Stony Brook University

Synthesis of Novel Fused Tricyclic and Tetracyclic Skeletons Through Rh(I)-Catalyzed [2+2+2+1] Cycloaddition of Enediyne Derivatives with Carbon Monoxide

A Dissertation Presented

by

Joseph Junior Kaloko

to

The Graduate School

In partial fulfillment of the

requirements

for the Degree of

Doctor of Philosophy

in

Chemistry

Stony Brook University

December 2010

Stony Brook University

The Graduate School

Joseph Junior Kaloko

We, the dissertation committee for the above candidate for the

Doctor of Philosophy degree, hereby recommend

acceptance of this thesis

Professor Iwao Ojima
Dissertation Advisor
Department of Chemistry

Professor Dale G. Drueckhammer
Chairman
Department of Chemistry

Professor Nancy Goroff
Third Member
Department of Chemistry

Dr. Ramesh Gupta
Outside Member
Vice President, Chem-Master International

This dissertation is accepted by the Graduate School

Lawrence Martin
Dean of the Graduate School

Abstract of the Dissertation

Synthesis of Novel Fused Tricyclic and Tetracyclic Skeletons Through Rh(I)-Catalyzed [2+2+2+1] Cycloaddition of Enediyne Derivatives with Carbon Monoxide

Joseph J. Kaloko

Doctor of Philosophy

in Chemistry

Stony Brook University

2010

Natural products (NP) and their metabolites isolated from diverse origins have been an extraordinary source of active pharmaceuticals, agrochemicals and other applications. Often, (NP) also serve as templates to obtain more potent and selective agents through structure-activity relationship (SAR) studies. A ubiquitous feature of (NP) and their metabolites is that they often contain fascinating fused-ring skeletons. Unfortunately, the vast majority of (NP) cannot be isolated in large quantities from their natural source. Consequently, the need to develop highly efficient synthetic methods that provide access to fused ring-skeletons with handles for further modification is necessary. Transition metal-catalyzed carbocyclization and cycloaddition reactions have proven to be among the most efficient methods for (NP) synthesis as well as constructing "natural product-like" (NPL) and "drug-like" (DL) skeletons.

As part of ongoing studies by the Ojima lab into transition metal catalyzed carbocyclizations and higher-order cycloaddition reactions, the Rh(I)-catalyzed [2+2+2+1] cycloaddition of enediyne derivatives was investigated. The reaction of cyclohexene-diynes in the presence of $[Rh(CO)_2Cl]_2$ and CO (2 atm) gave novel 5-7-6-5 fused tetracyclic products while the reaction of cyclopentene-diynes under similar conditions gave the corresponding 5-7-5-5 fused tetracyclics in good to excellent yields. In addition to the expected products, the diene shifted regioisomers were obtained for all 1-silyl-substituted cycloalkenyl-diyne substrates investigated. γ-Butyrolactones are prominent constituents in a diverse class of biologically active compounds. Thus, the Rh(I)-catalyzed [2+2+2+1] cycloaddition of 1-methyl-dodec-11-ene-8-oxo-1,6-diynes which afforded 5-7-5 tricyclic products with fused γ-butyrolactones was also

investigated. The reaction variables as well as the mechanism for the formation of these fused products are presented.

Dedicated to my late Grandfather Sinneh A. M. Bangura
and
my Parents, Brothers, Sisters, Aunts and Uncles

TABLE OF CONTENTS

CHAPTER 3

Formation of novel 5-7-5-5 fused tetracyclic skeletons through Rh(I)-catalyzed [2+2+2+1]cycloaddition of cyclopentene-diynes and carbon monoxide

CHAPTER 4

Formation of 5-7-5 fused tricyclic γ-Lactones *via* Rh(I)-catalyzed [2+2+2+1] cycloaddition of enediynes with carbon monoxide

CHAPTER 5

Progress on the enantioselective synthesis of β-Lactams

APPENDICES

LIST OF FIGURES

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

LIST OF SCHEMES

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

LIST OF TABLES

CHAPTER 2

CHAPTER 3

CHAPTR 4

CHAPTER 5

LIST OF ABBREVIATIONS

Ac	-	acetyl
Atm	-	atmosphere
BINAP	-	2,2’-bis(diphenylphosphino)-1-1’-binapthyl
Boc	-	*tert*-butyl carbonate
Bu	-	butyl
BQ	-	Benzoylquinine
CH_2Cl_2	-	dichloromethane
COD	-	cyclooctadiene
CO	-	carbon monoxide
D	-	doublet
DCC	-	dicyclohexylcarbodiimide
DIAD	-	diisopropylazodicarboxylate
DIC	-	diisopropylcarbodiimide
DCE	-	1,2-dichloroethane
DCM	-	dichloromethane
dd	-	doublet of doublets
DMAP	-	4-dimethylaminopyridine
DMF	-	dimethylformamide
dppp	-	diphenylphosphino propane
EDG	-	electron donating group
ee	-	enantiomeric excess
ES	-	electrospray ionization
Et	-	ethyl
EWG	-	electron withdrawing group
EtOAc	-	ethyl acetate
FIA	-	flow-injection analysis
g	-	grams
GC- MS	-	gas chromatography mass spectrometry
h	-	hour

HPLC	-	high performance liquid chromatography
HRMS	-	high resolution mass spectrometry
Hz	-	hertz
i-Bu	-	*iso*-butyl
IR	-	infrared spectroscopy
L	-	liter
Kj	-	kilo joules
LC-MS	-	liquid chromatography mass spectrometry
LDA	-	lithium diisopropylamide
LiHMDS	-	lithium hexamethyldisilizane
m	-	multiplet
MeOH	-	methanol
Mmol	-	millimole
M	-	molarity
Mg	-	milligram
MHz	-	mega hertz
mL	-	milliliter
mp	-	melting point
MS	-	mass spectrometry
MW	-	microwave
NMR	-	nuclear magnetic resonance
NP	-	natural product
Ph	-	phenyl
Pht	-	Phthalimido
PMP	-	*para*-methoxyphenyl
PPM	-	parts per million
r.t.	-	room temperature
s	-	singlet
SAR	-	structure activity relationship
t	-	triplet
t-Bu	-	*tert*-butyl

TEA	-	triethylamine
Tf	-	triflate
TFA	-	trifluroacetic acid
TFE	-	2,2,2-trifluoroethanol
THF	-	tetrahydrofuran
TESCl	-	triethylsilyl chloride
TLC	-	thin layer chromatography
TMS	-	trimethylsilyl
Ts	-	tosylate
p-TSA	-	*p*-toluenesulfonic acid

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my thesis advisor professor Iwao Ojima for giving me the opportunity to work in his research lab. I thank him for his guidance, patience, support and encouragement throughout the course of my graduate career; I truly benefitted under his mentorship. I wish to thank the members of my ACC committee: Professor Dale G. Drueckhammer and Professor Nancy Goroff for their insightful comments, support and advice throughout the course of my graduate career. I clearly benefited greatly in my interactions with each of them. I especially like to thank Dr. Ramesh Gupta for taking the time to serve as my Outside Member. A special thank you to Mrs. Patricia Marinaccio "the Ojima Group Mom" for her support, lots of thoughtful advice and encouragement during fun times and tough times. I wish to also thank Mrs. Yoko Ojima for her wonderful hospitality and kindness.

I would like to thank my mentors; Dr. Liang Sun, Dr. Xianrui "Ray" Zhao and Ms. Ilaria Zanadi for all their help during my years in the Ojima group. To Ojima Group alumni Dr. Bruno Chapsal, Dr. Stephen J. Chaterpaul, Dr. Ce Shi, Dr. Shuyi Chen, Dr. Jin Chen, and Dr. Stanislav Jaracz; thank you for your support, encouragement and the many discussions on my research projects. I wish to thank all the current members of the Ojima Lab; Gary Teng, Edison Zuniga, Chi-Feng Lin, Chih-Wei Chien, Alexandra Athan, William Berger, Dr. Olivier Marrec, Joshua Seitz, Tao Wang, Lucy Li, Wen Chen, Winnie Situ, Bora Park, Yang Zang, and Kunal Kumar for their support and help with every aspect of research. I am greatly indebted to Dr. Stephen Chaterpaul, Gary Teng, Edison Zuniga, Chi-Feng Lin, Chih-Wei Chien and Alexandra Athan for helping me get through the many tough days with lots of laughter, support and encouragement; I am truly lucky to have worked so closely with you all. A special thank you to Dr. Olivier Marrec, Gary Teng, Edison Zuniga, Alexandra Athan and Dr. Stephen Chaterpaul for proofreading and helping me write a better dissertation.

I wish to thank the members of the faculty of the Chemistry Department and especially Prof. Drueckhammer, Prof. Tonge, Prof. Ojima, Prof. Parker and Prof. Fowler for a great foundation during my course work. A special thank you to Dr. James Marecek

for his help with various NMR experiments and countless discussions on research problems. Thanks also to Dr. Alvin Silverstein and Mr. Micheal Teta for keeping the chemistry building in working order. Thanks also to the entire staff of the chemistry department's main office Ms. Carol Brekke, Ms. Charmaine Yapchin and especially to Ms. Katherine Hughes for keeping me on track with program requirements. Thank you to the National Science Foundation for funding my research. Special thanks to the W. Burghardt Turner Fellowship at Stony Brook University for a graduate fellowship.

A special thank you is extended to Henry and Stephanie Causey, Samsad Pavel, Anna Basovich, Francis Roberts, Charles Kalimba, Fatu Bangura and my many more friends for their friendships, support and encouragement throughout this adventure. Finally, I would like to express my deepest gratitude to my entire family; my parents, brothers Mohamed, Fuhard, and Abraham, sisters Rugiatu and Aminata, my aunts and uncles who all believed in me, supported me, encouraged me and always stood by me. This thesis is especially for them.

Chapter 1

Carbonylative carbocyclization and cycloaddition reactions

Table of Contents

§ 1.1. Introduction

The development of highly efficient catalytic processes for the synthesis of bioactive compounds or building blocks for organic materials remains a central focus in modern organic chemistry.[1] Moreover, the use of carbon-carbon or carbon-heteroatom bond forming reactions to generate new ring systems is a key part of contemporary organic synthesis.[2] One of the most efficient approaches is the application of transition-metal catalyzed cyclization reactions. Using relatively simple but appropriately designed precursors, monocyclic, bicyclic and complex polycyclic molecules, which may be difficult to access from classical pericyclic reactions or other classical carbon-carbon bond forming reactions, can be synthesized under mild conditions often in a single step.[3] In addition, transition metal catalyzed cyclization reactions provide high atom economy, while often requiring relatively mild reaction conditions. The distribution of products often can be controlled based on the reaction conditions or the transition metal used in the reaction.[3-4]

Among catalytic cyclization processes, the carbocyclization of eneynes, dienes, enediynes, trienes, triynes, and their hetero-atom derivatives are extremely important and useful for the syntheses of a variety of carbocyclic and heterocyclic compounds.[1-3] Additionally, cascade carbocyclization of tethered olefins is a powerful method for rapid access to polycyclic skeletons in one step. The term "carbocyclization" has been used to describe an annulation process involving carbon-carbon bond formation via carbometallation a process that is fundamentally different from radical cyclization as well as thermal and photochemical cycloadditions.[5] When the carbocyclization process incorporates carbon monoxide, the process is categorized as carbonylative carbocyclization and provides efficient routes to cyclic and fused ketones.

Transition metal-catalyzed cycloaddition reactions also provide easy access to a variety of carbocyclic and heterocyclic compounds. Sometimes, the products are indistinguishable from those obtained from transition metal-catalyzed carbocyclization reactions though the mechanistic pathways are distinctive for the two processes. As with carbonylative carbocyclization reactions, transition metal catalyzed cycloaddition reactions performed in the presence of carbon monoxide also provide ketone products.

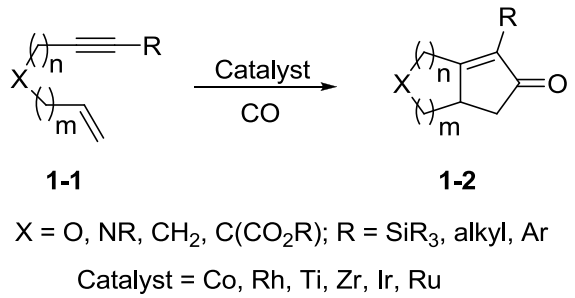
Mechanistic studies of various transition metal catalyzed carbocyclization and cycloaddition reactions have been carried out over the years and the versatilities of intermediate species have also been exploited.[6] Thus, over the past decade, a variety of otherwise forbidden or difficult to achieve reactions have been realized including [5+2+1],[7] [4+2+2],[4] and other higher order cycloadditons.[1, 5, 8] Various reviews, covering different aspects on transition metal catalyzed and mediated cycloadditions[2, 9] and carbocyclizations[10] have been reported in the literature.

This chapter provides an overview of carbonylation (incorporation of carbon monoxide) reactions by highlighting a few examples of carbonylative cycloaddition reactions; namely the Pauson-Khand (PK) and PK-type reactions from the recent literature, with particular emphasis on substrate type, application to natural product synthesis and heterocyclic compounds. Additionally, novel silicon-initiated carbocyclization (SiCaC), carbonylative carbobicyclization (CO-SiCaB), and carbonylative carbotricyclization (CO-SiCaT) reactions as well as higher-order [2+2+2+1] cycloaddition reactions pioneered in Ojima's laboratory are also discussed.

§ 1.2. Carbonylative carbocyclization and cycloaddition

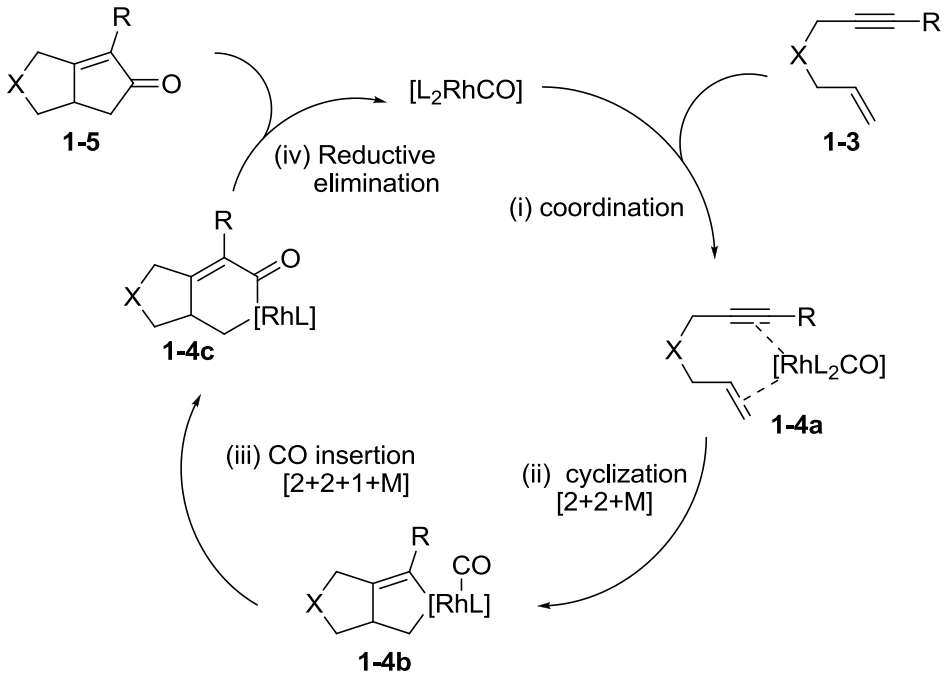
§ 1.2.1 Catalytic Pauson-Khand and Pauson-Khand type reactions

The Pauson-Khand reaction (PKR) was first reported in 1973. The PKR is formally a cobalt mediated [2+2+1] cycloaddition involving an alkene, an alkyne and carbon monoxide forming a cyclopentenone.[11] The synthetic utility of the PKR was initially limited due to the poor regioselectivity observed in the intermolecular reaction when unsymmetrical alkynes and alkenes are used.[12] However, the inherent regiocontrol of the intramolecular variant of the PKR has considerably expanded the synthetic utility of the reaction (**Scheme 1-1**).[12]



Scheme 1-1: Intramolecular Pauson-Khand reaction (PKR)

A variety of transition metals have been shown to catalyze the PK reaction including Co, Rh, Ti Zr, Ir, and Ru.[9b, 13] A proposed mechanism for the PK reaction of 1,6-enynes **1-3** catalyzed by Rh is outlined in **Scheme 1-2**.[14]

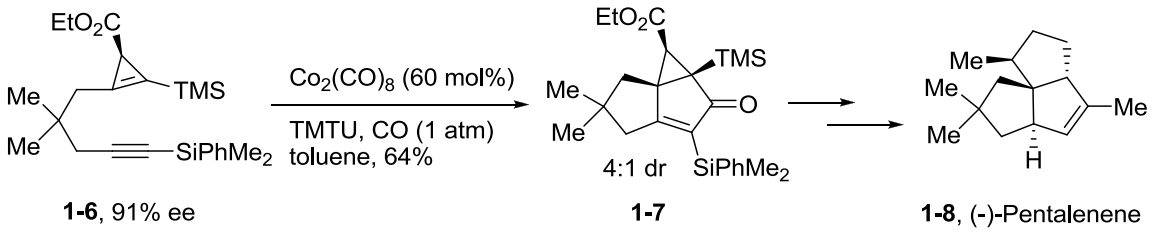


Scheme 1-2: Proposed mechanism of the PK reaction catalyzed by Rh-complex[14]

The reaction starts with (i) coordination of the active Rh catalyst to the enyne **1-3**, giving intermediate **1-4a**, (ii) intermediate **1-4a** is converted to rhodacyclopentene **1-4b** ([2+2+M]), (iii) migratory insertion of CO into the Rh-C bond gives 5-6 rhodacycle **1-4c** ([2+2+1+M]), and (iv) reductive elimination yields the PK reaction product **1-5**. A number of detailed reviews on the PKR and PK type reaction have been reported in the

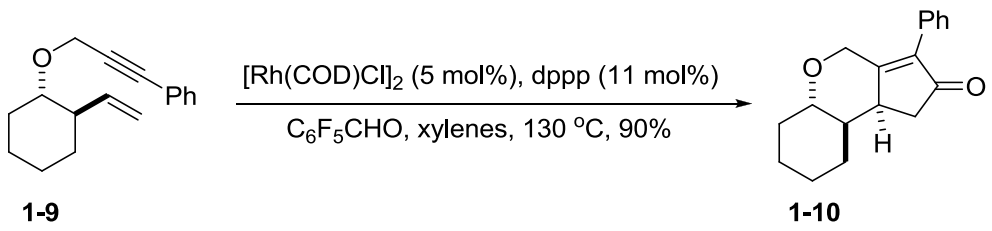
literature.[9b, 13, 15] The PK type reaction refers to [2+2+1] cycloaddition reactions in which either the olefin or alkyne has been replaced by other unsaturated moieties such as allenes and carbodiimides. A few recent examples of PKR and PK type reactions are covered here to highlight the scope of this very useful reaction, especially in the course of their application to natural product synthesis.

The intramolecular PKR was used to obtain a key intermediate in the enantioselective synthesis of (-)-Pentalenene **1-8**, the unnatural enantiomer of the angular triquinane natural product.[16] Using $Co_2(CO)_8$ (60 mol%) as catalyst in toluene and 1 atm of CO, enantiomerically enriched (91% ee) cyclopropene **1-6** gave the PK adduct **1-7** (4:1 dr) in 64% isolated yield (**Scheme 1-3**). The use of the known PKR promoter tetramethylthiourea (TMTU) was found to be critical in obtaining a good yield of the desired tricyclic product **1-7**.



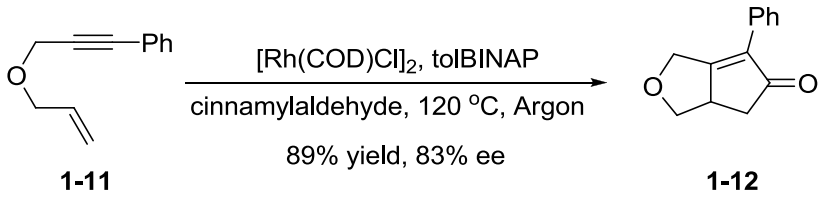
Scheme 1-3: Total synthesis of (-)-Pentalenene **1-8** *via* the PKR

The use of highly toxic carbon monoxide (CO) remains a drawback in cyclocarbonylation reactions. Recently, two independent groups reported the use of aldehydes as CO source. First, Kakiuchi and coworkers[17] reported a catalytic PK type reaction of eneynes using pentafluorobenzaldehyde (200 mol%), $[Rh(COD)Cl]_2$ (5 mol%), diphenylphosphino propane (dppp) (11 mol%) in xylenes under a nitrogen atmosphere. Several eneynes gave the [2+2+1] cycloadducts, but aryl substituted eneynes were generally more efficient under the reported reaction conditions. Specifically, cyclohexane tethered eneyne **1-9** gave the PK cycloadduct **1-10** in 90% yield as a single stereoisomer (**Scheme 1-4**).



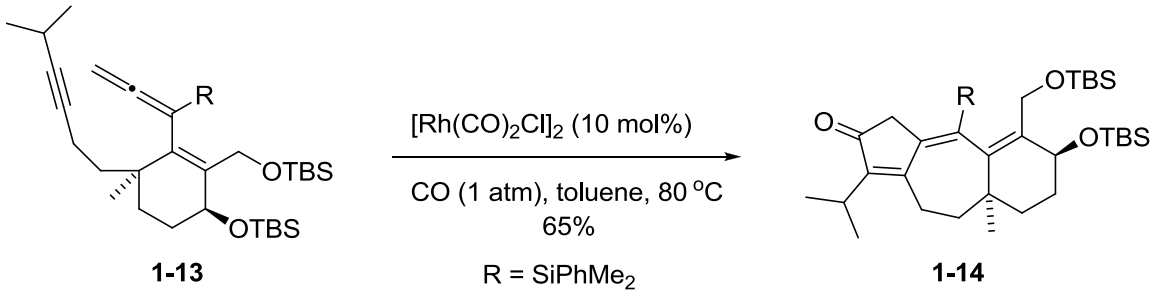
Scheme 1-4: The PKR of **1-9** using pentafluorobenzaldehyde as CO source

In the other example, cinnamylaldehyde was found to be the most efficient aldehyde in a solvent free system.[18] Using [Rh(dppp)$_2$Cl] (5 mol%) as the catalyst, commonly used eneynes were converted to the cyclopentenones adducts in high yields. Perhaps more encouraging was that a preliminary experiment under asymmetric conditions using [Rh(COD)Cl]$_2$ and (*R*)-(+)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl (tolBINAP) as chiral ligand gave the cycloadduct product **1-12** in 89% yield and 83% ee (**Scheme 1-5**).



Scheme 1-5: The PK reaction of **1-11**using cinnamylaldehyde as CO source

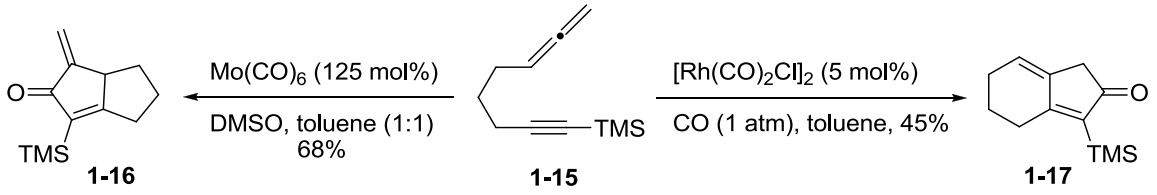
Seven-membered rings can also be obtained from the intramolecular cyclocarbonylation of allenynes with the appropriate number of atoms on the tether. The tricyclic skeleton of Guanacastepene A was obtained in an efficient manner using the PK type reaction of cyclohexene-tethered alleneyne **1-13** (**Scheme 1-6**).[19] Similar reaction conditions have also been applied to other cyclohexane-tethered allenenynes yielding linearly and angularly fused [6-7-5] ring systems.[20]



1-13 **1-14**

Scheme 1-6: Synthesis of the Guanacastepene A tricyclic core **1-14** *via* the PK reaction

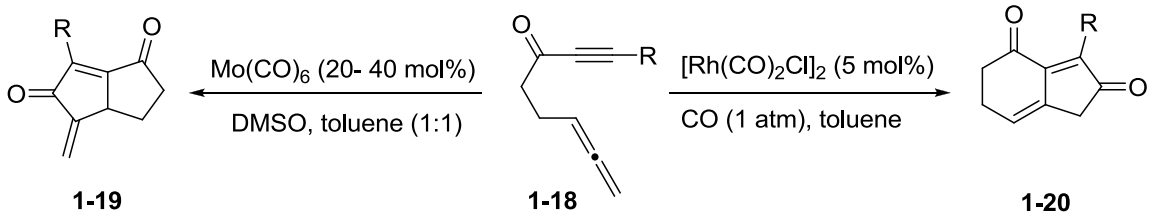
The products obtained from the PK type reaction of allenynes have been shown to be dependent on the transition metal used in the reaction. The use of $Mo(CO)_6$ as catalyst results in the exclusive reaction of the proximal double bond of the allene yielding α-alkylidene cyclopentenones **1-16**. Alternatively, using $[Rh(CO)_2Cl]_2$ as catalyst gives 4-alkylidene cyclopentenones **1-17** from reaction of the distal double bond of the allene (**Scheme 1-7**).[21]



1-16 **1-15** **1-17**

Scheme 1-7: The intramolecular PK-type reaction of allenenynes **1-15**

The scope of this regioselective cyclocarbonylation reaction has been extended to the preparation of bicyclic dienediones **1-19** and **1-20** from allenyl alkynones **1-18** (**Scheme 1-8**).[21] The $Mo(CO)_6$ catalyzed reactions gave bicyclo [3.3.0] octadienediones **1-19** while the $[Rh(CO)_2Cl]_2$ catalyzed reactions gave bicyclo [4.3.0] nonadienediones **1-20** (**Scheme 1-8**).

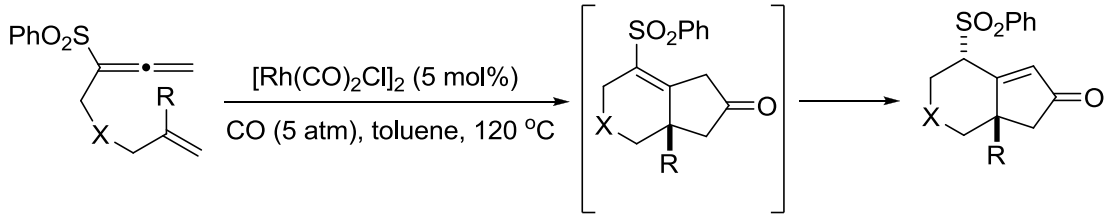


1-19 **1-18** **1-20**

Entry	R	yield [Mo] (%)	yield [Rh] (%)
1	TMS	76	51
2	n-Bu	70	61
3	Ph	84	55

Scheme 1-8: The intramolecular PK type reaction of allenyl alkynones **1-18**

Allenenes have also been shown to be effective substrates in the PK-type cycloaddition. An intramolecular Rh(I)-catalyzed [2+2+1] cycloaddition of phenylsulfonyl substituted allenenes **1-21,** yielding bicycle [4.3.0] nonenones **1-23** skeletons, was reported by Mukai and coworkers (**Scheme 1-9**).[22] The reaction was found to be selective for the distal π-bond of the allenyl moiety, leading initially to [4.3.0] non-1-en-8-one derivatives **1-22**, which isomerized to the α,β-unsaturated ketones **1-23**.

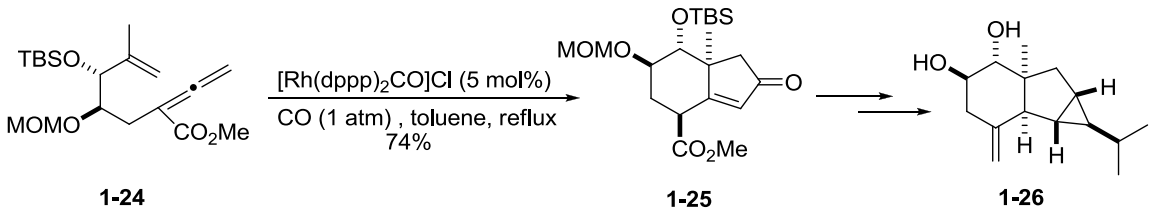


1-21 **1-22** **1-23**

Entry	X	R	yield (%)	*cis*/*trans*
1	NTs	H	89	71:29
2	O	H	63	82:18
3	$C(CO_2Me)_2$	Me	85	0:100
4	$C(CO_2Me)_2$	CH_2CH_2OMe	69	0:100
5	NTs	Me	58	0:100

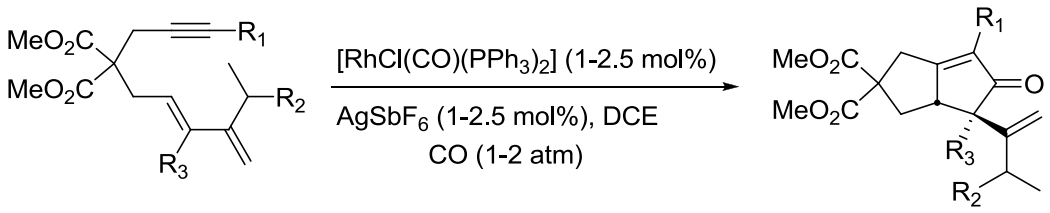
Scheme 1-9: The intramolecular PK type reaction of allenenes **1-21**

The PK type reaction of the allenene derivative **1-24** was used as a key step in the first total synthesis of the cyclopropane fused tricyclic sesquiterpene (1*S*,3*R*,4*R*,5*R*,6*S*,9*R*,10*R*)-9,10-dihydroxy -1-methyl-4-(1-methylethyl)-7-methylidenetricyclo[4.4.0.03,5]decane, **1-26**, that was isolated from *Jatropha neopauciflora*.[23] Treatment of the allenene precursor **1-24** (obtained from dimethyl D-tartrate) with cationic $[Rh(dppp)_2CO]Cl$ (5 mol%) under an atmosphere of CO in refluxing toluene afforded the cycloadduct **1-25** in 74% isolated yield (**Scheme 1-10**).



Scheme 1-10: Total synthesis of (1*S*,3*R*,4*R*,5*R*,6*S*,9*R*,10*R*)-9,10-dihydroxy -1-methyl-4-(1-methylethyl)-7-methylidenetricyclo[4.4.0.03,5]decane **1-26** *via* the PK type reaction

Dieneynes are also effective substrates in the PKR. Using $[RhCl(CO)(PPh_3)_2]$ (1-2.5 mol%), $AgSbF_6$ (1-2.5 mol%) in dichloroethane under CO (1-2 atm), a series of dieneynes **1-27** were converted to the corresponding alkenyl cyclopentenones **1-28** in good to excellent yields and as single diastereomers (**Scheme 1-11**).[24] Internal alkynes were found to react more efficiently than terminal alkynes. Substitution on the diene component was also well tolerated and was found to have a significant effect on the rate of the reaction. The intermolecular version of the reaction yielding highly functionalized cyclopentenones has also been reported.[25]

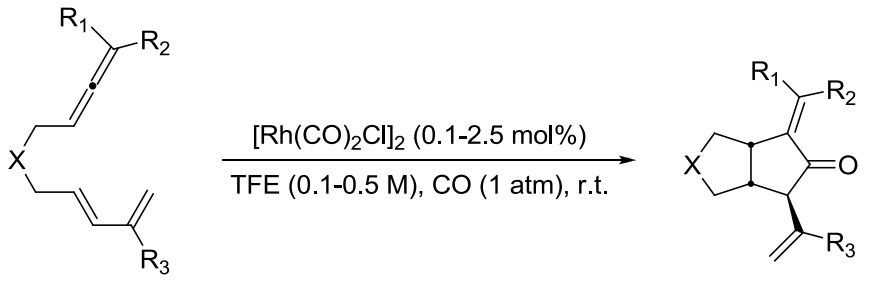


1-27 **1-28**

Entry	R_1	R_2	R_3	yield (%)
1	Me	Me	H	89
2	TMS	Me	H	85
3	H	Me	H	43
4	H	H	H	42
5	Me	H	H	86

Scheme 1-11: The PKR of dieneynes **1-27**

Diene-allenes **1-29** have also been subjected to the [2+2+1] cycloaddition yielding α-methylene cyclopentanones **1-30** in moderate to excellent yields (**Scheme 1-12**).[26] Substrates containing ether, amine and diester tethers were converted to the PK type adducts in good to excellent yields. Significant rate enhancement was observed when the reactions were performed in trifluoroethanol (TFE) or in the presence of certain Brønsted acids. Wender and coworkers suggested that possible co-catalysis involving protonation of CO in the migratory insertion step may explain the role of TFE.[26]

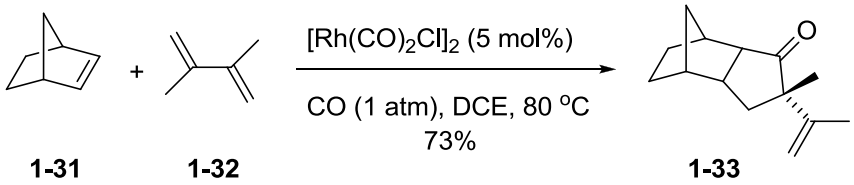


1-29 **1-30**

Entry	X	R_1	R_2	R_3	yield (%)
1	NTs	Me	Me	Me	97
2	$C(CO_2Me)_2$	Me	Me	i-Pr	92
3	O	Me	Me	H	97
4	NTs	H	Me	i-Pr	39

Scheme 1-12: The PKR of diene-allenes **1-29**

Using $[Rh(CO)_2Cl]_2$ as catalyst, the corresponding trienes have also been shown to undergo the PK type cycloaddition yielding the products also as single diastereomers.[27] However, 1,3-disubstitution on the diene component was not well tolerated for the intramolecular version of the reaction. The intermolecular reaction could be performed as exemplified by the reaction of norbornene **1-31** and 2,3-dimethyl butadiene **1-32** under a CO atmosphere yielding the tricyclic ketone **1-33** in 73% yield (**Scheme 1-13**).

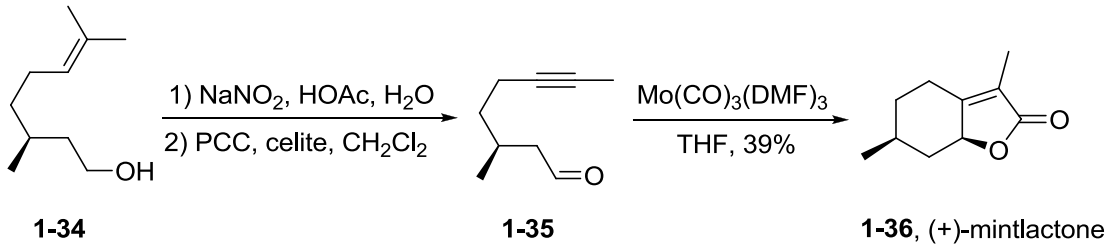


1-31 **1-32** **1-33**

Scheme 1-13: The intermolecular PK type reaction of trienes **1-31** and **1-32**

As shown in the examples above, the PKR and PK type reactions traditionally yield cyclopentenone derivatives. Recently, the use of heteroalkene counterparts such as aldehydes,[28] or ketones[29] and imines[30] leading to γ-butyrolactones and γ-lactams respectively has also been developed. The hetero-PK reaction was used by Zhai and coworkers in a short and efficient synthesis of (+)-mintlactone **1-36**, a bicyclic

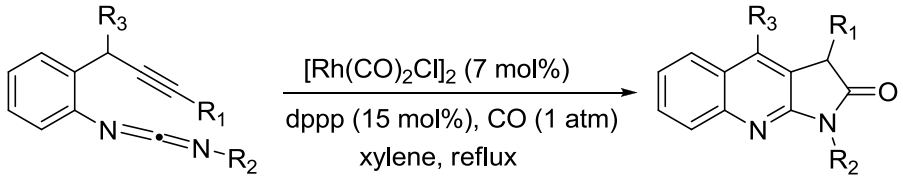
monoterpene-γ-lactone natural product. The treatment of 1,6-yn-al **1-35** (obtained from (-)-citronellol) **1-34** with freshly prepared $Mo(CO)_3(DMF)_3$ gave (+)-mintlactone **1-36** in 39% yield (**Scheme 1-14**). It is truly remarkable that a new stereogenic center, three covalent bonds (1 C-O and 2 C-C) and two rings were formed in this single operation.



1-34 **1-35** **1-36**, (+)-mintlactone

Scheme 1-14: Total synthesis of (+)-Mintlactone *via* hetero-PKR

Carbodiimides also serve as reactive olefin counterparts in the hetero-PK reaction.[31] Under optimized reaction conditions, $[Rh(CO)_2Cl]_2$ (7 mol%), dppp (15 mol%), CO (1 atm) in refluxing xylene, *N*-[2-(2-alkyn-1-yl)phenyl]carbodiimides **1-37** gave pyrrolo [2,3-b]quinolines **1-38**, whose motifs are often found in biologically active compounds (**Scheme 1-15**).[31a] Substitutions at the alkyne and carbodiimide were well tolerated with increased in both reaction rates and yields noted for substrates with increased steric bulk at the alkyne terminus. The pyrrolo[2,3-b]inole-2-one[31c] and thieno[2,3-b]indol-2-one[32] skeletons have also been obtained from the corresponding alkynylphenylcarbodiimides and alkynylphenyl isothiocyanates respectively.



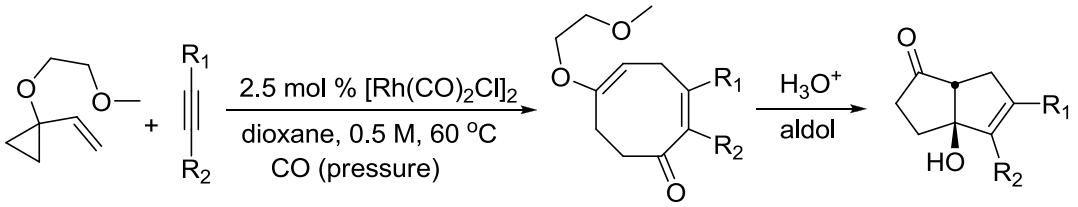
1-37 **1-38**

Entry	R_1	R_2	R_3	yield [%]
1	*n*-pent	Pr	H	80
2	*n*-pent	Bn	H	70
3	Me	Ph	H	41
4	Ph	Bn	H	71
5	TBS	Pr	H	75
6	TBS	Bn	H	58
7	Me	Pr	Me	52
8	Me	Ph	Me	61

Scheme 1-15: The hetero-PK reaction of carbodiimides

§ 1.2.2 Cyclocarbonylation of vinylcyclopropane derivatives

Vinylcyclopropane (VCP) derivates are very reactive species owing to the ring strain of the cyclopropane ring. Thus, cyclopropane derivatives serve as effective three carbon components in many cycloaddition and carbocyclization reactions. A three component [5+2+1] cycloaddition of VCP **1-39**, alkynes **1-40** and carbon monoxide using $[Rh(CO)_2Cl]_2$ as catalyst was reported by Wender and coworkers.[7] The process initially leads to an eight membered ring **1-41** which upon hydrolytic workup yields bicyclo [3.3.0] octenone products **1-42** in good to excellent yields (**Scheme 1-16**). The process was found to be more efficient with the use of carbonyl activated alkynes. NMR and x-ray studies of products indicated that CO insertion occurred distal to the carbonyl functionality of the alkyne resulting in single regioisomers of products.

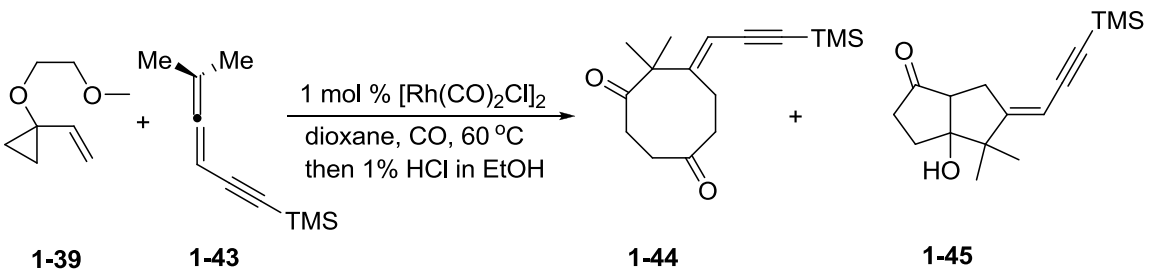


1-39 **1-40** **1-41** **1-42**

Entry	R_1	R_2	CO [atm]	yield [%]
1	$COCH_3$	Et	2	97
2	$COCH_3$	TMS	1	54
3	$COCH_3$	Ph	1	88
4	$CONH_2$	Ph	1	96
5	CHO	Ph	2	69
6	CO_2Et	Ph	1	79
7	CO_2Et	TMS	1	67
8	CO_2Et	Me	1	85
9	CO_2Me	CO_2Me	1	48

Scheme 1-16: Intermolecular [5+2+1] cycloaddition of vinylcyclopropane **1-39** with alkynes **1-40**

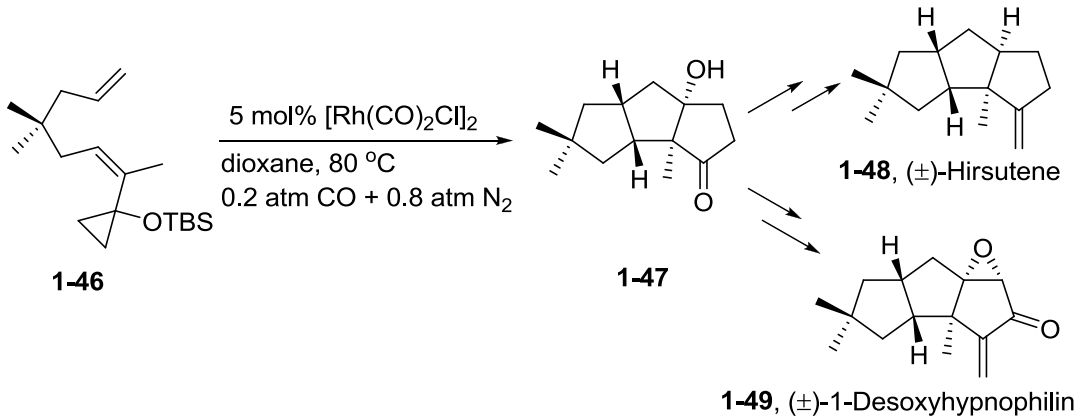
VCP **1-39** was also found to react with allene **1-43** under similar conditions to yield cyclooctanedione **1-44** and its transannular aldol product hydroxybicyclo[3.3.0] octanone **1-45** (**Scheme 1-17**).[33] Increasing the CO pressure to 2 atm resulted in higher yield but a longer reaction time and modest change in product ratio was observed.



Entry	Time (h)	CO [atm]	Ratio (1-36:1-37)
1	1	1	1:2.2
2	15	2	1:1.3

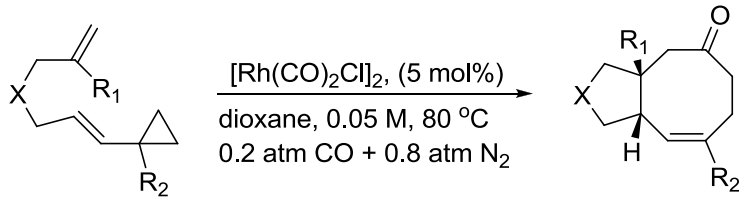
Scheme 1-17: Intermolecular [5+2+1] cycloaddition of vinylcyclopropane **1-39** with allene **1-43**

The linear triquinanes, (±)-Hirsutene **1-48** and (±)-1- Desoxyhypnophilin **1-49** have displayed promising biological activities including antibiotic and antitumor activities.[34] These compounds possess novel architecture characterized by *cis-anti-cis* fused cyclopentane skeleton. A very efficient, tandem [5+2+1] cycloaddition/ aldol reaction was used in the key step to obtain a common intermediate **1-47** enroute to the total synthesis of both triquinanes (**Scheme 1-18**).[35] (*Z*)-siloxy-ene-VCP **1-46** gave a single diastereomer of the tricyclic product **1-47** with the required *cis-anti-cis* configuration.



Scheme 1-18: Total synthesis of (+/-)-Hirsutene **1-48** and (+/-)-Desoxyhypnophilin **1-49** *via* [5+2+1] cycloaddition of ene-vinylcylopropane **1-46**

The intramolecular reaction of vinylcyclopropanes tethered to alkenes **1-50** yielding fused bicyclic products **1-51** has also been applied to the [5+2+1] cycloaddition (**Scheme 1-19**).[36] In this case, a low partial pressure of CO was found to be effective. Substrates with sulfonamides (**entries 2, 5 and 7**), ethers (**entries 3, 6 and 8**) and germinal diesters (**entries 1 amd 4**) tethers were effective in the cycloaddition. In addition, substitutions on either the olefinic component or the VCP component were tolerated yielding 5-8 fused ring products with high diastereoselectivity. The *E/Z* olefin geometry of the VCP moieties of the substrates was found to directly affect the *cis*/*trans* stereochemistry of the bicyclic products suggesting the conservation of the olefin geometry throughout the cycloaddition process.



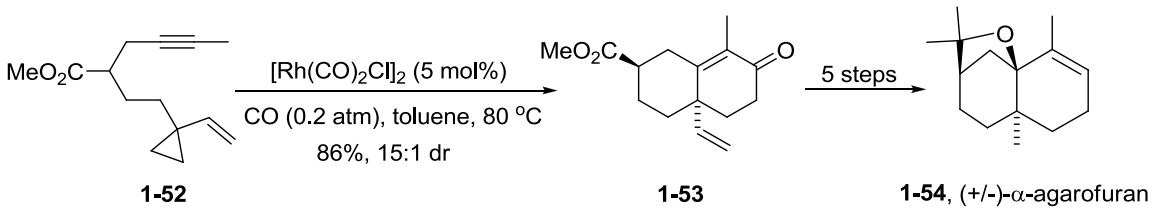
1-50 **1-51**

Entry	X	R_1	R_2	yield [%]
1	$C(CO_2Me)_2$	H	H	70
2	NTs	H	H	81
3	O	H	H	90
4	$C(CO_2Me)_2$	Me	H	29
5	NTs	Me	H	71
6	O	Me	Ph	78
7	NTs	H	H	92
8	O	H	Ph	73

Scheme 1-19: Intramolecular [5+2+1] cycloaddition of ene- vinylcyclopropanes **1-50**

Alkyne tethered VCPs have also been shown to undergo cyclocarbonylation.[37] In the example reported by Jiao[37] and coworkers, the vinyl group was found to be critical in facilitating the ring opening of the cyclopropane under mild conditions. However, in this example, the vinyl group did not participate in the cycloaddition as other examples have

shown. Interestingly, the optimized conditions were found to be a partial pressure of carbon monoxide (0.2 atm) in toluene and $[Rh(CO)_2Cl]_2$ as catalyst. A variety of substrates with diverse tethers gave both 5,6 and 6,6-bicyclic cyclohexenone products with quaternary stereocenters. In addition, both terminal and internal alkynes were found to be compatible with the reaction conditions. Olefin tethered VCPs were also found to be viable substrates providing the corresponding bicyclic cyclohexanone products albeit with longer reaction times. The synthetic utility of the process was demonstrated in the key step in the total synthesis of the furanoid sesquiterpene natural product, (+/-)-α-agarofuran **1-54**. Thus the monoester substituted 1-yne-VCP **1-52** afforded bicyclic cyclohexenone **1-53** in 86% yield with good diastereoselectivity (15:1, *trans*:*cis*) (**Scheme 1-20**). The cycloadduct **1-53** was then converted to (+/-)-α-agarofuran **1-54** in five additional steps.

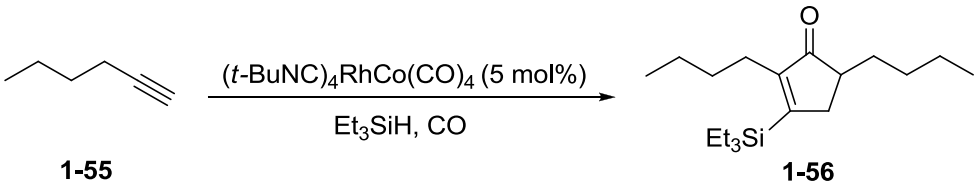


1-52 **1-53** **1-54**, (+/-)-α-agarofuran

Scheme 1-20: total synthesis of (+/-)-α-Agarofuran **1-54** *via* [3+2+1] cycloaddition of yne-vinylcyclopropane **1-52**

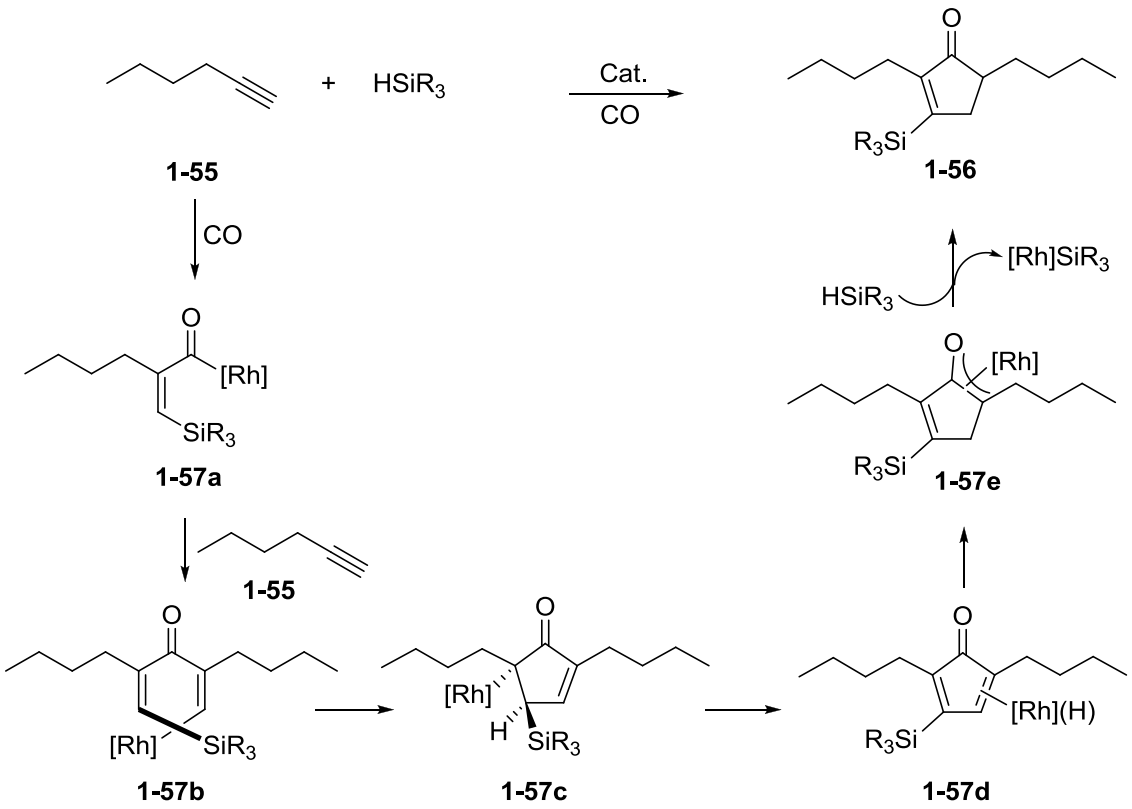
§ 1.3. Silicon initiated carbocyclizations and carbonylative carbocyclizations

The Rh-catalyzed carbonylative silylcarbocyclization (CO-SiCaC) reaction of 1-hexeyne **1-55** gave silylcyclopentenone **1-56** (**Scheme 1-21**). Compound **1-56** was isolated as a minor product during studies on the mechanism, scope and limitation of the silylformylation of 1-hexyne **1-55** with dimethylphenylsilane catalyzed by $Co_2Rh_2(CO)_{12}$ or $Rh_4(CO)_{12}$ (**Scheme 1-21**).[38] Under optimized conditions using Et_3SiH and $(t\text{-BuNC})_4RhCo(CO)_4$ as the catalyst at 60 °C, **1-56** was isolated in 54% yield.[38b]



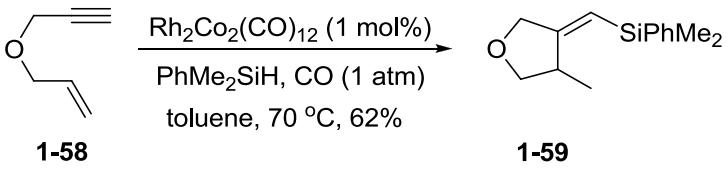
Scheme 1-21: Synthesis of silylcyclopentenone **1-56** *via* CO-SiCaC reaction

A possible mechanism proposed by Ojima and coworkers for this intermolecular CO-SiCaC reaction is outlined in **Scheme 1-22**.[38b] In the mechanism, the formation of **1-56** was proposed to proceed *via* intermolecular trapping of the β-silylacryloyl-[Rh] complex **1-57a** by a second molecule of 1-hexyne **1-55** to give intermediate **1-57b**. Subsequent carbocyclization gives intermediate **1-57c** which then undergoes β-hydride elimination to form cyclopentadienone-[Rh]H complex **1-57d**. Highly regioselective hydrometallation of the olefin moiety at the sterically less congested site gives intermediate **1-57e** and subsequent reductive elimination affords **1-56** (**Scheme 1-22**). It should be noted that Matsude *et. al*. have proposed a similar mechanism for the intermolecular CO-SiCaC reaction of phenylacetylene catalyzed by $Rh_4(CO)_{12}$, which gave silylcyclopentenones.[39]



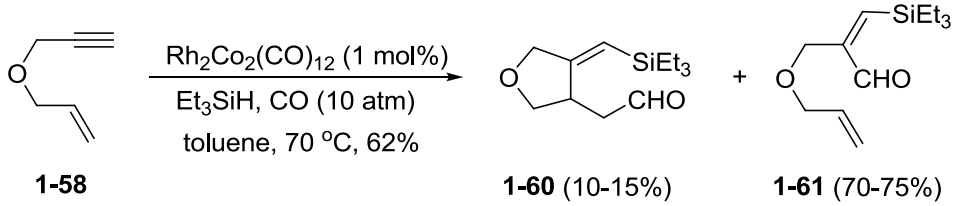
Scheme 1-22: Proposed mechanism for the formation of silylcyclopentenone **1-56**

Analysis of the proposed mechanism outlined in **Scheme 1-22** indicated that β-silylethenyl-[Rh]intermediate **1-57a** (**Scheme 1-22**) could be trapped by an unsaturated moiety in an intramolecular fashion. Thus, following the discovery of the intermolecular CO-SiCaC reaction of 1-hexyne, the intramolecular version of the CO-SiCaC and silylcarbocyclization (SiCaC) reactions were investigated using 1,6-eneynes.[38b] For example, the reaction of allyl propargyl ether **1-58** with $PhMe_2SiH$ catalyzed by $Rh_2Co_2(CO)_{12}$ (1 mol%) gave 3-(silylmethylene)-4-methylhydrofuran **1-59** in 62% yield (**Scheme 1-23**). This result clearly supports the observation that the β-silylethenyl-[Rh] species **1-57a** (**Scheme 1-22**) could be efficiently trapped in an intramolecular fashion by the olefin moiety.



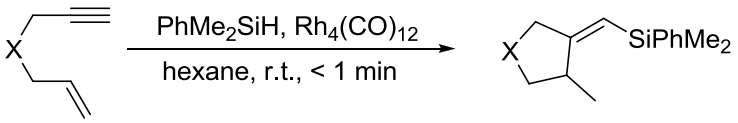
Scheme 1-23: SiCaC reaction of 1,6-eneyne **1-58**

When the reaction of **1-58** was carried out under 10 atm of CO using Et_3SiH, the CO-SiCaC reaction took place to give the corresponding aldehyde **1-60** as a minor product (15-20 %) together with the silylformylation product **1-61** (70-75 %) (**Scheme 1-24**).[38b] In this case, the higher CO pressure favored the carbonylated products.



Scheme 1-24: CO-SiCaC reaction of 1,6-eneyne **1-58**

The Ojima group has thus investiaged the SiCaC reaction of eneynes in detail, and has applied it to a wide range of substrates. Rhodium carbonyl clusters, such as $Rh_4(CO)_{12}$, and bimetallic clusters such as $Rh_2Co_2(CO)_{12}$ have been found to be very effective catalysts in promoting this transformation. The reaction of 1,6-eneynes **1-62** with $PhMe_2SiH$ catalyzed by $Rh_4(CO)_{12}$ was complete within 1 minute at room temperature, and gave the corresponding silylmethylene-2-methylcyclopentanes **1-63** in good to excellent yields (**Scheme 1-25**). [40]

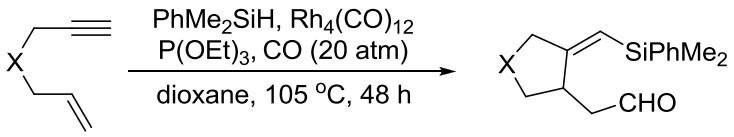


1-62 **1-63**

Entry	X	yield (%)
1	$C(CO_2Et)_2$	99
2	$C(CH_2OH)_2$	52
3	$C(CH_2OMe)_2$	96
4	$C(CH_2OAc)_2$	90
5	NTs	86
6	NBn	83

Scheme 1-25: SiCaC reaction of 1,6-eneynes **1-62**

When the reaction of **1-62** catalyzed by $Rh_4(CO)_{12}$/ $P(OEt)_3$ was carried out under 20 atm of CO, the CO-SiCaC reaction took place almost exclusively and gave **1-64** in good to excellent yields (**Scheme 1-26**).[40] A variety of substrates including methylethers and sulfonamides tethers were shown to be effective in the Rh-catalyzed SiCaC and CO-SiCaC reactions and thus provide efficient methods for the construction of synthetically useful substituted cyclopentane and pyrrolidine products. Fukuta and coworkers also reported the CO-SiCaC of 1,6-eneynes catalyzed by $Rh_4(CO)_{12}$ under 20 atm of CO in benzene, albeit in lower yields (37 – 89%).[41]

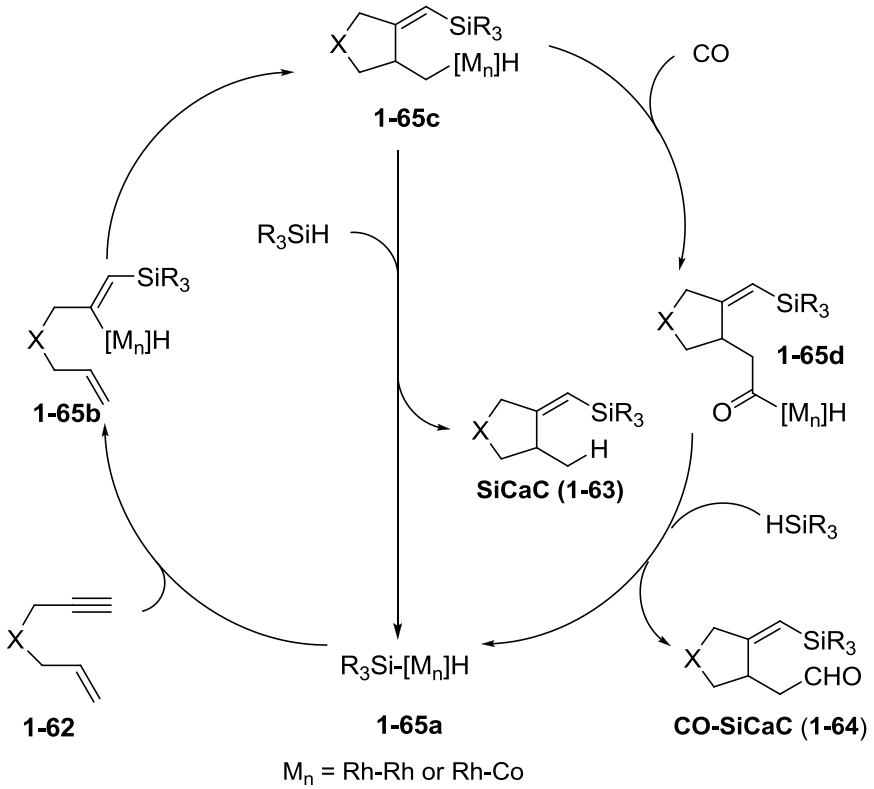


1-62 **1-64**

Entry	X	yield (%)
1	$C(CO_2Et)_2$	91
2	$C(CH_2OH)_2$	89
3	$C(CH_2OMe)_2$	83
4	$C(CH_2OAc)_2$	91
5	NTs	85
6	NMs	56

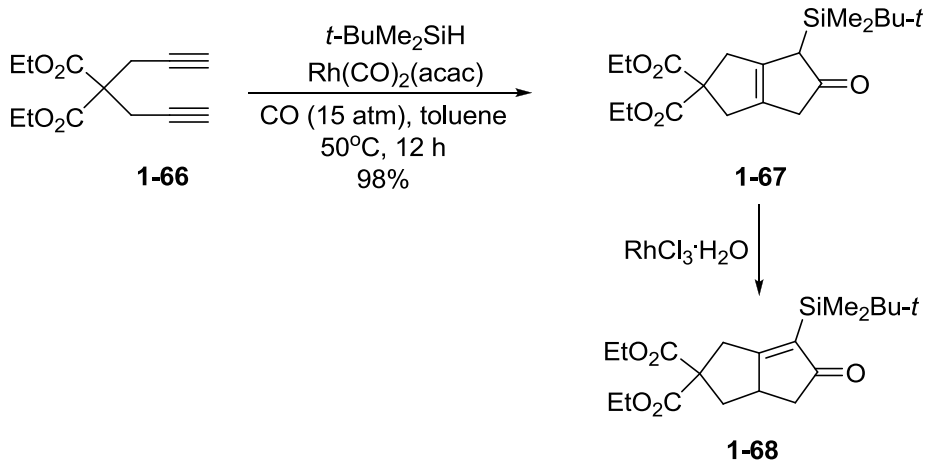
Scheme 1-26: CO-SiCaC reaction of 1,6-eneynes **1-62**

The proposed mechanism for the SiCaC and CO-SiCaC reactions of 1,6-eneynes **1-62** is illustrated in **Scheme 1-27**. The reaction should begin with the formation of the active catalyst species $R_3Si[M]H$ complex **1-65a**, followed by regioselective insertion of the acetylene moiety of eneyne **1-62** to generate *β*-silylvinyl-[Rh] complex **1-65b**. Coordination of the olefin moiety of **1-65b**, followed by intramolecular carbometallation, leads to the formation of *exo*-methylenecyclopentylmethyl-[Rh] complex **1-65c**. At this point, the pathways leading to the formation of SiCaC **1-63** and CO-SiCaC **1-64** products diverge. Since SiCaC product **1-63** does not require CO, hydrosilane-promoted reductive elimination occurs to give SiCaC product **1-63** and regenerates silyl-[Rh] complex **1-65a**. At higher CO concentration, migratory insertion of CO into the alkyl-[Rh] bond of **1-65c** leads to the formation of acyl-[Rh] complex **1-65d**. Subsequent hydrosilane-promoted reductive elimination affords CO-SiCaC product **I-56** and regenerates the active catalyst species **1-65a**. Though a CO atmosphere is not essential for the formation of the SiCaC product, the use of a CO atmosphere appears to stabilize the active [Rh] catalyst species, especially when Rh and Rh-Co carbonyl clusters are used for a prolonged period of time.



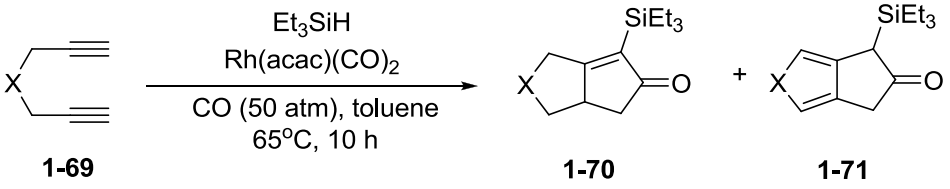
Scheme 1-27: Proposed SiCaC and CO-SiCaC mechanisms

The carbonylative silylcarbobicyclization (CO-SiCaB) reaction of 1,6-diynes was also investigated. The reaction of 4,4-*gem*-bis(carbethoxy)hepta-1,6-diyne **1-66** with *t*-BuMe$_2$SiH at 50 ^{o}C and 15 atm of CO afforded 2-silylbicyclo[3,3,0]oct-$\Delta^{1,5}$-en-3-one **1-67** in 98% yield (**Scheme 1-28**).[42] Cycloadduct **1-67** was quantitatively isomerized to the more stable 2-silylbicyclo[3,3,0]oct-1-en-3-one **1-68** using a catalytic amount of $RhCl_3 \cdot 3H_2O$.



Scheme 1-28: CO-SiCaB of 1,6-diyne of **1-66**

A different type of CO-SiCaB reaction was observed when the tether was a basic amine moiety. For example, the reactions of *N*-benzyl-, *N*-*n*-hexyl- or *N*-allyldipropargylamine **1-69** with Et_3SiH (1.6 equiv.) catalyzed by $Rh(acac)(CO)_2$ at 65 °C and 50 atm of CO gave the corresponding 2-silyl-7-azabicyclo[3.3.0]octa-5,8-dien-3-one **1-70** as the predominant or sole product (**Scheme 1-29**).

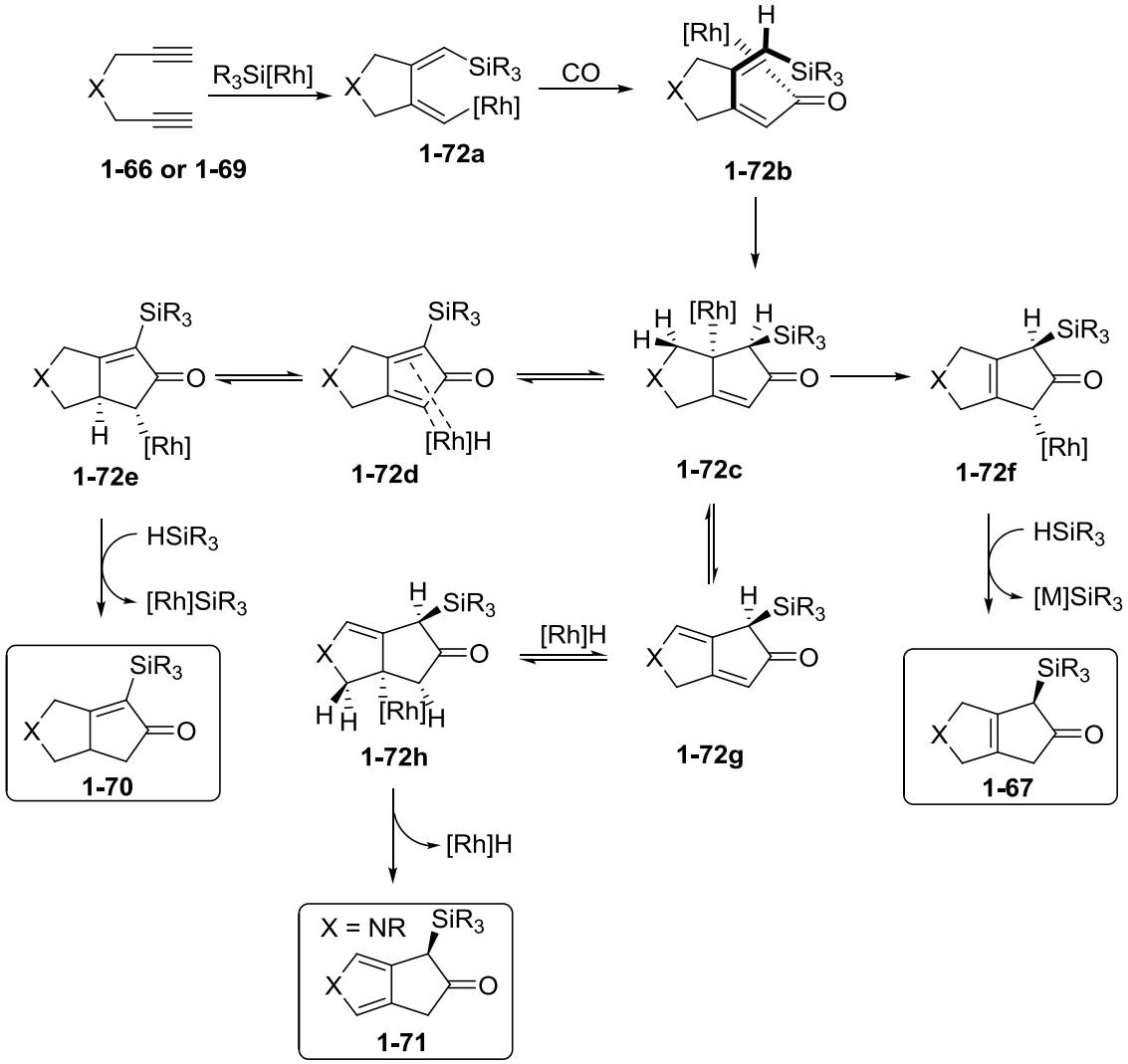


Entry	X	Yield (%)	**1-70/1-71**
1	*N*-benzyl	66	97/3
2	*N*-hexyl	58	100/0
3	*N*-allyl	62	100/0

Scheme 1-29: CO-SiCaB of 4- amino-1,6-diynes **1-69**

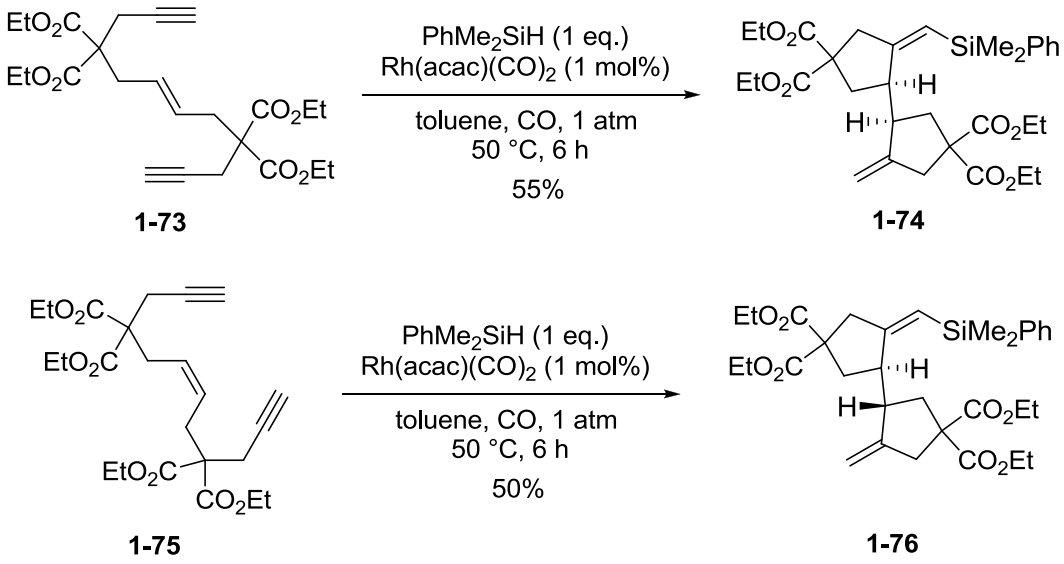
Possible pathways to the formation of **1--67**, **1-70** and **1-71** are illustrated in **Scheme 1-30**.[42b] The proposed mechanism includes acyl-[Rh] complex **1-72b**, which is formed via a pathway similar to that of the CO-SiCaC reaction (*vide supra*). Intermediate **1-72b** undergoes the second carbocyclization to give bicyclic alkyl-[Rh]

complex **1-72c**. The β-hydride elimination from **1-72c** affords bicyclic diene-[Rh]H complex **1-72d** and/or bicyclic diene **1-72g**. The regioselective addition of [Rh]-H species to the olefin moiety of **1-72d** in the less hindered side gives intermediate **1-72e**, whereas the addition of [M]-H species to **1-72g** affords intermediate **1-72h**. These β-hydride elimination and [Rh]-H addition are potentially reversible processes. Reductive elimination of R_3Si-[Rh] species from **1-72e** affords **1-70.** The β-hydride elimination of [Rh]-H species from **1-72h** affords **1-71**. The 1,3-shift of [Rh] in **1-72c** gives **1-72f** and then **1-67** through hydrosilane promoted reductive elimination of R_3Si-[Rh] (**Scheme 1-30**).



Scheme 1-30: Proposed mechanism for CO-SiCaB of 1,6-diynes **1-66** and **1-69**

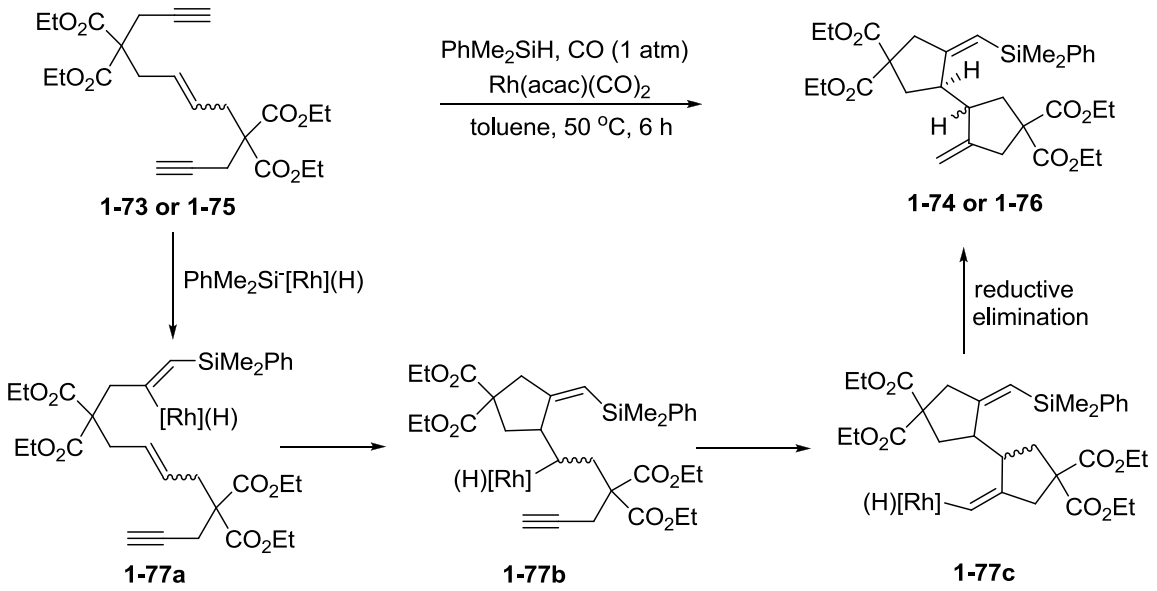
Based on the results of the SiCaC study on 1,6-eneynes, Ojima and coworkers postulated that the alkyl-[Rh](H) intermediate **1-65c** (**Scheme 1-27**), formed after the first carbocyclization could be trapped by an appropriately placed alkene or alkyne moiety as long as the competing reductive elimination is slower than the carbometallation. The resulting cascade carbocyclization would provide polycyclic frameworks from relatively simple starting materials. Indeed this hypothesis was confirmed when (6*E*)-dodec-6-ene-1,11-diyne **1-73** reacted with $PhMe_2SiH$, catalyzed by $Rh(acac)(CO)_2$ at 50 ^oC and atmospheric pressure of CO afforded (*R*,*R*)-bis(*exo*-methylenecyclopentyl) **1-74** in 55% isolated yield (**Scheme 1-31**).[6a] In a similar manner, the reaction of (6*Z*)-dodec-6-ene-1,11-diyne **1-75** gave (*S*,*R*)-bis(*exo*-methylenecyclopentyl) **1-76** in 50% isolated yield (**Scheme 1-31**). Thus, these cascade reactions proceeded stereospecifically.[6a]



Scheme 1-31: SiCaC of dodec-6-ene-1,11-diynes **1-73** and **1-75**

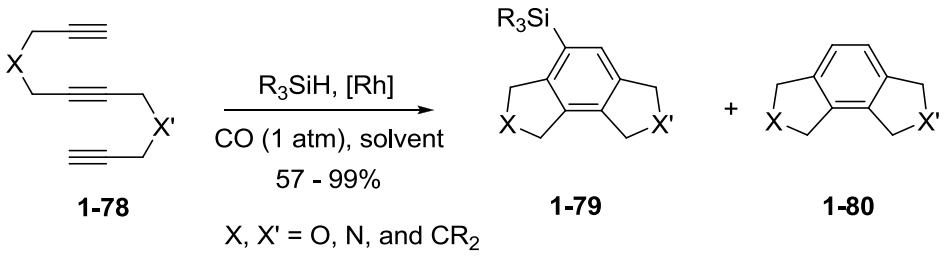
The proposed mechanism for the SiCaC reaction is depicted in **Scheme 1-32**. The reaction begins with the insertion of the an alkyne moiety of **1-73** or **1-75** into the Si-[Rh] bond of the hydrosilane-Rh oxidative adduct to give intermediate **1-77a** which then undergoes the first carbocyclization to form intermediate **1-77b**. Then the alkyl-[Rh](H) of intermediate **1-77b** is trapped by the second acetylene moiety to form the vinyl-[Rh](H) intermediate **1-77c**. Reductive elimination gives **1-73** or **1-75**. Although carbometallation of the vinylsilane moiety with the vinyl-[Rh] species of **1-77c** to form

the corresponding fused tricyclic skeleton was conceptually possible in this reaction, such a cyclization was not observed. Instead, reductive elimination occurred to give **1-74** or **1-76**. This result may well be attributable to the rotational freedom about the bond connecting the two cyclopentyl units.[6a]



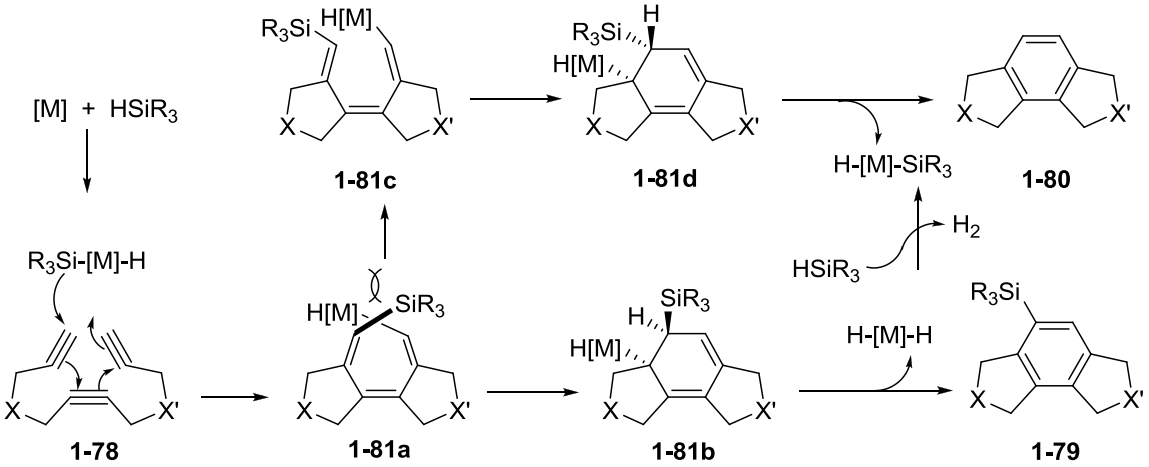
Scheme 1-32: Proposed mechanism for SiCaC of dodec-6-ene-1,11-diynes **1-73** and **1-75**

It was anticipated that restricting the rotational freedom about the bond of intermediate **1-77b** (**Scheme 1-32**) by the introduction of a carbon-carbon double bond would generate a rigid framework that would facilitate the subsequent carbometallation which would then lead to a third carbocyclization. This anticipation led to the investigation of the cascade SiCaC reaction of dodec-1,6,11-triynes **1-78**. Thus, a novel silicon-initiated cascade carbotricyclization (SiCaT) of triynes **1-78** catalyzed by rhodium complexes such as $Rh(acac)(CO)_2$, $[Rh(COD)Cl]_2$, $[Rh(NBD)Cl]_2$, $Rh_4(CO)_{12}$ and $Rh_2Co_2(CO)_{12}$ gave the corresponding fused tricyclic benzene derivatives **1-79** and **1-80** in good to excellent yields (**Scheme 1-33**).[43] The SiCaT reaction is applicable to 1,7,12- and 1,7,13-triynes affording 6-6-5 and 6-6-6 fused tricyclic benzene derivatives, respectively.



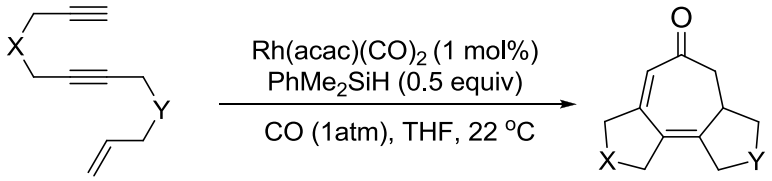
Scheme 1-33: SiCaT of 1,7,11-triynes **1-78**

A proposed mechanism for the SiCaT reaction using the 1,7,11-triyne system is illustrated in **Scheme 1-34**. The reaction proceeds through insertion of one of the terminal alkynes of **1-78** into the preformed Si-[Rh] complex generating an ethenyl-[Rh] intermediate which undergoes addition to the second and third alkyne moieties to form intermediate **1-81a**. Subsequent carbocyclization followed by β-hydride elimination gives the tricyclic silylbenzene derivative **1-79**. Alternatively, ethenyl-[Rh] intermediate **1-81a** is isomerized to the thermodynamically more favorable intermediate **1-81c** *via* a zwitterionic carbene species, i.e., the "Ojima-Crabtree mechanism".[44] Subsequent carbocyclization gives **1-81d**. In this intermediate, the metal and the C-4 hydrogen are *trans* to each other, precluding *β*-hydride elimination. Instead, β-silyl elimination takes place to give nonsilylated SiCaT product **1-80**.



Scheme 1-34: Proposed mechanism for SiCaT of 1,7,11-triynes **1-78**

When the olefin is at the terminal position of an enediyne system, carbonylative carbotricyclization (CO-SiCaT) reaction takes place, incorporating CO into the product.[45] As **Scheme 1-35** shows, the reaction of dodec-11-ene-1,6-diynes **1-82** catalyzed by $Rh(acac)(CO)_2$ under atmospheric pressure of CO gave the corresponding cyclopenta[*e*]azulenes **1-83** in good to excellent yields (**Scheme 1-35**).



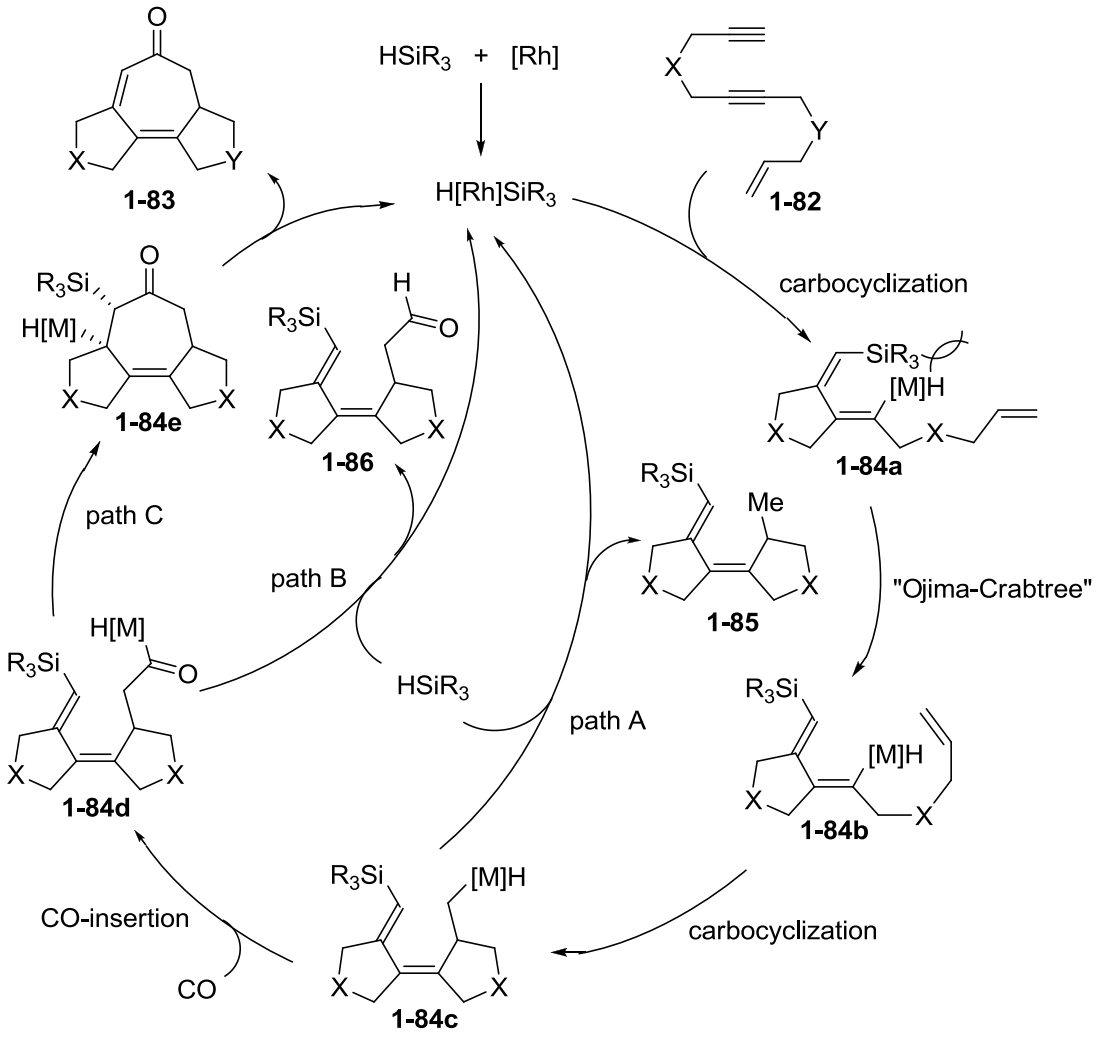
1-82 **1-83**

Entry	X	Y	Yield [%]
1	$C(CO_2Et)_2$	$C(CO_2Et)_2$	88
2	O	O	50
3	O	$C(CO_2Et)_2$	91
4	NTs	NTs	85
5	$C(CO_2Et)_2$	NTs	84
6	NTs	$C(CO_2Et)_2$	82
7	NBoc	$C(CO_2Et)_2$	86
8	$C(CH_2OMe)_2$	$C(CH_2OMe)_2$	89
9	$C(CH_2OBn)_2$	$C(CH_2OBn)_2$	87
10	$C(CH_2OAc)_2$	$C(CH_2OAc)_2$	81
11	$C(CH_2OH)_2$	$C(CH_2OH)_2$	62

Scheme 1-35: CO-SiCaT of dodec-11-ene-1,6-diynes **1-82**

A proposed mechanism for the CO-SiCaT reaction is illustrated in **Scheme 1-36**.[45] The reaction begins with the insertion of the terminal alkyne moiety of **1-82** into the Si-[Rh] bond of the hydrosilane-Rh oxidative adduct. Carbocyclization then occurs to give (*Z*)-dienyl[Rh](H) intermediate **1-84a**. Because of the steric hindrance between the vinylsilane and the vinyl-[Rh] moieties, **1-84a** isomerizes to **1-84b** through the "Ojima- Crabtree mechanism". Subsequent carbocyclization gives common intermediate

1-84c. Reductive elimination of **1-84c** should give **1-85** (**path A**). The CO insertion to **1-84c** gives acyl-[Rh](H) intermediate **1-84d** and reductive elimination of **1-84d** should yield aldehyde **1-86** (**path B**). Carbocyclization of **1-84d** gives tricyclic intermediate **1-84e** that has the silicon and the [Rh] moieties in *syn* positions (**path C**). Subsequent *β*-silyl elimination takes place to afford the fused 5-7-5 tricyclic product **1-83** and to regenerate the active catalyst species, R_3Si- [Rh](H).



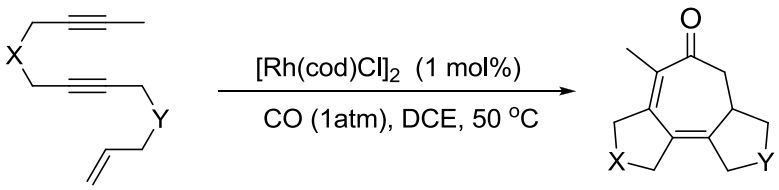
Scheme 1-36: Proposed mechanism for CO-SiCaT of dodec-11-ene-1,6-diynes **1-82**

When one or more equivalent of hydrosilane is used, reductive elimination, i.e., hydride shift, is accelerated so that products **1-85** (**path A**) and **1-86 (path B**) are obtained besides **1-83**. This is because the hydrosilane promoted reductive elimination pathways from either intermediate **1-84c** or **1-84d** leading to hydrosilylated product **1-85**

(**path A**) or silyl-formylated product **1-86** (**path B**), are bimolecular processes. As such, the presence of stoichiometric or excess amount of hydrosilane and high reaction concentration leads to products **1-85** and **1-86**. It is noteworthy that cyclopenta[*e*]azulene **1-83** is exclusively formed under optimized conditions using a catalytic amount of hydrosilane and high dilution conditions (**path C**). The reactions of enediynes substituted at the terminal position did not yield the carbonylated products but rather the 5-6-5 tricyclic products.[45b]

§ 1.4. Rh(I)-catalyzed [2+2+2+1] cycloaddition

During the studies on the scope and limitations of the CO-SiCaT reaction, it was found that the reaction of 1-susbstituted dodec-11-ene-1,6-diynes **1-87** catalyzed by $[Rh(COD)Cl]_2$ in the *absence of a hydrosilane* also gave carbonylative fused tricyclic products **1-88** in good to excellent yields.[45b, 46] This process turned out to be the first example of an intramolecular [2+2+2+1] cycloaddition (**Scheme 1-37**).

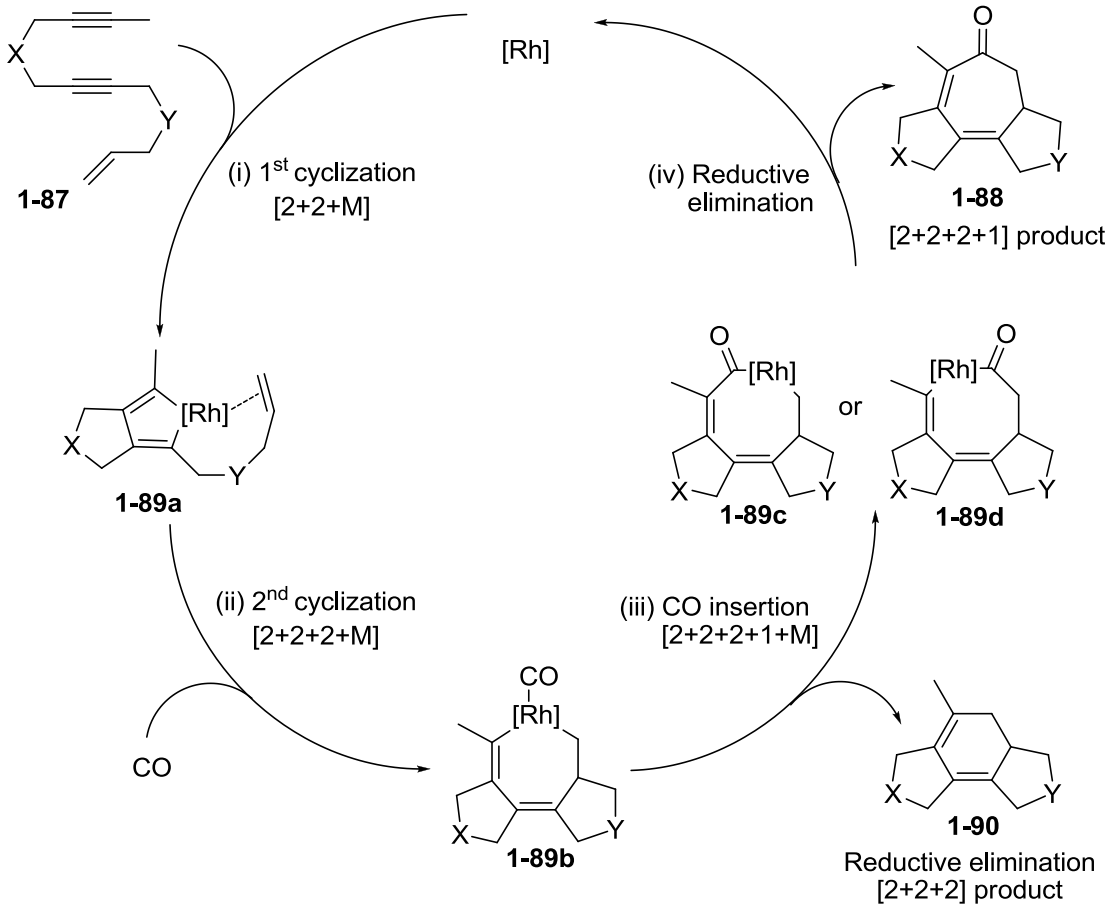


1-87 **1-88**

Entry	X	Y	Yield [%]
1	$C(CO_2Et)_2$	$C(CO_2Et)_2$	88
2	O	O	53
3	O	$C(CO_2Et)_2$	79
4	NTs	NTs	84
5	$C(CO_2Et)_2$	NTs	69
6	NTs	$C(CO_2Et)_2$	88
7	$C(CO_2Et)_2$	NBoc	70
8	$C(CH_2OMe)_2$	$C(CH_2OMe)_2$	92
9	$C(CH_2OBn)_2$	$C(CH_2OBn)_2$	91
10	$C(CH_2OAc)_2$	$C(CH_2OAc)_2$	82

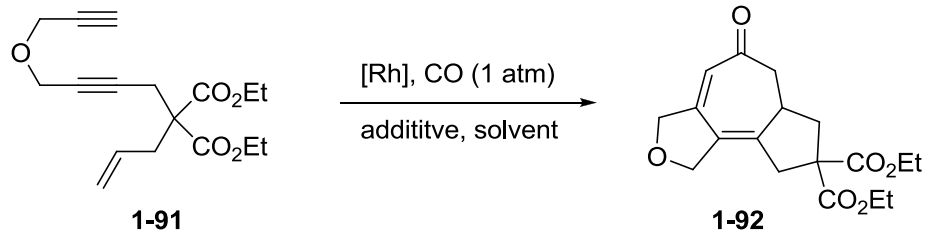
Scheme 1-37: [2+2+2+1] cycloaddition of 1-methyl-dodec-11-ene-1,6-diynes

Scheme 1-38 illustrates the proposed mechanism of this novel process.[45b, 46] The proposed mechanism includes (i) selective coordination of the diyne moiety of enediyne **1-87** to the active Rh catalyst species, forming metallacycle **1-89a** [2+2+M]), (ii) insertion of the olefin moiety of **1-87** into the Rh-C bond followed by CO coordination to the Rh metal forms the fused 5-7-5 tricyclic rhodacycle **1-89b** ([2+2+2+M]), (iii) migratory insertion of CO into the Rh-C bond gives 5-8-5 rhodacycle **1-89c** or **1-89d** ([2+2+2+1+M]), and (iv) reductive elimination gives the [2+2+2+1] cycloadduct **1-88** and regenerates the active Rh catalyst species. Reductive elimination from the 5-7-5 rhodacycle **1-89b** prior to CO insertion gives the [2+2+2] cycloadduct **1-90**. Since this reaction is believed to proceed through a series of metallacycles, it is thus different from that of the CO-SiCaT reaction, which is believed to be a stepwise process involving sequential carbocyclizations.



Scheme 1-38: Proposed mechanism for [2+2+2+1] cycloaddition of 1-methyl-dodec-11-ene-1,6-diynes **1-87**

Interestingly, the reaction of un-substituted dodec-11-ene-1,6-diyne **1-91** under the optimized [2+2+2+1] cycloaddition conditions proceeded slowly (3 days) to give the tricyclic adduct **1-92** in 51% yield (**Scheme 1-39, entry 2**).[45b] In contrast, the CO-SiCaT of enediyne **1-91** gave **1-92** in 91% isolated in 24 h (**Scheme 1-39, entry 1**).[45b] Thus, the two carbonylation reactions are complimentary with respect to substrate type.

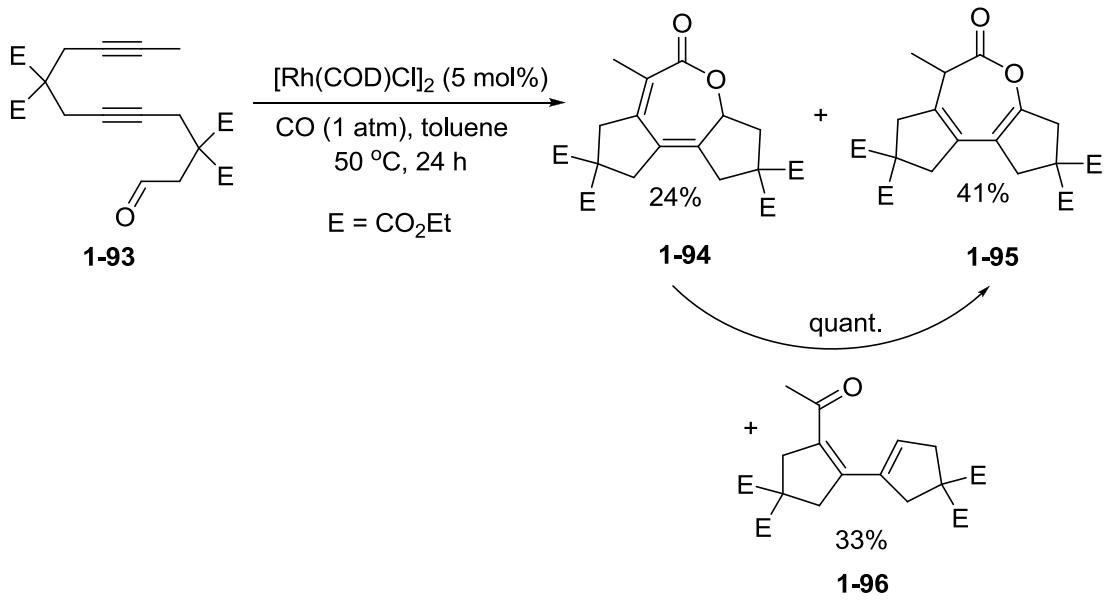


1-91 **1-92**

Entry	Additive	[Rh]	Solvent	Yield(%)
1	Me_2PhSiH	$Rh(acac)(CO)_2$	THF	91
2	none	$[Rh(COD)Cl]_2$	DCE	51

Scheme 1-39: CO-SiCaT and [2+2+2+1] cycloaddition of dodec-11-ene-1,6-diyne **1-91**

The [2+2+2+1] cycloaddition reaction of dodeca-5,10-diyn-1-al **1-93** carried out with $[Rh(COD)Cl]_2$ (5 mol%) at 50 ^oC and ambient pressure of CO in toluene, gave cycloadducts **1-94** and **1-95** (65% combined yield) as well as acetylbis(cyclopentenyl) **1-96** from the [2+2+2] cycloaddition in 33% yield (**Scheme 1-40**).[45b]

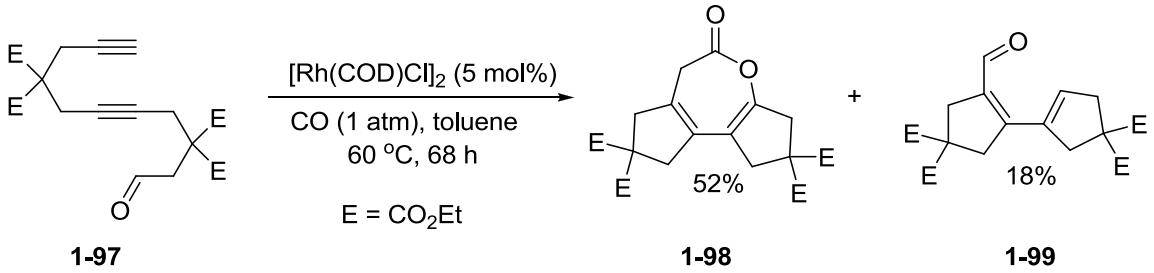


1-93 **1-94** **1-95** **1-96**

Scheme 1-40: [2+2+2+1] cycloaddition of 1-methyl-dodeca-5,10-diyn-1-al **1-93**

Upon monitoring the reaction, Ojima and coworkers found that fused 5-7-5 tricyclic lactone **1-94** was the kinetic product, and observed the complete isomerization of **1-94** to **1-95** by leaving a mixture of **1-94** and **1-95** in $CDCl_3$ in an NMR tube for two weeks at ambient temperature.

However, the tricyclization of terminal diyne-al **1-97** at 60 ^{o}C for 68 h gave fused 5-7-5 lactone **1-98** and aldehyde **1-99** (**Scheme 1-41**).[45b] The kinetic product was not isolated in this case. Thus, the preferential formations of **1-95** (**Scheme 1-40**) and **1-98** (**Scheme 1-41**) indicate that the two *endo*-double bond system is substantially more favorable than the two *exo*-double bond system.



1-97 **1-98** **1-99**

Scheme 1-41: [2+2+2+1] cycloaddition of dodeca-5,10-diyn-1-al **1-97**

The CO-SiCaT and Rh(I)-catalyzed [2+2+2+1] cycloaddition of enediyne derivatives, pioneered in Ojima's laboratory, provides a straight-forward and complimentary method to fused ketones and lactones. The products are also clearly amendable to further functionalization. These methods offer broad access to other fused products. For instance, tetracyclic products could be envisioned if the olefinic component was part of a ring system. As part of ongoing studies on the development of the novel higher-order cycloaddition process, the [2+2+2+1]cycloaddition of cycloalkenyl-diynes which provided the carbonylative tetracyclic products in good to excellent yields were investigated. The details of these studies are presented in the subsequent chapters.

§ 1.5. References

1. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J., Transition metal-catalyzed carbocyclizations in organic synthesis. *Chem. Rev.* **1996,** *96*, 635-662.

2. Kotha, S.; Brahmachary, E.; Lahiri, K., Transition metal-catalyzed [2+2+2] cycloaddition and application in organic synthesis. *Eur. J. Org. Chem.* **2005**, 4741-4767.

3. Nakamura, I.; Yamamoto, Y., Transition-metal-catalyzed reactions in heterocyclic synthesis. *Chem. Rev.* **2004,** *104*, 2127-2198.

4. Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N., Intermolecular transition metal-catalyzed [4+2+2] cycloaddition reactions: A new approach to the construction of eight-membered rings. *J. Am. Chem. Soc.* **2002,** *124*, 8782-8783.

5. Bonafoux, D.; Lee, S.-Y.; Ojima, I., Cyclizations by homogeneous catalysts. In *Encyclopedia of Catalysis*, Horvath, I., Ed. John Wiley: Colorado Springs, **2003**; Vol. 2, pp 706-766.

6. (a) Ojima, I.; McCullagh, J. V.; Shay, W. R., New cascade silylcarbocyclization (SiCaC) of enediynes. *J. Organomet. Chem.* **1996,** *521*, 421-423; (b) Negishi, E.-I.; Coperet, C.; Ma, S.; Liou, S. Y.; Liu, F., Cyclic carbopalladation. A versatile synthetic methodology for the construction of cyclic organic compounds. *Chem. Rev.* **1996,** *96*, 365-394; (c) Brummond, K. M.; McCabe, J. M., The rhodium(I)-catalyzed Alder-ene reaction. In *Modern Rhodium-Catalyzed Organic Reactions* Evans, A. P., Ed. Wiley-VCH Verlag GmbH & Co: **2005**; pp 151-172.

7. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L., Three-component cycloadditions: The first transition metal-catalyzed [5+2+1] cycloaddition reactions. *J. Am. Chem. Soc.* **2002,** *124*, 2876-2877.

8. (a) Chen, Y.; Kiattansakul, R.; Ma, B.; Snyder, J. K., Transition metal-catalyzed [4+2+2] cycloadditions of bicyclo[2.2.1]hepta-2,5-dienes (Norbornadienes) and bicyclo[2.2.2]octa-2,5-dienes. *J. Org. Chem.* **2001,** *66*, 6932-6942; (b) Gilbertson, S. R.; DeBoef, B., Rhodium catalyzed [4+2+2] Cycloaddition and alkyne insertion: A new route to eight-membered rings. *J. Am. Chem. Soc.* **2002,** *124*, 8784-8785.

9. (a) Gibson, S. E.; Lewis, S. E.; Mainolfi, N., Transition metal-mediated routes to cyclopentenones. *J. Organomet. Chem.* **2004,** *689*, 3873-3890; (b) Shibata, T., Recent advances in the catalytic Pauson-Khand-type reaction. *Adv. Synth. Cat.* **2006,** *348*, 2328-2336.

10. (a) Fujiwara, M.; Ojima, I., Rhodium(I)-catalyzed cycloisomerization and cyclotrimerization reactions. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, A. P., Ed. Wiley-VCH Verlag GmbH & Co: **2005**; pp 129-149; (b) Ojima, I., New cyclization reactions in organic syntheses. *Pure Appl. Chem.* **2002,** *74*, 159-166; (c) Evans, P. A.; Leahy, D. K., Recent developments in rhodium-catalyzed allylic substitution and carbocyclization reactions. *Chemtracts* **2003,** *16*, 567-578; (d) Robinson, J. E., Rhodium(I)-catalyzed [4+2] and [4+2+2] carbocyclizations. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, P. A., Ed. Wiley-VCH Verlag GmbH & Co.: **2005**; pp 241-262; (e) Varchi, G.; Ojima, I., Synthesis of heterocycles through hydrosilylation, silylformylation, silylcarbocyclization and cyclohydrocarbonylation reactions. *Curr. Org. Chem* **2006,** *10*, 1341-1362.

11. (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E., Organocobalt complexes. Part I. Arene complexes derived from dodecacarbonyltetracobalt. *J. Chem. Soc., Perkin Trans. 1,* **1973**, 975-977; (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I., Organocobalt complexes. Part II. Reaction of acetylenehexacarbonyldicobalt complexes, $(R^1C_2R^2)Co_2(CO)_6$, with norbornene and its derivatives. *J. Chem. Soc., Perkin Trans. 1,* **1973**, 977-981.

12. Schore, N. E.; Croudace, M. C., Preparation of bicyclo[3.3.0]oct-1-en-3-one and bicyclo[4.3.0]non-1(9)-en-8-one via intramolecular cyclization of alpha-omega-enynes. *J. Org. Chem.* **1981,** *46*, 5436-5438.

13. Brummond, K. M.; Kent, J. L., Recent advances in the Pauson-Khand reaction and related [2+2+1] cycloadditions. *Tetrahedron* **2000,** *56*, 3263-3283.

14. Jeong, N.; Sung, B. K.; Kim, J. S.; Park, S. B.; Seo, S. D.; Shin, J. Y.; In, K. Y.; Choi, Y. K., Pauson-Khand-type reaction mediated by Rh(I) catalysts. *Pure Appl. Chem.* **2002,** *74*, 85-91.

15. (a) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A., Regioselectivity, stereoselectivity and catalysis in intermolecular Pauson-Khand reactions: Teaching an old dog new tricks. *Synlett* **2005**, 2547-2570; (b) Park, J. H.; Chang, K.-M. C.; Keun, Y., Catalytic Pauson-Khand-type reactions and related carbonylative cycloaddition reactions. *Coord. Chem. Rev.* **2009,** *253*, 2461-2480; (c) Croatt, M. P.; Wender, P. A., The diene effect. The design, development, and mechanistic investigation of metal-catalyzed diene-yne, diene-ene, and diene-allene [2+2+1] cycloaddition reactions. *Eur. J. Org. Chem.* **2010**, 19-32; (d) Lee, H.-W.; Kwong, F.-Y., A Decade of advancements in Pauson-Khand-type reactions. *Eur. J. Org. Chem.* **2010**, 789-811; (e) Susan E. Gibson; Stevenazzi, A., The Pauson-Khand Reaction: the catalytic age is here! *Angew. Chem. Int. Ed.* **2003,** *42*, 1800-1810.

16. Pallerla, M. K.; Fox, J. M., Enantioselective synthesis of (−)-Pentalenene. *Org. Lett.* **2007,** *9*, 5625-5628.

17. Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K., CO-Transfer carbonylation reactions. A catalytic Pauson−Khand-type reaction of enynes with aldehydes as a source of carbon monoxide. *J. Am. Chem. Soc.* **2002,** *124*, 3806-3807.

18. Shibata, T.; Toshida, N.; Takagi, K., Catalytic Pauson-Khand-Type Reaction Using Aldehydes as a CO Source. *Org. Lett.* **2002,** *4*, 1619-1621.

19. Brummond, K. M.; Chen, D.; Davis, M. M., A general synthetic route to differentially functionalized angularly and linearly fused [6−7−5] ring systems: A Rh(I)-catalyzed cyclocarbonylation reaction. *J. Org. Chem.* **2008,** *73*, 5064-5068.

20. (a) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J., An allenic Pauson−Khand-type reaction: A reversal in π-bond selectivity and the formation of seven-membered rings. *Org. Lett.* **2002,** *4*, 1931-1934; (b) Brummond, K. M.; Kerekes, A. D.; Wan, H., Chiral nonracemic α-alkylidene and α-silylidene cyclopentenones from chiral allenes using an intramolecular allenic Pauson−Khand-type cycloaddition. *J. Org. Chem.* **2002,** *67*, 5156-5163.

21. Brummond, K. M.; Chen, D., $Mo(CO)_6$ and $[Rh(CO)_2Cl]_2$ catalyzed allenic cyclocarbonylation reactions of alkynones: Efficient access to bicyclic dienediones. *Org. Lett.* **2008,** *10*, 705-708.

22. Inagaki, F.; Mukai, C., Rhodium(I)-catalyzed intramolecular Pauson−Khand-type [2+2+1] cycloaddition of allenenes. *Org. Lett.* **2006,** *8*, 1217-1220.

23. Hayashi, Y.; Miyakoshi, N.; Kitagaki, S.; Mukai, C., Stereoselective total syntheses of uncommon sesquiterpenoids isolated from Jatropha neopauciflora. *Org. Lett.* **2008,** *10*, 2385-2388.

24. Wender, P. A.; Deschamps, N. M.; Gamber, G. G., The dienyl Pauson–Khand reaction. *Angew. Chem. Int. Ed.* **2003,** *42*, 1853-1857.

25. Wender, P. A.; Deschamps, N. M.; Williams, T. J., Intermolecular dienyl Pauson-Khand reaction. *Angew. Chem. Int. Ed.* **2004,** *43*, 3076-3079.

26. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Metal-catalyzed [2+2+1] cycloadditions of 1,3-dienes, allenes, and CO. *Angew. Chem. Int. Ed.* **2006,** *45*, 2459-2462.

27. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Rhodium(I)-catalyzed [2+2+1] cycloadditions of 1,3-dienes, alkenes, and CO. *J. Am. Chem. Soc.* **2004,** *126*, 5948-5949.

28. (a) Adrio, J.; Carretero, J. C., Butenolide synthesis by Molybdenum-mediated hetero-Pauson−Khand reaction of alkynyl aldehydes. *J. Am. Chem. Soc.* **2007,**

129, 778-779; (b) Gao, P.; Xu, P.-F.; Zhai, H., Expeditious construction of (+)-Mintlactone via intramolecular hetero-Pauson-Khand reaction. *J. Org. Chem.* **2009,** *74*, 2592-2593.

29. Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S., $Ru_3(CO)_{12}$-catalyzed intermolecular cyclocoupling of ketones, alkenes or alkynes, and carbon monoxide. [2+2+1] Cycloaddition strategy for the synthesis of functionalized γ-butyrolactones. *J. Am. Chem. Soc.* **2000,** *122*, 12663-12674.

30. (a) Morimoto, T.; Chatani, N.; Murai, S., The first catalytic carbonylative [4+1] cycloaddition using a 1,3-conjugated system. A new transformation of α,β-unsaturated imines to unsaturated γ-lactams catalyzed by $Ru_3(CO)_{12}$. *J. Am. Chem. Soc.* **1999,** *121*, 1758-1759; (b) Göbel, A.; Imhof, W., One-pot ruthenium catalyzed synthesis of spiro[pyrrolidin-2-one] derivatives by a [2+2+1] cycloaddition of ketimines, carbon monoxide and ethylene *Chem. Commun.* **2001**, 593-594.

31. (a) Saito, T.; Furukawa, N.; Otani, T., A facile synthesis of pyrrolo[2,3-b]quinolines via a Rh(I)-catalyzed carbodiimide-Pauson–Khand-type reaction. *Org. Biomol. Chem.* **2010,** *8*, 1126-1132; (b) Aburano, D.; Yoshida, T.; Miyakoshi, N.; Mukai, C., Synthesis of hexahydropyrrolo[2,3-b]indole alkaloids based on the aza-Pauson−Khand-type reaction of alkynecarbodiimides. *J. Org. Chem.* **2007,** *72*, 6878-6884; (c) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A., $Co_2(CO)_8$-catalyzed intramolecular hetero-Pauson−Khand reaction of alkynecarbodiimide: Synthesis of (±)-Physostigmine. *Org. Lett.* **2006,** *8*, 83-86; (d) Saito, T.; Sugizaki, K.; Otani, T.; Suyama, T., Rhodium-catalyzed intramolecular alkyne-carbodiimide Pauson−Khand-type reaction. *Org. Lett.* **2007,** *9*, 1239-1241.

32. Saito, T.; Nihei, H.; Otani, T.; Suyama, T.; Furukawa, N.; Saito, M., Thiocarbonyl induced heterocumulenic Pauson–Khand type reaction: expedient synthetic method for thieno[2,3-b]indol-2-ones. *Chem. Commun.* **2008**, 172-174.

33. Wegner, H. A.; deMeijere, A.; Wender, P. A., Transition metal-catalyzed intermolecular [5+2] and [5+2+1] cycloadditions of allenes and vinylcyclopropanes. *J. Am. Chem. Soc.* **2005,** *127*, 6530-6531.

34. Mehta, G.; Srikrishna, A., Synthesis of polyquinane natural products: An update. *Chem. Rev.* **1997,** *97*, 671-720.

35. Jiao, L.; Yuan, C.; Yu, Z.-X., Tandem Rh(I)-catalyzed [(5+2)+1] cycloaddition/Aldol reaction for the construction of linear triquinane skeleton: Total syntheses of (±)-Hirsutene and (±)-1-Desoxyhypnophilin. *J. Am. Chem. Soc.* **2008,** *130*, 4421-4430.

36. Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z. X., A computationally designed Rh(I)-catalyzed two-component [5+2+1] cycloaddition of ene-vinylcyclopropanes and CO for the synthesis of cyclooctenones. *J. Am. Chem. Soc.* **2007,** *129*, 10060-10061.

37. Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X., Rh(I)-catalyzed [(3+2)+1] cycloaddition of 1-yne/ene-vinylcyclopropanes and CO: Homologous Pauson−Khand reaction and total synthesis of (±)-α-Agarofuran. *Org. Lett.* **2010,** *12*, 2528-2531.

38. (a) Ojima, I.; Ingallina, P.; Donovan, R. J.; Clos, N., Silylformylation of 1-hexyne catalyzed by Rhodium-Cobalt mixed-metal carbonyl clusters. *Organometallics* **1991,** *10*, 38-41; (b) Ojima, I.; Donovan, R. J.; Eguchi, M.; Shay, W. R.; Ingallina, P.; Korda, A.; Zeng, Q., Silylformylation catalyzed by Rh and Rh-Co mixed metal complexes and its application to the synthesis of pyrrolizidine alkaloids. *Tetrahedron* **1993,** *49*, 5431-5444.

39. Matsuda, I.; Fukuta, Y.; Tsuchihashi, T.; Nagashima, H.; Itoh, K., Rhodium-catalyzed silylformylation of acetylenic bonds: Its scope and mechanistic considerations. *Organometallics* **1997,** *16*, 4327-4345.

40. Ojima, I.; Vu, A. T.; Lee, S. Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H., Rhodium-catalyzed silylcarbocyclization (SiCaC) and carbonylative silylcarbocyclization (CO-SiCaC) reactions of enynes. *J. Am. Chem. Soc.* **2002,** *124*, 9164-9174.

41. Fukuta, Y.; Matsuda, I.; Itoh, K., Rhodium-catalyzed domino silylformylation of enynes involving carbocyclization. *Tetrahedron Lett.* **1999,** *40*, 4703-4706.

42. (a) Ojima, I.; Fracchiolla, D. A.; Donovan, R. J.; Banerji, P., Silylcarbobicyclization of 1,6-Diynes: A novel catalytic route to bicyclo[3.3.0]octenones. *J. Org. Chem.* **1994,** *59*, 7594-7595; (b) Ojima, I.; Zhu, J.; Vidal, E. S.; Kass, D. F., Silylcarbocyclizations of 1,6-diynes. *J. Am. Chem. Soc.* **1998,** *120*, 6690-6697.

43. Ojima, I.; Vu, A. T.; McCullagh, J. V.; Kinoshita, A., Rhodium-catalyzed intramolecular silylcarbotricyclization (SiCaT) of triynes. *J. Am. Chem. Soc.* **1999,** *121*, 3230-3231.

44. (a) Ojima, I.; Clos, N.; Donovan, R. J.; Ingallina, P., Hydrosilylation of 1-hexyne catalyzed by rhodium and cobalt-rhodium mixed-metal complexes. Mechanism of apparent trans addition. *Organometallics* **1990,** *9*, 3127-3133; (b) Tanke, R. S.; Crabtree, R. H., Unusual activity and selectivity in alkyne hydrosilylation with an iridium catalyst stabilized by an oxygen-donor ligand. *J. Am. Chem. Soc.* **1990,** *112*, 7984-7989.

45. (a) Ojima, I.; Lee, S.-Y., Rhodium-catalyzed novel carbonylative carbotricyclization of enediynes. *J. Am. Chem. Soc.* **2000,** *122*, 2385-2386; (b) Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I., Silicon-initiated carbonylative carbotricyclization and [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *J. Am. Chem. Soc.* **2005,** *127*, 17756-17767.

46. Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2+2+2+1] cycloaddition of enediynes catalyzed by Rhodium complexes. *Org. Lett.* **2004,** *6*, 3589-3591.

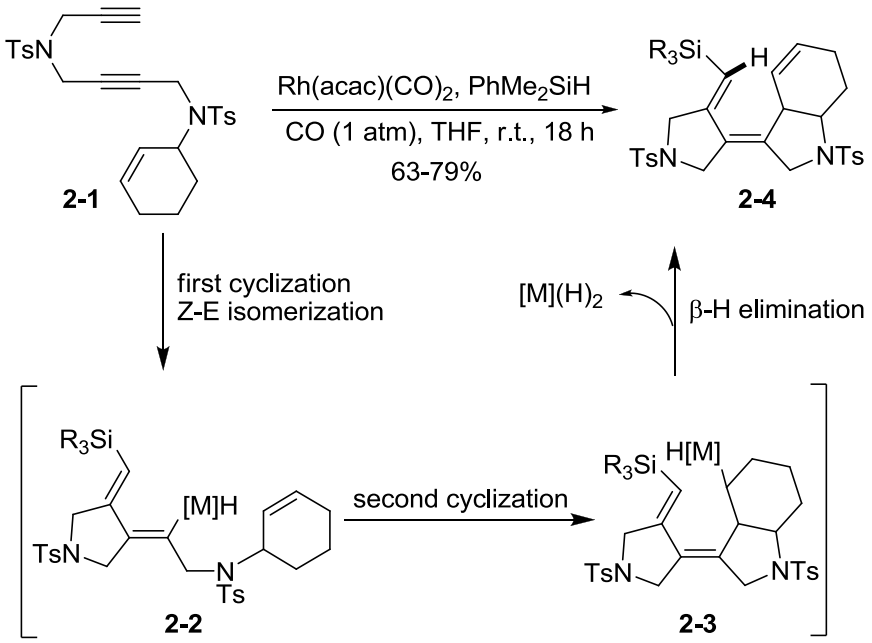
Chapter 2

Formation of novel 5-7-6-5 fused tetracyclic skeletons through Rh(I)-catalyzed [2+2+2+1]cycloaddition of cyclohexene-diynes and carbon monoxide

Table of Contents

§ 2.1. Introduction

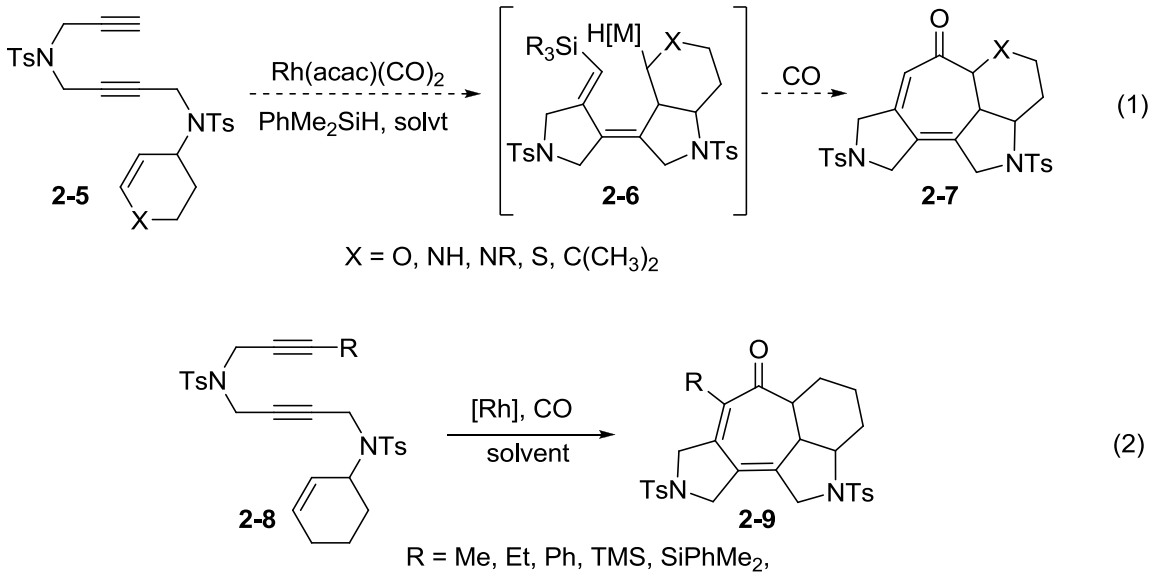
The development of novel reactions and efficient catalysts to effect the formation of carbon-carbon and carbon-heteroatom bonds is an important activity in organic chemistry. In particular, transition metal-catalyzed carbocyclization and cycloaddition reactions have proven to be among the most efficient methods for constructing complex polycyclic systems.[1] The treatment of cyclohexene-diyne **2-1** under carbonylative silylcarbotricylizaton (CO-SiCaT) conditions afforded *bis* pyrrolidine-triene **2-4** in good yield.[2] It should be noted that the observed product **2-4** was correctly predicted based on a possible β-hydride elimination pathway of the key intermediate **2-3** (**Scheme 2-1**).[2] The formation of product **2-4** without the observation of the 5-7-6-5 fused tetracyclic product indicates that the β-hydride elimination pathway is much faster than CO insertion under the reaction conditions.



Scheme 2-1: Carbonylative silylcarbotricylizaton of cyclohexene-diyne **2-1**

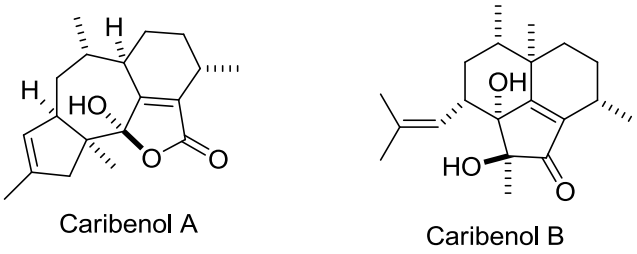
Undoubtedly the olefins and vinylsilane present in product **2-4** provide an opportunity for further functional group manipulation. The formation of product **2-4** also shows the limitation of the CO-SiCaT process with this substrate type. A close evaluation

of the proposed mechanism (**Scheme 2-1**) provides a hint at substrate modification for the formation of the 5-7-6-5 fused tetracyclic compounds. The introduction of a heteroatom or *gem*-disubstitution on the cyclohexenyl moiety provides a means to blocking the facile β-hydride elimination process, and thus, should facilitate the formation of the 5-7-6-5 fused system **2-7** *via* intermediate **2-6** (**Scheme 2-2**, **reaction 1**). The proposed substrate modification should yield either compound **2-7** in the presence of carbon monoxide or the non-carbonylated 5-6-6-5 product since the facile β-hydride elimination process leading to **2-4** *via* intermediate **2-3** is blocked. Alternatively, cyclohexene-diyne **2-8** substituted at the terminal acetylene could be subjected to previously developed [2+2+2+1] cycloaddition conditions[2-3] to form the 5-7-6-5 fused tetracyclics **2-9** (**Scheme 2-2, reaction 2**).



Scheme 2-2: Proposed synthesis of 5-7-6-5 fused tetracyclics

Recently Rodriguez and coworkers[4] reported the structures of the norditerpenes Caribenol A and B (**Figure 1-1**), metabolites of the West Indian Gorgonian Octocroal *Pseudopterogorgia elisabethae*. Caribenol A possesses a novel 5-7-6-5 fused tetracyclic core that was previously *not* known in natural product chemistry.[4] More importantly, both Caribenol A and B were found to posses strong inhibitory activity against *Mycobacterium tuberculosis.*[4]



Caribenol A Caribenol B

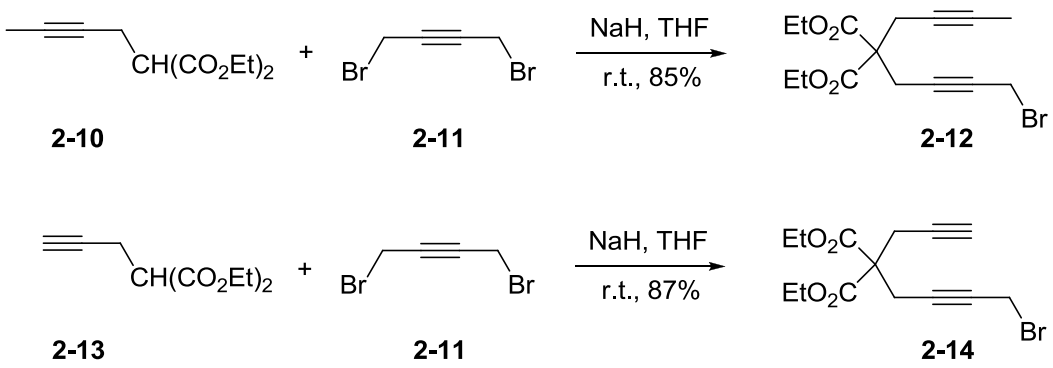
Figure 2-1: Caribenol A and Caribenol B

Intrigued by these findings, we set out to develop a highly efficient synthetic route to the 5-7-6-5 tetracyclic skeleton *via* a single step process from cyclohexene-diynes. An advantage of this approach is that from simple and readily accessible starting materials, a variety of richly functionalized natural product-like compounds with modifiable functional groups can be obtained in a few steps. As part of our ongoing investigations into Rh(I)-catalyzed higher-order cycloadditon of enediyne derivatives, we applied the previously developed [2+2+2+1] cycloaddition process[2-3] to substituted cyclohexene-diyne substrates, and found that the reaction afforded the desired 5-7-6-5 fused tetracyclic products in good to excellent yields and as single diastereomers.[5]

§ 2.2. Results and discussion

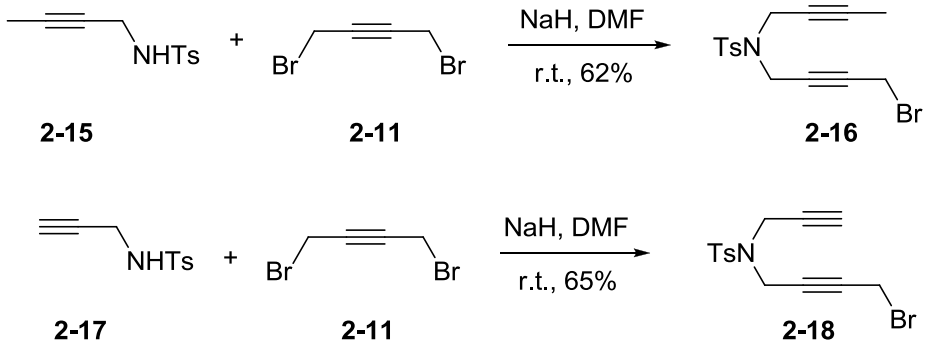
§ 2.2.1. Synthesis of cyclohexene-diynes

Our investigation into the formation of 5-7-6-5 fused tetracyclics began with the synthesis of cyclohexene-diyne substrates. Thus, soduim hydride (NaH) mediated coupling of diethyl -2-(but-2-ynyl)malonate[2] **2-10** with 1,4-dibromobut-2-yne **2-11** in THF gave the desired methyl substituted bromo-diyne **2-12** in 85% isolated yield (**Scheme 2-3**). The propargyl derivative **2-14** was also obtained in a similar manner (**Scheme 2-3**).



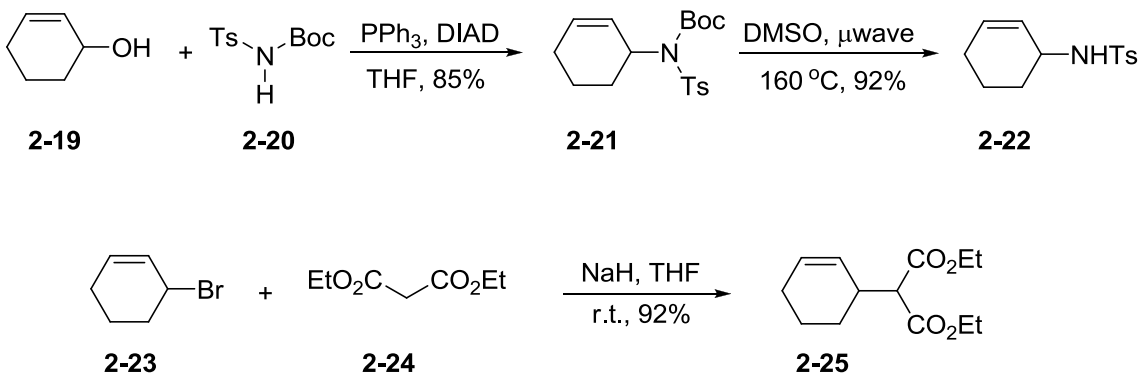
Scheme 2-3: Synthesis of bromo-diynes **2-12** and **2-14**

The *N*-tosyl tethered bromo diynes **2-16** and **2-18** were obtained from coupling of *N*-butynyl-*N*-tosylamide **2-15** and *N*-propargyl-*N*-tosylamide **2-17** with 1,4-dibromobut-2-yne **2-11** respectively (**Scheme 2-4**).



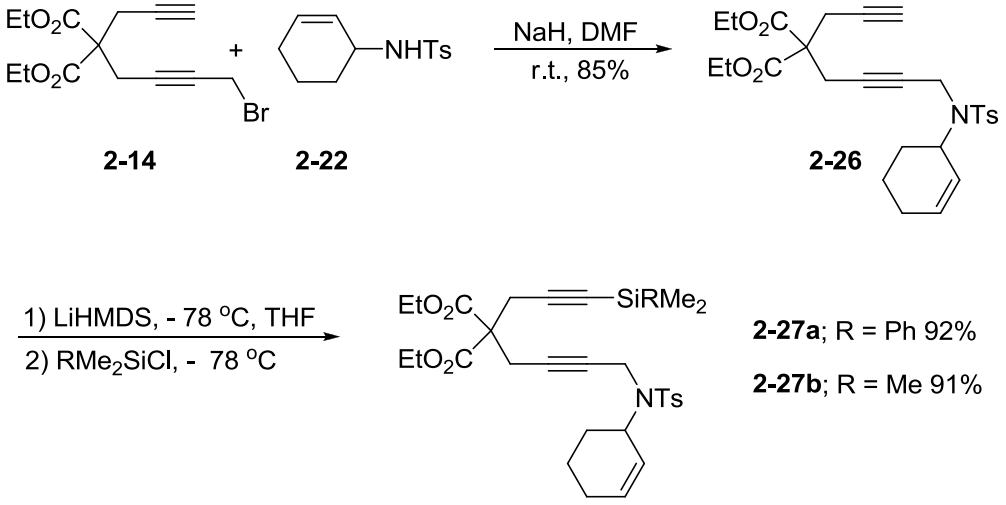
Scheme 2-4: Synthesis of bromo-diynes **2-16** and **2-18**

The synthesis of *N*-cyclohex-2-enyl sulfonamide **2-22** was accomplished in two steps (**Scheme 2-5**). Coupling of 2-cyclohexen-1-ol **2-19** with *N*-Boc-*N*-tosylamide **2-2** under Mitsunobu conditions afforded the desired product **2-21** in 85% yield. Subsequent Boc thermolysis under microwave irradiation conditions gave the desired product **2-22** in excellent yield. Diethyl 2-(cyclohex-2-enyl) malonate **2-25** was obtained in excellent yield from the coupling of bromocyclohexene **2-23** with diethyl malonate **2-24** in the presence of NaH (**Scheme 2-5**).



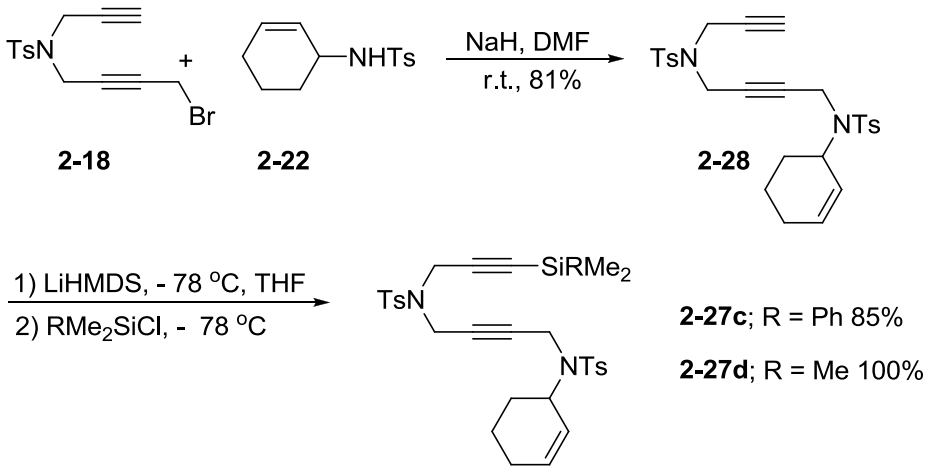
Scheme 2-5: Synthesis of *N*-cyclohex-2-enyl sulfonamide (**2-22)** and diethyl 2-(cyclohex-2-enyl) malonate (**2-25)**

With the various substrate components in hand, a variety of cyclohexene-diyne substrates were prepared. The terminal cyclohexene-diyne **2-26** was obtained in 85% yield from coupling of bromo-diyne **2-14** with *N*-cyclohexenyl tosylamide **2-22**. Treatment of cyclohexene-diyne **2-26** with chlorodimethylphenyl silane or chloro-trimethyl silane in the presence of LiHMDS gave the desired substrates **2-27a** and **2-27b** in high yields (**Scheme 2-6**).



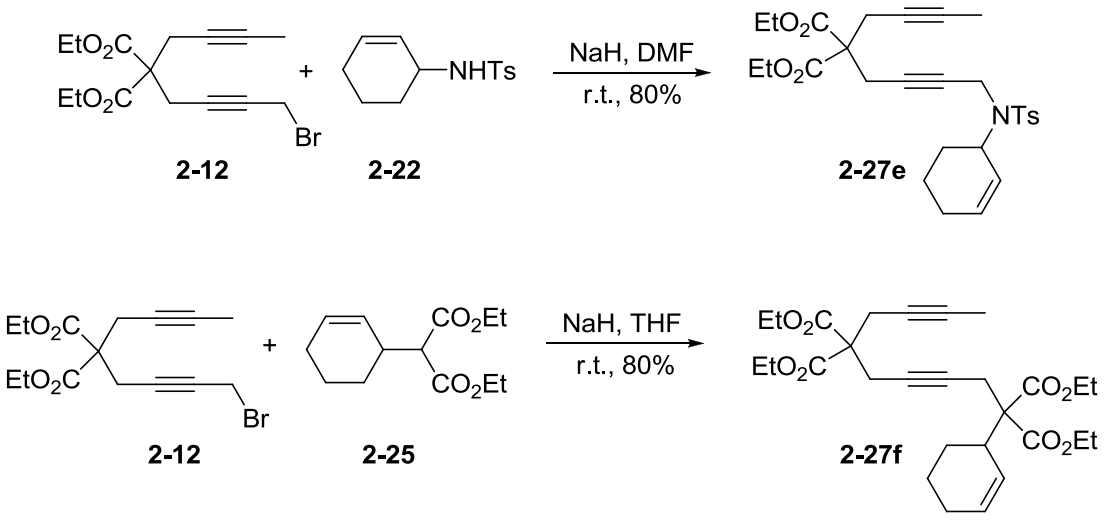
Scheme 2-6: Synthesis of cyclohexene-diynes **2-27a** and **2-27b**

The bis *N*-tosyl tethered substrates **2-27c** and **2-27d** were obtained in 85% and quantitative yields respectively from treatment of cyclohexene-diyne **2-28** with the corresponding chlorosilanes in the presence of LiHMDS (**Scheme 2-7**).



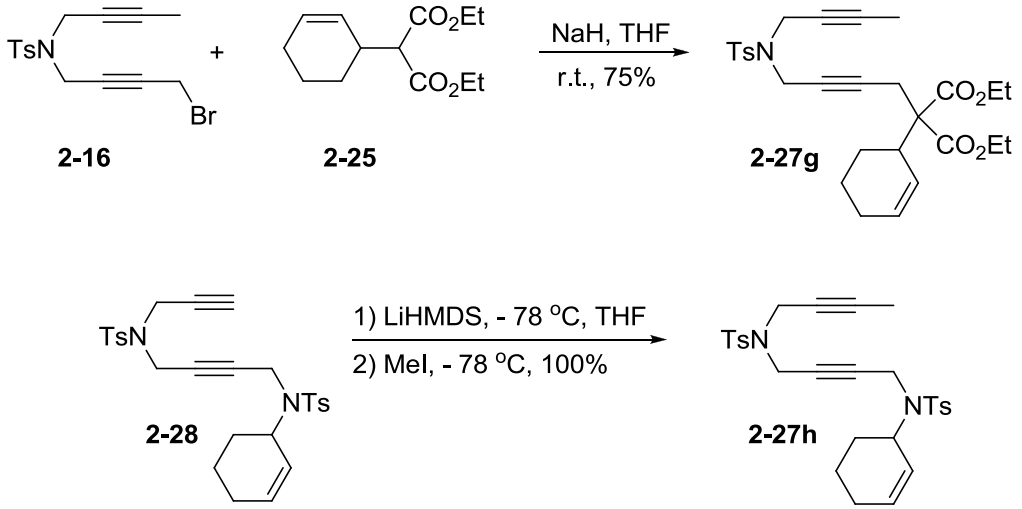
Scheme 2-7: Synthesis of cyclohexene-diynes **2-27c** and **2-27d**

Methyl substituted substrates **2-27e** and **2-27f** were obtained in good yields from NaH mediated nucleophilic substitution of bromo-diyne **2-12** with *N*-cyclohex-2-enyl sulfonamide **2-22** and diethyl 2-(cyclohex-2-enyl) malonate **2-25** respectively (**Scheme 2-8**).



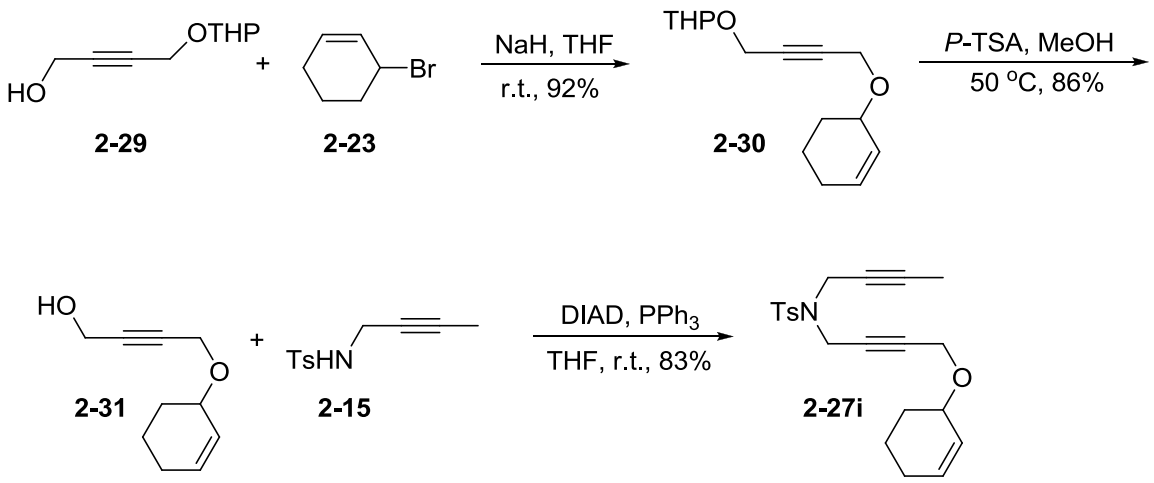
Scheme 2-8: Synthesis of cyclohexene-diynes **2-27e** and **2-27f**

The treatment of bromo-diyne **2-16** with 2-(cyclohex-2-enyl) malonate **2-25** in the presence of NaH gave substrate **2-27g** in 75% yield (**Scheme 2-9**), while substrate **2-27h** was obtained in quantitative yield after treatment of cyclohexene-diyne **2-28** with methyl iodide in the presence of LiHMDS (**Scheme 2-9**).



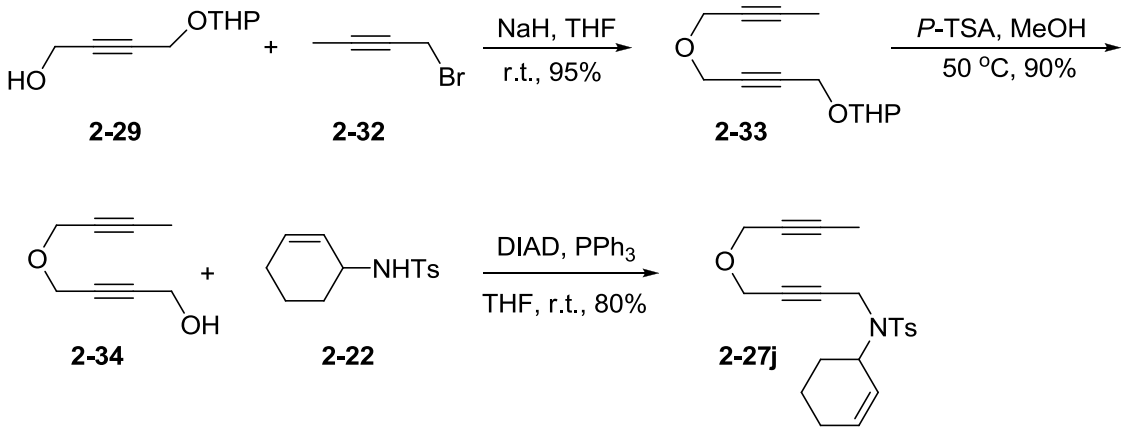
Scheme 2-9: Synthesis of cyclohexene-diynes **2-27g** and **2-27h**

The synthesis of methyl substituted cyclohexene-diyne **2-27i** is outlined in **Scheme 2-10**. Compound **2-31** was obtained in high yield after coupling of bromocyclohexene **2-23** with mono-tetrahydropyran (THP) protected 2-butyndiol **2-29** and subsequent THP deprotection. The desired cyclohexene-diyne **2-27i** was then obtained in good yield *via* Mitsunobu reaction of *N*-butynyl-tosylamide **2-15** with eneyne **2-31** (**Scheme 2-10**).



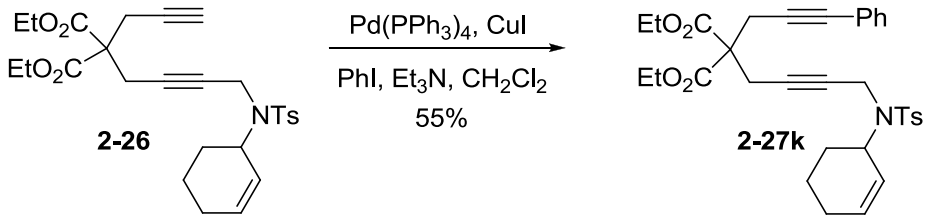
Scheme 2-10: Synthesis of cyclohexene-diyne 2-27i

The synthesis of substrate **2-27j** began with the formation of diyne **2-33** through NaH mediated coupling of mono-THP protected 2-butyndiol **2-29** with 1-bromo-2-butyne **2-32**. Subsequent deprotection of the THP followed by Mitsunobu coupling of the resultant alcohol **2-34** with *N*-cyclohex-2-enyl sulfonamide **2-22** afforded cyclohexene-diyne **2-27j** in good yield (**Scheme 2-11**).



Scheme 2-11: Synthesis of cyclohexene-diyne **2-27j**

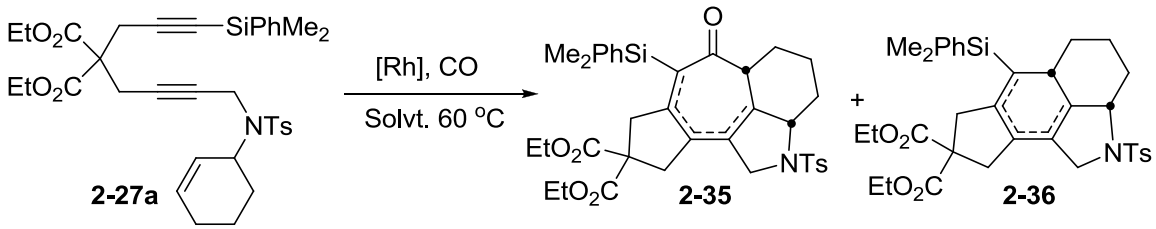
The treatment of cyclohexene-diyne **2-26** with iodobenzene under Sonagashira conditions gave the corresponding phenyl-substituted cyclohexene-diyne **2-27k** in 55% yield (**Scheme 2-12**).



Scheme 2-12: Synthesis of cyclohexene-diyne **2-27k**

§ 2.2. 2. Optimization of [2+2+2+1] cycloaddition reaction and substrate scope

The optimization studies for the formation of 5-7-6-5 fused tetracyclics started with phenyldimethylsilyl ($SiPhMe_2$) substituted substrate **2-27a**. Subjecting substrate **2-27a** to previously reported conditions for the formation of the [2+2+2+1] products ($[Rh(COD)Cl]_2$, 1 atm of CO in dichloroethane (DCE) at 60 ^oC)[3], gave the desired fused tetracyclic product **2-35** along with a small amount of the [2+2+2] cycloadduct **2-36** (ca. 11.5:1) in 89% combined yield but with low catalyst turnover (i.e. 50 h) (**Scheme 2-13**, **Table 2-1, entry 1**).



Scheme 2-13: [2+2+2+1] cycloaddition of cyclohexene-diyne **2-27a** with CO

Table 2-1: Optimization of [2+2+2+1] cycloaddition of **2-27a** with CO

Entry	Solvent	[Rh] cat.	Press (atm)	Conv. (%)[a]	Ratio (**2-35**:**2-36**)[a]	Comb. Yield (%)[b]
1	DCE	$[Rh(COD)Cl]_2$	1	100[d]	92:8	89
2	DCE	$[Rh(CO)_2Cl]_2$	1	100	90:10	86
3	DCE	$[Rh(CO)_2Cl]_2$	2	75	93:7	ND[c]
4	DCE	$[Rh(CO)_2Cl]_2$	3	90[d]	93:7	ND[c]
5	TFE	$[Rh(CO)_2Cl]_2$	2	100	100:0	70
6	DCE/TFE (1:1)	$[Rh(CO)_2Cl]_2$	2	100	100:0	81
7	DCE/TFE (5:1)	$[Rh(CO)_2Cl]_2$	2	100	100:0	91
8	**DCE/TFE (10:1)**	**$[Rh(CO)_2Cl]_2$**	**2**	**100**	**100:0**	**92**

DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol; [a] Determined by reverse phase HPLC analysis (CH_3CN:H_2O, Phenomenex, Jupiter 10µ Proteo 90A) for 20 h reaction.[b] Isolated yield. [c] Not determined. [d] At 50 h.

Moreover, the conditions for high selectivity for the carbonylated product **2-35a** could not be extended to other substrates. Thus, the reaction conditions were further optimized to improve the product selectivity as well as the rate of the reaction (**Table 2-1**). Using $[Rh(CO)_2Cl]_2$ as the catalyst significantly increased the rate of the reaction (i.e., completion in 20 h) but with decreased selectivity (**Table 2-1, entry 2**). Increasing the CO pressure resulted in lower conversion but excellent selectivity (**entries 3 & 4**). Trifluoroethanol (TFE) has been shown to increase the rate of carbonylation reactions.[6] Using TFE as solvent at 2 atm of CO pressure, **2-35a** was obtained exclusively with complete conversion in 20 h but in 70% yield (**entry 5**). A combination of DCE and TFE as solvent also gave exclusive selectivity for the carbonylated product **2-35a** (**entries 6-8**). The combination of $[Rh(CO)_2Cl]_2$ as catalyst and 2 atm of CO pressure in DCE/TFE (10:1) gave the desired carbonylated product **2-35a** exclusively and in excellent yield after 20 h (**Table 2-1, entry 8**).

Following purification of **2-35a**, NMR, HPLC and LC-MS analysis indicated that **2-35a** was a 1:1 mixture of two isomers, which were isolated by preparative HPLC (**Figure 2**). The two isolated compounds were studied by proton and carbon NMR. The proton count for both compounds were equal and suggested regioisomeric products. The carbon count for both fractions were also equal but the chemical shifts

for the carbonyls of the two compounds were revealing (207 ppm for fraction one and 199 ppm for fraction two); suggesting non-conjugated and conjugated carbonyls respectively.[7]

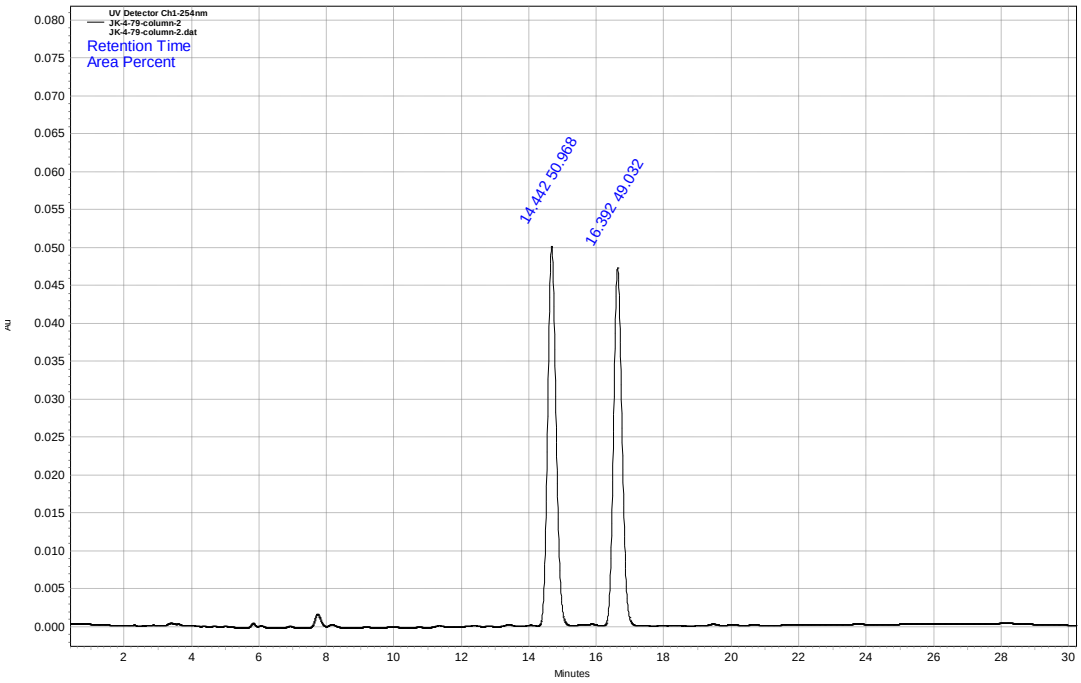


Figure 2-2: HPLC trace of isolated product **2-37a** (first peak) and **2-35a** (second peak) from [2+2+2+1] cycloaddition of cyclohexene-diyne **2-27a** with CO

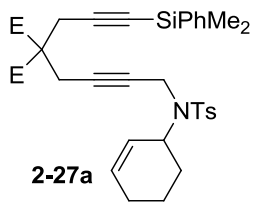
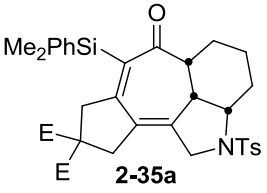
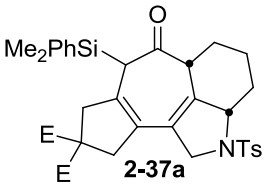
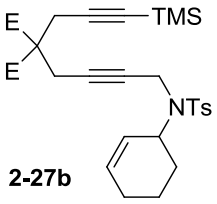
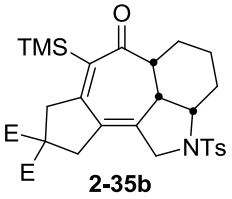
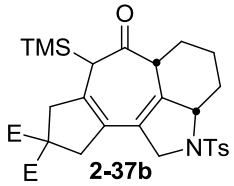
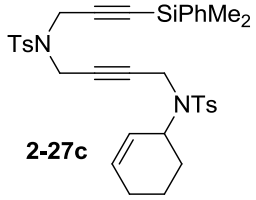
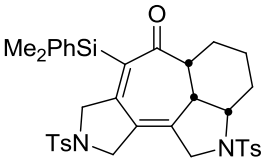
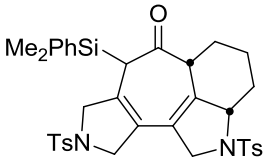
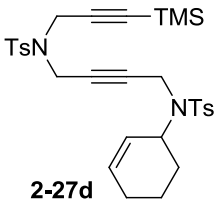
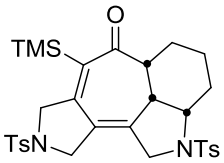
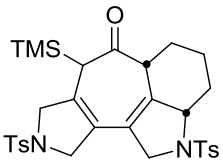
The mass spectral analysis of each isolated product showed molecular mass consistent with the carbonylated product (i.e. 662 daltons; M+H). However, a difference in the molecular mass base peaks for the two fractions was noted. The molecular mass base peak for the first fraction was 585 daltons (M+H-Ph), while that for the second fraction was 662 daltons (M+H). The molecular mass difference turns out to correspond to the ionization of the phenyl ring on the dimethylphenyl silyl substituent of the first fraction.

Further analysis by LC-MS supported the NMR experiments. Thus, a mixture of the two products was monitored at 254 nm and 305 nm, respectively. It was expected that ultraviolet (UV) absorption of the less conjugated regioisomer would be lower at higher wavelengths. While both compounds could be observed at 254 nm in a

1:1 ratio, the absorption for fraction one is significantly diminished at 305 nm, while the absorption for fraction two remained strong at 305 nm. This suggested that fraction one contained the non-conjugated carbonylated isomer, while the second fraction contained the α,β-conjugated carbonylated isomer.

Based on the evidence, the compound in fraction two was assigned as the anticipated α,β-conjugated carbonylated product **2-35a**, while the other was its diene-shifted regioisomer **2-37a** (**Table 2-2, entry 1**). It should be noted that **2-35a** and **2-37a** were isolated as single diastereomers. The *syn* relationship of the three methine protons were confirmed by NOE experiments. Similar results were obtained for the reactions of substrates bearing $PhMe_2Si$ or Me_3Si group at the terminal ethynyl moiety, affording the carbonylated products, also as 1:1 mixture of regioisomers (**Table 2-2, entries 2-4**). The structures of the regioisomeric products were analogously assigned. TMS-capped substrates **2-27b** gave a mixture of products **2-35b** and **2-37b** in a combined 92% yield (**entry 2**), while **2-27d** gave **2-35d** and **2-37d** in 87% combined yield. The $PhMe_2Si$ capped substrate **2-27c** with bis- *p*-toluenesulfonamide tethers gave the regioisomeric products **2-35c** and **2-37c** in a combined 77% isolated yield.

Table 2-2: Formation of 5-7-6-5tetracyclics **2-35a-d** and **2-37a-d** through [2+2+2+1] cycloaddition of **2-27a-d** with CO

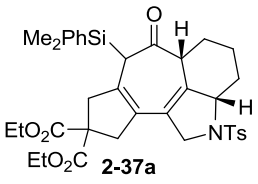
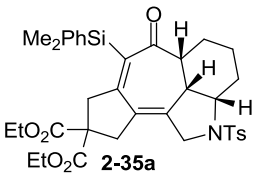
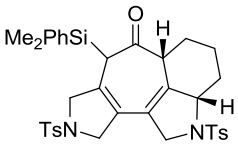
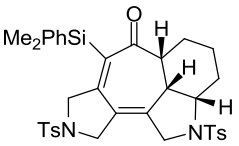
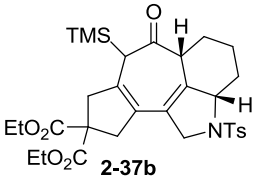
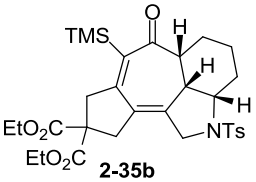
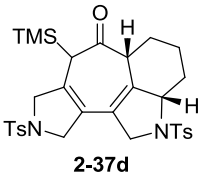
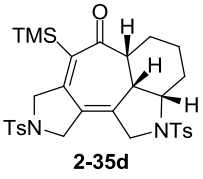
Entry	Substrate	Product 1	Product 2	Yield (%)[a]
(1)	 **2-27a**	 **2-35a**	 **2-37a**	(92)
(2)	 **2-27b**	 **2-35b**	 **2-37b**	(92)
(3)	 **2-27c**	 **2-35c**	 **2-37c**	(77)
(4)	 **2-27d**	 **2-35d**	 **2-37d**	(87)[b]

E = CO_2Et

[a] Averaged combined isolated yield of regioisomeric products based on at least two runs using 50-100 mg of substrate, 5 mol% $[Rh(CO)_2Cl]_2$, CO (2 atm) in DCE/TFE (10:1) at [0.05] for 20 h at 60 °C. Isomeric products can be separated by prep HPLC. [b] [2+2+2] product was observed in 6% yield.

Molecular modeling studies (PM3 and MNDO; PC Spartan 08, version 1.20) on **2-35a-d** and **2-37a-d** indicated that the diene-shifted regioisomers should be energetically more favorable than the α,β-conjugated isomers (**Table 2-3**). However, attempted diene isomerization with extended reaction time did not result in any appreciable change in product ratios. Further details into the reaction mechanism and discussions into the isomerized products will be presented later in this chapter.

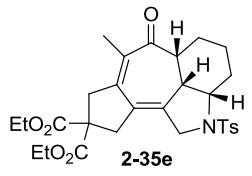
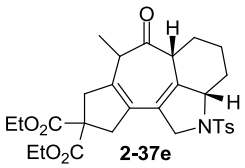
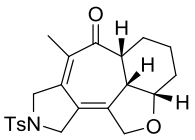
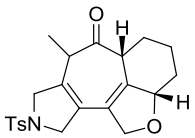
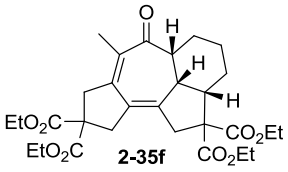
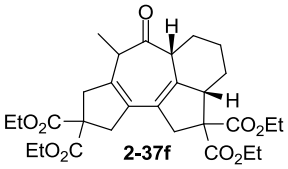
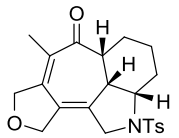
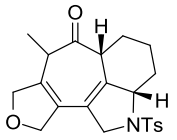
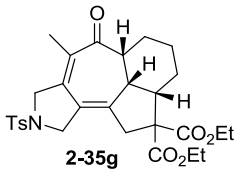
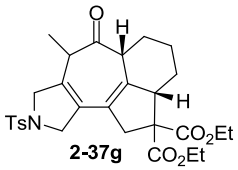
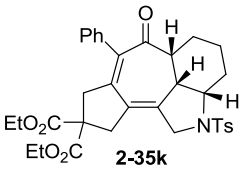
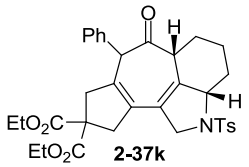
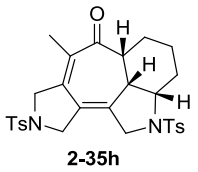
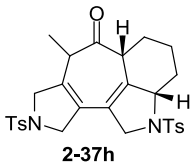
Table 2-3: Heat of formation calculations for **2-35a-d** and **2-37a-d**

 **2-37a**	 **2-35a**	 **2-37c**	 **2-35c**
Relative energy (kJ/mol) 0 0	15.4 (PM3) 3.3 (MNDO)	0 0	16.0 (PM3) 2.4 (MNDO)
 **2-37b**	 **2-35b**	 **2-37d**	 **2-35d**
Relative energy (kJ/mol) 0 0	15.9 (PM3) 5.7 (MNDO)	0 0	15.7 (PM3) 6.3 (MNDO)

Calculations were carried out using PC Spartan 08, version 1.20 from MM2 energy minimized structures

Computational studies also predicted the carbonyl-conjugated products to be more favorable for alkyl substituted substrates (**Table 2-4**). Therefore, the heteroatom and functional group tolerance of this process for alkyl substituted substrates **2-27e-k** was investigated. Gratifyingly, various cyclohexenyl-1,6-diynes containing sulfonamide, ether and malonate tethers were found to be well tolerated in this [2+2+2+1] cycloadditon process, affording the desired 5-7-6-5 fused tetracyclic cycloadducts **2-35e-k** in good to excellent yields, with very high to exclusive selectivity for the carbonylated products (**Table 2-5**).

Table 2-4: Heat of formation calculations for **2-35e-k** and **2-37e-k**

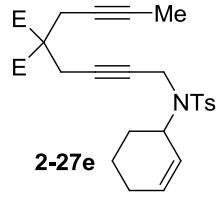
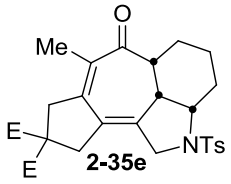
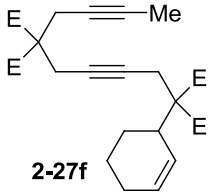
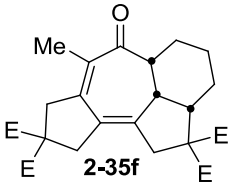
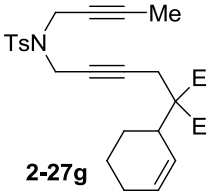
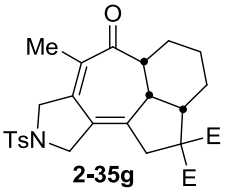
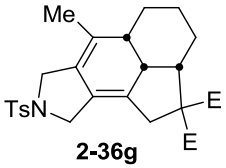
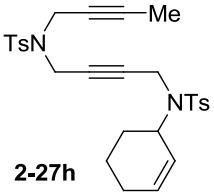
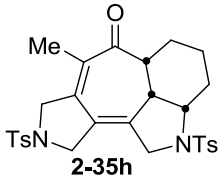
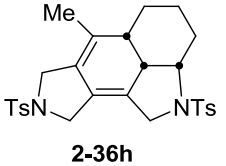
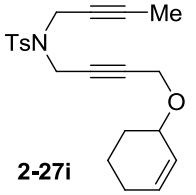
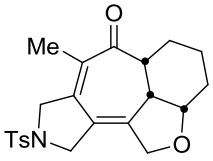
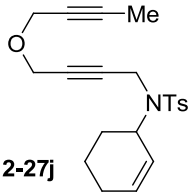
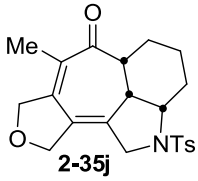
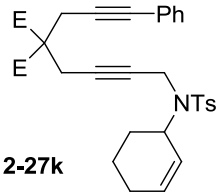
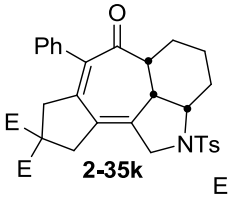
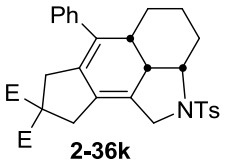
 **2-35e**	 **2-37e**	 **2-35i**	 **2-37i**
Relative energy (kJ/mol) 0 0	5.3 (PM3) 0.6 (MNDO)	Relative energy (kJ/mol) 0 0	11.0 (PM3) 4.3 (MNDO)
 **2-35f**	 **2-37f**	 **2-35j**	 **2-37j**
Relative energy (kJ/mol) 0 0	5.1 (PM3) 4.0 (MNDO)	Relative energy (kJ/mol) 0 0	7.7 (PM3) 8.7 (MNDO)
 **2-35g**	 **2-37g**	 **2-35k**	 **2-37k**
Relative energy (kJ/mol) 0 0	4.4 (PM3) 1.5 (MNDO)	Relative energy (kJ/mol) 0 0	10.8 (PM3) 11.6 (MNDO)
 **2-35h**	 **2-37h**		
Relative energy (kJ/mol) 0 0	4.0 (PM3) 3.1 (MNDO)		

Calculations were carried out using PC Spartan 08, version 1.20 from MM2 energy minimized structures

As predicted by computational studies, only the α,β-congugated products **2-35e-k** were obtained, also as single diastereomers. Cyclohexene-diyne **2-27e** with *p*-toluenesulfonamide and malonate tethers afforded the tetracyclic adduct **2-35e** exclusively (**Table 2-5, entry 1**), while its tether isomer **2-27g** gave a mixture of 5-7-6-5 **2-35g** (83%) and 5-6-6-5 **2-36g** (6%) products respectively (**entry 3**). Cyclohexene-diyne **2-27f**, bearing malonate tethers, also gave the desired tetracyclic adduct **2-35f** exclusively in 85% isolated yield (**entry 2**). The bis *p*-toluenesulfonamide tethered substrate **2-27h** gave a mixture of carbonylated product **2-35h** and non-carbonylated product **2-36h** in excellent combined yield (**entry 4**). The reaction of **2-27i** bearing a methyl group at the terminal ethynyl moiety with *p*-toluenesulfonamide and an ether tether afforded only the

5-7-6-5 tetracyclic adduct **2-35i** in 91% isolated yield (**entry 5**) with no trace of the [2+2+2] cycloadditon product. Its tether isomer **2-27j** also gave the desired product **2-35j** exclusively, albeit in lower isolated yield (74%, **entry 6**). The phenyl substituted cyclohexene-diyne **2-27k** was also investigated under the optimized conditions. However, no selectivity was observed, with both the 5-7-6-5 **2-35k** and 5-6-6-5 **2-36k** cycloadducts isolated in 44 % yield respectively. The lack of selectivity for this substrate is most likely due to the small energy difference between the two products.

Table 2-5: Formation of tetracyclics **2-35e-k** and **2-36g,h,k** through [2+2+2+1] cycloaddition of **2-27e-k** with CO

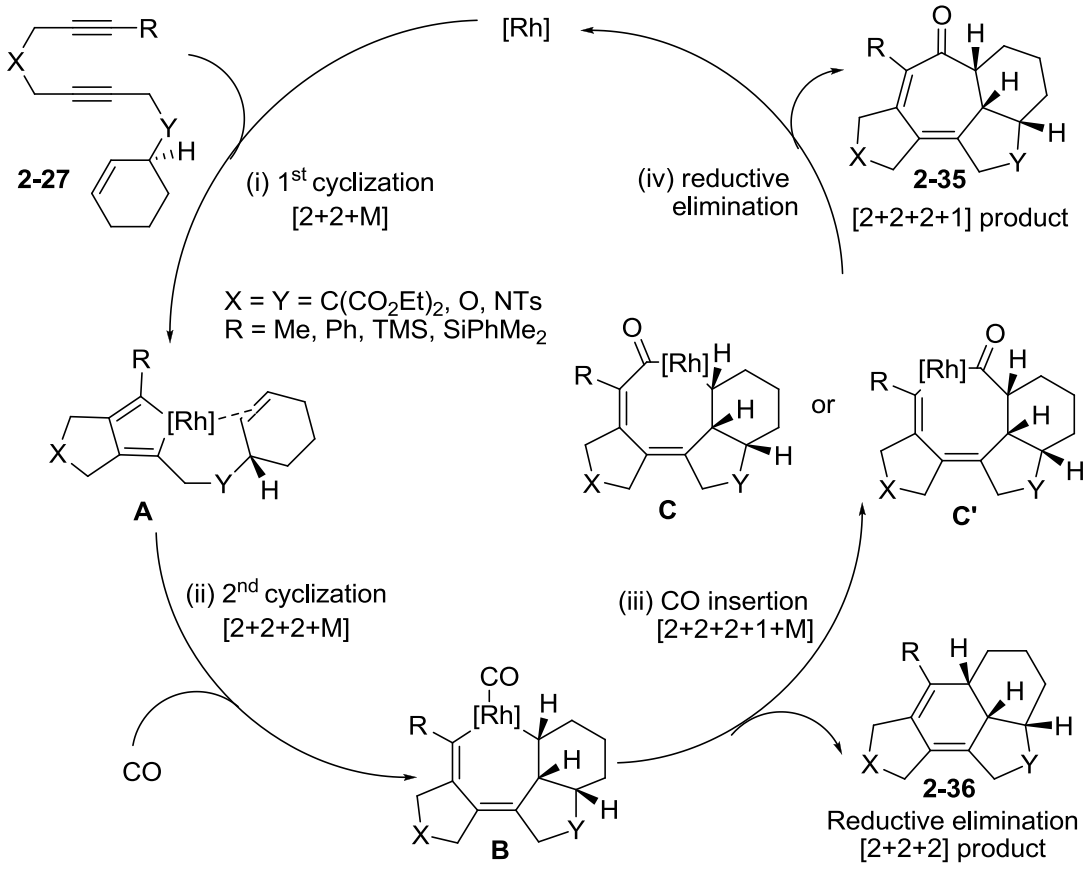
Entry	Substrate	Product 1 (yield %)[a]		Product 2 (Yield %)[a]	
(1)	 **2-27e**	 **2-35e**	(78)	(--)	
(2)	 **2-27f**	 **2-35f**	(85)	(--)	
(3)	 **2-27g**	 **2-35g**	(83)	 **2-36g**	(6)
(4)	 **2-27h**	 **2-35h**	(85)	 **2-36h**	(8)
(5)	 **2-27i**	 **2-35i**	(91)	(--)	
(6)	 **2-27j**	 **2-35j**	(74)	(--)	
(7)	 **2-27k**	 **2-35k**	(44)	 **2-36k**	(44)

E = CO_2Et

Averaged combined isolated yield of regioisomeric products based on at least two runs using 50-100 mg of substrate, 5 mol% $[Rh(CO)_2Cl]_2$, CO (2 atm) in DCE/TFE (10:1) at [0.05] for 20 h at 60 ^oC.

§ 2.2.3. Proposed mechanism for [2+2+2+1] cycloaddition

The key to the rapid construction of the 5-7-6-5 fused tetracyclic skeleton in one step from cyclohexene-diynes **2-27a-k** and CO lies in the mechanism of the [2+2+2+1] cycloaddition process.[5] As illustrated in **Scheme 2-14**, the reaction is presumed to proceed through a series of cycloadditions.



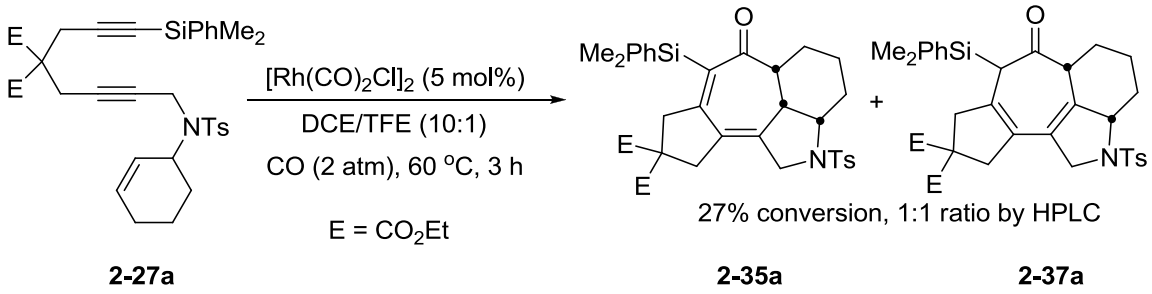
Scheme 2-14: Proposed mechanism for formation of 5-7-6-5 fused tetracyclic **2-35**

The reaction begins with the (i) selective coordination of the diyne moiety of enediyne **2-27** to the active Rh-catalyst species forming metallocycle **A** ([2+2+M]), (ii) insertion of the olefin moiety of **A** into the Rh-C bond gives the 5-7-6-5 fused tetracyclic rhodacycle **B** (2+2+2+M]), (iii) coordination of CO to the [Rh] metal followed by migratory insertion of CO into the Rh-C bond gives 5-8-6-5 rhodacycle **C** or **C'** ([2+2+2+1+M]), (iv) finally, reductive elimination gives the [2+2+2+1] cycloadduct **2-35** and regenerates the active Rh-catalyst species. Reductive elimination from rhodacycle **B**

prior to CO insertion gives [2+2+2] cycloadduct **2-36**.[2-3] The observed diastereoselectivity of the products is proposed to originate from the *endo* insertion of the olefin moiety of the cyclohexene group of **A** to form rhodacycle **B**. The formation of rhodacycle **B** also prevents the β-hydride elimination that occurred in intermediate **2-3** (**Scheme 2-1**) as the most facile pathway. Thus, this newly found feature has significantly expanded the scope of the [2+2+2+1] cycloaddition process.

The proposed mechanism for the formation of the 5-7-6-5 tetracyclics does not account for the formation of the diene-shifted isomers in cases of silyl-substituted substrates. It was initially thought that these products resulted from a Rh-catalyzed olefin isomerization of the predicted products.[7] However, with computational results indicating energy difference in favor of the diene-shifted regioisomer, at this point, it is not clear why an equal amount of products are obtained even after extending the reaction time.

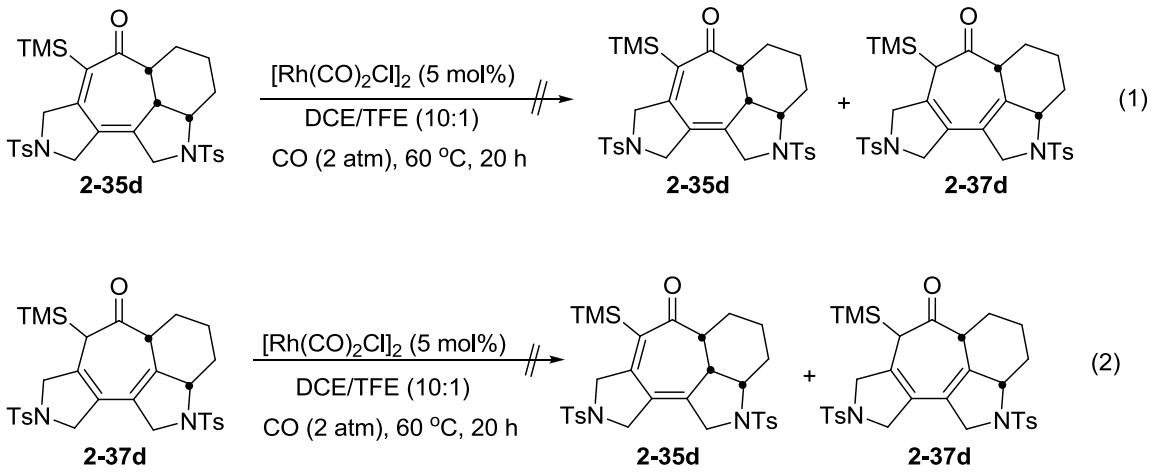
To ascertain the origins of the regioisomeric products, the reaction of **2-27a** under the optimized conditions was stopped after 3 h and the reaction mixture analyzed by HPLC. The HPLC analysis showed a 27% conversion of substrate but most important was that both products **2-35a** and **2-37a** were present in a 1:1 mixture (**Scheme 2-15**).



Scheme 2-15: [2+2+2+1] cycloaddition of cyclohexene-diyne **2-27a** with CO

Thus, the results suggest that both products are formed quite early during the reaction and the ratio of products remains relatively constant during the course of the reaction. Therefore, it is possible that the regioisomer arise either from the expected 5-7-6-5 silyl-substituted product through a [Rh]-catalyzed isomerization or from a distinctly different reaction mechanism. If these products arise from the former case, then subjecting the pure products of the less energetically favored isomers **2-35a-d** to the

reaction conditions should result in at least a mixture of regioisomeric products. To test this possibility, tetracyclic product **2-35d** isolated by preparatory HPLC, was subjected to the reaction conditions and the reaction mixture analyzed by HPLC (**Scheme 2-16, reaction 1**). Analysis of the crude reaction mixture by HPLC indicated only the presence of compound **2-35d** with no trace of the regioisomer **2-37d**. In a separate experiment, the energetically more favorable isomer **2-37d** was also subjected to the reaction conditions and HPLC analysis of the crude reaction mixture also showed no trace of isomer formation (**Scheme 2-16, reaction 2**).

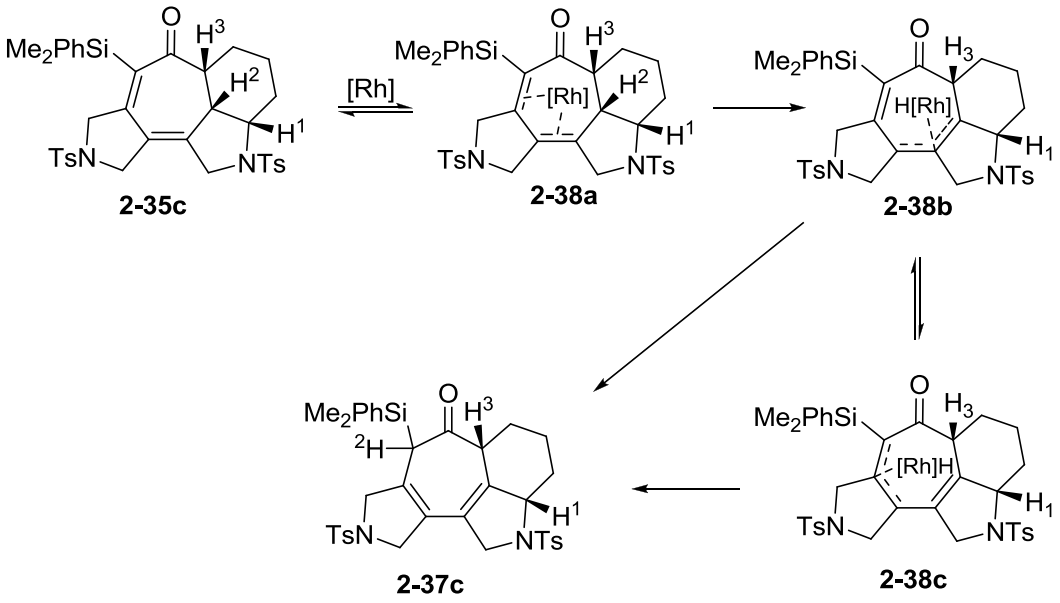


Scheme 2-16: Attempted isomerization of 5-7-6-5 tetracyclics **2-35a** and **2-37a**

These results suggest that the isomeric products may in fact be obtained from a distinctly different reaction mechanism that is only operative when silyl-substituted substrates are used in the cycloaddition reaction. In considering an alternate mechanism, products **2-35a-d** would be formed if the first cycloaddition occurred between the olefin and the internal alkyne (i.e. Pauson-Khand type reaction), followed by a second cycloaddition, CO insertion and subsequent reductive elimination. With such a scenario, the Pauson-Khand (PK) type product could also be formed. However, NMR studies of products **2-37a-d** do not support the formation of the PK type product. If such products were obtained, the quaternary carbon count on the ^{13}C NMR spectra would be expected to be two less than that found for compounds **2-37a-d**. In addition, since the second cycloaddition would not be expected to occur if the PK type products were formed, the

acetylenic carbons would be evident in the ^{13}C NMR spectra of the products; but no such observations were found.

The observed regioisomeric products **2-37a-d** could arise from a C-H activation type mechanism.[8] The current proposed mechanism using compound **2-35c** is depicted in **Scheme 2-17**. After the reductive elimination step that gives compound **2-35c** (**See step (iv) in scheme 2-14**), the catalyst coordinates to the olefins of **2-35c**, forming complex **2-38a**. Then, complex **2-38a**, undergoes C-H activation (H^2 in complex **2-38a**), giving Rh-π-allyl complex **2-38b**. Isomerization of Rh-π-allyl complex **2-38b** gives Rh-π-allyl complex **2-38c** which is stabilized by the silicon substituent through hyper-conjugation. The regioisomeric product **2-37c** is formed either from intermediate **2-38**b through a net 1,5-hydride shift from **2-38b**, followed by decomplexation or from intermediate **2-38c** through reductive elimination of **2-38c**, followed by decomplexation. Clearly, more detailed studies are needed to elucidate the mechanism for the formation of the regioisomeric products when silyl-substituted substrates are used in the cycloaddition reaction.



Scheme 2-17: Proposed mechanism for formation of compounds **2-37a-d**

§ 2.3. Conclusion

In summary, the formation of novel 5-7-6-5 fused tetracyclics from the [2+2+2+1] cycloaddition of cyclohexene-diynes with carbon monoxide was described. The carbonylated products were obtained in very high to exclusive selectivity, in good to excellent yields, and as single diastreomers. Interestingly, silyl-substituted substrates gave regioisomeric products; while alkyl substituted substrates gave single products. The process is operationally simple and thus, it is clear that this novel [2+2+2+1] cycloaddition process has opened an avenue for possible rapid construction of a library of fused tetracyclic compounds using unsaturated carbocycles and heterocycles as the *ene* component. Further studies on the scope and application as well as mechanistic studies of this unique process are underway.

§ 2.4. Experimental section

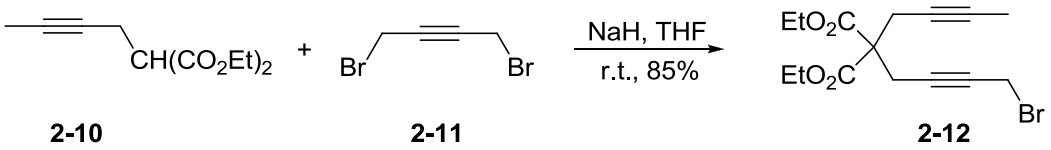
§ 2.4.1. General methods

All reactions were carried out under nitrogen or carbon monoxide in oven dried glassware using standard Schlenk techniques unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents using Fisher silica gel (60 μm particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. Analytical high performance liquid chromatography (HPLC) was performed with a Shimadzu LC 2010A system using a phenomenex Jupiter 10μ proteo 90A column (4.5 x 250 mm/mm) and gradient from 100% acetonitrile to 95:5 acetonitrile:water over 24 min with a flow rate of 1mL/min. Preparative HPLC was carried out on a Shimadzu semi-preparative LC-6AD HPLC system using a phenomenex Jupiter 10μ proteo 90A column (21.2 x 250 mm/mm) and gradient from 100% acetonitrile to 95:5 acetonitrile:water over 24 min with a flow rate of 20 mL/min. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Shimadzu FTIR-84005 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Inova-500 (500 MHz), 400 (400 MHz) or a Gemini-300 (300 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova-400 (100 MHz) or a Gemini-300 (75 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 77.0 ppm). High resolution mass spectrometry (HRMS) was carried out at the Mass Spectrometry Facility, the University of Illinois Urbana Champaign. **Caution:** Carbon monoxide is a toxic gas and thus all reactions should be carried out in a fume hood with sufficient ventilation. Solvents were reagent grade and freshly distilled before use. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from DrySolv® and used without further purification. Dichloroethane (DCE) and trifluoroethanol (TFE) were purchased from Fischer and used without purification. Carbon monoxide was purchased from Liquid Carbonic Specialty

Gases, Oak Brook, Illinois and passed through Drierite® before use. $[Rh(CO)_2Cl]_2$ was prepared by the literature method.[9]

§ 2.4.2. Synthesis of bromo-diynes

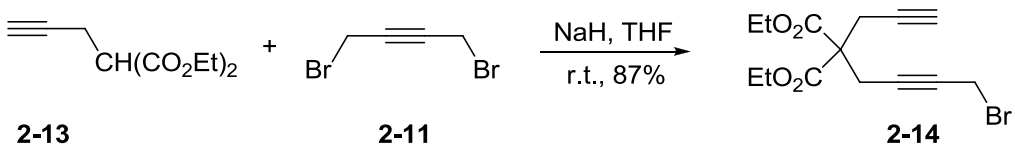
Diethyl 2-(4-Bromobut-2-ynyl)-2-(but-2-ynyl)malonate, (2-12):[2,3]



2-10 **2-11** **2-12**

Diethyl 2-(but-2-ynyl)malonate[10] **2-10** (5.00 g, 23.6 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 1.00 g, 23.6 mmol) in 80 mL of THF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of 1,4-dibromobut-2-yne **2-11** (15.0 g, 70.7 mmol) in 100 mL of THF *via* cannula over 2.5 h. The mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield yellow oil. The excess dibromobutyne **2-11** was recovered by distillation (100 ^oC/4 mmHg). The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give product **2-12** as yellow oil (6.88 g, 85%); TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.52); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 6H, *J* = 7.2 Hz), 1.75 (t, 2H, *J* = 2.7 Hz), 2.88 (q, 2H, *J* = 2.7 Hz), 3.02 (t, 2H, *J* = 2.1 Hz), 3.87 (t, 2H, *J* = 2.1 Hz), 4.25 (q, 4H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.45, 14.02, 14.69, 22.74, 22.99, 56.70, 61.69, 61.87, 72.94, 78.20, 79.14, 82.23, 168.86. All data are in agreement with those reported in the literature.[2,3]

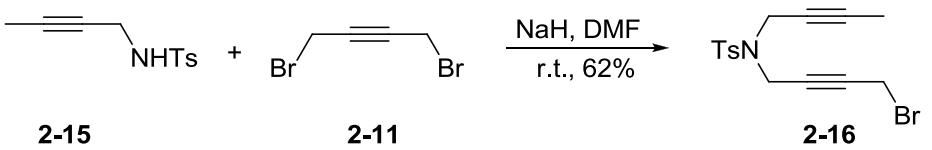
Diethyl 2-(4-Bromobut-2-ynyl)-2-(prop-2-ynyl)malonate, (2-14):[2,3]



2-13 **2-11** **2-14**

Diethyl 2-(prop-2-ynyl)malonate[11] **2-13** (6.50 g, 32.8 mmol) in 40 mL of THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 1.70 g, 42.4 mmol) in 30 mL of THF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of dibromobut-2-yne **2-11** (17.7 g, 83.4 mmol) in 50 mL of THF *via* cannula over the period of 2.5 h. The mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield dark oil. The excess dibromobutyne **2-11** was recovered by distillation (100 ^oC/4 mmHg). The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give bromodiyne **2-14** as light yellow oil (9.39 g, 87%); TLC (SiO_2, hexanes:EtOAc = 4:1, R_f = 0.33); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 6 H, *J* = 7.1 Hz), 2.03 (t, 1 H, *J* = 2.7 Hz), 2.97 (d, 2 H, *J* = 2.7 Hz), 3.05 (t, 2 H, *J* = 2.2 Hz), 3.87 (t, 2 H, *J* = 2.5 Hz), 4.24 (q, 4 H, *J* = 7.1 Hz). All data are in agreement with those reported in the literature.[2,3]

***N*-(4-Bromobut-2-ynyl)-*N*-(but-2-ynyl)-4-Methylbenzenesulfonamide, (2-16):**[2,3]

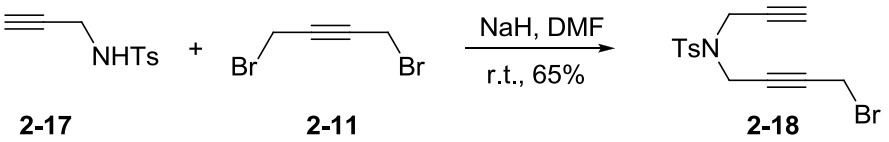


2-15 **2-11** **2-16**

N-(But-2-ynyl)-4-methylbenzenesulfonamide **2-15** (500 mg, 2.24 mmol) in 5 mL of DMF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 107 mg, 2.69 mmol) in 5 mL of DMF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of 1,4-dibromobut-2-yne **2-11**(1.50 g, 7.07 mmol) in 5 mL of DMF *via* cannula and the resulting mixture stirred at room temperature for 18 h. The mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to

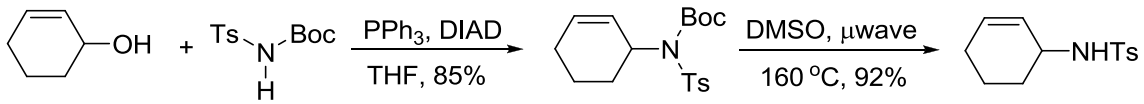
yield yellow oil. The excess dibromobutyne **2-11** was recovered by distillation (100 ^{o}C/4 mmHg). The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give bromodiyne **2-16** as viscous yellow oil (490 mg, 62%). TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (t, 3 H, *J* = 2.4 Hz), 2.43 (s, 3 H), 3.72 (t, 2 H, *J* = 2.1 Hz), 4.06 (q, 2 H, *J* = 2.4 Hz), 4.21 (d, 2 H, *J* = 2.1 Hz), 7.32 (d, 2 H, *J* = 8.4 Hz), 7.72 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.38, 13.69, 21.51, 36.49, 36.96, 71.33, 79.63, 80.43, 82.02, 127.89, 129.42, 135.30, 143.72. All data are in agreement with those reported in the literature.[2,3]

***N*-(4-Bromobut-2-ynyl)-*N*-(prop-2-ynyl)-4-methylbenzenesulfonamide, (2-18):**[2,3]



N-(Prop-2-ynyl)-4-methylbenzenesulfonamide[12] **2-17** (4.30 g, 20.1 mmol) in 25 mL of DMF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 1.15 g, 28.7 mmol) in 40 mL of DMF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of 1,4-dibromobut-2-yne **2-11** (13.1 g, 61.5 mmol) in 20 mL of DMF *via* cannula. The mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield yellow oil. The excess dibromobutyne **2-11** was recovered by distillation (100 ^{o}C/4 mmHg). The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give bromodiyne **2-18** as a yellow oil (4.23 g, 62%); TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.48); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (t, 1 H, *J* = 2.4 Hz), 2.43 (s, 3 H), 2.44 (s, 3 H), 3.71 (d, 2 H, *J* = 6.6 Hz), 3.89 (d, 2 H, *J* = 2.4 Hz), 3.90 (d, 1 H, *J* = 2.4 Hz), 3.91 (d, 1 H, *J* = 2.4 Hz), 3.96 (d, 1 H, *J* = 2.4 Hz), 3.97 (d, 1 H, *J* = 2.4 Hz), 5.18 (dd, 1 H, *J* = 1.5, 11.4 Hz), 5.20 (dd, 1 H, *J* = 1.5, 17.7 Hz), 5.68 (ddt, 1 H, *J* = 6.6, 11.4, 17.7 Hz), 7.26 (d, 2 H, *J* = 12.6 Hz), 7.30 (d, 2 H, *J* = 16.8 Hz), 7.64 (d, 2 H, *J* = 13.5 Hz), 7.68 (d, 2 H, *J* = 13.5 Hz). All data are in agreement with those reported in the literature.[2,3]

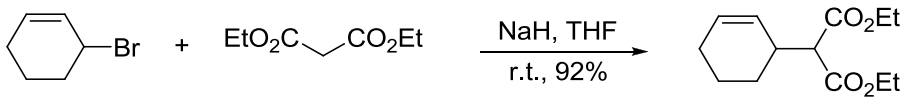
***N*-(Cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide, (2-22):**[13b]



2-19 **2-20** **2-21** **2-22**

A mixture of triphenylphosphine (4.41 g, 16.8 mmol) and diisopropylazodicarboxylate (DIAD) (3.58 g, 16.8 mmol) in THF (50 mL) was stirred for 10 min until a precipitate formed. Then, *N*-Boc-*N*-tosylamide (4.15 g, 15.3 mmol) in 30 mL of THF was added dropwise, followed by cyclohex-3-enol (1.50 g, 15.3 mmol) in 30 mL of THF. The resulting mixture was stirred overnight. The mixture was concentrated and purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleunt to give **2-21** (4.57 g, 85%) as a white solid. This product (6.14 g, 17.5 mmol) was dissolved in DMSO (30 mL) and heated in a microwave reactor at 160 ^{o}C for 4 min. Water was added and the mixture extracted with ether (3 x 50 mL). The organic layers were combined, washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to give **2-22** as a white solid(4.04 g, 92%); mp 100 -101 ^{o}C (lit.[13] 101-102 ^{o}C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60-1.52 (m, 3H), 1.79-1.76 (m, 1H), 1.91-1.93 (m, 2H), 2.43 (s, 1H), 3.79-3.85 (m, 1H), 4.48 (d, 1H, *J* = 8.4 Hz), 5.32-5.37 (m, 1H), 5.74-5.78 (m, 1H), 7.32 (d, 2H, *J* = 8.7 Hz), 7.78 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.27, 21.51, 24.48, 30.28, 48.96, 126.97, 127.03, 129.68, 131.59, 138.37, 143.24. All spectral data were consistent with that reported in the literature.[13b]

Diethyl 2-(cyclohex-2-enyl)malonate, (2-25):[14]



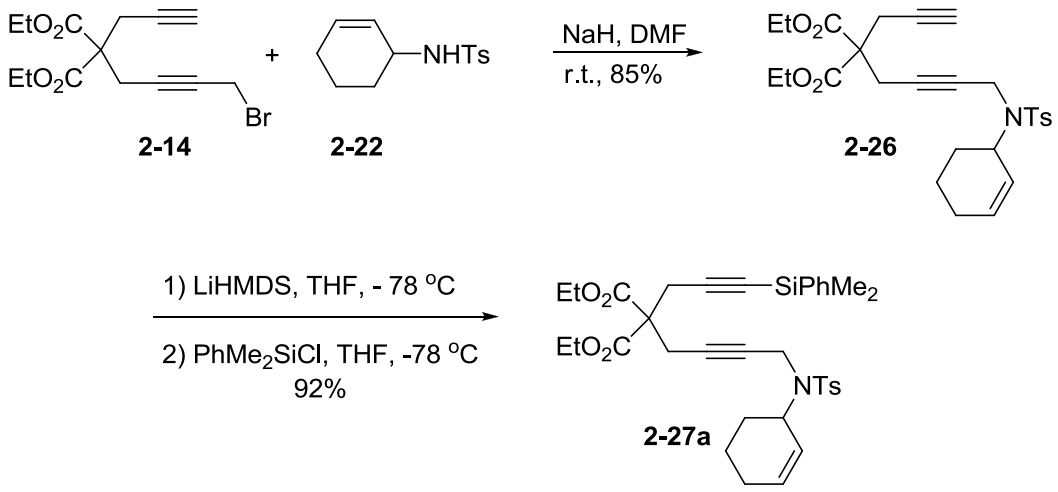
2-23 **2-24** **2-25**

Diethyl malonate **2-24** (21.00 g, 131.1 mmol) in 40 mL of THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 2.00 g, 50.0 mmol) in 100 mL of THF. The resulting mixture was stirred for 1 h at room temperature. Then 1-bromo-2-cyclohexene **2-23** (8.00 g, 49.7 mmol) in 20 mL of THF was added. The

mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield yellow oil. The product was purified by distillation (140 ^oC, 4mmHg) to give **2-25** as colorless oil (11.1g, 93%); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24-1.27 (m, 6H), 1.36-1.43 (m, 1H), 1.51-1.59 (m, 1H), 1.69-1.81 (m, 2H), 1.96-2.01 (m, 2H), 2.83-2.92 (m, 1H), 3.26 (d, 1H, *J* = 9.3 Hz), 4.18-4.21 (m, 4H), 5.52-5.56 (m, 1H), 5.73-5.78 (m, 1H). All spectral data were consistent with that reported in the literature.[14]

§ 2.4.3. Synthesis of Cyclohexene-diynes

1-Aza-1-(cyclohex-2-en-1-yl)-6,6,-dicarbethoxy-9-dimethylphenylsilyl-1-(4-methylbenzene-sulfonyl)nona-3,8-diyne, (2-27a):



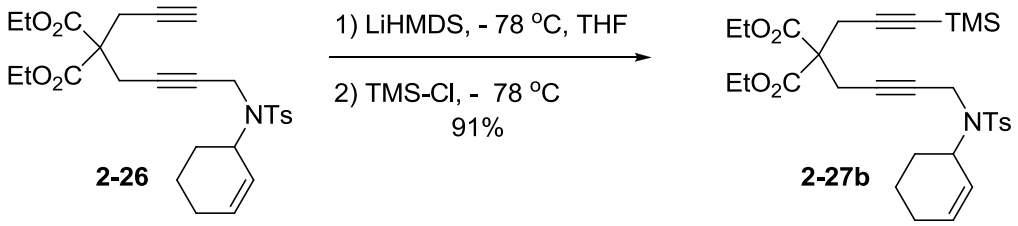
Cyclohexenylsulfonamide **2-22** (2.26 g, 8.99 mmol) in 20 mL of DMF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.440 g, 10.9 mmol) in 10 mL of DMF. The resulting solution was stirred at room temperature for 45 min and then bromodiyne **2-14** (2.96 g, 8.99 mmol) in 25 mL of DMF was added dropwise and the mixture was stirred for an additional 5 h. Water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent

gave cyclohexenediyne **2-26** as yellow oil (3.81 g, 85% yield): TLC (SiO_2, hexanes:EtOAc = 4:1, R_f = 0.34); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, 6H, *J* = 7.2 Hz), 1.48-1.55 (m, 2H), 1.65-1.72 (m, 2H), 1.92-1.95 (m, 2H), 1.99 (t, 1H, *J* = 2.4 Hz), 2.39 (s, 3H) 2.79 (t, 2H, *J* = 2.0 Hz), 2.84 (d, 2H, *J* = 2.4 Hz), 2.87 (t, 2H, *J* = 2.1 Hz), 3.90 (dt, 1H, *J* = 2.1 Hz), 4.10 (dt, 1H, *J* = 2.1 Hz), 4.15-4.21 (m, 4H), 4.40-4.43 (m, 1H), 5.29 (dd, 1H, *J* = 1.8, 10.5 Hz), 5.81-5.86 (m, 1H), 7.29 (d, 2H, *J* = 8.7 Hz), 7.77 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.87, 21.38, 21.39, 22.46, 22.67, 24.26, 27.82, 32.78, 54.82, 56.15, 61.85, 71.4, 77.99, 78.46, 80.08, 126.84, 127.17, 127.23, 129.36, 129.54, 132.73, 138.04, 142.97, 168.49; IR (neat, cm^{-1}) 3276, 2935, 1737, 1596, 1444, 1334, 1288, 1209, 1161, 1095, 1053, 1031.

To a cold solution of cyclohexenyldiyne **2-26** (0.930 g, 1.85 mmol) in 20 mL of THF was added dropwise 1 M LiHMDS (2.80 mL) in THF at -78 ^{o}C. The resulting mixture was stirred at -78 ^{o}C for 45 min and then dimethylphenylsilyl chloride (0.470 g, 2.78 mmol) in 10 mL of THF was added dropwise. The resulting mixture was then warmed slowly to -40 ^{o}C and stirred for 4 h. The reaction mixture was diluted with ether, followed by the addition of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to afford silyl-terminal cyclohexenediyne **2-27a** (1.07 g, 92% yield) as yellow oil; TLC (SiO_2, hexanes:EtOAc = 4:1, R_f = 0.40); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.37 (s, 6H), 1.25 (t, 6H, *J* = 7.2), 1.54-1.56 (m, 2H), 1.77-1.71 (m, 2H), 1.92-1.95 (m, 2H), 2.38 (s, 3H) 2.91 (t, 2H, *J* = 1.8 Hz), 2.95 (s, 2H), 3.93 (dd, 1H, *J* = 2.1, 14.1 Hz), 4.05-4.19 (m, 5H), 4.40-4.42 (m, 1H), 5.31 (d, 1H, *J* = 10.2 Hz), 5.83-5.87 (m, 1H), 7.34-7.41 (m, 5H), 7.57-7.61 (m, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ – 0.84, 13.98, 21.47, 22.88, 24.05, 24.37, 27.92, 32.91, 54.91, 56.54, 61.91, 78.22, 80.14, 86.23, 102.88, 127.28, 127.34, 127.81, 129.37, 129.44, 132.81, 133.59, 136.89, 138.12, 143.07, 168.59; IR (neat, cm^{-1}) 2979, 2937, 2358, 2179, 1735, 1334, 1207, 1161; HRMS (ES) m/z calcd for $C_{35}H_{44}NO_6SSi$ $(M + H)^+$ 634.2659, found 634.2687 (Δ 2.8 ppm).

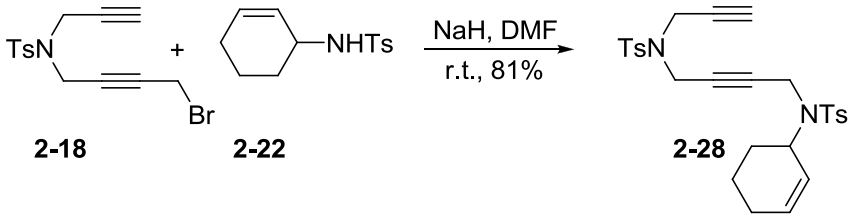
In the same manner 9-trimethylsilyl derivative **2-27b** was synthesized.

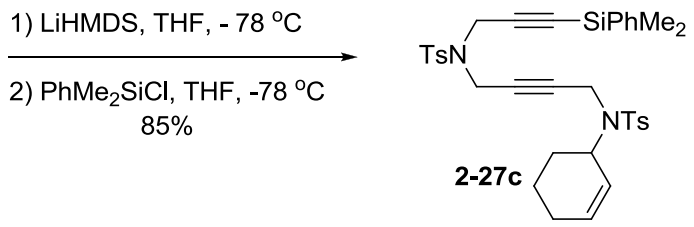
1-Aza-1-(cyclohex-2-en-1-yl)-6,6,-dicarbethoxy-9-trimethylsilyl-1-(4-methylbenzene-sulfonyl)nona-3,8-diyne, (2-27b):



Synthesized using LiHMDS (3.0 mL of 1 M solution in THF), cyclohexenyldiyne **2-26** (1.0 g, 2.0 mmol) and trimethylsilyl chloride (0.33g, 3.0 mmol) in 91% yield as yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.52); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 9H), 1.26 (t, 6H, *J* = 7.2 Hz), 1.48-1.55 (m, 2H), 1.65-1.74 (m, 2H), 1.92-1.95 (m, 2H), 2.43 (s, 3H) 2.89 (m, 4H), 3.91 (dt, 1H, *J* = 2.0 Hz), 4.11 (dt, 1H, *J* = 2.0 Hz), 4.14-4.21 (m, 4H), 4.41-4.44 (m, 1H), 5.31 (dd, 1H, *J* = 2.0, 10.0 Hz), 5.84-5.89 (m, 1H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.79 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -0.06, 14.03, 21.52, 22.79, 23.94, 24.39, 27.92, 32.94, 54.92, 56.57, 61.87, 78, 80.04, 88.19, 100.97, 127.29 127.36, 129.45, 132.79, 138.14, 143.05, 168.61; IR (neat, cm^{-1}) 2979, 2937, 2177, 1739, 1336, 1207, 1163; HRMS (ES) m/z calcd for $C_{30}H_{42}NO_6SSi$ $(M + H)^+$ 572.2502, found 572.2501 (Δ - 0.1 ppm).

1,6-Bis(4-methylbenzenesulfonyl)-1-(cyclohex-2-en-1-yl)-1,6-diaza-9-dimethylphenylsilylnona-3,8-diyne, (2-27c):





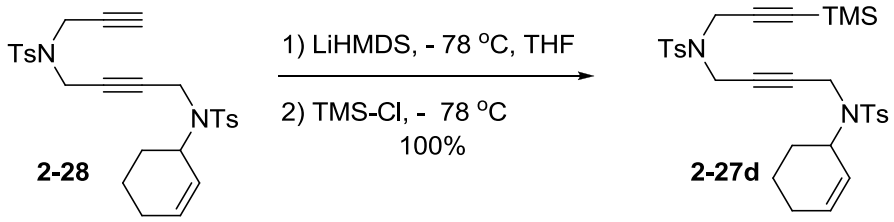
Cyclohexenylsulfonamide **2-22** (1.22 g, 4.84 mmol) in 10 mL of DMF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.240 g, 6.05 mmol) in DMF (5 mL). The resulting solution was stirred at room temperature for 45 min and then bromodiyne **2-18** (2.06 g, 6.05 mmol) in 10 mL of DMF was added dropwise and the mixture was stirred for an additional 5 h. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 15% EtOAc in hexanes as eluent gave cyclohexenediyne **2-28** as a white solid (2.01 g, 81%): mp 96-98 ^oC; TLC (SiO_2, hexanes:EtOAc = 4:1, R_f = 0.25); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54-1.69 (m, 2H), 1.71-1.75 (m, 2H), 1.92-1.95 (m, 2H), 2.09 (t, 1H, *J* = 2.7 Hz), 2.43 (s, 3H), 3.87 (dt, 1H, *J* = 2.4 Hz), 4.02 (dt, 1H, *J* = 2.4 Hz), 4.03 (d, 4H, *J* = 2.4 Hz), 4.43-4.47 (m, 1H), 5.27 (dd, 1H, *J* = 1.8, 10.5 Hz), 5.83-5.86 (m, 1H), 7.31 (dd, 4H, *J* = 2.4, 9.0 Hz), 7.76 (m 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.64, 21.78, 24.59, 28.18, 32.95, 36.34, 36.69, 55.18, 74.11, 74.16, 76.45, 82.76, 127.37, 127.52, 128.06, 129.79, 133.25, 135.45, 138.22, 143.57, 144.19; IR (in $CHCl_3$, cm^{-1}) 3272, 2929, 1596, 1448, 1350, 1163, 1095, 1031.

To a cold solution of cyclohexenyldiyne **2-28** (0.650 g, 1.27 mmol) in 15 mL of THF was added dropwise 1 M LiHMDS (1.90 mL) in THF at -78 ^oC. The resulting mixture was stirred at -78 ^oC for 45 min and then dimethylphenylsilyl chloride (0.330 g, 1.90 mmol) in 5 mL of THF was added dropwise. The resulting mixture was then warmed slowly to -40 ^oC and stirred for 4 h. The reaction mixture was diluted with ether, followed by the addition of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to afford silyl-terminal cyclohexenediyne **2-27c** as yellow oil (0.70 g, 85% yield); TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.43); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.27 (s, 6H), 1.56-1.60 (m, 2H), 1.71-1.74 (m, 2H), 1.90-1.92(m, 2H), 2.34 (s, 3H), 2.40 (s, 3H), 3.88 (dt, 1H, *J*

= 2.1 Hz), 4.00-4.13 (m, 5H), 4.40-4.46 (m, 1H), 5.28 (dd, 1H, *J* = 1.5, 12.0 Hz), 5.81-5.87 (m, 1H), 7.21 (d, 2H, *J* = 8.1 Hz), 7.37-7.48 (m, 7 H), 7.69 (d, 2H, *J* = 8.1 Hz), 7.78 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ – 1.15, 21.38, 21.49, 24.34, 27.94, 32.76, 36.51, 37.13, 54.92, 76.36, 82.36, 89.27, 99.14, 127.15, 127.28, 127.78, 127.88, 129.56, 129.59, 129.68, 133.01, 133.49, 135.27, 136.20, 137.98, 143.35, 143.80; IR (neat, cm^{-1}) 2952, 2929, 2177, 1597, 1429, 1334, 1163; HRMS (ES) m/z calcd for $C_{35}H_{41}N_2O_4S_2Si$ $(M + H)^+$ 645.2277, found 645.2247 (Δ - 3.0 ppm).

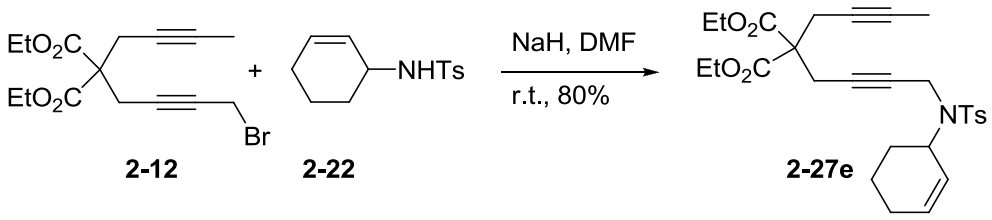
In the same manner 9-trimethylsilyl derivative **2-27d** was synthesized.

1,6-Bis(4-methylbenzenesulfonyl)-1-(cyclohex-2-en-1-yl)-1,6-diaza-9-trimethylsilylnona-3,8-diyne, (2-27d):



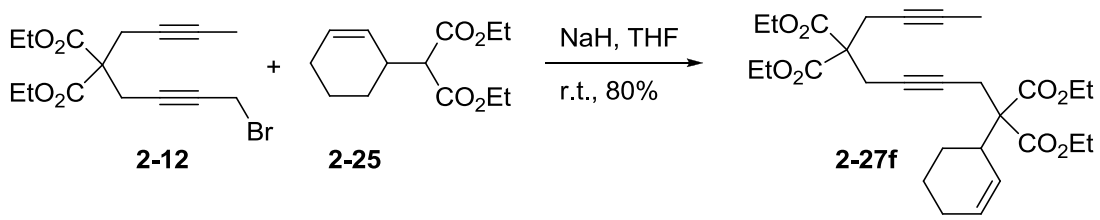
Synthesized using LiHMDS (3.0 mL of 1 M solution in THF), cyclohexenyldiyne **2-28** (0.50 g, 0.098 mmol) and trimethylsilyl chloride (0.21 g, 1.96 mmol) in 100% yield as white solid; mp = 88-89 °C; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.43); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 9H), 1.51-1.56 (m, 2H), 1.62-1.71 (m, 2H), 1.89 (bs, 2H), 2.36 (s, 3H), 2.38 (s, 3H), 3.83 (dt, 1H, *J* = 2.4 Hz), 4.00 (m, 5H), 4.40-4.43 (m, 1H), 5.24 (dd, 1H, *J* = 1.5, 12.0 Hz), 5.78-5.82 (m, 1H), 7.38 (m, 4H), 7.64 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -0.40, 21.41, 21.53, 24.36, 27.93, 32.76, 36.43, 37.06, 54.91, 76.46, 82.25, 91.18, 97.34, 127.21, 127.32, 127.85, 129.59, 133.04, 135.39, 138.04, 143.36, 143.78; IR (in $CHCl_3$, cm^{-1}) 3026, 2958, 2177, 1647, 1596, 1494, 1350, 1249, 1163, 1095, 1032; HRMS (ES) m/z calcd for $C_{30}H_{39}N_2O_4S_2Si$ $(M + H)^+$ 583.2121, found 583.2104 (Δ - 1.7 ppm).

1-Aza-1-(cyclohex-2-en-1-yl)-6,6-dicarbethoxy-1-(4-methylbenzenesulfonyl)nona-3,8-diyne, (2-27e):



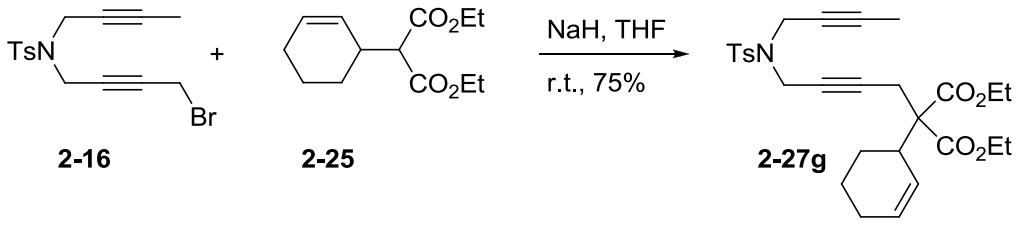
N-Cyclohexenyl-*N*-tosylamide **2-22** (0.40 g, 1.6 mmol) in 4 mL of DMF was added dropwise to a suspension of NaH, (60% dispersion in mineral oil 82 mg, 2.1 mmol) in 3 mL of DMF. The resulting solution was stirred at room temperature for 45 min and then # (0.55 g, 1.6 mmol) in 5 mL of DMF was added dropwise and the mixture was stirred for an additional 5 h. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent gave cyclohexene-diyne **2-27e** as light yellow oil (0.65 g, 80 %); TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.46); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21-1.24 (m, 6H), 1.48-1.55 (m, 2H), 1.67-1.74 (m, 5H), 1.93-1.94 (m, 2H), 2.42 (s, 3H) 2.79 (t, 2H, *J* = 2.0 Hz), 2.86 (t, 2H, *J* = 2.0 Hz), 3.90 (dt, 1H, *J* = 2.0 Hz), 4.10 (dt, 1H, *J* = 2.0 Hz), 4.15-4.22 (m, 4H), 4.40-4.43 (m, 1H), 5.30 (d, 1H, *J* = 10.4 Hz), 5.83-5.86 (m, 1H), 7.30 (d, 2H, *J* = 8.8 Hz), 7.78 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.42, 13.95, 21.45, 22.70, 22.75, 22.88, 24.32, 27.86, 32.89, 54.87, 56.55, 61.66, 61.70, 73.09, 78.42, 78.83, 79.89, 127.28, 127.35, 129.39, 132.74, 138.13, 142.99, 168.93; IR (neat, cm^{-1}) 2979, 2921, 1734, 1326, 1290, 1209, 1161, 1095, 1051; HRMS (ES) m/z calcd for $C_{28}H_{36}NO_6S$ $(M + H)^+$ 514.2263, found 514.2255 (Δ = -0.8 ppm).

1-(Cyclohex-2-en-1-yl)-,1,16,6-tetracarbethoxydeca-3,8-diyne, (2-27g):



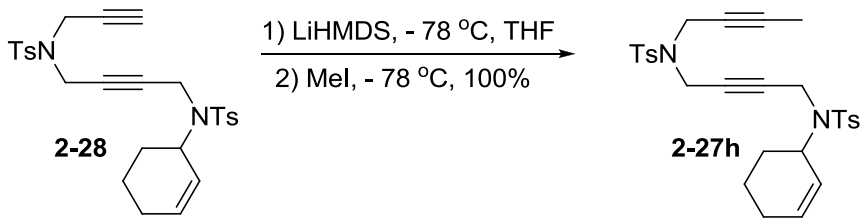
Diethyl 2-(cyclohex-2-en-1-yl) malonate **2-25** (0.650 g, 2.73 mmol) in 10 cm^3 of THF was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil 0.130 g, 3.28 mmol) in THF (10 mL). The resulting solution was stirred at room temperature for 30 min and then **2-12** (0.940 g, 2.73 mmol) in 10 mL of THF was added dropwise and the mixture was stirred for additional 5 h. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent gave **2-27f** (1.10 g, 80%) as yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.52); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20-1.28 (m, 12H), 1.52-1.59 (m, 2H), 1.74 (t, 3H, *J* = 2.7 Hz), 1.76-1.80 (m, 2H), 1.90-1.94 (m, 2H), 2.82 (dt, 2H, *J* = 2.4 Hz), 2.85-2.90 (m, 4H), 3.03-3.08 (m, 1H), 4.12-4.25 (m, 8H), 5.73 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.44, 13.97, 14.01, 14.05, 22.25, 22.70, 22.76, 24.16, 24.89, 38.35, 56.71, 60.06, 61.16, 61.22, 61.68, 73.24, 77.41, 78.35, 78.72, 128.01, 128.47, 169.04, 169.72, 169.88; IR (neat, cm^{-1}) 3033, 2979, 2935, 2181, 1737, 1733, 1367, 1193; HRMS (ES) m/z calcd for $C_{28}H_{39}O_8$ $(M + H)^+$ 503.2645, found 503.2638 (Δ = -0.7 ppm).

6-Aza-1-(cyclohex-2-en-1-yl)-,1,1-dicarbethoxy-6-(4-methylbenzenesulfonyl)deca-3,8-diyne, (2-27g):



Diethyl 2-(cyclohex-2-enyl) malonate **2-25** (0.41 g, 1.7 mmol) in 5 mL of THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 88 mg, 2.2 mmol) in THF (5 mL). The resulting solution was stirred at room temperature for 30 min and then bromodiyne **2-16** (0.60 g, 1.7 mmol) in 5 mL of THF was added dropwise and the mixture was stirred for an additional 5 h. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent gave **2-27g** (0.65 g, 75%) as white solid; mp 69-70 ^oC; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.40); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19-1.29 (m, 7H), 1.48-1.54 (m, 1H), 1.62 (t, 3 H, *J* = 2.4 Hz), 1.69-1.76 (m, 2H), 1.91-1.94 (m, 2H), 2.41 (s, 3H), 2.69 (dt, 1H, *J* = 2.1 Hz), 2.78 (dt, 1H, *J* = 2.1 Hz), 2.98-3.02 (m, 1H), 4.02-4.07 (m, 4H), 4.12-4.22 (m, 4H), 5.64-5.70 (m, 2H), 7.32 (d, 2H, *J* = 8.7 Hz), 7.70 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.31, 14.04, 21.47, 22.24, 22.52, 24.16, 24.84, 36.46, 36.52, 38.63, 59.94, 61.29, 61.33, 71.39, 75.53, 81.30, 81.64, 127.66, 127.89, 128.71, 129.29, 135.49, 143.47, 169.54, 169.73; IR (in $CHCl_3$, cm^{-1}) 2979, 2933, 2178, 1726, 1352, 1163; HRMS (ES) m/z calcd for $C_{28}H_{36}NO_6S$ $(M + H)^+$ 514.2263, found 514.2261 (Δ - 0.2 ppm).

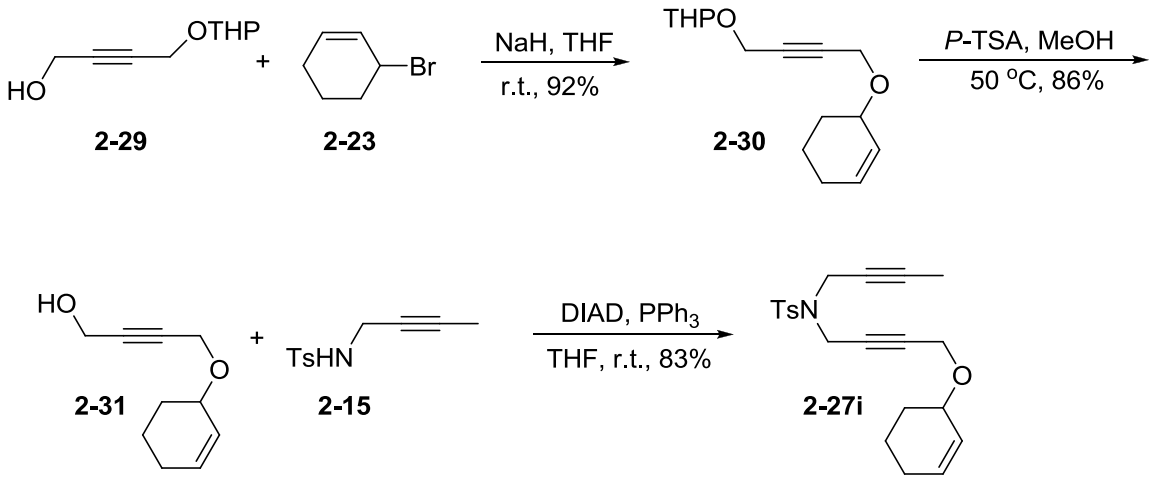
1,6-Bis(4-methylphenylsulfonyl)-1-(cyclohex-2-en-1-yl)- 1,6-diazadeca-3,8-diyne, (2-27h):



To a cold solution of **2-28** (0.500 g, 0.098 mmol) in 10 mL of THF was added dropwise 1.2 M LiHMDS (1.63 mL) in THF at -78 ^oC. The resulting mixture was stirred at -78 ^oC for 45 min and then methyl iodide (0.560 g, 3.92 mmol) was added dropwise. The resulting mixture was warmed slowly to -40 ^oC and stirred for 4 h. The reaction mixture was diluted with ether, followed by the addition of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer was washed with brine, dried

over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to give methyl-terminal cyclohexenediyne **2-27h** (0.513 g, 100% yield) as viscous yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.31); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46-1.53 (m, 5H), 1.64-1.67 (m, 2H), 1.86 (bs, 2H), 2.34 (s, 6H), 3.76 (dt, 1H, *J* = 2.4 Hz), 3.92 (m, 5H), 4.37-4.38 (m, 1H), 5.22 (d, 1H, *J* = 10.0 Hz), 5.75-5.78 (m, 1H), 7.38 (d, 4H, *J* = 8.0 Hz), 7.62 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.19, 21.24, 21.36, 24.19, 27.75, 32.62, 36.28, 36.52, 54.77 71.11, 76.44, 81.71, 82.03, 126.96, 127.12, 127.74, 129.24, 129.39, 132.84, 135.19, 137.82, 143.19, 143.56; IR (in $CHCl_3$, cm^{-1}) 3028, 2921, 1627, 1596, 1348, 1161, 1095, 1031; HRMS (ES) m/z calcd for $C_{28}H_{33}N_2O_4S_2$ $(M + H)^+$ 525.1882, found 525.1902 (Δ 2.0 ppm).

6-Aza-1-(4-cyclohex-2-en-1-yl)-6-(4-methylbenzenesulfonyl)-1-oxadeca-3,8-diyne, (2-27i):



1-Tetrahydropyranyl(THP)butyne-1,4-diol[15] **2-29** (775 mg, 4.56 mmol) in 15 mL of THF was added dropwise to a suspension of NaH, (60% dispersion in mineral oil 237 mg, 5.93 mmol) in THF (5 mL). The resulting solution was stirred at room temperature for 30 min and then 3-bromocyclohex-1-ene **2-23** (734 mg, 4.56 mmol) in 10 mL of THF was added dropwise and the mixture was stirred overnight. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude

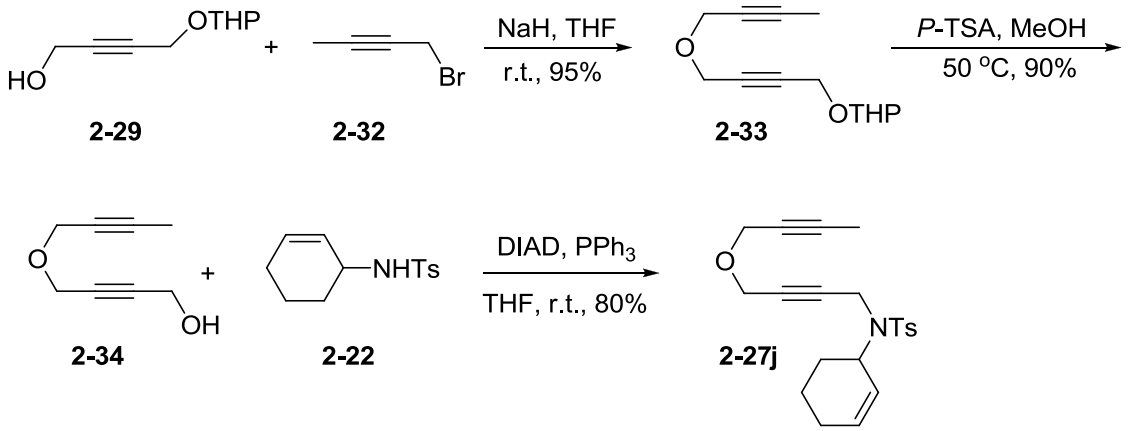
product by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent gave 1-THP-4-(cyclohex-2-en-1-yl)but-2-yne-1,4-diol **2-30** (1.05 g, 92%) as light yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.64); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1. 84-1.94 (m, 10H), 1.95-1.98 (m, 1H), 2.00-2.04 (m, 1H), 3.49-3.54 (m, 1H), 3.80-3.86 (m, 1H), 4.05-4.07 (m, 1H), 4.23-4.24 (m, 2H), 4.27-4.28 (m, 1H), 4.30-4.32 (m, 1H), 4.81 (t, 1H, *J* = 3.2 Hz), 5.74-5.79 (m, 1H), 5.85-5.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.04, 19.06, 25.15, 25.33, 28.04, 30.23, 54.43, 55.56, 62.01, 71.67, 81.74, 82.58, 96.83, 127.13, 131.41.

p-Toluenesulfonic acid (*p*-TSA, 372 mg, 1.96 mmol) was added to a solution of eneyne-THP ether **2-30** (980 mg, 3.91 mmol) in MeOH (50 mL). The solution was then heated at 50 ^{o}C overnight. The solution was cooled to room temperature and then solid $NaHCO_3$ was added portionwise. The mixture was then diluted with water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 25% EtOAc in hexanes as eluent gave 1-(cyclohex-2-en-1-yl)but-2-yne-1,4-diol **2-31** (559 mg, 86 %) as yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.24); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54- 1.59 (m, 1H), 1.64-1.83 (m, 3H), 1.95-2.04 (m, 2H), 4.03-4.07 (m, 1H), 4.17-4.24 (m, 2H), 4.29-4.31 (m, 2H), 5.74-5.74 (m, 1H), 5.85-5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.01, 25.13, 28.00, 51.11, 55.47, 71.87, 82.37, 84.07, 126.96, 131.57.

Diisopropyl azodicarboxylate (DIAD) (694 mg, 3.26 mmol) was added to a solution of triphenylphosphine (856 mg, 3.26 mmol) in 10 mL of THF. After formation of a solid, *N*-(but-2-ynyl)-*N*-(4-methylbenzene) sulfonamide **2-15** (583 mg, 2.61 mmol) in 10 mL of THF was added, followed by the addition of eneynol **2-31** (434 mg, 2.61 mmol) in 5 cm^3 of THF. The resulting mixture was stirred overnight and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to give **2-27i** (802 mg, 83%) as colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.48); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55-1.61 (m, 1H), 1.63-1.65 (m, 4H), 1.67-1.75 (m, 2H), 1.96-2.03 (m, 2H), 2.41 (s, 3H), 3.92 (m, 1H), 4.08 (m, 4H), 4.17(t, 2H, *J* = 1.8 Hz), 5.66-5.71

(1H), 5.83-5.88 (m, 1H), 7.30 (d, 2H, J = 8.4 Hz), 7.72 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.36, 18.97, 21.50, 25.13, 27.99, 36.51, 36.79, 55.28, 71.43, 71.59, 78.42, 81.89, 82.25, 126.96, 127.97, 129.33, 131.50, 135.48, 143.56; IR (neat, cm^{-1}) 3026, 2929, 2179, 1596, 1350, 1163; HRMS (ES) m/z calcd for $C_{21}H_{26}NO_3S$ $(M + H)^+$ 372.1633, found 372.1638 (Δ = 0.5 ppm).

1-(Cyclohex-3-en-1-yl)-1-(4-methylbenzenesulfonyl)-6-oxadeca-3,8-diyne, (2-27j):

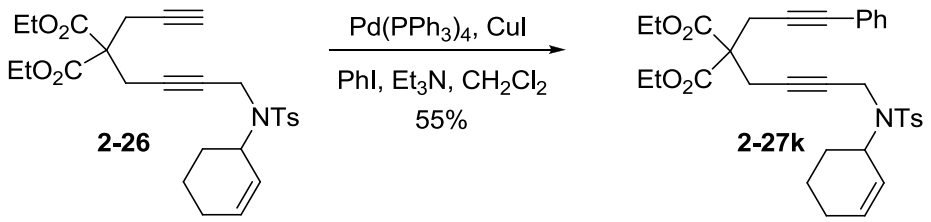


1-Tetrahydropyranyl (THP)-butynediol **2-29** (2.00 g, 11.8 mmol) in 25 mL of THF was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil 0.611 g, 15.3 mmol) in THF (10 mL). The resulting solution was stirred at room temperature for 30 min and then 1-bromobut-2-yne **2-32** (1.56 g, 11.8 mmol) in 15 mL of THF was added dropwise and the mixture was stirred overnight. Water was added to quench the reaction and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent gave 1-THP-*O*-5-oxanona-2,7-diyne (**2-33**, 2.48 g, 95%) as light yellow oil; TLC (SiO_2, hexanes:EtOAc = 2:1, R_f = 0.66); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (m, 4H), 1.81 (m, 2H), 1.85 (t, 3H, J = 2.4 Hz), 3.50-3.55 (m, 1H), 3.78-3.86 (m, 1H), 4.19 (q, 2H, J = 2.4 Hz), 4.27-4.31 (m, 3H), 4.35 (t, 1H, J = 1.8 Hz), 4.80 (t, 1H, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.56, 19.01, 25.32, 30.21, 54.24, 56.63, 57.13, 61.98, 74.31, 81.34, 82.68, 83.08, 96.83.

p-Toluenesulfonic acid (*p*-TSA) (1.28 g, 6.73 mmol) was added to a solution of **2-33** (2.35 g, 10.6 mmol) in MeOH (40 mL). The solution was then heated at 50 ^{o}C overnight. The resulting solution was cooled to room temperature and then solid $NaHCO_3$ was added portionwise. The mixture was diluted with water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 25% EtOAc in hexanes as eluent gave 1-hydroxy-5-oxanona-2,7-diyne **2-34** (1.32 g, 90%) as yellow oil. TLC (SiO_2, hexanes:EtOAc = 2:1, R_f = 0.30); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 (t, 3H, *J* = 1.2 Hz), 3.01 (bs, 1H), 4.16 (q, 2H, *J* = 1.2 Hz), 4.22 (t, 2H, *J* = 1.8 Hz), 4.25 (t, 2H, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.53, 50.97, 56.50, 57.17, 74.15, 81.09, 83.23, 84.92.

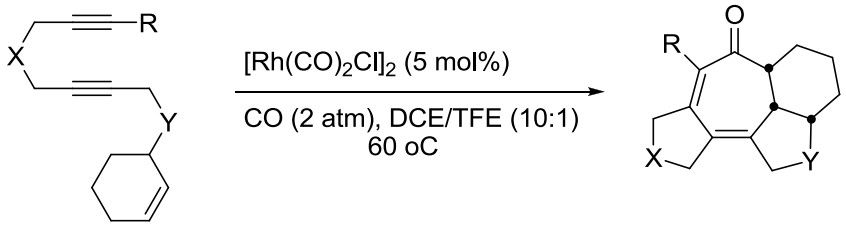
DIAD (614 mg, 3.04 mmol) was added to a solution of triphenylphosphine (796 mg, 3.04 mmol) in 10 mL of THF. After formation of a solid, **2-22** (637 mg, 2.53 mmol) in 10 mL of THF and then hydroxydiyne **2-34** (350 mg, 2.53 mmol) in 10 mL of THF were added. The resulting mixture was stirred overnight and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to give **2-27j** (752 mg, 80%) as light yellow viscous oil; TLC (SiO_2, hexanes:EtOAc = 2:1, R_f = 0.52); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55-1.61 (m, 2H), 1.69-1.79 (m, 2H), 1.87 (t, 3H, *J* = 2.4 Hz), 1.93-1.97 (m, 2H), 2.42 (s, 3H), 3.99 (dt, 1H, *J* = 2.1 Hz), 4.09 (q, 2H, *J* = 2.4 Hz), 4.12-4.18 (m, 3H), 4.48-4.55 (m, 1H), 5.32 (d, 1H, *J* = 10.3 Hz), 5.83-5.85 (m, 1H), 7.31 (d, 2H, *J* = 8.4 Hz), 7.81 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.57, 21.42, 21.48, 24.34, 27.98, 32.94, 55.03, 56.52, 56.96, 74.31, 79.19, 82.97, 83.32, 127.19, 127.38, 129.40, 133.01, 138.12, 143.11; IR (neat, cm^{-1}) 2921, 1627, 1340, 1161, 1095, 1074, 1031; HRMS (ES) m/z calcd for $C_{21}H_{26}NO_3S$ $(M + H)^+$ 372.1633, found 372.1648 (Δ = 1.5 ppm).

1-Aza-1-(cyclohex-2-en-1-yl)-6,6,-dicarbethoxy-1-(4-methylbenzenesulfonyl)-9-phenylnona-3,8-diyne, (2-27k):



Iodobenzene (0.24 g, 1.2 mmol) in 4 mL of CH_2Cl_2 was added to a mixture of $Pd(PPh_3)_4$ (0.035 g, 0.05 mmol) and CuI (0.02 g, 0.10 mmol) in 10 mL of CH_2Cl_2 and 5 mL of Et_3N. Then cyclohexenediyne **2-26** (0.50 g, 1.0 mmol) in 4 mL of CH_2Cl_2 was added dropwise via syringe. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and then washed with saturated NH_4Cl solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to yield phenyl-terminal cyclohexenediyne **2-27k** (0.32 g, 55% yield) as yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.47); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (dt, 6H, *J* = 0.8, 7.2 Hz), 1.54-1.56 (m, 2H), 1.71-1.77 (m, 2H), 1.92-1.95 (m, 2H), 2.35 (s, 3H) 2.95 (t, 2H, *J* = 2.0 Hz), 3.10 (s, 2H), 3.95 (dd, 1H, *J* = 1.6, 18.4 Hz), 4.14 (dd, 1H, *J* = 1.6, 18.4 Hz), 4.20-4.27 (m, 4H), 4.41-4.45 (m, 1H), 5.25 (d, 1H, *J* = 10.4 Hz), 5.86-5.89 (m, 1H), 7.30 (m, 5H), 7.37 (m, 2H), 7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.01, 21.38, 21.46, 22.95, 23.49, 24.35, 27.90, 32.90, 54.90, 56.63, 61.89, 78.30, 80.15, 83.58, 84.00, 123.05, 127.29, 127.32, 128.02, 128.19, 129.40, 131.57, 132.78, 138.11, 143.06, 168.74; IR (neat, cm^{-1}) 3026, 2935, 1733, 1730, 1652, 1596, 1558, 1490, 1423, 1328, 1193, 1161, 1095, 1051, 1031; HRMS (ES) m/z calcd for $C_{33}H_{38}NO_6S$ $(M + H)^+$ 576.2420, found 576.2410 (Δ - 1.0 ppm).

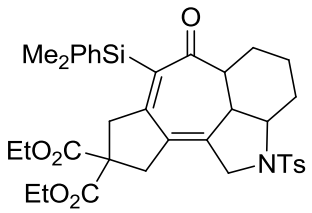
§ 2.4.4. [2+2+2+1] Cycloaddition of Cyclohexene-diynes with Carbon Monoxide



Typical procedure is described for the reaction of cyclohexene-diyne **2-35a**: A 25 mLround bottomed flask charged with an **2-27a** (100 mg, 0.19 mmol) in DCE/TFE (10:1) (3.90 mL, [0.05 M] and $[Rh(CO)_2Cl]_2$ (3.8 mg, 0.009 mmol) was transferred to a 125 mL stainless steel autoclave and purged with CO and released (4x) (**Caution must be done in a well ventilated fume hood**) and then charged with CO to 2 atm. The autoclave was immersed in an oil bath at 60 ^oC for 20 h. The autoclave was allowed to cool to room temperature, followed by release of the gas in a well ventilated fume hood. The reaction mixture was concentrated under reduced pressure and the resulting crude product was purified by column chromatography on silica gel using EtOAc/hexanes (15/85) as eluent to give fused tetracyclic product **2-35a** (86 mg, 92%) as light yellow oil.

For **2-35a-d** arising from 9-silyl-cyclohexene-diynes **2-27a-d**, two regioisomers were separated by preparative HPLC using a phenomenex Jupiter 10µ proteo 90A column (21.2 x 250 mm/mm) and gradient from 100% acetonitrile to 95:5 acetonitrile:water over 24 min with a flow rate of 20 mL/min.

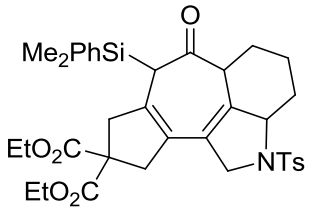
7-[Dimethyl(phenyl)silyl]-2,9-bis[(4-methylphenyl)sulfonyl]-2,2a,3,4,5,5a,8,9,10,10c-decahydroazuleno[4,5,6-*cd*]indole-9,9(1*H*)-dicarboxylate, (2-35a):



Colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.24); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.40 (s, 3H), 0.43 (s, 3H), 0.85-1.13 (m, 3H), 1.54 (t, 1H, *J* = 9.6 Hz), 1.59-1.62 (m, 1H), 1.93-2.04 (m, 2H), 2.13-2.17 (m, 1H), 2.42 (s, 3H), 2.45 (s, 3H), 3.27 (d, 1H, *J* =

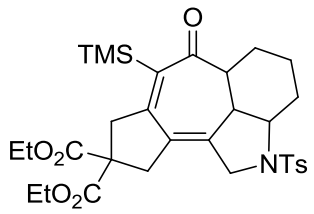
11.2 Hz), 3.63-3.68 (m, 1H), 3.75-3.89 (m, 5H), 7.23 (d, 2H, *J* = 8.0 Hz), 7.27-7.43 (m, 9H), 7.73 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.11, -1.43, 21.54, 28.49, 30.12, 36.93, 41.16, 47.00, 50.34, 53.69, 55.44, 58.39, 61.39, 127.05, 127.15, 128.14, 129.62, 129.87, 133.71, 134.02, 135.61, 136.72, 140.12, 141.35, 143.59, 143.86, 199.65; HRMS (ES) m/z calcd for $C_{36}H_{44}NO_7SiS$ $(M + H)^+$ 662.2226, found 662.2242 (Δ 1.6 ppm).

Diethyl-7-[dimethyl(phenyl)silyl]-2-[(4-methylphenyl)sulfonyl]-6-oxo-2,2a,3,4,5,5a,6,7,8,10-decahydroazuleno[4,5,6-*cd*]indole-9,9(1*H*)-dicarboxylate, (2-37a):



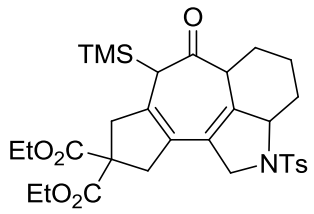
Colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.28); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.40 (d, 6H, *J* = 7.8 Hz), 1.10-1.28 (m, 8H), 1.45-1.61 (m, 4H), 1.72-1.76 (m, 1H), 2.02-2.09 (m, 1H), 2.43 (s, 3H), 2.49-2.53 (m, 1H), 2.70-2.87 (m, 4H), 3.92-4.15 (m, 6H), 7.29-7.33 (m, 5H), 7.54 (d, 2H, *J* = 8.7 Hz), 7.72 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -1.49, -1.15, 13.86, 13.94, 21.52, 21.62, 23.72, 28.76, 39.25, 42.17, 44.98, 48.97, 50.79, 57.35, 60.51, 61.77, 61.81, 127.00, 127.92, 129.16, 129.99, 132.07, 133.85, 136.04, 137.25, 137.82, 143.74, 150.55, 179.18, 170.57, 207.10; IR (neat, cm^{-1}) 2977, 2929, 1734, 1731, 1664, 1251, 1161; IR (neat, cm^{-1}) 2935, 1743, 1731, 1662, 1301, 1251, 1161; HRMS (ES) m/z calcd for $C_{36}H_{44}NO_7SiS$ $(M + H)^+$ 662.2608, found 662.2609 (Δ 0.1 ppm).

Diethyl-2-[(4-methylphenyl)sulfonyl]-6-oxo-7-(trimethylsilyl)-2,2a,3,4,5,5a,6,8,10,10c-decahydroazuleno[4,5,6-*cd*]indole-9,9(1*H*)-dicarboxylate, (2-35b):



Colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.37); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 9H), 0.85-1.07 (m, 3H), 1.26 (t, 6H, *J* = 7.2 Hz), 1.64 (t, 2H, *J* = 9.6 Hz), 2.01 (m, 2H), 2.09-2.16 (m, 1H), 2.43 (s, 3H), 2.77-2.83 (m, 2H), 3.06 (dd, 1H, *J* = 1.8 Hz), 3.35 (dd, 1H, *J* = 1.8 Hz), 3.40 (d, 1H, *J* = 11.4 Hz), 3.79 (d, 1H, *J* = 11.4 Hz), 3.87-3.96 (m, 1H), 4.13-4.22 (m, 4H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.75 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -1.02, 13.97, 21.65, 28.54, 30.14, 36.43, 36.49, 40.33, 41.32, 46.87, 55.76, 58.41, 60.16, 61.88, 61.95, 62.25, 127.16, 129.73, 136.03, 142.78, 143.41, 143.52, 170.98, 171.27, 201.15; IR (neat, cm^{-1}) 2948, 2869, 2256, 1766, 1728, 1598, 1463, 1348, 1251, 1164, 1093, 1058; HRMS (ES) m/z calcd for $C_{31}H_{42}NO_7SiS$ $(M + H)^+$ 600.2451, found 600.2454 (Δ 0.3 ppm).

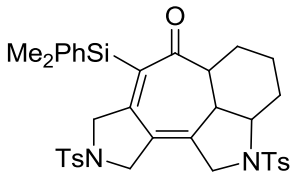
Diethyl-2-[(4-methylphenyl)sulfonyl]-6-oxo-7-(trimethylsilyl)-2,2a,3,4,5,5a,6,7,8,10-decahydroazuleno[4,5,6-*cd*]indole-9,9(1*H*)-dicarboxylate, (2-37b):



Colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.37); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 9H), 1.18-1.28 (m, 8H), 1.32-1.52 (m, 2H), 1.68-1.70 (m, 1H), 1.98-2.02 (m, 1H), 2.42 (s, 3H), 2.45-2.49 (m, 1H), 2.67-2.93 (m, 3H), 3.04 (d, 1H, *J* = 16.5 Hz), 3.21 (d, 1H, *J* = 16.5 Hz), 3.89-4.00 (m, 3H), 4.14-4.24 (m, 4H), 7.31 (d, 2H, *J* = 8.1 Hz), 7.71 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.03, 13.97, 14.03, 21.49, 21.54,

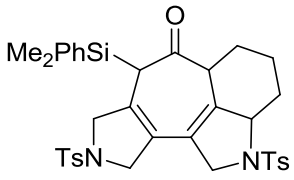
23.58, 28.74, 39.35, 42.01, 44.98, 48.81, 50.74, 57.69, 60.45, 61.94, 61.97, 126.99, 129.97, 131.85, 136.03, 137.18, 139.13, 143.70, 148.84, 170.22, 170.69, 207.64; IR (neat, cm^{-1}) 2937, 2538, 1734, 1731, 1662, 1446, 1346, 1249, 1161; HRMS (ES) m/z calcd for $C_{31}H_{42}NO_7SiS$ $(M + H)^+$ 600.2451, found 600.2438 (Δ - 1.3 ppm).

7-[Dimethyl(phenyl)silyl]-2,9-bis[(4-methylphenyl)sulfonyl] 2,2a,3,4,5,5a,8,9,10,10cdecahydropyrrolo[3',4':6,7]cyclohepta[1,2,3-*cd*]indol-6(1*H*)-one, (2-35c):



Colorless oil; TLC (SiO2, hexanes:EtOAc = 3:1, Rf = 0.24); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.40 (s, 3H), 0.43 (s, 3H), 0.85-1.13 (m, 3H), 1.54 (t, 1H, *J* = 9.6 Hz), 1.59-1.62 (m, 1H), 1.93-2.04 (m, 2H), 2.13- 2.17 (m, 1H), 2.42 (s, 3H), 2.45 (s, 3H), 3.27 (d, 1H, *J* = 11.2 Hz), 3.63-3.68 (m, 1H), 3.89-3.75 (m, 5H), 7.23 (d, 2H, *J* = 8.0 Hz), 7.27-7.43 (m, 9H), 7.73 (d, 2H, *J* = 8.0 Hz); 13C NMR (CDCl3, 100 MHz) δ - 3.11, -1.43, 21.54, 28.49, 30.12, 36.93, 41.16, 47.00, 50.34, 53.69, 55.44, 58.39, 61.39, 127.05, 127.15, 128.14, 129.62, 129.87, 133.71, 134.02, 135.61, 136.72, 140.12, 141.35, 143.59, 143.86, 199.65; HRMS (ES) m/z calcd for $C_{36}H_{41}N_2O_5SiS_2$ (M + H)+ 673.2226, found 673.2242 (Δ 1.6 ppm).

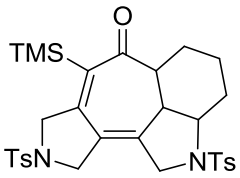
7-[Dimethyl(phenyl)silyl]-2,9-bis[(4-methylphenyl)sulfonyl]-2,2a,3,4,5,5a,7,8,9,10-decahydropyrrolo[3',4':6,7]cyclohepta[1,2,3-*cd*]indol-6(1*H*)-one, (2-37c):



Colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.24); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.34 (s, 3H), 0.45 (s, 3H), 1.09-1.22 (m, 3H), 1.48-1.52 (m, 1H), 1.62-1.66 (m, 1H), 1.96-2.01 (m, 1H), 2.41 (s, 3H), 2.43 (s, 3H), 2.48-2.54 (m, 1H), 2.67 (bs, 1H), 3.53 (s,

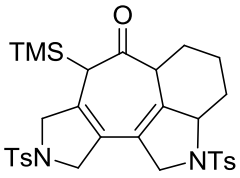
2H), 3.55-3.64 (m, 1H), 3.73-3.80 (m, 1H), 3.85-3.96 (m, 2H), 7.23 (d, 2H, *J* = 7.8 Hz), 7.29-7.35 (m, 4H), 7.38-7.53 (m, 5H), 7.70 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -2.14, -1.69, 21.44, 21.54, 23.31, 28.48, 45.12, 48.67, 50.21, 51.33, 53.78, 60.17, 127.03, 127.79, 128.28, 128.93, 129.66, 129.74, 130.05, 131.86, 134.02, 135.76, 136.88, 137.21, 138.40, 143.96, 146.45, 206.12; IR (neat, cm^{-1}) 3066, 2941,1718,1666, 1596, 1448, 1305, 1163; HRMS (ES) m/z calcd for $C_{36}H_{41}N_2O_5SiS_2$ $(M + H)^+$ 673.2226, found 673.2205 (Δ - 2.1 ppm).

2,9-Bis[(4-methylphenyl)sulfonyl]-7-(trimethylsilyl)-2,2a,3,4,5,5a,8,9,10,10c-decahydropyrrolo-[3',4':6,7]cyclohepta[1,2,3-*cd*]indol-6(1*H*)-one, (2-35d):



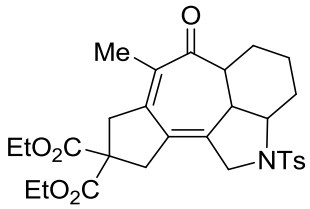
Colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.20); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.09 (s, 9H), 0.82-1.03 (m, 3H), 1.51-1.63 (m, 2H), 1.89-1. 94 (m, 2H), 2.10-2.15 (m, 1H), 2.43 (s, 3H), 2.46 (m, 3H), 3.29 (d, 1H, *J* = 11.4 Hz), 3.77 (d, 1H, *J* = 11.4 Hz), 3.84-3.89 (m, 2H), 4.06-4.15 (m, 2H), 4.24-4.31 (m, 1H), 7.32 (d, 2H, *J* = 7.8 Hz), 7.36 (d, 2H, *J* = 7.5 Hz), 7.63 (d, 2H, *J* = 7.5 Hz), 7.74 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -1.04, 21.53, 28.35, 30.11, 36.44, 41.12, 47.07, 50.54, 53.66, 55.16, 58.24, 61.40, 127.10, 127.16, 129.83, 129.93, 134.21, 135.63, 140.68, 141.22, 143.77, 143.94, 199.92; IR (neat, cm^{-1}) 2948, 2867, 1770, 1596, 1346, 1163, 1091; HRMS (ES) m/z calcd for $C_{31}H_{39}N_2O_5SiS_2$ $(M + H)^+$ 611.2070, found 611.2042 (Δ - 2.8 ppm).

2,9-Bis[(4-methylphenyl)sulfonyl]-7-(trimethylsilyl)-2,2a,3,4,5,5a,7,8,9,10-decahydropyrrolo-[3',4':6,7]cyclohepta[1,2,3-*cd*]indol-6(1*H*)-one, (2-37d):



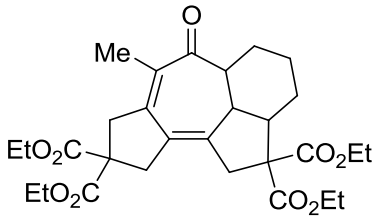
Colorless oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.20); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 9H), 1.05-1.8 (m, 3H), 1.41-1.45 (m, 1H), 1.59-1.63 (m, 1H), 1.93-2.01 (m, 1H), 2.43-2.49 (m, 7H), 2.64 (bs, 1H), 3.65-3.71 (m, 1H), 3.87-3.96 (m, 5H), 4.23 (d, 1H, 15.3 Hz), 7.29-7.35 (m, 4H), 7.67-7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -0.05, 21.38, 21.49, 23.18, 28.49, 45.23, 48.55, 50.19, 51.47, 53.45, 60.11, 127.06, 127.84, 128.89, 129.95, 130.06, 132.41, 135.78, 137.85, 138.92, 143.96, 144.30, 145.10, 206.69; IR (neat, cm^{-1}) 2945, 2358, 1662, 1346, 1163; HRMS (ES) m/z calcd for $C_{31}H_{39}N_2O_5SiS_2$ $(M + H)^+$ 611.2070, found 611.2079 (Δ 0.9 ppm).

Diethyl-7-methyl-2-[(4-methylphenyl)sulfonyl]-6-oxo-2,2a,3,4,5,5a,6,8,10,10c-dec ahydroazuleno[4,5,6-*cd*]indole-9,9(1*H*)-dicarboxylate, (2-35e):



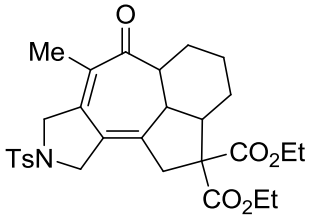
82% yield; yellow oil; TLC (SiO_2, hexanes:EtOAc = 2:1, R_f = 0.36); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22-1.28 (m, 6H), 1.38-1.45 (m, 2H), 1.63-1.71 (m, 3H), 1.85 (s, 3H), 1.87-1.96 (m, 1H), 2.41 (s, 3H), 2.62-2.65 (m, 1H), 2.80-2.84 (m, 2H), 3.00-3.16 (m, 3H), 3.94-3.97 (m, 1H), 4.08 (s, 2H), 4.15-4.24 (m, 4H), 7.31 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.99, 17.12, 21.52, 22.39, 23.79, 28.19, 39.86, 41.89, 43.76, 50.51, 50.72, 57.03, 60.69 , 61.95, 127.02, 129.95, 130.23, 130.65, 136.29, 136.92, 143.68, 145.03, 170.47, 170.86, 200.72; IR (neat, cm^{-1}) 2979, 2860, 1730, 1734, 1652, 1596, 1444, 1344, 1261, 1161, 1093; HRMS (ES) m/z calcd for $C_{29}H_{36}NO_7S$ $(M + H)^+$ 542.2212, found 542.2206 (Δ - 0.6 ppm).

Tetraethyl-7-methyl-6-oxo-1,2a,3,4,5,5a,6,8,10,10c-decahydrobenzo[*cd*]cyclopenta[*h*]azulene-2,2,9,9-tetracarboxylate, (2-35f):



85% yield; light yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.30); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21-1.26 (m, 13H), 1.37-1.46 (m, 3H), 1.70-1.78 (m, 2H), 1.86 (s, 3H), 2.76 (m, 2H), 2.86 (d, 1H, *J* = 20 Hz), 2.97 (d, 1H, *J* = 16.4 Hz), 3.06-3.25 (m, 4H), 3.43 (d, 1H, *J* = 20 Hz), 4.10- 4.24 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.93, 13.97, 14.07, 16.87, 23.69, 23.87, 23.90, 38.36, 40.33, 42.49, 44.07, 45.22, 51.16, 57.02, 61.62, 61.69, 61.75, 62.29, 129.25, 129.97, 140.69, 146.49, 169.12, 170.87, 170.98, 171.18, 201.13; IR (neat, cm^{-1}) 2979, 2935, 1731, 1367, 1257, 1159; HRMS (ES) m/z calcd for $C_{29}H_{39}O_9$ $(M + H)^+$ 531.2594, found 531.2576 (Δ - 1.8 ppm).

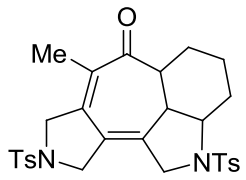
Diethyl-7-methyl-9-[(4-methylphenyl)sulfonyl]-6-oxo-2a,3,4,5,5a,6,8,9,10,10c-decahydrobenzo[1,8]azuleno[4,5-*c*]pyrrole-2,2(1*H*)-dicarboxylate, (2-35g):



83% yield; white solid; mp = 86-88 ^{o}C; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.28); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21-1.27 (m, 8H), 1.39-1.42 (m, 2H), 1.67-1.71 (m, 2H), 1.78 (s, 3H), 2.43 (s, 3H), 2.71-2.79 (m, 3H), 3.21 (d, 1H, *J* = 12.0 Hz), 3.32 (d, 1H, *J* = 12.0 Hz), 3.89 (d, 1H, *J* = 13.2 Hz), 4.02 (d, 1H, *J* = 16 Hz), 4.09-4.26 (m, 6H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.75 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.91, 14.06, 16.29, 21.51, 23.59, 23.65, 23.75, 37.79, 44.16, 45.04, 50.62, 52.81, 54.34, 61.79, 61.87, 62.31, 126.64, 127.79, 128.75, 129.84, 132.63, 141.37, 141.85, 144.06, 168.70, 170.69, 200.04; IR (in $CHCl_3$, cm^{-1}) 2983, 2906, 2255, 1741, 1731, 1373, 1266, 1096, 1046;

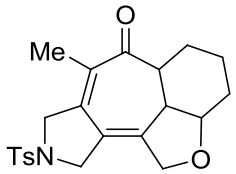
HRMS (ES) m/z calcd for $C_{29}H_{36}NO_7S$ $(M + H)^+$ 542.2212, found 542.2192 (Δ - 2.0 ppm).

7-Methyl-2,9-bis[(4-methylphenyl)sulfonyl]-2,2a,3,4,5,5a,8,9,10,10c-decahydropyrrolo[3',4':6,7]cyclohepta[1,2,3-*cd*]indol-6(1*H*)-one, (2-35h):



85% yield; mp = 200 -201 ^oC; TLC (SiO_2, hexanes:EtOAc = 2:1, R_f = 0.20); white solid; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11-1.22 (m, 3H), 1.38-1.40 (m, 1H), 1.62-1.71 (m, 1H), 1.77 (s, 3H), 1.91-1.95 (m, 2H), 2.42 (s, 3H), 2.43 (s, 3H), 2.62-2.65 (m, 1H), 2.79 (bs, 1H), 3.37 (d, 1H, *J* = 10 Hz), 3.89-3.99 (m, 3H), 4.10 (d, 1H, *J* = 14 Hz), 4.24 (d, 1H, *J* = 14 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 7.71 (d, 2H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.58, 21.55, 22.17, 23.64, 27.95, 29.67, 43.92, 50.06, 52.20, 53.81, 60.44, 126.83, 127.07, 127.79, 129.97, 130.02 , 130.25, 132.39, 136.08, 137.58, 140.73, 143.91, 144.33, 199.52; IR (in $CHCl_3$, cm^{-1}) 2923, 2854, 1733, 1596, 1346, 1163; HRMS (ES) m/z calcd for $C_{29}H_{33}N_2O_5S_2$ $(M + H)^+$ 553.1831, found 553.1818 (Δ - 1.3 ppm).

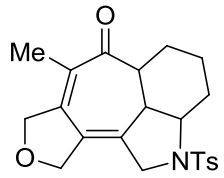
7-Methyl-9-[(4-methylphenyl)sulfonyl]-1,2a,3,4,5,5a,8,9,10,10c-decahydro-6*H*-[1]benzofuro[3',4':3,4,5]cyclohepta[1,2-*c*]pyrrol-6-one, (2-35i):



91% yield; white solid; mp = 182-183 ^oC; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.12); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18-1.28 (m, 3H), 1.38-1.44 (m, 1H), 1.63-1.69 (m, 1H), 1.81 (s, 3H), 2.39-2.45 (m, 4H), 2.72-2.79 (m, 1H), 3.23 (bs, 1H), 3.61-3.67 (m, 1H), 3.95-4.38 (m, 5H), 7.36 (d, 2H, *J* = 7.8 Hz), 7.74 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.55, 21.56, 21.92, 23.84, 26.57, 44.27, 49.86, 51.91, 53.90, 68.91, 79.10,

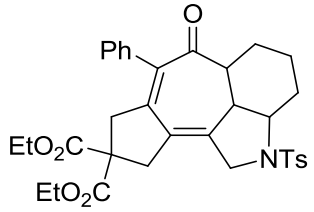
124.37, 127.79, 129.74, 129.87, 129.95, 141.34, 141.77, 144.24, 199.41; IR (in $CHCl_3$, cm^{-1}) 2939, 2864, 1724, 1596, 1346, 1163; HRMS (ES) m/z calcd for $C_{22}H_{26}NO_4S$ $(M + H)^+$ 400.1583, found 400.1569 (Δ - 1.4 ppm).

7-Methyl-2-[(4-methylphenyl)sulfonyl]-2,2a,3,4,5,5a,10,10c-octahydro-1*H*-furo[3', 4':6,7]cyclohepta[1,2,3-*cd*]indol-6(8*H*)-one, (2-35j):



74% yield; white solid; mp = 191-193 ^oC; TLC (SiO_2, hexanes:EtOAc = 2:1, Rf = 0.24); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22-1.30 (m, 2H), 1.46-1.52 (m, 2H), 1.75 (s, 3H), 1.96-2.01 (m, 2H), 2.42 (s, 3H), 2.66-2.74 (m, 1H), 2.88 (bs, 1H), 3.94-4.07 (m, 3H), 4.38 (dt, 1H, *J* = 2.1 Hz)), 4.49-4.67 (m, 3H), 7.31 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.97, 21.51, 22.35, 23.99, 28.31, 43.99, 49.69, 50.48, 60.42, 72.18, 73.58, 127.00, 127.85, 129.63, 130.00, 135.05, 136.14, 143.81, 144.46, 199.74; IR (in $CHCl_3$, cm^{-1}) 2929, 2856, 1721, 1654, 1596, 1342, 1159; HRMS (ES) m/z calcd for $C_{22}H_{26}NO_4S$ $(M + H)^+$ 400.1583, found 400.1569 (Δ - 1.4 ppm).

Diethyl-7-phenyl-2-[(4-methylphenyl)sulfonyl]-6-oxo-2,2a,3,4,5,5a,6,8,10,10c-dec ahydroazuleno[4,5,6-*cd*]indole-9,9(1*H*)-dicarboxylate, (**2-35k**):



44% yield; light yellow oil; TLC (SiO_2, hexanes:EtOAc = 3:1, R_f = 0.23); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 6H, *J* = 7.2 Hz), 1.56-1.66 (m, 4H), 1.75-1.79 (m, 1H), 1.97-2.01 (m, 1H), 2.44 (s, 3H), 2.67-2.75 (m, 1H), 2.87-2.94 (m, 4H), 3.09 (d, 1H, *J* = 14.0 Hz), 3.99-4.03 (m, 1H), 4.12-4.19 (m, 6H), 7.04 (dd, 2H, *J* = 8.4, 1.5 Hz), 7.27-7.37 (m, 5H), 7.75 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.93, 13.99, 21.54, 22.23, 23.69, 28.37, 40.05, 42.62, 44.24, 50.19, 50.82, 57.32, 60.66, 61.89, 127.04,

127.43, 128.42, 128.68, 130.01, 130.15, 136.08, 136.21, 138.66, 138.71, 143.77, 145.31, 170.22, 170.59, 200.37; IR (neat, cm^{-1}) 2960, 2860, 2358, 1735, 1728, 1723, 1650, 1444, 1365, 1344, 1263, 1159, 1093, 1053, 1016; HRMS (ES) m/z calcd for $C_{34}H_{38}NO_7S$ $(M + H)^+$ 604.2369, found 604.2348 (Δ - 2.1 ppm).

§ 2.5. References

1. (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J., Transition metal-catalyzed carbocyclizations in organic synthesis. *Chem. Rev.* **1996,** *96*, 635-662; (b) Lautens, M.; Klute, W.; Tam, W., Transition metal-mediated cycloaddition reactions. *Chem. Rev.* **1996,** *96*, 49-92.

2. Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I., Silicon-initiated carbonylative carbotricyclization and [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *J. Am. Chem. Soc.* **2005,** *127*, 17756-17767.

3. Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *Org. Lett.* **2004,** *6*, 3589-3591.

4. Wei, X.; Rodriguez, I. I.; Rodriguez, A. D.; Barnes, C. L., Caribenols A and B, sea whip derived norditerpenes with novel tricarbocyclic skeletons. *J. Org. Chem.* **2007,** *72*, 7386-7389.

5. Kaloko, J. J.; Teng, Y.-H. G.; Ojima, I., One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. *Chem. Commun.* **2009**, 4569 - 4571.

6. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Metal-catalyzed [2+2+1] cycloadditions of 1,3-dienes, allenes, and CO. *Angew. Chem. Int. Ed.* **2006,** *45*, 2459-2462.

7. Faitg, T.; Soulié, J.; Lallemand, J.-Y.; Mercier, F.; Mathey, F., Asymmetric isomerisation of a cyclic diene: a comparative study of BINAP and BIPNOR-rhodium(I) catalysts. *Tetrahedron* **2000,** *56*, 101-104.

8. Aïssa, C.; Fürstner, A., A rhodium-catalyzed C−H activation/cycloisomerization tandem. *J. Am. Chem. Soc.* **2007,** *129*, 14836-14837.

9. McCleverty, J. A.; Wilkinson, G., Dichlorotetracarbonyldirhodium (rhodium carbonyl chloride). *Inorg. Syn. 8*, 211-214.

10. Brummond, K. M.; Chen, H.; Sill, P.; You, L., A rhodium(I)-catalyzed formal allenic Alder Ene reaction for the rapid and stereoselective assembly of cross-conjugated trienes. *J. Am. Chem. Soc.* **2002,** *124*, 15186-15187.

11. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L., Three-component cycloadditions: the first transition metal-catalyzed [5+2+1] cycloaddition reactions. *J. Am. Chem. Soc.* **2002,** *124*, 2876-2877.

12. Cerezo, S.; Cortès, J.; Galvan, D.; Lago, E.; Marchi, C.; Molins, E.; Moreno-Mañas, M.; Pleixats, R.; Torrejón, J.; Vallribera, A., Preparation of nitrogen-

containing 15-membered triolefinic macrocycles: (*E*,*E*,*E*)-1,6,11-tris(arylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-trienes. *Eur. J. Org. Chem.* **2001**, 329-337.

13. (a) Sharpless, K. B.; Hori, T., Allylic amination of olefins and acetylenes by imido sulfur compounds. *J. Org. Chem.* **1976,** *41*, 176-177; (b) Taylor, J. G.; Whittall, N.; Hii, K. K., Copper-catalyzed intermolecular hydroamination of alkenes. *Org. Lett.* **2006,** *8*, 3561-3564.

14. Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L., Scope of the intramolecular titanocene-catalyzed Pauson−Khand type reaction1. *J. Am. Chem. Soc.* **1999,** *121*, 5881-5898.

15. Khan, A. T.; Choudhury, L. H.; Ghosh, S., Cupric sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$): a mild and efficient catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols. *Tetrahedron Lett.* **2004,** *45*, 7891-7894.

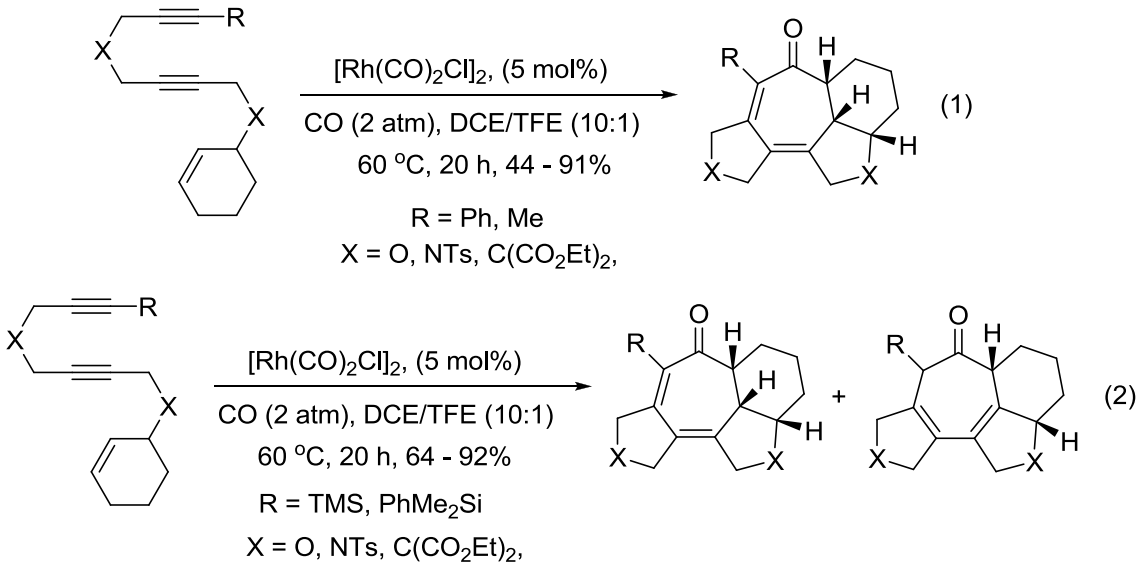
Chapter 3

Formation of novel 5-7-5-5 fused tetracyclic skeletons through Rh(I)-catalyzed [2+2+2+1]cycloaddition of cyclopentene-diynes and carbon monoxide

Table of Contents

§ 3.1. Introduction

As described in the previous chapter, the [2+2+2+1] cycloaddition of substituted cyclohexene-diynes with carbon monoxide gave fused 5-7-6-5 tetracyclics in good to excellent yields (**Scheme 3-1**).[1] During our studies into the formation 5-7-6-5 tetracyclic products, we observed that along with the expected products, the diene-shifted regioisomers were also obtained for all silyl-substituted substrates investigated in a calculated 1:1 ratio (**Scheme 3-1, reaction 2**).



Scheme 3-1: Formation of 5-7-6-5 fused tetracyclics

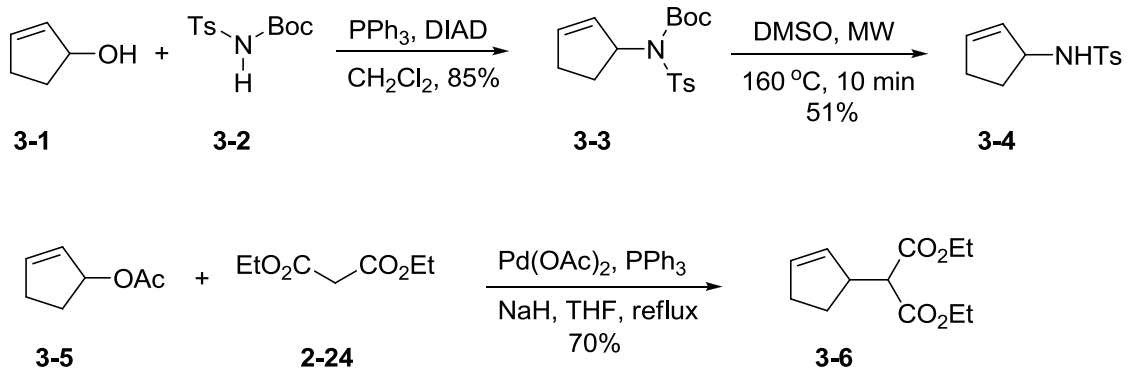
With the goal of expanding the cyclo-alkene component of the enediyne substrates, we wondered if silyl-substituted cyclopentene-diynes which should afford the corresponding 5-7-5-5 fused tetracyclics would also yield regioisomers for silyl-substituted substrates. As part of ongoing studies on higher-order cycloaddition reactions, the formation of 5-7-5-5 tetracyclic products *via* Rh-catalyzed [2+2+2+1] of cyclopentene-diynes with carbon monoxide was also investigated. Indeed, the desired 5-7-5-5 products were obtained in high yields and as single diastereomers. Moreover, along with the expected fused tetracyclic products, the diene shifted regioisomers were also obtained for all silyl-substrates investigated in a calculated 4:1 ratio in favor of the regioisomers. It should be noted that these fused tetracyclic products can be further

elaborated for the synthesis of natural product like compounds. The results of the study on the formation of 5-7-5-5 tetracyclics are detailed below.

§ 3.2. Results and discussion

§ 3.2.1. Synthesis of cyclopentene-diynes

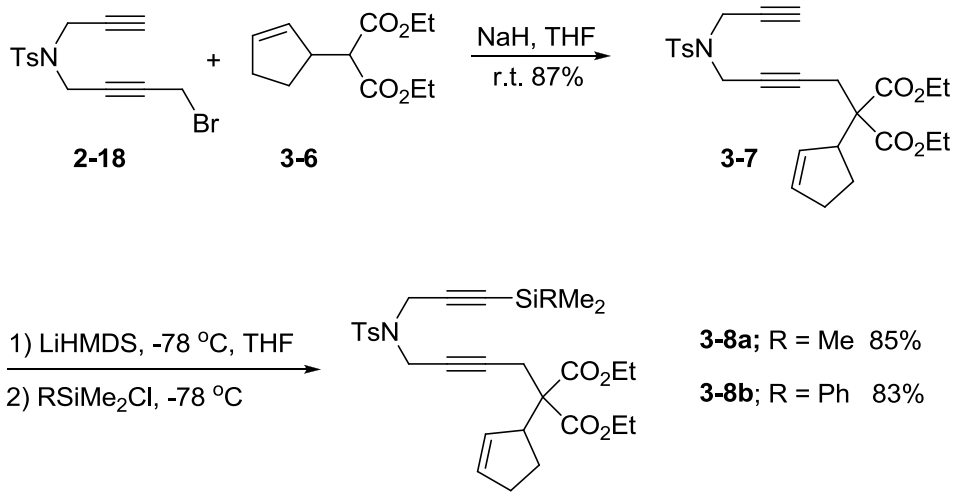
The preparation of cyclopentene-diynes involved coupling of the cyclopentenyl components to diyne bromides (See chapter 2 for synthesis of diyne bromides). The synthesis of *N*-cyclopent-2-enyl sulfonamide **(3-4)** was accomplished in two steps (**Scheme 3-2**). Coupling of 2-cyclopenten-1-ol **(3-1)** with *N*-Boc-*N*-tosylamide **(3-2)** under Mitsunobu conditions gave the desired product **3-3** in 85% yield. Subsequent Boc thermolysis using microwave irradiation gave the desired product **3-4** in moderate yield.



Scheme 3-2: Synthesis of *N*-cyclopent-2-enyl sulfonamide **(3-4)** and diethyl 2-(cyclopent-2-enyl) malonate **(3-6)**

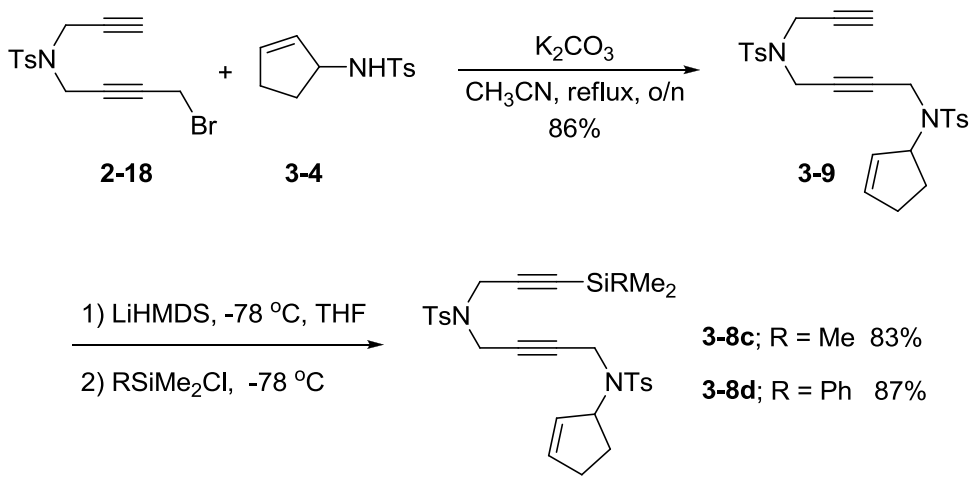
In addition to the desired product **3-4**, a second product later identified as *p*-toluenesulfonamide was also obtained (not shown). The formation of this second product also indicated the formation of 1,3-cyclopentadiene which could not be isolated. Other synthetic methods to access compound **3-4** were explored, but these methods involved multiple steps and the overall yields were comparable or lower than that obtained with the method depicted in **Scheme 3-2**. Diethyl 2-(cyclopent-2-enyl) malonate **(3-6)** was obtained in good yield from the reaction of cyclopent-2-enyl acetate **(3-5)** with diethyl malonate **2-24** *via* allylic alkylation (**Scheme 3-2**).

The treatment of bromo-diyne **2-18** with diethyl 2-(cyclopent-2-enyl) malonate **(3-6)** afforded the desired *N*-tosyl-malonate tethered cyclopentene-diyne **3-7** in 87% yield (**Scheme 3-3**). The trimethylsilyl (TMS) and dimethylphenyl silyl ($SiPhMe_2$) capped cyclopentene-diynes **3-8a** and **3-8b** were obtained in good yields from the reaction of **3-7** with the corresponding chlorosilanes in the presence of LiHMDS (**Scheme 3-3**).



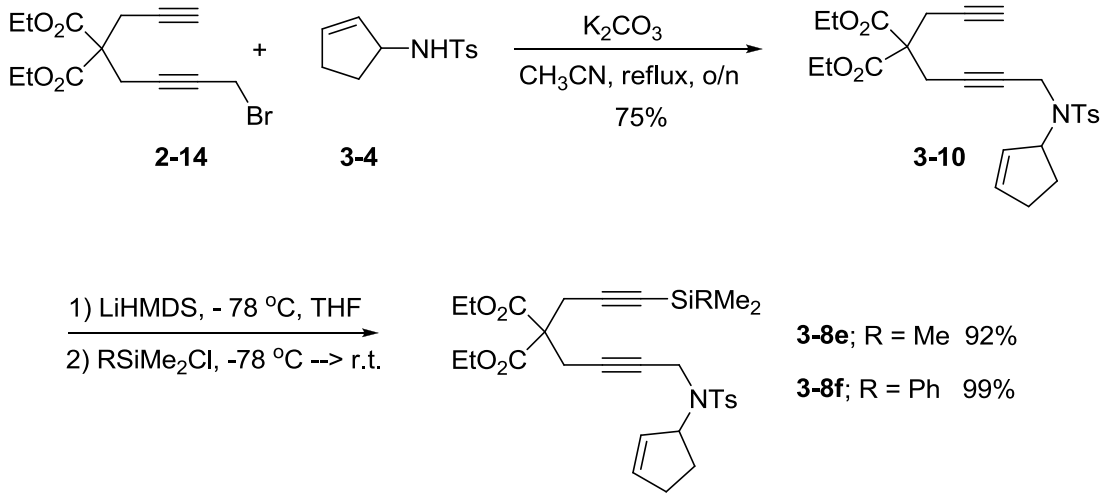
Scheme 3-3: Synthesis of cyclopentene-diynes **3-8a** and **3-8b**

Similarly, the bis *N*-tosyl tethered substrates **3-8c** and **3-8d** were obtained in 83% and 87% yields respectively from treatment of cyclopentene-diyne **3-9** with the corresponding chlorosilanes in the presence of LiHMDS (**Scheme 3-4**).



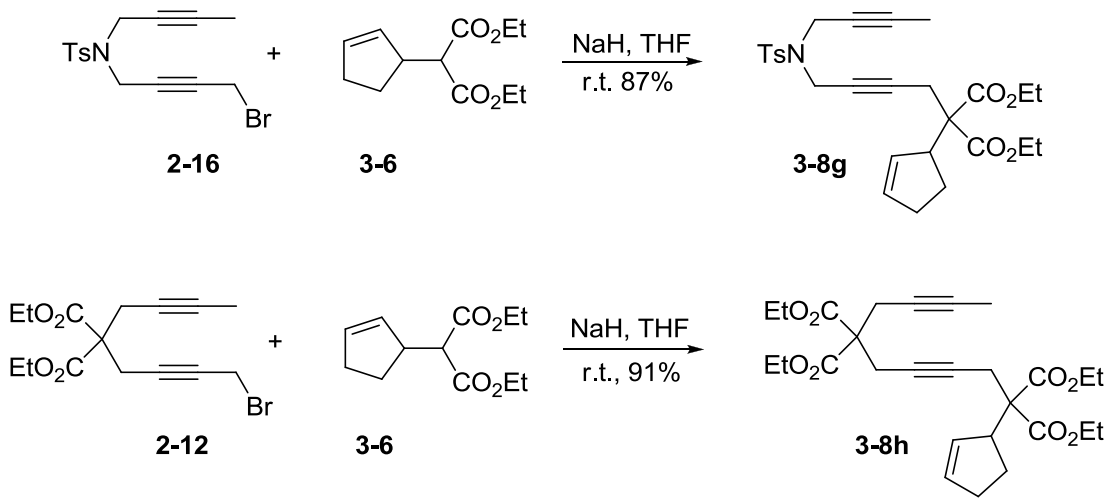
Scheme 3-4: Synthesis of cyclopentene-diynes **3-8c** and **3-8d**

Cyclopentene-diyne **3-10** was obtained in 75% yield from nucleophilic substitution of bromo-diyne **2-14** with *N*-cyclopent-2-enyl sulfonamide **(3-4)** (**Scheme 3-5**). Treatment of compound **3-10** with either trimethyl chlorosilane or dimethylphenyl chlorosilane, in the presence of LiHMDS as base, afforded TMS and $SiPhMe_2$-capped substrates **3-8e** and **3-8f** in 92% and 99% isolated yields, respectively (**Scheme 3-5**).



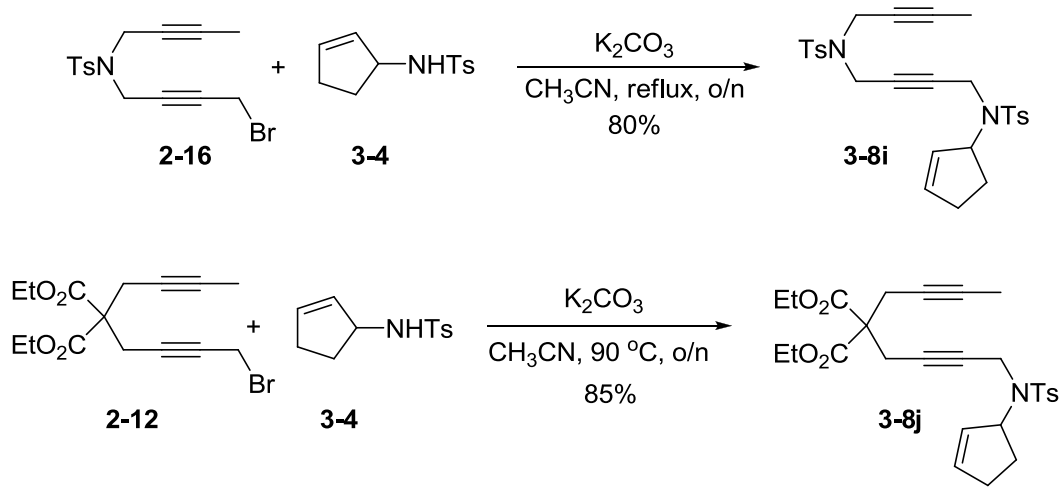
Scheme 3-5: Synthesis of cyclopentene-diynes **3-8e** and **3-8f**

Methyl-substituted substrates **3-8g** and **3-8h** were obtained in good yields from NaH-mediated coupling of bromo-diynes **2-16** and **2-12** with diethyl 2-(cyclopent-2-enyl) malonate **(3-6)**, respectively (**Scheme 3-6**).



Scheme 3-6: Synthesis of cyclopentene-diynes **3-8g** and **3-8h**

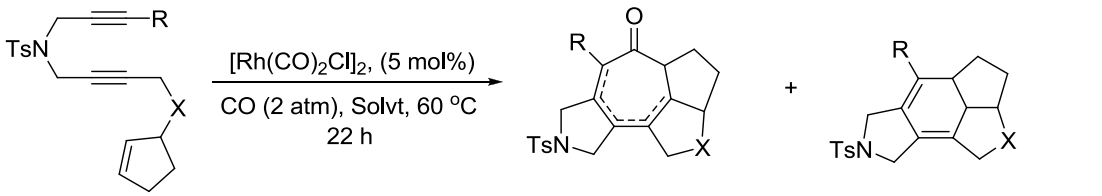
The reactions of bromo-diynes **2-16** and **2-12** with *N*-cyclopent-2-enyl sulfonamide **(3-4)** in the presence of potassium carbonate in refluxing acetonitrile afforded substrate **3-8i** and **3-8j** in 80% and 85% yields, respectively (**Scheme 3-7**).



Scheme 3-7: Synthesis of cyclopentene-diynes **3-8i** and **3-8j**

§ 3.2.2. Optimization of [2+2+2+1] cycloaddition reaction and substrate scope

With cyclopentene-diyne substrates in hand, we began the optimization studies for the formation of 5-7-5-5 tetracyclic compounds. Since previous experience showed that the optimum conditions for one substrate could not necessarily be extended to other substrates, two substrates were used in the optimization studies. TMS-capped substrate **3-8a** was subjected to previously optimized conditions for the formation of 5-7-6-5 products ($[Rh(CO)_2Cl]_2$, 2 atm of CO in 1,2-dichloroethane (DCE)/2,2,2-trifluoroethanol (TFE) (10:1) at 60 ^oC. Under these conditions, the fused tetracyclic product **3-11a** along with the [2+2+2] cycloadduct **3-12a** were obtained in a 94:6 ratio, as determined by HPLC (**Scheme 3-8, Table 3-1, entry 1**). The $SiPhMe_2$-capped substrate **3-8d** gave products **3-11d** and **3-12d** in 83:17 ratio as determined by HPLC (**entry 2**).



3-8a X = $C(CO_2Et)_2$, R = TMS

3-8d X = NTs, R = $SiPhMe_2$

3-11a X = $C(CO_2Et)_2$

3-11d X = NTs, R = $SiPhMe_2$

3-12a X = $C(CO_2Et)_2$, R = TMS

3-12d X = NTs, R = $SiPhMe_2$

Scheme 3-8: [2+2+2+1] cycloadditon of cyclopentene-diyne **3-8a** and **3-8d** with CO

Table 3-1: Optimization of [2+2+2+1] cycloaddition of **3-8a** and **3-8d** with CO

Entry	X	R	Compound	Solvent	Conc. [M]	Ratio (**3-11**:**3-12**)[a]
1	$C(CO_2Et)_2$	TMS	3-8a	DCE/TFE (10:1)	0.050	94:6
2	NTs	$SiPhMe_2$	3-8d	DCE/TFE (10:1)	0.050	83:17
3	$C(CO_2Et)_2$	TMS	3-8a	DCE/TFE (10:1)	0.025	95:5
4	NTs	$SiPhMe_2$	3-8d	DCE/TFE (10:1)	0.025	90:10
5	$C(CO_2Et)_2$	TMS	3-8a	TFE	0.025	100:0*
6	$C(CO_2Et)_2$	TMS	3-8a	DCE/TFE (5:1)	0.025	100:0*
7	NTs	$SiPhMe_2$	3-8d	DCE/TFE (5:1)	0.025	100:0*
8	**$C(CO_2Et)_2$**	**TMS**	**3-8a**	**DCE/TFE (8:1)**	**0.025**	**100:0**
9	**NTs**	**$SiPhMe_2$**	**3-8d**	**DCE/TFE (8:1)**	**0.025**	**100:0**

DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol; [a] Determined by reverse phase HPLC analysis (MeOH:H_2O, Phenomenex, Jupiter 10μ Proteo 90A) for 20 h reaction. * desilylated product **3-7** was also obtained aling with the desired product.

Performing the reactions of substrates **3-8a** and **3-8d** under more dilute conditions resulted in improved selectivity only for substrate **3-8d** (**Table 3-1**,**entries 3 and 4**). The reaction of **3-8a** in 2,2,2-trifluoroethanol (TFE) at 0.025M afforded the carbonylated product exclusively. However, a significant amount of desilylated product **3-7** was also observed (**entry 5**). It is assumed that **3-7** was formed through protodesilylation of **3-8a** by TFE under the reaction conditions. Although desilylation was observed to a lesser extent, similar results were also observed for substrates **3-8a** and **3-8d** when a 5:1 ratio of 1,2-dichloroethane (DCE)/TFE was used as solvent (**entries 6 and 7**). Fortunately, increasing the amount of DCE in the reaction mixture resulted in exclusive formation of carbonylated products **3-11a** and **3-11d** with no trace of the desilylated products (**entries 8 and 9**). Thus, the current optimum conditions with $[Rh(CO)_2Cl]_2$ (5 mol%) under 2 atm of CO in DCE/TFE (8:1) at 60 ^oC for 22 h afforded 5-7-5-5 cycloadducts **3-11a** and **3-11d** exclusively in 98% and 92% isolated yields respectively (**Table 3-2, entries 1 and 4**). It should be noted that the carbonylated products **3-11a** (**See Figure 3-1**) and **3-11d** as well as other silyl-substituted substrates were obtained as regioisomers (1:4) and as single diastereomers as was observed for 5-7-6-5 tetracyclic products (**See chapter 2**).

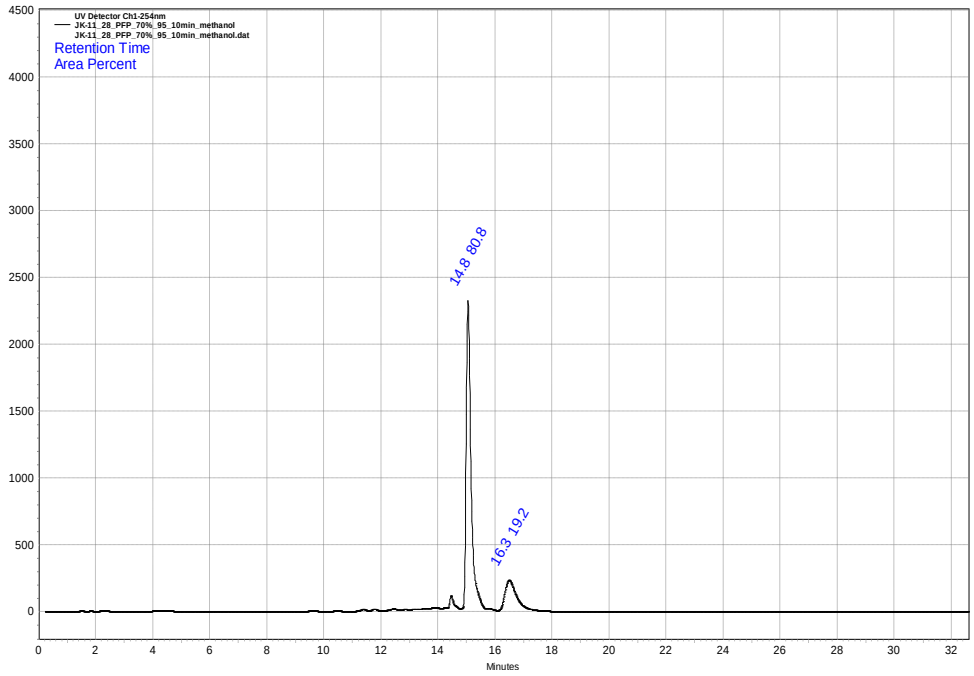


Figure 3-1: HPLC trace of isolated product **3-13a** (first peak) and **3-11a** (second peak) from [2+2+2+1] cycloaddition of cyclopentene-diyne **3-8a** with CO

In an experiment similar to that done for 5-7-6-5 fused tetracylic products (**See Chapter 2**), the mixture of carbonylated products **3-11a** and **3-13a** was also analyzed by LC-MS while monitoring at 254 nm and 305 nm respectively (**Figure 3-2**). It was predicted that the ultraviolet (UV) absorption for the non-conjugated carbonylated isomer **3-13a** would be diminshed at higher wavelengths. As **Figure 3-2** shows, both products **3-13a** (first peak) and **3-11a** (second peak) are clearly observed at 254 nm (Top spectrum in **Figure 3-2)**. However, the abosorption of the first product **3-13a** at 305 nm is significantly diminshed, suggesting that this peak represents the non-conjugated carbonylated isomer **3-13a**, while the second peak represents the α,β-conjugated carbonylated isomer **3-11a**.

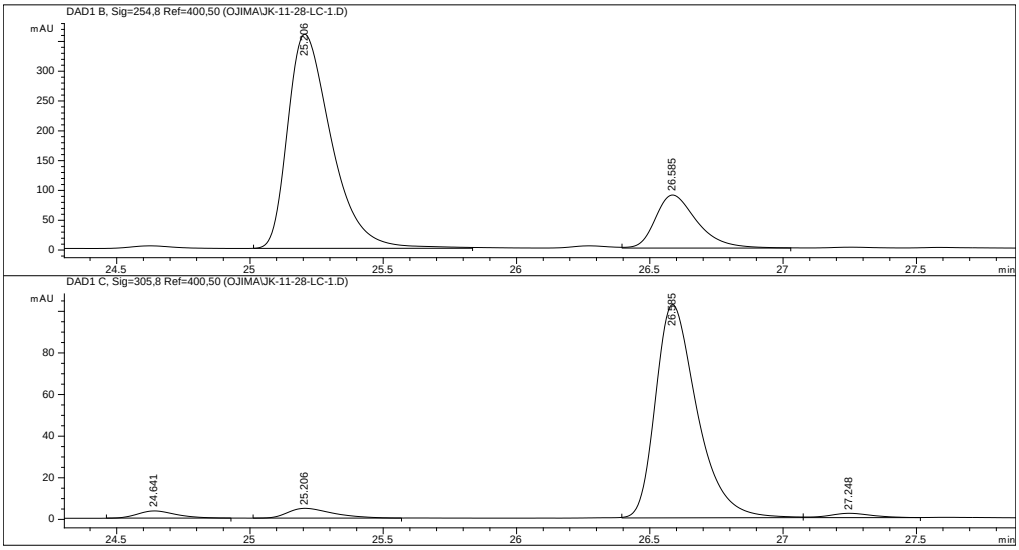
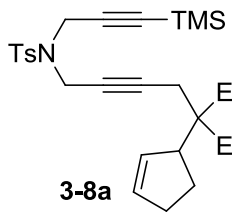
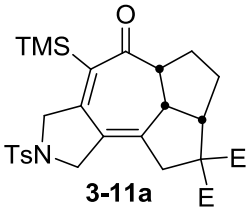
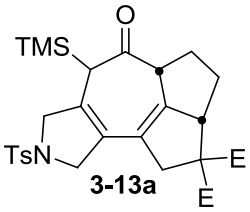
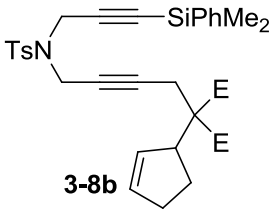
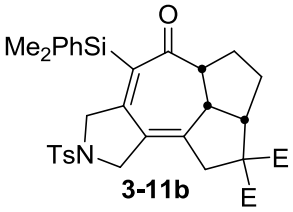
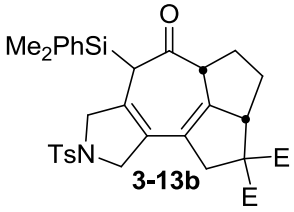
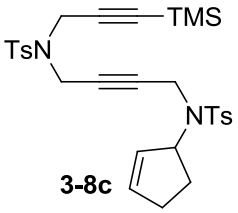
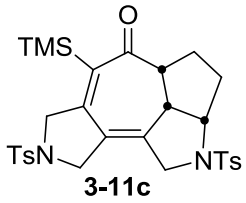
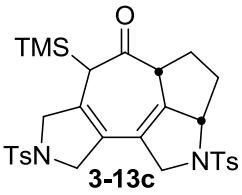
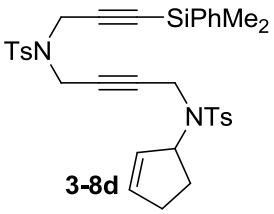
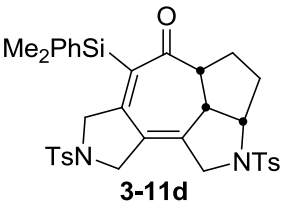
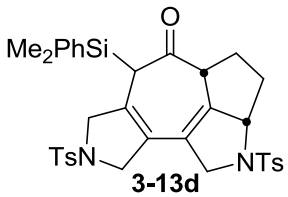
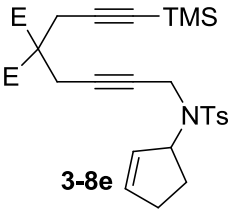
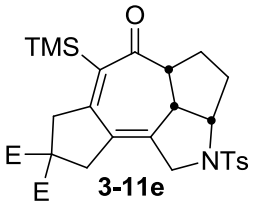
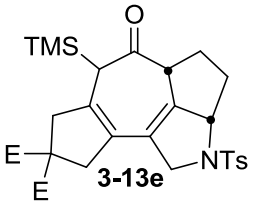
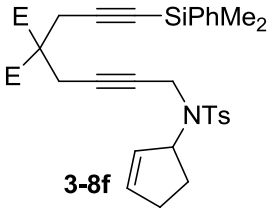
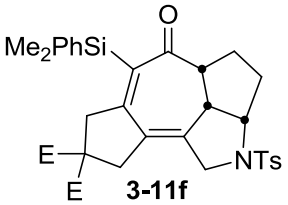
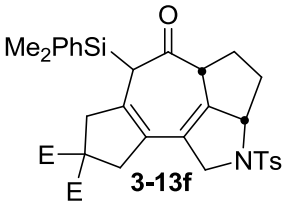


Figure 3-2: LC-MS trace of product **3-13a** (first peak) and **3-11a** (second peak) at 254 nm and 305 nm respectively

Exclusive selectivity in favor of the carbonylated products was also observed for other sily-substituted cyclopentene-diyne substrates. Thus, $PhMe_2Si$ capped substrates **3-8b** and **3-8f** with *p*-toluenesulfonamide and malonate tethers gave the regioisomeric products **3-11b** and **3-13b** as well as **3-11f** and **3-13f** in 94% and 86% isolated yields respectively (**entries 2 and 6**). The reaction of TMS-capped *bis p*-toluenesulfonamide tethered substrate **3-8c** also gave the carbonylated products **3-11c** and **3-13c** in high yield (**entry 3**). It is worthy of note that computational studies showed the diene-shifted 5-7-5-5 regioisomers to be more energetically favorable as was observed in the case of 5-7-6-5 regioisomeric products (**See chapter 2**).

Table 3-2: Formation of 5-7-5-5tetracyclics **3-11a-f** and **3-13a-f** through [2+2+2+1] cycloaddition of **3-8a-f** with CO

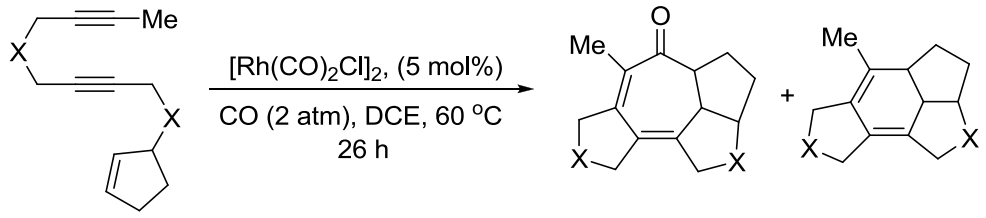
Entry	Substrate	Product 1	Product 2	Yield (%)[a]
(1)	 **3-8a**	 **3-11a**	 **3-13a**	(98)
(2)	 **3-8b**	 **3-11b**	 **3-13b**	(94)
(3)	 **3-8c**	 **3-11c**	 **3-13c**	(84)
(4)	 **3-8d**	 **3-11d**	 **3-13d**	(92)
(5)	 **3-8e**	 **3-11e**	 **3-13e**	(94)
(6)	 **3-8f**	 **3-11f**	 **3-13f**	(86)

E = CO_2Et_2

[a] Averaged combined isolated yield of regioisomeric products based on at least two runs using 80 mg of substrate, 5 mol% $[Rh(CO)_2Cl]_2$, CO (2 atm) in DCE/TFE (8:1) at [0.05] for 22 h at 60 ^oC. Isomeric products can be separated by prep HPLC.

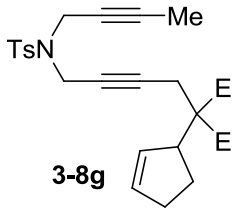
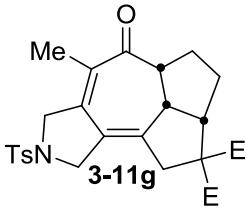
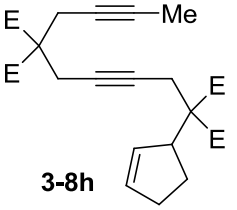
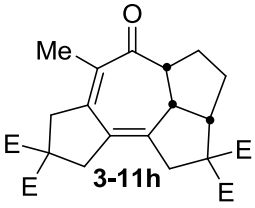
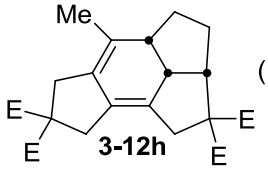
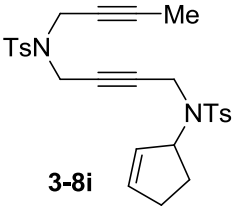
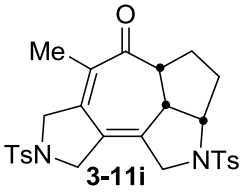
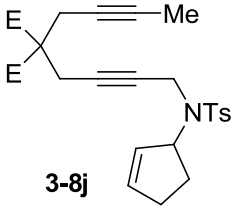
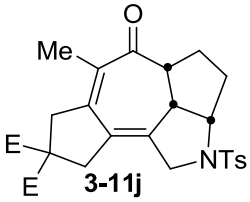
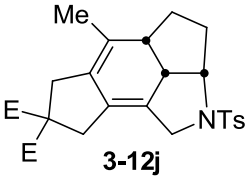
Alkyl substituted cyclopentene-diyne subsbrates were also investigated. However, the reaction of **3-8j** under the current optimized conditions ($[Rh(CO)_2Cl]_2$ (5 mol%) under 2 atm of CO in DCE/TFE (8:1) at 60 ^oC for 22 h) for 5-7-5-5 tetracyclic formation gave a complex mixture as determined by HPLC. Other methyl substituted substrates either gave complex reaction mixtures or showed no selectivity for the desired carbonylated tetracyclic products. Thus, the conditions for selective formation of the carbonylated products for methyl substituted substrates were investigated. It turned out that using DCE as solvent gave satisfactory results for the methyl substrates **3-8g-j** investigated, although a longer reaction time was required (**Scheme 3-9, Table 3-3**). As was the case for 5-7-6-5 tetracyclics, only the expected α,β-congugated products **3-11g-j** were obtained also as single diastereomers.

The reaction of **3-8g** gave the desired 5-7-5-5 tetracyclic product **3-11g** in 94% isolated yield with no trace of the [2+2+2] cycloadduct (**entry 1**). The *bis* malonate tethered substrate **3-8h** gave the carbonylated product **3-11h** in good yield (85%), but the non-carbonylated product **3-12h** was also obtained in 12% yield (**entry 2**). The *bis p*-toluenesulfonamide tethered substrate **3-8i** also gave the carbonylated products **3-11i** in moderate yield. The reaction of cyclopentene-diyne **3-11j** afforded the 5-7-5-5 tetracyclic adduct **3-11j** and the 5-6-5-5 product **3-12j** in 81% and 9% isolated yields respectively (**entry 4**).



Scheme 3-9: [2+2+2+1] cycloadditon of cyclopentene-diyne **3-8g-j** with CO

Table 3-3: Formation of 5-7-5-5tetracyclics **3-11g-j** through [2+2+2+1] cycloaddition of **3-8g-j** with CO

Entry	Substrate	Product 1 (yield %)[a]	Product 2 (Yield %)[a]
(1)	 **3-8g**	 **3-11g** (94)	(–)
(2)	 **3-8h**	 **3-11h** (85)	 **3-12h** (12)
(3)	 **3-8i**	 **3-11i** (60)	(--)
(4)	 **3-8j**	 **3-11j** (81)	 **3-12j** (9)

E = CO_2Et

Averaged isolated yield of products based on at least two runs using 80 mg of substrate, 5 mol% $[Rh(CO)_2Cl]_2$, CO (2 atm) in DCE at [0.025] for 26 h at 60 °C.

§ 3.3. Conclusion

In summary, the formation of novel 5-7-5-5 fused tetracyclics from the [2+2+2+1] cycloaddition of cyclopentene-diynes with carbon monoxide was described. The carbonylated products were obtained exclusively, in good to excellent yields, and as single diastereomers for all silyl-substituted substrates investigated. High to exclusive selectivities were observed for methyl-substituted substrates, providing the carbonylated products in moderate to excellent yields and as single diastereomers. The reaction of silyl-substituted substrates gave regioisomeric carbonylated products, while alkyl substituted substrates gave single carbonylated products. This novel [2+2+2+1] cycloaddition process could be applied to the preparation of fused tetracyclic compounds using a variety of unsaturated carbocycles and heterocycles as the *ene* component.

§ 3.4 Experimental section

§ 3.4.1 General methods

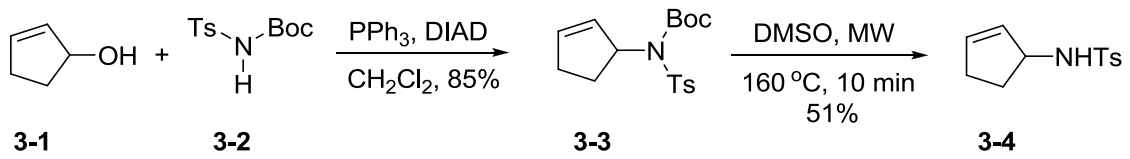
All reactions were carried out under nitrogen or carbon monoxide in oven dried glassware using standard Schlenk techniques unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents using Fisher silica gel (60 μm particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. Analytical high performance liquid chromatography (HPLC) was performed with a Shimadzu LC 2010A system using a phenomenex Jupiter 10μ proteo 90A column (4.5 x 250 mm/mm) and gradient from 70% methanol to 95:5 methanol:water over 30 min with a flow rate of 1mL/min. Preparative HPLC was carried out on a Shimadzu semi-preparative LC-6AD HPLC system using a phenomenex Jupiter 10μ proteo 90A column (21.2 x 250 mm/mm) and gradient from 70% methanol to 95:5 methanol:water over 30 min with a flow rate of 20 mL/min. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Shimadzu FTIR-84005 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Inova-500 (500 MHz), 400 (400 MHz) or a Gemini-300 (300 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova-500 (125 MHz) 400 (100 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 77.0 ppm). High resolution mass spectrometry (HRMS) was carried out at the Mass Spectrometry Facility, the University of Illinois Urbana Champaign. **Caution:** Carbon monoxide is a toxic gas and thus all reactions should be carried out in a fume hood with sufficient ventilation. Solvents were reagent grade and freshly distilled before use. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from DrySolv® and used without further purification. Dichloroethane (DCE) and trifluoroethanol (TFE) were purchased from Fischer and used without purification. Carbon monoxide was purchased

from Liquid Carbonic Specialty Gases, Oak Brook, Illinois and passed through Drierite® before use. $[Rh(CO)_2Cl]_2$ was prepared by the literature method.[2]

Materials. Bromo-diynes **2-12**, **2-14**, **2-16** and **2-18** were prepared according to the procedures in chapter 2 of this document.

§ 3.4.2. Synthesis of cyclopentene-diynes

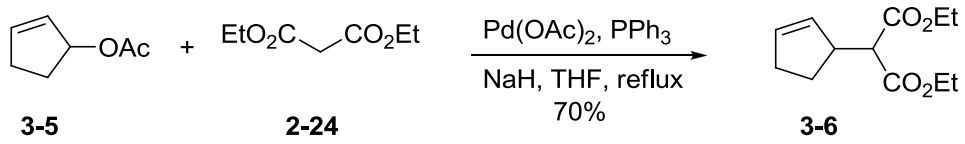
***N*-(Cyclopent-2-enyl)-4-methylbenzenesulfonamide, (3-4)**:[3]



Triphenylphosphine (11.7 g, 44.7 mmol), DIAD (9.51 g, 44.7 mmol) and *N*-tosylamide **3-2** (10.1 g, 37.2 mmol) in CH_2Cl_2 (85 mL) were stirred for 20 min at room temperature. Then 2-cyclopenten-1-ol **(3-1)** (3.13 g, 37.2 mmol) diluted in 15 mL of CH_2Cl_2 was added dropwise. The resulting mixture was stirred for 4 h at room temperature. The mixture was concentrated and purified by flash chromatography on silica gel using 8% EtOAc in hexanes as eleunt to give **3-3** (11.69 g, 85%) of the product as a white solid; mp = 85-86 ^oC. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 9H), 2.04-2.09 (m, 1H), 2.37-2.43 (m, 5H), 2.46-2.58 (m, 1H), 5.61-5.64 (m, 2H), 5.88-5.90 (m, 1H), 7.32 (d, 2H, *J* = 8.7 Hz), 7.80 (d, 2H, *J* = 8.7 Hz).

The tosylamide **3-3** (4.50 g, 13.3 mmol) was dissolved in 20 mL of DMSO and heated in a microwave reactor at 160 ^oC for 10 min. Water was added and the mixture extracted with CH_2Cl_2 (3x50 mL). The organic layers were combined and washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to give the product **3-4** (1.60 g, 51%) as a white solid; mp = 73-73 ^oC. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46-1.52 (m, 1H), 2.04-2.08 (m, 2H), 2.18-2.42 (m, 1H), 2.44 (s, 3H), 4.43 (bs, 1H), 4.71 (bs, 1H), 5.41-5.44 (m, 1H), 5.83-5.86 (m, 1H), 7.32 (d, 2H, *J* = 8.7 Hz), 7.79 (d, 2H, *J* = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.50, 30.79, 31.53, 59.80, 127.08, 129.69, 130.45, 135.04, 138.12, 143.29. Spectral data are consistent with those reported in the literature.[3]

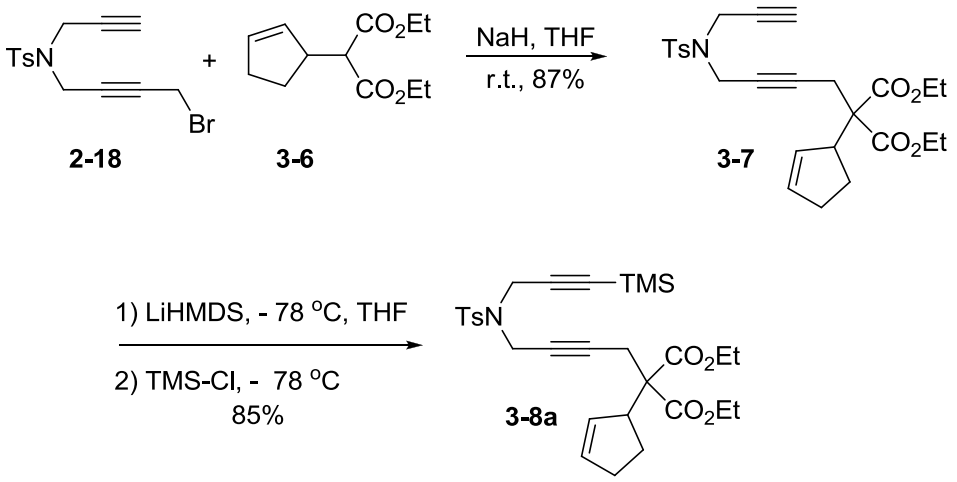
Diethyl 2-(cyclopent-2-enyl) malonate, (3-6):[4]



3-5 **2-24** **3-6**

To a suspension of NaH (951 mg, 23.7 mmol,) in THF (60 mL) was added diethylmalonate **(2-24)** (3.85 g, 23.7 mmol) and the resulting mixture stirred for 10 min. To this was added $Pd(OAc)_2$ (110 mg, 0.496 mmol) and PPh_3 (520 mg, 1.98 mmol), followed by cyclopent-2-enyl acetate **(3-5)** (2.50 g, 19.8 mmol). The resulting solution was heated under reflux overnight. The mixture was then partitioned between Et_2O and H_2O. The organic layer was separated, and the aqueous extracted with Et_2O (3 x 40 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to give diethyl-2-(cyclopent-2-enyl) malonate **(3-6)** (3.14 g, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24-1.28 (m, 6H), 1.58-1.63 (m, 1H), 2.09-2.16 (m, 1H), 2.30-2.36 (m, 2H), 3.24 (d, 1H, *J* = 9.3 Hz), 3.33-3.38 (m, 1H), 4.16-4.23 (m, 4H), 5.65-5.68 (m, 1H), 5.80-5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.07, 27.76, 31.72, 45.33, 57.06, 61.17, 131.50, 132.82, 168.70, 168.75. Spectral data are consistent with those reported in the literature.[4]

1-Aza-1-(cyclopent-2-en-1-yl)-(4-methylbenzene-sulfonyl)-9-trimethylsilyl-6,6,-dicarbethoxy-1nona-3,8-diyne, (3-8a):



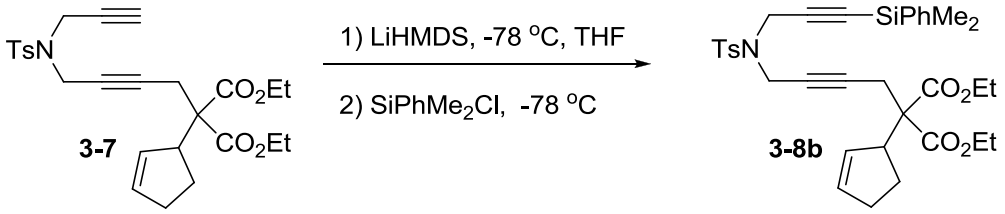
2-18 **3-6** **3-7** **3-8a**

Diethyl 2-(cyclopent-2-enyl) malonate **(3-6)** (1.66 g, 7.35 mmol) in 10 mL of THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.353 g, 8.82 mmol) in 40 mL of THF. The resulting mixture was stirred for 30 min at room temperature. Bromo-diyne **2-18** (2.50 g, 7.35 mmol) diluted in 10 mL of THF was added and the mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield dark oil. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give cyclopentene-diyne **3-7** as light yellow oil (3.11 g, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.26 (m, 6H), 1.62-1.71 (m, 1H), 1.91-2.01 (m, 1H), 2.10 (t, 1H, *J* = 1.8 Hz), 2.23-2.28 (m, 2H), 2.42 (s, 3H), 2.68 (t, 2H, *J* = 2.4 Hz), 3.42-3.50 (m, 1H), 4.08-4.21 (m, 8H), 5.71-5.78 (m, 2H), 7.30 (d, 2H, *J* = 8.4 Hz), 7.70 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.00, 14.04, 21.50, 23.14, 25.02, 31.67, 35.95, 36.53, 48.72, 59.78, 61.30, 61.36, 73.71, 75.09, 76.31, 81.62, 127.79, 129.47, 131.09, 132.40, 135.33, 143.76, 169.71, 169.88;

To a solution of cyclopentene-diyne **3-7** (600 mg, 1.24 mmol) in 20 mL of THF was added dropwise 1 M LiHMDS (1.85 mL) in THF at -78 ^{o}C. The resulting mixture was stirred at -78 ^{o}C for 45 min and then trimethylchloro silane (165 mg, 1.49 mmol) in 10 mL of THF was added dropwise. The resulting mixture was then warmed slowly to -40 ^{o}C and stirred for 4 h. The reaction mixture was diluted with ether, followed by the addition of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to afford silyl-terminal cyclopentene-diyne **3-8a** as white solid (586 mg, 85% yield) ; mp = 70-71 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s,9H), 1.21-1.26 (m, 6H), 1.64-1.71 (m, 1H), 1.95-2.04 (m, 1H), 2.23-2.29 (m, 2H), 2.41 (s, 3H), 2.70 (t, 2H, *J* = 2.4 Hz), 3.42-3.50 (m, 1H), 4.11(t, 2H, *J* = 2.4 Hz), 4.11-4.21 (m, 6H), 5.71-5.78 (m, 2H), 7.29 (d, 2H, *J* = 8.4 Hz), 7.69 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -0.43, 14.05, 14.07, 21.50, 23.11, 25.03, 31.70, 36.50, 36.91, 48.76, 59.82, 61.31, 61.36, 75.25, 81.41, 90.93, 97.46, 127.83, 129.49, 131.15, 132.40, 135.41, 143.59, 169.76, 169.91.

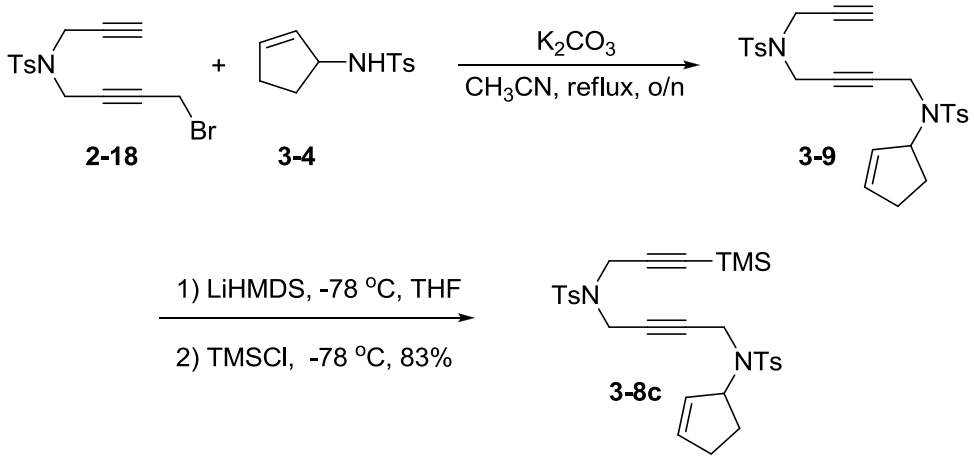
In the same manner 9-dimethylphenylsilyl derivative **3-8b** was synthesized.

1-Aza-1-(cyclopent-2-en-1-yl)-(4-methylbenzene-sulfonyl)-9- dimethylphenylsilyl-6,6,-dicarbethoxy-1nona-3,8-diyne, (3-8b):



Synthesized using LiHMDS (1.85 mL of 1 M solution in THF), cyclopentene-diyne **3-7** (0.60 g, 1.24 mmol) and dimethylphenylsilyl chloride (0.22 g, 1.24 mmol); 640 mg, 83% yield) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 6H), 1.17-1.24 (m, 6H), 1.62-1.71 (m, 1H), 1.94-2.02 (m, 1H), 2.26-2.41 (m, 2H), 2.32 (s, 3H), 2.71 (t, 2H, *J* = 2.1 Hz), 3.49-3.52 (m, 1H), 4.06-4.23 (m, 8H), 5.72-5.76 (m, 2H), 7.19 (d, 2H, *J* = 8.4 Hz), 7.34-7.39 (m, 3H), 7.45-7.48 (m, 2H), 7.68 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.00, 15.23, 22.64, 24.32, 26.21, 32.87, 37.77, 38.15, 49.93, 60.99, 62.48, 62.54, 76.39, 82.71, 90.21, 100.51, 128.96,129.00, 130.65, 130.68, 132.29, 133.60, 134.67, 136.50, 137.49, 144.80, 170.91, 171.07.

1,6-Bis(4-methylbenzenesulfonyl)-1-(cyclopent-2-en-1-yl)-1,6-diaza-9-trimethylsilylnona-3,8-diyne, (3-8c):

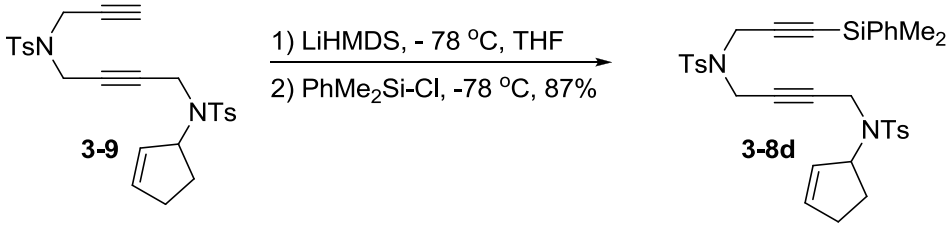


A suspension of *N*-(cyclopent-2-ynyl)-4-methylbenzenesulfonamide **(3-4)** (1.38 g, 5.81 mmol) and potassium carbonate (K_2CO_3, 1.58 g, 11.4 mmol) in 40 mL of CH_3CN was heated at reflux for 15 min. A solution of diyne-bromide **2-18** (1.94 g, 5.70 mmol) in 10 mL of CH_3CN was added and the resulting mixture was refluxed overnight. The mixture was cooled to room temperature, filtered over celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give **3-9** as white solid (2.43 g, 86%); mp = 115-116 ^oC. ^1H NMR (300 MHz, $CDCl_3$) δ 1.63-1.71 (m, 1H), 2.02-2.09 (m, 2H), 2.24-2.29 (m, 1H), 2.43 (s, 6H), 3.73-4.01 (m, 6H), 5.02-5.08 (m, 1H), 5.38-5.40 (m, 1H), 5.95-5.97 (m, 1H), 7.31 (d, 4H, *J* = 8.1 Hz), 7.69 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.53, 27.41, 31.38, 32.37, 36.11, 36.39, 64.15, 73.95, 76.03, 76.15, 82.19, 127.42, 127.80, 129.02, 129.37, 129.52, 129.57, 135.19, 136.47, 137.53, 143.38, 143.97;

To a solution of cyclopentene-diyne **3-9** (550 mg, 1.11 mmol) in 20 mL of THF was added dropwise 1 M LiHMDS (1.66 mL) in THF at -78 ^oC. The resulting mixture was stirred at -78 ^oC for 45 min and then trimethylchloro silane (135 mg, 1.22 mmol) in 10 mL of THF was added dropwise. The resulting mixture was then warmed slowly to -40 ^oC and stirred for 4 h. The reaction mixture was diluted with ether, followed by the addition of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to afford silyl-terminal cyclopentene-diyne **3-8c** as yellow oil (523 mg, 83% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 1.70-1.75 (m, 1H), 2.01-2.08 (m, 2H), 2.34-2.40 (m, 1H), 2.42(s, 3H), 2.44 (s, 3H), 3.76-4.00 (m, 6H), 5.03-5.09 (m, 1H), 5.40-5.43 (m, 1H), 5.96-5.98 (m, 1H),7.33 (m, 4H), 7.68 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -0.40, 21.53, 27.44, 31.42, 32.45, 36.37, 37.05, 64.14, 76.26, 81.91, 91.21, 97.27, 127.43, 127.82, 129.05, 129.53, 129.58, 135.33, 136.46, 137.57, 143.39, 143.78.

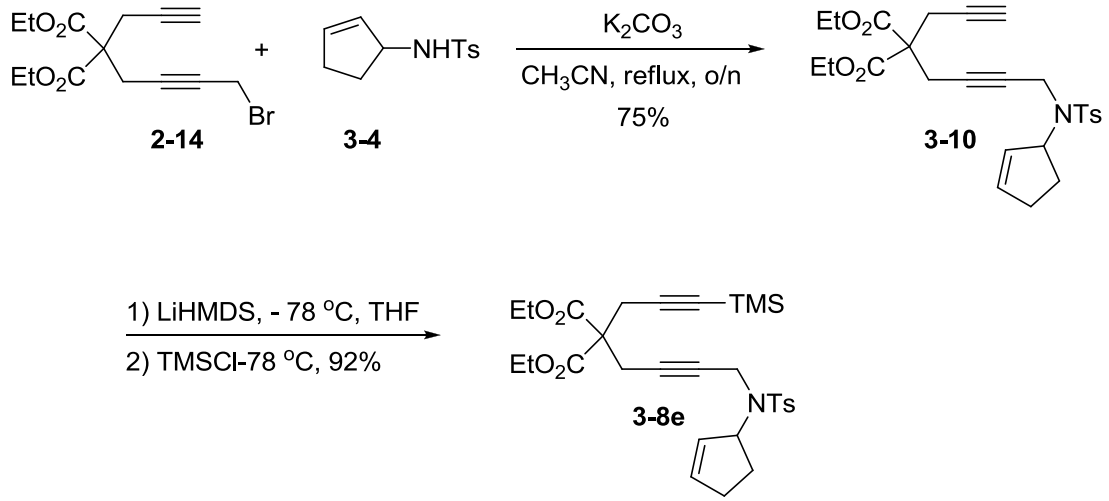
In the same manner 9-dimethylphenylsilyl derivative **3-8d** was synthesized.

1,6-Bis(4-methylbenzenesulfonyl)-1-(cyclopent-2-en-1-yl)-1,6-diaza-9-dimethylphenylsilyl -3,8-diyne, (3-8d):



Synthesized using LiHMDS (1. 50 mL of 1 M solution in THF), cyclopentene-diyne **3-9** (0.49 g, 0.98 mmol) and dimethylphenylsilyl chloride (0.17 g, 0.98 mmol); (540 mg, 87% yield) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 6H), 1.68-1.75 (m, 1H), 2.01-2.09 (m, 1H), 2.20-2.34 (m, 1H), 2.31-2.38 (m, 4H), 2.41 (s, 3H), 3.76-3.97 (m, 4H), 4.08 (s,2H), 5.04-5.07 (m, 1H), 5.40-5.43 (m, 1H), 5.92-5.97 (m, 2H),7.21 (d, 2H, *J* = 8.1 Hz),7.27-7.47(m, 7H), 7.67(d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -1.16, 21.50, 27.44, 31.40, 32.42, 36.45, 37.12, 64.14, 76.17, 82.04, 89.33, 99.07, 127.41, 127.77, 127.88, 129.03, 129.52, 129.60, 133.50, 135.21, 136.17, 136.49, 137.54, 143.39, 143.83;

1-Aza-1-(cyclopent-2-en-1-yl)-6,6,-dicarbethoxy-9-trimethylsilyl-1-(4-methylbenzene-sulfonyl)nona-3,8-diyne, (3-8e):



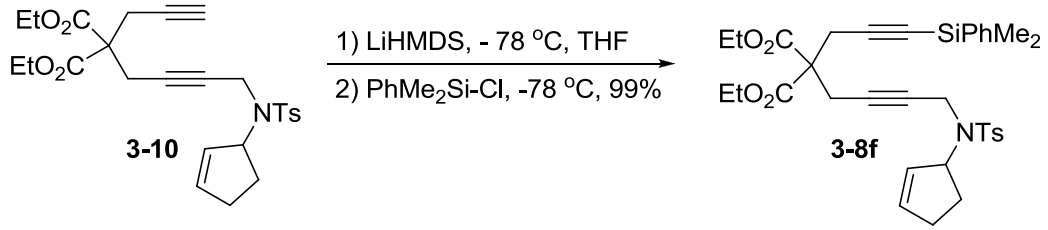
A suspension of *N*-(cyclopent-2-ynyl)-4-methylbenzenesulfonamide **(3-4)** (0.820

g, 3.46 mmol) and potassium carbonate (K_2CO_3, 0.956 g, 6.92 mmol) in 30 mL of CH_3CN was heated at reflux for 15 min. A solution of the diyne-bromide **2-14** (1.14 g, 3.46 mmol) in 10 mL of CH_3CN was added and the resulting mixture was refluxed overnight. The mixture was cooled to room temperature, filtered over celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give **3-10** as viscous yellow oil (1.26 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.27 (m, 6H), 1.75-1.77 (m, 1H), 2.01-2,09 (m, 2H), 2.20-2.27 (m, 1H), 2.43 (s, 3H), 2.83-2.85 (m, 4H), 3.85-3.94 (m, 2H), 4.10-4.24 (m, 4H), 5.01-5.06 (m, 1H), 5.43-5.46 (m, 1H), 5.97-5.99 (m, 1H), 7.32 (d, 2H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.95, 21.49, 22.54, 22.73, 27.37, 29.29, 31.36, 32.54, 56.19, 61.97, 64.10, 71.52, 77.86, 78.53, 79.84, 127.41, 127.46, 129.12, 129.42, 136.31, 137.70, 143.09, 168.57.

To a solution of cyclopentene-diyne **3-10** (0.620 g, 1.28 mmol) in 20 mL of THF was added dropwise 1 M LiHMDS (1.92 mL) in THF at -78 ^{o}C. The resulting mixture was stirred at -78 ^{o}C for 45 min and then trimethylsilyl chloride (0.210 g, 1.92 mmol) in 10 mL of THF was added dropwise. The resulting mixture was then warmed slowly to -40 ^{o}C and stirred for 4 h. The reaction mixture was diluted with ether, followed by the addition of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eleuent to afford silyl-terminal cyclohexenediyne **3-8e** as yellow oil (0. 66 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.21-1.29 (m, 6H), 1.73-1.81 (m, 1H), 1.99-2.06 (m, 1H), 2.22-2.54 (m, 1H), 2.37-2.40 (m, 1H), 2.43 (s, 3H), 2.82-2.84 (m, 4H), 3.79-4.00 (m, 2H), 4.04-4.21 (m, 4H), 5.00-5.04 (m, 1H), 5.42-5.46 (m, 1H), 5.96-5.99 (m, 1H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -0.07, 14.01, 21.52, 22.76, 23.93, 27.39, 31.41, 32.61, 56.49, 61.89, 64.11, 78.11, 79.74, 88.25, 100.92, 127.50, 129.15, 129.44, 136.32, 137.73, 143.12, 168.61.

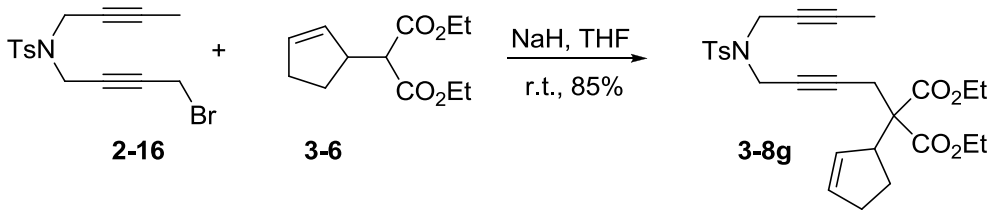
In the same manner 9-dimethylphenylsilyl derivative **3-8f** was synthesized.

1-Aza-1-(cyclopent-2-en-1-yl)-6,6,-dicarbethoxy-9-dimethylphenylsilyl-1-(4-methylbenzene-sulfonyl)nona-3,8-diyne (3-8f):



Synthesized using LiHMDS (1.92 mL of 1 M solution in THF), cyclopentene-diyne **3-10** (0.62 g, 1.28 mmol) and dimethylphenylsilyl chloride (0.33 g, 1.92 mmol); (0. 79 g, 99% yield) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.36 (s, 6H), 1.19-1.28 (m, 6H), 1.73-1.81 (m, 1H), 1.99-2.10 (m, 1H), 2.23-2.31 (m, 1H), 2.38-2.43 (m, 4H), 2.85-2.91 (m, 4H), 3.83-4.05 (m, 2H), 4.17-4.20 (m, 4H), 5.00-5.02 (m, 1H), 5.43-5.46 (m, 1H), 5.94-5.99 (m, 1H), 7.29-7.40 (m, 5H), 7.62 (d, 2H, *J* = 8.1 Hz), 7.78 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -0.85, 13.97, 21.45, 22.84, 24.03, 27.39, 31.38, 32.57, 56.46, 61.92, 64.09, 78.01, 79.81, 86.27, 102.80, 127.45, 127.80, 127.84, 129.11, 129.37, 133.58, 136.30, 136.87, 137.70, 143.11, 168.56.

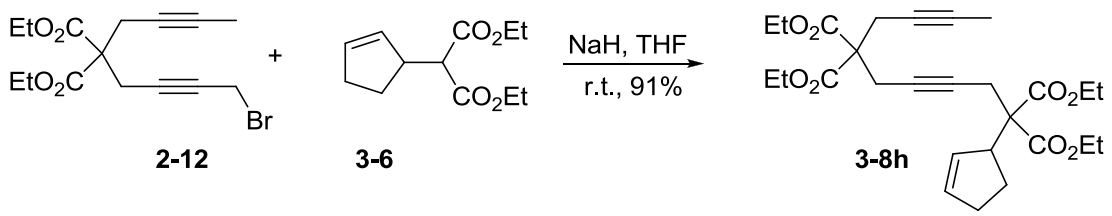
6-Aza-1-(cyclopent-2-en-1-yl)-,1,1-dicarbethoxy-6-(4-methylbenzenesulfonyl)deca-3,8-diyne, (3-8g):



Diethyl 2-(cyclopent-2-enyl) malonate **(3-6)** (268 mg, 1.19 mmol) in 10 mL of THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 57 mg, 1.4 mmol) in 10 mL of THF. The resulting mixture was stirred for 30min at room temperature. Bromodiyne **2-16** (420 mg, 1.19 mmol) in 5 mL of THF was added and the mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over

$MgSO_4$, filtered and concentrated to yield dark oil. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give cyclopentene-diyne **3-8g** as light yellow viscous oil (514 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.26 (m, 6H), 1.62 (t, 3H, *J* = 2.4 Hz), 1.65-1.69 (m, 1H), 1.93-2.01 (m, 1H), 2.21-2.28 (m, 2H), 2.41 (s, 3H), 2.67 (t, 2H, *J* = 2.4 Hz), 3.44-3.48 (m, 1H), 4.05-4.20 (m, 8H), 5.70-5.79 (m, 2H), 7.29 (d, 2H, *J* = 8.7 Hz), 7.69 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.30, 13.98, 14.10, 21.48, 23.15, 25.04, 31.69, 36.49, 48.73, 59.81, 61.29, 61.34, 71.43, 75.44, 81.26, 81.63, 127.89, 129.29, 131.17, 132.36, 135.53, 143.47, 169.75, 169.91.

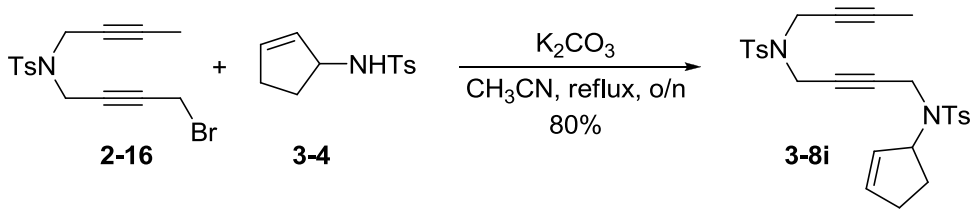
1-(Cyclopent-2-en-1-yl)-,1,16,6-tetracarbethoxydeca-3,8-diyne, (3-8h):



2-12 **3-6** **3-8h**

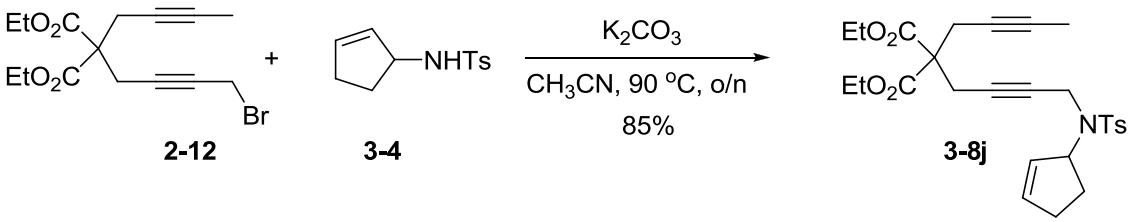
Diethyl 2-(cyclopent-2-enyl) malonate **(3-6)** (363 mg, 1.60 mmol) in 10 mL of THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 77 mg, 1.9 mmol) in 10 mL of THF. The resulting mixture was stirred for 30min at room temperature. Bromodiyne **2-12** (550 mg, 1.60 mmol) in 5 mL of THF was added and the mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield dark oil. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give cyclopentene-diyne **3-8h** as light yellow oil (709 mg, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.27 (m,12H), 1.66-1.73 (m, 4H), 2.00-2.06 (m, 1H), 2.23-2.28 (m, 2H), 2.76 (t, 2H, *J* = 2.4 Hz), 2.86 (q, 2H, *J* = 2.4 Hz), 2.90 (t, 2H, *J* = 2.4 Hz), 3.54-3.57 (m, 1H), 4.14-4.22 (m, 8H), 5.74-5.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.39, 13.95, 14.03, 22.74, 22.77, 23.30, 25.07, 31.65, 48.59, 56.71, 59.88, 61.14, 61.22, 61.64, 73.21, 78.37, 78.71, 131.49, 132.07, 169.02, 169.86, 170.02.

1,6-Bis(4-methylphenylsulfonyl)-1-(cyclopent-2-en-1-yl)- 1,6-diazadeca-3,8-diyne, (3-8i):



A suspension of *N*-(cyclopent-2-ynyl)-4-methylbenzenesulfonamide **(3-4)** (320 mg, 1.36 mmol) and potassium carbonate (K_2CO_3, 376 mg, 2.72 mmol) in 30 mL of CH_3CN was heated at reflux for 15 min. A solution of diyne-bromide **2-16** (481 g, 1.36 mmol) in 10 mL of CH_3CN was added and the resulting mixture was refluxed overnight. The mixture was cooled to room temperature, filtered over celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 10% EtOAc in hexanes as eluent to give **3-8i** as viscous yellow oil (554 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61-1.72 (m, 4H), 2.01-2.06 (m, 1H), 2.22-2.38 (m, 2H), 2.42 (s, 3H), 2.43 (s, 3H), 3.74-3.99 (m, 6H), 5.02-5.05 (m, 1H), 5.37-5.41 (m, 1H), 5.93-5.97 (m, 1H), 7.27-7.32 (m, 4H), 7.66-7.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.35, 21.52, 27.39, 31.38, 32.43, 36.37, 36.66, 64.14, 71.29, 76.42, 81.83, 81.85, 127.43, 127.89, 129.04, 129.38, 129.50, 135.41, 136.46, 137.54, 143.37, 143.66.

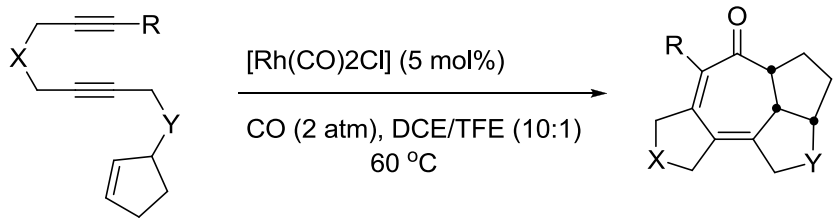
1-Aza-1-(cyclopent-2-en-1-yl)-6,6-dicarbethoxy-1-(4-methylbenzenesulfonyl)nona-3,8-diyne, (3-8j);



A suspension of *N*-(cyclopent-2-ynyl)-4-methylbenzenesulfonamide **(3-4)** (691 mg, 2.91 mmol) and potassium carbonate (K_2CO_3, 804 mg, 5.82 mmol) in 30 mL of CH_3CN was heated at reflux for 15 min. A solution of the diyne-bromide **2-12** (1.00 g, 2.91 mmol) in 10 mL of CH_3CN was added and the resulting mixture was refluxed

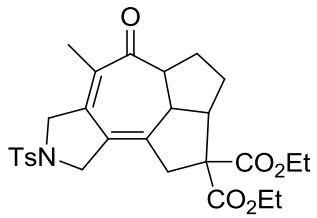
overnight. The mixture was cooled to room temperature, filtered over celite and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as eluent to give **3-8j** as yellow oil (1.24 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.25 (m, 6H), 1.74-1.81 (m, 4H), 2.01-2.05 (m, 1H), 2.14-2.24 (m, 1H), 2.38-2.41 (m, 1H), 2.43 (s, 3H), 2.77 (q, 2H, *J* = 2.4 Hz), 2.83 (t, 2H, *J* = 2.1 Hz), 3.79-4.04 (m, 2H), 4.10-4.22 (m, 4H), 5.01-5.03 (m, 1H), 5.43-5.45 (m, 1H), 5.96-5.98 (m, 1H), 7.32 (d, 2H, *J* = 8.7 Hz), 7.79 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.41, 13.95, 21.47, 22.74, 22.89, 27.32, 31.33, 32.57, 56.51, 61.74, 64.07, 73.07, 78.19, 78.86, 79.55, 127.45, 129.08, 129.37, 136.28, 137.69, 143.04, 168.91.

§ 3.4.3. [2+2+2+1] Cycloaddition of cyclopentene-diynes with carbon monoxide



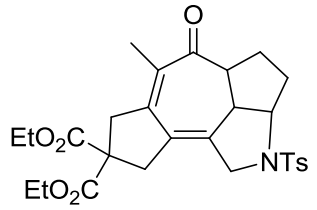
Typical procedure is described for the reaction of cyclohexene-diyne **4a**: A 25 cm^3 round bottomed flask charged with an **4a** (100 mg, 0.19 mmol) in DCE/TFE (10:1) (3.90 cm^3, [0.05 M] and $[Rh(CO)_2Cl]_2$ (3.8 mg, 0.009 mmol) was transferred to a 125 cm^3 stainless steel autoclave and purged with CO and released (4x) (**Caution must be done in a well ventilated fume hood**) and then charged with CO to 2 atm. The autoclave was immersed in an oil bath at 60 ^{o}C for 20 h. The autoclave was allowed to cool to room temperature, followed by release of the gas in a well ventilated fume hood. The reaction mixture was concentrated under reduced pressure and the resulting crude product was purified by column chromatography on silica gel using EtOAc/hexanes (15/85) as eluent to give fused tetracyclic products.

Diethyl-6-methyl-2-[(4-methylphenyl)sulfonyl]-5-oxo-2a,3,4,5,5a,6,8,9,9c-nona ahydrobenzo[1,8]azuleno[4,5-*c*]pyrrole-2,2(1*H*)-dicarboxylate, (3-11g):



94% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22-1.31 (m, 8H), 1.66 (s, 3H), 1.71-1.87 (m, 3H), 2.33 (d, 1H, *J* = 14.1 Hz), 2.43 (s, 3H), 2.48-2.54 (m, 1H), 2.93 (t, 1H, *J* = 6.6 Hz), 3.17-3.24 (m, 1H), 3.62 (d, 1H, *J* = 6.6 Hz), 3.92 (d, 1H, *J* = 15.3 Hz), 4.03-4.12 (m, 1H), 4.17-4.35 (m, 5H), 7.36 (d, 2H, *J* = 7.8 Hz), 7.73 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.10, 21.54, 27.17, 29.26, 34.14, 44.36, 46.48, 48.05, 50.35, 51.67, 54.66, 57.13, 61.55, 61.71, 127.45, 129.95, 132.21, 133.49, 144.05, 171.06, 172.00, 208.60.

Diethyl-6-methyl-2-[(4-methylphenyl)sulfonyl]-5-oxo-2,2a,3,4,5,5a,6,8,9,9c-nona ahydroazuleno[4,5,6-*cd*]indole-9,9(1*H*)-dicarboxylate, (3-11j):



Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18-1.27 (m, 7H), 1.63-1.69 (m, 1H), 1.78-1.89 (m, 5H), 2.43 (s, 3H), 2.73-3.01 (m, 3H), 3.10-3.30 (m, 2H), 4.03-4.06 (m, 1H), 4.15-4.21 (m, 4H), 4.31-4.37 (m, 1H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.99, 21.52, 26.91, 31.32, 39.88, 41.51, 47.23, 52.59, 56.82, 56.91, 61.95, 62.03, 65.32, 127.46, 129.85, 130.45, 132.60, 134.91, 136.76, 143.76, 146.43, 170.56, 170.69, 199.10;

§ 3.5. References

1. Kaloko, J. J.; Teng, Y.-H. G.; Ojima, I., One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. *Chem. Commun.* **2009**, 4569 - 4571.

2. McCleverty, J. A.; Wilkinson, G., Dichlorotetracarbonyldirhodium (rhodium carbonyl chloride). *Inorg. Syn. 8*, 211-214.

3. Kim, D. Y.; Kim, H. S.; Choi, Y. J.; Mang, J. Y.; Lee, K., Transformation of allyl stannanes into allyl amines using [*N*-(p-toluenesulfonyl)imino]-phenyliodinane. *Synth. Commun.* **2001,** *31*, 2463-2469.

4. Adamczyk, M.; Grote, J.; Douglas, J.; Dubler, R.; Harrington, C., Synthesis of conjugates for a barbiturate screening assay. *Bioconjugate Chem.* **1992,** *8*, 281-288.

Chapter 4

Formation of 5-7-5 fused tricyclic γ-lactones *via* Rh(I)-catalyzed [2+2+2+1] cycloaddition of enediynes with carbon monoxide

Table of Contents

§ 4.1. Introduction

Natural products and their metabolites isolated from diverse origins have been an extraordinary source in the development of active pharmaceuticals, agrochemicals and other applications. Often, natural products also serve as templates to obtain more potent and selective agents through structure-activity relationship (SAR) studies. A ubiquitous feature of natural products and their metabolites is that they often contain fascinating fused-ring skeletons. Carbocyclic seven-membered rings fused with γ-butyrolactones are prominent constituents in a wide variety of biologically active compounds.[1] Among them, the guaianolides **4-1** and **4-2**, pseudoguaianoides **4-3** and **4-4** and tremulanes **4-5** (**Figure 4-1**) possessing a tricyclic 5-7-5 ring system, are a widely distributed class of sesquiterpene lactones displaying a broad range of biological activity.[1a, b, 1d, 2]

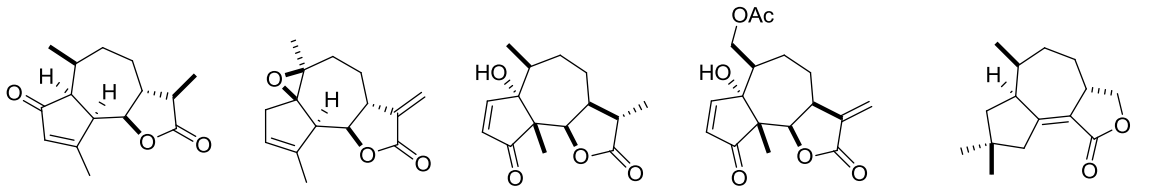


Figure 4-1: Natural products with 5-7-5 fused lactone skeletons

The key difference between the guaianolides **4-1** and **4-2** and pseudoguaianoides **4-3** and **4-4** lies in the stereochemical orientation of the lactone. The γ-butyrolactone moiety is generally *trans* in guaianolides, while the pseudoguaianolides are generally found to contain a *cis*-fused α-methyl or α-methylene γ-butyrolactones.

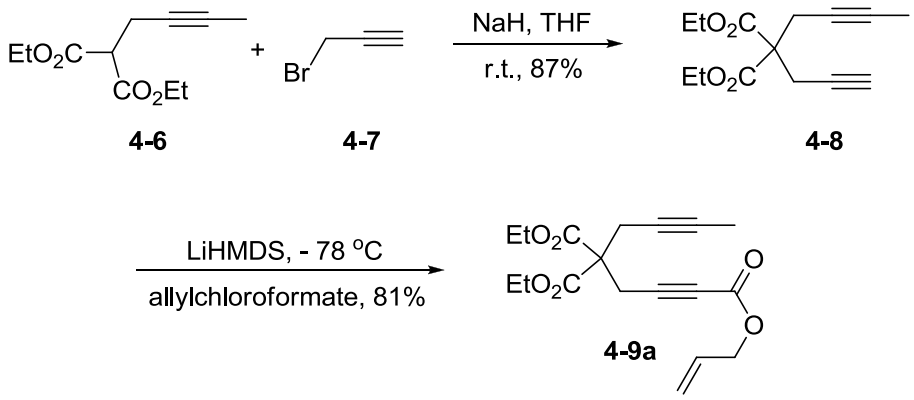
Unfortunately, the vast majority of natural products cannot be isolated in large quantities from their natural source. Consequently, the need to develop highly efficient synthetic methods that provide access to fused-ring skeletons with handles for further modification is necessary. Transition metal-catalyzed carbocyclization and cycloaddition reactions have proven to be among the most efficient methods for natural products synthesis as well as constructing "natural product-like" and "drug-like" skeletons.[3]

As a part of continuing studies on higher order cycloaddition reactions, the Rh(I)-catalyzed [2+2+2+1] cycloaddition of 1-substituted dodec-11-ene-8-oxo-1,6-diynes to yield 5-7-5 tricyclic products with fused γ-lactones was investigated. Tricyclic products with modifiable functional groups were obtained from simple linear starting materials in a single reaction and in good to excellent yields.

§ 4.2. Result and discussion

§ 4.2.1. Synthesis of 1-substituted dodec-11-ene-8-oxo-1,6-diynes

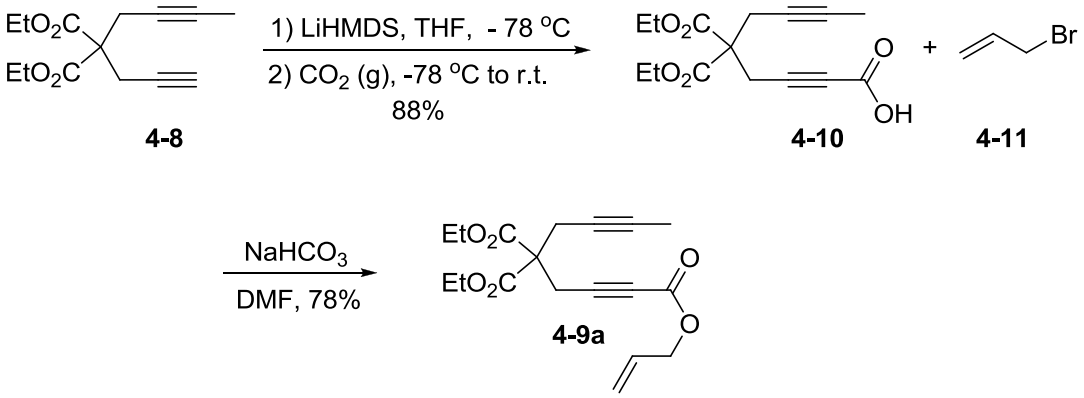
The synthesis of 9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne **(4-9a)** began with the coupling of butynyl malonate **(4-6)** with propargyl bromide **(4-7)** in the presence of NaH in THF, and afforded the desired *bis*-propargylic malonate **4-8** in 87% yield (**Scheme 4-1**). The treatement of malonate **4-8** with allyl chloroformate in the presence of LiHMDS afforded the desired enediyne derivative **4-9a** in 81% isolated yield (**Scheme 4-1**).



Scheme 4-1: Synthesis of 9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne **(4-9a)**

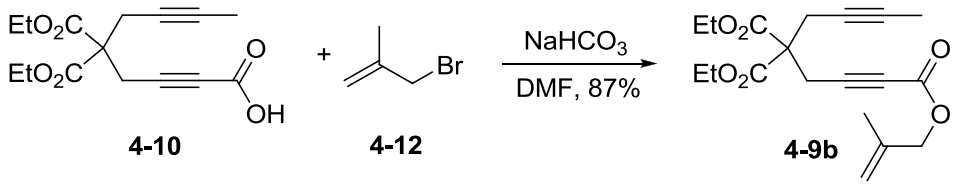
Though the desired oxo- enediyne **4-9a** could be obtained easily as described in **Scheme 4-1**, it was necessary to develop a more general method that would permit the preparation of substrates with diverse allyl substituents. We envisioned that such substrates could be easily accessed by esterification from the corresponding acid derivative. Thus, treatment of *bis*-propargylic malonate **4-8** with LiHMDS in THF at –

78 ^{o}C, followed by quenching the resulting acetylide with gaseous carbon dioxide gave acid **4-10** in 88% isolated yield (**Scheme 4-2**). The desired oxo-enediyne **4-9a** was then obtained in 78% yield by coupling of acid **4-10** with allyl bromide **4-11** in the presence of $NaHCO_3$ in DMF (**Scheme 4-2**).

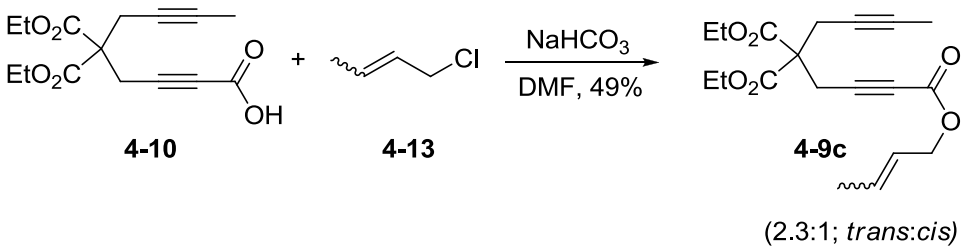


Scheme 4-2: Synthesis of 9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne **(4-9a)**

In a similar manner, oxo-enediynes **4-9b** and **4-9c** were obtained in 87% and 49% yields respectively from the treatment of acid **4-10** with methylallyl bromide **4-12** and crotyl chloride **4-13** respectively (**Schemes 4-3 and 4-4**).

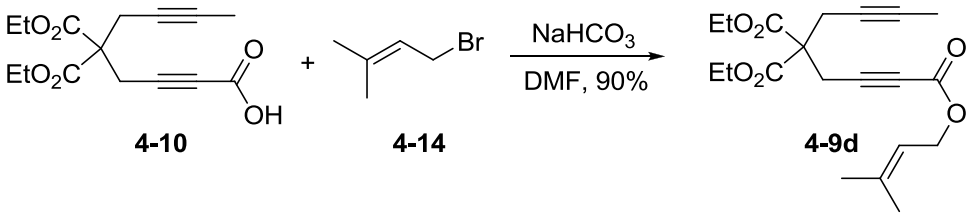


Scheme 4-3: Synthesis of 2-methyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne **(4-9b)**

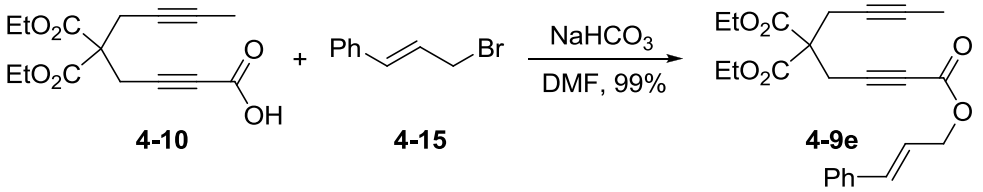


Scheme 4-4: 10,10-di(carbethoxy)-5-oxo-6-oxa-tetradeca-2-ene-7,12-diyne **(4-9c)**

The enediynes **4-9d** and **4-9e**, with dimethyl and phenyl substituents respectively on the allyl component were similarly synthesized from the reaction of acid **4-10** with prenyl bromide **4-14** and cinnamyl bromide **4-15**, respectively, in excellent isolated yields (**Schemes 4-5 and 4-6**).

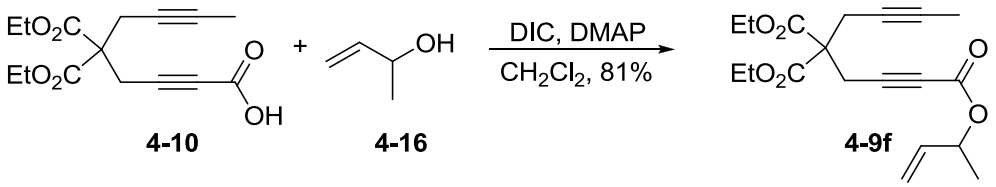


Scheme 4-5: Synthesis of 2-methyl-10,10-di(carbethoxy)-5-oxo-6-oxa-tetradeca-2-ene-7,12-diyne **(4-9d)**

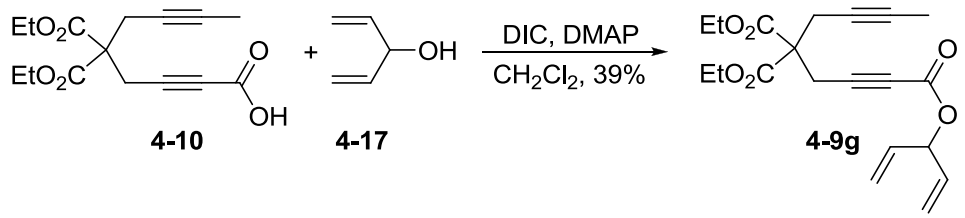


Scheme 4-6: Synthesis of 1-phenyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne **(4-9e)**

Substrates **4-9f** and **4-9g** were obtained in 81% and 39% yields respectively from the *N*,*N*-diisopropylcarbodiimide (DIC) mediated esterification of acid **4-10** with racemic but-3-en-2-ol **4-16** and 1,4-pentadien-3-ol **4-17** respectively (**Schemes 4-7 and 4-8**).

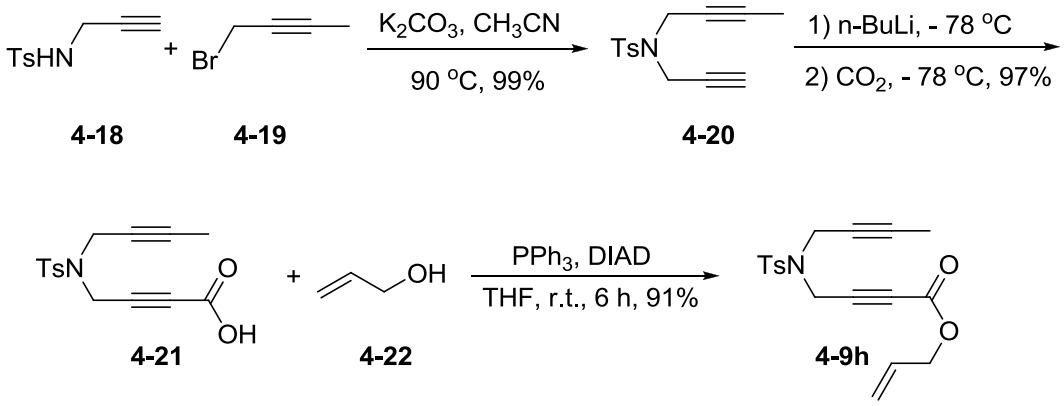


Scheme 4-7: Synthesis of 3-methyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne **(4-9f)**



Scheme 4-8: Synthesis of 3-vinyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne **(4-9g)**

N-tosyl tethered oxo-enediyne substrates were also prepared. The synthesis began with the nucleophilic substitution of bromo-butyne **4-19** with *N*-propargyl-*N*-tosyl amine **4-18** in the presence of potassium carbonate which afforded the desired *N*-butynyl-*N*-tosyl-*N*-propargyl amine **4-20** in 99% yield (**Scheme 4-9**).

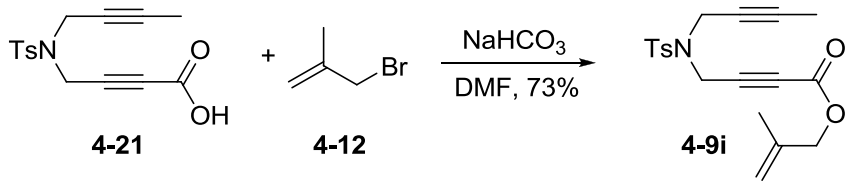


Scheme 4-9: Synthesis of 9-(4-methylbenzenesulfonyl)-4-oxo-5-oxa-9-azatrideca-1-ene-6,11-diyne **(4-9h)**

The attempted coupling of compound **4-20** with allylchloroformate in the presence of LiHMDS resulted in a 1:1 mixture of desired product **4-9h** and starting material **4-20** which could not be separated by column chromatography. Furthermore, the use of a large excess of base and varying the reaction temperature did not result in complete conversion to the desired product **4-9h**. Thus, compound **4-20** was converted to acid **4-21** *via* treatment of the preformed acetylide with gaseous carbon dioxide, in excellent yield. Attempted coupling of acid **4-21** with allyl alcohol **4-22** mediated either by DCC or EDC failed to give any of the desired product **4-9h**. The *N*-tosyl tethered substrate **4-9h** was

finally obtained *via* Mitsunobu esterification of acid **4-21** with allyl alcohol **4-22** in 91% yield (**Scheme 4-9**).

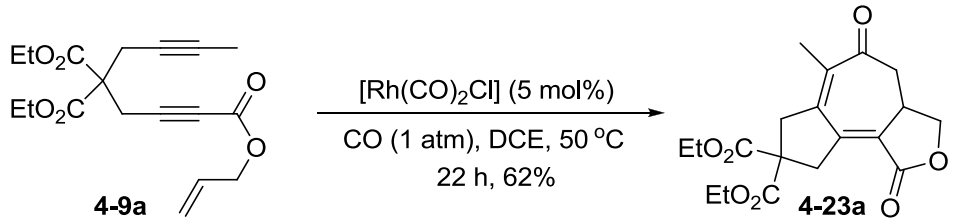
The methylallyl substituted substrate **4-9i** was also prepared from the reaction of acid **4-21** with methylallyl bromide **4-12** in the presence of $NaHCO_3$ in DMF (**Scheme 4-10**).



Scheme 4-10: Synthesis of 2-methyl-9-(4-methylbenzenesulfonyl)-4-oxo-5-oxa-9-azatrideca-1-ene-6,11-diyne **(4-9i)**

§ 4.2.2. Optimization of [2+2+2+1] cycloaddition reaction

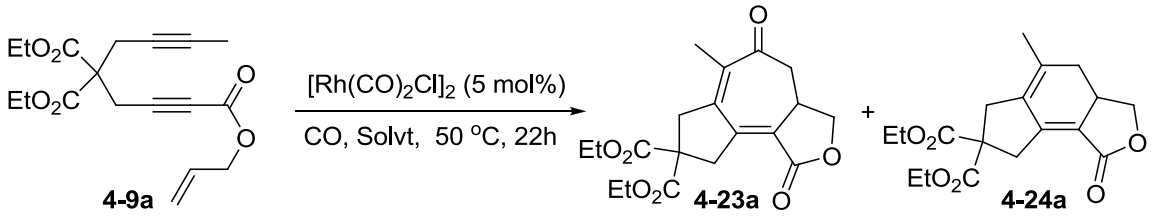
With the enediyne substrates in hand, the Rh(I)-catalyzed [2+2+2+1] cycloaddition of this new substrate type was investigated. We were pleased to find that the reaction of enediyne **4-9a** with 5 mol% $[Rh(CO)_2Cl]_2$ and 1 atm of CO in DCE, at 50 ^oC, gave the desired tricyclic product **4-23a**, in 62% isolated yield (**Scheme 4-11**).[4]



Scheme 4-11: Formation of 8,8-Bis(carbethoxy)-6-methyl-1,5-dioxo-3a,4,5,7,9-pentahydro-3H-2-oxacyclopenta-[*e*]azulene, **(4-23a)**

Analysis of the crude reaction mixture by HPLC indicated a clean reaction with two major peaks (**Entry 1, Table 1**). Further analysis by LC-MS showed molecular masses consistent with the desired [2+2+2+1] product **4-23a** and [2+2+2] product **4-24a** or enediyne substrate **4-9a**. When the reaction was ran in toluene, at 1 atm of CO and 50 ^oC in similar concentration, a significant increase of the [2+2+2+1] product **4-23a** was

noted, as determined by HPLC (i.e. 88:12 vs. 70:30 ratio) (**entry 1 vs 2, Table 1**). Further increase in selectivity for the carbonylated product **4-23a** was observed under more dilute conditions, with toluene as solvent (**entry 3**). Increasing the pressure of carbon monoxide to 2 atm gave similar results to that at 1 atm of CO pressure (**entries 3 and 6**). Trifluoroethanol (TFE) has been shown to be an effective solvent in cyclocarbonylation reactions.[5] Thus, performing the reaction in TFE as solvent at [0.025 M] gave similar results to that of toluene (**entries 2 and 7**), but the reaction in TFE was found to be "cleaner" than in toluene. Therefore, the optimium conditions to date include a concentration of [0.025] in TFE and 1 atm of CO pressure, at 50 ^{o}C, for 22 h.



Scheme 4-12: [2+2+2+1] Cycloaddition of enediyne **4-9a** with carbon monoxide

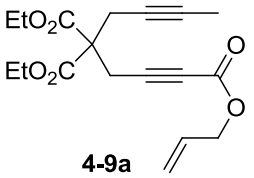
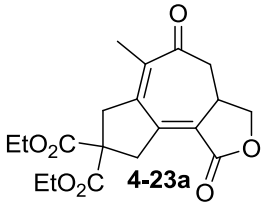
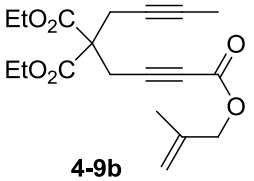
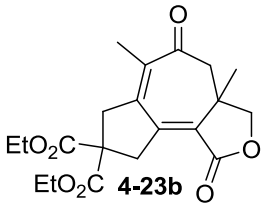
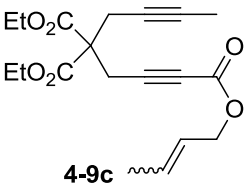
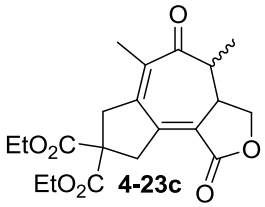
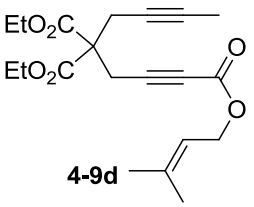
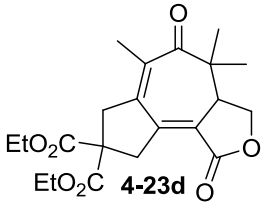
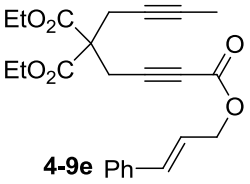
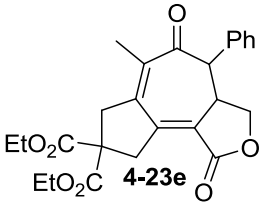
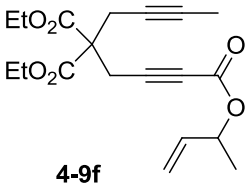
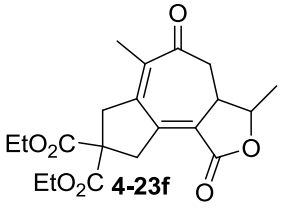
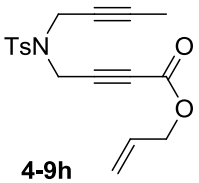
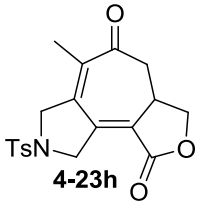
Table 4-1: Optimization of [2+2+2+1] cycloaddition of enediyne **4-9a** with CO

Entry	Solvent	Conc. [M]	Press (atm)	Ratio (**4-23a**:**4-24a**)[a]
1	dichloroethane	0.05	1	70:30
2	toluene	0.05	1	88:12
3	toluene	0.025	1	94:6
4	dichloroethane	0.025	1	80:20
5	toluene	0.0125	1	87:13
6	toluene	0.025	2	92:8
7	trifluoroethanol	0.025	1	93:7

[a] Determined by reverse phase HPLC analysis (CH_3CN:H_2O, Phenomenex, Jupiter 10µ Proteo 90A)

With optimized conditions found, the enediyne substrates on hand were then subjected to the carbonylation reaction. Substrate **4-9a**, which was used in the optimization studies, gave the corresponding tricyclic fused lactone **4-23a** in 96% isolated yield (**Table 4-2, entry 1**). It should be noted that no [2+2+2] product was detected by LC/MS or HPLC analysis of the crude reaction mixture. The methylallyl-substitued enediyne **4-9b** gave the desired fused γ-lactone **4-23b** with a quaternary stereocenter in 80% isolated yield (**entry 2**). The crotyl substituted enediyne **4-9c** (*trans*/*cis* = 2.3:1) gave two products as determined by HPLC (**entry 3**). LC/MS of the crude reaction mixture showed only the mass corresponding to the carbonylated product **4-23c**. ^{1}H NMR of the crude reaction mixture also indicated two products. Therefore, it is possible that the carbonylation reaction is stereospecific; however, at this point more experiments need to be done to ascertain this possibility. The product mixture **4-23c** was isolated in 81% yield by column chromatography (**entry 3**). The separation of the mixture by preparatory HPLC would need to be done in order for the structures to be confirmed by NMR studies. It should be noted that two contiguous chiral centers resulted from this single transformation.

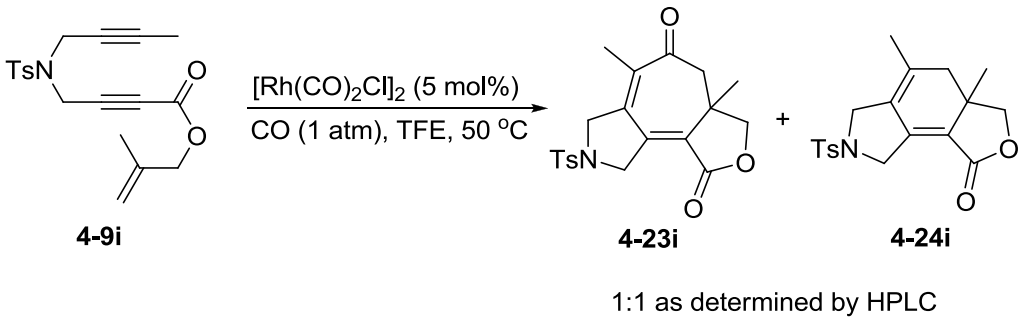
Table 4-2: [2+2+2+1] cycloaddition of enediynes **4-9a-g** with CO

Entry	Substrate	Product	(yield %)[a]
(1)	 **4-9a**	 **4-23a**	(96)
(2)	 **4-9b**	 **4-23b**	(80)
(3)	 **4-9c**	 **4-23c**	(81)
(4)	 **4-9d**	 **4-23d**	(NR)
(5)	 **4-9e** Ph	 **4-23e**	(NR)
(6)	 **4-9f**	 **4-23f**	(90)
(7)	 **4-9h**	 **4-23h**	(40)

Reactions were ran using 50 mg of substrate, 5 mol% $[Rh(CO)_2Cl]_2$, CO (1 atm) TFE at [0.025] for 20 h at 50 °C. [a] isolated yield. NR = no reaction.

The prenyl and phenyl substituted enediynes **4-9d** and **4-9e** failed to react under the current optimized conditions, probably due to the steric effects of the dimethyl and phenyl substituents (**entries 4 and 5**). Performing the reactions either in toluene or TFE at elevated temperature (80 ^{o}C) resulted in no conversion, as determined by HPLC and ^{1}H NMR. These results clearly show the sensitivity of the reaction with respect to steric effects at the allylic position. Tricyclic fused lactone **4-23f** bearing two contiguous tertiary chiral centers was obtained in excellent yield (90%) from the reaction of enediyne **4-9f** (**Table 2, entry 6**).

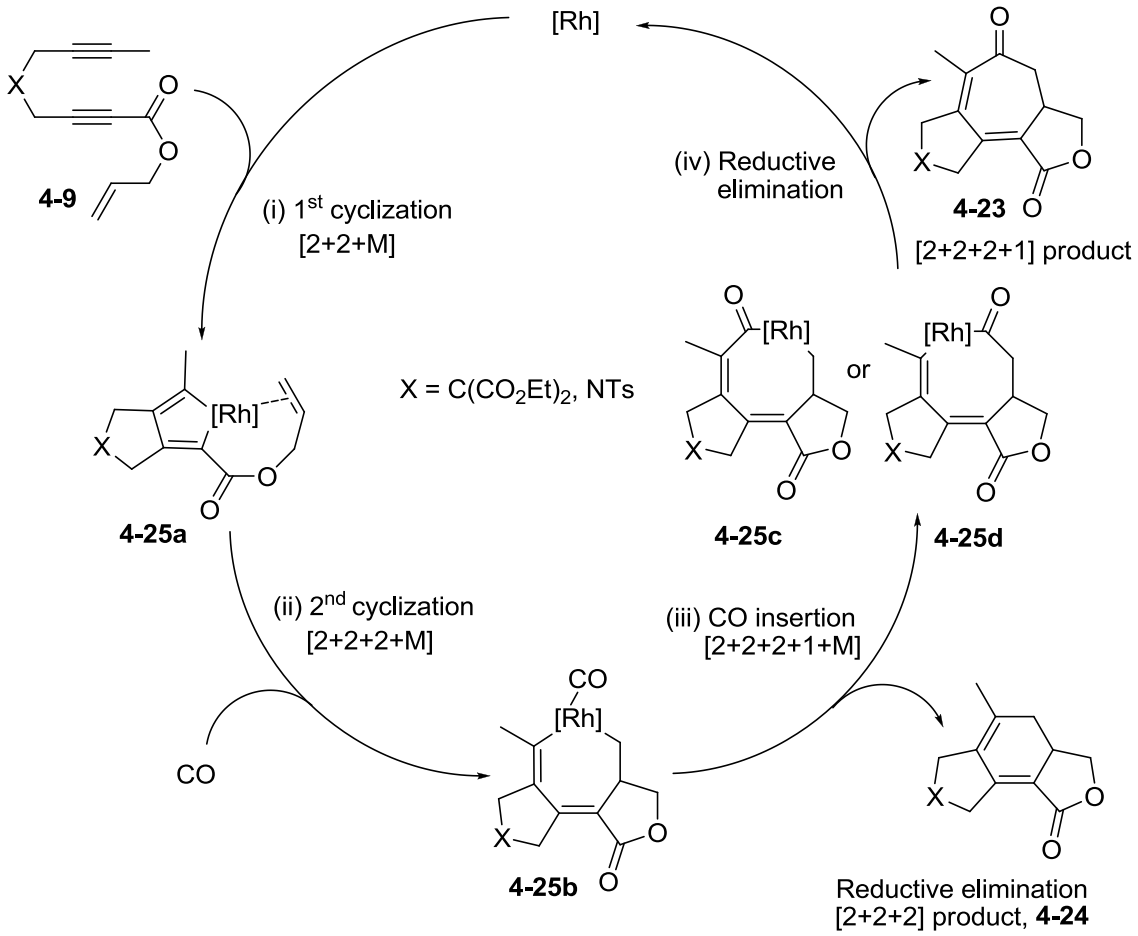
The treatment of *N*-tosyl tethered enediyne **4-9h** with $[Rh(CO)_2Cl]_2$ (5 mol%), under 1 atm of CO in TFE at 0.025 M, gave the carbonylated product **4-23h** in 40% isolated yield (**Table 4-2, entry 7**). A very complex mixture was obtained when the reaction was carried out in toluene at 0.025 M. Analysis of the crude reaction mixture by LC-MS indicated the desired product along with the [2+2+2] cycloadduct. In addition, a compound with the molecular weight corresponding to the "dimer" of compound **4-9h** was also detected. A slight decrease in the dimeric product was noted when dichloroethane (DCE) was used as solvent, but an increase in the [2+2+2] product was noted. Subjecting the *N*- methylallyl enediyne **4-9i** to the optimium conditions gave a 1:1 ratio of [2+2+2+1] **4-9i** and [2+2+2] **4-24i** products as determined by HPLC (**Scheme 4-13**). Therefore, investigations aimed at optimizing the reaction conditions for these substrates are ongoing.



Scheme 4-13: [2+2+2+1] cycloaddition of enediyne **4-9i** with CO

The proposed mechanism for the formation of 5-7-5 fused γ-lactones is outlined in **Scheme 4-14**. The proposed mechanism includes (i) selective coordination of the diyne moiety of enediyne **4-9** to the active Rh catalyst species, forming metallacycle **4-**

25a [2+2+M]); (ii) insertion of the olefin moiety of **4-25a** into the Rh-C bond followed by CO coordination to the metal forms the fused 5-7-5 tricyclic rhodacycle **4-25b** ([2+2+2+M]), (iii) migratory insertion of CO into the Rh-C bond gives 5-8-5 rhodacycle **4-25c** or **4-25d** ([2+2+2+1+M]), and (iv) reductive elimination gives the [2+2+2+1] cycloadduct **4-23** and regenerates the active Rh catalyst species. Reductive elimination from the 5-7-5 rhodacycle **4-25b** prior to CO insertion gives the [2+2+2] cycloadduct **4-24**.



Scheme 4-14: Proposed mechanism for [2+2+2+1] cycloaddition of enediynes **4-9a-h**

§ 4.3. Conclusion

In continuing studies on the Rh(I)-catalyzed higher order cycloaddition of enediynes, 8-oxo-enediyne derivatives were synthesized and found to afford the desired 5-7-5 fused tricyclic γ-lactone products in good to excellent yields. The skeletons of the products obtained are commonly found in natural products. Thus, this method could be used in the preparation of natural products and analogs for structure activity relationship studies. In terms of substrate scope, the substituents on both the terminal acetylene and the allyl component can be expanded. Additionally, this method can easily be extended to the preparation of diketone and γ-lactam products, which may also serve as platforms for natural product synthesis.

§ 4.4. Experimental section

§ 4.4.1. General methods

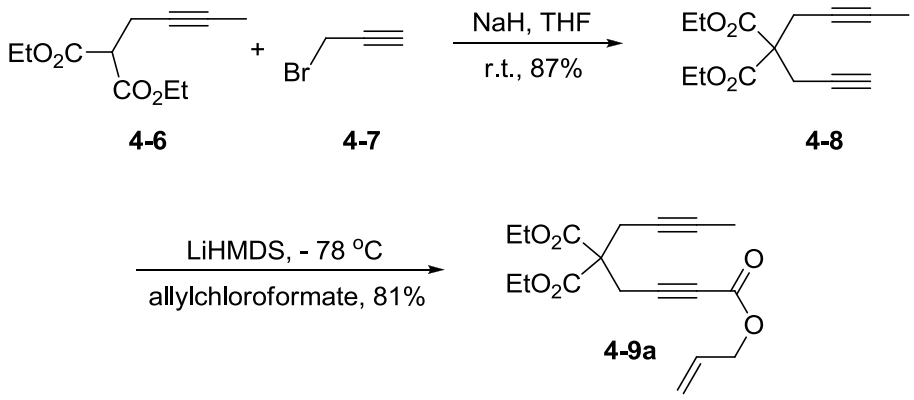
All reactions were carried out under nitrogen or carbon monoxide in oven dried glassware using standard Schlenk techniques unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents using Fisher silica gel (60 μm particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. Analytical high performance liquid chromatography (HPLC) was performed with a Shimadzu LC 2010A system using a phenomenex Jupiter 10μ Proteo 90A column (4.5 x 250 mm/mm) and gradient from 100% acetonitrile to 95:5 acetonitrile:water over 30 min with a flow rate of 1 mL/min. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Shimadzu FTIR-84005 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Inova-500 (500 MHz), 400 (400 MHz) or a Gemini-300 (300 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova-500 (125 MHz) or 400 (100 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 77.0 ppm). High resolution mass spectrometry (HRMS) was carried out at the Mass Spectrometry Facility, the University of Illinois Urbana Champaign. **Caution:** Carbon monoxide is a toxic gas and therefore all reactions should be carried out in a fume hood with sufficient ventilation.

Materials. Solvents were reagent grade and freshly distilled before use. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen. Toluene was freshly distilled from calcium hydride under nitrogen. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from DrySolv® and used without further purification. Dichloroethane (DCE) and trifluoroethanol (TFE) were purchased from Aldrich and used without purification. Carbon monoxide was purchased from Liquid

Carbonic Specialty Gases, Oak Brook, Illinois and passed through Drierite® before use. $[Rh(CO)_2Cl]_2$ was prepared by the literature method.[6]

§ 4.4.2. Synthesis of 1-methyl dodec-11-ene-8-oxo-1,6-diynes

9,9-Di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne; (4-9a):

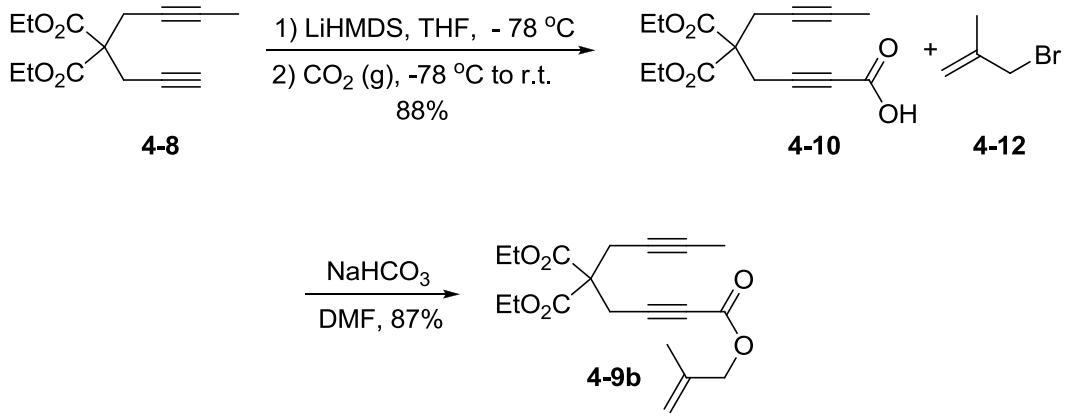


Diethyl 2-(but-2-ynyl)malonate **4-6** (2.20 g, 10.4 mmol) dissolved in 10 mL of THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.502 g, 12.4 mmol) in 30 mL of THF. After stirring at room temperature for 15min, propargyl bromide **(4-7)** (80% solution in toluene, 1.36 g, 11.4 mmol) diluted in 10 mL of THF was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by flash chromatography on silica gel using 5% EtOAc in hexanes as eluent to give product **4-8** as colorless liquid (2.26 g, 87 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22-1.26 (m, 6H), 1.74 (t, 3H, *J* = 2.7 Hz), 2.09 (t, 1H, *J* = 2.7 Hz), 2.90 (q, 2H, *J* = 2.7 Hz), 2.95 (d, 2H, *J* = 2.7 Hz), 4.17-4.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.42, 13.97, 22.49, 22.83, 56.58, 61.61, 61.82, 71.34, 72.94, 78.74, 79.04, 168.91.

LiHMDS (4.50 mL of 1 M solution in THF) was added dropwise to a (-78 ^{o}C) cold solution of diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl) malonate **(4-8)** (750 mg, 3.00 mmol) in 30 mL of THF. The resulting mixture was stirred at -78 ^{o}C for 30 min and then allylchloroformate (542 mg, 4.50 mmol) diluted in 5 mL of THF was added dropwise and the resulting mixture was stirred for 3 h at – 78 ^{o}C, and then warmed slowly to room

temperature. The mixture was diluted with ether followed by addition of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel pre-treated with Et_3N using 7% EtOAc in hexanes as eluent to yield compound **4-9a** as colorless oil (810 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23-1.27 (m, 6H), 1.74 (t, 3H, *J* = 2.4 Hz), 2.91 (q, 2H, *J* = 2.4 Hz), 3.11 (s, 2H), 4.20-4.25 (m, 4H), 4.61-4.63 (m, 2H), 5.25-5.36 (m, 2H), 5.86-5.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.43, 13.97, 22.85, 23.26, 56.39, 62.16, 66.37, 72.59, 75.25, 79.62, 83.86, 119.21, 131.17, 152.86, 168.45.

2-Methyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne, **(4-9b):**

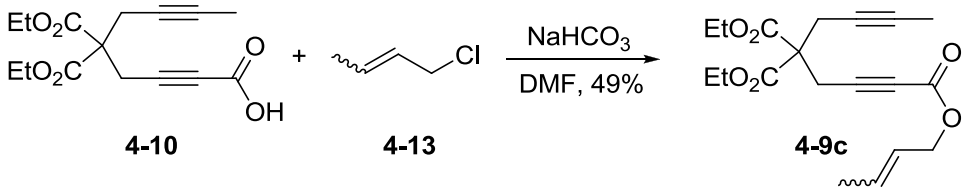


To a cold (-78 °C) solution of malonate **4-8** (3.15 g, 12.6 mmol) in 60 mL of THF was added dropwise 1 M LiHMDS in THF (19 mL, 19.0 mmol). After 20 min at -78 °C, a balloon of CO_2 (g) equipped with a syringe was introduced to the reaction. The reaction was stirred at -78 °C for 2 h and then allowed to warm to room temperature before being poured into 5% citric acid solution. The layers were separated and the aqueous phase was acidified to pH 4 by addition of 2 M HCl solution and then extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel using 20% EtOAc in hexanes as eluent to give the desired product **4-10** as light yellow oil (3.30 g, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 6H, *J* = 4.8 Hz), 1.75 (t, 3H, *J* = 2.4 Hz), 2.90 (q, 2H, *J* = 2.4 Hz), 4.27 (q, 4H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 125

MHz) δ 3.40, 13.94, 22.94, 23.32, 56.36, 62.27, 72.45, 74.86, 79.56, 86.33, 156.73, 168.45.

A mixture of acid **4-10** (600 mg, 2.04 mmol) and sodium bicarbonate ($NaHCO_3$, 257 mg, 3.06 mmol) in 10 mL of DMF was stirred at room temperature for 15 min. Then, methylallyl bromide **4-12** (413 mg, 3.06 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give the product **4-9b** as colorless oil (620 mg, 87 %). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23-1.29 (m, 6H), 1.75 (t, 6H, *J* = 2.7 Hz), 2.91 (q, 2H, *J* = 2.7 Hz), 3.12 (s, 2H), 4.19-4.19 (m, 4H), 4.54 (s, 2H), 4.94-4.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.12, 16.65, 22.09, 25.54, 25.95, 59.09, 64.82, 71.65, 75.29, 77.94, 82.29, 86.55, 116.57, 141.62, 155.61, 171.12.

10,10-Di(carbethoxy)-5-oxo-6-oxa-tetradeca-2-ene-7,12-diyne, (4-9c):



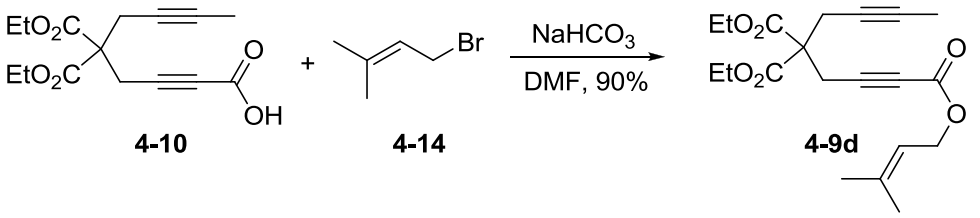
4-10 **4-13** **4-9c**

(2.3:1; *trans*:*cis)*

A mixture of acid **4-10** (450 mg, 1.53 mmol) and sodium bicarbonate ($NaHCO_3$, 257 mg, 3.06 mmol) in 8 mL of DMF was stirred at room temperature for 15 min. Then, crotyl chloride **(4-13)** (2.3:1 *trans*:*cis*) (166 mg, 1.84 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give product **4-9c** as colorless oil (261 mg, 49 %). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 6H, *J* = 7.2 Hz), 1.74 (m, 6H), 2.91 (q, 2H, *J* = 2.7 Hz), 3.10 (s, 2H), 4.26 (q, 4H, *J* = 7.2 Hz), 4.56 (d, 1.35H, *J* = 5.7 Hz, trans isomer), 4.70 (d, 0.65 H, *J* = 6.6 Hz, cis isomer), 5.54-5.60 (m, 1H), 5.74-5.78 (m, 1H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 3.41, 13.94, 17.71, 22.81, 23.22, 56.36, 61.32, 62.12, 66.49, 72.61, 75.36, 79.57, 83.44, 83.55, 123.24, 124.14, 130.50, 132.56, 153.02, 153.15, 168.43.

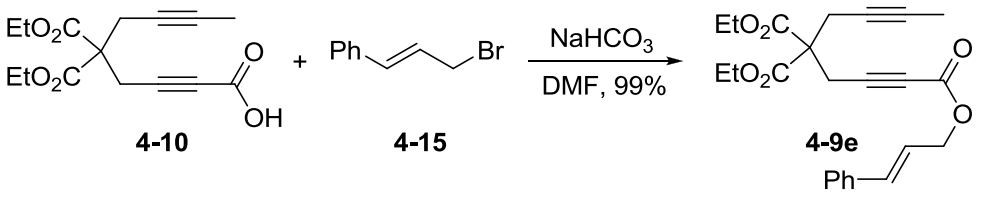
2-Methyl-10,10-di(carbethoxy)-5-oxo-6-oxa-tetradeca-2-ene-7,12-diyne, (4-9d):



4-10 **4-14** **4-9d**

A mixture of acid **4-10** (450 mg, 1.53 mmol) and sodium bicarbonate ($NaHCO_3$, 257 mg, 3.06 mmol) in 10 mL of DMF was stirred at room temperature for 15 min. Then, prenyl bromide **(4-14)** (273 mg, 1.83 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give product **4-9d** as colorless oil (500 mg, 90 %). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, 6H, *J* = 7.5 Hz), 1.70-1.75 (m, 9H), 2.90 (d, 2H, *J* = 2.5 Hz), 3.10 (s, 2H), 4.24 (q, 4H, *J* = 7.0 Hz), 4.62 (d, 2H, *J* = 7.0 Hz), 5.31-5.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.40, 13.94, 17.99, 22.81, 23.23, 25.72, 56.38, 62.11, 62.64, 72.64, 75.47, 79.56, 83.28, 117.66, 140.15, 153.26, 168.45.

1-Phenyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne, (4-9e):

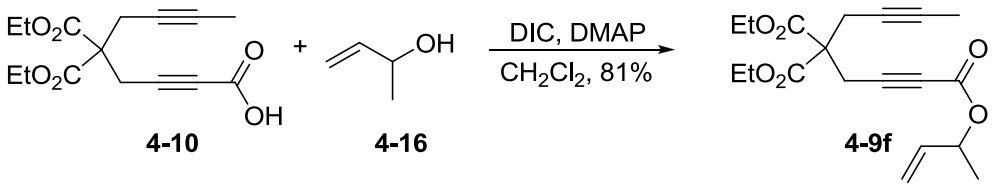


4-10 **4-15** **4-9e**

To a mixture of acid **4-10** (600 mg, 2.04 mmol) and sodium bicarbonate ($NaHCO_3$, 257 mg, 3.06 mmol) in 12 mL of DMF was added cinnamyl bromide **(4-15)** (413 mg, 3.06 mmol) and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by flash

chromatography on silica gel using 10% EtOAc in hexanes as eluent to give product **4-9e** as colorless oil (825 mg, 99 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23-1.28 (m, 6H), 1.75 (t, 3H, *J* = 2.4 Hz), 2.92 (q, 2H, *J* = 2.4 Hz), 3.13 (s, 2H), 4.27 (q, 4H, *J* = 6.9 Hz), 4.80 (dd, 2H, *J* = 1.2, 8.7 Hz), 6.24-6.31 (m, 1H), 6.69 (d, 1H, *J* = 15.6 Hz), 7.27-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.12, 14.66, 23.55, 23.95, 57.07, 62.84, 67.04, 73.29, 75.98, 80.31, 84.60, 122.74, 127.37, 128.91, 129.29, 135.86, 136.67, 153.67, 169.13.

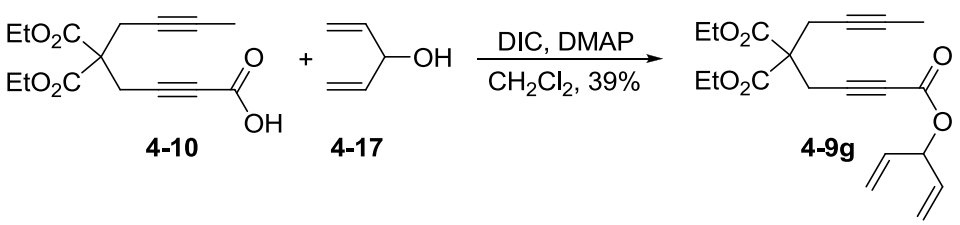
3-Methyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne, (4-9f):



4-10 **4-16** **4-9f**

To a solution of acid **4-10** (450 mg, 1.53 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC was added diisopropylcarbodiimide (DIC, 232 mg, 1.84 mmol). After 5 min, a solution of (+/-) but3-en-2-ol **(4-16)** (110 mg, 1.53 mmol) and dimethylamino pyridine (DMAP, 56 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) was added to the mixture which was then stirred overnight at room temperature. The mixture was concentrated under reduced pressure and purified by chromatography on silica gel using 10% EtOAc in hexanes as eluent to give the product **4-9f** as colorless oil (432 mg, 81 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 6H, *J* = 7.2 Hz), 1.35 (d, 3H, *J* = 6.6 Hz), 1.75 (t, 3H, *J* = 2.4 Hz), 2.92 (q, 2H, *J* = 2.4 Hz), 3.11 (s, 2H), 4.27 (m, 4H), 5.14-5.29 (m, 2H), 5.31-5.38 (m, 1H), 5.78-5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.40, 13.95, 19.73, 22.84, 23.26, 56.40, 62.12, 72.64, 72.92, 75.59, 79.57, 83.32, 116.66, 136.71, 152.44, 168.45.

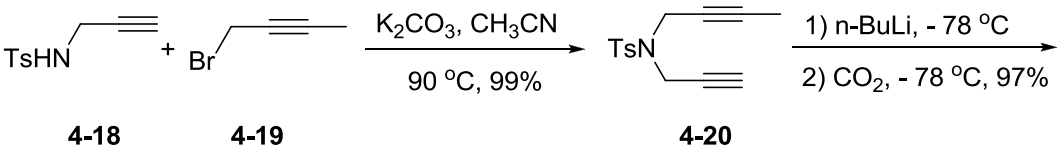
3-Vinyl-9,9-di(carbethoxy)-4-oxo-5-oxa-trideca-1-ene-6,11-diyne, (4-9g):



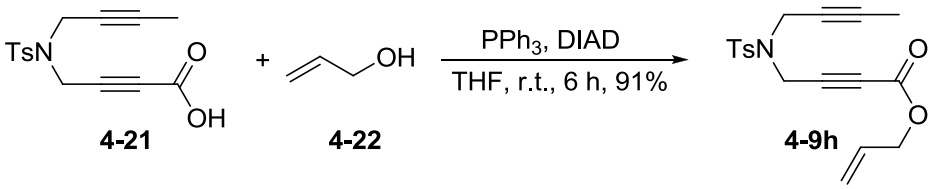
4-10 **4-17** **4-9g**

To a solution of acid **4-10** (480 mg, 1.63 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC was added diisopropylcarbodiimide (DIC, 247 mg, 1.96 mmol). After 5 min, a solution of penta-1,4-dien-3-ol **(4-17)** (206 mg, 2.46 mmol) and DMAP (100 mg, 0.82 mmol) diluted in CH_2Cl_2 (5 mL) was added to the mixture which was then stirred overnight at room temperature. The mixture was concentrated under reduced pressure and purified by chromatography on silica gel using 10% EtOAc in hexanes as eluent to give the product **4-9g** as colorless oil (230 mg, 39 %). ^1H NMR ($CDCl_3$, 300 MHz) δ1.23-1.29 (m, 6H), 1.75 (t, 3H, *J* = 2.7 Hz), 2.92 (q, 2H, *J* = 2.4 Hz), 3.12 (s, 2H), 4.26 (q, 4H, *J* = 7.2 Hz), 5.24-5.35 (m, 4H), 5.71-5.74 (m, 1H), 5.77-5.88 (m, 2H), 5.78-5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.42, 13.96, 22.87, 23.27, 56.40, 62.15,72.62, 75.38, 76.68, 79.61, 83.83, 118.30, 134.18, 152.13, 168.44.

9-(4-Methylbenzenesulfonyl)-4-oxo-5-oxa-9-azatrideca-1-ene-6,11-diyne, (4-9h):



4-18 **4-19** **4-20**



4-21 **4-22** **4-9h**

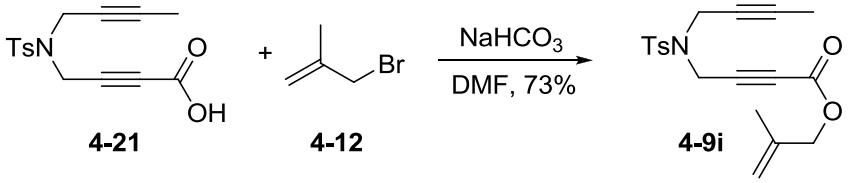
A suspension of *N*-(prop-2-ynyl)-4-methylbenzenesulfonamide[7] **(4-18)** (3.50 g, 16.7 mmol) and potassium carbonate (K_2CO_3, 5.80 g, 41.8 mmol) in 50 mL of CH_3CN was refluxed at 90 ^oC for 15 min. A solution of 1-bromobut-2-yne **(4-19)** (2.70 g, 20.1 mmol) in 5 mL of CH_3CN was added and the resulting mixture was refluxed overnight. The mixture was cooled to room temperature, filtered over celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give **4-20** as viscous colorless oil (4.33 g, 97%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (t, 3H, *J* = 2.1 Hz), 2.14 (t, 1H, *J* = 2.4 Hz), 2.42 (s, 3H), 4.10 (q, 2H, *J* = 2.1 Hz), 4.14 (d, 2H, *J* = 2.4 Hz), 7.30 (d, 2H, *J* = 7.8 Hz), 7.72 (d, 2H, *J*

= 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.34, 2149, 36.09, 36.68, 71.28, 73.64, 76.53, 81.93, 127.92, 129.35, 135.37, 143.67.

n-BuLi (2.2 M in hexanes, 3.72 mL, 8.20 mmol) was added dropwise to a cold (- 78 ^{o}C) solution of **4-20** in 35 mL of THF. After 20 min at -78 °C, a balloon of CO_2 ($_g$) equipped with a syringe was introduced to the reaction. The reaction was stirred at -78 °C for 2 h and then allowed to warm to room temperature before being added to 5% citric acid solution. The layers were separated, and the aqueous phase was acidified to pH 4 by addition of 2 M HCl solution and then extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 4-(*N*-(but-2-ynyl)-4-methylphenylsulfonamide)but-2-ynoic acid **4-21** as red viscous oil (2.32, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67, (t, 3H, *J* = 2.4 Hz), 2.41 (s, 3H), 4.07 (q, 2H, *J* = 2.4 Hz), 4.31 (s, 2H), 7.32 (d, 2H, *J* = 8.1 Hz), 7.72 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.38, 21.51, 36.25, 37.49, 70.88, 76.35, 82.86, 83.16, 127.88, 129.67, 134.79, 144.27, 156.20.

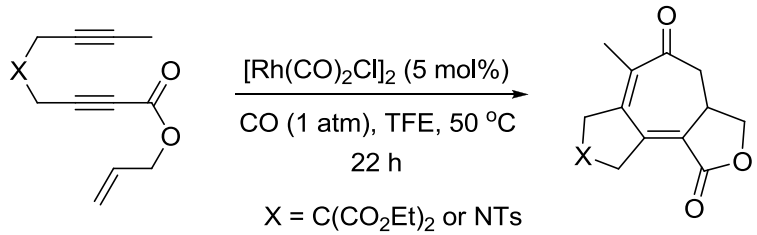
Diisopropylazodicarboxylate (DIAD, 753 mg, 3.54 mmol) was added to a solution of triphenylphosphine (938 mg, 3.54 mmol) in 10 mL of THF. After formation of a solid (10 min), 4-(*N*-(but-2-ynyl)-4-methylphenylsulfonamide)but-2-ynoic acid **(4-21)** (900 mg, 2.95 mmol) in 15 mL of THF was added followed by allyl alcohol **(4-22)** (342 mg, 5.89 mmol) in 5 mL of THF. The resulting mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel using 8% EtOAc in hexanes as eluent to give the desired product **4-9h** as light yellow oil (920 mg, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67 (t, 3H, *J* = 2.4 Hz), 2.41 (s, 3H), 4.08 (q, 2H, *J* = 2.4 Hz), 4.29 (s, 2H), 4.59-4.62 (m, 2H), 5.27-5.37 (m, 2H), 5.82-5.93 (m, 1H), 7.32 (d, 2H, *J* = 8.7 Hz), 7.73 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.37, 21.52, 36.19, 37.36, 66.49, 70.98, 76.86, 80.63, 82.67, 119.41, 127.89, 129.59, 130.93, 134.96, 144.03, 152.30.

2-Methyl-9-(4-methylbenzenesulfonyl)-4-oxo-5-oxa-9-azatrideca-1-ene-6,11-diyne, (4-9i):



A suspension of acid **4-21** (650 mg, 2.13 mmol) and sodium bicarbonate ($NaHCO_3$, 358 mg, 4.26 mmol) in 10 mL of DMF was stirred at room temperature for 15 min. Then, methylallyl bromide **4-12** (432 mg, 3.20 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by flash chromatography on silica gel using 10% EtOAc in hexanes as eluent to give product **4-9i** as colorless oil (560 mg, 73 %). ^1H NMR ($CDCl_3$, 300 MHz) δ1.66 (t, 3H, *J* = 2.4 Hz), 1.75 (d, 3H, *J* =1.2 Hz), 2.40 (s, 3H), 4.07 (q, 2H, *J* = 2.7 Hz), 4.29 (s, 2H), 4.52 (s, 2H), 4.96-4.98 (m, 2H), 7.31 (d, 2H, *J* = 8.7 Hz), 7.72 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.33, 19.36, 21.48, 36.19, 37.33, 69.07, 70.96, 76.86, 80.61, 82.65, 114.05, 127.85, 129.55, 134.95, 138.70, 144.03, 152.34.

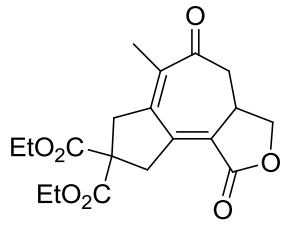
§ 4.4.3. [2+2+2+1] Cycloaddition of 1-methyl dodec-11-ene-8-oxo-1,6-diynes



Typical procedure is described for the reaction of **4-9a**: A 100 mL round bottomed flask charged with **4-9a** (50 mg, 0.15 mmol) in TFE (6.00 mL, [0.025 M] and $[Rh(CO)_2Cl]_2$ (2.9 mg, 0.007 mmol) was transferred to a 250 mL stainless steel autoclave and purged with CO and released (4x) (**Caution must be done in a well**

ventilated fume hood) and then charged with CO to 1 atm. The autoclave was immersed in an oil bath preset at 50 ^{o}C for 22 h. The autoclave was allowed to cool to room temperature, followed by release of the gas in a well ventilated fume hood. The reaction mixture was concentrated under reduced pressure and the resulting crude product was purified by flash chromatography on silica gel using 20% EtOAc in hexanes as eluent to give fused tricyclic product **4-23a** as light yellow oil (52 mg, 96%).

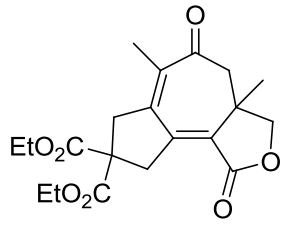
8,8-Bis(carbethoxy)-6-methyl-1,5-dioxo-3a,4,5,7,9-pentahydro 3H 2-oxacyclopenta-[*e*]azulene, **(4-23a):**



Light yellow oil (96%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24-1.30 (m, 6H), 2.03 (s, 3H), 2.73 (dd, 1H, *J* = 2.7 Hz), 2.88 (t, 1H, *J* = 14.7 Hz), 3.24 (s, 2H), 3.31-3.39 (m, 1H), 3.57 (dd, 1H, *J* = 3.6 Hz), 3.86-3.97 (m, 2H), 4.18-4.26 (m, 4H), 4.61 (t, 1H, *J* = 9.3 Hz); ^{13}C NMR ($CDCl_3$, 100 M Hz) δ 13.96, 29.67, 34.43, 39.09, 41.58, 44.11, 57.08, 62.06, 69.27, 127.15, 137.76, 147.58, 148.77, 170.53, 170.68, 195.07.

In a similar manner, the reactions of **4-9b**-**4-9h** were performed and **4-23b**-**4-23h** were obtained as products.

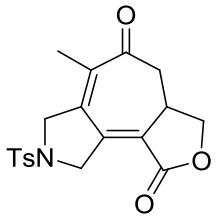
Diethyl(6Z,9a*E*)-3a,6-dimethyl-1,5-dioxo-3,3a,4,5,7,9-hexahydroazuleno[4,5-c]furan-8,8(1H)-dicarboxylate, (4-23b):



Colorless oil (80%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.22-1.27 (m, 6H), 2.02 (s, 3H), 2.61 (d, 1H, *J* = 13.5 Hz), 2.94 (d, 1H, *J* = 13.5 Hz), 3.22-3.24 (m, 2H), 3.60 (d,

1H, *J* = 18.9 Hz), 3.86 (d, 1H, *J* = 18.9 Hz), 3.94 (d, 1H, *J* = 9.0 Hz), 4.08 (d, 1H, *J* = 9.0 Hz), 4.17-4.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 M Hz) δ 13.96, 16.95, 19.86, 39.05, 39.67, 41.82, 48.12, 56.98, 62.02, 62.04, 76.38, 132.23, 137.89, 146.08, 146.88, 169.54, 170.46, 170.78, 194.98.

6-Methyl-8-[(4-methylphenyl)sulfonyl]-3a,7,8,9 tetrahydrofuro[3',4':3,4]cyclohepta[1,2-*c*]pyrrole-1,5(3*H*,4*H*)-dione, (4-23h):



Colorless oil (40%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (s, 3H), 2.36-2.45 (m, 4H), 2.72 (t, 1H, *J* = 8.4 Hz), 3.25-3.30 (m, 1H), 3.91 (t, 1H, *J* = 8.4 Hz), 4.11 (d, 1H, *J* = 16.0 Hz), 4.31 (d, 1H, *J* = 16.0 Hz), 4.53 (dd, 1H, *J* = 17.6, 4.0 Hz), 4.61 (t, 1H, *J* = 8.4 Hz), 4.74 (dd, 1H, *J* = 17.6, 4.0 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.76 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 M Hz) δ 16.72, 21.54, 34.36, 42.63, 52.32, 53.21, 69.60, 127.26, 127.93, 129.95, 132.41, 137.61, 142.64, 143.89, 144.37, 168.73, 194.19.

§ 4.5. References

1. (a) Schall, A.; Reiser, O., Synthesis of biologically active guaianolides with a trans-annulated lactone moiety. *Eur. J. Org. Chem.* **2008**, 2353-2364; (b) Higuchi, Y.; Shimoma, F.; Ando, M., Synthetic method and biological activities of cis-fused α-methylene γ-lactones. *J. Nat. Prod.* **2003,** *66*, 810-817; (c) Watanabe, K.; Oguri, Y.; Miyakado, M.; Ohno, N.; Mabry, T. J., Structure and fungicidal activity of four pseudoguaianolides isolated from Helenium quadridentatum Labill. *J. Agric. Food Chem.* **1985,** *33*, 83-86; (d) Hu, J.-F.; Patel, R.; Li, B.; Garo, E.; Hough, G. W.; Goering, M. G.; Yoo, H.-D.; O'Neil-Johnson, M.; Eldridge, G. R., Anti-HCV bioactivity of pseudoguaianolides from Parthenium hispitum. *J. Nat. Prod.* **2007,** *70*, 604-607.

2. (a) Shimoma, F.; Kusaka, H.; Azami, H.; Wada, K.; Suzuki, T.; Hagiwara, H.; Ando, M., Total syntheses of (+/-)-Hymenolin and (+/-)-Parthenin. *J. Org. Chem.* **1998,** *63*, 3758-3763; (b) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Böhm, C.; Reiser, O., Facile Asymmetric synthesis of the core nuclei of xanthanolides, guaianolides, and eudesmanolides. *Org. Lett.* **2003,** *5*, 941-944; (c) Ashfeld, B. L.; Martin, S. F., Enantioselective syntheses of Tremulenediol A and Tremulenolide A. *Org. Lett.* **2005,** *7*, 4535-4537; (d) Bruno, M.; Rosselli, S.; Maggio, A.; Raccuglia, R. A.; Bastow, K. F.; Lee, K.-H., Cytotoxic activity of some natural and synthetic guaianolides. *J. Nat. Prod.* **2005,** *68*, 1042-1046; (e) Recio, M. C.; Giner, R. M.; Uriburu, L.; Máñez, S.; Cerdá, M.; De La Fuente, J. R.; Ríos, J. L., In vivo activity of pseudoguaianolide sesquiterpene lactones in acute and chronic inflammation. *Life Sci.* **2000,** *66*, 2509-2518.

3. (a) Kotha, S.; Brahmachary, E.; Lahiri, K., Transition metal-catalyzed [2+2+2] cycloaddition and application in organic synthesis. *Eur. J. Org. Chem.* **2005**, 4741-4767; (b) Lautens, M.; Klute, W.; Tam, W., Transition metal-mediated cycloaddition reactions. *Chem. Rev.* **1996,** *96*, 49-92; (c) Nakamura, I.; Yamamoto, Y., Transition-metal-catalyzed reactions in heterocyclic synthesis. *Chem. Rev.* **2004,** *104*, 2127-2198.

4. Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *Org. Lett.* **2004,** *6*, 3589-3591.

5. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Metal-catalyzed [2+2+1] cycloadditions of 1,3-dienes, allenes, and CO. *Angew. Chem. Int. Ed.* **2006,** *45*, 2459-2462.

6. McCleverty, J. A.; Wilkinson, G., Dichlorotetracarbonyldirhodium (rhodium carbonyl chloride). *Inorg. Syn. 8*, 211-214.

7. Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I., Silicon-initiated carbonylative carbotricyclization and [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *J. Am. Chem. Soc.* **2005,** *127*, 17756-17767.

Chapter 5

Progress on the enantioselective synthesis of β-Lactams

Table of Contents

§ 5.1. Introduction

The β-lactam skeleton is the key structural unit responsible for the antibacterial properties of the most widely used antibiotics including the penams **5-1**, cephems **5-2**, monobactams **5-3** and carbapenems **5-4** (**Figure 1**).[1]

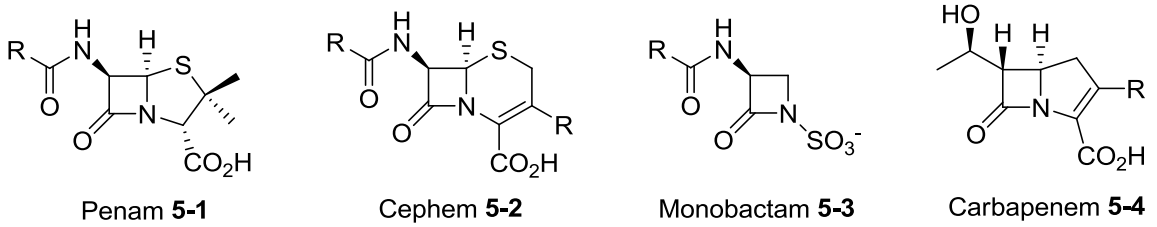
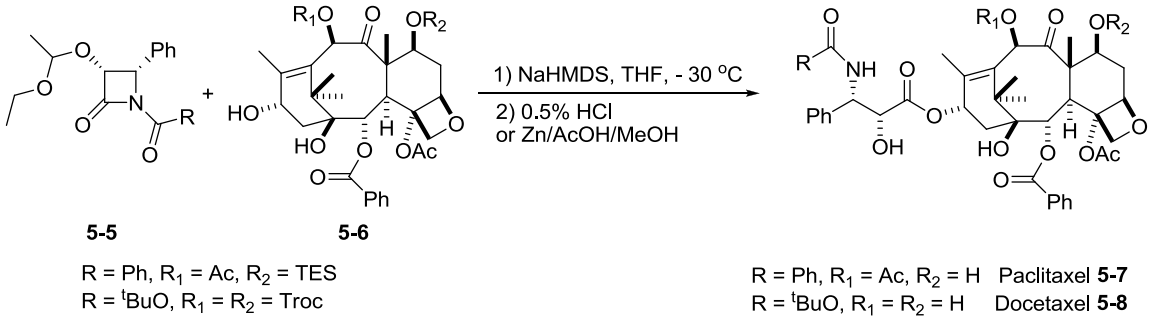


Figure 5-1: β-Lactam antibiotics

The need for development of new bioactive β-lactam compounds to combat drug resistance against the traditional antibiotics has kept interest in the β-lactam skeleton.[2] In addition, β-lactams have been shown to be useful chiral starting materials for the synthesis of natural and unnatural products.[1, 3] A variety of natural and unnatural amino acids, peptides, peptidomimetics and other types of compounds of biological interest have been synthesized *via* enantiopure β-lactam intermediates (β-Lactam Synthon Method).[1a] Notably, Ojima *et. al.* used β-lactams as key intermediates in the semi-synthesis of antitumor taxoids Paclitaxel (**5-7)** and Docetaxel (**5-8)** (**Scheme 5-1**).[4] It is worthy to note that structure activity relationship (SAR) studies showed the C_{13} amino acid moiety of antitumor taxoids to be crucial for the strong antitumor activities displayed by these compounds.[4a]



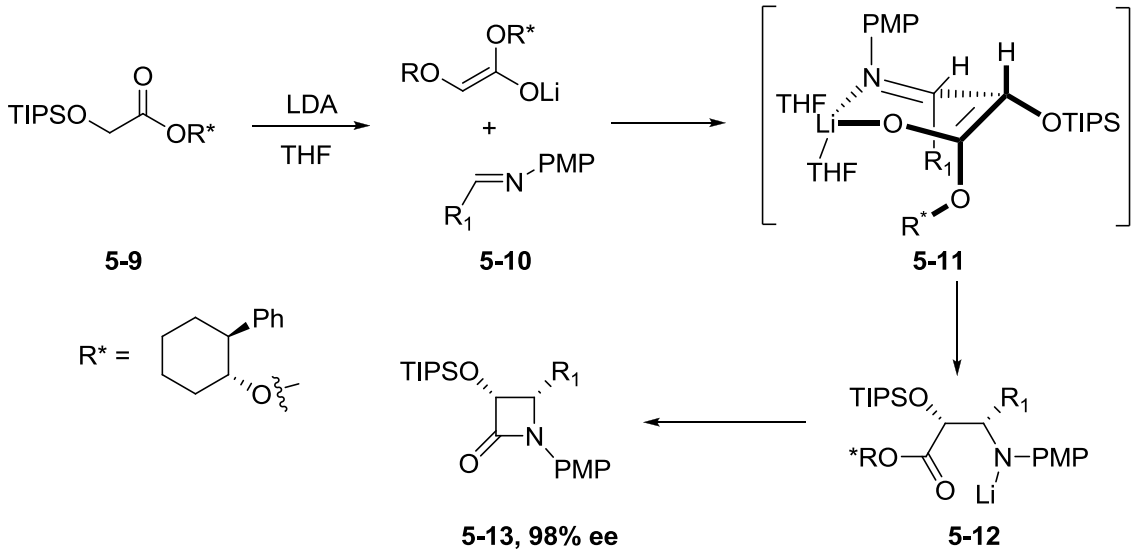
Scheme 5-1: Semi-synthesis of antitumor taxoids Paclitaxel (**5-7)** and Docetaxel (**5-8)**

In addition to their antibiotic activities, β-lactams are also useful in the development of mechanism based inhibitors of serine protease including β-lactamases,[5] prostate specific antigen[6] and as inhibitors of acyl-CoA cholesterol acyltransferase (ACAT), an enzyme implicated in the development of artherosclerotic coronary heart disease.[7]

§ 5.2. Synthetic approaches to enantiopure β-lactams

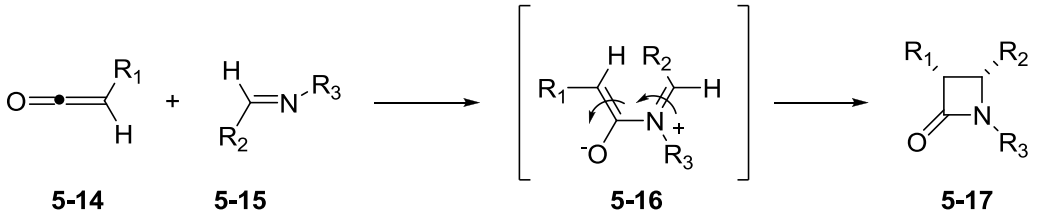
As a consequence of the versatility of β-lactams as intermediates in synthesis, a number of synthetic methods have been developed and numerous reviews covering different aspects of β-lactam chemistry have been published.[1-3, 8] The hydroxamate cyclization,[9] the metalloester enolate-imine condensation (Gilman-Speeter reaction),[10] the reaction of nitrones with copper acetylides (Kinugasa reaction),[11] the chromium carbine-imine reaction[12] and the ketene-imine [2+2] cycloaddition (Staudinger reaction)[13] are some of the approaches used for the synthesis of the azetidin-2-one ring system. The ester enolate-imine cyclocondensation and the ketene-imine [2+2] cycloaddition (Staudinger reaction) are two of the most common approaches for the synthesis of β-lactams.[1a, 3, *8b*]

The use of a chiral auxiliary in the ester enolate-imine cyclocondensation method can provide enantiomerically enriched β-lactams.[14] If the chiral auxiliary is attached to the ester component, it is cleaved during the C-N bond forming step of the reaction. Thus, no additional steps are needed for chiral auxiliary removal and recovery of the chiral auxiliary is possible. The chiral ester enolate-imine cyclocondensation method was utilized by Ojima *et. al.* to synthesize enantiopure β-lactams that were then coupled to suitably protected baccatin III for the semi-syntheses of the anticancer taxoids Paclitaxel (**5-7)** and **Docetaxel (**5-8) (**See Scheme 5-1**).[4] The treatment of TIPS ester **5-9** appended with (-) phenylcyclohexanol (Whitesell's Chiral Auxiliary) with imine **5-10** in the presence of lithium diisopropyl amide (LDA) gave the desired β-lactam products **5-13** with excellent enantiomeric excess (ee) (**Scheme 5-2**). The chiral induction was proposed to occur via the chair-like transition state **5-11** in which the chiral auxiliary is situated in the more favorable *endo* position.



Scheme 5-2: Synthesis of β-lactams **5-13** *via* the chiral ester enolate-imine cyclocondensation reaction

The Staudinger reaction remains the most versatile method for β-lactam synthesis (**Scheme 5-3**). This is mainly due to the ready availability of a variety of both imines and ketenes and operationally simple procedures.



Scheme 5-3: The Staudinger cycloaddition reaction

In the classical Staudinger reaction, the ketene **5-14** is generated in situ by the dehydrohalogenation of an acid chloride possessing α-hydrogens, in the presence of a tertiary amine base. Nucleophilic attack by the imine **5-15** onto the ketene **5-14** generates a zwitterionic intermediate **5-16** that undergoes conrotatory electrocyclic ring closure to furnish the β-lactam product **5-17** (**Scheme 5-3**). The Staudinger cycloaddition reaction is stereoselective for *cis* β-lactams due to electronic (torqueselectivity) rather than steric effects in the transition state.[2] Studies by Cossio *et. al*. have shown that conrotatory ring

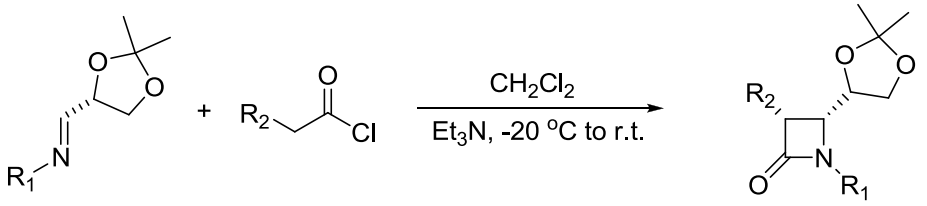
closure is favored by 8 – 12 kcal / mol when the R_1 (**Scheme 5-3**) substituent is electron donating and adopts an "outward" configuration upon imine attack leading to the formation of the *cis* β-lactams selectively.[15] These studies also showed that when R_1 (**Scheme 5-3**) is electron withdrawing, the "inward" configuration of this substituent is favored by 12 – 15 kcal / mol leading to the formation of *trans* β-lactams.

A number of modified versions of this reaction have been developed, in which a variety of activated compounds such as α-diazoketones instead of acid chlorides are used as ketene precursors.[2] The racemic products obtained are often separated by enzymatic kinetic resolution. The need for racemate separation presents drawbacks both in terms of cost and yields since the overall yield of a desired enantiomer is reduced to a maximum of fifty percent. Several asymmetric approaches to the Staudinger reaction have been reported in the literature.[1a, 3, 8b] Asymmetric induction of the Staudinger reaction can be effected with imines derived from either chiral aldehydes or chiral amines.[1a, 3] However, low levels of enantio and diastereoselectivities are generally observed with the use of enantiopure imines derived from chiral amines and achiral aldehydes.[1a, 2] Though a few exceptions are known, the substrate scope has been shown to be rather limited.[16] The observed low levels of selectivities for chiral imines derived from chiral amines may be due largely to the remote distance of the chiral moiety to the reaction center, thus leading to non-selective transition states.[1a, 16a] The asymmetric Staudinger reaction can also be effected by chiral ketene precursors in which the chirality is derived from a chiral auxiliary attached to the ketene precursor. Recently, catalytic asymmetric versions of the Staudinger reaction were reported in the literature.[1a, 3, 8b] A few examples of the common approaches used to access enantio and diastereomerically pure β-lactams are presented below.

§ 5.2.1. Asymmetric induction from the imine component

As stated above, asymmetric induction in the Staudinger reaction of chiral imines with achiral ketenes is effected with imines derived from chiral aldehydes as well as from chiral amines. In general, higher stereoselectivities are attained when imines derived from chiral aldehydes are used. The most common approaches use chiral aldehydes derived from sugars. The *cis* β-lactams are usually obtained in high to excellent ee's.

Using chiral imines **5-18** derived from D-glyceraldehyde acetonide, a wide variety of 3,4-disubstituted 2-azetidinones **5-20** were prepared in moderate to good yields (**Scheme 5-4**).[17] For instance, 2-azidoacetyl chloride reacted with *N-para*-methoxyphenyl imine and gave the 3-azido-β-lactam in 55% yield (**entry 1**). In a similar manner, the 3-hydroxyacetyl substituted azetidinone was obtained in 70% yield from the reaction of acetoxyacetyl chloride with *N-para*-methoxyphenyl imine (**entry 6**). More importantly, the *cis* β-lactams **5-20** were isolated as single enantiomers for all substrates tested.[17]

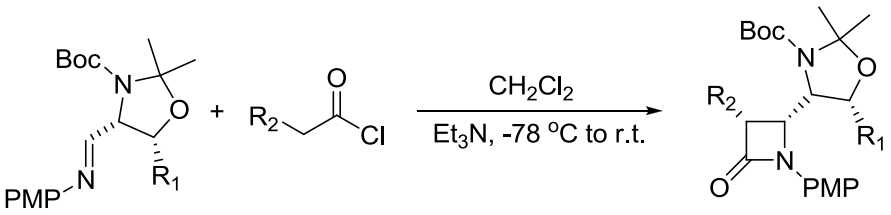


5-18 **5-19** **5-20**

Entry	R_1	R_2	yield%
1	PMP	N_3	55
2	PMP	Pht	57
3	CH_2CO_2Me	N_3	55
4	PMP	OMe	54
5	CH_2CO_2Me	OMe	57
6	PMP	OAc	70
7	PMP	OBn	69
8	PMP	OPh	67
9	Bn	OMe	55

Scheme 5-4: Asymmetric synthesis of β-lactams **5-20** from imine **5-18**

The use of *N*-Boc-α-amino imines **5-21** in the Staudinger reaction also leads to the β-lactam products **5-23** in high diastereoselectivity.[18] The treatment of imine **5-21** with either acetoxyacetyl chloride or benzyloxyacetyl chloride and triethylamine in CH_2Cl_2 at – 78 ^oC, gave the corresponding β-lactams **5-23** as single diastereomers in good to excellent yields (**Scheme 5-5, entries 1-6**). The reaction of imine **5-21** with phthalimidoacetyl (pht) chloride also afforded the respective β-lactam as a single diastereomer but in only 41% yield (**entry 7**).

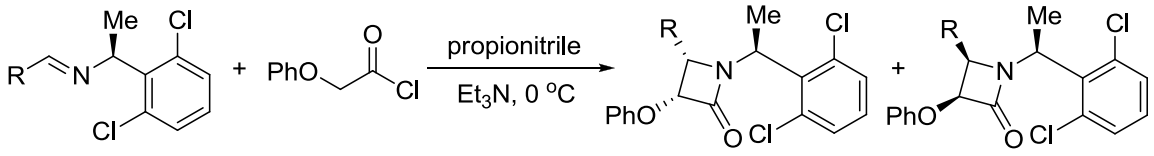


5-21 **5-22** **5-23**

Entry	R_1	R_2	yield%
1	H	OAc	70
2	Me	OAc	50
3	H	OBn	85
4	Me	OBn	86
5	H	OH	98
6	H	OMe	74
7	H	Pht	41

Scheme 5-5: Asymmetric synthesis of β-lactams **5-23** from imine **5-21**

The asymmetric Staudinger reaction of imines derived from chiral amines and achiral aldehydes usually gives the products with low diastereoselectivity, due to the distance between the chiral moiety and the reaction center.[1a, 2] However, (*S*)-1-(2,6-dichlorophenyl)ethylamine was found to be an effective chiral auxiliary in the [2+2] cycloaddition reaction.[16a] Using propionitrile as solvent at 0 ^oC, the β-lactam products **5-26** were obtained in good yields and selectivities in favor of the *cis* isomers (**Scheme 5-6**). Aromatic imines with both electron-withdrawing and donating groups were equally effective under the reaction conditions (**entries 2-3**). In addition, non-enolizeable aliphatic and olefinic imines also reacted smoothly (**entries 4-5**).

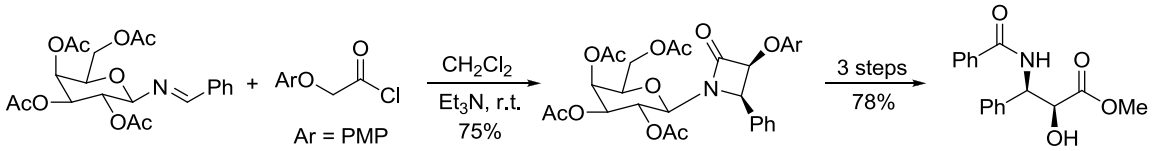


5-24 **5-25** **5-26** ***diast.*-5-26**

Entry	R	yield (%)	**5-26**: ***diast.*-5-26**
1	Ph	89	85:15
2	4-$MeOC_6H_4$	76	88:12
3	4-ClC_6H_4	83	85:15
4	PhCH=CH	60	88:12
5	t-Bu	56	91:9

Scheme 5-6: Asymmetric synthesis of β-lactams **5-26** from imine **5-24**

The reaction of imine **5-27** derived from 2,3,4,6-tetra-O-acetyl-β-D-galactoseamine with acid chloride **5-28** gave β-lactam **5-29** as a single diastereomer in 75% yield (**Scheme 5-7**).[16b] Hydrolysis of the sugar chiral auxiliary followed by *N*-benzoylation and oxidative dearylation gave (2*S*,3*R*) phenylisoserine methylester (**5-30)** in good yield.



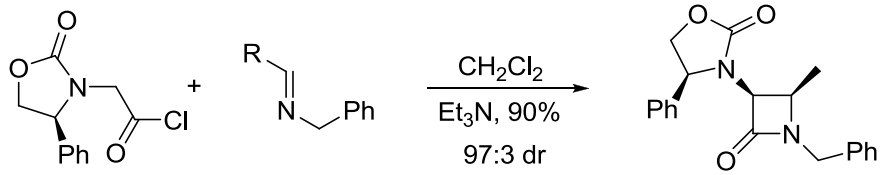
5-27 **5-28** **5-29** **5-30** (2*S*,3*R*)

Scheme 5-7: Asymmetric synthesis of 2*S*,3*R* phenylisoserine methylester (**5-30)**

The product from this reaction is the enantiomer of the phenylisoserine side chain of the antitumor agent Paclitaxel (**5-7)**. Accordingly, the (2*R*,3*S*) phenylisoserine could be obtained from imines derived from either D-arabinose or L-fucose.[16b]

§ 5.2.2. Asymmetric induction from the ketene component

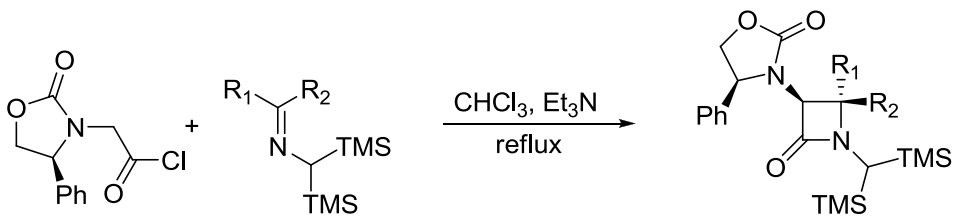
Another strategy for the synthesis of diastereomerically pure β-lactams involves attaching a chiral auxiliary to the ketene component. This method has been shown to be very effective for the preparation of 3-amino-β-lactams.[1a] Oxazolidinones derived from either (*S*) or (*R*)-phenylglycine have been demonstrated to be excellent chiral auxiliaries in the Staudinger reaction. For instance, the reaction of (*S*)-oxazolidinon-3-ylacetyl chloride **5-31** with *N*-benzylimine **5-32** in the presence of triethyl amine gave the β-lactam **5-33** in 90% yield and 97:3 diasteromeric ratio (dr) (**Scheme 5-8**).[19]



5-31 **5-32** **5-33**

Scheme 5-8: Asymmetric synthesis of β-lactam **5-33** from imine **5-31**

Oxazodinone **5-31** was also used in the synthesis of β-lactams with quaternary stereogenic centers at C_4 using imines **5-34** derived from ketones **(Scheme 5-9**).[20] While symmetrical aliphatic imines afforded the products with almost complete diastereoselectivity (**Scheme 5-9, entries 1-3**), unsymmetrical imines gave mixtures of β-lactams **5-35** epimeric at C_4, with low levels of diastereoselection (**entries 4-5**). The *bis*(trimethylsilyl) methyl group can be removed by treatment with ceric (IV) ammonium nitrate (CAN). The *N*-bis(trimethylsilyl)methylimines **5-34** did not enolize to the corresponding enamine under the reaction conditions.

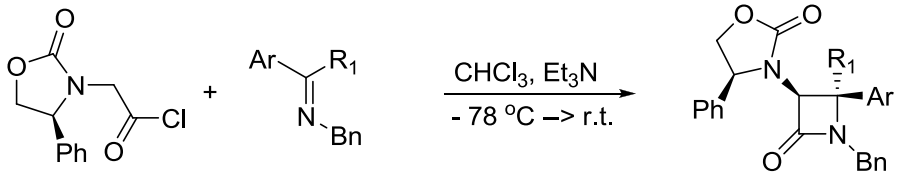


5-31 **5-34** **5-35**

Entry	R1	R2	yield%	dr%
1	Me	Me	70	99:1
2	Et	Et	69	99:1
3	Pr	Pr	70	98:1
4	Me	Et	80	70:30
5	Me	CH_2CH_2Ph	60	56:44

Scheme 5-9: Asymmetric synthesis of β-lactams **5-35** from imine **5-34**

The treatment of *N*-benzyl imines **5-36** derived from aryl ketones with (*S*)-oxazolidinon-3-ylacetyl chloride (**5-31)** gave essentially single diastereomers of the β-lactam products **5-37** in good yields (**Scheme 5-10**).[20]

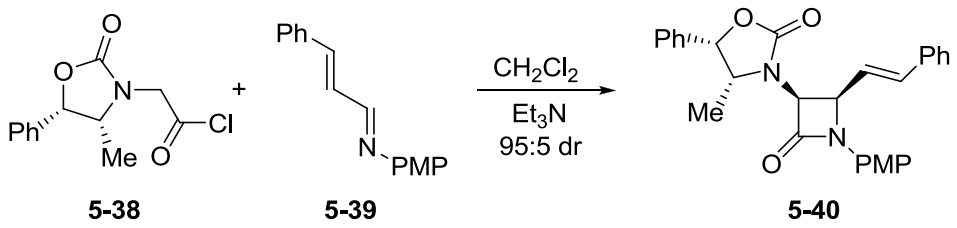


5-31 **5-36** **5-37**

Entry	Ar	R_1	yield%	dr%
1	Ph	Me	65	99:1
2	PMP	Me	65	99:1

Scheme 5-10: Asymmetric synthesis of β-lactams **5-37** from imine **5-31**

Similarly high diastereomeric ratio was obtained when the norephedrine derived chiral ketene precursor **5-38** was reacted with α,β-unsaturated imine **5-39**, giving the desired β-lactam **5-40** in 90% dr (**Scheme 5-11**).[21]

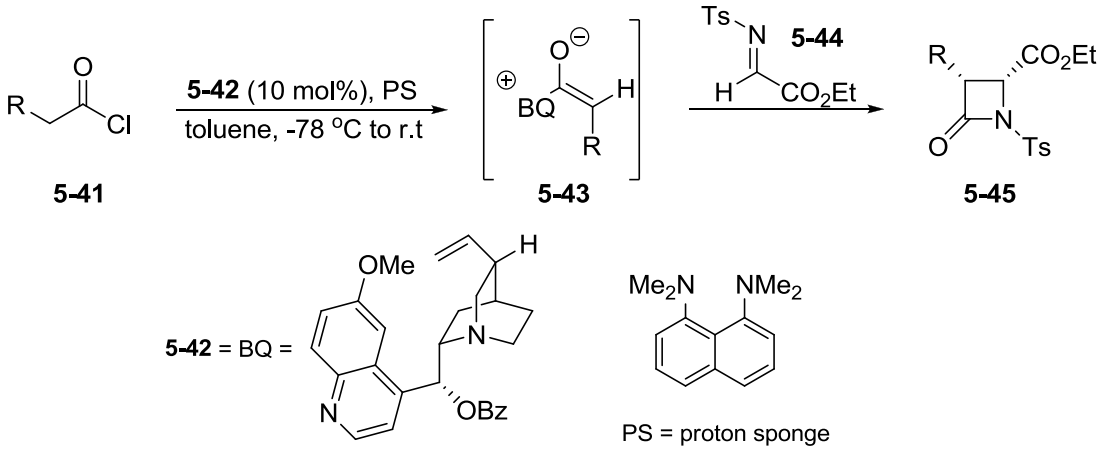


5-38 **5-39** **5-40**

Scheme 5-11: Asymmetric synthesis of β-lactam **5-40** from imine **5-38**

§ 5.2.3. Asymmetric induction from a chiral tertiary amine catalyst

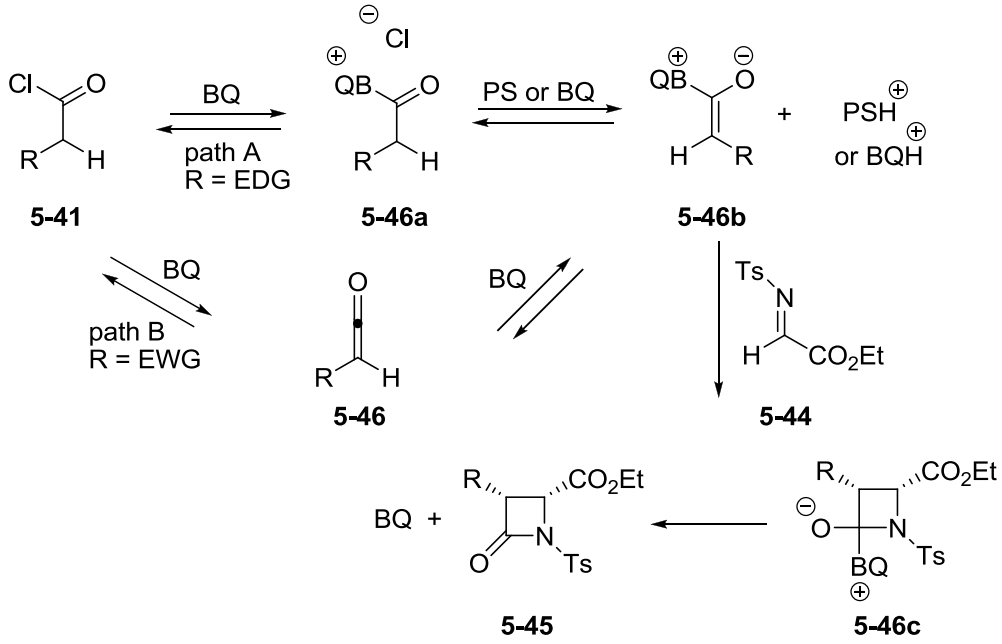
Compared to the reported methods for the asymmetric synthesis of β-lactams from chiral imines and ketenes, catalytic asymmetric variants of the Staudinger reaction are rare.[22] Lectka *et. al.* reported a method for the catalytic asymmetric synthesis of β-lactams from mono-substituted ketenes (**Scheme 5-12**).[23] The method is an umpolung version of the classical Staudinger reaction. That is, the ketene is nucleophilic while the imine is electrophilic. Using benzoylquinine (**5-42)** (BQ) as catalyst, the enantiomerically enriched 3-substituted-4-carboxyethyl products **5-45** were obtained in moderate to good yields with 95-99% enantiomeric excess (ee) and 99:1 diasteromeric ratio (dr) (**Scheme 5-12**). While the range of the ketene components that could be used was fairly broad, the reaction only worked with the highly electrophilic *N*-tosylimine **5-44**.



Entry	R	yield%	ee%	dr
1	Ph	65	96	99:1
2	Et	57	99	99:1
3	OPh	45	99	99:1
4	OAc	61	98	>99:1
5	OBn	56	95	99:1

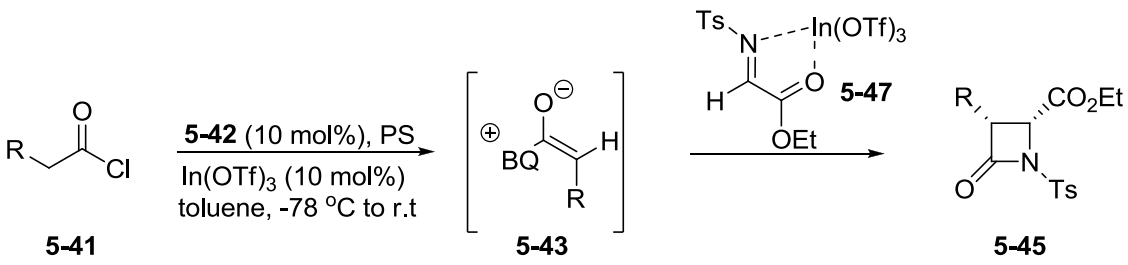
Scheme 5-12: BQ **5-42** catalyzed asymmetric synthesis of β-lactams **5-45**

The proposed mechanism for the transformation is illustrated in **Scheme 5-13**.[8b] According to Lectka and coworkers, the cinchona alkaloid derivative BQ (**5-42)** played two distinct roles depending on the type of acyl chloride used in the reaction. For acid chlorides with electron-donating groups (EDG), discrete ketene formation is not necessary. Instead, acylation of the acid chloride by BQ (**5-42)** forming **5-46a** followed by enolate **5-46b** formation occurs (**path A**). Cycloaddition between enolate **5-46b** and *N*-tosyl imine **5-44** gives the β-lactam product **5-45** and regenerates the active catalyst BQ (**5-42)**. For acid chloride with electron-withdrawing substituents (EWG), dehydrohalogenation by BQ (**5-42)** to form the ketene **5-46** followed by β-lactam formation predominates with PS acting as a secondary base (**path B**). Thus, BQ (**5-42)** acts as the kinetically active base in the dehydrohalogenation; while PS plays the role of the thermodynamic base by deprotonating BQ and regenerating the active catalyst.



Scheme 5-13: Proposed mechanism for BQ (**5-42)** catalyzed synthesis of β-lactams **5-45**

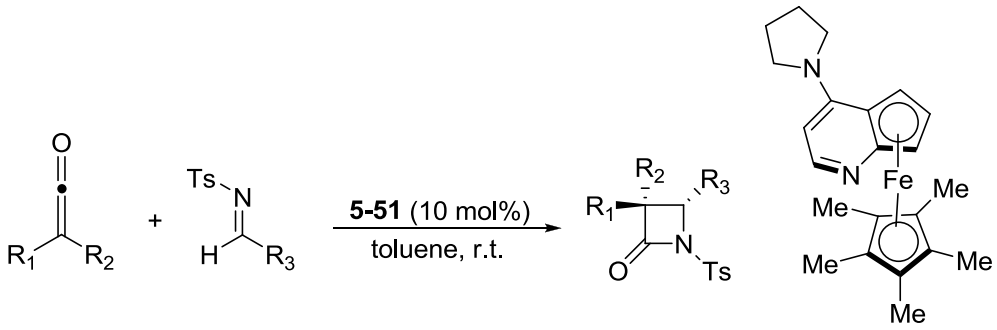
In a subsequent finding, the use of indium (III) triflate, $In(OTf)_3$, as a Lewis acid co-catalyst significantly improved the yield of the reactions. While the ee's for the modified reaction conditions remained largely unchanged, significant erosion of dr was observed (**Scheme 5-14**).[24] The dramatic rise in reaction yield was attributed to the metal co-catalyst binding to the imine, forming complex **5-47** (**Scheme 5-14**), thereby activating it to subsequent attack by the weakly nucleophilic ammonium enolate complex **5-43**.[24b]



Entry	R	yield%	ee%	dr
1	Ph	95	98	60:1
2	Bn	94	98	9:1
3	OPh	93	97	22:1
4	OAc	92	98	34:1
5	OBn	98	96	11:1

Scheme 5-14: BQ and In(III)OTf co-catalyzed asymmetric synthesis of β-lactams **5-45**

The Staudinger reaction of ammonium enolates derived from planar chiral ferrocenyl catalyst **5-51** with *N*-tosyl imines **5-49** gave highly substituted β-lactams **5-50** in good to excellent chemical yields and excellent ee's (**Scheme 5-15**).[25] High enantio and diastereoselectivity was observed for the reaction of *N*-tosyl imines **5-49** with both symmetrical and unsymmetrical disubstituted ketenes **5-48**. Imines derived from aromatic (**entries 1,4-6**), olefinic (**entry 3**) and aliphatic (**entries 2 and 7**) aldehydes gave the β-lactam products **5-50** in uniformly high yields and ee's. The mechanism for this reaction is proposed to proceed through ketene formation and is thus similar to that outlined in **Scheme 5-13** (**path B**).[8b]

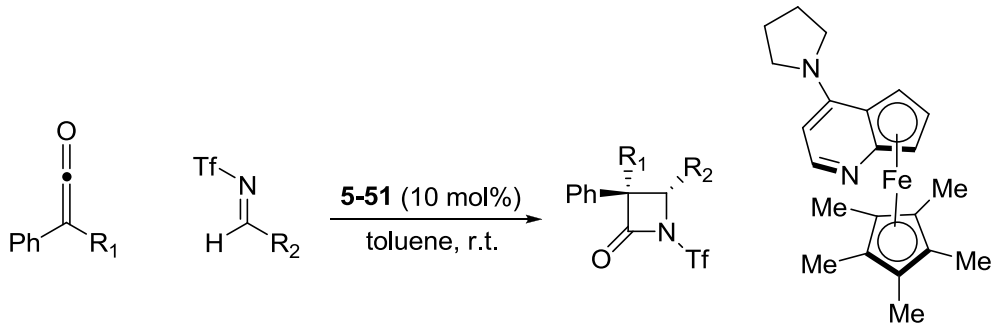


5-48 **5-49** **5-50** **5-51**

Entry	R1	R2	R3	yield%	ee%
1	-$(CH_2)_6$		2-furyl	90	92
2	-$(CH_2)_6$		cyclohexyl	76	94
3	Et	Et	1-styryl	83	92
4	Ph	i-Bu	Ph	88	98
5	Ph	i-Bu	2-furyl	97	98
6	Ph	Et	2-furyl	97	95
7	Ph	Et	*n*-propyl	97	98

Scheme 5-15: Asymmetric synthesis of β-lactams **5-50** catalyzed by **5-51**

An interesting reversal in diastereoselectivity was achieved when *N*-trifluoromethane sulfonyl (Tf) imines **5-53** instead of *N*-tosyl imines **5-49** were used with the same catalyst **5-51** (**Scheme 5-16**).[26] A broad range of disubstituted ketenes **5-52** and *N*-triflyl imines **5-53** gave the β-lactam products **5-54** in high yields, but with moderate to excellent selectivities.

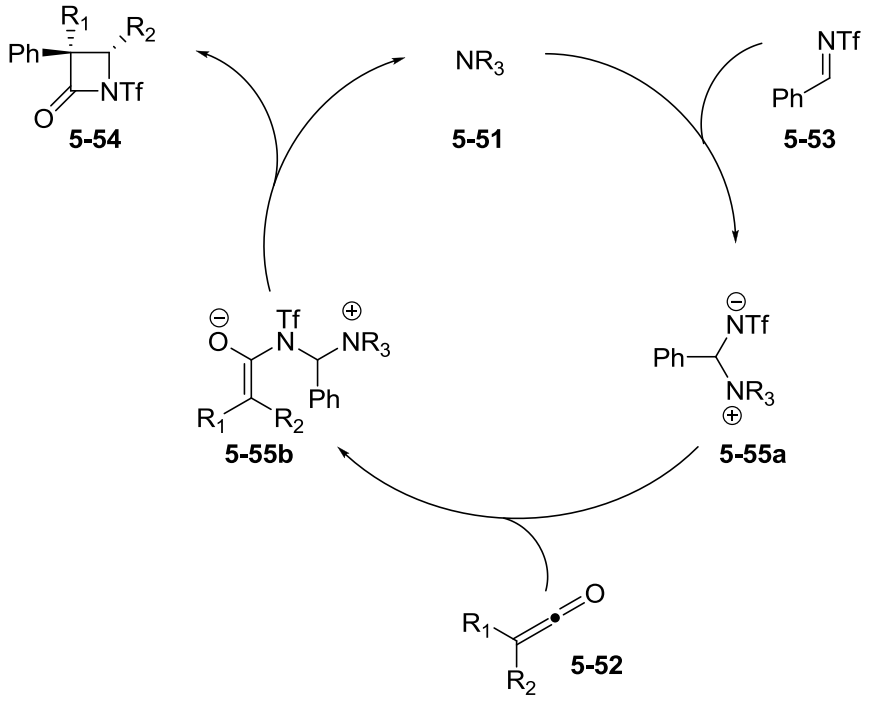


5-52 **5-53** **5-54** **5-51**

Entry	R_1	R_2	yield%	ee%	dr
1	Et	Ph	60	63	86:14
2	Me	Ph	83	81	98:2
3	*i*-Bu	Ph	72	63	97:3
4	Me	4-F-C_6H_4	80	85	96:4
5	Me	*o*-tolyl	89	99	81:19
6	Me	2-BrC_6H_4	79	84	80:20
7	Ph	Ph	62	98	–

Scheme 5-16: Asymmetric synthesis of β-lactams **5-54** catalyzed by **5-51**

The mechanism proposed by Fu and coworkers for the switch in selectivity is outlined below (**Scheme 5-17**).[26] The tetrahedral triflimide intermediate **5-55a** is generated by attack of the nucleophilic catalyst **5-51** at the highly electrophilic imine carbon **5-53**. The formation of intermediate **5-55a** was fully supported by ^{1}H NMR studies which showed that the catalyst **5-51** reacts quantitatively with *N*-triflyl imine **5-53**. Intermediate **5-55a** then attacks the ketene **5-52**, forming ammonium enolate **5-55b**. Displacement of the catalyst **5-51** by the enolate then forms the β-lactam **5-54**. A rational for the reversal in selectivity is still under investigation. However, it could be due to the intramolecular nature of the C-C bond formation in this case, as opposed to the intermolecular C-C bond formation in the classical Staudinger reaction.[22]



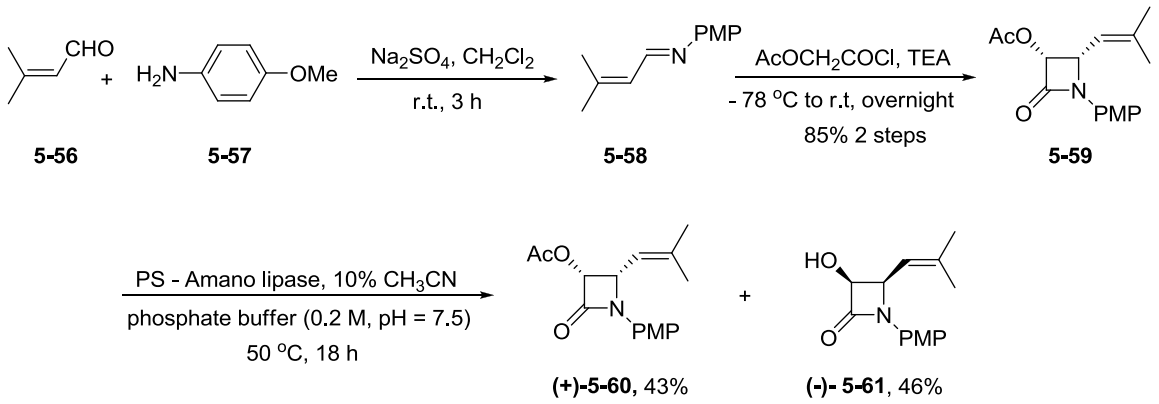
Scheme 5-17: Proposed mechanism for **5-51** catalyzed synthesis of β-lactams **5-54**

§ 5.3. Enantioselective approach to β-Lactams

As mentioned above, β-lactams are critical intermediates in the semi-synthesis of antitumor taxoids. During the course of studies on the structure activity relationship (SAR) of taxol, the Ojima lab developed a general method for the synthesis of a variety of β-lactams, which were then coupled to the appropriately modified baccatin III core to yield novel taxoids.[4] The synthesis of (+)-4-*iso*-butenyl-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy azetidin-2-one **(5-64)**, the side-chain precursor for novel second and third generation taxoids, is outlined below. The taxoids derived from coupling of compound **5-64** to appropriately modified baccatins have been shown to be several orders of magnitude more potent than Paclitaxel (**5-7)**.[27]

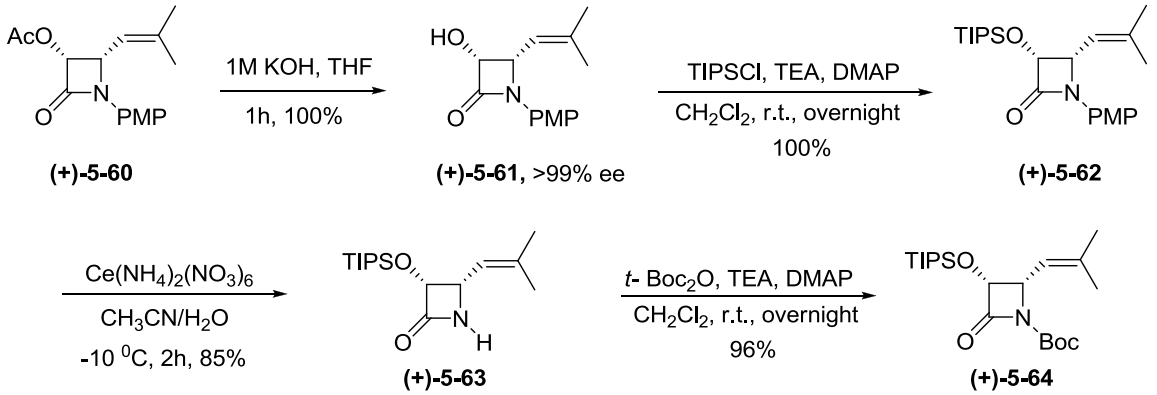
The condensation of 3-methylbut-2-enal (**5-56)** with *p*-methoxyaniline (**5-57)** gave imine **5-58**. Racemic β-lactam **(+/-)-5-59** was obtained *via* the Staudinger [2+2] cycloaddition of imine **5-58** and ketene, generated from the treatment of acetoxyacetyl chloride with triethylamine in 85% yield (2 steps) after chromatographic purification.

PS-Amano lipase catalyzed hydrolysis of racemate **(+/-)-5-59** resulted in the hydrolysis of the acetyl moiety at C-3 of the (*3S,4R*)- enantiomer yielding β-lactams **(+)-5-60** in 43% yield and **(-)-5-61** in 46% yield respectively (**Scheme 5-18**).



Scheme 5-18: Synthesis of (2*S*,3*R*)- 3-acetoxy-1-(4-methoxyphenyl)-4-(2-methylprop-1-enyl)- azetidin-2-one **(+)-(5-60)**

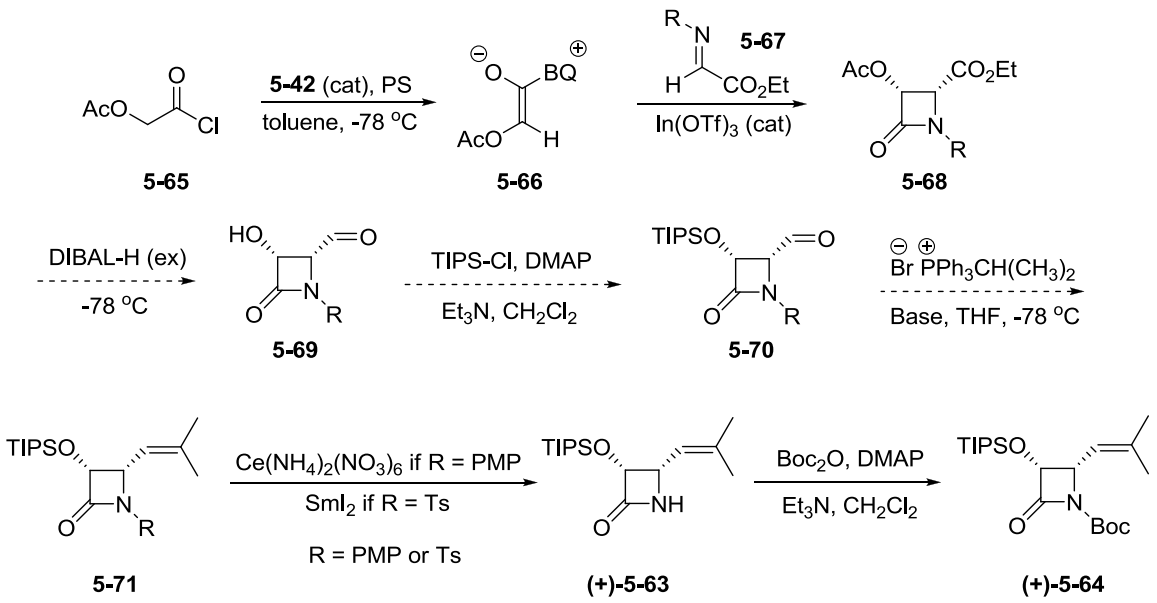
Deacetylation of β-lactam **(+)-5-60** followed by TIPS protection gave β-lactam **(+)-5-62** in quantitative yield for both steps**.** The enantiomeric excess (ee) was determined at this stage and was found to be 99% ee. Oxidative cleavage of the *p*-methoxyphenyl (PMP) group *via* treatment of β-lactam **(+)-5-62** with ceric ammonium nitrate (CAN) and subsequent acylation with *tert*-butylcarbonate in the presence of a catalytic amount of DMAP gave the desired *β*-lactam, 4-*iso*-butenyl-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy azetidin-2-one **(+)-(5-64)** in excellent yield (**Scheme 5-19**).



Scheme 5-19: Synthesis of 4-*iso*-butenyl-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy azetidin-2-one **(+)-(5-64)**

Though the desired β-lactam **(+)-5-64** could be obtained in enantiomerically pure form, it is obvious that the synthetic process could be improved; namely the enzymatic step which severely reduces the overall yield of the process. Thus, we were interested in preparing our desired β-lactam **(+)-5-64** in an asymmetric fashion. The catalytic asymmetric method reported by Lectka *et. al.* [23-24] was a very attractive choice for two reasons, besides the catalytic nature of the method. First, the tertiary amine catalyst is easily accessible in one step from commercially available quinine.[23b] Second, our desired β-lactam could be obtained in a few steps from a known intermediate.[23] Our proposed synthetic scheme is outlined in **Scheme 5-20**.

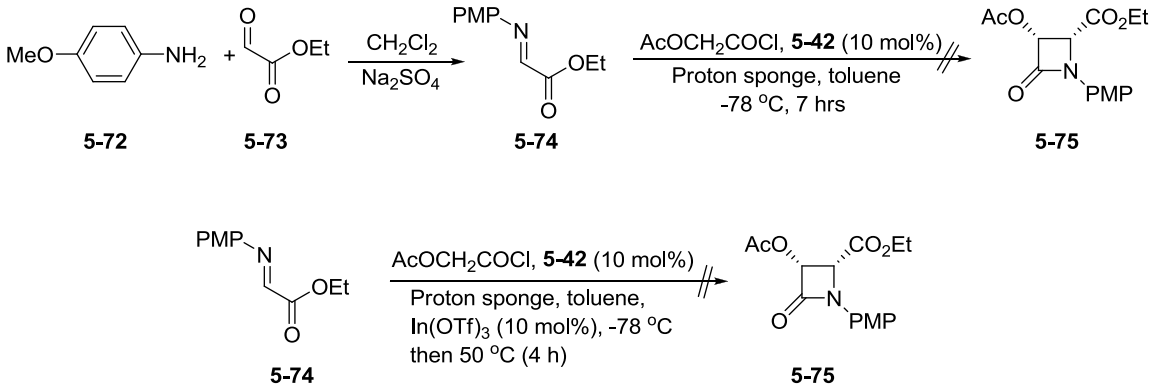
β-Lactam **5-68** would be formed through the reported method from iminoester **5-67** (R = Ts or PMP) and acetoxyacetyl chloride **5-65** with high enantio purity. Treatment of **5-68** with excess diisobutylaluminum hydride (DIBAL-H) is expected to give the hydroxy β-lactam **5-69**, which would be protected as the TIPS ether to give the known compound (R = PMP) **5-70**. Wittig olefination, followed by oxidative deprotection mediated by either ceric (IV) ammonium nitrate (CAN if R = PMP) or samarium diiodide (if R = Ts) and Boc protection of the amide nitrogen would give the desired *β*-lactam, 4-*iso*-butenyl-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy azetidin-2-one **(+)-(5-64)**. The results of the proposed process are discussed below.



Scheme 5-20: Proposed catalytic asymmetric synthesis of 4-*iso*-butenyl-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy azetidin-2-one **(+)-(5-64)**

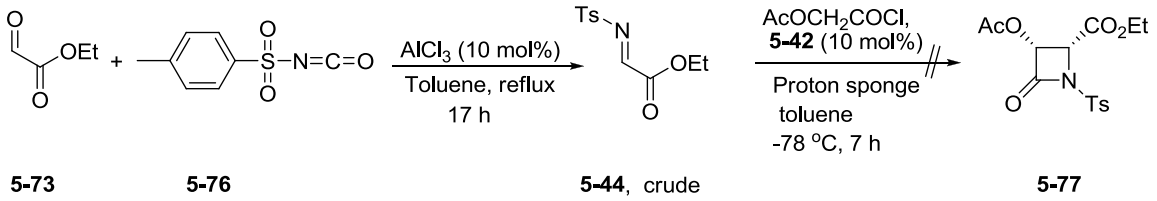
§ 5.4. Results and discussion

Our attempt at the catalytic asymmetric synthesis of **(+)-5-64**, started with the preparation of PMP iminoester **5-73** *via* condensation of ethyl glyoxylate (**5-73)** with *p*-methoxyanaline (**5-72)** (**Scheme 5-21**).[24b, 28] Reaction of the imine **5-74** with acetoxyacetyl chloride in the presence of catalytic amounts of benzoylquinine (**5-42)** (prepared from quinine, benzoyl chloride and triethyl amine) under the reported conditions, did not yield the expected β-lactam product **5-75**. Hoping to activate imine **5-74** to nucleophilic attack, $In(OTf)_3$ was used as a co-catalyst under similar conditions. However, no conversion was observed even after heating the reaction mixture at 50 °C (**Scheme 5-21**).



Scheme 5-21: Attempted synthesis of β-lactam **5-75**

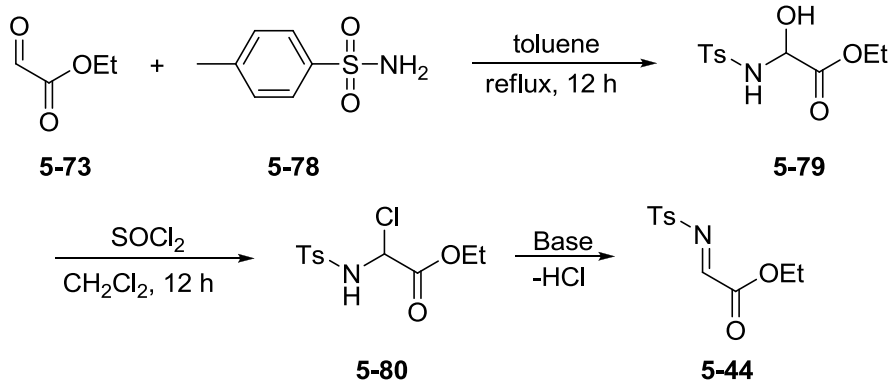
Since the reported method discussed above (**see Schemes 5-12 and 5-14**) used a tosyl iminoester, it is possible that our PMP-iminoester **5-74** does not possess the electrophilic character required for the desired transformation. Thus, we attempted the synthesis of the tosyl iminoester **5-44** according to a procedure reported by Weinreb (**Scheme 5-22**).[29] However, purification of this product proved difficult. Therefore, the crude product containing polymeric ethyl glyoxylate and the desired tosyl iminoester **5-44** was used in the β-lactam forming reaction according to the reported procedure. However, no desired product was obtained (**Scheme 5-22**).



Scheme 5-22: Attempted synthesis of β-lactam **5-77**

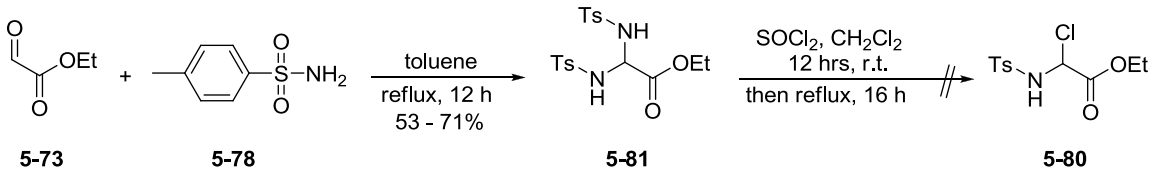
To avoid the purification issues associated with the Weinreb procedure, we explored the synthesis of the tosyl iminoester **5-44** by a three-step method reported by Lectka *et. al.* (**Scheme 5-23**).[30] Accordingly, the reaction of ethyl glyxoylate (**5-73)** with *p*-toluenesulfonyl amide (**5-78)** in refluxing toluene gave *N-p*-toluenesulfonylhydroxyglycine ethyl ester (**5-79)**. Chlorination of this compound

followed by base mediated dehydrohalogenation was reported to give the desired tosyl iminoester **5-44** (**Scheme 5-23**).



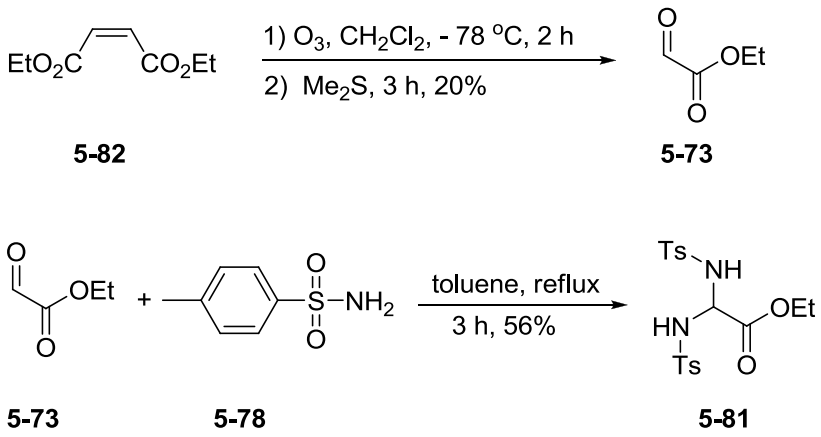
Scheme 5-23: Reported synthesis of *N*-tosyl iminoester **5-44**

However in our hands, the reaction of commercially available ethyl glyoxylate (**5-73)** with *p*-toluenesulfonyl amide (**5-78)** consistently yielded the *bis*-tosyl substituted ethyl ester **5-81** as the only product (**Scheme 5-24**). The formation of the *bis*-*N*-tosylester **5-81** indicated that the desired imine product was initially formed from the reaction of the monomeric form of the aldehyde **5-73** with the sulfonyl amide **5-78**. However, the subsequent reaction of the desired tosyl-imine with sulfonyl amide **5-78** present in the reaction mixture indicates that this second reaction may be faster than depolymerization of aldehyde **5-73**. Thus the aldehyde was distilled and used immediately in the reaction for the synthesis of compound **5-79**. However, prior distillation and varying the ratio of aldehyde to sulfonyl amide (i.e. using two to three equivalents of the aldehyde) along with slow addition of the sulfonyl amide had no effect, as only *bis*-tosylester **5-81** was always isolated as the lone product. We hoped that chlorination of the *bis*-tosylester product **5-81** would give the desired chloroester **5-80**. But no conversion was observed after 12 h at room temperature or after 16 h under refluxing conditions (**Scheme 5-24**).



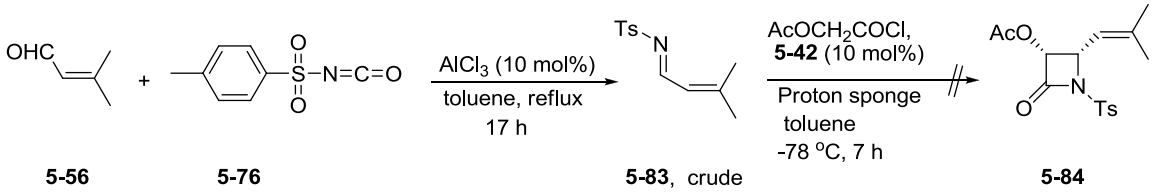
Scheme 5-24: Attempted synthesis of *N*-tosyl iminoester **5-44**

The preparation of fresh ethyl glyoxylate **5-73** from diethyl maleate **5-82** *via* ozonolysis and subsequent reaction with tosyl amide **5-78** also gave the *di*-substituted ethyl ester **5-81** in 56% isolated yield (**Scheme 5-25**).



Scheme 5-25: Attempted synthesis of *N*-tosyl iminoester **5-44**

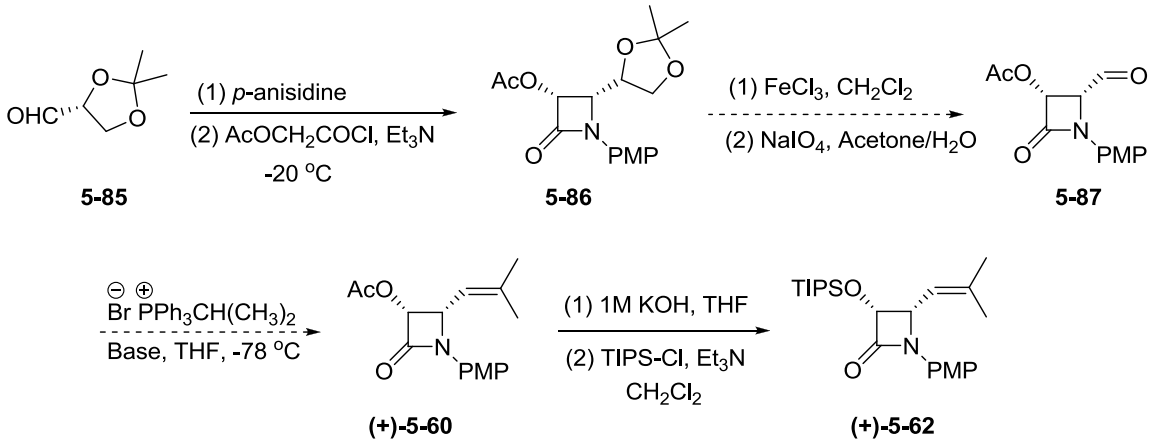
We also sought to obtain 3-acetoxy, 4-isobutenyl β-lactam **5-84** directly, using the method reported by Lectka *et. al*. Thus *N*-tosyl isobutenyl imine **5-83** was prepared from the reaction of *p*-toluene isocyanate (**5-76)** with 3-methyl-2-butenal (**5-56)** according to a known procedure (**Scheme 5-26**).[29] However, no product was obtained in the subsequent β-lactam forming reaction.



Scheme 5-26: Attempted catalytic asymmetric synthesis of (2*S*,3*R*)-3-acetoxy-4-(2-methylprop-1-enyl)- 1-*p*-toluenesulfonyl-azetidin-2-one **(5-84)**

Since no success was achieved in obtaining the desired β-lactams from the catalytic asymmetric approach, we therefore sought other methods to synthesize our desired target. After extensive literature search, we decided to utilize a method reported by Wagle *et. al*.[17] In this method, the key stereogenic center is derived from *D*-mannitol.

Our revised synthetic approach is outlined below (**Schemes 5-27 and 5-28**). The known β-Lactam **5-86** (**See scheme 5-4, entry 6**) would be formed *via* [2+2] cycloaddition of PMP-iminoacetal and the ketene generated from the reaction of acetoxyacetyl chloride with triethyl amine in high enantiomeric purity (**Scheme 5-27**).

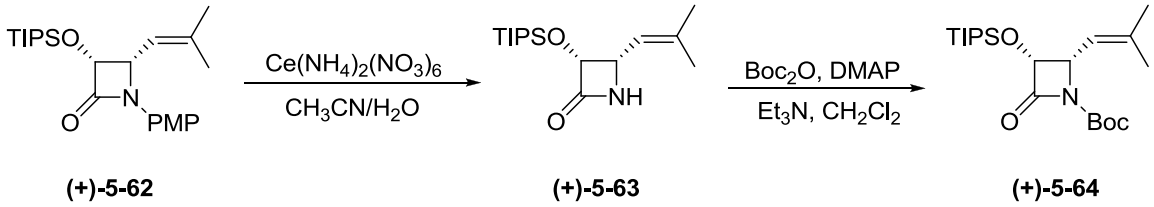


5-85 **5-86** **5-87**

(+)-5-60 **(+)-5-62**

Scheme 5-27: Proposed asymmetric synthesis of (2*S*,3*R*)-1-(4-methyoxyphenyl)-4-(2-methylprop-1-enyl)-3-(triisopropylsilyloxy)-azetidin-2-one **(+)-(5-62)**

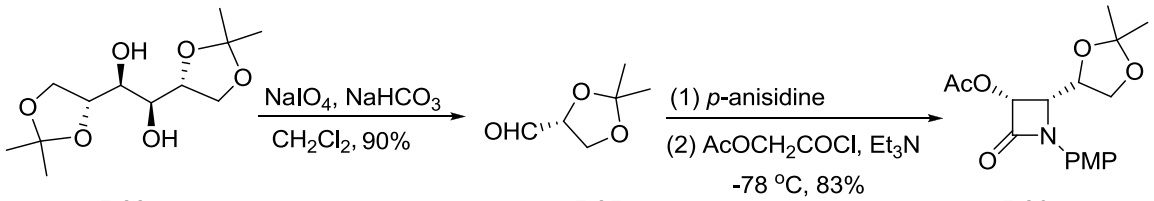
Deprotection of the acetonide and subsequent oxidative cleavage of the resulting diol would give aldehyde **5-87**.[31] Wittig olefination[32] followed by hydrolysis and TIPS protection of the alcohol would give the known β-lactam **(+)-5-62** (**Scheme 5-27**). Cerium ammonium nitrate (CAN) mediated reductive cleavage of the *para*-methoxyphenyl (PMP) group followed by Boc protection of the amide nitrogen would give the desired β-lactam **(+)-5-64** (**Scheme 5-28**).



(+)-5-62 **(+)-5-63** **(+)-5-64**

Scheme 5-28: Proposed asymmetric synthesis of 4-*iso*-butenyl-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy azetidin-2-one **(+)-(5-64)**

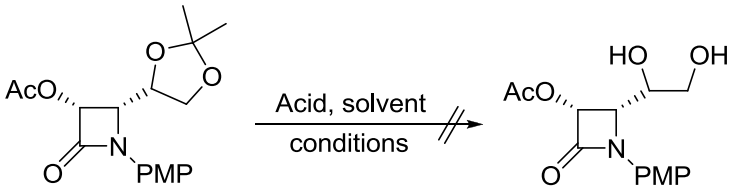
Our studies began with the preparation of aldehyde **5-85** which was obtained in 90% yield after oxidative cleavage of commercially available *bis*-acetonide derivative **5-88** of D-mannitol (**Scheme 5-29**). β-Lactam **5-86** was obtained in 83% yield (2 steps) as a single diastereomer after reaction of aldehyde **5-85** with *p*-anisidine and subsequent [2+2] cycloaddition of the chiral imine with acetoxyacetyl chloride in the presence of triethyl amine.[17]



5-88 **5-85** **5-86**

Scheme 5-29: Synthesis of (3*R*,4*S*)-1-(4-methyoxyphenyl)-3-acetoxy-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-azetidin-2-one (**5-86)**

The acetonide deprotection under a variety of acidic conditions was next investigated (**Scheme 5-30, Table 5-1**) and surprisingly turned out to not be trivial. As **Table 5-1** shows, treatment of β-lactam **5-86** with different Brønsted acids[18, 32] (**entries 1-6**) or Tin(II) chloride (entry 7) either resulted in no reaction or gave undesired products.



5-86 **5-89**

Scheme 5-30: Attepmpted acetonide deprotection of **5-86**

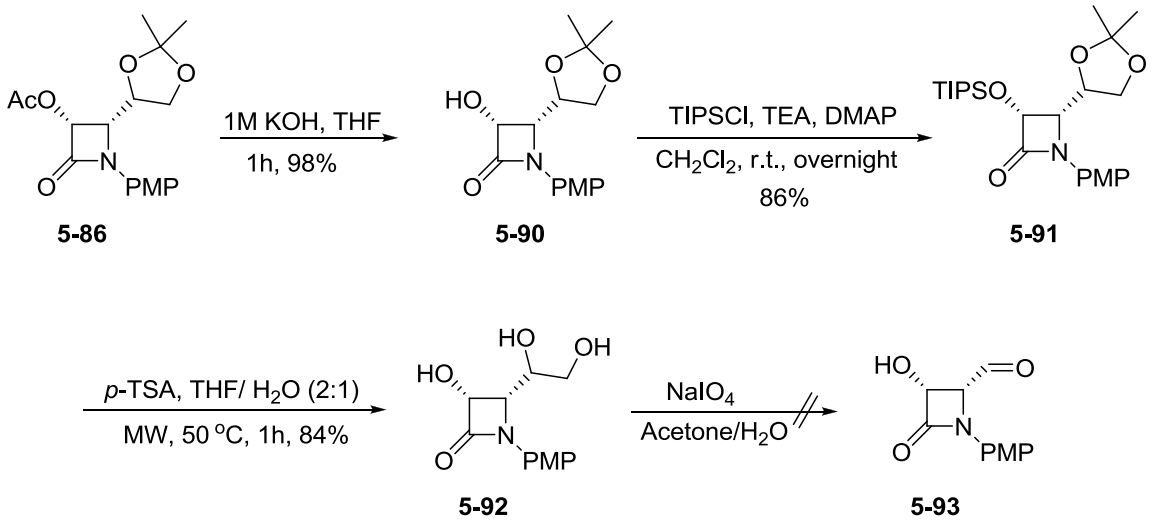
Table 5-1: Conditions explored for acetonide deprotection

Entry	Acid	Solvent	Conditions	Result
1	TFA	CH_2Cl_2	r.t., o/n	no reaction
2	75% AcOH	none	r.t., o/n	no reaction
3	*p*-TSA.$2H_2O$	CH_3OH	r.t., o/n	deacetylation
4	CH_3COCl	CH_2Cl_2, MeOH	r.t., o/n	no reaction
5	50% AcOH	none	MW, 50 ^oC, 1h	complex mixture
6	*p*-TSA.$2H_2O$	THF	MW, 50 ^oC, 1h	complex mixture
7	$SnCl_2$	CH_2Cl_2	r.t., o/n	no reaction

Specifically, the deprotection using trifluoroacetic acid (TFA) or 75% aqueous acetic acid only resulted in the recovery of compound **5-86** (**entries 1 and 2**). The reaction of β-lactam **5-86** with *para*-toluenesulfonic acid (*p*-TSA) in methanol (CH_3OH) resulted in hydrolysis of the acetyl group (**entry 3**). The attempt to generate hydrochloric acid (HCl) in-situ also resulted in only the recovery of **5-86** (**entry 4**). Next, the reaction was done under microwave irradiation conditions; using either 50% aqueous acetic acid or *p*-TSA, at 50 ^oC for 1 h resulted in a complex mixture as determined by ^1H NMR. Mass spectrometry analysis of these reaction mixtures indicated the desired product along with the corresponding triol resulting from concomitant acetyl hydrolysis (**entries 5 and 6**).

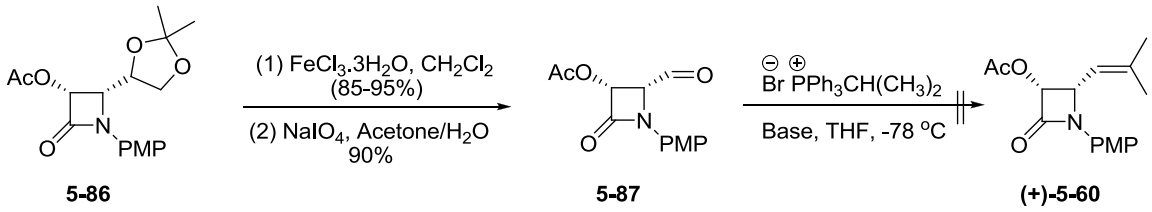
The deacetylated product observed under *p*-TSA/CH_3OH conditions (**Table 5-1, entry 3**) prompted an investigation into possible modification of the proposed synthetic route to β-lactam (+)-**5-64.** Thus, compound **5-86** was hydrolyzed under basic conditions and subsequent TIPS protection gave compound **5-91** in high overall yield (**Scheme 5-**

31). Acetonide hydrolysis with *p*-TSA under microwave irradiation conditions gave triol **5-92**. However, attempted oxidation of triol **5-92** gave a very complex reaction mixture (**Scheme 5-31**).



Scheme 5-31: Attempted synthesis of (3*R*,4*R*)-1-(4-methyoxyphenyl)-3-hydroxy-4 formyl-azetidin-2-one (**5-93)**

After extensive studies into the acetonide deprotection, we found $FeCl_3$ to be the best reagent and gave the desired diol in 85-95% yield.[31] Subsequent oxidative cleavage of the diol gave aldehyde **5-87** in high yield. Unfortunately, the Wittig olefination[32] could not be effected under a variety of conditions. The explorations of other methods aimed at obtaining β-lactam **(+)-5-60** are ongoing.



Scheme 5-32: Attepmted synthesis of 3-acetoxy-4-*iso*-butenyl-1-(*tert*-butoxycarbonyl) azetidin-2-one **(+)-(5-60)**

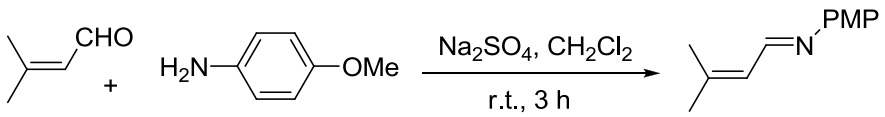
§ 5.5. Conclusion

The importance of β-lactams in the semi-synthesis of novel potent antitumor taxoids prompted us to develop an asymmetric approach to our desired β-lactams. We applied two reported approaches; the first being a catalytic asymmetric approach while in the second approach, the chirality was derived from a sugar auxiliary. The chiral auxiliary approach was found to be more reliable and gave a key intermediate for our desired β-lactams in high yields and excellent enantiopurity. The synthesis of the desired β-lactam is still under investigation.

§ 5.5. Experimental Section

General Methods: All reactions were carried out under nitrogen in oven dried glassware using standard Schlenk techniques unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents using Fisher silica gel (particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. Analytical high performance liquid chromatography (HPLC) was performed with a Shimadzu LC 2010A system using a phenomenex Curosil-B column, employing CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Shimadzu FTIR-84005 spectrophotometer. ^1H NMR spectra were recorded on a Varian Inova-500 (500 MHz), 400 (400 MHz) or a Gemini-300 (300 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova-400 (100 MHz) or a Gemini-300 (75 MHz) at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 77.0 ppm). High resolution mass spectrometry (HRMS) was carried out at the Mass Spectrometry Facility, the University of Illinois Urbana Champaign. Solvents were reagent grade and freshly distilled before use. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen.

***N*-(4-Methoxyphenyl)-3-methyl-2-butenaldimine, (5-58):**[27c]

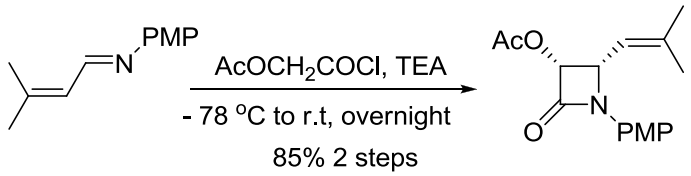


5-56 **5-57** **5-58**

3-Methylbut-2-enal (5.63 mL, 59.0 mmol) was added dropwise to a solution of *p*-anisidine (6.00 g, 49.0 mmol) and anhydrous Na_2SO_4 (27.84 g, 196 mmol) in 120 mL CH_2Cl_2, and the resulting reaction mixture was stirred at room temperature for 3 h. After

filtration, the mixture was evaporated under vacuum to yield imine as yellow **5-58** as viscous yellow oil, which was immediately used in the synthesis of β-lactam without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (s, 3 H), 2.01 (s, 3 H), 3.80 (s, 3 H), 6.20 (d, *J* = 9.5 Hz, 1 H), 6.89 (d, *J* = 7.0 Hz, 2 H), 7.11 (d, *J* = 7.0 Hz, 2 H), 8.38 (d, *J* = 9.5 Hz, 1 H). ^{1}H NMR data was consistent with that reported in the literature.[27c]

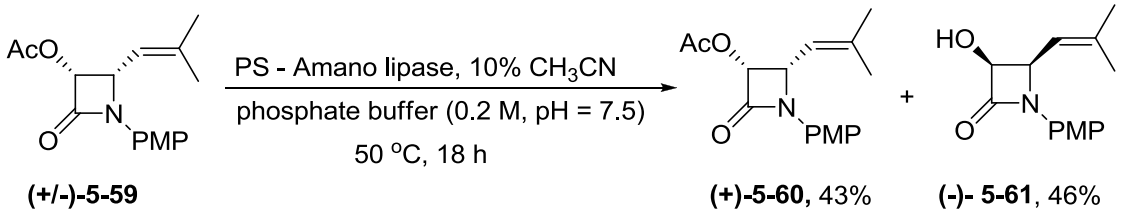
(±)-1-(4-Methoxyphenyl)-3-acetoxyl-4-(2-methylprop-1-enyl)azetidin-2-one, (+/-)-(5-59):[27c]



5-58 **5-59**

To the resulting imine **5-58** diluted with CH_2Cl_2 (250 mL), was added triethylamine (10.2 mL, 74.0 mmol) and the solution was cooled to -78 ˚C. Acetoxyacetyl chloride (6.34 mL, 59.0 mmol) in 20 mL of CH_2Cl_2 was added dropwise over 15 min and the reaction mixture was warmed to room temperature overnight. The reaction mixture was diluted with 150 mL of CH_2Cl_2 and 100 mL of water and the layers separated. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography of the residue on silica gel (hexanes/ ethyl acetate = 4/1) afforded the titled compound **(+/-)-5-59** (11.97 g, 85 %, two steps) as yellow solid; mp 107-109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70 (s, 3 H), 1.72 (s, 3 H), 2.01 (s, 3 H), 3.67 (s, 3 H), 4.83 (dd, *J* = 9.9 Hz, 4.8 Hz, 1 H), 5.02 (d, *J* = 9.3 Hz, 1 H), 5.67 (d, *J* = 4.8 Hz, 1 H), 6.74 (d, *J* = 8.9 Hz, 2 H), 7.20 (d, *J* = 8.9 Hz, 2 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 20.2, 27.0, 76.1, 114.3, 117.5, 118.4, 130.7, 141.8, 156.4, 161.3, 169.3. All data were consistent with literature precedent.[27c]

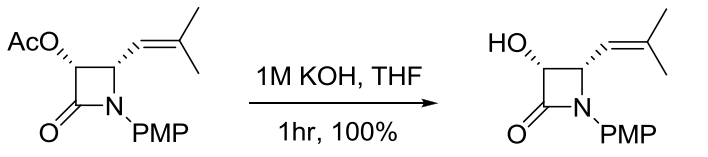
(+)-*cis*-(3*R*,4*S*)-3-Acetoxy-1-(4-methoxyphenyl)-4-(2-methylprop-1-enyl)azetidin-2-one, (+/-)-(5-60):[33]



(+/-)-5-59 **(+)-5-60,** 43% **(-)- 5-61**, 46%

While stirring, PS-Amano lipase (6.50 g) was added to a suspension of the racemic *β*-lactam **(+/-)-5-59** (11.9 g, 41.0 mmol) in 750 mL of 0.2 M sodium phosphate buffer (pH = 7.5) and 75 mL of acetonitrile, and the mixture was vigorously stirred at 50 ^{o}C. After 18 h, the ^{1}H NMR of an aliquot showed the conversion of the reaction was 54%. The mixture was filtered through a bed of celite and the filtrate was extracted with ethyl acetate (4 x 100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 4/1 and then 1% MeOH in CH_2Cl_2) to give (+)-*cis*-l-(4-methoxyhenyl)-3-acetoxy-4-(2-methylprop-1-enyl)-2-one (**(+)- 5-60**, 3.92 g, 43%) with 99% ee as colorless oil and (-)-*cis*-l-(4-methoxyhenyl)-3-hydroxy-4-(2-methylprop-1-enyl)-2-one (**(-)-5-61**, 5.73 g, 46%). **(+)-5-60:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (d, *J* = 8.4 Hz, 9 H), 2.12 (s, 3 H), 3.78 (s, 3 H), 4.95 (dd, *J* = 6.0 Hz, 1 H), 5.12 (d, *J* = 1.2 Hz), 5.80 (d, *J* = 3.0 Hz, 1 H), 6.84 (d, *J* = 9.0 Hz, 2 H), 7.31 (d, *J* = 6.0 Hz, 2 H). All data were consistent with literature precedent.[27c]

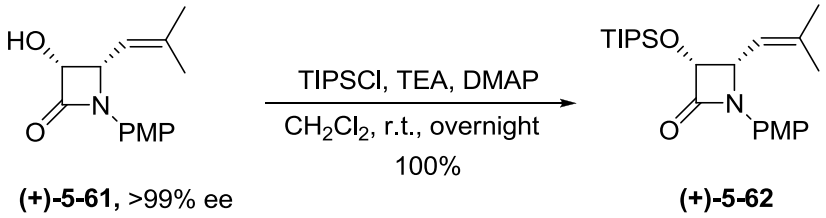
(+)-(*3R,4S*)-1-(4-Methoxyphenyl)-3-hydroxy-4-(2-methylprop-1-enyl)azetidin-2-one, (+)-(5-61).[27c]



(+)-5-60 **(+)-5-61,** >99% ee

To a cooled (0 ^{o}C) solution of **(+)-5-60** (2.00 g, 6.92 mmol) in 90 mL of THF was added dropwise 1 M aqueous solution of KOH (69 mL) *via* an addition funnel over 20 min. The mixture was stirred at 0 °C for 1 h and then 40 mL of saturated NH_4Cl was added. The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give **(+)- 5-61** (1.71 g, 100%) as white solid that was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (s, 6H), 3.75 (s, 3 H), 4.63 (d, 1H, *J* = 7.5 Hz), 4.86 (dd, 1H, *J* = 5.2, 9.2 Hz), 5.04 (dd, 1H, *J* = 5.2, 7.0 Hz, 1 H), 5.33 (d, 1H, *J* = 9.2 Hz), 6.79 (d, 2H, *J* = 9.0 Hz), 7.27 (d, 2H, *J* = 9.0 Hz). All data were consistent with that reported in the literature.[27c]

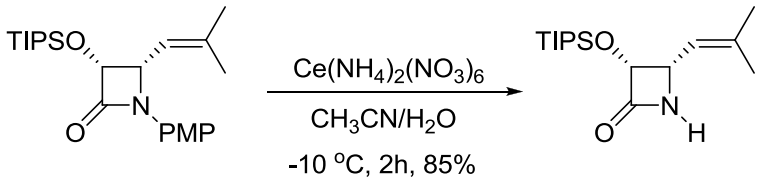
(+)-1-*p*-Methoxyphenyl-3-triisopropylsiloxy-4-(2-methylpropen-2-yl)azetidin-2-one, (+)-(5-62):[27c]



(+)-5-61, >99% ee **(+)-5-62**

Chlorotriisopropylsilane (1.50 mL, 6.80 mmol) was added to a solution of **(+)- 5-61** (1.12 g, 4.53 mmol), DMAP (0.11 g, 0.09 mmol) and Et_3N (2.53 mL, 18.1 mmol) in 35 mL of CH_2Cl_2. The reaction mixture was stirred overnight at room temperature and quenched with 30 mL of saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2 (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 18/1) to give 1-*p*-methoxyphenyl-3-triisopropylsiloxy-4-(2-methylpropen-2-yl)azetidin-2-one (**(+)- 5-62,** 1.83 g, 100%) as white solid; mp = 78-80 ^{o}C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97-1.24 (m, 21 H), 1.88 (d, *J* = 2.3 Hz, 3 H), 1.84 (d, *J* = 2.3 Hz, 3 H), 3.77 (s, 3 H), 4.82 (dd, *J* = 9.9, 5.1 Hz, 1 H), 5.04 (d, *J* = 5.1 Hz, 1 H), 5.33 (d, *J* = 9.9 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.7 Hz, 2 H). All data are in agreement with literature values.[27c]

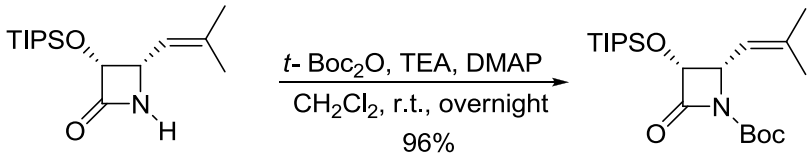
(+)-3-Triisopropylsilyloxy-4-(2-methylpropen-2-yl)azetidin-2-one, (+)-(5-63):[27c]



(+)-5-62, **(+)-5-63**

Cerium ammonium nitrate (CAN) in 8 mL of water was added dropwise over to a solution of **(+)-1-6** (1.69 g, 4.18 mmol) in 104 mL of acetonitrile, and 104 mL of water at -10 ^{o}C. The reaction mixture was stirred for 2 h at the indicated temperature and then quenched with 45 mL of saturated aqueous Na_2SO_3 and filtered. The filtrate was extracted with ethyl acetate (3 x 60 mL) and the combined organic layers was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate = 5/1) yielding the titled compound **(+)-5-63** as white solid (1.060 g, 85 % yield; mp = 85-86 ^{o}C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97-1.21 (m, 21 H), 1.68 (d, *J* = 2.3 Hz, 3 H), 1.19 (d, *J* = 2.3 Hz, 3 H), 4.43 (dd, *J* = 9.5, 4.7 Hz, 1 H), 4.98 (dd, *J* = 4.7, 2.3 Hz, 1 H), 5.31 (d, *J* = 9.5 Hz, 1 H). All data are in agreement with that reported in the literature.[27c]

(+)-1-(*tert*-Butoxycarbonyl)-3-triisopropylsiloxy-4-(2-methylpropen-2-yl)azetidin-2-one, (+)-(5-64):[27c]

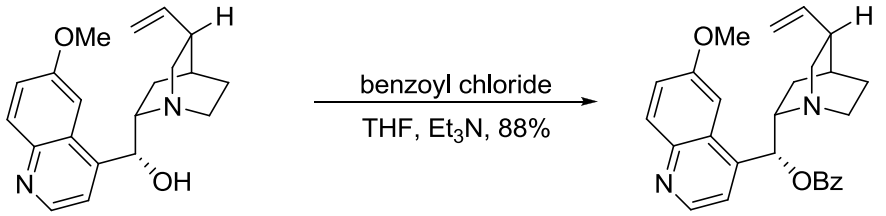


(+)-5-63 **(+)-5-64**

To a solution of 3-triisopropylsiloxy-4-(2- methylprop-2-enyl) azetidin-2-one (**(+)-5-63,** (1.06 g, 3.55 mmol), triethylamine (1.48 mL, 10.7 mmol) , and a catalytic amount of dimethylaminopyridine (DMAP) (0.09 g, 0.70 mmol) in 24 mL CH_2Cl_2, was added di-*tert*-butyl dicarbonate (0.93 g, 4.26 mmol) in 10 mL of CH_2Cl_2. The reaction

mixture was stirred overnight at room temperature, quenched with 30 mL saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate = 25/1) to yield 1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-(2-methylprop-2-enyl)-azetidin-2-one (**(+)-5-64)** as clear oil (1.35 g, 96% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02-1.2 (m, 21 H), 1.48 (s, 9 H), 1.77 (d, *J* = 1.0 Hz, 3 H), 1.79 (d, *J* = 1.0 Hz, 3 H), 4.75 (dd, *J* = 9.8, 5.6 Hz, 1 H), 4.98 (d, *J* = 5.6 Hz, 1 H), 5.28 (dd, *J* = 9.8, 1.0 Hz, 1 H). All data are in agreement with literature values.[27c]

Benzoylquinine, (5-42):[23b]

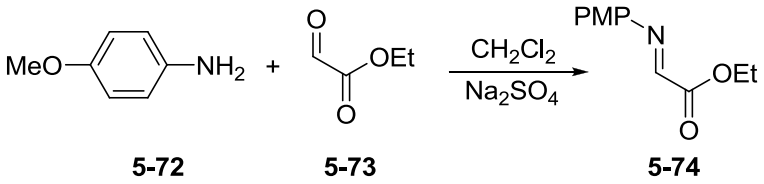


5-42

Quinine (1.50 g, 4.62 mmol) was dissolved in 15 mL of THF and triethylamine (3.22 mL, 23.1 mmol) and cooled to 0 ^{o}C. Benzoyl chloride (0.81 mL, 6.94 mmol) was added by syringe over 5 min and the reaction was allowed to warm to room temperature overnight. After evaporation under reduced pressure, the crude residue was dissolved in 20 mL CH_2Cl_2 and then washed three times with 10 mL 25% (w/w) aqueous NaOH solution. The combined aqueous fractions were back extracted with 30 mL CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified on a short plug of silica with 95% EtOAc with 5% triethylamine to yield a white solid (foam). The solid was recrystallized from boiling Et_2O/hexanes to yield benzoylquinine **5-42** as white solid (1.74 g, 88% yield): [mp = 136 – 138 ^{o} C; $[\alpha]_D^{20}$ = + 109.5; C = 0.04 in ethanol; (lit mp = 141.5 – 143 ^{o} C;[45] $[\alpha]_D^{23}$ = + 119.5]; C = 1.0 in ethanol).[34] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63 (m, 1 H), 1.80 (m, 2 H), 1.95 (m, 2H), 2.35 (m, 1H), 2.73 (m, 2H), 3.13 (m, 1H), 3.27 (m, 1H), 3.53 (m, 1H), 4.01 (s, 3H), 5.04 (m, 2H), 5.86 (m, 1H), 6.74 (d, 1H, *J* = 6.6 Hz), 7.40 (dd, 1H, *J* = 9.2, 2.7 Hz), 7.44 (d, ,

1H, *J* = 4.6 Hz), 7.50 (m, 2 H), 7.63 (m, 1 H), 8.04 (d, 1H, *J* = 9.0 Hz), 8.15 (m, 2 H), 8.74 (d, 1H, *J* = 4.5 Hz). Proton NMR data was consistent with the literature.[35]

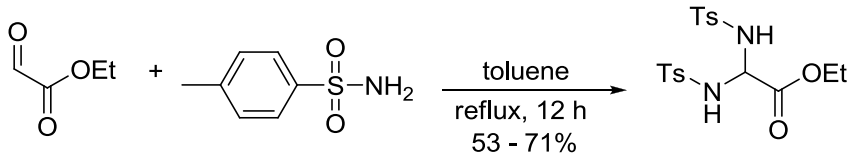
***N*-(Ethoxycarbonylmethylidene)4-methoxyaniline, (5-74)**:[28]



5-72 **5-73** **5-74**

A solution of ethyl glyoxylate (0.20 g, 1.95 mmol) in CH_2Cl_2 (2 mL) was treated with anhydrous sodium sulfate (0.55 g, 3.90 mmol) and *p*-methoxyaniline (0.12 g, 0.097 mmol) and the resulting mixture was stirred at room temperature for 3 h. Then the mixture was filtered and concentrated *in vacuo* to yield the product as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.4 (t, *J* = 7 Hz, 3 H), 3.7 (s, 3 H), 4.3 (q, *J* = 7 Hz, 2 H), 6.8 (d, *J* = 9 Hz, 2 H), 7.2 (d, *J* = 9 Hz, 2 H), 7.8 (s, 1 H). ^{1}H NMR data was consistent with literature precedent.[28]

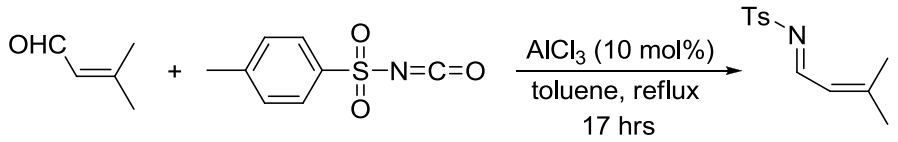
***N, N'*-Bis-(*p*-toluenesulfonyl)glycine ethyl ester, (5-81)**:[36]



5-73 **5-78** **5-81**

Ethyl glyoxylate (1.35 g, 13.2 mmol) and *p*-toluenesulfonylamide (2.26 g, 13.2 mmol) were refluxed in toluene (14 mL) for 12–16 h. A white precipitate formed as the mixture was cooled to room temperature. The solid was filtered and recrystallized from ethyl acetate to give the product as crystalline white solid: mp = 179 – 181 ^{o}C; (Lit 178 – 180 ^{o}C).[36] 1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, 3 H), 2.41 (s, 6 H), 4.06 (q, 2 H), 5.23 (t, *J* = 7.8, 1 H), 5.53 (d, *J* = 7.8, 2 H), 7.28 (d, *J* = 8.5, 4 H), 7.72 (d, *J* = 8.5, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.80, 29.02, 62.71, 64.45, 127.68, 130.10, 139.52, 143.83, 167.40. ^{1}H NMR Spectral data was consistent with the literature precedent.[36]

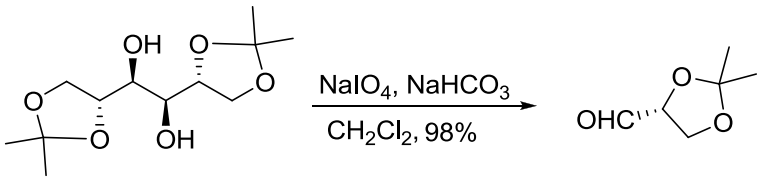
***N*-*p*-Toluenesulfonylisobutenyllimine, (5-83)**:



5-56 **5-76** **5-83**

To a solution of 3-methyl-2-butenal (0.18 g, 2.1 mmol) and *p*-toluene isocyanate (0.41 g, 2.1 mmol) in 4.0 mL of toluene was heated to reflux. To this mixture was carefully added anhydrous aluminum chloride (0.008 g, 0.08 mmol) in small portions and the resulting mixture was refluxed overnight. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude product **2-7** was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 2.10 (s, 3 H), 2.19 (s, 3H), 2.49 (s, 3H), 6.28 dd, 1H, *J* = 10.2, 1.2 Hz), 7.40 (d, 2H, *J* = 7.0 Hz), 7.90 (d, 2H, *J* = 7.0 Hz), 9.05 (d, 1H, *J* = 10.2 Hz). This compound has been reported in the literature.[37]

2,3-Isopropylidene-D-glyceraldehyde, (5-85):[38]

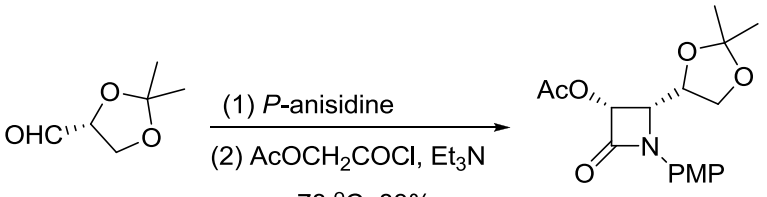


5-88 **5-85**

A solution of 1,2,5,6-Diisopropylidene-D-mannitol (6.70 g, 25.5 mmol) and saturated aqueous $NaHCO_3$ (2.7 mL) in dichloromethane (60 mL) was placed in a reaction vessel (250 mL) equipped with a magnetic stirrer. $NaIO_4$ (10.9 g, 51.0 mmol) was added, and the mixture was stirred for 1.5 h at room temperature. After decantation, dichloromethane was removed and the residue was extracted with more dichloromethane (30 mL). The solvent was distilled at room temperature and the residue was purified by distillation under reduced pressure (30 mbar, 55 ^{o}C). Pure aldehyde **5-85** (6.50 g) was obtained in 98% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (s, 3 H), 1.45 (s, 3 H), 4.08 (dd, IH, *J* = 4.85, 8.73 Hz), 4.16 (dd, 1H, *J* = 7.34, 8.68 Hz), 4.37 (ddd, 1H, *J* = 1.86,

4.87, 7.27 Hz), 9.70 (d, 1H, *J* = 1.86 Hz). Spectral data was consistent with the literature precedent.[38]

(3*R*,4*S*)-l-(4-methoxyphenyl)-3-acetoxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one, (5-86):[17]



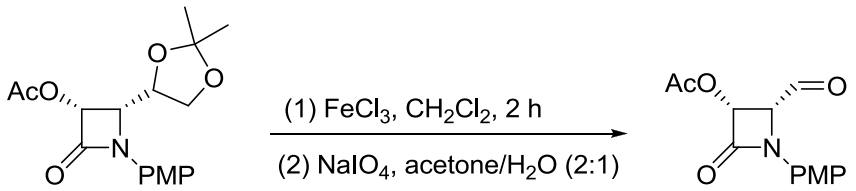
5-85 **5-86**

2,3-isopropylidene-D-glyceraldehyde **5-85** (1.30 g, 10.0 mmol) was added dropwise to a solution of *p*-anisidine (1.23 g, 10.0 mmol) and anhydrous Na_2SO_4 (5.68 g, 40.0 mmol) in 40 mL CH_2Cl_2, and the reaction mixture was stirred at room temperature for 3 h. The mixture was filtered, evaporated and then put under vacuum to yield imine as yellow, viscous oil which was immediately used in the synthesis of β-lactam without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 3H), 1.49 (s, 3H), 3.82 (s, 3H), 4.08-4.03 (m, 1H), 4.31-4.26 (m, 1H), 4.76 (q, 1H, *J* = 6.0 Hz), 6.91 (d, 2H, *J* = 9.0 Hz), 7.11(d, 2H, *J* = 9.0 Hz).

The resulting imine **5-85** was diluted with CH_2Cl_2 (80 mL), triethylamine (2.43 g, 24.0 mmol) was added, and the solution was cooled to -78 ˚C. Acetoxyacetyl chloride (1.29 mL, 12.0 mmol) in 40 mL of CH_2Cl_2 was added dropwise over 30 min at – 78 ^{o}C, and the reaction mixture was warmed to room temperature over 3 h. The reaction mixture was diluted with 100 mL of saturated $NaHCO_3$ solution and the layers separated. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography of the residue on silica gel (hexanes/ ethyl acetate = 4/1) afforded the titled compound **5-86** as white solid (2.74 g, 83 % over two steps); mp = 162-163 ^{o}C, (Lit Mp = 163 ^{o}C); $[\alpha]^{25}_D$ +100.9 (c = 0.5, MeOH), (lit $[\alpha]^{26}_D$ +101.3 (c = 0.5, MeOH).[17] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3 H), 1.50 (s, 3 H), 2.15 (s, 3 H), 3.65 (m, 1 H), 3.8 (s, 3 H), 4.05 (m, 1 H), 4.45 (m, 2 H), 6.05 (d, *J* = 5.7 Hz, 1 H), 7.75-6.9 (dd, 4 H); ^{13C} NMR ($CDCl_3$, 125 MHz) δ 20.45, 24.89, 26.52, 55.46,

61.53, 66.39, 73.11, 76.55, 114.0, 119.80, 157.10, 161.81, 169.31. All data was consistent with the literature precedent.[17]

(3*R*,4*R*)-3-Acetoxy-4-formyl-1-(4-methoxyphenyl) azetidin-2-one, (5-87):



5-86 **5-87**

To a solution of the β-Lactam (1.00 g, 2.98 mmol) in dichloromethane (45 mL) was added anhydrous $FeCl_3$ (0.968 g, 5.96 mmol) at room temperature and the resulting mixture was stirred for 2 h. After completion of the reaction (TLC) the reaction mixture was filtered through a bed of celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes as eluent to give the diol (860 mg, 98%) as white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20(s, 3H), 3.65 (d, 2H, *J* = 5.1 Hz), 3.79 (s, 3H), 4.12 (q, 1H, *J* = 5.1 Hz), 4.52 (t, 1H, *J* = 5.4Hz), 6.04 (d, 1H, *J* = 5.4 Hz), 6.90 (d, 2H, *J* = 9.0 Hz), 7.47 (d, 2H, *J* = 9.0 Hz).

To a solution of the diol (0.500 g, 1.69 mmol) in acetone–water (2:1, 40 mL) was added $NaIO_4$ (0.722 g, 3.38 mmol) and the solution was stirred at room temperature for 6 h. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel using 30% EtOAc in hexanes as eluent to obtained compound **5-87** (400 mg, 90%) as white solid; mp = . ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (s, 3H), 3.77 (s, 3H), 4.74 (q, 1H, *J* = 3.0 Hz), 5.99 (d, 1H, *J* = 5.1 Hz), 6.88 (d, 2H, *J* = 9.0 Hz), 7.25 (d, 2H, *J* = 9.0 Hz), 9.71 (d, 1H, *J* = 3.0 Hz).

§ 5.6. References

1. (a) Ojima, I.; Delaloge, F., Asymmetric synthesis of building-blocks for peptides and peptidomimetics by means of the β-lactam synthon method. *Chem. Soc. Rev.* **1997,** *26*, 377-386; (b) Ojima, I., Recent advances in the β-lactam synthon method. *Acc. Chem. Res.* **1995,** *28*, 383-389.

2. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M., Asymmetric synthesis of β-lactams by Staudinger ketene-imine cycloaddition reaction. *Eur. J. Org. Chem.* **1999**, 3223-3235.

3. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M., Asymmetric synthesis of β-lactams through the Staudinger reaction and their use as building blocks of natural and non-natural products. *Curr. Med. Chem.* **2004,** *11*, 1837-1872.

4. (a) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T., New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of β-lactam synthon method. *Tetrahedron* **1992,** *48*, 6985-7012; (b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R., Efficient and practical asymmetric synthesis of the taxol C-13 side chain, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine, and its analogs via chiral 3-hydroxy-4-aryl-β-lactams through chiral ester enolate-imine cyclocondensation. *J. Org. Chem.* **1991,** *56*, 1681-1683.

5. Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D. W.; Aplin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J., Mechanistic insights into the inhibition of serine proteases by monocyclic lactams. *Biochemistry* **1999,** *38*, 7989-7998.

6. Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L., Design and synthesis of novel monocyclic β-lactam inhibitors of prostate specific antigen. *Bioorg. Med.Chem. Lett.* **1997,** *7*, 1689-1694.

7. (a) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. A., Discovery of 1-(4-fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)- hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): A designed, potent, orally active inhibitor of cholesterol absorption. *J. Med. Chem.* **1998,** *41*, 973-980; (b) Wu, G.; Tormos, W., A catalytic asymmetric synthesis of a

spirofused azetidinone as a cholesterol absorption inhibitor. *J. Org. Chem.* **1997,** *62*, 6412-6414.

8. (a) Alcaide, B.; Almendros, P., Recent advances in the stereocontrolled synthesis of Bi- and tricyclic-β-lactams with non-classical structure. *Curr. Org. Chem.* **2002,** *6*, 245-264; (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T., Advances in the catalytic asymmetric synthesis of β-lactams. *Acc. Chem. Res.* **2004,** *37*, 592-600; (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M., β-Lactams as versatile intermediates in α- and β-amino acid synthesis. *Synlett* **2001**, 1813-1826.

9. Miller, M. J., Hydroxamate approach to the synthesis of β-lactam antibiotics. *Acc. Chem. Res.* **1986,** *19*, 49-56.

10. (a) Gilman, H.; Speeter, M., The Reformatsky reaction with benzalaniline. *J. Am. Chem. Soc* **1943,** *65*, 2255 - 2256; (b) Hart, D. J.; Ha, D. C., The ester enolate-imine condensation route to β-lactams. *Chem. Rev.* **1989,** *89*, 1447-1465.

11. (a) Kinugasa, M.; Hashimoto, S., The reactions of copper(I) phenylacetylide with nitrones. *J. Chem. Soc. Chem. Commun.* **1972**, 466-467; (b) Marco-Contelles, J., β-Lactam synthesis by the Kinugasa reaction. *Angew. Chem. Int. Ed.* **2004,** *43*, 2198-2200; (c) Miura, M.; Enna, M.; Okuro, K.; Nomura, M., Copper-catalyzed reaction of terminal alkynes with nitrones. Selective synthesis of 1-aza-1-buten-3-yne and 2-azetidinone derivatives. *J. Org. Chem.* **1995,** *60*, 4999-5004.

12. Hegedus, L. S., Synthesis of amino acids and peptides using chromium carbene complex photochemistry. *Acc. Chem. Res.* **1995,** *28*, 299-305.

13. Staudinger, H., Ketenes. 1. Diphenylketene. *Justus Liebigs Ann. Chem.* **1907,** *356*, 51-123.

14. Hart, D. J.; Ha, D.-C., The ester enolate-imine condensation route to β-lactams. *Chem. Rev.* **1989,** *89*, 1447 - 1465.

15. (a) Fernando, P.; Cossio, A. A.; Begona, L.; Ugalde, J. M., Chiral Control in the Staudinger Reaction between Ketenes and Imines. A theoretical SCF-MO study on asymmetric torquoselectivity. *J. Am. Chem. Soc.* **1994,** *116*, 2085 - 2093; (b) Cossío, F. P.; Arrieta, A.; Sierra, M. A., The mechanism of the ketene−imine (Staudinger) reaction in its centennial: still an unsolved problem? *Acc. Chem. Res.* **2008,** *41*, 925-936.

16. (a) Hashimoto, Y.; Kai, A.; Saigo, K., 1-(2,6-Dichlorophenyl)ethylamine: A new and efficient chiral auxiliary for the Staudinger β-lactam synthesis. *Tetrahedron Lett.* **1995,** *36*, 8821-8824; (b) Georg, G. I.; Mashava, P. M.; Akgun, E.; Milstead, M. W., Asymmetric synthesis of β-lactams and *N*-benzoyl-3-phenylisoserines via the Staudinger reaction. *Tetrahedron Lett.* **1991,** *32*, 3151-3154.

17. Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K., Studies on lactams. 81. Enantiospecific synthesis and absolute configuration of substituted β-lactams from D-glyceraldehyde acetonide. *J. Org. Chem.* **1988,** *53*, 4227-4236.

18. Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martinez-Ripoll, M., Contribution to the development of new substitution patterns of optically active β-lactams: synthesis of homochiral 4-(1-aminoalkyl)azetidin-2-ones from *N*-(tert-butyloxycarbonyl) α-amino aldehyde-derived imines *via* asymmetric Staudinger reaction. *J. Am. Chem. Soc* **1992,** *114*, 9360-9369.

19. Evans, D. A.; Sjogren, E. B., The asymmetric synthesis of β-lactam antibiotics - I. application of chiral oxazolidones in the Staudinger reaction. *Tetrahedron Lett.* **1985,** *26*, 3783-3786.

20. Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Galarza, R.; Legido, M.; Urchegui, R.; Roman, P.; Luque, A.; Server-Carrio, J.; Linden, A., Construction of quaternary stereogenic centers via [2+2] cycloaddition reactions. Synthesis of homochiral 4,4-disubstituted 2-azetidinones and imine substituent effects on β-lactam formation. *J. Org. Chem.* **1997,** *62*, 2070-2079.

21. Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B., Chiral control of the Staudinger reaction. *pure Appl. Chem.* **1987,** *59*, 485-492.

22. Gaunt, M. J.; Johansson, C. C. C., Recent developments in the use of catalytic asymmetric ammonium enolates in chemical synthesis. *Chem. Rev.* **2007,** *107*, 5596-5605.

23. (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T., Catalytic asymmetric synthesis of β-lactams. *J. Am. Chem. Soc.* **2000,** *122*, 7831-7832; (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T., The development of the first catalyzed reaction of ketenes and imines:

catalytic asymmetric synthesis of β-lactams. *J. Am. Chem. Soc.* **2002,** *124*, 6626-6635.

24. (a) France, S.; Wack, H.; Hafez, A., M.; Taggi, A., E.; Witsil, D., R.; Lectka, T., Bifunctional Asymmetric Catalysis: A tandem nucleophile/Lewis acid promoted synthesis of β-lactams. *Org. lett.* **2002,** *4*, 1603-1605; (b) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T., Bifunctional Lewis acid-nucleophile-based asymmetric catalysis: mechanistic evidence for imine activation working in tandem with chiral enolate formation in the synthesis of β-lactams. *J. Am. Chem. Soc* **2005,** *127*, 1206-1215.

25. Hodous, B. L.; Fu, G. C., Enantioselective Staudinger synthesis of β-lactams catalyzed by a planar-chiral nucleophile. *J. Am. Chem. Soc* **2002,** *124*, 1578-1579.

26. Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C., Catalytic asymmetric Staudinger reactions to form β-lactams: an unanticipated dependence of diastereoselectivity on the choice of the nitrogen substituent. *J. Am. Chem. Soc* **2005,** *127*, 11586-11587.

27. (a) Ojima, I.; Wang, T.; Miller, M. L.; Lin, S.; Borella, C. P.; Geng, X.; Pera, P.; Bernacki, R. J., Synthesis and structure-activity relationships of new second-generation taxoids. *Bioorg. Med. Chem. Lett.* **1999,** *9*, 3423-3428; (b) Ojima, I.; Slater, J. C.; Michaud, E.; Kuduk, S. D.; Bounaud, P. Y.; Vrignaud, P.; Bissery, M. C.; Veith, J. M.; Pera, P.; Bernacki, R. J., Syntheses and structure-activity relationships of the second-generation antitumor taxoids: exceptional activity against drug-resistant cancer cells. *J. Med. Chem.* **1996,** *39*, 3889-3896; (c) Ojima, I.; Slater, J. C.; Kuduk, S. D.; Takeuchi, C. S.; Gimi, R. H.; Sun, C. M.; Park, Y. H.; Pera, P.; Veith, J. M.; Bernacki, R. J., Syntheses and structure-activity relationships of raxoids derived from 14-hydroxy-10-deacetylbaccatin III. *J. Med. Chem.* **1997,** *40*, 267 - 278; (d) Ojima, I.; Geng, X.; Wu, X.; Qu, C.; Borella, C. P.; Xie, H.; Wilhelm, S. D.; Leece, B. A.; Bartle, L. M.; Goldmacher, V. S.; Chari, R. V. J., Tumor-specific novel taxoid-monoclonal antibody conjugates. *J. Med. Chem.* **2002,** *45*, 5620-5623; (e) Ojima, I.; Borella, C. P.; Wu, X.; Bounaud, P.-Y.; Oderda, C. F.; Sturm, M.; Miller, M. L.; Chakravarty, S.; Chen, J.; Huang, Q.; Pera, P.; Brooks, T. A.; Baer, M. R.; Bernacki, R. J., Design, synthesis and structure-activity relationships of novel taxane-based multidrug resistance reversal agents. *J. Med. Chem.* **2005,** *48*, 2218-2228.

28. Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Ahlgren, M. E., Monocyclic β-lactam inhibitors of human leukocyte elastase. *Tetrahedron* **1990,** *46*, 2255 - 2262.

29. Tschaen, D. M.; Turos, E.; Weinreb, S. M., Stereochemical studies of thermal intermolecular and intramolecular *N*-sulfonylimine Ene reactions. *J. Org. Chem.* **1984,** *49*, 5058 - 5064.

30. Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T., Asymmetric catalysis on sequentially-linked columns. *J. Am. Chem. Soc.* **2001,** *123*, 10853-10859.

31. Chincholkara, P. M.; Puranikb, V. G.; . Deshmukh, A. R. A., An efficient synthesis of azetidine-2,3-diones from L-(+)-diethyl tartrate. *Synlett* **2007,** *2007*, 2242-2246.

32. Li, L.; Thomas, S. A.; Klein, L. L.; Yeung, C. M.; Maring, C. J.; Grampovnik, D. J.; Lartey, P. A.; Plattner, J. J., Synthesis and biological evaluation of C-3'-modified analogs of 9(*R*)-dihydrotaxol. *J. Med. Chem.* **1994,** *37*, 2655-2663.

33. Brieva, R.; Crich, J. Z.; Sih, C. J., Chemoenzymic synthesis of the C-13 side chain of taxol: optically active 3-hydroxy-4-phenyl β-lactam derivatives. *J. Org. Chem.* **1993,** *58*, 1068-1075.

34. Pracejus, H.; Maetje, H., Organic Catalysts. LXXI. Asymmetric syntheses with ketenes. 4. Relationship between the stereochemistry of some alkaloidal catalysts and their stereospecific effects in the asymmetric synthesis of esters. *J. Prakt. Chem.* **1964,** *24*, 195-205.

35. Hutzler, J. M.; Walker, G. S.; Wienkers, L. C., Inhibition of cytochrome P450 2D6: structure-activity studies using a series of quinidine and quinine analogues. *Chem. Res. Toxicol.* **2003,** *16*, 450-459.

36. Ferraris, D.; Young, B.; Dudding, T.; Drury, W. J.; Lectka, T., Catalytic, enantioselective alkylations of *N*,O- and *N*, *N*-acetals and hemiacetals. *Tetrahedron* **1999,** *55*, 8869-8882.

37. Yamago, S.; Yanagawa, M.; Nakamura, E., Thermal hetero [3 + 2] cycloaddition of dipolar trimethylenemethane to *N*-sulfonyl and *N*-acyl imines. Synthesis of gama-amino acid derivatives. *Chem. Lett.* **1999**, 879 - 880.

38. Sugisaki, Claudia H.; Ruland, Y.; Baltas, M., Direct access to furanosidic eight-membered ulosonic esters from *cis*-α,β-epoxy aldehydes. *Eur. J. Org. Chem.* **2003**, 672-688.

Bibliography

Chapter 1

1. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J., Transition metal-catalyzed carbocyclizations in organic synthesis. *Chem. Rev.* **1996,** *96*, 635-662.

2. Kotha, S.; Brahmachary, E.; Lahiri, K., Transition metal-catalyzed [2+2+2] cycloaddition and application in organic synthesis. *Eur. J. Org. Chem.* **2005**, 4741-4767.

3. Nakamura, I.; Yamamoto, Y., Transition-metal-catalyzed reactions in heterocyclic synthesis. *Chem. Rev.* **2004,** *104*, 2127-2198.

4. Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N., Intermolecular transition metal-catalyzed [4+2+2] cycloaddition reactions: A new approach to the construction of eight-membered rings. *J. Am. Chem. Soc.* **2002,** *124*, 8782-8783.

5. Bonafoux, D.; Lee, S.-Y.; Ojima, I., Cyclizations by homogeneous catalysts. In *Encyclopedia of Catalysis*, Horvath, I., Ed. John Wiley: Colorado Springs, **2003**; Vol. 2, pp 706-766.

6. (a) Ojima, I.; McCullagh, J. V.; Shay, W. R., New cascade silylcarbocyclization (SiCaC) of enediynes. *J. Organomet. Chem.* **1996,** *521*, 421-423; (b) Negishi, E.-I.; Coperet, C.; Ma, S.; Liou, S. Y.; Liu, F., Cyclic carbopalladation. A versatile synthetic methodology for the construction of cyclic organic compounds. *Chem. Rev.* **1996,** *96*, 365-394; (c) Brummond, K. M.; McCabe, J. M., The rhodium(I)-catalyzed Alder-ene reaction. In *Modern Rhodium-Catalyzed Organic Reactions* Evans, A. P., Ed. Wiley-VCH Verlag GmbH & Co: **2005**; pp 151-172.

7. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L., Three-component cycloadditions: The first transition metal-catalyzed [5+2+1] cycloaddition reactions. *J. Am. Chem. Soc.* **2002,** *124*, 2876-2877.

8. (a) Chen, Y.; Kiattansakul, R.; Ma, B.; Snyder, J. K., Transition metal-catalyzed [4+2+2] cycloadditions of bicyclo[2.2.1]hepta-2,5-dienes (Norbornadienes) and bicyclo[2.2.2]octa-2,5-dienes. *J. Org. Chem.* **2001,** *66*, 6932-6942; (b) Gilbertson, S. R.; DeBoef, B., Rhodium catalyzed [4+2+2] Cycloaddition and alkyne insertion: A new route to eight-membered rings. *J. Am. Chem. Soc.* **2002,** *124*, 8784-8785.

9. (a) Gibson, S. E.; Lewis, S. E.; Mainolfi, N., Transition metal-mediated routes to cyclopentenones. *J. Organomet. Chem.* **2004,** *689*, 3873-3890; (b) Shibata, T., Recent

advances in the catalytic Pauson-Khand-type reaction. *Adv. Synth. Cat.* **2006,** *348*, 2328-2336.

10. (a) Fujiwara, M.; Ojima, I., Rhodium(I)-catalyzed cycloisomerization and cyclotrimerization reactions. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, A. P., Ed. Wiley-VCH Verlag GmbH & Co: **2005**; pp 129-149; (b) Ojima, I., New cyclization reactions in organic syntheses. *Pure Appl. Chem.* **2002,** *74*, 159-166; (c) Evans, P. A.; Leahy, D. K., Recent developments in rhodium-catalyzed allylic substitution and carbocyclization reactions. *Chemtracts* **2003,** *16*, 567-578; (d) Robinson, J. E., Rhodium(I)-catalyzed [4+2] and [4+2+2] carbocyclizations. In *Modern Rhodium-Catalyzed Organic Reactions*, Evans, P. A., Ed. Wiley-VCH Verlag GmbH & Co.: **2005**; pp 241-262; (e) Varchi, G.; Ojima, I., Synthesis of heterocycles through hydrosilylation, silylformylation, silylcarbocyclization and cyclohydrocarbonylation reactions. *Curr. Org. Chem* **2006,** *10*, 1341-1362.

11. (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E., Organocobalt complexes. Part I. Arene complexes derived from dodecacarbonyltetracobalt. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 975-977; (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I., Organocobalt complexes. Part II. Reaction of acetylenehexacarbonyldicobalt complexes, $(R^1C_2R^2)Co_2(CO)_6$, with norbornene and its derivatives. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 977-981.

12. Schore, N. E.; Croudace, M. C., Preparation of bicyclo[3.3.0]oct-1-en-3-one and bicyclo[4.3.0]non-1(9)-en-8-one via intramolecular cyclization of alpha-omega-enynes. *J. Org. Chem.* **1981,** *46*, 5436-5438.

13. Brummond, K. M.; Kent, J. L., Recent advances in the Pauson-Khand reaction and related [2+2+1] cycloadditions. *Tetrahedron* **2000,** *56*, 3263-3283.

14. Jeong, N.; Sung, B. K.; Kim, J. S.; Park, S. B.; Seo, S. D.; Shin, J. Y.; In, K. Y.; Choi, Y. K., Pauson-Khand-type reaction mediated by Rh(I) catalysts. *Pure Appl. Chem.* **2002,** *74*, 85-91.

15. (a) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A., Regioselectivity, stereoselectivity and catalysis in intermolecular Pauson-Khand reactions: Teaching an old dog new tricks. *Synlett* **2005**, 2547-2570; (b) Park, J. H.; Chang, K.-M. C.; Keun, Y., Catalytic Pauson-Khand-type reactions and related carbonylative cycloaddition reactions. *Coord. Chem. Rev.* **2009,** *253*, 2461-2480; (c) Croatt, M. P.; Wender, P. A., The diene effect. The design, development, and mechanistic investigation of metal-catalyzed diene-yne, diene-ene, and diene-allene [2+2+1] cycloaddition reactions. *Eur. J. Org. Chem.* **2010**, 19-32; (d) Lee, H.-W.; Kwong, F.-Y., A Decade of advancements in Pauson-Khand-type reactions. *Eur. J. Org. Chem.* **2010**, 789-811; (e) Susan E. Gibson; Stevenazzi, A., The

Pauson-Khand Reaction: the catalytic age is here! *Angew. Chem. Int. Ed.* **2003,** *42*, 1800-1810.

16. Pallerla, M. K.; Fox, J. M., Enantioselective synthesis of (−)-Pentalenene. *Org. Lett.* **2007,** *9*, 5625-5628.

17. Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K., CO-Transfer carbonylation reactions. A catalytic Pauson−Khand-type reaction of enynes with aldehydes as a source of carbon monoxide. *J. Am. Chem. Soc.* **2002,** *124*, 3806-3807.

18. Shibata, T.; Toshida, N.; Takagi, K., Catalytic Pauson-Khand-Type Reaction Using Aldehydes as a CO Source. *Org. Lett.* **2002,** *4*, 1619-1621.

19. Brummond, K. M.; Chen, D.; Davis, M. M., A general synthetic route to differentially functionalized angularly and linearly fused [6−7−5] ring systems: A Rh(I)-catalyzed cyclocarbonylation reaction. *J. Org. Chem.* **2008,** *73*, 5064-5068.

20. (a) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J., An allenic Pauson−Khand-type reaction: A reversal in π-bond selectivity and the formation of seven-membered rings. *Org. Lett.* **2002,** *4*, 1931-1934; (b) Brummond, K. M.; Kerekes, A. D.; Wan, H., Chiral nonracemic α-alkylidene and α-silylidene cyclopentenones from chiral allenes using an intramolecular allenic Pauson−Khand-type cycloaddition. *J. Org. Chem.* **2002,** *67*, 5156-5163.

21. Brummond, K. M.; Chen, D., $Mo(CO)_6$ and $[Rh(CO)_2Cl]_2$ catalyzed allenic cyclocarbonylation reactions of alkynones: Efficient access to bicyclic dienediones. *Org. Lett.* **2008,** *10*, 705-708.

22. Inagaki, F.; Mukai, C., Rhodium(I)-catalyzed intramolecular Pauson−Khand-type [2+2+1] cycloaddition of allenenes. *Org. Lett.* **2006,** *8*, 1217-1220.

23. Hayashi, Y.; Miyakoshi, N.; Kitagaki, S.; Mukai, C., Stereoselective total syntheses of uncommon sesquiterpenoids isolated from Jatropha neopauciflora. *Org. Lett.* **2008,** *10*, 2385-2388.

24. Wender, P. A.; Deschamps, N. M.; Gamber, G. G., The dienyl Pauson–Khand reaction. *Angew. Chem. Int. Ed.* **2003,** *42*, 1853-1857.

25. Wender, P. A.; Deschamps, N. M.; Williams, T. J., Intermolecular dienyl Pauson-Khand reaction. *Angew. Chem. Int. Ed.* **2004,** *43*, 3076-3079.

26. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Metal-catalyzed [2+2+1] cycloadditions of 1,3-dienes, allenes, and CO. *Angew. Chem. Int. Ed.* **2006,** *45*, 2459-2462.

27. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Rhodium(I)-catalyzed [2+2+1] cycloadditions of 1,3-dienes, alkenes, and CO. *J. Am. Chem. Soc.* **2004,** *126*, 5948-5949.

28. (a) Adrio, J.; Carretero, J. C., Butenolide synthesis by Molybdenum-mediated hetero-Pauson−Khand reaction of alkynyl aldehydes. *J. Am. Chem. Soc.* **2007,** *129*, 778-779; (b) Gao, P.; Xu, P.-F.; Zhai, H., Expeditious construction of (+)-Mintlactone via intramolecular hetero-Pauson-Khand reaction. *J. Org. Chem.* **2009,** *74*, 2592-2593.

29. Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S., $Ru_3(CO)_{12}$-catalyzed intermolecular cyclocoupling of ketones, alkenes or alkynes, and carbon monoxide. [2+2+1] Cycloaddition strategy for the synthesis of functionalized γ-butyrolactones. *J. Am. Chem. Soc.* **2000,** *122*, 12663-12674.

30. (a) Morimoto, T.; Chatani, N.; Murai, S., The first catalytic carbonylative [4+1] cycloaddition using a 1,3-conjugated system. A new transformation of α,β-unsaturated imines to unsaturated γ-lactams catalyzed by $Ru_3(CO)_{12}$. *J. Am. Chem. Soc.* **1999,** *121*, 1758-1759; (b) Göbel, A.; Imhof, W., One-pot ruthenium catalyzed synthesis of spiro[pyrrolidin-2-one] derivatives by a [2+2+1] cycloaddition of ketimines, carbon monoxide and ethylene *Chem. Commun.* **2001**, 593-594.

31. (a) Saito, T.; Furukawa, N.; Otani, T., A facile synthesis of pyrrolo[2,3-b]quinolines via a Rh(I)-catalyzed carbodiimide-Pauson–Khand-type reaction. *Org. Biomol. Chem.* **2010,** *8*, 1126-1132; (b) Aburano, D.; Yoshida, T.; Miyakoshi, N.; Mukai, C., Synthesis of hexahydropyrrolo[2,3-b]indole alkaloids based on the aza-Pauson−Khand-type reaction of alkynecarbodiimides. *J. Org. Chem.* **2007,** *72*, 6878-6884; (c) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A., $Co_2(CO)_8$-catalyzed intramolecular hetero-Pauson−Khand reaction of alkynecarbodiimide: Synthesis of (±)-Physostigmine. *Org. Lett.* **2006,** *8*, 83-86; (d) Saito, T.; Sugizaki, K.; Otani, T.; Suyama, T., Rhodium-catalyzed intramolecular alkyne-carbodiimide Pauson−Khand-type reaction. *Org. Lett.* **2007,** *9*, 1239-1241.

32. Saito, T.; Nihei, H.; Otani, T.; Suyama, T.; Furukawa, N.; Saito, M., Thiocarbonyl induced heterocumulenic Pauson–Khand type reaction: expedient synthetic method for thieno[2,3-b]indol-2-ones. *Chem. Commun.* **2008**, 172-174.

33. Wegner, H. A.; deMeijere, A.; Wender, P. A., Transition metal-catalyzed intermolecular [5+2] and [5+2+1] cycloadditions of allenes and vinylcyclopropanes. *J. Am. Chem. Soc.* **2005,** *127*, 6530-6531.

34. Mehta, G.; Srikrishna, A., Synthesis of polyquinane natural products: An update. *Chem. Rev.* **1997,** *97*, 671-720.

35. Jiao, L.; Yuan, C.; Yu, Z.-X., Tandem Rh(I)-catalyzed [(5+2)+1] cycloaddition/Aldol reaction for the construction of linear triquinane skeleton: Total syntheses of (±)-Hirsutene and (±)-1-Desoxyhypnophilin. *J. Am. Chem. Soc.* **2008,** *130*, 4421-4430.

36. Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z. X., A computationally designed Rh(I)-catalyzed two-component [5+2+1] cycloaddition of ene-vinylcyclopropanes and CO for the synthesis of cyclooctenones. *J. Am. Chem. Soc.* **2007,** *129*, 10060-10061.

37. Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X., Rh(I)-catalyzed [(3+2)+1] cycloaddition of 1-yne/ene-vinylcyclopropanes and CO: Homologous Pauson−Khand reaction and total synthesis of (±)-α-Agarofuran. *Org. Lett.* **2010,** *12*, 2528-2531.

38. (a) Ojima, I.; Ingallina, P.; Donovan, R. J.; Clos, N., Silylformylation of 1-hexyne catalyzed by Rhodium-Cobalt mixed-metal carbonyl clusters. *Organometallics* **1991,** *10*, 38-41; (b) Ojima, I.; Donovan, R. J.; Eguchi, M.; Shay, W. R.; Ingallina, P.; Korda, A.; Zeng, Q., Silylformylation catalyzed by Rh and Rh-Co mixed metal complexes and its application to the synthesis of pyrrolizidine alkaloids. *Tetrahedron* **1993,** *49*, 5431-5444.

39. Matsuda, I.; Fukuta, Y.; Tsuchihashi, T.; Nagashima, H.; Itoh, K., Rhodium-catalyzed silylformylation of acetylenic bonds: Its scope and mechanistic considerations. *Organometallics* **1997,** *16*, 4327-4345.

40. Ojima, I.; Vu, A. T.; Lee, S. Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H., Rhodium-catalyzed silylcarbocyclization (SiCaC) and carbonylative silylcarbocyclization (CO-SiCaC) reactions of enynes. *J. Am. Chem. Soc.* **2002,** *124*, 9164-9174.

41. Fukuta, Y.; Matsuda, I.; Itoh, K., Rhodium-catalyzed domino silylformylation of enynes involving carbocyclization. *Tetrahedron Lett.* **1999,** *40*, 4703-4706.

42. (a) Ojima, I.; Fracchiolla, D. A.; Donovan, R. J.; Banerji, P., Silylcarbobicyclization of 1,6-Diynes: A novel catalytic route to bicyclo[3.3.0]octenones. *J. Org. Chem.* **1994,** *59*, 7594-7595; (b) Ojima, I.; Zhu, J.; Vidal, E. S.; Kass, D. F., Silylcarbocyclizations of 1,6-diynes. *J. Am. Chem. Soc.* **1998,** *120*, 6690-6697.

43. Ojima, I.; Vu, A. T.; McCullagh, J. V.; Kinoshita, A., Rhodium-catalyzed intramolecular silylcarbotricyclization (SiCaT) of triynes. *J. Am. Chem. Soc.* **1999,** *121*, 3230-3231.

44. (a) Ojima, I.; Clos, N.; Donovan, R. J.; Ingallina, P., Hydrosilylation of 1-hexyne catalyzed by rhodium and cobalt-rhodium mixed-metal complexes. Mechanism of apparent trans addition. *Organometallics* **1990,** *9*, 3127-3133; (b) Tanke, R. S.; Crabtree, R. H., Unusual activity and selectivity in alkyne hydrosilylation with an iridium catalyst stabilized by an oxygen-donor ligand. *J. Am. Chem. Soc.* **1990,** *112*, 7984-7989.

45. (a) Ojima, I.; Lee, S.-Y., Rhodium-catalyzed novel carbonylative carbotricyclization of enediynes. *J. Am. Chem. Soc.* **2000,** *122*, 2385-2386; (b) Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I., Silicon-initiated carbonylative carbotricyclization and [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *J. Am. Chem. Soc.* **2005,** *127*, 17756-17767.

46. Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2+2+2+1] cycloaddition of enediynes catalyzed by Rhodium complexes. *Org. Lett.* **2004,** *6*, 3589-3591.

Chapter 2

1. (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J., Transition metal-catalyzed carbocyclizations in organic synthesis. *Chem. Rev.* **1996,** *96*, 635-662; (b) Lautens, M.; Klute, W.; Tam, W., Transition metal-mediated cycloaddition reactions. *Chem. Rev.* **1996,** *96*, 49-92.

2. Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I., Silicon-initiated carbonylative carbotricyclization and [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *J. Am. Chem. Soc.* **2005,** *127*, 17756-17767.

3. Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *Org. Lett.* **2004,** *6*, 3589-3591.

4. Wei, X.; Rodriguez, I. I.; Rodriguez, A. D.; Barnes, C. L., Caribenols A and B, sea whip derived norditerpenes with novel tricarbocyclic skeletons. *J. Org. Chem.* **2007,** *72*, 7386-7389.

5. Kaloko, J. J.; Teng, Y.-H. G.; Ojima, I., One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. *Chem. Commun.* **2009**, 4569 - 4571.

6. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Metal-catalyzed [2+2+1] cycloadditions of 1,3-dienes, allenes, and CO. *Angew. Chem. Int. Ed.* **2006,** *45*, 2459-2462.

7. Faitg, T.; Soulié, J.; Lallemand, J.-Y.; Mercier, F.; Mathey, F., Asymmetric isomerisation of a cyclic diene: a comparative study of BINAP and BIPNOR-rhodium(I) catalysts. *Tetrahedron* **2000,** *56*, 101-104.

8. Aïssa, C.; Fürstner, A., A rhodium-catalyzed C−H activation/cycloisomerization tandem. *J. Am. Chem. Soc.* **2007,** *129*, 14836-14837.

9. McCleverty, J. A.; Wilkinson, G., Dichlorotetracarbonyldirhodium (rhodium carbonyl chloride). *Inorg. Syn. 8*, 211-214.

10. Brummond, K. M.; Chen, H.; Sill, P.; You, L., A rhodium(I)-catalyzed formal allenic Alder Ene reaction for the rapid and stereoselective assembly of cross-conjugated trienes. *J. Am. Chem. Soc.* **2002,** *124*, 15186-15187.

11. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L., Three-component cycloadditions: the first transition metal-catalyzed [5+2+1] cycloaddition reactions. *J. Am. Chem. Soc.* **2002,** *124*, 2876-2877.

12. Cerezo, S.; Cortès, J.; Galvan, D.; Lago, E.; Marchi, C.; Molins, E.; Moreno-Mañas, M.; Pleixats, R.; Torrejón, J.; Vallribera, A., Preparation of nitrogen-containing 15-membered triolefinic macrocycles: (*E*,*E*,*E*)-1,6,11-tris(arylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-trienes. *Eur. J. Org. Chem.* **2001**, 329-337.

13. (a) Sharpless, K. B.; Hori, T., Allylic amination of olefins and acetylenes by imido sulfur compounds. *J. Org. Chem.* **1976,** *41*, 176-177; (b) Taylor, J. G.; Whittall, N.; Hii, K. K., Copper-catalyzed intermolecular hydroamination of alkenes. *Org. Lett.* **2006,** *8*, 3561-3564.

14. Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L., Scope of the intramolecular titanocene-catalyzed Pauson−Khand type reaction1. *J. Am. Chem. Soc.* **1999,** *121*, 5881-5898.

15. Khan, A. T.; Choudhury, L. H.; Ghosh, S., Cupric sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$): a mild and efficient catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols. *Tetrahedron Lett.* **2004,** *45*, 7891-7894.

Chapter 3

1. Kaloko, J. J.; Teng, Y.-H. G.; Ojima, I., One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. *Chem. Commun.* **2009**, 4569 - 4571.

2. McCleverty, J. A.; Wilkinson, G., Dichlorotetracarbonyldirhodium (rhodium carbonyl chloride). *Inorg. Syn. 8*, 211-214.

3. Kim, D. Y.; Kim, H. S.; Choi, Y. J.; Mang, J. Y.; Lee, K., Transformation of allyl stannanes into allyl amines using [*N*-(p-toluenesulfonyl)imino]-phenyliodinane. *Synth. Commun.* **2001,** *31*, 2463-2469.

4. Adamczyk, M.; Grote, J.; Douglas, J.; Dubler, R.; Harrington, C., Synthesis of conjugates for a barbiturate screening assay. *Bioconjugate Chem.* **1992,** *8*, 281-288.

Chapter 4

1. (a) Schall, A.; Reiser, O., Synthesis of biologically active guaianolides with a trans-annulated lactone moiety. *Eur. J. Org. Chem.* **2008**, 2353-2364; (b) Higuchi, Y.; Shimoma, F.; Ando, M., Synthetic method and biological activities of cis-fused α-methylene γ-lactones. *J. Nat. Prod.* **2003,** *66*, 810-817; (c) Watanabe, K.; Oguri, Y.; Miyakado, M.; Ohno, N.; Mabry, T. J., Structure and fungicidal activity of four pseudoguaianolides isolated from Helenium quadridentatum Labill. *J. Agric. Food Chem.* **1985,** *33*, 83-86; (d) Hu, J.-F.; Patel, R.; Li, B.; Garo, E.; Hough, G. W.; Goering, M. G.; Yoo, H.-D.; O'Neil-Johnson, M.; Eldridge, G. R., Anti-HCV bioactivity of pseudoguaianolides from Parthenium hispitum. *J. Nat. Prod.* **2007,** *70*, 604-607.

2. (a) Shimoma, F.; Kusaka, H.; Azami, H.; Wada, K.; Suzuki, T.; Hagiwara, H.; Ando, M., Total syntheses of (+/-)-Hymenolin and (+/-)-Parthenin. *J. Org. Chem.* **1998,** *63*, 3758-3763; (b) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Böhm, C.; Reiser, O., Facile Asymmetric synthesis of the core nuclei of xanthanolides, guaianolides, and eudesmanolides. *Org. Lett.* **2003,** *5*, 941-944; (c) Ashfeld, B. L.; Martin, S. F., Enantioselective syntheses of Tremulenediol A and Tremulenolide A. *Org. Lett.* **2005,** *7*, 4535-4537; (d) Bruno, M.; Rosselli, S.; Maggio, A.; Raccuglia, R. A.; Bastow, K. F.; Lee, K.-H., Cytotoxic activity of some natural and synthetic guaianolides. *J. Nat. Prod.* **2005,** *68*, 1042-1046; (e) Recio, M. C.; Giner, R. M.; Uriburu, L.; Máñez, S.; Cerdá, M.; De La Fuente, J. R.; Ríos, J. L., In vivo activity of pseudoguaianolide sesquiterpene lactones in acute and chronic inflammation. *Life Sci.* **2000,** *66*, 2509-2518.

3. (a) Kotha, S.; Brahmachary, E.; Lahiri, K., Transition metal-catalyzed [2+2+2] cycloaddition and application in organic synthesis. *Eur. J. Org. Chem.* **2005**, 4741-4767; (b) Lautens, M.; Klute, W.; Tam, W., Transition metal-mediated cycloaddition reactions. *Chem. Rev.* **1996,** *96*, 49-92; (c) Nakamura, I.; Yamamoto, Y., Transition-metal-catalyzed reactions in heterocyclic synthesis. *Chem. Rev.* **2004,** *104*, 2127-2198.

4. Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *Org. Lett.* **2004,** *6*, 3589-3591.

5. Wender, P. A.; Croatt, M. P.; Deschamps, N. M., Metal-catalyzed [2+2+1] cycloadditions of 1,3-dienes, allenes, and CO. *Angew. Chem. Int. Ed.* **2006,** *45*, 2459-2462.

6. McCleverty, J. A.; Wilkinson, G., Dichlorotetracarbonyldirhodium (rhodium carbonyl chloride). *Inorg. Syn. 8*, 211-214.

7. Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I., Silicon-initiated carbonylative carbotricyclization and [2+2+2+1] cycloaddition of enediynes catalyzed by rhodium complexes. *J. Am. Chem. Soc.* **2005,** *127*, 17756-17767.

Chapter 5

1. (a) Ojima, I.; Delaloge, F., Asymmetric synthesis of building-blocks for peptides and peptidomimetics by means of the β-lactam synthon method. *Chem. Soc. Rev.* **1997,** *26*, 377-386; (b) Ojima, I., Recent advances in the β-lactam synthon method. *Acc. Chem. Res.* **1995,** *28*, 383-389.

2. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M., Asymmetric synthesis of β-lactams by Staudinger ketene-imine cycloaddition reaction. *Eur. J. Org. Chem.* **1999**, 3223-3235.

3. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M., Asymmetric synthesis of β-lactams through the Staudinger reaction and their use as building blocks of natural and non-natural products. *Curr. Med. Chem.* **2004,** *11*, 1837-1872.

4. (a) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T., New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of β-lactam synthon method. *Tetrahedron* **1992,** *48*, 6985-7012; (b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R., Efficient and practical asymmetric synthesis of the taxol C-13 side chain, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine, and its analogs via chiral 3-hydroxy-4-aryl-β-lactams through chiral ester enolate-imine cyclocondensation. *J. Org. Chem.* **1991,** *56*, 1681-1683.

5. Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D. W.; Aplin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J., Mechanistic insights into the inhibition of serine proteases by monocyclic lactams. *Biochemistry* **1999,** *38*, 7989-7998.

6. Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L., Design and synthesis of novel monocyclic β-lactam inhibitors of prostate specific antigen. *Bioorg. Med.Chem. Lett.* **1997,** *7*, 1689-1694.

7. (a) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. A., Discovery of 1-(4-fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): A designed, potent, orally active inhibitor of cholesterol absorption. *J. Med. Chem.* **1998,** *41*, 973-980; (b)

Wu, G.; Tormos, W., A catalytic asymmetric synthesis of a spirofused azetidinone as a cholesterol absorption inhibitor. *J. Org. Chem.* **1997,** *62*, 6412-6414.

8. (a) Alcaide, B.; Almendros, P., Recent advances in the stereocontrolled synthesis of Bi- and tricyclic-β-lactams with non-classical structure. *Curr. Org. Chem.* **2002,** *6*, 245-264; (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T., Advances in the catalytic asymmetric synthesis of β-lactams. *Acc. Chem. Res.* **2004,** *37*, 592-600; (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M., β-Lactams as versatile intermediates in α- and β-amino acid synthesis. *Synlett* **2001**, 1813-1826.

9. Miller, M. J., Hydroxamate approach to the synthesis of β-lactam antibiotics. *Acc. Chem. Res.* **1986,** *19*, 49-56.

10. (a) Gilman, H.; Speeter, M., The Reformatsky reaction with benzalaniline. *J. Am. Chem. Soc* **1943,** *65*, 2255 - 2256; (b) Hart, D. J.; Ha, D. C., The ester enolate-imine condensation route to β-lactams. *Chem. Rev.* **1989,** *89*, 1447-1465.

11. (a) Kinugasa, M.; Hashimoto, S., The reactions of copper(I) phenylacetylide with nitrones. *J. Chem. Soc. Chem. Commun.* **1972**, 466-467; (b) Marco-Contelles, J., β-Lactam synthesis by the Kinugasa reaction. *Angew. Chem. Int. Ed.* **2004,** *43*, 2198-2200; (c) Miura, M.; Enna, M.; Okuro, K.; Nomura, M., Copper-catalyzed reaction of terminal alkynes with nitrones. Selective synthesis of 1-aza-1-buten-3-yne and 2-azetidinone derivatives. *J. Org. Chem.* **1995,** *60*, 4999-5004.

12. Hegedus, L. S., Synthesis of amino acids and peptides using chromium carbene complex photochemistry. *Acc. Chem. Res.* **1995,** *28*, 299-305.

13. Staudinger, H., Ketenes. 1. Diphenylketene. *Justus Liebigs Ann. Chem.* **1907,** *356*, 51-123.

14. Hart, D. J.; Ha, D.-C., The ester enolate-imine condensation route to β-lactams. *Chem. Rev.* **1989,** *89*, 1447 - 1465.

15. (a) Fernando, P.; Cossio, A. A.; Begona, L.; Ugalde, J. M., Chiral Control in the Staudinger Reaction between Ketenes and Imines. A theoretical SCF-MO study on asymmetric torquoselectivity. *J. Am. Chem. Soc.* **1994,** *116*, 2085 - 2093; (b) Cossío, F. P.; Arrieta, A.; Sierra, M. A., The mechanism of the ketene−imine (Staudinger) reaction in its centennial: still an unsolved problem? *Acc. Chem. Res.* **2008,** *41*, 925-936.

16. (a) Hashimoto, Y.; Kai, A.; Saigo, K., 1-(2,6-Dichlorophenyl)ethylamine: A new and efficient chiral auxiliary for the Staudinger β-lactam synthesis. *Tetrahedron Lett.* **1995,** *36*, 8821-8824; (b) Georg, G. I.; Mashava, P. M.; Akgun, E.; Milstead, M. W., Asymmetric synthesis of β-lactams and *N*-benzoyl-3-phenylisoserines via the Staudinger reaction. *Tetrahedron Lett.* **1991,** *32*, 3151-3154.

17. Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K., Studies on lactams. 81. Enantiospecific synthesis and absolute configuration of substituted β-lactams from D-glyceraldehyde acetonide. *J. Org. Chem.* **1988,** *53*, 4227-4236.

18. Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martinez-Ripoll, M., Contribution to the development of new substitution patterns of optically active β-lactams: synthesis of homochiral 4-(1-aminoalkyl)azetidin-2-ones from *N*-(tert-butyloxycarbonyl) α-amino aldehyde-derived imines *via* asymmetric Staudinger reaction. *J. Am. Chem. Soc* **1992,** *114*, 9360-9369.

19. Evans, D. A.; Sjogren, E. B., The asymmetric synthesis of β-lactam antibiotics - I. application of chiral oxazolidones in the Staudinger reaction. *Tetrahedron Lett.* **1985,** *26*, 3783-3786.

20. Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Galarza, R.; Legido, M.; Urchegui, R.; Roman, P.; Luque, A.; Server-Carrio, J.; Linden, A., Construction of quaternary stereogenic centers via [2+2] cycloaddition reactions. Synthesis of homochiral 4,4-disubstituted 2-azetidinones and imine substituent effects on β-lactam formation. *J. Org. Chem.* **1997,** *62*, 2070-2079.

21. Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B., Chiral control of the Staudinger reaction. *pure Appl. Chem.* **1987,** *59*, 485-492.

22. Gaunt, M. J.; Johansson, C. C. C., Recent developments in the use of catalytic asymmetric ammonium enolates in chemical synthesis. *Chem. Rev.* **2007,** *107*, 5596-5605.

23. (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T., Catalytic asymmetric synthesis of β-lactams. *J. Am. Chem. Soc.* **2000,** *122*, 7831-7832; (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T., The development of the first catalyzed reaction of ketenes and imines: catalytic asymmetric synthesis of β-lactams. *J. Am. Chem. Soc.* **2002,** *124*, 6626-6635.

24. (a) France, S.; Wack, H.; Hafez, A., M.; Taggi, A., E.; Witsil, D., R.; Lectka, T., Bifunctional Asymmetric Catalysis: A tandem nucleophile/Lewis acid promoted synthesis of β-lactams. *Org. lett.* **2002,** *4*, 1603-1605; (b) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T., Bifunctional Lewis acid-nucleophile-based asymmetric catalysis: mechanistic evidence for imine activation working in tandem with chiral enolate formation in the synthesis of β-lactams. *J. Am. Chem. Soc* **2005,** *127*, 1206-1215.

25. Hodous, B. L.; Fu, G. C., Enantioselective Staudinger synthesis of β-lactams catalyzed by a planar-chiral nucleophile. *J. Am. Chem. Soc* **2002,** *124*, 1578-1579.

26. Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C., Catalytic asymmetric Staudinger reactions to form β-lactams: an unanticipated dependence of diastereoselectivity on the choice of the nitrogen substituent. *J. Am. Chem. Soc* **2005,** *127*, 11586-11587.

27. (a) Ojima, I.; Wang, T.; Miller, M. L.; Lin, S.; Borella, C. P.; Geng, X.; Pera, P.; Bernacki, R. J., Synthesis and structure-activity relationships of new second-generation taxoids. *Bioorg. Med. Chem. Lett.* **1999,** *9*, 3423-3428; (b) Ojima, I.; Slater, J. C.; Michaud, E.; Kuduk, S. D.; Bounaud, P. Y.; Vrignaud, P.; Bissery, M. C.; Veith, J. M.; Pera, P.; Bernacki, R. J., Syntheses and structure-activity relationships of the second-generation antitumor taxoids: exceptional activity against drug-resistant cancer cells. *J. Med. Chem.* **1996,** *39*, 3889-3896; (c) Ojima, I.; Slater, J. C.; Kuduk, S. D.; Takeuchi, C. S.; Gimi, R. H.; Sun, C. M.; Park, Y. H.; Pera, P.; Veith, J. M.; Bernacki, R. J., Syntheses and structure-activity relationships of raxoids derived from 14-hydroxy-10-deacetylbaccatin III. *J. Med. Chem.* **1997,** *40*, 267 - 278; (d) Ojima, I.; Geng, X.; Wu, X.; Qu, C.; Borella, C. P.; Xie, H.; Wilhelm, S. D.; Leece, B. A.; Bartle, L. M.; Goldmacher, V. S.; Chari, R. V. J., Tumor-specific novel taxoid-monoclonal antibody conjugates. *J. Med. Chem.* **2002,** *45*, 5620-5623; (e) Ojima, I.; Borella, C. P.; Wu, X.; Bounaud, P.-Y.; Oderda, C. F.; Sturm, M.; Miller, M. L.; Chakravarty, S.; Chen, J.; Huang, Q.; Pera, P.; Brooks, T. A.; Baer, M. R.; Bernacki, R. J., Design, synthesis and structure-activity relationships of novel taxane-based multidrug resistance reversal agents. *J. Med. Chem.* **2005,** *48*, 2218-2228.

28. Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Ahlgren, M. E., Monocyclic β-lactam inhibitors of human leukocyte elastase. *Tetrahedron* **1990,** *46*, 2255 - 2262.

29. Tschaen, D. M.; Turos, E.; Weinreb, S. M., Stereochemical studies of thermal intermolecular and intramolecular *N*-sulfonylimine Ene reactions. *J. Org. Chem.* **1984,** *49*, 5058 - 5064.

30. Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T., Asymmetric catalysis on sequentially-linked columns. *J. Am. Chem. Soc.* **2001,** *123*, 10853-10859.

31. Chincholkara, P. M.; Puranikb, V. G.; . Deshmukh, A. R. A., An efficient synthesis of azetidine-2,3-diones from L-(+)-diethyl tartrate. *Synlett* **2007,** *2007*, 2242-2246.

32. Li, L.; Thomas, S. A.; Klein, L. L.; Yeung, C. M.; Maring, C. J.; Grampovnik, D. J.; Lartey, P. A.; Plattner, J. J., Synthesis and biological evaluation of C-3'-modified analogs of 9(*R*)-dihydrotaxol. *J. Med. Chem.* **1994,** *37*, 2655-2663.

33. Brieva, R.; Crich, J. Z.; Sih, C. J., Chemoenzymic synthesis of the C-13 side chain of taxol: optically active 3-hydroxy-4-phenyl β-lactam derivatives. *J. Org. Chem.* **1993,** *58*, 1068-1075.

34. Pracejus, H.; Maetje, H., Organic Catalysts. LXXI. Asymmetric syntheses with ketenes. 4. Relationship between the stereochemistry of some alkaloidal catalysts and their stereospecific effects in the asymmetric synthesis of esters. *J. Prakt. Chem.* **1964,** *24*, 195-205.

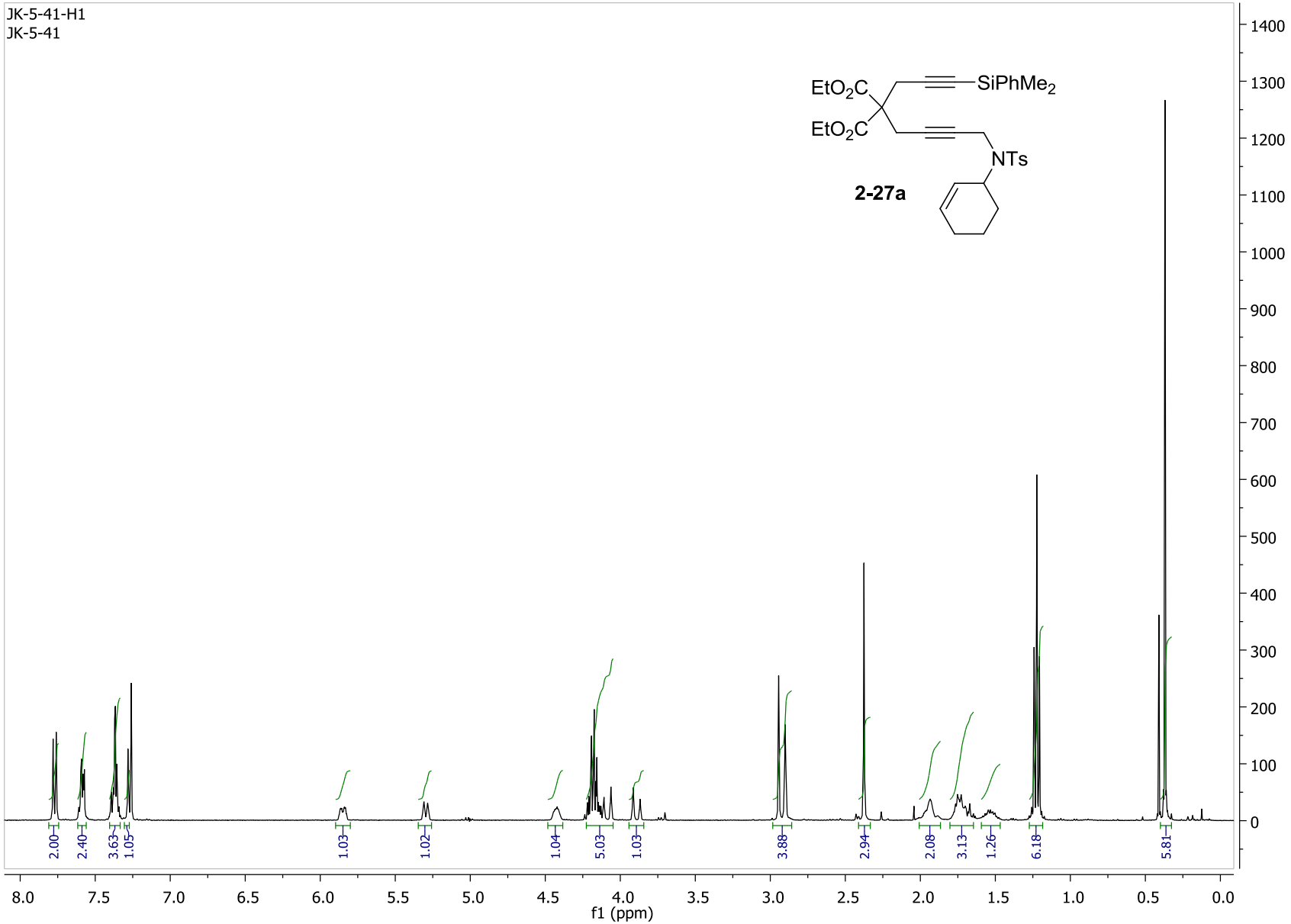
35. Hutzler, J. M.; Walker, G. S.; Wienkers, L. C., Inhibition of cytochrome P450 2D6: structure-activity studies using a series of quinidine and quinine analogues. *Chem. Res. Toxicol.* **2003,** *16*, 450-459.

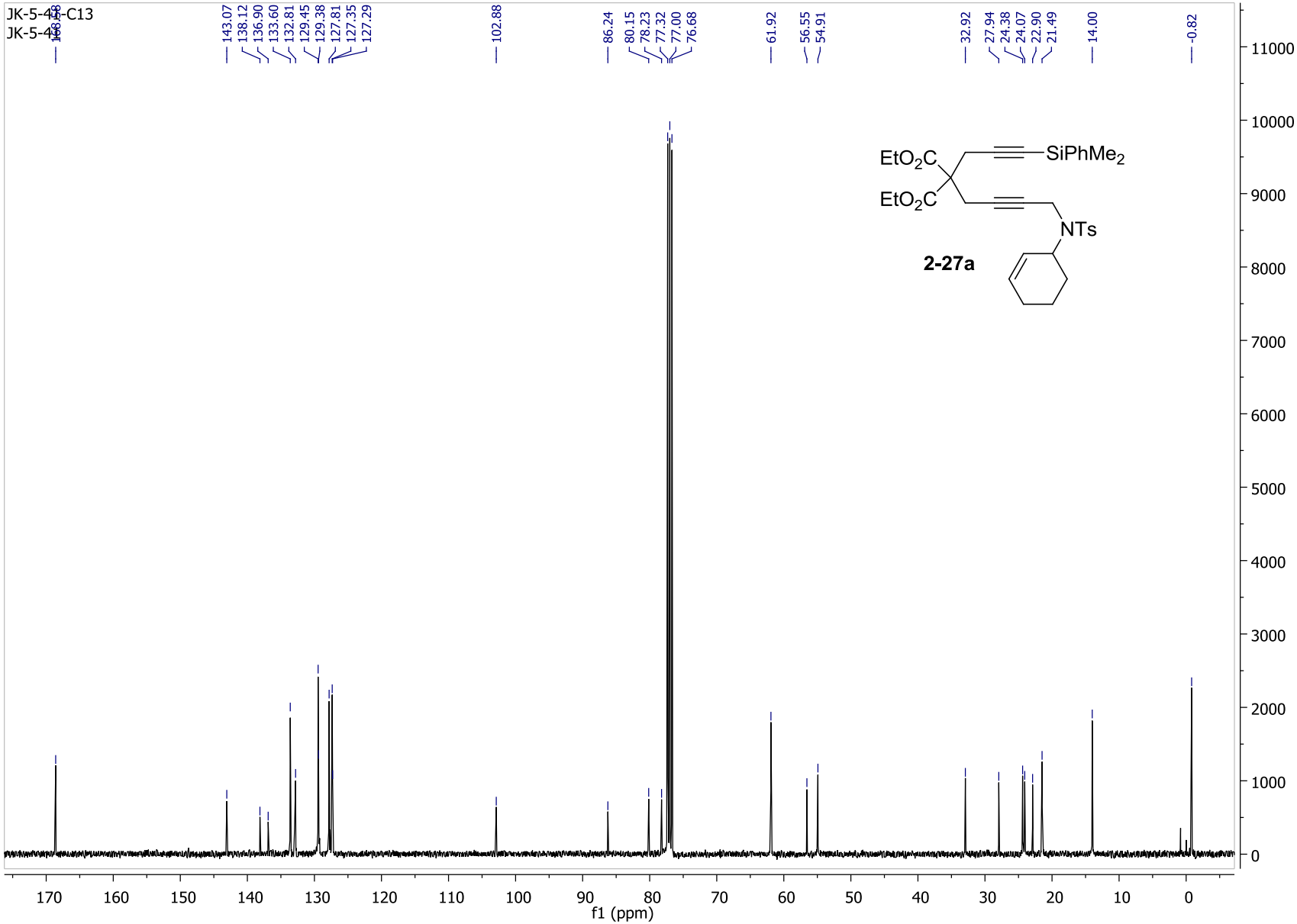
36. Ferraris, D.; Young, B.; Dudding, T.; Drury, W. J.; Lectka, T., Catalytic, enantioselective alkylations of *N*,O- and *N*, *N*-acetals and hemiacetals. *Tetrahedron* **1999,** *55*, 8869-8882.

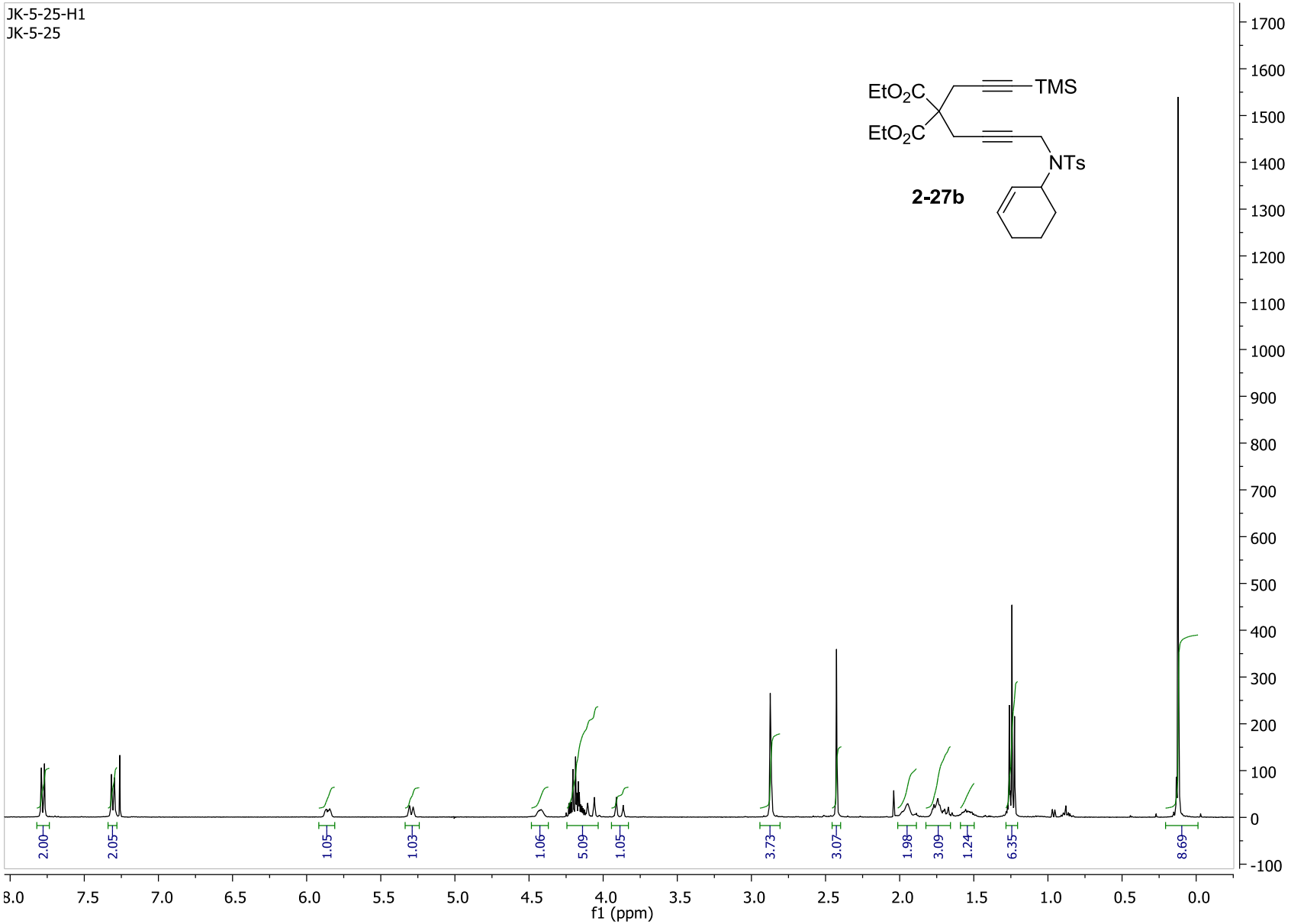
37. Yamago, S.; Yanagawa, M.; Nakamura, E., Thermal hetero [3 + 2] cycloaddition of dipolar trimethylenemethane to *N*-sulfonyl and *N*-acyl imines. Synthesis of gama-amino acid derivatives. *Chem. Lett.* **1999**, 879 - 880.

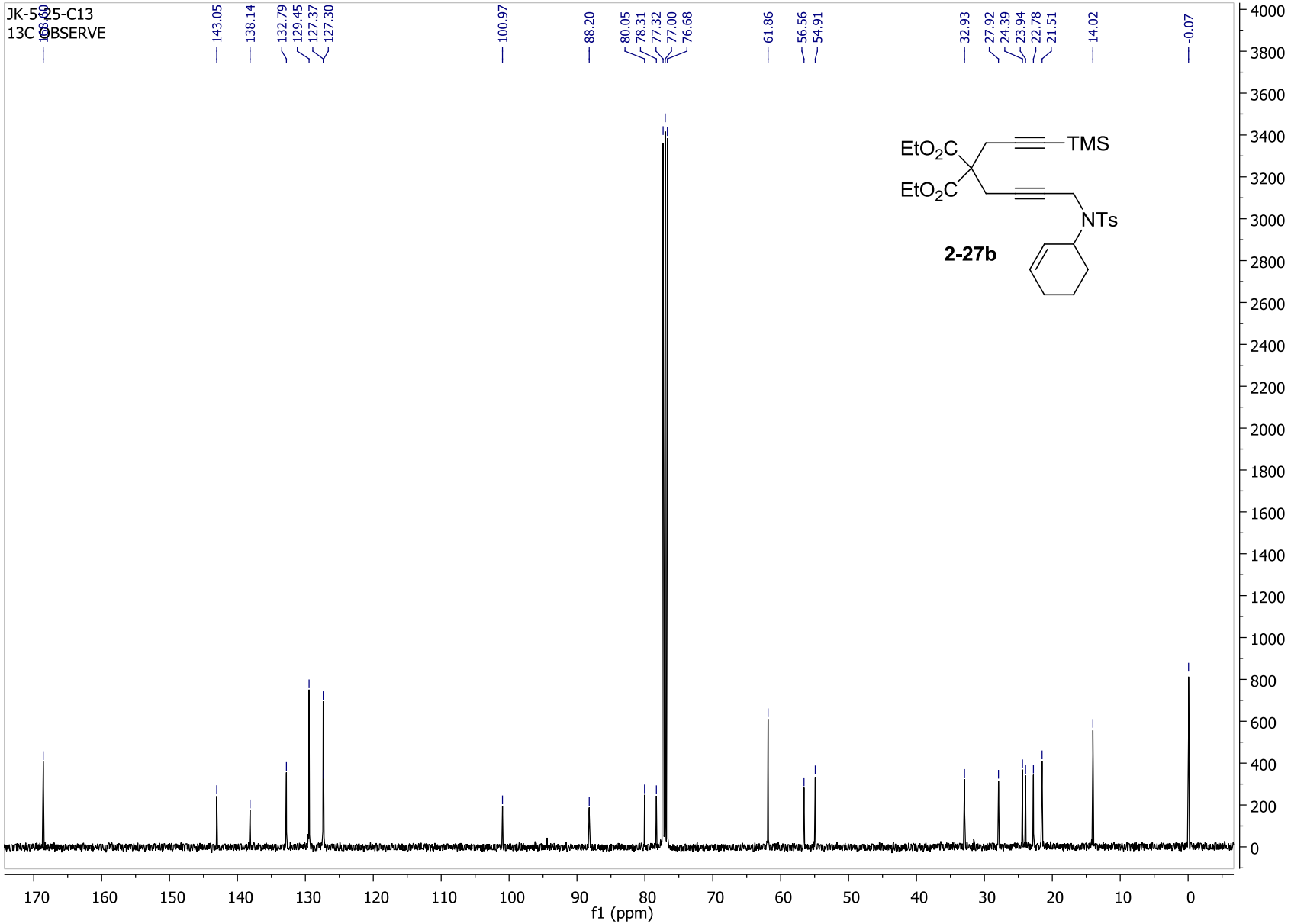
38. Sugisaki, Claudia H.; Ruland, Y.; Baltas, M., Direct access to furanosidic eight-membered ulosonic esters from *cis*-α,β-epoxy aldehydes. *Eur. J. Org. Chem.* **2003**, 672-688.

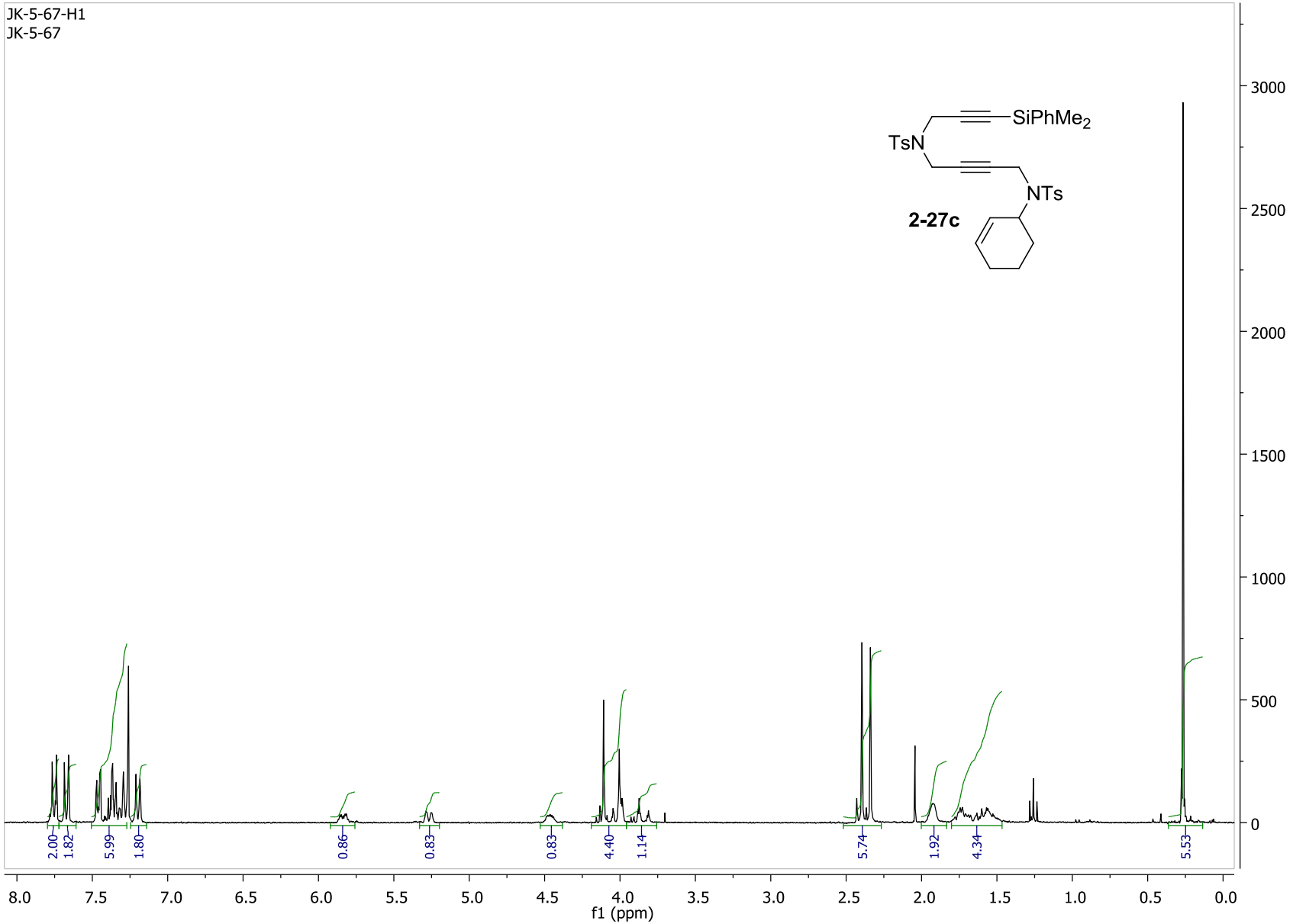
APPENDIX

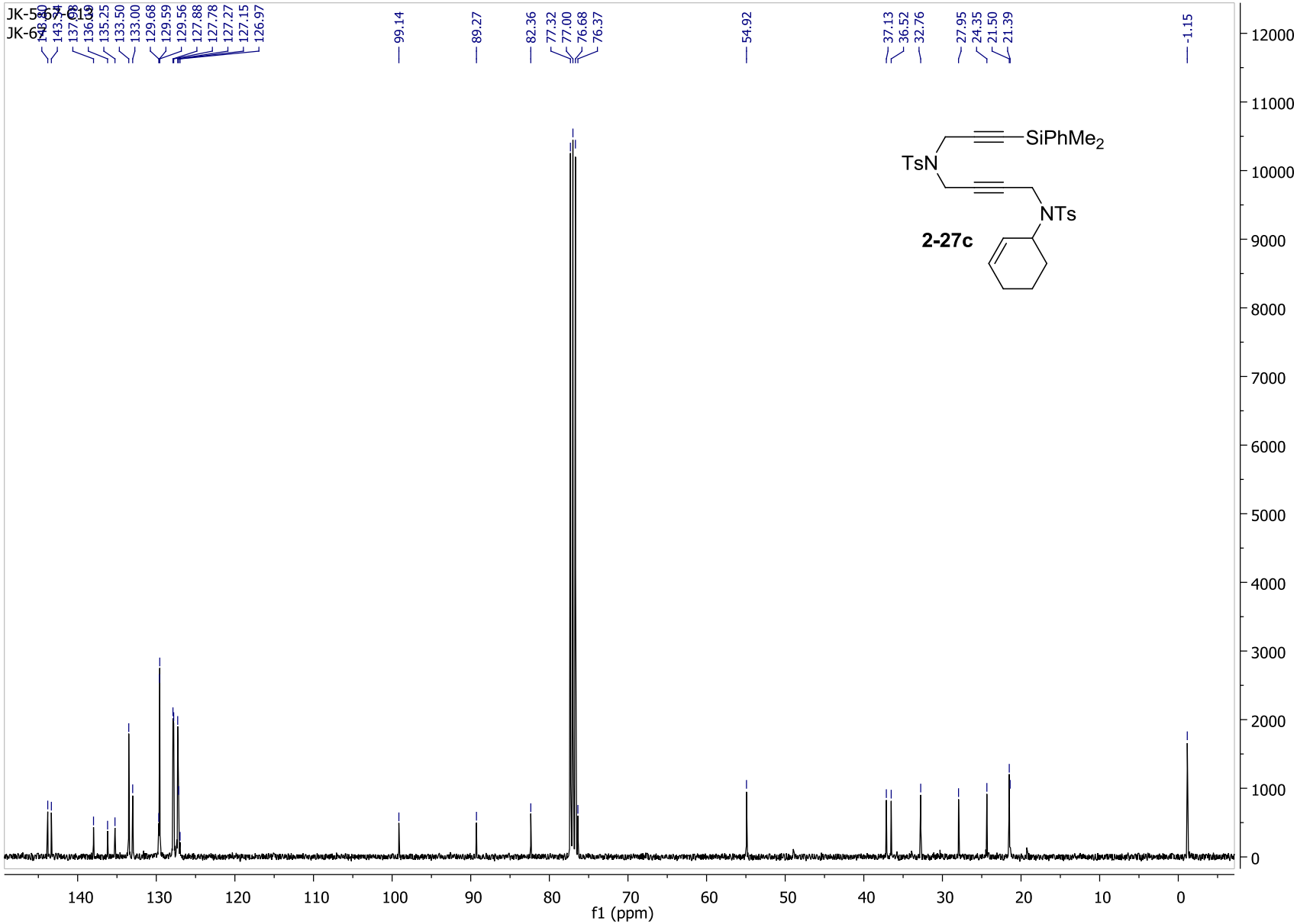

JK-5-41-H1
JK-5-41
EtO2C
EtO2C
SiPhMe2
NTs
2-27a
2.00
2.40
3.63
1.05
1.03
1.02
1.04
5.03
1.03
3.88
2.94
2.08
3.13
1.26
6.18
5.81
f1 (ppm)

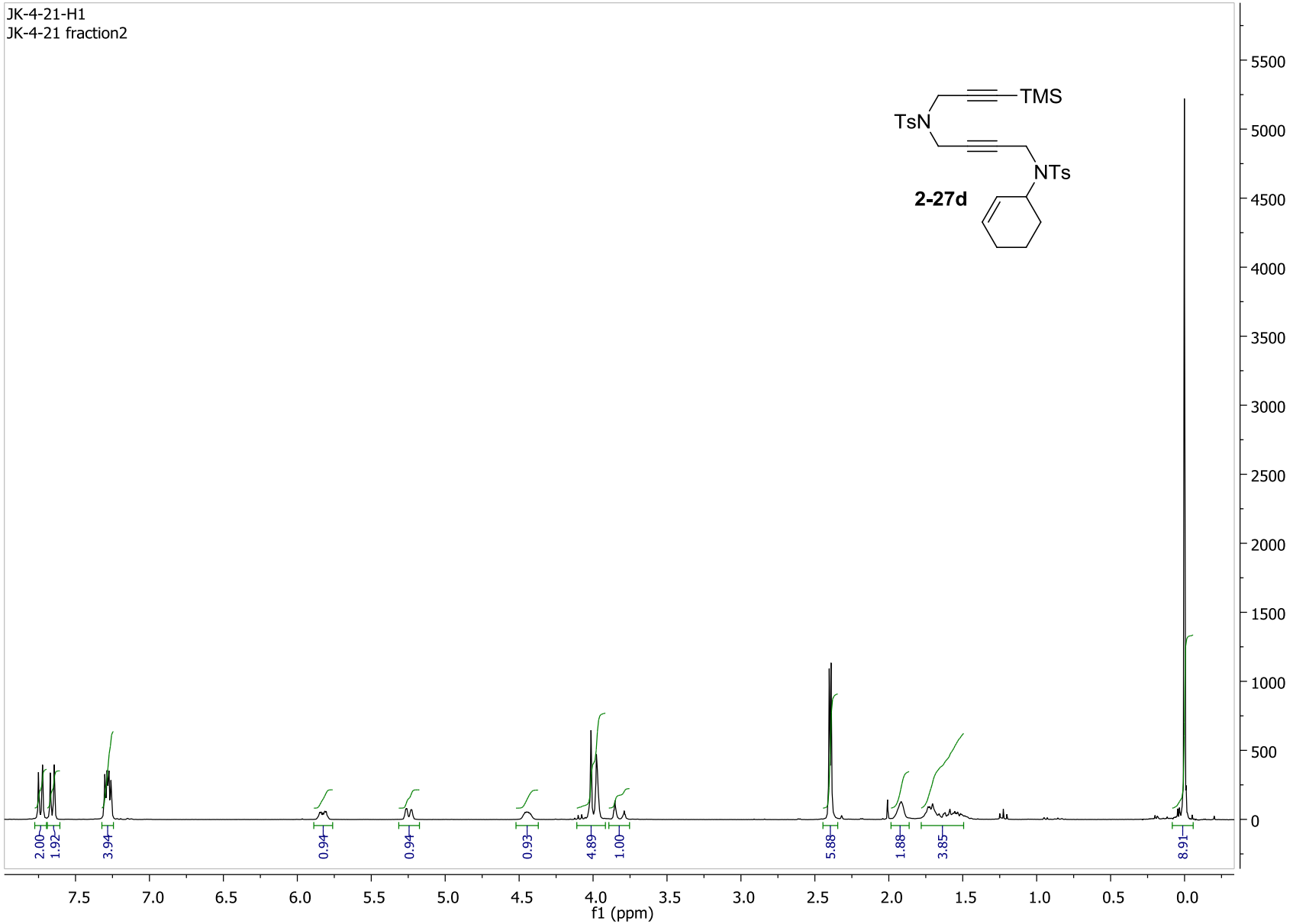

JK-5-45-C13
JK-5-45
143.07
138.12
136.90
133.60
132.81
129.45
129.38
127.81
127.35
127.29
102.88
86.24
80.15
78.23
77.32
77.00
76.68
61.92
56.55
54.91
32.92
27.94
24.38
24.07
22.90
21.49
14.00
-0.82
EtO2C
EtO2C
SiPhMe2
NTs
2-27a
f1 (ppm)

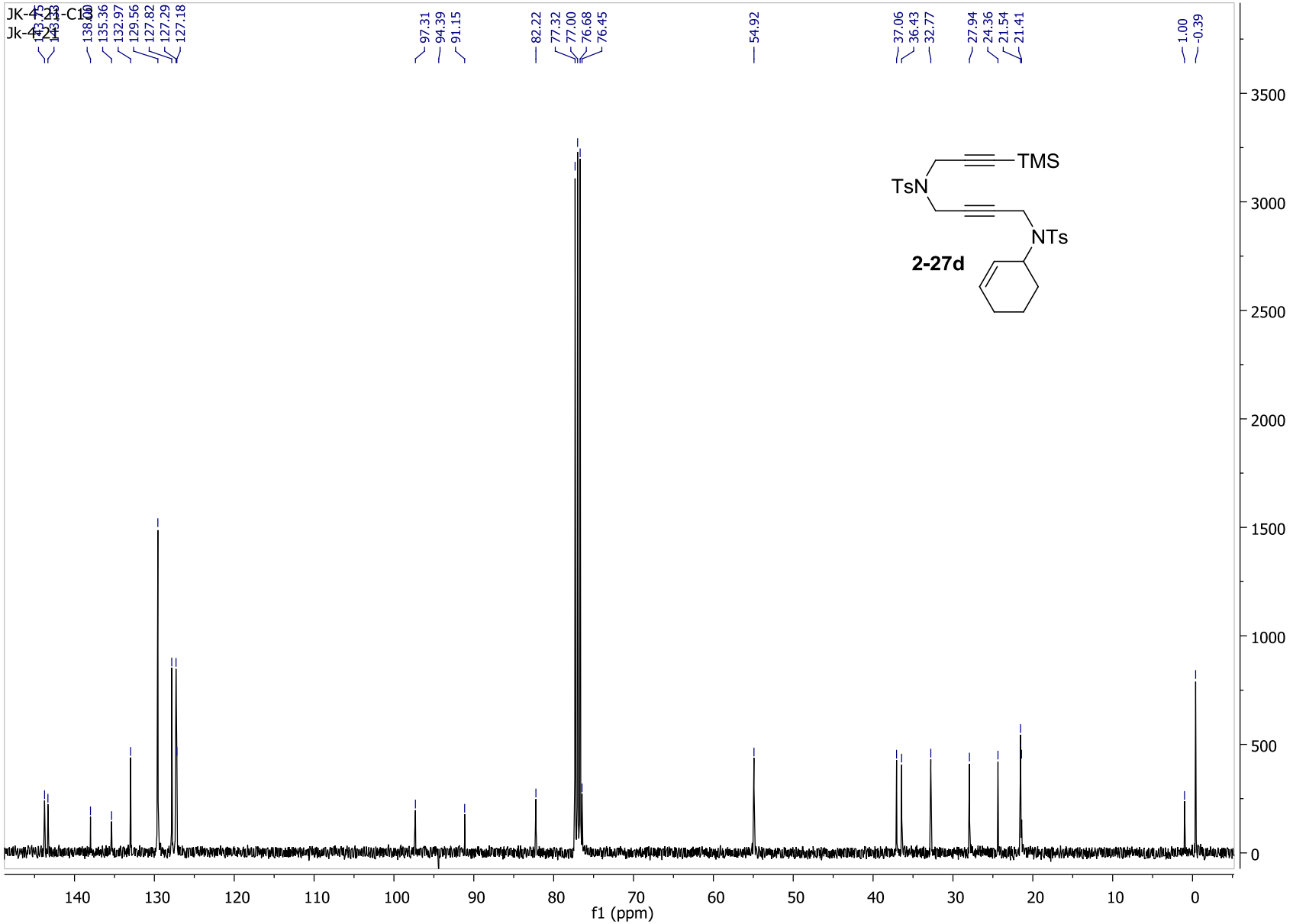

JK-5-25-H1
JK-5-25
EtO2C
EtO2C
TMS
NTs
2-27b
f1 (ppm)

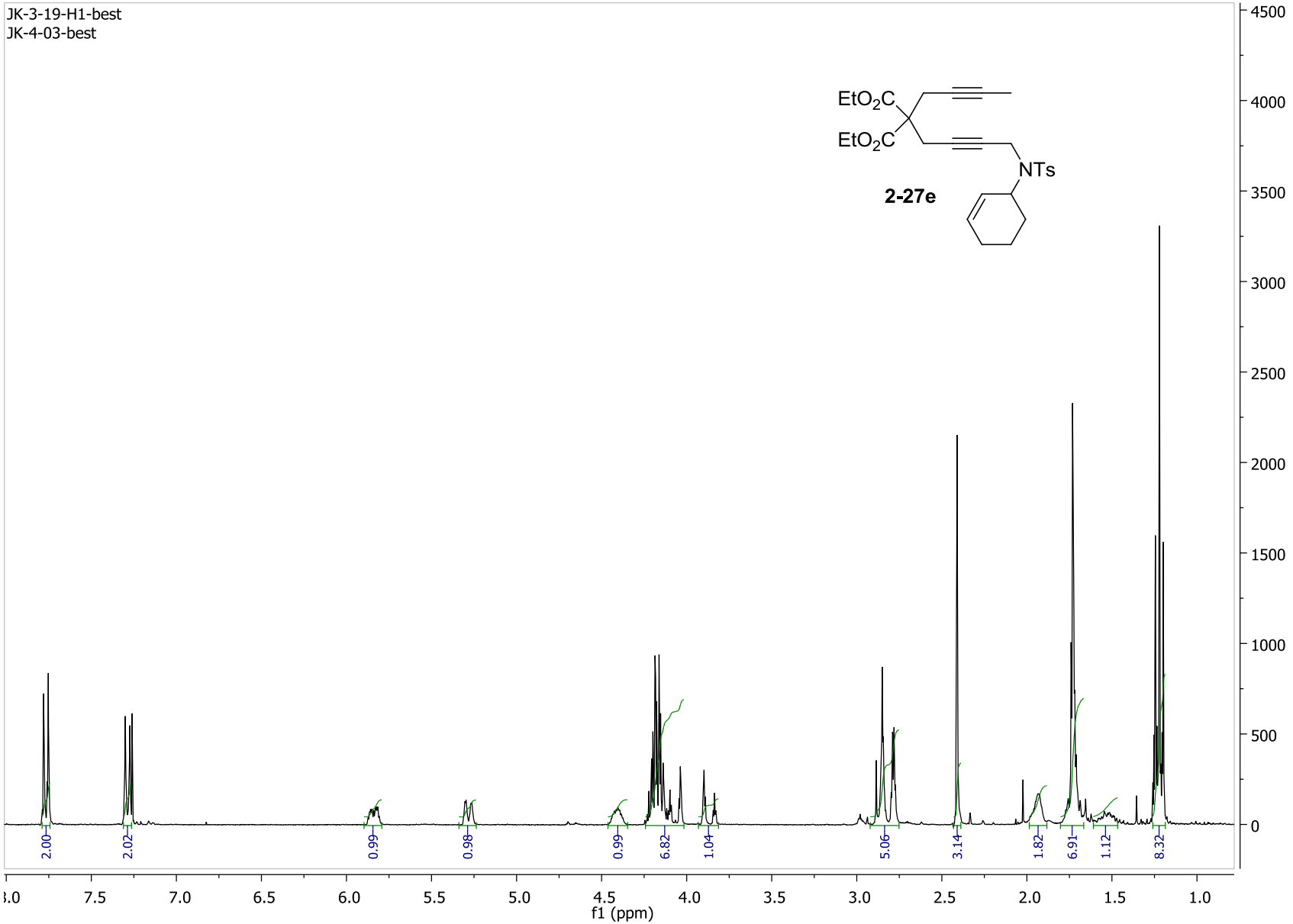

JK-5-25-C13
13C OBSERVE
168.60
143.05
138.14
132.79
129.45
127.37
127.30
100.97
88.20
80.05
78.31
77.32
77.00
76.68
61.86
56.56
54.91
32.93
27.92
24.39
23.94
22.78
21.51
14.02
-0.07
EtO2C
EtO2C
TMS
NTs
2-27b
f1 (ppm)

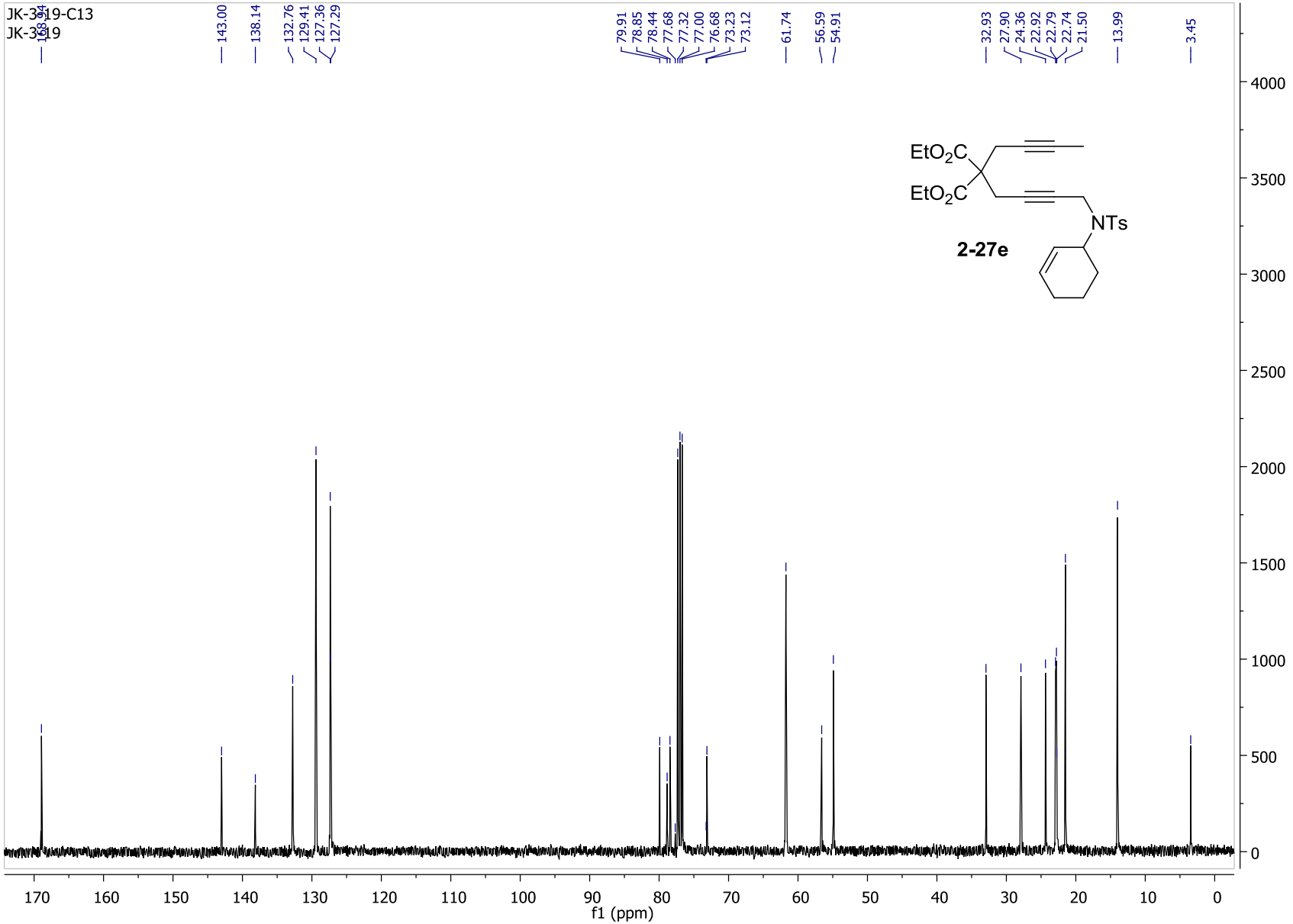

JK-5-67-H1
JK-5-67
SiPhMe2
TsN
NTs
2-27c
3000
2500
2000
1500
1000
500
0
2.00
1.82
5.99
1.80
0.86
0.83
0.83
4.40
1.14
5.74
1.92
4.34
5.53
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

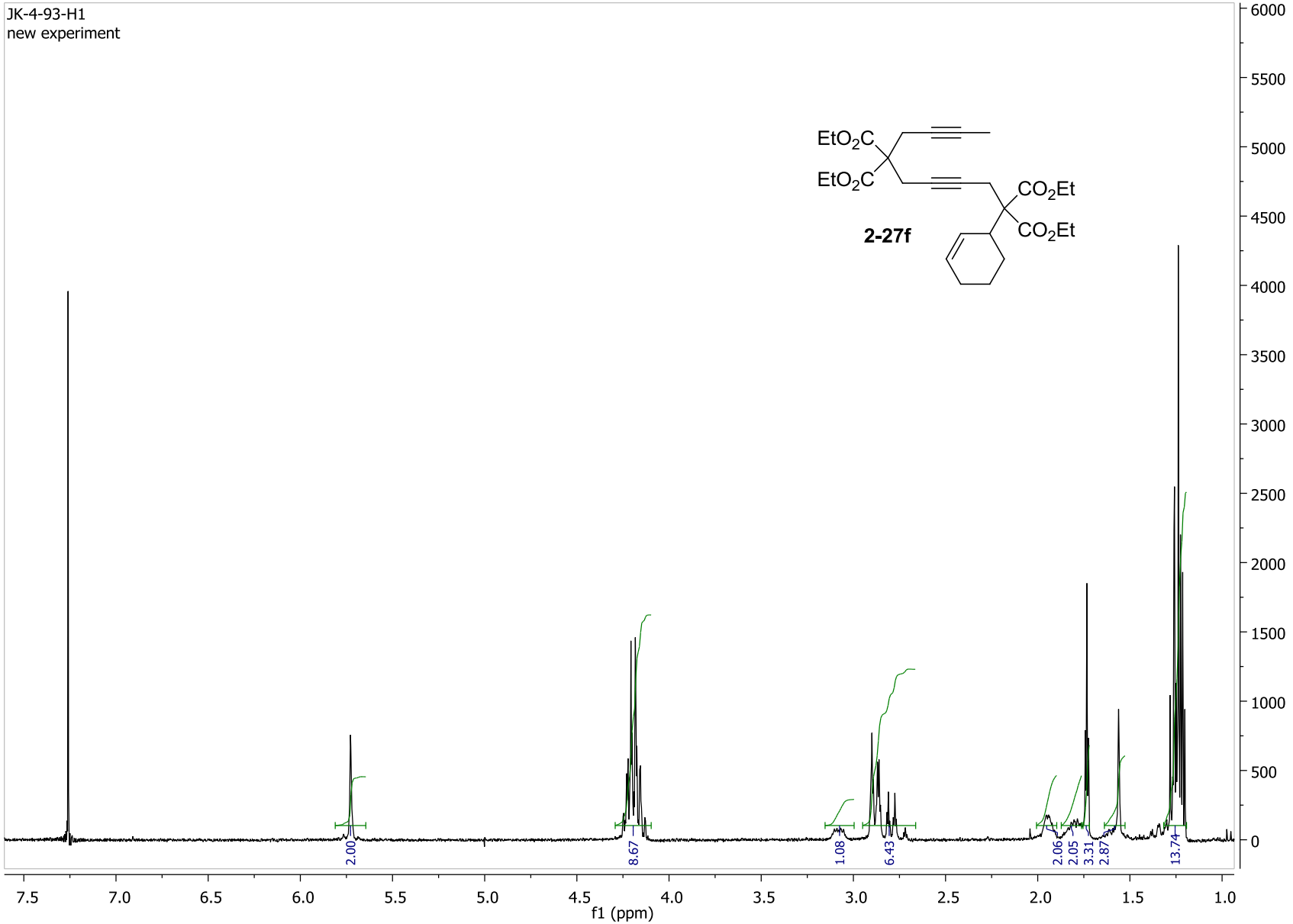

JK-5863-C13
JK-67
143.54
137.68
136.13
135.25
133.50
133.00
129.68
129.59
129.56
127.88
127.78
127.27
127.15
126.97
99.14
89.27
82.36
77.32
77.00
76.68
76.37
54.92
37.13
36.52
32.76
27.95
24.35
21.50
21.39
-1.15
SiPhMe2
TsN
NTs
2-27c
f1 (ppm)

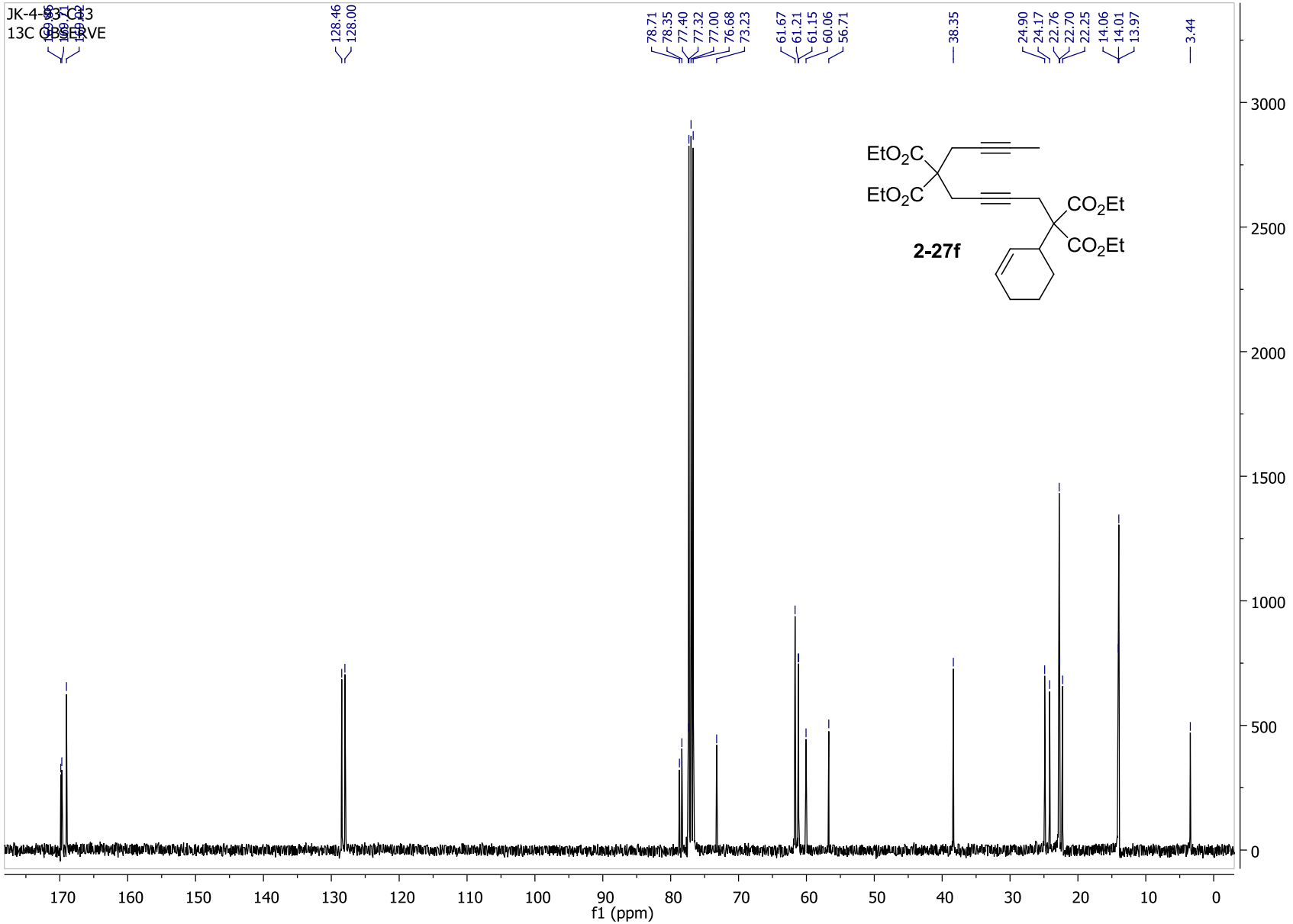

JK-4-21-H1
JK-4-21 fraction2
TMS
TsN
NTs
2-27d
2.00
1.92
3.94
0.94
0.94
0.93
4.89
1.00
5.88
1.88
3.85
8.91
f1 (ppm)

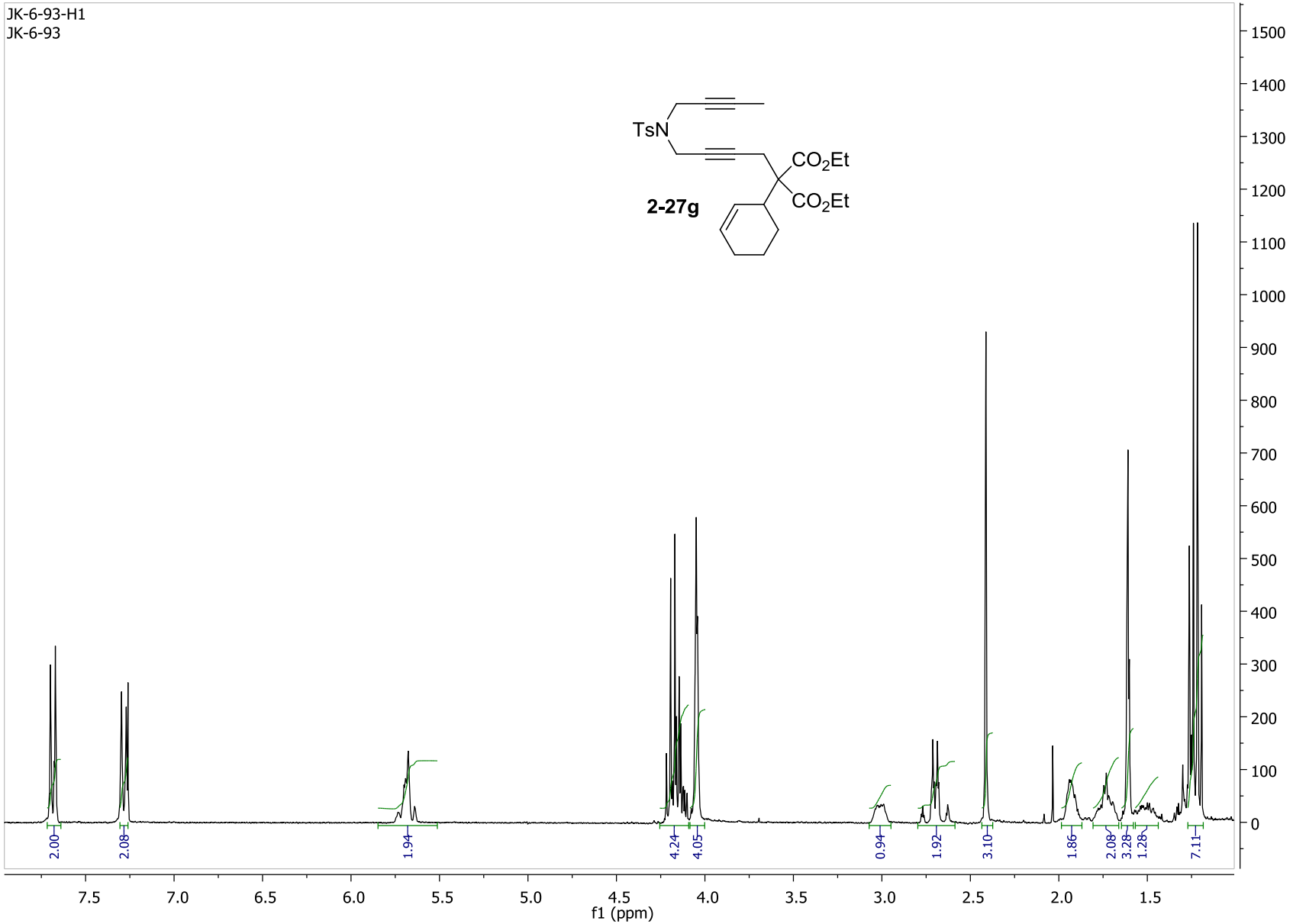

JK-4-21-C13
Jk-4-21
138.00
135.36
132.97
129.56
127.82
127.29
127.18
97.31
94.39
91.15
82.22
77.32
77.00
76.68
76.45
54.92
37.06
36.43
32.77
27.94
24.36
21.54
21.41
1.00
-0.39
TMS
TsN
NTs
2-27d
f1 (ppm)

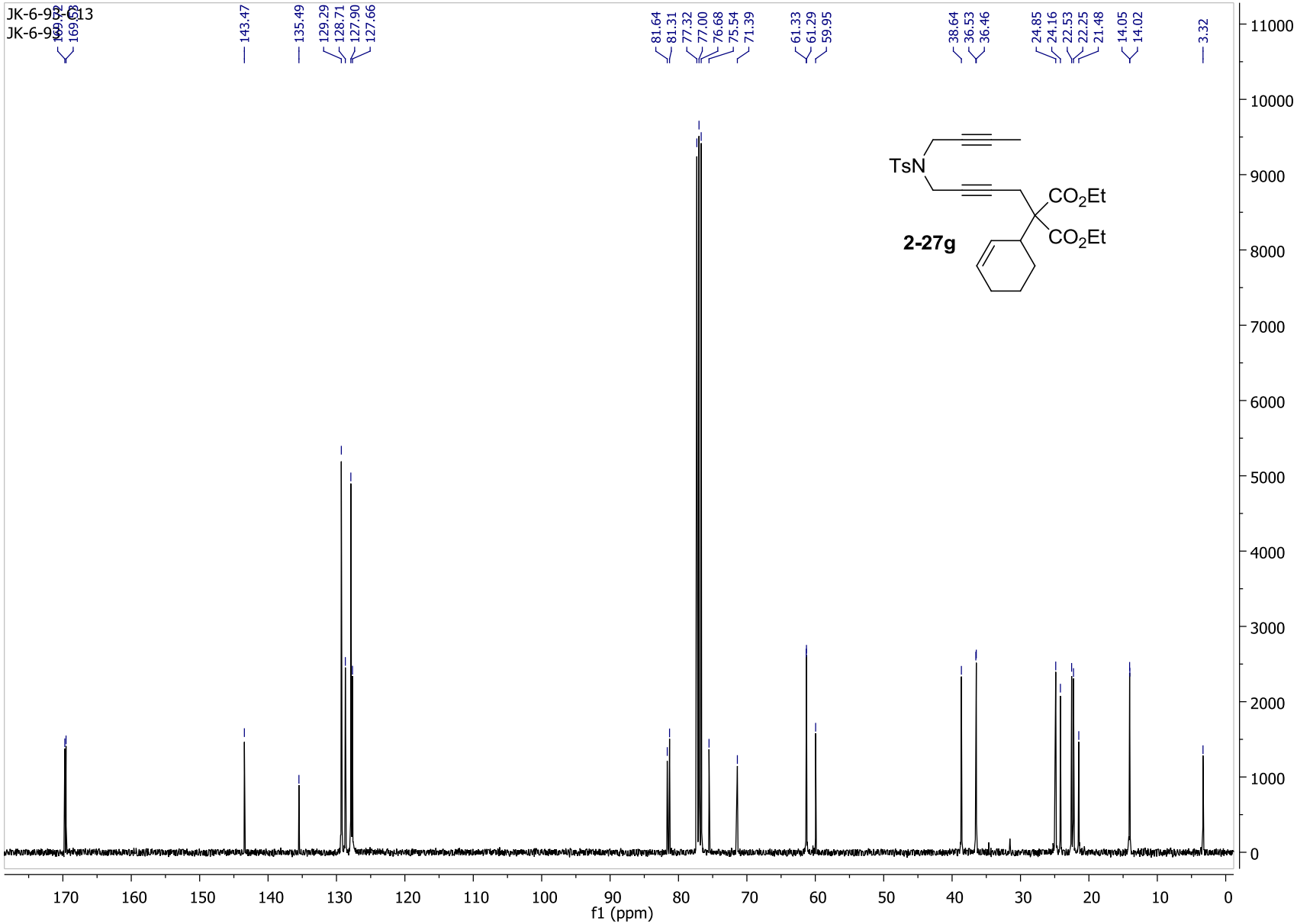

JK-3-19-H1-best
JK-4-03-best
EtO2C
EtO2C
NTs
2-27e
2.00
2.02
0.99
0.98
0.99
6.82
1.04
5.06
3.14
1.82
6.91
1.12
8.32
f1 (ppm)

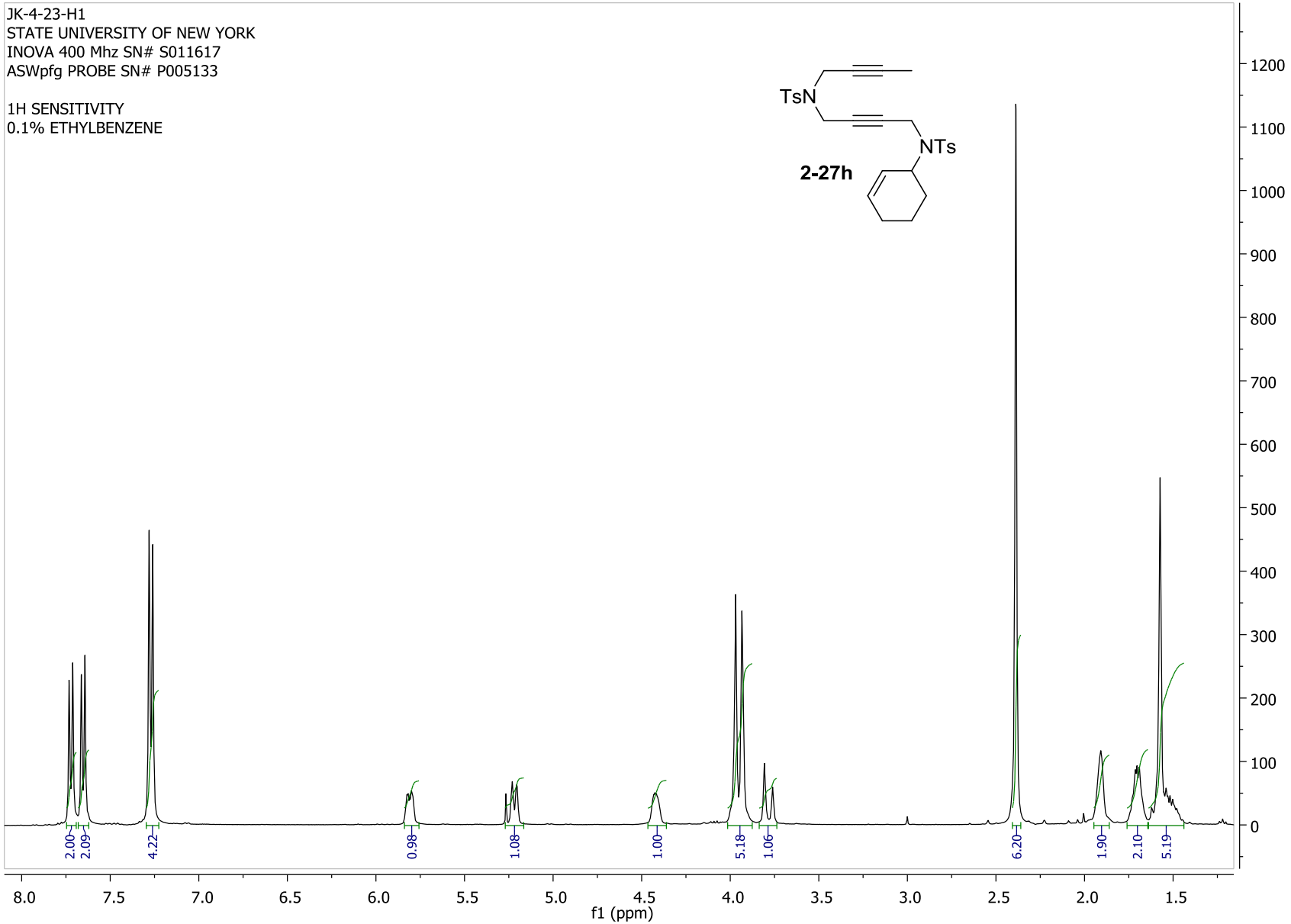

JK-3-19-C13
JK-3-19
168.84
143.00
138.14
132.76
129.41
127.36
127.29
79.91
78.85
78.44
77.68
77.32
77.00
76.68
73.23
73.12
61.74
56.59
54.91
32.93
27.90
24.36
22.92
22.79
22.74
21.50
13.99
3.45
EtO2C
EtO2C
NTs
2-27e
f1 (ppm)

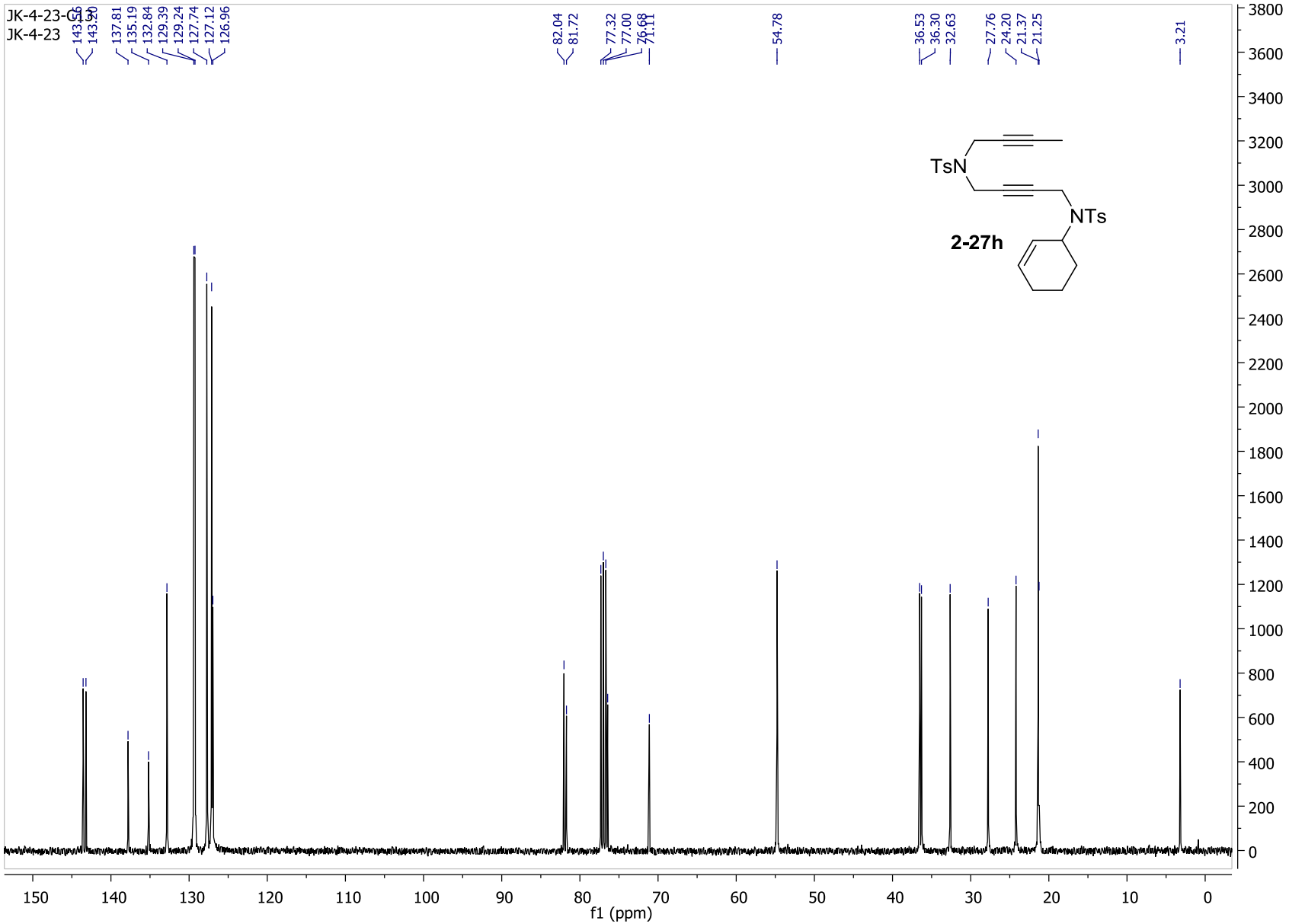

JK-4-93-H1
new experiment
EtO2C
EtO2C
CO2Et
CO2Et
2-27f
2.00
8.67
1.08
6.43
2.06
2.05
3.31
2.87
13.74
f1 (ppm)

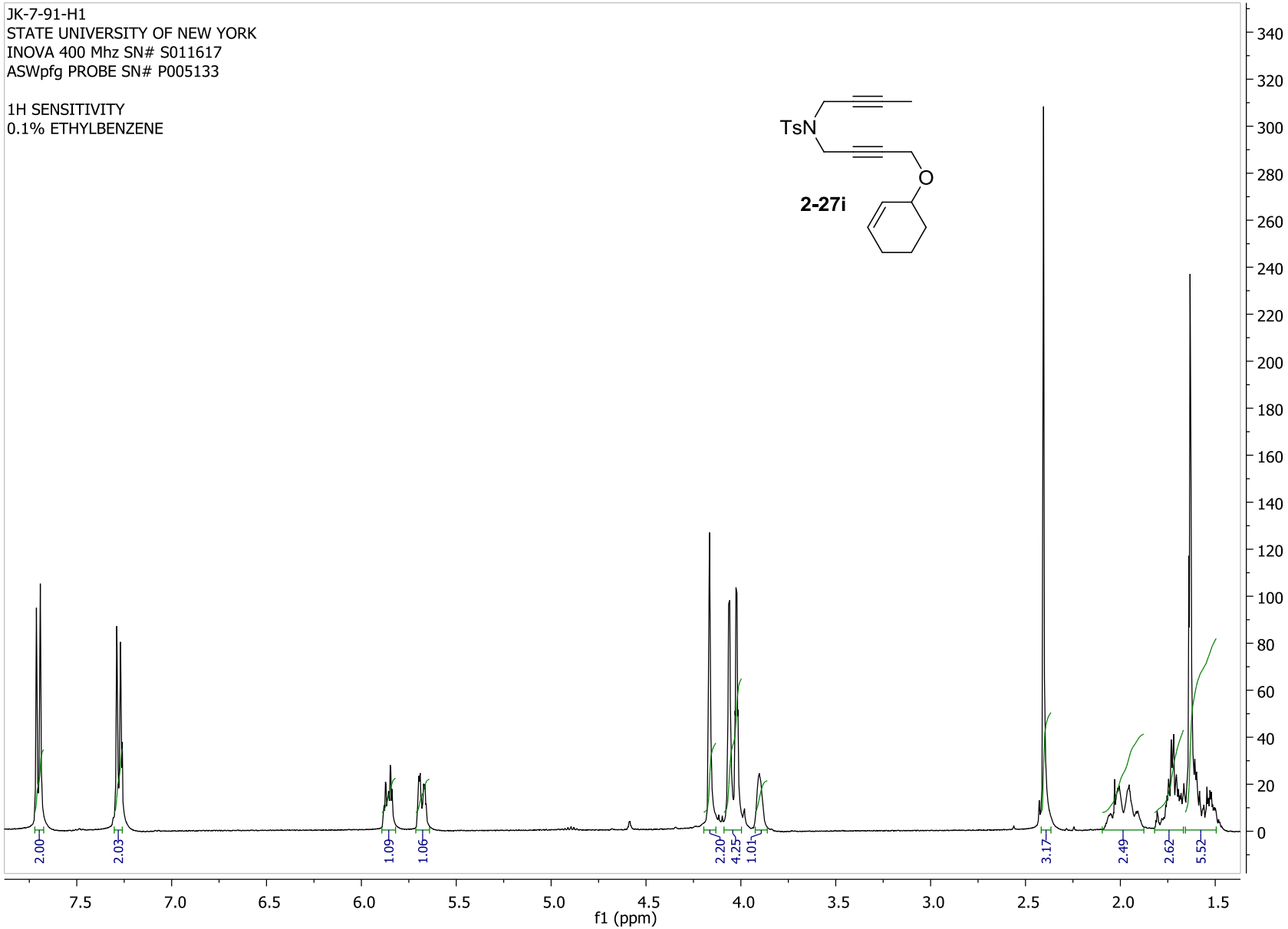

JK-4-93-C13
13C OBSERVE
128.46
128.00
78.71
78.35
77.40
77.32
77.00
76.68
73.23
61.67
61.21
61.15
60.06
56.71
38.35
24.90
24.17
22.76
22.70
22.25
14.06
14.01
13.97
3.44
EtO2C
EtO2C
CO2Et
CO2Et
2-27f
f1 (ppm)

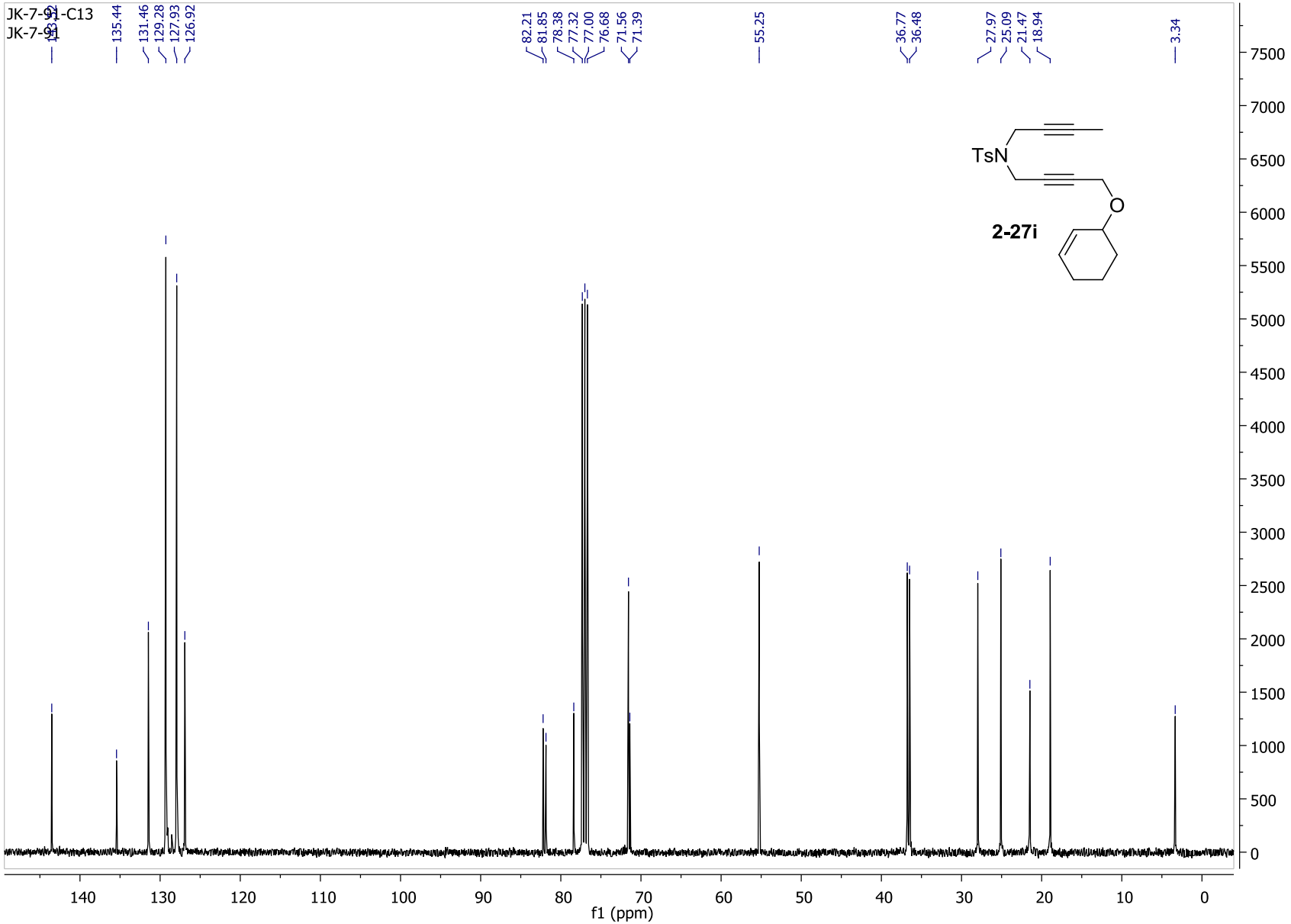

JK-6-93-H1
JK-6-93
TsN
CO2Et
CO2Et
2-27g
2.00
2.08
1.94
4.24
4.05
0.94
1.92
3.10
1.86
2.08
3.28
1.28
7.11
f1 (ppm)

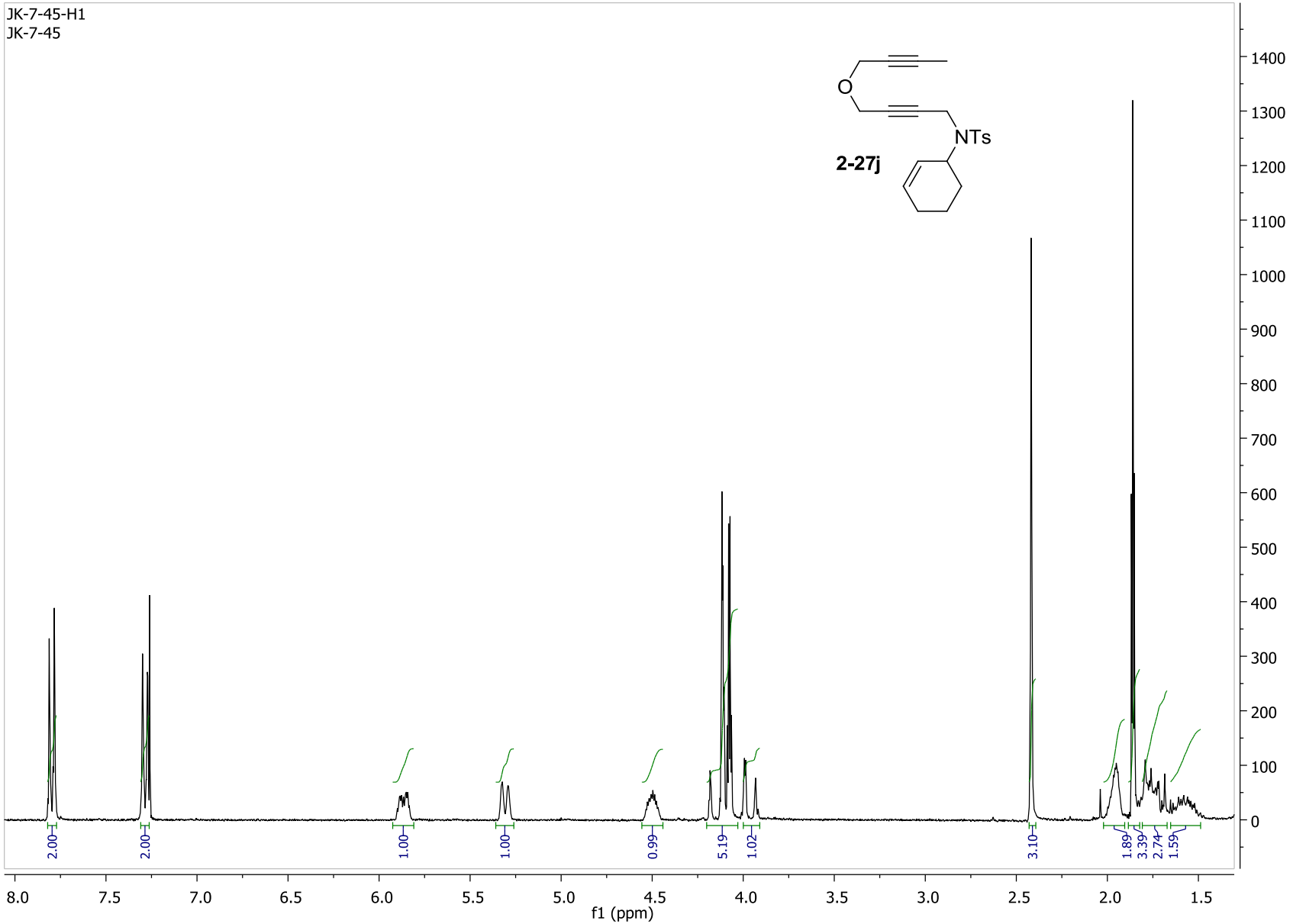

JK-6-93-C13
JK-6-93-C13
169.68
143.47
135.49
129.29
128.71
127.90
127.66
81.64
81.31
77.32
77.00
76.68
75.54
71.39
61.33
61.29
59.95
38.64
36.53
36.46
24.85
24.16
22.53
22.25
21.48
14.05
14.02
3.32
TsN
CO2Et
CO2Et
2-27g
f1 (ppm)

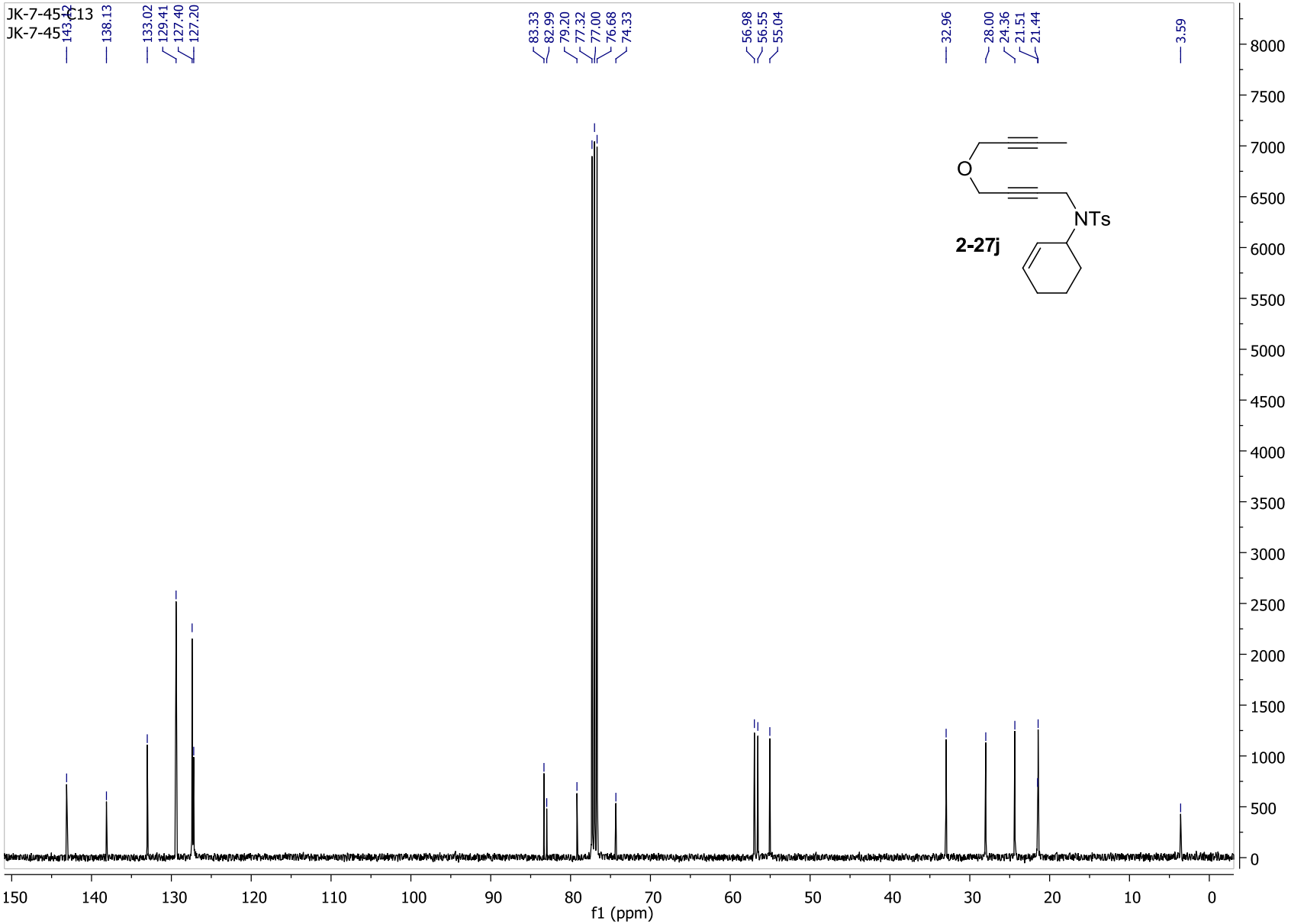

JK-4-23-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
TsN
NTs
2-27h
2.00
2.09
4.22
0.98
1.08
1.00
5.18
1.06
6.20
1.90
2.10
5.19
f1 (ppm)

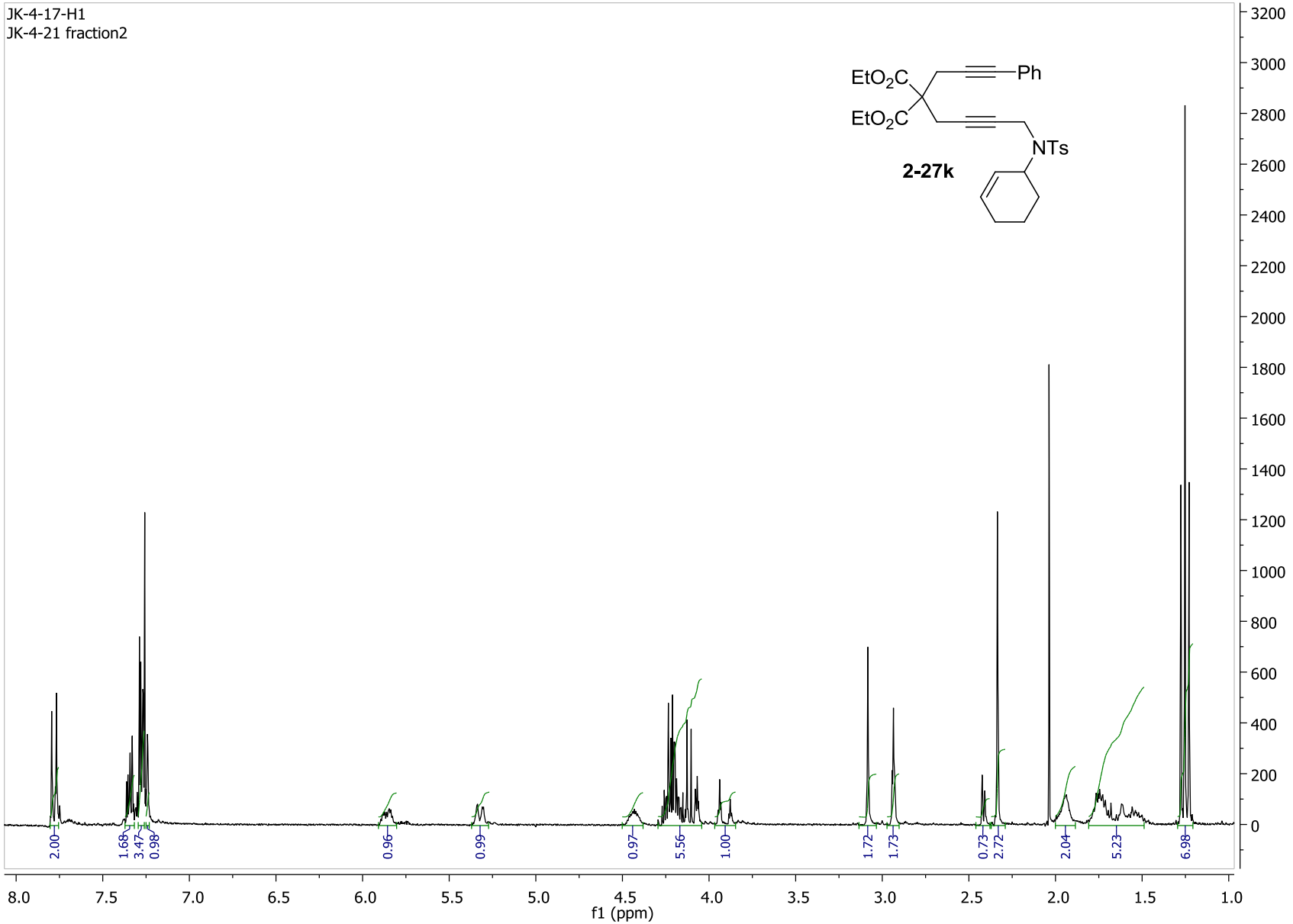

JK-4-23-C13
JK-4-23
143.56
143.20
137.81
135.19
132.84
129.39
129.24
127.74
127.12
126.96
82.04
81.72
77.32
77.00
76.68
71.11
54.78
36.53
36.30
32.63
27.76
24.20
21.37
21.25
3.21
TsN
NTs
2-27h
f1 (ppm)

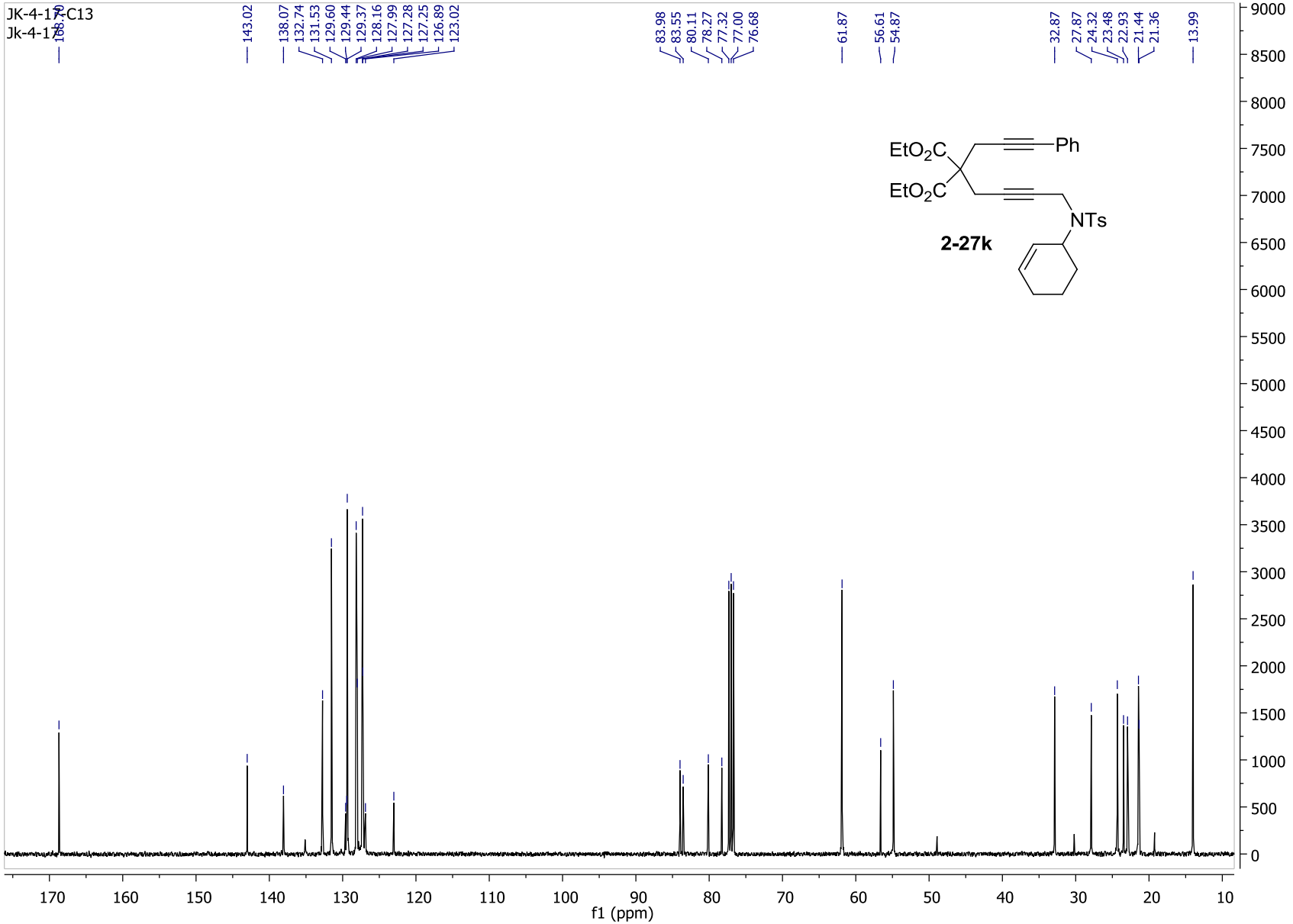

JK-7-91-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
TsN
O
2-27i
2.00
2.03
1.09
1.06
2.20
4.25
1.01
3.17
2.49
2.62
5.52
f1 (ppm)

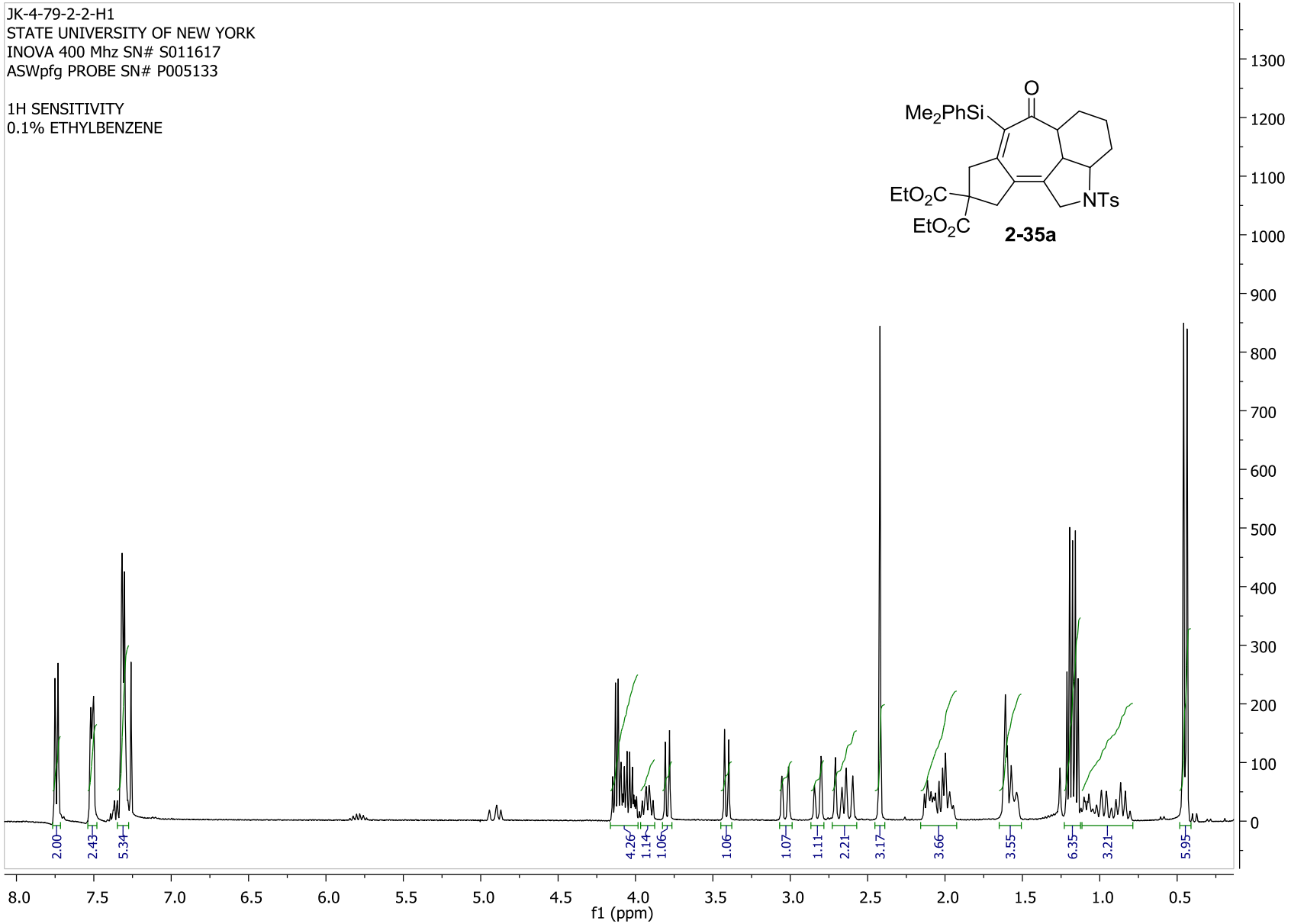

JK-7-91-C13
JK-7-91
143.92
135.44
131.46
129.28
127.93
126.92
82.21
81.85
78.38
77.32
77.00
76.68
71.56
71.39
55.25
36.77
36.48
27.97
25.09
21.47
18.94
3.34
TsN
O
2-27i
f1 (ppm)

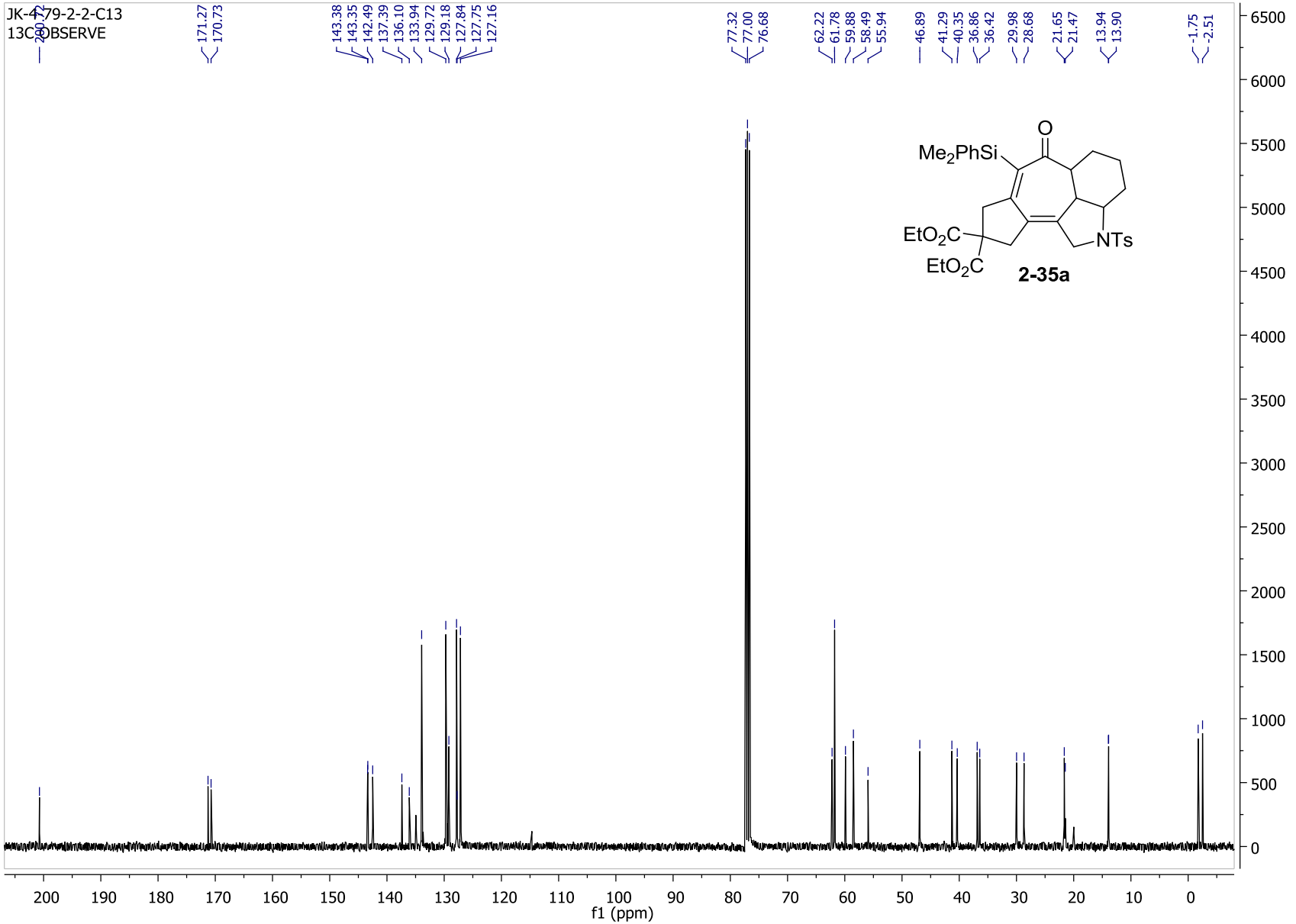

JK-7-45-H1
JK-7-45
O
NTs
2-27j
2.00
2.00
1.00
1.00
0.99
5.19
1.02
3.10
1.89
3.39
2.74
1.59
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0

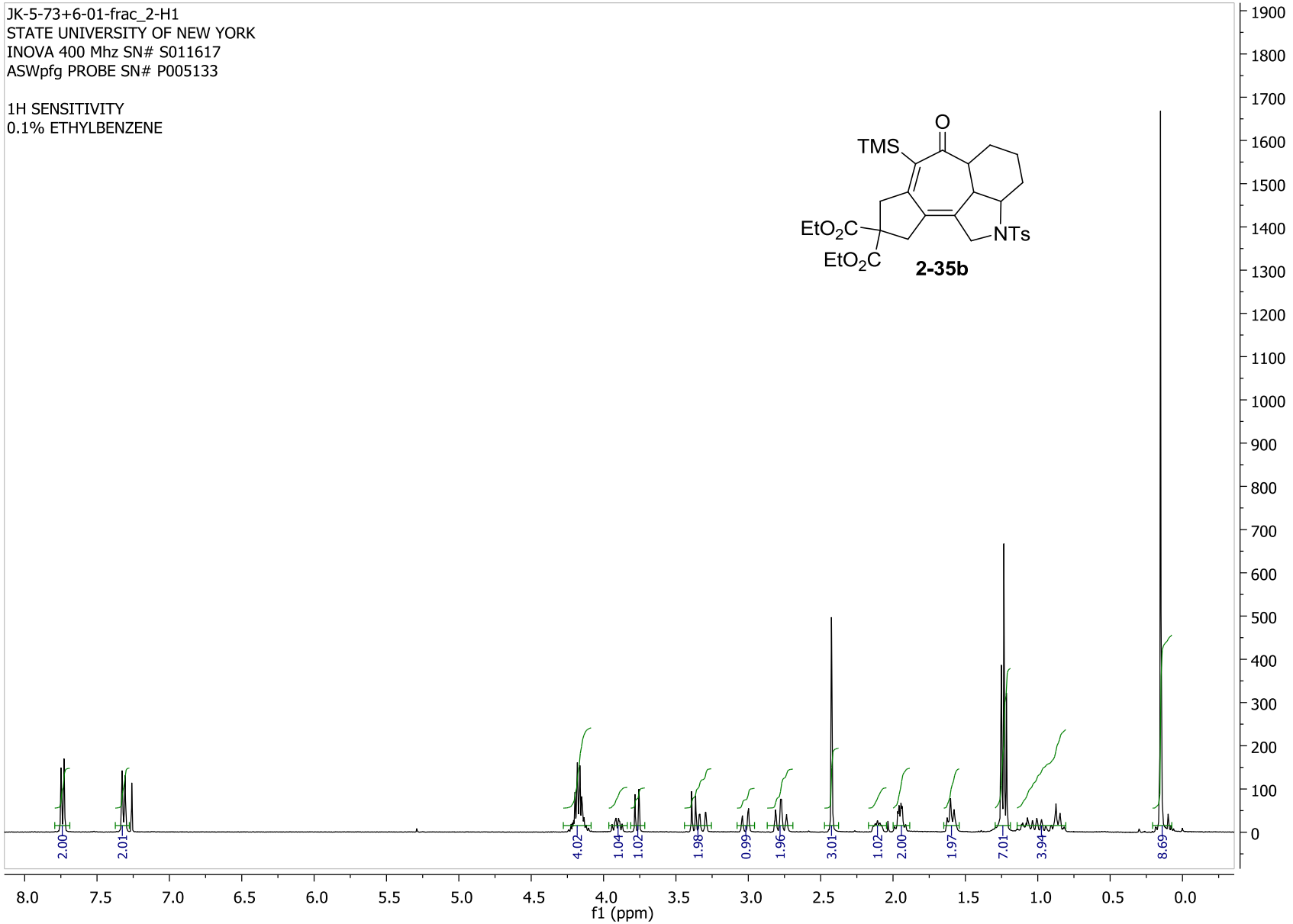

JK-7-45-C13
JK-7-45
143.42
138.13
133.02
129.41
127.40
127.20
83.33
82.99
79.20
77.32
77.00
76.68
74.33
56.98
56.55
55.04
32.96
28.00
24.36
21.51
21.44
3.59
O
NTs
2-27j
f1 (ppm)

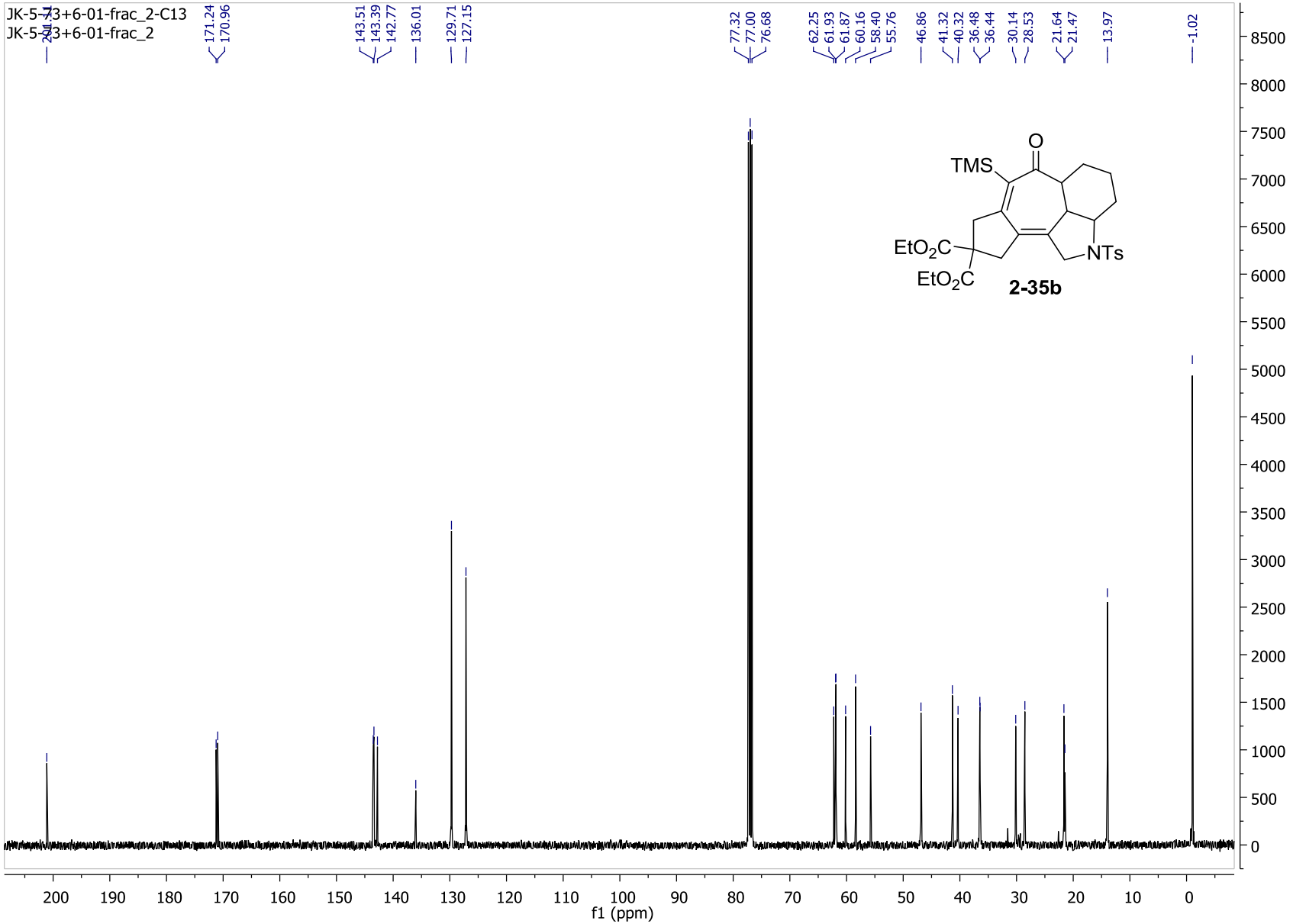

JK-4-17-H1
JK-4-21 fraction2
EtO2C
EtO2C
Ph
NTs
2-27k
f1 (ppm)

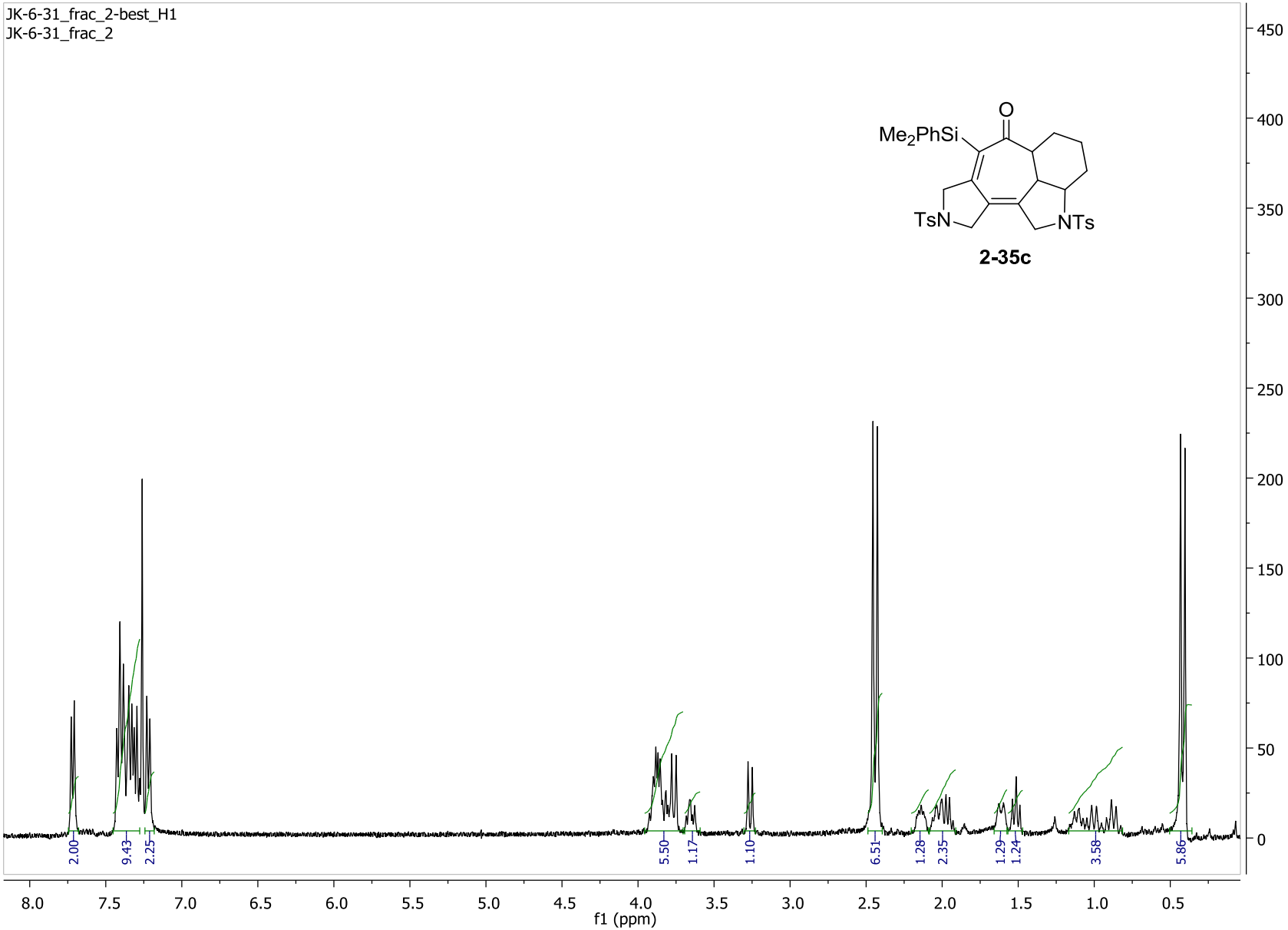

JK-4-17-C13
Jk-4-17
169.83
143.02
138.07
132.74
131.53
129.60
129.44
129.37
128.16
127.99
127.28
127.25
126.89
123.02
83.98
83.55
80.11
78.27
77.32
77.00
76.68
61.87
56.61
54.87
32.87
27.87
24.32
23.48
22.93
21.44
21.36
13.99
EtO2C
EtO2C
Ph
NTs
2-27k
f1 (ppm)

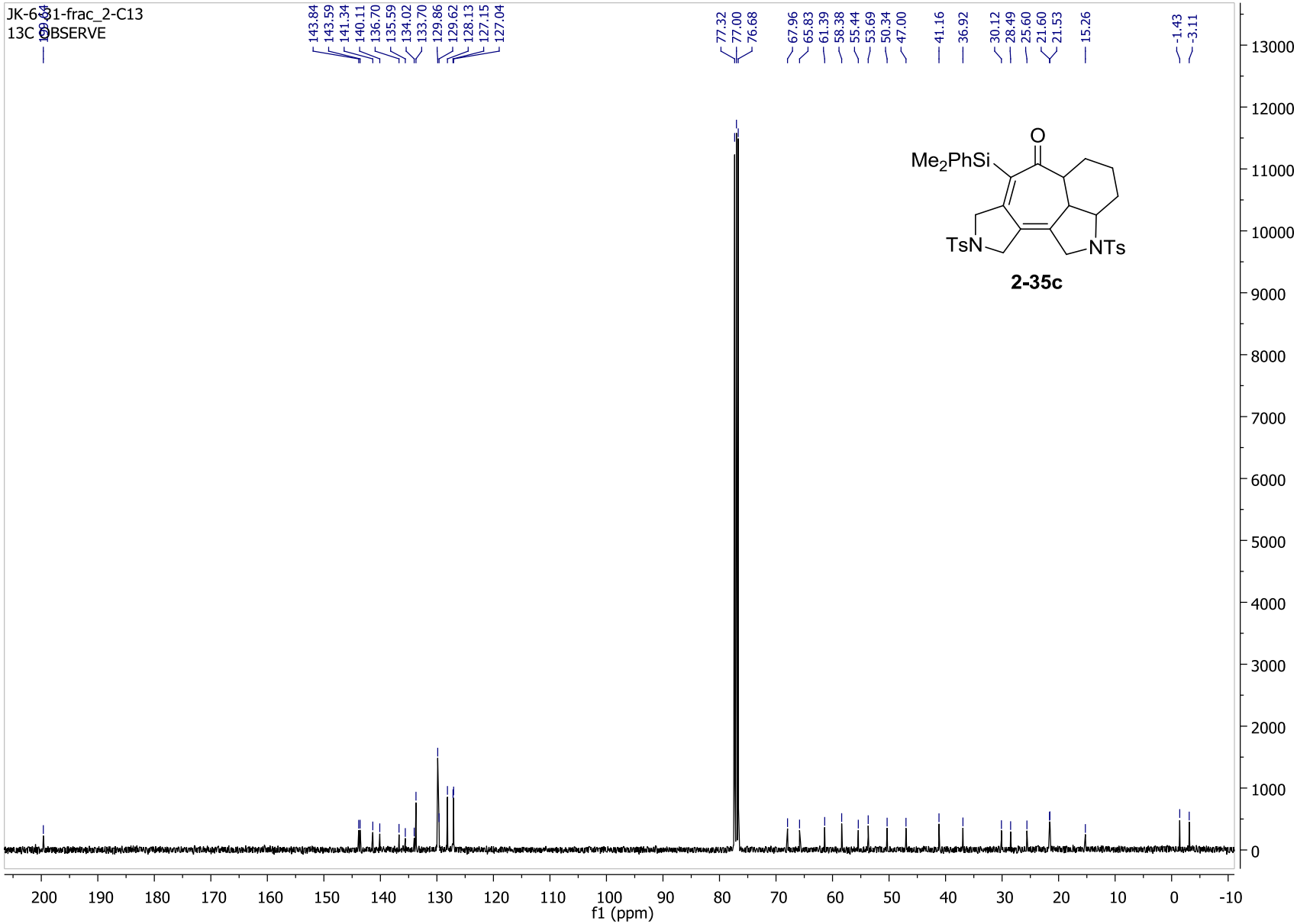

JK-4-79-2-2-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Me2PhSi
O
EtO2C
EtO2C
NTs
2-35a
2.00
2.43
5.34
4.26
1.14
1.06
1.06
1.07
1.11
2.21
3.17
3.66
3.55
6.35
3.21
5.95
f1 (ppm)

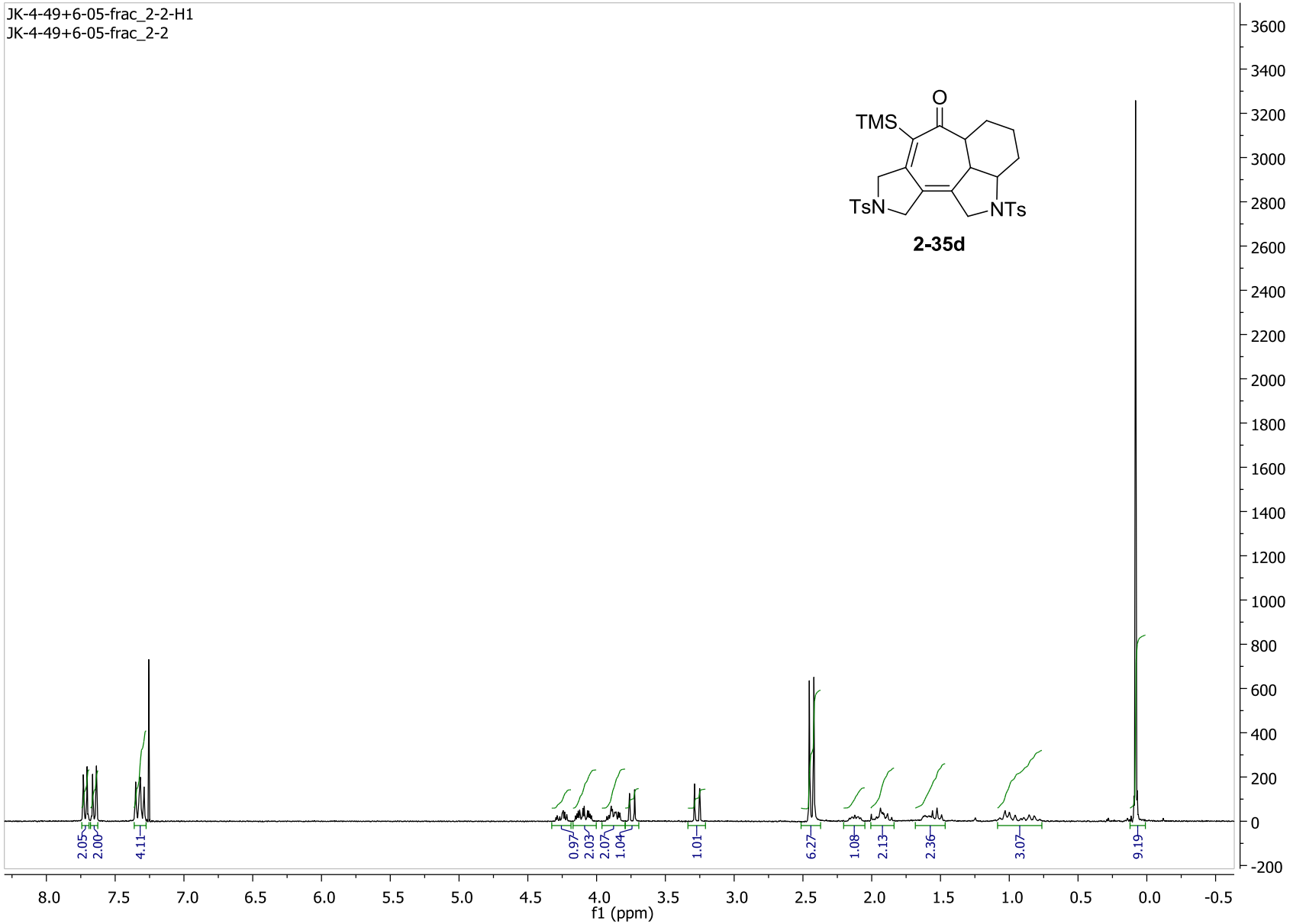

JK-4-79-2-2-C13
13C OBSERVE
200.09
171.27
170.73
143.38
143.35
142.49
137.39
136.10
133.94
129.72
129.18
127.84
127.75
127.16
77.32
77.00
76.68
62.22
61.78
59.88
58.49
55.94
46.89
41.29
40.35
36.86
36.42
29.98
28.68
21.65
21.47
13.94
13.90
-1.75
-2.51
Me2PhSi
O
EtO2C
EtO2C
NTs
2-35a
f1 (ppm)

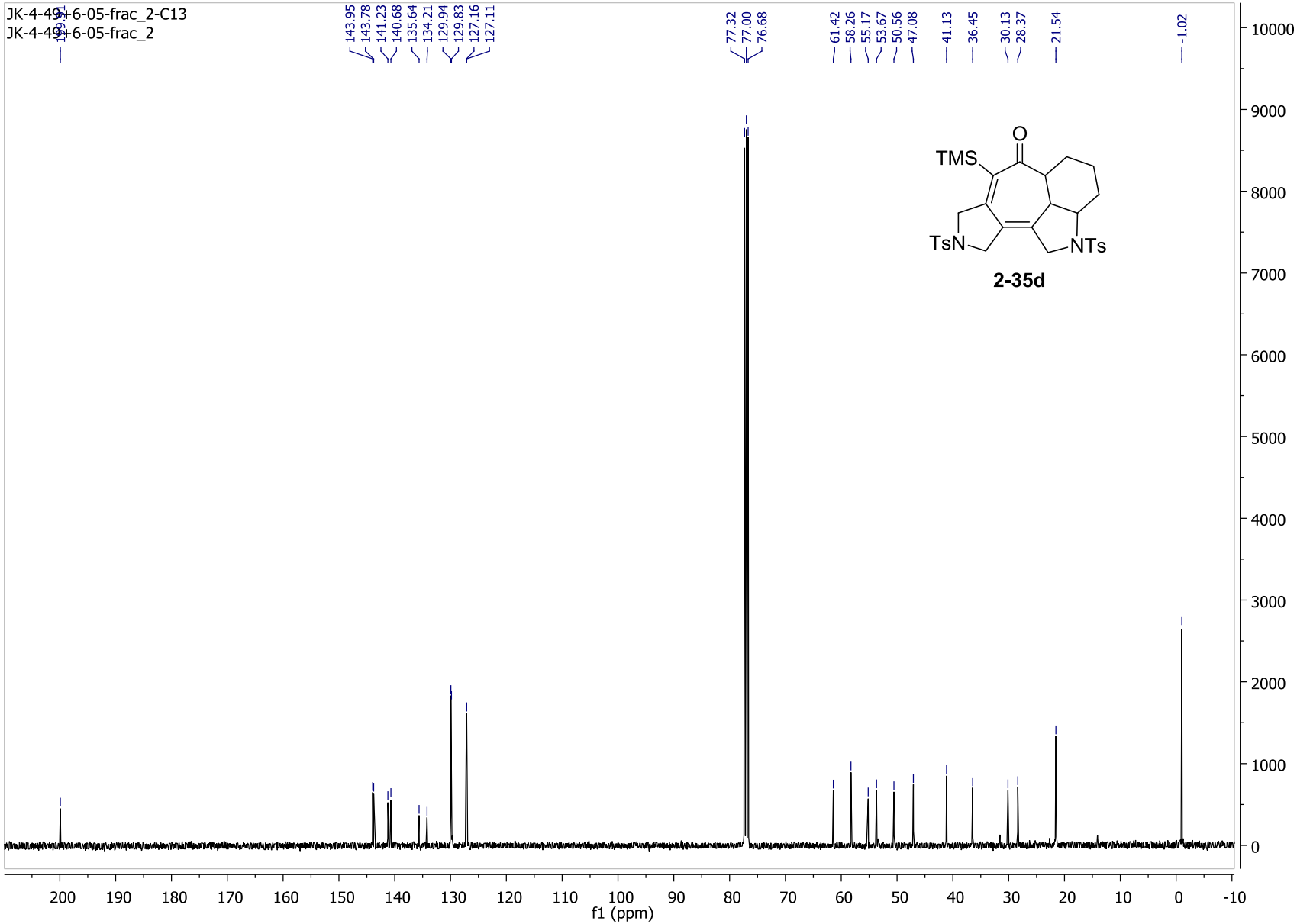

JK-5-73+6-01-frac_2-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
TMS
O
EtO2C
EtO2C
NTs
2-35b
2.00
2.01
4.02
1.04
1.02
1.98
0.99
1.96
3.01
1.02
2.00
1.97
7.01
3.94
8.69
f1 (ppm)

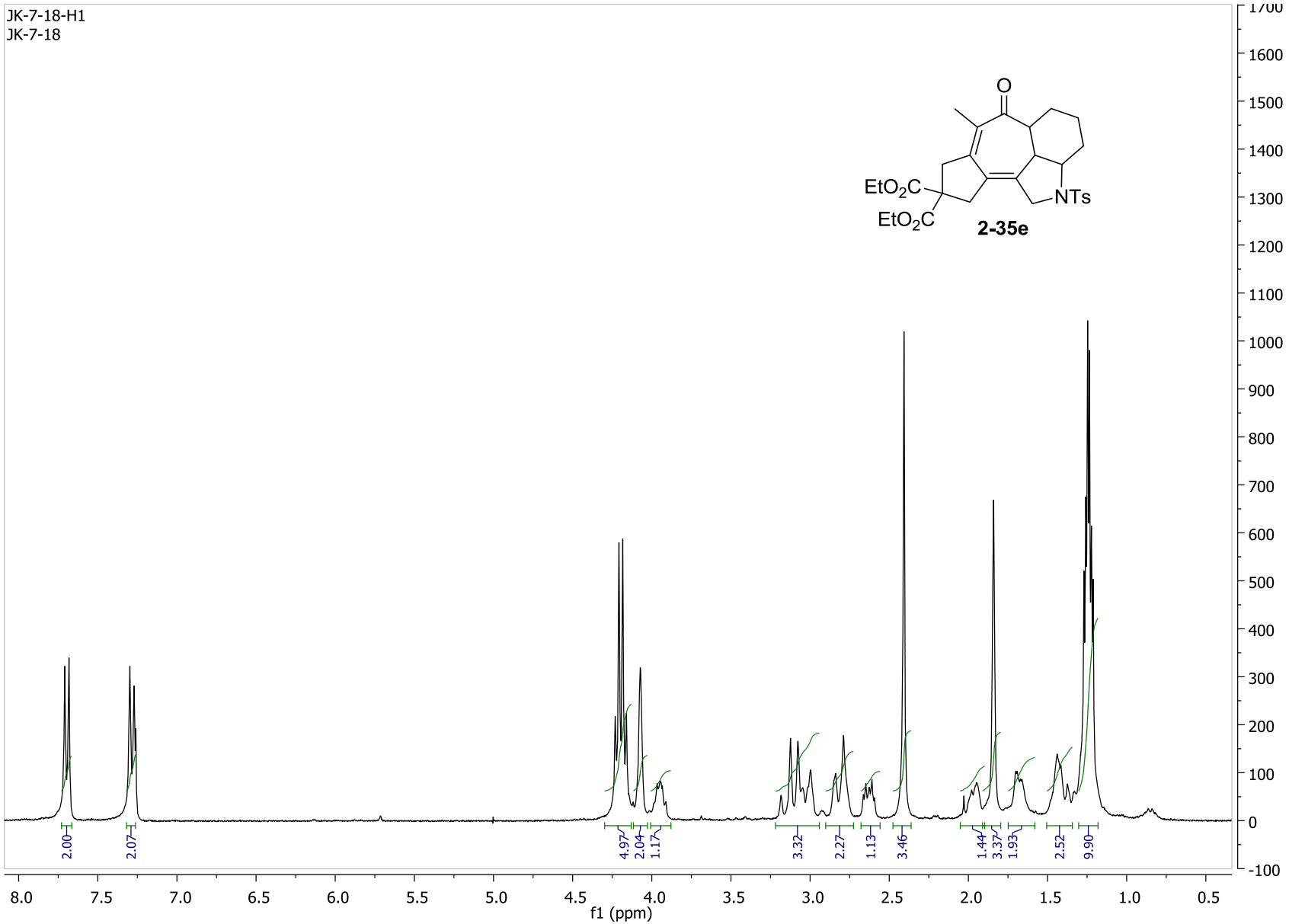

JK-5-73+6-01-frac_2-C13
JK-5-73+6-01-frac_2
171.24
170.96
143.51
143.39
142.77
136.01
129.71
127.15
77.32
77.00
76.68
62.25
61.93
61.87
60.16
58.40
55.76
46.86
41.32
40.32
36.48
36.44
30.14
28.53
21.64
21.47
13.97
-1.02
TMS
O
EtO2C
EtO2C
NTs
2-35b
f1 (ppm)

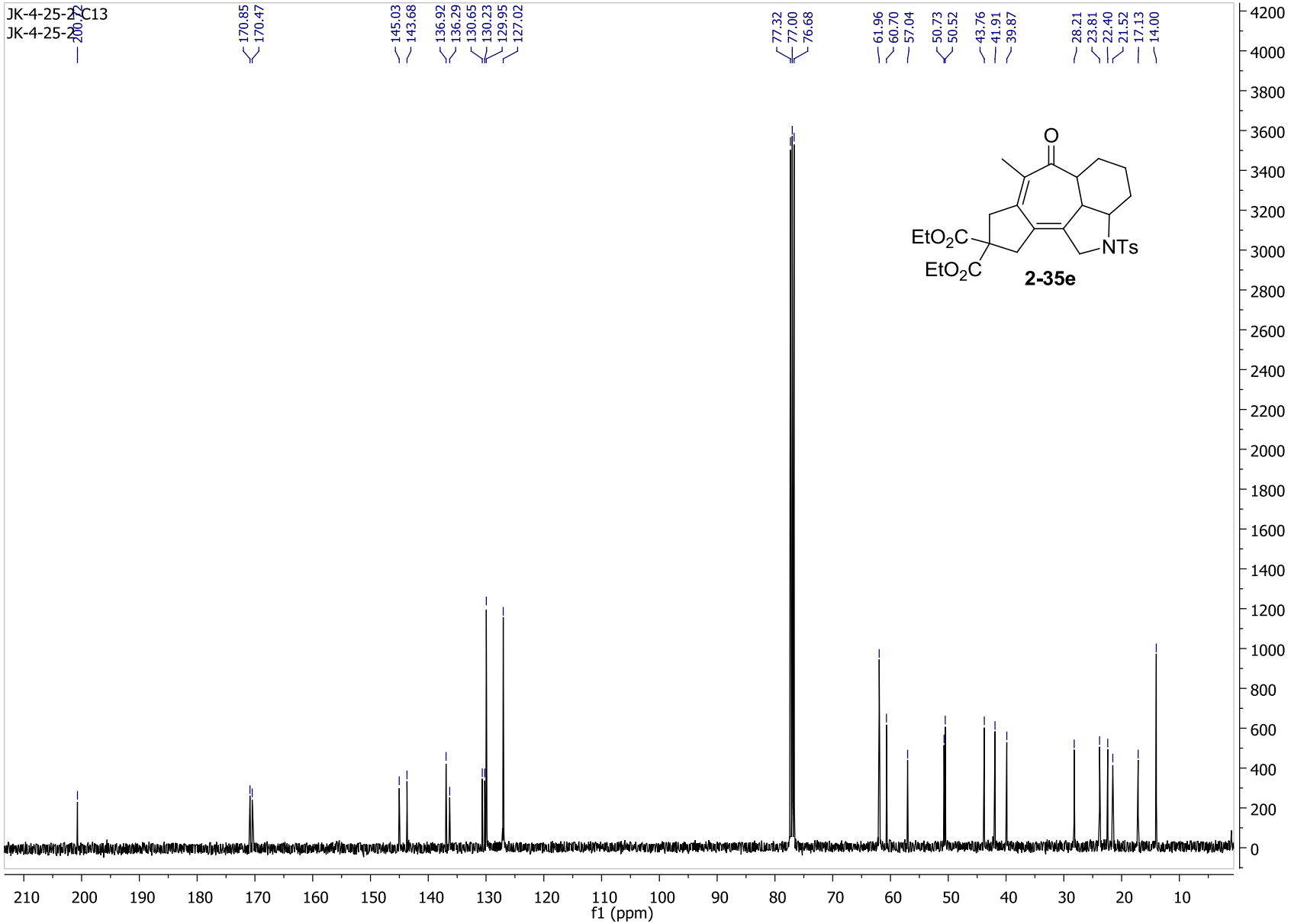

JK-6-31_frac_2-best_H1
JK-6-31_frac_2
Me2PhSi
O
TsN
NTs
2-35c
2.00
9.43
2.25
5.50
1.17
1.10
6.51
1.28
2.35
1.29
1.24
3.58
5.86
f1 (ppm)

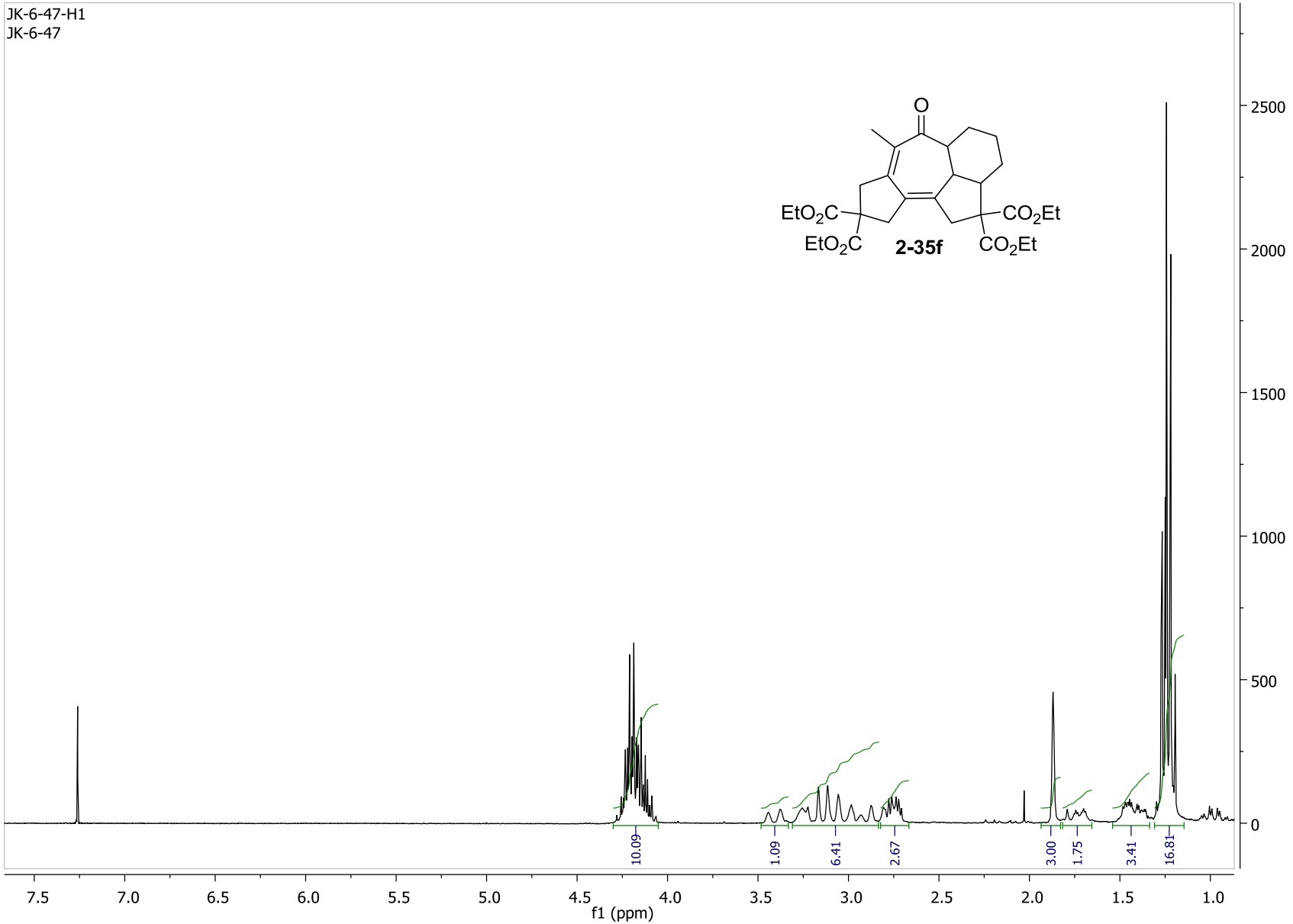

JK-6-31-frac_2-C13
13C OBSERVE
199.98
143.84
143.59
141.34
140.11
136.70
135.59
134.02
133.70
129.86
129.62
128.13
127.15
127.04
77.32
77.00
76.68
67.96
65.83
61.39
58.38
55.44
53.69
50.34
47.00
41.16
36.92
30.12
28.49
25.60
21.60
21.53
15.26
-1.43
-3.11
Me2PhSi
O
TsN
NTs
2-35c
f1 (ppm)

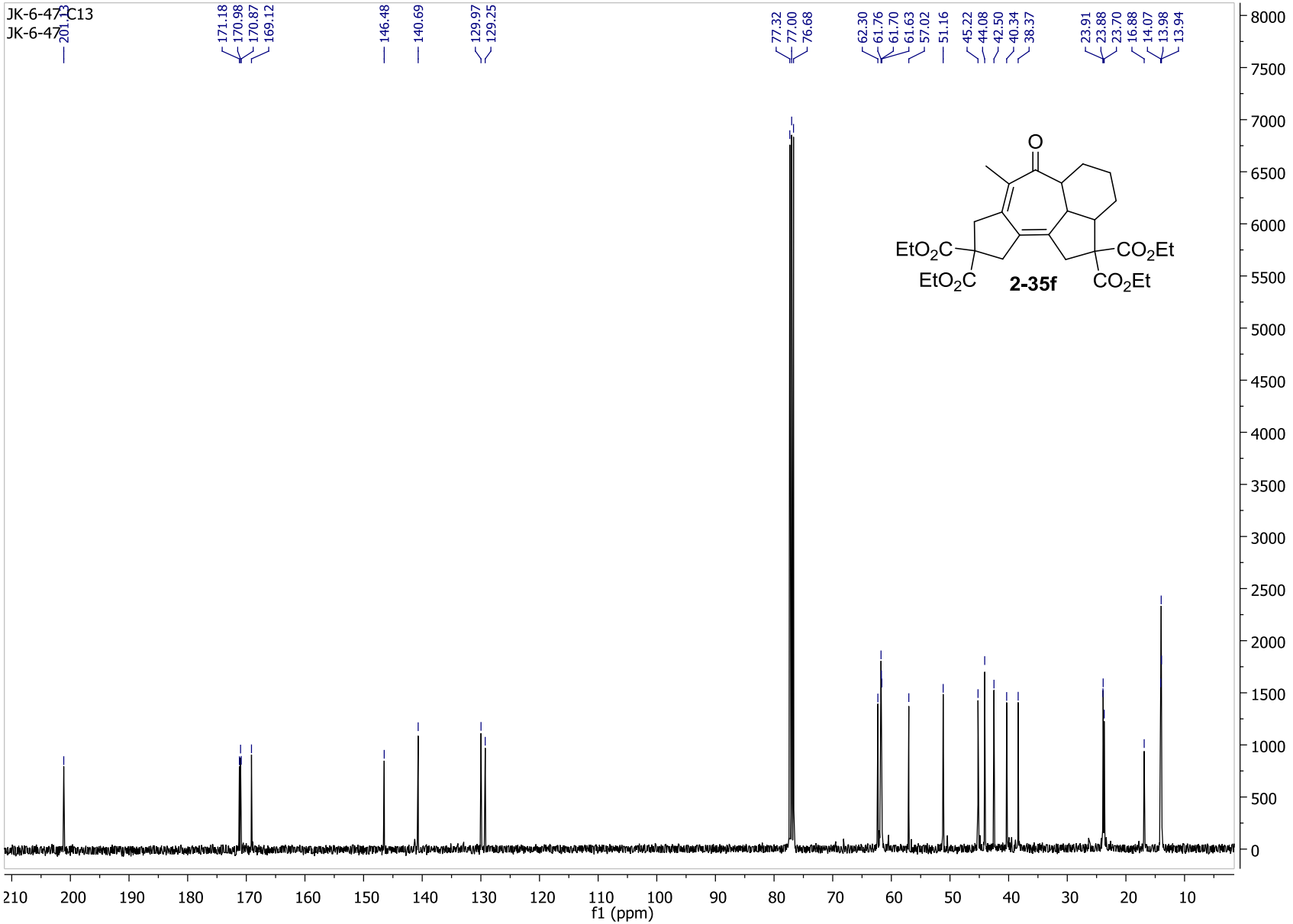

JK-4-49+6-05-frac_2-2-H1
JK-4-49+6-05-frac_2-2
TMS
O
TsN
NTs
2-35d
2.05
2.00
4.11
0.97
2.03
2.07
1.04
1.01
6.27
1.08
2.13
2.36
3.07
9.19
f1 (ppm)

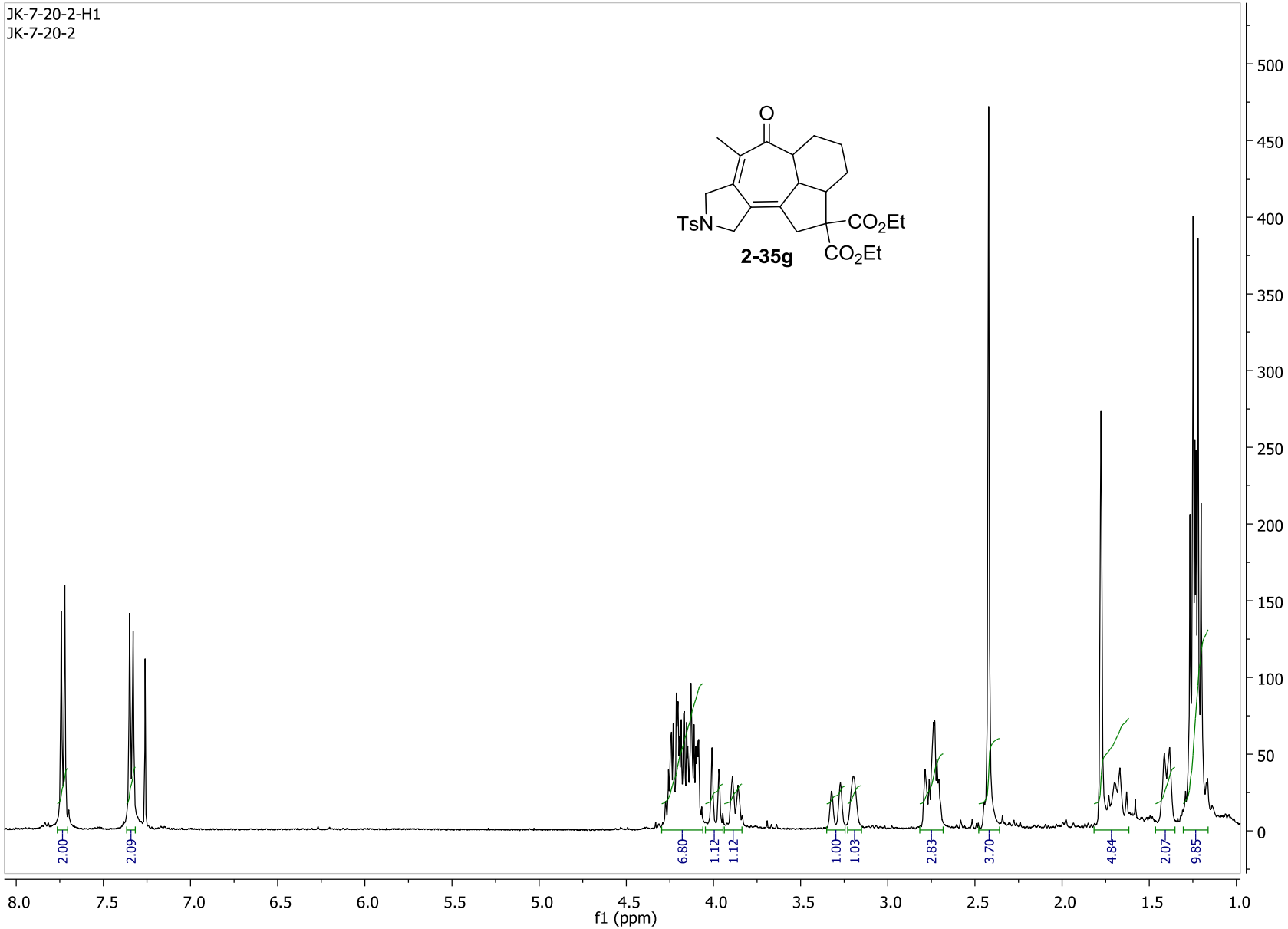

JK-4-49-6-05-frac_2-C13
JK-4-49-6-05-frac_2
199.91
143.95
143.78
141.23
140.68
135.64
134.21
129.94
129.83
127.16
127.11
77.32
77.00
76.68
61.42
58.26
55.17
53.67
50.56
47.08
41.13
36.45
30.13
28.37
21.54
-1.02
O
TMS
TsN
NTs
2-35d
f1 (ppm)

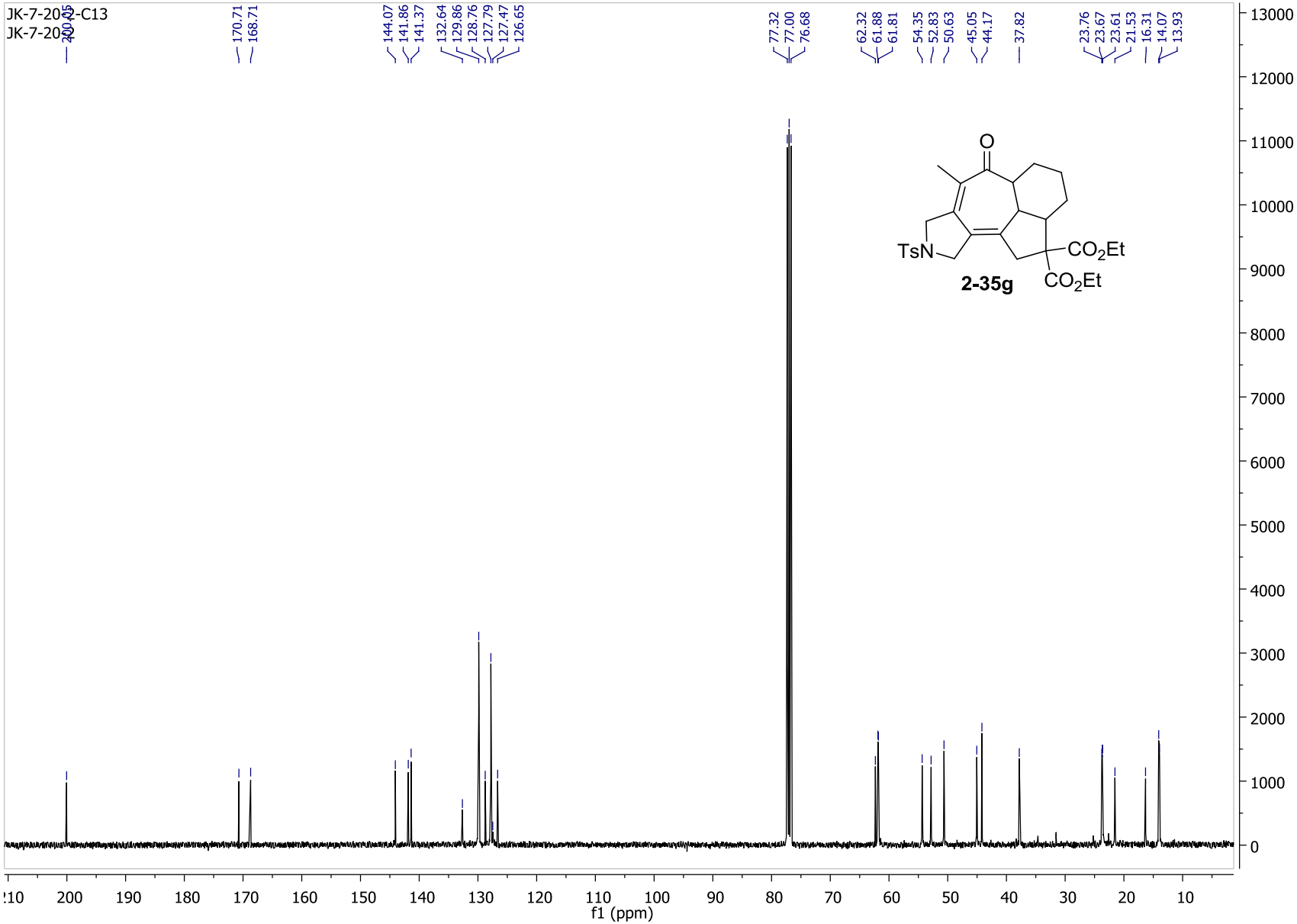

JK-7-18-H1
JK-7-18
O
EtO2C
EtO2C
NTs
2-35e
2.00
2.07
4.97
2.04
1.17
3.32
2.27
1.13
3.46
1.44
3.37
1.93
2.52
9.90
f1 (ppm)

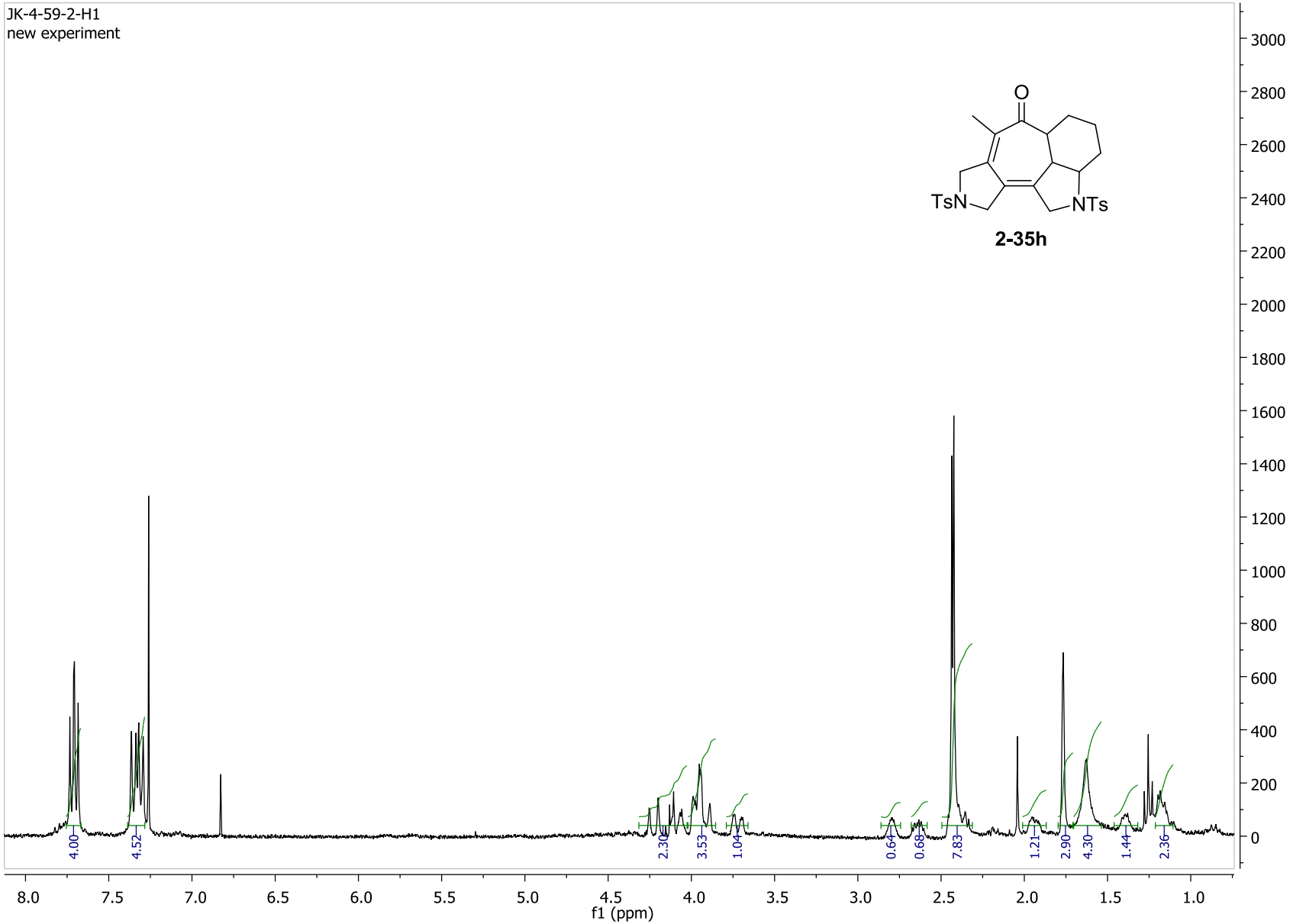

JK-4-25-2-C13
JK-4-25-2
200.72
170.85
170.47
145.03
143.68
136.92
136.29
130.65
130.23
129.95
127.02
77.32
77.00
76.68
61.96
60.70
57.04
50.73
50.52
43.76
41.91
39.87
28.21
23.81
22.40
21.52
17.13
14.00
O
EtO2C
EtO2C
NTs
2-35e
f1 (ppm)

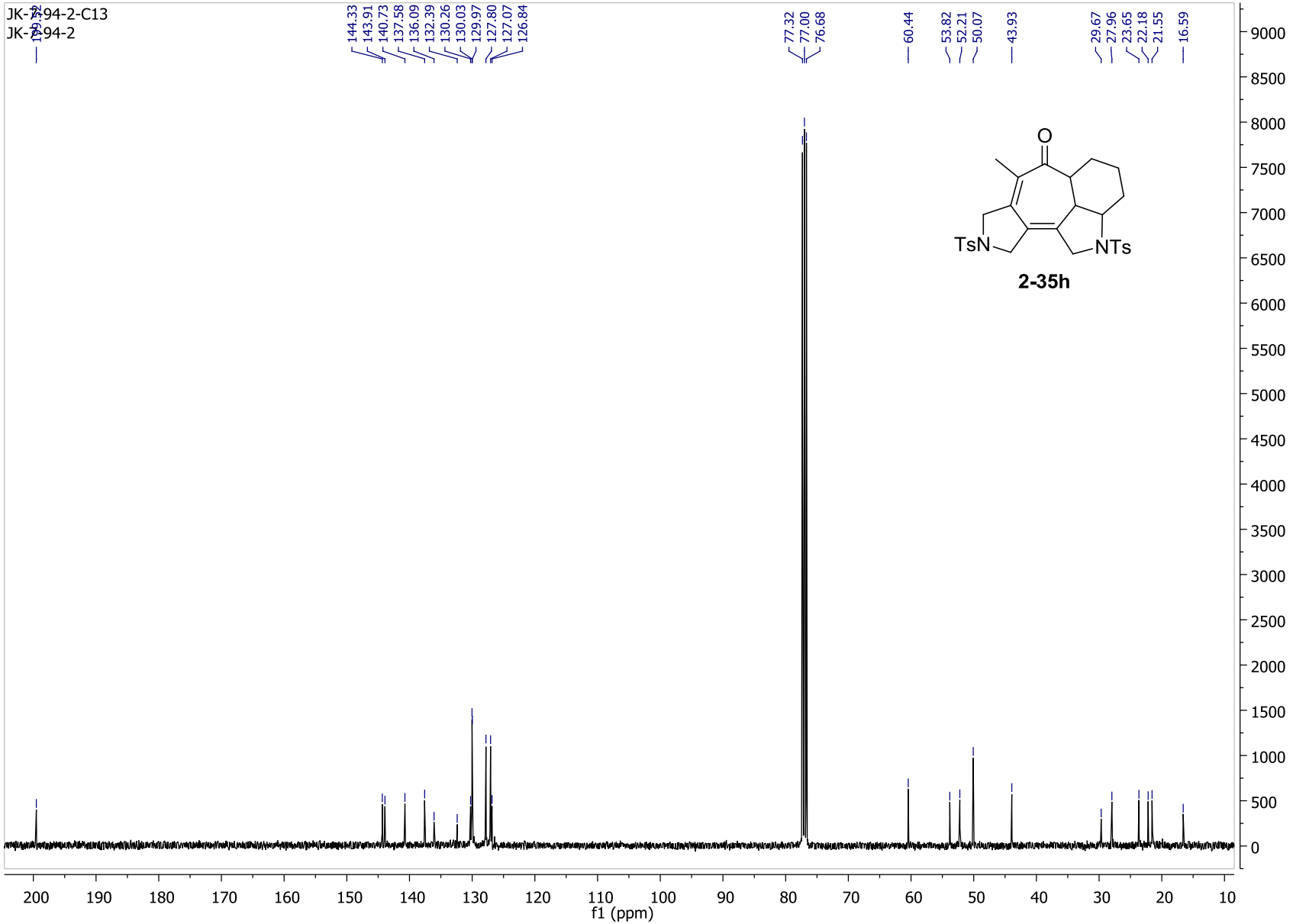

JK-6-47-H1
JK-6-47
O
EtO2C
CO2Et
EtO2C
CO2Et
2-35f
2500
2000
1500
1000
500
0
10.09
1.09
6.41
2.67
3.00
1.75
3.41
16.81
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

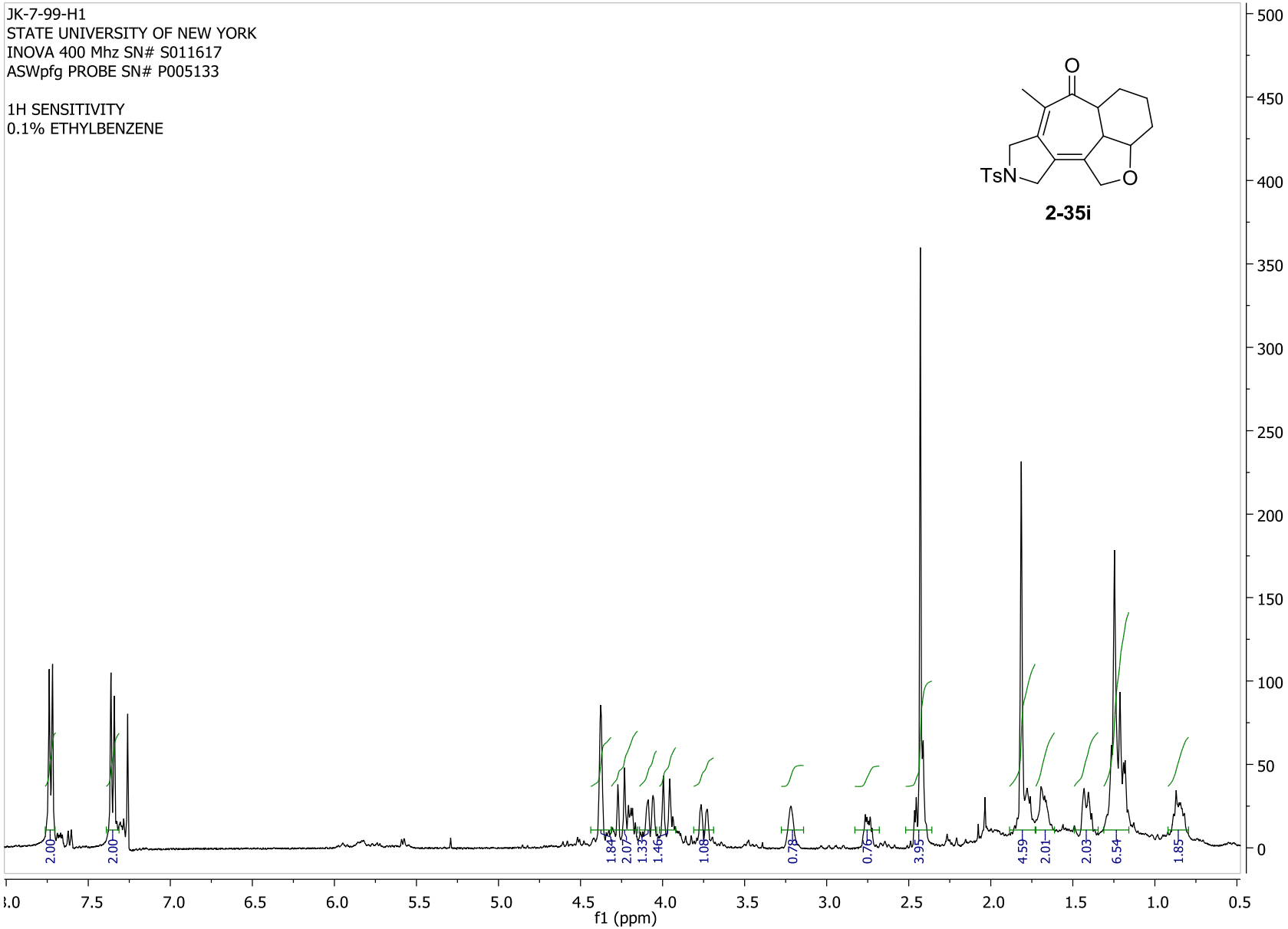

JK-6-47-C13
JK-6-47
201.23
171.18
170.98
170.87
169.12
146.48
140.69
129.97
129.25
77.32
77.00
76.68
62.30
61.76
61.70
61.63
57.02
51.16
45.22
44.08
42.50
40.34
38.37
23.91
23.88
23.70
16.88
14.07
13.98
13.94
O
EtO2C
EtO2C
CO2Et
CO2Et
2-35f
f1 (ppm)

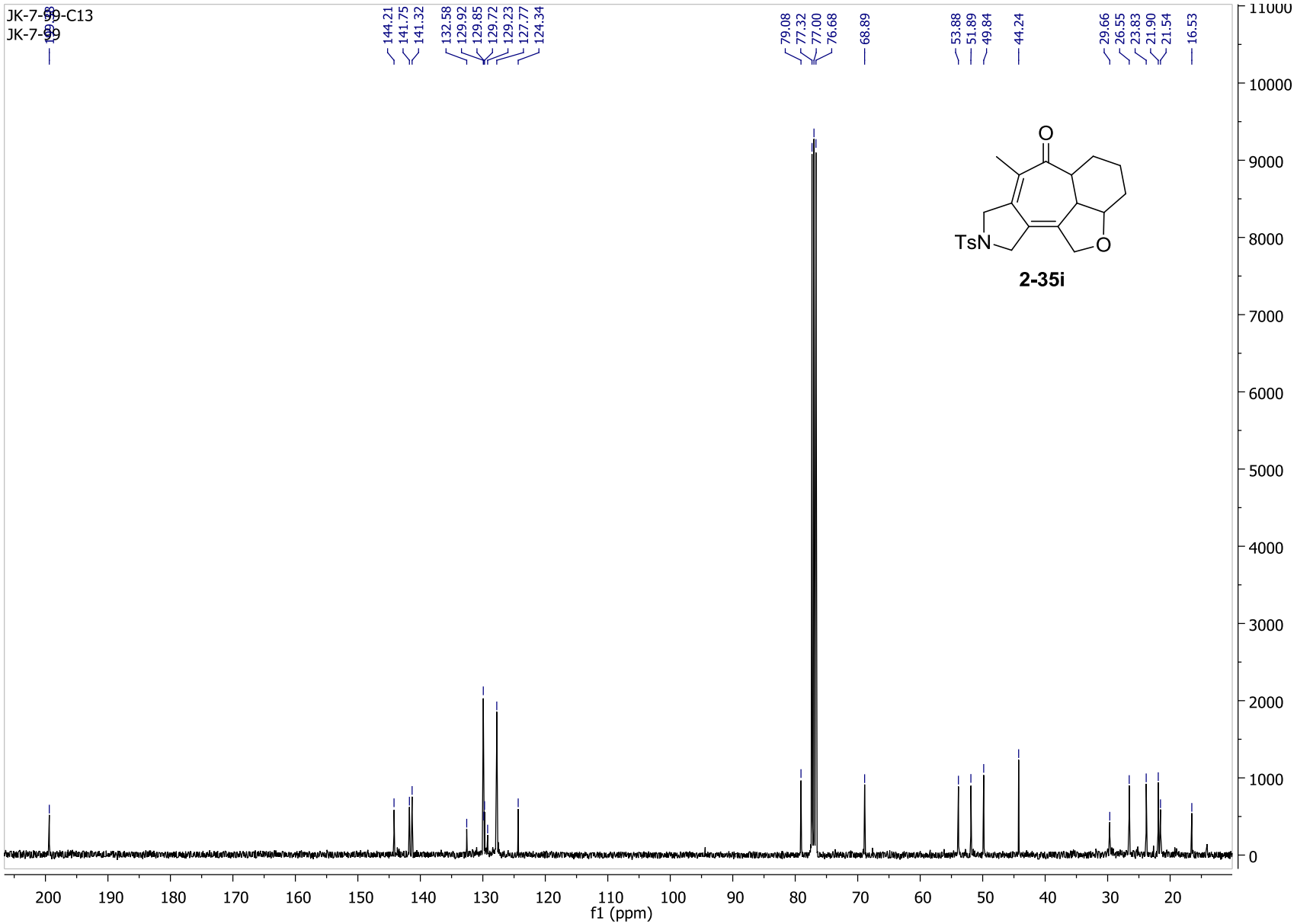

JK-7-20-2-H1
JK-7-20-2
O
TsN
CO2Et
CO2Et
2-35g
2.00
2.09
6.80
1.12
1.12
1.00
1.03
2.83
3.70
4.84
2.07
9.85
f1 (ppm)

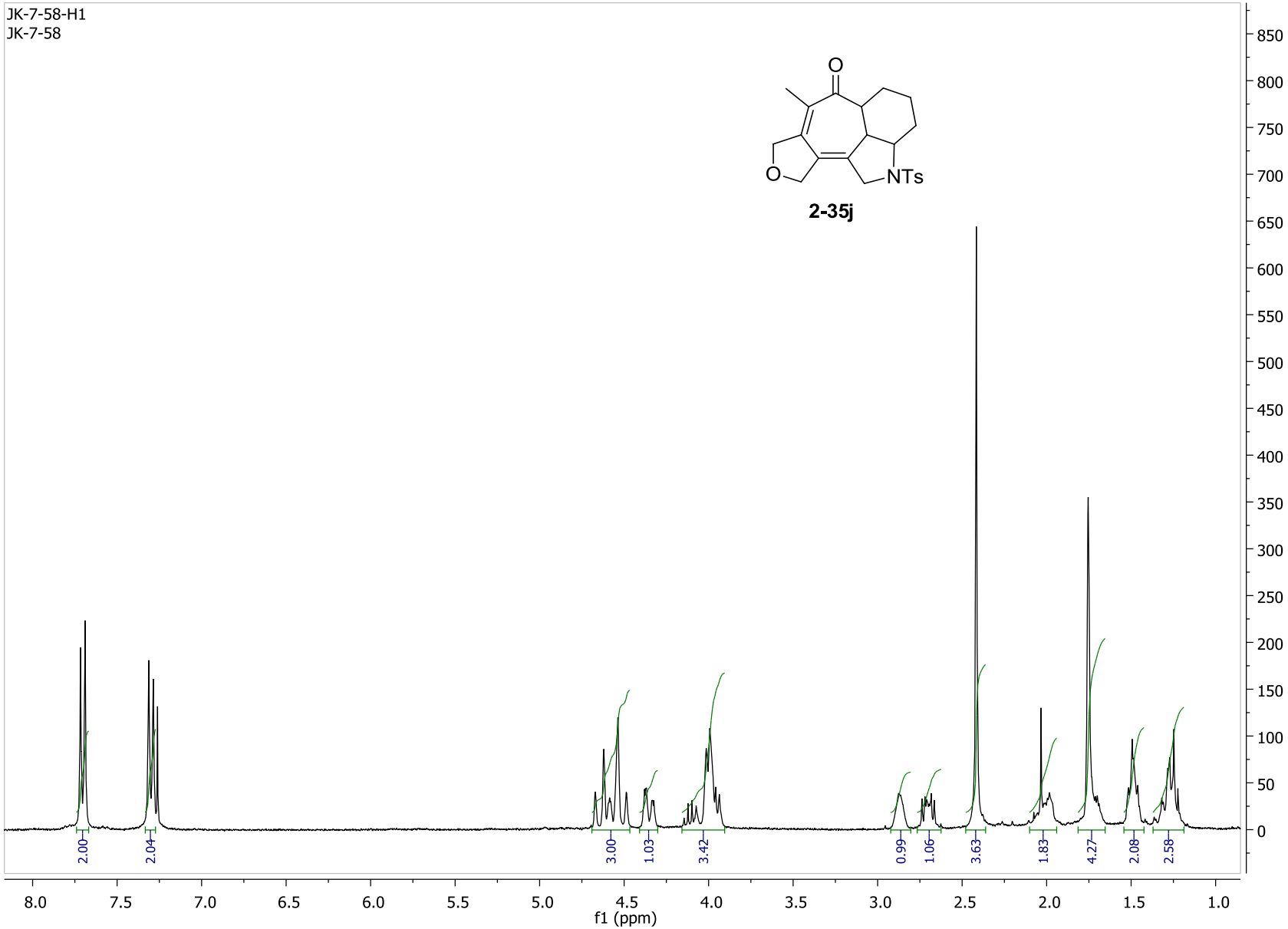

JK-7-202-C13
JK-7-202
200.05
170.71
168.71
144.07
141.86
141.37
132.64
129.86
128.76
127.79
127.47
126.65
77.32
77.00
76.68
62.32
61.88
61.81
54.35
52.83
50.63
45.05
44.17
37.82
23.76
23.67
23.61
21.53
16.31
14.07
13.93
O
TsN
CO2Et
CO2Et
2-35g
f1 (ppm)

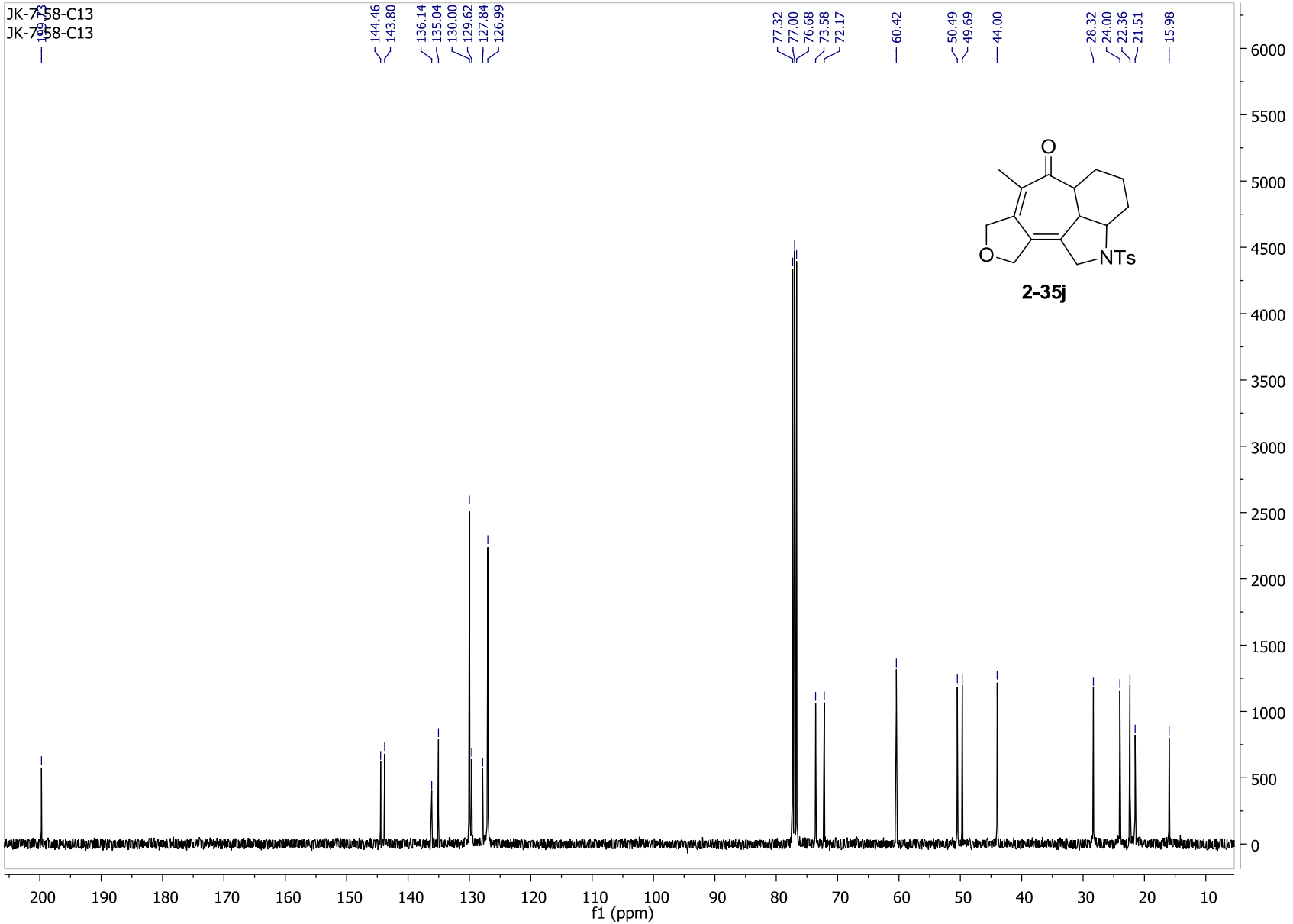

JK-4-59-2-H1
new experiment
O
TsN
NTs
2-35h
4.00
4.52
2.30
3.53
1.04
0.64
0.68
7.83
1.21
2.90
4.30
1.44
2.36
f1 (ppm)

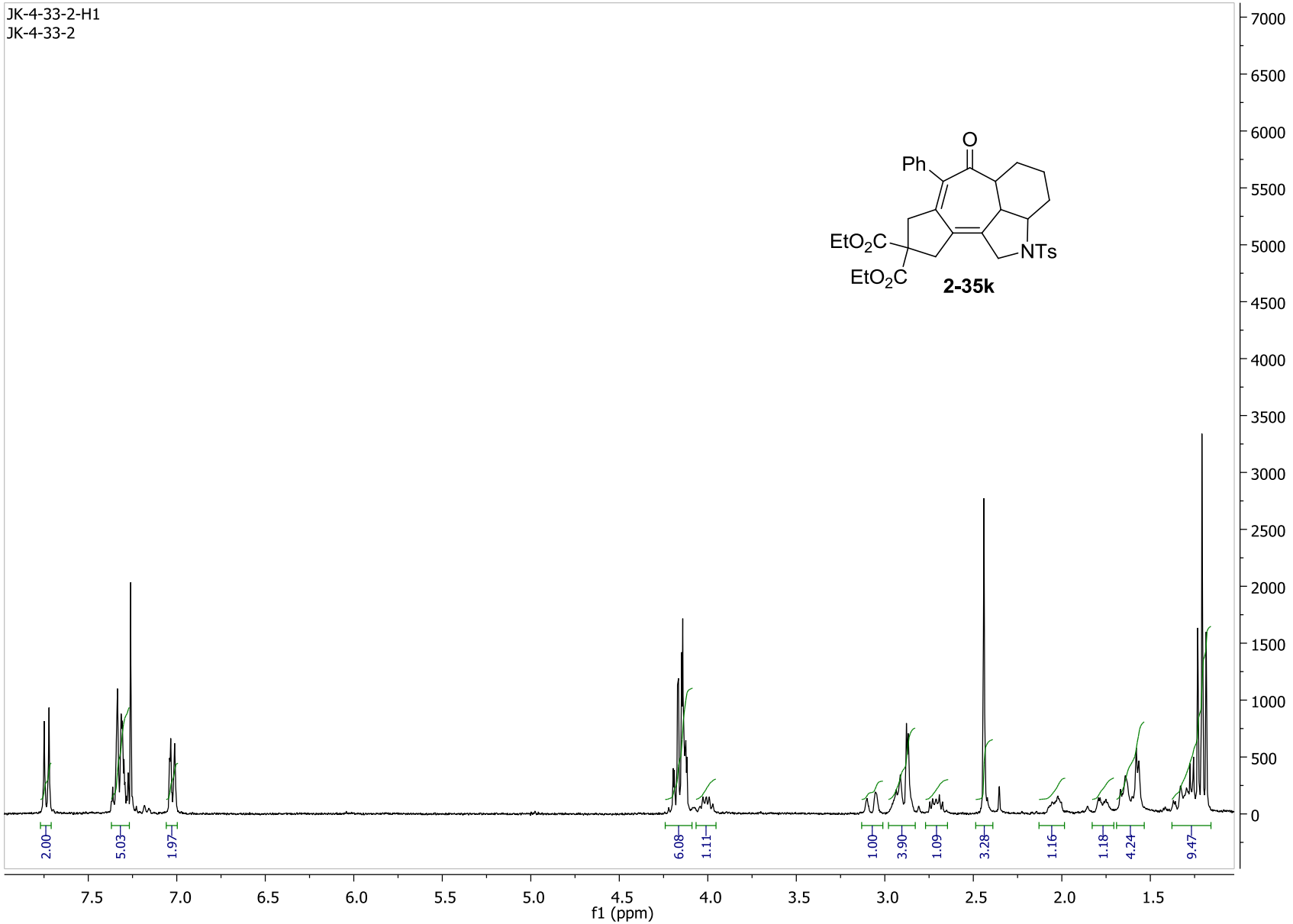

JK-2-94-2-C13
JK-2-94-2
199.29
144.33
143.91
140.73
137.58
136.09
132.39
130.26
130.03
129.97
127.80
127.07
126.84
77.32
77.00
76.68
60.44
53.82
52.21
50.07
43.93
29.67
27.96
23.65
22.18
21.55
16.59
O
TsN
NTs
2-35h
f1 (ppm)

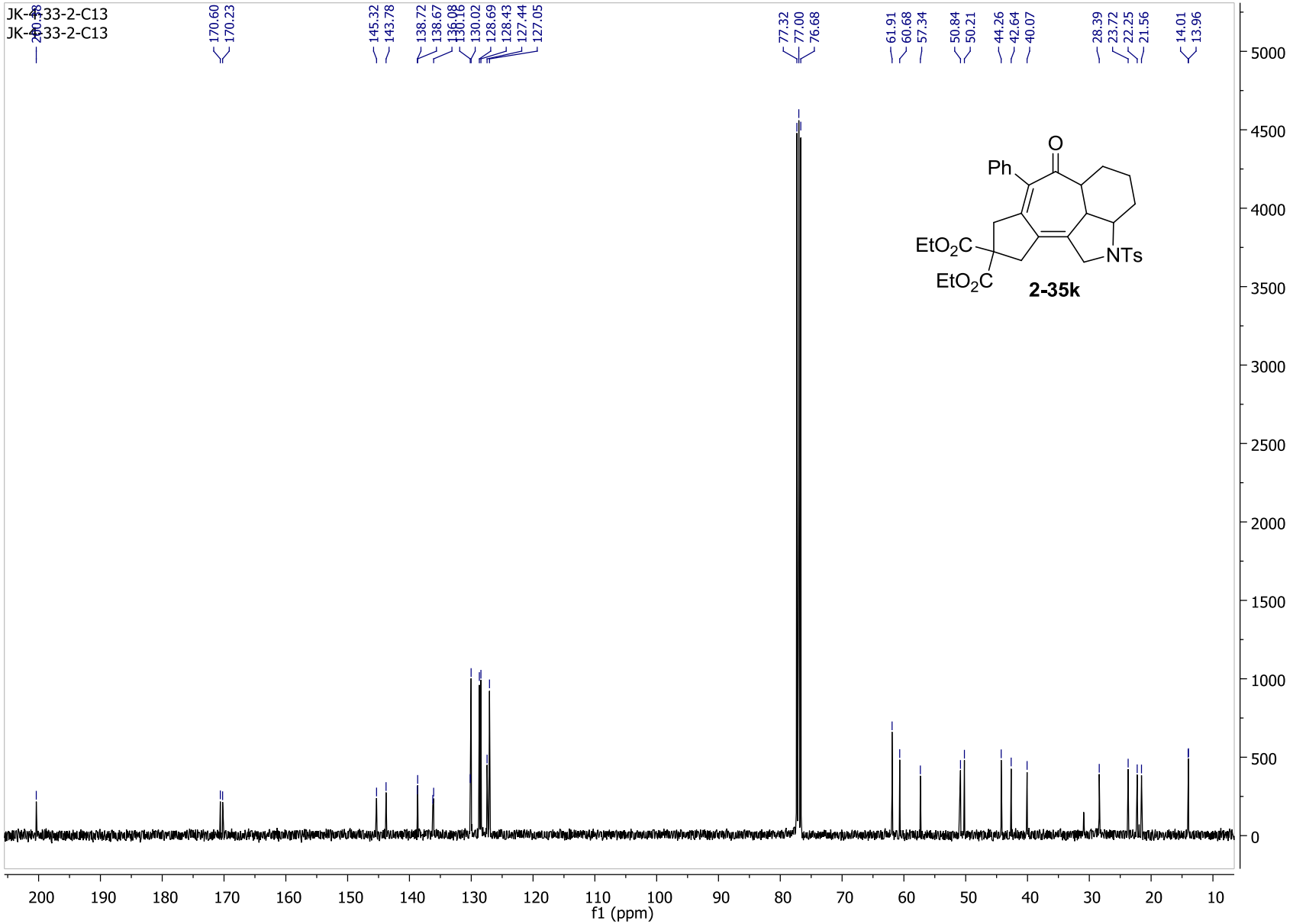

JK-7-99-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
O
TsN
O
2-35i
2.00
2.00
1.84
2.07
1.33
1.46
1.08
0.79
0.76
3.95
4.59
2.01
2.03
6.54
1.85
f1 (ppm)

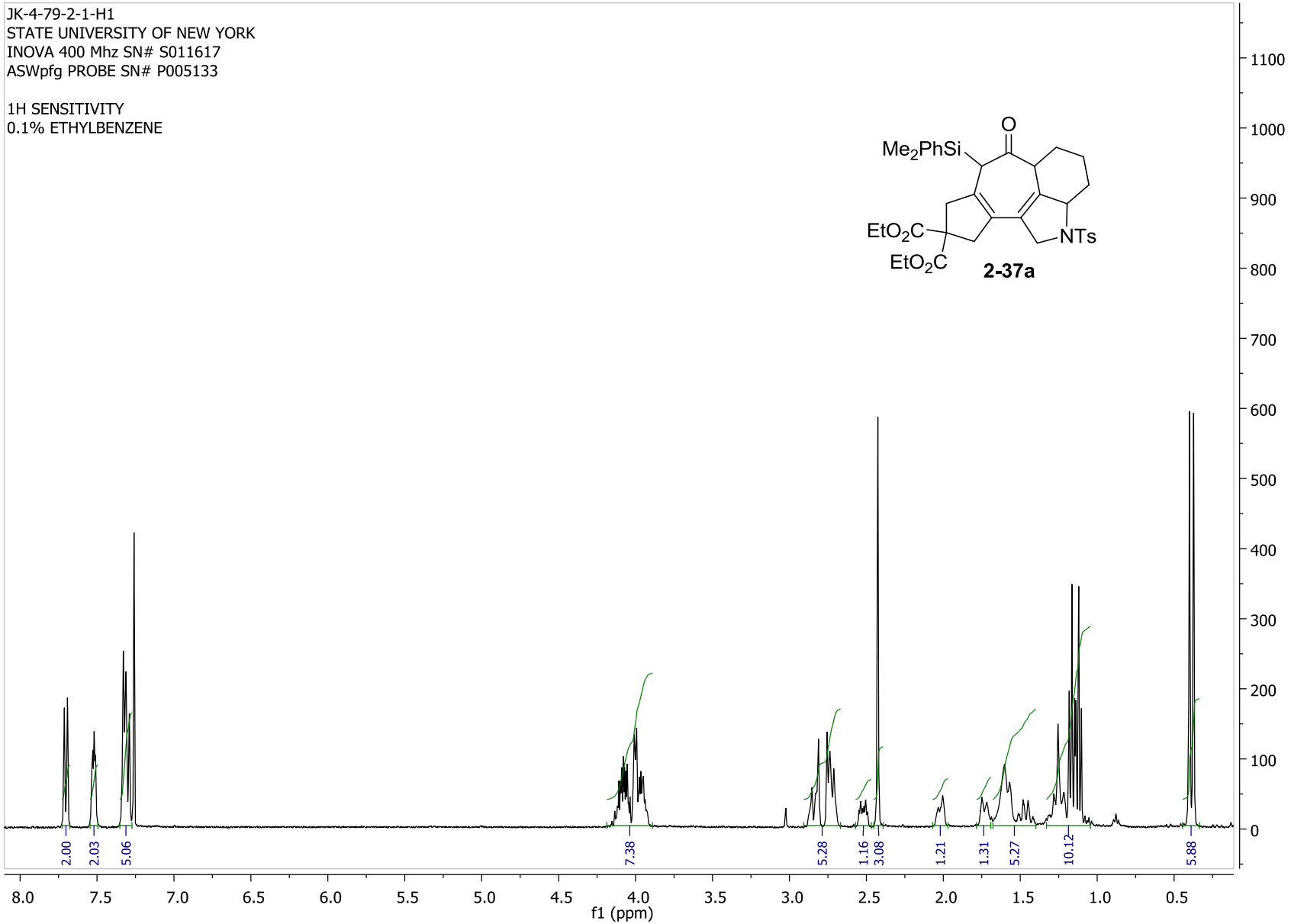

JK-7-99-C13
JK-7-99
144.21
141.75
141.32
132.58
129.92
129.85
129.72
129.23
127.77
124.34
79.08
77.32
77.00
76.68
68.89
53.88
51.89
49.84
44.24
29.66
26.55
23.83
21.90
21.54
16.53
TsN
O
O
2-35i
f1 (ppm)

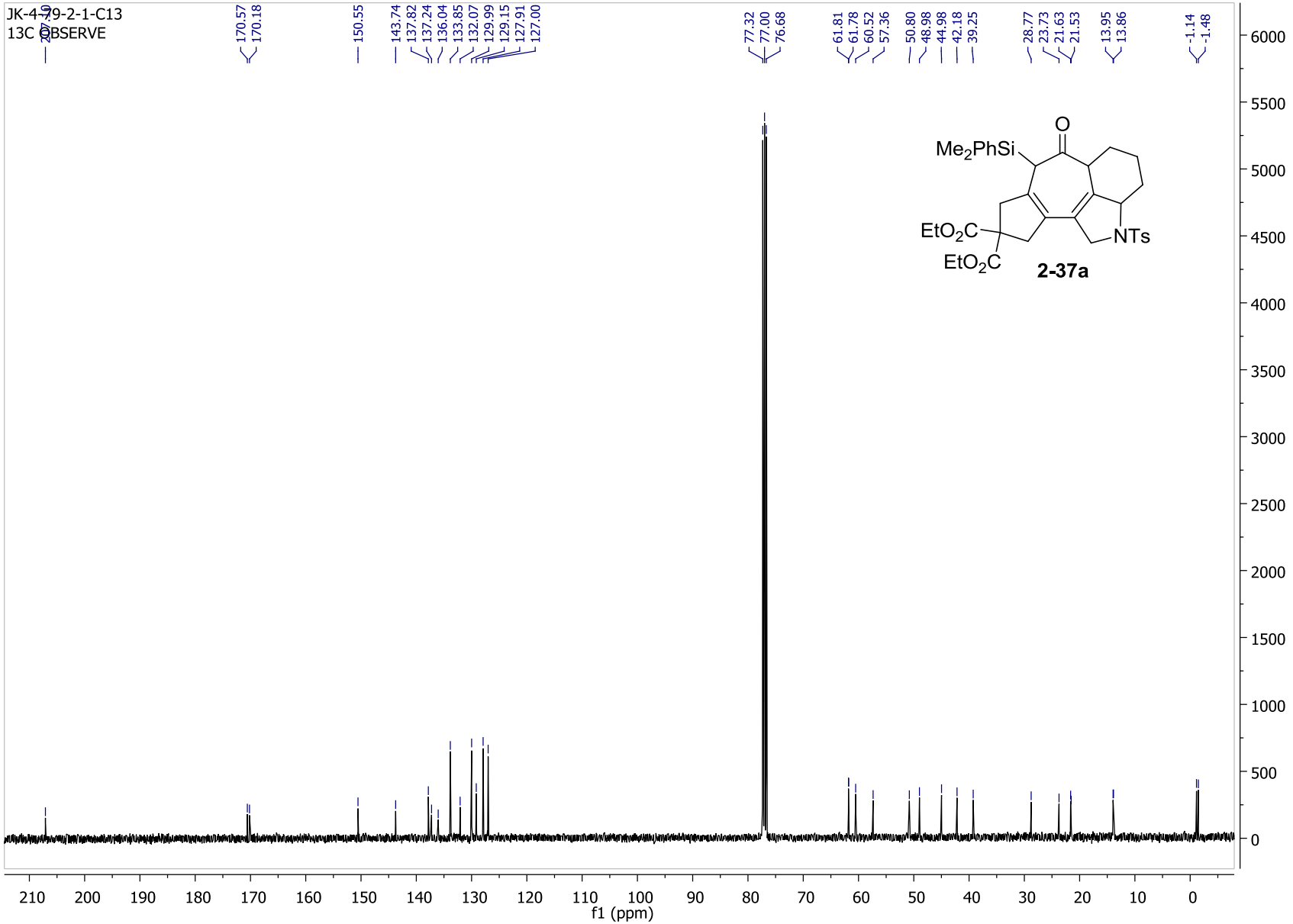

JK-7-58-H1
JK-7-58
O
O
NTs
2-35j
2.00
2.04
3.00
1.03
3.42
0.99
1.06
3.63
1.83
4.27
2.08
2.58
f1 (ppm)

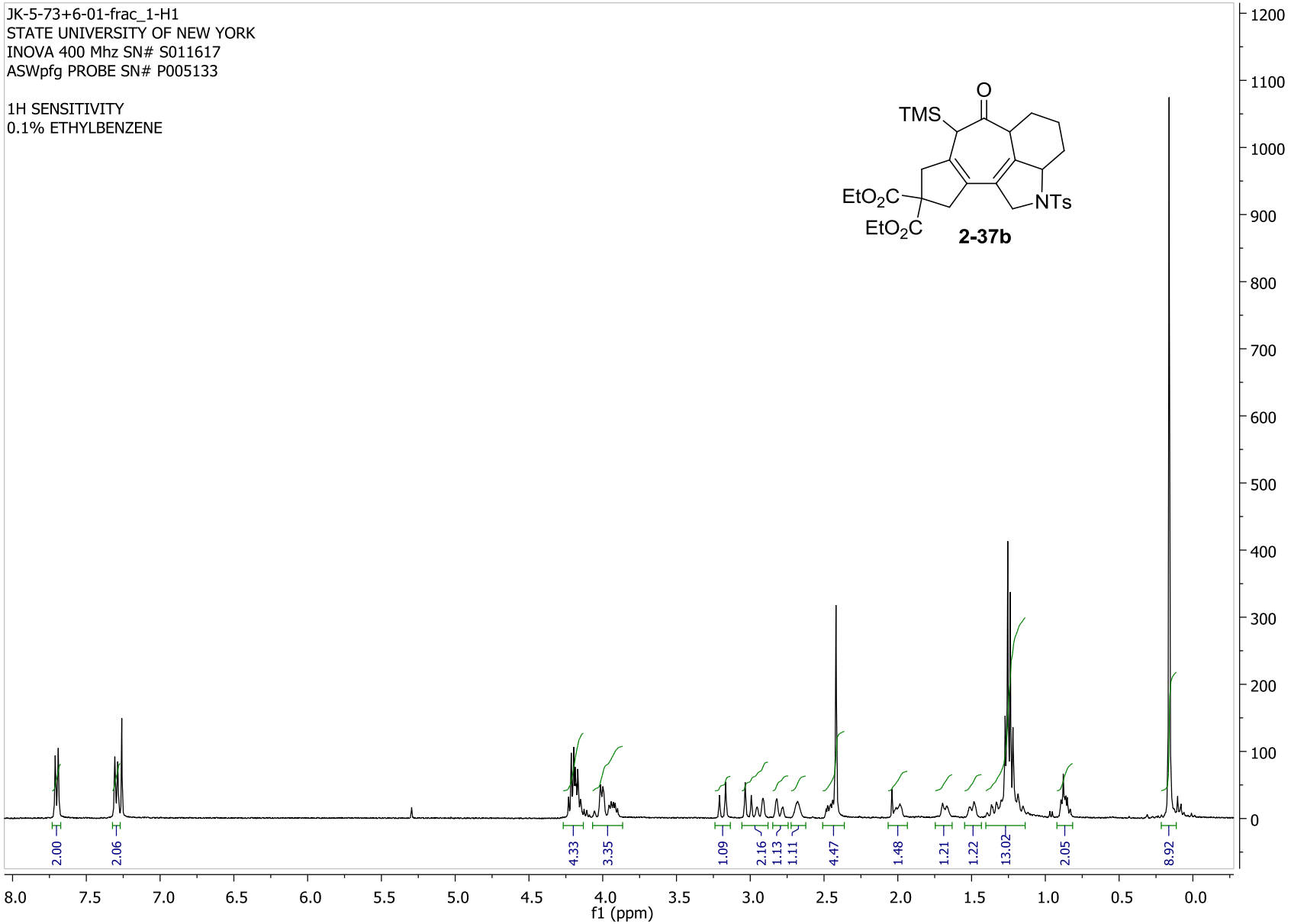

JK-7-58-C13
JK-7-58-C13
144.46
143.80
136.14
135.04
130.00
129.62
127.84
126.99
77.32
77.00
76.68
73.58
72.17
60.42
50.49
49.69
44.00
28.32
24.00
22.36
21.51
15.98
O
O
NTs
2-35j
f1 (ppm)

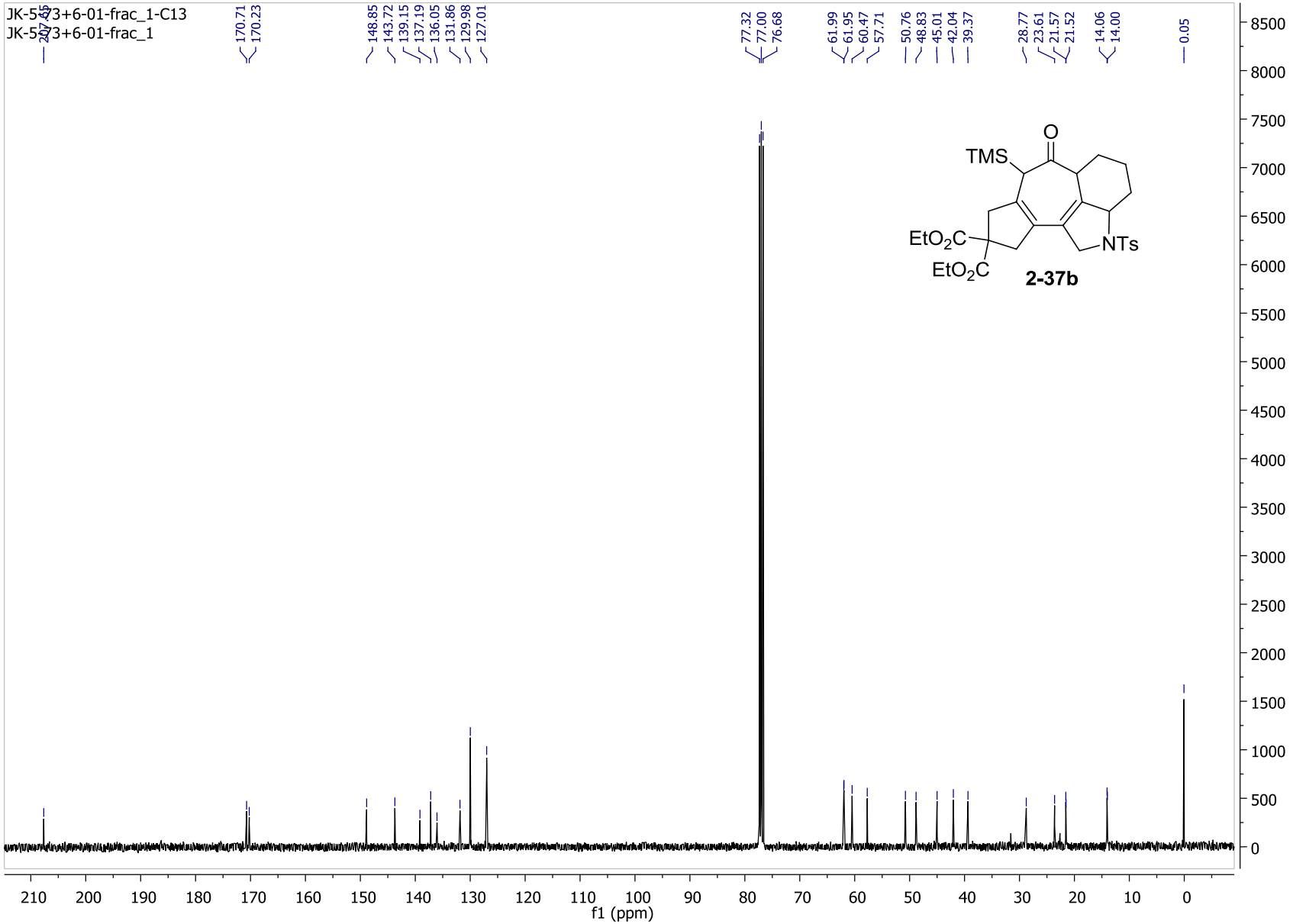

JK-4-33-2-H1
JK-4-33-2
O
Ph
EtO2C
EtO2C
NTs
2-35k
2.00
5.03
1.97
6.08
1.11
1.00
3.90
1.09
3.28
1.16
1.18
4.24
9.47
f1 (ppm)

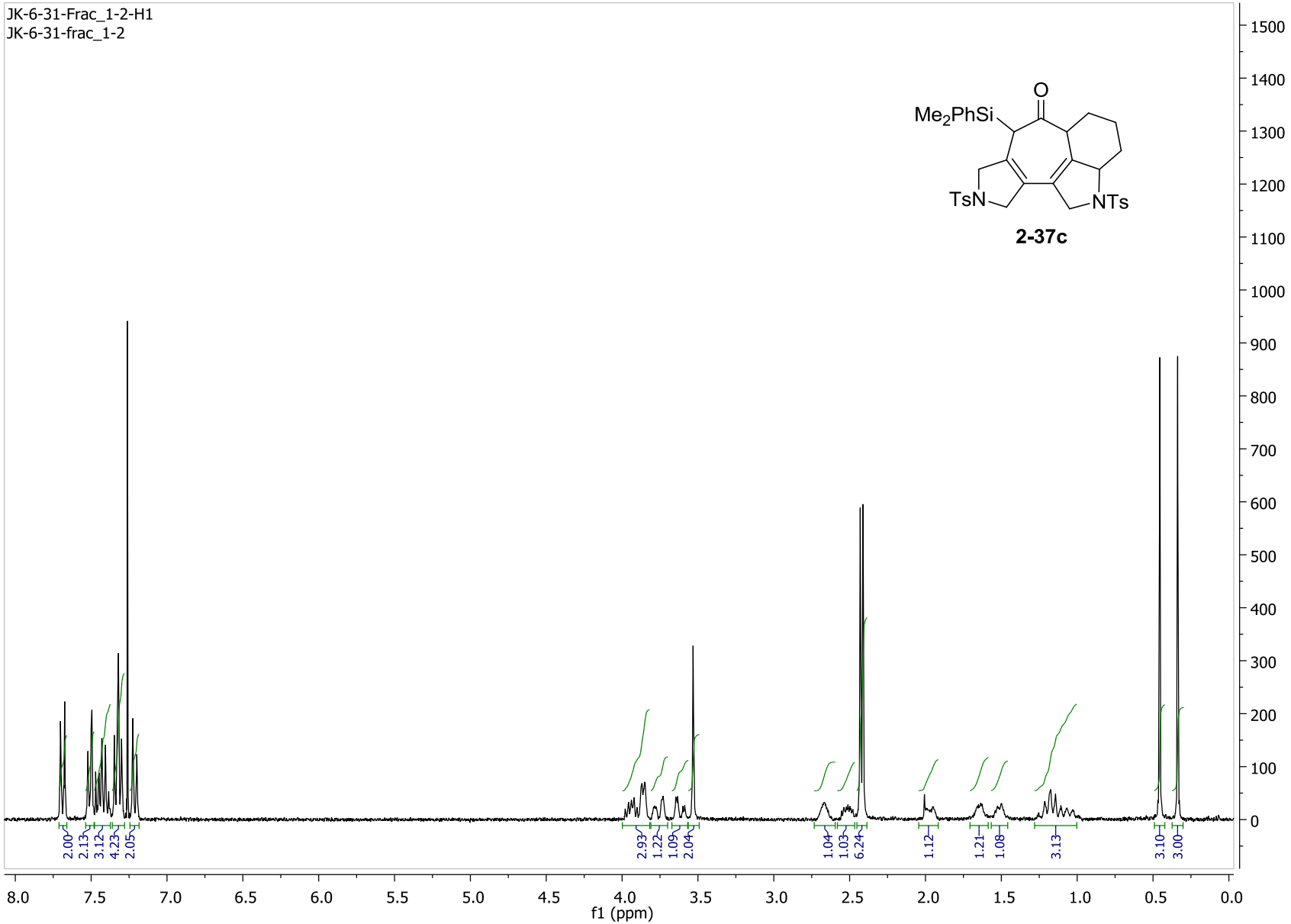

JK-4-33-2-C13
JK-4-33-2-C13
170.60
170.23
145.32
143.78
138.72
138.67
136.08
136.16
130.02
128.69
128.43
127.44
127.05
77.32
77.00
76.68
61.91
60.68
57.34
50.84
50.21
44.26
42.64
40.07
28.39
23.72
22.25
21.56
14.01
13.96
O
Ph
EtO2C
EtO2C
NTs
2-35k
f1 (ppm)

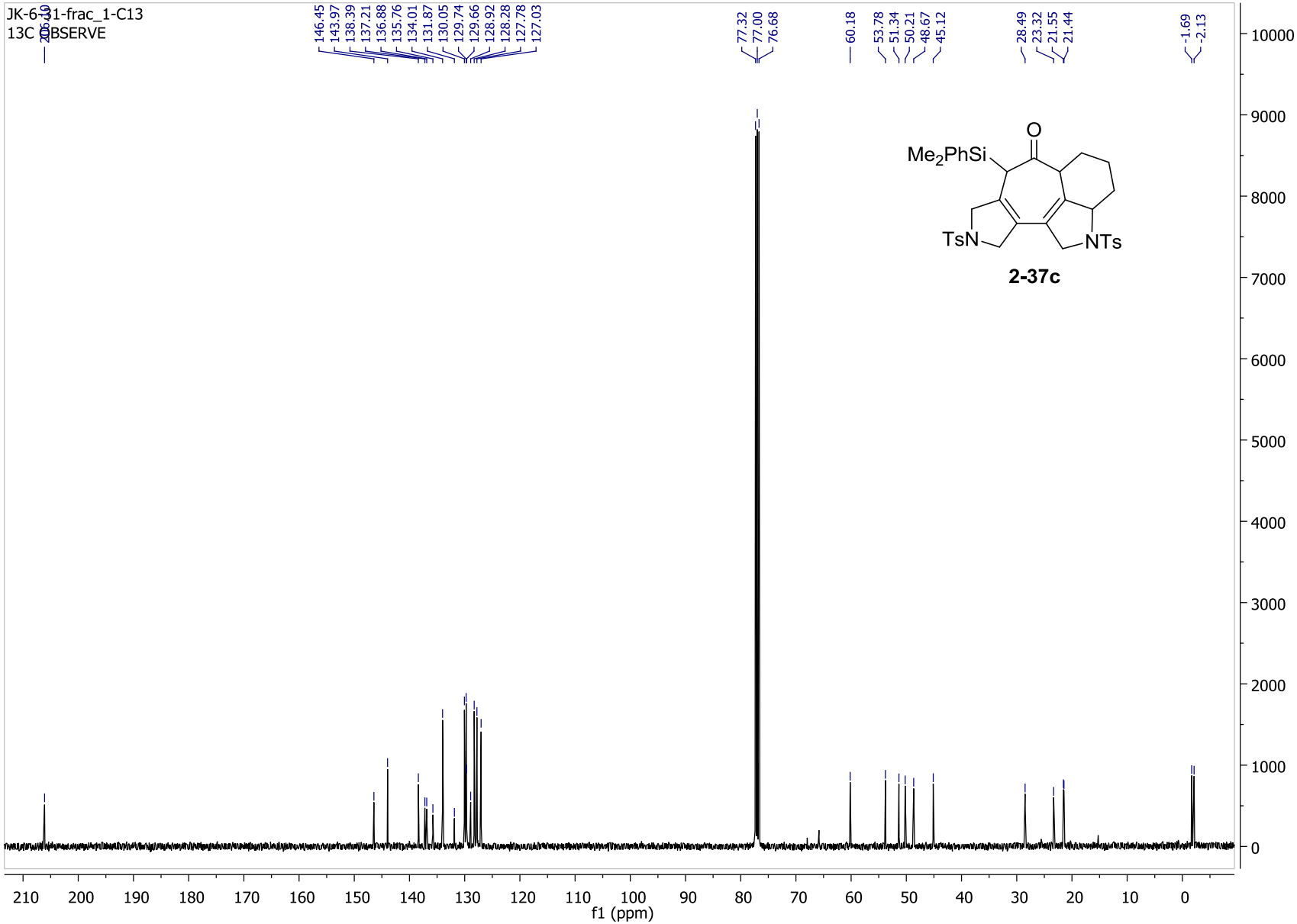

JK-4-79-2-1-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Me2PhSi
O
EtO2C
EtO2C
NTs
2-37a
2.00
2.03
5.06
7.38
5.28
1.16
3.08
1.21
1.31
5.27
10.12
5.88
f1 (ppm)

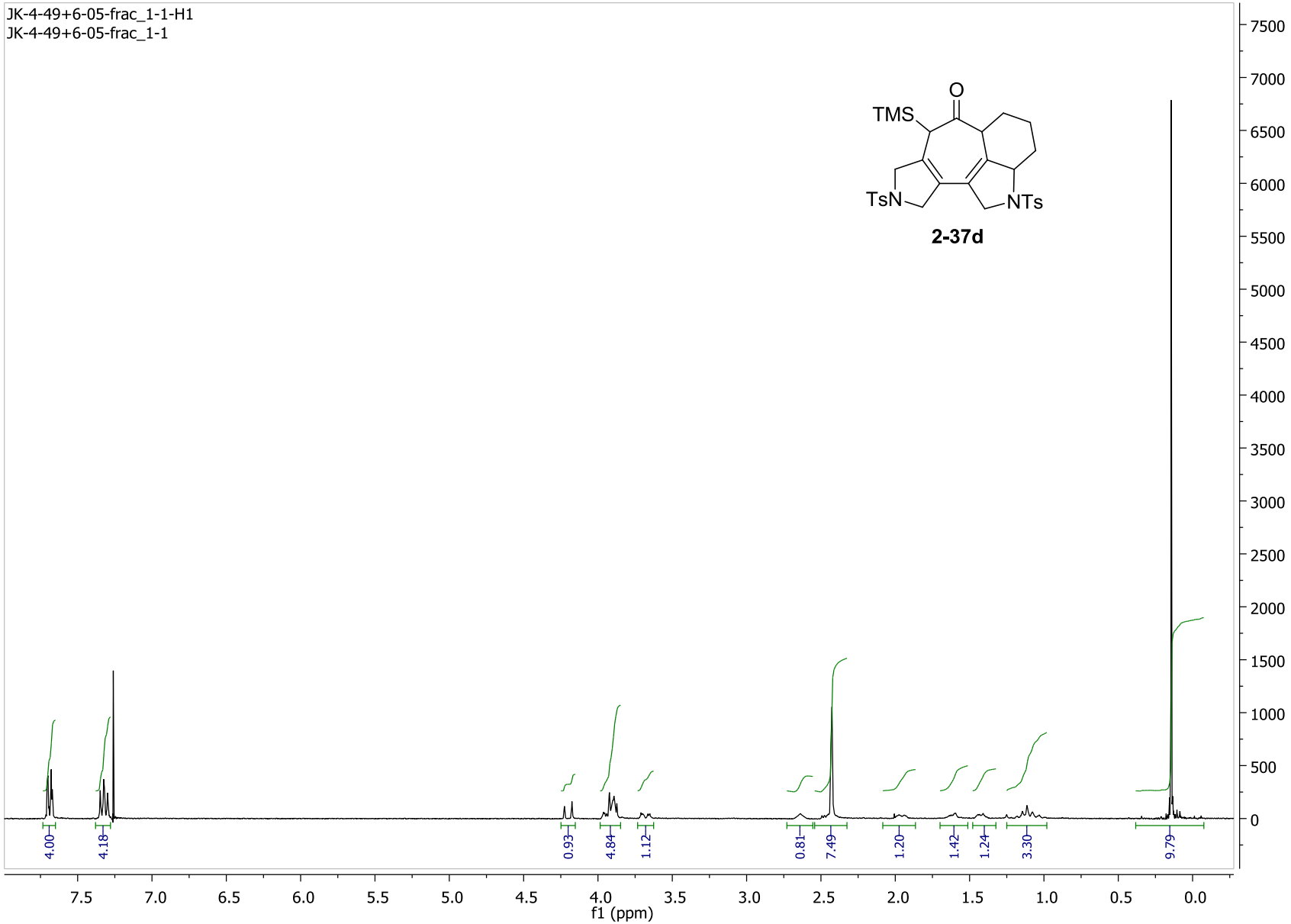

JK-4-79-2-1-C13
13C OBSERVE
170.57
170.18
150.55
143.74
137.82
137.24
136.04
133.85
132.07
129.99
129.15
127.91
127.00
77.32
77.00
76.68
61.81
61.78
60.52
57.36
50.80
48.98
44.98
42.18
39.25
28.77
23.73
21.63
21.53
13.95
13.86
-1.14
-1.48
Me2PhSi
O
EtO2C
EtO2C
NTs
2-37a
f1 (ppm)

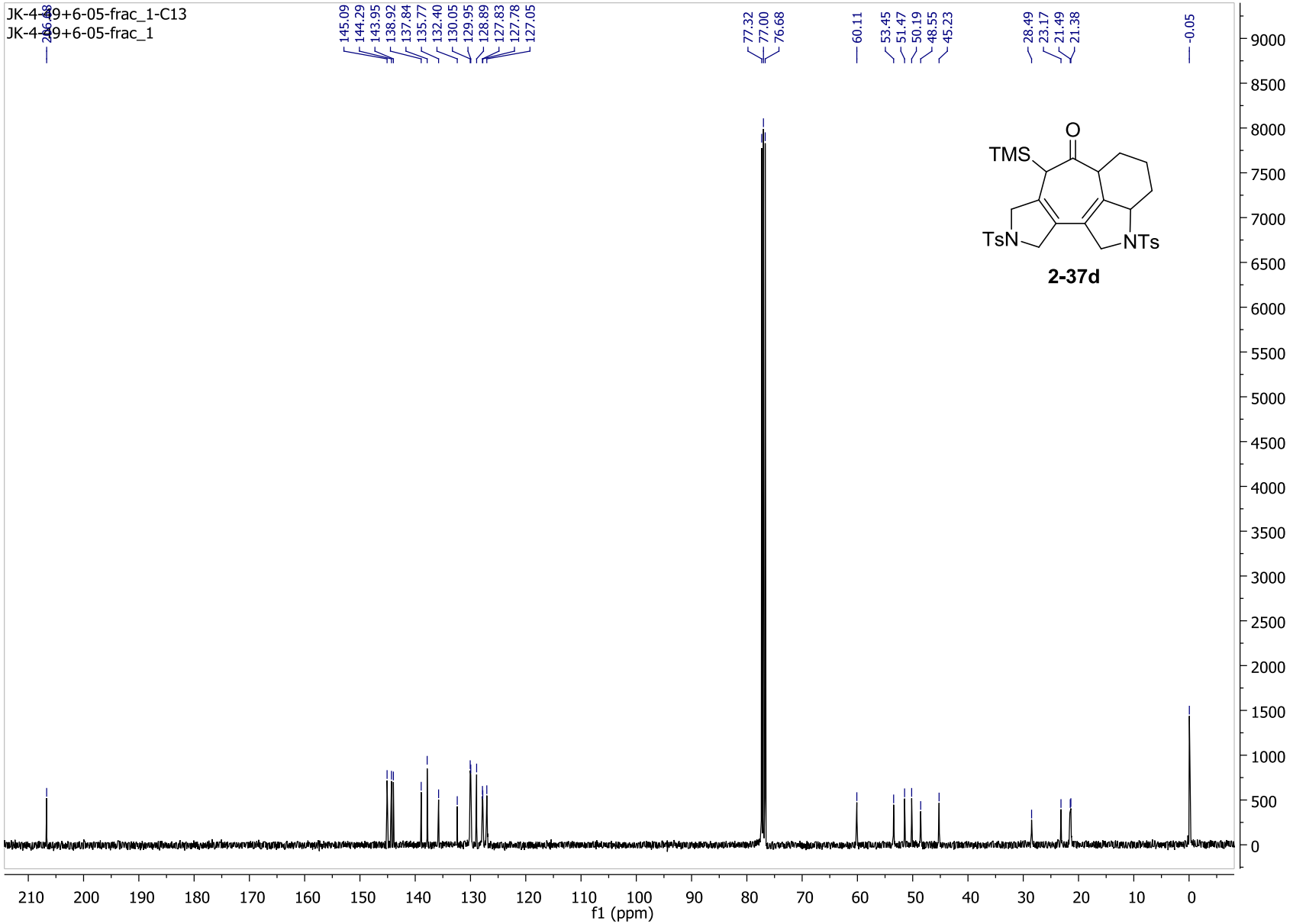

JK-5-73+6-01-frac_1-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
TMS
O
EtO2C
EtO2C
NTs
2-37b
2.00
2.06
4.33
3.35
1.09
2.16
1.13
1.11
4.47
1.48
1.21
1.22
13.02
2.05
8.92
f1 (ppm)

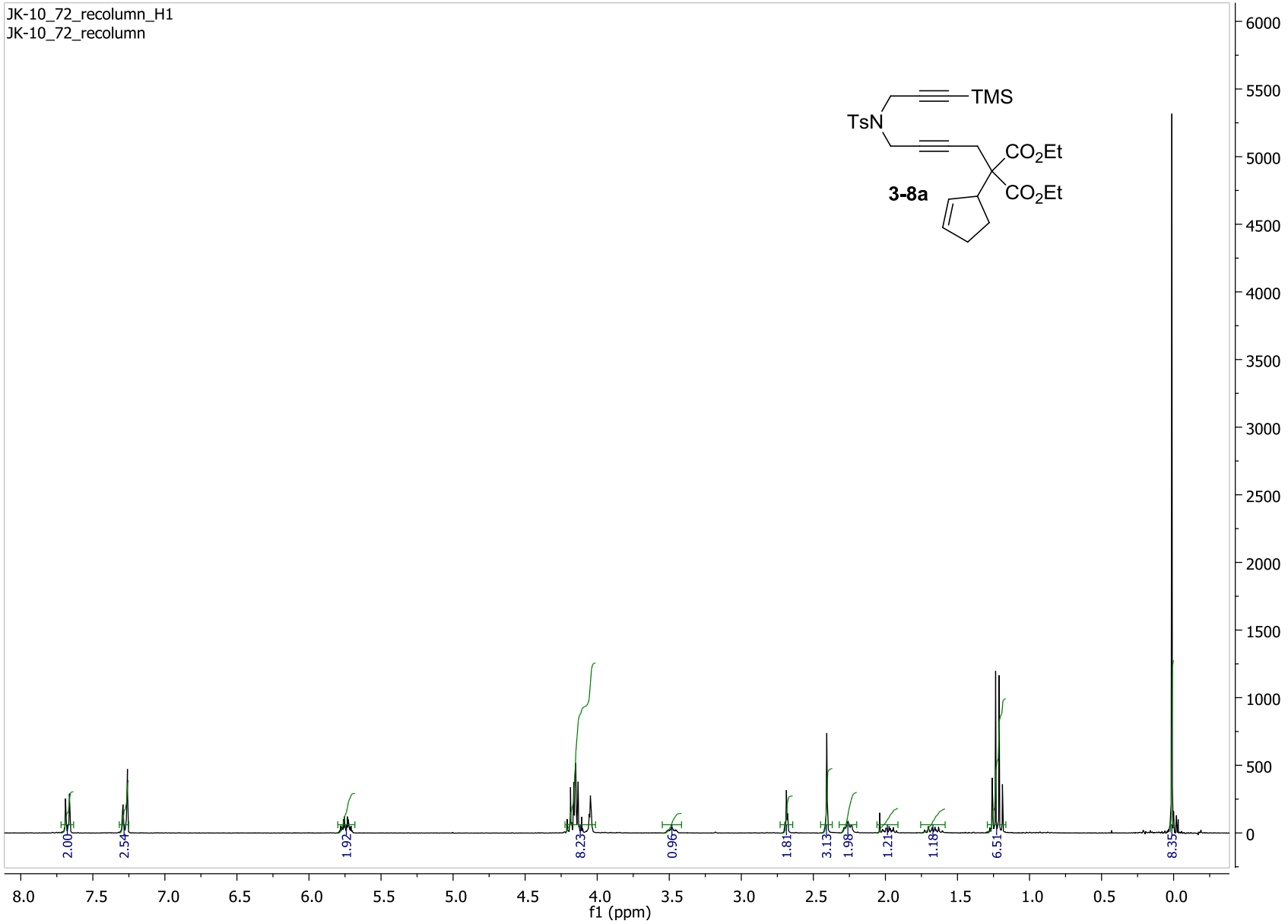

JK-5-73+6-01-frac_1-C13
JK-5-73+6-01-frac_1
170.71
170.23
148.85
143.72
139.15
137.19
136.05
131.86
129.98
127.01
77.32
77.00
76.68
61.99
61.95
60.47
57.71
50.76
48.83
45.01
42.04
39.37
28.77
23.61
21.57
21.52
14.06
14.00
0.05
TMS
O
EtO2C
EtO2C
NTs
2-37b
f1 (ppm)

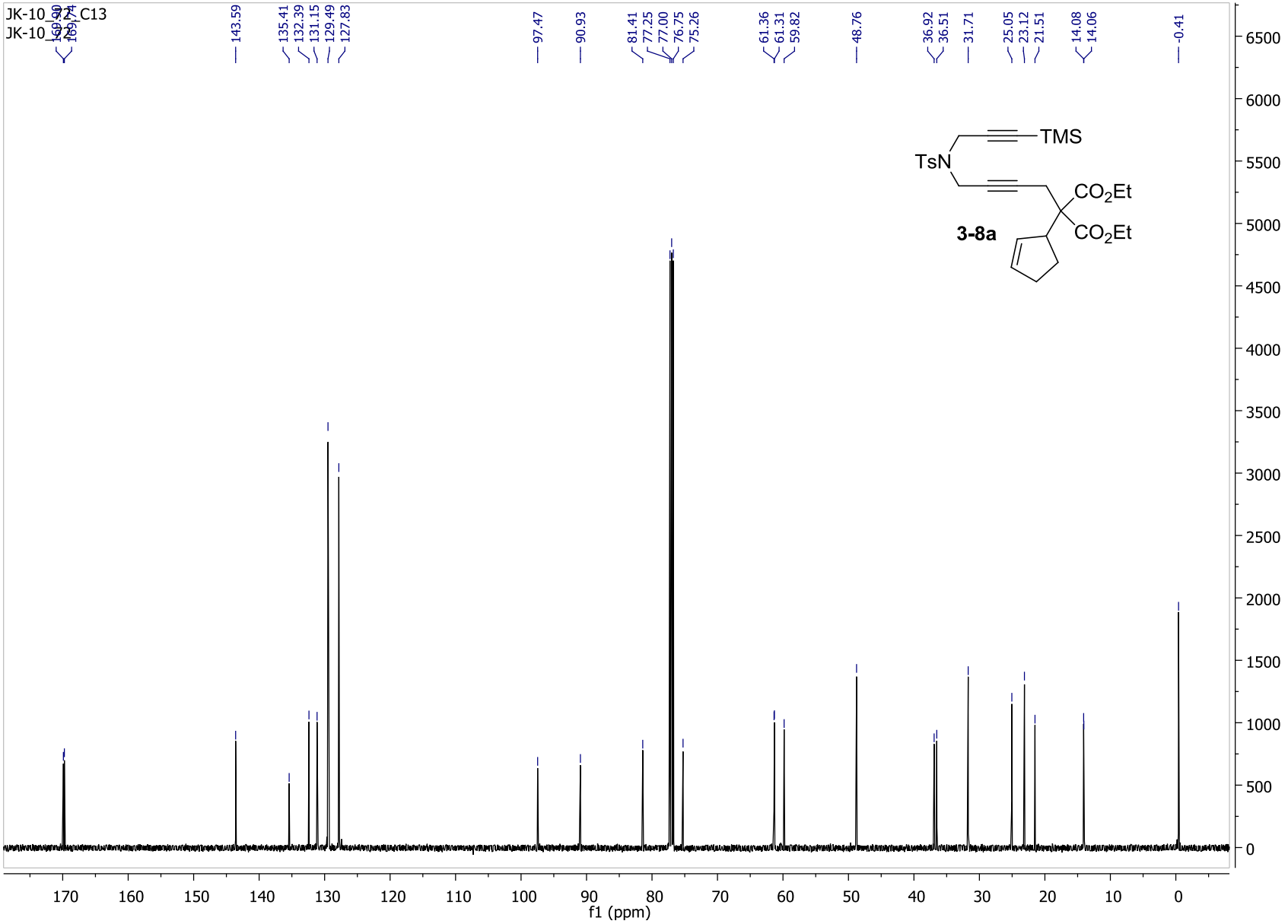

JK-6-31-Frac_1-2-H1
JK-6-31-frac_1-2
Me2PhSi
O
TsN
NTs
2-37c
f1 (ppm)

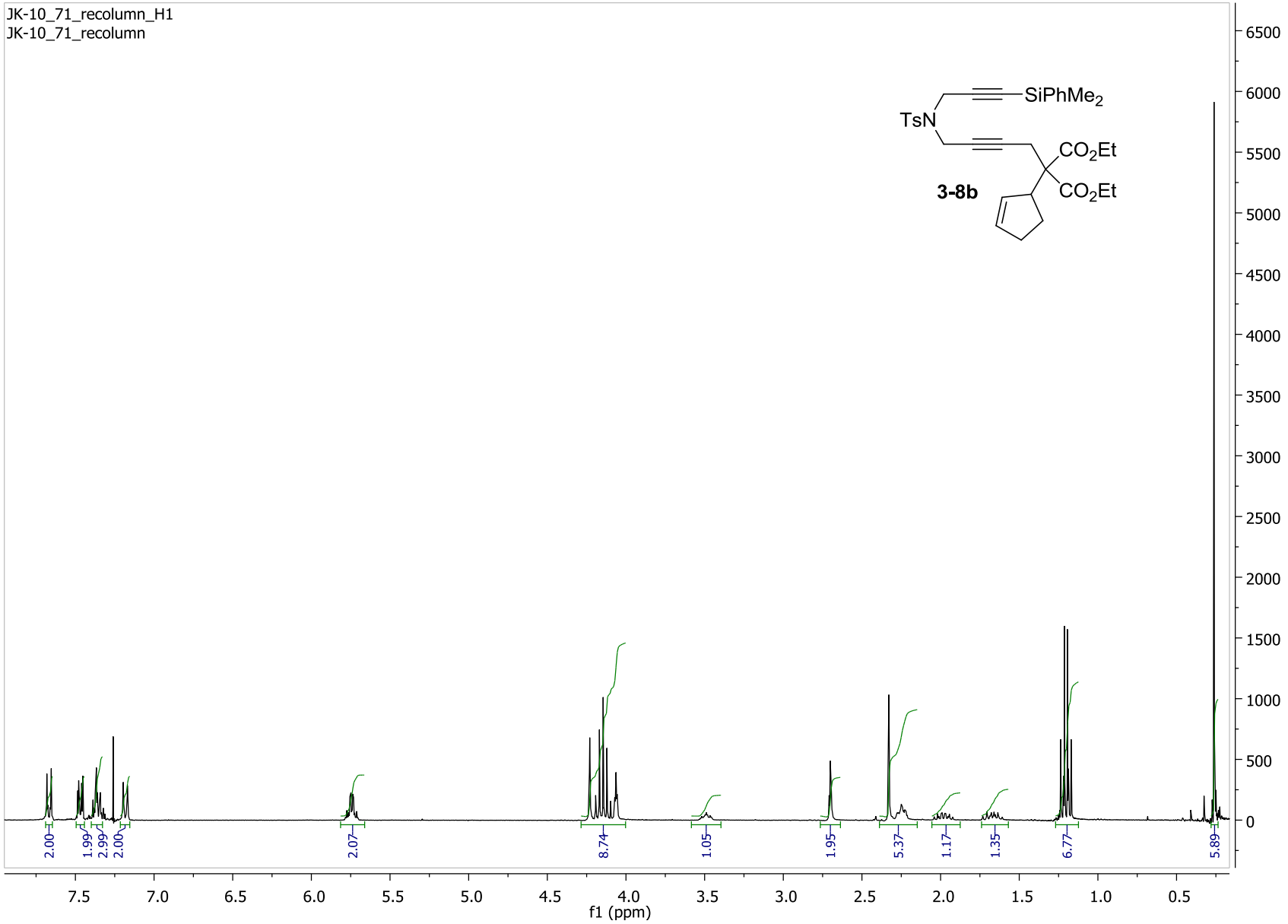

JK-6-31-frac_1-C13
13C OBSERVE
206.30
146.45
143.97
138.39
137.21
136.88
135.76
134.01
131.87
130.05
129.74
129.66
128.92
128.28
127.78
127.03
77.32
77.00
76.68
60.18
53.78
51.34
50.21
48.67
45.12
28.49
23.32
21.55
21.44
-1.69
-2.13
Me2PhSi
O
TsN
NTs
2-37c
f1 (ppm)

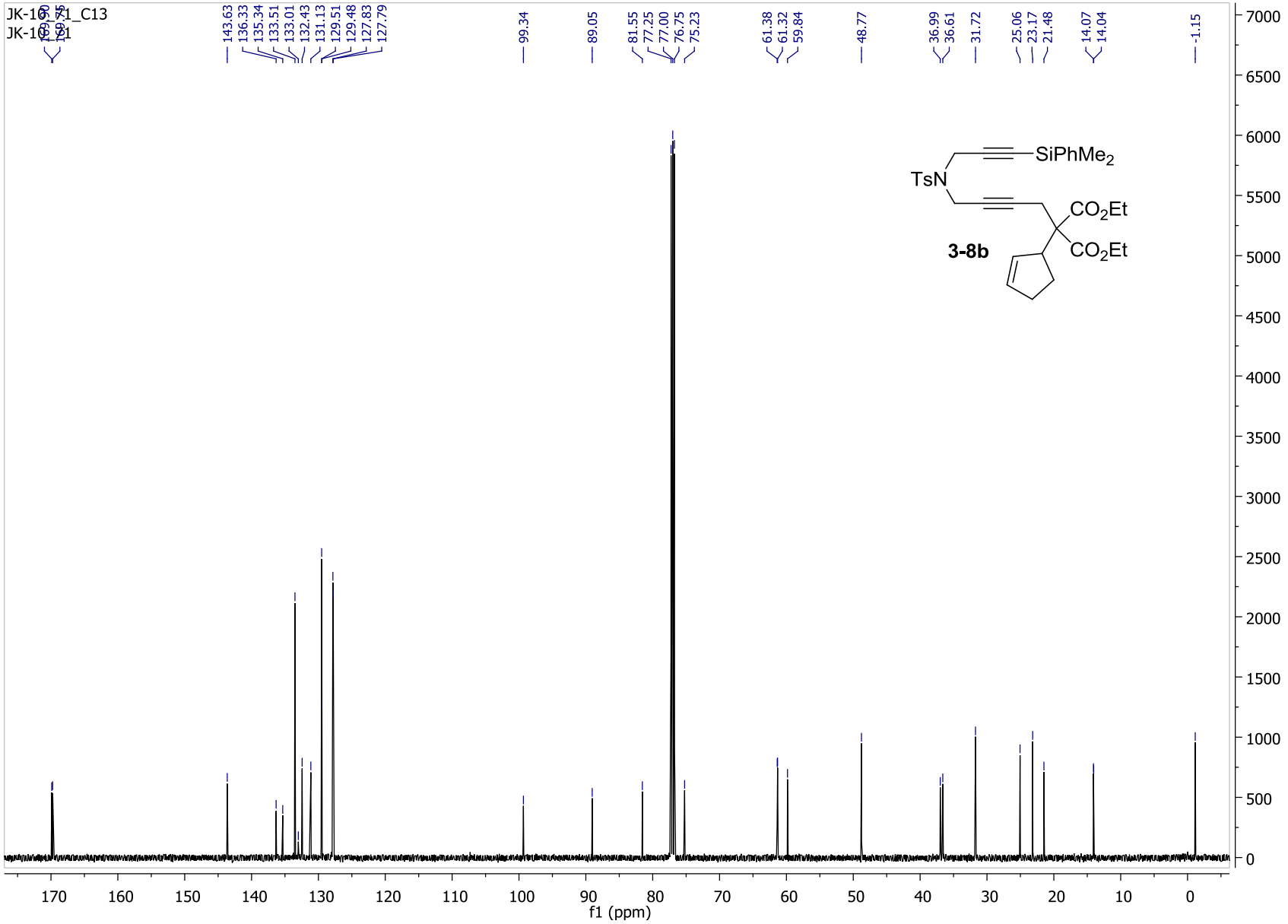

JK-4-49+6-05-frac_1-1-H1
JK-4-49+6-05-frac_1-1
TMS
O
TsN
NTs
2-37d
4.00
4.18
0.93
4.84
1.12
0.81
7.49
1.20
1.42
1.24
3.30
9.79
f1 (ppm)

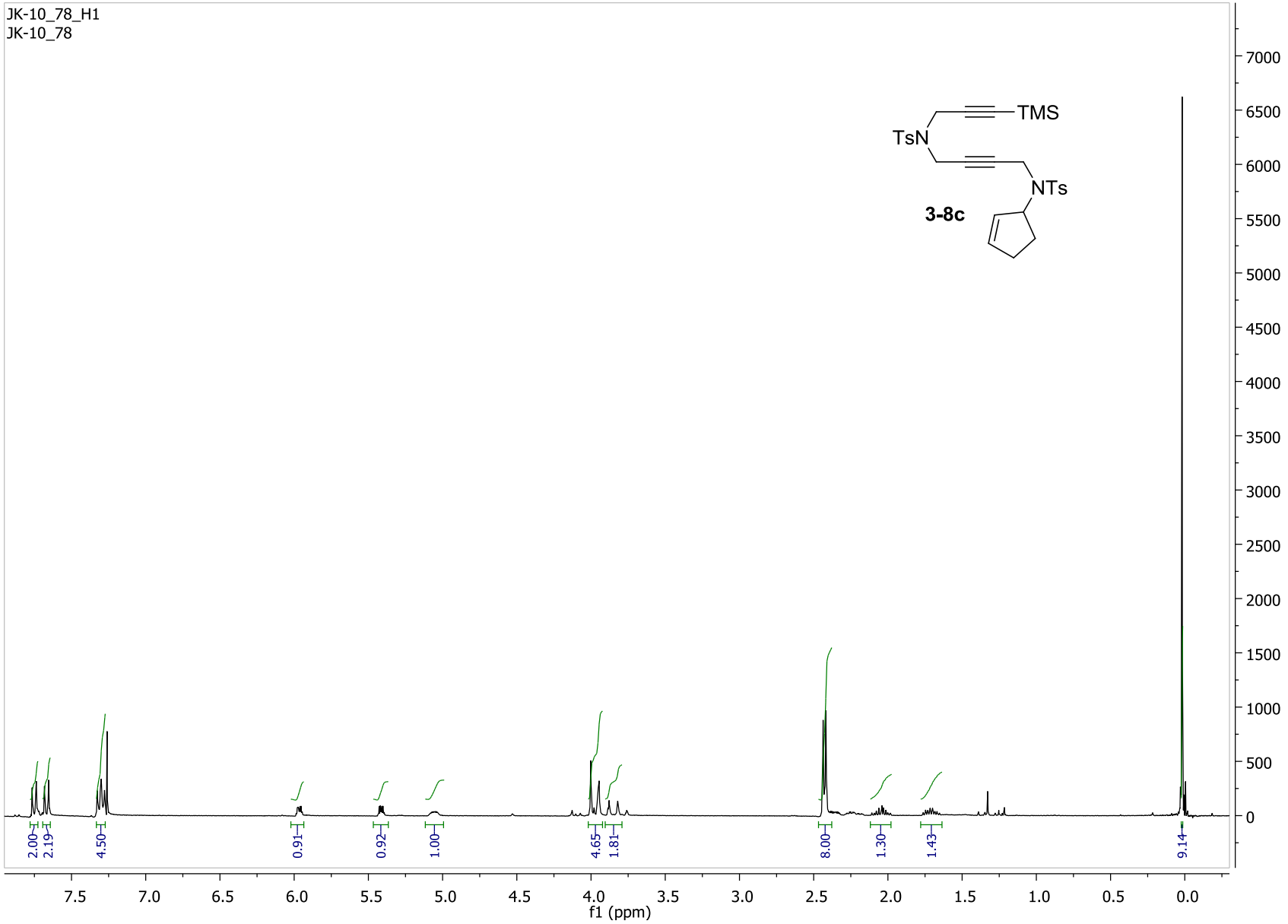

JK-4-49+6-05-frac_1-C13
JK-4-49+6-05-frac_1
145.09
144.29
143.95
138.92
137.84
135.77
132.40
130.05
129.95
128.89
127.83
127.78
127.05
77.32
77.00
76.68
60.11
53.45
51.47
50.19
48.55
45.23
28.49
23.17
21.49
21.38
-0.05
TMS
O
TsN
NTs
2-37d
f1 (ppm)

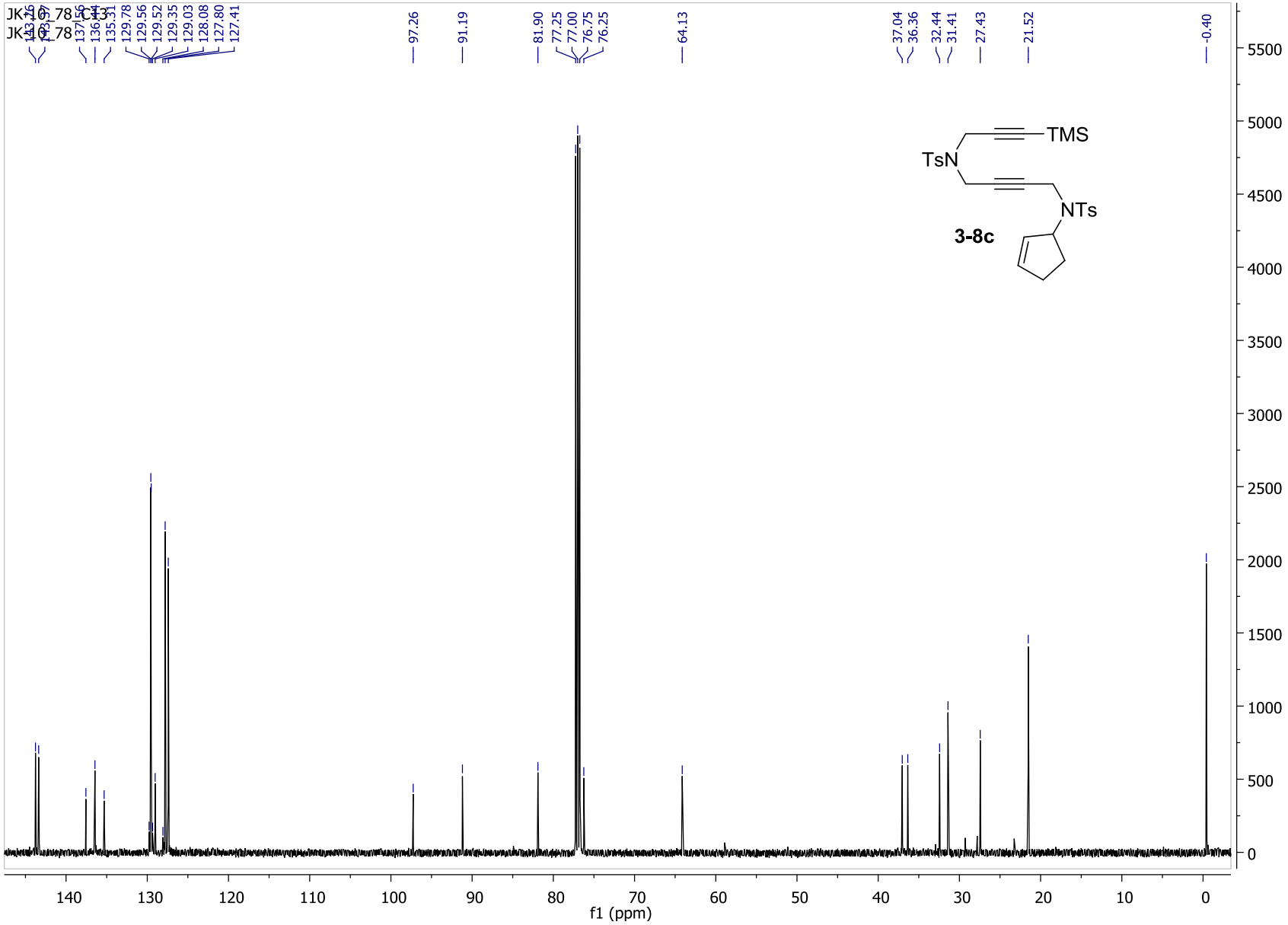

JK-10_72_recolumn_H1
JK-10_72_recolumn
TMS
TsN
CO_2Et
CO_2Et
3-8a
2.00
2.54
1.92
8.23
0.96
1.81
3.13
1.98
1.21
1.18
6.51
8.35
f1 (ppm)

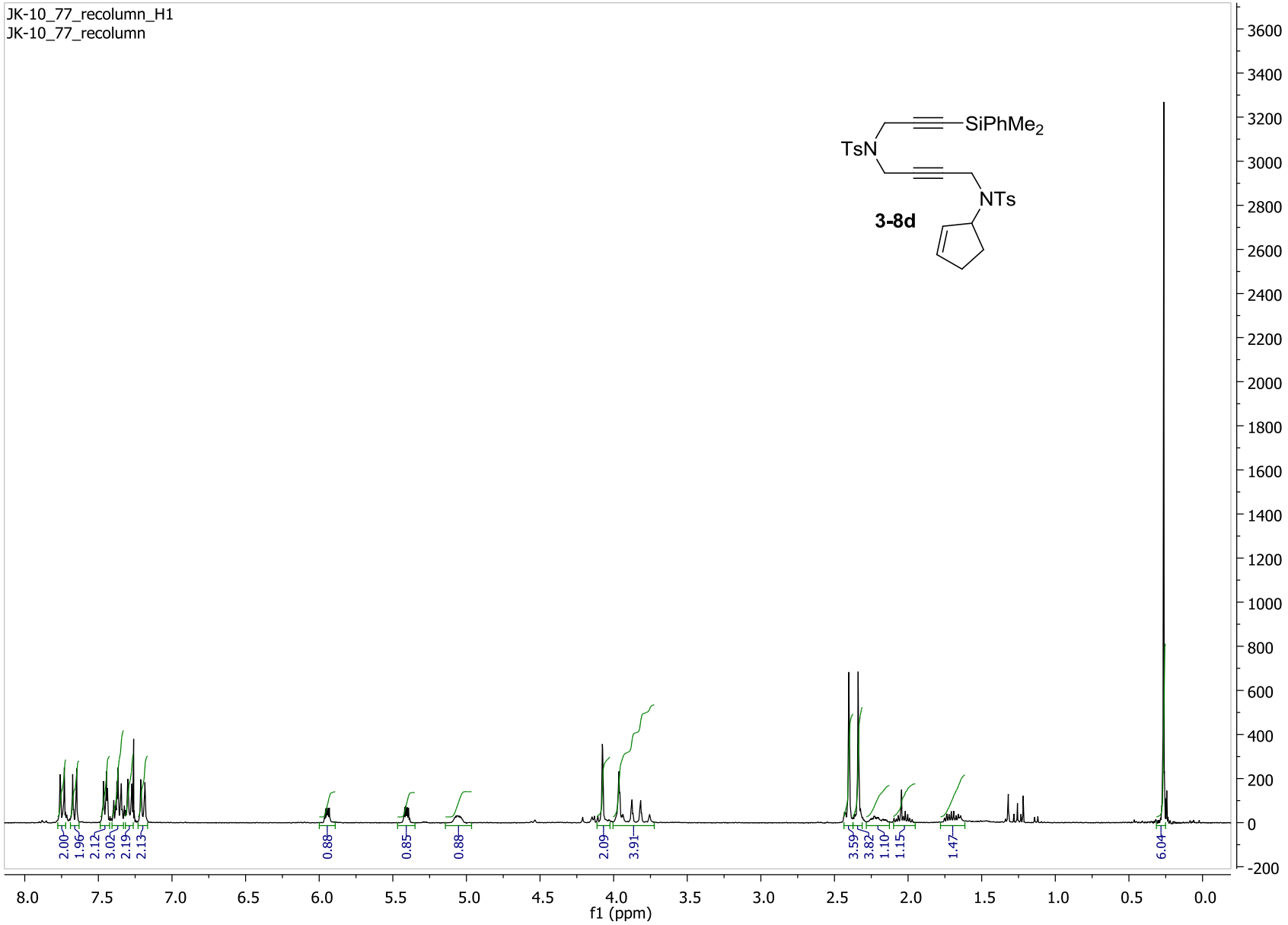

JK-10_22_C13
JK-10_22_1
170.30
169.74
143.59
135.41
132.39
131.15
129.49
127.83
97.47
90.93
81.41
77.25
77.00
76.75
75.26
61.36
61.31
59.82
48.76
36.92
36.51
31.71
25.05
23.12
21.51
14.08
14.06
-0.41
TMS
TsN
CO2Et
CO2Et
3-8a
f1 (ppm)

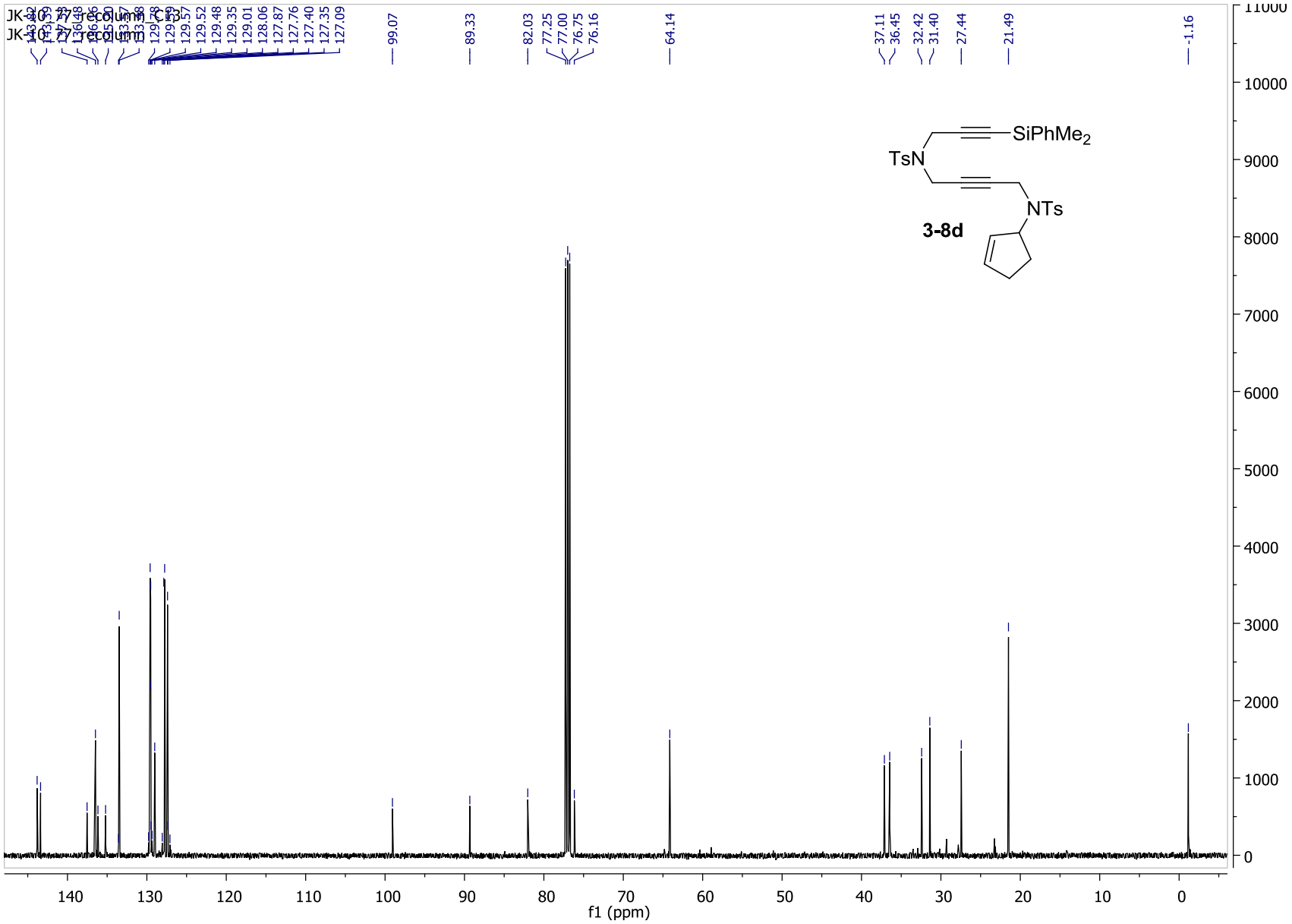

JK-10_71_recolumn_H1
JK-10_71_recolumn
SiPhMe2
TsN
CO2Et
CO2Et
3-8b
2.00
1.99
2.99
2.00
2.07
8.74
1.05
1.95
5.37
1.17
1.35
6.77
5.89
f1 (ppm)

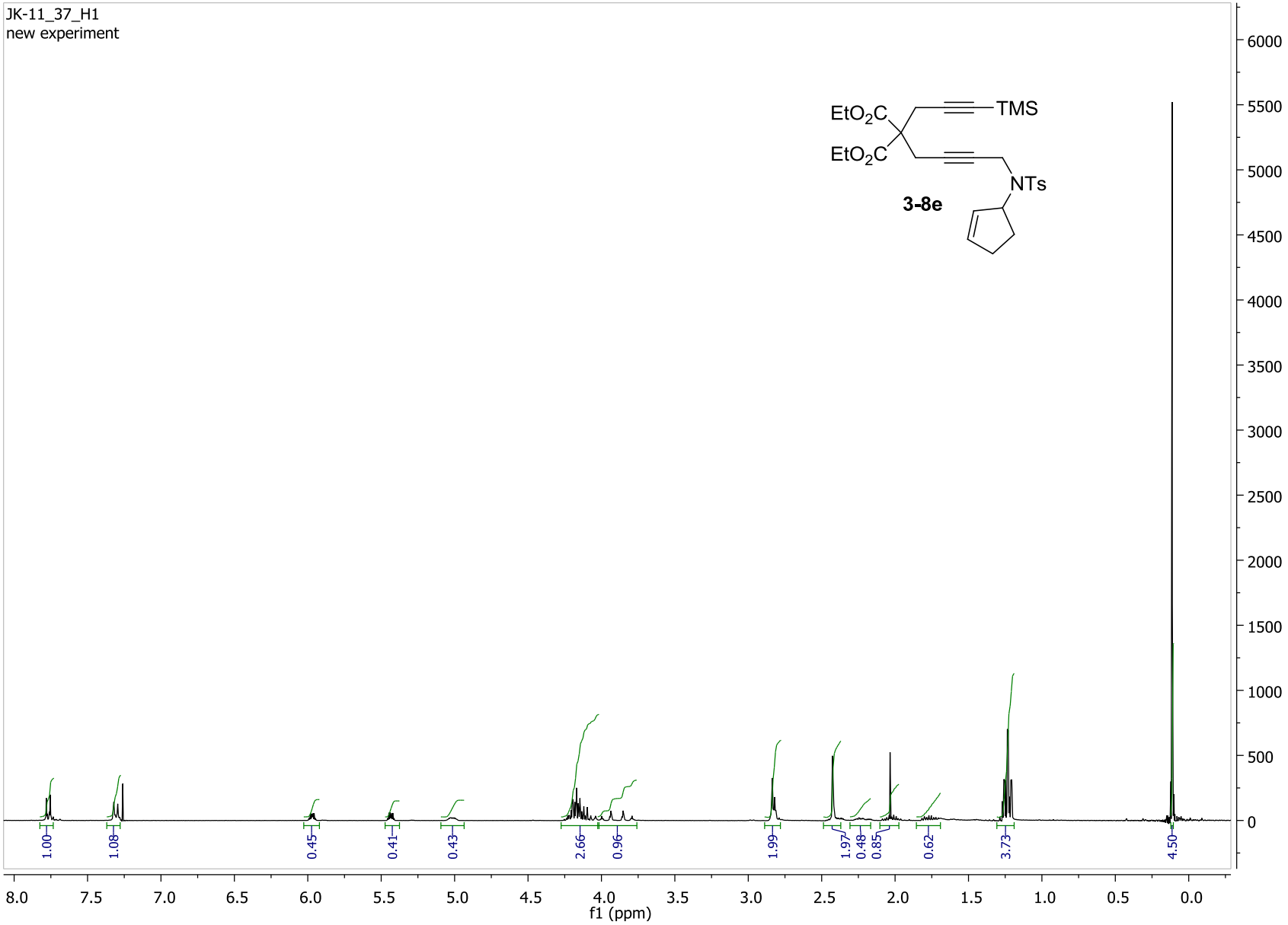

JK-16-71_C13
JK-16-71
143.63
136.33
135.34
133.51
133.01
132.43
131.13
129.51
129.48
127.83
127.79
99.34
89.05
81.55
77.25
77.00
76.75
75.23
61.38
61.32
59.84
48.77
36.99
36.61
31.72
25.06
23.17
21.48
14.07
14.04
-1.15
SiPhMe2
TsN
CO2Et
CO2Et
3-8b
f1 (ppm)

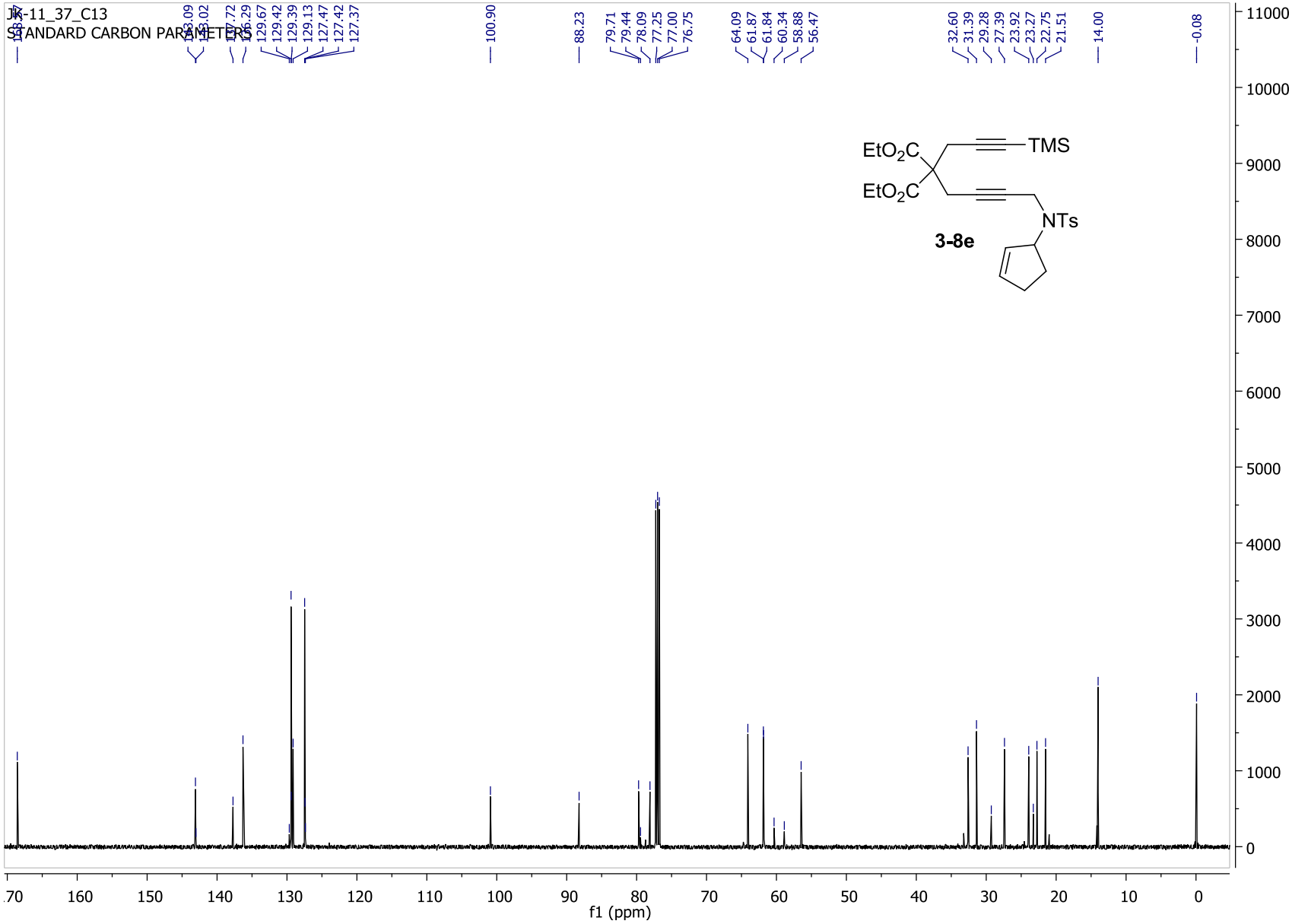

JK-10_78_H1
JK-10_78
TMS
TsN
NTs
3-8c
2.00
2.19
4.50
0.91
0.92
1.00
4.65
1.81
8.00
1.30
1.43
9.14
f1 (ppm)

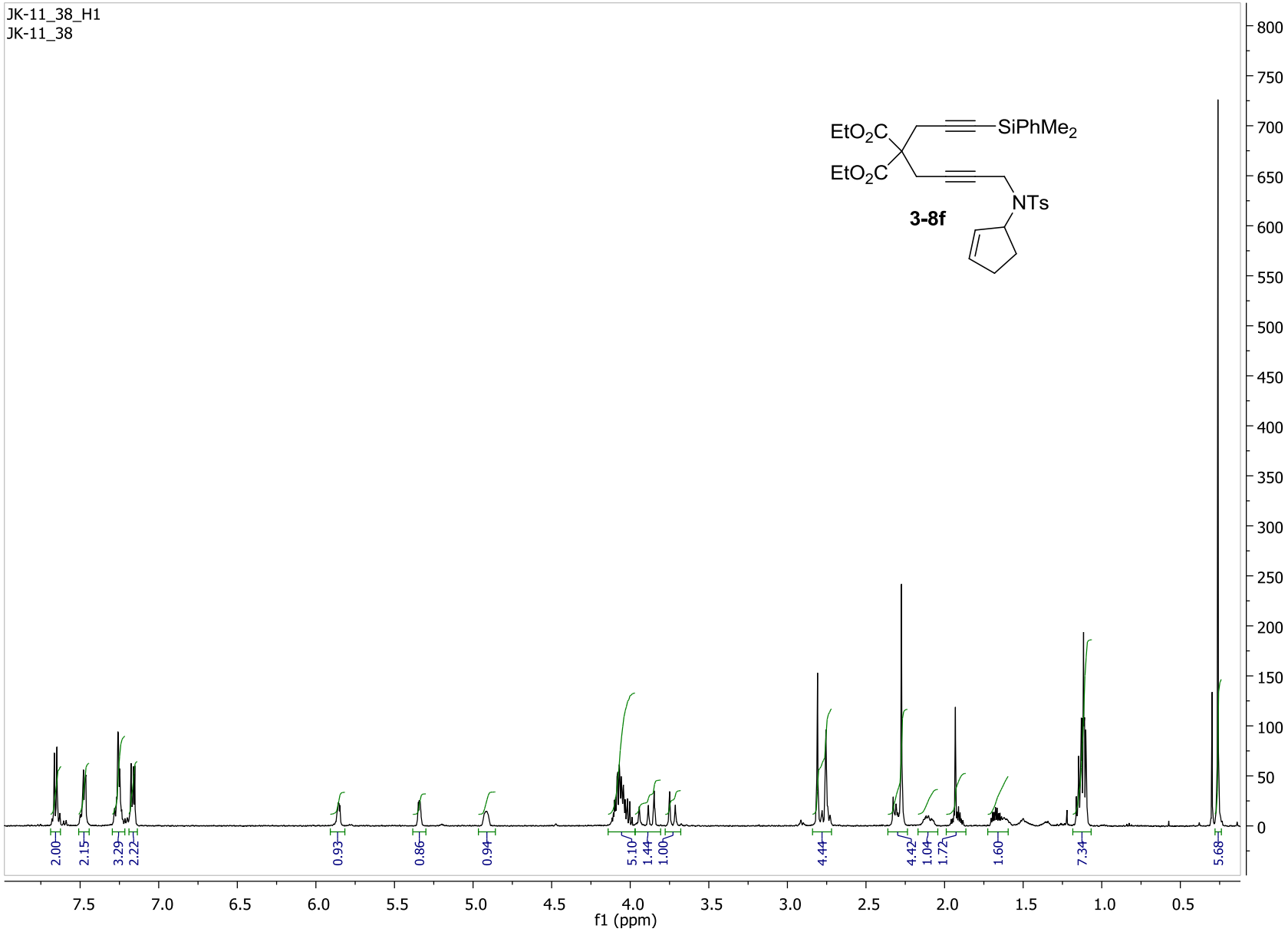

JK-10_78_C13
JK-10_78_C13
143.16
143.07
137.56
136.04
135.31
129.78
129.56
129.52
129.35
129.03
128.08
127.80
127.41
97.26
91.19
81.90
77.25
77.00
76.75
76.25
64.13
37.04
36.36
32.44
31.41
27.43
21.52
-0.40
TMS
TsN
NTs
3-8c
f1 (ppm)

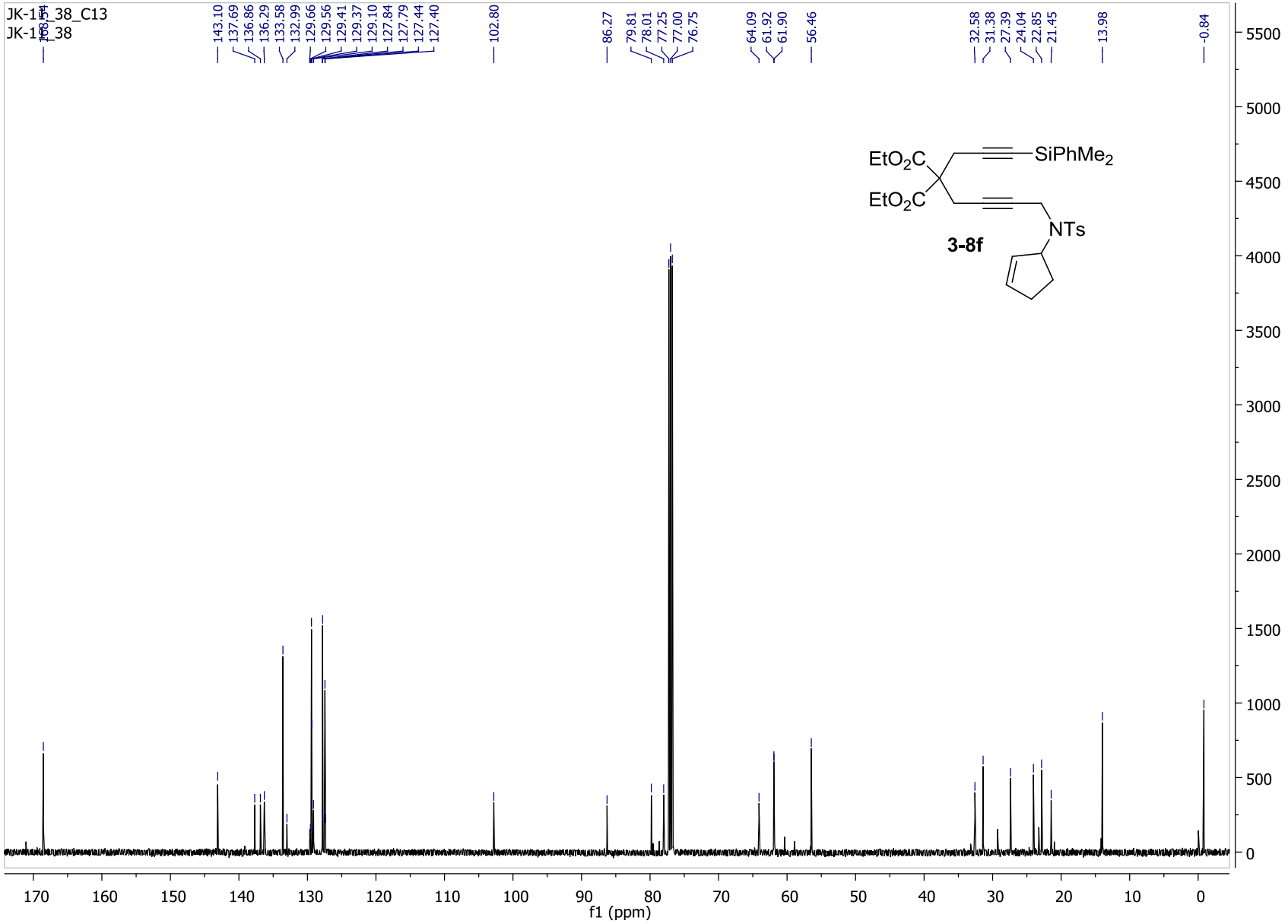

JK-10_77_recolumn_H1
JK-10_77_recolumn
SiPhMe2
TsN
NTs
3-8d
2.00
1.96
2.12
3.02
2.19
2.13
0.88
0.85
0.88
2.09
3.91
3.59
3.82
1.10
1.15
1.47
6.04
f1 (ppm)

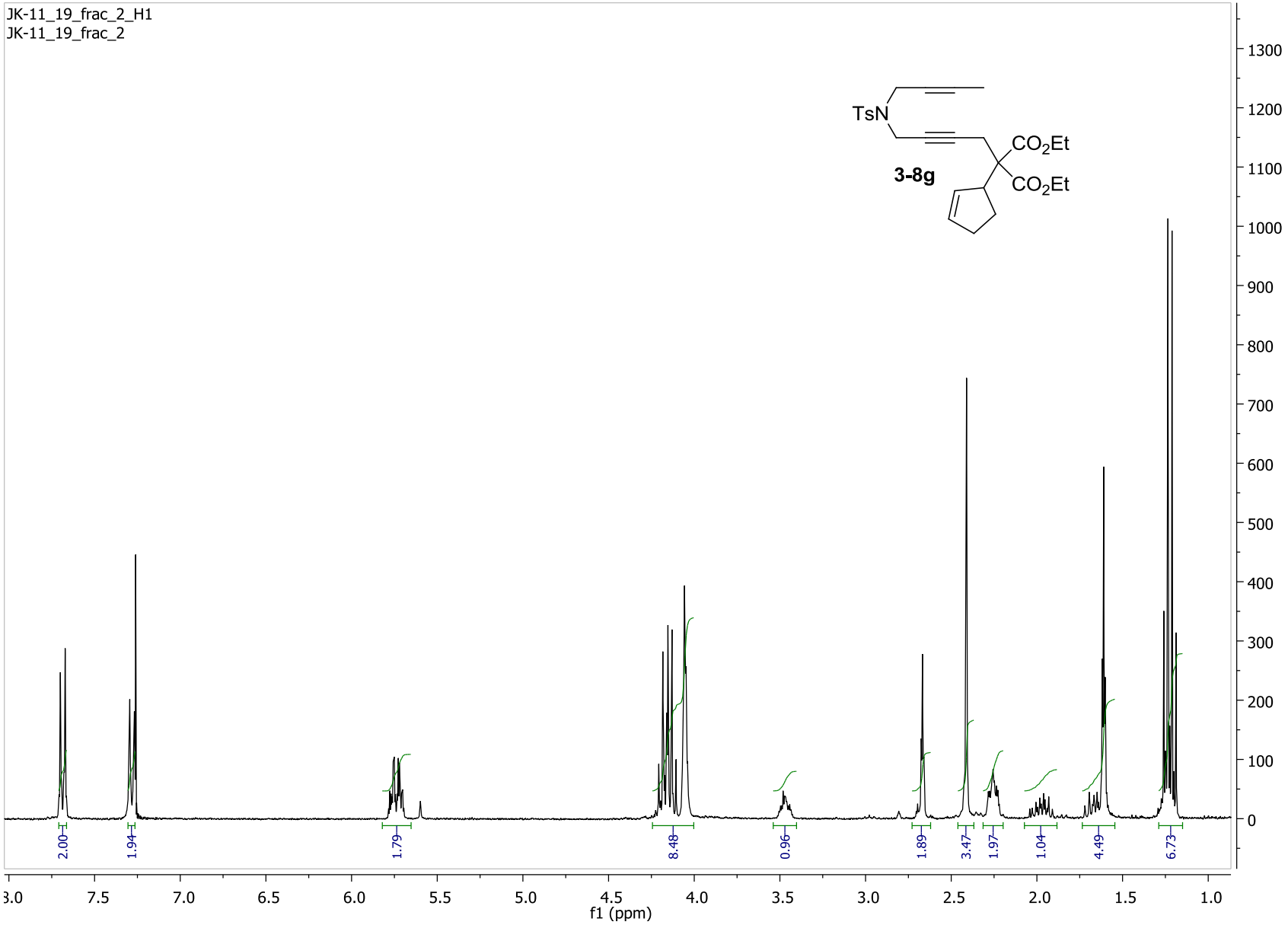

JK-10-77 recolumn (C13)
JK-10-77 recolumn (C13)
99.07
89.33
82.03
77.25
77.00
76.75
76.16
64.14
37.11
36.45
32.42
31.40
27.44
21.49
-1.16
SiPhMe2
TsN
NTs
3-8d
f1 (ppm)

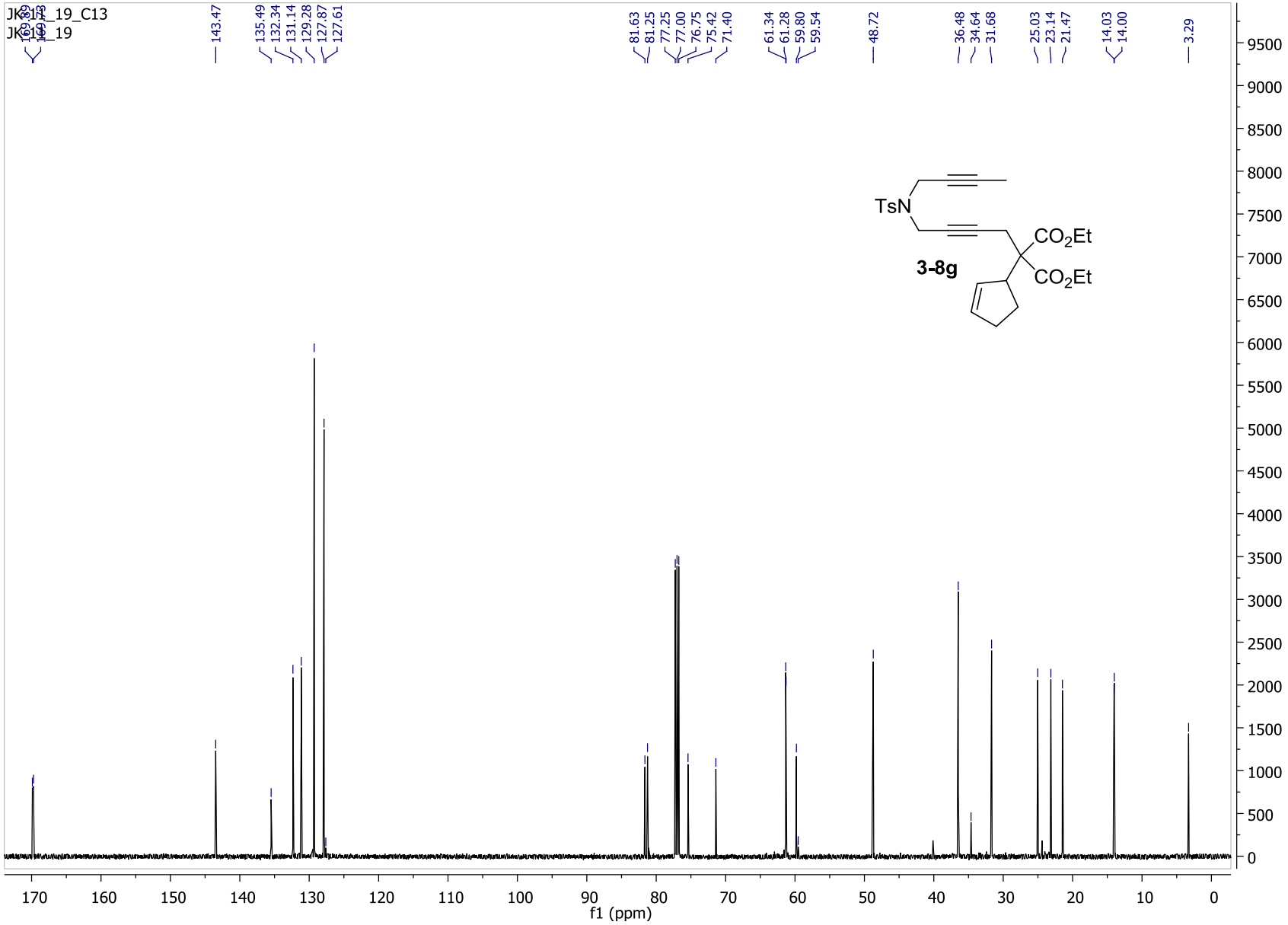

JK-11_37_H1
new experiment
EtO2C
EtO2C
TMS
NTs
3-8e
1.00
1.08
0.45
0.41
0.43
2.66
0.96
1.99
1.97
0.48
0.85
0.62
3.73
4.50
f1 (ppm)

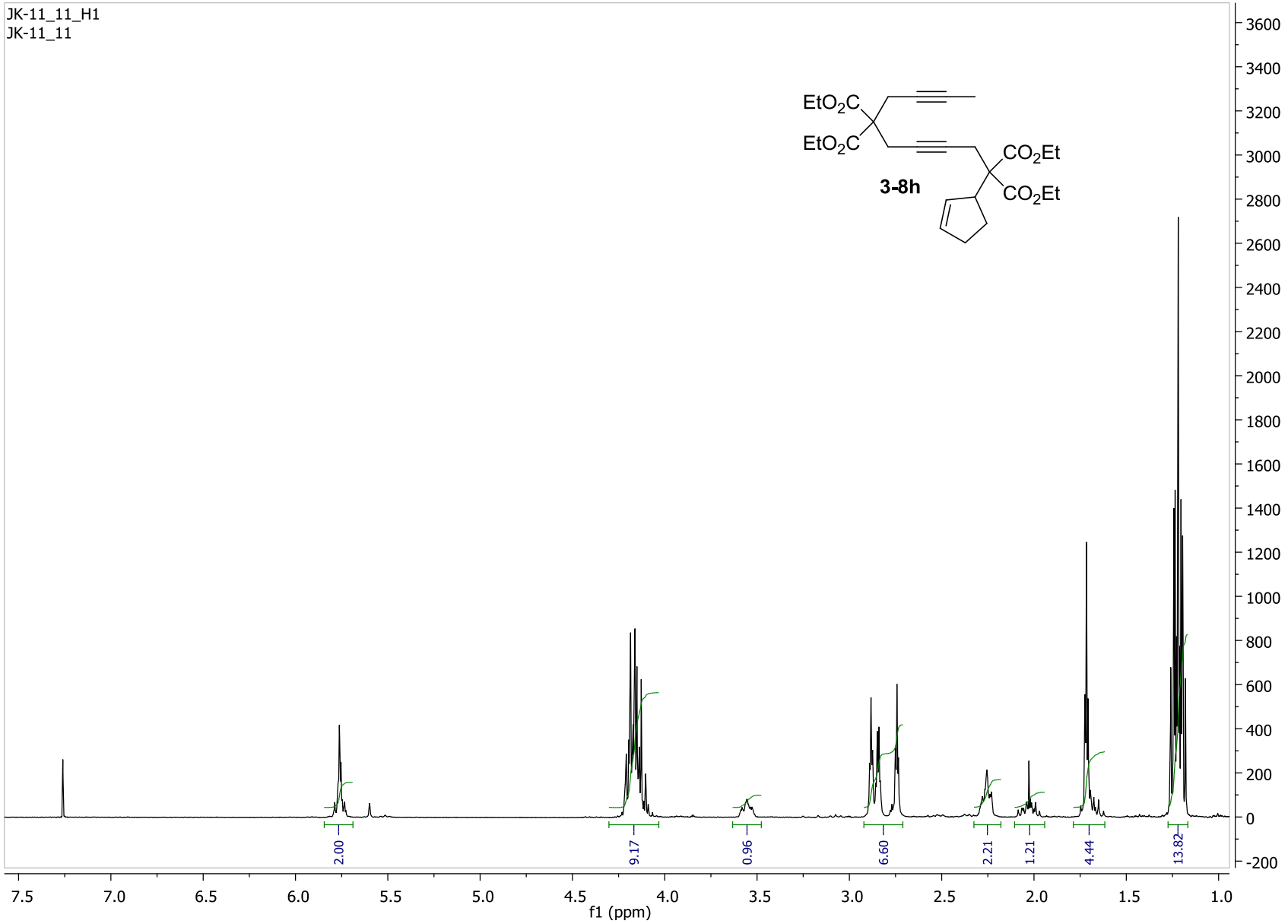

JK-11_37_C13
STANDARD CARBON PARAMETERS
168.09
143.02
137.72
136.29
129.67
129.42
129.39
129.13
127.47
127.42
127.37
100.90
88.23
79.71
79.44
78.09
77.25
77.00
76.75
64.09
61.87
61.84
60.34
58.88
56.47
32.60
31.39
29.28
27.39
23.92
23.27
22.75
21.51
14.00
-0.08
EtO2C
EtO2C
TMS
NTs
3-8e
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

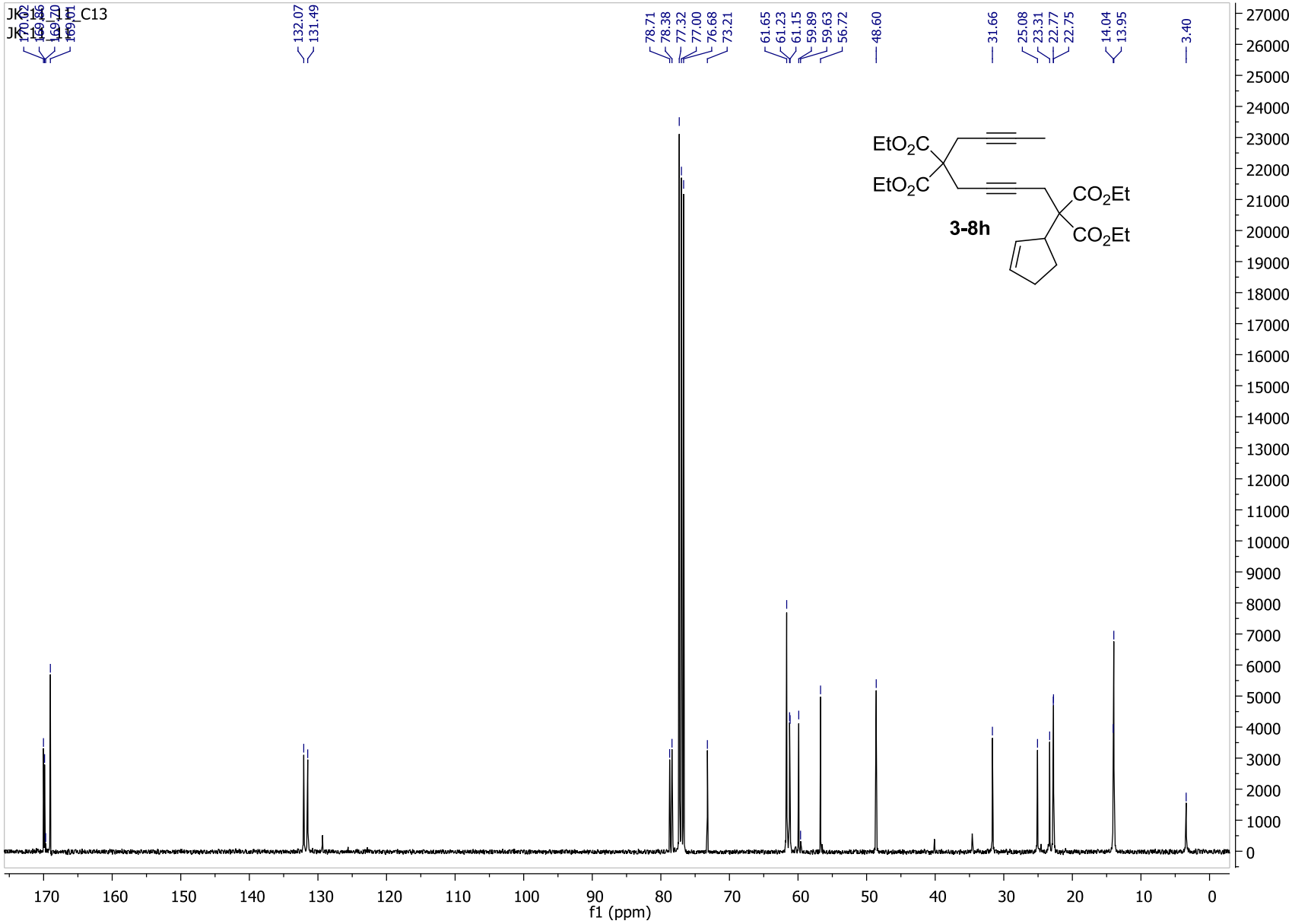

JK-11_38_H1
JK-11_38
EtO2C
EtO2C
SiPhMe2
NTs
3-8f
2.00
2.15
3.29
2.22
0.93
0.86
0.94
5.10
1.44
1.00
4.44
4.42
1.04
1.72
1.60
7.34
5.68
f1 (ppm)

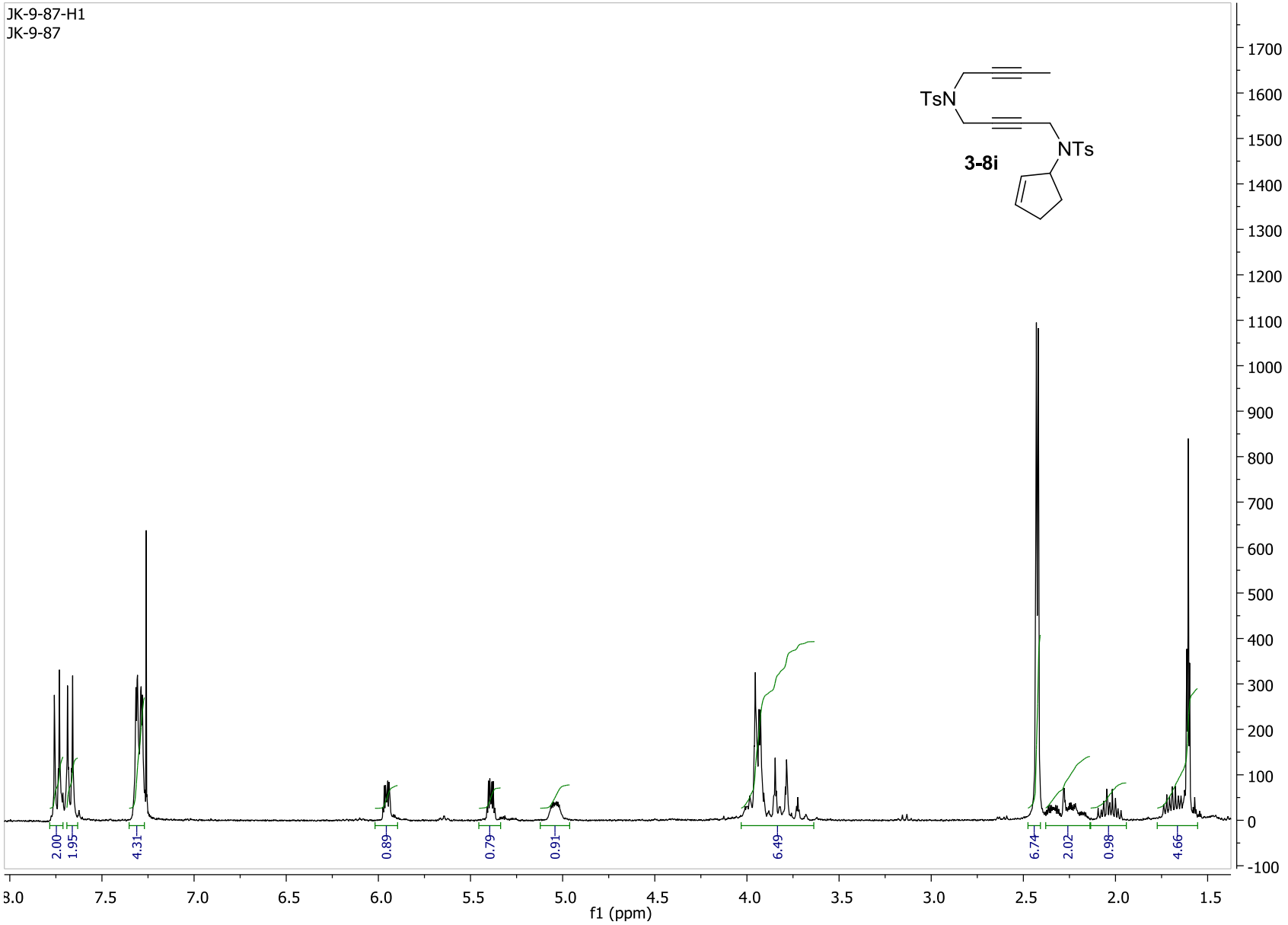

JK-1f_38_C13
JK-1f_38
168.54
143.10
137.69
136.86
136.29
133.58
132.99
129.66
129.56
129.41
129.37
129.10
127.84
127.79
127.44
127.40
102.80
86.27
79.81
78.01
77.25
77.00
76.75
64.09
61.92
61.90
56.46
32.58
31.38
27.39
24.04
22.85
21.45
13.98
-0.84
EtO2C
EtO2C
SiPhMe2
NTs
3-8f
f1 (ppm)

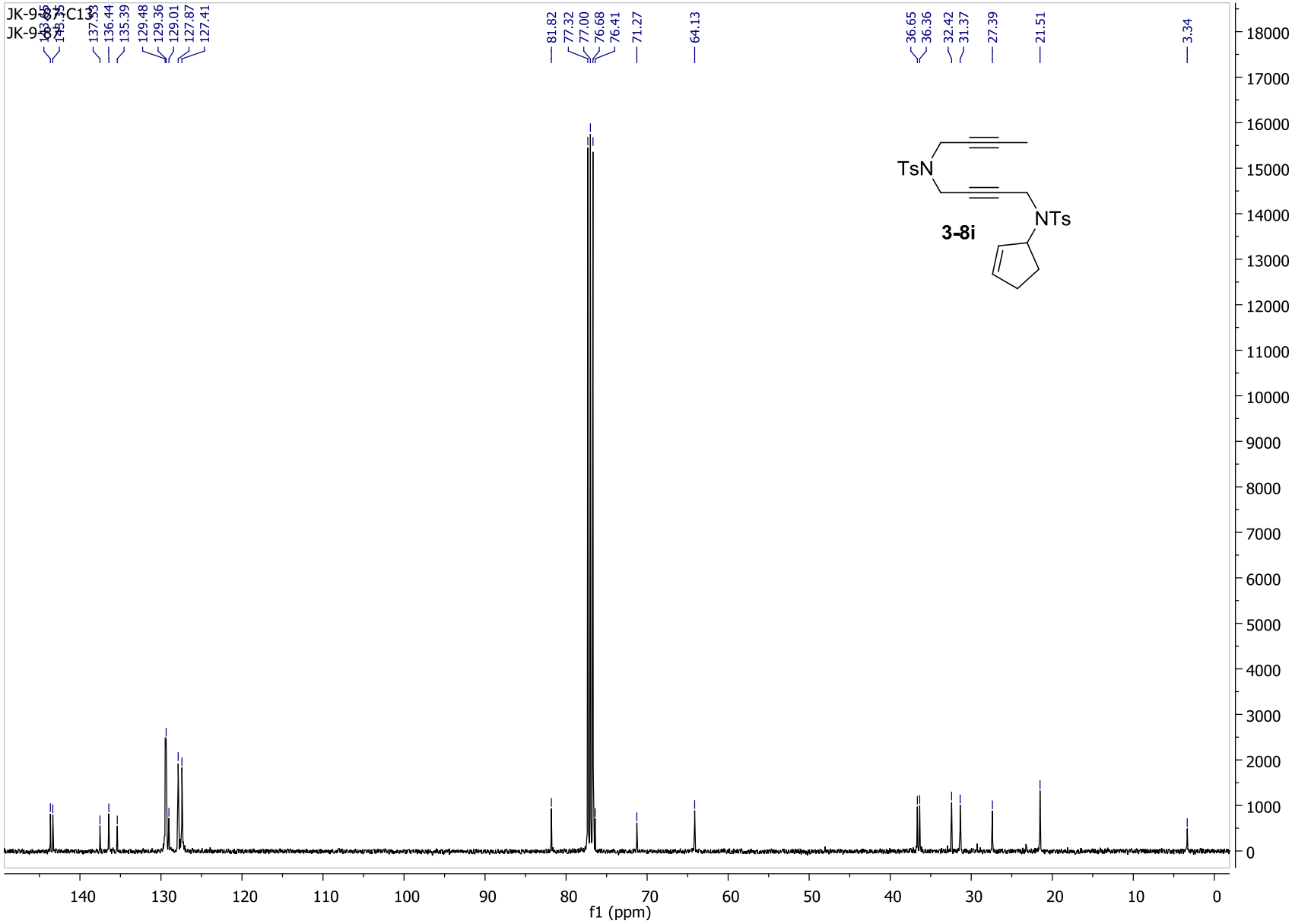

JK-11_19_frac_2_H1
JK-11_19_frac_2
TsN
CO2Et
CO2Et
3-8g
2.00
1.94
1.79
8.48
0.96
1.89
3.47
1.97
1.04
4.49
6.73
f1 (ppm)

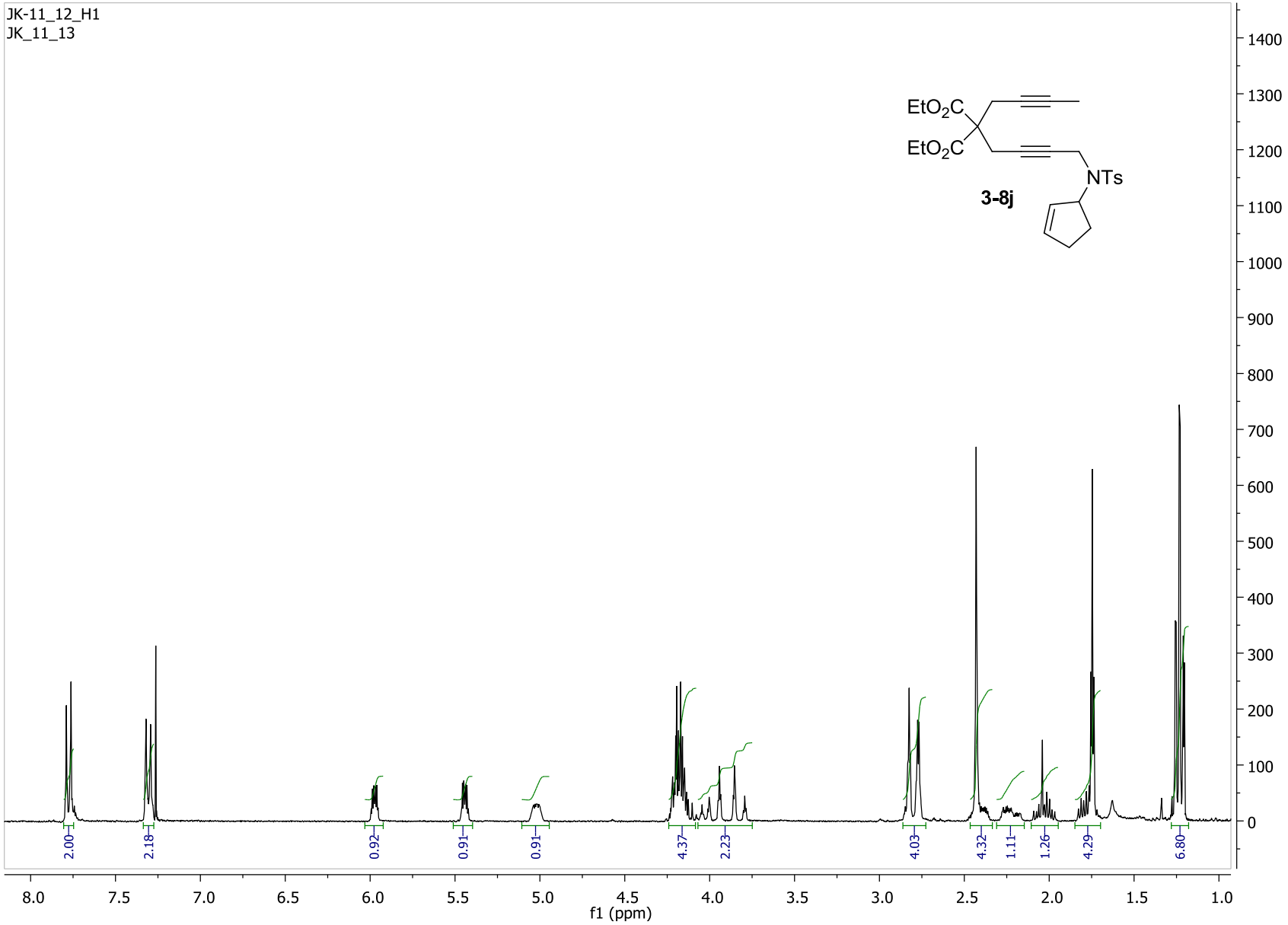

JK-3-19_C13
JK-3-19
143.47
135.49
132.34
131.14
129.28
127.87
127.61
81.63
81.25
77.25
77.00
76.75
75.42
71.40
61.34
61.28
59.80
59.54
48.72
36.48
34.64
31.68
25.03
23.14
21.47
14.03
14.00
3.29
TsN
CO2Et
CO2Et
3-8g
f1 (ppm)

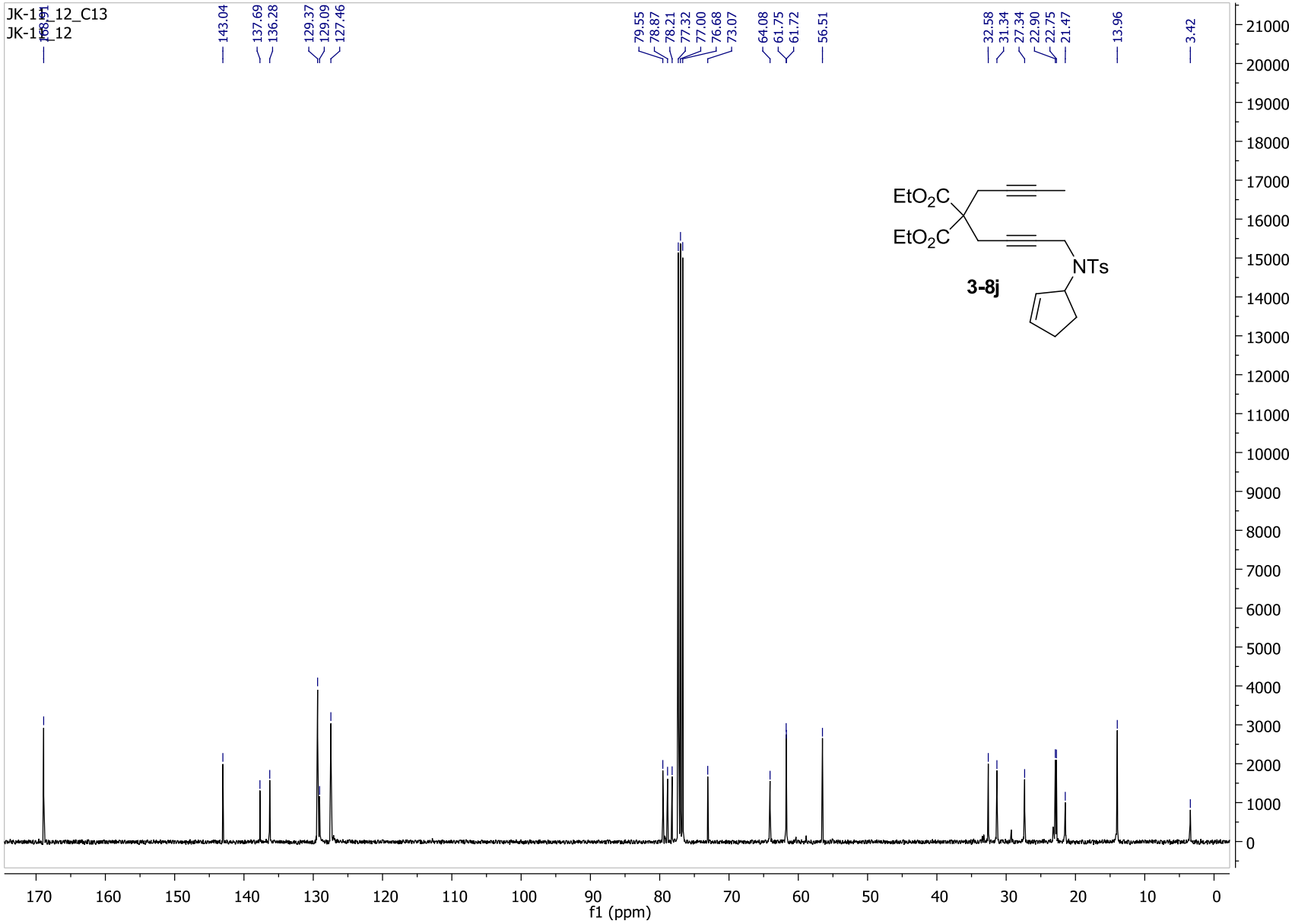

JK-11_11_H1
JK-11_11
EtO2C
EtO2C
CO2Et
CO2Et
3-8h
2.00
9.17
0.96
6.60
2.21
1.21
4.44
13.82
f1 (ppm)

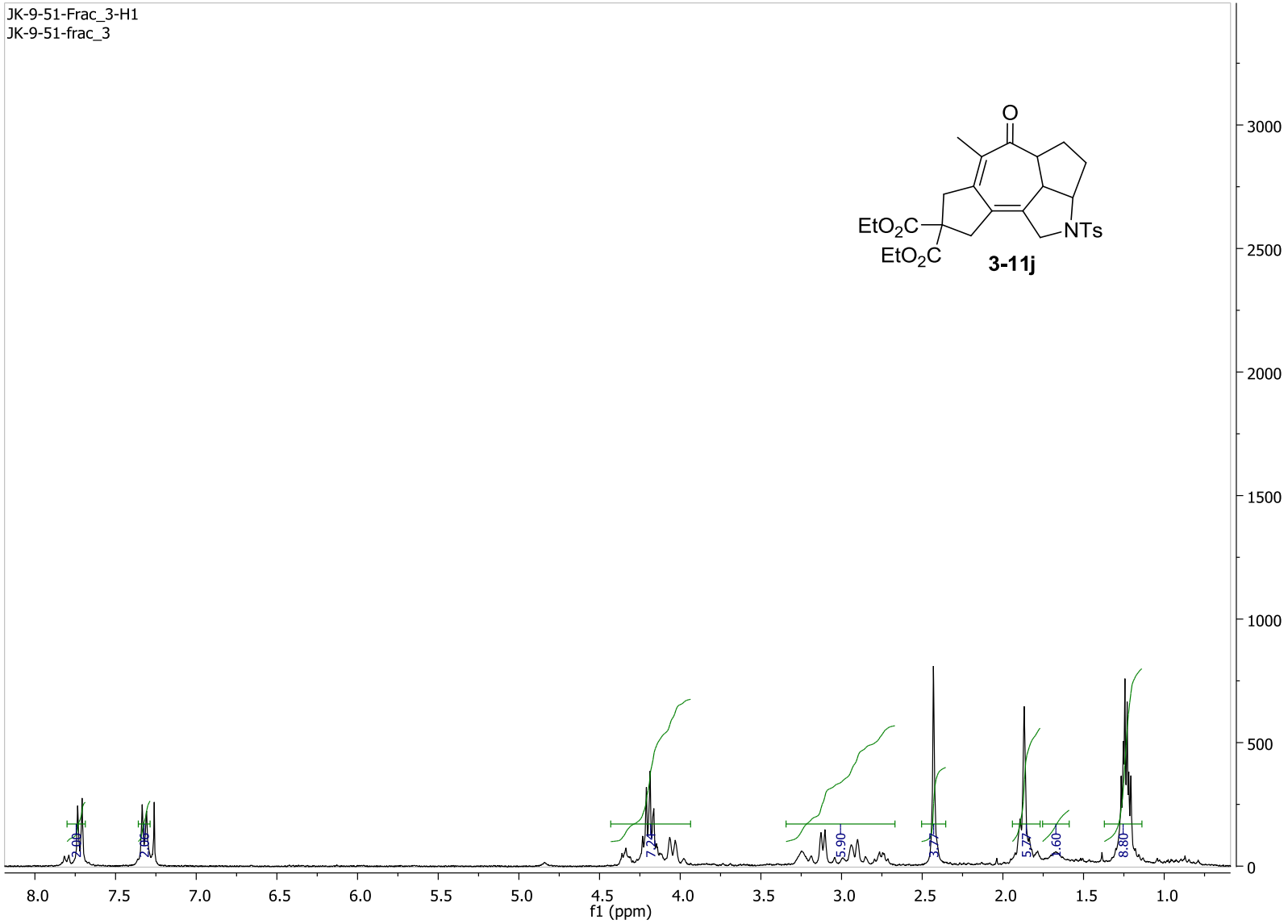

JK_C13
JK_C13
170.62
169.86
169.70
169.01
132.07
131.49
78.71
78.38
77.32
77.00
76.68
73.21
61.65
61.23
61.15
59.89
59.63
56.72
48.60
31.66
25.08
23.31
22.77
22.75
14.04
13.95
3.40
EtO2C
EtO2C
CO2Et
CO2Et
3-8h
f1 (ppm)

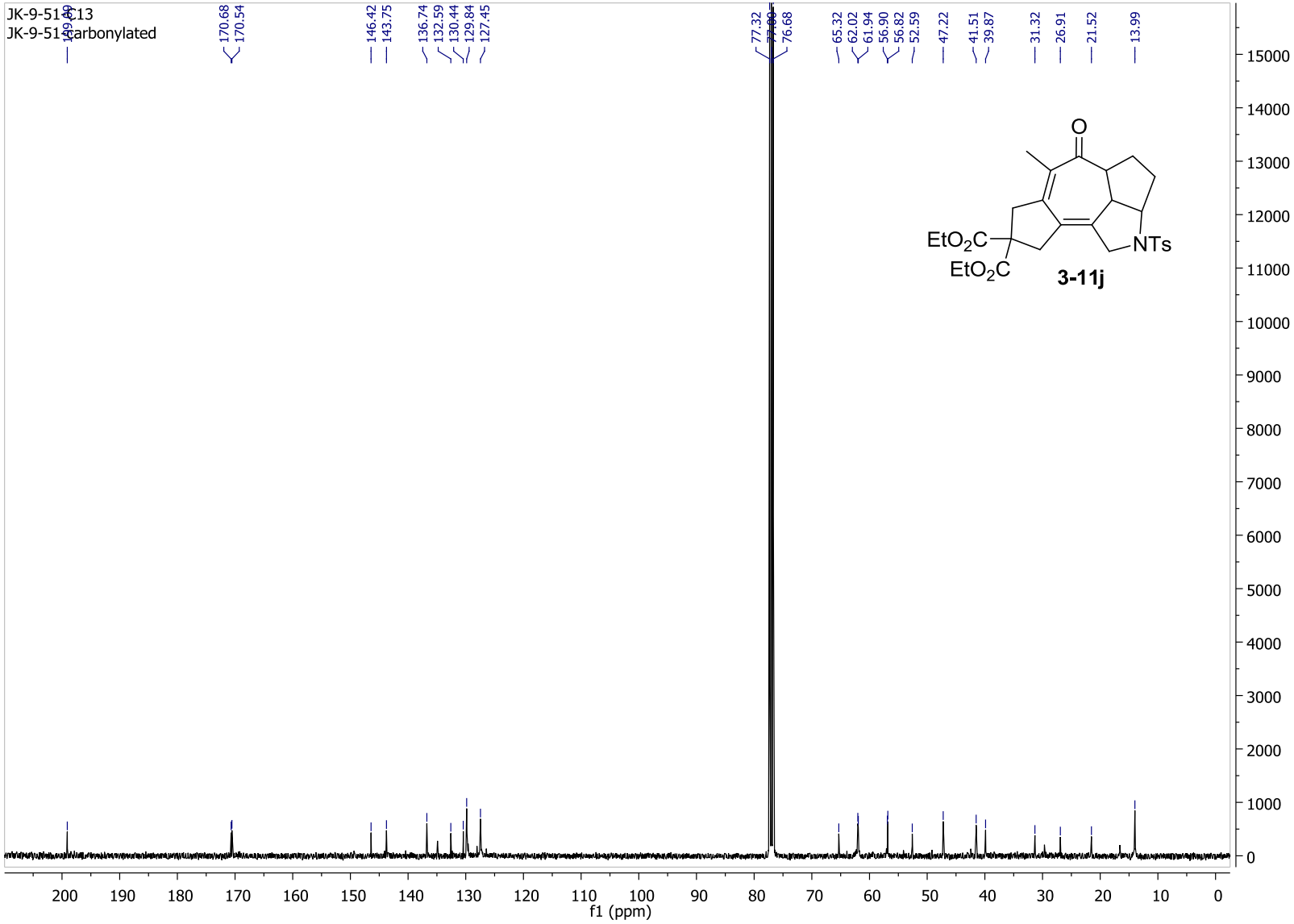

JK-9-87-H1
JK-9-87
TsN
NTs
3-8i
2.00
1.95
4.31
0.89
0.79
0.91
6.49
6.74
2.02
0.98
4.66
f1 (ppm)

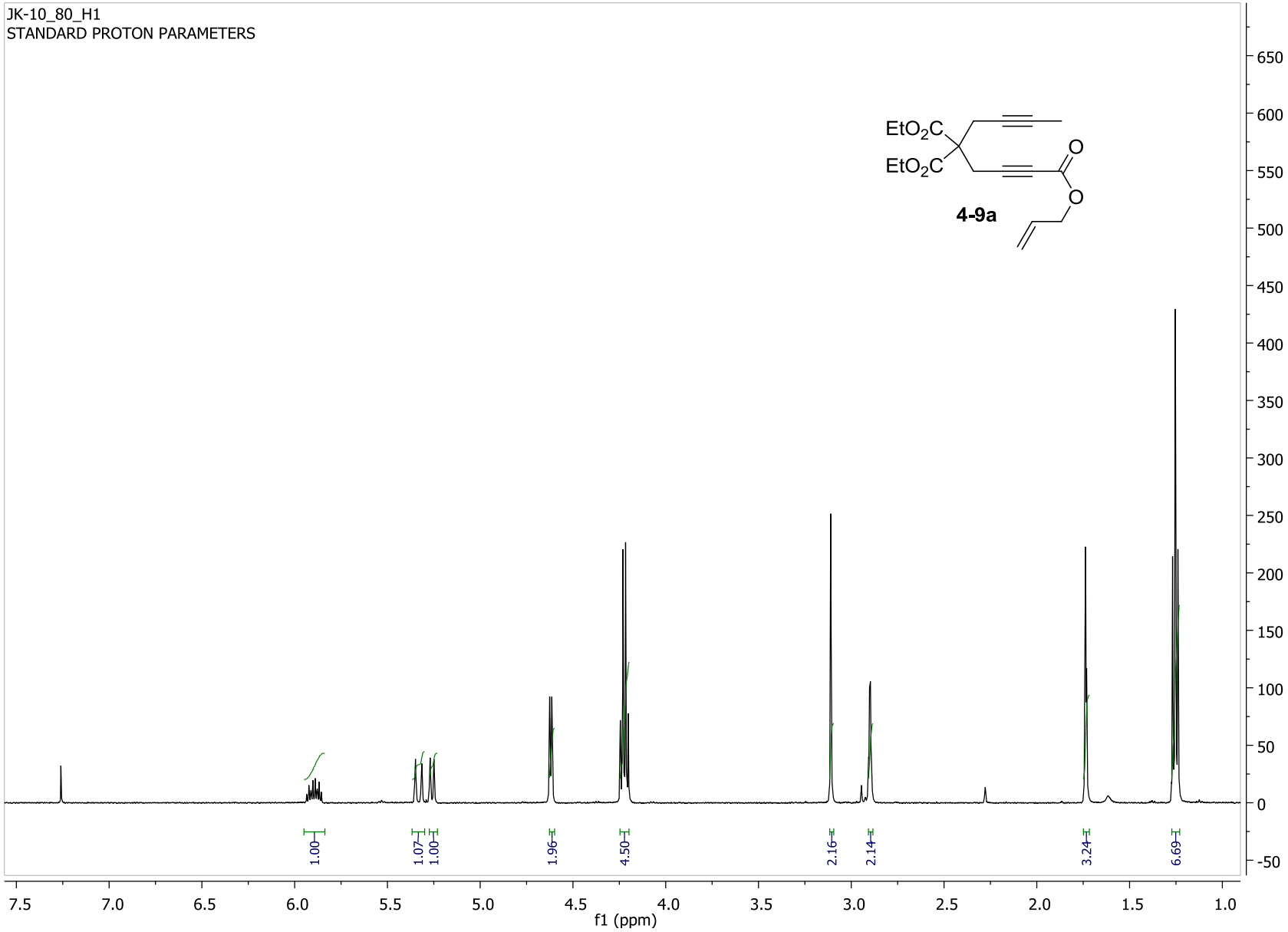

JK-9-87-C13
JK-9-87
143.83
137.55
136.44
135.39
129.48
129.36
129.01
127.87
127.41
81.82
77.32
77.00
76.68
76.41
71.27
64.13
36.65
36.36
32.42
31.37
27.39
21.51
3.34
TsN
NTs
3-8i
f1 (ppm)

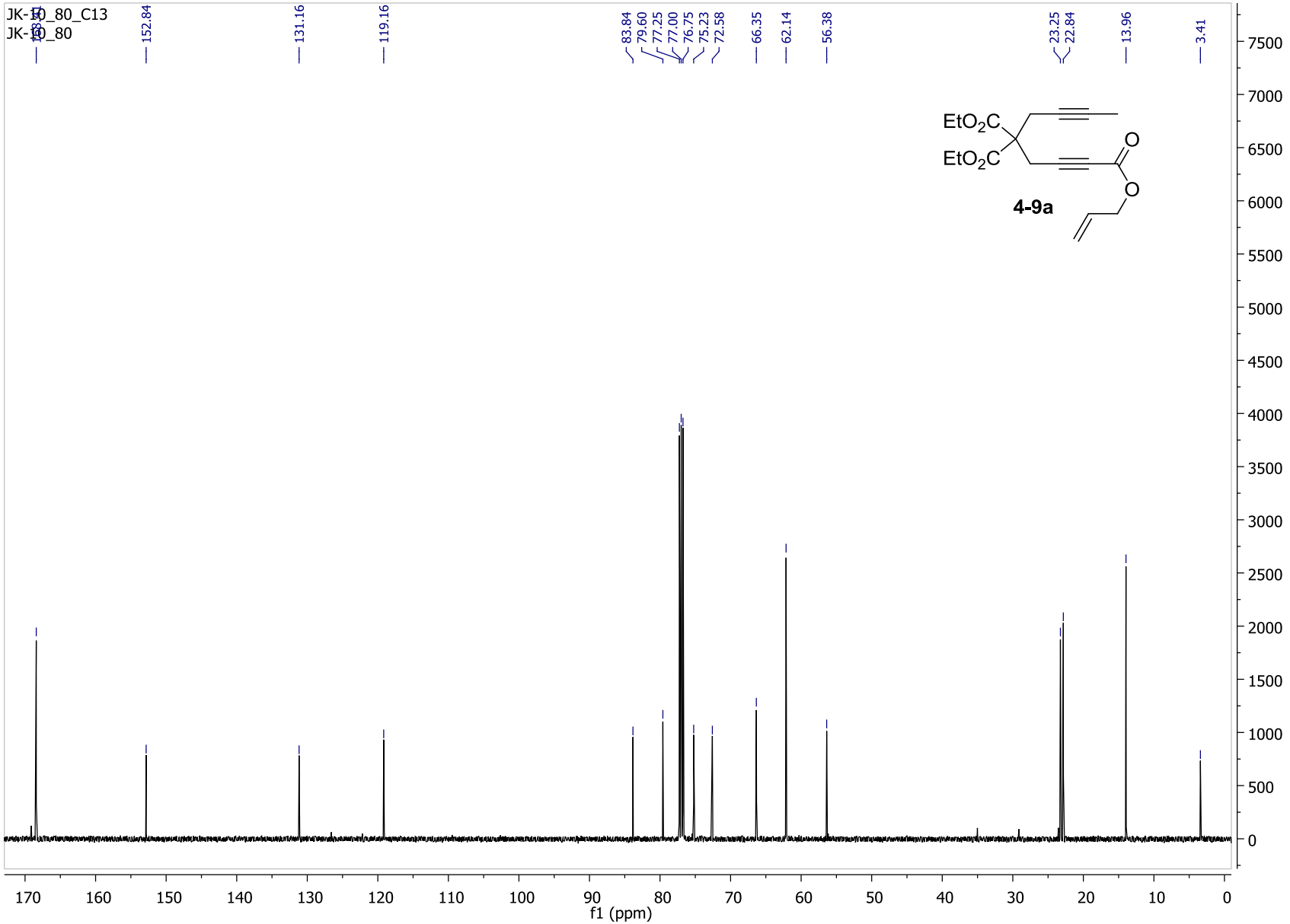

JK-11_12_H1
JK_11_13
EtO2C
EtO2C
NTs
3-8j
2.00
2.18
0.92
0.91
0.91
4.37
2.23
4.03
4.32
1.11
1.26
4.29
6.80
f1 (ppm)

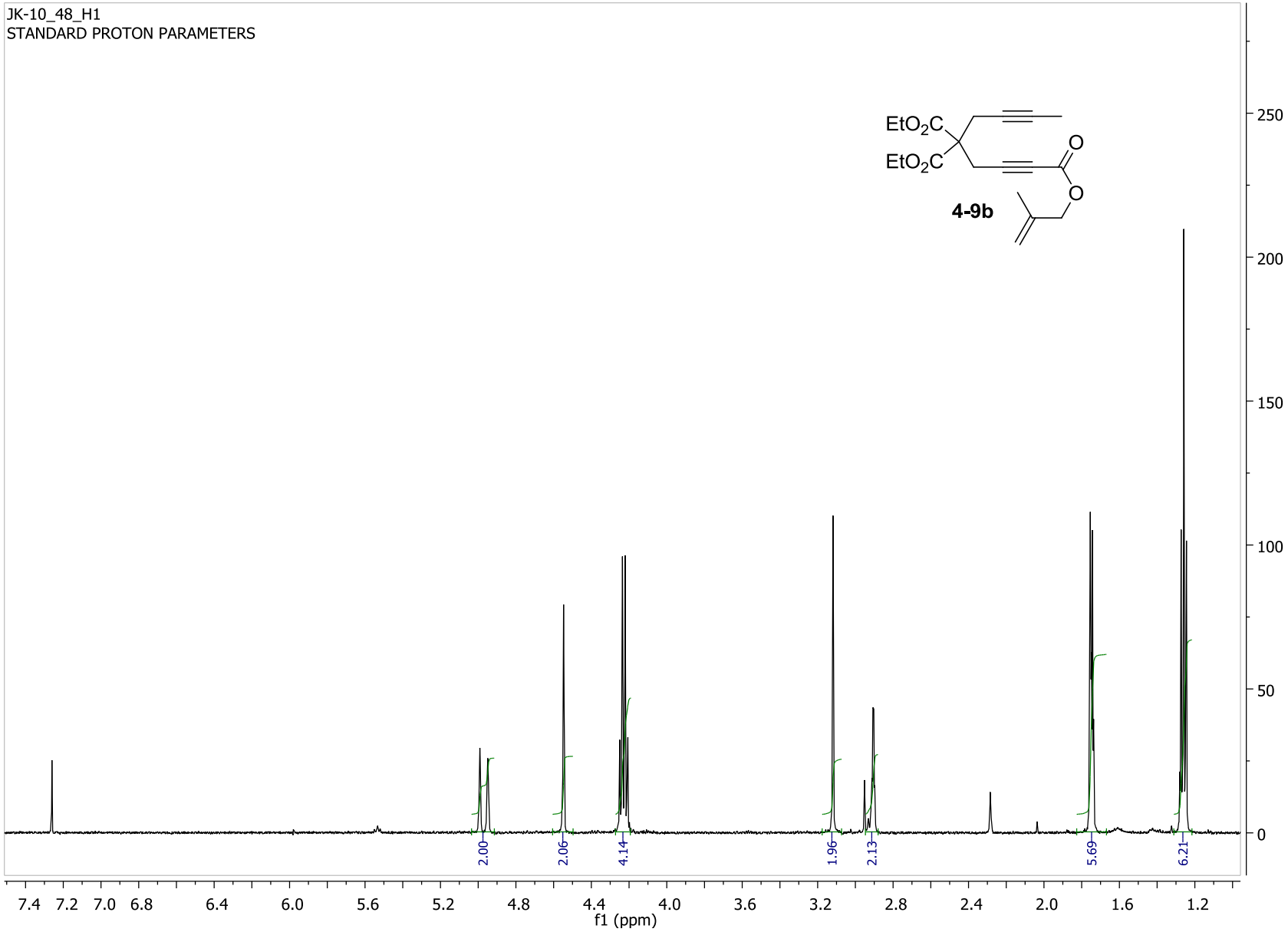

JK-11_12_C13
JK-11_12
168.91
143.04
137.69
136.28
129.37
129.09
127.46
79.55
78.87
78.21
77.32
77.00
76.68
73.07
64.08
61.75
61.72
56.51
32.58
31.34
27.34
22.90
22.75
21.47
13.96
3.42
EtO2C
EtO2C
NTs
3-8j
f1 (ppm)

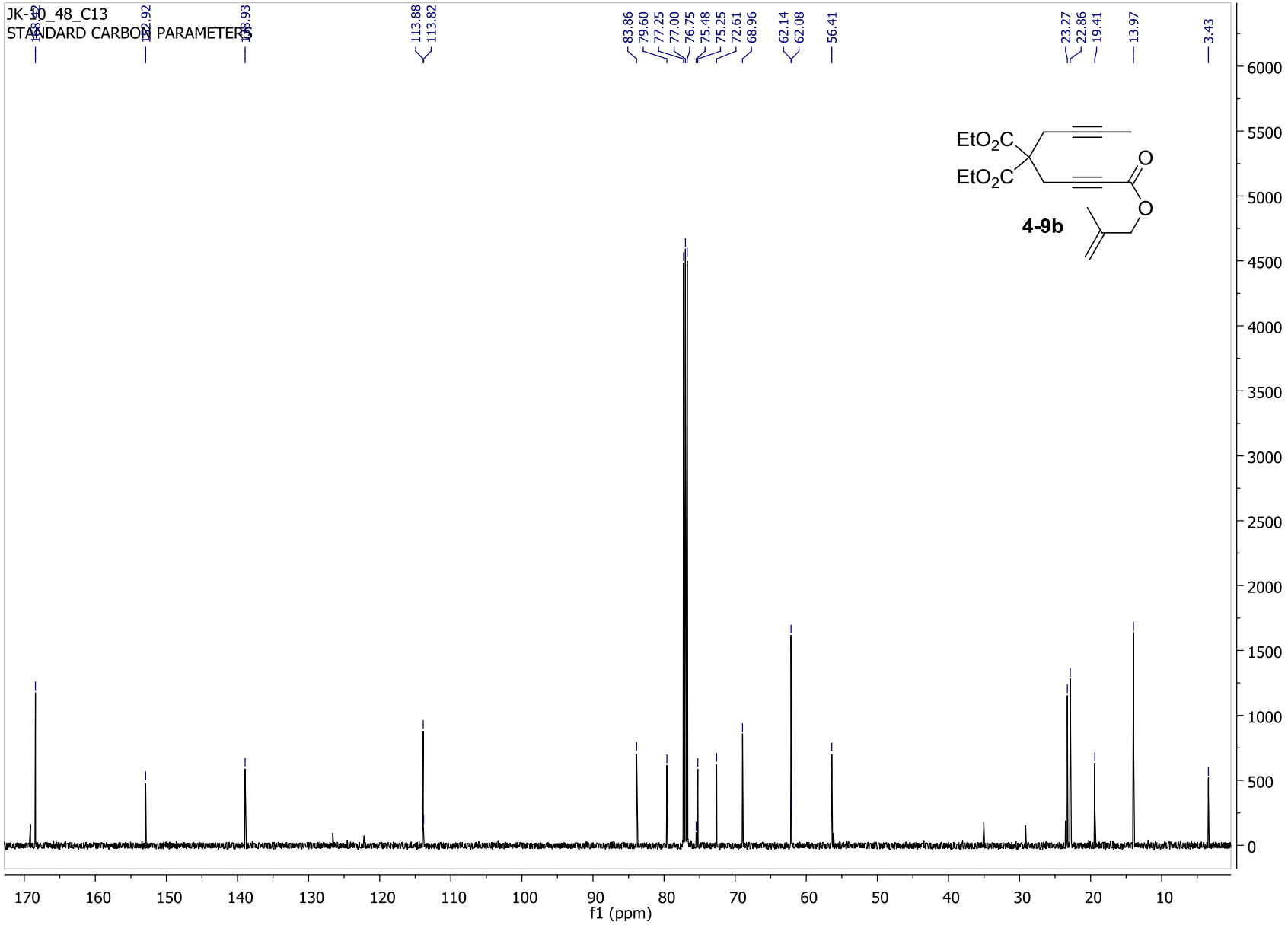

JK-9-51-Frac_3-H1
JK-9-51-frac_3
O
EtO2C
EtO2C
NTs
3-11j
3000
2500
2000
1500
1000
500
0
2.00
2.00
7.24
5.90
3.77
5.74
1.60
8.80
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

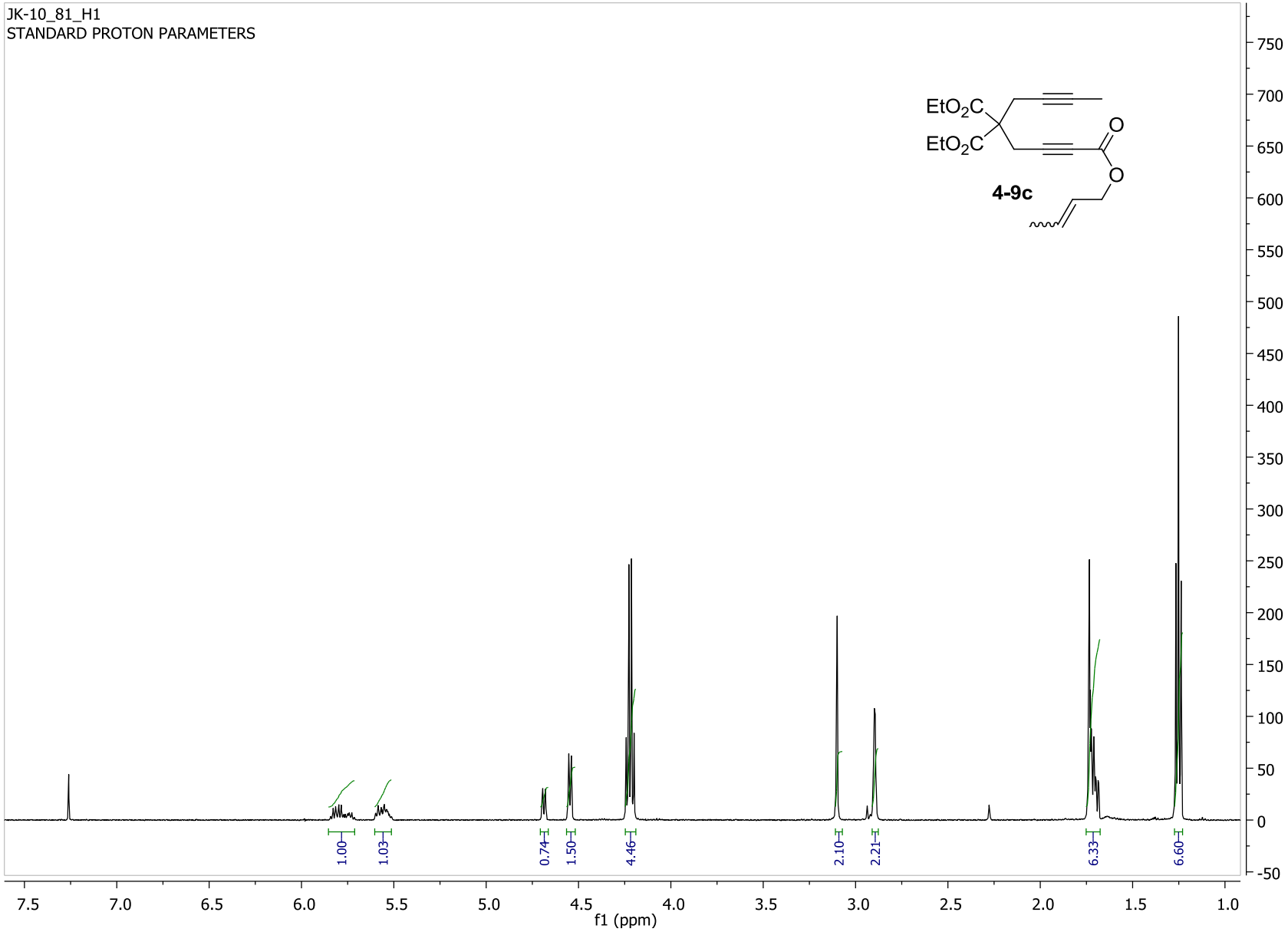

JK-9-51-C13
JK-9-51-carbonylated
199.40
170.68
170.54
146.42
143.75
136.74
132.59
130.44
129.84
127.45
77.32
77.00
76.68
65.32
62.02
61.94
56.90
56.82
52.59
47.22
41.51
39.87
31.32
26.91
21.52
13.99
O
EtO2C
EtO2C
NTs
3-11j
f1 (ppm)

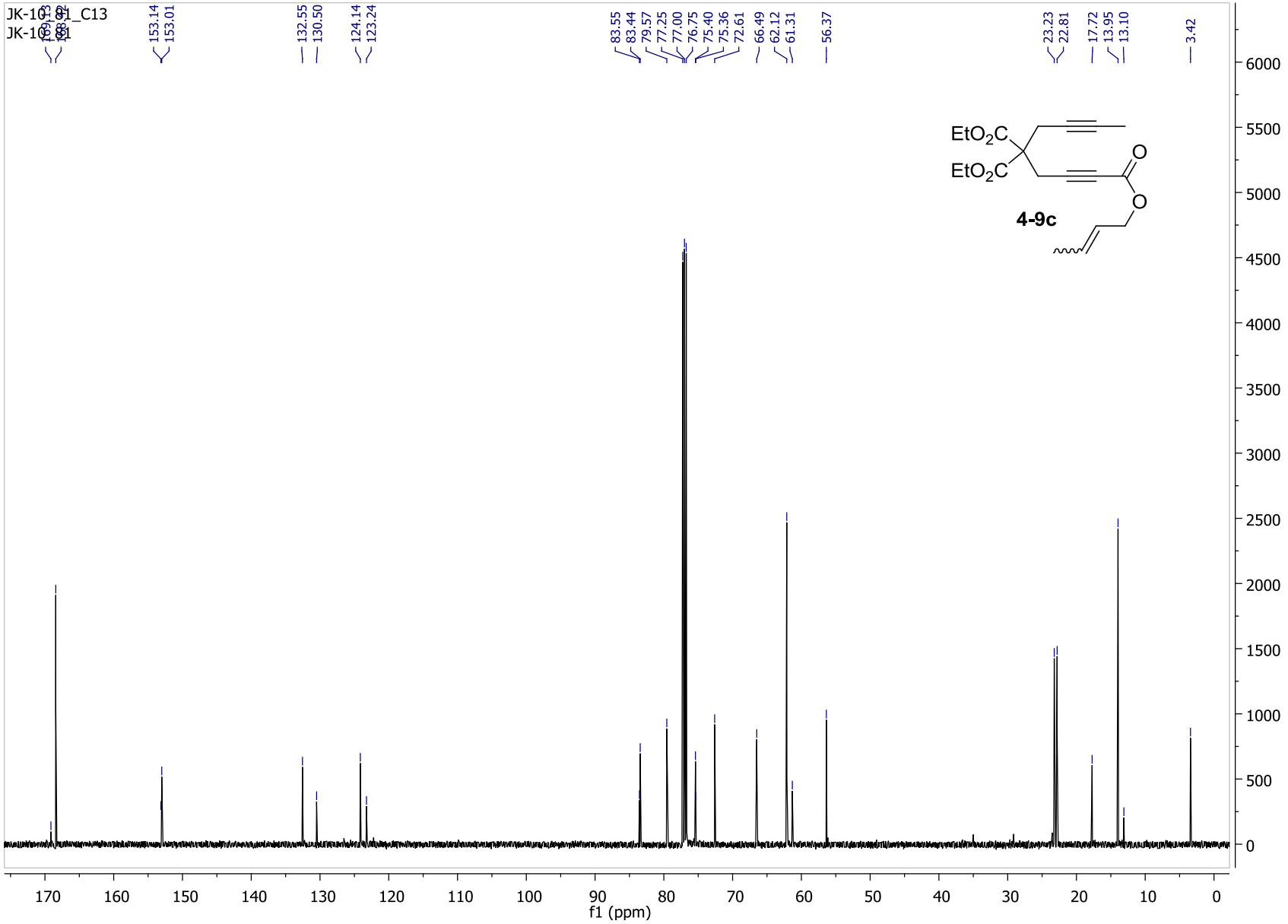

JK-10_80_H1
STANDARD PROTON PARAMETERS
EtO2C
EtO2C
O
O
4-9a
1.00
1.07
1.00
1.96
4.50
2.16
2.14
3.24
6.69
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50

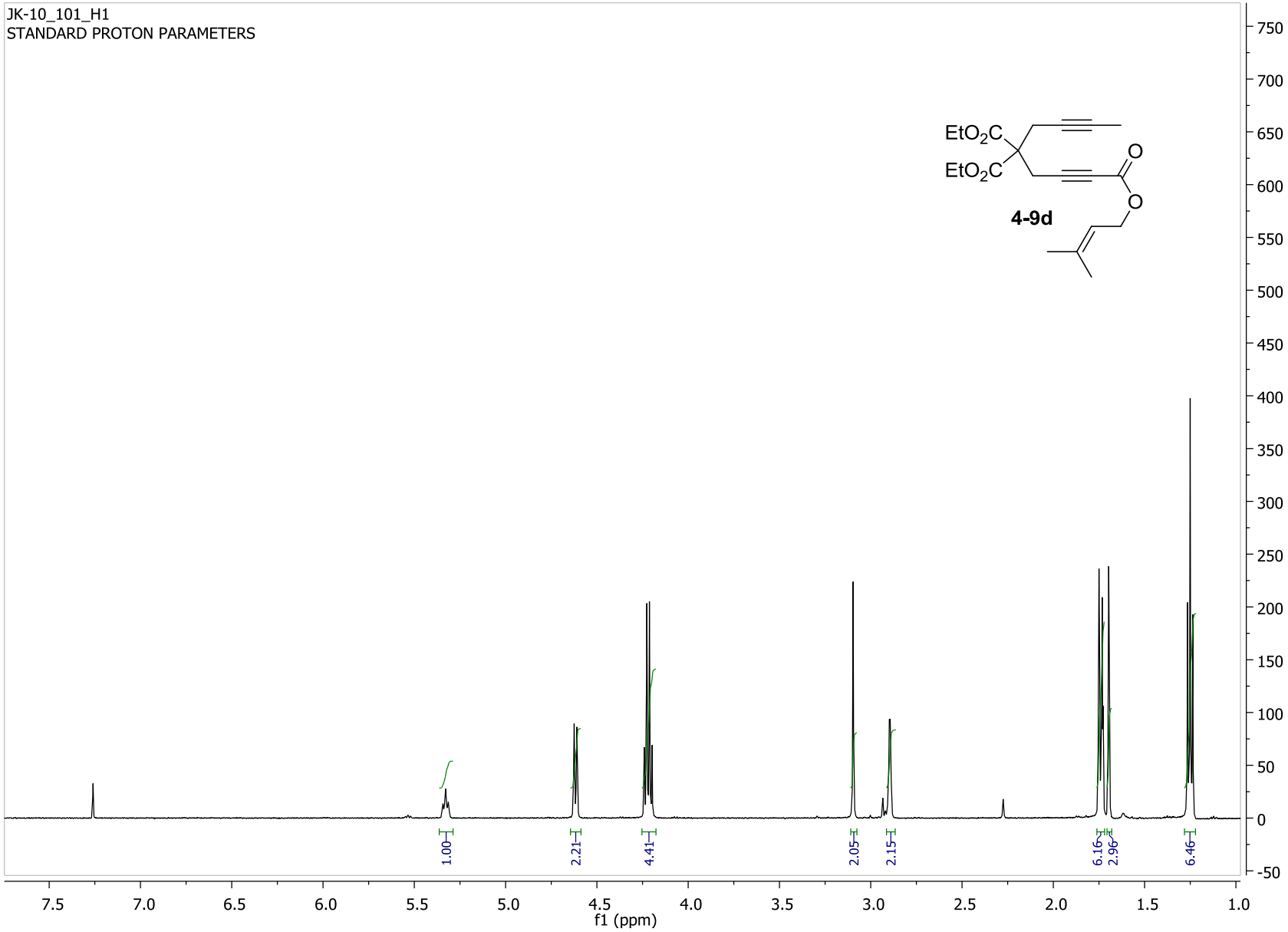

JK-10_80_C13
JK-10_80
168.41
152.84
131.16
119.16
83.84
79.60
77.25
77.00
76.75
75.23
72.58
66.35
62.14
56.38
23.25
22.84
13.96
3.41
EtO2C
EtO2C
O
O
4-9a
f1 (ppm)

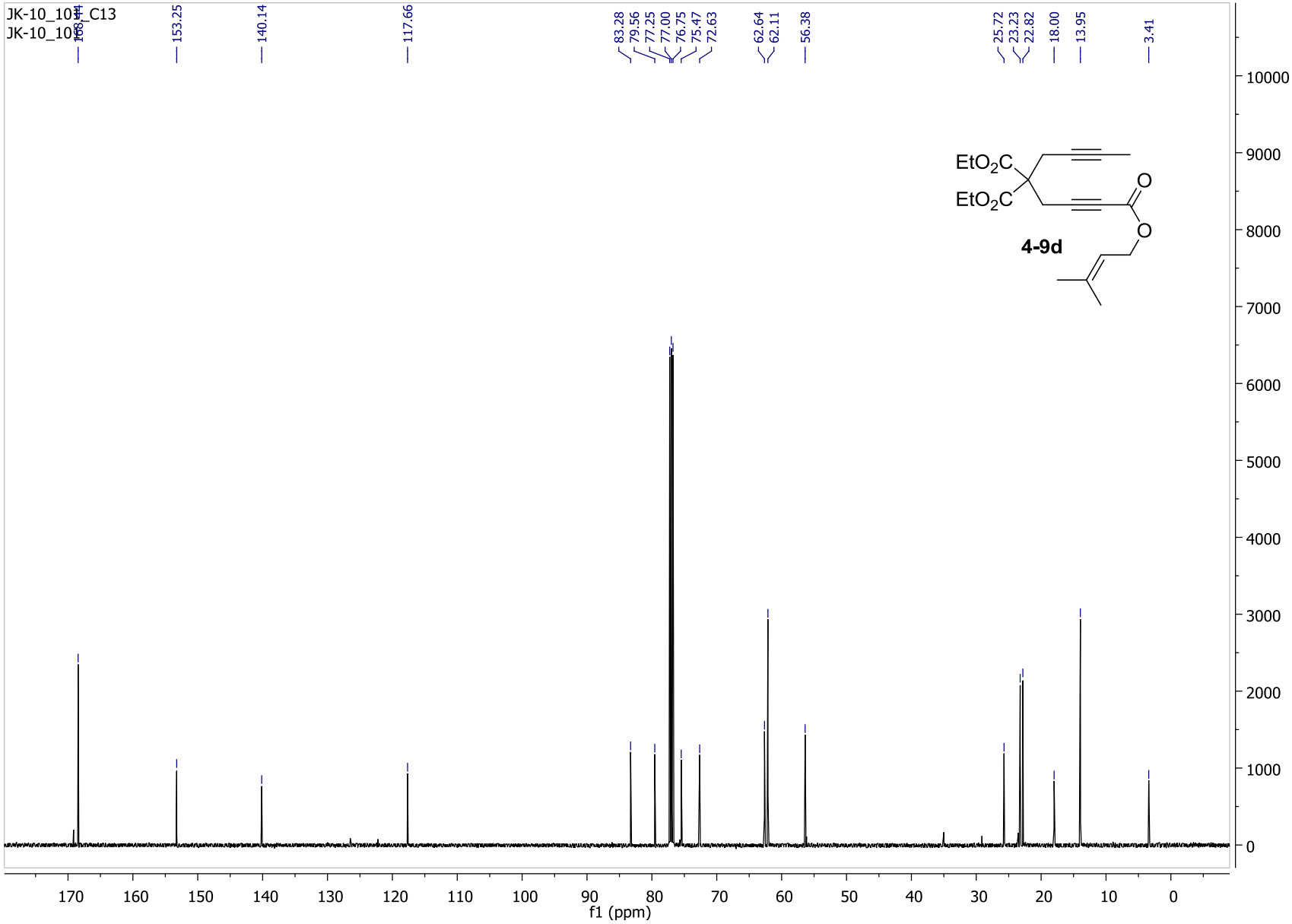

JK-10_48_H1
STANDARD PROTON PARAMETERS
EtO2C
EtO2C
O
O
4-9b
250
200
150
100
50
0
2.00
2.06
4.14
1.96
2.13
5.69
6.21
7.4 7.2 7.0 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2
f1 (ppm)

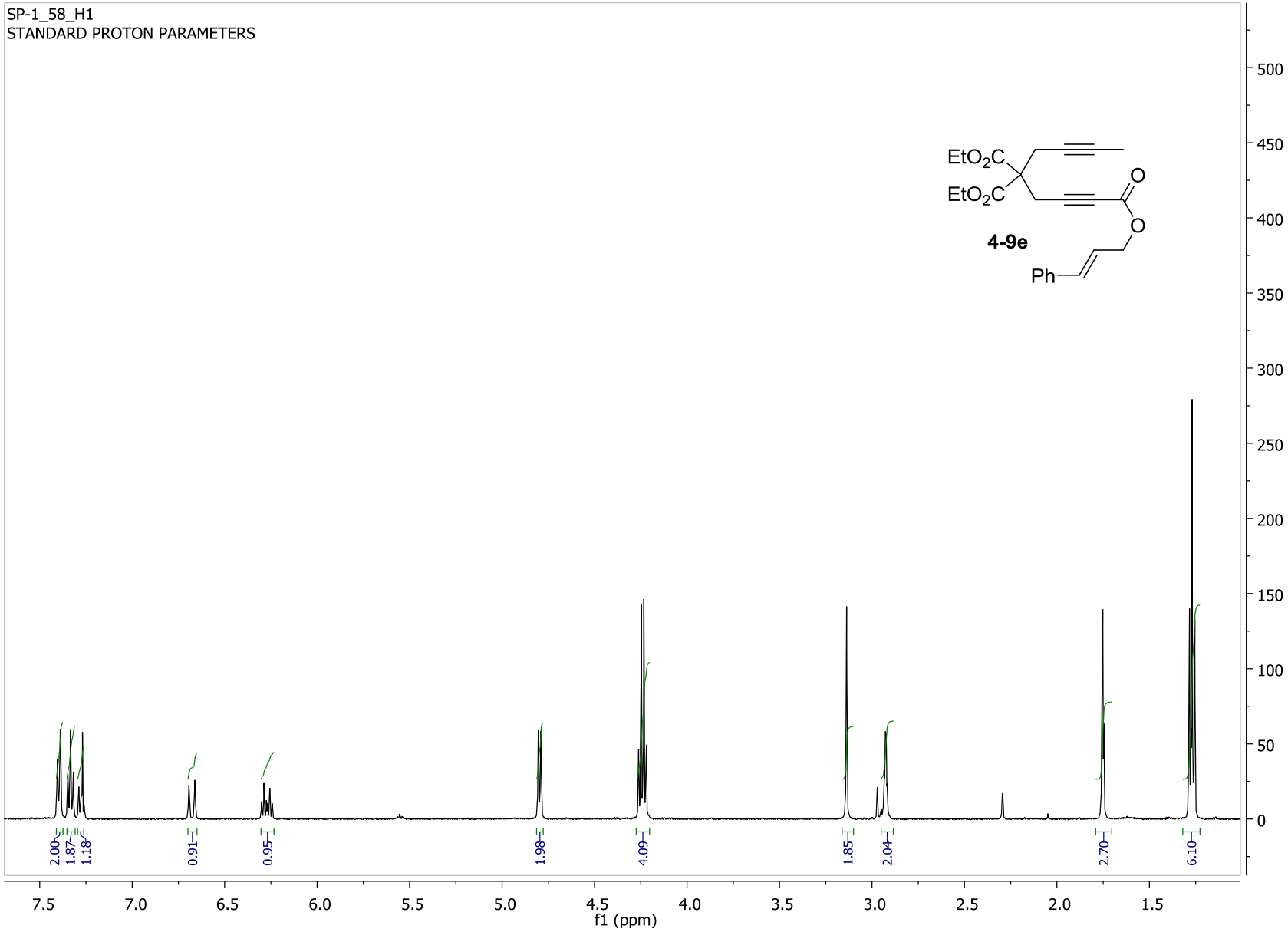

JK-10_48_C13
STANDARD CARBON PARAMETERS
152.92
138.93
113.88
113.82
83.86
79.60
77.25
77.00
76.75
75.48
75.25
72.61
68.96
62.14
62.08
56.41
23.27
22.86
19.41
13.97
3.43
EtO2C
EtO2C
O
O
4-9b
f1 (ppm)

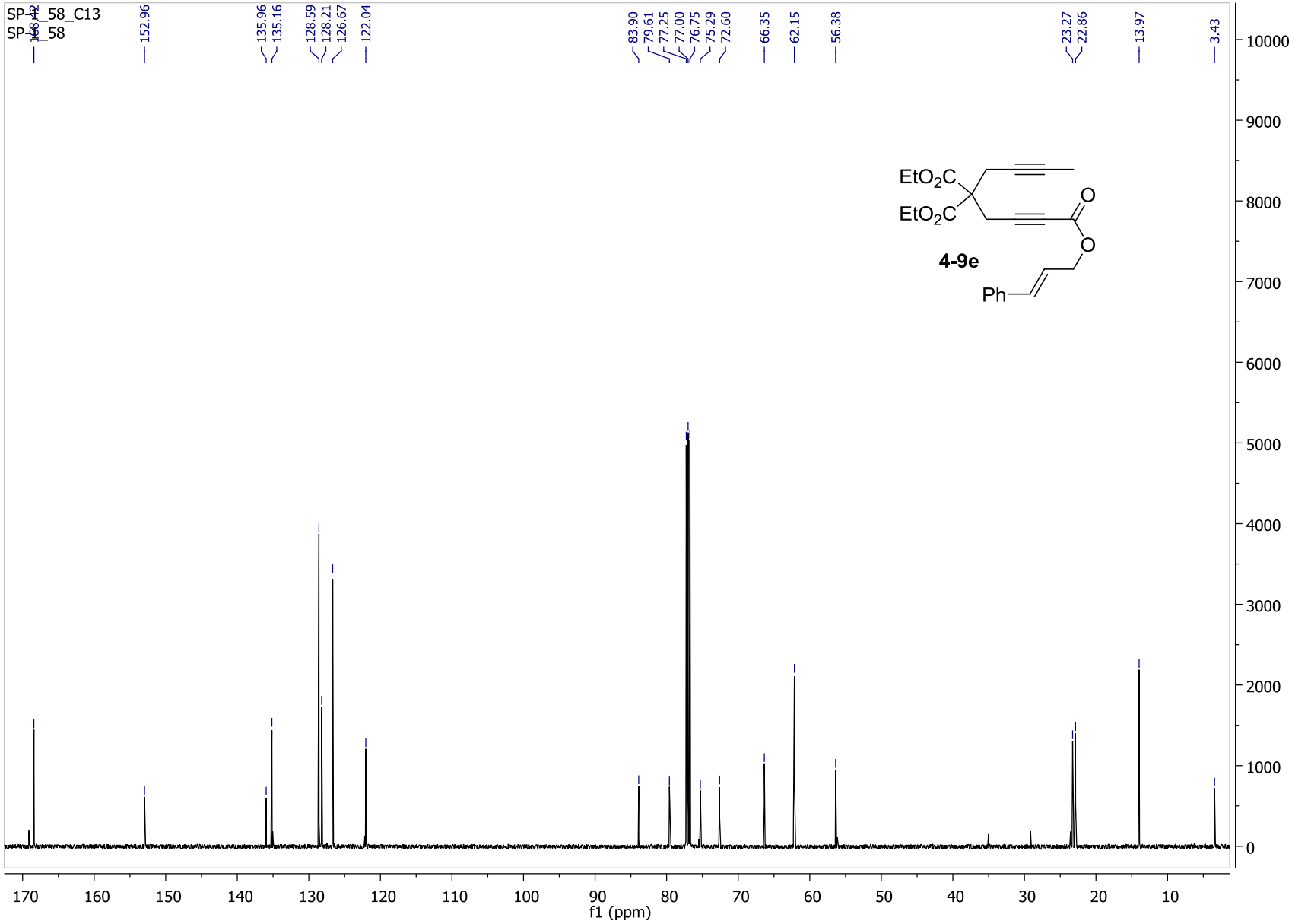

JK-10_81_H1
STANDARD PROTON PARAMETERS
EtO2C
EtO2C
O
O
4-9c
1.00
1.03
0.74
1.50
4.46
2.10
2.21
6.33
6.60
f1 (ppm)

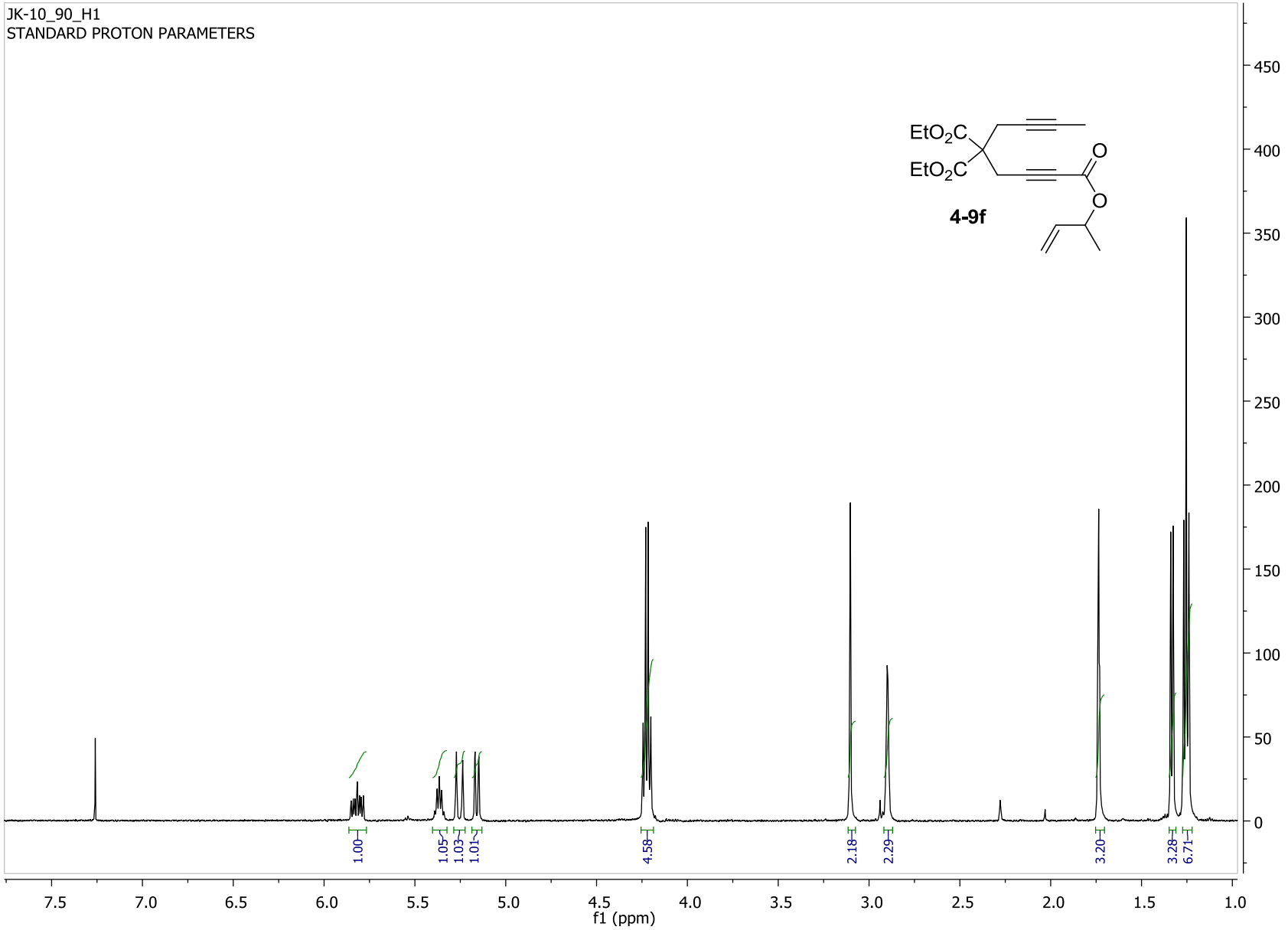

JK-10-81_C13
JK-10-81
169.82
169.68
153.14
153.01
132.55
130.50
124.14
123.24
83.55
83.44
79.57
77.25
77.00
76.75
75.40
75.36
72.61
66.49
62.12
61.31
56.37
23.23
22.81
17.72
13.95
13.10
3.42
EtO2C
EtO2C
O
O
4-9c
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

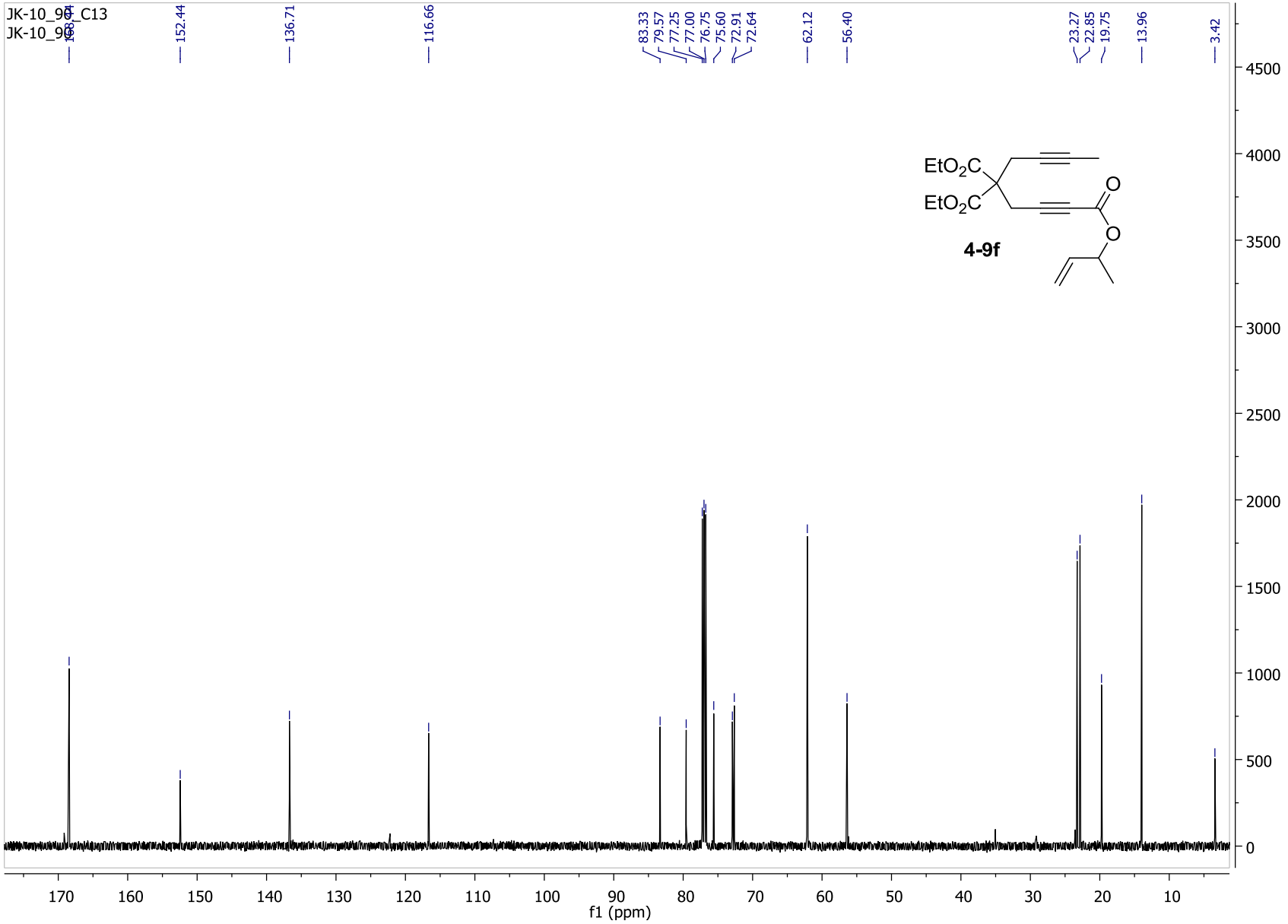

JK-10_101_H1
STANDARD PROTON PARAMETERS
EtO2C
EtO2C
O
O
4-9d
1.00
2.21
4.41
2.05
2.15
6.16
2.96
6.46
f1 (ppm)

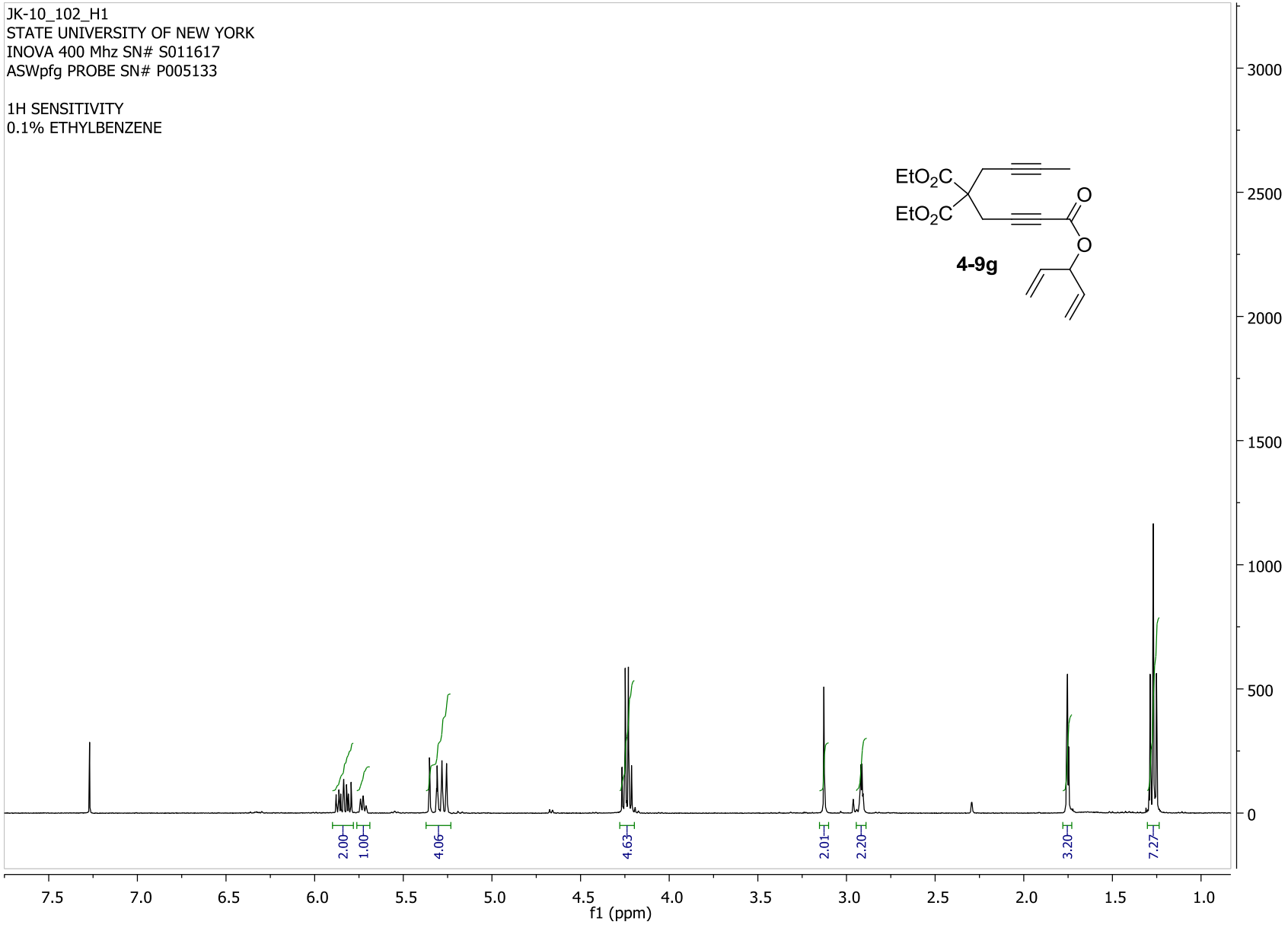

JK-10_104_C13
JK-10_104
168.44
153.25
140.14
117.66
83.28
79.56
77.25
77.00
76.75
75.47
72.63
62.64
62.11
56.38
25.72
23.23
22.82
18.00
13.95
3.41
EtO2C
EtO2C
O
O
4-9d
f1 (ppm)

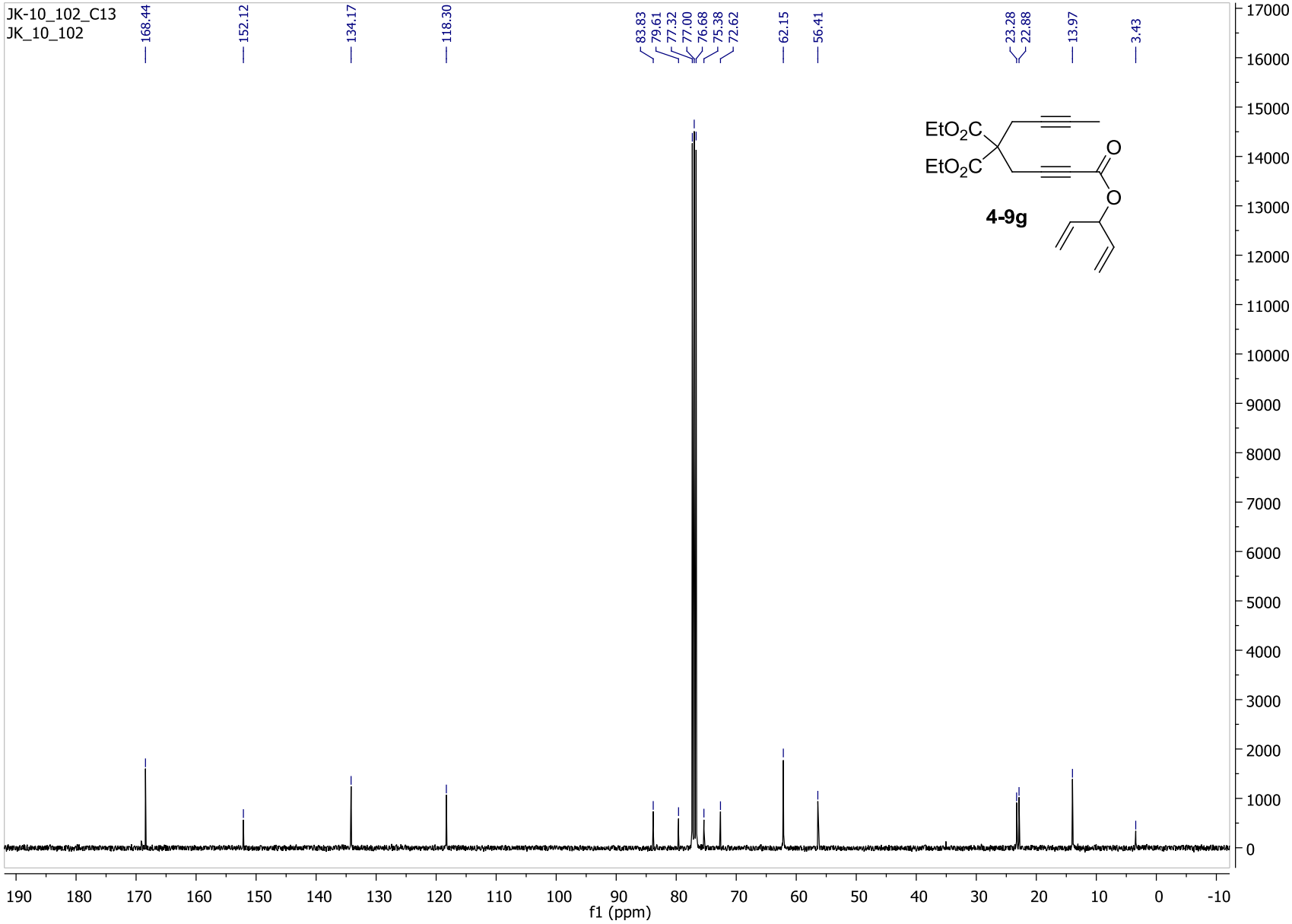

SP-1_58_H1
STANDARD PROTON PARAMETERS
EtO2C
EtO2C
O
O
4-9e
Ph
2.00
1.87
1.18
0.91
0.95
1.98
4.09
1.85
2.04
2.70
6.10
f1 (ppm)

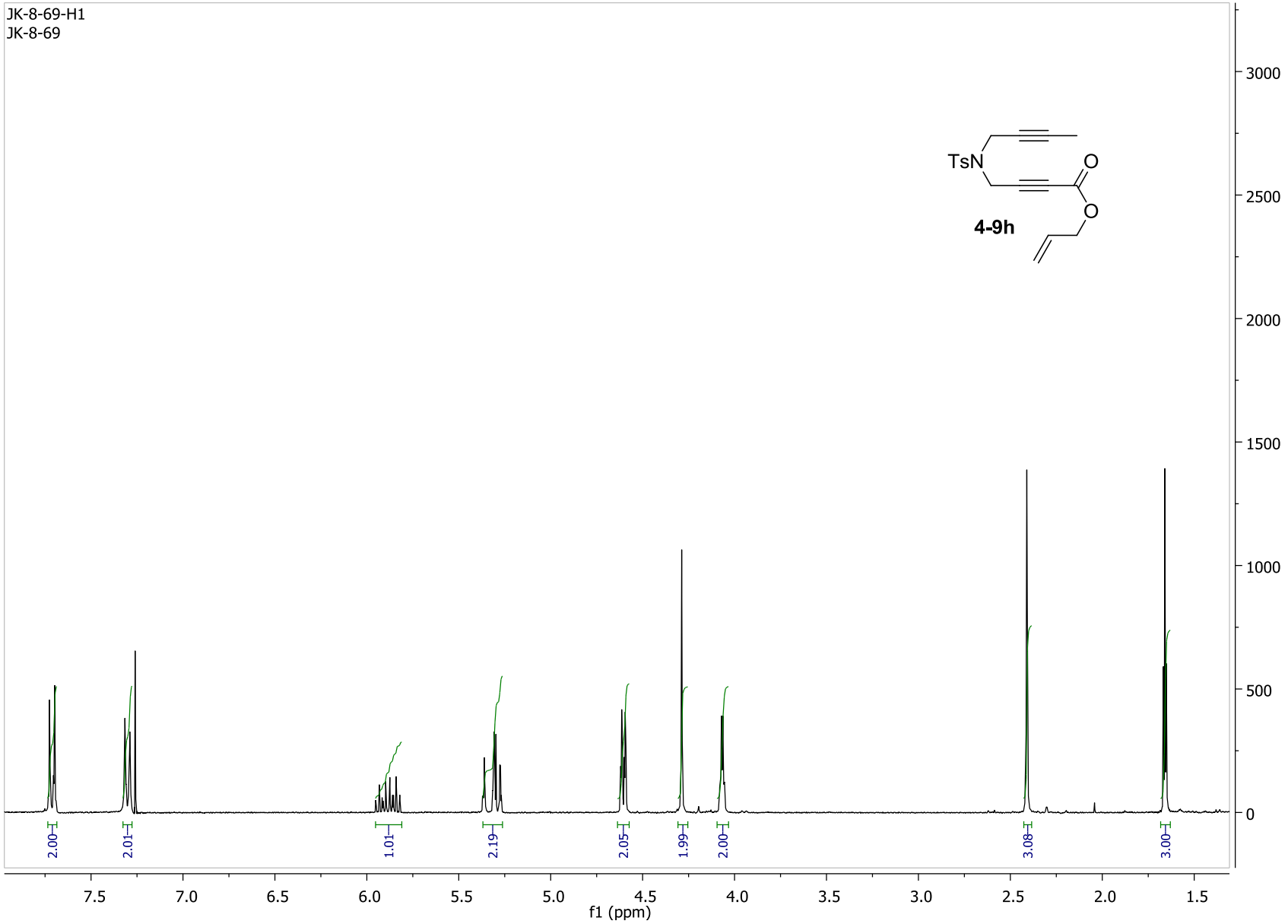

SP-4_58_C13
SP-4_58
168.42
152.96
135.96
135.16
128.59
128.21
126.67
122.04
83.90
79.61
77.25
77.00
76.75
75.29
72.60
66.35
62.15
56.38
23.27
22.86
13.97
3.43
EtO2C
EtO2C
O
O
4-9e
Ph
f1 (ppm)

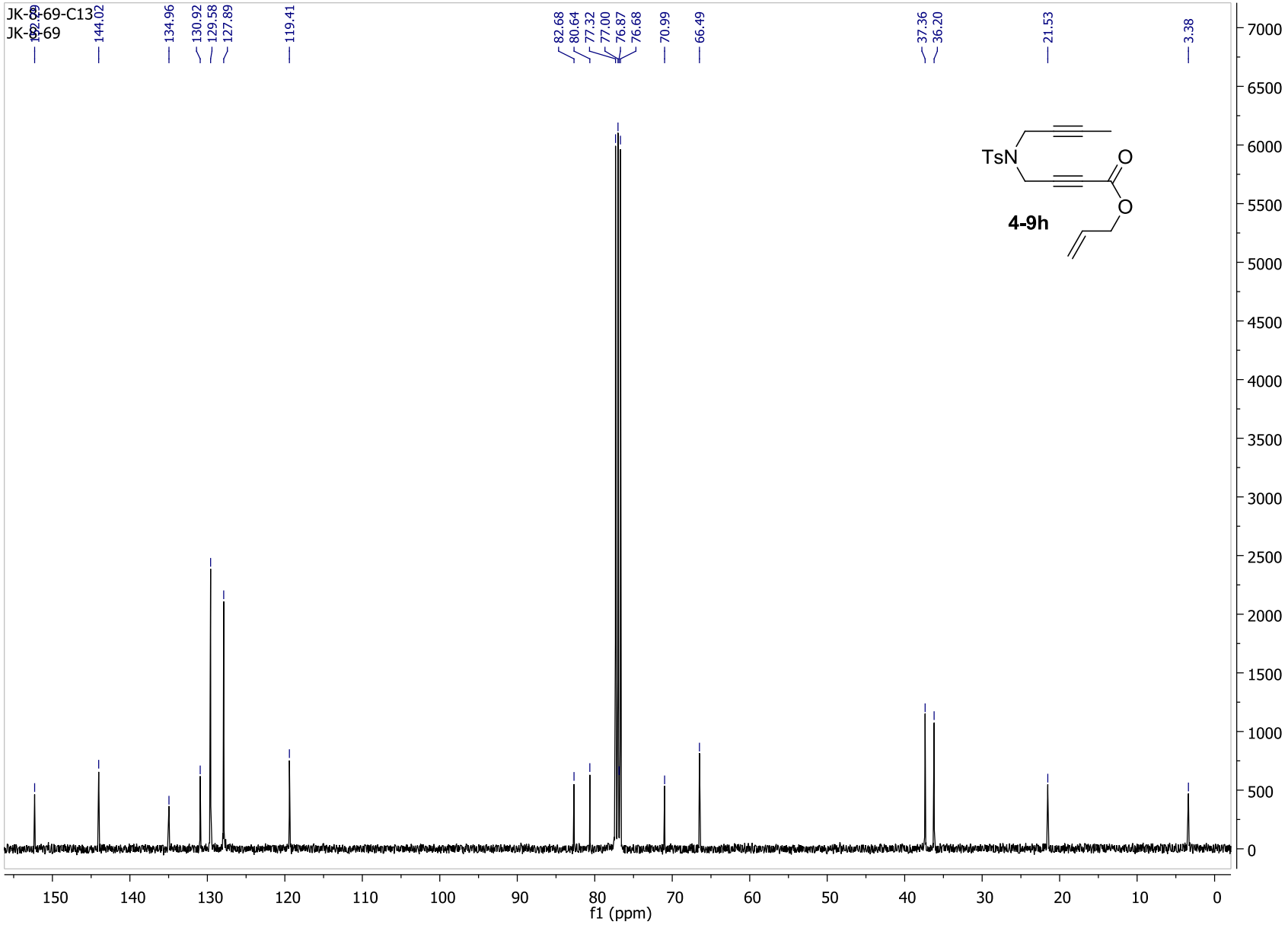

JK-10_90_H1
STANDARD PROTON PARAMETERS
EtO2C
EtO2C
O
O
4-9f
1.00
1.05
1.03
1.01
4.58
2.18
2.29
3.20
3.28
6.71
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
450
400
350
300
250
200
150
100
50
0

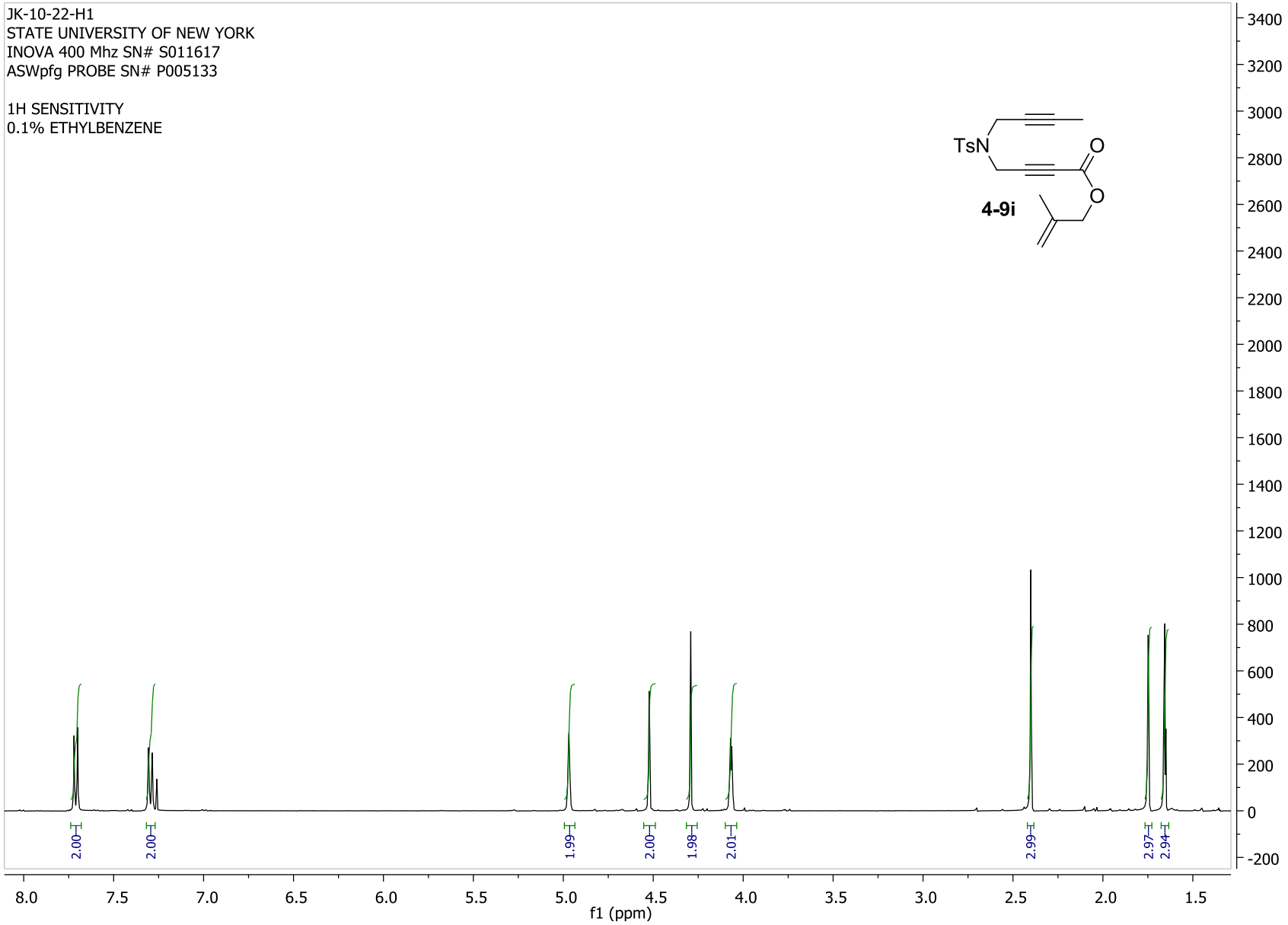

JK-10_9f_C13
JK-10_9f
168.84
152.44
136.71
116.66
83.33
79.57
77.25
77.00
76.75
75.60
72.91
72.64
62.12
56.40
23.27
22.85
19.75
13.96
3.42
EtO2C
EtO2C
O
O
4-9f
4500
4000
3500
3000
2500
2000
1500
1000
500
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

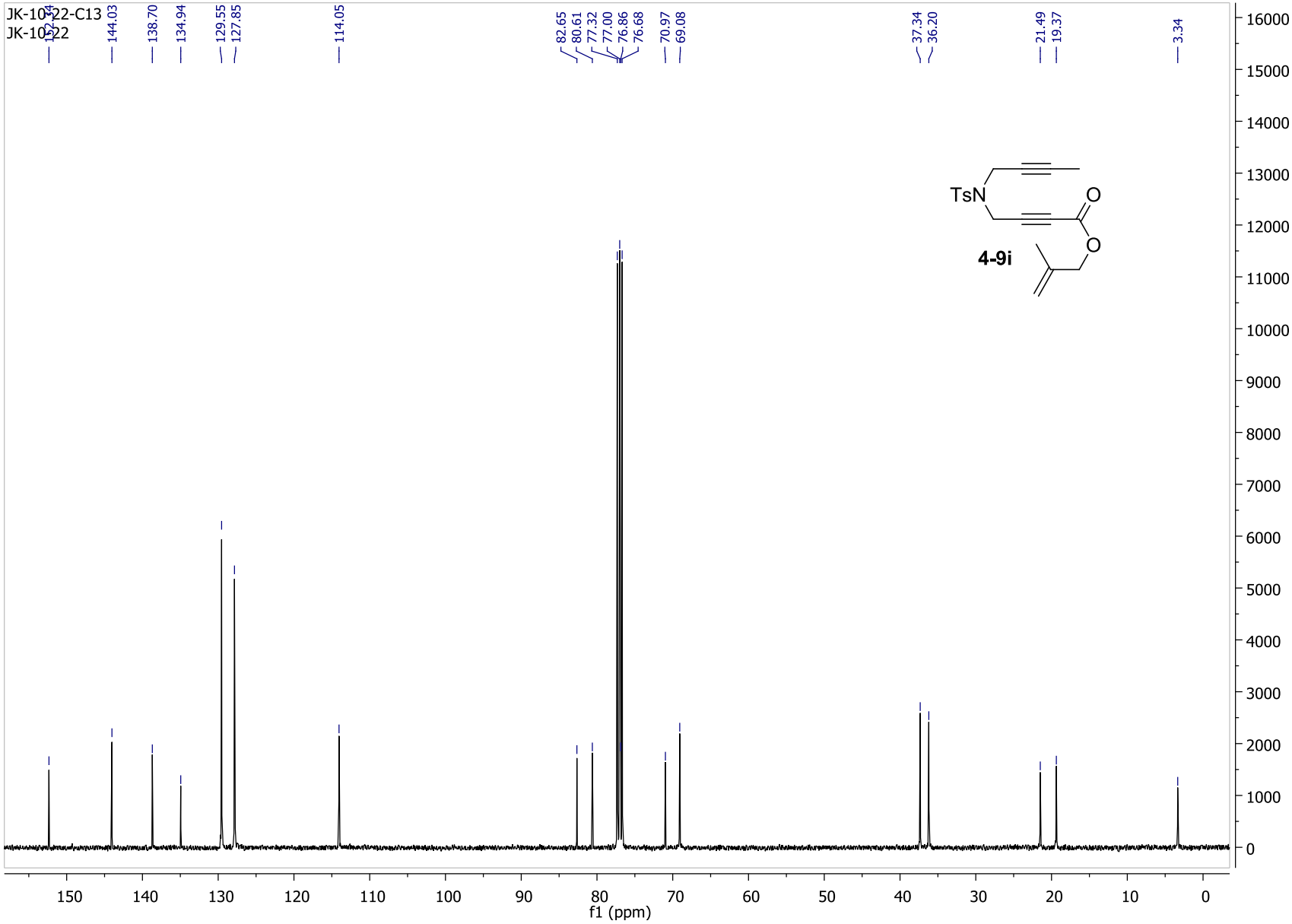

JK-10_102_H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
EtO2C
EtO2C
O
O
4-9g
2.00
1.00
4.06
4.63
2.01
2.20
3.20
7.27
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
3000
2500
2000
1500
1000
500
0

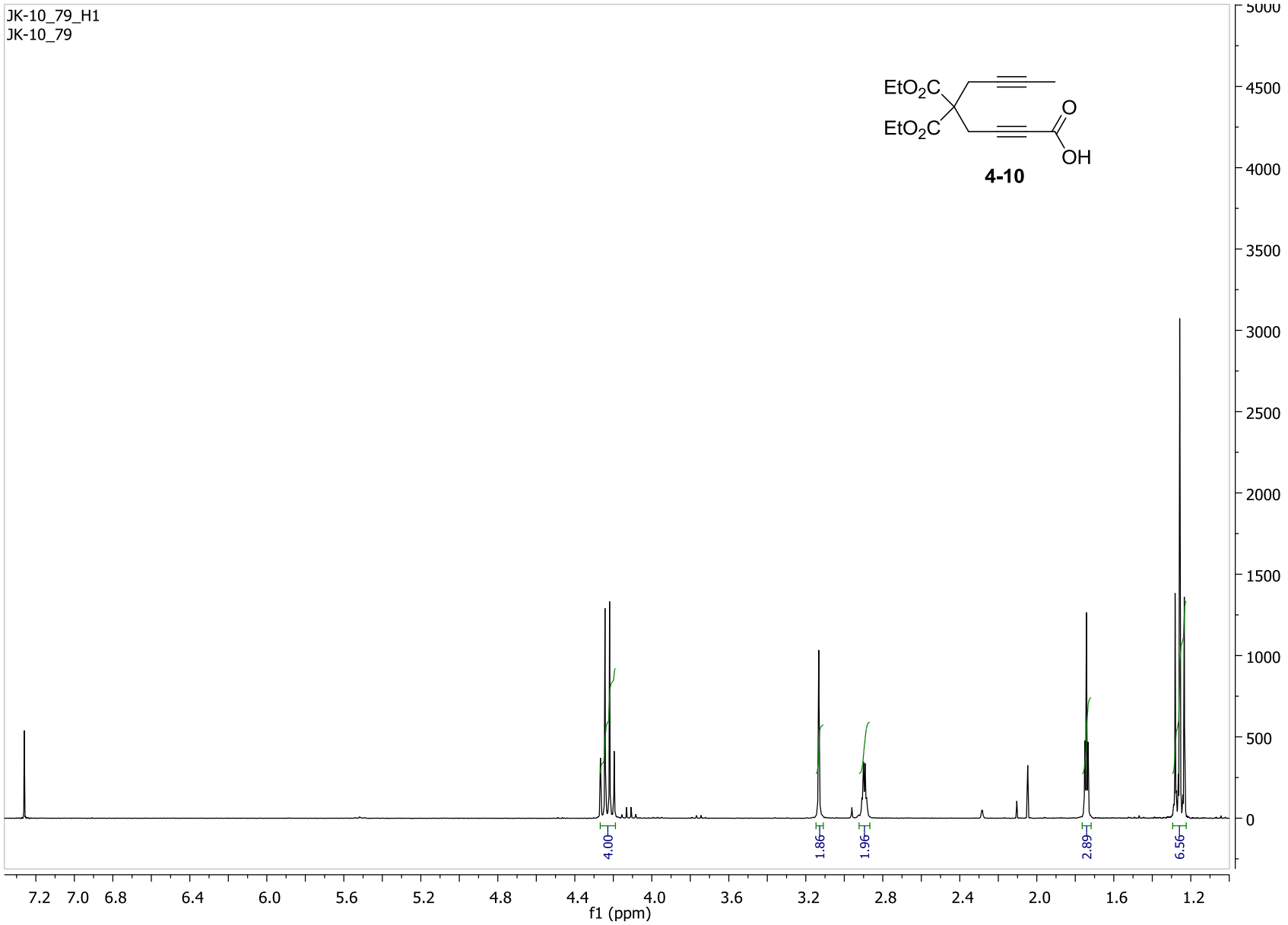

JK-10_102_C13
JK_10_102
168.44
152.12
134.17
118.30
83.83
79.61
77.32
77.00
76.68
75.38
72.62
62.15
56.41
23.28
22.88
13.97
3.43
EtO2C
EtO2C
O
O
4-9g
f1 (ppm)

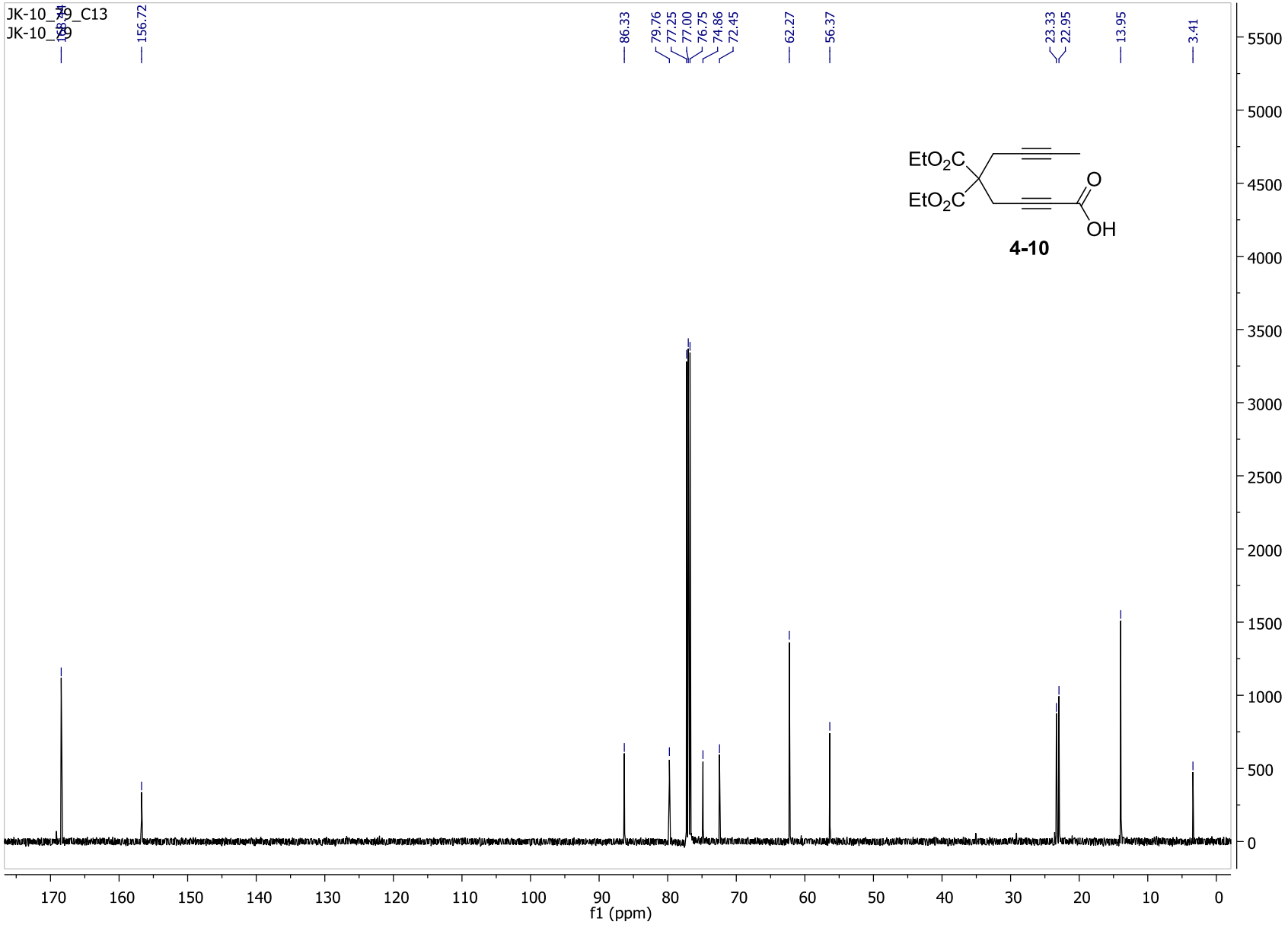

JK-8-69-H1
JK-8-69
TsN
O
O
4-9h
3000
2500
2000
1500
1000
500
0
2.00
2.01
1.01
2.19
2.05
1.99
2.00
3.08
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

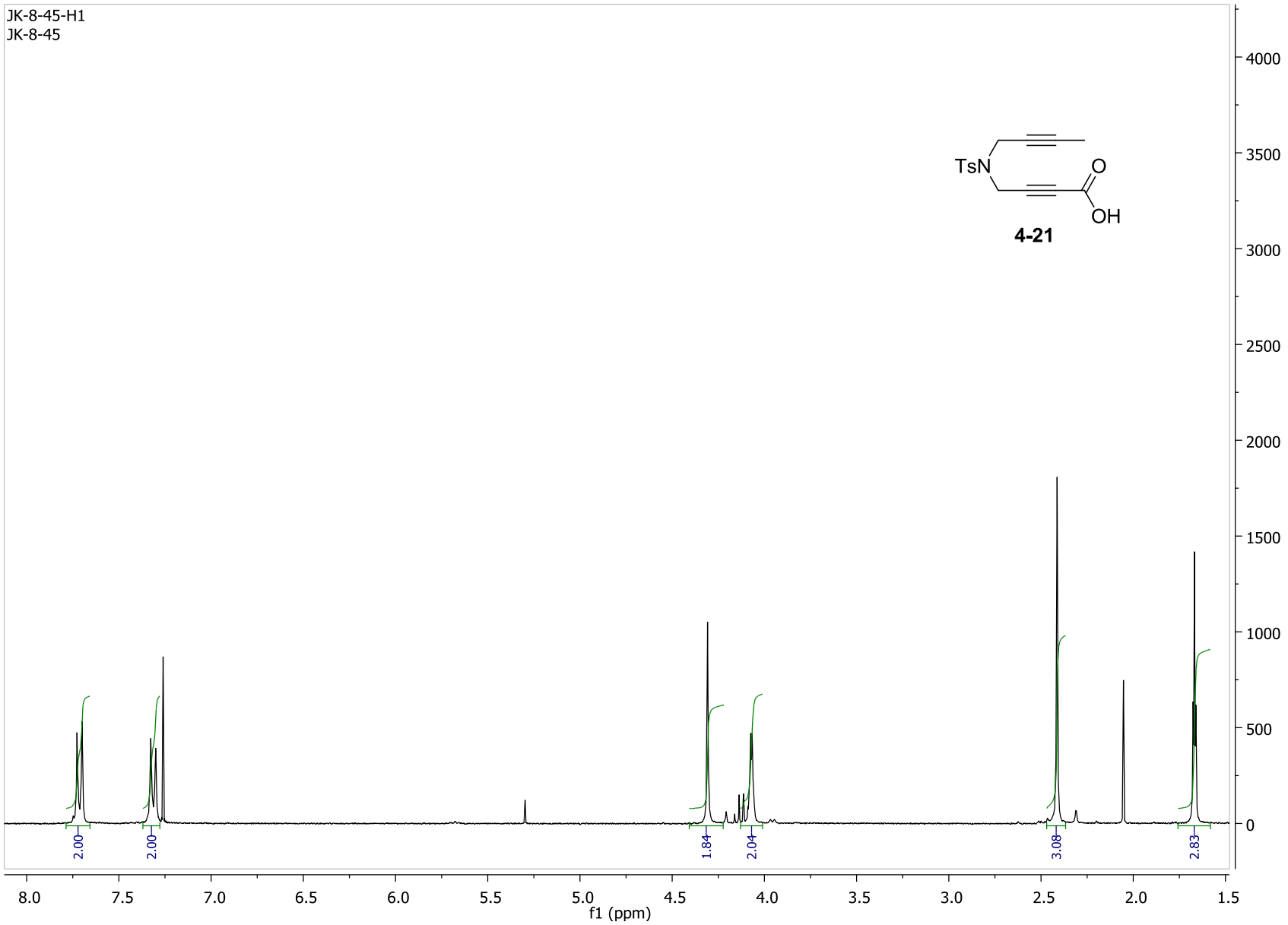

JK-8-69-C13
JK-8-69
144.02
134.96
130.92
129.58
127.89
119.41
82.68
80.64
77.32
77.00
76.87
76.68
70.99
66.49
37.36
36.20
21.53
3.38
TsN
O
O
4-9h
f1 (ppm)

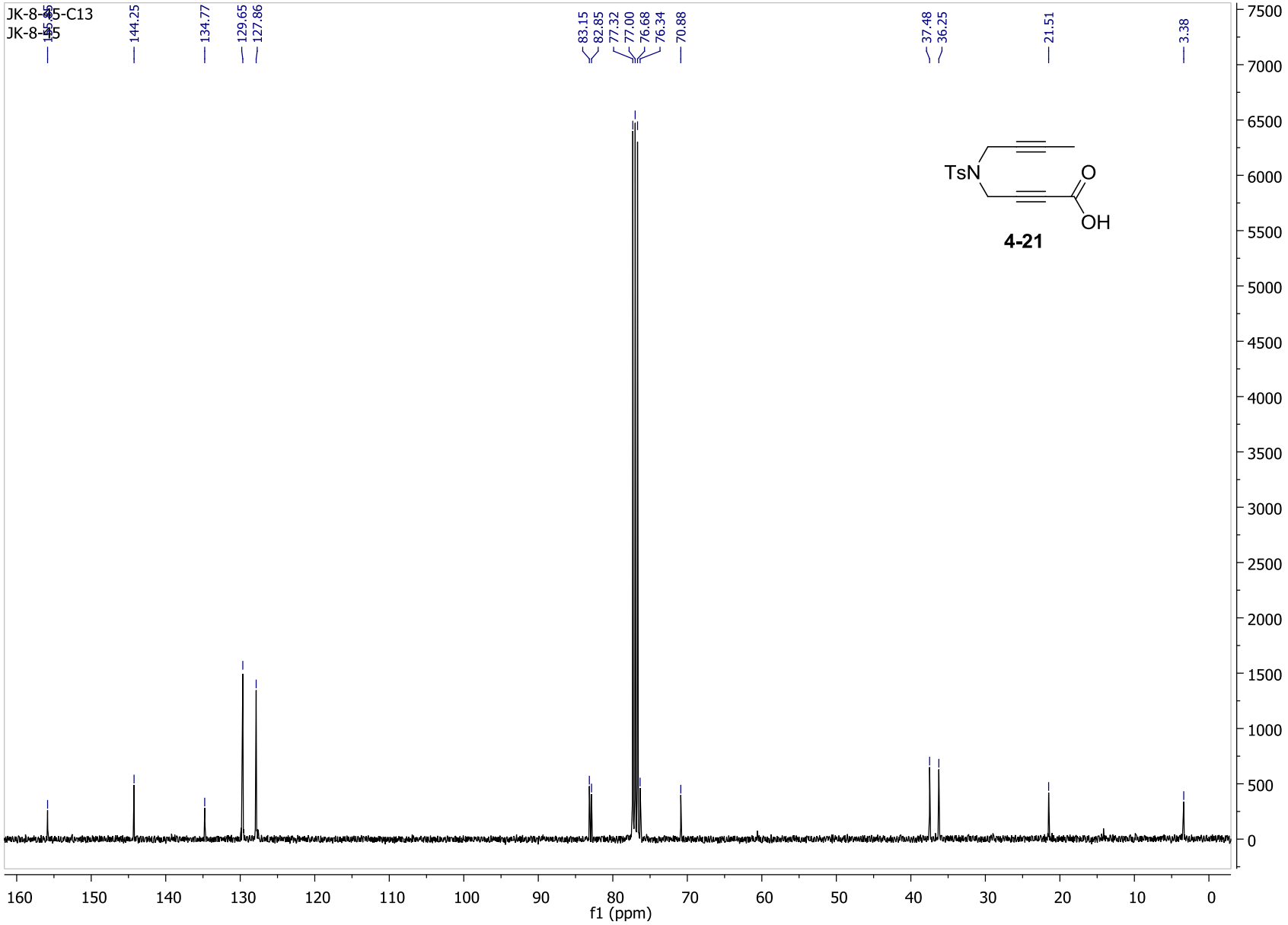

JK-10-22-H1
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
TsN
O
O
4-9i
2.00
2.00
1.99
2.00
1.98
2.01
2.99
2.97
2.94
f1 (ppm)

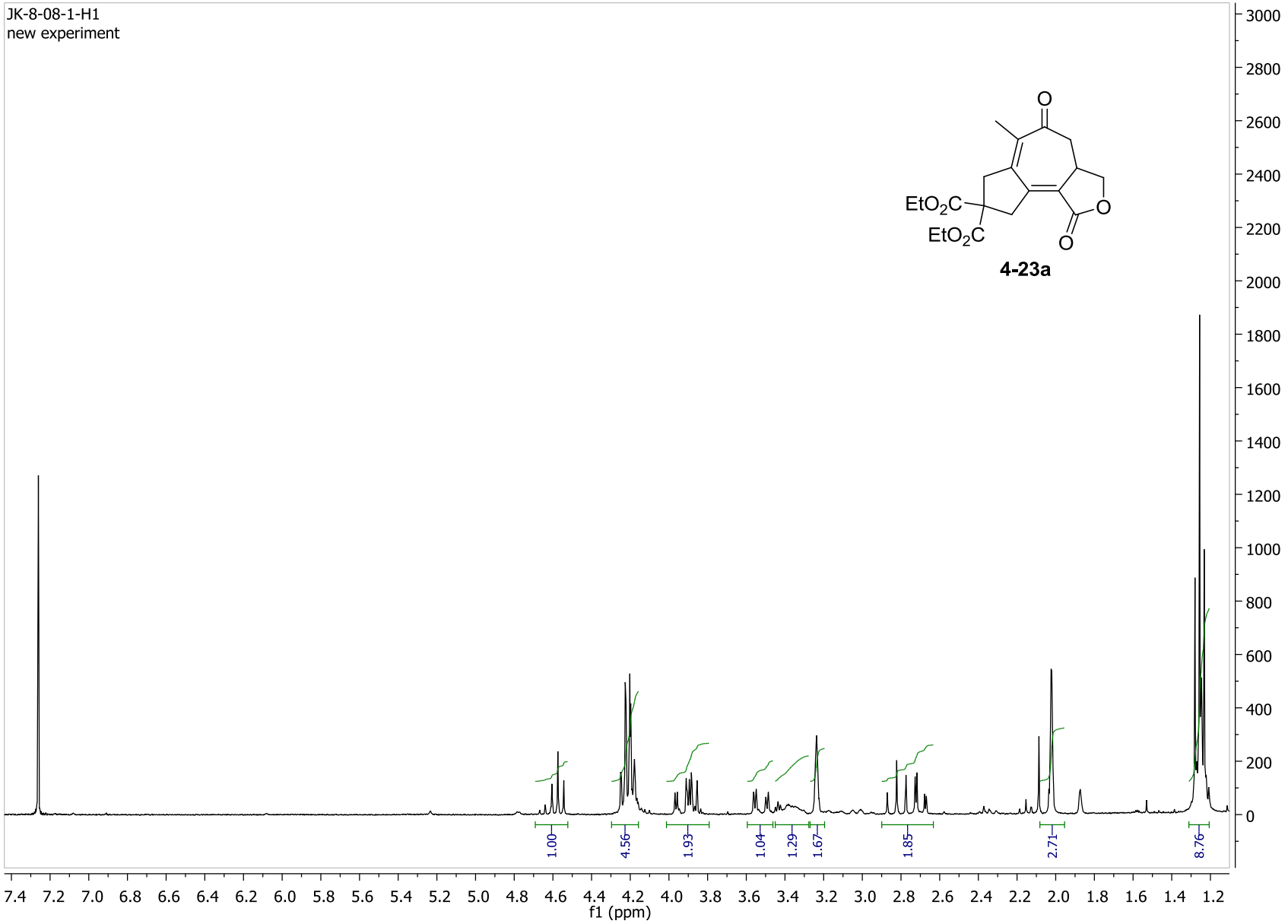

JK-10-22-C13
JK-10-22
152.44
144.03
138.70
134.94
129.55
127.85
114.05
82.65
80.61
77.32
77.00
76.86
76.68
70.97
69.08
37.34
36.20
21.49
19.37
3.34
TsN
O
O
4-9i
f1 (ppm)

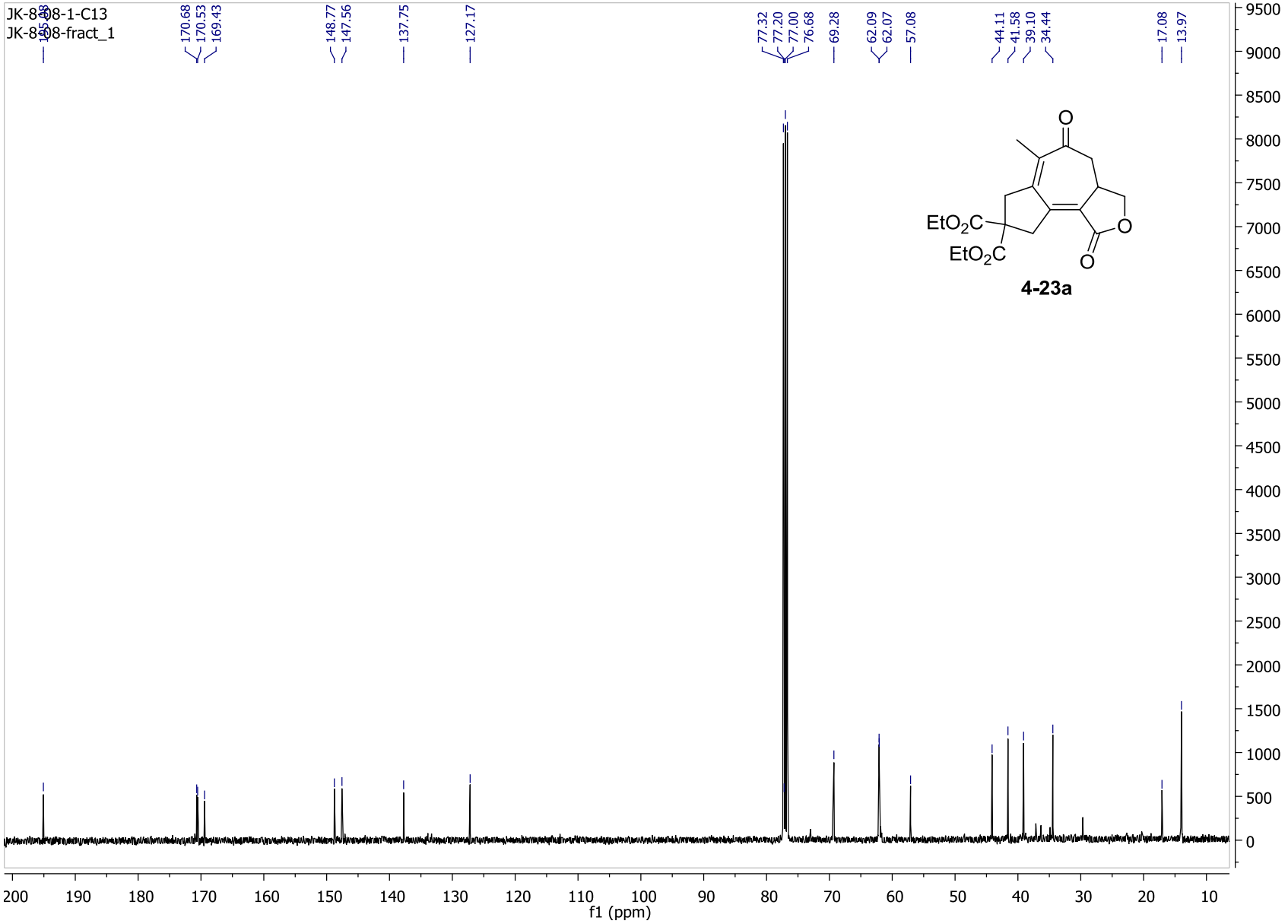

JK-10_79_H1
JK-10_79
EtO2C
EtO2C
O
OH
4-10
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
4.00
1.86
1.96
2.89
6.56
7.2 7.0 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2
f1 (ppm)

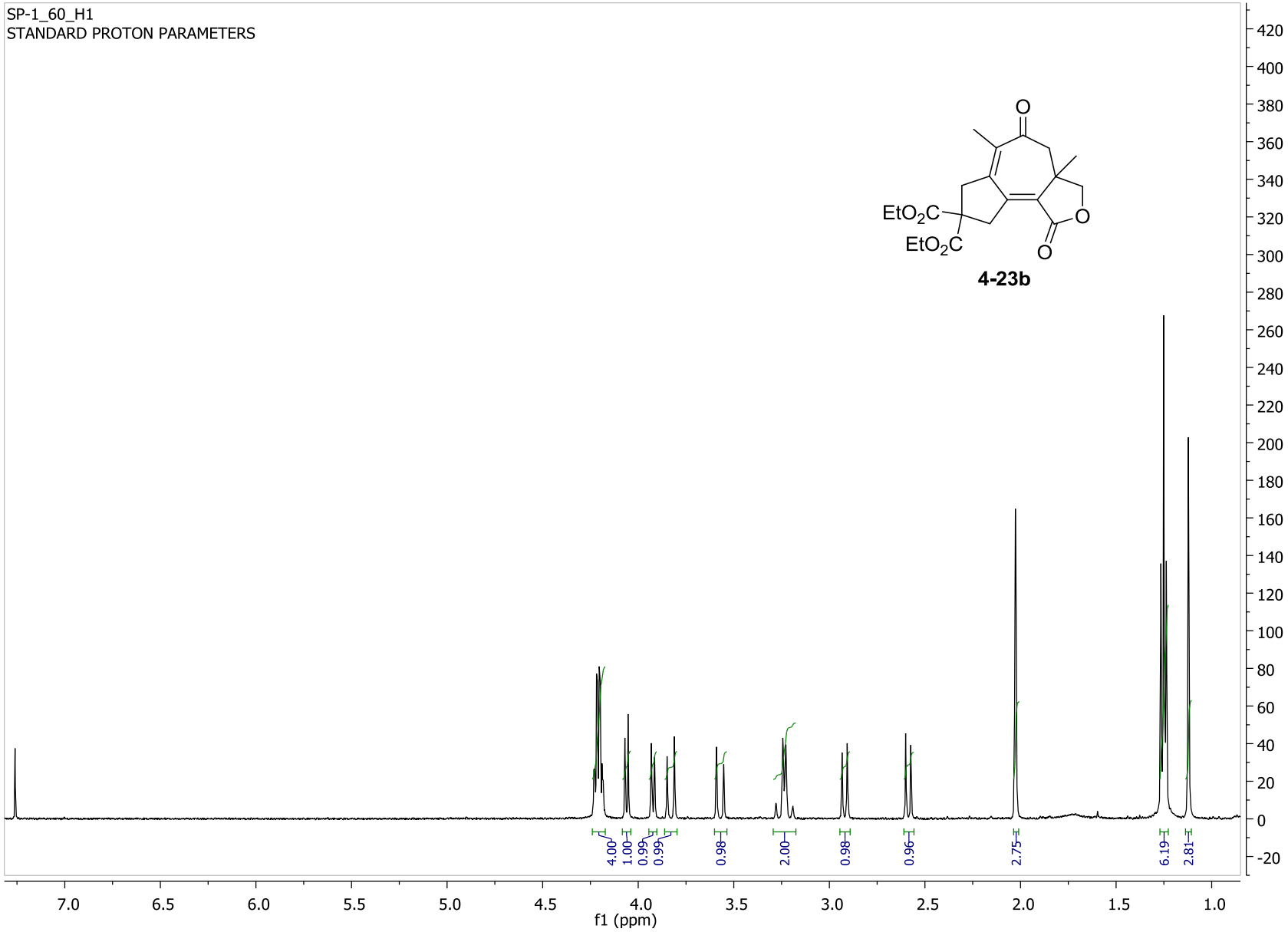

JK-10_79_C13
JK-10_79
156.72
86.33
79.76
77.25
77.00
76.75
74.86
72.45
62.27
56.37
23.33
22.95
13.95
3.41
EtO2C
EtO2C
O
OH
4-10
f1 (ppm)

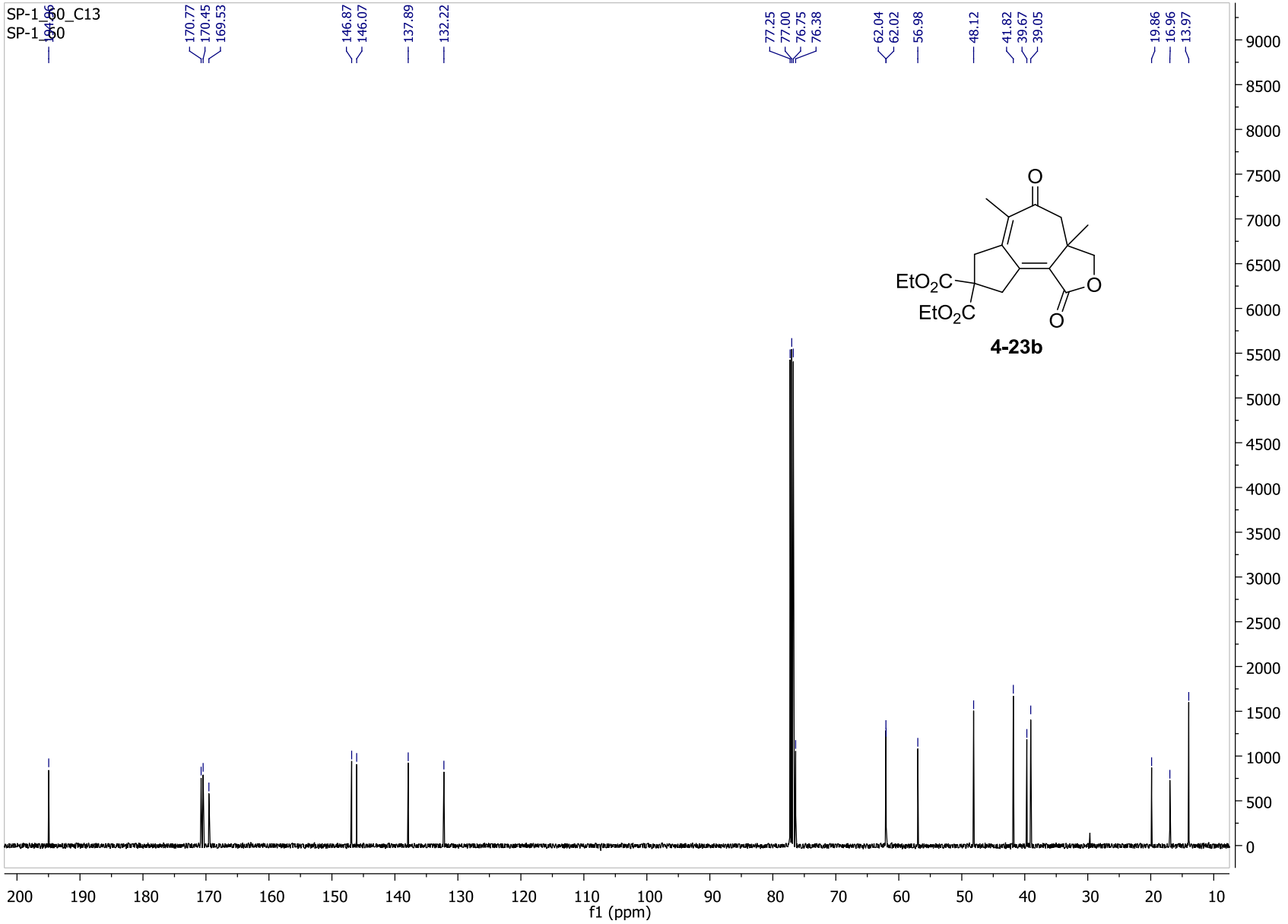

JK-8-45-H1
JK-8-45
TsN
O
OH
4-21
2.00
2.00
1.84
2.04
3.08
2.83
f1 (ppm)

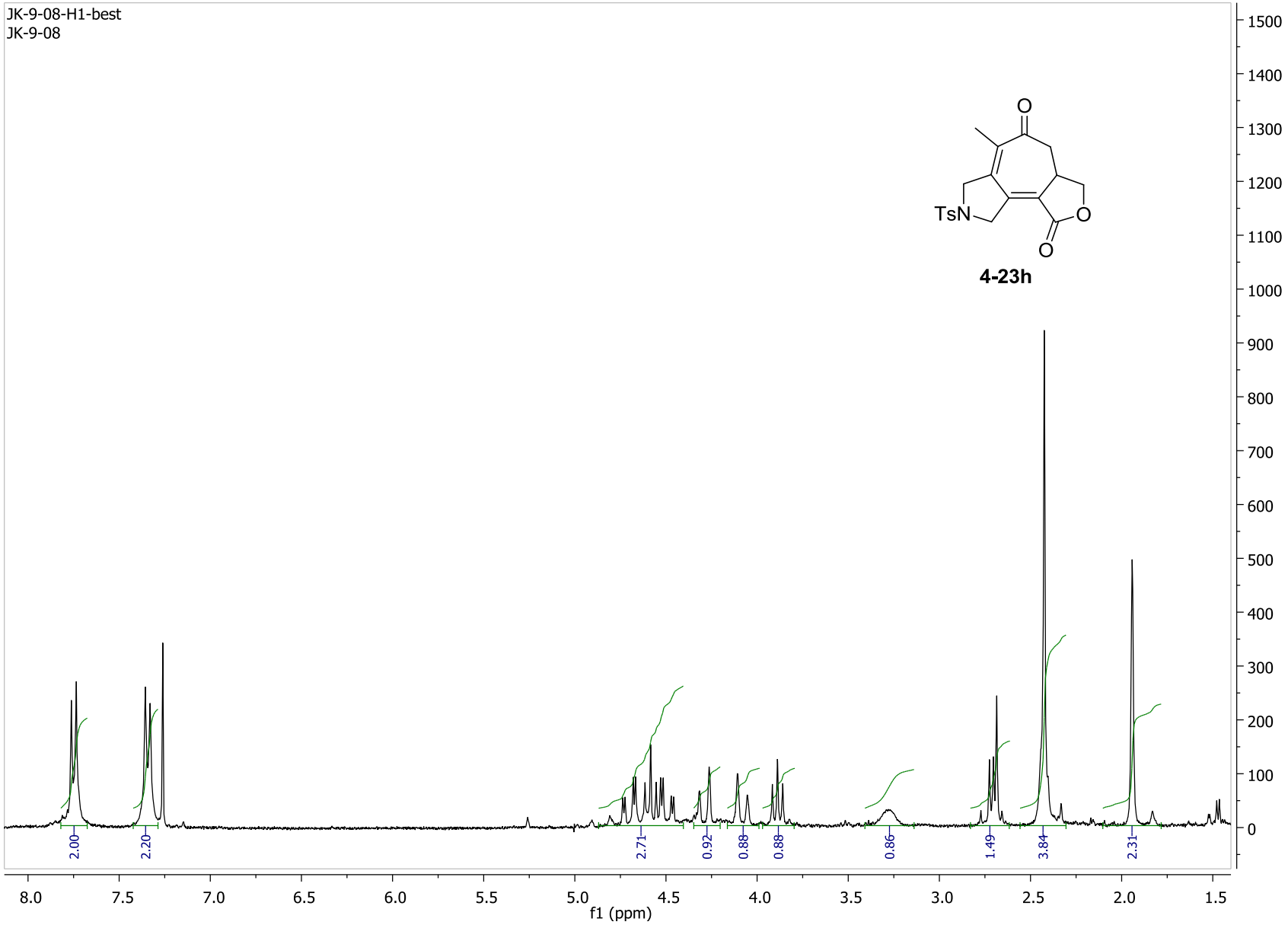

JK-8-45-C13
JK-8-45
144.25
134.77
129.65
127.86
83.15
82.85
77.32
77.00
76.68
76.34
70.88
37.48
36.25
21.51
3.38
TsN
O
OH
4-21
f1 (ppm)

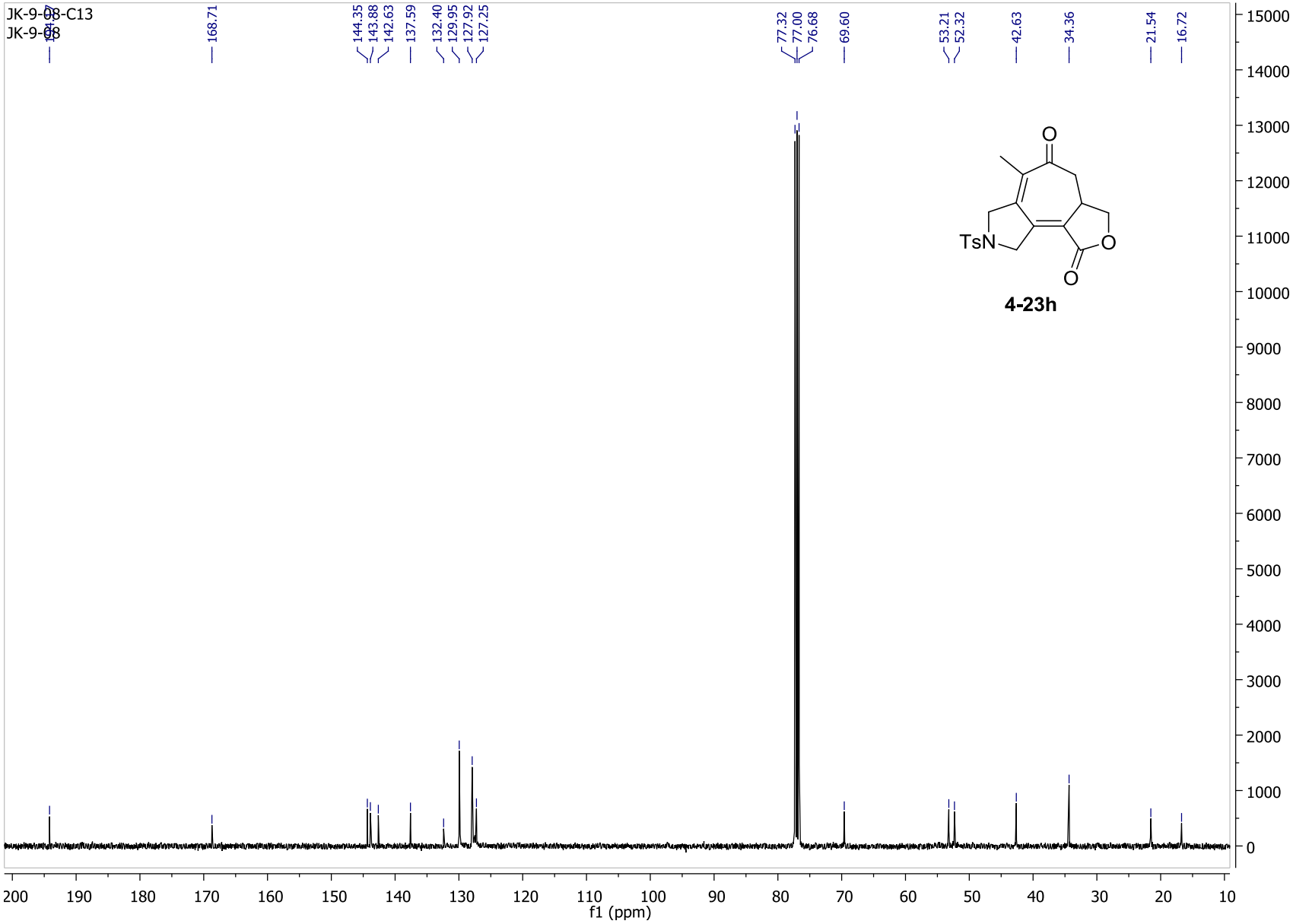

JK-8-08-1-H1
new experiment
O
EtO2C
EtO2C
O
O
4-23a
1.00
4.56
1.93
1.04
1.29
1.67
1.85
2.71
8.76
f1 (ppm)


JK-8508-1-C13
JK-8508-fract_1
165.88
170.68
170.53
169.43
148.77
147.56
137.75
127.17
77.32
77.20
77.00
76.68
69.28
62.09
62.07
57.08
44.11
41.58
39.10
34.44
17.08
13.97
EtO2C
EtO2C
O
O
O
4-23a
f1 (ppm)


SP-1_60_H1
STANDARD PROTON PARAMETERS
O
EtO2C
EtO2C
O
O
4-23b
4.00
1.00
0.99
0.99
0.98
2.00
0.98
0.96
2.75
6.19
2.81
f1 (ppm)


SP-1_60_C13
SP-1_60
194.86
170.77
170.45
169.53
146.87
146.07
137.89
132.22
77.25
77.00
76.75
76.38
62.04
62.02
56.98
48.12
41.82
39.67
39.05
19.86
16.96
13.97
EtO2C
EtO2C
O
O
O
4-23b
f1 (ppm)


JK-9-08-H1-best
JK-9-08
TsN
O
O
O
4-23h
2.00
2.20
2.71
0.92
0.88
0.88
0.86
1.49
3.84
2.31
f1 (ppm)


JK-9-08-C13
JK-9-08
168.71
144.35
143.88
142.63
137.59
132.40
129.95
127.92
127.25
77.32
77.00
76.68
69.60
53.21
52.32
42.63
34.36
21.54
16.72
TsN
O
O
O
4-23h
f1 (ppm)