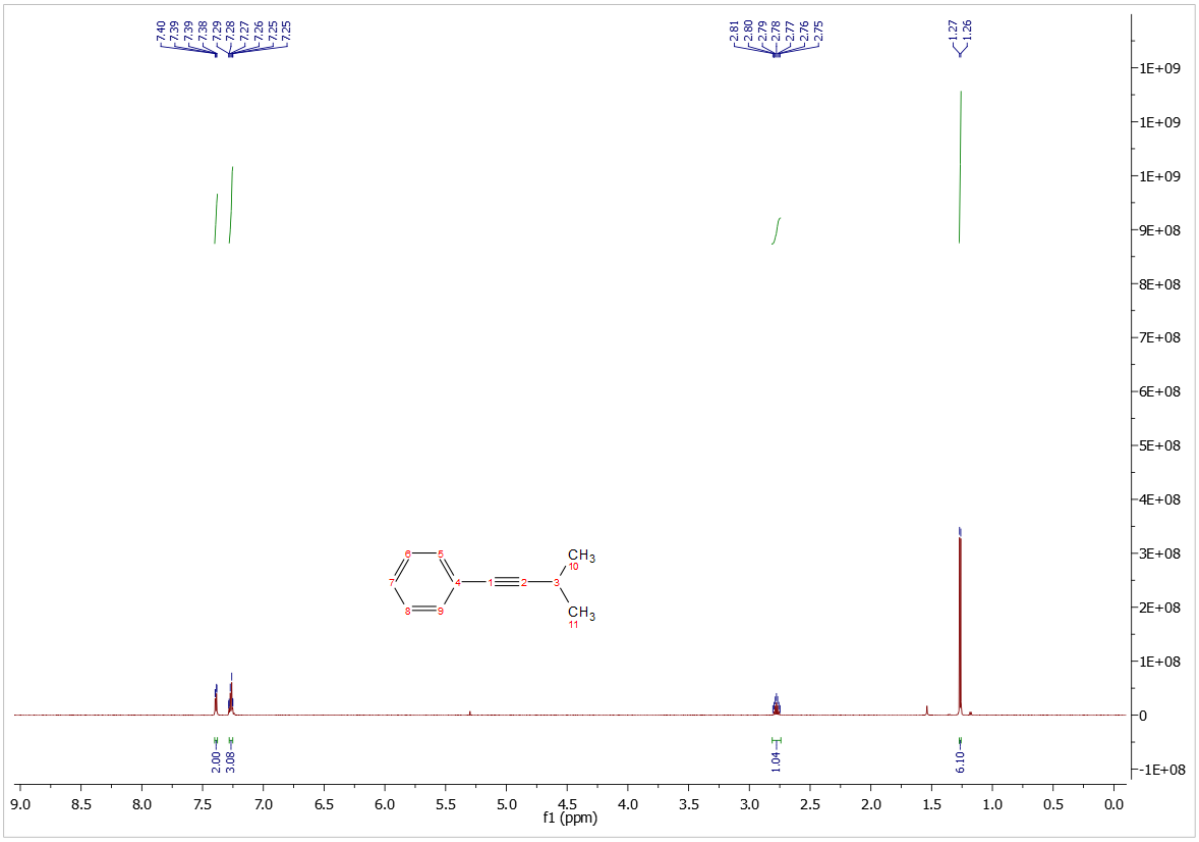

196.94
167.05
139.94
136.55
133.57
130.08
129.76
129.02
128.90
128.69
52.23
45.54
f1 (ppm)

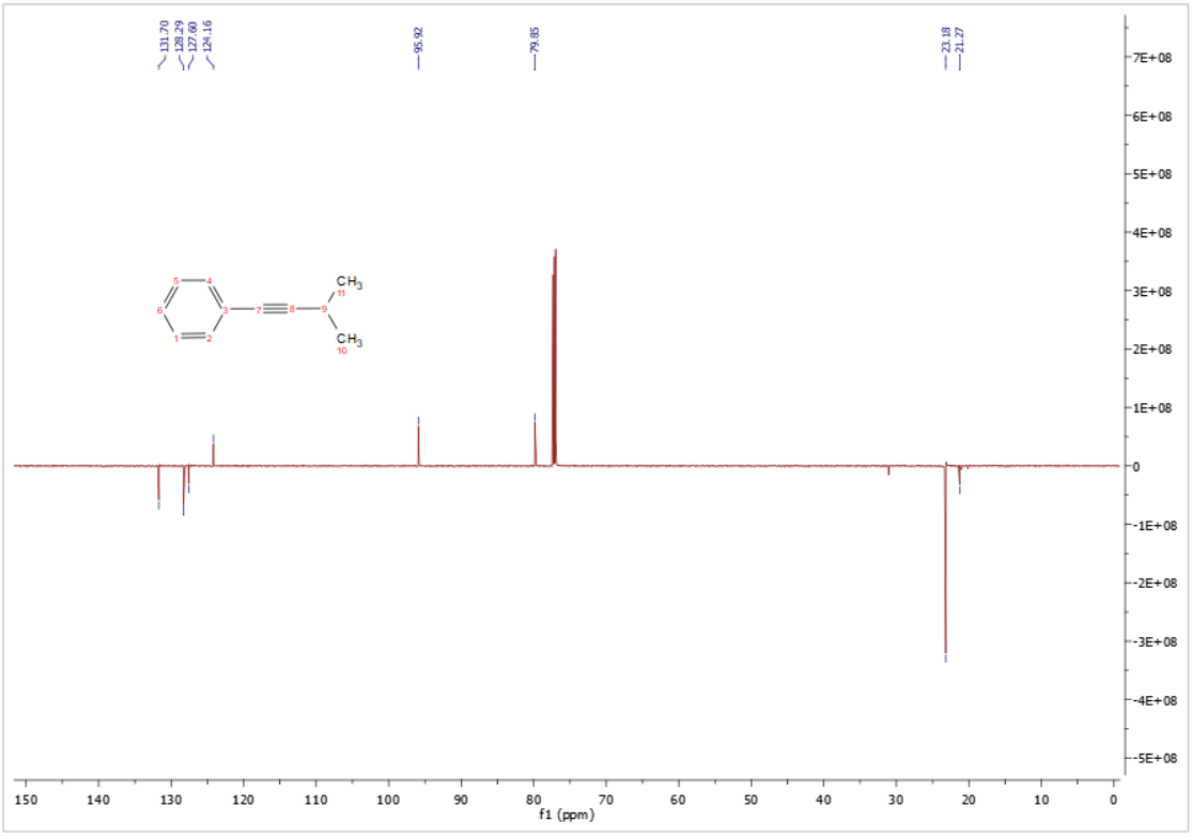

7.40
7.40
7.39
7.39
7.29
7.29
7.28
7.27
7.27
7.26
2.40
2.39
2.38
1.66
1.65
1.64
1.63
1.62
1.61
1.06
1.05
1.04
CH3
1.97
2.99
2.00
2.03
3.06
f1 (ppm)

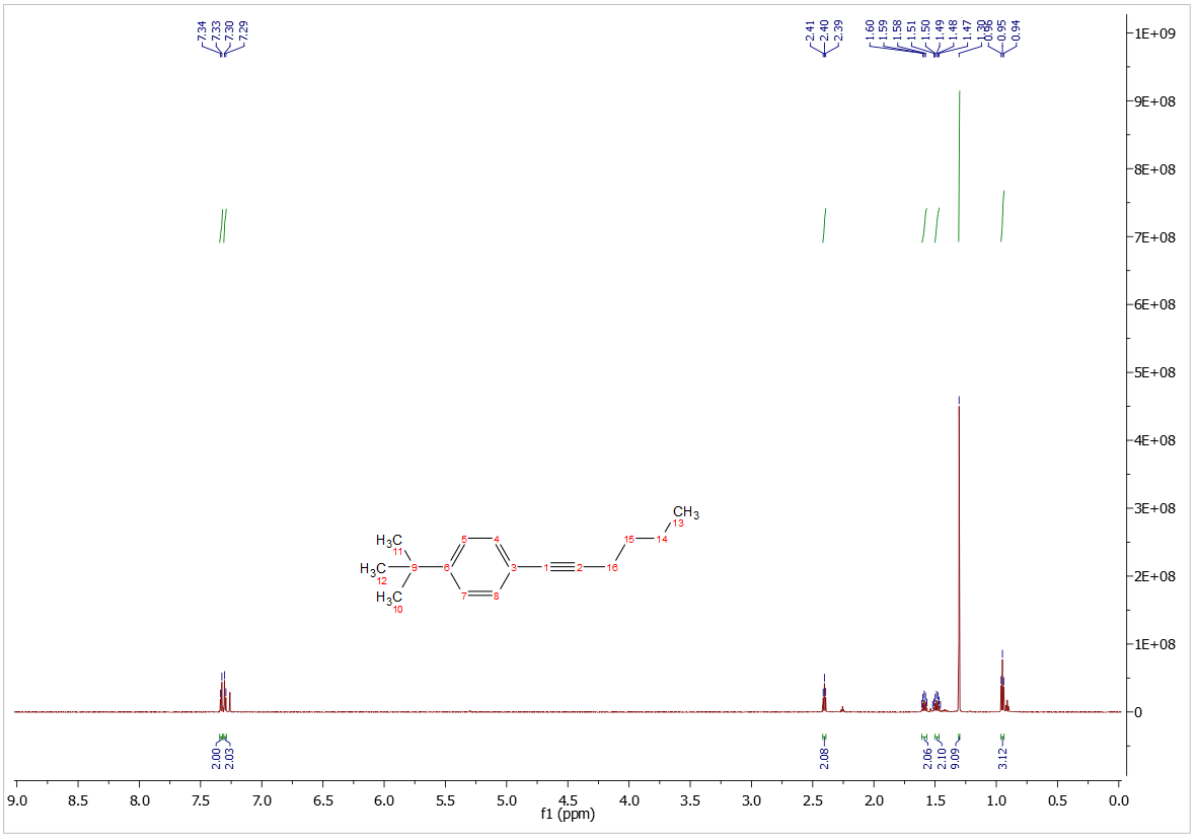

131.69
128.32
127.61
124.24
90.40
80.85
22.37
21.54
13.70
CH3
f1 (ppm)

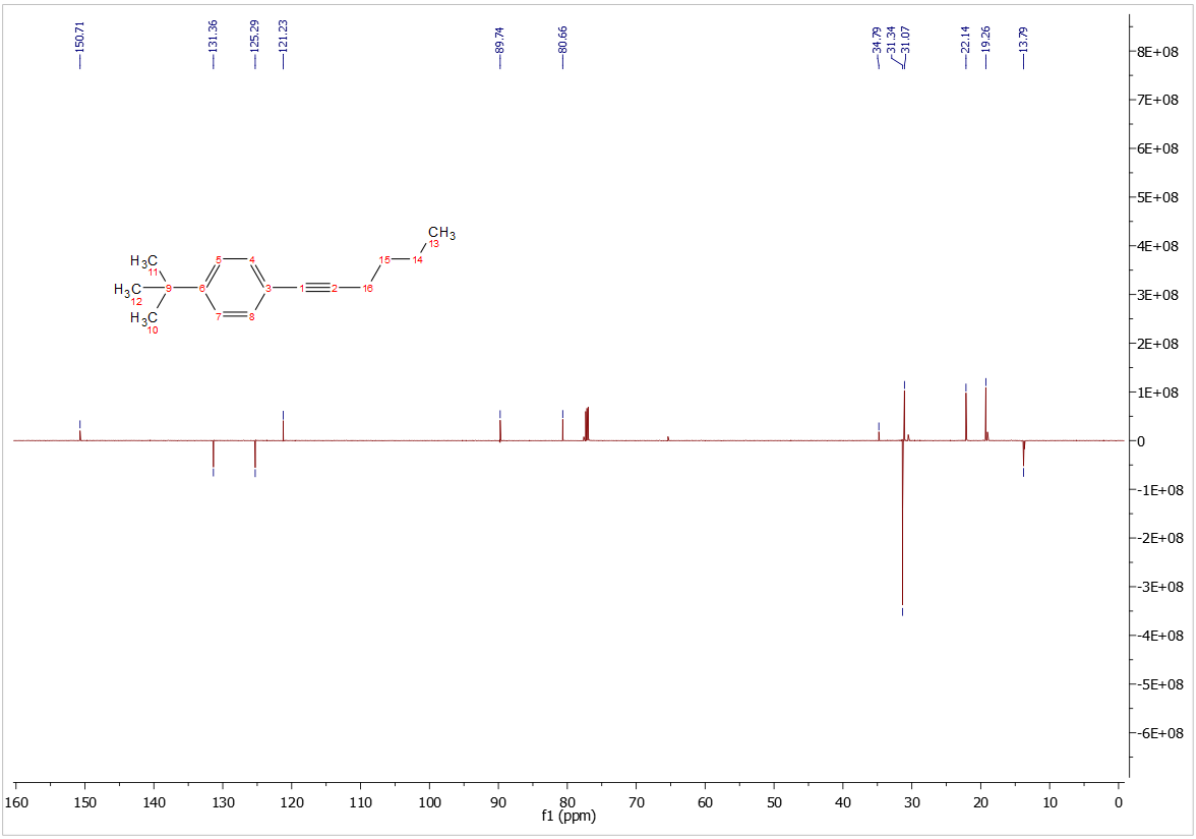

7.40
7.39
7.38
7.38
7.28
7.27
7.26
7.25
2.42
2.41
2.40
1.60
1.59
1.58
1.57
1.51
1.50
1.49
1.48
0.96
0.95
0.94
CH3
1.95
3.06
2.00
2.06
2.10
2.99
f1 (ppm)

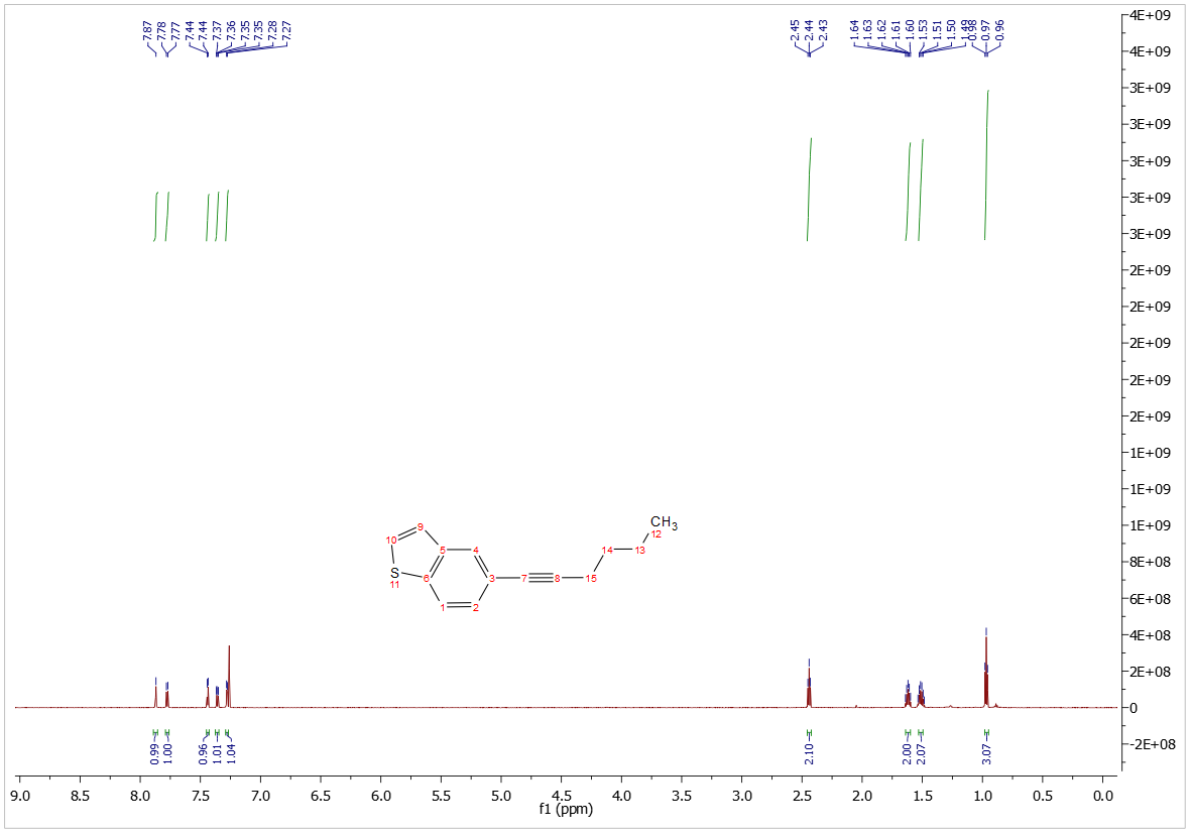

131.69
128.32
127.59
124.26
90.56
80.69
31.01
22.17
19.25
13.80
CH3
f1 (ppm)

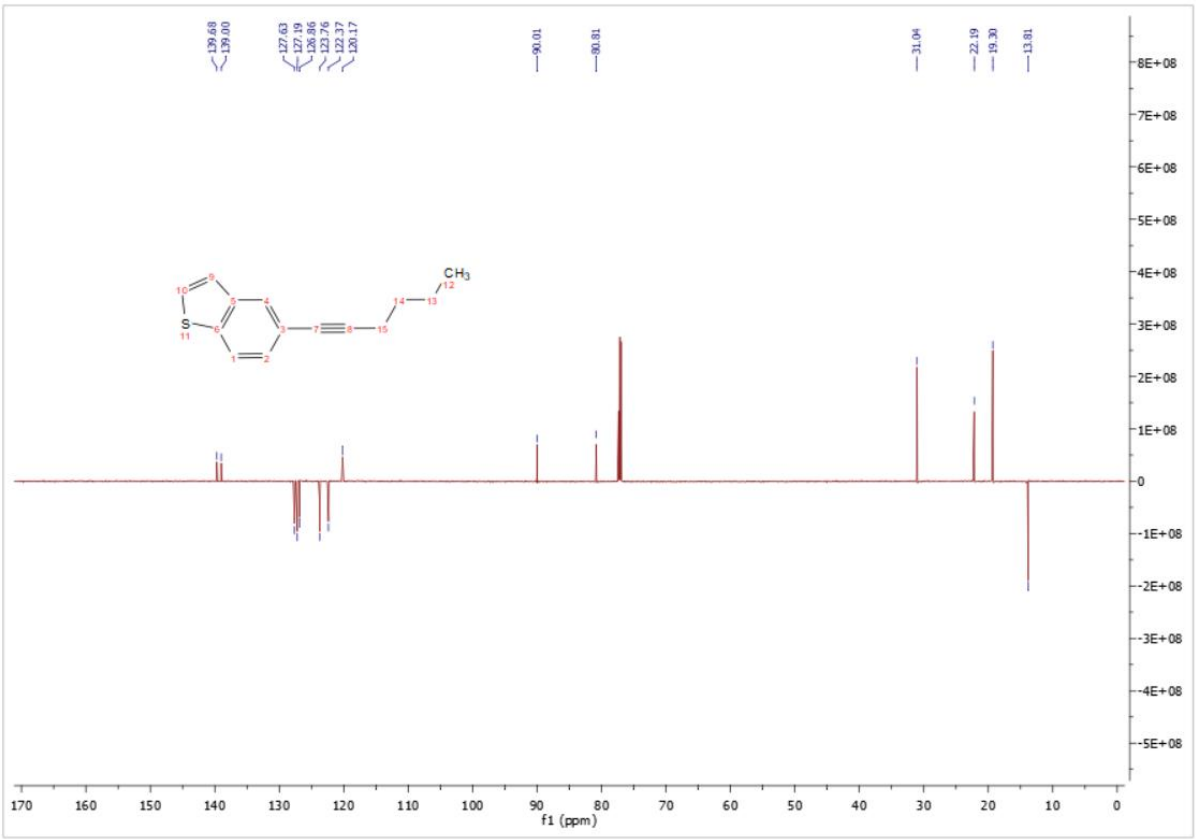

7.40
7.39
7.39
7.38
7.29
7.28
7.27
7.26
7.25
7.25
2.81
2.80
2.79
2.78
2.77
2.76
2.75
1.27
1.26
CH3
10
CH3
11
2.00
3.08
1.04
6.10
f1 (ppm)

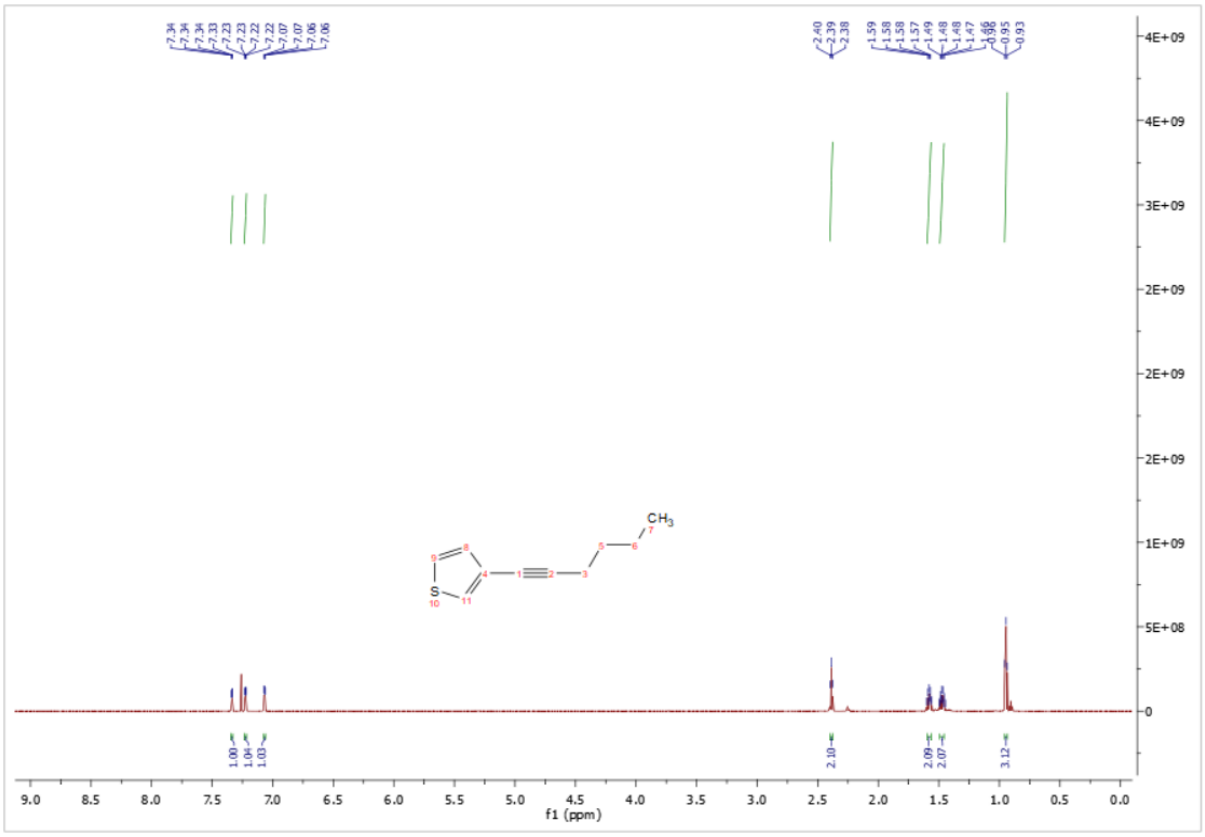

131.70
128.29
127.60
124.16
95.92
79.85
23.18
21.27
CH3
11
CH3
10
f1 (ppm)

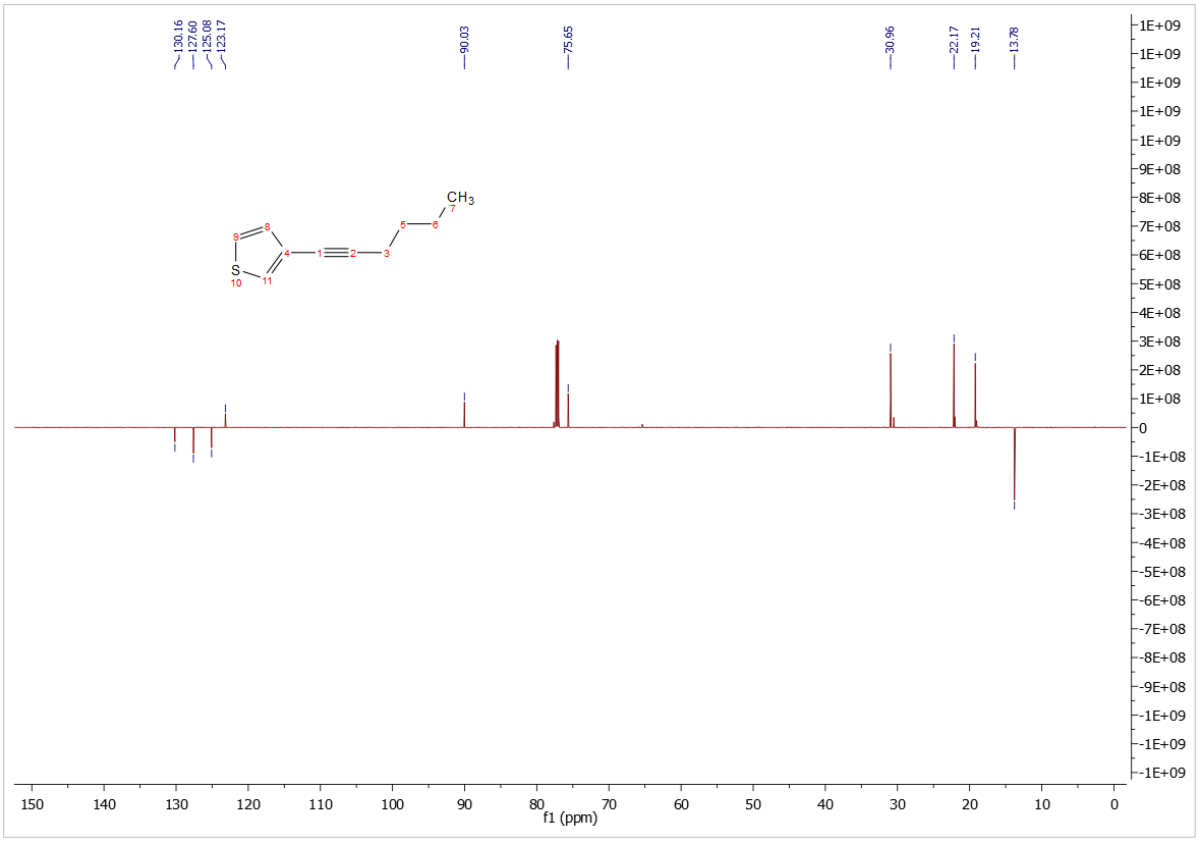

7.34
7.33
7.30
7.29
2.41
2.40
2.39
1.60
1.59
1.58
1.51
1.50
1.49
1.48
1.47
1.30
0.98
0.95
0.94
CH3
13
H3C
11
H3C
12
H3C
10
2.00
2.03
2.08
2.06
2.10
9.09
3.12
f1 (ppm)

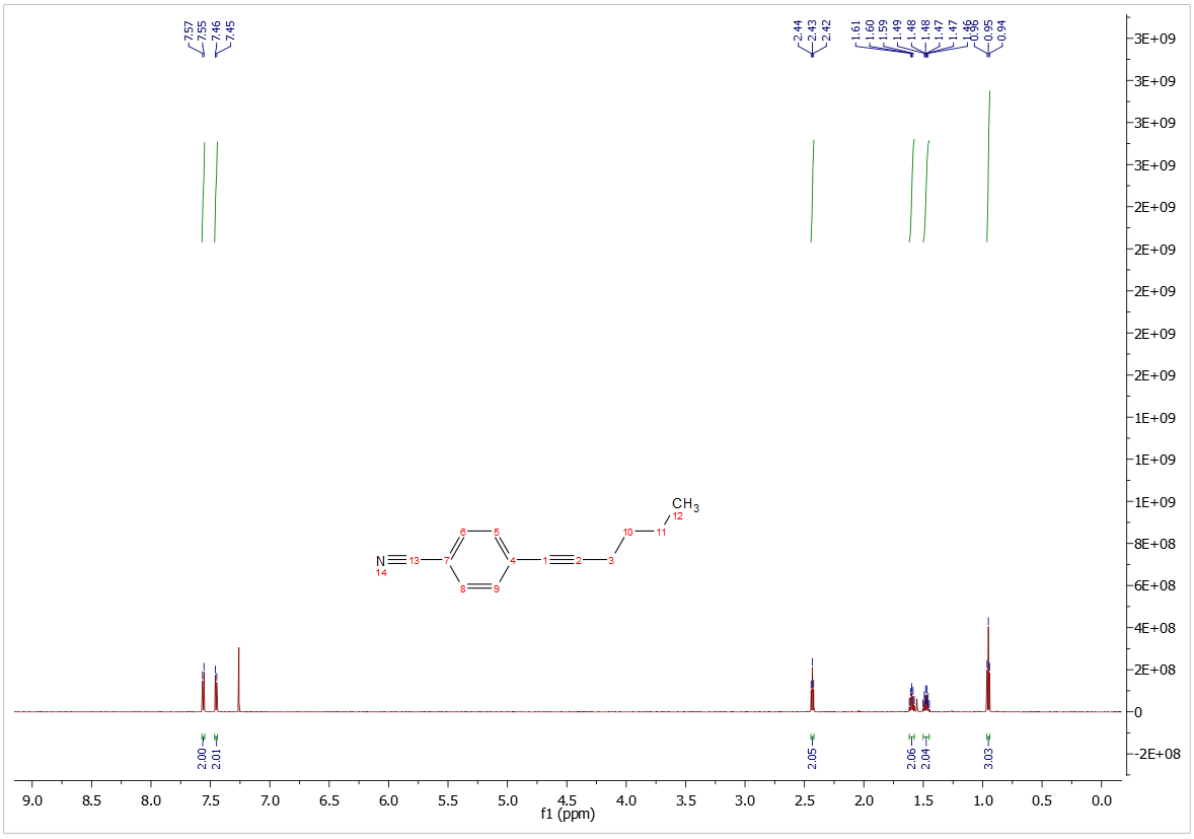

150.71
131.36
125.29
121.23
89.74
80.66
34.79
31.34
31.07
22.14
19.26
13.79
CH3
13
H3C
11
H3C
12
H3C
10
f1 (ppm)

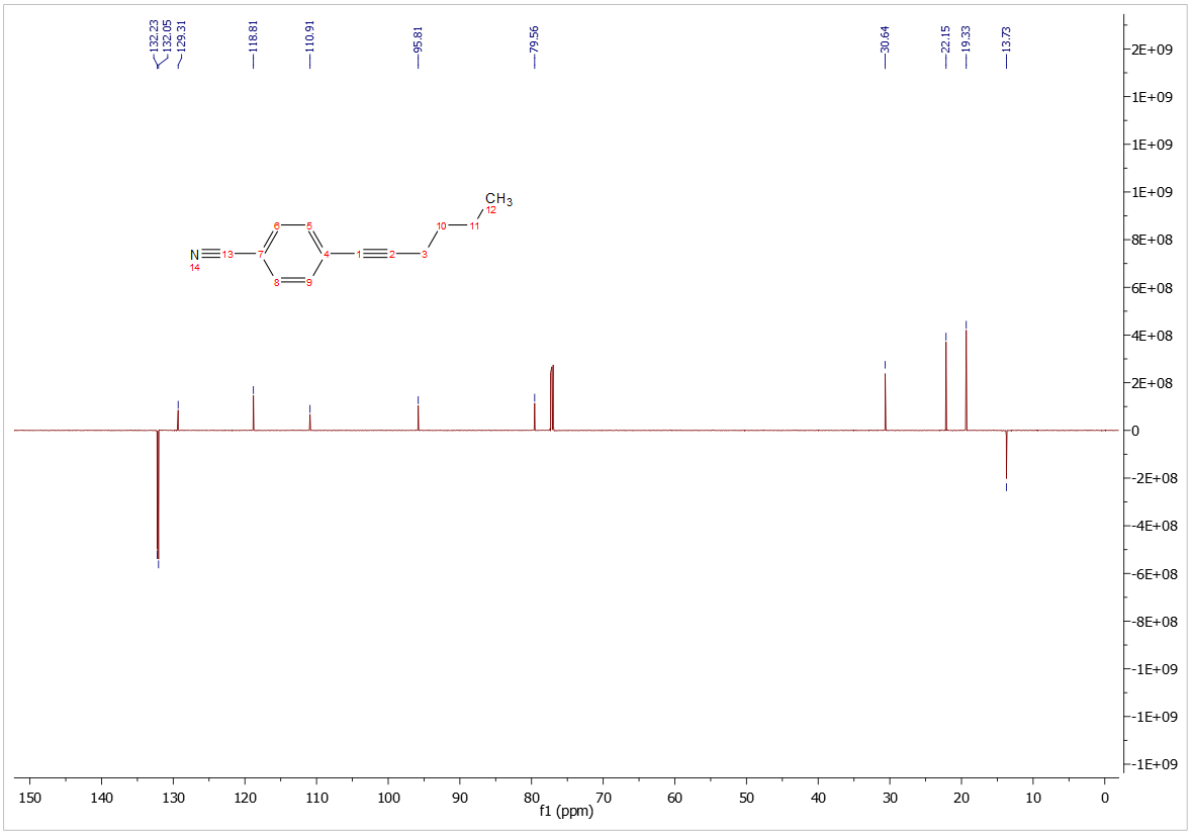

7.87
7.78
7.77
7.44
7.44
7.37
7.36
7.35
7.35
7.28
7.27
2.45
2.44
2.43
1.64
1.63
1.62
1.61
1.60
1.53
1.51
1.50
1.48
0.98
0.97
0.96
CH3
0.99
1.00
0.96
1.01
1.04
2.10
2.00
2.07
3.07
f1 (ppm)

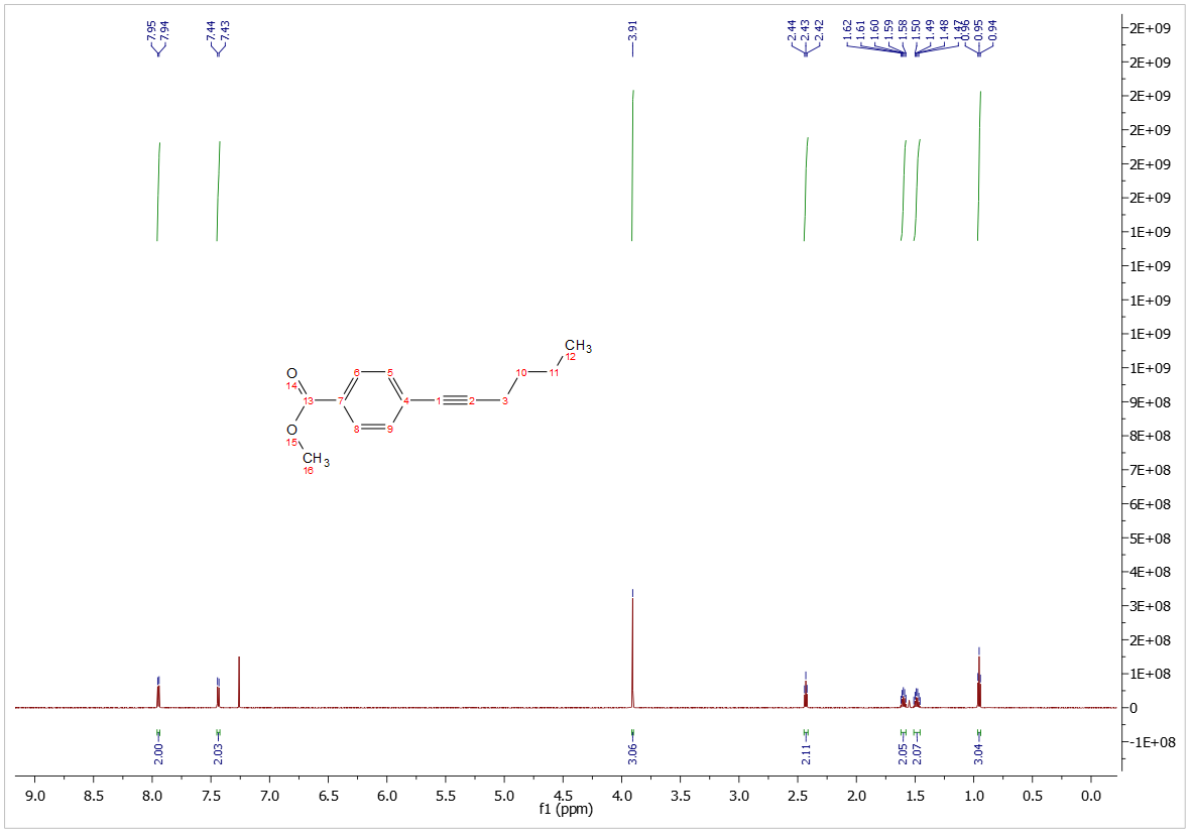

139.68
139.00
127.63
127.19
126.86
123.76
122.37
120.17
90.01
80.81
31.04
22.19
19.30
13.81
CH3
f1 (ppm)

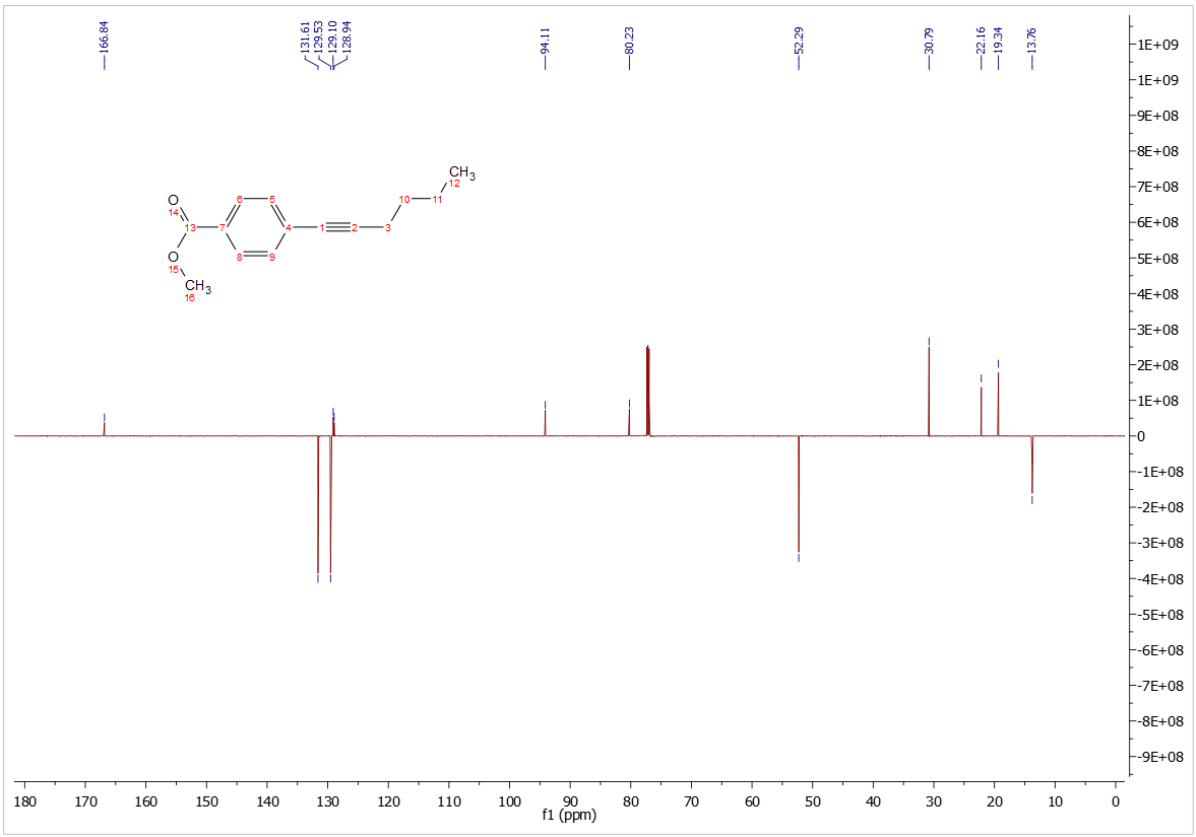

7.34
7.34
7.34
7.33
7.23
7.23
7.22
7.22
7.07
7.07
7.06
7.06
2.40
2.39
2.38
1.59
1.58
1.58
1.57
1.49
1.48
1.48
1.47
0.96
0.95
0.93
CH3
1.00
1.04
1.03
2.10
2.09
2.07
3.12
f1 (ppm)

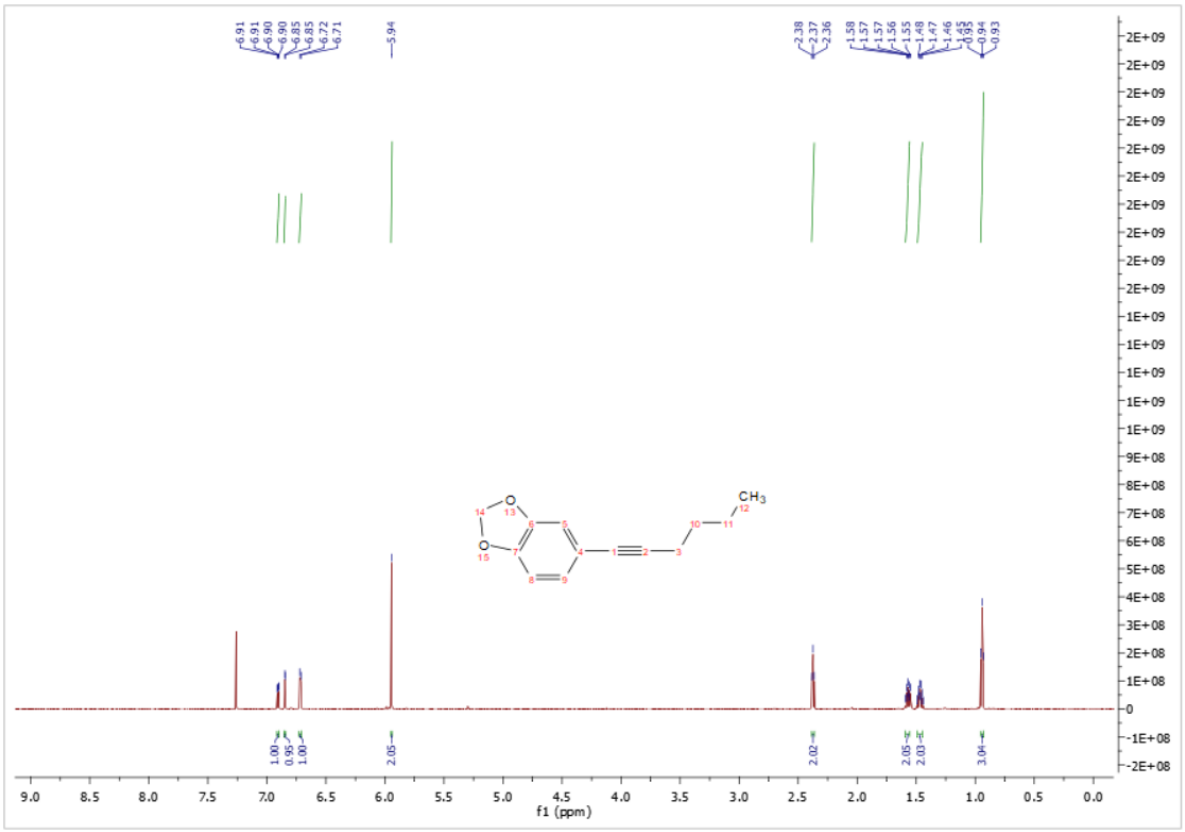

130.16
127.60
125.08
123.17
90.03
75.65
30.96
22.17
19.21
13.78
CH3
f1 (ppm)

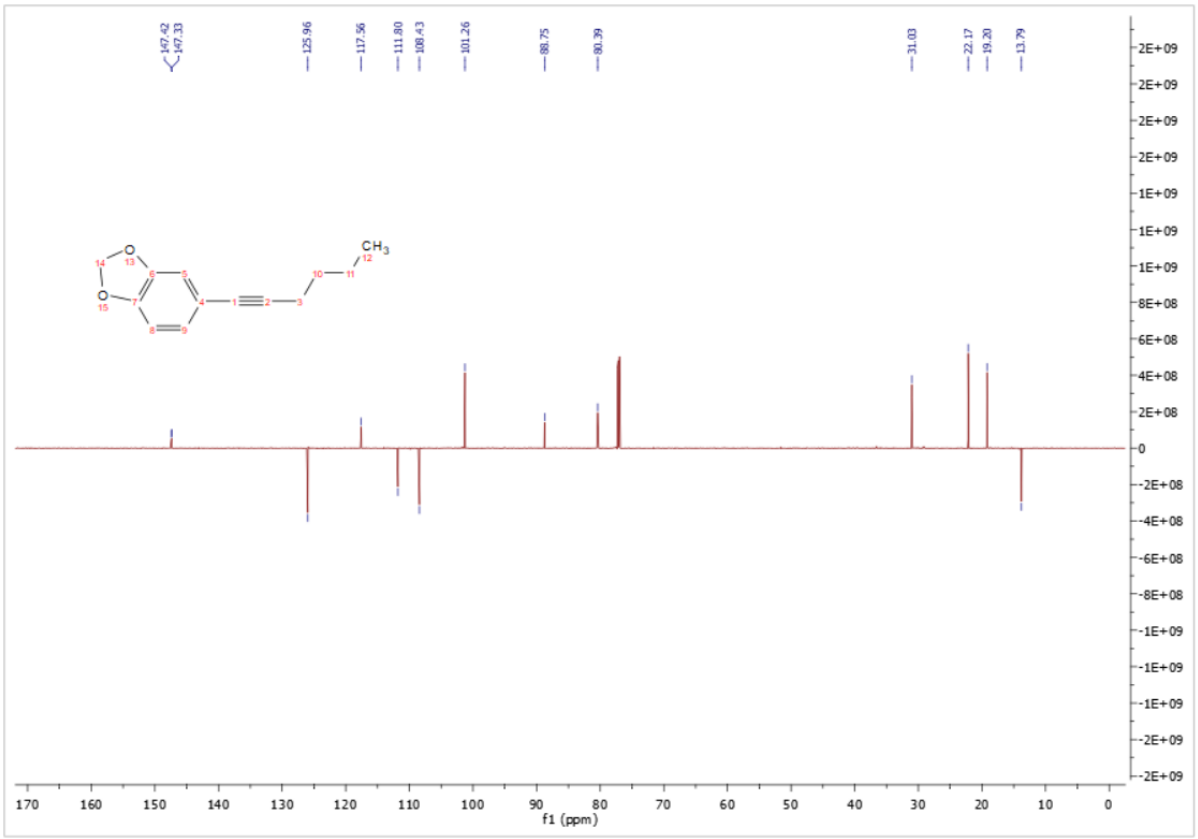

7.57
7.55
7.46
7.45
2.44
2.43
2.42
1.61
1.60
1.59
1.49
1.48
1.47
0.96
0.95
0.94
CH3
12
N
14
2.00
2.01
2.05
2.06
2.04
3.03
f1 (ppm)

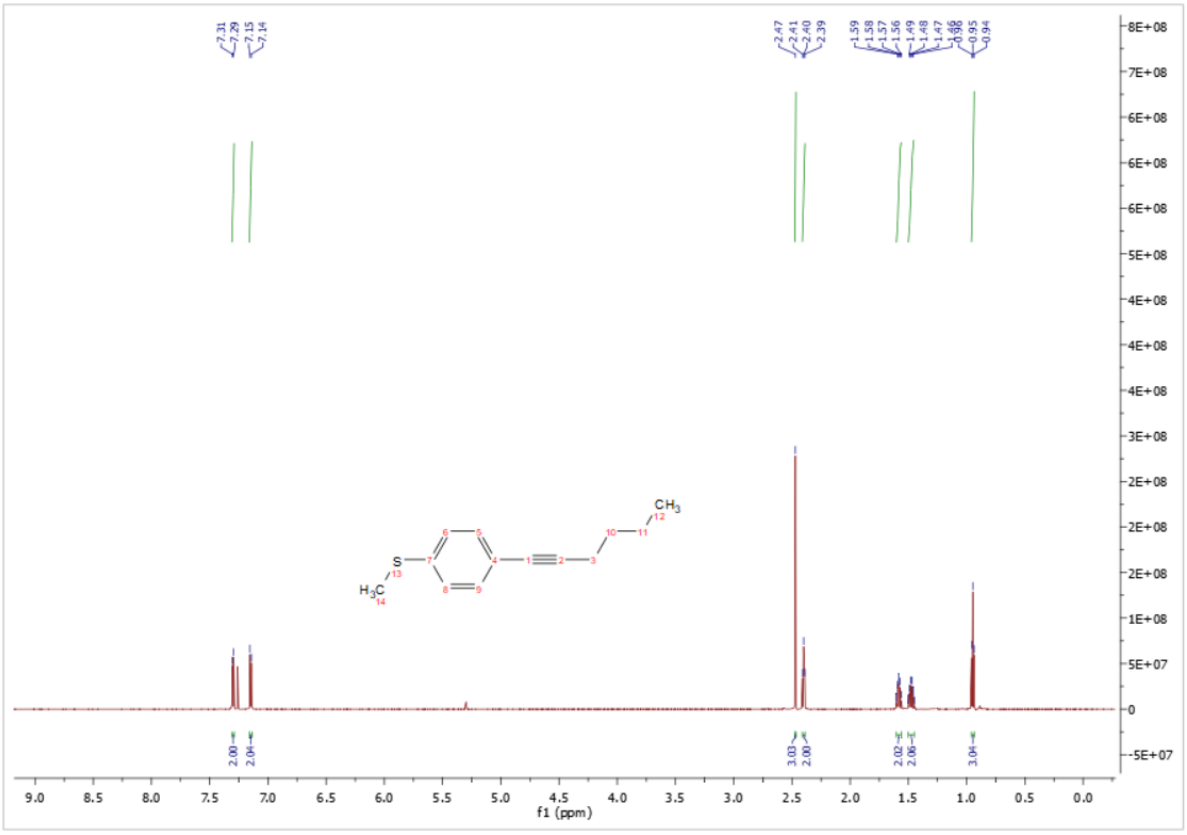

132.23
132.05
129.31
118.81
110.91
95.81
79.56
30.64
22.15
19.33
13.73
CH3
12
N
14
f1 (ppm)

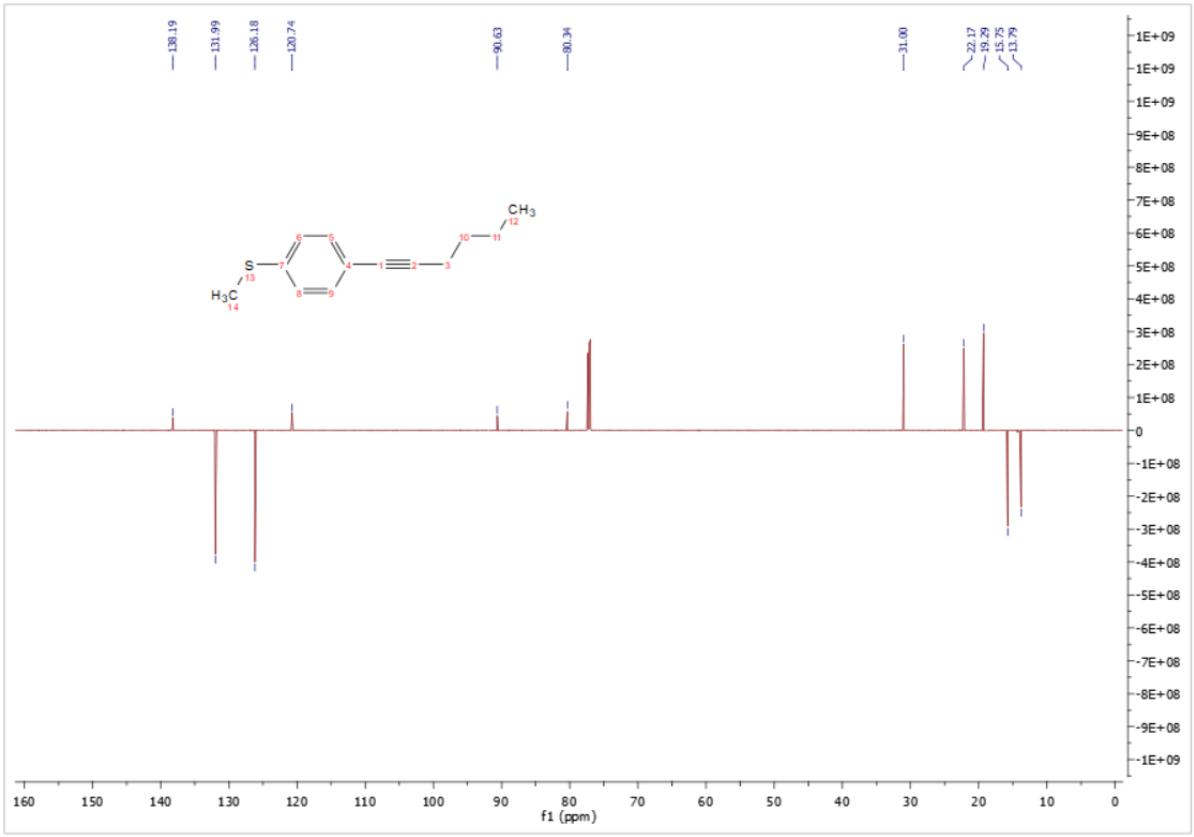

7.95
7.94
7.44
7.43
3.91
2.44
2.43
2.42
1.62
1.61
1.60
1.59
1.58
1.50
1.49
1.48
0.95
0.94
CH3
12
O
14
13
7
6
5
4
1
2
3
10
11
O
15
CH3
16
8
9
2.00
2.03
3.06
2.11
2.05
2.07
3.04
f1 (ppm)

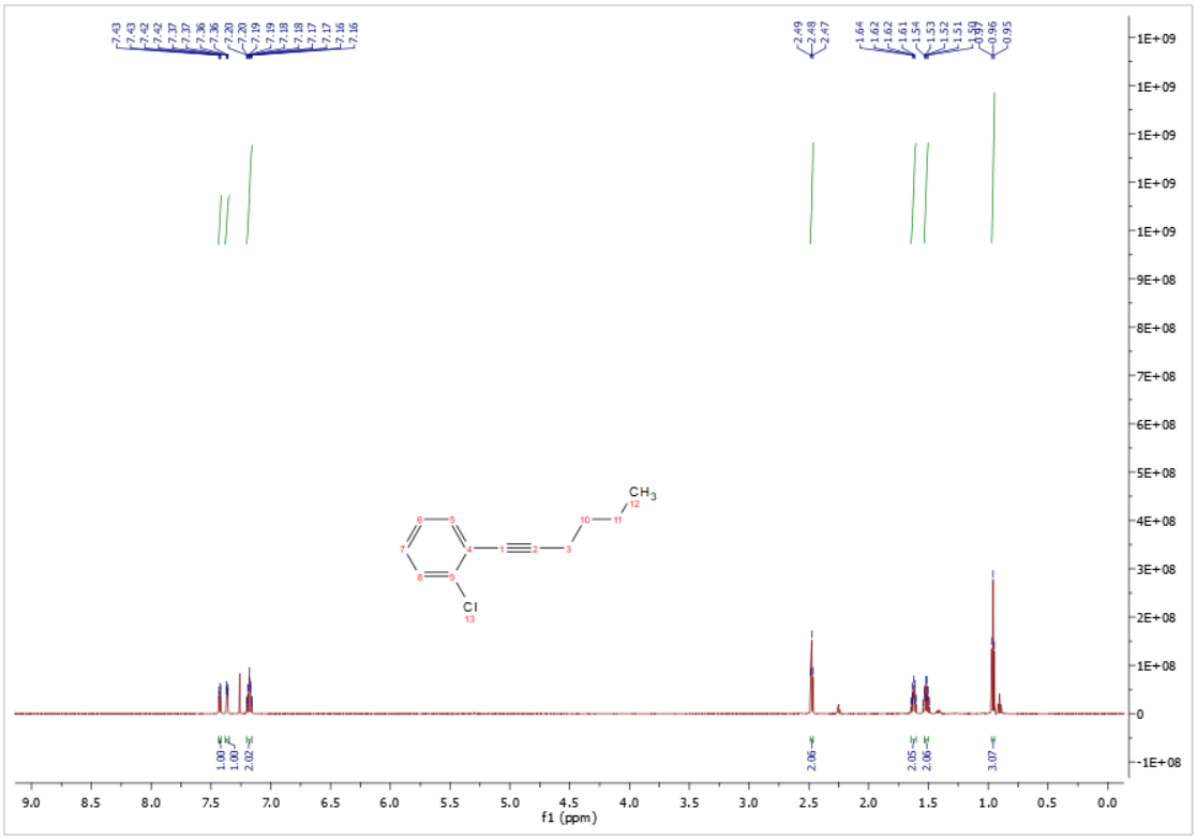

166.84
131.61
129.53
129.10
128.94
94.11
80.23
52.29
30.79
22.16
19.34
13.76
CH3
12
O
14
13
7
6
5
4
1
2
3
10
11
O
15
CH3
16
8
9
f1 (ppm)

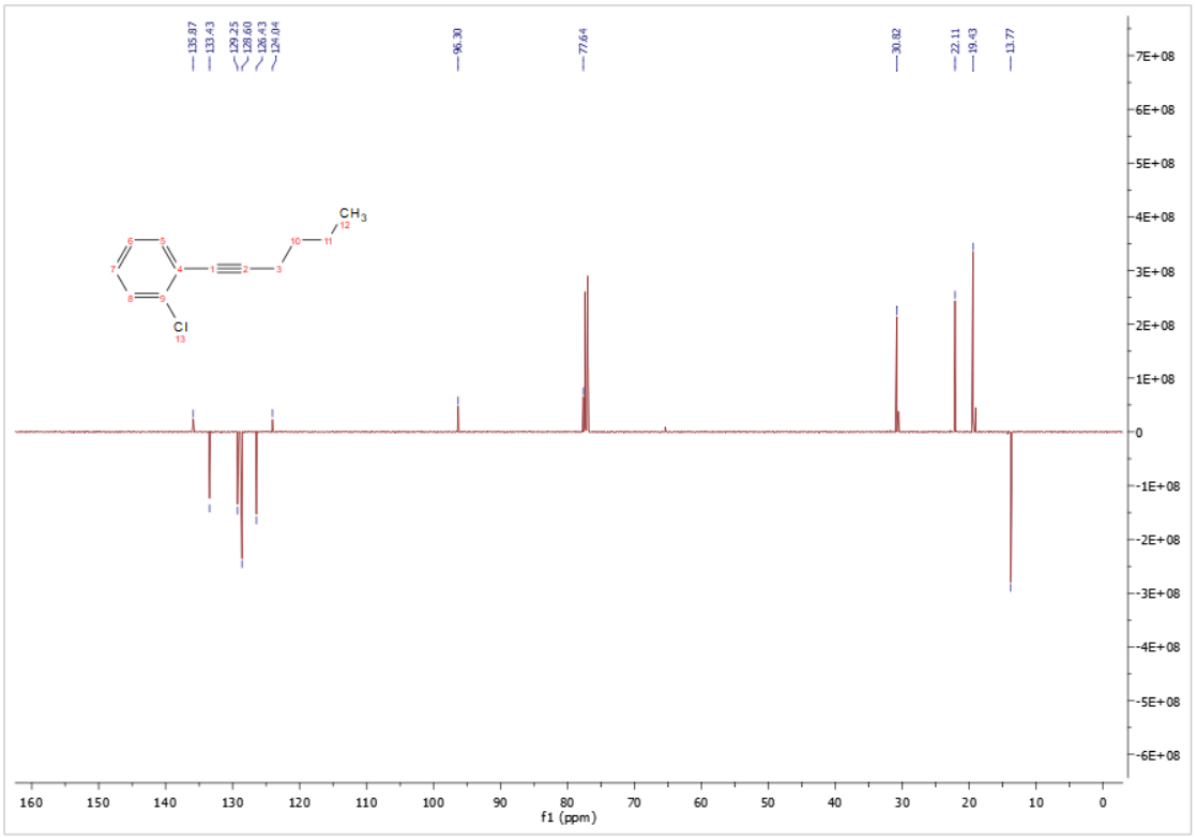

6.91
6.91
6.90
6.90
6.85
6.85
6.72
6.71
5.94
2.38
2.37
2.36
1.58
1.57
1.57
1.56
1.55
1.48
1.47
1.46
0.95
0.94
0.93
CH3
1.00
0.95
1.00
2.05
2.02
2.05
2.03
3.04
f1 (ppm)

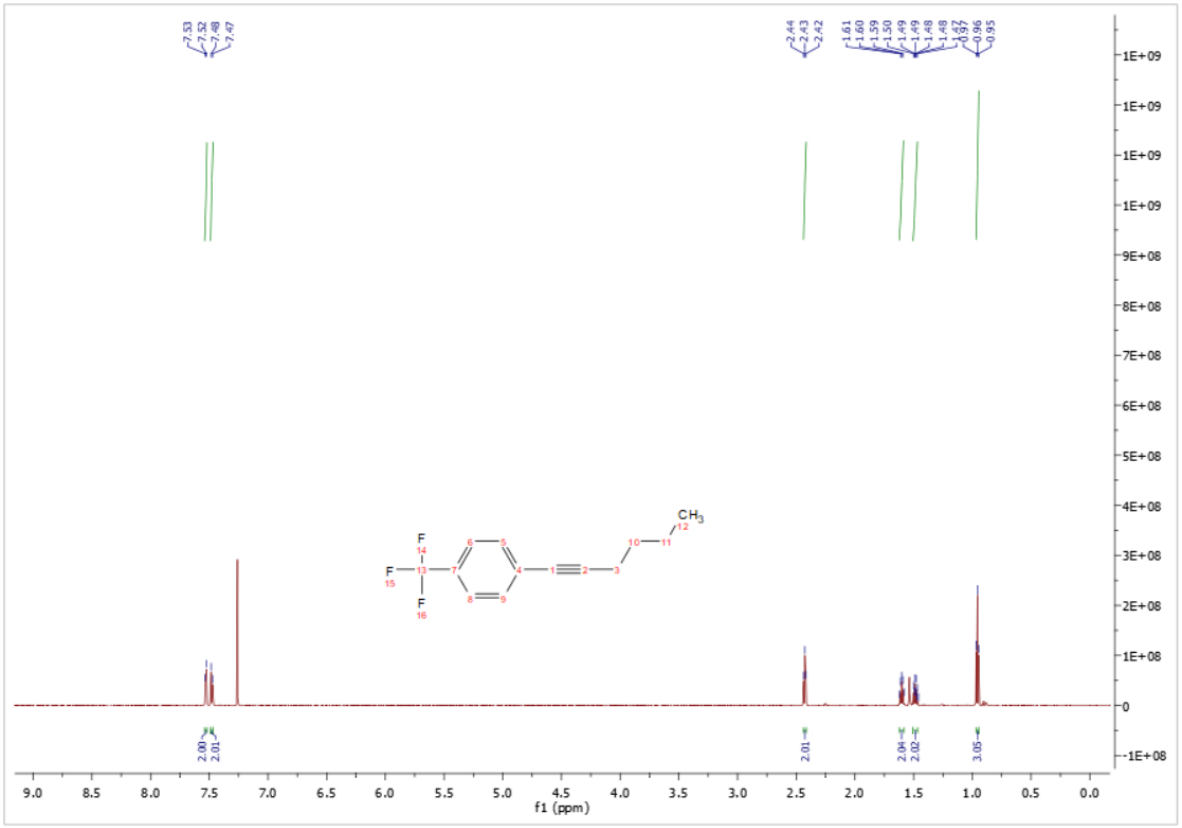

147.42
147.33
125.96
117.56
111.80
108.43
101.26
88.75
80.39
31.03
22.17
19.20
13.79
CH3
f1 (ppm)

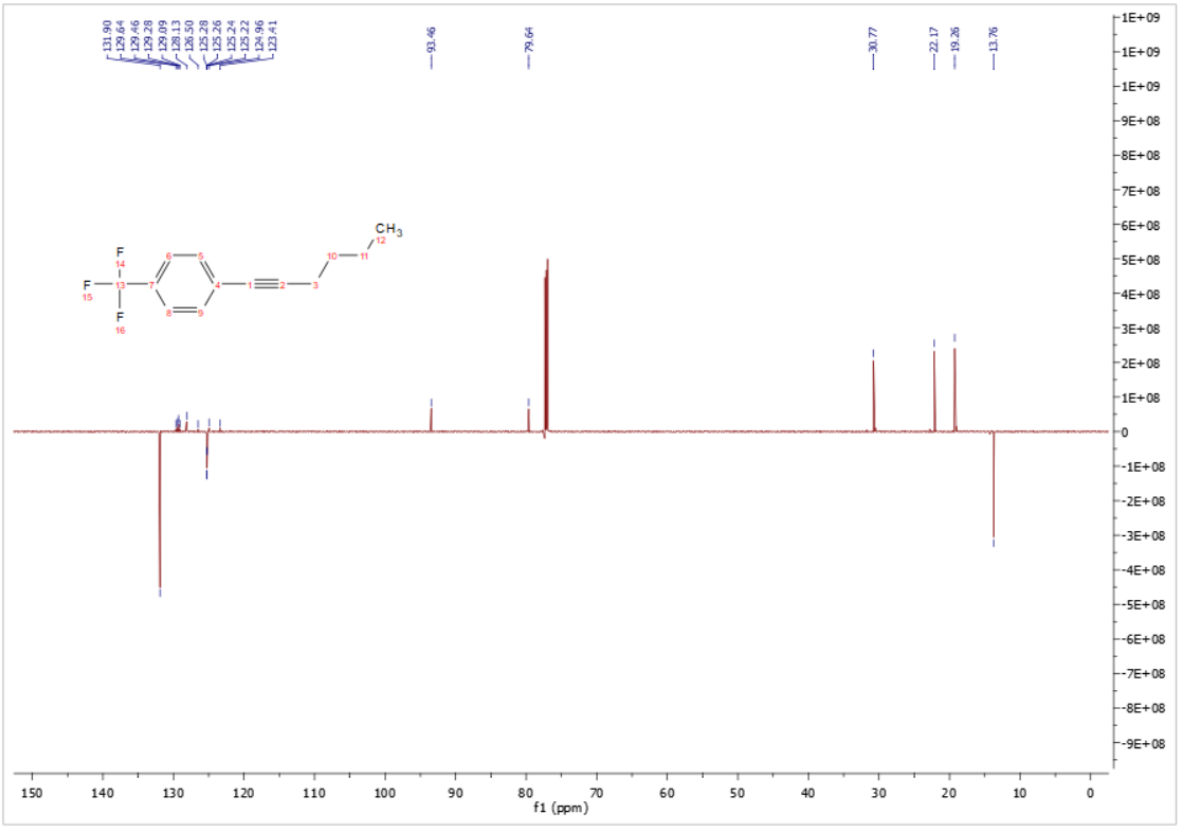

7.31
7.29
7.15
7.14
2.47
2.41
2.40
2.39
1.59
1.58
1.57
1.56
1.49
1.48
1.47
0.96
0.95
0.94
CH3
12
S
13
H3C
14
2.00
2.04
3.03
2.00
2.02
2.06
3.04
f1 (ppm)

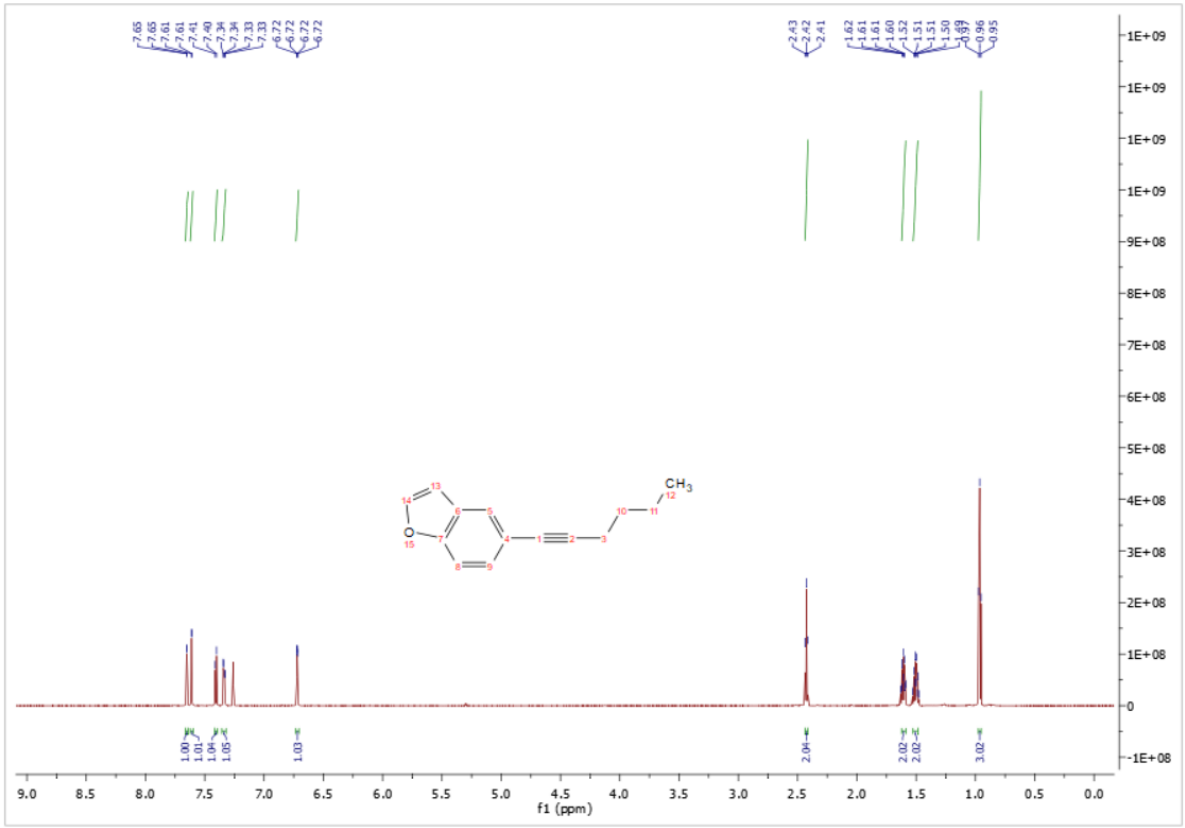

138.19
131.99
126.18
120.74
90.63
80.34
31.00
22.17
19.29
15.75
13.79
CH3
12
S
13
H3C
14
f1 (ppm)

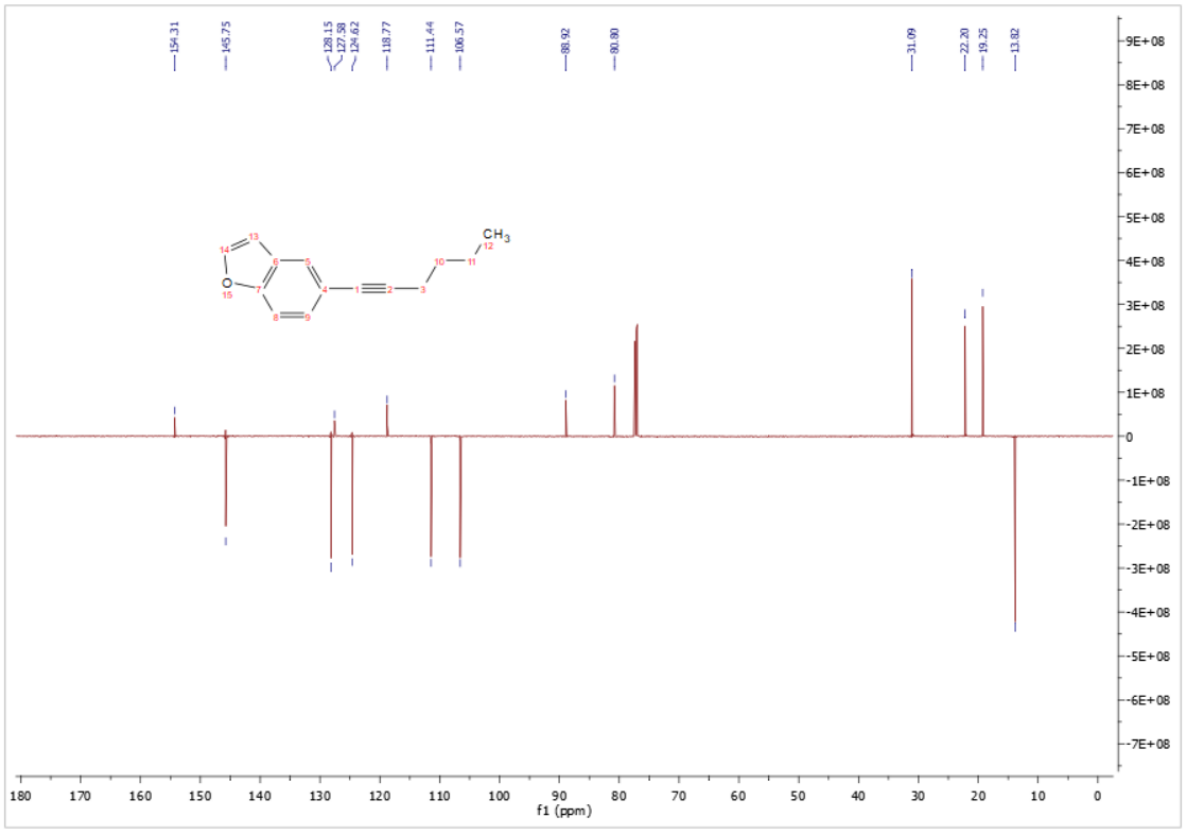

7.43
7.42
7.37
7.36
7.20
7.19
7.18
7.17
7.16
2.49
2.48
2.47
1.64
1.62
1.61
1.54
1.53
1.52
1.51
0.97
0.96
0.95
CH3
12
Cl
13
1.00
1.00
2.02
2.06
2.05
2.06
3.07
f1 (ppm)

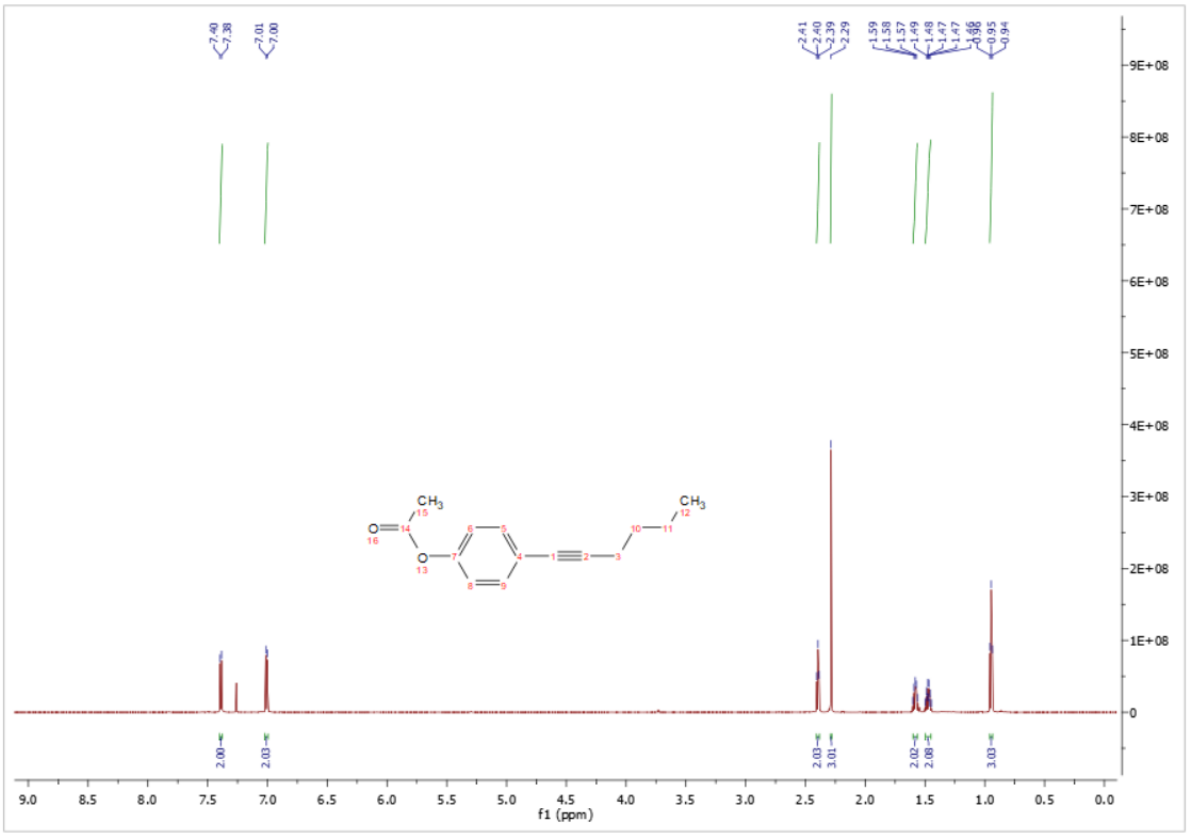

135.87
133.43
129.25
128.60
126.43
124.04
96.30
77.64
30.82
22.11
19.43
13.77
CH3
12
Cl
13
f1 (ppm)

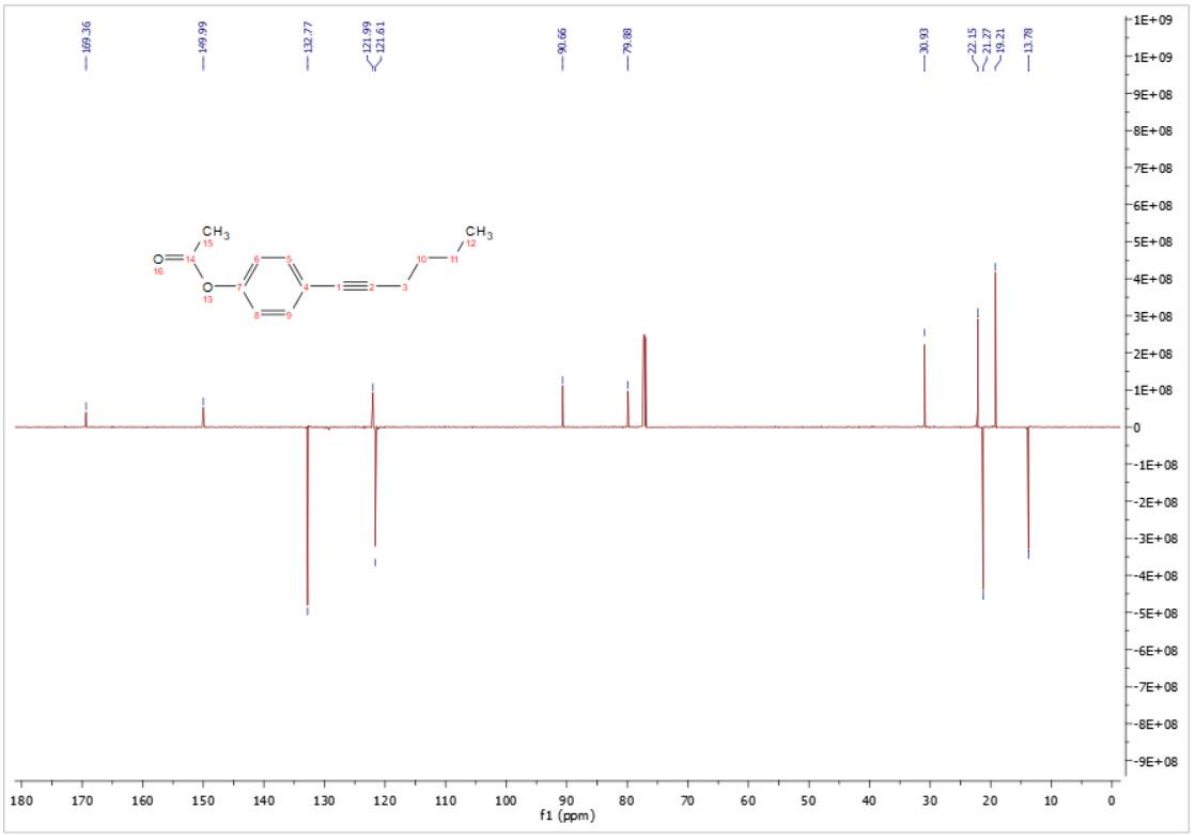

7.53
7.52
7.48
7.47
2.44
2.43
2.42
1.61
1.60
1.59
1.50
1.49
1.49
1.48
1.48
0.97
0.96
0.95
F
F
F
CH3
2.00
2.01
2.01
2.04
2.02
3.05
f1 (ppm)

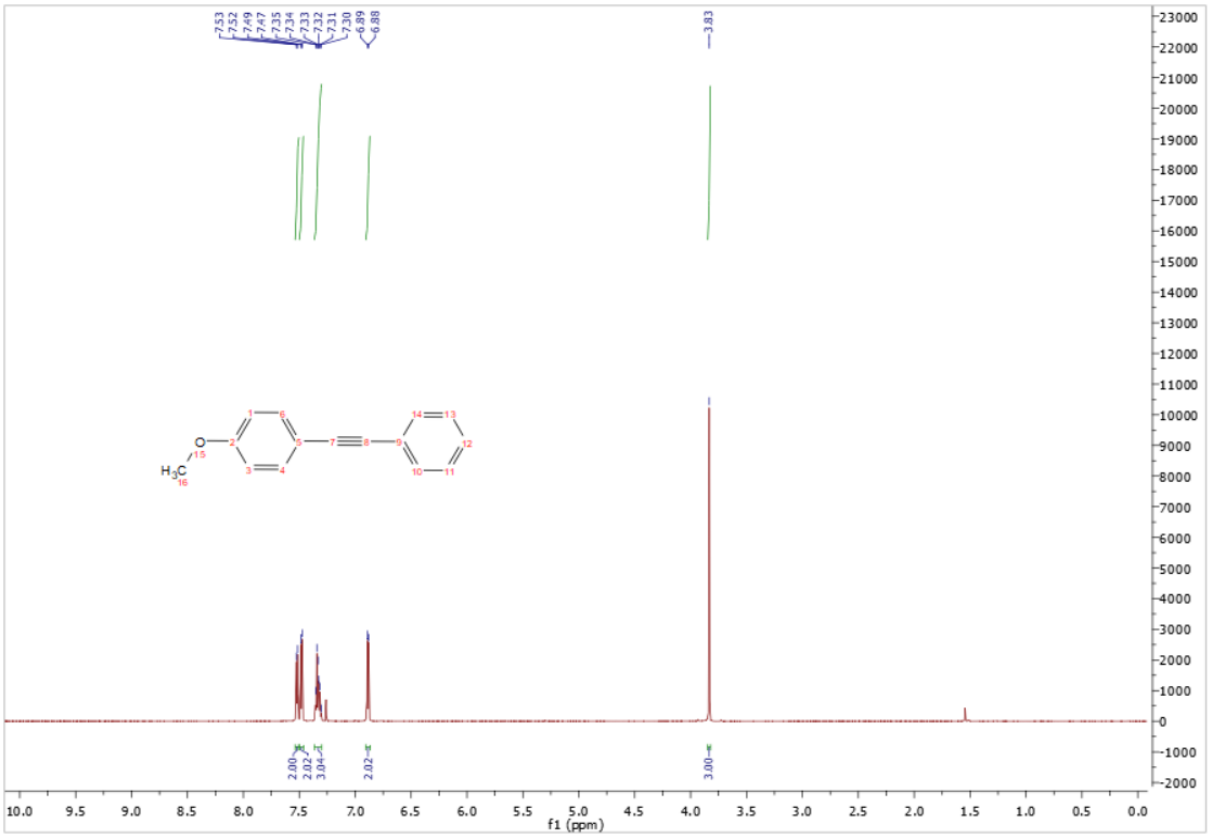

131.90
129.64
129.46
129.28
129.09
128.13
126.50
125.28
125.26
125.24
125.22
124.96
123.41
93.46
79.64
30.77
22.17
19.26
13.76
F
F
F
CH3
f1 (ppm)

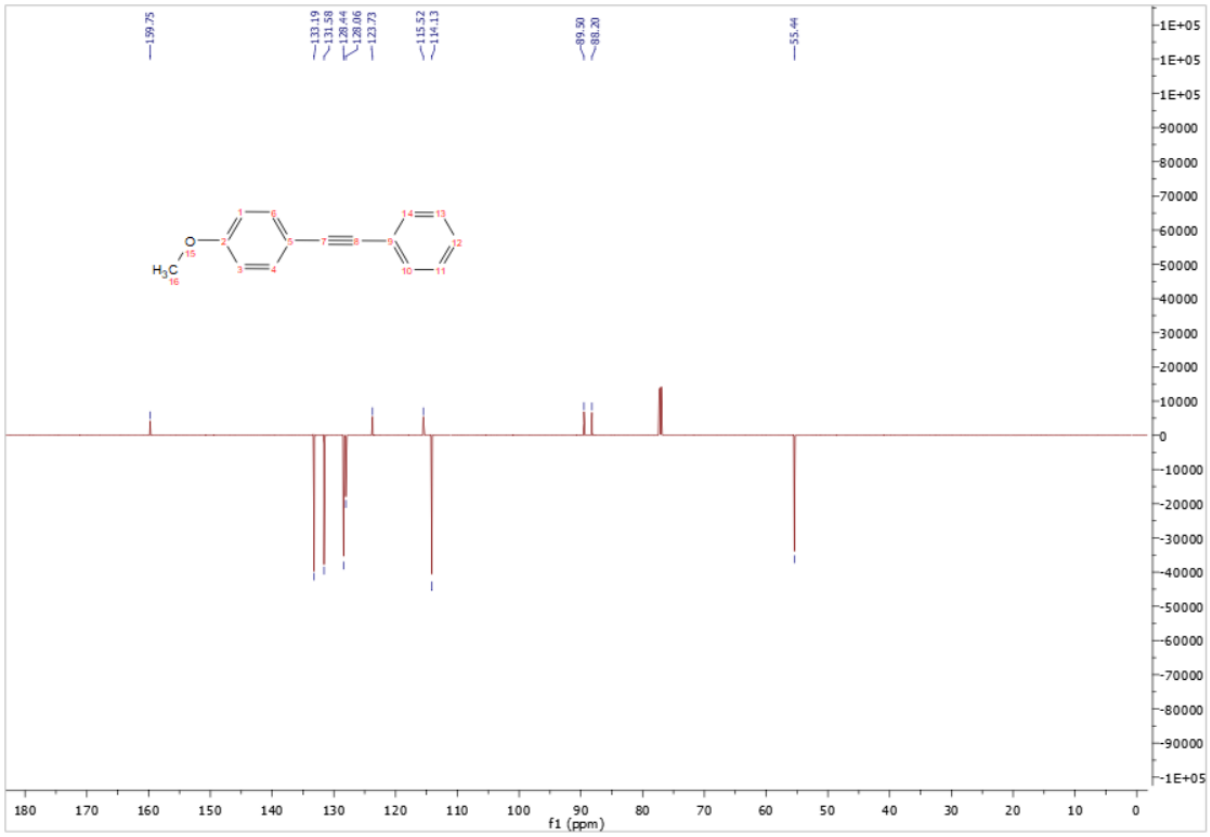

7.65
7.61
7.41
7.40
7.34
7.33
6.72
2.43
2.42
2.41
1.62
1.61
1.60
1.52
1.51
1.50
0.96
0.95
CH3
1.00
1.01
1.04
1.05
1.03
2.04
2.02
2.02
3.02
f1 (ppm)

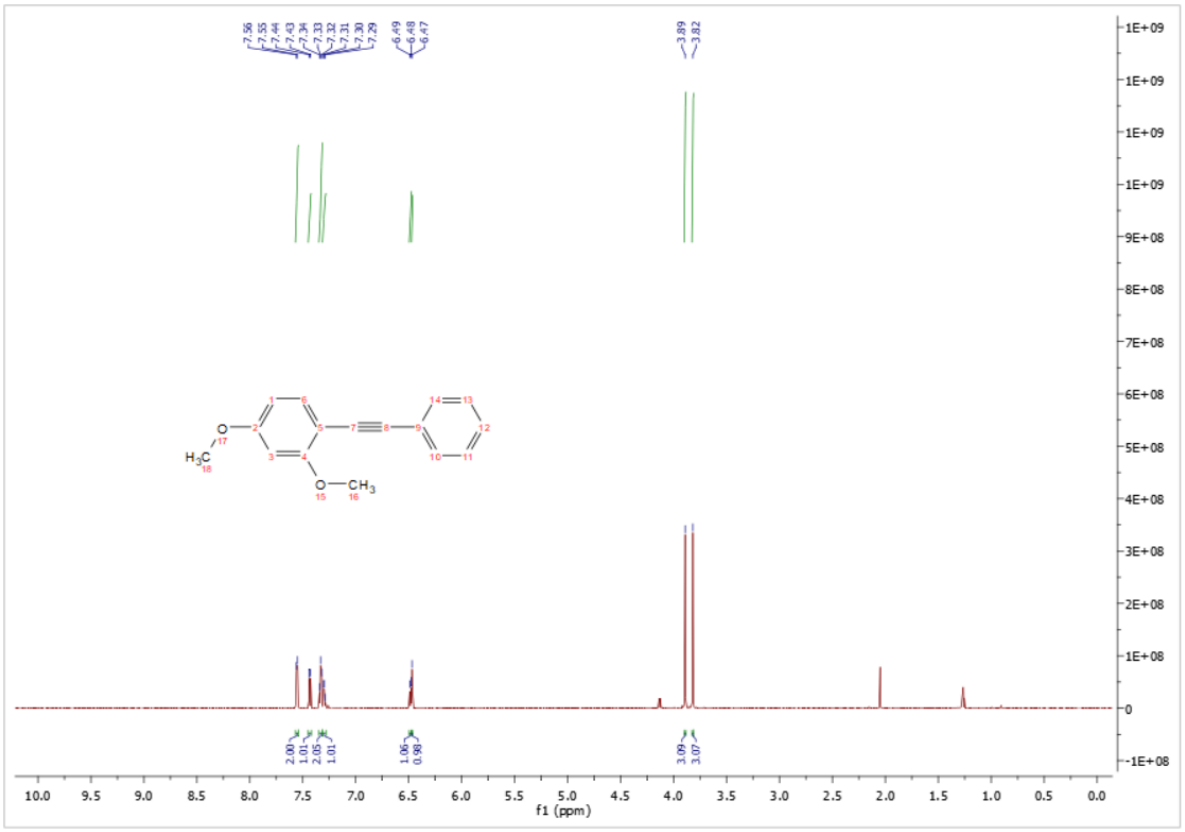

154.31
145.75
128.15
127.58
124.62
118.77
111.44
106.57
88.92
80.80
31.09
22.20
19.25
13.82
CH3
f1 (ppm)

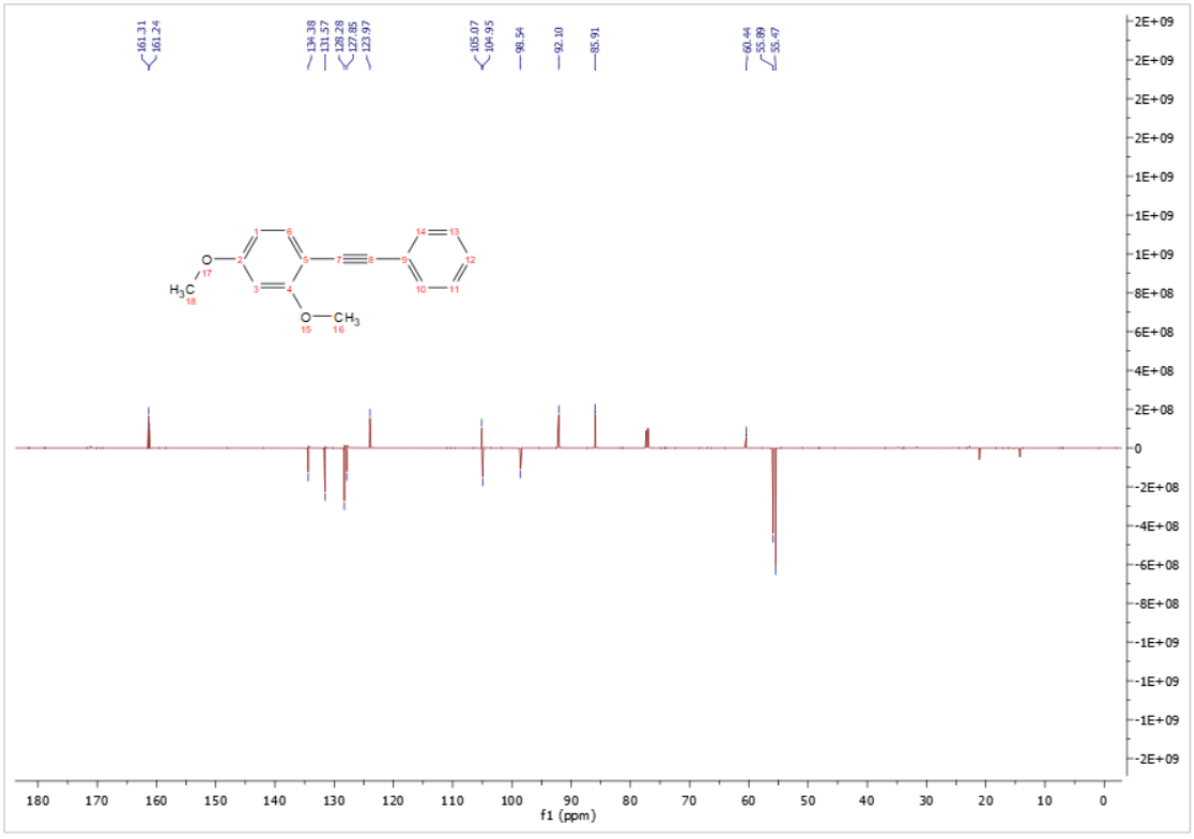

7.40
7.38
7.01
7.00
2.41
2.40
2.39
2.29
1.59
1.58
1.57
1.49
1.48
1.47
1.47
0.96
0.95
0.94
CH3
CH3
2.00
2.03
2.03
3.01
2.02
2.08
3.03
f1 (ppm)

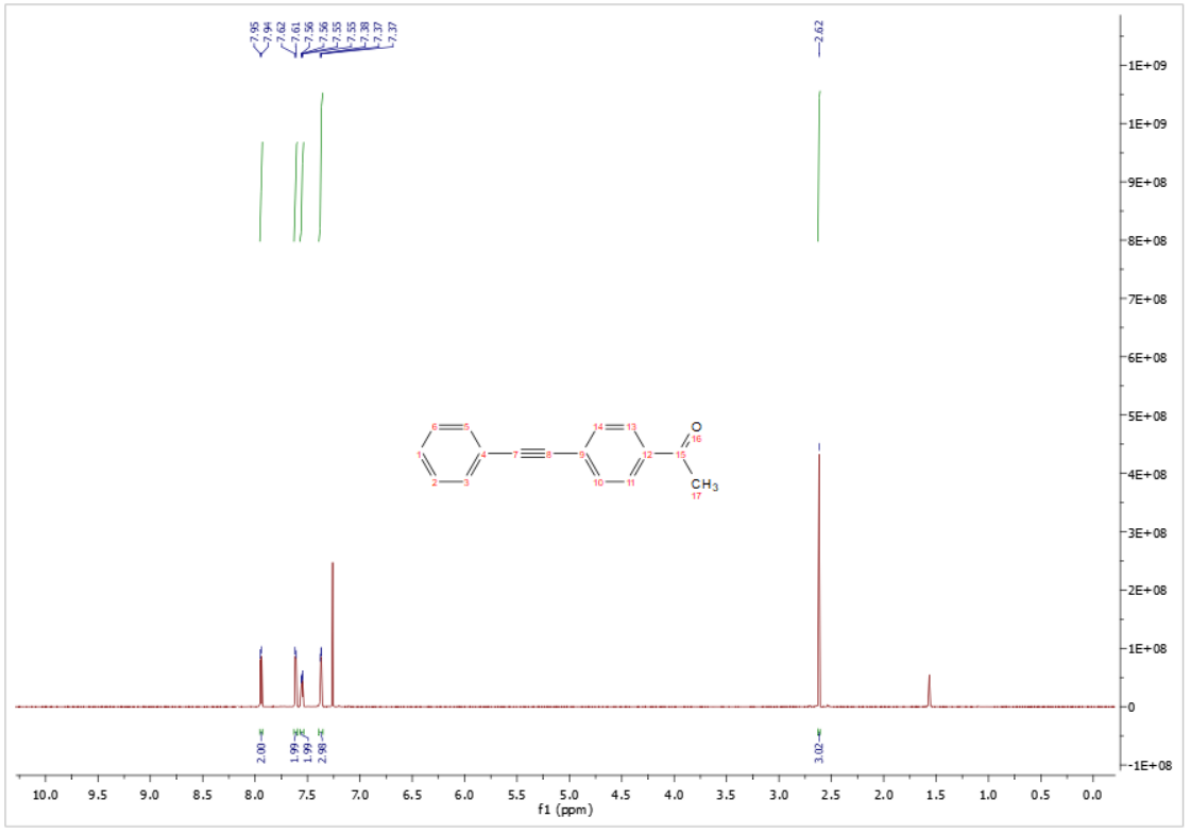

169.36
149.99
132.77
121.99
121.61
90.66
79.88
30.93
22.15
21.27
19.21
13.78
CH3
CH3
f1 (ppm)

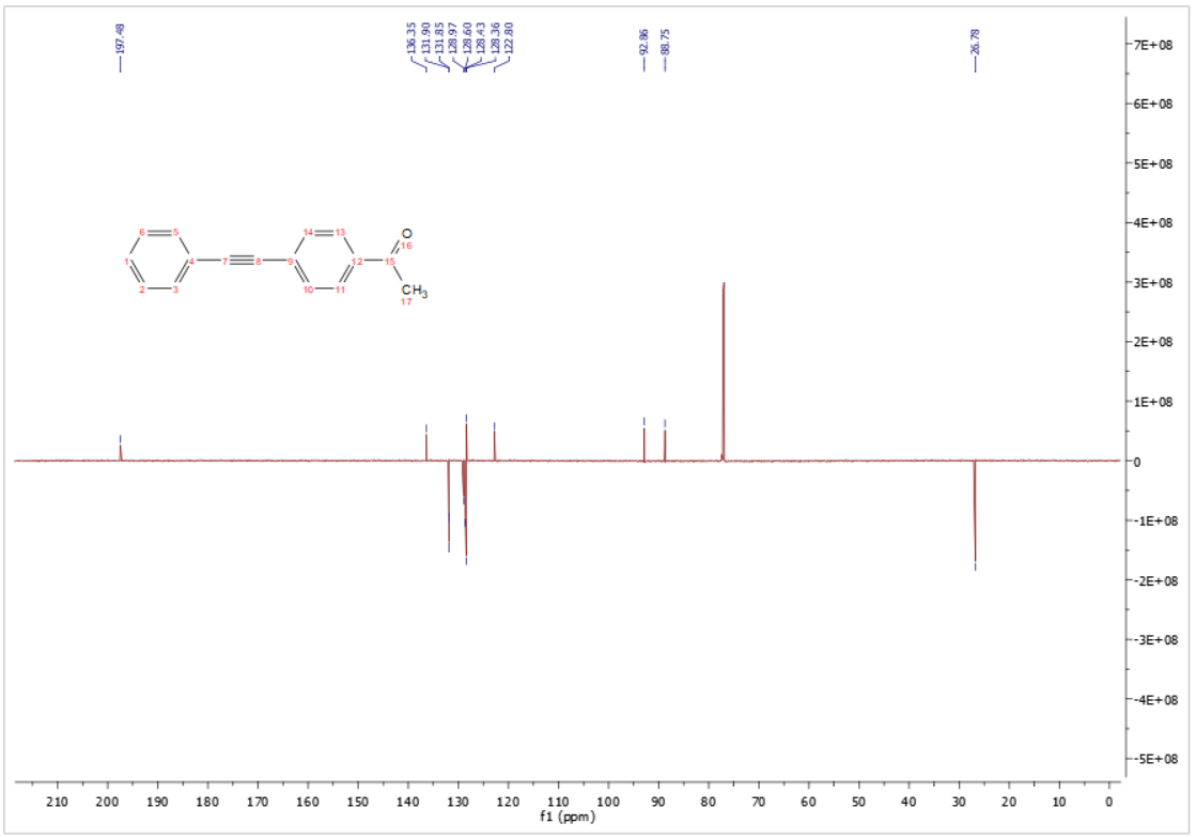

7.53
7.52
7.49
7.47
7.35
7.34
7.33
7.32
7.31
7.30
6.89
6.88
3.83
2.00
2.02
3.04
2.02
3.00
f1 (ppm)

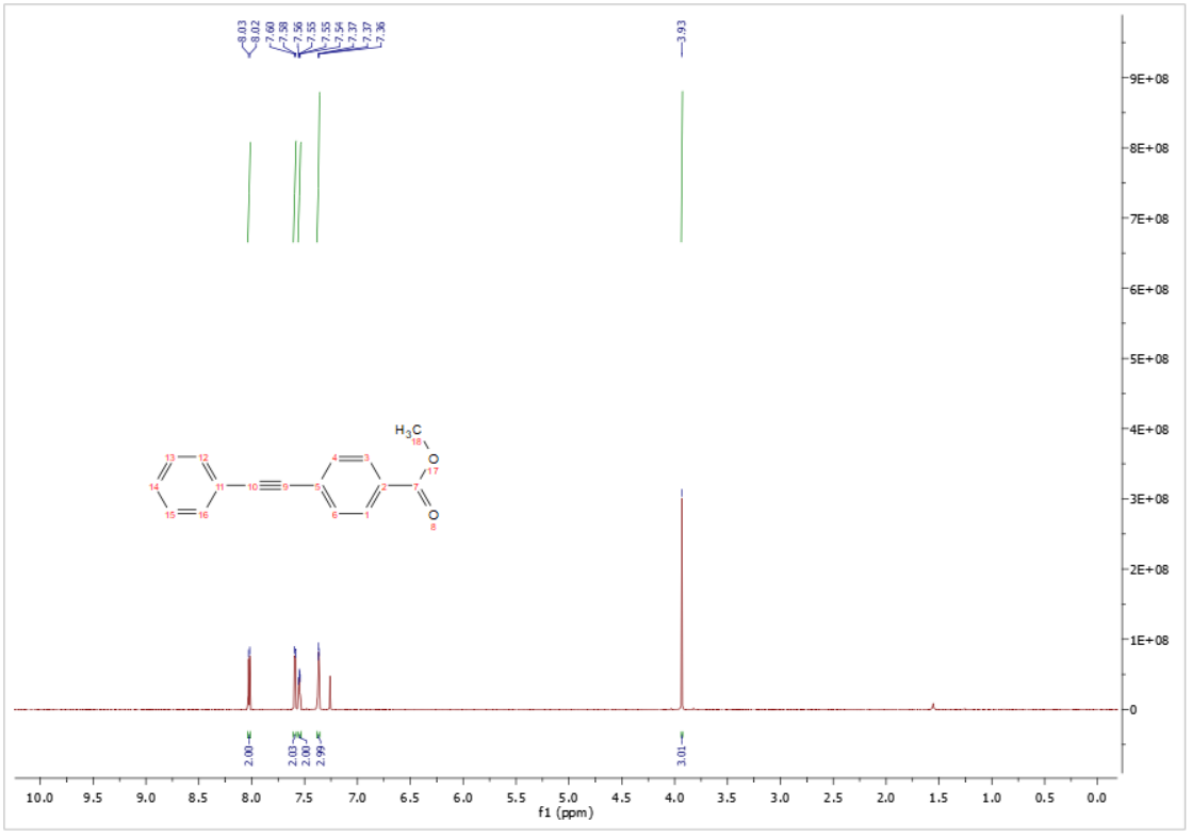

159.75
133.19
131.58
128.44
128.06
123.73
115.52
114.13
89.50
88.20
55.44
f1 (ppm)

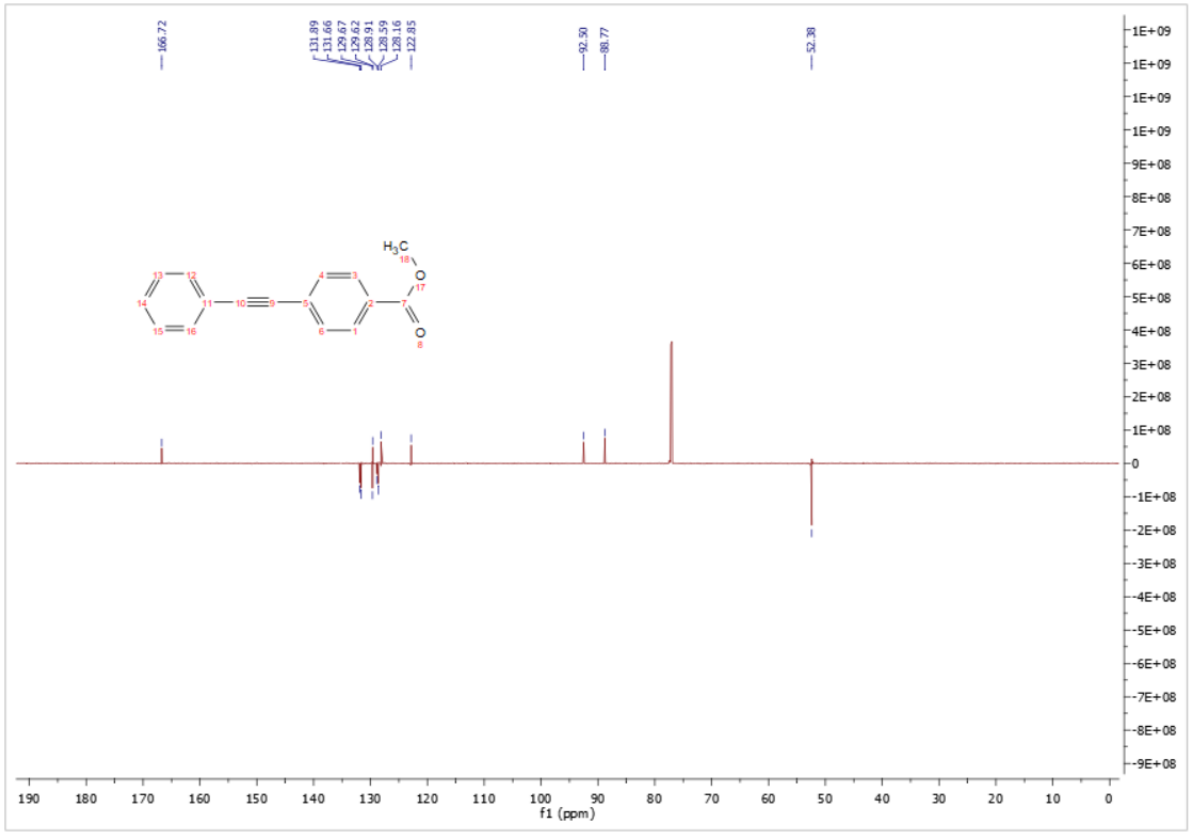

7.56
7.55
7.44
7.43
7.34
7.33
7.32
7.31
7.30
7.29
6.49
6.48
6.47
3.89
3.82
2.00
1.01
2.05
1.01
1.06
0.98
3.09
3.07
f1 (ppm)


161.31
161.24
134.38
131.57
128.28
127.85
123.97
105.07
104.95
98.54
92.10
85.91
60.44
55.99
55.47
f1 (ppm)


7.95
7.94
7.62
7.61
7.56
7.56
7.55
7.55
7.38
7.37
7.37
2.62
2.00
1.99
1.99
2.98
3.02
f1 (ppm)


197.48
136.35
131.90
131.85
128.97
128.60
128.43
128.36
122.80
92.86
88.75
26.78
f1 (ppm)


8.03
8.02
7.60
7.58
7.56
7.55
7.55
7.54
7.37
7.37
7.36
3.93
2.00
2.03
2.00
2.99
3.01
f1 (ppm)


166.72
131.89
131.66
129.67
129.62
128.91
128.59
128.16
122.85
92.50
88.77
52.38
f1 (ppm)