Rhodium and Platinum Catalyzed Cycloadditions from Propargylic Esters and Ethers

by

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A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

(Chemistry)

at the

UNIVERSITY OF WISCONSIN-MADISON

2013

Date of final oral examination: 06/11/13

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Under the Supervision of Professor Weiping Tang

at the University of Wisconsin-Madison

ABSTRACT: The past decade has witnessed a "gold rush" due to the novel π-acidity of gold. On the other hand, rhodium is well known for traditional organometallic reactivities such as oxidative addition, reductive elimination, and carbonylation, which makes rhodium widely utilized in industrial processes such as hydroformylation and Monsanto acetic acid synthesis. My Ph.D. research combines π-acidity of rhodium with traditional reactivities of rhodium. In particular, we use π-acidic Rh-complexes to activate propargylic esters and ethers for cycloadditions.

Propargylic esters can undergo either 1,3- or 1,2-acyloxy migration in the presence of rhodium to form allenes and vinyl metal carbenes respectively. By taking advantage of the Rh-catalyzed 1,3-acyloxy migration, I developed a [5+1] cycloaddition starting from cyclopropyl propargylic esters. By taking advantage of

Rh-catalyzed 1,2-acyloxy migration, I contributed to the synthesis of 7- and 8-membered rings starting from vinyl propargylic esters.

Vinyl metal carbenes could also be obtained from propargylic esters tethered with a nucleophile. By employing either platinum or rhodium metal complexes, I developed a tandem indole annulation and [4+3] cycloaddition with dienes and furans involving vinyl metal carbene intermediates. Biologically interesting bisindoles were also synthesized through a similar indole annulation followed by intermolecular nucleophilic trap of external indoles.

ACKNOWLEDGEMENTS

Above all, I would like to express my special appreciation and thanks to my advisor Professor Dr. Weiping Tang, you have been a tremendous mentor for me. I would like to thank you for encouraging my research and help in all the aspects. I have greatly benefited from his approach to educate a graduate student by allowing them enough flexibility to grow as an independent researcher as well as guiding them when necessary. I am also indebted to him for supporting me as a research assistant during most of my graduate career. Without his support, I would not have been possible to write this doctoral thesis.

I would also like to thank many professors at UW-Madison who inspired and taught me during my graduate program. First, I would like to thank Professor Richard Hsung. I have benefited a lot from him during joint group meeting and class. I would also like to thank Professor Steve Burke, Professor Shannon Stahl, and Professor Tehshik Yoon, not only for serving as my committee members, but also teaching and inspiring me during past few years. I would thank Professor Jennifer Schomaker for her kindness to be my committee member and take time to read my thesis. Finally, I would like to thank Professor Steve Nelsen for teaching my physical organic chemistry, from whom I gained a lot insight in organic chemistry.

I am grateful to have worked with all the former and current members in Tang group. The close relationship has made my graduate career an enjoyable experience.

I am also indebted to my undergraduate supervisors Professor Zhen Yang and Professor Jiahua Chen, who guided me when I entered the area of organic chemistry. I am also thankful for Dr. Bo Liang and Dr. Jing Liu, who taught me all the techniques and knowledge when I first joined an organic research group.

My family has always been the most important part of my life. My thanks go to my dear parents, who have supported me throughout my life. I am grateful to my grandparents as well as my uncles, aunts, and cousins.

I am also grateful for the beautiful friendship with all the friends in Madison in the past several years, particularly Casi, Yang, Kuang and Tianning.

Abbreviations and Acronyms

4 Å MS = 4 Å molecular sieves

Ac = Acetyl

AcO = Acetate

Ar = Aryl

BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Bn = Benzyl

Boc = tert-Butoxycarbonyl

Bu or n-Bu = n-Butyl

t-Bu or tBu = tert-Butyl

Cod = Cyclooctadiene

Cp = Cyclopentadienyl

CSA = Camphorsulphonic acid

DABCO = 1,4-Diazabicyclo[2.2.2]octane, Triethylendiamine

DBU = 1,8-Diazabyciclo[5.4.0]undec-7-ene

DCC = 1,3-Dicyclohexylcarbodiimide

DCM = Dichloromethane

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL = Diisobutylaluminium hydride

DMAP = 4-Dimethylaminopyridine

DMF = N,N-Dimethylformamide

DMP = Dess-Martin periodinaneDMPM = 3,4-Dimethoxybenzyl

DMSO = Dimethylsulphoxide

Dppe = 1,2-bis(diphenylphosphino)ethane

dppp = 1,3-bis(diphenylphosphino)propane

Et2O = Diethyl ether

HMPA = Hexamethylphosphoramide

KHMDS = Potassium bis(trimethylsilyl)amide

LAH = Lithium aluminium hydride

LDA = Lithium diisopropylamide

Me = Methyl

PDC = Pyridinium dichlorochromate

PCC = Pyridinium chlorochromate

Ph = Phenyl

Piv = Pivaloyl, 2,2-dimethylacetyl

PTSA = p-Toluenesulphonic acid

Py = Pyridine

TBAF = Tetrabutylammonium fluoride

TBDMS = tert-Butyldimethylsilyl

TBDPS = tert-Butyldiphenylsilyl

TBS = tert-Butyldimethylsilyl

TES = Triethylsilyl

TfO = Trifluoromethanesulfonate

TFA = Trifluoroacetic acid

THF = Tetrahydrofurane

TIPS = Triisopropylsilyl

TMS = Trimethylsilyl

Ts = p-Toluenesulphonyl

p-TsOH = p-Toluenesulphonic acid

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Chapter 1

Transition Metal-Catalyzed Cycloadditions Involving 1,3 and 1,2-Acyloxy Migration of Propargylic Esters

1.1 Introduction

The first decade in the 21st century witnessed a "gold rush" for gold-, platinum- and related π-acidic transition metal catalysis. Since the first comprehensive review by Hashmi in 2004, dozens of reviews have been published on homogeneous gold catalysis.[1] Numerous novel reactivities and new reaction modes have been discovered, among which one of the most important transformations is the gold-, platinum- and related π-acidic metal-catalyzed acyloxy migration of propargylic esters to form allene or vinyl carbene intermediates.

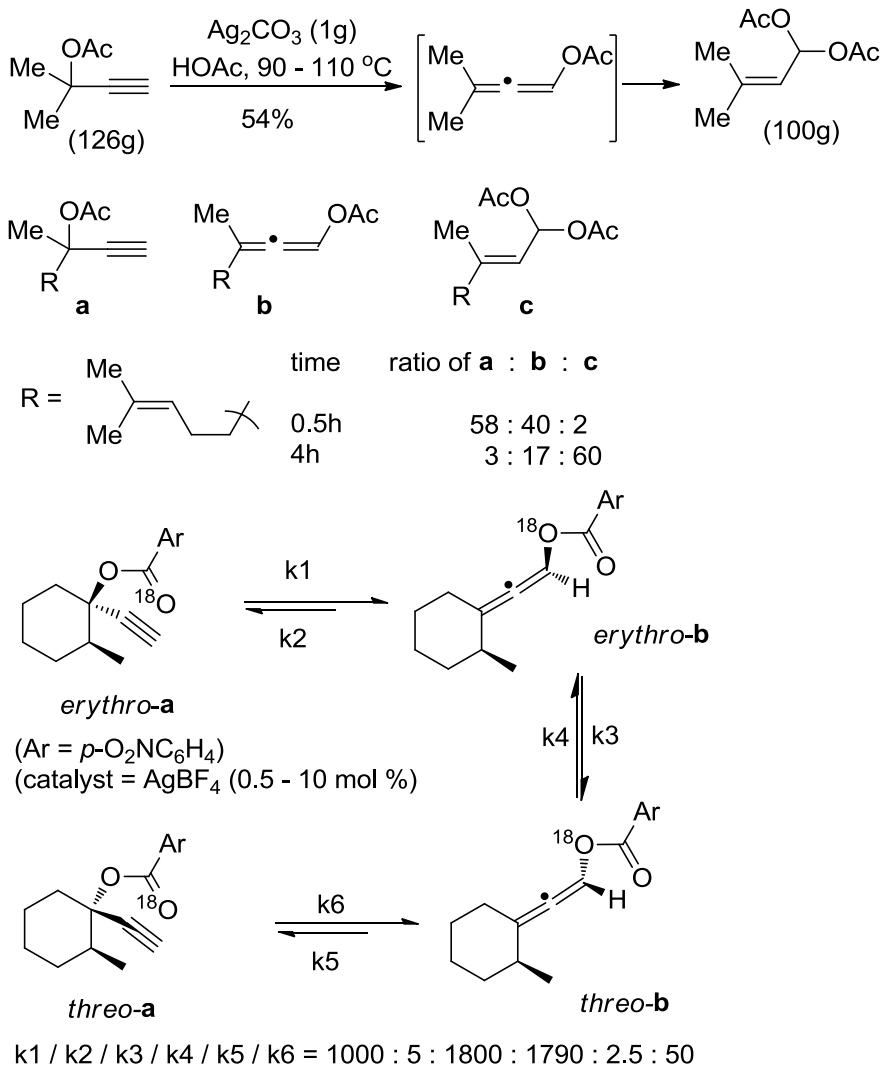
By forming at least two bonds in one operation, cycloaddition is an efficient way to construct carbo- and heterocycles. Classical cycloadditions have proven to be a powerful method. However, the scope of classical cycloaddition is often limited to substrates with matched electronic properties. On the other hand, cycloadditions that are not feasible under thermal or photolytic conditions can often be promoted by transition metals.[2,3] Among many transition metals, rhodium, ruthenium, nickel and palladium complexes are most involved in the transition metal-catalyzed cycloadditions prior to the recent "gold rush". More and more Au- and Pt-catalyzed cycloadditions have been developed in recent years.[4,5] More recently, rhodium catalyzed-cycloaddition involving acyloxy migration of propargylic esters has emerged as a new research area.[6]

1.2 Historical Discovery of 1,3- and 1,2-Acyloxy Migration of Propargylic Esters

Saucy and Marbet found in 1959 that by treating propargylic acetates with catalytic amount of copper powder, copper oxide, copper and silver salts, diacetates could be prepared (Scheme 1-1).[6] The authors also isolated and characterized some of the allenylic

acetate intermediates by IR. They studied the distribution of propargylic acetate **a**, allenylic acetate **b**, and diacetate **c** over the course of the reaction. They also hydrolyzed both allenylic acetates and diacetates to their corresponding α,β-unsaturated aldehydes.

Scheme 1-1. 1,3-Acyloxy Migration of Propargylic Esters and Related Mechanistic Study.

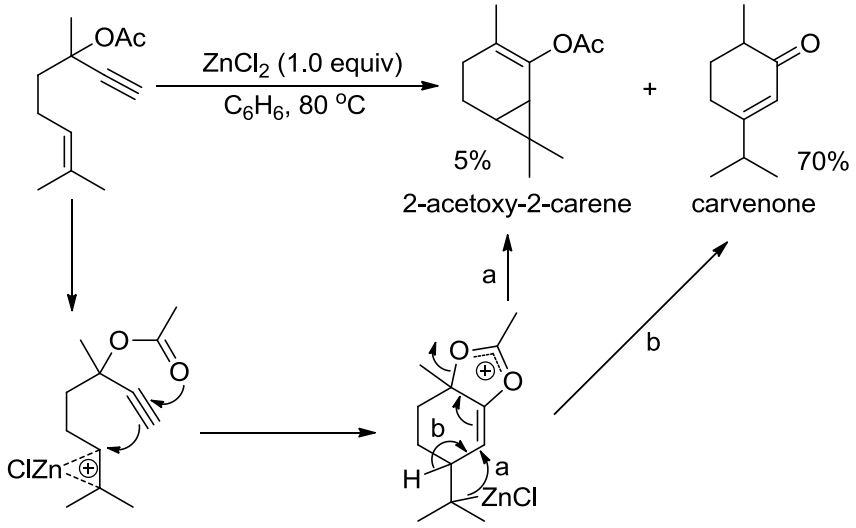


Later in 1973, the mechanism of silver-catalyzed Saucy-Marbet rearrangement was studied in detail using ^{14}C and ^{18}O-labelled substrates as well as optically active

propargylic esters.[7] In a cross coupling experiment, no mixed product was observed. Optically active propargylic esters underwent rearrangement to form a mixture of racemic allenylic esters. Interestingly, in the presence of a silver catalyst, allenylic esters *erythro*-**b** and *threo*-**b** epimerized rapidly (Scheme 1-1). The authors also found that the rate of epimerization is faster than the rearrangement. The ^{18}O-label was not randomized during the rearrangement and epimerization and ^{18}O-carbonyl label in the reactant was found exclusively in the alkoxy part of the allene product and. Kinetic studies revealed that complexation of the silver ion to substrates was found to be the rate-determining step. The rearrangement became slower when the reaction was run in coordinative solvents or adding cyclohexene. Based on the above findings, the authors proposed a [3,3]-sigmatropic rearrangement facilitated by silver catalyst.

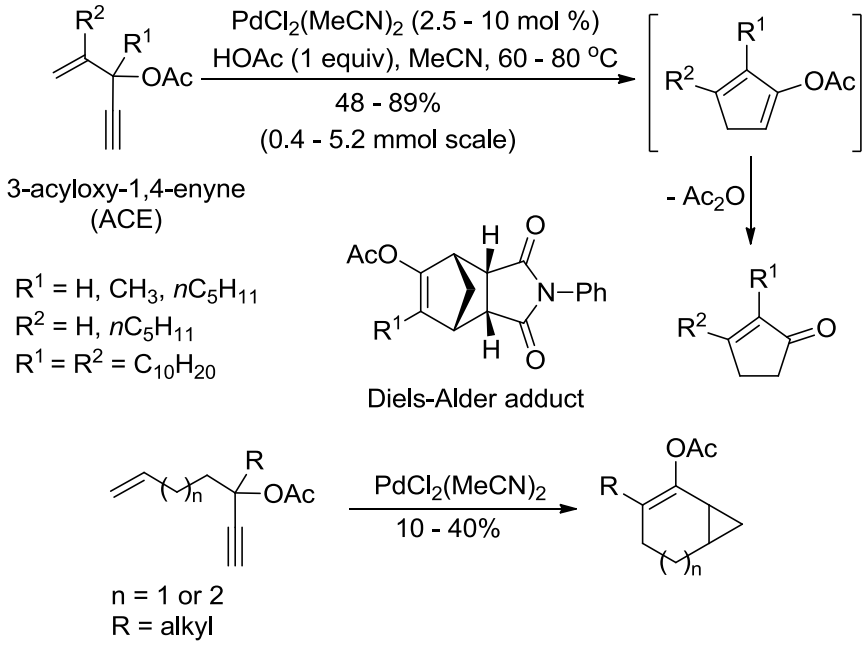
In 1976, Ohloff reported that by using $ZnCl_2$, an enyne could undergo cycloisomerization to form 2-acetoxy-2-carene and carvenone (Scheme 1-2).[8] It was proposed that the cycloisomerization was initiated by complexation of zinc chloride to the olefin moiety of the enyne. Cyclization and 1,2-acyloxy migration would generate an acetoxonium ion, which could undergo cyclopropanation to form 2-acetoxy-2-carene through pathway a or deprotonation to form a diene intermediate. The diene intermediate could undergo protonation followed by hydrolysis of the enol acetate to afford major product carvenone.

Scheme 1-2. 1,2-Acyloxy Migration of Propargylic Esters.



In 1984, Rautenstrauch reported the cycloisomerization of 3-acyloxy-1,4-enynes to cyclopentenones in the presence of a palladium catalyst (Scheme 1-3).[9] Among the metals examined, $PtCl_2(MeCN)_2$ was also found to catalyze this transformation. Various alkyl groups could be tolerated for R^1 and R^2 substituents. However, no other places on the alkene or the alkyne could be substituted. *N*-phenylmaleimide was found to trap the proposed cyclopentadiene intermediate to form Diels-Alder adduct as shown in Scheme 1-3. The author also reported cyclopropanation of a tethered alkene to from bicyclic compounds ssing the same Pd(II) catalyst, albeit in low yield (Scheme 1-3).[9]

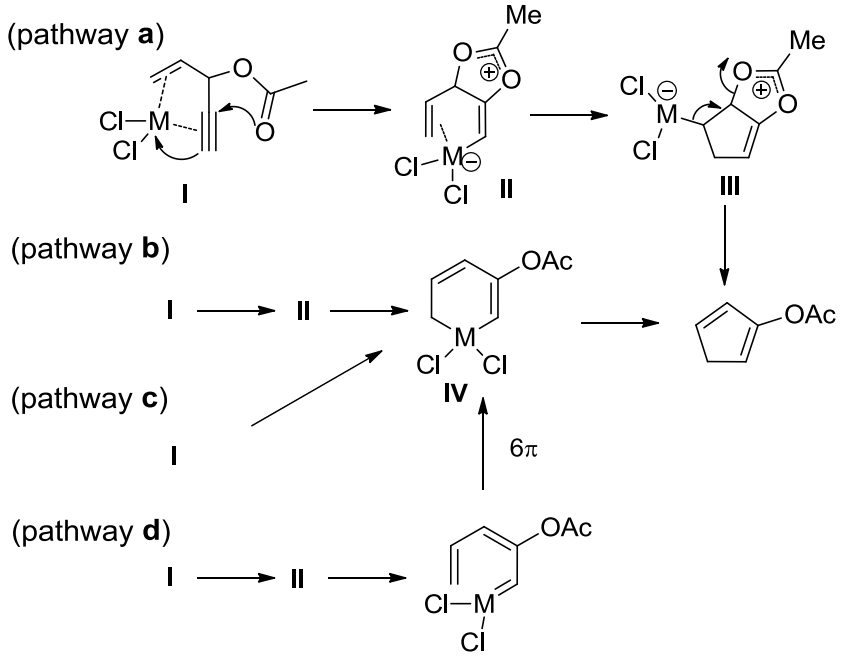
Scheme 1-3. Discovery of Pd-catalyzed 1,2-Acyloxy Migration of Propargylic Esters.



Rautenstrauch proposed that the initial step of the cycloisomerization was the complexation of the metal (Pd or Pt) to both the alkene and the alkyne parts of 3-acyloxy-1,4-enynes (Scheme 1-4). For the conversion of metal complex **I** to cyclopentadiene product, four potential pathways were outlined. In most pathways, acetoxonium ion **II** was proposed to be involved as an intermediate. In pathway **a**, acetoxonium ion **II** was formed, which gave bicyclic intermediate **III** after insertion of an olefin to the carbon-metal bond. The bicyclic intermediate **III** then underwent elimination to afford diene product. In pathways **b**, **c** and **d**, metallacyclohexadiene **IV** was proposed as a common intermediate to undergo reductive elimination to form cyclopentadiene**.** Metallacyclohexadiene **IV** could be derived from metal complex **I** in three pathways: a cyclization of acetoxonium ion **II** (pathway **b**), a concerted oxidative cyclization of complex **I** combined with 1,2-acyloxy migration (pathway **c**), or a 6-π electrocyclization of a carbene intermediate (pathway **d**). Formation of palladium carbene intermediates

from 1,2-acyloxy migration of propargylic esters was supported by the isolation of cyclopropanation products (Scheme 1-4).

Scheme 1-4. Mechanism of 1,2-Acyloxy Migration of Propargylic Esters Proposed by Rautenstrauch.



This is the first example of late transition metal-catalyzed 1,2-acyloxy migration of propargylic esters. Recent experimental and computational evidences as discussed in later sections supported some of the proposed mechanisms.

1.3 Mechanistic Studies on Transition Metal-mediated 1,3- and 1,2-Acyloxy Migration of Propargylic Esters

The synthetic potential of transition metal-catalyzed 1,3- and 1,2-acyloxy migration of propargylic esters were not realized until recently in spite of the discovery several

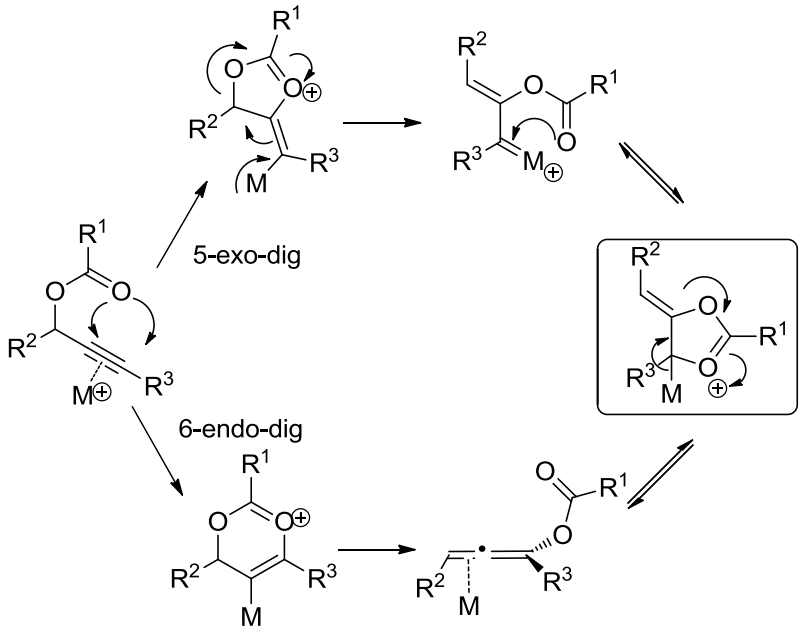
decades ago. In 2007, Marion and Nolan briefly reviewed gold-catalyzed 1,2- and 1,3-acyloxy migration of propargylic esters.[10] In the same year, the metal-catalyzed 1,2-acyloxy migration process was reviewed by Marco-Contelles and Soriano in more details.[11] In 2010, gold-catalyzed 1,3-acyloxy migration of propargylic esters was reviewed by Zhang.[12]

Based on the research studies, the selectivity for 1,3- and 1,2-acyloxy migration depends on the substitution pattern of the propargyl moiety as well as the metal catalyst. For propargylic esters with internal alkynes, the 1,3-acyloxy migration is generally favoured, while the 1,2-acyloxy migration is usually limited to terminal alkynes or internal alkynes with electron withdrawing groups(R^3 = H and EWG, Scheme 1-5) with propargylic esters derived from tertiary or benzylic alcohols. It was suggested that the change of regioselectivity was due to electronic effect in Au- and Pt-catalyzed reactions through the calculation by Soriano and Marco-Contelles.[13] They found that for terminal alkynes, 1,2-acyloxy migration was considerably kinetically favored. The R^3 alkyl substituent in the internal alkyne allows a faster 1,3-acyloxy migration since it enhances the electrophilicity of that acetylenic atom. The 1,3-acyloxy migration was consisted of a first rate-limiting 6-endo-dig cyclization to form a six-membered heterocycle followed by ring opening.

The mechanism for 1,3- and 1,2-acyloxy migration of propargylic esters is controversial based on recent studies. In a 2008 calculation study, double 1,2-shift through the circled intermediate in Scheme 1-5 was suggested as a preferred pathway for gold-catalyzed 1,3-acyloxy migration.[14] It was also mentioned that the intermediates might be in rapid equilibrium since the preference was not particularly strong. A 1,3-shift

followed by a retro 1,2-migration may also account for an apparent 1,2-acyloxy migration. In 2009, Toste showed the allene intermediate was derived from a direct 1,3-shift in gold-catalyzed reactions by ^{18}O labelling study, which was in accordance with results from previous studies shown in Scheme 1-2.[15] In the same year, labelling studies suggested that both direct 1,3- and double 1,2-acyloxy migration occurred randomly in the case of Au(I) and Au(III)-catalyzed reactions, while a direct 1,3-acyloxy migration occurred in Ag-catalyzed reactions.[16] In earlier studies on a tandem reaction for the formation of furans, double 1,2-acyloxy migration was also proposed as a possible pathway.[17]

Scheme 1-5. Mechanism of 1,3 and 1,2-Acyloxy Migration of Propargylic Esters.



Investigation on the the ring expansion reaction from propargylic esters with a chiral cyclopropyl probe indicated that 1,3-acyloxy migration propargylic esters was reversible and chirality transfer was not complete.[15,18] In a dynamic kinetic asymmetric

transformation, racemic propargylic esters could be converted to chiral chromenes.[19]

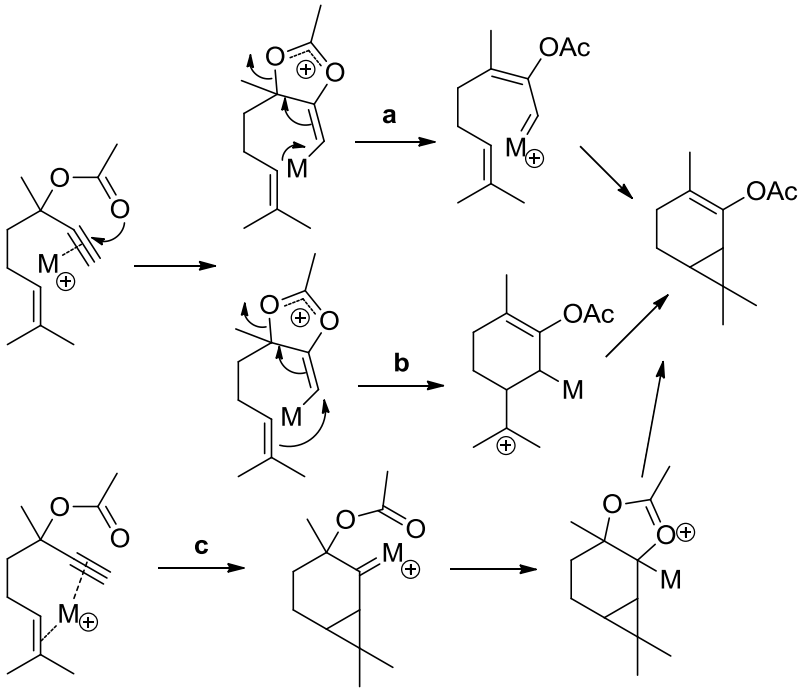
Recently, in an investigation on factors controlling the equilibrium of Pt-catalyzed 1,3- and 1,2-acyloxy migration of propargylic esters,[20] Cho found that the equilibrium was dependent on reaction temperature, alkyne substituent pattern, and catalysts. Sarpong and Zhang's research studies showed that 1,2-acyloxy migration becomes favored when R^3 (Scheme 1-5) is an electron-withdrawing ester or halogen substituent in Pt and Au-catalyzed reactions.[21,22]

1.4 Gold-, Platinum-, and Other π-acidic Metals-catalyzed Cycloadditions to Form Three-membered Rings Involving 1,3 and 1,2-Acycloxy Migration of Propargylic Esters

After initial discovery by Ohlof, the intramolecular cyclopropanation of alkenes using propargylic esters as the vinylcarbene precursors was further studied using transition metal catalysts such as Pt, Au, and Cu. Compared to earlier results shown in Schemes 1-3 and 1-5, better yields were generally obtained. By employing this method, several sesquiterpene natural products such as cubebol, cubebene, sesquicarene, sesquisabinene, and sesquithujene were synthesized.[23,24] Several reviews are available regarding these reseaches.[10,11,25] Computational studies were also performed for this process,[13,16] and three main mechanistic pathways have been proposed (Scheme 1-6). Either 1,2-acyloxy migration-cyclopropanation sequence or cyclopropanation-1,2-acyloxy migration sequence was proposed. In pathways **a** and **c**, carbene intermediates were proposed. In all of them, coordination of the metal to alkyne was proposed as the initial step, which is

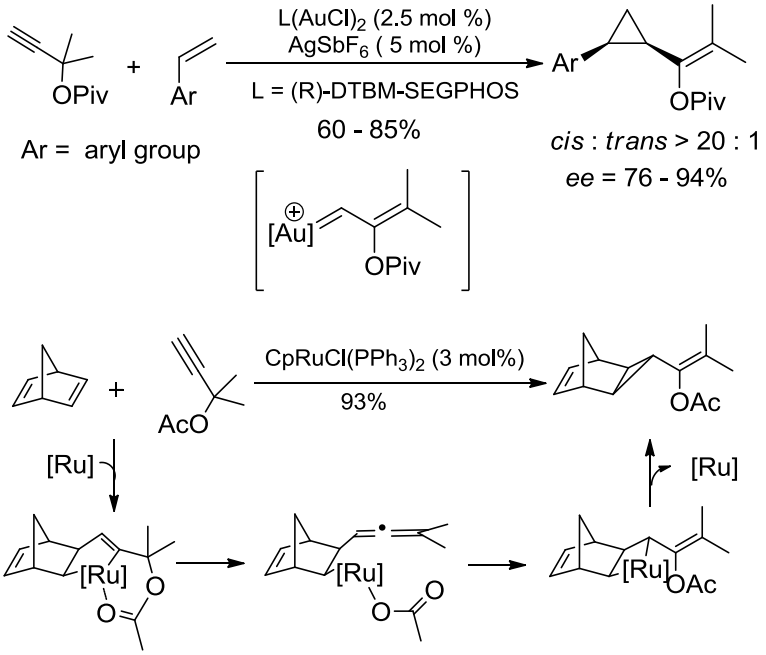
similar to Rautenstrauch's proposal (Scheme 1-6) but different from what Ohloff proposed (Scheme 1-2).

Scheme 1-6. Three Pathways Proposed for the Ohloff Process.



In 2003, Ohe and Uemura reported intermolecular cyclopropanation of alkenes using propargylic esters as vinylcarbene precursors using several transition metal catalysts including Ru(II), Rh(II), Au(III), Pt(II) and Ir(I) for.[26] The ratio for *cis*/*trans* cyclopropanes ranged from 94:6 to 36:64 using $[RuCl_2(CO)_3]_2$ catalyst. Toste demonstrated that by using chiral gold complexes, highly diastereoselective and enantioselective cyclopropanation of alkenes favoring the *cis*-isomer could be achieved (Scheme 1-7).[27] Using gold catalysts, enantioselective intramolecular cyclopropanation of alkenes to form medium-sized rings was also realized.[28]

Scheme 1-7. Au and Ru-catalyzed Intermolecular Cyclopropanation.



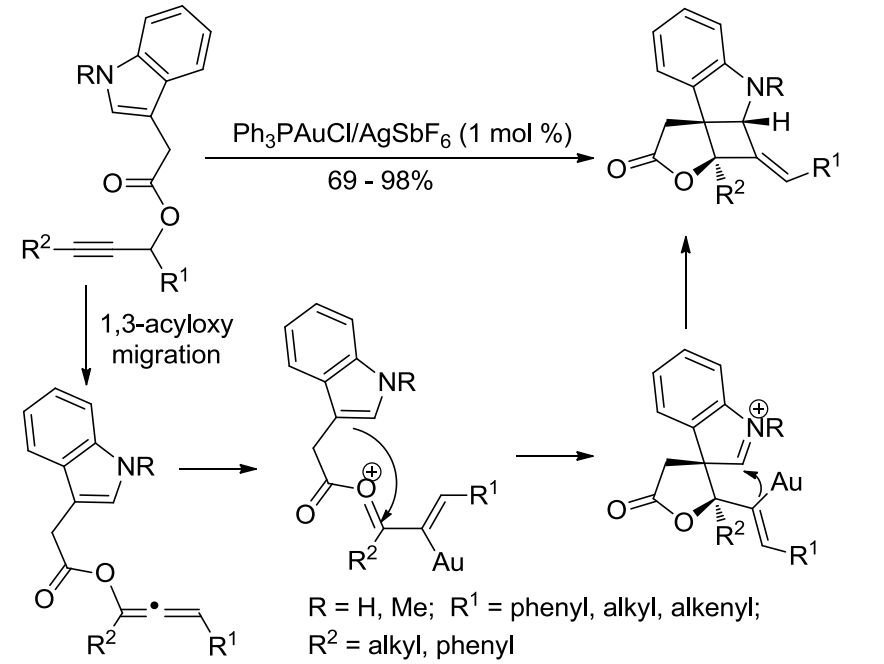
In 2006, Tenaglia reported an interesting $CpRuCl(PPh_3)_2$-catalyzed cyclopropanation of bicyclic alkenes (Scheme 1-7).[29] A cycloaddition isomerization mechanism involving allene intermediate was proposed.

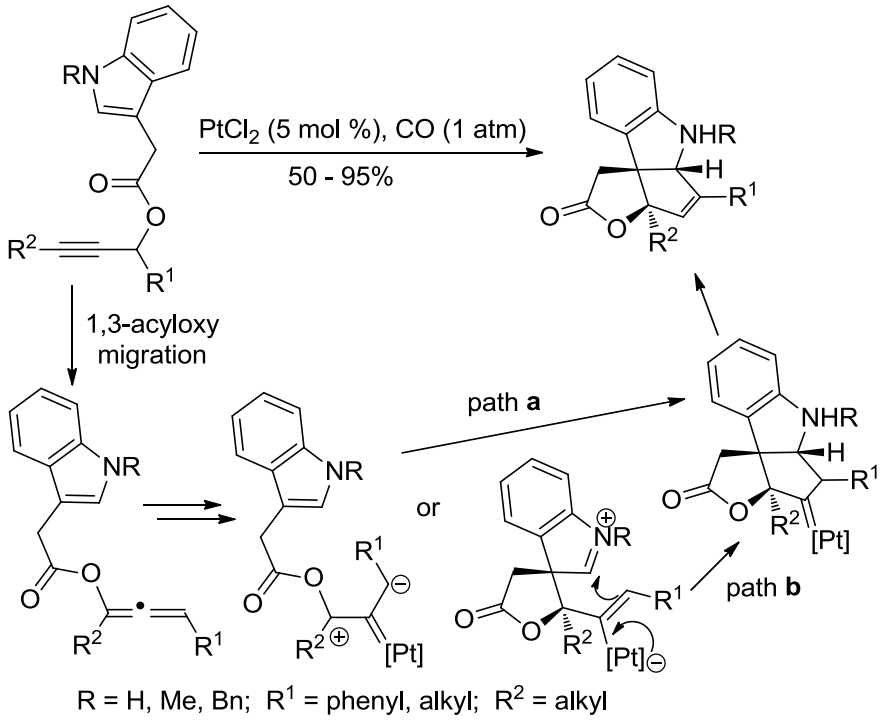
The intermolecular cyclopropanation could be futher coupled with other reactions. For example, Cope rearrangement of divinylcyclopropanes may yield cycloheptadienes (a formal stepwise [4+3] cycloaddition).[26,30] and ring expansion of vinylcyclopropanes may afford cyclopentenes (a formal stepwise [3+2] cycloaddition).[30] It was proposed by Gung that a concerted [4+3] cycloaddition occurred between dienes and gold-stabilized vinylcarbenes derived from propargylic esters.[31] Toste realized a formal stepwise [4+3] and [4+2] cycloadditions for the synthesis of benzonorcaradienes,[32] fluorenes, and styrenes from functionalized cyclopropane intermediates.[33]

1.5 Gold-, Platinum-, and Other π-acidic Metals-catalyzed Cycloadditions to Form Four-membered Rings Involving 1,3 and 1,2-Acycloxy Migration of Propargylic Esters

In 2005, Zhang reported a gold(I)-catalyzed [2+2] cycloaddition to form tetracyclic dihydroindole derivatives (Scheme 1-8).[34] Zhang proposed an allenylic ester as the initial intermediate after gold-catalyzed 1,3-acyloxy migration. Activation of the allene by gold allowed a following nucleophilic attack. Trapping of the iminium ion by alkenyl gold furnished the [2+2] cycloaddition product. When the reaction was stopped at shorter time the author observed the allenylic ester. Independently prepared allenylic ester also underwent reaction smoothly, which support that allenylic ester was involved in the [2+2] cycloaddition.

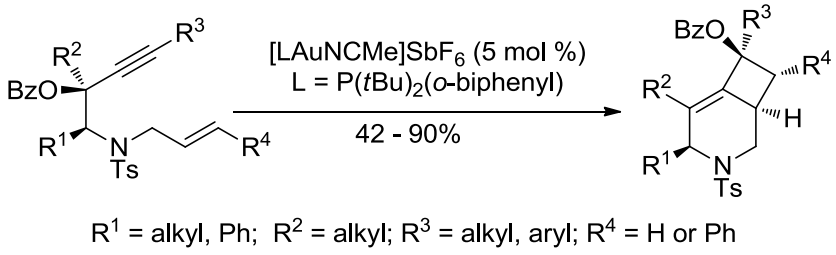
Scheme 1-8. Gold(I)-catalyzed [2+2] and [3+2] Cycloaddition with Indoles.





Recently, Chan demonstrated that in the presence of a gold catalyst, the allenylic ester could also undergo [2+2] cycloaddition with terminal alkenes or styrenes (Scheme 1-9).[35]

Scheme 1-9. Gold(I)-catalyzed [2+2] Cycloaddition with Alkenes.



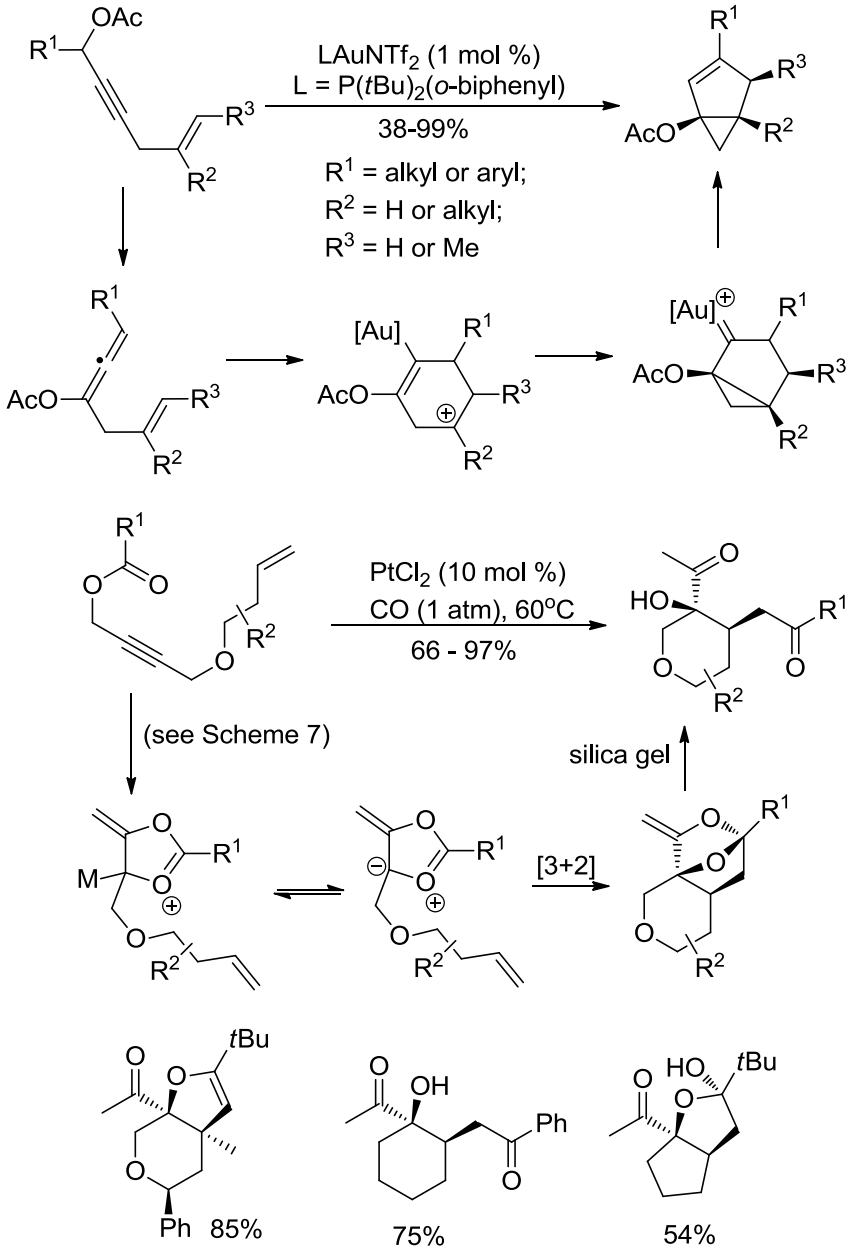
R^1 = alkyl, Ph; R^2 = alkyl; R^3 = alkyl, aryl; R^4 = H or Ph

1.6 Gold-, Platinum-, and Other π-acidic Metals-catalyzed Cycloadditions to Form Five-membered Rings Involving 1,3 and 1,2-Acycloxy Migration of Propargylic Esters

1.6.1 [3+2] Cycloaddition Involving 1,3-Acyloxy Migration

In 2006, Gagosz found that in the presence of cationic gold catalyst, 5-en-2-yn-1-yl acetates could undergo 1,3-acyloxy migration and cycloisomerization to form bicyclic[3.1.0]hexenes (Scheme 1-10).[36] The postulated allene intermediate was independently prepared and converted to the bicyclic product under the same condition. This process represented a formal intramolecular [3+2] cycloaddition of allene with alkene.[5] By adding alcohol nucleophile, cyclohexenes was observed from trapping the proposed carbocation. The author also observed that the chirality of the propargylic ester (99% *ee*) could be transferred to the bicyclic product (90% *ee*).

Scheme 1-10. Gold(I) and Platinum-catalyzed [3+2] Cycloaddition with Alkenes.



Zhang found that indoline-fused cyclopentenes could be obtained from [3+2] cycloaddition of allenylic ester and the tethered indole by changing the catalyst from gold to platinum (Scheme 1-8).[37] The author proposed that the reaction may proceed via a concerted dipolar cycloaddition (**a**) or a stepwise cyclization (**b**). The comparison in scheme 1-8 suggests substantial difference in the reactivities of alkenylplatinum and

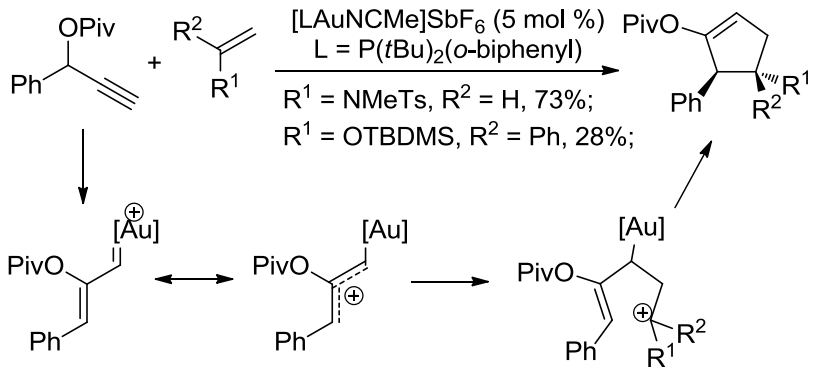
alkenylgold intermediates.

It was suggested by computational studies that a dipole intermediate might be involved in the equilibrium of acyloxy migration.[14] It was showed by She's group that this intermediate could be trapped by a tethered terminal alkene in a Pt-catalyzed [3+2] cycloaddition (Scheme 1-10).[38] Up to 58% yield could be obtained by using gold catalysts. Substrates with different tethers and substrates with a 1,1-disubstituted alkene also worked well. Nitrogen tethers were also examined in a later study.[39]

Wang found that the same dipole intermediate could be trapped by a tethered cyclohexadienones in a gold-catalyzed tandem reaction involving [3+2] cycloaddition, hydrolytic Michael addition, and retro-Aldol reaction.[40]

1.6.2 [3+2] Cycloaddition Involving 1,2-Acyloxy Migration.

Scheme 1-11. Au-catalyzed [3+2] Cycloaddition Involving 1,2-Acyloxy Migration.



It was found that [3+2] cycloaddition products could be obtained when certain electron-rich alkenes were employed in a study for Au-catalyzed cyclopropanation between propargylic esters with vinyl derivatives, (Scheme 1-11).[41] In most cases, vinyl derivatives afforded the cyclopropanation products. In one case, both cyclopentene and

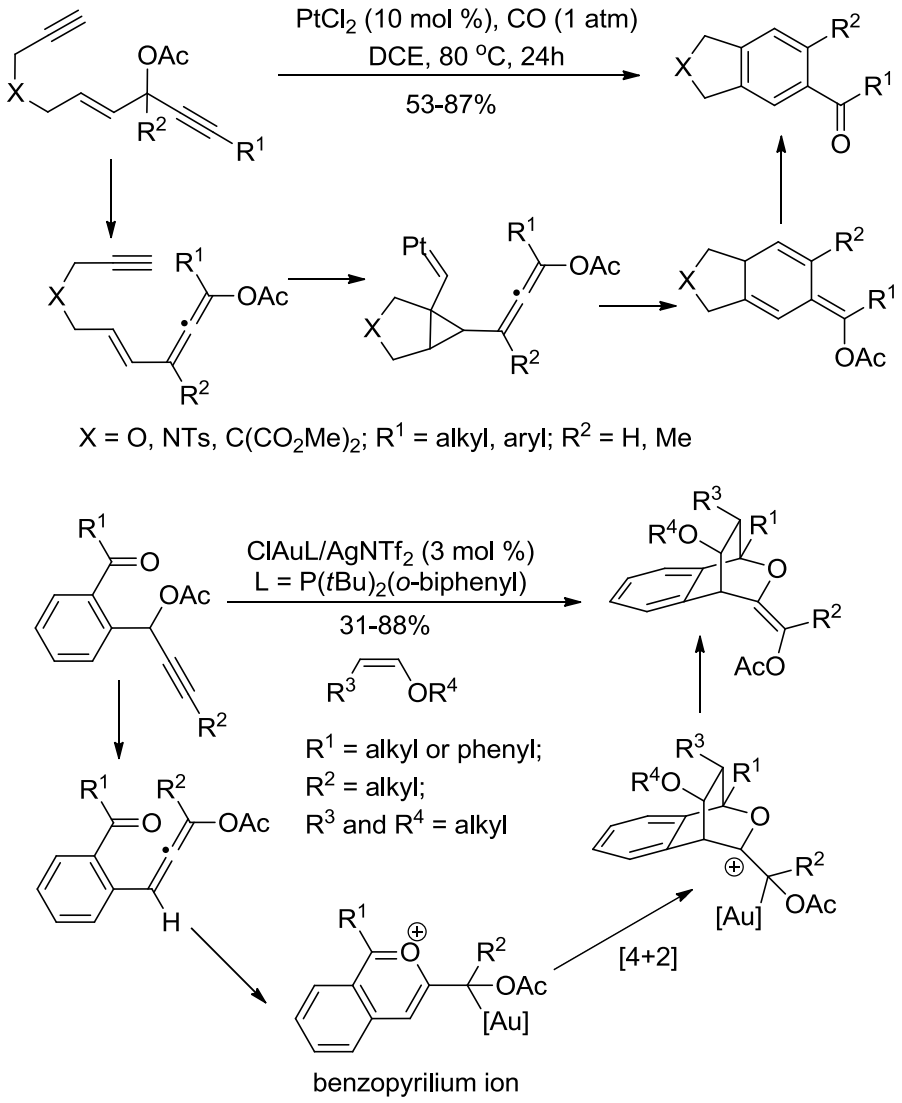
cyclopropane products were observed and the cyclopropane could not be converted to the corresponding cyclopentene. Based on this observation, a direct [3+2] cycloaddition mechanism was therefore proposed.

1.7 Gold-, Platinum-, and Other π-acidic Metals-catalyzed Cycloadditions to Form Six-membered Rings Involving 1,3- and 1,2-Acycloxy Migration of Propargylic Esters

1.7.1 [4+2] Cycloaddition Involving 1,3-Acyloxy Migration

Liang reported a Pt-catalyzed [4+2] cycloaddition involving 1,3-acyloxy migration(Scheme 1-12).[42] Low yields were obtained with Au(III) or Au(I) catalysts (8-11%) and aromatic products were isolated in all cases. For the 2C-component, only terminal alkynes were examined in call cases and no reaction occurred for propargylic esters with a terminal alkyne. The author proposed a Pt-mediated enyne cycloisomerization mechanism involving a cyclopropyl Pt-carbene.

Scheme 1-12. Pt and Gold-catalyzed [4+2] Cycloaddition.



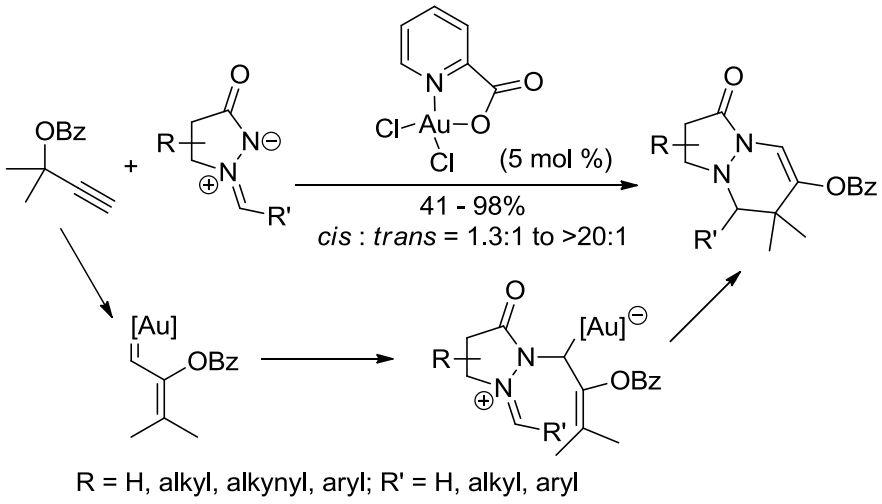
Liu reported a synthesis of bicyclic compounds fused with a benzene through a 1,3-acyloxy migration [4+2] cycloaddition sequence (Scheme 1-12).[43] The author proposed after Au-catalyzed nucleophilic attack of the carbonyl oxygen to allene, a benzopyrilium intermediate was proposed.

1.7.2 [3+3] Cycloaddition Involving 1,2-Acyloxy Migration

Toste demonstrated that azomethine imides could trap the carbene intermediates

generated from Au-catalyzed 1,2-acyloxy migration for [3+3] cycloadditions (Scheme 1-13).[44] The reaction also worked well with secondary propargylic esters. As the author pointed out, the Au-stabilized vinyl carbene served as three carbon component in reactions with 1,3-diploes, while the reaction of alkenyl Fischer carbene with 1,3-dipoles typically proceeds via [3+2] cycloaddition mode.

Scheme 1-13. Au-catalyzed [3+3] Dipolar Cycloaddition.

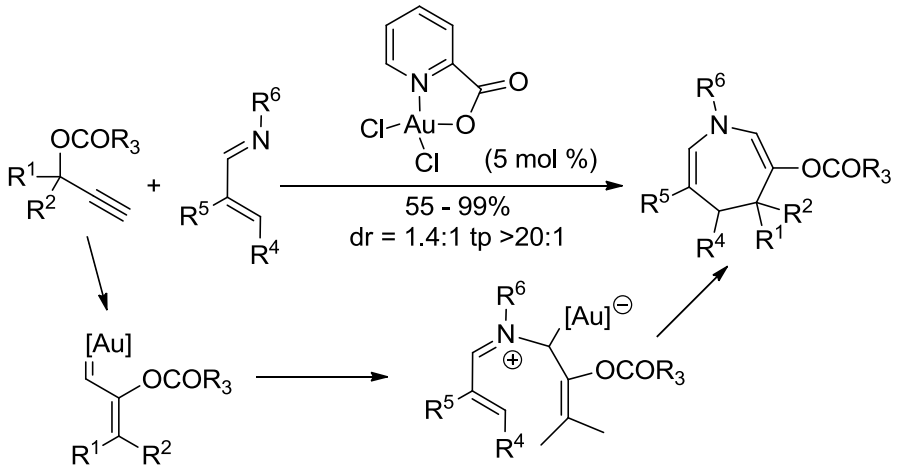


1.8 Gold-, Platinum-, and Other π-acidic Metals-catalyzed Cycloadditions to Form Seven-membered Rings Involving 1,3- and 1,2-Acycloxy Migration of Propargylic Esters

A [4+3] cycloaddition was realized by Toste for the synthesis of azepines when the carbene intermediates generated from Au-catalyzed 1,2-acyloxy migration is trapped by α,β-unsaturated imines, (Scheme 1-14).[45] As the author pointed out, this is analogy to [4+3] cycloadditions of rhodium and Fischer carbenes with α,β-unsaturated imines.

However, the stereochemistry of the Au-catalyzed [4+3] cycloaddition is different from [4+3] cycloadditions involving Fischer carbenes.

Scheme 1-14. Au-catalyzed [4+3] Cycloaddition.



R^1 and R^2 = H, alkyl or aryl; R^3 = Ph or *t*Bu; R^4 = alkyl, aryl;
R^5 = alkyl or Br; R^6 =aryl

1.9 Summary and Outlook

In summary, π-acidic metals, especially gold and platinum, could effectively catalyze a 1,3 or 1,2-acyloxy migration of propargylic esters depending on the substitution of alkyne. 1,3-Acyloxy migration would be preferred if the alkyne is substituted with an alkyl group, while a 1,2-acyloxy migration would occur when alkyne is attached with electron withdrawing group or hydrogen. Both allene and metal carbene, derived from 1,3-acyloxy migration and 1,2-acyloxy migration respectively, could be trapped by nucleophiles to undergo various cycloadditions.

Recenly, rhodium was found to be an effective π-acid for 1,3 and 1,2-acyloxy migrations of propargylic esters. With the unique redox and carbonyl insertion

reactivities, which are uncommon for traditional π-acidic metals like gold and platinum, rhodium might provide new opportunities for these types of cycloadditions.

1.10 Reference

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Chapter 2

Rhodium-catalyzed [5+1] Cycloaddition Involving 1,3-Acycloxy Migration of Cyclopropyl Propargylic Esters

This work has been published under the following:

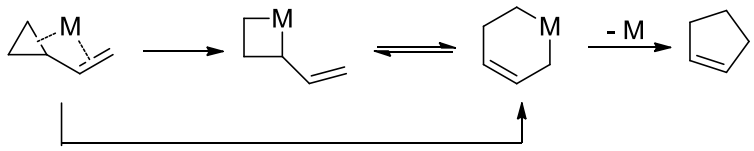
Shu, D.; Li, X.; Zhang,M.; Robichaux, P.; Tang, W. *Angew.Chem.Int.Ed*. **2011**, *50*, 1346.

Shu, D.; Li, X.; Zhang,M.; Robichaux, P.; Guzei, L.; Tang, W. *J.Org.Chem*. **2012**, *77*, 6463.

2.1 Introduction

Metal free ring expansion of simple vinylcyclopropanes to cyclopentenes without polar substituents generally require high temperatures and tend to produce mixtures of products.[1] Many transition metals (i.e., Pd, Rh, and Ni) have been utilized to catalyze this transformation (Scheme 2-1).[2] The mechanism involves metal-promoted cleavage of C-C bond via oxidative addition to form a vinylmetallacyclobutane.[3] The vinylmetallacyclobutane could then rearrange to a metallacyclohexene intermediate, which could undergo further reductive elimination to generate the cyclopentene. A direct oxidative coupling of vinyl cyclopropane to metallacyclohexene without involving of vinylmetallacyclobutane was also proposed for rhodium-catalyzed reactions based on calculation.[4]

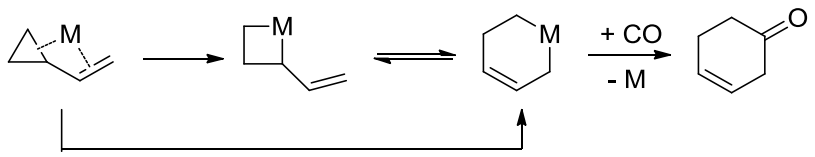
Scheme 2-1. **Transition Metal Catalyzed Vinylcyclopropane Cyclopentene Rearrangement.**



In the presence of CO, the intermediate metallacyclohexene can undergo CO insertion to form the [5+1] product cyclohexenone (Scheme 2-2). As early as 1969-1970, Sarel et al.[5] and Aumann[6] reported a stoichiometric reaction of vinylcyclopropane with $Fe(CO)_5$ forming cyclohexenone. More recently, Taber utilized this transformation to synthesize enantiomerically pure cyclohexenones.[7] Catalytic versions of this transformation have also been developed. Ito et al. reported an iridium-catalyzed [5+1] cycloaddition of

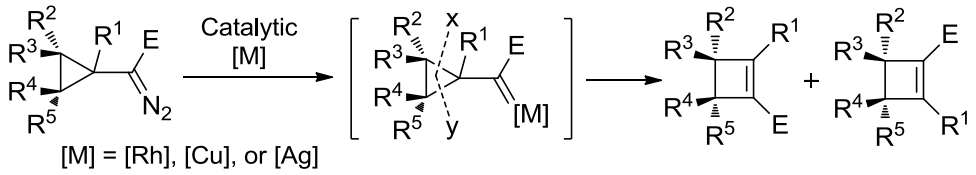
allenylcyclopropane and CO.[8] While Murai et al. found that cyclopropyl ketimines underwent $Ru_3(CO)_{12}$-catalyzedcycloaddition with CO to give six-membered unsaturated lactams.[9] The latter two transformations, however, require long reaction time and high temperature. Meijere found that $Co_2(CO)_8$ and $[Rh(CO)_2Cl]_2$ can be utilized to transfer vinylcyclopropanes into cyclohexenones, but the substrate scope is quite limited.[10] A more general rhodium-catalyzed [5+1] cycloaddition of vinylcyclopropane with CO was reported by Yu in 2012.[11]

Scheme 2-2. **Transition Metal Mediated [5+1] Cycloaddition.**

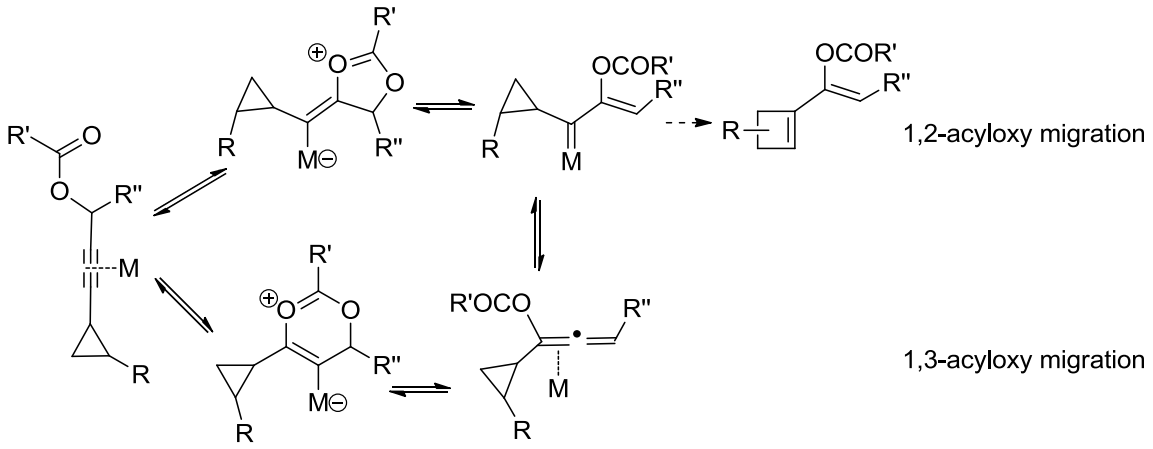


In 2008, our group reported a synthesis of highly substituted cyclobutenes from cyclopropyl metal carbenes derived from transition metal catalyzed decomposition of diazo compounds (Scheme 2-3).[12] Since diazo compounds are explosive and hard to handle, we proposed a more convenient and atom-economical way to generate metal carbene intermediates through a 1,2-acyloxy migration of propargylic esters (Scheme 2-4). During our investigation, an unexpected cyclohexenone **2-2a** was isolated in about 30% yield when $[Rh(CO)_2Cl]_2$ was employed (Scheme 2-5).

Scheme 2-3. Transition Metal Catalyzed Synthesis of Cyclobutenes through Ring Expansion of Cyclopropanes.

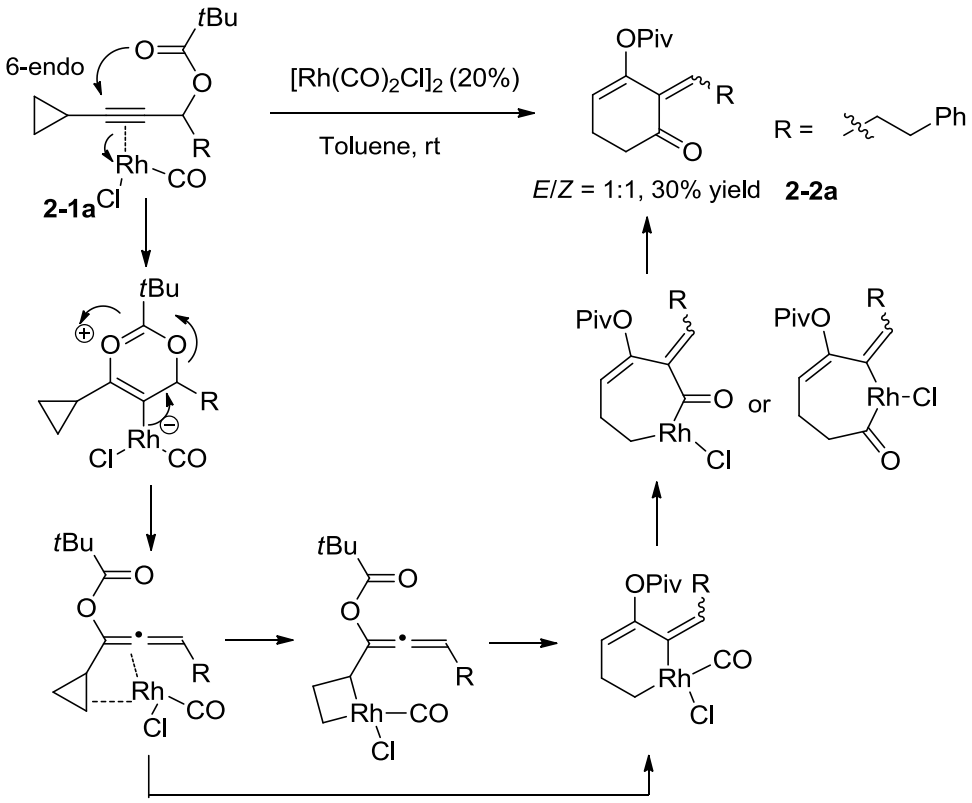


Scheme 2-4. **Proposed One-pot Synthesis of Cyclobutenes through 1,2-Acycloxy Migration and Ring Expansion Sequence.**



The possible mechanism involves an initial rhodium-catalyzed 1,3-acyloxy migration of propargylic ester followed by allenylcyclopropane [5+1] cycloaddition. It involves metal-promoted cleavage of C-C bond via oxidative addition to form an allenylmetallacyclobutane. The allenylmetallacyclobutane could then rearrange to a metallacyclohexene intermediate, which could undergo further CO insertion and reductive elimination to generate the cyclohexenone. A direct oxidative coupling of allenyl cyclopropane to metallacyclohexene without involving of metallacyclobutane is also possible.

Scheme 2-5. **Proposed Mechanism for the Rhodium-catalyzed Tandem 1,3-Acyloxy Migration and [5+1] Cycloaddition**.



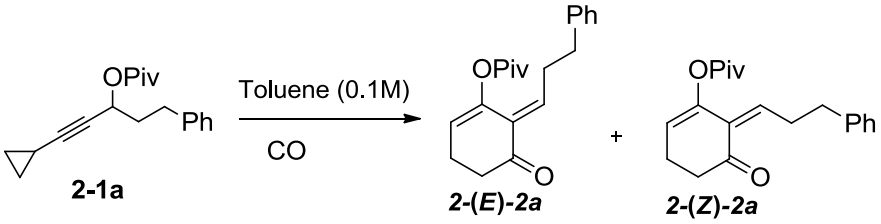
This transformation combines π-acidity with traditional redox reactivities of rhodium. While many π-acidic metals, such as gold and platinum, are superior to facilitate events like acyloxy migration. However, they are reluctant to undergo transformations involving redox chemistry.[13] The coupling of π-acidity of rhodium with its traditional oxidative addition, migratory insertion, and reductive elimination reactivities may lead to ample new opportunities for the design of new reactions.

2.2 Results and Discussion

2.2.1 Optimization of Catalyst and Reaction Conditions for the Tandem 1,3-Acyloxy Migration and [5+1] Cycloadditions

The initial yield was low with substoichiometric amount of $[Rh(CO)_2Cl]_2$. We then chose to run the reaction under one atm of CO (table 2-1). The conversion was low when the reaction was run under 1 atm of CO at room temperature. After increasing the temperature to 60 ^oC, complete conversion was observed. We found that by lowering the pressure of CO, complete conversion was also observed. Inhibition of the reaction by higher CO pressure may be due to competitive binding of CO to rhodium catalyst or slower oxidative addition with more electron-withdrawing CO ligand on the metal. In all the runs, *E*/*Z* selectivity is around 1:1.

Table 2-1. Effect of CO Pressure and Temperature.[a]

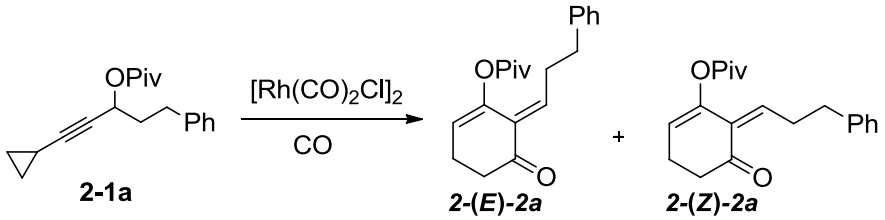


Entry	Condition	Conversion(*E*/*Z*)
1	$[Rh(CO)_2Cl]_2$, 1 atm CO, r.t., overnight	26% (1:1.3)
2	$[Rh(CO)_2Cl]_2$, 1 atm CO, 60 ^oC, 2h	complete conversion to product (1:1.3)
3	$[Rh(CO)_2Cl]_2$, 0.1 atm CO, r.t., overnight	complete conversion to product (1:1.3)

[a] $[Rh(CO)_2Cl]_2$ (5 mol%).

The solvent effect was also investigated. As shown in table 2-2, toluene, ethyl acetate and dioxane gave the best result. THF and CH_2ClCH_2Cl give moderate yield. The reaction was completely inhibited when CH_3CN or DMF was used as the solvent. In all the cases, *E*/*Z* selectivity is low. It is apparent that coordinative solvent is detrimental for this reaction, presumably due to competitive binding of these solvents to the rhodium catalyst.

Table 2-2. Effects of Solvent on Yield and *E*/*Z* Selectivity.[a]

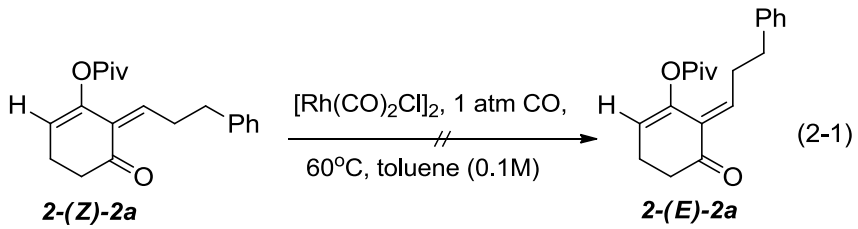


Entry	Solvent	Yield[b] (*E*/*Z*)
1	Toluene	Quantitative (1:1)
2	EtOAc	Quantitative (1:1)
3	dioxane	Quantitative (1:1)
3	THF	75% (1:1)
4	CH_2ClCH_2Cl	70% (2:1)
5	CH_3CN	No reaction
6	DMF	No reaction

[a] Condition: $[Rh(CO)_2Cl]_2$ (5%), CO (1 atm), 60 ^oC, concentration (0.1 M), 2h. [b] NMR yield.

2.2.2 Investigation of *E*/*Z* Selectivity

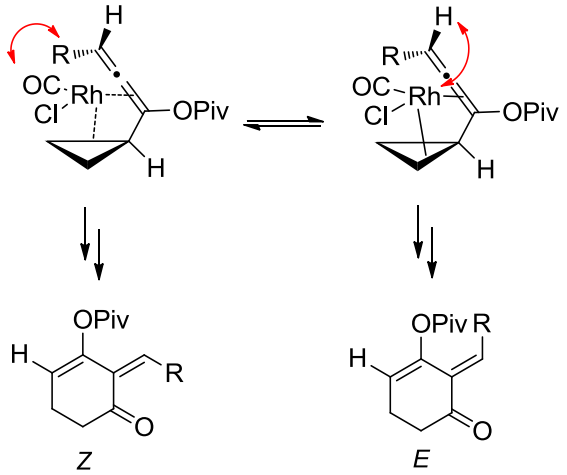
First we investigated whether the *E*/*Z* selectivity was kinetically or thermodynamically controlled (eq 2-1). Both *E* and *Z* isomers were isolated and treated under the same reaction condition separately. Double bond isomerization was not observed, indicating that the *E*/*Z* selectivity was kinetically controlled.



(2-1)

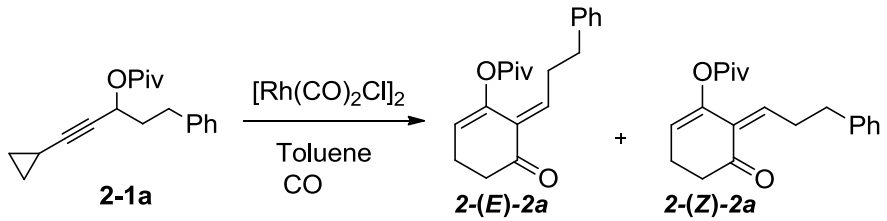
Based on the above results, we proposed a model in Scheme 2-6. Rhodium catalyst could coordinate from the back side, which would lead to *Z* isomer. If rhodium coordinates from the front side, *E* isomer would be obtained.

Scheme 2-6. Proposed Model for *E*/*Z* Selectivity



Based on the model, the low *E*/*Z* selectivity observed may be due to the fact that there is not enough steric interaction between R substituent and catalyst. Different ligands were screened to increase the steric interaction (Table 2-3). In most cases, the ligand inhibited the reaction, and *E*/*Z* selectivity was not improved even when desired product was observed. When thiourea was employed, a triene byproduct was observed.

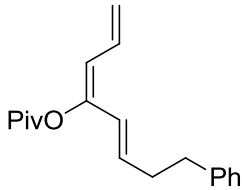
Table 2-3. Effect of Ligands.[a]



Entry	Ligand	Yield (*E*/*Z* selectivity)[b]
1	PPh_3	0%
2[c]	PPh_3	45% (1:1)
3[c]	$P(OPh)_3$	0%

4 [c]	$P(OMe)_3$	0%
5	pyridine	0%
6	urea	55% (1:1)
7	thiourea	30% (1:1)[d]

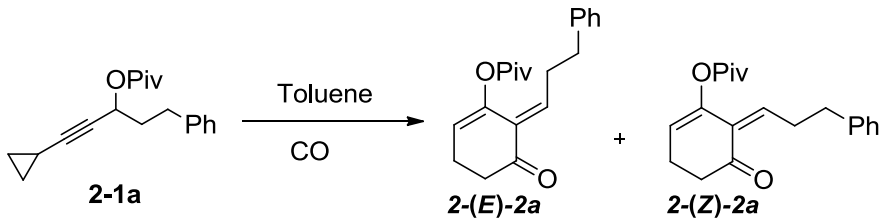
[a] Condition: $[Rh(CO)_2Cl]_2$ (5%), CO (1 atm), 60 °C, toluene (0.1 M), 2h. [b] NMR yield; the selectivity was determined based on NMR. [c] $[Rh(CO)_2Cl]_2$ (5%), CO (0.1 atm), 60 °C, toluene (0.1 M), 2h. [d] Triene byproduct **2-3** was observed in 30% yield.



2-3

Different catalysts were also screened (table 2-4). When cationic rhodium catalyst was employed, enone was observed (eq 2-2). The enone was presumably derived from the hydrolysis of an allene intermediate.

Table 2-4. Catalyst Screening.[a]

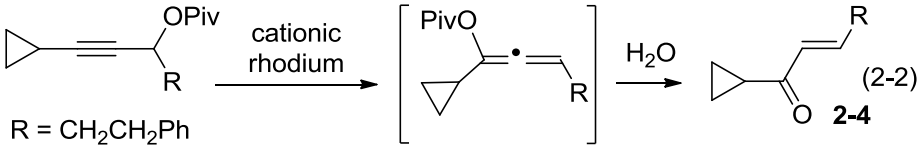


2-1a **2-(*E*)-2a** **2-(*Z*)-2a**

Entry	Catalyst	Yield (*E*/*Z* selectivity)[b]
1	$[Rh(CO)_2Cl]_2$ (5%), $AgBF_4$ (10%)	0%[c]

2	$[Rh(cod)_2]BF_4$ (5%)	0% [c]
3	$[Rh(cod)_2]BF_4$ (5%), dppp (10%)	0%
4	$[Rh(cod)Cl]_2$ (10%)	70% (1:1)
5	$[Rh(cod)Cl]_2$ (10%), $AgBF_4$ (10%), dppp (20%)	0% [c]
6	$[Rh(cod)Cl]_2$ (10%), $P(OMe)_3$(20%)	0%

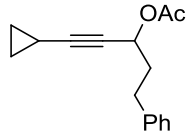
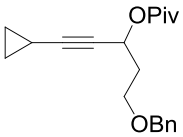
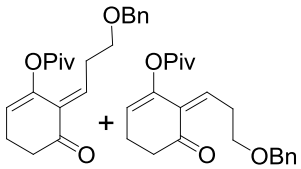
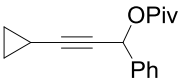
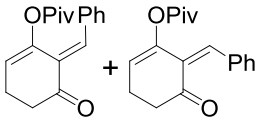
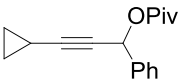
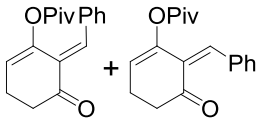
[a] Condition: CO (1 atm), 60 °C, toluene (0.1 M), 2h. [b] NMR yield; the selectivity was determined based on NMR. [c] substantial amount of enone byproduct was observed.

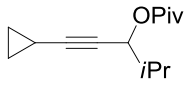
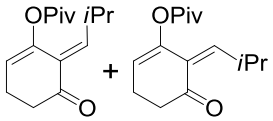
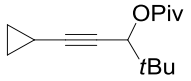
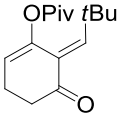
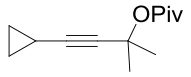
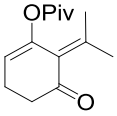
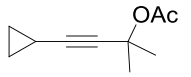
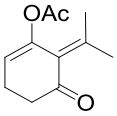
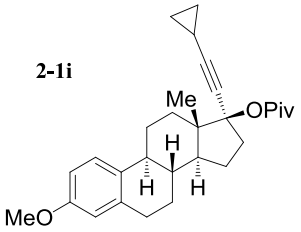
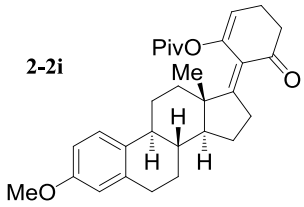


The *E*/*Z* selectivity of this tandem 1,3-acyloxy migration [5+1] cycloaddition was first examined with substrates **2-1b** to **2-1i** (Table 2-5), all derived from cyclopropyl acetylene. The reaction worked at rt with reduced CO pressure, but conducting it under 1 atm of CO at 60 °C is faster and provided us consistent results. No reaction occurred for secondary propargylic acetate **2-1b**, indicating that the migration group has a significant effect on the reactivity. For substrates with a tertiary ester, the [5+1] cycloaddition worked well when the propargylic ester was changed from pivalate to acetate (e.g. **2-1h**). Good *E*/*Z* selectivity could be achieved for propargylic esters with sterically demanding substituents (e.g. **2-1f** and **2-1i**). Highly functionalized product **2-2i** could also be obtained from

substrate **2-1i**, which was prepared from a steroid derivative. The structure of the exo-cyclic olefin of product **2-2f** was further confirmed by x-ray analysis.

Table 2-5. Scope of Substrates with non-Substituted Cyclopropanes.[a]

Substrates	Products	Yield[b] (*E*/*Z*)
2-1a	**2-(*E*)-2a + 2-(*Z*)-2a**	93% (1:1.3)
2-1b 	–	0%
2-1c 	 2-(*E*)-**2c** 2-(*Z*)-**2c**	81% (1:1.3)
2-1d 	 **2-(*E*)-2d** **2-(*Z*)-2d**	95% (2:1)
2-1d 	 **2-(*E*)-2d** **2-(*Z*)-2d**	70%[d,e] (3.5:1)

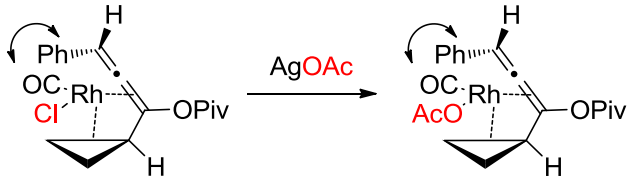
2-1e 	 **2-(*E*)-2e** **2-(*Z*)-2e**	87% (1:1)
2-1f 	**2-2f** 	92% (10:1)
2-1g 	**2-2g** 	88%[c]
2-1h 	**2-2h** 	85%
2-1i 	**2-2i** 	91% (13:1)

[a] Conditions: 5 mol % $[Rh(CO)_2Cl]_2$, CO (1 atm), toluene (0.1M), 60 °C, 5h. [b] Isolated yields of both isomers. [c] 2.5 mol % catalyst, 60 °C, 1h. [d] Condition: 5 mol % $[Rh(CO)_2Cl]_2$, 10 mol % AgOAc, CO (1 atm), toluene, 60 °C, 5h.[e.] NMR yield.

For substrate **2-1b**, we found that the *E*/*Z* selectivity could be improved from 2:1 to 3.5:1 by adding AgOAc. One possible explanation is that by replacing chloride with acetate, the steric interaction between phenyl and catalyst increases, leading to a higher

selectivity (Scheme 2-7). We could not improve the selectivity further by examining more sterically demanding counter ions.

Scheme 2-7. AgOAc effect.

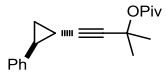
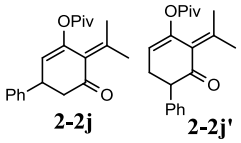
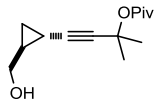
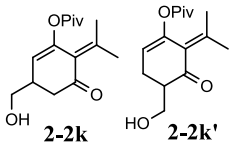
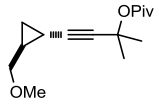
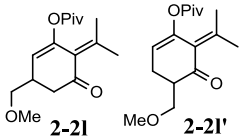
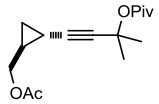
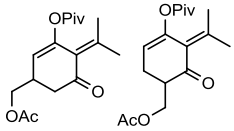
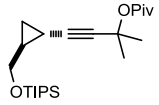
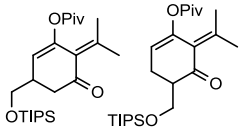


2.2.3 Investigation of Regioselectivity

For unsymmetrically substituted cyclopropanes, the cleavage of different cyclopropane C-C σ-bonds may lead to different isomers. Based on studies from our lab[15] and others,[7,16] the regioselectivity for the cleavage of C-C σ-bonds in cyclopropanes was determined by the electronic and steric properties of the substituents, the stereochemistry of the cyclopropane ring, and the metal catalysts.

We prepared a series of *trans*-substituted cyclopropyl propargylic esters to investigate the regioselectivity of the C-C σ-bond cleavage (table 2-6). Opposite regioselectivity was observed for **2-*trans*-1j and 2-*trans*-1k**, which had a phenyl and an alkyl substituent on the cyclopropane ring respectively. The regioselectivity was increased when the free hydroxyl group in **2-1k** was functionalized to methyl ether **2-1l**, acetate **2-1m**, or silyl ether **2-1n**,

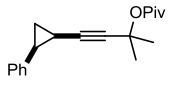
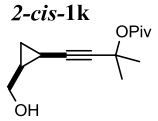
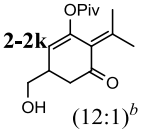
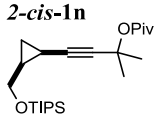
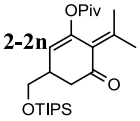
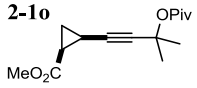
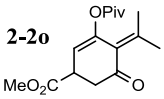
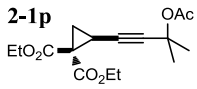
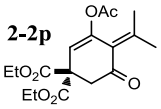
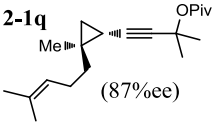
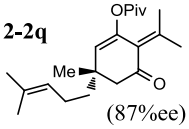
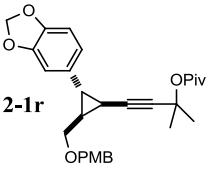
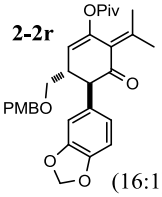
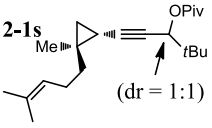
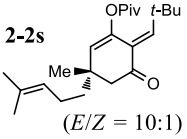
Table 2-6. Regioselectivity for the Cleavage of C-C σ-Bond in *trans*-Disubstituted Cyclopropanes.[a]

Substrates	Products	Yield[c]
***2-trans*-1j** 	 **2-2j** **2-2j'** (**2-2j** : **2-2j'** = 1 : 2.5)[b]	90%[d]
***2-trans*-1k** 	 **2-2k** **2-2k'** (**2-2k** : **2-2k'** = 3.5 : 1)[b]	64%
***2-trans*-1l** 	 **2-2l** **2-2l'** (**2-2l** : **2-2l'** = 6 : 1)[b]	68%
***2-trans*-1m** 	 **2-2m** **2-2m'** (**2-2m** : **2-2m'** = 6 : 1)[b]	78%
***2-trans*-1n** 	 **2-2n** **2-2n'** (**2-2n** : **2-2n'** = 10 : 1)[b]	91%

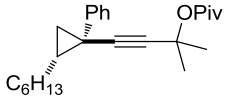
[a] Conditions: see Table 2-5, note a, unless noted otherwise. [b] Regioisomeric ratios were determined by ^{1}H NMR of the crude products. [c] Yields are isolated yields of the major isomer unless noted otherwise. [d] Yields are combined yields of **2-2j** and **2-2j'**.

Opposite regioselectivity was observed for cyclopropanes **2-*trans*-1j** and **2-*cis*-1j**, both of which had a phenyl substituent on the cyclopropane ring (Tables 2-6 and 2-7). Good regioselectivity was observed for alkyl substituted **2-*cis*-1k** and **2-*cis*-1n**. For substrate **2-*cis*-1n**, the 1,3-acyloxy migration [5+1] cycloaddition cascade reaction worked even at rt with 1 atm of CO. A 16:1 ratio was observed for this substrate at 60 ^{o}C. The ratio could further be improved to over 20:1 at rt. We also found the same trend of regioselectivity for other substituted cyclopropanes (e.g. **2-1o – 2-1s**). Only one isomer was obtained from cyclopropanes with a quaternary carbon, such as compounds **2-1p** and **2-1q.** For 1,2,3-trisubstituted cyclopropane **2-1r**, a 16:1 regioisomeric ratio was observed. Based on regioselectivity observed for substrates **2-*trans*-1j** and **2-*cis*-1n**, the *trans*-aryl group and *cis*-PMBOCH$_2$ group in cyclopropane **2-1r** should direct the cleavage of the same C-C σ-bond. We observed that the chirality in substrate **2-1q** was completely transferred to the corresponding cyclohexenone product, which paved a way for enantioselective synthesis of highly substituted cyclohexenones from optical pure cyclopropanes. In contrast, the chirality was not completely transferred in gold-catalyzed cyclopropane ring opening reactions.[17a-c]

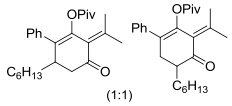
Table 2-7. Regioselectivity for the Cleavage of C-C σ-bond in *cis*-Disubstituted and Trisubstituted Cyclopropanes.[a]

Substrates	Products	Yield[c]
***2-cis*-1j**  	(**2-2j** : **2-2j'** = 3.5 : 1)[b]	95%[d]
***2-cis*-1k**  	**2-2k**  (12:1)[b]	79%
***2-cis*-1n**  	**2-2n**  (>20 : 1)[b]	93%[e]
2-1o  	**2-2o**  	76%
2-1p  	**2-2p**  	74%
2-1q  (87%ee)	**2-2q**  (87%ee)	86%
 	**2-2r**  (16:1)[b]	80%
2-1s  (dr = 1:1)	**2-2s**  (*E*/*Z* = 10:1)	74%[f]

2-1t



2-2t +2-2t'



99%

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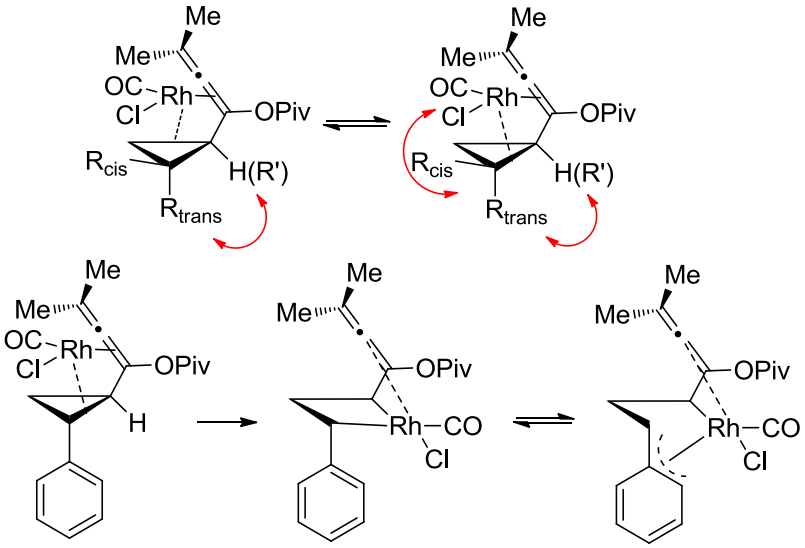
[a] Conditions: see Table 2-5, note a, unless noted otherwise. [b] Regioisomeric ratios were determined by ^{1}H NMR of the crude products. [c] Yields are isolated yields of the major isomer unless noted otherwise. [d] Yields are combined yields of **2-2j and 2-2j'**. [e] The reaction was run at rt. [f] 80 ^{o}C, 24h.

The less hindered C-C σ-bond was selectively cleaved for all *trans*-substituted cyclopropanes except **2-*trans*-1j** in Table 2.6, presumably because of the steric interaction between the substituent R and the rhodium complex in intermediate **2-*trans*-8-1** (Scheme 2-8). We observed higher regioselectivity for more sterically demanding substituent (e.g. 2-*trans*-**1k** to 2-*trans*-**1n**). For the same reason, the less hindered C-C σ-bond was also selectively cleaved for all *cis*-disubstituted cyclopropanes in Table 2-7. In general, substrates with a *cis* substituent to the propargylic ester group had higher regioselectivity than the corresponding *trans*-substituent (e.g. 2-*trans*-**1k** *vs* 2-*cis*-**1k** and 2-*trans*-**1n** *vs* 2-*cis*-**1n**). This can be explained by the more significant steric interactions between the R group and rhodium complex in intermediate 2-*cis*-**8-1** than that in 2-*trans*-**8-1** (Scheme 2-8). The C-C σ-bond that was adjacent to aryl group was selectively cleaved for substrate 2-*trans*-**1j**, presumably because of the electronic effect of the adjacent π-system. The adjacent phenyl group led to a more facile oxidative addition. The overall low and opposite regioselectivity observed for *trans*- and *cis*-phenyl substituted cyclopropanes 2-**1j** may be due to competing steric and electronic effects. The

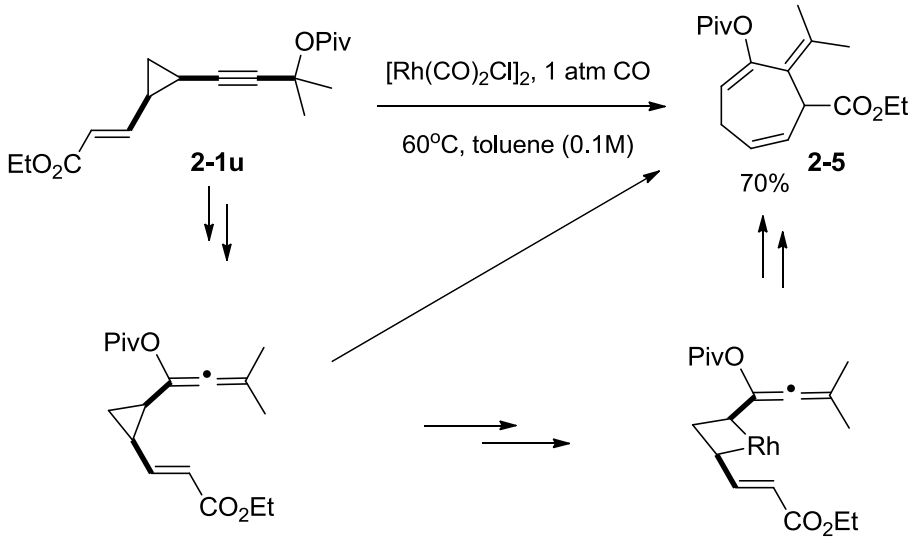
observed 1:1 regioselectivity for 1,1,2-trisubstituted cyclopropane 2-**1s** may be due to the competing steric effects (Scheme 2-8). The steric interaction between catalyst and *trans*-C_6H_{13} would favor the cleavage of less hindered C-C σ-bond, while the repulsion between phenyl (R') and *trans*-C_6H_{13} would favor the cleavage of more hindered C-C σ-bond.

Scheme 2-8. Steric and Electronic Effect on the Regioselectivity.



When **2-1u** was applied as substrate, an unexpected seven-membered ring was formed (Scheme 2-9). The reaction presumably undergoes an initial 1,3-acyloxy migration, followed by either thermal Cope rearrangement or rhodium-catalyzed stepwise Cope rearrangement.

Scheme 2-9. Cope Rearrangement Product.

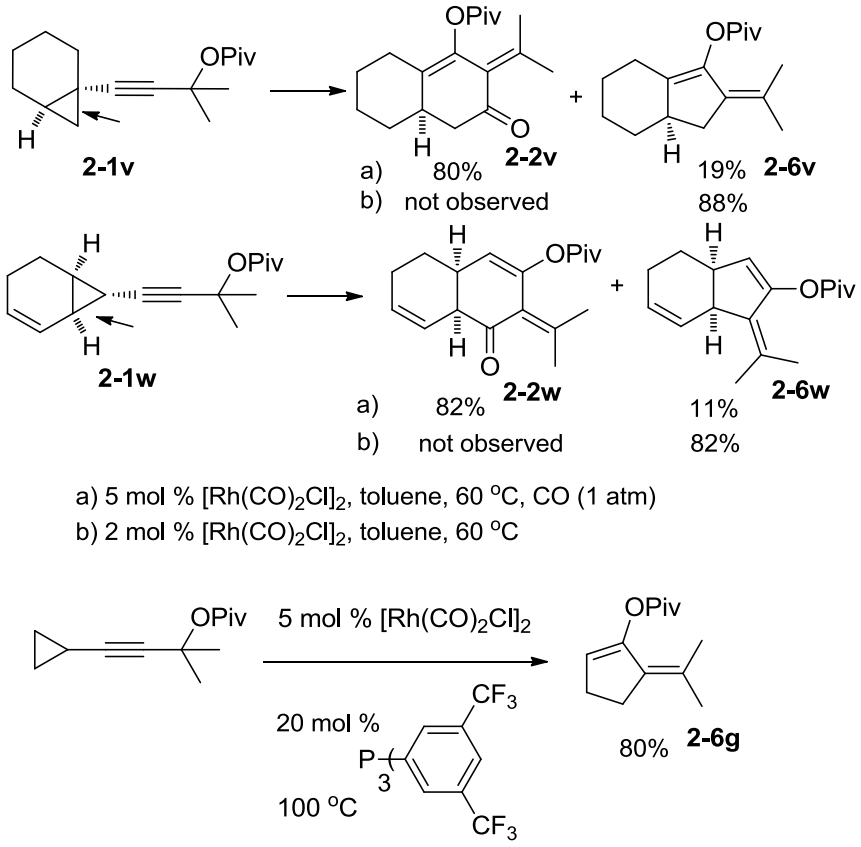


2.2.4 Formation of Five-membered Ring

Decalin derivatives 2-**2v** and **2-2w** were isolated in 80% and 82% yields respectively with high regioselectivity from bicyclic substrates 2-**1v** and 2-**1w** (Scheme 2-10). In these two cases, We also isolated the five-membered isomerization products **2-6v** and **2-6w** in 19% and 11% yields respectively under the standard condition. We could isolate the 5-6 fused bicyclic compounds **2-6v** and **2-6w** in good yields by running the reaction in the absence of external CO with a lower catalyst loading. The C-C σ-bond that was adjacent to alkene was exclusively cleaved for the formation of both products **2-2w** and **2-6w** from cyclopropane **2-1w**, presumably because of the electronic effect of the adjacent π-system to form a more stable π-allyl rhodium intermediate. It is interesting to note that we did not observe any five-membered isomerization product in the monocyclic system even in the absence of a CO balloon. However, with the addition of electron poor phosphine ligand and higher temperature, five-membered ring product could be isolated in good

yield. This ligand effect is similar to the CO insertion of Pt where electron donating ligand favors CO insertion and electron poor ligand disfavors CO insertion.[17d]

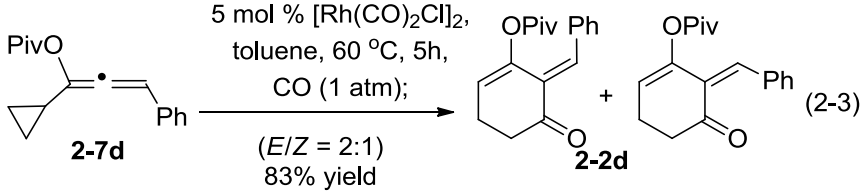
Scheme 2-10. Rh-Catalyzed Ring Expansion of Cyclopropanes in Bicyclic Systems.



2.2.5 Mechanistic study

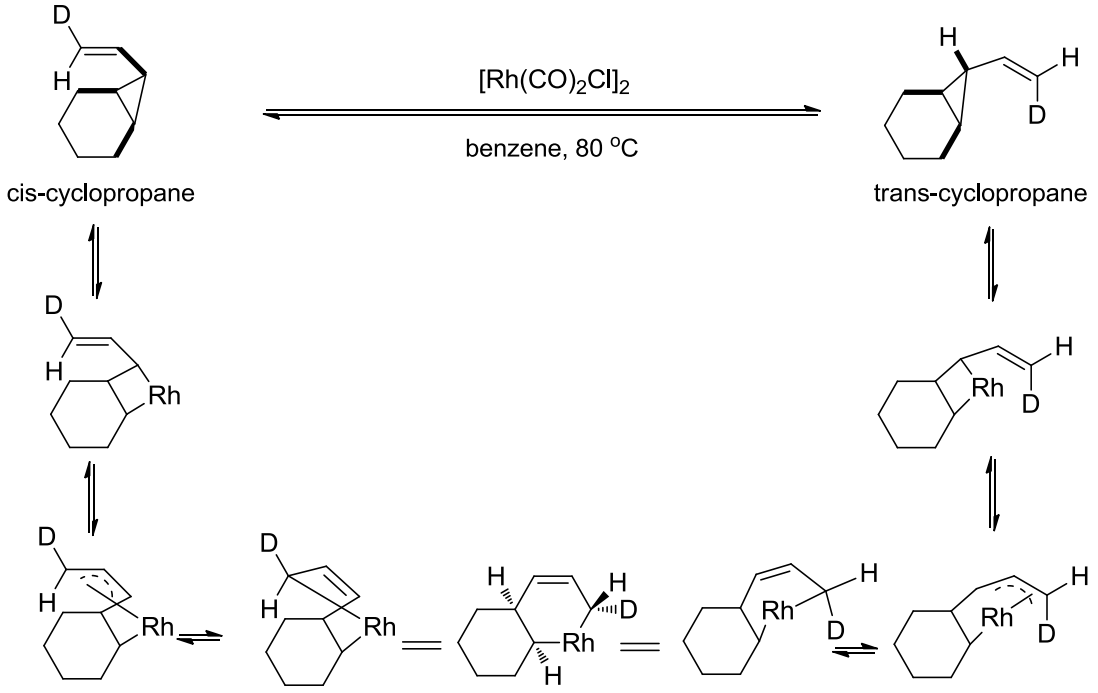
Allenyl cyclopropane was an intermediate in the proposed mechanism (Scheme 2-5). allene **2-7d** was prepared from propargylic ester 2-**1d** using a silver catalyst. Under standard conditions, product 2-**2d** was obtained in a similar yield (eq 2-3). Same *E*/*Z* ratio of alkylidene cyclohexenone 2-**2d** was observed as products directly derived from 2-**1d**

using a Rh(I) catalyst (Table 2-5). This result provided strong evidence for the mechanism we proposed in Scheme 2-5.



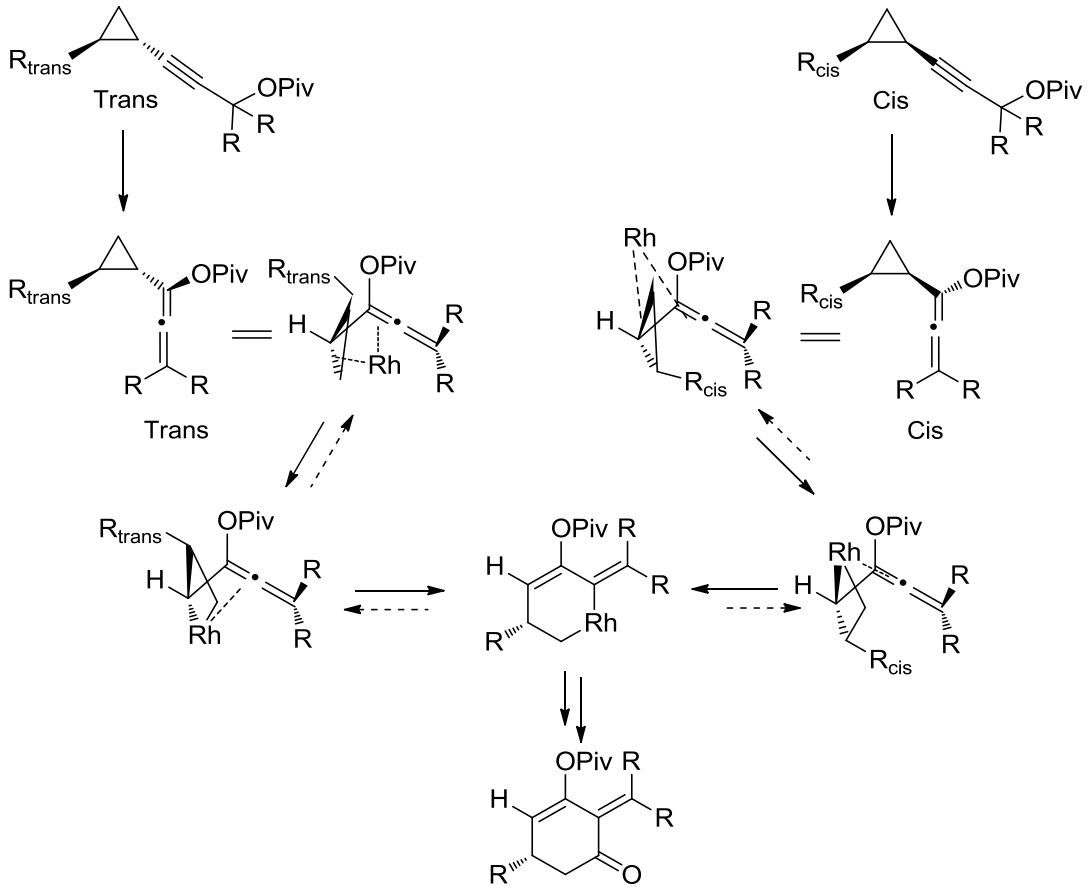
In the proposed mechanism (scheme 2-5), the ring expansion step from allenyl cyclopropane to metallayclohexene is the regioselectivity and *E*/*Z* selectivity generating step. If irreversible, then it is also the regioselectivity and *E*/*Z* selectivity determining step. Based on literature[4], it could be either a one-step oxidative coupling, or a two-step process involving allenylmetallacyclobutane intermediate. According to a study by Soloman and coworkers (Scheme 2-11)[18], vinylcyclopropane could undergo cis and trans isomerization in the presence of $[Rh(CO)_2Cl]_2$ catalyst. The authors also proposed a mechanism which involves a conformational inversion of metallacyclohexene. By deuterium labeling, the authors found that the cyclopropane cis to trans inversion was accompanied by a double bond isomerization.

Scheme 2-11. Rhodium-catalyzed Vinylcycloproane cis and trans Isomerization.



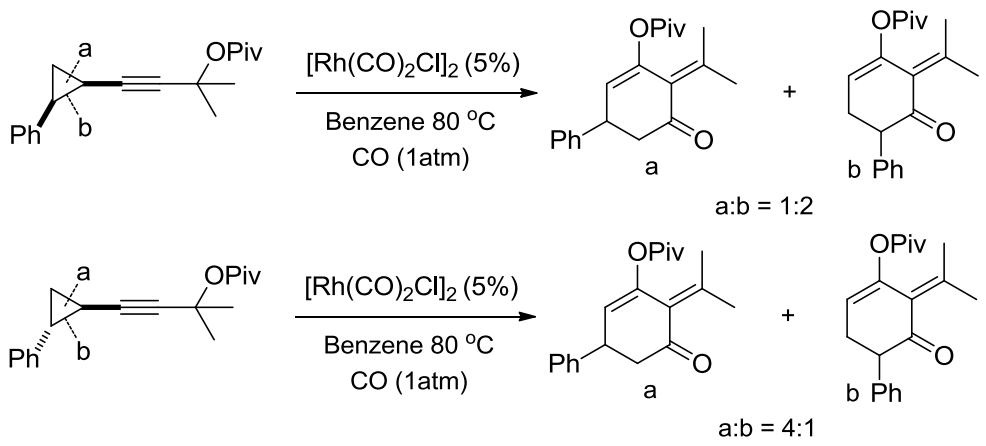
In our [5+1] cycloaddition, the cis and trans allenylcyclopropane isomerization is also possible (scheme 2-12). After initial 1,3-acycloxy migration, trans and cis allenylcyclopropanes could be generated from trans and cis cyclopropylpropargylic esters respectively. The trans and cis allenylcyclopropanes could then undergo ring expansion to form metallacyclohexenes through either a one-step or two-step process. If this ring expansion step is reversible, the trans and cis allenylcyclopropane intermediates would be in equilibrium, which implies the trans and cis cyclopropylpropargylic ester would result in same regioselectivity.

Scheme 2-12. Scrambling of Allenylcyclopropane Stereochemistry.



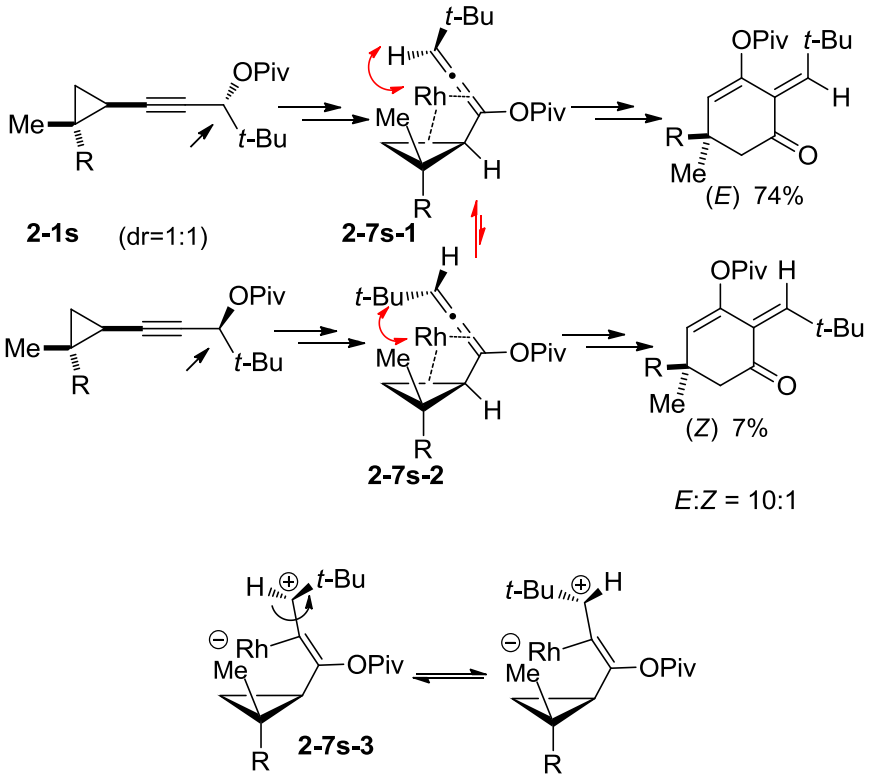
Under the identical reaction condition as the literature, we found that the 2-trans-1d and 2-cis-1d provide opposite regioselectivity (scheme 2-13). This result suggests that the ring expansion step is presumably irreversible.

Scheme 2-13. Mechanistic Investigation of the Reversibility of Ring Expansion Step.



We observed 10:1 *E*/*Z* selectivity for product 2-**2s** starting from a 1:1 diastereomeric mixture of cyclopropane 2-**1s**. It has been shown that the two *E/Z* isomers of alkylidene cyclohexenone product 2-**2a** do not isomerize under the reaction conditions (eq 2-1). As shown in Scheme 2-14, one would predict a 1:1 *E*/*Z* ratio for product 2-**2s** if the Rh-catalyzed 1,3-acyloxy migration of the propargylic ester was stereospecific and the configuration of the resulting allenes **(2-7s-1** and **2-7s-2)** was stable under the condition. Our result indicated that either the two diastereomeric allenes could interconvert to each other or the Rh-catalyzed 1,3-acyloxy migration was not stereospecific. We propose that allenes **2-7s-1** and **2-7s-2** may interconvert to each other through ionic intermediate **2-7s-3** as shown in Scheme 2-14. Due to steric interaction between *tert*-butyl group and the metal catalyst in isomer **2-7s-2,** coordination of rhodium to isomer 2-**7s-1** is favored. This may explain why 2-(*E*)-**2s** is the major product. The proposed isomerization between 2-7**s-1** and **2-7s-2** is consistent with previous results from gold-catalyzed 1,3-acyloxy migrations of chiral propargylic esters.[19] In fact, a dynamic kinetic transformation of racemic propargylic ester was recently realized by Toste using a chiral-gold complex as the catalyst.[20]

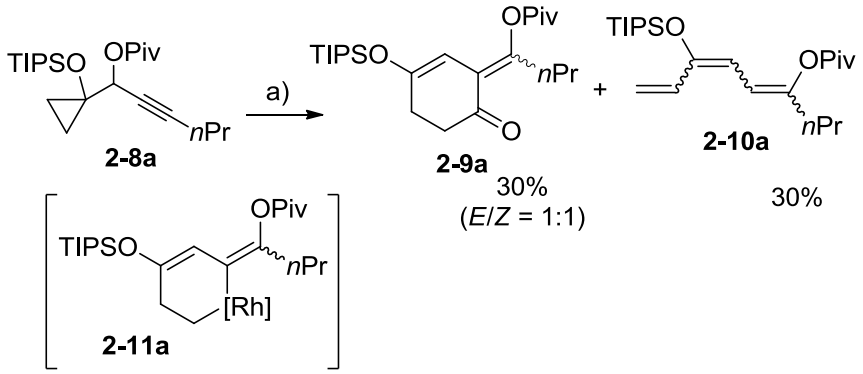
Scheme 2-14. Racemization of Allene Stereochemistry.



2.2.6 [5+1] Cycloaddition Involving Different Types of 1,3-Acyloxy Migrations

After we developed the Rh-catalyzed 1,3-acyloxy migration [5+1] cycloaddition of cyclopropyl substituted propargylic esters **1** with CO to form product **2**, we envisioned that we could rearrange the acyloxy group and place it between the cyclopropane and the alkyne (e.g. substrate **2-8a**, Scheme 2-15). We found that the reaction only afforded 30% yield of the desired product **2-9a** and another 30% yield of a mixture of inseparable trienes 2-**10a** under previously optimized condition. The triene byproducts are presumably derived from metallacycle 2-**11a** through a β-H elimination. We also obtained a mixture of [5+1] cycloaddition product and triene byproducts for substrate **2-8b** (Table 2-8) without the siloxy substituent.

Scheme 2-15. Rh-Catalyzed 1,3-Acyloxy Migration [5+1] Cycloaddition for Substrates 2-8a.

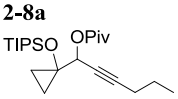
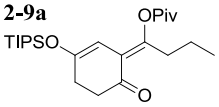
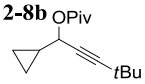
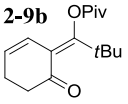
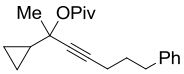
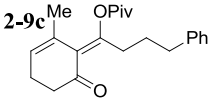
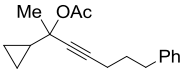
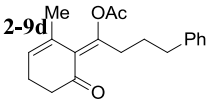
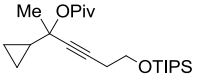
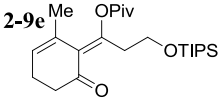
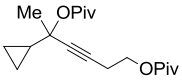
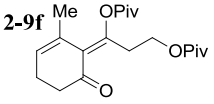
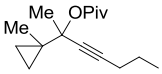
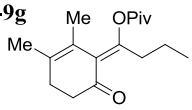


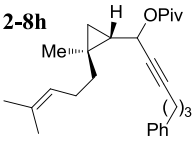
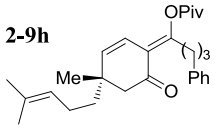
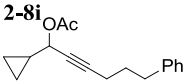
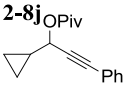
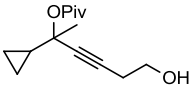
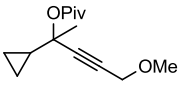
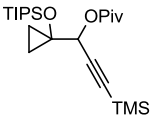
a) $[Rh(CO)_2Cl]_2$ (5 mol%), Toluene, CO(1 atm), 60 ^oC, 2h.

We decided to increase the amount of [5+1] cycloaddition product by changing the pressure of CO from 1 atm to 10 atm in order to suppress the formation triene byproducts. The desired cycloaddition product **2-9a** could be isolated in 70% yield and the triene byproduct was not observed under this condition (Table 2-8). The reaction takes longer time indicating a lower reactivity under higher CO pressure. This is reminiscent of the industrial $HCo(CO)_4$ catalyzed hydroformylation where higher CO pressure is required to increase the selectivity, albeit decrease reactivity. We then investigated the scope of this Rh-catalyzed 1,3-acyloxy migration [5+1] cycloaddition for the formation of product **9** from propargylic ester **8**. The reaction required higher temperature for substrate **2-8b** with a sterically demanding *tert*-butyl group. Lowering the temperature to 50 ^oC was necessary to achieve a higher yield for substrates with a tertiary ester. It was demonstrated that substituents on the cyclopropane ring could be tolerated. For substrates with a tertiary ester, the tandem reaction worked well when the propargylic ester was changed from pivalate to acetate. Functional groups such as siloxy group and ester could

be tolerated. In the case of product **2-9g**, we only isolated the *E* isomer. The *Z* isomer decomposed during workup. The two diastereomers of substrate 2-**8h** could be separated and each of them worked smoothly to yield identical results. This observation again indicated that the allenyl cyclopropane could be racemized under the reaction condition. We observed no reaction for secondary acetate **2-8i**, which was consistent with previous observation for substrate 2-**1b**. A complex mixture was obtained for substrate **2-8j, 2-8k, 2-8l**. No reaction was observed for substrate with a silyl substituent **2-8m**.

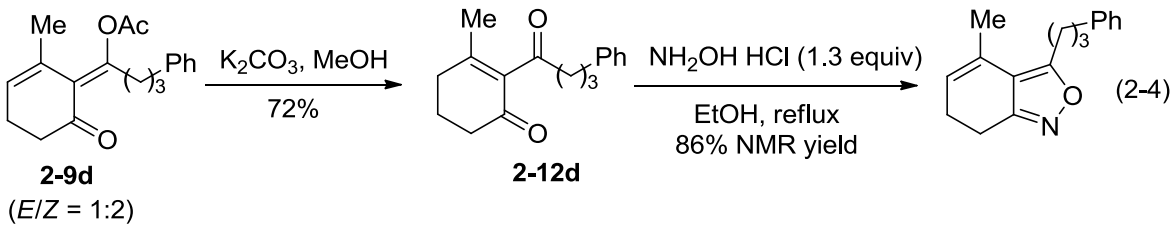
Table 2-8. Scope of Rh-Catalyzed 1,3-Acyloxy Migration [5+1] Cycloaddition for Substrates 2-8a - 2-8m.[a]

Substrates	Products	Yield (*E*/*Z*)
2-8a 	**2-9a** 	70%[b] (1:1)
2-8b 	**2-9b** 	72%[c] (2:1)[d]
2-8c 	**2-9c** 	86%[e] (1.8:1)
2-8d 	**2-9d** 	84%[e] (1:2)
2-8e 	**2-9e** 	91%[e] (2:1)
2-8f 	**2-9f** 	84%[e] (3.3:1)
2-8g 	**2-9g** 	52%[e,f] (2:1)

2-8h 	**2-9h** 	62%[e,g] (2:1)[d,h]
2-8i 	–	no reaction
2-8j 	–	complex mixture
2-8k 	–	complex mixture
2-8l 	–	complex mixture
2-8m 	–	no reaction

[a] Conditions: 5 mol % $[Rh(CO)_2Cl]_2$, CO (10 atm), toluene (0.05M), overnight. All *E*/*Z* ratios were determined by ^{1}H NMR of the crude product unless noted otherwise. [b] 70 ^{o}C. [c] 100 ^{o}C. [d] The stereochemistry of the exo-cyclic olefin could not be determined by ^{1}H NMR. [e] 50 ^{o}C. [f] Isolated yield of *E*-isomer. [g] 1 atm CO. [h] The ratio was determined by ^{13}C NMR.

The *E*/*Z* stereoselectivity for the exo-cyclic alkene in products **2-9a - 2-9h** is not high, but it is inconsequential after hydrolysis. Diketone **2-12d** could be obtained in good yield from the corresponding acetate **2-9d** (eq 2-4).

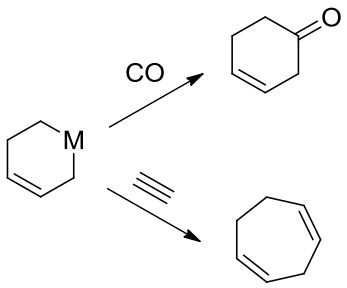


(2-4)

2.2.7 [5+2] Cycloaddition from Cyclopropyl Propargylic Esters

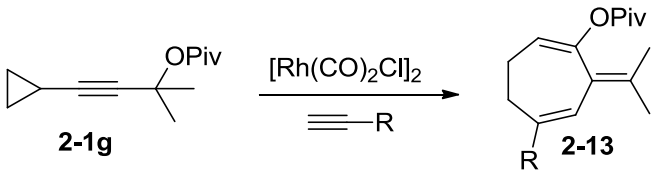
In addition to [5+1] cycloaddition with CO,the metallahexene intermediate could also be trapped by alkyne in a [5+2] cycloaddition (scheme 2-16).

Scheme 2-16. [5+1] and [5+2] Cycloaddition.



To test the feasibility of Rh-catalyzed tandem 1,3-acyloxy migration and [5+2] cycloaddition, different alkynes were screened (table 2-9). Alkynes with electron withdrawing group do not provide any desired product (entry 1-3). The conversion is low when internal alkynes are used. Alkynes with coordinating group tend to give higher yield (entry 7-10).

Table 2-9. Screening of Alkynes for [5+2] Cycloaddition.[a]



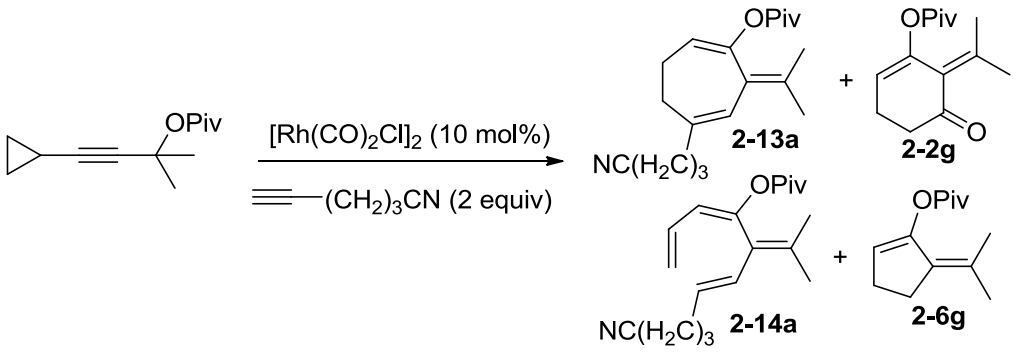
Entry	Alkyne	Solvent	Temperature (^oC)	Yield [b]
1	≡—COOEt	toluene	60	0%
2	Me—≡—COOEt	CH_2ClCH_2Cl	80	0%
3	MeOOC—≡—COOMe	toluene	60	0%
4	Ph—≡	toluene	80	0%
5	*n*Pr—≡—*n*Pr	toluene	40	sub recovery
6[c]	Ph—≡—Ph	toluene	60	15%
7	≡—CH_2OH	toluene	60	20%
8	≡—$(CH_2)_3CN$	toluene	60	25%
9[d]	≡—$(CH_2)_3CN$	toluene	60	18%
10	HOH_2C—≡—CH_2OH	dioxane	60	28%

[a] Condition: $[Rh(CO)_2Cl]_2$ (10 mol%), alkyne (2 equiv), solvent (0.1 M), 2h. [b] NMR yield.[c] longer time leads to messy reaction. [d] alkyne (1.3 equiv).

Since alkyne in entry 8 and 9 gives higher yield and cleaner reaction. We tried to optimize the yield by screening different solvents (table 2-10). Toluene and EtOAc were

found to be the best solvents for this reaction. We also observed that higher equivalent of alkyne led to the formation of more five-membered ring products (entry 2).

Table 2-10. Solvent Screening for [5+2] Cycloaddition.[a]

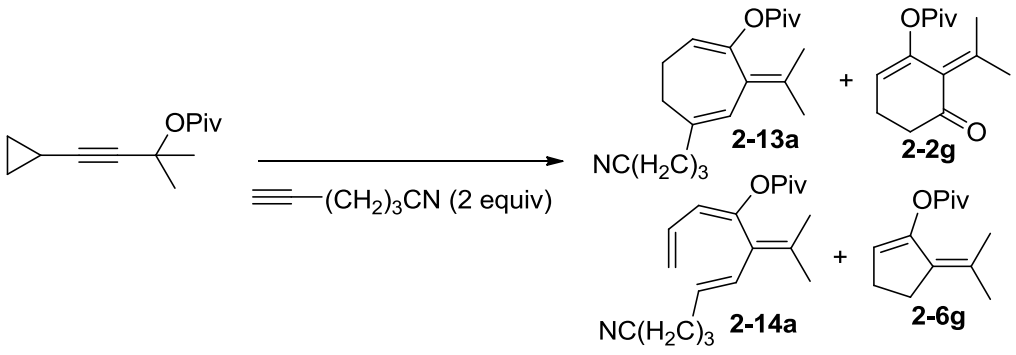


Entry	Solvent	Yield [b]	Selectivity (**2-13a/2-2g/2-14a/2-6g**)
1	toluene	25%	1/1/1/0
2[c]	toluene	18%	1/1/1.5/1
3[d]	toluene	22%	1/0.8/1.2/0
4	dioxane	23%	1/1.2/1.2/0
5	EtOAc	25%	1/1/1/0
6	CH_2ClCH_2Cl	16%	1/1.7/2/0
7[e]	CH_2ClCH_2Cl	messy	
8	$CHCl_3$	15%	1/1.3/1.7
9	benzene	13%	1/1/1

[a] Condition: $[Rh(CO)_2Cl]_2$ (10 mol%), alkyne (2 equiv), solvent (0.1 M), 60 ^oC, 2h. [b] NMR yield.[c] alkyne (4 equiv). [d] toluene (0.5 M). [e] mixed with 5% of CF_3CH_2OH.

Different catalysts and ligands were also screened (table 2-11). Other rhodium and iridium based catalysts did not provide desired product.

Table 2-11. Catalysts and Ligands Screening.[a]

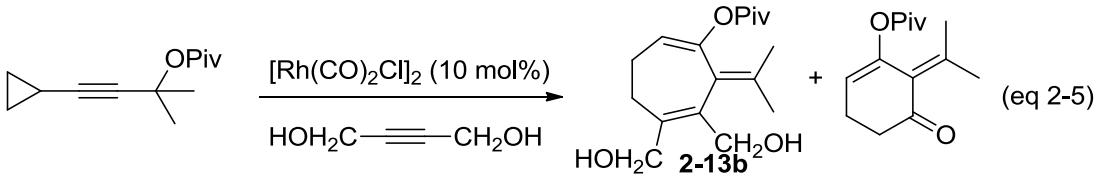


Entry	Catalyst	Ligand	Yield [b]	Selectivity (**2-13a/2-2g/2-14a/2-6g**)
1[c]	$[Rh(cod)Cl]_2$		messy	
2[c]	$Rh(CO)_2acac$		messy	
3[c]	$IrCl(CO)(PPh_3)_2$		messy	
4[c]	$Rh(PPh_3)_3Cl$		messy	
5[d]	$[Rh(CO)_2Cl]_2$		5%	
6[e]	$[Rh(CO)_2Cl]_2$		30%	1/0.6/1.6/0
7	$[Rh(CO)_2Cl]_2$	PPh_3	27%	11/0.8/1.2/0
8	$[Rh(CO)_2Cl]_2$	$P(C_6F_5)_3$	30%	1/1/1/0
9	$[Rh(CO)_2Cl]_2$	$P[OCH(CF_3)_2]_3$	0%	
10	$[Rh(CO)_2Cl]_2$	$P[OCH_2CF_3]_3$	0%	

11	$[Rh(CO)_2Cl]_2$	$P(C_6H_4CF_3)_3$	32%	1/1/1/0
12	$[Rh(CO)_2Cl]_2$	$P[C_6H_3(CF_3)_2]_3$	25%	1/1/0/1

[a] Condition: Catalyst (10 mol%), Ligand (20%), alkyne (2 equiv), solvent (0.1 M), 60 °C, 2h. [b] NMR yield.[c] 80 °C. [d] Catalyst (1mol%). [e] Catalyst (20 mol%).

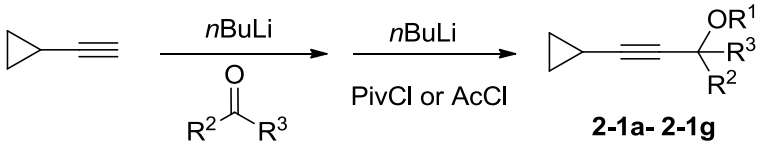
When propargylic alcohol (entry 10, table 2-9) was used, no β-H elimination product was observed and the desired [5+2] cycloaddition product could be obtained in about 25% yield based on NMR (eq 2-5). Various ligands were screened and no further improvement could be achieved.



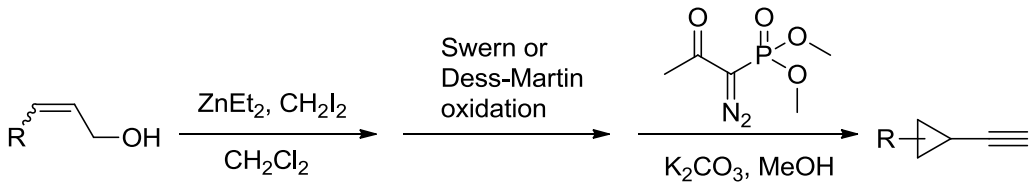
2.2.8 Synthesis of Substrate

Substrates **2-1a – 2-1g** were synthesized according to scheme 2-17.[21,22] More substituted substrates were generally synthesized from allylic alcohols via cyclopropanation[23], oxidation, and Seyferth-Gilbert Homologation[24] according to scheme 2-18.[25]

Scheme 2-17. Synthesis of Substrates 2-1a- 2-1g.

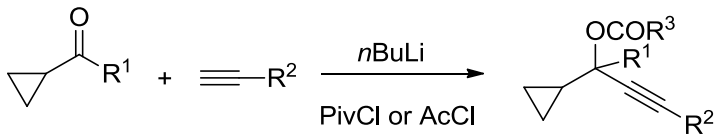


Scheme 1-18. Synthesis of Substituted Cyclopropyl Alkynes.



Substrates (**2-8a – 2-8m**) in the second version of [5+1] cycloaddition were synthesized from commercially available cyclopropyl ketones and aldehydes (scheme 2-19).

Scheme 2-19. Synthesis of Substrate.



2.3 Experimental Section

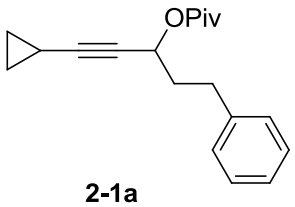
All reactions in non-aqueous media were conducted under a positive pressure of dry argon in glassware that had been oven dried prior to use unless noted otherwise. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Thin layer chromatography was performed using precoated silica gel plates (EMD Chemical Inc. 60, F254). Flash column chromatography was performed with silica gel (Silicycle, 40-63 μm). Infrared spectra (IR) were obtained on a Bruker Equinox 55 Spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Varian Unity-

Inova 400 MHz or 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in $CDCl_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint),or multiplet (m), with coupling constants (*J*) in hertz. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer. The optical rotation was determined using a Perkin–Elmer 241 Polarimeter.

General procedures for the Rh-catalyzed 1,3-acyl migration [5+1] cycloaddition:

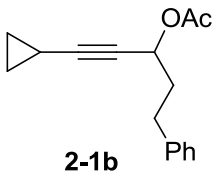
*Method for substrate **2-1**.* To an oven-dried flask attached with a CO balloon was added $[Rh(CO)_2Cl]_2$ (1.9 mg, 0.005 mmol), anhydrous toluene (1 mL), and cyclopropyl propargyl ester (0.1 mmol). The oil bath was heated to 60 ^oC. The reaction was monitored by TLC. After the reaction is complete, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel.

*Method for substrate **2-8***. To an oven-dried vial was added $[Rh(CO)_2Cl]_2$ (1.9 mg, 0.005 mmol), anhydrous toluene (2 mL), and cyclopropyl propargyl ester (0.1 mmol). The vial was placed in a high pressure reactor which was subsequently filled with 10 atm of CO. The reaction was heated overnight. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel.



2-1a

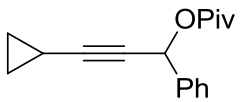
2,2-Dimethyl-propionic acid 3-cyclopropyl-1-phenethyl-prop-2-ynyl ester (2-1a). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.68 (m, 2H), 0.77 (m, 2H), 1.21 (s, 9H), 1.26 (m, 1H), 2.03 (m, 2H), 2.73 (m, 2H), 5.32 (td, *J* = 5.2, 1.5 Hz, 1H), 7.18 (m, 3H), 7.27 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.3, 8.58, 8.59, 27.2, 31.6, 36.9, 38.9, 63.9, 72.9, 89.5, 126.2, 128.61, 128.67, 141.3, 177.5. IR (film): ν 2963, 2246, 1731, 1479, 1455, 1366, 1278, 1146, 1030, 911 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{19}H_{24}NaO_2$ $(M+Na)^+$ 307.1668, found 307.1666.



2-1b

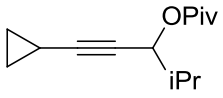
1-cyclopropyl-5-phenylpent-1-yn-3-yl acetate (2-1b). To an oven-dried flask was added THF (50 mL), cyclopropyl acetylene (10 mmol) and the solution was cooled to -78 ^{o}C. *n*-BuLi (6.3 mL, 10 mmol) was added and the solution was stirred at -78 ^{o}C for 10 min. 3-Phenyl propanal (1.3 ml, 10 mmol) was added and the solution was allowed to warm to room temperature. The reaction was quenched with water, extracted with EtOAc for three times, dried over $MgSO_4$. The solvent was evaporated and the crude alcohol intermediate was used for next step without further purification. To an oven-dried flask was added THF (50 mL) and the above alcohol. The solution was cooled to -78 ^{o}C. *n*-BuLi (6.3 mL, 10 mmol) was added and the solution was stirred for 10 min. PivCl (1.2 mL, 10 mmol) was added dropwise and the solution was allowed to warm to room temperature. The reaction was quenched with water, extracted with EtOAc for three times, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by

chromatography (EtOAc/Hexane = 1:50) to yield a colorless oil (1.92 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.70 (m, 2H), δ 0.76 (m, 2H), 1.28 (m, 1H), 2.04 (m, 2H), 2.05 (s, 3H), 2.74 (d, *J* = 8.0 Hz, 2H), 5.33 (td, *J* = 6.8, 2.0 Hz, 1H), 7.16 (m, 3H), 7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.4. 8.5, 21.3, 31.5, 36.8, 64.2, 72.7, 89.9, 126.2, 128.55, 128.62, 141.1, 170.2. IR (film): ν 3027, 2936, 2360, 2247, 1738, 1496, 1454, 1369, 1229, 1175, 1018, 958, 909, 813, 730, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{16}H_{18}O_2$ $(M+Na)^+$ 265.1199, found 265.1190.



2-1d

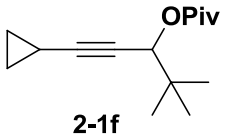
3-cyclopropyl-1-phenylprop-2-ynyl pivalate (2-1d). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.71 (m, 2 H), 0.78 (m, 2 H), 1.20 (s, 9H), 1.30 (m, 1 H), 6.40 (d, *J*=1.7 Hz, 1 H), 7.34 (m, 3 H), 7.46 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 8.8, 27.4, 39.1, 66.1, 72.5, 91.3, 127.6, 128.78, 128.82, 138.4, 177.6. IR: ν 2976, 2362, 2342, 1732, 1271, 1137 cm^{-1}. HRMS (ESI) for $C_{17}H_{20}NaO_2$ (M+23) 279.1356 (Calc.), found 279.1361.



2-1e

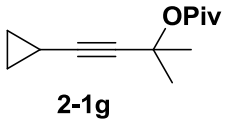
1-cyclopropyl-4-methylpent-1-yn-3-yl pivalate (**2-1e**). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.66 (m, 2H), 0.75 (m, 2H), 0.97 (d, *J* = 6.9 Hz, 6H), 1.21 (s, 9H), 1.26 (m, 1H), 1.93 (m, 1H), 5.14 (dd, *J* = 5.6, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 8.85,

18.2, 18.6, 27.6, 33.2, 39.3, 69.6, 72.1, 89.8, 177.9. IR: ν 2968, 2362, 2343, 1781, 1281, 1147 cm^{-1}. HRMS (ESI) for $C_{14}H_{22}O_2$ (M+1) 223.1693 (Calc.), found 223.1691.



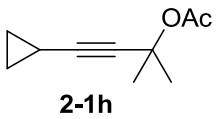
2-1f

2,2-Dimethyl-propionic acid 1-tert-butyl-3-cyclopropyl-prop-2-ynyl ester (2-1f). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 0.65 (m, 2H), 0.75 (m, 2H), 0.97 (s, 9H), 1.22 (s, 9H), 1.23 (m, 1H), 5.00 (d, *J* = 1.5Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.3, 8.5, 25.8, 27.2, 35.5, 39.1, 71.7, 72.2, 89.3, 177.5. IR (film): ν 2972, 2245, 1733, 1147 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{15}H_{24}NaO_2$ $(M+Na)^+$ 259.1668, found 259.1669.



2-1g

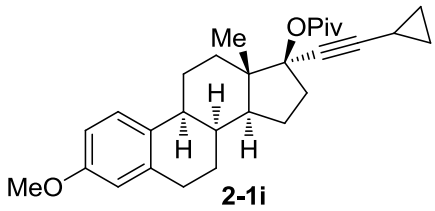
2,2-Dimethyl-propionic acid 3-cyclopropyl-1,1-dimethyl-prop-2-ynyl ester (2-1g). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 0.65 (m, 2H), 0.73 (m, 2H), 1.16 (s, 9H), 1.24 (m, 1H), 1.59 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.2, 8.8, 27.5, 29.7, 39.5, 72.5, 77.0, 87.7, 177.1. IR (film): ν 2980, 2240, 1732, 1117, 912, 856, 812 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{13}H_{20}NaO_2$ $(M+Na)^+$ 231.1355, found 231.1360.



2-1h

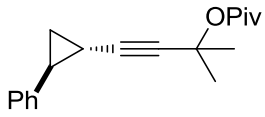
4-cyclopropyl-2-methylbut-3-yn-2-yl acetate (2-1h). ^1H NMR (400 MHz, $CDCl_3$,

TMS): δ 0.63 (m, 2H), 0.71 (m, 2H), 1.21 (m, 1H), 1.58 (s, 6H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 8.9, 22.7, 29.8, 73.1, 77.0, 88.2, 169.9. IR: ν 2942, 2361, 2343, 1743, 1365, 1266, 1243, 1138, 1123 cm^{-1}. HRMS (ESI) for $C_{10}H_{14}NaO_2$ $(M+Na)^+$ 189.0886 (Calc.), found 189.0885.



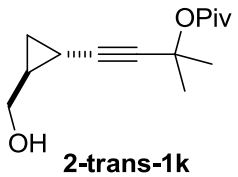
2-1i

2,2-Dimethyl-propionic acid 17-cyclopropylethynyl-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl ester (2-1i). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.66 (m, 2H), 0.76 (m, 2H), 0.89 (s, 9H), 1.29 (m, 2H), 1.42 (m, 2H), 1.69 (m, 1H), 1.80 (m, 2H), 1.90 (m, 1H), 1.99 (m, 2H), 2.23 (m, 1H), 2.36 (m, 1H), 2.70 (ddd, *J* = 15.2, 9.6, 6.0 Hz, 1H), 2.86 (m, 2H), 3.78 (s, 3H), 6.64 (d, *J* = 3.5 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.1, 8.83, 8.85, 13.9, 23.6, 26.6, 27.3, 27.6, 30.1, 33.6, 37.6, 39.3, 39.4, 43.8, 48.1, 48.5, 55.4, 75.0, 84.9, 90.2, 111.7, 114.0, 126.6, 132.7, 126.6, 132.7, 138.1, 157.7, 176.8. IR (film): ν 2937, 2243, 1733, 1500, 1156, 1029, 908, 729 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{29}H_{38}NaO_3$ $(M+Na)^+$ 457.2713, found 457.2714. $[\alpha]_D^{25}$ = -108.6 (*c* 1, $CHCl_3$).



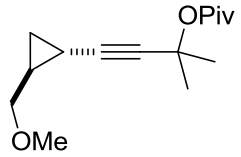
2-trans-1j

2,2-Dimethyl-propionic acid 1,1-dimethyl-3-(2-phenyl-cyclopropyl)-prop-2-ynyl ester (2-trans-1j). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.18 (s, 9H), 1.20 (m, 1H), 1.28 (m, 1H), 1.53 (ddd, *J* = 6.8, 5.5, 4.5 Hz, 1H), 1.62 (s, 6H), 2.20 (ddd, *J* = 7.2, 6.0, 4.5 Hz, 1H), 7.06 (m, 2H), 7.16 (m, 1H), 7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.5, 18.3, 26.5, 27.3, 29.3, 29.4, 39.2, 72.2, 78.1, 86.0, 126.0, 126.3, 128.5, 141.1, 176.9. IR (film): ν 2981, 2246, 1733, 1479, 1285, 1172, 1117, 860, 748, 697 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{19}H_{24}NaO_2$ $(M+Na)^+$ 307.1668, found 307.1678.



2-trans-1k

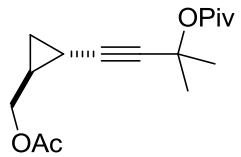
2,2-Dimethyl-propionic acid 3-(2-hydroxymethyl-cyclopropyl)-1,1-dimethyl-prop-2-ynyl ester (2-*trans*-1k). To a solution of **2-*trans*-1n**[4] (1.19 g, 3.0 mmol) in THF (45 ml) at 0 ^{o}C was added a solution of TBAF in THF (1.2 ml, 3.6 mmol, 3M). The solution was warmed to room temperature and stirred overnight. The reaction was quenched with water, extracted with EtOAc for three times, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography (EtOAc/Hexane = 1:4) to yield a colorless oil (661 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.73 (ddd, *J* = 8.8, 5.6, 4.4 Hz, 1H), 0.88 (dt, *J* = 8.8, 4.8 Hz, 1H), 1.16 (s, 9H), 1.20 (m, 1H), 1.42 (m, 1H), 1.59 (s, 6H), 1.75 (br, 1H), 3.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.3, 13.2, 24.4, 27.2, 29.32, 29.35, 39.3, 65.5, 72.2, 76.9, 86.2, 177.0 IR (film): ν 2981, 2241, 1733, 1288, 1176, 1128, 1062, 1028 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{14}H_{22}O_3$ $(M+Na)^+$ 261.1461, found 261.1465.



2-trans-1l

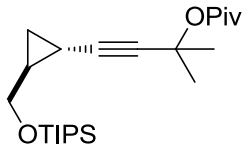
2,2-Dimethyl-propionic acid 3-(2-methoxymethyl-cyclopropyl)-1,1-dimethyl-prop-2-ynyl ester (2-*trans*-1l).

To an oven dried flask was added NaH (15mg, 0.37 mmol) and THF (1.25ml). The solution was cooled to 0 ^{o}C and ***2-trans*-1k** (40 mg, 0.17 mmol) was added. The solution was stirred at 0 ^{o}C for 0.5h, raised to room temperature, and stirred for 1h. MeI (52 uL, 0.84 mmol) was added and the reaction was stirred for another hour. The reaction was quenched with saturated NH_4Cl, extracted with EtOAc and dried over MgSO4. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc/Hexane = 1:20) to provide 12.1 mg (29%) of product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.71 (ddd, *J* = 8.5, 5.5, 4.5 Hz, 1H), 0.88 (dt, *J* = 8.5, 4.5 Hz, 1H), 1.16 (s, 9H), 1.17 (m, 1H), 1.38 (m, 1H), 1.59 (s, 6H), 3.25 (m, 2H), 3.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 5.5, 13.5, 21.7, 27.3, 29.4, 39.3, 58.7, 72.3, 75.2, 77.7, 86.1, 176.9. IR (film): ν 2984, 2244, 1734, 1115 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{15}H_{24}O_3$ $(M+Na)^+$ 275.1618, found 275.1624.



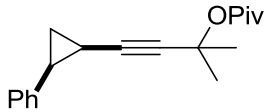
2-trans-1m

2,2-Dimethyl-propionic acid 3-(2-acetoxymethyl-cyclopropyl)-1,1-dimethyl-prop-2-ynyl ester (2-*trans*-1m). To a solution of **2-*trans*-1k** (42 mg, 0.17 mmol), pyridine (0.84 ml, 10.4 mmol), DMAP (17 mg, 0.14 mmol) was added acetyl chloride (0.12 ml, 1.68 mmol) at 0 ^{o}C. The solution was allowed to room temperature and stirred for 2h. The solvent was evaporated and the residue was purified by chromatography (EtOAc/Hexane = 1:20) to yield a colorless oil (46 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.80 (ddd, *J* = 9.0, 6.0, 5.0 Hz, 1H), 0.94 (dt, *J* = 9.0, 5.0 Hz, 1H), 1.20 (s, 9H), 1.27 (m, 1H), 1.48 (m, 1H), 1.62 (s, 6H), 2.10 (s, 3H), 3.91 (dd, *J* = 11.5, 7.0 Hz,1H), 3.99 (d, *J* = 11.5, 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 5.9, 13.8, 20.8, 21.2, 27.3, 29.4, 39.3, 67.0, 72.1, 78.0, 85.5, 171.3, 176.9. IR: ν 2976, 2243, 1733, 1231, 1116 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{16}H_{24}O_4$ $(M+Na)^+$ 303.1566, found 303.1571.



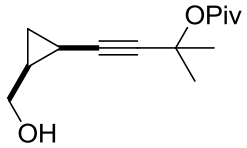
2-trans-1n

2,2-Dimethyl-propionic acid 1,1-dimethyl-3-(2-triisopropylsilanyloxymethyl-cyclopropyl)-prop-2-ynyl ester (2-trans-1n). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.80 (m, 2H), 1.04 (m, 21H), 1.16 (s, 9H), 1.39 (s, 6H), 1.26 (m, 1H), 1.31 (m, 1H), 1.60 (s, 6H), 3.66 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.72 (dd, *J* = 10.4, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.8, 12.2, 12.5, 18.1, 24.2, 27.2, 29.41, 29.42, 39.2, 63.6, 72.3, 76.9, 86.8, 176.8. IR (film): ν 2943, 2244, 1736, 1462, 1286, 1116, 881, 796, 681 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{23}H_{42}SiNaO_3$ $(M+Na)^+$ 417.2795, found 417.2798.



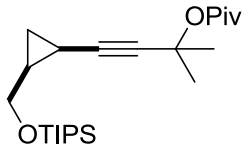
2-cis-1j

2,2-Dimethyl-propionic acid 1,1-dimethyl-3-(2-phenyl-cyclopropyl)-prop-2-ynyl ester (2-cis-1j). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.11 (s, 9H), 1.16 (ddd, *J* = 7.2, 6.4, 5.6 Hz, 1H), 1.32 (td, *J* = 8.4, 5.2 Hz, 1H), 1.39 (s, 6H), 1.78 (td, *J* = 8.4, 6.0 Hz, 1H), 2.27 (td, *J* = 8.4, 6.8 Hz, 1H), 7.16-7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.7, 15.0, 23.8, 27.2, 28.9, 29.1, 39.2, 72.0, 81.3, 83.8, 126.2, 127.8, 128.6, 138.3, 176.7. IR (film): ν 1735, 1288, 1119, 911, 698 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{19}H_{24}NaO_2$ $(M+Na)^+$ 307.1668, found 307.1682.



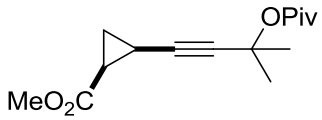
2-cis-1k

2,2-Dimethyl-propionic acid 3-(2-hydroxymethyl-cyclopropyl)-1,1-dimethyl-prop-2-ynyl ester (2-cis-1k). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.60 (ddd, *J* = 5.2, 5.2, 5.2 Hz, 1H), 0.96 (td, *J* = 7.6, 4.8 Hz,1H), 1.17 (s, 9H), 1.43 (m, 2H), 1.60 (s, 6H), 2.88 (s, 1H), 3.45 (dd, *J* = 11.6, 8.4 Hz, 1H), 3.99 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 4.5, 12.6, 21.2, 27.2, 28.8, 29.5, 39.4, 63.5, 72.1, 78.5, 84.9, 177.9. IR (film): ν 2985, 2244, 1723, 1129, 915 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{14}H_{22}NaO_3$ $(M+Na)^+$ 261.1461, found 261.1473.



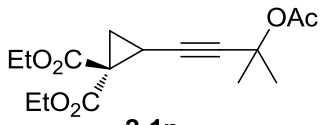
2-cis-1n

2,2-Dimethyl-propionic acid 1,1-dimethyl-3-(2-triisopropylsilanyloxymethyl-cyclopropyl)-prop-2-ynyl ester (2-cis-1n). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.53 (ddd, *J* = 5.5, 5.5, 5.5 Hz, 1H), 0.98 (m, 1H), 1.08 (m, 21H), 1.16 (s, 9H), 1.27 (m, 1H), 1.46 (m, 1H), 1.59 (s, 6H), 3.62 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.94 (dd, *J* = 10.5, 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 4.8, 12.2, 12.5, 13.5, 18.2, 20.6, 27.2, 29.2, 29.3, 39.1, 64.7, 72.1, 79.1, 84.0, 176.5. IR (film): ν 2944, 2868, 1736, 1463, 1286, 1129, 883, 772, 682 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{23}H_{42}SiNaO_3$ $(M+Na)^+$ 417.2795, found 417.2803.



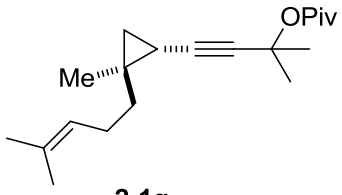
2-1o

2-[3-(2,2-Dimethyl-propionyloxy)-3-methyl-but-1-ynyl]-cyclopropanecarboxylic acid methyl ester (2-1o). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.17 (s, 9H), 1.19 (m, 1H), 1.41 (ddd, *J* = 6.8, 6.4, 4.8 Hz, 1H), 1.59 (s, 3H), 1.60 (s, 3H), 1.81 (td, *J* = 8.8, 7.2 Hz, 1H), 1.93 (ddd, *J* = 8.4, 7.6, 6.0 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.5, 14.5, 21.5, 27.2, 29.1, 29.3, 39.2, 51.9, 71.9, 80.5, 81.4, 170.6, 176.8. IR (film): ν 2981, 2245, 1732, 1197, 1074 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{15}H_{22}NaO_4$ $(M+Na)^+$ 289.1410, found 261.1424.

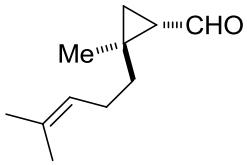


2-1p

Diethyl 2-(3-acetoxy-3-methylbut-1-ynyl)cyclopropane-1,1-dicarboxylate (2-1p). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.24 (t, *J* = 8.0 Hz, 3H), 1.31 (t, *J* = 8.0 Hz, 3H), 1.53 (dd, *J* = 9.2, 4.5 Hz, 1H), 1.56 (s, 6H), 1.77 (dd, *J* = 7.2, 4.5 Hz, 1H), 1.97 (s, 3H), 2.46 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.21 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 14.3, 16.7, 22.1, 29.2, 36.4, 61.9, 62.1, 72.1, 80.4, 81.5, 166.5, 168.9, 169.4. IR: ν 2986, 2359, 2344, 1733, 1371, 1321, 1243, 1202, 1137, 1017 cm^{-1}. HRMS (ESI) for $C_{16}H_{22}NaO_6$ $(M+Na)^+$ 333.1309 (Calc.), found 333.1316.

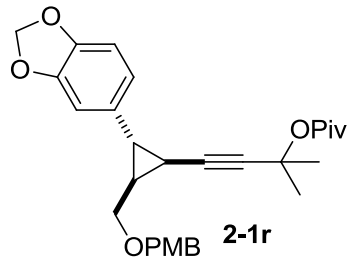


2-1q



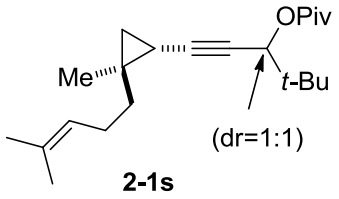
2,2-Dimethyl-propionic acid 1,1-dimethyl-3-[2-methyl-2-(4-methyl-pent-3-enyl)-cyclopropyl]-prop-2-ynyl ester (2-1q). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.46 (dd, *J* = 5.0, 5.0 Hz, 1H), 0.73 (dd, *J* = 9.0, 4.0 Hz, 1H), 1.11 (dd, *J* = 8.5, 5.0 Hz, 1H), 1.16 (s, 9H), 1.16 (s, 3H), 1.17-1.31 (m, 2H), 1.60 (s, 3H), 1.62 (s, 6H), 1.67 (s, 3H), 2.03 (m, 2H), 5.07 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.4, 17.8, 18.8, 22.7, 23.4, 25.5, 25.9, 27.3, 29.5, 29.6, 39.3, 40.1, 72.5, 79.2, 85.5, 124.5, 131.6, 176.8. IR (film): ν 2969, 2238, 1736, 1286, 1172, 1114 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{20}H_{32}NaO_2$

$(M+Na)^+$ 327.2945, found 327.2305. $[\alpha]_D^{25}$ = +73.8 (*c* 1, $CHCl_3$). The enantiomeric excess (87%) of substrate **2-1q** was determined by HPLC analysis of the precursor aldehyde shown above. (Chiralcel OJ-H; eluent: pure hexane; flow rate: 0.7 mL/min; detection: at 210 nm): retention times t_1 = 20.2 min t_2=23.8 min. Compound **2-1q** was prepared according to general procedures in Schemes 1 and 2. The enantioselective cyclopropanation was conducted according to literature procedure.



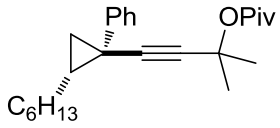
2-1r

2,2-Dimethyl-propionic acid 3-[2-benzo[1,3]dioxol-5-yl-3-(4-methoxybenzyloxymethyl)-cyclopropyl]-1,1-dimethyl-prop-2-ynyl ester (2-1r). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.17 (s, 9H), 1.61 (s, 6H), 1.65 (m, 1H), 1.71 (dd, *J* = 8.4, 5.2 Hz, 1H), 1.96 (t, *J* = 5.2 Hz, 1H), 3.70 (dd, *J* = 6.0, 1.6 Hz, 2H), 3.79 (s, 3H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.56 (d, *J* = 10.4 Hz, 1H), 5.90 (s, 2H), 6.52 (d, *J* = 2.0 Hz, 1H), 6.56 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.87 (m, 2H), 7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 27.3, 27.6, 29.3, 31.1, 39.3, 55.5, 70.1, 72.1, 72.7, 80.8, 82.7, 101.1, 106.8, 108.3, 114.0, 119.7, 129.6, 130.9, 134.1, 146.3, 147.9, 159.4, 176.8. IR (film): ν 1731, 1513, 1250, 1038, 756 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{29}H_{34}NaO_6$ $(M+Na)^+$ 501.2247, found 501.2246.



2-1s

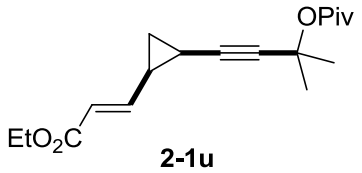
2,2-Dimethyl-propionic acid 1-tert-butyl-3-[2-methyl-2-(4-methyl-pent-3-enyl)-cyclopropyl]-prop-2-ynyl ester (2-1s, 1:1 diastereoisomers). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.45 (dd, *J* = 4.5, 4.5Hz, 1H), 0.74 (dd, *J* = 8.5, 4.0 Hz, 1H), 0.99 (s, 9H), 1.13 (m, 1H), 1.16 (m, 3H), 1.21 (s, 9H), 1.23 (m, 2H), 1.60 (s, 3H), 1.67 (s, 3H), 2.04 (m, 2H), 5.04 (d, *J* = 2.0 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5, 17.8, 19.1, 19.1, 22.73, 22.76, 23.37, 23.43, 25.5, 25.92, 25.94, 25.96, 27.3, 35.56, 35.60, 39.1, 40.03, 40.05, 72.50, 72.57, 74.2, 87.32, 87.37, 124.4, 131.7, 177.5. IR (film): ν 2973, 2239, 1735, 1479, 1279, 1150, 1032 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{22}H_{36}NaO_2$ $(M+Na)^+$ 355.2607, found 355.2610.



2-1t

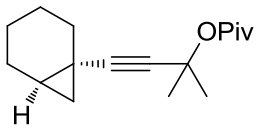
4-((1R,2R)-2-hexyl-1-phenylcyclopropyl)-2-methylbut-3-yn-2-yl pivalate. (2-1t) ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.45 (dd, *J* = 4.5, 4.5Hz, 1H), 0.74 (dd, *J* = 8.5, 4.0 Hz, 1H), 0.99 (s, 9H), 1.13 (m, 1H), 1.16 (m, 3H), 1.21 (s, 9H), 1.23 (m, 2H), 1.60 (s, 3H), 1.67 (s, 3H), 2.04 (m, 2H), 5.04 (d, *J* = 2.0 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5, 17.8, 19.1, 19.1, 22.73, 22.76, 23.37, 23.43, 25.5, 25.92, 25.94, 25.96, 27.3, 35.56, 35.60, 39.1, 40.03, 40.05, 72.50, 72.57, 74.2, 87.32, 87.37,

124.4, 131.7, 177.5. IR (film): ν 2973, 2239, 1735, 1479, 1279, 1150, 1032 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{22}H_{36}NaO_2$ $(M+Na)^+$ 355.2607, found 355.2610.



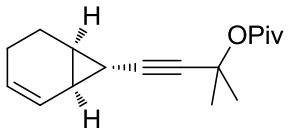
2-1u

(E)-ethyl 3-((1R,2R)-2-(3-methyl-3-(pivaloyloxy)but-1-yn-1-yl)cyclopropyl)acrylate (2-1u). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 0.97 (dt, *J* = 5.5, 5.5 Hz, 1H), 1.17 (s, 9H), 1.28 (t, *J* = 9.0 Hz, 3H), 1.32 (td, *J* = 8.5, 5.0 Hz, 1H), 1.61 (s, 3H), 1.62 (s, 3H), 1.82 (m, 2H), 4.09 (m, 2H), 5.96 (d, *J* = 15.5 Hz, 1H), 6.75 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.9, 14.4, 17.5, 21.4, 27.2, 29.2, 29.3, 39.2, 60.2, 71.9, 80.9, 82.9, 121.4, 149.0, 166.3, 176.8. IR (film): ν 2982, 2249, 1720, 1650, 1286, 1176, 1129 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{21}H_{32}NaO_3$ $(M+Na)^+$ 329.1723, found 329.1737.



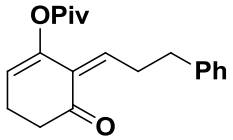
2-1v

4-((1R,6R)-bicyclo[4.1.0]heptan-1-yl)-2-methylbut-3-yn-2-yl pivalate (2-1v). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 0.48 (m, 1H), 0.90 (m, 2H), 1.10 (m, 1H), 1.15 (s, 9H), 1.23 (m, 3H), 1.52 (m, 1H), 1.57 (s, 3H), 1.58 (s, 3H), 1.85 (m, 1H), 1.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 20.4, 20.5, 21.2, 23.4, 27.3, 29.5, 29.6, 39.3, 72.5, 76.2, 92.2, 176.8. IR: ν 2976, 2935, 2863, 2364, 2234, 1733, 1285, 1172, 1120 cm^{-1}. HRMS (ESI) for $C_{17}H_{26}O_2$ (M+1) 263.2006 (Calc.), found 263.2002.



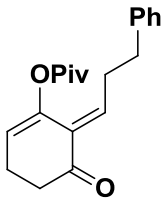
2-1w

4-((1S,6R,7S)-bicyclo[4.1.0]hept-2-en-7-yl)-2-methylbut-3-yn-2-yl pivalate (2-1w). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.17 (s, 9H), 1.27 (d, *J* = 1.0 Hz, 1H), 1.46 (m, 1H), 1.51 (m, 1H), 1.60 (s, 6H), 1.61 (m, 1H), 1.71 (m, 1H), 2.00 (m, 2H), 5.46 (m, 1H), 6.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 17.9, 20.8, 22.1, 24.9, 26.7, 27.3, 29.4, 39.3, 72.3, 78.3, 86.1, 124.4, 126.4, 176.9. IR: ν 2983, 2935, 2806, 2360, 2244, 1734, 1172, 1126, 1098 cm^{-1}. HRMS (ESI) for $C_{17}H_{24}O_2$ (M+1) 261.1849 (Calc.), found 261.1846.



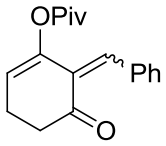
2-Z-2a

(*Z*)-2,2-Dimethyl-propionic acid 5-oxo-6-(3-phenyl-propylidene)-cyclohex-1-enyl ester (c). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.23 (s, 9H), 2.49 (td, *J* = 6.5, 5.0 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.97 (dt, *J* = 7.5, 7.5 Hz,2H), 5.58 (t, 5.0Hz, 1H), 5.92 (t, *J* = 7.5 Hz, 1H), 7.17 (m, 3H), 7.26 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 27.3, 30.5, 35.5, 39.2, 39.8, 115.6, 126.1, 128.5, 128.7, 129.6, 137.1, 141.2, 146.0, 176.4, 199.3. IR (film): ν 2972, 1753, 1702, 1373, 1119, 914, 700 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{20}H_{24}NaO_3$ $(M+Na)^+$ 335.1617, found 335.1632.



2-E-2a

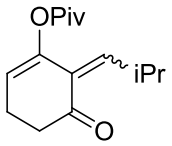
(*E*)-2,2-Dimethyl-propionic acid 5-oxo-6-(3-phenyl-propylidene)-cyclohex-1-enyl ester (2-E-2a). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.22 (s, 9H), 2.45 (td, *J* = 6.0, 5.2 Hz, 2H), 2.59 (t, *J* = 6.0 Hz, 2H), 2.68 (dt, *J* = 7.6, 7.6 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 5.63 (t, *J* = 5.2Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 7.17 (m, 3H), 7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 27.3, 30.7, 35.4, 37.1, 39.2, 118.5, 126.3, 128.4, 128.6, 129.7, 137.7, 141.0, 147.0, 177.0, 198.4. IR (film): ν 2971, 1751, 1705, 1266, 1120, 914, 735 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{20}H_{24}NaO_3$ $(M+Na)^+$ 335.1617, found 335.1614.



2-2d

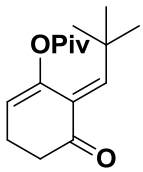
(*E/Z*)-6-benzylidene-5-oxocyclohex-1-enyl pivalate (2-2d). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): For *E*-isomer: δ 0.76 (s, 9H), 2.53 (m, 2H), 2.63 (t, *J* = 6.2 Hz, 2H), 5.87 (td, *J* = 5.3, 1.2 Hz, 1H, one isomer), 7.31 (m, 4H), 7.43 (m, 1H), 7.58 (s, 1H). For *Z*-isomer: δ 1.35 (s, 9H), 2.58 (m, 2H), 2.73 (t, *J* = 6.4 Hz, 2H), 5.73 (t, *J* = 4.5 Hz, 1H), 6.67 (s, 1H), 7.31 (m, 4H), 7.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 26.7, 36.7, 40.3, 120.3, 128.2, 129.1, 130.4, 131.6, 134.2, 135.4, 146.5, 176.4, 199.5. IR: ν 2975, 2361, 2342,

1749, 1702, 1162, 1112 cm^{-1}. HRMS (ESI) for $C_{18}H_{20}O_3$ (M+1) 285.1485 (Calc.), found 285.1481.



2-2e

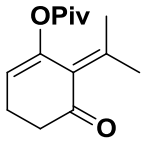
(*E*/*Z*)-6-(2-methylpropylidene)-5-oxocyclohex-1-enyl pivalate (2-2e). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): For *E*-isomer: δ 0.98 (d, *J* = 6.6 Hz, 6H), 1.30 (s, 9H), 2.45 (m, 2H), 2.59 (m, 2H), 3.46 (m, 1H), 5.59 (m, 1H), 6.46 (d, *J* = 10.7 Hz, 1H). For *Z*-isomer: δ 0.97 (d, *J* = 6.6 Hz, 6H), 1.28 (s, 9H), 2.45 (m, 2H), 2.59 (m, 2H), 2.96 (m, 1H), 5.58 (m, 1H), 5.70 (d, *J* = 9.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 21.4, 22.7, 22.8, 27.3, 27.4, 27.5, 27.7, 37.3, 39.34, 39.35, 40.0, 115.6, 118.4, 127.0, 127.4, 145.1, 145.2, 146.0, 146.9, 176.4, 177.0, 199.0, 199.3. IR: ν 2973, 2361, 2342, 1751, 1704, 1114 cm^{-1}. HRMS (ESI) for $C_{15}H_{22}O_3$ (M) 251.1642 (Calc.), found 251.1639.



2-2f

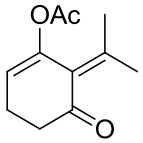
2,2-Dimethyl-propionic acid 6-(2,2-dimethyl-propylidene)-5-oxo-cyclohex-1-enyl ester (2-2f). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.15 (s, 9H), 1.26 (s, 9H), 2.38 (dt, *J* = 6.0, 6.0Hz, 2H), 2.50 (t, *J* = 6.8Hz, 2H), 5.74 (td, *J* = 5.2, 1.2Hz, 1H), 6.69 (d, *J* = 1.2Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 27.4, 29.9, 33.2, 35.9, 39.2, 119.0,

129.5, 146.2, 148.9, 177.3, 201.4. IR (film): ν 2963, 1749, 1703, 1110 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{16}H_{24}NaO_3$ $(M+Na)^+$ 287.1617, found 287.1615.



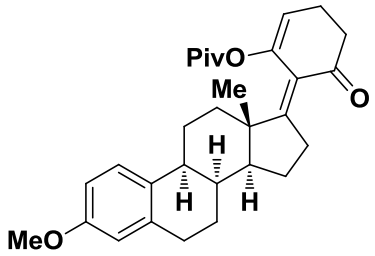
2-2g

2,2-Dimethyl-propionic acid 6-isopropylidene-5-oxo-cyclohex-1-enyl ester (2-2g). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.27 (s, 9H), δ 1.97 (s, 3H), δ 2.15 (s, 3H), δ 2.36 (dt, *J* = 6.0, 6.0 Hz, 2H), δ 2.51 (t, *J* = 6.4Hz, 2H), δ 5.62 (t, *J* = 5.2Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2, 24.3, 25.2, 27.4, 38.5, 39.2, 116.7, 128.6, 146.5, 147.3, 176.6, 201.7. IR (film): ν 2974, 1747, 1690, 1267, 1149, 1112 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{14}H_{20}NaO_3$ $(M+Na)^+$ 259.1304, found 259.1302.



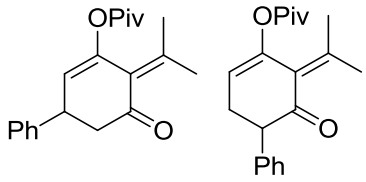
2-2h

5-oxo-6-(propan-2-ylidene)cyclohex-1-enyl acetate (2-2h). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.99 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 2.39 (m, 2H), 2.53 (t, *J* = 6.5 Hz, 2H), 5.66 (t, *J* = 5.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 21.1, 24.8, 38.9, 117.1, 128.1, 146.4, 146.7, 168.7, 201.4. IR: ν 2906, 2361, 2342, 1756, 1689, 1205, 1149 cm^{-1}. HRMS (ESI) for $C_{11}H_{14}O_3$ (M+1) 195.1016 (Calc.), found 195.1015.



2-2i

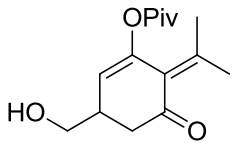
2,2-Dimethyl-propionic acid 6-(3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta[a]phenanthren-17-ylidene)-5-oxo-cyclohex-1-enyl ester (2-2i). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.96 (s, 3H), 1.27 (s, 9H), 1.28-1.60 (m, 6H), 1.83 (m, 1H), 1.95 (m, 1H), 2.17-2.50 (m, 6H), 2.63 (m, 2H), 2.87 (m, 2H), 3.00 (dd, *J* = 20.8, 8.0 Hz, 1H), 3.78 (s, 3H), 5.70 (dd, *J* = 7.2, 3.6 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.71 (dd, *J* = 8.1, 2.8 Hz, 1H), δ 7.20 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8, 19.8, 23.8, 26.9, 27.5, 27.7, 30.0, 32.6, 33.6, 37.2, 38.7, 39.1, 43.6, 47.2, 54.3, 55.4, 111.7, 113.9, 116.6, 124.6, 126.4, 132.6, 138.0, 147.3, 157.7, 164.9, 177.1, 202.9. IR (film): ν 2937, 1746, 1689, 1500, 1254, 1112, 910, 731 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{30}H_{38}NaO_4$ $(M+Na)^+$ 485.2662, found 457.2656. $[\alpha]_D^{25}$ = -48.0 (*c* 1, $CHCl_3$).



2-2j, 2-2j'

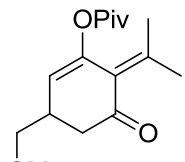
2,2-Dimethyl-propionic acid 6-isopropylidene-5-oxo-3(4)-phenyl-cyclohex-1-enyl ester (2-2j, 2-2j'). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.28 (s, 9H, isomer **2-2j**), 1.29 (s, 9H, isomer **2-2j'**), 2.00 (s, 3H, isomer **2-2j'**), 2.04 (s, 3H, isomer **2-2j**), 2.05 (s, 3H,

isomer **2-2j'**), 2.16 (s, 3H, isomer **2-2j**), 2.64-2.86 (m, 2H), 3.74 (t, *J* = 8.0 Hz, 1H, isomer 16), 3.84 (m, 1H, isomer **2-2j**), 5.65 (d, *J* = 4.0 Hz, 1H, isomer **2-2j**), 5.66 (t, *J* = 6.0 Hz, 1H, isomer **2-2j'**), 7.18-7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 24.6, 25.0, 25.2, 27.4, 28.6, 38.6, 39.3, 47.8, 54.0, 115.9, 121.0, 127.1, 127.2, 127.4, 128.1, 128.7, 128.7, 129.0, 143.0, 147.1, 147.5, 176.6, 200.0. IR (film): ν 2976, 1747, 1690, 1271, 1109, 911, 763, 731, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{20}H_{24}NaO_3$ $(M+Na)^+$ 335.1617, found 335.1627.



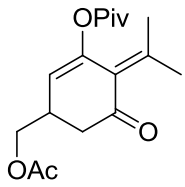
2-2k

2,2-Dimethyl-propionic acid 3-hydroxymethyl-6-isopropylidene-5-oxo-cyclohex-1-enyl ester (2-2k). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.27 (s, 9H), 1.99 (s, 3H), 2.14 (s, 3H), 2.48 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.62 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.77 (m, 1H), 3.63 (d, *J* = 6.0 Hz, 1H), 5.52 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.2, 27.3, 35.4, 39.2, 41.9, 65.4, 118.0, 128.1, 147.0, 148.0, 176.8, 200.5. IR (film): ν 3500, 2977, 2001, 1747, 1688, 1119, 732 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{15}H_{22}NaO_4$ $(M+Na)^+$ 289.1410, found 261.1416.



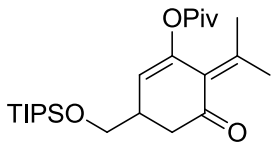
2-2l

2,2-Dimethyl-propionic acid 6-isopropylidene-3-methoxymethyl-5-oxo-cyclohex-1-enyl ester (2-2l). Yield 8.0 mg, 68%; colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.27 (s, 9H), 1.98 (s, 3H), 2.15 (s, 3H), 2.40 (dd, *J* = 16.5, 8.5 Hz, 1H), 2.56 (dd, *J* = 16.0, 5.5 Hz, 1H), 2.83 (m, 1H), 3.35 (s, 3H), 3.35 (m, 2H), 5.55 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.5, 25.4, 27.5, 32.9, 39.3, 41.9, 59.2, 75.3, 118.5, 128.4, 147.3, 147.8, 176.6, 200.6. IR (film): ν 2983, 1749, 1692, 1109, 916 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{16}H_{24}O_4$ $(M+Na)^+$ 303.1567, found 303.1572.



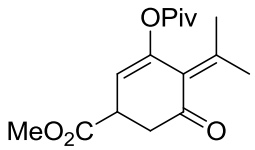
2-2m

2,2-Dimethyl-propionic acid 3-acetoxymethyl-6-isopropylidene-5-oxo-cyclohex-1-enyl ester (2-2m). Yield 36.0mg, 78%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.27 (s, 9H), 1.99 (s, 3H), 2.05 (s, 3H), 2.16 (s, 3H), 2.42 (dd, *J* = 16.4, 7.6 Hz, 1H), 2.62(dd, *J* = 16.4, 5.6 Hz, 1H), 2.89 (m, 1H), 4.06 (d, *J* = 6.4 Hz, 2H), 5.52 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 24.5, 25.4, 27.4, 31.9, 39.3, 41.7, 66.1, 117.0, 128.1, 148.3, 148.4, 171.1, 176.4, 199.8. IR: ν 2974, 1744, 1692, 1229, 1116 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{17}H_{24}O_5$ $(M+Na)^+$ 331.1516, found 331.1525.



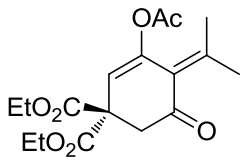
2-2n

2,2-Dimethyl-propionic acid 6-isopropylidene-5-oxo-3-triisopropylsilanyloxymethyl-cyclohex-1-enyl ester (2-2n). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.04 (m, 21H), 1.23 (s, 9H), 1.97 (s, 3H), 2.14 (s, 3H), 2.45 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.60 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.75 (m, 1H), 3.63 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.68 (dd, *J* = 9.6, 6.4 Hz, 1H), 5.54 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 18.1, 24.4, 25.2, 27.3, 35.5, 39.2, 41.9, 66.1, 118.5, 128.4, 146.6, 147.6, 176.5, 200.9. IR (film): ν 2944, 1752, 1693, 1463, 1107, 882, 734, 684 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{24}H_{42}SiNaO_4$ $(M+Na)^+$ 445.2744, found 445.2730.



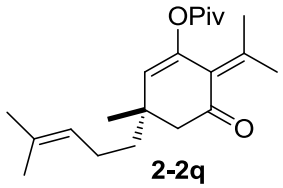
2-2o

3-(2,2-Dimethyl-propionyloxy)-4-isopropylidene-5-oxo-cyclohex-2-enecarboxylic acid methyl ester (2-2o). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.27 (s, 9H), 1.99 (s, 3H), 2.18 (s, 3H), 2.73 (m, 2H), 3.50 (m, 1H), 3.72 (s, 3H), 5.76 (d, *J* = 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.5, 27.3, 37.6, 39.2, 40.6, 52.6, 114.5, 127.7, 148.5, 149.4, 172.4, 176.2, 198.5. IR (film): ν 2976, 1740, 1693, 1107 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{16}H_{22}NaO_5$ $(M+Na)^+$ 317.1359, found 261.1369.



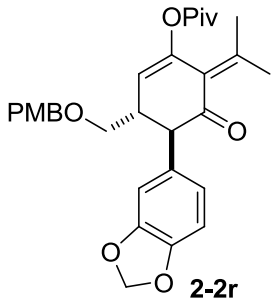
2-2p

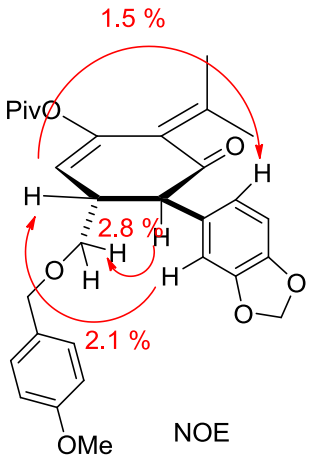
Diethyl 3-acetoxy-5-oxo-4-(propan-2-ylidene)cyclohex-2-ene-1,1-dicarboxylate (2-2p). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.25 (t, *J* = 7.1 Hz, 6H), 1.99 (s, 3H), 2.18 (s, 3H), 2.23 (s, 3H), 2.90 (s, 2H), 4.21 (m, 4H), 6.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.9, 24.9, 25.3, 44.1, 53.2, 62.5, 114.9, 126.1, 148.9, 151.2, 168.0, 168.8, 195.8. IR: ν 2985, 2361, 2344, 1733, 1697, 1266, 1187 cm^{-1}. HRMS (ESI) for $C_{17}H_{22}O_7$ (M+1) 339.1438 (Calc.), found 339.1437.



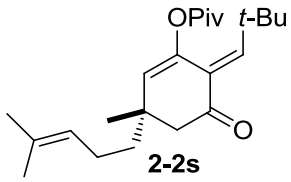
2-2q

2,2-Dimethyl-propionic acid 6-isopropylidene-3-methyl-3-(4-methyl-pent-3-enyl)-5-oxo-cyclohex-1-enyl ester (2-2q). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.10 (s, 3H), 1.27 (s, 9H), 1.40 (m, 2H), 1.58 (s, 3H), 1.66 (s, 3H), 1.97 (m, 2H), 1.99 (s, 3H), 2.15 (s, 3H), 2.36 (d, *J* = 15.0 Hz, 1H), 2.51 (d, *J* = 15.0 Hz, 1H), 5.06 (t, *J* = 7.0 Hz, 1H), 5.36 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8, 23.3, 24.8, 25.3, 25.9, 26.8, 27.4, 35.3, 39.2, 42.1, 52.3, 124.3, 126.4, 127.6,131.9, 146.0, 146.4, 176.7, 201.0. IR (film): ν 2967, 1751, 1693, 1273, 1111 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{21}H_{32}NaO_3$ $(M+Na)^+$ 355.2243, found 355.2251. $[\alpha]_D^{25}$ = -10.7 (*c* 0.3, $CHCl_3$); The enantiomeric excess (87%) of product **29** was determined by HPLC analysis of an alcohol derived from reduction of ketone group in **29**. (Chiralcel AS-H; eluent: pure hexane; flow rate: 0.7 mL/min; detection: at 210 nm): retention times t_1 = 6.8 min t_2=7.2 min.



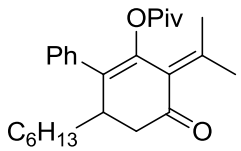


2,2-Dimethyl-propionic acid 4-benzo[1,3]dioxol-5-yl-6-isopropylidene-3-(4-methoxy-benzyloxymethyl)-5-oxo-cyclohex-1-enyl ester (2-2r). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.28 (s, 9H), 1.98 (s, 3H), 2.02 (s, 3H), 2.93 (m, 1H), 3.28 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.36 (dd, *J* = 9.0, 4.5 Hz, 1H), 3.58 (d, *J* = 8.5 Hz, 1H), 3.80 (s, 3H), 4.33 (d, *J* = 9.6 Hz, 1H), 4.40 (d, *J* = 9.2 Hz, 1H), 5.63 (d, *J* = 3.0 Hz, 1H), 5.93 (s, 2H), 6.58 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.65 (d, *J* = 1.5 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 1H), 6.85 (m, 2H), 7.19 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3, 24.9, 27.4, 39.3, 40.3, 55.5, 56.3, 70.9, 73.0, 101.2, 108.5, 109.3, 114.0, 118.6, 122.7, 128.4, 129.5, 130.3, 132.2, 146.5, 146.7, 146.9, 148.0, 159.5, 176.5, 200.5. IR (film): ν 1749, 1513, 1248, 1125, 1037 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{30}H_{34}NaO_7$ $(M+Na)^+$ 529.2196, found 529.2198.



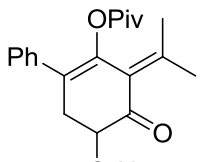
2,2-Dimethyl-propionic acid 6-(2,2-dimethyl-propylidene)-3-methyl-3-(4-methyl-pent-3-enyl)-5-oxo-cyclohex-1-enyl ester (2-2s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ

1.11 (s, 3H), 1.19 (s, 9H), 1.30 (s, 9H), δ 1.41 (m, 2H), 1.58 (d, *J* = 0.4 Hz, 3H), 1.66 (d, *J* = 1.2 Hz, 3H), 1.97 (m, 2H), 2.37 (d, *J* = 16.0 Hz, 1H), 2.48 (d, *J* = 16.0 Hz, 1H), 5.05 (tqq, *J* = 7.2, 1.2, 0.4 Hz, 1H), 5.51 (d, *J* = 1.2 Hz, 1H), 6.76 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 23.4, 25.8, 26.3, 27.5, 30.1, 33.0, 34.7, 39.3, 41.8, 49.8, 124.1, 128.5, 128.9, 132.0, 144.9, 148.8, 177.4, 200.5. IR (film): ν 2962, 1752, 1703, 1479, 1107 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{23}H_{36}NaO_3$ $(M+Na)^+$ 383.2556, found 383.2564.



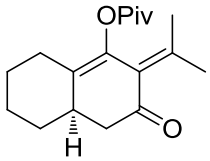
2-2t

6-hexyl-4-oxo-3-(propan-2-ylidene)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl pivalate (2-2t). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88 (t, *J* = 7.2 Hz, 1H), 0.98 (s, 9H), 1.25-1.40 (m, 8H), 1.55 (m, 1H), 1.94 (m, 1H), 2.02 (s, 3H), 2.14 (s, 3H), 2.56 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.74 (m, 1H), 2.90 (dd, *J* = 16.4, 6.0 Hz, 1H), 7.23-7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.7, 24.4, 25.9, 27.0, 27.6, 29.2, 31.8, 33.7, 38.7, 38.9, 44.2, 127.4, 128.1, 128.6, 128.9, 134.5, 138.3, 141.8, 148.0, 175.6, 201.4. IR (film): ν 2928, 1747, 1691, 1111 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{23}H_{36}NaO_3$ $(M+Na)^+$ 419.2556, found 419.2557.



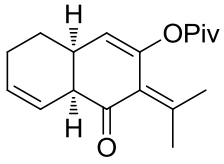
2-2t'

5-hexyl-4-oxo-3-(propan-2-ylidene)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl pivalate (2-2t'). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.81 (t, *J* = 6.8 Hz, 1H), 0.91 (s, 9H), 1.10-1.30 (m, 8H), 1.35 (m, 1H), 1.52 (m, 1H), 2.05 (s, 3H), 2.22 (s, 3H), 2.47 (dd, *J* = 15.6, 8.0 Hz, 1H), 2.55 (m, 1H), 2.75 (dd, *J* = 15.6, 5.6 Hz, 1H), 7.21-7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 24.0, 25.2, 27.1, 27.4, 29.5, 30.7, 31.9, 33.3, 39.0,47.6, 127.5, 128.1, 128.3, 128.4, 129.4, 138.5, 141.0, 145.8, 175.8, 203.9. IR (film): ν 2923, 1742, 1686, 1270, 1113 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{23}H_{36}NaO_3$ $(M+Na)^+$ 419.2556, found 419.2567.



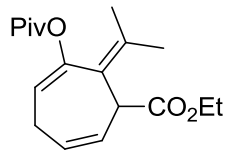
2-2v

(R)-3-oxo-2-(propan-2-ylidene)-2,3,4,4a,5,6,7,8-octahydronaphthalen-1-yl pivalate (2-2v). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.24 (s, 9H), 1.26 (m, 1H), 1.34 (m, 2H), 1.70 (m, 3H), 1.80 (m, 1H), 1.87 (s, 6H), 2.26 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.44 (m, 2H), 2.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.0, 25.8, 26.9, 27.7, 35.3, 36.9, 39.3, 47.1, 53.7, 123.8, 129.8, 130.2, 137.8, 175.7, 200.7. IR: ν 2975, 2933, 2860, 2361, 1745, 1704, 1271, 1111 cm^{-1}. HRMS (ESI) for $C_{18}H_{26}O_3$ (M+1) 291.1955 (Calc.), found 291.1967.



2-2w

(4aS,8aS)-4-oxo-3-(propan-2-ylidene)-3,4,4a,7,8,8a-hexahydronaphthalen-2-yl pivalate (2-2w). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.24 (s, 9H), 1.43 (m, 1H), 1.74 (m, 1H), 1.94 (s, 3H), 2.02 (s, 3H), 2.03 (m, 2H), 2.70 (m, 1H), 3.15 (m, 1H), 5.46 (d, *J* = 5.6 Hz, 1H), 5.74 (m, 1H), 5.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.17, 24.22, 24.5, 26.3, 27.4, 32.6, 39.2, 48.4, 120.3, 124.2, 128.1, 129.3, 144.3, 146.0, 176.5, 201.8. IR: ν 2976, 2922, 2874, 2360, 2343, 1750, 1688, 1159, 1113 cm^{-1}. HRMS (ESI) for $C_{18}H_{24}O_3$ (M+1) 289.1798 (Calc.), found 289.1796.

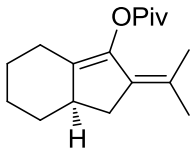


2-5

ethyl 6-(pivaloyloxy)-7-(propan-2-ylidene)cyclohepta-2,5-dienecarboxylate (2-5). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.21 (s, 9H), 1.17 (s, 9H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.80 (s, 3H), 1.81 (s, 3H), 2.81 (m, 1H), 2.95 (m, 1H), 4.08 (m, 1H), 4.18 (m, 1H), 4.28 (m, 1H). 5.53 (dd, *J* = 7.0,3.5 Hz, 1H), 5.78 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4, 20.8, 23.2, 26.9, 27.4, 39.2, 46.8, 61.1, 117.1, 126.4, 126.7, 128.7, 135.6, 135.6, 146.8, 172.0, 176.1. IR (film): ν 2973, 1742, 1128 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{21}H_{32}NaO_3$ $(M+Na)^+$ 329.1723, found 329.1733.

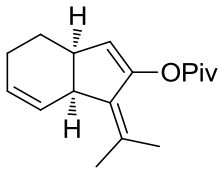
General Procedures for the synthesis of compound 2-6vand 2-6w. To an oven-dried flask was added $[Rh(CO)_2Cl]_2$ (2 mol %), anhydrous toluene (0.1 M), and 1 equiv of cyclopropyl propargyl ester. The oil bath was heated to 60 ^{o}C. The reaction was monitored by TLC. After the reaction is complete, the solvent was evaporated and the

residue was purified by flash column chromatography on silica gel (EtOAc/Hexane = 50:1).



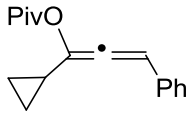
2-6v

(R)-2-(propan-2-ylidene)-2,4,5,6,7,7a-hexahydro-1H-inden-3-yl pivalate (2-6v). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.09 (m, 2H), 1.28 (m, 2H), 1.31 (s, 9H), 1.64 (s, 3H), 1.76 (s, 3H), 1.77 (m, 2H), 1.96 (m, 1H), 2.06 (d, br, *J* = 15.2 Hz, 1H), 2.22 (m, 1H), 2.47 (m, 1H), 2.73 (dd, *J* = 16.0, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 23.2, 25.2, 25.9, 26.2, 27.6, 35.1, 35.7, 39.2, 39.4, 119.2, 131.2, 137.9, 142.5, 176.3. IR: ν 2976, 2930, 2858, 2360, 2342, 1751, 1120 cm^{-1}. HRMS (ESI) for $C_{17}H_{26}O_2$ (M+1) 263.2006 (Calc.), found 263.2017.



2-6w

(3aR,7aS)-1-(propan-2-ylidene)-3a,4,5,7a-tetrahydro-1H-inden-2-yl pivalate (2-6w).^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.28 (s, 9H), 1.66 (m, 2H), 1.80 (s, 3H), 1.83 (s, 3H), 2.11 (m, 2H), 3.14 (s, br, 1H), 3.44 (s, br, 1H), 5.52 (m, 1H), 5.54 (s, 1H), 5.80 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 19.8, 21.7, 23.5, 26.1, 36.5, 38.1, 40.0, 122.2, 122.8, 126.3, 126.4, 133.6, 150.1, 175.1. IR: ν 2977, 2362, 2343, 1712, 1362, 1222 cm^{-1}. HRMS (ESI) for $C_{17}H_{24}O_2$ (M+1) 261.1849 (Calc.), found 261.1840.

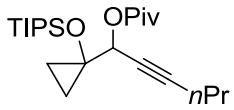


2-7d

1-cyclopropyl-3-phenylpropa-1,2-dienyl pivalate (2-7d). Yield 49 mg, 49%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.62-0.64 (m, 2H), 0.75-0.78 (m, 2H), 1.26 (s, 9H), 1.54-1.60 (m, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 7.24-7.26 (m, 1H), 7.31-7.35 (m, 2H), 7.41-7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.8, 6.3, 12.3, 27.4, 39.4, 105.0, 128.1, 128.2, 128.5, 128.9, 134.2, 176.2, 196.8. HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}O_2$ $(M+Na)^+$ 279.1356, found 279.1360.

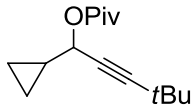
General procedures for the synthesis of compound 8. To an oven-dried flask was added THF (0.2 M), diisopropylamine (1.0 equiv) and the solution was cooled to 0 ^{o}C. A solution of *n*-BuLi (1.0 equiv) was added and the resulting mixture was stirred at 0 ^{o}C for 10 min and then cooled to -78 ^{o}C. The alkyne (1.0 equiv) was added dropwise and stirred for 30 min. The aldehyde or ketone (1.0 equiv) was added and the solution was allowed to warm to room temperature. The reaction was quenched with water, extracted with EtOAc for 3 times, dried over $MgSO_4$. The solvent was evaporated and the crude alcohol intermediate was used for next step without purification. To an oven-dried flask was added THF (0.2 M) and the above alcohol. The solution was cooled to -78 ^{o}C. A solution of *n*-BuLi (1.0 equiv) was added and the solution was stirred for 10 min. PivCl or acetic anhydride (1.1 equiv) was added dropwise and the solution was allowed to warm to room temperature. The reaction was quenched with water, extracted with EtOAc for three times,

and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography.



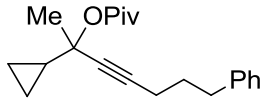
2-8a

6-phenyl-1-(1-((triisopropylsilyl)oxy)cyclopropyl)hex-2-yn-1-yl pivalate (2-8a). Yield 174 mg, 88%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.77-0.97 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 1.04 (m, 21H), 1.22 (s, 9H), 1.49 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.13 (td, *J* = 7.2, 2.0 Hz, 2H), 6.00 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3, 12.8, 13.0, 13.5, 18.30, 18.32, 20.9, 22.0, 27.2, 39.0, 58.2, 69.5, 76.1, 86.0, 177.7. IR (film): ν 2964, 2868, 1723, 1462, 1279, 1216, 1145, 1044, 1015, 955, 882, 668 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{23}H_{42}O_3Si$ $(M+Na)^+$ 417.2795, found 417.2791.



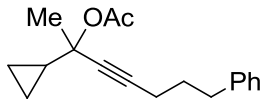
2-8b

1-cyclopropyl-4,4-dimethylpent-2-yn-1-yl pivalate (2-8b). Yield 484 mg, 62%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.38-0.55 (m, 4H), 1.19 (s, 9H), 1.19 (m, 1H), 1.21 (s, 9H), 5.30 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 1.9, 3.1, 14.4, 27.2, 27.5, 31.0, 38.9, 67.5, 74.1, 94.4, 177.7. IR (film): ν 2971, 2361, 1727, 1479, 1364, 1279, 1152, 1029, 954, 849, 667 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{15}H_{24}O_2$ $(M+Na)^+$ 259.1668, found 259.1662.



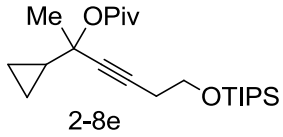
2-8c

2-cyclopropyl-7-phenylhept-3-yn-2-yl pivalate (2-8c). Yield 986 mg, 79%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.50 (m, 3H), δ 0.72 (m, 1H), 1.18 (s, 9H), 1.34 (m, 1H), 1.73 (s, 3H), 1.78 (m, 2H), 2.19 (t, *J* = 8.5 Hz, 2H), 2.70 (t, *J* = 10.0 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.3, 3.0, 18.2, 20.4, 27.3, 27.6, 30.6, 34.8, 39.4, 77.5, 78.7, 85.3, 126.0, 128.5, 128.8, 141.9, 176.8. IR (film): ν 2983, 2360, 1732, 1478, 1455, 1363, 1281, 1141, 1070, 1051, 927, 743, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{21}H_{28}O_2$ $(M+Na)^+$ 335.1982, found 335.1994.



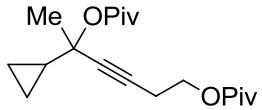
2-8d

2-cyclopropyl-7-phenylhept-3-yn-2-yl acetate (2-8d). Yield 165 mg, 60%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.50 (m, 3H), δ 0.72 (m, 1H), 1.37 (m, 1H), 1.75 (s, 3H), 1.78 (m, 2H), 2.02 (s, 3H), 2.19 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 7.18 (m, 3H), 7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.5, 3.3, 18.3, 20.1, 22.4, 27.7, 30.5, 34.9, 78.0, 78.7, 85.9, 126.1, 128.5, 128.7, 141.8, 169.6. IR (film): ν 2936, 1737, 1366, 1238, 1148, 1071, 1012, 910, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{18}H_{22}O_2$ $(M+Na)^+$ 293.1512, found 293.1526.



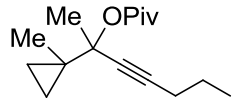
2-8e

2-cyclopropyl-6-((triisopropylsilyl)oxy)hex-3-yn-2-yl pivalate (2-8e). Yield 429 mg, 47%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.48 (m, 3H), δ 0.68 (m, 1H), 1.06 (m, 21H), 1.17 (s, 9H), 1.34 (m, 1H), 1.70 (s, 3H), 2.43 (t, *J* = 7.2 Hz, 2H), 3.75 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.3, 2.9, 12.2, 18.2, 20.3, 23.4, 27.3, 27.5, 39.4, 62.3, 77.6, 79.0, 82.7, 176.9. IR (film): ν 2958, 2867, 1736, 1462, 1366, 1283, 1143, 1109, 1071, 917, 856, 681 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{23}H_{42}O_3Si$ $(M+Na)^+$ 417.2795, found 417.2790.



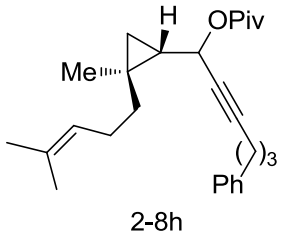
2-8f

5-cyclopropylhex-3-yne-1,5-diyl bis(2,2-dimethylpropanoate) (2-8f). Yield 50.7 mg, 79%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.48 (m, 3H), δ 0.68 (m, 1H), 1.17 (s, 9H), 1.21 (s, 9H), 1.34 (m, 1H), 1.70 (s, 3H), 2.52 (t, *J* = 6.8 Hz, 2H), 4.11 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 2.3, 3.0, 19.4, 20.3, 27.3, 27.4, 27.5, 38.9, 39.4, 62.5, 77.5, 79.5, 81.4, 176.8, 178.5. IR (film): ν 2975, 1730, 1480, 1281, 1143, 1071, 769 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{19}H_{30}O_4$ $(M+Na)^+$ 345.2036, found 345.2032.



2-8g

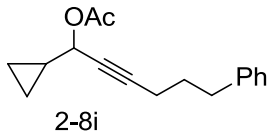
2-(1-methylcyclopropyl)hept-3-yn-2-yl pivalate (2-8g). Yield 52.3 mg, 72%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.25(m, 1H), δ 0.33(m, 1H), δ 0.73 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 3H), 1.02 (m, 1H), 1.12 (s, 3H), 1.16 (s, 9H), 1.48 (m, 2H), 1.67 (s, 3H), 2.13 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 12.6, 13.5, 19.8, 20.8, 22.3, 22.9, 25.0, 27.3, 39.6, 78.6, 79.0, 85.3, 176.4. IR (film): ν 2965, 2361, 1738, 1284, 1158, 1065, 913, 873, 860, 658 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{16}H_{26}O_2$ $(M+Na)^+$ 273.1825, found 273.1824.



2-8h

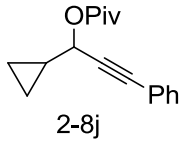
(R)-1-((1S,2S)-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopropyl)-6-phenylhex-2-yn-1-yl pivalate (2-8h). Yield 50.3mg, 38%; colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.34 (t, *J* = 5.0 Hz, 1H), 0.67 (t, *J* = 9.0, 5.0 Hz, 1H), 1.01 (m, 1H), 1.02 (s, 3H), 1.15 (ddd, *J* = 10.0, 9.0, 5.0 1H), 1.23 (s, 9H), 1.40 (ddd, *J* = 13.5, 10.5, 7.0 Hz, 1H), 1.60 (s, 3H), 1.67 (s, 3H). 1.81 (pentet, *J* = 7.0 Hz, 2H), 2.03 (m, 2H), 2.21 (td, *J* = 7.0, 2.0 Hz, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 4.88 (dt, *J* = 10.0, 2.0 Hz, 1H), 5.10 (tt, *J* = 7.0, 1.5 Hz, 1H), 7.16-7.30 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 17.8, 18.3, 18.7, 21.5, 25.5, 25.9, 27.3, 28.4, 30.3, 34.8, 38.8, 41.2, 66.0, 79.1, 84.5, 124.6, 126.1, 128.5, 128.8, 131.6,

141.8, 177.3. IR (film): ν 2929, 2359, 1729, 1454, 1287, 1149, 1134, 934, 745, 698 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{27}H_{38}O_2$ $(M+Na)^+$ 417.2764, found 417.2746.



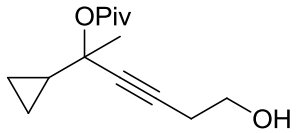
2-8i

1-cyclopropyl-6-phenylhex-2-yn-1-yl acetate (2-8i). Yield 526 mg, 78%; colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 0.51 (m, 4H), δ 1.26 (m, 1H), 1.81 (pentet, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 2.21 (td, *J* = 7.2, 2.0 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 5.28 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.19 (m, 3H), 7.27(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.3, 3.6, 14.7, 18.3, 21.4, 30.3, 34.9, 68.1, 76.2, 86.1, 126.1, 128.6, 128.7, 141.7, 170.4. IR (film): ν 2938, 1735, 1496, 1454, 1367, 1230, 1026, 965, 894, 746, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}O_2$ $(M+Na)^+$ 279.1355, found 279.1344.



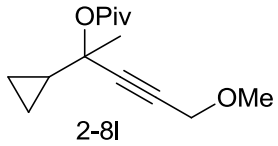
2-8j

1-cyclopropyl-3-phenylprop-2-yn-1-yl pivalate (2-8j). Yield 494 mg, 77%; colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 0.58 (m, 4H), δ 1.24 (s, 9H), 1.36 (m, 1H), 5.43(d, *J* = 6.8 Hz, 1H), 7.30(m, 3H), 7.42(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.4, 3.5, 14.9, 27.3, 39.0, 67.7, 85.1, 85.2, 122.6, 128.4, 128.7, 132.1, 177.8. IR (film): ν 2973, 1728, 1490, 1479, 1277, 1144, 1070, 1029, 697 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}O_2$ $(M+Na)^+$ 279.1355, found 279.1353.



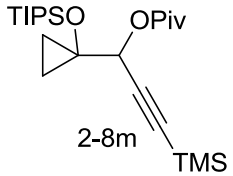
2-8k

2-cyclopropyl-6-hydroxyhex-3-yn-2-yl pivalate (**2-8k**). ^{1}H NMR (400 MHz, CDCl3, TMS): δ 0.46 (m, 3H), 0.66 (m, 1H), 1.15 (s, 9H), 1.23 (m, 1H), 1.66 (s, 3H), 2.39 (m, 2H), 2.66 (b, 1H), 3.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.0, 3.0, 20.3, 23.4, 27.2, 27.4, 39.5, 61.1, 76.9, 80.7, 83.4, 177.6. IR (film): ν 2974, 1717, 1479, 1286, 1216, 1145, 1050, 666 cm^{-1}.



2-8l

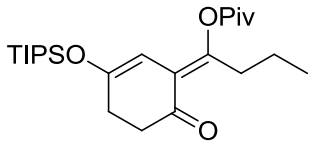
2-cyclopropyl-5-methoxypent-3-yn-2-yl pivalate (**2-8l**). ^{1}H NMR (500 MHz, CDCl3, TMS): δ 0.53 (m, 3H), 0.70 (m, 1H), 1.17 (s, 9H), 1.36 (m, 1H), 1.72 (s, 3H), 3.36 (s, 3H), 4.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.2, 3.0, 20.3, 27.1, 27.2, 39.4, 57.5, 60.0, 76.6, 81.0, 84.7, 176.7. IR (film): ν 2978, 1734, 1479, 1461, 1395, 1361, 1281, 1140, 1102, 1027, 933, 905, 863, 831, 767 cm^{-1}.



2-8m

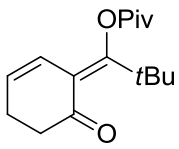
1-(1-((triisopropylsilyl)oxy)cyclopropyl)-3-(trimethylsilyl)prop-2-yn-1-yl pivalate (**2-8m**). ^{1}H NMR (500 MHz, CDCl3, TMS): δ 0.13 (s, 9H), 0.86 (m, 4H), 1.04 (m, 21H), 1.22 (s,

9H), 5.54 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.1, 11.5, 12.8, 12.9, 18.35, 18.36, 27.1, 38.9, 58.0, 69.3, 90.3, 101.1, 177.5. IR (film): ν 2945, 2868, 1736, 1462, 1308, 1278, 1250, 1223, 1143, 1062, 1014, 842, 758, 665 cm^{-1}.



2-9a

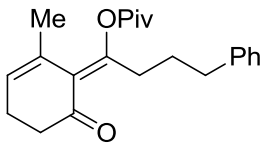
1-(6-oxo-3-((triisopropylsilyl)oxy)cyclohex-2-en-1-ylidene)-4-phenylbutyl pivalate (2-9a, a mixture *E* and *Z* isomers). Yield 42.8 mg, 70%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.93 (m, 3H), δ 0.93 (m, 3H), 1.09 (m, 21H), 1.09 (m, 21H), 1.30 (s, 9H), 1.30 (s, 9H), 1.50 (m, 2H), 1.50 (m, 2H), 2.21 (t, *J* = 7.6 Hz, 2H), 2.55 (m, 2H), 2.55 (m, 4H), 2.66 (m, 2H), 2.66 (m, 2H), 5.61 (s, 1H), 5.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 12.9, 14.1, 18.10, 18.11, 20.0, 21.0, 27.3, 29.6, 29.9, 33.6, 39.2, 39.4, 39.7, 40.3, 102.7, 103.2, 121.0, 122.0, 147.9, 153.0, 153.69, 153.74, 175.7, 176.6, 197.3, 199.3. IR (film): ν 2962, 2868, 1744, 1701, 1638, 1598, 1462, 1375, 1253, 1107, 998, 881, 684, 666 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{24}H_{42}O_4Si$ $(M+Na)^+$ 445.2744, found 445.2734.



2-9b

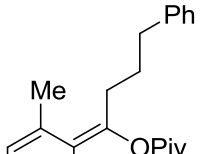
2,2-dimethyl-1-(6-oxocyclohex-2-en-1-ylidene)propyl pivalate (2-9b, a mixture *E* and *Z* isomers). Yield 70 mg, 72%; colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.17 (s, 9H), δ 1.21 (s, 9H), 1.23 (s, 9H), 1.33 (s, 9H), 2.38 (m, 4H), 2.60 (m, 4H), 5.74 (m,

1H), 5.79 (dt, *J* = 10.0, 4.0 Hz, 1H), 5.84 (m, 1H), 6.10 (dt, *J* = 10.0, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.3, 25.4, 26.9, 27.1, 27.5, 28.4, 28.8, 37.9, 39.0, 39.5, 41.5, 44.7, 122.5, 124.0, 125.1, 125.2, 125.3, 128.5, 145.8, 159.0, 175.9, 176.1, 202.4, 210.4. IR (film): ν 2970, 1746, 1694, 1478, 1122, 1096, 731, 707 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{16}H_{24}O_3$ $(M+Na)^+$ 287.1617, found 287.1610.



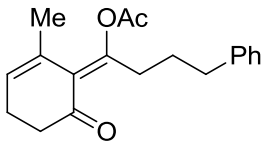
2-E-9c

(*E*)-1-(2-methyl-6-oxocyclohex-2-en-1-ylidene)-4-phenylbutyl pivalate (2-*E*-9c). Yield 37.3 mg, 55%; colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.23 (s, 9H), δ 1.86 (m, 2H), 1.89 (q, *J* = 1.5 Hz, 3H), 2.38(m, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.65 (t, *J* = 8.0 Hz, 2H), 5.73 (tq, *J* = 4.5, 1.5 Hz, 1H), 7.16 (m, 3H), 7.26 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5, 23.9, 27.3, 29.9, 32.8, 35.8, 38.9, 39.4, 126.0, 127.5, 128.2, 128.5, 128.6, 132.5, 142.2, 155.9, 175.9, 203.1. IR (film): ν 2972, 1744, 1696, 1603, 1454, 1269, 1104, 910, 731, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{22}H_{28}O_3$ $(M+Na)^+$ 363.1931, found 363.1938.



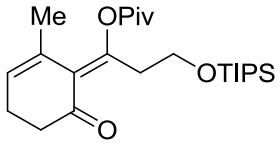
2-Z-9c

(*Z*)-1-(2-methyl-6-oxocyclohex-2-en-1-ylidene)-4-phenylbutyl pivalate (2-*Z*-9c). Yield 21.3 mg, 31%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.18 (s, 9H), δ 1.67 (d, *J* = 1.2 Hz, 3H), 1.92 (pentet, *J* = 7.6 Hz, 2H), 2.29(m, 4H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 5.49 (m, 1H), 7.17 (m, 3H), 7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 23.1, 25.4, 26.1, 27.1, 35.4, 39.1, 43.9, 121.3, 126.2, 128.4, 128.59, 128.63, 129.0, 141.7, 148.0, 176.2, 205.0. IR (film): ν 2935, 1748, 1697, 1453, 1364, 1276, 1252, 1229, 1107, 909, 730, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{22}H_{28}O_3$ $(M+Na)^+$ 363.1931, found 363.1945.



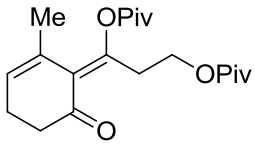
2-9d

1-(2-methyl-6-oxocyclohex-2-en-1-ylidene)-4-phenylbutyl acetate (2-9d, a mixture *E* and *Z* isomers). Yield 36.3 mg, 84%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.68 (q, *J* = 1.2 Hz, 3H), δ 1.84 (m, 2H), 1.92 (s, 3H), 1.94(m, 2H), 2.03 (s, 3H), 2.15 (s, 3H), 2.27 (m, 2H), 2.36 (m, 4H), 2.48(m, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.64 (m, 6H), 5.50 (m, 1H), 5.76 (tq, *J* = 4.8, 1.2 Hz, 1H), 7.18(m, 3H), 7.18(m, 3H), 7.27 (m, 2H), 7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 20.9, 21.4, 22.1, 23.1, 23.7, 25.4, 26.3, 29.5, 32.7, 35.3, 35.7, 38.7, 43.7, 121.5, 126.0, 126.2, 127.2, 128.49, 128.57, 128.58, 128.65, 128.8, 129.0, 132.2, 141.7, 142.2, 148.3, 155.5, 168.1, 168.4, 202.9, 204.7. IR (film): ν 2941, 1762, 1695, 1602, 1453, 1367, 1208, 1187, 1037, 1013, 700 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{19}H_{22}O_3$ $(M+Na)^+$ 321.1461, found 321.1482.



2-9e

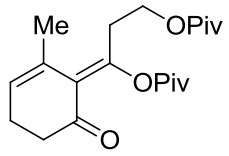
1-(2-methyl-6-oxocyclohex-2-en-1-ylidene)-3-((triisopropylsilyl)oxy)propyl pivalate (2-9e, a mixture *E* and *Z* isomers). Yield 39 mg, 91%; colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.10 (m, 21H), δ 1.10 (m, 21H), 1.29 (s, 9H), 1.33 (s, 9H), 1.77(s, 3H), 1.95 (q, *J* = 1.5Hz, 3H), 2.33 (m, 4H), 2.42 (m, 2H), 2.53 (m, 2H), 2.84(m, 4H), 3.91 (t, *J* = 7.0 Hz, 2H), 4.03 (t, *J* = 6.5 Hz, 2H), 5.54 (m, 1H), 5.78 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1, 12.2, 18.16, 18.19, 19.6, 22.5, 23.1, 23.8, 26.3, 27.2, 27.3, 37.4, 38.7, 39.2, 39.4, 47.9, 59.0, 62.1, 121.2, 128.3, 128.5, 129.5, 132.4, 148.7, 153.4, 176.0, 176.1, 202.8, 203.4. IR (film): ν 2942, 2866, 1747, 1698, 1462, 1382, 1271, 1096, 1027, 935, 881, 680 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{24}H_{42}O_4Si$ $(M+Na)^+$ 445.2744, found 445.2735.



2-E-9f

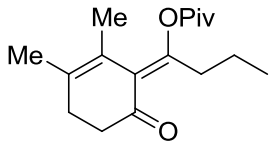
(*E*)-1-(2-methyl-6-oxocyclohex-2-en-1-ylidene)propane-1,3-diyl bis(2,2-dimethylpropanoate) (2-*E*-9f). Yield 41.0mg, 84% combined yield; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.10 (s, 9H), δ 1.29 (s, 9H), 1.91 (q, *J* = 1.6Hz, 3H), 2.40 (m, 2H), 2.51 (t, *J* = 6.8 Hz, 2H), 2.89 (t, *J* = 6.8 Hz, 2H), 4.22 (t, *J* = 7.2 Hz, 2H), 5.78 (tq, *J* = 4.8, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 23.7, 27.3, 27.4, 32.9,

38.6, 38.8, 39.4, 62.1, 128.9, 130.0, 132.2, 151.7, 176.0, 178.5, 202.6. IR (film): ν 2971, 1727, 1698, 1281, 1147, 1097, 1031 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{20}H_{30}O_5$ $(M+Na)^+$ 373.1985, found 373.1979.



2-*Z*-9f

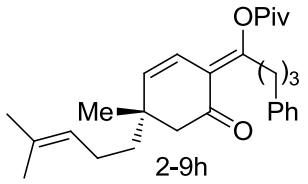
(*Z*)-1-(2-methyl-6-oxocyclohex-2-en-1-ylidene)propane-1,3-diyl bis(2,2-dimethylpropanoate) (2-*Z*-9f). Yield 41.0mg, 84% combined yield; colorless oil. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 1.17 (s, 9H), δ 1.25 (s, 9H), 1.72 (q, *J* = 1.5Hz, 3H), 2.31 (m, 4H), 2.89 (t, *J* = 6.5 Hz, 2H), 4.34 (t, *J* = 6.5 Hz, 2H), 5.52 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6, 23.1, 26.4, 27.2, 27.4, 38.9, 39.2, 43.3, 59.5, 121.6, 127.9, 129.1, 149.5, 176.1, 178.5, 201.4. IR (film): ν 2973, 1726, 1480, 1363, 1282, 1151, 1106, 133, 909, 729 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{20}H_{30}O_5$ $(M+Na)^+$ 373.1985, found 373.1979.



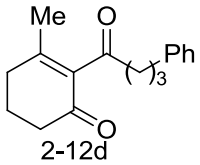
2-*E*-9g

(*E*)-1-(2,3-dimethyl-6-oxocyclohex-2-en-1-ylidene)butyl pivalate (2-*E*-9g). Yield 30.3mg, 52%; colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 0.93 (t, *J* = 7.6 Hz, 3H), δ 1.28 (s, 9H), 1.52 (sextet, *J* = 7.6 Hz, 2H), 1.78 (s, 3H), 1.79 (s, 3H), 2.31 (m, 2H), 2.39 (m, 2H), 2.55 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 17.8, 19.9, 21.3,

27.4, 29.4, 33.9, 37.6, 39.3, 124.5, 129.5, 134.7, 154.2, 175.5, 204.0. IR (film): ν 2963, 1744, 1696, 1608, 1479, 1461, 1273, 1101, 1027, 914, 731 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{17}H_{26}O_3$ $(M+Na)^+$ 301.1774, found 301.1771.



(S)-1-(4-methyl-4-(4-methylpent-3-en-1-yl)-6-oxocyclohex-2-en-1-ylidene)-4-phenylbutyl pivalate (2-9h, a mixture *E* and *Z* isomers). Yield 67 mg, 62%; colorless oil. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 1.06 (s, 3H), 1.28 (s, 9H), 1.37 (m, 2H), 1.57 (s, 3H), 1.65 (s, 3H), 1.83 (m, 2H), 1.93 (m, 2H), 2.37 (m, 1H), 2.37 (d, *J* = 14.0 Hz, 1H), 2.56 (d, *J* = 14.0, 1H), 2.65 (t, *J* = 8.0 Hz, 2H), 2.80 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 5.05 (m, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 6.21 (d, *J* = 10.0 Hz, 1H), 7.16-7.30 (m, 5H). The two isomers have nearly identical ^1H NMR. ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8, 23.3, 25.84, 25.85, 27.27, 27.34, 29.2, 31.8, 35.4, 35.8, 39.3, 39.5, 39.9, 42.4, 53.3, 120.8, 122.3, 124.2, 126.0, 126.2, 128.5, 128.58, 128.60, 132.0, 138.2, 142.2, 157.5, 175.7, 176.0, 200.0. IR (film): ν 2967, 1712, 1454, 1361, 1220, 1123, 914, 732, 700 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{28}H_{38}O_3$ $(M+Na)^+$ 445.2613, found 445.2607.



3-methyl-2-(4-phenylbutanoyl)cyclohex-2-enone (2-12d). To a round bottom flask was added compound **2-9d** (60.2 mg, 0.20 mmol), 2 mL of MeOH, and K_2CO_3 (28 mg, 0.2 mmol). The reaction was stirred for 10 min. About 5 mL of Et_2O and 5 mL of H_2O were added and the aqueous phase was extracted with 5 mL of Et_2O for 3 times. The combined organic solution was dried over $MgSO_4$, evaporated under vacuum and the residue was purified by flash column chromatography (EtOAc/Hexane = 1:4) to provide a colorless oil (40.2 mg, 0.144 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.89 (s, 3H), 1.97 (m, 4H), 2.39 (m, 4H), 2.64 (q, *J* = 7.2 Hz, 4H), 7.18 (m, 3H), 7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 25.3, 32.3, 35.4, 37.6, 43.7, 126.1, 128.5, 128.7, 139.9, 142.0, 159.6, 197.2, 207.0. IR (film): ν 2931, 2360, 1698, 1661, 1378, 1181, 907, 727, 700 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}O_2$ $(M+Na)^+$ 279.1356, found 279.1355.

2.4 Referrence

1. Baldwin, J. E. *Chem.Rev.* **2003**, *103*, 1197.
2. Pd catalyzed vinylcyclopropane cyclopentene rearrangement: (a) Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1982**, *23*, 2871. (b) Fugami, K.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*. 857. (c) Burgess, K. *J. Org. Chem*. **1987**, *52*, 2046. (d) Burgess, K. *Tetrahedron Lett*. **1985**, *26*, 3049.

   Rh catalyzed vinylcyclopropane cyclopentene rearrangement: (a) Grigg, R.; Hayes, R.; Sweeney, A. *J. Chem. Soc., Chem. Commun*. **1971**, 1248. (b) Alcock, N. W.; Brown. J. M.; Golding, J. A.; Williamson, D. H. *J. Chem. Soc., Chem. Commun*. **1975**, 792. (c) Aris, V.; Brown, J. M.; Conneely, J. A.; Golding, B. T.; Williamson, D. H.

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Chapter 3

Rhodium-catalyzed Eight-membered Ring Formation and [5+2] Cycloaddition Involving 1,2-Acycloxy Migration of Vinyl Propargylic Esters

This work has been published under the following:

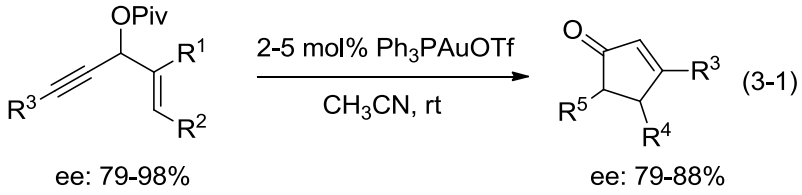
Shu, X.; Huang, S.; Shu, D.; Tang, W. *Angew.Chem.Int.Ed*. **2011**, *50*, 8153.

Shu, X.-z; Li, X.; Shu, D.; Huang, S.; Schienebeck, C. M.; Zhou, X.; Robichaux, P. J.; Tang, W. *J. Am. Chem. Soc.* **2012**, *134*, 5211.

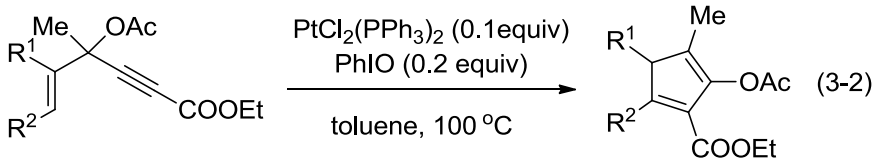
3.1 Introduction

In 1984, Rautenstrauch first reported that 3-acyloxy-1,4-enynes could undergo cycloisomerization to form cyclopentenones and release acetic anhydride in the presence of a palladium catalyst. [1]

In 2005, the scope of Rautenstrauch rearrangement was expanded using gold[2] and platinum[3] catalysts to synthesize functionalized five-membered rings. In the gold-catalyzed Rautenstrauch rearrangement, Toste found that optical pure cyclopentenones could be prepared from chiral starting material (eq 3-1). Different substituents (R^1, R^2 and R^3) could be tolerated.



Sarpong reported a platinum-catalyzed Rautenstrauch rearrangement (eq 3-2). The experimental results support a possible intermediacy of Pt (IV) catalyst.



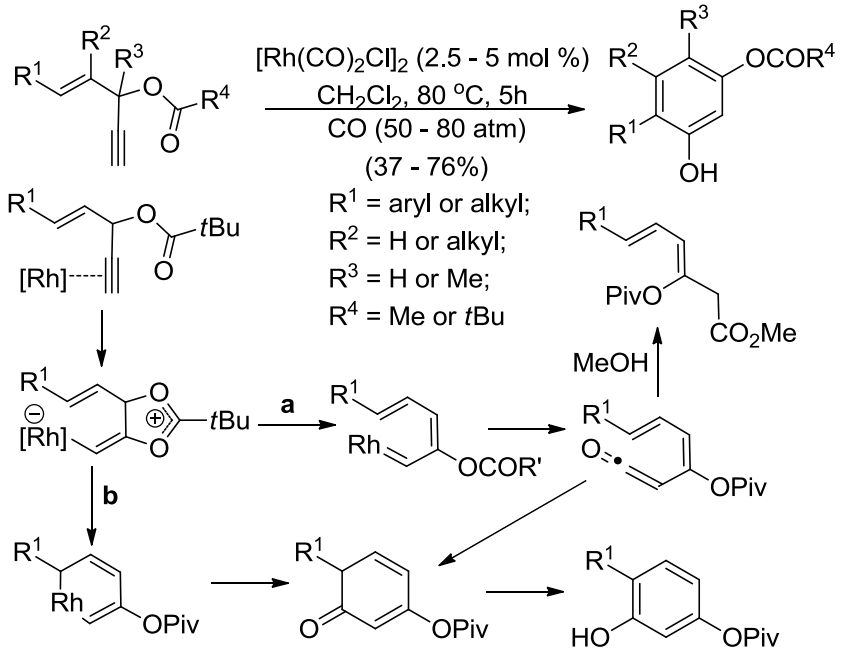
In 2010, research groups of Fukuyama, Ryu, Fensterbank, and Malacria reported a Rh-catalyzed tandem 1,2-acyloxy migration [5+1] cycloaddition of 3-acyloxy-1,4-enynes with CO (scheme 3-1).[4,5] This method provided access to various functionalized

resorcinol derivatives from readily available 3-acyloxy-1,4-enynes.

Various transition metals were screened. Gold and platinum salts led to either recovered starting materials or cyclopentenones *via* Rautenstrauch rearrangement. A mixtures of cyclopentenones and resorcinol derivatives were found when $Rh_2(OAc)_4$ or $[RhCp^*Cl_2]_2$ was employed as the catalyst. Other rhodium complexes, such as $Rh_6(CO)_{16}$, $Rh(acac)(CO)_2$, and $RhCl(PPh_3)_3$, did not catalyze the [5+1] cycloaddition.

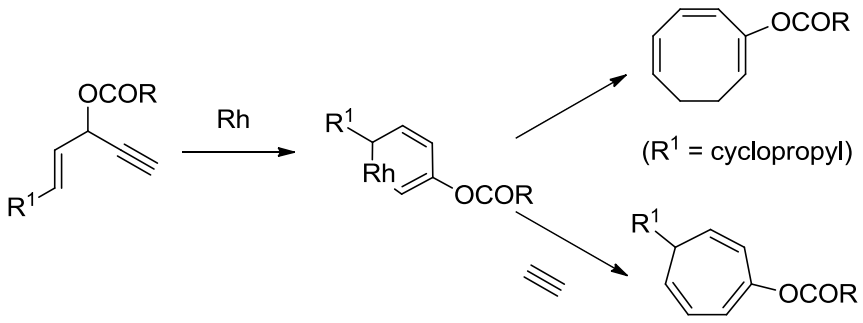
In the initial report, the author proposed two mechanisms,[4] both of which involve Rh-catalyzed 1,2-acyloxy migration through a zwitterionic vinyl rhodium intermediate. In pathway **a**, formation of a vinyl rhodium-carbene intermediate was proposed. It was then followed by a sequence of CO insertion to form ketene, 6π-electrocyclization, and aromatization. In pathway **b**, a six-membered metallacycle was proposed, which was then followed by CO insertion, reductive elimination, and aromatization. Since the ketene intermediate could be trapped by methanol, only pathway **a** was proposed in a later report.[5]

Scheme 3-1. Rhodium-catalyzed [5+1] Cycloaddition Involving 1,2-Acyloxy Migration.



Based on the 1,2-migration of propargylic esters, our group recently developed a method for the formation of eight-membered rings from cyclopropanes and a [5+2] cycloaddition (Scheme 3-2).[6,7]

Scheme 3-2. Eight-membered Ring Formation and [5+2] Cycloaddition.

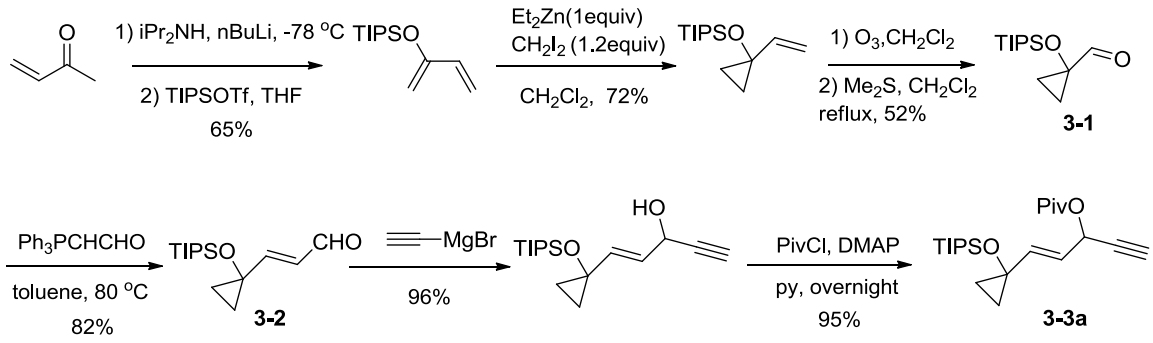


3.2 Rhodium-catalyzed Eight-membered Ring Formation

3.2.1 Optimization of Catalyst and Condition

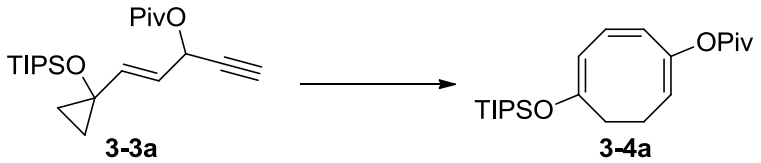
Substrate **3-3a** was synthesized according to the procedures outlined in scheme 3-3.

Scheme 3-3. Synthetic Procedures for Substrate 3-3a Preparation.



Different catalysts and conditions were screened (table 3-1). When $[Rh(PPh_3)_3]Cl$ and $[Rh(cod)_2]BF_4$ were employed, either no reaction or a complex mixture was observed. $[Rh(CO)_2Cl]_2$ provided 20% NMR yield when running the reaction in DCE (entry 6). When reaction was run under 1 atm of CO, significant amount of [5+1] product was observed (entry 9). The yield could be improved to 42% in toluene, which could be further improved at a higher temperature. Under optimized condition, 74% isolated yield could be achieved when reaction was run at 140 ^oC in toluene (entry 11).

Table 3-1. Catalyst and Condition Optimization.[a]



Entry	Catalyst	Solvent	Temperature(^oC)	Yield[b]

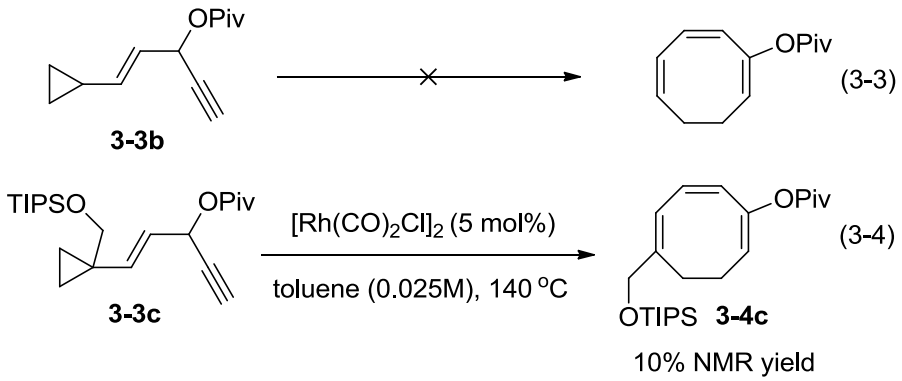
1	$[Rh(PPh_3)_3Cl$	CF_3CH_2OH	90	complex
2	$[Rh(PPh_3)_3Cl$	toluene	90	complex
3	$[Rh(PPh_3)_3Cl$, $AgSbF_6$(5%)	toluene	90	no reaction
4	$[Rh(cod)_2]BF_4$	CH_2ClCH_2Cl	90	No reaction
5	$[Rh(cod)_2]BF_4$	toluene	90	complex
6	$[Rh(CO)_2Cl]_2$	CH_2ClCH_2Cl	60	20%
7	$[Rh(CO)_2Cl]_2$	toluene	60	42%
8	$[Rh(CO)_2Cl]_2$	toluene	90	51%
9[c]	$[Rh(CO)_2Cl]_2$, CO (1 atm)	toluene	90	33%
10	$[Rh(CO)_2Cl]_2$	toluene	110	66%
11	$[Rh(CO)_2Cl]_2$	toluene	140	74%[d]
12	$[Rh(CO)_2Cl]_2$, $P(C_6F_5)_3$ (10%)	toluene	110	47%
13	$[Rh(CO)_2Cl]_2$	dioxane	110	45%
14	$PdCl_2$	MeCN	60	0%

[a] Condition: catalyst (5%), concentration (0.025M). [b] NMR yield. [c] significant amount of [5+1] product was observed.[d] isolated yield.

3.2.2 Investigation of the Substrate Scope

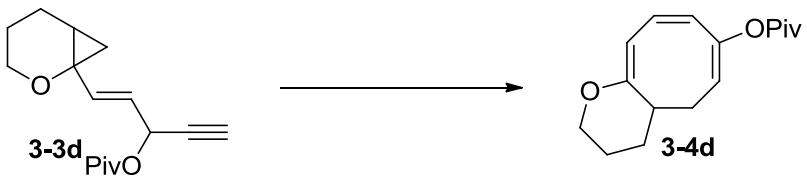
For the substrate without any activation group on the cyclopropane, no desired eight-membered ring product was observed under various conditions (eq 3-3). According to the

calculation results from Houk and Wender, the substitution on cyclopropyl position could enhance the reactivity of cyclopropane ring cleavage due to both conformation and electronic effect.[8] So we decided to investigate whether alkyl substituent on the cyclopropane would help the reaction (eq 3-4). Eight-membered ring product was indeed observed, however the reaction was messy and the yield was low. The result indicates that alkoxy substituent is much more effective than the alkyl substituent, presumably due to the conjugation between oxygen and forming double bond in the transition state.



Since oxygen substituent is necessary for the reaction, we synthesized bicyclic substrate to investigate the scope of the reaction (table 3-2).[9] After extensive optimizations, , only 30% yield of desired bicyclic product could be achieved.

Table 3-2. Catalyst and Condition Optimization.[a]



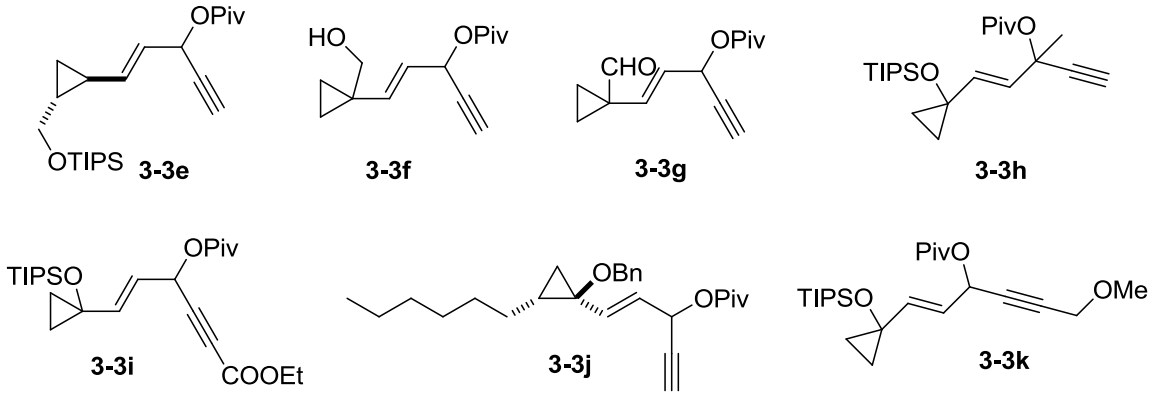
Entry	Catalyst	Solvent	Temperature(°C)	Yield[b]

1[c]	$[Rh(CO)_2Cl]_2$	Toluene	60	15%
2	$[Rh(CO)_2Cl]_2$	Toluene	110	30%
3	$[Rh(CO)_2Cl]_2$	Toluene	140	30%
4[d]	$[Rh(CO)_2Cl]_2$	Toluene	140	28%
5	$[Rh(CO)_2Cl]_2$	xylene	140	28%
6	$[Rh(CO)_2Cl]_2$	dioxane	140	15%
7	$[Rh(CO)_2Cl]_2$	benzene	140	20%
8	$[Rh(CO)_2Cl]_2$	CH_2ClCH_2Cl	140	10%
9	$[Rh(CO)_2Cl]_2$, dppp(5%)	toluene	110	No reaction
10[e]	$[Rh(CO)_2Cl]_2$, $P(C_6H_4CF_3)_3$	toluene	110	No reaction
11	$IrClCO(PPh_3)_2$	toluene	110	No reaction

[a] Condition: catalyst (5%), concentration (0.025M), 20 min. [b] NMR yield. [c] significant amount of [5+1] product was observed.[d] catalyst (2%). [e] starting material decomposes after 4h.

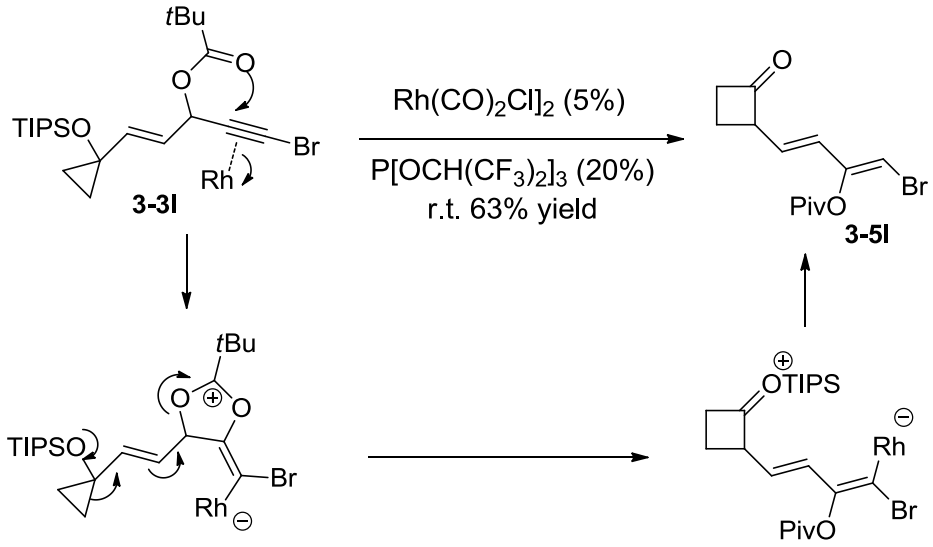
Other substrates were found unsuccessful for this reaction (scheme 3-4).

Scheme 3-4. Unsuccessful Substrates.



When the terminal position of alkyne was substituted by a bromine, a novel cyclobutanone product was obtained in a 63% yield (scheme 3-5). We propose that after an initial 5-exo-dig attack, the reaction undergoes a ring expansion to form the cyclobutanone structure.

Scheme 3-5. Formation of Cyclobutanone.

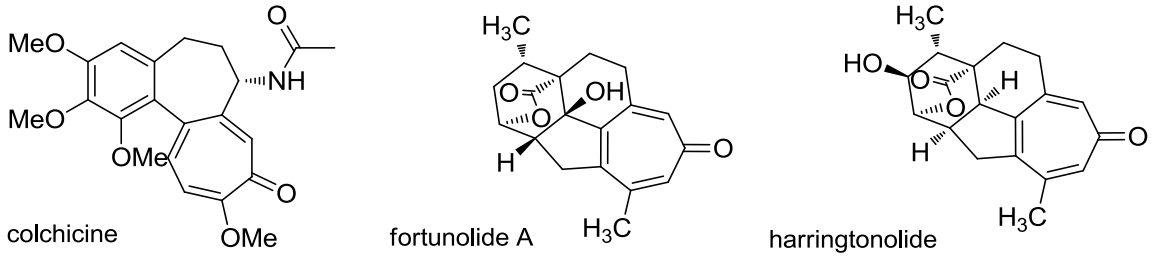


3.3 Rhodium-catalyzed [5+2] Cycloadditions

3.3.1 Introduction

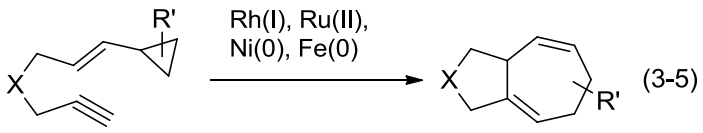
Six and seven-membered rings are common structure motifs in natural products (Scheme 3-6). There are three types of two-component cycloadditions exist for the synthesis of seven-membered rings: [4 + 3],[10-12] [5 + 2],[13] and [6 + 1][14] cycloadditions. Since diverse two-carbon (2C) alkenes, alkynes, and allenes are readily available, it would be highly desirable to discover new five-carbon (5C) synthons for the development of novel cycloaddition reactions that can lead to functionalized seven-membered rings.

Scheme 3-6. Selected Natural Products with Seven-membered Rings.



Among the various cycloaddition reactions developed for seven-membered ring formation, transition metal catalyzed [5+2] cycloadditions are one of the most powerful ways to construct the seven-membered ring. It has been realized using different transition metal catalysts for the [5 + 2] cycloaddition of vinylcyclopropanes (VCPs) and alkynes (eq 3-5) in the research groups of Wender,[15] Trost,[16] Louie,[17]

Fürstner,[18] Yu,[19,20] and Murai.[21,22-26] The intramolecular [5 + 2] cycloaddition of VCPs and alkynes has been applied to the synthesis of several natural products.[27-36] It has been extensively investigated by Houk, Wender, and Yu[37-41] regarding the mechanism of this novel cycloaddition. Stryker[42-44] and Tanino[45] discovered other 5C synthons for [5 + 2] cycloadditions by employing stoichiometric amount of cobalt.



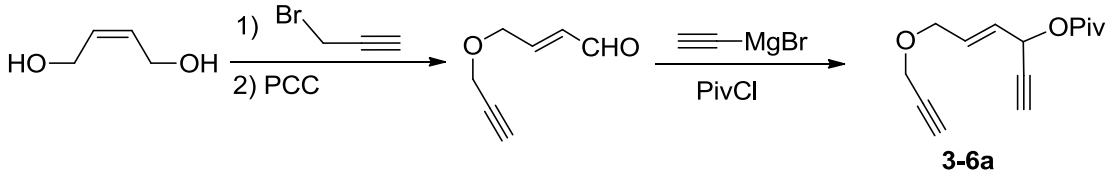
(3-5)

As 5C synthons, ACEs have been used for the synthesis of five- and six-membered rings in transition-metal-catalyzed reactions (eq 3-1, eq 3-2, and scheme3-1). We anticipated that ACE could also be utilized for a [5+2] cycloaddition.

3.3.2 Intramolecular [5+2] Cycloaddition

In an effort to use ACE as a 5C component for [5+2] cycloaddition, Dr. Shu in our gruop synthesized substrate **3-6a** via a four step process(scheme 3-7).

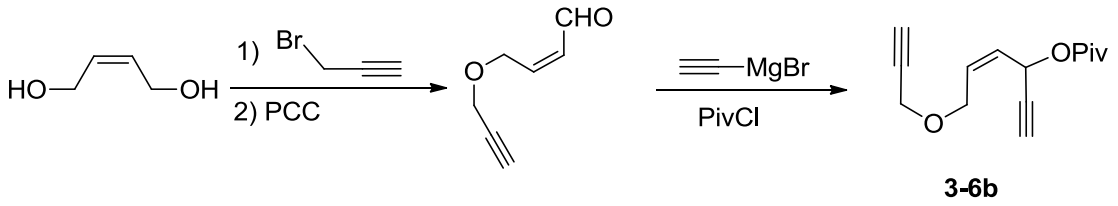
Scheme 3-7. Synthetic Route for Substrate 3-6a.



3-6a

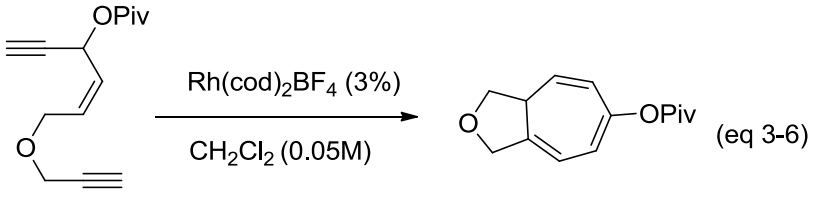
Various rhodium catalysts as well as other π-acidic metals were examined by Dr. Shu for the intramolecular [5+2] cycloaddition. He found that the reaction could be catalyzed by cationic Rh(I) complex at room temperature.

Scheme 3-8. Synthetic Route for Substrate 3-6b.



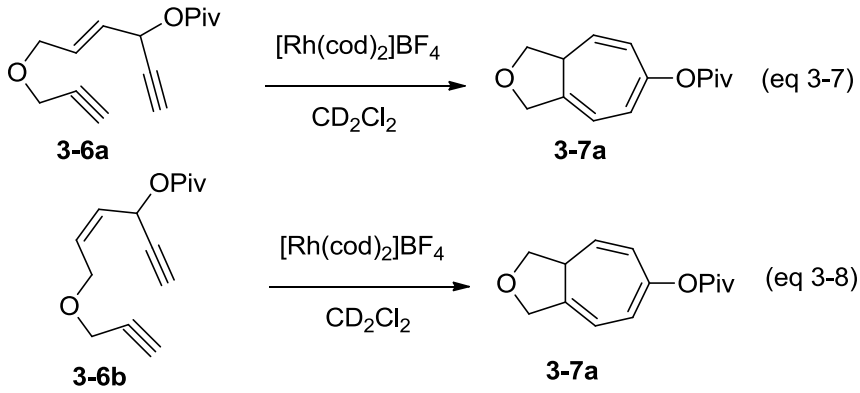
3-6b

I synthesized substrate 3-6b following a similar four-step procedure (scheme 3-8). Based on literature, there is often a dramatic difference between cis and trans substrate.[4,5] We tested this cis substrate with the optimized condition. We were pleased to find that same product was isolated in a similar yield (eq 3-6).



3-6b **3-7a** (eq 3-6)

We further investigated the kinetics of the [5+2] cycloaddition from both trans **3-6a** and cis **3-6b**. We found that same rate was observed for these two reactions under the detection by NMR. No double bond isomerization was observed during the reaction. We are currently collaborating with Houk's group to study the mechanism of this reaction.

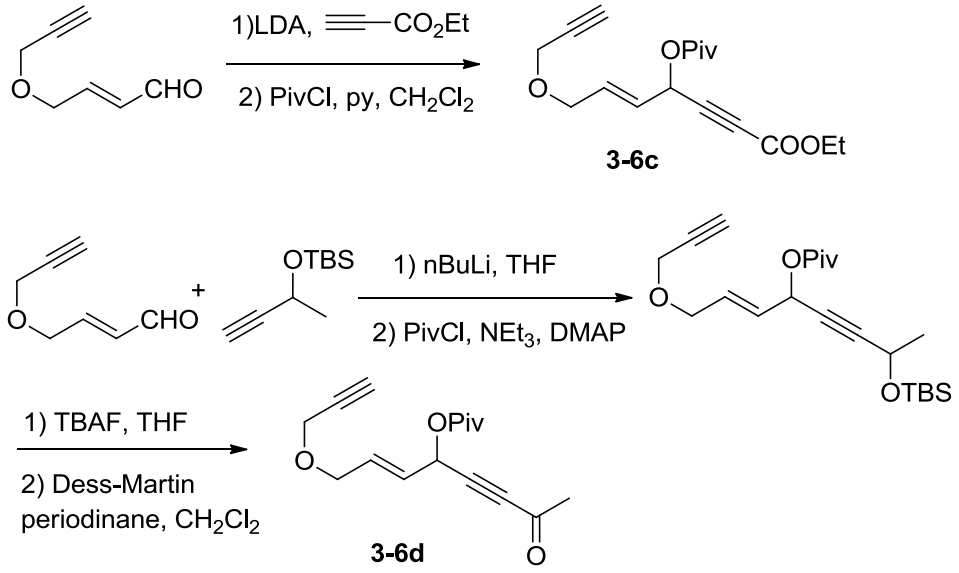


3-6a **3-7a** (eq 3-7)

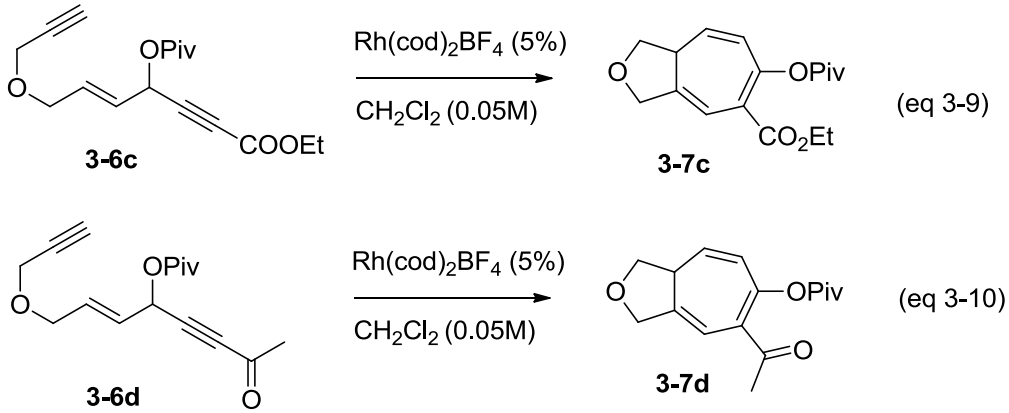
3-6b **3-7a** (eq 3-8)

Electron-withdrawing esters have been reported to facilitate the 1,2-acyloxy migration of propargyl esters. Following synthetic procedures described in scheme 3-9, I synthesized substrate **3-6c** and **3-6d**.

Scheme 3-9. Synthetic Route for Substrate 3-6c and 3-6d.

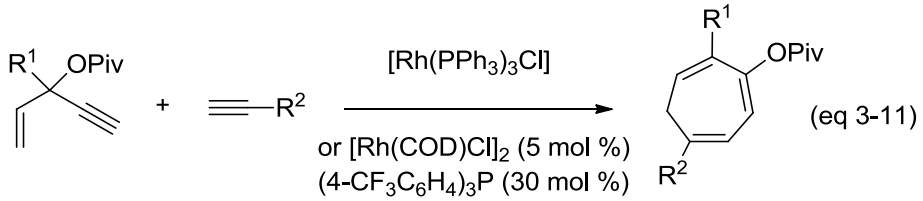


Indeed, I obtained good yield of bicyclic product **3-7c** from ACE **3-6c** with an ester group at the terminal position of the alkyne upon treatment with the cationic Rh(I) catalyst (eq 3-9). Other electron-withdrawing group such as ketone also afforded desired [5+2] cycloaddition product in moderate to good yield (eq 3-10).



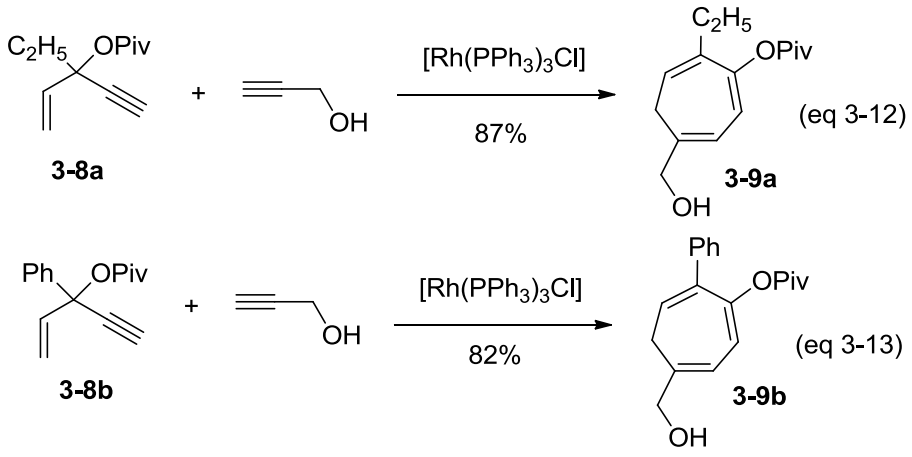
3.3.3 Intermolecular [5+2] Cycloaddition

Dr. Shu also investigated the potential of ACE as a 5C component in the intermolecular [5+2] cycloaddition. He found that by using either Wilkinson's catalyst $Rh(PPh_3)_3Cl$ or a combination of $[Rh(COD)Cl]_2$ and $(4\text{-}CF_3C_6H_4)_3P$, good yields of seven-membered ring product could be observed (eq 3-11).



(eq 3-11)

During the study of the scope of the 5C synthon, I prepared substrates 3-8a and 3-8b with a substituent at the 3-positionI found that good yield and excellent regioselectivity could be achieved (eq 3-12 and eq 3-13).

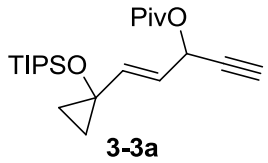


(eq 3-12)

(eq 3-13)

3.4 Experimental Section

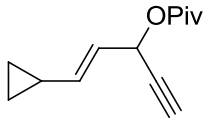
All reactions in non-aqueous media were conducted under a positive pressure of dry argon in glassware that had been oven dried prior to use unless noted otherwise. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Thin layer chromatography was performed using precoated silica gel plates (EMD Chemical Inc. 60, F254). Flash column chromatography was performed with silica gel (Silicycle, 40-63 μm). Infrared spectra (IR) were obtained on a Bruker Equinox 55 Spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Varian Unity-Inova 400 MHz or 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in $CDCl_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint),or multiplet (m), with coupling constants (*J*) in hertz. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer. The optical rotation was determined using a Perkin–Elmer 241 Polarimeter.



3-3a

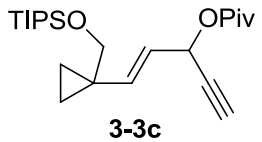
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.80 (m, 2H), 1.03-1.13 (m, 21H), 1.21 (s, 9H), 2.51 (d, *J* = 2.0 Hz, 1H), 5.77 (m, 2H), 5.87 (dd, *J* = 4.5, 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 13.0, 17.02, 17.04, 18.4, 27.1, 38.9, 56.3, 63.6, 74.7, 80.0, 121.4,

141.1, 177.3. IR (film): ν 2944, 2867, 1731, 1463, 1275, 1141, 1041, 908, 881, 674 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{22}H_{38}NaO_3Si$ $(M+Na)^+$ 401.2482, found 401.2471.



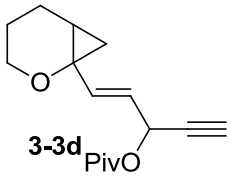
3-3b

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.42 (m, 2H), 0.75 (m, 2H), 1.19 (s, 9H), 1.41 (m, 1H), 2.49 (d, *J* = 2.0 Hz, 1H), 5.46 (dd, *J* = 15.2, 8.8 Hz, 1H), 5.58 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.77 (dd, *J* = 6.4, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.26, 7.27, 27.1, 38.8, 63.9, 74.5, 80.3, 122.2, 140.6, 177.3.



3-3c

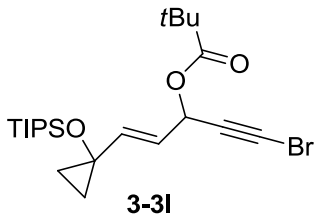
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.60 (m, 2H), 0.80 (m, 2H), 1.05 (m, 21H), 1.20 (s, 9H), 2.50 (d, *J* = 2.4 Hz,1H), 3.73 (s, 2H), 5.54 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.81 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 12.00, 12.03, 12.20, 18.3, 23.6, 26.7, 27.2, 38.8, 64.2, 66.7, 74.6, 80.3, 121.5, 140.3, 177.4.



3-3d

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.92 (m, 2H), 1.20 (m, 1H), 1.22 (s, 9H), 1.47 (m, 2H), 1.95 (m, 2H), 2.52 (d, *J* = 2.0 Hz, 1H), 3.28 (m, 2H), 3.68 (m, 2H), 5.55 (m, 1H),

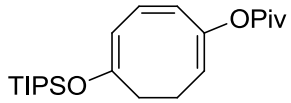
5.82 (m, 1H), 5.90 (m, 1H) . ^{13}C NMR (125 MHz, $CDCl_3$): δ 1.1, 20.01, 20.08, 20.16, 21.6, 27.1, 38.8, 59.10, 59.14, 63.5, 63.6, 64.5, 74.5, 74.7, 80.0, 80.3, 120.6, 120.8, 139.3, 139.5, 177.3, 177.4. IR (film): ν 2969, 2933, 2861, 1729, 1479, 1272, 1141, 1075, 956, 910, 800, 732 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{16}H_{22}NaO_3$ $(M+Na)^+$ 285.1461, found 285.1464.



3-3l

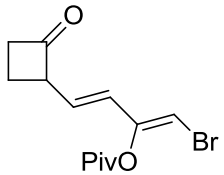
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 0.80 (m, 2H), 1.03-1.13 (m, 23H), 1.19 (s, 9H), 5.74 (m, 2H), 5.87 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 17.11, 17.16, 18.4, 27.2, 39.0, 47.2, 56.4, 64.5, 76.5, 121.4, 141.1, 177.3. IR (film): ν 2944, 2867, 1734, 1478, 1463, 1305, 1274, 1141, 1043, 882 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{22}H_{37}BrNaO_3Si$ $(M+Na)^+$ 479.1586, found 479.1588.

General Procedure for the rhodium catalyzed 8 member ring formation. To an oven-dried flask was added $[Rh(CO)_2Cl]_2$ (0.005mmol) and anhydrous toluene (2.5 ml), substrate (0.1 mmol) was added and the oil bath was heated to 140 ^{o}C. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and the residue was further purified by flash chromatography.



3-4a

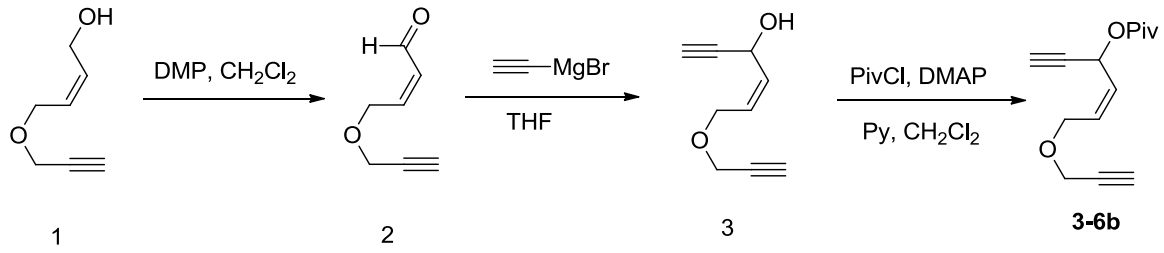
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.09 (m, 18H), 1.21 (m, 3H), 1.23 (s, 9H), 2.38 (m, 2H), 2.58 (dd, *J* = 14.0, 5.2 Hz, 2H), 5.26 (d, *J* = 5.6 Hz, 1H), 5.36 (d, *J* = 12.0 Hz, 1H), 5.52 (t, *J* = 5.2 Hz, 1H), 5.96 (dd, *J* = 12.0, 5.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9, 18.1, 18.2, 27.3, 27.7, 31.7, 38.9, 105.0, 120.2, 121.0, 129.6, 145.0, 160.7, 177.7. IR (film): ν 2961, 2867, 1743, 1641, 1462, 1266, 1165, 1130, 1046, 881, 699 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{22}H_{38}NaO_3Si$ $(M+Na)^+$ 401.2482, found 401.2462.



3-5l

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.37 (s, 9H), 1.93 (m, 1H), 2.34 (qd, *J* = 10.5, 5.5 Hz, 1H), 2.98 (dddd, *J* = 17.5, 10.0, 5.0, 2.5 Hz, 1H), 3.12 (m, 1H), 4.01 (m, 1H), 5.75 (dd, *J* = 15.5, 6.0 Hz, 1H), 6.13 (dd, *J* = 15.5, 2.0 Hz, 1H), 6.14 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 27.5, 39.7, 45.3, 62.2, 100.0, 110.0, 124.3, 125.8, 149.2, 174.5, 206.8. IR (film): ν 2973, 1781, 1755, 1479, 1265, 1106, 912, 732 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{13}H_{17}BrNaO_3$ $(M+Na)^+$ 323.0253, found 323.0249.

Substrate **3-6b** was synthesized through the following steps.

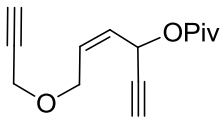


1 2 3 **3-6b**

Aldehyde (2). Alcohol 1 (252 mg, 2 mmol) was dissolved in 10 ml dichloromethane, and DMP (1.27g, 3 mmol) was added. The reaction was stirred under Argon protection for 2h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The solution was dried over magnesium sulfate. The solvent was evaporated and the residue was purified by chromatography (Hexane/Ethyl acetate=25:1, Rf=0.4 in Hexane/Ethyl acetate=4:1) to provide 105 mg (42%) colorless oil.

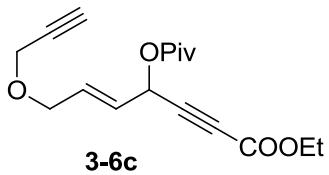
Alcohol (3). Aldehyde 2 (248 mg, 2 mmol) was dissolved in 2 ml anhydrous THF in an oven dried flask and the solution was cooled to -78 ^{o}C. Ethynyl magnesium bromide THF solution (8 ml, 4 mmol) was added dropwise and the solution was warmed to room temperature. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The solution was dried over magnesium sulfate. The solvent was evaporated and the residue was purified by chromatography (Hexane/Ethyl acetate=10:1) to provide 265 mg (88%) colorless oil.

Ester (4). Alcohol 3 (80 mg, 0.53 mmol) and DMAP (12mg, 0.2 mmol) was dissolved in anhydrous dichloromethane. Pivaloyl chloride (0.1 ml, 0.75 mmol) and pyridine (0.1 ml, 1.15 mmol) was added and the solution was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography (Hexane/Ethyl acetate=50:1) to provide 115 mg (93%) colorless oil.



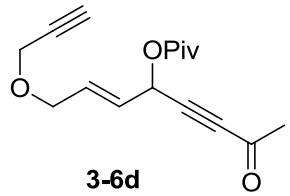
3-6b

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.26 (s, 9H), 2.50 (t, *J* = 2.5 Hz, 1H), 2.55 (d, *J* = 2.5 Hz, 1H), 4.20 (d, *J* = 2.5 Hz, 2H), 4.31 (m, 2H), 5.74 (m, 1H), 5.81 (m, 1H), 6.11 (dd, *J* = 9.0, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.1, 38.9, 57.7, 59.7, 65.4, 74.2, 75.0, 79.5, 80.2, 128.1, 130.8, 177.1. IR (film): ν 3295, 2974, 1729, 1479, 1273, 1140, 1086, 1031, 978, 929, 769 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{19}H_{24}NaO_2$ $(M+Na)^+$ 257.1148, found 257.1161.



3-6c

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.23 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H), 2.45 (t, *J* = 2.4 Hz, 1H), 4.12 (dt, *J* = 5.2, 1.6 Hz, 2H), 4.17 (t, *J* = 2.4 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 5.82 (ddt, *J* = 15.2, 6.0, 1.6 Hz, 1H), 5.98 (dq, *J* = 6.0, 1.2 Hz, 1H), 6.07 (dtd, *J* = 15.2, 5.2, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 27.2, 39.0, 57.8, 62.5, 62.7, 68.8, 75.1, 78.0, 79.5, 82.1, 125.8, 131.9, 153.1, 177.0. IR (film): ν 2981, 2916, 2249, 1714, 1249, 1135, 1030, 961, 910, 731 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{17}H_{22}NaO_5$ $(M+Na)^+$ 329.1359, found 329.1367.

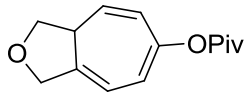


3-6d

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.23 (s, 9H), 2.36 (s, 3H), 2.47 (t, *J* = 2.5 Hz, 1H), 4.13 (m, 2H), 4.17 (d, *J* = 2.5 Hz, 2H), 5.83 (m, 1H), 6.00 (m, 1H), 6.06 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.2, 32.9, 39.1, 57.9, 62.9, 68.9, 75.1, 79.5, 85.2, 86.3, 125.9, 131.9, 177.1, 183.9. IR (film): ν 2974, 2216, 1734, 1681, 1479, 1360, 1271, 1223, 1135, 1031, 956, 936 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{16}H_{20}NaO_4$ $(M+Na)^+$ 299.1354, found 299.1364.

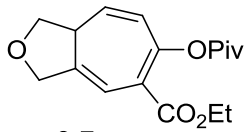
General procedures for the Rh-catalyzed cycloaddition: To a solution of $[Rh(COD)_2]BF_4$ (2.5 mg, 3 mol %) in CH_2Cl_2 (0.05 M) was added propargylic ester (0.2

mmol). The solution was stirred at room temperature until the reaction was complete as determined by TLC analysis. The solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding cycloheptatriene.



3-7a

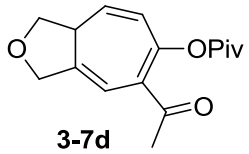
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (s, 9 H), 2.67-2.69 (m, 1 H), 4.09 (dd, *J* = 4.8, 9.2 Hz, 1 H), 4.29 (dd, *J* = 7.2, 9.2 Hz, 1 H), 4.41 (d, *J* = 14.4 Hz, 1 H), 4.47 (d, *J* = 14.4 Hz, 1 H), 5.22 (dd, *J* = 4.4, 9.6 Hz, 1 H), 5.91 (d, *J* = 9.6 Hz, 1 H), 6.06-6.09 (m, 1 H), 6.32 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.3, 39.1, 43.2, 71.0, 74.7, 112.3, 120.1, 123.7, 125.7, 139.5, 150.6, 177.7. IR (film): ν 912, 1124, 1277, 1480, 1742, 2872, 2972 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{14}H_{18}O_3$ $(M+Na)^+$ 257.1148, found 257.1145.



3-7c

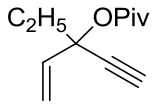
Yield: 72%, 44 mg, oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.31 (s, 9H), 1.32 (t, *J* = 7.5 Hz, 3H), 2.66 (m, 1H), 4.18 (m, 3H), 4.31 (qd, *J* = 7.0, 11.0 Hz, 1H), 4.46 (t, *J* = 1.5 Hz, 2H), 5.50 (dd, *J* = 4.5, 10.0 Hz, 1H), 5.89 (qd, *J* = 2.0, 10.0 Hz, 1H), 6.51 (q, *J* =

1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 27.3, 39.2, 42.8, 61.4, 70.8, 74.4, 112.4, 123.9, 124.8, 131.6, 140.5, 152.1, 166.2, 176.8. IR (film): ν 2976, 1750, 1721, 1479, 1395, 1366, 1256, 1226, 1163, 1131, 1103, 1035, 924, 861, 730 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{17}H_{22}NaO_5$ $(M+Na)^+$ 329.1359, found 329.1368.



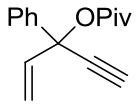
3-7d

Yield: 60%, 33 mg, oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.31 (s, 9H), 2.38 (s, 3H), 2.66 (m, 1H), 4.15 (dd, *J* = 9.0, 3.5 Hz, 1H), 4.23 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.45 (t, *J* = 2.0 Hz, 2H), 5.49 (dd, *J* = 10.0, 5.0 Hz, 1H), 5.85 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.42 (q, *J* = 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.2, 30.9, 39.3, 42.9, 70.8, 74.4, 111.8, 123.7, 131.0, 132.6, 140.7, 150.6, 176.9, 200.4. IR (film): ν 2975, 1747, 1690, 1479, 1396, 1355, 1265, 1101, 1026, 909, 728 cm^{-1}. For $C_{16}H_{20}NaO_4$ $(M+Na)^+$ 299.1354, found 299.1362.



3-8a

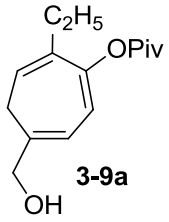
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 9H), 1.85 (m,1H), 1.99 (m, 1H), 2.65 (s, 1H), 5.27 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.56 (dd, *J* = 16.4, 0.2 Hz, 1H), 5.83 (dd, *J* = 16.4, 10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.3, 27.2, 34.3, 39.3, 75.5, 77.6, 81.3, 116.5, 137.7, 176.4. IR (film): ν 3286, 2976, 2360, 1740, 1479, 1278, 1152, 936 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{12}H_{18}NaO_2$ $(M+Na)^+$ 217.1199, found 217.1210.



3-8b

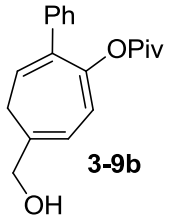
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.24 (s, 9H), 2.90 (s, 1H), 5.26 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.58 (dd, *J* = 16.8, 0.2 Hz, 1H), 6.05 (dd, *J* = 16.8, 10.4 Hz, 1H), 7.32 (m, 1H), 7.35 (m, 2H), 7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2, 39.4, 77.7, 77.8, 80.8, 115.5, 125.8, 128.3, 128.6, 138.8, 140.5, 175.7. IR (film): ν 3284, 2973, 1742, 1277, 1132, 979, 934, 762, 696 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{16}H_{18}NaO_2$ $(M+Na)^+$ 265.1199, found 265.1204.

General Procedure for Intermolecular [5+2] Cycloaddition: To a solution of Rh(PPh3)3Cl catalyst (18.5 mg, 10 mol %) in $CHCl_3$ (1 mL) were added the ACE (0.2 mmol) and alkyne (0.4 mmol). The reaction mixture was allowed to stir at 65 ℃ under argon until the reaction was complete, as determined by TLC analysis. After the solvent was removed under reduced pressure, the residue was purified by chromatography on silica gel to afford the corresponding product.



3-9a

2,2-Dimethyl-propionic acid 7-ethyl-4-hydroxymethyl-cyclohepta-1,3,6-trienyl ester. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.31 (s, 9H), 1.85 (b,1H), 2.10 (q, *J* = 7.2 Hz, 2H), 2.43 (d, *J* = 7.2 Hz, 2H), 4.24 (s, 2H), 5.28 (t, *J* = 7.2 Hz, 1H), 6.06 (dt, *J* = 6.4, 1.2 Hz, 1H), 6.22 (d, *J* = 6.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 25.0, 27.3, 29.0, 39.1, 66.1, 118.3, 119.2, 119.8, 136.9, 137.8, 151.7, 177.4. IR (film): ν 3361, 2967, 1745, 1278, 1125, 912 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{15}H_{22}NaO_3$ $(M+Na)^+$ 273.1461, found 273.1473.



3-9b

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.89 (s, 9H), 1.68 (b, 1H), 2.63 (d, *J* = 7.6 Hz, 2H), 4.28 (s, 2H), 5.54 (t, *J* = 7.6 Hz, 1H), 6.19 (dt, *J* = 6.4, 1.2 Hz, 1H), 6.48 (d, *J* = 6.4 Hz, 1H), 7.20-7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 29.5, 38.7, 66.1, 118.6, 121.1, 122.2, 127.6, 128.1, 129.4, 137.8, 138.0, 138.4, 150.3, 176.9. IR (film): ν 3356, 2966, 1744, 1278, 1130, 1013, 765, 731, 698 cm^{-1}. HRMS (ESI) *m/z* calcd. For $C_{19}H_{22}NaO_3$ $(M+Na)^+$ 321.1461, found 321.1468.

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Chapter 4

Rhodium and Platinum-catalyzed Tandem Indole Annulation and [4+3] Cycloadditions

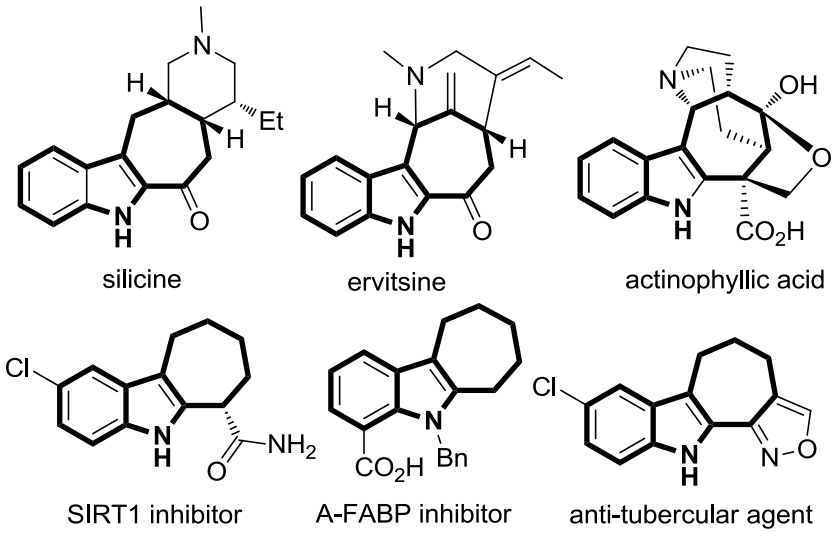
This work has been published under the following:

Shu, D.; Song, W.; Li, X.; Tang, W. *Angew.Chem.Int.Ed*. **2013**, *11*, 3237.

4.1 Introduction

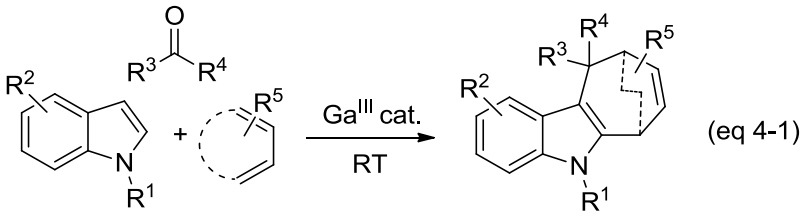
Indole fused seven-membered rings, cyclohepta[*b*]indoles, are present in many bioactive natural products such as ervitsine,[1]silicine,[2] and actinophyllic acid (Figure 4-1).[3,4] They are also important structural motifs in numerous pharmaceutical agents with different pharmacological properties such as inhibition of adipocyte fatty-acid binding protein (A-FABP),[5]inhibition of deacetylase SIRT1,[6] and anti-tubercular activity.[7]

Figure 4-1. Representative Indole Alkaloids with a Fused Seven-membered Ring.



Due to the importance of cyclohepta[*b*]indoles structure, many efforts have been devoted to develop efficient ways to access this structure. [8-10] Traditional ways to access cyclohepta[*b*]indoles have focused on building the seven-membered ring from a pre-existing indole ring.[5,6,11-17] In 2012, Wu reported an elegant three-component [4 + 3] cycloaddition for the synthesis of cyclohepta[*b*]indoles from indoles, aldehydes

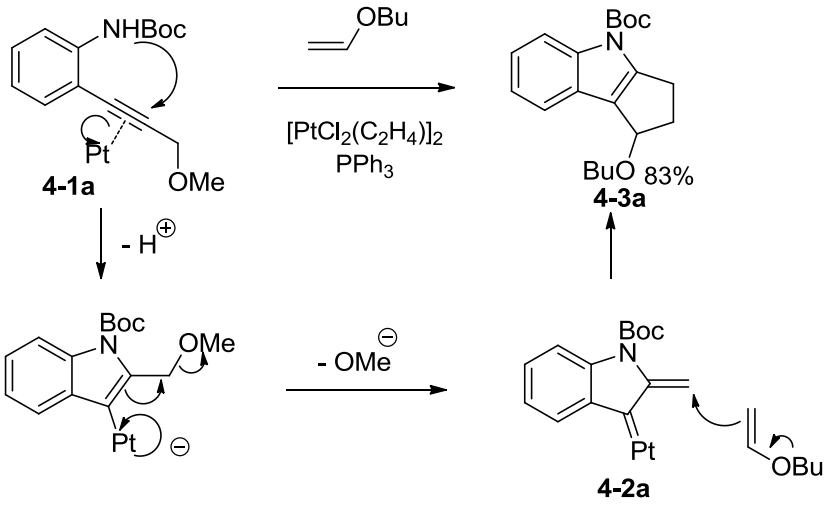
and dienes.[18] It represents the first example of a [4 + 3] cycloadditions where indole is the 2π component (eq 4-1).



(eq 4-1)

In 2011, Iwasawa reported a novel way to generate vinyl platinum carbene from propargylic ether derivatives (scheme 4-1).[19] The vinyl platinum carbene could then be trapped by electron rich olefins to undergo a [3+2] cycloaddition to form indole fused five-membered ring structures.

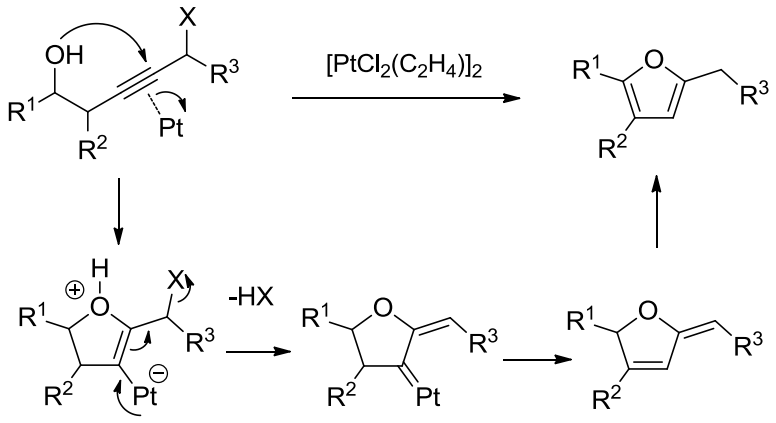
Scheme 4-1. Platinum-catalyzed [3+2] Cycloaddition.



At the same year, Ferreira reported a similar strategy to generate vinyl platinum carbene from a homopropargylic alcohol (scheme 4-2).[20] In their study, different leaving groups X were also investigated. They found OH and OMe were the best

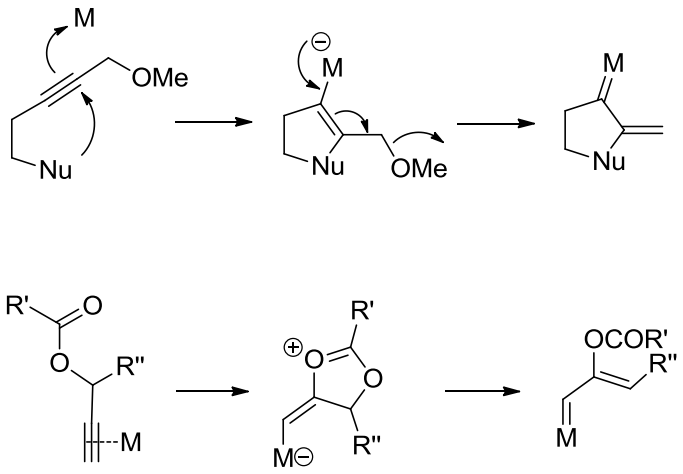
choices and provided highest yield, while Cl and OAc only provided trace amount of desired product.

Scheme 4-2. Platinum-catalyzed Furan Formation.



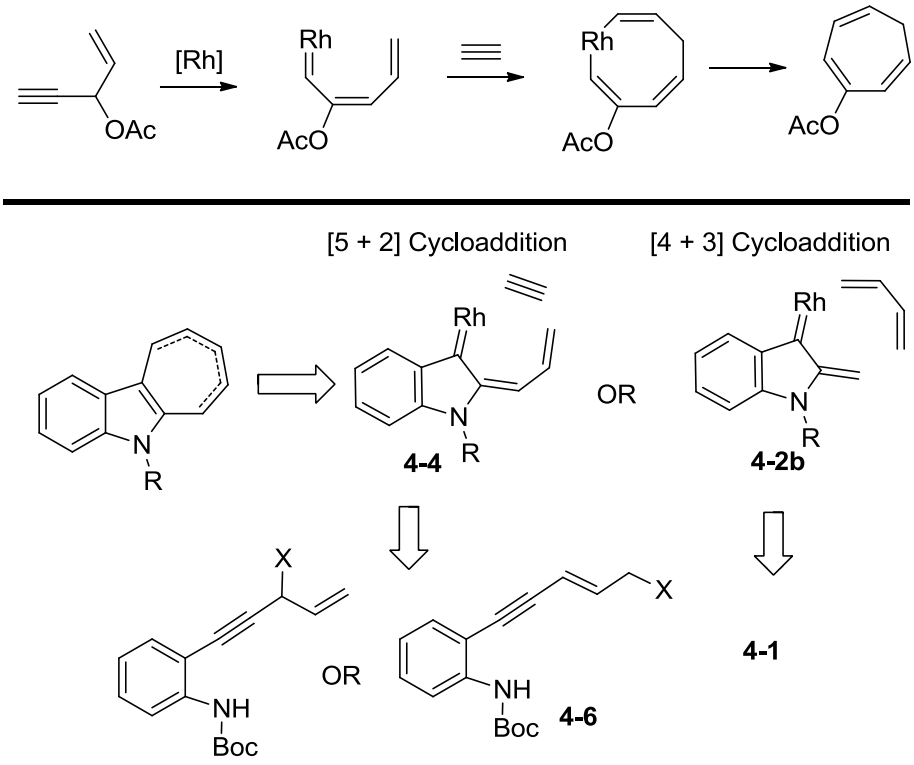
The strategy to separate nucleophile and leaving group provides a new way to generate vinyl metal carbene. We envisioned that since similar vinyl metal carbene will be formed from either propargylic ether or propargylic ester (scheme 4-3), we could also use this propargylic ether as a platform for the development of a new type of [5+2] cycloaddition. As shown in scheme 4-4, by simply attaching another double bond, the key six-membered metallacycle could potentially be formed.

Scheme 4-3. Vinyl Metal Carbene Formation from Propargylic Ether and Propargylic Ester.



Alternatively, we could also use a [4+3] strategy to access cyclohepta[*b*]indoles (scheme 4-4). It is well documented that vinyl metal carbenes generated from vinyl diazo compounds can react with dienes through a sequence of cyclopropanation/Cope rearrangement to undergo formal [4 + 3] cycloadditions.[21,22,23-26] Vinyl Fisher carbenes[27-34] or vinyl gold carbenes derived from 1,2-acyloxy migration of propargylic esters could also undergo formal [4 + 3] cycloadditions with dienes to form various seven-membered rings.[35-37]

Scheme 4-4. Proposed Cyclohepta[b]indoles Synthesis from [5+2] and [4+3] Cycloadditions.



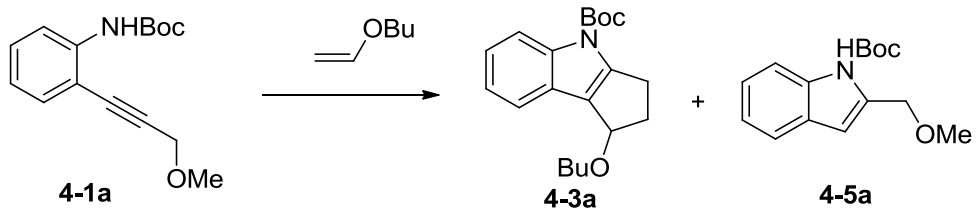
4.2 Rhodium and Platinum-catalyzed Indole Fused Seven-membered Ring Formation

4.2.1 Initial Effort on Rhodium-catalyzed [5+2] Cycloaddition

First of all, various rhodium catalysts were screened to see whether the reported [3+2] cycloaddition could be realized (table 4-1). To our surprise, platinum complex similar to the reported catalyst did not provide any desired product. It appeared that the ethylene ligand was necessary in Iwasawa's [3+2] cycloaddition. When $[Rh(CO)_2Cl]_2$ was employed, a complex mixture was observed. For most rhodium complexes, we observed complete substrate recovery. We were pleased to find that electron deficient phosphite ligand promoted the reaction. We isolated the [3+2] cycloaddition product in 58% yield, together with 15% yield of simple indole

annulation product. We also observed that electron deficient phosphine ligands, such as $P(C_6F_5)_3$ and $P[C_6H_3(CF_3)_2]_3$, also promoted the reaction. No reaction was observed when electron rich vinyl butyl ether was replaced by electron neutral alkenes or alkynes.

Table 4-1. Catalyst Screening for the [3+2] Cycloaddition.[a]



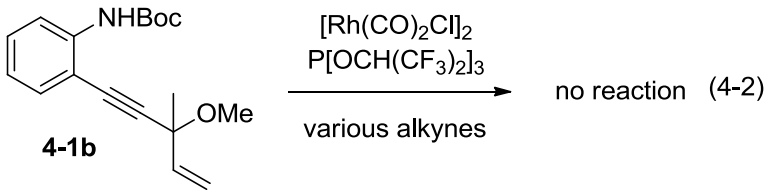
4-1a **4-3a** **4-5a**

Entry	Catalyst	Yield of **4-3a**
1	$Pt(PPh_3)_2Cl_2$	0[b]
2	$[Rh(CO)_2Cl]_2$	0[c]
3	$[Rh(cod)Cl]_2$	0[b]
4	$[Rh(CO)_2Cl]_2$, PPh_3	0[b]
5	$[Rh(CO)_2Cl]_2$, $P[OCH(CF_3)_2]_3$	58%[d]
6	$Rh(PPh_3)_3Cl$	0[b]

[a]Conditions: Catalyst (5 mol %), ligand (10%), dioxane (0.20 M), Na_2CO_3 (1.5 equiv), vinyl butyl ether (10 equiv), 100 ^oC, overnight. [b]substrate recovery. [c]complex mixture. [d]isolated yield, **4-5a** was obtained in 15% isolated yield.

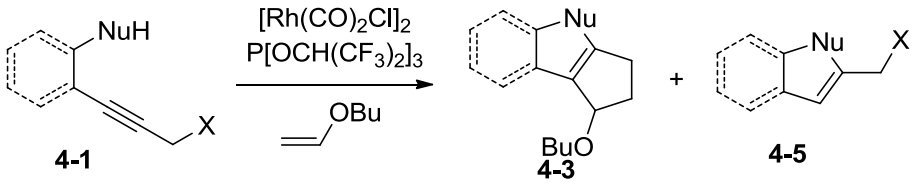
The result indicated that we could access vinyl rhodium carbene intermediate **4-2b**. With this result in hand, we moved on to investigate the [5+2] cycloaddition. First we synthesized substrate **4-1b** and tested it with the optimized conditions (eq 4-2). To our

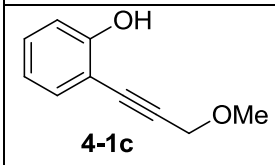
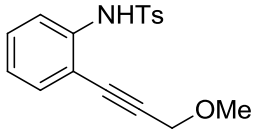
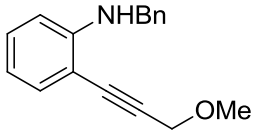
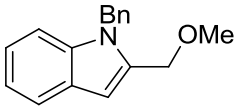
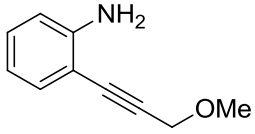
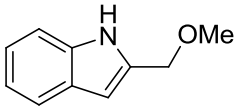
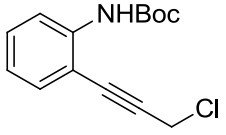
disappointment, no reaction was observed. We anticipated that the low reactivity may be due to the more steric hindrance of the tertiary ether in **4-1b** compared to the previous primary ether in **4-1a**.

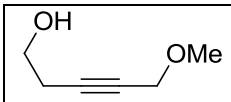
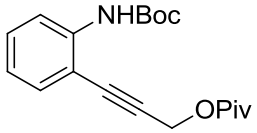


We envisioned that by adjusting the nucleophiles and leaving group in the substrate, it may provide us opportunity to overcome the steric hindrance. Substrates with different nucleophiles and leaving groups were synthesized and tested (Table 4-2). Substrates **4-1c** and **4-1d** with acidic protons on nitrogen completely inhibited the reaction, presumably due to the coordination between rhodium and nitrogen anions formed under basic condition. For substrates **4-1e** and **4-1f** with increased nucleophilicity, the reaction provided indole annulations products **4-5e** and **4-5f** in good yields. We reasoned that due to the increased aromaticity of the indole **4-5e** and **4-5f**, the rhodium intermediates underwent protonation instead of elimination. Replacing MeO with Cl led to complex reaction. We did not observe any reaction when free hydroxy group was utilized as the nucleophile. These results showed that Boc protected amine has the right nucleophilicity to undergo nucleophilic attack as well as right aromaticity for the following elimination.

Table 4-2. [3+2] Cycloaddition with Different Substrates.[a]



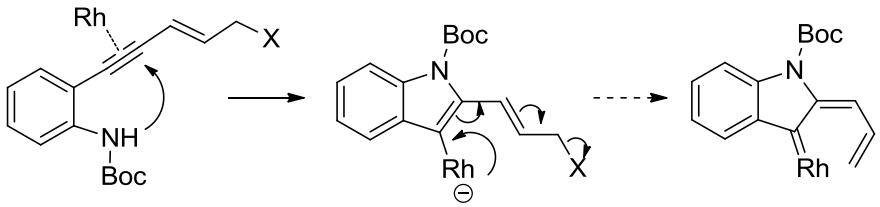
Substrate	Product	Yield[b]
 **4-1c**	–[c]	
 **4-1d**	–[c]	
 **4-1e**	 **4-5e**	90%
 **4-1f**	 **4-5f**	60%
 **4-1g**	–[d]	

 **4-1h**	–[c]	
 **4-1i**	–[d]	

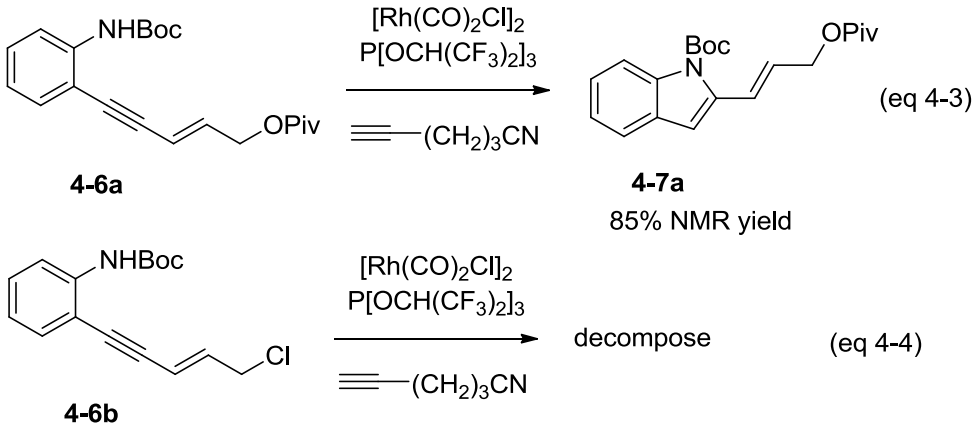
[a]Conditions: Catalyst (5 mol %), ligand (10%), dioxane (0.20 M), Na_2CO_3 (1 equiv), vinyl butyl ether (10 equiv), 100 ^{o}C, overnight. [b]NMR yield. [c]substrate recovery. [d]complex mixture.

Without any success in adjusting nucleophiles and leaving groups, we switched to another strategy by inserting an additional double bond between leaving group and alkyne (scheme 4-5). In principle, similar six-membered metallacycle could be formed.

Scheme 4-5. Six-membered Metallacycle Formation from Vinylogous Propargylic Ether.



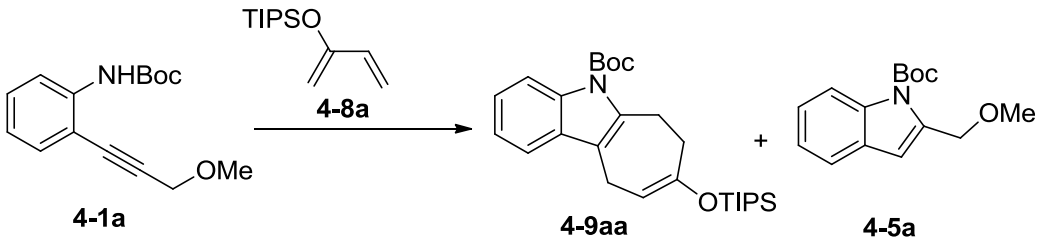
To test this hypothesis, substrates **4-6a** and **4-6b** were synthesized (eq 4-3 and eq 4-4). Under the optimized condition, **4-6a** provided only the simple indole annulation product in good yield; presumably the elimination step is slowed down the additional double bond. On the other hand, substrate **4-6b** with a better leaving group, led to a complex mixture.



4.2.2 Optimization of Catalyst and Conditions for [4+3] Cycloadditions

Initial optimization of [4+3] cycloaddition was focused on reaction between propargylic ether **4-1a** and diene **4-8a**.Three categories of catalysts were screened: rhodium, platinum and other π-acidic metals.

Table 4-3. Rhodium-catalyzed [4+3] Cycloaddition between Propargylic Ether 4-1a and Diene 4-8a.[a]



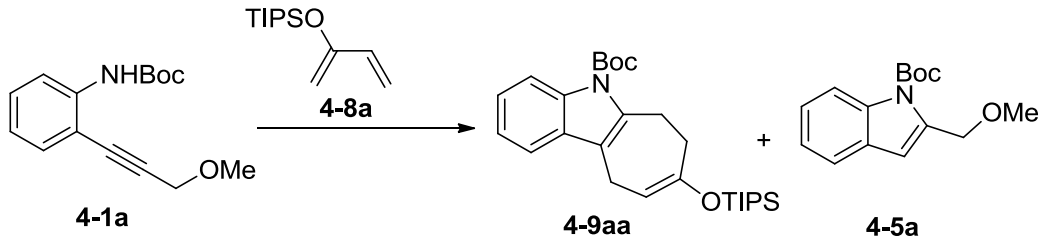
Entry	Catalyst	Yield[b]
1	$[Rh(CO)_2Cl]_2$, $P[OCH(CF_3)_2]_3$	66%[c]
2[d]	$[Rh(CO)_2Cl]_2$, $P[OCH(CF_3)_2]_3$	56%
3[e]	$[Rh(CO)_2Cl]_2$, $P[OCH(CF_3)_2]_3$	28%
4	$[Rh(CO)_2Cl]_2$, $P(C_6F_5)_3$	45%

5	$[Rh(CO)_2Cl]_2$, $P[3,5\text{-}(C_6H_3(CF_3)_2]_3$	38%
6	$[Rh(cod)Cl]_2$, $P[OCH(CF_3)_2]_3$	20%
7[f]	$[Rh(CO)_2Cl]_2$, $P[OCH(CF_3)_2]_3$	0%

[a]Conditions: Catalyst (10 mol %), ligand (20%), dioxane (0.20 M), Na_2CO_3 (1 equiv), diene **4-8a** (2 equiv), 100 °C, overnight. [b]NMR yield. [c]**4-5a** was observed. [d]120 °C. [e]80 °C, 14% substrate recovery. [f]Na_2CO_3 was replaced by DBU, NEt_3 or proton sponge.

We were pleased to find that the $[Rh(CO)_2Cl]_2$ and $P[OCH(CF_3)_2]_3$ combination provided desired product in 66% NMR yield (entry 1, table 4-3). Increased temperature led to lower yield and lower temperature led to incomplete conversion. Electron deficient ligands, such as $P(C_6F_5)_3$ $P[3,5\text{-}(C_6H_3(CF_3)_2]_3$, also promoted the reaction, albeit in lower yield. The reaction was completely shut down when Na_2CO_3 was replaced by DBU, NEt_3 or proton sponge.

Table 4-4. Platinum-catalyzed [4+3] Cycloaddition between Propargylic Ether 4-1a and Diene 4-8a.[a]



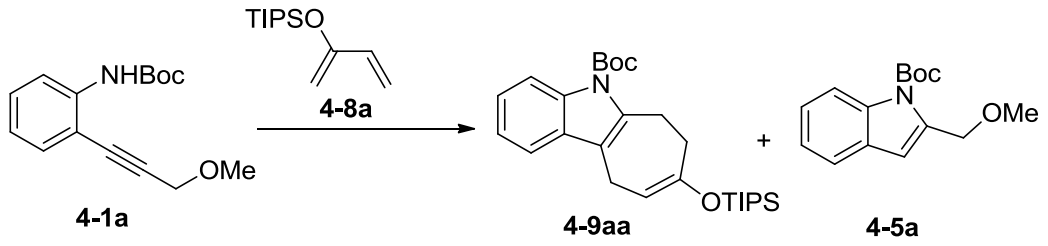
Entry	Catalyst	Yield (**4-9aa**:**4-5a**)[b]
1	$Pt(PPh_3)_2Cl_2$	0%[c]
2	$PtCl_2$	0%[d]
3	PtO_2	0%[c]

4	$PtCl_4$ + $P[OCH(CF_3)_2]_3$	0%[d]
5	$PtCl_2$ + $P[OCH(CF_3)_2]_3$	30% (5:1)
6[e]	$PtCl_2$ + $P[OCH(CF_3)_2]_3$	33%
7[f]	$PtCl_2$ + $P[OCH(CF_3)_2]_3$	0%[d]
8[g]	$PtCl_2$ + $P[OCH(CF_3)_2]_3$	0%[c]
9	$PtCl_2$ + octene(1equiv),60 ^oC	13%
10	$PtCl_2$ + CO(1 atm) ,60 ^oC:	15% (1.5:1)
11	$PtCl_2$ + $P[3,5\text{-}(C_6H_3(CF_3)_2]3$,60 ^oC	22% (4:1)
12	$PtCl_2$ + $P(C_6F_5)_3$, 80 ^oC	55%

[a]Conditions: Catalyst (10 mol %), ligand (20%), dioxane (0.20 M), Na_2CO_3 (1 equiv), diene **4-8a** (2 equiv), 100 ^oC, overnight. [b]NMR yield. [c]substrate recovery. [d]complex mixture. [e]80 ^oC. [f] no Na_2CO_3 was added. [g]Na_2CO_3 was replaced by ^{t}BuOK.

Various platinum catalysts were also screened (table 4-4). $PtCl_2$ was found to be the most effective platinum catalyst and electron deficient ligands were again found to promote to reaction. $P(C_6F_5)_3$ was identified as the best ligand and 80 ^oC was the best temperature.

Table 4-5. Other π-acid Catalyzed [4+3] Cycloaddition between Propargylic Ether 4-1a and Diene 4-8a.[a]



Entry	Catalyst	Yield[b]
1	$[Ir(cod)Cl]_2$, $P(C_6F_5)_3$	0%[c]
2	$PdCl_2$, $P(C_6F_5)_3$	0%[c]
3	$IrCl(CO)(PPh_3)_2$	0%[c]
4	AuCl(*p*-$C_6H_4CF_3$)	0%[c]
5	$NaAuCl_4$	0%[d]
6	$AuBr_3.H_2O$	0%[d]
7	$AuCl(SEt_2)$ + $P[OCH(CF_3)_2]_3$	0%
8	$[Ir(cod)Cl]_2$+ $P[OCH(CF_3)_2]_3$	15%
9	$Rh_2(OAc)_4$ + $P[OCH(CF_3)_2]_3$	0%[c]

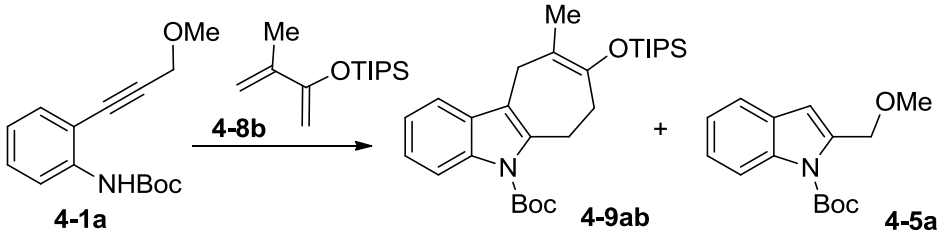
[a]Conditions: Catalyst (10 mol %), ligand (20%), dioxane (0.20 M), Na_2CO_3 (1 equiv), diene **4-8a** (2 equiv), 100 ^oC, overnight. [b]NMR yield. [c]substrate recovery. [d]complex mixture.

Other π-acidic metals were also screened (table 4-5). Most metal catalysts provided either substrate recovery or complex mixture.

Since the yield could not be further improved with diene **4-8a**, we switched to diene **4-8b** (table 4-6). When a mixture of propargylic ether **4-1a** and diene **4-8b** was treated with $[Rh(CO)_2Cl]_2$ at 80 ^oC, no reaction occurred (entry 1). We have previously found that electron-deficient phosphine or phosphite ligands increase the acidity of rhodium catalysts. Indeed, a mixture of [4 + 3] cycloaddition product **4-9ab** and simple indole **4-5a** was observed when **4-1a** was treated with $[Rh(CO)_2Cl]_2$ in the presence of such ligands (entries 2-4). The amount of indole **4-5a** could be minimized by employing a

greater excess of dienes (entry 4). A 67% isolated yield of tricyclic product **4-9ab** could be obtained in the presence of Rh(I) metal complex and electron-deficient phosphite ligand.

Table 4-6. Optimization for the Reaction between 4-1a and 4-8b.



Entry	Conditions	Yield of **4-9ab**[b] (ratio of **4-9ab**/**4-5a**)
1[c]	$[Rh(CO)_2Cl]_2$	No reaction
2[c]	$[Rh(CO)_2Cl]_2$, $P[(CF_3)_2C_6H_3]_3$	35% (1:1)
3[c]	$[Rh(CO)_2Cl]_2$, $P(C_6F_5)_3$	53% (2:1)
4	$[Rh(CO)_2Cl]_2$, $P[OCH(CF_3)_2]_3$	70%, (67%),[d] (4:1)
5	$PtCl_2$	28% (1.6:1)
6	$PtCl_2$, octene	21% (2:1)
7	$Pt(PPh_3)_2Cl_2$	No reaction
8	$PtCl_2$, CO (1 atm)	18% (4:1)
9	$PtCl_2$, $P[OCH(CF_3)_2]_3$	66% (8:1)
10	$PtCl_2$, $P[(CF_3)_2C_6H_3]_3$	31% (10:1)
11	$PtCl_2$, $P(C_6F_5)_3$	(85%)[d] (> 20:1)

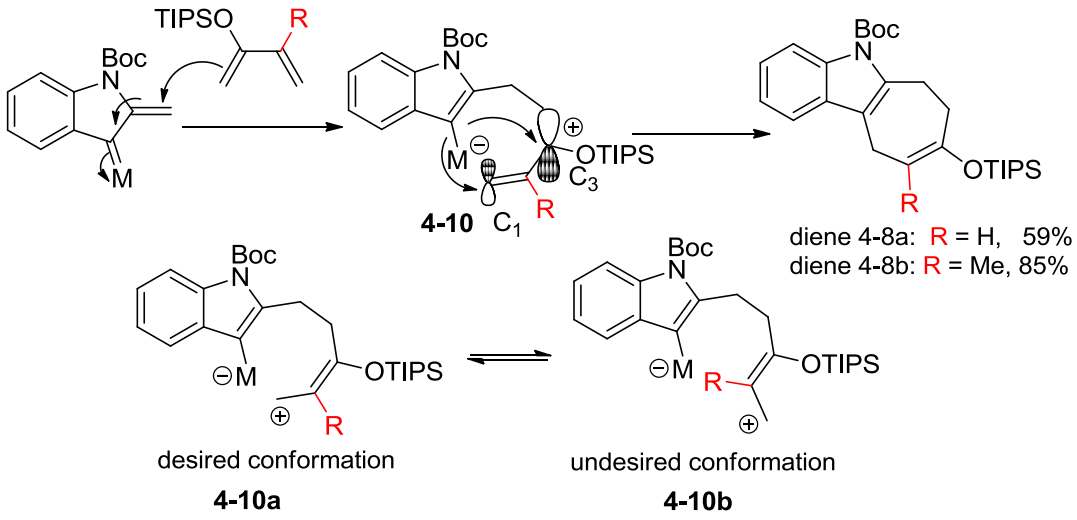
12	$IrCl(CO)(PPh_3)_2$	No reaction
13	$PdCl_2$	No reaction
14	$AuClP[(p\text{-}CF_3)C_6H_4]_3$	No reaction

[a] Conditions: 10 mol% metal catalyst, 20 mol% ligand, diene **4-8b** (5 equiv), 80 ^oC, dioxane, Na_2CO_3, 12 h, unless noted otherwise. [b] Yields based on ^1H NMR. [c] 2 equiv of diene **4-8b**. [d] Isolated yield.

We also examined $PtCl_2$-PPh_3 complex, $PtCl_2$, and $PtCl_2$-alkene complex, and all of which have been used in the generation of vinyl platinum carbenes from propargylic ethers. However, either low yield of product **4-9ab** or no product, was observed using these catalysts (entries 5-8). Then we added electron-deficient phosphite or phosphine ligands to further enhance the reactivity of $PtCl_2$ catalyst (entries 9-11). Indeed, the yield of product **4-9ab** was increased dramatically. Electron deficient $P(C_6F_5)_3$ ligand provided the highest isolated yield of product **4-9ab** (entry 11). Other metal catalysts did not afford the desired product (entries 12-14).

We proposed the increased yield for diene **4-8b** compared to **4-8a** was due to the conformation effect. As shown in scheme 4-6, after the nucleophilic attack, zwitterion intermediate **4-10** would be formed which exists in two different conformation—the desired conformation **4-10a** and undesired conformation **4-10b**. When R group was switched from H to Me, the $A_{1,3}$ interaction in conformation **4-10b** increases, which pushes the equilibrium towards the desired conformation **4-10a**.

Scheme 4-6. Proposed Model for [4+3] Cycloaddition.



Another intriguing aspect of this [4+3] cycloaddition is the preferred formation of seven-membered ring instead of five-membered ring as shown in scheme 4-6. It is well-known that five-membered ring cyclization is much faster than seven-membered ring. We also performed a preliminary calculation which showed the coefficient of the LUMO of C_3 is much larger than that of C_1. Since both conformation and electronic factor favor the formation of five-membered ring, the observed seven-membered ring formation should be caused by steric effect since C_1 has less steric hindrance compared to C_3.

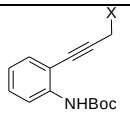
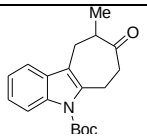
4.2.3 Investigation of Substrate Scope

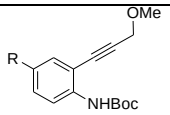
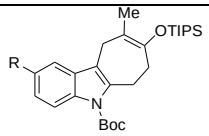
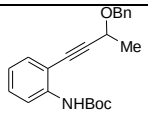
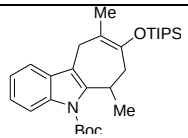
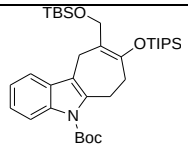
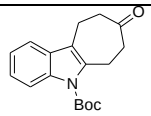
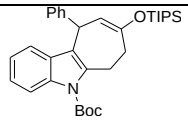
With the two optimized catalysts in hand, we then studied the scope of this tandem indole annulation/[4 + 3] cycloaddition with different propargylic ethers and dienes (Table 4-7). Ketone **4-10ab** could be isolated in 82% yield after in-situ hydrolysis of the silyl enol ether (entry 1). Substrate **4-1j** with a benzyl ether worked equally well (entry 2). We also investigated different electron-withdrawing or donating groups on the benzene ring, which could change the nucleophilicity of the aniline nitrogen. We found that the

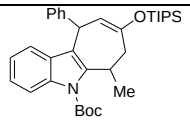
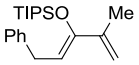
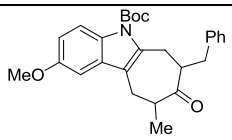
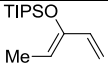
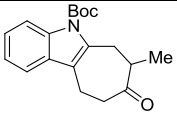
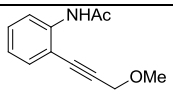
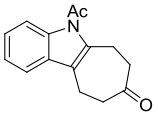
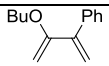
efficiency of the indole annulation/[4 + 3] cycloaddition was not affected by either type of substituent (entries 3 and 4). Substrate with a free hydroxyl group led to a lower yield (entry 5). The tandem reaction was not interfered by a formyl group (entry 6). Secondary propargylic ether also participated in the tandem reaction and yielded product **4-9ob** (entry 7). We found the yield was lower when we switched Boc to Ac (entry 14).

We also investigated the scope of acyclic dienes that could be used in this process.[38] More functionalized 2,3-disubstituted diene **4-8c** afforded product **4-9ac** in high yield (entry 8, Table 4-7). Mono-substituted diene **4-8a** produced ketone **10-aa** in 59% yield employing Rh-catalyst (entry 9). We obtained lower yields when various Pt-catalysts were employed in this case. The same trend was also observed for diene **4-8d** (entry 10). When Pt catalysts were employed, we only observed 42% NMR yield of product **4-9ad**. We observed a complex mixture when substrate **4-1a** was treated with 2-methyl-1,3-butadiene in the presence of either Pt- or Rh-catalyst, suggesting that the siloxy substituent is critical for the reactivity of acyclic dienes. A complex mixture was also observed when diene **4-8g** was employed (entry 15).

Table-4-7. Scope of Propargylic Ethers and Acyclic Dienes.[a]

Entry	Aniline 4-**1**	Diene **4-8**	Product and Yield
			
1[b]	**4-1a** (X = OMe)	**4-8b**	**4-10ab** (82%)
2[b]	**4-1j** (X = OBn)	**4-8b**	**4-10ab** (80%)

			
3	**4-1k** (R = CO_2Et)	**4-8b**	**4-9kb** (83%)
4	**4-1l**(R = OMe)	**4-8b**	**4-9lb** (86%)
5	**4-1m**(R = CH_2OH)	**4-8b**	**4-9mb**(52%)
6	**4-1n**(R = CHO)	**4-8b**	**4-9nb** (83%)
7[c]	 **4-1o**	**4-8b**	 **4-9ob**(56%)
8	**4-1a**	 **4-8c**	 **4-9ac** (90%)
9[b,d]	**4-1a**	 **4-8a**	 **4-10aa** (59%)
10[d]	**4-1a**	 **4-8d**	 **4-9ad** (66%)

11	**4-1o**	**4-8d**	 **4-9od** (50%, dr = 3:1)
12	**4-1l**	 **4-8e**	 **4-10le** (51%, dr = 9:1)
13[d]	**4-1a**	 **4-8f**	 **4-10af** (56%)
14	 **4-1p**	**4-8b**	 **4-10pb** (10%)
15	**4-1a**	 **4-8g**	0%

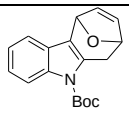
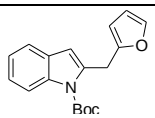
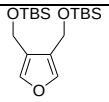
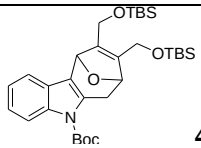
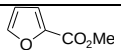
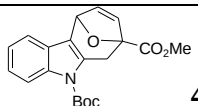
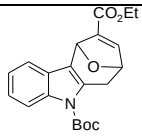
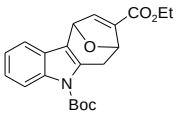
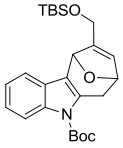
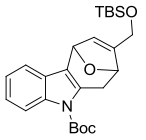
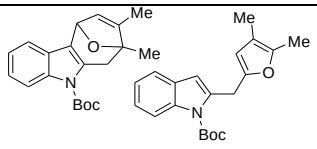
[a] Conditions: $PtCl_2$ (10 mol%), $P(C_6F_5)_3$ (20 mol%), diene **4-8** (5.0 equiv), 80 ^oC, dioxane, Na_2CO_3, 12 h. Yields are isolated yields. [b] The resulting product was treated with

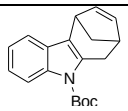
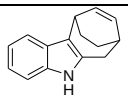
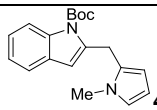
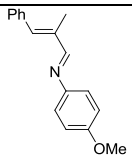
aqueous HCl (4M). [c] 1.5 equiv of diene **4-8**. [d] $[Rh(CO)_2Cl]_2$ (5 mol%) and $P[OCH(CF_3)_2]_3$ (20 mol%) were employed.

We found that furan **4-11a** participated in the tandem reaction and afforded tetracyclic product **4-12a** in 71% yield (entry 1, Table 4-8) together with the arylation product **4-13a** in 14% yield. For 3,4-disubstituted furan **4-11b**, a single product **4-12b** was observed (entry 2). The yields for electron deficient ester-substituted furan **4-11c** and **4-11d** were slightly lower (entries 3 and 4). Two regioisomers were obtained for non-symmetric furans **4-11d** and **4-11e** (entries 4 and 5). 2,3-Dimethylfuran **4-11f** only afforded one regioisomeric product (entry 6) together with 30% of **4-13f**. To our surprise, simple cyclopentadiene **4-11g** could also undergo tandem reaction to provide tetracyclic product **4-12g** in 63% yield (entry 7). Free indole **4-12h** could be prepared from **c**yclohexadiene after removing the Boc-protecting group (entry 8). When pyrrole was employed, only arylation product was observed, which is consistent with the previous literature report (entry 9).[39]Boc and Ts protected pyrroles were also prepared to weaken the aromaticity. However, we did not observe any [4+3] cycloaddition product. When unsaturated imine **4-11j** was employed, no reaction was observed.

Table 4-8. Scope of Cyclic Dienes for the Tandem Reaction with Propargylic Ether 4-1a.[a]

Entry	Diene **4-11**	Products and Yields

1[b]	 **4-11a**	  **4-12a**, 71%; **4-13a**, 14%
2	 **4-11b**	 **4-12b**, 79%
3	 **4-11c**	 **4-12c**, 52%
4	 **4-11d**	  **4-12d**, 44%; **4-12d'**, 23%
5	 **4-11e**	  **4-12e** + **4-12e'**, 83% (**4-12e** : **4-12e'** = 1:1.5)
6	 **4-11f**	 **4-12f**, 58%; **4-13f**, 30%

7	 **4-11g**	 **4-12g**, 63%
8	 **4-11h**	 **4-12h**, 61%[c]
9	 **4-11i**	 **4-13i**, 68%
10	 **4-11j**	0%

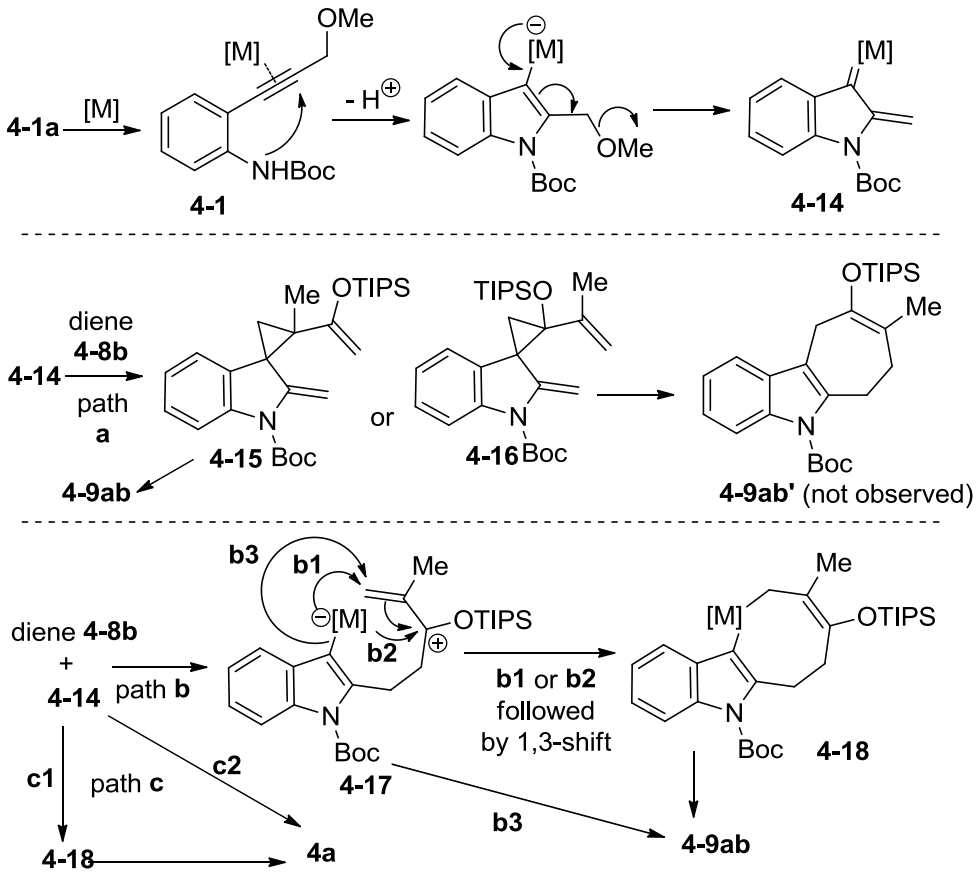
[a] Conditions: $PtCl_2$ (10 mol%), $P(C_6F_5)_3$ (20 mol%), diene **4-11** (1.5-5.0 equiv), 80 ^oC, dioxane, Na_2CO_3, 12 h. [b] $PtCl_2$ (5 mol%), $P(C_6F_5)_3$ (10 mol%) [c] The Boc-protecting group was removed by the treatment of TFA. The yield is the overall yield for two steps.

Possible mechanisms for the tandem indole annulations and [4 + 3] cycloaddition are described in Scheme 4-7. Metal carbene **4-14** can be formed by an initial 5-endo-cyclization and following elimination of methanol.[19,20] Several potential pathways can be responsible for the cycloaddition. In pathway **a**, cyclopropanation of diene **4-8b** would afford divinylcyclopropanes **4-15** or **4-16**. These two cyclopropanes could then undergo

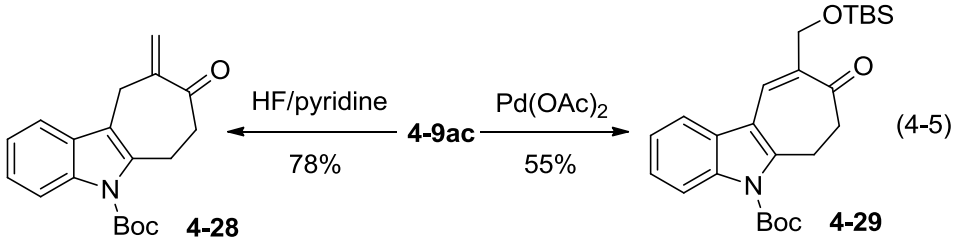
Cope rearrangement to produce products **4-9ab** or **4-9ab'**, respectively. In pathway **b**, nucleophilic attack of the silyl enol ether to vinyl carbene would generate ionic intermediate **4-17**. Metallacycle **4-18** can be formed through either pathway **b1** directly or from a six-membered metallacycle through pathway **b2** followed by a 1,3-shift. Product **4-9ab** could then be formed from reductive elimination of metallacycle **4-18**. Alternatively, product **4-9ab** could be produced from cyclization through pathway **b3** directly. In pathway **c1**, a concerted [4 + 4] cycloaddition between carbene **4-14** and diene **4-8b** may also lead to metallacycle **4-18**. A [4+3] cycloaddition with a concomitant elimination of the metal through pathway **c2** may yield product **4-9ab** directly.

Cyclopropanation of diene **4-8b** should occur on the electron-rich silyl enol ether selectively and afford cyclopropane **16** based on the regioselectivity reported previously,[21-26]which would produce isomeric product **4-9ab'**. Since only regioisomer **4-9ab** was observed, [4 + 3] cycloaddition through pathways **b** or **c** are more likely for dienes **4-8** and **4-11**.

Scheme 4-7. Proposed Mechanisms for the [4 + 3] Cycloaddition Accompanied by an Indole Annulation.



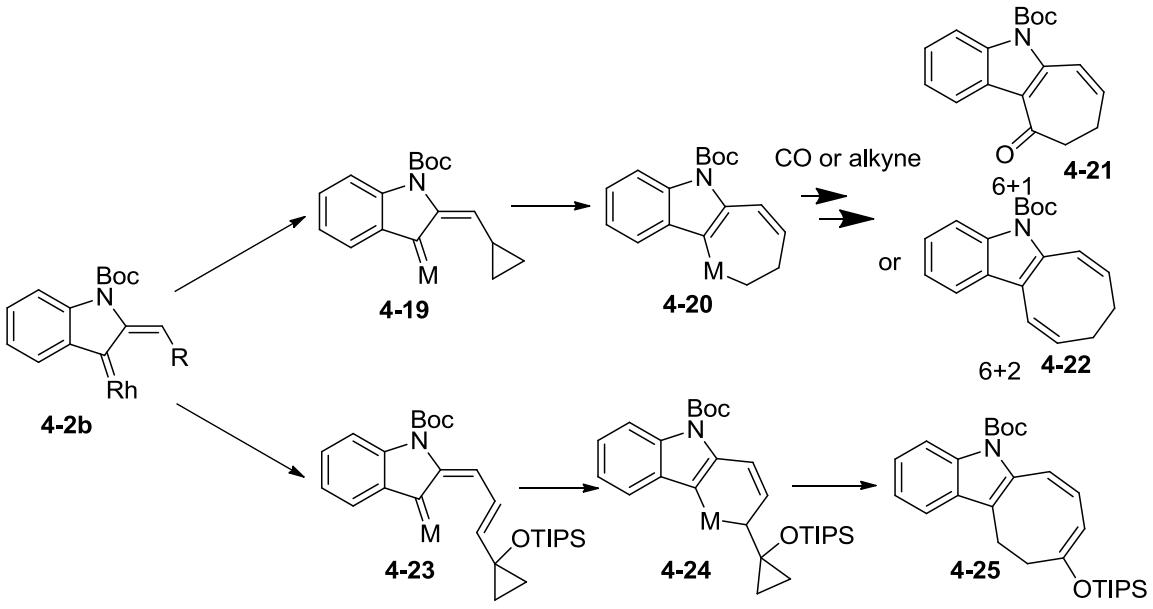
Treatment of product **4-9ac** with HF/pyridine provided enone **4-28**, which could be easily further functionalized Saegusa oxidation[40] of the same silyl enol ether yielded enone **4-29**.



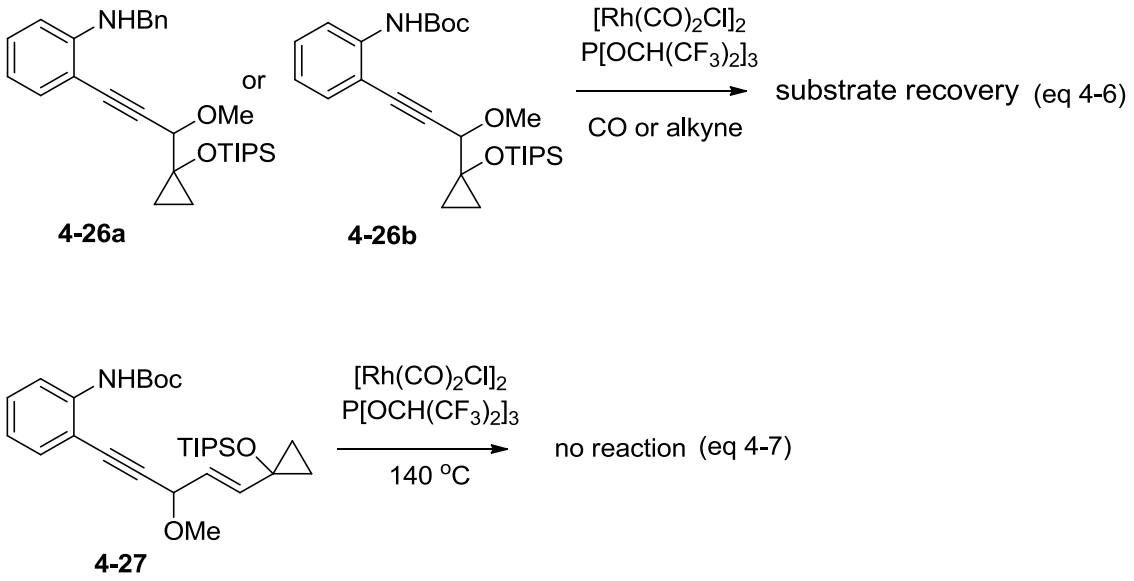
4.2.4 Other Reactions Involving the Generation of Vinyl Rhodium Carbene from Propargylic Ethers

We also designed several other reactions based on the vinyl rhodium carbene intermediate **4-2b** (scheme 4-8). When R is a cyclopropyl group, **4-19** may undergo ring expansion to form **4-20**, which could potentially undergo either [6+1] or [6+2] cycloaddition to form **4-21** or **4-22**. On the other hand, if intermediate **4-23** could be formed, it may undergo previous described eight-membered ring formation to form **4-25**.

Scheme 4-8. Proposed [6+1], [6+2] and Eight-membered Ring Formation.



To test the hypothesis, substrate **4-26a** and **4-26b** were synthesized. Under various conditions, we observed only substrate recovery (eq 4-6). Substrate **4-27** did not undergo any transformation even at 140 ^{o}C (eq 4-7).

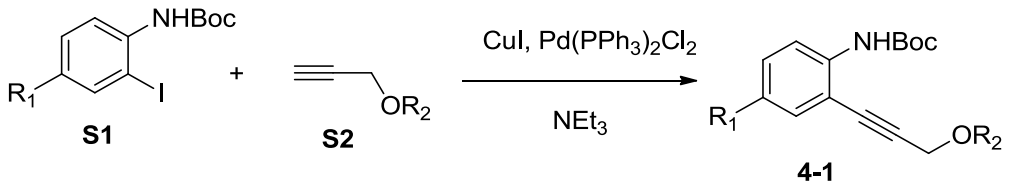


4.3 Experimental Section

All reactions in non-aqueous media were conducted under a positive pressure of dry argon in glassware that had been oven dried prior to use unless noted otherwise. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Thin layer chromatography was performed using precoated silica gel plates (EMD Chemical Inc. 60, F254). Flash column chromatography was performed with silica gel (Silicycle, 40-63 μm). Infrared spectra (IR) were obtained on a Bruker Equinox 55 Spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Varian Unity-Inova 400 MHz or 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in $CDCl_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint),or multiplet (m), with coupling constants (*J*) in hertz.

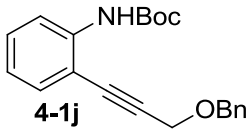
High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer. The optical rotation was determined using a Perkin–Elmer 241 Polarimeter.

All propargylic ether substrates were synthesized from the corresponding iodoanaline **S1** and propargyl ether **S2** following the scheme shown below.



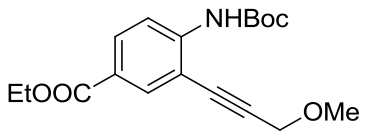
To an oven dried flask were added iodoanaline **S1** (1 equiv), propargyl ether **S2** (1 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), CuI (0.1equiv) and NEt_3 (3 ml/ mmol). The solution was stirred for 2h. The solvent were evaporated and the residue was purified by flash column chromatography.

Propargylic ethers **4-1a**, **4-1c** and **4-1l** are known compounds.(Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc*. **2011**, *133*, 689)



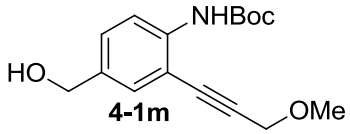
tert-butyl (2-(3-(benzyloxy)prop-1-yn-1-yl)phenyl)carbamate (4-1j). Yield 300 mg, 88%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.52 (s, 9H), 4.47 (s, 2H), 4.69

(s, 2H), 6.95 (td, *J* = 6.0, 0.8 Hz, 1H), 7.24 (br, 1H), 7.29-7.41 (m, 7H), 8.15 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):28.5, 58.0, 71.9, 81.0, 82.1, 92.1, 110.6, 117.8, 122.2, 128.2, 128.3, 128.7, 130.0, 132.3, 127.4, 139.9, 152.5. IR (film): ν 3403, 2932, 1731, 1579, 1514, 1447, 1237, 1152, 1050, 752, 736, 697 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}NO_3$ $(M+Na)^+$ 360.1570, found 360.1576.



4-1k

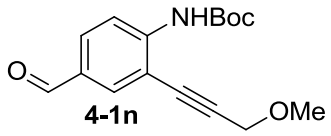
ethyl 4-((tert-butoxycarbonyl)amino)-3-(3-methoxyprop-1-yn-1-yl)benzoate (4-1k). Yield 195 mg, 90%; colorless oil.^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.33 (d, *J* = 7.2 Hz, 3H), 1.49 (s, 9H), 3.43 (s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.36 (s, 2H), 7.36 (br, 1H), 7.93 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 28.3, 57.9, 60.4, 61.0, 80.9, 81.6, 92.7, 110.2, 116.7, 124.1, 131.3, 133.7, 143.5, 151.9, 165.6. IR (film): ν 2980, 1736, 1714, 1579, 1519, 1466, 1413, 1367, 1293, 1234, 1214, 1150, 1100, 1021, 849, 765, 730 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{18}H_{23}NO_5Si$ $(M+Na)^+$ 356.1468, found 356.1463.



4-1m

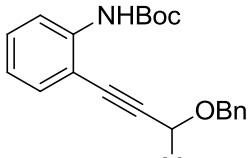
tert-butyl (4-(hydroxymethyl)-2-(3-methoxyprop-1-yn-1-yl)phenyl)carbamate (4-1m). Yield 195 mg, 98%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.50 (s, 9H), 2.30 (br, 1H), 3.44 (s, 3H), 4.36 (s, 2H), 4.54 (s, 2H), 7.19 (br, 1H), 7.25 (dd, *J* = 8.8,

2.0 Hz, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.4, 57.8, 60.5, 64.5, 81.1, 81.9, 91.8, 110.7, 117.9, 128.8, 130.8, 134.9, 139.1, 152.5. IR (film): ν 3408, 2979, 1730, 1518, 1240, 1153, 1096, 903 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{16}H_{21}NO_4$ $(M+Na)^+$ 314.1363, found 314.1350.



4-1n

tert-butyl (4-formyl-2-(3-methoxyprop-1-yn-1-yl)phenyl)carbamate (4-1n). Yield 40 mg, 85%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.55 (s, 9H), 3.49 (s, 3H), 4.42 (s, 2H), 7.48 (br, 1H), 7.82 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 8.36 (d, *J* = 8.8 Hz, 1H), 9.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.3, 58.0, 60.5, 80.6, 82.1, 93.4, 110.9, 117.2, 130.6, 131.7, 134.0, 144.9, 151.9, 190.3. IR (film): ν 3398, 2981, 2359, 1737, 1694, 1575, 1518, 1239, 1152, 910 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{16}H_{19}NO_4$ $(M+Na)^+$ 312.1206, found 312.1212.



4-1o

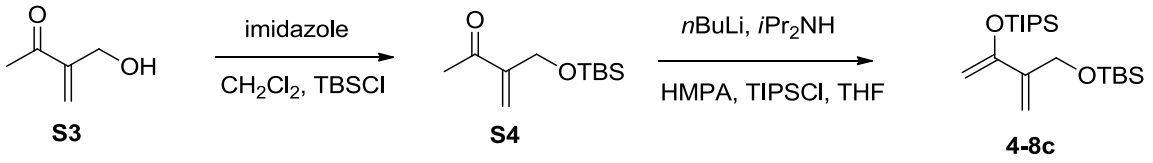
tert-butyl (2-(3-(benzyloxy)but-1-yn-1-yl)phenyl)carbamate (4-1o). Yield 278 mg, 93%; colorless oil.[1] ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.61 (s, 9H), 1.60 (d, *J* = 6.4 Hz, 3H), 4.50 (q, *J* = 6.4 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.86 (d, *J* = 11.6 Hz, 1H),

6.96 (td, *J* = 7.6, 1.2 Hz, 1H), 7.25-7.41(m, 8H), 8.13 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):22.4, 28.4, 65.1, 71.0, 80.8, 81.0, 96.2, 110.7, 117.7, 122.2, 128.0, 128.2, 128.64, 128.66, 129.9, 132.0, 137.8, 139.8, 152.5. IR (film): ν 3404, 2979, 1732, 1579, 1515, 1447, 1236, 1152, 1094, 751, 697 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}NO_3$ $(M+Na)^+$ 374.1727, found 360.1740.

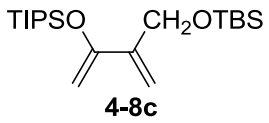
Procedures for the preparation of diene substrates:

Dienes **4-11a**, **c**, **d**, **f**, **g**, and **h** are commercially available. Dienes **4-8a**, **b**, **d**,**f**, **4-11b**, **e, i, j** are known compounds and were prepared according to the following references.(Mukherjee, S.; Corey, E. *Org. Lett*. **2010**, *12*, 632.; Rivera, J.; Martin, T.; Rebek Jr., J. *J. Am. Chem. Soc*. **2001**, *123*, 5213.)

Diene **3b** was prepared following the scheme shown below.



S3 **S4** **4-8c**



4-8c

9,9-diisopropyl-2,2,3,3,10-pentamethyl-6,7-dimethylene-4,8-dioxa-3,9-disilaundecane (4-8c). Diene **4-8c** was synthesized from known compound **S3** (He, Z.; Tang, X.; Chen, Y.; He, Z. *Adv. Synth. Cat*. **2006**. *348*. 413-417.) To 5 ml anhydrous CH_2Cl_2 was added 3-(hydroxymethyl)but-3-en-2-one (1.3 mmol, 130 mg), imidazole

(1.95 mmol, 133 mg), and TBSCl (1.56 mmol, 234mg). The solution was stirred overnight at room temperature and evaporated. The residue was purified by flash column chromatography (Hexane/EtOAc = 10/1) to provide 250 mg **S4** (yield: 90%). Next, To 4 ml THF was added *i*Pr_2NH (0.25ml, 1.76 mmol) and *n*BuLi (0.7 ml, 1.76 mmol) at 0 ^oC. The solution was stirred for 10 min and cooled to -78 ^oC and HMPA (0.31 ml, 1.76 mmol) was added. **S4** (250 mg, 1.17 mmol) was added dropwise and stirred at -78^oC for 0.5h and TIPSCl (0.26 ml, 1.28 mmol) was added over 5 min. The solution was stirred at -78 ^oC for 45 min and gradually warmed to room temperature and quenched with $NaHCO_3$ solution. The solution was extracted with hexane, evaporated and the residue was purified by flash column chromatography (pure hexane) to provide **4-8c.** Yield 296 mg, 68%; colorless oil. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 0.08 (s, 6H), 0.92 (s, 9H), 1.10 (d, *J* = 6.0 Hz, 18H), 1.24 (m, 3H), 4.21 (m, 4H), 5.33(s, 1H), 5.63 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$):-5.16, 13.0, 18.2, 18.5, 26.1, 62.8, 90.9, 112.1, 143.6, 154.4. IR (film): ν 2947, 2867, 1589. 1463, 1253, 1096, 1020, 914, 882, 836, 775, 679 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{20}H_{42}O_2Si_2$ $(M+Na)^+$ 393.2616, found 393.2616.

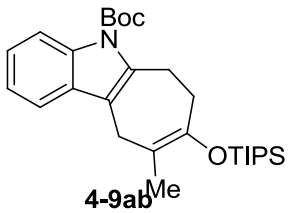
General procedure for Rh-catalyzed indole annulations and [4+3] cycloaddition:

To an oven-dried flask was added $[Rh(CO)_2Cl]_2$ (1.9 mg, 0.005 mmol), Na_2CO_3 (16mg, 0.15 mmol), $P[OCH(CF_3)_2]_3$ (6.3 μl, 0.02 mmol), diene **4-8b** (121mg, 0.5 mmol), analine **4-1a** (26.3mg, 0.1 mmol) and dioxane (0.5 ml). The flask was degassed with Ar, sealed and heated to 100 ^oC overnight. After the reaction was complete, the solvent was evaporated. For silyl enol ether, the residue was purified by flash column chromatography on silica gel (pure hexane to hexane: NEt_3 = 50:1). For ketone, the

residue was stirred in 0.5 ml THF and 0.5 ml 4M HCl for 0.5h, extracted with EtOAc, evaporated and purified by flash column chromatography (hexane : EtOAc = 15:1).

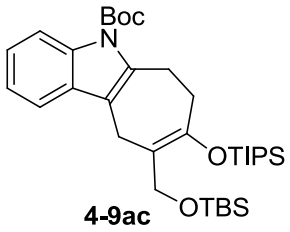
General procedure for Pt-catalyzed indole annulations and [4+3] cycloaddition:

To an oven-dried flask was added $PtCl_2$ (2.7 mg, 0.01 mmol), Na_2CO_3 (16mg, 0.15 mmol), $P[C_6F_5]_3$ (10.5 mg, 0.02 mmol), diene **4-8b** (125mg, 0.5 mmol), analine **4-1a** (26.3mg, 0.1 mmol) and dioxane (0.5 ml). The flask was degassed with Ar, sealed and heated to 80 ^oC overnight. After the reaction was complete, the solvent was evaporated. For silyl enol ether, the residue was purified by flash column chromatography on silica gel (pure hexane to hexane: NEt_3 = 50:1). For ketone, the residue was stirred in 0.5 ml THF and 0.5 ml 4M HCl for 0.5h, extracted with EtOAc, evaporated and purified by flash column chromatography (hexane : EtOAc = 15:1).



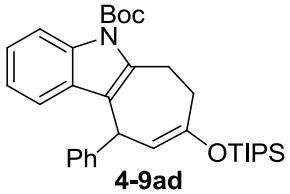
4-9ab

tert-butyl 9-methyl-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-5(10H)-carboxylate (4-9ab). Yield 39.9 mg, 85%; colorless oil.^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.13 (m, 21H), 1.65 (s, 9H), 1.77 (s, 3H), 2.66 (m, 2H), 3.21 (m, 2H), 3.29 (s, 2H), 7.21 (m, 2H), 7.43 (m, 1H), 8.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 18.1, 18.2, 27.50, 27.53, 28.4, 31.8, 83.5, 113.6, 115.4, 116.9, 117.4, 122.4, 123.5, 130.5, 135.0, 136.3, 146.8, 150.9. IR (film): ν 2944, 2866, 1727, 1456, 1354, 1248, 1165, 1134, 1116, 1095, 986, 883, 744, 681 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{28}H_{43}NO_3Si$ $(M+Na)^+$ 492.2904, found 492.2904.



4-9ac

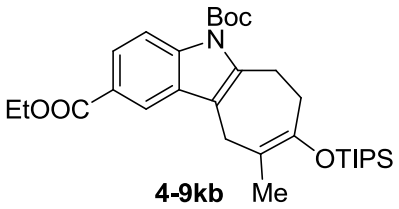
tert-butyl 9-(((tert-butyldimethylsilyl)oxy)methyl)-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-5(10H)-carboxylate (4-9ac). Yield 54.0 mg, 90%; white solid, m.p. 96-97 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.16 (m, 21H), 1.69 (s, 9H), 2.71 (m, 2H), 3.26 (m, 2H), 3.45 (s, 2H), 4.35 (s, 2H), 7.24 (m, 2H), 7.50 (m, 1H), 8.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.1, 13.4, 18.2, 18.5, 21.7, 26.1, 27.1, 28.5, 31.9, 60.7, 83.4, 115.3, 117.3, 117.7, 117.9, 122.4, 123.5, 130.4, 134.9, 136.0, 147.9, 150.9. IR (film): ν 2947, 2866, 1728, 1457, 1354, 1250, 1167, 1133, 1054, 1009, 908, 836, 680 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{34}H_{57}NO_4Si_2$ $(M+Na)^+$ 622.3718, found 622.3721.



4-9ad

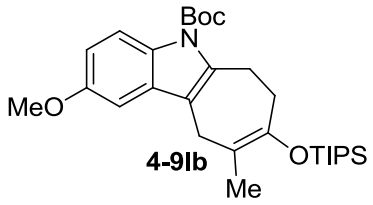
(E)-tert-butyl 1-styryl-1-((triisopropylsilyl)oxy)-2,3-dihydrocyclopenta[b]indole-4(1H)-carboxylate (4-9ad). Yield 35.2 mg, 66%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.07 (m, 21H), 1.68 (s, 9H), 2.23 (ddd, *J* = 15.2, 7.2, 3.2 Hz, 1H), 2.63 (ddd, *J* = 15.2, 11.6, 3.2 Hz, 1H), 3.19 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 3.41 (ddd, *J* = 17.2, 11.6, 3.2 Hz, 1H), 4.87 (d, *J* = 9.2 Hz, 1H), 5.55 (d, *J* = 9.2 Hz, 1H), 7.25 (m, 8H),

8.07 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.8, 18.2, 25.9, 28.5, 31.7, 37.1, 83.8, 107.8, 115.4, 118.1, 119.6, 122.6, 123.6, 125.8, 127.7, 128.1, 130.6, 135.2, 138.0, 144.5, 150.9, 154.9. IR (film): ν 2944, 2866, 1728, 1664, 1457, 1353, 1211, 1158, 1143, 1116, 906, 882, 850, 729, 698 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{33}H_{45}NO_3Si$ $(M+H)^+$ 532.3241, found 532.3241.



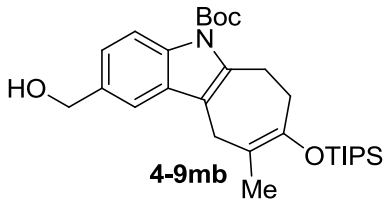
4-9kb

5-tert-butyl 2-ethyl 9-methyl-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-2,5(10H)-dicarboxylate (4-9kb). Yield 45.2 mg, 83%; white solid, m.p. 107 – 108 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.12 (m, 21H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.65 (s, 9H), 1.79 (s, 3H), 2.66 (m, 2H), 3.20 (m, 2H), 3.33 (s, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 7.92 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.10 (d, *J* = 1.6 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 14.6, 17.9, 18.0, 18.2, 27.3, 27.4, 28.4, 31.6, 60.9, 84.1, 113.7, 115.0, 117.3, 119.6, 124.6, 124.8, 130.2, 137.6, 137.7, 146.7, 150.5, 167.4. IR (film): ν 2944, 2867, 1714, 1451, 1337, 1273, 1234, 1166, 1136, 1087, 1010, 908, 882, 769, 680 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{31}H_{47}NO_5Si$ $(M+Na)^+$ 564.3115, found 564.3108.



4-9lb

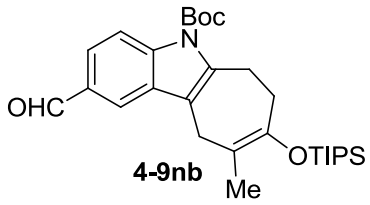
tert-butyl 2-methoxy-9-methyl-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-5(10H)-carboxylate (4-9lb). Yield 43.0 mg, 86%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.13 (m, 21H), 1.64 (s, 9H), 1.78 (s, 3H), 2.65 (m, 2H), 3.21 (m, 2H), 3.24 (s, 2H), 3.87 (s, 3H), 6.82 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 17.9, 18.1, 18.2, 27.5, 27.6, 28.4, 31.7, 55.9, 83.3, 100.7, 111.4, 113.5, 116.2, 116.7, 129.6, 131.3, 137.2, 146.8, 150.8, 155.9. IR (film): ν 2944, 2867, 1720, 1476, 1366, 1167, 1124, 906, 881, 729, 679 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{29}H_{45}NO_4Si$ $(M+Na)^+$ 522.3010, found 522.3004.



4-9mb

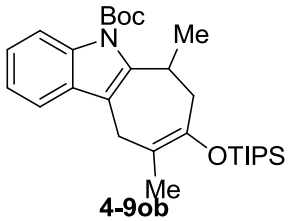
tert-butyl 2-(hydroxymethyl)-9-methyl-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-5(10H)-carboxylate (4-9mb).). Yield 25.9 mg, 52%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.12 (m, 21H), 1.65 (s, 9H), 1.77 (s, 3H), 2.35 (br, 1H), 2.66 (m, 2H), 3.20 (m, 2H), 3.29 (s, 2H), 4.78 (s, 2H), 7.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 18.1, 18.2, 27.50, 27.52, 28.4, 31.7, 66.0, 83.6, 113.6, 115.5, 116.1, 116.9,

122.9, 130.7, 134.6, 135.1, 136.9, 146.8, 150.8. IR (film): ν 2943, 2866, 1727, 1683, 1453, 1356, 1248, 1163, 1124, 1092, 1008, 913, 881, 679 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{29}H_{45}NO_4Si$ $(M+Na)^+$ 522.3010, found 522.3004.



4-9nb

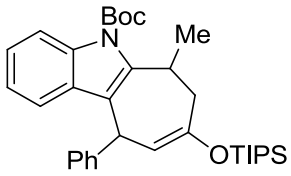
tert-butyl 2-formyl-9-methyl-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-5(10H)-carboxylate (4-9nb). Yield 41.5 mg, 83%; white solid, 66-67 ^oC. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.13 (m, 21H), 1.66 (s, 9H), 1.79 (s, 3H), 2.68 (m, 2H), 3.21 (m, 2H), 3.34 (s, 2H), 7.75 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.99 (d, *J* = 1.6 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 10.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 18.0, 18.2, 27.3, 27.5, 28.4, 31.6, 84.5, 113.6, 115.7, 117.5, 119.9, 125.3, 130.7, 131.4, 138.3, 138.8, 146.8, 150.3, 192.5. IR (film): ν 2943, 2866, 1733, 1692, 1607, 1451, 1337, 1251, 1200, 1154, 1125, 909, 881, 814, 730, 681 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{29}H_{43}NO_4Si$ $(M+Na)^+$ 520.2853, found 520.2842.



4-9ob

tert-butyl 6,9-dimethyl-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-5(10H)-carboxylate(4-9ob). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.07 (m, 21H), 1.24

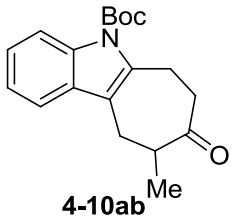
(d, *J* = 6.4 Hz, 2H), 1.62 (s, 9H), 1.73 (s, 3H), 2.43 (d, *J* = 14.4, 8.4 Hz, 1H), 2.73 (d, *J* = 14.4, 2.8 Hz, 1H), 3.22 (s, 2H), 3.79 (m, 1H), 7.16 (m, 2H), 7.38 (m, 1H), 8.00 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.4, 18.1, 18.2, 21.8, 27.9, 28.4, 30.8, 39.8, 83.5, 113.7, 115.5, 116.7, 117.6, 122.4, 123.6, 130.4, 135.4, 141.2, 145.8, 150.7. IR (film): ν 2943, 1729, 1457, 1354, 1258, 1182, 1136, 1102, 1016, 798, 742, 680 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{29}H_{45}NO_3Si$ $(M+Na)^+$ 506.3061, found 506.3047.



4-9od

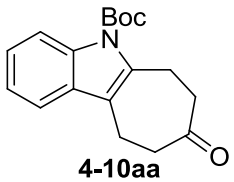
tert-butyl 6-methyl-10-phenyl-8-((triisopropylsilyl)oxy)-6,7-dihydrocyclohepta[b]indole-5(10H)-carboxylate(3:1 diastereoisomeric ratio). Yield 20.0 mg, 50%; white solid, m.p. 98-99 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): Major isomer: δ 1.00 (m, 21H), 1.30 (d, *J* = 6.0Hz), 1.64 (s, 9H), 1.93 (ddd, *J* = 14.0, 6.0, 2.4 Hz, 1H), 2.88 (d, *J* = 14.0 Hz, 1H), 3.91 (m, 1H), 4.77 (d, *J* = 9.2Hz, 1H), 5.48 (d, J = 9.2Hz, 1H), 6.99 – 7.15 (m, 8H), 8.00 (d, *J* = 8.4 Hz, 1H). Minor isomer: δ 1.00 (m, 21H), 1.30 (d, *J* = 6.4Hz), 1.62 (s, 9H), 2.28 (m, 2H), 3.91 (m, 1H), 4.84 (d, *J* = 7.6Hz, 1H), 5.42 (d, *J* = 7.6Hz, 1H), 6.99 – 7.15 (m, 8H), 7.97 (d, *J* = 8.4 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 12.8, 18.22, 18.25, 20.3, 22.7, 28.45, 28.49, 29.7, 30.4, 37.4, 38.2, 38.6, 39.9, 83.8, 107.3, 109.1, 115.0, 115.6, 117.4, 118.51, 118.59, 119.4, 122.60, 122.63, 123.7, 123.8, 125.7, 125.9, 127.5, 127.8, 128.1, 128.2, 130.7, 130.8, 135.5, 135.7, 142.4, 143.0, 144.6, 144.8, 150.8, 152.1, 153.8. IR (film): ν 2946, 2866, 1730, 1667, 1458, 1356,

1314, 1250, 1145, 884, 743 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{34}H_{47}NO_3Si$ $(M+H)^+$ 546.3427, found 546.3430.



4-10ab

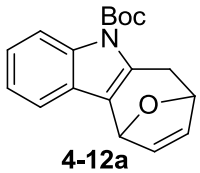
tert-butyl 9-methyl-8-oxo-7,8,9,10-tetrahydrocyclohepta[b]indole-5(6H)-carboxylate (4-10ab). Yield 25.7 mg, 82%; white solid, m.p. 91 -92 ^oC. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.21 (d, *J* = 6.8 Hz, 3H), 1.67 (s, 9H), 2.88 (m, 3H), 3.03 (ddd, *J* = 13.2, 9.2, 5.2 Hz, 1H), 3.12 (m, 1H), 3.45 (m, 2H), 7.25 (m, 2H), 7.43 (m, 1H), 8.06 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 16.9, 26.4, 27.3, 28.4, 39.4, 47.0, 84.1, 115.6, 117.6, 117.7, 122.7, 124.2, 130.1, 135.3, 135.5, 150.7, 214.9. IR (film): ν 2976, 1726, 1704, 1455, 1354, 1304, 1252, 1137, 1116, 839, 743 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{19}H_{23}NO_3$ $(M+Na)^+$ 336.1570, found 336.1573.



4-10aa

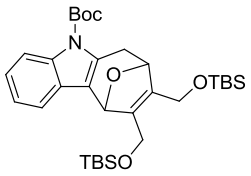
tert-butyl 8-oxo-7,8,9,10-tetrahydrocyclohepta[b]indole-5(6H)-carboxylate (4-10aa). Yield 17.7mg, 59%; colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.67 (s, 9H), 2.83 (m, 2H), 2.98 (m, 2H), 3.08 (m, 2H), 3.44 (m, 2H), 7.25 (m, 2H), 7.43 (m, 1H), 8.06

(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.2, 25.9, 28.5, 40.6, 43.0, 84.2, 115.6, 117.6, 118.6, 122.7, 124.2, 129.7, 135.5, 150.7, 213.0. IR (film): ν 2922, 1726, 1707, 1457, 1358, 1319, 1156, 1137, 1116, 745 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{18}H_{21}NO_3$ $(M+Na)^+$ 322.1413, found 322.1407.



4-12a

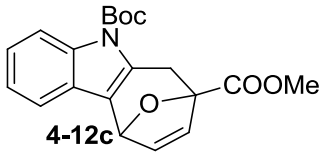
tert-butyl 6,7-dihydro-7,10-epoxycyclohepta[b]indole-5(10H)-carboxylate (4-12a). Yield 42.2 mg, 71%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.65 (s, 9H), 2.76 (d, *J* = 18.0 Hz, 1H), 3.55 (dd, *J* = 18.0, 6.0 Hz, 1H), 5.19 (dt, *J* = 6.0, 1.6 Hz, 1H), 5.63 (d, *J* = 0.4 Hz, 1H), 6.00 (dd, *J* = 6.0, 1.6 Hz, 1H), 6.60 (ddd, *J* = 6.0, 1.6, 0.4 Hz, 1H), 7.22 (m, 2H), 7.42 (m, 1H), 8.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.4, 30.3, 74.7, 77.5, 83.9, 115.8, 117.1, 120.3, 122.8, 123.4, 126.3, 127.0, 130.1, 134.7, 138.4, 150.3. IR (film): ν 2975, 1726, 1478, 1353, 1313, 1154, 1129, 909, 733, 706 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{18}H_{19}NO_3$ $(M+Na)^+$ 320.1257., found 320.1247.



4-12b

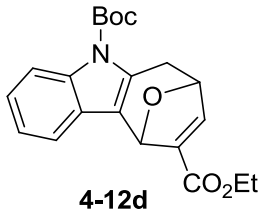
tert-butyl 8,9-bis(((tert-butyldimethylsilyl)oxy)methyl)-6,7-dihydro-7,10-epoxycyclohepta[b]indole-5(10H)-carboxylate (4-12b). Yield 46.3 mg, 79%; colorless

oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.02 (m, 12H), 0.84 (s, 9H), 0.88 (s, 9H), 1.69 (s, 9H), 2.90 (d, *J* = 12 Hz, 1H), 3.46 (m, 1H), 4.10 (d, *J* = 12 Hz, 1H), 4.35 (m, 3H), 5.26 (d, *J* = 4 Hz, 1H), 5.62 (s, 1H), 7.18 (m, 2H), 7.40 (d, *J* = 4 Hz, 1H), 8.12 (d, *J* = 4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.28, -5.25, -5.14, -5.12, 18.4, 18.5, 26.10, 26.12, 28.4, 30.1, 57.2, 57.6, 76.5, 80.1, 83.8, 115.8, 117.4, 120.6, 122.8, 123.4, 126.8, 130.8, 132.8, 134.8, 146.4, 150.4. IR (film): ν 2954, 2856, 1732, 1454, 1358, 1254, 1130, 1079, 836, 776 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{32}H_{51}NO_5Si_2$ $(M+Na)^+$ 608.3198, found 608.3223.



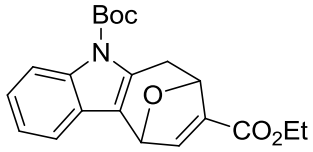
4-12c

5-tert-butyl 7-methyl 6,7-dihydro-7,10-epoxycyclohepta[b]indole-5,7(10H)-dicarboxylate (4-12c). Yield 18.5 mg, 52%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.66 (s, 9H), 3.22 (dd, *J* = 18.0 Hz, 1H), 3.60 (d, *J* = 18.0 Hz, 1H), 3.90 (s, 3H), 5.81 (t, *J* = 1.6 Hz, 1H), 6.01 (d, *J* = 5.6 Hz, 1H), 6.89 (dd, *J* = 5.6, 1.6 Hz, 1H), 7.24 (m, 2H), 7.45 (m, 1H), 8.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.4, 33.4, 52.9, 76.4, 84.4, 85.8, 115.9, 117.3, 119.3, 123.0, 123.8, 126.0, 126.6, 130.5, 134.8, 139.6, 150.3, 171.0. IR (film): ν 2919, 1729, 1453, 1356, 1116, 1055, 910, cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{20}H_{21}NO_5$ $(M+Na)^+$ 378.1311., found 378.1306.



4-12d

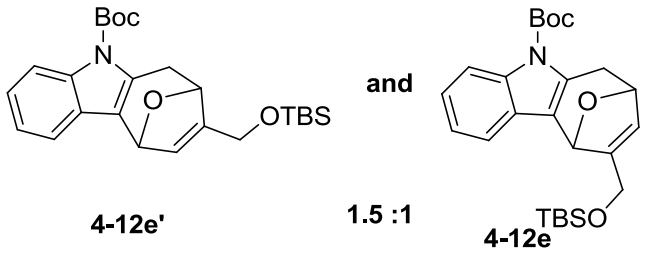
5-tert-butyl 9-ethyl 6,7-dihydro-7,10-epoxycyclohepta[b]indole-5,9(10H)-dicarboxylate (4-12d). Yield 15.7 mg, 44%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.26 (t, *J* = 8 Hz, 3H), 1.66 (s, 9H), 2.85 (d, *J* = 12 Hz, 1H), 3.64 (m, 1H), 4.15 (q, *J* = 8 Hz, 2H), 5.31 (d, *J* = 4 Hz, 1H), 5.84 (s, 1H), 6.82 (s, 1H), 7.23 (m, 2H), 7.59 (m, 1H), 8.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 28.4, 29.4, 61.0, 74.6, 78.7, 84.1, 115.7, 118.4, 119.8, 122.9, 123.6, 126.4, 129.7, 134.7, 136.9, 145.8, 150.4, 162.7. IR (film): ν 2978, 1713, 1356, 1240, 1130, 1096, 745 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}NO_5$ $(M+Na)^+$ 392.1468, found 392.1466.



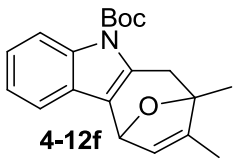
10d'

5-tert-butyl 8-ethyl 6,7-dihydro-7,10-epoxycyclohepta[b]indole-5,8(10H)-dicarboxylate (4-12d'). Yield 8.1 mg, 23%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.28 (t, *J* = 4 Hz, 3H), 1.66 (s, 9H), 3.00 (d, *J* =16 Hz, 1H), 3.60 (m, 1H), 4.21 (m, 2H), 5.45 (d, *J* = 8 Hz, 1H), 5.73 (m, 1H), 7.25 (m, 2H), 7.41 (m, 2H), 8.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 28.4, 30.2, 60.8, 76.0, 77.3, 84.3, 116.0, 117.1, 117.5, 123.0, 123.8, 126.1, 131.6, 133.9, 134.9, 147.8, 150.2, 163.5. IR (film): ν 2978,

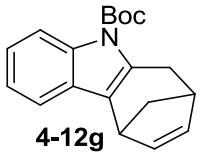
2359, 1712, 1454, 1355, 1130, 1115, 742 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}NO_5$ $(M+Na)^+$ 392.1468, found 392.1466.



tert-butyl 8-(((tert-butyldimethylsilyl)oxy)methyl)-6,7-dihydro-7,10-epoxycyclohepta[b]indole-5(10H)-carboxylate (4-12e + 4-12e'). Yield 36.7 mg, 83%; colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 0.04 (m, 6H), δ 0.92 (m, 9H), 1. 65 (s, 9H), 2.81 (m, 1H), 3.54 (m, 1H), 4.26 (m, 2H), 5.19 (d, *J* = 8 Hz, 1H), 5.55 (d, *J* = 12 Hz, 1H), 6.00 (m, 1H), 7.22 (m, 2H), 7.41 (m, 1H), 8.14 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.25, -5.20, -5.1, 18.50, 18.53, 26.05, 26.07, 28.4, 30.2, 30.5, 59.2, 59.4, 74.8, 75.4, 78.2, 78.3, 83.91, 83.93, 115.9, 117.1, 117.2, 119.5, 120.2, 120.8, 122.8, 122.9, 123.4, 126.4, 126.7, 130.4, 130.7, 133.1, 134.7, 134.8, 142.1, 150.4, 154.3. IR (film): ν 2947, 2861, 1728, 1457, 1357, 1133, 836, 740 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{25}H_{35}NO_4Si$ $(M+Na)^+$ 464.2227, found 464.229.

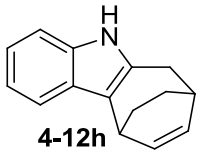


tert-butyl 7,8-dimethyl-6,7-dihydro-7,10-epoxycyclohepta[b]indole-5(10H)-carboxylate (4-12f). Yield 18.9 mg, 58%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.58 (s, 3H), 1.66 (s, 9H), 1.76 (m, 3H), 2.93 (d, *J* = 16.4 Hz, 1H), 3.15 (d, *J* = 16.4 Hz, 1H), 5.48 (s, 1H), 6.16 (m, 1H), 7.20 (m, 2H), 7.40 (m, 1H), 8.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 11.2, 23.4, 28.4, 35.5, 74.2, 83.9, 84.5, 115.9, 117.2, 121.4, 122.8, 123.3, 126.5, 132.8, 133.0, 134.7, 139.8, 150.6. IR (film): ν 2973, 1727, 1453, 1356, 1156, 1126, 1114 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{20}H_{23}NO_3$ $(M+Na)^+$ 348.1570, found 348.1570.



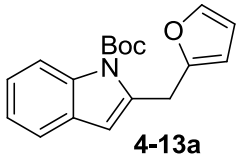
4-12g

tert-butyl 6,7-dihydro-7,10-methanocyclohepta[b]indole-5(10H)-carboxylate (4-12g). Yield 18.6 mg, 63%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.65 (s, 9H), 1.83 (d, *J* = 9.6 Hz, 1H), 2.17 (m, 1H), 2.83 (dd, *J* = 18.4, 1.2 Hz, 1H), 3.10 (m, 1H), 3.26 (dd, *J* = 18.4, 5.6 Hz, 1H), 3.61 (dd, *J* = 4.0, 2.8 Hz, 1H), 5.79 (dd, *J* = 5.2, 2.8 Hz, 1H), 6.36 (dd, *J* = 5.2, 2.8 Hz, 1H), 7.20 (m, 2H), 7.47 (m, 1H), 8.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.5, 30.6, 35.8, 39.1, 41.4, 83.4, 115.7, 117.1, 122.5, 122.9, 123.1, 128.1, 130.4, 131.8, 135.0, 140.3, 150.7. IR (film): ν 2983, 2365, 1727, 1454, 1358, 1328, 1139, 1113, 728 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}NO_2$ $(M+Na)^+$ 318.1465., found 318.1467.



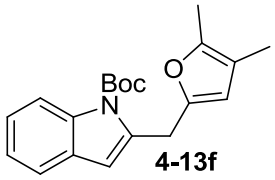
4-12h

5,6,7,10-tetrahydro-7,10-ethanocyclohepta[b]indole (4-12h). Yield 12.8 mg, 61%; green solid, 157 – 158 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.81 (m, 1H), 1.93 (m, 2H), 2.12 (m, 1H), 2.84 (m, 1H), 2.88 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.00 (d, *J* = 16.0 Hz, 1H), 3.65 (dt, *J* = 8.0, 3.5 Hz, 1H), 6.05 (t, *J* = 8.0 Hz, 1H), 6.33 (t, *J* = 8.0 Hz, 1H), 7.06 (m, 2H), 7.22 (m, 1H), 7.50 (m, 1H), 7.57 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 25.3, 29.4, 30.4, 32.3, 33.9, 110.3, 115.9, 117.3, 119.1, 120.8, 127.0, 129.2, 132.5, 134.8, 139.6. IR (film): ν 3389, 2930, 1463, 1344, 907 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{15}H_{15}N$ $(M+H)^+$ 210.1277, found 210.1280.



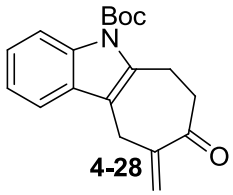
4-13a

tert-butyl 2-(furan-2-ylmethyl)-1H-indole-1-carboxylate (4-13a). Yield 8.4 mg, 14%; colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.60 (s, 9H), 4.38 (s, 2H), 6.01 (dd, *J* = 3.0, 1.0 Hz, 1H), 6.28 (s, 1H), 6.31 (dd, *J* = 3.0, 2.0 Hz, 1H), 7.18 (td, *J* = 7.0, 1.0 Hz, 1H), 7.25 (td, *J* = 7.0, 1.5 Hz, 1H), 7.36 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.44 (d, *J* = 7.0 Hz, 1H), 8.14 (dd, *J* = 7.0, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 28.2, 29.7, 84.1, 106.7, 109.2, 110.6, 115.7, 120.2, 122.8, 123.8, 129.1, 137.0, 137.4, 141.3, 150.5, 153.1. IR (film): ν 2918, 1730, 1486, 1237, 1158, 1095, 984, 728 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{18}H_{19}NO_3$ $(M+Na)^+$ 320.1257., found 320.1259.



4-13f

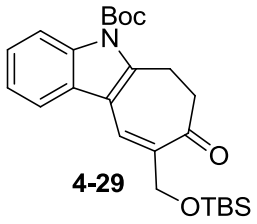
tert-butyl 2-((4,5-dimethylfuran-2-yl)methyl)-1H-indole-1-carboxylate (4-13f). Yield 9.8 mg, 30%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.61 (s, 9H), 1.88 (s, 3H), 2.18 (s, 3H), 4.27 (s, 2H), 5.78 (s, 1H), 6.29 (s, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (td, *J* = 7.6, 1.2 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 10.0, 11.5, 28.2, 29.7, 84.1, 109.0, 109.0, 114.7, 115.6, 120.1, 122.8, 123.7, 129.2, 137.0, 138.1, 146.0, 149.7, 150.6. IR (film): ν 2923, 1732, 1454, 1370, 1328, 1162, 1116, 1084, 908 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{20}H_{23}NO_3$ $(M+Na)^+$ 348.1570, found 348.1568.



4-28

tert-butyl 9-methylene-8-oxo-7,8,9,10-tetrahydrocyclohepta[b]indole-5(6H)-carboxylate (4-28). To 34.7 mg of Compound **4-9ac** in 1 ml THF at 0 ^{o}C was slowly added 0.12 ml of HF-Py solution. The solution was stirred at room temperature for 1h and then poured into $NaHCO_3$ solution. The solution was extracted with EtOAc, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography column (Hexane : EtOAc = 15:1). Yield 18.0 mg, 78%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.66 (s, 9H), 3.11 (m, 2H), 3.44 (m, 2H), 3.85 (s, 2H), 5.39 (d, *J* = 1.2 Hz, 1H),

6.07 (d, *J* = 1.2 Hz, 1H), 7.27 (m, 2H), 7.48 (m, 1H), 8.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.5, 28.4, 28.5, 39.3, 84.2, 115.7, 116.3, 117.4, 122.2, 122.7, 129.2, 134.3, 135.7, 144.8, 150.6, 201.4. IR (film): ν, 2944, 1729, 1646, 1455, 1358, 908 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}NO_3$ $(M+Na)^+$ 334.1414, found 334.1403.



4-29

tert-butyl 9-(((tert-butyldimethylsilyl)oxy)methyl)-8-oxo-7,8-dihydrocyclohepta[b]indole-5(6H)-carboxylate(4-29). To a solution of **4-9ac** (30 mg, 0.1 mmol) in 2 ml MeCN was added $Pd(OAc)_2$ (22mg, 0.1 mmol). The solution was heated to 50 ^{o}C overnightp. The solvent was evaporated and purified by flash chromatography column (Hexane : EtOAc = 30/1 to 10/1) to provide colorless oil (24.3 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.15 (s, 6H), 1.00 (s, 9H), 1.71 (s, 9H), 2.91 (m, 2H), 3.51 (m, 2H), 4.58 (d, *J* = 2.0 Hz, 2H), 7.32 (m, 2H), 7.64 (m, 1H), 7.68 (t, *J* = 2.0 Hz, 1H), 8.06 (m, 1H). ^{13}C NMR (100MHz, $CDCl_3$): -5.0, 18.6, 22.3, 26.2, 28.4, 40.8, 62.0, 85.3, 115.7, 116.6, 117.4, 123.7, 124.7, 128.5, 129.1, 135.5, 136.3, 143.0, 150.3, 199.6. IR (film): ν 2930, 1737, 1644, 1457, 1371, 1346, 1302, 1145, 1122, 908, 839 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{25}H_{35}NO_4Si$ $(M+Na)^+$ 464.2228, found 464.2230.

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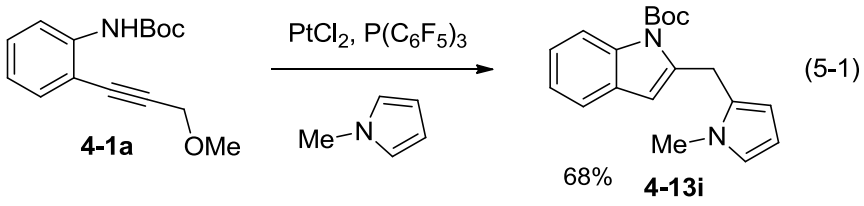
Chapter 5

Platinum-catalyzed Synthesis of Bisindole involving Indole Annulation from Propargylic Ethers

5.1 Introduction

Indole is one of the most common heterocycles in alkaloids and other natural products as well as pharmaceutical agents. Not surprisingly, it has been a continuous focus for the synthetic community and numerous efforts have been devoted to the preparation of indoles in different ways and from diverse range of starting materials.[1] Most synthetic effort, however, have focused on simple indole annulation.[1a-d] If the event of indole annulation is coupled with other transformations in a cascade manner, the efficiency of the synthesis can be improved dramatically. We previously developed a tandem indole annulation/[4+3] cycloaddition for the synthesis of cyclohepta[*b*]indoles by constructing both indole and seven-membered ring simultaneously (chapter IV).[2] During our investigation, we found that when we employed pyrrole as the 4-π component, only arylation product **4-13i** was observed (eq 5-1).



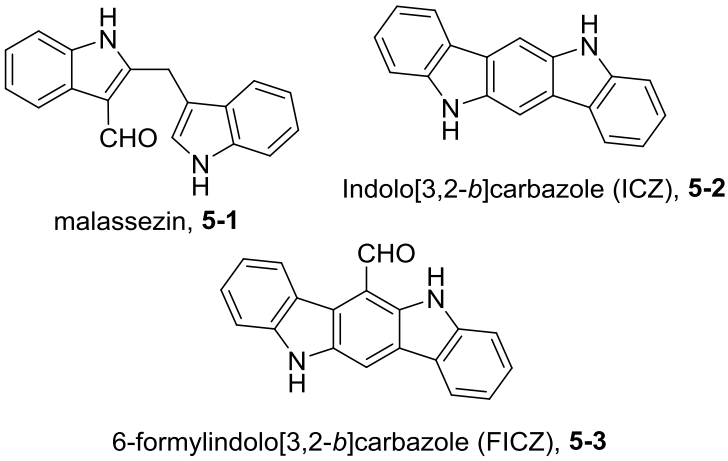
(5-1)

Diindolylmethanes are present in natural products such as malassezin**5-1**[3] shown in Figure 5-1.[4] They are also important precursors for other naturally occurring heterocycles such as indolocarbazoles **5-2** and **5-3.**[5] Indolo[3,2-*b*]carbazoles are also core structure of an important class of organic electroluminescent compounds.[4,6]

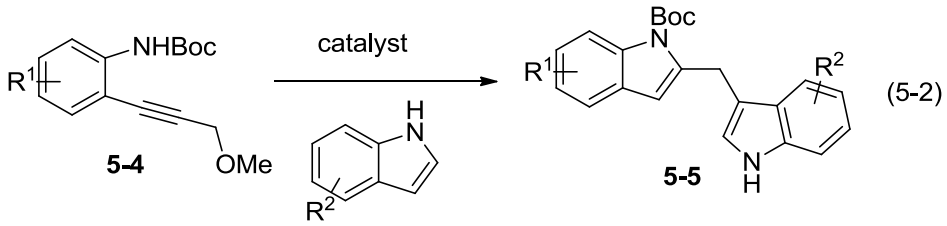
It has been realized using iodine as the catalyst to promote the rearrangement of the symmetrical 3,3'-diindolylmethanes to 2,3-diindolylmethanes.[7] However, when

substituted indoles were employed as the substrates, low yields were observed. Based on current method, it requires the joining of two different indoles to synthesize non-symmetric 2,3-diindolylmethanes in multiple steps.[8]

Figure 5-1. Natural Products and Pharmaceutical Agents Containing Diindolylmethanes and Indolo[3,2-*b*]carbazoles.



Inspired by both the observed reactivity in eq 5-1 and the importance of diindolylmethanes, we devised a bisindole formation protocol (eq 5-2). The preexisting indole would utilize C3 position to attack the vinyl metal carbene intermediate derived from **5-4**, to afford 2,3- symmetrical and unsymmetrical diindolylmethanes **5-5**.

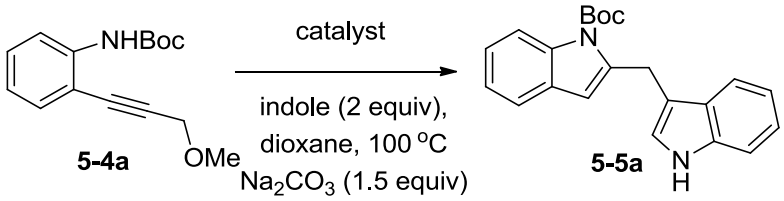


5.2 Platinum-catalyzed Bisindole Formation

5.2.1 Optimization of Catalyst and Conditions

We first examined the conditions that we employed previously for indole annulation/[4+3] cycloadditions (entry 1, Table 5-1).[2] 84% NMR yield was observed. We were pleased to find that $PtCl_2$ alone could also catalyze the reaction effectively. **5-5a** was isolated in 83% yield. We found the yield was lower when we decreased the catalyst loading (entries 3-4). We also examined rhodium catalyst and only 56% NMR yield was observed. Silver and copper complexes did not afford any desired product.

Table 5-1. Catalysts and Conditions Optimization.[a]



Entry	Catalyst	Yield
1	**$PtCl_2$ (10 mol %), $P(C_6F_5)_3$(20 mol %)**	**84%**
2	**$PtCl_2$ (10 mol %)**	**83%**[b]
3	**$PtCl_2$ (5 mol %), $P(C_6F_5)_3$(10 mol %)**	**77 %**
4	**PtCl2 (5 mol %)**	**76 %**
5	**$AgBF_4$**	**0%(sub recovery)**
6	**AgOTf**	**0 %**
7	**Cu(OTf)**	**0 %**
8	**$[Rh(CO)_2Cl]_2$(10 mol %), $P[OCH(CF_3)_2]_3$ (20**	**56%**

	mol %)	
9	**AgOTf (10 mol %), $P(C_6F_5)_3$(20 mol %),**	**0 %**
10	**CuOTf (10 mol %), $P(C_6F_5)_3$(20 mol %),**	**0 %**

a. Unless noted otherwise, the yield of **5-5a** was determined by ^{1}H NMR. *b.* Isolated yield.

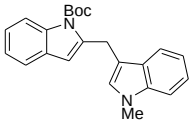
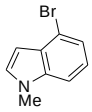
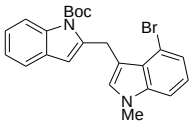
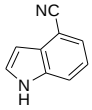
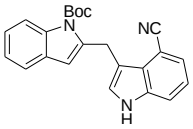
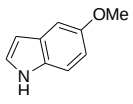
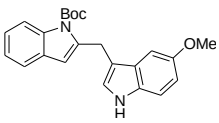
5.2.2 Investigation of Substrate Scope

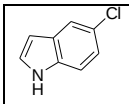
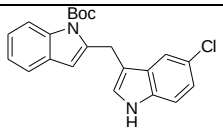
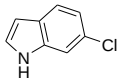
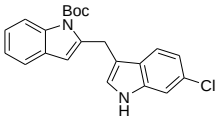
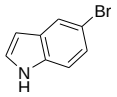
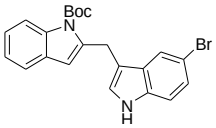
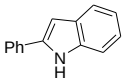
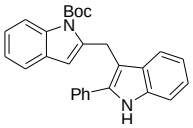
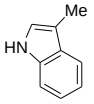
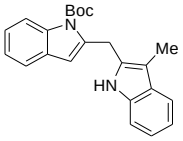
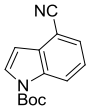
With the optimized condition in hand, we then examined the scope of different indoles for the tandem indole annulation/arylation using propargylic ether **5-4a** as the starting material (Table 5-2). *N*-Methyl indole **5-6b** afforded 88% yield of the 2,3'-diindolyl methane product **5-5b**. The yield was much lower for 4-Br substituted *N*-methylindole **5-5c**. We observed that the 4-cyano substituted indole **5-6d** did not interfere with the efficiency of the tandem reaction. Electron-donating methoxy or halogen substituents on the 5- or 6-position of the indole could also be tolerated in the indole annulation/arylation reaction.

We also studied the substituent effect on the 2- and 3-position of indole **5-6**. 2,2'-Diindolylmethane was obtained in lower yield when the 3-position of the indole is blocked in substrate **5-6j**. With a 2-phenyl substituent on indole **5i**, the yield of product **5-5i** is comparable to **5-6a**.

We also examined protecting group on indole nitrogen. It was found that when the indole was protected with Boc, no reaction was observed. The result indicated that the nucleophilicity of indole is responsible for the efficiency of the reaction.

Table 5-2. Scope of Indoles for Pt-Catalyzed Tandem Indole Annulation/Arylation of Propargylic Ether 5-4a.[a]

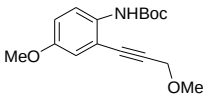
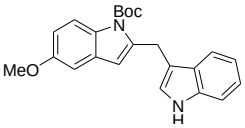
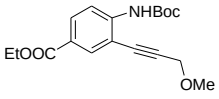
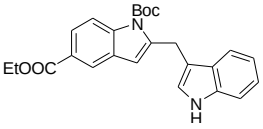
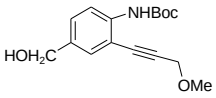
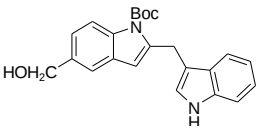
Indole Substrates	**Products**	**Yield(%)**[b]
5-6b 	**5-5b** 	**88**
5-6c 	**5-5c** 	**68**
5-6d 	**5-5d** 	**81**
5-6e 	**5-5e** 	**77**
5-6f	**5-5f**	**84**

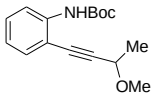
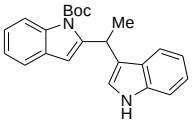
		
5-6g 	**5-5g** 	**85**
5-6h 	**5-5h** 	**82**
5-6i 	**5-5i** 	**80**
5-6j 	**5-5j** 	**60**
5-6k 	**--**	**0**

a. Conditions: $PtCl_2$ (10 mol %), $P(C_6F_5)_3$(20 mol %),100 ^oC, dixoane, Na_2CO_3 (1.5 equiv), 12h. *b.* Isolated yield.

The scope propargylic ethers with different substituents were also investigated (table 5-3).[9] We focused on the *para*-position of the aniline since the nucleophilicity of the aniline nitrogen can be systematically examined. We were pleased to find anilines with both electron-donating methoxy group and electron-withdrawing ester group on the *para*-position participated in the tandem reaction with similar efficiency. For substrate **5-7c** with a free hydroxyl group, the yield dropped to 55%. When propargylic ether **5-7d** was employed, diindolylethane **5-8d** could also be prepared efficiently.

Table 5-3. Scope of Propargylic Ether for Pt-Catalyzed Tandem Indole Annulation/Arylation.[a]

Indole Substrates	**Products**	**Yield**[b]
5-7a 	**5-8a** 	**77%**
5-7b 	**5-8b** 	**62%**
5-7c 	**5-8c** 	**55%**

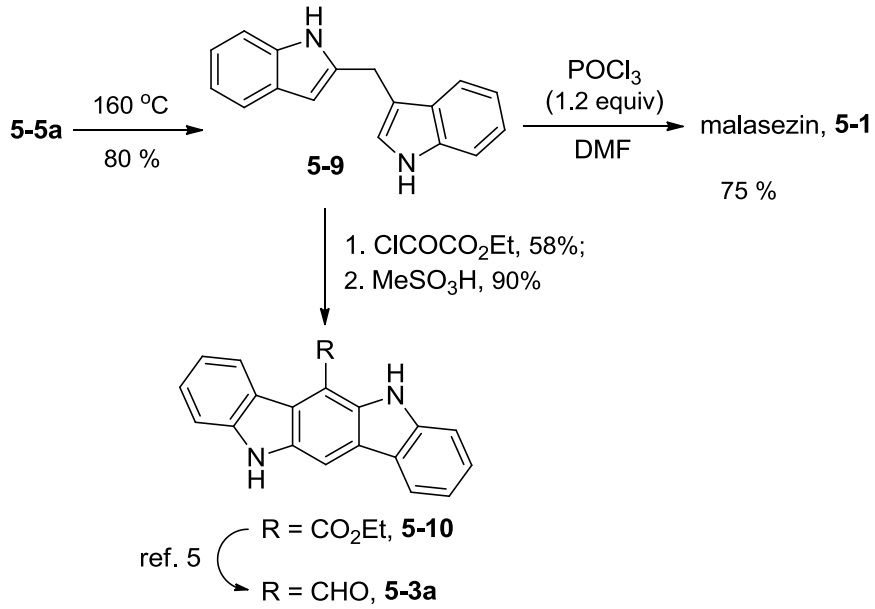
5-7d	5-8d	
		**70%**

[a]See Table 5-2 for conditions. [b.] Isolated yield.

5.2.3 Synthesis of Malassezin and FICZ

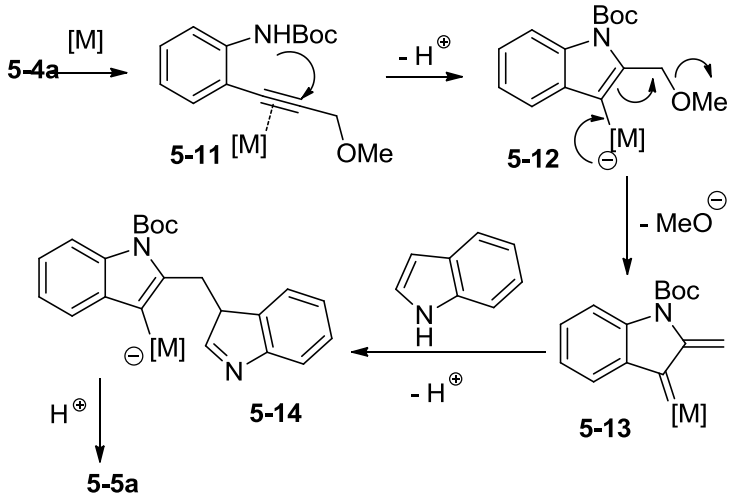
Removal of the Boc-protection group in product **5-5a** was unsuccessful under various conditions using TFA. We were pleased to find under thermal conditions, diindolylmethane **5-9** could be obtained in good yield, which then can undergo formylation to afford natural product malasezin **5-1** (Scheme 5-1). Indolo[3,2-*b*]carbazole **5-10** could be obtained by acylation of diindolylmethane **5-9** followed by acid-mediated cyclization. This represents a formal synthesis of natural product FICZ **5-3a**.[5]

Scheme 5-1. Synthesis of Malassezin and FICZ.



A possible mechanism for the indole annulation/arylation is depicted in Scheme 5-2. After substrate **5-4a** is activated by the coordination of metal catalyst, metal carbene **5-13** can be formed by initial 5-endo-cyclization to form intermediate **5-12** followed by elimination.[2,10] This electrophilic metal carbene can then be attacked by indole nucleophiles to form **5-14**, which could further undergo protonation and aromatization can then lead to diindolylmethane product **5-5a**.

Scheme 5-2. Proposed Mechamism for Indole Annulation/Arylation.



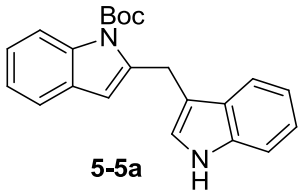
5.3 Experimental Section

General Remarks

All reactions in non-aqueous media were conducted under a positive pressure of dry argon in glassware that had been oven dried prior to use unless noted otherwise. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Thin layer chromatography was performed using precoated silica gel plates (EMD Chemical Inc. 60,

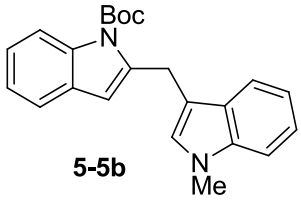
F254). Flash column chromatography was performed with silica gel (Silicycle, 40-63 μm). Infrared spectra (IR) were obtained on a Bruker Equinox 55 Spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Varian Unity-Inova 400 MHz or 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in $CDCl_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint),or multiplet (m), with coupling constants (*J*) in hertz. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer. The optical rotation was determined using a Perkin–Elmer 241 Polarimeter.

General procedures for the Pt-catalyzed tandem indole annulation/arylation: To an oven-dried flask was added $PtCl_2$ (2.7 mg, 0.01 mmol), Na_2CO_3 (16mg, 0.15 mmol), indole **5a** (23.4mg, 0.2 mmol), **4** (26.3mg, 0.1 mmol) and dioxane (0.5 ml). The flask was degassed with Ar, sealed and heated to 100 ^{o}C overnight. After the reaction was complete, the solvent was evaporated. The residue was purified by flash column chromatography on silica.



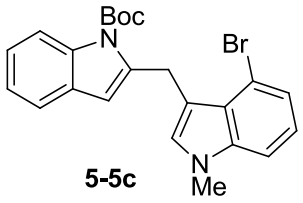
5-5a

tert-butyl 2-((1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 205 mg, 83% yield; brown solid, m.p.=134 – 135 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.60 (s, 9H), 4.49 (s, 2H), 6.17 (s, 1H), 7.01 (d, *J*= = 2.4 Hz, 1H), 7.09 (ddd,*J* = 8.0, 6.8, 1.2 Hz, 1H), 7.14 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.21 (m, 2H), 7.33 (m, 1H), 7.39 (m, 1H), 7.56 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.00 (br, 1H), 8.11 (dd, *J* = 8.4, 0.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 26.7, 28.3, 83.9, 108.7, 111.3, 113.8, 115.6, 119.4, 119.5, 120.0, 122.2, 122.7, 122.8, 123.4, 127.6, 129.4, 136.4, 137.0, 141.0, 150.9. IR (film): ν 3418, 2979, 1727, 1454, 1370, 1326, 1159, 1115, 1083, 906 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}N_2O_2$ $(M+Na)^+$ 369.1573, found 369.1580.



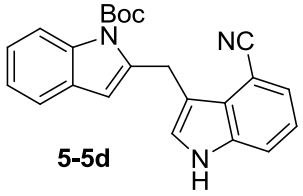
5-5b

tert-butyl 2-((1-methyl-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 49 mg, 88% yield; gray soild, m.p.=92-94 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.64 (s, 9H), 3.78 (s, 3H), 4.51 (s, 2H), 6.20 (s, 1H), 6.90 (s, 1H), 7.12 (ddd, *J* = 8.0, 7.2, 0. 8 Hz, 1H), 7.18 (td, *J* = 8.0, 1.2 Hz, 1H), 7.26 (m, 2H), 7.36 (m, 2H), 7.58 (dt, *J* = 8.0, 1.2 Hz, 1H), 8.16 (dd, *J* = 8.0, 0.8 Hz, 1H). ^{13}C NMR (100MHz, $CDCl_3$): 26.6, 28.3, 32.8, 83.8, 108.7, 109.3, 112.2, 115.6, 119.0, 119.5, 120.0, 121.7, 122.7, 123.4, 127.6, 128.0, 129.4, 137.0, 137.2, 141.3, 150.9. IR (film): ν 2976, 1727, 1453, 1369, 1324, 1156, 1114, 1081, 907 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{23}H_{25}N_2O_2$ $(M+H)^+$ 361.1911, found 361.1916.



5-5c

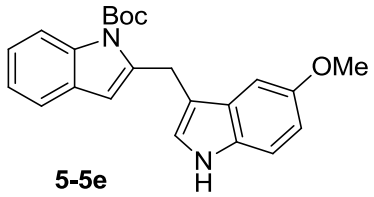
tert-butyl 2-((4-bromo-1-methyl-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 66 mg, 68% yield; brown soild, m.p.=161-162 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.61 (s, 9H), 3.76 (s, 3H), 4.79 (s, 2H), 6.19 (s, 1H), 6.79 (s, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H), 7.31 (m, 3H), 7.44 (d, *J* = 7.0 Hz, 1H), 8.26 (dd, *J* = 8.0, 1.0 Hz, 1H). ^{13}C NMR (125MHz, $CDCl_3$): 150.9, 141.6, 138.5, 137.2, 129.5, 128.9, 125.9, 123.5, 123.4, 122.7, 122.6, 120.0, 115.6, 114.8, 113.8, 109.1, 108.7, 83.8, 33.0, 29.9, 28.2. IR (film): ν 2916, 1728, 1454, 1369, 1334, 1162, 1115, 1082, 908, 769, 736 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{23}H_{24}BrN_2O_2$ $(M+H)^+$ 439.1016, found 439.1016.



5-5d

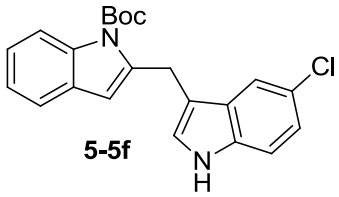
tert-butyl 2-((4-cyano-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 62 mg, 81% yield; yellow solid, m.p.=155-157 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.52 (s, 9H), 4.75(s, 2H), 6.20 (s, 1H), 6.99 (s, 1H), 7.20 (m, 3H), 7.38 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.45 (dd, J = 7.2, 0.8 Hz, 1H), 7.57 (dd, *J* = 8.0, 0.8 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.46 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 150.8, 140.2, 137.2, 136.6, 129.3, 126.7, 126.4, 125.7, 123.6, 122.7, 121.8, 120.0, 119.3, 116.3, 115.7, 114.6, 109.0, 102.3, 83.9, 28.2, 26.5. IR

(film): ν 3359, 2980, 2217, 1728, 1454, 1325, 1159, 1114, 1082, 907 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{23}H_{22}N_3O_2$ $(M+H)^+$ 372.1707, found 372.1706.



5-5e

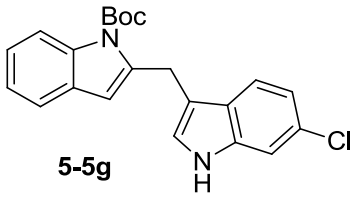
tert-butyl 2-((5-methoxy-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 56 mg, 77% yield.; yellow soild, m.p.=98-99 ^oC. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 1.60 (s, 9H), 3.86 (s, 3H), 4.51 (s, 2H), 6.23 (s, 1H), 6.94 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.03 (t, *J* = 2.5 Hz, 2H), 7.22 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.30 (m, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.98 (br, 1H), 8.20 (dd, *J* = 8.0, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 26.8, 28.3, 56.1, 83.9, 101.1, 108.7, 112.0, 112.5, 113.5, 115.6, 120.1, 122.7, 123.4, 123.6, 128.0, 129.4, 131.6, 137.0, 141.0, 150.9, 154.2. IR (film): ν 3418, 2979, 1727, 1485, 1453, 1369, 1326, 1215, 1160, 1115, 1082, 907 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{23}H_{25}N_2O_3$ $(M+H)^+$ 377.1860, found 377.1855.



5-5f

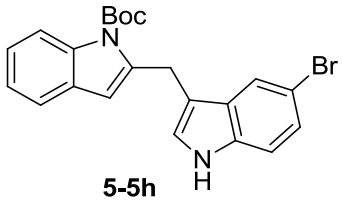
tert-butyl 2-((5-chloro-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 200 mg, 84% yield; yellow solid, m.p.=162-163 ^oC. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.60 (s, 9H),

4.43 (s, 2H), 6.13 (s, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 7.23 (m, 4H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 8.01 (br, 1H), 8.11 (dd, *J* = 8.4, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 150.9, 140.6, 137.0, 134.8, 129.3, 128.7, 125.4, 124.2, 123.6, 122.8, 122.5, 120.1, 118.8, 115.6, 113.7, 112.3, 108.7, 84.0, 28.3, 26.5. IR (film): 3416, 2981, 1728, 1707, 1453, 1368, 1327, 1220, 1157, 1115, 1080, 797, 746. HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}ClN_2O_2$ $(M+H)^+$ 381.1365, found 381.1348.



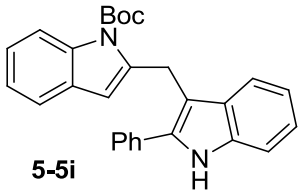
5-5g

tert-butyl 2-((6-chloro-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 65 mg, 85%. yield; white soild, m.p.=155-156 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.61 (s, 9H), 4.47 (s, 2H), 6.16 (s, 1H), 6.95 (m, 1H), 7.08 (m, 1H), 7.18 (m, 1H), 7.25 (m, 1H), 7.35 (m, 2H), 7.46 (m, 1H), 7.98 (br, 1H), 8.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 150.9, 140.6, 137.0, 136.8, 129.3, 128.1, 126.2, 123.6, 123.4, 122.8, 120.39, 120.33, 120.1, 115.6, 114.1, 111.2, 108.7, 84.0, 28.3, 26.6. IR (film): ν 3427, 2977, 1728, 1453, 1393, 1325, 1157, 1115, 1063, 905, 803 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}ClN_2O_2$ $(M+H)^+$ 381.1365, found 381.1360.



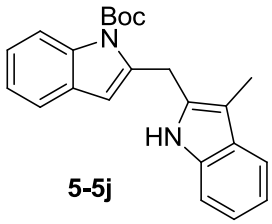
5-5h

tert-butyl 2-((5-bromo-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 70 mg, 82% yield; brown soild, m.p.=159-160 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.62 (s, 9H), 4.34(s, 2H), 6.04 (s, 1H), 6.86 (s, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.15 (m, 3H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.96 (br, 1H), 8.07 (dd, *J* = 8.0, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 150.9, 140.6, 137.0, 135.0, 129.38, 129.32, 125.1, 124.1, 123.6, 122.8, 121.9, 120.1, 115.6, 113.5, 112.9, 112.8, 108.7, 84.0, 28.3, 26.5. IR (film): 3421, 2980, 1728, 1454, 1369, 1327, 1156, 1115, 1084, 907, 795. HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}BrN_2O_2$ $(M+H)^+$ 425.0860, found 425.0860.



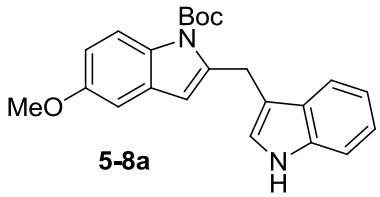
5-5i

tert-butyl 2-((2-phenyl-1H-indol-3-yl)methyl)-1H-indole-1-carboxylate. 270 mg, 80%.yield; white soild, m.p.=145-146 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.68 (s, 9H), 4.55 (s, 2H), 6.05 (s, 1H), 7.11 (m, 2H), 7.21-7.41 (m, 7H), 7.49 (m, 3H), 8.14 (br, 2H), 8.17 (dd, *J* = 8.4, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 26.6, 28.5, 84.1, 108.9, 109.7, 111.0, 115.7, 119.6, 120.0, 120.1, 122.6, 122.7, 123.4, 127.7, 128.0, 129.1, 129.5, 132.7, 135.8, 136.1, 137.1, 141.6, 151.1. IR (film): ν 3412, 2997, 2974, 1730, 1454, 1369, 1326, 1248, 1161, 1114, 1082, 908, 737, 698 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{28}H_{27}N_2O_2$ $(M+H)^+$ 423.2068, found 423.2059.



5-5j

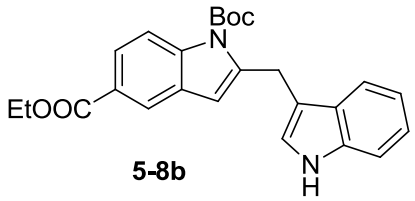
tert-butyl 2-((3-methyl-1H-indol-2-yl)methyl)-1H-indole-1-carboxylate. 105 mg, 60% yield; brown solid, m.p.=144-145 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.76 (s, 9H), 2.37 (s, 3H), 4.56(s, 2H), 6.31 (s, 1H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1H), 7.19 (td, *J* = 7.0, 1.5 Hz, 1H), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H), 7.29 (m, 2H), 7.46 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.23 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 151.2, 138.9, 136.6, 135.3, 131.7, 129.3, 129.3, 123.8, 123.0, 121.5, 120.2, 119.1, 118.5, 115.8, 110.6, 109.2, 108.4, 84.6, 28.4, 27.3, 8.7. IR (film): 3418, 2980, 1732, 1454, 1371, 1330, 1163, 1117, 1083, 909. HRMS (ESI) *m/z* calcd. for $C_{23}H_{25}N_2O_2$ $(M+H)^+$ 361.1911, found 361.1901.



5-8a

tert-butyl 2-((1H-indol-3-yl)methyl)-5-methoxy-1H-indole-1-carboxylate. 58 mg, 77% yield; yellow solid, m.p.=97-98 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.62 (s, 9H), 3.80 (s, 3H), 4.48 (s, 2H), 6.10 (s, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.85 (dd, J = 9.2, 2.8 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 7.39 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 8.11 (br, 1H), 8.02 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 155.9, 150.8, 141.8, 136.4, 131.7, 130.2,

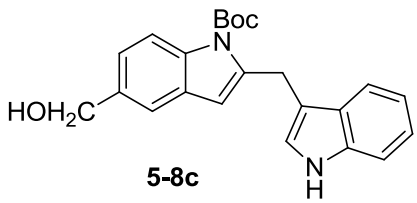
127.6, 122.8, 122.2, 119.5, 119.4, 116.4, 113.8, 111.9, 111.3, 108.6, 102.8, 83.7, 55.8, 28.3, 26.8. IR (film): 3414, 2979, 1727, 1477, 1450, 1370, 1162, 1122, 1084, 908, 734. HRMS (ESI) *m/z* calcd. for $C_{23}H_{24}N_2O_3Na$(M+Na) 399.1680, found 399.1666.



5-8b

2-(1H-Indol-3-ylmethyl)-indole-1,5-dicarboxylic acid 1-tert-butyl ester 5-ethyl ester.

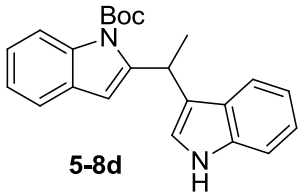
49 mg, 62% yield; green solid, m.p.=100-102 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.08 Hz, 3H), 1.6 (s, 9H), 4.36 (q, *J* = 7.16 Hz, 2H), 4.48 (s, 2H), 6.25 (s, 1H), 6.99 (d, *J* =2.32, 1H), 7.09 (ddd, *J* = 8.00, 7.09, 1.00 Hz, 1H), 7.22(ddd, *J* = 8.16, 7.00, 1.2 Hz, 1H) 7.38 (d, *J* =8.2, 1H), 7.54 (d, *J* = 7.92 Hz,1H), 7.94(dd, *J* = 8.84, 1.80 Hz, 1H) 8.08 (d, *J* = 1.6 Hz, 2H), 8.15(d, *J* = 8.84 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.61, 26.81, 28.33, 60.94, 84.67, 109.09, 111.42, 113.47, 115.26, 119.36, 119.71, 122.24, 122.36, 122.90, 124.88, 125.01, 127.53, 129.13, 136.55, 139.80, 142.50, 150.62, 161.39. IR (film) 730.94, 906.99, 1086.17, 1159.77, 1242.33, 1370.15, 1709.71 ν cm^{-1}. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_2O_4$ $(M+H)^+$ 419.1966, found 419.1980.



5-8c

5-Hydroxymethyl-2-(1H-indol-3-ylmethyl)-indole-1-carboxylic acid tert-butyl ester

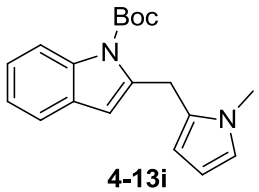
25 mg, 55% yield; brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 9H), 4.46 (s, 2H), 4.69 (s, 2H), 6.14 (s, 1H), 6.94 (d, *J* =2.40 Hz, 1H), 7.08 (ddd, *J* = 7.96, 7.00, 1.04 Hz, 1H), 7.17-7.23 (m, 2H) 7.38(d, *J* =1.04, 1H), 7.36 (dt, *J* = 8.16, 1.00 Hz, 1H), 7.56(dq, *J* = 7.92, 1.00 Hz, 1H) 8.03 (s, 1H), 8.09(d, *J* = 9.64 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.82, 28.38, 65.92, 84.13, 108.77, 111.38, 113.79, 115.78, 118.80, 119.44, 119.63, 122.27, 122.88, 1229, 127.61, 129.64, 135.47, 136.54, 136.70, 141.67, 150.90. IR (film) 731.67, 908.08, 1032.86, 1252.46, 1315.52, 1726.58 ν cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{24}N_2O_3$ $(M+H)^+$ 377.1860, found 377.1863.



5-8d

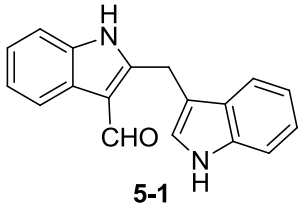
tert-butyl 2-(1-(1H-indol-3-yl)ethyl)-1H-indole-1-carboxylate. 25 mg, 70% yield, brown solid, 141-142 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.47 (s, 9H), 1.75 (d, *J* = 7.2 Hz, 3H), 5.19 (q, J = 7.2 Hz, 1H), 6.35 (s, 1H), 6.78 (dd, J = 2.4, 0.8 Hz, 1H), 7.07 (ddd, *J* = 8.0, 6.7, 0.8 Hz, 1H), 7.17 (m, 2H), 7.23 (ddd, *J* = 8.8, 6.8, 1.6 Hz, 1H), 7.34 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.40 (ddd, *J* = 7.6, 1.6, 0.8 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.90 (br, 1H), 8.10 (dd, *J* = 8.4, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 150.7, 146.0, 137.3, 136.7, 129.2, 126.8, 123.5, 122.6, 122.1, 121.3, 121.0, 120.2, 119.8, 119.4, 115.5, 111.3, 107.3, 83.8, 30.8, 28.1, 21.4. IR (film): ν 3421, 2976, 2362, 1728, 1454, 1368,

1326, 1156, 1116, 908 cm^{-1}.HRMS (ESI) *m/z* calcd. for $C_{23}H_{24}N_2O_2$ $(M+H)^+$ 361.1911, found 361.1908.



4-13i

tert-butyl 2-((1-methyl-1H-pyrrol-2-yl)methyl)-1H-indole-1-carboxylate. 21 mg, 63% yield; brown oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.66 (s, 9H), 3.52 (s, 3H), 4.29 (s, 2H), 5.92 (s, 1H), 5.98 (m, 1H), 6.12 (m, 1H), 6.64 (m, 1H), 7.22 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.1, 28.4, 33.8, 84.1, 107.0, 108.2, 108.6, 115.7, 120.1, 121.8, 122.8, 123.6, 129.3, 129.7, 136.9, 140.1, 150.8. IR (film): ν 2976, 1729, 1454, 1369, 1161, 1081, 744 cm^{-1}. HRMS (ESI) *m/z* calcd. for $C_{19}H_{22}N_2O_2$ $(M+Na)^+$ 333.1573, found 333.1575.

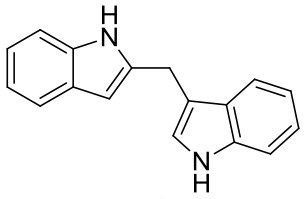


5-1

Compound **5-5a** (49 mg, 0.18 mmol) was heated at 160 ^oC for 45 min, the residue was purified by flash column chromatography (Hexane/EtOAc = 8:1 to 4:1) to provide 25 mg of free bisindole **5-9** (70%). To 0.3 mL of DMF was added $POCl_3$ (10 ul, 0.11 mmol) dropwise over 5 min at 0 ^oC. After 10 min, a solution of bisindole **5-9** (25 mg, 0.1 mmol) in 0.2 ml of DMF was added. The solution was stirred at room temperature overnight and

was poured into $NaHCO_3$ solution, extracted with ether, washed with 0.1 M NaOH solution, dried over $MgSO_4$ and purified by flash column chromatography (Hexane/EtOAc = 1.5:1) to provide pinkish product.

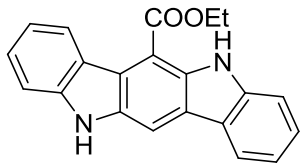
2-((1H-indol-3-yl)methyl)-1H-indole-3-carbaldehyde 20.5 mg, 75% yield; pinkish solid, 235-236 ^{o}C. ^{1}H NMR (400 MHz, CCl_4:DMSO-d_6 = 1:4): δ 4.52 (s, 2H), 6.92 (t, *J* = 6.8 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.11(m, 2H), 7.21(s, 1H), 7.33 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 8.03 (m, 1H), 10.23 (s, 1H), 10.92 (br, 1H), 11.85 (br, 1H). ^{13}C NMR (100 MHz, CCl_4:DMSO-d_6 = 1:4): 185.1, 152.0, 137.1, 136.3, 127.4, 126.4, 124.5, 123.4, 122.6, 122.0, 121.1, 119.4, 119.0, 113.9, 112.5, 112.3, 111.6, 22.9. IR (film): 3412, 2910, 1643, 1465, 1390, 1246, 822. All spectroscopic data are in accordance with literature.[13]



5-9

3-((1H-indol-2-yl)methyl)-1H-indole. Compound **5-5a** (49 mg, 0.18 mmol) was heated at 160 ^{o}C for 45 min, the residue was purified by flash column chromatography (Hexane/EtOAc = 8:1 to 4:1) to provide 25 mg of free bisindole **5-9** (70%). Pinkish solid; 136–137 ^{o}C. . ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.26(s, 2H), 6.38 (m, 1H), 7.00 (m, 1H), 7.07 (m, 3H), 7.20 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.53 (m, 2H), 7.79 (br, 1H), 7.92 (br, 1H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.19 (s, 2H), 6.17(s, 1H), 6.95 (m, 3H), 7.07 (td, *J* = 6.4, 0.8 Hz, 1H), 7.24 (d, *J* = 1.6 Hz, 1H), 7.27(d, *J* = 6.4 Hz, 1H), 7.37 (d, *J* = 6.4 Hz, 1H), 7.39 (d, *J* = 6.4Hz, 1H), 7.50 (d, *J* = 6.4 Hz, 1H), 10.89 (br, 2H). ^{13}C

NMR (100 MHz, $CDCl_3$): 138.4, 136.6, 136.1, 129.0, 127.4, 122.8, 122.5, 121.1, 120.0, 119.9, 119.7, 119.2, 113.0, 111.4, 110.6, 100.2, 24.6. IR (film): 3403,2926, 1458, 1418, 1342, 1285, 908 cm^{-1}. All spectroscopic data are in accordance with literature.[30]



5-10

To a solution of bisindole **5-9** (57mg, 0.23 mmol) in 1.5 ml of THF at 0 ^oC under Ar was added 0.03 ml of pyridine quickly followed by ethyl oxalyl chloride (0.054 ml, 0.35 mmol) slowly over 10 min. The reaction was stirred for 6 h. The mixture was diluted with EtOAc, washed with 1 M HCl, then $NaHCO_3$ and dried over $MgSO_4$. The residue was purified by flash column chromatography (Hexane/EtOAc = 3:1 to 2:1). The purified intermediate was dissolved in 4 mL of dioxane and 0.1 mL of $MeSO_3H$ was added dropwise. The solution was heated to reflux for 1h and then cooled down to room temperature. Silica was added and the residue was purified by flash column chromatography (Hexane/CH_2Cl_2 = 1:1).

ethyl 5,11-dihydroindolo[3,2-b]carbazole-6-carboxylate. 40 mg, 52% for two steps, yellow solid; 217-218 ^oC. ^1H NMR (400 MHz, acetone-d_6): δ 1.43 (t, *J* = 6.8 Hz, 3H), 4.57 (q, *J* = 6.8 Hz, 2H), 7.04 (qd, J = 7.6, 0.8 Hz, 2H), 2.95 (td, J = 7.2, 1.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H), 8.83 (d, J = 8.0 Hz, 1H), 10.40 (br, 2H). ^{13}C NMR (100 MHz, acetone-d_6): 168.9, 143.4,

142.7, 138.3, 137.1, 127.7, 127.6, 127.2, 125.1, 123.7, 123.5, 122.5, 121.5, 120.3, 119.4, 112.5, 111.9, 108.2, 106.7, 62.2, 15.5. IR (film): 3393, 2976, 1675, 1610, 1510, 1455, 1416, 1295, 1111, 908, 870. All spectroscopic data are in accordance with literature.[30]

5.4 Reference

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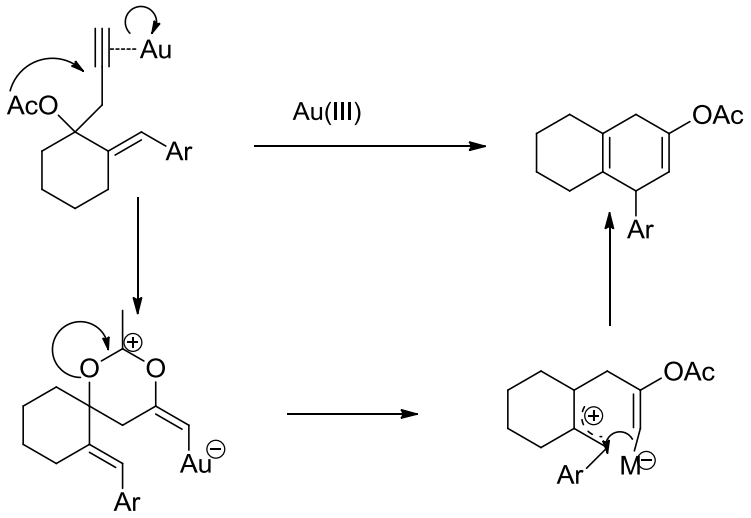
Appendix 1

Rhodium and Iridium-catalyzed 1,4-Acyloxy Migration

While π-acidic metal-promoted 1,2- and 1,3-acyloxy migration of propargylic esters are common, 1,4-acycloxy migration is rare. In 2006, Zhang first reported a novel 1,4-acycloxy migration catalyzed by gold (scheme A1-1).[1] The reaction involves an initial 1,4-acyloxy migration promoted by gold to generate a stabilized carbocation, followed by cyclization to form a six-membered ring.

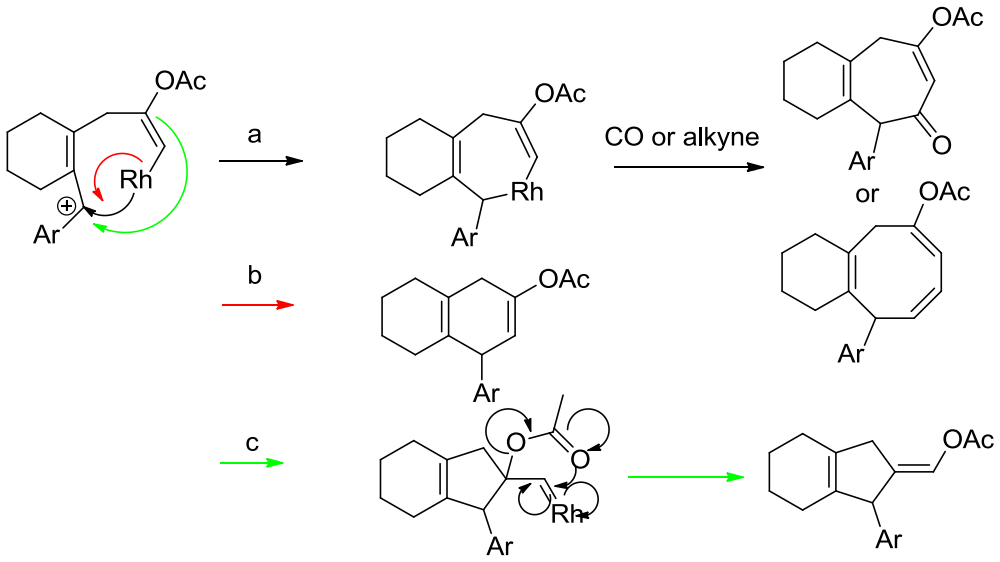
Scheme A1-1. Gold-catalyzed Cycloisomerization Involving 1,4-Acyloxy Migration.



Inspired by Zhang's work, we anticipated that certain rhodium complexes may also promote a similar 1,4-acyloxy migration. Unlike gold, rhodium is well known for its redox reactivity, which may allow a following CO or alkyne insertion and reductive elimination (pathway **a**, scheme A1-2). We also anticipated that the

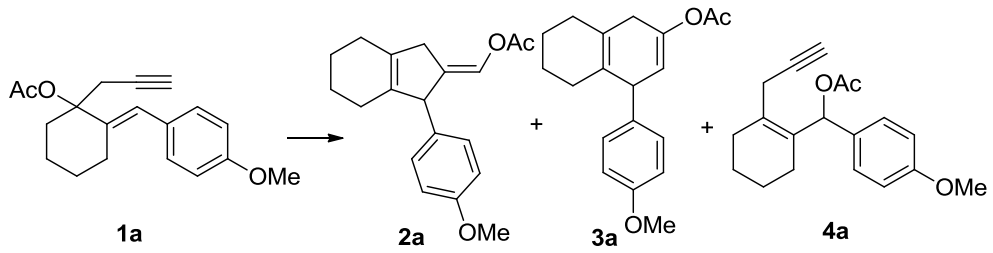
reaction might follow pathway **b** to generate a six-membered ring, or pathway **c** to form a five-membered ring.

Scheme A1-2. Proposed Rhodium-catalyzed Reactions Involving 1,4-Acyloxy Migration.



With all of these possible pathways in mind, we Prepared substrate **1** and screened various metal complexes (table A1-1). Cationic rhodium catalyst led to no desired product, instead allylic acetate isomerization was observed (entries 1-2). $[Rh(CO)_2Cl]_2$ in CH_2ClCH_2Cl provided us six-membered ring **3a** in 50% yield. However, no desired [6+1] product was observed. Platinum complexes led to either no reaction or a complex mixture. With iridium catalysts, we observed five-membered ring **2a** for the first time, together with six-membered ring **3a**. The ratio could be improved to 8:1 by employing $[Ir(cod)Cl]_2$ as the catalyst.

Table A1-1. Catalyst and Condition Screening for Substrate 1a.

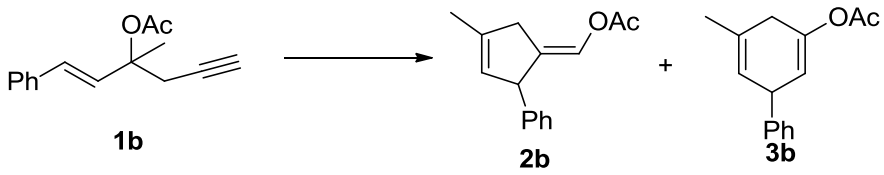


Entry	Catalyst and Condition	NMR Yield
1	$[Rh(cod)_2]BF_4$ (5%), toluene (0.015M), 90 ^oC, 4h	0%
2	$[Rh(cod)_2]BF_4$ (5%), toluene (0.015M), 80 ^oC, CO, 8h	**4a** (45%)
3	$[Rh(CO)_2Cl]_2$ (5%), Toluene(0.015M), 90 ^oC, 4h	complex
4	$[Rh(CO)_2Cl]_2$(5%), toluene (0.015M), 90 ^oC, CO(1atm)	complex
5	**$[Rh(CO)_2Cl]_2$(5%), CH_2ClCH_2Cl (0.015M), CO, 60 ^oC, overnight**	**3a** (50%)
6	$PtCl_2$(10%), CO, toluene (0.015M), 80 ^oC, 8h	substrate recovery
7	$PtCl_4$ (10%), CO, 2h, toluene (0.015M), 80 ^oC	complex
8	$IrCl(CO)(PPh_3)_2$ (5%), toluene(0.015M), 60 ^oC, CO, 4.5h	**2a** (45%), **3a** (35%)
9	**$IrCl(CO)(PPh_3)_2$ (5%), toluene(0.015M), 60 ^oC, Ar, 4.5h**	**2a** (45%), **3a** (35%)
10	**$[Ir(cod)Cl]_2$(5%), toluene(0.015M), 60 ^oC, Ar,**	**2a** (50%),

	overnight	**2a**:**3a**=8:1

Since yield and selectivity could not be further improved for substrate **1a**, we switched to substrate **1b**. To our disappointment, no reaction was observed under the optimized conditions (table A1-2).

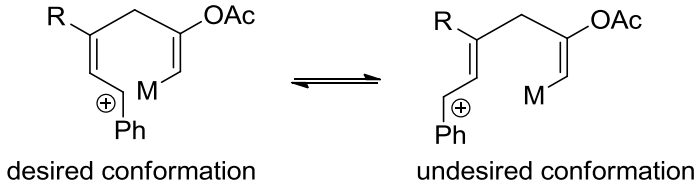
Table A1-2. Catalyst and Condition Screening for Substrate 1b.



Entry	Catalyst and Condition	NMR Yield
1[a]	.$[Rh(CO)_2Cl]_2$(5%), CH_2ClCH_2Cl (0.015M), CO	0%
2[a]	$IrCl(CO)(PPh_3)_2$ (5%), toluene (0.015M), Ar	0%
3[a]	$[Ir(cod)Cl]_2$ (5%), toluene (0.015M). Ar	0%
4[b]	$[Cp^*RhCl_2]_2$(5%), toluene (0.015M), CO	0%

[a]substrate recovery at 60 ^oC for 8h, decompose at 90 ^oC overnight. [b]substrate recovery at 90 ^oC.

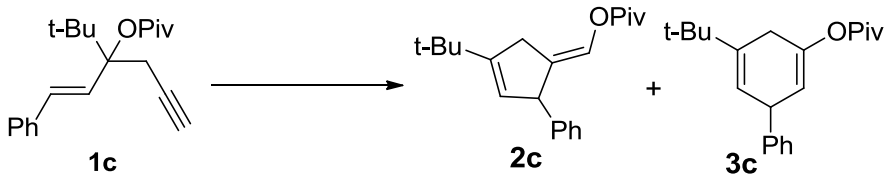
Scheme A1-3. Equilibrium between Desired and Undesired Conformation.



desired conformation undesired conformation

Based on literature, the low reactivity of substrate **1b** may be due to the unfavorable conformation of the intermediate (scheme A1-3). Thus we synthesized substrate **1c**. Indeed, this substrate with a bulky tert-butyl group decrease the impact of undesired conformation and we observed better yields (table A1-3).

Table A1-3. Catalyst and Condition Screening for Substrate 1c.



Entry	Catalyst and Condition	NMR Yield
1	**$[IrCl(CO)(PPh_3)_2]$ (5%), Ar, 80 ^oC**	**2c** (60%), **3c** (20%)
2	**$[Ir(cod)Cl]_2$ (5%), toluene (0.02M), 100 ^oC, Ar, 8h**	**2c**(40%), **2c**:**3c** = 10:1
3	$[Ir(cod)_2]BF_4$ (5%), toluene(0.02M), 100 ^oC, 8h	0%
4	$[Cp^*IrCl_2]$ (5%), toluene (0.02M), 8h, 100 ^oC, 8h	**2c** (30%), **2c**:**3c** = 10:1

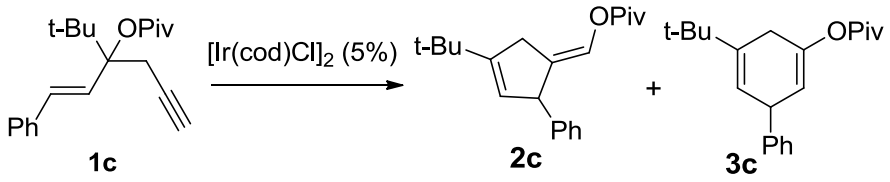
5[a]	**$[Rh(CO)_2Cl]_2$ (5%), CH_2ClCH_2Cl(0.02M), 80 °C, CO, overnight**	**3c** (30%). **2c**:**3c** = 1:3

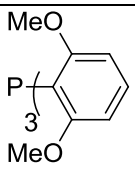
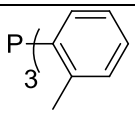
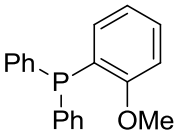
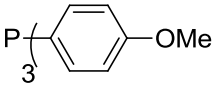
[a]only 60% conversion was observed.

For substrate **1c**, $[IrCl(CO)(PPh_3)_2]$ provided the best combined yield. $[Ir(cod)Cl]_2$ provided best **2c**:**3c** selectivity. $[Rh(CO)_2Cl]_2$ together with CO provided the best yield of **3c**. It was noteworthy that five-membered ring 2 was more favored from **3a** compared to the results from **1a**. For example, $[IrCl(CO)(PPh_3)_2]$ alone provided 3:1 selectivity in favor of 2c (entry 1, table A1-3), while in the previous case almost 1:1 ratio was observed (entry 9, table A1-2).

Since catalyst $[Ir(cod)Cl]_2$ provided us the best **2c**:**3c** selectivity, we screened different ligands to improve the yield of **2c** (table A1-4). When PPh3 was added as the ligand, results were similar to the one found using $[IrCl(CO)(PPh_3)_2]$ (entry1, table A1-3). A 2:1 catalyst to ligand ratio was found to be most effective (entry 2, table A1-4). Bidentate ligands inhibited the reaction (entries 4-5). Steric bulky ligand also slowed down the reaction, no conversion or little conversion was observed (entries 6-8). Electron donating ligand inhibited the reaction, while electron withdrawing ligand led to a complex mixture.

Table A1-4. Catalyst and Condition Screening for Substrate 1c.[a]



Entry	Ligand and Condition	NMR Yield (**2c**:**3c**)
1	PPh_3 (10%)	58% (3.5:1)
2	**PPh_3(20%)**	**2c**(64%), **2c**:**3c** = 4:1
3	PPh_3 (40%)	0%[b]
4	BINAP (10%),	0%
5	dppp or dppb (20%)	0%[b]
6		0%[b]
7		0%[b]
8		**2c**(15%), **2c**:**3c** = 4:1
9		0%[b]
10	P(*p*CF_3-Ph)$_3$	2c (32%), **2c**:**3c** = 5:1[c]
11	$P(C_6F_5)_3$	complex

12	$P(OCH(CF_3)_2)_3$	complex
13	$P(OEt)_3$	**2c**:**3c** = 2:1[d]

[a]unless noted, otherwise 20% ligand was added, toluene (0.02M), 80 °C, CO(1atm). [b]substrate recovery.[c]50% conversion. [d]majority is substrate recovery.

During the investigation, we also found that substrate **4a** underwent a 1,4-acycloxy migration to form diene **5a** (scheme A1-4). A possible mechanism was proposed which involves an initial 1,4-acyloxy migration followed by either a E1 elimination or β-H elimination. Various catalysts were screened for the transformation of **4a** to **5a** (table A1-5). 70% yield was obtained using $[Ir(cod)Cl]_2$ as the catalyst in toluene in the presence of CO (entry 6).

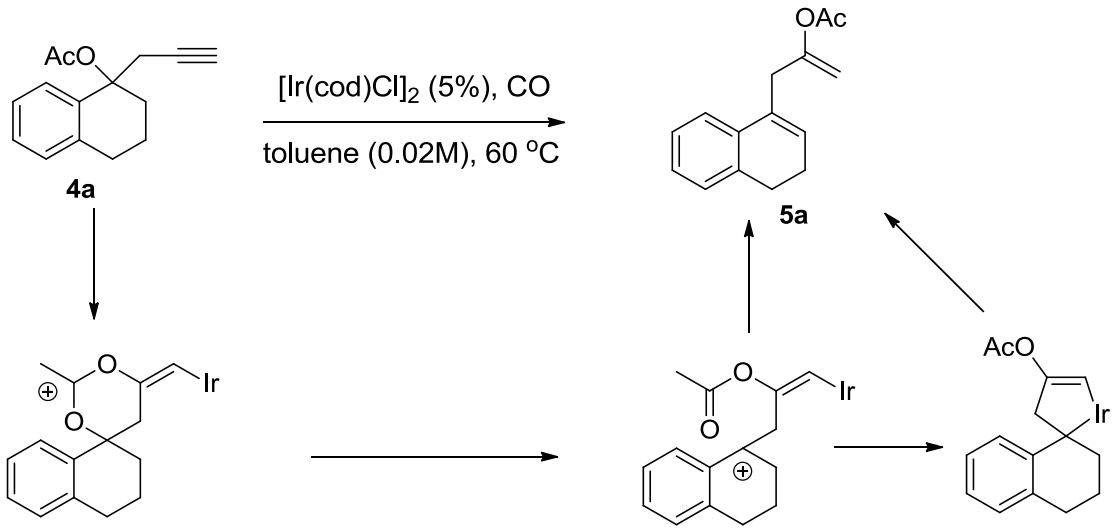
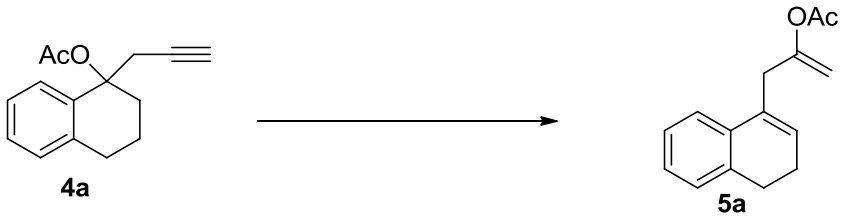


Table A1-5. Catalyst and Condition Screening for Substrate 4a.[a]



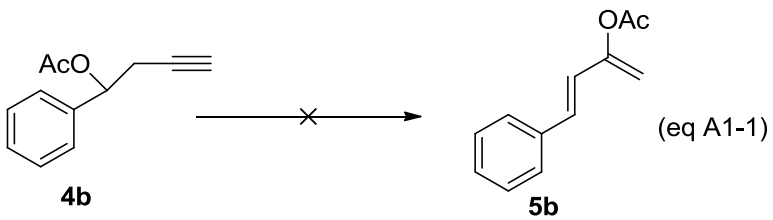
4a **5a**

Entry	Catalyst and Condition	NMR Yield
1	.$[Rh(CO)_2Cl]_2$, CH_2ClCH_2Cl, CO	messy
2	.$[Rh(CO)_2Cl]_2$, toluene, CO	messy
3	.$[Rh(CO)_2Cl]_2$, toluene, Ar	10%
4	$[Cp^*RhCl_2]_2$, toluene, CO	0%[b]
5	$IrCl(CO)(PPh_3)_2$,toluene	20%
6	$[Ir(cod)Cl]_2$, toluene,CO	70%
7	$[Rh(cod)_2]BF_4$ (5%), CH_2ClCH_2Cl	messy

[a]unless noted, otherwise 20% ligand was added, toluene (0.02M), 80 ^oC, CO(1atm).

[b]substrate recovery.

We also tested the optimized condition with substrate **4b**, no reaction was observed under various conditions (eq A1-1).



4b **5b** (eq A1-1)

In conclusion, we found that rhodium and iridium could promote a 1,4-acyloxy migration. In the following cyclization event, rhodium catalyzes a six-membered ring

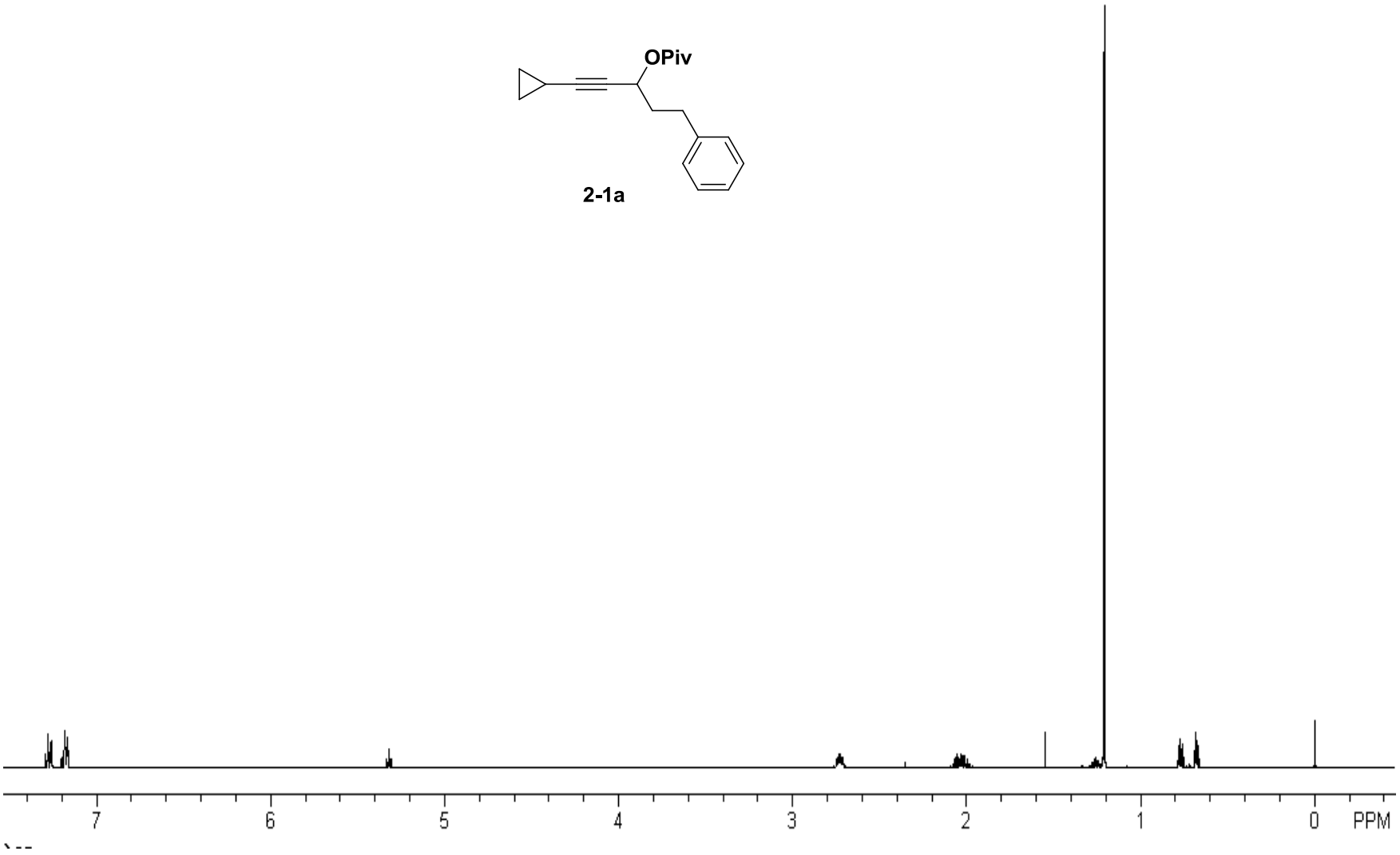
closure, while iridium generally prefers a five-membered ring formation to form iridium carbene.

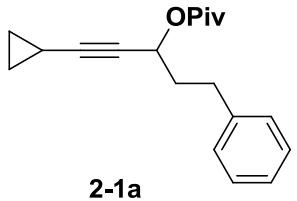
Reference

(1) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274.

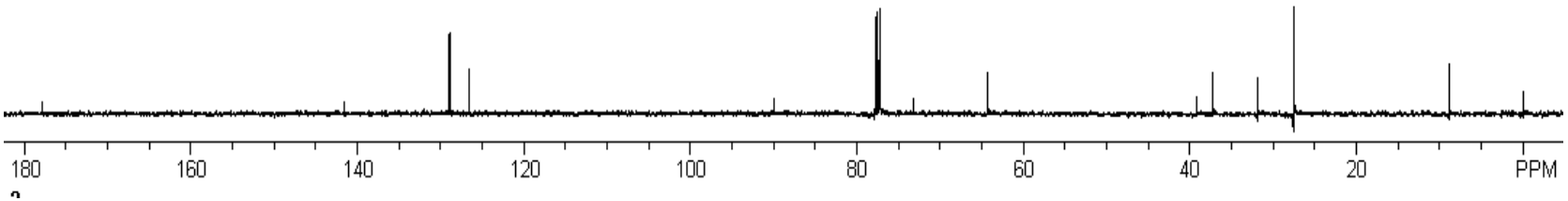
Appendix 2

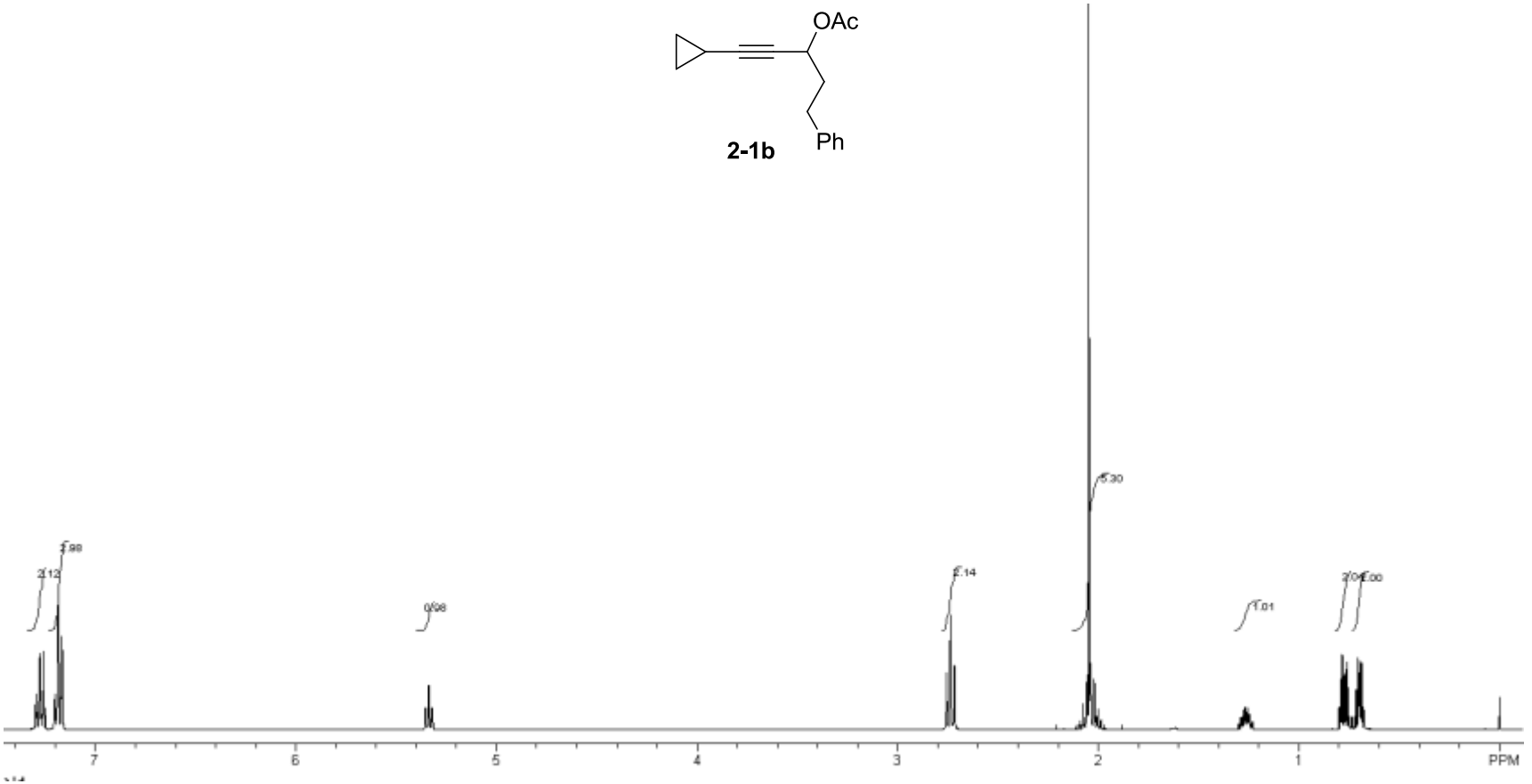
NMR Spectra of Compounds

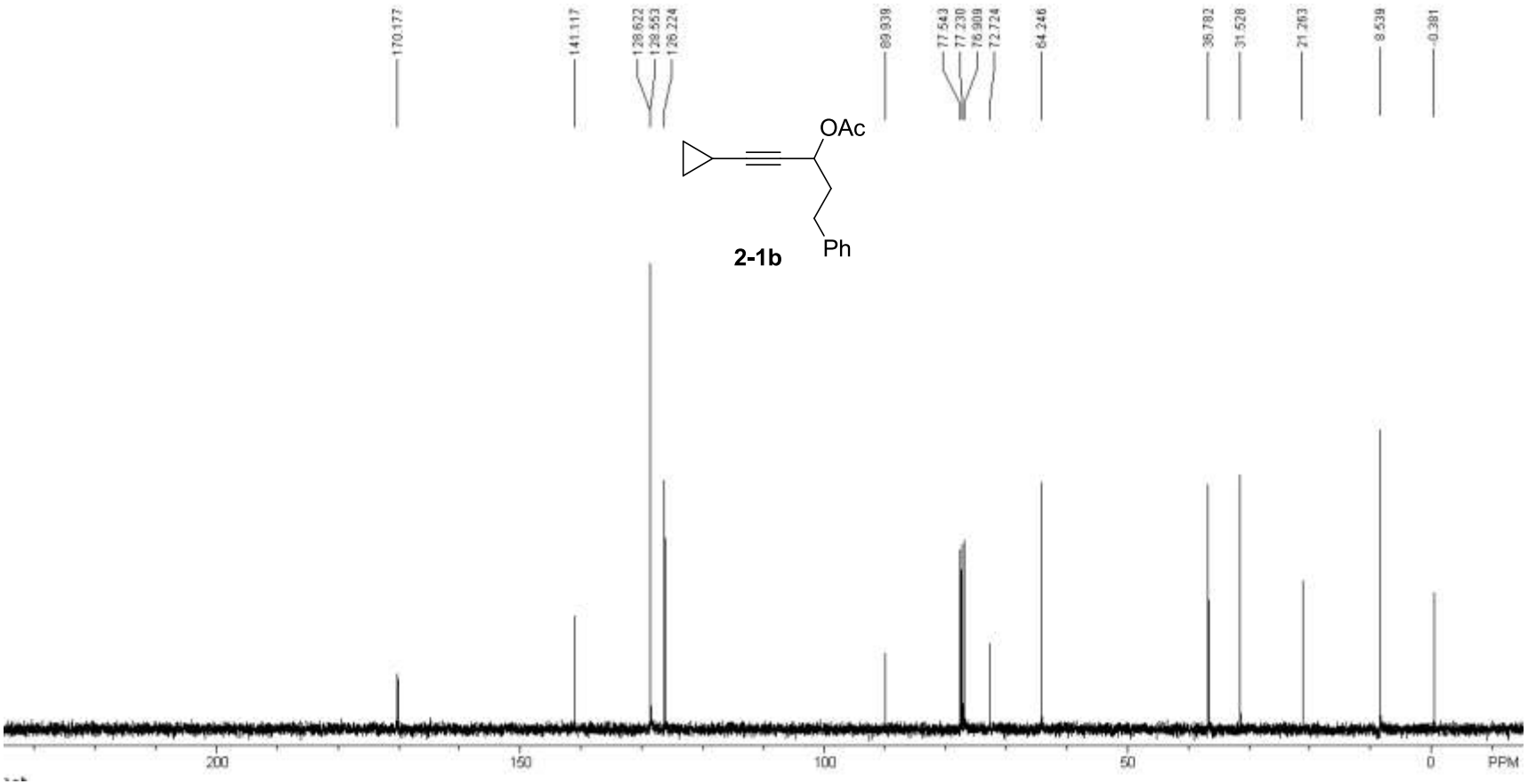

OPiv
2-1a
7
6
5
4
3
2
1
0
PPM

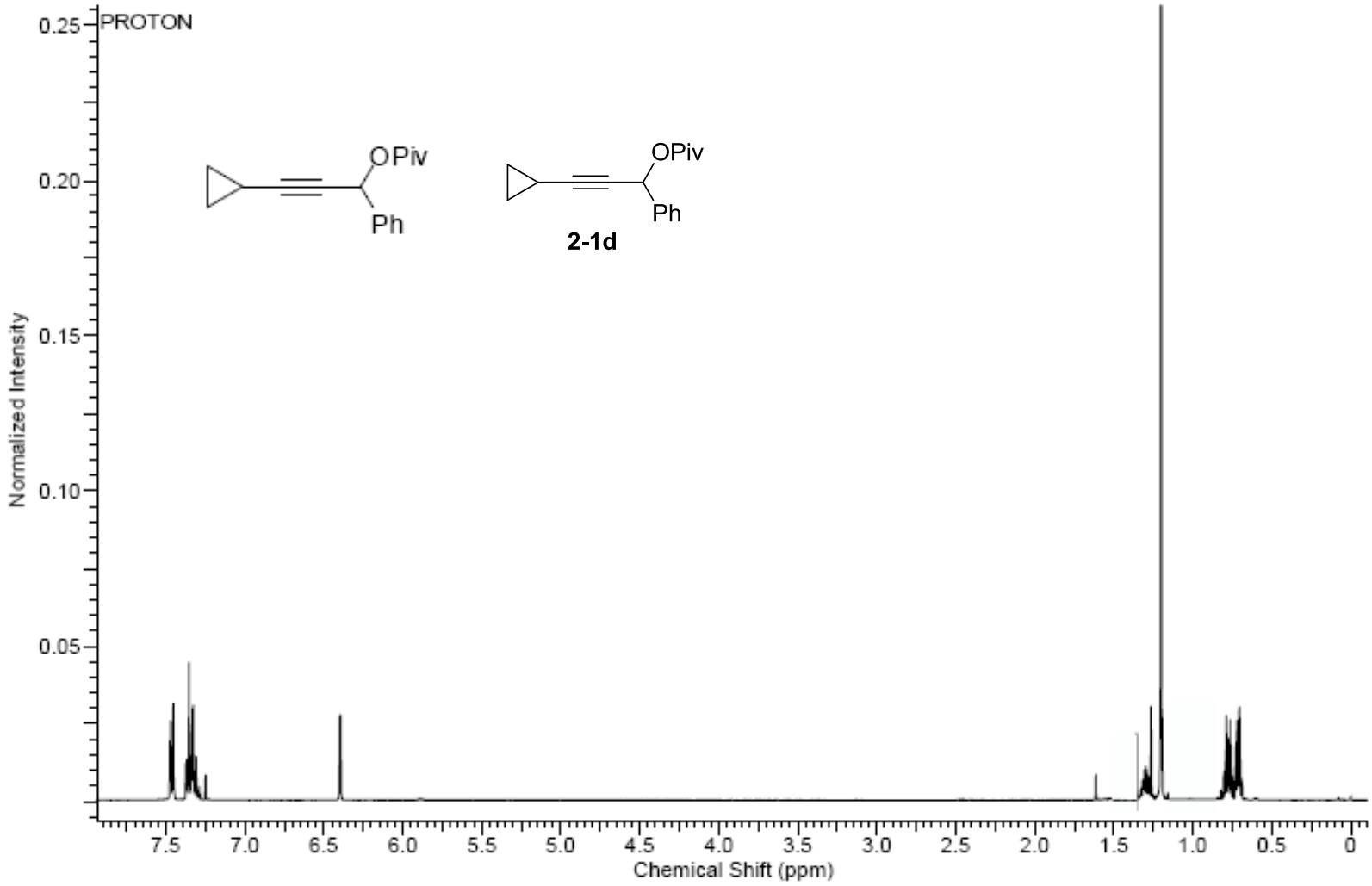


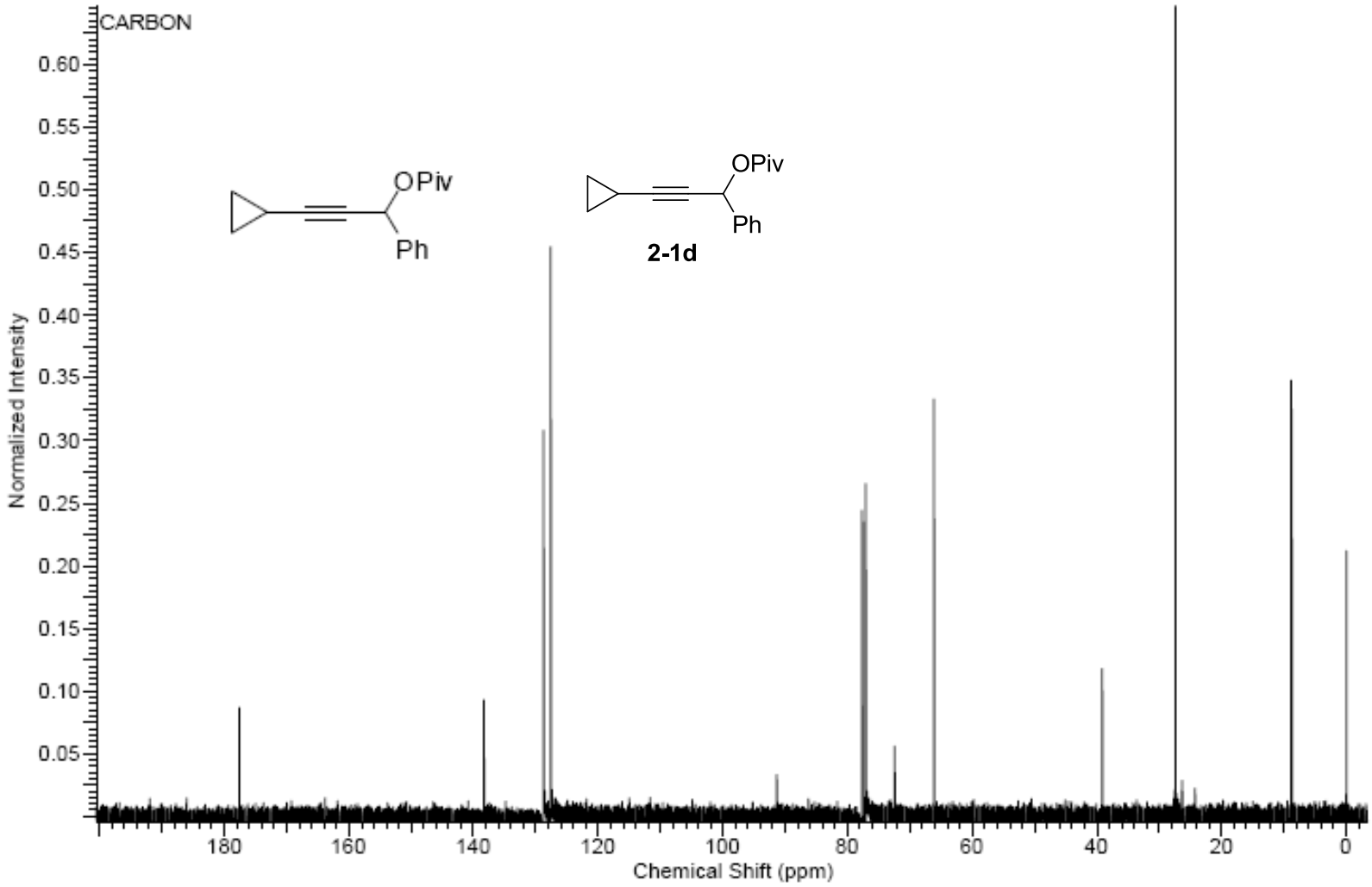
2-1a




OAc
Ph
2-1b
PPM


170.177
141.117
128.622
128.553
126.224
89.939
77.543
77.230
76.909
72.724
64.246
36.782
31.528
21.263
8.539
-0.381
OAc
Ph
2-1b
200
150
100
50
0
PPM


PROTON
OPiv
Ph
OPiv
Ph
2-1d
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)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OPiv
Ph
OPiv
Ph
2-1d
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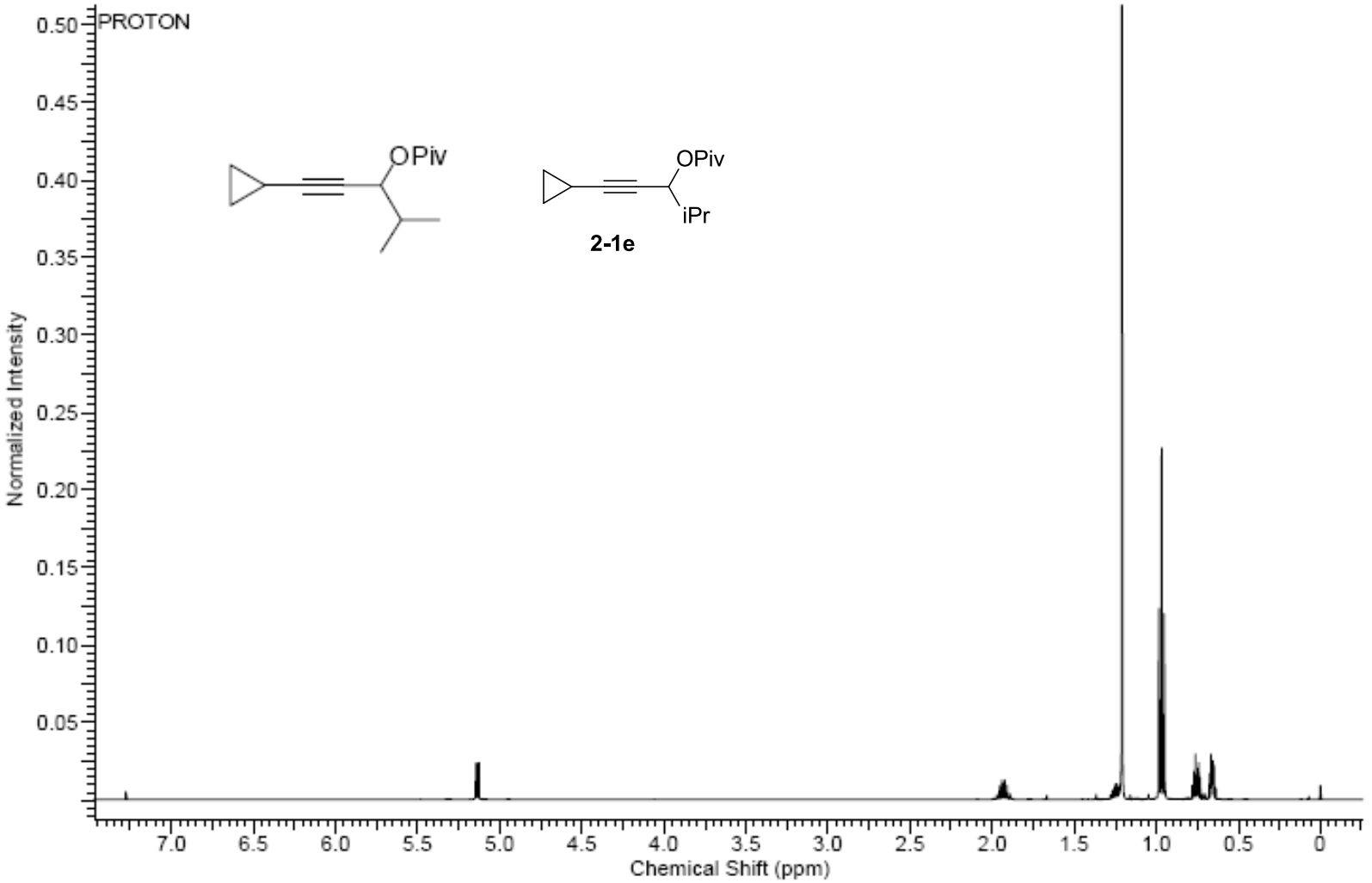
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


PROTON
OPiv
OPiv
iPr
2-1e
Normalized Intensity
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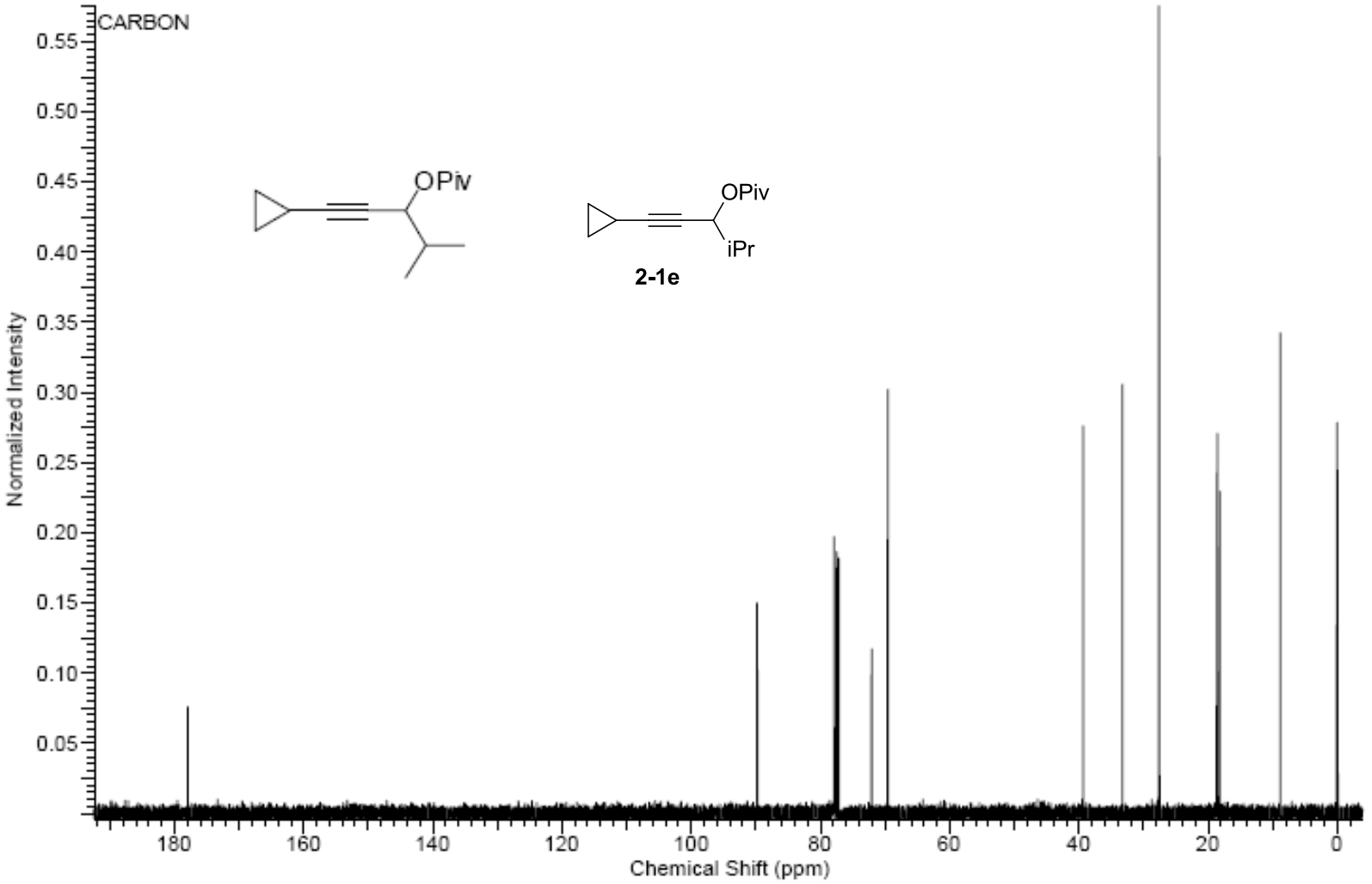
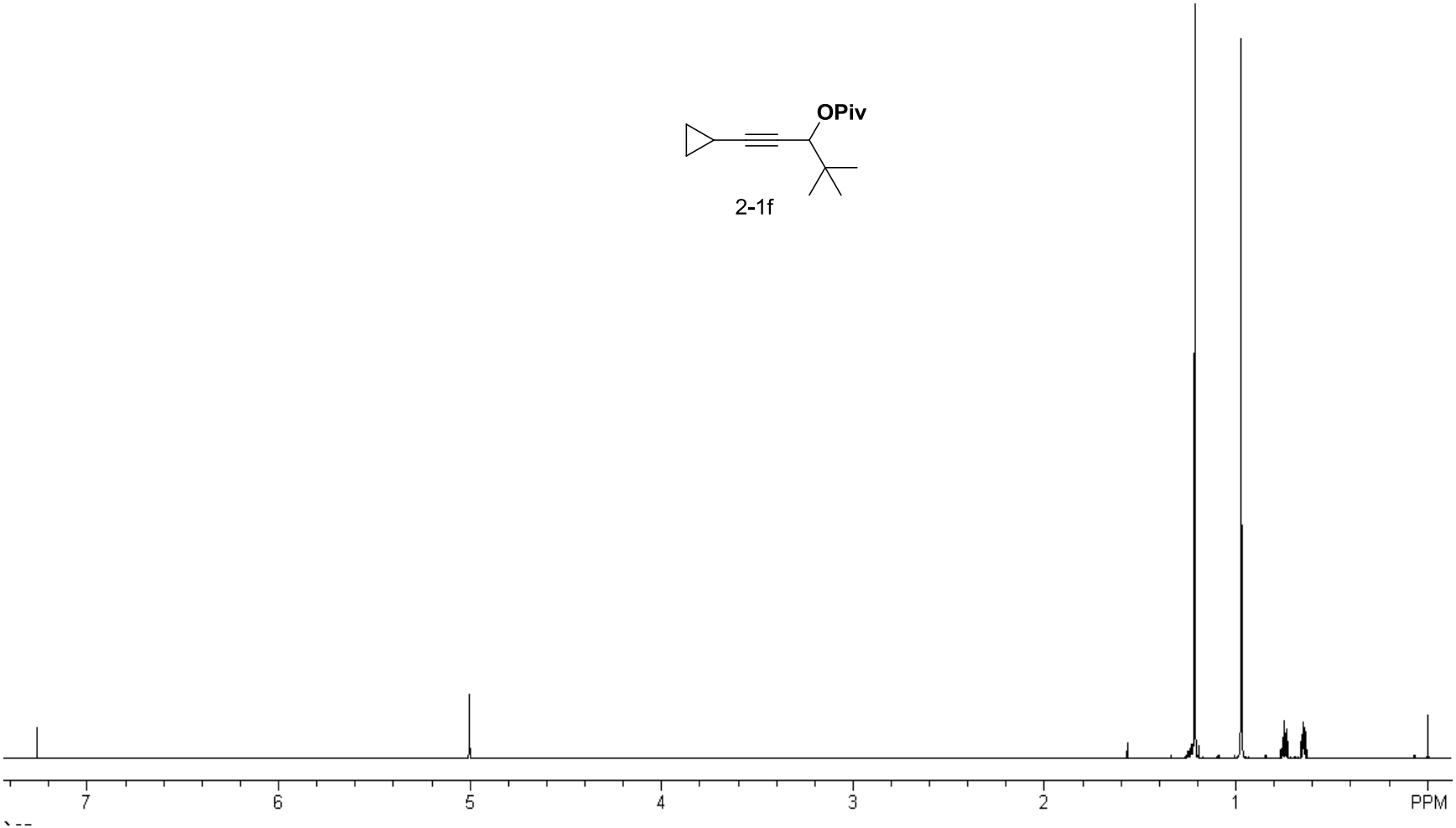
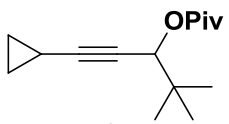
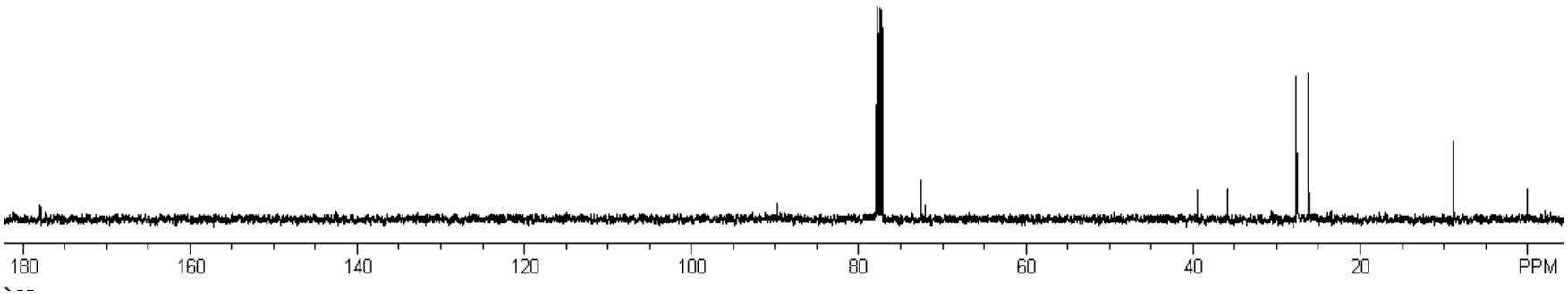
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

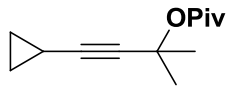

CARBON
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
OPiv
OPiv
iPr
2-1e
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


OPiv
2-1f
7
6
5
4
3
2
1
PPM

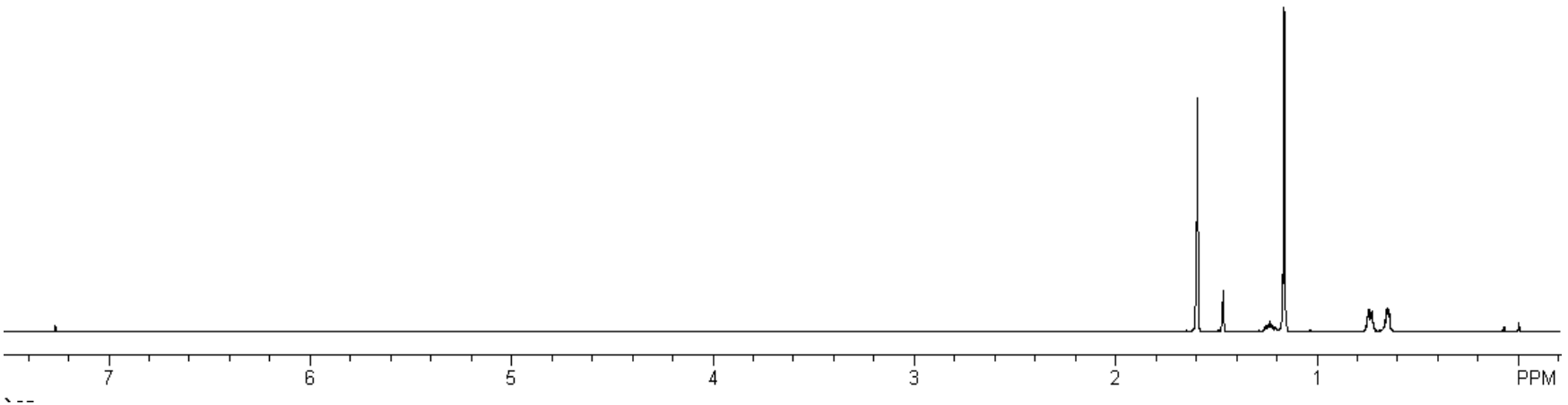


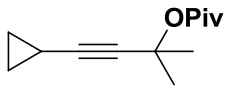
2-1f



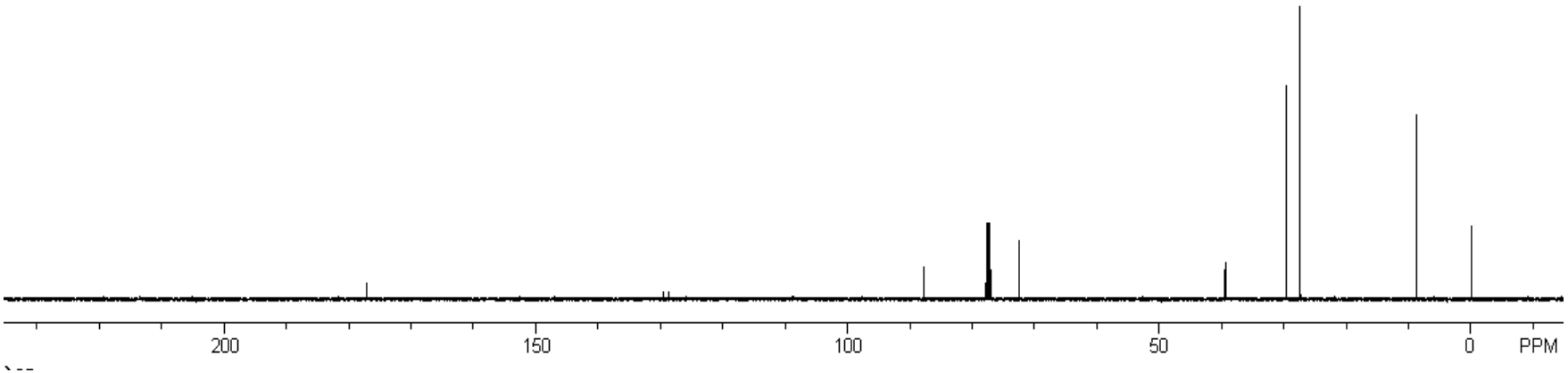


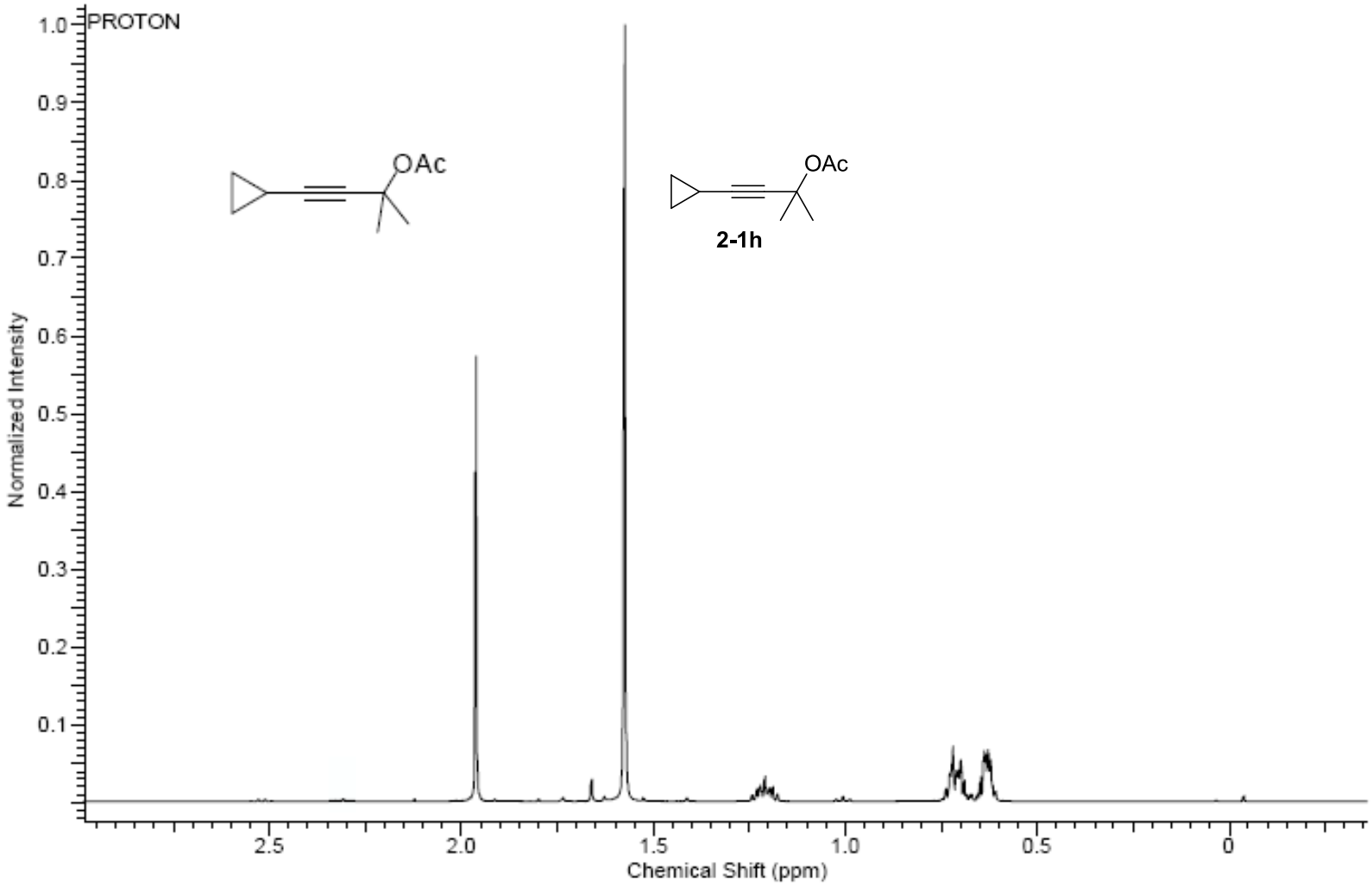
2-1g





2-1g




PROTON
OAc
OAc
2-1h
Normalized Intensity
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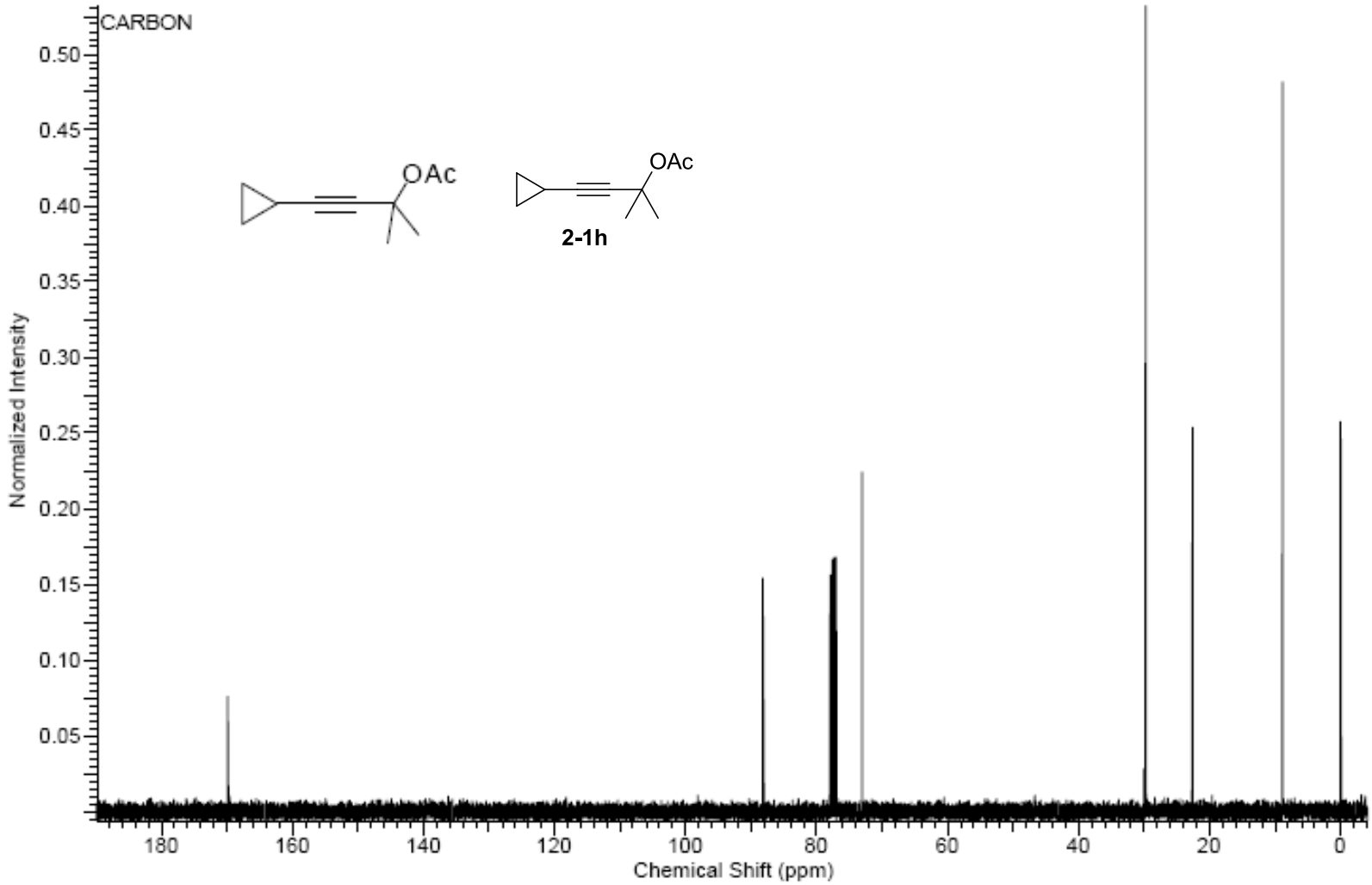
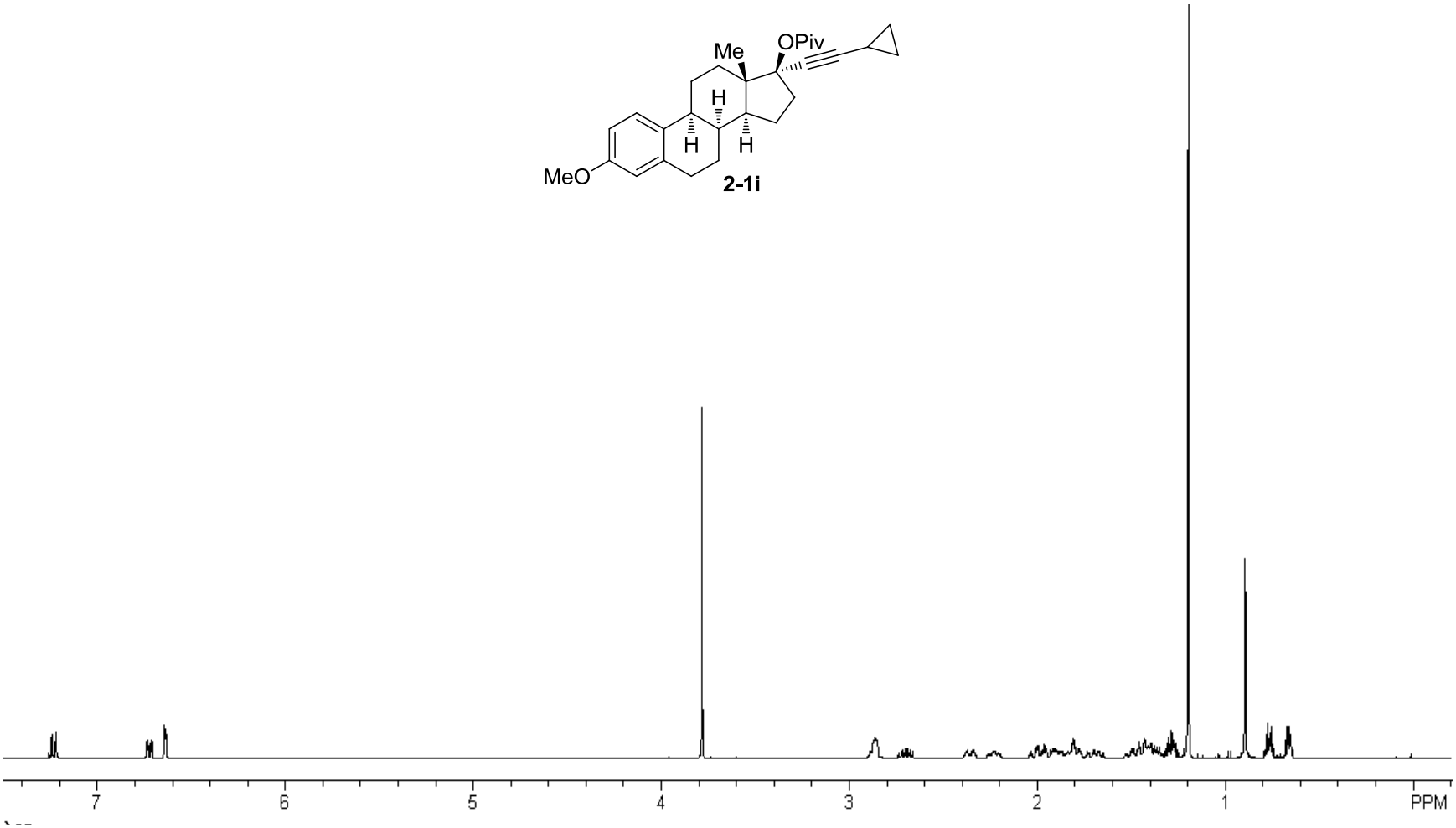
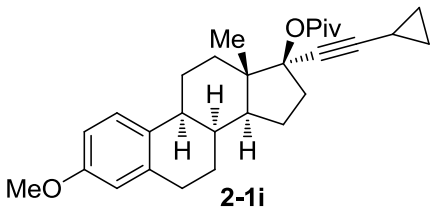
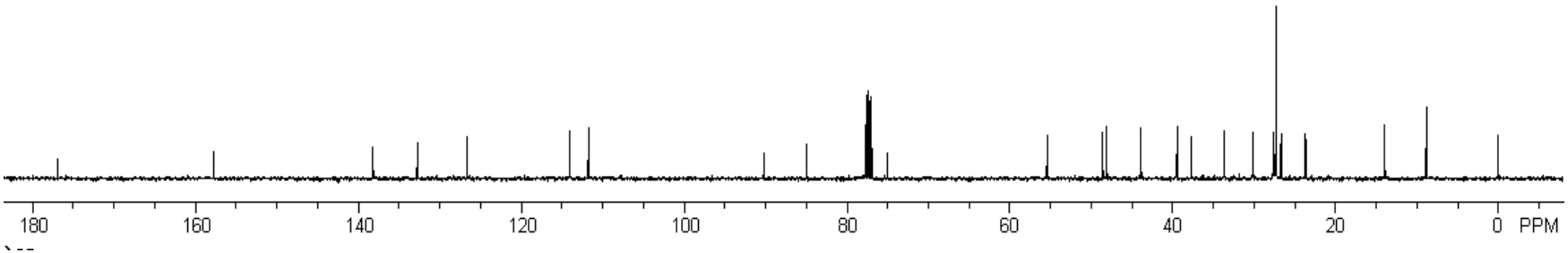
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

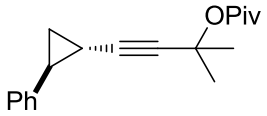

CARBON
OAc
OAc
2-1h
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


Me
OPiv
H
H
H
MeO
2-1i
7
6
5
4
3
2
1
PPM

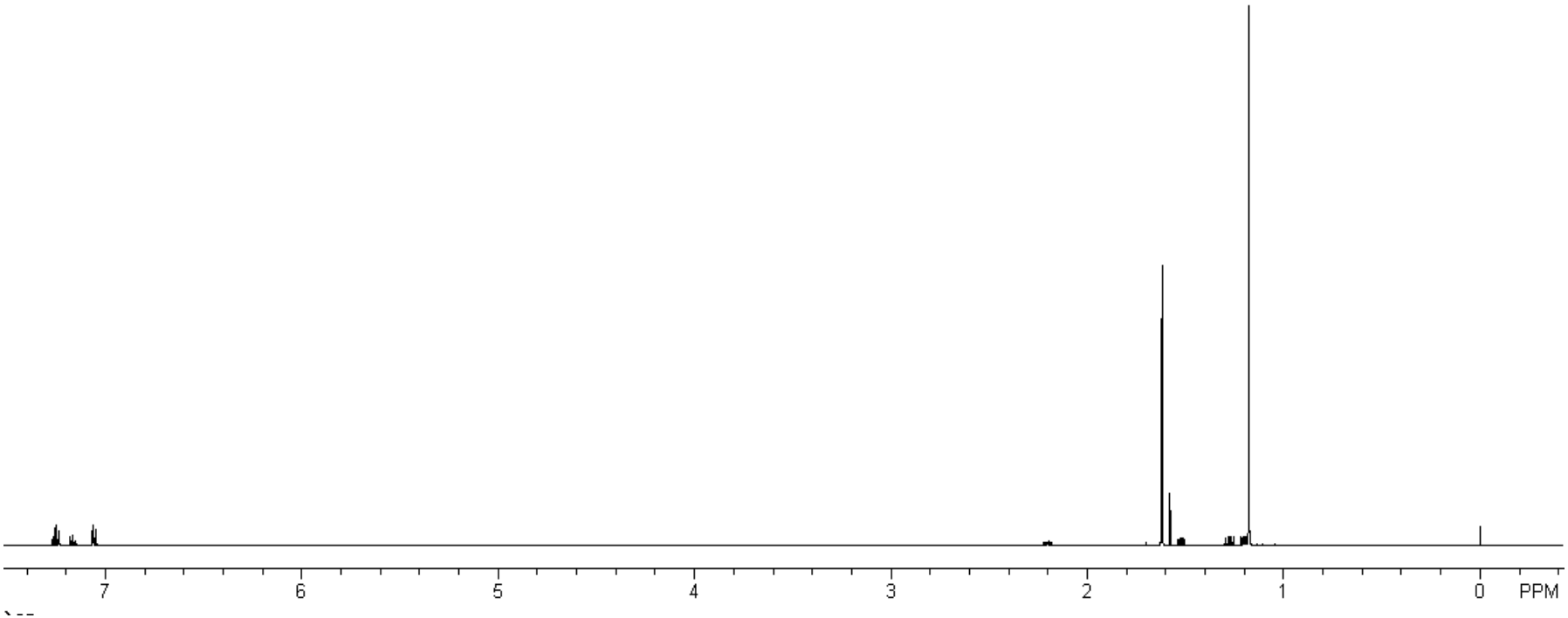


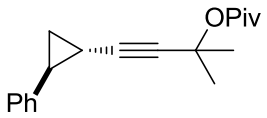
2-1i



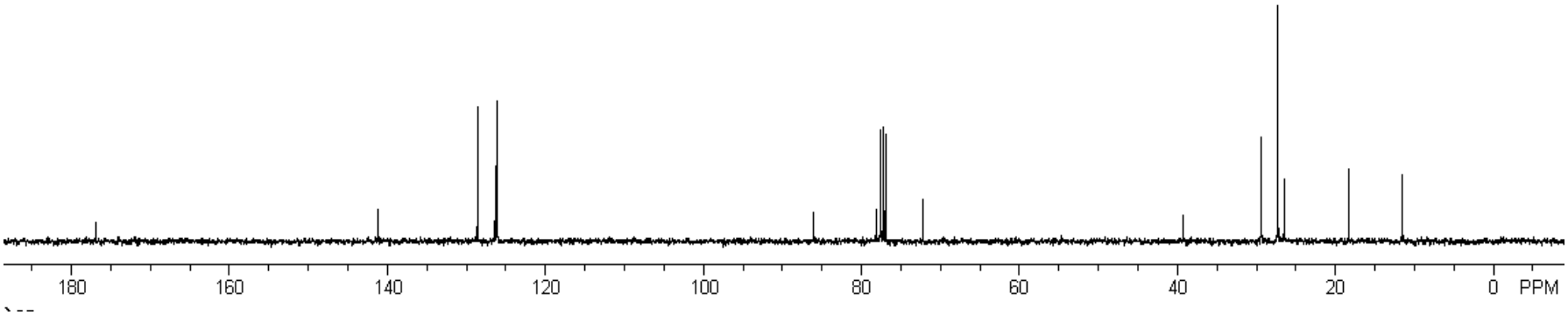


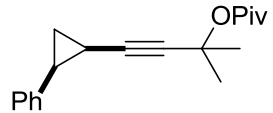
2-trans-1j



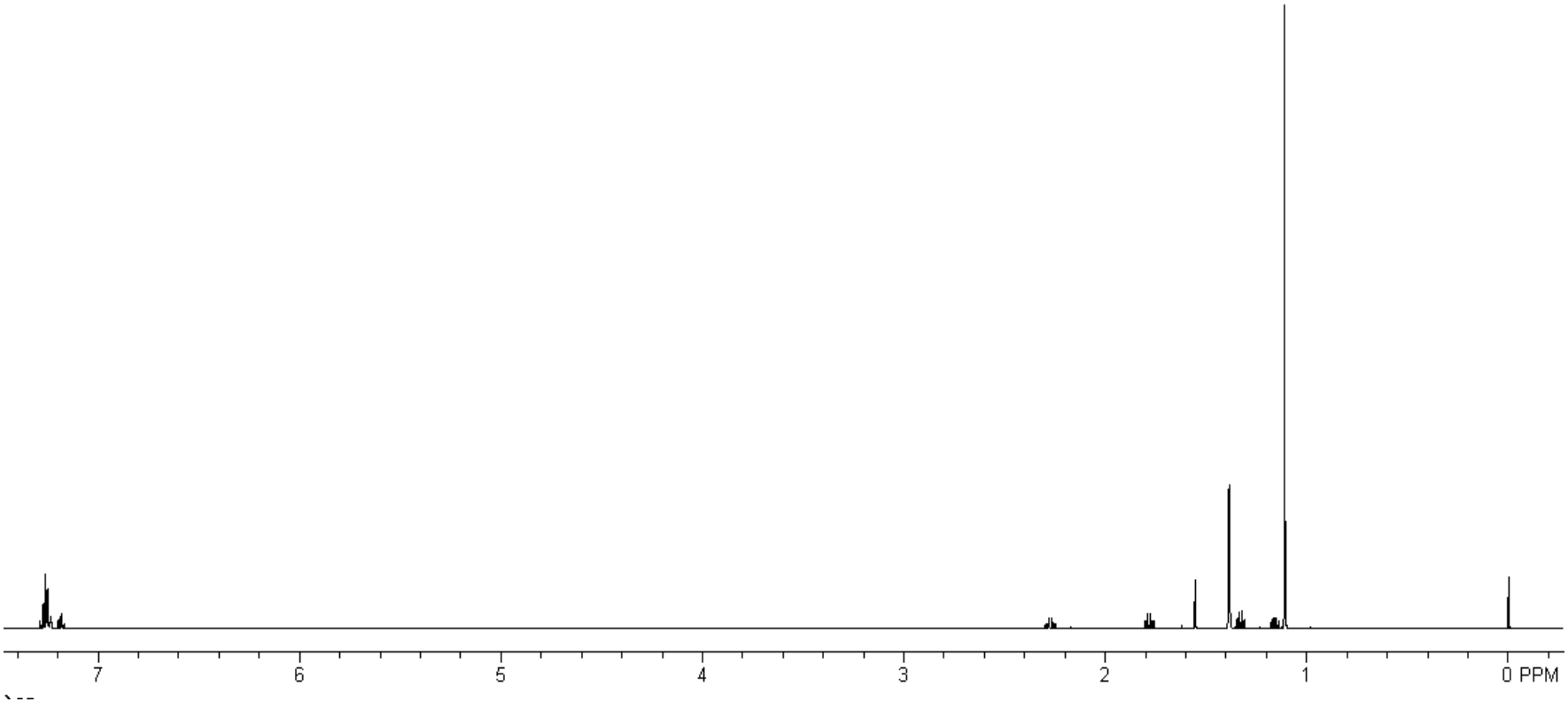


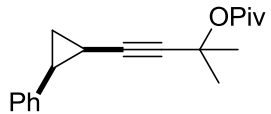
2-trans-1j



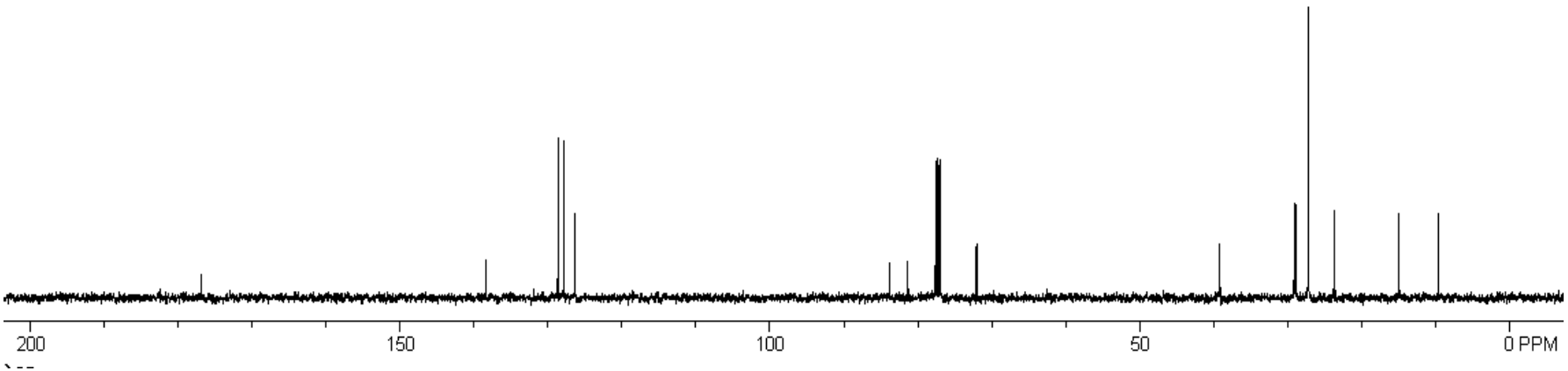


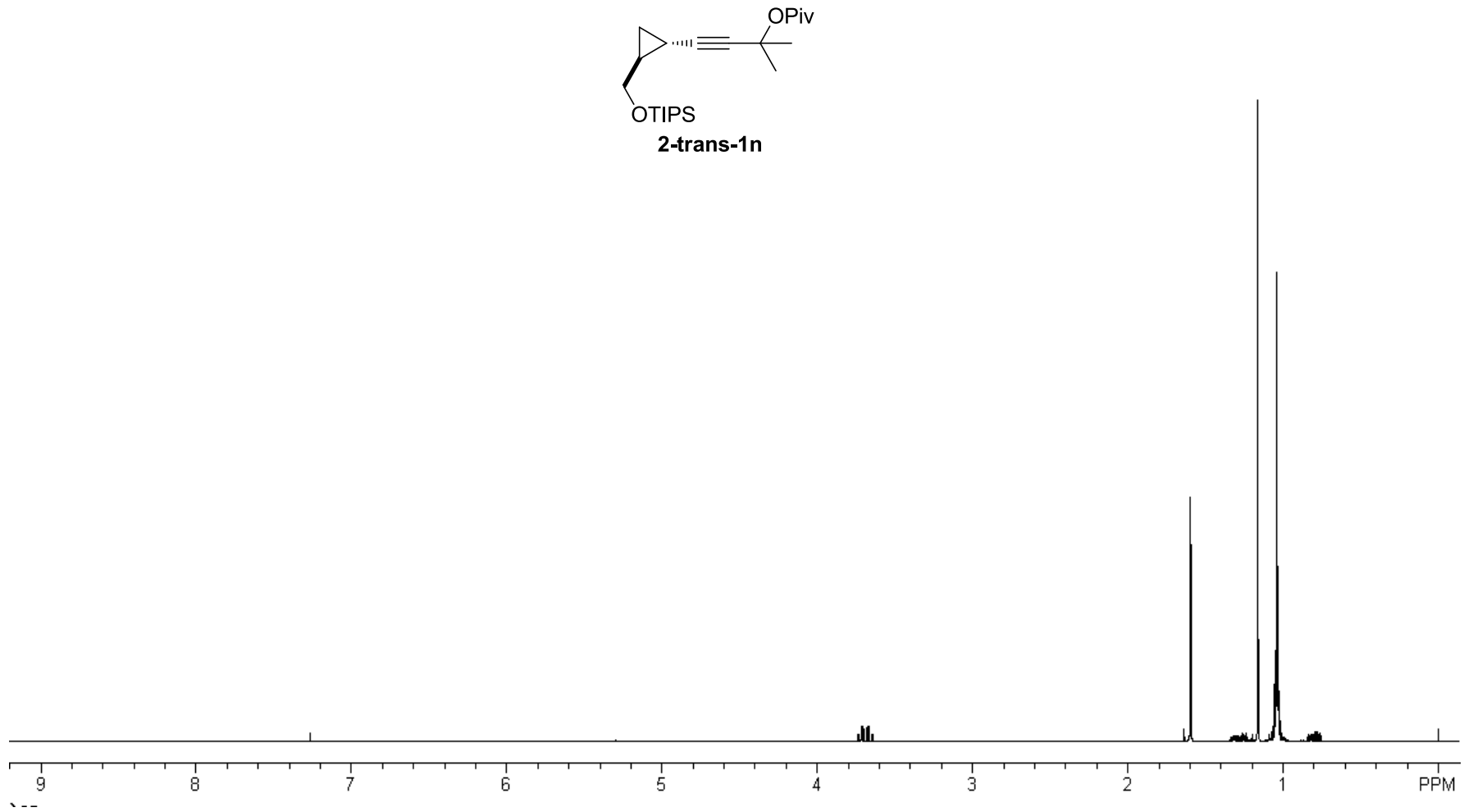
2-cis-1j

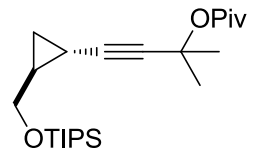




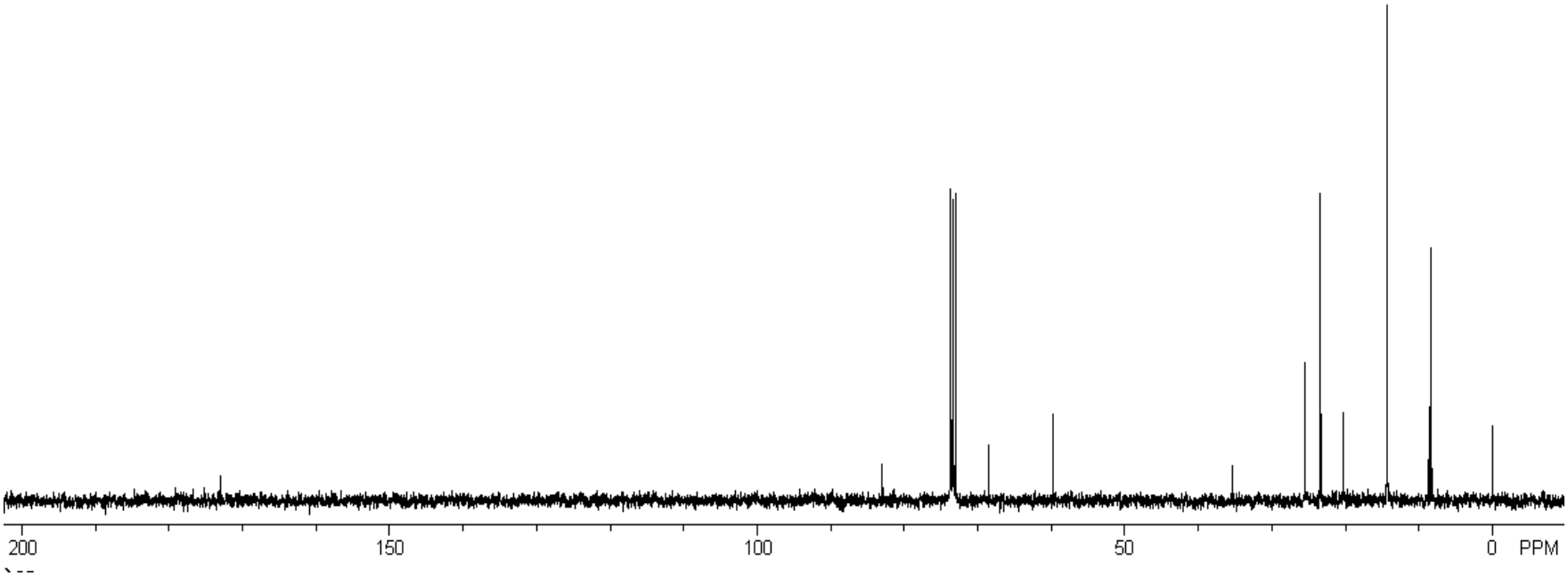
2-cis-1j

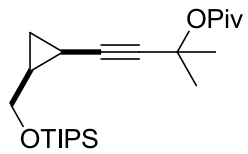



OPiv
OTIPS
2-trans-1n
9
8
7
6
5
4
3
2
1
PPM



2-trans-1n





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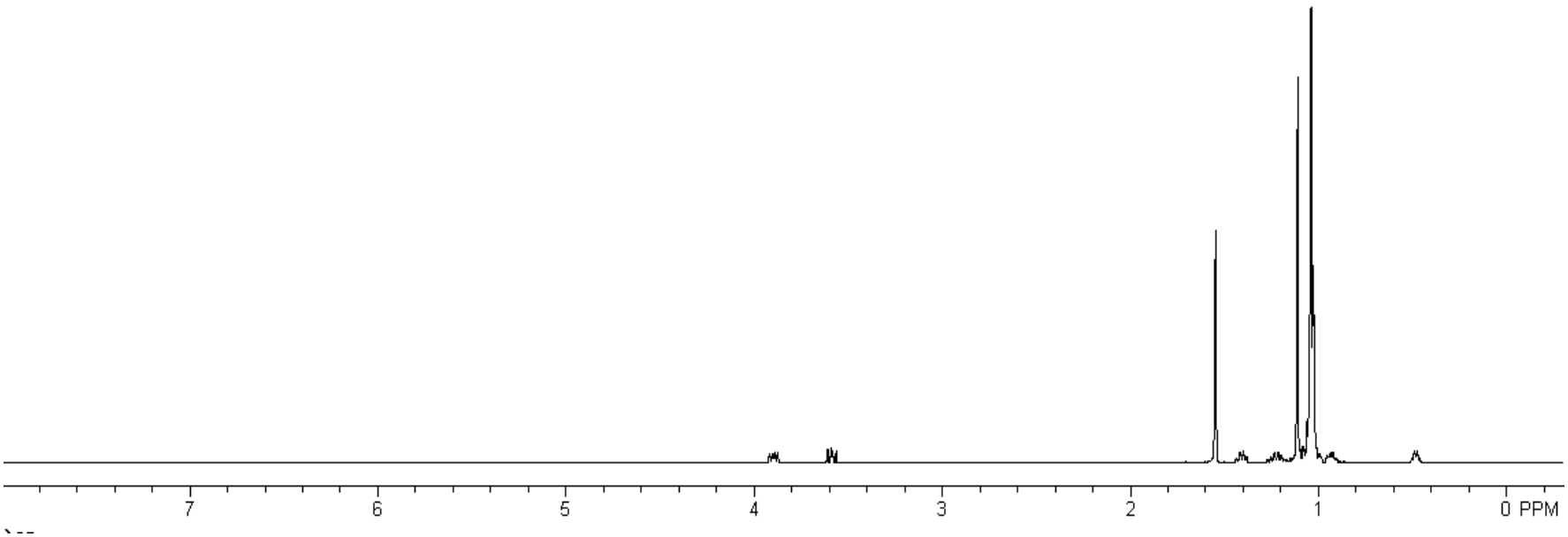
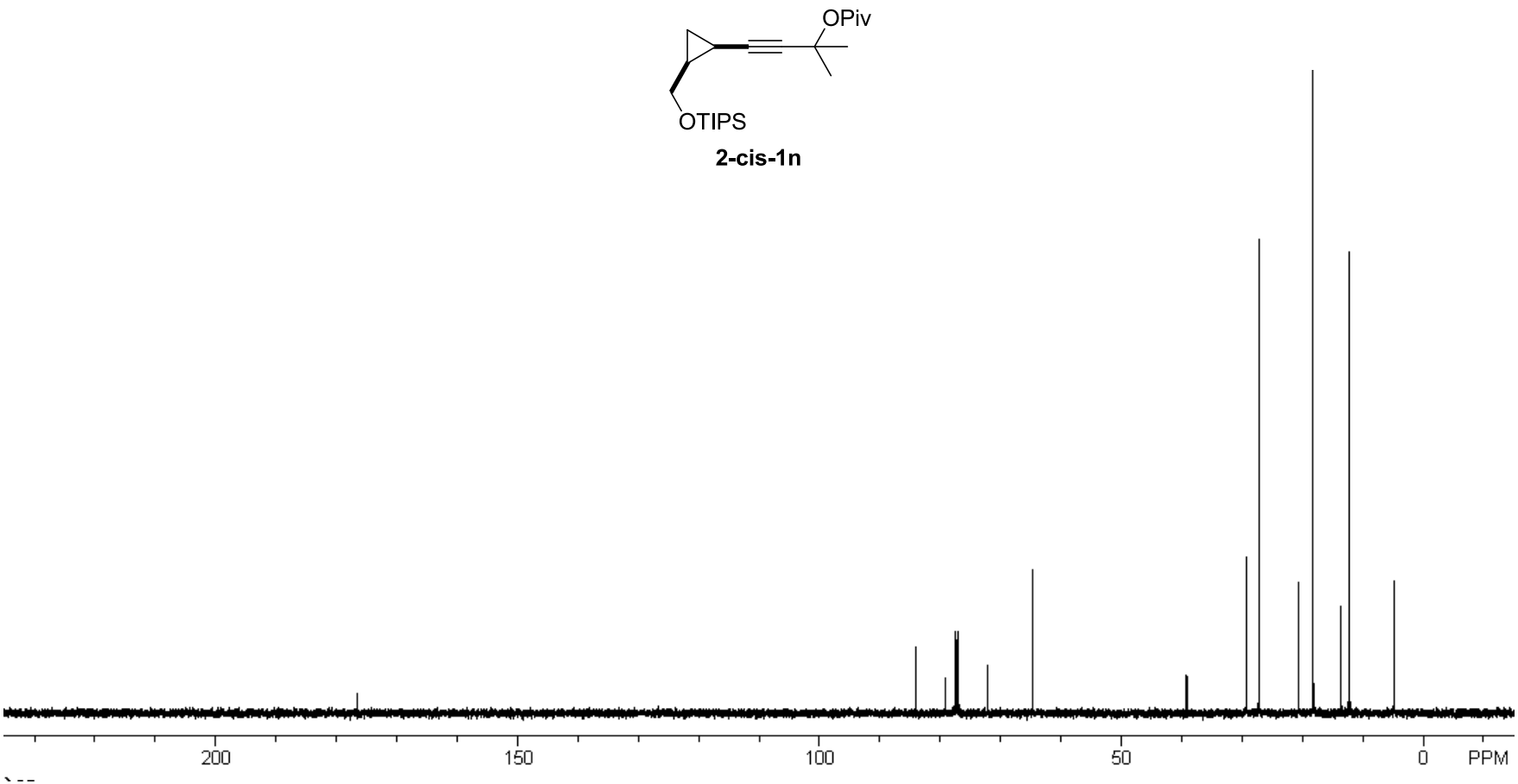
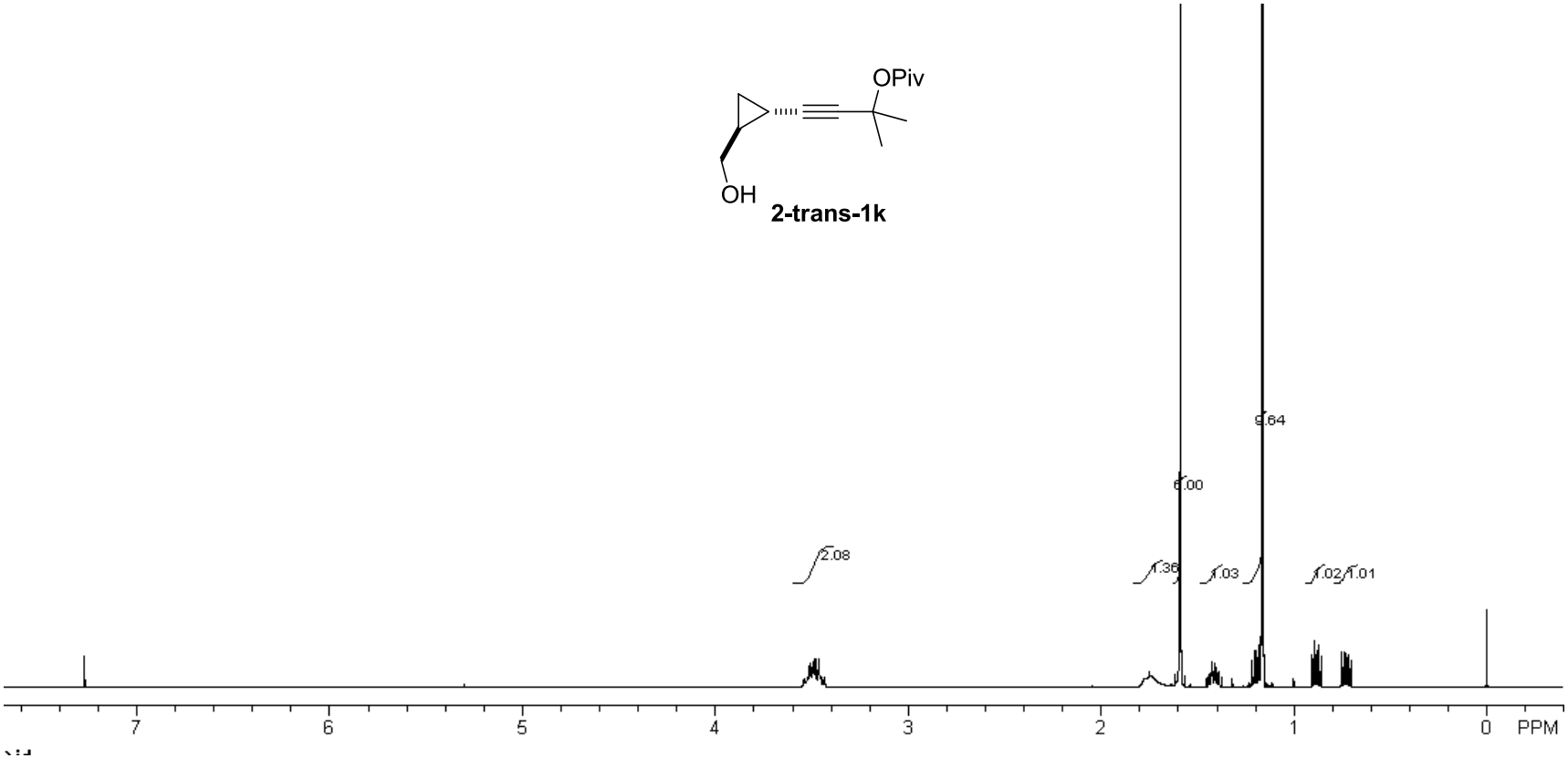
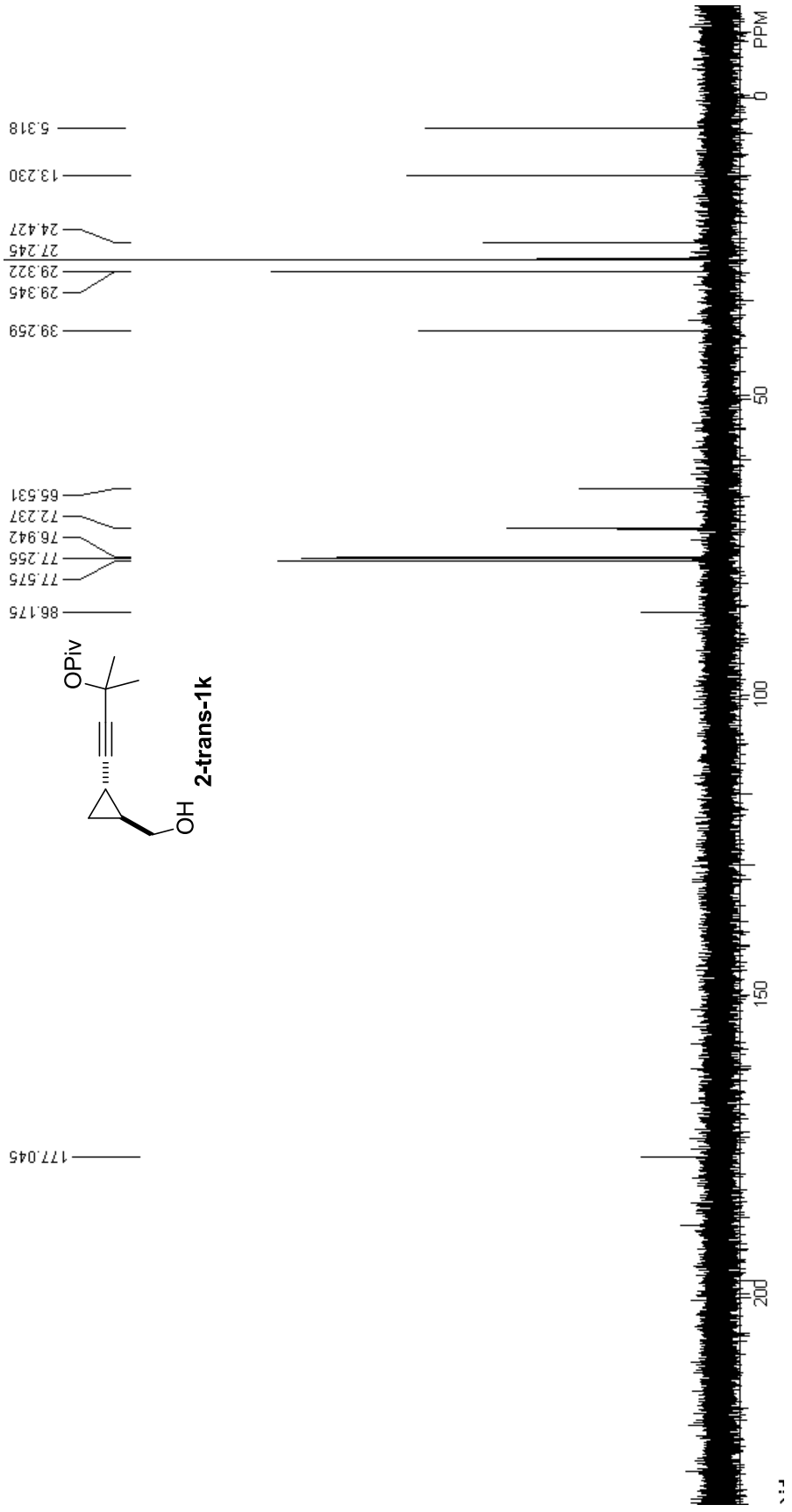



OPiv
OTIPS
2-cis-1n
200
150
100
50
0
PPM


OPiv
OH
2-trans-1k
2.08
1.36
6.00
1.03
9.64
1.02
1.01
7
6
5
4
3
2
1
0
PPM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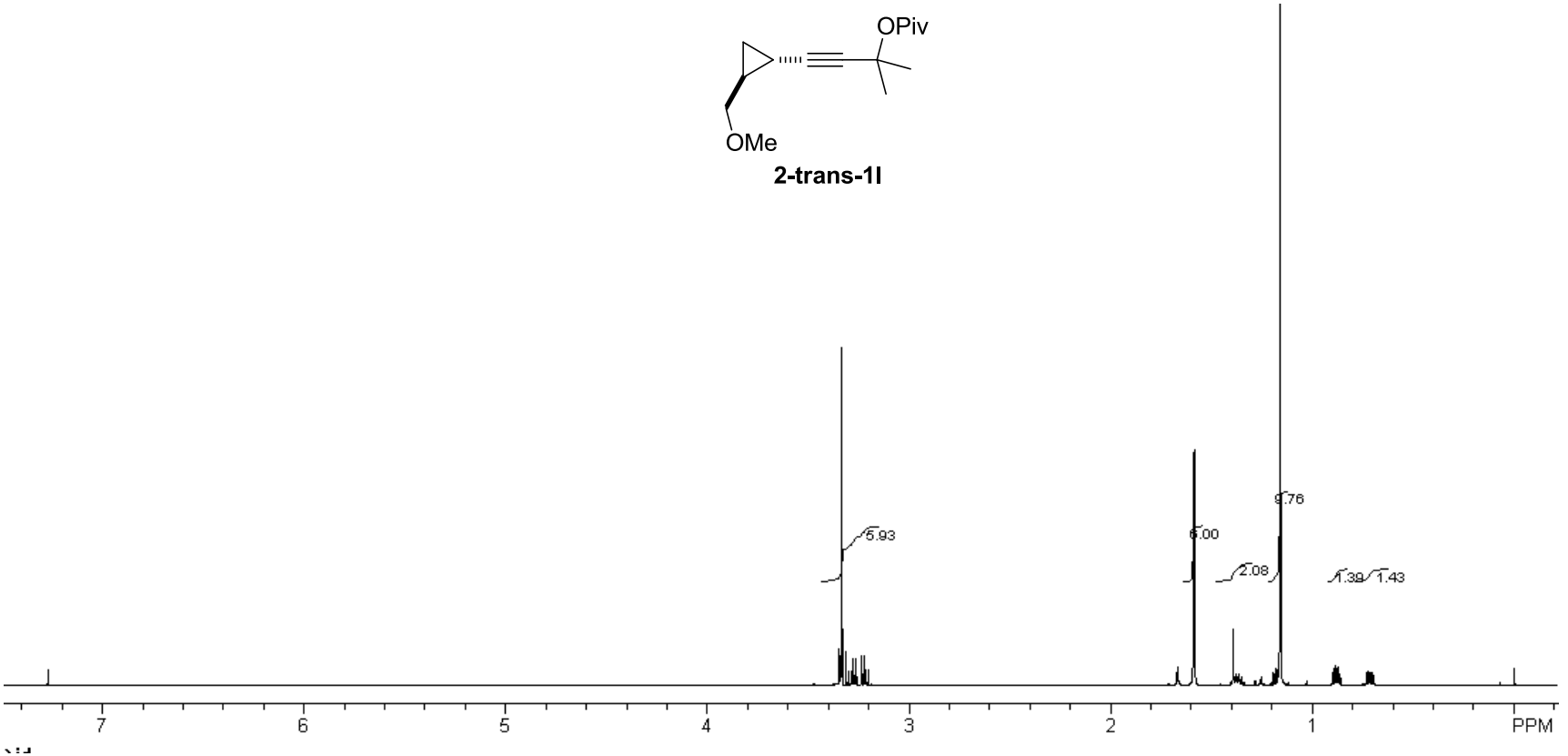
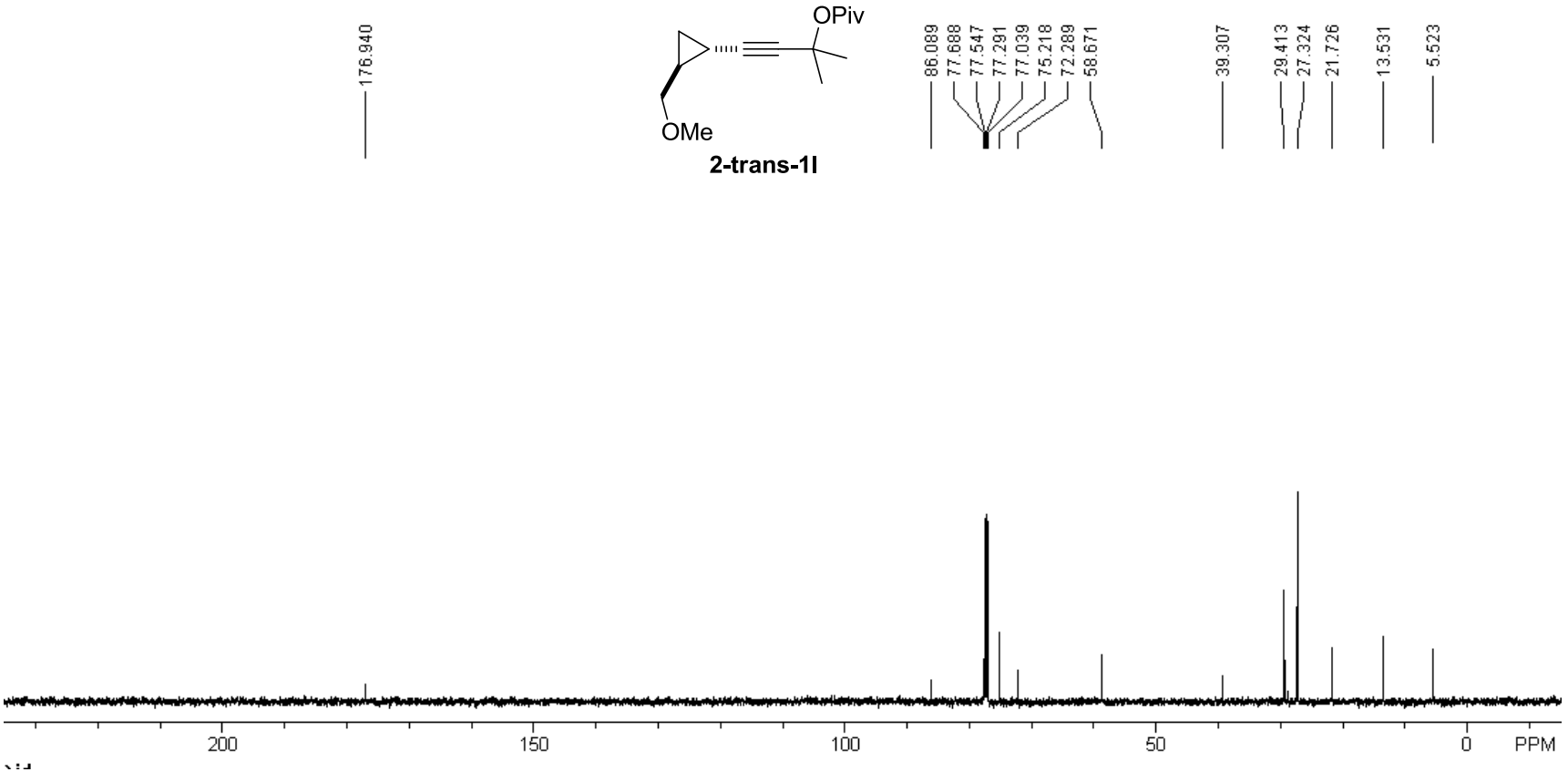
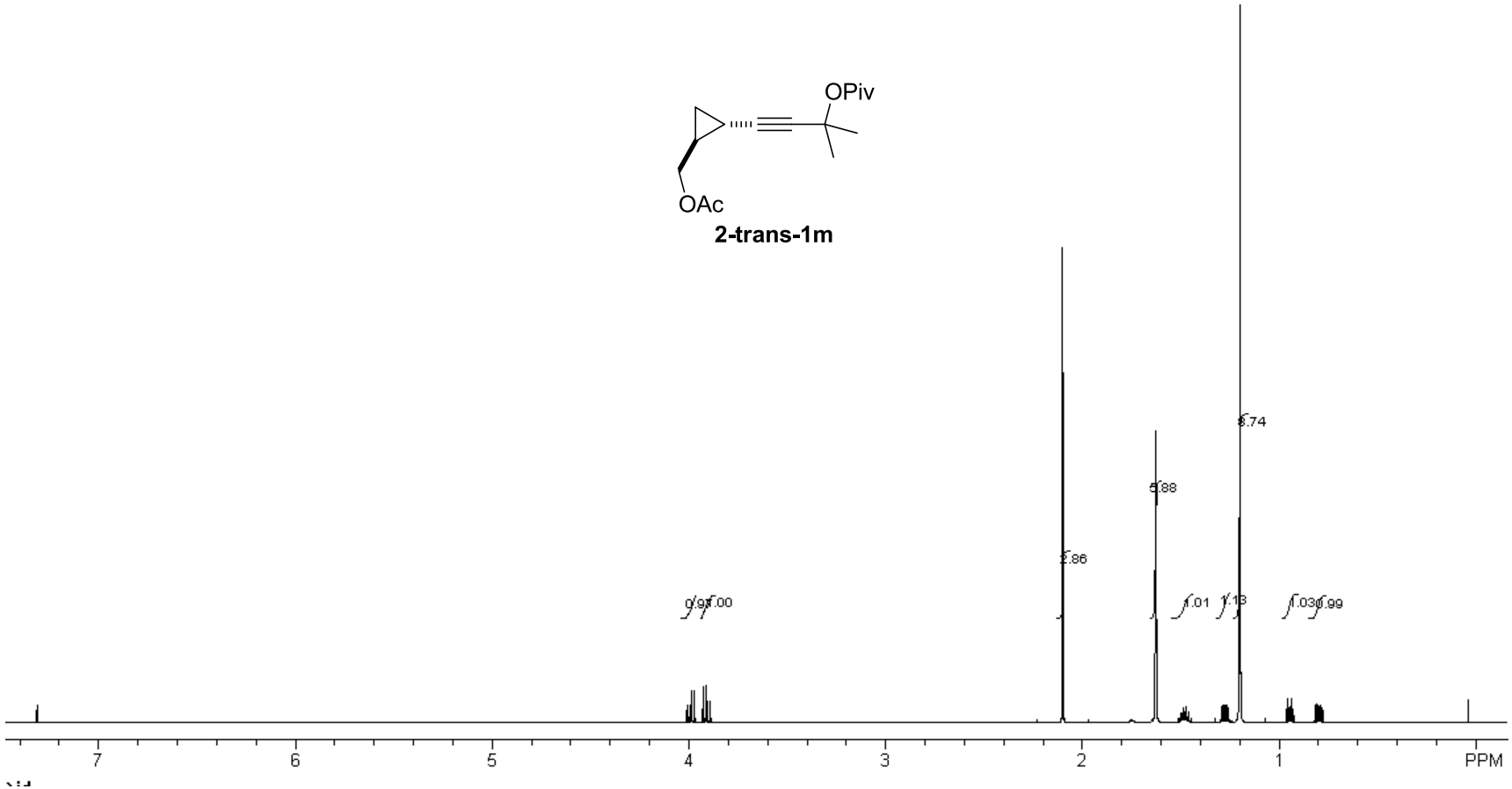
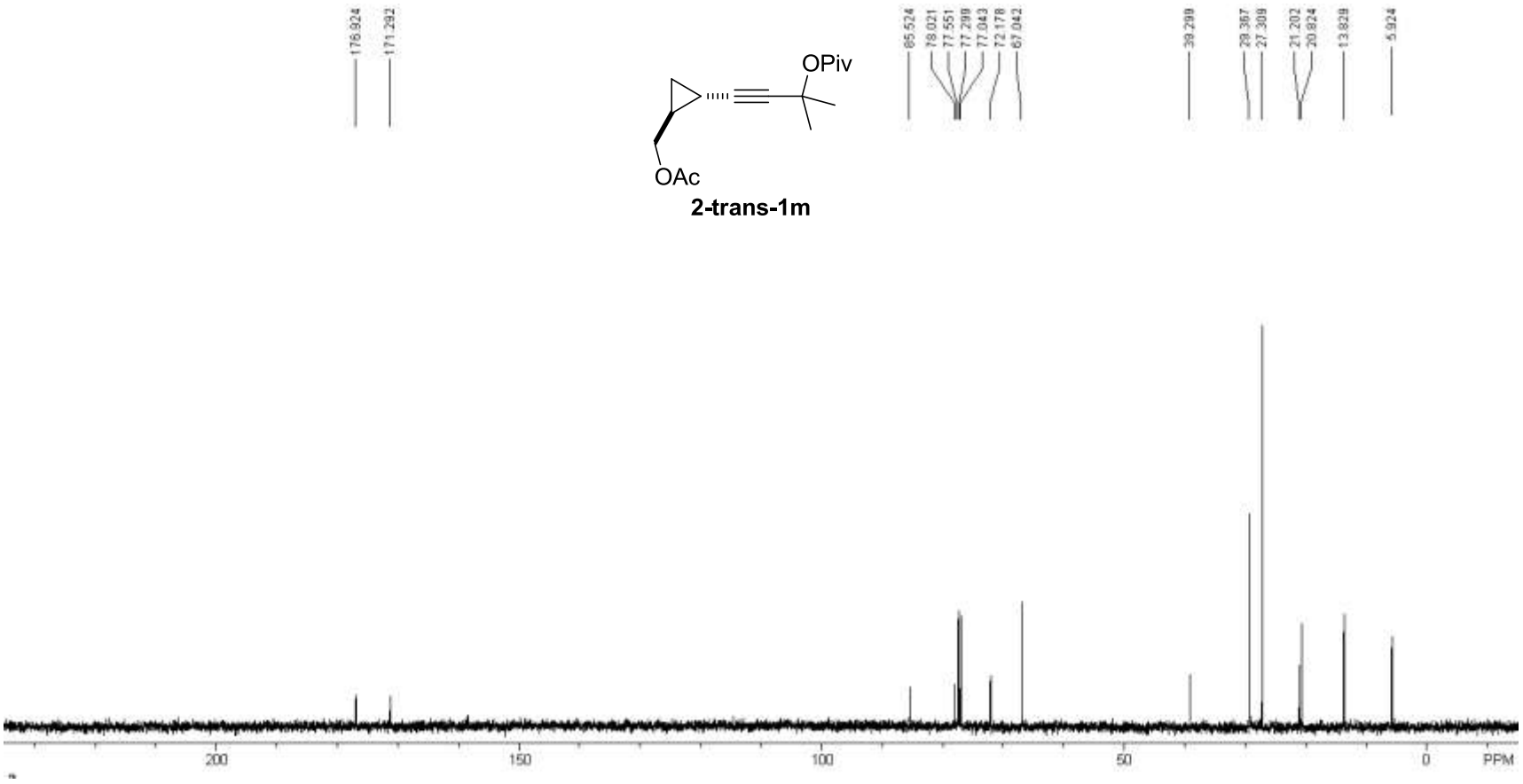
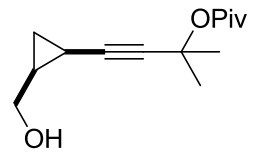
13.230
24.427
27.245
29.322
29.345
39.259
65.531
72.237
76.942
77.255
77.575
86.175
177.045
OPiv
OH
2-trans-1k
PPM
0
50
100
150
200


OPiv
OMe
2-trans-1l
6.93
6.00
9.76
2.08
1.39
1.43
7
6
5
4
3
2
1
PPM

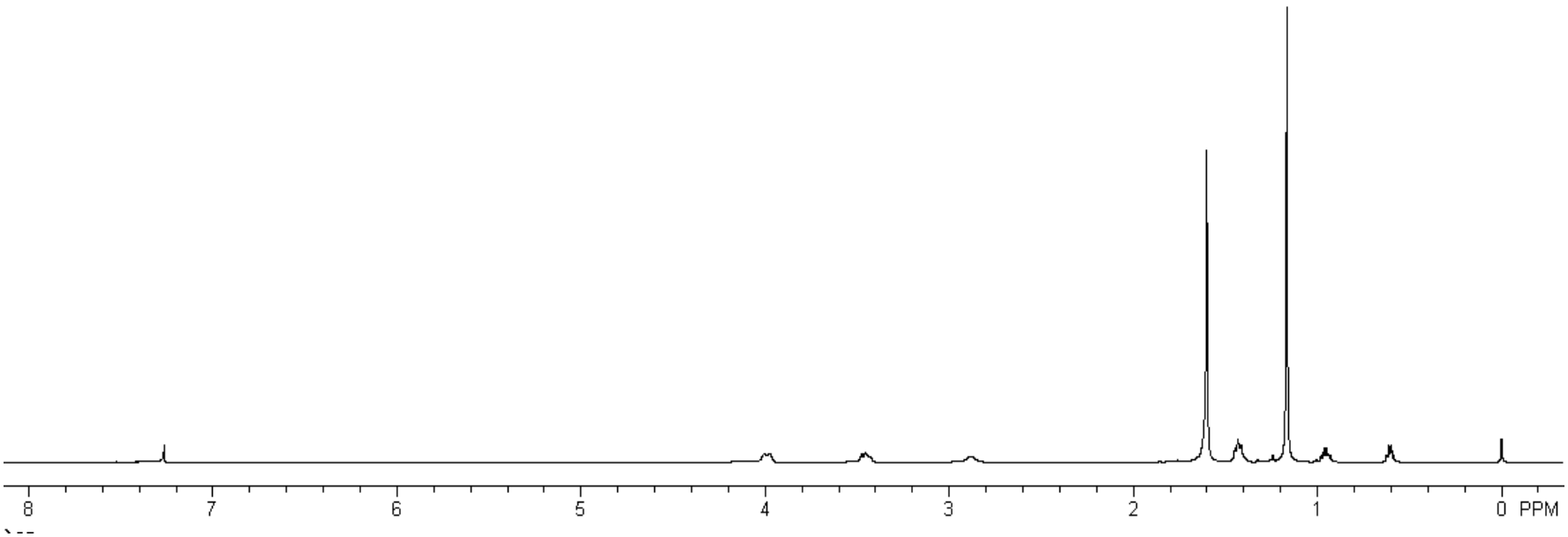

176.940
OPiv
OMe
2-trans-1l
86.089
77.688
77.547
77.291
77.039
75.218
72.289
58.671
39.307
29.413
27.324
21.726
13.531
5.523
200
150
100
50
0
PPM

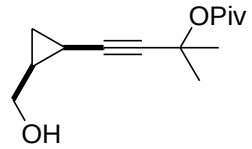

OPiv
OAc
2-trans-1m
8.74
5.88
2.86
0.97
1.00
1.01
1.13
1.03
0.99
7
6
5
4
3
2
1
PPM

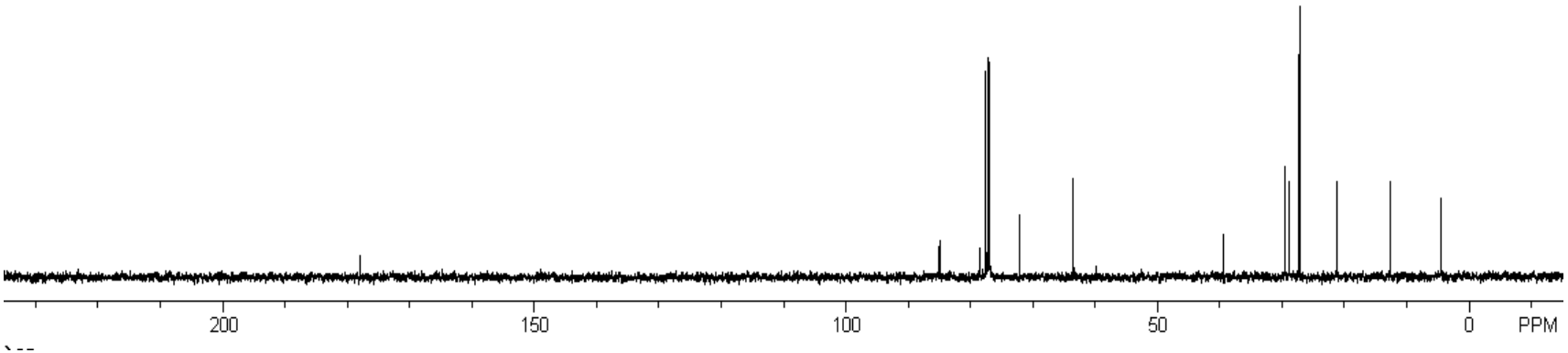

176.924
171.292
65.524
78.021
77.551
77.299
77.043
72.178
67.042
39.299
29.367
27.309
21.202
20.824
13.829
5.924
OPiv
OAc
2-trans-1m
200
150
100
50
0
PPM

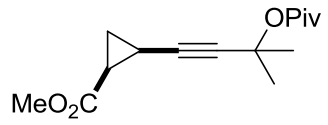


2-cis-1k

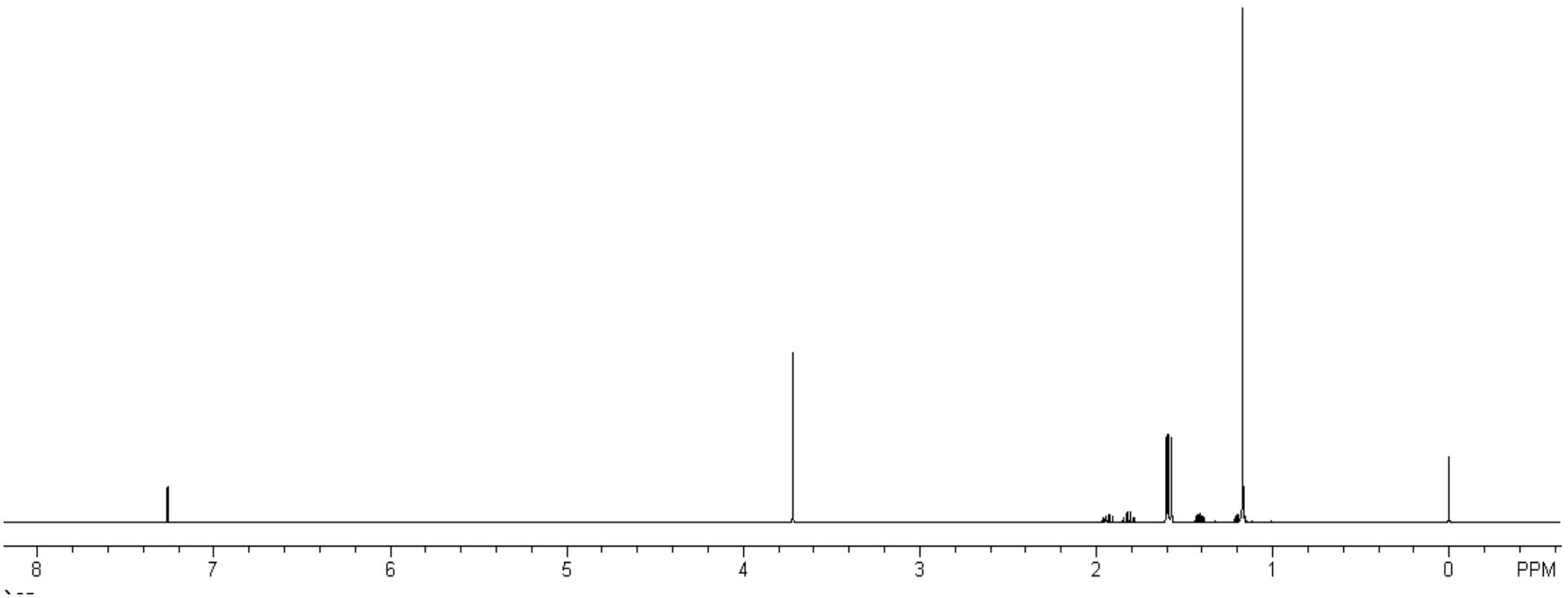


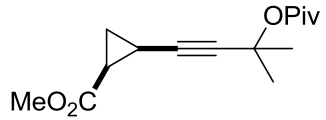

OPiv
OH


200
150
100
50
0
PPM

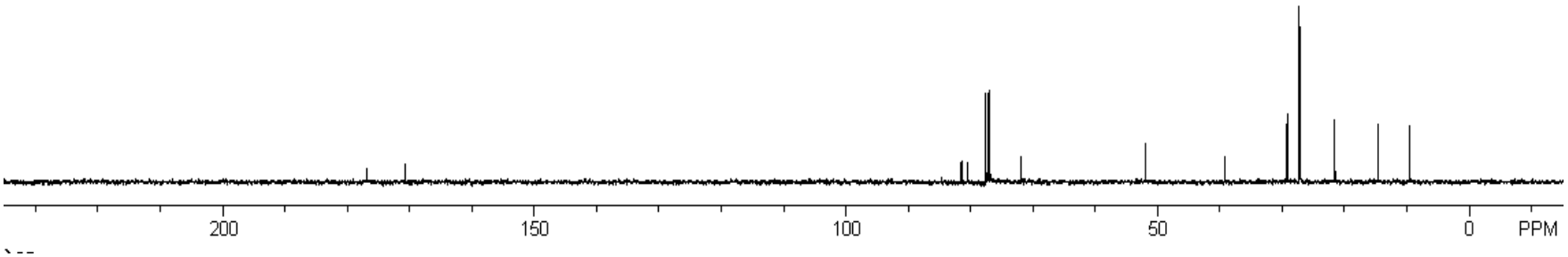


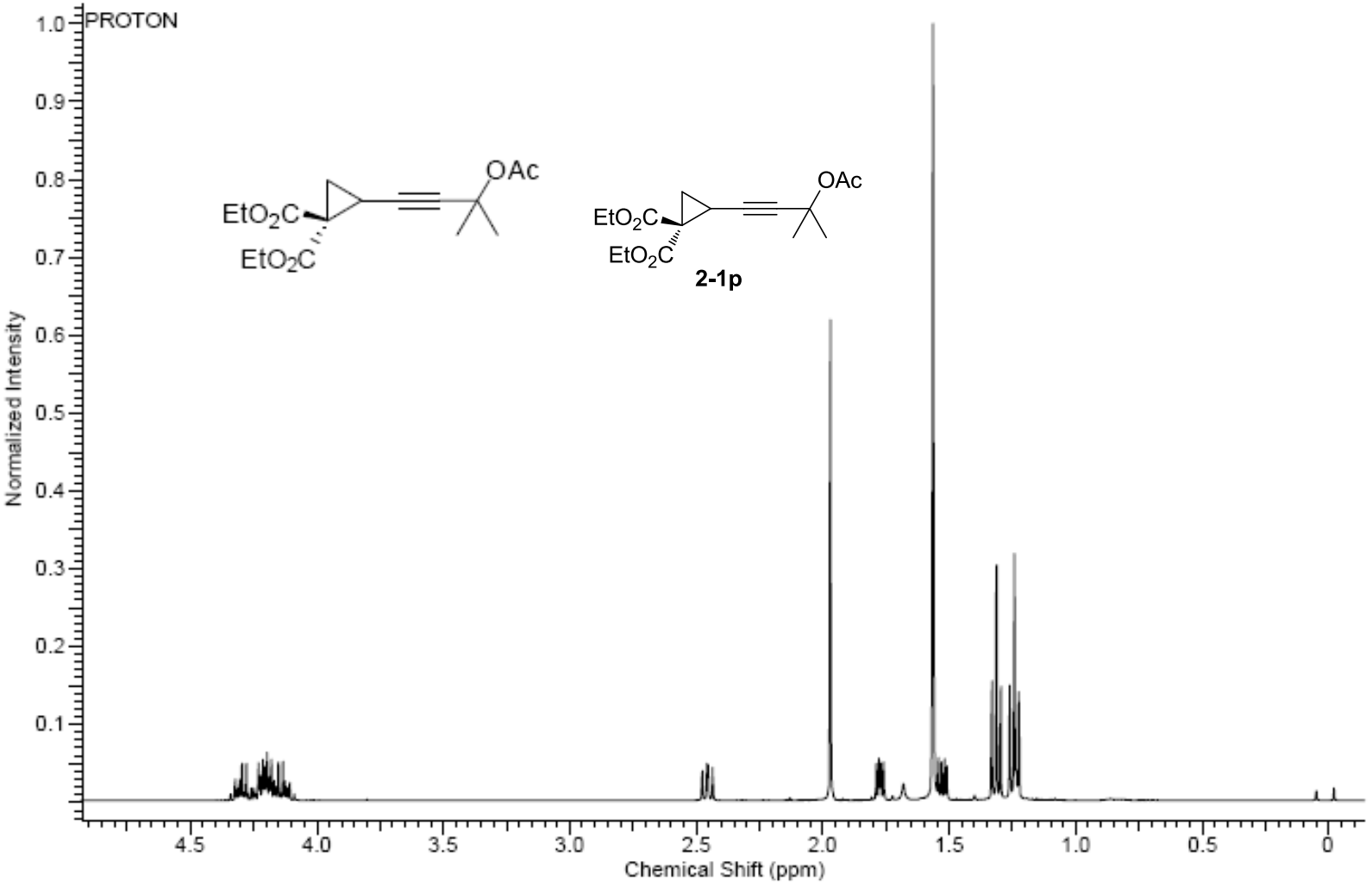
2-1o

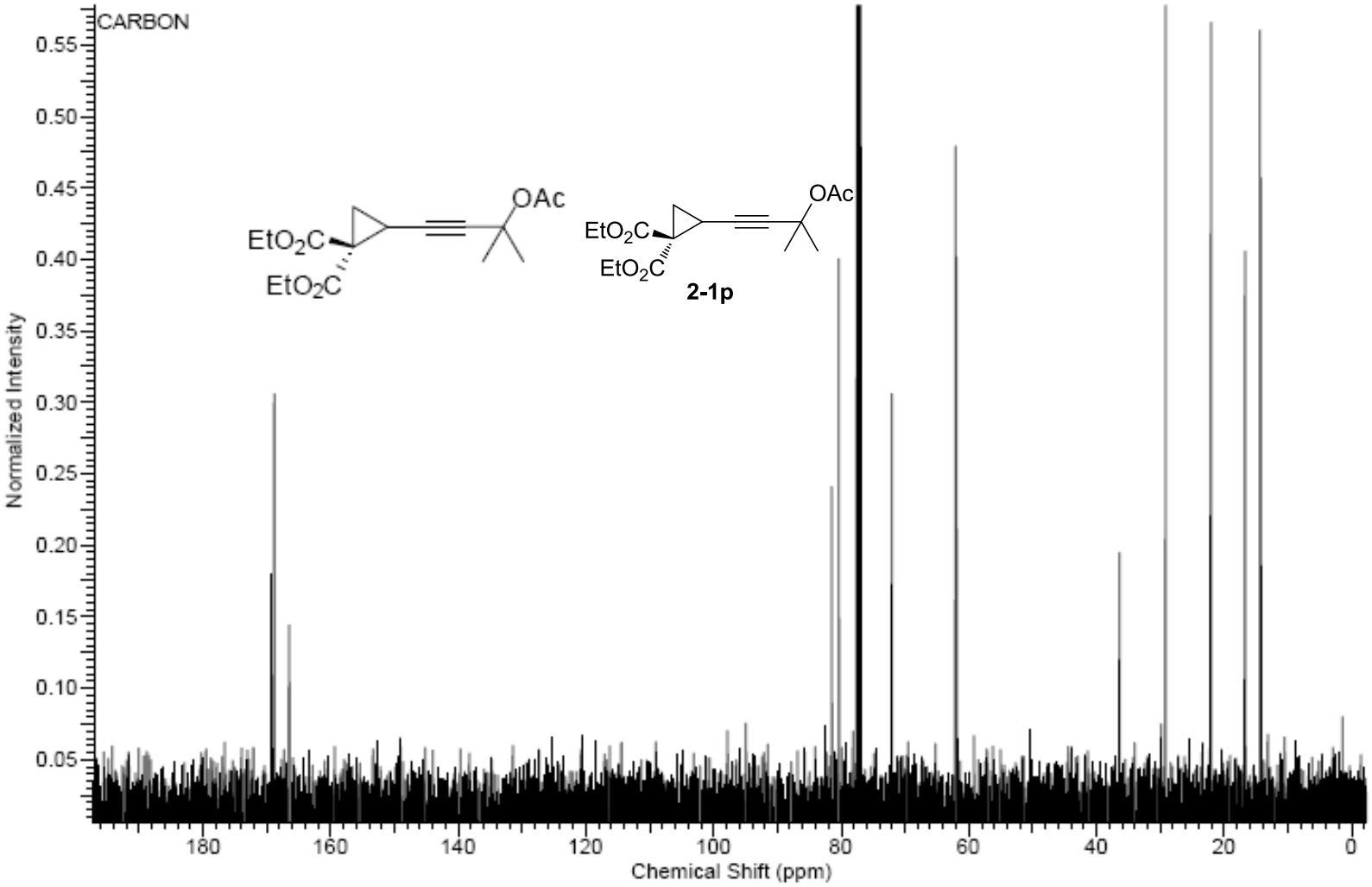




2-1o




PROTON
OAc
EtO2C
EtO2C
OAc
EtO2C
EtO2C
2-1p
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


CARBON
Normalized Intensity
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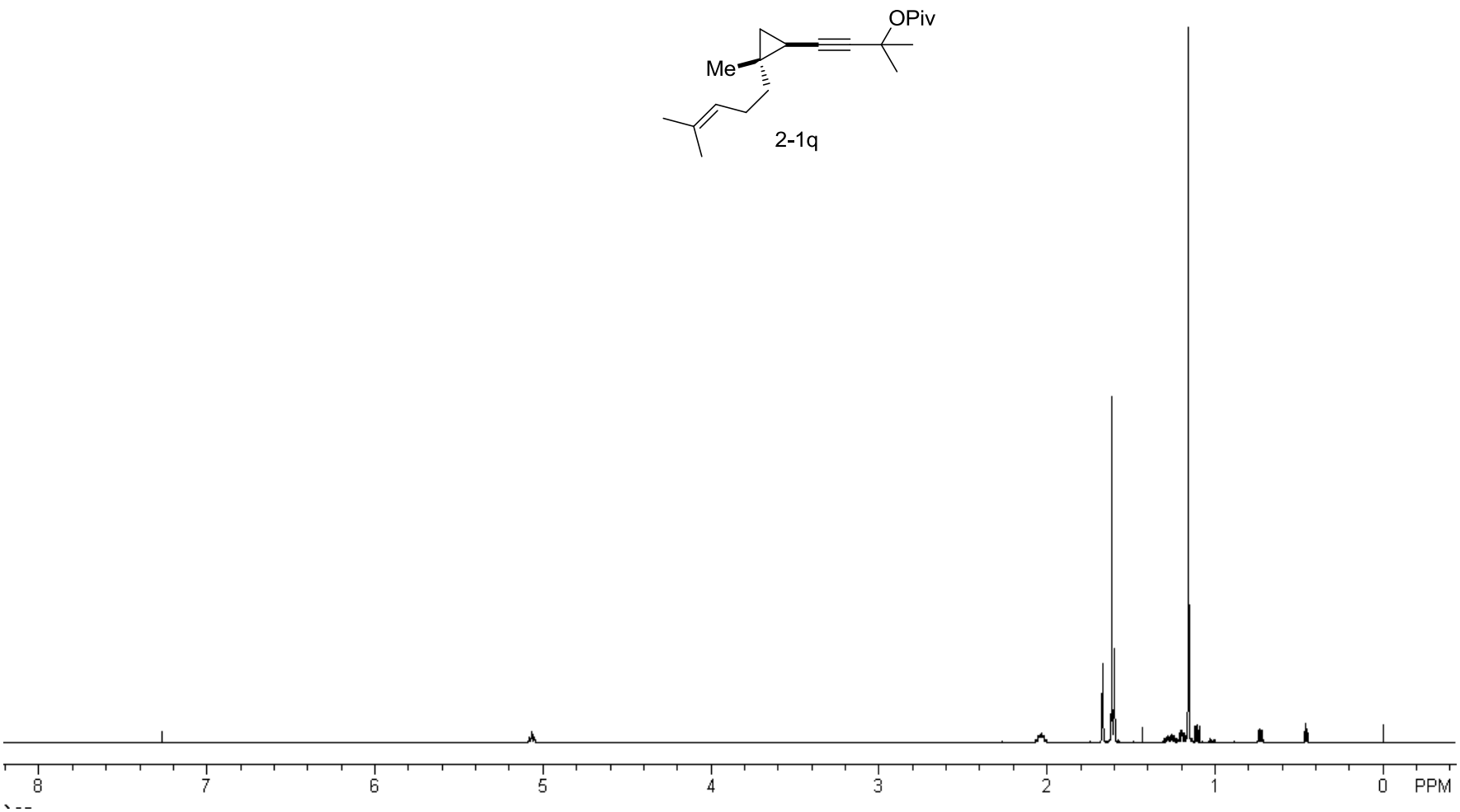
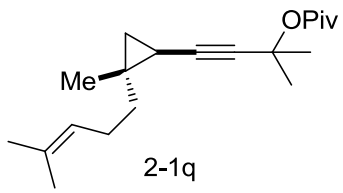
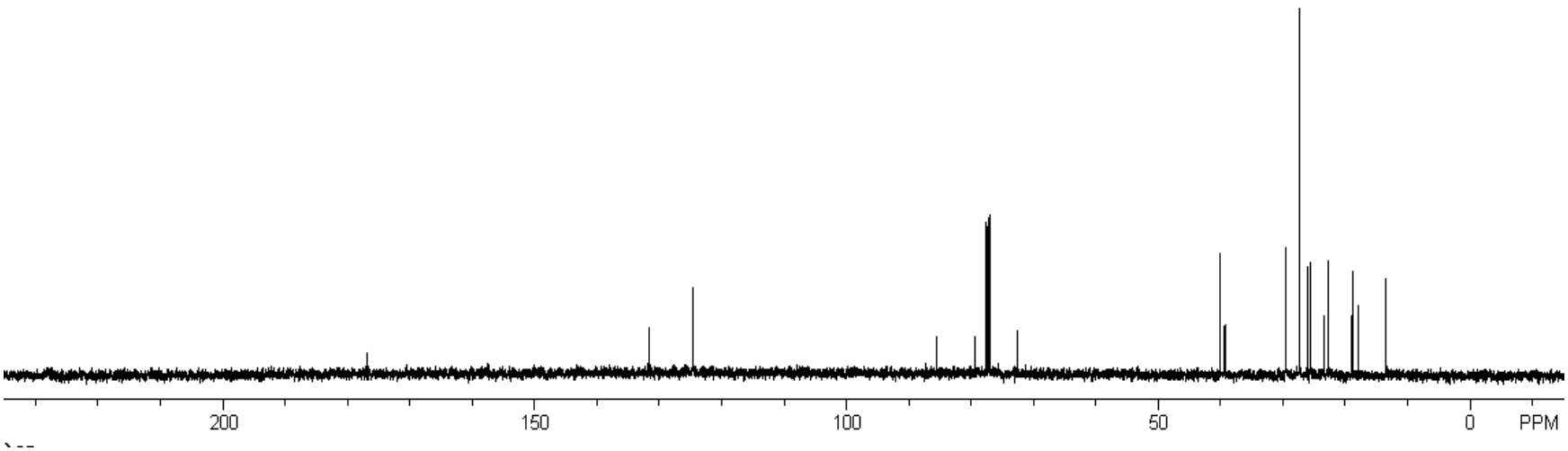
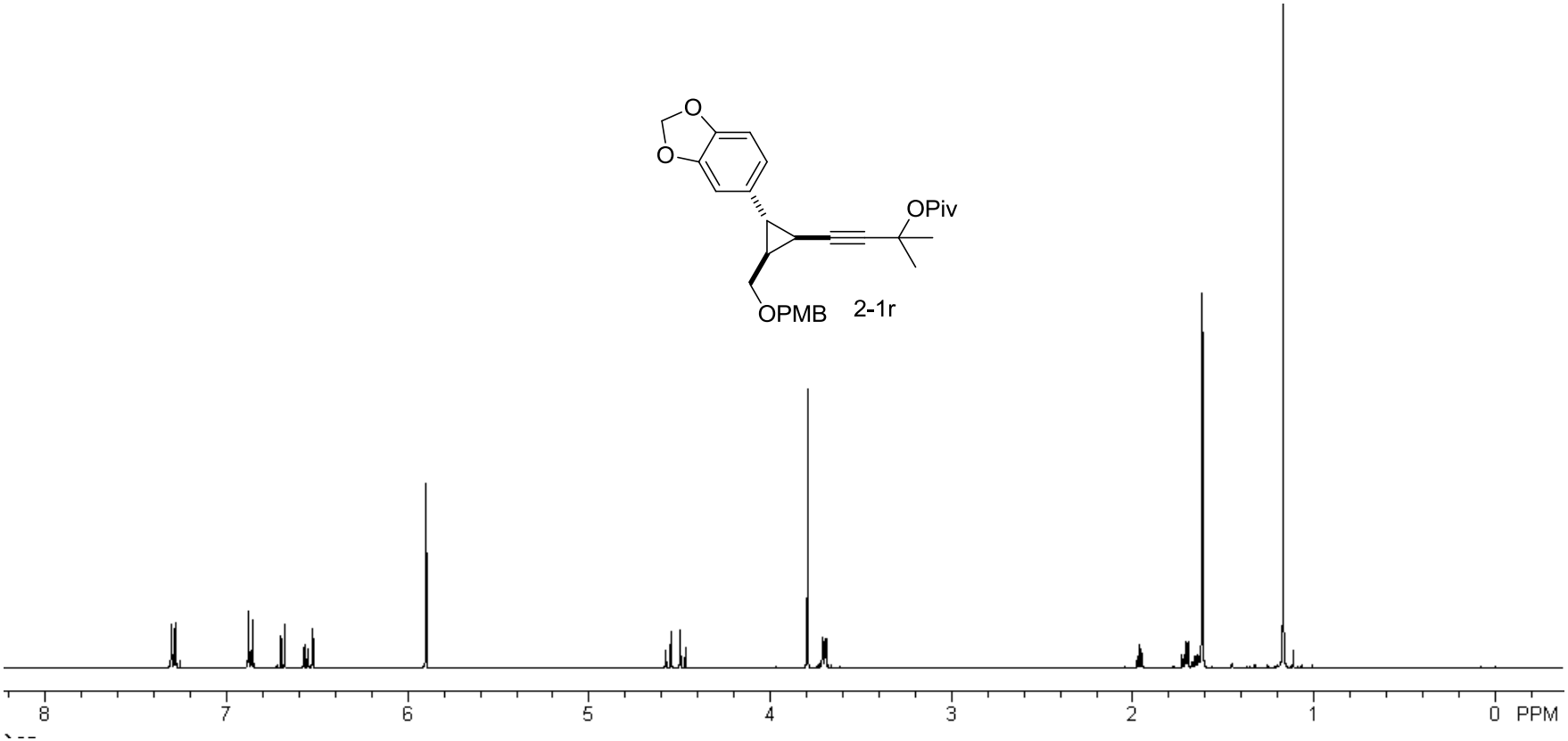
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
EtO2C
EtO2C
OAc
EtO2C
EtO2C
OAc
2-1p

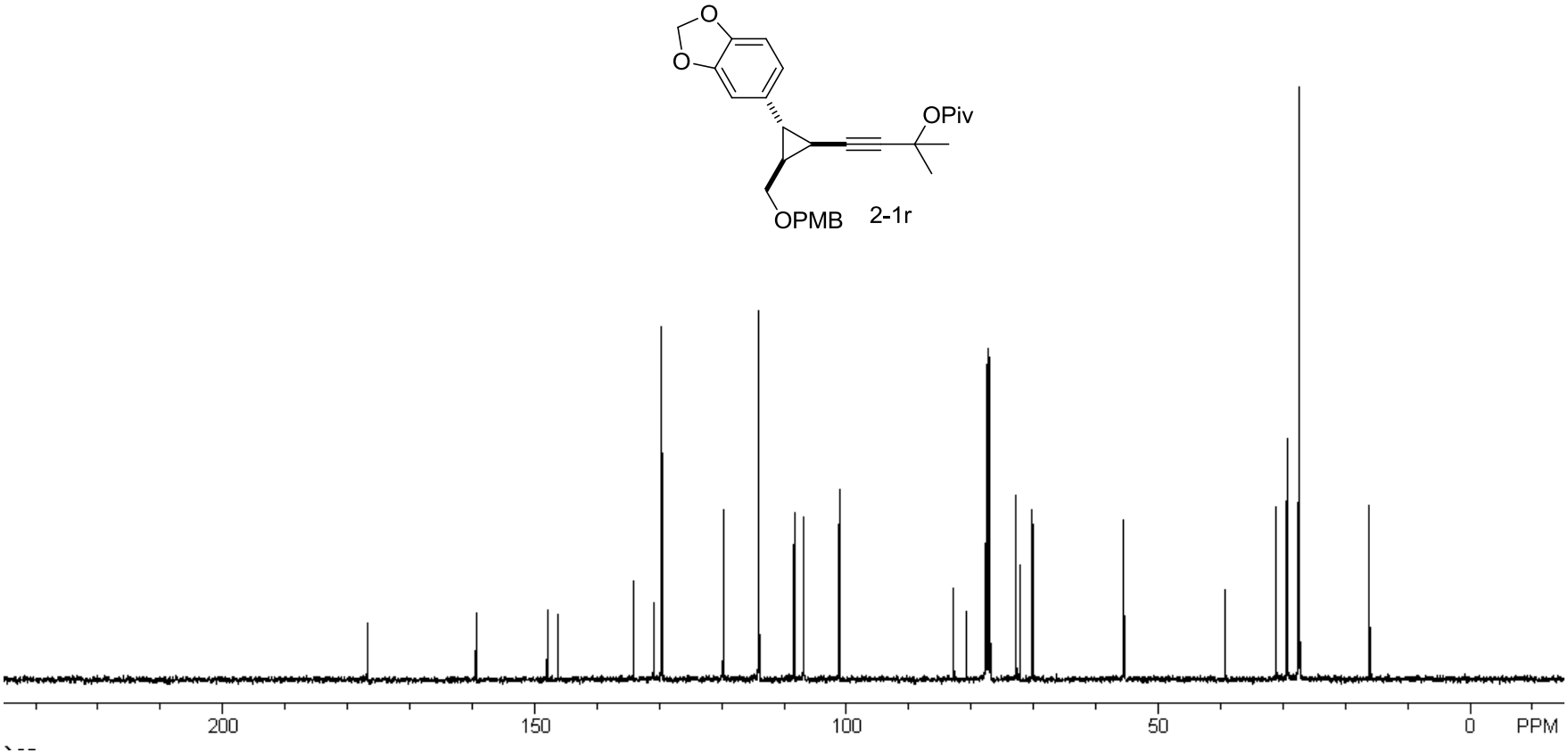

OPiv
Me
2-1q
8
7
6
5
4
3
2
1
0
PPM

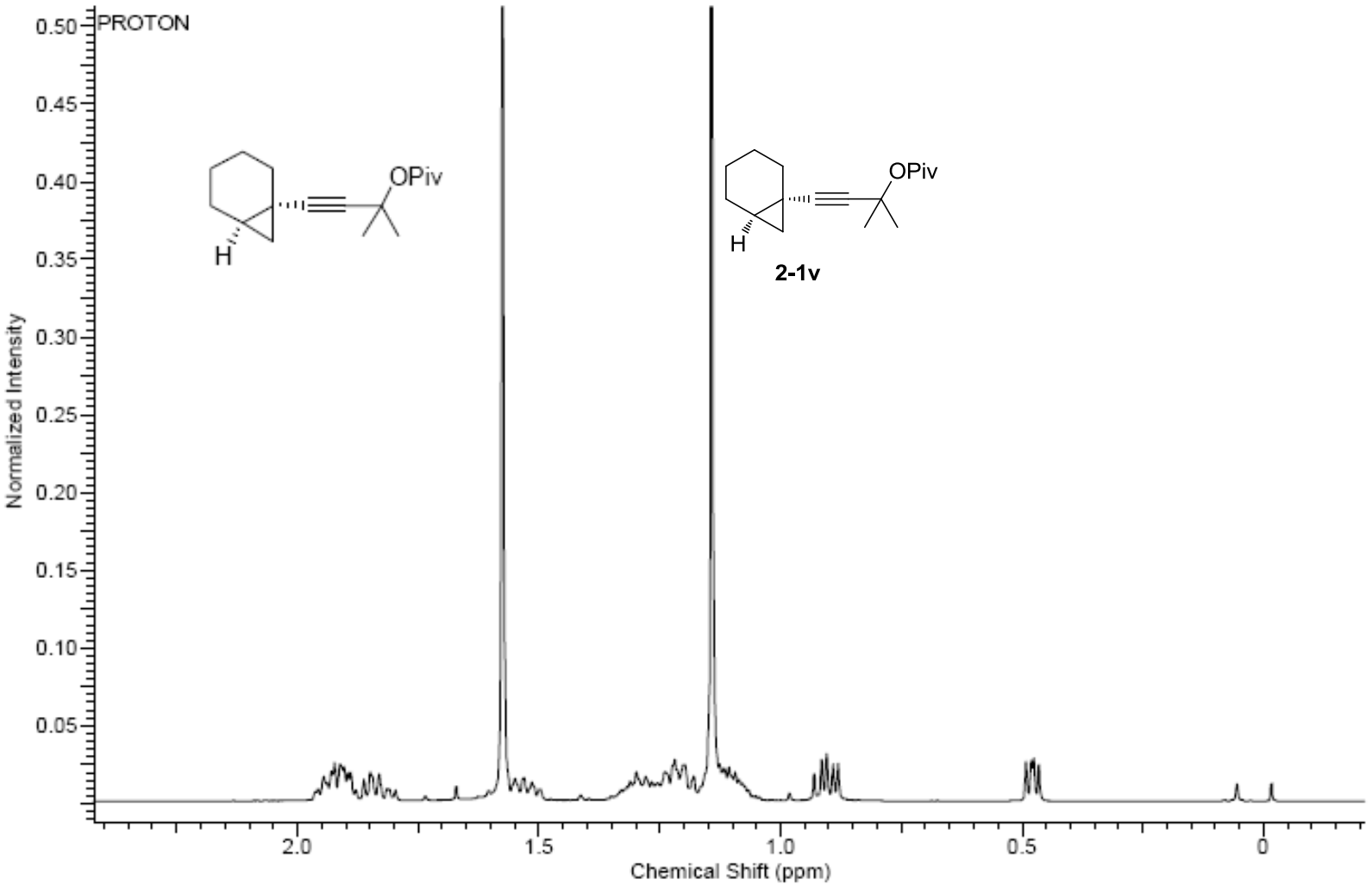


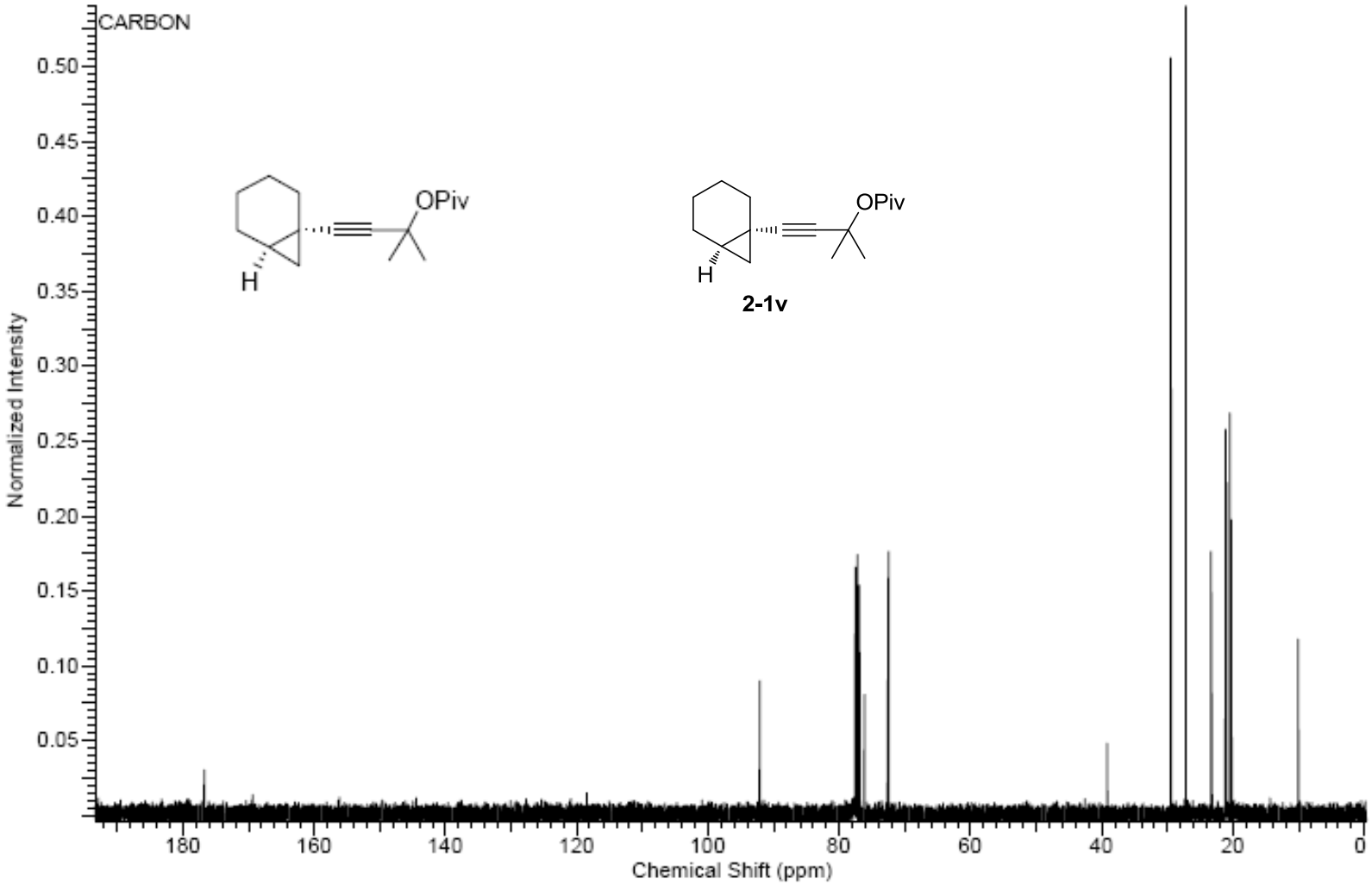
2-1q

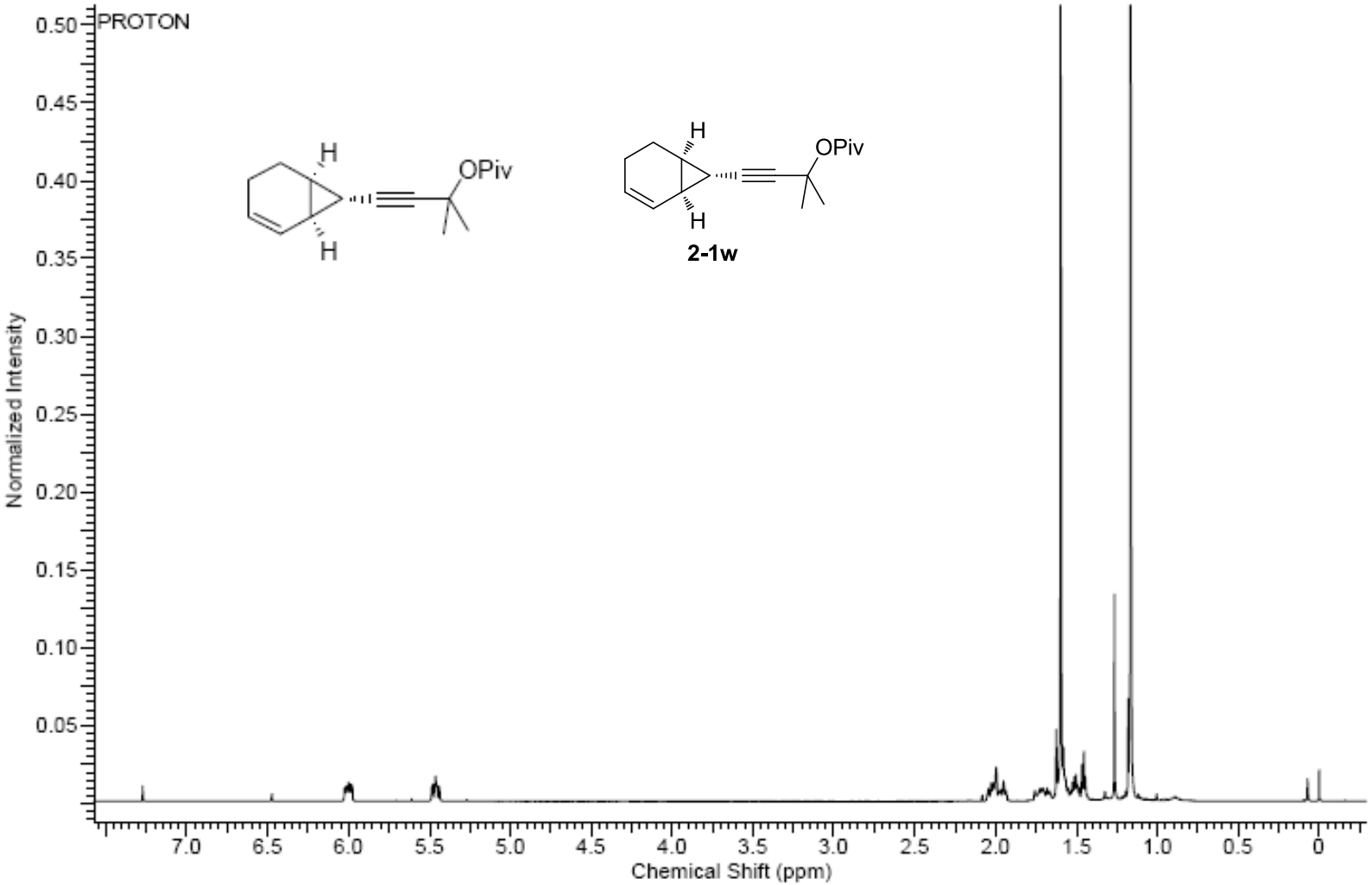


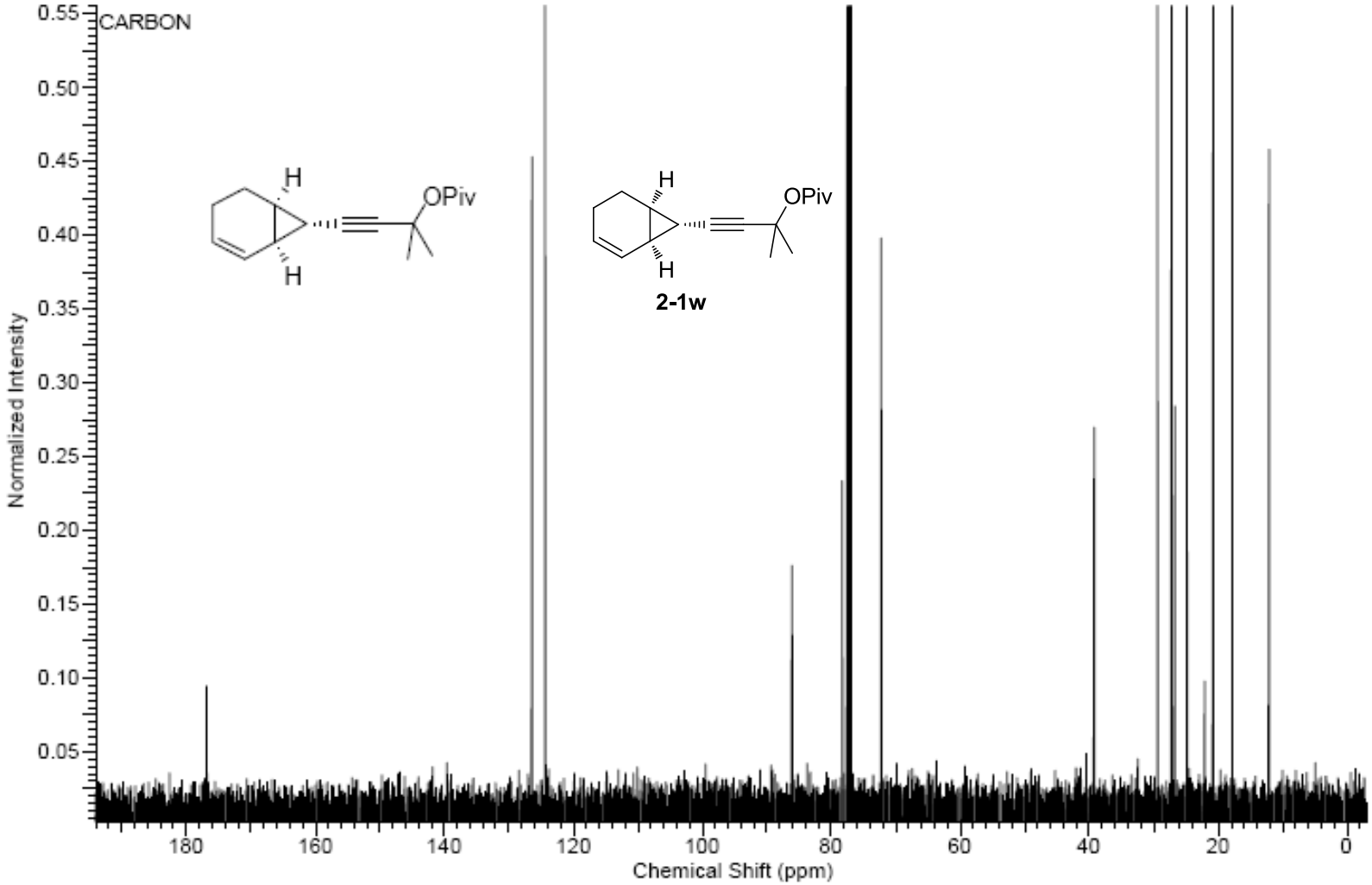

O
O
OPiv
OPMB
2-1r
8
7
6
5
4
3
2
1
0
PPM

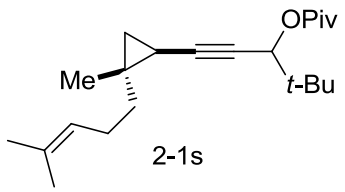

O
O
OPiv
OPMB
2-1r
200
150
100
50
0
PPM


PROTON
OPiv
H
OPiv
H
2-1v
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

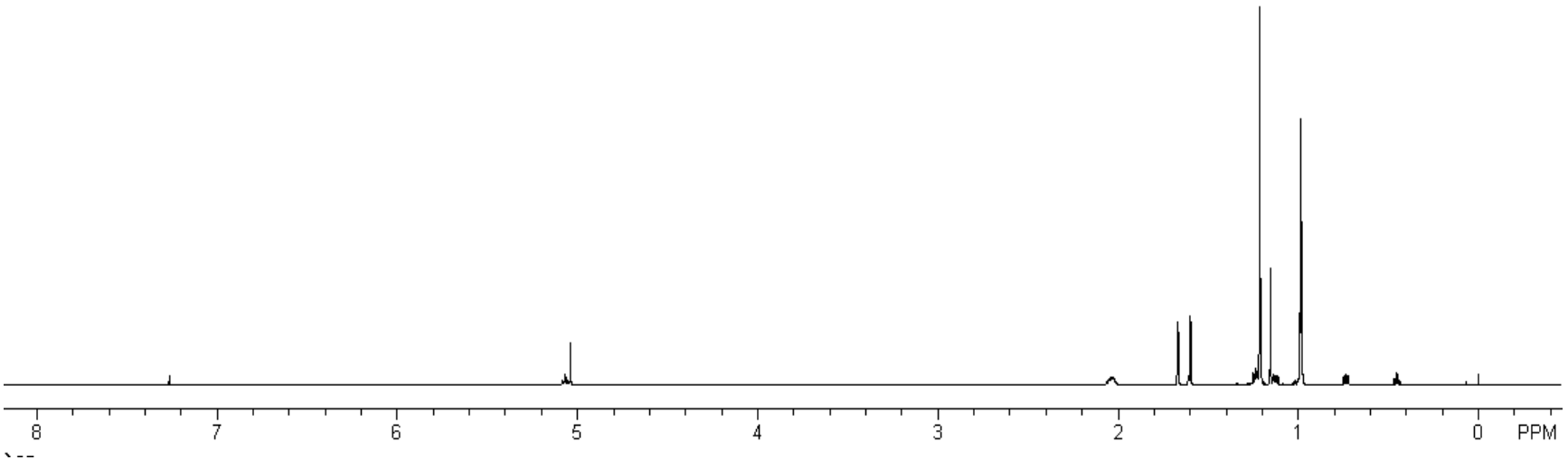

CARBON
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
OPiv
H
OPiv
H
2-1v
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

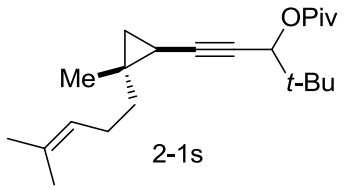

PROTON
H
H
OPiv
H
H
OPiv
2-1w
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


CARBON
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
H
OPiv
H
H
OPiv
H
2-1w



2-1s





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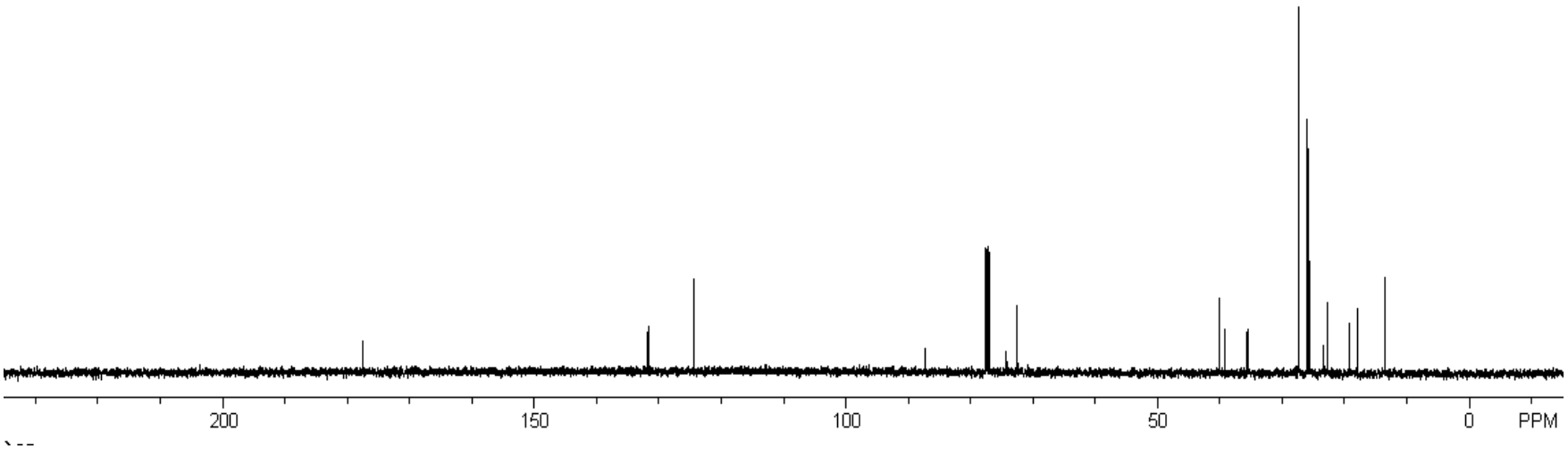
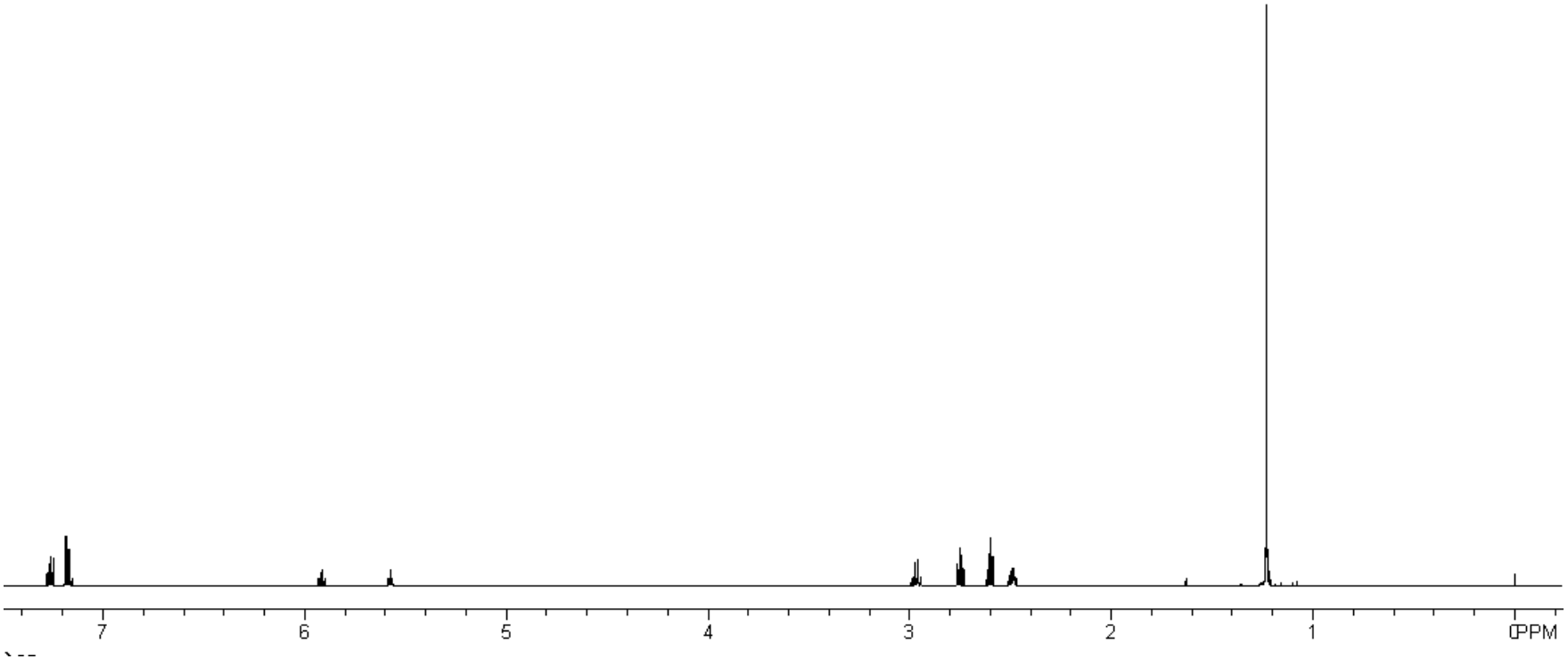
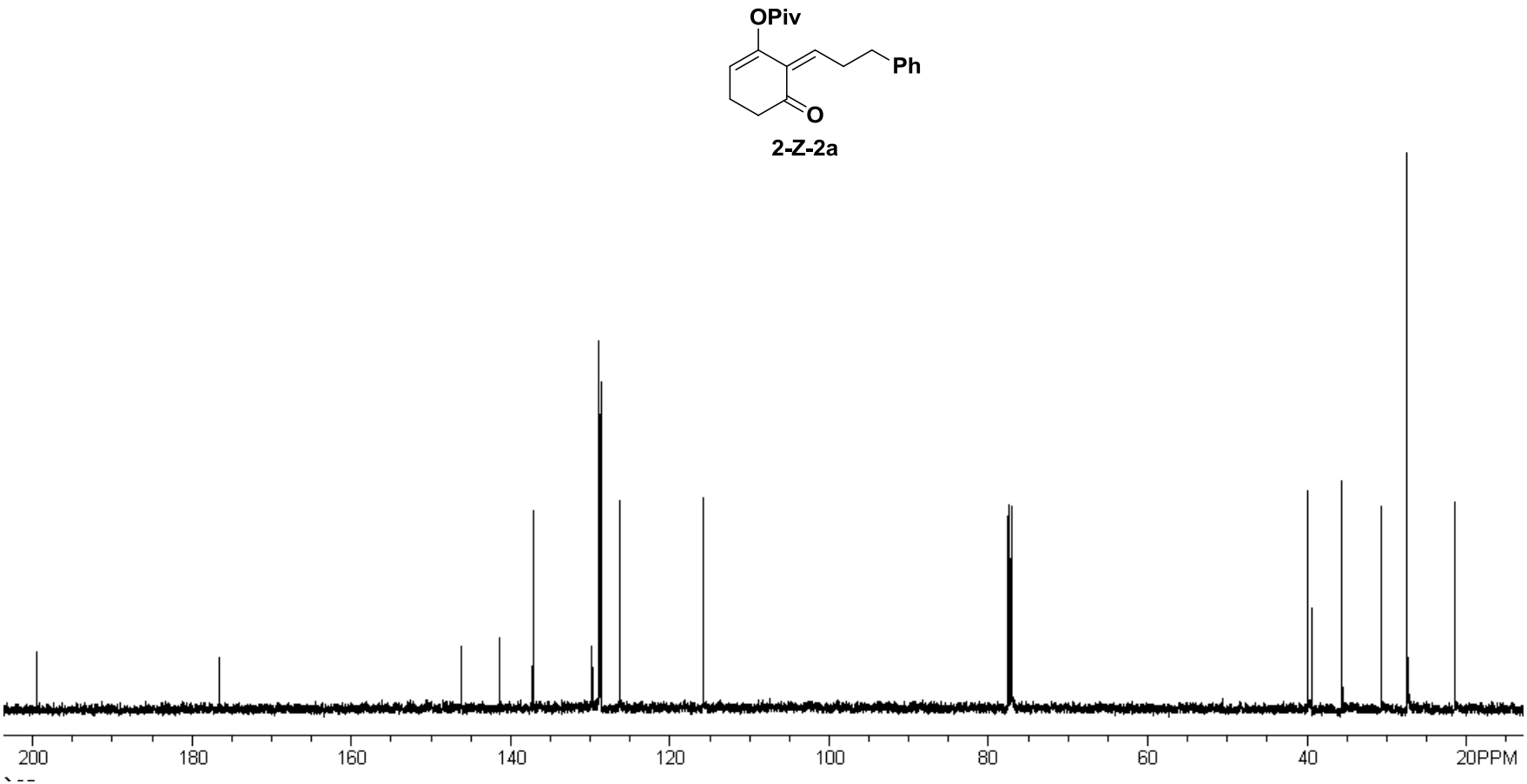


2-Z-2a

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200
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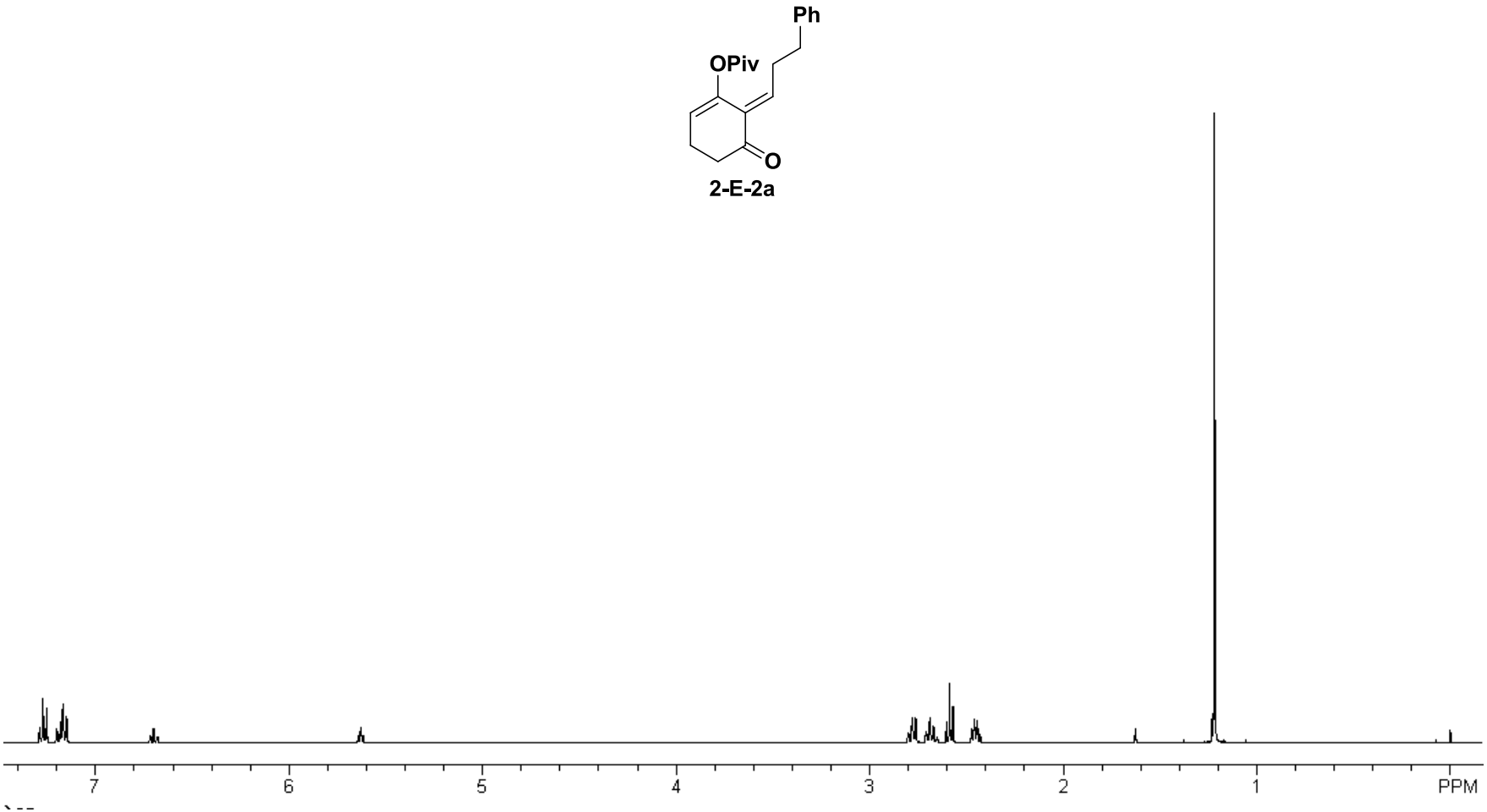
20PPM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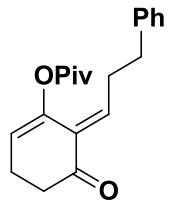
PPM



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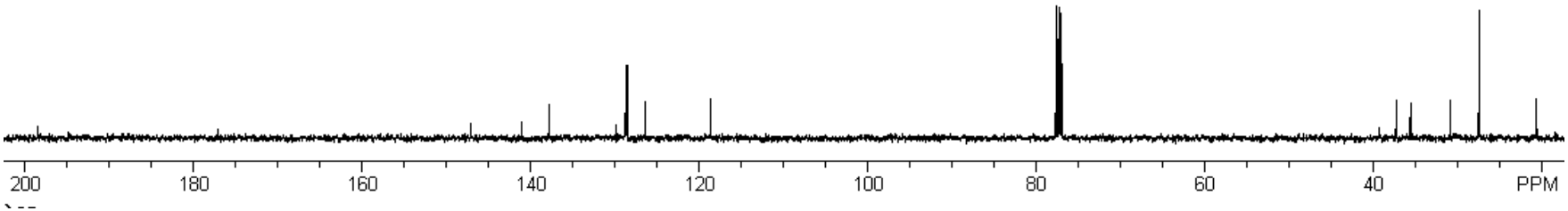

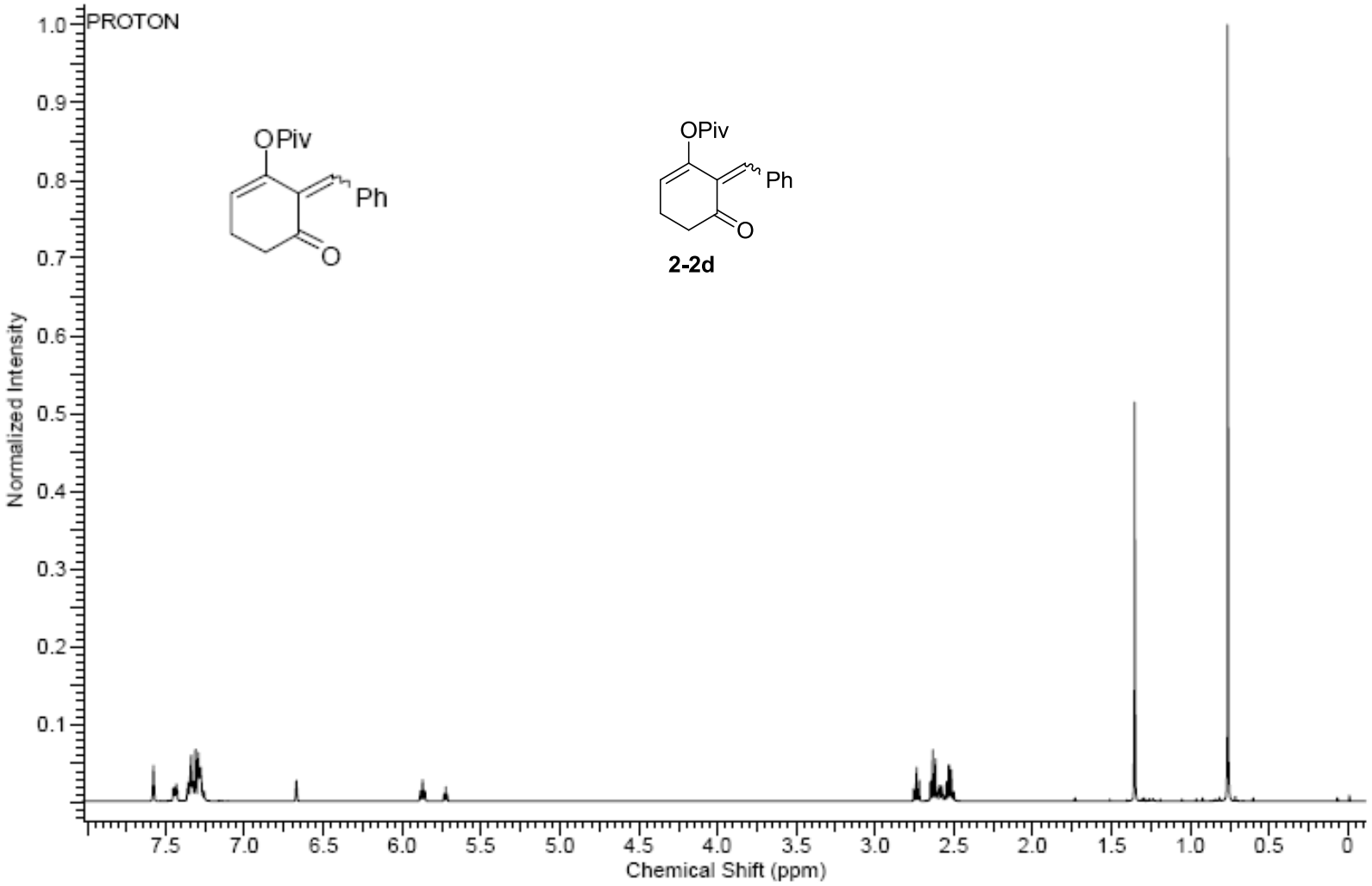
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OPiv
Ph
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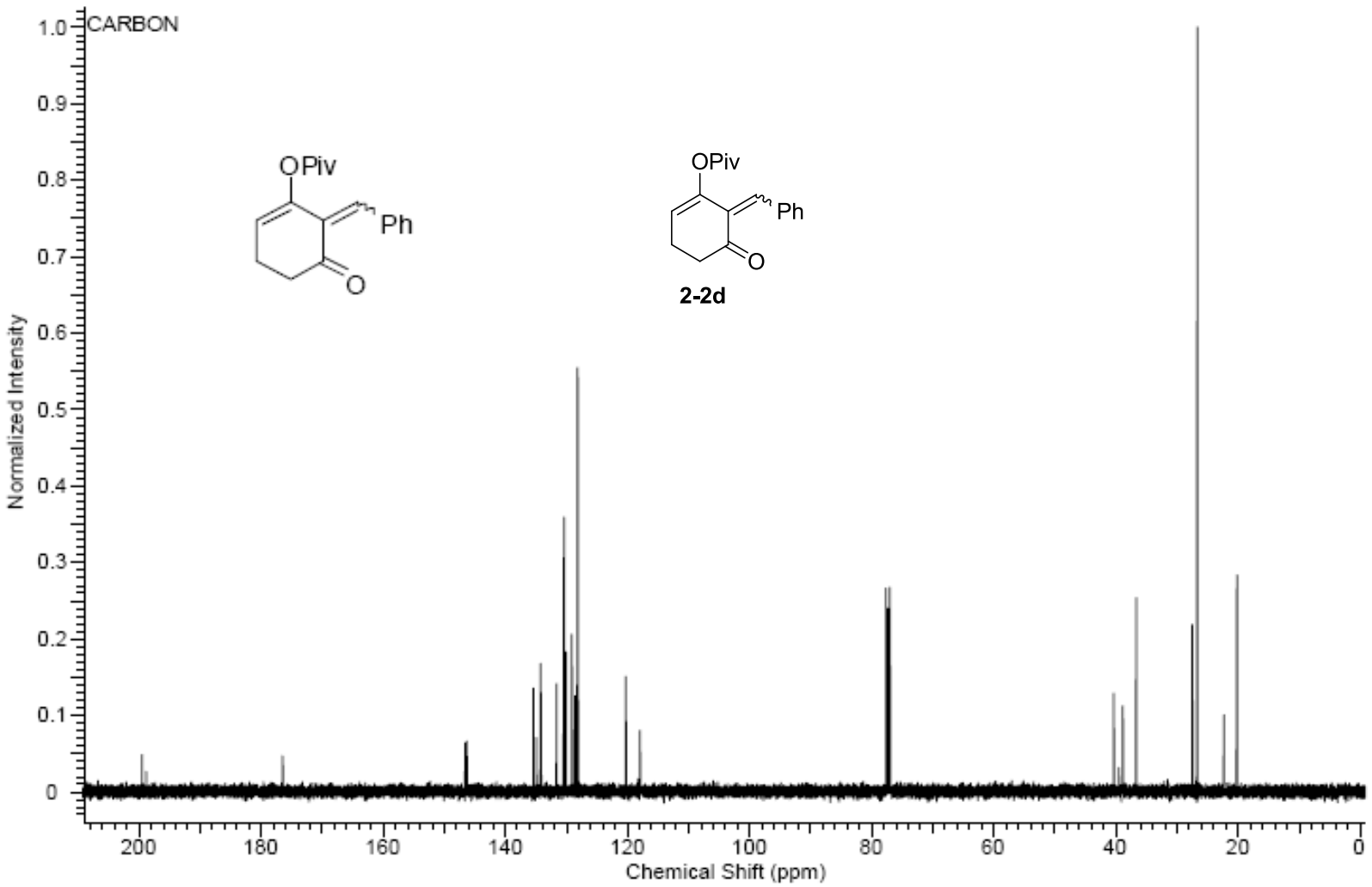
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Ph
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Ph
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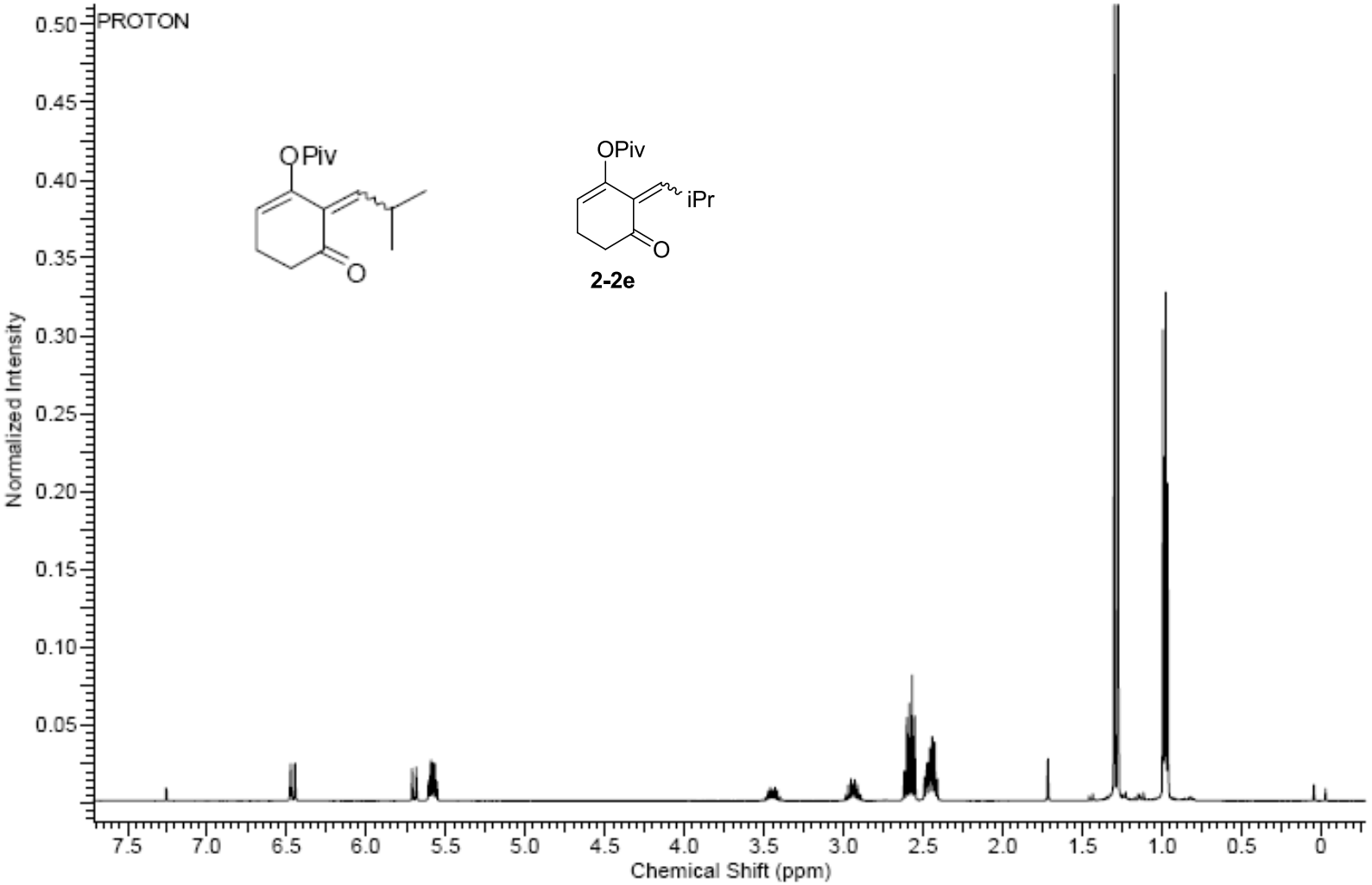
Chemical Shift (ppm)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OPiv
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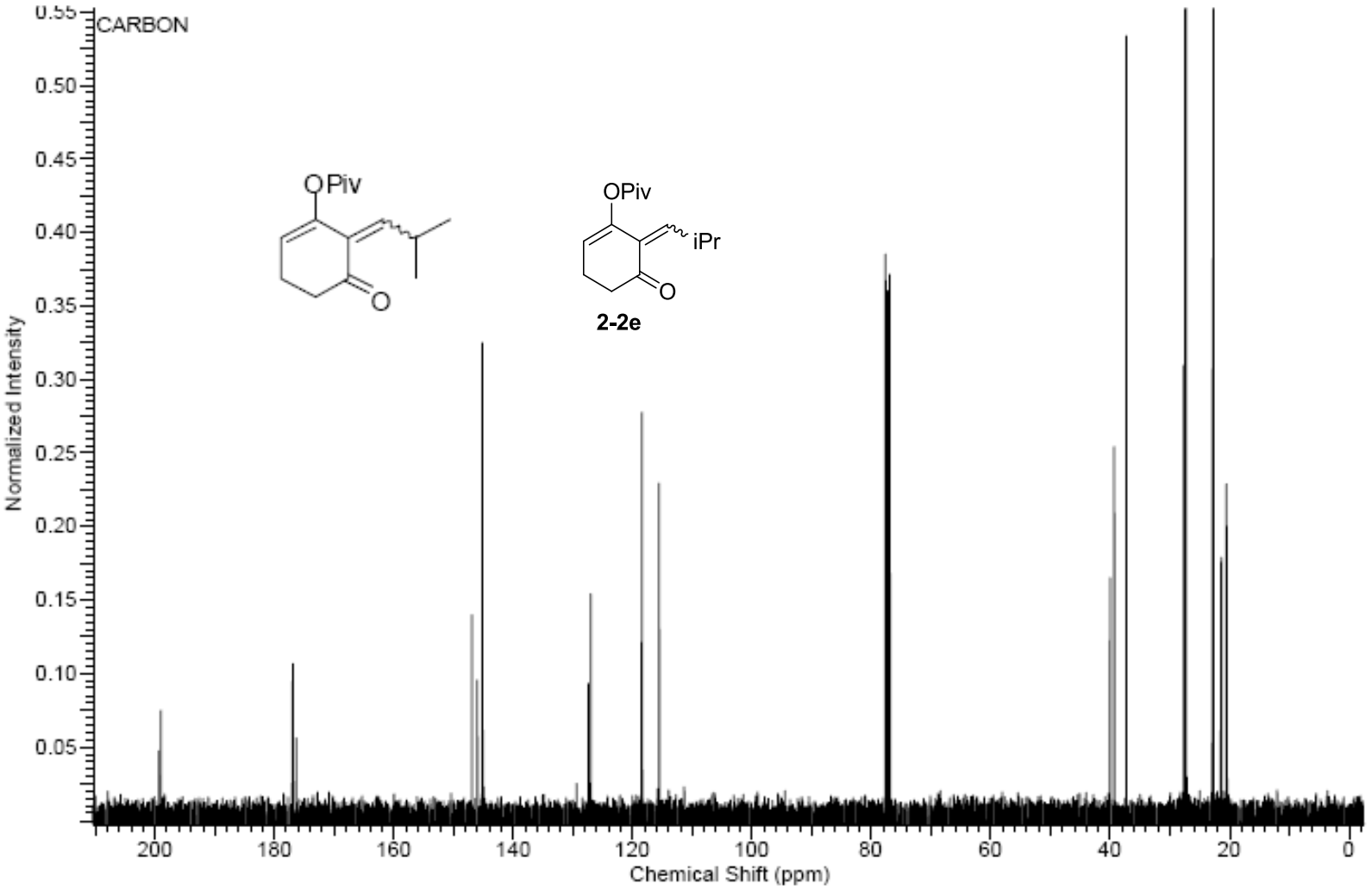
Chemical Shift (ppm)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OPiv
iPr
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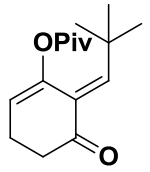

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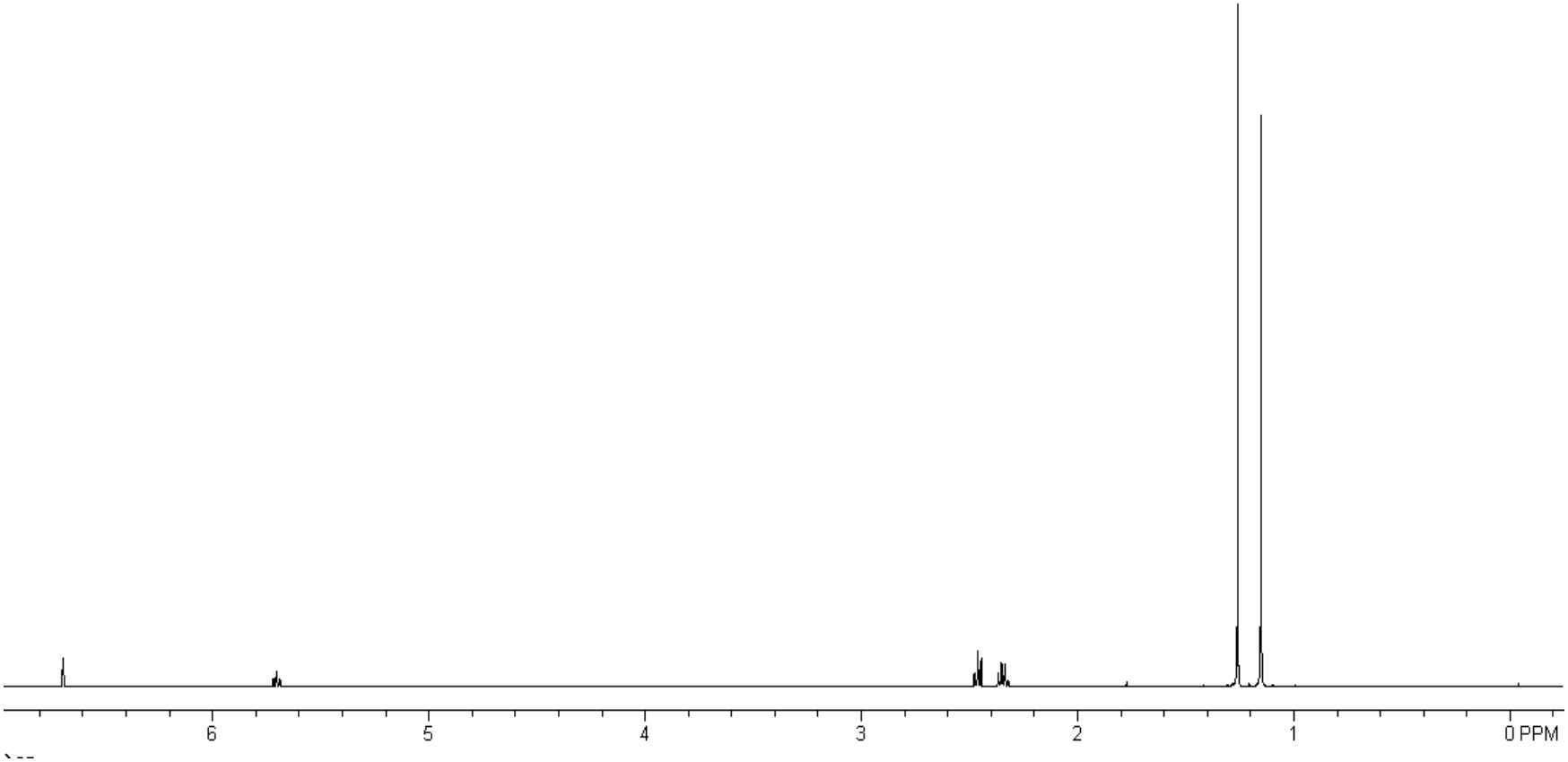

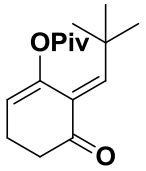

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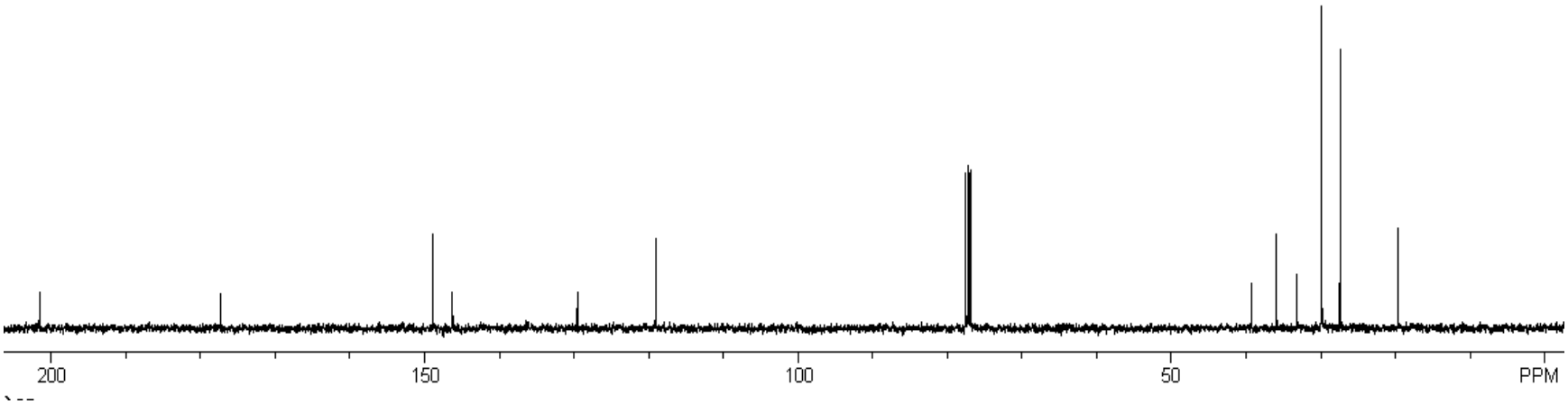

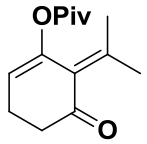

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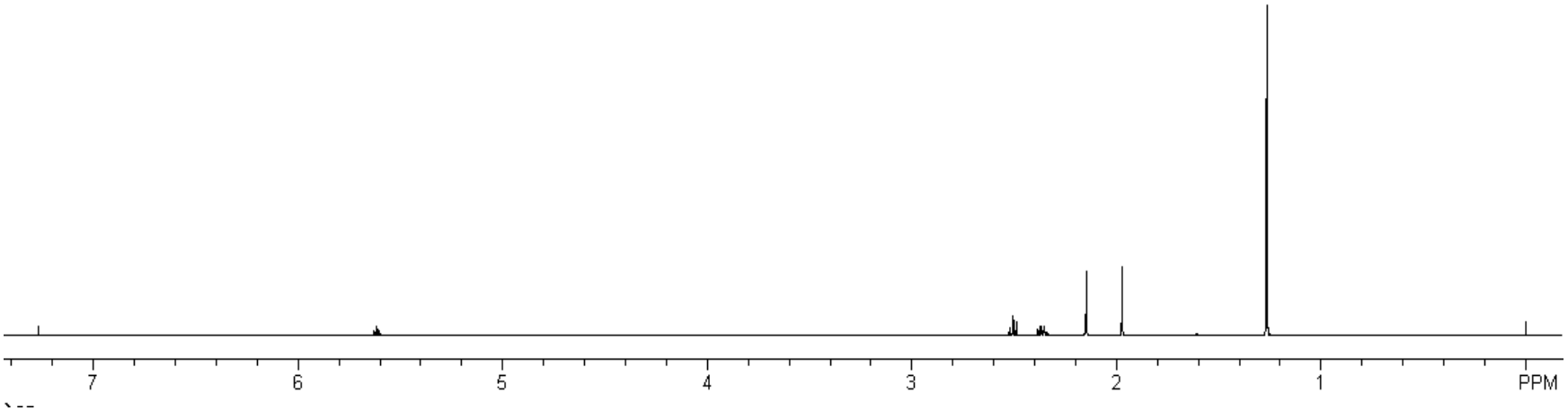

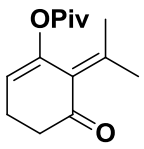

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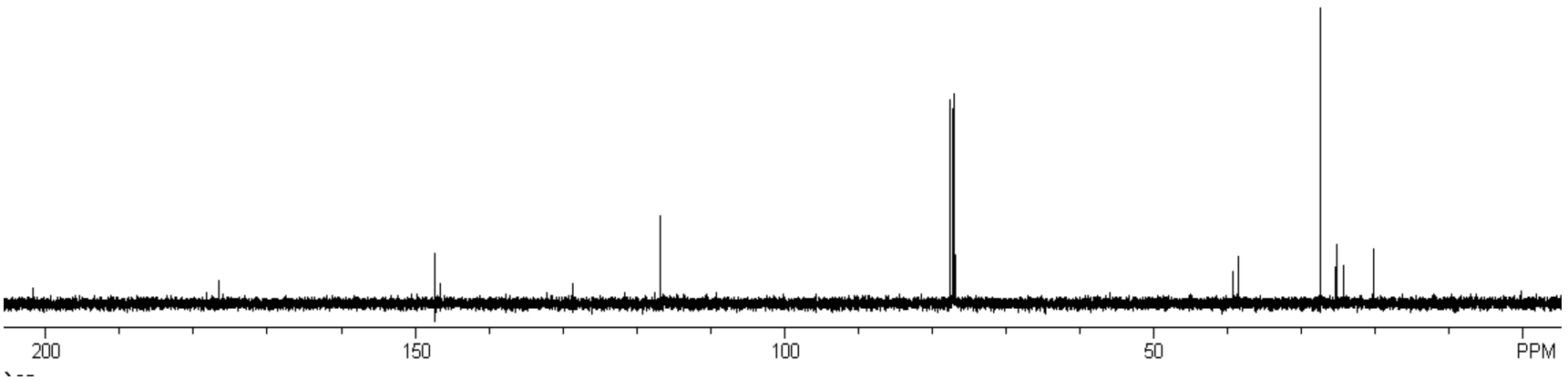

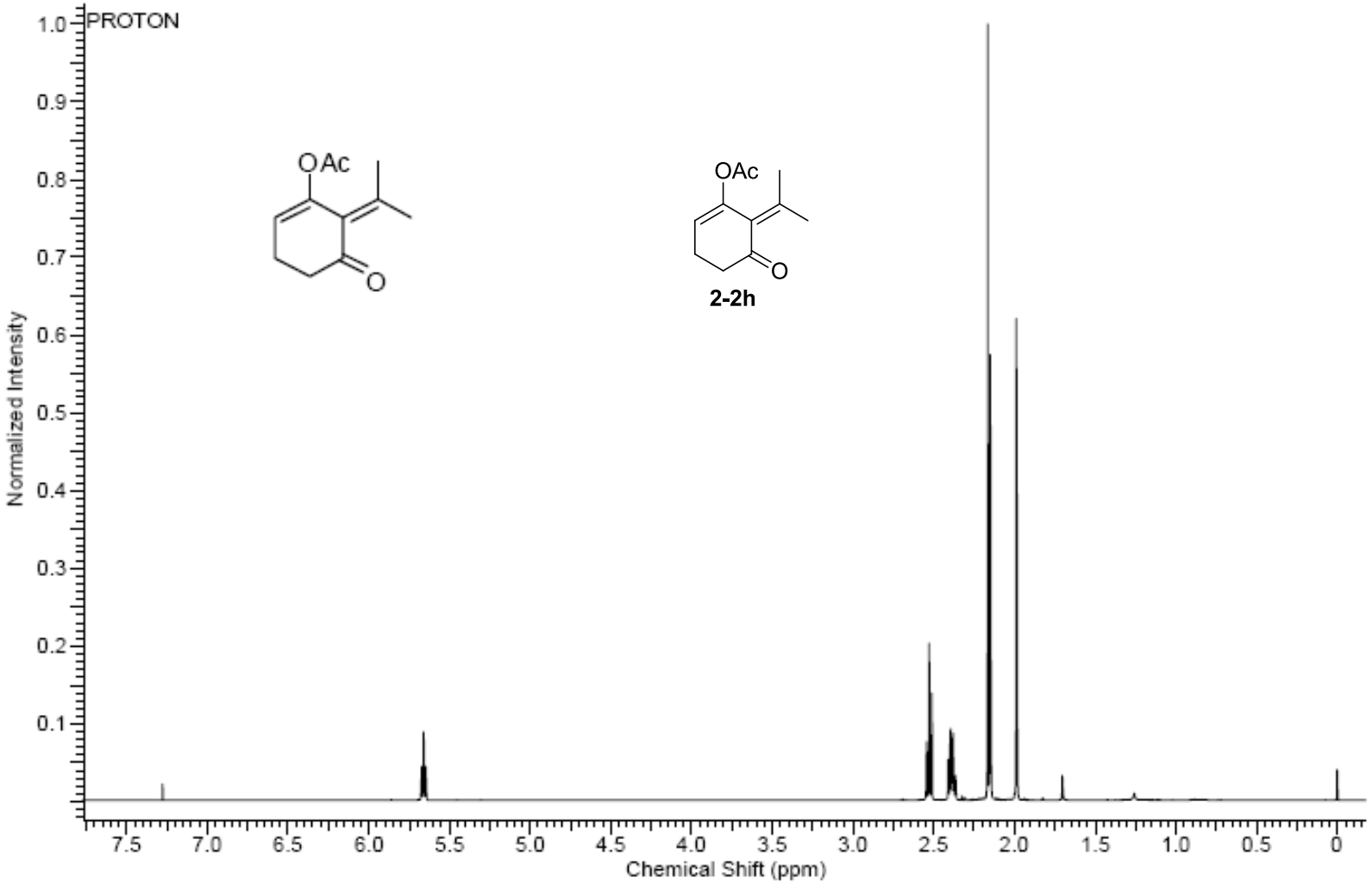
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OAc
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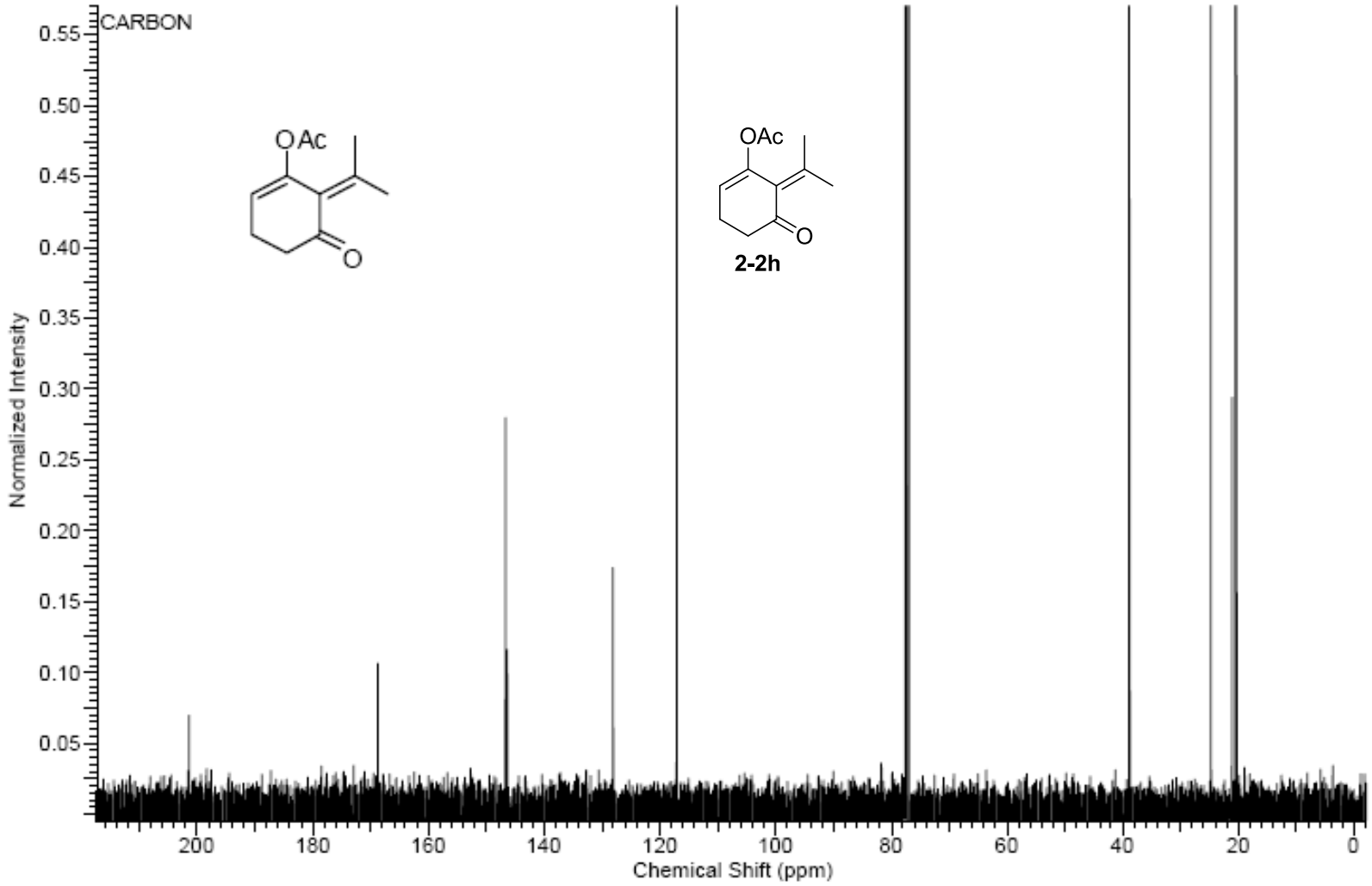
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OAc
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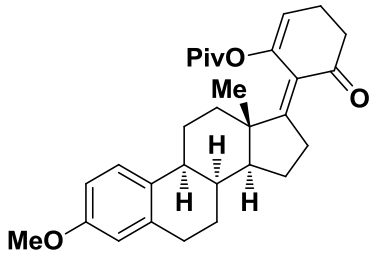

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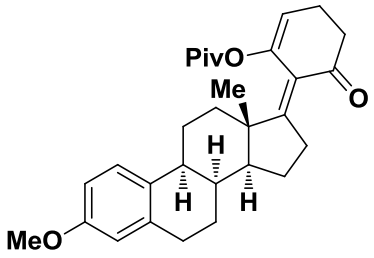
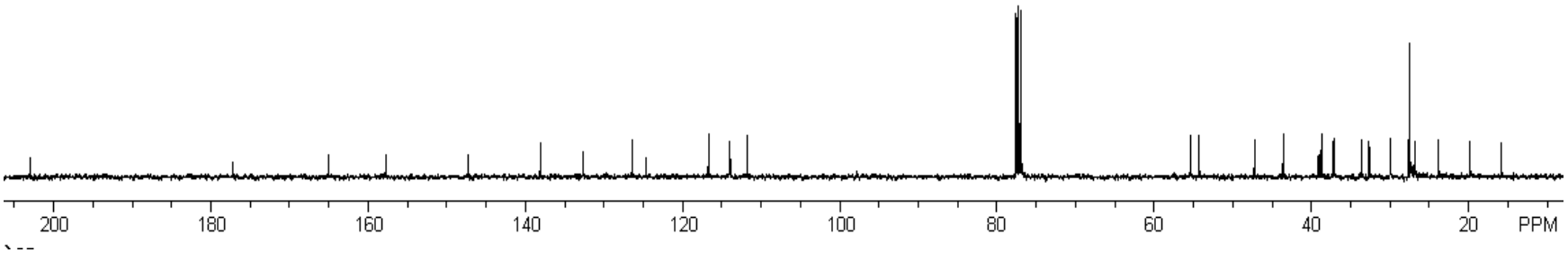
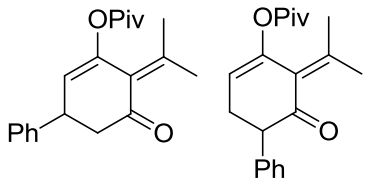


2-2i





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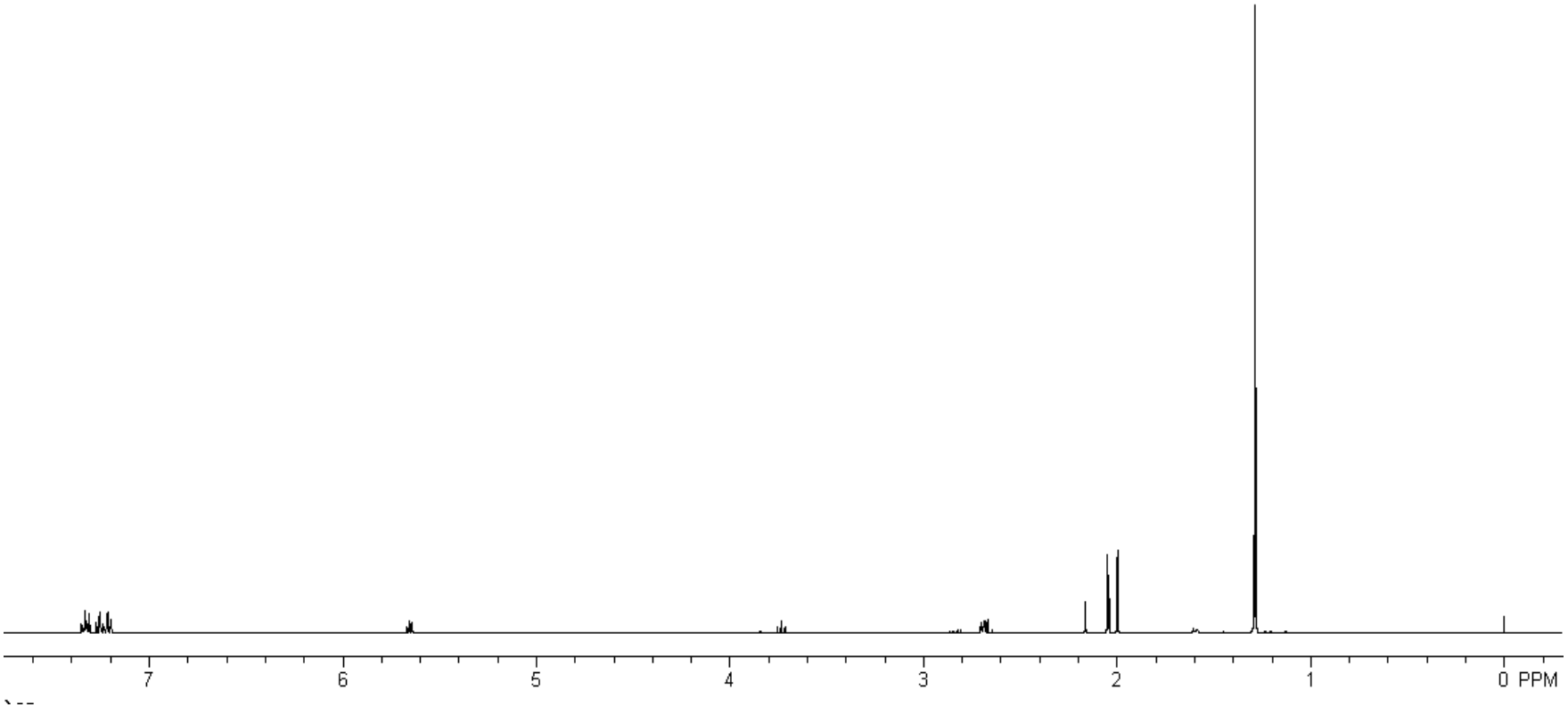

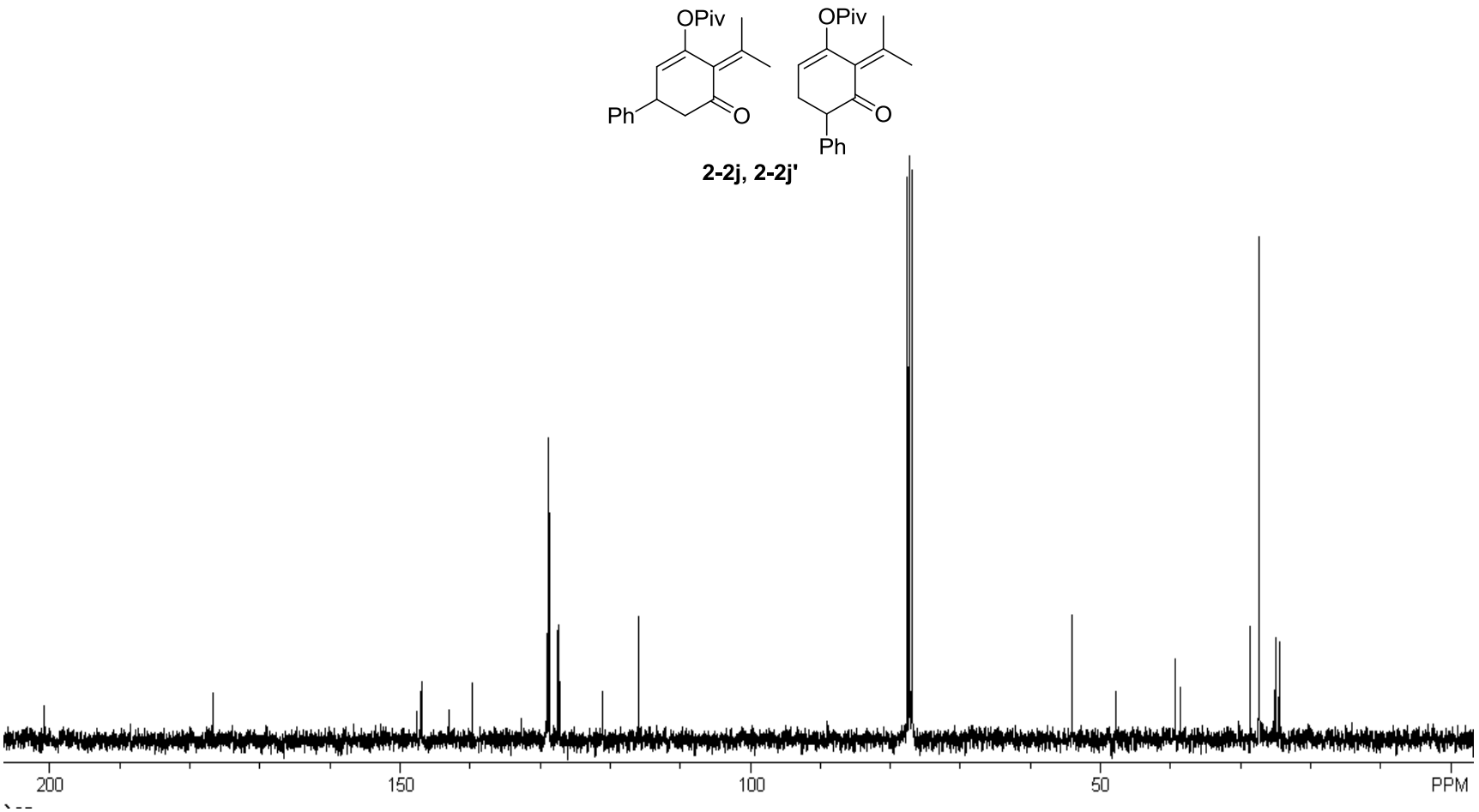

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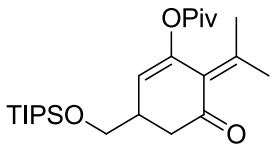

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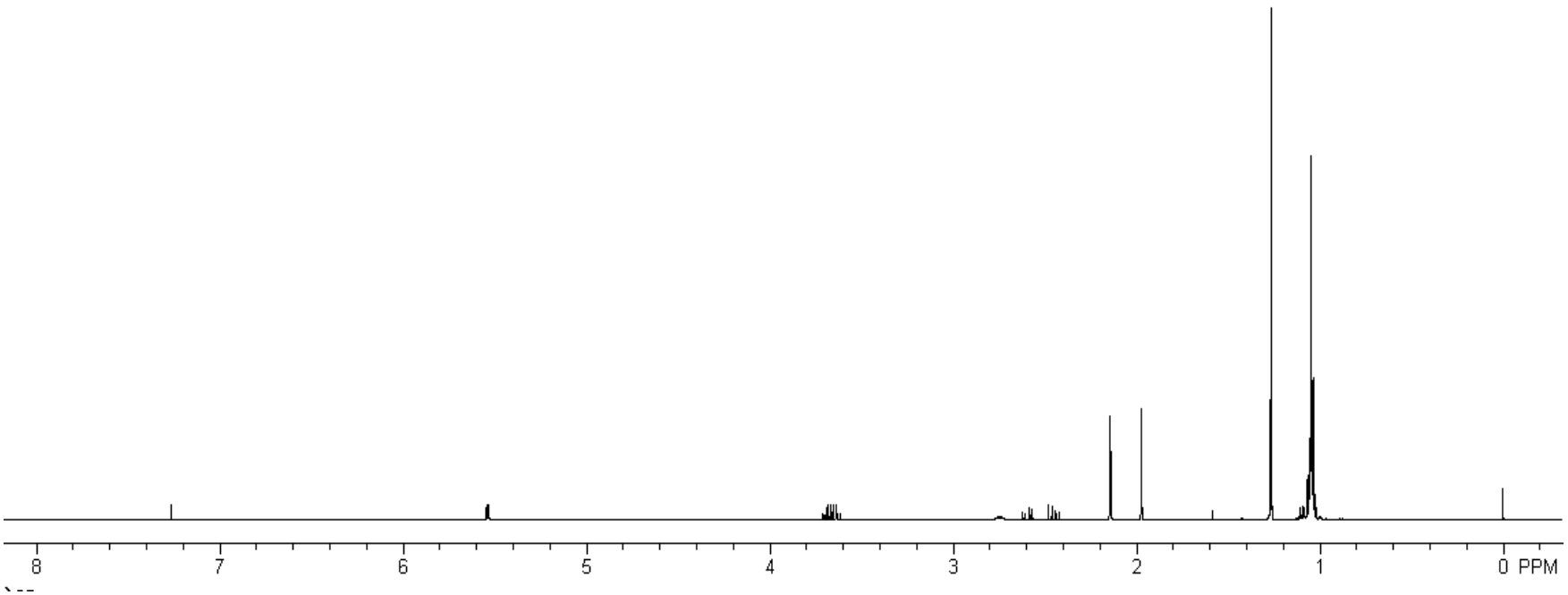

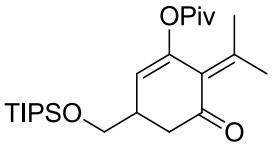

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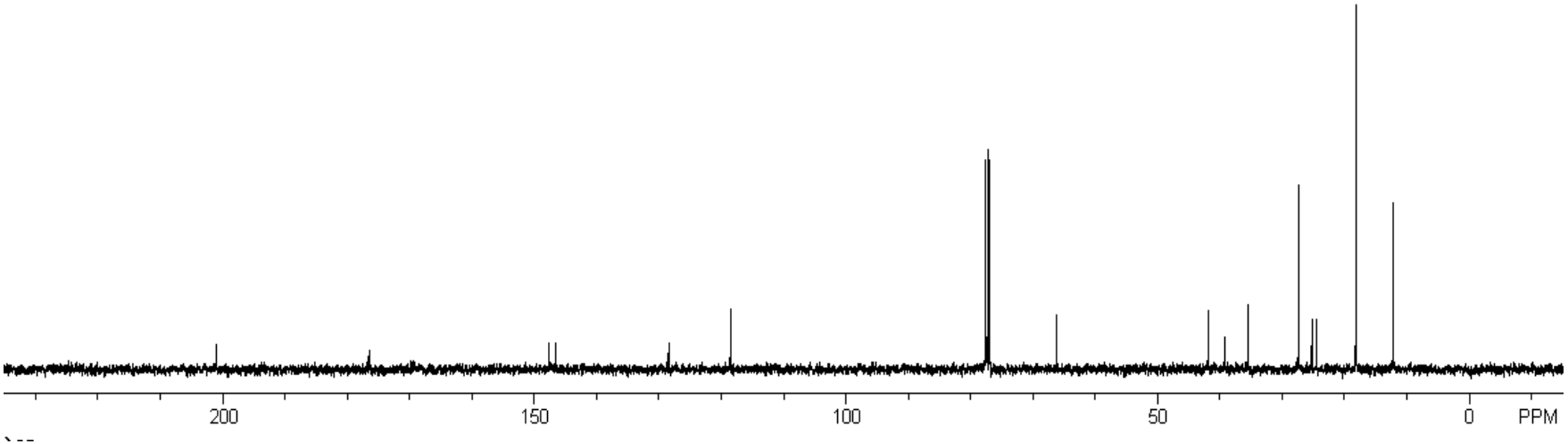
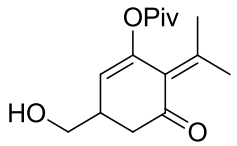
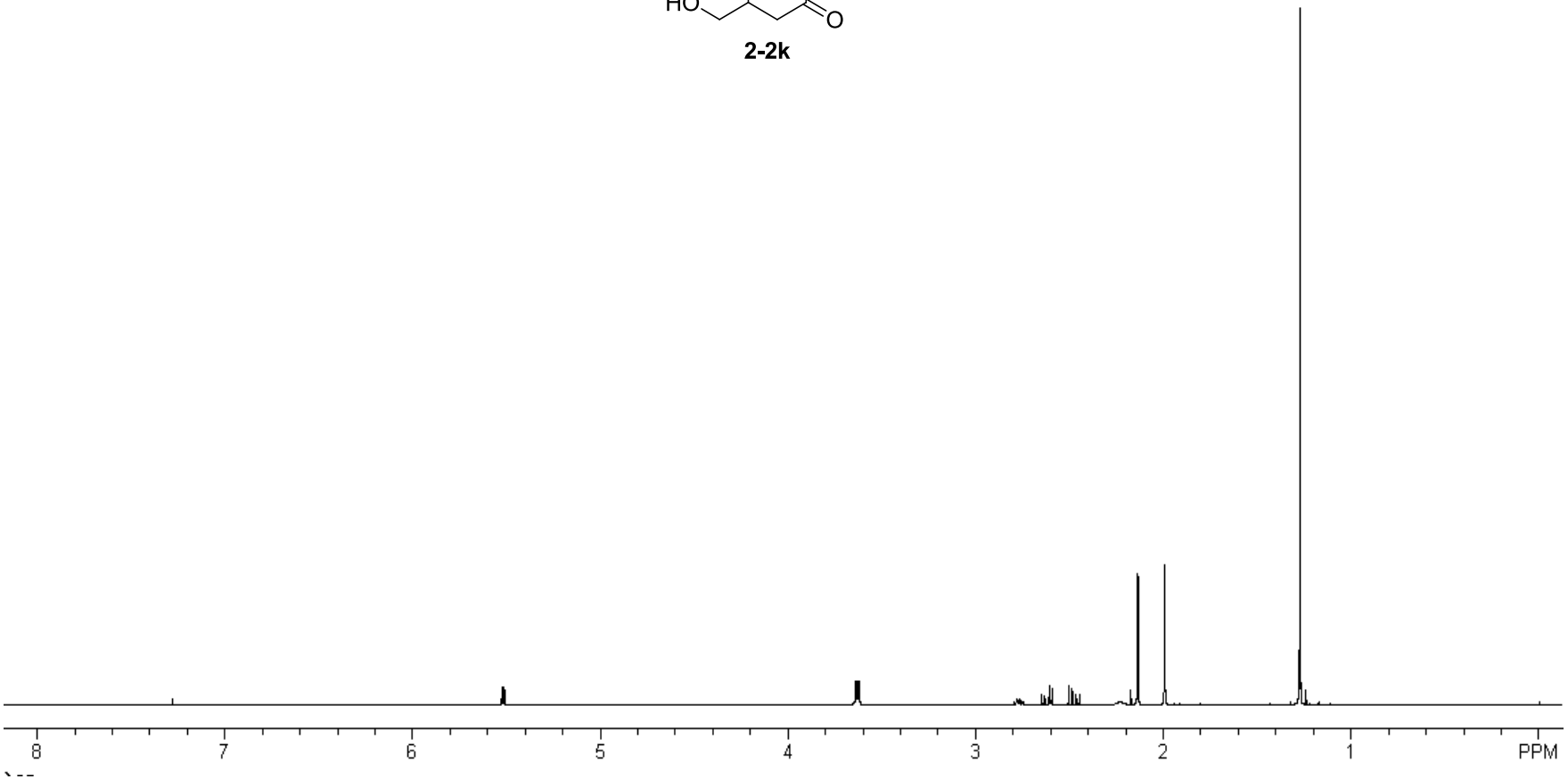
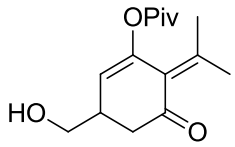




2-2k





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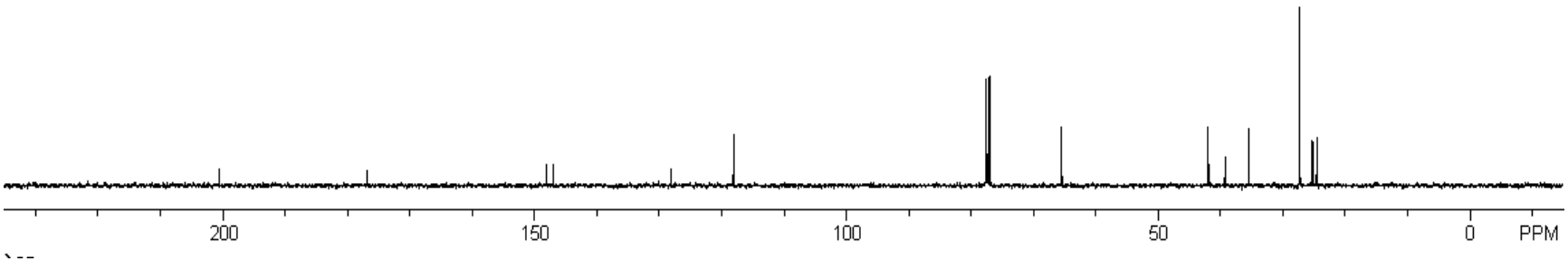

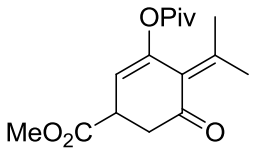

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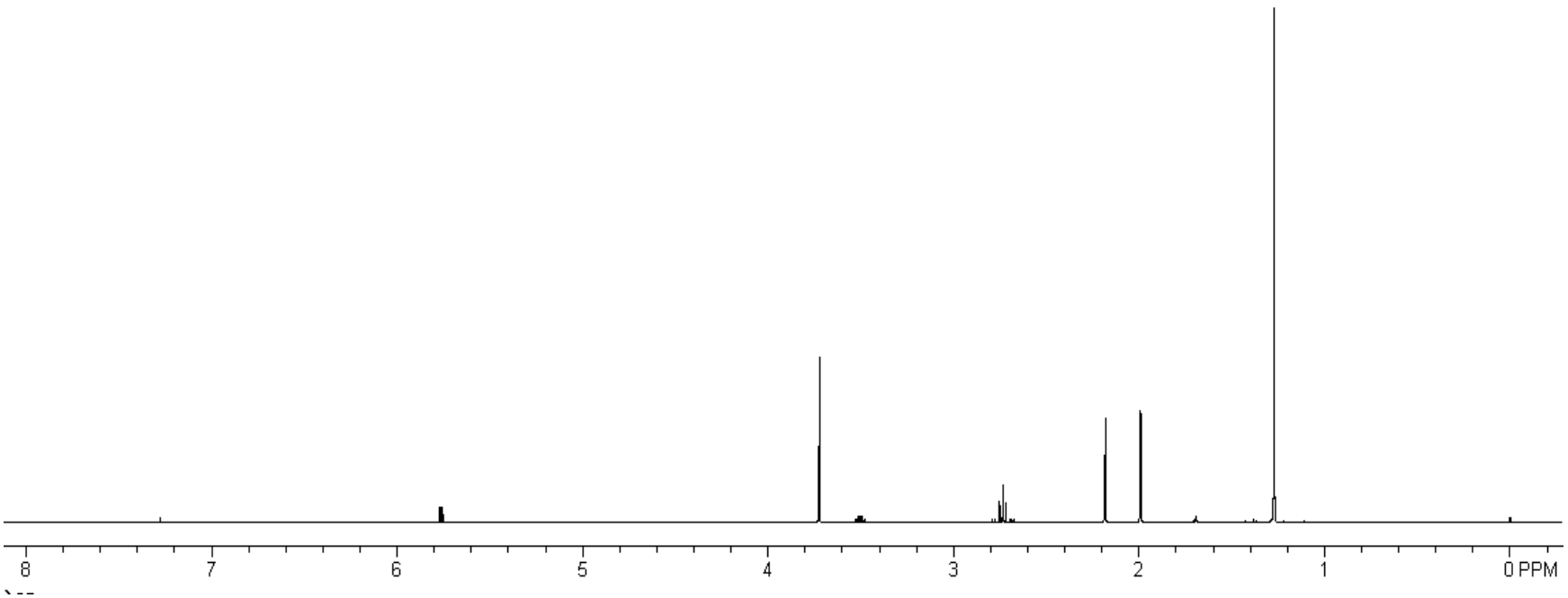

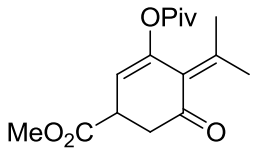

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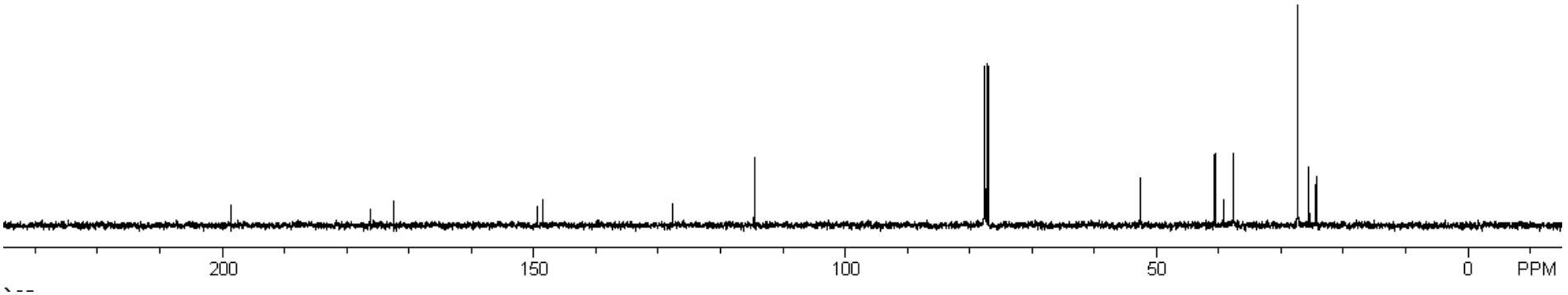

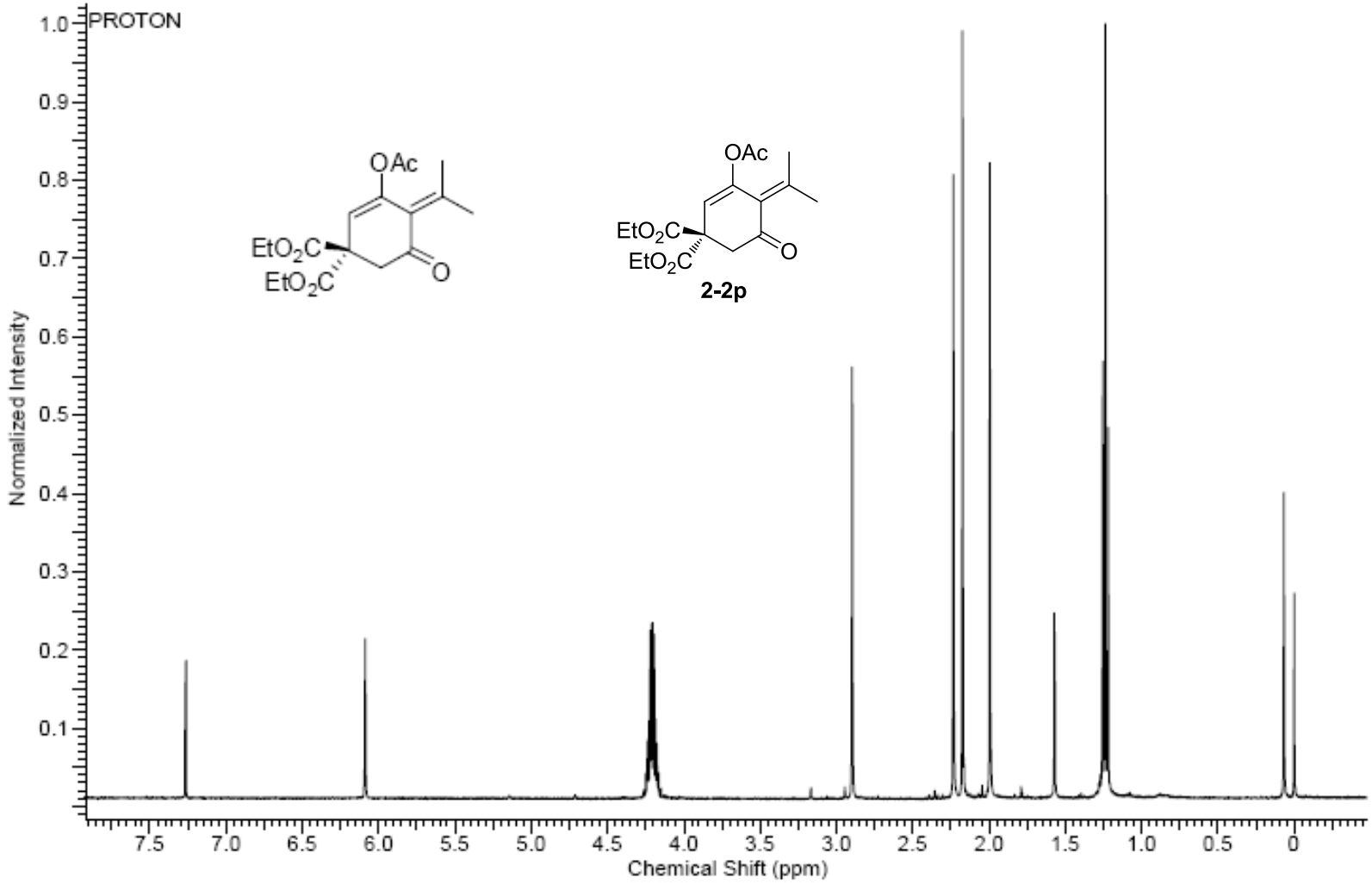
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EtO2C
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OAc
EtO2C
EtO2C
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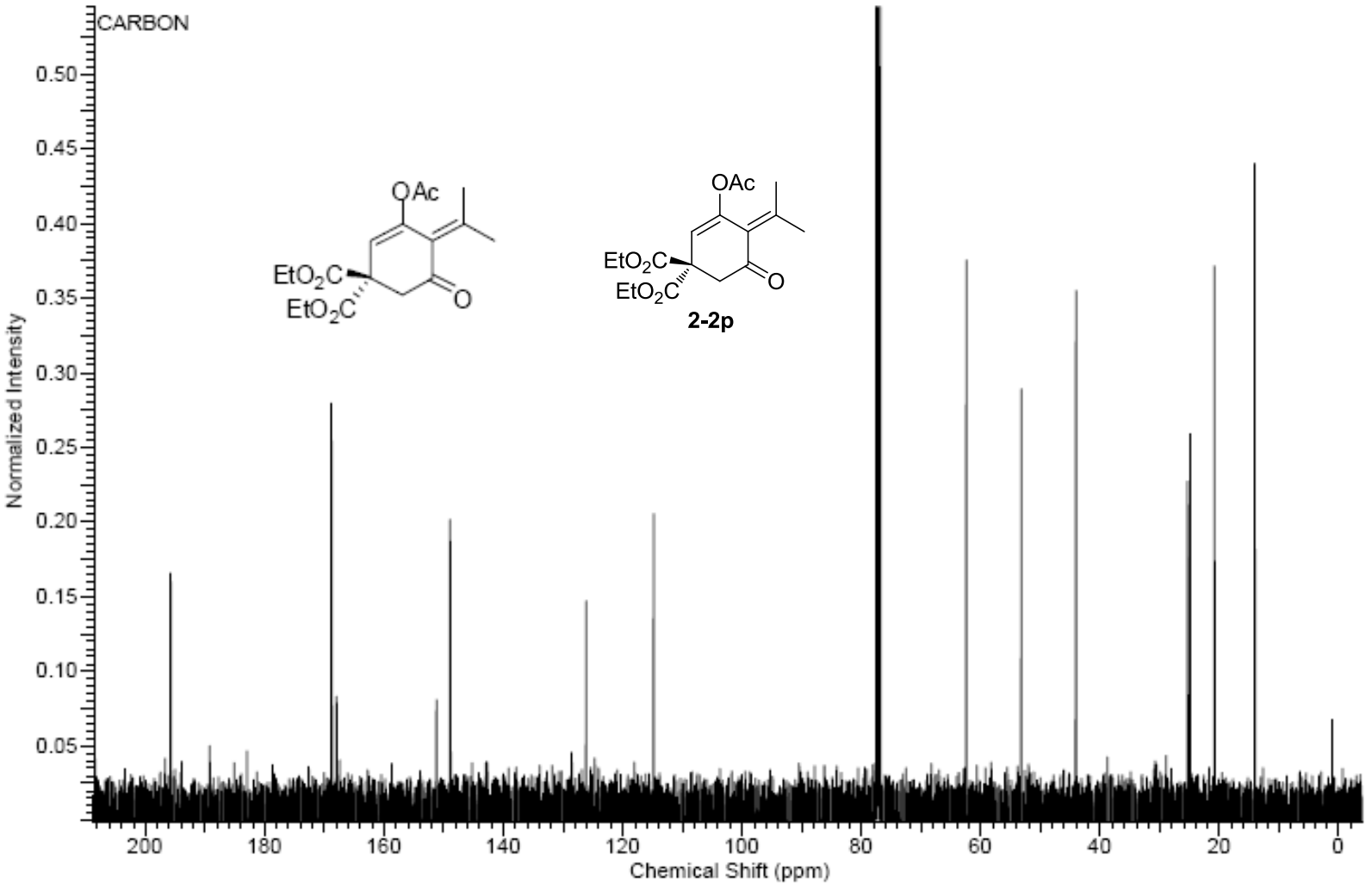
Chemical Shift (ppm)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140
120
100
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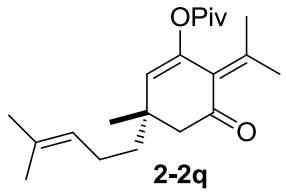
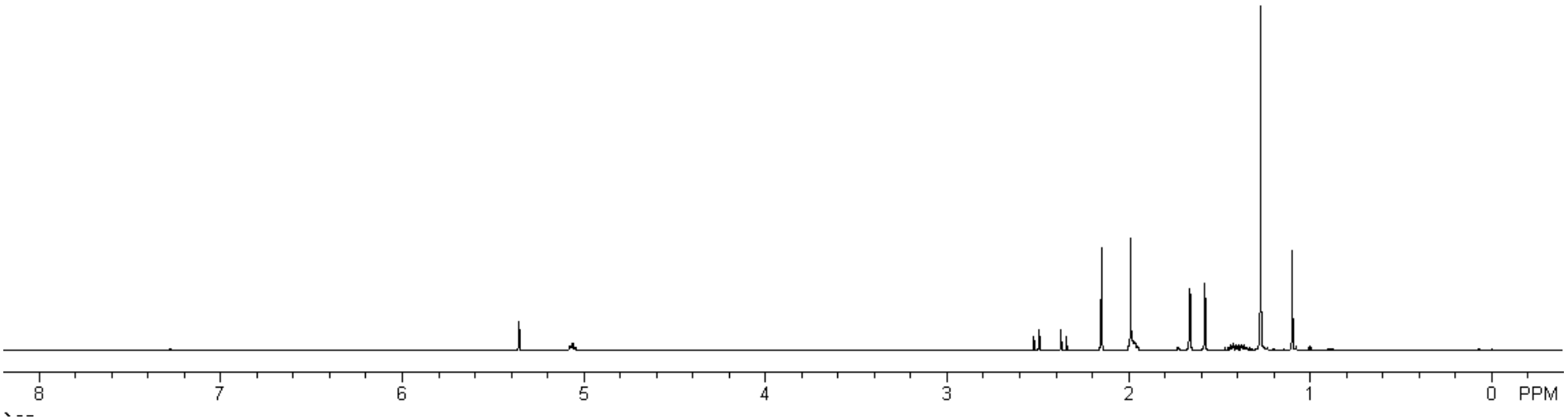
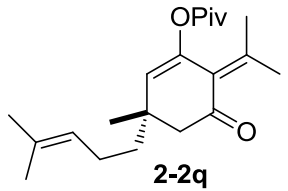
60
40
20
0
Chemical Shift (ppm)
OAc
EtO2C
EtO2C
O
OAc
EtO2C
EtO2C
O
2-2p

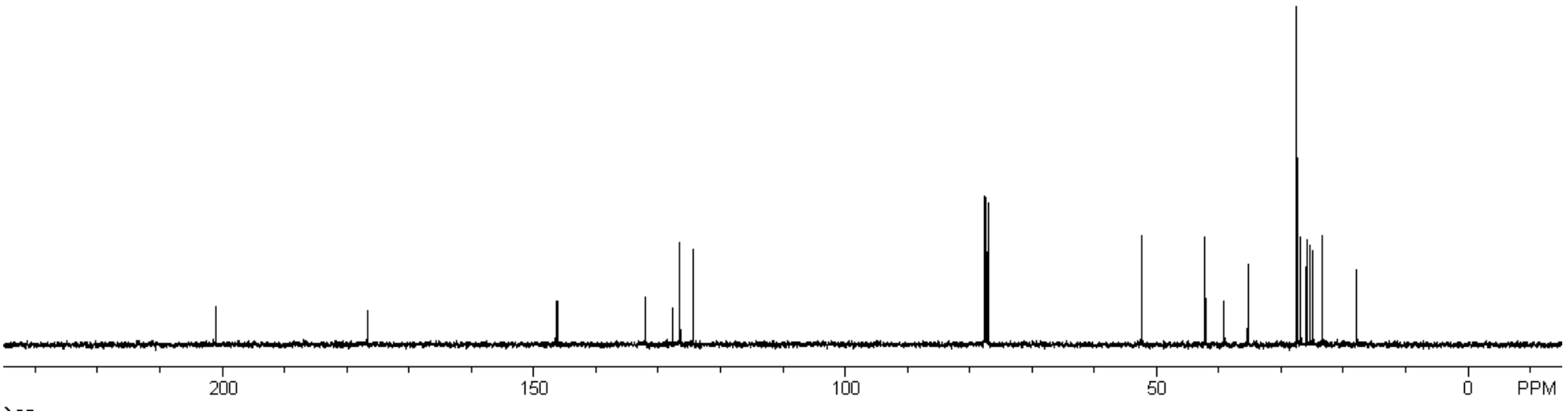


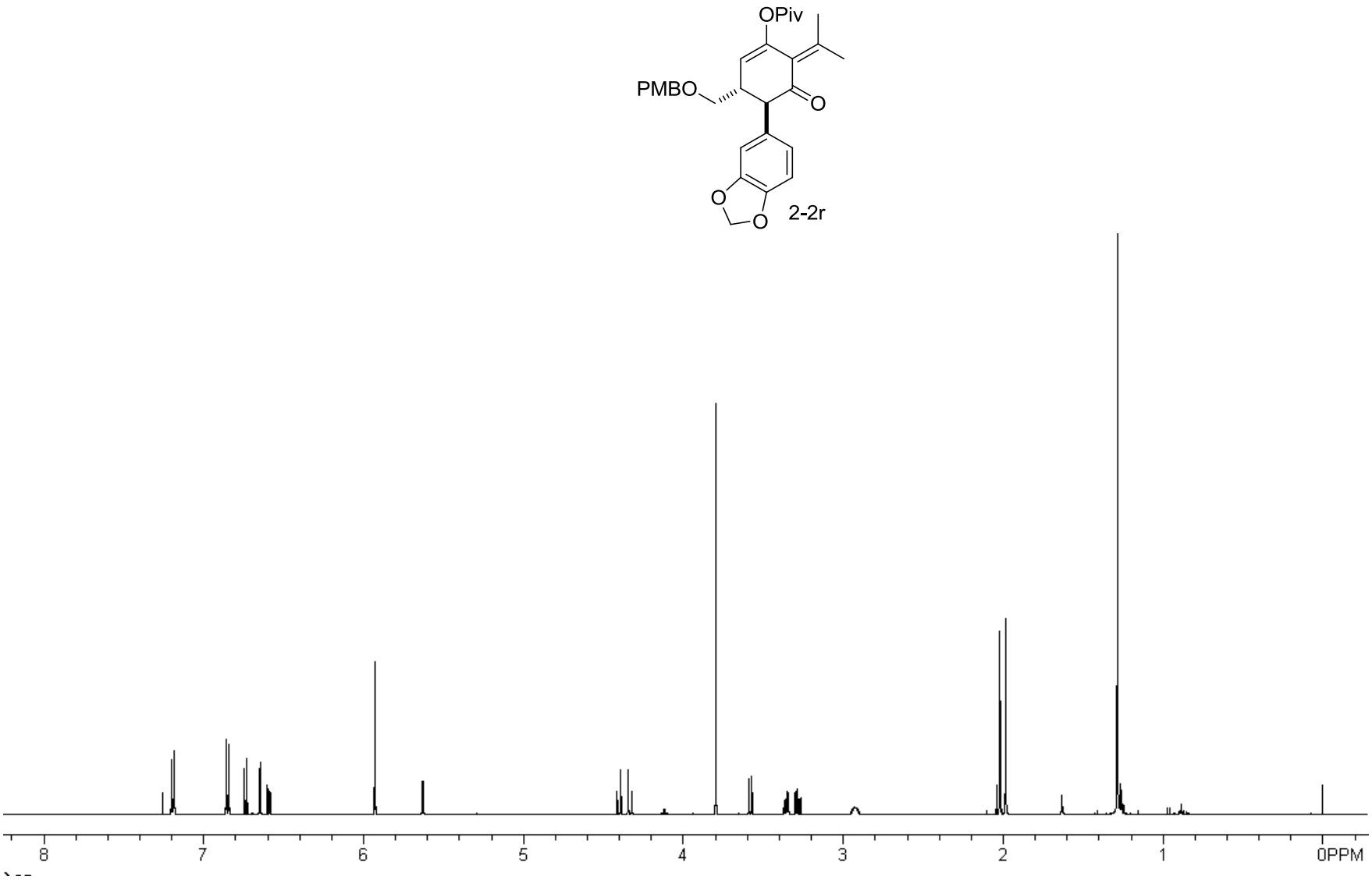
2-2q

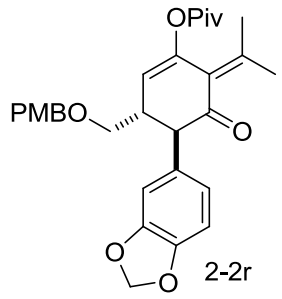


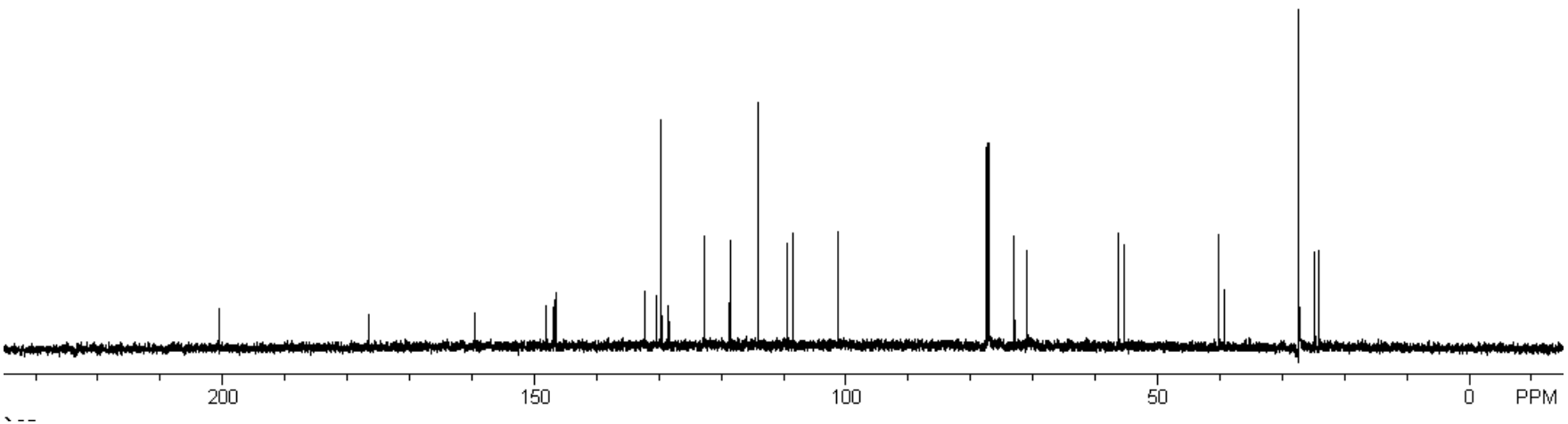


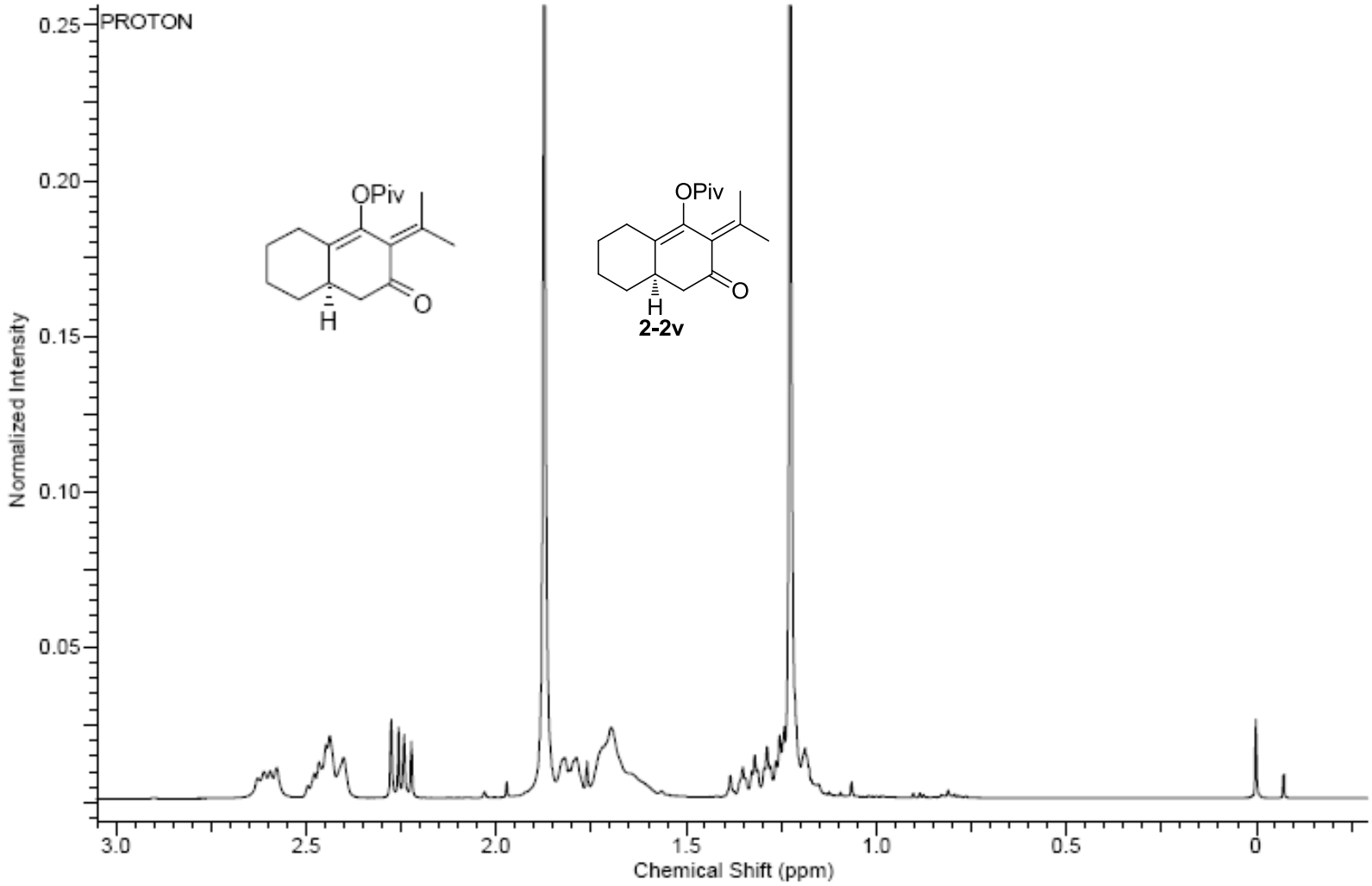
2-2q

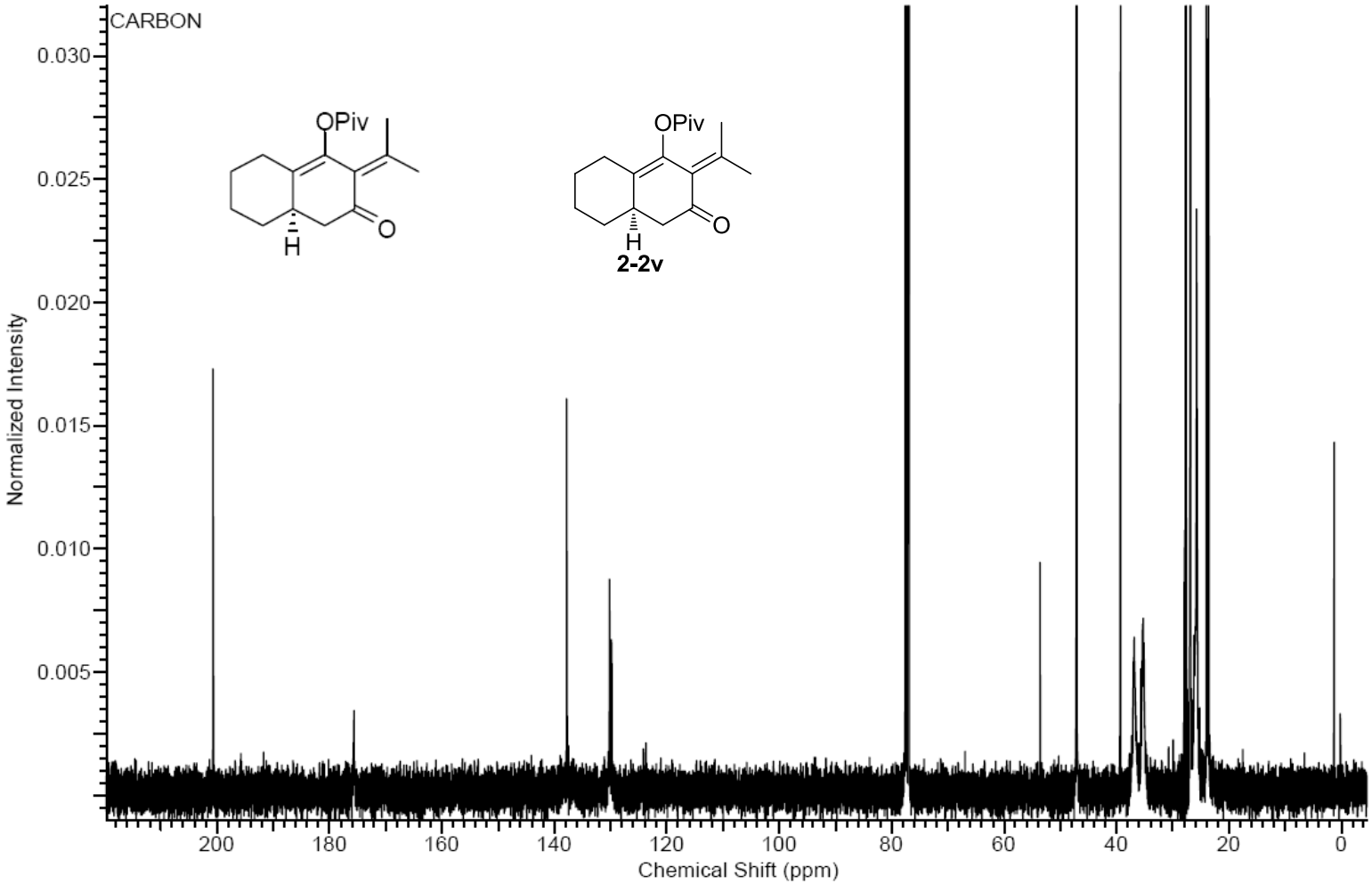


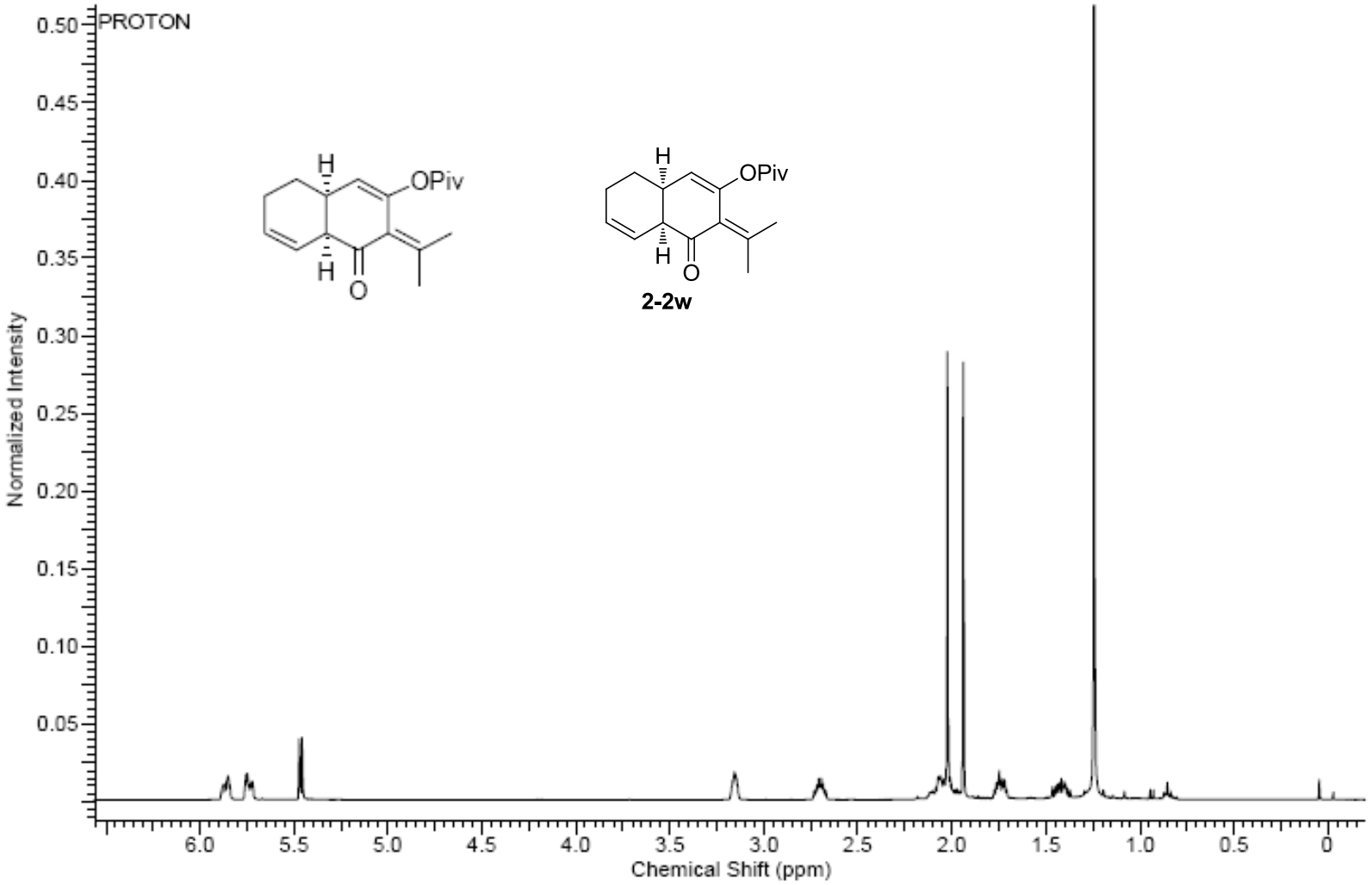

OPiv
PMBO
O
O
O
2-2r
8
7
6
5
4
3
2
1
0PPM

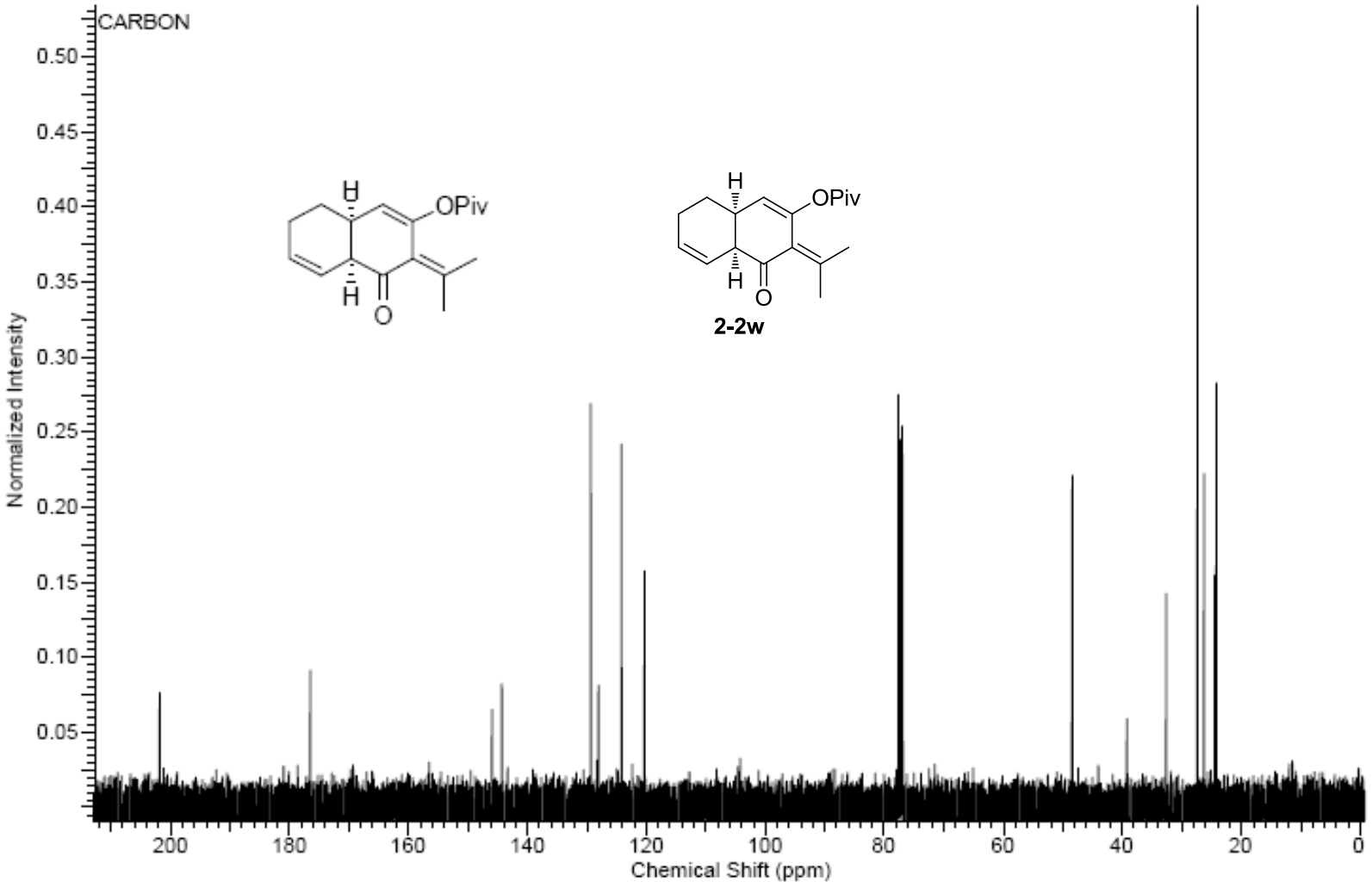

OPiv
PMBO
O
O
O
2-2r


200
150
100
50
0
PPM

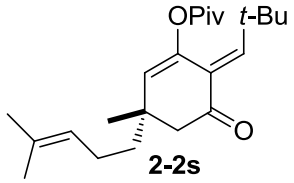

PROTON
OPiv
O
H
OPiv
O
H
2-2v
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


CARBON
OPiv
O
H
OPiv
O
H
2-2v
Normalized Intensity
0.030
0.025
0.020
0.015
0.010
0.005
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

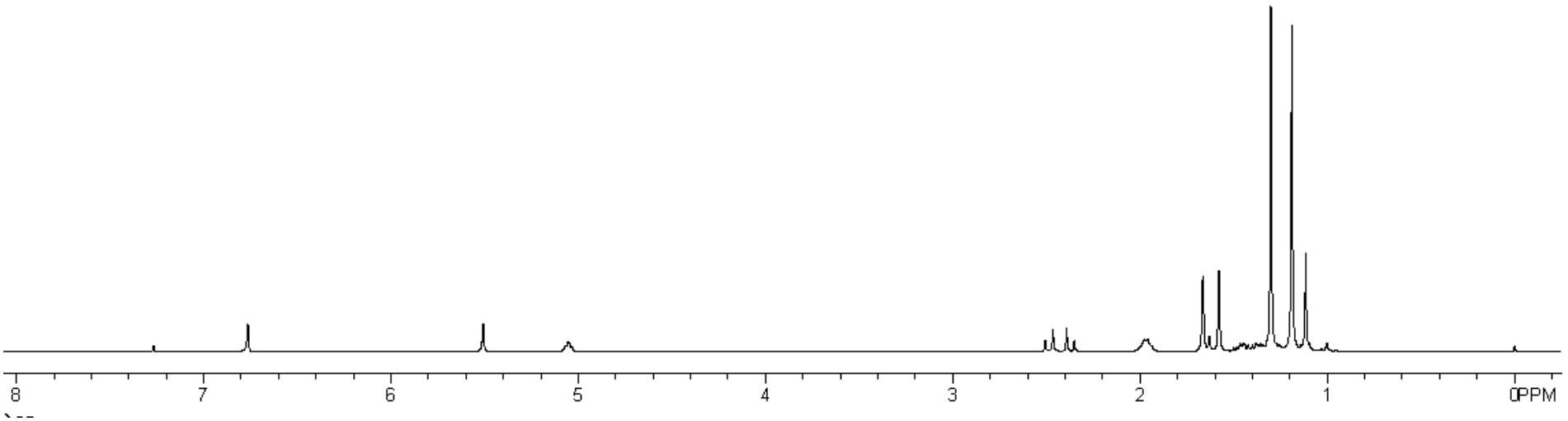

PROTON
H
OPiv
H
O
H
OPiv
H
O
2-2w
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

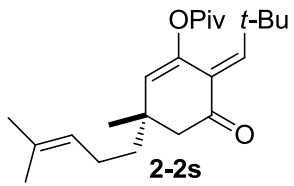

CARBON
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
H
OPiv
H
O
H
OPiv
H
O

2-2w

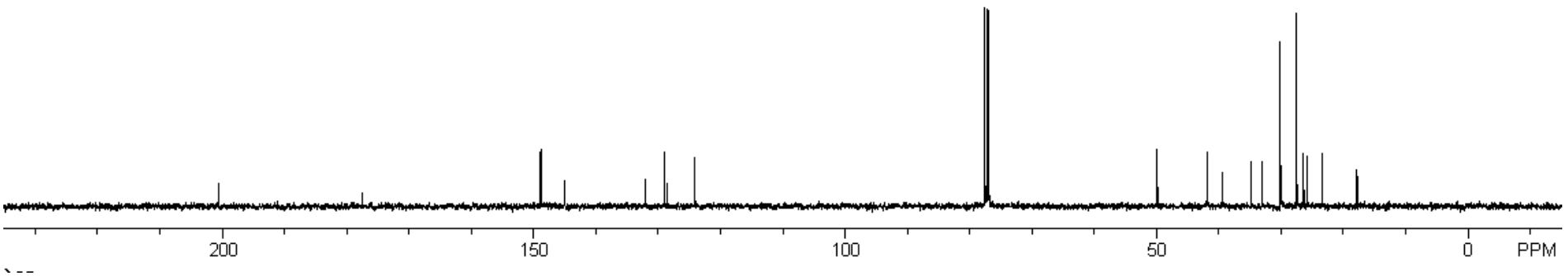


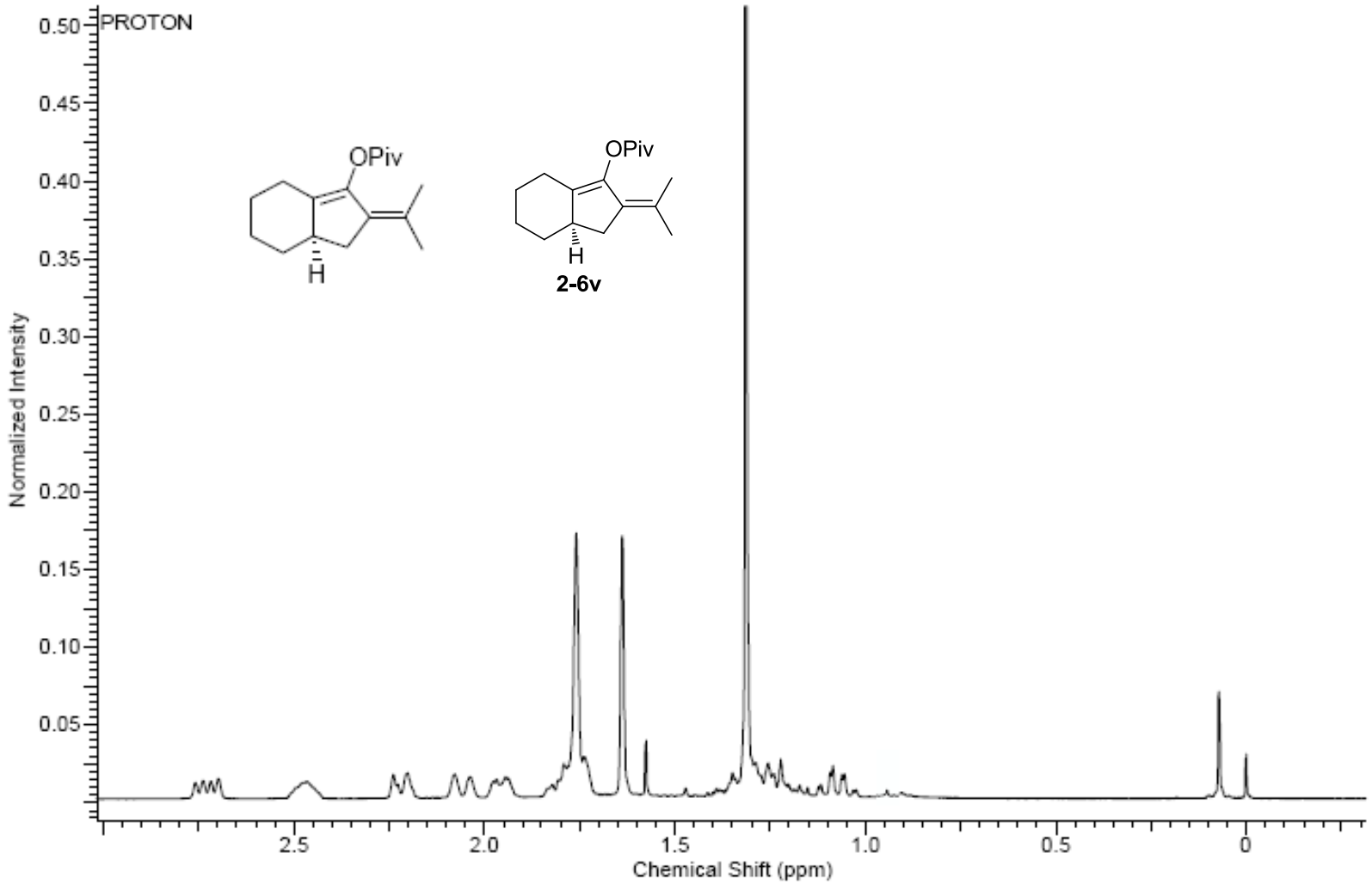
2-2s

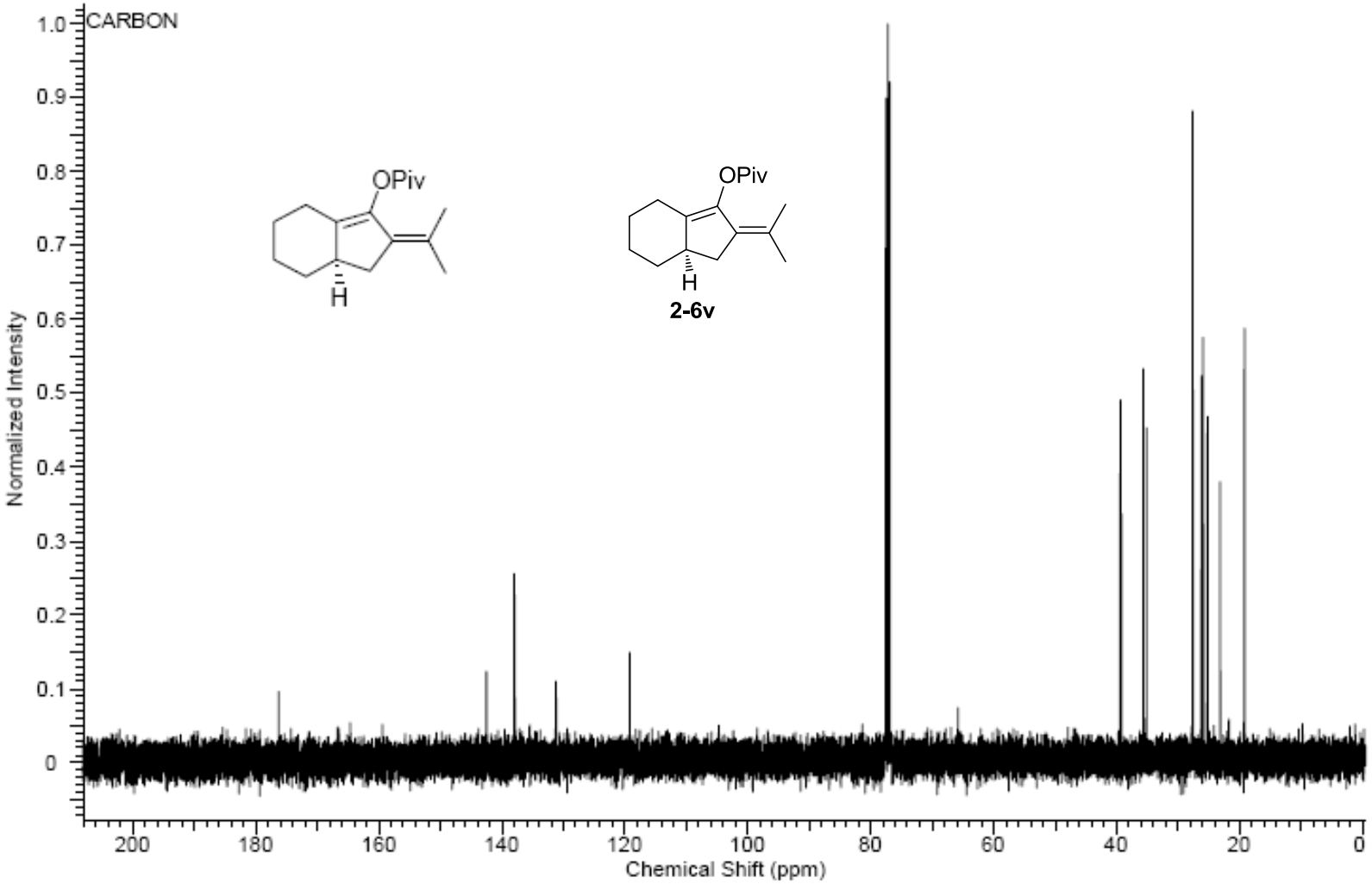


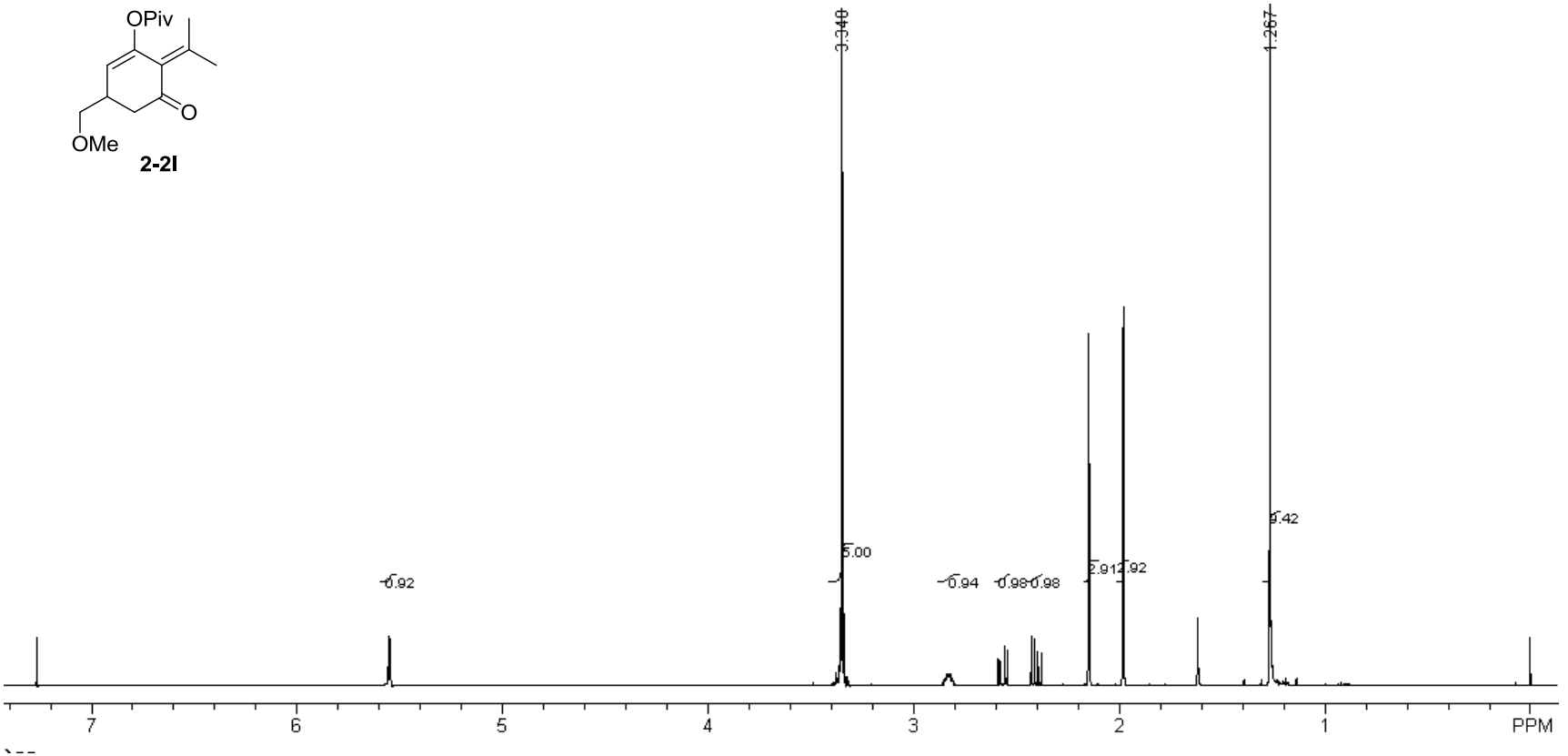


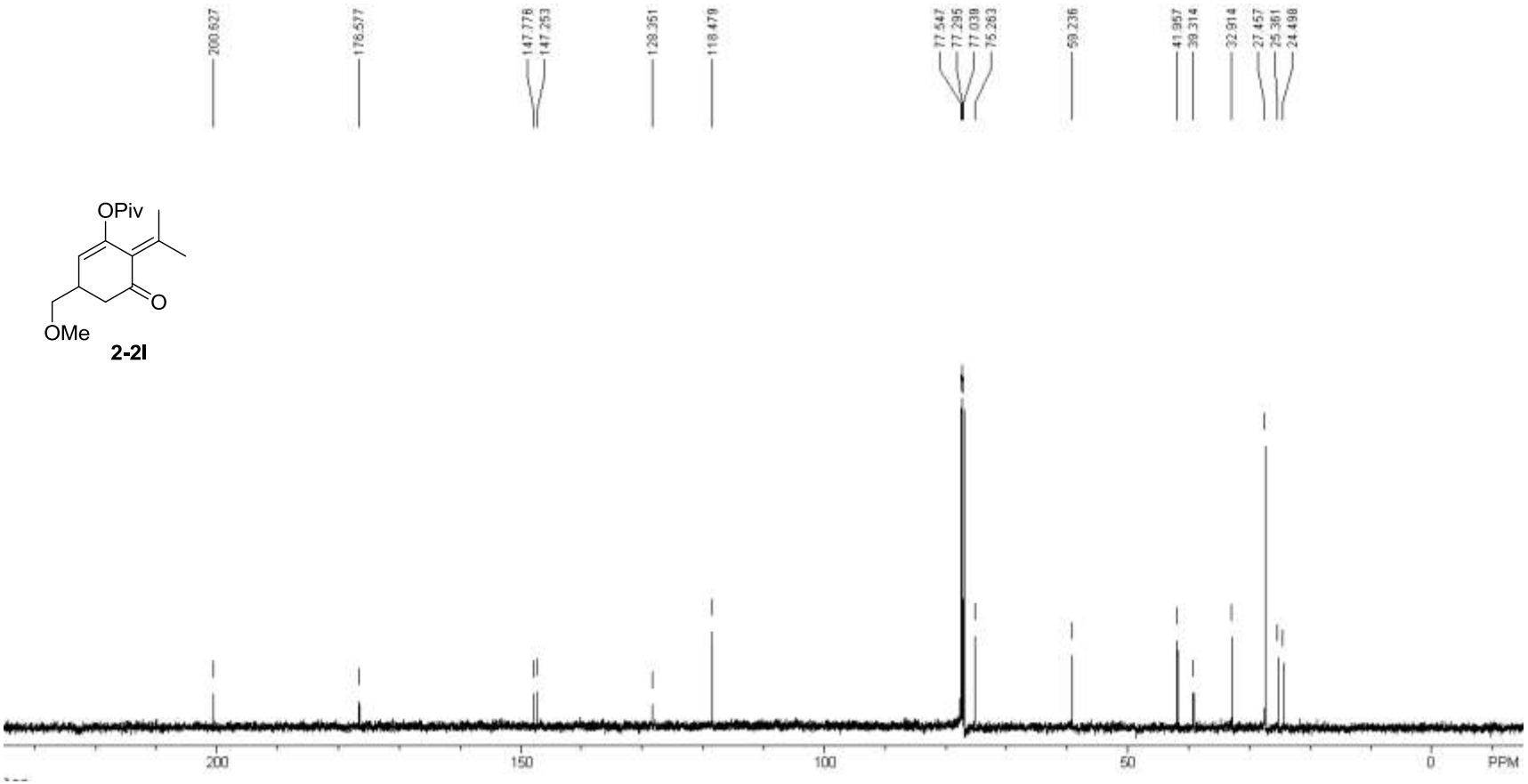
2-2s

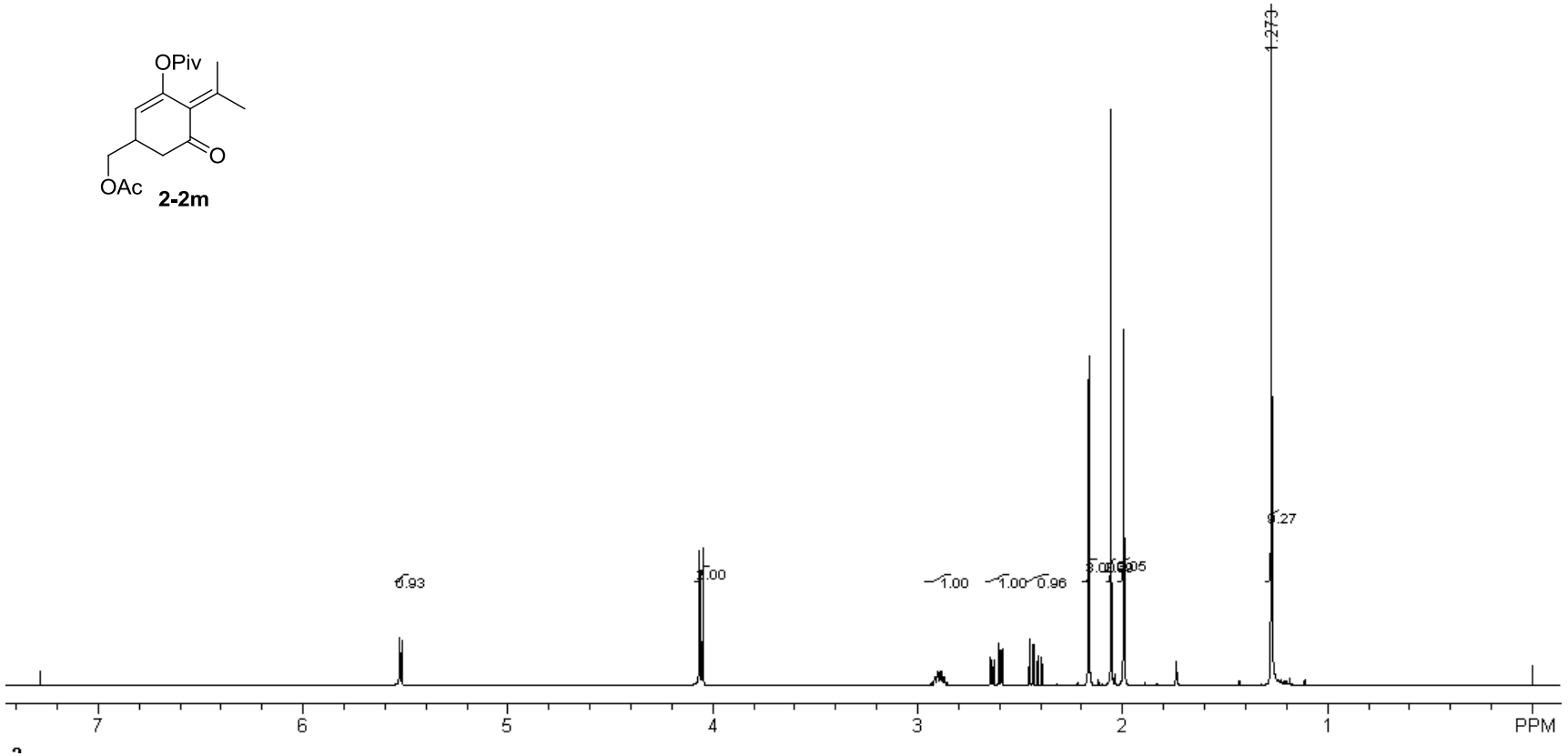


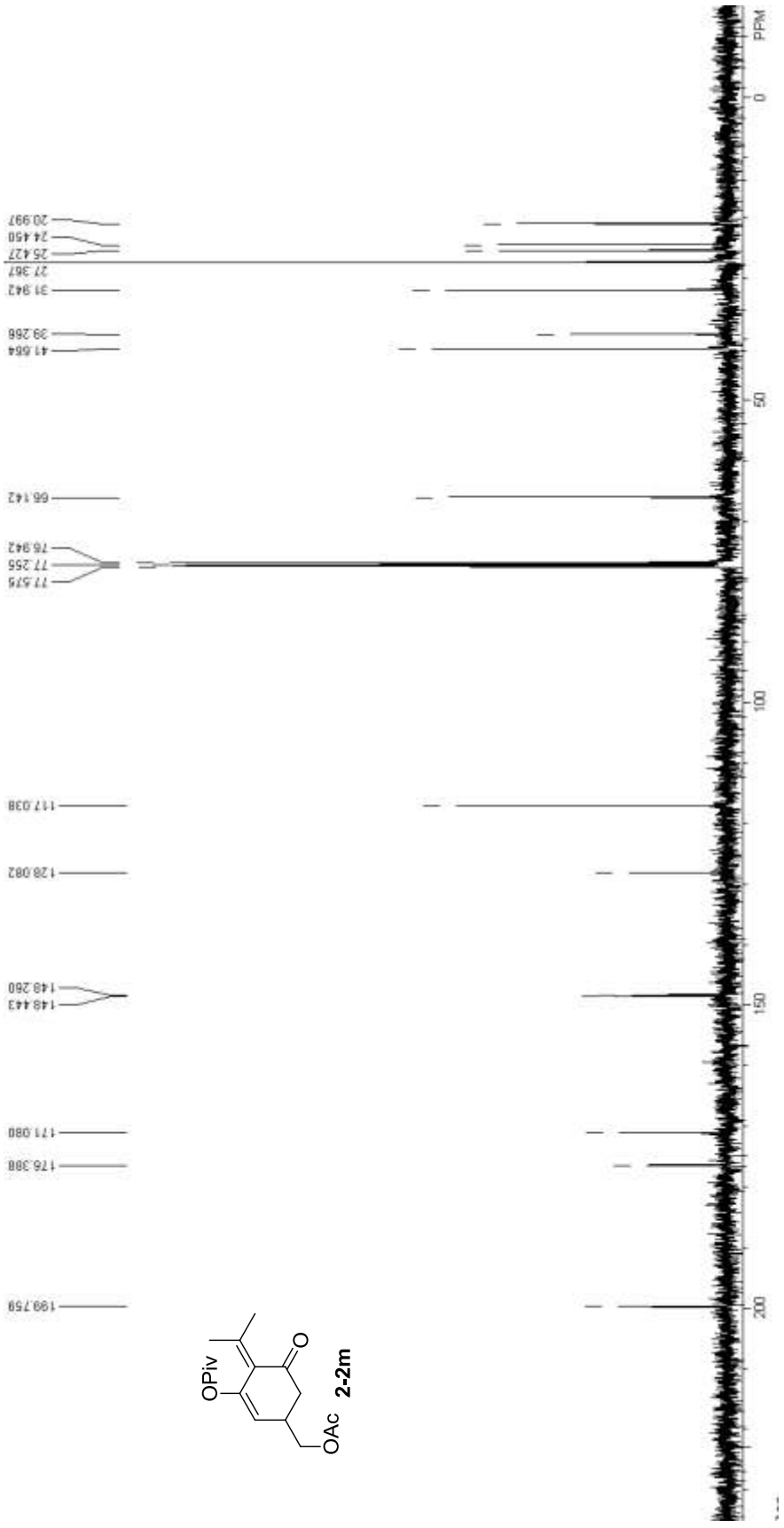

PROTON
OPiv
H
OPiv
H
2-6v
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

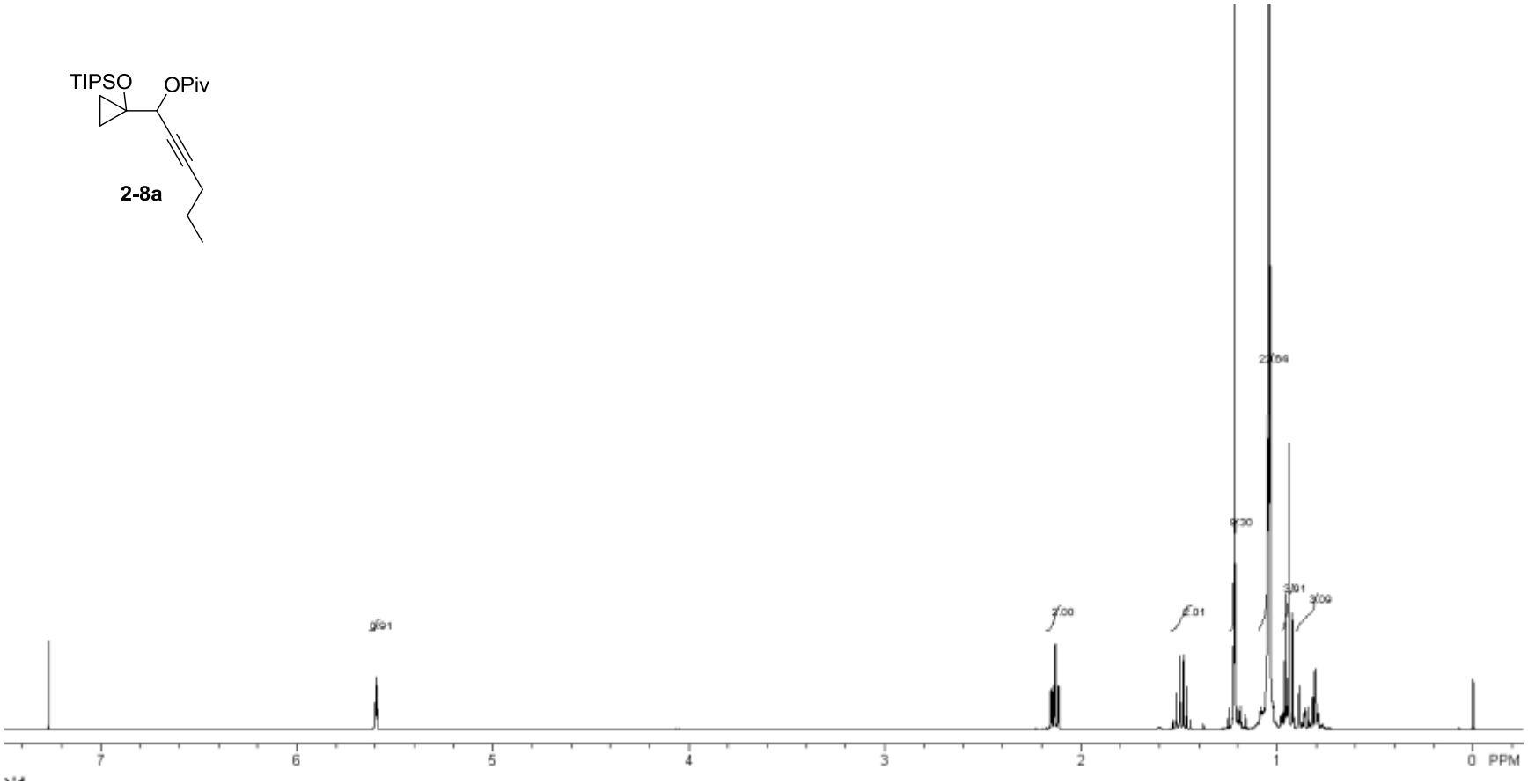

CARBON
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
OPiv
H
OPiv
H
2-6v
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

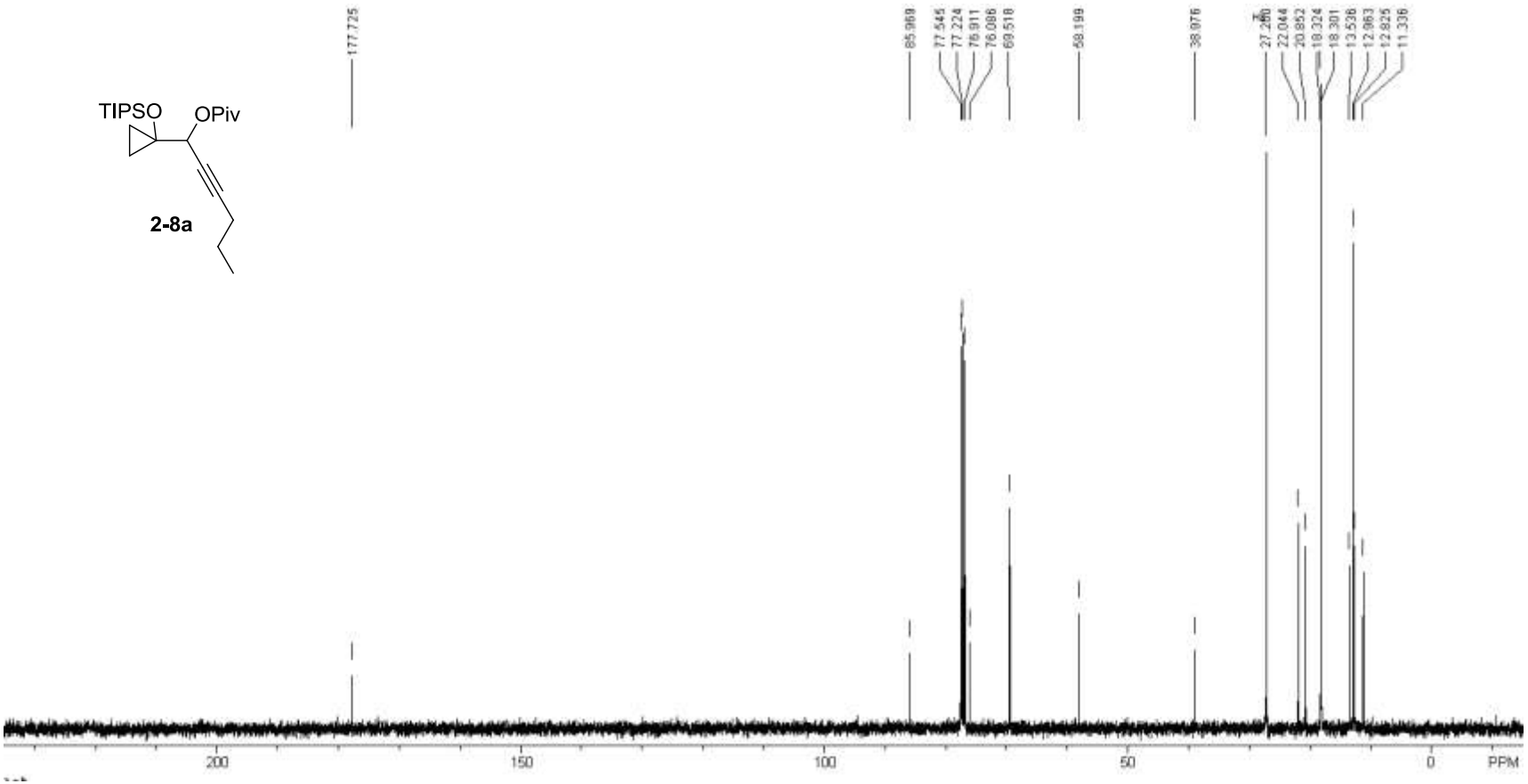

OPiv
O
OMe
2-2l
3.348
1.267
0.92
5.00
0.94
0.98
0.98
2.91
2.92
9.42
7
6
5
4
3
2
1
PPM

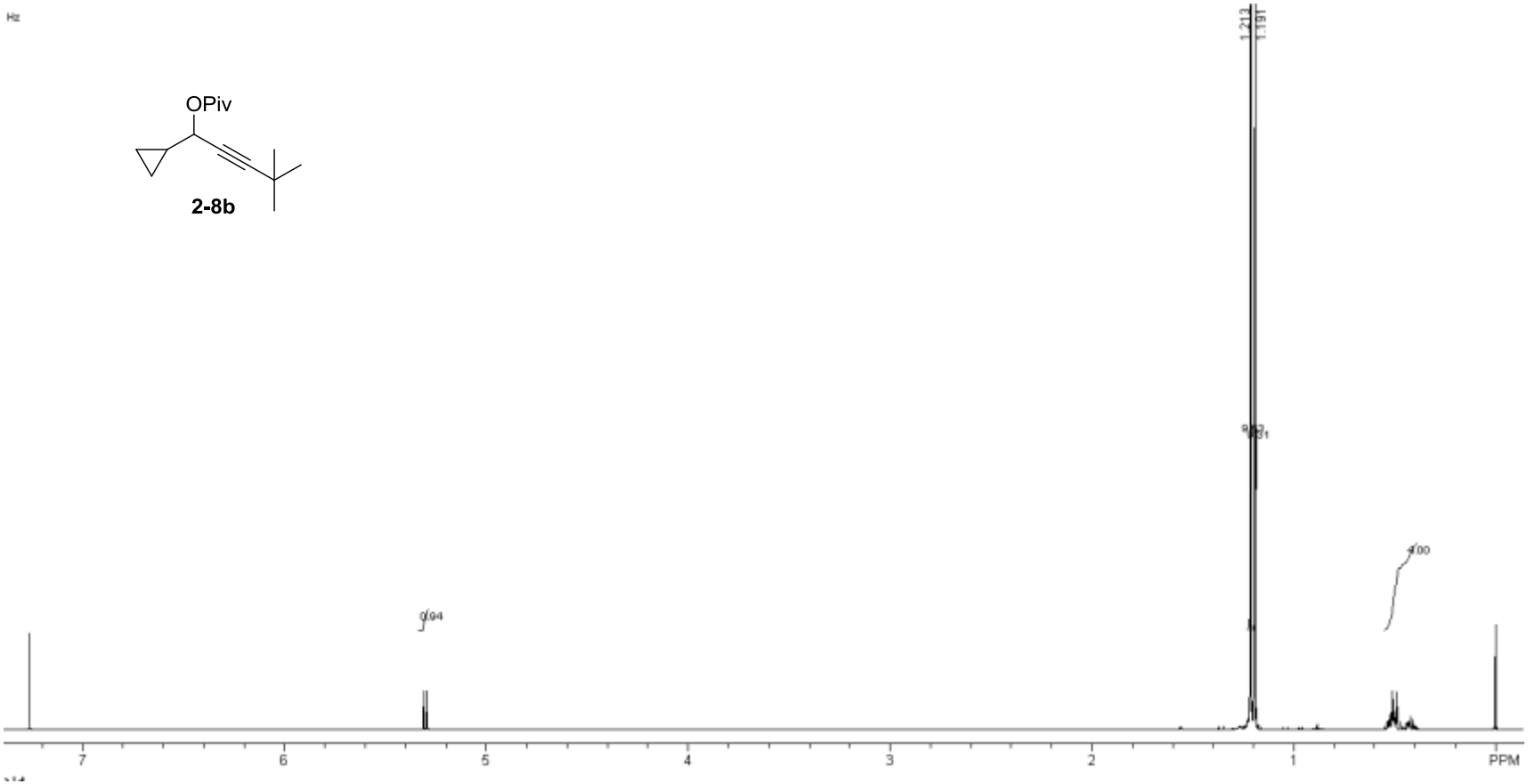

200.627
176.577
147.778
147.253
128.351
118.479
77.547
77.295
77.039
75.263
59.236
41.957
39.314
32.914
27.457
25.361
24.498
OPiv
O
OMe
2-2l
200
150
100
50
0
PPM

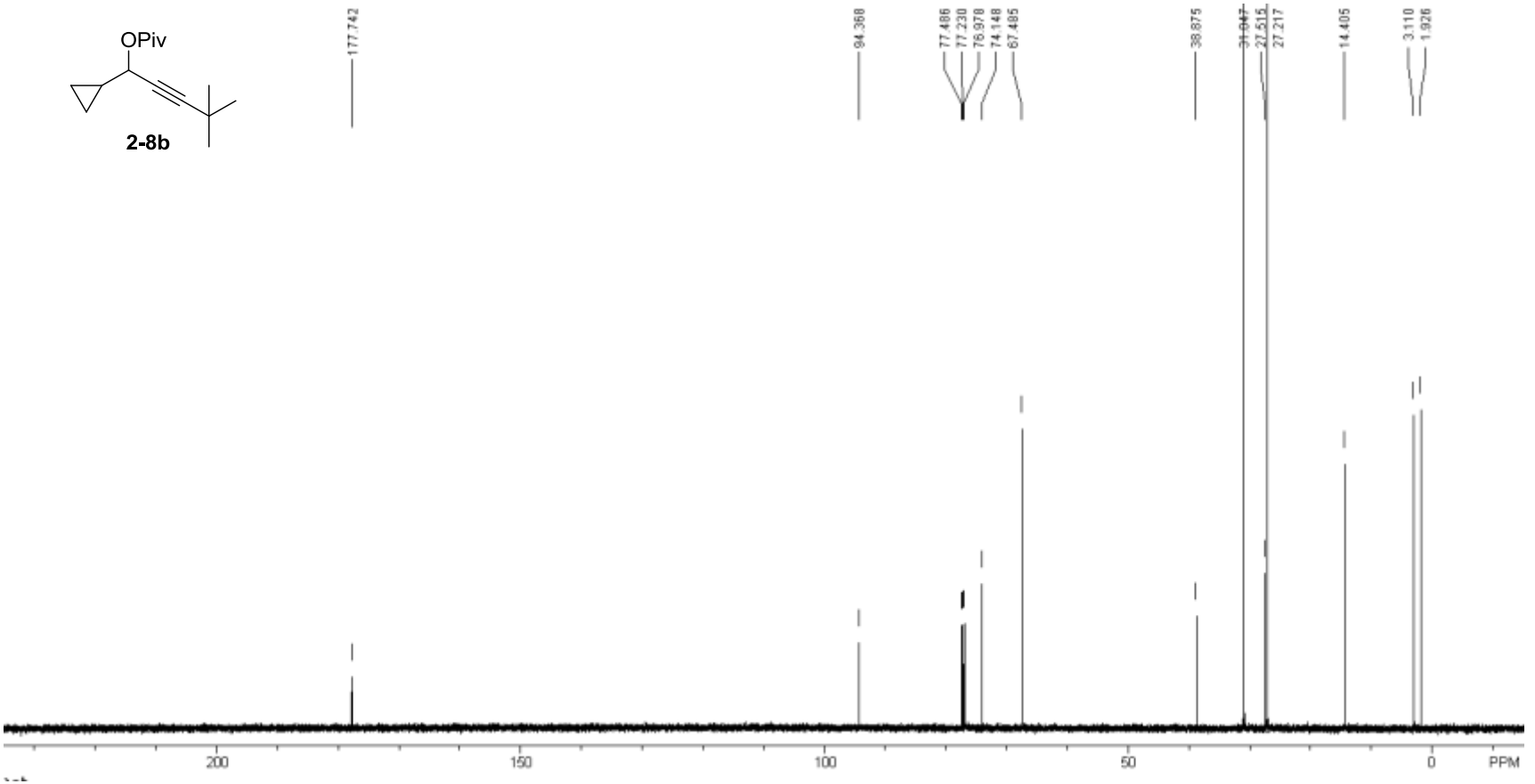

OPiv
O
OAc
2-2m
6.93
1.00
1.00
1.00
0.96
3.05
9.27
1.273
7
6
5
4
3
2
1
PPM

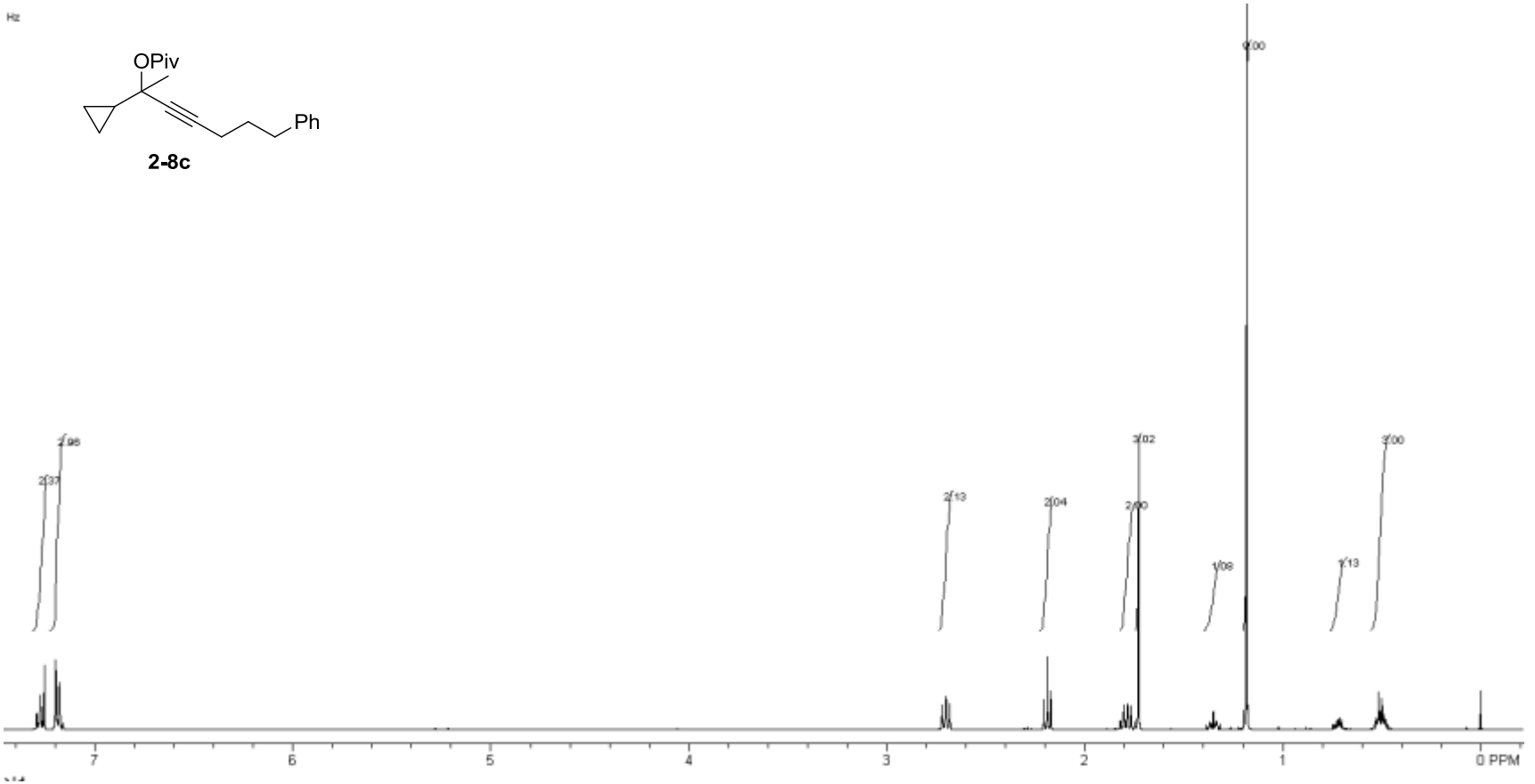

PPM
0
50
100
150
200
20.997
24.450
25.427
27.367
31.942
39.268
41.664
66.142
76.942
77.255
77.575
117.038
128.082
148.260
148.443
171.080
176.388
190.759
OPiv
O
OAc
2-2m

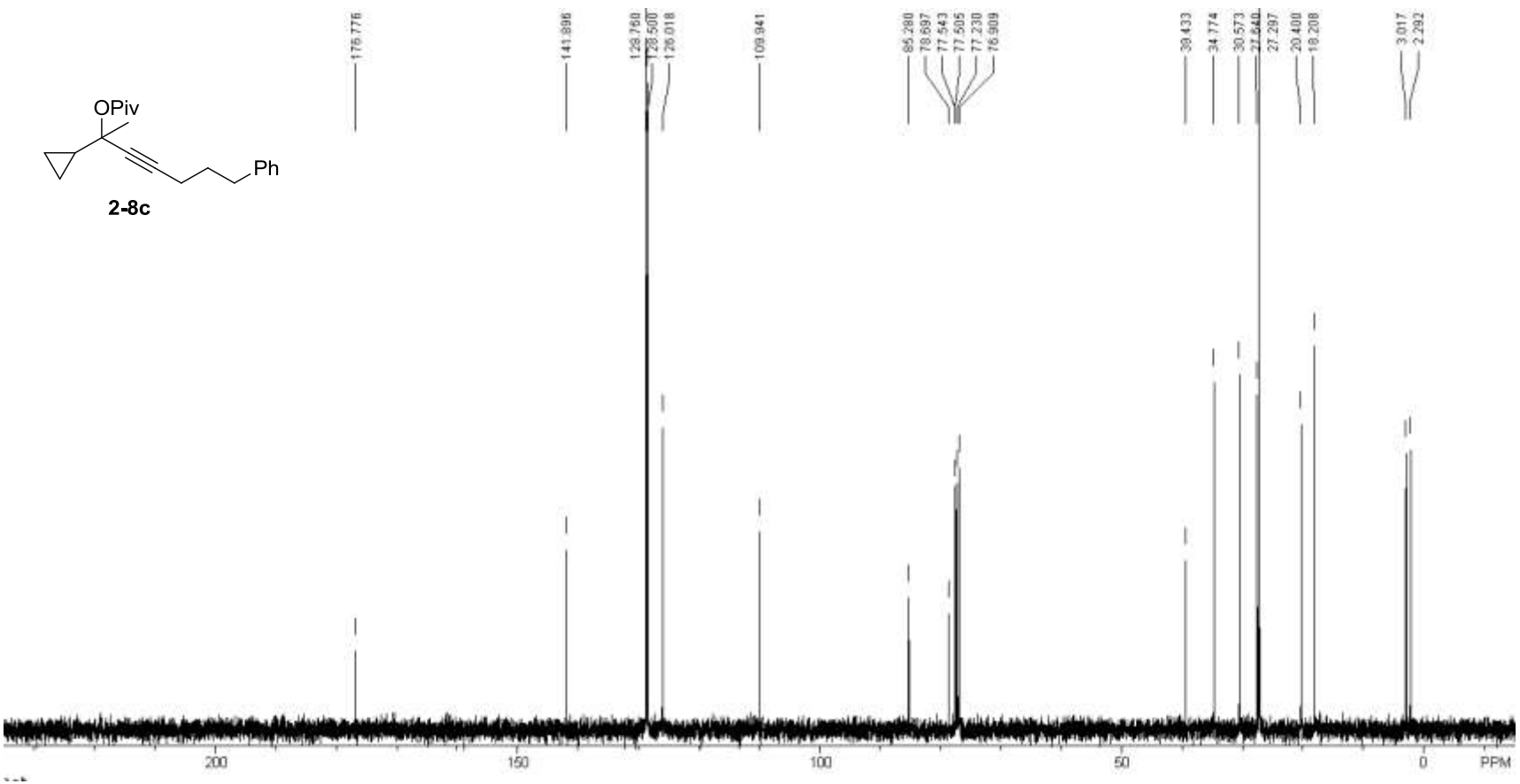

TIPSO
OPiv
2-8a
9.30
7
6
5
4
3
2
1
0 PPM

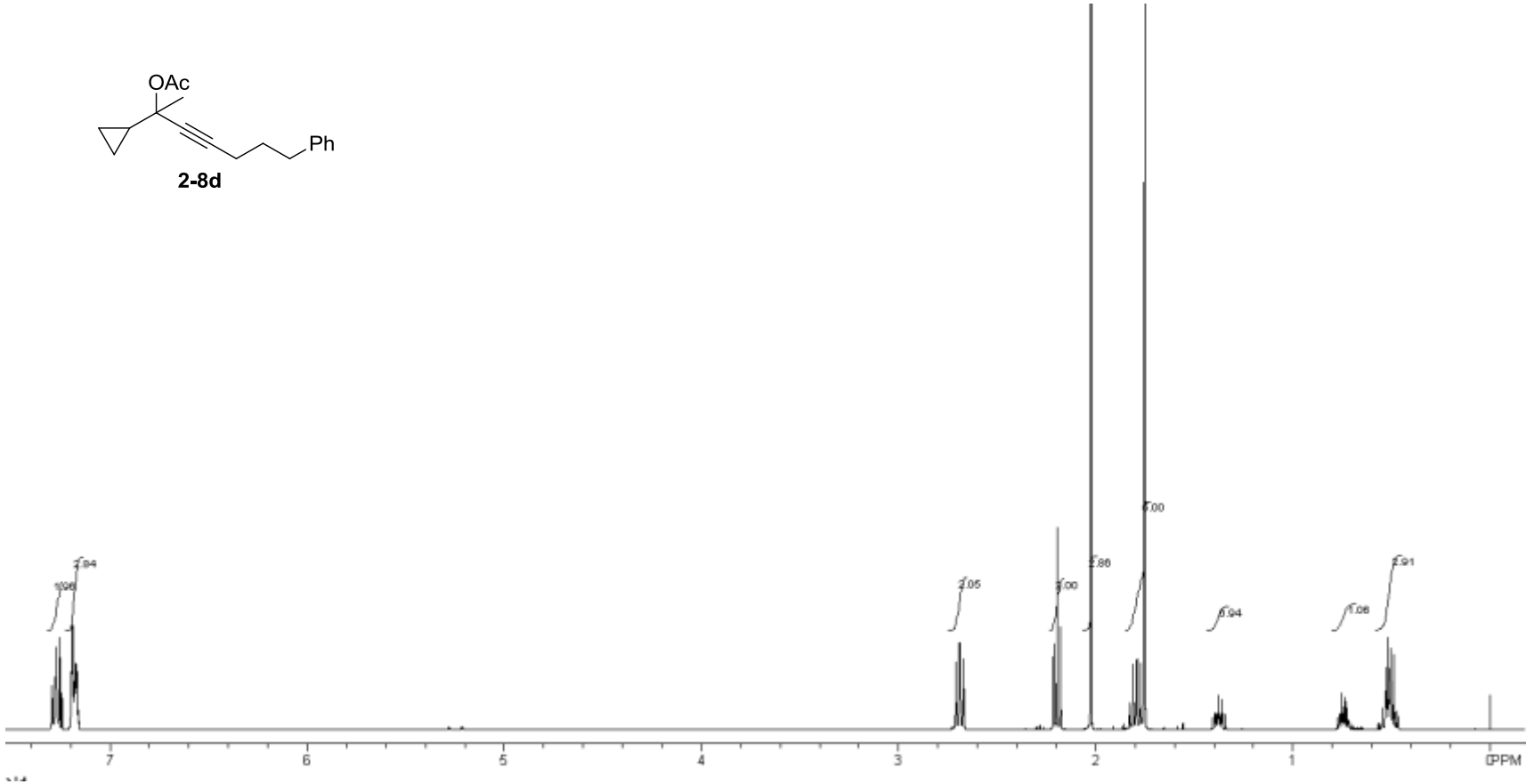

TIPSO
OPiv
2-8a
177.725
85.969
77.545
77.224
76.911
76.086
69.518
58.199
38.976
27.260
22.044
20.852
18.324
18.301
13.536
12.863
12.825
11.336
200
150
100
50
0
PPM

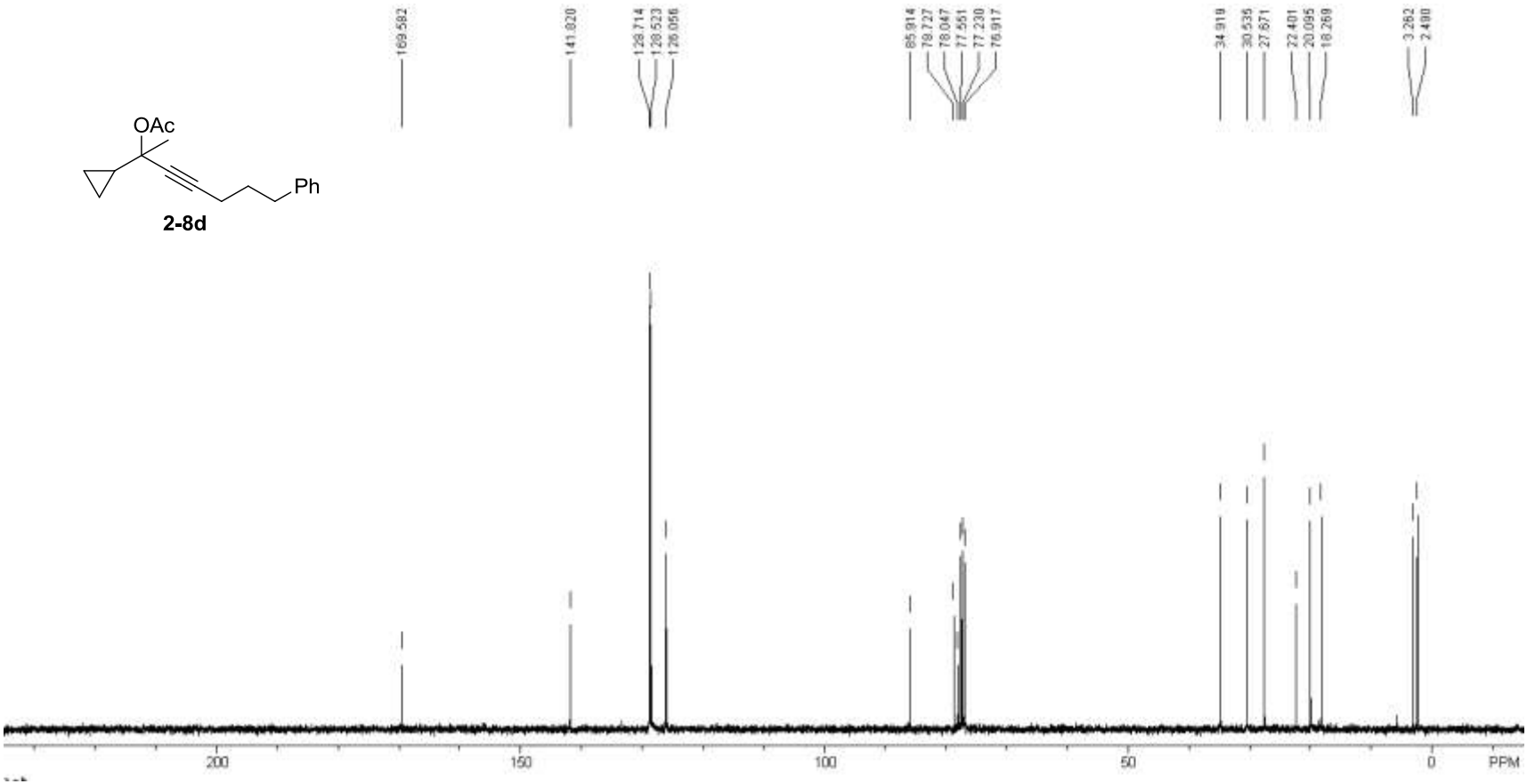

OPiv
2-8b
1.213
1.191
0.94
4.00
7
6
5
4
3
2
1
PPM

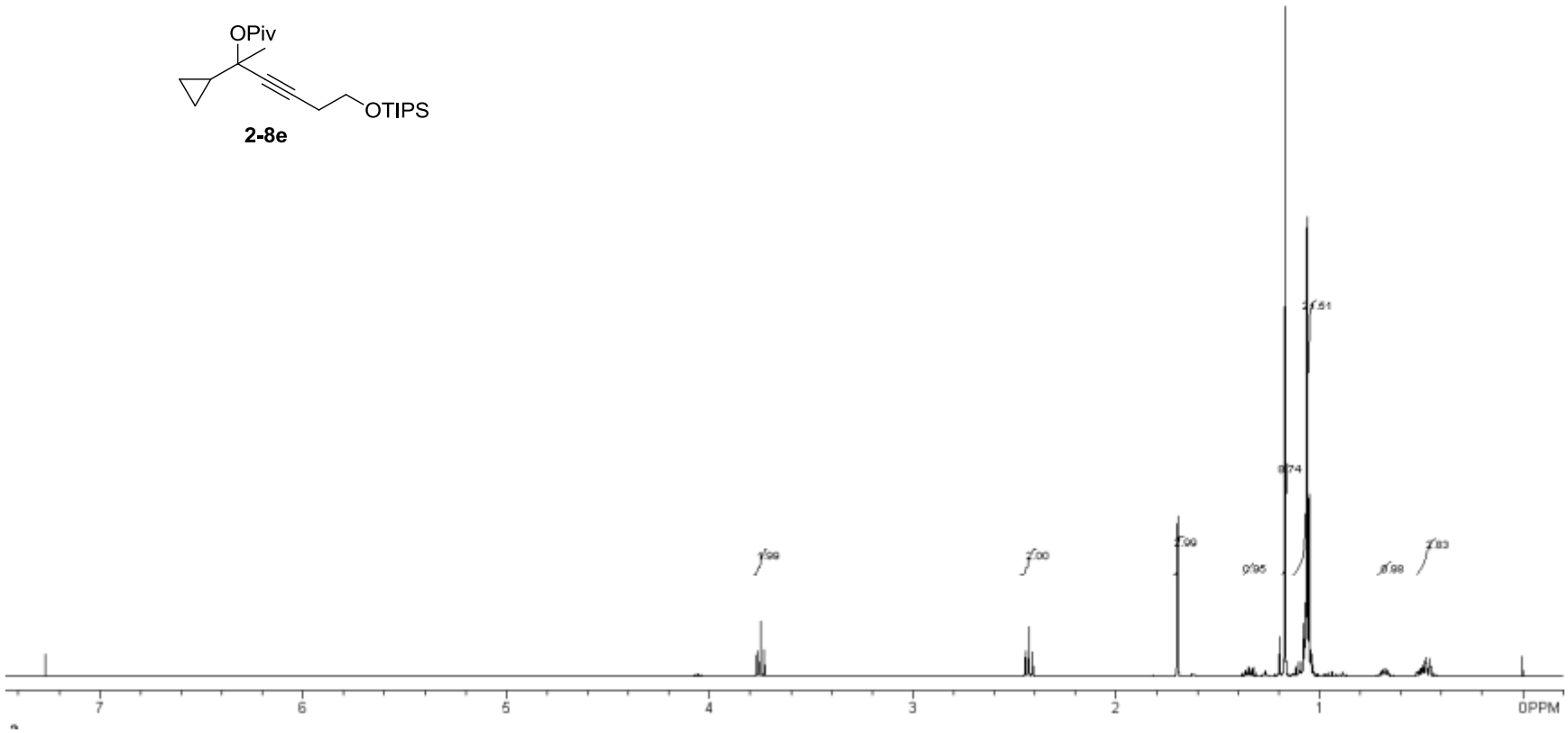

OPiv
2-8b
177.742
94.368
77.486
77.230
76.978
74.148
67.485
38.875
31.647
27.515
27.217
14.405
3.110
1.926
200
150
100
50
0
PPM

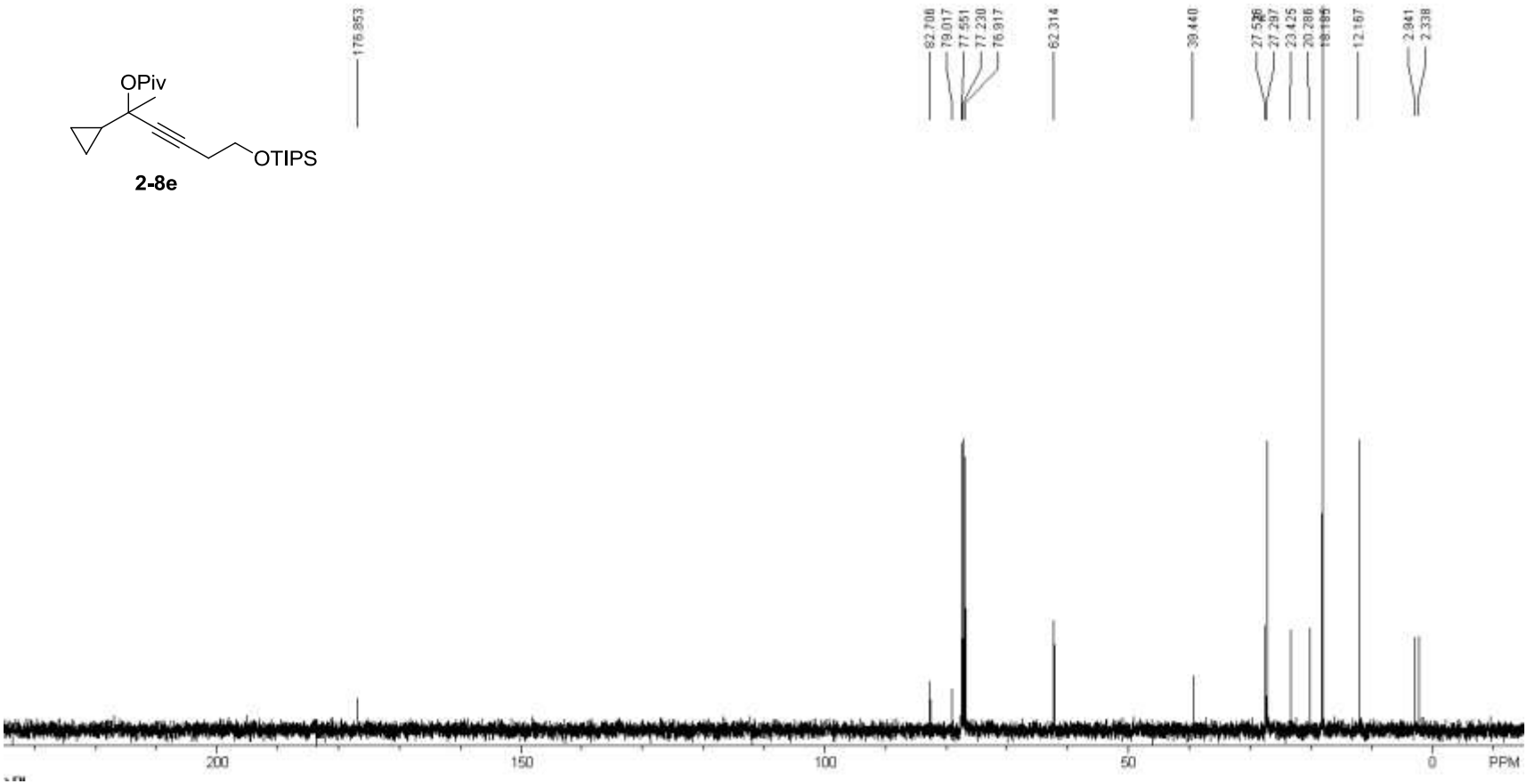

Hz
OPiv
Ph
2-8c
9.00
3.02
3.00
2.98
2.37
2.13
2.04
2.00
1.08
1.13
7
6
5
4
3
2
1
0 PPM

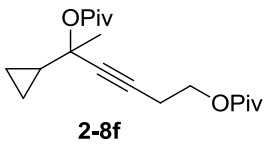

OPiv
Ph
2-8c
176.776
141.896
128.760
128.500
126.018
109.941
85.280
78.697
77.543
77.505
77.230
76.909
39.433
34.774
30.573
27.640
27.297
20.400
18.208
3.017
2.292
200
150
100
50
0
PPM


OAc
Ph
2-8d
1.96
1.94
2.05
2.00
2.86
3.00
0.94
1.08
1.91
7
6
5
4
3
2
1
0PPM

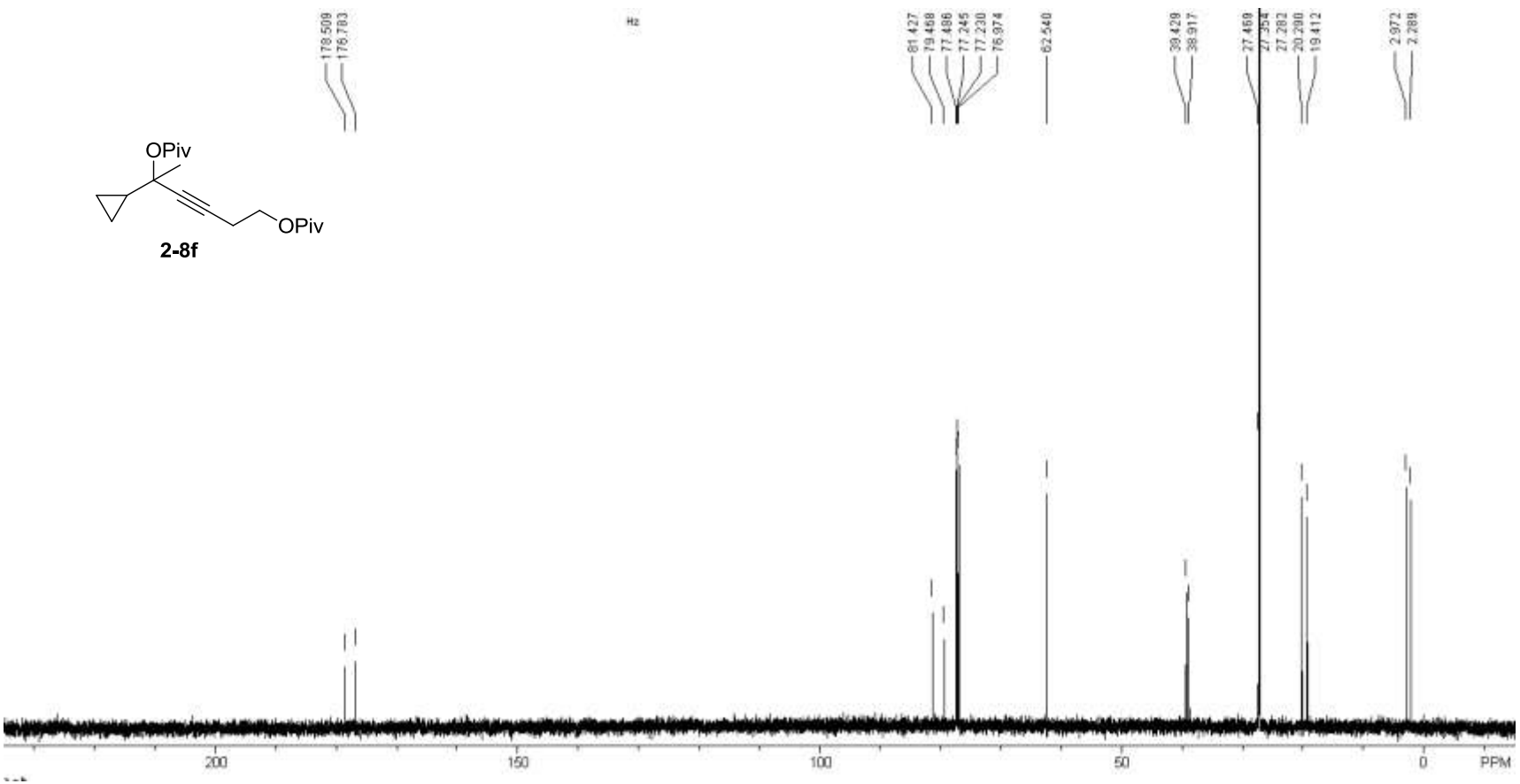

OAc
Ph
2-8d
169.582
141.020
128.714
128.523
126.056
85.914
78.727
78.047
77.551
77.230
76.917
34.919
30.535
27.671
22.401
20.095
18.269
3.262
2.498
200
150
100
50
0
PPM

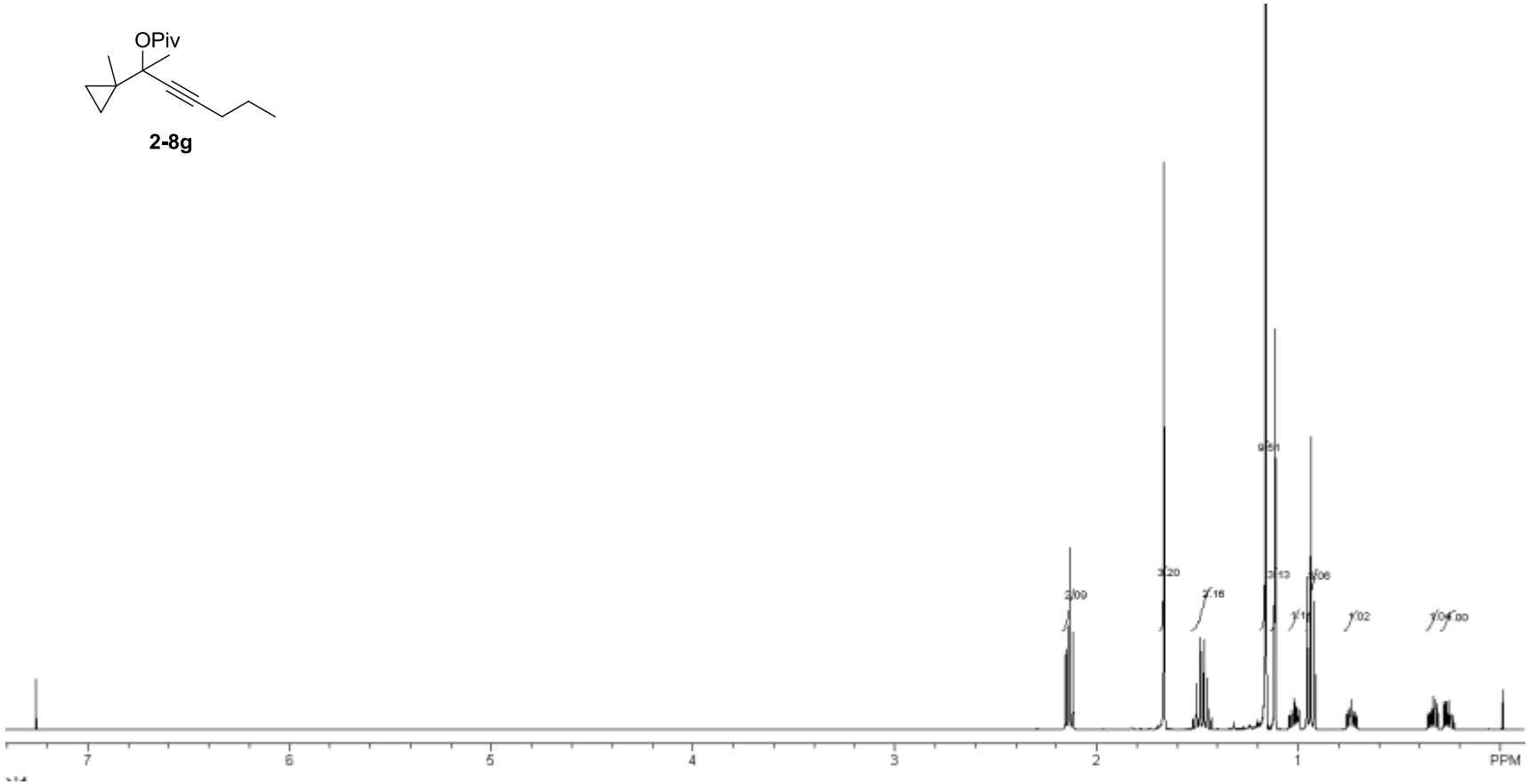

OPiv
OTIPS
2-8e
7
6
5
4
3
2
1
0PPM

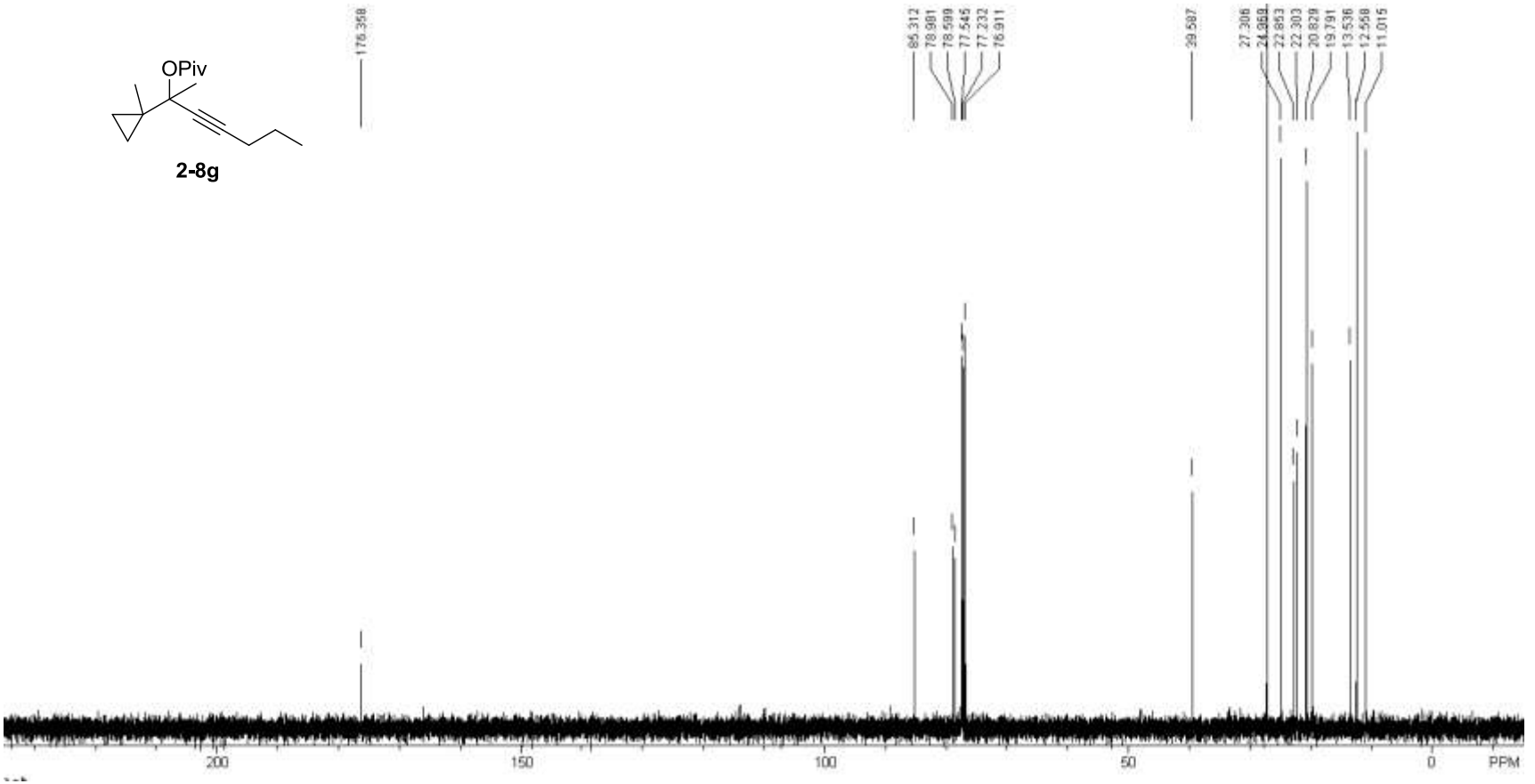

OPiv
OTIPS
2-8e
176.853
82.706
79.017
77.551
77.230
76.917
62.314
39.440
27.526
27.297
23.425
20.286
18.189
12.157
2.941
2.338
200
150
100
50
0
PPM

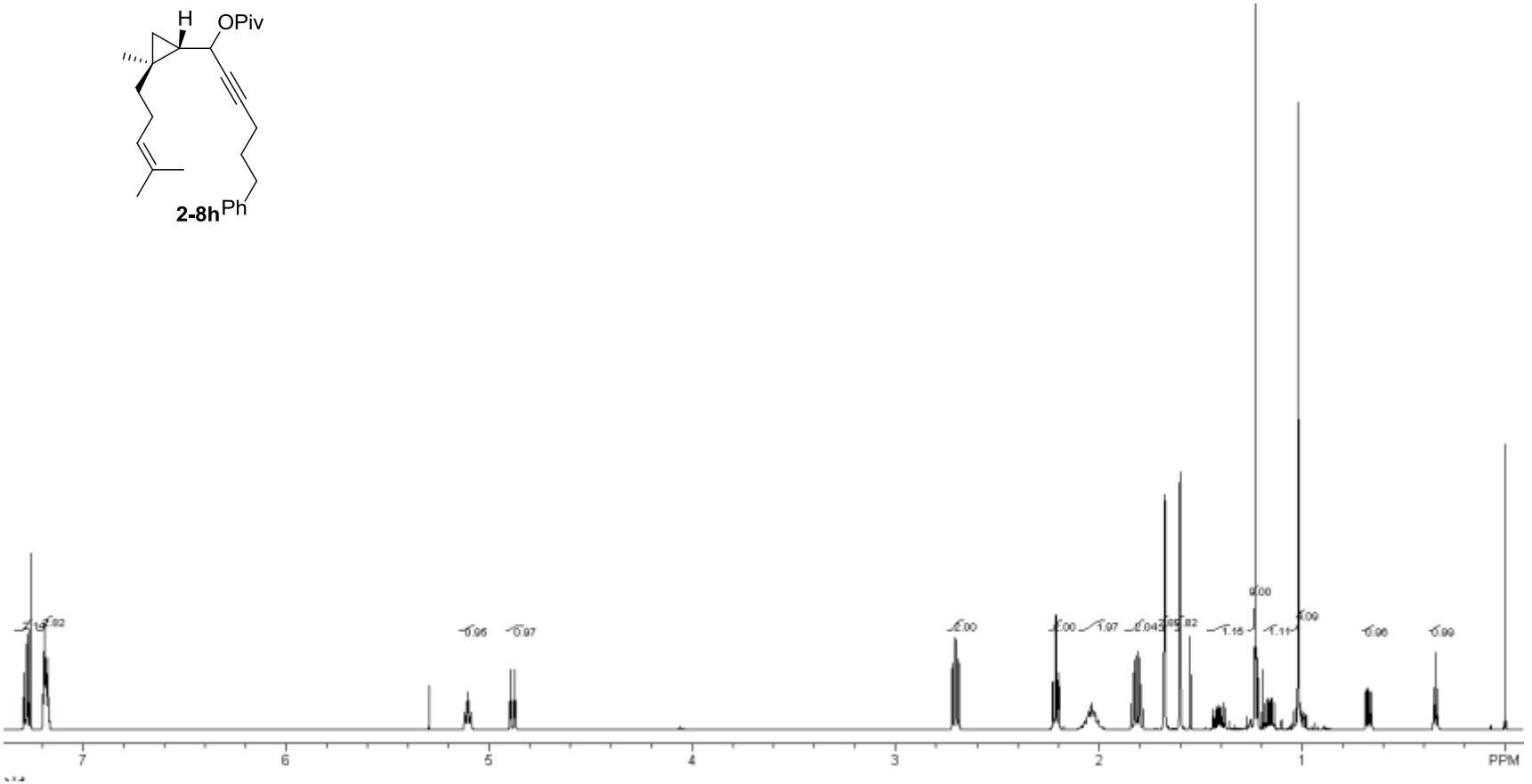


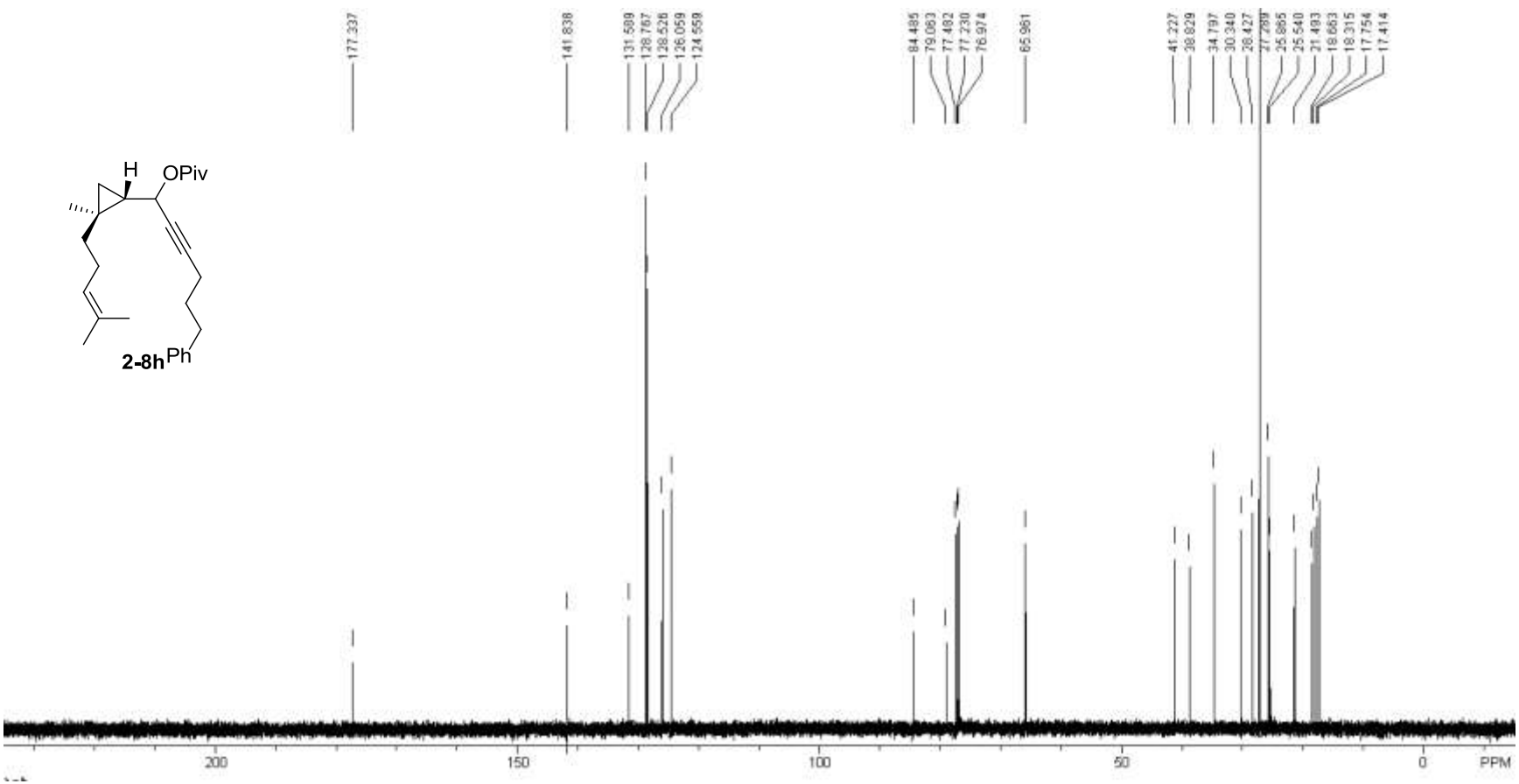
2-8f

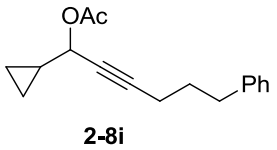

OPiv
OPiv
2-8f
178.509
176.783
81.427
79.458
77.486
77.245
77.230
76.974
62.540
39.429
38.917
27.469
27.354
27.282
20.290
19.412
2.972
2.289
200
150
100
50
0
PPM


OPiv
2-8g
3.09
3.20
2.18
9.51
3.13
3.06
1.02
7
6
5
4
3
2
1
PPM

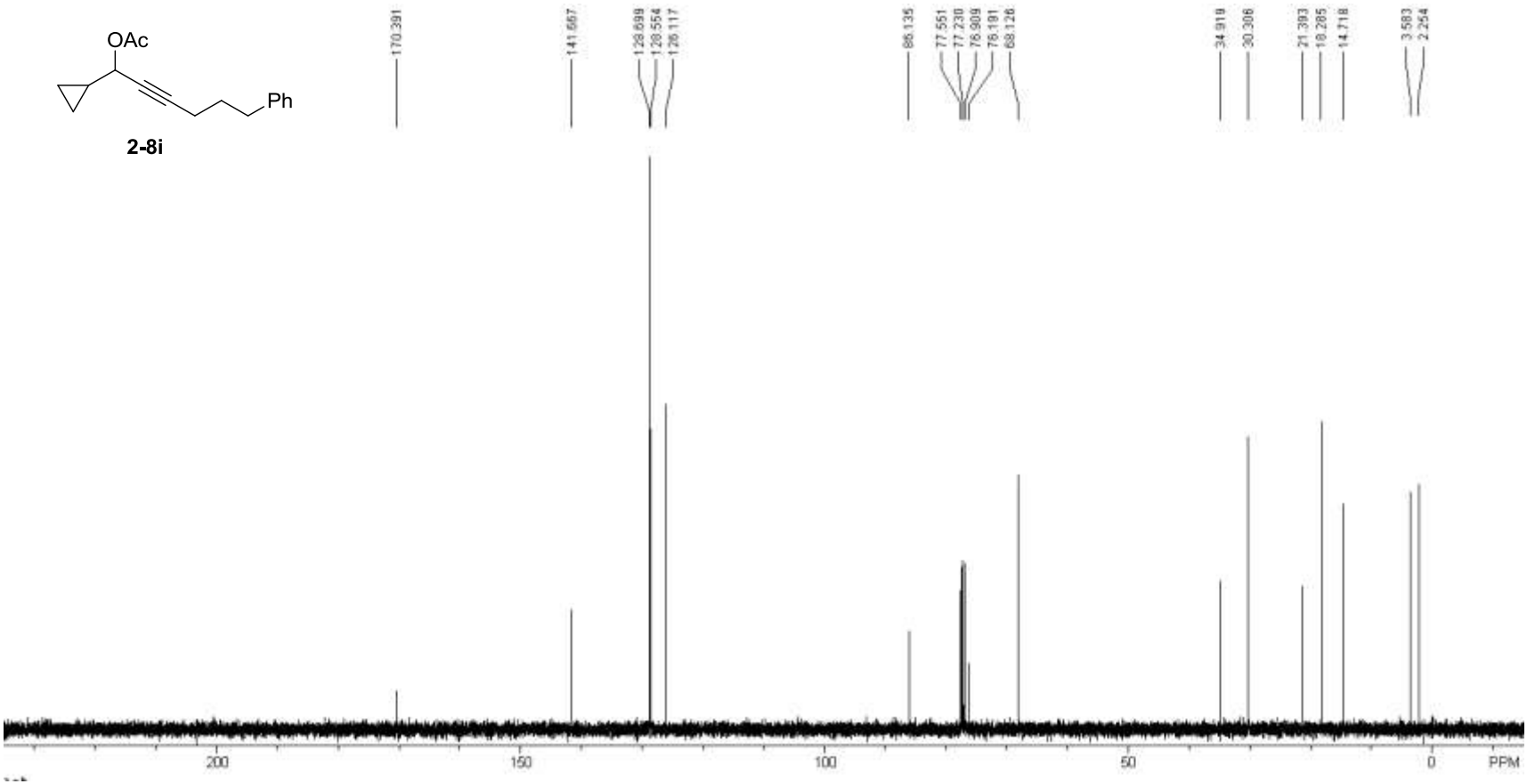

OPiv
2-8g
176.358
85.312
78.981
78.599
77.545
77.232
76.911
39.587
27.306
24.869
22.853
22.303
20.829
19.791
13.536
12.558
11.015
200
150
100
50
0
PPM

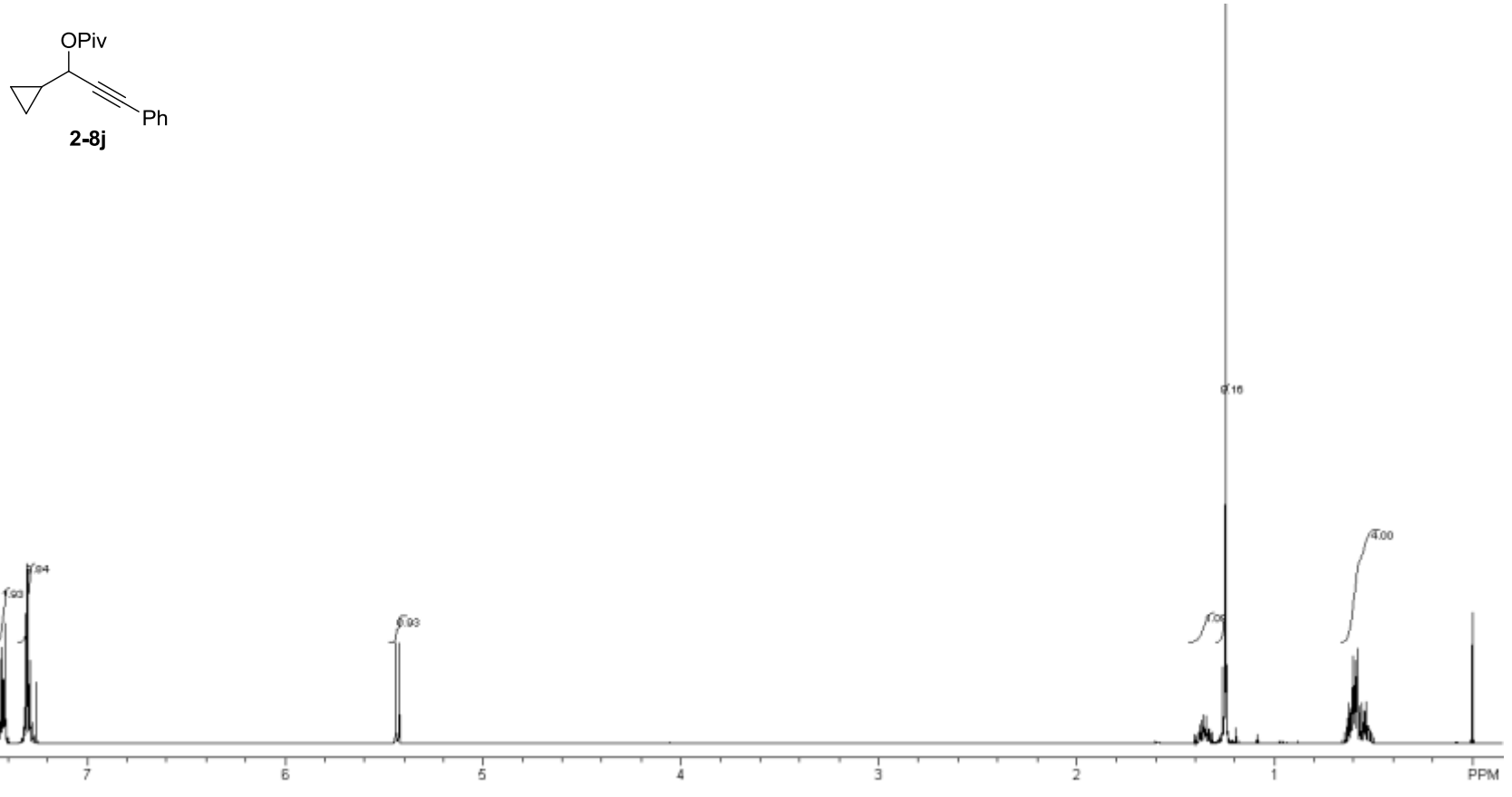

H
OPiv
2-8h
Ph
0.96
0.97
2.00
2.00
1.97
2.04
3.82
1.15
9.00
1.11
3.09
0.98
0.99
7
6
5
4
3
2
1
PPM

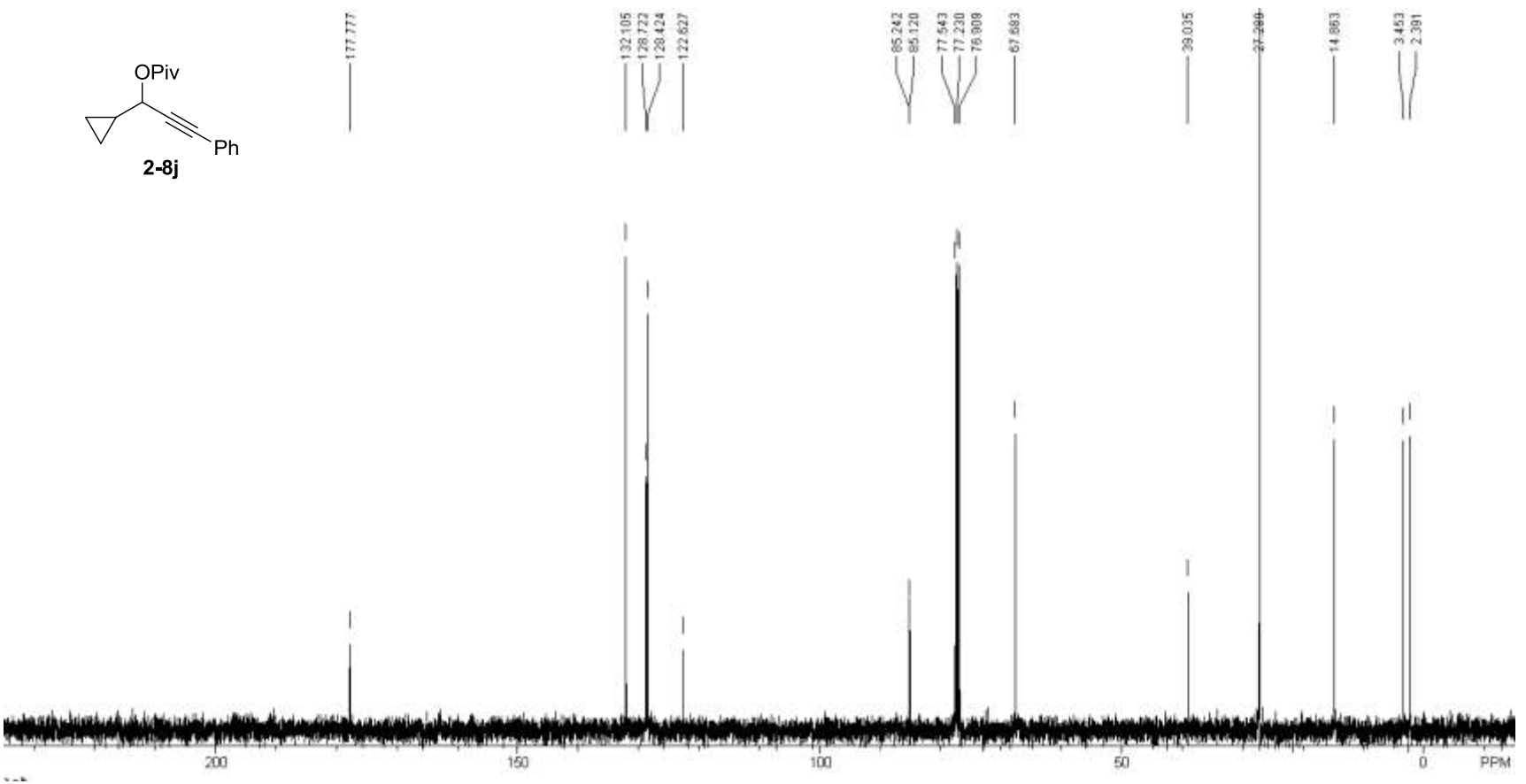

H
OPiv
2-8hPh
177.337
141.838
131.589
128.767
128.526
126.059
124.559
84.485
79.063
77.462
77.230
76.974
65.961
41.227
38.829
34.797
30.340
28.427
27.269
25.865
25.540
21.493
18.663
18.315
17.754
17.414
200
150
100
50
0
PPM

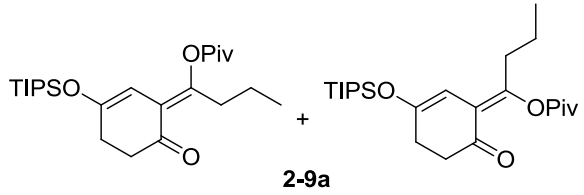


2-8i

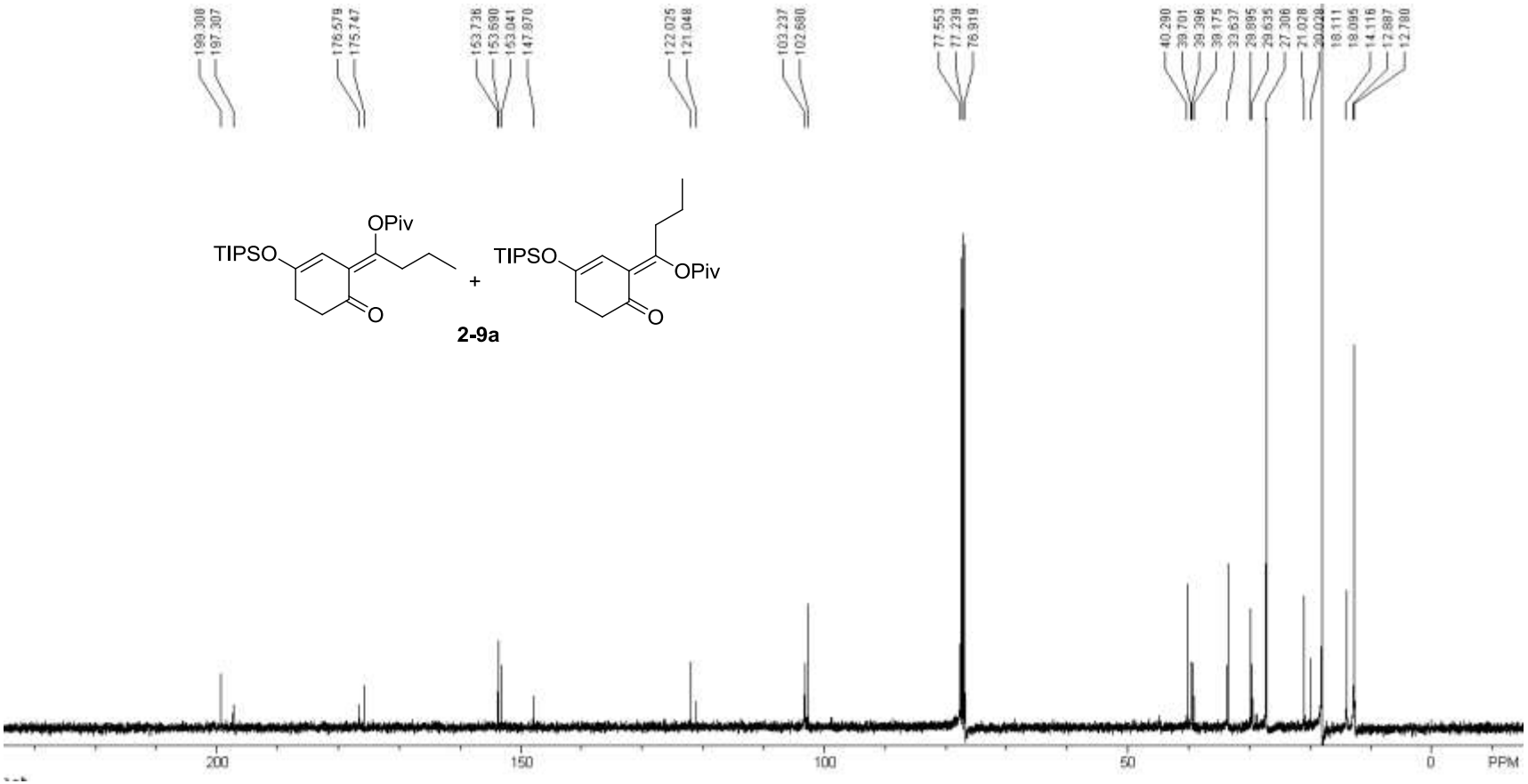

OAc
Ph
2-8i
170.391
141.667
128.699
128.554
126.117
86.135
77.551
77.230
76.909
76.191
68.126
34.919
30.306
21.393
19.285
14.718
3.583
2.254
200
150
100
50
0
PPM

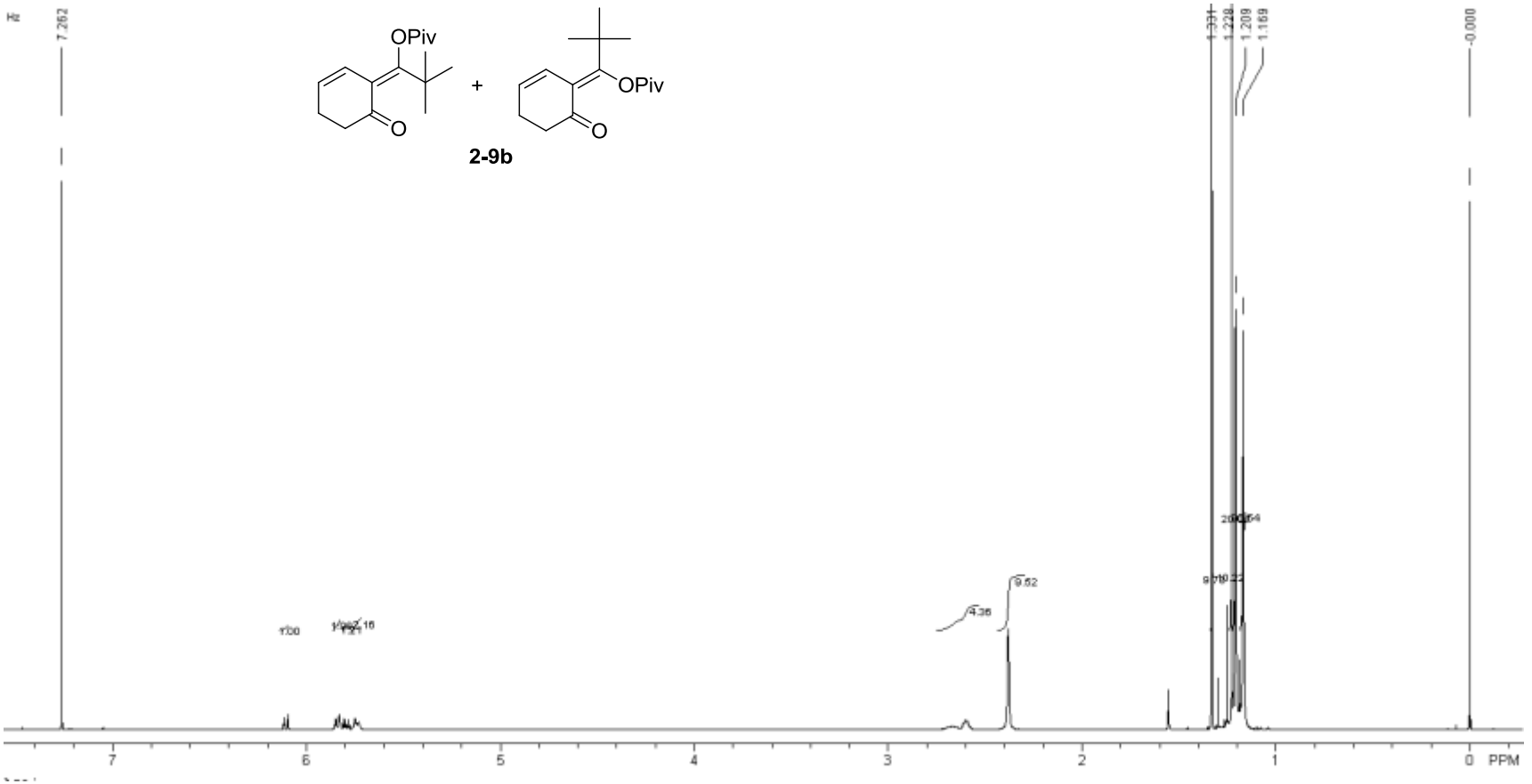

OPiv
Ph
2-8j
7
6
5
4
3
2
1
PPM

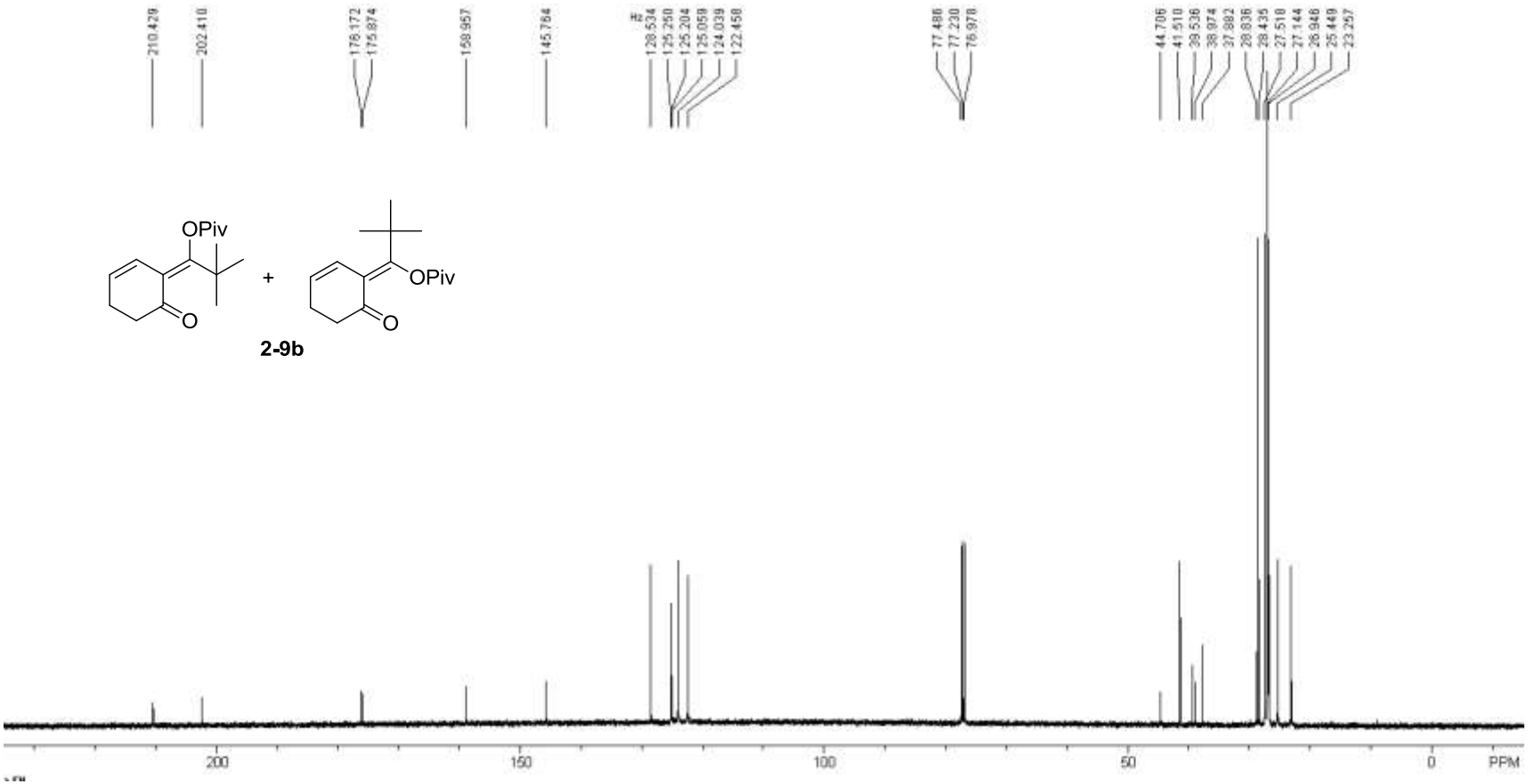

OPiv
Ph
2-8j
177.777
132.105
128.722
128.424
122.627
85.242
85.120
77.543
77.230
76.909
67.683
39.035
27.289
14.863
3.453
2.391
200
150
100
50
0
PPM

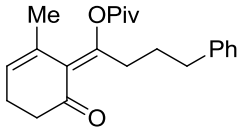


2-9a

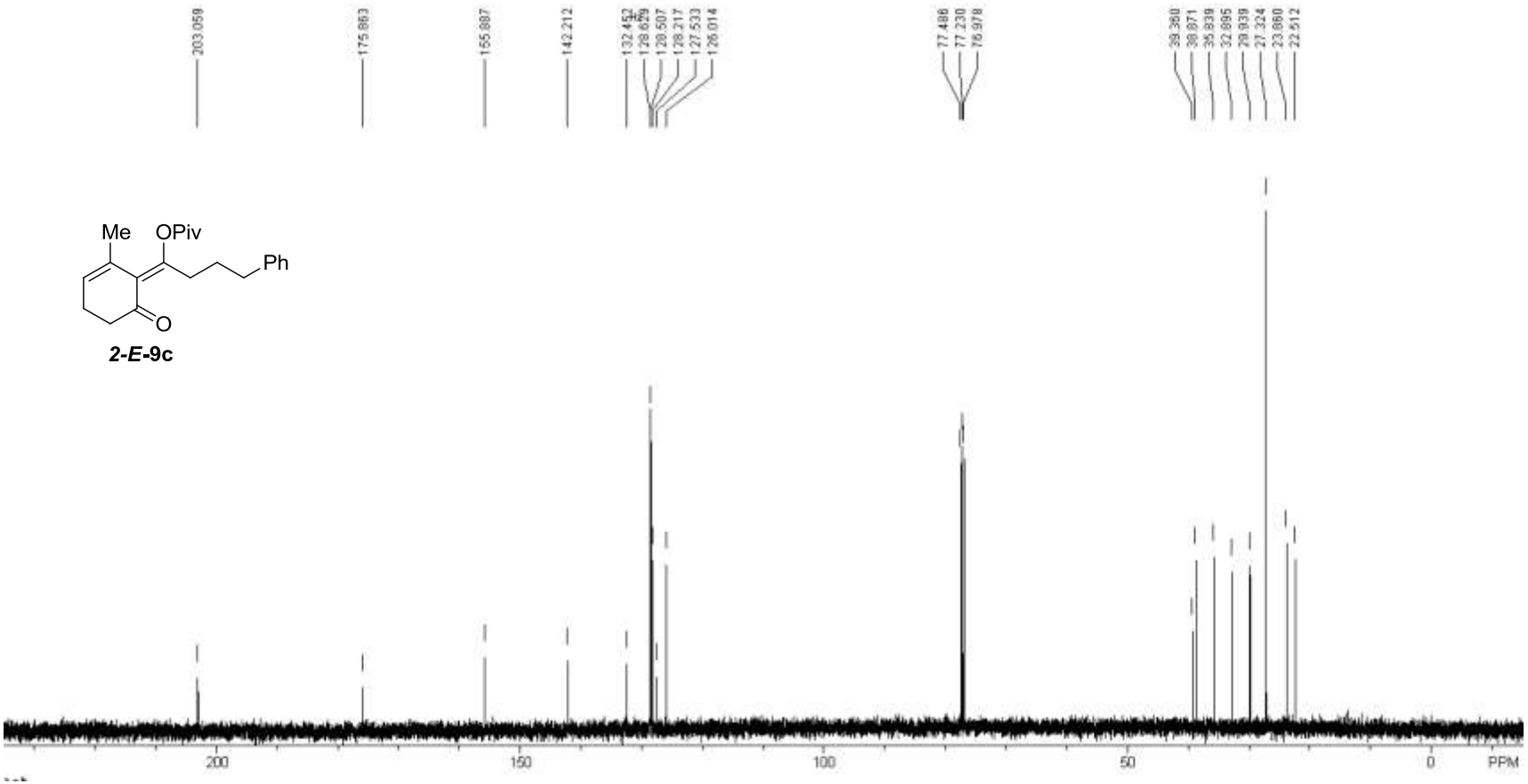

199.308
197.307
176.579
175.747
153.738
153.690
153.041
147.870
122.025
121.048
103.237
102.680
77.553
77.239
76.919
40.290
39.701
39.396
39.175
33.637
28.995
29.635
27.306
21.028
20.028
18.111
18.095
14.116
12.887
12.780
TIPSO
OPiv
O
+
TIPSO
OPiv
O
2-9a
200
150
100
50
0
PPM


OPiv
+
OPiv
O
O
2-9b
7.262
1.331
1.228
1.209
1.169
0.000
9.52
4.36
7
6
5
4
3
2
1
0
PPM

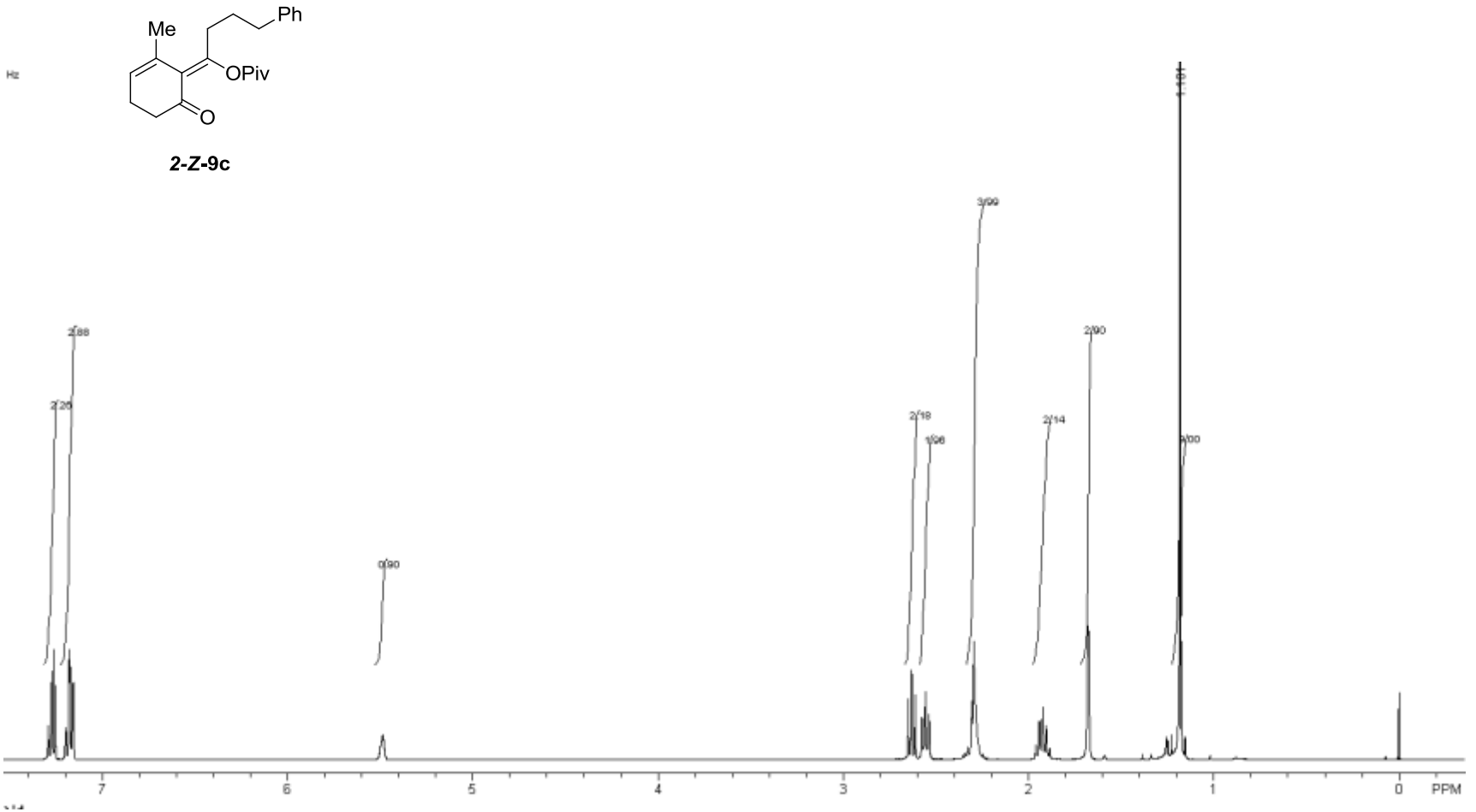

210.429
202.410
176.172
175.874
158.957
145.764
128.534
125.250
125.204
125.059
124.039
122.458
77.486
77.230
76.978
44.706
41.510
39.536
38.974
37.882
28.836
28.435
27.510
27.144
26.946
25.449
23.257
OPiv
O
+
OPiv
O
2-9b
200
150
100
50
0
PPM

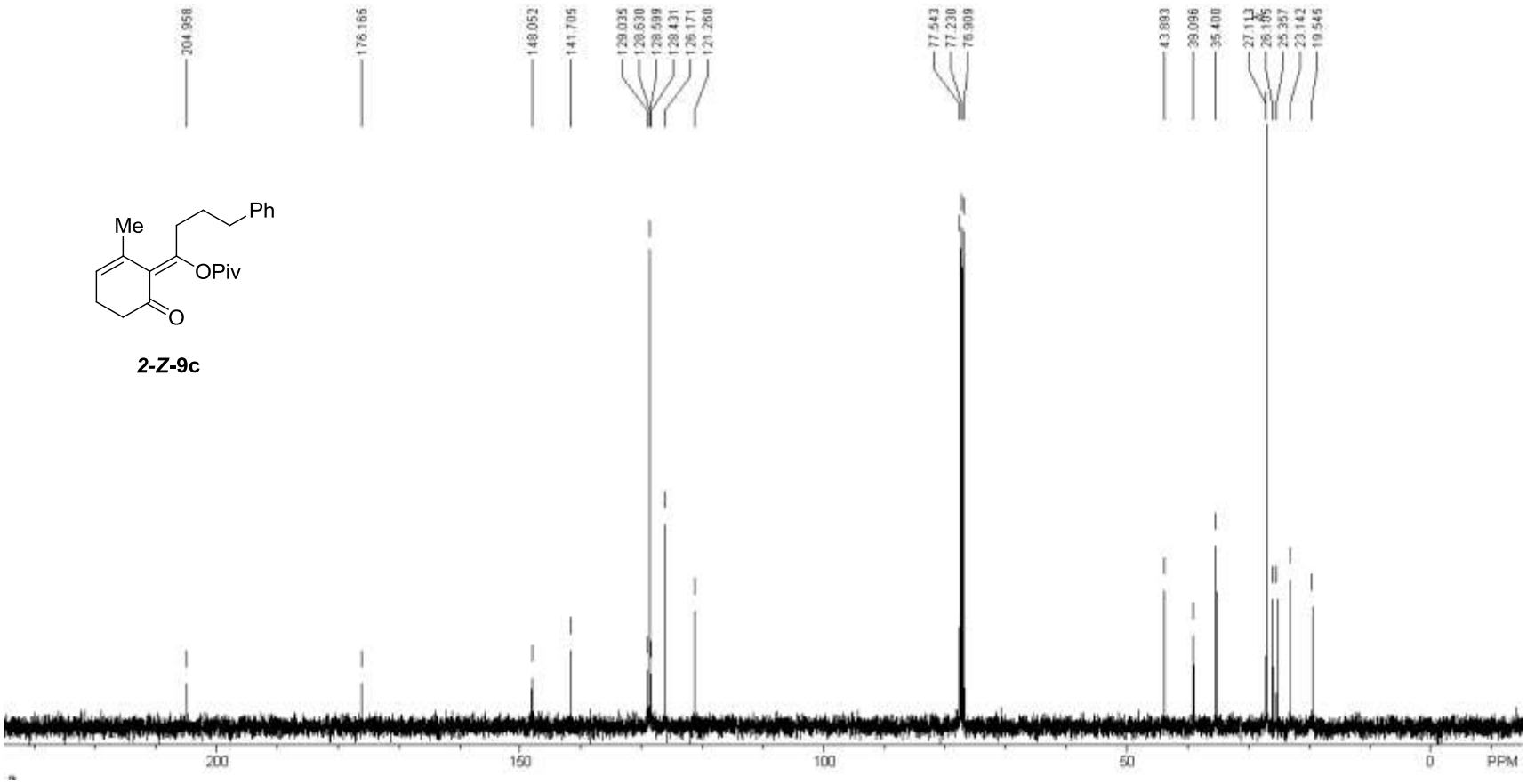


***2-E*-9c**

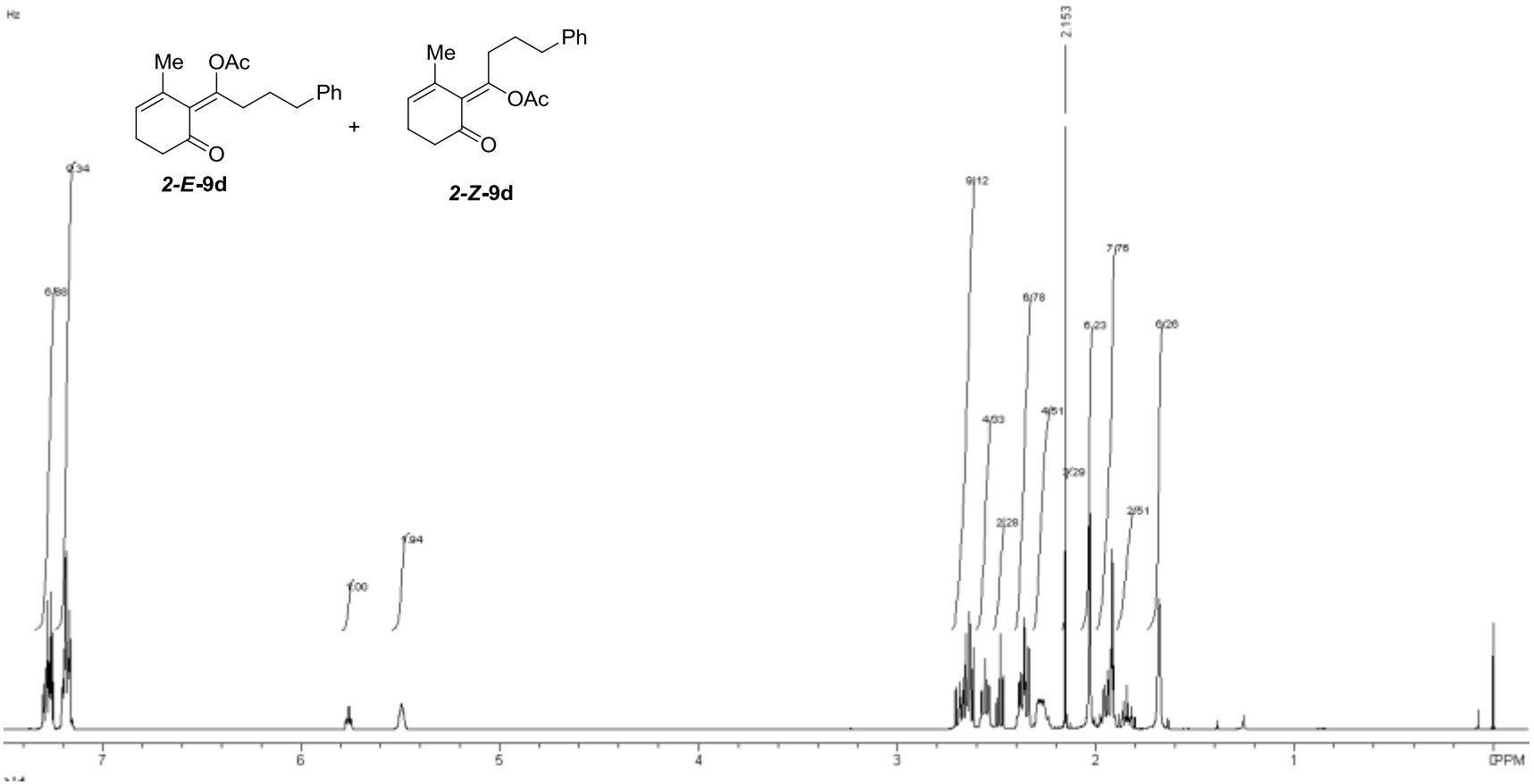

203.059
175.863
155.887
142.212
132.452
128.629
128.507
128.217
127.533
126.014
77.486
77.230
76.978
39.360
38.871
35.839
32.695
29.939
27.324
23.860
22.512
Me
OPiv
Ph
O
200
150
100
50
0
PPM

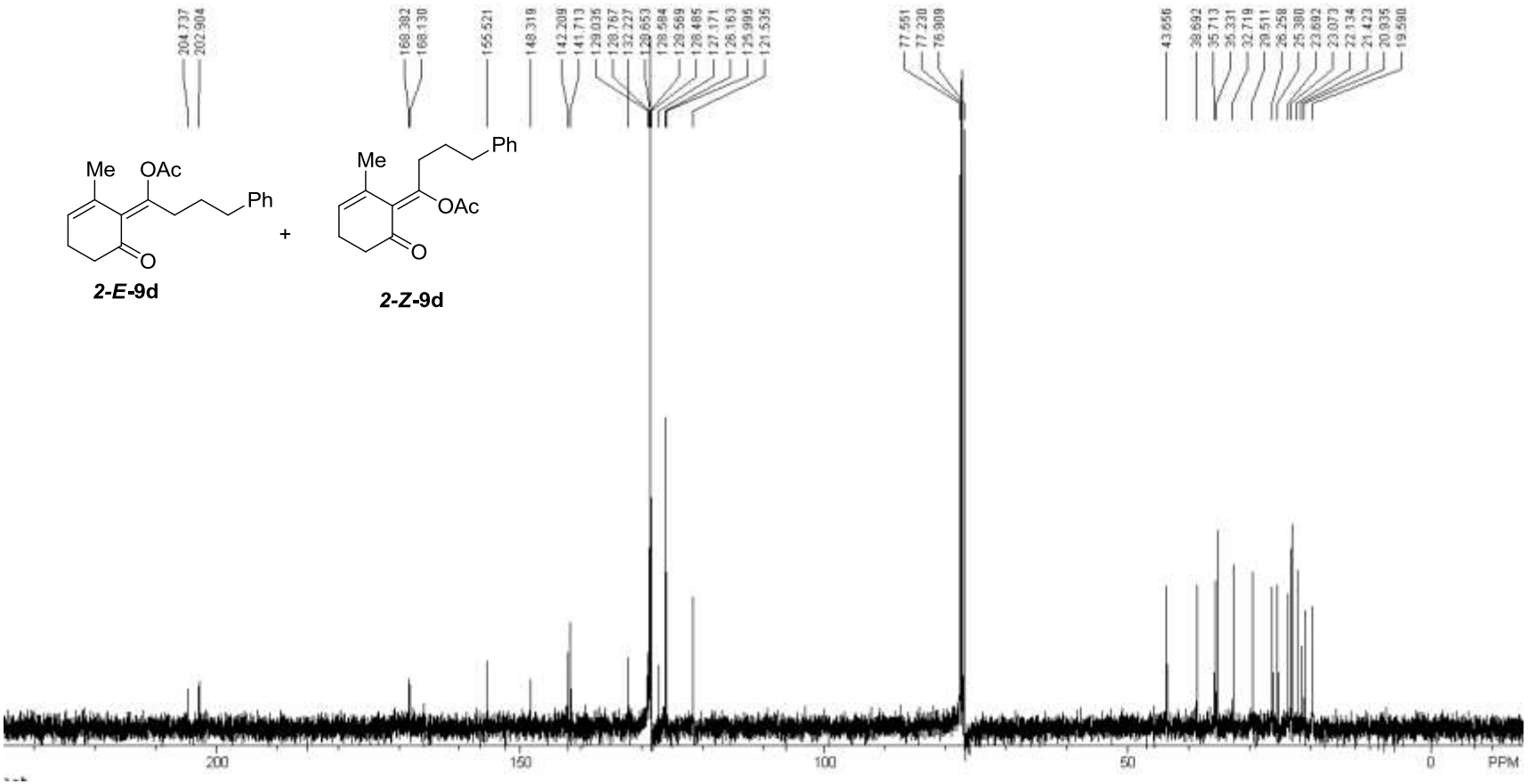
***2-E*-9c**

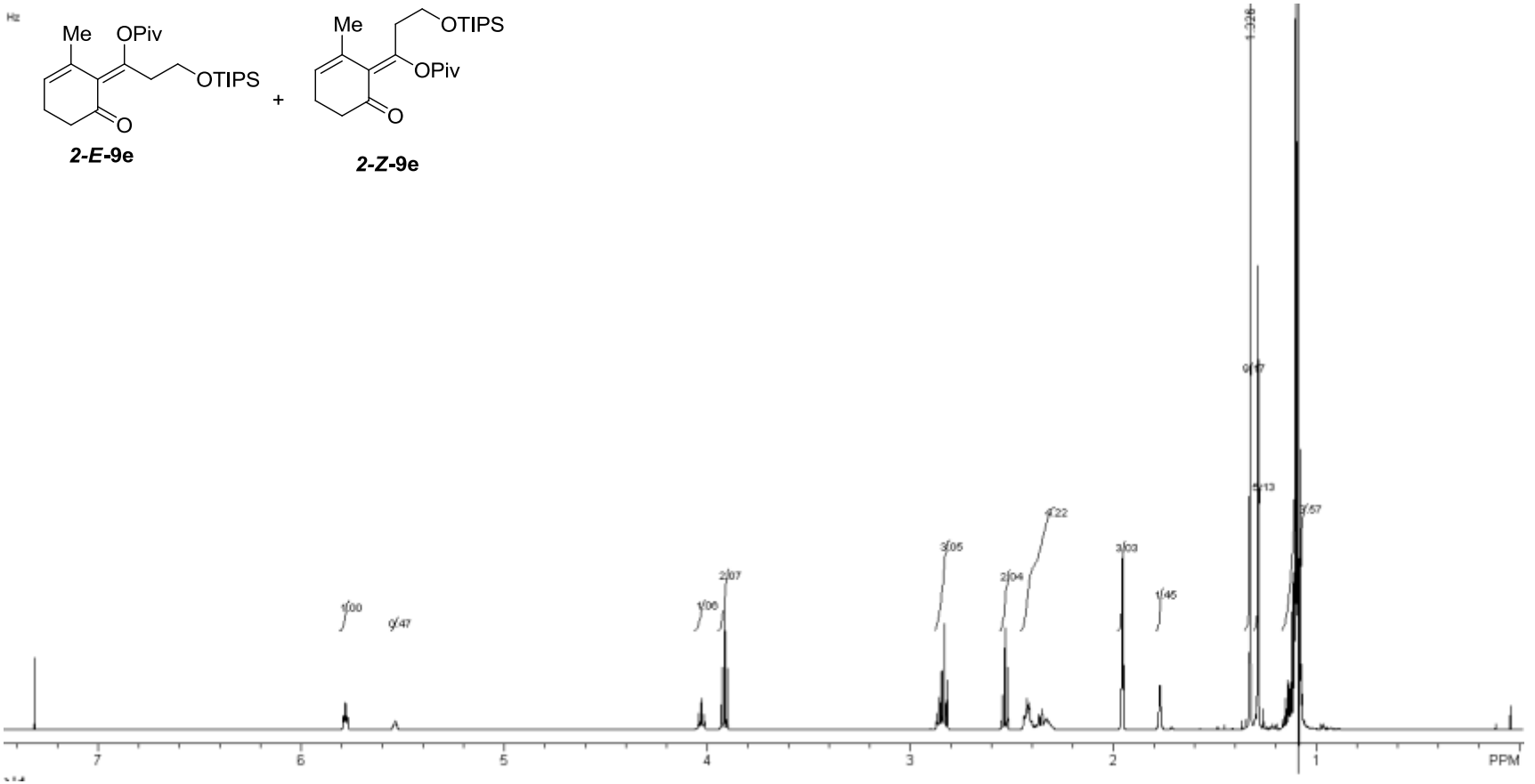

Me
Ph
OPiv
O
2-Z-9c
Hz
2.88
2.26
0.90
3.99
2.18
1.08
2.14
2.00
1.00
7
6
5
4
3
2
1
0
PPM

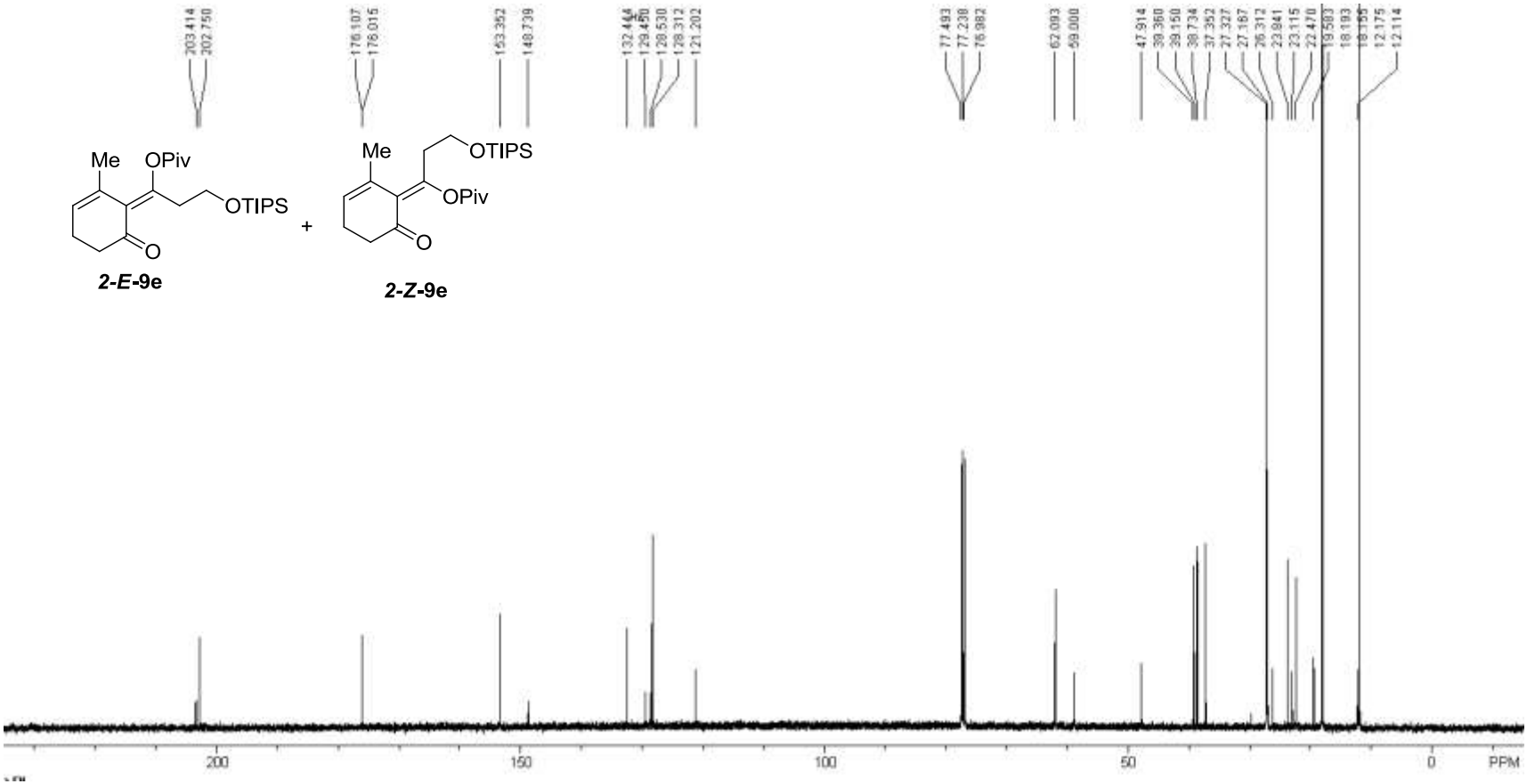

204.958
176.165
148.052
141.705
129.035
128.630
128.599
128.431
126.171
121.260
77.543
77.230
76.909
43.893
39.096
35.400
27.113
26.185
25.357
23.142
19.545
Me
Ph
OPiv
O
200
150
100
50
0
PPM

2-Z-9c

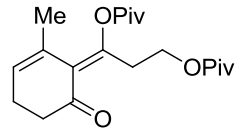

Me
OAc
Ph
O
2-E-9d
+
Me
Ph
OAc
O
2-Z-9d
2.153
9.12
9.34
6.88
7.75
6.78
6.23
6.26
4.33
4.51
3.29
2.28
2.51
1.94
1.00
7
6
5
4
3
2
1
0
PPM


204.737
202.904
168.382
168.130
155.521
148.319
142.209
141.713
129.035
128.787
128.227
128.053
128.584
128.569
128.485
127.171
126.163
125.995
121.535
77.551
77.230
76.909
43.656
38.692
35.713
35.331
32.719
29.511
26.258
25.380
23.692
23.073
22.134
21.423
20.935
19.590
Me
OAc
Ph
O
2-E-9d
+
Me
Ph
OAc
O
2-Z-9d
200
150
100
50
0
PPM

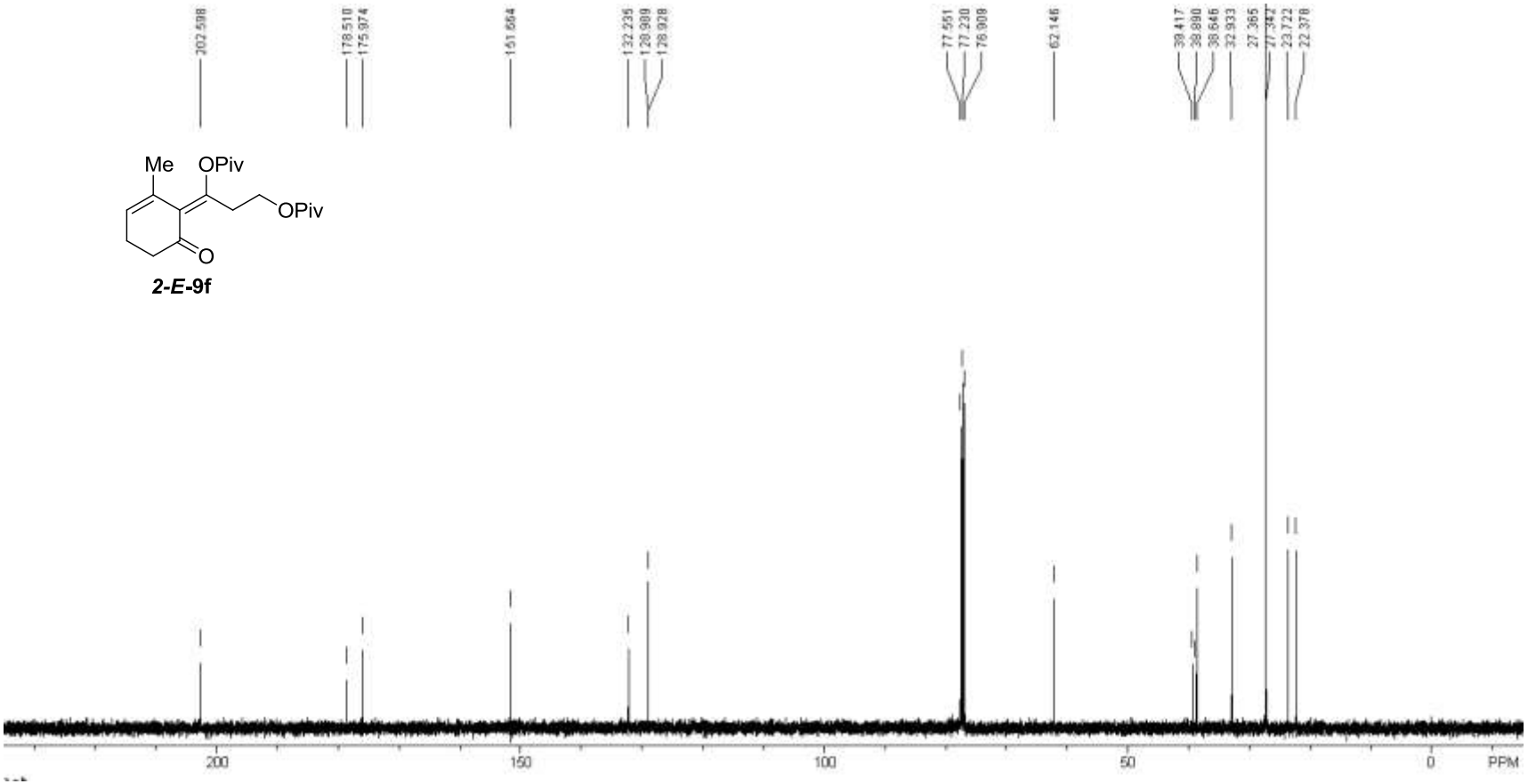

Me
OPiv
OTIPS
O
2-E-9e
+
Me
OTIPS
OPiv
O
2-Z-9e
1.00
0.47
2.07
1.06
3.05
2.04
4.22
3.03
1.45
9.17
5.13
3.57
7
6
5
4
3
2
1
PPM

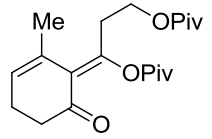

203.414
202.750
176.107
176.016
153.352
148.739
132.444
129.450
128.530
128.312
121.202
77.493
77.238
76.982
62.093
59.000
47.914
39.360
39.150
38.734
37.352
27.327
27.167
26.312
23.841
23.115
22.470
19.503
18.193
18.155
12.175
12.114
Me
OPiv
OTIPS
O
+
Me
OTIPS
OPiv
O
200
150
100
50
0
PPM

2-*E*-9e + **2-*Z*-9e**

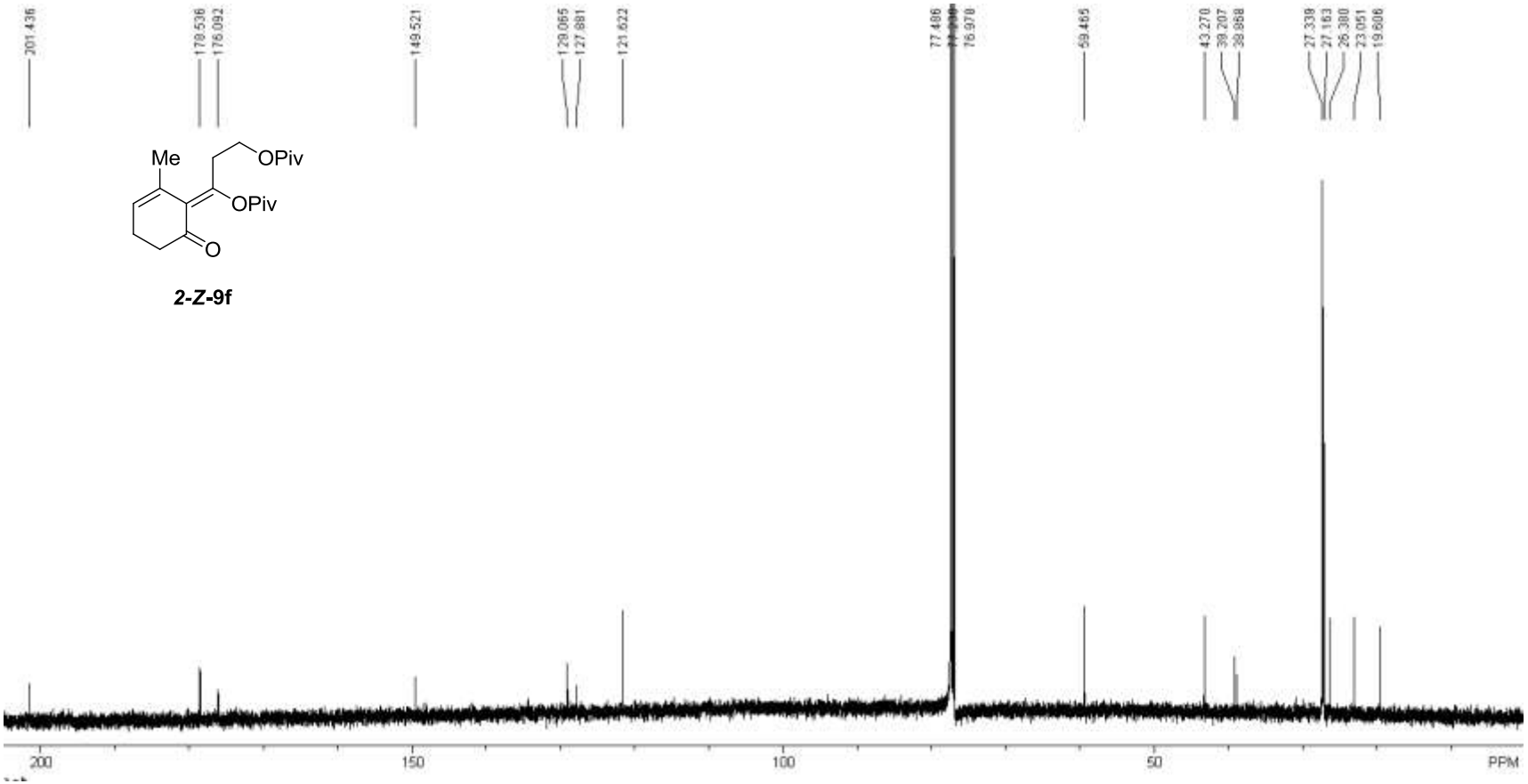


***2-E*-9f**

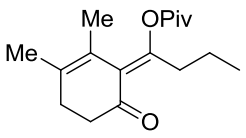

202.598
178.510
175.974
151.664
132.235
129.989
128.928
77.551
77.230
76.909
62.146
39.417
38.890
38.646
32.933
27.365
27.347
23.722
22.378
Me
OPiv
OPiv
O
2-E-9f
200
150
100
50
0
PPM



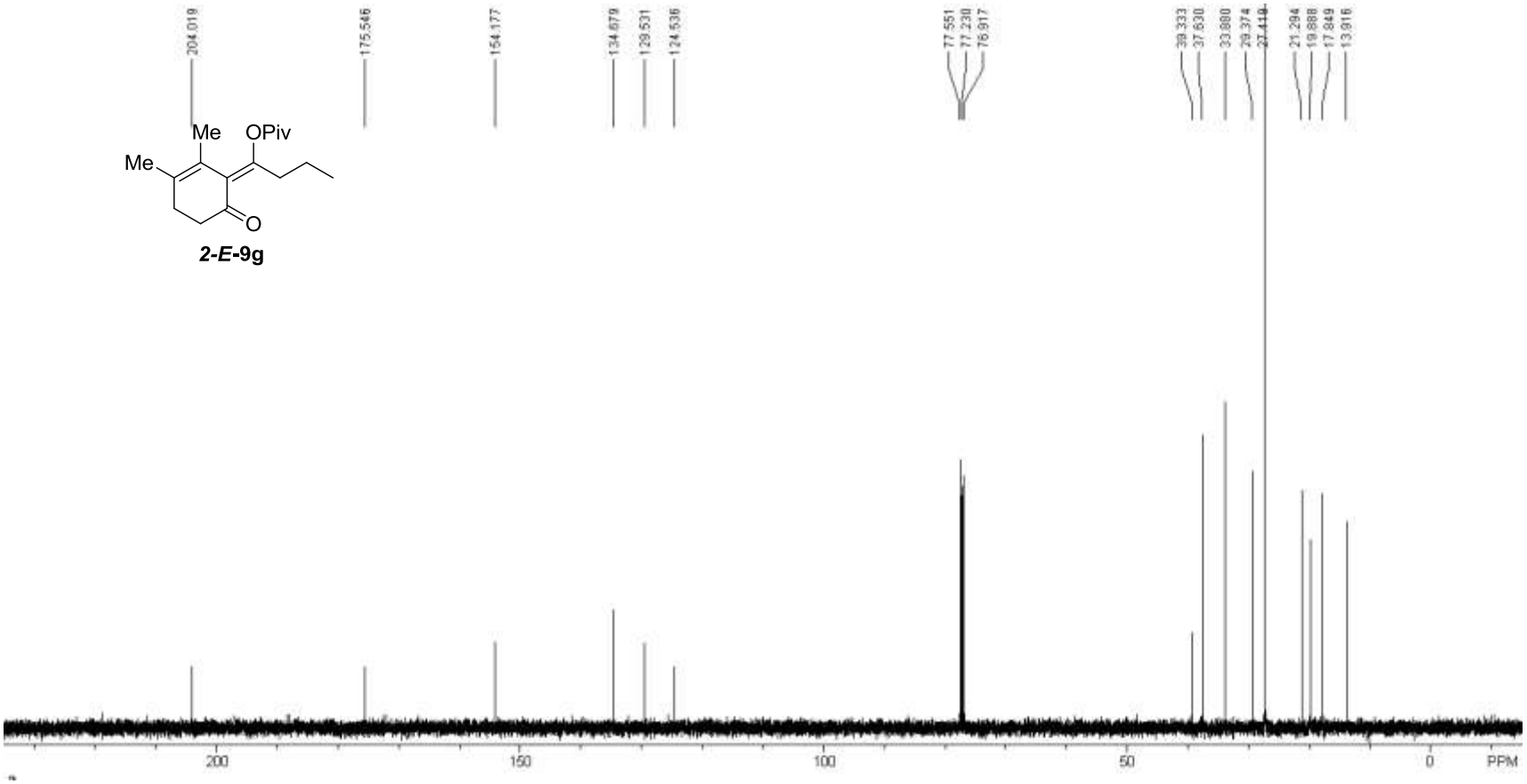
2-*Z*-9f

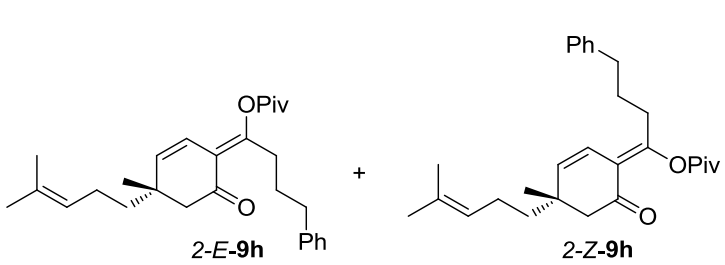

201.436
178.536
176.092
149.521
129.065
127.881
121.622
77.486
76.970
59.465
43.270
39.207
38.868
27.339
27.163
26.380
23.051
19.606
Me
OPiv
OPiv
O
200
150
100
50
PPM

2-*Z*-9f



***2-E*-9g**

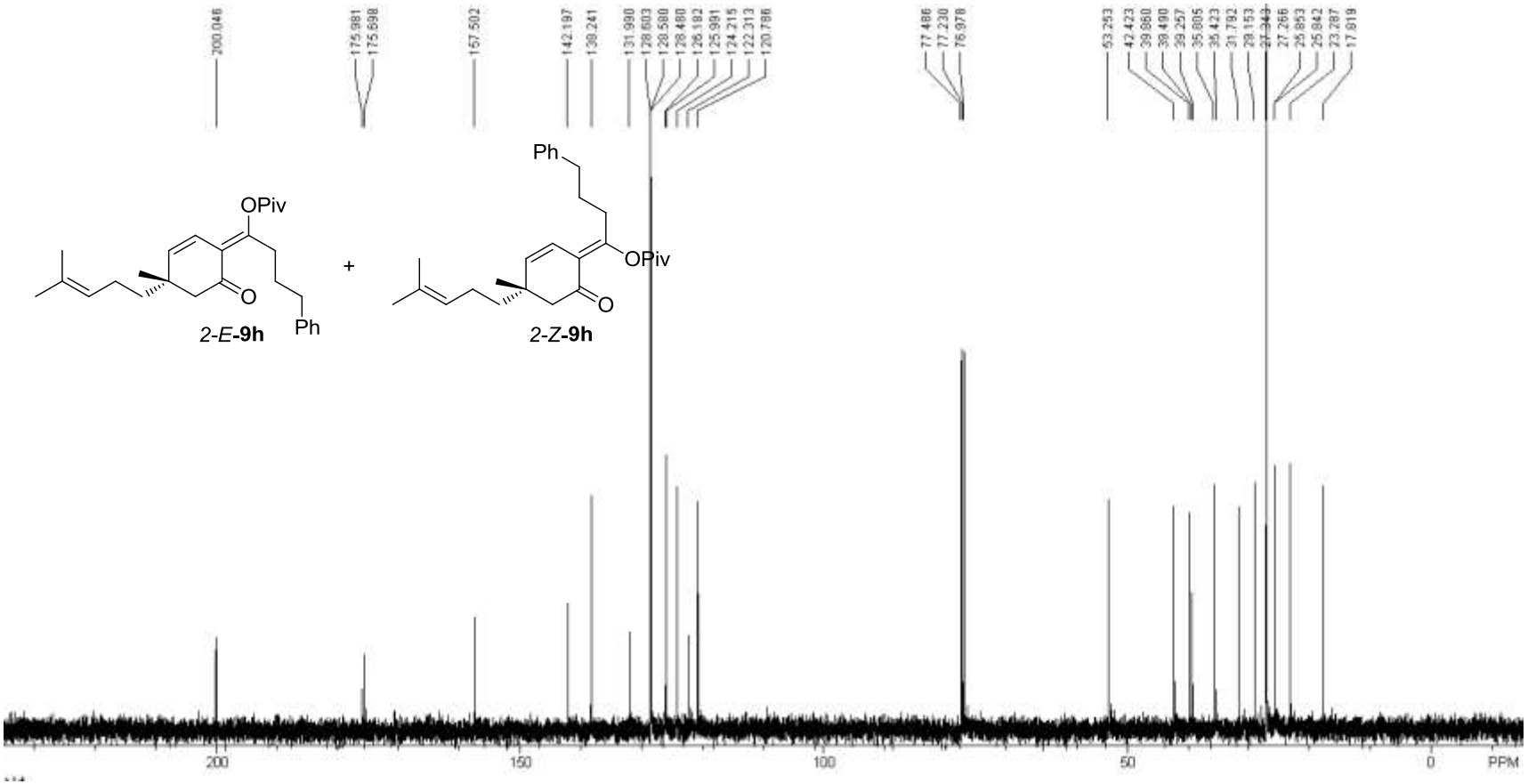

204.019
175.546
154.177
134.679
129.531
124.536
77.551
77.230
76.917
39.333
37.630
33.680
29.374
27.418
21.294
19.888
17.849
13.916
Me
OPiv
Me
O
2-E-9g
200
150
100
50
0
PPM

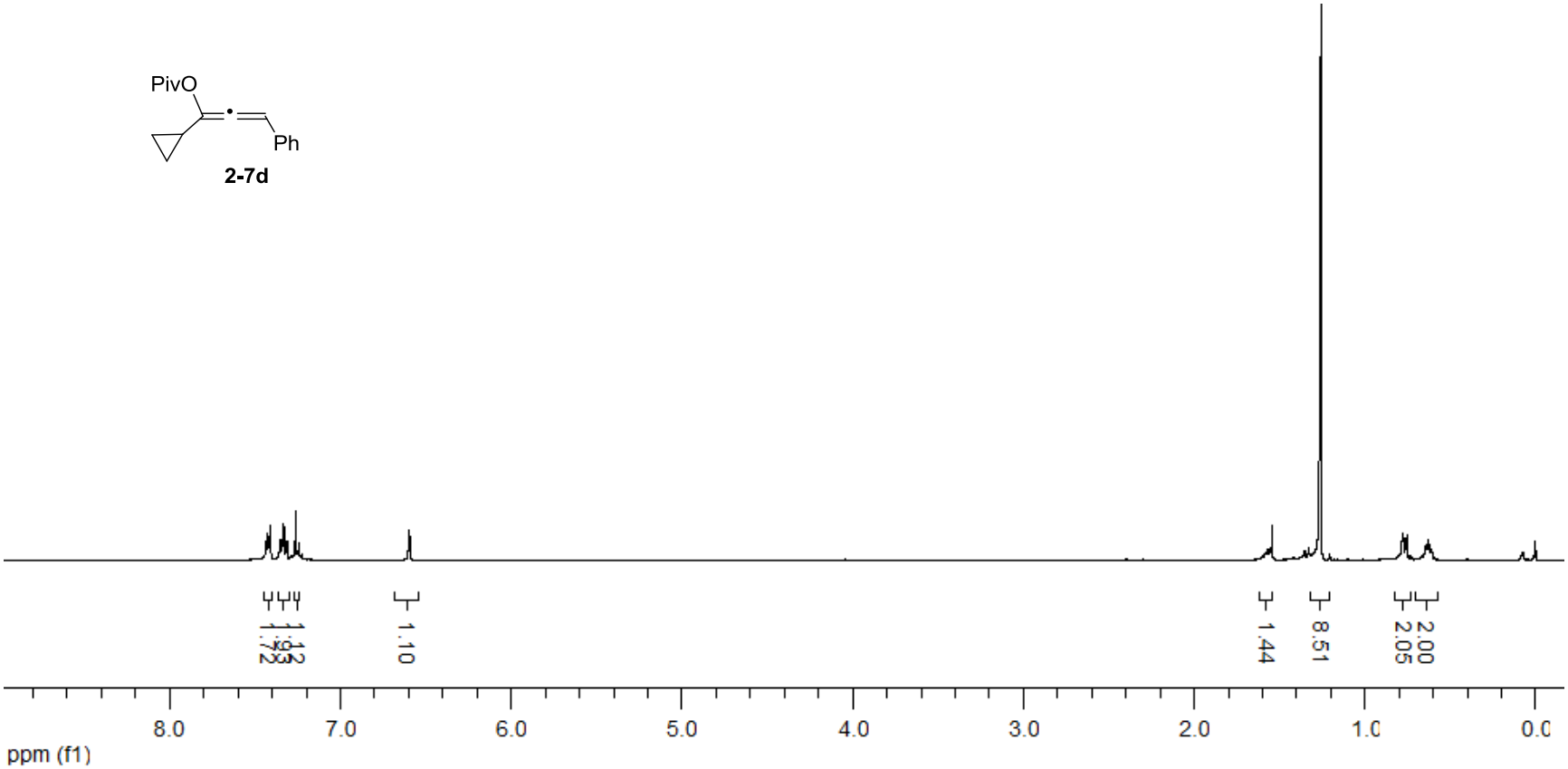


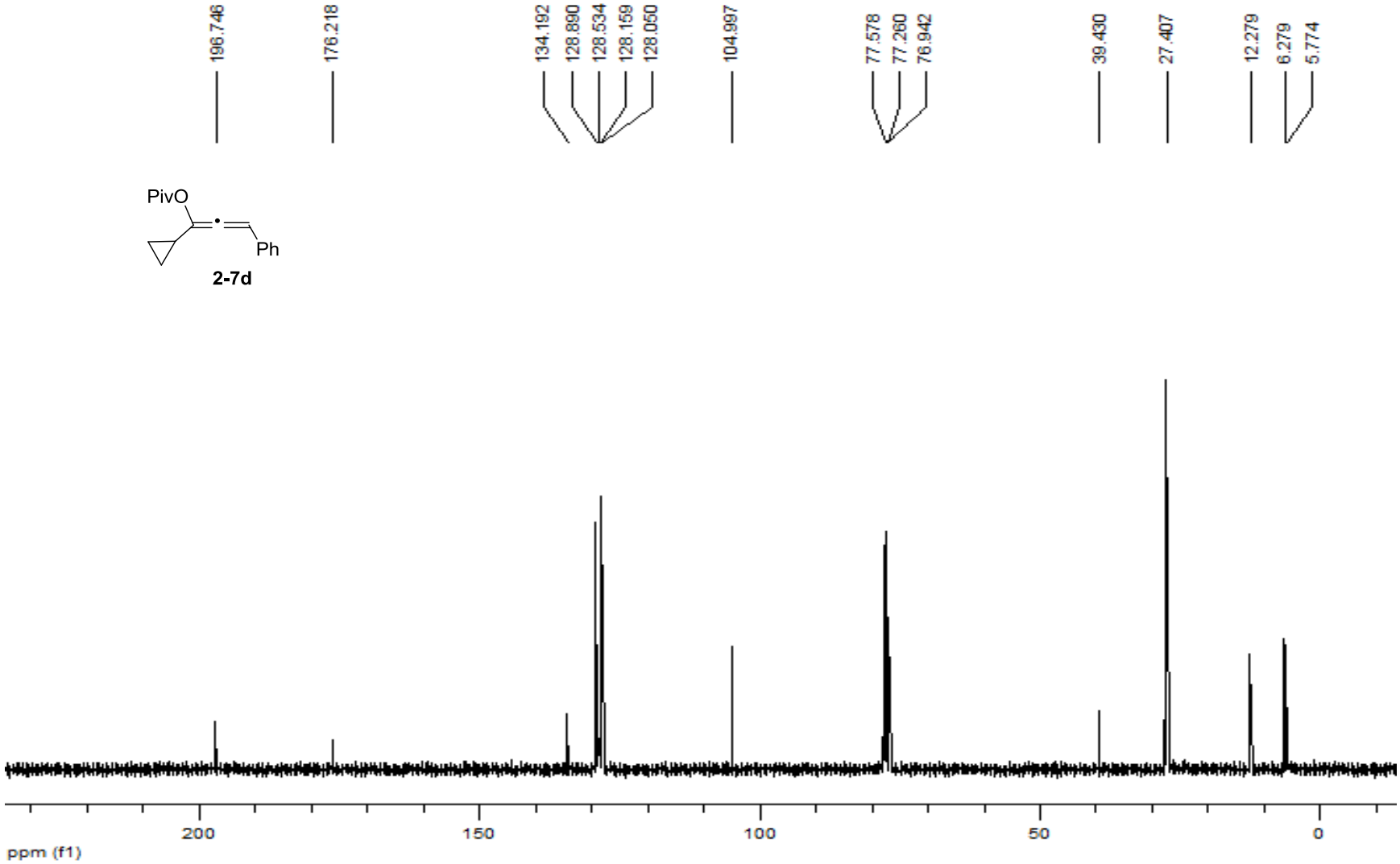
2-E-**9h**

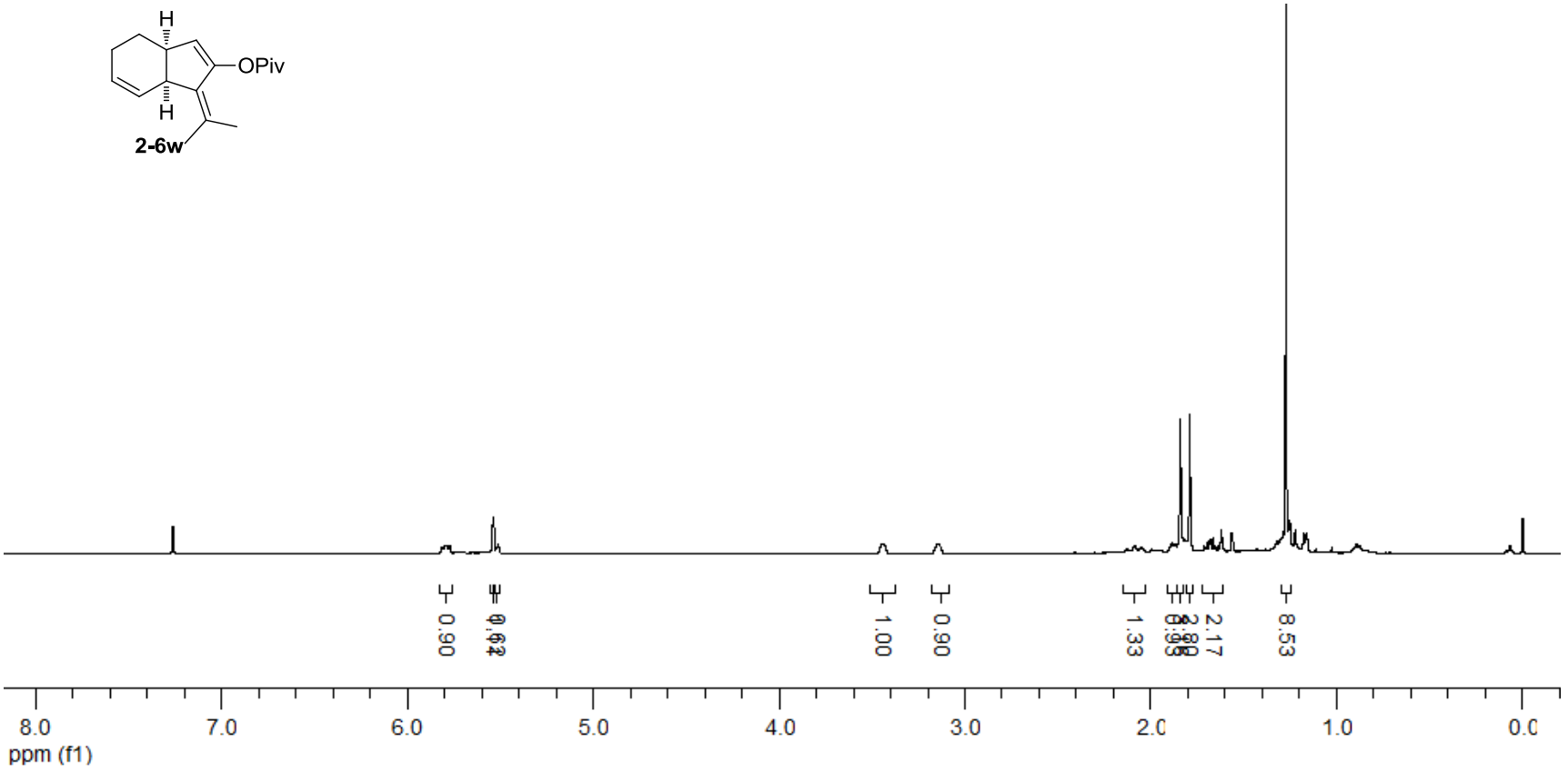
+

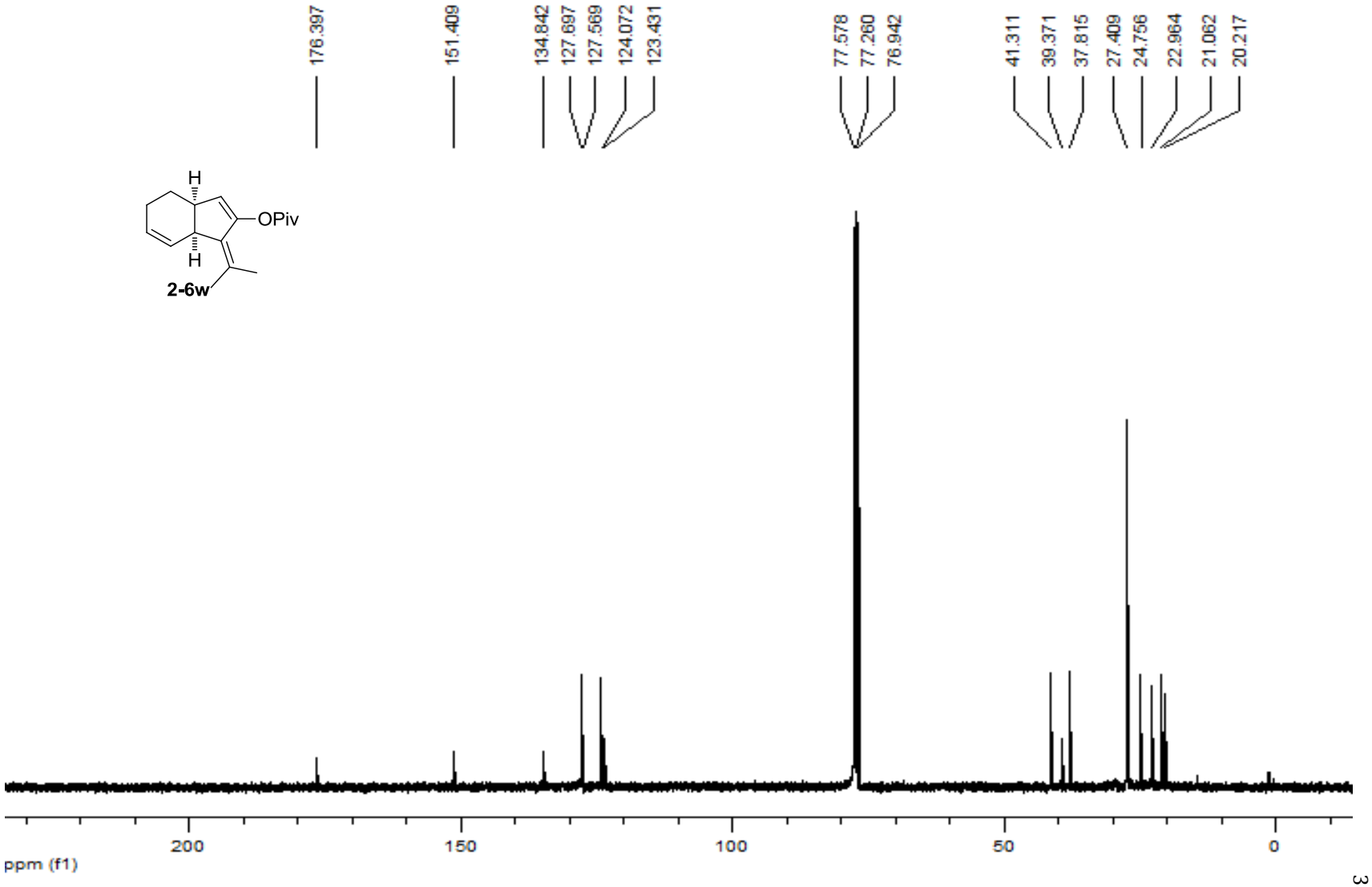
2-Z-**9h**

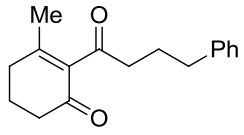

200.046
175.981
175.598
157.502
142.197
138.241
131.990
128.603
128.580
128.480
126.182
125.991
124.215
122.313
120.786
77.486
77.230
76.978
53.253
42.423
39.860
39.490
39.257
35.805
35.423
31.792
29.153
27.343
27.266
25.853
25.842
23.287
17.819
OPiv
O
Ph
+
Ph
OPiv
O
2-E-9h
2-Z-9h
200
150
100
50
0
PPM


PivO
Ph
2-7d
1.10
1.44
8.51
2.00
2.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

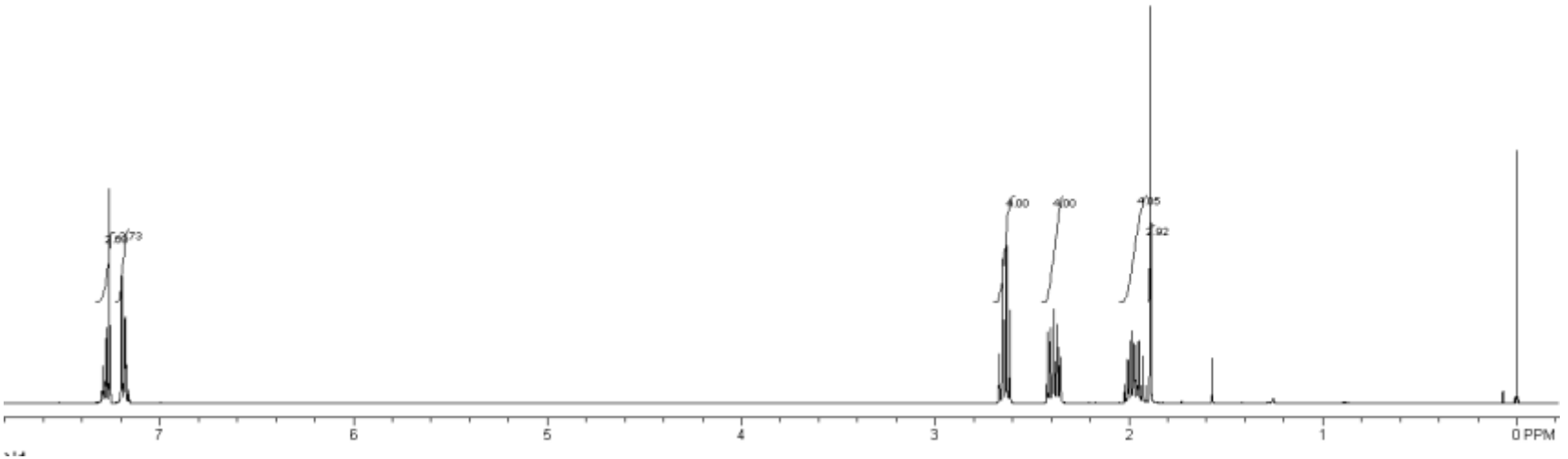

196.746
176.218
134.192
128.890
128.534
128.159
128.050
104.997
77.578
77.260
76.942
39.430
27.407
12.279
6.279
5.774
PivO
Ph
2-7d
200
150
100
50
0
ppm (f1)

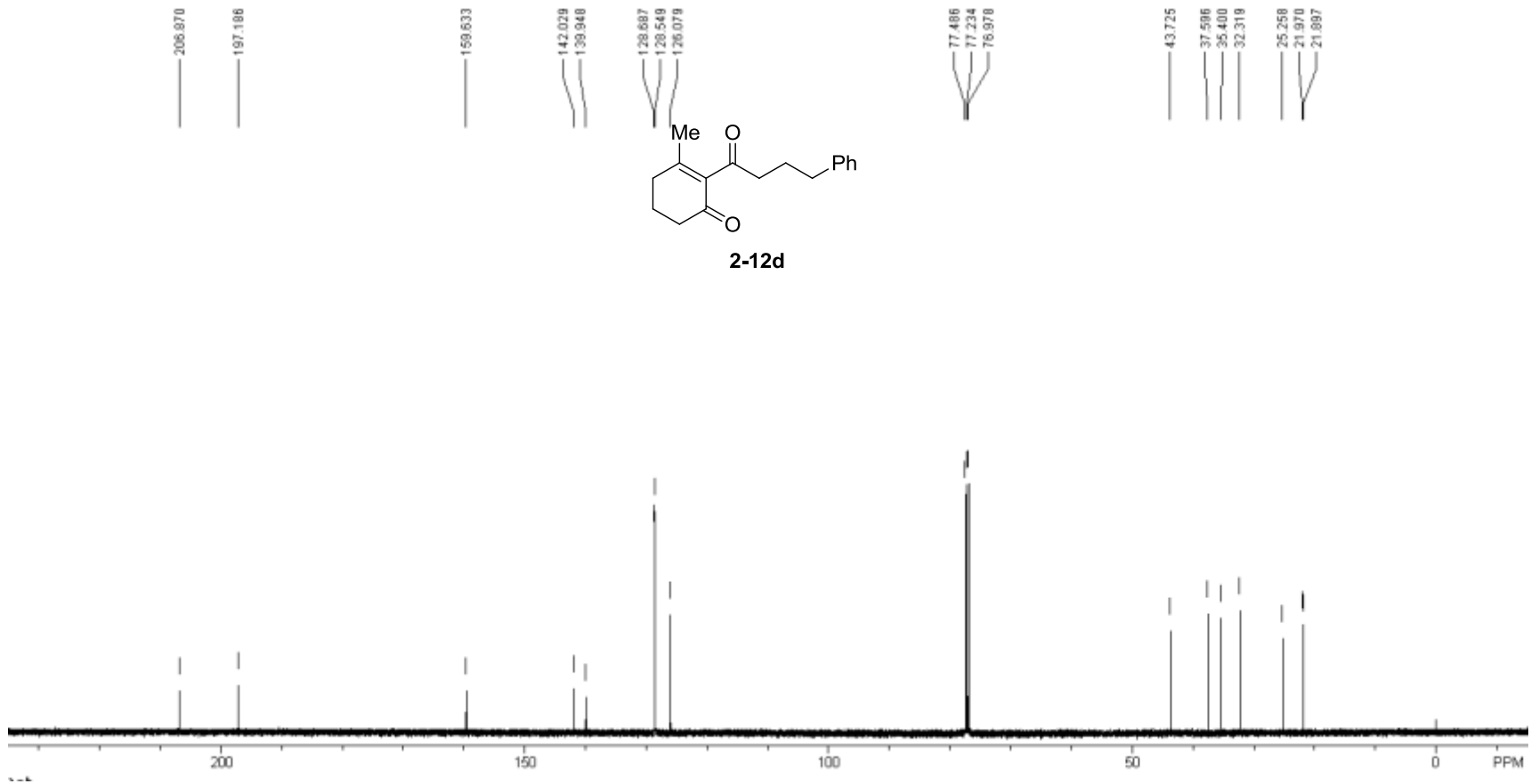

H
OPiv
H
2-6w
0.90
1.00
0.90
1.33
2.17
8.53
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


176.397
151.409
134.842
127.697
127.569
124.072
123.431
77.578
77.260
76.942
41.311
39.371
37.815
27.409
24.756
22.964
21.062
20.217
H
OPiv
H
2-6w
200
150
100
50
0
ppm (f1)



2-12d




206.870
197.186
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142.029
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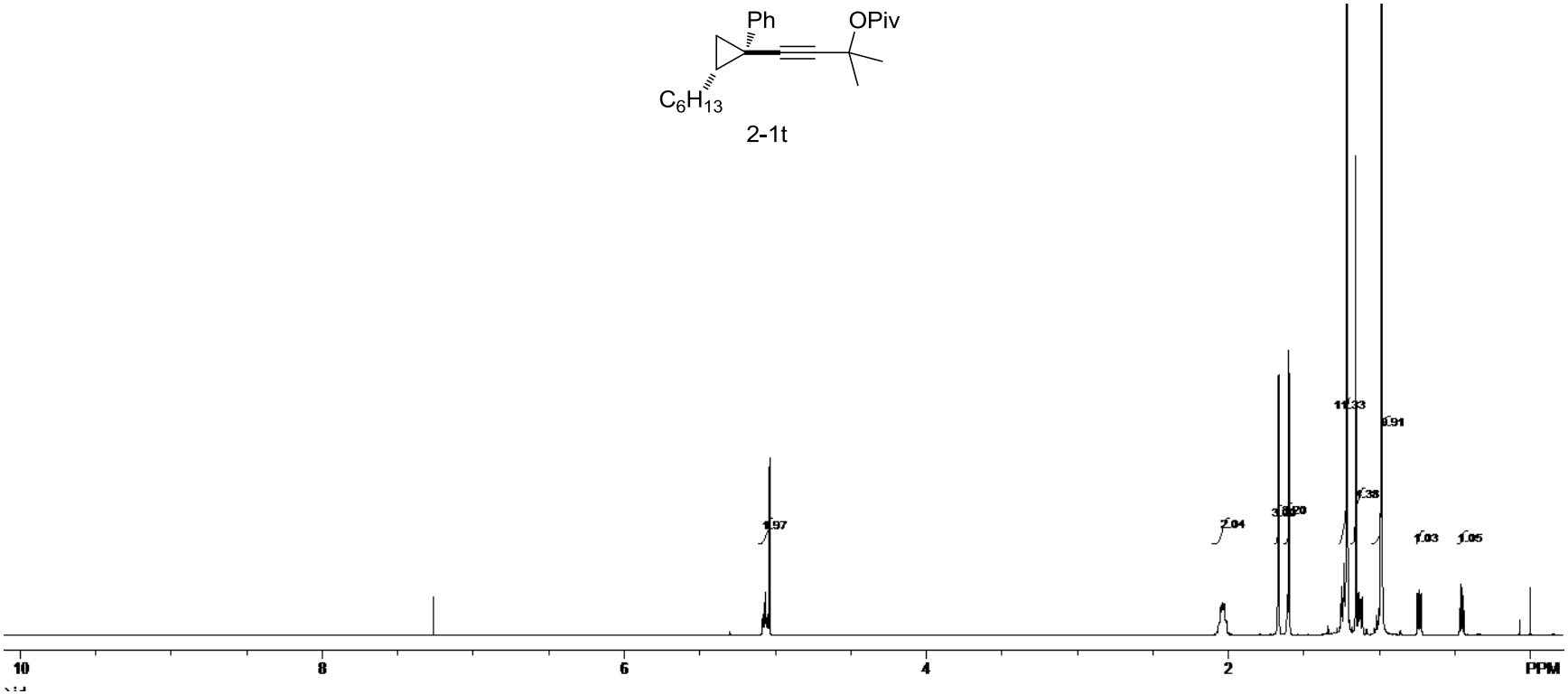
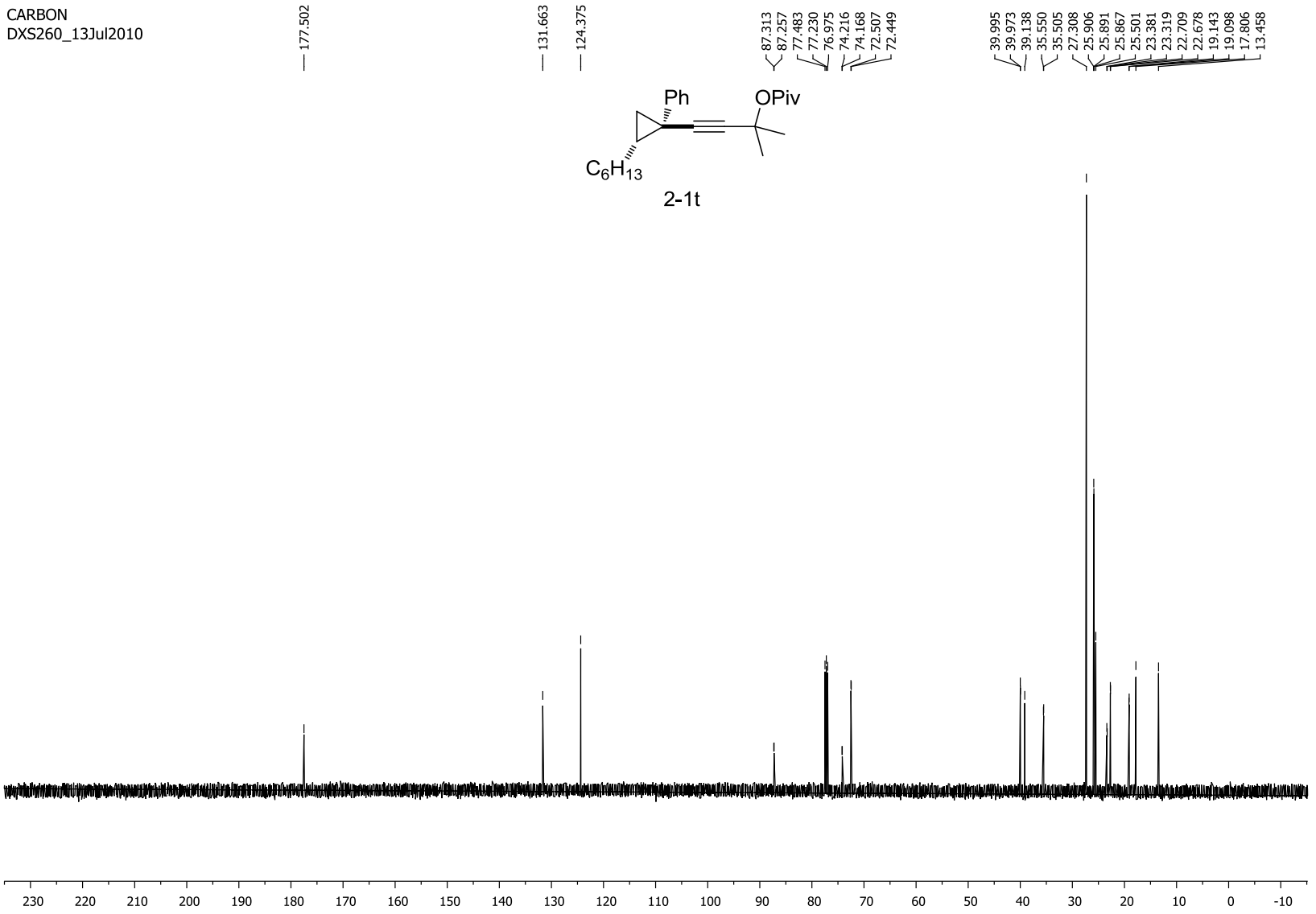
128.549
126.079
77.486
77.234
76.978
43.725
37.596
35.400
32.319
25.258
21.970
21.897
Me
O
Ph
O
200
150
100
50
0
PPM

2-12d


Ph
OPiv
C6H13
2-1t
1.97
2.04
11.33
9.91
1.38
1.03
1.05
10
8
6
4
2
PPM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131.663
124.375
87.313
87.257
77.483
77.230
76.975
74.216
74.168
72.507
72.449
39.995
39.973
39.138
35.550
35.505
27.308
25.906
25.891
25.867
25.501
23.381
23.319
22.709
22.678
19.143
19.098
17.806
13.458
Ph
OPiv
C6H13
2-1t
230
220
210
200
190
180
170
160
150
140
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120
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100
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60
50
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30
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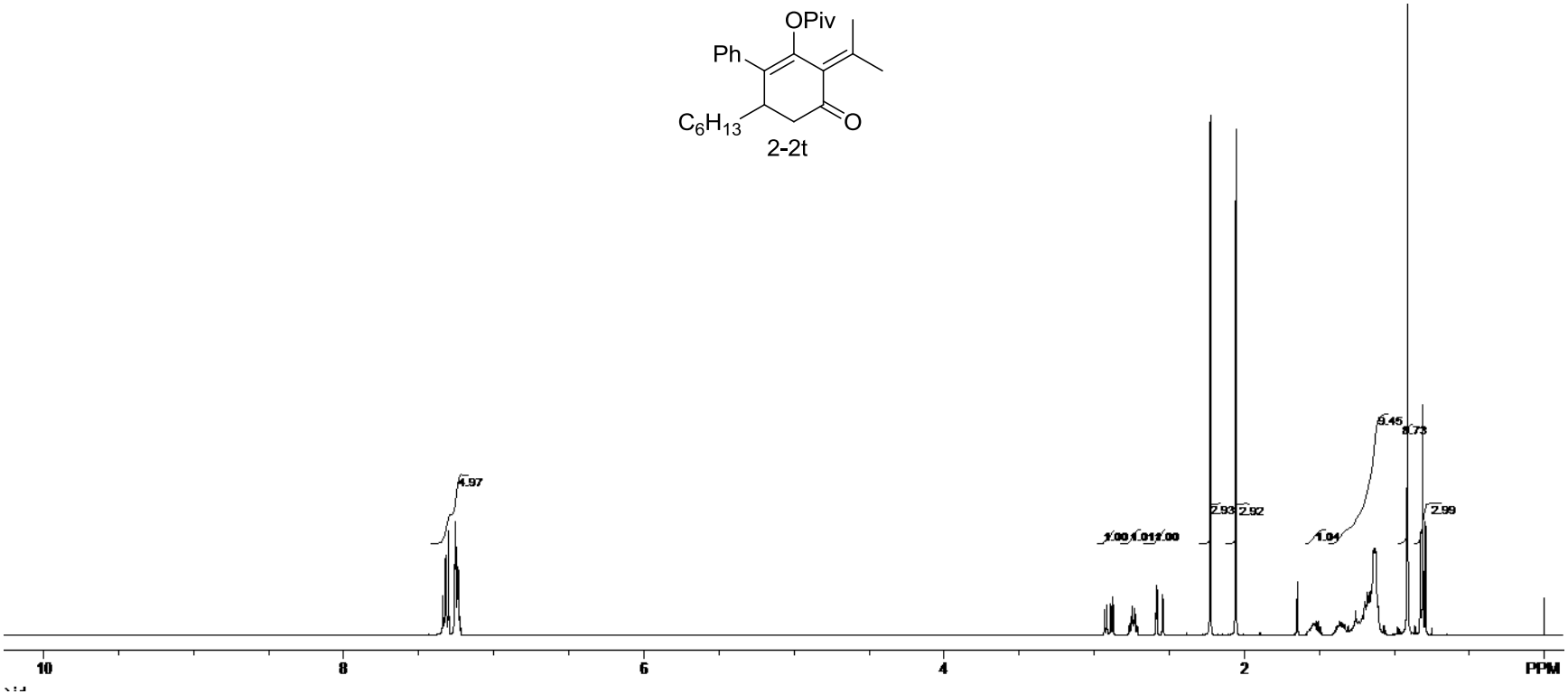
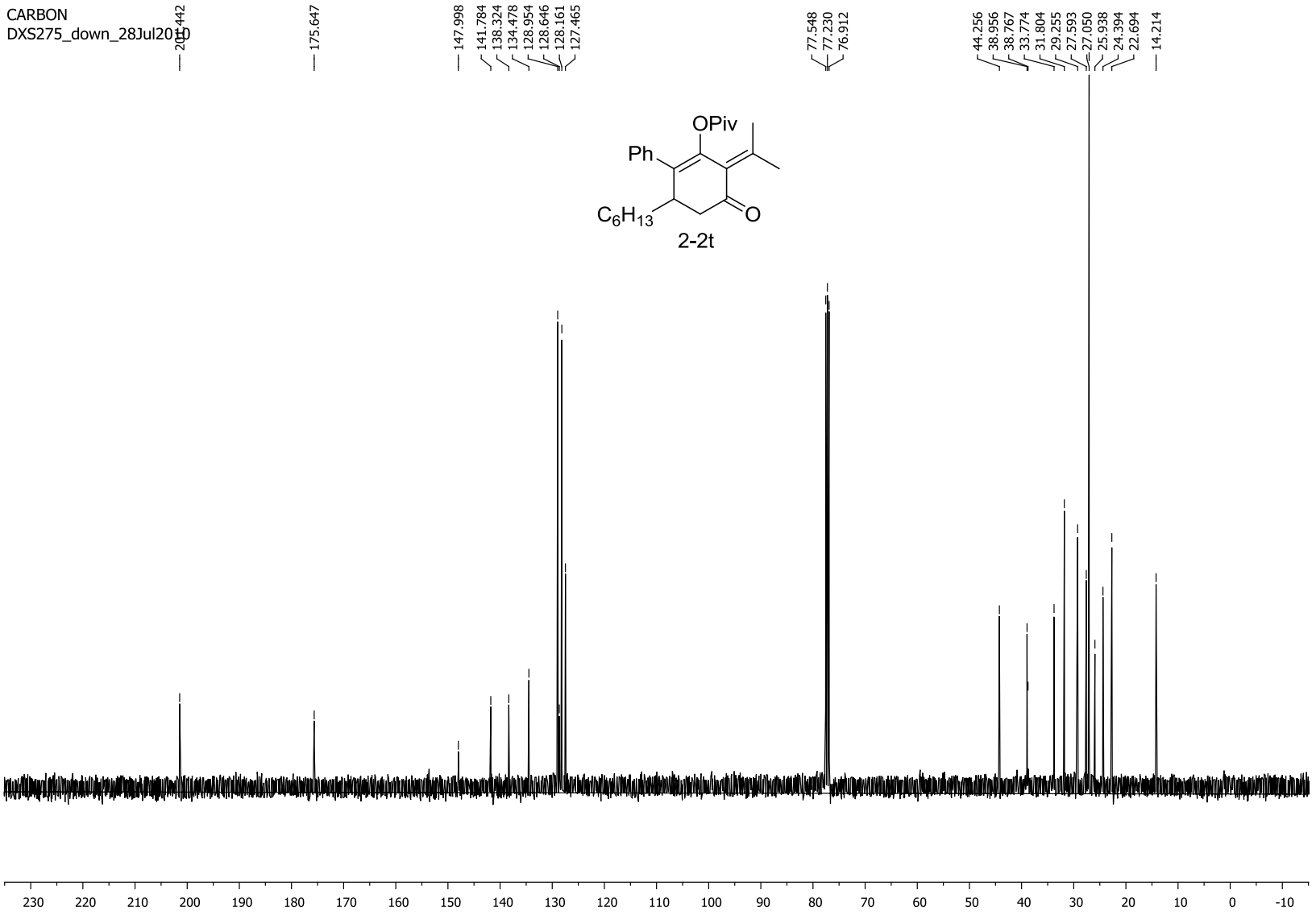
0
-10


OPiv
Ph
C_6H_{13}
O
2-2t
4.97
1.00
1.01
2.00
2.93
2.92
1.04
5.45
8.73
2.99
10
8
6
4
2
PPM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DXS275_down_28Jul2015
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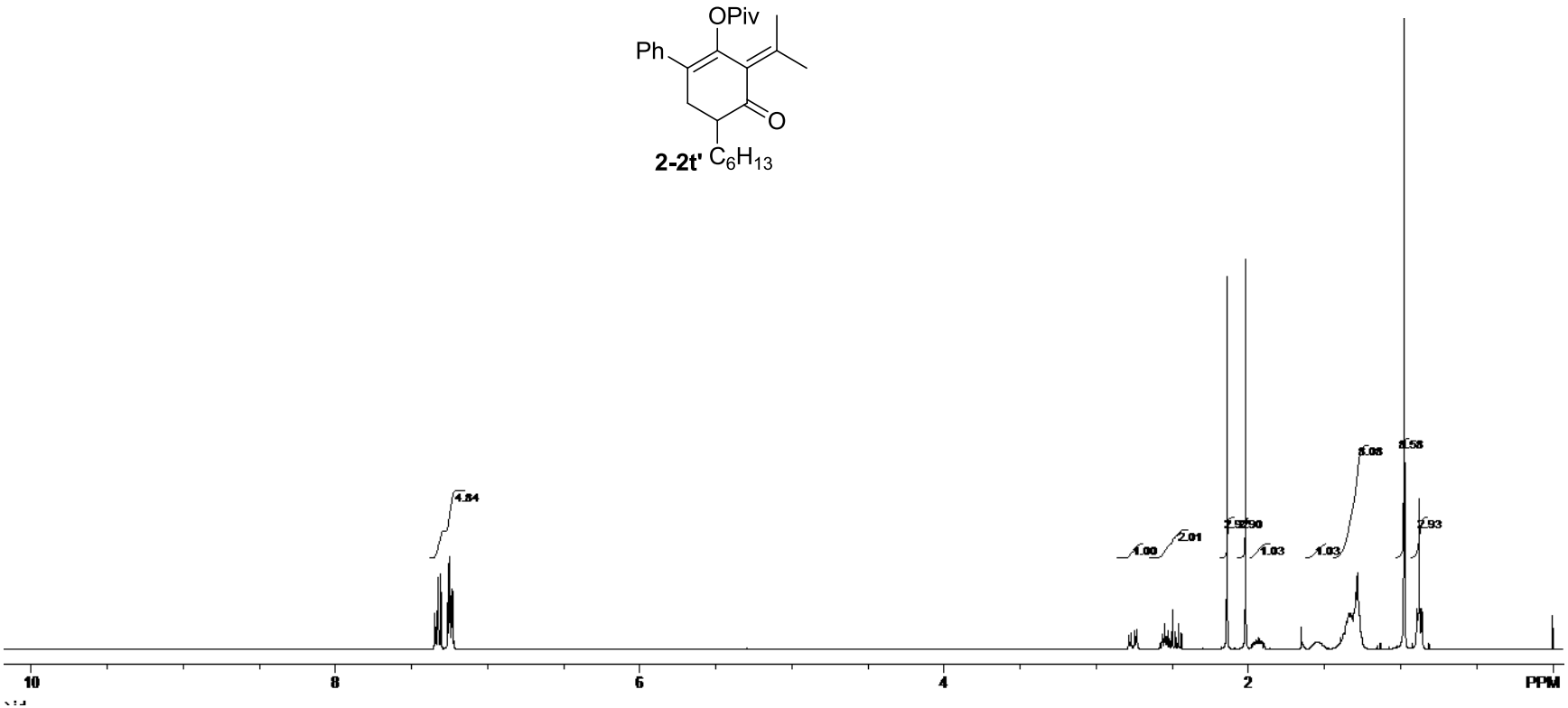
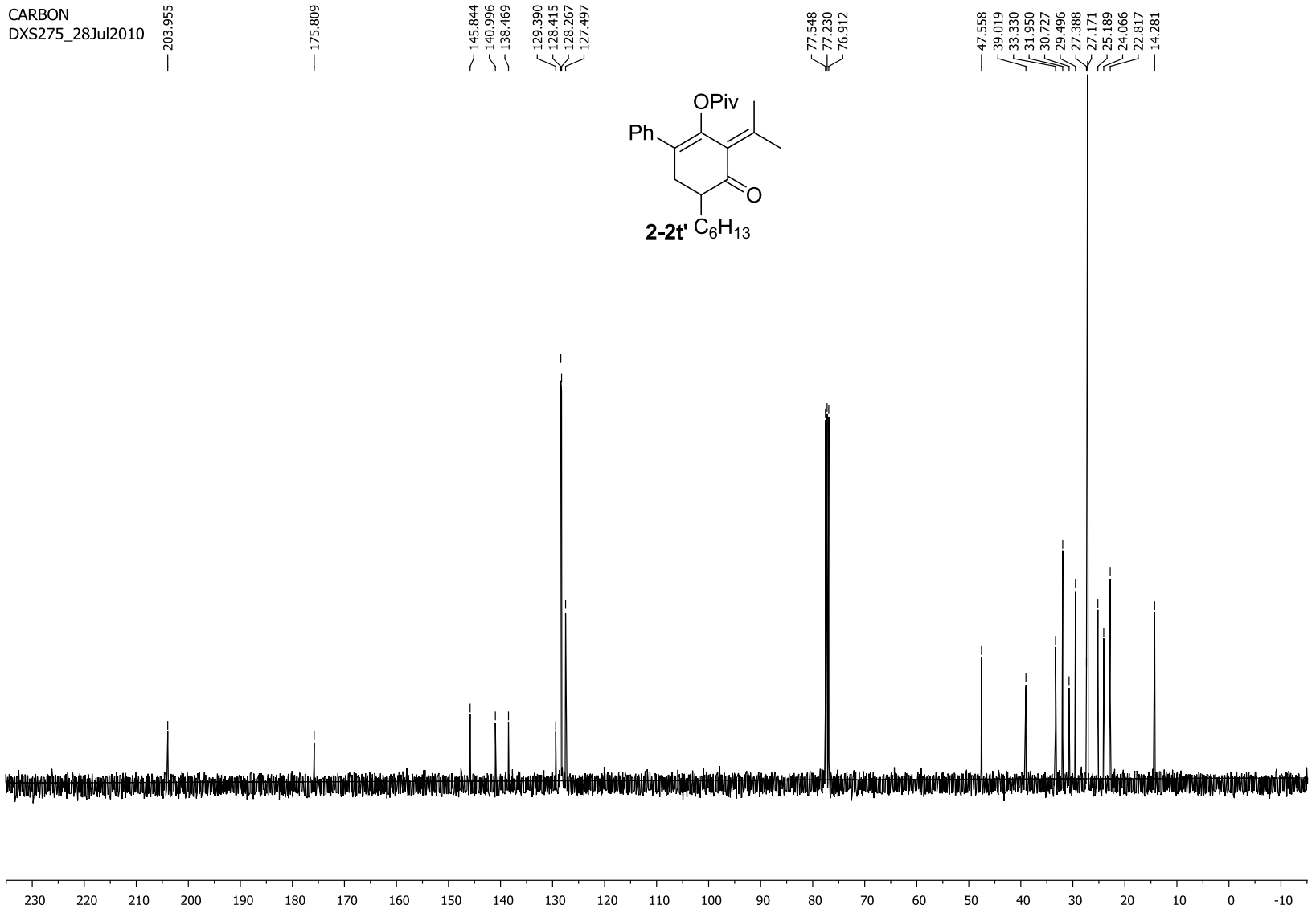
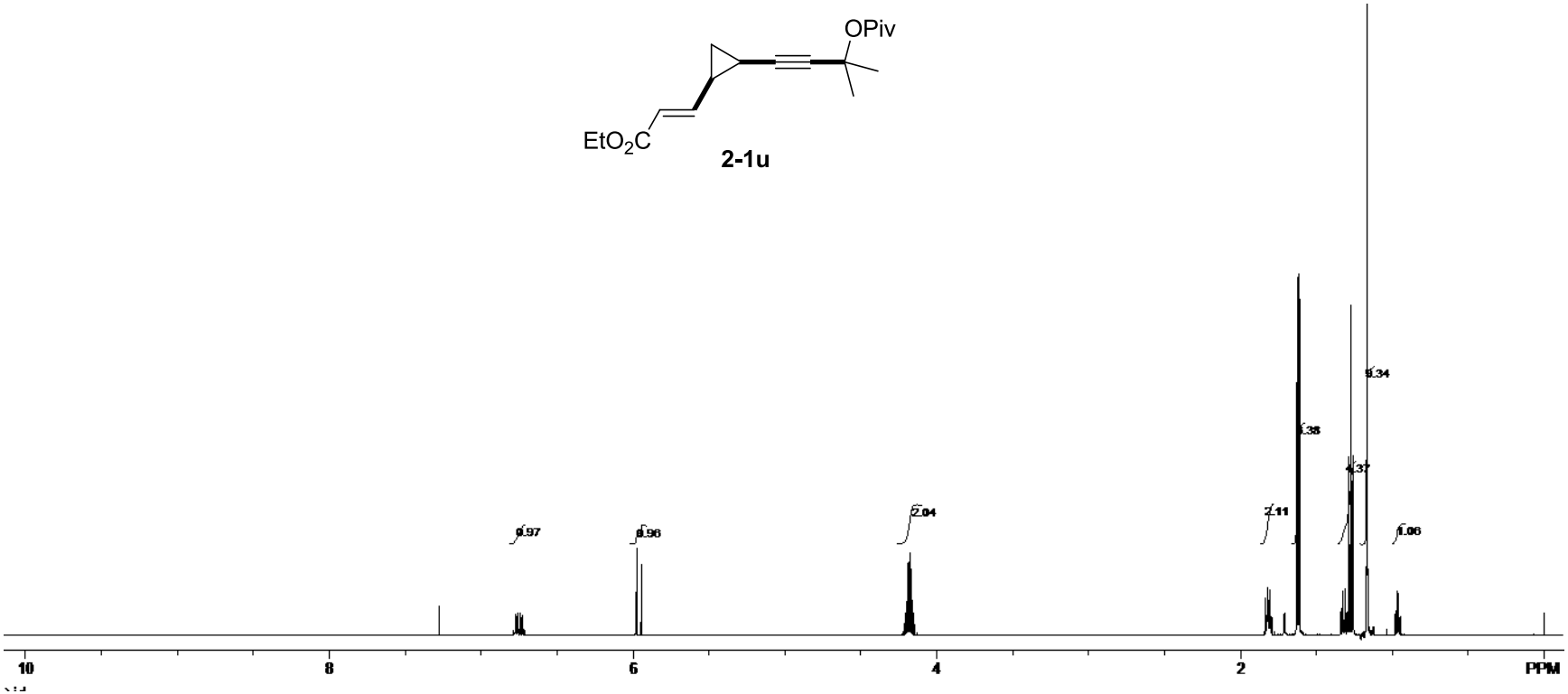
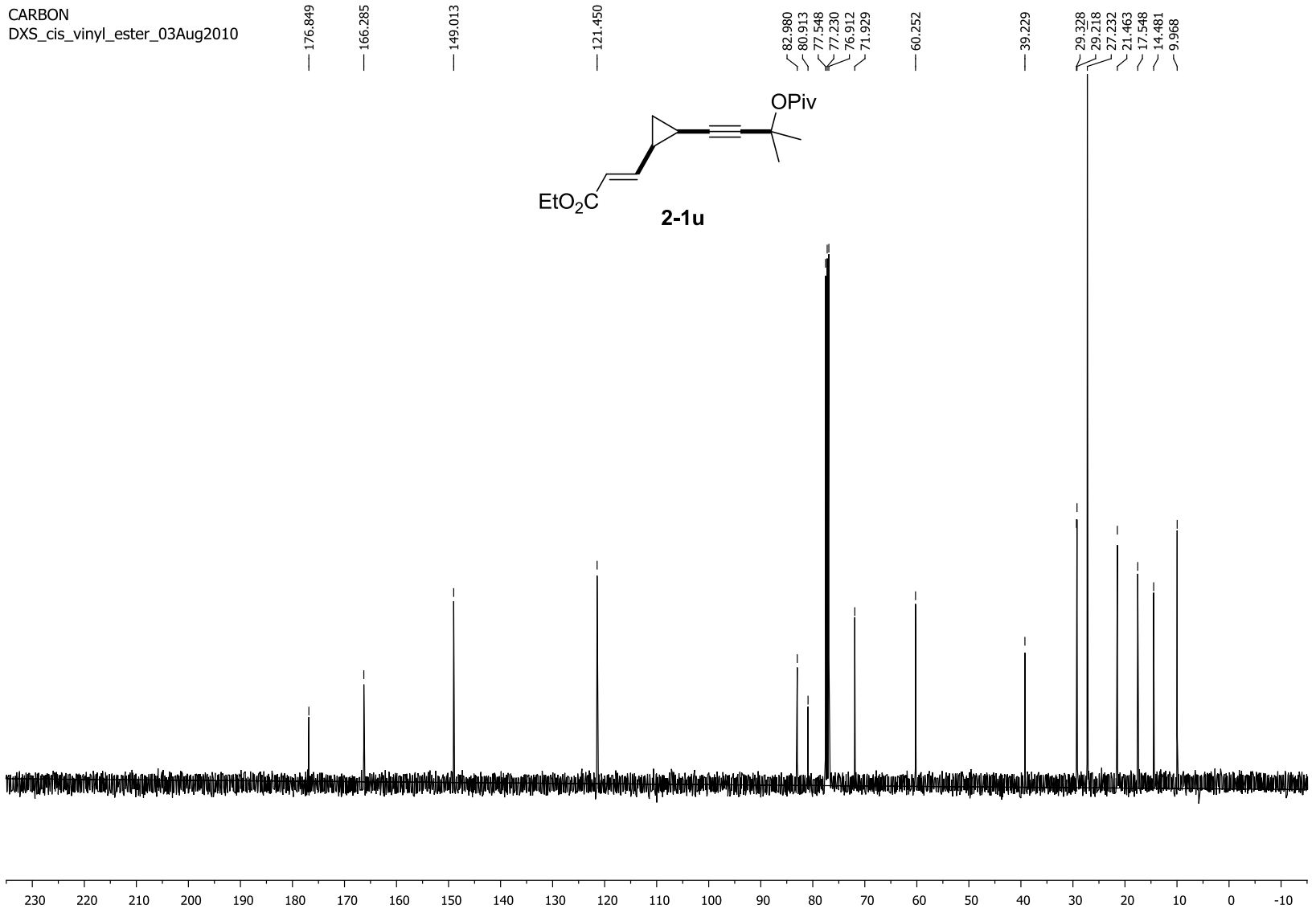
175.647
147.998
141.784
138.324
134.478
128.954
128.646
128.161
127.465
77.548
77.230
76.912
44.256
38.956
38.767
33.774
31.804
29.255
27.593
27.050
25.938
24.394
22.694
14.214
OPiv
Ph
C6H13
O
2-2t
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


OPiv
Ph
O
2-2t' C6H13
4.84
1.00
2.01
2.92
2.90
1.03
1.03
5.05
5.58
2.93
10
8
6
4
2
PPM


CARBON
DXS275_28Jul2010
203.955
175.809
145.844
140.996
138.469
129.390
128.415
128.267
127.497
77.548
77.230
76.912
47.558
39.019
33.330
31.950
30.727
29.496
27.388
27.171
25.189
24.066
22.817
14.281
OPiv
Ph
O
2-2t' C6H13
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


OPiv
EtO2C
2-1u
0.97
0.96
2.04
2.11
3.38
4.37
5.34
1.06
10
8
6
4
2
PPM


CARBON
DXS_cis_vinyl_ester_03Aug2010
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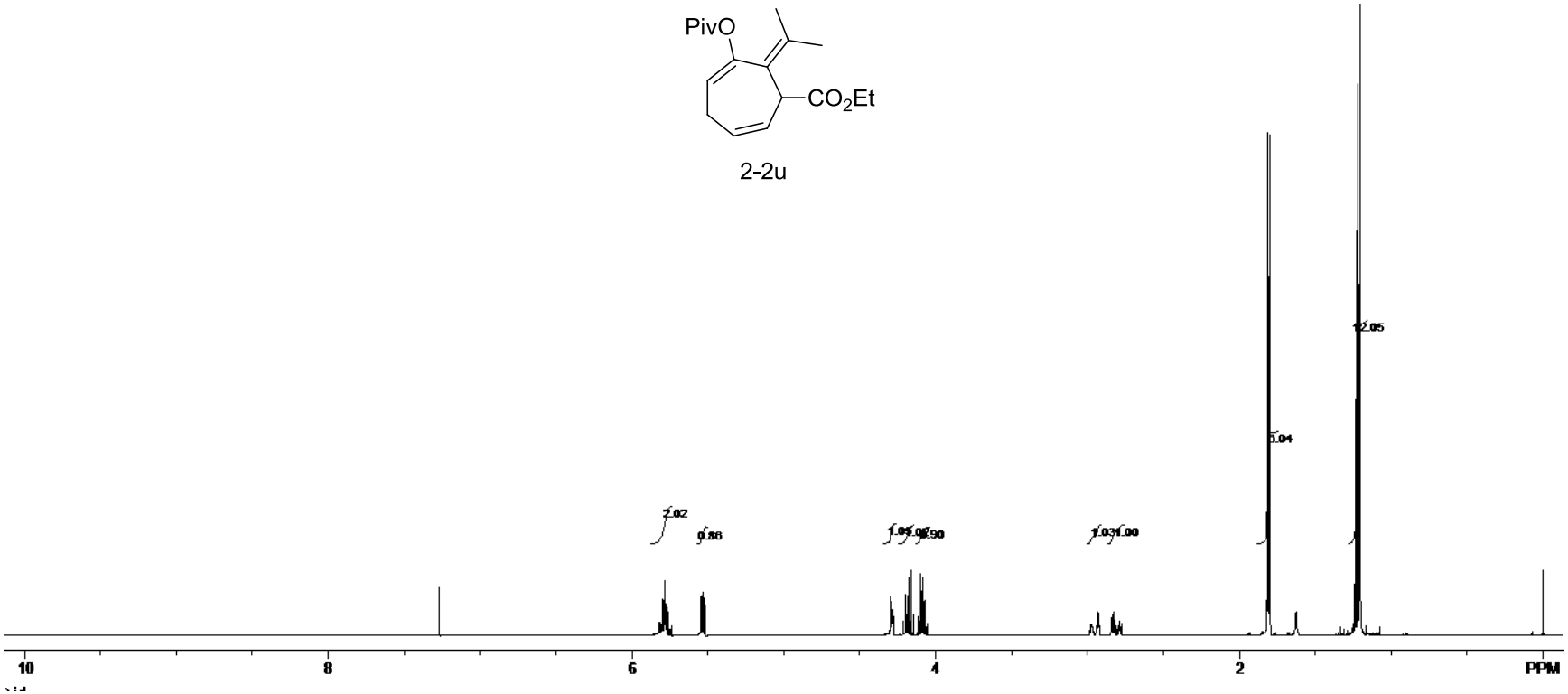
166.285
149.013
121.450
82.980
80.913
77.548
77.230
76.912
71.929
60.252
39.229
29.328
29.218
27.232
21.463
17.548
14.481
9.968
OPiv
EtO2C
2-1u
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


PivO
CO2Et
2-2u
2.02
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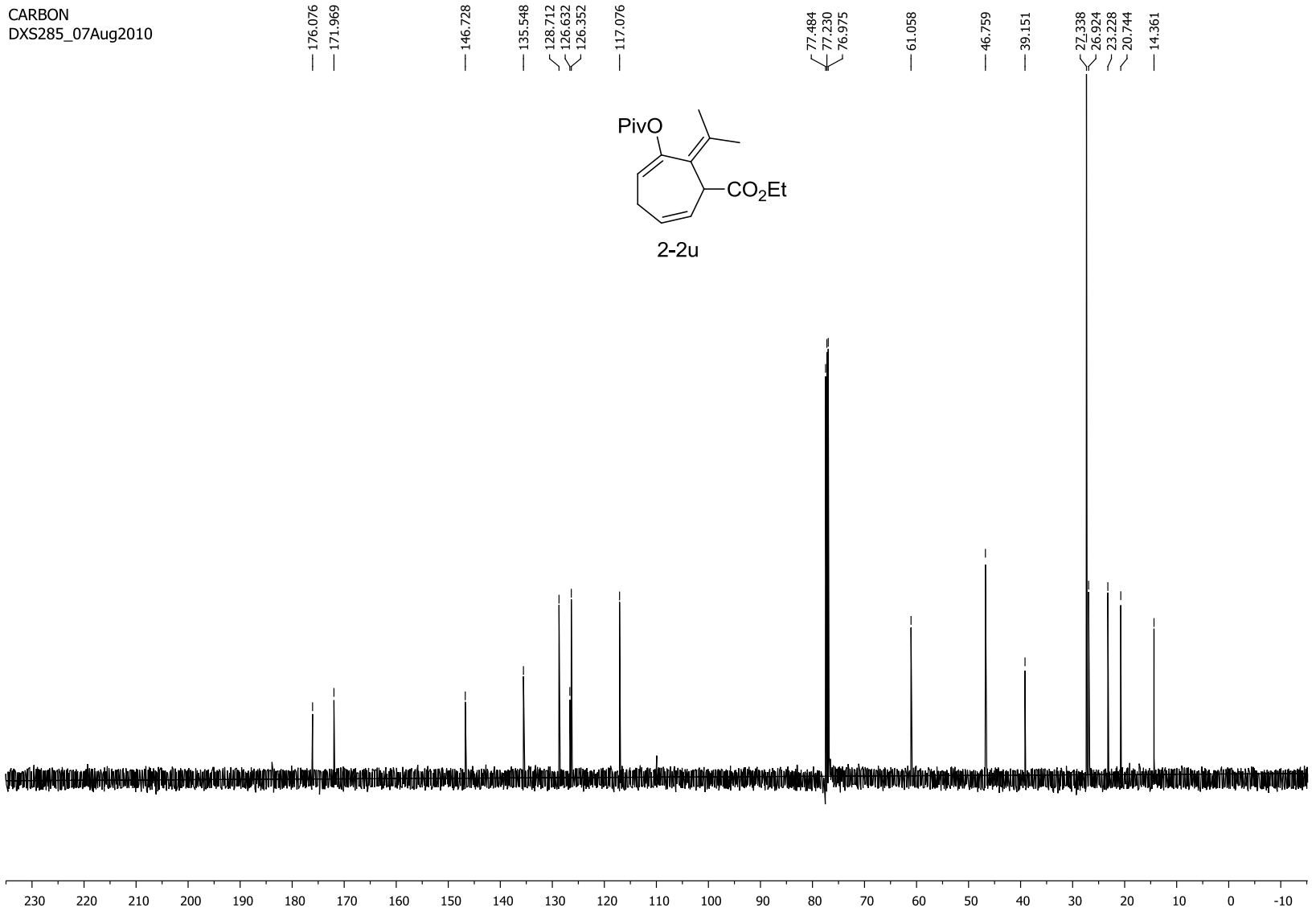
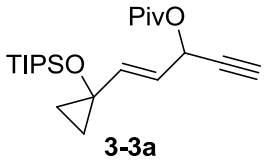
1.00
6.04
12.05
10
8
6
4
2
PPM

CARBON
DXS285_07Aug2010



Chapter III NMR Spectrum



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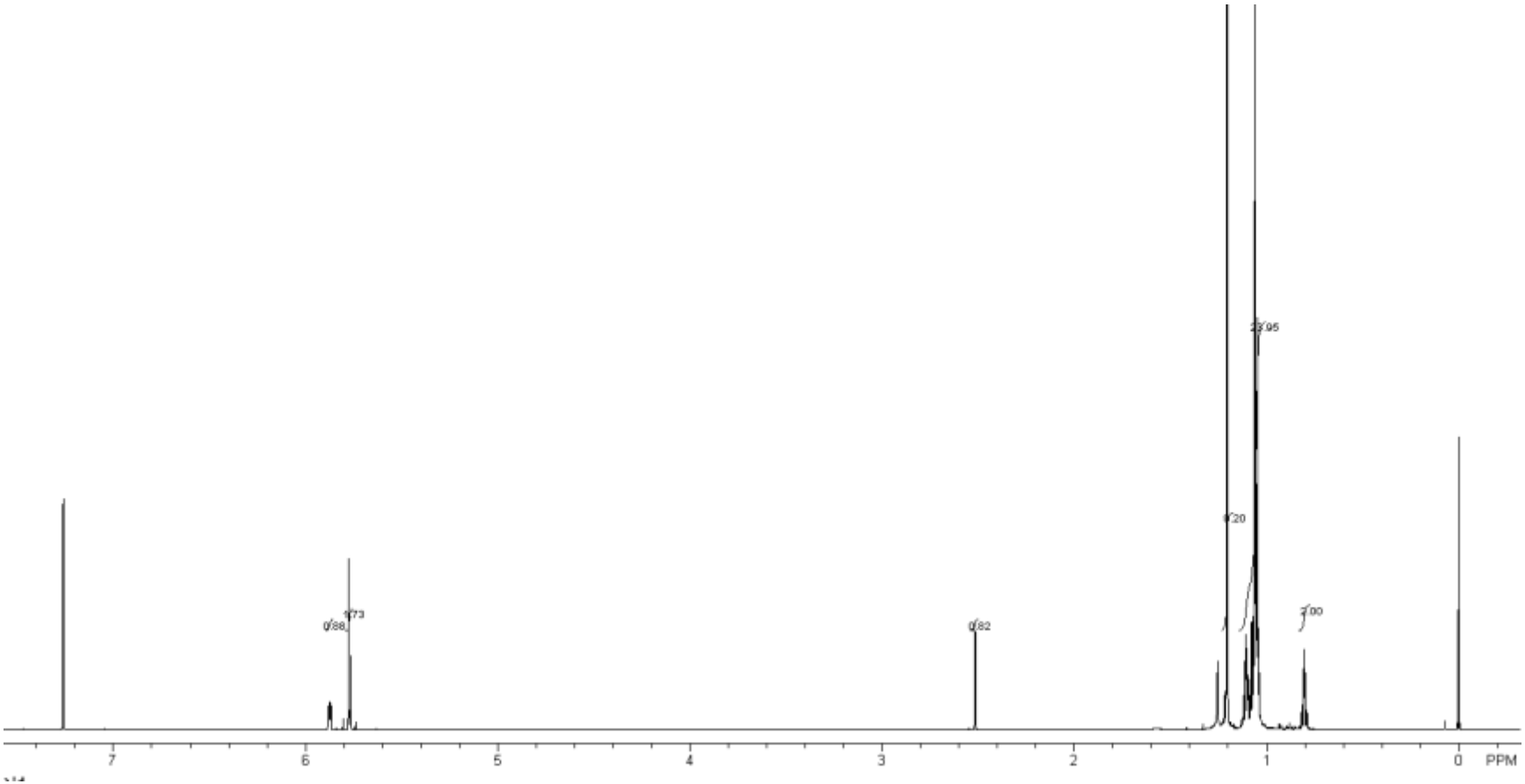
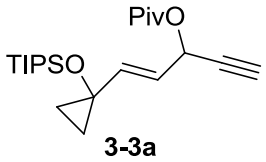
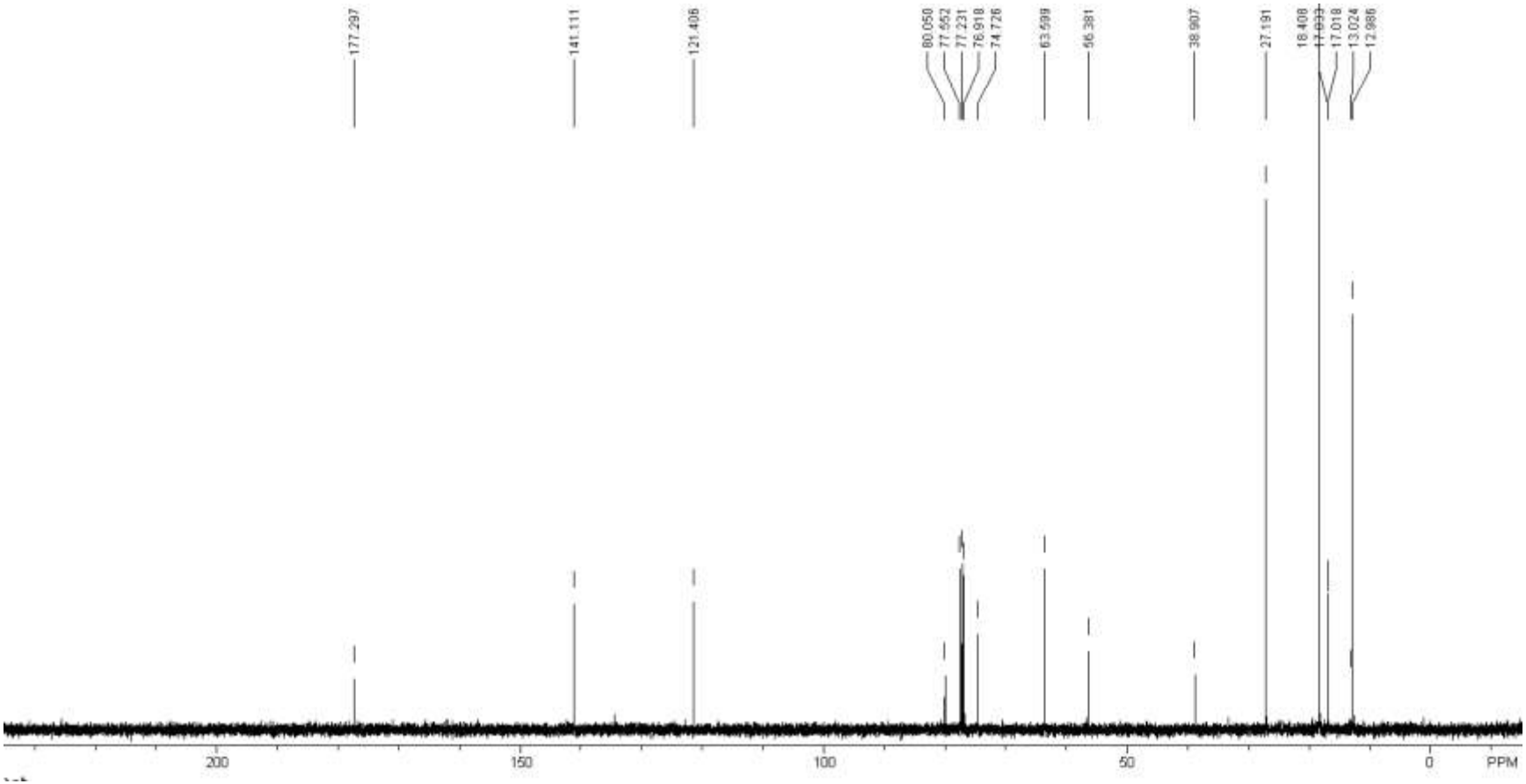



PivO
TIPSO

3-3a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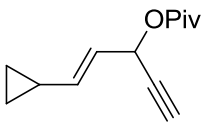
141.111
121.406
80.050
77.552
77.231
76.918
74.726
63.599
56.381
38.907
27.191
18.408
17.018
13.024
12.986
200
150
100
50
0
PPM



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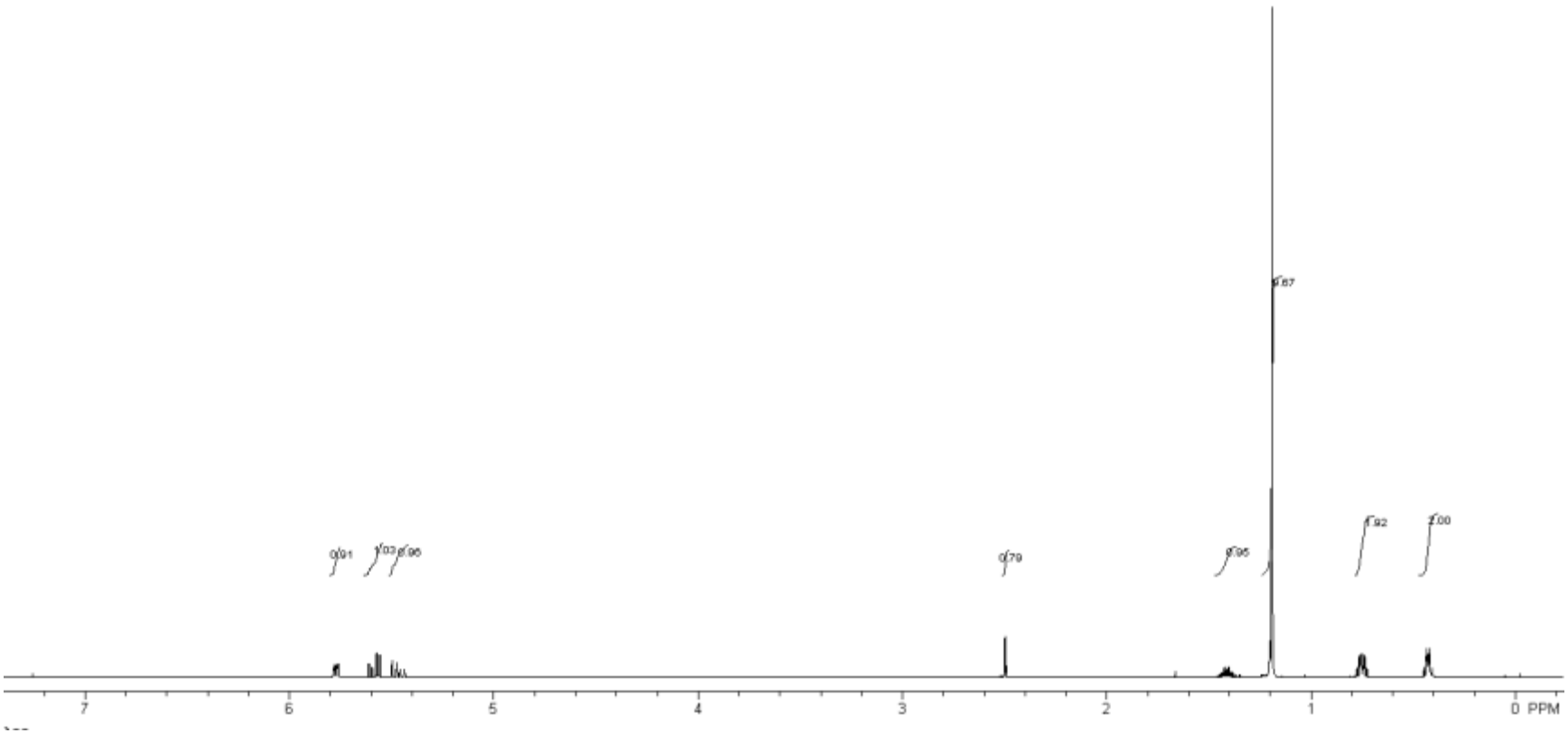
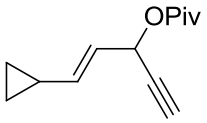
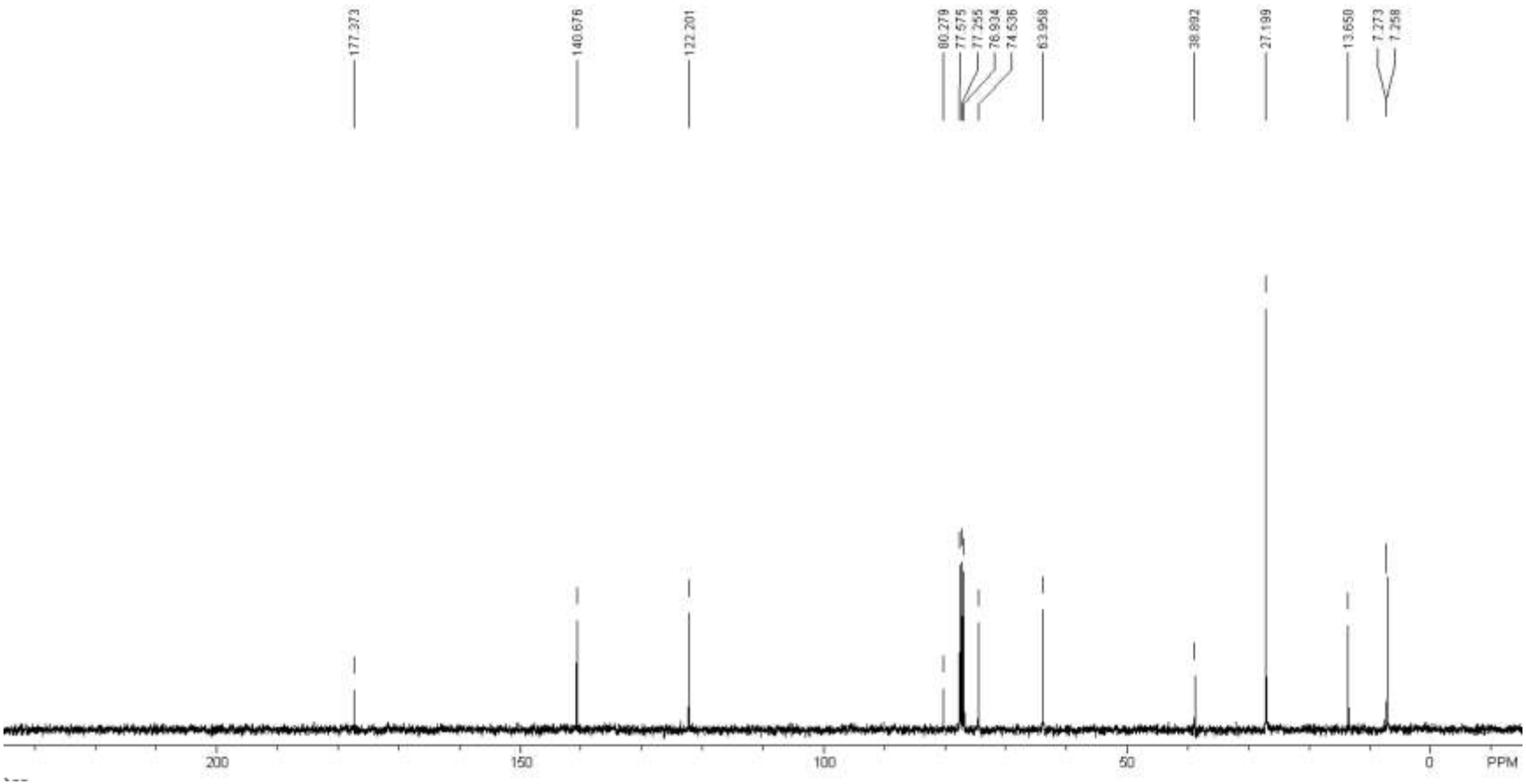



OPiv

3-3b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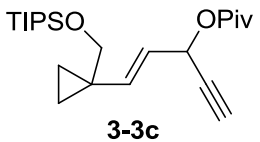
140.676
122.201
80.279
77.575
77.255
76.934
74.536
63.958
38.892
27.199
13.650
7.273
7.258
200
150
100
50
0
PPM



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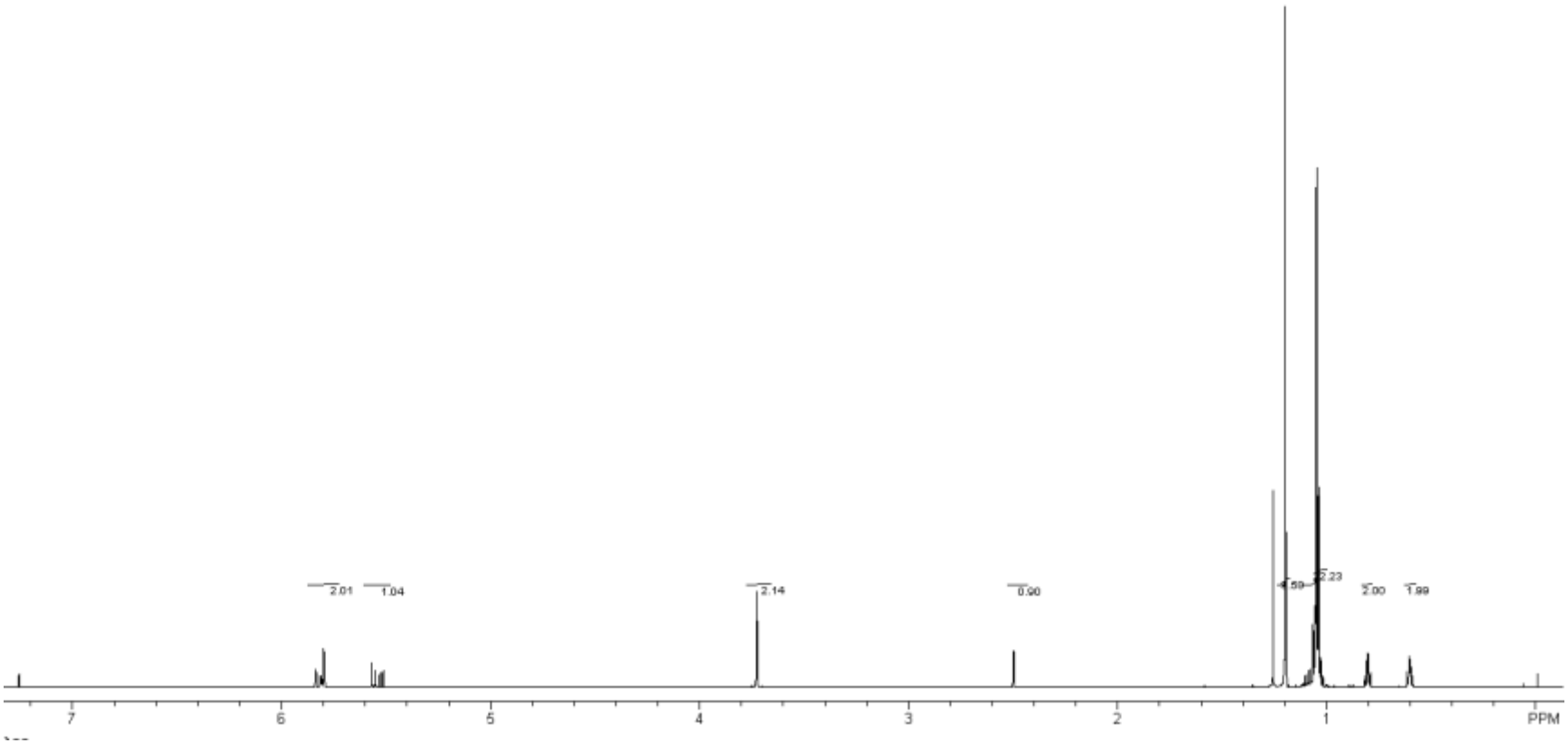
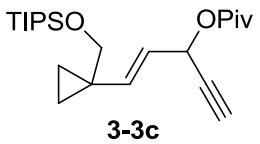
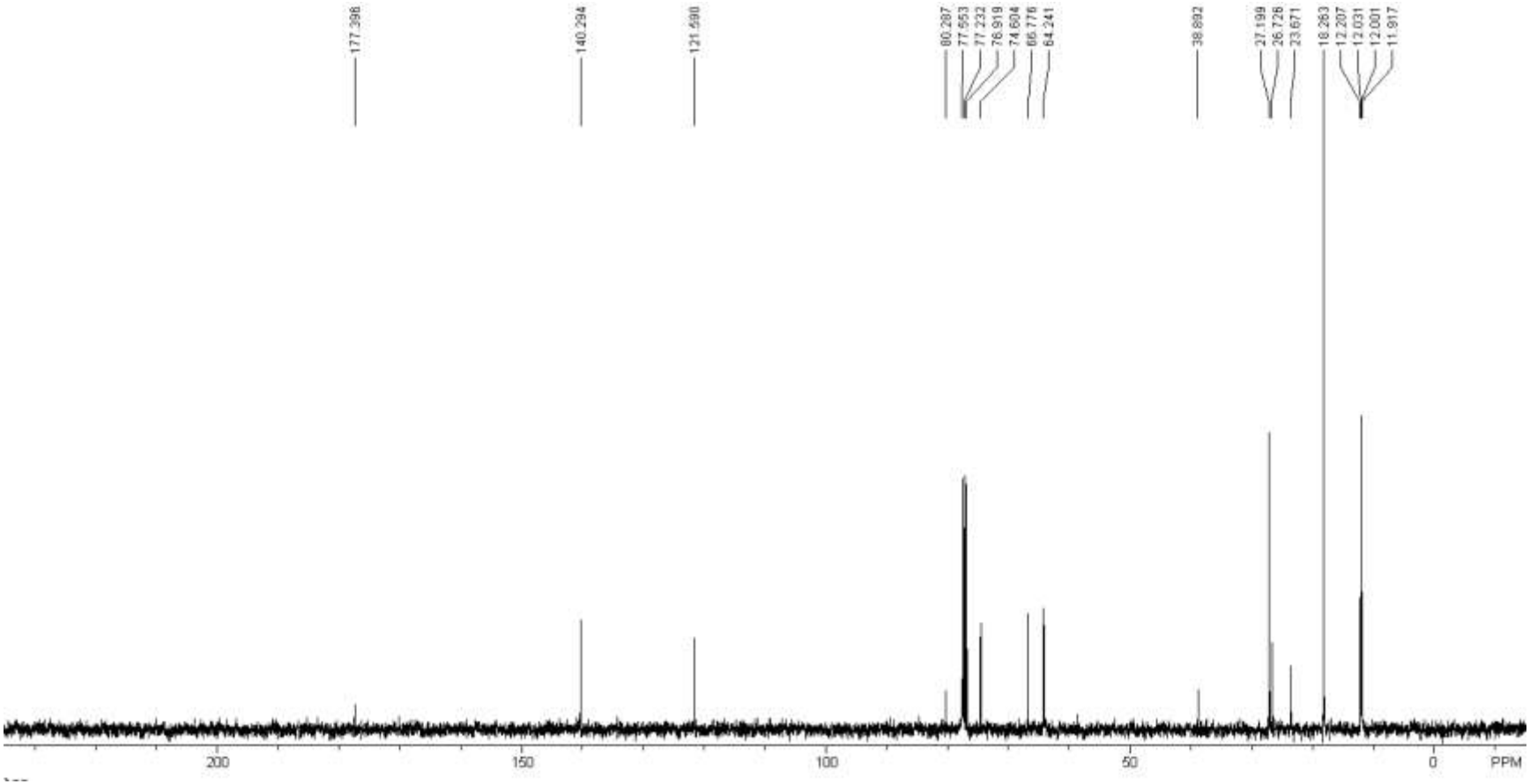



TIPSO
OPiv

3-3c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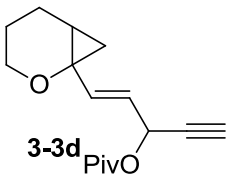
80.287
77.553
77.232
76.919
74.604
66.776
64.241
38.892
27.199
26.726
23.671
18.263
12.207
12.031
12.001
11.917
200
150
100
50
0
PPM



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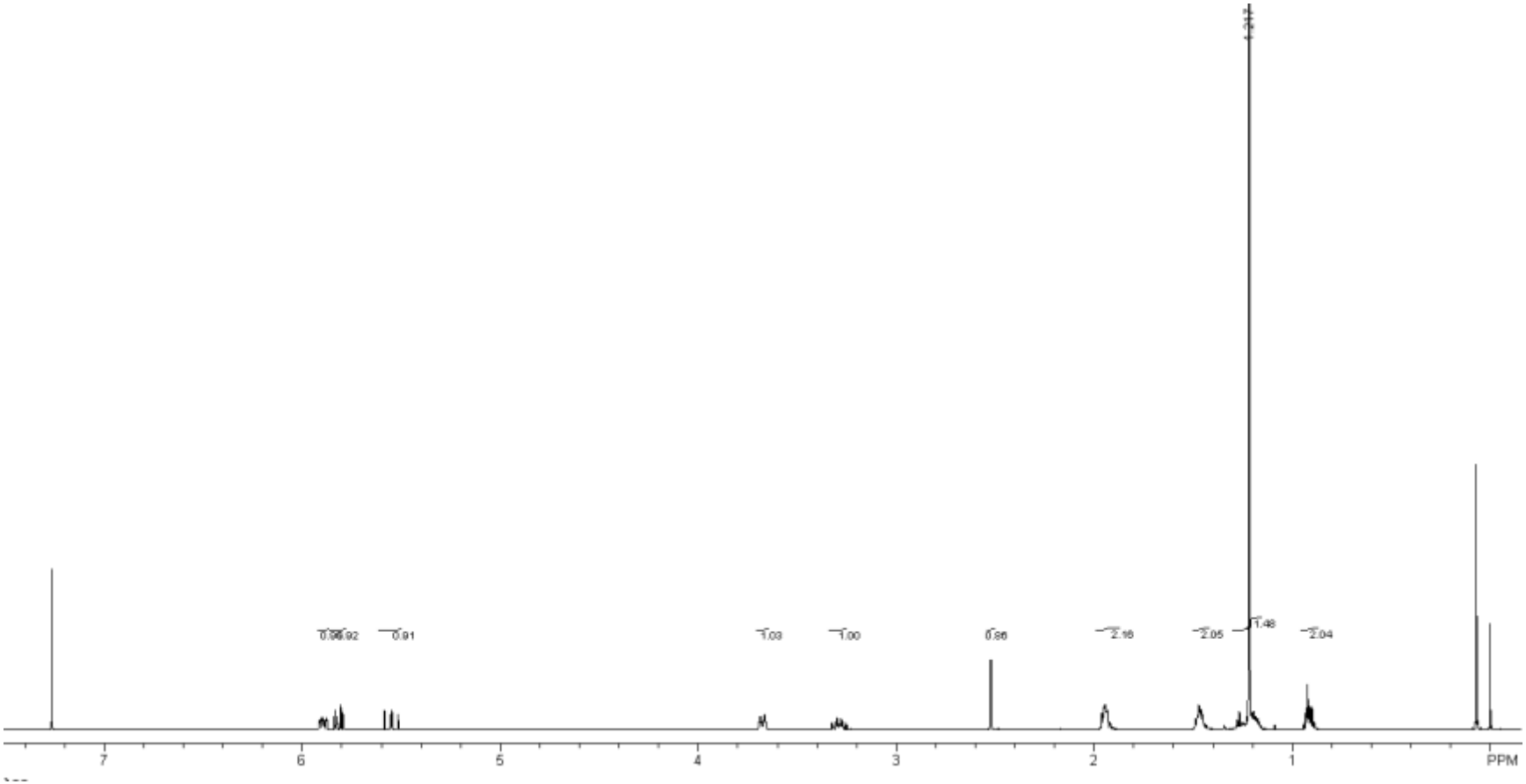
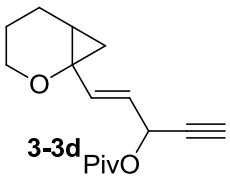
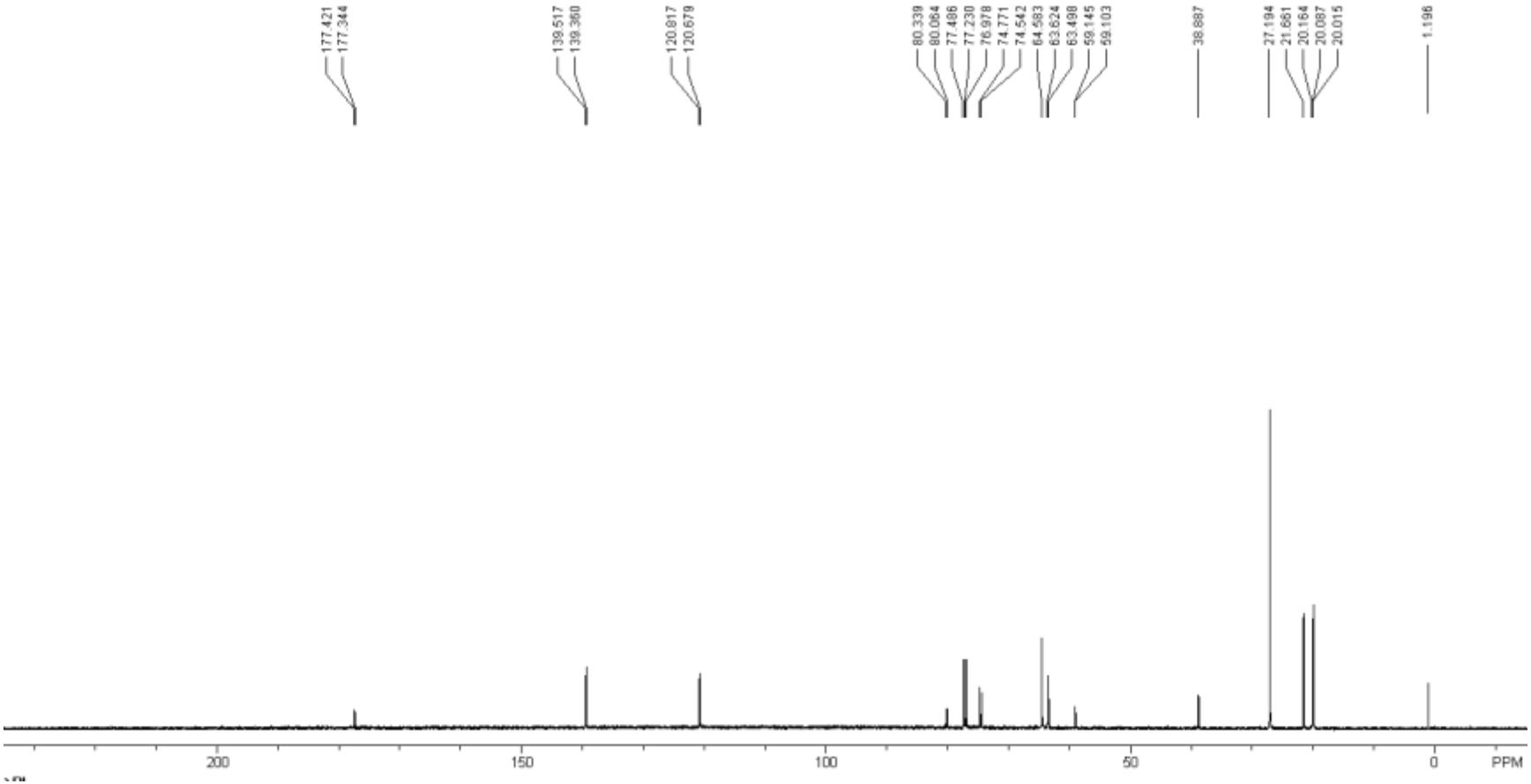



O
3-3d
PivO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177.344
139.517
139.360
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120.679
80.339
80.064
77.486
77.230
76.978
74.771
74.542
64.583
63.624
63.498
59.145
59.103
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27.194
21.661
20.164
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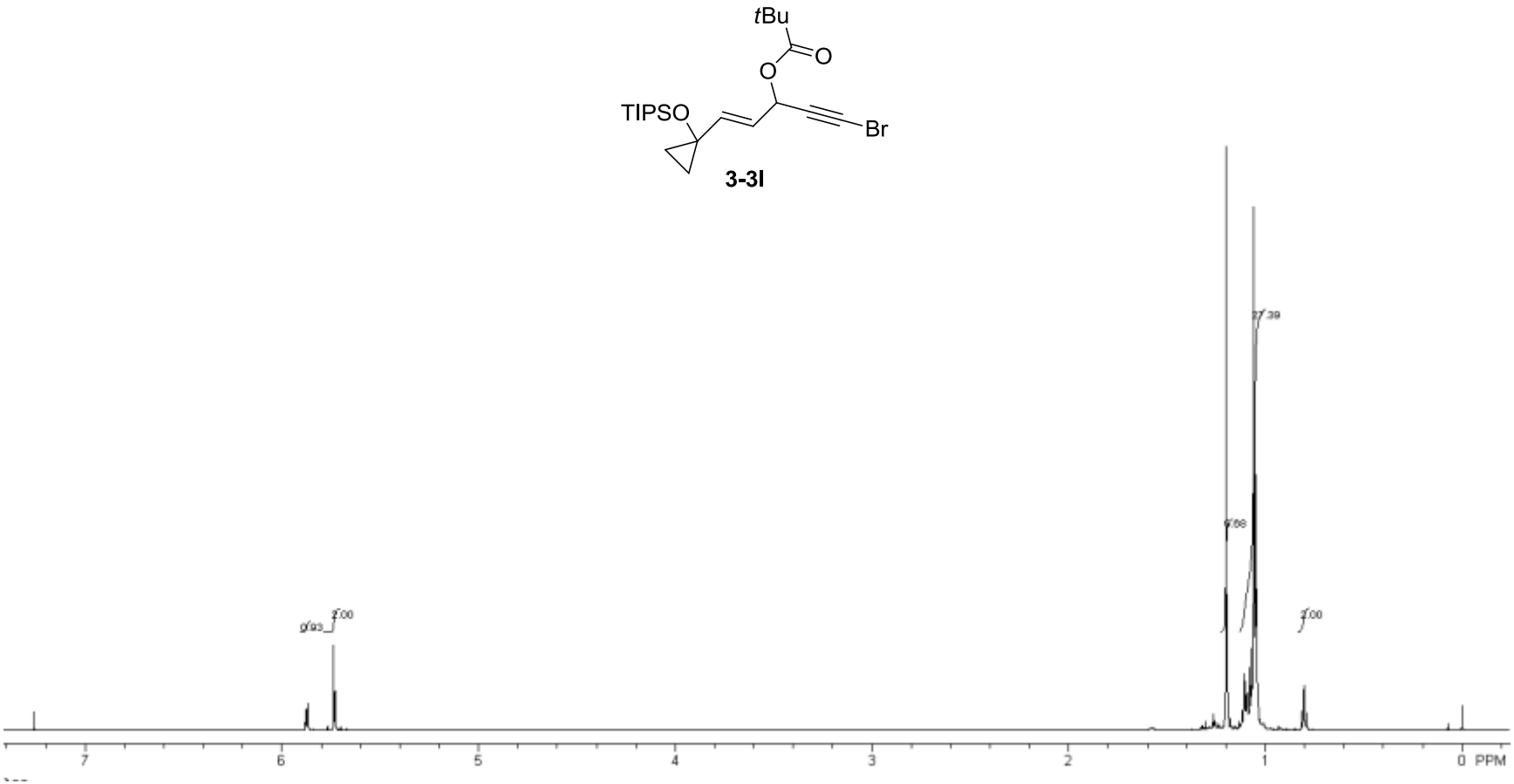
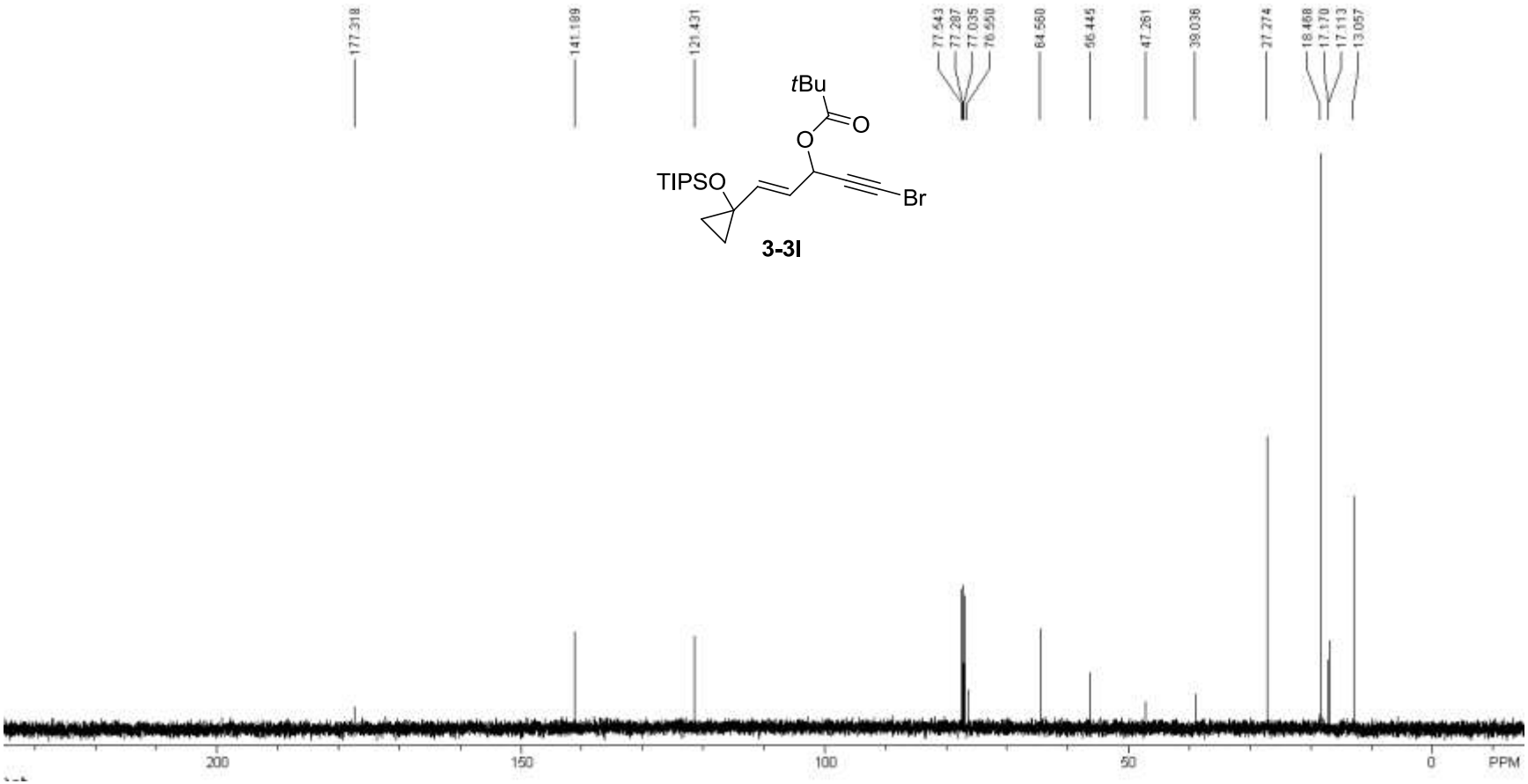
20.015
1.196
200
150
100
50
0
PPM


tBu
O
O
TIPSO
Br
3-3l
9.08
7.39
2.00
0.93
2.00
7
6
5
4
3
2
1
0 PPM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141.189
121.431
77.543
77.287
77.035
76.550
64.560
56.445
47.261
39.036
27.274
18.458
17.170
17.113
13.057
tBu
O
O
TIPSO
Br
3-3l
200
150
100
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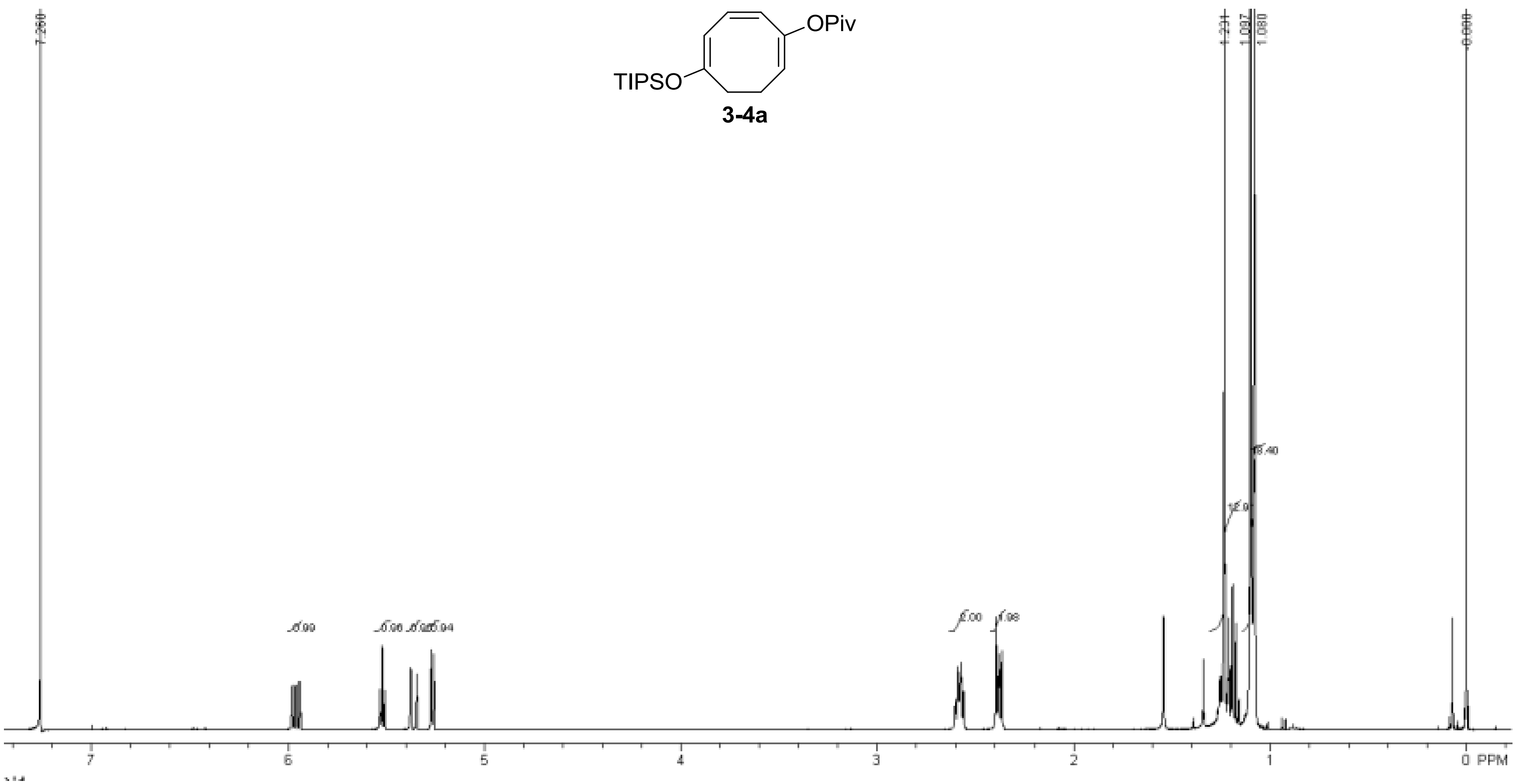
0
PPM


TIPSO
OPiv
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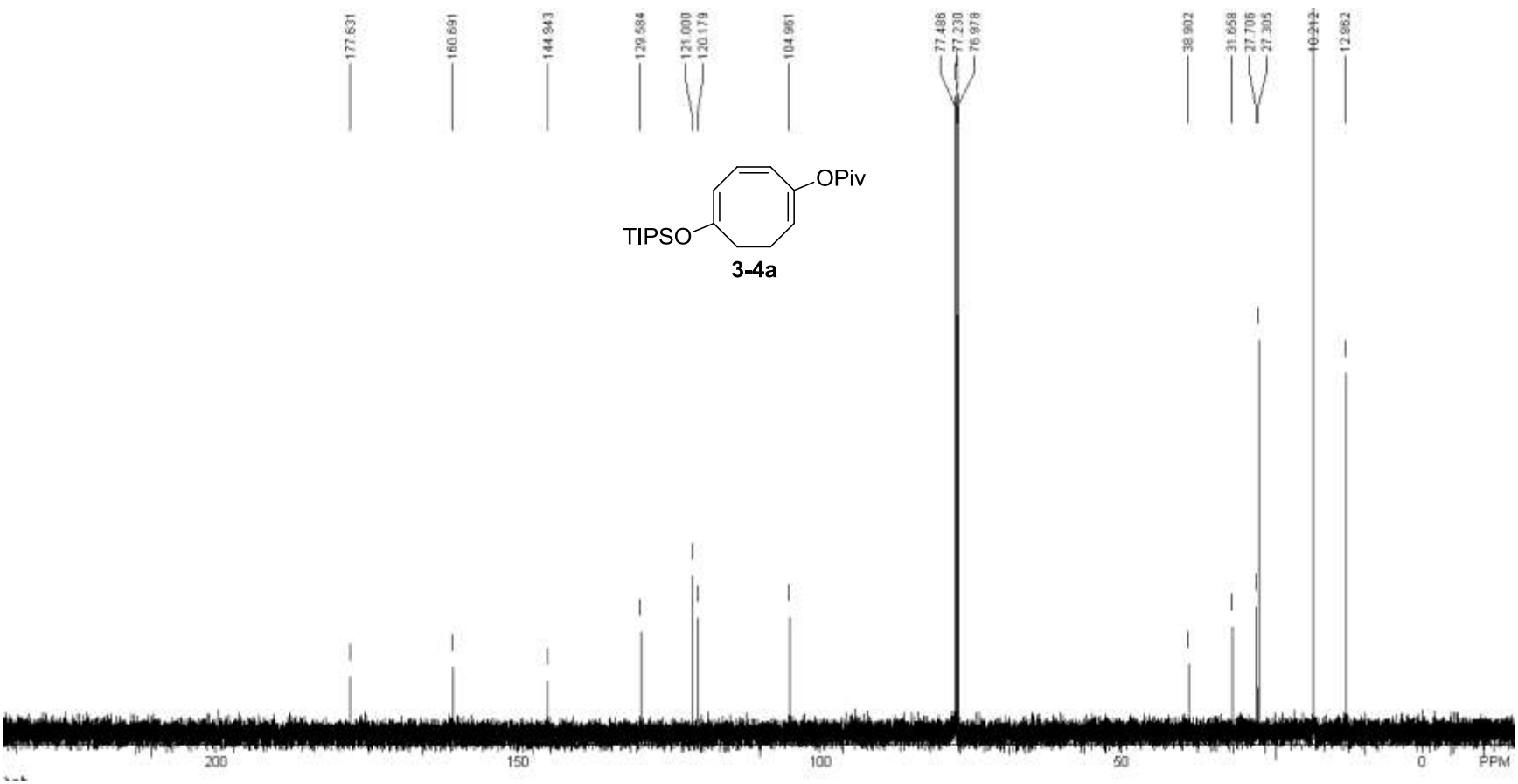
1.080
0.000
2.00
1.98
18.40
7
6
5
4
3
2
1
0 PPM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129.584
121.000
120.179
104.961
77.486
77.230
76.978
38.902
31.658
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27.305
19.212
12.862
OPiv
TIPSO
3-4a
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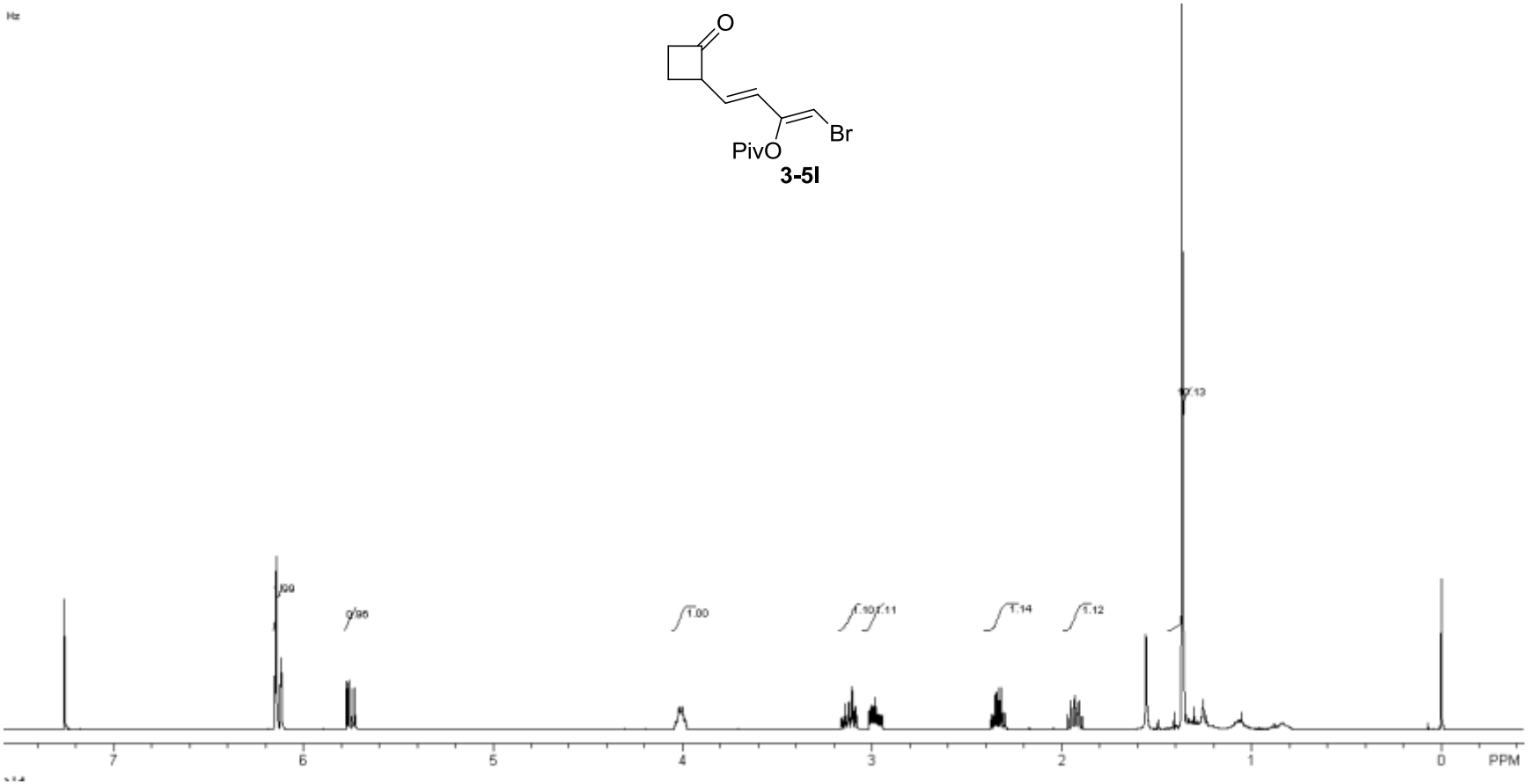
150
100
50
0
PPM


O
Br
PivO
3-5l
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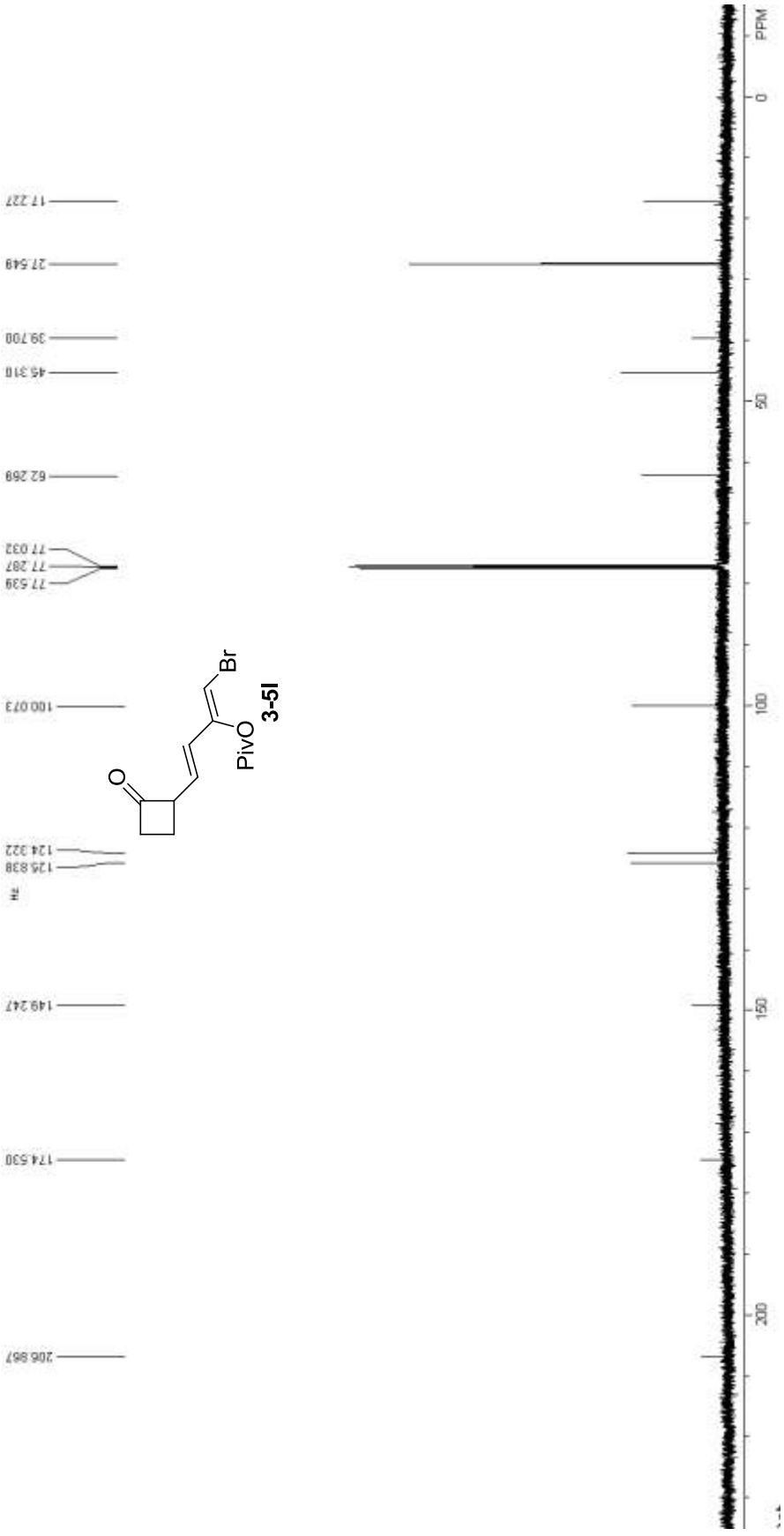
1.00
1.10
1.11
1.14
1.12
9.13
7
6
5
4
3
2
1
0
PPM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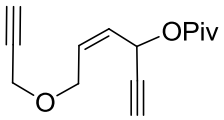
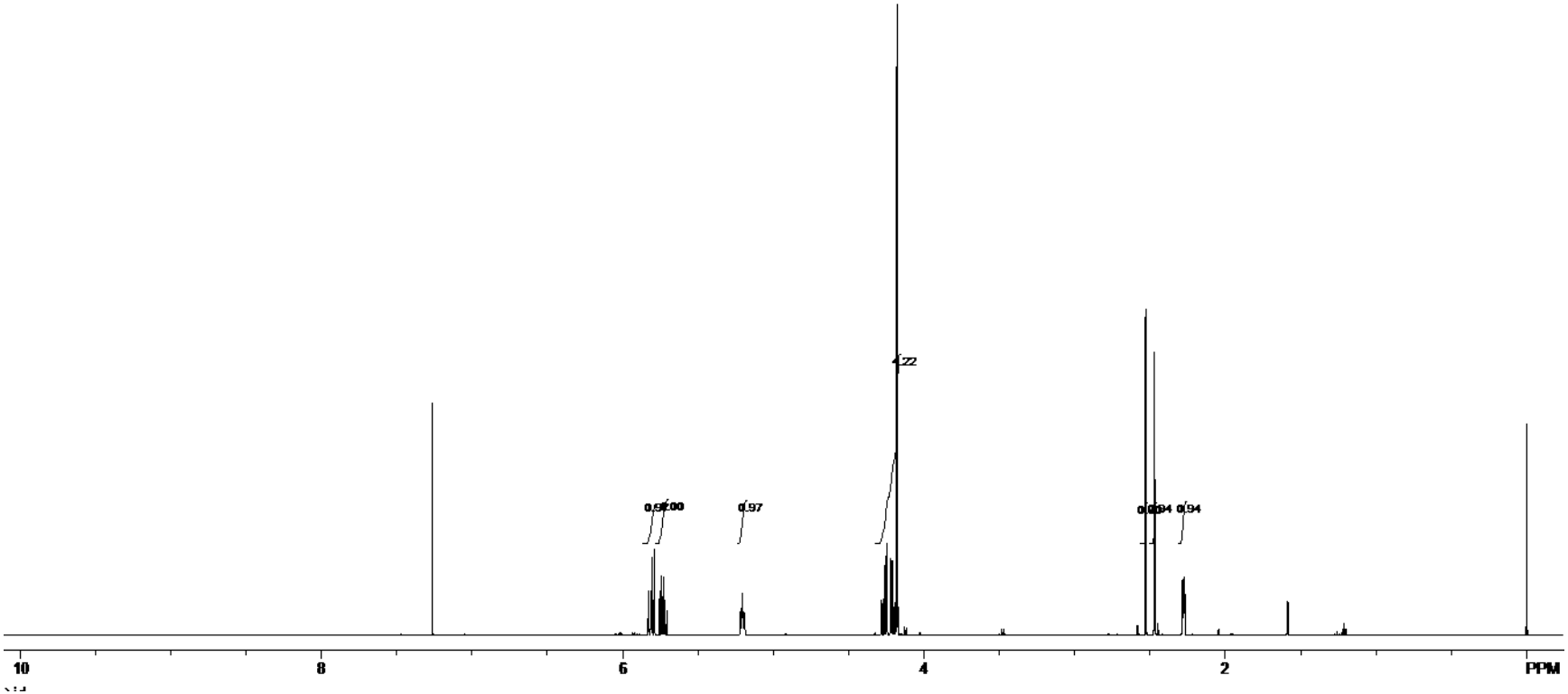
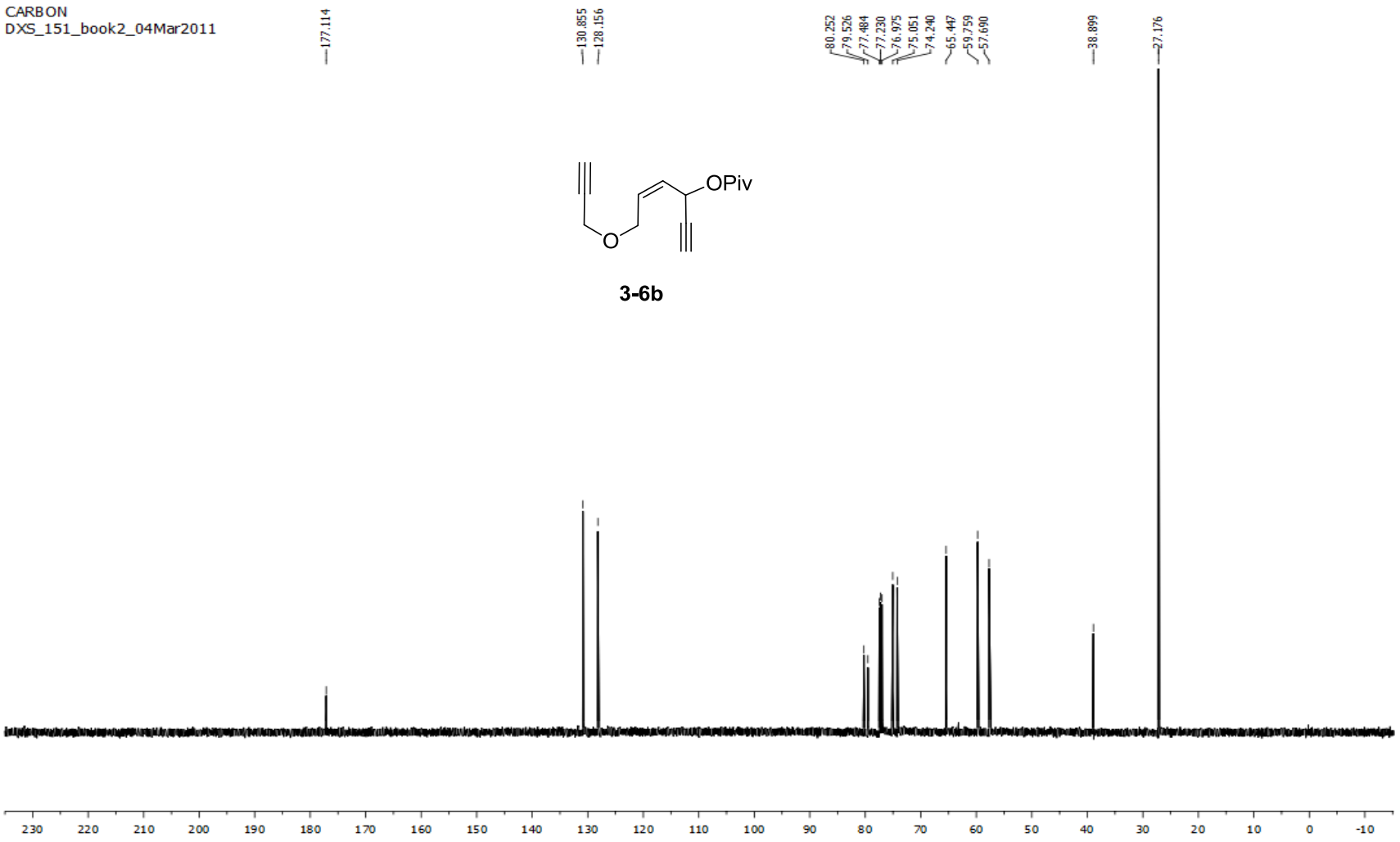
39.700
45.310
62.269
77.032
77.287
77.539
100.073
124.322
125.838
149.247
174.530
206.867
PPM
0
50
100
150
200
Br
PivO
O
3-5l

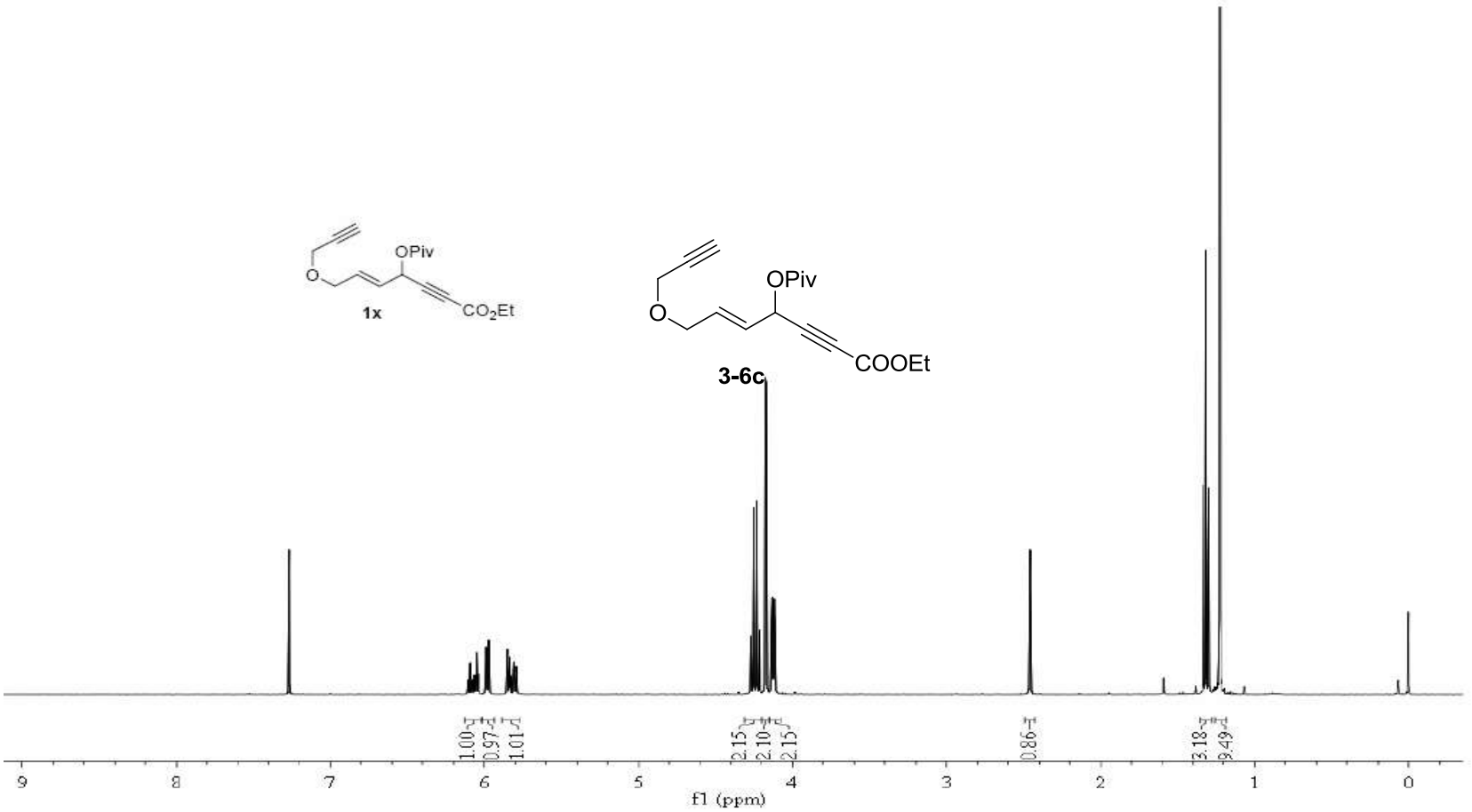


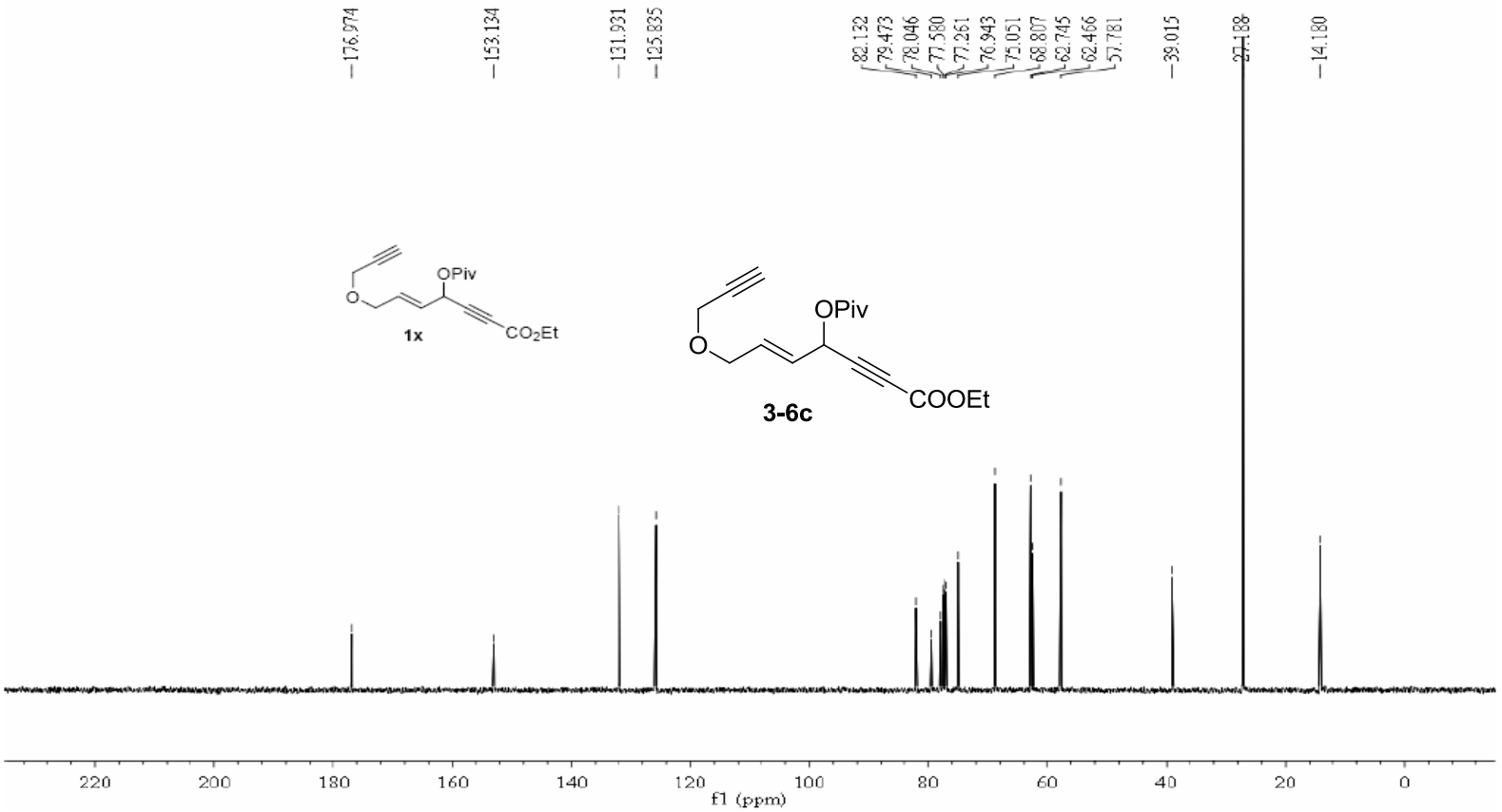
3-6b

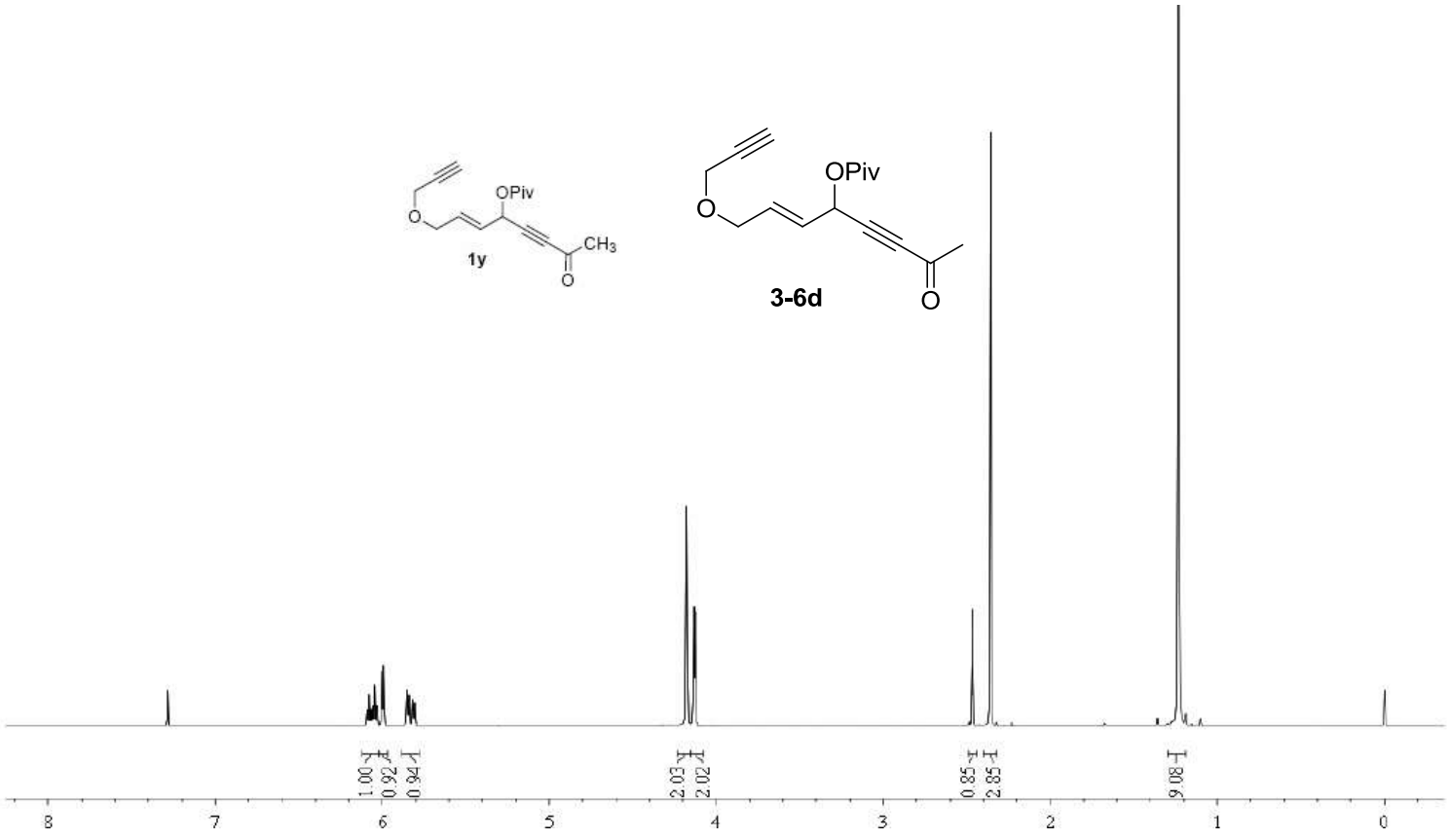


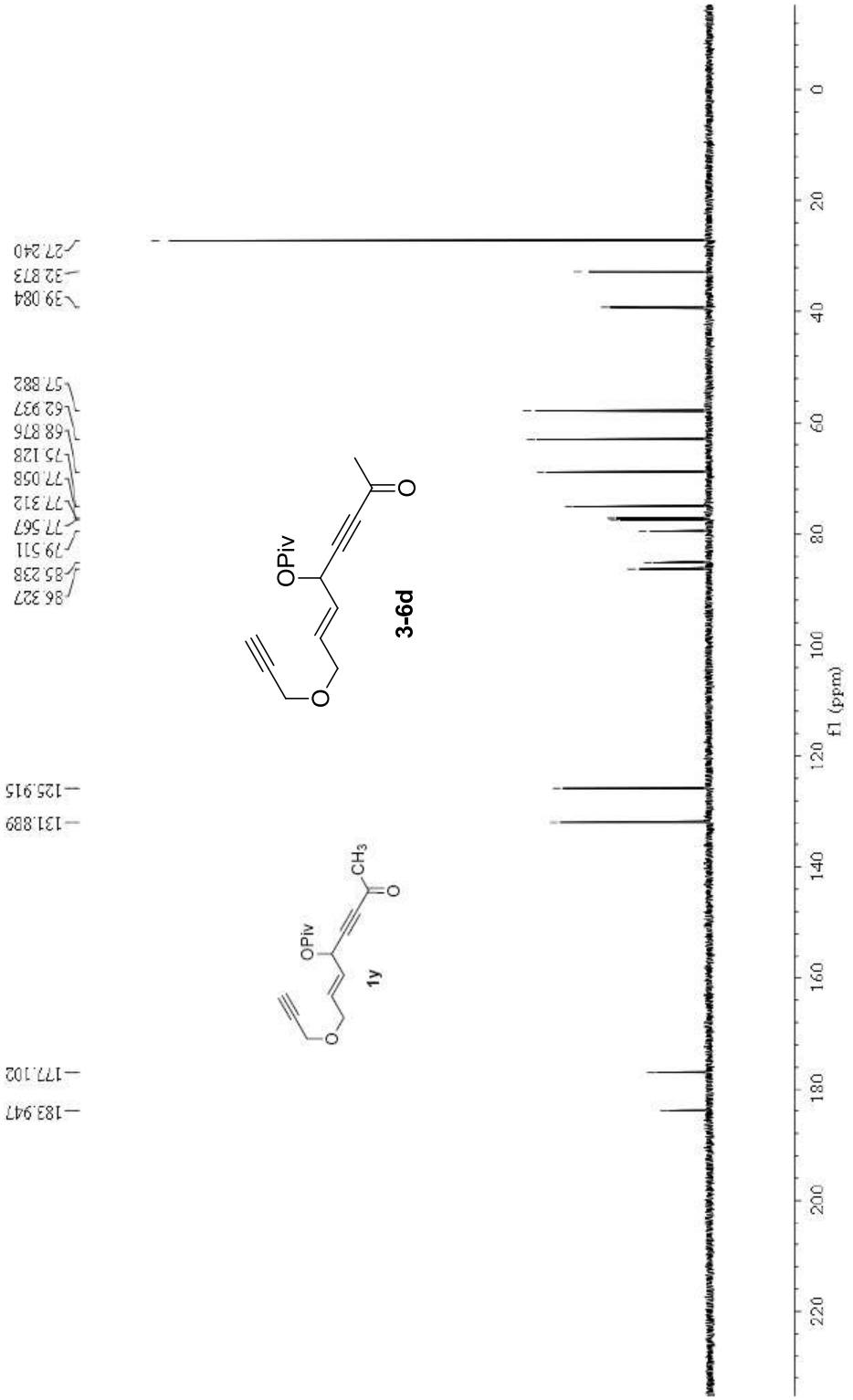

CARBON
DXS_151_book2_04Mar2011
177.114
130.855
128.156
80.252
79.526
77.484
77.230
76.975
75.051
74.240
65.447
59.759
57.690
38.899
27.176
OPiv
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

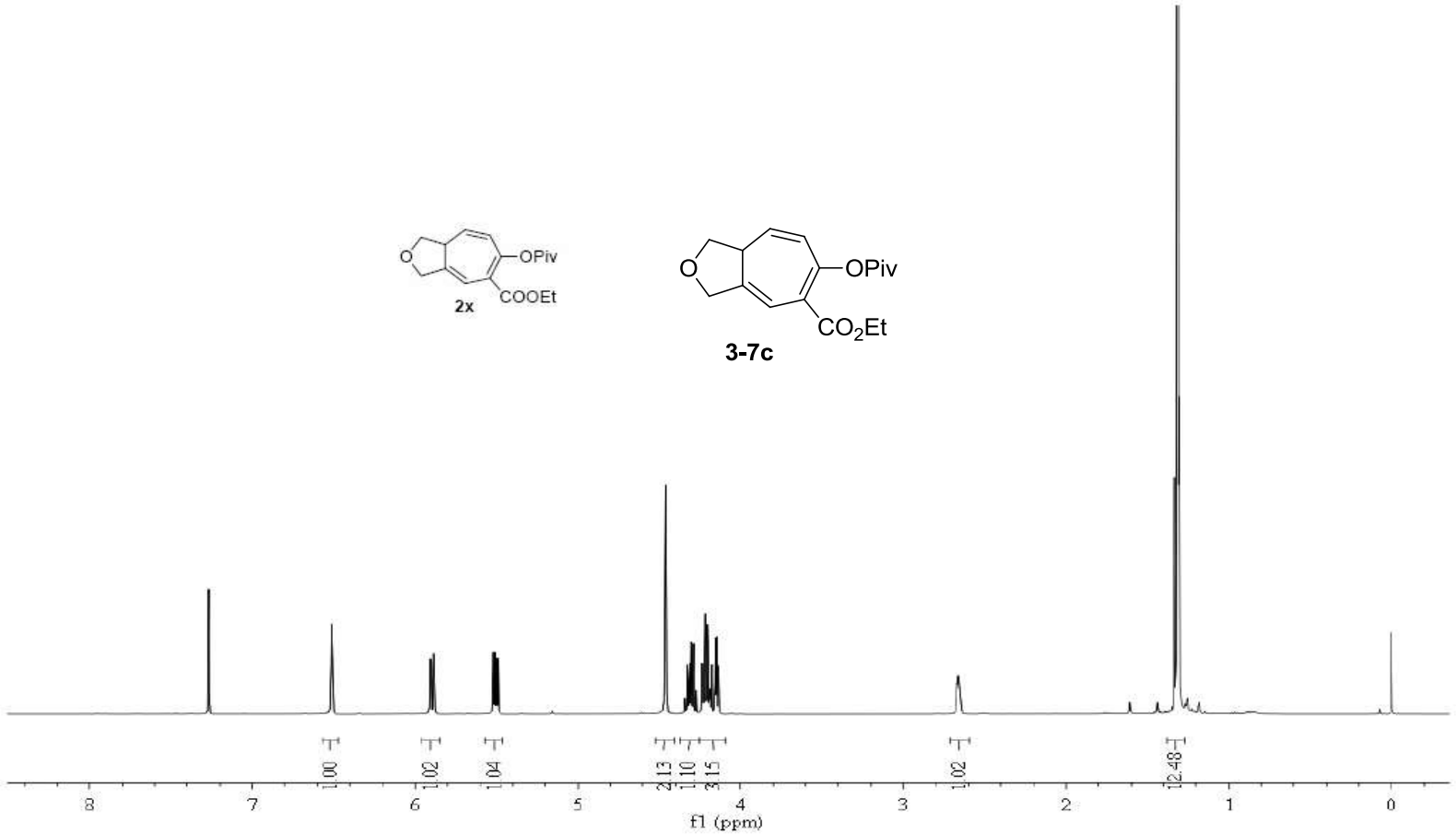
3-6b

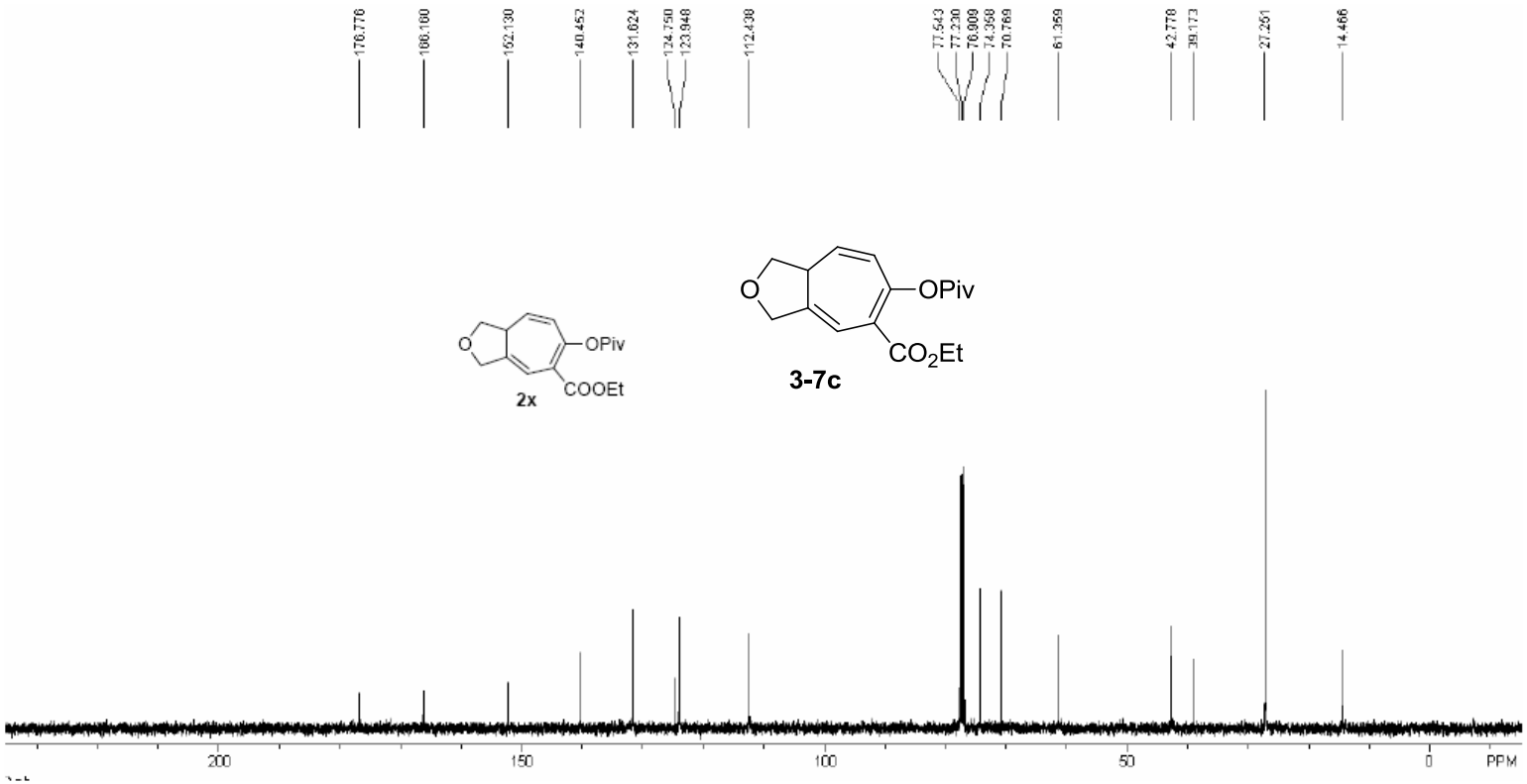

OPiv
O
1x
CO2Et
OPiv
O
COOEt
3-6c
1.00
0.97
1.01
2.15
2.10
2.15
0.86
3.18
9.49
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

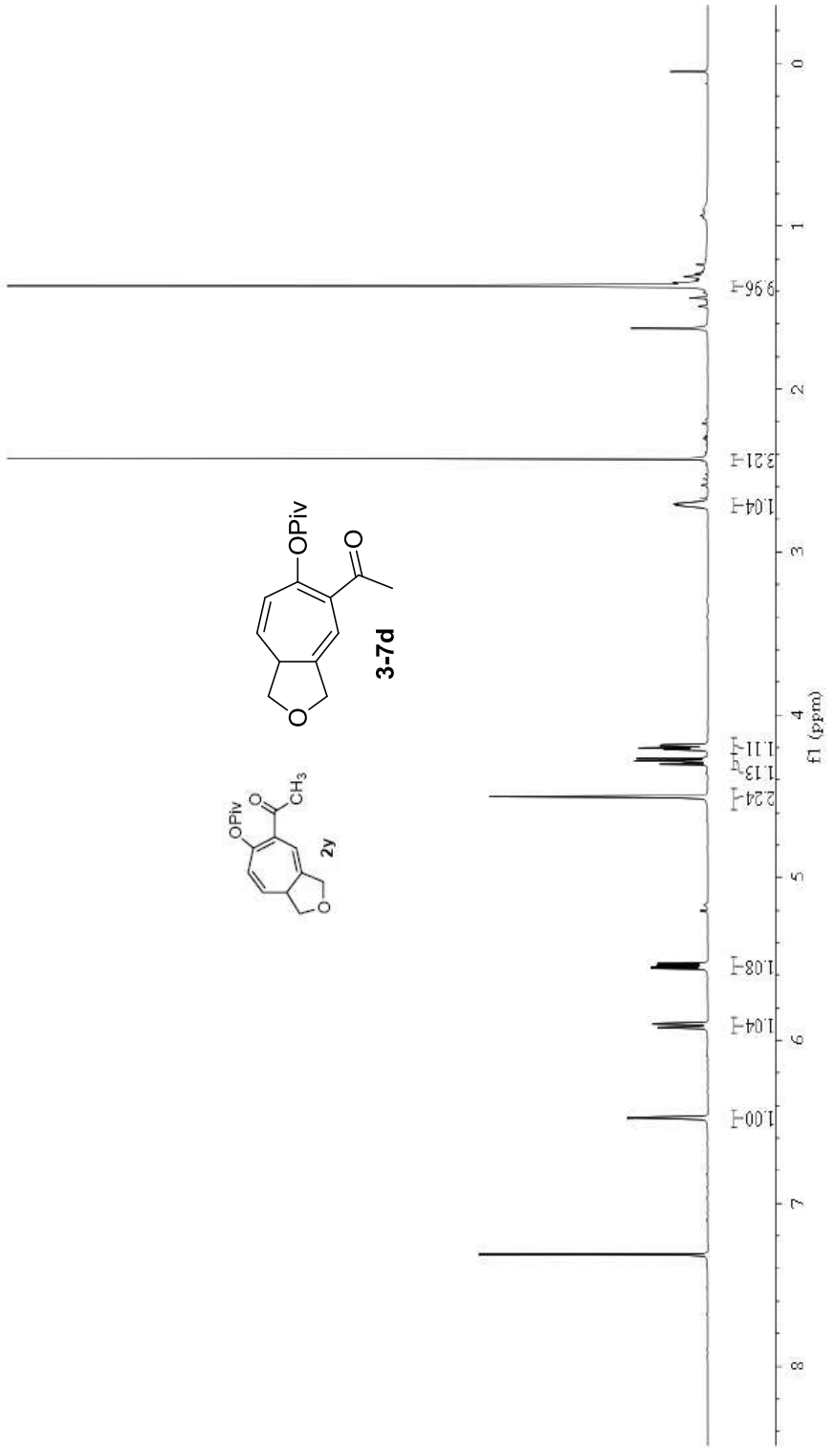

176.974
153.134
131.931
125.835
82.132
79.473
78.046
77.580
77.261
76.943
75.051
68.807
62.745
62.466
57.781
39.015
27.188
14.180
OPiv
O
CO2Et
1x
OPiv
O
COOEt
3-6c
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

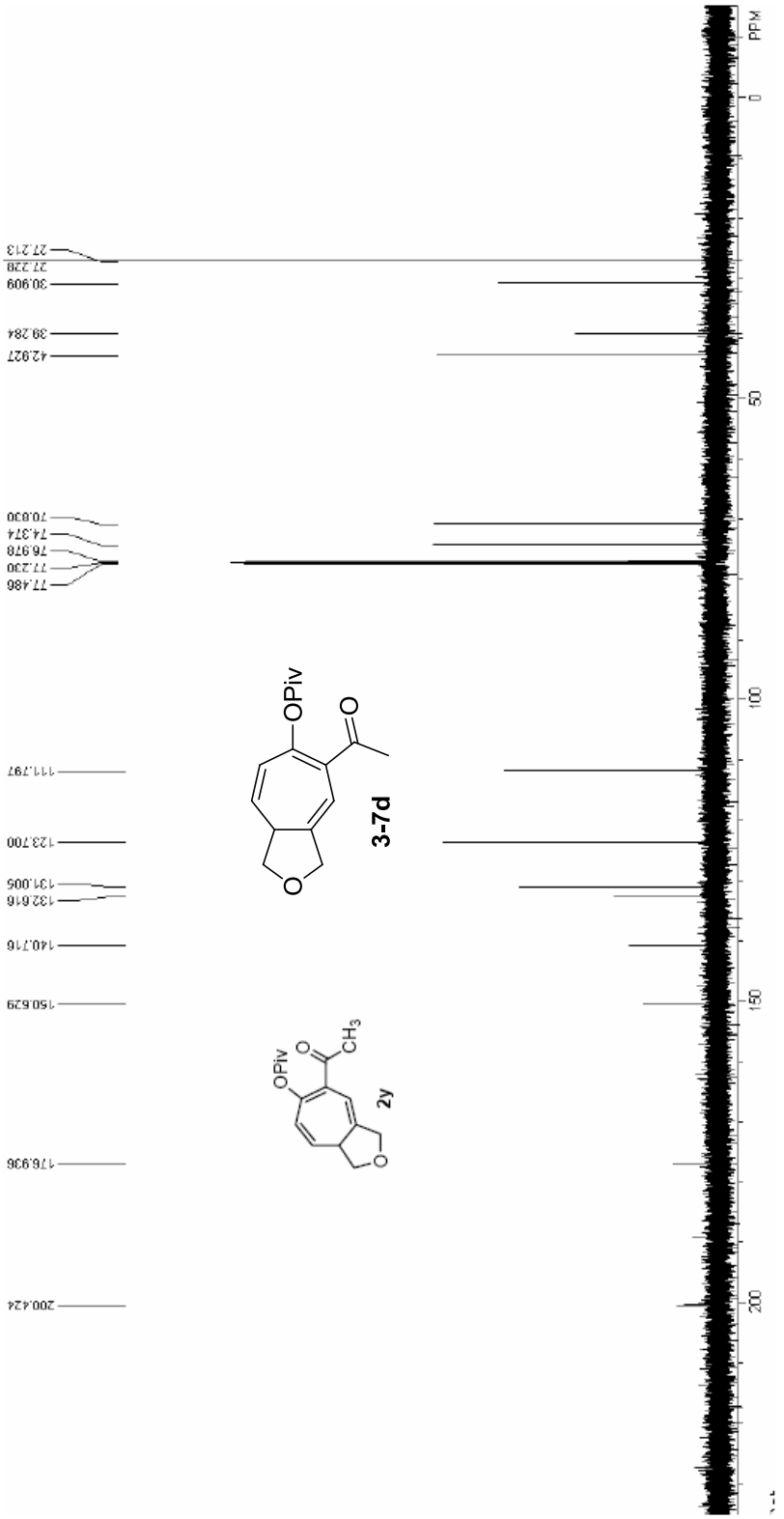

OPiv
O
CH3
O
1y
OPiv
O
O
3-6d
1.00
0.92
0.84
2.03
2.02
0.85
2.85
9.08
8
7
6
5
4
3
2
1
0

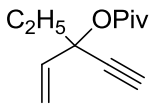

27.240
32.873
39.084
57.882
62.937
68.876
75.128
77.058
77.312
77.567
79.511
85.238
86.327
125.915
131.889
177.102
183.947
OPiv
3-6d
OPiv
1y
CH3
O
f1 (ppm)


OPiv
COOEt
2x
OPiv
CO2Et
3-7c
1.00
1.02
1.04
2.13
1.10
3.15
1.02
12.48
8
7
6
5
4
3
2
1
0
f1 (ppm)

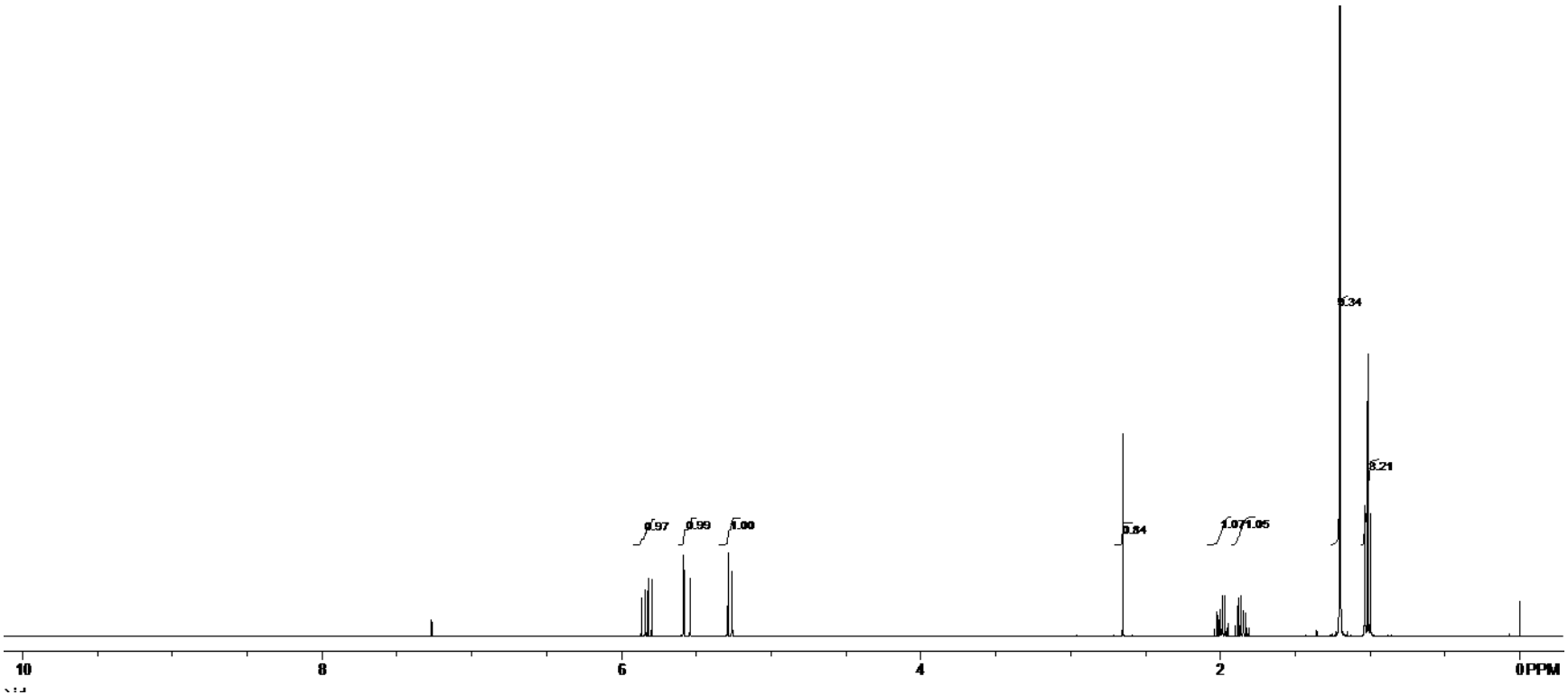

176.776
166.160
152.130
140.452
131.624
124.750
123.948
112.438
77.543
77.230
76.909
74.358
70.769
61.359
42.778
39.173
27.251
14.466
O
OPiv
COOEt
2x
O
OPiv
CO2Et
3-7c
200
150
100
50
0
PPM


OPiv
O
3-7d
OPiv
O
CH3
2y
9.96
3.21
1.04
1.11
1.13
2.24
1.08
1.04
1.00
0
1
2
3
4
5
6
7
8
f1 (ppm)

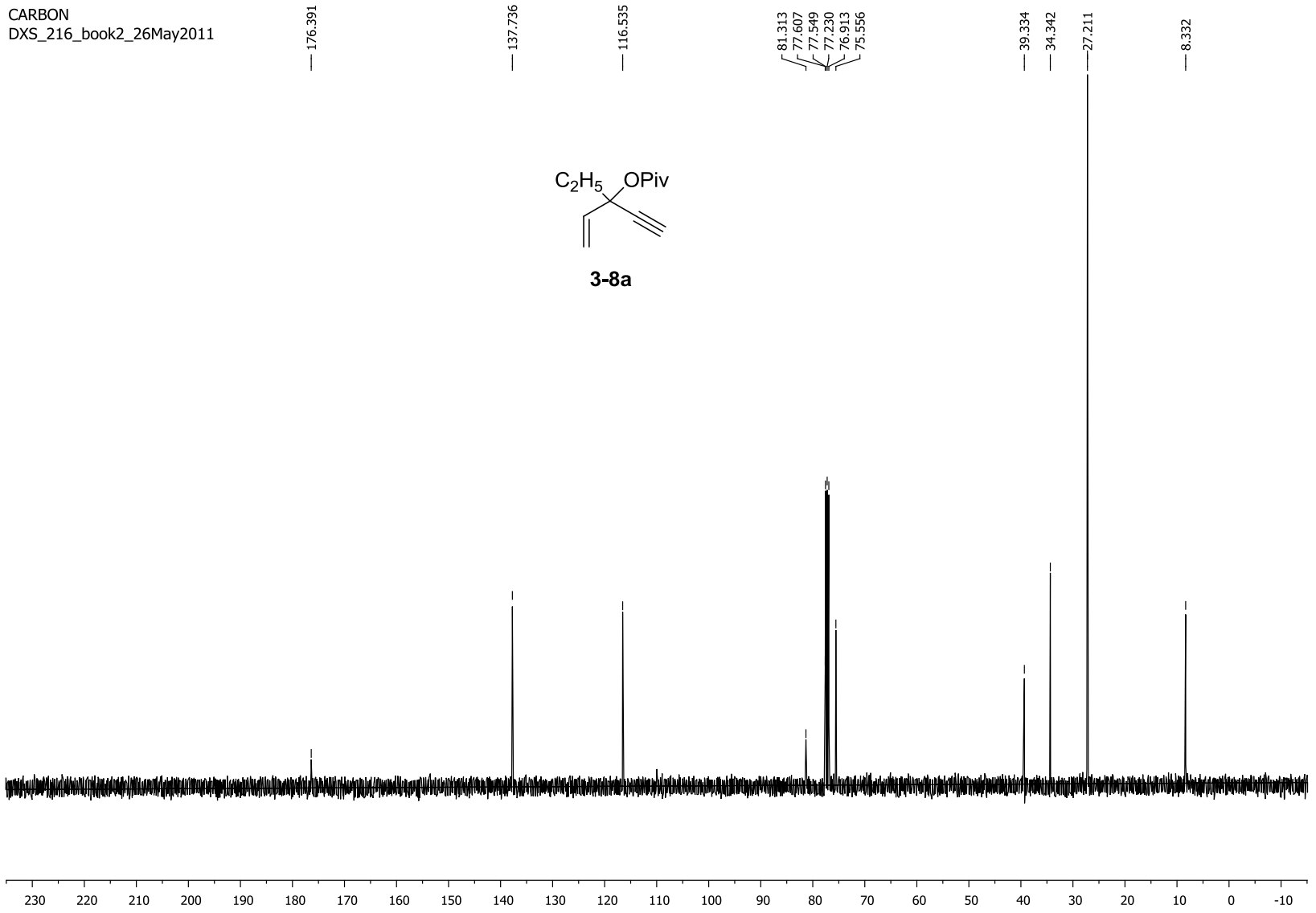

27.213
27.228
30.909
39.284
42.927
70.830
74.374
76.978
77.230
77.486
111.797
123.700
131.005
132.616
140.716
150.629
176.936
200.424
PPM
0
50
100
150
200
OPiv
O
O
3-7d
OPiv
O
CH3
O
2y



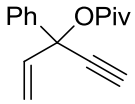
3-8a



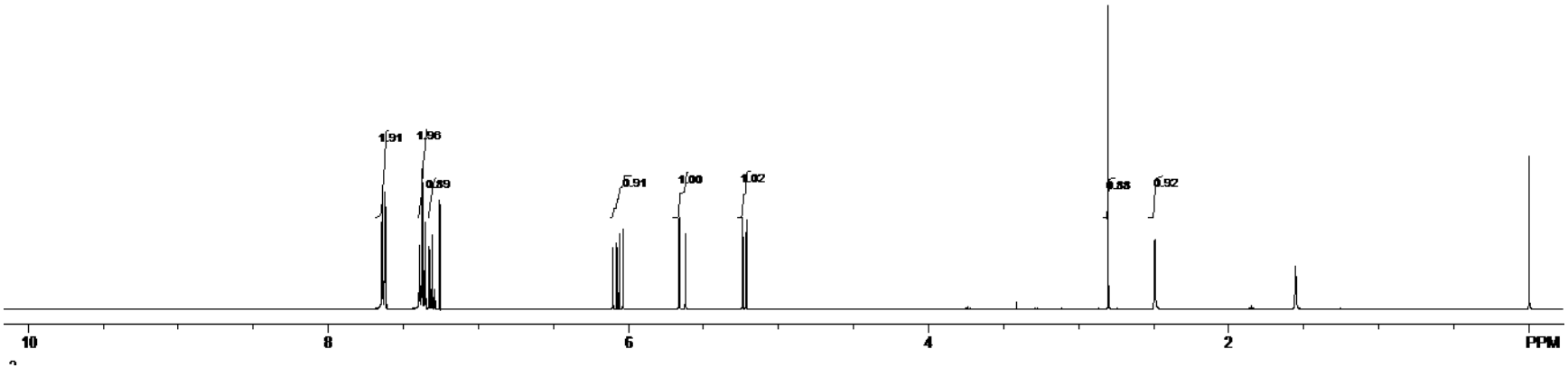
CARBON
DXS_216_book2_26May2011



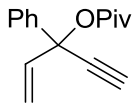
3-8a



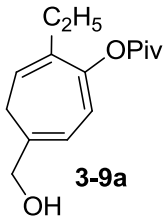
3-8b



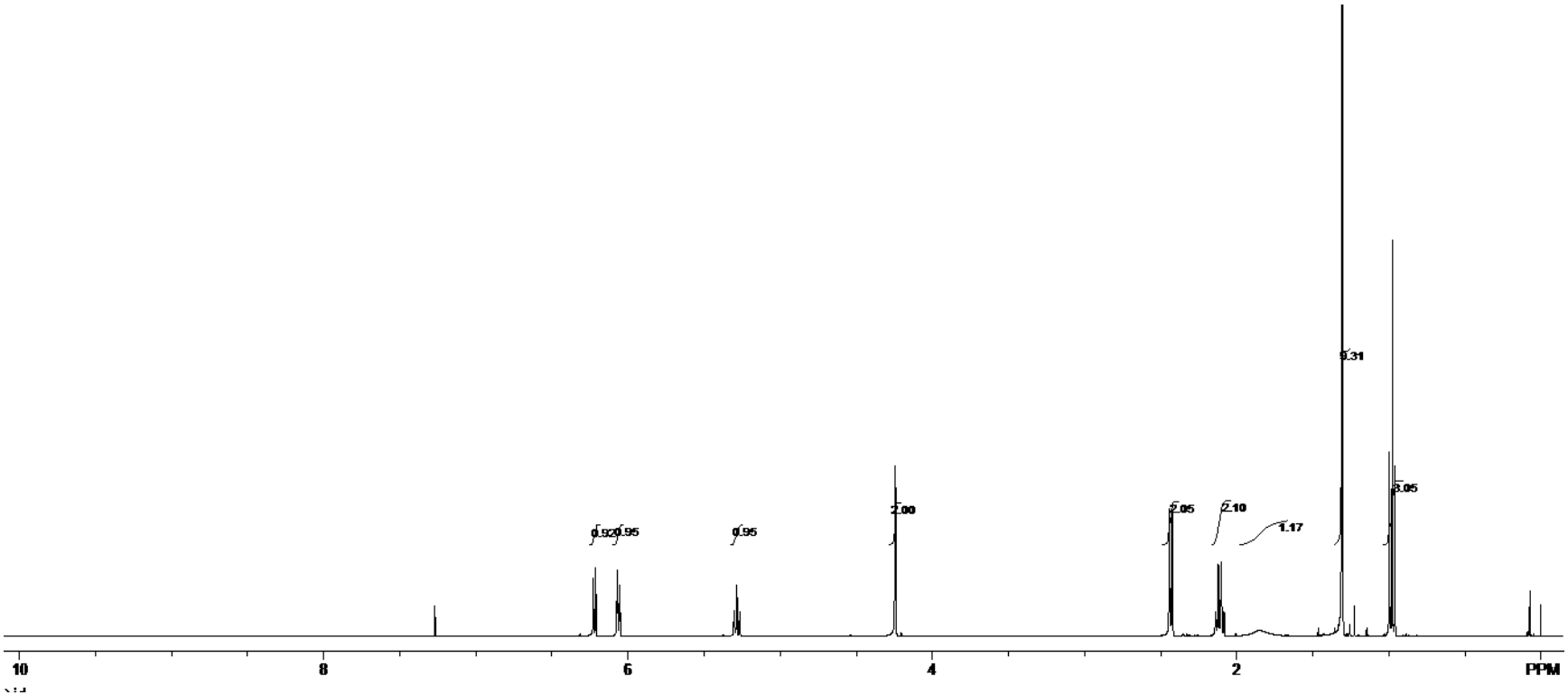
CARBON
DXS_234_book2_Al_16Jun2011



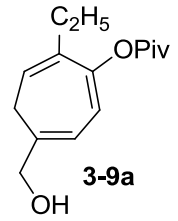
3-8b



3-9a

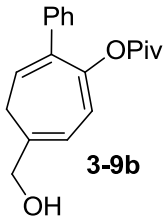


CARBON
DXS_220_book2_29May2011

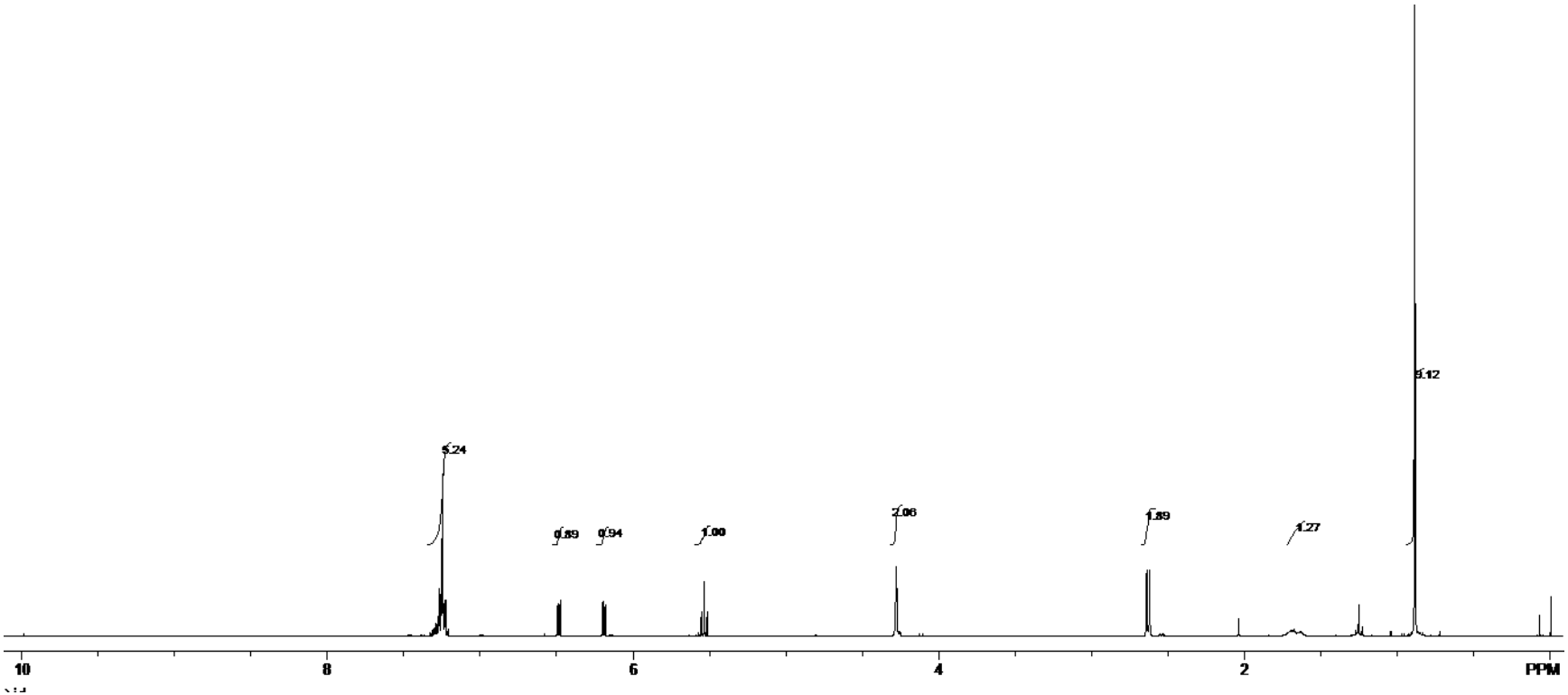


3-9a

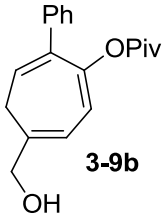
177.366
151.692
137.770
136.905
119.844
119.256
118.272
77.547
77.230
76.912
66.112
39.135
28.981
27.329
24.996
13.504



3-9b

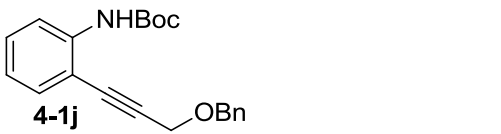


CARBON
DXS_236_book2_17Jun2011

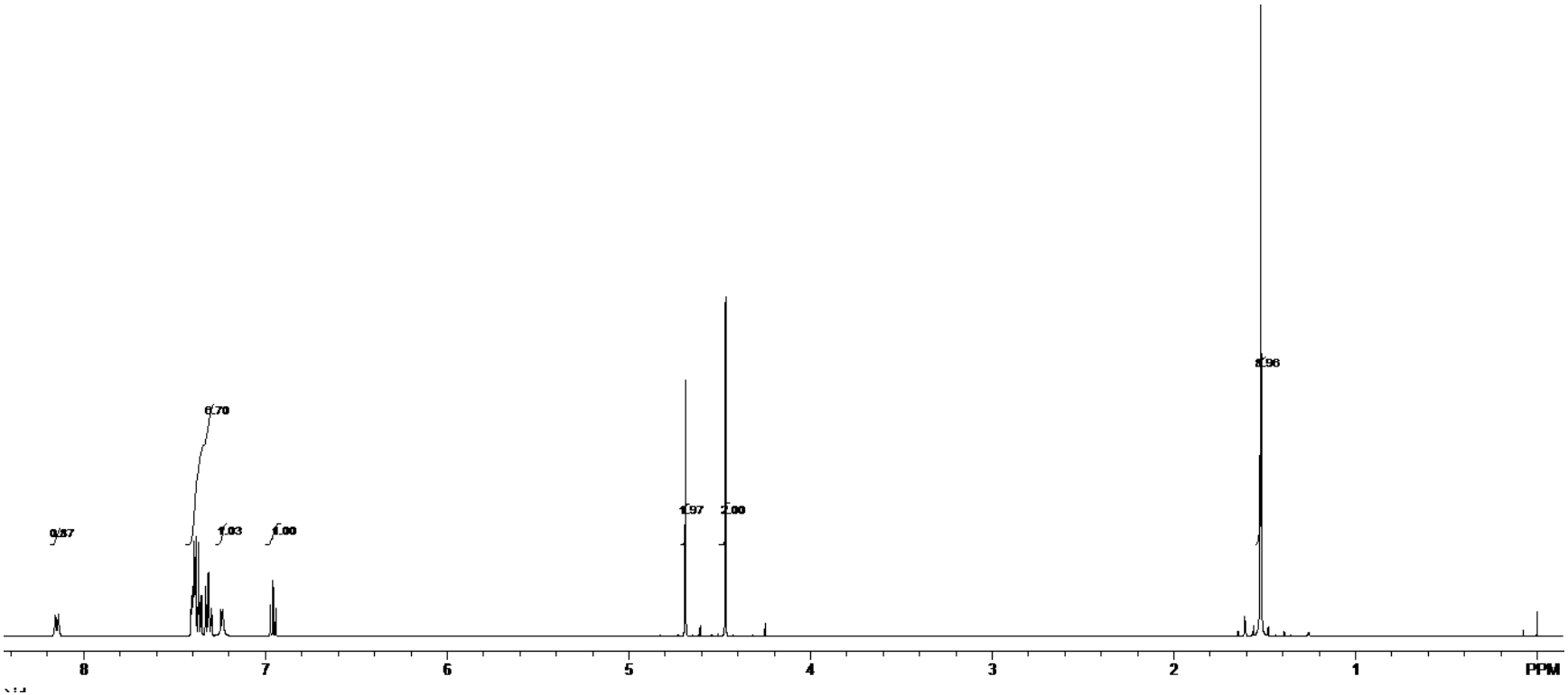


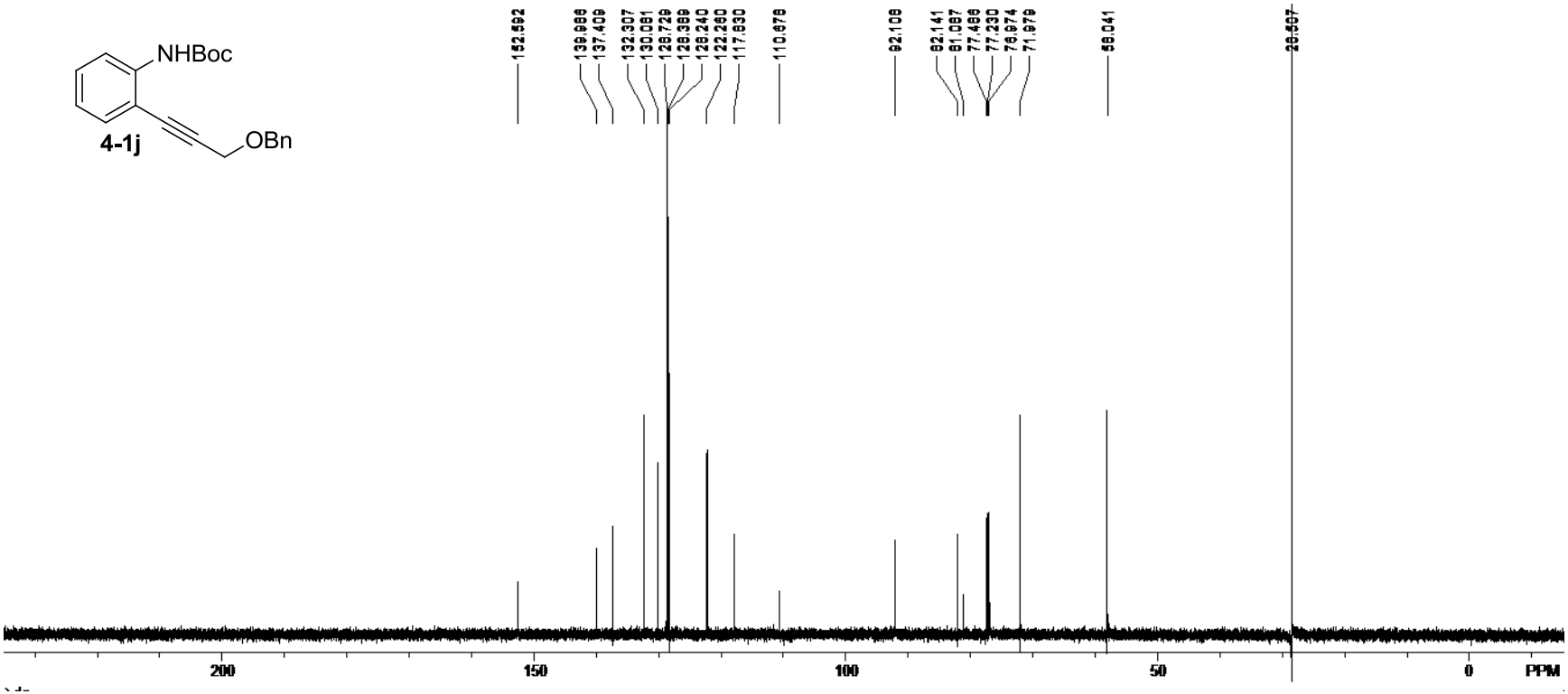
3-9b

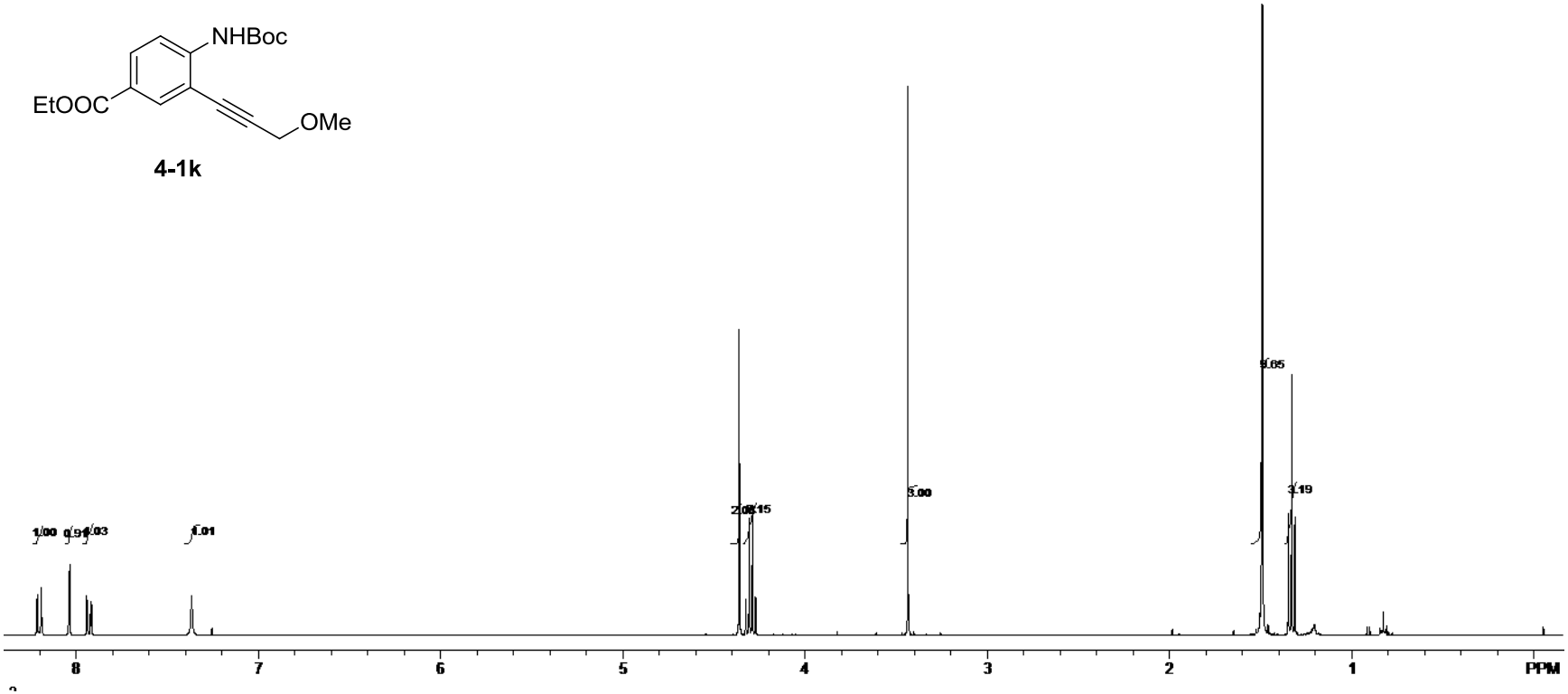
Chapter IV NMR Spectrum

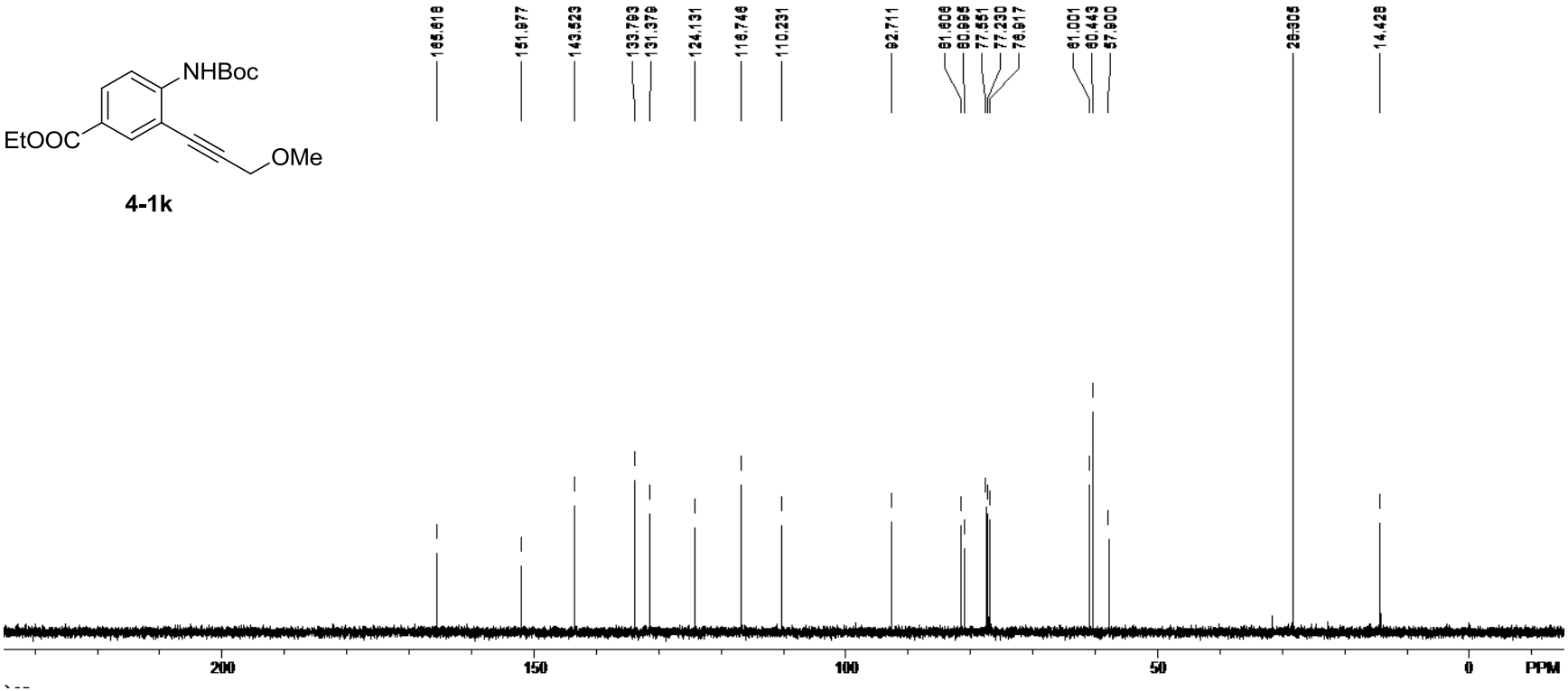


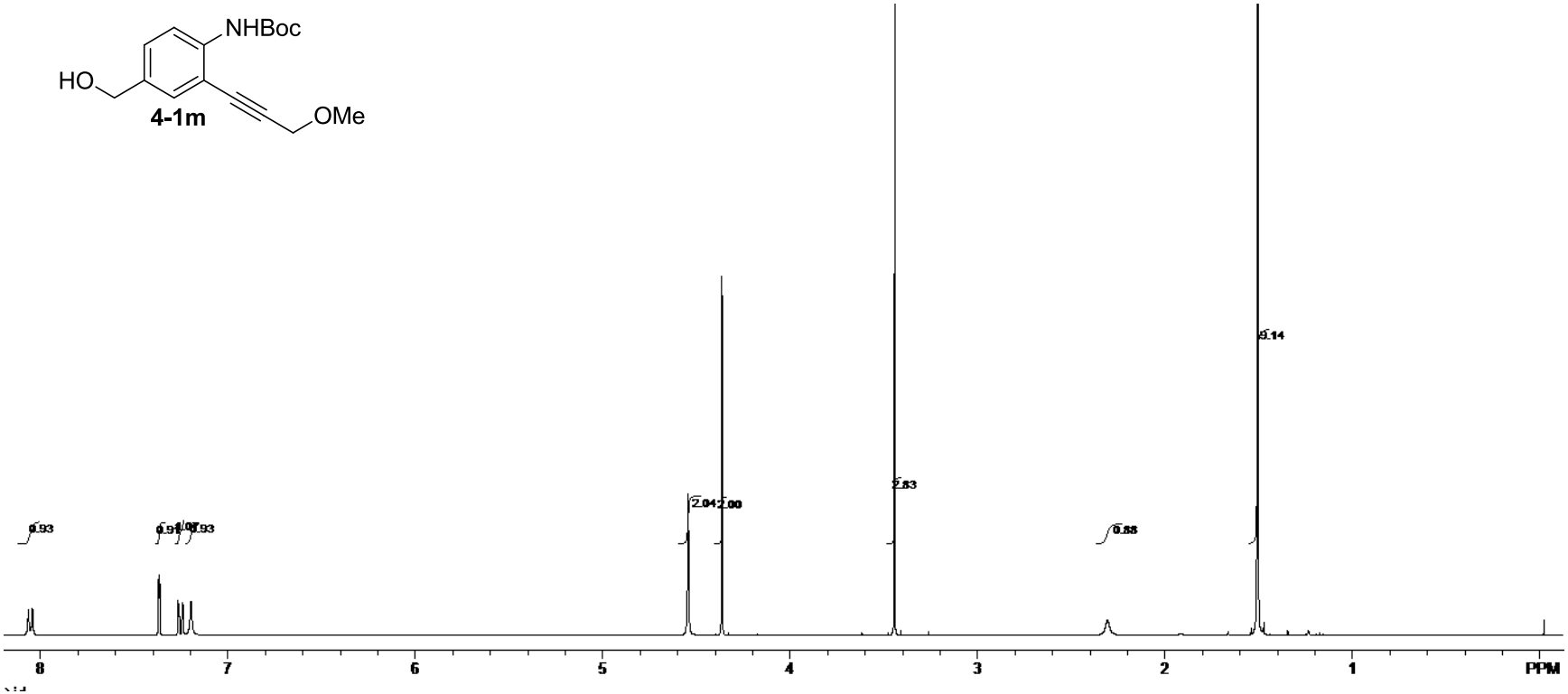
4-1j

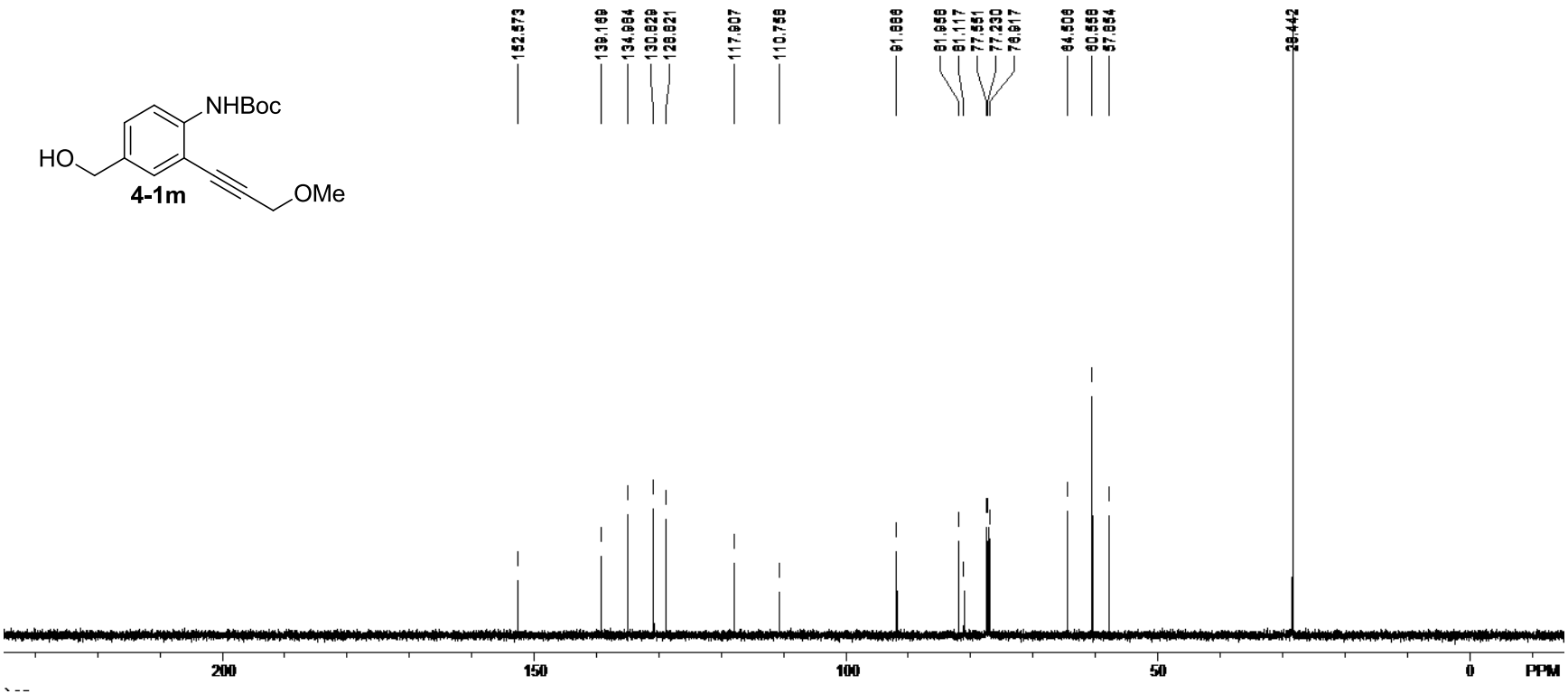


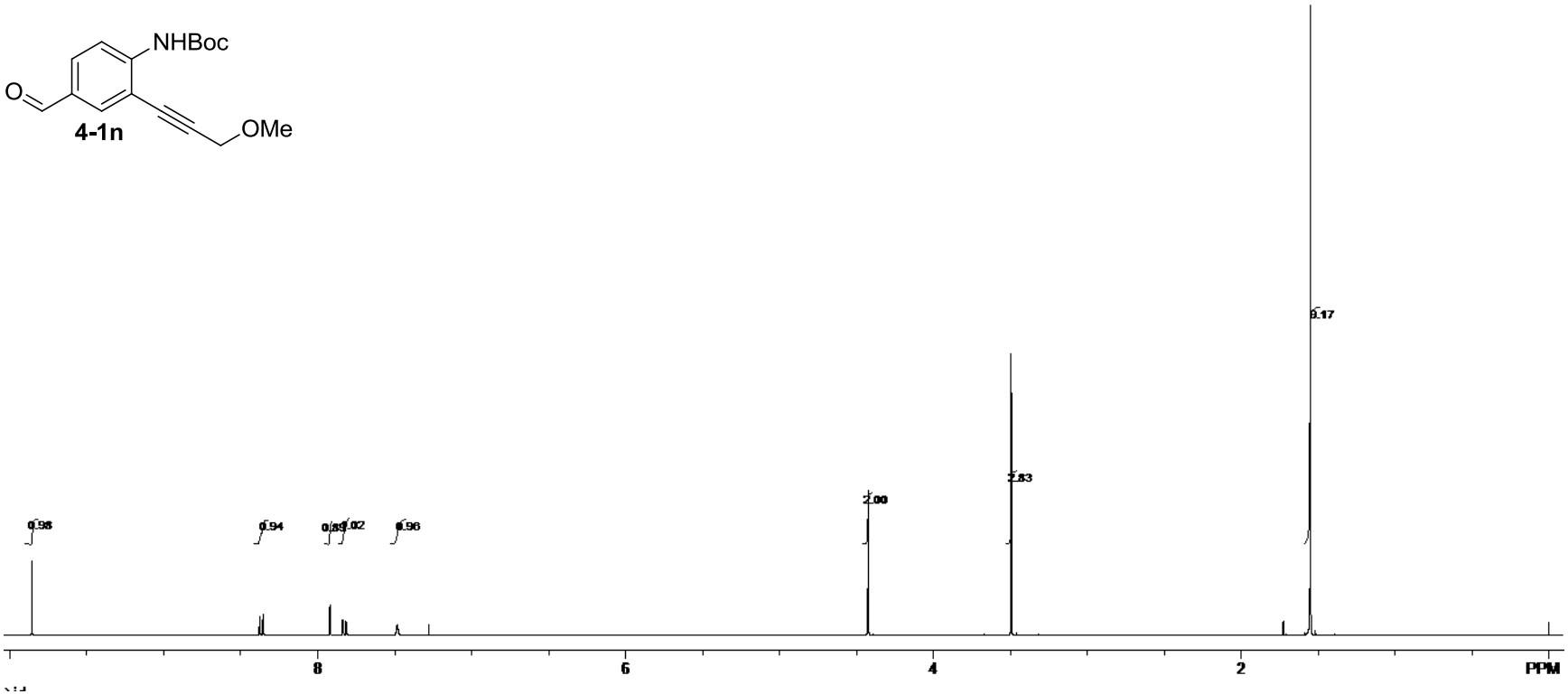

NHBoc
OBn
4-1j
152.592
139.666
137.409
132.307
130.081
128.729
128.386
126.240
122.260
117.630
110.078
82.108
82.141
81.087
77.486
77.230
76.974
71.979
58.041
29.697
200
150
100
50
0
PPM

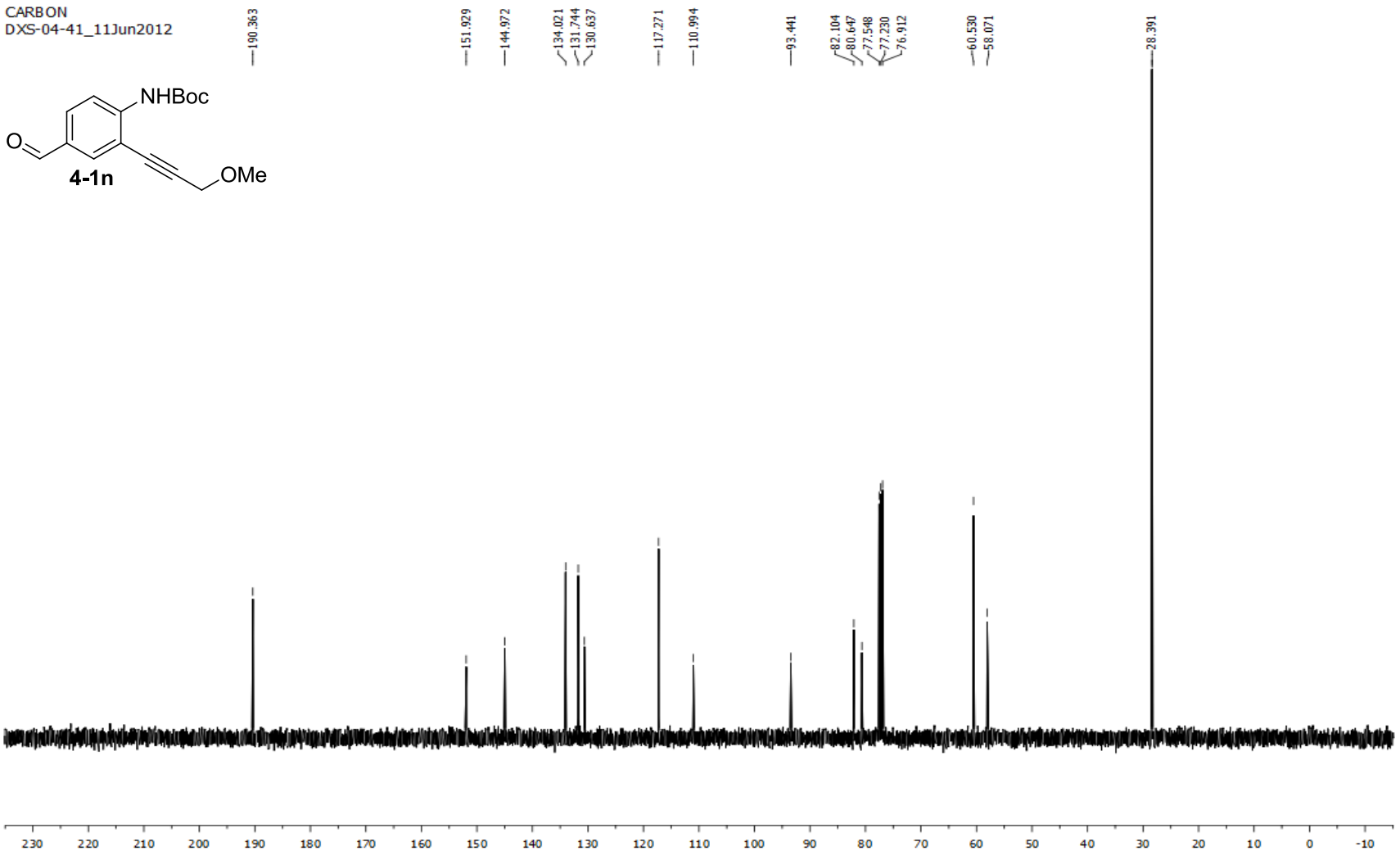

NHBoc
EtOOC
OMe
4-1k
1.00
0.94
1.03
1.01
2.08
2.15
5.00
9.65
3.19
8
7
6
5
4
3
2
1
PPM

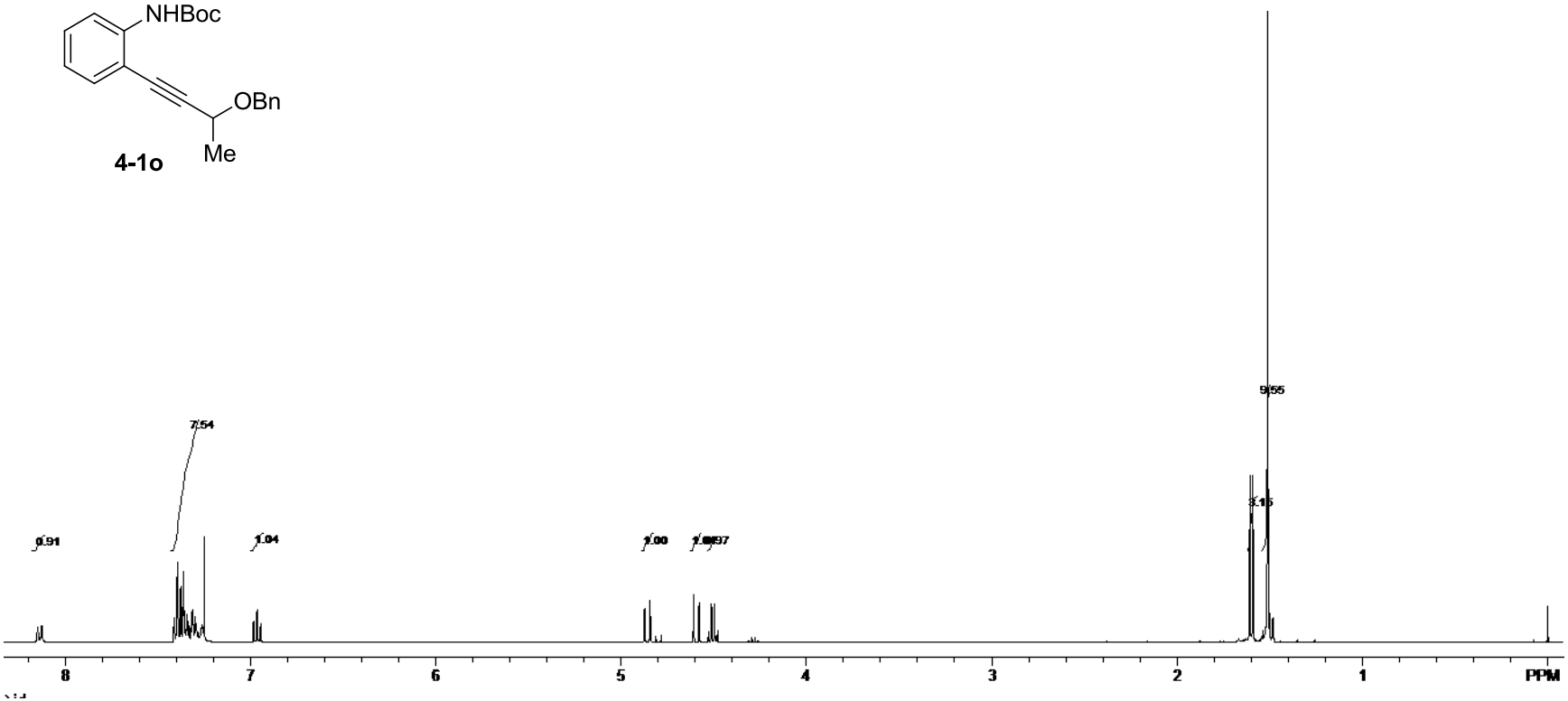

NHBoc
EtOOC
OMe
4-1k
165.618
151.877
143.523
133.763
131.379
124.131
118.748
110.231
92.711
61.606
60.995
77.551
77.230
76.917
61.001
60.443
57.600
28.305
14.426
200
150
100
50
0
PPM

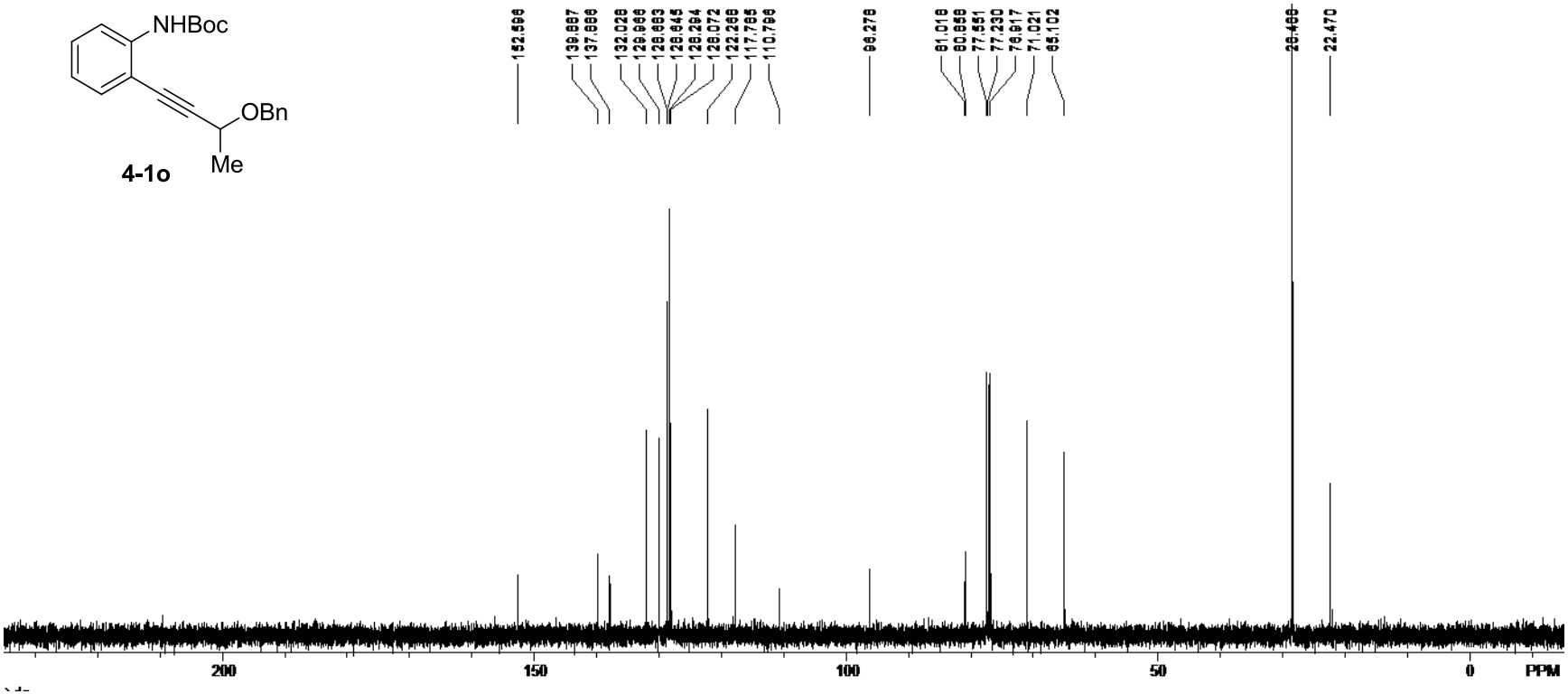

NHBoc
HO
OMe
4-1m
9.14
8
7
6
5
4
3
2
1
PPM

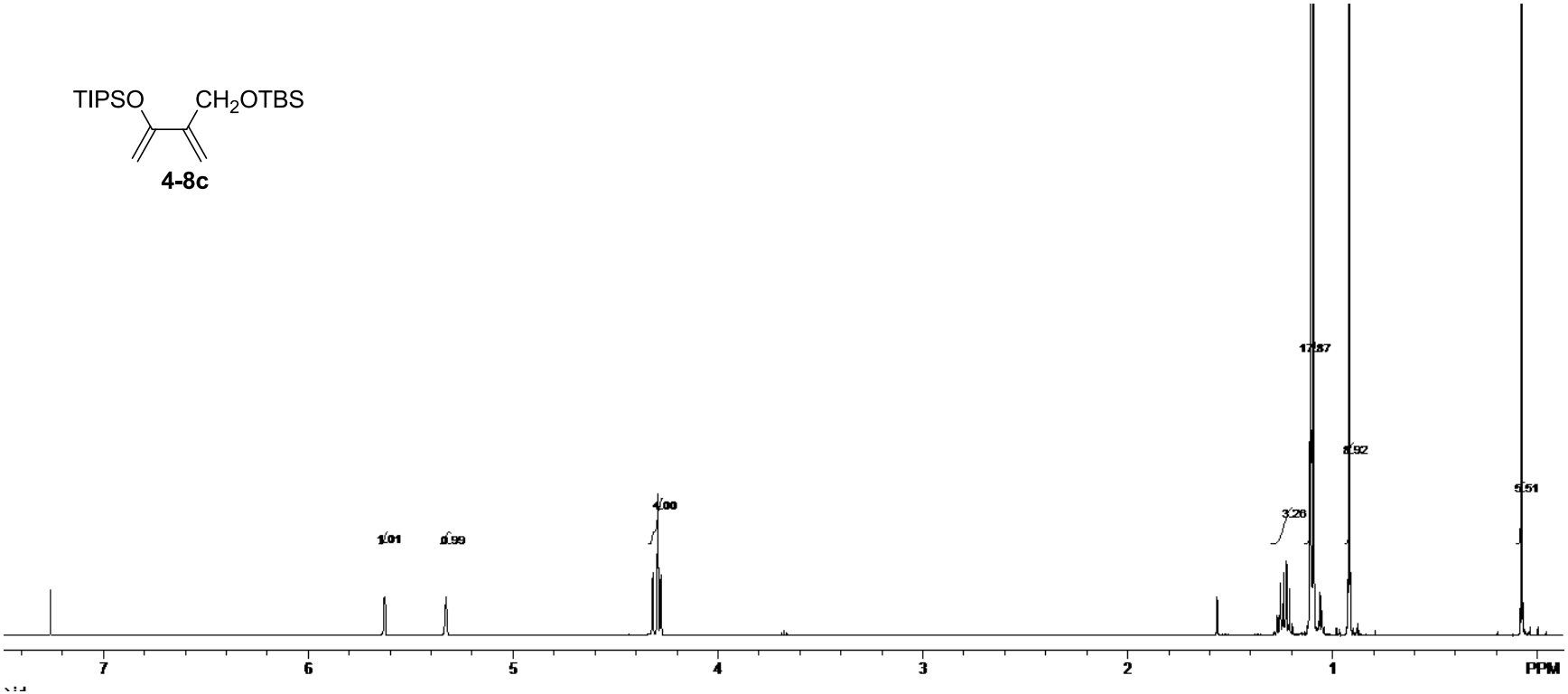

NHBoc
HO
OMe
4-1m
152.573
139.169
134.984
130.629
128.821
117.607
110.758
91.666
81.958
81.117
77.551
77.230
76.917
64.506
60.559
57.854
39.442
200
150
100
50
0
PPM

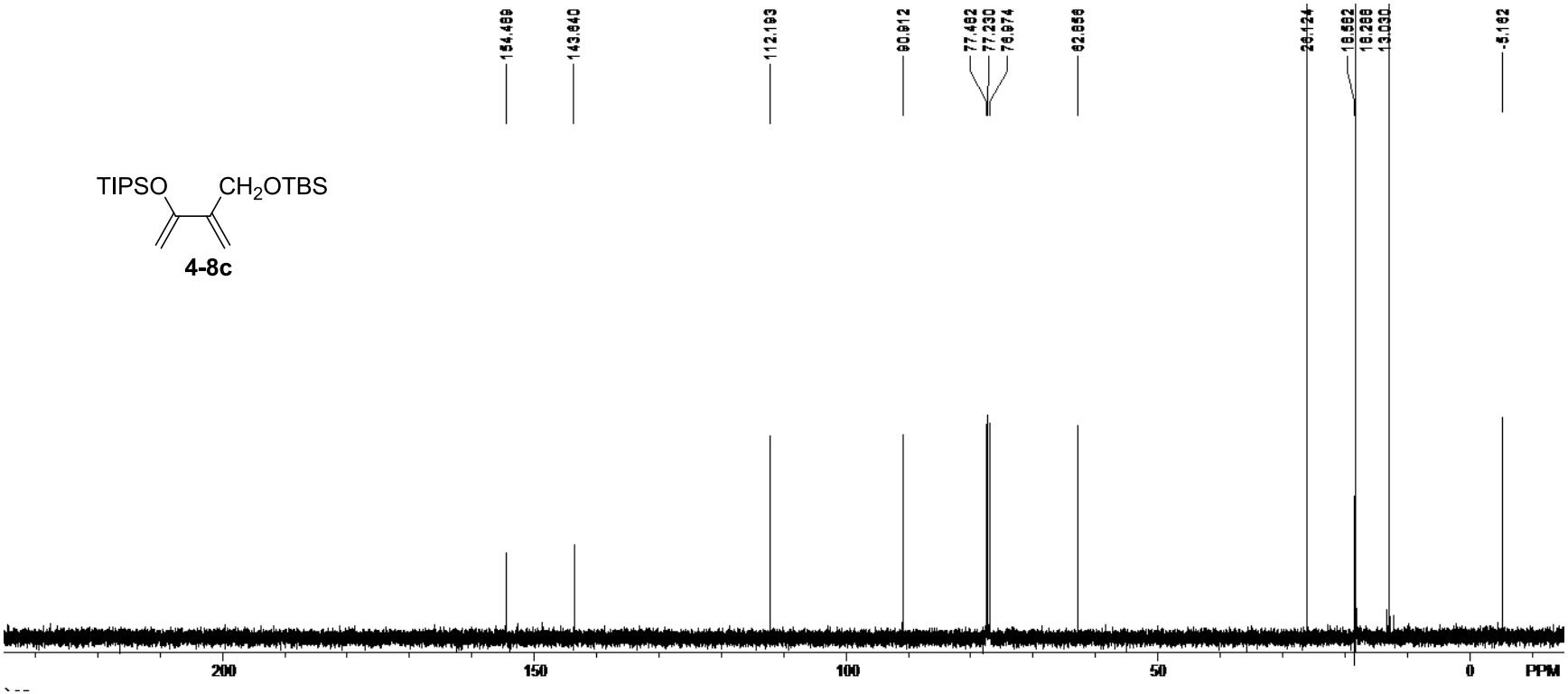

NHBoc
O
OMe
4-1n
0.98
0.94
1.02
0.96
2.00
2.83
9.17
8
6
4
2
PPM

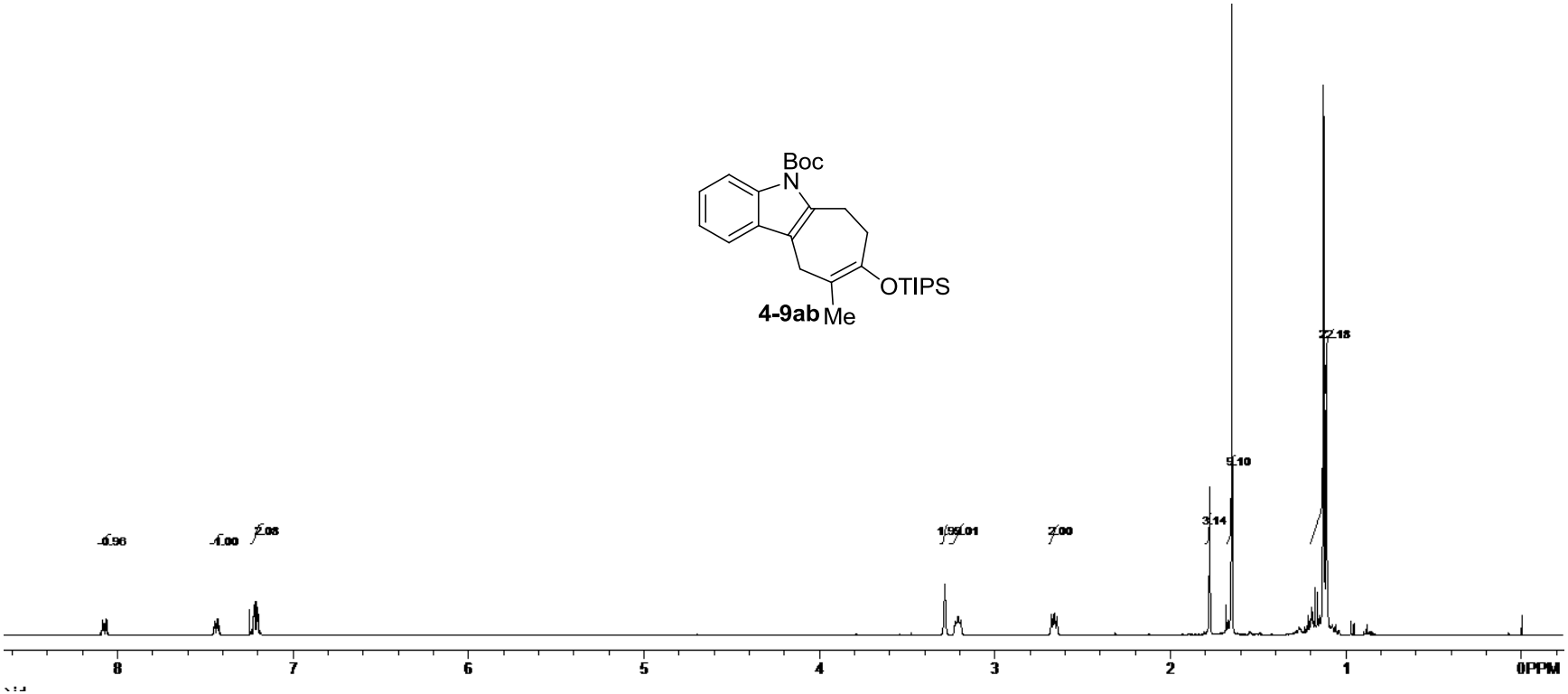

CARBON
DXS-04-41_11Jun2012
190.363
151.929
144.972
134.021
131.744
130.637
117.271
110.994
93.441
82.104
80.647
77.548
77.230
76.912
60.530
58.071
28.391
NHBoc
O
OMe
4-1n
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

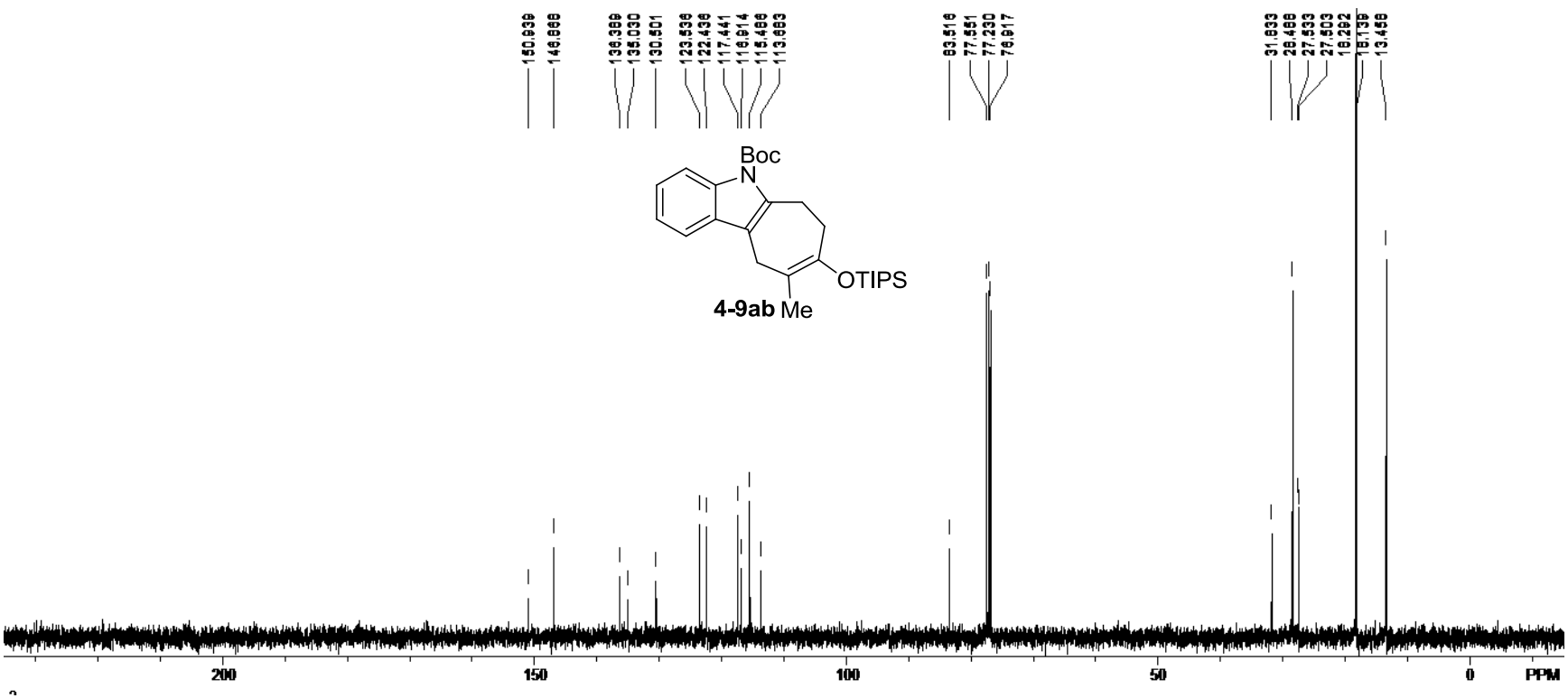

NHBoc
OBn
Me
4-1o
7.54
9.55
PPM


NHBoc
OBn
Me
4-1o
152.596
139.887
137.986
132.028
129.066
128.883
128.645
128.264
128.072
122.266
117.785
110.766
94.278
81.016
80.856
77.551
77.230
76.917
71.021
65.102
28.466
22.470
200
150
100
50
0
PPM


TIPSO
CH2OTBS
4-8c
1.01
0.99
4.00
3.26
12.57
8.92
5.51
7
6
5
4
3
2
1
PPM


154.489
143.640
112.163
90.912
77.462
77.230
76.974
62.858
29.124
18.562
18.266
13.030
-5.162
TIPSO
CH2OTBS
4-8c
200
150
100
50
0
PPM


Boc
N
OTIPS
4-9ab Me
0.96
4.00
2.08
1.99
1.01
2.00
3.14
9.10
22.15
8
7
6
5
4
3
2
1
0PPM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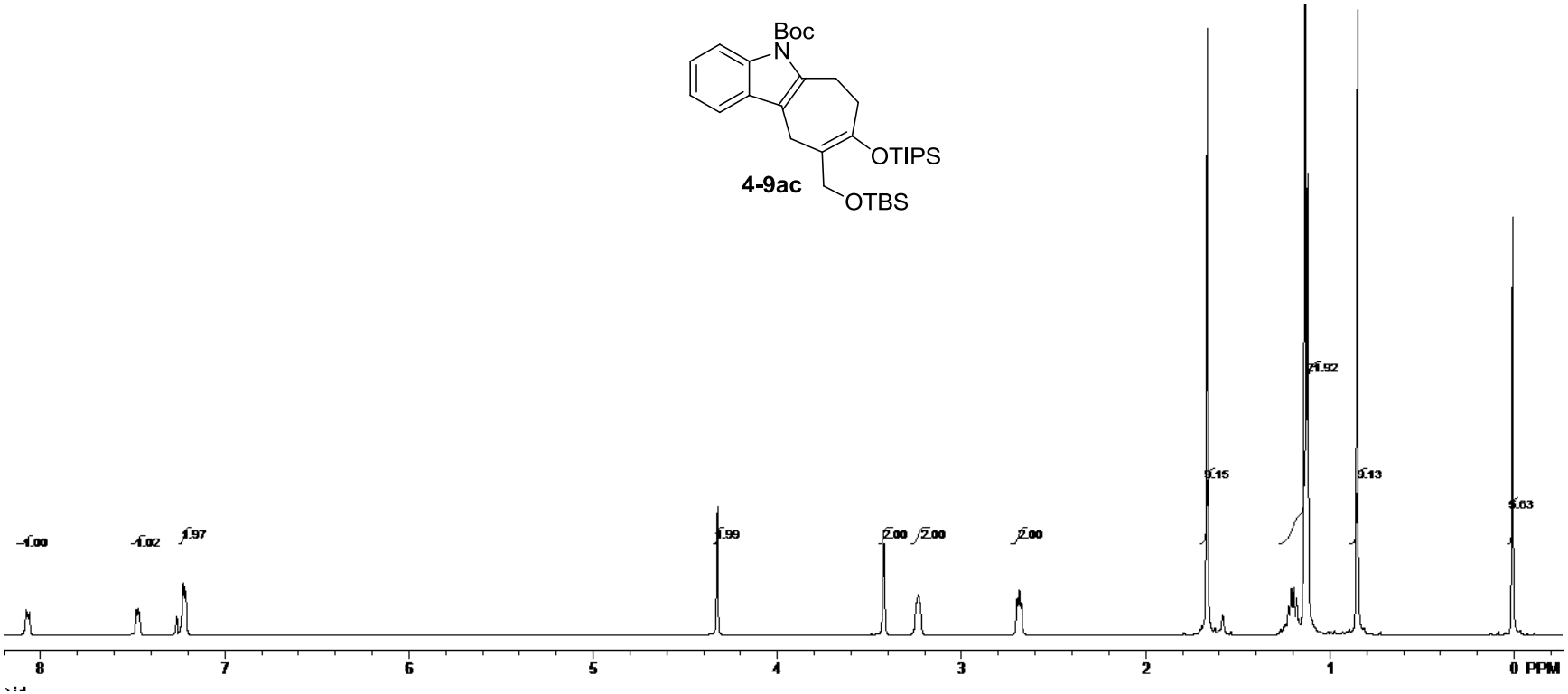
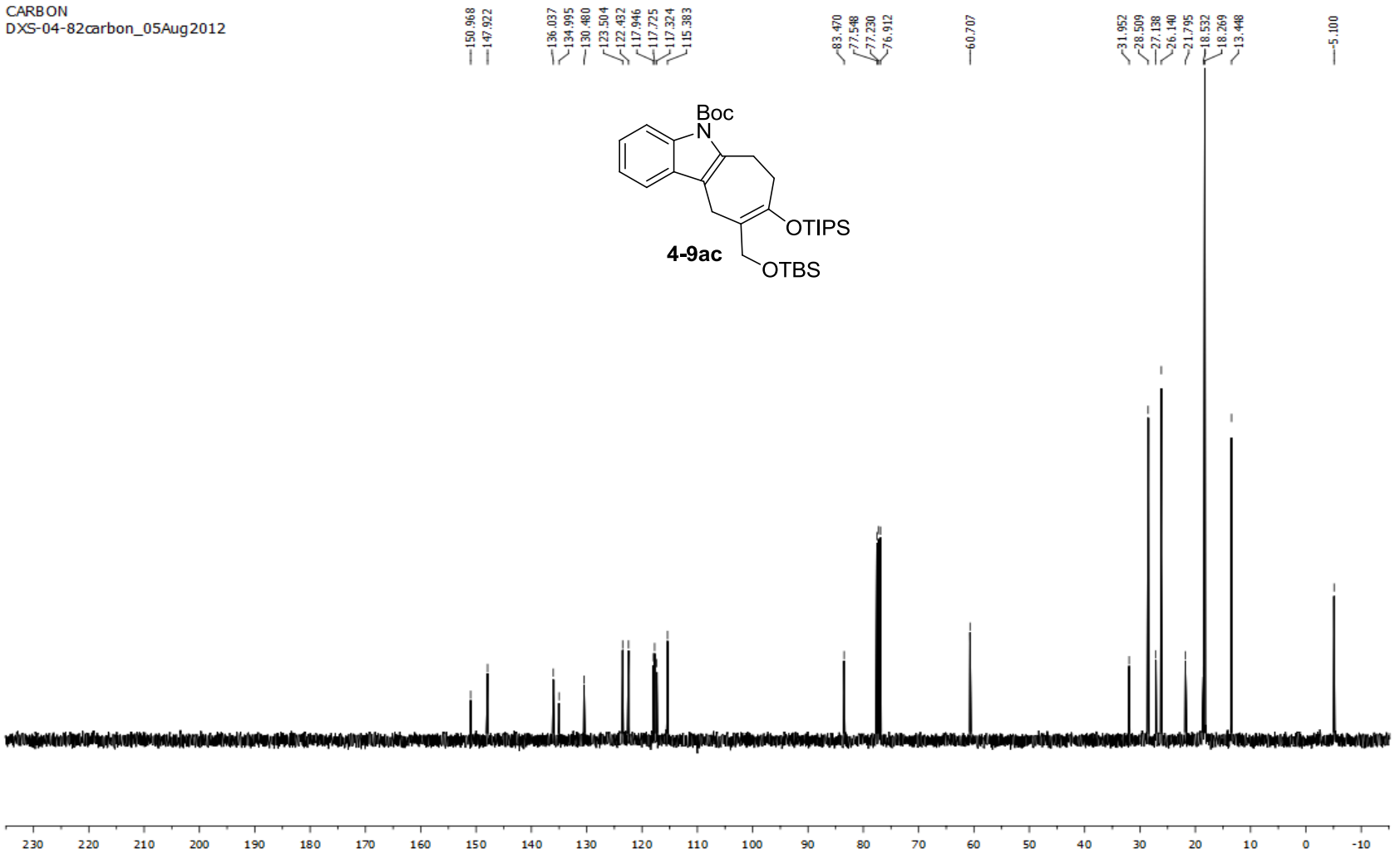
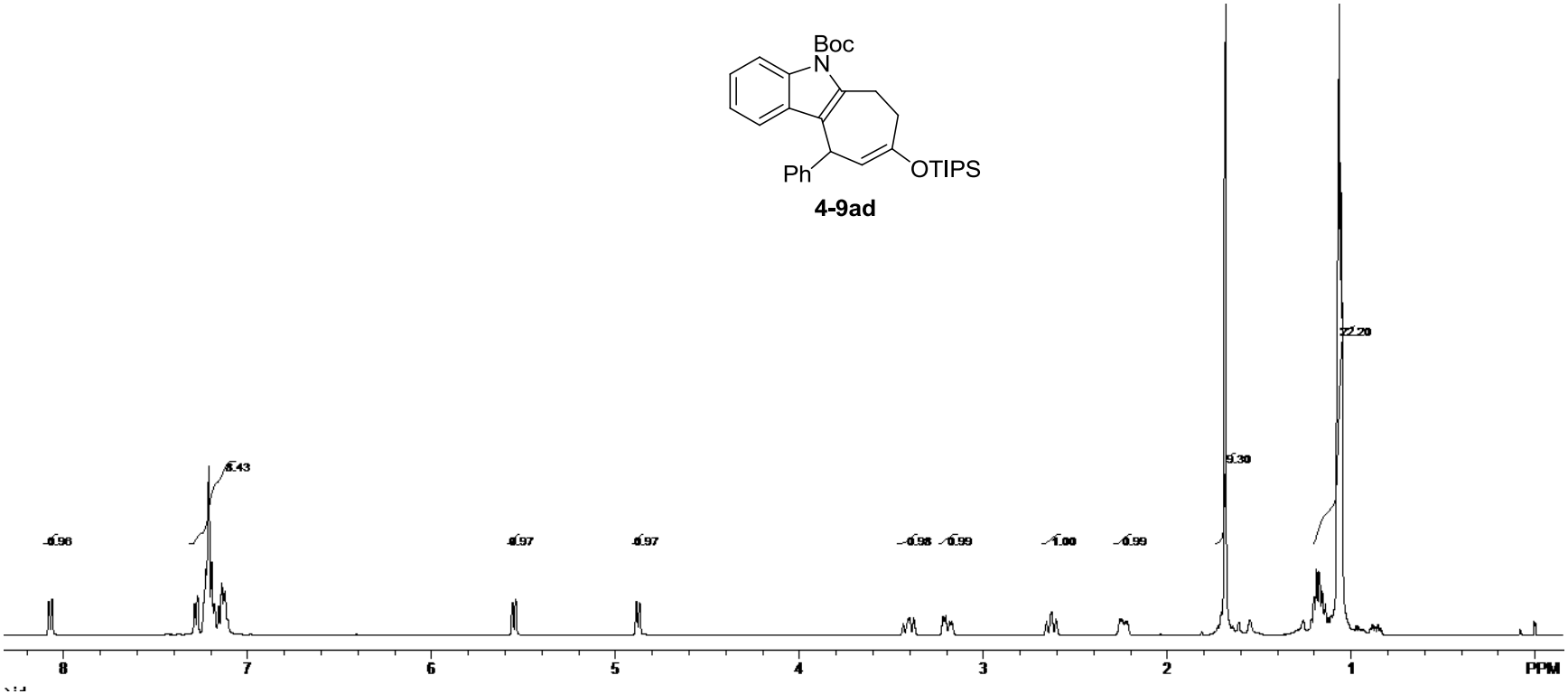
136.389
135.030
130.501
123.536
122.436
117.441
116.814
115.486
113.863
83.516
77.551
77.230
76.917
31.633
28.486
27.533
27.503
18.292
18.136
13.456
Boc
N
OTIPS
4-9ab Me
200
150
100
50
0
PPM

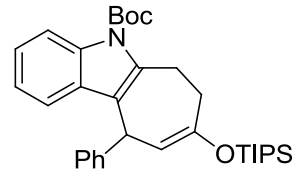

Boc
N
OTIPS
OTBS
4-9ac
4.00
4.02
1.97
1.99
2.00
2.00
2.00
9.15
21.92
9.13
5.63
8
7
6
5
4
3
2
1
0 PPM


CARBON
DXS-04-82carbon_05Aug2012
150.968
147.922
136.037
134.995
130.480
123.504
122.432
117.946
117.725
117.324
115.383
83.470
77.548
77.230
76.912
60.707
31.952
28.509
27.138
26.140
21.795
18.532
18.269
13.448
-5.100
Boc
N
OTIPS
OTBS
4-9ac
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Boc
N
Ph
OTIPS
4-9ad
6.43
0.96
0.97
0.97
0.98
0.99
1.00
0.99
9.30
22.20
8
7
6
5
4
3
2
1
PPM

CARBON
DXS-3-291-pure_06Mar2012

154.934
150.981
144.592
138.039
135.211
130.655
128.185
127.730
125.897
123.648
122.696
119.666
118.154
115.433
107.877
83.866
77.548
77.230
76.912
37.187
31.768
28.537
25.937
18.236
12.800



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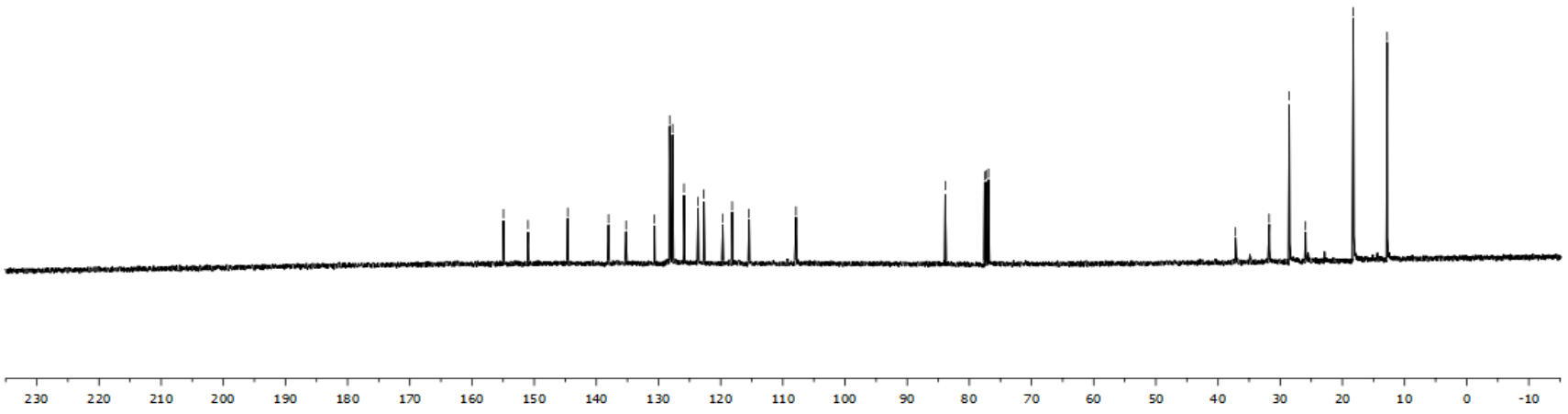
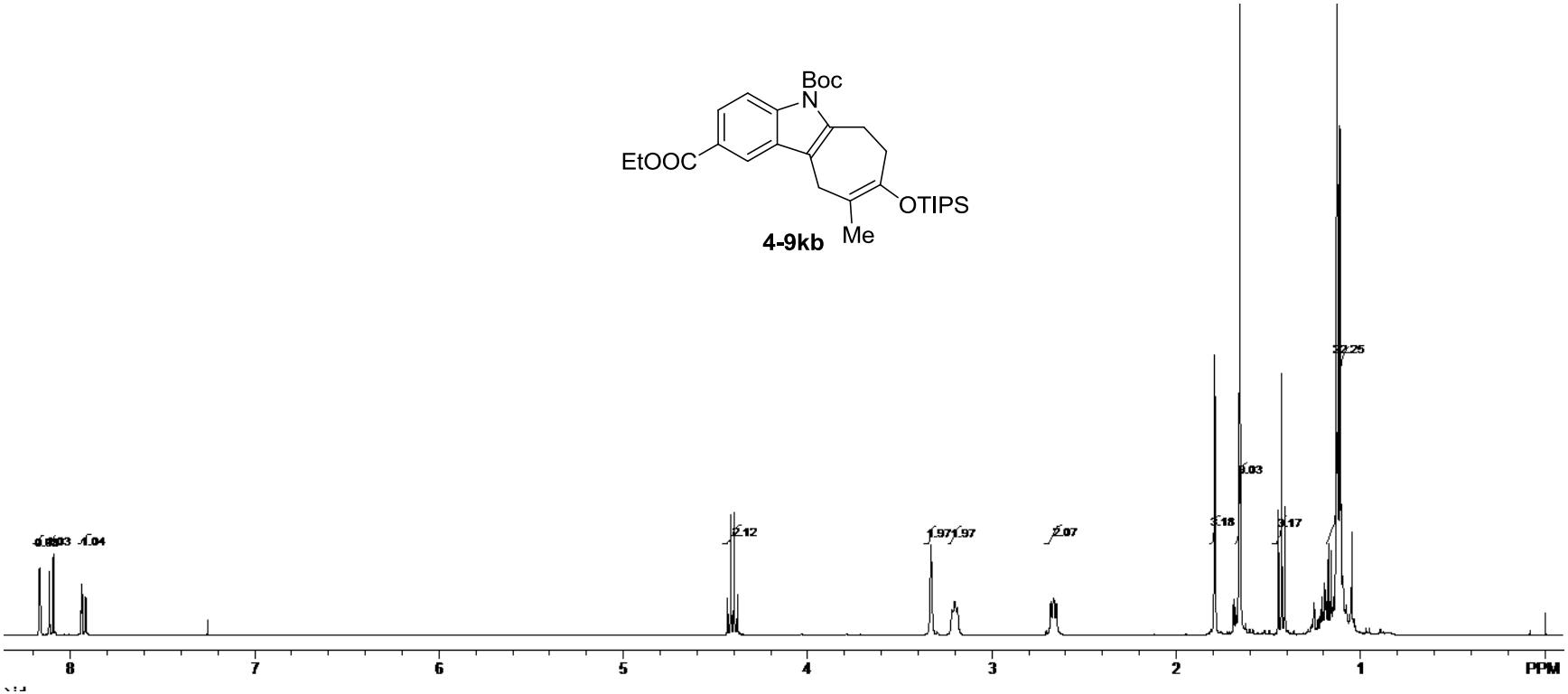
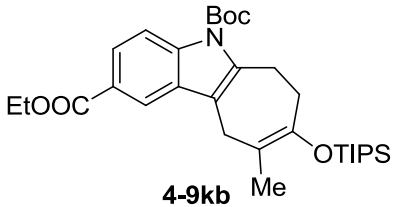


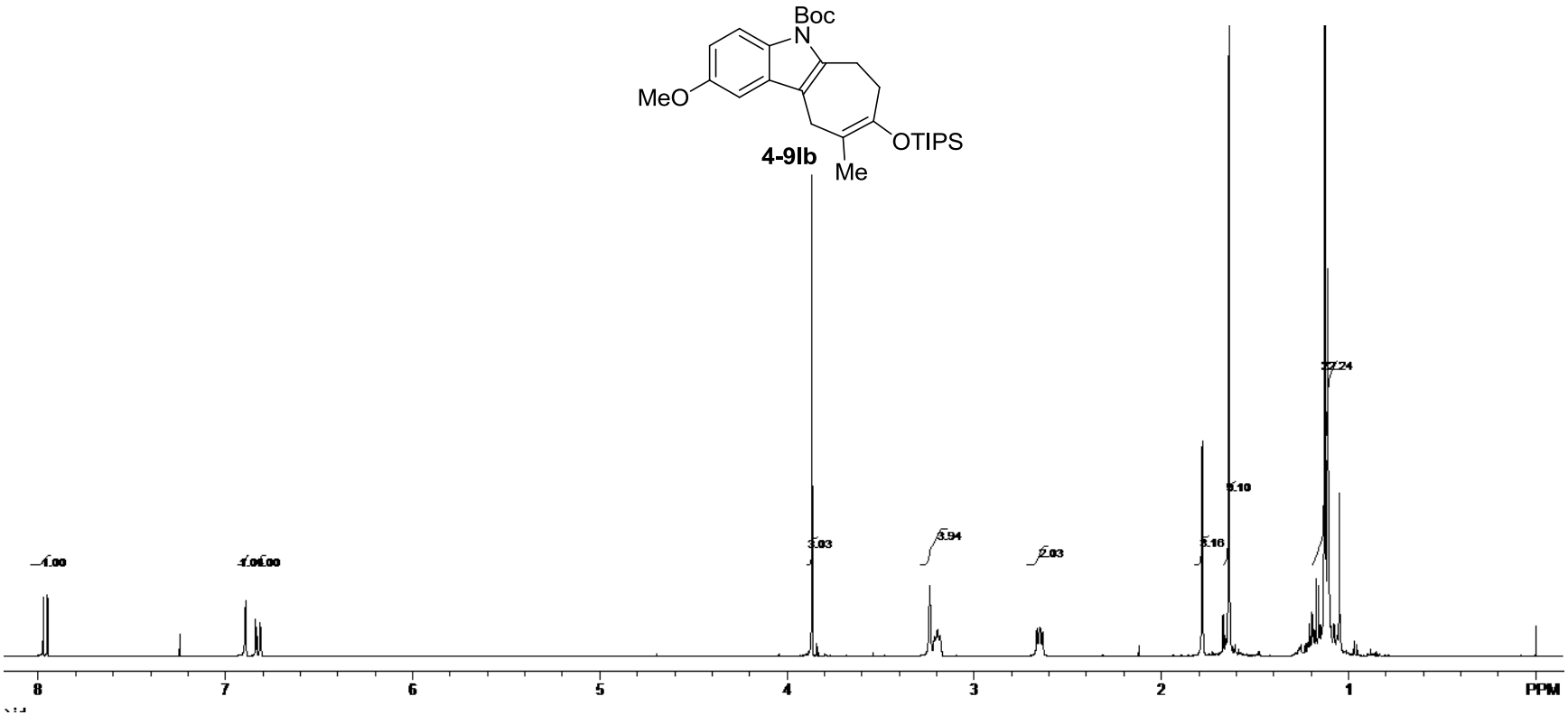

Boc
N
EtOOC
OTIPS
Me
4-9kb
1.04
2.12
1.97
1.97
2.07
3.18
9.03
3.17
22.25
8
7
6
5
4
3
2
1
PPM

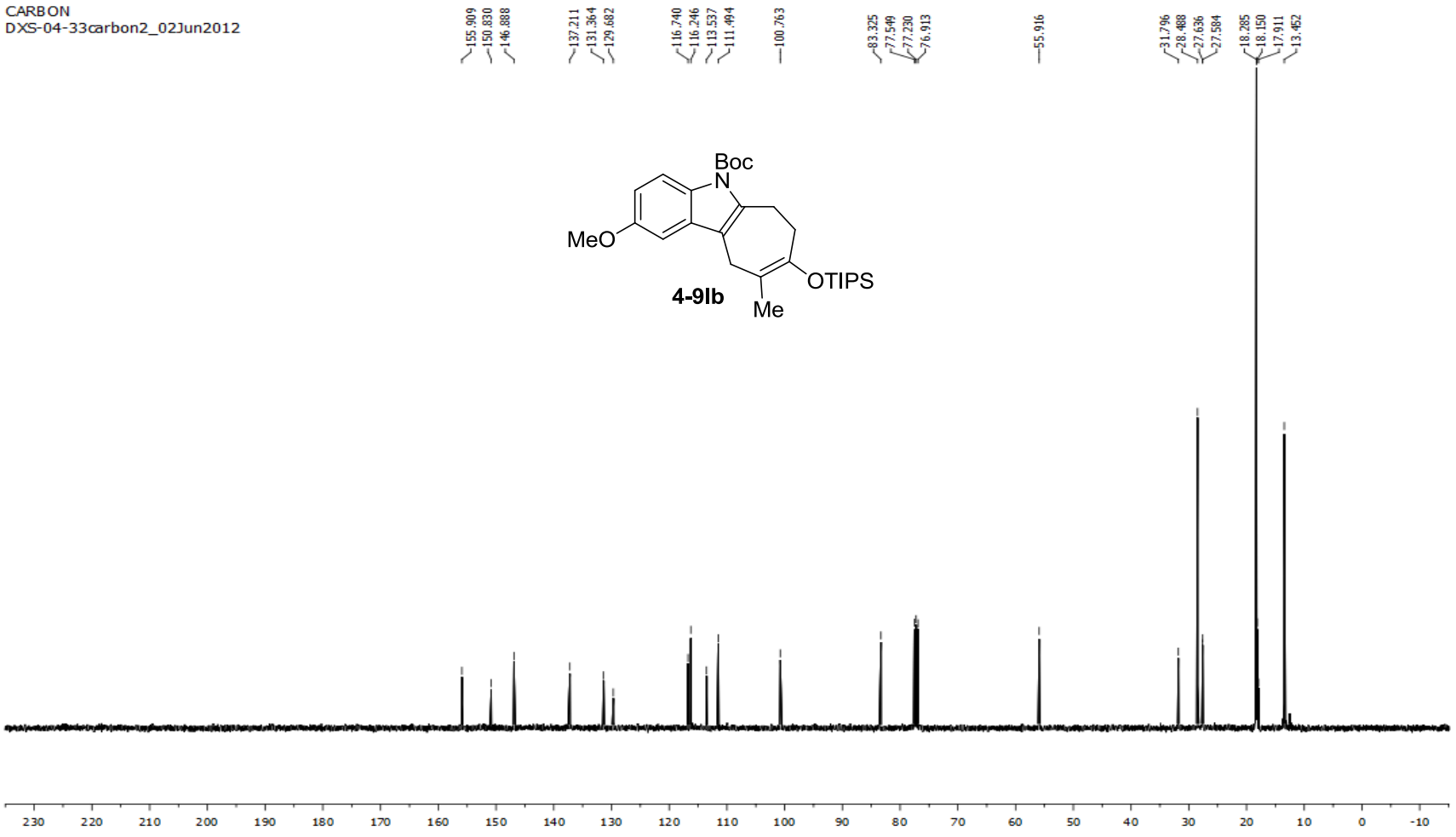
CARBON
DXS-04-22puretweo_24May2012

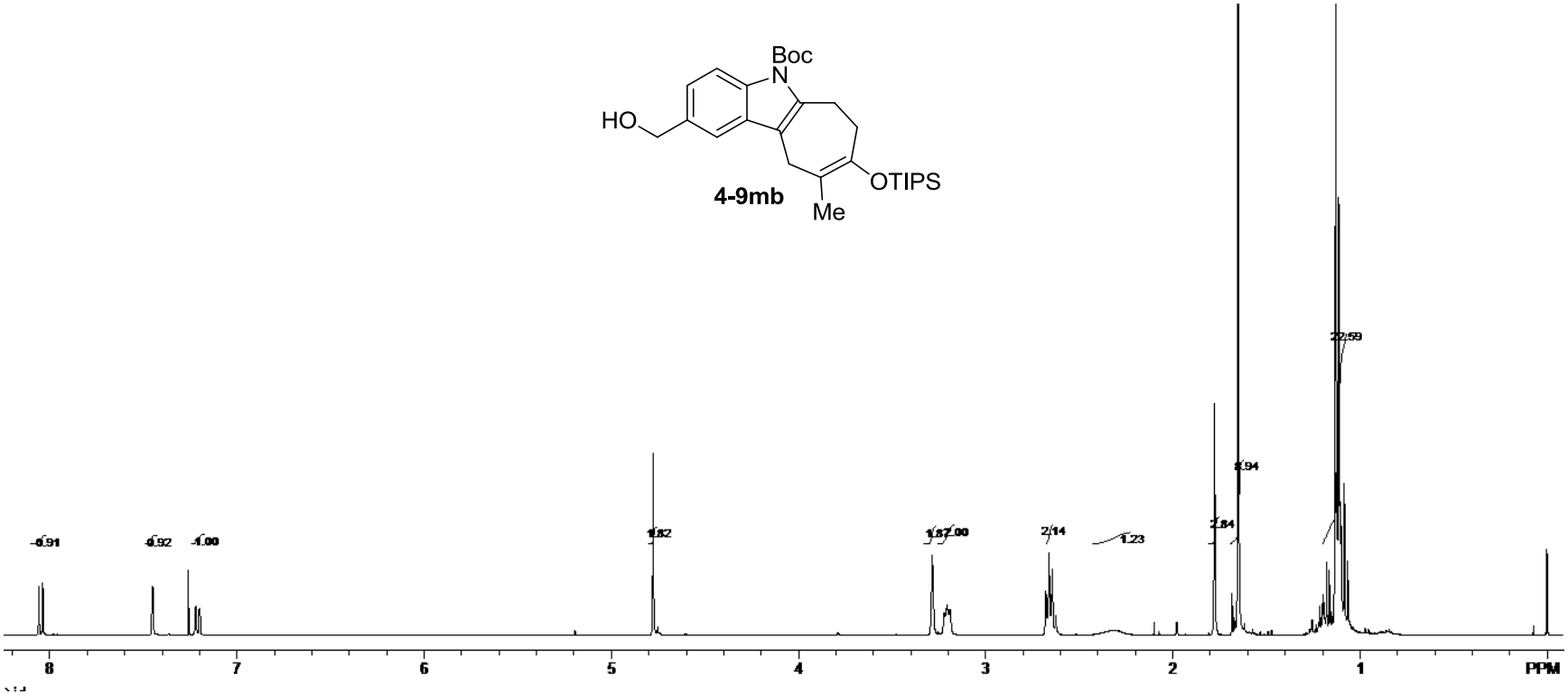
167.486
150.530
146.783
137.775
137.627
130.256
124.889
124.654
119.631
117.372
115.026
113.722
84.169
77.548
77.230
76.912
60.962
31.652
28.403
27.498
27.372
18.255
18.068
17.902
14.654
13.419



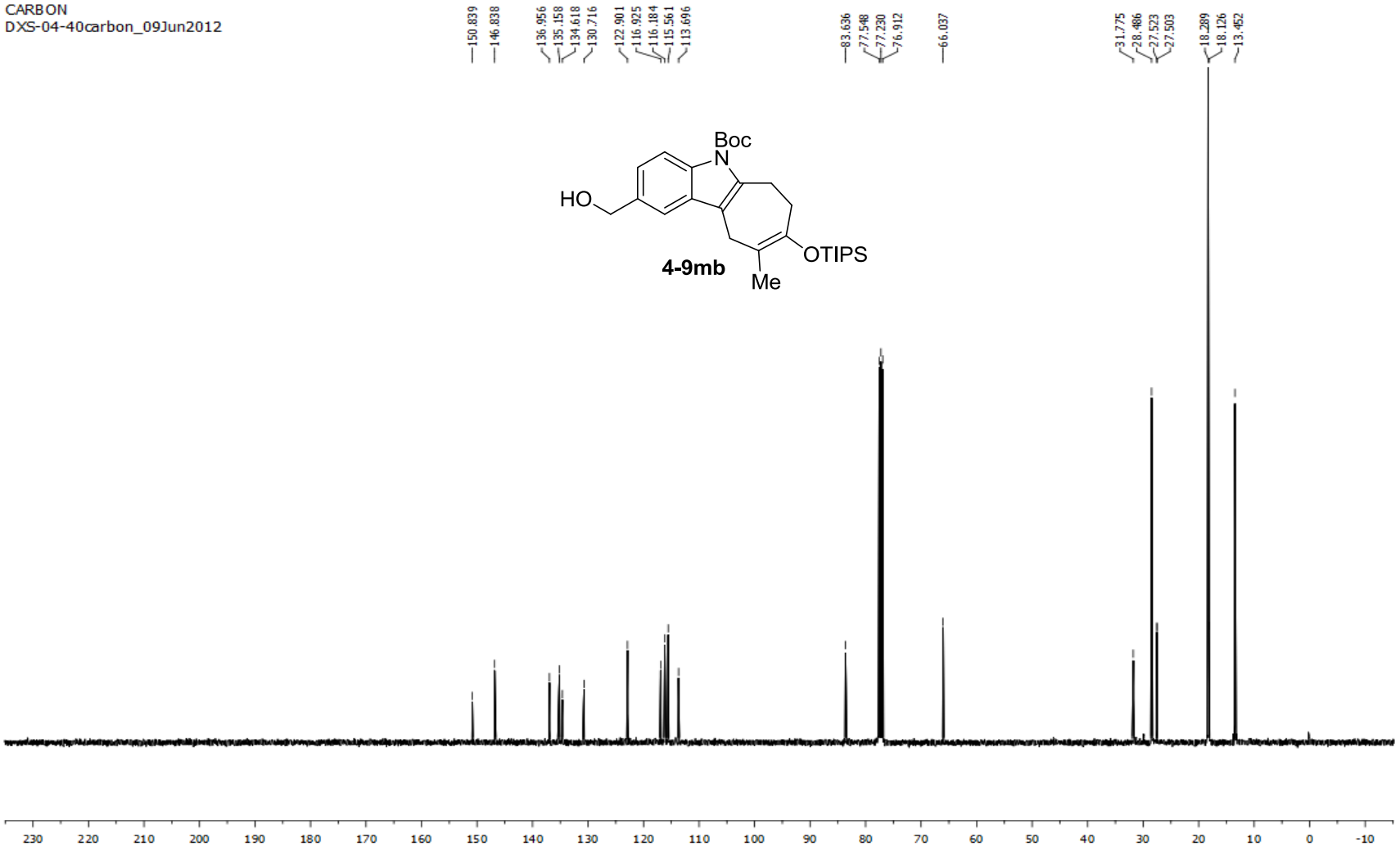
4-9kb

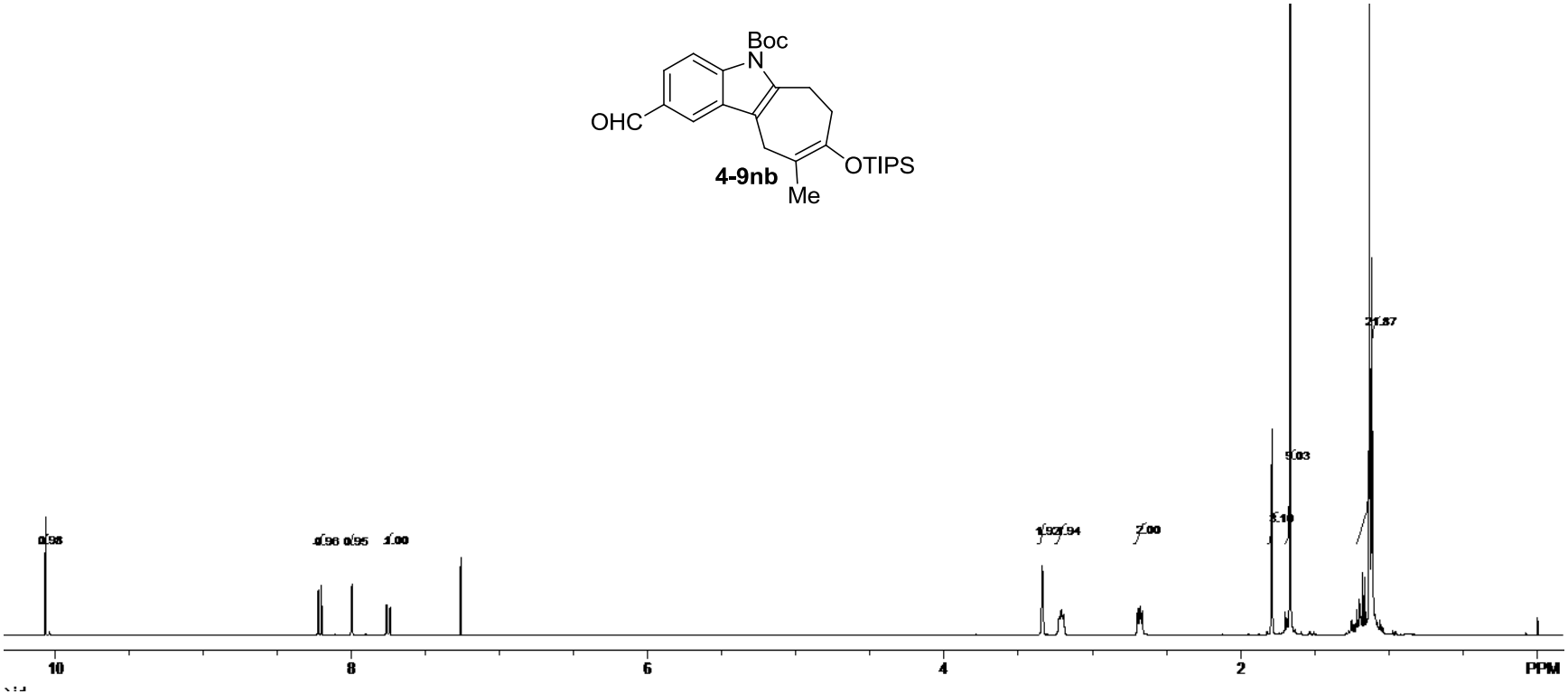

Boc
N
MeO
OTIPS
Me
4-9lb
1.00
4.06
3.03
3.94
2.03
5.16
9.10
22.24
8
7
6
5
4
3
2
1
PPM

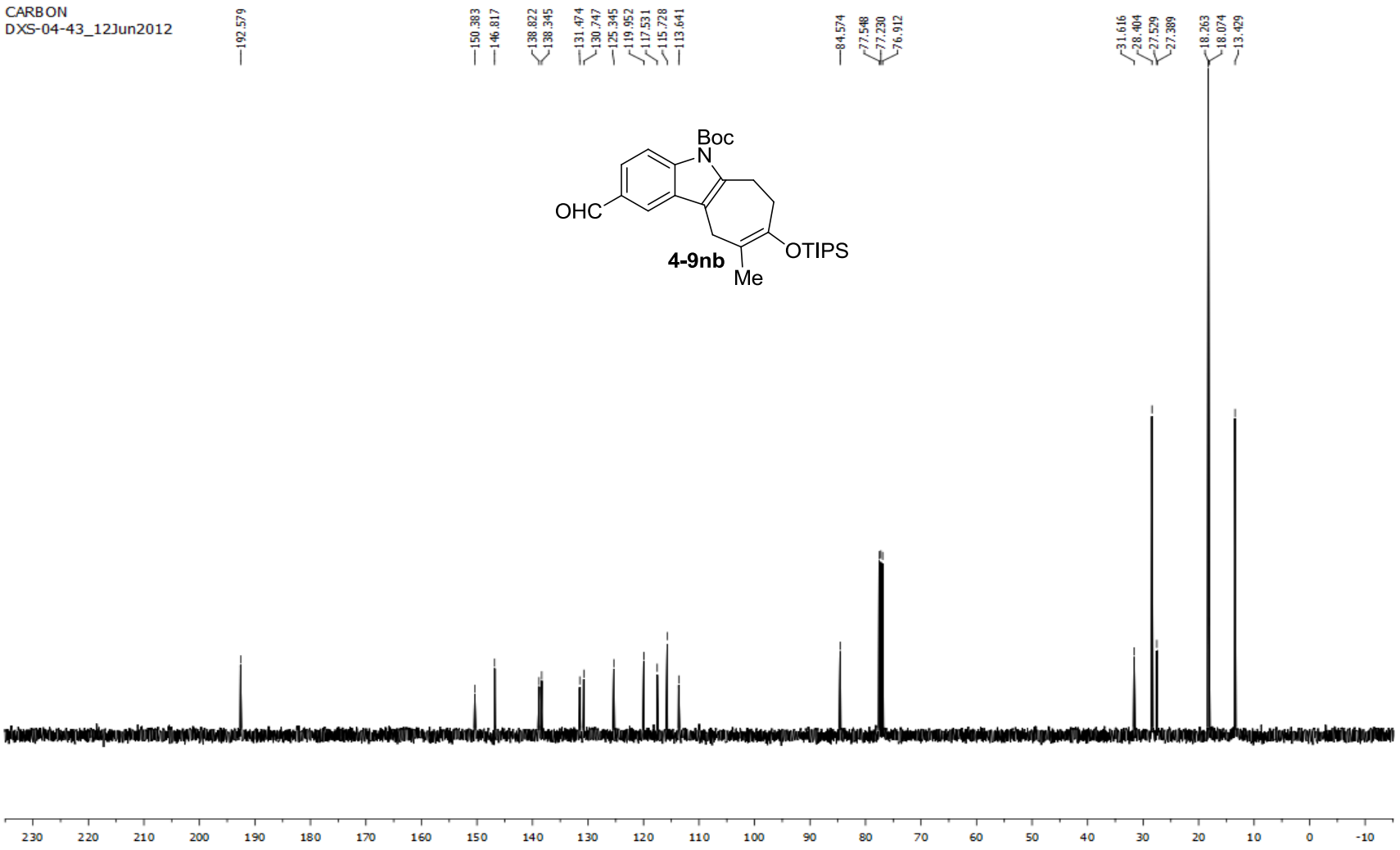

CARBON
DXS-04-33carbon2_02Jun2012
155.909
150.830
146.888
137.211
131.364
129.682
116.740
116.246
113.537
111.494
100.763
83.325
77.549
77.230
76.913
55.916
31.796
28.488
27.636
27.584
18.285
18.150
17.911
13.452
Boc
N
MeO
OTIPS
Me
4-9Ib
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

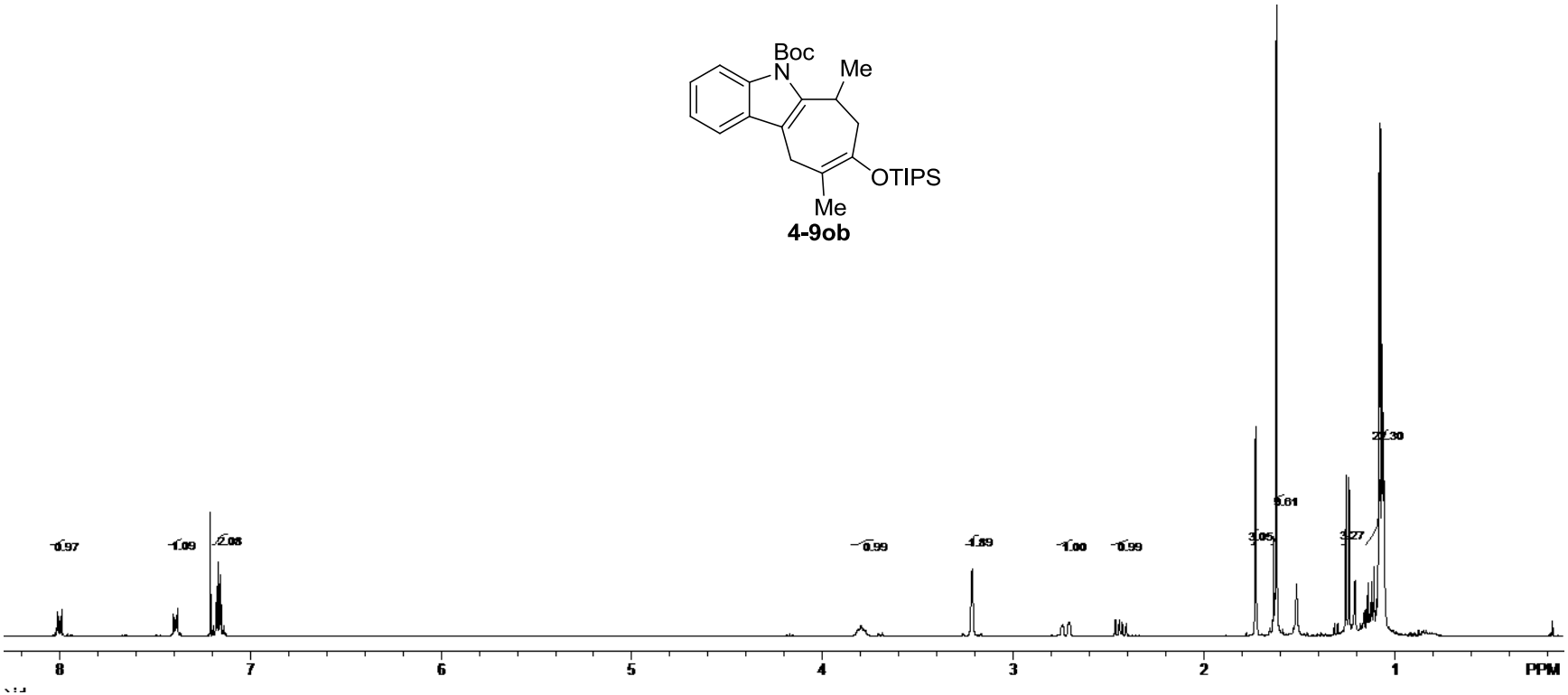

Boc
N
HO
OTIPS
Me
4-9mb
0.91
0.92
1.00
1.82
2.14
1.23
2.84
3.94
22.59
8
7
6
5
4
3
2
1
PPM

CARBON
DXS-04-40carbon_09Jun2012




Boc
N
OHC
OTIPS
Me
4-9nb
0.98
0.96
0.95
1.00
1.92
1.94
7.00
5.10
9.03
21.87
10
8
6
4
2
PPM

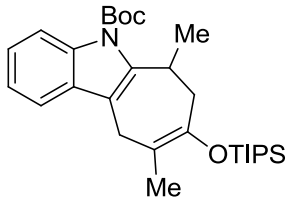

CARBON
DXS-04-43_12Jun2012
192.579
150.383
146.817
138.822
138.345
131.474
130.747
125.345
119.952
117.531
115.728
113.641
84.574
77.548
77.230
76.912
31.616
28.404
27.529
27.389
18.263
18.074
13.429
Boc
N
OHC
OTIPS
4-9nb
Me
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Boc
N
Me
OTIPS
Me
0.97
1.09
2.08
0.99
4.89
1.00
0.99
3.05
9.61
3.27
22.30
8
7
6
5
4
3
2
1
PPM

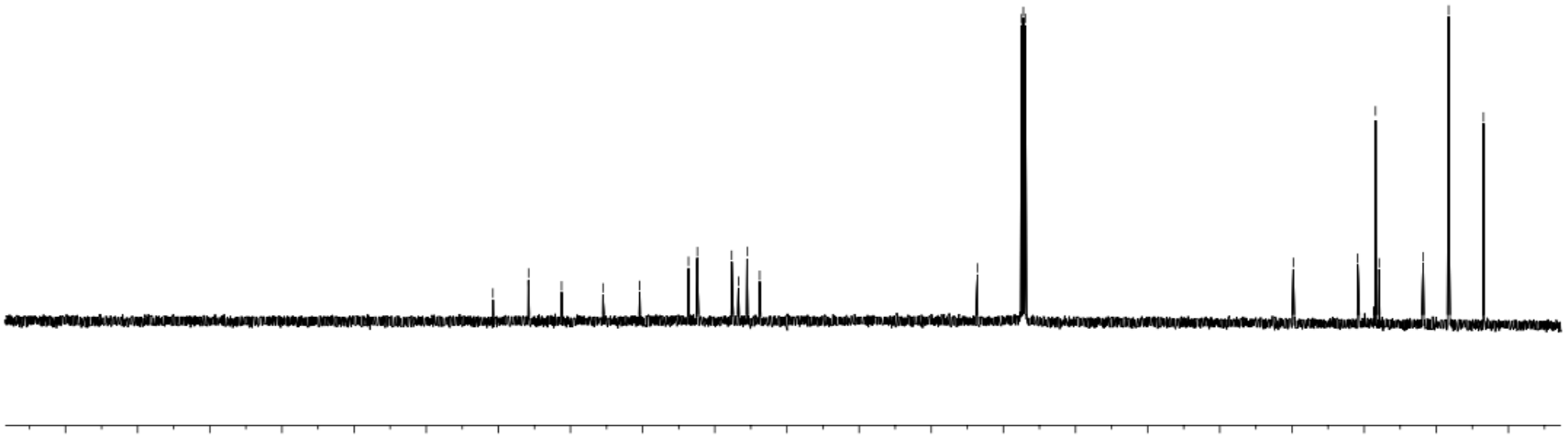
4-9ob

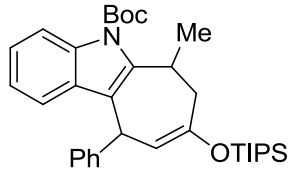
CARBON
DXS-04-101carbon_09Sep2012

150.760
145.804
141.234
135.493
130.411
123.652
122.414
117.657
116.713
115.510
113.780
83.590
77.484
77.230
76.975
39.810
30.879
28.419
27.918
21.814
18.285
18.187
13.464

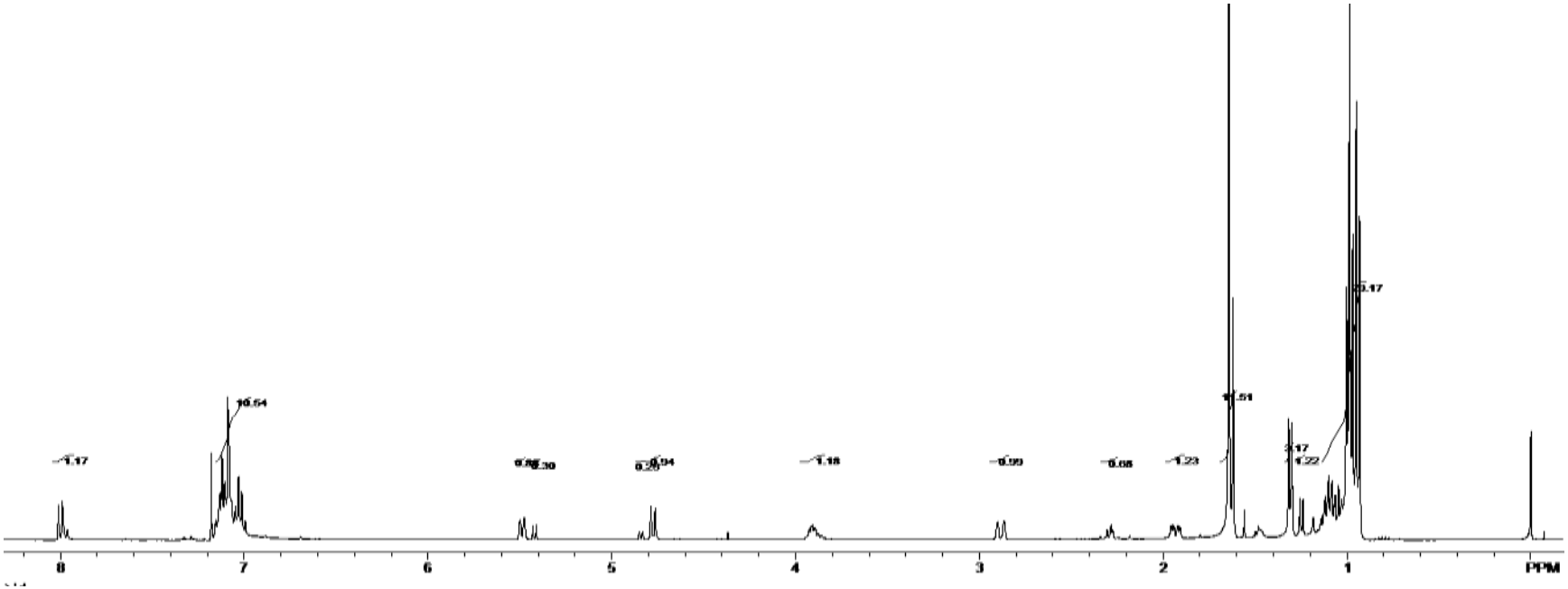


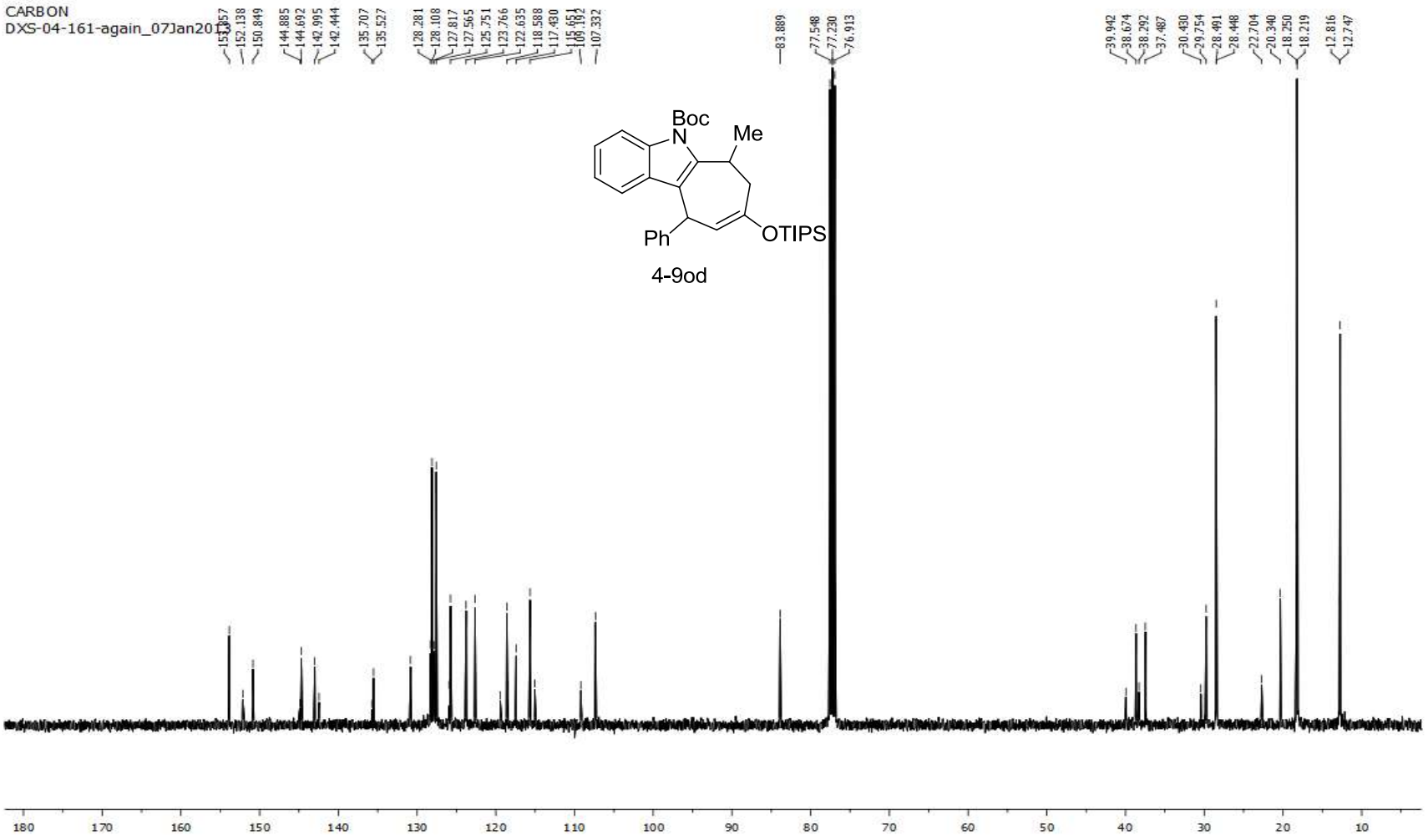
4-9ob

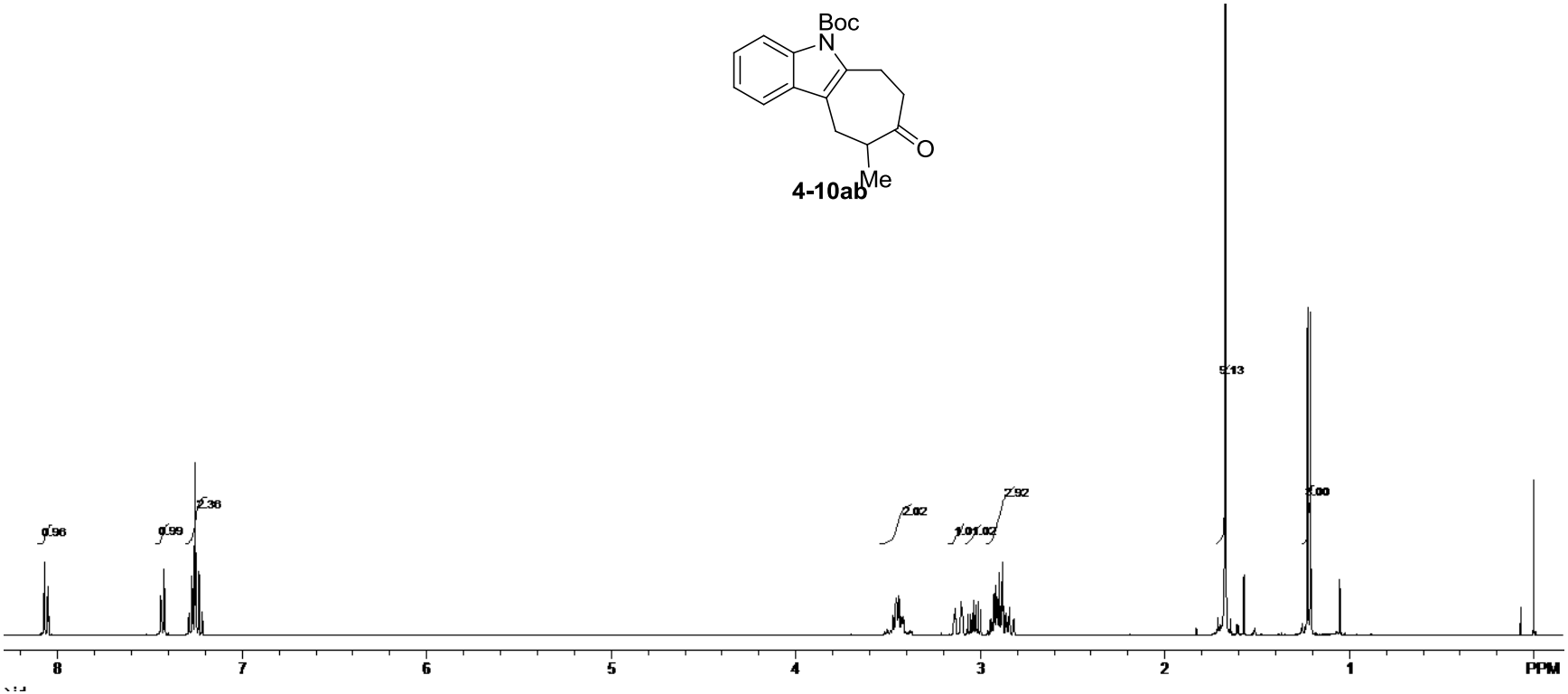


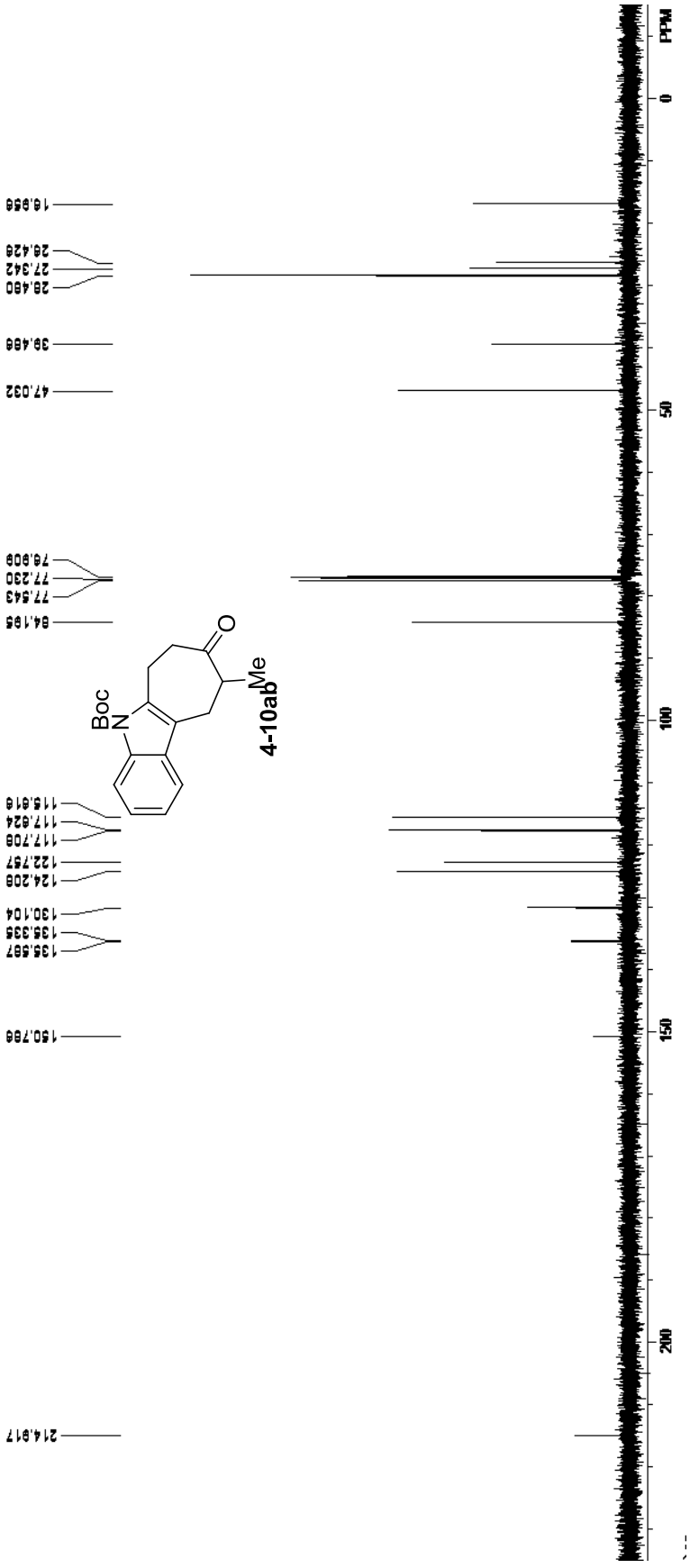

Boc
N
Me
Ph
OTIPS

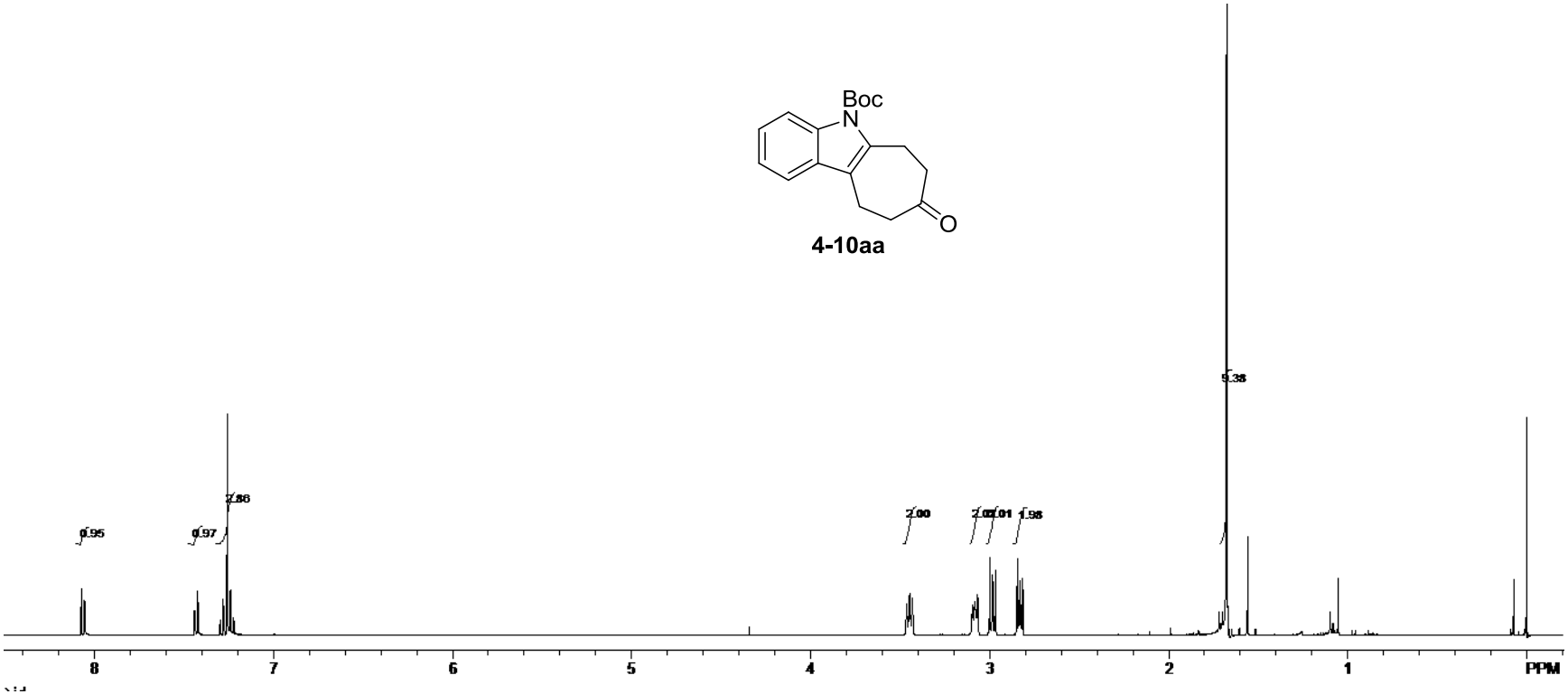
4-9od

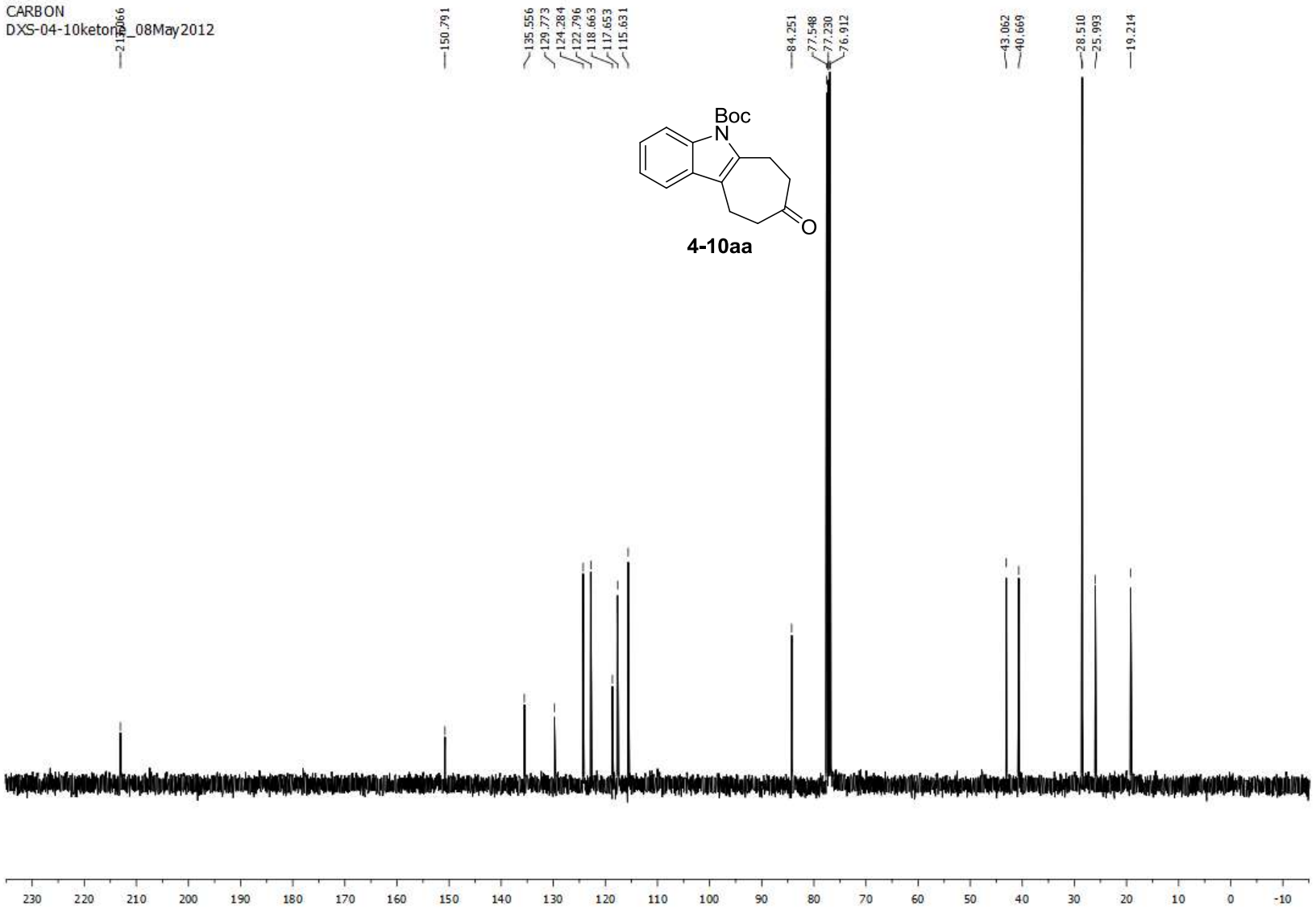

1.17
10.64
0.98
0.94
1.18
0.99
0.68
1.23
11.51
3.17
1.22
5.17
8
7
6
5
4
3
2
1
PPM


CARBON
DXS-04-161-again_07Jan2013
153.057
152.138
150.849
144.885
144.692
142.995
142.444
135.707
135.527
128.281
128.108
127.817
127.565
125.751
123.766
122.635
118.588
117.430
115.651
109.192
107.332
83.889
77.548
77.230
76.913
39.942
38.674
38.292
37.487
30.480
29.754
28.491
28.448
22.704
20.340
18.250
18.219
12.816
12.747
Boc
N
Me
Ph
OTIPS
4-9od
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


Boc
N
O
Me
4-10ab
0.96
0.99
2.36
2.02
2.92
9.13
3.00
8
7
6
5
4
3
2
1
PPM


PPM
0
50
100
150
200
214.917
150.786
138.587
136.335
130.104
124.208
122.757
117.708
117.624
115.816
84.185
77.543
77.230
76.908
47.032
39.488
28.480
27.342
26.428
18.956
Boc
N
O
Me
4-10ab


Boc
N
O
4-10aa
9.38
7.86
0.95
0.97
2.00
1.98
8
7
6
5
4
3
2
1
PPM


CARBON
DXS-04-10ketone_08May2012
213.066
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135.556
129.773
124.284
122.796
118.663
117.653
115.631
84.251
77.548
77.230
76.912
43.062
40.669
28.510
25.993
19.214
Boc
N
O
4-10aa
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
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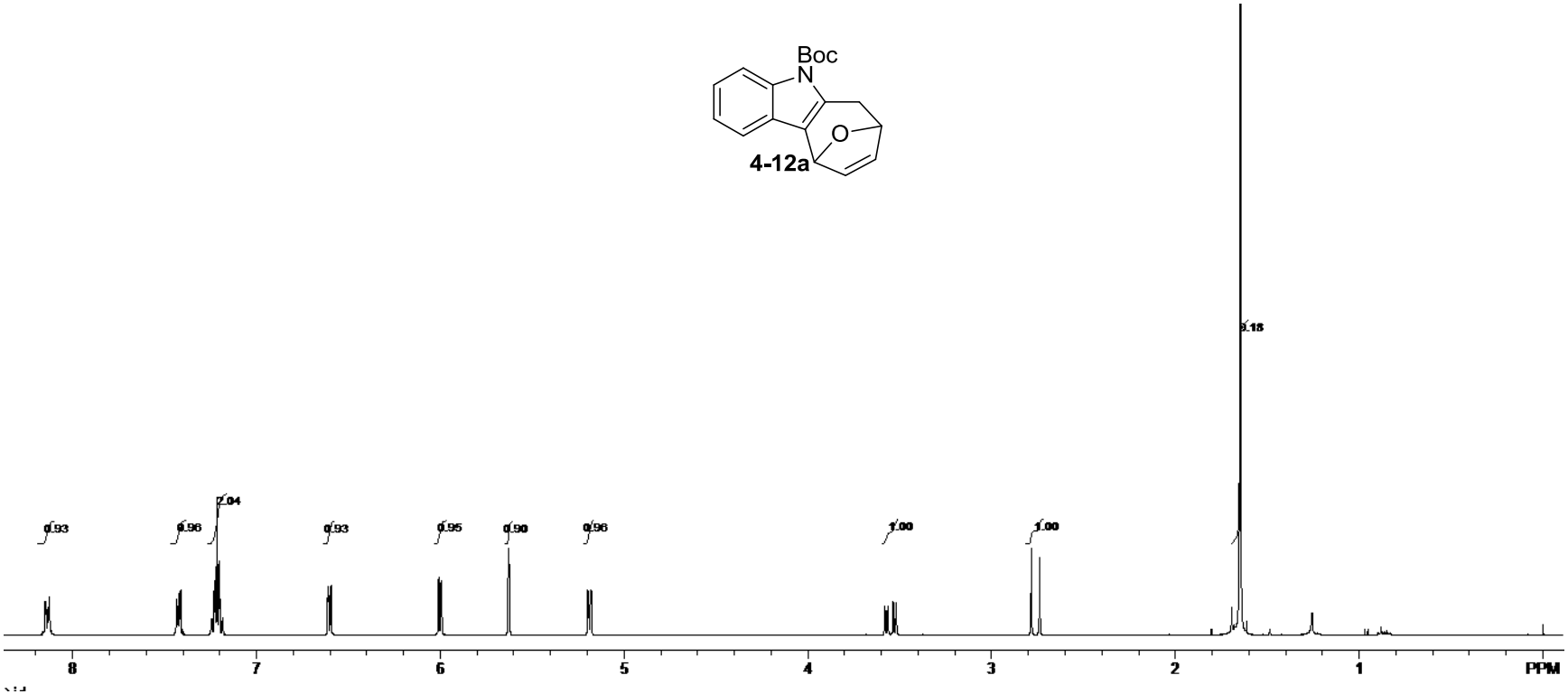
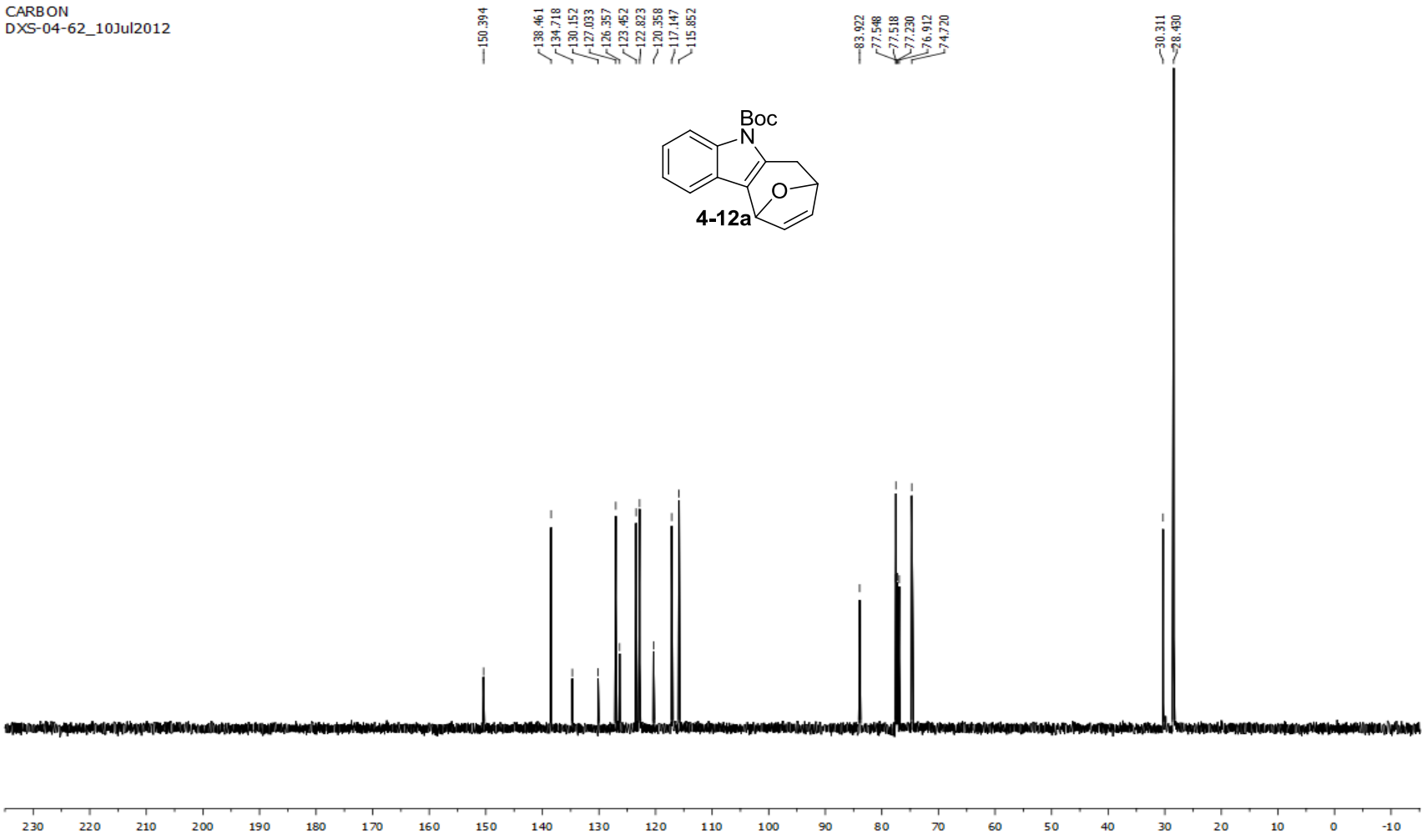
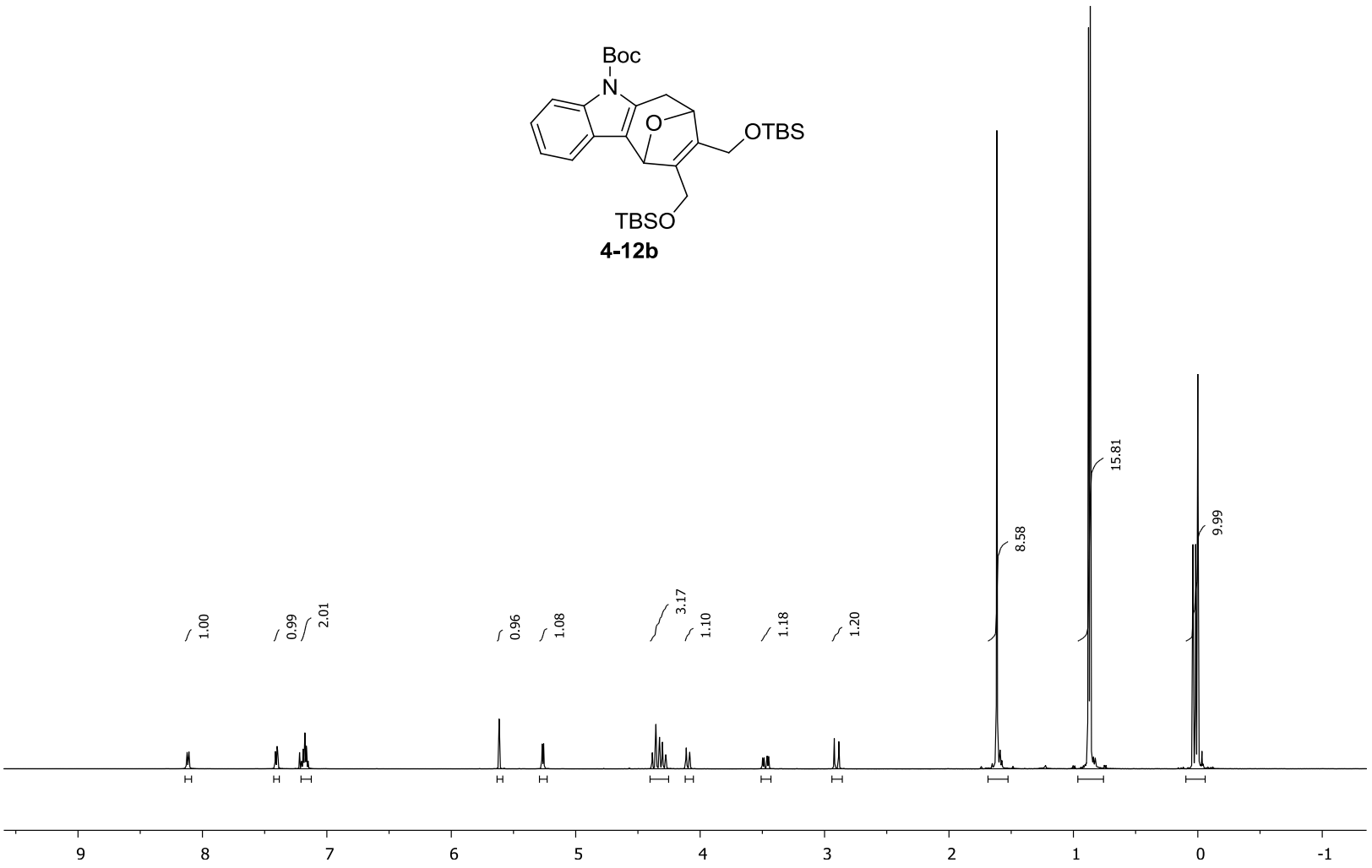
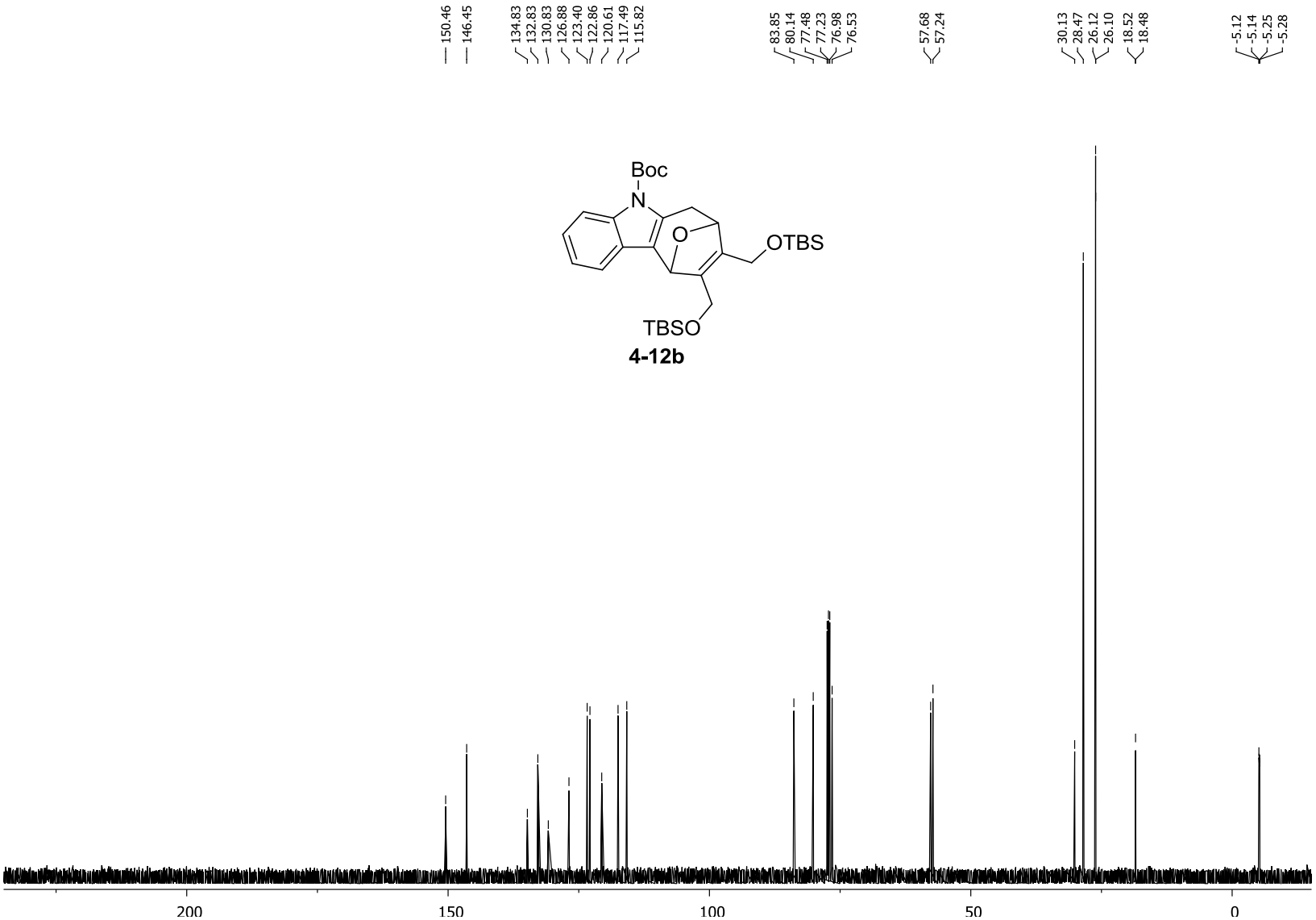
30
20
10
0
-10


Boc
N
O
4-12a
0.93
0.96
2.04
0.93
0.95
0.90
0.96
1.00
1.00
9.18
8
7
6
5
4
3
2
1
PPM


CARBON
DXS-04-62_10Jul2012
150.394
138.461
134.718
130.152
127.033
126.357
123.452
122.823
120.358
117.147
115.852
83.922
77.548
77.518
77.230
76.912
74.720
30.311
28.430
Boc
N
O
4-12a
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Boc
N
O
OTBS
TBSO
4-12b
1.00
0.99
2.01
0.96
1.08
3.17
1.10
1.18
1.20
8.58
15.81
9.99
9
8
7
6
5
4
3
2
1
0
-1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146.45
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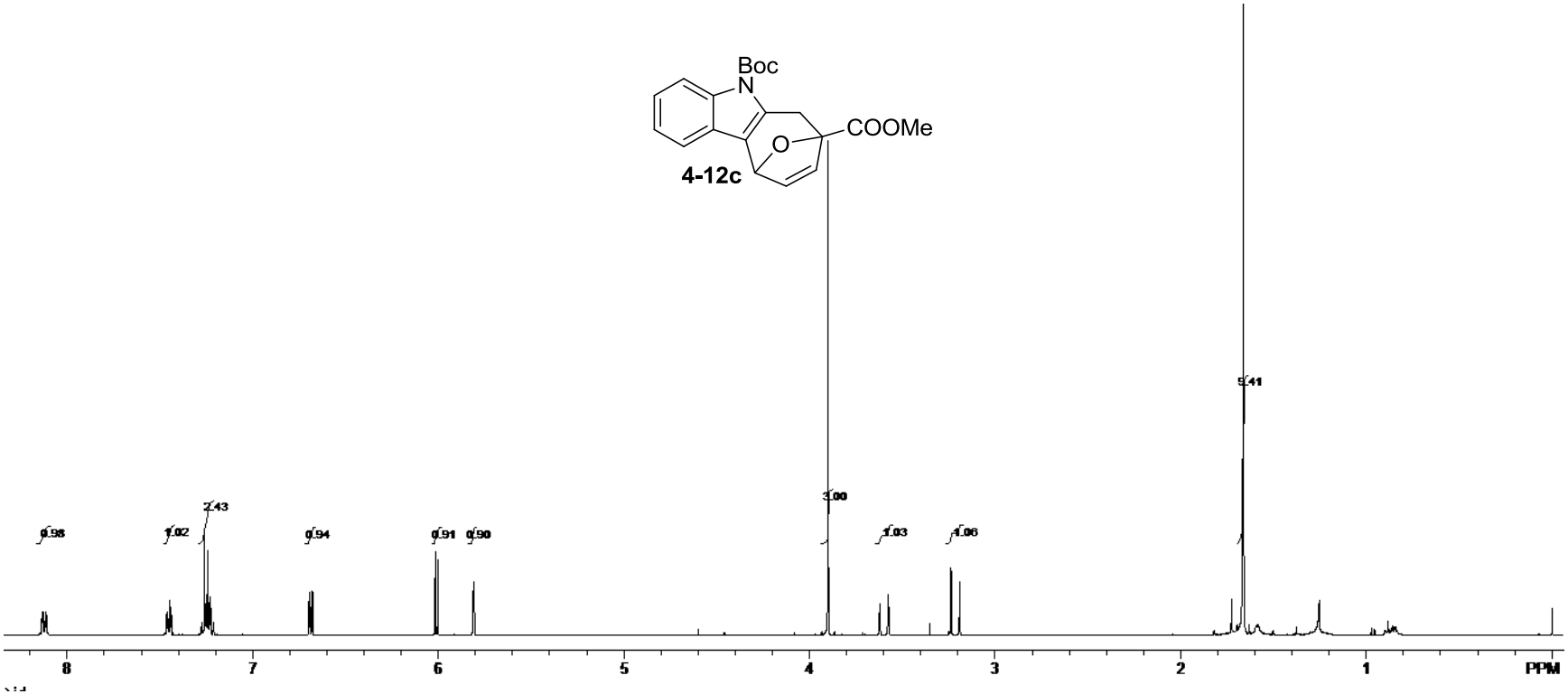
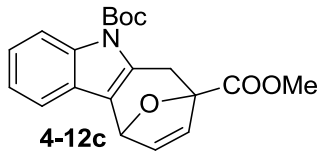
132.83
130.83
126.88
123.40
122.86
120.61
117.49
115.82
83.85
80.14
77.48
77.23
76.98
76.53
57.68
57.24
30.13
28.47
26.12
26.10
18.52
18.48
-5.12
-5.14
-5.25
-5.28
Boc
N
O
OTBS
TBSO
4-12b
200
150
100
50
0

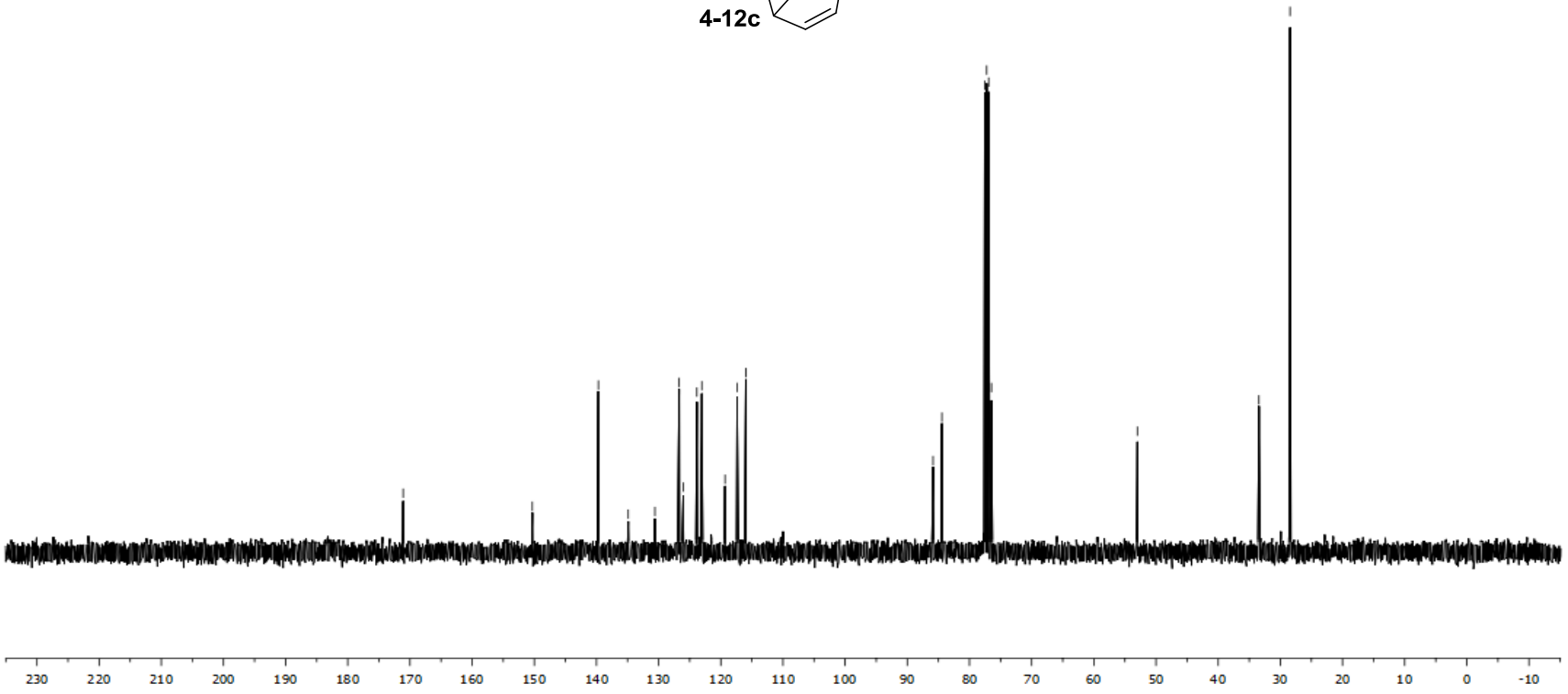

Boc
N
O
COOMe
4-12c
0.98
1.02
2.43
0.94
0.91
0.90
3.00
1.03
1.06
9.41
8
7
6
5
4
3
2
1
PPM

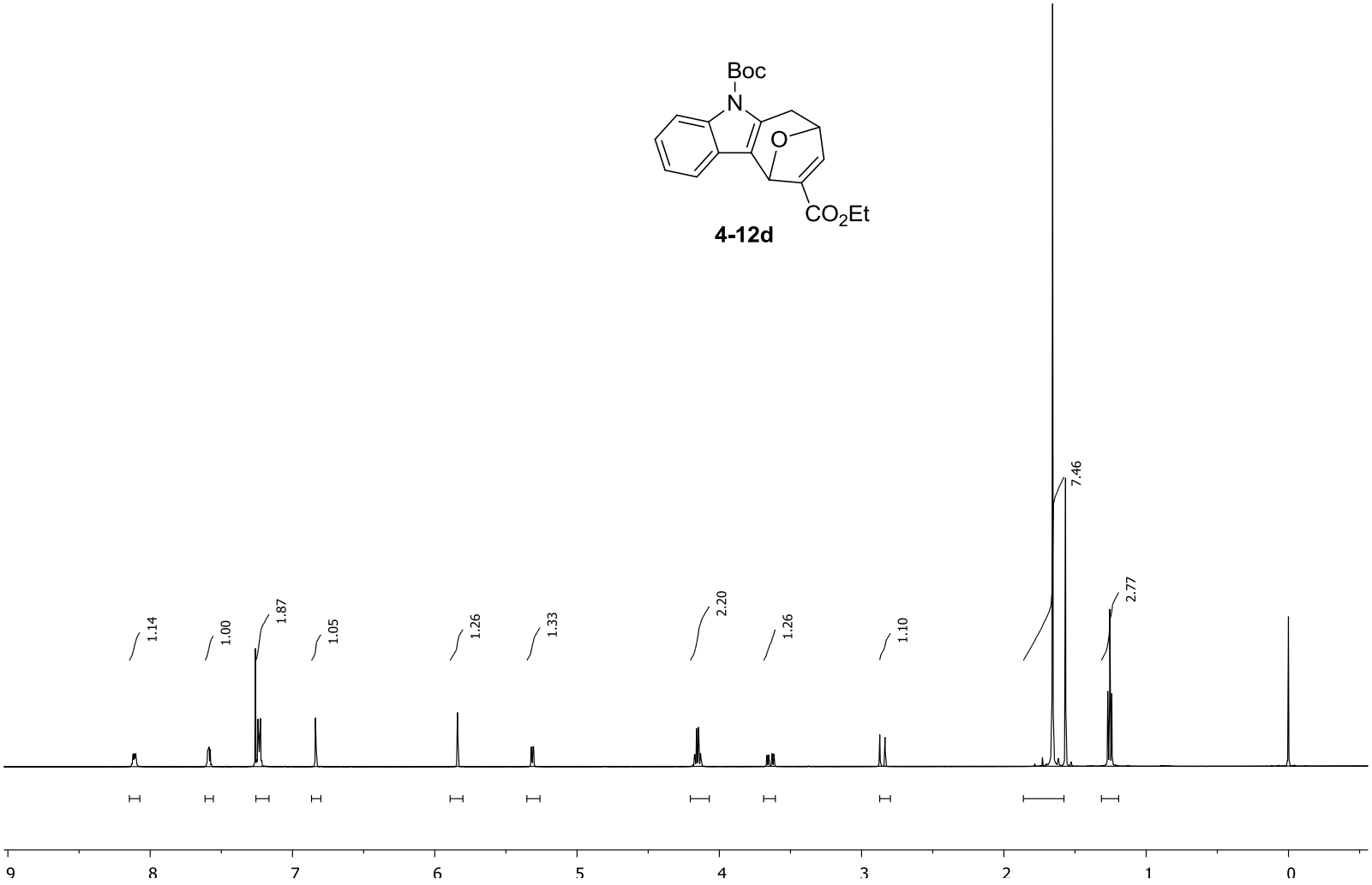
CARBON
DXS-04-65_17Jul2012

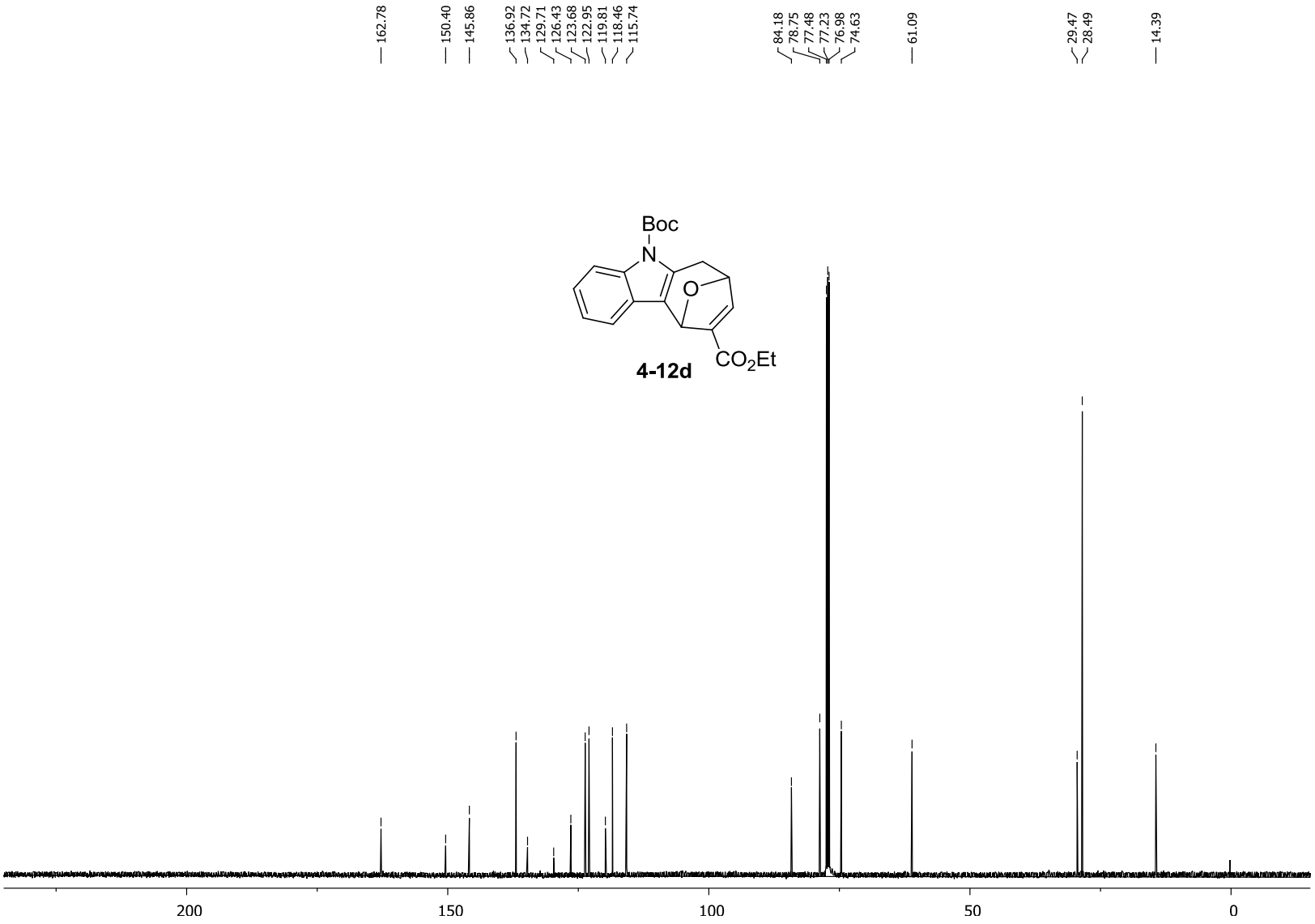
171.091
150.324
139.697
134.884
130.593
126.699
126.041
123.846
123.045
119.315
117.371
115.974
85.861
84.429
77.548
77.230
76.912
76.458
52.992
33.441
28.440

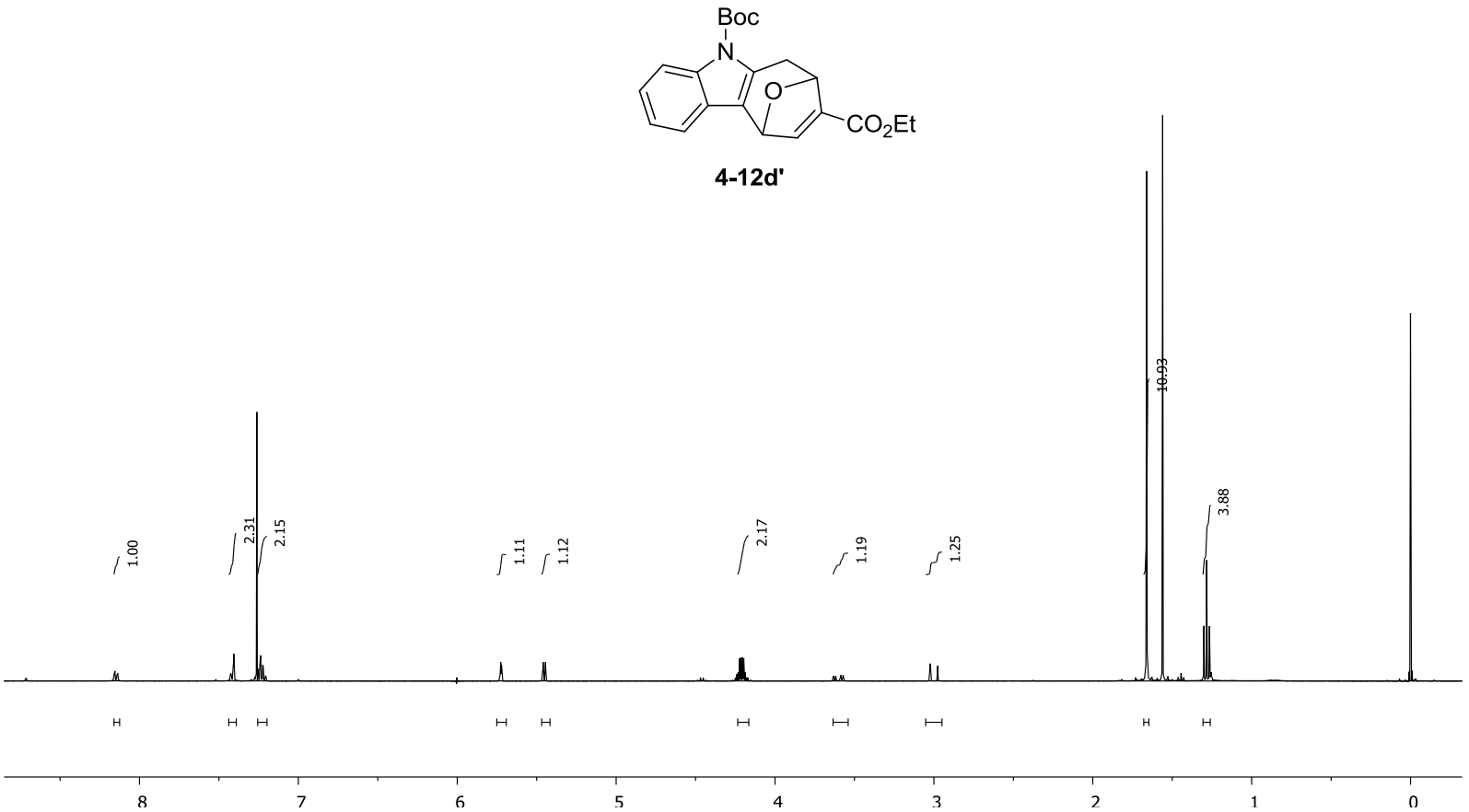


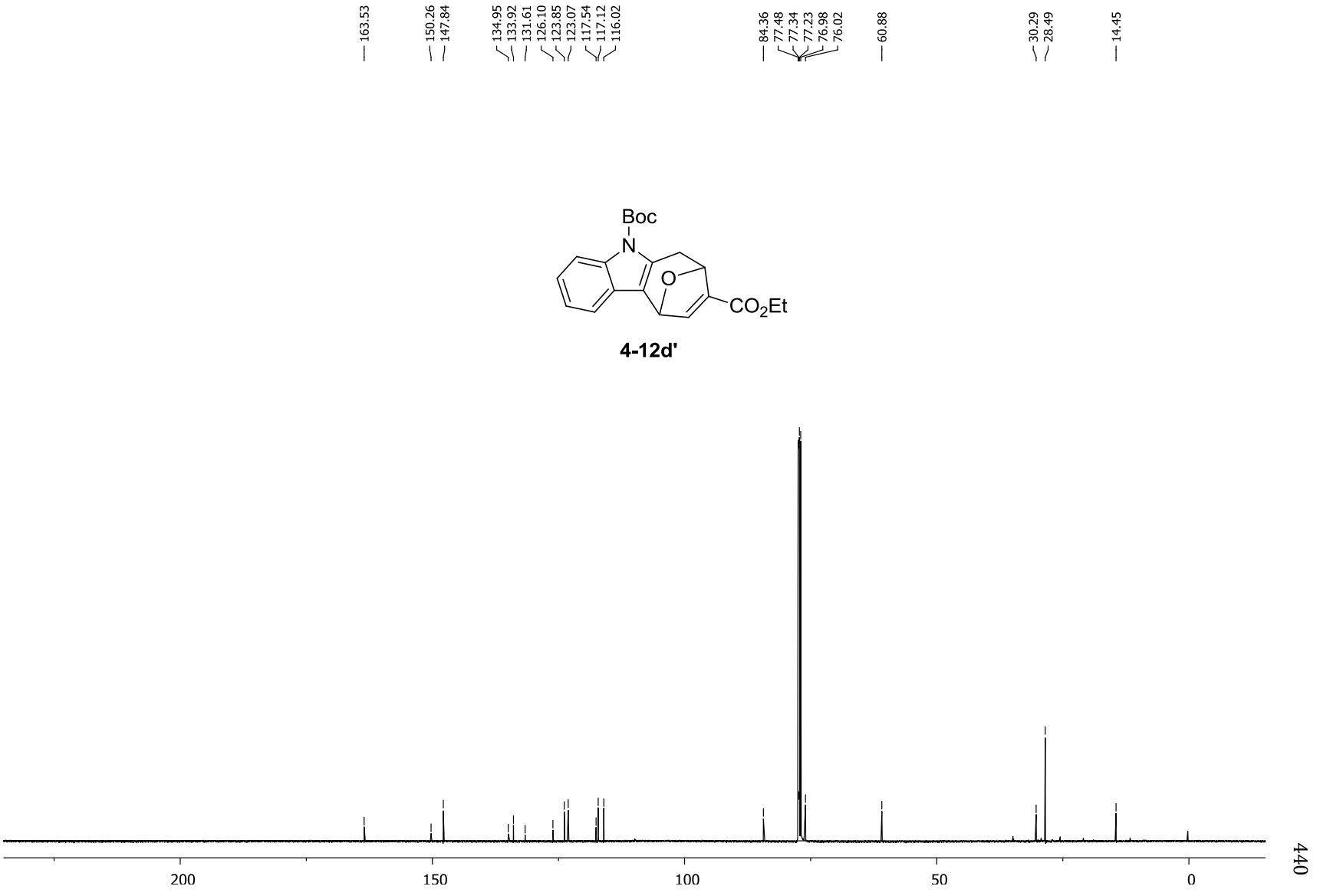
4-12c



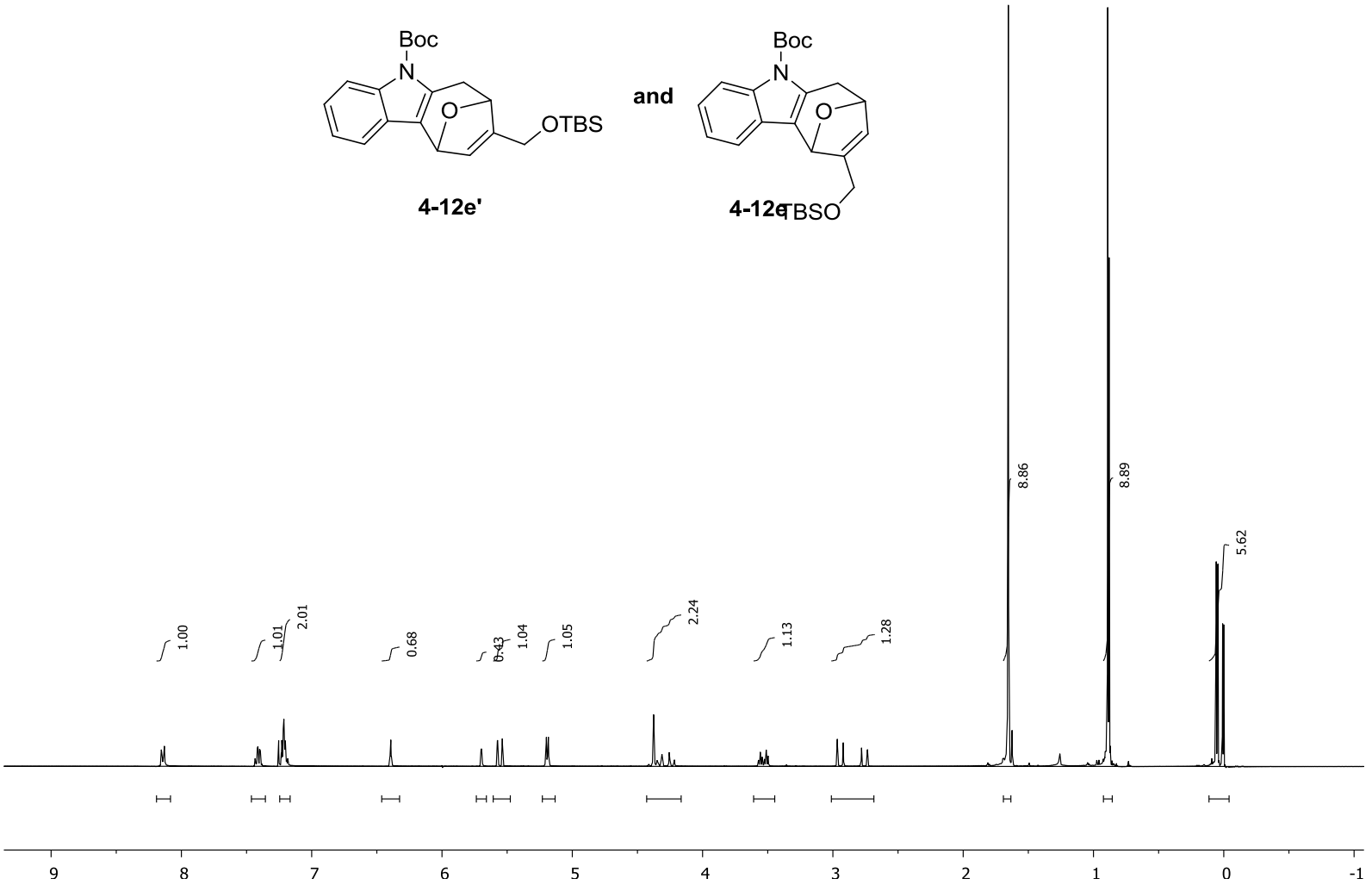

Boc
N
O
CO2Et
4-12d
1.14
1.00
1.87
1.05
1.26
1.33
2.20
1.26
1.10
7.46
2.77
9
8
7
6
5
4
3
2
1
0

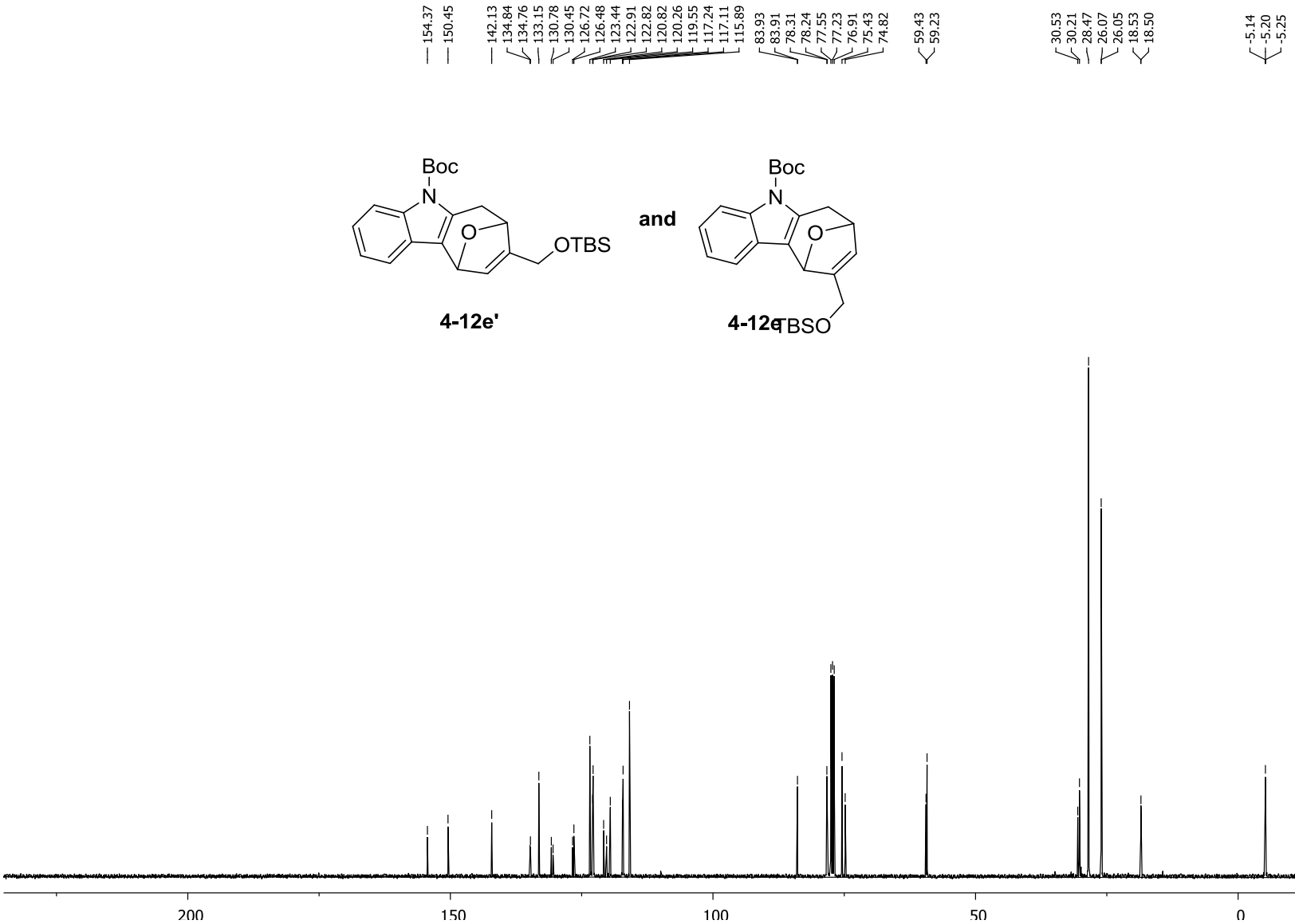

162.78
150.40
145.86
136.92
134.72
129.71
126.43
123.68
122.95
119.81
118.46
115.74
84.18
78.75
77.48
77.23
76.98
74.63
61.09
29.47
28.49
14.39
Boc
N
O
CO2Et
4-12d
200
150
100
50
0

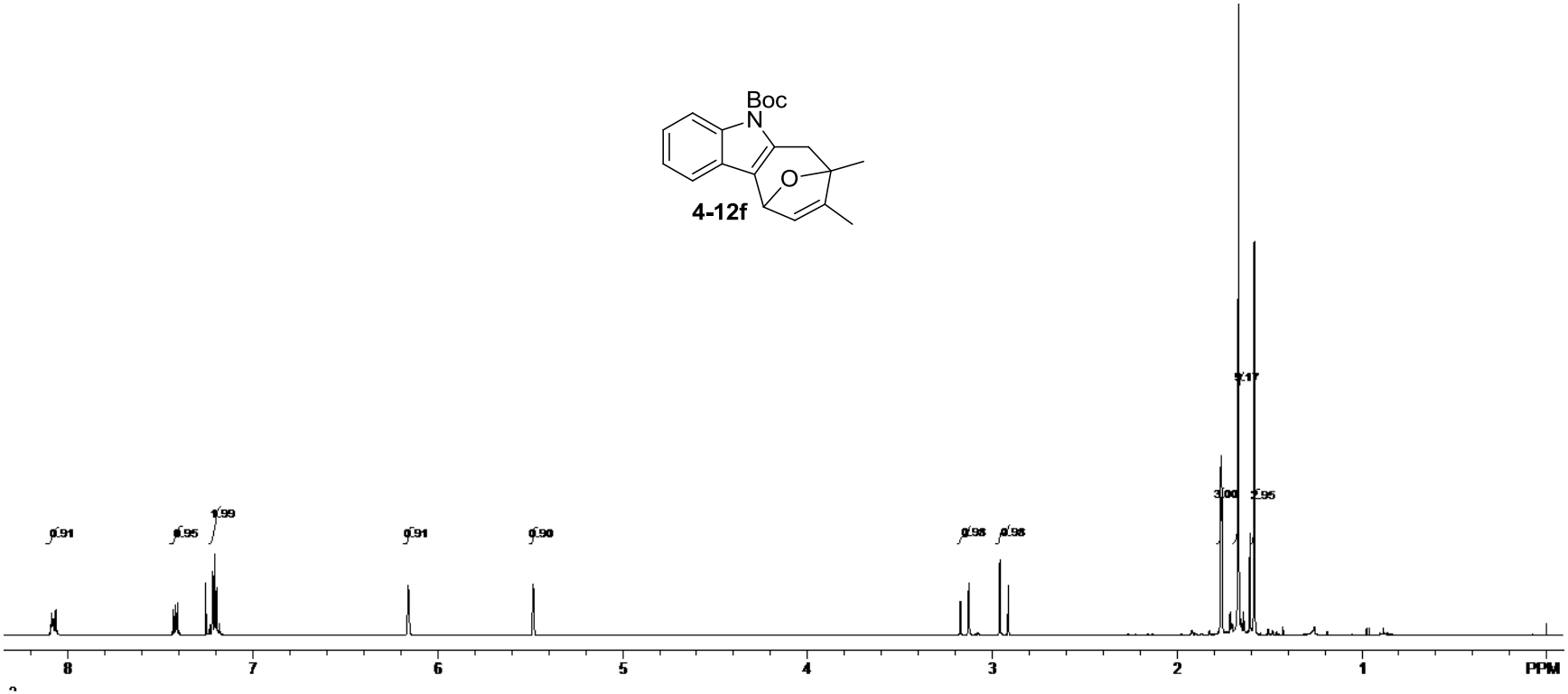

Boc
N
O
CO2Et
4-12d'
1.00
2.31
2.15
1.11
1.12
2.17
1.19
1.25
10.93
3.88
8
7
6
5
4
3
2
1
0


163.53
150.26
147.84
134.95
133.92
131.61
126.10
123.85
123.07
117.54
117.12
116.02
84.36
77.48
77.34
77.23
76.98
76.02
60.88
30.29
28.49
14.45
Boc
N
O
CO2Et
200
150
100
50
0

4-12d'

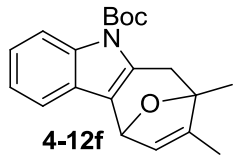

Boc
N
O
OTBS
4-12e'
and
Boc
N
O
TBSO
4-12e
1.00
1.01
2.01
0.68
0.43
1.04
1.05
2.24
1.13
1.28
8.86
8.89
5.62
9
8
7
6
5
4
3
2
1
0
-1


154.37
150.45
142.13
134.84
134.76
133.15
130.78
130.45
126.72
126.48
123.44
122.91
122.82
120.82
120.26
119.55
117.24
117.11
115.89
83.93
83.91
78.31
78.24
77.55
77.23
76.91
75.43
74.82
59.43
59.23
30.53
30.21
28.47
26.07
26.05
18.53
18.50
-5.14
-5.20
-5.25
Boc
N
O
OTBS
and
Boc
N
O
TBSO
4-12e'
4-12e
200
150
100
50
0


Boc
N
O
4-12f
0.91
0.95
1.99
0.91
0.90
0.98
0.98
9.17
3.00
2.95
8
7
6
5
4
3
2
1
PPM

CARBON
DXS-04-70_24Jul2012

150.635
139.815
134.738
133.012
132.888
126.513
123.350
122.807
121.401
117.267
115.906
84.502
83.979
77.547
77.230
76.912
74.262
35.524
28.496
23.411
11.276



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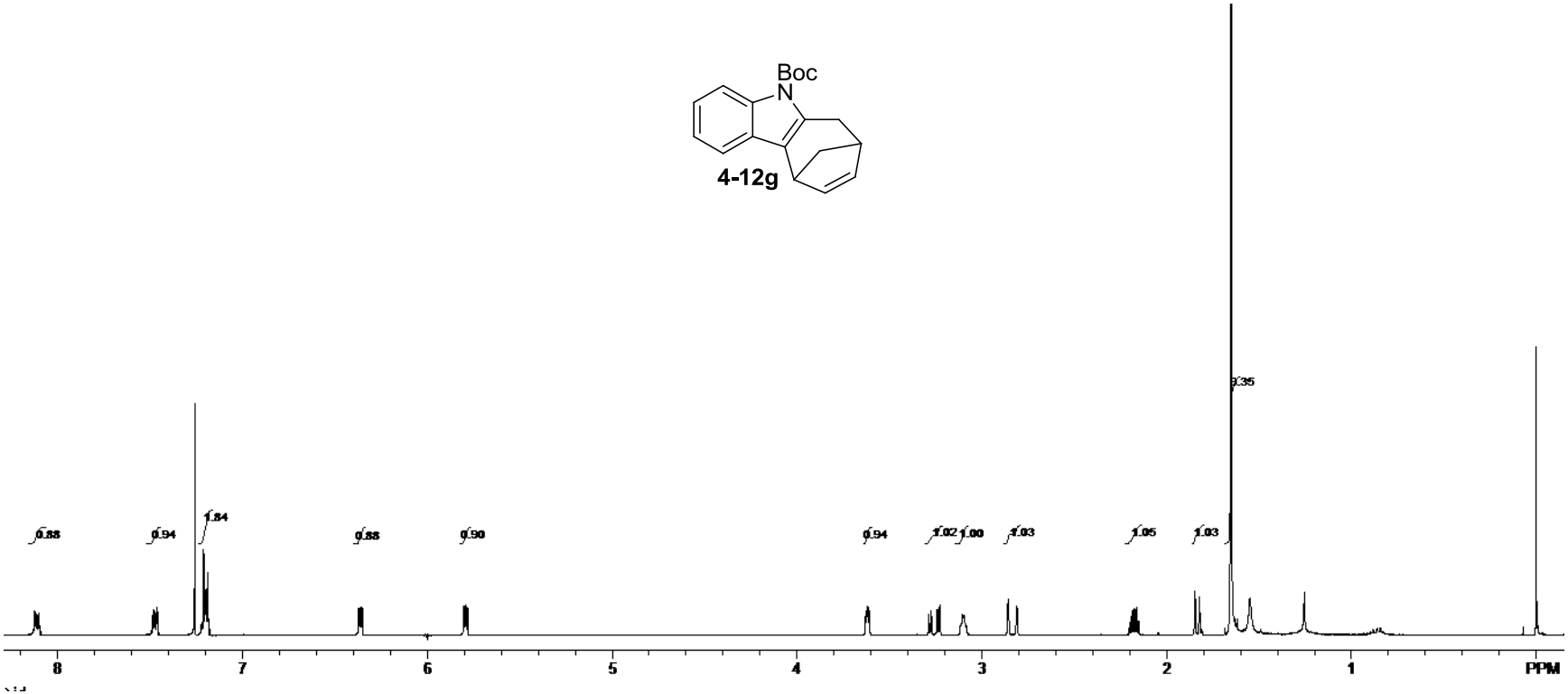
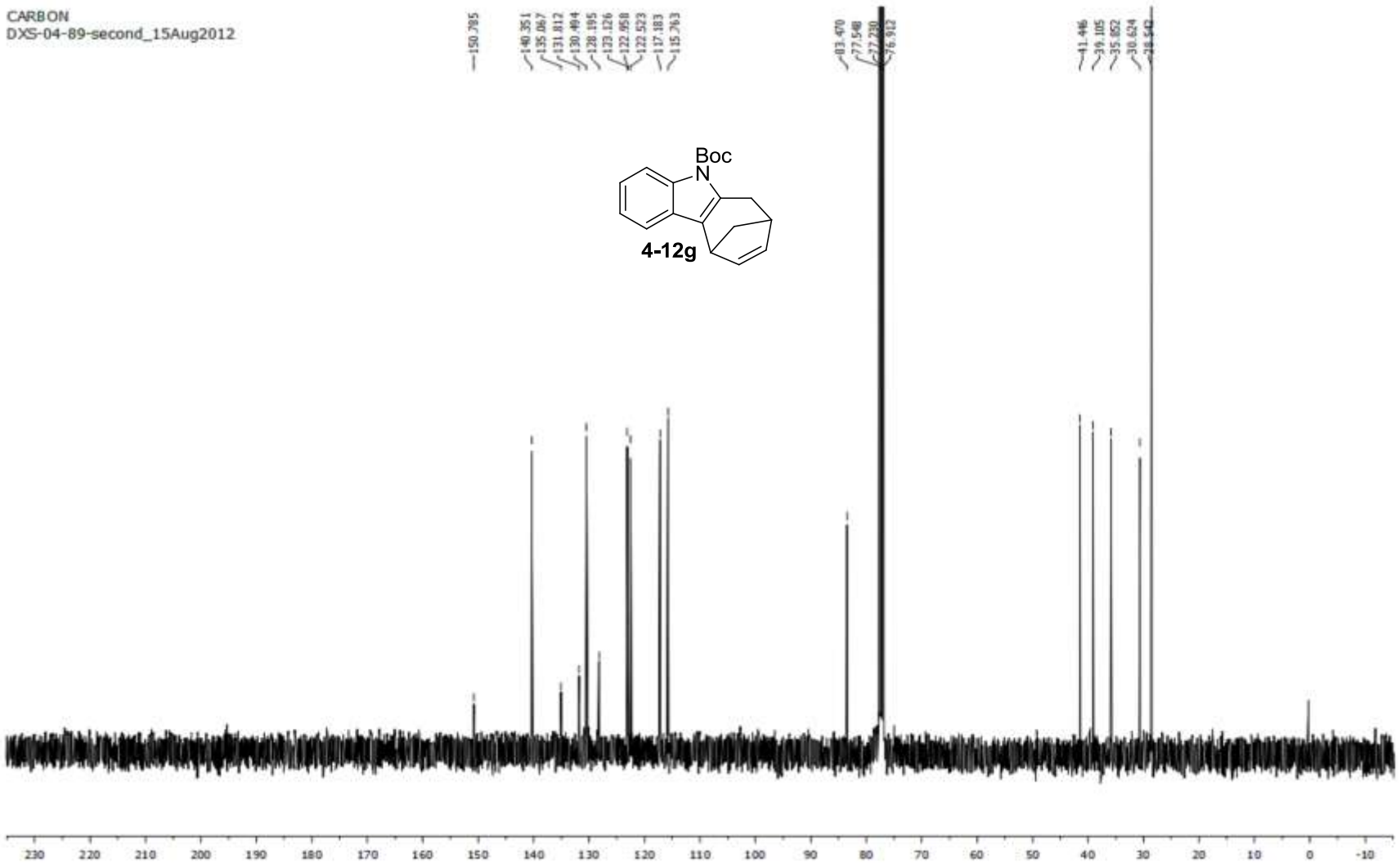
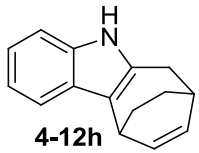
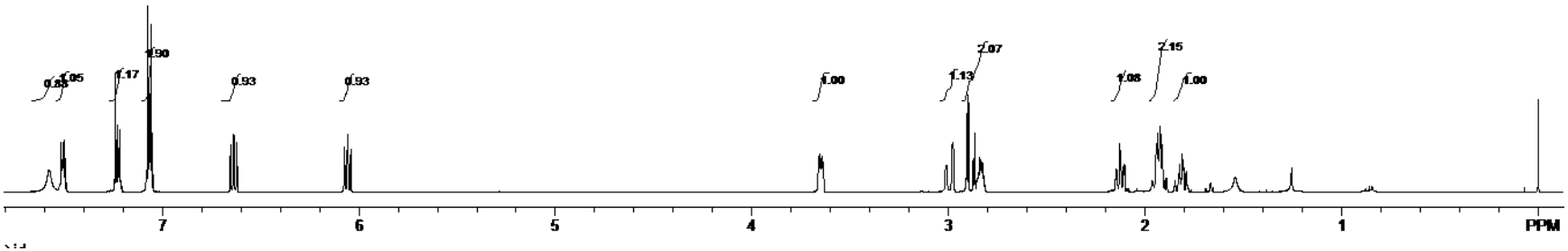
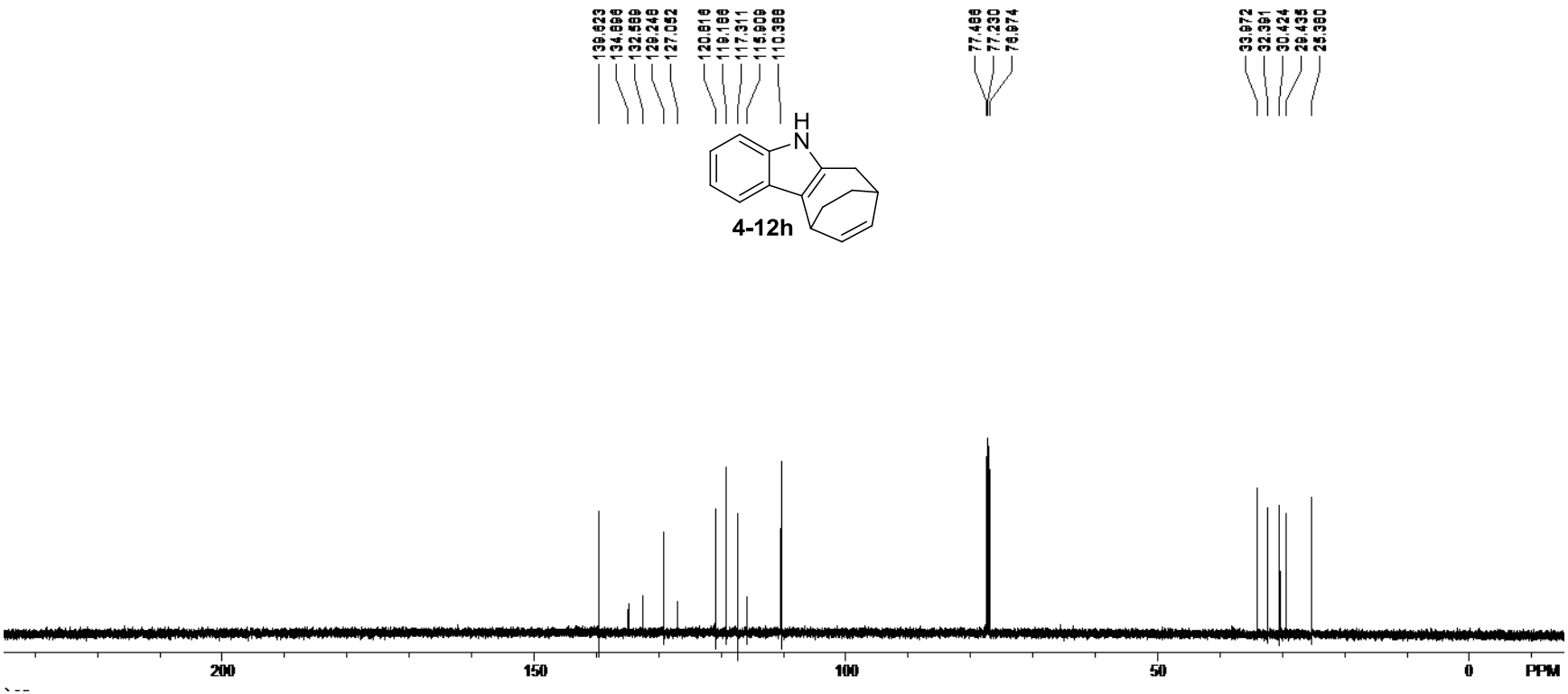

Boc
N
4-12g
9.35
PPM

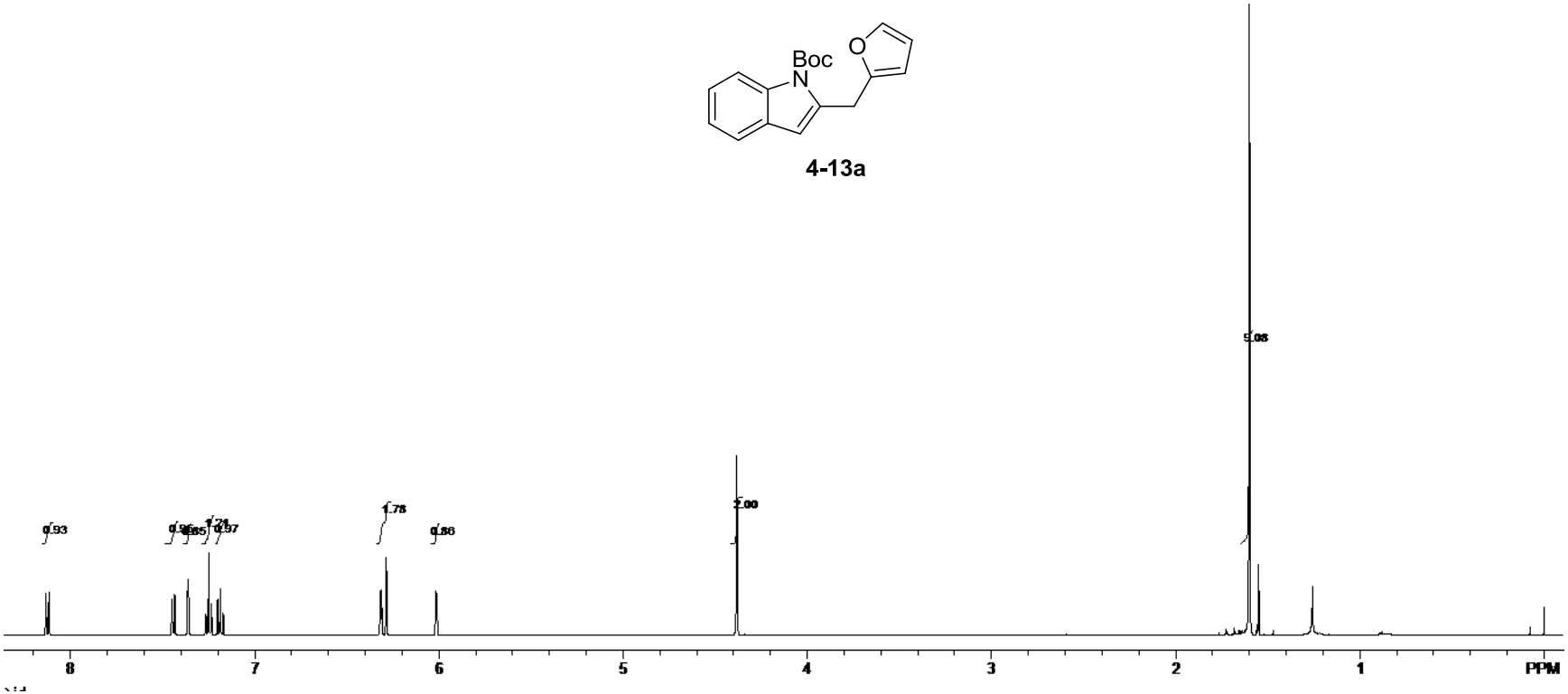

CARBON
DXS-04-89-second_15Aug2012
150.785
140.351
135.067
131.812
130.494
128.195
123.126
122.958
122.523
117.183
115.763
83.470
77.548
77.230
76.912
41.446
39.105
35.852
30.624
28.542
Boc
N
4-12g
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

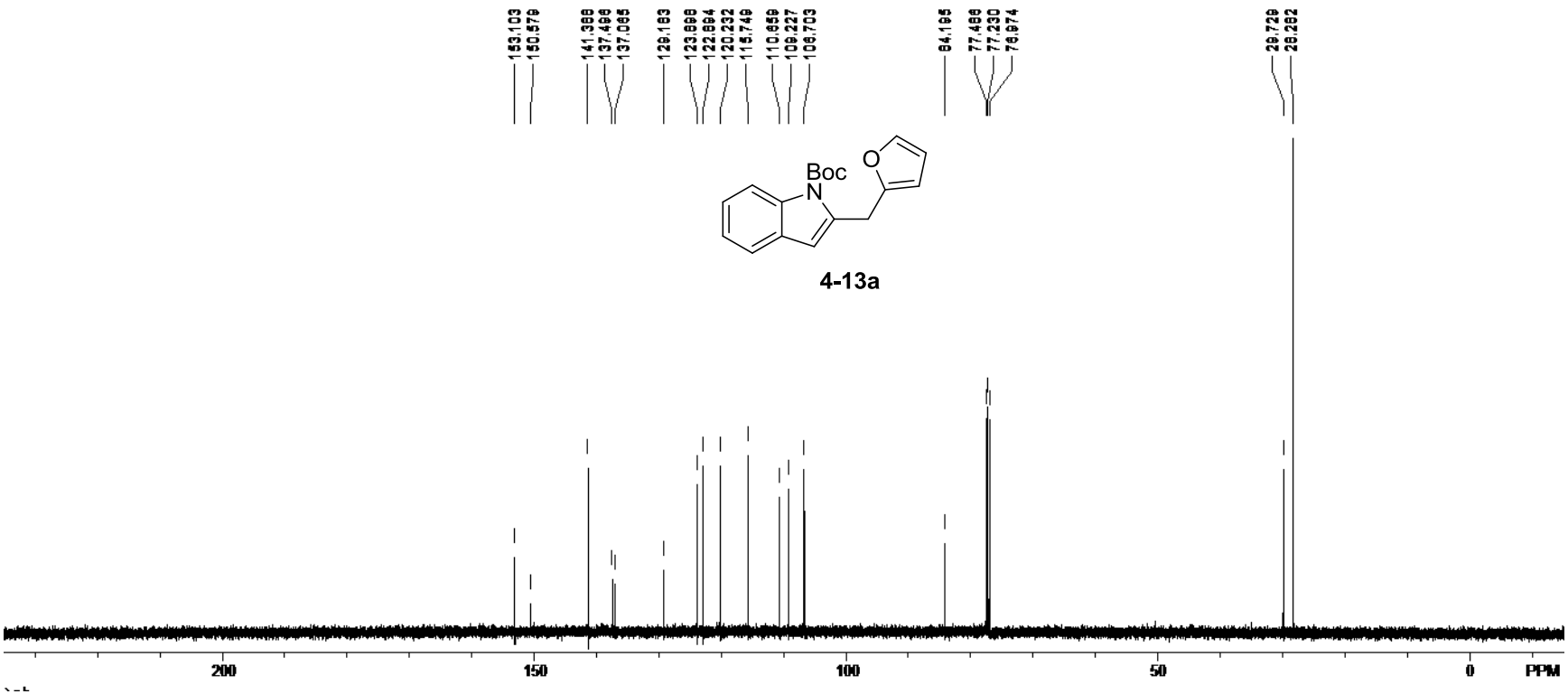


4-12h

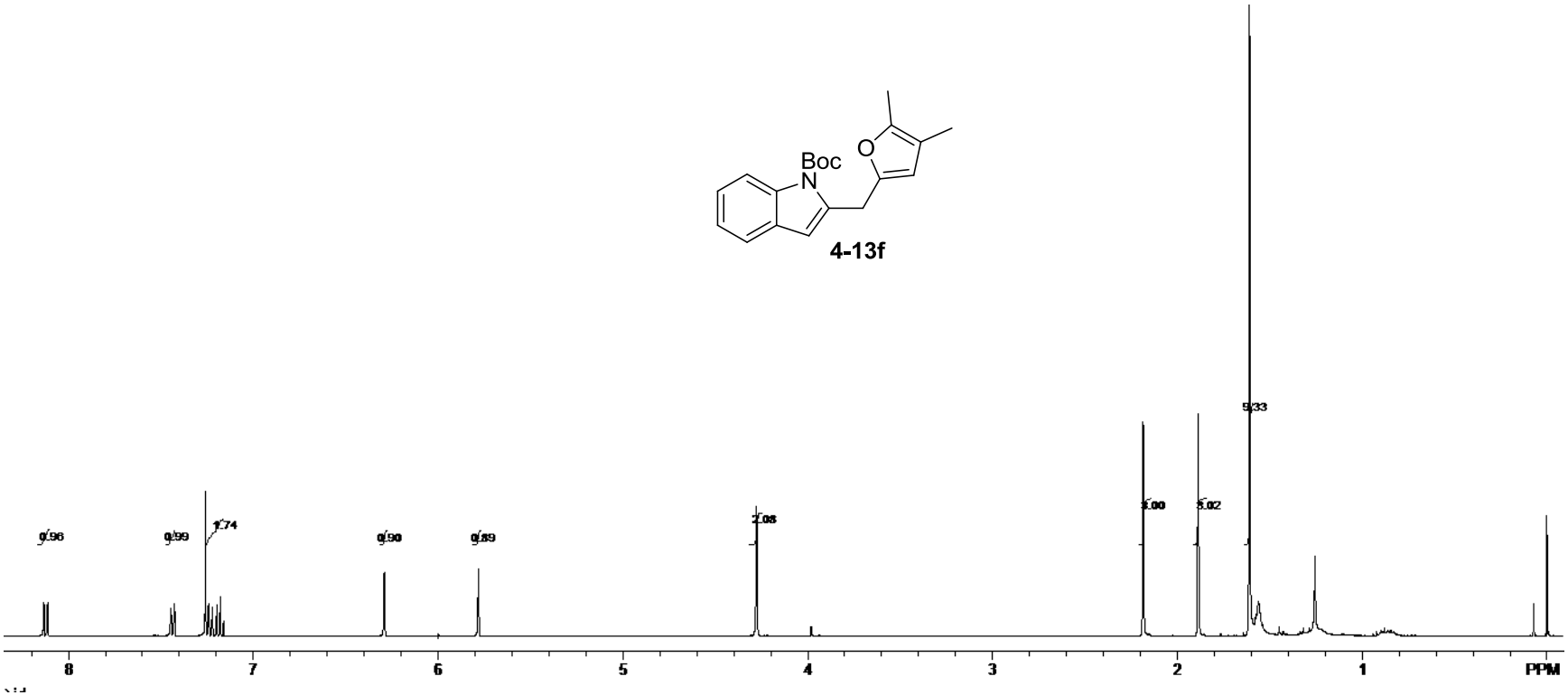


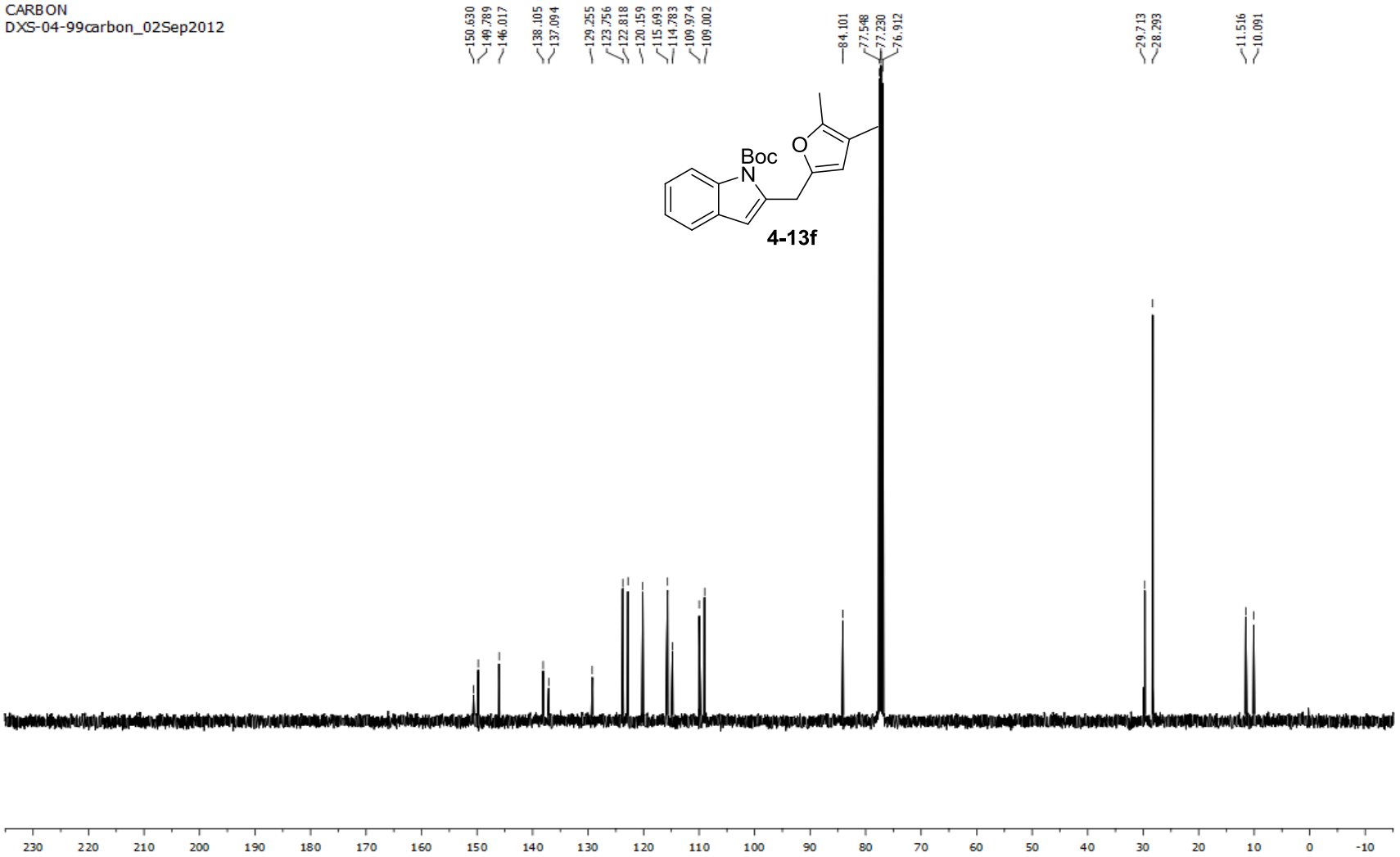

139.623
134.666
132.589
129.248
127.052
120.818
119.166
117.311
115.809
110.388
77.486
77.230
76.974
33.972
32.361
30.424
28.435
26.380
H
N
4-12h
200
150
100
50
0
PPM

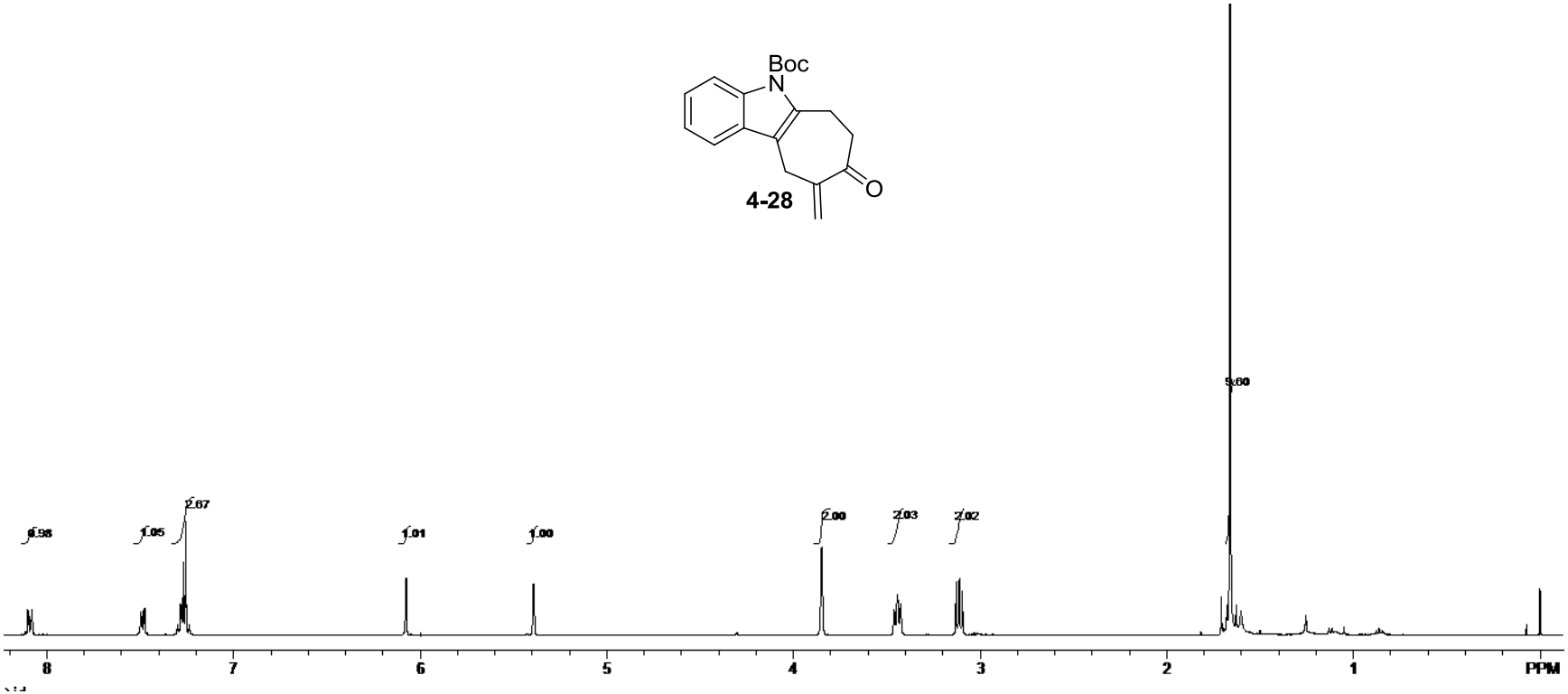

Boc
N
O
4-13a
0.93
1.78
0.86
2.00
5.05
8
7
6
5
4
3
2
1
PPM


153.103
150.579
141.366
137.466
137.065
128.163
123.866
122.864
120.232
115.746
110.659
109.227
105.703
84.165
77.486
77.230
76.974
28.729
28.282
Boc
N
O
200
150
100
50
0
PPM

4-13a

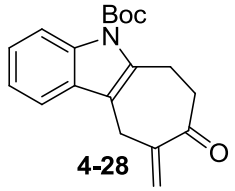

Boc
N
O
4-13f
0.96
0.99
1.74
0.90
0.89
2.08
3.00
5.02
9.33
8
7
6
5
4
3
2
1
PPM


CARBON
DXS-04-99carbon_02Sep2012
150.630
149.789
146.017
138.105
137.094
129.255
123.756
122.818
120.159
115.693
114.783
109.974
109.002
84.101
77.548
77.230
76.912
29.713
28.293
11.516
10.091
Boc
N
O
4-13f
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

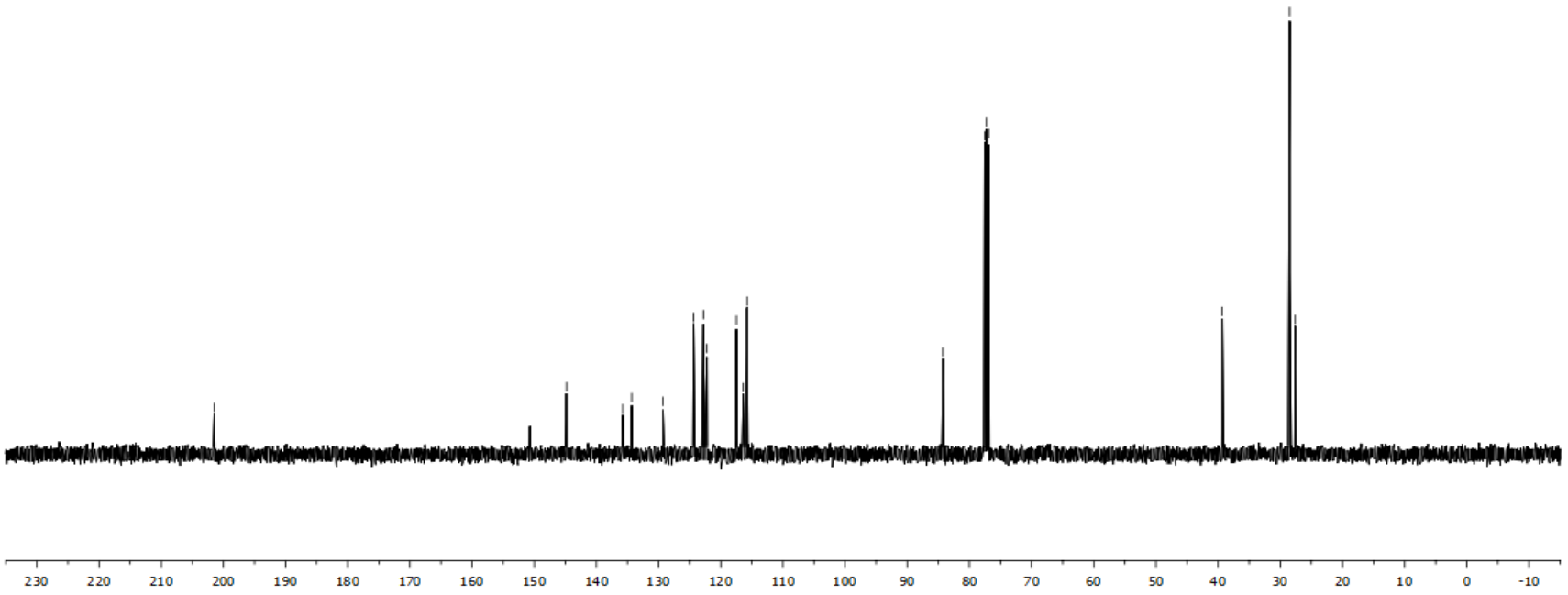

Boc
N
O
4-28
0.98
1.05
2.67
1.01
1.00
2.00
2.03
2.02
9.60
8
7
6
5
4
3
2
1
PPM

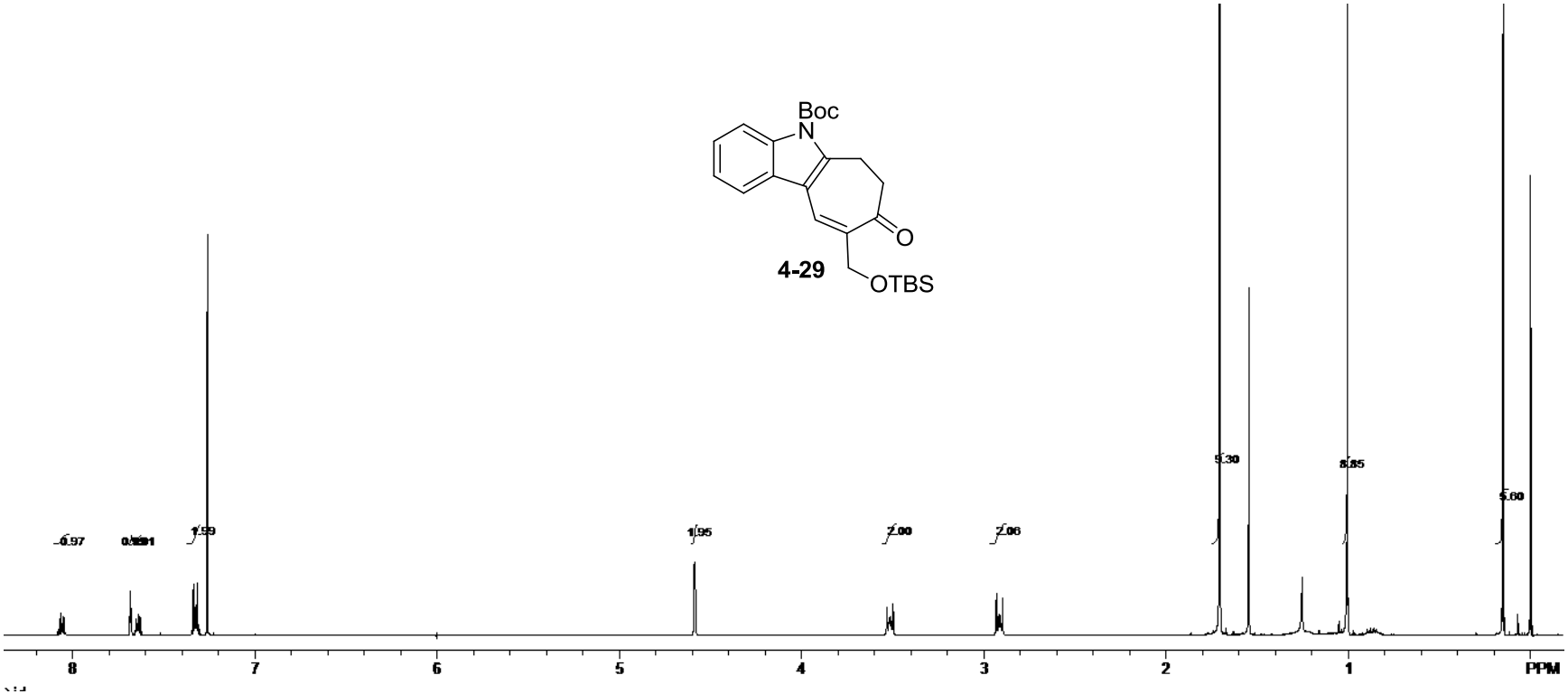
CARBON
DXS-04-92-3_24Aug2012

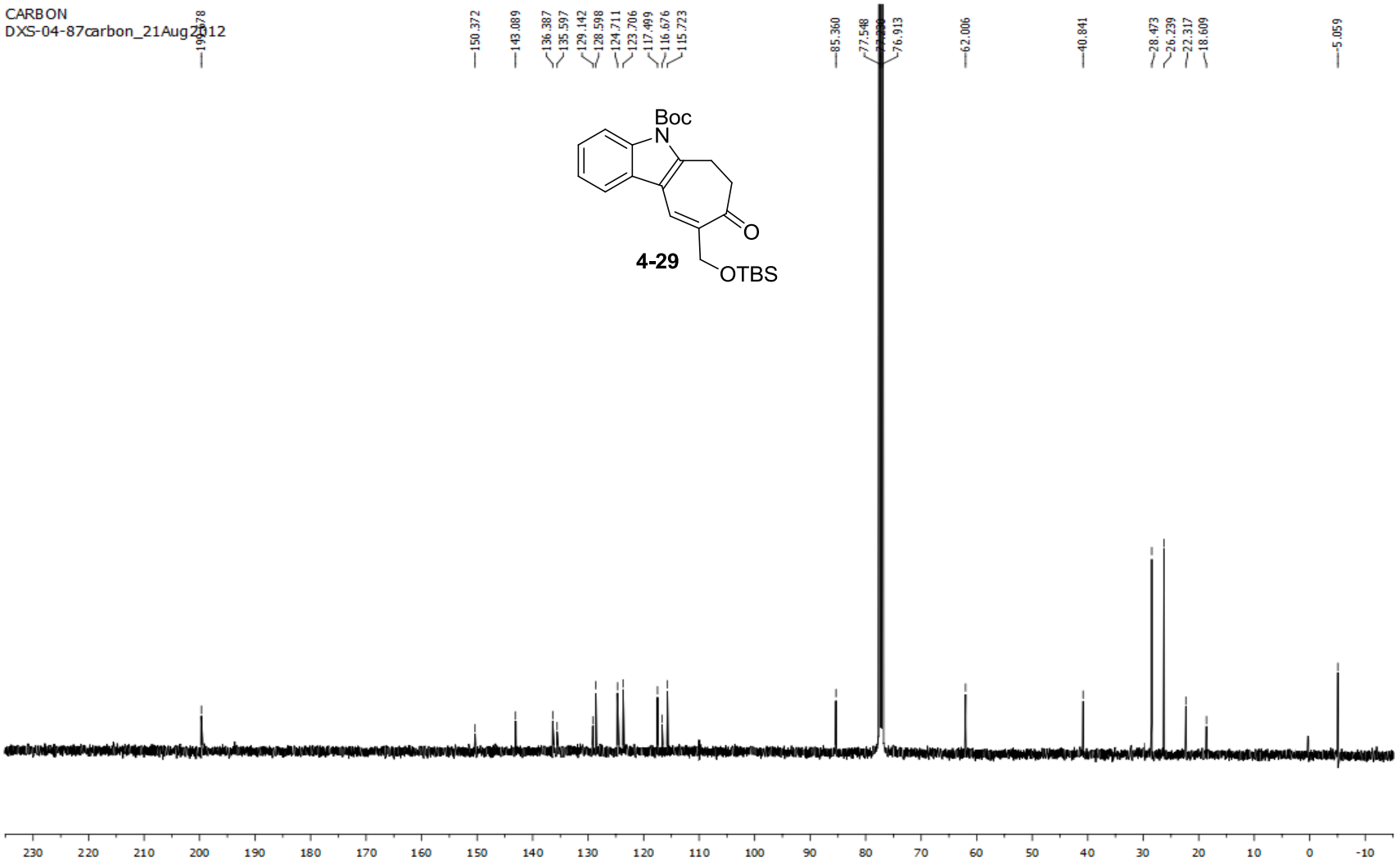
201.966
150.677
144.830
135.741
134.329
129.289
124.362
122.794
122.233
117.464
116.378
115.774
84.256
77.547
77.230
76.912
39.319
28.547
28.484
27.579



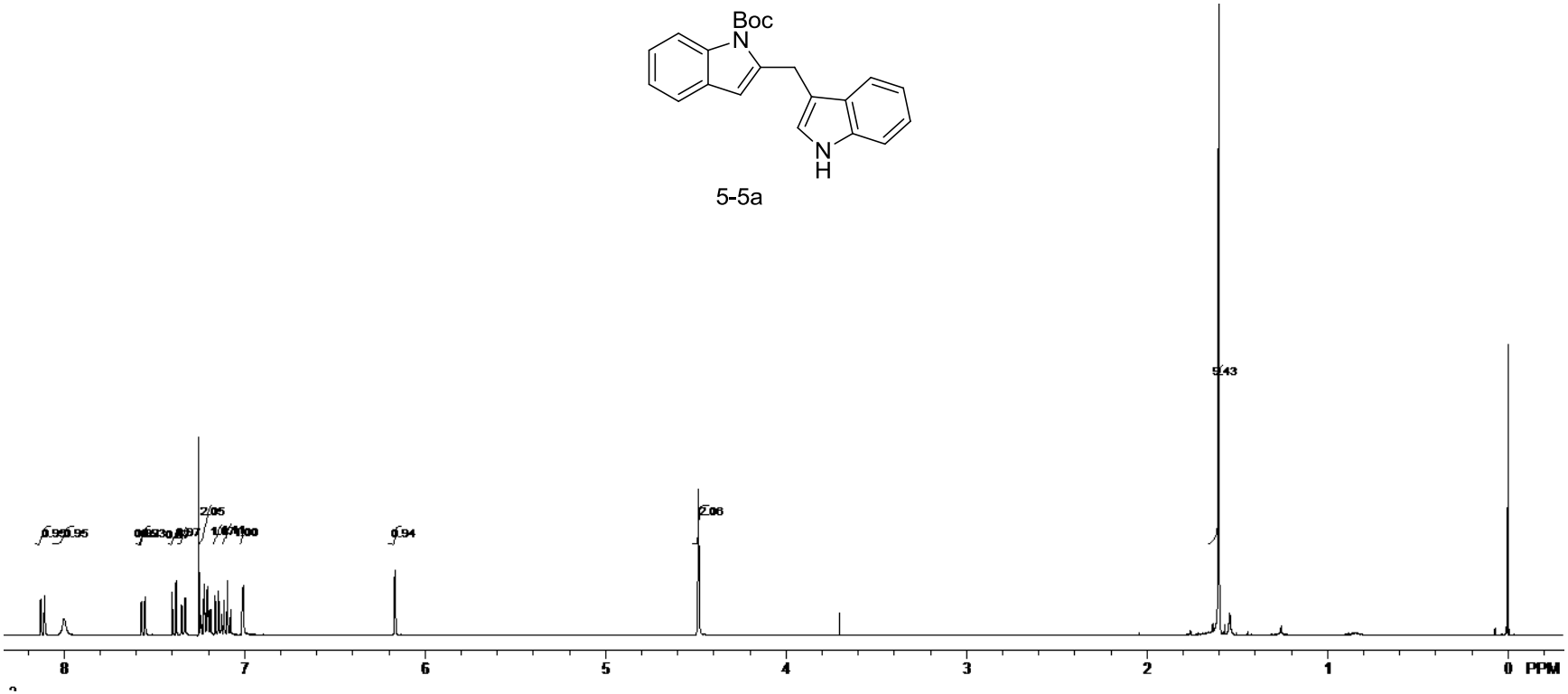
4-28



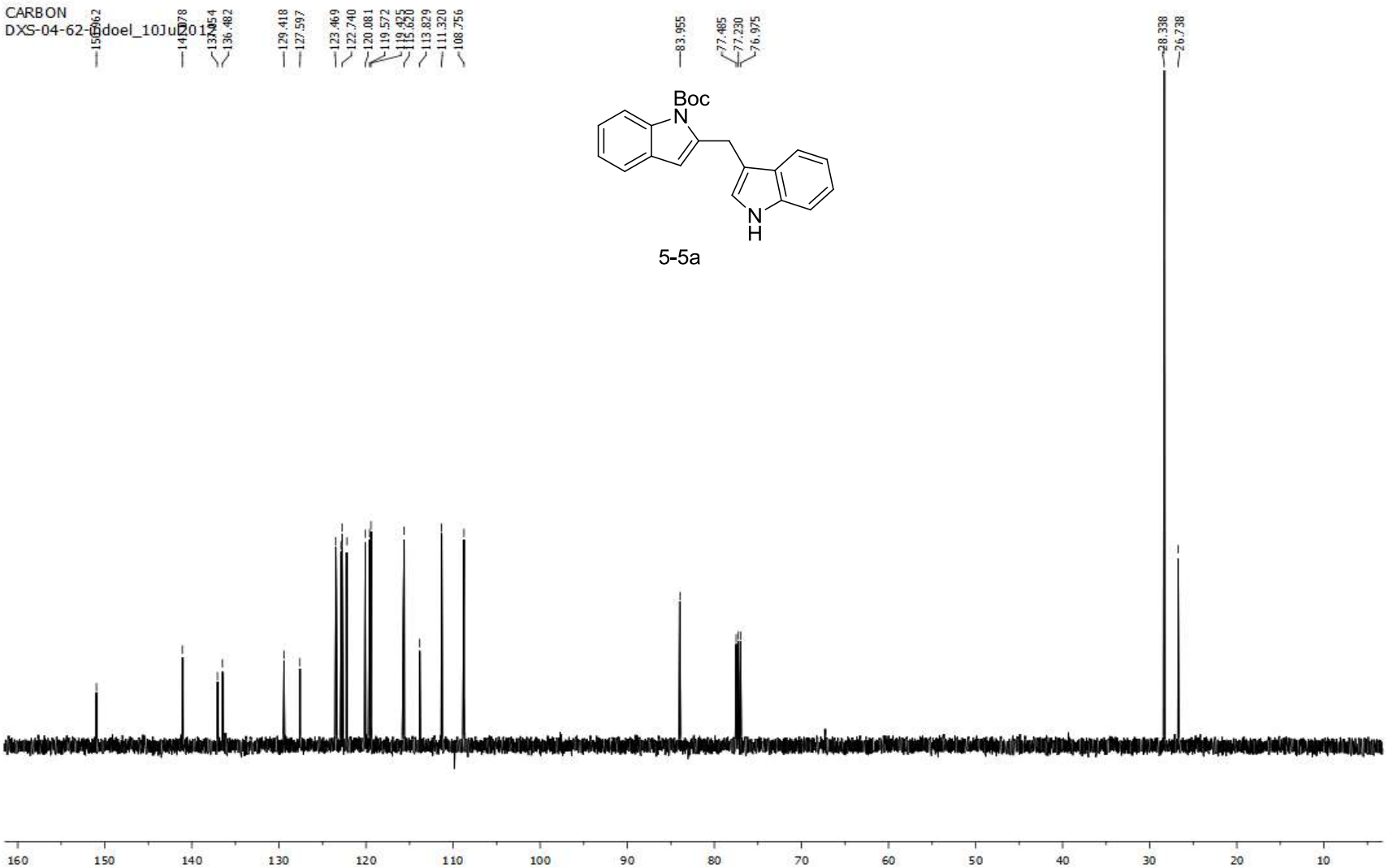

Boc
N
O
OTBS
4-29
6.97
1.99
1.95
2.00
2.06
5.30
8.85
5.60
8
7
6
5
4
3
2
1
PPM

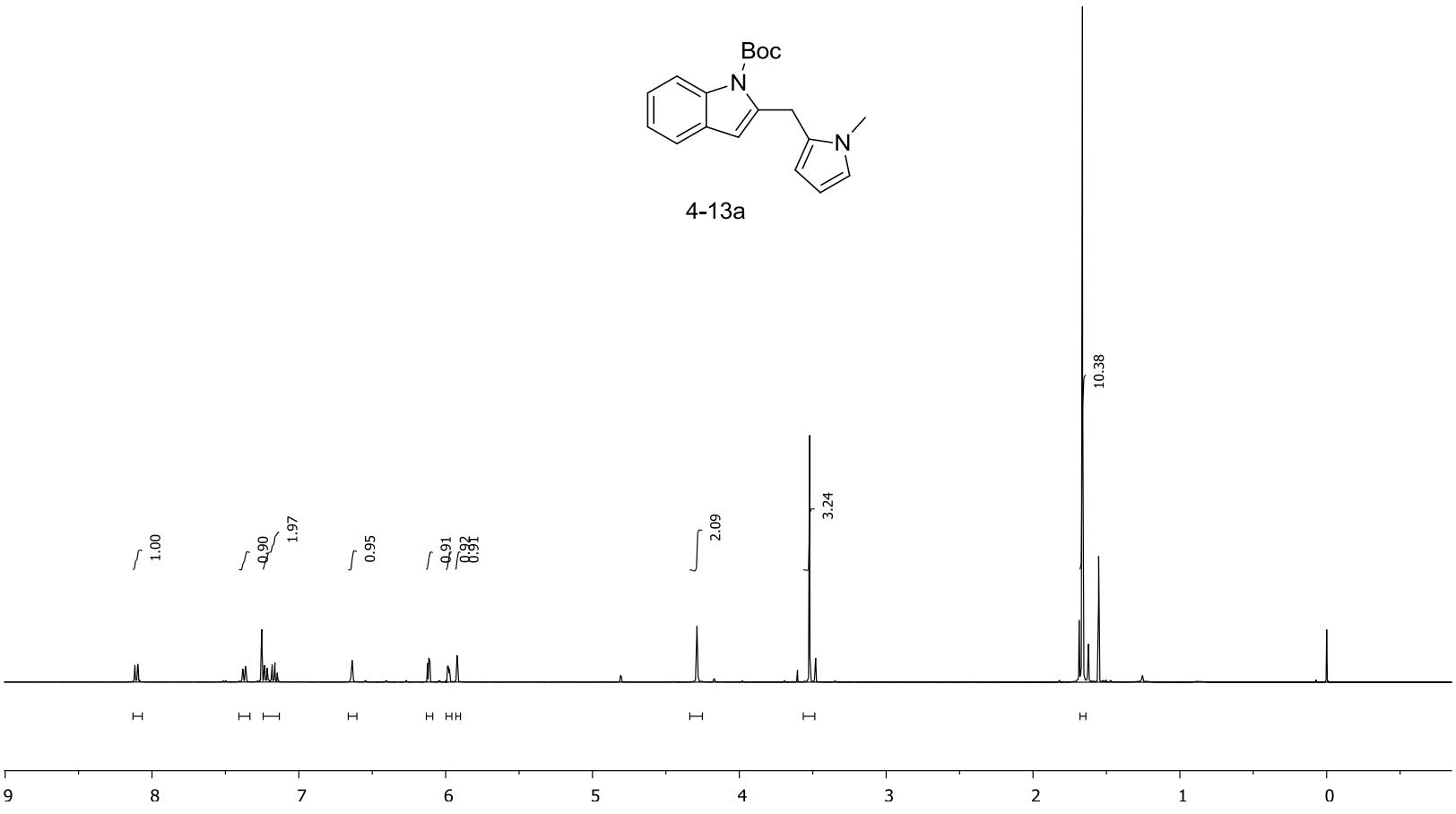

CARBON
DXS-04-87carbon_21Aug2012
199.678
150.372
143.089
136.387
135.597
129.142
128.598
124.711
123.706
117.499
116.676
115.723
85.360
77.548
76.913
62.006
40.841
28.473
26.239
22.317
18.609
5.059
Boc
N
O
OTBS
4-29
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

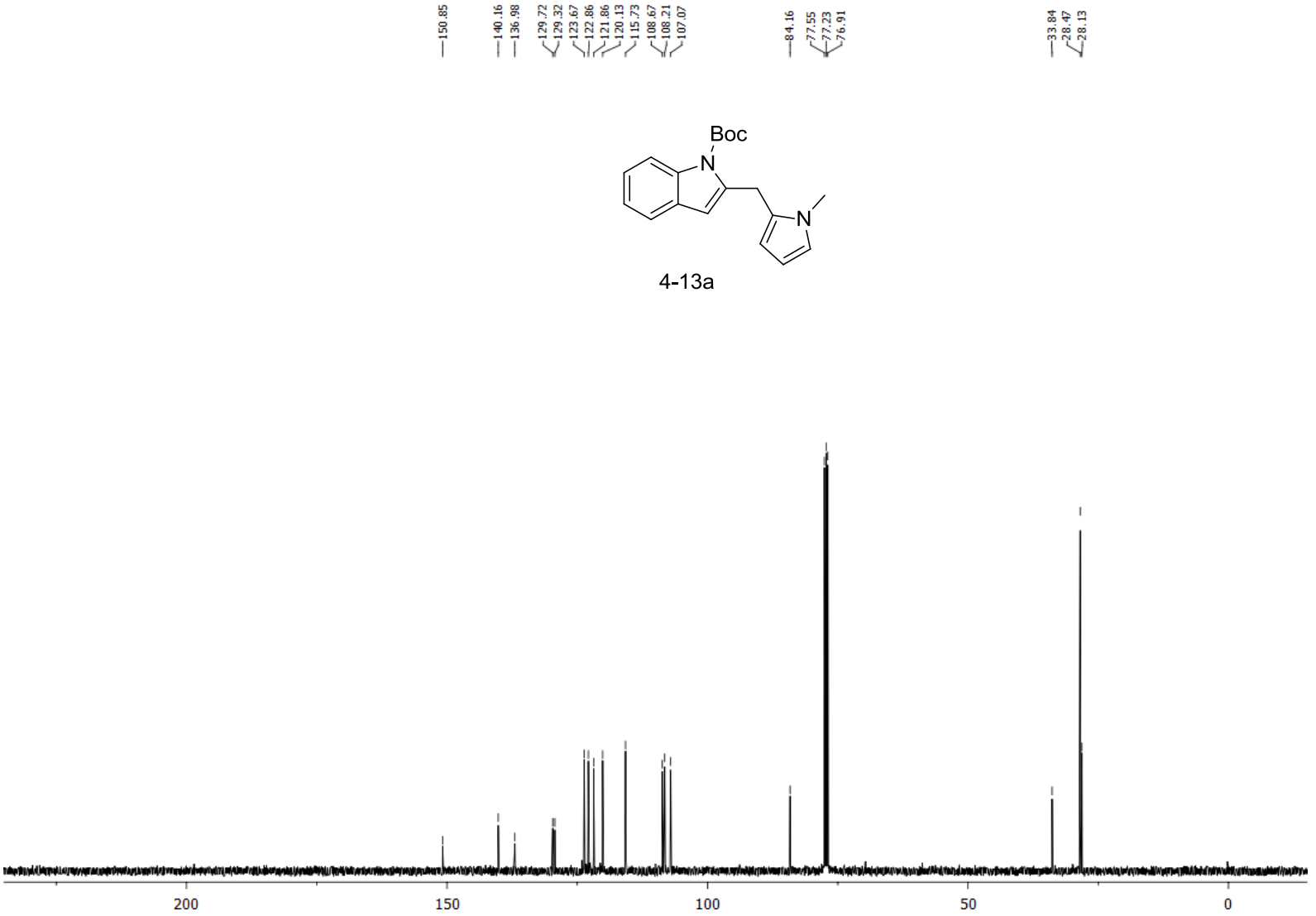
Chapter V NMR Spectrum



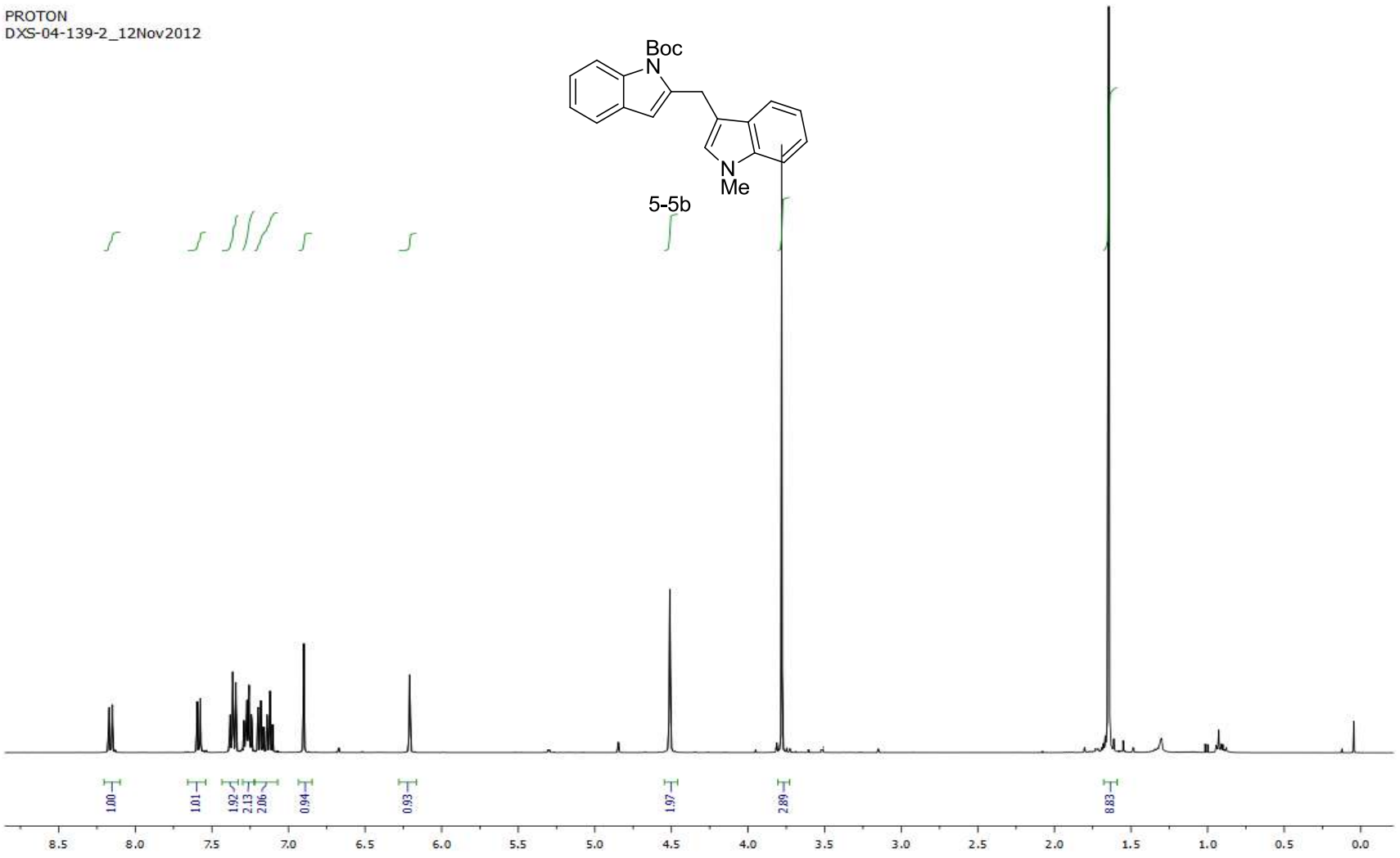
5-5a

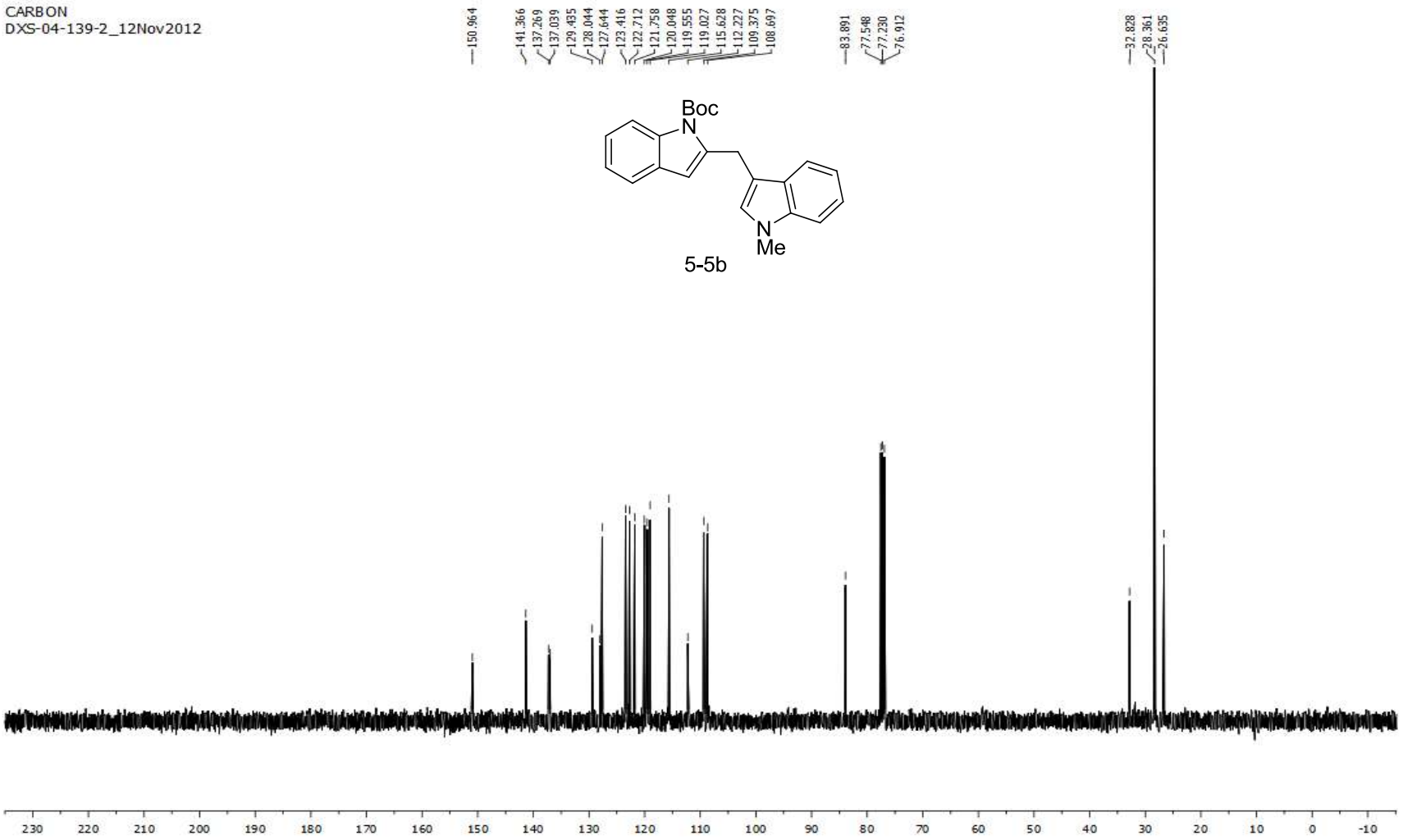

CARBON
DXS-04-62-Cdoel_10Jul2013
150.962
141.078
133.954
136.482
129.418
127.597
123.469
122.740
120.081
119.572
83.955
77.485
77.230
76.975
28.338
26.738
Boc
N
N
H
5-5a
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


Boc
N
N
4-13a
1.00
0.90
1.97
0.95
0.91
0.92
0.91
2.09
3.24
10.38
9
8
7
6
5
4
3
2
1
0

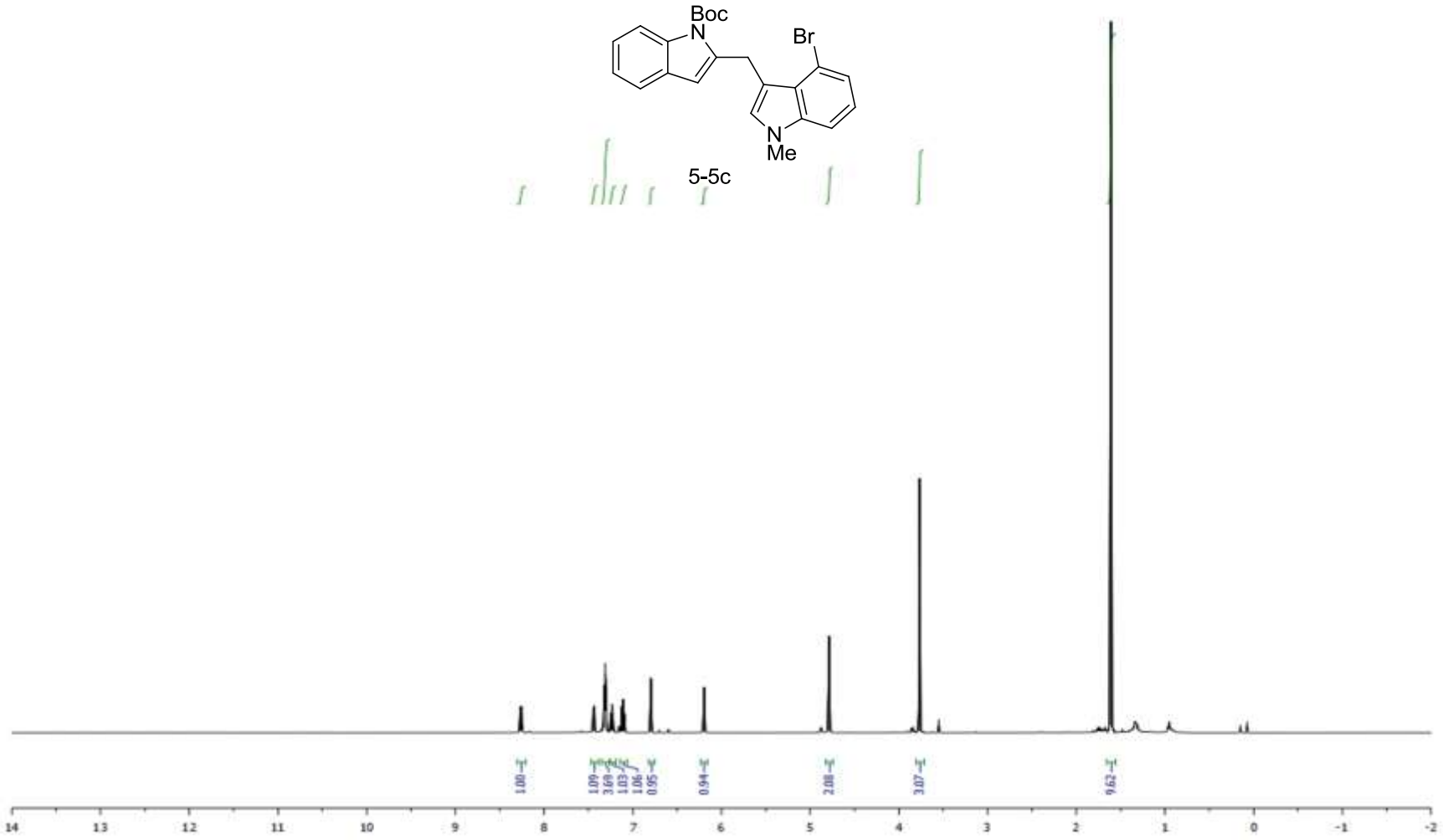

150.85
140.16
136.98
129.72
129.32
123.67
122.86
121.86
120.13
115.73
108.67
108.21
107.07
84.16
77.55
77.23
76.91
33.84
28.47
28.13
Boc
N
N
200
150
100
50
0

4-13a


PROTON
DXS-04-139-2_12Nov2012
Boc
N
N
Me
5-5b
1.00
1.01
1.92
2.13
2.06
0.94
0.93
1.97
2.89
8.83
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

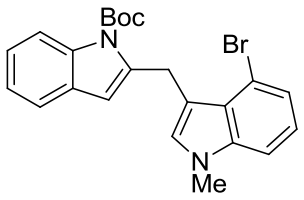

CARBON
DXS-04-139-2_12Nov2012
150.964
141.366
137.269
137.039
129.435
128.044
127.644
123.416
122.712
121.758
120.048
119.555
119.027
115.628
112.227
109.375
108.697
83.891
77.548
77.230
76.912
32.828
28.361
26.635
Boc
N
N
Me
5-5b
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

PROTON
DXS-04-142-2_09Dec2012

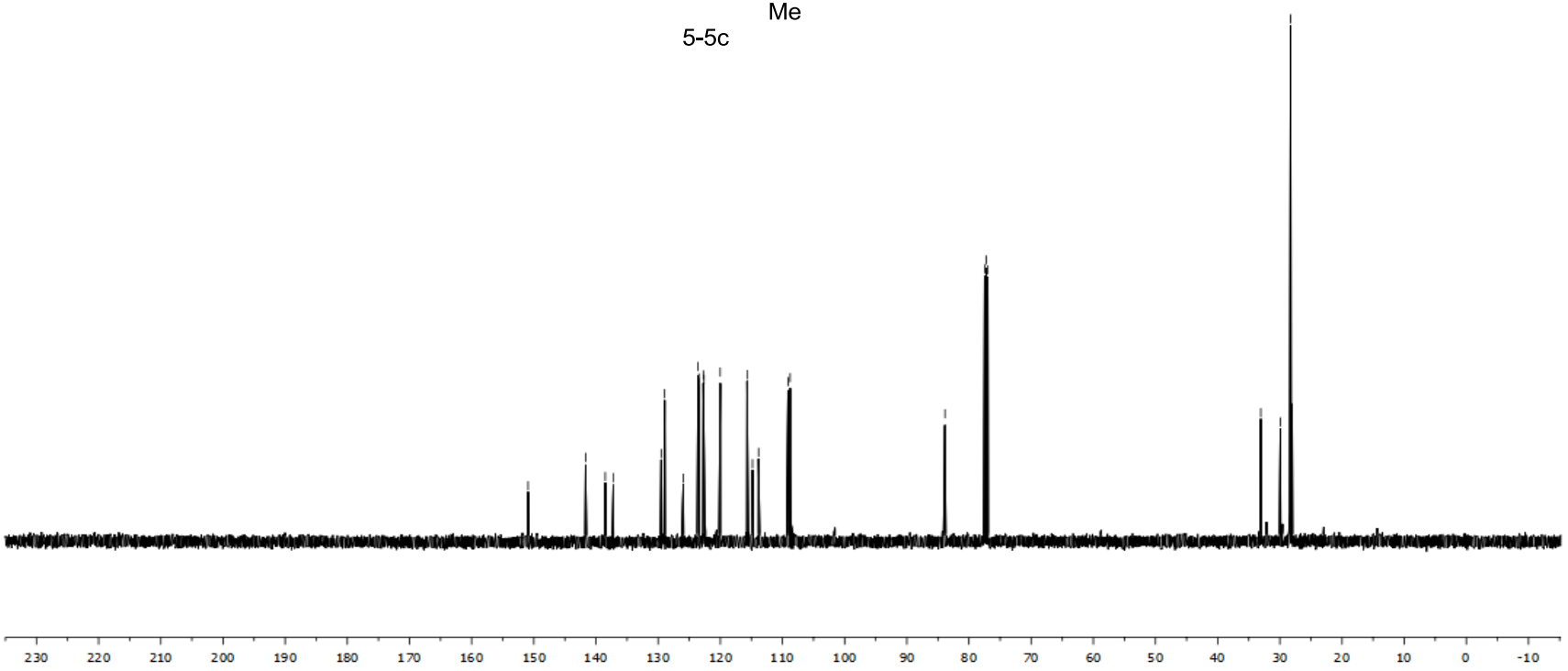


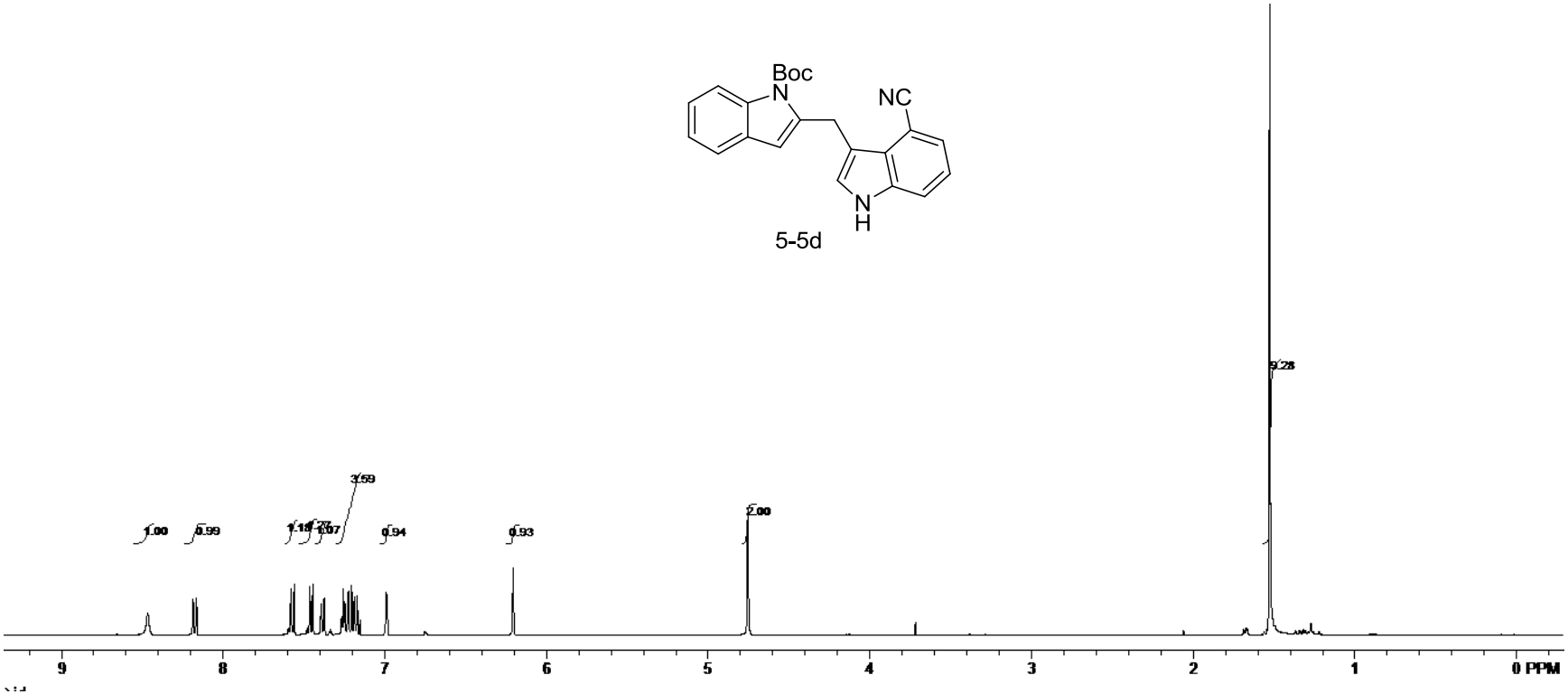
CARBON
DXS-04-142-2_09Dec2012

150.919
141.666
138.501
137.214
129.504
128.954
125.959
123.590
123.445
122.721
122.625
120.024
115.682
114.832
113.834
109.099
108.772
83.856
77.484
77.230
76.976
33.065
29.917
28.266

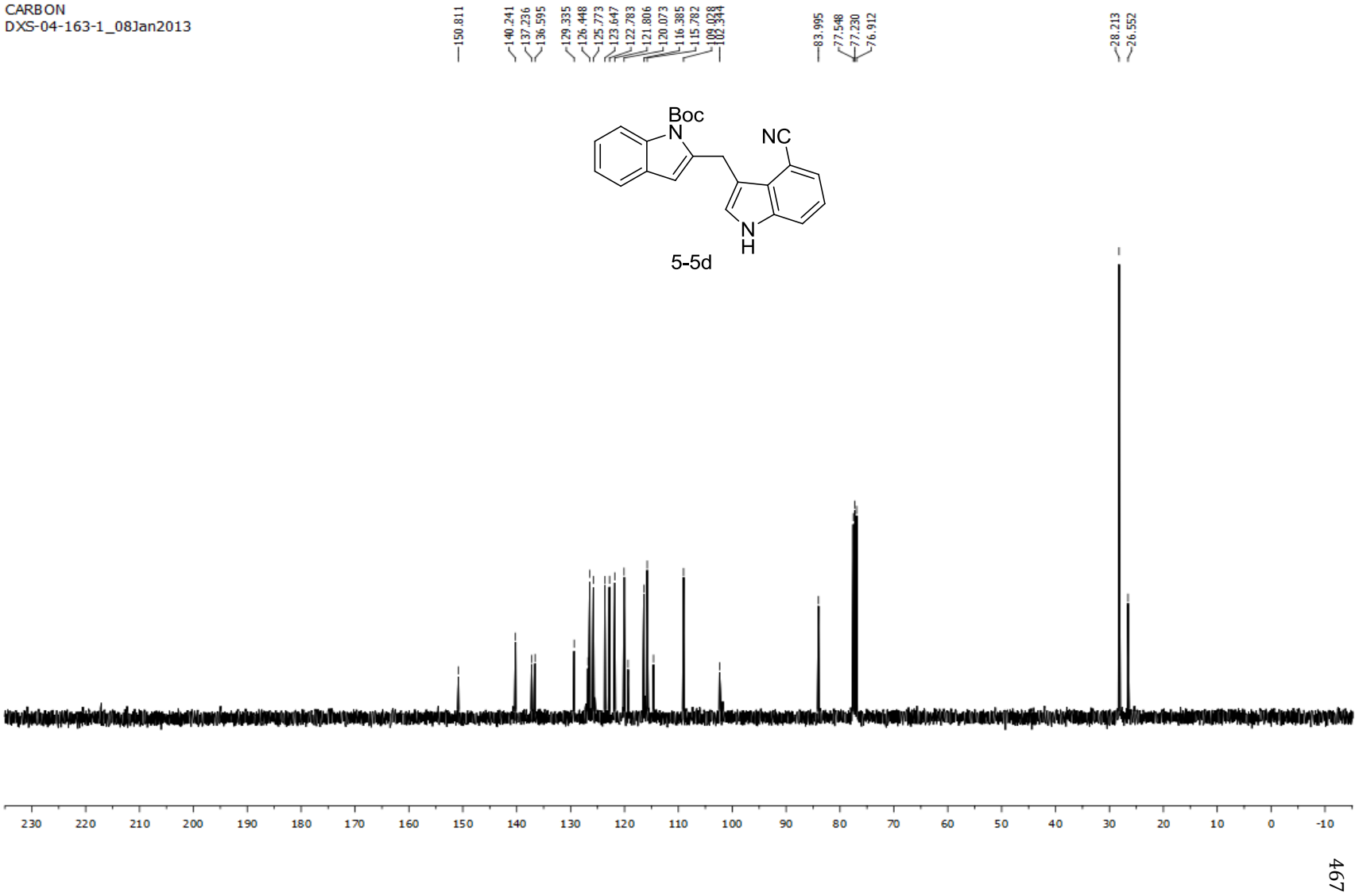


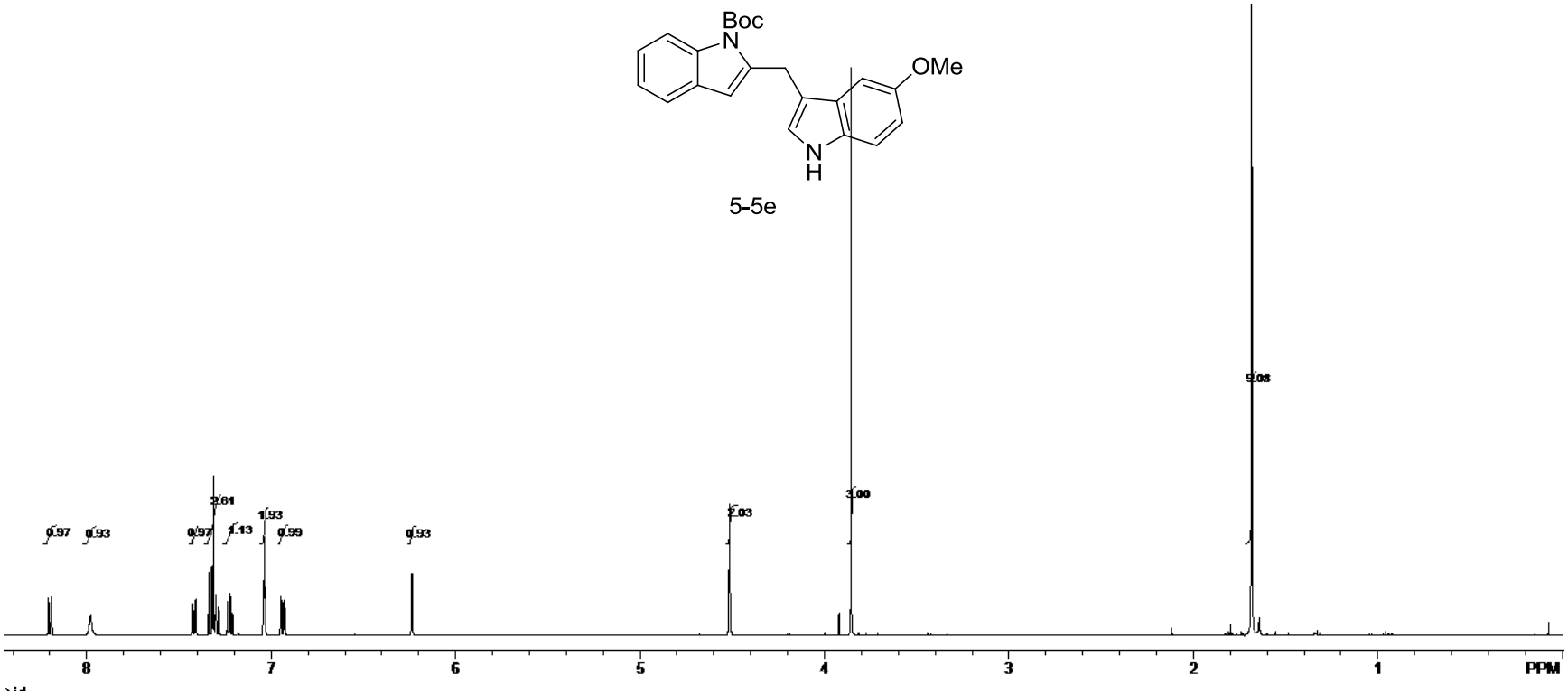
5-5c



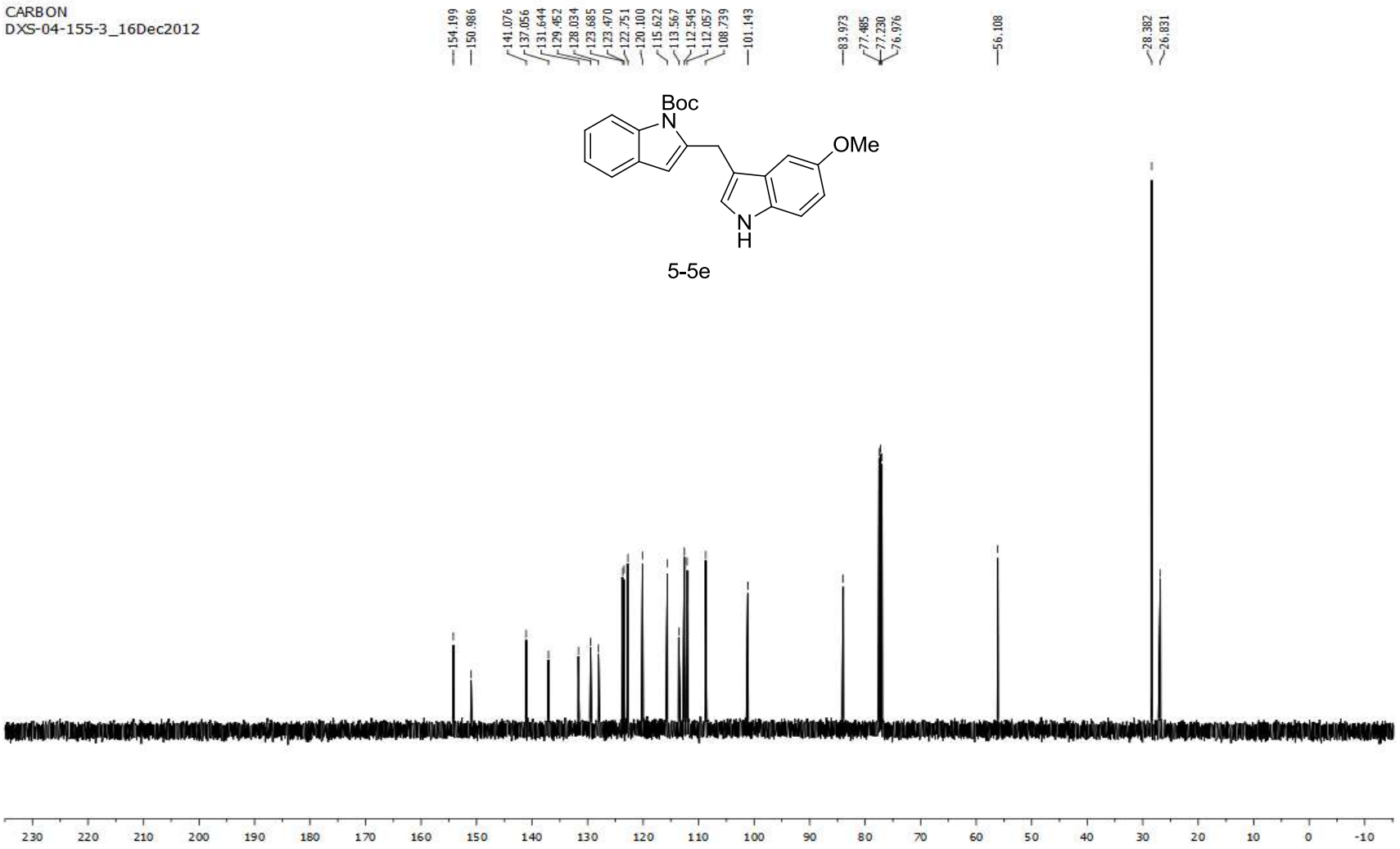

Boc
N
NC
N
H
5-5d
1.00
0.99
3.59
0.94
0.93
2.00
9.28
9
8
7
6
5
4
3
2
1
0 PPM

CARBON
DXS-04-163-1_08Jan2013

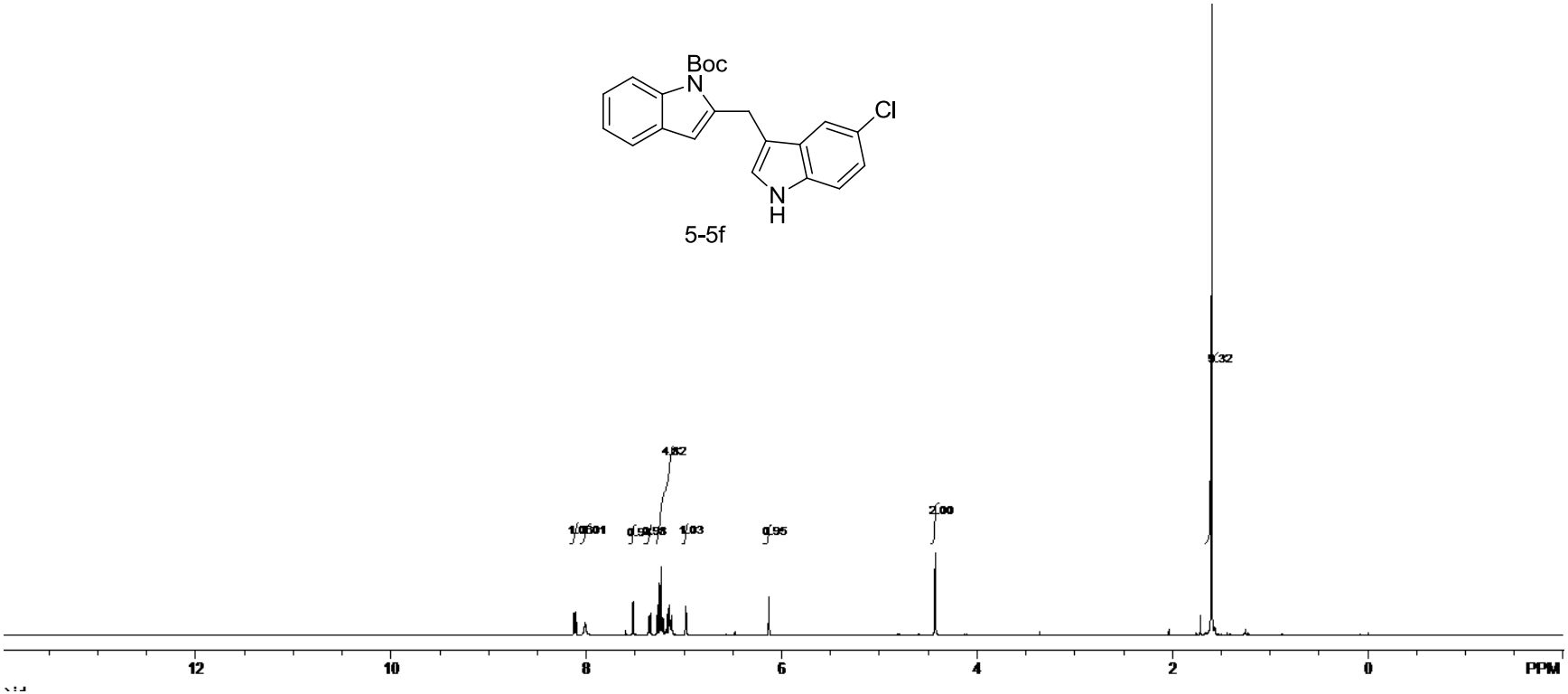



Boc
N
OMe
N
H
5-5e
0.97
0.93
0.97
1.13
2.61
1.93
0.99
0.93
2.03
3.00
9.08
8
7
6
5
4
3
2
1
PPM

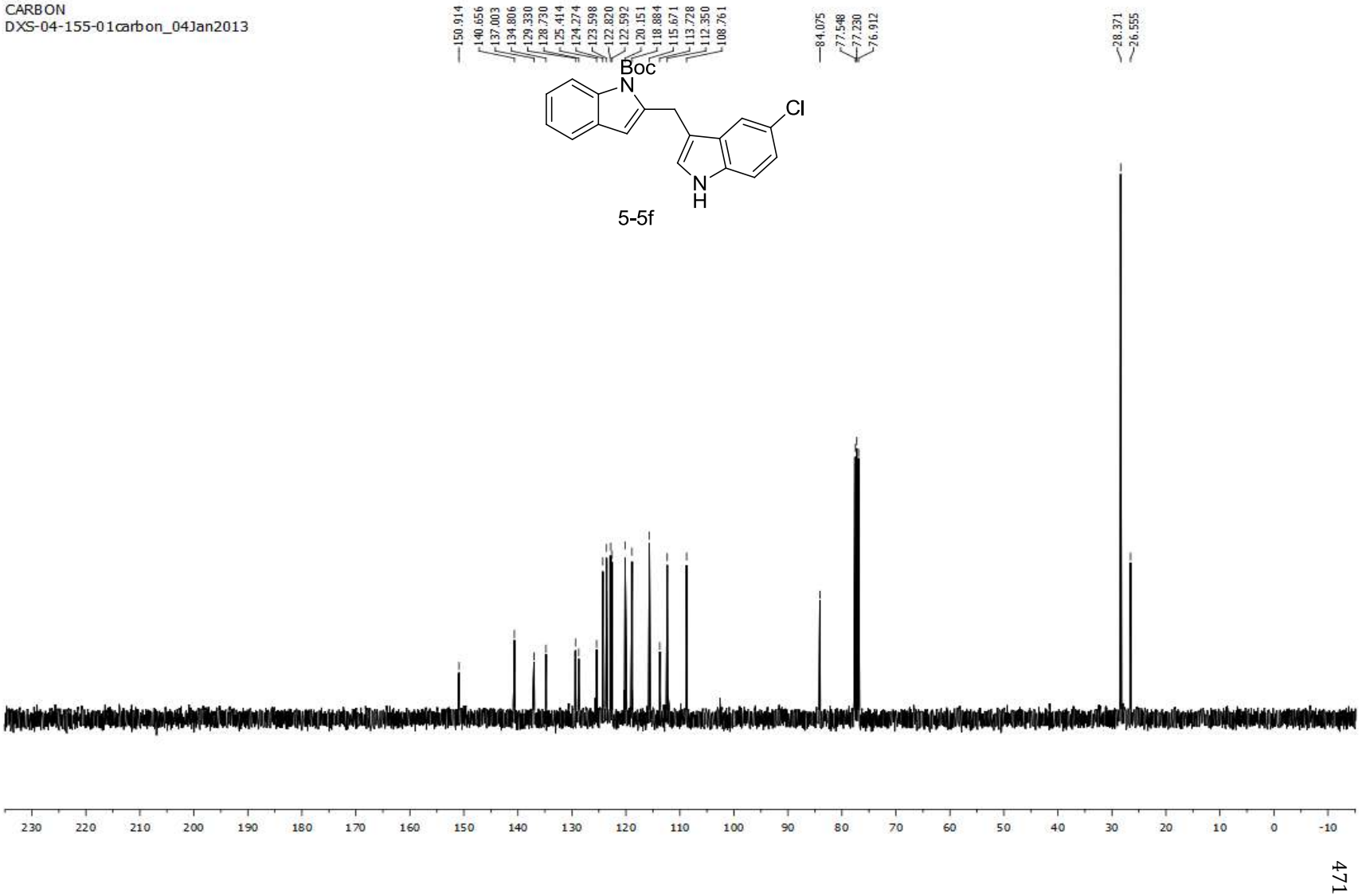
CARBON
DXS-04-155-3_16Dec2012

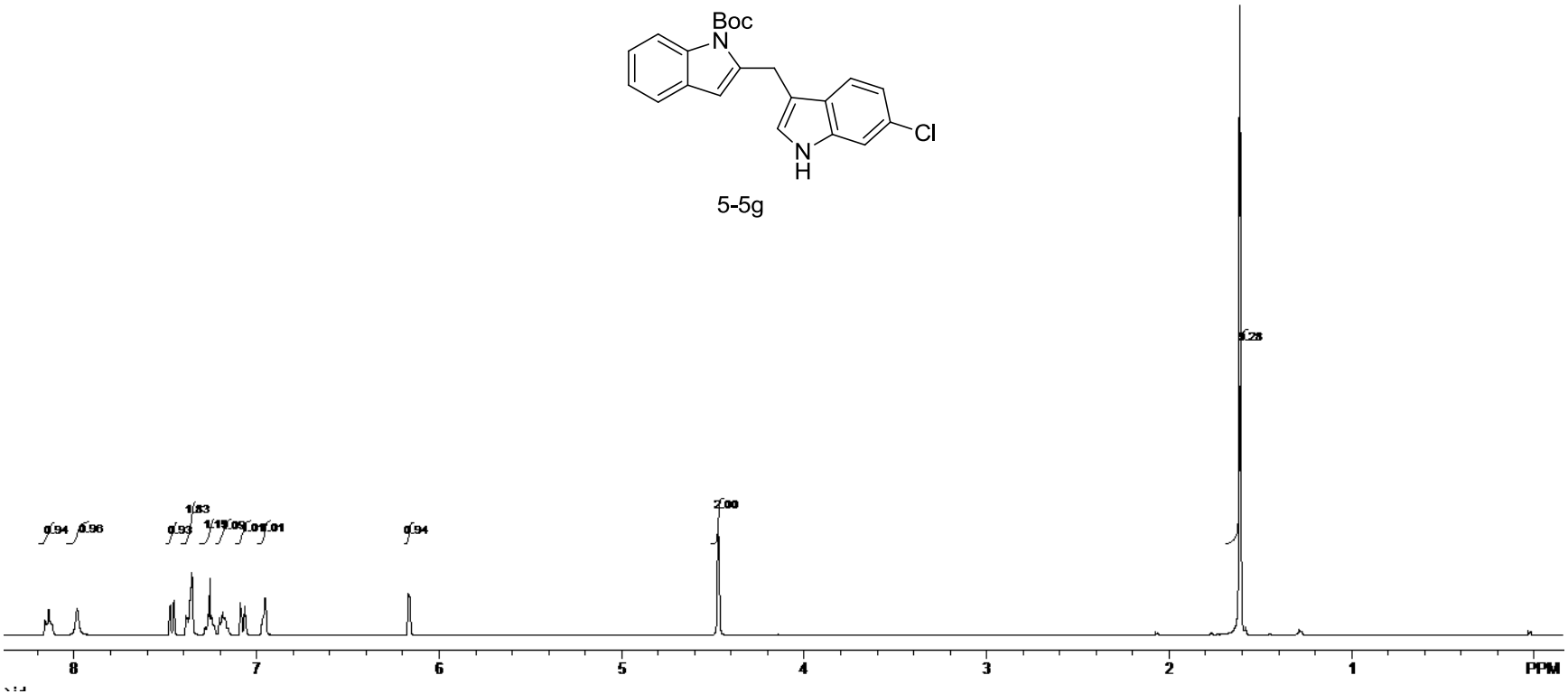


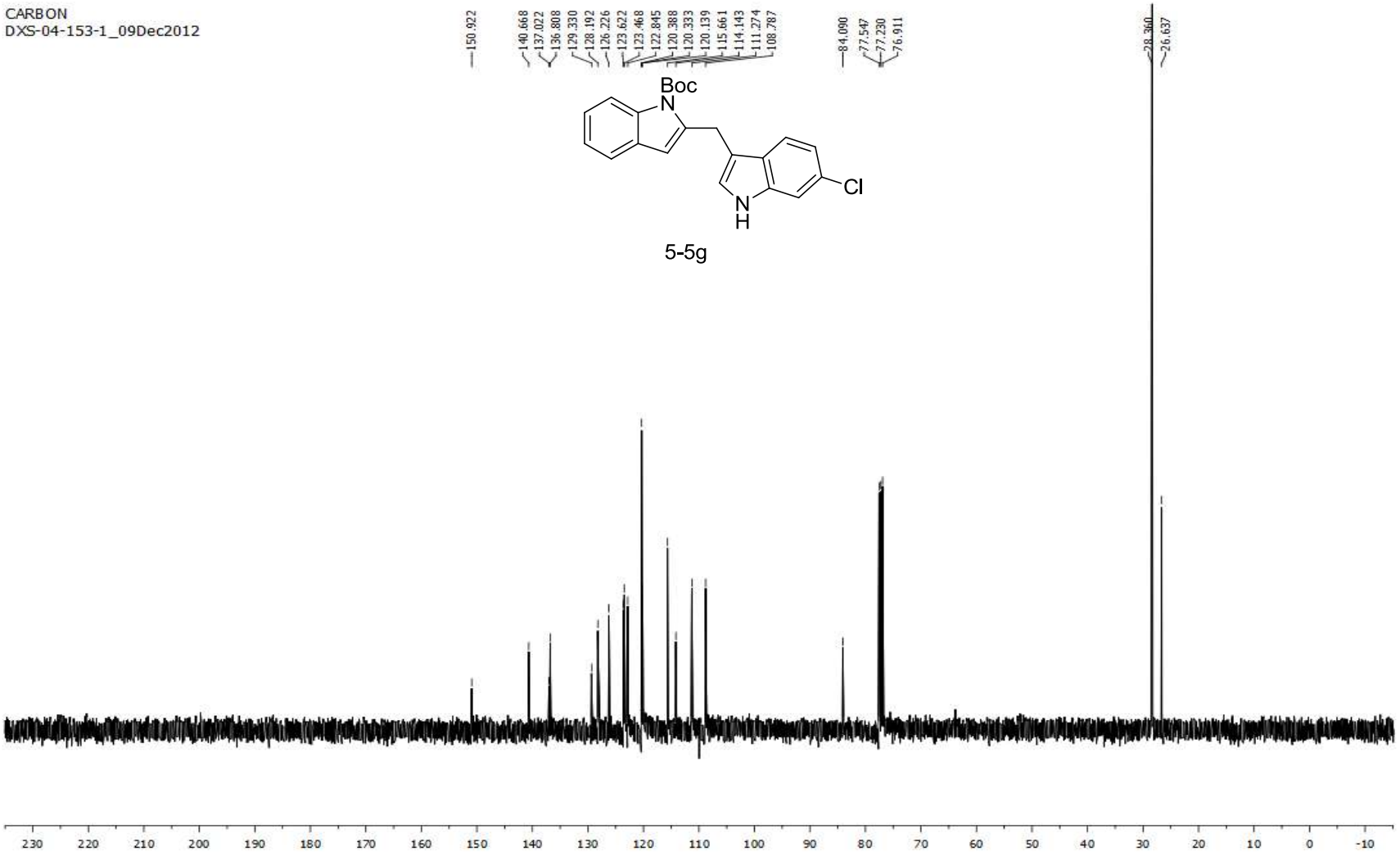
5-5e

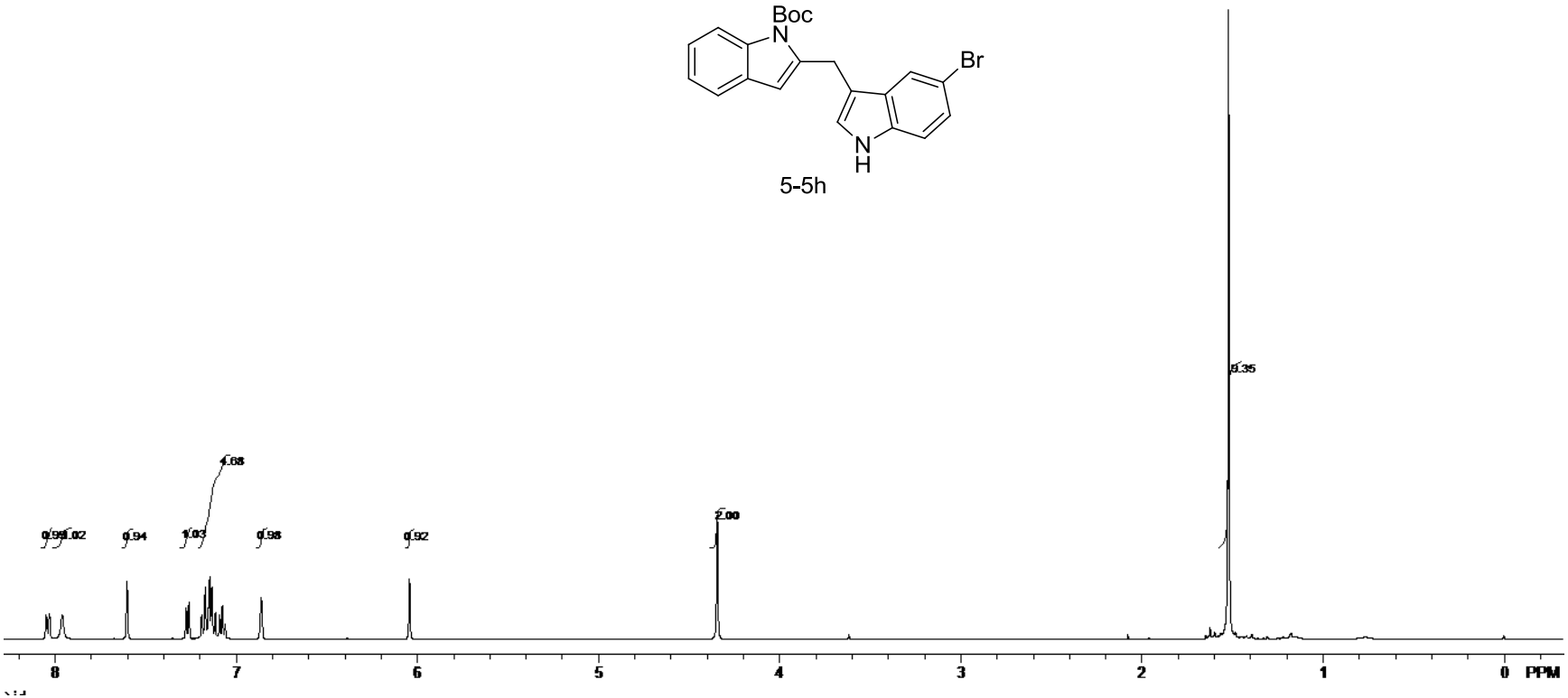

Boc
N
Cl
N
H
5-5f
9.32
4.82
2.00
1.03
0.95
12
10
8
6
4
2
0
PPM

CARBON
DXS-04-155-01carbon_04Jan2013




Boc
N
N
H
Cl
5-5g
0.94
0.96
1.83
0.93
1.19
1.05
1.01
1.01
0.94
2.00
5.28
8
7
6
5
4
3
2
1
PPM


CARBON
DXS-04-153-1_09Dec2012
150.922
140.668
137.022
136.808
129.330
128.192
126.226
123.622
123.468
122.845
120.388
120.333
120.139
115.661
114.143
111.274
108.787
84.090
77.547
77.230
76.911
28.360
26.637
Boc
N
N
H
Cl
5-5g
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Boc
N
Br
N
H
5-5h
9.35
4.68
2.00
0.92
0.98
1.03
0.94
1.02
8
7
6
5
4
3
2
1
0
PPM

CARBON
DXS-04-168-characteirzatin_16Jan2013

150.903
140.642
136.996
135.075
129.377
129.323
125.102
124.128
123.597
122.821
121.934
120.156
115.664
113.587
112.928
112.810
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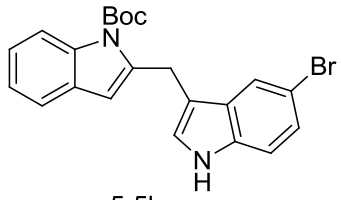
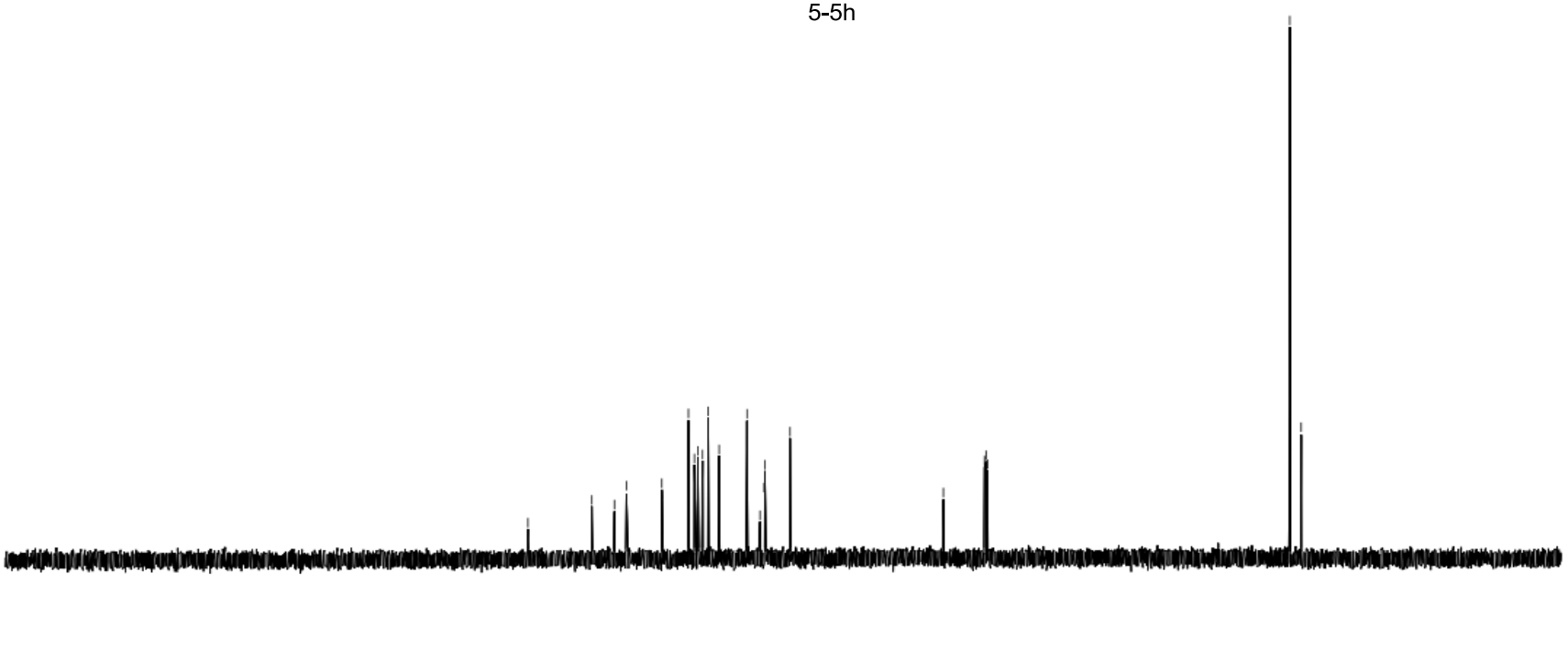
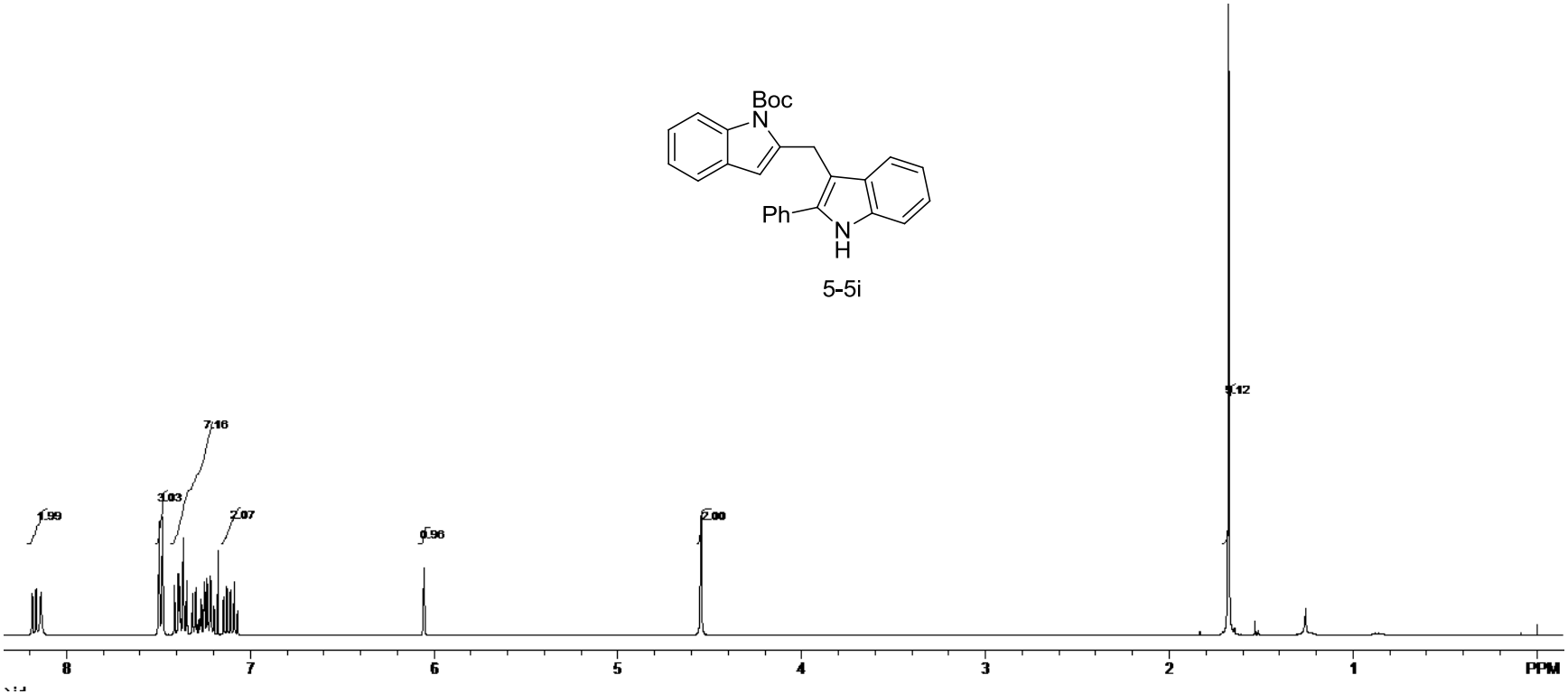
84.091
77.484
77.230
76.975
28.367
26.529



5-5h

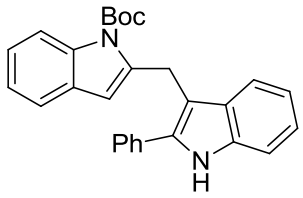


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

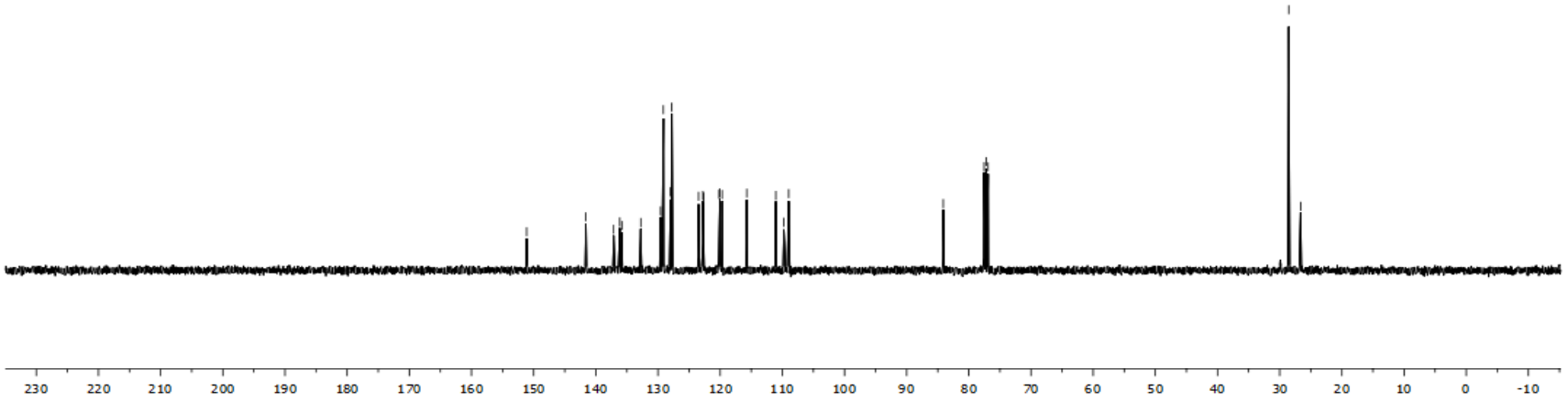

Boc
N
Ph
N
H
5-5i
1.99
3.03
7.16
2.07
0.96
2.00
9.12
8
7
6
5
4
3
2
1
PPM

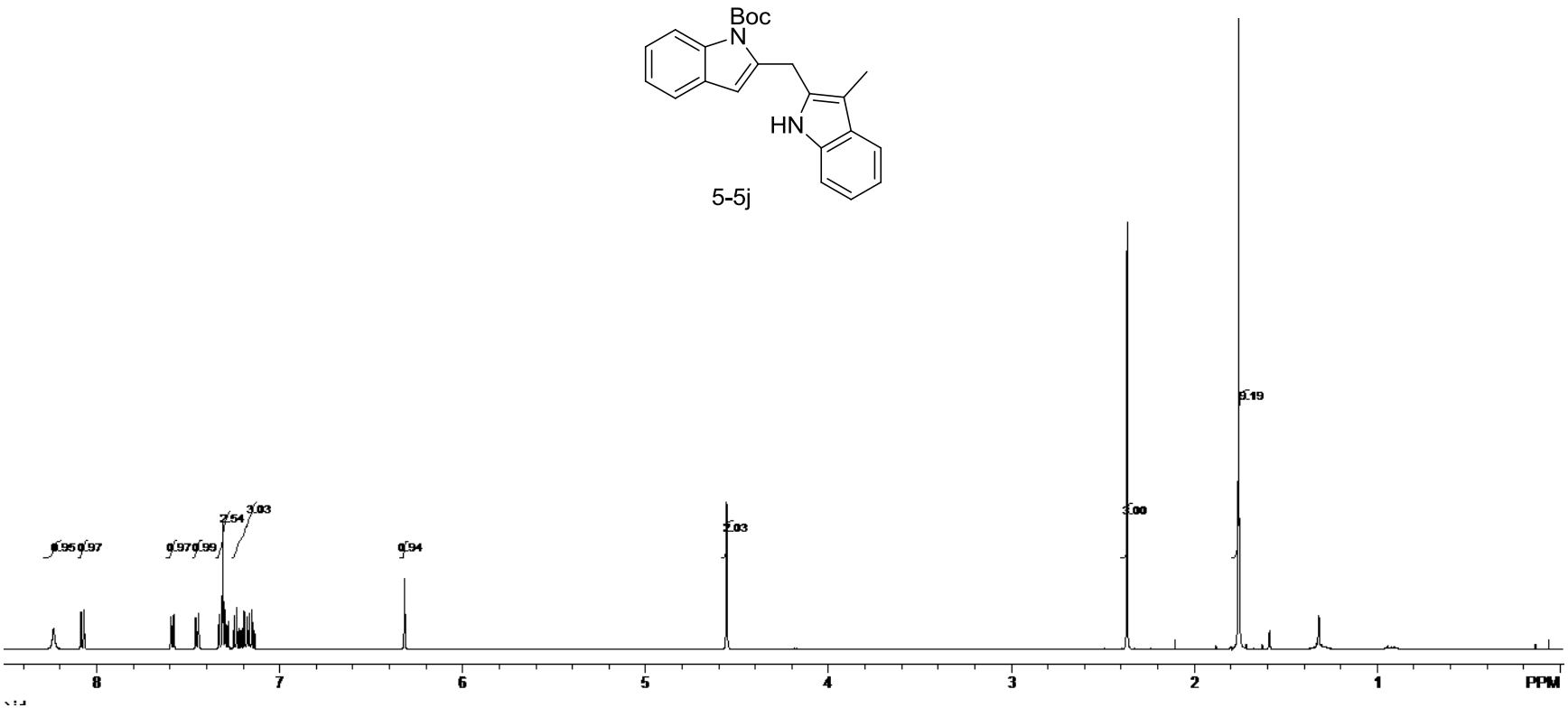
CARBON
DXS-04-153-2second_11Dec2012

151.119
141.601
137.132
136.150
135.823
132.770
129.583
129.141
127.996
127.770
123.475
122.779
122.673
120.183
120.064
119.685
115.708
111.041
109.742
108.967
84.123
77.548
77.230
76.913
28.537
26.633

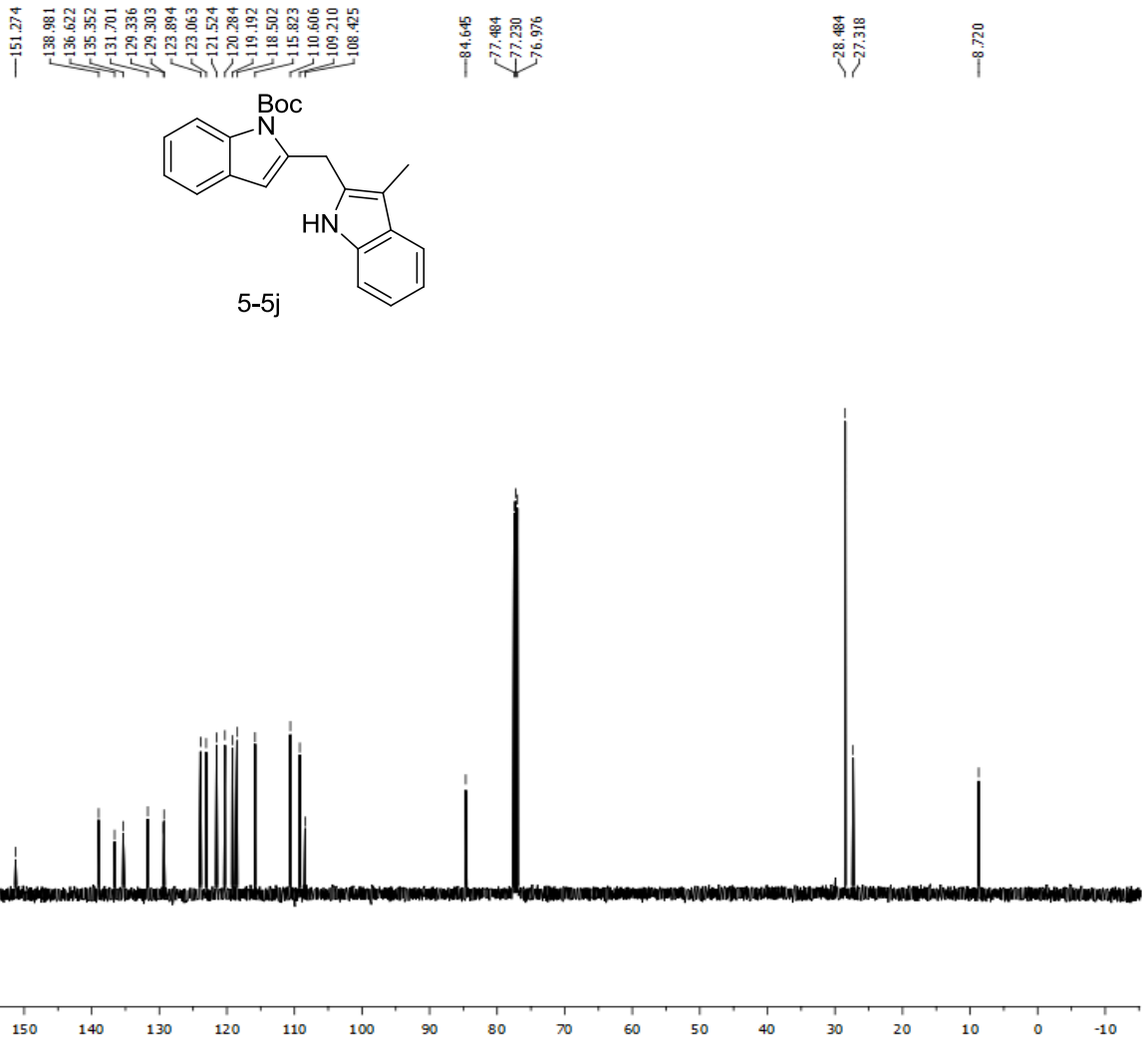


5-5i

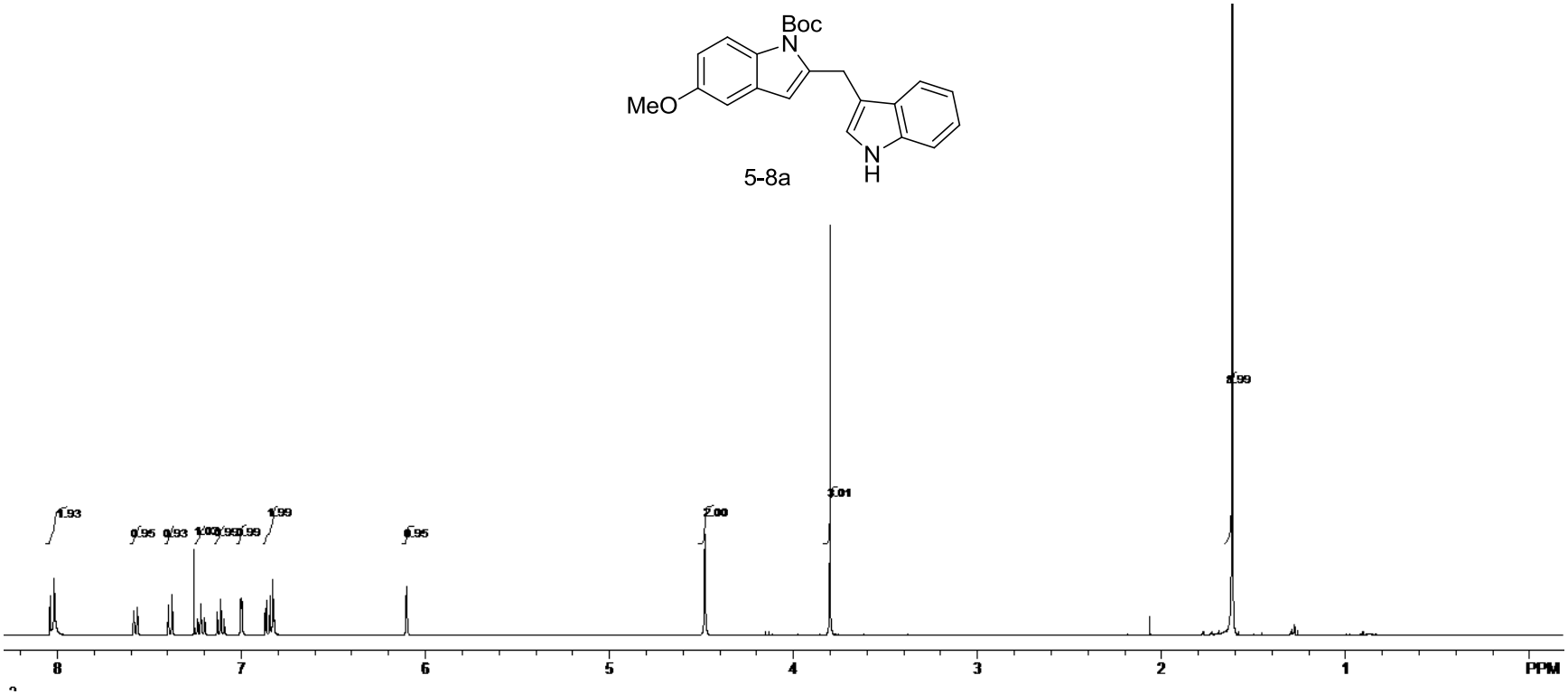



Boc
N
HN
5-5j
0.95
0.97
0.97
0.99
2.54
3.03
0.94
2.03
3.00
3.19
8
7
6
5
4
3
2
1
PPM

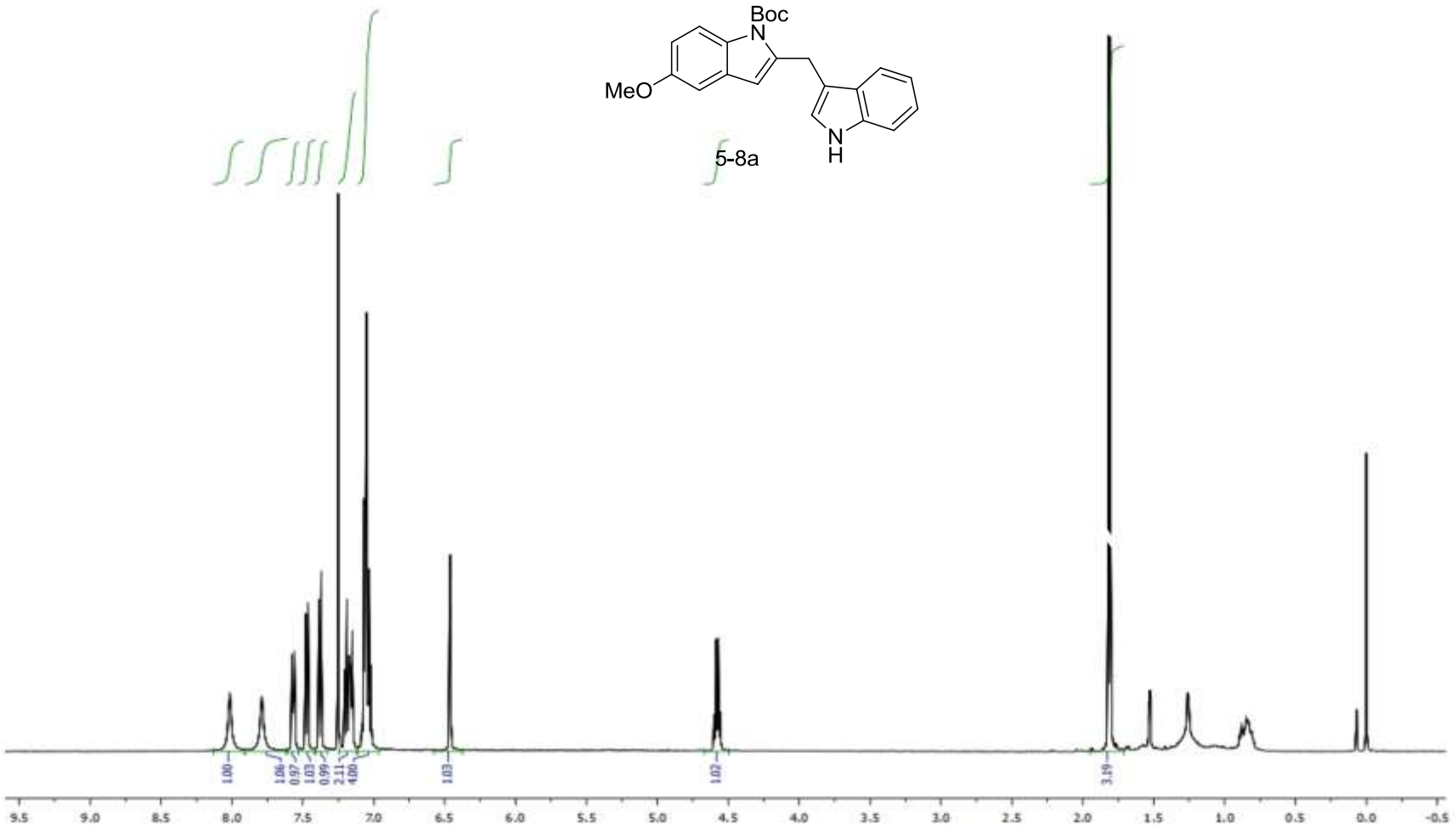
CARBON
DXS-04-155-2_06Jan2013

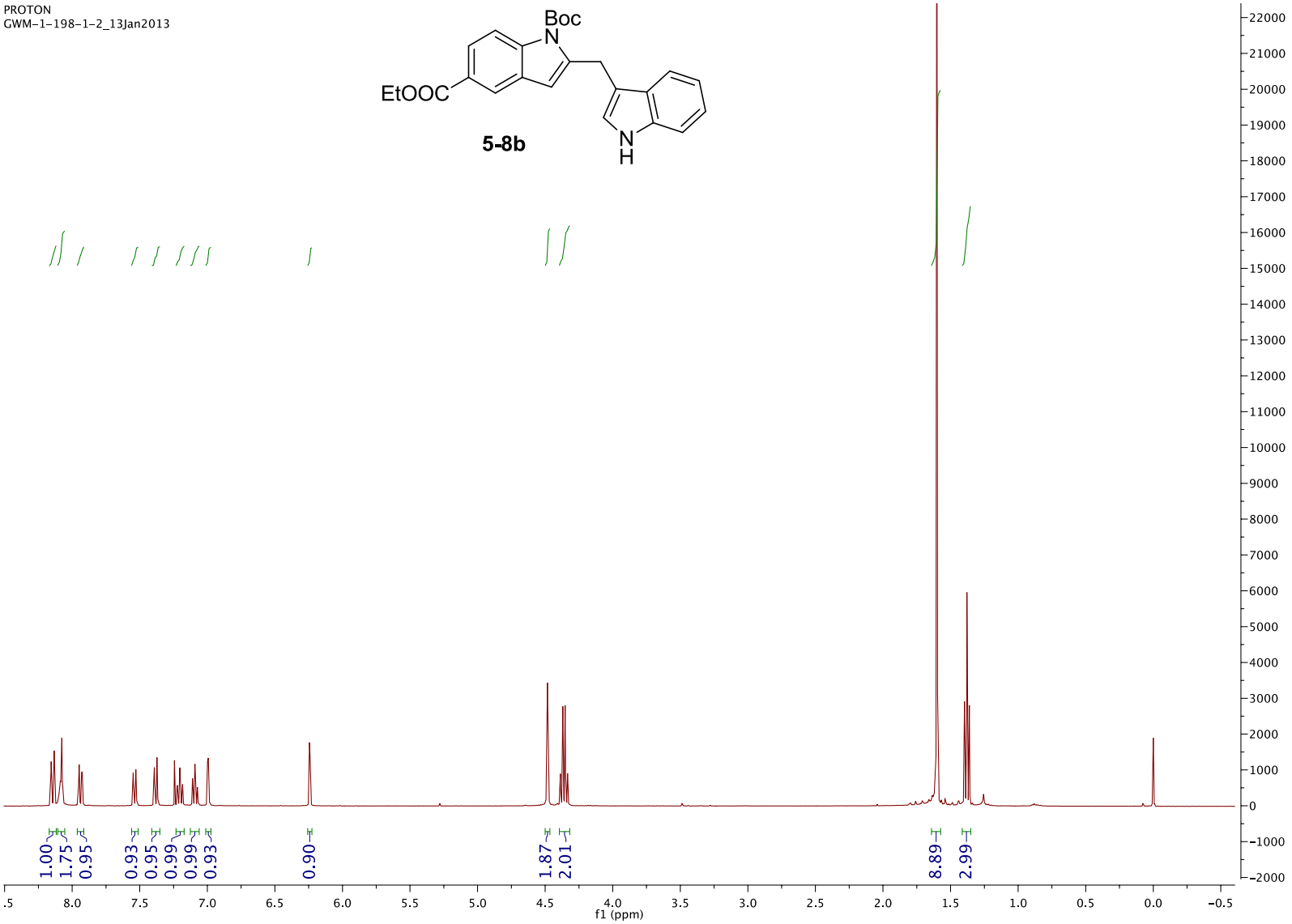


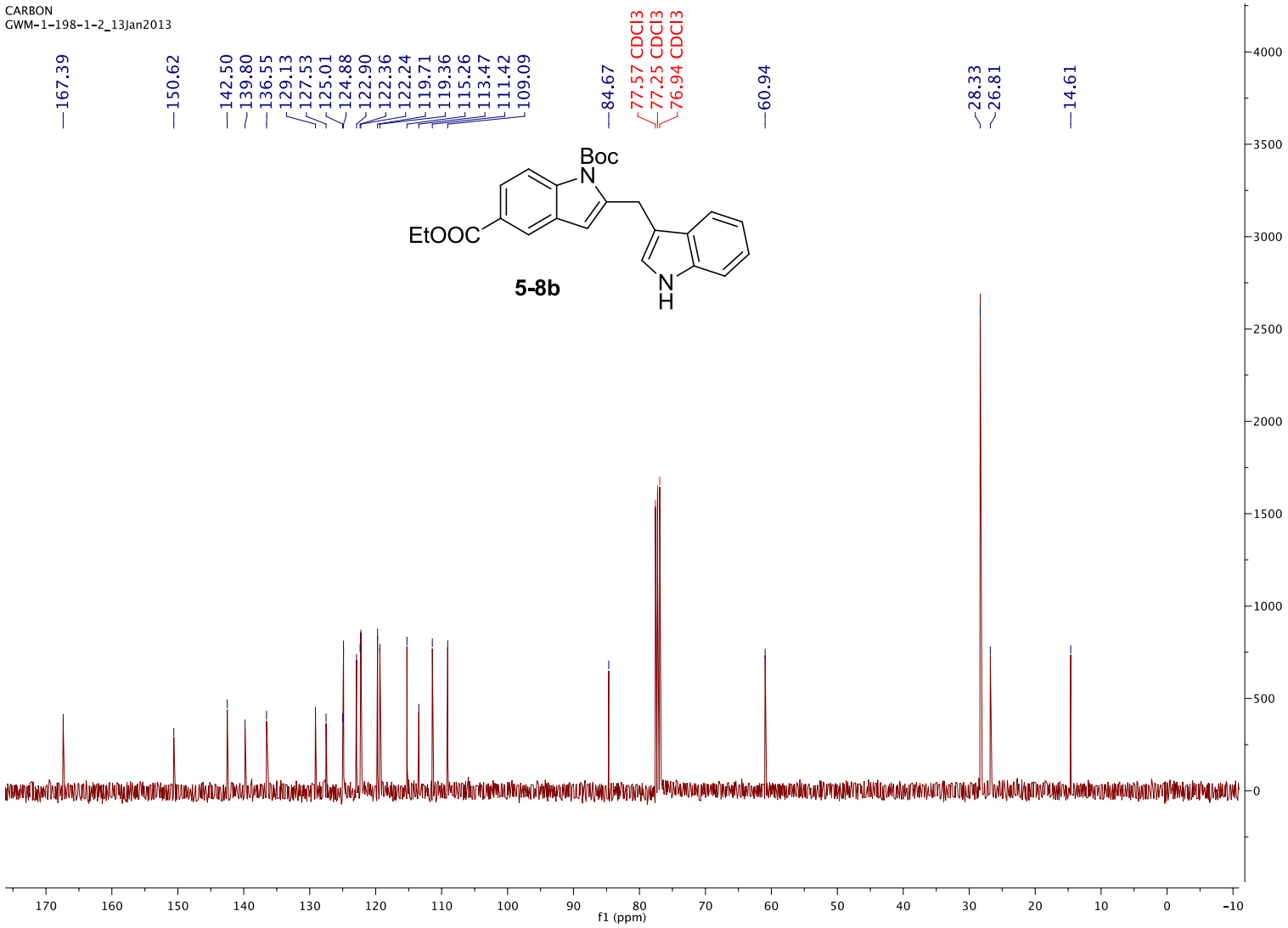
5-5j

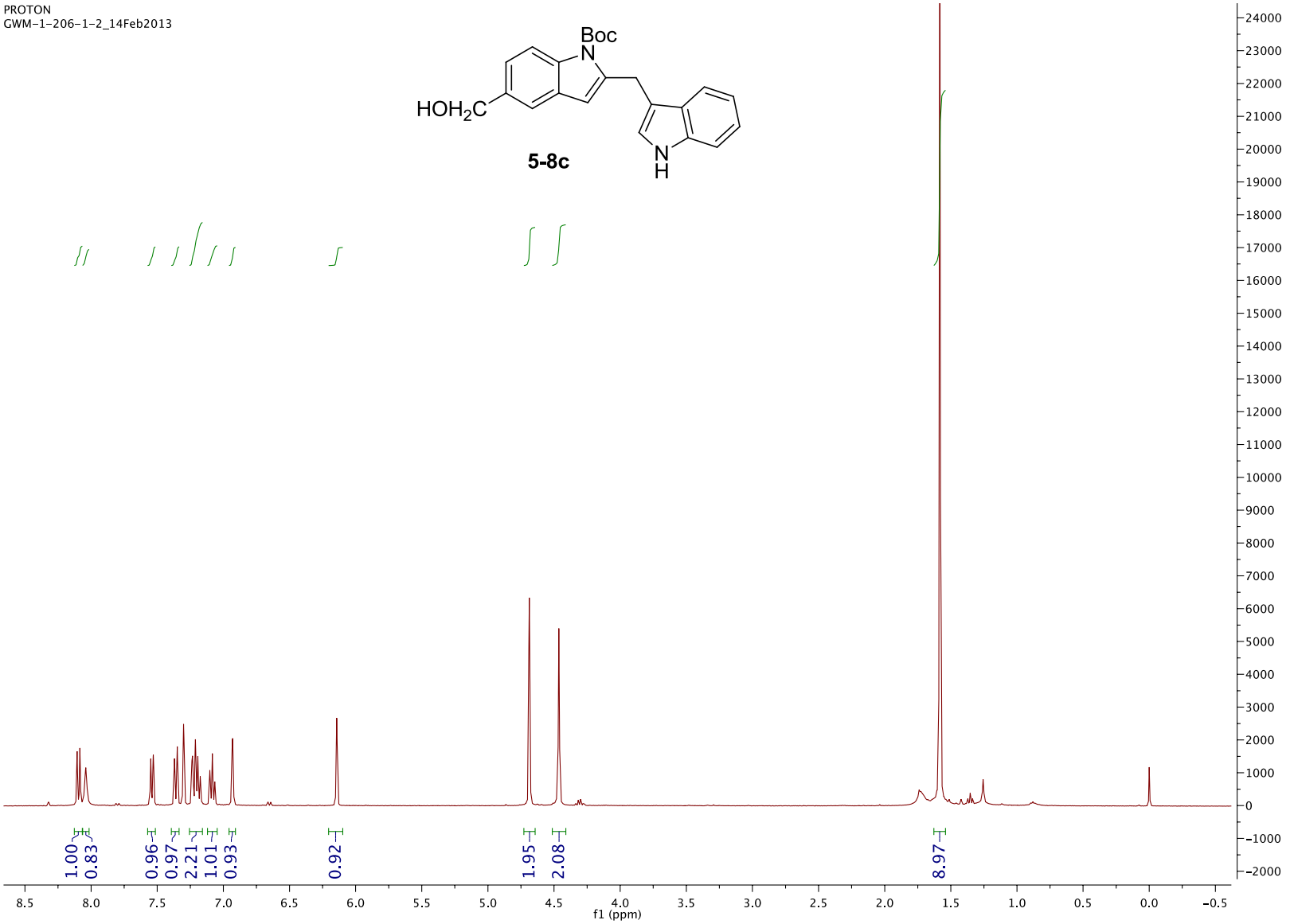

Boc
N
MeO
N
H
5-8a
1.93
0.95
0.93
1.99
0.95
2.00
3.01
2.99
8
7
6
5
4
3
2
1
PPM

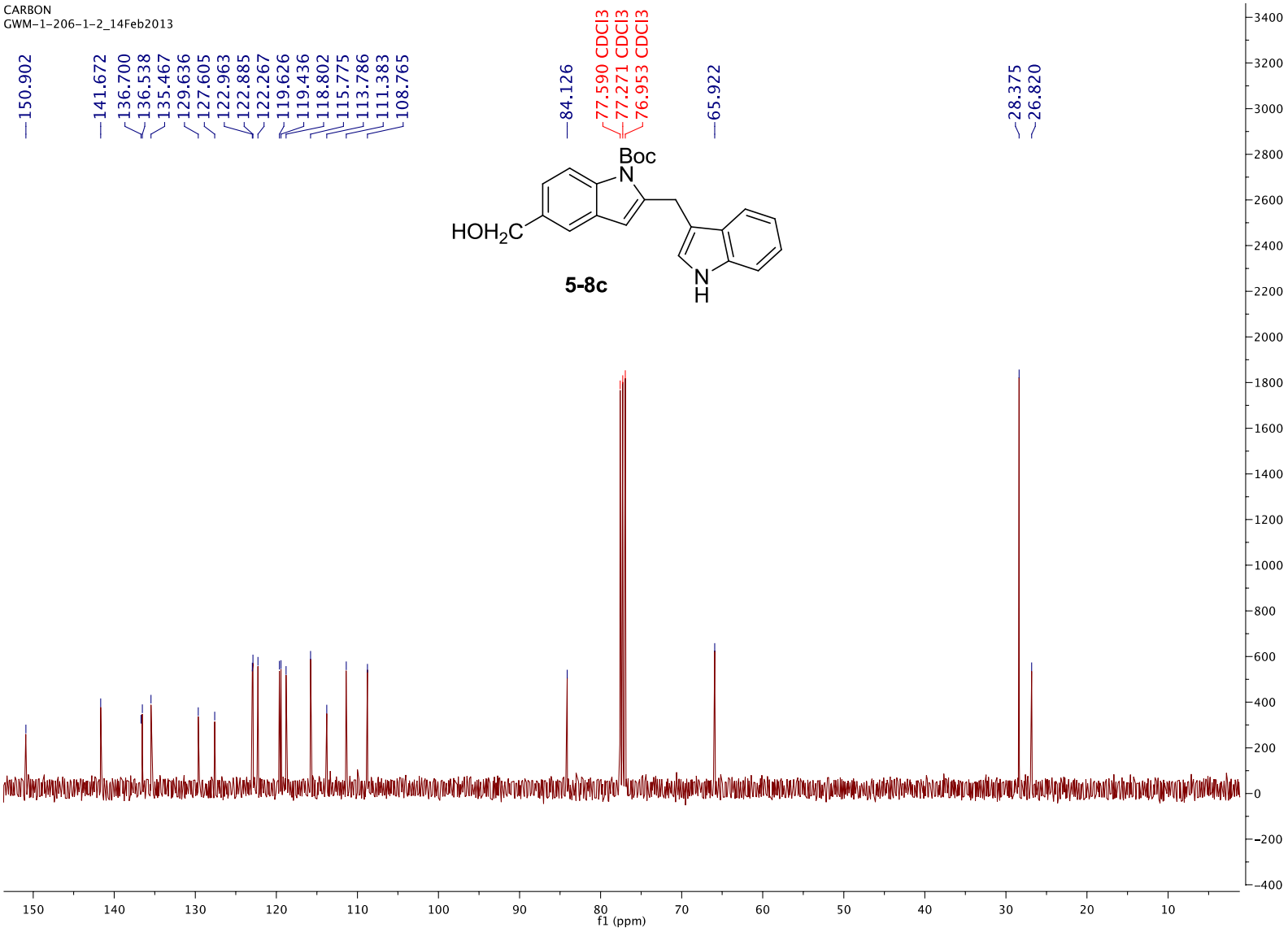
PROTON
DXS-04-141-2_16Nov2012

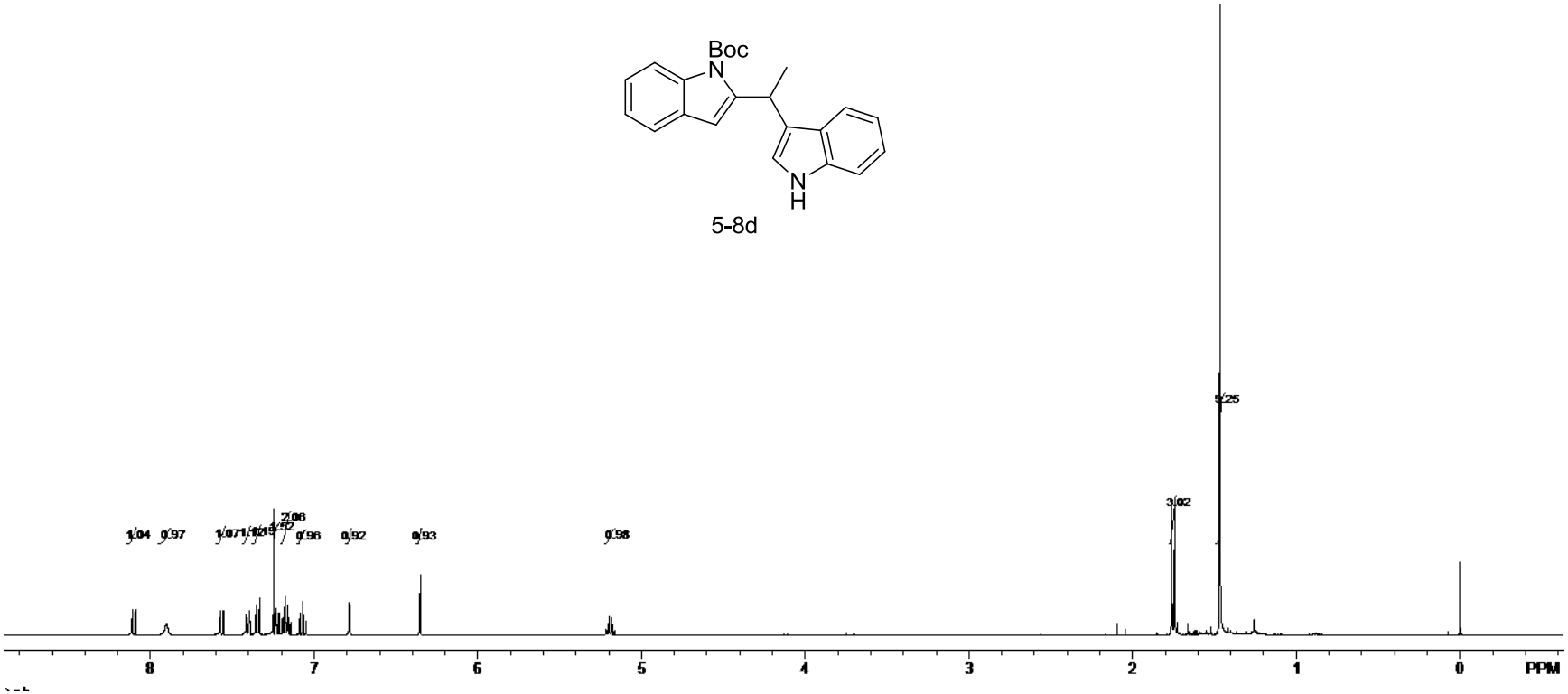



PROTON
GWM-1-198-1-2_13Jan2013
Boc
N
EtOOC
N
H
5-8b
1.00
1.75
0.95
0.93
0.95
0.99
0.99
0.93
0.90
1.87
2.01
8.89
2.99
f1 (ppm)


CARBON
GWM-1-198-1-2_13Jan2013
167.39
150.62
142.50
139.80
136.55
129.13
127.53
125.01
124.88
122.90
122.36
122.24
119.71
119.36
115.26
113.47
111.42
109.09
84.67
77.57 CDCl3
77.25 CDCl3
76.94 CDCl3
60.94
28.33
26.81
14.61
Boc
N
EtOOC
N
H
5-8b
f1 (ppm)

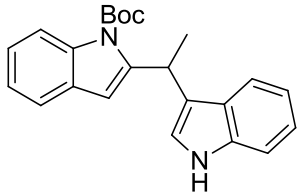

PROTON
GWM-1-206-1-2_14Feb2013
Boc
N
HOH2C
N
H
5-8c
1.00
0.83
0.96
0.97
2.21
1.01
0.93
0.92
1.95
2.08
8.97
f1 (ppm)


CARBON
GWM-1-206-1-2_14Feb2013
150.902
141.672
136.700
136.538
135.467
129.636
127.605
122.963
122.885
122.267
119.626
119.436
118.802
115.775
113.786
111.383
108.765
84.126
77.590 CDCl3
77.271 CDCl3
76.953 CDCl3
65.922
28.375
26.820
Boc
N
HOH2C
N
H
5-8c
f1 (ppm)

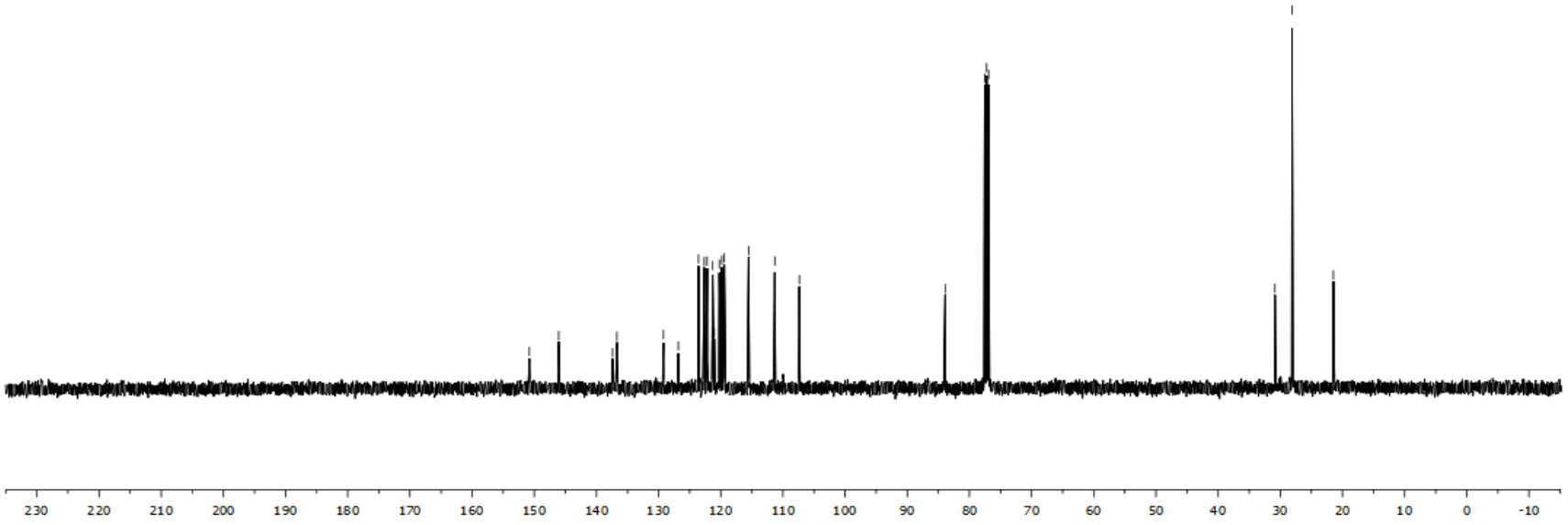

Boc
N
N
H
5-8d
1.04
0.97
1.07
2.06
0.96
0.92
0.93
0.98
3.02
5.25
8
7
6
5
4
3
2
1
0
PPM

CARBON
DXS-04-179_14Mar2013

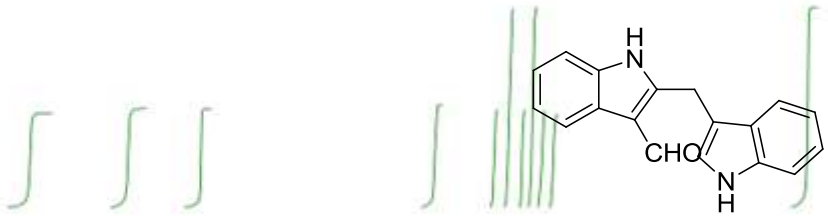
150.787
146.065
137.390
136.707
129.222
126.832
123.581
122.648
122.191
121.303
121.044
120.229
119.828
119.429
115.513
111.314
107.356
83.890
77.548
77.230
76.912
30.863
28.108
21.448



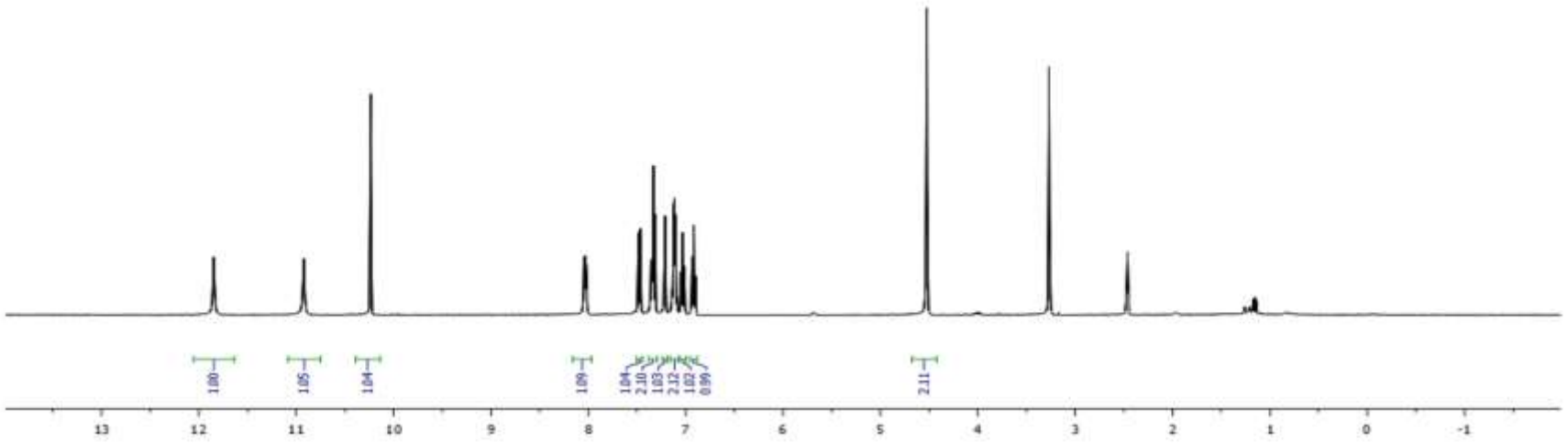
5-8d



PROTON
DXS-04-166_14Jan2013

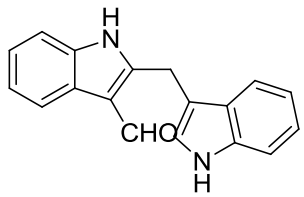


5-1

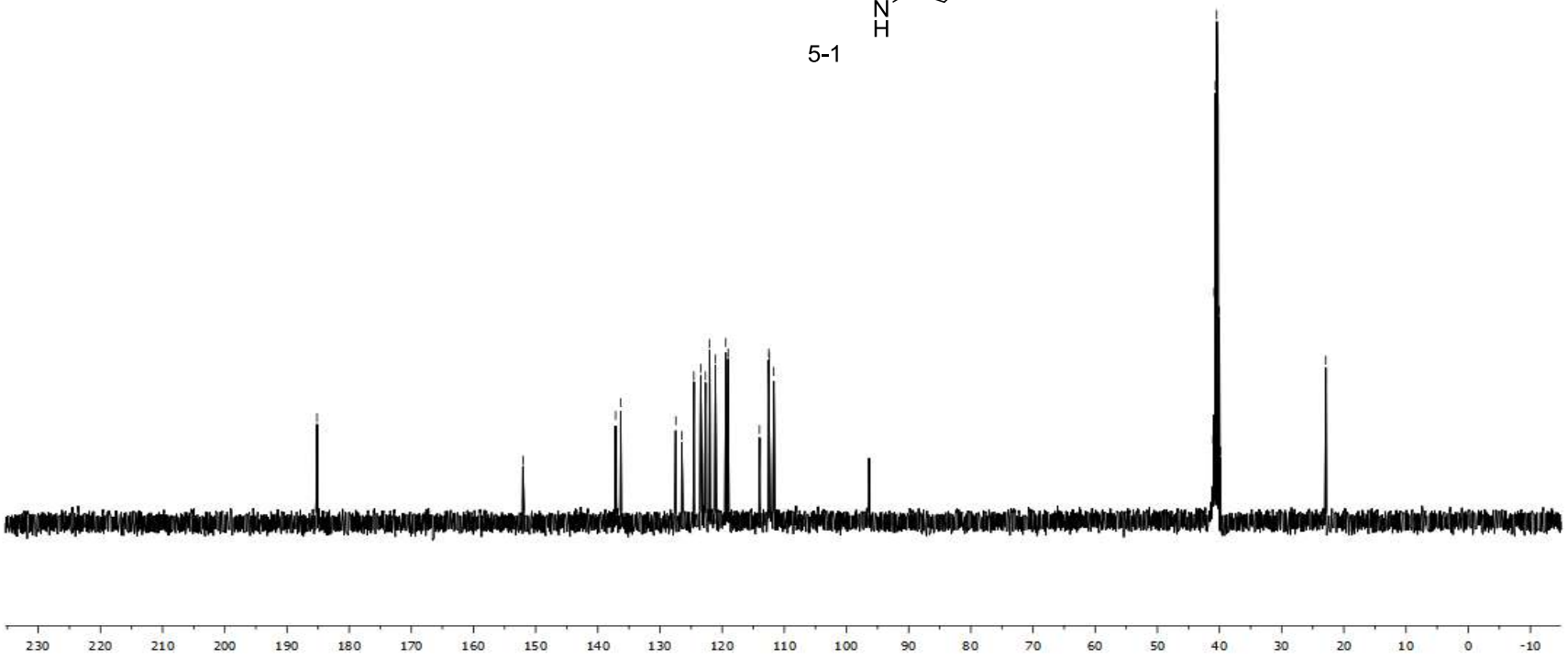


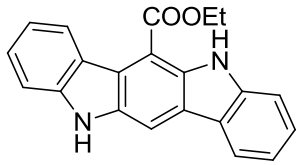
CARBON
DXS-04-166_14Jan2013

185.172
152.046
137.132
136.315
127.468
126.492
124.549
123.459
122.681
122.013
121.097
119.416
119.051
113.994
112.504
112.387
111.692
41.073
40.867
40.658
40.450
40.241
40.031
39.825
22.901

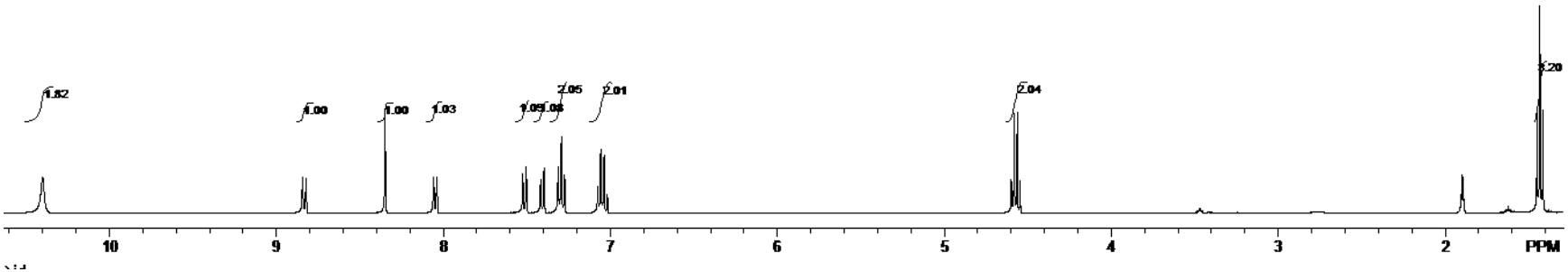


5-1

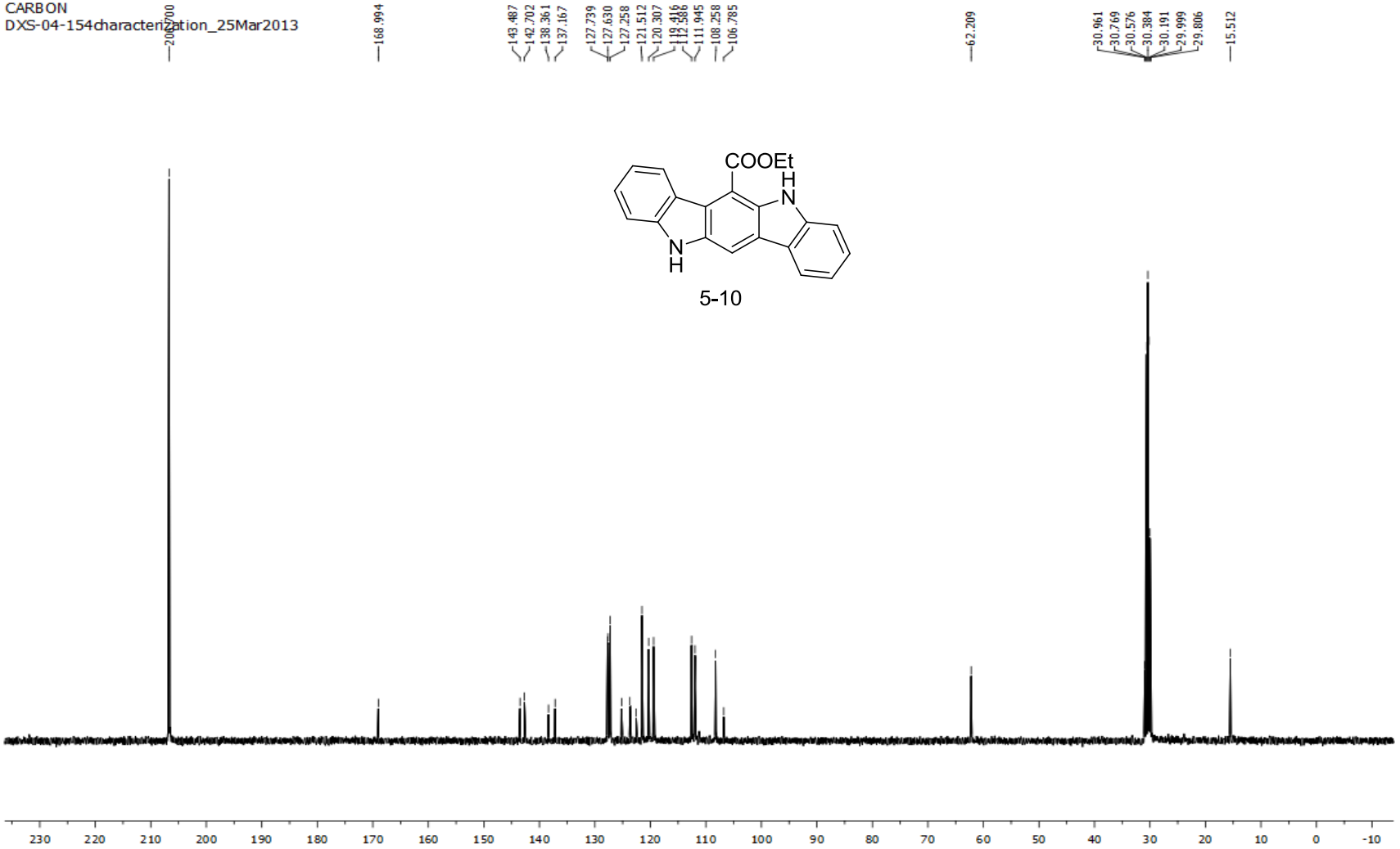



COOEt
H
N
N
H

5-10


1.82
1.00
1.00
1.03
1.05
1.08
2.05
2.01
2.04
3.20
10
9
8
7
6
5
4
3
2
PPM

CARBON
DXS-04-154characterization_25Mar2013



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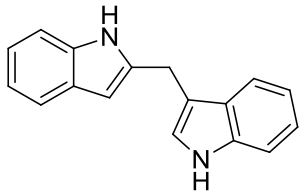

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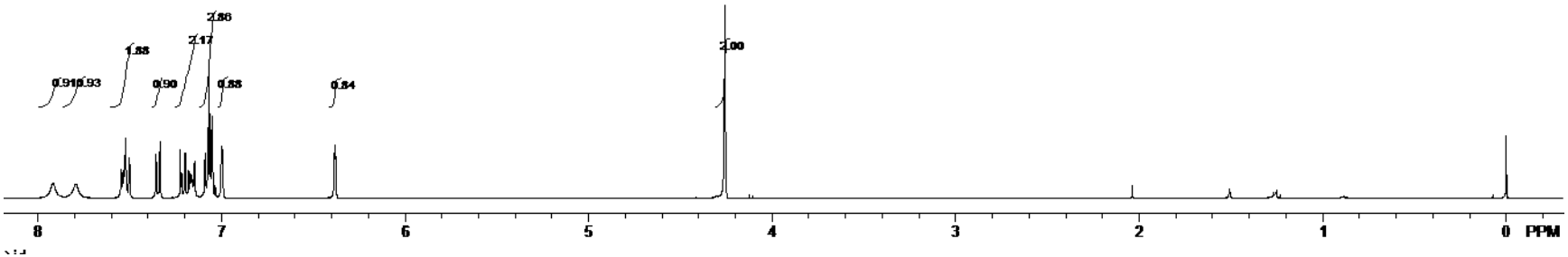

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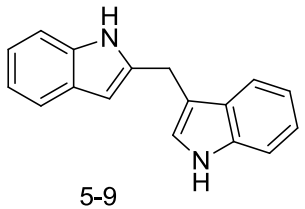

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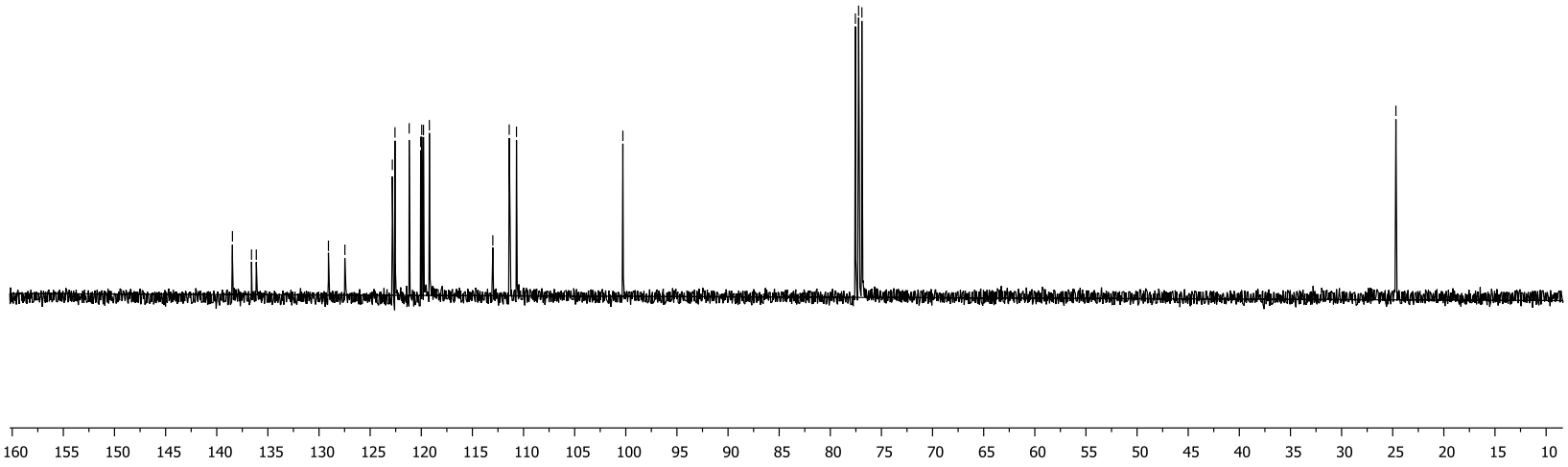

Appendix 3

X-ray Crystal Structure Determination

Data collection and structural solutions performed by Dr. Ilia A. Guzei and Lara C. Spencer

Unversity of Wisconsin-Madison

Data Collection

A colorless crystal with approximate dimensions 0.23 x 0.21 x 0.08 mm3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker SMART APEXII diffractometer with Cu K_α (λ = 1.54178 Å) radiation and the diffractometer to crystal distance of 4.03 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 25 frames collected at intervals of 1 ºin a 25 ºrange about ω with the exposure time of 5 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9968 strong reflections from the actual data collection.

The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.82 Å. A total of 23125 data were harvested by collecting 19 sets of frames with 0.8 ºscans in ω and φ with an exposure time of 5-10 sec per frame. These highly redundant datasets were corrected for Lorentz and

polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group $P2_1/n$ that yielded chemically reasonable and computationally stable results of refinement [2-4].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The final least-squares refinement of 178 parameters against 2835 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0361 and 0.1310, respectively. The final difference Fourier map was featureless.

The molecular diagram are drawn with 50% probability ellipsoids.

References

[1] Bruker-AXS. (2007) APEX2, SADABS, and SAINT Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

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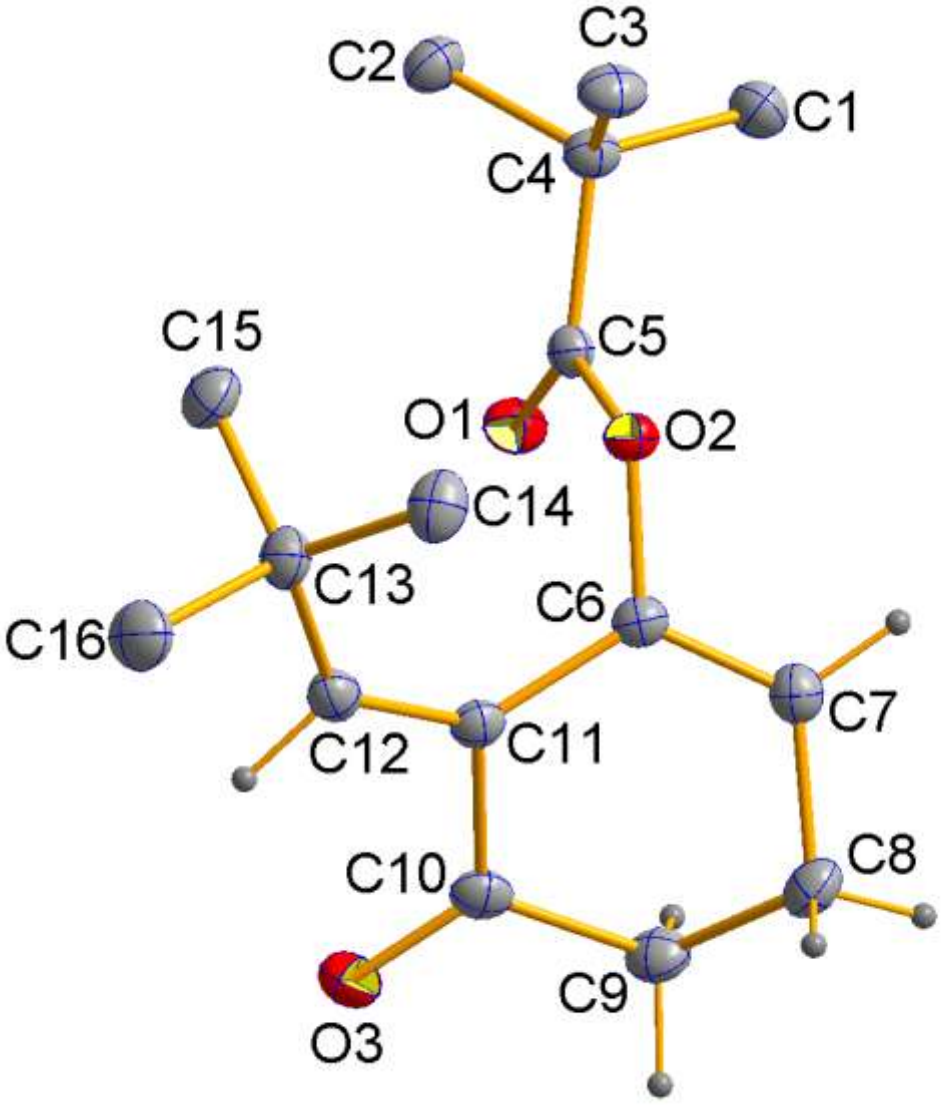
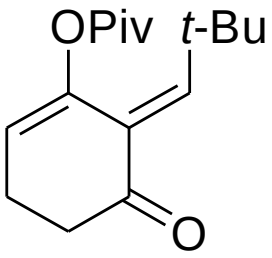
[3] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. "OLEX2: a complete structure solution, refinement and analysis program". *J. Appl. Cryst.* (2009) **42**, *339-341*.

[4] Guzei, I.A. (2006-2008). Internal laboratory computer programs "Inserter", "FCF_filter", "Modicifer".

[5] Pennington, W.T. (1999) *J. Appl. Cryst.* **32**(5), 1028-1029.



A molecular drawing of **2f**. All H atoms attached to the t-butyl groups are omitted for clarity.



2f

Table 1. Crystal data and structure refinement for **2f**.

Identification code	**2f**	
Empirical formula	$C_{16}H_{24}O_3$	
Formula weight	264.35	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.5042(2) Å	= 90 °.
	b = 6.09200(10) Å	= 95.8150(10) °.

	c = 24.0074(4) Å = 90 °.
Volume	1528.37(5) $Å^3$
Z	4
Density (calculated)	1.149 Mg/m^3
Absorption coefficient	0.619 mm^{-1}
F(000)	576
Crystal size	0.33 x 0.15 x 0.13 mm^3
Theta range for data collection	3.70 to 69.54 °.
Index ranges	-12<=h<=12, -7<=k<=7, -28<=l<=23
Reflections collected	23125
Independent reflections	2835 [R(int) = 0.0269]
Completeness to theta = 67.00 °	99.0 %
Absorption correction	Analytical with SADABS
Max. and min. transmission	0.9238 and 0.8217
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2835 / 0 / 178

Goodness-of-fit on F^2	1.173
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.1272
R indices (all data)	R1 = 0.0388, wR2 = 0.1310
Largest diff. peak and hole	0.310 and -0.196 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2f**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3779(1)	156(1)	527(1)	21(1)
O(2)	3715(1)	2808(1)	1179(1)	17(1)
O(3)	8057(1)	736(1)	1045(1)	26(1)
C(1)	1064(1)	2070(2)	399(1)	24(1)
C(2)	1445(1)	-1596(2)	866(1)	23(1)
C(3)	1357(1)	1816(2)	1448(1)	23(1)
C(4)	1764(1)	859(2)	904(1)	18(1)
C(5)	3186(1)	1162(2)	846(1)	15(1)

C(6)	4980(1)	3410(2)	1090(1)	16(1)
C(7)	5146(1)	5266(2)	817(1)	19(1)
C(8)	6461(1)	5942(2)	695(1)	23(1)
C(9)	7221(1)	3904(2)	556(1)	23(1)
C(10)	7193(1)	2068(2)	978(1)	19(1)
C(11)	6046(1)	1984(2)	1312(1)	17(1)
C(12)	6188(1)	770(2)	1782(1)	19(1)
C(13)	5380(1)	456(2)	2264(1)	21(1)
C(14)	4741(1)	2578(2)	2439(1)	25(1)
C(15)	4378(1)	-1337(2)	2107(1)	24(1)
C(16)	6276(1)	-347(2)	2770(1)	29(1)

—

Table 3. Bond lengths [Å] and angles [º] for **2f**.

O(1)-C(5)	1.2024(13)	C(3)-H(3B)	0.9800
O(2)-C(5)	1.3653(12)	C(3)-H(3C)	0.9800
O(2)-C(6)	1.4156(12)	C(4)-C(5)	1.5254(13)
O(3)-C(10)	1.2156(13)	C(6)-C(7)	1.3260(15)
C(1)-C(4)	1.5407(14)	C(6)-C(11)	1.4743(14)
C(1)-H(1A)	0.9800	C(7)-C(8)	1.4989(15)
C(1)-H(1B)	0.9800	C(7)-H(7)	0.9500
C(1)-H(1C)	0.9800	C(8)-C(9)	1.5310(15)
C(2)-C(4)	1.5332(14)	C(8)-H(8A)	0.9900
C(2)-H(2A)	0.9800	C(8)-H(8B)	0.9900
C(2)-H(2B)	0.9800	C(9)-C(10)	1.5112(15)
C(2)-H(2C)	0.9800	C(9)-H(9A)	0.9900
C(3)-C(4)	1.5295(14)	C(9)-H(9B)	0.9900
C(3)-H(3A)	0.9800	C(10)-C(11)	1.5144(14)

C(11)-C(12)	1.3441(14)	C(14)-H(14C)	0.9800
C(12)-C(13)	1.5162(14)	C(15)-H(15A)	0.9800
C(12)-H(12)	0.9500	C(15)-H(15B)	0.9800
C(13)-C(14)	1.5347(15)	C(15)-H(15C)	0.9800
C(13)-C(15)	1.5371(15)	C(16)-H(16A)	0.9800
C(13)-C(16)	1.5381(15)	C(16)-H(16B)	0.9800
C(14)-H(14A)	0.9800	C(16)-H(16C)	0.9800
C(14)-H(14B)	0.9800		

C(5)-O(2)-C(6)	115.74(7)	C(4)-C(2)-H(2B)	109.5
C(4)-C(1)-H(1A)	109.5	H(2A)-C(2)-H(2B)	109.5
C(4)-C(1)-H(1B)	109.5	C(4)-C(2)-H(2C)	109.5
H(1A)-C(1)-H(1B)	109.5	H(2A)-C(2)-H(2C)	109.5
C(4)-C(1)-H(1C)	109.5	H(2B)-C(2)-H(2C)	109.5
H(1A)-C(1)-H(1C)	109.5	C(4)-C(3)-H(3A)	109.5
H(1B)-C(1)-H(1C)	109.5	C(4)-C(3)-H(3B)	109.5
C(4)-C(2)-H(2A)	109.5	H(3A)-C(3)-H(3B)	109.5

C(4)-C(3)-H(3C)	109.5	C(8)-C(7)-H(7)	120.0
H(3A)-C(3)-H(3C)	109.5	C(7)-C(8)-C(9)	109.33(8)
H(3B)-C(3)-H(3C)	109.5	C(7)-C(8)-H(8A)	109.8
C(5)-C(4)-C(3)	113.14(8)	C(9)-C(8)-H(8A)	109.8
C(5)-C(4)-C(2)	108.83(8)	C(7)-C(8)-H(8B)	109.8
C(3)-C(4)-C(2)	110.14(9)	C(9)-C(8)-H(8B)	109.8
C(5)-C(4)-C(1)	105.24(8)	H(8A)-C(8)-H(8B)	108.3
C(3)-C(4)-C(1)	109.71(9)	C(10)-C(9)-C(8)	114.12(9)
C(2)-C(4)-C(1)	109.64(9)	C(10)-C(9)-H(9A)	108.7
O(1)-C(5)-O(2)	122.73(9)	C(8)-C(9)-H(9A)	108.7
O(1)-C(5)-C(4)	124.91(9)	C(10)-C(9)-H(9B)	108.7
O(2)-C(5)-C(4)	112.28(8)	C(8)-C(9)-H(9B)	108.7
C(7)-C(6)-O(2)	117.89(9)	H(9A)-C(9)-H(9B)	107.6
C(7)-C(6)-C(11)	123.22(9)	O(3)-C(10)-C(9)	121.16(10)
O(2)-C(6)-C(11)	118.87(8)	O(3)-C(10)-C(11)	122.07(10)
C(6)-C(7)-C(8)	120.06(9)	C(9)-C(10)-C(11)	116.77(9)
C(6)-C(7)-H(7)	120.0	C(12)-C(11)-C(6)	130.08(10)

C(12)-C(11)-C(10)	115.86(9)	C(13)-C(15)-H(15A)	109.5
C(6)-C(11)-C(10)	113.85(9)	C(13)-C(15)-H(15B)	109.5
C(11)-C(12)-C(13)	133.42(10)	H(15A)-C(15)-H(15B)	109.5
C(11)-C(12)-H(12)	113.3	C(13)-C(15)-H(15C)	109.5
C(13)-C(12)-H(12)	113.3	H(15A)-C(15)-H(15C)	109.5
C(12)-C(13)-C(14)	113.39(9)	H(15B)-C(15)-H(15C)	109.5
C(12)-C(13)-C(15)	108.97(9)	C(13)-C(16)-H(16A)	109.5
C(14)-C(13)-C(15)	110.98(9)	C(13)-C(16)-H(16B)	109.5
C(12)-C(13)-C(16)	107.31(9)	H(16A)-C(16)-H(16B)	109.5
C(14)-C(13)-C(16)	107.53(9)	C(13)-C(16)-H(16C)	109.5
C(15)-C(13)-C(16)	108.47(9)	H(16A)-C(16)-H(16C)	109.5
C(13)-C(14)-H(14A)	109.5	H(16B)-C(16)-H(16C)	109.5
C(13)-C(14)-H(14B)	109.5		
H(14A)-C(14)-H(14B)	109.5		
C(13)-C(14)-H(14C)	109.5		
H(14A)-C(14)-H(14C)	109.5		
H(14B)-C(14)-H(14C)	109.5		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2f**. The anisotropic displacement factor exponent takes the form: $-2\ ^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	20(1)	23(1)	22(1)	-5(1)	5(1)	0(1)
O(2)	15(1)	18(1)	18(1)	-2(1)	3(1)	-1(1)
O(3)	18(1)	26(1)	35(1)	1(1)	4(1)	2(1)
C(1)	20(1)	24(1)	26(1)	3(1)	-1(1)	0(1)
C(2)	24(1)	19(1)	26(1)	-1(1)	4(1)	-4(1)
C(3)	20(1)	26(1)	24(1)	-5(1)	7(1)	-1(1)
C(4)	17(1)	18(1)	19(1)	-2(1)	2(1)	-1(1)
C(5)	17(1)	16(1)	14(1)	1(1)	1(1)	1(1)
C(6)	17(1)	18(1)	13(1)	-2(1)	2(1)	-2(1)
C(7)	22(1)	19(1)	18(1)	0(1)	1(1)	1(1)
C(8)	27(1)	21(1)	22(1)	4(1)	4(1)	-4(1)

C(9)	21(1)	28(1)	19(1)	2(1)	5(1)	-3(1)
C(10)	16(1)	21(1)	20(1)	-5(1)	-1(1)	-4(1)
C(11)	16(1)	16(1)	18(1)	-2(1)	1(1)	-3(1)
C(12)	17(1)	17(1)	21(1)	-1(1)	-1(1)	0(1)
C(13)	24(1)	20(1)	18(1)	4(1)	2(1)	1(1)
C(14)	34(1)	24(1)	17(1)	0(1)	5(1)	2(1)
C(15)	28(1)	22(1)	22(1)	5(1)	4(1)	-3(1)
C(16)	30(1)	34(1)	23(1)	8(1)	0(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2f**.

	x	y	z	U(eq)
H(1A)	1296	3629	417	35
H(1B)	138	1917	408	35
H(1C)	1315	1434	51	35
H(2A)	1694	-2186	513	34
H(2B)	523	-1801	880	34
H(2C)	1913	-2369	1181	34
H(3A)	1845	1107	1768	35
H(3B)	441	1555	1465	35
H(3C)	1526	3398	1459	35

H(7)	4431	6167	700	23
H(8A)	6903	6700	1024	28
H(8B)	6400	6972	374	28
H(9A)	6873	3347	184	27
H(9B)	8122	4335	531	27
H(12)	6956	-66	1819	22
H(14A)	5397	3699	2533	37
H(14B)	4282	2289	2767	37
H(14C)	4137	3099	2130	37
H(15A)	3791	-841	1789	36
H(15B)	3894	-1630	2428	36
H(15C)	4809	-2683	2005	36
H(16A)	6675	-1734	2675	44
H(16B)	5782	-574	3090	44
H(16C)	6941	755	2866	44

Table 6. Torsion angles [°] for **2f**.

C(6)-O(2)-C(5)-O(1)	5.77(13)
C(6)-O(2)-C(5)-C(4)	-171.10(8)
C(3)-C(4)-C(5)-O(1)	162.66(10)
C(2)-C(4)-C(5)-O(1)	39.89(13)
C(1)-C(4)-C(5)-O(1)	-77.56(12)
C(3)-C(4)-C(5)-O(2)	-20.55(12)
C(2)-C(4)-C(5)-O(2)	-143.32(9)
C(1)-C(4)-C(5)-O(2)	99.23(9)
C(5)-O(2)-C(6)-C(7)	104.54(10)
C(5)-O(2)-C(6)-C(11)	-76.72(11)
O(2)-C(6)-C(7)-C(8)	-177.95(9)
C(11)-C(6)-C(7)-C(8)	3.37(15)
C(6)-C(7)-C(8)-C(9)	37.00(13)
C(7)-C(8)-C(9)-C(10)	-50.22(12)
C(8)-C(9)-C(10)-O(3)	-153.63(10)

C(8)-C(9)-C(10)-C(11)	26.02(12)
C(7)-C(6)-C(11)-C(12)	144.47(12)
O(2)-C(6)-C(11)-C(12)	-34.20(15)
C(7)-C(6)-C(11)-C(10)	-29.96(14)
O(2)-C(6)-C(11)-C(10)	151.37(8)
O(3)-C(10)-C(11)-C(12)	17.44(14)
C(9)-C(10)-C(11)-C(12)	-162.21(9)
O(3)-C(10)-C(11)-C(6)	-167.30(9)
C(9)-C(10)-C(11)-C(6)	13.06(12)
C(6)-C(11)-C(12)-C(13)	-2.93(19)
C(10)-C(11)-C(12)-C(13)	171.41(10)
C(11)-C(12)-C(13)-C(14)	-38.60(16)
C(11)-C(12)-C(13)-C(15)	85.54(13)
C(11)-C(12)-C(13)-C(16)	-157.20(11)

Symmetry transformations used to generate equivalent atoms: