# GENERATION OF METAL CARBENOIDS AND THE TOTAL SYNTHESIS AND STRUCTURAL REVISION OF PIPERCYCLOBUTANAMIDE A AND PIPERCHABAMIDE G

By

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*To my wife, Zhenzi, who tolerates much and gives more, with love*

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**GENERATION OF METAL CARBENOIDS AND THE TOTAL SYNTHESIS**

**AND STRUCTURAL REVISION OF PIPERCYCLOBUTANAMIDE A AND PIPERCHABAMIDE G**

RENHE LIU

Under the Supervision of Professor Weiping Tang

At the University of Wisconsion-Madison

Metal carbenoids are versatile intermediates in organic synthesis and they are involved in numerous reactions such as cyclopropanation, C-H insertion and metathesis reactions. We have developed a general strategy for the diastereo- and enantioselective introduction of four different substituents to a cyclobutane ring: the three substituents on the cyclopropane ring could be transferred regioselectively and stereospecifically to the cyclobutenoate product via a cyclopropyl metal carbenoid intermediate. A $Rh^{I}$-catalyzed conjugate addition of aryl boronic acid to this cyclobutenoate afforded the fourth substituent diastereoselectively. Proposed

structures for pipercyclobutanamide A and piperchabamide G were completed and they were revised to their six-membered ring isomers chabamide and nigramide F, respectively. The structures of natural products pipercyclobutanamide B and piperchabamide H were also revised to their six-membered ring isomers.

Decomposition of diazo compounds or related derivatives is still one of the most frequently used and efficient methods to generate metal carbenoids. However, considering the hazardous and potential explosive nature of diazo compounds, other alternative carbene precursors are highly desirable. We developed two efficient methods to generate α-imino and oxo metal carbenoids respectively.

1. *N*-sulfonyl-1,2,3-triazoles can act as the carbene precursor. We developed an efficient method for the preparation of highly substituted cyclobutenes from alkynyl cyclopropanes which involved α-imino metal carbenoid as the key intermediate. The tandem process was facilitated by a dual catalyst system (CuTc and AgOTf). Various cyclobutenes with aldehyde or sulfonamide functionality could be prepared.
2. Metal complex $[Rh(CO)_2Cl]_2/P[OCH(CF_3)_2]_3$ is acidic enough to active ynamide for the addition of pyridine followed by the cleavage of N-O bond to generate α-oxo Rh(I) carbenoid intermediates. The α-oxo Rh(I) carbenoids could undergo ring expansion with adjacent cyclopropanes to afford cyclobutenes, or metathesis with a tethered alkyne to form 2-oxo-pyrrolidines, and cyclopropanation with a tethered alkene to afford 3-azabicyclo[3.1.0]hexanes.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| [α] | specific rotation |
| ℃ | degrees Celsius |
| Ac | acetyl |
| aq | aqueous |
| Ar | aryl |
| atm | atmosphere |
| Bn | benzyl |
| d | day(s); doublet(for NMR spectroscopy) |
| DIBAL | di-*iso*-butylaluminum hydride |
| DMAP | 4-dimethylaminopyridine |
| DMF | dimethylformamide |
| DMP | Dess-Martin peiodinane |
| *dr* | diastereomeric ratio |
| E | entgegen ("opposite") |
| EDG | electron-donating group |
| ee | enantiomeric excess |

EI electron impact (mass spectrometry)

equiv. equivalent

ESI electrospray ionization

Et ethyl

$Et_2O$ diethyl ether

EWG electron-withdrawing group

g gram(s)

h hour(s)

HMPA hexamethylphosphoramide

Hz hertz (cycloes per second)

*i*-Pr isopropyl

IR infrared

*J* coupling constant (for NMR spectroscopy)

m meta

M molarity (moles per liter)

Me methyl

mg milligram(s)

MHZ megahertz

min minute(s)

mL milliliter(s)

mol mole

MS mass spectrometry

Ms methanessulfonyl

MW molecular weight

NBS N-bromosuccinimide

n number (1,2,3...)

*n*-Bu *normal*-butyl

*n*-BuLi *n*-butyllithium

NMR nuclear magnetic resonance

nOe nuclear Overhauser effect/enhancement

NR no reaction

*o* *ortho*

Ph phenyl

ppm parts per million

q quartet (for NMR spectroscopy)

R rectus

Rf retention factor

rt room temperature

s singlet

S sinister

t triplet (for NMR spectroscopy)

TBDPS *tert*-butyldiphenylsilyl

*t*-Bu *tert*-butyl

THF tetrahydrofuran

TLC thin layer chromatography

TMS trimethylsilyl

Ts *para*-toluenesulfonyl

Z zusammen ("together")

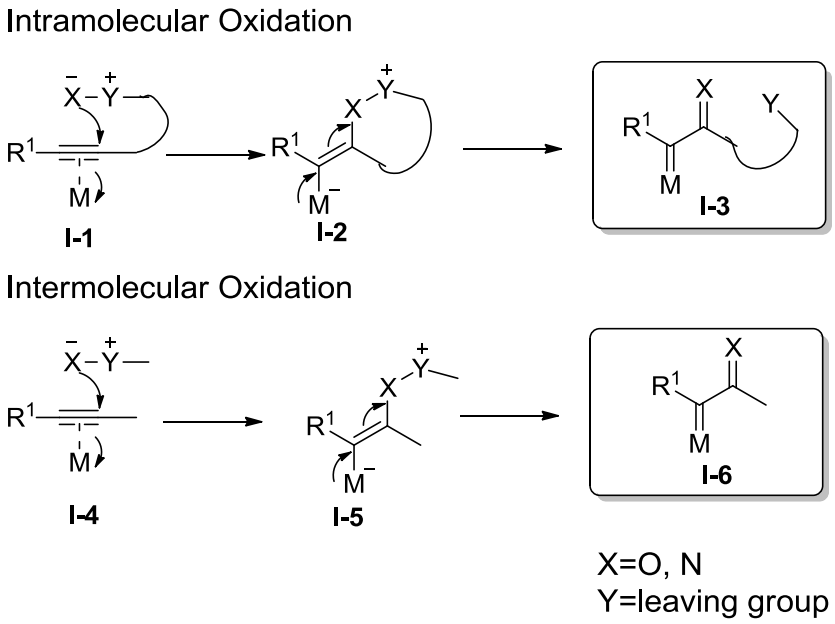
δ chemical shift (for NMR spectroscopy)

# CHAPTER I α-OXO AND α-IMINO METAL CARBENOIDS GENERATED FROM ALKYNES

## 1.1 INTRODUCTIONS

Metal carbenoid is one of the most versatile intermediates for synthetic chemistry[1]. Among different metal carbenoids , α-oxo and imino metal carenoids are well studied and widely used due to their accessibility and stability[2]. They are involved in numerous reactions such as cyclopropanation, C-H insertion and dipolar cycloaddition[3]. Decomposition of diazo compounds or related derivatives by transition metal catalysts is still the most common method to prepare metal carbenoids. Recent rapid development of transition metal catalysis especially gold catalysis offers the opportunities to generate α-oxo and imino metal carenoids via alkyne oxidation[4]. In **Scheme I-1**, it shows the common way to access α-oxo and imino metal carenoids. There are three key parts for the generation of metal carbenoids from alkyne derivatives: a) metal catalysts that can activate alkyne towards nucleophilic addition, b) suitable nucleophiles (X) and c) good leaving group (Y). A comprehensive review has been published for the generation of α-oxo metal carenoids by intramolecular oxygen transfer. [5] In this chapter, we will focus on intermolecular oxygen transfer and nitrogen transfer from azido group.

**Scheme I-1:** Intra- and Intermolecular Oxidative Metal Carbenoids formation



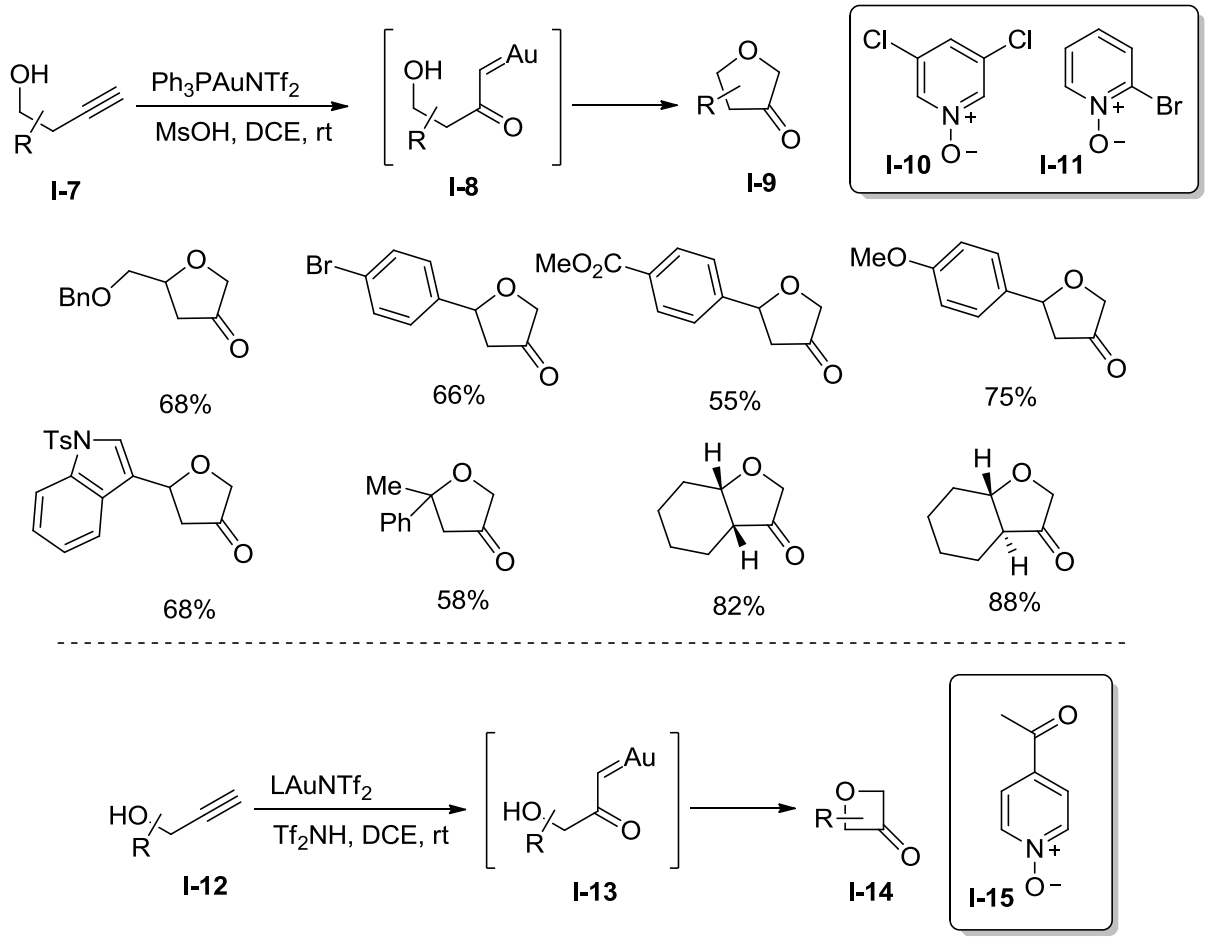

## 1.2 INTERMOLECULAR OXYGEN ATOM TRANSFOR TO ALKYNES

### 1.2.1 OXYGEN ATOM TRANSFER FROM PYRIDINE N-OXIDES

In 2010, Zhang and co-workers reported the first example of generating α-oxo gold carbenoids via intermolecular oxidation of terminal alkynes[6] (**Scheme I-2**). In this case, terminal alkyne (**I-7**) activated by $Ph_3PAuNTf_2$ catalyst was attacked by external oxidant pyridine N-oxide to generate α-oxo gold intermediate **I-8**, which was trapped by a homopropargyl alcohol. 4,5-Dichloropyridine N-oxide (**I-10**) and 2-bromopyridine N-oxide(**I-11**) proved to be the most efficient and the presence of MsOH was necessary to achieve good yields. Many functional groups were tolerated and the yields ranged from 55% to 88%. Compared to the intramolecular reaction, this strategy provided much more synthetic flexibility, which makes it competitive to diazo compounds.

Zhang and co-workers later expanded the scope of this reaction to propargyl alcohols[7]. Based on the same concept, various strained oxetan-3-ones (**I-14**), which are a valuable drug intermediates, were prepared in one step. Instead of $Ph_3PAuNTf_2$, [(2-biphyl)$Cy_2PAu$]$NTf_2$ proved to be a more efficient catalyst. Oxidative reagent **I-15** and additive $Tf_2NH$ are important for high yields..

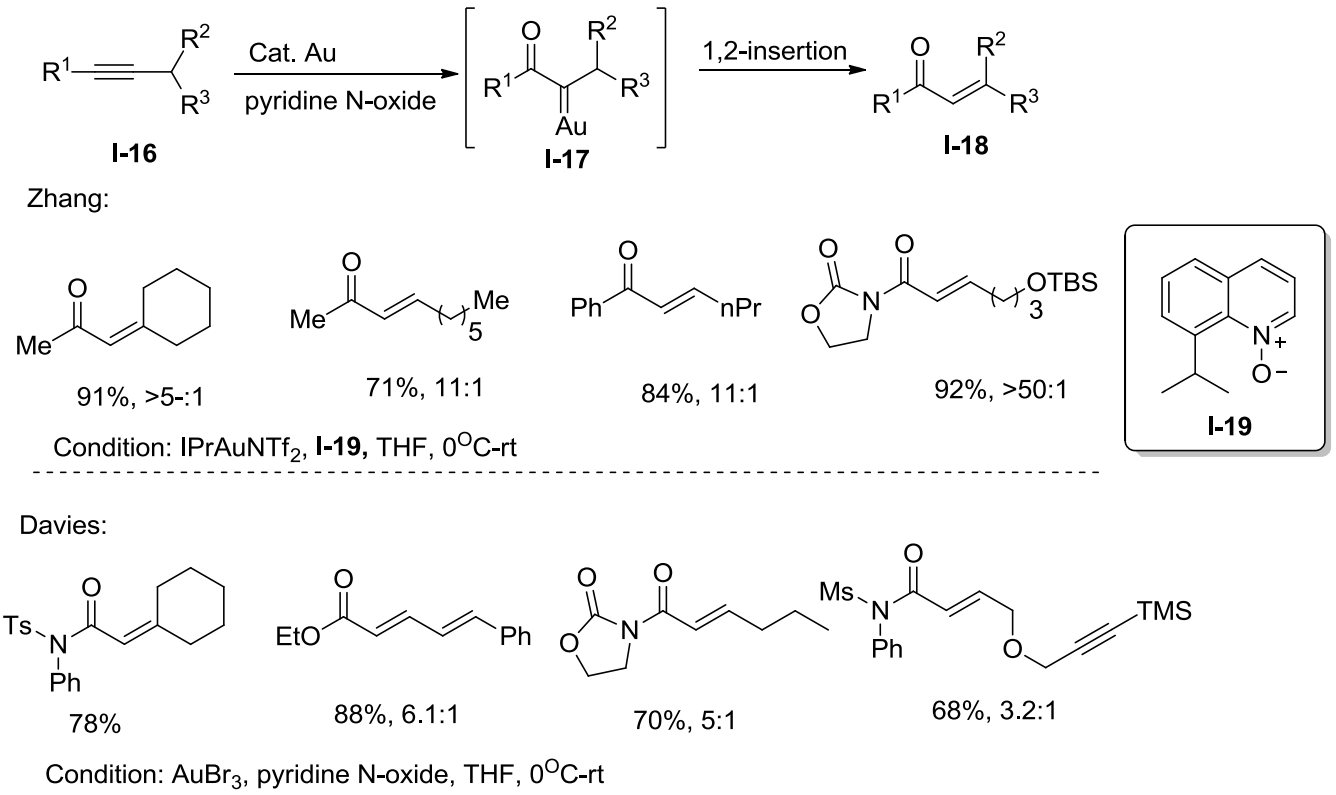
**Scheme I-2:** Gold-catalyzedGeneration of α-Oxo Gold Carbenes and Their Reaction with Alcohols



In 2011, the groups of Zhang[8] and Davies[9] reported gold-catalyzed regioselective α-oxo carbenoids formation and 1,2-insertion independently. In Zhang's work, $IPrAuNTf_2$ and 8-alkylqinoline N-oxide (**I-19**) were used to achieve good regioselectivity. A range of sensitive functional groups were tolerated leading to synthetically useful α,β-unsaturated carbonyls (**I-18**) with excellent E-selectivity.

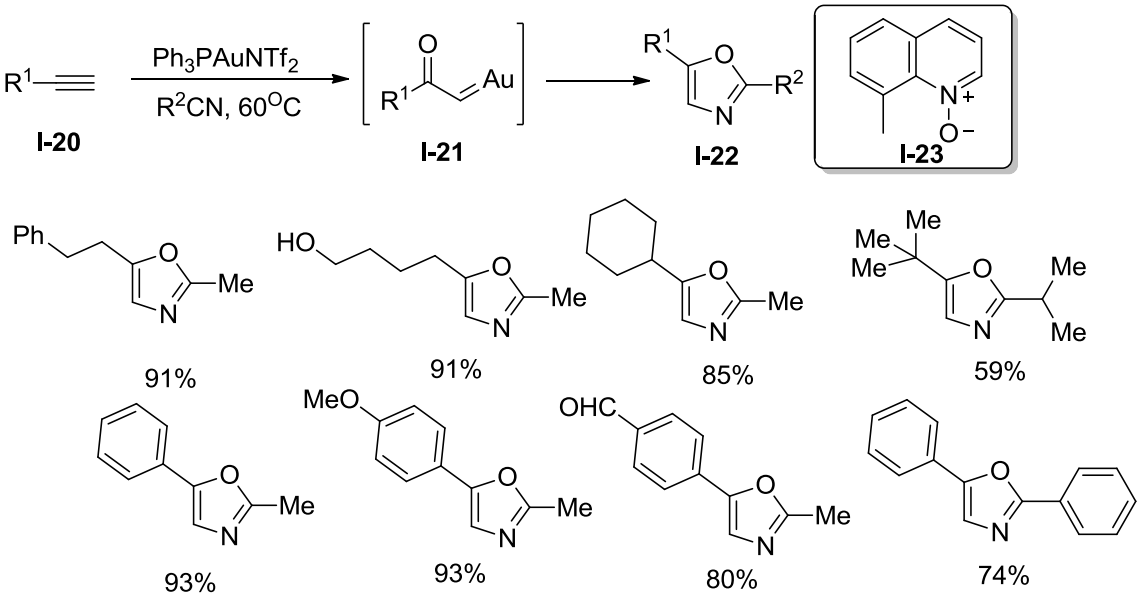
Ynamides and ynol esters were used in Davies' cases to control the regioselectivity. The electrophilic carbon of ynamides and ynol esters is the one adjacent to hetero-atom due to the electron density contributed from gold-ketene-iminium resonance structure. After screening different conditions, gold (III) showed the best reactivity and E/Z selectivity. This method provided an efficient way to generate α-oxo gold carbenoids for the preparation of α,β-unsaturated carboxylic ester and imide derivatives. Overall, Zhang's method afforded broader substrate scope and better E/Z selectivity.

**Scheme I-3:** Regioselective α-Oxo Carbenois Formation and 1,2-Insertion




Zhang and co-workers[10] also developed the first intermolecular reaction between the α-oxo gold carbenes derived from alkyne oxidation and nitriles to yield various 2,5-disubstituted oxazoles (**Scheme I-4**). This three-component reaction can be catalyzed $Ph_3PAuNTf_2$ with a range of nitriles and terminal alkynes. Overall, it is a formal [2+2+1] annulation reaction.

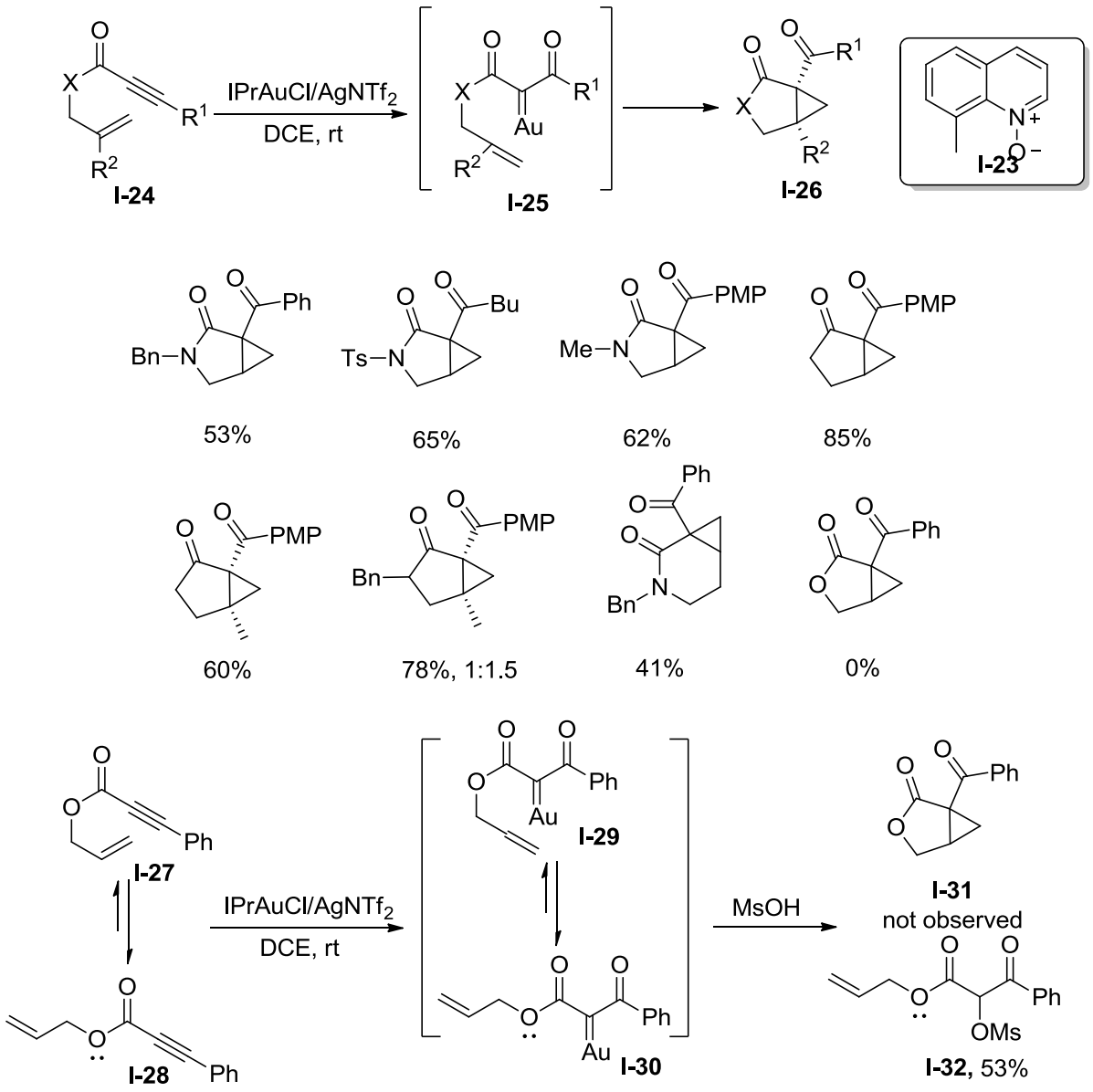
**Scheme I-4:** Synthesi of 2,3-Disubstituted Oxazoles




In 2011, Zhang and co-workers reported a gold-catalyzed tandem oxidation followed by cyclopropanation of 1,6-enynes with external oxidants[11] (**Scheme I-5**). For gold carbenes generated from alkynes oxidation in previous examples, electron-rich terminal alkynes are generally used. In this case, electron deficient keto-alkynes (**I-24**) was used as starting material and good yields were obtained.

Interestingly, cyclopropanation product **I-31** was not observedwhen the substrates had an ester linker. Instead, linear product **I-32** was isolated in 51% yield. The stereoelectronic effects makes the s-trans conformation of ester more stable and the ring-closing step becomes very difficult.

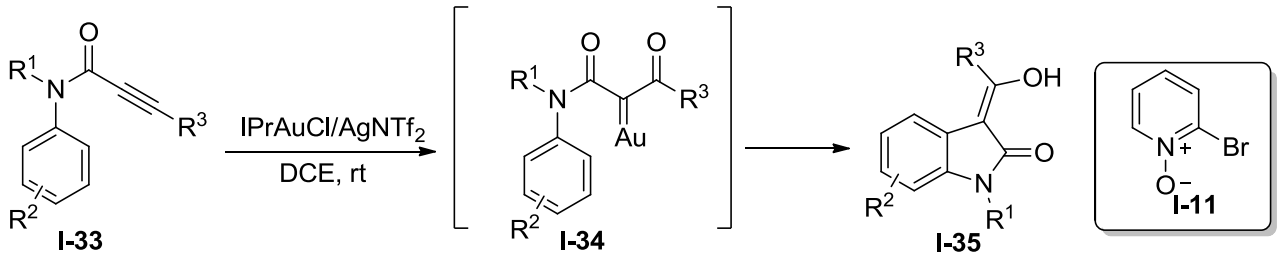
**Scheme I-5:** Gold-catalyzed oxidative cyclopropanation

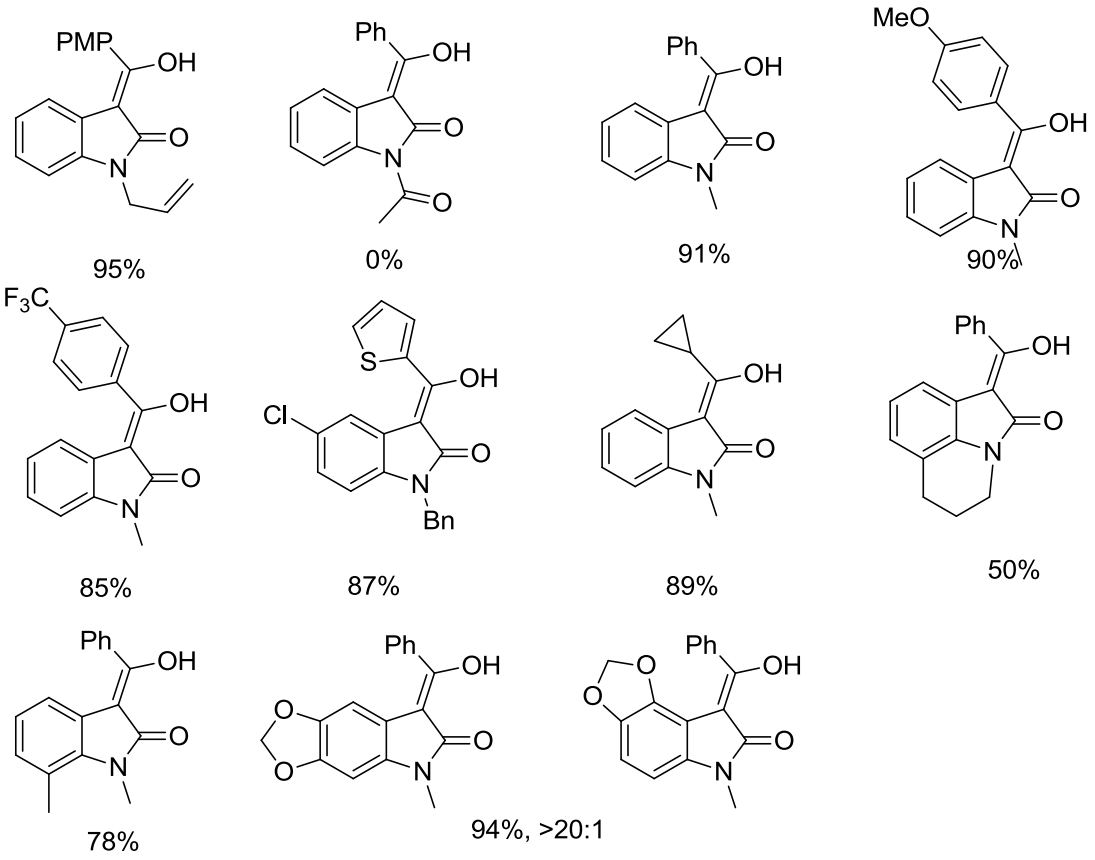



During Zhang's previous studies, N-phenyl-N-allyl-propoplamide did not yield desired cyclopropantion product but afforded an unexpected oxoindole (**Scheme I-6**). The gold carbene

intermediate reacted with the aromatic ring.[12] This reaction can be carried out under mild conditions with excellent yields. It provided an efficient route for acyloxindoles (**I-35**).

**Scheme I-6:** Catalytic Oxidation/C-H funtionalization

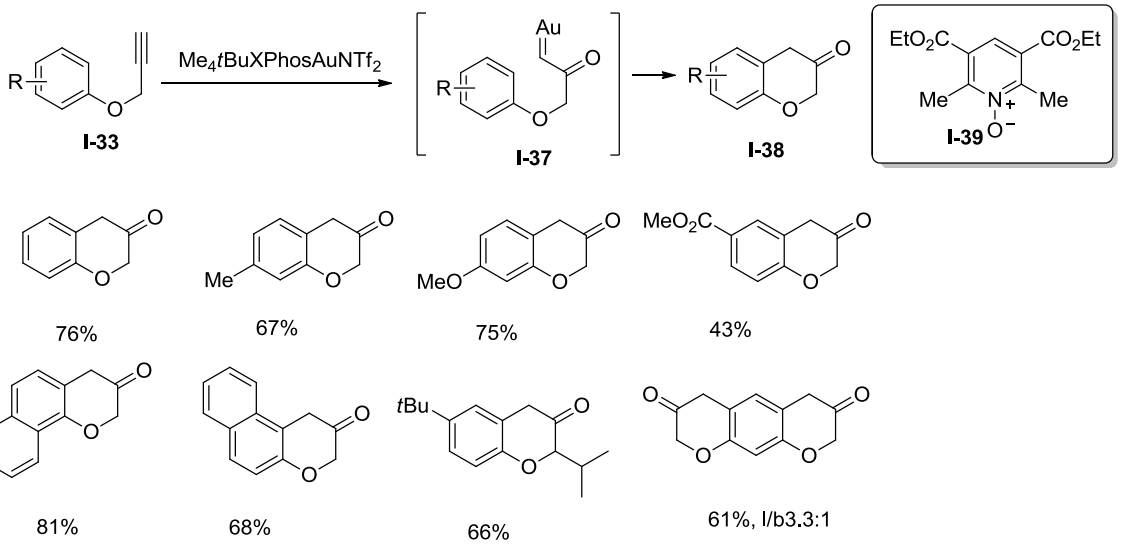



Using alkyne as an alternative carbene precursor, Zhang and co-workers also prepared chroman-3-one, which has also been prepared using diazo compounds[13] (**Scheme I-7**). It is

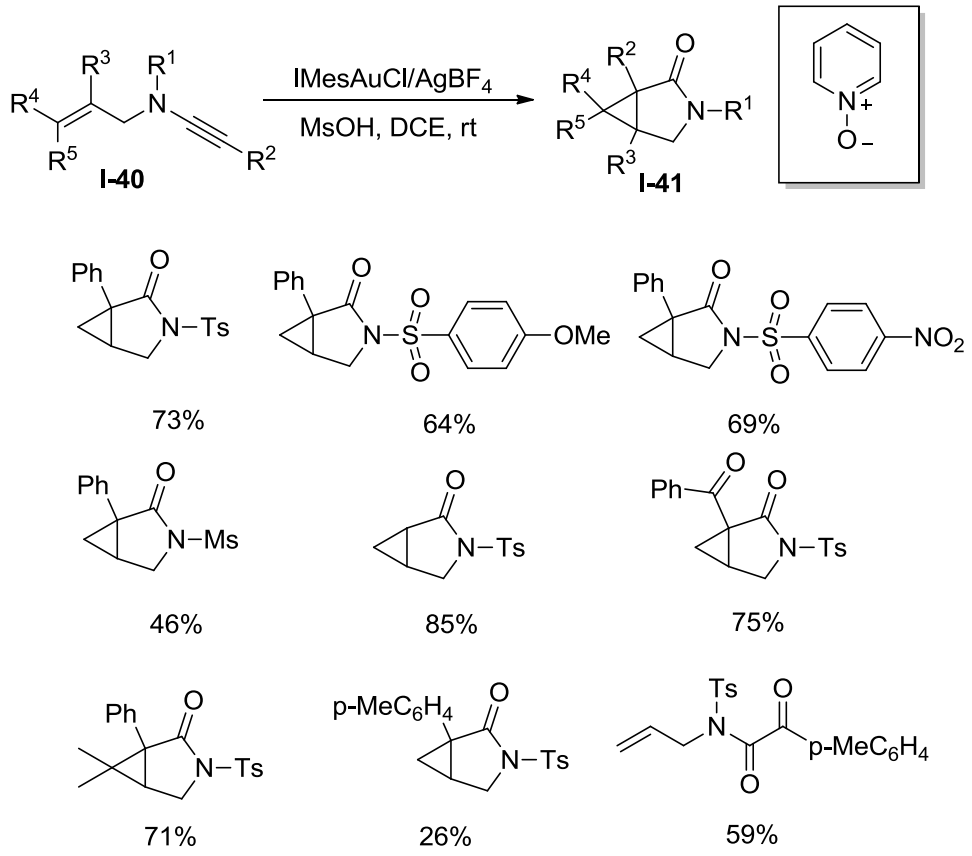
known that biphenylphosphine gold catalysts will be more effective if the biphenyl part is more sterically demanding . $Me_4$tBuXPhosAuNT$f_2$ proved to be the best catalyst for this reaction. Common oxidative reagents were examined and did not improve the reaction at all. The authors therefore made more hindered and electron deficient N-oxides (**I-39**), which turned out to be better. Substituted chroman-3-ones were prepared from propargyl aryl esters in one step with excellent yields.

**Scheme I-7:** Gold-catalyzed Oxidation of Propargyl Aryl Esters




Recently, Li and co-workers reported a gold-catalyzed oxidative cyclopropanation of N-allylynamides andproduced 3-aza-bicyclo[3.1.0]-hexan-2-one derivatives[14] (**Scheme I-8**). When sulfoxides were employed, a 1,2-dicarbonyl compound was the major product, while pyridine N-oxide gave the cyclopropanation products (**I-41**). The aromatic substituent on the alkyne played an important role for the chemoselectivity. When there was an electron-rich group, dicarbonyl compounds became major products.

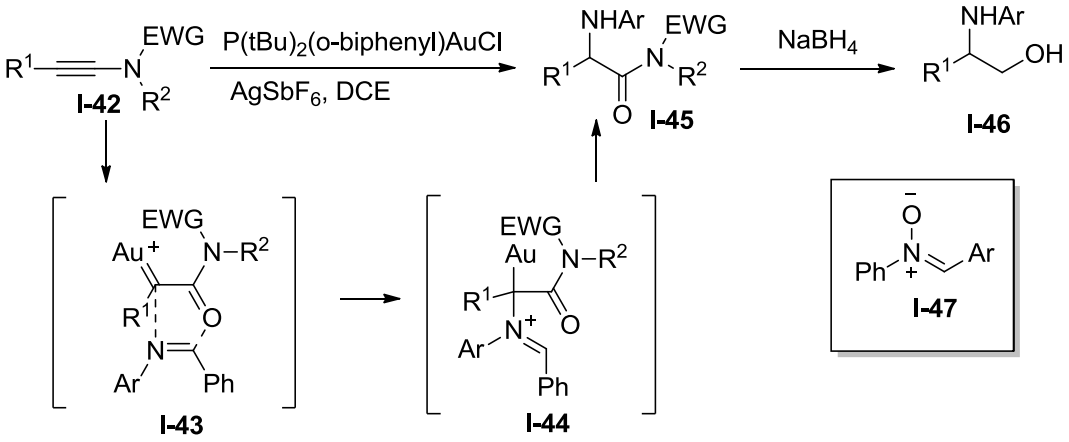
**Scheme I-8:** Gold-catalyzed Oxidative Cyclopropanation of N-Allylnamides




### 1.2.2 OXYGEN ATOM TRANSFER FROM NITRONES AND NITROSOBENZENES

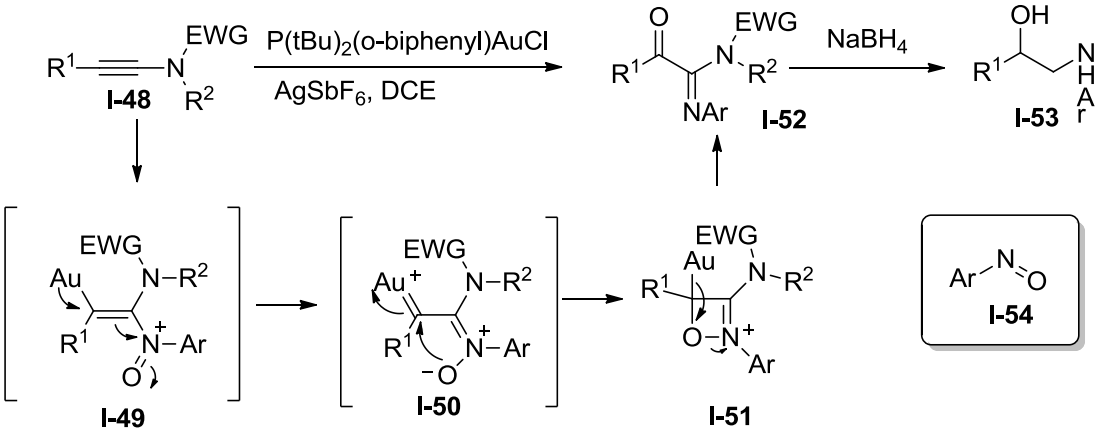
Liu and co-workers[15] developed an efficient rout for the oxidative 1,2-difunctinalizations of alkynes (**I-42**) with nitrones (**I-47**). In the presence of $P(tBu)_{2(}$o-biphenyl)AuCl/$AgSbF_6$, nitrones (**I-47**) could react with ynamide (**I-42**) to form intermediate **I-44**. In-situ reduction then afforded alcohol **I-46**.

**Scheme I-9:** Gold-catalyzed Oxidative 1,2-Difunctinalizaion of Alkynes With Nitrones




Nitrosobenzene provided different reactivity from nitrones,[15] in which case nitrogen atom of nitrosobenzene attacked the ynamide to afford intermediate **I-49**. A novel metathesis occurred to deliver 2-oxoiminylamides (**I-52**), which could be reduced in situ to yield **I-53**. This provided product (**I-46**) with opposite regioselectivity compared with nitrones (**Scheme 10)**.

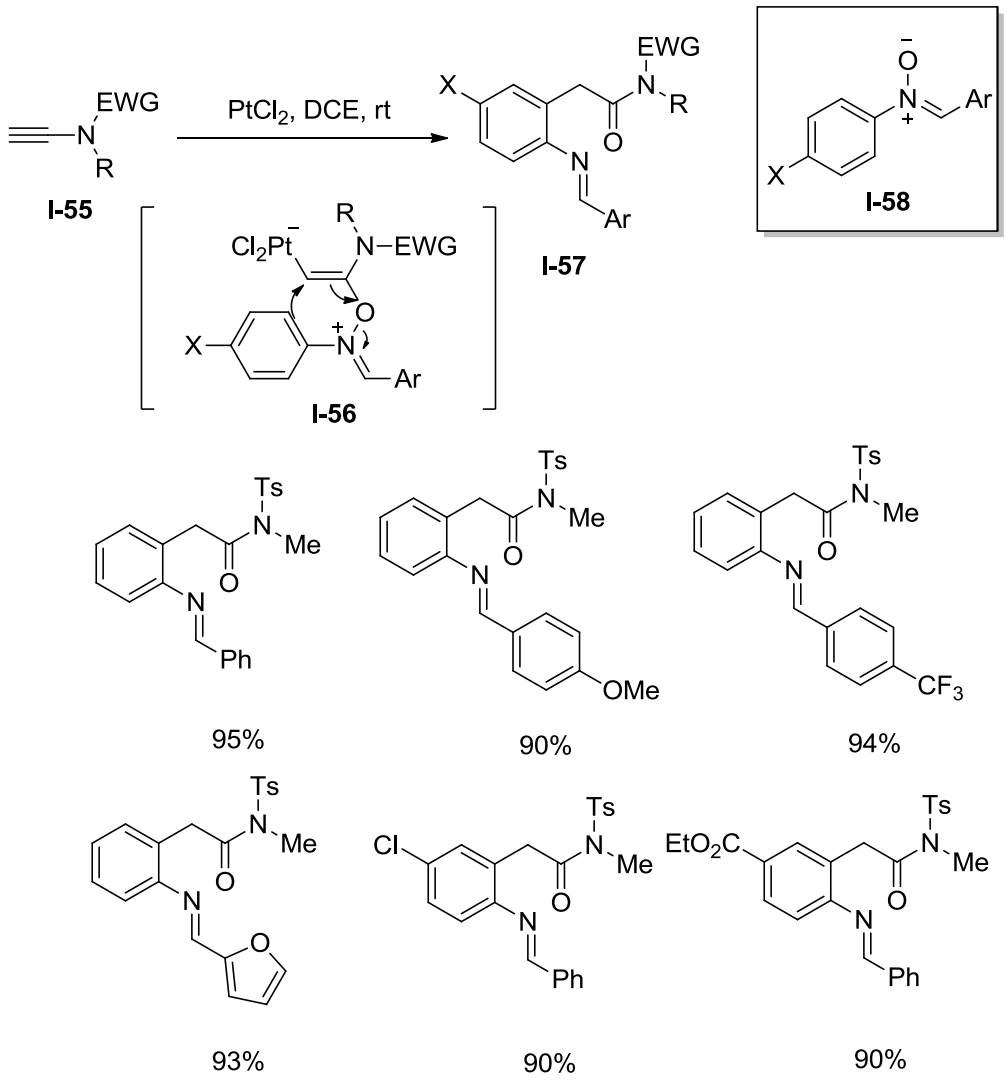
**Scheme I-10:** Gold-catalyzed Oxidative 1,2-difunctinalizaion of Alkynes With Nitrosobenzene




Various conditions were explored for the reaction between ynamides and nitrones in Liu's group. A new type product **I-57** was observed when platinum catalyst was employed.[16] The

mechanism for platinum-catalyzed reactions was shown in **Scheme I-11**. After oxidative addition, a subsequent [3,3] sigmatropic rearrangement of intermediate **I-56** occurred. .

**Scheme I-11:** Platinum-Catalyzed Oxoarylations of Ynamides with Nitrones

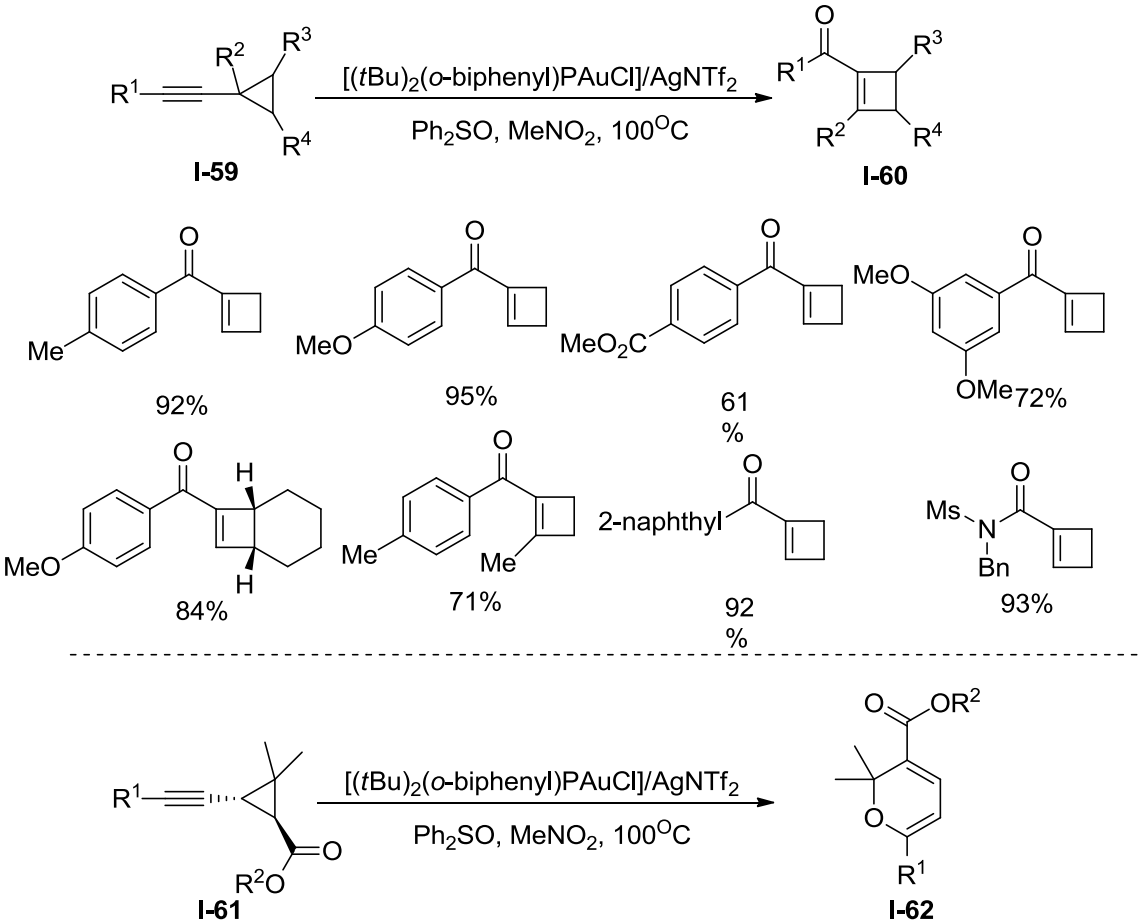



### 1.2.3 OXYGEN TRANSFER FROM SULFOXIDES

Sulfoxide is also a commonly used oxidant. Intramolecular addition of sulfoxides to alkynes catalyzed by goldfor the generation of gold carbenoids was reported by Toste[17] and Zhang[18]

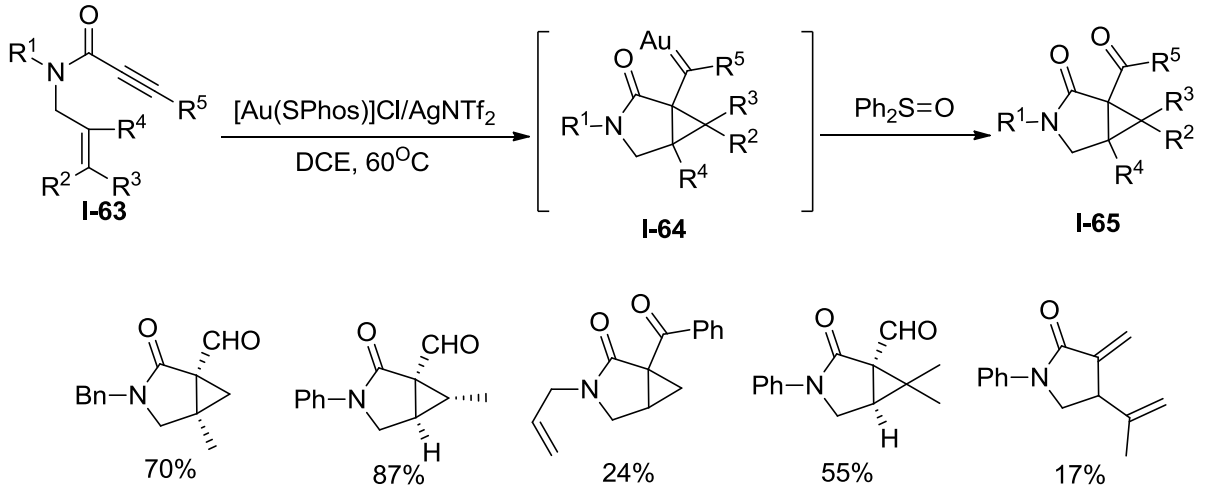
independently. In 2012, Liu and co-workers reported gold-catalyzed oxidative ring expansion of cyclopropylalkynes using diphenylsulfoxide as the oxidative reagent[19]. A-oxo gold carbene was formed and then underwent ring expansion with the adjacent cyclopropane ring to yield cyclobutene (**I-60**) in a regioselective manner. Interestingly, when there was trans ester group on the cyclopropane ring, oxidative cleavage reaction occurred to form 2H-pyrans (**I-62**) with reasonable substrate scope.

**Scheme I-12:** Gold-Catalyzed Oxidative Ring Expansion and Ring Cleavages by diphenylsulfoxides



Recently Shin and co-workers showed interesting results for gold-catalyzed oxidative cyclopropanation of 1,6-enynes[20](**Scheme I-13**). Comparing to Zhang's work (**Scheme I-5**), the same substrate exposed to cationic gold catalyst with different ligands and different oxidants results different types of products due to different mechanistic pathways. In Shin's system, gold carbene **I-64** was generated from gold catalyzed enyne cycloisomerizaion. While in Zhang's condition, α-oxo gold carbene was formed. In this case diphenylsulfoxides rather than pyridine N-oxide was served as the oxidant and it also played an important role on the chemoselectivity.

**Scheme I-13:** Gold-Catalyzed Oxidative Ring Cyclopropanation of 1,6-Enynes



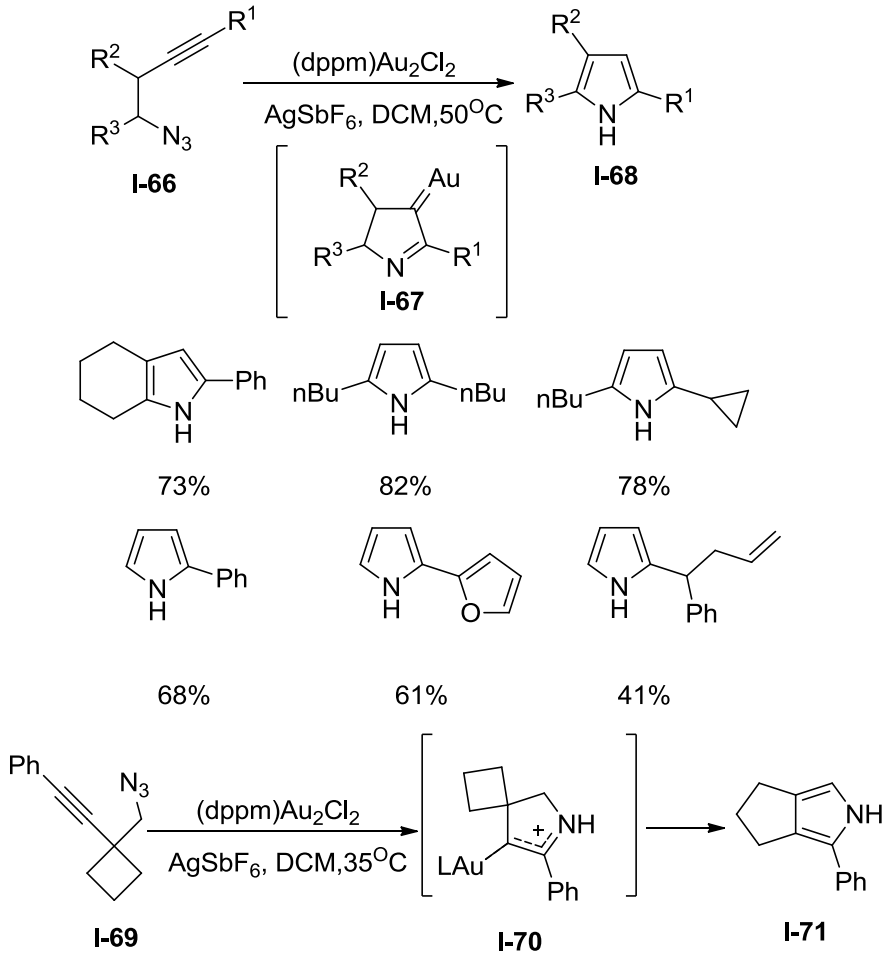

## 1.3 NITROGEN ATOM TRANSFER TO ALKYNES

### 1.3.1 INTRAMOLECULAR NITROGEN ATOM TRANSFER

In 2005, Toste[21] and co-workers reported gold-catalyzed acetylenic Schmidt reaction of homopropargyl azides to afford substituted pyrroles which allowed for regiospecific

substitution at each position of the pyrrole ring (**Scheme I-14**). The authors proposed a mechanism involving the addition of the nitrogen of the azide to the alkyne and subsequent loss of nitrogen gas to afford gold carbenoid **I-67**. Based on the proposed mechanism, cyclobutyl azide **I-67** was prepared and it underwent rearrangement to deliver the trisubstituted pyrrole **I-71** in 80% yield.

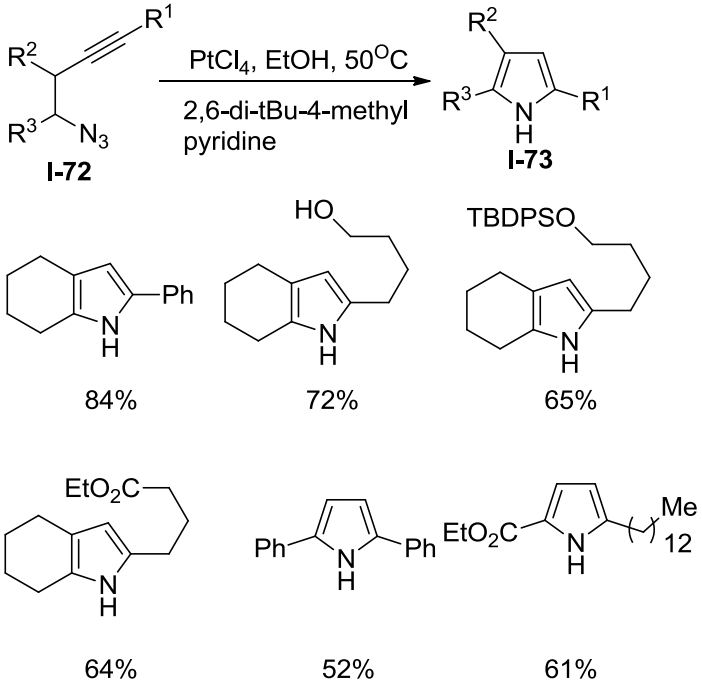
**Scheme I-14:** Gold-Catalyzed Intramolecular Acetylenic Schmidt Reaction




One year later, platinum-catalyzed cyclization reaction of homopropargyl azide was realized by Hiroya and co-workers[22] (**Scheme I-15**). Platinum catalyst showed similar reactivity as gold

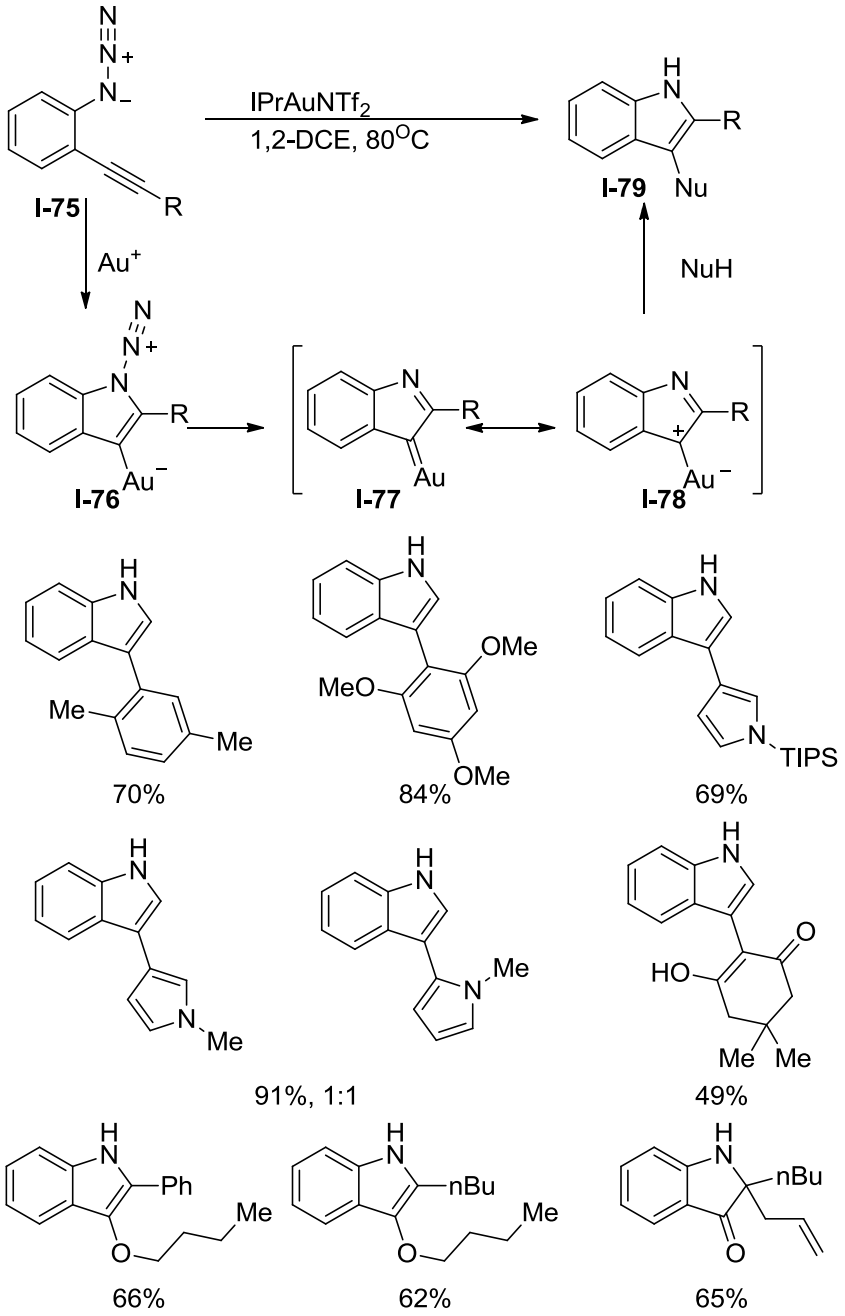
catalyst (**Scheme I-14**). 2,6-Di-tert-butyl-4-methylpyridine was found to be the best base for the ring-closing step.

**Scheme I-15:** Platinum-Catalyzed Cyclization Reactions of Homopropargyl Azide Derivatives




In 2011, umpolung reactivity of indole type α-imino gold carbene was realized by the group of Zhang[23] and Gagosz[24] (**Scheme 16**). *O*-Azidoaryalkynes mediated an intramolecular nitrene transfer for the azido group to the alkyne Cyclic α-imino gold carbene **I-77** was then formed. tUmplung reactivity at 3-position was chiaved through α-imino gold carbenoid **I-78**. Various nucleophiles could react at the 3-position and it provided a range of functional indoles **I-79**.

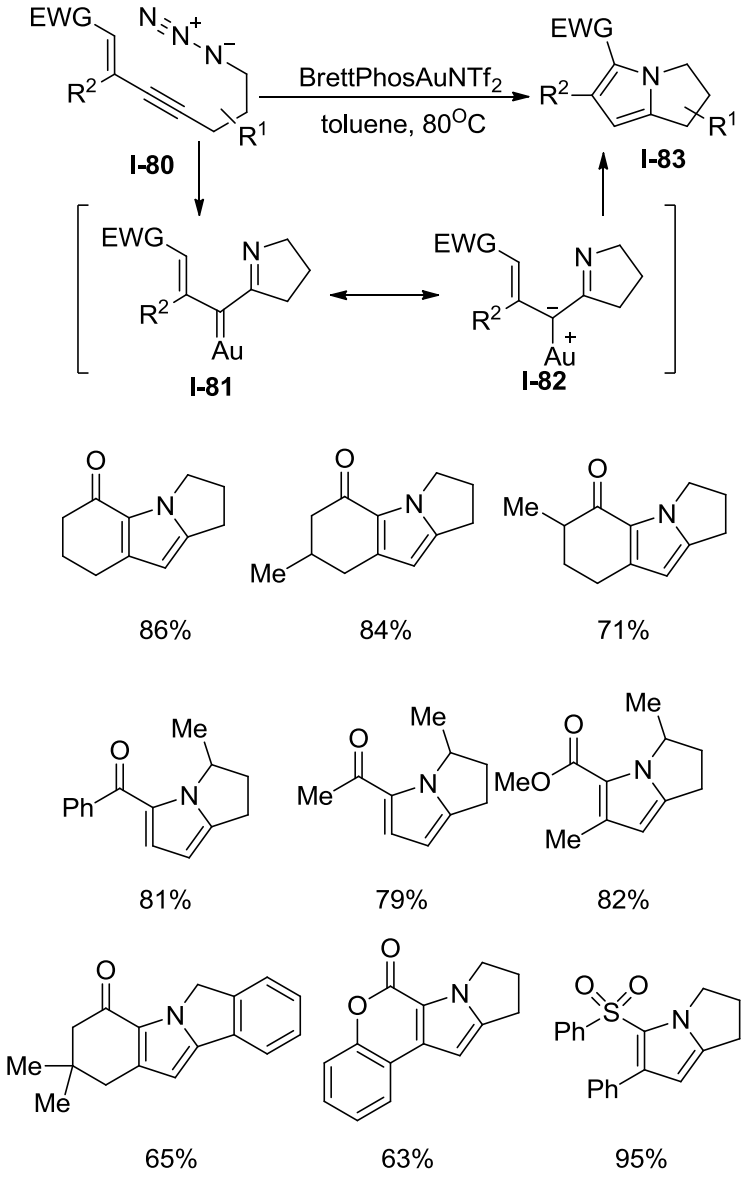
**Scheme I-16:** Umpolung Reactivity of Indole through Gold Catalysis




In 2012, Zhang and co-workers reported a gold-catalyzed synthesis of pyrrolizines with electron withdrawing groups in the 5-position[25] (**Scheme I-17**). The linear azidoenynes (**I-80**)

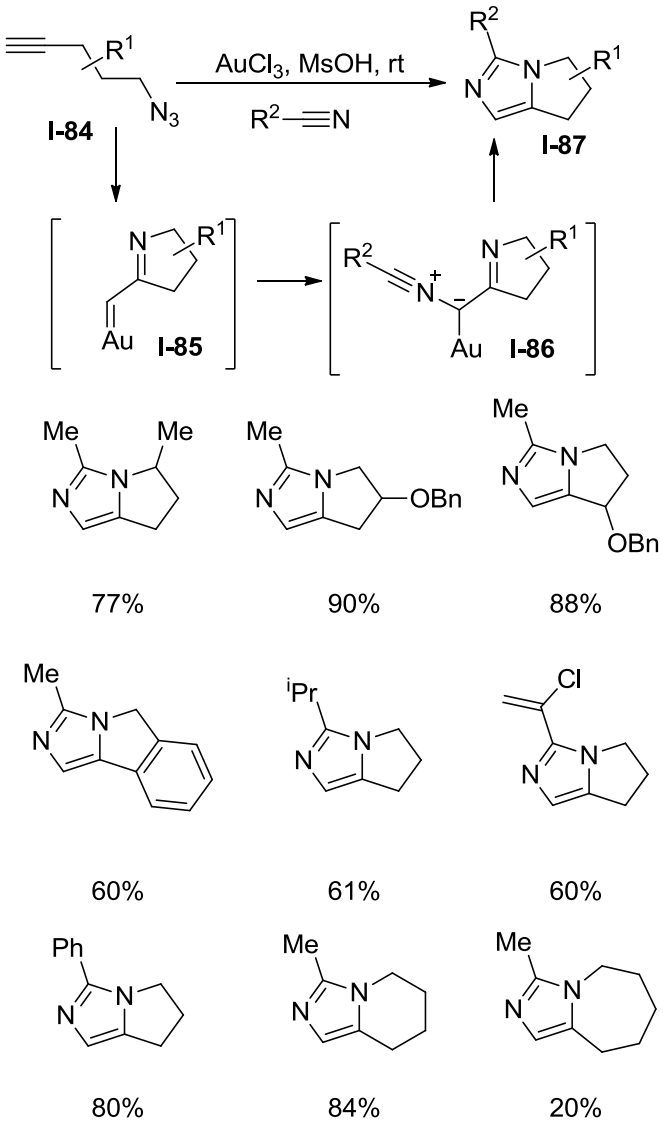
could be easily prepared by the Sonogashira coupling. The azido group could be treated as nitrene precursor. In the presence of gold catalyst, the α-imino gold carbene (**I-81**) was generated, and it was followed by an electrocyclic ring closure to afford pyrrole product (**I-83**).

**Scheme I-17:** Gold-catalyzed Construction of 2,3-Dihydro-1H-Pyrrolizines



α-Imino gold carbenes could be trapped by various functional groups. Cycloaddition of nitriles and α-imino gold carbene was published by Zhang and co-workers[26] (**Scheme 18**). Au(III) and MsOH were necessary for good yields. The cyclic α-imino gold carbene **I-85** was generated in situ through nitrene transfer from azido group to the tethered terminal alkyne. Nitriles, used as the solvent, could undergo nucleophilic attack to gold carbene to yield intermediate **I-86**, which could undergo further cyclization to afford imidazole **I-87** efficiently.

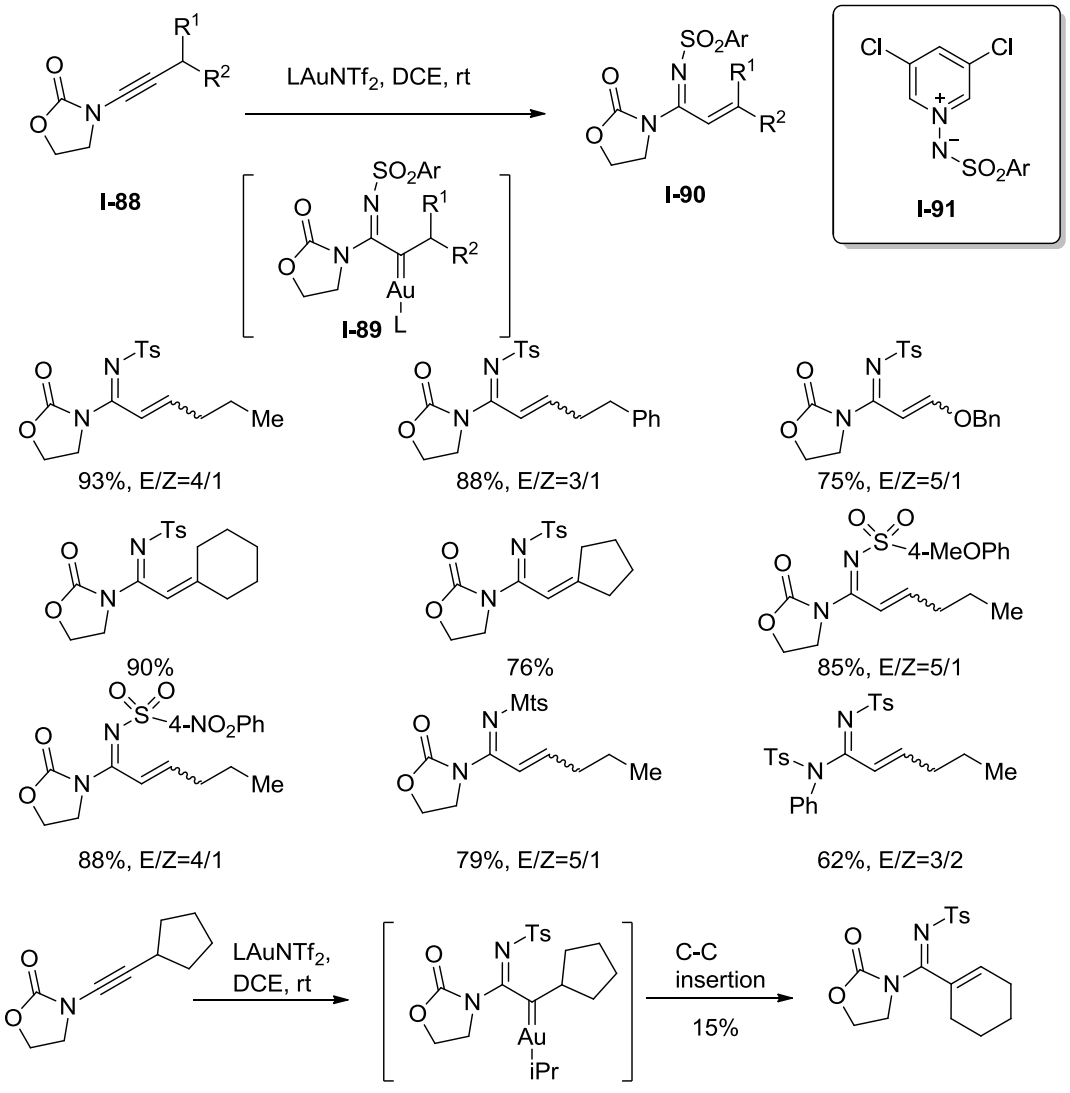
**Scheme I-18:** Gold-catalyzed Synthesis of Bicyclic Imidazoles



### 1.3.2 INTERMOLECULAR NITROGEN ATOM TRANSFER

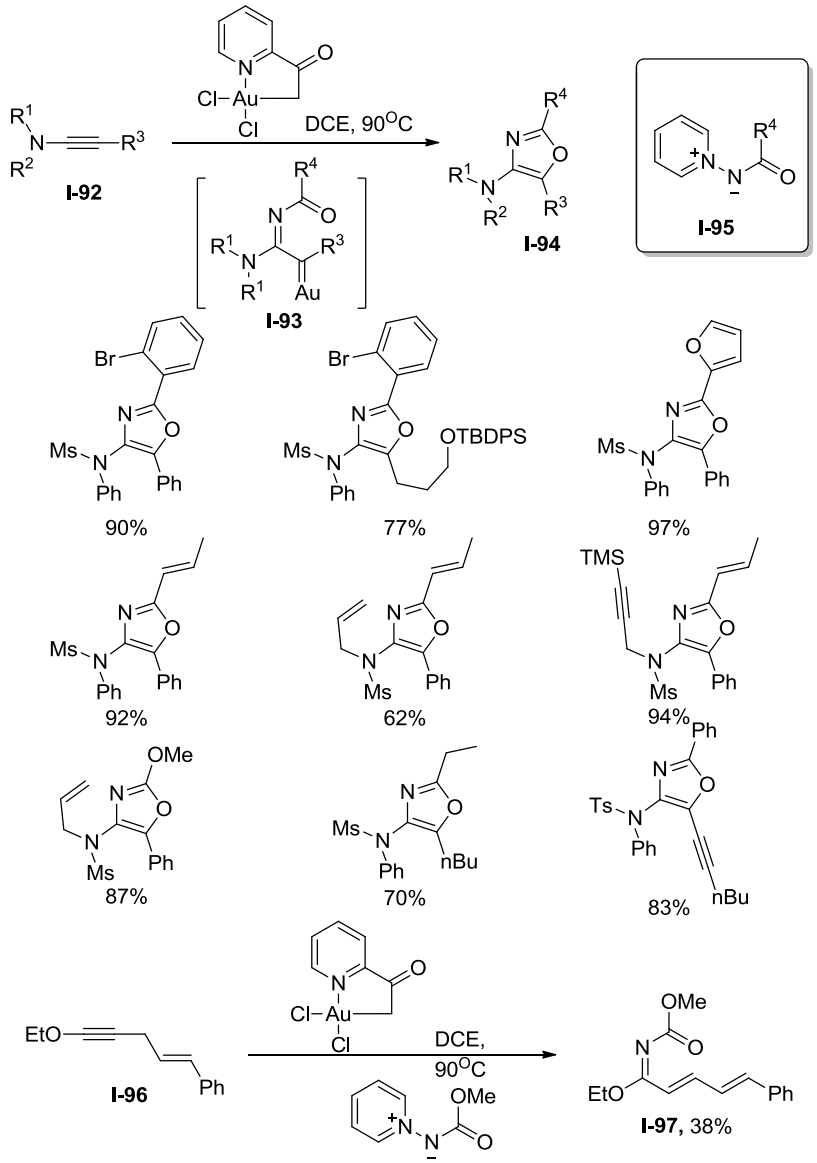
In 2011, Zhang and co-workers reported the first examples of gold-catalyzed intermolecular nitrene transfer to alkynes[8] (**Scheme I-19**). After examining various nitrene transfer reagents, 3,5-dichloropyridine derivative (**I-91**) proved to be highly effective. α-Imino gold carbene intermediate **I-89** was generated from **I-88**. The resulting metal carbenes underwent 1,2 C-H insertion to deliver α,β-unsaturated amidines (**I-90**) in good yields.

**Scheme I-19:** Gold-catalyzed Nitrene Transfer to Activated Alkynes



Davies[27] and co-workers developed a regioselective intermolecular [3+2] cycloaddition via α-imino gold carbenoid intermediate **I-93** (**Scheme I-20**). Further cyclization occurred to afford oxazole product **I-94**. A variety of substituents such as aryl groups can be tolerated. However, when ynol enyne I-96 was exposed to the reaction condition, no desired product was observed. Linear product (**I-97**) before cyclization was obtained in a 38% yield.

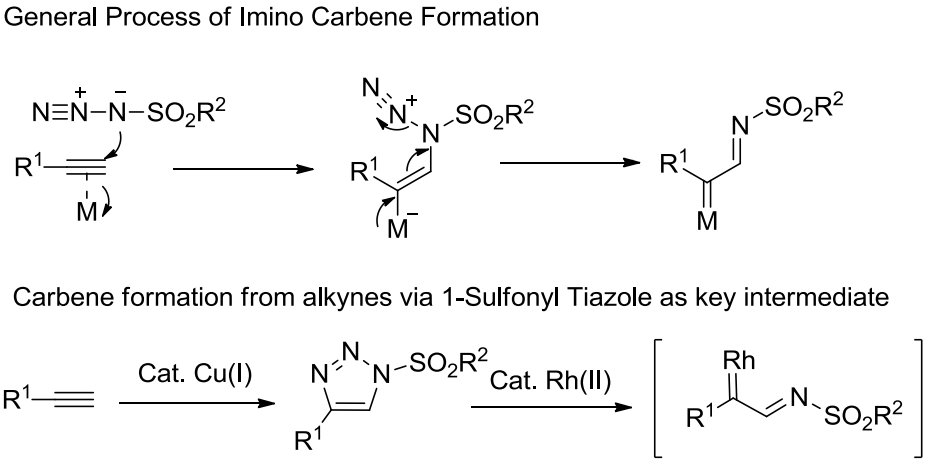
**Scheme I-20:** Gold-catalyzed Formal [3+2] Cycloaddition



### 1.3.3 NITROGEN ATOM TRANSFER FROM AZIDE VIA 1,2,3-TRIZAOLES INTERMEDIATES

1-Sulfonyl 1,2,3-trazoles can be easily prepared by cycloaddition between sulfonyl azides and terminal alkynes in the presence of copper catalysts under mild conditions. Recently the study involving 1-sulfonyl 1,2,3-trazoles draws a lot of attentions[28]. 1-Sulfonyl triazole could serve as precursors of diazoimines, which could be transferred to metal α-imino carbene species. In some cases, dual catalysts could be employed to achieve the triazole formation and carbene generation in one pot. The overall process can be treated as nitrene transfer from azides to alkynes (**Scheme I-21**). There are several comprehensive reviews on transannulation[29] from triazoles to other heterocyclic systems. Here we will focus on other unique reactivity of 1-sulfonyl 1,2,3-trazoles.

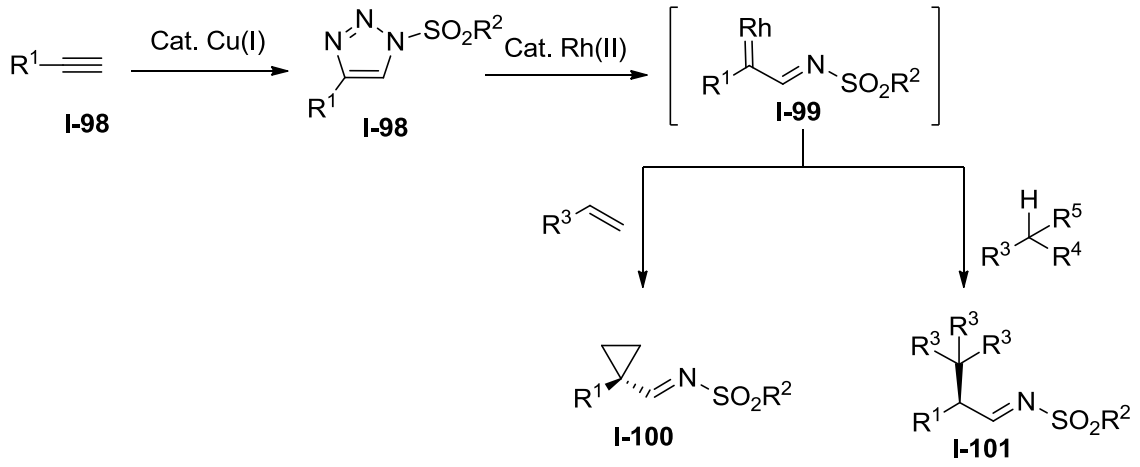
**Scheme I-21:** Comparison of Different Ways to Generate α-Imino Carbenes




Fokin and co-workers[30] reported that Rh(II) α-imino carbenes (**I-99**) underwent cyclopropanation with olefins inh high diastereo and enantioselectivity under mild conditions.

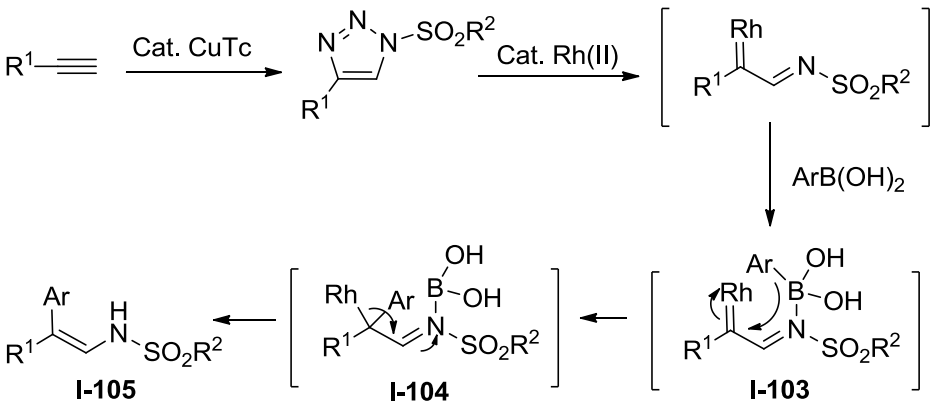
In 2011, Fokin's group developed a highly enantioselective C-H functionalizaiont reaction,[31] which involved the α-imino Rhodium (II) carbenes derived from triazoles (**Scheme I-22**).

**Scheme I-22:** Cyclopropanation and C-H Insertion of α-imino Rhodium (II) carbenes



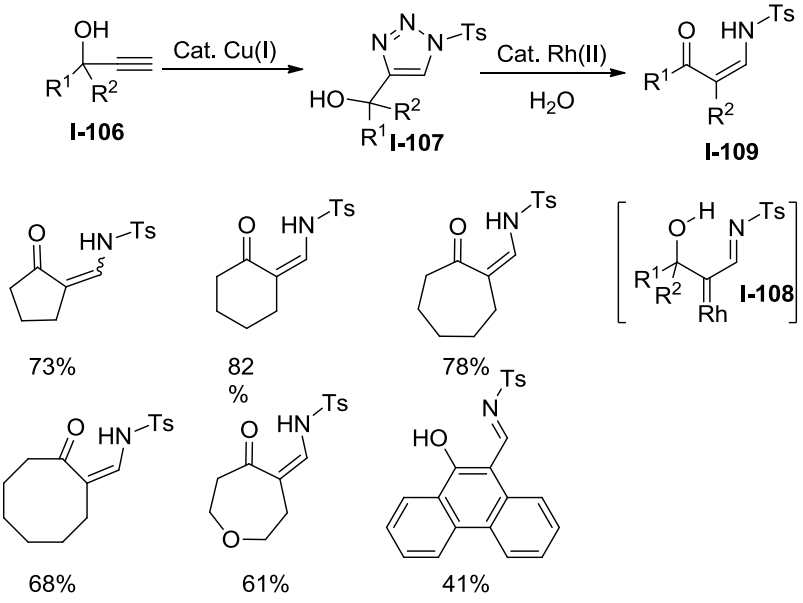

Inspired by the reaction between dizao compounds and arylboronic acid nucleophiles,(ref) Fokin's group recently developed the arylation of α-imino Rhodium (II) carbenes with boronic acid to afford substituted enamines[32] (**Scheme I-23**). α-Imino Rhodium (II) carbenes was generated from 1,2,3-trazoles. The authors proposed that the lone pair of nitrogen reversibly coordinates to the empty orbital of boron atom to generate intermediate (**I-103**), which was followed by aryl group transfer from boron atom to Rhodium (II) carbene carbon to form intermediate (**I-104**). After dissociation of rhodium and protonolysis, substituted emaine **I-105** was prepared.

**Scheme I-23:** Arylation of α-Imino Rhodium (II) Carbenes with Boronic Acid




The ring expansion reaction is very common for rhodium species derived from diazo compounds. In 2012, the groups of Murakami[33] and Fokin[34] reported the ring expansion of substituted 1-sulfony-1,2,3-triazoles catalyzed by rhodium (II) catalyst. As shown in **Scheme I-24**, the product was prepared via the rearrangement of intermediate **I-108** with broad substrate scope and acceptable yields.

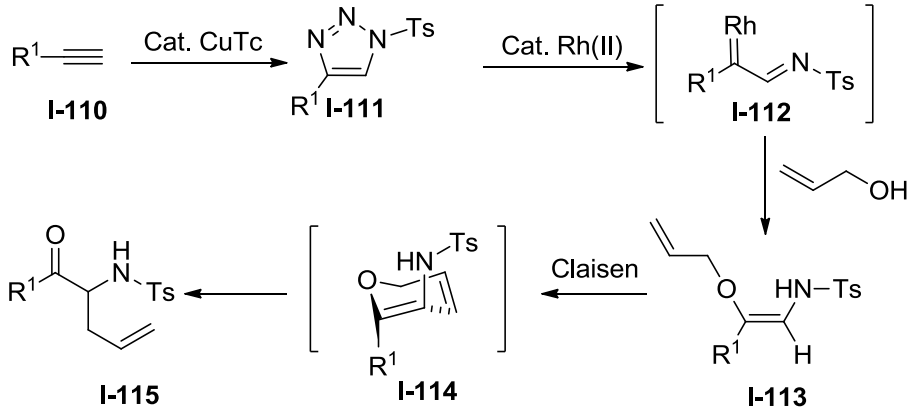
**Scheme I-24:** Ring Expansion of α-Imino Rhodium (II) Carbenes



In 2013, Murakami and co-workers[35] reported an interesting one-pot three-step reaction to introduce three different bonds onto terminal alkynes via 1,2,3-triazole intermediates (**Scheme I-25**).

It involved three steps for the transfer from terminal alkynes to α-substituted α-amino ketones: 1. azide-alkyne cycloaddition catalyzed by CuTc (**I-110** to **I-111**); 2. α-Imino Rhodium (II) carbene formation and subsequent O-H insertion (**I-111** to **I-113**); finally, Claisen rearrangement to afford products (**I-113** to **I-115**) .

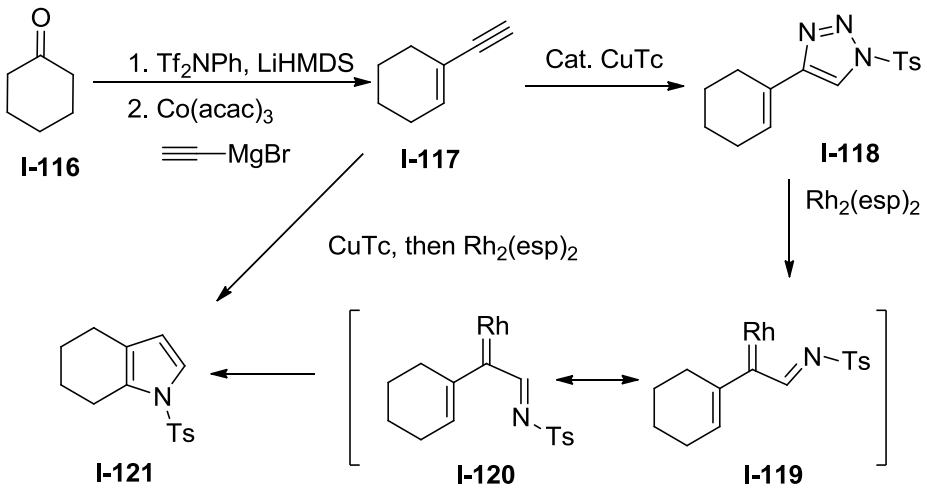
**Scheme I-25:** One-Pot Procedure for the Preparation of α-Amino Ketones from Terminal Alkynes




Recently Davies and co-workers developed an efficient route to prepare 2,3-fused pyrroles from cyclic ketones (**Scheme I-26**). Enyne (**I-117**) was synthesized by a sequence of vinyl triflate formation and cobalt-catalyzed Kumada-type coupling with ethynylmagnesium bromide. Copper-catalyzed azide-alkyne cycloaddition yielded triazole (**I-118**), which was treated with rhodium (II) catalyst to form α-imino Rh (II) carbenes (**I-119** and **I-120**). A 4π electrocycliztion

occurred to give 2,3-fused pyrrole (**I-121**). One-pot pyrrole synthesis was also achieved from enyne (**I-117**).

**Scheme I-26:** Coversion of Cyclic Ketones to 2,3-Fused Pyrroles




## 1.4 CONCLUSION

In summary, we have described various reactions involving α-oxo and α-imino metal carbenoids generated from alkynes. For α-oxo metal carbenoids, we discussed intermolecular oxygen transfer from pyridine N-oxide, nitrones, nitrosobenzenes and sulfoxides. α-Imino metal carbenoids were mainly generated by the nitrene transfer from azido groups to alkynes. 1-Sulfonyl 1,2,3-triazoles could be treated as an intermediate from alkyne to α-imino carbenoid. Most of the chemistry presented in this chapter was developed in the past few years and all the discoveries were based on the understanding of known metal carbonoid chemistry as well as bringing new concepts into well-studied fields.

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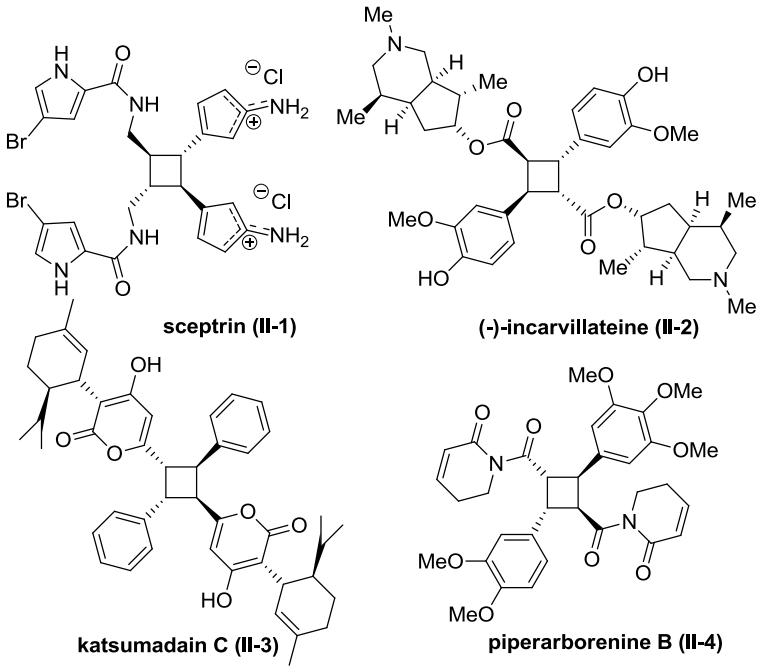
# CHAPTER II TOTAL SYNTHESIS AND STRUCTURE REVISION OF CYCLOBUTANE-CONTAINING NATURAL PRODUCTS

## 2.1 ADVANCES IN TOTAL SYNTHESIS OF TETRASUBSTITUTED CYCLOBUTANE-CONTAINING NATURAL PRODUCTS

### 2.1.1 INTRODUCTIONS

Cyclobutane-containing compounds are abundant in nature and have diverse bioactivities (**Scheme II-1**). For example, sceptrin[1] (**II-1**) showed broad bioactivity such as antiviral, antimuscarinic, antibacterial and antihistaminic. Incarvillateine (**II-2**) isolated from the aerial parts of *Incarvillea sinensis Lam* shows potent analgesic properties[2,3]. Katsumadain C[4] (**II-3**) exhibited broad antitumor activity against several human tumor cell lines. Piperarborenine B (**II-4**)was isolated from *Piper arborescens* and exhibits *in vitro* cytotoxicity against several cancer cell lines[5].

**Scheme II-1:** Selected Bioactive Cyclobutane-based Natural Products




In this section, we will discuss the reported synthesis of tetrasubstituted cyclobutane-containing natural products.[6] We divided this section into three parts: 1) photochemical [2+2] cycloaddition in solutions; 2) photochemical [2+2] cycloaddition in solid state; 3) Introduction of substituents by C-H activation.

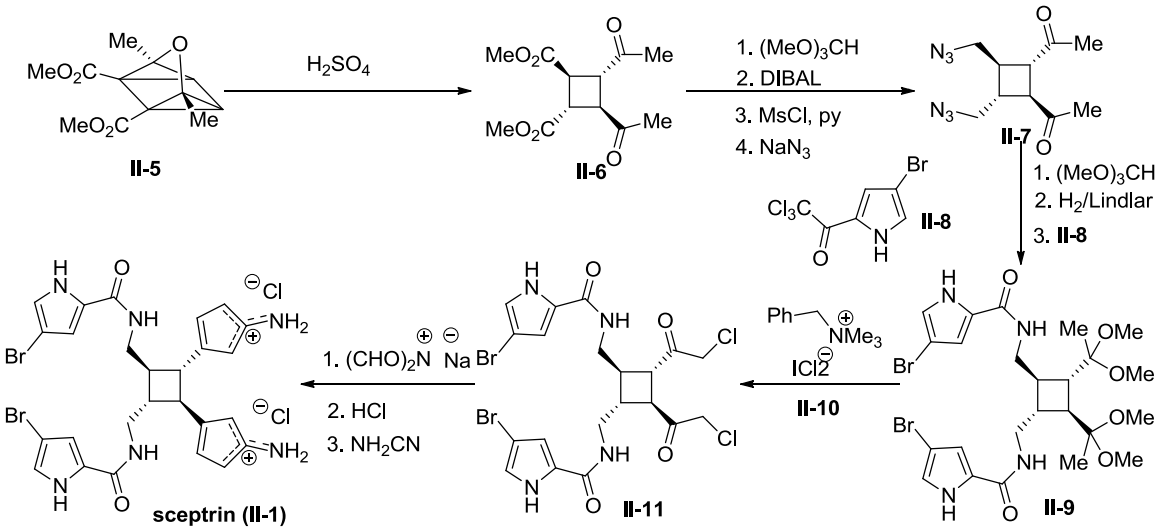
## 2.1.2 PHOTOCHEMICAL [2+2] CYCLOADDTION IN SOLUTIONS

### 2.1.2.1 Baran's total synthesis of sceptrin[7]

Sceptrin (**II-1**) and related alkaloid dibromosceptrin (**II-16**) was isolated from *Agelas sceptrum* and showed a broad range of biological activities such as antibacterial, antiviral and antimuscarinic. Sceptrin is also a somatostratin inhibitor. In 1981, sceptrin was isolated and characterized by Faulkner and Clardy. In 2004, Baran and co-workers completed the first total

synthesis (**Scheme II-2**). They took advantage of the rearrangement observed by Laing and Nelson: 3-oxaquadricyclane (**II-5**) underwent the rearrangement to afford trans, trans, trans-cyclobutane diester (**II-6**) without chromatography. After the reduction, oxidation and substitution displacement, the diazide cyclobutane (**II-7**) was prepared from diester (**II-6**). When diketone on the cyclobutane diester (**II-6**) was protected, azide could be reduced and then reacted with pyrrole (**II-8**) to yield cyclobutane **II-11**. Using benzyltrimethylammonium dichloroiodate (**II-10**), **II-9** was converted to dichloride **II-11** with great chemo- and regioselectivity. After threesteps involving just one-flask cyclization, sceptrin (**II-1**) was synthesized. Overall, this is a beautiful synthesis which could be operated on large scale without HPLC or flash chromatography.

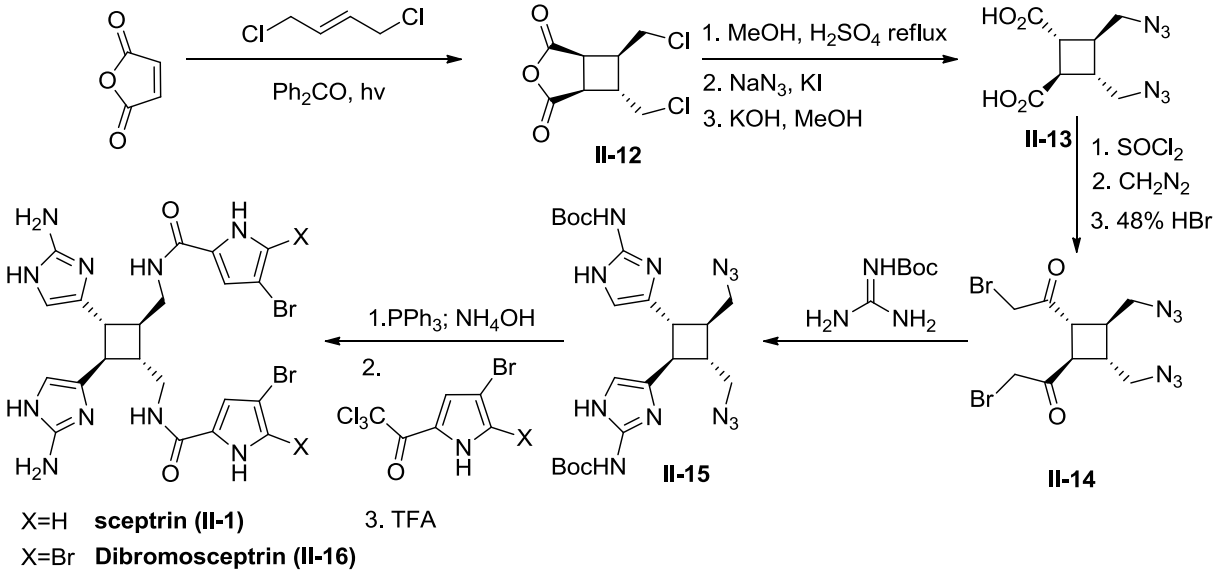
**Scheme II-2:** Baran's Total Synthesis of Sceptrin



### 2.1.2.2 Birman's total synthsis of sceptrin alkaloids[8]

In 2004, Birman and co-workers disclosed a concise synthetic route to sceptrin and dibromosceptrin (**Scheme II-3**). Compared to Baran's synthesis, Birman and coworkers used the known photocycloadditio of maleic anhydride with trans-1, 4-dichloro-2-butene to construct the cyclobutane main core (**II-12**). Unlike Baran's strategy, which introduced the pyrroles at the beginningBirman and co-workers first installed the 1-aminoimidazole subunits to obtain **II-15** after the formation of diketone. After azide reduction by triphenylphosphine, subsequent acylation with pyrrole and deprotection, total synthesis of sceptrin (**II-1**) was completed. Dibromosceptrin (**II-16**) was also synthesized in the same route.

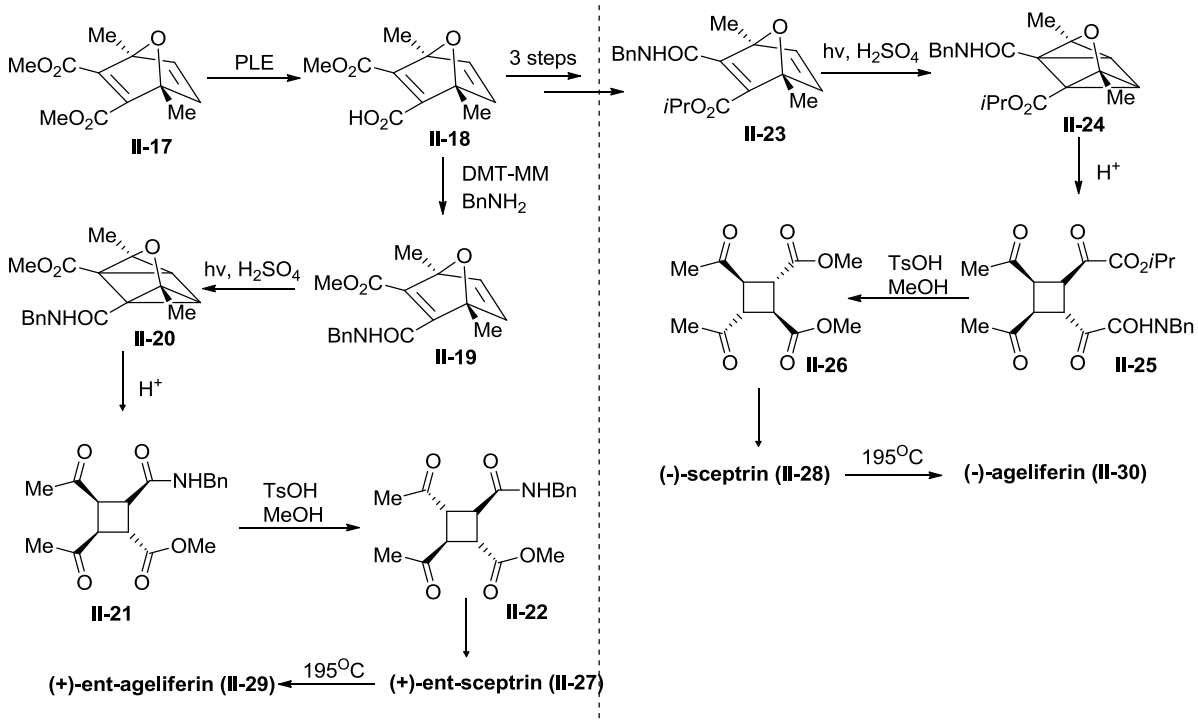
**Scheme II-3:** Birman's Total Synthsis of Sceptrin Alkaloids



### 2.1.2.3 Baran's enantioselective totally synthesis of sceptrin and ageliferin[9]

Later Baran and co-workers reported the enantioselective total synthesis of sceptrin and ageliferin by programmed fragmentation of an oxaquadricyclane (**Scheme II-4**). Enzymatic desymmetrization of meso-diester (**II-17**) using pig liver esterase (PLE) yielded monoester (**II-18**) with 75% ee. Monoester (**II-18**) was treated by DMT-MM to afford the monobenzylamide (**II-19**). After irradiation and rearrangement, cis, trans, trans-cyclobutane (**II-21**) was prepared with 75% ee (>95%% after recrystallization). Debenzylation, esterification and epimerization was achieved in one pot using TsOH and MeOH to give tetrasubstituted cyclobutane (**II-22**), which could produce (+)-ent-sceptrin according to known procedures. The naturally sceptrin could be made by converting monoacid to amide (**II-18**) following the similar conditions. The key was the preparation of monobenzylamide **II-23**. Enantioselective synthesis of ageliferin was also completed according to literature precedures.

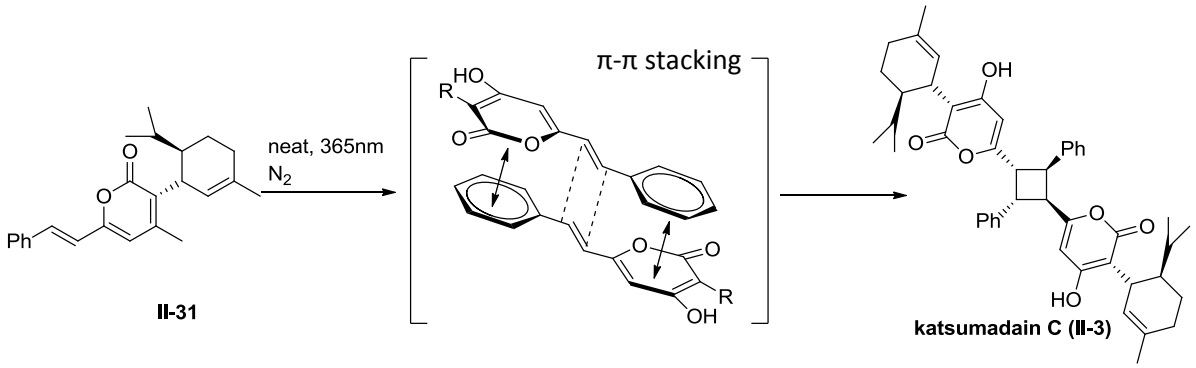
**Scheme II-4:** Baran's Enantioselective Totally Synthesis of Sceptrin and Ageliferin




### 2.1.2.4 Yang and Tang's total synthesis of Katsumadain C[4]

In 2011, Yang and coworkers reported the enantioseletive total synthesis of katsumadain C through a biomimetic approach (**Scheme II-5**). Katsumadain C was isolated *from Alpinia katsumadiai* by Kong and co-workers and exhibited broad antitumor activity against several human tumor cell lines. Photo-induced topochemical [2+2] dimerization afforded katsumadain C **(II-3**) in neat condition which involved π-π stacking interaction between the phenyl ring and the 2-pyranone ring.

**Scheme II-5:** Yang and Tang's Total Synthesis of Katsumadain C

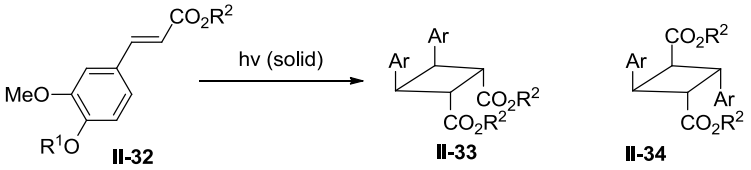



## 2.1.3 PHOTOCHEMICAL [2+2] CYCLOADDTION IN SOLID STATE

### 2.1.3.1 Kibayashi's total synthesis of (-)-incarvillateine[10]

In 2004, Kabayashi and co-workers described the photodimerization of ferulic acid derivatives in crystalline forms and so called "topochemical rules" could be used to predict the reactivity and stereoselectivity in crystal controlled photochemical [2+2] cycloadditions. The results of the photodimerization of ferulic acid derivatives were shown in **Table II-1**. When 4-o-tosylferulic acid was employed (**entry 8**), the desired α-truxillic product (**II-34-8**) was formed in great yield.

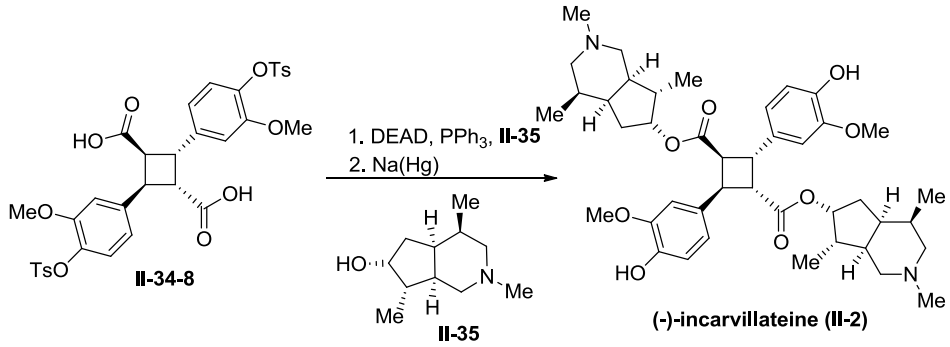
**Table II-1:** Photodimerization of the Ferulic Acid Derivatives




| Entry | $R^1$ | $R^2$ | Photodimer | Yield **head-to-tail (α-truxillic)** |
|---|---|---|---|---|
| 1 | H | p-$NO_2$Ph | **II-33**-1 | 63 |
| 2 | Ac | Me | na | |
| 3 | PhCO | Me | na | |
| 4 | Ms | Me | **II-34-4** | 35 |
| 5 | $PhSO_2$ | Me | na | |
| 6 | o-Ns | Me | **II-34-6** | 56 |
| 7 | Ts | Me | **II-34-7** | 60 |
| 8 | Ts | H | **II-34-8** | 98 |

With the phtodimerization condition in hand, α-truxillic cyclobutane dicarboxylic acid **II-34-8** was prepared in large scale. The condensation of this dicarboxylic acid with (+)-6-*epi*-incarvilline (**II-35**) afforded tosyl protected incarvillatein. Deprotection using sodium amalgam gave (-)-incarvillateine (**II-2**).

**Scheme II-6:** Kabayashi's total synthesis of (-)-incarvillateine



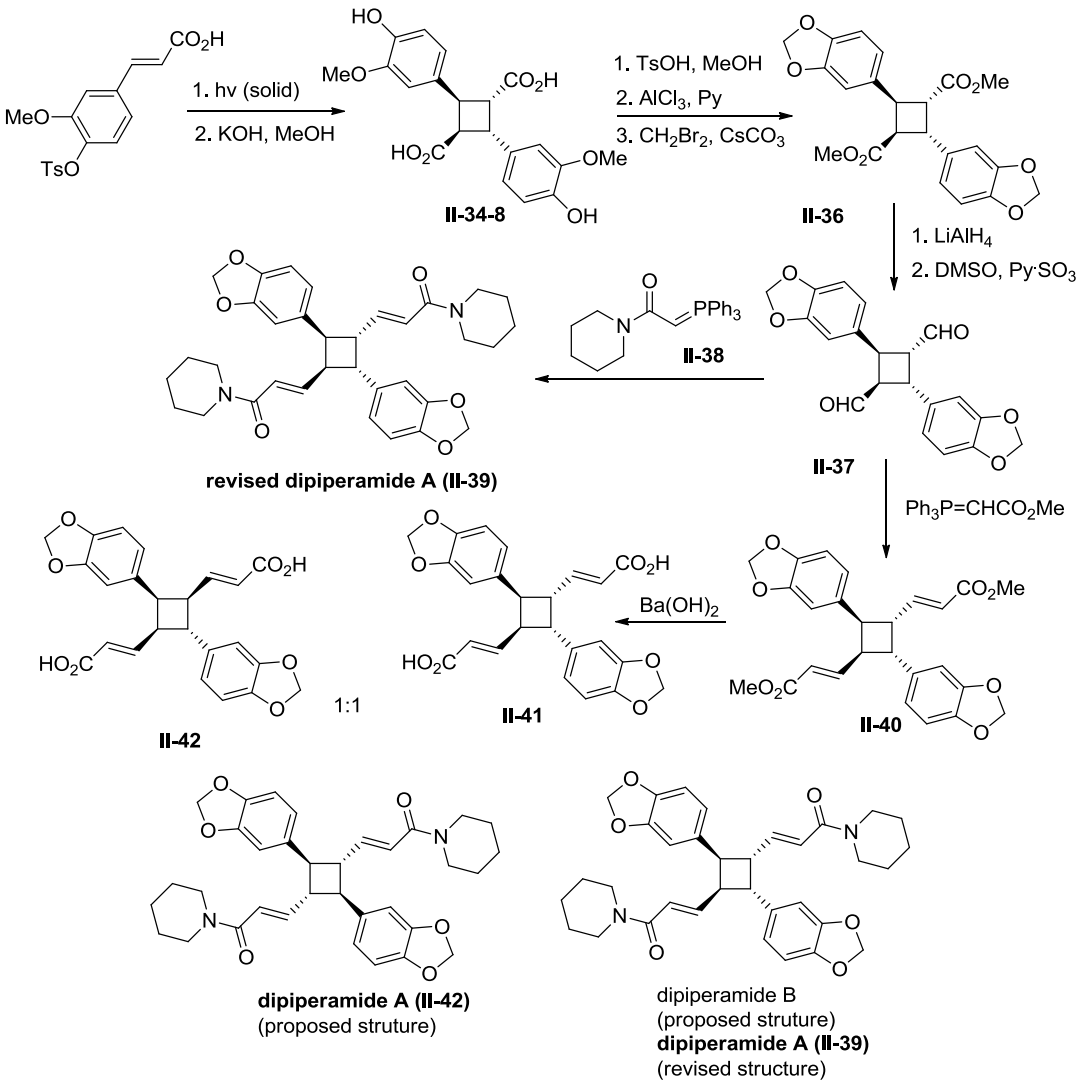

Later, Bergman, Ellman and Jia described the total synthesis of (-)-incarvillateine independently by constructing the cyclobutane main core following Kibayashi's protocol[10].

### 2.1.3.2 Kibayashi's total synthesis and structure revision of dipiperamide A[11]

In 2005, Kibayashi and co-workers reported the total synthesis and structure revision of dipiperamide A using the crystal controlled photochemical [2+2] cycloadditions described above. Tetrosubstituted cyclobutane (**II-36**) could not be observed from direct photochemical [2+2] cycloadditions of 3,4-methylenedioxycinnamic acid. Instead, after three steps, **II-34-8** was converted to tetrasubstituted cyclobutane (**II-36**). Dialdehyde (**II-37**) was prepared in two steps. Wittig olifinaion of **II-37** with triphenylphosphoranylidenacetate gave diolefin (**II-40**), which was hydrolyzed by $Ba(OH)_2$ to give a 1:1 mixture of **II-41** and **II-42**; while direct Wittig olifination of **II-37** with **II-38** gave **II-39** without epimerization.

However, the data ($^{1}$HNMR and $^{13}$CNMR) of synthetic sample (**II-39**) was not consistent with the reported data of dipieramide B, but consistent with those reported for dipiperamide A. So the authors claimed the proposed structure of dipiperamide B should be the revised to the structure of dipiperamide A.

**Scheme II-7:** Kibayashi's Total Synthesis and Structure Revision of Dipiperamide A

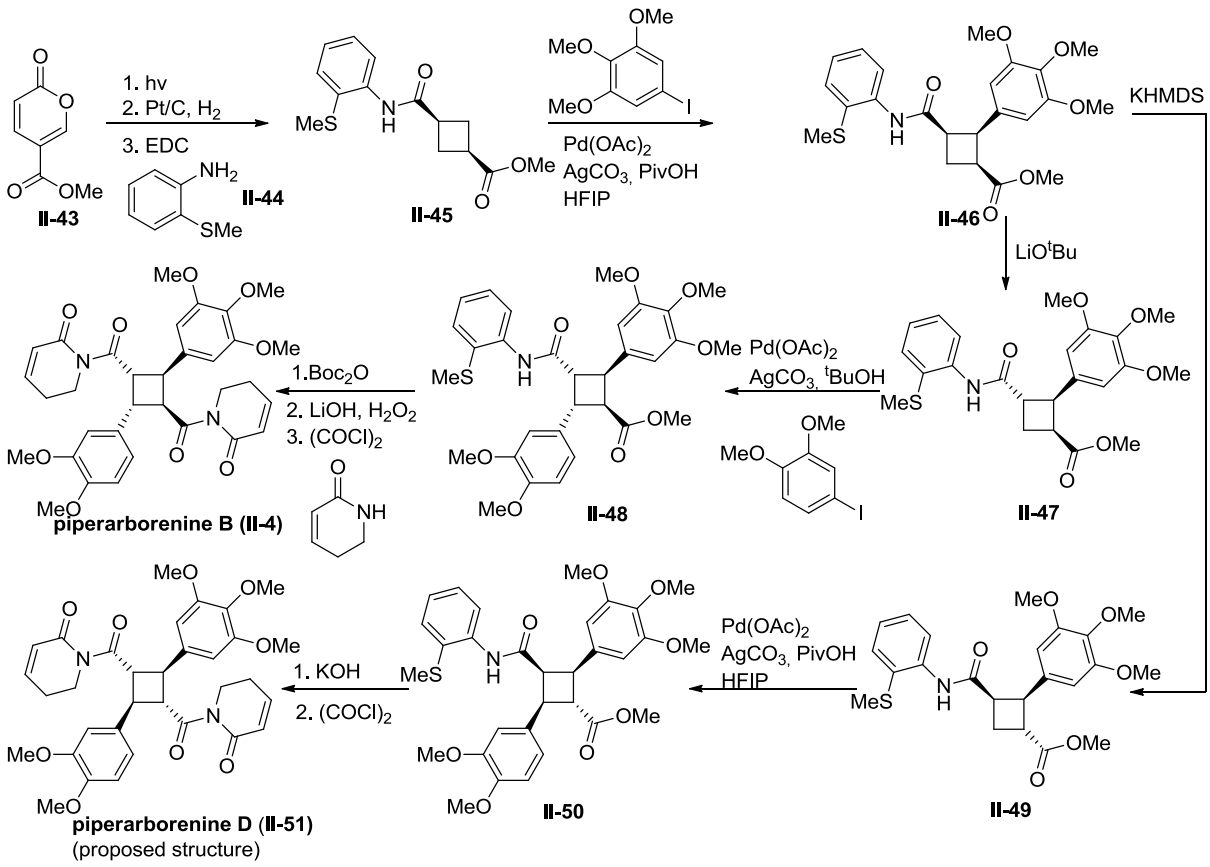



## 2.1.4 INTRODUCTION OF SUBSTITUENTS BY C-H ACTIVATION

### 2.1.4.1 Baran's total synthesis and structure revision of piperarborenine B and D[12]

Recently, Baran and co-workers reported a new strategy to access unsymmetrical cyclobutane natural products by applying metal-catalyzed functionlizaion of cyclobutane C ($sp^3$)-H bond (**Scheme II-8**). The 1,3-dicarboxylate cyclobutane (**II-45**) was prepared from commercially available methyl comalate (**II-43**) as a single diastereoisomer in one-pot.It involved photochemical 4π electron cyclization, reduction and subsequent amide formation to introduce the directing group for the C-H activation. After optimizing the C-H activation conditions, 3,4,5-trimethoxyiodobenzene was introduced to the disubstituted cyclobutane (**II-45**). The addition of both PivOH and hexafluoroisopropanol (HFIP) was found to be crucial for this C-H activation reaction. Amide on the cyclobutane (**II-46**) was selectively epimerized under Li*O*tBu condition. Further arylation with 3,4-dimethoxyiodobenzene occurred to give tetrasubstituted cyclobutane (**II-47**) under the similar C-H activation condition as above. Surprisingly, both PivOH and hexafluoroisopropanol (HFIP) were found to be not necessary in this case. Treatment of tetrasubstituted cyclobutane (**II-48**) with $Boc_2O$ and subsequent hydrolysis of both amide and ester provided a dicarboxylic acid, which was coupled with dihydropyridone to afford piperarborenine B.

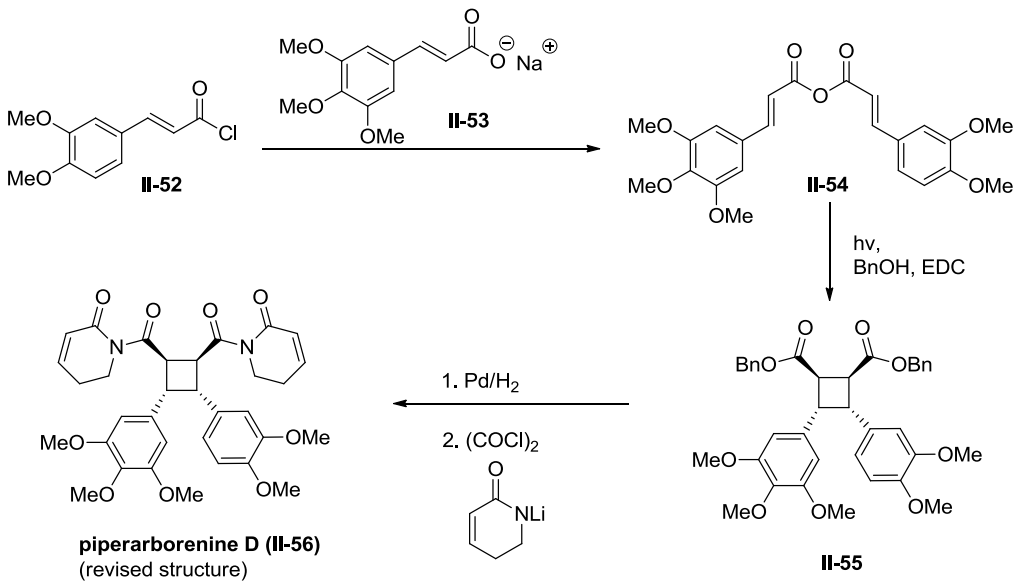
**Scheme II-8:** Baran's Total Synthesis and Structure Revision of Piperarborenine B and D




Selective epimerization of ester using KHMDS yielded trisubstituted cyclobutane (**II-49**), which was converted to arylated product (**II-50**) under the C-H activation conditions described before. After further epimerization of the amide on tetrasubstituted cyclobutane (**II-50**), hydrolysis and formation of an amide, proposed structure of poperarborenine D was completed.

However, the data ($^{1}$HNMR and $^{13}$CNMR) of synthetic piperarborenine D was not consistent with the literature data. So the authors proposed a revised head to head dimerizaion structure (**II-56**) which was confirmed by synthesis using an intramolecular [2+2] photocyloaddition approach (**Scheme II-9**).

**Scheme II-9:** Baran's Total Synthesis of Revised Structure of Piperarborenine D

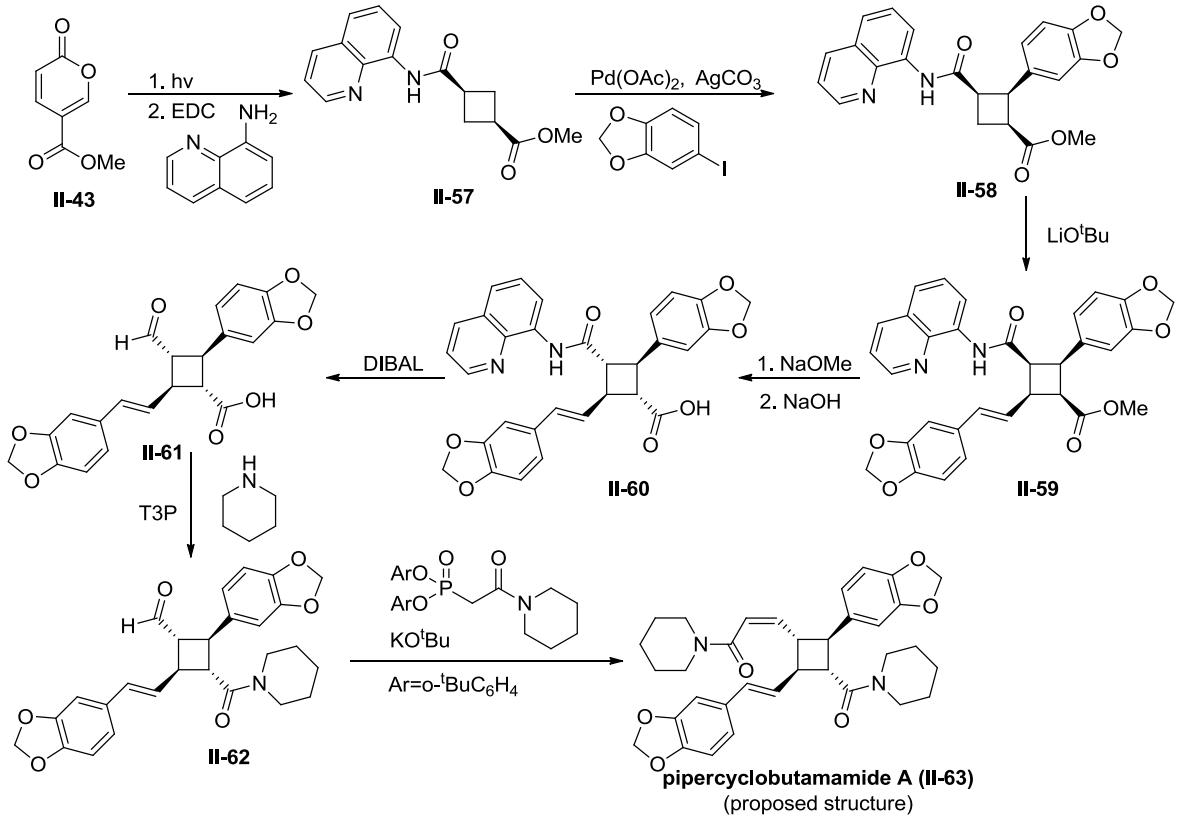



### 2.1.4.2 Baran's total synthesis of proposed structure of pipercyclobutanamide A[13]

In 2012, Baran and co-workers completed the synthesis of pipercyclobutanamide A using sequential C($sp^3$)-H arylation and olefination (**Scheme II-10**), which further showed the power of C-H activation for the synthesis of tetrasubstituted cyclobutane natural products. Starting with similar dicarboxylate cyclobutane (**II-57**), 1-iodo-3,4-methylene-dioxybenzene was coupled to the cyclobutane using aminoquinoline amide as directing group. Second C-H olefination occurred between trisubstituted cyclobutane (**II-58**) and styrenyl iodide under the similar C-H activation condition to give the all-cis tetrasubstituted cyclobutane (**II-59**). After epimerization and formation of trans- and cis- olefins, all-cis cyclobutane was converted to proposed structure of pipercyclobutanamide A. Baran's group and we reported the synthesis of the

proposed structure of pipercyclobutanamide A at the same time by back-to-back communications.(ref)

**Scheme II-10:** Baran's Total Synthesis of Proposed Structure of Pipercyclobutanamide A



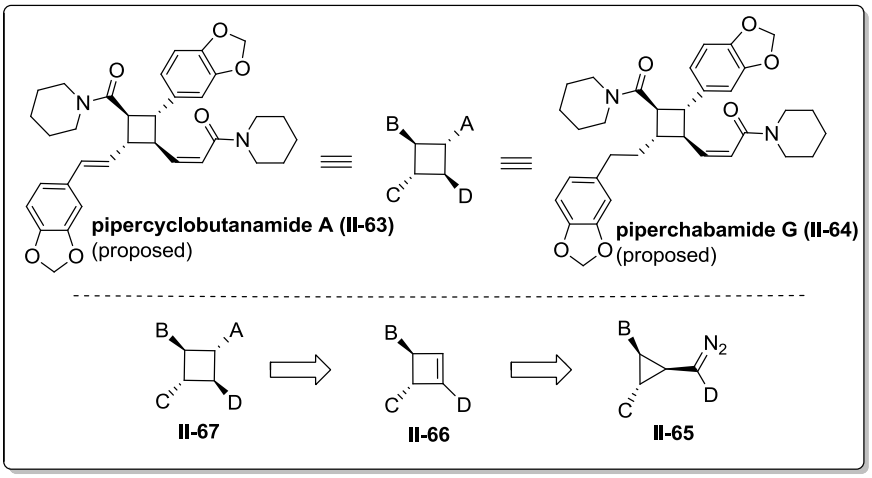

## 2.2 GENERAL RETROSYNTHETIC PLAN FOR THE SYNTHESIS OF PIPERCYCLOBUTANAMDE A AND PIPERCHABAMIDE G

Pipercyclobutanamides[14-16] and piperchabamides are two classes of tetrasubstituted cyclobutane natural products isolated from *Piper nigrum* and *Piper chaba*, the source of white

and black pepper. Pipercyclobutanamide A[14,] (**II-63**) is a selective inhibitor for CYP2D6, one of the main P450 enzymes for drug metabolism in liver; while Piperchabamide G[17] (**II-64**) is an inhibitor for D-GalN/tumor necrosis factor and has hepatoprotective effect.

We envisioned that both pipercyclobutanamide A (**II-63**) and piperchabamide G (**II-63**) could be simplified to the models shown in **Scheme II-11** (**II-65, 66 and 67**) and A-D represents four different substitutions attached on the cyclobutane. The fourth substitution A on tetrasubstituted cyclobutane (**II-67**) could be introduced by the conjugate addition of A to the cyclobutene II-66. Cyclobutene **II-66** can be prepared from cyclopropyl dizao compound **II-65** through metal catalyzed ring expansion reaction developed in our lab[18,19].

**Scheme II-11:** General Retrosynthetic Plan for the Synthesis

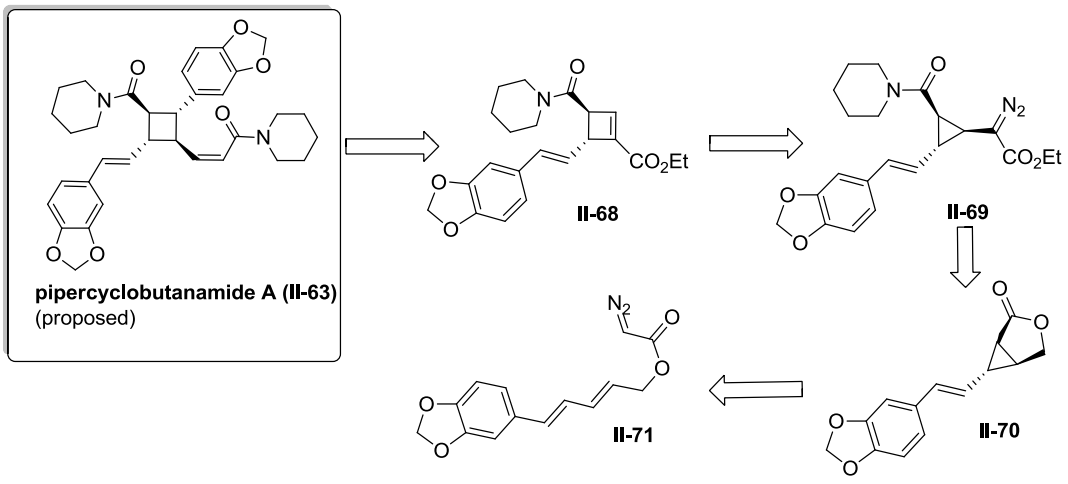



## 2.3 FIRST GENERATION ROUTE TOWARDS THE SYNTHESIS OF PIPERCYCLOBUTANAMIDE

### 2.3.1 RETROSYNTHETIC PLAN FOR THE SYNTHESIS OF PIPERCYCLOBUTANAMIDE A

The first generation of retrosynthetic plan of pipercyclobutanamide A (**II-63**) was shown in **Scheme II-12**. Pipercyclobutanamide A (**II-63**) was constructed by introducing 3,4-methylene-dioxybenzene to cyclobutene II-68 and subsequent cis-olefination. Cyclobutene **II-68** can be synthesized from cyclopropyl dizao compound **II-69** through ring expansion reaction which involves a cyclopropyl metal carbene intermediate derived from transition metal-catalyzed decomposition of diazo compounds. Dizao compound **II-69** was obtained by lactone opening of bicyclic **II-70** and several steps of functional group manipulations . Bicyclic lactone **II-70** was constructed through an intramolecular cyclopropanation of **II-71**.

**Scheme II-12:** First Generation Retrosynthetic Plan for the Synthesis of Piperbutanamide A

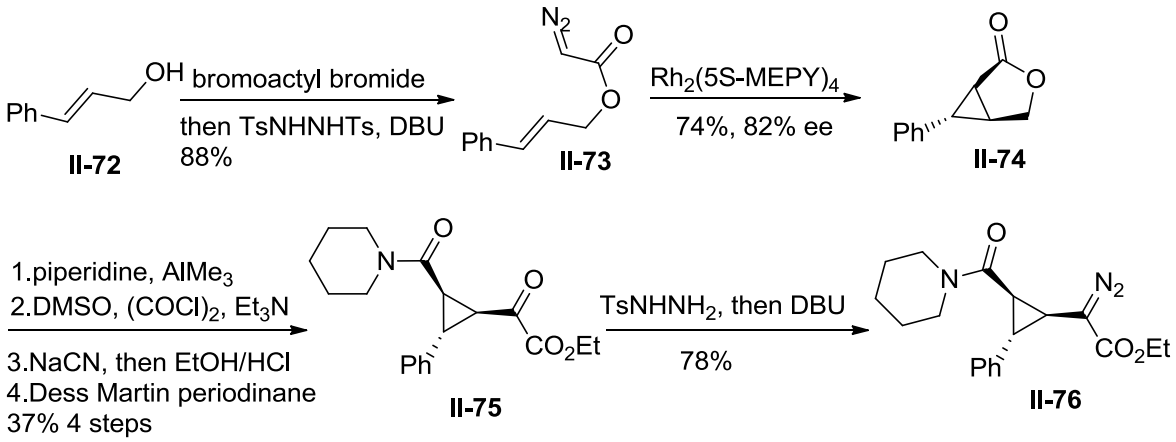



## 2.2.2 MODEL STUDY TOWARDS THE SYNTHESIS OF PIPERCYCLOBUTANAMDE A

Before pursuing pipercyclobutanamide A (**II-63**), we chose commercially available cinnamyl alcohol (**II-72**) as the starting material to perform a model study. Following literature procedures, we prepared known compound **II-74** in two steps. Lactone opening and oxidation of primary alcohol under Swern oxidation condition yielded an aldehyde, which was converted

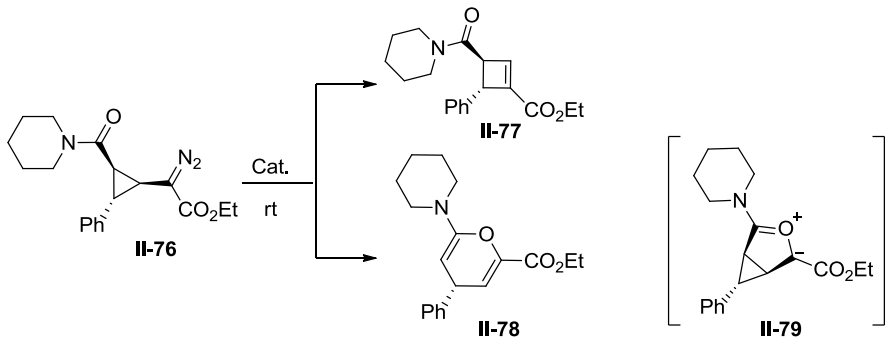
to diazo compound **II-76** through ketoester **II-75** according to procedures we developed previously.

**Scheme II-13:** Model Study for the Synthesis of Piperbutanamide A




With diazo compound **II-76** in hand, we further screened conditions for the ring expansion reaction (**Table II-2**). We have reported that the regioselectivity was dependent on different catalysts and the substituents of the cyclopropane ring. The C-C bond that was adjacent to the electron-donating group or away from the electron-withdrawing group could be selectively cleaved when a silver(I) catalyst was employed. In the case of cyclopropane **II-76**, we predicted that cyclobutene **II-77** would be observed. As we expected, great regioselectivity was observed when diazo compound **II-76** was treated with different transition metal catalysts. We were glad to find the silver (I) catalyst gave us desired cyclobutene product **II-77** as a single isomer with perfect regioselectivity based on $^{1}$H NMR of the crude product; while Rhodium (II) catalyst produced pyran product **II-78** through ylide intermediate **II-79**.

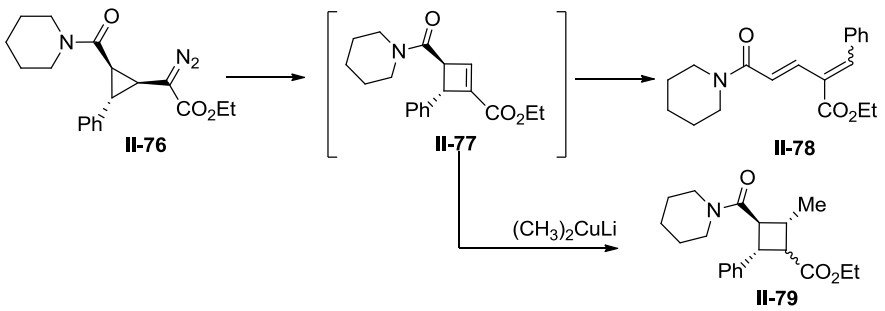
**Table II-2:** Screening of Conditions for Ring Expansion Reaction (Compound numbers in the Table are wrong.)




| Entry | Condition | Ratio II-77/78 |
|---|---|---|
| 1 | $Rh_2(OAc)_4$, DCM | 1:20 |
| 2 | $Cu(MeCN)_4PF_6$, DCM | UNKNOWN |
| 3 | $AgSbF_6$, DCM | 20:1 |

We fail to isolate cyclobutane **II-77** because it was not stable in solution at room temperature. We also tried to trap it with methyl cuprate reagent. However, we only obtained trace amount tetrasubstituted cyclobutane product and diene II-78, (this number was designated to pyran product in Table II-2) which was the product of ring opening of cyclobuene. We realized that amide and phenyl groups on the cyclobuene formed a push-pull system to accelerate the ring opening process. In our original plan for pipercyclobutanamide A (**II-63**) shown in **Scheme II-12**, 3,4-methylene-dioxybenzene on the cyclobutene **II-68** is much more electron rich than phenyl group. This will make the cyclobuene **II-68** even less stable.

**Scheme II-13:** Attempt to Trap the Cyclobutene

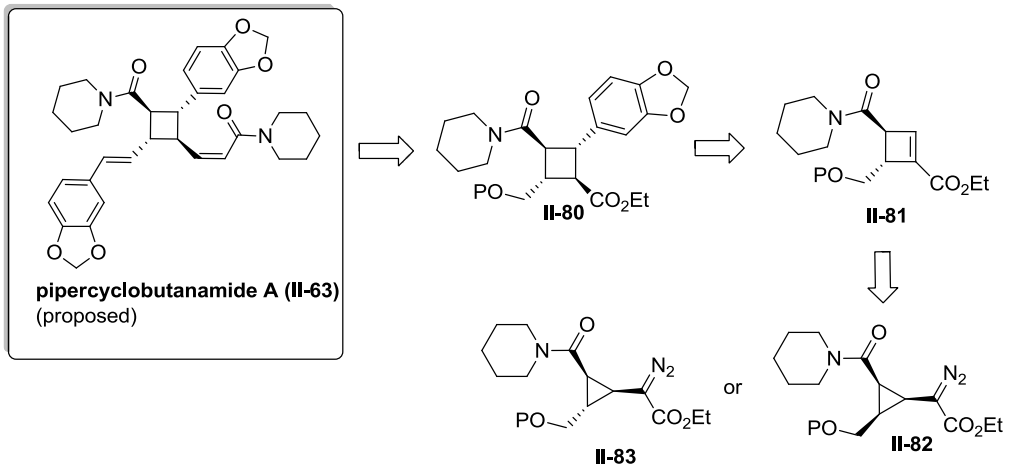



## 2.4 SECOND GENERATION ROUTE TOWARDS THE SYNTHESIS OF PIPERCYCLOBUTANAMIDE A

### 2.4.1 SECOND GENERATION OF RETROSYNTHETIC PLAN FOR THE SYNTHESIS OF PIPERCYCLOBUTANAMIDE A

We then designed a new strategy for the synthesis of pipercyclobutanamide A (**II-63**). We chose the protected primary alcohol as the precursor of the trans-olefin on the pipercyclobutanamide A (**II-63**) instead of installing it in the starting material (II-71). This new approach for pipercyclobutanamide A (**II-63**) is shown in **Scheme II-14**. The protected primary hydroxyl group and ester group in cyclobutane **II-80** served as cis- or trans-olefin precursors, respectively. Conjugate addition of an aryl group to cyclobutenoate **II-81** might give the tetrasubstituted cyclobutane **II-80**. Because of potential steric interactions with the adjacent amide, the aryl group would approach the cyclobutenoate **II-81** from the α-face. Cyclobutenoate **II-81** could be prepared from cyclopropyl dizao compound **II-82** or **83**by ring expansion reaction.

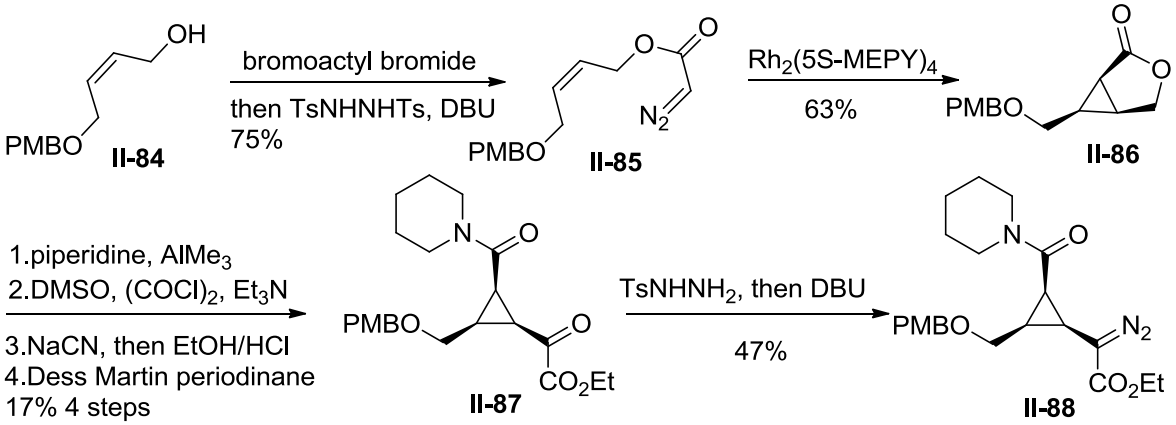
**Scheme II-14:** Second Generation Retrosynthetic Plan for the Synthesis of Piperbutanamide A




## 2.4.2 CIS-MONOPROTECTED DIOL AS STARTING MATERIAL

Our synthesis started from mono-protected cis-diol **II-84** (**Scheme II-15**). After the same transformations described in the model study (**Scheme II-13**), the cyclopropyl diazo compound **II-88** was prepared.

**Scheme II-15:** Synthesis of Cyclopropyl Dizao **II-88**



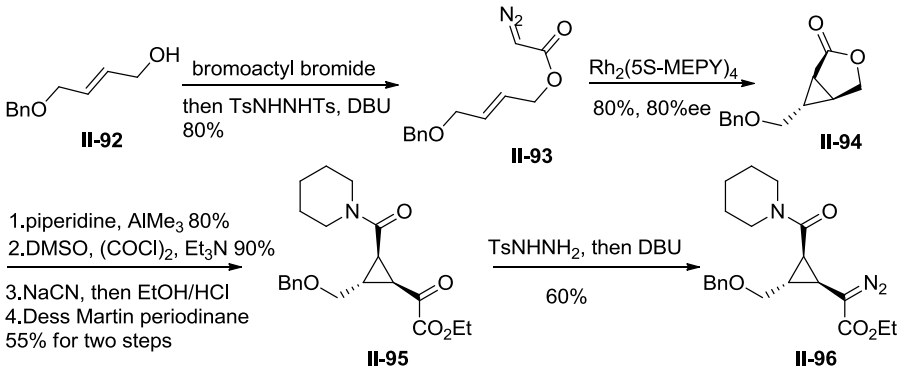
With diazo compound **II-88** in hand, we further screened conditions for the ring expansion reaction (**Scheme**). Unfortunately, in all case, we did not observed the desired cyclobuene product.

### 2.4.3 TRANS-MONOPROTECTED DIOL AS STARTING MATERIAL

#### 2.4.3.1 SYNTHESIS OF CYCLOPROPYL DIAZO COMPOUND

We started our synthesis from mono-protected trans-diol 13 (Scheme 2). After the same transformations described in the model study (**Scheme II-13**), the cyclopropyl diazo compound **II-96** was prepared. By taking advantage of the well-documented Rh(II) catalyzed enantioselective intermolecular cyclopropanation, bicyclic lactone **II-94** was prepared in a 80% yield and 80% ee

**Scheme II-17:** Synthesis of Cyclopropyl Dizao Compound **II-96**

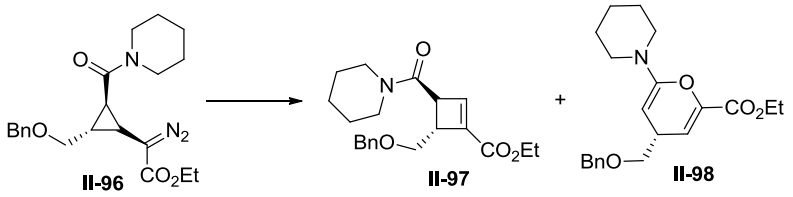



#### 2.4.3.2 COMPLETION OF SYNTHESIS OF PIPERCYCLOBUTANAMIDE A

After examining different metal catalysts, a similar trend was found for cyclopropyl diazo compound **II-96** as **II-76** (**Table II-3**). Excellent regioselectivity was always observed when diazo

compound **II-96** was treated with different transition metal catalysts. Silver (I) catalyst yielded desired cyclobutane product **II-97**; while rhodium (II) catalyst produced 4*H*-pyran product II-**98**. Interestingly, copper catalyst gave a 1:1 mixture of **II-97** and **98**.

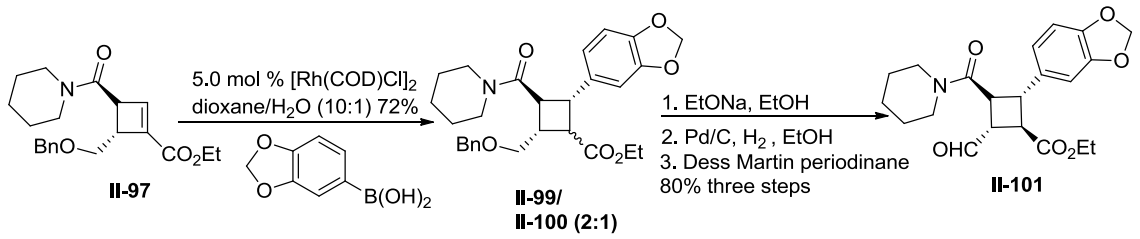
**Table II-3:** Screening of Conditions for Ring Expansion Reaction



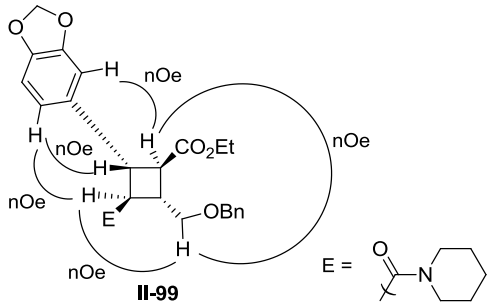

| Entry | Condition | Ratio |
|---|---|---|
| 1 | $Rh_2(Oct)_4$, DCM | 1:20 |
| 2 | $Cu(MeCN)_4PF_6$, DCM | 1:1 |
| 3 | AgOTf, DCM | 20:1 |

With cyclobutenoate **II-97** in hand, we investigated the conjugate addition of an aryl group to this enoate (**Scheme II-18**). Under various conditions, aryl cuprate reagent failed to give any conjugate addition product. We then examined other transition metal catalysts and found that Rhodium (I)-catalyzed addition of arylboronic acid to this enoate gave the tetrasubstituted cyclobutanes 99 and 100 (Scheme II-18). The aryl group should approach the cyclobutene ring selectively from the face away from the amide substituent. The mixture of diastereomers **II-99** and **100** was obtained with a ratio of 2:1 favoring β-isomer **II-99**. Treating this mixture with NaOEt afforded the thermodynamically more stable β-isomer **II-99** as a single stereoisomer, which was confirmed by nOe analysis (**Scheme II-19**). Removal of the benzyl group followed by oxidation provided aldehyde **II-101**.

**Scheme II-18:** Synthesis of Cyclobutane Aldehyde **II-101**

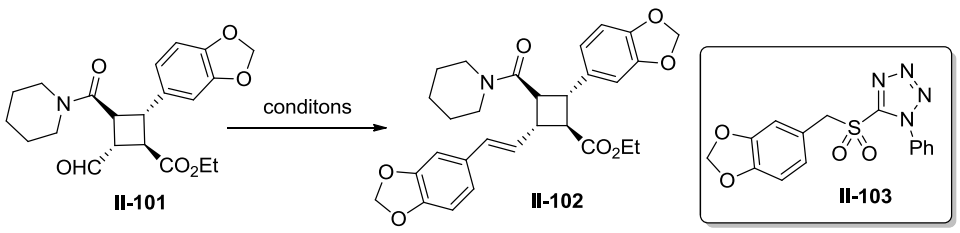



**Scheme II-19:** nOe Analysis of **II-99**




The installation of the *E*-olefin in pipercyclobutanamide (**II-63**) by Julia-Kocienski olefination seemed very straightforward. However, under the typical condition (**entry 1 Table II-4**), cyclobutane aldehyde **II-101** reacted with **II-103** gave 2:1 *E*/*Z* ratios even at low temperature. Finally both polar solvent DMF and HMPA additive were found to be critical to achieve high *E*/*Z* ratios (**entry 5**). Trans-olefination product **II-102** was obtained as a single isomer but contaminated with byproduct derived from reagent **II-103**.

**Table II-4:** Screening of Conditions for Trans-olefination

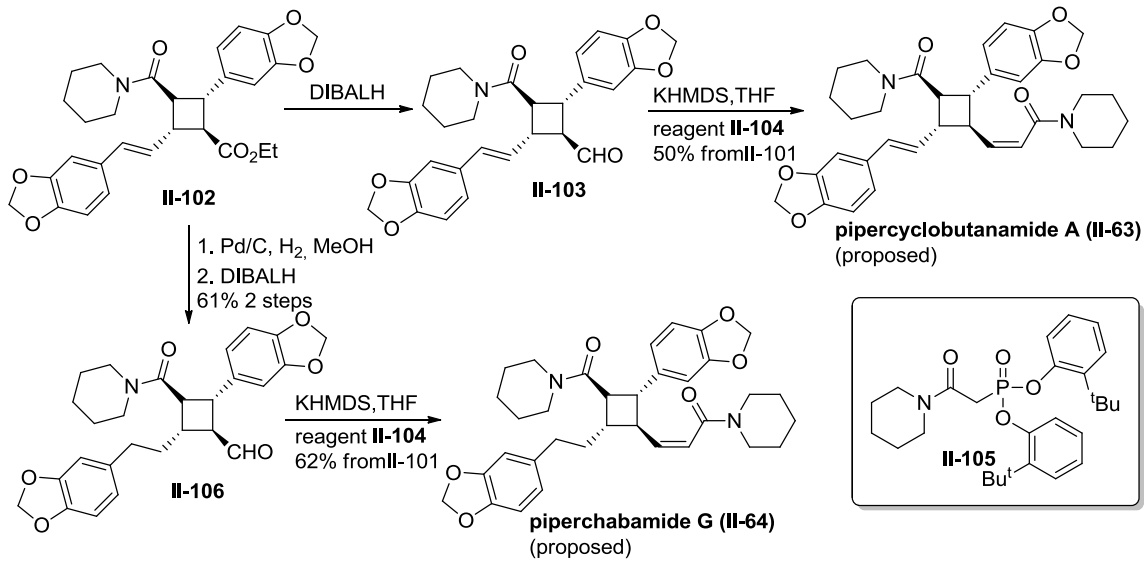



| Entry | Condition | E/Z ratio |
|---|---|---|
| 1 | NaHMDS, THF, -78$^{o}$C-r.t. | 2:1 |
| 2 | KHMDS, THF, -78$^{o}$C-r.t. | 3:1 |
| 3 | LiHMDS, THF, -78$^{o}$C-r.t. | 3:1 |
| 4 | LiHMDS, DMF, -78$^{o}$C-r.t. | 4:1 |
| 5 | LiHMDS, DMF/HMPA (4/1, v/v), -78$^{o}$C-r.t. | >20:1 |

DIBAL reduction gave the cyclobutane aldehyde **II-103**, which reacted with Ando's reagent **II-105** to furnish the *Z*-olefin and complete the synthesis of pipercyclobutanamide A (**II-63**) with great *Z*/*E* selectivity (*Z*/*E*>20:1). A *Z*/*E* ratio of 2:1 was obtained when the Still-Gennari olefination protocol was employed.

We also completed the total synthesis of piperchabamide G (**II-64**), which did not have the styrene olefin compared to pipercyclobutanamide A (**II-63**). Hydrogenation of trans-olefin in cyclobutane **II-102** followed by reduction and olefination with Ando's reagent II-104 as described above produced piperchabamide G (**II-64**) (Z/E>20:1).

**Scheme II-20:** Completion of the Synthesis

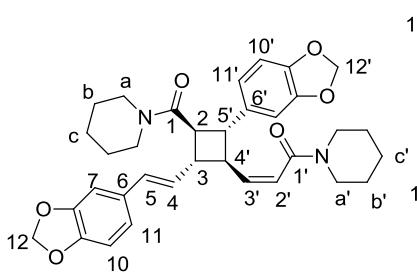



## 2.5 STRUCTURE REVISION OF CYCLOBUTANE-CONTAINING NATURAL PRODUCTS

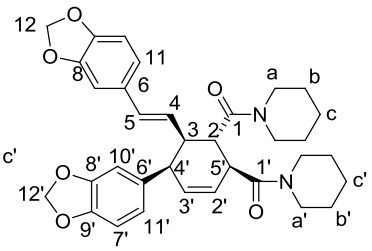
Our data ($^{1}$H and $^{13}$C NMR) for synthetic pipercyclobutanamide A (**II-63**) were not consistent with those reported in literature for pipercyclobutanamide A. We then further characterized our synthetic compound by COSY, HMBC, HSQC, ROESY, and HRMS. All of our spectral data matched the proposed structure of pipercyclobutanamide A (**II-63**).

We compared our data and those in literature carefully and found that we did have any signal between 5.0 ppm and 5.5 ppm in the $^{1}$H NMR of synthetic compound. These signals supposed to be the β-styrene hydrogen H4. After analyzing similar natural products in the literature, we found that chemical shifts for this type of β-styrene hydrogen ranged from 6.10 to 6.29 ppm.

**Table II-5:** $^{1}$H NMR and $^{13}$C NMR Spectral Data for the Core Structures



**pipercyclobutanamide A (II-63)**
(proposed)



**chabamide II-107**
(revised structure of
pipercyclobutanamide A )

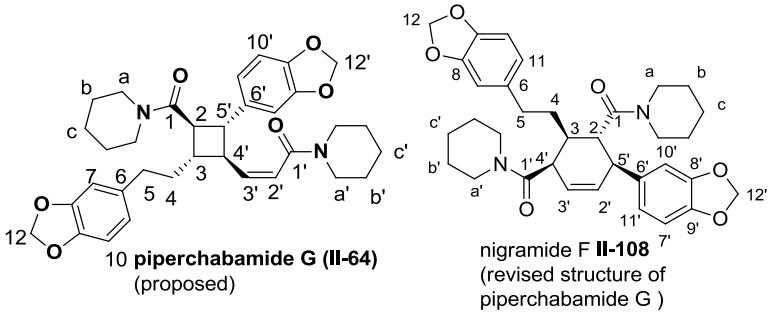
| Position | δH / δC of synthetic II-63 | δH / δC of II-63 (literature)[16] | δH / δC of II-107 (literature) |
|---|---|---|---|
| 1 | — / 170.2 | — / 172.2 | — / 172.2 |
| 2 | 3.03 / 49.7 | 3.66 / 37.7 | 3.64 / 37.7 |
| 3 | 3.03 / 45.6 | 2.93 / 45.4 | 2.91 / 45.4 |
| 4 | 6.16 / 128.6 | 5.21 / 128.0 | 5.19 / 128.1 |
| 5 | 6.48 / 130.7 | 6.32 / 131.0 | 6.29 / 131.0 |
| 1′ | — / 165.8 | — / 171.1 | — / 171.1 |
| 2′ | 6.03 / 120.4 | 5.75 / 125.5 | 5.73 / 125.5 |
| 3′ | 5.92 / 140.5 | 5.86 / 130.3 | 5.84 / 130.3 |
| 4′ | 3.78 / 43.4 | 3.48 / 45.9 | 3.45 / 45.9 |
| 5′ | 3.48 / 46.5 | 4.14 / 42.8 | 4.12 / 42.9 |

Our spectral data ($^{1}$H NMR and $^{13}$C NMR) for piperchabamide G (**II-64**) again did not match the data in literature. All of our spectral data (COSY, HMBC, HSQC, ROESY, and HRMS) were consistent with the proposed structure.

After failing to find cyclobutane isomers that could match the spectral data of natural products pipercyclobutanamide A and piperchabamide G, we then carefully analyzed all spectroscopic differences between our synthetic compounds and natural products (Tables **II-5**). We found that $^{13}$C chemical shifts of 172.2 and 171.1 ppm were assigned to the two carbonyl carbons in natural product pipercyclobutanamide A. We observed $^{13}$C chemical shifts of 170.2 and 165.8 ppm for carbonyl carbons 1 and 1′, respectively, in our synthetic compound. In a related natural product, dipiperamide E, $^{13}$C chemical shifts of 169.1 and 165.2 ppm were

assigned to the non-conjugated amide carbonyl carbon and the conjugated amide carbonyl carbon, respectively. Our assignments for the two carbonyl carbons in synthetic product **II-63** were also consistent with other closely related natural products. It appeared that the two carbonyl groups in natural product pipercyclobutanamide A were both non-conjugated. Furthermore, the comparison of $^{13}C$ chemical shifts of the cis-alkene in natural product pipercyclobutanamide A, our synthetic compound, and related natural products suggested that the cis-alkene in natural product pipercyclobutanamide A was likely not conjugated to a carbonyl group.

**Table II-6:** $^{1}H$ NMR and $^{13}C$ NMR Spectral Data for the Core Structures



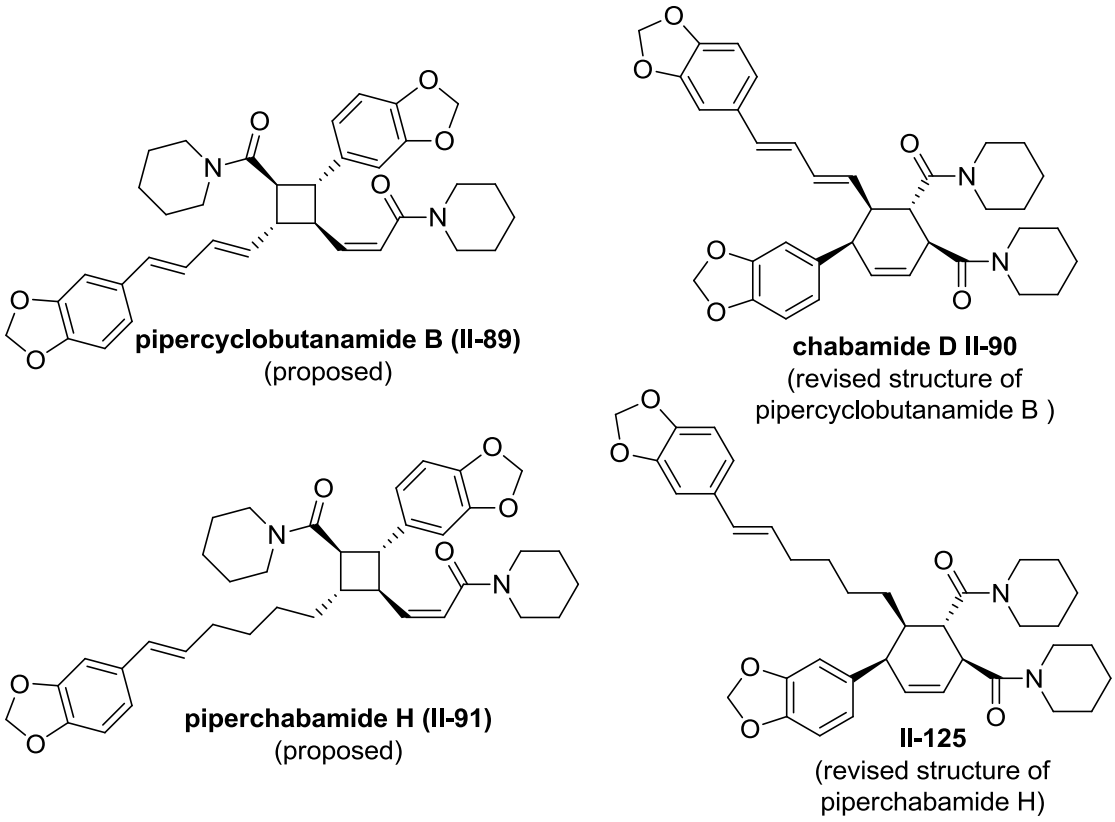

| Position | δH / δC of synthetic II-64 | δH / δC of II-64 (literature) | δH / δC of II-108 (literature) |
|---|---|---|---|
| 1 | — / 170.9 | — / 173.2 | — / 173.2 |
| 1’ | — / 165.9 | — / 170.4 | — / 170.4 |
| 2’ | 5.98 / 123.1 | 5.84 / 134.0 | 5.85 / 134.1 |
| 3’ | 5.93 / 142.0 | 5.71 / 123.2 | 5.71 / 123.2 |

Based on the above analysis, we turned our attention to six-membered ring isomers of structures **II-63** and **II-64**. After examining all known six-membered ring natural products isolated from *Piper nigrum* and *Piper Chaba*, we were pleased to find that spectral data ($^{1}H$ NMR and $^{13}C$ NMR) of natural product chabamide (**II-107**) was identical to that of natural

product pipercyclobutanamide A, as shown in **Table II-5**. We also found that spectral data ($^{1}$H NMR and $^{13}$C NMR) of natural product nigramide F was identical to that of natural product piperchabamide G, within experimental error. We therefore propose that structures of pipercyclobutanamide A should be revised to chabamide and piperchabamide G should be revised to nigramide F based on our analysis.

We further carefully analyzed the related cyclobutane-containing natural products. We found the spectral data ($^{1}$H NMR and $^{13}$C NMR) of natural product chabamide D (**II-90**) was identical to that of natural product pipercyclobutanamide B within experimental error. We propose that structures of pipercyclobutanamide B should be revised to chabamide D. Based on our analysis, the spectral data ($^{1}$H NMR and $^{13}$C NMR) of piperchabamide H did not support the proposed structure (**Scheme 21**) which contains cyclobutane and a cis-olefin. Unfortunately, we could not find the identical six-memberd ring known natural product. Therefore, we proposed an unknown six-membered ring structure **II-125** which contains a cis-olefin and basically match spectral data[17] (HMBC and nOe) in the isolation paper.

**Scheme II-21:** Proposed Structures and Structural Revision of Pipercyclobutanamide B and Piperchabamide H

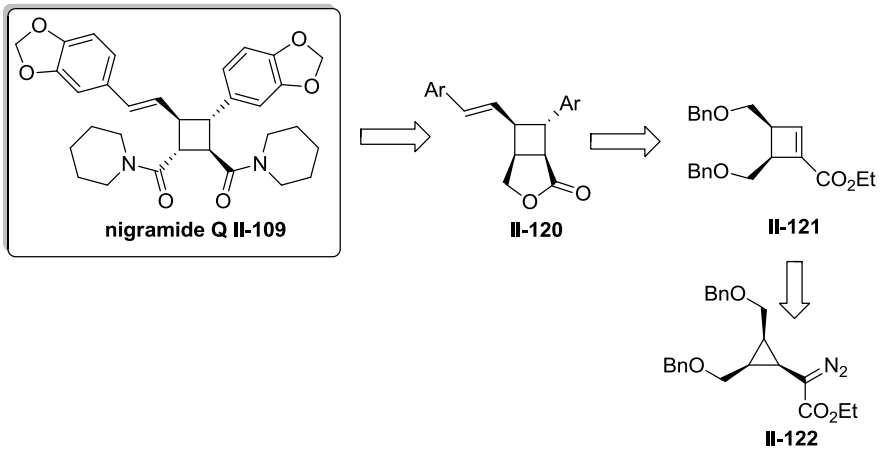



## 2.6 SYNTHETIC STUDY TOWARD THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF NIGRAMIDE Q

### 2.6.1 RETROSYNTHETIC PLAN FOR THE SYNTHESIS OF NIGRAMIDE Q

The retrosynthetic plan for the synthesis of nigramide Q was shown in **Scheme II-22**. We want to take advantage of cylopropanation method developed by Charette[20,21] to construct meso-cyclopropyl diazo compound **II-122**, which can potentially undergo enantioseletive desymmetrization.

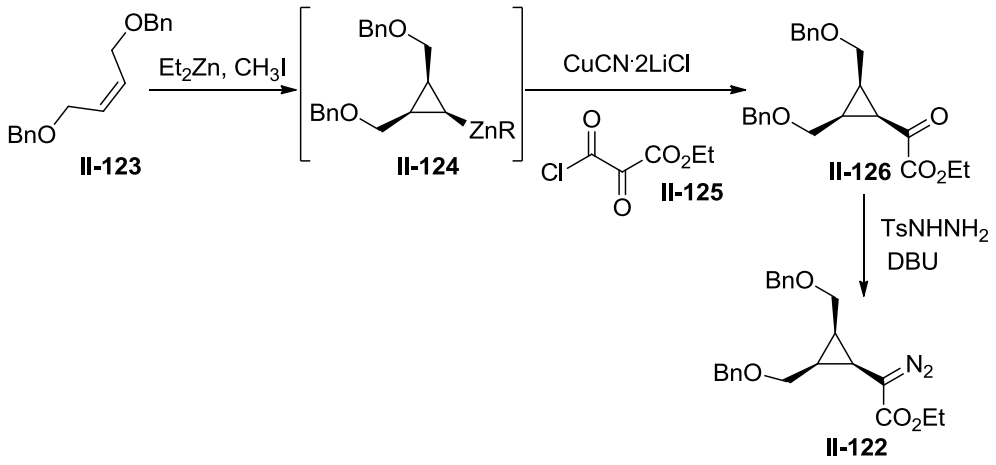
**Scheme II-22:** Retrosynthetic Plan for the Synthesis of Nigramide Q




## 2.6.2 ENANTIOSELECTIVE SYNTHESIS OF CYCLOBUTAENE II-121

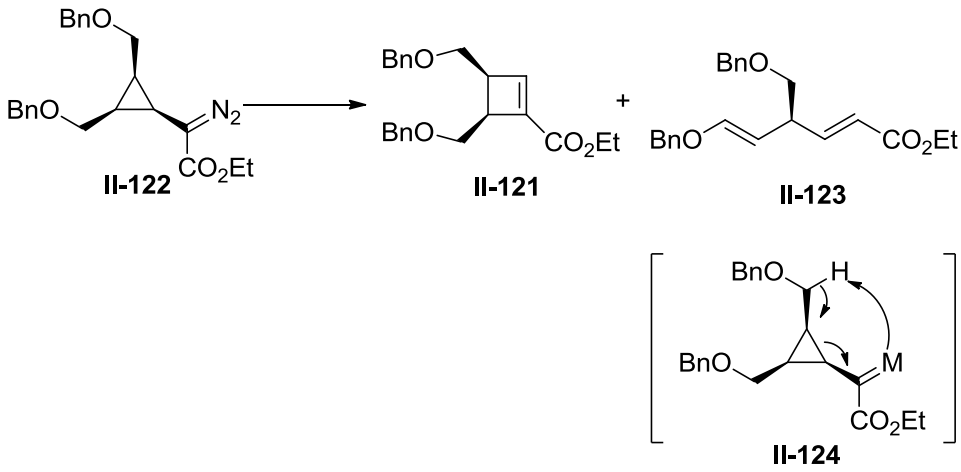
Charette and co-workers established the method to accesssubstituted cyclopropanes stereoselectively via gem-dizinc carbenoid (**II-124**). Treating protected 2-butene-1,4-diols **II-123** with $Et_2Zn$ and $CH_3I$ afforded the cyclopropylzinc intermediate **II-124** which could undergo transmetalation with $CuCN_2LiCl$. The resulting cuprate reagent could be trapped by electrophile **II-125** to yield cyclopropyl ketoester **II-126** in a moderate yield (52%). Ketoester **II-126** was converted to dizao compound **II-122** by condensation with tosylhydrazine followed by DBU.

**Scheme II-23:** Synthesis of Cyclopropyl Diazo **II-122**




With diazo compound **II-122** in hand, we first screened different metal catalysts and conditions for the ring expansion reaction (**Table II-7**). As described before, the chemo- and regioselectivity were dependent on catalysts and the substituents of the cyclopropane ring. The C-H bond on the methylene group could react with the carbenoid to produce skipped diene **II-123** through an ene type mechanism (**II-124**) when a Rh(II) catalyst was employed. We were glad to find that copper(I) catalyst gave us desired cyclobutane product **II-121** as a single isomer with perfect regioselectivity; while silver (I) catalyst gave a mixture of **II-121** and **123** with a ratio of 5:4**.**

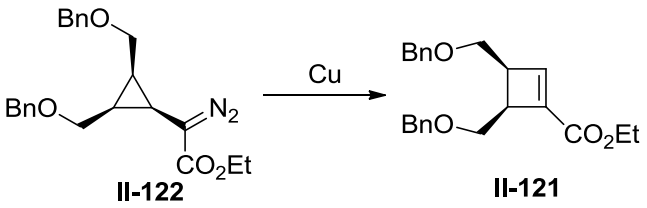
**Table II-7:** Catalyst Screening for Ring Expansion Reaction




| Entry | Condition | Ratio |
|---|---|---|
| 1 | $Rh_2(Oct)_4$, DCM | 1:18 |
| 2 | AgOTf, DCM | 5:4 |
| 3 | $Cu(MeCN)_4PF_6$, DCM | 18:1 |

The enantioselective ring expansion reaction was first carried out in the presence of copper catalysts and chiral ligands in dichloromethane at room temperature. As shown in Table II-8, copper (II) with S-BINAP afforded 20% ee and Feringa's ligand gave the same results (**entry 1** and **2**). Using less polar solvent such as toluene, the reaction went well with excellent yield and a slightly higher ee (28%, **entry 3**) . NaBArF greatly increased the enantioselectivity from 28% to 45%, which is the best results we observed (**entry 4**). No reaction occurred when copper (I) catalysts were employed with ligands(**entry 5**). The ring expansion could be catalyzed by silver (I) catalysts with ligand, however, no enantioselectivity was observed (**entry 6**).

**Table II-8:** Screening of Conditions for Enantioselective Ring Expansion Reaction

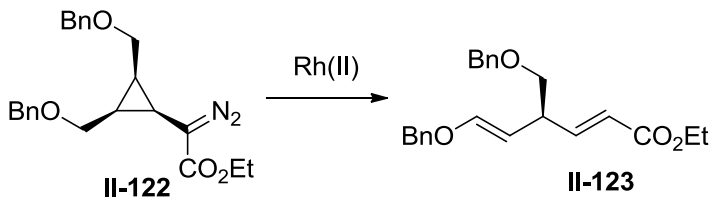



**II-122** **II-121**

| Entry | Condition | ee(yield) |
|---|---|---|
| 1 | $Cu(OTf)_2$, S-BINAP, DCM, r.t. | 20% |
| 2 | $Cu(OTf)_2$, Feringa's ligand, DCM, r.t. | 20% |
| 3 | $Cu(OTf)_2$, Feringa's ligand, Tol., r.t. | 28%(80%) |
| 4 | $Cu(OTf)_2$, Feringa's ligand, NaBArF, Tol., r.t. | 45%(82%) |
| 5 | Cu(I), Feringa's ligand | N.R. |
| 6 | AgOTf, S-BINAP, Tol., r.t. | 0% |

For the ene-type reaction, we screened three commercially available Rhodium (II) catalysts (**Table II-9**). Surprisingly, no reaction occurred when $Rh_2$(4s-MEPY)$_4$ was employed (**entry 1**). $Rh_2$(s-DOSP)$_4$ and $Rh_2$(s-PTAD)$_4$ could catalyze the reaction and gave similar results (**entry 2** and **3**). Similar to the ring expansion reaction, less polar solvent such as toluene improved the enantioselectivity to 47%. Temperature plays a critical role. A 80% ee was achieved in the presence of $Rh_2$(s-PTAD)$_4$ in toluene at -40°C.

**Table II-9:** Screening of Conditions for Enantioselective Ene-type Reaction




**II-122** **II-123**

| Entry | Condition | ee(yield) |
|---|---|---|
| 1 | $Rh_2$(4S-MEPY)$_4$, DCM, r.t. | N.R. |
| 2 | $Rh_2$(S-DOSP)$_4$, DCM, r.t. | 20% |
| 3 | $Rh_2$(S-PTAD)$_4$, DCM, r.t. | 28%(78%) |
| 4 | $Rh_2$(S-PTAD)$_4$, Tol., r.t. | 47%(82%) |
| 5 | $Rh_2$(S-PTAD)$_4$, Tol., -40$^o$C | 80%(86%) |

## 2.7 CONCLUSION

We have developed a general strategy for the diastereo- and enantioselective introduction of four different substituents to a cyclobutane ring: the three substituents on the cyclopropane ring could be transferred regioselectively and stereospecifically to the cyclobutenoate product. A $Rh^I$-catalyzed conjugate addition of aryl boronic acid to this cyclobutenoate afforded the fourth substituent diastereoselectively. Proposed structures for pipercyclobutanamide A (**II-63**) and piperchabamide G (**II-64**) were completed and they were revised to their six-membered ring isomers chabamide (**II-107**) and nigramide F (**II-108**), respectively. The structures of natural products pipercyclobutanamide B and piperchabamide H were also revised to their six-membered ring isomers.

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# CHAPTER III RING EXPANSION OF ALKYNYL CYCLOPROPANES TO HIGHLY SUBSTITUTED CYCLOBUTENES

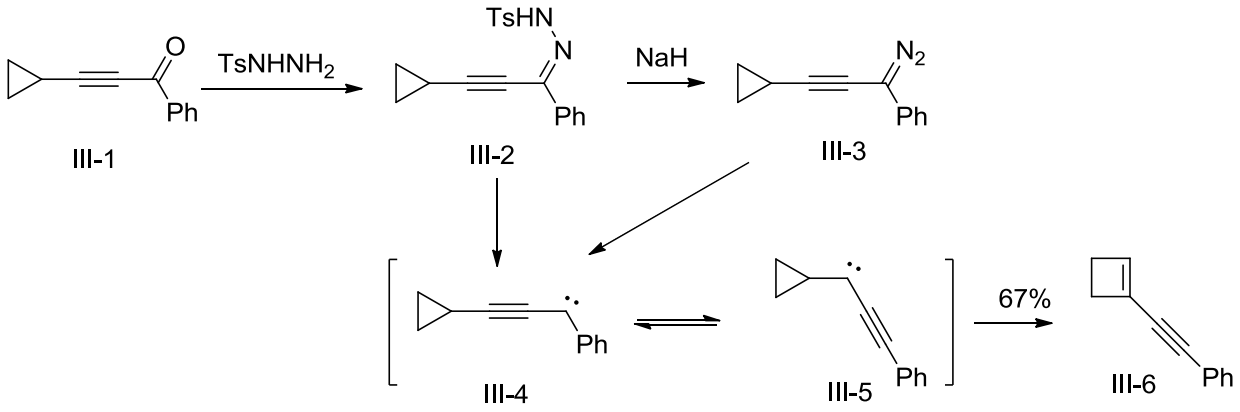
Cyclobutane is a common structural motif that is presented in numerous bioactive compounds and it is also often employed as key intermediate for the synthesis of complex targets.[1, 2] We previously developed a method for the synthesis of highly substituted cyclobutenes from cyclopropyl metal carbenes derived from Rh(II), Ag(I), or Cu(I)-catalyzed decomposition of diazo compounds.[3,4] We took advantage of the well-documented stereoselective cyclopropanation methods[2, 5] and transferred the substituents and stereochemistry of cyclopropanes to cyclobutenes.[6] However, cyclopropyl diazo compound is not very stable and its preparation is often lengthy. Alternative precursors that can provide general and efficient access to cyclopropyl metal carbenes and therefore cyclobutenes are highly desirable.

## 3.1 RING EXPANSION OF ALKYNYL CYCLOPROPANES TO CYCLOBUTENES VIA AN N-TOSYLHYDRAZONES INTERMIDIATE

N-tosylhydrazone is a typical precursor of diazo compound. Recently, Wang group developed a one pot method to generated diazo compounds in-situ by using this carbene precursor.[7] We prepared N-tosylhydrazone **III-2** by condensing keto **III-1** and $TsNHNH_2$ under thermo condition. When we treated N-tosylhydrazone **III-2** with bases, instead of diazo compound **III-3**, cyclobutene III-6 was generated. In this transformation, free carbene intermediate **III-4** might be formed and it was then isomerized to carbene intermediate **III-5**,

which underwent ring expansion to yield cyclobutene **III-6 in 67% yield**. The reaction failed when there was substitution on cyclopropane.

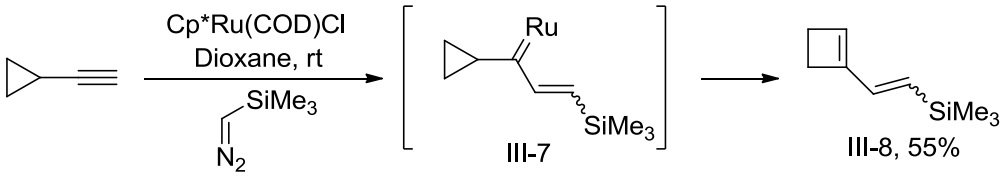
**Scheme III-1:** Ring Expansion of Alkynyl Cyclopropanes to Cyclobutenes via N-hydrozones




## 3.2 RING EXPANSION OF ALKYNYL CYCLOPROPANES TO CYCLOBUTENES VIA RUTHENIUM CARBENOIDS TRANSFER

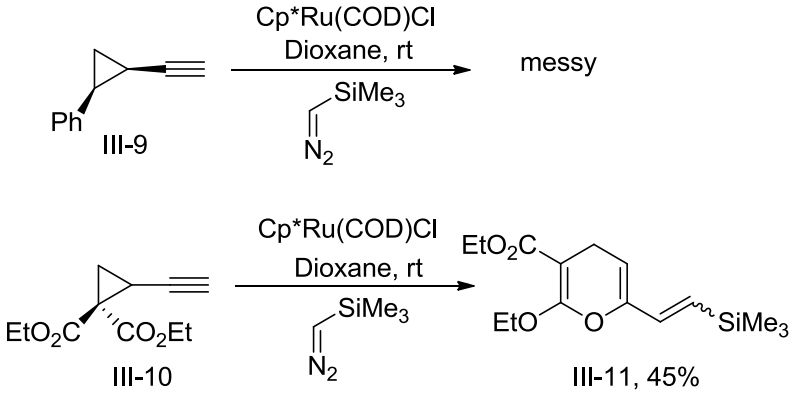
Ruthenium catalysts have shown high efficiency for the dimerization of diazo compounds. In the presence of Cp*Ru(COD)Cl precatalyst, the reaction of alkynes with $N_2CHTMS$ leads to conjugated dienes.[8] When we used cyclopropyl acetylene as starting material and similar conditions in literature, the ruthenium carbenoid intermediate **III-7** was formed and then underwent ring expansion to generate cyclobutene **III-8** in a moderate yield. We screened different solvents and a variety of Rhodium and Ruthenium catalysts. In most cases there were no desired products. When $N_2CHCO_2Et$ was used instead of $N_2CHTMS$, the reaction was complex based on $^1$HNMR and the yield is much lower.

**Scheme III-2:** Ring Expansion of Alkynyl Cyclopropanes to Cyclobutenes Catalyzed by Cp*Ru(COD)Cl




Under the conditions in Scheme III-2, we briefly investigated the scopes of the reaction (**Scheme III-3**). When there was a phenyl group on cyclopropyl ring (**III-9**), the reaction was slower and very complex based on TLC and $^{1}$HNMR. Diesters gave pyran type product which was consistent with previous results.

**Scheme III-3:** Scope Test of Ring Expansion Catalyzed by Cp*Ru(COD)Cl




**3.3 RING EXPANSION OF ALKYNYL CYCLOPROPANES TO HIGHLY SUBSTITUTED CYCLOBUTENES VIA A TRIZAOLE INTERMEDIATE**

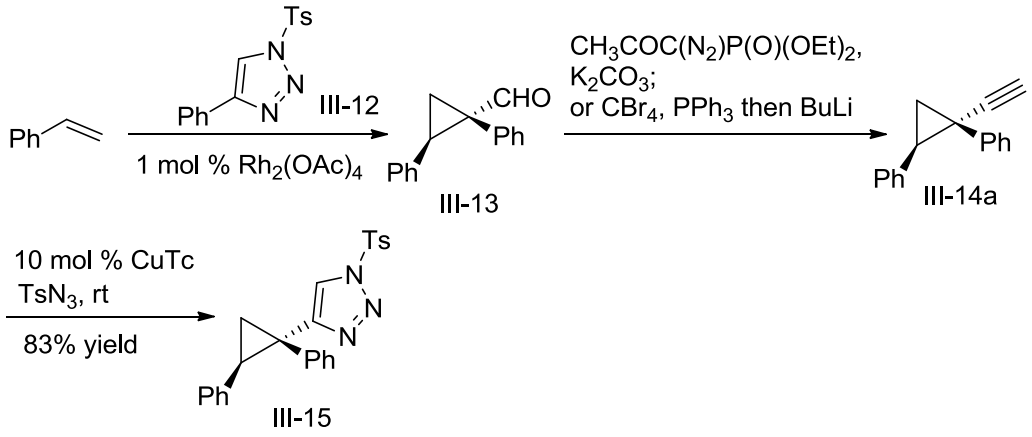
In order to find a more convenient and general precursor for cyclopropyl carbenes, we then

turned our attention to *N*-sulfonyl 1,2,3-triazoles,[9] a diazo compound equivalent developed by Fokin and Gevorgyan for annulation, cyclopropanation and C-H insertion reactions. In most cases, *N*-sulfonyl 1,2,3-triazoles can be activated by Rh, Ni and other transition metal catalysts which showed similar reactivity as diazo compound.[10,11,12]

### 3.3.1 SYNTHESIS OF SUBSTITUTED CYCLOPROPANES FROM ALKENES

Aldehyde **III-13** was prepared by cyclopropanation of styrene with tosyl triazole **III-12** according to the literature precedure.[11,12] Homologation of aldehyde **III-13** afforded cyclopropyl acetylene **III-15** (**Scheme III-4**).[13] The acetylene III-14 could be converted to tosyl triazole III-15 following literature procedure.[14]

**Scheme III-4:** Preparation of Substituted Cyclopropanes from Alkenes

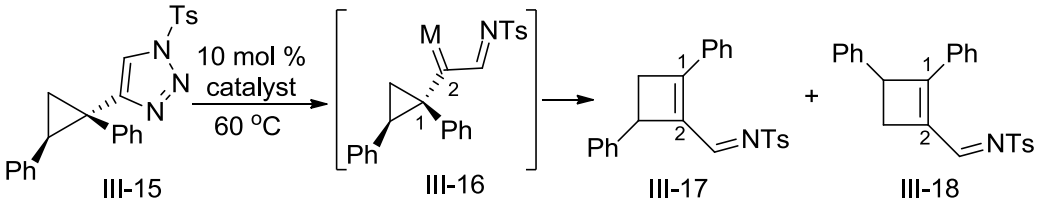



### 3.3.2 RING EXPANSION OF ALKYNYL CYCLOPROPANES TO HIGHLY SUBSTITUTED CYCLOBUTENES VIA A TRIZAOLE INTERMEDIATE

With Triazole **III-15** in hand, we started to test the ring expansion reaction. First, Triazole **III-**

**15** was treated with three catalysts that we previously used for the decomposition of cyclopropyl diazo compounds (**Scheme III-5**). In our previous study, these three catalysts gave similar results for the simple non-substituted cyclopropane substrates. In triazole system, $Rh_2(Oct)_4$ showed higher reactivity than AgOTf and $Cu(MeCN)_4PF_6$.On the other hand, AgOTf and $Cu(MeCN)_4PF_6$ provided much higher regioselectivity for the formation of cyclobutene **III-17** over isomer **III-18**.

**Scheme III-5:** Effect of Catalysts on the Regioselectivity of Ring Expansion



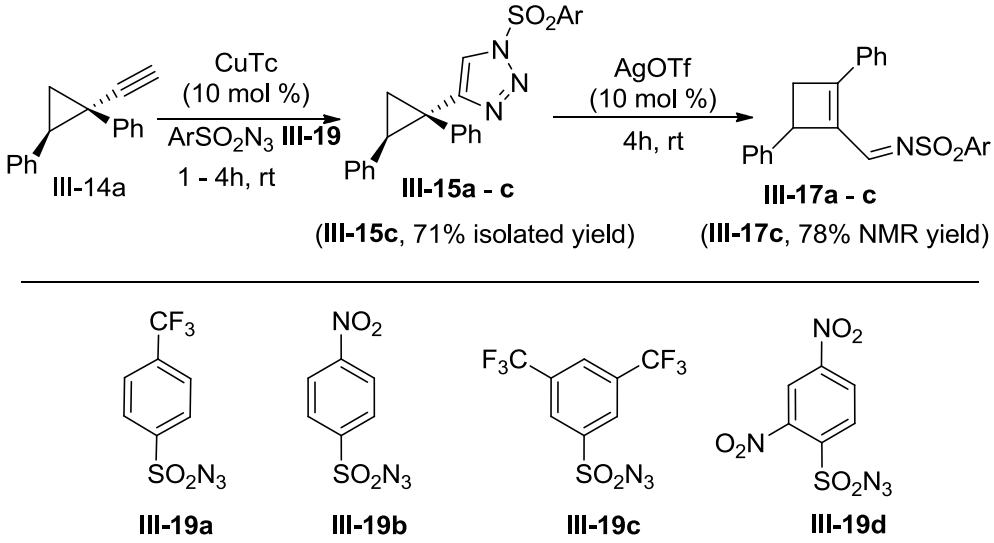

III-15 III-16 III-17 III-18

| Entry | Condition | Time | Yield | Ratio 17/18 |
|---|---|---|---|---|
| 1 | $Rh_2(Oct)_4$ | 1h | 82% | 1.2:1 |
| 2 | AgOTf | 4h | 76% | >20:1 |
| 3 | $Cu(MeCN)_4PF_6$ | 8h | 50% | >20:1 |

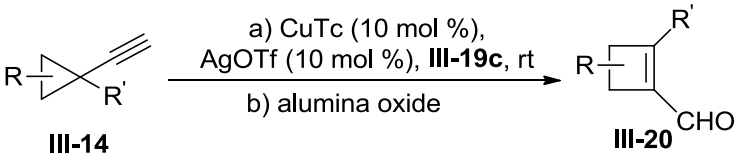
Fokin's group reported that when the tosyl group was replaced by triflate, the reactivity of *N*-sulfonyl 1,2,3-triazole was increased and its stability was decreased. We then examined the effect of arylsulfonyl azide on triazole formation and ring expansion (**Scheme III-6**). We prepared triazoles **III-15a-c** from alkyne **III-14** and azides **III-19a-c**. The trend was similar toliterature. In the presence of a AgOTf catalyst, the ring expansion of triazole **III-15c** could be completed in 4h at room temperature, while low conversions were observed for triazoles **III-15a** and **III-15b** under the same condition. In the absence of any catalyst, no

reaction was observed at room temperature after 24h. Triazole **14d** derived from alkyne **III-14** and azide **III-19d** was not stable enough to be isolated. Finally we were pleased to find that Triazole **III-15c** had the balanced reactivity and stability.

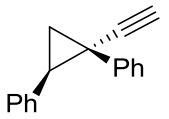
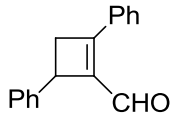
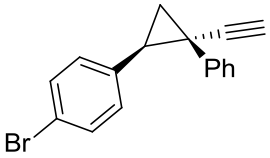
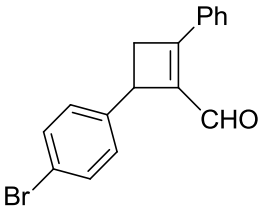
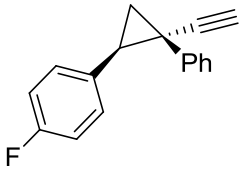
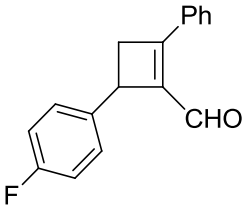
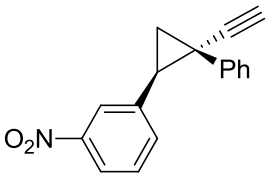
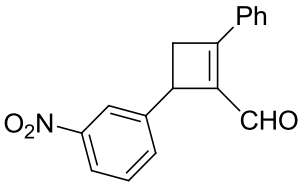
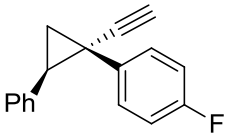
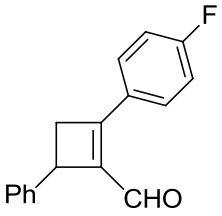
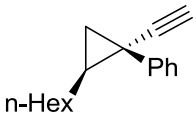
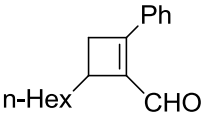
**Scheme III-6:** Effect of Azides on Ring Expansion




During the preparation of triazole **III-15c**, we also observed small amount of cyclobutene product **III-17c**, which suggested that CuTc was capable of catalyzing the ring expansion reaction. However, even though we extended the reaction time from 4h to 12h, significant amount of starting material was recovered (the ratio of **III-17c/III-15c** was only about 1:2). Results in **Scheme III-5** suggested that the order of reactivity is AgOTf > $Rh_2(Oct)_4$ > $Cu(MeCN)_4PF_6$. We then decided to treat cyclopropyl acetylene **III-14a** with azide **III-19c** in the presence of both CuTc and AgOTf catalysts. We were pleased to find that these two catalysts did not interfere with each other and cyclobutene carboxyaldehyde **III-20a** was isolated in good yield and selectivity (**entry 1**, **Table III-1**).**Table III-1:** Synthesis of Cyclobutene Carboxyaldehyde From Cyclopropyl Acetylene




III-14 III-20

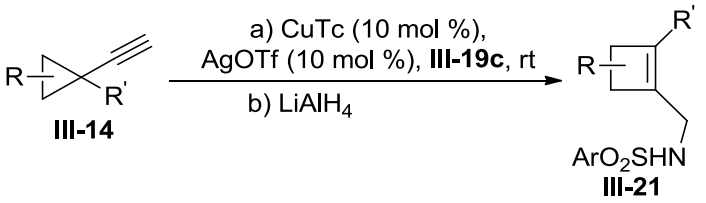
| Entry | Substrate | Productb | Yield |
|---|---|---|---|
| 1 |  III-14a |  III-20a | 85% |
| 2 |  III-14b |  III-20b | 80% |
| 3 |  III-14c |  III-20c | 80% |
| 4 |  III-14d |  III-20d | 70% |
| 5 |  III-14e |  III-20e | 82% |
| 6 |  III-14f |  III-20f | 86% |

a Conditions: 1) CuTc (10 mol % ), AgOTf (10 mol %), **III-19c** (1 equivalent), rt, 4-8h; 2) alumina oxide; b. Regioselectivity (>20:1) was determined by $^{1}$H NMR of the crude product.

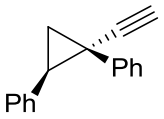
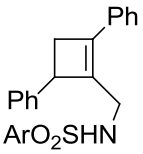
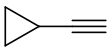
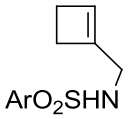
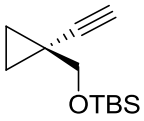
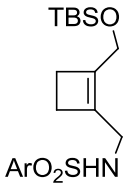
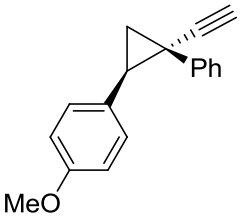
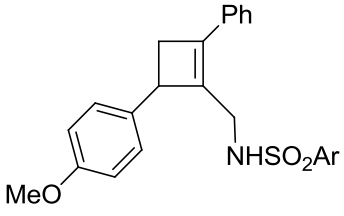
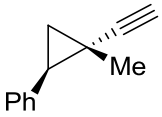
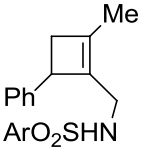
We then tested the scope of the ring expansion of different cyclopropyl acetylenes facilitated by the CuOTc/AgOTf dual catalysts in the presence of azide **III-19c** (**Table III-1**). Different aryl groups on the 2- and 1-position of the cyclopropane ring (entries 2-5) were examined and high regioselectivity (>20:1) was observed in all cases. Alkyl groups could also be tolerated on the 2-position of cyclopropanes (**entry 6**).

Imine intermediate **III-17c** could also be reduced in-situ to form sulfonamide **III-21a** (**Table III-2**). In this case the chirality in cyclopropane **III-14a** was also successfully transferred from alkynyl cyclopropane to product cyclobutene sulfonamides (**entry 1**). This provided a practical method for enantioselective synthesis of four-membered rings from chiral alkynyl cyclopropanes. Commercially available cyclopropyl acetylene **III-14g** could be converted to sulfonamide **III-21g** in 85% yield in one step (**entry 2**). Alkyl substituent on the 1-position of cyclopropane could also be tolerated (**entry 3**). While we found that the cyclobutenyl aldehyde derived from acetylene **III-14i** was not very stable at room temperature, direct reduction of the imine intermediate afforded stable sulfonamide **III-21i** in good yield and high regioselectivity (**entry 4**). Substrate **III-14j** with an alkyl group on the 1-position and aryl group on the 2-position of the cyclopropane also worked well (**entry 5**).

**Table III-2:** Synthesis of Cyclobutene Sulfonamides **16** from Alkynyl Cyclopropanes (Ar = 3,5-$(CF_3)_2C_6H_3$)[a]




**III-14** **III-21**

| Entry | Substrate | Product[b] | Yield |
|---|---|---|---|
| 1 |  **III-14a** (81% *ee*)[c] |  **III-21a** (80% *ee*) | 81% |
| 2 |  **III-14g** |  **III-21g** | 85% |
| 3 |  **III-14h** |  **III-21h** | 80% |
| 4 |  **III-14i** |  **III-21i** | 78% |
| 5 |  **III-14j** |  **III-21j** | 76% |

a Conditions: CuTc (10 mol % ), AgOTf (10 mol %), **III-19c** (1 equivalent), rt, 1-8h; 2) $LiAlH_4$; b. Regioselectivity (>20:1) was determined by $^1H$ NMR of the crude product. c. This is based on the ee of the aldehyde precursor.

## 3.4 CONLUSION

In summary, we have developed an efficient method for the preparation of highly substituted cyclobutenes from alkynyl cyclopropanes selectively. The tandem process was facilitated by a dual catalyst system (CuTc and AgOTf). This new protocol avoided isolating unstable diazo or triazole intermediates which could be problematic in some cases. Various cyclobutenes with aldehyde or sulfonamide functionality could be prepared. The synthesis of cyclobutenes is greatly simplified by using *N*-sulfonyl-1,2,3-triazoles as the carbene precursor for both cyclopropanation of alkene and ring expansion of cyclopropanes.

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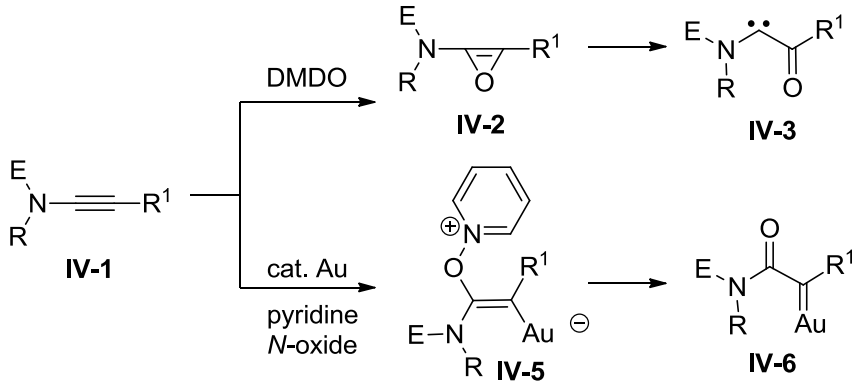
## CHAPTER IV RODIUM-CATALYZED OXIDATIVE CYCLOISOMERZATION

Metal carbenoids are versatile intermediates in organic synthesis and they are involved in numerous reactions such as cyclopropanation, C-H insertion and metathesis reactions.[1-6,7-9] Decomposition of diazo compounds or related derivatives is one of the most frequently used methods to generate metal carbenoids. Considering the hazardous and potential explosive nature of diazo compounds, other alternative carbene precursors are highly desirable. Recently, carbenoids derived from readily available ynamides[10, 11] have attracted lots of attention. Hsung's group reported that readily available ynamides could be oxidized by dimethyl dioxirane (DMDO)[28-30] to afford push-pull α-oxo carbene **IV-3** through oxriene intermediate **IV-2**. In 2010, Zhang[14, 15] and Liu[16] reported that in the presence of gold catalysts and mild external oxidants (e.g. pyridine *N*-oxide),[16-21] α-oxo gold carbenoid was formed *via* intermediate **IV-6** (**Scheme IV-1**) from yanmides.[22-27] Prior to these studies, Zhang[12] and Toste[13] also reported that gold carbenes could be generated from normal alkynes with a tethered sulfoxide. We envisioned that the metal catalysts and their surrounding ligands would have significant impact on the reactivity of carbenoids generated from alkynes including ynamides. Based on previous works in our lab[31], we became interested in exploring the possibility of generating Rh(I) carbenoids from normal alkynes or ynamides and their unique reactivities.

**Scheme IV-1:** Carbenes from Ynamides

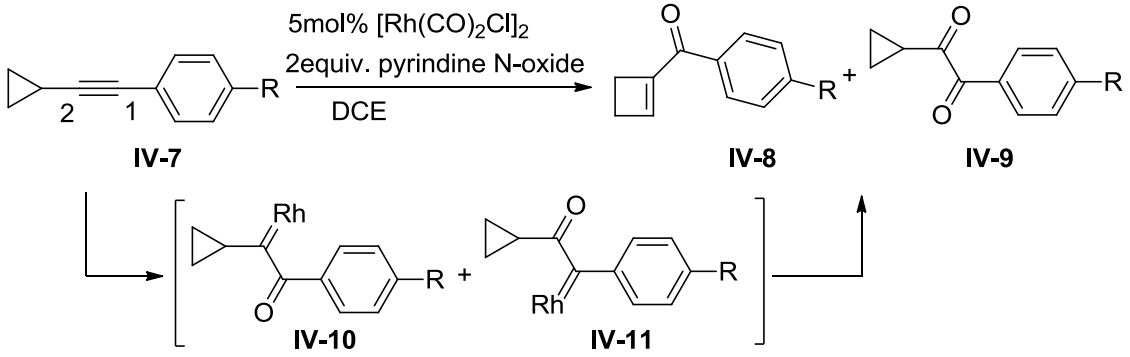



## 4.1 RODIUM-CATALYZED OXIDATIVE RING EXPANSION

We previously reported a method for the synthesis of highly substituted cyclobutenes from cyclopropyl metal carbenes derived from Rh(II), Ag(I), or Cu(I)-catalyzed decomposition of diazo compounds.31,32 We therefore chose the ring expansion reaction to initiate our investigation.

In the presence of 5mol% of [Rh(CO)2Cl]2 catalyst, substrate IV-7 was treated with 2 equivalent of pyridine N-oxide in DCE (**Scheme IV-2**). At room temperature, no reaction occurred when R was hydrogen or para-methoxy group (**entry 1 and 3**) At higher temperature (100°C), when R was hydrogen (**entry 2**), the ratio of **IV-8**/**9** was 1:4. When R was para-methoxy group, the ratio was increased to 1:2. These results suggested that the electron-donating group gave higher selectivity for desired product **IV-8**. α-Oxo gold carbenoids IV-10 and IV-11 were formed when pyridine N-oxide attacked carbon 1 and 2, respectively. Product IV-8 was generated from intermediate IV-10, while IV-9 could be obtained *via both* intermediate IV-10 and IV-11. In addition, the rate is faster for the substrate with an electron-donating group.

**Scheme IV-2:** Rhodium(I) Catalyzed Oxidative Ring Expansion

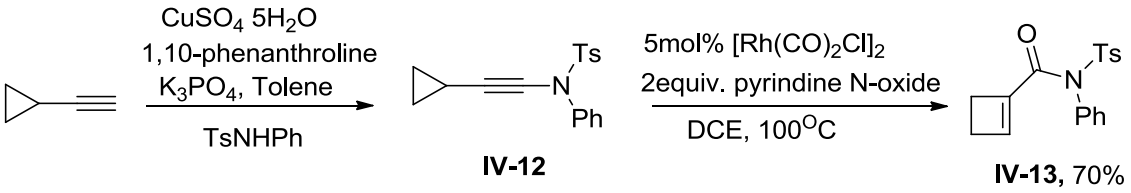



| Entry | R | Temperature | Conversion | Ratio **IV-8/9** |
|---|---|---|---|---|
| 1 | H | rt | 0 | — |
| 2 | H | 100$^{O}$C | 50% | 1:4 |
| 3 | OMe | rt | 0 | — |
| 4 | OMe | 100$^{O}$C | 50% | 1:2 |

To achieve higher reactivity and regioselectivity, we turned our attention to more electron-rich ynamides, which showed good reactivity and regioselectivity in gold-catalyzed reactions[16]. We prepared ynamide **IV-12** from commercially available cyclopropyl acetylene and TsNHPh (**Scheme IV-3)**. We were pleased to find that ynamide **IV-12** gave perfect regioselectivity and a 70% yield of cyclobutene ketoamide IV-13.

This initial study demonstrated that Rh(I) carbenoids could be generated from oxidative addition to ynamides conveniently. We did not further study the scope of this ring reaction as the same transformation was reported by Liu using gold-catalyst[16].

**Scheme IV-3:** Rhodium(I) Catalyzed Oxidative Ring Expansion of Ynamides

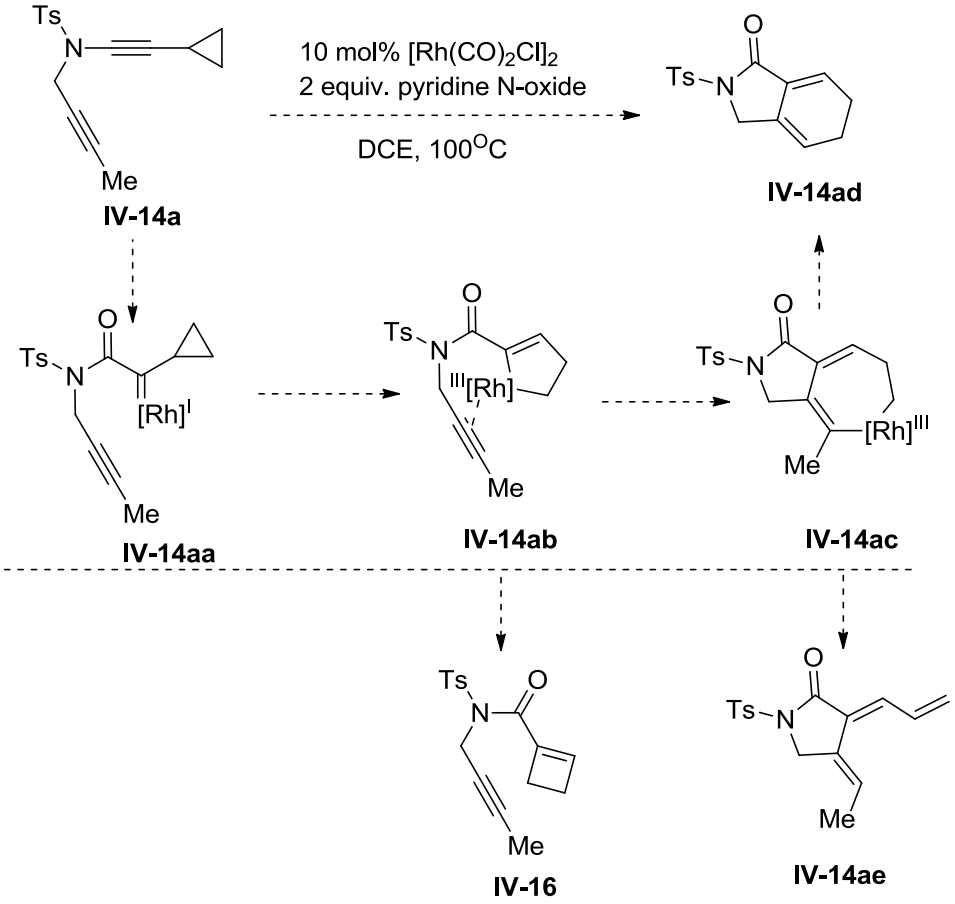



## 4.2 RODIUM-CATALYZED OXIDATIVE CYCLOISOMERIZATION OF DIYNES

Because of our interests in cyclopropyl metal carbenoids[31-34] and π-acidic Rh(I) complexes,[35] we began to investigate the possibility of generating Rh(I) carbenoids[36-40] from ynamide and its reactivity with a tethered alkyne.

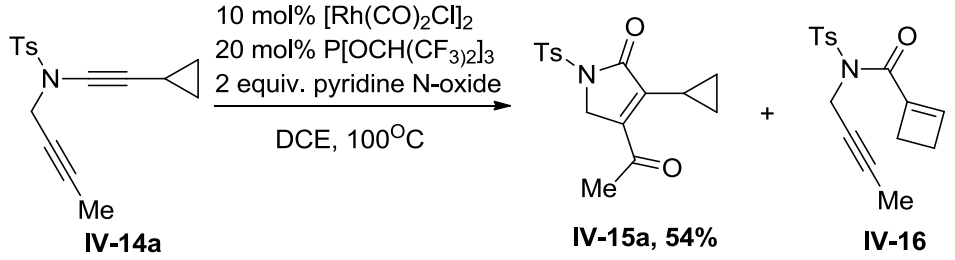
We proposed a Rh(I)-catalyzed formal [4+2] oxiditive cycloaddition reaction in **Scheme IV-4**. An oxo-Rhodium (I) carbenoid (**IV-14aa**) similar to intermediate **IV-6** could be generated from ynamide **IV-14a** through the mechanism shown in **Scheme IV-1**. Ring expansion of this metal carbenoid intermediate would produce metallacyclopentene **IV-14ab**. Migratory insertion of the alkyne might give the metallacycle **IV-14ac** , which could undergo reductive elimination to form a 5-6 fused bicyclic compound **IV-14ad**. Cyclobutene **IV-16** and diene **IV-14ae** are two possible byproducts generated from direct reductive elimination of **IV-14ab** and β-hydrogen elimination of **IV-14ac** followed by reductive elimination, respectively.

**Scheme IV-4:** Proposed Rh(I)-catalyzed Formal [4+2] Oxiditive Cycloaddtion



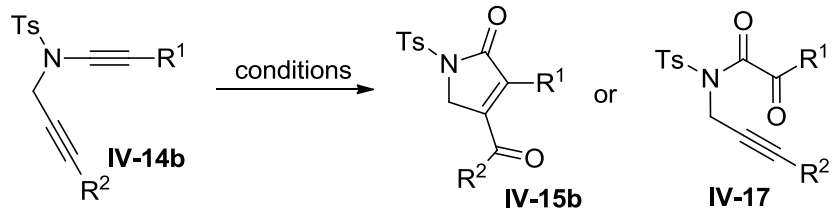

We prepared ynamide **IV-14a** and treated it with pyridine *N*-oxide and $[Rh(CO)_2Cl]_2$, which was the same condition used for ynamide ring expansion (**Scheme IV-3**). Surprisingly, unexpected compound **IV-15a** was isolated as the major product and ring expansion product cyclobutene **IV-16** was also observed as the minor product. In our previous studies, a complex of $[Rh(CO)_2Cl]_2/P[OCH(CF_3)_2]_3$ was shown to successfully promote acyloxy migration of propargylic esters, a process that was typically catalyzed by π-acidic transition metals. Under this condition, the yield of **IV-15a** was improved to 54% (**Scheme IV-5**).

**Scheme IV-5:** Rhodium (I) Catalyzed Oxidative Cycloisomerization of Diyne




We replaced cyclopropyl group with other substituents to avoid the formation of cyclobutene. Indeed, product **IV-15b** was obtained in a 62% yield from diyne **IV-14b** under conditions employed for diyne **IV-14a** (**entry 1, Table IV-1**). The structure of product **IV-15b** was unambiguously assigned by X-ray analysis. The oxidative cycloisomerization of diyne **IV-14b** was then optimized under different conditions. When the phosphite ligand was removed, ketoamide **IV-17b** was observed (**entry 2**). No desired product was obtained when $[Rh(COD)Cl]_2$, Wilkinson's catalyst, or $[Rh(COD)BF_4]$ were employed. Other phosphine or phosphite ligands gave worse results (**entry 3 and 4**). Using $Rh_2(OAc)_4$ as the catalyst, no reaction occurred even at higher temperature (**entry 5**). Interestingly, only ketoamide **IV-17** was observed when gold catalyst was employed (entry 6). $PtCl_2$ catalyst provided a complex mixture (entry 7). We then screened different substituted pyridine *N*-oxides, such as *p*-methoxy-, *p*-nitro-, 2,6-dichloro-, and 3,5- dichloropyridine *N*-oxides. Among them, 3,5-dichloropyridine *N*-oxide provided the best result (**entry 8**). Among all solvents that we examined, dioxane afforded the highest yield (**entry 9**).

**Table IV-1:** Screening of Catalysts and Conditions for the Oxidative Cycloisomerization of Diyne **IV-14b**[a]




$R^1$ = Ph, $R^2$ = *p*-$MeOC_6H_4$

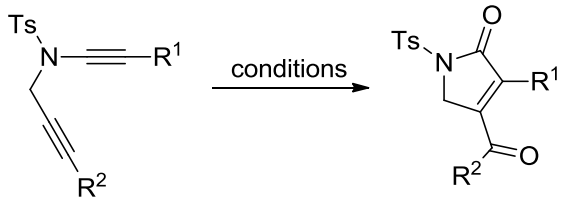
| Entry | Conditions | 8b / 12b[b] | Yield[c] |
|---|---|---|---|
| 1 | $[Rh(CO)_2Cl]_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (20 mol%) | 1 : 0 | 62% |
| 2 | $[Rh(CO)_2Cl]_2$ (5 mol%) | 5 : 1 | - |
| 3 | $[Rh(CO)_2Cl]_2$ (5 mol%), $P(OPh)_3$ (20 mol%) | no reaction | |
| 4 | $[Rh(CO)_2Cl]_2$ (5 mol%), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (20 mol%) | 5 : 1 | - |
| 5 | $Rh_2(OAc)_4$ (5 mol%) | no reaction | |
| 6 | $Au(PPh_3)Cl$ (10 mol%), AgOTf (10 mol%) | 0 : 1 | - |
| 7 | $PtCl_2$ (5 mol%) | complexmixture | |
| 8 | $[Rh(CO)_2Cl]_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (20 mol%), 3,5-dichloropyridine *N*-oxide (3 equiv) | 1 : 0 | 70% |
| 9[d] | Same as above. | 1 : 0 | 78% |

a.Conditions: pyridine N-oxide (3 equiv), $ClCH_2CH_2Cl$, 80 $^oC$, 4h, unless noted otherwise. b. The ratio was determined by 1H NMR of crude product. c. Isolated yield of 8b. d. Dioxane was used as the solvent instead of $ClCH_2CH_2Cl$.

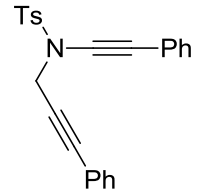
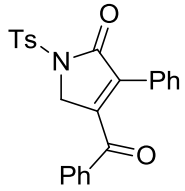
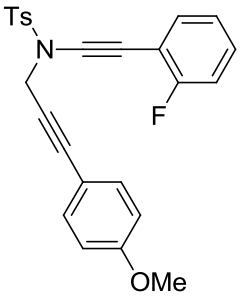
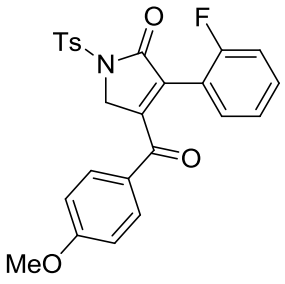
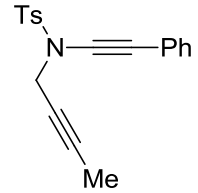
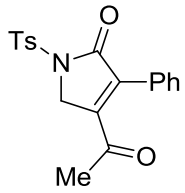
With the optimized condition in hand, the scope of oxidative cycloisomerization of diyne **IV-14** was examined (**Table IV-2**). The yield of product **IV-14c** became slightly lower than that of **IV-14b** when $R^2$ was a phenyl group (**entry 1**). $R^1$ could tolerate aryl groups with an *ortho* substituent (**entry 2**). When $R^2$ was a methyl group, the yield of product **IV-14e** became slightly

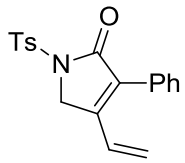
lower while product **IV-18** was isolated in about 10% yield (**entry 3**). When $R^2$ was electron-deficient aryl group (e.g. *p*-$ClC_6H_4$, *p*-$NO_2C_6H_4$), a complex mixture was obtained. When $R^1$ was hydrogen, the Rhodium (I) carbenoid became more reactive and the reaction could be completed at room temperature (**entry 4**). When $R^1$ was an alkyl group, **IV-15g** was still the major product while 1,2-hydrogen migration product **IV-19** was isolated in about 11% yield.

**Table IV-2:** Scope of Oxidative Cycloisomerization of Diynes[a]



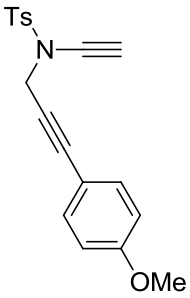

**IV-14** **IV-15**

| Entry | Substrate 4 | Product 8 | Yield[b] |
|---|---|---|---|
| **1** |  **IV-14c** |  **IV-15c** | **67%** |
| **2** |  **IV-14d** |  **IV-15d** | **75%** |
| **3** |  **IV-14e** |  **IV-15e** | **56%** |

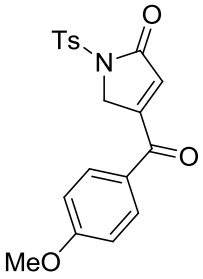



**IV-18** **(10%)[d]**

**4[c]**

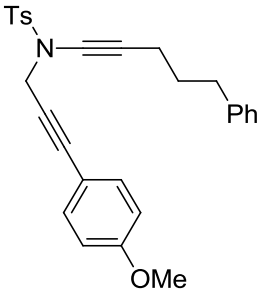



**IV-14f**

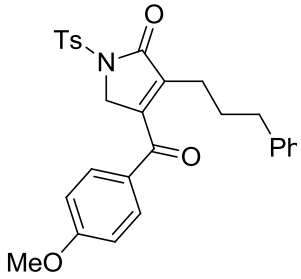



**IV-15f** **80%**

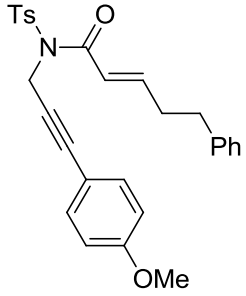
**5**




**IV-14g**




**IV-15g** **67%**




**IV-19** **(11%)[d]**

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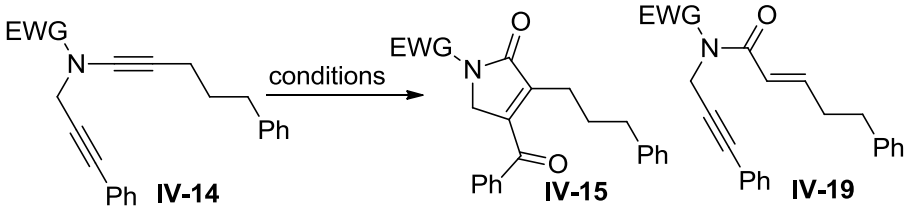
a.Conditions: $[Rh(CO)_2Cl]_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (20 mol%), 3,5-dichloropyridine N-oxide (3 equiv), dioxane, 80 $^{o}$C, 4h. b. Isolated yields. c. rt, 3h. d. Yield of byproduct

In entries 3 and 5, although desired products **IV-15e** and **IV-15g** were the major ones, there were significant amount of 1,2-hydrogen migration products **IV-18** and **IV-19**. We then examined the effect of arylsulfonyl groups on oxidative cycloisomerization of diynes (**Scheme IV-6**). When the Ts was replaced by Ms, the ratio became 1:4, which meant 1,2-migration product was the major product (**entry 2**). When E was Ns, a complex mixture was obtained and conversion was lower than that of Ts and Ms (**entry 3**). 1,2-Migration product became dominant if the ynamide had a strong electron donating group (**entry 4)**.

**Scheme IV-6:** Effects of Electron Withdrawing Groups



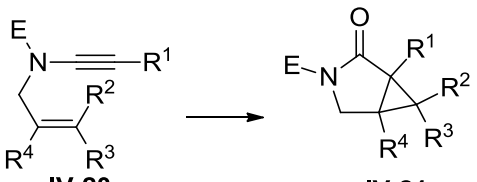

| Entry | EWG | Conversion | Ratio **IV-15/19** |
|---|---|---|---|
| 1 | Ts | 100% | 7:1 |
| 2 | Ms | 100% | 1:4 |
| 3 | Ns | 90% | messy |
| 4 | p-OMe | 80% | 1:20 |

## 4.3 RODIUM-CATALYZED OXIDATIVE CYCLOISOMERIZATION OF ENYNES

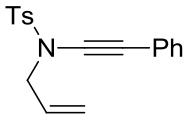
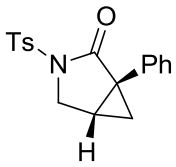
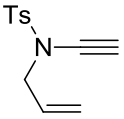
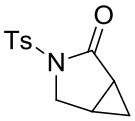
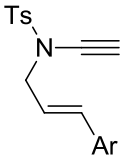
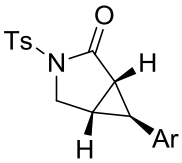
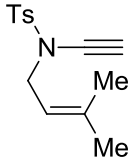
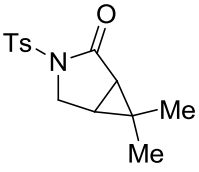
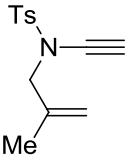
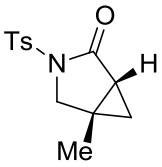
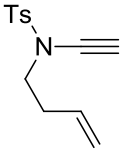
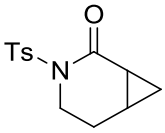
We next examined the reactivity of α-oxo Rhodium (I) carbenoids derived from ynamides with tethered alkenes (**Table IV-3**). Under previously optimized conditions for oxidative cycloisomerization of diynes, a yield of 78% was obtained for cyclopropanation product **IV-21a** from enyne **IV-20a** (**entry 1**). No improvement was observed after screening different Rh(I) complexes, ligands, and pyridine N-oxides.

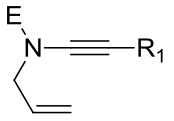
The scope of oxidative cycloisomerization of enyne **IV-20** was then investigated. The reaction could be carried out at even room temperature for terminal ynamides (**entries 2-9**). Terminal alkene **IV-21b** produced the best yield (**entry 2**). Compound **IV-21c** was obtained in a 70% yield by cyclopropanating a non-substituted styrene (**entry 3**). It has been shown that α-oxo Rh(I) carbenoid derived from 1,2-acyloxy migration of propargylic esters only reacts with electron-deficient alkynes or alkenes[41].In our previous oxidative diyne cycloisomerization, $R^2$ in **IV-14** needs to be an electron-neutral or -rich aryl group to make the adjacent alkyne reactive enough for Rhodium (I) carbenoid. To our delight, both electron-rich and electron-poor styrenes underwent cyclopropanation to form bicyclic products **IV-21d** and **IV-21e**, respectively (**entries 4 and 5**). Alkenes with a *gem*-dimethyl substituent or a methyl group in the internal position participated in the cyclopropanation and yielded products **IV-21f** and **IV-21g**, respectively (**entries 6 and 7**). A six-atom tether could also be tolerated and bicyclic product **IV-21h** was prepared in a 78% yield (**entry 8**).

**Table IV-3:** Oxidative Cycloisomerization of Enynes[a]

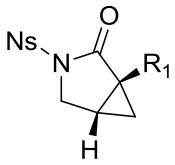



**IV-20** **IV-21**

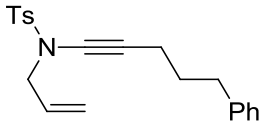
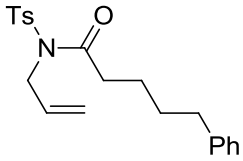
| Entry | Substrate 5 | Product 9 | Yield[b] |
|---|---|---|---|
| **1**[c] |  **IV-20a** |  **IV-21a** | **78%** |
| **2** |  **IV-20b** |  **IV-21b** | **88%** |
| |  **(IV-20c - e)** |  **(9c - 9e)** | |
| **3** | **5c, Ar = Ph** | **IV-21c** | **70%** |
| **4** | **5d, Ar = *p*-MeOC$_6$H$_4$** | **IV-21d** | **62%** |
| **5** | **5e, Ar = *p*-NO$_2$C$_6$H$_4$** | **IV-21e** | **63%** |
| **6** |  **IV-20f** |  **IV-21f** | **87%** |
| **7** |  **IV-20g** |  **IV-21g** | **72%** |
| **8** |  **IV-20h** |  **IV-21h** | **78%** |



**(IV-20i – l)**



**(IV-21i – l)**

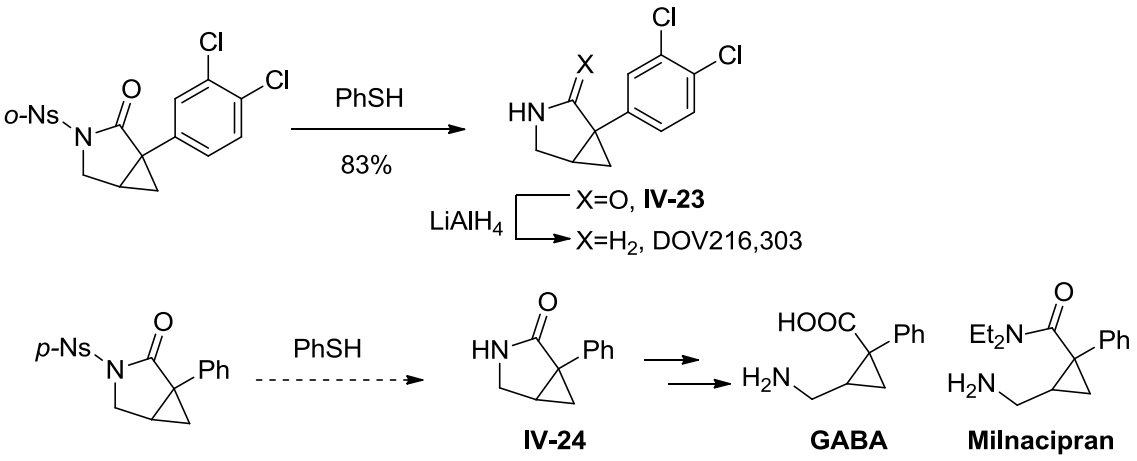
| | | | |
|---|---|---|---|
| **9** | **IV-20i, E = *p*-Ns, $R^1$ = H** | **IV-21i** | **80%** |
| **10**[c] | **IV-20j, E = *p*-Ns, $R^1$ = Ph** | **IV-21j** | **76%** |
| **11**[c] | **IV-20k, E = *p*-Ns, $R^1$ = *p*-$CH_3C_6H_4$** | **IV-21k** | **60%** |
| **12**[c] | **IV-20l, E = *o*-Ns, $R^1$ = 3,4-$Cl_2C_6H_3$** | **IV-21l** | **81%** |
| **13**[c] |  **IV-20m** |  **IV-22** | **68%** |

a.Conditions: $[Rh(CO)_2Cl]_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (20 mol%), 3,5-dichloropyridine N-oxide (1.0 equiv), dioxane, rt., 2h. b. Isolated yields. c. 80 $^oC$, 4-8 h. p-Ns = (para-nitrophenyl)sulfonyl. o-Ns = (ortho-nitrophenyl)sulfonyl.

Generally, nosyl group is easier to be removed than tosyl group. We prepared substrates **IV-20i** and **IV-20j** and found that yields for products **IV-21i** and **IV-21j** (**entries 9 and 10**) were comparable to their tosyl counterparts (**entries 1 and 2**). The nosyl group in product **IV-21l** was easily removed under mild conditions to yield compound **IV-23** (**Scheme IV-7**), which is the precursor for triple reuptake inhibitor DOV216,303[42-44]. Similarly, the nosyl group in product **IV-21j** could be removed under the same condition to afford **IV-24**, which is the precursor of GABA (γ-amino butyric acid, an analogue of the inhibitory neurotransmitter)[45] and Milnacipran (a clinically useful antidepressant).[46] The 3-azabicyclo[3.1.0]hexane skeleton[47] is also present in

numerous other pharmaceuticals with broad biological activities, such as analgesic, antibacterial, and inhibition of aromatase. When $R^1$ in substrate **IV-20** was an alkyl group, hydrolysis product **IV-22** was obtained (**entry 13**).

**Scheme IV-7:** Applications of **IV-21**

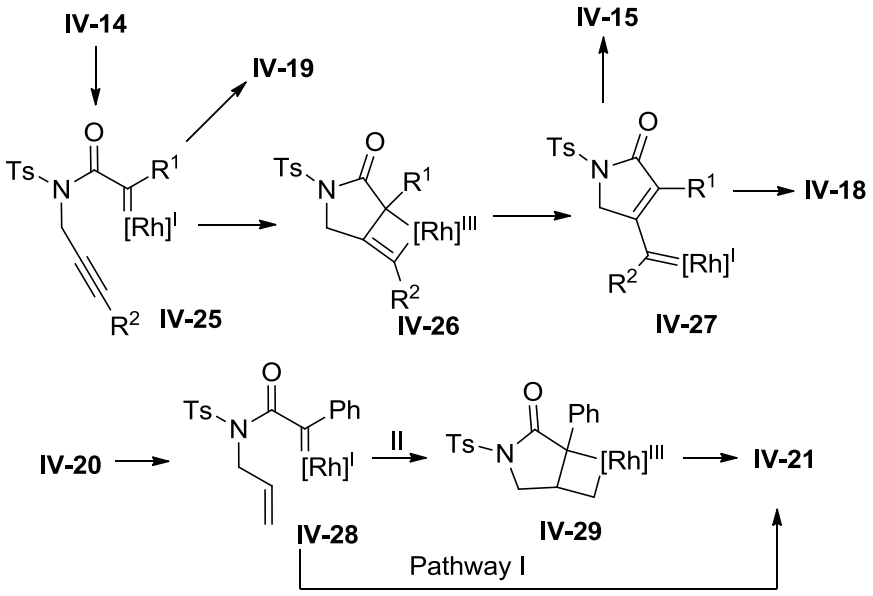



## 4.4 MECHANISOM FOR THE RHODIUM-CATALYZED OXIDATIVE CYCLOISOMERIZATION OF DIYNES AND ENYNES

The mechanism for the oxidative cycloisomerization of diynes and enynes is proposed in **Scheme IV-8**. Metal carbenoids **IV-25** and **IV-28** can be formed from ynamides **IV-14** and **IV-20**, respectively. Metathesis of metal carbenoid **IV-25** with the tethered alkyne via metallacyclobutene intermediate **IV-26** may afford carbenoid **IV-27**,[48-50] which could be oxidized by another molecule of pyridine *N*-oxide to yield oxidative diyne cycloisomerization

product **IV-18**. When $R^1$ or $R^2$ was an alkyl group, 1,2-hydrogen migration occurred and yielded byproducts **IV-19** or **IV-18**, respectively.

**Scheme IV-8:** Proposed Mechanism for Oxidative Cycloisomerization of Diynes and Enynes




Rhodium (I) carbenoid **IV-28** derived from ynamide **IV-20** might react with tethered alkenes via two possible pathways. In pathway I, Rh(I) carbenoid **IV-28** goes through a concerted cyclopropanation mechanism to afford product **IV-21** directly. In pathway II, Rh(I) carbenoid **IV-28** may undergo a metathesis reaction with the tethered alkene to form metallacyclobutane **IV-29**. Reductive elimination of this metallacycle may also afford product **IV-21**. Density function theory (DFT) calculations indicated that pathway I was preferred because the reductive elimination from the metallocyclobutane intermediate in pathway II was relatively difficult (**Figure IV-1** and **2**).

**Figure IV-1:** The Free Energy Surfaces for the Direct Cyclopropanation of Carbenoid **IV-25** With the Tethered Alkene (Pathway I)

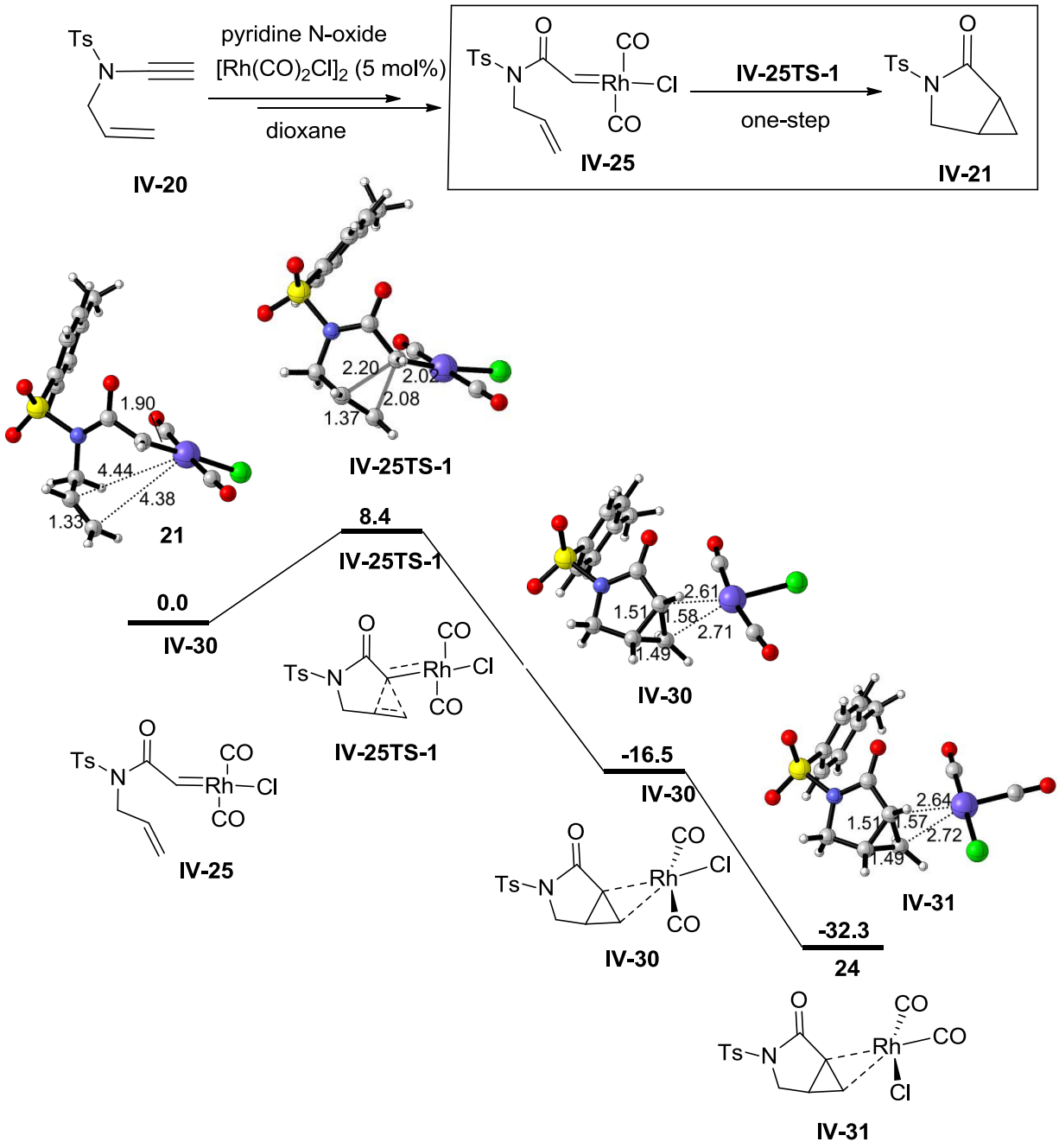
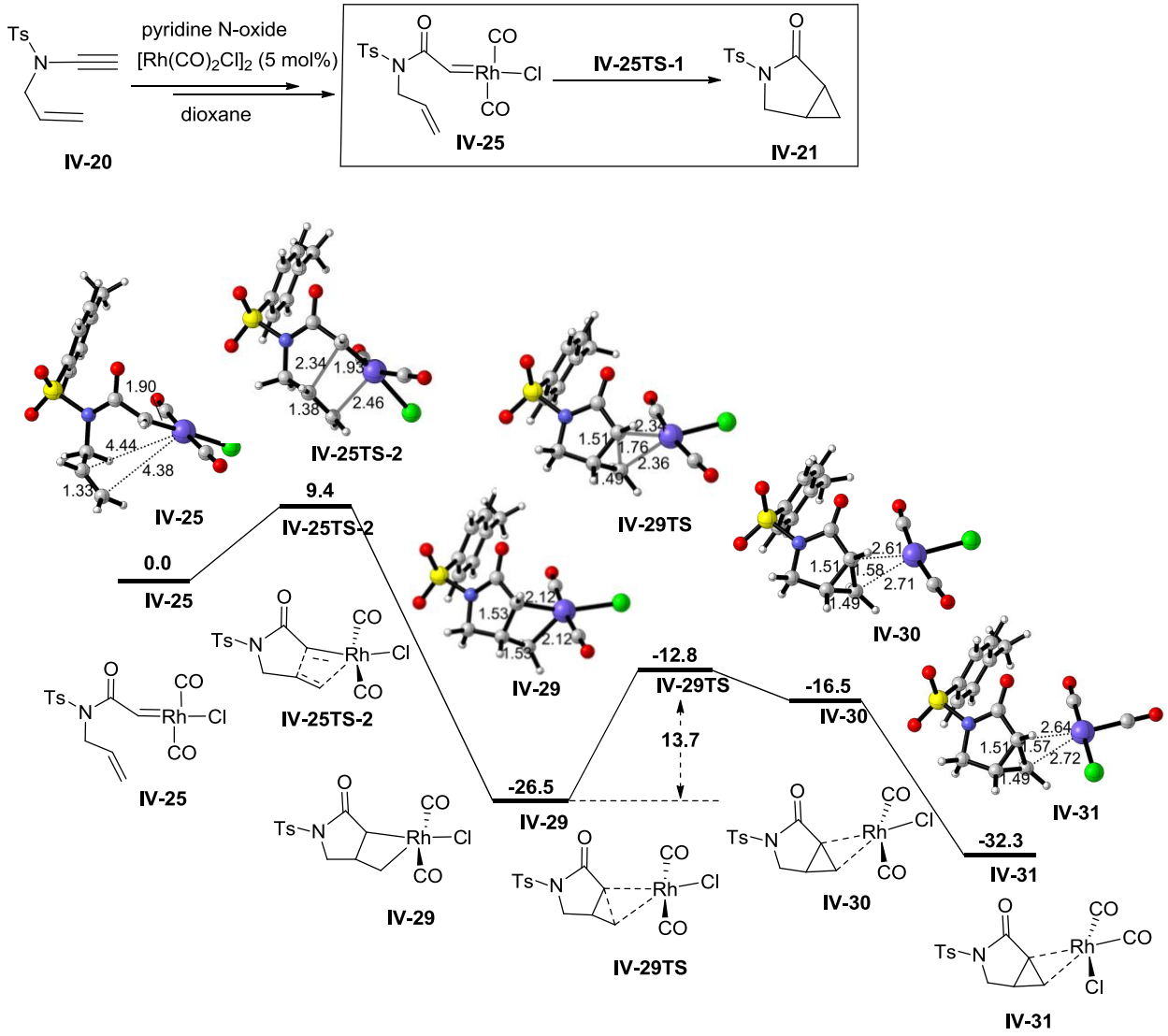


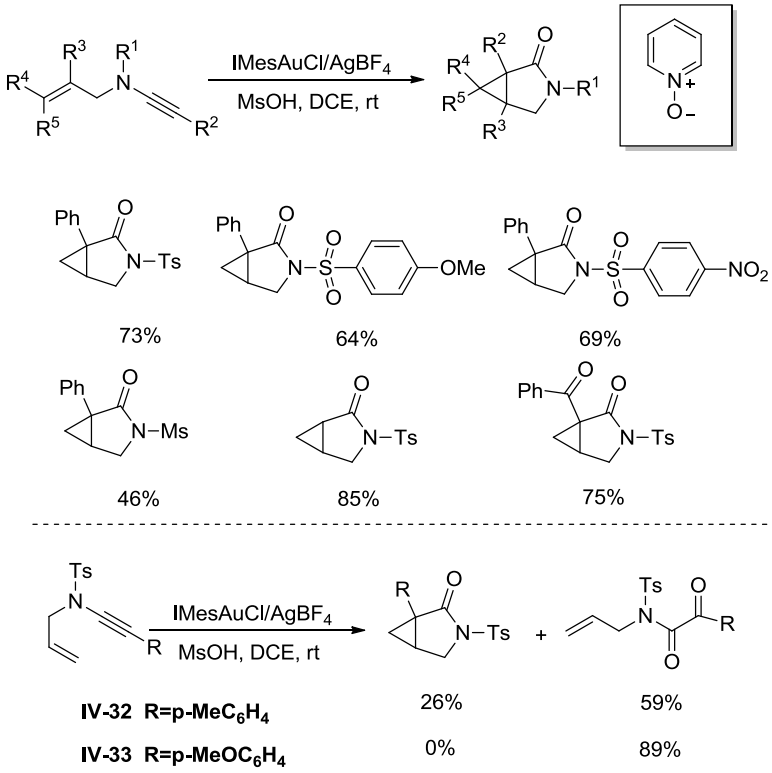
**Figure IV-2:** The free energy surfaces for the metathesis of carbenoids 21 with the tethered alkene via intermediate 22 (Pathway II)




About the same time, Li and co-workers[21] also studied gold-catalyzed oxidative cycloisomerization of enynes containing an ynamide s (**Scheme IV-9**). Initially, they also observed ketoamide as the major product under various conditions using gold as the catalyst, which is consistent to our observation. After extensive screenings, they found that 3-aza-

bicyclo[3.1.0]-hexan-2-one could be obtained as the major product when IMes ligand and pyridine oxide were employed. The aromatic substituent on the alkyne played an important role for the chemoselectivity. When the aryl group adjacent to the alkyne contained an electron-donating substituent such as methyl or methoxy group, ketoamides became the major product. They did not examine substrates with an electro-deficient aryl group on the position adjacent to the alkyne. Under our conditions using Rh(I) as the catalyst, both electron-donating and electron-withdrawing substituents could be tolerated on the aryl group adjacent to the alkyne and afforded corresponding cyclopropanation products .

**Scheme IV-9:** Gold-catalyzed Oxidative Cyclopropanation of N-Allylnamides (by Li Group)



## 4.5 CONLUSION

In summary, we have demonstrated that metal complex $[Rh(CO)_2Cl]_2/P[OCH(CF_3)_2]_3$ is acidic enough to active ynamides for the addition of external nucleophiles. The addition of pyridine *N*-oxide to activated ynamides followed by the cleavage of N-O bond then generated α-oxo Rh(I) carbenoid intermediates under mild conditions. The Rh(I) carbenoids could undergo ring expansion with adjacent cyclopropanes to afford cyclobutenes, or metathesis with a tethered alkyne to form 2-oxo-pyrrolidines, and cyclopropanation with a tethered alkene to afford 3-azabicyclo[3.1.0]hexanes.

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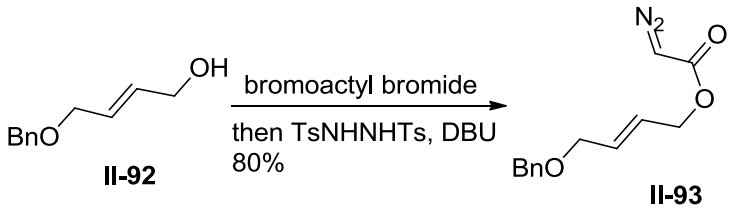
## APPENDIX I: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION

### General remarks

All reactions in non-aqueous media were conducted under a positive pressure of dry argon in glassware that had been oven dried prior to use unless noted otherwise. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Reagents were purchased from Aldrich, Acros, TCI, or VWR unless otherwise noted. Thin layer chromatography was performed using precoated silica gel plates (EMD Chemical Inc. 60,F254). Flash column chromatography was performed with silica gel (Sillicycle, 40-63μm). Infrared spectra (IR) were obtained as neat oils on a Bruker Equinox 55 spectrophotometer. $^{1}H$ and $^{13}C$ Nuclear Magnetic Resonance (NMR) spectra were obtained on a Varian Unity-Inova 400 MHz or 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in $CDCl_3$, $CD_3OD$. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), or multiplet (m), with coupling constants (*J*) in hertz. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer. Enantiomeric excess was determined by chiral HPLC analysis. The optical rotation was determined by Perkin–Elmer 241 Polarimeter.

**CHAPTER II TOTAL SYNTHESIS AND STRUCTURE REVISION OF CYCLOBUTANE-CONTAINING NATURAL PRODUCTS**

**Experimental procedures and characterization data:**

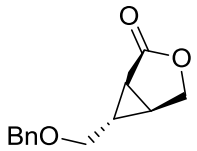



**II-92** **II-93**

To a 250 mL round bottom flask was added alcohol **II-92** (5 g, 28 mmol), $NaHCO_3$ (7.1 g, 84 mmol), and acetonitrile (100 mL). To the above solution was added bromoacetyl bromide (3.7mL, 42 mmol) slowly at 0 °C. After stirring for 10 min at the same temperature, the reaction was quenched by water. The solution was extracted with $CH_2Cl_2$ three times. The combined organic phases was washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the residue was used in the next step without further purification. To the solution of the above bromoacetate in THF (100 mL) was added N, N'- ditosylhydrazine (19 g, 56 mmol) and DBU (21mL, 140 mmol) dropwise at 0 °C. The reaction was stirred at the same temperature for 10 minutes. After quenching of the reaction by the addition of saturated $NaHCO_3$ solution, the organic layers was separated and the aqueous layer was extracted with $Et_2O$ three times. The combined organic phases was washed with brine, dried over $Na_2SO_4$ and evaporated to give the crude diazoacetate. Purification of the crude diazoacetate was performed with neutral silica gel to give **II-93** as a yellow oil (5.21 g, 80% yield). $R_f$ = 0.5 (silica gel, hexanes:EtOAc, 4:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ 4.04 (2H, d, *J* = 3.2 Hz), 4.52 (2H, s), 4.67 (2H, d, *J* = 4.8 Hz), 4.76 (1H, s), 5.87 (2H, q, *J* = 4 Hz), 7.29 (1H, m), 7.33 (4H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 45.99, 64.31, 69.54,

72.20, 126.33, 127.49, 127.55, 128.22, 130.83, 137.92. IR ($CHCl_3$) ν 2114, 1707, 1360, 1222, 1092, 739 $cm^{-1}$.

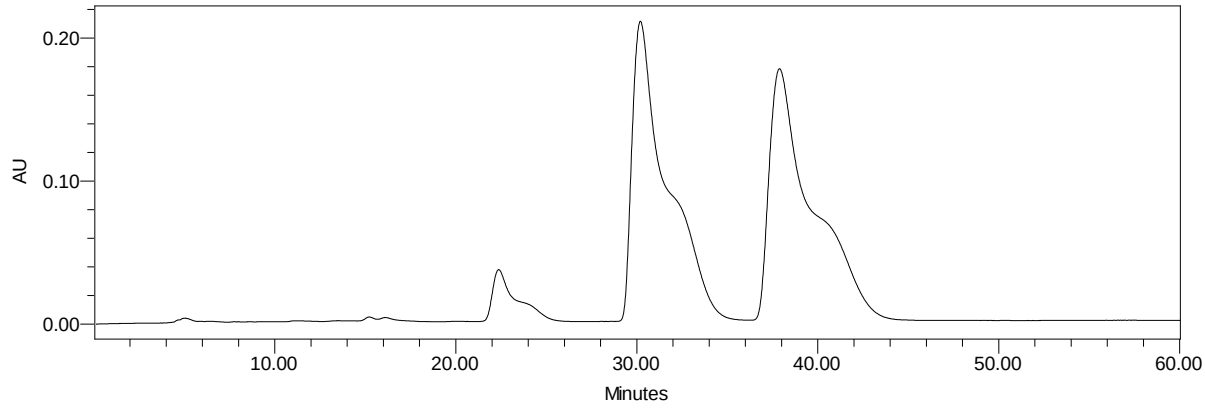



**II-94**

To a solution of diazo compound **II-93** (2 g, 8.6 mmol) in $CH_2Cl_2$ (400mL) was added the solution of $Rh_2$(5S-MEPY)$_4$ (75 mg, 0.086 mmol) in $CH_2Cl_2$ (200 mL) with syringe pump (10 mL/hour) at 50 °C. After the addition was completed, the reaction mixture was stirred for another 2h under the same temperature. After evaporating the solvent, the residue was purified by flash column chromatography with ethyl acetate/hexane (1/8 -1/2) as eluent to give compound **II-94** (1.48 g, 80% yield) as an oil. $R_f$ = 0.35 (silica gel, hexanes:EtOAc, 2:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.50 (1H, m), 2.05 (1H, m), 2.23 (1H, m), 3.37 (1H, dd, *J* = 10.4, 6.4 Hz), 3.58 (1H, dd, *J* = 10.4, 5.6 Hz) 4.22 (1H, dd, *J* = 9.6, 0.8 Hz), 4.32 (1H, dd, *J* = 9.6, 4.8 Hz), 4.50 (2H, s), 7.26-7.37 (5H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.83, 22.09, 24.96, 68.70, 69.17, 72.89, 127.58, 127.79, 128.42, 137.62, 175.44. IR ($CHCl_3$) ν 1772, 1360, 1135, 752 $cm^{-1}$. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_3$ $(M+Na)^+$ 241.0823, found 241.0846. $[\alpha]_D^{20}$ =+39 (c=1.0, $CHCl_3$).

Racemic sample




| | Retention Time | Area | % Area |
|---|---|---|---|
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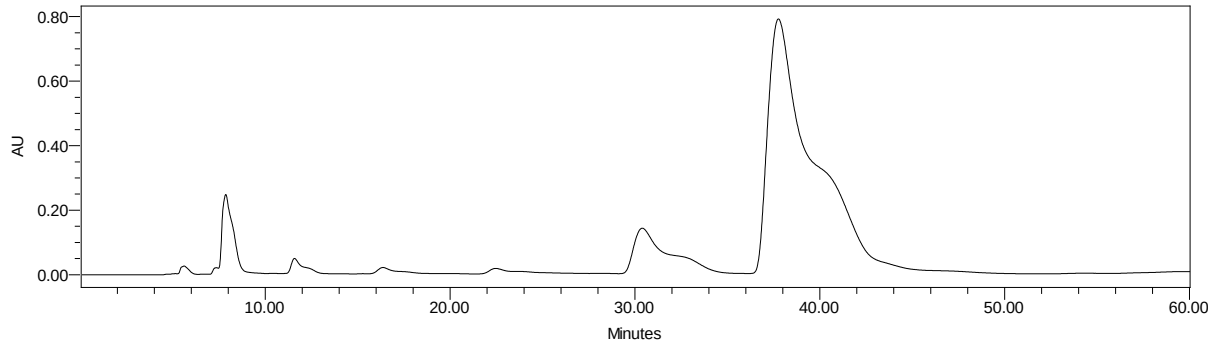
| 2 | 37.888 | 28552738 | 50.70 |

Chiral sample




| | Retention Time | Area | % Area |
|---|---|---|---|
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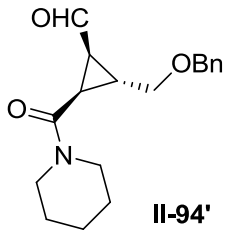
| 2 | 37.761 | 134301635 | 89.95 |



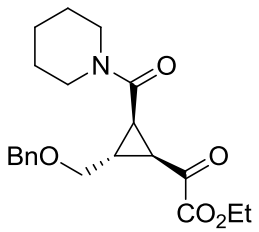

**II-94'**

To a solution of piperidine (12.7 mL, 12.8 mmol) in anhydrous $CH_2Cl_2$ (15 mL) was added $AlMe_3$ (3.3 g, 6.4 mmol, 25% W/W solvent in hexane) under argon atmosphere at 0°C. The resulting solution was stirred at this temperature for 10 min. To the reaction mixture was added a solution of lactone **II-94** (1.4 g, 6.4 mmol) in $CH_2Cl_2$ (10 mL). The resulting solution was stirred for 20h at room temperature, quenched carefully with water and saturated $NH_4Cl$ solution at 0°C, and then extracted with $CH_2Cl_2$ three times. The combine organic phases was dried over anhydrous $Na_2SO_4$ and evaporated to give the crude product. The residue was then purified by flash column chromatography with ethyl acetate/hexane (1/4 to 2/1) as eluent to give the corresponding alcohol as a colorless oil (1.56 g, 80% yield).

To a stirred solution of oxalyl chloride (1.08 mL, 12.8 mmol) in anhydrous $CH_2Cl_2$ (15 mL) was added a solution of DMSO (1.8 mL, 25.6 mmol) in anhydrous $CH_2Cl_2$ (5 mL) at -78°C. The mixture was stirred at this temperature for 20 min. To this mixture was added a solution of the alcohol from the previous step (1.94 g, 6.4 mmol) in anhydrous $CH_2Cl_2$ (10 mL) and the reaction mixture was stirred at -78°C for 2h. After the addition of triethylamine (4.5 mL, 32 mmol) at -78°C, the mixture was gradually warmed to room temperature and stirred for 1h. The reaction mixture was quenched by saturated $NH_4Cl$ aqueous solution and then extracted with $CH_2Cl_2$ three times. The combine organic phases was dried over anhydrous $Na_2SO_4$, and evaporated to give the crude product. The resulting

residue was purified by flash column chromatography with ethyl acetate/hexane (1/4 to 2/1) as eluent to give **II-94'** as a colorless oil (1.74 g, 90% yield). $R_f$ = 0.4 (silica gel, hexanes:EtOAc, 4:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.40-1.66 (6H, m), 2.07 (1H, ddd, *J* = 8.9, 6.6, 6.6 Hz), 2.38 (1H, dd, *J* = 8.9, 6.6 Hz), 2.60 (1H, m), 3.40-3.65 (6H, m), 4.50 (2H, s), 7.22-7.35 (5H, m), 9.12 (1H, d, *J* = 6.6 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 24.29, 25.23, 25.38, 26.46, 27.09, 33.80, 43.22, 46.75, 68.45, 72.74, 127.52, 127.69, 128.33, 137.63, 165.70, 199.27. IR ($CHCl_3$) ν 1704, 1631, 1446, 1281, 1113, 751 cm$^{-1}$. HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_3$ $(M+Na)^+$ 324.1570, found 324.1583. $[\alpha]_D^{20}$ =-3.7 (c=1.0, $CHCl_3$).




**II-95**

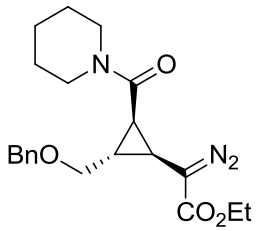
To a stirred suspension of NaCN (230 mg, 4.65 mmol) in a mixture of methanol (10 mL) and water (5 mL) was added acetic acid (280 mg, 4.65 mmol) at room temperature. After stirring at this temperature for 10 min, the homogeneous solution was transferred to a flask containing a solution of aldehyde **II-94'** (1.4 g, 4.65 mmol) in anhydrous $CH_2Cl_2$ (5 mL). This reaction mixture was stirred at room temperature for 2h. The reaction was monitored by TLC. Brine and a solution of sodium bicarbonate were added sequentially to the reaction mixture before being extracted by $CH_2Cl_2$ three times. The combined extracts were dried over $Na_2SO_4$, concentrated under reduced pressure to give the crude product.

To a solution of the above crude compound in absolute ethanol (3 mL) was added a solution of hydrogen chloride in dioxane(3 mL, 4 M, 12 mmol). The resulting reaction mixture was stirred at 0°C for 10 min before resting in a freezer for 2 days. The volatile substances were removed under

reduced pressure to give the crude imidate which was then mixed with water (10 mL). The reaction mixture was stirred overnight at room temperature before extracting with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and evaporated to give the crude hydroxyester.

To the crude hydroxyester in a flask was added a solution of Dess-Martin reagent (4.24 g, 10 mmol) in $CH_2Cl_2$ (50 mL). The solution was stirred for 2h at room temperature. The solid was removed by filtration through a thin silica gel pad. The resulting solution was concentrated under reduced pressure to afford an oily residue which was purified by column chromatography to give ketoester **II-95** as a colorless oil (955 mg, 55% yield). $R_f$ = 0.5 (silica gel, hexanes:EtOAc, 4:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 7.2 Hz), 1.48 (4H, m), 1.59 (2H,m), 2.46 (2H, m), 2.80 (1H, dd, *J* = 8.4, 7.2Hz), 3.38-3.57 (5H, m), 3.71 (1H, m), 4.32 (2H, q, *J* = 7.2Hz), 4.51 (2H, s), 7.31 (5H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 13.98, 24.38, 25.40, 26.14, 26.29, 28.64, 31.68, 43.09, 46.77, 62.28, 69.17, 72.76, 127.54, 127.73, 128.39, 137.83, 160.86, 165.92, 189.75. IR ($CHCl_3$) ν 1748, 1721, 1626, 1445, 1092, 751 cm$^{-1}$. HRMS (ESI) *m/z* calcd for $C_{21}H_{27}NO_5$ $(M+H)^+$ 374.1962, found 374.1975. $[\alpha]_D^{20}$ =-14.8 (c=1.0, $CHCl_3$).

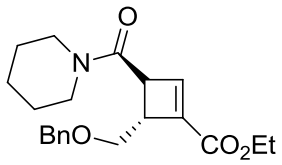



**II-96**

To a flask containing keto-ester **II-95** (1.3 g, 3.5 mmol) and $TsNHNH_2$ (650 mg, 3.5 mmol) was added anhydrous toluene (15 mL). After the reaction mixture was stirred at 100 °C for 5h, it was cooled to room temperature. DBU (1.58mL, 10.5 mmol) was added and the resulting mixture was stirred at

room temperature for 12h. After evaporating the solvent, the resulting residue was purified by flash column chromatography to give diazo compound **18** as a yellow oil (810 mg, 60% yield). $R_f$ = 0.45 (silica gel, hexanes:EtOAc, 4:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, *J* = 7.2 Hz), 1.40-1.66 (6H, m), 2.07-2.22 (3H, m), 3.46 (1H, m), 3.51-3.63 (5H, m), 4.17 (2H, q, *J* = 7.2 Hz), 4.52 (2H, s), 7.28-7.37 (5H, m); $^{13}$C NMR (CDCl3, 100 MHz): δ 14.49, 18.35, 23.26, 24.57, 25.04, 25.64, 26.24, 43.26, 46.77, 60.57, 69.55, 72.70, 109.74, 127.62, 127.68, 128.39, 137.96, 167.07. IR ($CHCl_3$) ν 3009, 2940, 2858, 2095, 1625, 1216, 746 cm$^{-1}$. HRMS (ESI) *m/z* calcd for $C_{21}H_{27}N_3O_4$ $(M+Na)^+$ 408.1899, found 408.1889. $[\alpha]_D^{20}$ =+55.8 (c=0.8, $CHCl_3$).

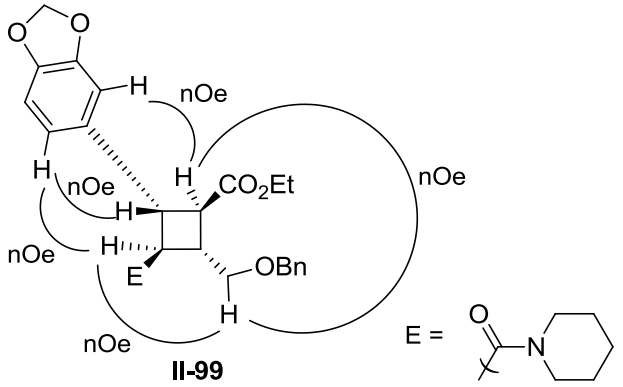



**II-97**

To a stirred suspension of AgOTf (25 mg, 0.1 mmol) mL) in $CH_2Cl_2$ (5 mL) was slowly added a solution of diazo compound **II-96** (385 mg, 1 mmol) in $CH_2Cl_2$ (10 mL). This reaction mixture was stirred at room temperature for 2h. The reaction was monitored by TLC. After the starting material was consumed, the volatile substances were removed under reduced pressure and the resulting residue was purified by flash column chromatography with ethyl acetate/hexane (1/4) as eluent to give cyclobutenoate **II-97** as a colorless oil (339 mg, 95% yield). $R_f$ = 0.4 (silica gel, hexanes:EtOAc, 4:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.26 (3H, t, *J* = 7.2 Hz), 1.40-1.64 (6H, m), 3.32-3.47 (4H, m), 3.60 (1H, m), 3.68 (2H, m), 3.86 (1H, dd, *J* = 10.1, 3.3 Hz), 4.18 (2H, q, *J* = 7.2 Hz), 4.53 (2H, s), 6.88 (1H, q, *J* = 1.2 Hz), 7.28-7.37 (5H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 14.07, 24.35, 25.38, 26.42, 42.64, 45.03, 46.25, 46.51, 60.10, 69.13, 73.09, 127.56, 127.69, 128.21, 138.01, 139.16, 144.46, 161.48, 168.86. IR

($CHCl_3$) ν 2934, 2856, 1715, 1629, 1442, 1102, 740 $cm^{-1}$. HRMS (ESI) *m/z* calcd for $C_{21}H_{27}NO_4$ $(M+H)^+$ 358.2013, found 358.2013. $[\alpha]_D^{20}$ =+105.4 (c=2.9, $CHCl_3$).




**II-99**

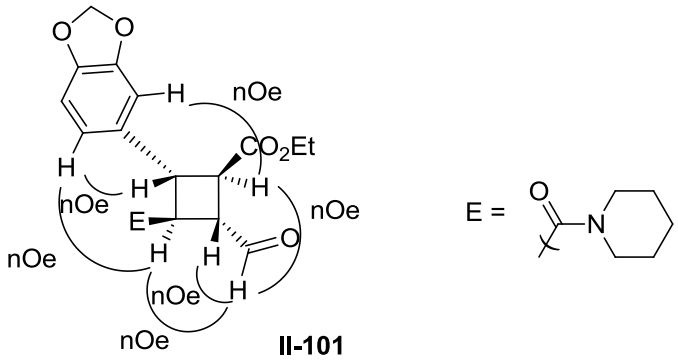
To a solution of compound **II-97** (357 mg, 1 mmol), was added aryl boronic acid shown above (830 mg, 5 mmol), $[Rh(COD)Cl]_2$ (25 mg, 0.05 mmol), a mixture of dioxane and water (10:1, 15 mL), and $Et_3N$ (253 mg, 2.5 mmol). The reaction was stirred at room temperature for 20h and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel to give a mixture of two stereoisomers (345 mg, 72% yield dr=2:1).

To a solution of the above diastereomeric mixture (300 mg, 0.8 mmol) in ethanol (5 mL) was added freshly prepared solution of EtONa (2 mmol) in ethanol (2 mL). After the reaction was stirred at room temperature for 10h, it was carefully neutralized by a solution of HCl (1M in Hexane), filtered to remove the salt and concentrated under reduced pressure.

For small scale reaction (45 mg of product **II-99**), a yield of 90% was obtained after flash column chromatography on silica gel. $R_f$ = 0.38 (silica gel, hexanes:EtOAc, 2:1). For the large scale reaction, the product was used in the next step without further purification.

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, *J* = 6.8 Hz), 1.22 (2H, m), 1.50 (4H,m), 3.03 (1H, tt, *J* = 6, 3.2 Hz), 3.11 (2H, dd, *J* = 11.6, 6.8Hz), 3.20 (1H, t, *J* = 9.2 Hz), 3.37 (1H, t, *J* = 8.8 Hz), 3.42 (1H, m), 3.58 (3H, m), 3.73 (1H, t, *J* = 9.6 Hz), 4.12 (2H, q, *J* = 6.8 Hz) 4.58 (2H, q, *J* = 12 Hz), 5.92 (2H, s), 6.71 (1H, d,

*J* = 8.0 Hz), 6.78 (1H, d, *J* = 8.0 Hz) 6.86 (1H, s), 7.33 (5H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 14.17, 24.40, 25.49, 26.61, 38.92, 42.05, 42.95, 43.15, 46.06, 60.36, 68.84, 73.08, 100.83, 107.37, 108.08, 120.32, 127.52, 128.30, 135.99, 138.23, 146.32, 147.68, 170.23, 173.09. IR ($CHCl_3$) ν 1772, 1664, 1045, 854 $cm^{-1}$. HRMS (ESI) *m/z* calcd for $C_{28}H_{33}NO_6$ $(M+Na)^+$ 480.2381, found 480.2375. $[\alpha]_D^{20}$ =-10.3 (c=3.0, $CHCl_3$).



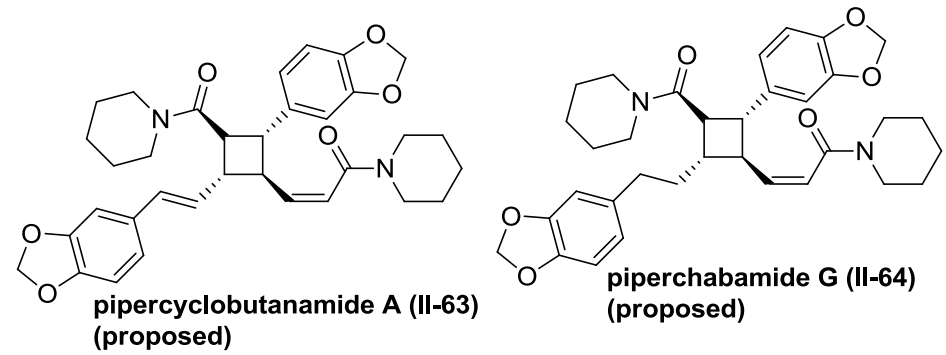

**II-101**

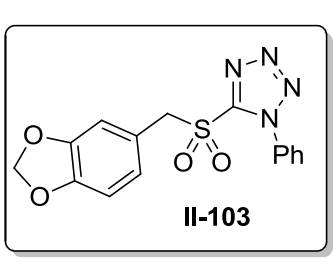


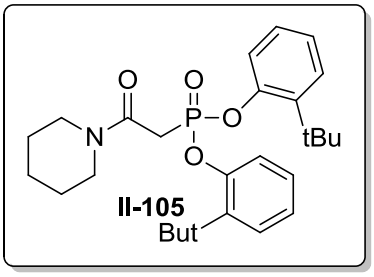

To a flask containing compound **II-99** (1.3 g, 3.5 mmol) and Pd/C 10% (130 mg) was added anhydrous methanol (15 mL) under a hydrogen balloon. The reaction mixture was stirred at room temperature for 15h. After the starting material was consumed, the mixture was filtered through a short bed of silica gel to remove the Pd/C and concentrated under reduced pressure. The alcohol was used in the next step without further purification.

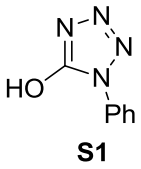
To a flask containing the crude alcohol from the previous step was added a solution of Dess-Martin reagent (3 g, 7 mmol) in $CH_2Cl_2$ (30 mL). The reaction mixture was stirred for 2h at room temperature. The solid was removed by filtration through a thin silica gel pad. The mixture was concentrated under reduced pressure to afford an oily residue which was purified by flash column chromatography on silica gel to give product **II-101** as a colorless oil (840 mg, 80% yield over 3 steps). $R_f$ = 0.4 (silica gel, hexanes:EtOAc, 3:1).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.17-1.32 (2H, m), 1.25 (3H, t, *J* = 7.2 Hz), 1.54 (4H, m), 3.12 (2H,t, *J* =9.2), 3.21 (1H, t, *J* = 9.6 Hz), 3.41 (1H, m), 3.49 (1H, t, *J* = 9.2Hz), 3.65 (1H, m), 3.76 (1H, t, *J* = 9.2 Hz), 3.99 (1H, t, *J* = 9.2 Hz), 4.17 (2H, qd, *J* = 7.8, 1.2 Hz), 5.96 (2H, s), 6.76 (2H, m), 6.79 (1H, m), 9.86 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 14.17, 24.33, 25.50, 26.53, 41.48, 43.54, 46.43, 46.74, 61.17, 101.13, 107.22, 108.40, 120.45, 134.39, 146.94, 148.04, 168.74, 171.62, 199.54. IR ($CHCl_3$) ν 2944, 1725, 1626, 1445, 756 cm$^{-1}$. HRMS (ESI) *m/z* calcd for $C_{21}H_{25}NO_6$ $(M+H)^+$ 388.1715, found 388.1719. $[\alpha]_D^{20}$ =+8.6 (c=1.3, $CHCl_3$).




To a solution of sulfone **II-103** shown above (110 mg, 0.3 mmol) in 0.4 mL of DMF/HMPA (3:1 v/v) was added KHMDS (0.5 M in THF, 0.72 mL, 0.36 mmol) at –35 °C. This was immediately followed by dropwise addition of aldehyde **II-101** (120 mg, 0.3 mmol) in 0.6mL of DMF/HMPA (3:1 v/v). The reaction was allowed to warm slowly to room temperature and stirred for 6 h. The reaction was monitored by TLC. After the starting material was consumed, the reaction was diluted by the addition of ether and water. The organic layer was separated and the aqueous layer was extracted with ether three times. The combined organic layers were washed with water and brine, dried over

$Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with ethyl acetate/hexane (1/4) as eluent to give product **II-102** contaminated with byproduct **S1** (total of 175 mg in a ratio of 2:1 by $^1$H NMR) as a colorless oil.

To a cooled (-78 °C) solution of ester **II-102** (120 mg, contaminated with byproduct **S1** in a ratio of 2:1, The calculated amount of **23** was 0.16 mmol.) obtained from previous step in 2.5 mL of toluene was added a solution of DIBALH (1.6 M in Hexane, 130 µL, 0.2 mmol). The reaction mixture was stirred at –78 °C for 30 min before it was quenched with 3 drops of MeOH. The resulting mixture was diluted by EtOAc and a solution of Rochelle salt. The solution was then extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with ethyl acetate/hexane (1/4) as eluent to give the aldehyde product (53 mg) as a colorless oil.

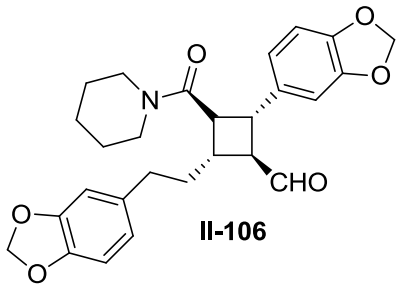
To a solution of reagent **II-105** shown above (47 mg, 0.1 mmol) in 0.4 mL of THF (3:1 v/v) was added KHMDS (0.5 M in THF, 0.24 mL, 0.12 mmol) at –78 °C. The mixture was stirred at this temperature for 30 min, followed by dropwise addition of aldehyde (25 mg, 0.05 mmol) in 0.6 mL of THF. The reaction was allowed to warm slowly to 0 °C and stirred at this temperature for 2h. The reaction was monitored by TLC. After the starting material was consumed, the reaction was diluted by the addition of ether and water. The mixture was extracted with ether three times. The combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with ethyl acetate/hexane (1/4) as eluent to give the final product **II-63** as a colorless oil (28 mg, 50% yield over three steps). $R_f$ = 0.5 (silica gel, hexanes:EtOAc, 2:1).

Reagent **II-105** was prepared according to literature procedure (K. Ando, S. Nagaya, Y. Tarumi, *Tetrahedron Lett.* **2009**, *50*, 5689.). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.38 (18H, s), 1.53 (2H, s, br), 1.63 (4H, s, br), 3.43 (2H, d, *J* = 22.2 Hz), 3.54 (4H, t, *J* = 5.3 Hz), 7.05-7.15(4H, m), 7.36 (2H, d, *J* = 7.8 Hz), 7.65 (2H, d, *J* = 8.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 24.25, 25.32, 26.24, 30.06, 34.64, 34.67 (d, *J* = 135.9 Hz), 43.25, 48.29, 119.62 (d, *J* = 2.3 Hz), 124.51, 127.24, 127.60, 139.31 (d, *J* = 8.5 Hz), 150.02 (d, *J* = 8.5 Hz), 161.31 (d, *J* = 5.4 Hz). IR ($CHCl_3$) ν 2943, 1642, 1440, 1256, 1178, 1083, 941, 726 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{27}H_{38}NO_4P$ $(M+H)^+$ 472.2611, found 472.2618.

Data for Compound **II-63**.

$^{1}$H NMR (600 MHz, $CDCl_3$): δ 1.28-1.52 (12H, m), 3.03 (2H, m), 3.17 (2H, m), 3.24 (2H, m), 3.48 (1H, m), 3.50 (3H, m) 3.65 (1H, m), 3.78 (1H, m), 5.92 (1H, m ), 5.94 (2H, d, 3.4), 5.96 (2H, s), 6.03 (1H, d, 11.4), 6.16 (1H, dd, 15.9, 6.8), 6.48 (1H, d, 15.9), 6.75 (1H, d, 8.0), 6.76 (1H, d, 8.0), 6.83 (1H, d, 8.0), 6.83 (1H, d, 8.0), 6.88 (1H, s), 6.93 (1H, s). $^{13}$C NMR (150 MHz, $CDCl_3$): δ 24.4, 24.5, 25.5, 25.9, 25.9, 26.7, 42.2, 43.1, 43.4, 45.6, 46.5, 46.6, 47.3, 49.7, 100.8, 101.0, 105.6, 107.7, 108.2, 108.2, 120.4, 121.0, 124.2, 128.6, 130.7, 131.6, 135.9, 140.5, 146.2, 147.0, 147.7, 147.9, 165.8, 170.2. IR ($CHCl_3$) ν 2361, 2253, 1710, 1362, 1223, 905, 728$cm^{-1}$. HRMS (ESI) *m/z* calcd for $C_{34}H_{38}N_2O_6$ $(M+Na)^+$ 593.26221, found 593.2650. $[\alpha]_D^{20}$ =+4.2 (c=0.5, $CHCl_3$). Note: The natural product was isolated as a racemic mixture.

Each proton and carbon of synthetic compound **1** (Table S1) was assigned based on $^{1}$H NMR, $^{13}$C NMR, HSQC, HMBC, COSY, and ROESY.




**II-106**

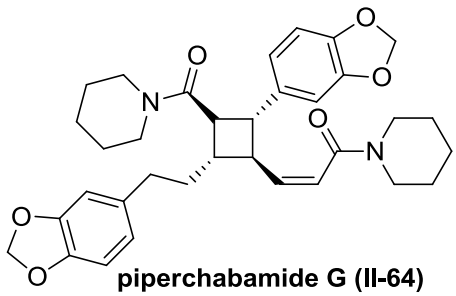
To a suspension of 10% Pd/C (10 mg) in anhydrous methanol (5 mL) under hydrogen gas atmosphere was added compound **II-102** (140 mg contaminated with byproduct **S1** in a ratio of 2:1. The calculated amount of **II-102** was 0.2 mmol.). The reaction mixture was stirred at room temperature for 15 h. After all the starting material was consumed, the mixture was filtered through a short bed of silica gel to remove the Pd/C and concentrated under reduced pressure. The resulting product was used in the next step without further purification.

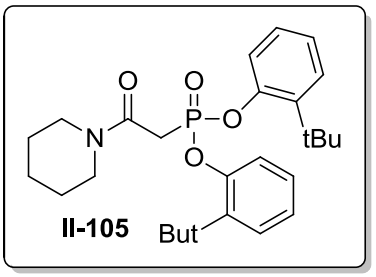
To a cooled (-78 °C) solution of ester obtained from above in toluene (2.5 mL) was added DIBALH (1.6 M in Hexane, 0.13 mL, 0.2 mmol). The reaction mixture was stirred at

–78 °C for 30 min before it was quenched with 3 drops of MeOH and diluted with EtOAc and Rochelle salt solution. After extraction with ethyl acetate, the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography with ethyl acetate/hexane (1/4) as eluent to give product **II-106** (56mg, 61% over 2 steps) as a colorless oil. $R_f$ = 0.42 (silica gel, hexanes:EtOAc, 2:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.16-1.32 (2H, m), 1.53 (4H, m), 1.87, (2H, m), 2.53 (2H, m), 2.80 (1H, m), 2.97 (2H, m), 3.12 (2H,m), 3.40 (1H, m), 3.70 (2H, m), 5.92 (2H, s), 5.95 (2H, s), 6.60 (1H, dd, J=7.8, 1.2Hz), 6.66 (1H, d, J=1.6Hz), 6.69-6.76 (4H, m), 9.69 (1H, d, J=3.1Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 24.4, 25.6, 26.7, 33.0, 36.1, 37.2, 41.5, 43.3, 46.5, 47.8, 56.2, 100.8, 101.1, 107.1, 108.2, 108.4, 108.7, 120.2, 121.0, 134.9, 135.1, 145.7, 146.8, 147.6, 148.0, 170.0, 201.1. IR ($CHCl_3$) ν 2964, 2300, 1725,

1629, 1445, 736 $cm^{-1}$. HRMS (ESI) *m/z* calcd for $C_{27}H_{29}NO_6$ $(M+H)^+$ 464.2073, found 464.2069. $[\alpha]_D^{20}$ = -3.2 (c=0.7, $CHCl_3$)



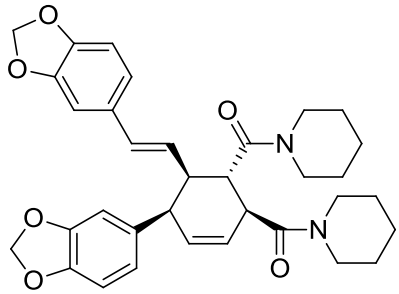




To a solution of reagent **II-105** shown above (24 mg, 0.05 mmol) in THF (0.3 mL) was added KHMDS (0.5 M in THF, 0.12 mL, 0.06 mmol) at –78 °C. After the mixture was stirred at this temperature for 30 min, a solution of aldehyde (13 mg, 0.025 mmol) in THF (0.3 mL) was added. The reaction was allowed to warm slowly to 0 °C and stirred at this temperature for 2 h. The reaction was monitored by TLC. After all the starting material was consumed, the reaction was diluted by the addition of ether and water. After extraction with ether three times, the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography with ethyl acetate/hexane (1/4) as eluent to give product **2** (8.9 mg, 62%) as a colorless oil. $R_f$ = 0.48 (silica gel, hexanes:EtOAc, 2:1).

$^1$H NMR (600 MHz, $CDCl_3$): δ 1.28 (4H, m), 1.45 (4H, m), 1.52 (4H, m), 1.84 (2H, m), 2.46, (1H, m), 2.50 (1H, m), 2.70 (1H, m), 2.82 (1H, m), 3.17 (2H, m), 3.24 (2H, m), 3.25 (1H, m), 3.42 (2H, m), 3.47 (1H, m) 3.65 (2H, m), 5.93 (2H, m), 5.93 (2H, s), 5.93 (1H, d, 11.4), 5.98 (1H, d, 11.4), 6.67 (1H, d, 8.0), 6.72 (1H, d, 8.0), 6.73 (2H, d, 8.0) 6.73 (1H, s), 6.80 (1H, s); $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 24.5, 25.6, 26.7, 32.6, 37.4, 41.5, 43.1, 44.4, 46.5, 47.5, 48.4, 100.6, 100.9, 107.5, 108.0, 108.1, 109.0, 120.4, 121.2, 123.1, 135.9, 136.3, 142.0, 145.4, 146.2, 147.4, 147.7, 165.9, 170.9. IR ($CHCl_3$) ν 2353, 2240,

1715, 1362, 1223, 908, 724cm$^{-1}$. HRMS (ESI) *m/z* calcd for $C_{34}H_{40}N_2O_6$ $(M+Na)^+$ 595.2784, found 595.2794. $[\alpha]_D^{20}$ =+5.6 (c=0.3, $CHCl_3$).

Each proton and carbon of synthetic compound **2** (Table S4) was assigned based on $^1$H NMR, $^{13}$C NMR, HSQC, HMBC, COSY, and ROESY.



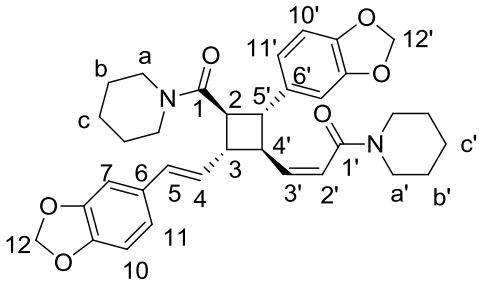
chabamide II-107
(revised structure of pipercyclobutanamide A )

Compound **II-107** was also prepared following procedures in the following literature.

K. Wei, W. Li, K. Koike, T. Nikaido, *Org. Lett.* **2005**, *7*, 2833. (ref 27 in manuscript)

$^1$H NMR (500 MHz, $CDCl_3$): δ 1.1-1.6 (8H, m), 1.62 (4H, m), 2.93 (1H, ddd, 11.2, 10.5, 5.6), 3.31 (4H, m), 3.48 (1H, m), 3.56 (4H, m), 3.66 (1H, dd, 11.8, 9.6), 4.14 (1H, dd, 9.5, 2.2), 5.21 (1H, dd, 15.6, 10.0), 5.75 (1H, d, 10.0), 5.86(1H, ddd, 10.0, 4.9, 2.7), 5.92 (2H, s), 5.96 (1H, d, 1.2), 5.99 (1H, d, 1.2), 6.32 (1H, d, 15.6), 6.64 (1H, dd, 8.0, 1.2), 6.65 (1H, s), 6.69 (1H, d, 8.0), 6.81 (2H, broad s), 6.83 (1H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 24.5, 24.6, 25.6, 25.8, 26.3, 26.7, 37.7, 42.8, 42.9, 43.3, 45.4, 45.9, 46.9, 47.1, 100.87, 100.9, 105.3, 107.9, 108.2, 110.8, 120.7, 123.4, 125.5, 128.1, 130.3, 131.0, 131.9, 133.5, 146.4, 146.7, 147.4, 147.8, 171.1, 172.1. IR ($CHCl_3$) ν 2939, 2857, 2341, 1625, 15.3, 1248, 906, 725 cm$^{-1}$.

**Table S1**. $^{13}C$ and $^{1}H$ NMR spectral data of natural product **II-63** (literature) and synthetic **II-63**



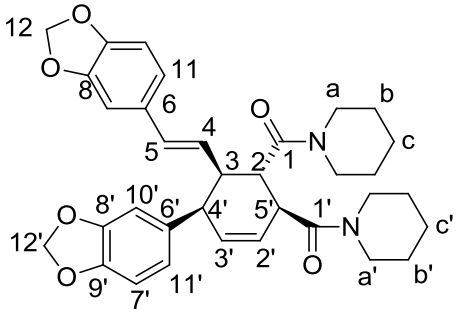

proposed structure
of pipercyclobutanamide A **II-63**

| position | $\delta_C$ of **II-63** (literature)[a] | $\delta_C$ of synthetic **II-63** | $\delta_H$ of **II-63** (literature)[a] | $\delta_H$ of synthetic **II-63** |
|---|---|---|---|---|
| 1 | 172.2 | 170.2 | --- | --- |
| 2 | 37.7 | 49.7 | 3.66 (dd, 11.7, 9.6) | 3.03 (1H, m) |
| 3 | 45.4 | 45.6 | 2.93 (ddd, 11.7, 10.2, 5.6) | 3.03 (1H, m) |
| 4 | 128.0 | 128.6 | 5.21 (dd, 15.6, 10.2) | 6.16 (1H, dd, 15.9, 6.8) |
| 5 | 131.0 | 130.7 | 6.32 (d, 15.6) | 6.48 (1H, d, 15.9) |
| 6 | 131.9 | 131.6 | --- | --- |
| 7 | 105.3 | 108.2 | 6.65 (d, 2.0) | 6.93 (1H, s) |
| 8 | 147.8 | 147.9 | --- | --- |
| 9 | 146.7 | 147.7 | --- | --- |
| 10 | 108.2 | 105.6 | 6.69 (d, 7.9) | 6.76 (1H, d, 8.0) |
| 11 | 120.8 | 121.0 | 6.64 (dd, 7.9, 2.0) | 6.83 (1H, d, 8.0) |
| 12 | 100.9 | 100.8 | 5.92 (s) | 5.94 (2H, d, 3.4) |
| 1' | 171.1 | 165.8 | --- | --- |
| 2' | 125.5 | 120.4 | 5.75 (dt, 10.0, 1.7) | 6.03 (1H, d, 11.4) |
| 3' | 130.3 | 140.5 | 5.86(ddd, 10.0, 4.9, 2.7) | 5.92 (1H, m) |
| 4' | 45.9 | 43.4 | 3.48 (dddd, 5.6, | 3.78 (1H, m) |

| | | | | |
|---|---|---|---|---|
| | | | 4.9, 2.7, 1.7) | |
| 5' | 42.8 | 46.5 | 4.14 (dddd, 9.6, 2.7, 2.7, 1.7) | 3.48 (1H, m) |
| 6' | 133.6 | 135.9 | --- | --- |
| 7' | 110.8 | 108.2 | 6.83 (d, 1.5) | 6.88 (1H, s) |
| 8' | 147.4 | 147 | --- | --- |
| 9' | 146.4 | 146.2 | --- | --- |
| 10' | 107.9 | 107.7 | 6.81 (s) | 6.75 (1H, d, 8.0) |
| 11' | 123.4 | 124.2 | 6.81 (d, 1.5) | 6.83 (1H, d, 8.0) |
| 12' | 100.9 | 101.0 | 5.96 (d, 1.4), 5.99 (d, 1.4) | 5.96 (2H, s) |
| a, a’ | 42.9, 46.9, 43.3, 47.1 | 43.1, 46.6 42.2, 47.3 | 3.31 (m), 3.56 (m), 3.31 (m), 3.56 (m) | 3.17 (2H, m), 3.24 (2H, m) 3.50 (3H, m) 3.65 (1H, m) |
| b, b’ | 25.6, 26.4, 25.8, 26.7 | 25.9, 26.7 25.5, 25.9 | 1.3-1.6 (m), 1.3-1.6 (m) | |
| c, c’ | 24.5, 24.7 | 24.4, 24.5 | 1.62 (m), 1.62 (m) | 1.28-1.52 (12H,m) |

[a.] Y. Fujiwara, K. Naithou, T. Miyazaki, K. Hashimoto, K. Mori, Y. Yamamoto, *Tetrahedron Lett.* **2001**, *42*, 2497. (ref 2 in manuscript)

**Table S2**. $^{13}$C NMR spectral data of natural product **1** (literature), natural product **II-107** (literature), and synthetic **II-107**




chabamide **II-107** (revised structure of pipercyclobutanamide A **II-63**)

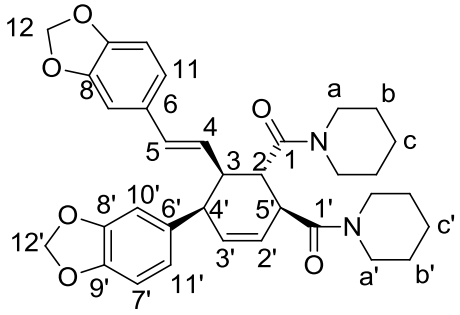
| position | $\delta_C$ of **II-63** (literature)[a] | $\delta_C$ of **II-107** (literature)[b] | $\delta_C$ difference between **1** and **25** (literature)[a,b] | $\delta_C$ of synthetic **II-63** |
|---|---|---|---|---|
| 1 | 172.2 | 172.2 | 0 | 172.1 |
| 2 | 37.7 | 37.7 | 0 | 37.7 |
| 3 | 45.4 | 45.4 | 0 | 45.4 |
| 4 | 128.0 | 128.1 | -0.1 | 128.1 |
| 5 | 131.0 | 131.0 | 0 | 131.0 |
| 6 | 131.9 | 131.9 | 0 | 131.9 |
| 7 | 105.3 | 105.3 | 0 | 105.3 |
| 8 | 147.8 | 147.8 | 0 | 147.8 |
| 9 | 146.7 | 146.7 | 0 | 146.7 |
| 10 | 108.2 | 108.2 | 0 | 108.2 |
| 11 | 120.8 | 120.7 | 0.1 | 120.7 |
| 12 | 100.9 | 100.89 | 0.01 | 100.87 |
| 1' | 171.1 | 171.1 | 0 | 171.1 |
| 2' | 125.5 | 125.5 | 0 | 125.5 |
| 3' | 130.3 | 130.3 | 0 | 130.3 |
| 4' | 45.9 | 45.9 | 0 | 45.9 |

| | | | | |
|---|---|---|---|---|
| 5' | 42.8 | 42.9 | -0.1 | 42.9 |
| 6' | 133.6 | 133.6 | 0 | 133.5 |
| 7' | 110.8 | 110.8 | 0 | 110.8 |
| 8' | 147.4 | 147.5 | -0.1 | 147.4 |
| 9' | 146.4 | 146.4 | 0 | 146.4 |
| 10' | 107.9 | 107.9 | 0 | 107.9 |
| 11' | 123.4 | 123.5 | 0.1 | 123.4 |
| 12' | 100.9 | 100.92 | -0.02 | 100.9 |
| a | 46.9, 42.9 | 46.9, 42.8 | 0, 0.1 | 46.9, 42.8 |
| b | 26.4, 25.6 | 26.4, 25.6 | 0, 0 | 26.3, 25.6 |
| c | 24.5 | 24.5 | 0 | 24.5 |
| a' | 43.3, 47.1 | 43.3, 47.1 | 0, 0 | 43.3, 47.1 |
| b' | 25.8, 26.7 | 25.8, 26.7 | 0, 0 | 25.8, 26.7 |
| c' | 24.7 | 24.6 | 0.1 | 24.6 |

[a.] Y. Fujiwara, K. Naithou, T. Miyazaki, K. Hashimoto, K. Mori, Y. Yamamoto, *Tetrahedron Lett.* **2001**, *42*, 2497. (ref 2 in manuscript)

[b.] T. Rukachaisirikul, S. Prabpai, P. Champung, A. Suksamrarn, *Planta Med.* **2002**, *68*, 853. (ref 26a in manuscript)

**Table S3**. $^{1}$H NMR spectral data of natural product **1** (literature), natural product **25** (literature), and synthetic **II-107**




chabamide **II-107**
(revised structure of
pipercyclobutanamide A **II-63**)

| position | $\delta_H$ of **II-63** (literature)[a] | $\delta_H$ of **II-107** (literature)[b] | $\delta_H$ of synthetic **II-107** |
|---|---|---|---|
| 1 | --- | --- | --- |
| 2 | 3.66 (dd, 11.7, 9.6) | 3.64 (1H, dd, 11.8, 9.6) | 3.66 (1H, dd, 11.8, 9.6) |
| 3 | 2.93 (ddd, 11.7, 10.2, 5.6) | 2.91 (1H, ddd, 11.8, 10.2, 5.7) | 2.93 (1H, ddd, 11.2, 10.5, 5.6) |
| 4 | 5.21 (dd, 15.6, 10.2) | 5.19 (dd, 15.6, 10.2) | 5.21 (1H, dd, 15.6, 10.0) |
| 5 | 6.32 (d, 15.6) | 6.29 (d, 15.6) | 6.32 (1H, d, 15.6) |
| 6 | --- | --- | --- |
| 7 | 6.65 (d, 2.0) | 6.60 (1H, d, 1.6) | 6.65 (1H, s) |
| 8 | --- | --- | --- |
| 9 | --- | --- | --- |
| 10 | 6.69 (d, 7.9) | 6.67 (1H, d, 6.9) | 6.69 (1H, d, 8.0) |
| 11 | 6.64 (dd, 7.9, 2.0) | 6.63 (1H, dd,.6.9, 1.6) | 6.64 (1H, dd, 8.0, 1.2) |
| 12 | 5.92 (s) | 5.899 (d, 1.6), 5.895 (d, 1.6) | 5.92 (2H, s) |
| 1' | --- | --- | --- |
| 2' | 5.75 (dt, 10.0, 1.7) | 5.73 (1H, ddd, 10.0, 2.3 2.3,) | 5.75 (1H, d, 10.0) |
| 3' | 5.86(ddd, 10.0, 4.9, 2.7) | 5.84 (1H, ddd, 10.0, 5.0, | 5.86(1H, ddd, 10.0, 4.9, |

| | | | |
|---|---|---|---|
| | | 2.3) | 2.7) |
| 4' | 3.48 (dddd, 5.6, 4.9, 2.7, 1.7) | 3.45 (1H, m) | 3.48 (1H, m) |
| 5' | 4.14 (dddd, 9.6, 2.7, 2.7, 1.7) | 4.12 (ddt, 9.6, 2.3, 2.3) | 4.14 (1H, dd, 9.5, 2.2) |
| 6' | --- | --- | --- |
| 7' | 6.83 (d, 1.5) | 6.79 (1H, br s) | 6.83 (1H, s) |
| 8' | --- | --- | --- |
| 9' | --- | --- | --- |
| 10' | 6.81 (s) | 6.80 (1H, d, 11.4) | 6.81 (1H, broad s) |
| 11' | 6.81 (d, 1.5) | 6.80 (1H, d, 11.4) | 6.81 (1H, broad s) |
| 12' | 5.96 (d, 1.4),<br>5.99 (d, 1.4) | 5.94 (d, 1.5),<br>5.96 (d, 1.5) | 5.96 (1H, d, 1.2),<br>5.99 (1H, d, 1.2) |
| a | 3.31 (m), 3.56 (m) | 3.26 (m), 3.33 (m) | 3.31 (m), 3.56 (m) |
| b | 1.3-1.6 (m) | 1.12 (1H, m), 1.25 (2H, m), 1.43 (1H, m) | 1.1-1.6 (m) |
| c | 1.62 (m) | 1.34 (1H, m), 1.43 (1H, m) | 1.62 (m) |
| a' | 3.31 (m), 3.56 (m) | 3.54 (2H, m) | 3.31 (m), 3.56 (m) |
| b' | 1.3-1.6 (m) | 1.51 (2H, m), 1.58 (2H, m) | 1.1-1.6 (m) |
| c' | 1.62 (m) | 1.63 (2H, m) | 1.62 (m) |

[a.] Y. Fujiwara, K. Naithou, T. Miyazaki, K. Hashimoto, K. Mori, Y. Yamamoto, *Tetrahedron Lett.* **2001**, *42*, 2497. (ref 2 in manuscript)

[b.] T. Rukachaisirikul, S. Prabpai, P. Champung, A. Suksamrarn, *Planta Med.* **2002**, *68*, 853. (ref 26a in manuscript)

**Figure S1**. Selected $^{1}$H-$^{1}$H COSY and HMBC correlations of synthetic **II-63**

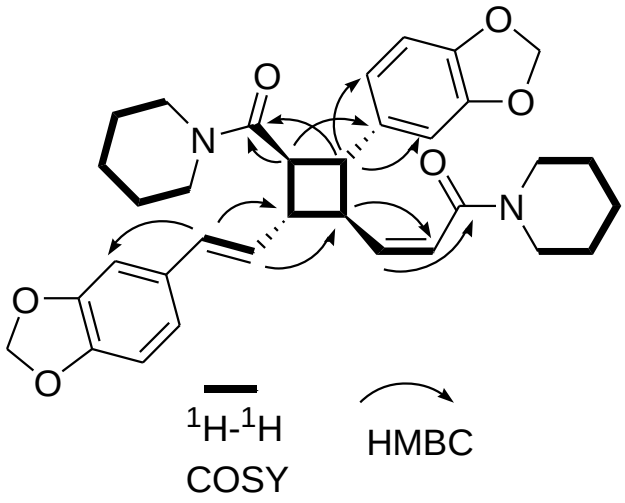



**Figure S2**. Selected nOe correlations based on ROESY of synthetic **II-63**

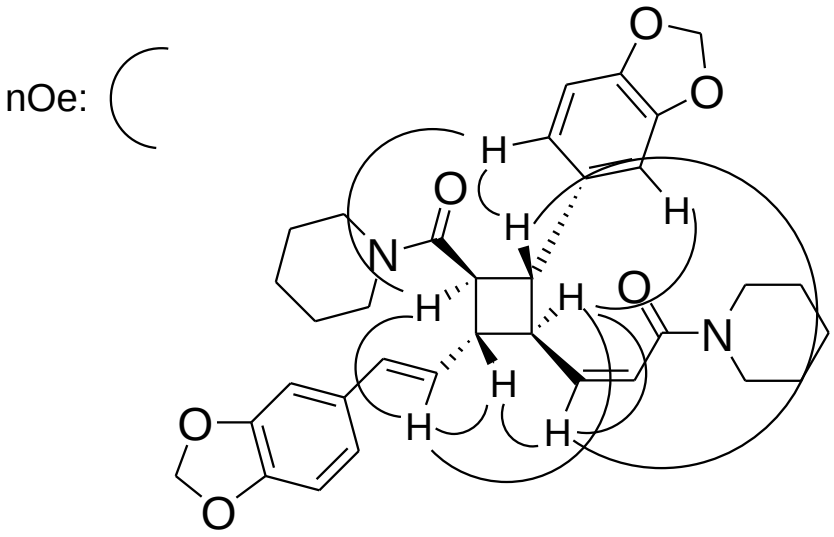
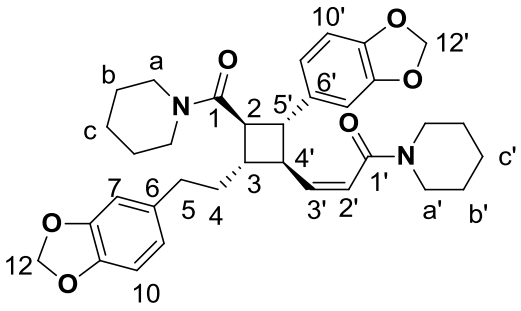


**Table S4**. $^{13}C$ and $^{1}H$ NMR spectral data of natural product **2** (literature) and synthetic **2**



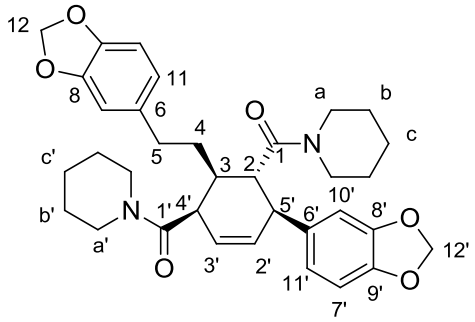

proposed structure of piperchabamide G **II-64**

| position | $\delta_C$ of **II-64** (literature)[a] | $\delta_C$ of synthetic **II-64** | $\delta_H$ of **II-64** (literature)[a] | $\delta_H$ of synthetic **II-64** |
|---|---|---|---|---|
| 1 | 173.2 | 170.9 | --- | --- |
| 2 | 45 | 48.4 | 4.05 (1H, dd, 9.7, 10.0) | 2.82 (1H, m) |
| 3 | 39.3 | 41.5 | 2.22 (1H, m) | 2.50 (1H, m) |
| 4 | 31.9 | 37.4 | 1.58 (1H, m), 1.67 (1H, m) | 1.84 (2H, m) |
| 5 | 33.5 | 32.6 | 2.40 (1H, m), 2.50 (1H, m) | 2.46,2.70 (2H, m) |
| 6 | 136 | 136.3 | --- | --- |
| 7 | 108.7 | 108.1 | 6.60 (1H, d, 1.5) | 6.73 (1H, s) |
| 8 | 147.5 | 147.7 | --- | --- |
| 9 | 145.5 | 147.4 | --- | --- |
| 10 | 108.1 | 109.0 | 6.68 (1H, br s) | 6.73 (1H, d, 8.0) |
| 11 | 120.9 | 121.2 | 6.56 (1H, dd,.1.5, 7.9) | 6.72 (1H, d, 8.0) |
| 12 | 100.7 | 100.9 | 5.90 (2H br s) | 5.93 (2H, m) |
| 1' | 170.4 | 165.9 | --- | --- |
| 2' | 134 | 123.1 | 5.84 (1H, d, 9.8) | 5.98 (1H, d, 11.4) |
| 3' | 123.2 | 142.0 | 5.71 (1H, ddd, 2.1, 5.1, 9.8) | 5.93 (1H, d, 11.4) |
| 4' | 38.3 | 44.4 | 3.60 (1H, br s) | 3.47 (1H, m) |

| | | | | |
|---|---|---|---|---|
| 5' | 46.6 | 47.5 | 3.68 (1H, ddd, 2.1, 2.1, 9.7) | 3.25 (1H, m) |
| 6' | 137.8 | 135.9 | --- | --- |
| 7' | 108.1 | 107.5 | 6.68 (1H, br s) | 6.80 (1H, s) |
| 8' | 147.5 | 146.2 | --- | --- |
| 9' | 146 | 145.4 | --- | --- |
| 10' | 108.9 | 108.0 | 6.74 (1H, d, 8.2) | 6.73 (1H, d, 8.0) |
| 11' | 121.4 | 120.4 | 6.68 (1H, br s) | 6.67 (1H, d, 8.0) |
| 12' | 100.7 | 100.6 | 5.87 (2H br s) | 5.93 (2H, s) |
| a | 42.9, 47.0 | 46.5 | 2.95 (1H, ddd, 2.4, 12.5, 12.5), 3.01 (1H, ddd, 3.1, 13.2, 13.2), 3.48(1H, br d, ca. 13), 3.98(1H, br d, ca. 13) | 3.17 (2H, m), 3.24 (2H, m) |
| b | 26.0, 27.1 | 26.7 | 1.15 (1H, m), 1.25 (2H, m) 1.43 (1H, m) | 1.45 (4H, m) |
| c | 24.6 | 24.5 | 1.43 (1H, m), 1.67 (1H, m) | 1.28 (2H, m) |
| a' | 42.9, 47.1 | 43.1 | 3.61 (2H, br s), 3.62 (2H, br s) | 3.42 (2H, m) 3.65 (2H, m) |
| b' | 25.9, 27.1 | 25.6 | 1.58 (4H, m) | 1.52 (4H, m) |
| c' | 24.6 | 24.5 | 1.43 (2H, m) | 1.28 (2H,m) |

[a.] H. Matsuda, K. Ninomiya, T. Morikawa, D. Yasuda, I. Yamaguchi, M. Yoshikawa, *Bioorg. Med. Chem.* **2009**, *17*, 7313. (ref 6 in manuscript)

**Table S5**. $^{13}$C NMR spectra data of natural product **2** (literature), natural product **26** (literature), and synthetic **26**



nigramide F **II-108**
(revised structure of
piperchabamide G **II-64**)

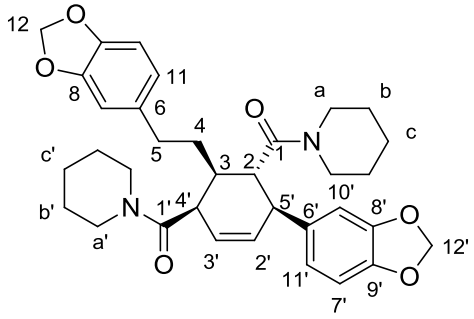
| position | $\delta_C$ of **II-64** (literature)[a] | $\delta_C$ of **II-108** (literature)[b] | $\delta_C$ difference between **II-64** and **II-108** (literature)[a,b] |
|---|---|---|---|
| 1 | 173.2 | 173.2 | 0 |
| 2 | 45.0 | 45.1 | -0.1 |
| 3 | 39.3 | 39.4 | -0.1 |
| 4 | 31.9 | 32.0 | -0.1 |
| 5 | 33.5 | 33.6 | -0.1 |
| 6 | 136.0 | 136.1 | -0.1 |
| 7 | 108.7 | 108.8 | -0.1 |
| 8 | 147.5 | 147.5 | 0 |
| 9 | 145.5 | 145.6 | -0.1 |
| 10 | 108.1 | 108.1 | 0 |
| 11 | 120.9 | 121.0 | -0.1 |
| 12 | 100.7 | 100.7 | 0 |
| 1' | 170.4 | 170.4 | 0 |
| 2' | 134.0 | 134.1 | -0.1 |
| 3' | 123.2 | 123.2 | 0 |
| 4' | 38.3 | 38.4 | -0.1 |
| 5' | 46.6 | 46.7 | -0.1 |

| | | | |
|---|---|---|---|
| 6' | 137.8 | 137.8 | 0 |
| 7' | 108.1 | 108.1 | 0 |
| 8' | 147.5 | 147.5 | 0 |
| 9' | 146.0 | 146.1 | -0.1 |
| 10' | 108.9 | 109.0 | -0.1 |
| 11' | 121.4 | 121.4 | 0 |
| 12' | 100.7 | 100.7 | 0 |
| a | 42.9, 47.0 | 43.0, 47.1 | -0.1, -0.1 |
| b | 26.0, 27.1 | 25.9, 27.2 | -0.1, -0.1 |
| c | 24.6 | 24.7 | -0.1 |
| a' | 42.9, 47.1 | 42.9, 47.1 | 0, 0 |
| b' | 25.9, 27.1 | 25.9, 26.1 | 0, 1.0 |
| c' | 24.6 | 24.7 | -0.1 |

[a.] H. Matsuda, K. Ninomiya, T. Morikawa, D. Yasuda, I. Yamaguchi, M. Yoshikawa, *Bioorg. Med. Chem.* **2009**, *17*, 7313. (ref 6 in manuscript)

[b.] K. Wei, W. Li, K. Koike, Y. J. Chen, T. Nikaido, *J. Org. Chem.* **2005**, *70*, 1164. (ref 5 in manuscript)

**Table S6**. $^{1}$H NMR spectral data of natural product **II-64** (literature), natural product **26** (literature), and synthetic **II-108**



nigramide F **II-108**
(revised structure of
piperchabamide G **II-64**)

| position | $\delta_H$ of **II-64** (literature)[a] | $\delta_H$ of **II-108** (literature)[b] |
|---|---|---|
| 1 | --- | --- |
| 2 | 4.05 (1H, dd, 9.7, 10.0) | 4.05 (1H, t, 10.4) |
| 3 | 2.22 (1H, m) | 2.20(1H, tdd, 10.5, 5.7, 4.5) |
| 4 | 1.58 (1H, m), 1.67 (1H, m) | 1.60 (1H, m), 1.67 (1H, m) |
| 5 | 2.40 (1H, m), 2.50 (1H, m) | 2.40 (1H, ddd, 13.5 10.7, 5.2), 2.48 (1H, ddd, 13.5, 10.3, 6.2) |
| 6 | --- | --- |
| 7 | 6.60 (1H, d, 1.5) | 6.60 (1H, d, 1.6) |
| 8 | --- | --- |
| 9 | --- | --- |
| 10 | 6.68 (1H, br s) | 6.69 (1H, d, 8.0) |
| 11 | 6.56 (1H, dd,.1.5, 7.9) | 6.56 (1H, dd,.1.6, 8.0) |
| 12 | 5.90 (2H br s) | 5.90 (2H, s) |
| 1' | --- | --- |

| | | |
|---|---|---|
| 2' | 5.84 (1H, d, 9.8) | 5.85 (1H, dt, 9.8, 1.9) |
| 3' | 5.71 (1H, ddd, 2.1, 5.1, 9.8) | 5.71 (1H, ddd, 2.7, 5.2, 9.8) |
| 4' | 3.60 (1H, br s) | 3.59 (1H, m) |
| 5' | 3.68 (1H, ddd, 2.1, 2.1, 9.7) | 3.69 (1H, dq, 1.9, 9.8) |
| 6' | --- | --- |
| 7' | 6.68 (1H, br s) | 6.68 (1H) |
| 8' | --- | --- |
| 9' | --- | --- |
| 10' | 6.74 (1H, d, 8.2) | 6.74 (1H, d, 1.1) |
| 11' | 6.68 (1H, br s) | 6.68 (1H) |
| 12' | 5.87 (2H br s) | 5.87 (2H, d, 1.3) |
| a | 2.95 (1H, ddd, 2.4, 12.5, 12.5), 3.01 (1H, ddd, 3.1, 13.2, 13.2), 3.48(1H, br d, ca. 13), 3.98(1H, br d, ca. 13) | 2.96(1H, ddd, 2.7, 9.8, 12.8), 3.02(1H, ddd, 3.0, 9.9, 13.3), 3.46(1H, 4.1 13.3), 3.96(1H, dt, 4.1, 12.8) |
| b | 1.15 (1H, m), 1.25 (2H, m) 1.43 (1H, m) | 1.15 (1H, m), 1.25 (1H, m), 1.50 (1H, m)1.43 (1H, m) |
| c | 1.43 (1H, m), 1.67 (1H, m) | 1.34 (1H, m), 1.43 (1H, m) |
| a' | 3.61 (2H, br s), 3.62 (2H, br s) | 3.62 (2H, m) |
| b' | 1.58 (4H, m) | 1.65 (2H, m), 1.61 (2H, m) |
| c' | 1.43 (2H, m) | 1.69 (2H, m) |

[a.] H. Matsuda, K. Ninomiya, T. Morikawa, D. Yasuda, I. Yamaguchi, M. Yoshikawa, *Bioorg. Med. Chem.* **2009**, *17*, 7313. (ref 6 in manuscript)

[b.] K. Wei, W. Li, K. Koike, Y. J. Chen, T. Nikaido, *J. Org. Chem.* **2005**, *70*, 1164. (ref 5 in manuscript)

**Figure S3**. Selected $^{1}$H-$^{1}$H COSY and HMBC correlations of synthetic **II-64**

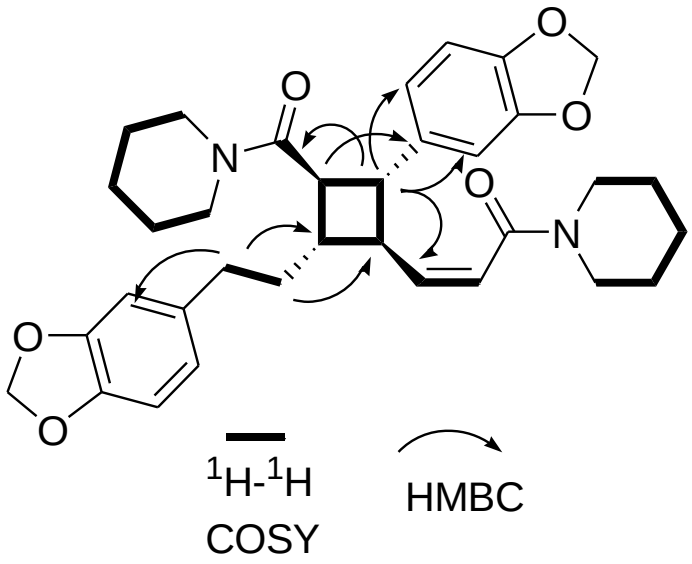



**Figure S4**. Selected nOe correlations based on ROESY of synthetic **II-64**

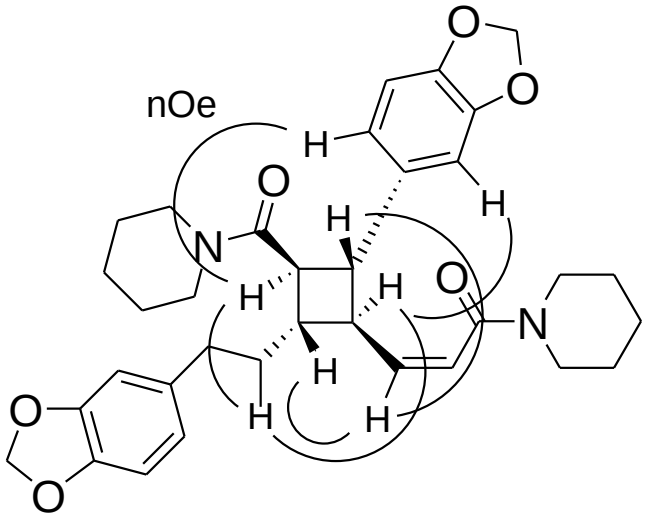
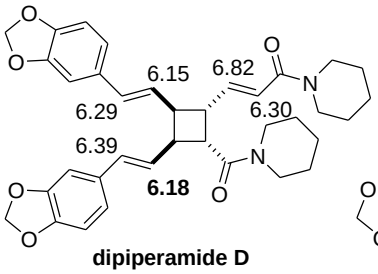
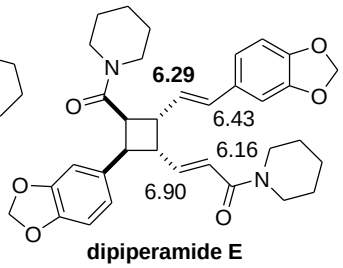


**Figure S5**. Selected $^{1}$H NMR spectral data of related natural products

*Bioorg. Med. Chem.* **2002**, *10,* 2981. (ref 4 in manuscript)

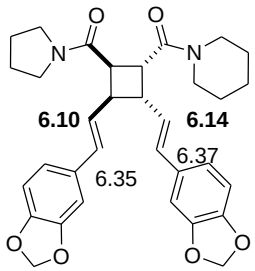



**dipiperamide D**



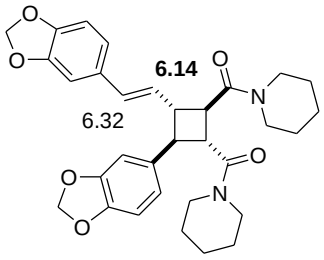

**dipiperamide E**

*Tetrahedron* **2002**, *58*, 1667. (ref 3 in manuscript)

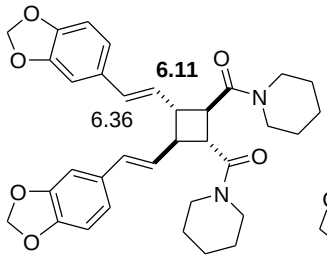



**dipiperamide C**

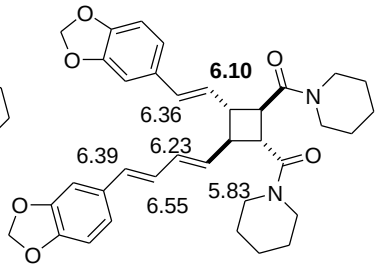
*J. Org. Chem.* **2005**, *70*, 1164. (ref 5 in manuscript)




**nigramide Q**



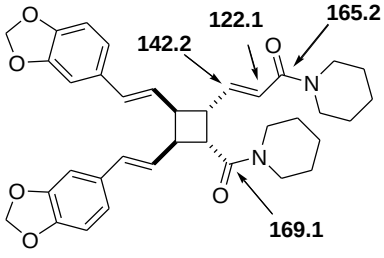

**nigramide R**



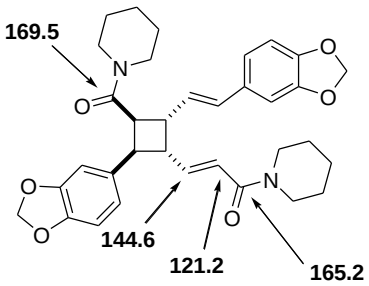

**nigramide S**

**Figure S6**. Selected $^{13}$C NMR spectral data of related natural products

*Bioorg. Med. Chem.* **2002**, *10,* 2981. (ref 4 in manuscript)




**dipiperamide D**

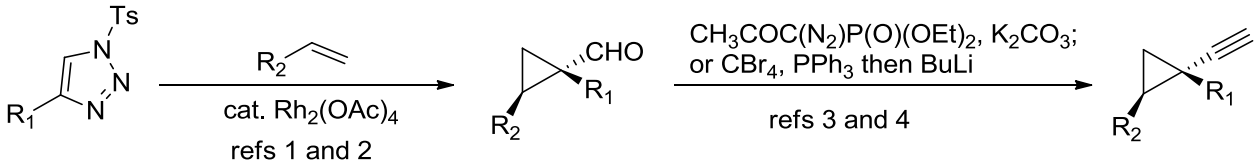



**dipiperamide E**

**CHAPTER III RING EXPANSION OF ALKYNYL CYCLOPROPANES TO HIGHLY SUBSTITUTED CYCLOBUTENES**

**Characterization data for alkynyl cyclopropane substrates:**

Unless noted otherwise, alkynyl cyclopropanes were prepared by cyclopropanation of alkenes followed by alkyne formation as shown below following literature procedures.



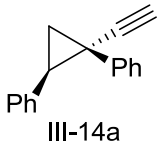

References:

1) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher and V. V. Fokin, *J. Am. Chem. Soc.*, 2009, **131**, 18034.

2) N. Grimster, L. Zhang and V. V. Fokin, *J. Am. Chem. Soc.*, 2010, **132**, 2510.

3) S. Muller, B. Liepold, G. J. Roth and H. J. Bestmann, *Synlett*, 1996, 521.

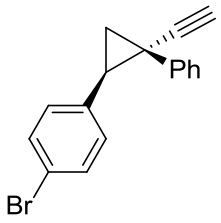
4) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, **13,** 3769.




**III-**14a

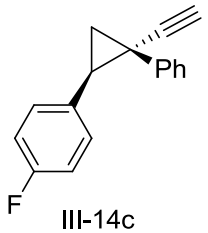
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.89 (dd, *J* = 8.97, 5.65 Hz, 1H), 1.97 (dd, *J* = 7.21, 5.46 Hz, 1H), 2.13 (s, 1H), 2.95 (dd, *J* = 9.1, 7.21 Hz, 1H), 6.91 (m, 2H), 7.05-7.21 (m, 8H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 19.94, 24.21, 34.44, 64.77, 89.77, 126.24, 126.63, 127.71, 127.92, 128.42, 129.26,

136.12, 136.63. IR ($CHCl_3$) ν 3289, 3028, 2113, 1712, 1498, 762, 695$cm^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{14}$ $(M+Na)^+$ 241.0988, found 241.0989.



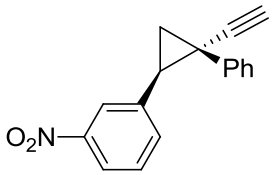

III-14b

$^1H$ NMR (400 MHz, $CDCl_3$): δ 1.89 (m, 2H), 2.11 (s, 1H), 2.85 (d, *J*=8.1Hz, 1H), 6.74 (d, *J*=8.2Hz, 2H), 7.09-7.17(m, 5H), 7.36 (d, *J*=8.5Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 20.04, 24.42, 33.79, 65.03, 89.37, 120.15, 126.92, 128.14, 129.24, 130.01, 130.82, 135.37, 136.24. IR ($CHCl_3$) ν 3294, 3027, 2925, 2114, 1712, 1489, 1009, 697$cm^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}Br$ $(M+Na)^+$ 319.0093, found 319.0094.



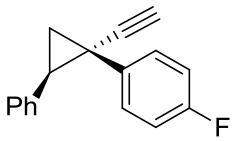

III-14c

$^1H$ NMR (400 MHz, $CDCl_3$): δ 1.89 (m, 2H), 2.11 (s, 1H), 2.89 (d, *J*=8.2Hz, 1H), 6.78 (t, *J*=8.77Hz, 2H), 6.85 (m, 2H), 7.08-7.17(m, 5H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 19.99, 24.05, 33.72, 64.91, 89.52, 114.63 (d, $^2J$=21.5 Hz), 126.74, 128.00, 129.13, 129.88 (d, $^3J$=8.5 Hz), 131.86 (d, $^4J$=3.1 Hz), 136.42, 161.42 (d, $^1J$=244.9 Hz). IR ($CHCl_3$) ν 3295, 3058, 2114, 1510, 1218, 836, 697$cm^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}F$ $(M+Na)^+$ 259.0894, found 259.0892.



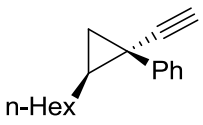

III-14d

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.95 (dd, *J*=8.85, 5.97Hz, 1H), 2.04 (t, *J*=6Hz, 1H), 2.12 (s, 1H), 2.96 (t, *J*=7.4Hz, 1H), 7.05-7.25 (m, 7H), 7.73 (s, 1H), 7.85 (d, *J*=7.8Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 19.83, 25.04, 33.57, 65.48, 88.67, 121.29, 123.02, 127.18, 128.26, 128.52, 129.19, 134.36, 135.57, 138.63, 147.72. IR ($CHCl_3$) ν 3294, 3027, 2356, 2116, 1527, 1347, 693cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}NO_2$ $(M+Na)^+$ 286.0839, found 286.0837.




III-14e

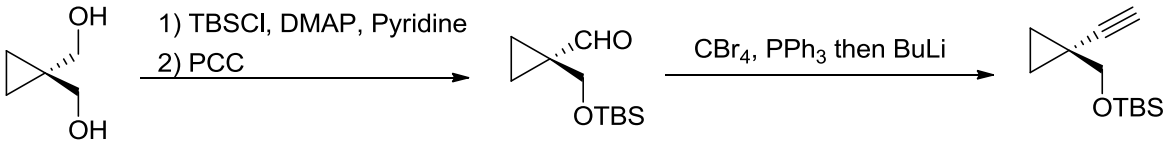
$^1$H NMR (500 MHz, $CDCl_3$): δ 1.94-2.00 (m, 2H), 2.20 (s, 1H), 3.02 (dd, *J*=9.0, 7.5Hz, 1H), 6.89-6.92 (m, 2H), 6.98 (d, *J*=12.0Hz, 2H), 7.16-7.23 (m, 5H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 20.21, 23.76, 34.50, 65.23, 89.67, 115.02 ($^2J$ = 21.4 Hz), 126.60, 128.04, 128.55, 131.09 ($^3J$ = 8.1Hz), 132.76 ($^4J$ = 3.1Hz), 136.07, 161.71 ($^1J$=244 Hz); IR ($CHCl_3$) ν 3300, 2114, 1509, 1221, 907, 731 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}F$ $(M+Na)^+$ 259.0894, found 259.0898.




III-14f

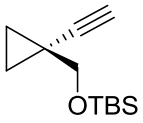
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.70 (m, 1H), 0.82 (t, *J*=7.4Hz, 3H), 1.10-1.33 (m, 10H), 1.38 (dd, *J*=8.8, 4.9Hz, 1H), 1.53 (m, 1H), 1.96 (s, 1H), 7.23 (m, 1H), 7.30 (m, 2H), 7.37 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 14.01, 19.90, 20.69, 22.49, 28.72, 28.92, 29.14, 29.99, 31.63, 63.69, 90.67, 126.67, 128.13, 129.10, 137.95. IR ($CHCl_3$) ν 3310, 2927, 2856, 2114, 1448, 909, 733, 698cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{22}$ $(M+H)^+$ 227.1794, found 227.1792.

Alkynyl cyclopropane **4h** was prepared in three steps following literature procedures.



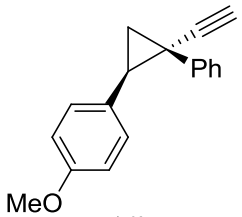

1) S. Zhou, M. N. Prichard, J. Zemlicka, *Tetrahedron*, 2007, **63**, 9406.

2) E. J. Corey and P. L. Fuchs, Tetrahedron *Lett.*, 1972, **13**, 3769.




III-14h

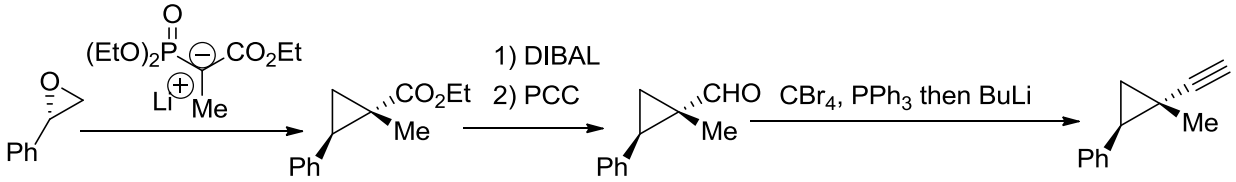
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.81 (m, 2H), 0.85 (m, 2H), 0.90 (s, 9H), 1.88 (s, 1H), 3.64 (s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ -5.31, 11.91, 13.58, 18.38, 25.88, 65.09, 66.10, 87.92. IR ($CHCl_3$) ν 3316, 2930, 2896, 2115, 1102, 835 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{12}H_{22}OSi$ $(M+Na)^+$ 233.1332, found 233.1325.




III-14i

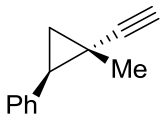
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.83 (m, 2H), 2.08 (s, 1H), 2.85 (t, *J*=8Hz, 1H), 3.68 (s, 3H), 6.61 (d, *J*=8.7Hz, 2H), 6.80 (d, *J*=8.6Hz, 2H), 7.04-7.16 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 20.08, 23.83, 33.96, 55.07, 64.65, 89.94, 113.22, 126.54, 127.92, 128.15, 129.16, 129.49, 136.81, 158.03. IR ($CHCl_3$) ν 3286, 3006, 2935, 2112, 1712, 1513, 697cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{16}O$ $(M+Na)^+$ 271.1093, found 271.1094.

Alkynyl cyclopropane **4j** was prepared in four steps following literature procedures.




1) C. D. Bray, F. Minicone , *Chem. Commun.*, 2010, **46**, 5867.

2) E. J. Corey and P. L. Fuchs, Tetrahedron *Lett.*, 1972, **13**, 3769.



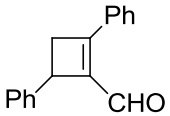

III-14j

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.09 (dd, *J*=6.82, 5.07Hz, 1H), 1.39 (dd, *J*=8.77, 4.87Hz, 1H), 1.94 (s, 1H), 2.53 (t, *J*=8.5 Hz, 1H), 7.18-7.31 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 13.00,

18.82, 19.91, 31.23, 63.51, 91.17, 126.51, 128.13, 129.15, 136.98. IR ($CHCl_3$) ν 2923, 2854, 2341, 1460, 1166, 736$cm^{-1}$. HRMS (ESI) m/z calcd for $C_{12}H_{12}(M+H)^+$ 157.1017, found 157.1011.

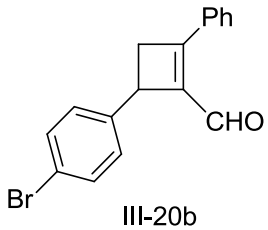
**General procedure for the ring expansion of alkynyl cyclopropanes to cyclobutene aldehydes:**

To a 4 mL vial equipped with a stirring bar, azide 13c (0.2 mmol), and alkyne (0.2 mmol) was added CuTc (0.02 mmol), AgOTf (0.02 mmol) and toluene (2 mL). The reaction mixture was stirred in the capped vial at room temperature for 4-8 h until starting material was completely consumed as determined by TLC analysis. Several drops of water and 20 mg alumina oxide were added to the reaction mixture. The resulting suspension was stirred for 1 h until hydrolysis of imine was completed. Solvents were removed under vacuum. The residue was purified by flash column chromatography with ethyl acetate/hexane (1/10 to 1/4) as eluent to give the corresponding cyclobutene aldehyde.



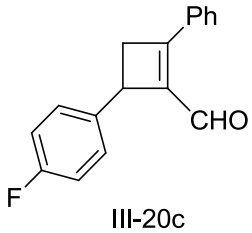
III-20a

$^1$H NMR (400 MHz, $CDCl_3$): δ 2.77 (dd, *J*=15.6, 2.8Hz, 1H), 3.38 (dd, *J*=15.6, 5.1Hz, 1H), 4.27 (d, *J*=5.1Hz, 1H), 7.24 (m, 3H), 7.31 (m, 2H), 7.46 (m, 5H), 10.04 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ.37.79, 41.84, 109.76, 126.73, 126.80, 128.44, 128.51, 128.58, 128.87, 131.09, 185.83. IR ($CHCl_3$) ν 3029, 2918, 1658, 907, 728$cm^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{14}O$ $(M+Na)^+$ 257.0937, found 257.0935.



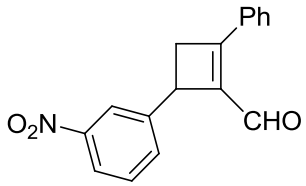

III-20b

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.74 (dd, *J*=15.6, 2.0Hz, 1H), 3.38 (dd, *J*=15.6, 5.1Hz, 1H), 4.22 (d, *J*=5.0Hz, 1H), 7.18 (d, *J*=8.6Hz, 2H), 7.41-7.52(m, 5H), 7.75 (m, 2H), 10.05 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 37.84, 41.46, 120.72, 128.75, 128.81, 129.19, 131.50, 131.88, 133.07, 139.29, 140.79, 159.45, 185.23. IR ($CHCl_3$) ν 2921, 1656, 1402, 907, 728cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}BrO$ $(M+Na)^+$ 335.0042, found 335.0038.



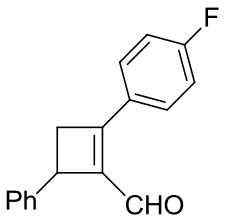

III-20c

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.72 (dd, *J*=15.6, 2.1Hz, 1H), 3.37 (dd, *J*=15.6, 5.2Hz, 1H), 4.21 (dd, *J*=5.1, 2.0Hz, 1H), 6.99 (m, 2H), 7.25 (m, 2H), 7.47 (m, 3H), 7.74 (m, 2H), 10.04 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 37.87, 41.07, 115.35 (d, $^{2}J$=20.7Hz), 128.26 (d, $^{3}J$=8.5Hz), 128.51, 128.93, 131.21, 132.9, 136.95 (d, $^{4}J$=3.1Hz), 139.34, 159.01, 161.71 (d, $^{1}J$=224.9Hz) 185.69. IR ($CHCl_3$) ν 2918, 2849, 1709, 1508, 1220, 692cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}FO$ $(M+Na)^+$ 275.0843, found 275.0839.



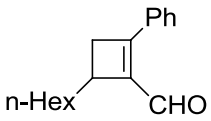

III-20d

$^1$H NMR (400 MHz, $CDCl_3$): δ 2.81 (dd, *J*=15.6, 1.6Hz, 1H), 3.46 (dd, *J*=15.6, 5.6Hz, 1H), 4.36 (dd, *J*=5.1, 1.8Hz, 1H), 7.44-7.55 (m, 4H), 7.65 (d, *J*=8.0Hz, 1H), 7.74 (m, 2H), 8.10 (d, *J*=8.0Hz, 1H), 8.14 (m, 1H),10.14 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 37.40, 41.15, 121.69, 121.85, 128.57, 129.04, 129.46, 131.53, 132.53, 133.29, 138.47, 143.43, 148.51, 159.18, 185.10. IR ($CHCl_3$) ν 3017, 2116, 1627, 1327, 693cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}NO_3$ $(M+Na)^+$ 302.0788, found 302.0783.




III-20e

$^1$H NMR (500 MHz, $CDCl_3$): 2.73 (dd, *J*=15.0, 1.5Hz, 1H), 3.34 (dd, *J*=16.0, 5.5Hz, 1H), 4.26(dd, *J*=5.0, 1.5Hz, 1H), 7.12-7.16(m, 2H), 7.22-7.25 (m, 1H), 7.28-7.33(m, 4H), 7.82-7.85(m, 2H), 9.86(s, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 38.06, 42.07, 116.23 ($^2J$ =21.8Hz), 127.00, 127.05, 128.85, 129.67 ($^4J$ =3.1Hz), 131.00 ($^3J$=8.6Hz), 138.68, 141.43, 157.47, 164.54 ($^1J$=251.9Hz), 186.2; IR ($CHCl_3$) ν 1598, 1231, 1158, 906 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{13}FO$ $(M+Na)^+$ 275.0843, found 275.0834.

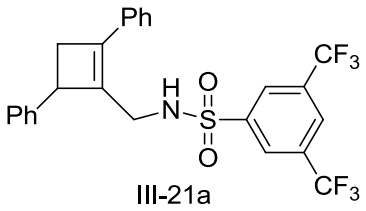



III-20f

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J*=6.6Hz, 3H), 1.18-1.56 (m, 10H), 2.43 (d, *J*=15.4Hz, 1H), 2.99 (dd, *J*=15.4, 4.7Hz, 1H), 3.06 (m, 1H), 7.42 (m, 3H), 7.64 (m, 2H), 10.05 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 14.08, 22.64, 27.46, 29.42, 31.83, 33.21, 34.21, 38.11, 128.21, 128.78, 130.58, 133.57, 141.83, 157.85, 186.06. IR($CHCl_3$) ν 2926, 2136, 1656, 1279, 758cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{22}O$ $(M+Na)^+$ 265.1563, found 265.1559.

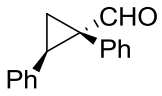
**General procedure for the ring expansion of alkynyl cyclopropanes to cyclobutene sulfonamides:**

To a 4 mL vial equipped with a stirring bar, azide (0.2 mmol), and alkyne (0.2 mmol) was added CuTc (0.02 mmol), AgOTf (0.02 mmol) and toluene (2 mL). The reaction mixture was stirred in the capped vial at room temperature for 1-8 h until starting material was completely consumed as determined by TLC analysis. The reaction mixture was cooled to -78$^{o}$C and a solution of $LiAlH_4$ in THF (2 mL, 0.2M, 0.4 mmol) was added slowly. The mixture was stirred at the same temperature for 1 h and warmed up to 0 $^{o}$C. The reaction was quenched by careful addition of methanol followed by water. The solid was removed by filtration through a thin silica gel pad. The resulting solution was concentrated under reduced pressure to afford an oily residue which was purified by column chromatography to give the corresponding cyclobutene sulfonamide.




III-21a

$[\alpha]_D^{20}$ =-23 (c=0.5, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): δ 2.50 (d, *J*=13.1Hz, 1H), 2.98 (dd, *J*=13.1, 4.9Hz, 1H), 3.57 (d, *J*=4.3Hz, 1H), 3.82 (dd, *J*=17.2, 5.3Hz, 1H), 4.20 (dd, *J*=15.2, 5.5Hz, 1H), 4.67 (t, *J*=5.5Hz, 1H), 7.08 (m, 2H), 7.17-7.39 (m, 8H), 8.00 (s, 1H), 8.18 (s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 36.75, 40.62, 43.99, 122.36 (d, $^1J$=272.6Hz), 126.17, 126.28, 126.55, 127.06, 127.29, 128.48, 128.69, 128.88, 132.77 (d, $^2J$=34.6Hz), 133.52, 136.01, 140.97, 142.88, 143.39. IR ($CHCl_3$) ν 3378, 2256, 1279, 908, 733cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{25}H_{19}F_6NO_2S$ $(M+Na)^+$ 534.0933, found 534.0928.

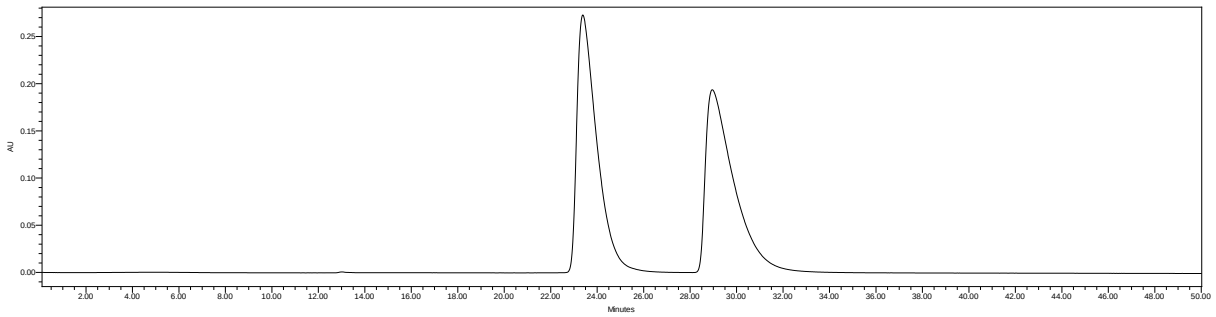



III-13

Racemic and chiral cyclopropanes **8** are known compounds and were prepared according to the following reference.

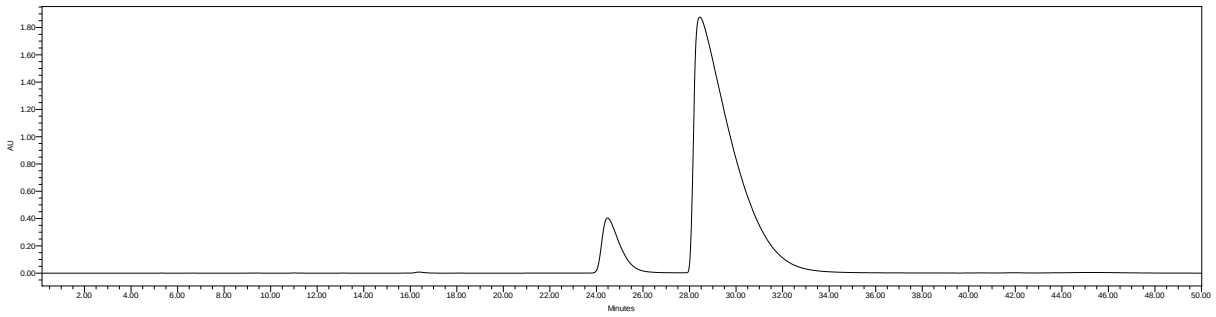
S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher and V. V. Fokin, *J. Am. Chem. Soc.*, 2009, **131**, 18034.

Racemic **III-14a**:



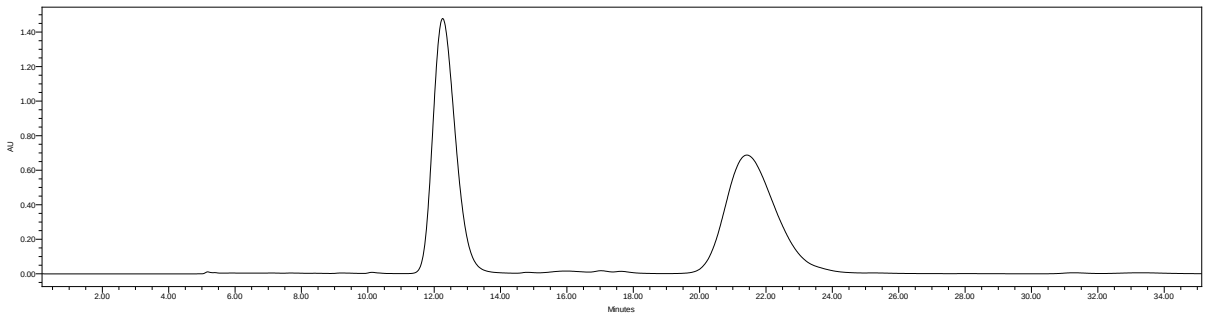

| | Retention Time | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 23.382 | 16286193 | 49.97 | 272843 |
| 2 | 28.957 | 16304775 | 50.03 | 193596 |

Chiral **III-14a** $[\alpha]_D^{20}$ =+130, (c=1, MeOH):



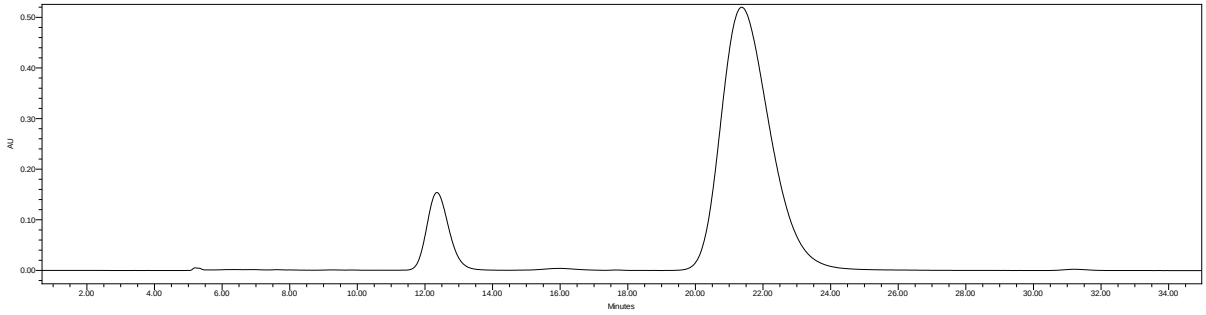

| | Retention Time | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 24.479 | 21520024 | 9.49 | 402980 |
| 2 | 28.442 | 205127815 | 90.51 | 1863761 |

Racemic **III-21a**:

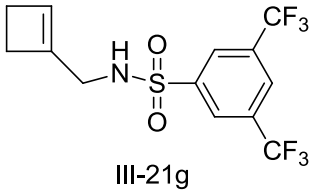



| | Retention Time | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 12.257 | 69966637 | 49.77 | 1476051 |
| 2 | 21.423 | 70602059 | 50.23 | 680665 |

Chiral **III-21a**:

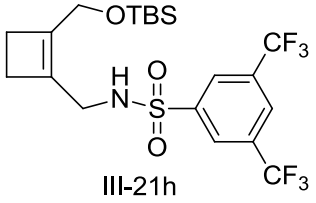



| | Retention Time | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 12.354 | 5939471 | 10.21 | 143624 |
| 2 | 21.370 | 52255960 | 89.79 | 519707 |



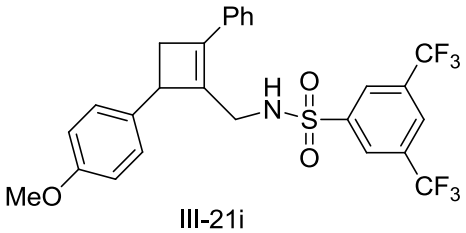
III-21g

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.28 (m, 4H), 3.69 (m, 2H), 4.80 (t, *J*=5.5Hz, 1H), 5.79 (m, 1H), 8.08 (s, 1H), 8.33 (s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 26.77, 29.74, 43.30, 122.44 (d, $^{1}J$=273.3Hz), 126.14, 127.42, 131.67, 132.92 (d, $^{2}J$=34.6Hz), 142.72, 143.27 . IR ($CHCl_3$) v 3303, 2929, 2258, 1278, 1142, 905, 730cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{13}H_{11}F_6NO_2S$ $(M+Na)^+$ 382.0307, found 382.0308.



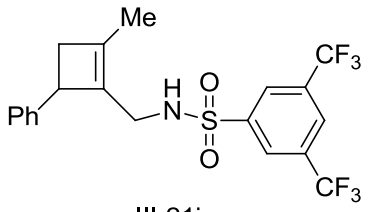
III-21h

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 6H), 0.92 (s, 9H), 2.09 (d, *J*=19Hz, 4H), 3.68 (br s, 2H), 4.01 (br s, 2H), 6.74 (m, 1H), 8.04 (s, 1H), 8.36 (s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ -5.57, 18.56, 25.91, 26.49, 27.53, 42.12, 62.00, 125.73, 127.29, 132.49, 132.83, 134.79, 141.00, 143.73. IR ($CHCl_3$) v 2367, 2331, 1724, 1280, 908, 734cm$^{-1}$.



III-21i

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.43 (d, *J*=13.1Hz, 1H), 2.94 (dd, *J*=13.1, 4.9Hz, 1H), 3.50 (d, *J*=4.1Hz, 1H), 3.77 (s, 3H), 3.82 (m, 1H), 4.20 (dd, *J*=15.2, 5.5Hz, 1H), 4.88 (t, *J*=5.5Hz, 1H), 6.78 (d, *J*=8.6Hz, 2H), 7.00 (d, *J*=8.7Hz, 2H), 7.24-7.37 (m, 5H), 8.00 (s, 1H), 8.20 (s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 37.02, 40.47, 43.20, 55.16, 114.23, 126.15, 126.25, 127.29, 127.35 (d, $^{1}J$=240.3Hz), 127.56, 128.38, 132.54, 132.82, 132.88, 136.18, 133.57, 142.89, 143.09, 158.57. IR ($CHCl_3$) ν 3278, 2839, 2256, 1358, 729cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{26}H_{21}F_6NO_3S$ $(M+Na)^+$ 564.1039, found 564.1041.

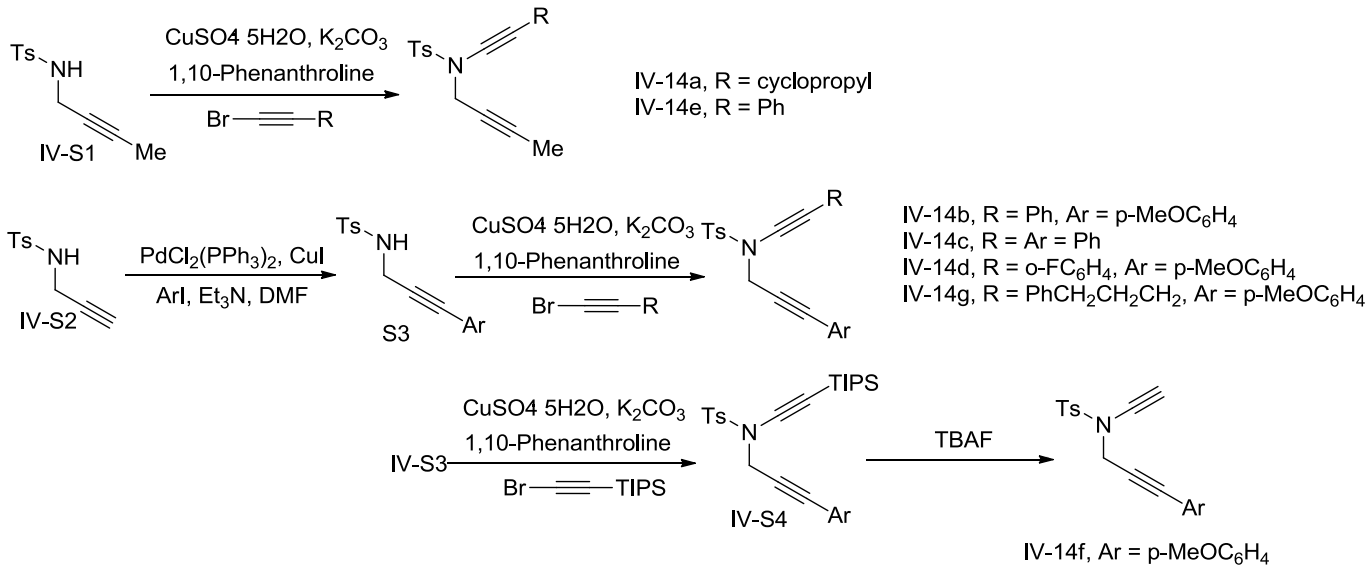



III-21j

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.74 (s, 3H), 2.12 (d, *J*=13.5Hz, 1H), 2.58 (dd, *J*=17.7, 4.5Hz, 1H), 3.35 (s, 1H), 3.53 (dd, *J*=20.5, 5.5Hz, 1H), 3.79 (dd, *J*=14.8, 5.3Hz, 1H), 4.52 (t, *J*=5.6Hz, 1H), 6.99 (m, 2H), 7.14-7.26 (m, 3H), 8.04 (s, 1H), 8.21 (s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 13.92, 39.98, 40.41, 44.48, 122.44 (d, $^{1}J$=274.1Hz), 126.06, 126.31, 126.74, 127.24, 128.71, 132.75 (d, $^{2}J$=34.6Hz), 136.23, 141.43, 143.22, 144.10. IR ($CHCl_3$) ν 3296, 2916, 1359, 1278, 1141, 906, 712cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{20}H_{17}F_6NO_2S$ $(M+Na)^+$ 472.0776, found 472.0761.

## CHAPTER IV RODIUM-CATALYZED OXIDATIVE CYCLOISOMERZATION

### General strategy for the synthesis of diyne substrates:




Sulfonamide **IV-S1** is a known compound [1] and sulfonamide **IV- S2** is commercially available.

### General procedure for the synthesis of IV-S3 from IV-S2[2]:

To a mixture of $PdCl_2(PPh_3)_2$ (190 mg, 0.271 mmol), CuI (114 mg, 0.598 mmol), aryliodide (13.6 mmol), and *N*-(2-propynyl)-*p*-toluenesulfonamide **IV-S2** (3.14 g, 15.0mmol) was added $Et_3N$ (40 mL) and DMF (5 mL) and the solution was stirred for 19 h at 50 °C. The volatile solvents were removed under vacuum and the residue was poured into water. This was extracted with $CH_2Cl_2$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (eluent: EtOAc and hexane) to afford the desired substrate **IV-S3**.

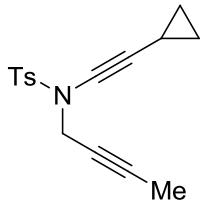
### General procedure for the coupling of sulfonamide (IV-S1 or IV-S3) and 1-bromoalkyne[3]:

To a mixture of a sulfonamide (1.0 equiv), $K_2CO_3$ (2.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.10 equiv), and 1,10-phenanthroline (0.20 equiv) in a reaction vial was added a solution of a respective 1-bromoalkyne (1.1 equiv, 1.0 M) in toluene. The reaction mixture was capped and heated in an oil bath at 65-75 °C for 32 h while being monitored with TLC analysis. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc and filtered through Celite, and the filtrate was concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (eluent: EtOAc and hexane) to afford the desired diyne substrate.

**General procedure for the removal of TIPS:**

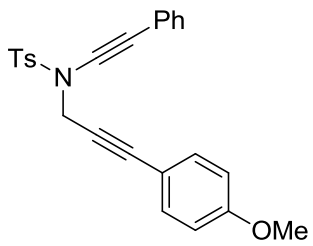
To a solution of N-((triisopropylsilyl) ethynyl) benzenesulfonamide **IV-S4** (2 mmol) in THF (20 mL) was added *n*-tetrabutyl ammonium fluoride (1.0M in THF, 3 mL, 3 mmol) at 0 °C, and the resulting mixture was stirred at rt for 1 h. The crude products were purified by flash column chromatography using silica gel (eluent: EtOAc and hexane) to afford the desired diyne substrate.

**Characterization data for diyne substrates:**



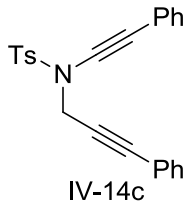

IV-14a

The product was obtained as an oil (120 mg, 71% in one step form sulfonamide **S1)**. $^1$H NMR (400 MHz, $CDCl_3$): δ 0.65 (m, 2H), 0.79 (m, 2H), 1.31 (m, 1H), 1.67 (t, *J* = 2.53 Hz, 3H), 2.45 (s, 3H), 4.13 (q, *J* = 2.53 Hz, 2H), 7.33 (d, *J* = 7.99 Hz, 2H), 7.81 (d, *J* = 8.19 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ -0.75, 3.40, 8.84, 21.60, 42.49, 68.37, 71.48, 75.10, 82.35, 128.18, 129.21, 134.43, 144.35. IR ($CHCl_3$) ν 690, 755, 1340, 1710, 2234cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{16}H_{17}NO_2S$ $(M+Na)^+$ 287.0980, found 287.0971.



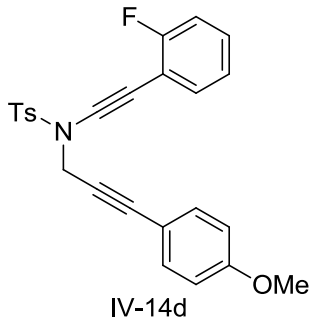

IV-14b

The product was obtained as an oil (300 mg, 43% in two steps form sulfonamide **S2)**. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.77 (s, 3H), 4.53 (s, 2H), 6.76 (d, *J* = 8.38 Hz, 2H), 7.11 (d, *J* = 8.38 Hz, 2H), 7.27 (m, 6H), 7.38 (m, 1H), 7.90 (d, *J* = 8.19 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.50, 42.93, 55.17, 71.06, 79.66, 82.05, 86.42, 113.69, 113.87, 113.98, 122.57, 127.84, 128.13, 129.49, 131.43, 133.04, 134.21, 144.75, 159.70. IR ($CHCl_3$) ν 691, 756, 1170, 1710, 2925 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{25}H_{21}NO_3S$ $(M+Na)^+$ 438.1134, found 438.1143.




IV-14c

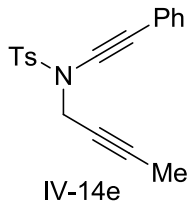
The product was obtained as an oil (80 mg, 38% in two steps form sulfonamide **S2)**. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.57 (s, 2H), 7.17 (d, *J* = 7.99 Hz, 2H), 7.22-7.34 (m, 7H), 7.39 (m, 3H), 7.92 (d, *J* = 8.19 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.55, 42.88, 71.15, 81.12, 82.00, 86.47, 116.81, 122.62, 127.94, 128.12, 128.24, 128.56, 129.55, 129.57, 131.55, 131.62, 134.27, 144.86. IR ($CHCl_3$) ν 692, 1170, 1710, 2235 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{24}H_{19}NO_2S$ $(M+Na)^+$ 408.1029, found 408.1038.




IV-14d

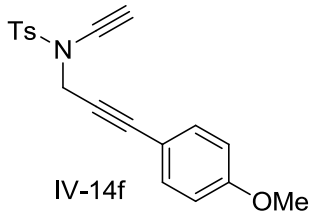
The product was obtained as a yellow solid (120 mg, 45% in two steps form sulfonamide **S2,** mp 72-74 °C). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.78 (s, 3H), 4.55 (s, 2H), 6.77 (d, *J* = 8.97 Hz, 2H), 7.09 (m, 4H), 7.27 (m, 3H), 7.38 (m, 1H), 7.94 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100

MHz): δ 21.49, 42.92, 55.16, 64.76, 79.42, 86.56, 86.75 (d, $J_{CF}$ = 3.07 Hz). 111.20 (d, $J_{CF}$ = 16.12 Hz), 113.65, 113.96, 115.31 (d, $J_{CF}$ = 20.73 Hz), 123.79 (d, $J_{CF}$ = 3.84 Hz), 128.18, 129.49, 129.54 (d, $J_{CF}$ = 6.14 Hz), 133.07, 133.23, 134.13, 144.87, 159.71, 162.54 (d, $J_{CF}$ = 251.06 Hz). IR ($CHCl_3$) ν 691, 748, 1362, 1711, 2225, 2923 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{25}H_{20}FNO_3S$ $(M+Na)^+$ 456.1040, found 456.1053.



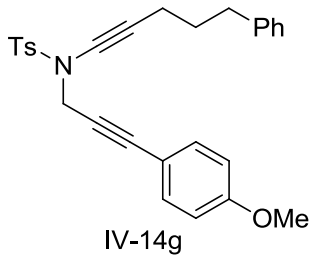
IV-14e

The product was obtained as an oil (82 mg, 75% in one step form sulfonamide **S1)**. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.65 (t, *J* = 2.53 Hz, 3H), 2.45 (s, 3H), 4.28 (q, *J* = 2.53 Hz, 2H), 7.23-7.40 (m, 7H), 7.89 (d, *J* = 8.19 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 3.43, 21.62, 42.58, 70.94, 71.23, 82.13, 82.83, 122.73, 127.80, 128.19, 128.23, 129.40, 131.40, 134.35, 144.68. IR ($CHCl_3$) ν 691, 748, 1120, 1350, 1710, 2950 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_2S$ $(M+Na)^+$ 346.0872, found 346.0877.



IV-14f

The product was obtained as an oil (65 mg, 32% in three steps form sulfonamide **S2)**. $^1H$ NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.79 (s, 1H), 3.79 (s, 3H), 4.46 (s, 2H), 6.76 (d, *J* = 8.97 Hz, 2H), 7.11 (d, *J* = 8.58 Hz, 2H), 7.29 (d, *J* = 8.19 Hz, 2H), 7.88 (d, *J* = 8.19 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 21.58, 42.52, 55.26, 59.56, 75.64, 79.35, 86.43, 113.73, 113.95, 128.21, 129.58, 133.16, 134.37, 144.90, 159.81. IR ($CHCl_3$) ν 691, 1360, 1712, 2230 $m^{-1}$. HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_3S$ $(M+Na)^+$ 362.0821, found 362.0872.



IV-14g

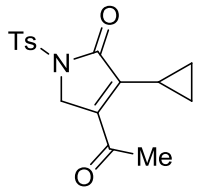
The product was obtained as an oil (95 mg, 44% in two steps form sulfonamide **S2)**. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.82 (m, 2H), 2.33 (t, *J* = 6.82 Hz, 2H), 2.36 (s, 3H), 2.69 (t, *J* = 7.60 Hz, 2H),

3.78 (s, 3H), 4.48 (s, 2H), 6.76 (d, *J* = 8.58 Hz, 2H), 7.12 (m, 4H), 7.19-7.31 (m, 5H), 7.92 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 17.72, 21.36, 30.21, 34.28, 42.74, 55.07, 70.29, 73.40, 79.90, 86.03, 113.58, 113.90, 125.61, 128.05, 128.08, 128.32, 129.30, 132.95, 134.17, 141.39, 144.43, 159.58. IR ($CHCl_3$) ν 691, 1360, 1723, 2238 $m^{-1}$. HRMS (ESI) m/z calcd for $C_{28}H_{27}NO_3S$ $(M+Na)^+$ 457.1712, found 457.1700.

**General procedure for the Rh-catalyzed oxidative cycloisomerization of diynes:**

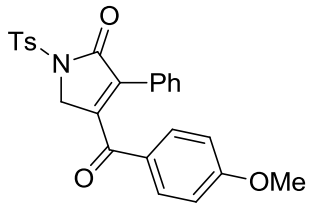
To a solution of $[Rh(CO)_2Cl]_2$ (4.0 mg, 5 mol %) in dioxane (4mL, 0.05M) was added $P[OCH(CF_3)_2]_3$ (20 mg, 20 mol %) and the mixture was stirred at room temperature for 5 min. The diyne substrate (0.2 mmol) and 3,5-dichloropyridine *N*-oxide (0.6 mmol) were then added sequentially. The reaction mixture was allowed to stir at 80 °C until the reaction was complete, as determined by TLC analysis. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel to afford the corresponding product.

**Characterization data for products from oxidative cycloisomerization of diynes:**



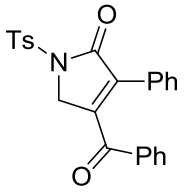

IV-15a

The product was obtained as an oil. $^1$H NMR (400 MHz, $CDCl_3$): δ 0.91 (m, 2H), 1.50 (m, 2H), 2.36 (m, 1H), 2.45 (m, 6H), 4.20 (s, 2H), 7.35 (d, *J* = 7.99 Hz, 2H), 7.93 (d, *J* = 8.19 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 7.77, 10.28, 21.70, 30.05, 49.33, 128.14, 129.85, 134.87, 144.50, 144.21, 145.49, 166.73, 194.68. IR ($CHCl_3$) ν 667, 758, 1170, 1630, 1558, 2853, 2925 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{16}H_{17}NO_4S$ $(M+Na)^+$ 319.0878, found 319.0855.



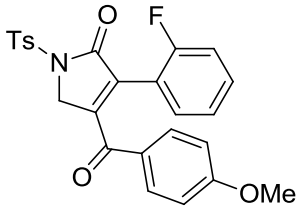

IV-15b

The product was obtained as a yellow solid (mp 168-170 °C). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.79 (s, 3H), 4.77 (s, 2H), 6.75 (d, *J* = 8.77 Hz, 2H), 7.18 (m, 2H), 7.36 (m, 5H), 7.68 (d, *J* = 8.77 Hz, 2H), 8.04 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.70, 50.76, 55.53, 114.09, 127.03, 128.17, 128.32, 128.36, 128.75, 129.07, 129.55, 129.87, 132.04, 135.04, 145.55, 148.52, 164.68, 166.70, 190.77. IR ($CHCl_3$) ν 667, 758, 1170, 1610, 2855, 2925 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{25}H_{21}NO_5S$ $(M+Na)^+$ 470.1038, found 470.1032.



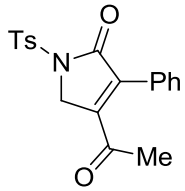

IV-15c

The product was obtained as a yellow solid (mp 158-160 °C). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 4.79 (s, 2H), 7.16 (m, 3H), 7.27 (m, 4H), 7.37 (d, *J* = 7.99 Hz, 2H), 7.45 (m, 1H), 7.67 (d, *J* = 8.38 Hz, 2H), 8.04 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.71, 50.63, 128.31, 128.36, 128.62, 128.71, 129.23, 129.45, 129.69, 129.90, 134.18, 134.43, 134.82, 136.37, 145.63., 147.65, 166.66, 192.56. IR ($CHCl_3$) ν 667, 758, 1170, 1610, 2845, 3100 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{24}H_{19}NO_4S$ $(M+Na)^+$ 440.0927, found 440.0934.



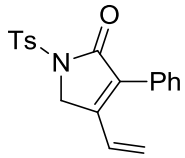

IV-15d

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.78 (s, 3H), 4.84 (s, 2H), 6.75 (m, 3H), 7.20 (m, 1H), 7.38 (m, 1H), 7.36 (d, *J* = 8.58 Hz, 2H), 7.45 (m, 1H), 7.64 (d, *J* = 8.58 Hz, 2H), 8.03 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.70, 51.00, 55.49, 113.81, 115.49 (d, $J_{CF}$ = 21.5 Hz), 117.26, 124.15 (d, $J_{CF}$ = 3.84 Hz), 127.29, 128.35, 129.90, 130.64 (d, $J_{CF}$ = 2.30 Hz), 130.71, 131.59 (d, $J_{CF}$ = 8.45 Hz), 131.76, 134.75, 145.63, 150.30 (d, $J_{CF}$ = 6.00 Hz), 159.63 (d, $J_{CF}$ = 250.29 Hz), 164.40, 166.30, 189.41 (d, $J_{CF}$ = 2.30 Hz). IR ($CHCl_3$) ν 667, 758, 1170, 1610, 2855, 2925$cm^{-1}$. HRMS (ESI) m/z calcd for $C_{25}H_{20}FNO_5S$ $(M+Na)^+$ 488.0938, found 488.0956.



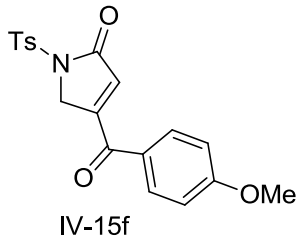

IV-15e

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.44 (s, 3H), 4.65 (s, 2H), 7.28-7.36 (m, 5H), 7.43 (m, 2H), 8.00 (d, *J* = 8.58 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.70, 29.57, 49.65, 128.06, 128.32, 128.68, 129.43, 129.77, 129.87, 130.22, 139.84, 145.59, 147.33, 167.22, 196.50. IR ($CHCl_3$) ν 667, 758, 1170, 1720, 2853, 2925 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_4S$ $(M+Na)^+$ 378.0770, found 378.0778.



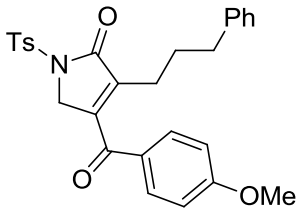

IV-18

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 4.67 (s, 2H), 5.56 (d, *J* = 10.92 Hz, 1H), 5.73 (d, *J* = 17.74 Hz, 1H), 6.85 (dd, *J* = 17.74, 11.11 Hz, 1H), 7.29-7.42 (m, 7H), 8.01 (d, *J* = 8.19 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.68, 49.16, 121.99, 128.22, 128.45, 128.66, 128.94, 129.43, 129.55, 129.78, 135.36, 132.23, 145.17, 148.20, 167.96. IR ($CHCl_3$) ν 667, 758, 1712, 2855, 3008 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{17}NO_3S$ $(M+Na)^+$ 362.0821, found 362.0827.




IV-15f

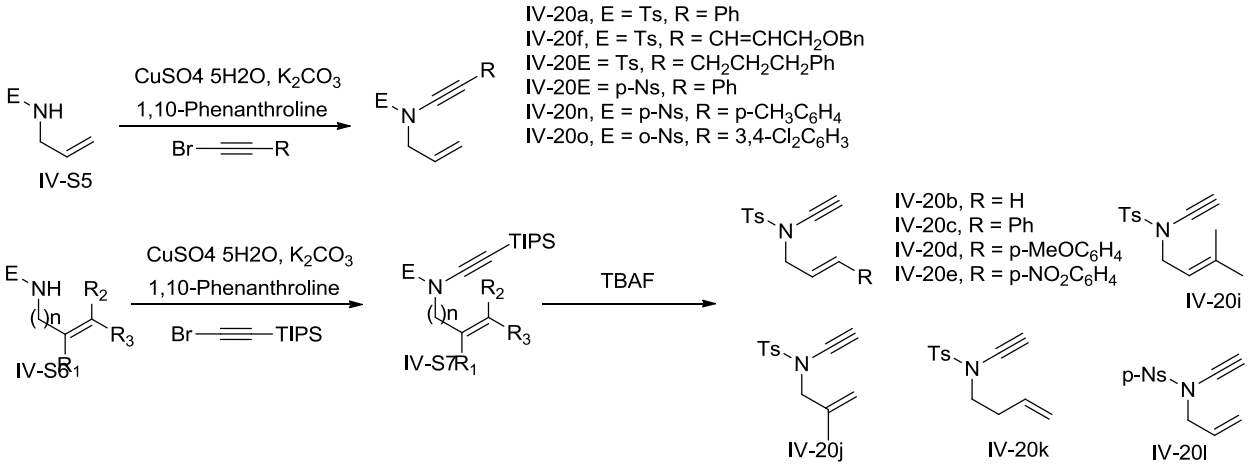
The product was obtained as a yellow solid (mp 154-155 °C). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.91 (s, 3H), 4.79 (s, 2H), 6.36 (t, *J* = 1.95 Hz, 1H), 6.98 (d, *J* = 8.97 Hz, 2H), 7.37 (d, *J* = 8.58 Hz, 2H), 7.84 (d, *J* = 8.97 Hz, 2H), 8.00 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.69, 51.91, 55.66, 114.32, 128.12, 128.33, 129.71, 129.89, 131.78, 134.98, 145.55, 154.17, 164.69, 167.14, 187.72. IR ($CHCl_3$) ν 667, 758, 1720, 2723, 2885 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_5S$ $(M+Na)^+$ 394.0720, found 394.0722.




IV-15g

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.71 (m, 2H), 2.18 (m, 2H), 2.41 (m, 2H), 2.45 (s, 3H), 3.91 (s, 3H), 4.62 (s, 2H), 6.95 (d, *J* = 8.97 Hz, 4H), 7.12 (m, 3H), 7.37 (d, *J* = 8.58 Hz, 2H), 7.75 (d, *J* = 8.77 Hz, 2H), 7.99 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.70, 24.85, 28.87, 35.48, 50.97, 55.67, 113.79, 114.38, 125.77, 128.14, 128.18, 128.52, 129.86, 131.73, 135.05, 138.09, 140.99, 145.43, 148.65, 164.87, 167.94, 190.46. IR ($CHCl_3$) ν 667, 758, 1720, 2623, 2893 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{28}H_{27}NO_5S$ $(M+Na)^+$ 489.1610, found 489.1577.

**General strategy for the synthesis of enyne substrates:**




**IV-S5** is commercially available and **IV-S6** is a known compound.[4,5]

**General procedure for the coupling of sulfonamide (IV-S5 or IV- S6) and 1-bromoalkyne[3]:**

To a mixture of an amide (1.0 equiv), $K_2CO_3$ (2.0 equiv), $CuSO_4{\cdot}5H_2O$ (0.10 equiv), and 1,10-phenanthroline (0.20 equiv) in a reaction vial was added a solution of 1-bromoalkyne (1.1 equiv, 1.0 M) in toluene. The reaction mixture was capped and heated in an oil bath at 65-75 °C for 32 h while being monitored with TLC analysis. Upon completion, the reaction mixture was cooled

to room temperature and diluted with EtOAc and filtered through Celite, and the filtrate was concentrated under vacuum. The crude products were purified by silica gel flash column chromatography (eluent: EtOAc and hexane) to afford the desired enyne substrate.

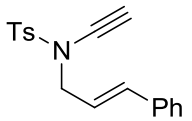
(*Note*: $K_3PO_4$ was used as the base for the preparation of substrates **IV-20d** and **IV-20e**.)

**General procedure for the removal of TIPS:**

To a solution of N-((triisopropylsilyl) ethynyl) benzenesulfonamide **IV-S7** (2 mmol) in THF (20 mL) was added *n*-tetrabutyl ammonium fluoride (1.0M in THF, 3 mL, 3 mmol) at 0 °C, and the resulting mixture was stirred at rt for 1 h. The crude products were purified by flash column chromatography using silica gel (eluent: EtOAc and hexane) to afford the desired diyne substrate.

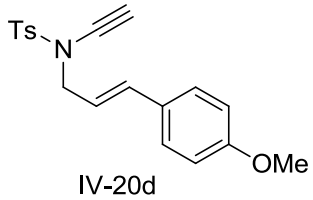
**Characterization data for enyne substrates:**

Substrates **IV-a**,[6] **IV-b**,[7] **7j**,[8] **IV-k**,[7] and **IV-l**[7] are known compounds.




IV-20c

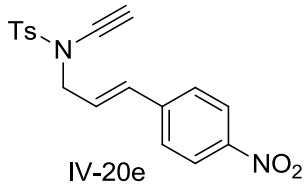
The product was obtained as an oil (80 mg, 64% in two steps form sulfonamide **S6)**. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.73 (s, 1H), 4.13 (d, *J* = 6.63 Hz, 2H), 6.02 (dt, *J* = 15.79, 6.82 Hz, 1H), 6.51 (d, *J* = 15.79 Hz, 1H), 7.22-7.35 (m, 7H), 7.82 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.58, 53.75, 59.38, 76.05, 121.34, 126.58, 127.78, 128.12, 128.51, 129.75, 134.76, 135.24, 135.87, 144.80. IR ($CHCl_3$) ν 682, 737, 1350, 1610, 3100 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{18}H_{17}NO_2S$ $(M+Na)^+$ 334.0872, found 334.0874.




IV-20d

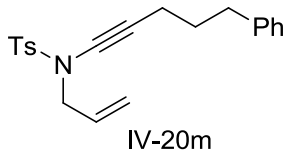
The product was obtained as an oil (67 mg, 46% in two steps form sulfonamide **S6)**. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.73 (s, 1H), 3.80 (s, 3H), 4.11 (d, *J* = 6.80 Hz, 2H), 5.89 (dt, *J* = 15.60, 6.80 Hz, 1H), 6.47 (d, *J* = 15.60 Hz, 1H), 6.82 (d, *J* = 8.80 Hz, 2H), 7.21 (d, *J* = 8.80 Hz, 2H),

7.32 (d, *J* = 8.01 Hz, 2H), 7.81 (d, *J* = 8.01 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ. 21.60, 53.96, 55.27, 59.35, 76.12, 113.92, 119.02, 127.79, 127.85, 128.65, 129.72, 134.85, 144.72, 159.59. IR ($CHCl_3$) 707.16, 813.36, 912.33, 1089.55, 1212.25, 151.86, 2134.06, 3292.51 ν $cm^{-1}$. HRMS (ESI) m/z calcd $C_{19}H_{19}NO_3S$ $(M+Na)^+$ 364.0984, found 364.0969.



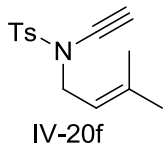

IV-20e

The product was obtained as an oil (140 mg, 60% in two steps form sulfonamide **S6)**. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 2H), 7.85 – 7.81 (m, 2H), 7.45 – 7.40 (m, 2H), 7.38 – 7.33 (m, 2H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.18 (dd, *J* = 6.4, 1.4 Hz, 2H), 2.77 (s, 1H), 2.44 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 147.49, 145.33, 142.48, 134.78, 132.81, 130.11, 128.02, 127.42, 126.84, 124.18, 76.14, 59.84, 53.56, 21.88. IR ( film ): 3304, 2135, 1596, 1517, 1365, 1341, 1266, 1167, 1109, 1090, 1017, 970, 918, 859, 832, 814, 735, 712, 676 $cm^{-1}$. IR ($CHCl_3$) ν 680, 737, 1352, 1610, 3108 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2O_4S$ $(M+Na)^+$ 379.0723, found 379.0724.




IV-20m

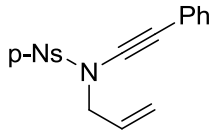
The product was obtained as an oil (110 mg, 82% in one step form sulfonamide **S5)**. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.94 (quint, *J* = 6.82 Hz, 2H), 2.26 (t, *J* = 6.82 Hz, 2H), 2.42 (s, 3H), 2.65 (t, *J* = 7.60 Hz, 2H), 3.94 (d, *J* = 6.73 Hz, 2H), 5.21 (m, 2H), 5.74 (m, 1H), 7.12-7.33 (m, 7H), 7.79 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 17.80, 21.54, 30.44, 34.52, 54.20, 69.91, 73.50, 119.59, 125.78, 127.65, 128.24, 128.42, 129.57, 131.16, 134.67, 141.54, 144.35. IR ($CHCl_3$) ν 691, 1370, 1440, 1723, 2238 $m^{-1}$. HRMS (ESI) m/z calcd for $C_{21}H_{23}NO_2S$ $(M+Na)^+$ 353.1449, found 353.1421.




IV-20f

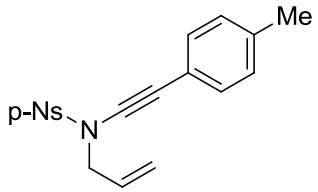
The product was obtained as an oil (35 mg, 33% in two steps form sulfonamide **S6)**. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 3H), 1.68 (s, 3H), 2.45 (s, 3H), 2.69 (s, 1H), 3.96 (d, *J* =7.61 Hz, 2H),

5.11-5.16 (m, 1H), 7.34 (d, *J* = 8.41 Hz, 2H), 7.79 (d, *J* = 8.80 Hz, 2H);$^{13}$C NMR ($CDCl_3$, 100 MHz): δ 17.96, 21.60, 25.64, 49.18, 58.78, 76.38, 116.69, 127.65, 129.60, 134.83, 139.20, 144.50. IR ($CHCl_3$) ν 728.26, 813.57, 845.93, 1088.62, 1165.53, 1293.63, 2359.67 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_2S$ $(M+Na)^+$ 286.0878, found 286.0866.



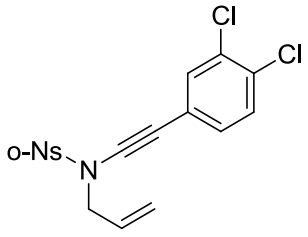

IV-20j

The product was obtained as a yellow solid (200 mg, 45% in one step form sulfonamide **S5,** mp 65-67 °C). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.48 – 8.35 (m, 2H), 8.23 – 8.10 (m, 2H), 7.42 – 7.27 (m, 5H), 5.91 – 5.69 (m, 1H), 5.36 – 5.25 (m, 2H), 4.13 (ddd, *J* = 6.4, 1.2, 1.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.86, 143.28, 131.80, 130.36, 129.25, 128.62, 124.62, 122.19, 121.06, 81.14, 71.75, 55.08. IR ( film ): 3106, 1708, 1607, 1532, 1350, 1312, 1173, 1125, 1086, 930, 855, 737, 700, 682 $cm^{-1}$. IR ($CHCl_3$) ν 681, 737, 1326, 1610, 3008 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{14}N_2O_4S$ $(M+Na)^+$ 365.0566, found 365.0554.




IV-20k

The product was obtained as an oil (100 mg, 28% in one step form sulfonamide **S5)**. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.12 (d, *J* = 6.41 Hz, 2H), 5.27 ( dd, *J* = 10.02, 1.21 Hz , 1 H), 5.32 (dd, *J* = 16.82, 1.21 Hz, 1H), 5.77-5.85 ( m, 1H), 7.12(d, *J* = 7.22 Hz, 2H), 7.25 (dd, *J* = 8.11, 1.62 Hz, 2H), 8.14 (dd, *J* = 8.82, 2.01 Hz, 2H), 8.40 (dd, *J* = 8.82, 2.02 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.45, 54.85, 71.52, 80.18, 118.76, 120.72, 124.32, 128.01, 129.12, 130.16, 131.65, 138.68, 143.05. IR ($CHCl_3$) 683.22, 734.74, 854.86, 1175.12, 1348.08, 1531.02, 2238. 62, 2360.80, 2929.09 ν $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2O_4S$ $(M+Na)^+$ 379.0729, found 379.0724.



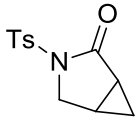

IV-20l

The product was obtained as a yellow solid (150 mg, 42% in one step form sulfonamide **S5,** mp 70-72 °C). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 1H), 7.86 – 7.72 (m, 3H), 7.40 (dd, *J* = 1.9, 0.5 Hz, 1H), 7.35 (dd, *J* = 8.3, 0.5 Hz, 1H), 7.15 (ddd, *J* = 8.3, 2.0, 0.8 Hz, 1H), 6.06 – 5.84 (m, 1H), 5.51 – 5.29 (m, 2H), 4.27 (ddd, *J* = 6.3, 1.3, 1.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.17, 133.02, 132.69, 132.59, 132.21, 132.15, 131.07, 130.97, 130.67, 130.55, 124.85, 122.56, 120.94, 82.75, 70.38, 55.09. IR ( film ): 2240, 1543, 1475, 1440, 1371, 1265, 1175, 1124, 1030, 987, 933, 879, 826, 754, 735, 682 $cm^{-1}$. IR ($CHCl_3$) ν $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{12}Cl_2N_2O_4S$ $(M+Na)^+$ 432.9787, found 432.9785.

**General procedure and for the Rh-catalyzed oxidative cycloisomerization of enynes:**

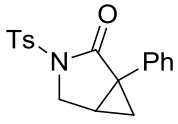
To a solution of $[Rh(CO)_2Cl]_2$ (4.0 mg, 5 mol %) in dioxane (4mL, 0.05M) was added $P[OCH(CF_3)_2]_3$ (20mg, 20 mol %) and the mixture was stirred at room temperature for 5 min. The substrate (0.2 mmol) and 3,5-dichloropyridine *N*-oxide (0.2 mmol equiv) were then added sequentially. The reaction mixture was allowed to stir at 80 °C until the reaction was complete, as determined by TLC analysis. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel to afford the corresponding product.

**Characterization data for products from oxidative cycloisomerization of enynes:**



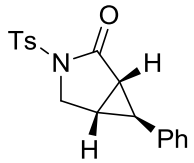

IV-21b

The product was obtained as a yellow solid (mp 142-143 °C). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.77 (m, 1H), 1.20 (m, 1H), 1.91 (m, 2H), 2.44 (s, 3H), 3.85 (dd, *J* = 10.14, 5.65 Hz, 1H), 3.95 (d, *J* = 10.14 Hz, 1H), 7.33 (d, *J* = 7.99 Hz, 2H), 7.90 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 12.06, 12.52, 20.79, 21.65, 48.66, 127.99, 129.63, 135.05, 145.04, 172.77. IR ($CHCl_3$) ν 698, 907, 1358, 1740, 2257 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{12}H_{13}NO_3S$ $(M+Na)^+$ 251.0616, found 251.0611.



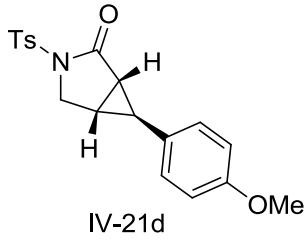

IV-21a

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 4.68 Hz, 1H), 1.51 (dd, *J* = 7.80, 4.87 Hz, 1H), 2.33 (m, 1H), 2.43 (s, 3H), 4.01 (m, 2H), 7.22-7.34 (m, 7H), 7.92 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 19.57, 20.10, 21.64, 34.48, 47.54, 127.65, 128.11, 128.45, 129.69, 134.10, 135.01, 145.10, 172.26. IR ($CHCl_3$) ν 698, 907, 1353, 1729, 2257cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{18}H_{17}NO_3S$ $(M+Na)^+$ 350.0821, found 350.0814.



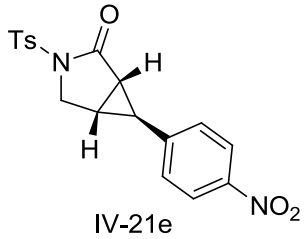

IV-21c

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.17 (m, 1H), 2.25 (m, 2H), 2.46 (s, 3H), 3.97 (m, 1H), 4.14 (d, *J* = 10.53 Hz, 1H), 7.00 (d, *J* = 7.02 Hz, 2H), 7.26 (m, 3H), 7.36 (d, *J* = 8.38 Hz, 2H), 7.82 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.32, 21.70, 29.43, 30.99, 49.09, 125.95, 127.16, 128.10, 128.71, 129.72, 134.98, 137.15, 145.23, 171.20. IR ($CHCl_3$) ν 698, 907, 1353, 1729, 2257 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{18}H_{17}NO_3S$ $(M+Na)^+$ 350.0821, found 350.0823.



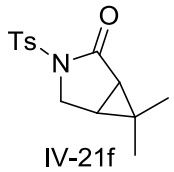

IV-21d

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.08-2.10 (m, 1H), 2.18-2.23 (m, 2H), 2.45, (s, 3H), 3.77 (s, 3H), 3.95(dd, *J* = 10.01, 5.20 Hz, 1H), 4.12 (d, *J* = 11.60 Hz, 1H), 6.81 (d, *J* = 8.80 Hz, 1H), 6.94 (d, *J* = 7.99 Hz, 2H), 7.36 (d, *J* = 8.81 Hz, 2H), 7.94 (d, *J* = 8.41 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 20.90, 21.68, 28.97, 30.76, 49.07, 55.30, 114.12, 127.17, 128.06, 128.97, 129.69, 134.99, 145.17, 158.76, 171.33. IR ($CHCl_3$) ν 687.93, 727.83, 907.57, 1031.75, 1169.02, 1356.46, 1516.16, 1729.80cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{19}H_{19}NO_4S$ $(M+Na)^+$ 380.0933, found 380.0919.



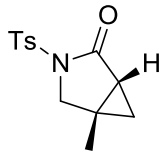

IV-21e

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.11 (m, 2H), 7.97 – 7.92 (m, 2H), 7.39 – 7.36 (m, 2H), 7.19 – 7.12 (m, 2H), 4.18 (dd, *J* = 10.6, 1.3 Hz, 1H), 4.00 (dd, *J* = 10.7, 5.0 Hz, 1H), 2.47 (s, 3H), 2.36 – 2.32 (m, 2H), 2.29 – 2.25 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.37, 147.18, 145.72, 145.14, 134.94, 130.02, 128.37, 126.80, 124.22, 49.13, 31.93, 29.05, 22.54, 21.95. IR ( film ): 1741, 1712, 1619, 1508, 1345, 1270, 1222, 1192, 1165, 1131, 1089, 1026, 1006, 886, 859, 815, 736, 667 $cm^{-1}$. IR ($CHCl_3$) ν 687, 727, 907, 1035, 1169, 1356, 1520, 1729 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2O_5S$ $(M+Na)^+$ 395.0672, found 395.0674.



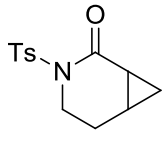

IV-21f

The product was obtained as an oil. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.09 (s, 3H), 1.72 (t, *J* = 6.80 Hz, 1H), 1.78 (dd, *J* = 6.41, 1.60 Hz, 1H), 2.43(s, 3H), 3.80 (dt, *J* = 10.81, 0.80 Hz, 1H), 3.93 (dd, *J* = 10.81, 6.40 Hz, 1H), 7.32 (d, *J* = 8.40 Hz, 2H), 7.91 (d, *J* = 8.80 Hz, 2H);$^{13}$C NMR ($CDCl_3$, 100 MHz): δ 13.56, 21.66, 23.50, 24.62, 25.97, 33.43, 45.82, 128.04, 129.56, 135.37, 145.04, 170.99. IR ($CHCl_3$) 671.86, 728.23, 908..48, 1047.74, 1168.24, 1357.08, 1721.98, ν $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_3S$ $(M+Na)^+$ 302.0798, found 302.0812.




IV-21b

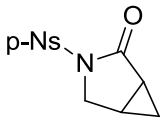
The product was obtained as a yellow solid (mp 166-168 °C). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 0.92 (m, 1H), 1.10 (dd, *J* = 8.77, 4.78 Hz, 1H), 1.31, (s, 3H), 1.66 (m, 1H), 2.44 (s, 3H), 3.57 (d, *J* = 9.94 Hz, 1H), 3.96 (d, *J* = 9.94 Hz, 1H), 7.33 (d, *J* = 7.99 Hz, 2H), 7.90 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 18.42, 19.01, 20.30, 21.65, 27.16, 53.28, 128.02, 129.64, 135.11, 145.00, 173.10. IR ($CHCl_3$) ν 685, 1036, 1703, 3416 $cm^{-1}$. HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_3S$ $(M+Na)^+$ 288.0665, found 288.0675.




IV-21h

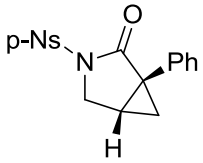
The product was obtained as a yellow solid (mp 148-150 °C). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.04 (m, 1H), 1.26 (m, 1H), 1.72 (m, 2H), 2.06 (m, 1H), 2.16 (m, 1H), 2.42 (s, 3H), 3.27 (td, *J* = 13.25,

4.09 Hz, 1H), 4.30 (dd, *J* = 13.45, 5.65 Hz, 1H), 7.30 (d, *J* = 8.58 Hz, 2H), 7.86 (d, *J* = 8.19 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 7.69, 15.72, 19.02, 21.63, 21.65, 40.60, 128.41, 129.27, 136.44, 144.55, 170.82. IR ($CHCl_3$) ν 683, 705, 907, 1111, 1683, 2256 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_3S$ $(M+Na)^+$ 288.0665, found 288.0674.



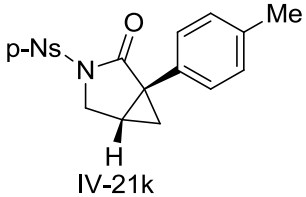

IV-21i

The product was obtained as a yellow solid (mp 156-158 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 0.87 (m, 1H), 1.30 (m, 1H), 1.93 (m, 1H), 2.03 (m, 1H), 3.87 (dd, *J* = 10.14, 5.46 Hz, 1H), 4.02 (d, *J* = 10.14 Hz, 1H), 8.23 (d, *J* = 8.58 Hz, 2H), 8.39 (d, *J* = 8.58 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 12.35, 12.98, 20.64, 48.76, 124.24, 129.55, 143.32, 150.97, 172.81. IR ($CHCl_3$) ν 683, 728, 1140, 1350, 1531, 1737, 2259, 3111 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{11}H_{10}N_2O_5S$ $(M+Na)^+$ 305.0203, found 305.0211.




IV-21j

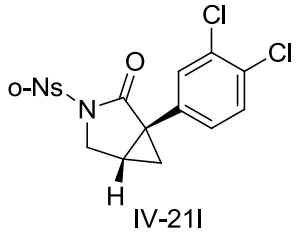
The product was obtained as a yellow solid (mp 143-145 °C). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.32 (m, 2H), 8.32 – 8.21 (m, 2H), 7.36 – 7.24 (m, 5H), 4.10 (d, *J* = 10.2 Hz, 1H), 4.01 (dd, *J* = 10.1, 5.3 Hz, 1H), 2.50 – 2.37 (m, 1H), 1.59 (dd, *J* = 7.6, 4.8 Hz, 1H), 1.29 (dd, *J* = 4.8, 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.72, 151.08, 143.49, 133.66, 129.89, 128.84, 128.73, 128.22, 124.48, 47.91, 34.75, 20.62, 20.04. IR ( film ): 2348, 1733, 1607, 1531, 1478, 1448, 1403, 1350, 1176, 1131, 1095, 1045, 994, 918, 855, 737, 699 cm$^{-1}$. IR ($CHCl_3$) ν 683, 728, 1140, 1350, 1531, 1750, 2250, 3008 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{14}N_2O_5S$ $(M+Na)^+$ 381.05015, found 381.0503.




IV-21k

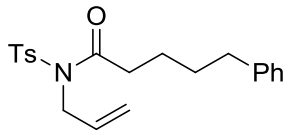
The product was obtained as a yellow solid (mp 140-144 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 4.18 Hz, 1H), 1.56 (dd, *J* = 7.60, 4.82 Hz, 1H), 2.30 (s, 3H), 2.37 (dt, *J* = 8.02, 4.82 Hz , 1H), 4.00 (dd, *J* = 10.01, 5.63 Hz, 1H), 4.09 (d, *J* = 8.11 Hz, 1H), 7.10 (d, *J* = 8.10 Hz, 2H), 7.16 (dt, *J* =

8.00, 2.01 Hz, 2H), 8.25 (dt, *J* = 9.20, 2.41 Hz, 2H), 8.36 (dt, *J* = 9.21, 2.41Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 19.75, 20.22, 21.06, 34.36, 47.71, 124.22, 128.49, 129.28, 129.64, 130.35, 137.90, 143.28, 150.81, 172.69. IR ($CHCl_3$) 669.11, 731.09, 907.52, 1108.65, 1178.16, 1350.29, 1502.02, 1728.90, 2342.44 ν cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2O_5S$ $(M+Na)^+$ 395.0678, found 395.0666.




IV-21l

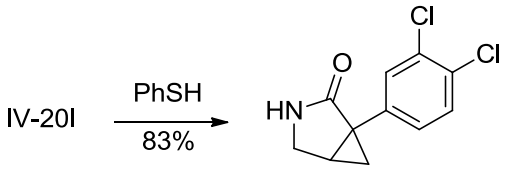
The product was obtained as a yellow solid (mp 144-146 °C). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.65 – 8.33 (m, 1H), 7.89 – 7.68 (m, 3H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.26 (dd, *J* = 10.3, 5.5 Hz, 1H), 4.12 (d, *J* = 10.3 Hz, 1H), 2.49 – 2.45 (m, 1H), 1.69 – 1.39 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.04, 135.40, 134.96, 134.33, 132.90, 132.36, 131.24, 130.83, 130.72, 128.12, 124.53, 47.62, 33.80, 20.47, 20.34. IR ( film ): 1730, 1542, 1479, 1441, 1368, 1305, 1264, 1245, 1175, 1127, 1096, 1031, 852, 780, 736, 703 cm$^{-1}$. IR ($CHCl_3$) ν 668, 731, 907, 1111, 1170, 1351, 1545, 1729, 2355 cm$^{-1}$. HRMS (ESI) m/z calcd for $C_{17}H_{12}Cl_2N_2O_5S$ $(M+Na)^+$ 448.9736, found 448.9735.




IV-22

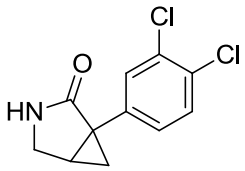
The product was obtained as an oil. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.56 (m, 4H), 2.44 (s, 3H), 2.56 (q, *J* = 6.63 Hz, 4H), 4.46 (d, *J* = 5.46 Hz, 2H), 5.24 (m, 2H), 5.89 (m, 1H), 7.10-7.28 (m, 5H), 7.31 (d, *J* = 8.58 Hz, 2H), 7.80 (d, *J* = 8.38 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 21.61, 24.07, 30.65, 35.57, 35.83, 48.49, 118.13, 125.74, 127.93, 128.32, 129.66, 130.67, 132.88, 136.80, 142.01, 144.76, 172.66. IR ($CHCl_3$) ν 691, 1370, 1440, 1723, 2238 m$^{-1}$. HRMS (ESI) m/z calcd for $C_{21}H_{25}NO_3S$ $(M+Na)^+$ 371.1555, found 371.1501.

**Procedure for removal of the nosyl group:**




IV-21l

To a solution of nosyl protected amide **IV-20l** (30 mg, 0.081 mmol) in DMF (0.8 ml, 0.1 M) was added potassium bicarbonate (33 mg, 0.242 mmol). To the above solution was added phenyl hydrosulfide (10 µL, 0.097 mmol) dropwise. The reaction was then stirred at room temperature for 90 minutes. The reaction was quenched with water (2ml) and allowed to stir for an additional 20 minutes. The reaction mixture was extracted 3 times with ethyl acetate. All organic phases were combined and dried over magnesium sulfate. The solvent was removed under reduced pressure and the final product was purified on silica gel (33% ethyl acetate in hexanes) to yield 16 mg (83%) of product **IV-21l** as an oil.




IV-21l

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.1 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.27 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.38 (br s, 1H), 3.63 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.39 (d, *J* = 10.4 Hz, 1H), 2.30 – 2.22 (m, 1H), 1.50 (dd, *J* = 7.9, 4.8 Hz, 1H), 1.20 (dd, *J* = 4.7, 4.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.40, 136.68, 132.62, 131.47, 130.80, 130.54, 128.26, 43.18, 32.66, 23.30, 20.20. IR ( film ): 3214, 2890, 2245, 1686, 1480, 1379, 1273, 1191, 1135, 1089, 1030, 906, 727, 677 $cm^{-1}$. The data are in accordance with the references [9, 10].

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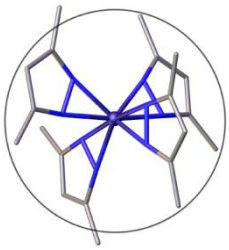
**APPENDIX II: X-RAY CRYSTALLIZATION DATA**



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Structural report on **IV-15b**

DECEMBER 19, 2011

Crystallographic Experimental Section

***Data Collection***

A colorless crystal with approximate dimensions 0.41 x 0.25 x 0.17 $mm^3$ was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

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

The initial cell constants were obtained from three series of $\omega$ scans at different starting angles. Each series consisted of 41 frames collected at intervals of 0.6º in a 25º range about $\omega$ with the exposure time of 5 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9911 strong reflections from the actual data collection.

The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.82 Å. A total of 19664 data were harvested by collecting 21 sets of frames with 0.6º scans in $\omega$ with an exposure time 8/15/20 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1]

**Structure Solution and Refinement**

The systematic absences in the diffraction data were consistent for the space groups $P\bar{1}$ and $P1$. The *E*-statistics strongly suggested the centrosymmetric space group $P\bar{1}$ that yielded chemically reasonable and computationally stable results of refinement [2-4].

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

The final least-squares refinement of 291 parameters against 3942 data resulted in residuals *R* (based on $F^2$ for $I \geq 2\sigma$) and *wR* (based on $F^2$ for all data) of 0.0332 and 0.0872, respectively. The final difference Fourier map was featureless.

The molecular diagram is drawn with 50% probability ellipsoids.

**References**

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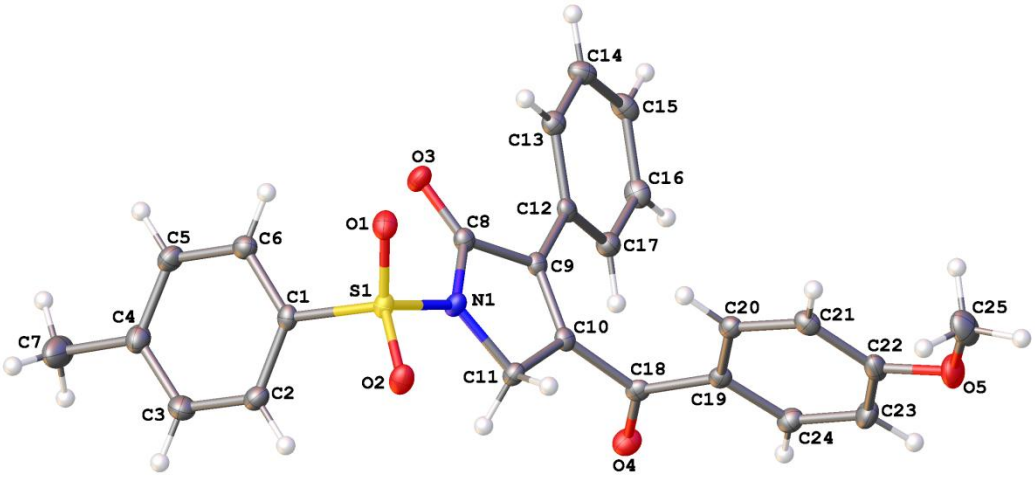


Figure 1. A molecular drawing of **IV-15b**.

Table 1. Crystal data and structure refinement for **8b**.

| | | |
|---|---|---|
| Identification code | **8b** | |
| Empirical formula | $C_{25}$ $H_{21}$ N $O_5$ S | |
| Formula weight | 447.49 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Triclinic | |
| Space group | $P\bar{1}$ | |
| Unit cell dimensions | a = 5.7897(6) Å | = 108.641(8)°. |
| | b = 12.9326(10) Å | = 93.241(6)°. |
| | c = 14.9376(20) Å | = 91.294(7)°. |
| Volume | 1057.12(19) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.406 $Mg/m^3$ | |
| Absorption coefficient | 1.688 $mm^{-1}$ | |
| F(000) | 468 | |
| Crystal size | 0.41 x 0.25 x 0.17 $mm^3$ | |
| Theta range for data collection | 3.13 to 72.19°. | |
| Index ranges | -7<=h<=7, -15<=k<=15, -18<=l<=16 | |
| Reflections collected | 19664 | |
| Independent reflections | 3942 [R(int) = 0.0206] | |
| Completeness to theta = 67.00° | 97.1 % | |
| Absorption correction | Numerical with SADABS | |
| Max. and min. transmission | 0.7577 and 0.5473 | |

| | |
|---|---|
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3942 / 0 / 291 |
| Goodness-of-fit on $F^2$ | 1.044 |
| Final R indices [I>2sigma(I)] | R1 = 0.0332, wR2 = 0.0870 |
| R indices (all data) | R1 = 0.0334, wR2 = 0.0872 |
| Largest diff. peak and hole | 0.449 and -0.460 e.$Å^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$)

for **8b**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(1) | 4005(1) | 8238(1) | -481(1) | 14(1) |
| O(1) | 6473(2) | 8214(1) | -459(1) | 19(1) |
| O(2) | 2814(2) | 8902(1) | -946(1) | 20(1) |
| O(3) | 5489(2) | 7591(1) | 1243(1) | 19(1) |
| O(4) | -1879(2) | 10240(1) | 2719(1) | 21(1) |
| O(5) | 3226(2) | 14888(1) | 4086(1) | 26(1) |
| N(1) | 3250(2) | 8696(1) | 629(1) | 15(1) |
| C(1) | 2842(2) | 6891(1) | -929(1) | 15(1) |
| C(2) | 645(2) | 6707(1) | -1390(1) | 18(1) |
| C(3) | -299(2) | 5649(1) | -1716(1) | 22(1) |
| C(4) | 899(2) | 4777(1) | -1586(1) | 22(1) |
| C(5) | 3115(2) | 4987(1) | -1132(1) | 20(1) |
| C(6) | 4103(2) | 6037(1) | -801(1) | 17(1) |
| C(7) | -200(3) | 3640(1) | -1936(2) | 36(1) |
| C(8) | 4140(2) | 8318(1) | 1351(1) | 14(1) |
| C(9) | 3040(2) | 8969(1) | 2225(1) | 13(1) |
| C(10) | 1581(2) | 9647(1) | 1987(1) | 13(1) |

| | | | | |
|---|---|---|---|---|
| C(11) | 1483(2) | 9503(1) | 947(1) | 14(1) |
| C(12) | 3582(2) | 8814(1) | 3150(1) | 14(1) |
| C(13) | 5711(2) | 8414(1) | 3349(1) | 16(1) |
| C(14) | 6210(2) | 8274(1) | 4222(1) | 19(1) |
| C(15) | 4617(2) | 8534(1) | 4912(1) | 20(1) |
| C(16) | 2495(2) | 8922(1) | 4717(1) | 20(1) |
| C(17) | 1971(2) | 9052(1) | 3842(1) | 17(1) |
| C(18) | 93(2) | 10488(1) | 2606(1) | 14(1) |
| C(19) | 1104(2) | 11615(1) | 3025(1) | 14(1) |
| C(20) | 3237(2) | 11939(1) | 2791(1) | 15(1) |
| C(21) | 4025(2) | 13027(1) | 3133(1) | 18(1) |
| C(22) | 2689(2) | 13797(1) | 3737(1) | 19(1) |
| C(23) | 604(2) | 13469(1) | 4018(1) | 21(1) |
| C(24) | -190(2) | 12397(1) | 3654(1) | 18(1) |
| C(25) | 5279(3) | 15286(1) | 3790(1) | 30(1) |

---

Table 3. Bond lengths [Å] and angles [°] for **8b**.

| | | | |
|---|---|---|---|
| S(1)-O(1) | 1.4286(10) | C(7)-H(7B) | 0.9800 |
| S(1)-O(2) | 1.4316(10) | C(7)-H(7C) | 0.9800 |
| S(1)-N(1) | 1.6605(11) | C(8)-C(9) | 1.4947(18) |
| S(1)-C(1) | 1.7573(13) | C(9)-C(10) | 1.3449(18) |
| O(3)-C(8) | 1.2129(16) | C(9)-C(12) | 1.4762(19) |
| O(4)-C(18) | 1.2147(17) | C(10)-C(11) | 1.5014(18) |
| O(5)-C(22) | 1.3600(17) | C(10)-C(18) | 1.5064(18) |
| O(5)-C(25) | 1.432(2) | C(11)-H(11A) | 0.9900 |
| N(1)-C(8) | 1.3973(17) | C(11)-H(11B) | 0.9900 |
| N(1)-C(11) | 1.4657(16) | C(12)-C(17) | 1.3969(19) |
| C(1)-C(2) | 1.3892(19) | C(12)-C(13) | 1.4003(19) |
| C(1)-C(6) | 1.3943(19) | C(13)-C(14) | 1.388(2) |
| C(2)-C(3) | 1.385(2) | C(13)-H(13) | 0.9500 |
| C(2)-H(2) | 0.9500 | C(14)-C(15) | 1.388(2) |
| C(3)-C(4) | 1.397(2) | C(14)-H(14) | 0.9500 |
| C(3)-H(3) | 0.9500 | C(15)-C(16) | 1.388(2) |
| C(4)-C(5) | 1.396(2) | C(15)-H(15) | 0.9500 |
| C(4)-C(7) | 1.506(2) | C(16)-C(17) | 1.388(2) |
| C(5)-C(6) | 1.3860(19) | C(16)-H(16) | 0.9500 |
| C(5)-H(5) | 0.9500 | C(17)-H(17) | 0.9500 |
| C(6)-H(6) | 0.9500 | C(18)-C(19) | 1.4817(18) |
| C(7)-H(7A) | 0.9800 | C(19)-C(20) | 1.3934(19) |

| | | | |
|---|---|---|---|
| C(19)-C(24) | 1.4045(18) | C(23)-H(23) | 0.9500 |
| C(20)-C(21) | 1.3910(19) | C(24)-H(24) | 0.9500 |
| C(20)-H(20) | 0.9500 | C(25)-H(25A) | 0.9800 |
| C(21)-C(22) | 1.394(2) | C(25)-H(25B) | 0.9800 |
| C(21)-H(21) | 0.9500 | C(25)-H(25C) | 0.9800 |
| C(22)-C(23) | 1.401(2) | | |
| C(23)-C(24) | 1.375(2) | | |
| O(1)-S(1)-O(2) | 119.99(6) | | |
| O(1)-S(1)-N(1) | 107.92(6) | | |
| O(2)-S(1)-N(1) | 104.65(6) | | |
| O(1)-S(1)-C(1) | 108.74(6) | | |
| O(2)-S(1)-C(1) | 109.42(6) | | |
| N(1)-S(1)-C(1) | 105.08(6) | | |
| C(22)-O(5)-C(25) | 117.86(12) | | |
| C(8)-N(1)-C(11) | 112.54(10) | | |
| C(8)-N(1)-S(1) | 123.94(9) | | |
| C(11)-N(1)-S(1) | 123.45(9) | | |
| C(2)-C(1)-C(6) | 121.49(12) | | |
| C(2)-C(1)-S(1) | 118.60(10) | | |
| C(6)-C(1)-S(1) | 119.90(10) | | |
| C(3)-C(2)-C(1) | 118.55(13) | | |
| C(3)-C(2)-H(2) | 120.7 | | |
| C(1)-C(2)-H(2) | 120.7 | | |
| C(2)-C(3)-C(4) | 121.49(13) | | |

| | | | |
|---|---|---|---|
| C(2)-C(3)-H(3) | 119.3 | | |
| C(4)-C(3)-H(3) | 119.3 | | |
| C(5)-C(4)-C(3) | 118.56(13) | | |
| C(5)-C(4)-C(7) | 121.42(13) | | |
| C(3)-C(4)-C(7) | 120.02(13) | | |
| C(6)-C(5)-C(4) | 121.08(13) | | |
| C(6)-C(5)-H(5) | 119.5 | | |
| C(4)-C(5)-H(5) | 119.5 | | |
| C(5)-C(6)-C(1) | 118.82(12) | C(9)-C(10)-C(18) | 129.24(12) |
| C(5)-C(6)-H(6) | 120.6 | C(11)-C(10)-C(18) | 118.22(11) |
| C(1)-C(6)-H(6) | 120.6 | N(1)-C(11)-C(10) | 100.97(10) |
| C(4)-C(7)-H(7A) | 109.5 | N(1)-C(11)-H(11A) | 111.6 |
| C(4)-C(7)-H(7B) | 109.5 | C(10)-C(11)-H(11A) | 111.6 |
| H(7A)-C(7)-H(7B) | 109.5 | N(1)-C(11)-H(11B) | 111.6 |
| C(4)-C(7)-H(7C) | 109.5 | C(10)-C(11)-H(11B) | 111.6 |
| H(7A)-C(7)-H(7C) | 109.5 | H(11A)-C(11)-H(11B) | 109.4 |
| H(7B)-C(7)-H(7C) | 109.5 | C(17)-C(12)-C(13) | 118.59(12) |
| O(3)-C(8)-N(1) | 124.68(12) | C(17)-C(12)-C(9) | 120.70(12) |
| O(3)-C(8)-C(9) | 129.55(12) | C(13)-C(12)-C(9) | 120.70(12) |
| N(1)-C(8)-C(9) | 105.75(11) | C(14)-C(13)-C(12) | 120.37(13) |
| C(10)-C(9)-C(12) | 130.15(12) | C(14)-C(13)-H(13) | 119.8 |
| C(10)-C(9)-C(8) | 107.93(12) | C(12)-C(13)-H(13) | 119.8 |
| C(12)-C(9)-C(8) | 121.92(11) | C(15)-C(14)-C(13) | 120.59(13) |
| C(9)-C(10)-C(11) | 112.54(11) | C(15)-C(14)-H(14) | 119.7 |

| | | | |
|---|---|---|---|
| C(13)-C(14)-H(14) | 119.7 | C(20)-C(21)-C(22) | 119.46(13) |
| C(16)-C(15)-C(14) | 119.36(13) | C(20)-C(21)-H(21) | 120.3 |
| C(16)-C(15)-H(15) | 120.3 | C(22)-C(21)-H(21) | 120.3 |
| C(14)-C(15)-H(15) | 120.3 | O(5)-C(22)-C(21) | 124.97(13) |
| C(15)-C(16)-C(17) | 120.40(13) | O(5)-C(22)-C(23) | 114.96(12) |
| C(15)-C(16)-H(16) | 119.8 | C(21)-C(22)-C(23) | 120.06(12) |
| C(17)-C(16)-H(16) | 119.8 | C(24)-C(23)-C(22) | 119.90(13) |
| C(16)-C(17)-C(12) | 120.66(13) | C(24)-C(23)-H(23) | 120.0 |
| C(16)-C(17)-H(17) | 119.7 | C(22)-C(23)-H(23) | 120.0 |
| C(12)-C(17)-H(17) | 119.7 | C(23)-C(24)-C(19) | 120.74(13) |
| O(4)-C(18)-C(19) | 122.52(12) | C(23)-C(24)-H(24) | 119.6 |
| O(4)-C(18)-C(10) | 120.06(12) | C(19)-C(24)-H(24) | 119.6 |
| C(19)-C(18)-C(10) | 117.37(11) | O(5)-C(25)-H(25A) | 109.5 |
| C(20)-C(19)-C(24) | 118.86(12) | O(5)-C(25)-H(25B) | 109.5 |
| C(20)-C(19)-C(18) | 122.67(12) | H(25A)-C(25)-H(25B) | 109.5 |
| C(24)-C(19)-C(18) | 118.42(12) | O(5)-C(25)-H(25C) | 109.5 |
| C(21)-C(20)-C(19) | 120.84(12) | H(25A)-C(25)-H(25C) | 109.5 |
| C(21)-C(20)-H(20) | 119.6 | H(25B)-C(25)-H(25C) | 109.5 |
| C(19)-C(20)-H(20) | 119.6 | | |

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **8b**. The anisotropic displacement factor exponent takes the form: $-2\ ^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| S(1) | 19(1) | 12(1) | 12(1) | 4(1) | 3(1) | 1(1) |
| O(1) | 20(1) | 17(1) | 19(1) | 4(1) | 5(1) | -1(1) |
| O(2) | 29(1) | 16(1) | 15(1) | 7(1) | 3(1) | 3(1) |
| O(3) | 24(1) | 16(1) | 17(1) | 5(1) | 2(1) | 7(1) |
| O(4) | 19(1) | 20(1) | 25(1) | 9(1) | 5(1) | 1(1) |
| O(5) | 33(1) | 14(1) | 28(1) | 3(1) | -1(1) | -3(1) |
| N(1) | 19(1) | 14(1) | 12(1) | 4(1) | 2(1) | 5(1) |
| C(1) | 19(1) | 13(1) | 12(1) | 3(1) | 3(1) | 0(1) |
| C(2) | 19(1) | 17(1) | 20(1) | 6(1) | 2(1) | 5(1) |
| C(3) | 17(1) | 22(1) | 25(1) | 5(1) | -1(1) | 1(1) |
| C(4) | 21(1) | 17(1) | 26(1) | 4(1) | 3(1) | 0(1) |
| C(5) | 22(1) | 16(1) | 24(1) | 7(1) | 2(1) | 4(1) |
| C(6) | 17(1) | 18(1) | 16(1) | 5(1) | 0(1) | 2(1) |
| C(7) | 27(1) | 19(1) | 58(1) | 7(1) | -4(1) | -2(1) |
| C(8) | 16(1) | 13(1) | 14(1) | 5(1) | 0(1) | -2(1) |
| C(9) | 14(1) | 11(1) | 14(1) | 4(1) | 1(1) | -2(1) |
| C(10) | 14(1) | 12(1) | 14(1) | 4(1) | 1(1) | -3(1) |
| C(11) | 17(1) | 13(1) | 13(1) | 4(1) | 2(1) | 3(1) |
| C(12) | 18(1) | 10(1) | 14(1) | 4(1) | -1(1) | -3(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(13) | 17(1) | 15(1) | 18(1) | 6(1) | 1(1) | -1(1) |
| C(14) | 17(1) | 20(1) | 22(1) | 11(1) | -3(1) | -2(1) |
| C(15) | 24(1) | 22(1) | 16(1) | 10(1) | -4(1) | -5(1) |
| C(16) | 22(1) | 22(1) | 16(1) | 6(1) | 4(1) | -2(1) |
| C(17) | 18(1) | 17(1) | 17(1) | 6(1) | 0(1) | 0(1) |
| C(18) | 16(1) | 16(1) | 12(1) | 8(1) | 1(1) | 3(1) |
| C(19) | 16(1) | 15(1) | 12(1) | 6(1) | 0(1) | 3(1) |
| C(20) | 16(1) | 17(1) | 12(1) | 5(1) | 0(1) | 2(1) |
| C(21) | 18(1) | 20(1) | 16(1) | 7(1) | -1(1) | -2(1) |
| C(22) | 25(1) | 14(1) | 17(1) | 5(1) | -5(1) | -1(1) |
| C(23) | 24(1) | 18(1) | 20(1) | 2(1) | 3(1) | 6(1) |
| C(24) | 18(1) | 19(1) | 17(1) | 7(1) | 4(1) | 3(1) |
| C(25) | 36(1) | 20(1) | 34(1) | 9(1) | -6(1) | -9(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **8b**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | -190 | 7295 | -1479 | 22 |
| H(3) | -1796 | 5514 | -2036 | 26 |
| H(5) | 3960 | 4399 | -1048 | 24 |
| H(6) | 5612 | 6173 | -493 | 21 |
| H(7A) | -1811 | 3663 | -1764 | 54 |
| H(7B) | 656 | 3170 | -1646 | 54 |
| H(7C) | -160 | 3348 | -2626 | 54 |
| H(11A) | -63 | 9220 | 636 | 17 |
| H(11B) | 1886 | 10195 | 831 | 17 |
| H(13) | 6819 | 8237 | 2883 | 20 |
| H(14) | 7655 | 7997 | 4348 | 23 |
| H(15) | 4976 | 8448 | 5512 | 24 |
| H(16) | 1394 | 9099 | 5186 | 24 |
| H(17) | 502 | 9305 | 3713 | 21 |
| H(20) | 4165 | 11410 | 2393 | 18 |
| H(21) | 5462 | 13244 | 2955 | 21 |
| H(23) | -261 | 13986 | 4458 | 26 |

| | | | | |
|---|---|---|---|---|
| H(24) | -1630 | 12182 | 3831 | 21 |
| H(25A) | 5194 | 15077 | 3098 | 46 |
| H(25B) | 6636 | 14970 | 4008 | 46 |
| H(25C) | 5412 | 16084 | 4063 | 46 |

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Table 6. Torsion angles [°] for **8b**.

| | | | |
|---|---|---|---|
| O(1)-S(1)-N(1)-C(8) | -47.04(12) | C(11)-N(1)-C(8)-O(3) | 174.23(12) |
| O(2)-S(1)-N(1)-C(8) | -175.90(10) | S(1)-N(1)-C(8)-O(3) | -2.78(19) |
| C(1)-S(1)-N(1)-C(8) | 68.86(12) | C(11)-N(1)-C(8)-C(9) | -4.40(14) |
| O(1)-S(1)-N(1)-C(11) | 136.27(10) | S(1)-N(1)-C(8)-C(9) | 178.59(9) |
| O(2)-S(1)-N(1)-C(11) | 7.41(12) | O(3)-C(8)-C(9)-C(10) | -177.07(13) |
| C(1)-S(1)-N(1)-C(11) | -107.83(11) | N(1)-C(8)-C(9)-C(10) | 1.46(14) |
| O(1)-S(1)-C(1)-C(2) | -152.72(11) | O(3)-C(8)-C(9)-C(12) | 2.5(2) |
| O(2)-S(1)-C(1)-C(2) | -19.94(13) | N(1)-C(8)-C(9)-C(12) | -179.00(11) |
| N(1)-S(1)-C(1)-C(2) | 91.94(12) | C(12)-C(9)-C(10)-C(11) | -177.57(12) |
| O(1)-S(1)-C(1)-C(6) | 28.58(13) | C(8)-C(9)-C(10)-C(11) | 1.91(14) |
| O(2)-S(1)-C(1)-C(6) | 161.36(11) | C(12)-C(9)-C(10)-C(18) | 2.0(2) |
| N(1)-S(1)-C(1)-C(6) | -86.76(12) | C(8)-C(9)-C(10)-C(18) | -178.51(12) |
| C(6)-C(1)-C(2)-C(3) | 0.7(2) | C(8)-N(1)-C(11)-C(10) | 5.25(13) |
| S(1)-C(1)-C(2)-C(3) | -177.98(11) | S(1)-N(1)-C(11)-C(10) | -177.72(9) |
| C(1)-C(2)-C(3)-C(4) | 0.4(2) | C(9)-C(10)-C(11)-N(1) | -4.29(14) |
| C(2)-C(3)-C(4)-C(5) | -1.2(2) | C(18)-C(10)-C(11)-N(1) | 176.08(11) |
| C(2)-C(3)-C(4)-C(7) | 178.95(15) | C(10)-C(9)-C(12)-C(17) | 26.2(2) |
| C(3)-C(4)-C(5)-C(6) | 1.0(2) | C(8)-C(9)-C(12)-C(17) | -153.22(12) |
| C(7)-C(4)-C(5)-C(6) | -179.17(15) | C(10)-C(9)-C(12)-C(13) | -154.63(13) |
| C(4)-C(5)-C(6)-C(1) | 0.0(2) | C(8)-C(9)-C(12)-C(13) | 25.94(18) |
| C(2)-C(1)-C(6)-C(5) | -0.9(2) | C(17)-C(12)-C(13)-C(14) | -0.97(19) |
| S(1)-C(1)-C(6)-C(5) | 177.76(11) | C(9)-C(12)-C(13)-C(14) | 179.85(12) |

| | | | |
|---|---|---|---|
| C(12)-C(13)-C(14)-C(15) | -0.4(2) | C(20)-C(19)-C(24)-C(23) | 1.5(2) |
| C(13)-C(14)-C(15)-C(16) | 1.0(2) | C(18)-C(19)-C(24)-C(23) | -175.95(12 |
| C(14)-C(15)-C(16)-C(17) | -0.3(2) | | |
| C(15)-C(16)-C(17)-C(12) | -1.1(2) | | |
| C(13)-C(12)-C(17)-C(16) | 1.74(19) | | |
| C(9)-C(12)-C(17)-C(16) | -179.08(12) | | |
| C(9)-C(10)-C(18)-O(4) | -91.20(17) | | |
| C(11)-C(10)-C(18)-O(4) | 88.36(16) | | |
| C(9)-C(10)-C(18)-C(19) | 91.26(17) | | |
| C(11)-C(10)-C(18)-C(19) | -89.19(14) | | |
| O(4)-C(18)-C(19)-C(20) | -170.69(13) | | |
| C(10)-C(18)-C(19)-C(20) | 6.79(18) | | |
| O(4)-C(18)-C(19)-C(24) | 6.6(2) | | |
| C(10)-C(18)-C(19)-C(24) | -175.88(12) | | |
| C(24)-C(19)-C(20)-C(21) | -3.4(2) | | |
| C(18)-C(19)-C(20)-C(21) | 173.95(12) | | |
| C(19)-C(20)-C(21)-C(22) | 1.7(2) | | |
| C(25)-O(5)-C(22)-C(21) | 2.0(2) | | |
| C(25)-O(5)-C(22)-C(23) | -177.02(13) | | |
| C(20)-C(21)-C(22)-O(5) | -177.22(13) | | |
| C(20)-C(21)-C(22)-C(23) | 1.8(2) | | |
| O(5)-C(22)-C(23)-C(24) | 175.45(13) | | |
| C(21)-C(22)-C(23)-C(24) | -3.7(2) | | |
| C(22)-C(23)-C(24)-C(19) | 2.0(2) | | |

Symmetry transformations used to generate equivalent atoms:

## APPENDIX III: MECHANISM COMPUTATIONAL STUDIS

### General remarks:

Pathways in Scheme 2 of the manuscript are computed using B3LYP/SDD-6-31G* with SMD solvation energy corrections for 1,4-dioxane.[1] For Figures S1-S5, energies are in kcal/mol and bond lengths are in Å.

Reference:

1. (a) The B3LYP hybrid functional with the 6-31G* (for H, C, O, N, S and Cl) and SDD (for Rh) basis sets were used for geometry optimization in gas phase and single point calculations with 1,4-dioxane solvent. (b) All the transition states have been verified by IRC (intrinsic reaction coordinate) calculations. (c) Frisch, M. J.; et al. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2010.

### Computational results for Rh-catalyzed oxidative cycloisomerization of diynes:

For the oxidative cycloisomerization of diynes, the calculated pathway (**Pathway I**, Figure S1) shows that the 16-electron (16e) rhodium carbenoid **18-1** adopts a square-planar geometry, in which the tethered alkyne moiety does not coordinate to Rh as evidenced by the calculated long distances between two carbon atoms of the alkyne moiety and the Rh atom (4.16 Å and 4.73 Å). A CO ligand is then dissociated and the tethered alkyne in **18-1** binds to the rhodium metal center, leading to the formation of the 16e rhodium carbenoid **18-2**. This alkyne coordination leads to a free energy increase of 10.3 kcal/mol. With the coordination of the tethered alkyne to metal carbene, **18-2** converts to metallacyclobutene **19-1** via the transition state **18TS**, in which the new forming C-C bond and Rh-C bond are 2.20 Å and 2.31 Å, respectively. This alkyne insertion step (from **18-1** to **18TS)** requires an overall activation free energy of 20.7 kcal/mol. Next, with the elongation of the old Rh-C bond in **19-1**, a stationary point **19-2**, where the four-membered metallacycle adopts a more planar conformation, is located on the free energy surface. Subsequently, the rupture of the old Rh-C bond leads to the new carbenoid **20**. This step requires an overall activation free energy of 14.0 kcal/mol from **19-1** to the transition state **19TS**, in which the breaking Rh-C bond is 2.53 Å.

Alternatively, metathesis of **18-1** may undergo another pathway (**Pathway II,** Figure S2) in which no CO dissociates from **18-1** and then follows the similar steps to those in **Pathway I**. But all efforts to search 18TS' failed. By carefully analyzing the electronic configuration of the speculated 18TS', we believe that such a transition state should be unavailable, which consequently rules out the possibility of **Pathway II.**

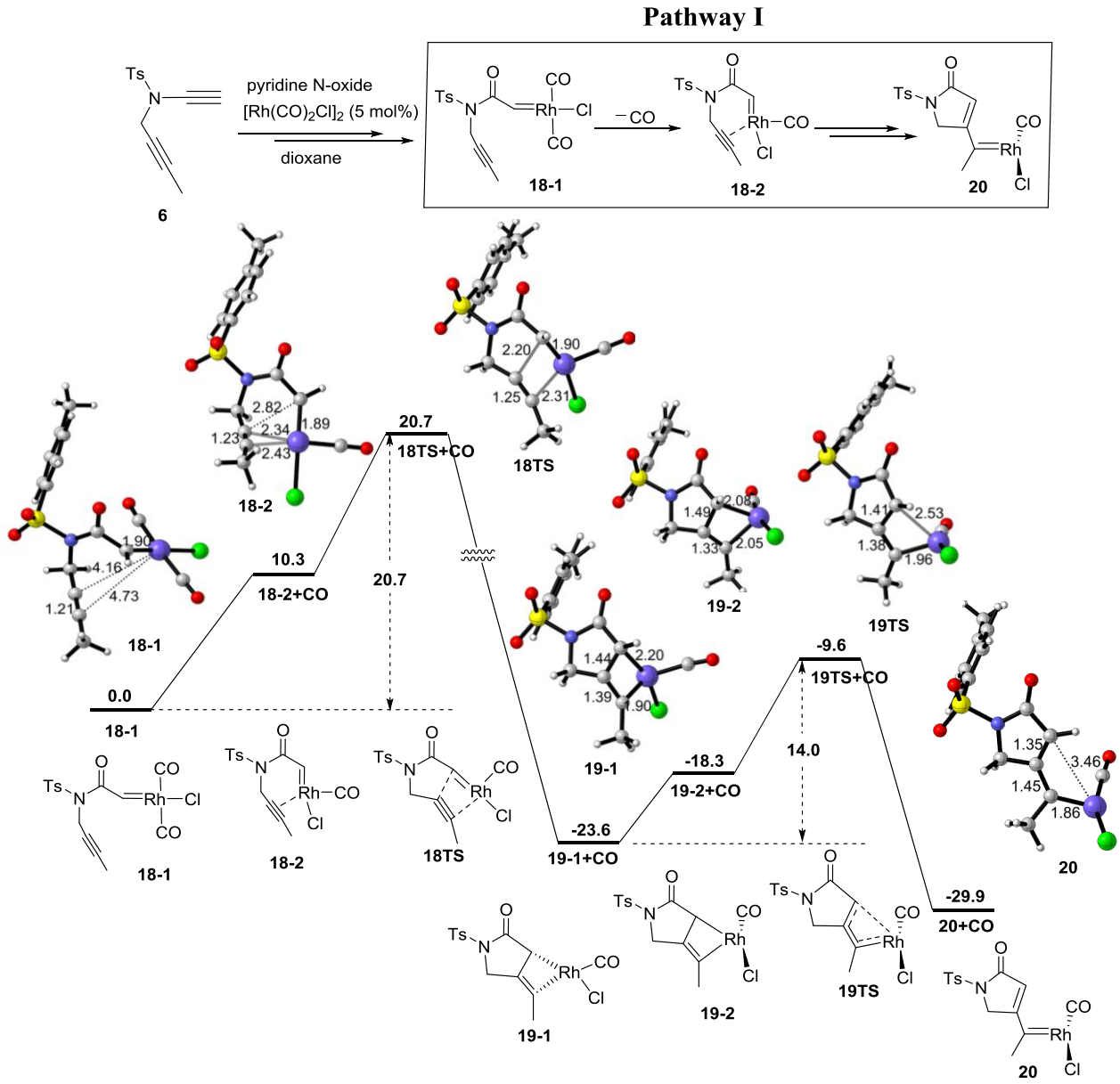



***Figure S1.*** The free energy surfaces for the metathesis of carbenoids **18-1** along **pathway I**.

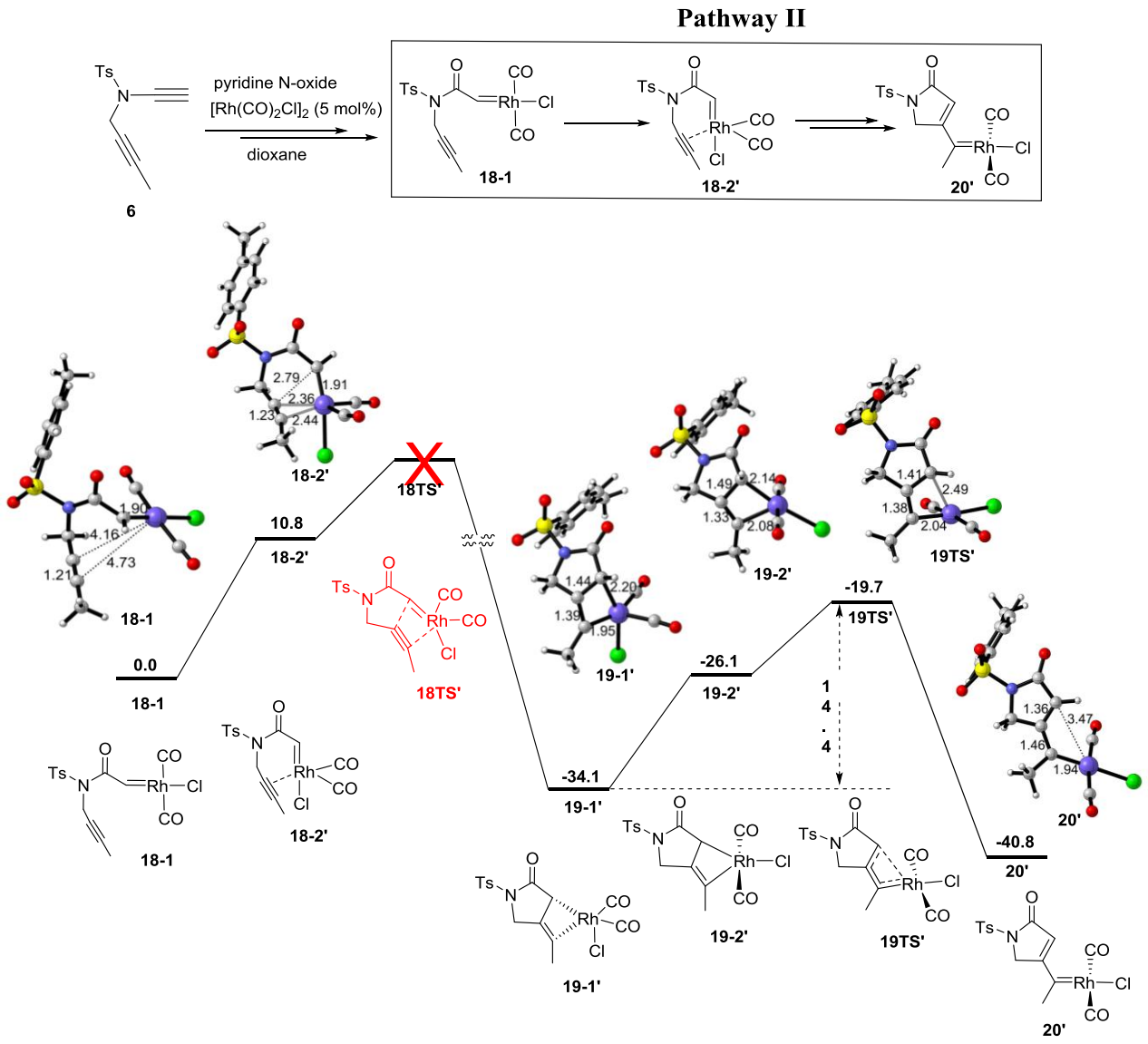



***Figure S2.*** The free energy surfaces for the metathesis of carbenoid **18-1** along **pathway II**.

**Computational results for Rh-catalyzed oxidative cycloisomerization of enynes:**

Similar to carbenoid **18-1**, 16e rhodium carbenoid **21** adopts a square-planar geometry in which the tethered alkene moiety does not coordinate to the rhodium metal center as evidenced by the long distances (4.38 Å and 4.44 Å) between the Rh atom and two carbon atoms of the alkene moiety.

For the oxidative cycloisomerization of enynes, two mechanisms (see Figures S3 and S4) have been considered. As shown in Figure S3, as the tethered alkene approaches the metal

carbene, carbenoid **21** can be directly converted to the cyclopropanation product complex **23** via a concerted transition state **21TS-1**, in which the two forming C-C bonds are 2.08 Å and 2.20 Å, respectively. This one-step process requires an activation free energy of 8.4 kcal/mol. Subsequently, product complex **23** isomerizes to a more stable product complex **24**, which can produce cyclopropanation product **9b** through ligand exchange.

Alternatively, carbenoid **21** can be converted to cyclopropanation product complex **23** through a stepwise pathway (Figure S4): Firstly, an intermediate metallacyclobutane **22** is formed via transition state **21TS-2,** in which the forming new C-C bond and Rh-C bond are 2.34 Å and 2.46 Å, respectively. Subsequently, metallacyclobutane **22** undergoes reductive elimination via **22TS** to afford cyclopropanation product complex **23**. In the transition state **22TS**, the forming C-C bond in the three-membered ring is 1.76 Å, and the two breaking Rh-C bonds are 2.34 Å and 2.36 Å, respectively. The free energy barriers for these two consecutive steps are 9.4 kcal/mol and 13.7 kcal/mol respectively, which are much higher than that for the one-step pathway. Therefore, the concerted one-step pathway is preferred for the oxidative cycloisomerization of enynes.

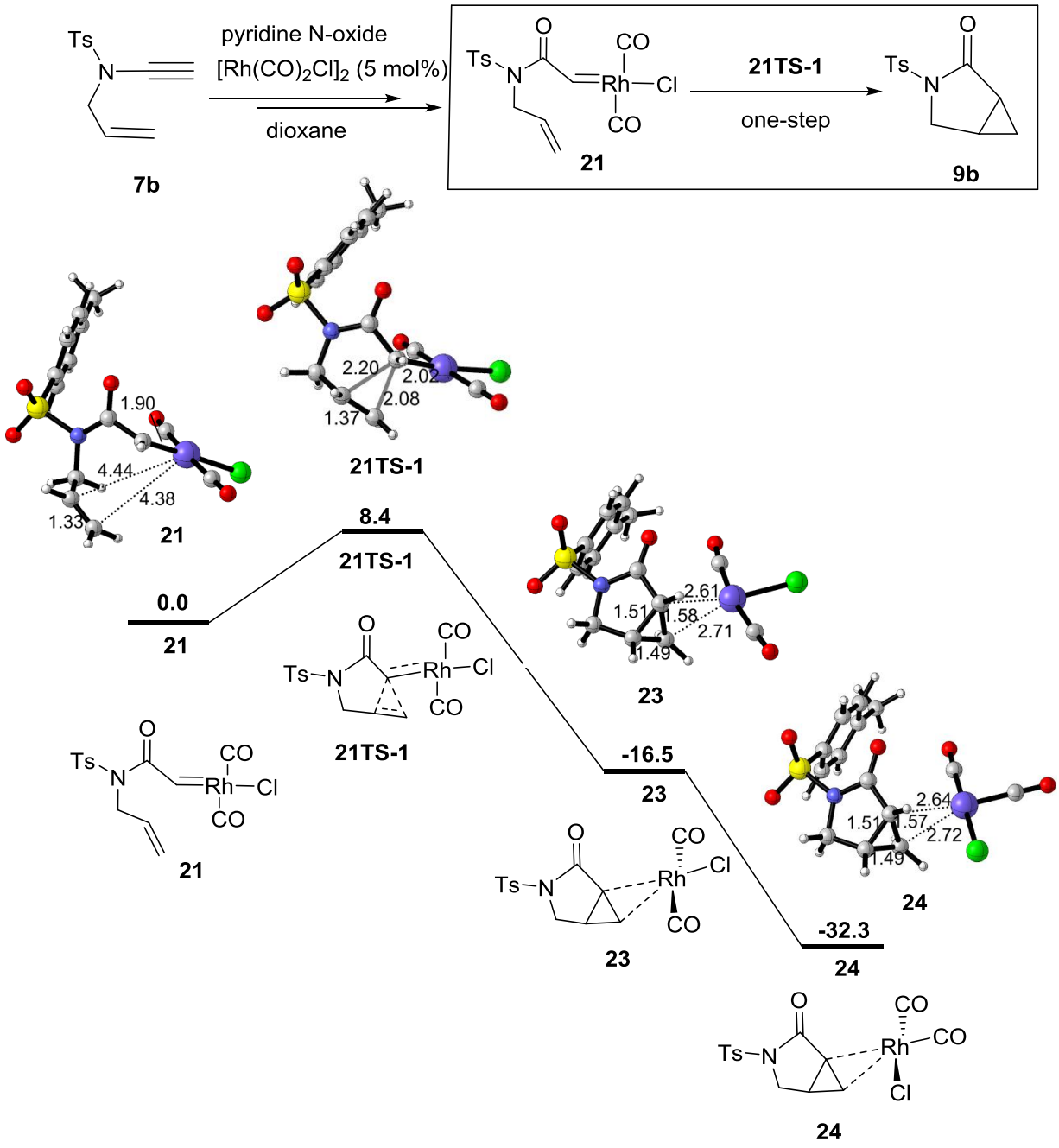



***Figure S3.*** The free energy surfaces for the direct cyclopropanation of carbenoid **21** with the tethered alkene.

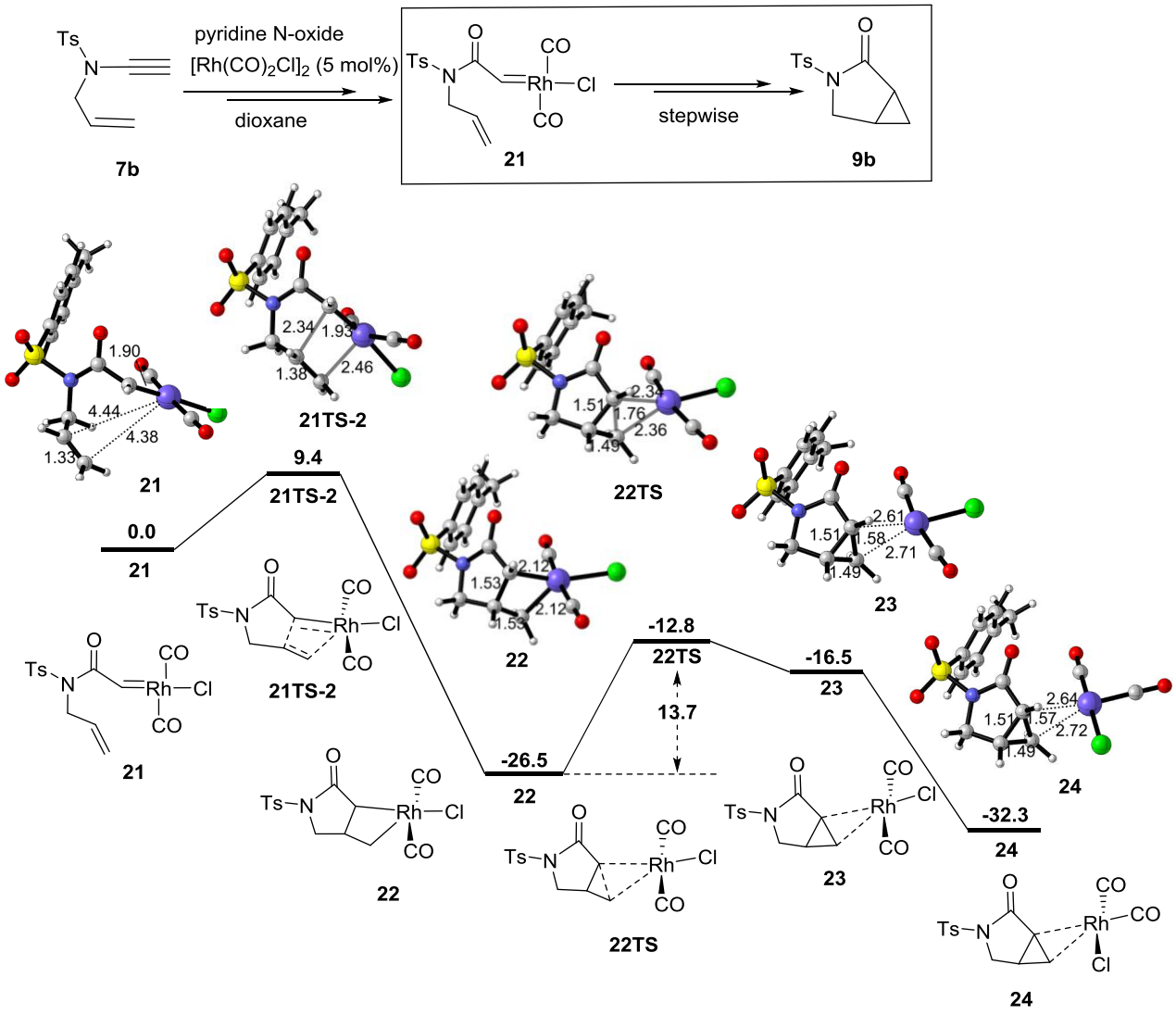



***Figure S4.*** The free energy surfaces for the metathesis of carbenoids **21** with the tethered alkene *via* intermediate **22**.

Dissociation of one CO from carbenoid **21** may generate carbenoid **21´** (Figure S5). Calculation result suggests that metathesis of carbenoid **21´** may not work at room temperature since it needs about an overall activation free energy of 30.0 kcal/mol.

All the free energy barriers shown in Figure 1 and 3 are lower than 21 kcal/mol, indicating that oxidative cycloisomerization of diynes and enynes involving metal carbenoids **18-1** and **21** can take place at room temperature.

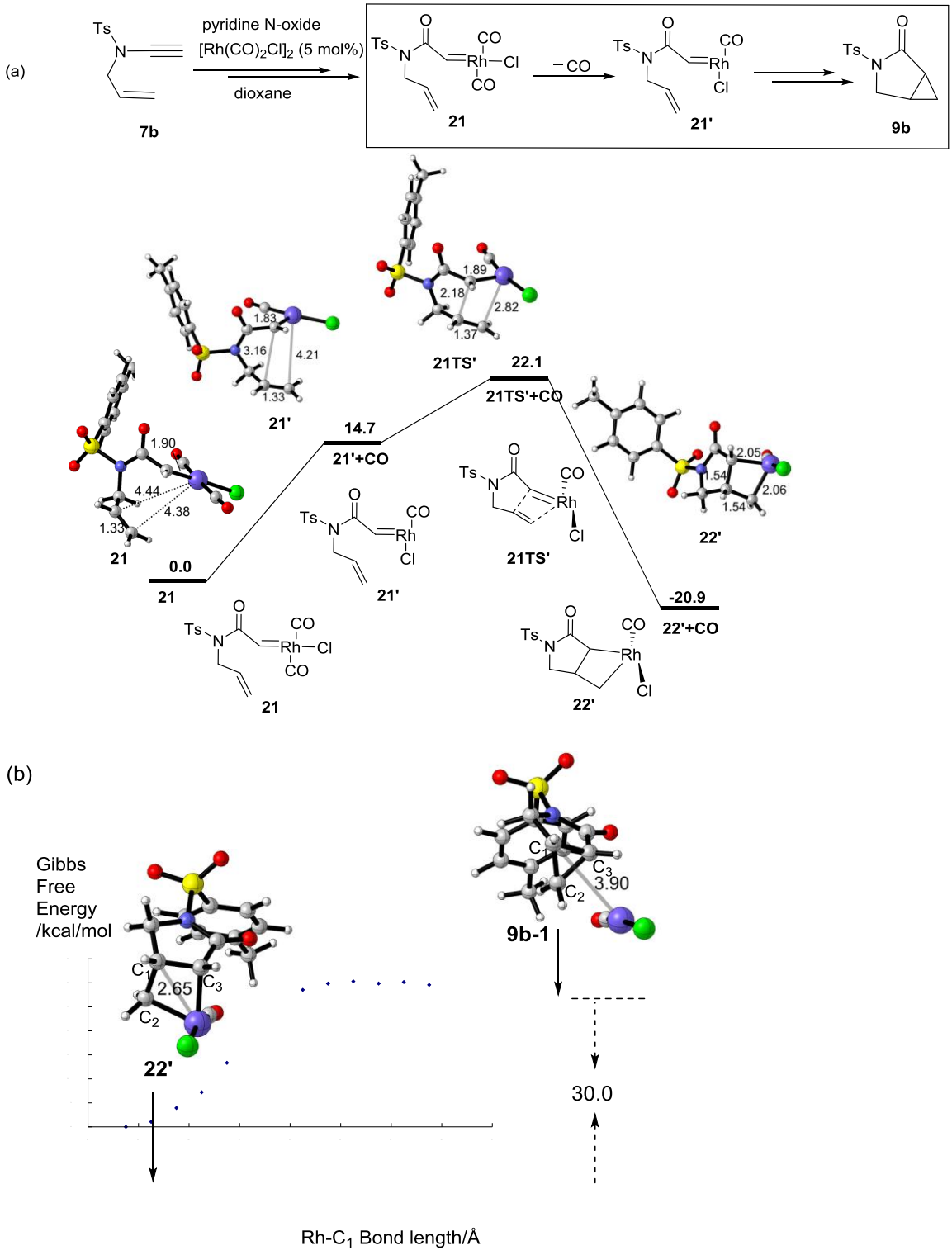



***Figure S5:*** (a) The free energy surface of the alkene insertion step in the metathesis of **21**´. (b) The scanned free energy surface for the reductive elimination of **22**´ with the increase of the

distance between Rh atom and $C_1$ atom. Energies are in kcal/mol and calculated using B3LYP/SDD-6-31G*/SMD (1,4-dioxane). Bond lengths are in Å.

*Note: we didn't locate the transition state for the reductive elimination of **22´** successfully, so we performed the scan of the free energy surface for the reductive elimination of **22´** to estimate the free energy barrier of this step. And the result indicates that the overall free energy barrier for the metathesis of **21´** is about 30.0 kcal/mol.*

**The Cartesian coordinates (Å), SCF energies and Gibbs free energies at 298K for the optimized structures.**

**18-1,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1979.1737681 a.u.
Thermal free energy correction in gas phase: 0.188072 a.u.
Gibbs free energy after correction at 298K: -1978.985696 a.u.
Gibbs free energy in gas phase at 298K: -1978.968421 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.01055600 | 0.01549600 | 0.01004700 |
| O | -0.01543500 | 0.02464800 | 1.23654900 |
| S | 2.70616200 | 0.01339700 | 0.00709400 |
| O | 2.72421300 | 1.17484000 | 0.88580700 |
| O | 3.63244400 | -0.10656400 | -1.12184200 |
| C | 2.78907600 | -1.48382000 | 0.97171100 |
| C | 2.41980600 | -1.46062600 | 2.31800500 |
| C | 3.27169500 | -2.64705300 | 0.36532600 |
| C | 2.52919200 | -2.63486500 | 3.05946500 |
| H | 2.05297300 | -0.54506100 | 2.76512800 |
| C | 3.36832900 | -3.80898900 | 1.12615000 |
| H | 3.58442600 | -2.63312600 | -0.67320200 |
| C | 2.99504900 | -3.82389900 | 2.47910300 |

| | | | |
|---|---|---|---|
| H | 2.24795100 | -2.62605200 | 4.10925800 |
| H | 3.74739100 | -4.71698100 | 0.66435400 |
| C | 3.07443100 | -5.09732900 | 3.28592200 |
| H | 2.14121800 | -5.66982500 | 3.20165000 |
| H | 3.88580800 | -5.74415600 | 2.93664600 |
| H | 3.23466400 | -4.88943800 | 4.34860200 |
| N | 1.11978000 | -0.06989700 | -0.77156800 |
| C | 1.04267700 | 0.02365200 | -2.25182200 |
| H | 0.50735500 | -0.85530900 | -2.62923500 |
| H | 2.07247100 | -0.03522100 | -2.61261800 |
| C | 0.39583300 | 1.25156800 | -2.71629200 |
| C | -0.13360100 | 2.26336400 | -3.11806600 |
| C | -0.74817400 | 3.49617000 | -3.60377400 |
| H | -0.13821200 | 3.95154700 | -4.39293300 |
| H | -1.74688500 | 3.31162100 | -4.01656600 |
| H | -0.84664500 | 4.23033800 | -2.79534800 |
| C | -1.34941100 | 0.05731400 | -0.64130900 |
| H | -1.73441900 | 1.08080900 | -0.62672000 |
| Cl | -3.77861800 | -3.21944300 | -1.93737100 |
| C | -3.83876000 | -0.19850000 | -1.74853800 |
| O | -4.69324000 | 0.48107000 | -2.07978600 |
| Rh | -2.41257800 | -1.41435800 | -1.19973600 |
| C | -1.08053000 | -2.74401900 | -0.67411400 |
| O | -0.35584800 | -3.57779200 | -0.38860400 |

**18-2,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1865.843779 a.u.

Thermal free energy correction in gas phase: 0.19045909 a.u.

Gibbs free energy after correction at 298K: -1865.65332 a.u.

Gibbs free energy in gas phase at 298K: -1865.636082 a.u.

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.16225400 | -0.27227200 | -0.55572600 |
| O | 0.41438000 | -0.93290100 | -1.41259600 |
| S | 2.06583600 | -0.45376000 | 0.99876100 |
| O | 2.06492200 | -1.90812300 | 0.89910600 |
| O | 2.36432900 | 0.21731100 | 2.26799000 |
| C | 3.09787100 | 0.24741300 | -0.27397900 |
| C | 3.39378100 | -0.50137600 | -1.41480400 |
| C | 3.63326100 | 1.52288800 | -0.07658500 |
| C | 4.23653700 | 0.05258200 | -2.37534100 |
| H | 2.96238500 | -1.48601000 | -1.54450100 |
| C | 4.47010400 | 2.05679600 | -1.05298900 |
| H | 3.40897600 | 2.07630800 | 0.82881800 |
| C | 4.78587300 | 1.33316700 | -2.21312700 |
| H | 4.47001200 | -0.52101900 | -3.26852400 |
| H | 4.88993300 | 3.04899900 | -0.90907200 |

| | | | |
|---|---|---|---|
| C | 5.72069000 | 1.90789400 | -3.24985400 |
| H | 6.75719900 | 1.60487500 | -3.05080200 |
| H | 5.46728200 | 1.55797500 | -4.25576900 |
| H | 5.69513100 | 3.00223000 | -3.25094700 |
| N | 0.45043000 | 0.15324200 | 0.61150600 |
| C | -0.35430300 | 0.71311100 | 1.71762200 |
| H | -0.68815000 | 1.72235600 | 1.46078100 |
| H | 0.30051900 | 0.78709400 | 2.58998100 |
| C | -1.48956500 | -0.17972800 | 1.99807800 |
| C | -2.21031000 | -1.13230700 | 2.27424200 |
| C | -2.96212900 | -2.27347900 | 2.79823300 |
| H | -2.46122900 | -2.65285700 | 3.69666700 |
| H | -3.98049300 | -1.96863900 | 3.05429900 |
| H | -3.01182500 | -3.08110500 | 2.06060900 |
| C | -1.59867700 | 0.06306200 | -0.80579400 |
| H | -1.67180500 | 0.34312700 | -1.86060200 |
| Rh | -3.11573000 | 0.00069300 | 0.32145400 |
| Cl | -4.99623400 | 0.31925300 | 1.75076500 |
| C | -4.20147700 | 0.49754500 | -1.12822700 |
| O | -4.87554300 | 0.80261900 | -2.00348700 |

**18TS,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1865.824817 a.u.

SMD solvation energy correction: 0.18812323 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1865.636694 a.u.

Gibbs free energy in gas phase at 298K: -1865.617435 a.u.

Imaginary frequency: -311.66 $cm^{-1}$

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.20094900 | -0.61816900 | -0.83563700 |
| O | 0.72484700 | -1.01754200 | -1.86737500 |
| S | 2.61986900 | -0.24613600 | 0.38856800 |
| O | 3.05004700 | -1.58292500 | 0.00438100 |
| O | 2.87199600 | 0.29220300 | 1.72671600 |
| C | 3.14470300 | 0.93885800 | -0.83139000 |
| C | 3.38376100 | 0.52260500 | -2.14353500 |
| C | 3.32526200 | 2.26881500 | -0.44042000 |
| C | 3.80346400 | 1.46850900 | -3.07546500 |
| H | 3.23134200 | -0.51250800 | -2.42309600 |
| C | 3.74424200 | 3.19546800 | -1.39133300 |
| H | 3.15549400 | 2.56475700 | 0.58910600 |
| C | 3.98958400 | 2.81273100 | -2.71902500 |
| H | 3.98763900 | 1.15599500 | -4.09995900 |
| H | 3.88608300 | 4.23191100 | -1.09678100 |
| C | 4.47176200 | 3.81980700 | -3.73473100 |
| H | 5.56911500 | 3.84976800 | -3.76286900 |
| H | 4.12673600 | 3.56833800 | -4.74268900 |

| | | | |
|---|---|---|---|
| H | 4.12335100 | 4.82936500 | -3.49506500 |
| N | 0.86850000 | -0.20334300 | 0.29660100 |
| C | 0.12772300 | 0.20400800 | 1.50193200 |
| H | 0.44573400 | 1.20486600 | 1.80848900 |
| H | 0.34588700 | -0.48474300 | 2.32533900 |
| C | -1.33078900 | 0.21036300 | 1.23331100 |
| C | -2.54797600 | 0.31997500 | 1.49291300 |
| C | -3.85942200 | 0.32105500 | 2.14504800 |
| H | -3.74458600 | 0.06634100 | 3.20605300 |
| H | -4.31681700 | 1.30902100 | 2.04827500 |
| H | -4.52157300 | -0.41668800 | 1.67782300 |
| C | -1.28472900 | -0.51954900 | -0.83645900 |
| H | -1.76399200 | -1.50129500 | -0.93018300 |
| Rh | -2.24122000 | 1.11535200 | -0.65543700 |
| Cl | -3.22923000 | 3.11866800 | 0.21232500 |
| C | -3.04427200 | 1.35835800 | -2.34683500 |
| O | -3.55690400 | 1.43167000 | -3.37177400 |

**19-1,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1865.898671a.u.

SMD solvation energy correction: 0.19139292 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1865.707278 a.u.

Gibbs free energy in gas phase at 298K: -1865.683878 a.u.

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.25780700 | -1.66839700 | -0.43381600 |
| O | 0.78255900 | -1.97366200 | -1.48497500 |
| S | 2.65535100 | -1.29039300 | 0.91316100 |
| O | 3.14079300 | -2.60031500 | 0.49630700 |
| O | 2.84395900 | -0.80141700 | 2.28149700 |
| C | 3.21472000 | -0.05263300 | -0.24007300 |
| C | 3.48880400 | -0.41305600 | -1.56150300 |
| C | 3.38258300 | 1.25978800 | 0.20964700 |
| C | 3.93140500 | 0.57099100 | -2.44239400 |
| H | 3.34268600 | -1.43524200 | -1.88835300 |
| C | 3.82627600 | 2.22581200 | -0.68996900 |
| H | 3.18184900 | 1.51064800 | 1.24563300 |
| C | 4.10730800 | 1.89879300 | -2.02542300 |
| H | 4.14246300 | 0.30202200 | -3.47412500 |
| H | 3.95978600 | 3.24921500 | -0.34900300 |
| C | 4.61592900 | 2.94736400 | -2.98521700 |
| H | 5.71322500 | 2.98887000 | -2.97264200 |
| H | 4.31006100 | 2.73061300 | -4.01375600 |
| H | 4.24877800 | 3.94441900 | -2.72167700 |
| N | 0.93489200 | -1.26195700 | 0.73350900 |
| C | 0.06763500 | -1.06529000 | 1.90451800 |
| H | 0.24577000 | -0.09865700 | 2.37971200 |

| | | | |
|---|---|---|---|
| H | 0.22547600 | -1.85511300 | 2.65068400 |
| C | -1.30950200 | -1.18203900 | 1.26821700 |
| C | -2.50942700 | -0.56146200 | 1.57523400 |
| C | -3.37955800 | -0.32645400 | 2.74400400 |
| H | -2.83289900 | -0.53279400 | 3.67409000 |
| H | -3.76248300 | 0.69767800 | 2.74424700 |
| H | -4.23840500 | -1.01116400 | 2.71140700 |
| C | -1.19952300 | -1.63733600 | -0.09217000 |
| H | -1.84091400 | -2.40017800 | -0.51814100 |
| Rh | -2.39361900 | 0.20867500 | -0.15302500 |
| Cl | -3.18448800 | 2.37510600 | 0.34230000 |
| C | -3.58092400 | -0.24453200 | -1.55752500 |
| O | -4.40150500 | -0.62107700 | -2.26789900 |

**19-2,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1865.892226 a.u.

SMD solvation energy correction: 0.19326724 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1865.698958 a.u.

Gibbs free energy in gas phase at 298K: -1865.675196 a.u.

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.30230200 | -1.44013900 | -1.76204200 |
| C | -0.11692700 | -1.13887500 | 0.66595200 |

| | | | |
|---|---|---|---|
| C | 1.28489900 | -1.26273700 | 0.10286200 |
| N | -0.97703300 | -1.28317100 | -0.43958100 |
| O | -0.46852600 | -0.98247100 | 1.81743600 |
| C | 1.09188300 | -1.02681600 | -1.35880800 |
| C | 1.96258500 | -0.08685200 | -1.71377600 |
| Rh | 2.81568500 | 0.13868300 | 0.13291800 |
| S | -2.67738400 | -1.57472900 | -0.28852500 |
| O | -2.87175700 | -2.62554400 | 0.70317200 |
| O | -3.10687600 | -1.73806000 | -1.67957100 |
| C | -3.32897800 | -0.03705200 | 0.34062600 |
| C | -3.86277000 | 0.88482700 | -0.56321500 |
| C | -3.33662200 | 0.20279400 | 1.71712000 |
| C | -4.40212700 | 2.07200600 | -0.07311900 |
| H | -3.87453300 | 0.66046600 | -1.62427400 |
| C | -3.87905900 | 1.39808100 | 2.18280900 |
| H | -2.91886300 | -0.52812100 | 2.39837200 |
| C | -4.41407700 | 2.35002300 | 1.30175800 |
| H | -4.82879400 | 2.79001700 | -0.76891300 |
| H | -3.89153400 | 1.59254300 | 3.25216800 |
| C | -4.97354300 | 3.65260100 | 1.82141900 |
| H | -5.40590100 | 3.53273800 | 2.82005300 |
| H | -5.74873900 | 4.04984800 | 1.15825600 |
| H | -4.18569600 | 4.41389100 | 1.89675700 |
| Cl | 4.53027400 | -1.34822300 | -0.15903000 |

| | | | |
|---|---|---|---|
| C | 1.64753700 | 1.55771400 | 0.54581700 |
| O | 0.98829800 | 2.45457200 | 0.83376200 |
| C | 2.23919800 | 0.75112400 | -2.90678200 |
| H | 2.12998900 | 1.81945500 | -2.68082400 |
| H | 1.54168300 | 0.49380700 | -3.71587700 |
| H | 3.26019800 | 0.59507300 | -3.27343500 |
| H | -0.37779800 | -2.47830400 | -2.10480500 |
| H | -0.76065100 | -0.78883800 | -2.50889700 |
| H | 1.78783800 | -2.17487700 | 0.43672200 |

**19TS,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1865.876341 a.u.

SMD solvation energy correction: 0.19128024 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1865.685061 a.u.

Gibbs free energy in gas phase at 298K: -1865.662782 a.u.

Imaginary frequency: -168.48 $cm^{-1}$

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.09742200 | -0.02025300 | 0.17672400 |
| C | 0.00672200 | 0.06853700 | 2.59402900 |
| C | 1.43872700 | 0.02217700 | 2.16874600 |
| N | -0.72751200 | 0.04924300 | 1.39652800 |
| O | -0.44932600 | 0.10376100 | 3.71974100 |

| | | | |
|---|---|---|---|
| C | 1.49020100 | 0.14850300 | 0.76193300 |
| C | 2.59409800 | 0.80649900 | 0.26561400 |
| Rh | 3.45556300 | 1.51249600 | 1.87322000 |
| S | -2.44273900 | -0.18811000 | 1.32067000 |
| O | -2.77938000 | -1.33155300 | 2.15903400 |
| O | -2.70667600 | -0.18171500 | -0.11988100 |
| C | -3.10395600 | 1.29993700 | 2.04613200 |
| C | -3.47585800 | 2.35007600 | 1.20303500 |
| C | -3.27180900 | 1.38033800 | 3.43123300 |
| C | -4.01502000 | 3.50437700 | 1.76610600 |
| H | -3.36494400 | 2.25054500 | 0.12871400 |
| C | -3.81165200 | 2.54533900 | 3.97020800 |
| H | -2.97679200 | 0.55276400 | 4.06447100 |
| C | -4.18582100 | 3.62331500 | 3.15344000 |
| H | -4.31573300 | 4.32275000 | 1.11704400 |
| H | -3.94789700 | 2.61670900 | 5.04619200 |
| C | -4.74274900 | 4.88977200 | 3.75768900 |
| H | -5.33936800 | 4.67845400 | 4.65110900 |
| H | -5.37295700 | 5.43157000 | 3.04536000 |
| H | -3.93287900 | 5.56679300 | 4.06037500 |
| Cl | 4.84631700 | -0.16459400 | 2.59160400 |
| C | 2.58410600 | 3.17367700 | 1.59918000 |
| O | 2.13065400 | 4.23144900 | 1.54449300 |
| C | 2.87555300 | 1.19252100 | -1.14237900 |

| | | | |
|---|---|---|---|
| H | 3.06819400 | 2.26988500 | -1.22471100 |
| H | 2.05141800 | 0.92026100 | -1.81567300 |
| H | 3.78506700 | 0.69009700 | -1.49580500 |
| H | -0.03983800 | -0.98444600 | -0.32719400 |
| H | -0.17745400 | 0.77219200 | -0.52539300 |
| H | 2.17571400 | -0.44146900 | 2.81231800 |

**20,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1865.907382 a.u.

SMD solvation energy correction: 0.19004001 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1865.717342 a.u.

Gibbs free energy in gas phase at 298K: -1865.693539 a.u.

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| S | -2.63928600 | -1.82558000 | 0.04413800 |
| O | -2.93769200 | -2.58014300 | 1.25387800 |
| O | -2.49927600 | -2.47480700 | -1.26121800 |
| O | -1.42040700 | 0.00107400 | 2.31993900 |
| N | -1.09737400 | -1.07331100 | 0.26247700 |
| C | -3.77288200 | -0.45768800 | -0.09829100 |
| C | -4.14859800 | -0.02643700 | -1.37284600 |
| H | -3.75225800 | -0.52078200 | -2.25309300 |
| C | -5.05104700 | 1.02870600 | -1.48557100 |

| | | | |
|---|---|---|---|
| H | -5.35119500 | 1.36919000 | -2.47323900 |
| C | -5.58238700 | 1.65352100 | -0.34768700 |
| C | -5.18482500 | 1.19412600 | 0.91736500 |
| H | -5.58572400 | 1.66885800 | 1.80915400 |
| C | -4.28693600 | 0.13893300 | 1.05659000 |
| H | -3.97543600 | -0.20801800 | 2.03427100 |
| C | -6.58316800 | 2.77611400 | -0.47945900 |
| H | -6.47502700 | 3.30058400 | -1.43407800 |
| H | -6.47332300 | 3.50765700 | 0.32781900 |
| H | -7.61023300 | 2.39063700 | -0.43160100 |
| C | -0.71566300 | -0.32353900 | 1.38512000 |
| C | 0.71409900 | 0.00872000 | 1.14992700 |
| C | 1.14151900 | -0.52209000 | -0.01986900 |
| C | 0.00376100 | -1.29691900 | -0.66892100 |
| H | -0.24014200 | -0.92151200 | -1.66990300 |
| H | 0.23342200 | -2.36444500 | -0.76168800 |
| C | 2.48871000 | -0.48080900 | -0.56395500 |
| H | 1.29679300 | 0.57729300 | 1.86303700 |
| Rh | 3.84673700 | 0.71346300 | -0.14775600 |
| Cl | 5.72687700 | -0.48674100 | 0.41839100 |
| C | 2.67243800 | 2.15634300 | -0.12323400 |
| O | 1.98457600 | 3.07996000 | -0.05106200 |
| C | 2.88202800 | -1.59009500 | -1.50076200 |
| H | 3.87028400 | -1.44306100 | -1.93597800 |

| | | | |
|---|---|---|---|
| H | 2.88794700 | -2.54459700 | -0.95258300 |
| H | 2.14514100 | -1.68255700 | -2.31202400 |

**21,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1941.105572 a.u.
Thermal free energy correction in gas phase: 0.1863185 a.u.
Gibbs free energy after correction at 298K: -1940.919253 a.u.
Gibbs free energy in gas phase at 298K: -1940.903245 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.00000000 | 0.00000000 | 0.00000000 |
| O | 0.00000000 | 0.00000000 | 1.22757201 |
| S | 2.71013880 | 0.00000000 | -0.00448877 |
| O | 2.73222611 | 1.16760567 | 0.86745015 |
| O | 3.64112993 | -0.12806056 | -1.12814347 |
| C | 2.78329130 | -1.49243089 | 0.96791861 |
| C | 2.40892953 | -1.46187478 | 2.31381607 |
| C | 3.26121475 | -2.66000975 | 0.36836751 |
| C | 2.50999530 | -2.63242923 | 3.06000761 |
| H | 2.04005256 | -0.54394095 | 2.75410441 |
| C | 3.34983000 | -3.81993938 | 1.13518986 |
| H | 3.57206945 | -2.65425544 | -0.67073381 |
| C | 2.97768668 | -3.82583301 | 2.48719809 |
| H | 2.21910152 | -2.61939045 | 4.10726638 |
| H | 3.71963371 | -4.73335403 | 0.67705482 |
| C | 3.09699294 | -5.07932986 | 3.31988298 |

| | | | |
|---|---|---|---|
| H | 3.24512026 | -5.96488091 | 2.69470884 |
| H | 3.94937095 | -5.01207589 | 4.00825817 |
| H | 2.20120122 | -5.23864456 | 3.93033523 |
| N | 1.12462570 | -0.06535867 | -0.78902924 |
| C | 1.04892944 | 0.05140695 | -2.26550827 |
| H | 0.38432838 | -0.73065079 | -2.64715998 |
| H | 2.05824596 | -0.15352864 | -2.63079902 |
| C | -1.35050767 | 0.03429705 | -0.62598366 |
| H | -1.73510806 | 1.05872142 | -0.61720211 |
| Rh | -2.42911550 | -1.43818002 | -1.15022662 |
| Cl | -3.80700375 | -3.24334932 | -1.86318290 |
| C | -1.06449911 | -2.76297901 | -0.69921781 |
| O | -0.32176357 | -3.59366907 | -0.45486787 |
| C | 0.58850140 | 1.41274697 | -2.71765333 |
| H | 1.15675668 | 2.25703320 | -2.32816425 |
| C | -0.42176030 | 1.61046595 | -3.56731438 |
| H | -0.69725024 | 2.60680964 | -3.90143048 |
| H | -0.99683803 | 0.78122415 | -3.97493048 |
| C | -3.89502816 | -0.23102804 | -1.60758130 |
| O | -4.77610859 | 0.43993314 | -1.88087533 |

**21TS-1,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1941.095861 a.u.
Thermal free energy correction in gas phase: 0.1899804 a.u.
Gibbs free energy after correction at 298K: -1940.905881 a.u.
Gibbs free energy in gas phase at 298K: -1940.883759 a.u.

Imaginary frequency: -302.6892 $cm^{-1}$
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.00000000 | 0.00000000 | 0.00000000 |
| O | 0.00000000 | 0.00000000 | 1.21969027 |
| S | 2.74555449 | 0.00000000 | -0.02987542 |
| O | 2.81060337 | 1.10785228 | 0.91411302 |
| O | 3.62415514 | -0.05863697 | -1.20106514 |
| C | 2.82388790 | -1.55048027 | 0.84098933 |
| C | 2.40888128 | -1.62029080 | 2.17424097 |
| C | 3.32772505 | -2.66848941 | 0.17168136 |
| C | 2.49197586 | -2.84361057 | 2.83314452 |
| H | 2.02014198 | -0.73964554 | 2.67003196 |
| C | 3.40169620 | -3.88086666 | 0.85354738 |
| H | 3.66604047 | -2.58411391 | -0.85527603 |
| C | 2.98476484 | -3.98923974 | 2.18817583 |
| H | 2.16532653 | -2.91043074 | 3.86762650 |
| H | 3.79108704 | -4.75640732 | 0.34107454 |
| C | 3.08222476 | -5.30211170 | 2.92662313 |
| H | 3.22277990 | -6.14044003 | 2.23790826 |
| H | 3.93119024 | -5.29763693 | 3.62265825 |
| H | 2.18012809 | -5.49358512 | 3.51775966 |
| N | 1.15193315 | -0.00094807 | -0.77015051 |
| C | 1.03939011 | 0.20118337 | -2.22626352 |
| H | 1.13977030 | -0.74981550 | -2.76135568 |

| | | | |
|---|---|---|---|
| H | 1.84130351 | 0.86287995 | -2.55908175 |
| C | -1.34651618 | -0.03508220 | -0.69643913 |
| H | -1.87294961 | 0.89878121 | -0.49575969 |
| Rh | -2.43161916 | -1.73922347 | -0.59644286 |
| Cl | -3.74467668 | -3.69675076 | -0.19940514 |
| C | -0.90041473 | -2.92851042 | -0.66884073 |
| O | -0.05453596 | -3.69764423 | -0.73111502 |
| C | -0.31252369 | 0.81680655 | -2.44756505 |
| H | -0.42044735 | 1.88003413 | -2.24937810 |
| C | -1.40237186 | 0.05430725 | -2.77252012 |
| H | -2.37351691 | 0.50464065 | -2.94907546 |
| H | -1.28902977 | -0.97181775 | -3.10108446 |
| C | -4.09738281 | -0.75728812 | -0.57875822 |
| O | -5.10828304 | -0.21983011 | -0.57551646 |

**23,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1941.13642 a.u.
Thermal free energy correction in gas phase: 0.1908831 a.u.
Gibbs free energy after correction at 298K: -1940.945537 a.u.
Gibbs free energy in gas phase at 298K: -1940.924321 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.00000000 | 0.00000000 | 0.00000000 |
| O | 0.00000000 | 0.00000000 | 1.21578404 |
| S | 2.75599315 | 0.00000000 | -0.22266352 |
| O | 2.87624555 | 1.12980585 | 0.68953605 |
| O | 3.54667713 | -0.08783834 | -1.45172602 |

| | | | |
|---|---|---|---|
| C | 2.90794724 | -1.52454759 | 0.68739766 |
| C | 2.54213203 | -1.56587958 | 2.03656732 |
| C | 3.41997358 | -2.64810206 | 0.03483966 |
| C | 2.68148815 | -2.76554484 | 2.72811463 |
| H | 2.14837825 | -0.68091780 | 2.52095858 |
| C | 3.55337774 | -3.83707554 | 0.75009317 |
| H | 3.72329257 | -2.58334255 | -1.00457074 |
| C | 3.18561874 | -3.91633117 | 2.10069277 |
| H | 2.39454235 | -2.80899712 | 3.77558431 |
| H | 3.95545760 | -4.71554024 | 0.25232301 |
| C | 3.33908217 | -5.20281116 | 2.87567969 |
| H | 3.62869820 | -6.03295780 | 2.22466660 |
| H | 4.10678010 | -5.10369782 | 3.65337671 |
| H | 2.40434607 | -5.47548757 | 3.37910061 |
| N | 1.12343065 | -0.03924988 | -0.81976275 |
| C | 0.84247018 | 0.15074157 | -2.25370225 |
| H | 1.36329857 | -0.60168202 | -2.85133947 |
| H | 1.17366573 | 1.14147615 | -2.58173923 |
| C | -1.20739784 | 0.01042234 | -0.90889581 |
| H | -2.05345058 | 0.62233658 | -0.60185080 |
| Rh | -3.07747212 | -1.44857780 | 0.17316874 |
| Cl | -4.75447868 | -2.40547482 | 1.49750557 |
| C | -1.84319202 | -2.31027142 | 1.42264959 |
| O | -1.20169479 | -2.86931135 | 2.18400181 |

| | | | |
|---|---|---|---|
| C | -0.67710418 | 0.03300835 | -2.32642882 |
| H | -1.19198755 | 0.61268066 | -3.08581862 |
| C | -1.30018410 | -1.24048485 | -1.86626554 |
| H | -2.24865164 | -1.50942454 | -2.31921069 |
| H | -0.65755125 | -2.08228250 | -1.62600647 |
| C | -4.53085690 | -0.73969132 | -0.87237773 |
| O | -5.43778483 | -0.34814348 | -1.45297407 |

**24,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1941.165774 a.u.
Thermal free energy correction in gas phase: 0.1950856 a.u.
Gibbs free energy after correction at 298K: -1940.970689 a.u.
Gibbs free energy in gas phase at 298K: -1940.951351 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.00000000 | 0.00000000 | 0.00000000 |
| O | 0.00000000 | 0.00000000 | 1.21615496 |
| S | 2.75464455 | 0.00000000 | -0.22913647 |
| O | 2.88793298 | 1.13188264 | 0.67895577 |
| O | 3.54559624 | -0.10170277 | -1.45694094 |
| C | 2.89529330 | -1.52135851 | 0.68931382 |
| C | 2.55563805 | -1.54632722 | 2.04451530 |
| C | 3.36945750 | -2.66074563 | 0.03413981 |
| C | 2.68573345 | -2.74438046 | 2.74251486 |
| H | 2.18736477 | -0.65058996 | 2.52923195 |
| C | 3.49317263 | -3.84678299 | 0.75418263 |
| H | 3.64977233 | -2.60949636 | -1.01250638 |

| | | | |
|---|---|---|---|
| C | 3.15452104 | -3.90830311 | 2.11436737 |
| H | 2.41793102 | -2.77533790 | 3.79540723 |
| H | 3.86396216 | -4.73756629 | 0.25361866 |
| C | 3.31859832 | -5.18986232 | 2.89537388 |
| H | 4.28418489 | -5.20741293 | 3.41789171 |
| H | 2.53691689 | -5.29781914 | 3.65446518 |
| H | 3.28442754 | -6.06666078 | 2.24116562 |
| N | 1.12291454 | -0.03076730 | -0.82242002 |
| C | 0.83473780 | 0.16489515 | -2.25558525 |
| H | 1.36228337 | -0.57749995 | -2.85955677 |
| H | 1.15370964 | 1.16159234 | -2.57755075 |
| C | -1.20607127 | -0.00281408 | -0.90700703 |
| H | -2.07237381 | 0.58539565 | -0.61064934 |
| Rh | -3.11852840 | -1.50036896 | 0.12920614 |
| Cl | -4.62471412 | -0.39561113 | -1.30455737 |
| C | -1.91130622 | -2.38212278 | 1.27325409 |
| O | -1.20711034 | -2.95829379 | 1.97472560 |
| C | -0.68410970 | 0.03167086 | -2.32431367 |
| H | -1.21384466 | 0.60506470 | -3.07711551 |
| C | -1.28817750 | -1.25098272 | -1.86240917 |
| H | -2.24874386 | -1.51013201 | -2.29871266 |
| H | -0.63093867 | -2.08560111 | -1.63381544 |
| C | -4.55121972 | -2.17769453 | 1.05448610 |
| O | -5.45992853 | -2.59319437 | 1.62023593 |

**21TS-2,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1941.095592 a.u.
Thermal free energy correction in gas phase: 0.1912844 a.u.
Gibbs free energy after correction at 298K: -1940.904307 a.u.
Gibbs free energy in gas phase at 298K: -1940.884907 a.u.
Imaginary frequency: -236.4274 $cm^{-1}$
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.28027600 | 0.93753800 | 1.21961300 |
| O | 0.35756000 | 0.63093000 | 2.21834900 |
| S | 1.95375700 | 2.00731500 | 0.07633200 |
| O | 2.24052800 | 2.77653900 | 1.27902900 |
| O | 2.10398300 | 2.58533400 | -1.26104100 |
| C | 2.81312700 | 0.44725300 | 0.12944200 |
| C | 3.19459500 | -0.09353800 | 1.35917100 |
| C | 3.10972900 | -0.19596100 | -1.07643200 |
| C | 3.87711800 | -1.30824700 | 1.36978400 |
| H | 2.94959200 | 0.42230300 | 2.27916300 |
| C | 3.79005100 | -1.40963900 | -1.03927300 |
| H | 2.82701200 | 0.25645300 | -2.02077900 |
| C | 4.18361300 | -1.98398500 | 0.17977100 |
| H | 4.17507900 | -1.73951400 | 2.32173400 |
| H | 4.02357500 | -1.91752600 | -1.97141700 |
| C | 4.94570800 | -3.28679500 | 0.20316500 |
| H | 4.60025900 | -3.96622600 | -0.58305700 |
| H | 6.01743600 | -3.11494400 | 0.03701700 |
| H | 4.84046500 | -3.79575500 | 1.16614300 |

| | | | |
|---|---|---|---|
| N | 0.24965400 | 1.57175100 | 0.11211500 |
| C | -0.57311000 | 1.87545400 | -1.07538000 |
| H | -0.37145200 | 1.14940600 | -1.87173700 |
| H | -0.27525500 | 2.85961900 | -1.44689200 |
| C | -1.72929600 | 0.59292000 | 1.19238400 |
| H | -2.27006100 | 1.16775600 | 1.94981900 |
| Rh | -2.64453400 | -0.73853600 | 0.13078000 |
| Cl | -3.89560400 | -2.18900600 | -1.38321600 |
| C | -1.05130100 | -1.59995800 | -0.58364400 |
| O | -0.17339300 | -2.20629000 | -0.99804700 |
| C | -2.04371100 | 1.87392900 | -0.73568300 |
| H | -2.40253300 | 2.66011300 | -0.07326800 |
| C | -2.95415300 | 1.12053500 | -1.44516700 |
| H | -4.02023700 | 1.29299500 | -1.34002000 |
| H | -2.64903600 | 0.52764700 | -2.30237100 |
| C | -4.29017500 | -0.62879700 | 1.16599000 |
| O | -5.26654900 | -0.65834200 | 1.76202600 |

**22,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1941.156485 a.u.
Thermal free energy correction in gas phase: 0.1950407 a.u.
Gibbs free energy after correction at 298K: -1940.961444 a.u.
Gibbs free energy in gas phase at 298K: -1940.941416 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.03339000 | -1.13525300 | 0.98761600 |
| O | -0.40031200 | -0.50958500 | 1.93912000 |

| | | | |
|---|---|---|---|
| S | -2.46040400 | -1.98592700 | 0.16804900 |
| O | -2.75490400 | -2.51106100 | 1.49653000 |
| O | -2.80646700 | -2.73208300 | -1.04436800 |
| C | -3.09804400 | -0.32520200 | 0.03013900 |
| C | -3.22590800 | 0.46819100 | 1.17379100 |
| C | -3.49405100 | 0.13811500 | -1.22655300 |
| C | -3.74810800 | 1.75187900 | 1.03997700 |
| H | -2.90819800 | 0.08714700 | 2.13637500 |
| C | -4.01517200 | 1.42613100 | -1.33513500 |
| H | -3.41097600 | -0.50699400 | -2.09464200 |
| C | -4.14979500 | 2.25095100 | -0.20912100 |
| H | -3.84680100 | 2.37818500 | 1.92299800 |
| H | -4.32869700 | 1.79363200 | -2.30885000 |
| C | -4.73794000 | 3.63645100 | -0.32804600 |
| H | -4.73757500 | 3.98573100 | -1.36509000 |
| H | -5.77697100 | 3.65226200 | 0.02606000 |
| H | -4.17977400 | 4.35999700 | 0.27611200 |
| N | -0.74735200 | -1.77998000 | 0.02168500 |
| C | 0.02647800 | -2.60794000 | -0.92506100 |
| H | -0.35807800 | -2.49147300 | -1.94061900 |
| H | -0.04201500 | -3.66703600 | -0.65130400 |
| C | 1.47647800 | -1.33794600 | 0.60031300 |
| H | 2.06024200 | -1.76054900 | 1.42118000 |
| Rh | 2.45582400 | 0.43531100 | -0.01541700 |

| | | | |
|---|---|---|---|
| Cl | 3.67114200 | 2.50190700 | 0.15605700 |
| C | 0.82857500 | 1.52317400 | -0.10123000 |
| O | -0.07486800 | 2.21181700 | -0.18039500 |
| C | 1.45669300 | -2.06037600 | -0.74980400 |
| H | 2.20447100 | -2.85345400 | -0.84309700 |
| C | 1.81603600 | -0.83344800 | -1.58421200 |
| H | 2.65766100 | -0.93333700 | -2.27131100 |
| H | 0.96534300 | -0.35466700 | -2.07103200 |
| C | 4.17398500 | -0.47603600 | 0.05241600 |
| O | 5.20181400 | -0.97012700 | 0.09072500 |

**22TS,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1941.13394 a.u.
Thermal free energy correction in gas phase: 0.194291 a.u.
Gibbs free energy after correction at 298K: -1940.939649 a.u.
Gibbs free energy in gas phase at 298K: -1940.918006 a.u.
Imaginary frequency: -204.3995 $cm^{-1}$
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.04020000 | -1.23470600 | 0.81335700 |
| O | -0.29532000 | -0.49146100 | 1.73994100 |
| S | -2.68408500 | -1.87193900 | 0.32583600 |
| O | -2.91004400 | -2.25309700 | 1.71457900 |
| O | -3.21709600 | -2.66321100 | -0.78498400 |
| C | -3.11493100 | -0.15928900 | 0.09414500 |
| C | -3.08448800 | 0.71616900 | 1.18298100 |
| C | -3.50735700 | 0.26825700 | -1.17689700 |

| | | | |
|---|---|---|---|
| C | -3.44043800 | 2.04654600 | 0.97826800 |
| H | -2.78140300 | 0.35910000 | 2.15943400 |
| C | -3.85892600 | 1.60411900 | -1.35644600 |
| H | -3.55603700 | -0.43848500 | -1.99840400 |
| C | -3.82457900 | 2.51318800 | -0.28834800 |
| H | -3.41946500 | 2.73543400 | 1.81863100 |
| H | -4.17264700 | 1.94473500 | -2.33972900 |
| C | -4.17508800 | 3.96647400 | -0.49652400 |
| H | -4.73108000 | 4.36978500 | 0.35646600 |
| H | -3.26664000 | 4.57285900 | -0.60735500 |
| H | -4.77909600 | 4.10983200 | -1.39778700 |
| N | -0.97151900 | -1.90283100 | 0.02277300 |
| C | -0.39245100 | -2.91715400 | -0.87441700 |
| H | -0.81597900 | -2.83328900 | -1.87844200 |
| H | -0.59517300 | -3.92562300 | -0.49825800 |
| C | 1.33388200 | -1.60992900 | 0.29173000 |
| H | 2.08984600 | -1.81325700 | 1.04531300 |
| Rh | 2.51090500 | 0.37725200 | -0.08475300 |
| Cl | 3.70437700 | 2.37110200 | 0.35959200 |
| C | 0.96282800 | 1.55675500 | -0.16361500 |
| O | 0.11677900 | 2.32206700 | -0.22466600 |
| C | 1.10126700 | -2.59989100 | -0.81865100 |
| H | 1.77469900 | -3.44931300 | -0.90252200 |
| C | 1.56585400 | -1.31786400 | -1.42648300 |

| | | | |
|---|---|---|---|
| H | 2.51949400 | -1.35840300 | -1.94330600 |
| H | 0.80258600 | -0.71661300 | -1.91068000 |
| C | 4.25100000 | -0.46183600 | -0.00519400 |
| O | 5.31237300 | -0.88880200 | 0.04278300 |

**18-2',** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1979.1629478 a.u.
Thermal free energy correction in gas phase: 0.194440 a.u.
Gibbs free energy after correction at 298K: -1978.968508 a.u.
Gibbs free energy in gas phase at 298K: -1978.950567 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.53414100 | -0.40579900 | 0.59332700 |
| O | 1.22677100 | -0.76095100 | 1.54054700 |
| S | 2.30835800 | 1.61181900 | 0.15129600 |
| O | 2.17271600 | 2.08309900 | 1.52392200 |
| O | 2.37785800 | 2.55548400 | -0.96913200 |
| C | 3.68075500 | 0.48029100 | 0.02496700 |
| C | 4.15034000 | -0.16919000 | 1.16796400 |
| C | 4.29031600 | 0.30268800 | -1.21992900 |
| C | 5.24775100 | -1.01879900 | 1.04835600 |
| H | 3.65620900 | -0.01729300 | 2.11928500 |
| C | 5.38294900 | -0.55488300 | -1.31516100 |
| H | 3.92304300 | 0.83668800 | -2.08956400 |
| C | 5.87894900 | -1.22615700 | -0.18684200 |
| H | 5.61876500 | -1.53199800 | 1.93164500 |

| | | | |
|---|---|---|---|
| H | 5.86237400 | -0.70089900 | -2.27972100 |
| C | 7.08431500 | -2.12876500 | -0.29568600 |
| H | 8.01259400 | -1.55866500 | -0.15742600 |
| H | 7.06703400 | -2.91366900 | 0.46702600 |
| H | 7.13995100 | -2.60719500 | -1.27891200 |
| N | 0.90402200 | 0.62570600 | -0.25555600 |
| C | -0.02230800 | 1.12361000 | -1.28874300 |
| H | -0.09757400 | 0.40191400 | -2.10725800 |
| H | 0.39948200 | 2.05074700 | -1.68552400 |
| C | -1.33777600 | 1.38483600 | -0.68772100 |
| C | -2.30192000 | 1.88927400 | -0.11780900 |
| C | -3.37833000 | 2.75584300 | 0.37071500 |
| H | -3.16203900 | 3.78992800 | 0.07878000 |
| H | -4.33091700 | 2.45477100 | -0.07672000 |
| H | -3.46347200 | 2.71859200 | 1.46164800 |
| C | -0.74726000 | -1.13548800 | 0.34438000 |
| H | -0.54955200 | -2.18704900 | 0.55991500 |
| Cl | -4.37865300 | -0.09875700 | -1.62702400 |
| C | -2.95116600 | -2.35541000 | -0.32278700 |
| O | -3.26544300 | -3.43562500 | -0.53230800 |
| Rh | -2.52657900 | -0.53432000 | 0.00834400 |
| C | -3.82303900 | -0.18563800 | 1.48192400 |
| O | -4.42826600 | -0.15702600 | 2.45286600 |

**18TS',** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1979.1509537 a.u.
Thermal free energy correction in gas phase: 0.192386 a.u.
Gibbs free energy after correction at 298K: -1978.958568 a.u.
Gibbs free energy in gas phase at 298K: -1978.941986 a.u.
Imaginary frequency: -301.6246 $cm^{-1}$
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.20259700 | 1.00797500 | 1.29510400 |
| O | 0.93831300 | 0.65957600 | 2.20972500 |
| S | 2.30952200 | 2.06167400 | -0.08520700 |
| O | 2.72003000 | 2.82561700 | 1.08512100 |
| O | 2.31754400 | 2.64676200 | -1.42747200 |
| C | 3.16200400 | 0.49841500 | -0.12607000 |
| C | 3.68037200 | -0.03970700 | 1.05346100 |
| C | 3.32336300 | -0.14466700 | -1.35750000 |
| C | 4.36218900 | -1.25308300 | 0.98866100 |
| H | 3.54425000 | 0.47961200 | 1.99393700 |
| C | 4.00567400 | -1.35689300 | -1.39552200 |
| H | 2.94061700 | 0.30857900 | -2.26545500 |
| C | 4.52934200 | -1.93226100 | -0.22673100 |
| H | 4.77187200 | -1.67940500 | 1.90044000 |
| H | 4.14044100 | -1.86150100 | -2.34868500 |
| C | 5.23987500 | -3.26293200 | -0.27952300 |
| H | 5.89703600 | -3.40210500 | 0.58430300 |
| H | 4.51698500 | -4.08926400 | -0.28043500 |
| H | 5.84306900 | -3.35906600 | -1.18856400 |
| N | 0.62071900 | 1.62342300 | 0.12421600 |

| | | | |
|---|---|---|---|
| C | -0.33120600 | 2.06813500 | -0.92724900 |
| H | 0.02085700 | 1.70298300 | -1.89633200 |
| H | -0.34707500 | 3.16381100 | -0.96612800 |
| C | -1.67668100 | 1.53431100 | -0.62577800 |
| C | -2.94295900 | 1.43716900 | -0.49701600 |
| C | -4.31322500 | 1.92942100 | -0.72789500 |
| H | -4.30917300 | 2.89071500 | -1.25464300 |
| H | -4.86585600 | 1.19093200 | -1.31763700 |
| H | -4.83774200 | 2.05383100 | 0.22719500 |
| C | -1.25088200 | 0.71873600 | 1.39459900 |
| H | -1.77959500 | 1.35895900 | 2.10552400 |
| Cl | -3.21835200 | -1.34024000 | -1.86103900 |
| C | -3.58625200 | -1.32170900 | 1.26318100 |
| O | -4.38478600 | -1.77200300 | 1.95218000 |
| Rh | -2.18280900 | -0.50268700 | 0.17769400 |
| C | -0.70119000 | -1.84063700 | 0.00572100 |
| O | 0.14479800 | -2.60463700 | -0.09242500 |

**19-1',** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1979.2369012 a.u.
Thermal free energy correction in gas phase: 0.196870 a.u.
Gibbs free energy after correction at 298K: -1979.040031 a.u.
Gibbs free energy in gas phase at 298K: -1979.021286 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.28465500 | -1.12382100 | 1.36853800 |
| O | -0.93592100 | -0.68238000 | 2.29437800 |

| | | | |
|---|---|---|---|
| S | -2.49032100 | -2.01090400 | -0.06505500 |
| O | -3.00755200 | -2.71130300 | 1.10394800 |
| O | -2.50449200 | -2.62079400 | -1.39693800 |
| C | -3.21379500 | -0.38407000 | -0.15474200 |
| C | -3.62907800 | 0.25300500 | 1.01686700 |
| C | -3.36517300 | 0.21797700 | -1.40719800 |
| C | -4.19705900 | 1.52165900 | 0.92042400 |
| H | -3.49300800 | -0.23079100 | 1.97632300 |
| C | -3.93628800 | 1.48601000 | -1.47767600 |
| H | -3.05463500 | -0.30611100 | -2.30465500 |
| C | -4.36020200 | 2.15645200 | -0.31968000 |
| H | -4.51865200 | 2.02812800 | 1.82670500 |
| H | -4.05853300 | 1.96134500 | -2.44758200 |
| C | -5.00385100 | 3.51903800 | -0.41213400 |
| H | -6.08257500 | 3.42965600 | -0.59704600 |
| H | -4.87696000 | 4.08591900 | 0.51545200 |
| H | -4.58098100 | 4.10704800 | -1.23329600 |
| N | -0.80867300 | -1.69246200 | 0.19211300 |
| C | 0.20486900 | -2.23806200 | -0.72556800 |
| H | 0.05079900 | -1.88556600 | -1.74739200 |
| H | 0.17965700 | -3.33573800 | -0.72941900 |
| C | 1.48475300 | -1.72092300 | -0.08853900 |
| C | 2.70796200 | -1.35646200 | -0.63728200 |
| C | 3.54390400 | -1.90836400 | -1.72416500 |

| | | | |
|---|---|---|---|
| H | 2.95835200 | -2.55993200 | -2.38757400 |
| H | 4.01250600 | -1.10801500 | -2.30168300 |
| H | 4.34038500 | -2.52648000 | -1.28468000 |
| C | 1.20369600 | -1.16872500 | 1.21183700 |
| H | 1.80206500 | -1.37669300 | 2.09089200 |
| Cl | 3.36622200 | 1.52090200 | -1.75439400 |
| C | 3.54618700 | 0.94936200 | 1.46078500 |
| O | 4.35917700 | 1.21104300 | 2.22575300 |
| Rh | 2.31102800 | 0.39353100 | 0.12569900 |
| C | 1.11506300 | 2.00761100 | 0.30722300 |
| O | 0.42721100 | 2.91725700 | 0.32987800 |

**19-2,** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1979.225355 a.u.
Thermal free energy correction in gas phase: 0.198145 a.u.
Gibbs free energy after correction at 298K: -1979.02721 a.u.
Gibbs free energy in gas phase at 298K: -1979.007046 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.11517000 | -2.22761000 | 1.02396900 |
| C | 0.23170300 | -0.89944400 | -1.03887700 |
| C | -1.23315800 | -1.09887600 | -0.71109800 |
| N | 0.95082100 | -1.57333800 | -0.02509900 |
| O | 0.74007100 | -0.32031500 | -1.97819100 |
| C | -1.19179500 | -1.54448600 | 0.71312700 |
| C | -2.06277500 | -0.77027100 | 1.34785100 |
| S | 2.63307900 | -1.94950500 | -0.14871500 |

| | | | |
|---|---|---|---|
| O | 2.88180300 | -2.52763400 | -1.46460600 |
| O | 2.89428500 | -2.70255600 | 1.08126600 |
| C | 3.44420800 | -0.36311500 | -0.03758400 |
| C | 3.90137100 | 0.07036000 | 1.20911800 |
| C | 3.64839600 | 0.39565900 | -1.19287400 |
| C | 4.56355400 | 1.29320300 | 1.29500300 |
| H | 3.76005500 | -0.55251200 | 2.08574600 |
| C | 4.31195100 | 1.61516600 | -1.08188300 |
| H | 3.28623400 | 0.03759200 | -2.14858100 |
| C | 4.77461500 | 2.08506600 | 0.15671800 |
| H | 4.93113700 | 1.63317000 | 2.25989400 |
| H | 4.47799600 | 2.21092500 | -1.97580700 |
| C | 5.46940700 | 3.42143700 | 0.26264800 |
| H | 6.06276400 | 3.63606400 | -0.63224300 |
| H | 6.13428400 | 3.46056000 | 1.13135000 |
| H | 4.73944500 | 4.23459300 | 0.37119800 |
| Cl | -4.22290400 | 2.24224400 | -0.05756300 |
| C | -1.19653600 | 1.71537600 | 0.07668200 |
| O | -0.38684100 | 2.49368900 | 0.26362200 |
| C | -2.47186500 | -0.47520500 | 2.74639500 |
| H | -2.25407100 | 0.56479100 | 3.01728200 |
| H | -1.92888100 | -1.13717200 | 3.43548900 |
| H | -3.54635800 | -0.62843000 | 2.89907000 |
| H | 0.09988100 | -3.31422900 | 0.87683800 |

| | | | |
|---|---|---|---|
| H | 0.50648100 | -2.01413900 | 2.02065400 |
| H | -1.68564100 | -1.77564100 | -1.44361800 |
| Rh | -2.65526700 | 0.43105400 | -0.24496100 |
| C | -4.13389000 | -0.77943000 | -0.56056500 |
| O | -5.01858000 | -1.47976600 | -0.72610300 |

**19TS',** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1979.212245 a.u.
Thermal free energy correction in gas phase: 0.195144 a.u.
Gibbs free energy after correction at 298K: -1979.017101 a.u.
Gibbs free energy in gas phase at 298K: -1978.996682 a.u.
Imaginary frequency: -137.2763 $cm^{-1}$
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.14707800 | -2.19217500 | 0.77559400 |
| C | 0.34482100 | -0.83389300 | -1.21766900 |
| C | -1.10562800 | -0.97518900 | -0.87114900 |
| N | 1.02386700 | -1.55092900 | -0.22083700 |
| O | 0.84512800 | -0.24897900 | -2.15710400 |
| C | -1.20792500 | -1.62649900 | 0.38039300 |
| C | -2.29121600 | -1.23645800 | 1.14590900 |
| S | 2.71567300 | -1.93394900 | -0.29307500 |
| O | 2.99825100 | -2.47080500 | -1.61804900 |
| O | 2.91904300 | -2.72658100 | 0.92139200 |
| C | 3.51106400 | -0.35074400 | -0.10399000 |
| C | 3.93629700 | 0.03950800 | 1.16812400 |
| C | 3.72475100 | 0.45569100 | -1.22602100 |

| | | | |
|---|---|---|---|
| C | 4.57765900 | 1.26780800 | 1.31363700 |
| H | 3.78603200 | -0.61770600 | 2.01775500 |
| C | 4.36563800 | 1.67941800 | -1.05398300 |
| H | 3.38522500 | 0.13234400 | -2.20227700 |
| C | 4.79678500 | 2.10708800 | 0.21155200 |
| H | 4.91999200 | 1.57610000 | 2.29806200 |
| H | 4.53597900 | 2.31363800 | -1.92005900 |
| C | 5.46611700 | 3.44955100 | 0.38070600 |
| H | 6.15166200 | 3.66135100 | -0.44682200 |
| H | 6.03219000 | 3.50176600 | 1.31578500 |
| H | 4.72205800 | 4.25665500 | 0.39908400 |
| Cl | -3.34746100 | 2.51979500 | -0.99203500 |
| C | -1.66865700 | 1.57870400 | 1.25877700 |
| O | -1.02692100 | 2.31261400 | 1.85172700 |
| C | -2.52917300 | -1.64134500 | 2.55880200 |
| H | -2.52737300 | -0.75500500 | 3.21009100 |
| H | -1.79533900 | -2.36502400 | 2.93852500 |
| H | -3.53064500 | -2.07793000 | 2.66730900 |
| H | 0.19736400 | -3.28422600 | 0.68652300 |
| H | 0.44971400 | -1.92300600 | 1.79167700 |
| H | -1.82546900 | -0.96378200 | -1.67970000 |
| Rh | -2.86978800 | 0.44742400 | 0.15352400 |
| C | -4.30361000 | -0.42061900 | -0.78929100 |
| O | -5.19249000 | -0.92013900 | -1.30712100 |

**20',** B3LYP/SDD-6-31G(d)
Total SCF energy in solvent 1,4-dioxane: -1979.2456251 a.u.
Thermal free energy correction in gas phase: 0.194870 a.u.
Gibbs free energy after correction at 298K: -1979.050755 a.u.
Gibbs free energy in gas phase at 298K: -1979.030260 a.u.
Charge and Multiplicity: 0 1
Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| S | -3.11021600 | -1.80596200 | 0.05214900 |
| O | -3.52286900 | -2.51701000 | 1.25506700 |
| O | -3.00643300 | -2.47561800 | -1.24654600 |
| O | -1.76516500 | -0.11822600 | 2.36263500 |
| N | -1.50494300 | -1.22278500 | 0.31194400 |
| C | -4.08771900 | -0.32640500 | -0.12683100 |
| C | -4.39119500 | 0.12677400 | -1.41221800 |
| H | -4.03272000 | -0.41714000 | -2.27937700 |
| C | -5.17502800 | 1.27048300 | -1.55337400 |
| H | -5.41913400 | 1.62880700 | -2.55003300 |
| C | -5.65822300 | 1.96117000 | -0.43313300 |
| C | -5.33597100 | 1.47674900 | 0.84473700 |
| H | -5.70199300 | 2.00121900 | 1.72371700 |
| C | -4.55810200 | 0.33481500 | 1.01210300 |
| H | -4.30305300 | -0.03223400 | 1.99879100 |
| C | -6.52649800 | 3.18612000 | -0.59113100 |
| H | -6.46968200 | 3.59129000 | -1.60596200 |
| H | -6.23304600 | 3.97602800 | 0.10902700 |
| H | -7.57880400 | 2.94871200 | -0.38762400 |

| | | | |
|---|---|---|---|
| C | -1.07439400 | -0.51423400 | 1.44457400 |
| C | 0.38449800 | -0.32601000 | 1.23932300 |
| C | 0.78833200 | -0.89748600 | 0.07890500 |
| C | -0.40808400 | -1.56402200 | -0.58861800 |
| H | -0.59017700 | -1.18242900 | -1.60035000 |
| H | -0.28397200 | -2.65013300 | -0.66248900 |
| C | 2.16197400 | -0.98823800 | -0.40570200 |
| H | 1.00397000 | 0.18083900 | 1.96845100 |
| Cl | 5.16887900 | 2.06711000 | 0.17736700 |
| C | 2.20251500 | 1.83758500 | -0.09303500 |
| O | 1.50674300 | 2.74320500 | -0.08444400 |
| C | 2.42930400 | -2.25482100 | -1.18109800 |
| H | 3.42222100 | -2.29106900 | -1.62763600 |
| H | 2.30509000 | -3.13422600 | -0.52925700 |
| H | 1.69298000 | -2.36938300 | -1.99046500 |
| Rh | 3.50030800 | 0.38264000 | -0.12282700 |
| C | 4.97362600 | -0.90168700 | -0.08302200 |
| O | 5.88164100 | -1.59233100 | -0.03442200 |

**21´,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1827.762211 a.u.

SMD solvation energy correction: 0.18238419 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1827.579827 a.u.

Gibbs free energy in gas phase at 298K: -1827.558629 a.u.

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.36828000 | 0.62593300 | -0.92619200 |
| O | -0.23620900 | 0.19731400 | -1.90429400 |
| S | -1.80922800 | 2.02833700 | -0.13798700 |
| O | -1.92010300 | 2.63747000 | -1.45684300 |
| O | -2.02082100 | 2.80674400 | 1.08374600 |
| C | -2.80251500 | 0.55124700 | -0.05860400 |
| C | -3.18924000 | -0.08540900 | -1.23977800 |
| C | -3.21399300 | 0.08480700 | 1.19312000 |
| C | -3.99519000 | -1.21807200 | -1.15305400 |
| H | -2.86154900 | 0.30009800 | -2.19731600 |
| C | -4.01602500 | -1.05136600 | 1.25385500 |
| H | -2.92919000 | 0.61478800 | 2.09556800 |
| C | -4.41374600 | -1.72251500 | 0.08714500 |
| H | -4.30535200 | -1.71821500 | -2.06671800 |
| H | -4.34518400 | -1.41877100 | 2.22228500 |
| C | -5.25702000 | -2.97196000 | 0.16619300 |
| H | -5.89908500 | -2.96804100 | 1.05284400 |
| H | -5.89314500 | -3.08287800 | -0.71772000 |
| H | -4.62209900 | -3.86584600 | 0.22599800 |
| N | -0.14874300 | 1.43572500 | 0.04909500 |
| C | 0.70803700 | 2.00198900 | 1.12330900 |

| | | | |
|---|---|---|---|
| H | 1.19244900 | 1.17568200 | 1.65370500 |
| H | 0.02396800 | 2.49773000 | 1.81574500 |
| C | 1.77809800 | 0.14962500 | -0.83452800 |
| H | 2.46234800 | 0.64096000 | -1.53390200 |
| Rh | 2.51009100 | -1.27452900 | 0.05820000 |
| Cl | 4.74340800 | -0.92145300 | -0.34105700 |
| C | 0.84599500 | -1.85360600 | 0.68530300 |
| O | -0.13403600 | -2.26552900 | 1.12965200 |
| C | 1.72899200 | 2.97102500 | 0.58719600 |
| H | 1.32858900 | 3.82192500 | 0.03673000 |
| C | 3.04464700 | 2.84071600 | 0.77200800 |
| H | 3.74601700 | 3.57671300 | 0.38922100 |
| H | 3.47047500 | 1.99845200 | 1.31272500 |

**21TS´,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1827.754022 a.u.

SMD solvation energy correction: 0.18598201 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1827.56804 a.u.

Gibbs free energy in gas phase at 298K: -1827.544589 a.u.

Imaginary frequency: -352.22 $cm^{-1}$

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.33105000 | 0.82752200 | 0.96115200 |

| | | | |
|---|---|---|---|
| O | 0.20112100 | 0.40900900 | 1.97710100 |
| S | 1.97114500 | 2.05006400 | 0.13565300 |
| O | 2.15601000 | 2.67802700 | 1.43655000 |
| O | 2.20459200 | 2.77885500 | -1.11281700 |
| C | 2.84680700 | 0.50028400 | 0.08076700 |
| C | 3.12484600 | -0.18049300 | 1.26888800 |
| C | 3.26813200 | 0.01108700 | -1.15888300 |
| C | 3.82776200 | -1.38080600 | 1.19936800 |
| H | 2.79239100 | 0.22251200 | 2.21748300 |
| C | 3.96973100 | -1.19068700 | -1.20174400 |
| H | 3.06858800 | 0.57404500 | -2.06419500 |
| C | 4.25407100 | -1.90719600 | -0.02930700 |
| H | 4.05111200 | -1.91710600 | 2.11787600 |
| H | 4.30769900 | -1.57552700 | -2.16032600 |
| C | 4.98590900 | -3.22596100 | -0.09009300 |
| H | 5.64329300 | -3.28061300 | -0.96365200 |
| H | 5.59221700 | -3.38970000 | 0.80660900 |
| H | 4.27624500 | -4.06081800 | -0.16102400 |
| N | 0.28079700 | 1.59524600 | -0.00369000 |
| C | -0.51172600 | 2.06980300 | -1.15168800 |
| H | -0.34395500 | 1.42707300 | -2.02419900 |
| H | -0.17567500 | 3.07672200 | -1.40893700 |
| C | -1.77869500 | 0.48931700 | 0.74275300 |
| H | -2.45699100 | 0.94120200 | 1.46997800 |

| | | | |
|---|---|---|---|
| Rh | -2.55212100 | -1.03982200 | -0.05824000 |
| Cl | -4.72082600 | -0.67730700 | 0.69321400 |
| C | -0.93996600 | -1.63850600 | -0.75696900 |
| O | 0.03028200 | -2.06803100 | -1.21578500 |
| C | -1.96914700 | 2.06466500 | -0.75707800 |
| H | -2.28972600 | 2.81729100 | -0.03931400 |
| C | -2.91256900 | 1.37535400 | -1.47330000 |
| H | -3.96982500 | 1.45685600 | -1.24436500 |
| H | -2.64045400 | 0.77733700 | -2.33797000 |

**22´,** B3LYP/SDD-6-31G(d)

Total SCF energy in solvent 1,4-dioxane: -1827.828409 a.u.

SMD solvation energy correction: 0.19187319 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -1827.636536 a.u.

Gibbs free energy in gas phase at 298K: -1827.612917 a.u.

Charge and Multiplicity: 0 1

Cartesian coordinates:

| ATOM | X | Y | Z |
|---|---|---|---|
| C | -0.12340100 | -0.34297600 | -0.34295000 |
| O | 0.31494700 | -0.58180700 | -1.45289700 |
| S | 1.80051000 | 1.54408200 | 0.25514000 |
| O | 1.98191200 | 2.28752700 | 1.50373100 |
| O | 1.53015200 | 2.21373100 | -1.01074600 |
| C | 3.17080200 | 0.41936100 | 0.05216100 |

| | | | |
|---|---|---|---|
| C | 4.01763900 | 0.18836100 | 1.13893300 |
| C | 3.39407000 | -0.18550400 | -1.18826300 |
| C | 5.09982600 | -0.67426700 | 0.97682700 |
| H | 3.84177500 | 0.69525300 | 2.08155000 |
| C | 4.48078700 | -1.04527500 | -1.32463700 |
| H | 2.72449300 | 0.01087900 | -2.01658900 |
| C | 5.34511500 | -1.30725500 | -0.25026900 |
| H | 5.76937800 | -0.85154800 | 1.81462100 |
| H | 4.66415200 | -1.51828400 | -2.28602100 |
| C | 6.50271500 | -2.26333700 | -0.40996300 |
| H | 6.93661800 | -2.20248200 | -1.41350500 |
| H | 7.29466000 | -2.06083600 | 0.31798500 |
| H | 6.17621600 | -3.30100800 | -0.25990500 |
| N | 0.44042600 | 0.53072600 | 0.59024200 |
| C | -0.16017000 | 0.45613300 | 1.93456800 |
| H | -0.27916400 | 1.45548900 | 2.35547900 |
| H | 0.48265000 | -0.12609300 | 2.60588800 |
| C | -1.35586600 | -0.92619700 | 0.30082000 |
| H | -1.42162800 | -2.01191800 | 0.22471200 |
| Rh | -3.15648900 | -0.22628000 | -0.39855100 |
| Cl | -4.38709500 | -1.94771500 | 0.51917700 |
| C | -2.43464200 | 1.19918700 | -1.38633000 |
| O | -2.08346400 | 2.08761300 | -2.02327800 |
| C | -1.50561000 | -0.26325900 | 1.67961700 |

| | | | |
|---|---|---|---|
| H | -1.74043500 | -0.98411500 | 2.46618300 |
| C | -2.70421500 | 0.66003900 | 1.40748600 |
| H | -3.57312600 | 0.50579100 | 2.04739800 |
| H | -2.45480400 | 1.71568400 | 1.29457900 |

**CO,** B3LYP/SDD-6-31G(d) 5d, 7f

Total SCF energy in solvent 1,4-dioxane: -113.3019022 a.u.

SMD solvation energy correction: -0.014102 a.u.

Gibbs free energy after SMD solvation energy correction at 298K: -113.3160042 a.u.

Gibbs free energy in gas phase at 298K: -113.321016 a.u.

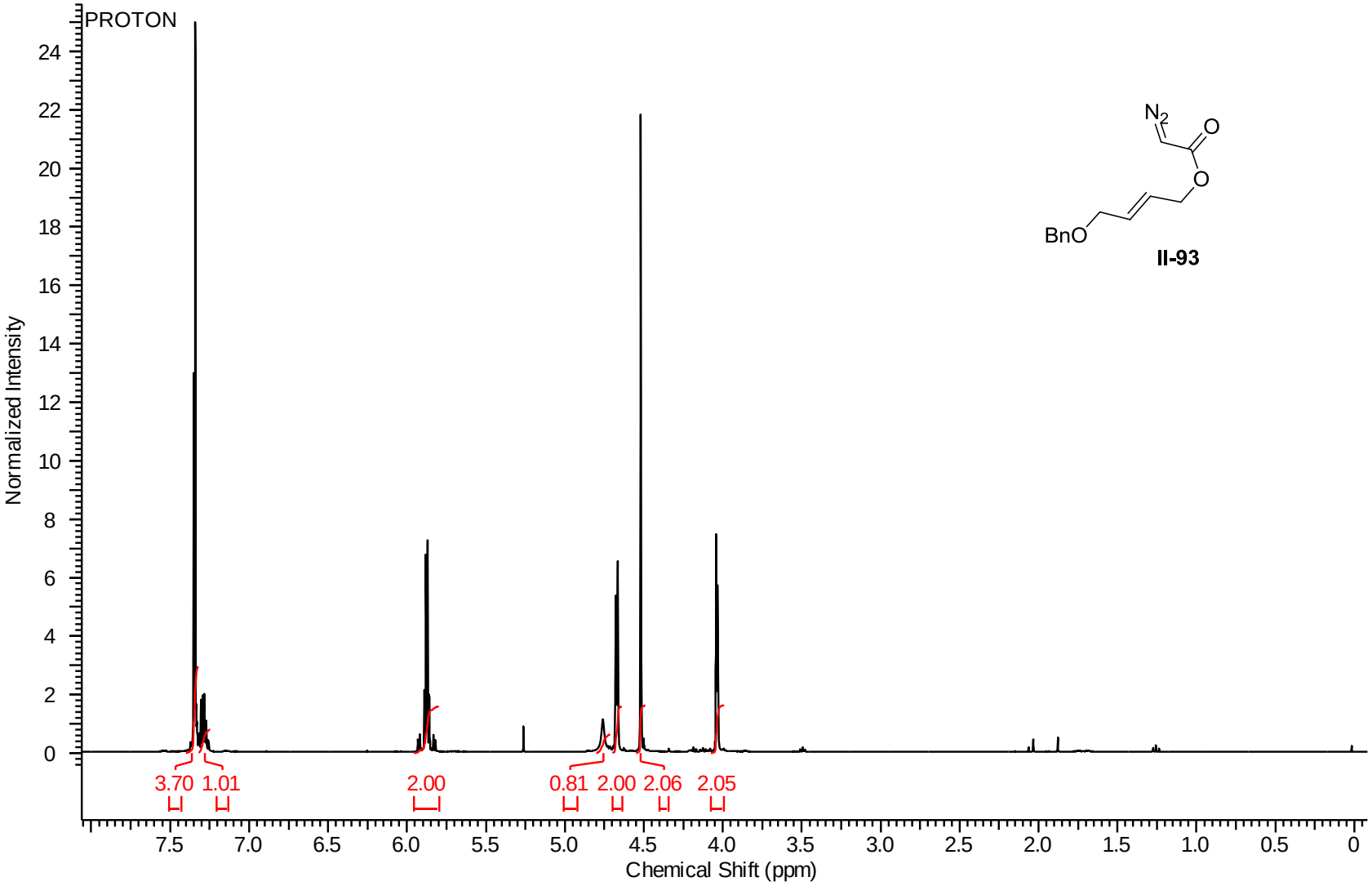
Charge and Multiplicity: 0 1

Cartesian coordinates:

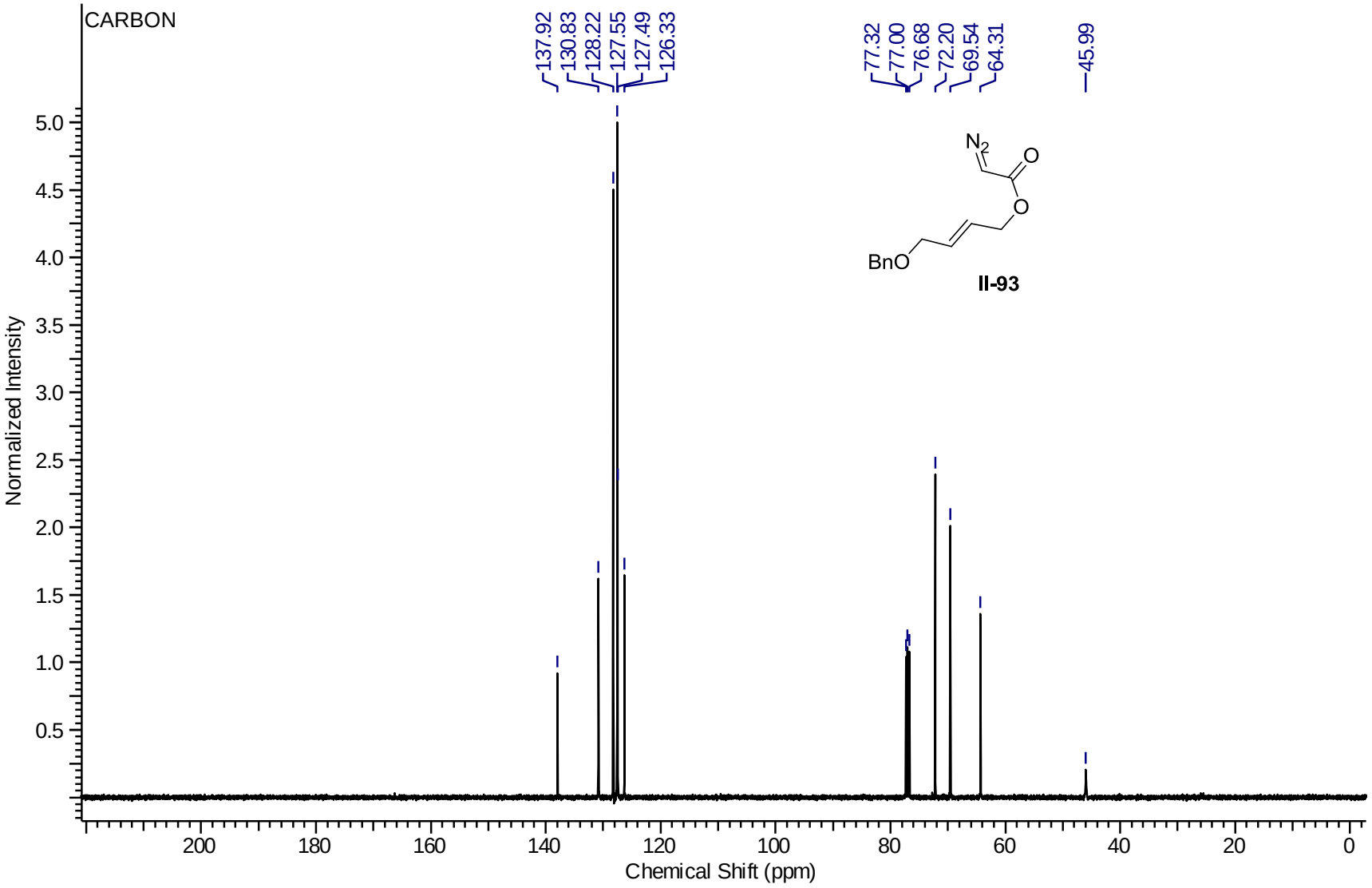
| ATOM | X | Y | Z |
|---|---|---|---|
| C | 0.00000000 | 0.00000000 | -0.65013500 |
| O | 0.00000000 | 0.00000000 | 0.48760200 |

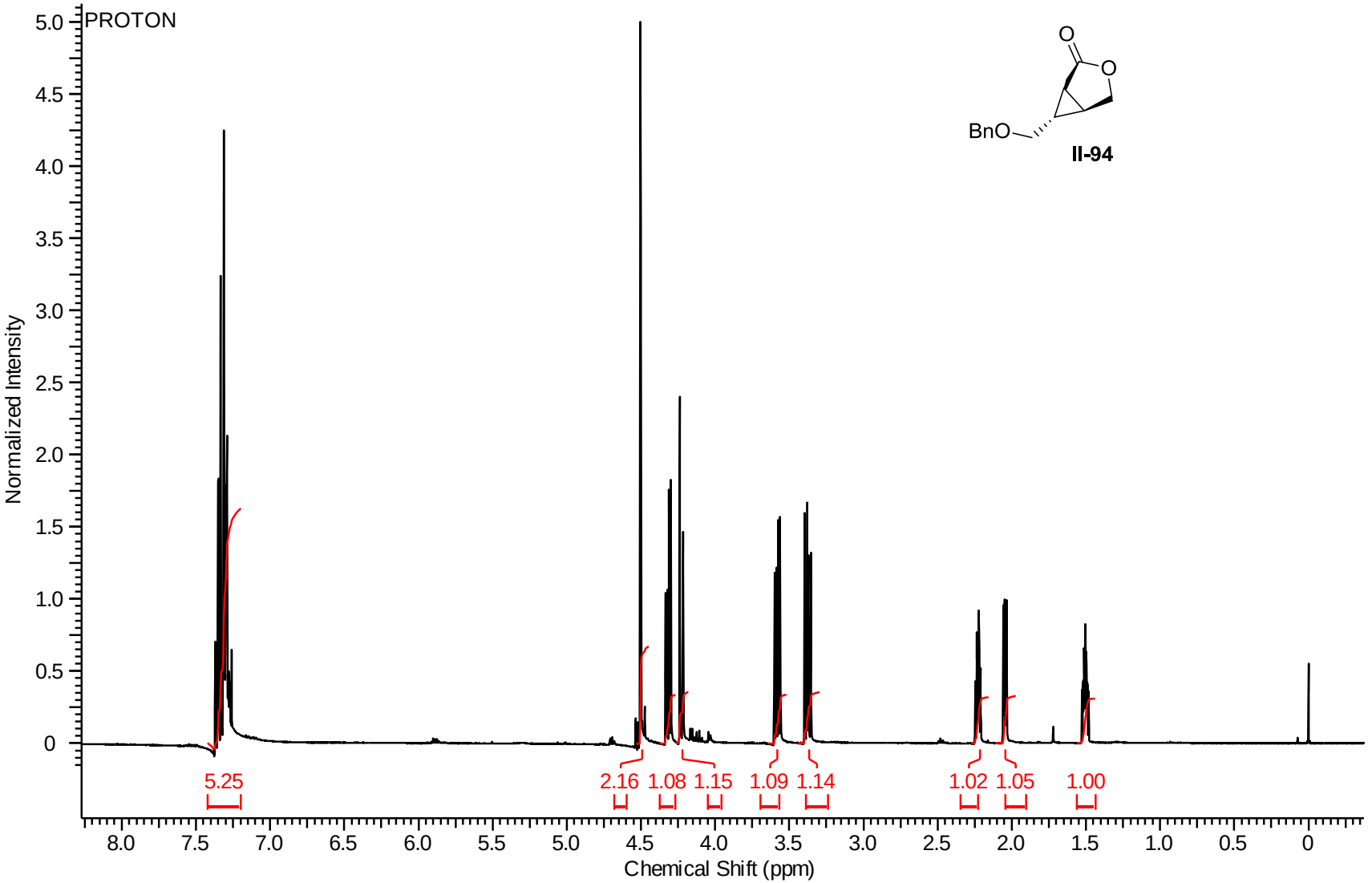
## APPENDIX IV: SELECTED $^{1}H$ AND $^{13}C$ NMR DATA

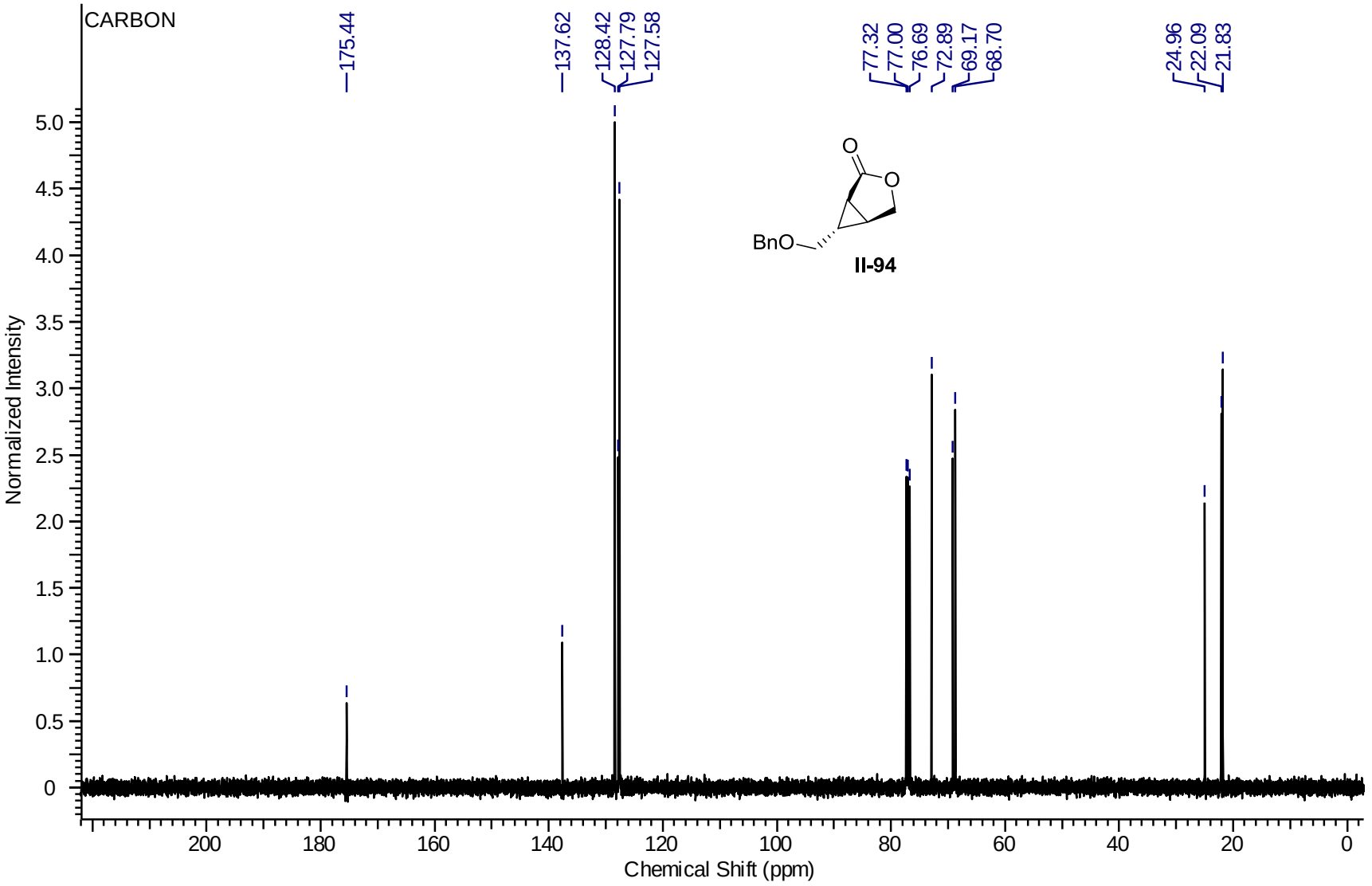
### CHAPTER I

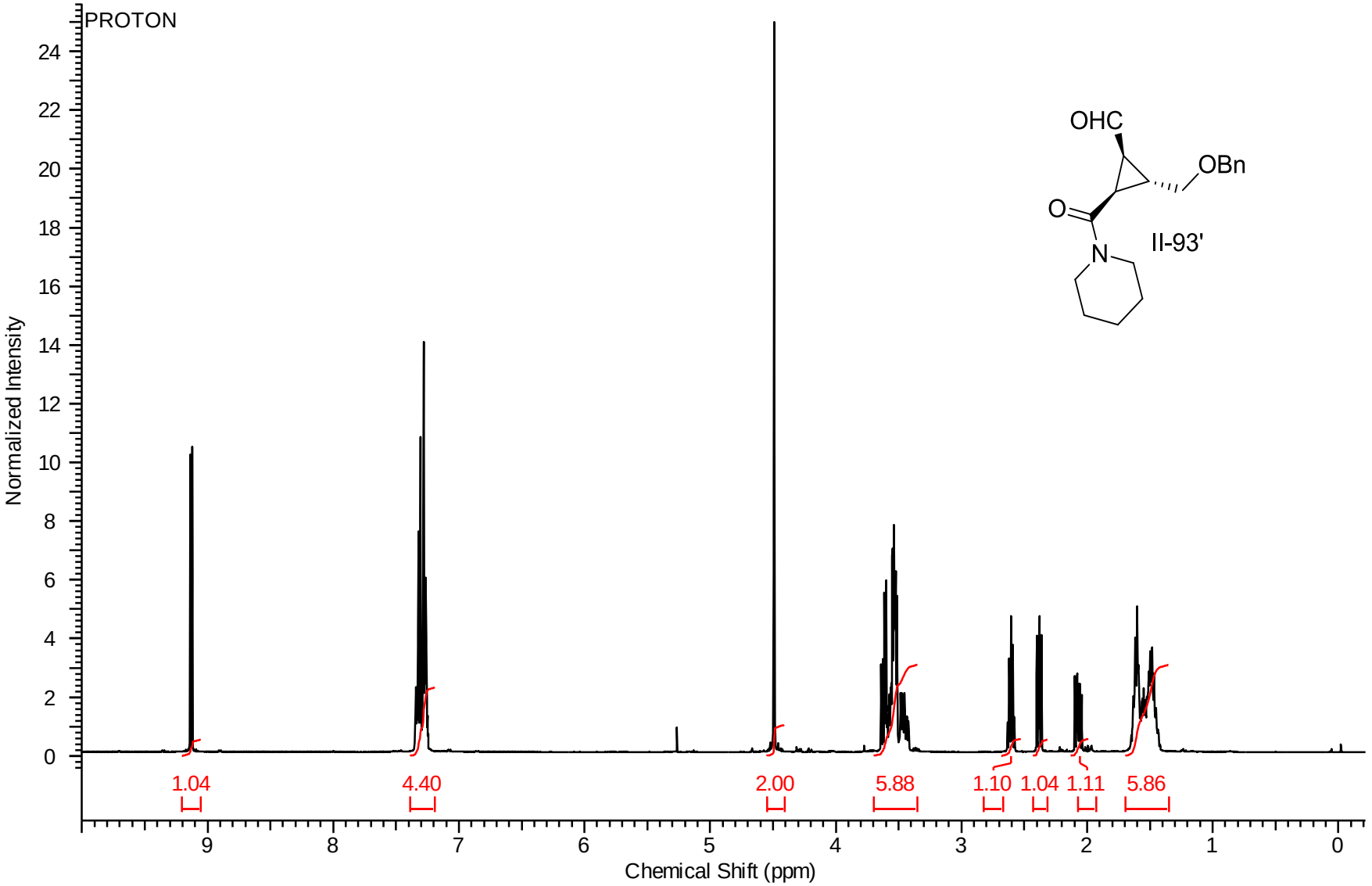


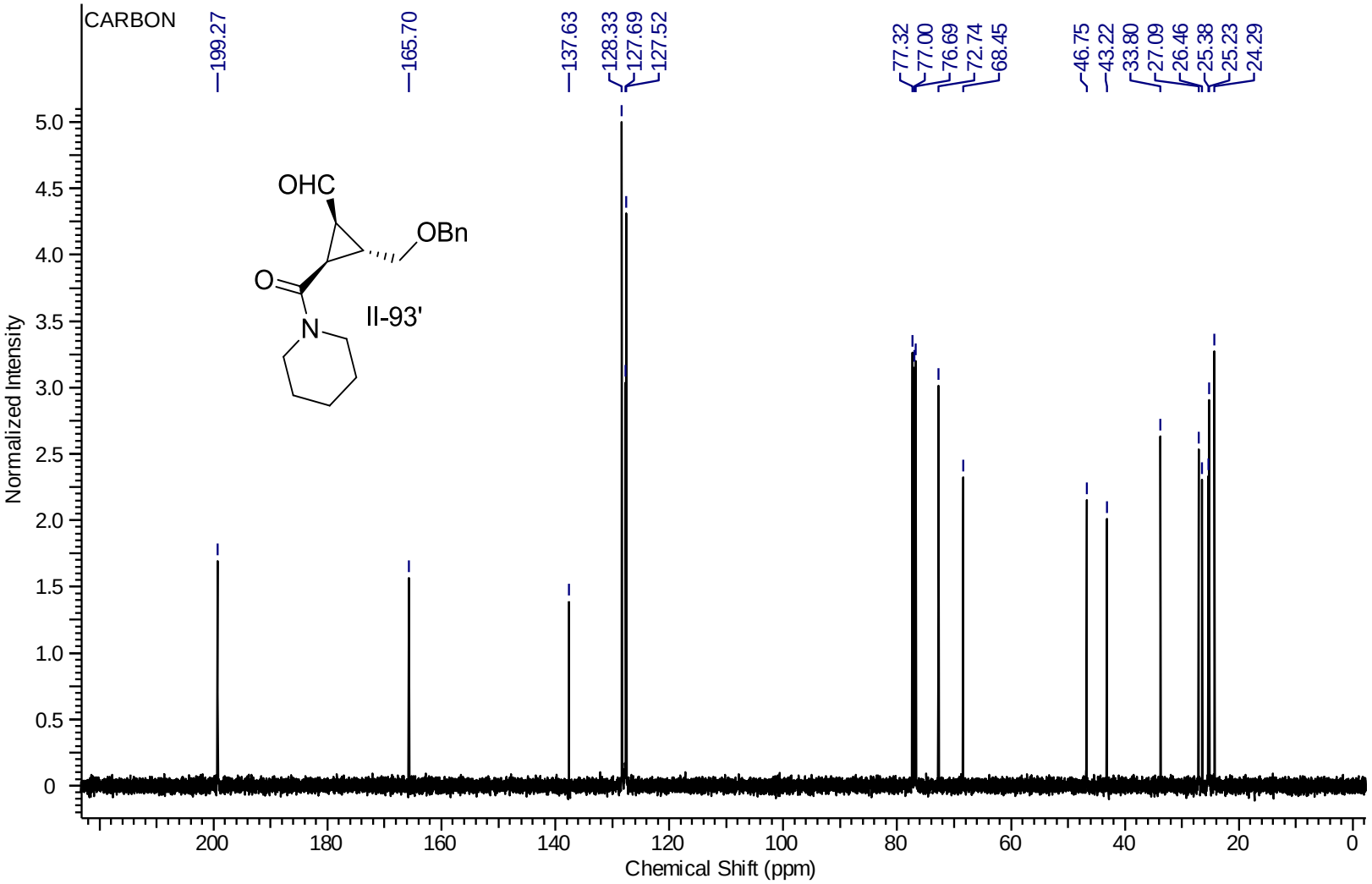

**II-93**

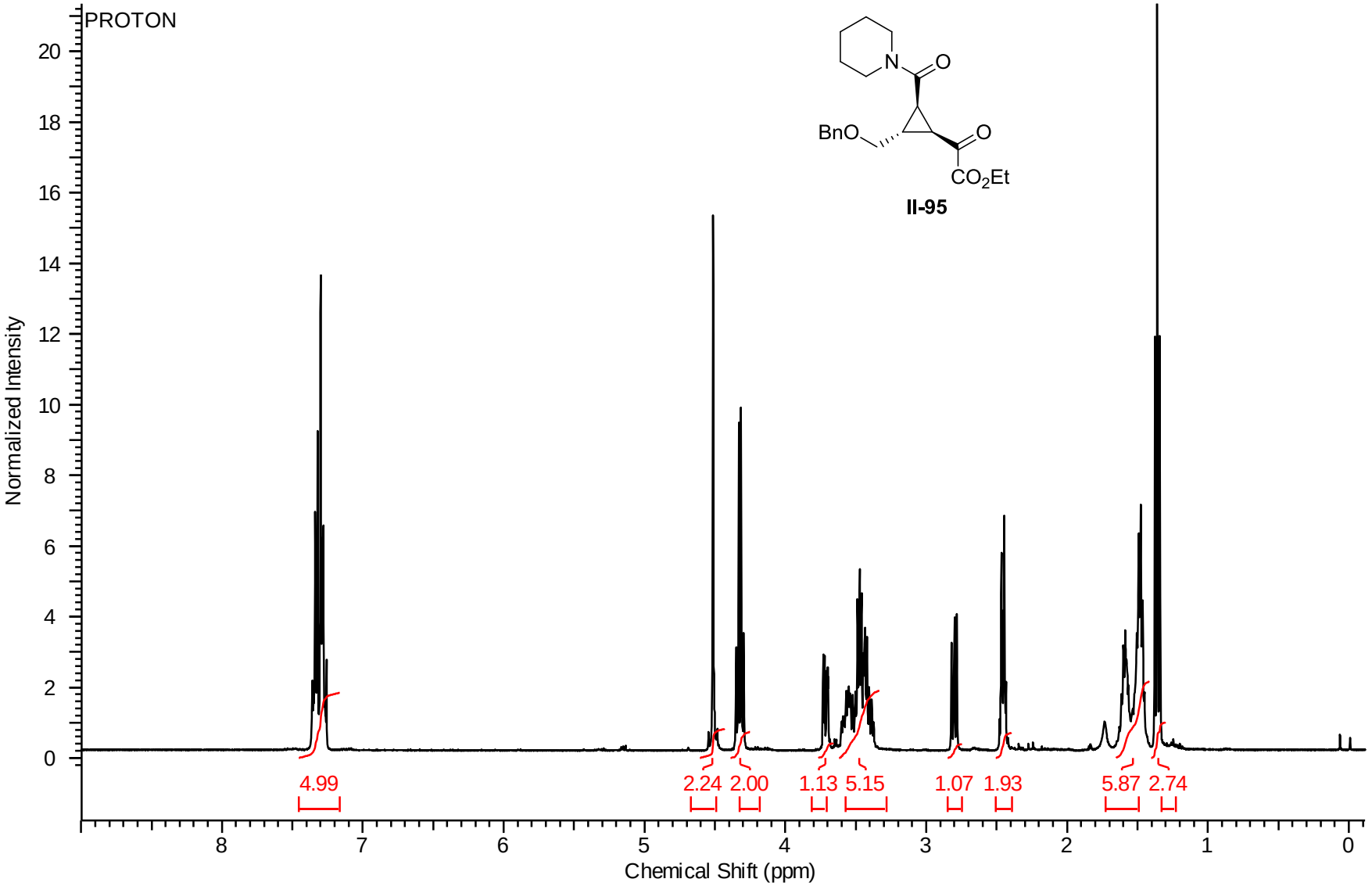

CARBON
137.92
130.83
128.22
127.55
127.49
126.33
77.32
77.00
76.68
72.20
69.54
64.31
45.99
N2
O
O
BnO
II-93
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

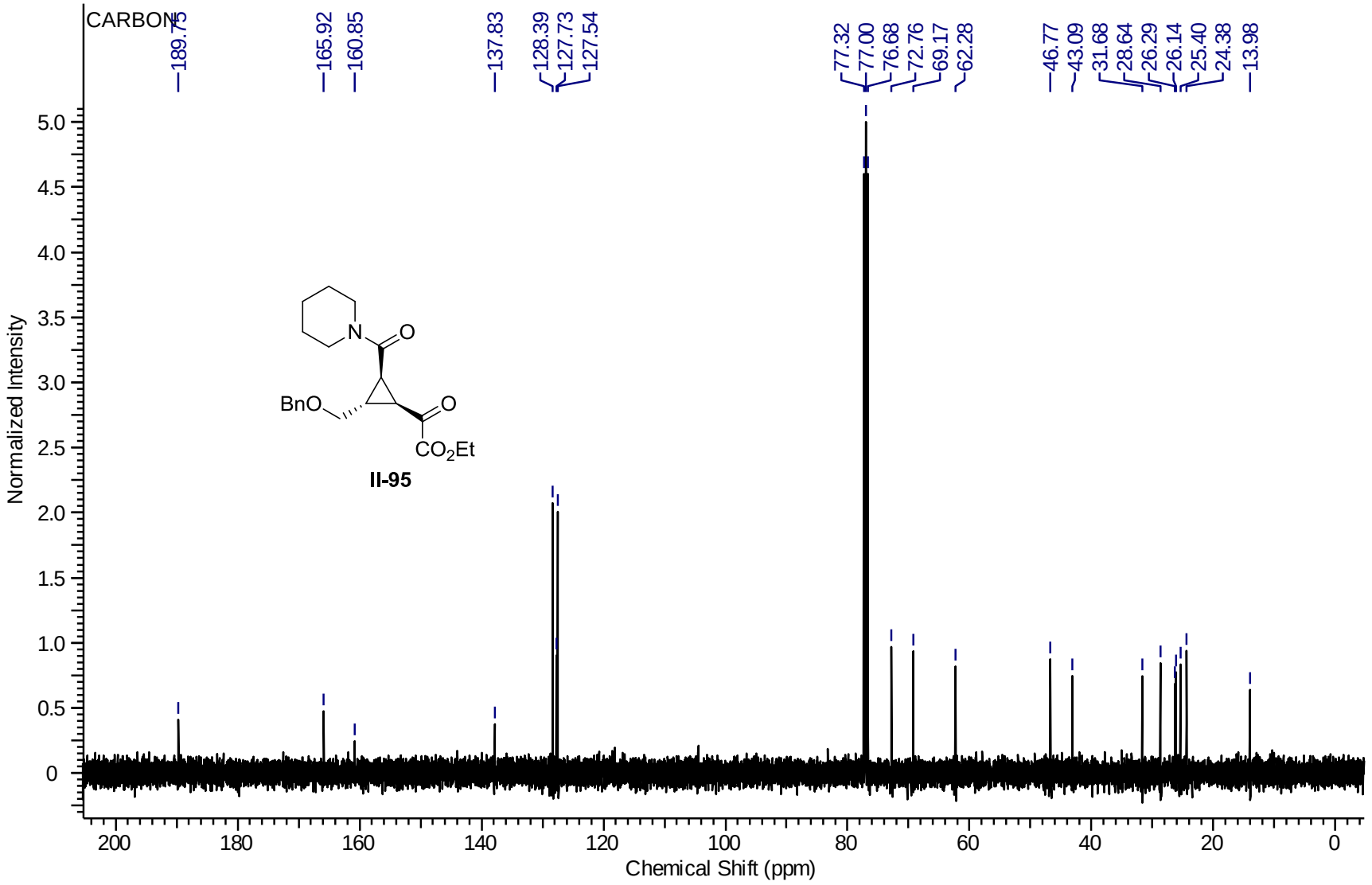

PROTON
Normalized Intensity
Chemical Shift (ppm)
5.25
2.16
1.08
1.15
1.09
1.14
1.02
1.05
1.00
BnO
O
O
II-94

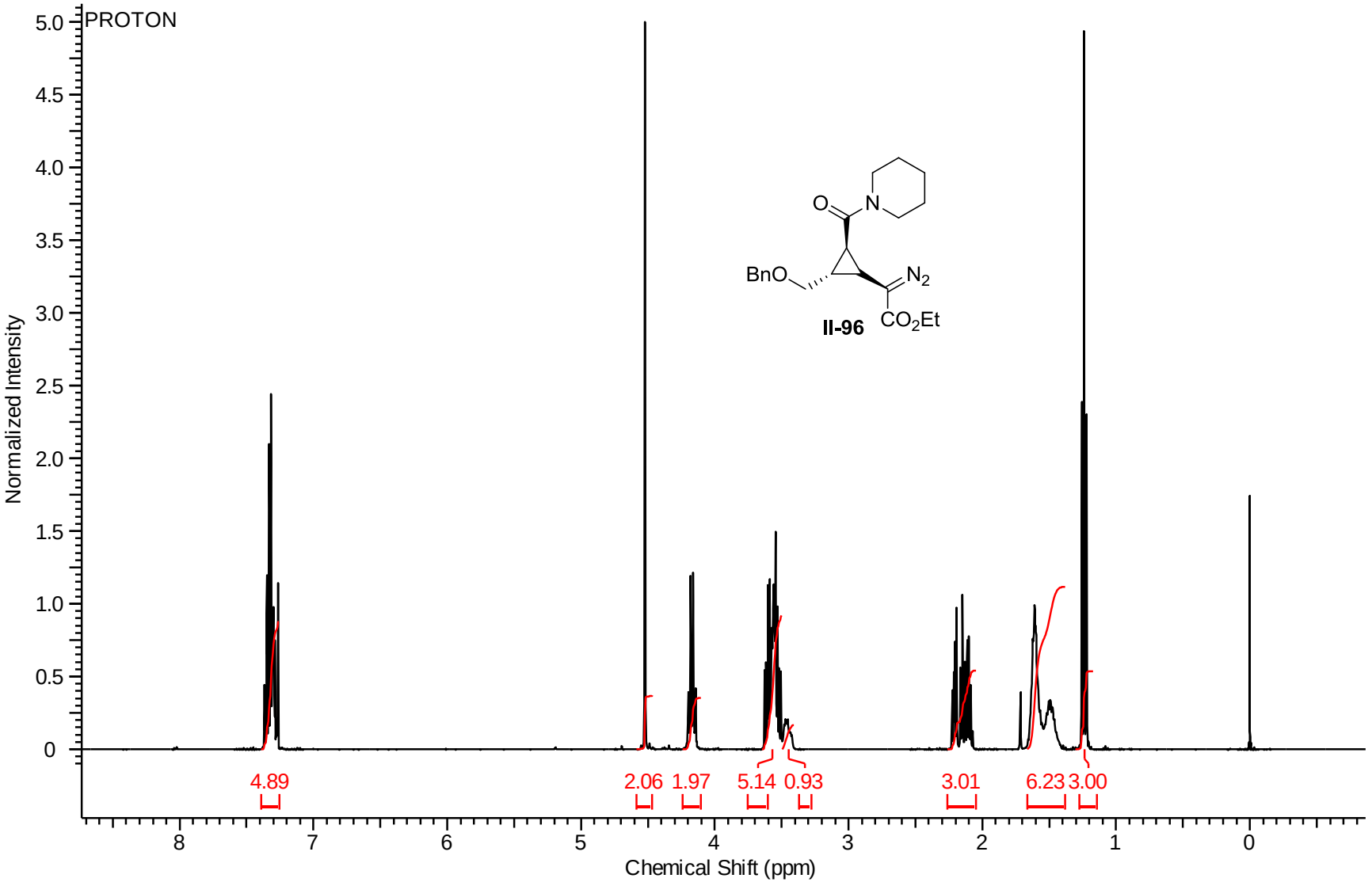

CARBON
175.44
137.62
128.42
127.79
127.58
77.32
77.00
76.69
72.89
69.17
68.70
24.96
22.09
21.83
O
O
BnO
II-94
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

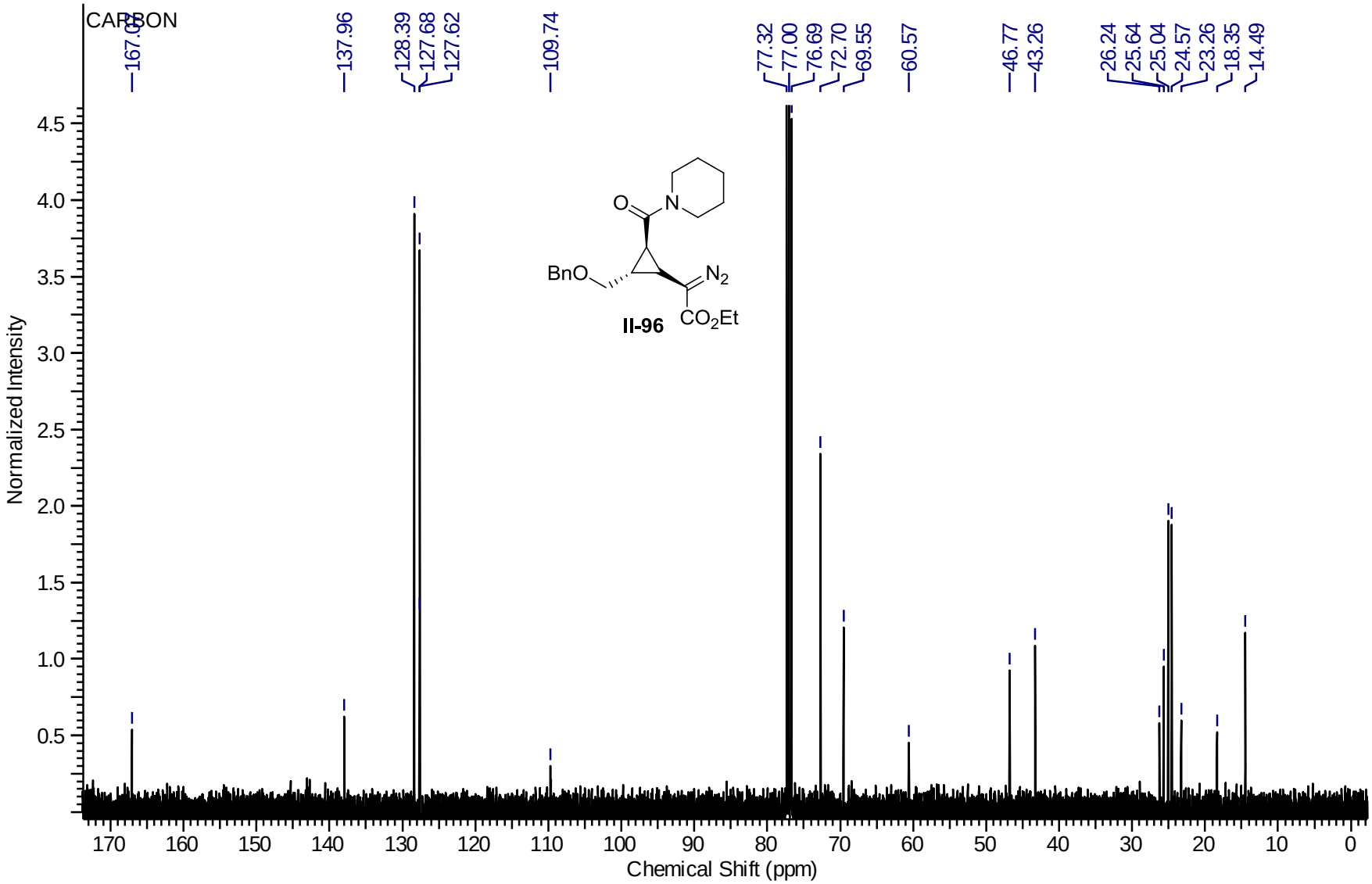

PROTON
Normalized Intensity
Chemical Shift (ppm)
OHC
OBn
O
N
II-93'
1.04
4.40
2.00
5.88
1.10
1.04
1.11
5.86

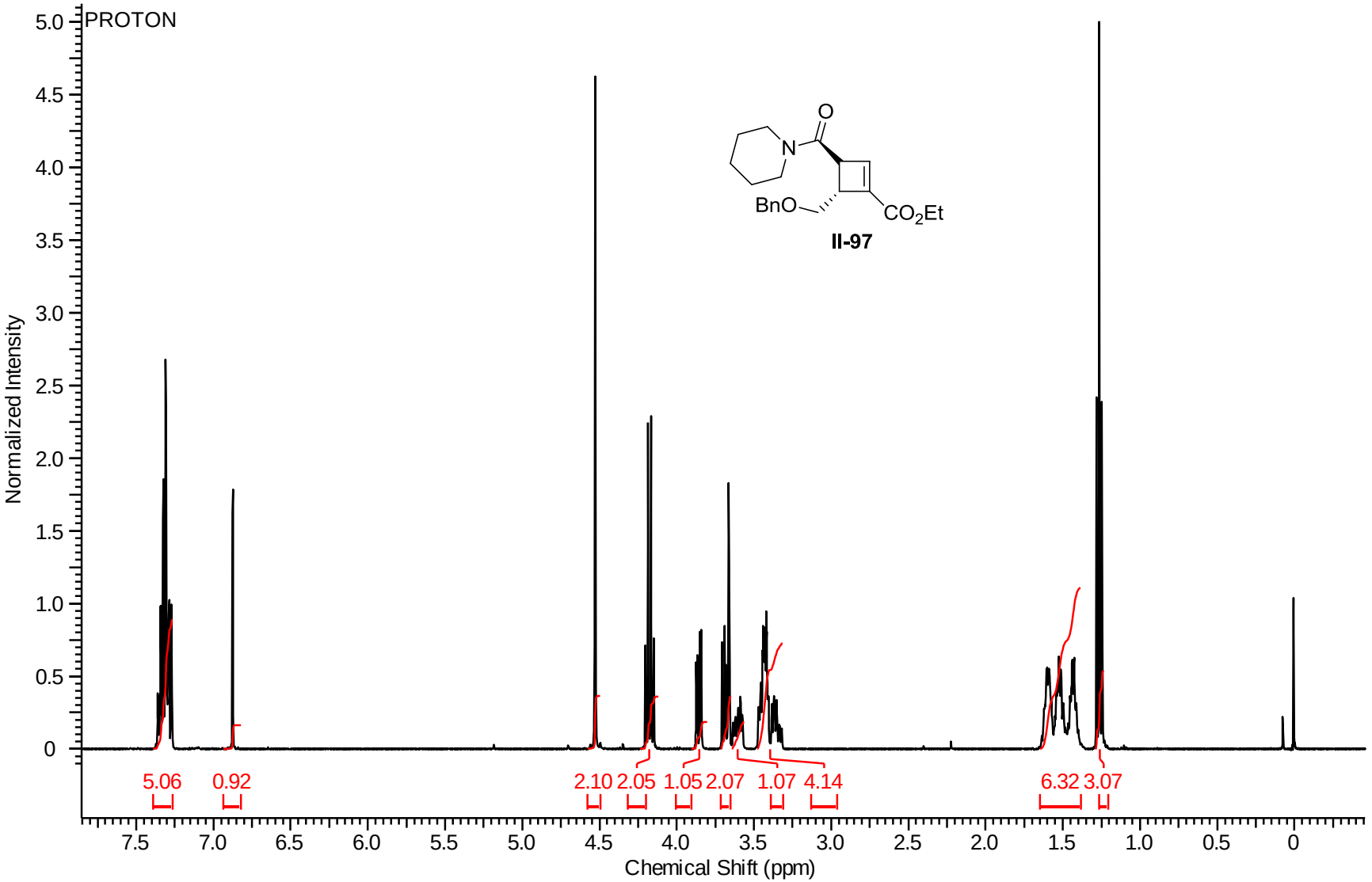

CARBON
199.27
165.70
137.63
128.33
127.69
127.52
77.32
77.00
76.69
72.74
68.45
46.75
43.22
33.80
27.09
26.46
25.38
25.23
24.29
OHC
OBn
O
N
II-93'
Normalized Intensity
Chemical Shift (ppm)

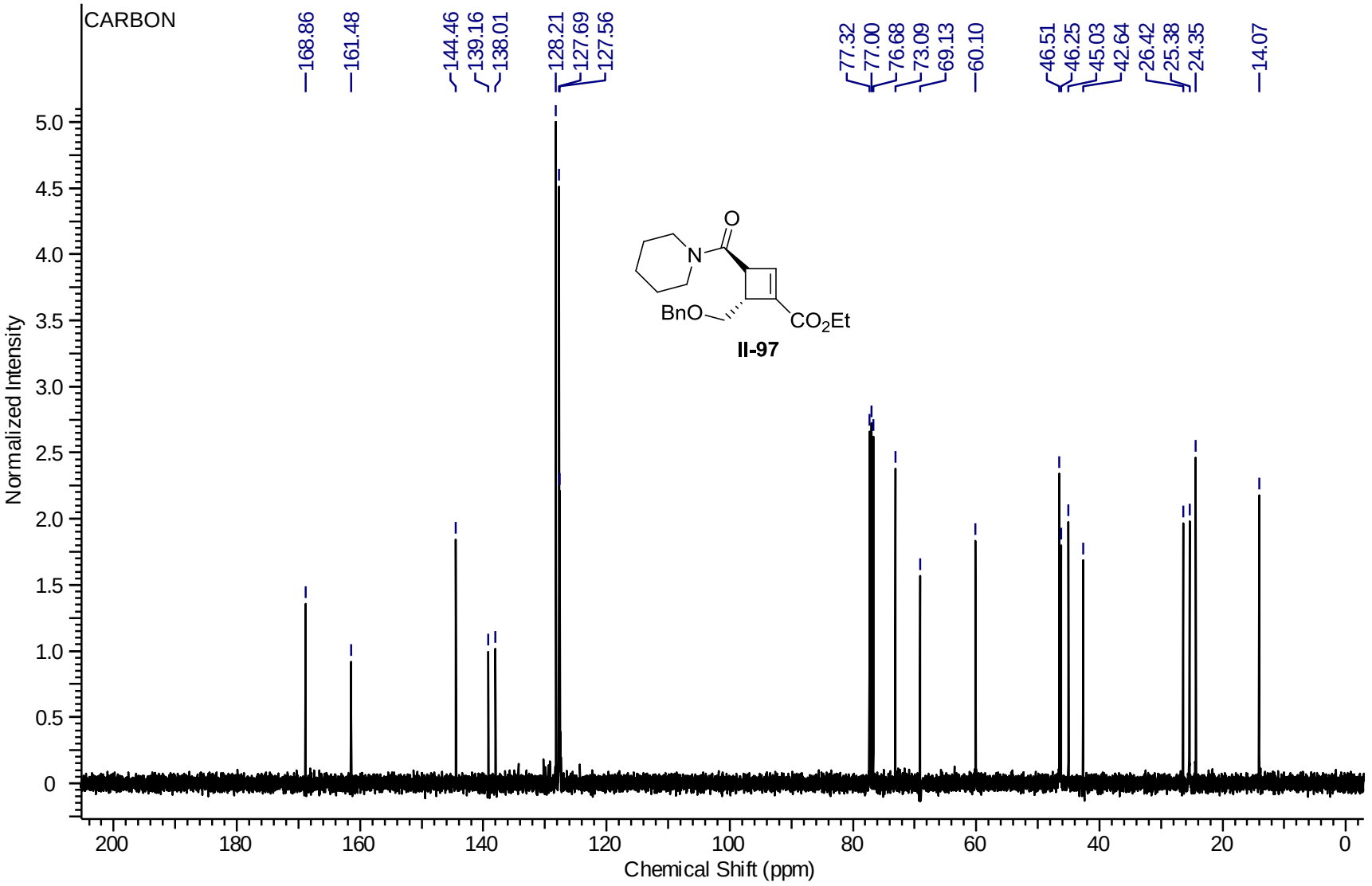

PROTON
Normalized Intensity
Chemical Shift (ppm)
BnO
O
N
O
O
$CO_2Et$
II-95
4.99
2.24
2.00
1.13
5.15
1.07
1.93
5.87
2.74

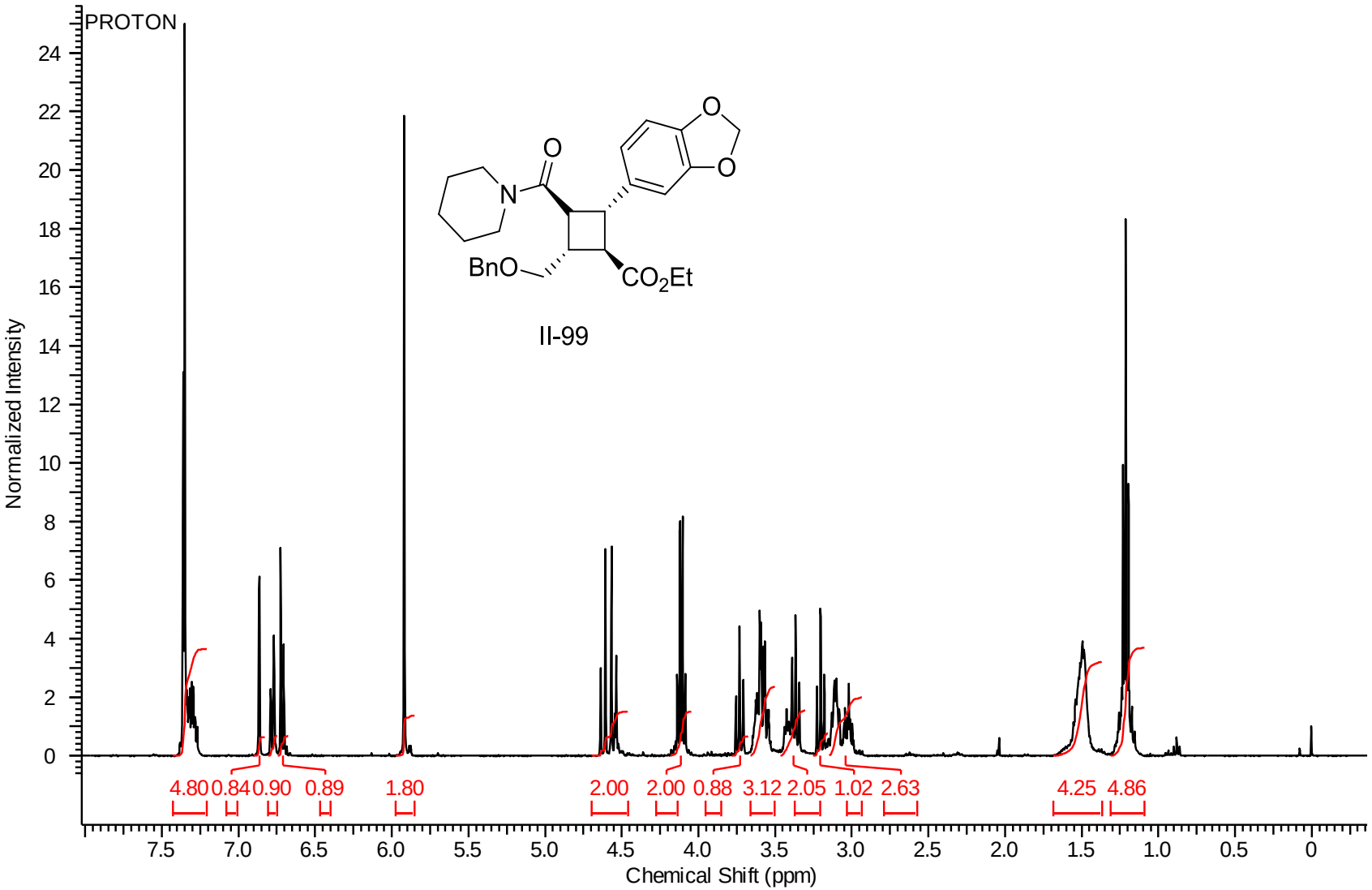

CARBON
189.75
165.92
160.85
137.83
128.39
127.73
127.54
77.32
77.00
76.68
72.76
69.17
62.28
46.77
43.09
31.68
28.64
26.29
26.14
25.40
24.38
13.98
Normalized Intensity
Chemical Shift (ppm)
BnO
N
O
O
CO2Et
II-95

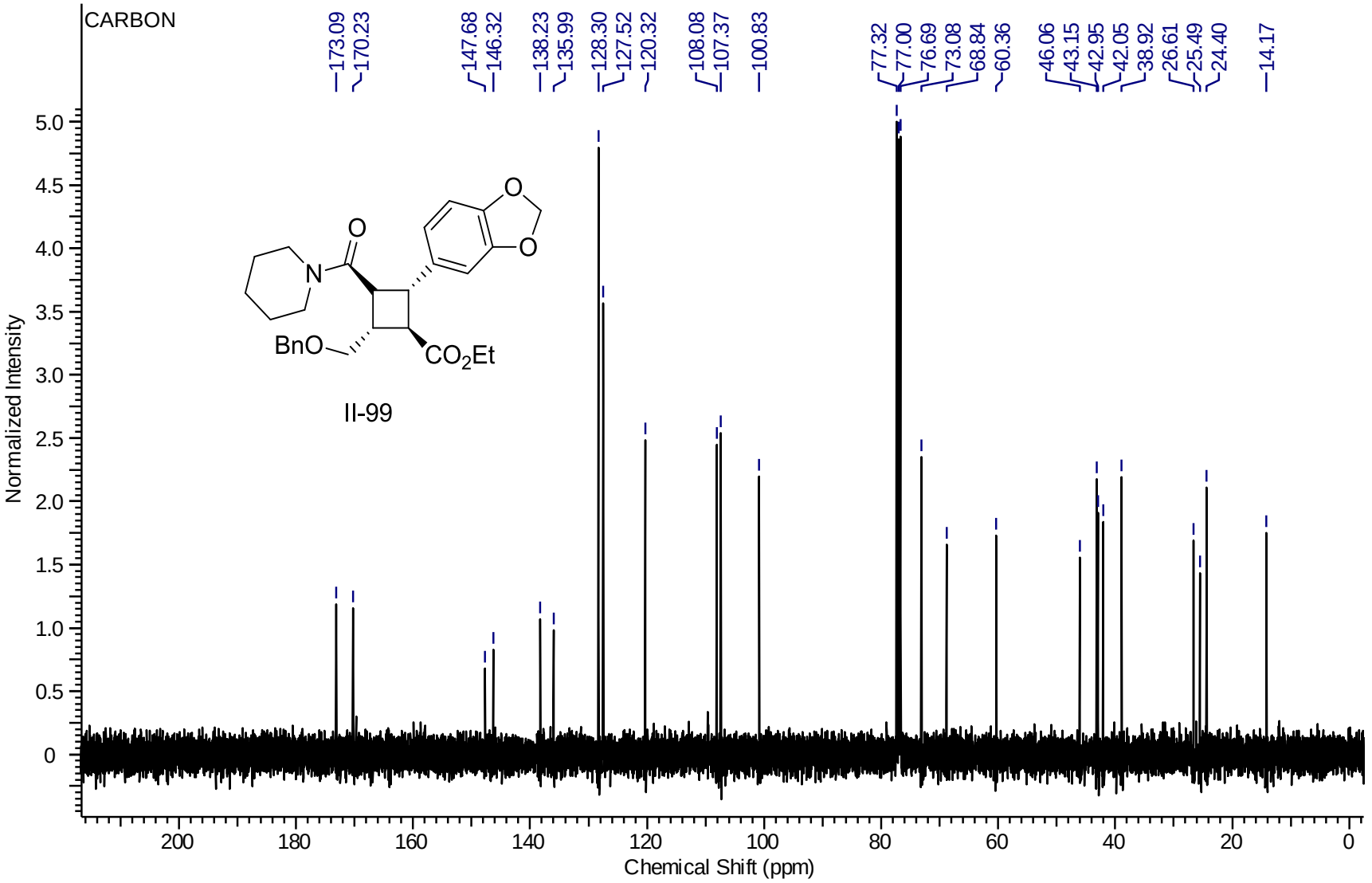

PROTON
Normalized Intensity
Chemical Shift (ppm)
4.89
2.06
1.97
5.14
0.93
3.01
6.23
3.00
BnO
N2
CO2Et
II-96

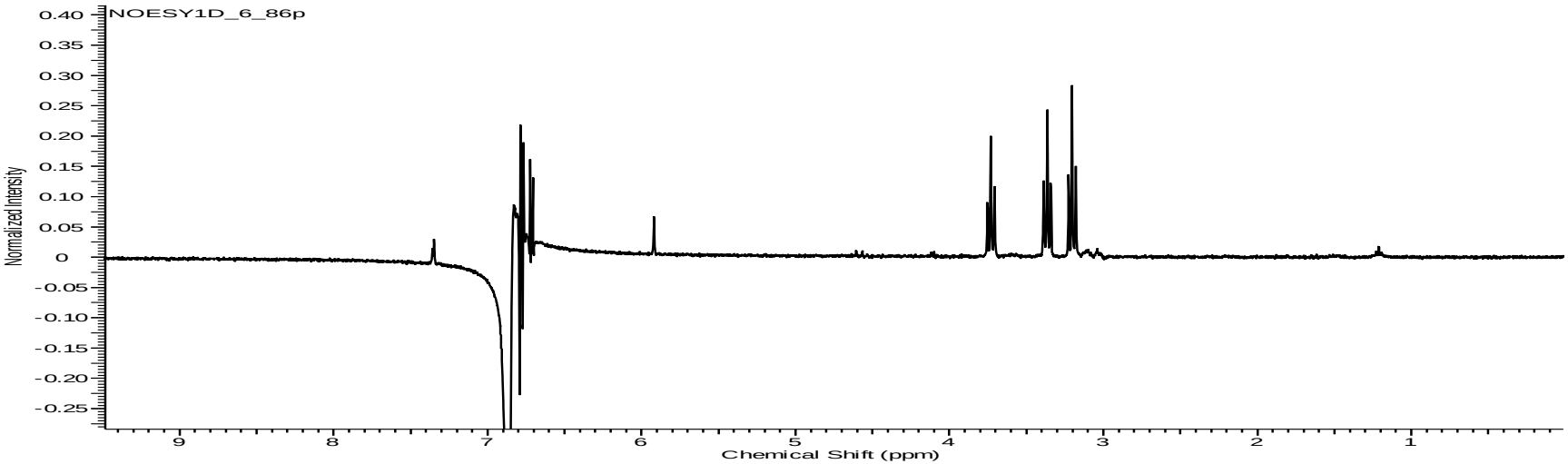

CARBON
167.08
137.96
128.39
127.68
127.62
109.74
77.32
77.00
76.69
72.70
69.55
60.57
46.77
43.26
26.24
25.64
25.04
24.57
23.26
18.35
14.49
O
N
BnO
N2
CO2Et
II-96
Normalized Intensity
Chemical Shift (ppm)

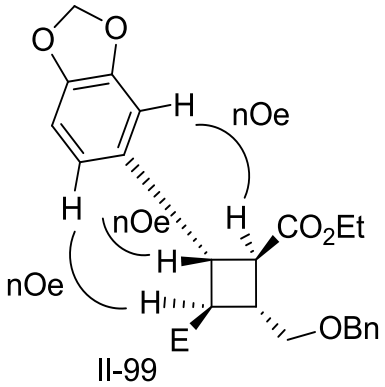

PROTON
Normalized Intensity
Chemical Shift (ppm)
5.06
0.92
2.10
2.05
1.05
2.07
1.07
4.14
6.32
3.07
O
N
BnO
CO2Et
II-97


CARBON
168.86
161.48
144.46
139.16
138.01
128.21
127.69
127.56
77.32
77.00
76.68
73.09
69.13
60.10
46.51
46.25
45.03
42.64
26.42
25.38
24.35
14.07
Normalized Intensity
Chemical Shift (ppm)
BnO
CO2Et
II-97

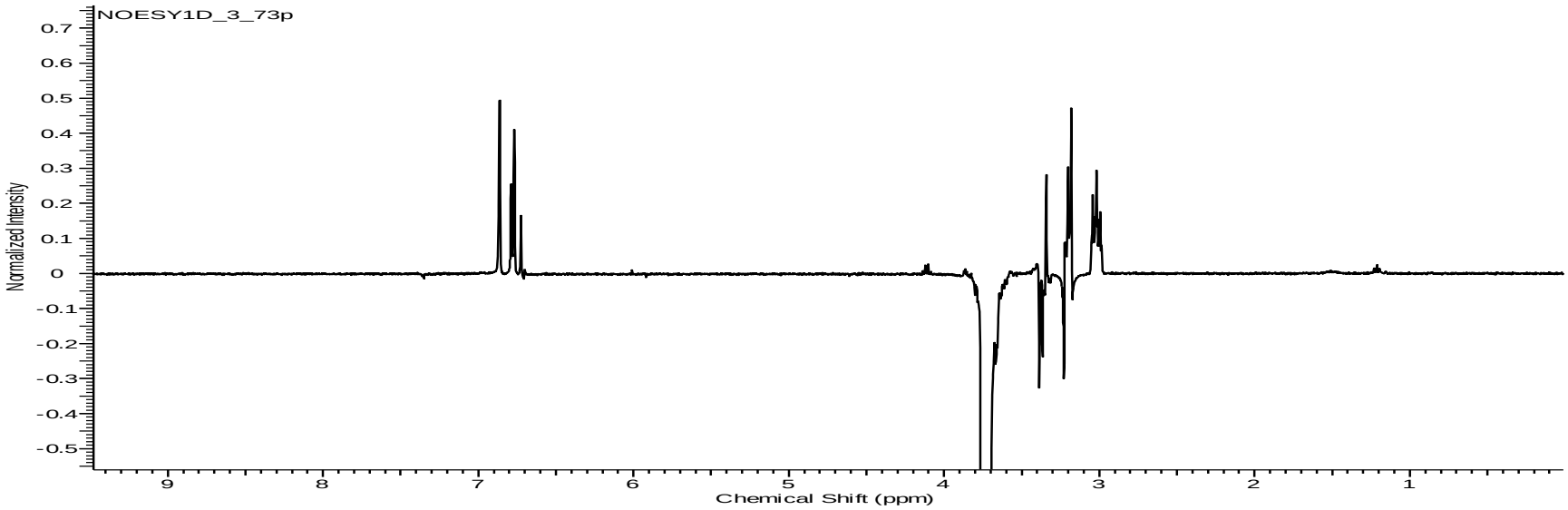

PROTON
Normalized Intensity
Chemical Shift (ppm)
II-99
BnO
CO2Et
4.80
0.84
0.90
0.89
1.80
2.00
2.00
0.88
3.12
2.05
1.02
2.63
4.25
4.86

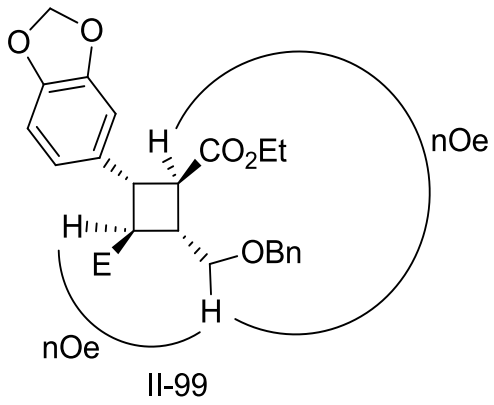

CARBON
173.09
170.23
147.68
146.32
138.23
135.99
128.30
127.52
120.32
108.08
107.37
100.83
77.32
77.00
76.69
73.08
68.84
60.36
46.06
43.15
42.95
42.05
38.92
26.61
25.49
24.40
14.17
O
O
O
N
BnO
CO2Et
II-99
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


NOESY1D_6_86p
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
-0.05
-0.10
-0.15
-0.20
-0.25
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

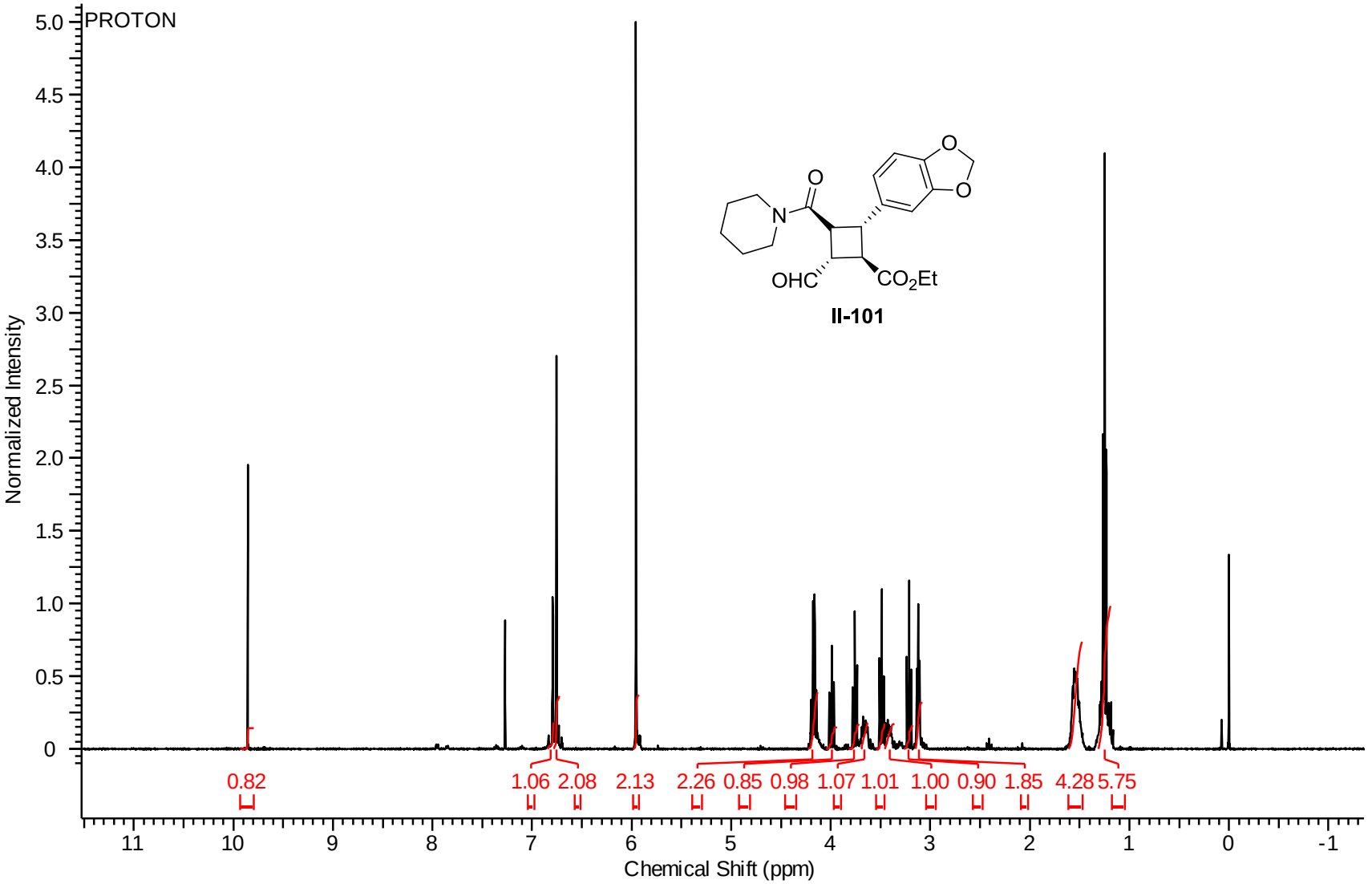

O
O
H
nOe
H
nOe
H
CO2Et
H
nOe
H
E
OBn

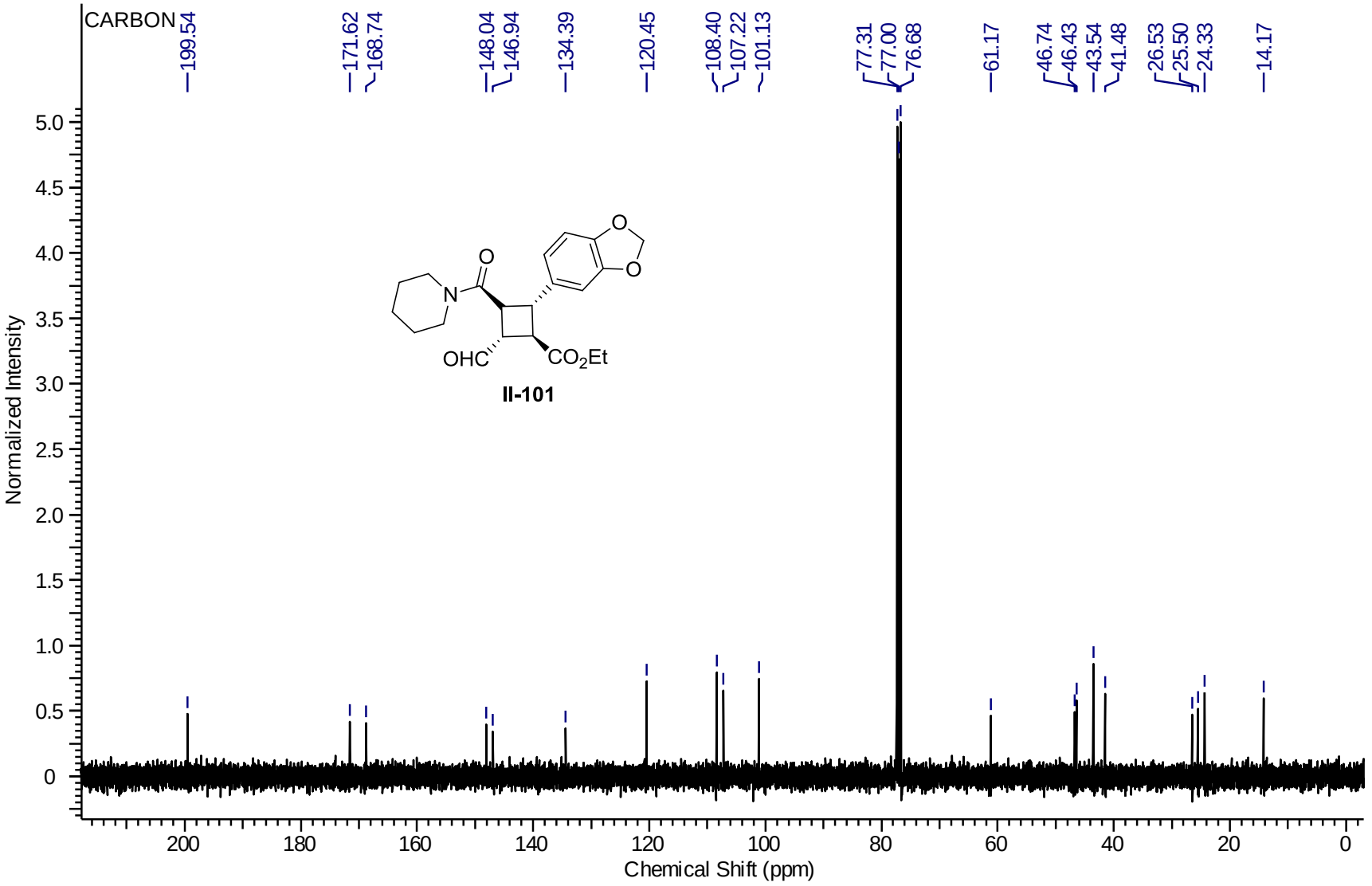
II-99

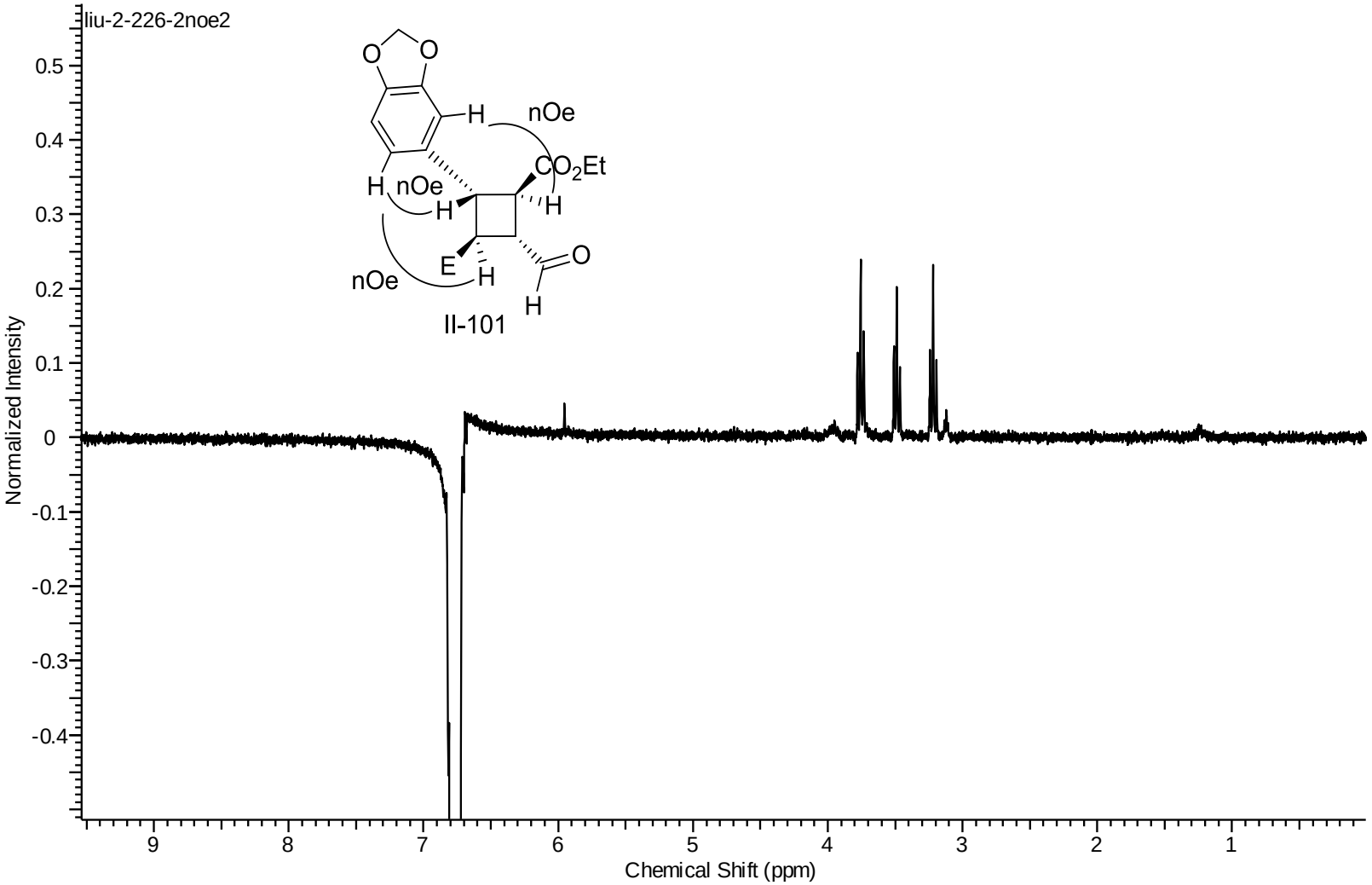

NOESY1D_3_73p
Normalized Intensity
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

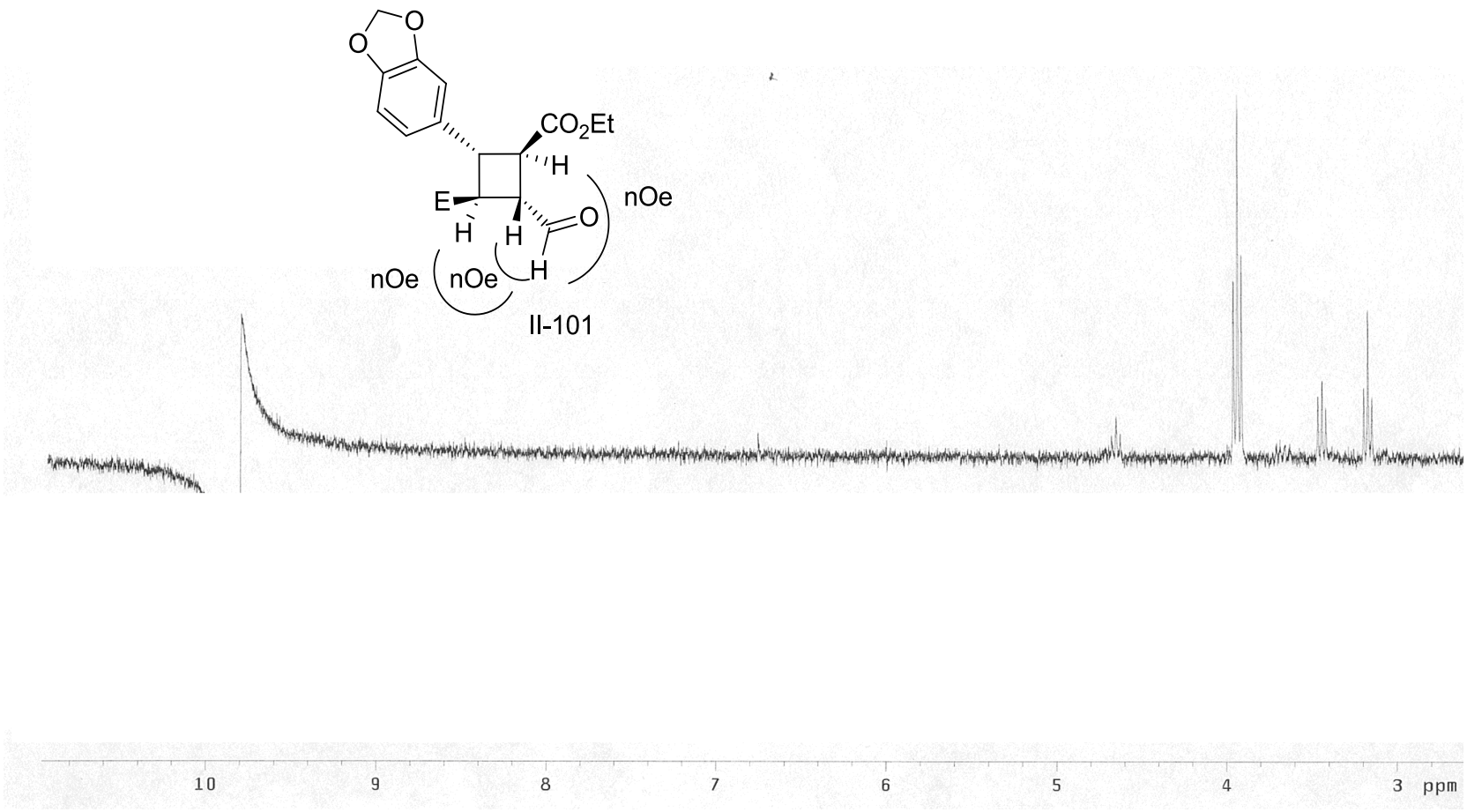

O
O
H
CO2Et
nOe
H
E
OBn
H
nOe

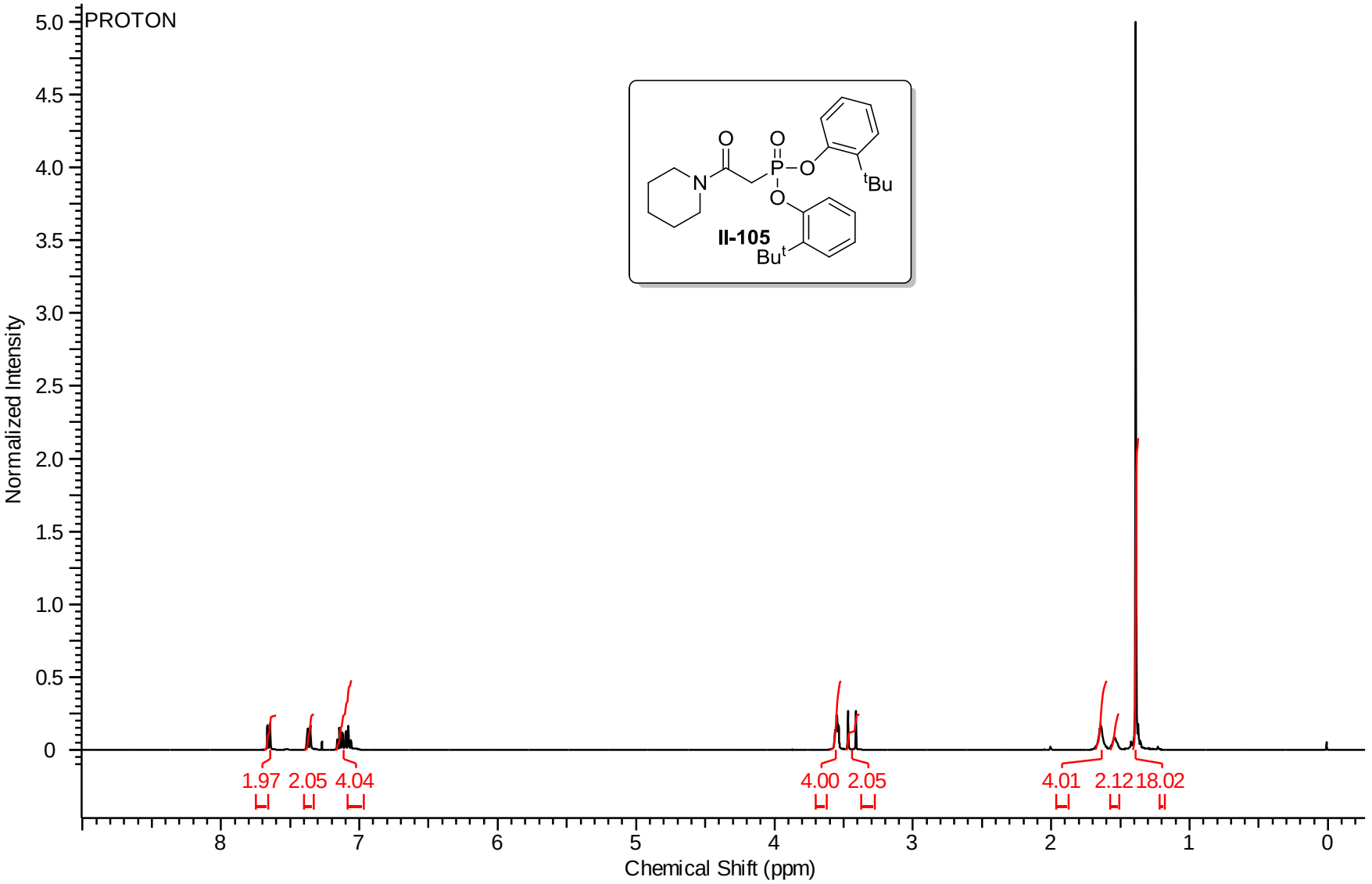
II-99

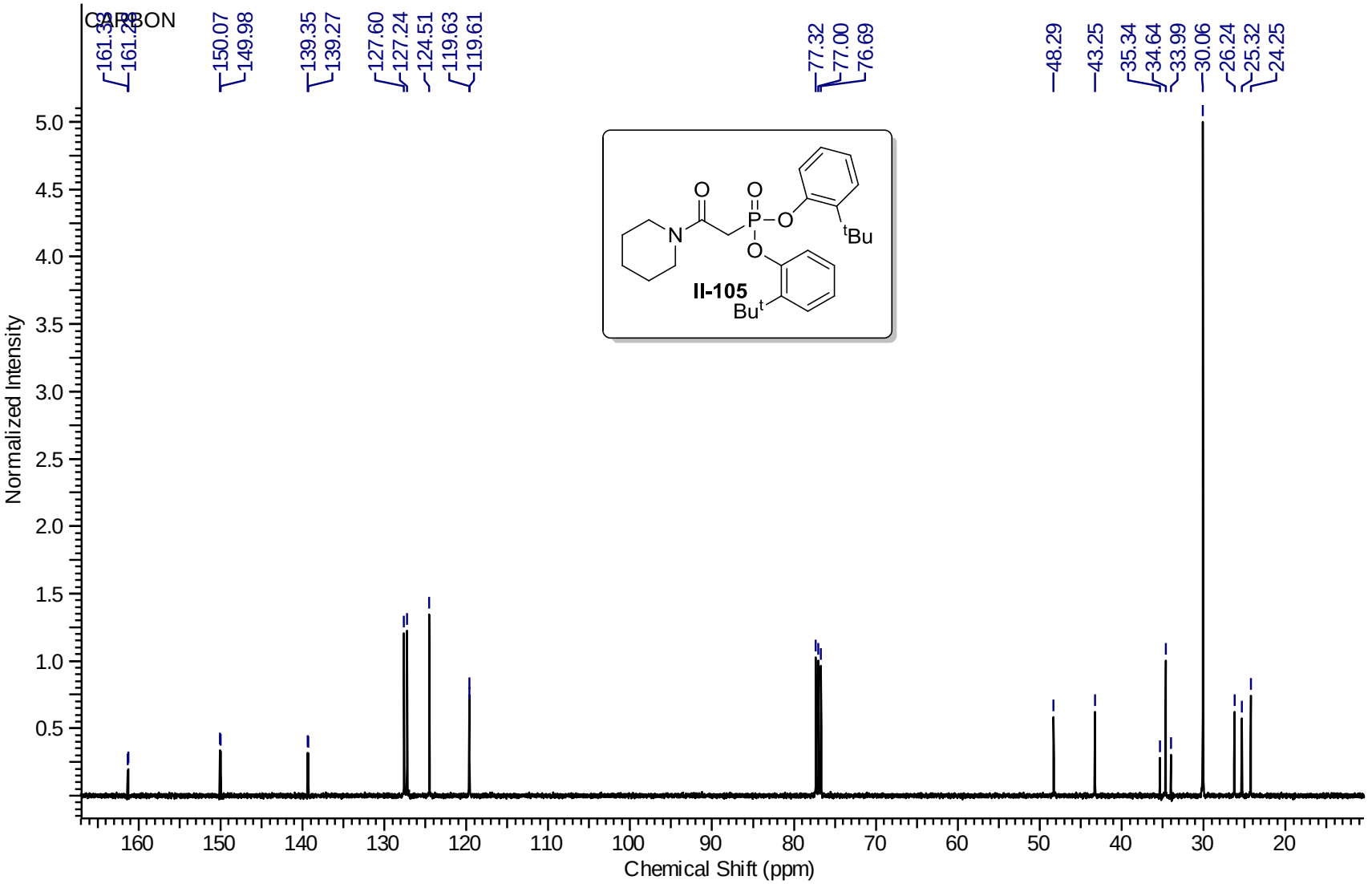

PROTON
Normalized Intensity
Chemical Shift (ppm)
0.82
1.06 2.08 2.13 2.26 0.85 0.98 1.07 1.01 1.00 0.90 1.85 4.28 5.75
OHC
CO2Et
II-101

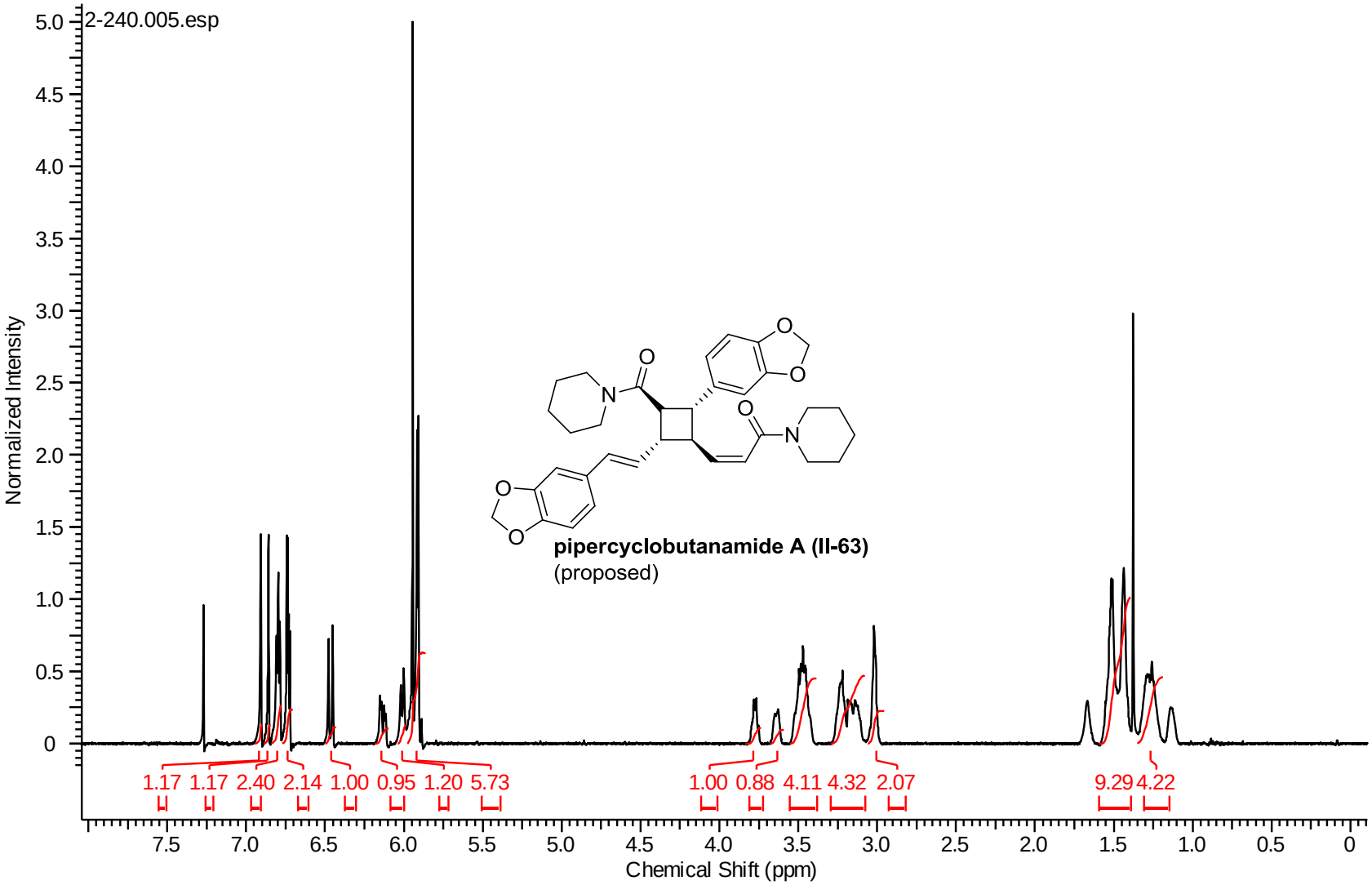

CARBON
199.54
171.62
168.74
148.04
146.94
134.39
120.45
108.40
107.22
101.13
77.31
77.00
76.68
61.17
46.74
46.43
43.54
41.48
26.53
25.50
24.33
14.17
Normalized Intensity
Chemical Shift (ppm)
OHC
CO2Et
II-101

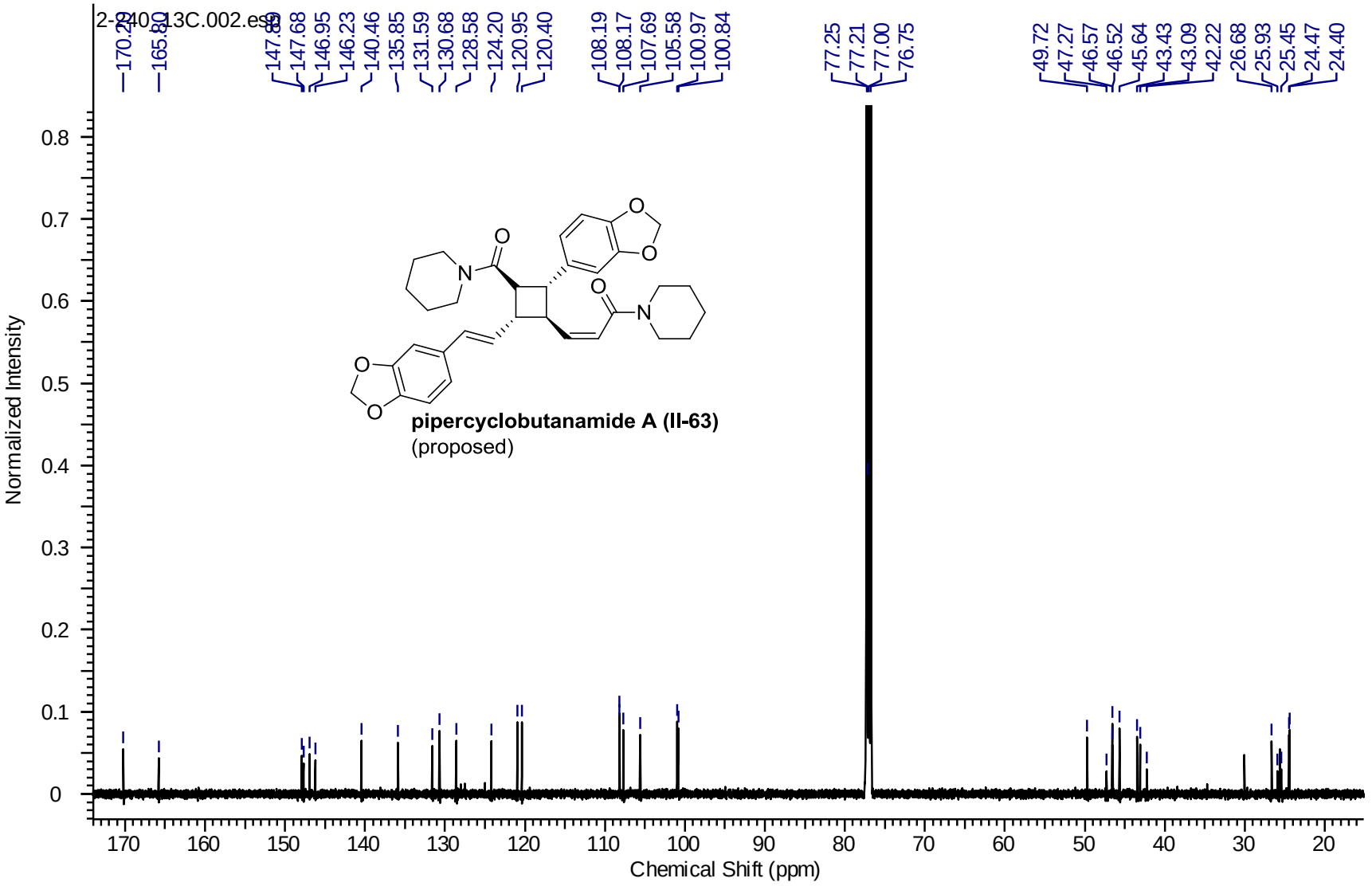

liu-2-226-2noe2
O
O
H
nOe
CO2Et
H nOe
H
H
E
H
O
nOe
H
II-101
Normalized Intensity
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

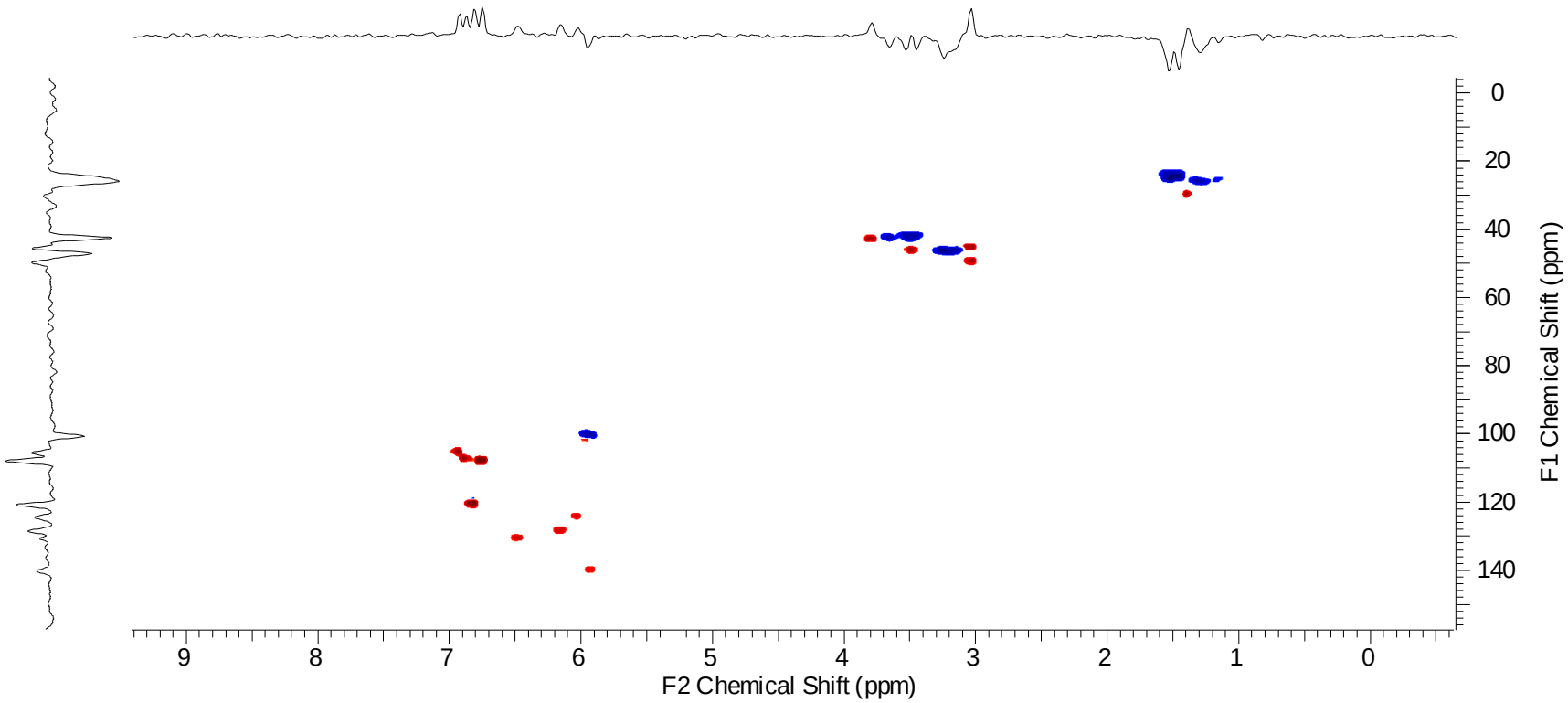

O
O
CO2Et
H
E
H
H
O
H
nOe
nOe
nOe
II-101
10
9
8
7
6
5
4
3
ppm

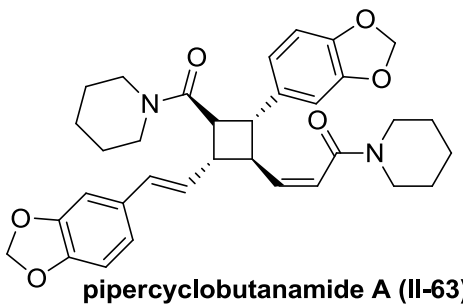

PROTON
Normalized Intensity
Chemical Shift (ppm)
II-105
1.97 2.05 4.04
4.00 2.05
4.01 2.12 18.02


CARBON
161.33
161.26
150.07
149.98
139.35
139.27
127.60
127.24
124.51
119.63
119.61
77.32
77.00
76.69
48.29
43.25
35.34
34.64
33.99
30.06
26.24
25.32
24.25
II-105
Normalized Intensity
Chemical Shift (ppm)

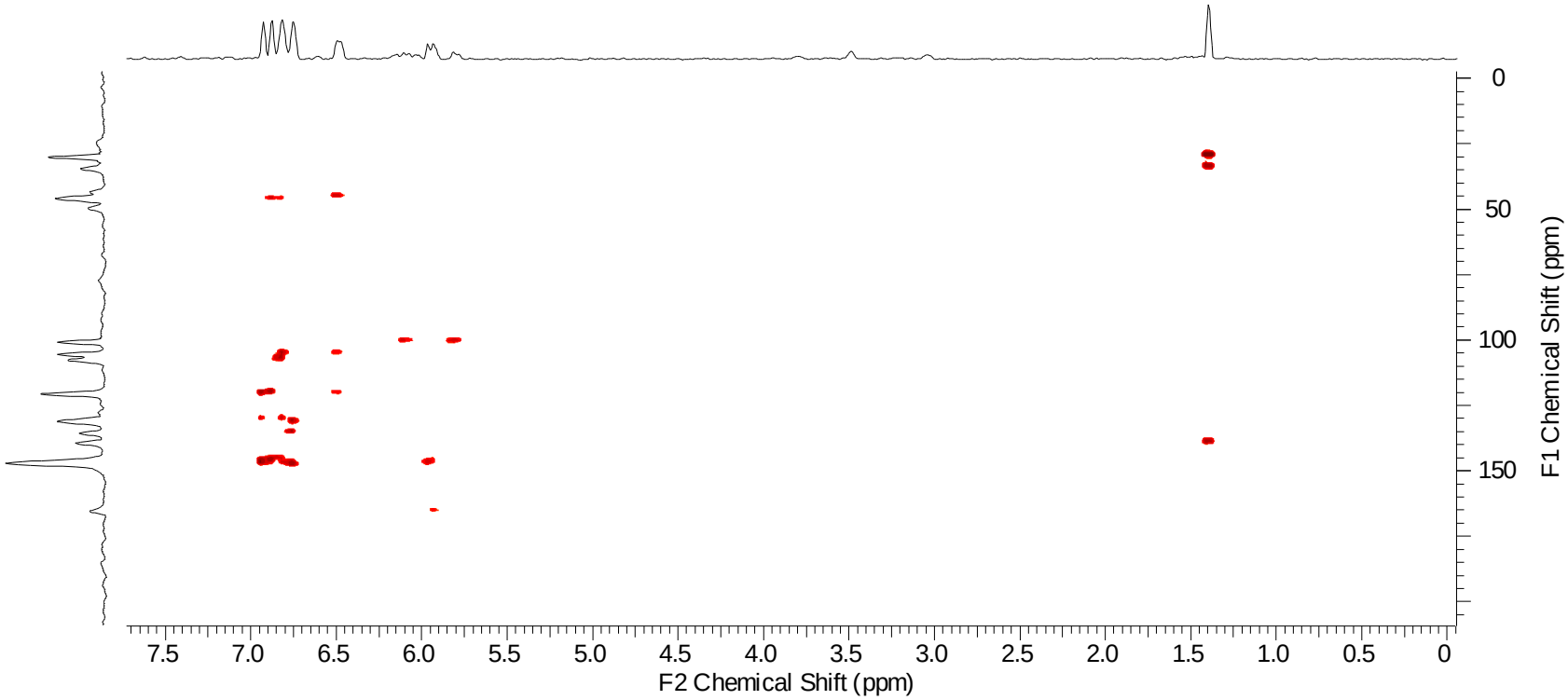

2-240.005.esp
Normalized Intensity
Chemical Shift (ppm)
pipercyclobutanamide A (II-63)
(proposed)
1.17 1.17 2.40 2.14 1.00 0.95 1.20 5.73
1.00 0.88 4.11 4.32 2.07
9.29 4.22

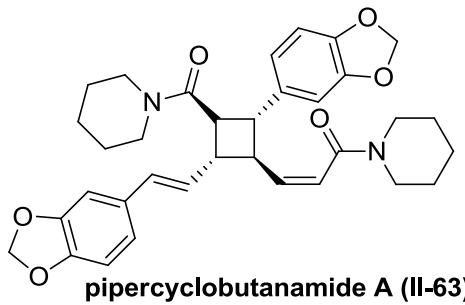

2-240-13C.002.esp
170.24
165.80
147.85
147.68
146.95
146.23
140.46
135.85
131.59
130.68
128.58
124.20
120.95
120.40
108.19
108.17
107.69
105.58
100.97
100.84
77.25
77.21
77.00
76.75
49.72
47.27
46.57
46.52
45.64
43.43
43.09
42.22
26.68
25.93
25.45
24.47
24.40
pipercyclobutanamide A (II-63)
(proposed)
Normalized Intensity
Chemical Shift (ppm)



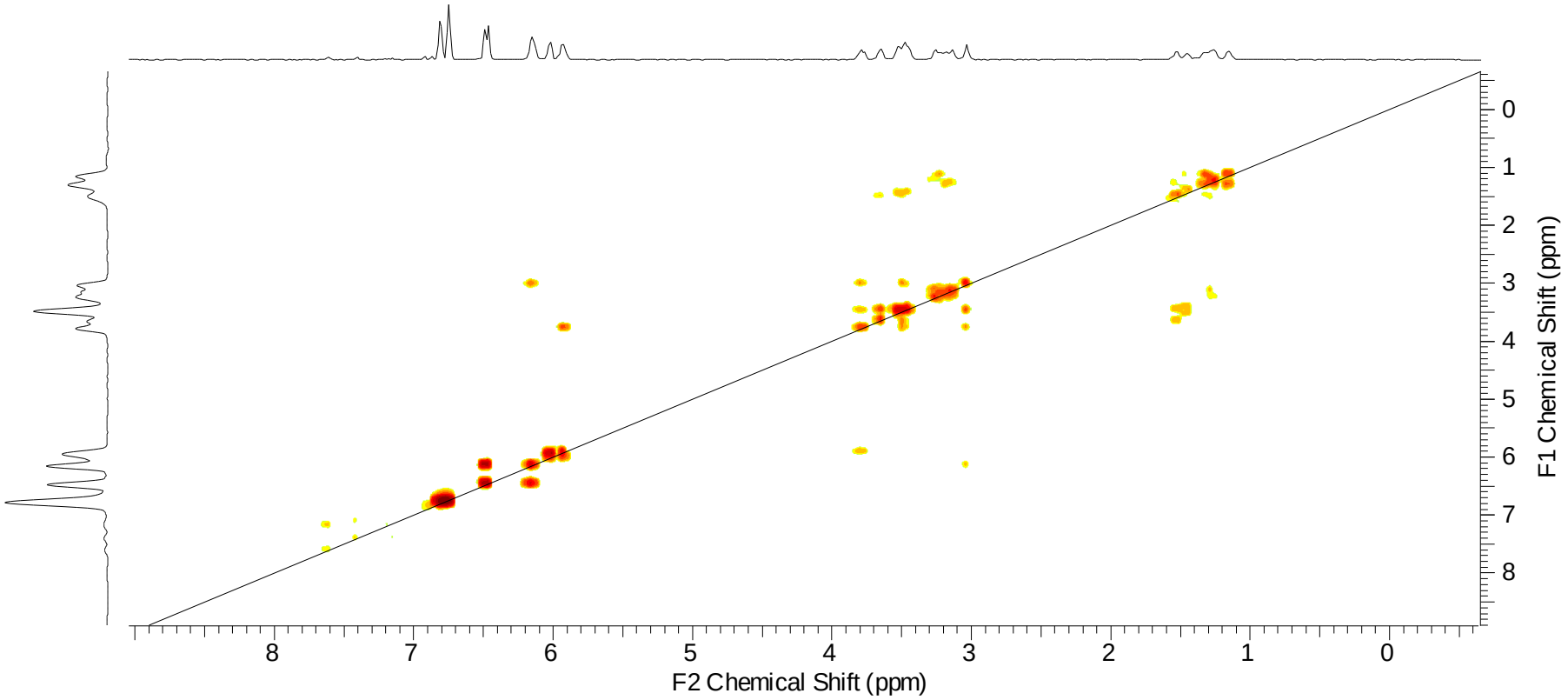



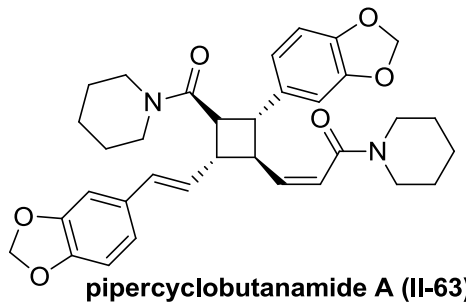

**pipercyclobutanamide A (II-63)**
(proposed)



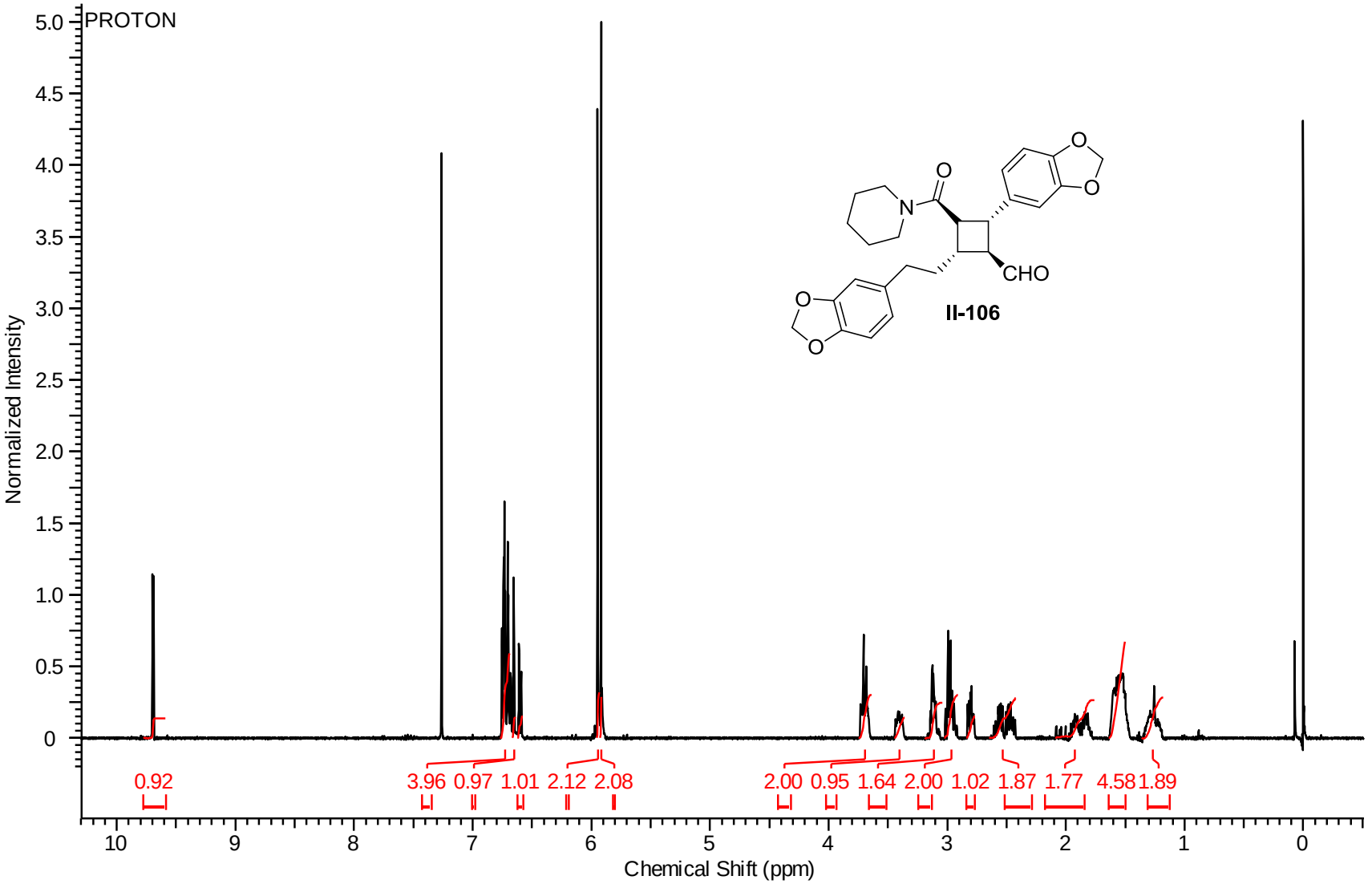



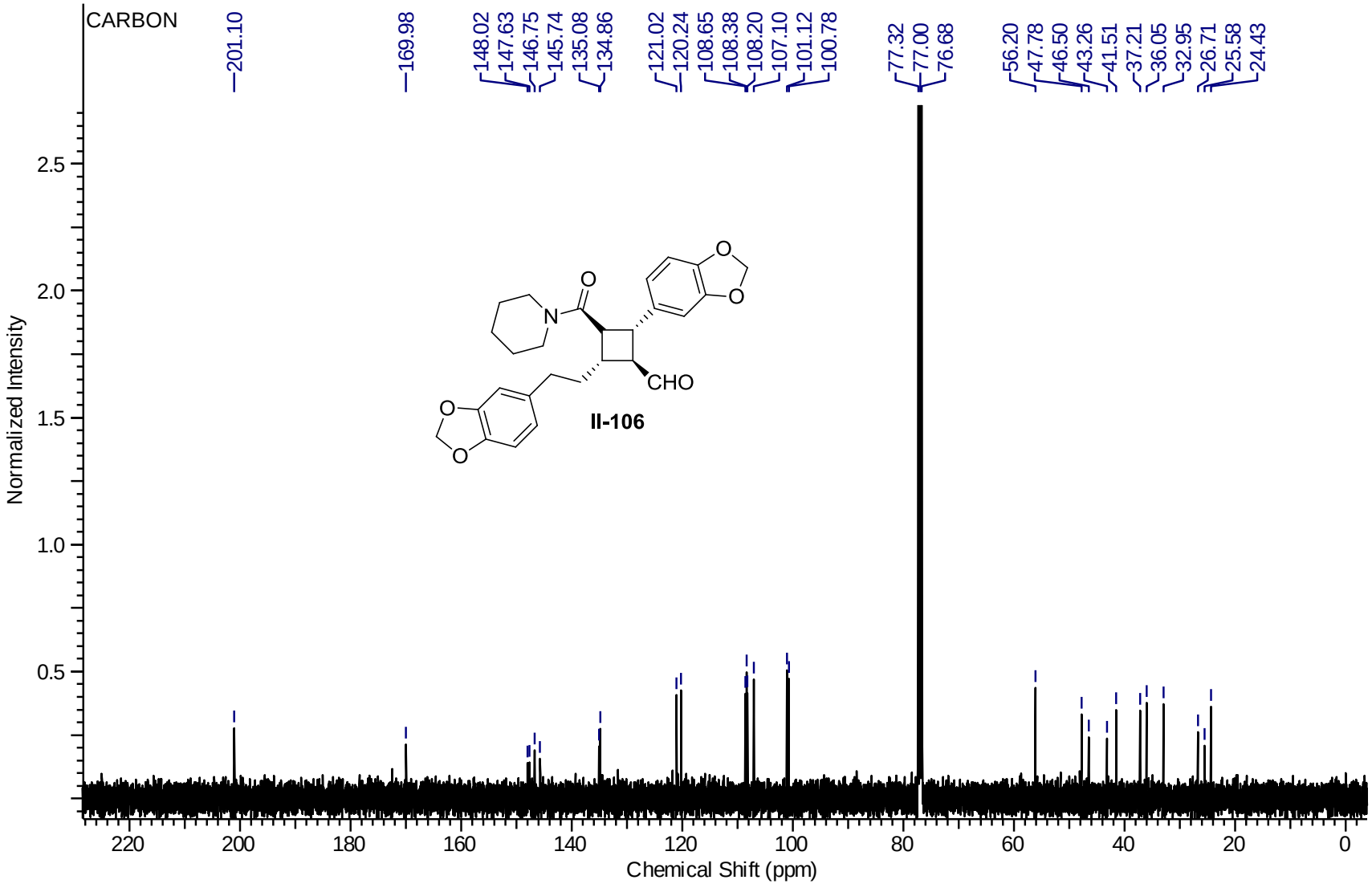

**pipercyclobutanamide A (II-63)**
(proposed)

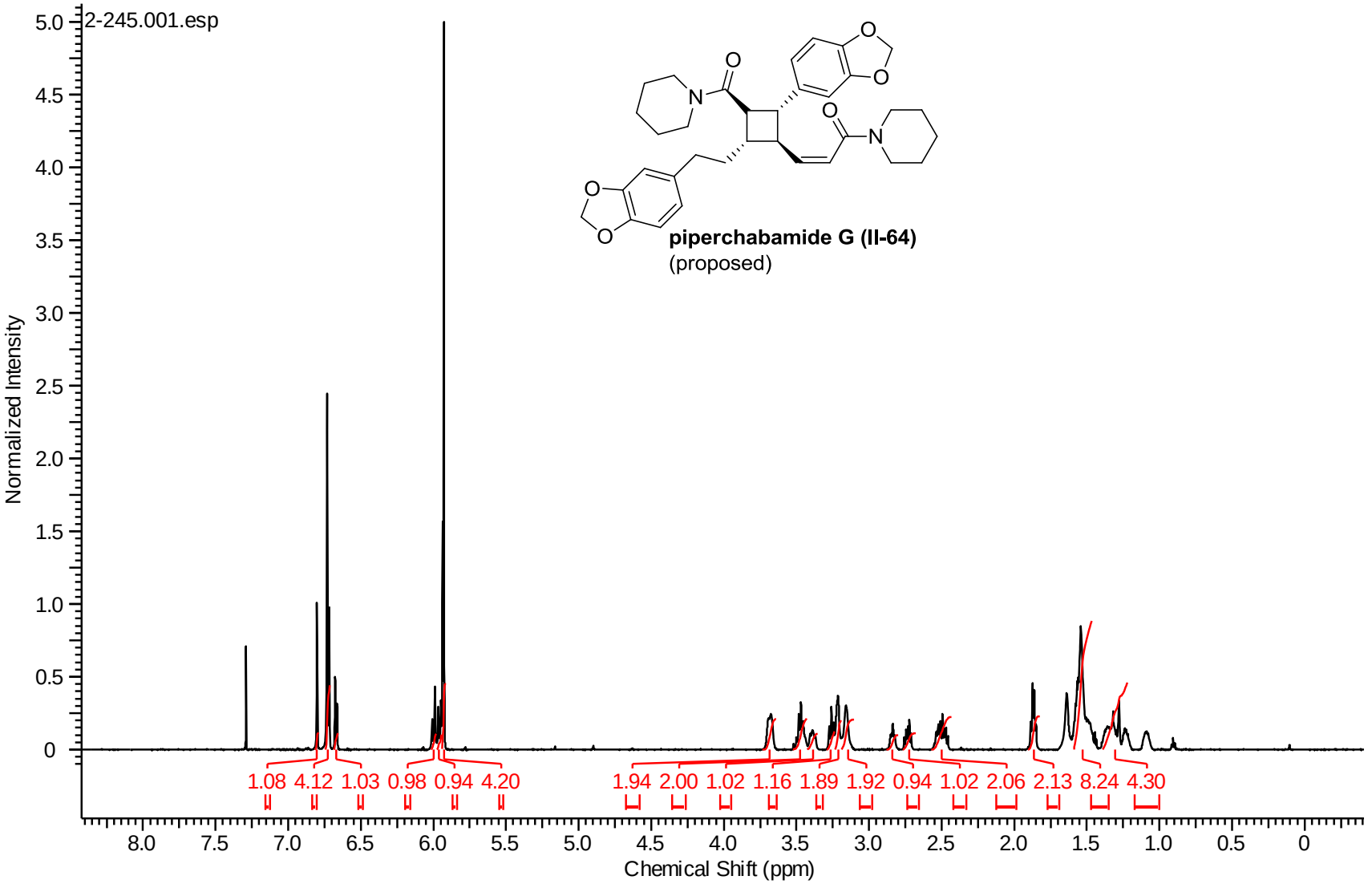


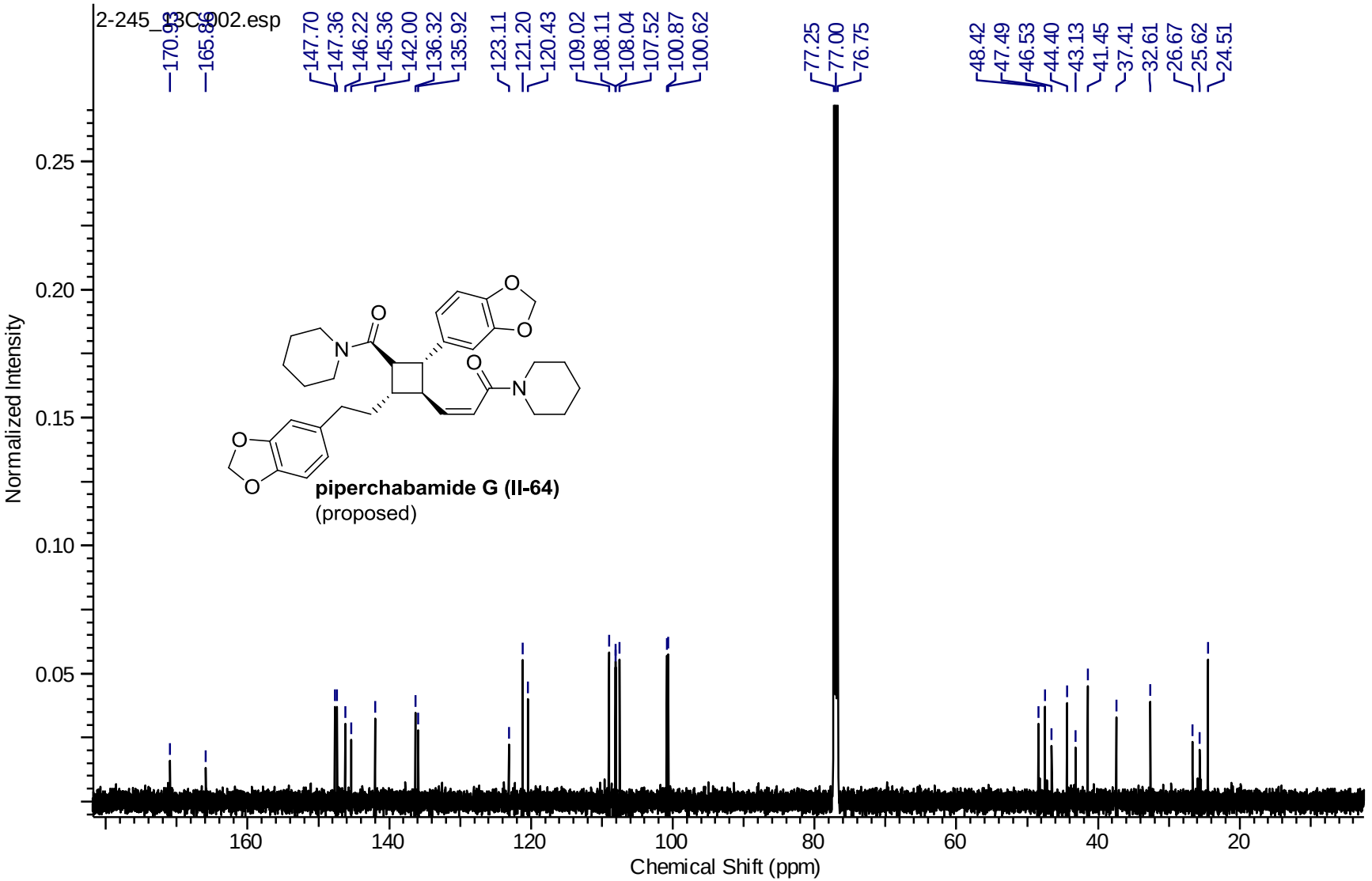



**pipercyclobutanamide A (II-63)**
(proposed)

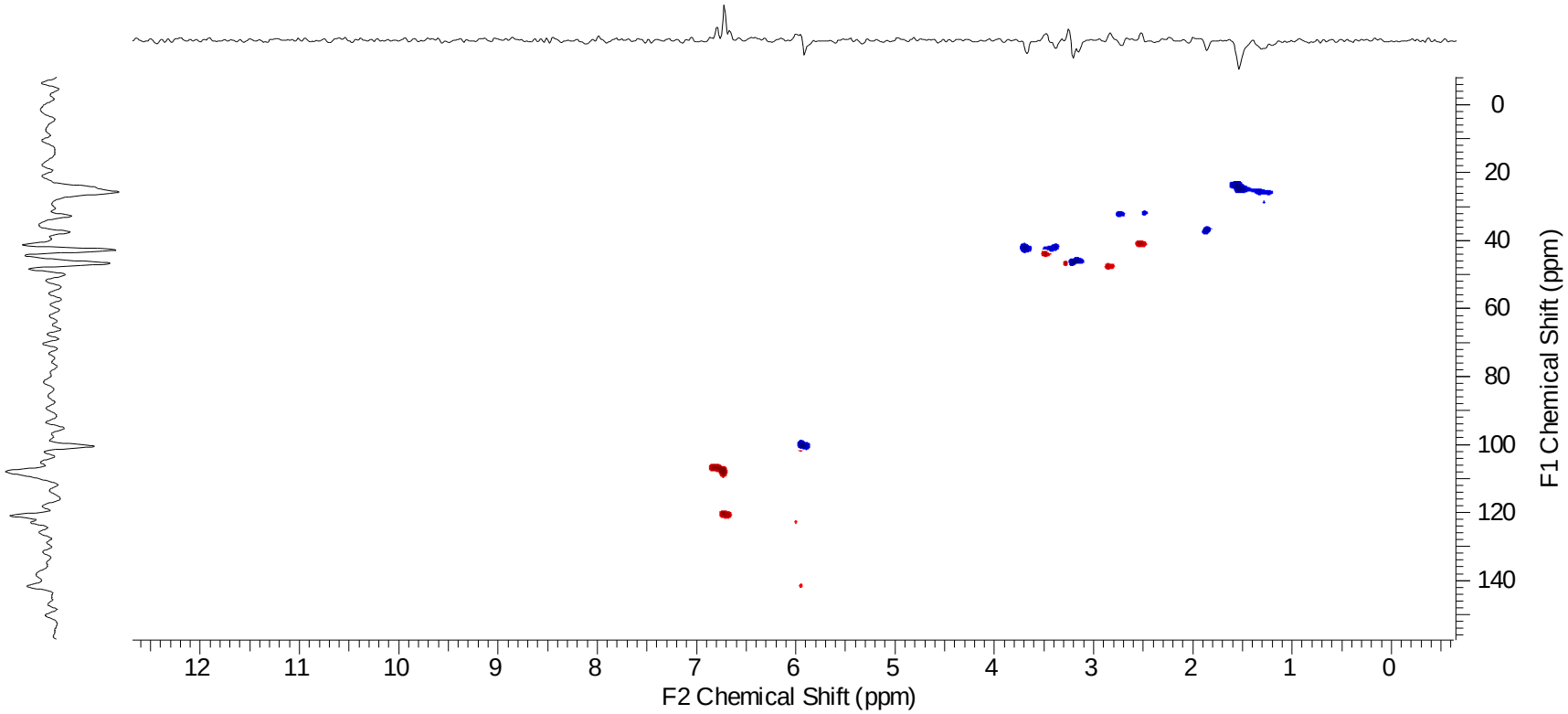

PROTON
Normalized Intensity
Chemical Shift (ppm)
0.92
3.96 0.97 1.01 2.12 2.08
2.00 0.95 1.64 2.00 1.02 1.87 1.77 4.58 1.89
II-106

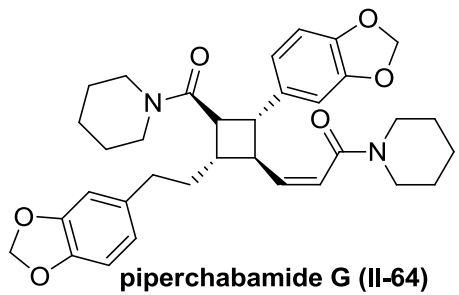

CARBON
201.10
169.98
148.02
147.63
146.75
145.74
135.08
134.86
121.02
120.24
108.65
108.38
108.20
107.10
101.12
100.78
77.32
77.00
76.68
56.20
47.78
46.50
43.26
41.51
37.21
36.05
32.95
26.71
25.58
24.43
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
O
N
O
O
CHO
O
O
II-106


2-245.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.08 4.12 1.03 0.98 0.94 4.20
1.94 2.00 1.02 1.16 1.89 1.92 0.94 1.02 2.06 2.13 8.24 4.30
piperchabamide G (II-64)
(proposed)


2-245_13CCPD02.esp
170.93
165.86
147.70
147.36
146.22
145.36
142.00
136.32
135.92
123.11
121.20
120.43
109.02
108.11
108.04
107.52
100.87
100.62
77.25
77.00
76.75
48.42
47.49
46.53
44.40
43.13
41.45
37.41
32.61
26.67
25.62
24.51
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
160
140
120
100
80
60
40
20
Chemical Shift (ppm)
piperchabamide G (II-64)
(proposed)

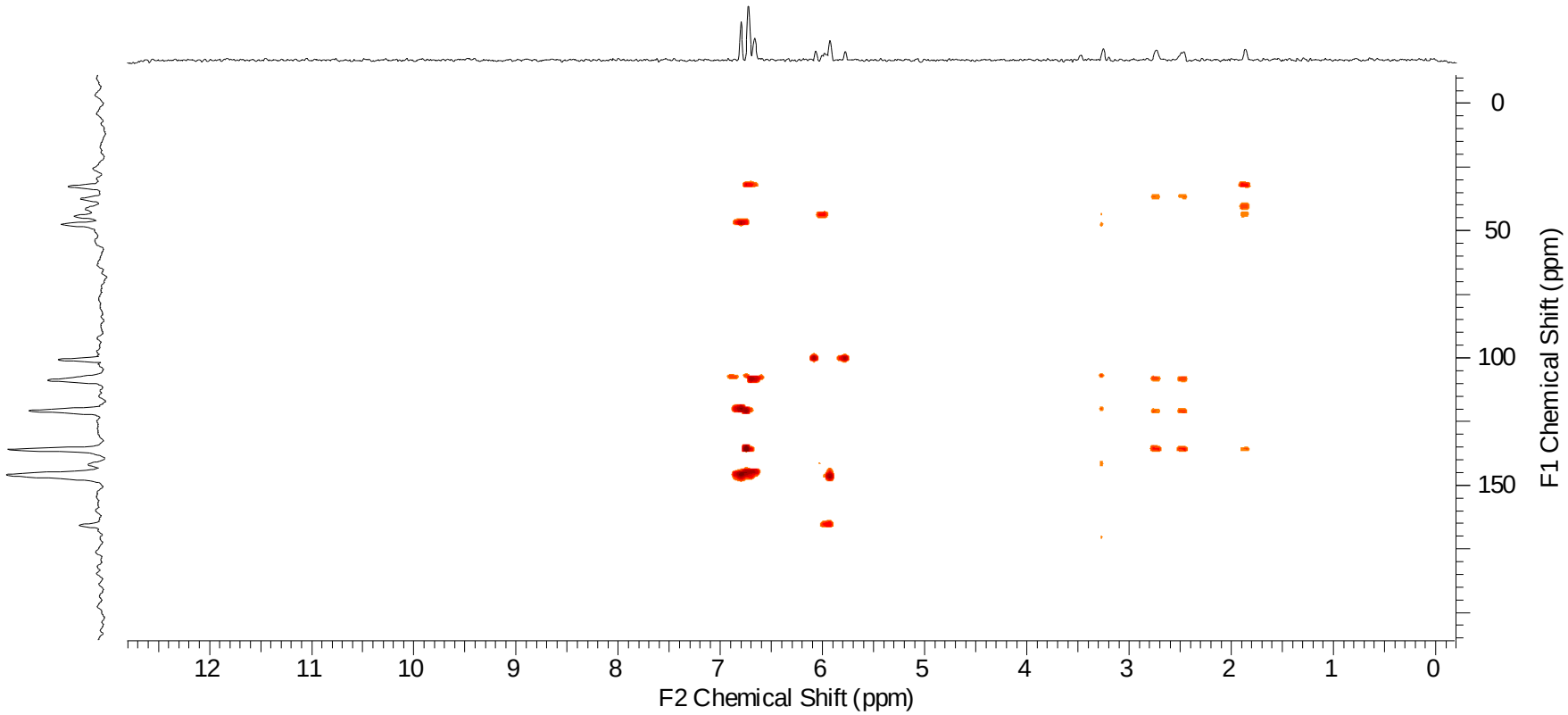
HSQC

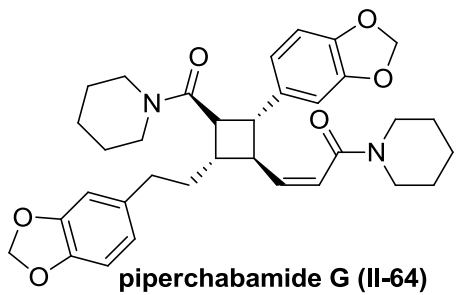



**piperchabamide G (II-64)**
(proposed)

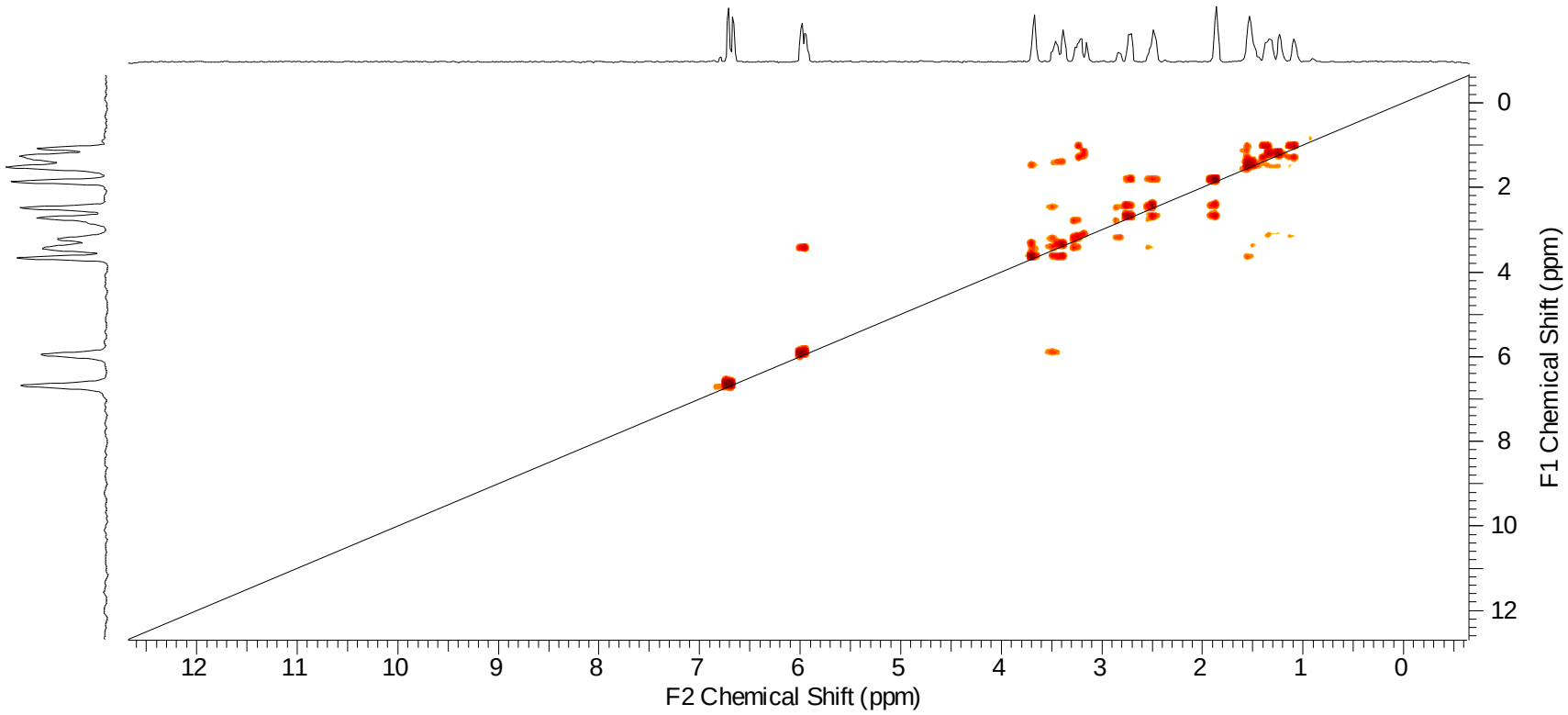
HMBC

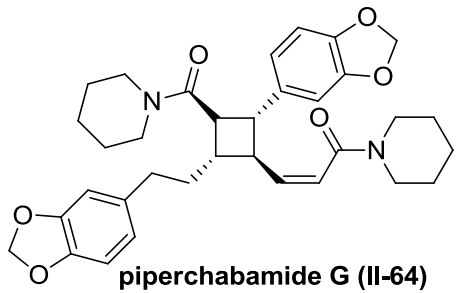


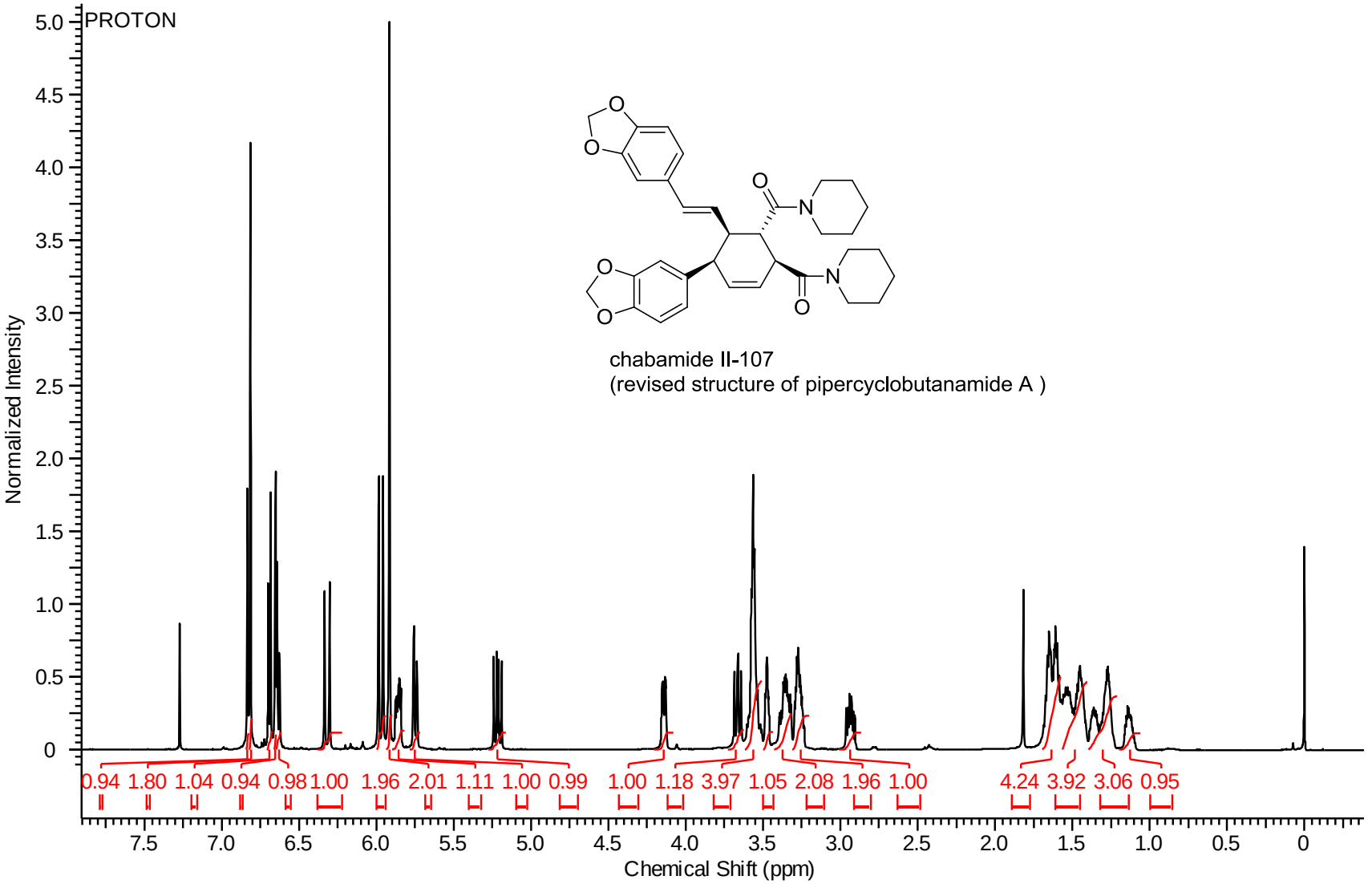

**piperchabamide G (II-64)**
(proposed)

COSY

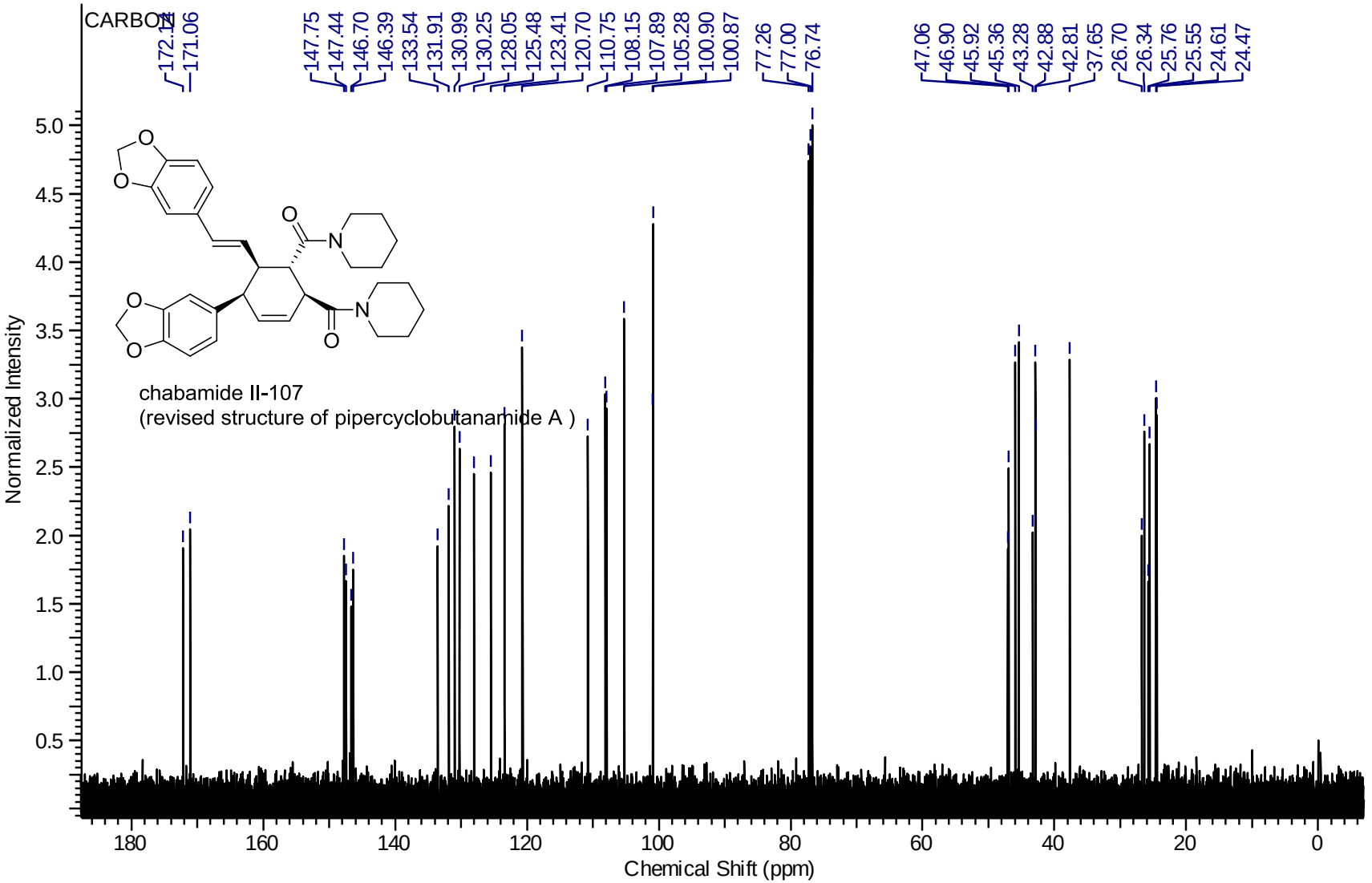


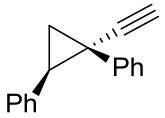



**piperchabamide G (II-64)**
(proposed)

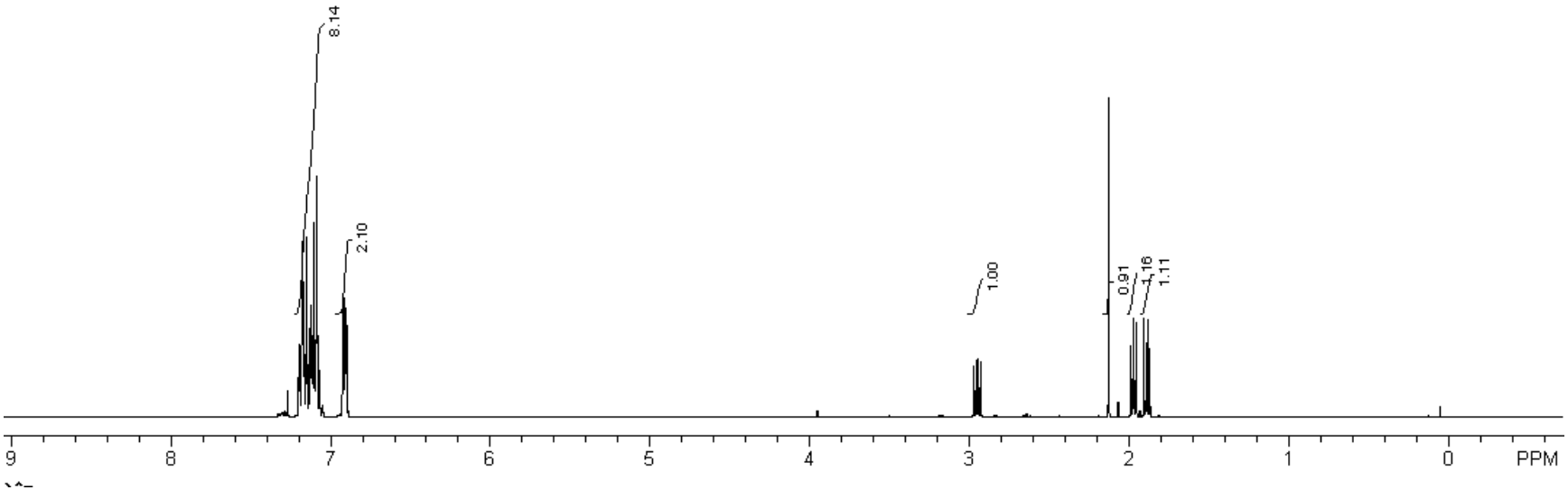


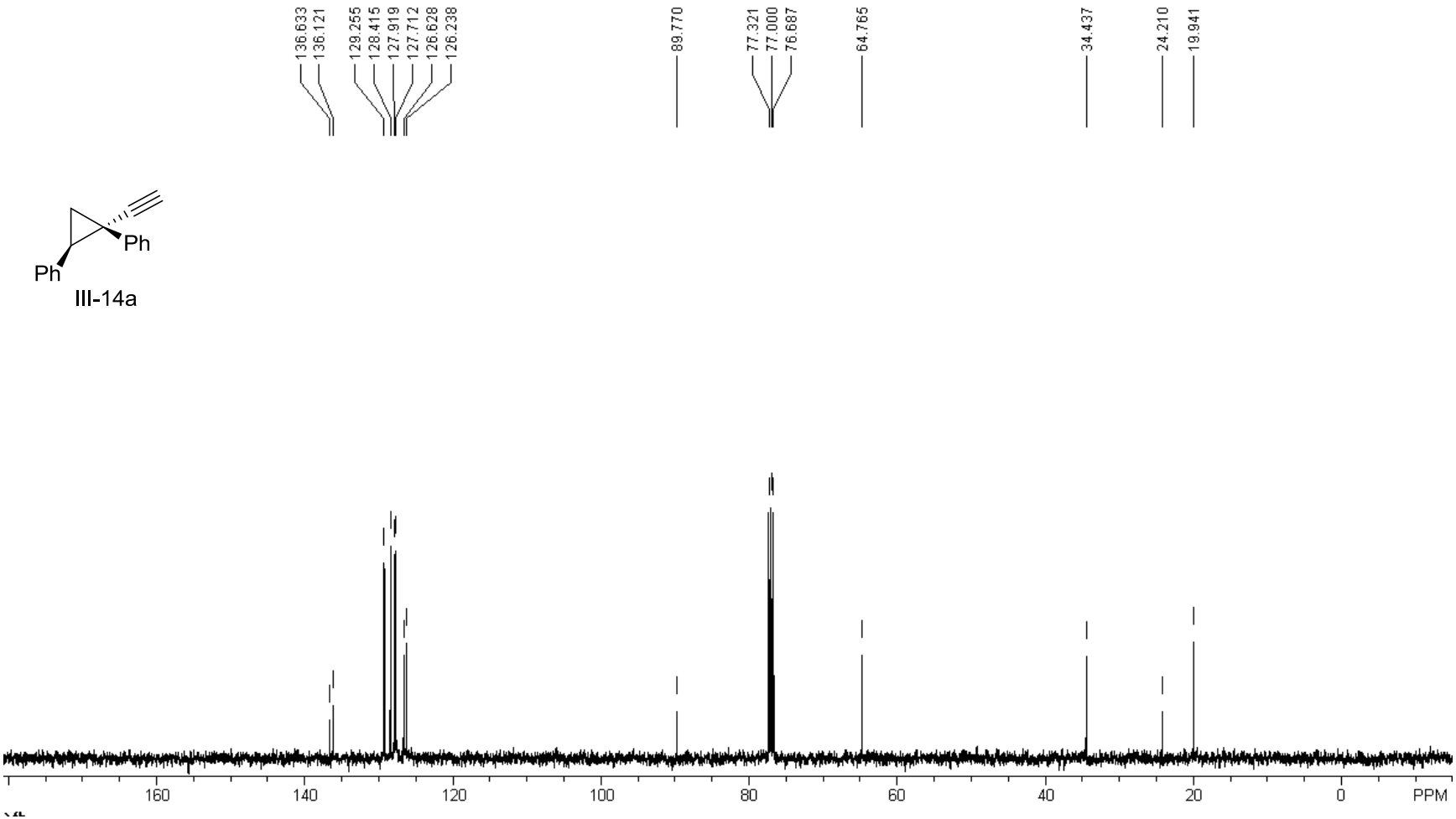

chabamide II-107
(revised structure of pipercyclobutanamide A )

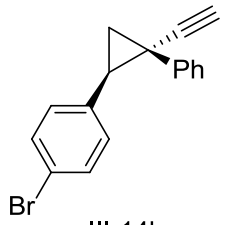

CARBON
172.12
171.06
147.75
147.44
146.70
146.39
133.54
131.91
130.99
130.25
128.05
125.48
123.41
120.70
110.75
108.15
107.89
105.28
100.90
100.87
77.26
77.00
76.74
47.06
46.90
45.92
45.36
43.28
42.88
42.81
37.65
26.70
26.34
25.76
25.55
24.61
24.47
chabamide II-107
(revised structure of pipercyclobutanamide A )
Normalized Intensity
Chemical Shift (ppm)



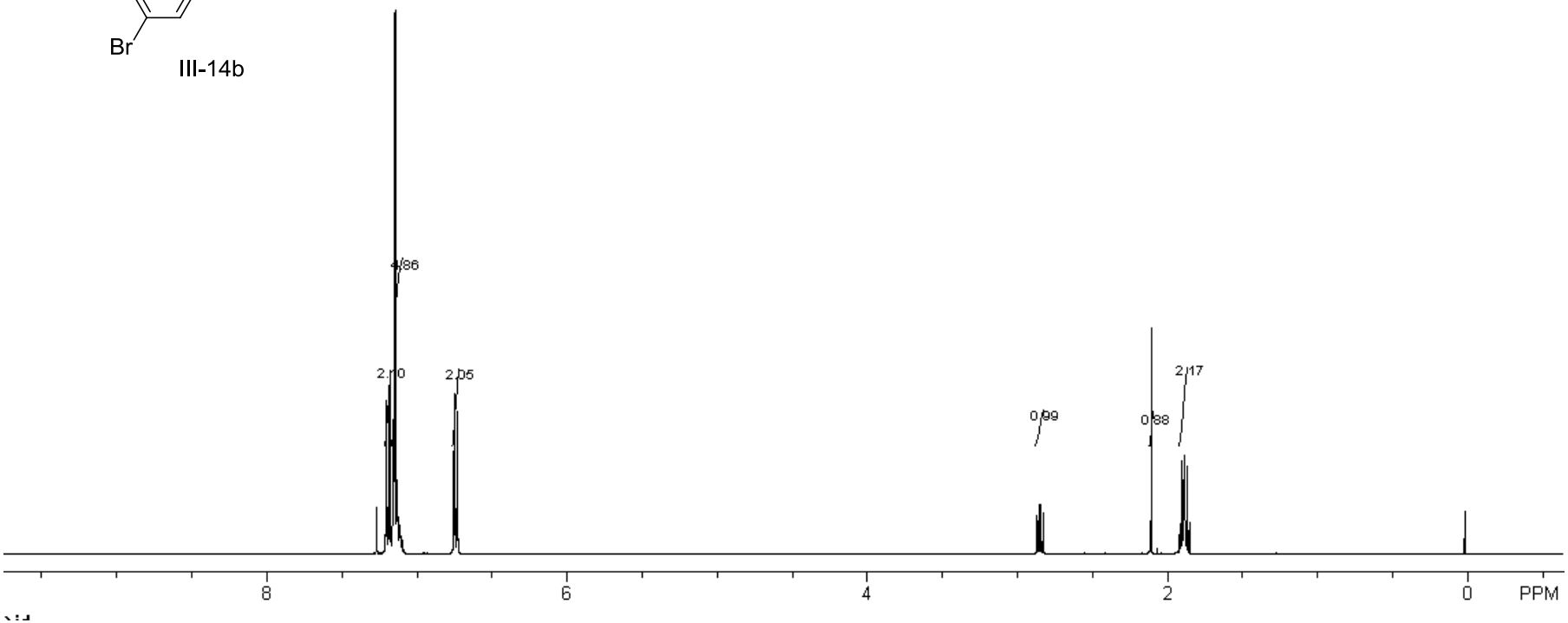

III-14a

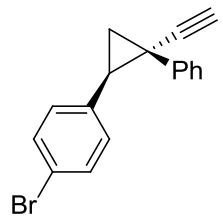



136.633
136.121
129.255
128.415
127.919
127.712
126.628
126.238
89.770
77.321
77.000
76.687
64.765
34.437
24.210
19.941
Ph
Ph
III-14a
160
140
120
100
80
60
40
20
0
PPM

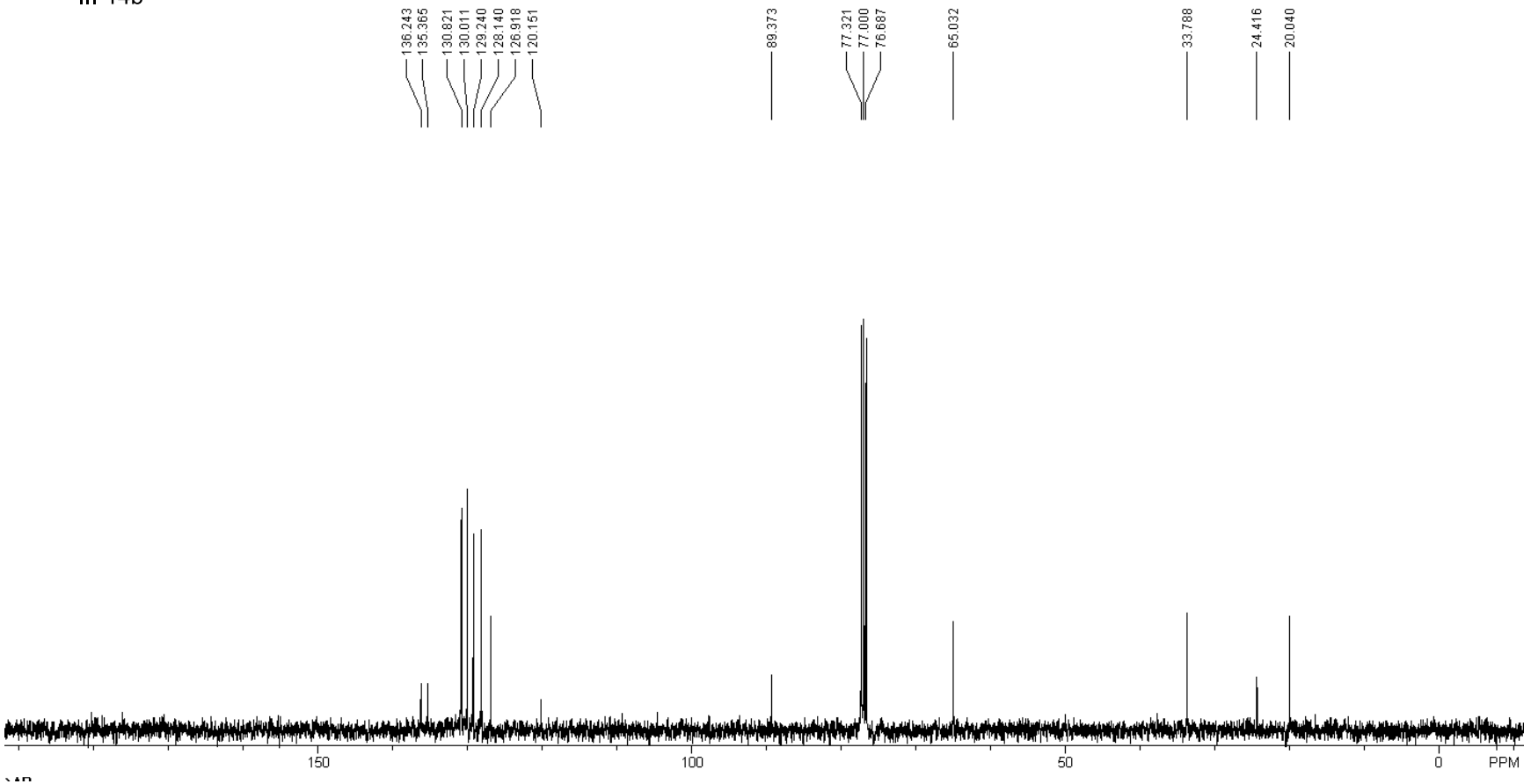


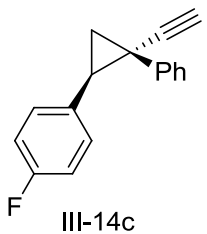

III-14b



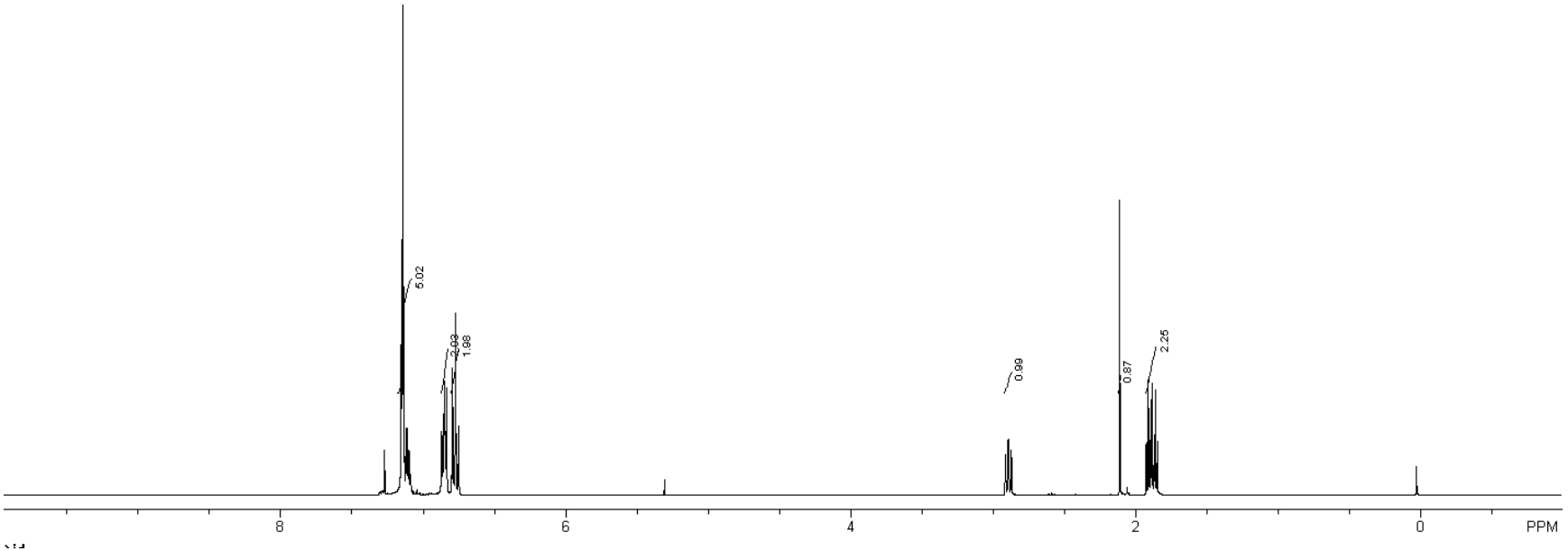

Ph
Br

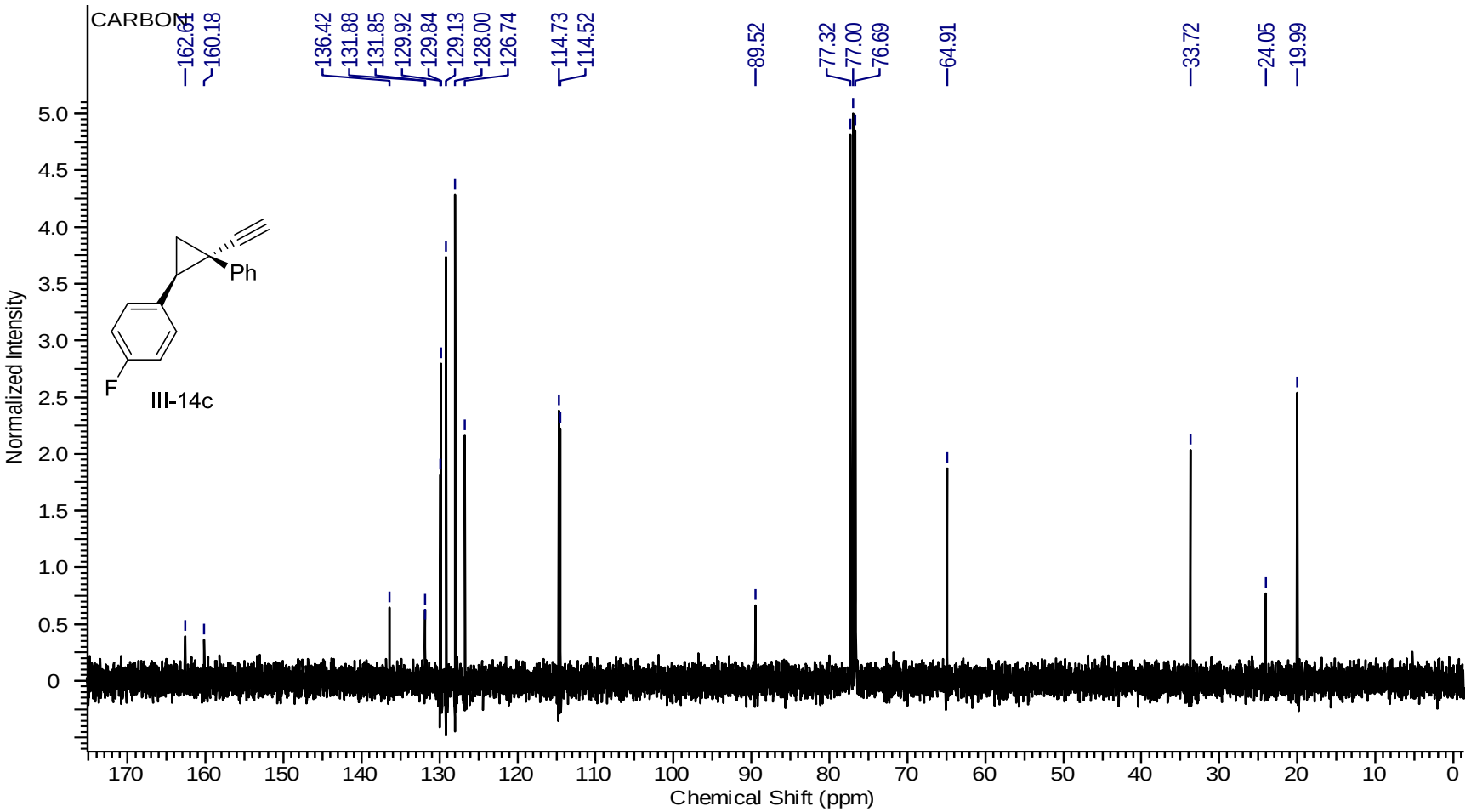
III-14b

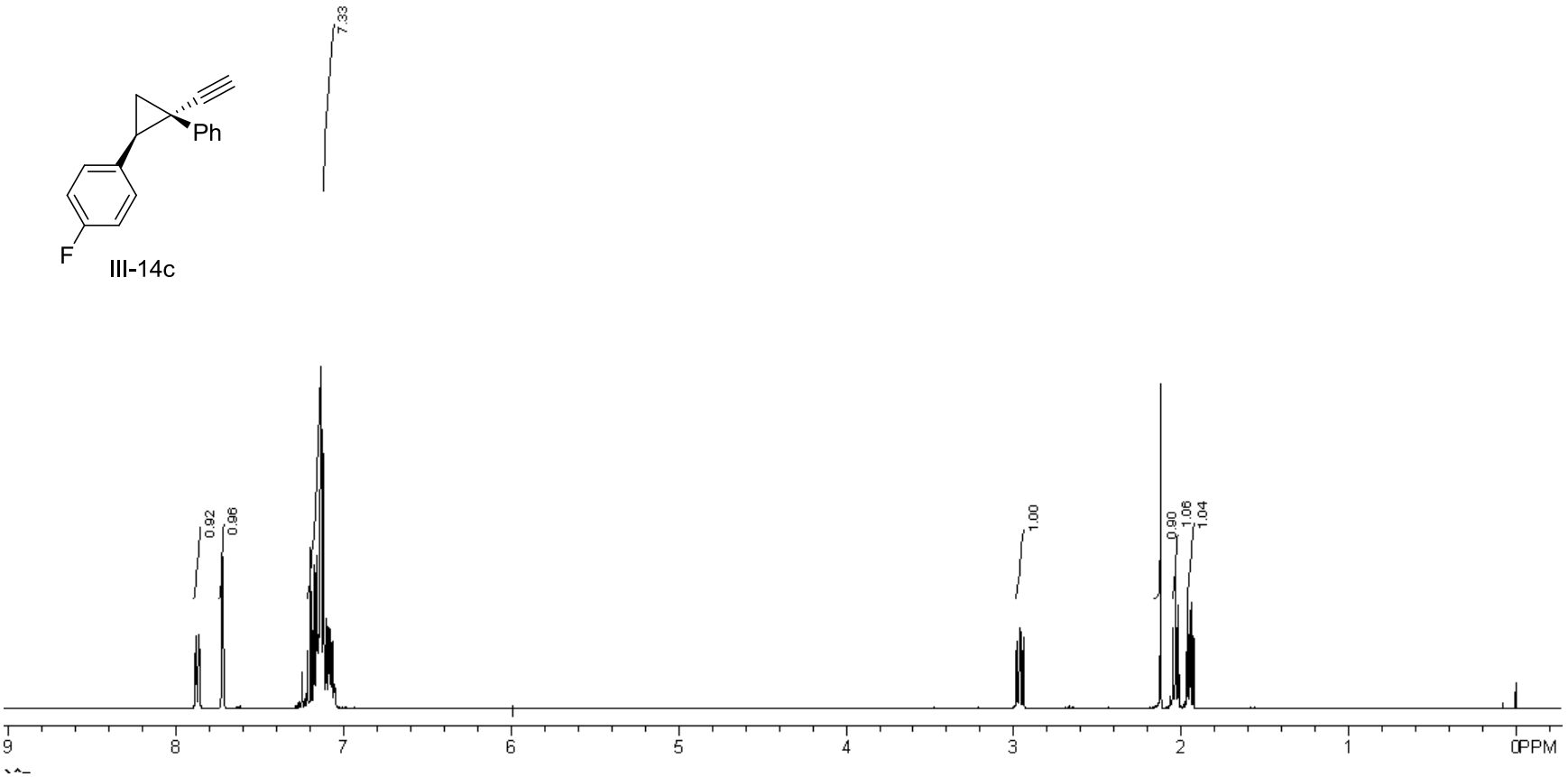

136.243
135.365
130.821
130.011
129.240
128.140
126.918
120.151
89.373
77.321
77.000
76.687
65.032
33.788
24.416
20.040
150
100
50
0
PPM

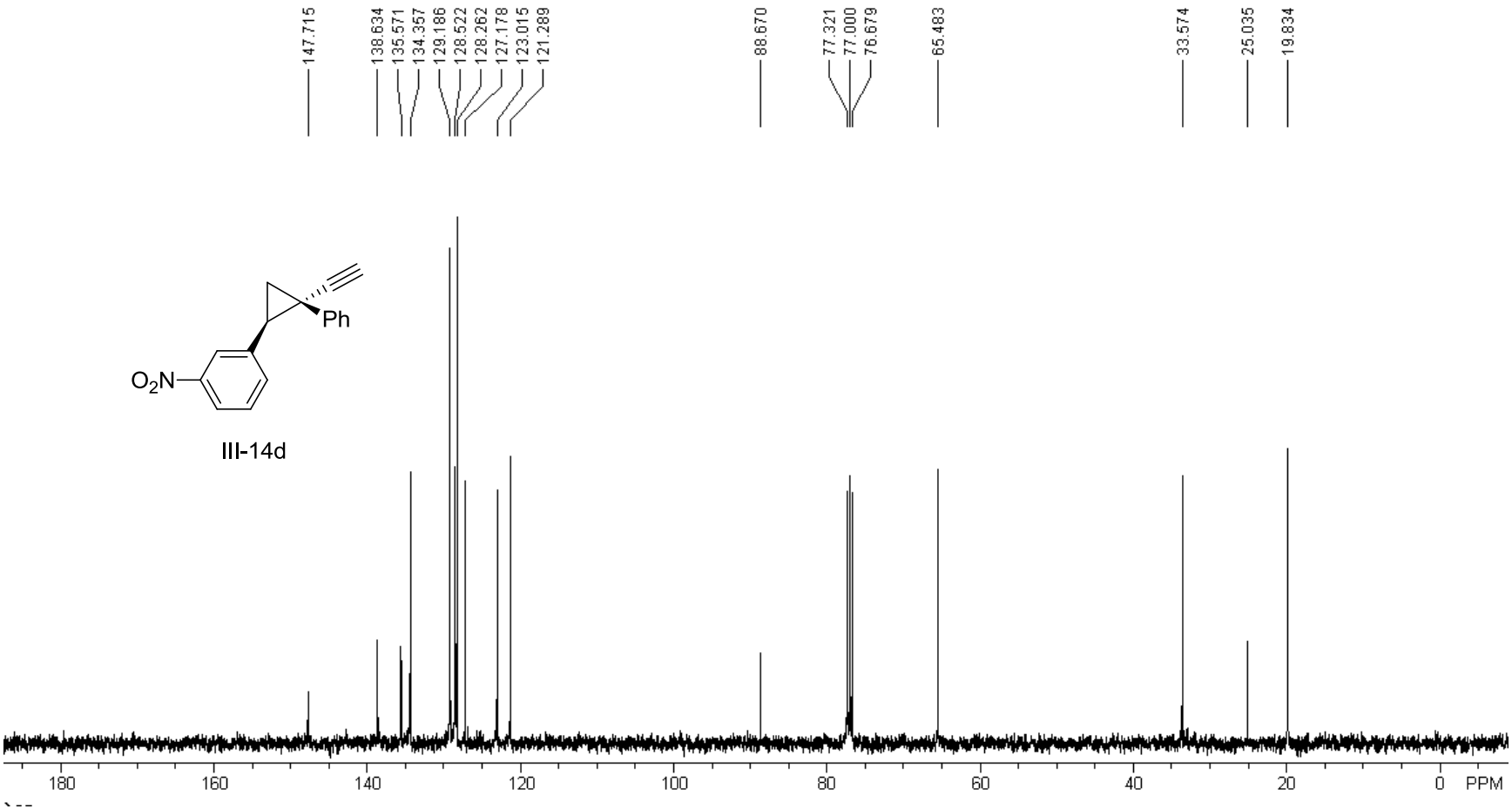


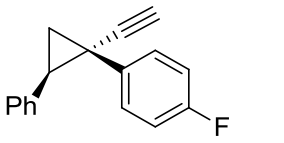

III-14c



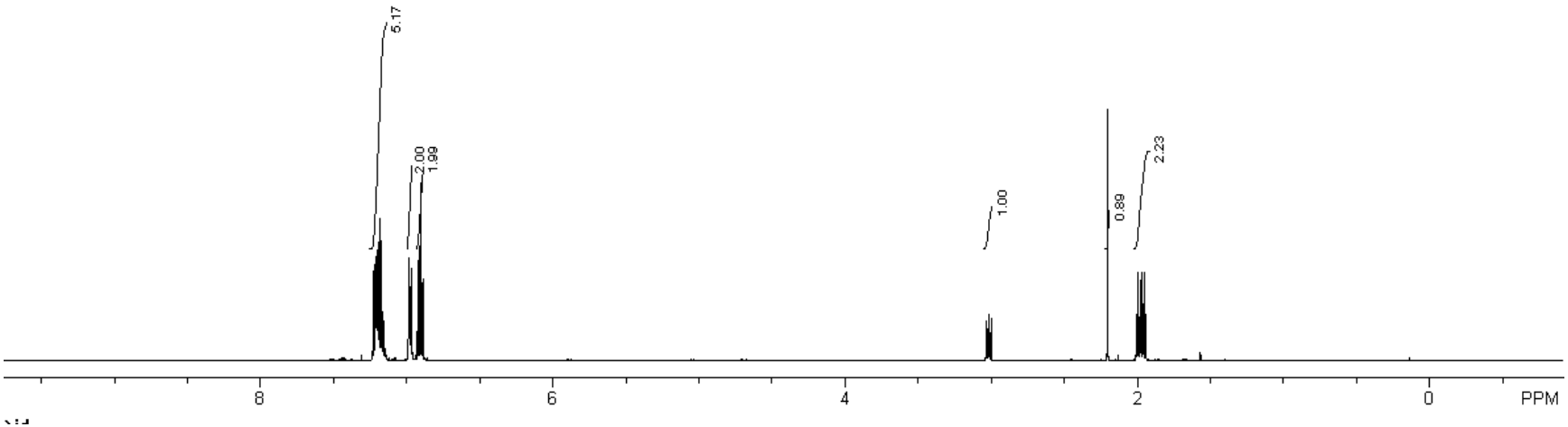

CARBON
162.64
160.18
136.42
131.88
131.85
129.92
129.84
129.13
128.00
126.74
114.73
114.52
89.52
77.32
77.00
76.69
64.91
33.72
24.05
19.99
Ph
F
III-14c
Normalized Intensity
Chemical Shift (ppm)

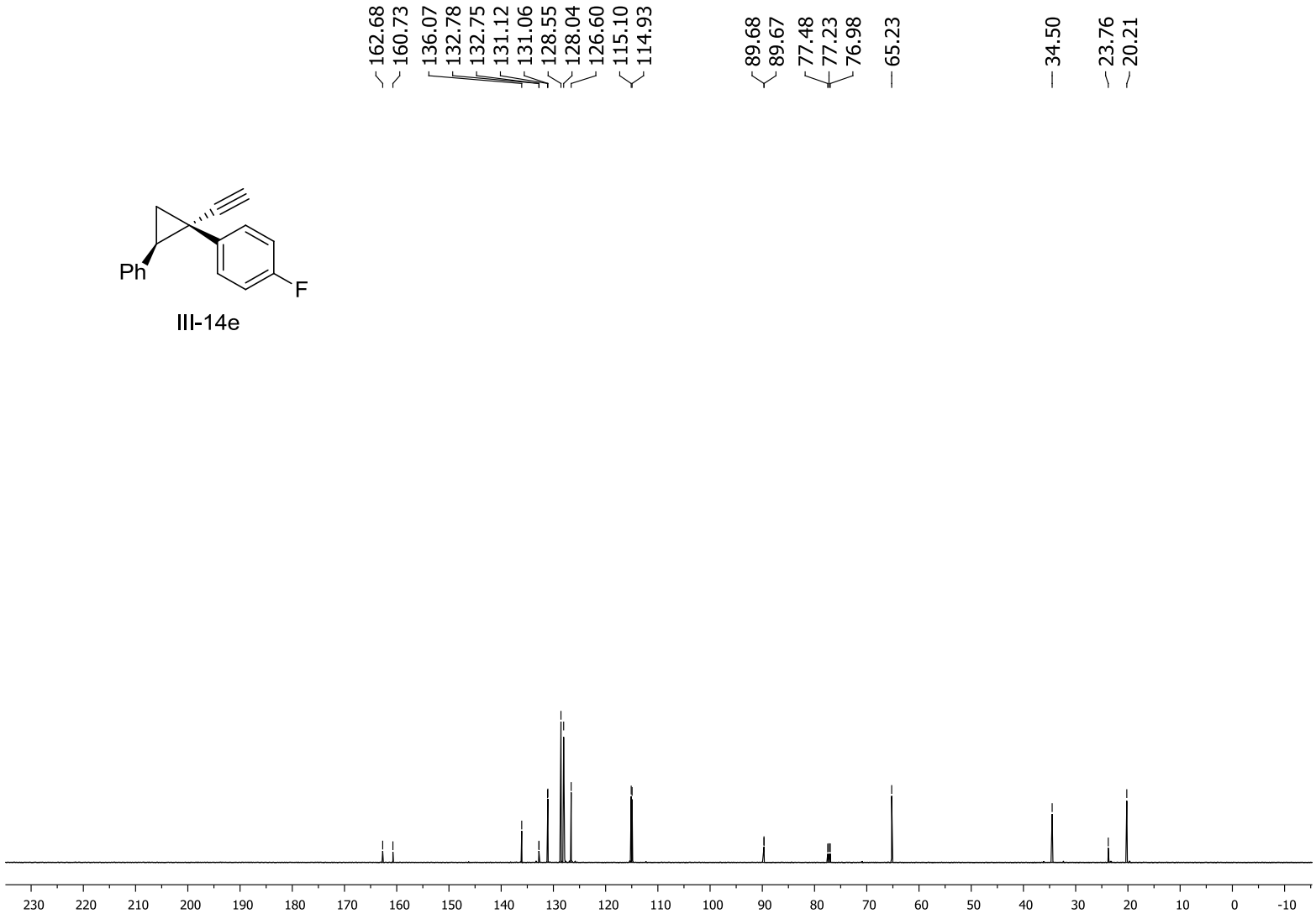

Ph
F
III-14c
7.33
0.92
0.96
1.00
0.90
1.06
1.04
9
8
7
6
5
4
3
2
1
0PPM

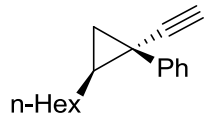

147.715
138.634
135.571
134.357
129.186
128.522
128.262
127.178
123.015
121.289
88.670
77.321
77.000
76.679
65.483
33.574
25.035
19.834
Ph
O2N
III-14d
180
160
140
120
100
80
60
40
20
0
PPM



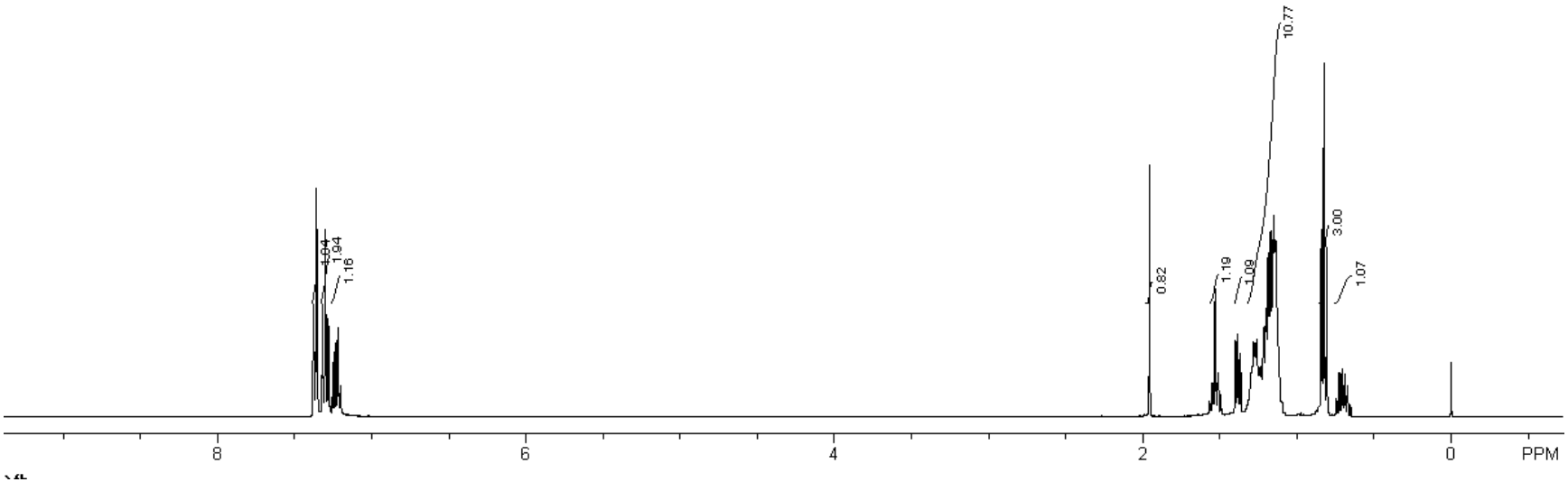

III-14e

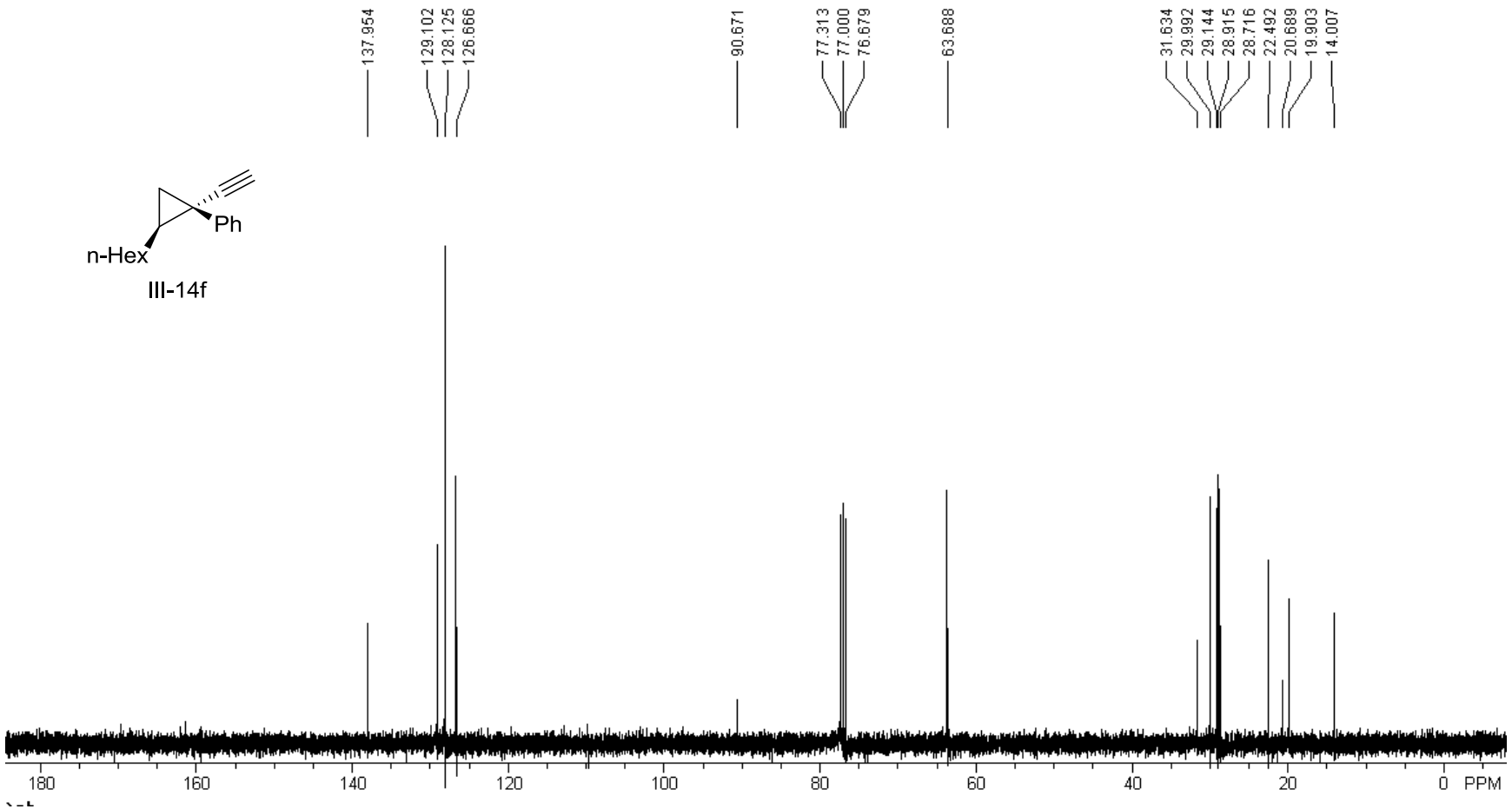


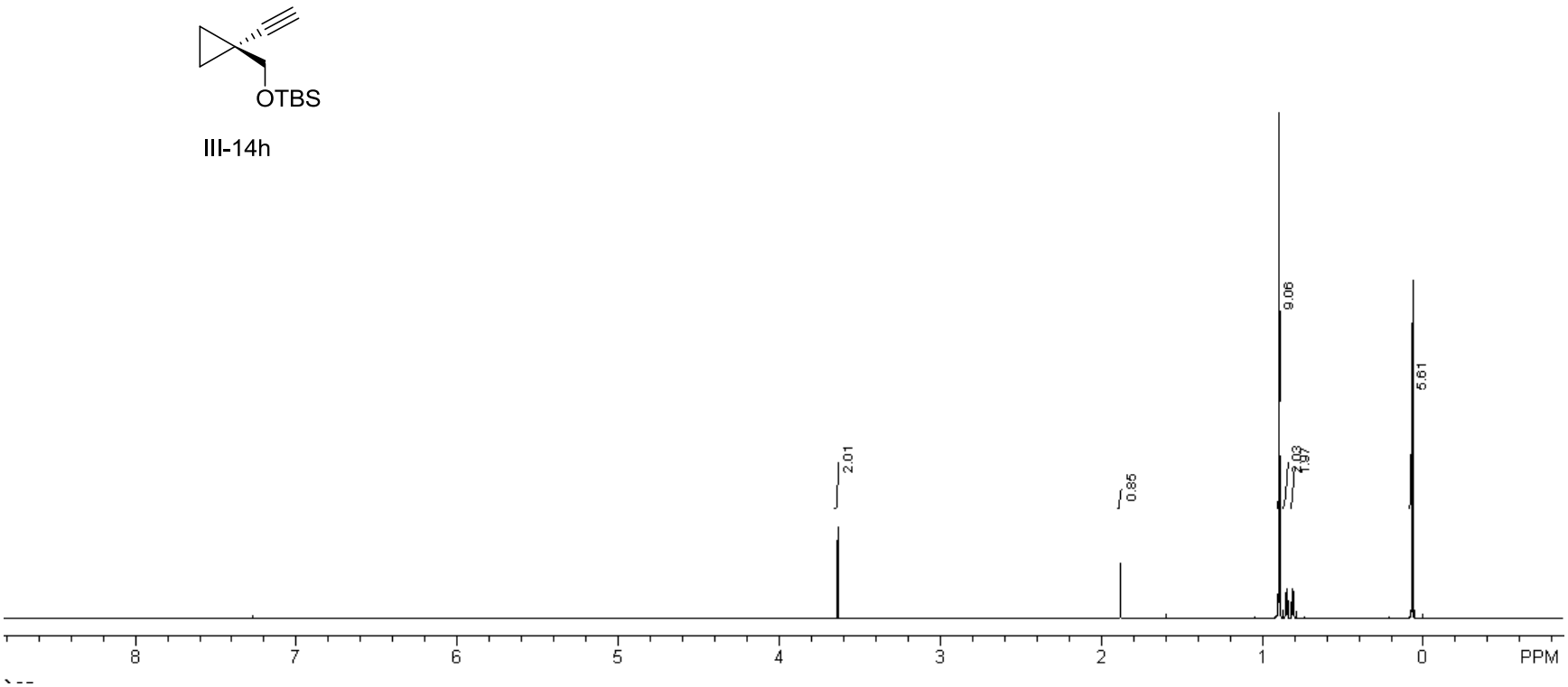

162.68
160.73
136.07
132.78
132.75
131.12
131.06
128.55
128.04
126.60
115.10
114.93
89.68
89.67
77.48
77.23
76.98
65.23
34.50
23.76
20.21
Ph
F
III-14e
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

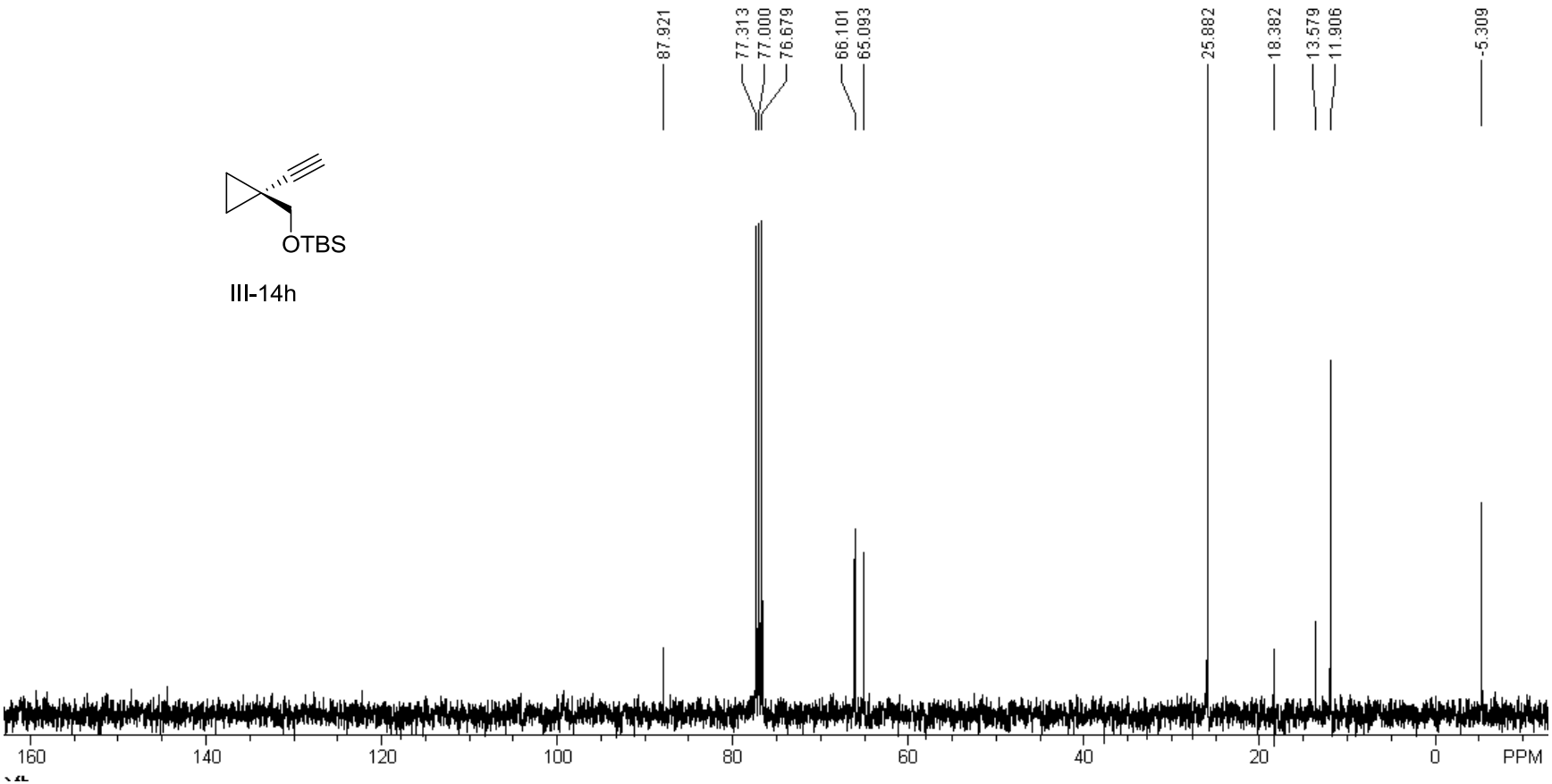


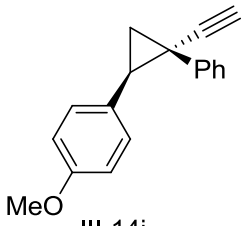

III-14f



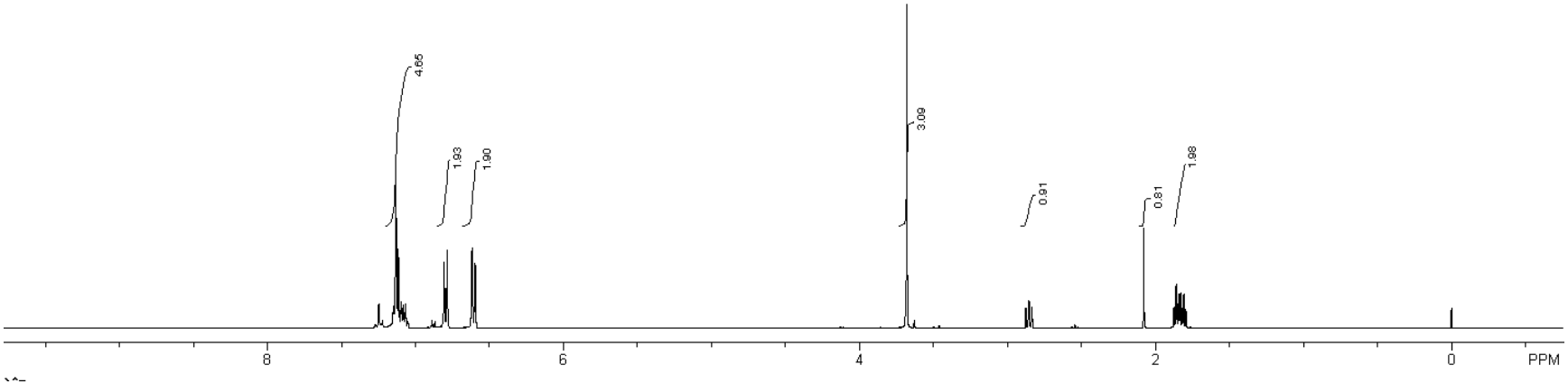

137.954
129.102
128.125
126.666
90.671
77.313
77.000
76.679
63.688
31.634
29.992
29.144
28.915
28.716
22.492
20.689
19.903
14.007
Ph
n-Hex
III-14f
180
160
140
120
100
80
60
40
20
0
PPM

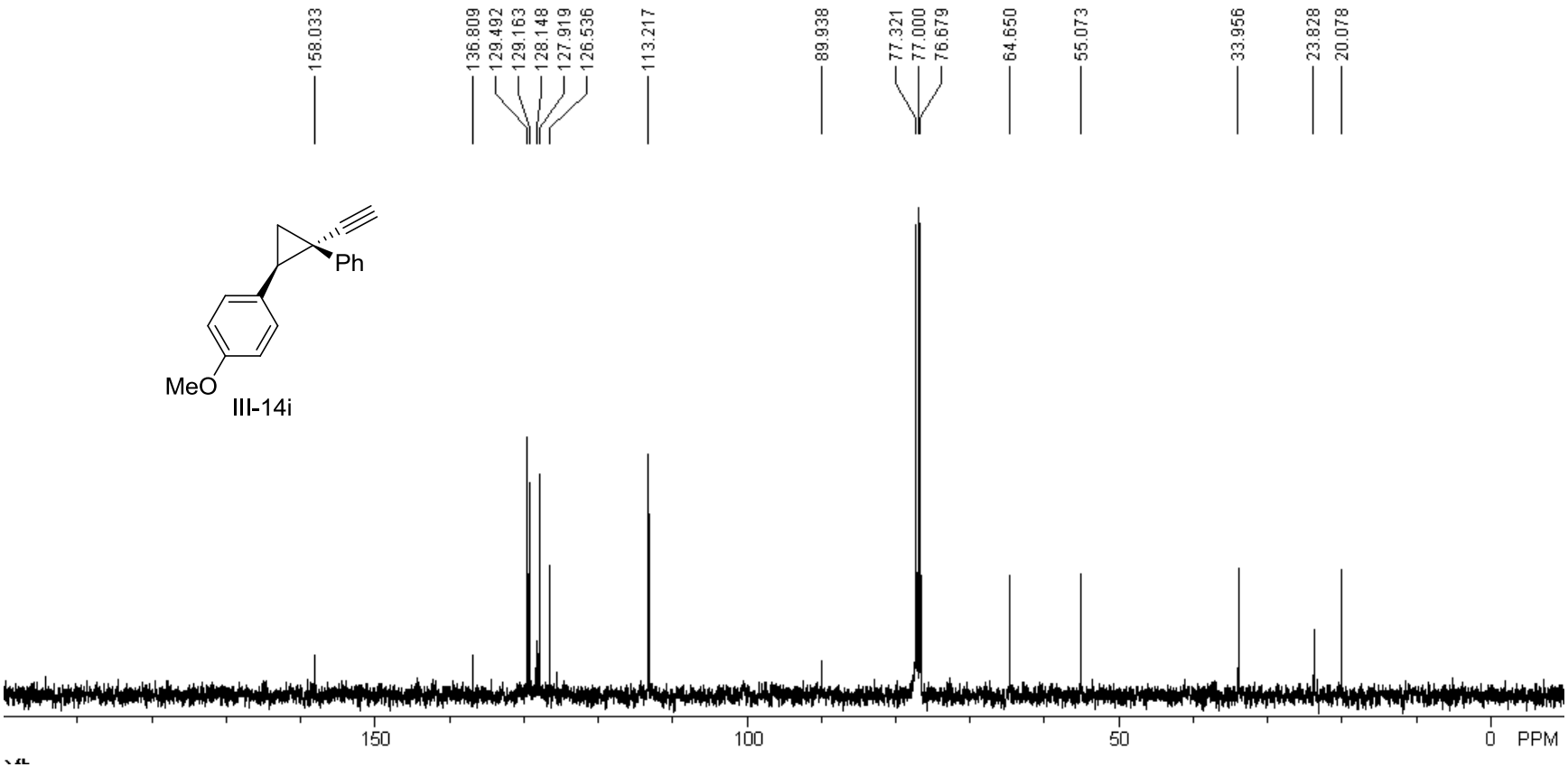

OTBS
III-14h
2.01
0.86
9.06
1.97
5.61
8
7
6
5
4
3
2
1
0
PPM

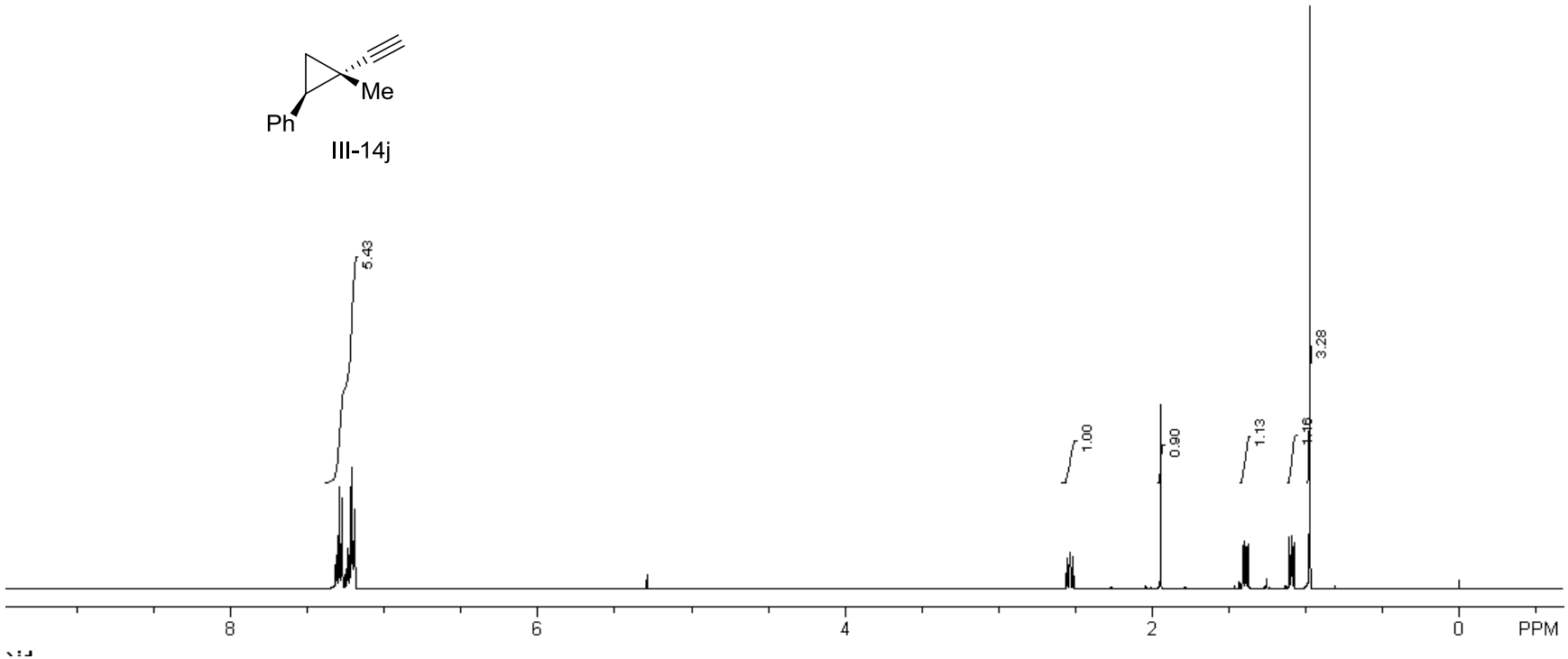

87.921
77.313
77.000
76.679
66.101
65.093
25.882
18.382
13.579
11.906
-5.309
OTBS
III-14h
160
140
120
100
80
60
40
20
0
PPM

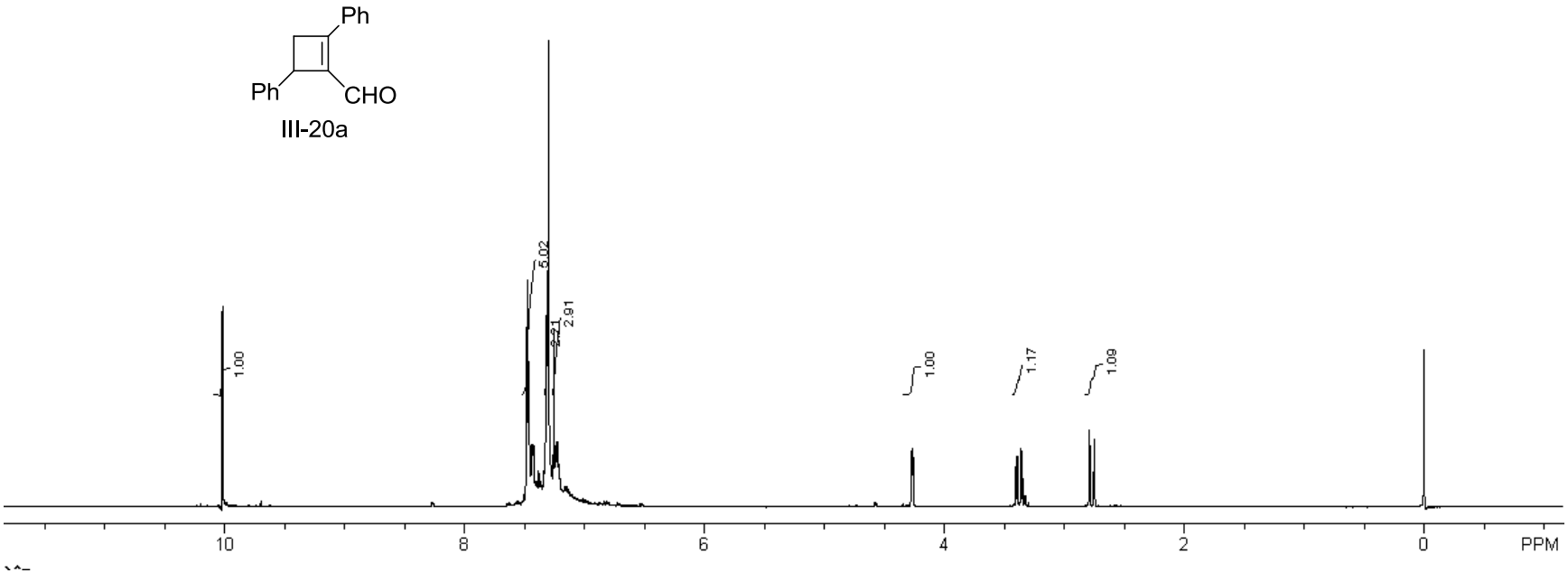


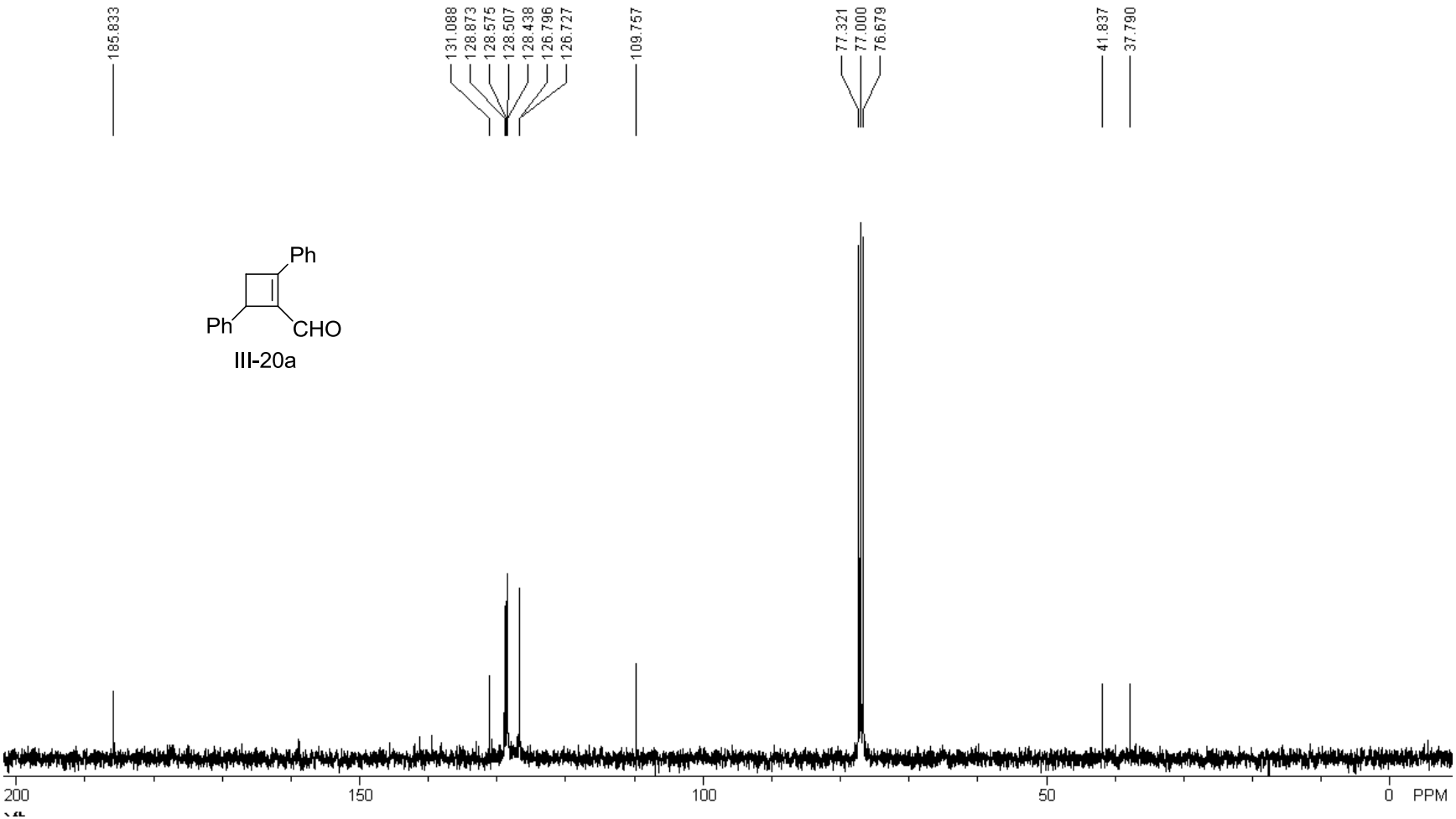

III-14i

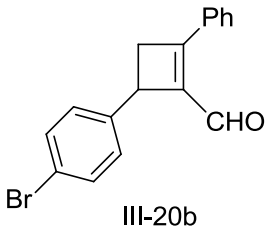



158.033
136.809
129.492
129.163
128.148
127.919
126.536
113.217
89.938
77.321
77.000
76.679
64.650
55.073
33.956
23.828
20.078
Ph
MeO
III-14i
150
100
50
0
PPM

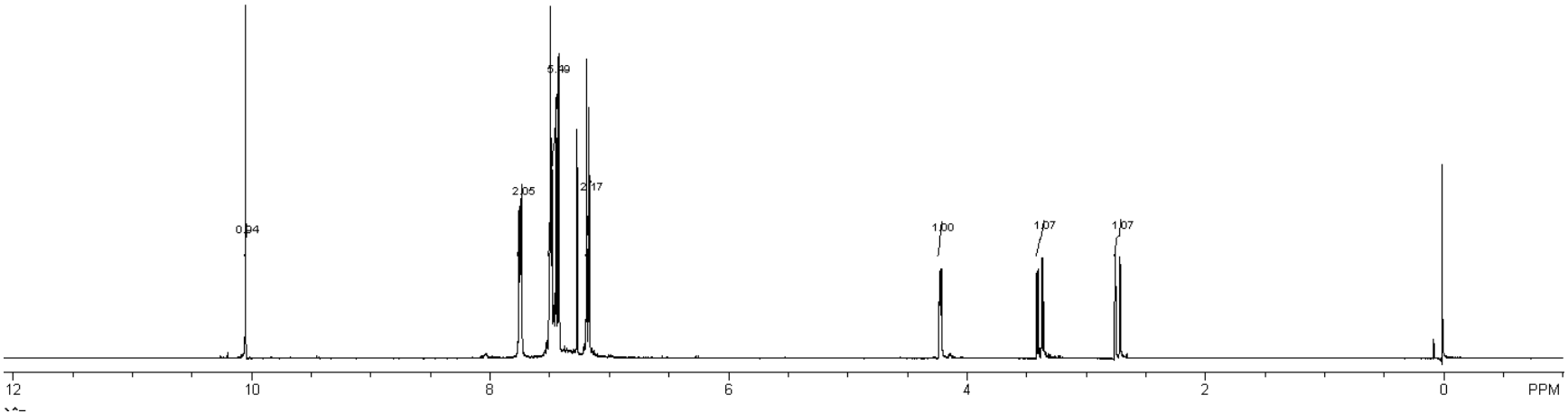

Me
Ph
III-14j
5.43
1.00
0.90
1.13
1.16
3.28
8
6
4
2
0
PPM

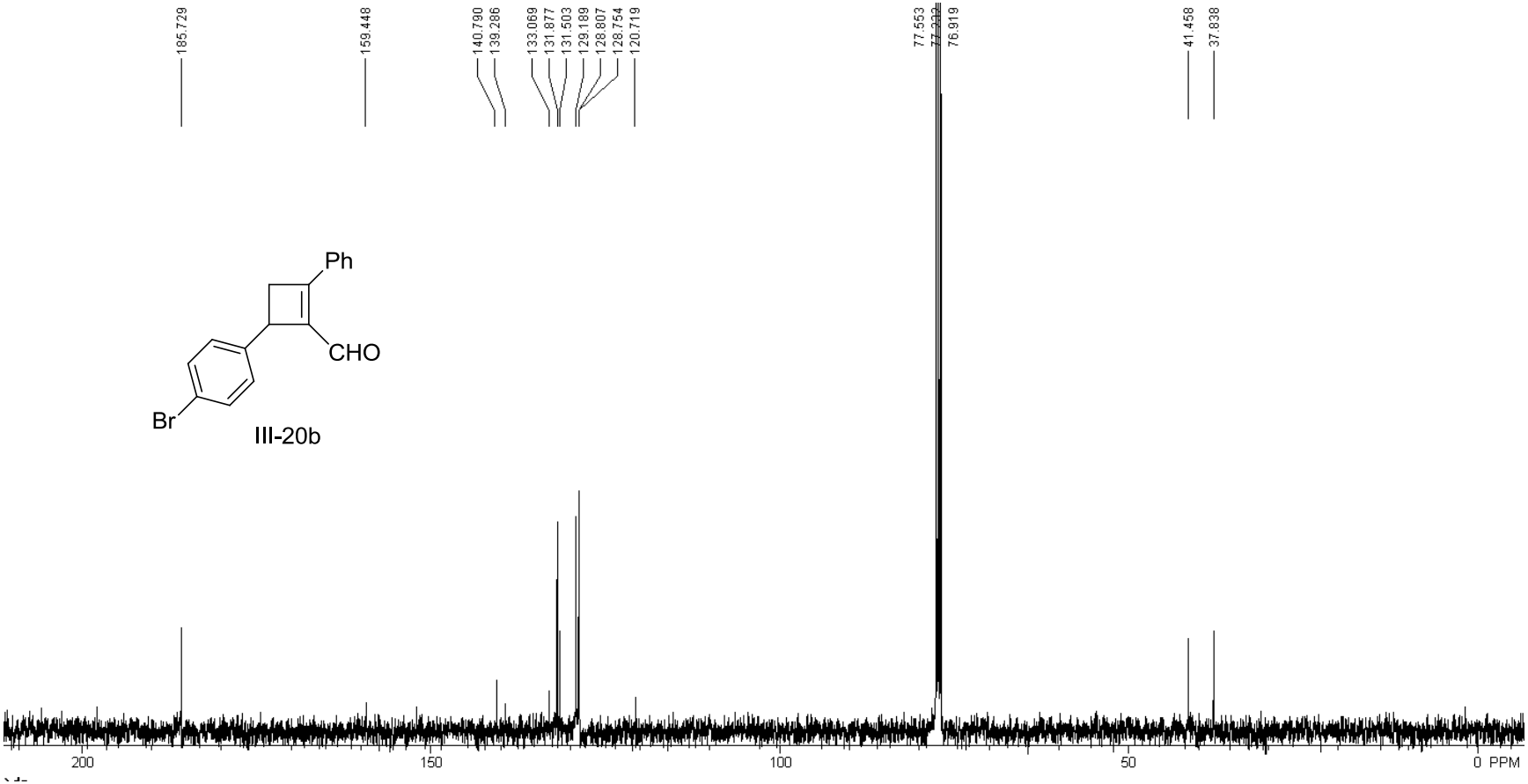

Ph
Ph
CHO
III-20a
1.00
5.02
2.21
2.91
1.00
1.17
1.09
10
8
6
4
2
0
PPM

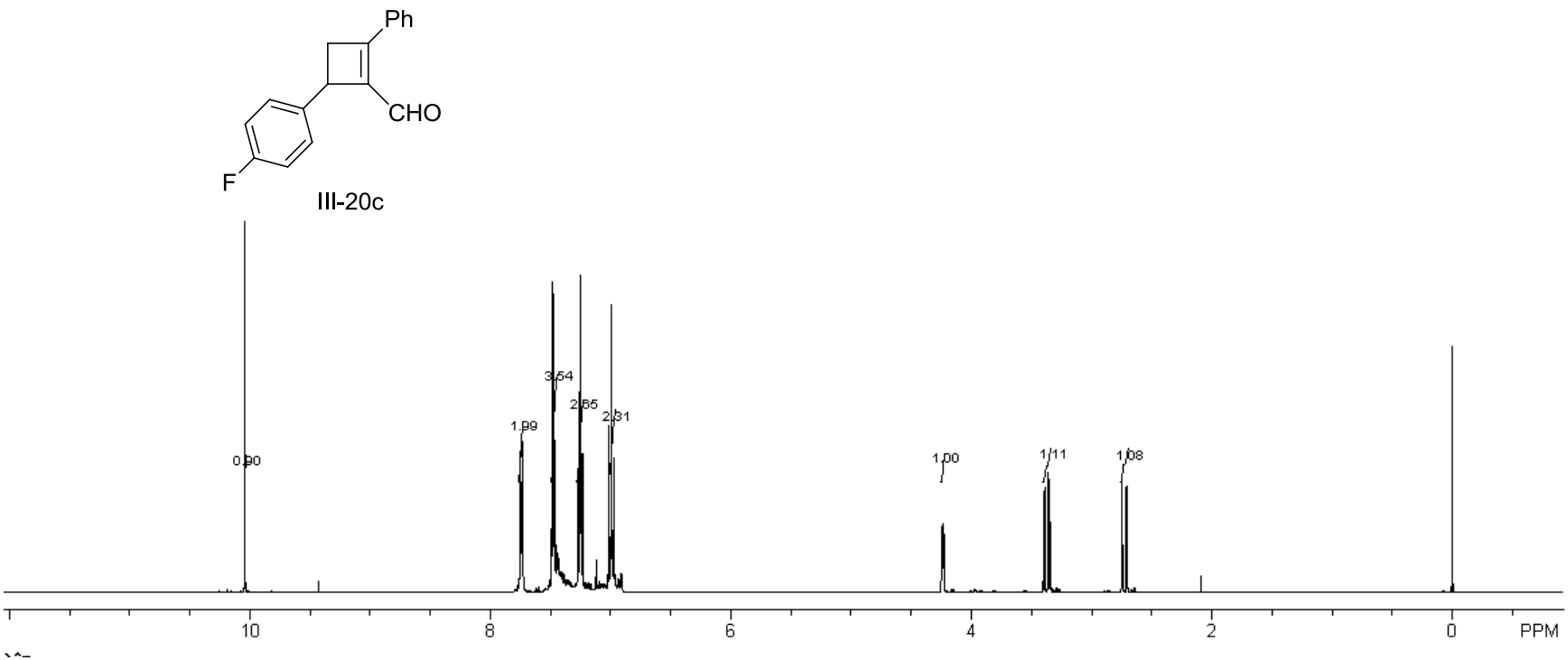

185.833
131.088
128.873
128.575
128.507
128.438
126.796
126.727
109.757
77.321
77.000
76.679
41.837
37.790
Ph
Ph
CHO
III-20a
200
150
100
50
0
PPM

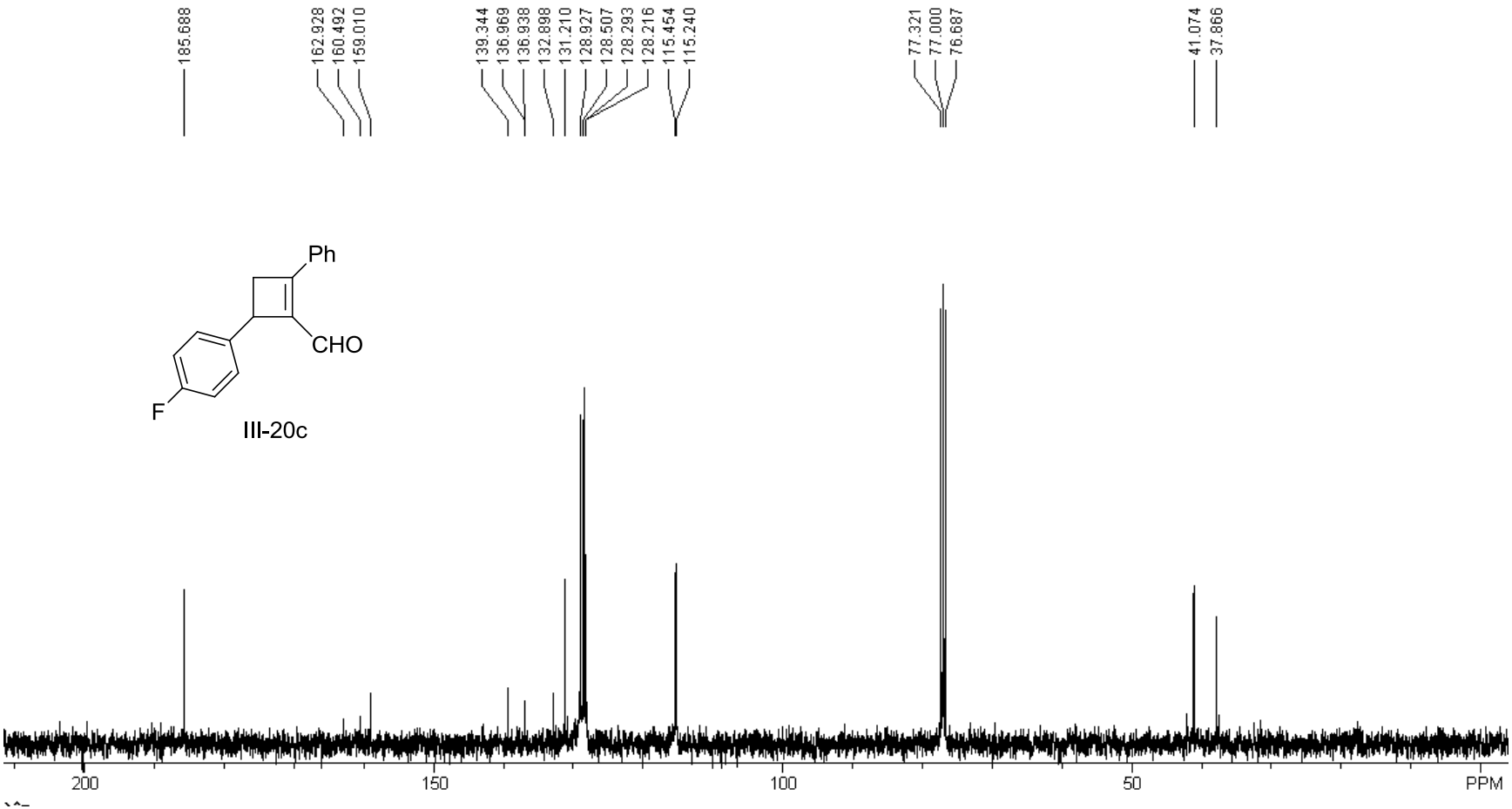


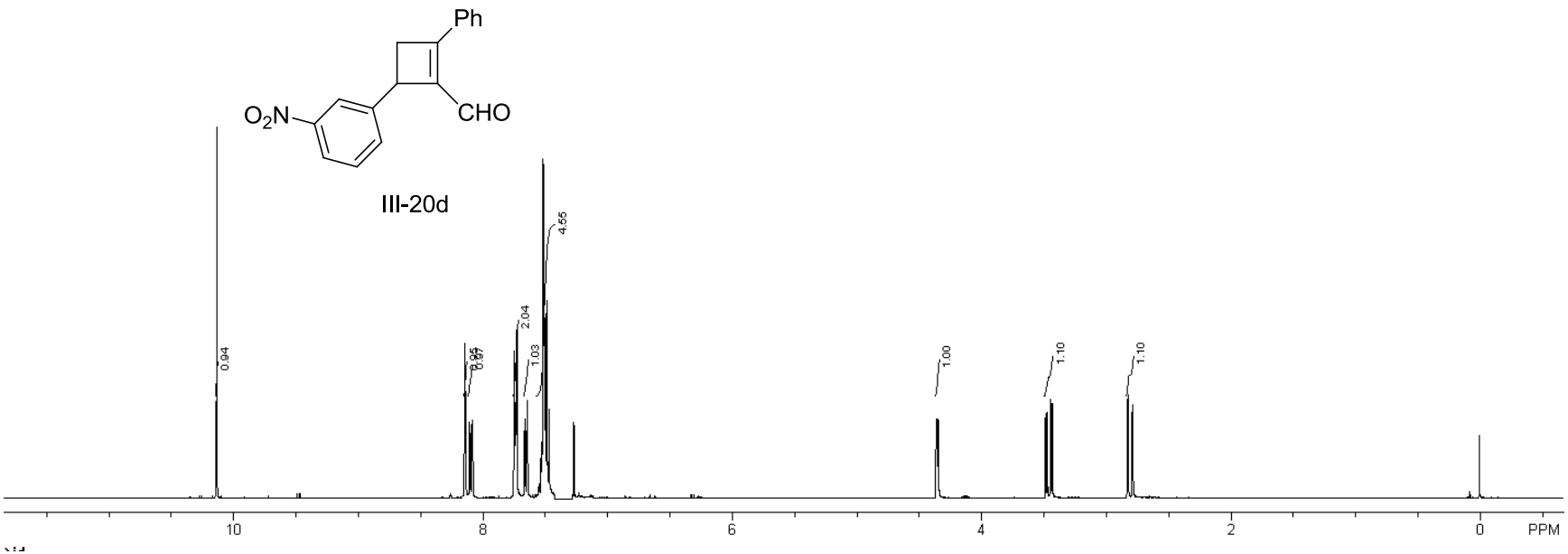

III-20b

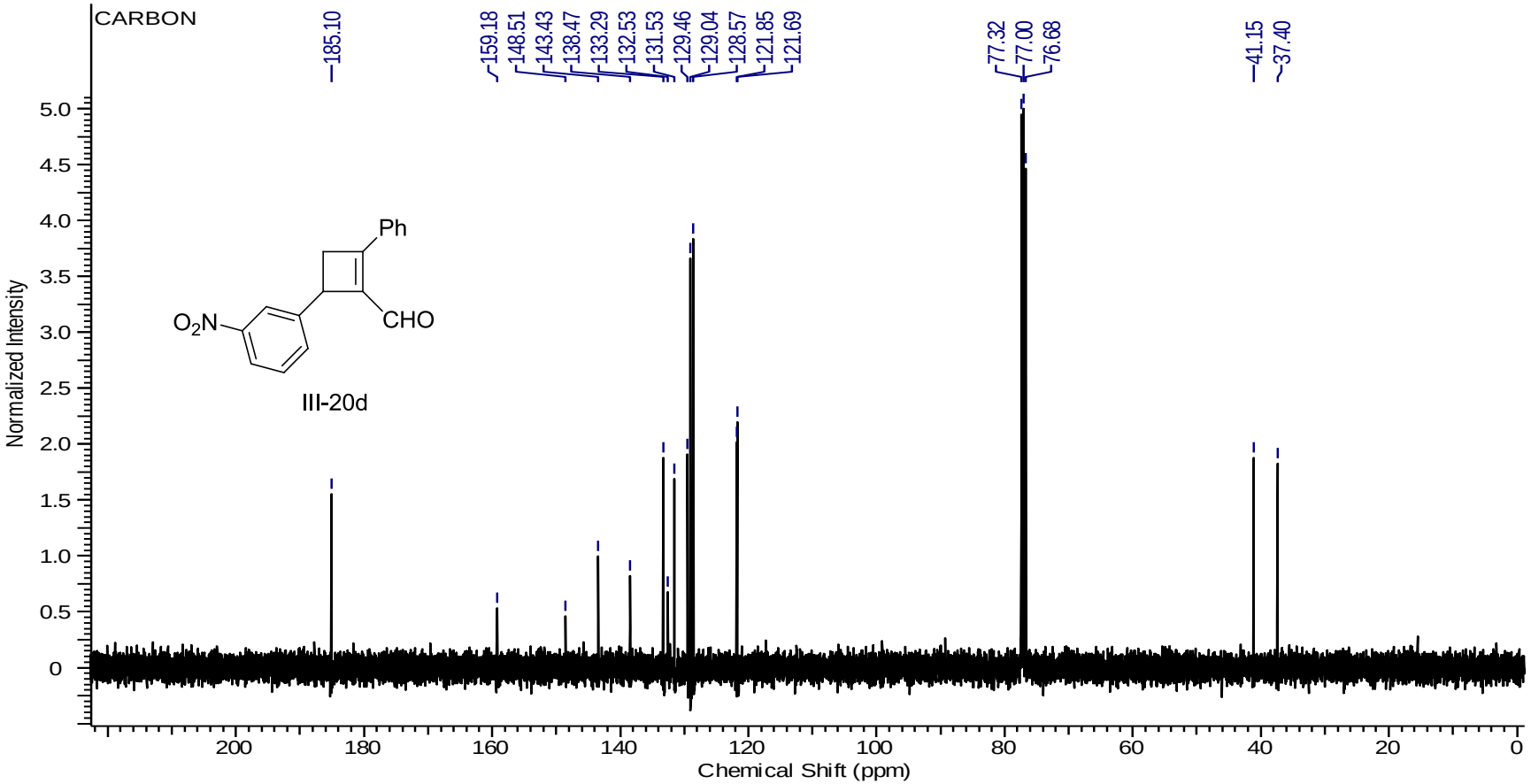


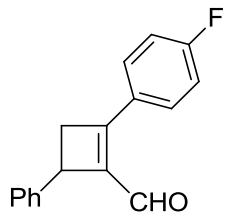

185.729
159.448
140.790
139.286
133.069
131.877
131.503
129.189
128.807
128.754
120.719
77.553
76.919
41.458
37.838
Ph
CHO
Br
III-20b
200
150
100
50
0 PPM


Ph
CHO
F
III-20c
0.90
1.99
3.54
2.65
2.31
1.00
1.11
1.08
10
8
6
4
2
0
PPM

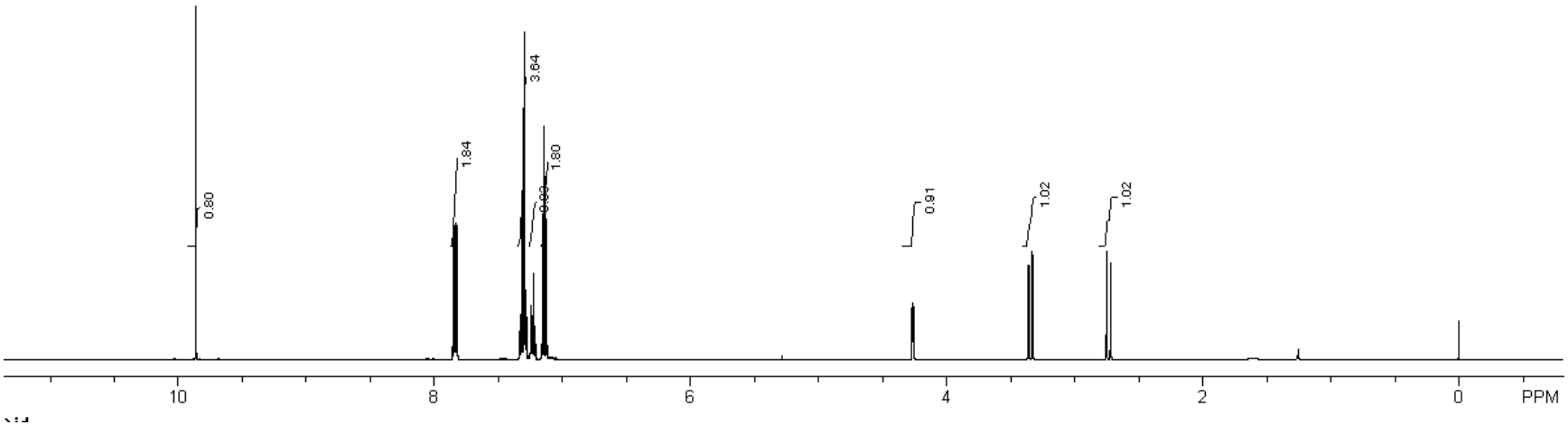

185.688
162.928
160.492
159.010
139.344
136.969
136.838
132.898
131.210
128.927
128.507
128.293
128.216
115.454
115.240
77.321
77.000
76.687
41.074
37.866
Ph
CHO
F
III-20c
200
150
100
50
PPM

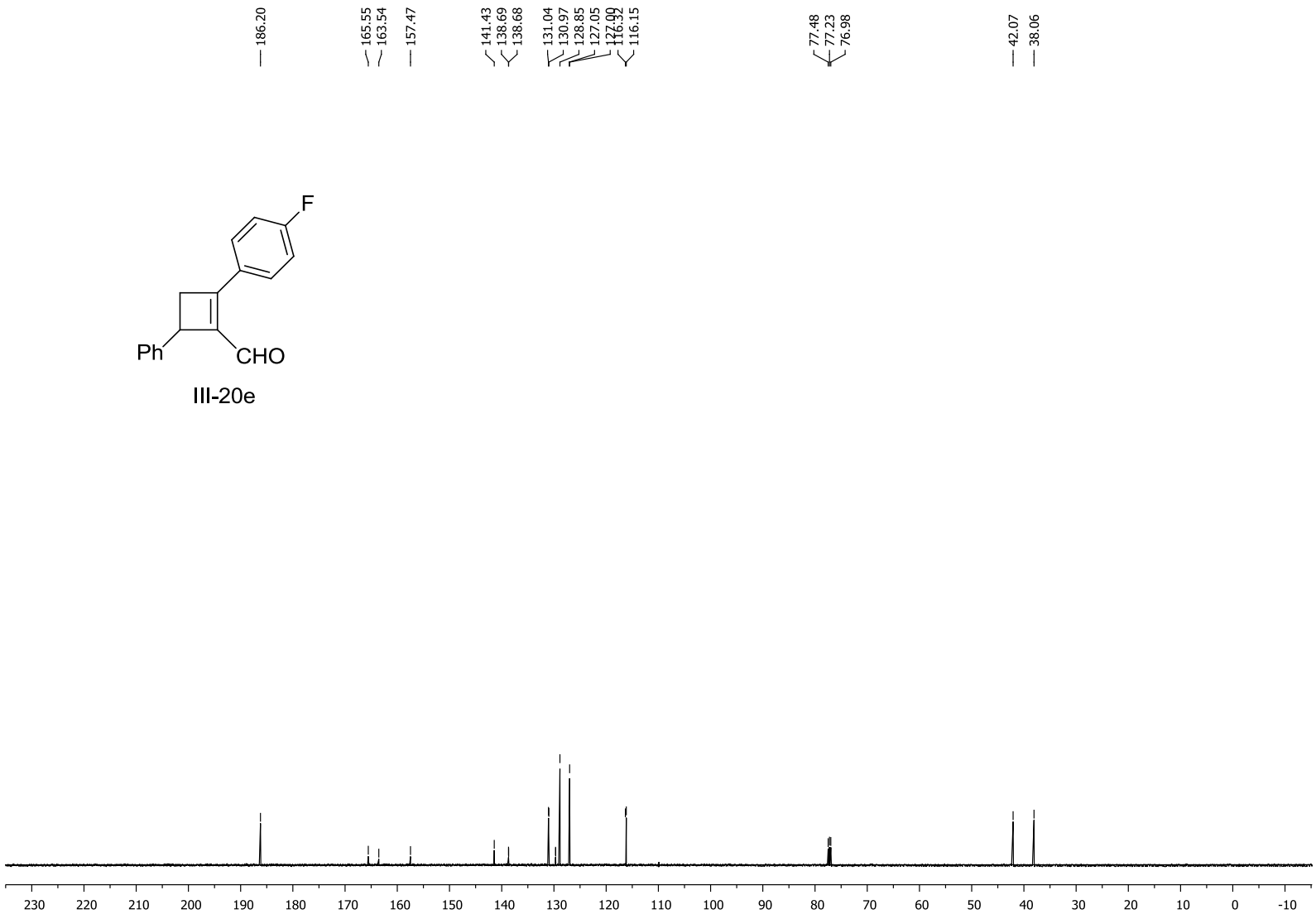

Ph
$O_2N$
CHO
III-20d
0.94
2.04
1.03
4.55
1.00
1.10
1.10
10
8
6
4
2
0
PPM

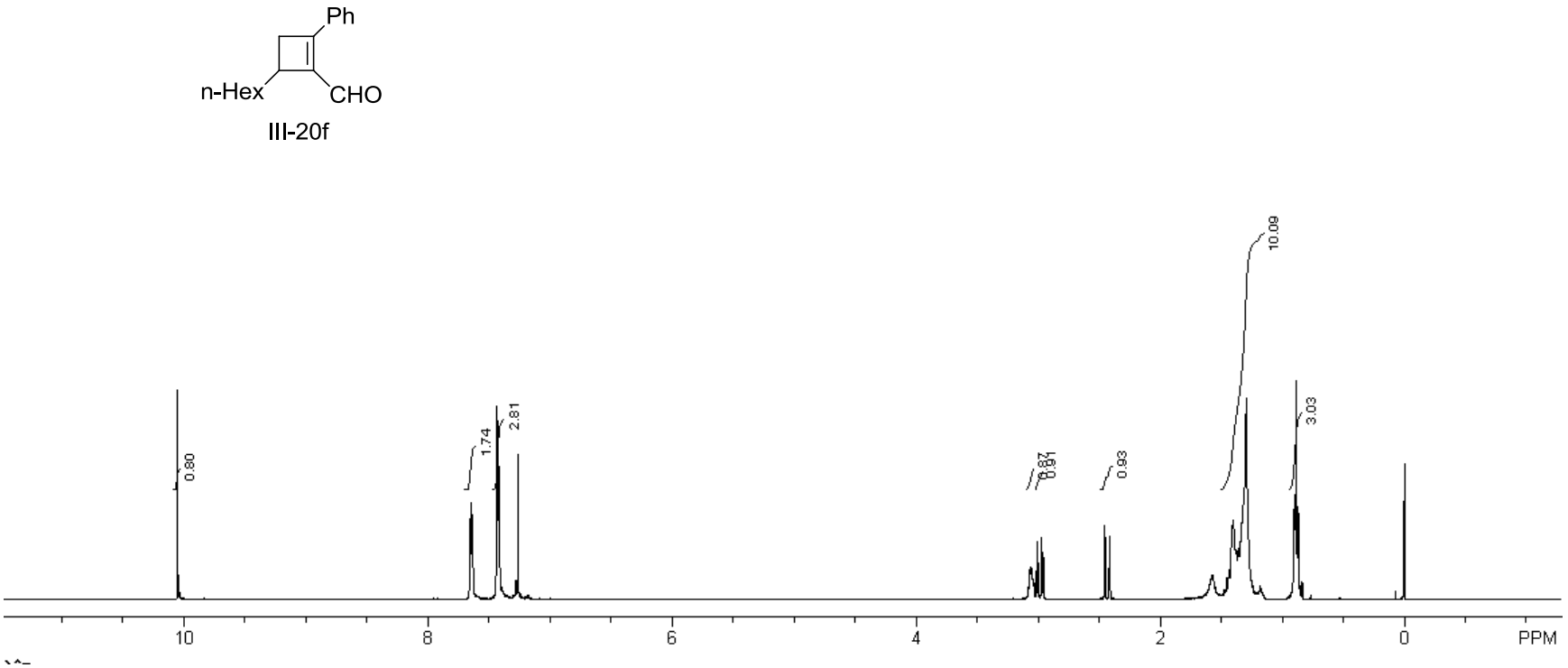

CARBON
185.10
159.18
148.51
143.43
138.47
133.29
132.53
131.53
129.46
129.04
128.57
121.85
121.69
77.32
77.00
76.68
41.15
37.40
Ph
O2N
CHO
III-20d
Normalized Intensity
Chemical Shift (ppm)

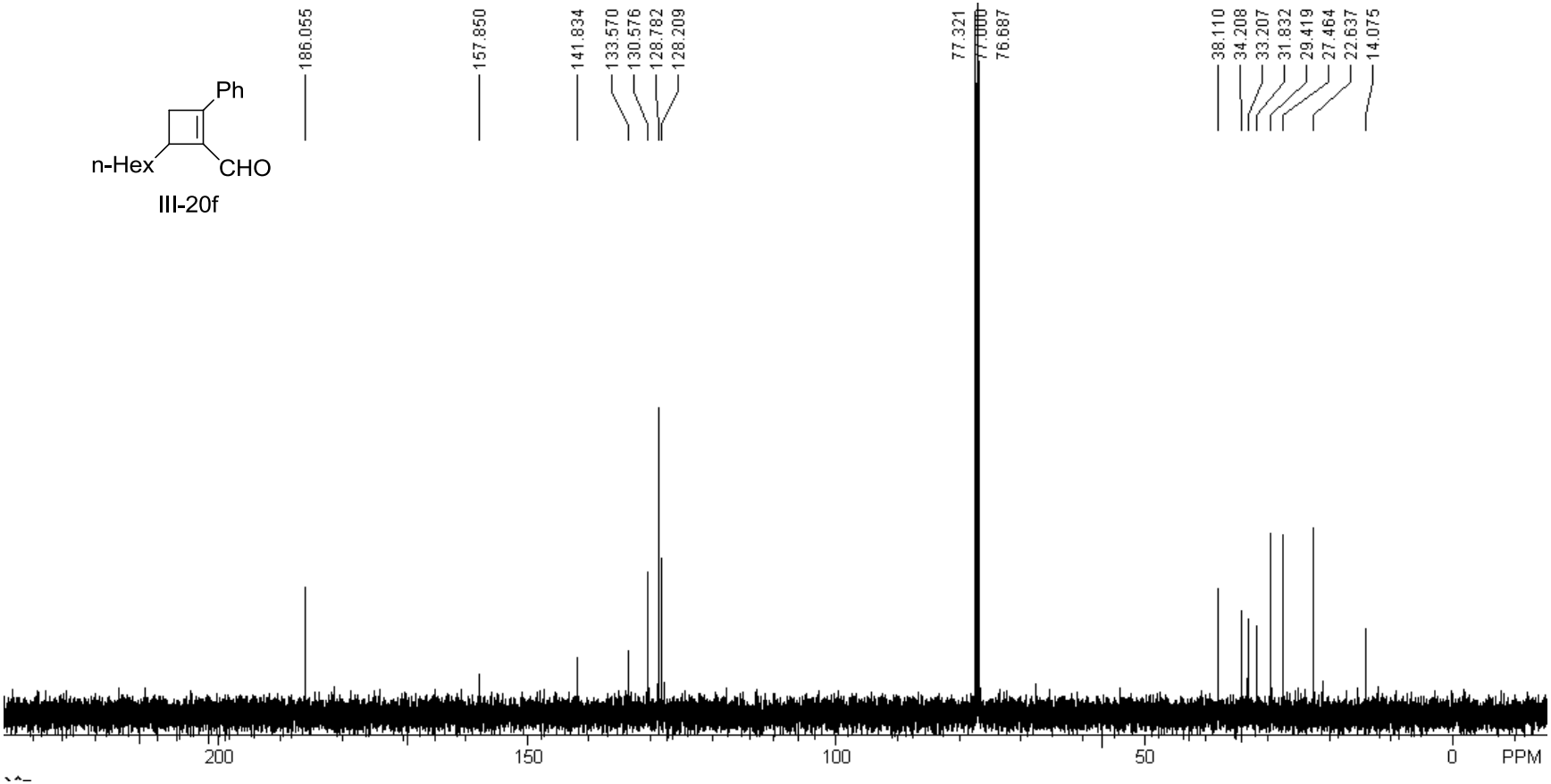


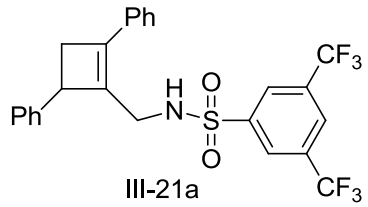

III-20e



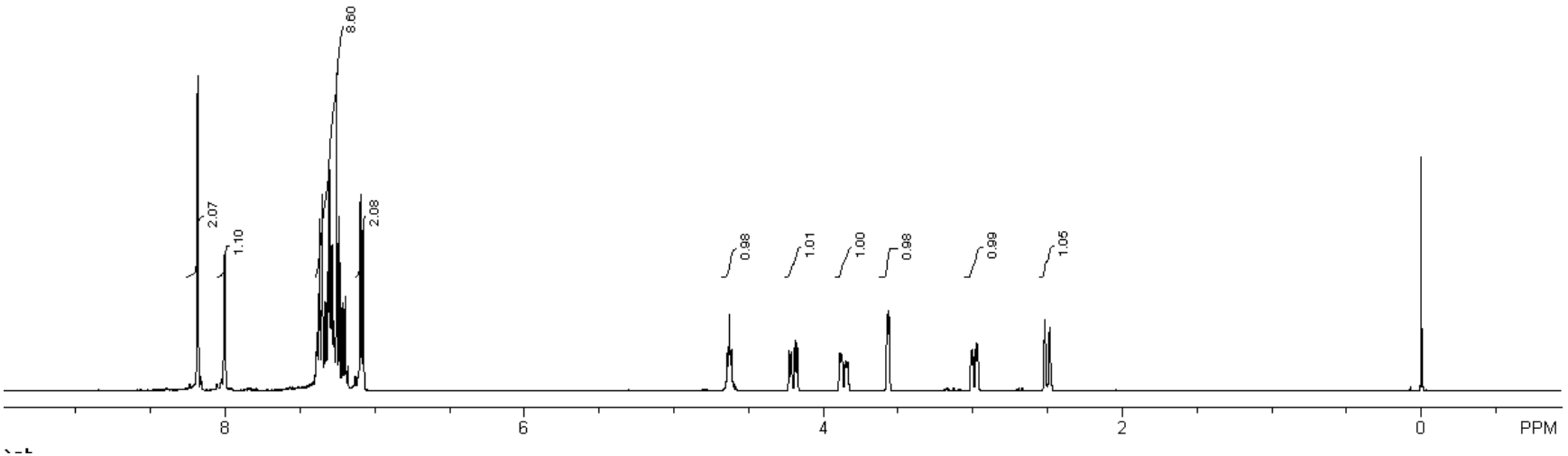

186.20
165.55
163.54
157.47
141.43
138.69
138.68
131.04
130.97
128.85
127.05
127.00
116.32
116.15
77.48
77.23
76.98
42.07
38.06
F
Ph
CHO
III-20e
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

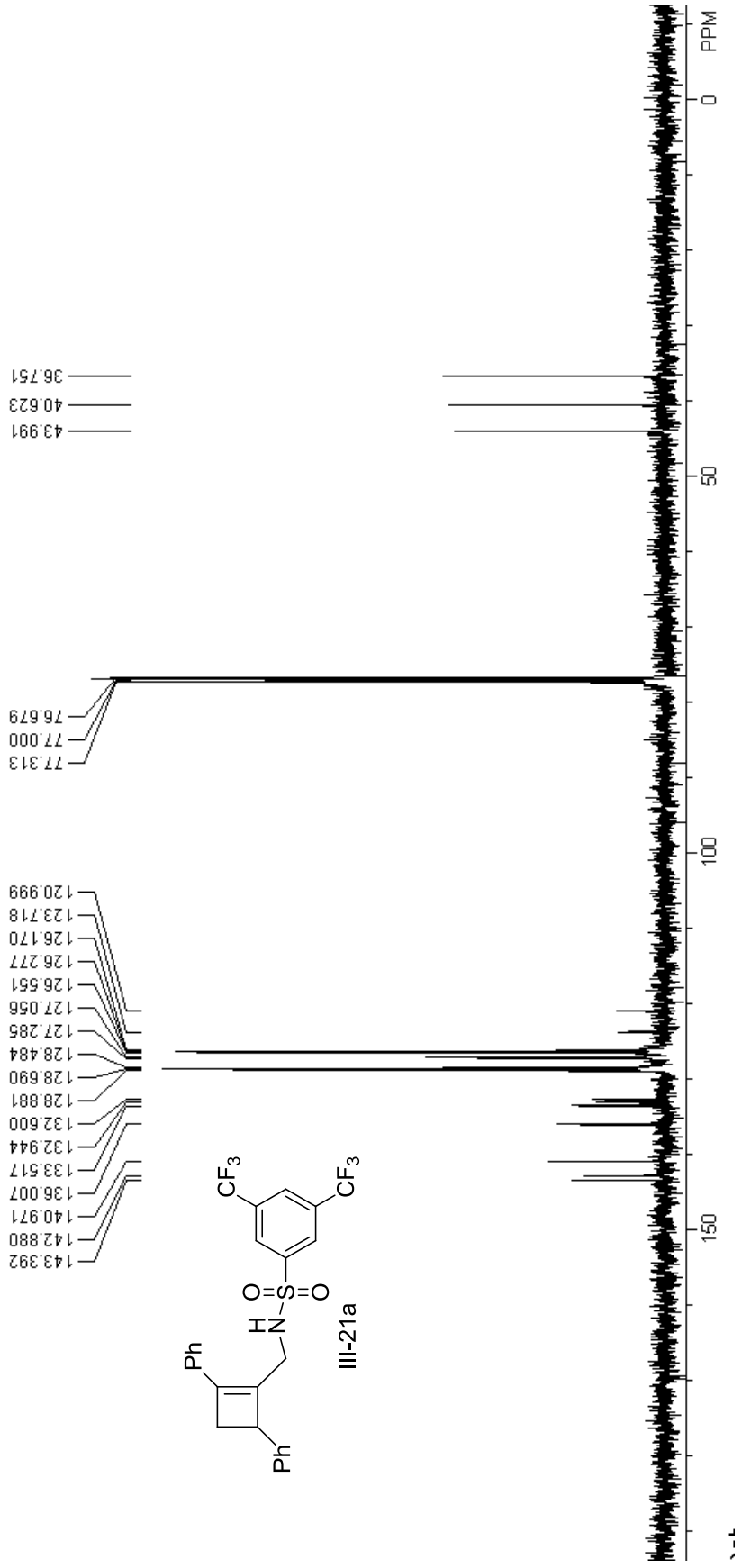

Ph
n-Hex
CHO
III-20f
0.80
1.74
2.81
0.87
0.87
0.93
10.09
3.03
10
8
6
4
2
0
PPM

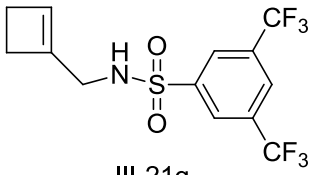

186.055
157.850
141.834
133.570
130.576
128.782
128.209
77.321
77.000
76.687
38.110
34.208
33.207
31.832
29.419
27.464
22.637
14.075
Ph
n-Hex
CHO
III-20f
200
150
100
50
0
PPM


Ph
Ph
H
N
O
S
O
CF3
CF3

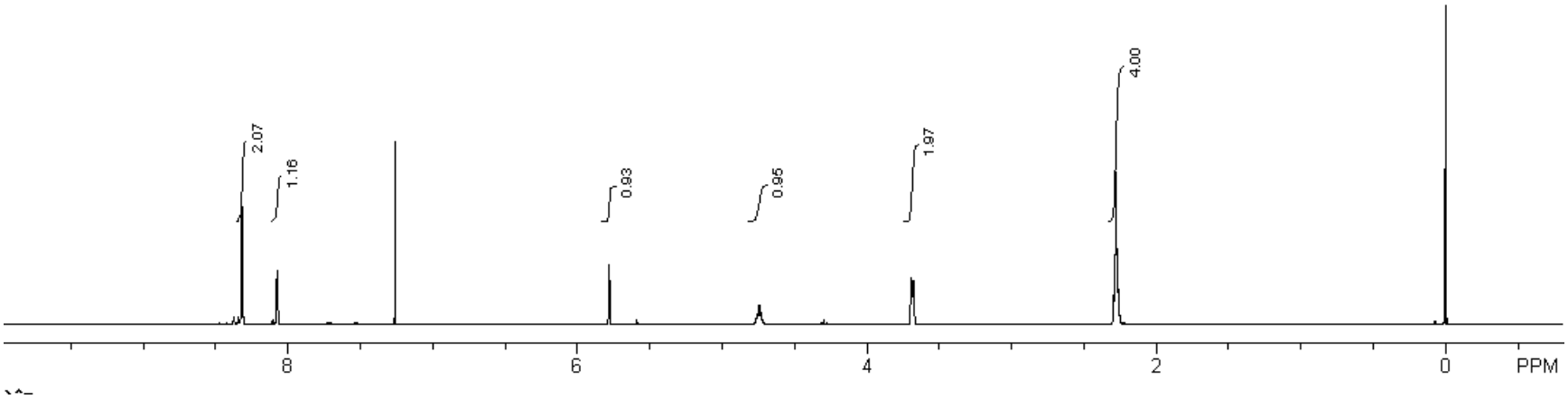
III-21a

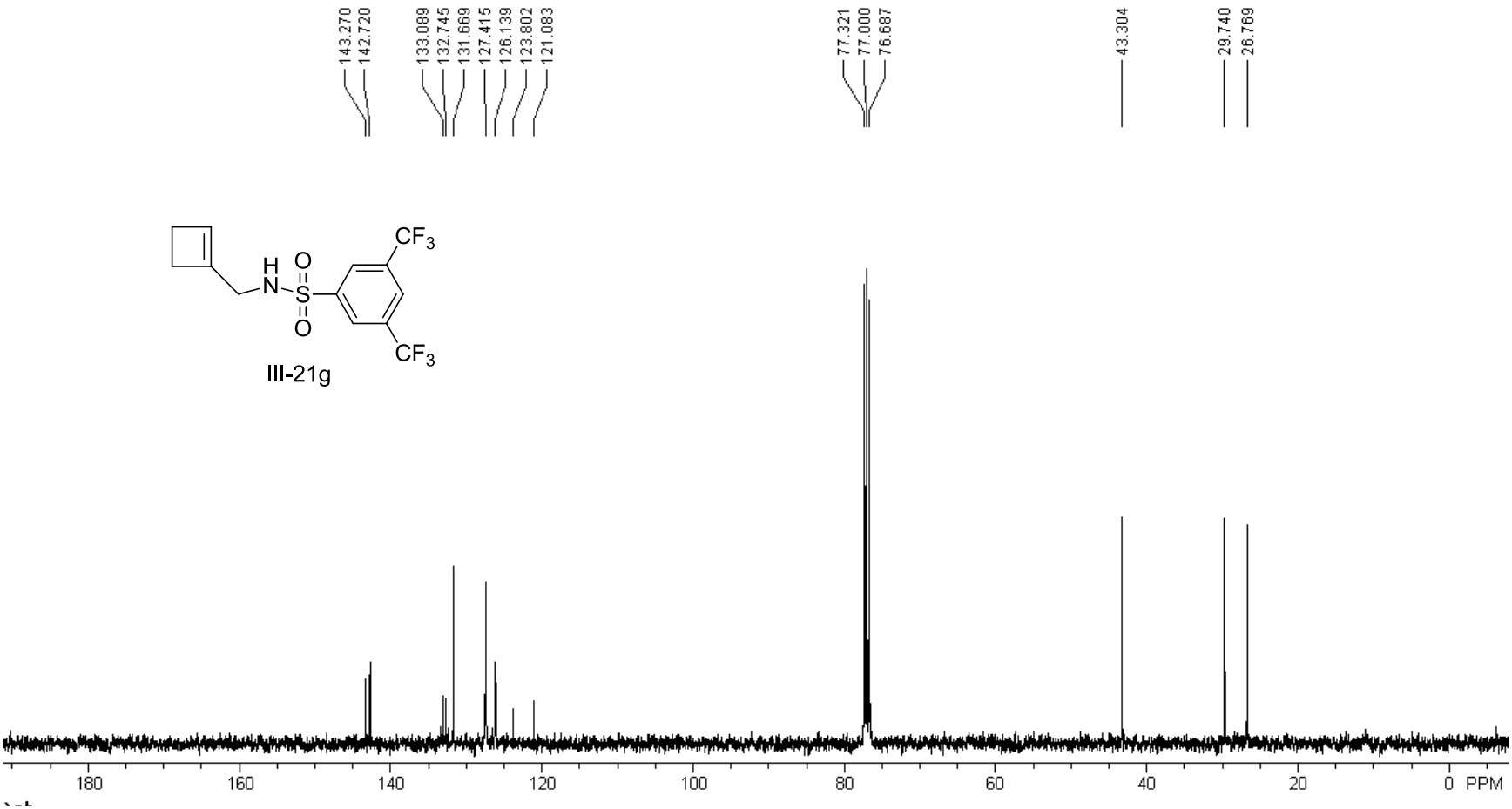

8.60
2.07
1.10
2.08
0.98
1.01
1.00
0.98
0.99
1.05
8
6
4
2
0
PPM


PPM
0
50
100
150
36.751
40.623
43.991
76.679
77.000
77.313
120.999
123.718
126.170
126.277
126.551
127.056
127.285
128.484
128.690
128.881
132.600
132.944
133.517
136.007
140.971
142.880
143.392
CF3
CF3
O=S=O
H
N
Ph
Ph
III-21a

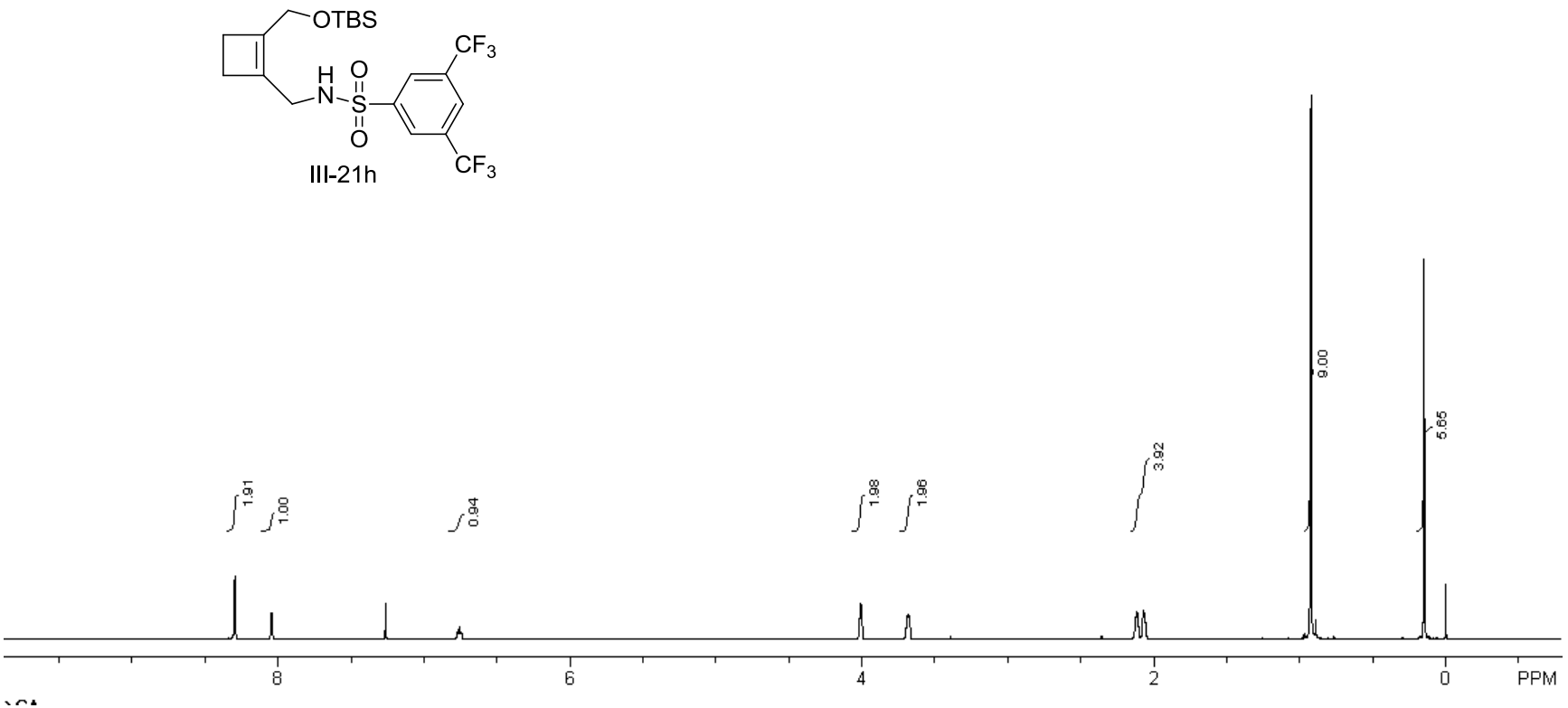


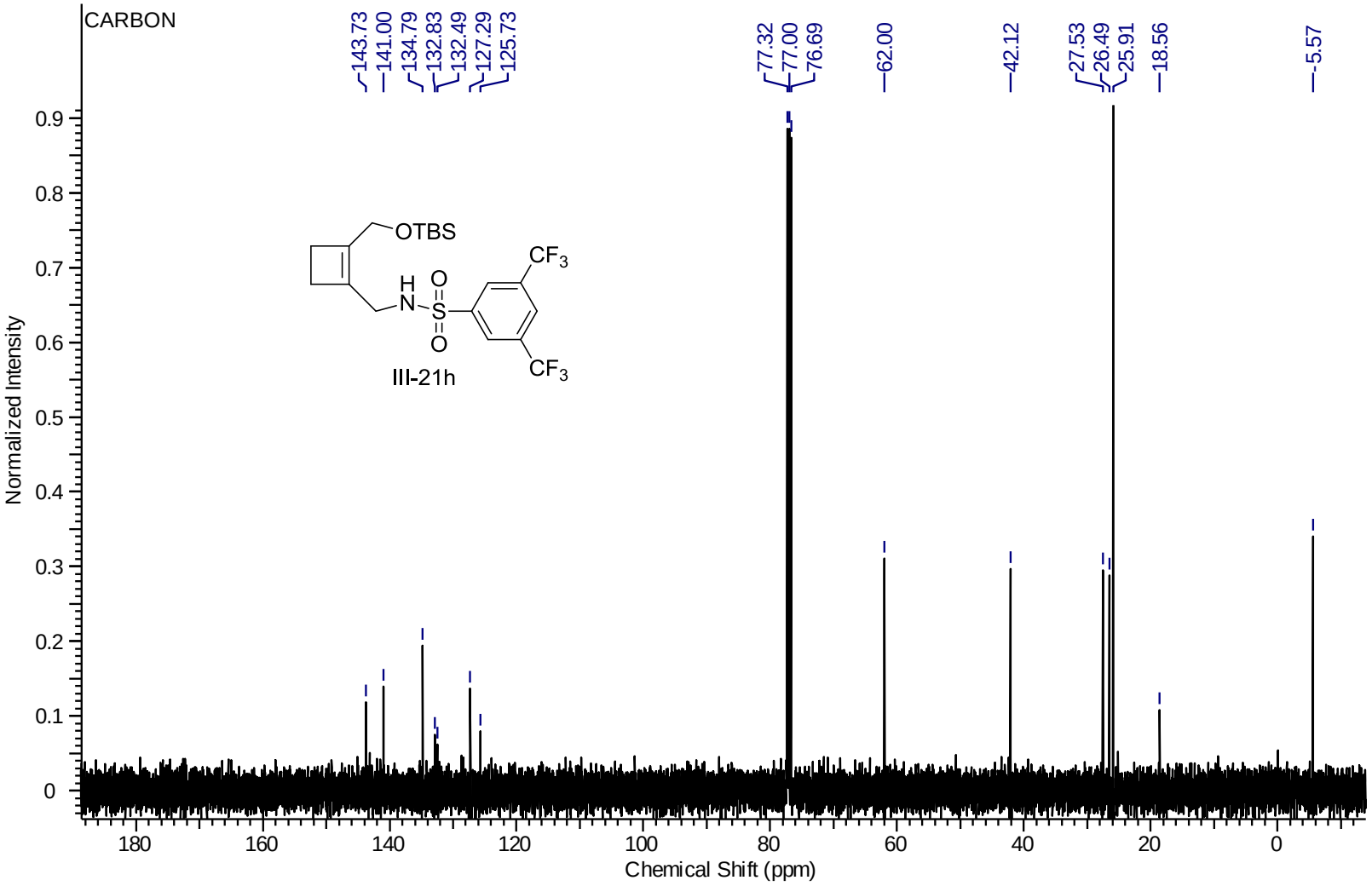

III-21g

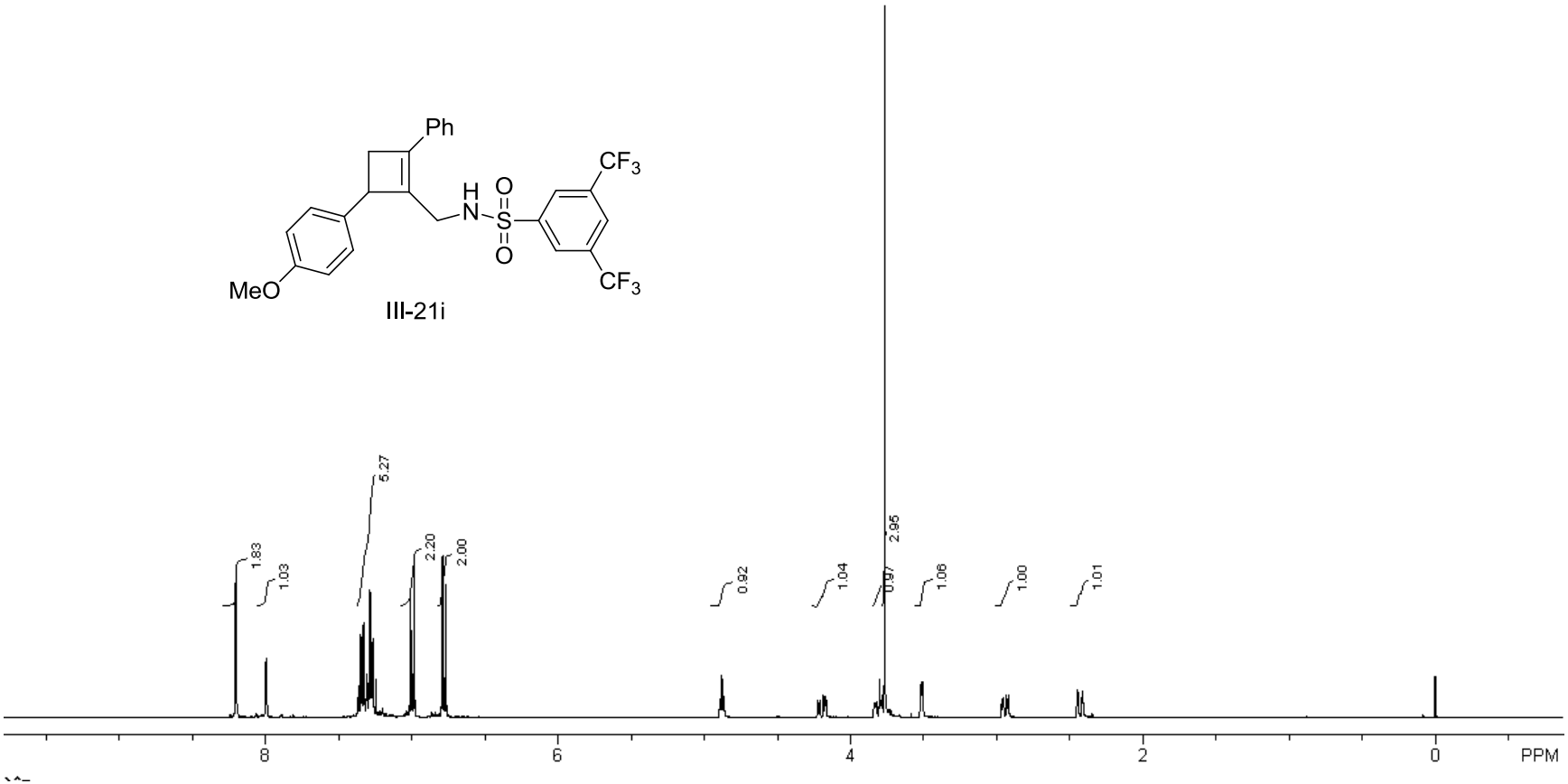


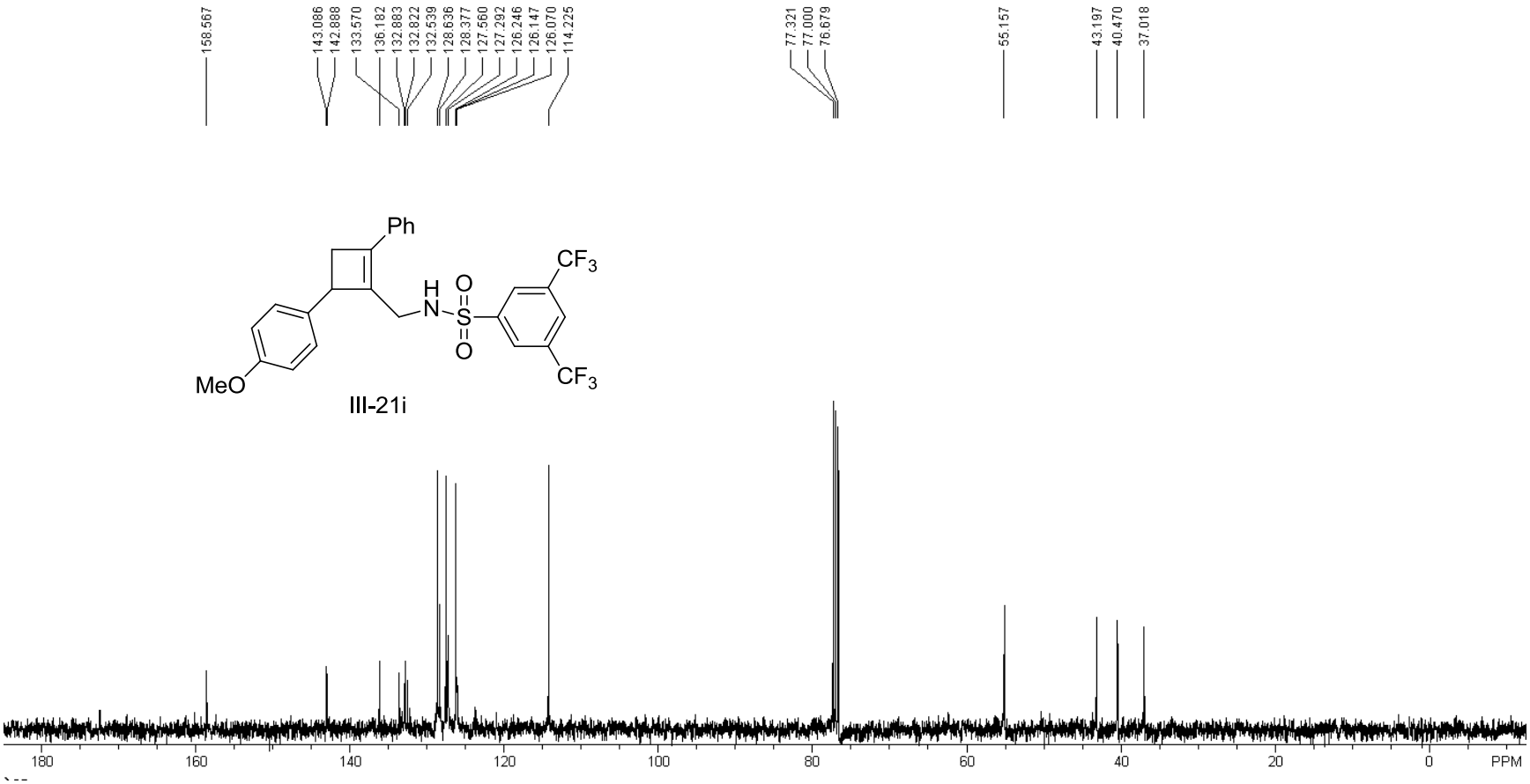

143.270
142.720
133.089
132.745
131.669
127.415
126.139
123.802
121.083
77.321
77.000
76.687
43.304
29.740
26.769
CF3
CF3
H
N
O
S
O
180
160
140
120
100
80
60
40
20
0 PPM

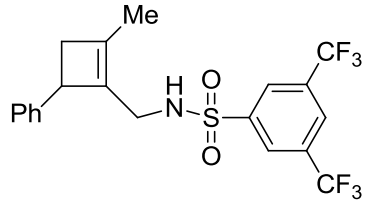
III-21g


OTBS
CF3
H
N
O
S
O
O
CF3
III-21h
1.91
1.00
0.94
1.98
1.96
3.92
9.00
5.65
8
6
4
2
0
PPM

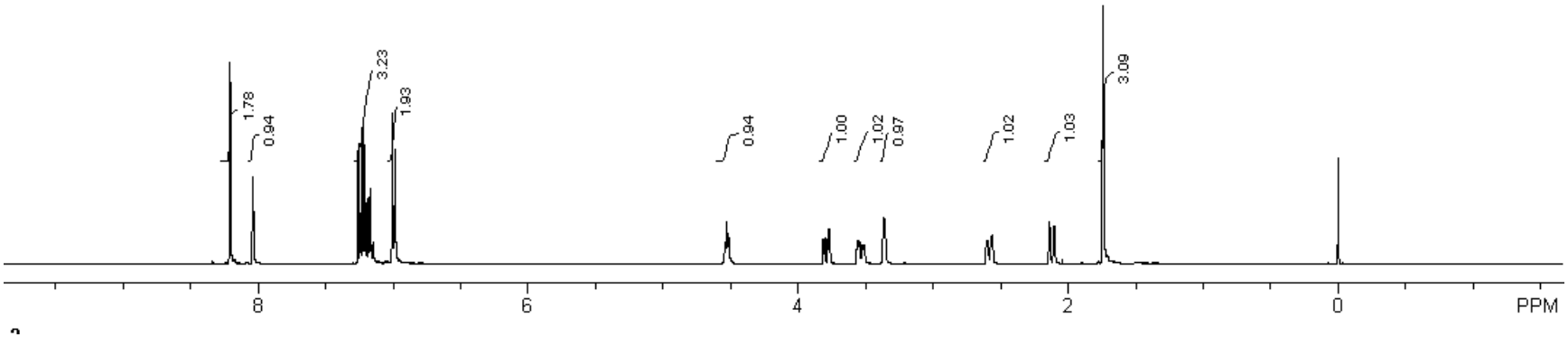

CARBON
143.73
141.00
134.79
132.83
132.49
127.29
125.73
77.32
77.00
76.69
62.00
42.12
27.53
26.49
25.91
18.56
-5.57
OTBS
CF3
H
N
O
S
O
O
CF3
III-21h
Normalized Intensity
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

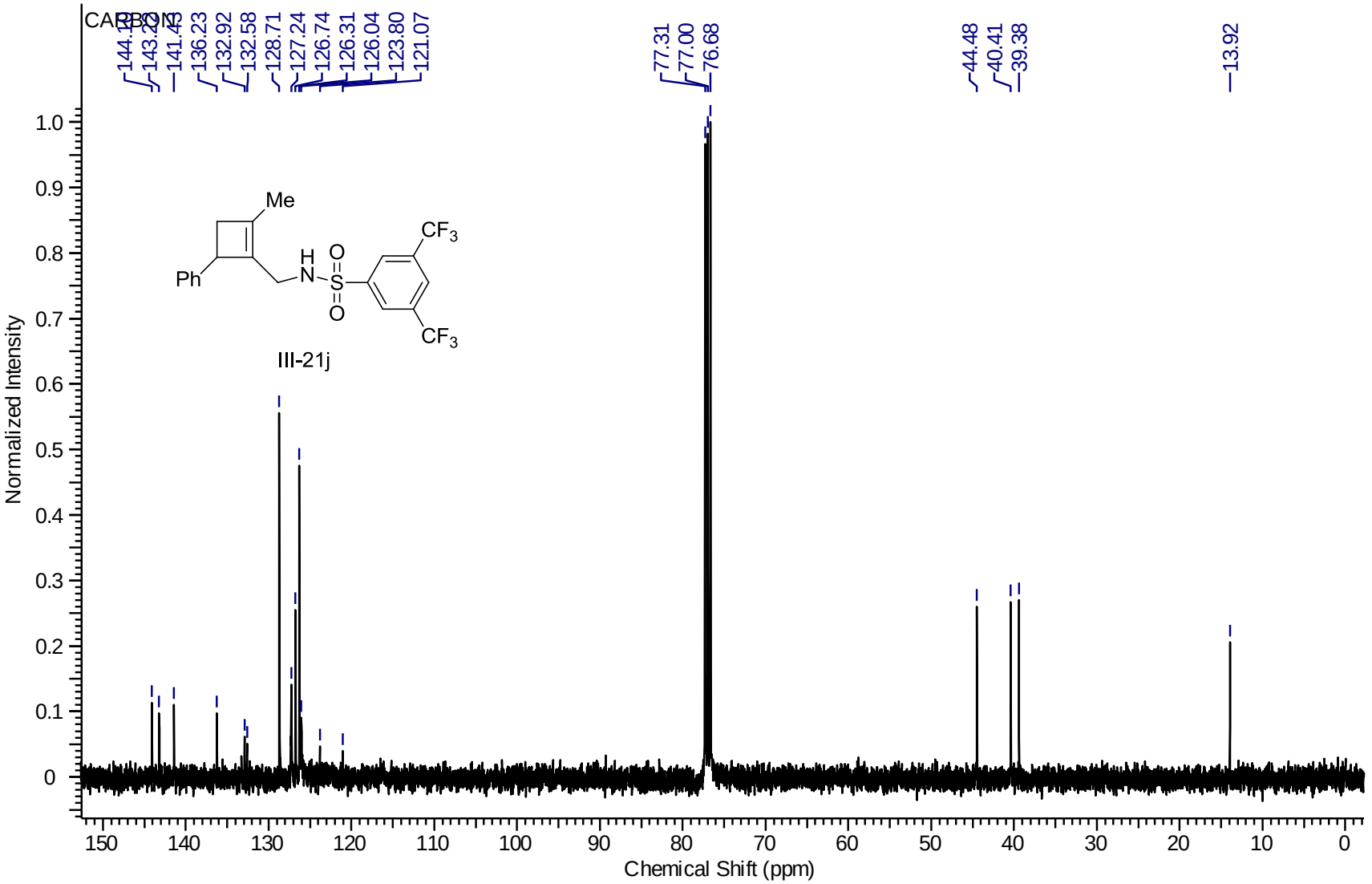

Ph
CF3
H
N
O
S
O
MeO
CF3
III-21i
1.83
1.03
5.27
2.20
2.00
0.92
1.04
0.97
2.95
1.06
1.00
1.01
8
6
4
2
0
PPM

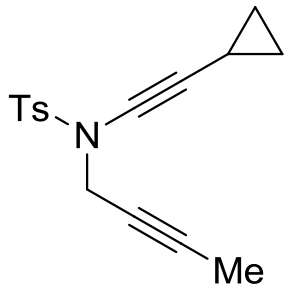

158.567
143.086
142.888
133.570
136.182
132.883
132.822
132.539
128.636
128.377
127.560
127.292
126.246
126.147
126.070
114.225
77.321
77.000
76.679
55.157
43.197
40.470
37.018
Ph
CF3
H
N
O
S
O
O
CF3
MeO
III-21i
180
160
140
120
100
80
60
40
20
0
PPM


Me
Ph
H
N
O
S
O
O
CF3
CF3

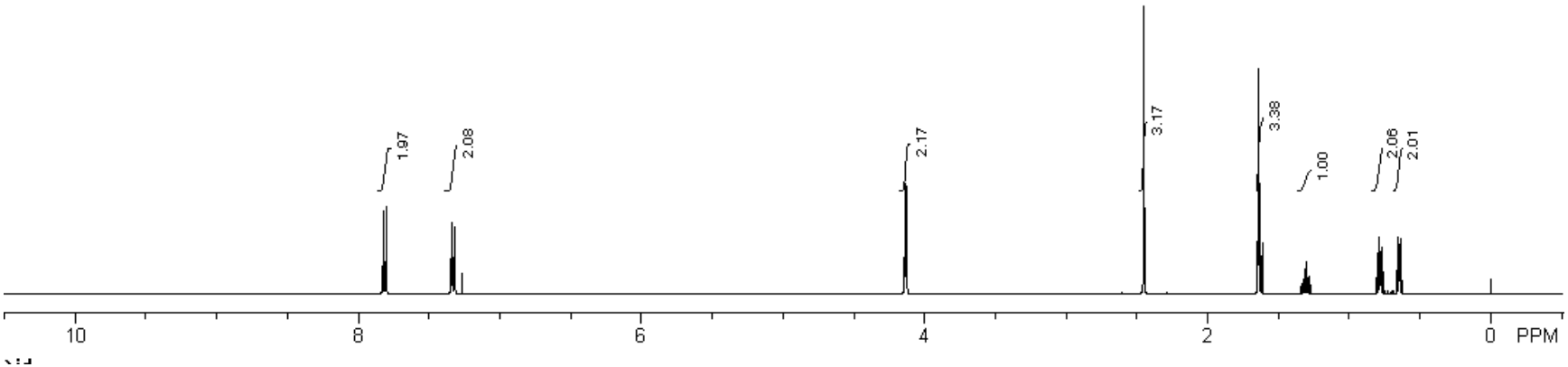
III-21j

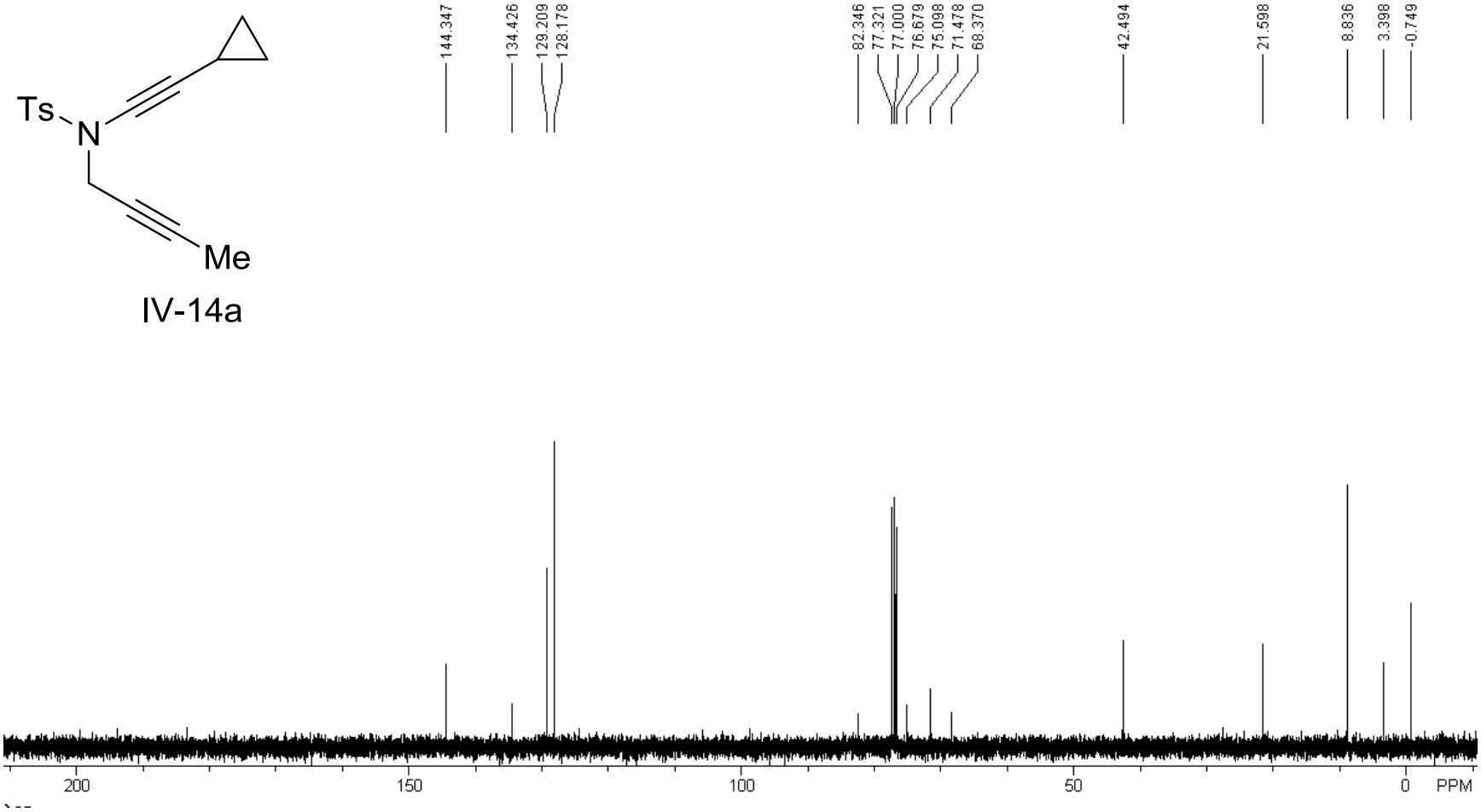

1.78
0.94
3.23
1.93
0.94
1.00
1.02
0.97
1.02
1.03
3.09
8
6
4
2
0
PPM


CARBON
144.18
143.23
141.42
136.23
132.92
132.58
128.71
127.24
126.74
126.31
126.04
123.80
121.07
77.31
77.00
76.68
44.48
40.41
39.38
13.92
Me
Ph
H
N
S
O
O
CF3
CF3
III-21j
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

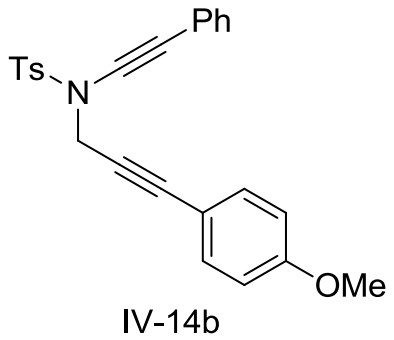



IV-14a

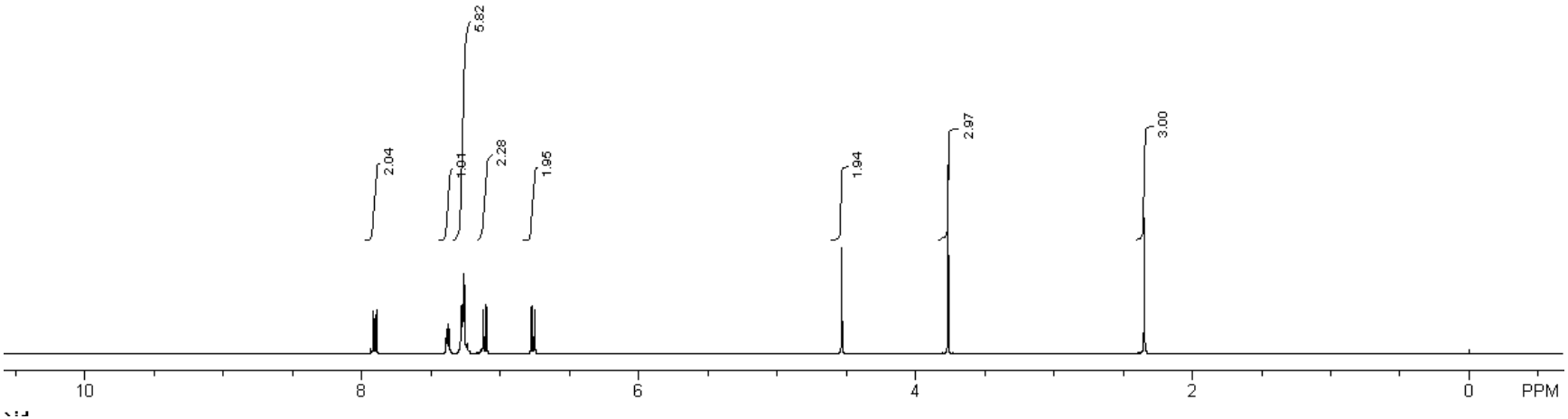


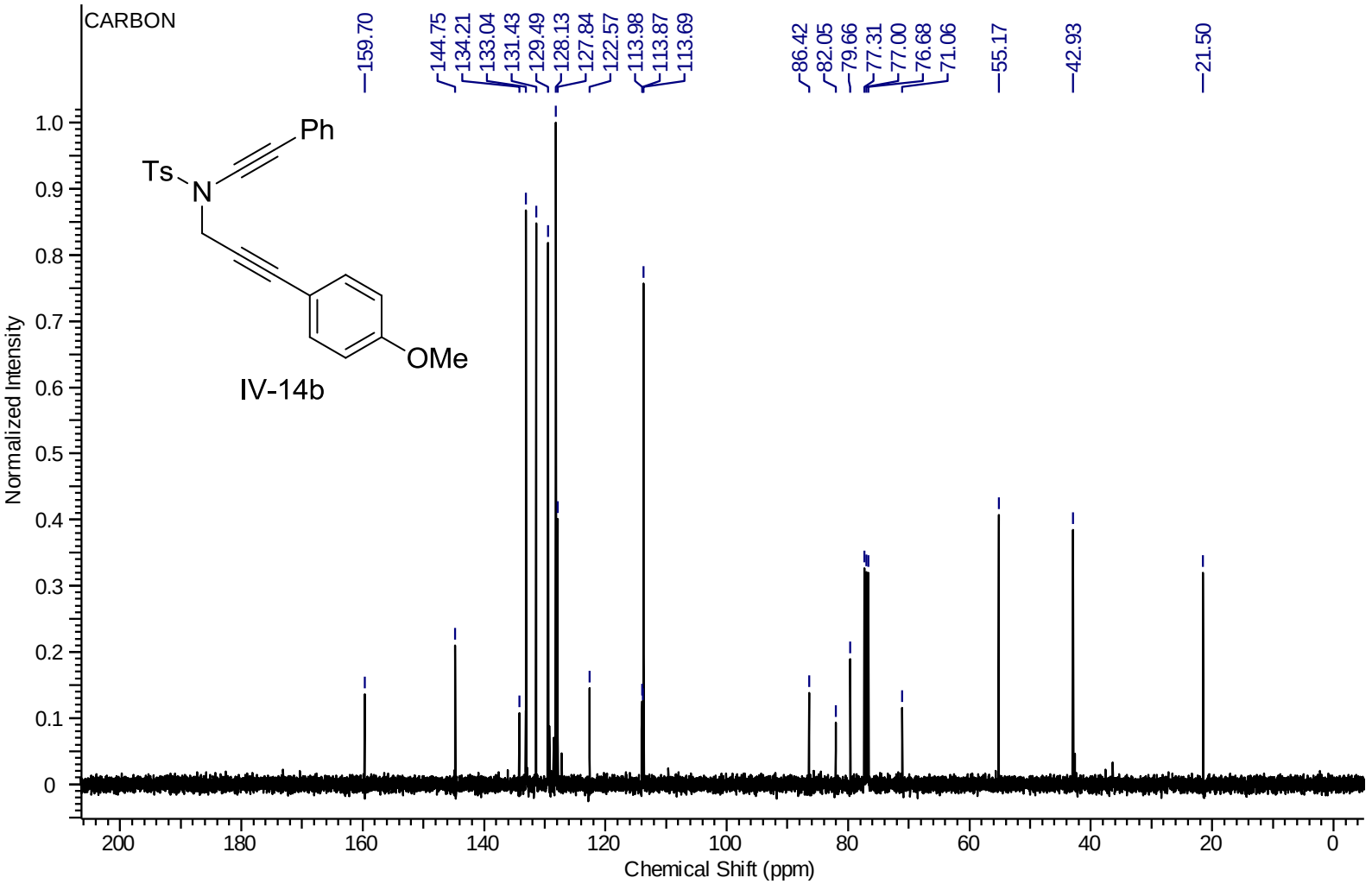

Ts
N
Me
144.347
134.426
129.209
128.178
82.346
77.321
77.000
76.679
75.098
71.478
68.370
42.494
21.598
8.836
3.398
-0.749
200
150
100
50
0
PPM

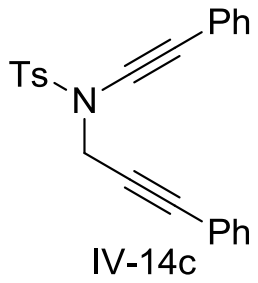
IV-14a



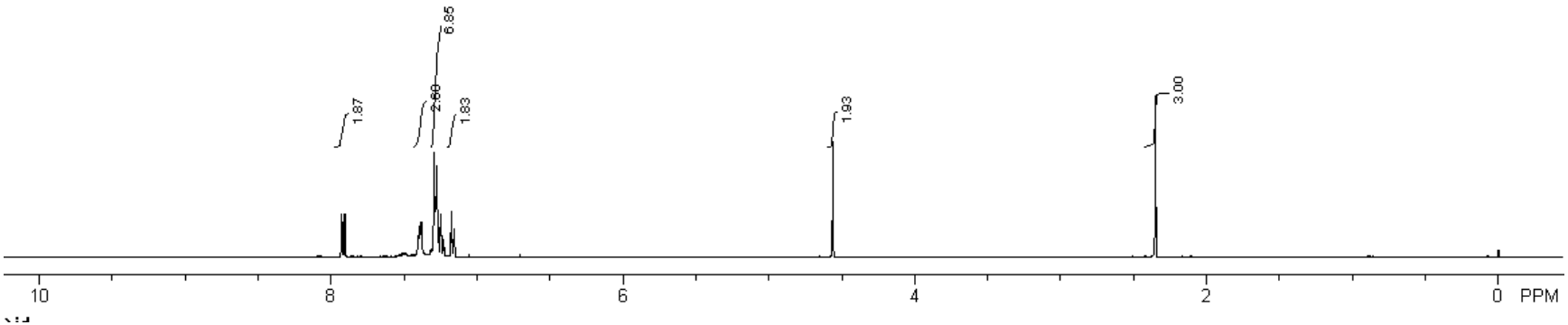

IV-14b

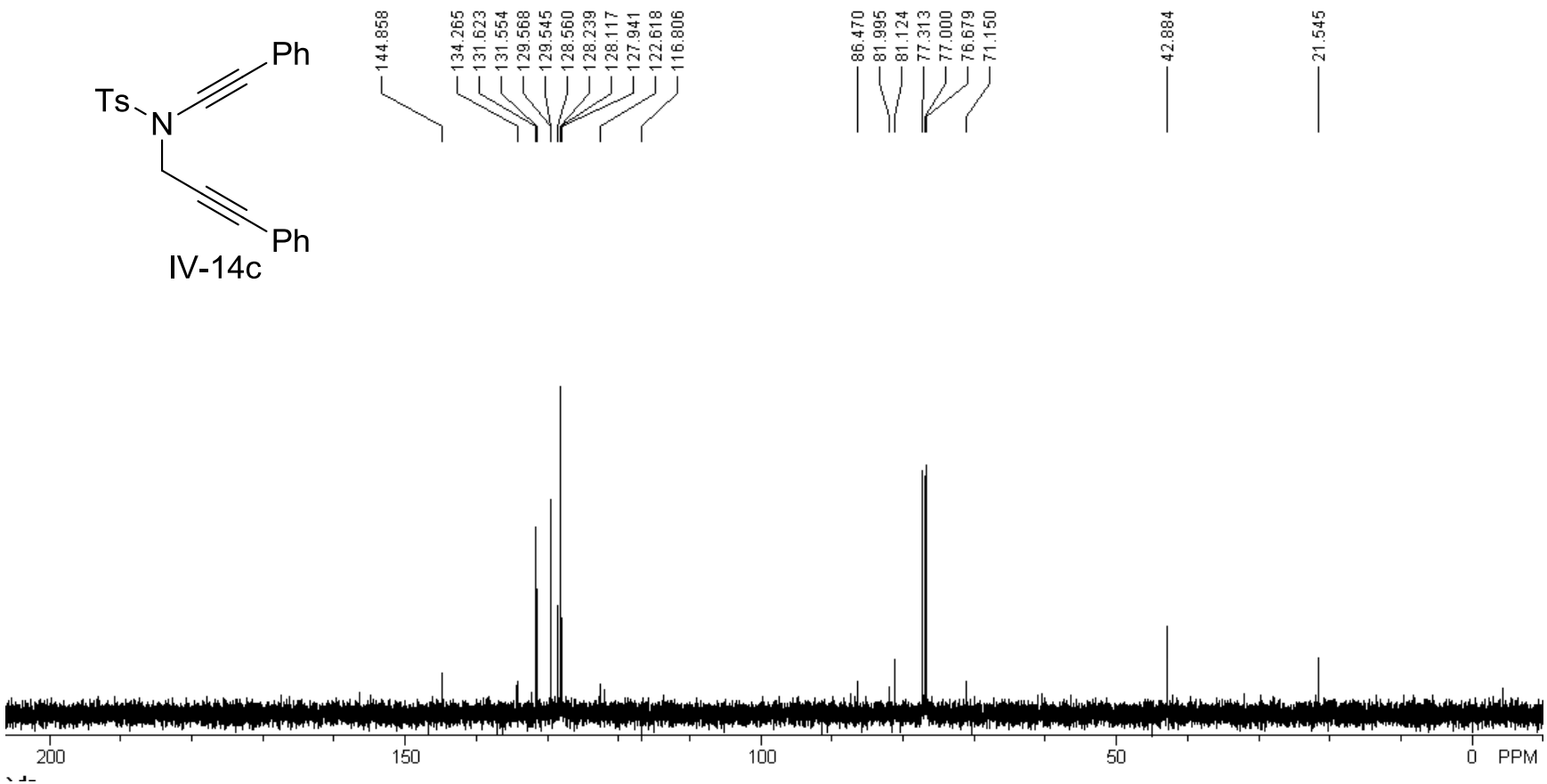


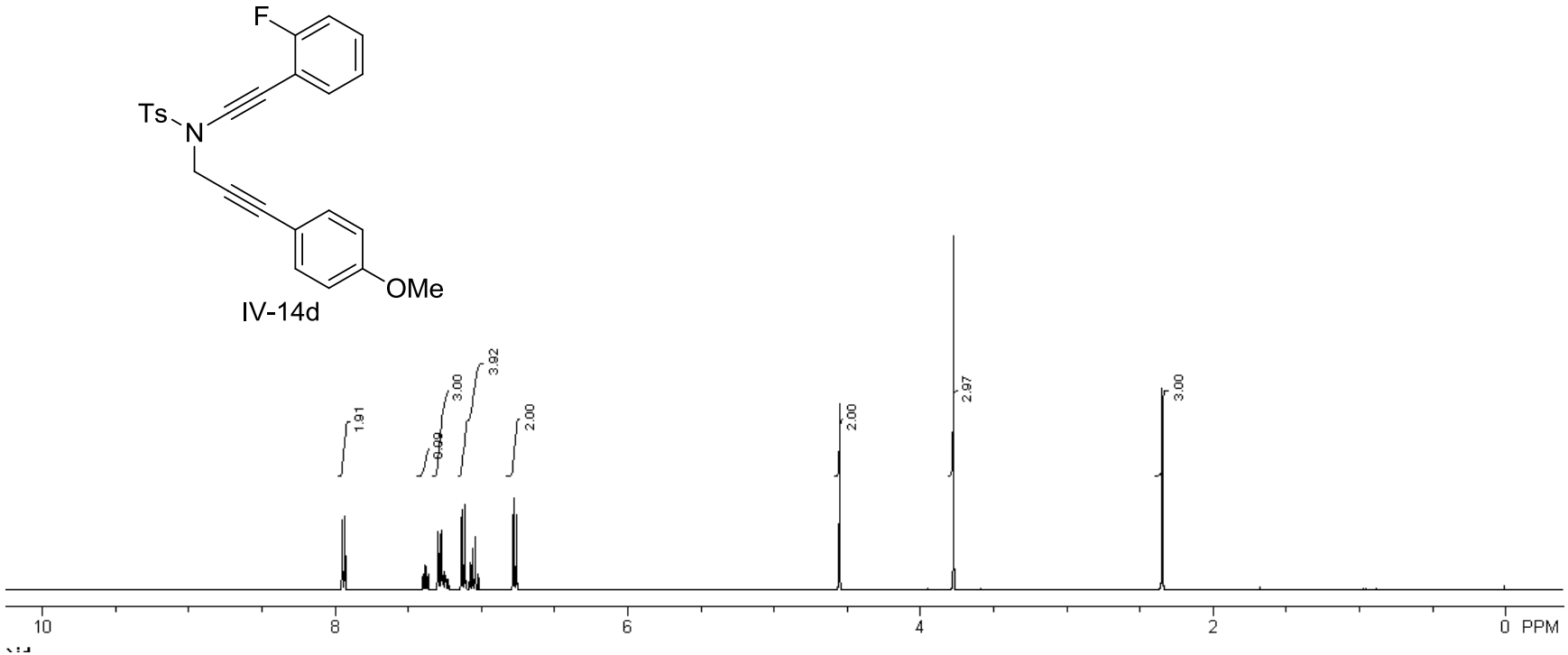

CARBON
159.70
144.75
134.21
133.04
131.43
129.49
128.13
127.84
122.57
113.98
113.87
113.69
86.42
82.05
79.66
77.31
77.00
76.68
71.06
55.17
42.93
21.50
Ph
Ts
N
OMe
IV-14b
Normalized Intensity
Chemical Shift (ppm)

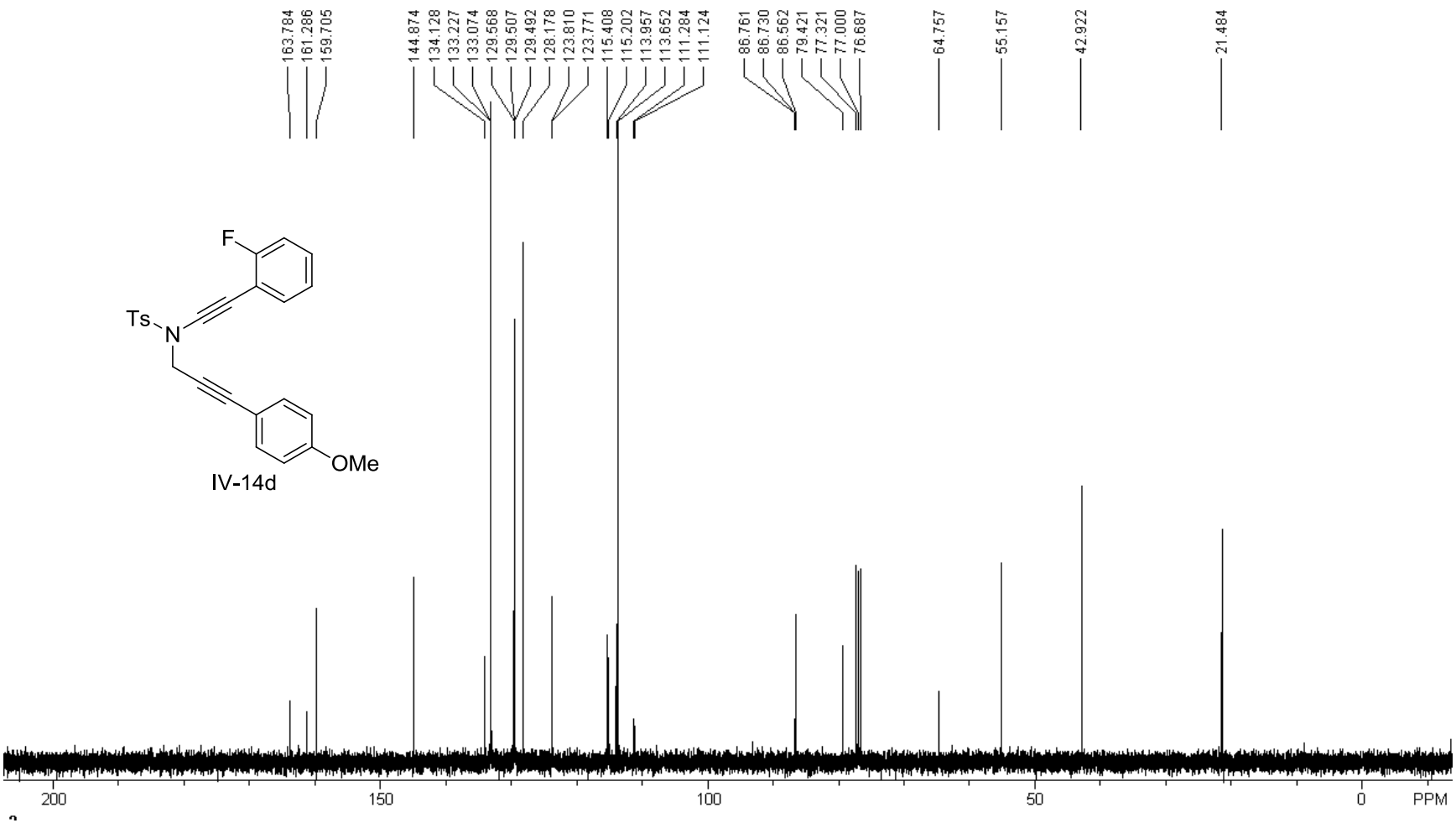


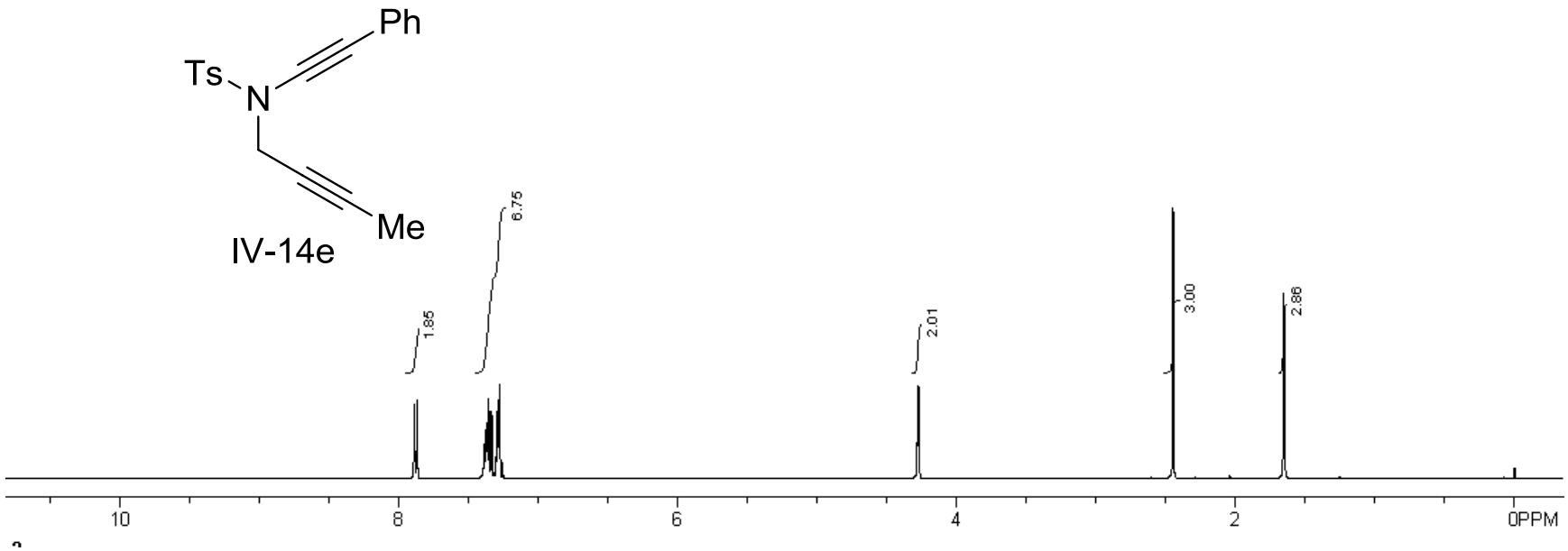

IV-14c

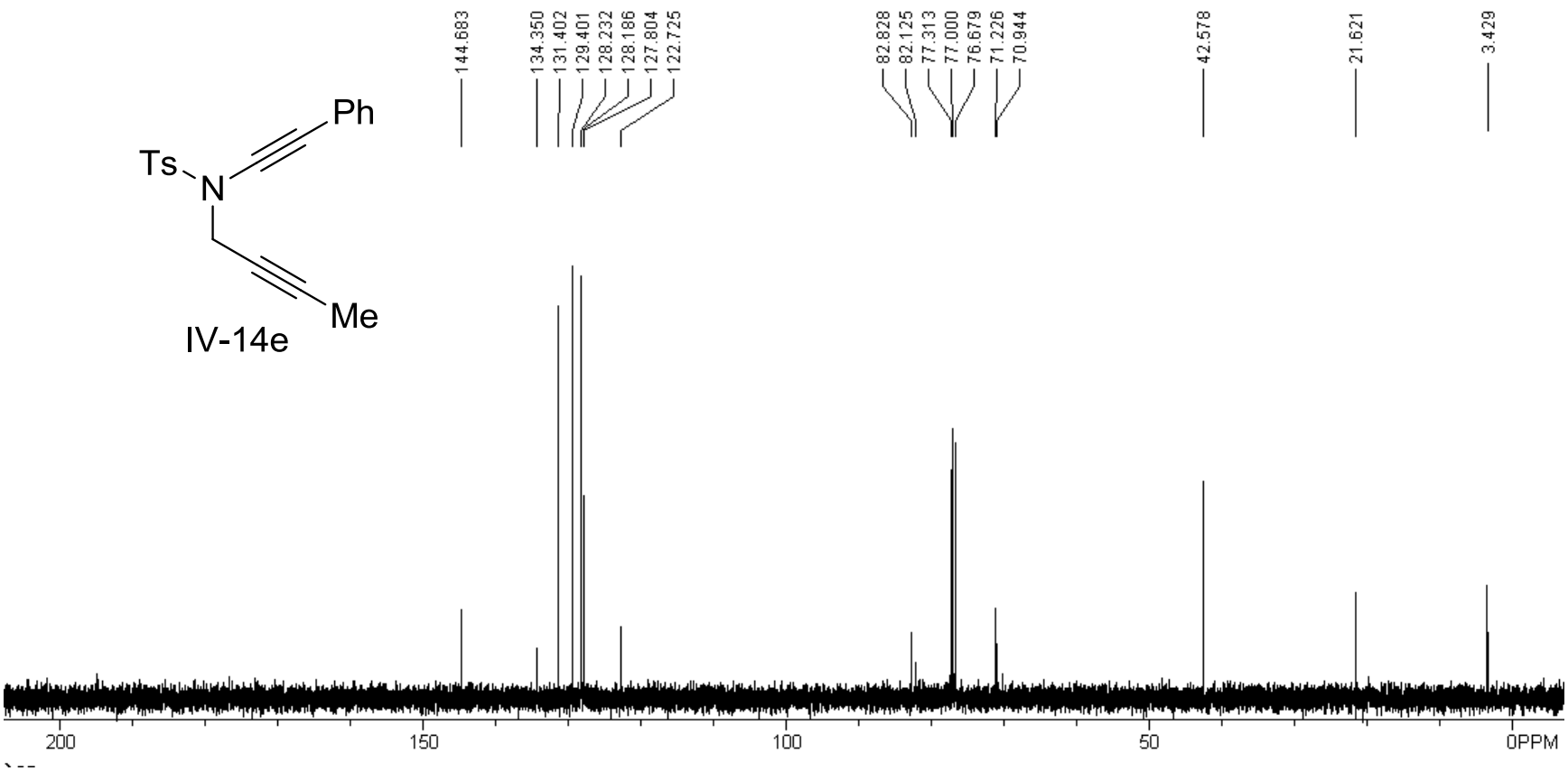


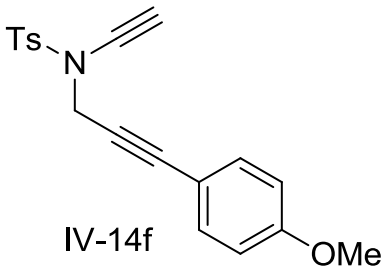

Ts
N
Ph
Ph
IV-14c
144.858
134.265
131.623
131.554
129.568
129.545
128.560
128.239
128.117
127.941
122.618
116.806
86.470
81.995
81.124
77.313
77.000
76.679
71.150
42.884
21.545
200
150
100
50
0
PPM


F
Ts
N
OMe
IV-14d
1.91
0.99
3.00
3.92
2.00
2.00
2.97
3.00
10
8
6
4
2
0 PPM

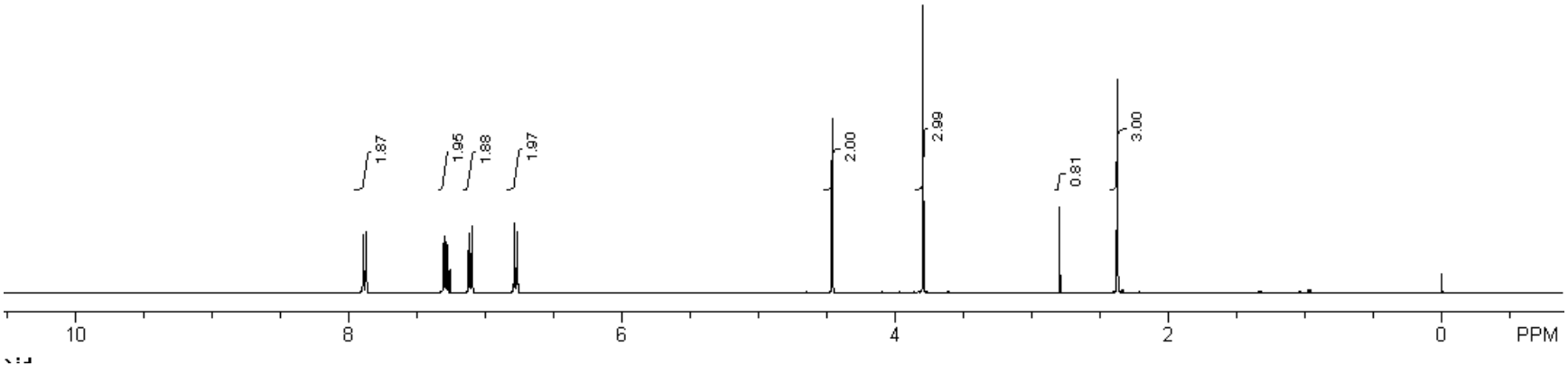

163.784
161.286
159.705
144.874
134.128
133.227
133.074
129.568
129.507
129.492
128.178
123.810
123.771
115.408
115.202
113.957
113.652
111.284
111.124
86.761
86.730
86.562
79.421
77.321
77.000
76.687
64.757
55.157
42.922
21.484
F
Ts
N
OMe
IV-14d
200
150
100
50
0
PPM

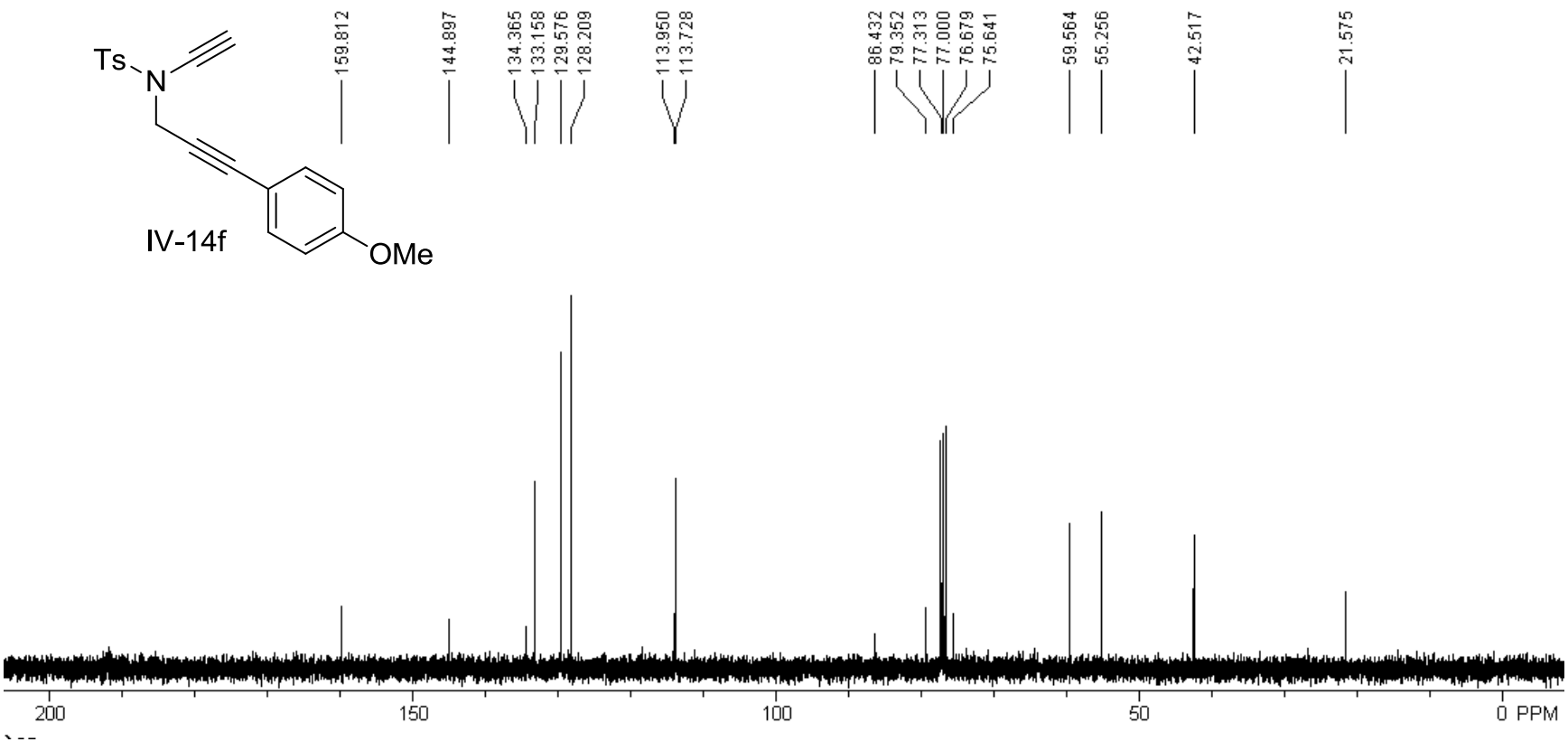

Ph
Ts
N
Me
IV-14e
1.85
6.75
2.01
3.00
2.86
10
8
6
4
2
0PPM

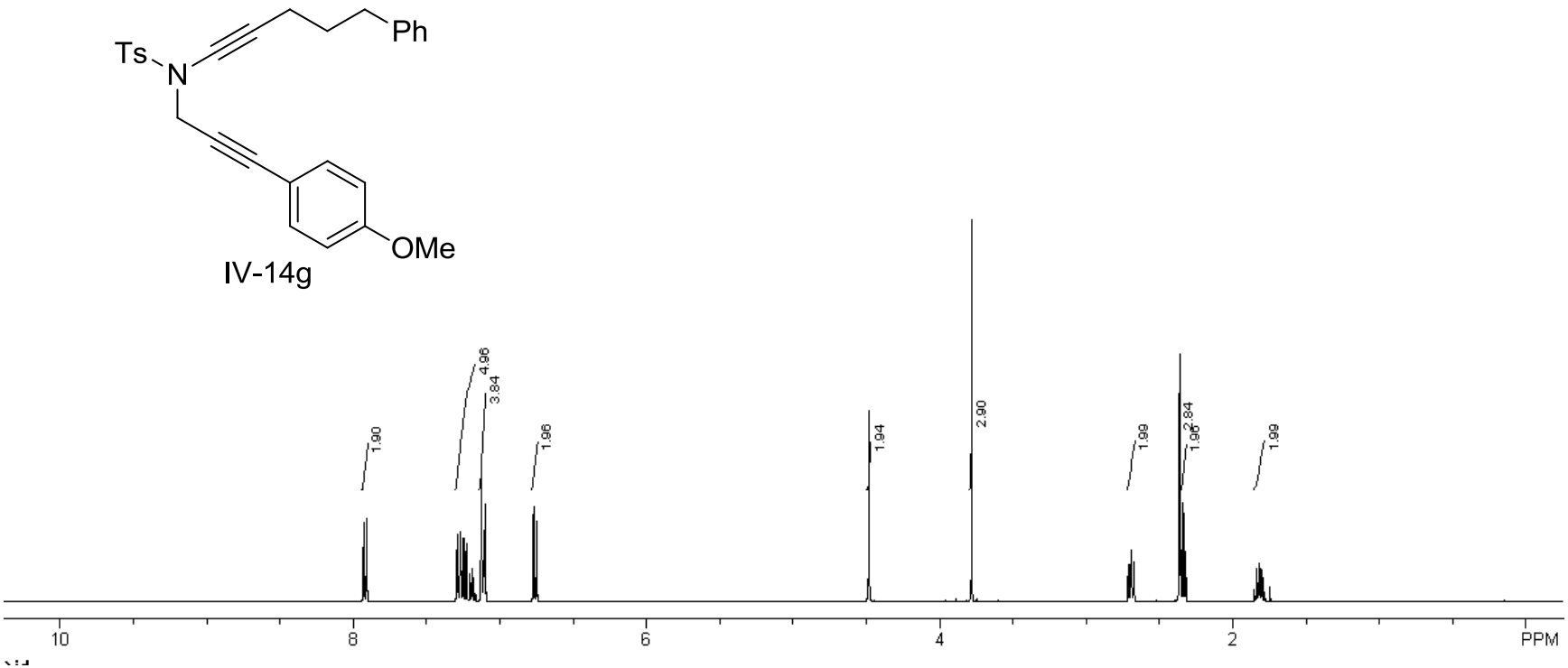

144.683
134.350
131.402
129.401
128.232
128.186
127.804
122.725
82.828
82.125
77.313
77.000
76.679
71.226
70.944
42.578
21.621
3.429
Ph
Ts
N
Me
IV-14e
200
150
100
50
0PPM

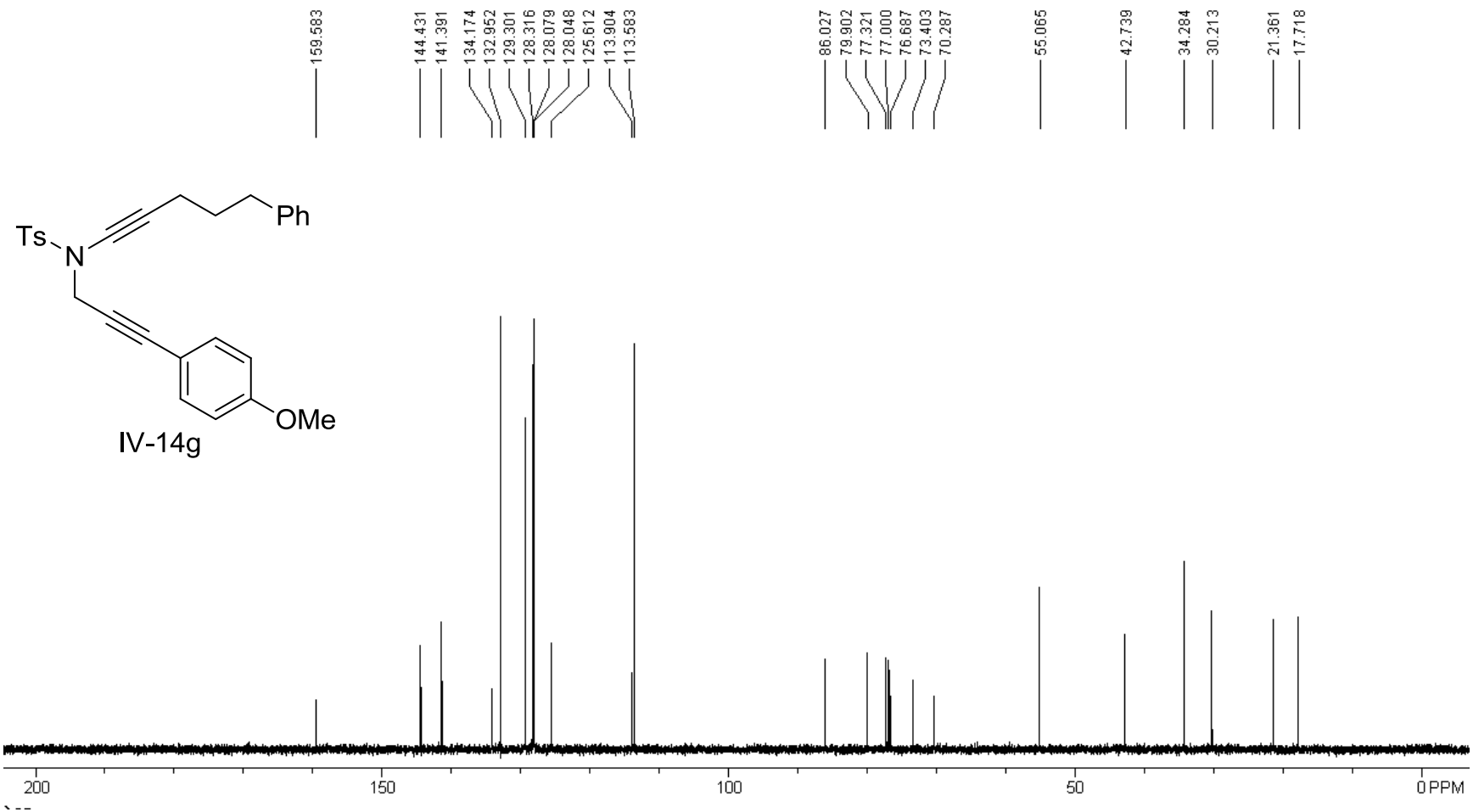


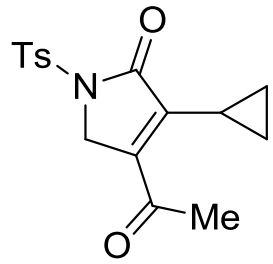

IV-14f



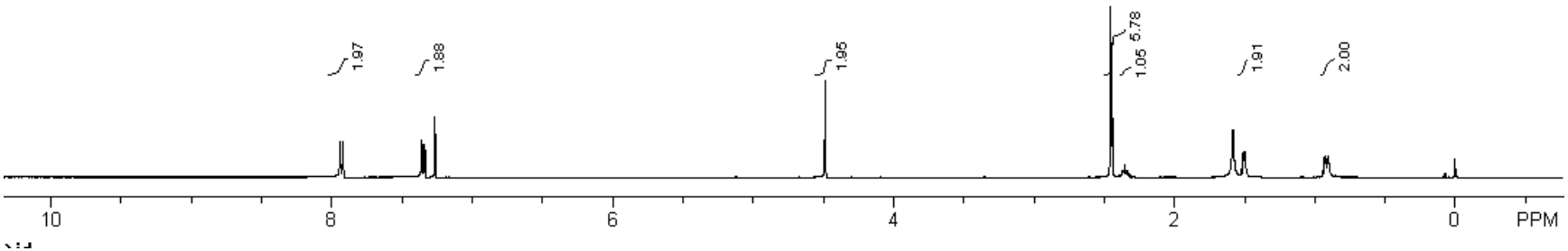

Ts
N
OMe
IV-14f
159.812
144.897
134.365
133.158
129.576
128.209
113.950
113.728
86.432
79.352
77.313
77.000
76.679
75.641
59.564
55.256
42.517
21.575
200
150
100
50
0 PPM

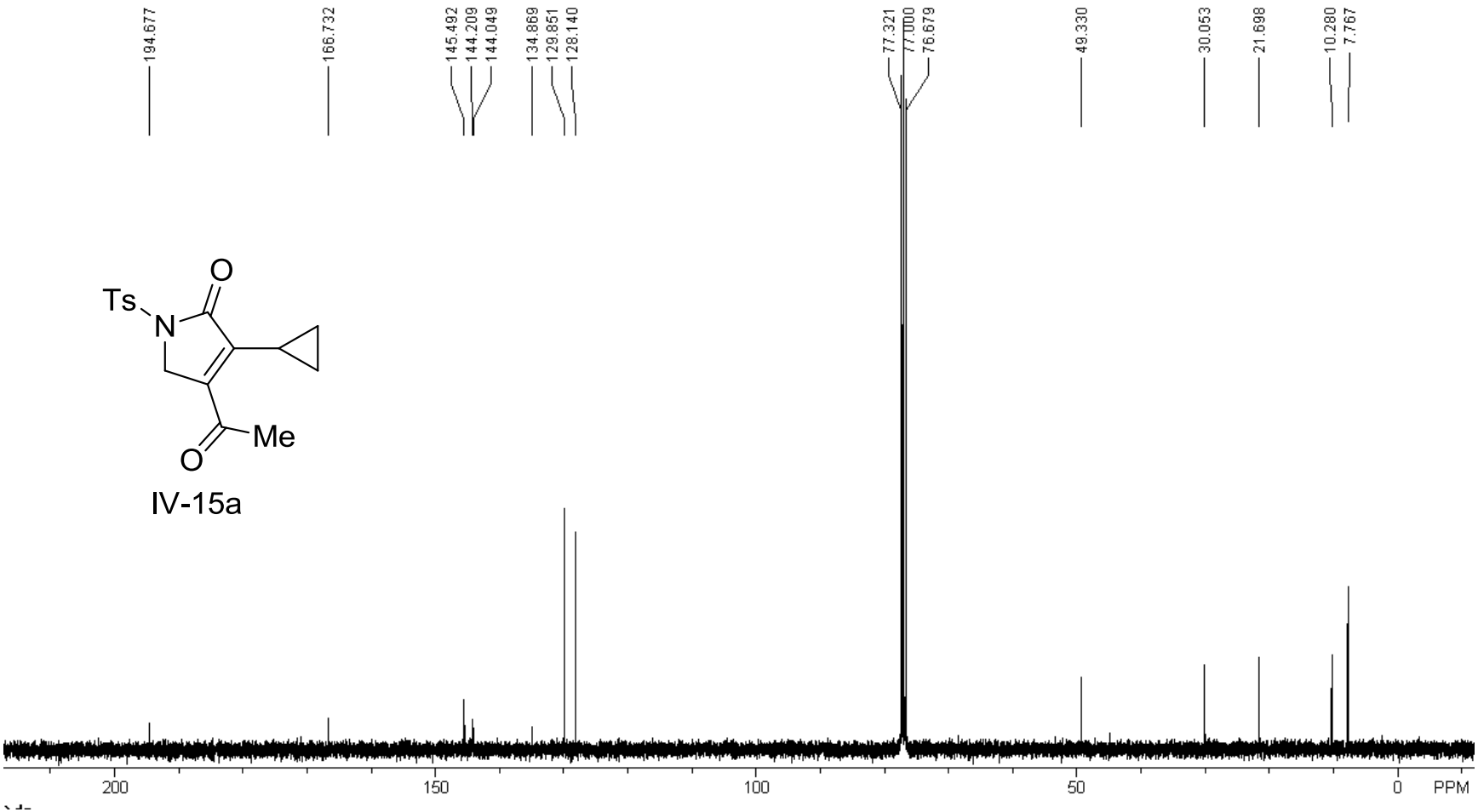

Ts
N
Ph
OMe
IV-14g
1.90
4.96
3.84
1.96
1.94
2.90
1.99
2.84
1.96
1.99
10
8
6
4
2
PPM


159.583
144.431
141.391
134.174
132.952
129.301
128.316
128.079
128.048
125.612
113.904
113.583
86.027
79.902
77.321
77.000
76.687
73.403
70.287
55.065
42.739
34.284
30.213
21.361
17.718
Ts
N
Ph
OMe
IV-14g
200
150
100
50
0 PPM

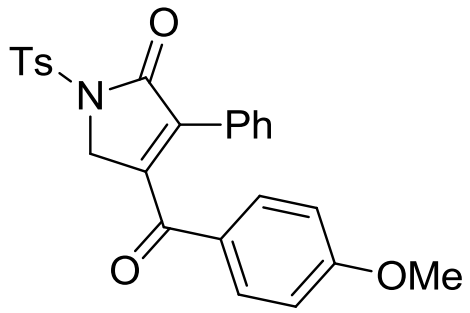



IV-15a

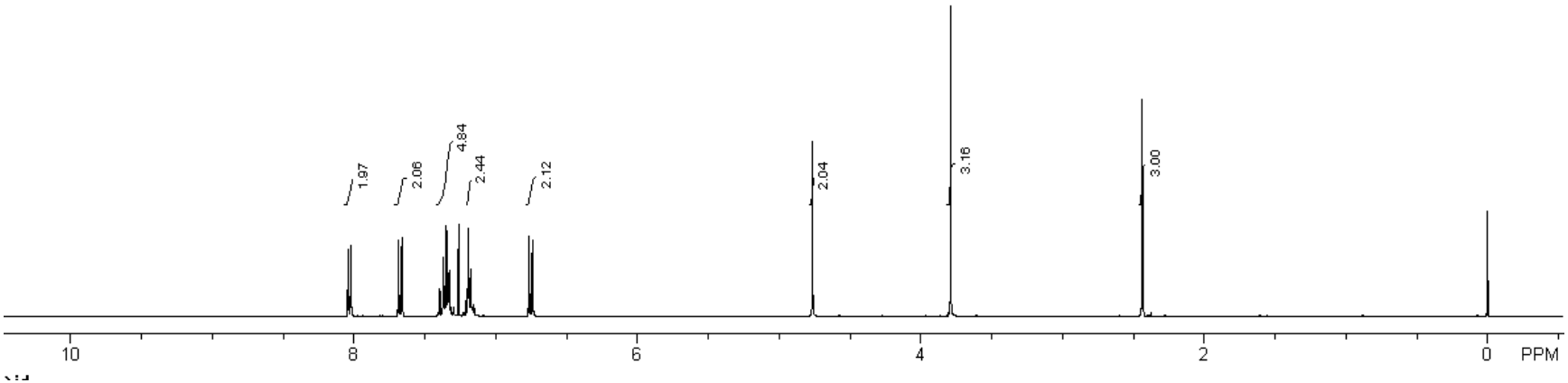


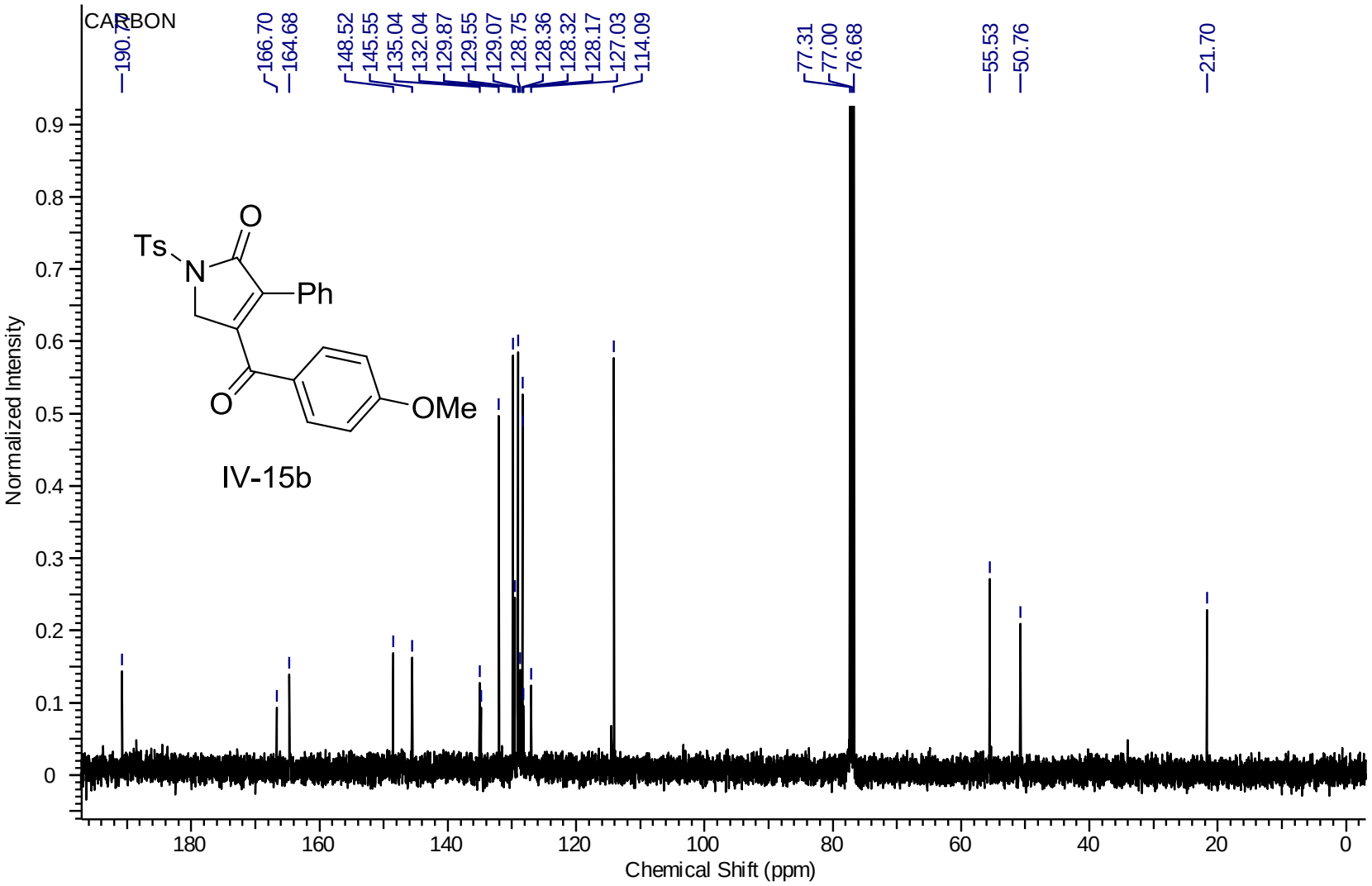

194.677
166.732
145.492
144.209
144.049
134.869
129.851
128.140
77.321
77.000
76.679
49.330
30.053
21.698
10.280
7.767
Ts
N
O
O
Me
200
150
100
50
0
PPM

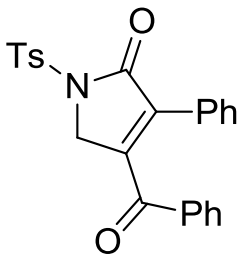
IV-15a



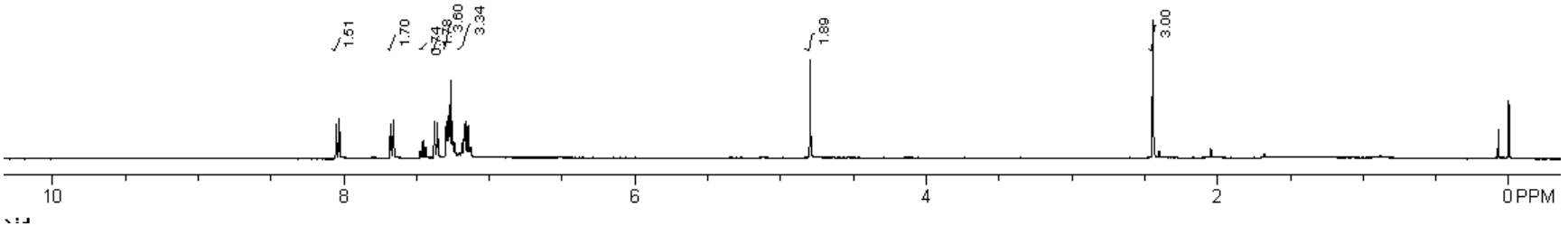

IV-15b

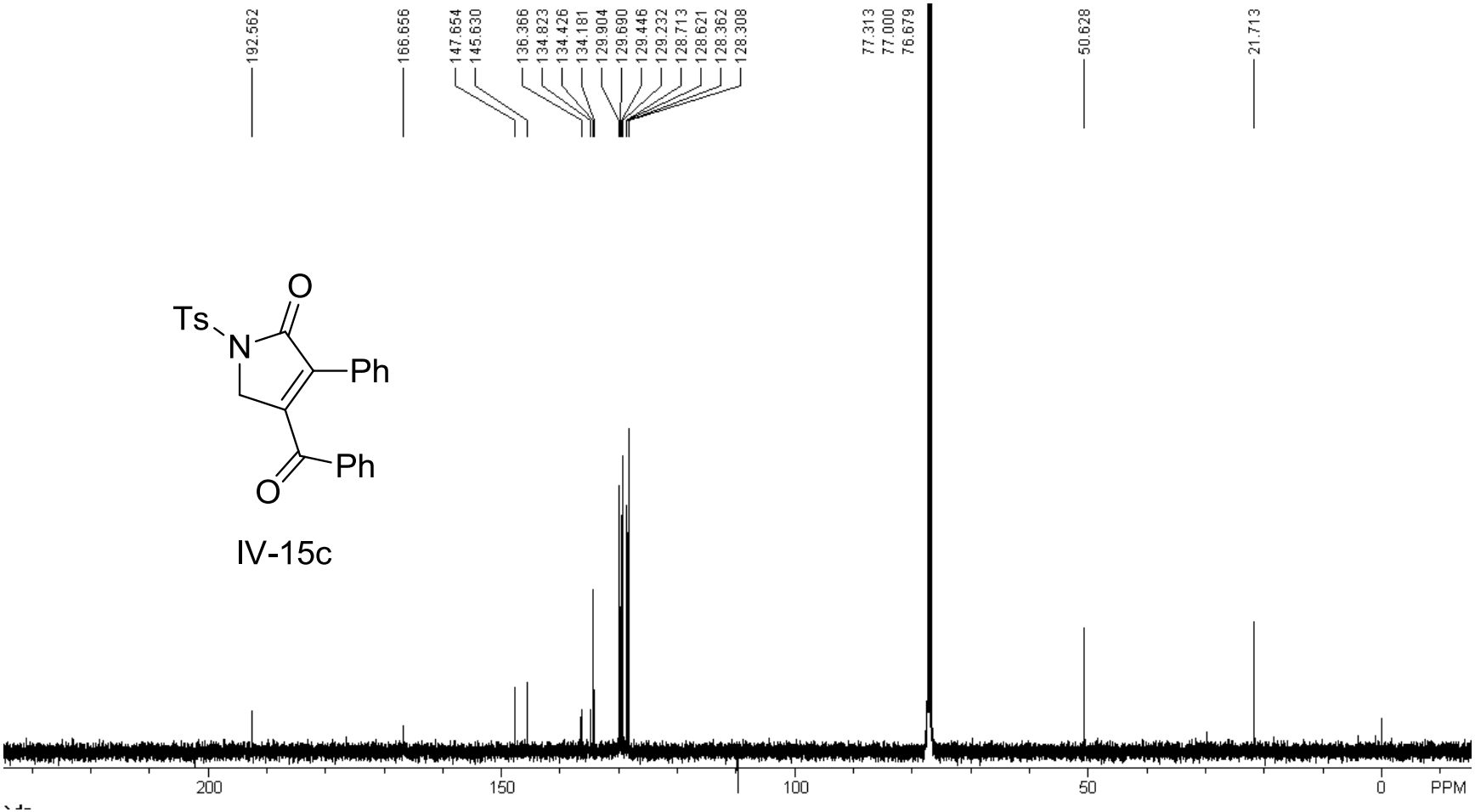


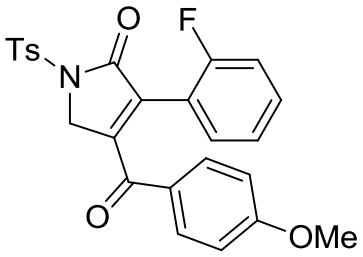

CARBON
190.78
166.70
164.68
148.52
145.55
135.04
132.04
129.87
129.55
129.07
128.75
128.36
128.32
128.17
127.03
114.09
77.31
77.00
76.68
55.53
50.76
21.70
Ts
N
O
O
Ph
OMe
IV-15b
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



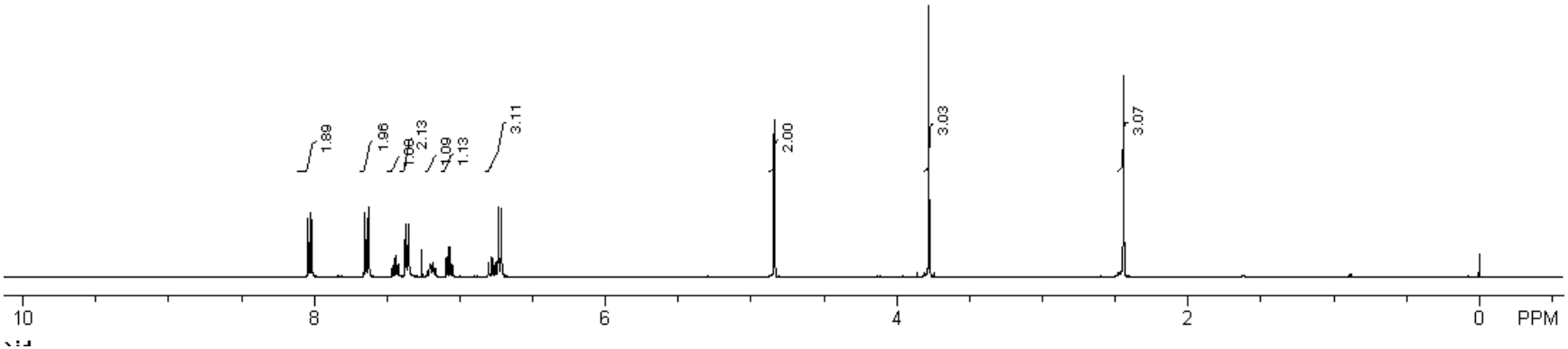

IV-15c

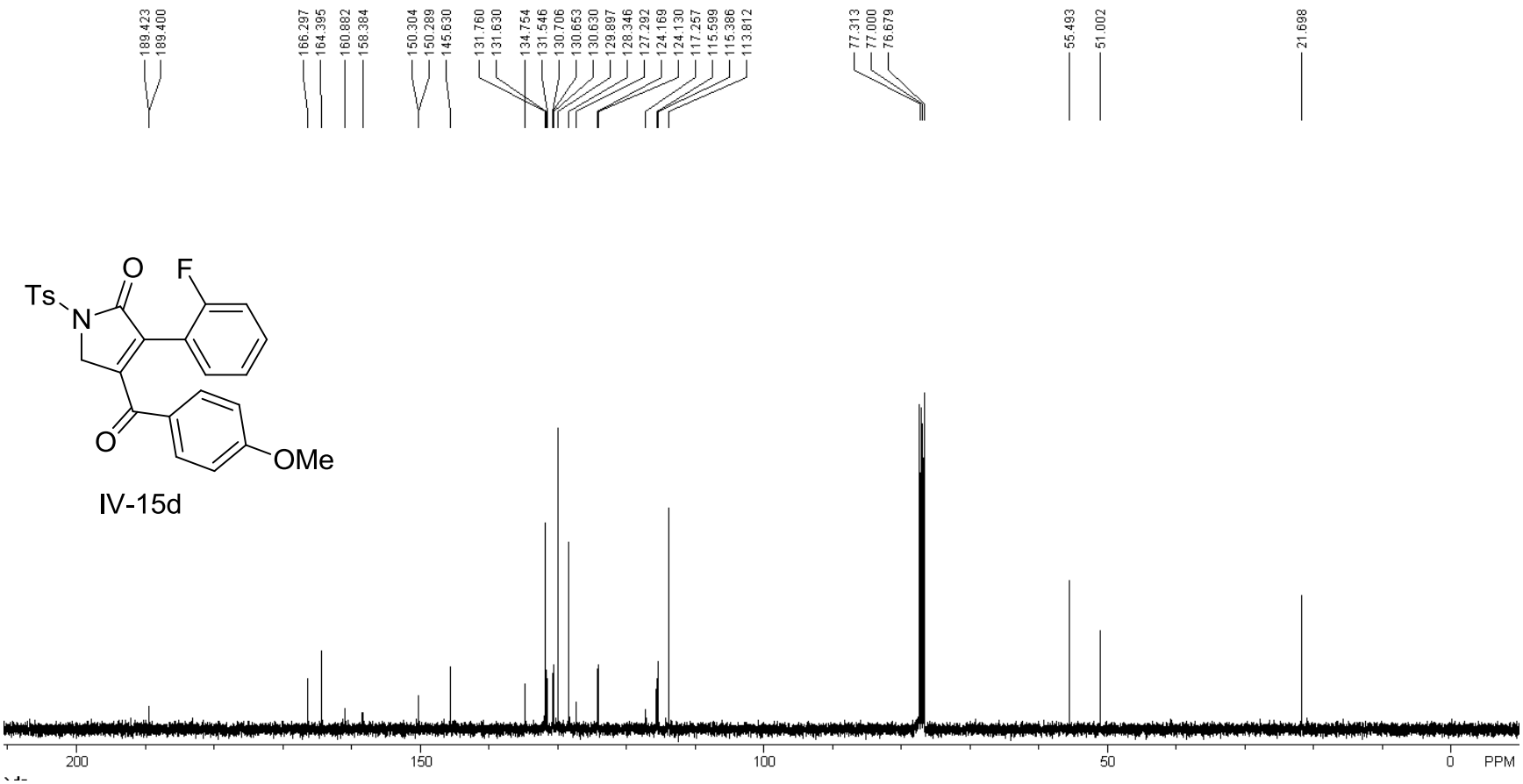


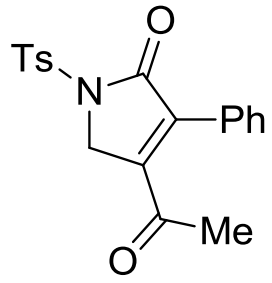

192.562
166.656
147.654
145.630
136.366
134.823
134.426
134.181
129.904
129.690
129.446
129.232
128.713
128.621
128.362
128.308
77.313
77.000
76.679
50.628
21.713
Ts
N
O
Ph
Ph
O
IV-15c
200
150
100
50
0
PPM



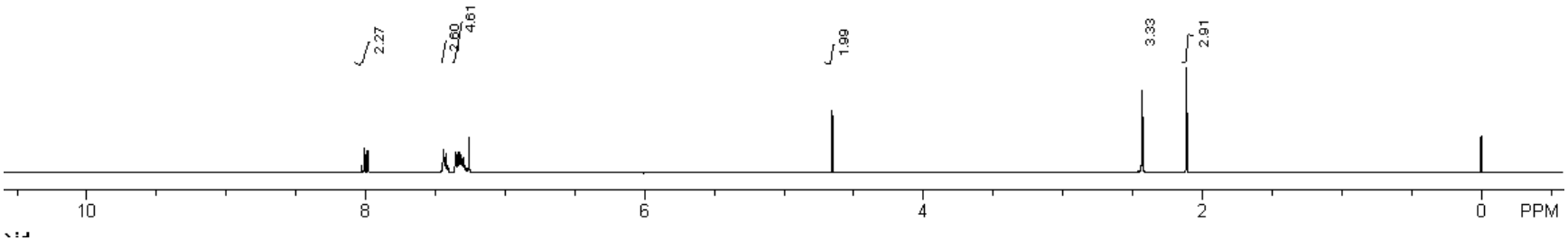

IV-15d

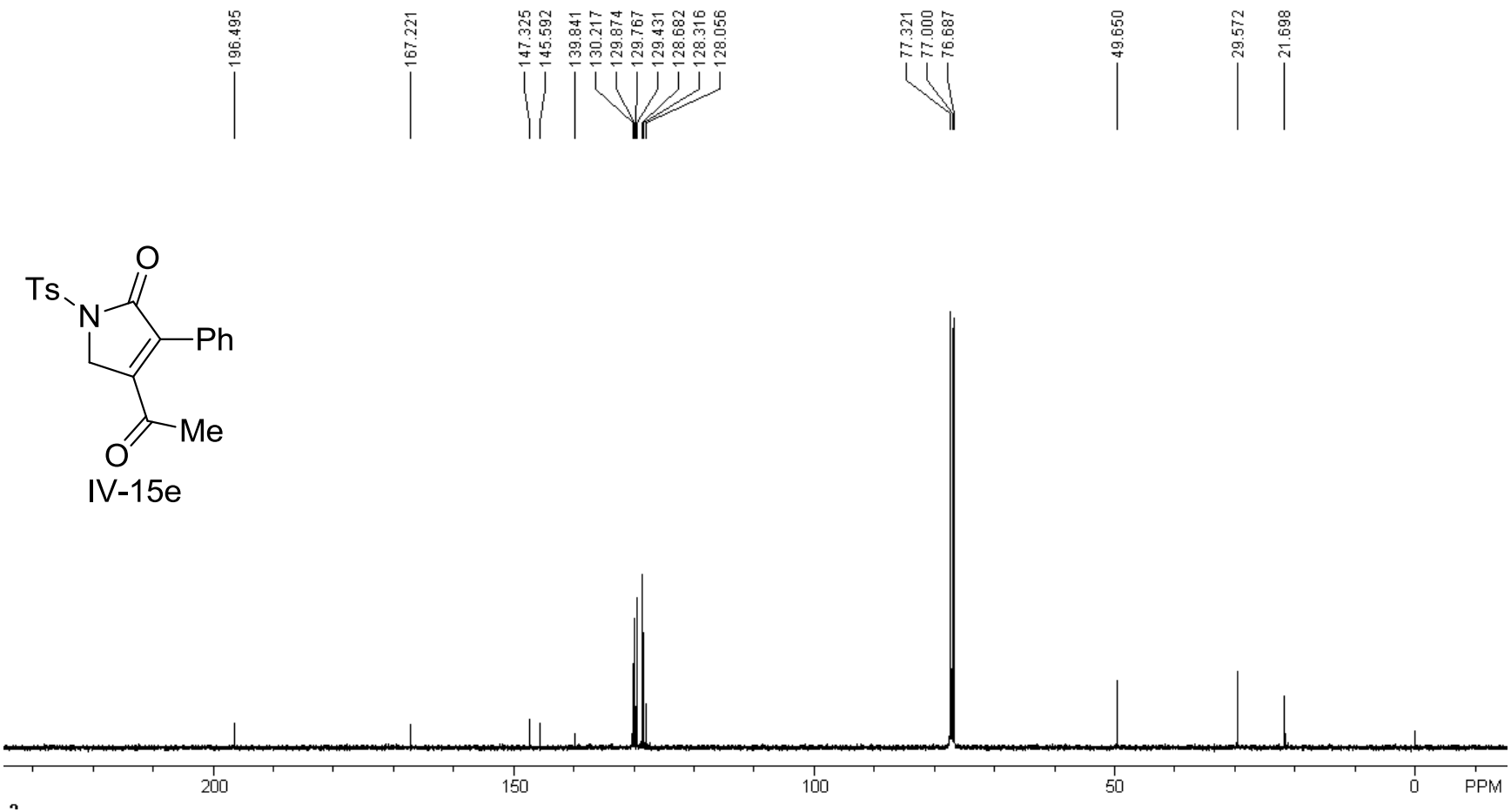



189.423
189.400
166.297
164.395
160.882
158.384
150.304
150.289
145.630
131.760
131.630
134.754
131.546
130.706
130.653
130.630
129.897
128.346
127.292
124.169
124.130
117.257
115.599
115.386
113.812
77.313
77.000
76.679
55.493
51.002
21.698
Ts
N
O
F
O
OMe
IV-15d
200
150
100
50
0
PPM

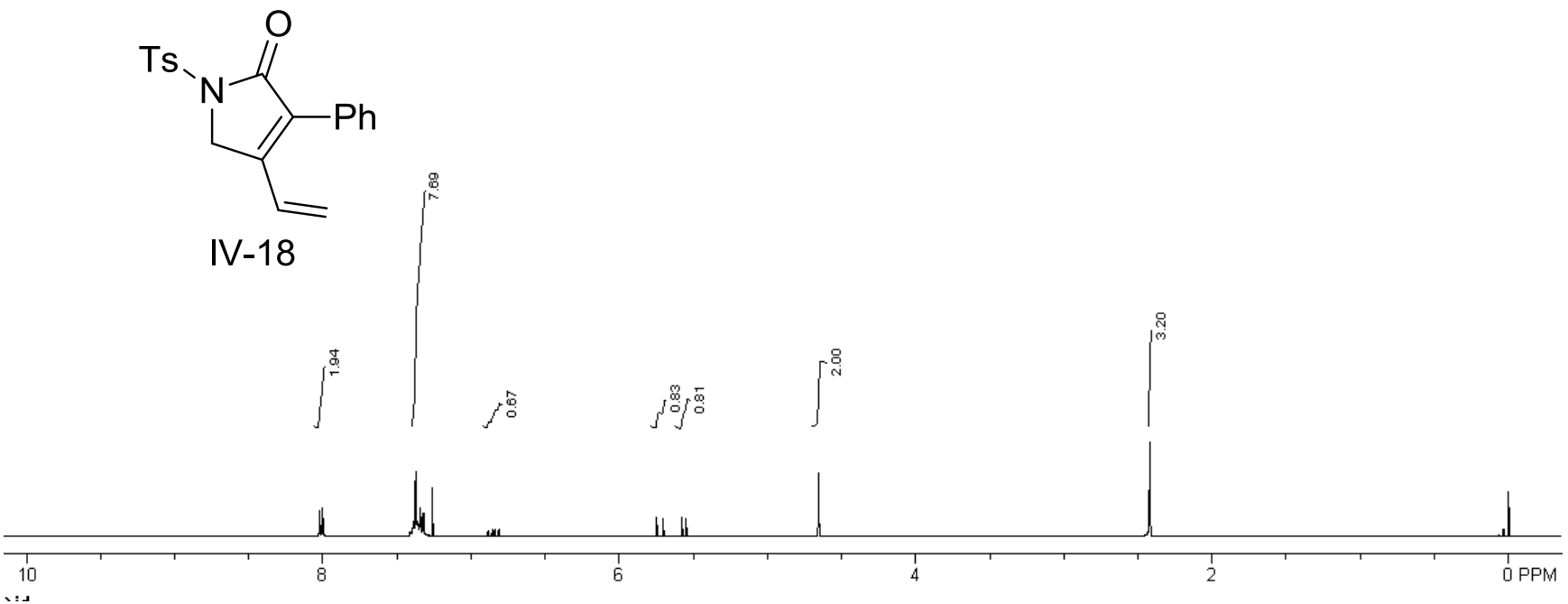


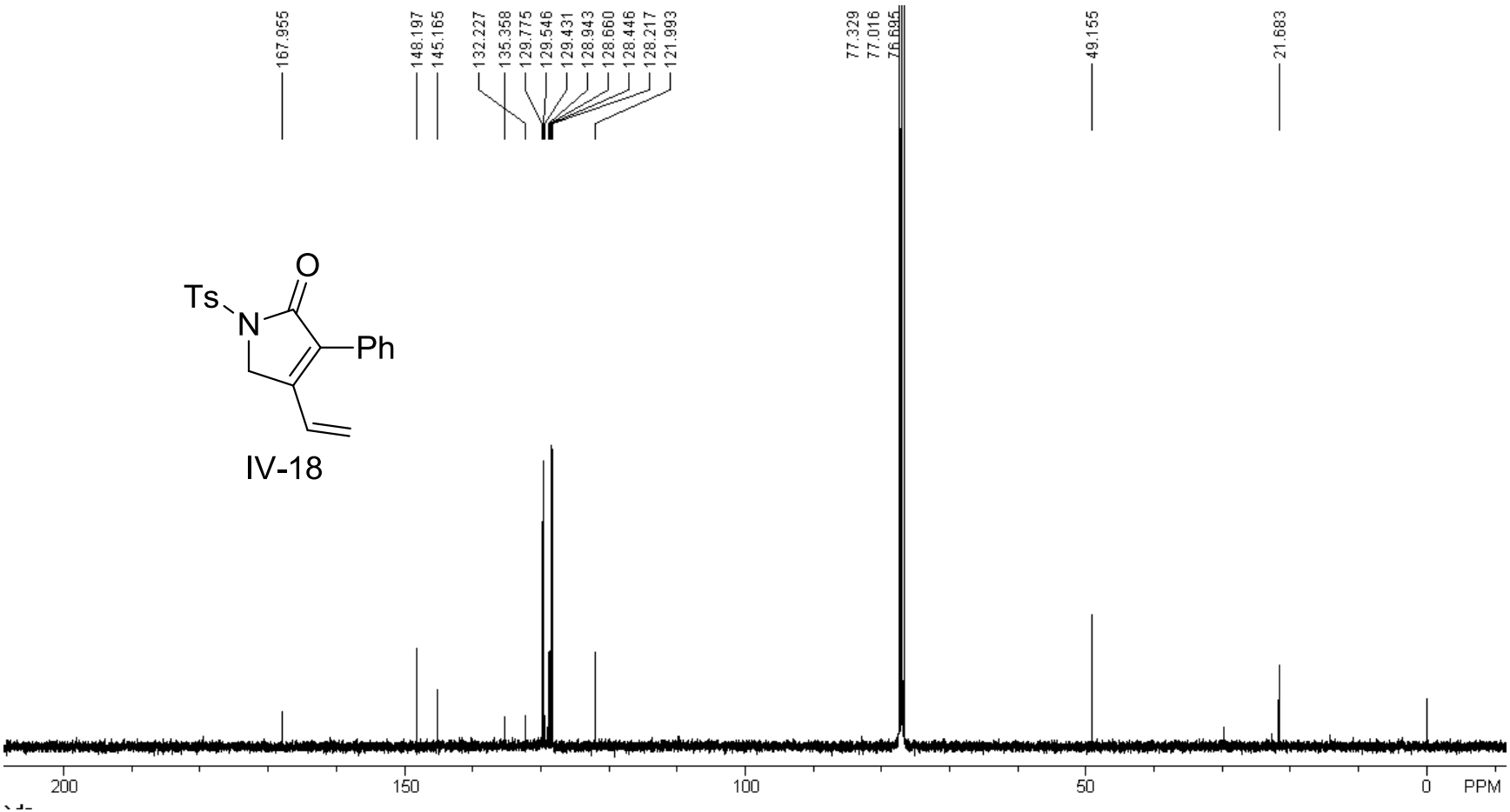

IV-15e

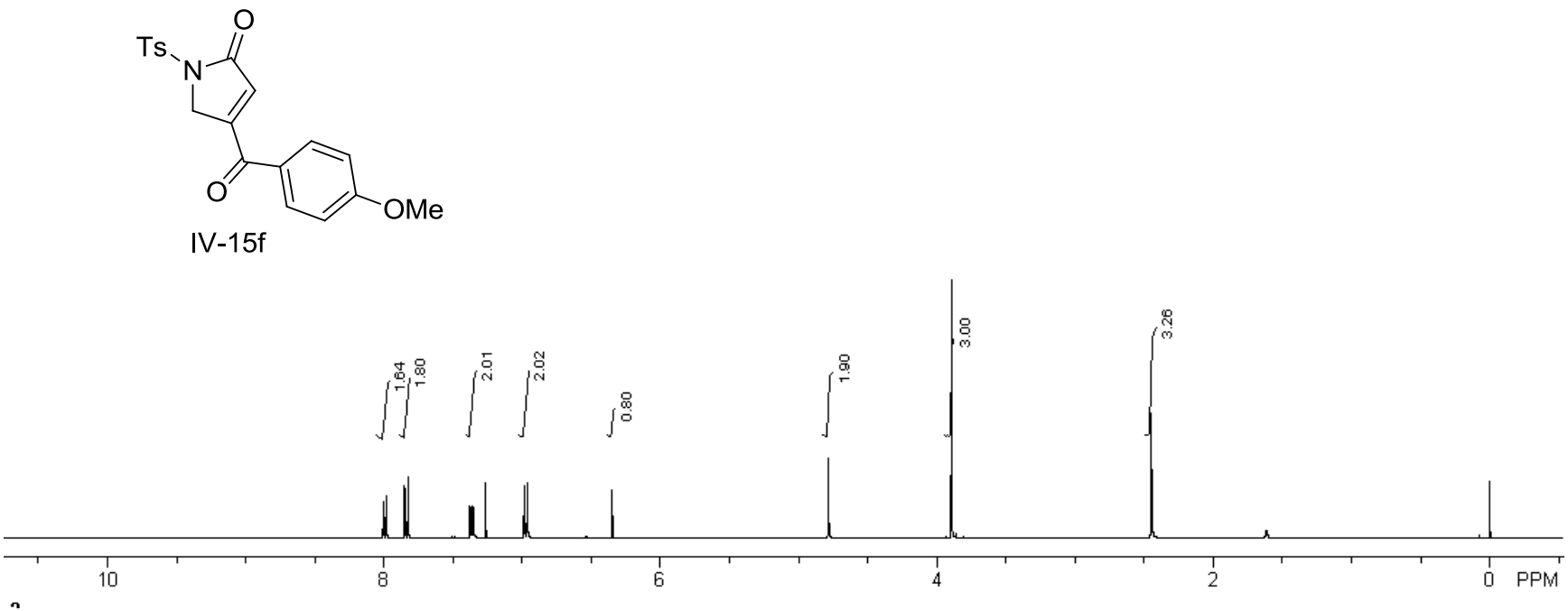



196.495
167.221
147.325
145.592
139.841
130.217
129.874
129.767
129.431
128.682
128.316
128.056
77.321
77.000
76.687
49.650
29.572
21.698
Ts
N
O
Ph
Me
O
200
150
100
50
0
PPM

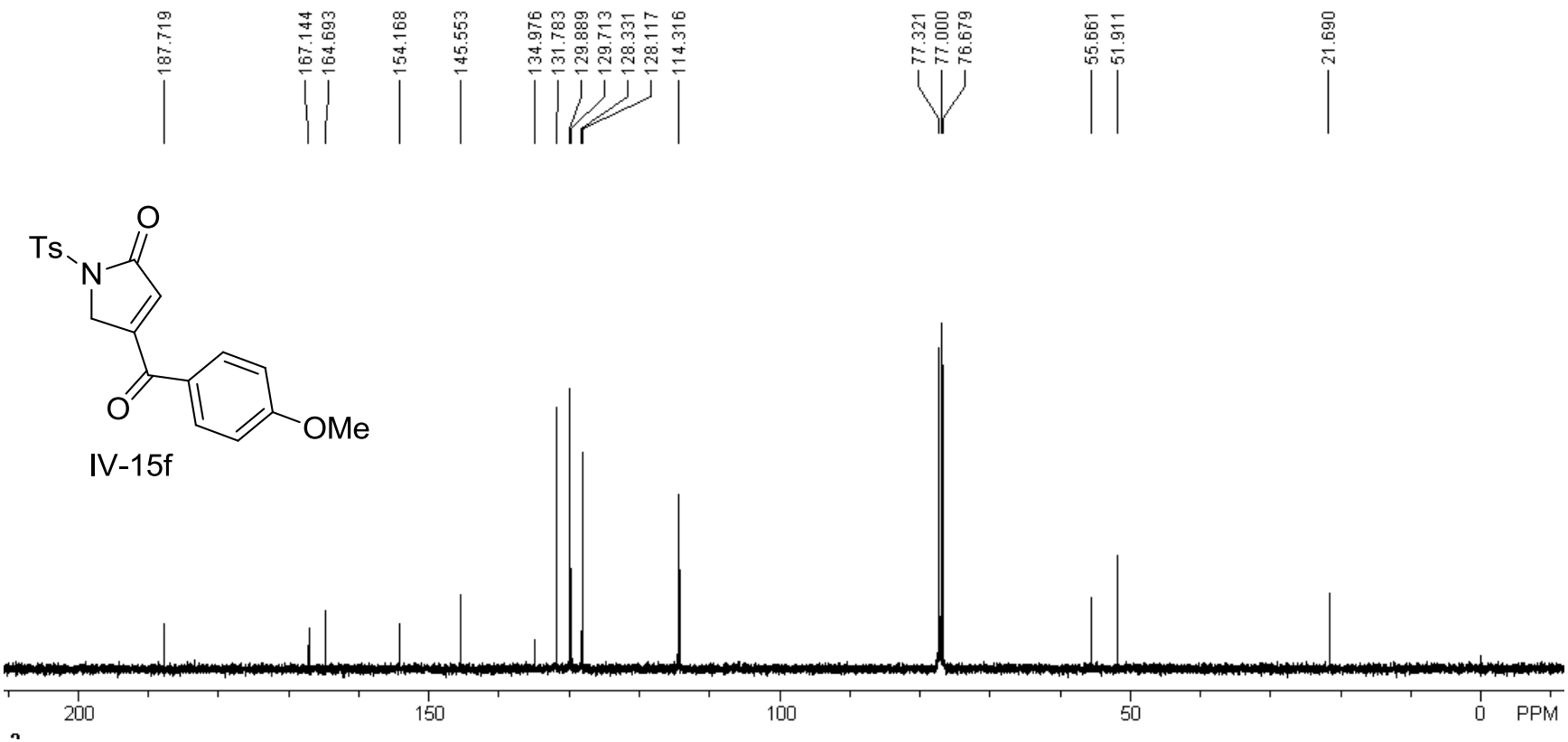
IV-15e

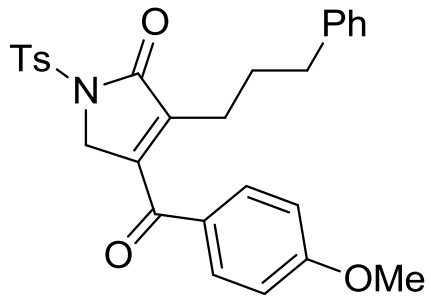

O
Ts
N
Ph
IV-18
1.94
7.69
0.67
0.83
0.81
2.00
3.20
10
8
6
4
2
0 PPM


167.955
148.197
145.165
132.227
135.358
129.775
129.546
129.431
128.943
128.660
128.446
128.217
121.993
77.329
77.016
76.695
49.155
21.683
O
Ts
N
Ph
IV-18
200
150
100
50
0
PPM

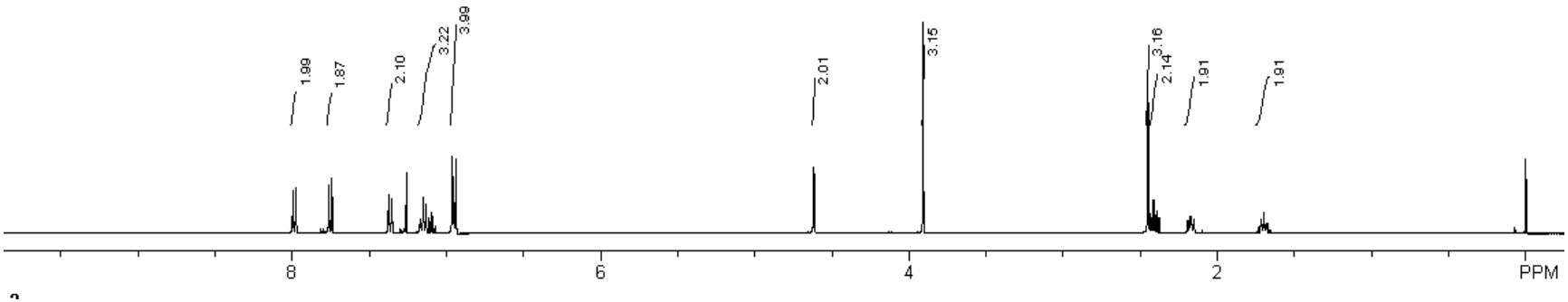


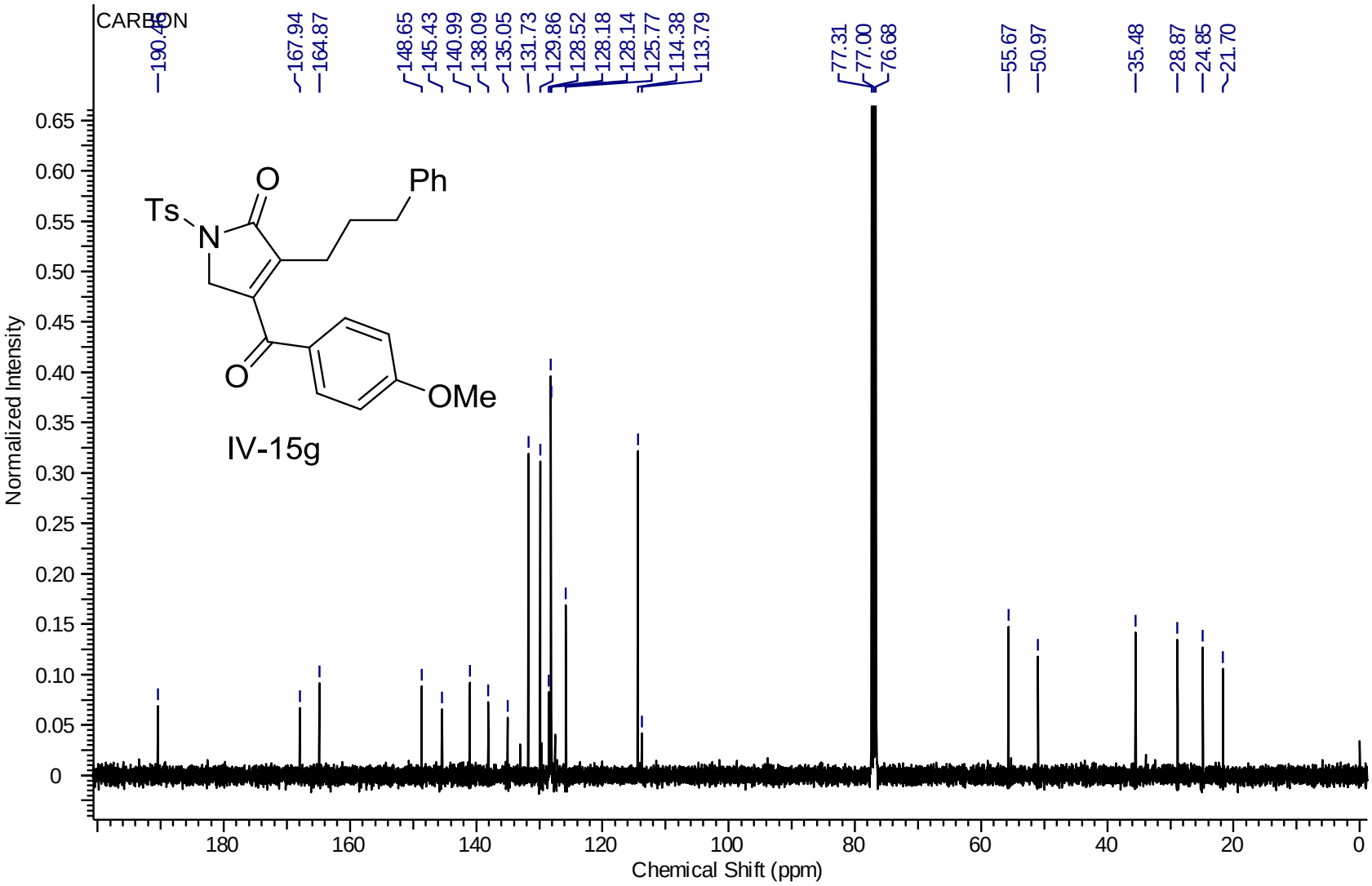

IV-15f

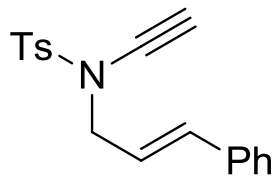

187.719
167.144
164.693
154.168
145.553
134.976
131.783
129.889
129.713
128.331
128.117
114.316
77.321
77.000
76.679
55.661
51.911
21.690
Ts
N
O
O
O
OMe
IV-15f
200
150
100
50
0
PPM


O
Ph
Ts
N
O
OMe

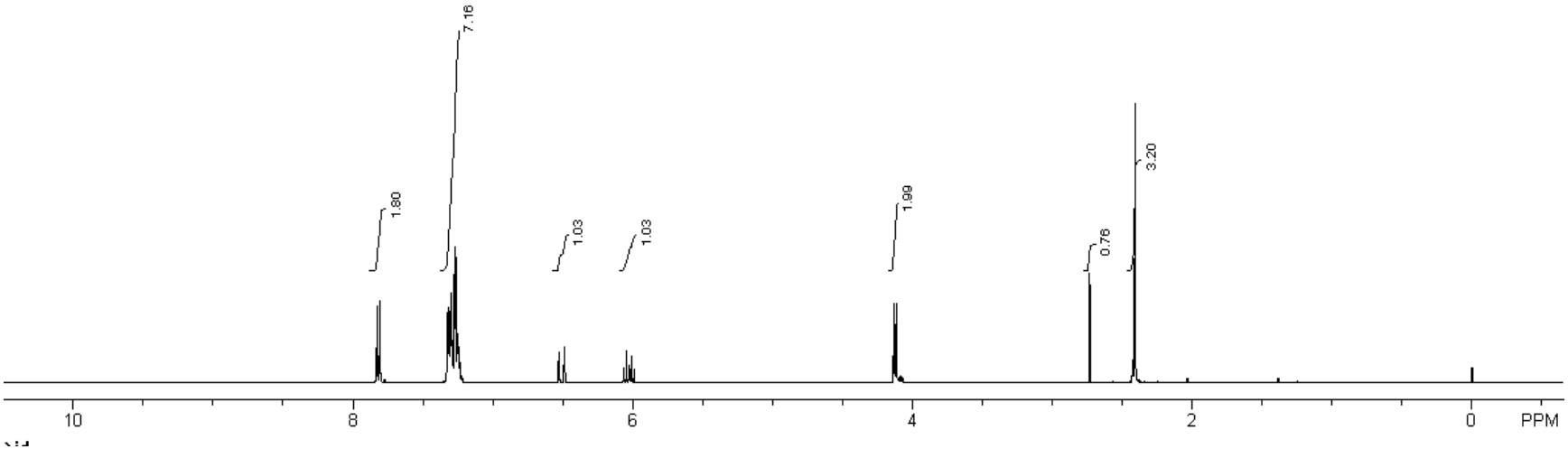
IV-15g

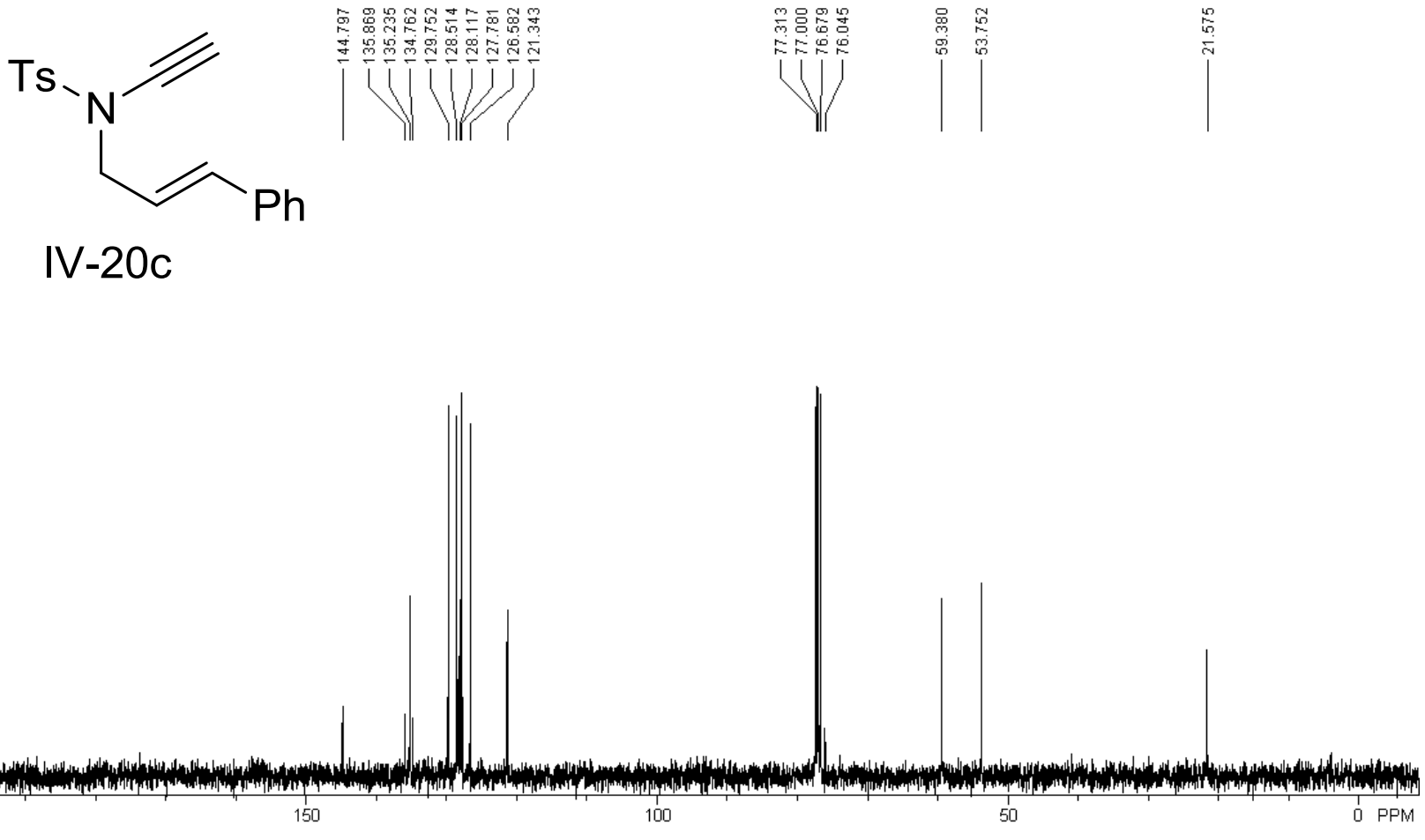

1.99
1.87
2.10
3.22
3.99
2.01
3.15
3.16
2.14
1.91
1.91
8
6
4
2
PPM


CARBON
190.45
167.94
164.87
148.65
145.43
140.99
138.09
135.05
131.73
129.86
128.52
128.18
128.14
125.77
114.38
113.79
77.31
77.00
76.68
55.67
50.97
35.48
28.87
24.85
21.70
Ts
N
O
O
Ph
OMe
IV-15g
Normalized Intensity
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

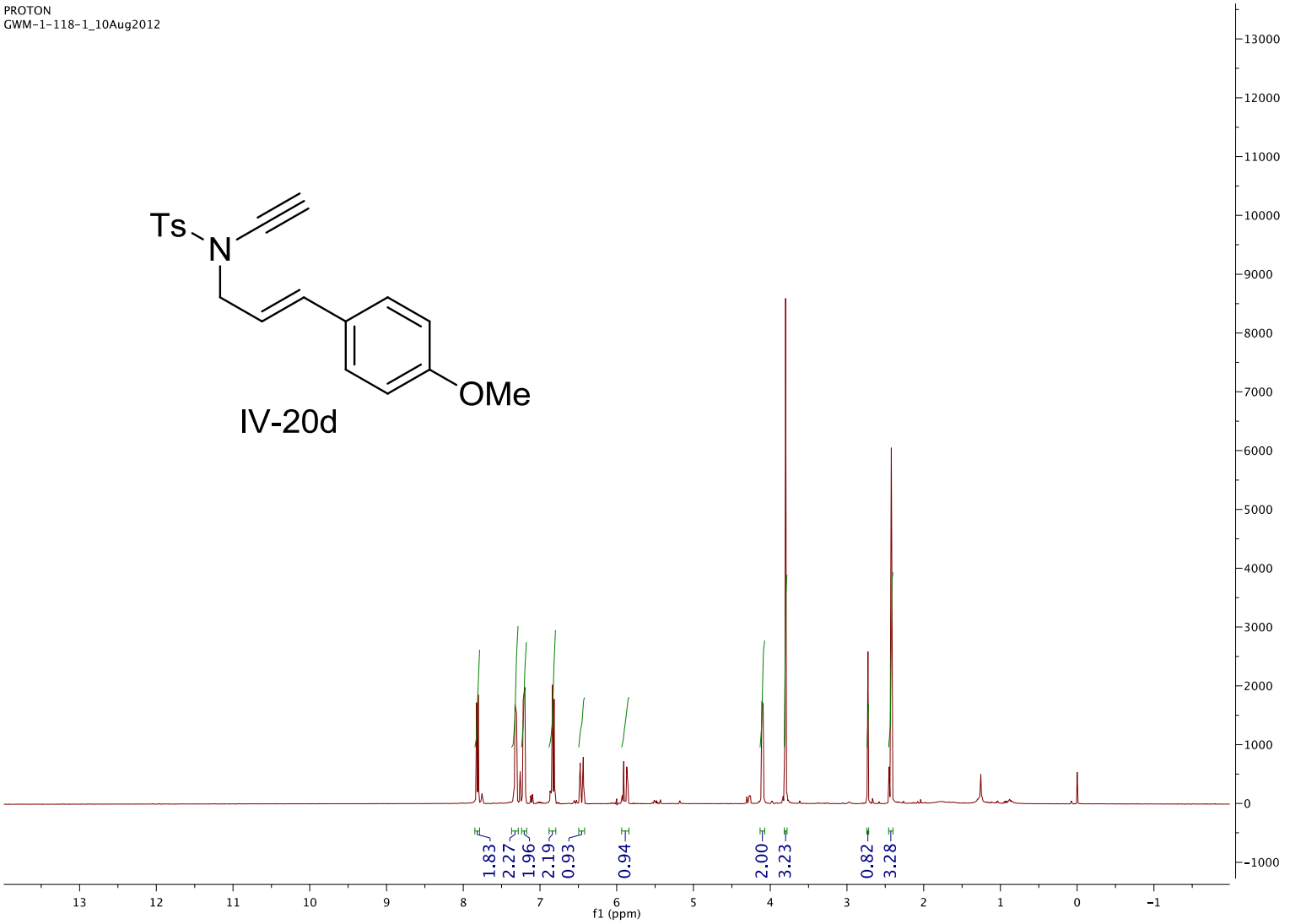


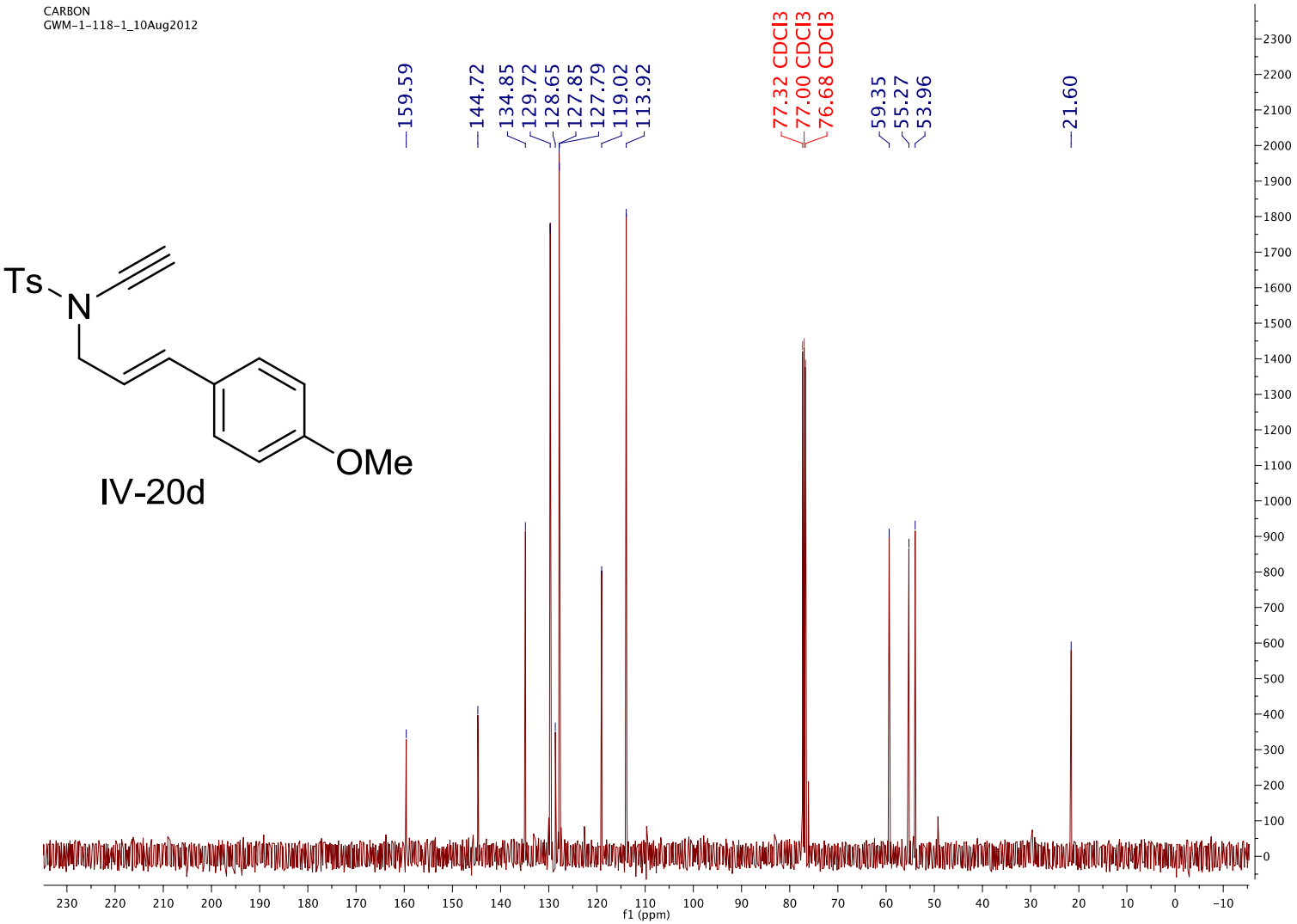

IV-20c

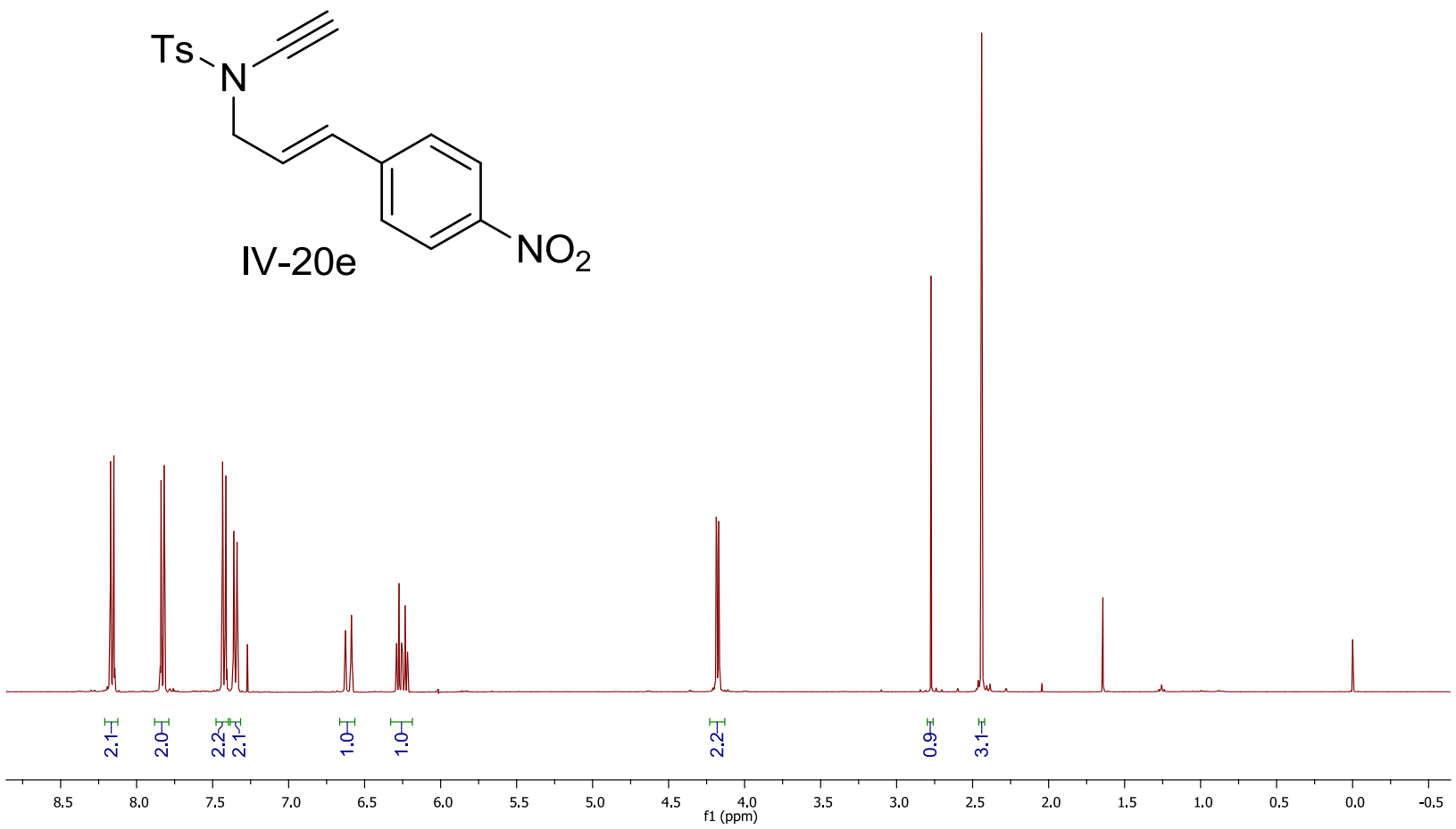


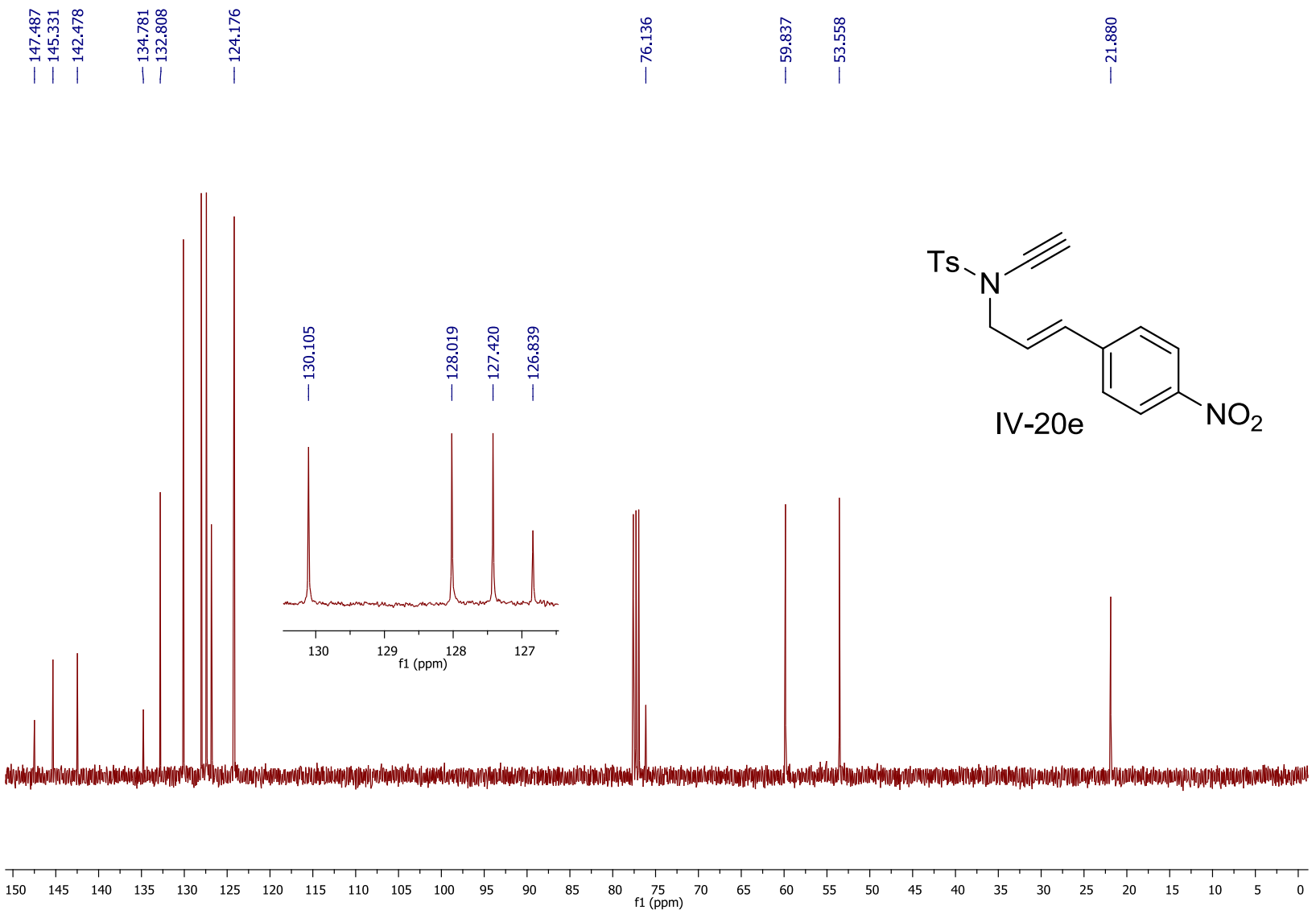

Ts
N
Ph
144.797
135.869
135.235
134.762
129.752
128.514
128.117
127.781
126.582
121.343
77.313
77.000
76.679
76.045
59.380
53.752
21.575
200
150
100
50
0 PPM

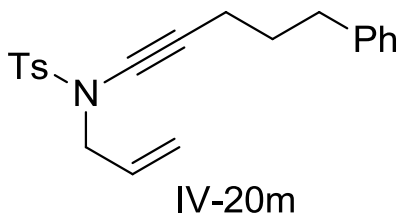
IV-20c


PROTON
GWM-1-118-1_10Aug2012
Ts
N
OMe
IV-20d
1.83
2.27
1.96
2.19
0.93
0.94
2.00
3.23
0.82
3.28
f1 (ppm)

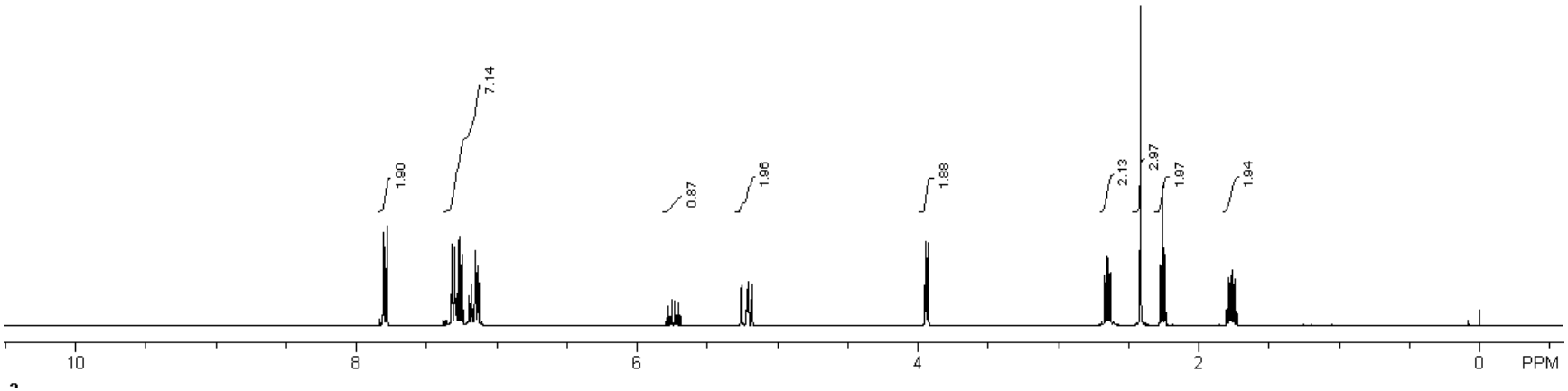

CARBON
GWM-1-118-1_10Aug2012
159.59
144.72
134.85
129.72
128.65
127.85
127.79
119.02
113.92
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
59.35
55.27
53.96
21.60
Ts
N
OMe
IV-20d
f1 (ppm)

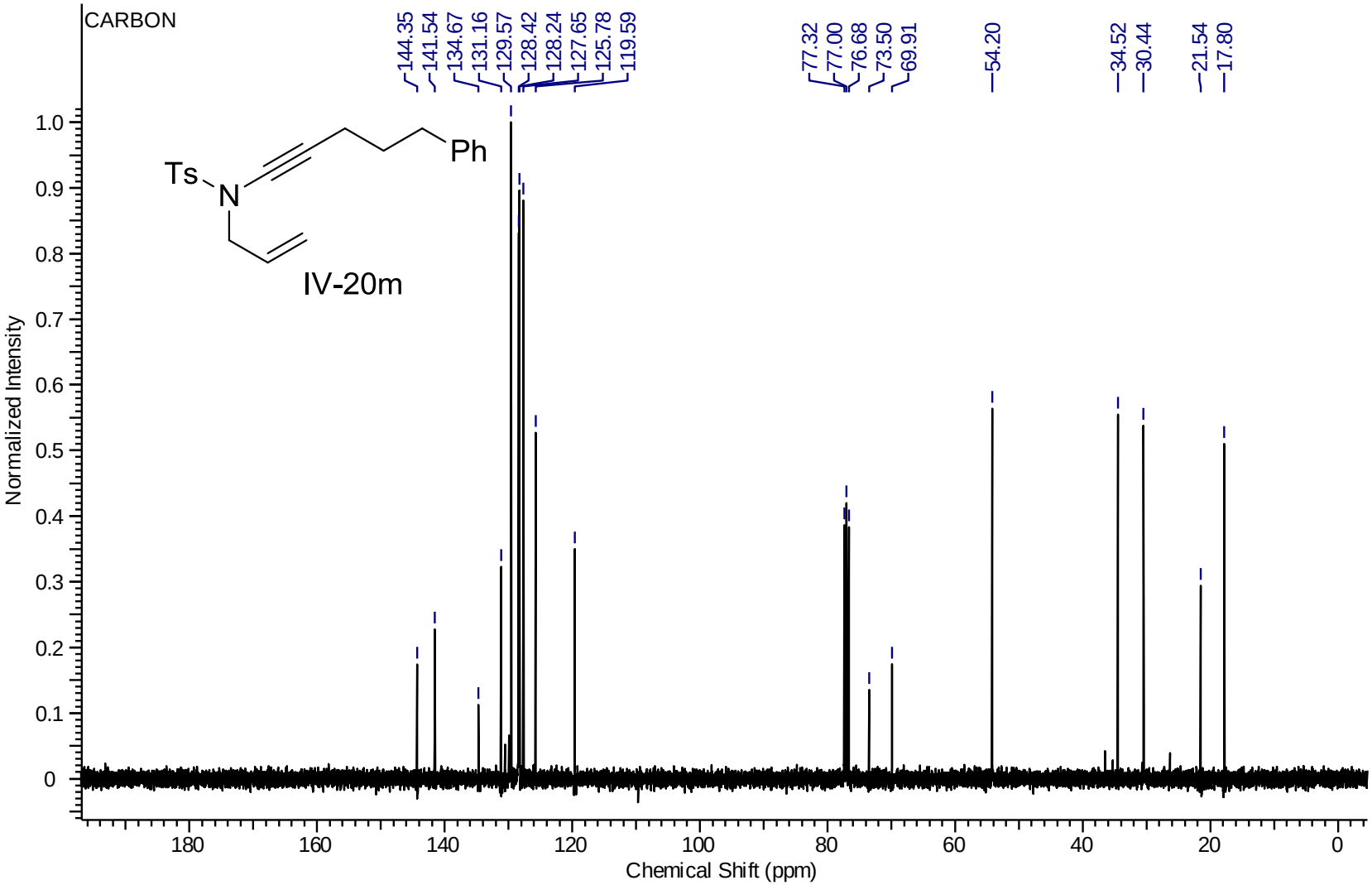

Ts
N
NO2
IV-20e
2.1
2.0
2.2
2.1
1.0
1.0
2.2
0.9
3.1
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


147.487
145.331
142.478
134.781
132.808
124.176
76.136
59.837
53.558
21.880
130.105
128.019
127.420
126.839
f1 (ppm)
f1 (ppm)
Ts
N
NO2
IV-20e

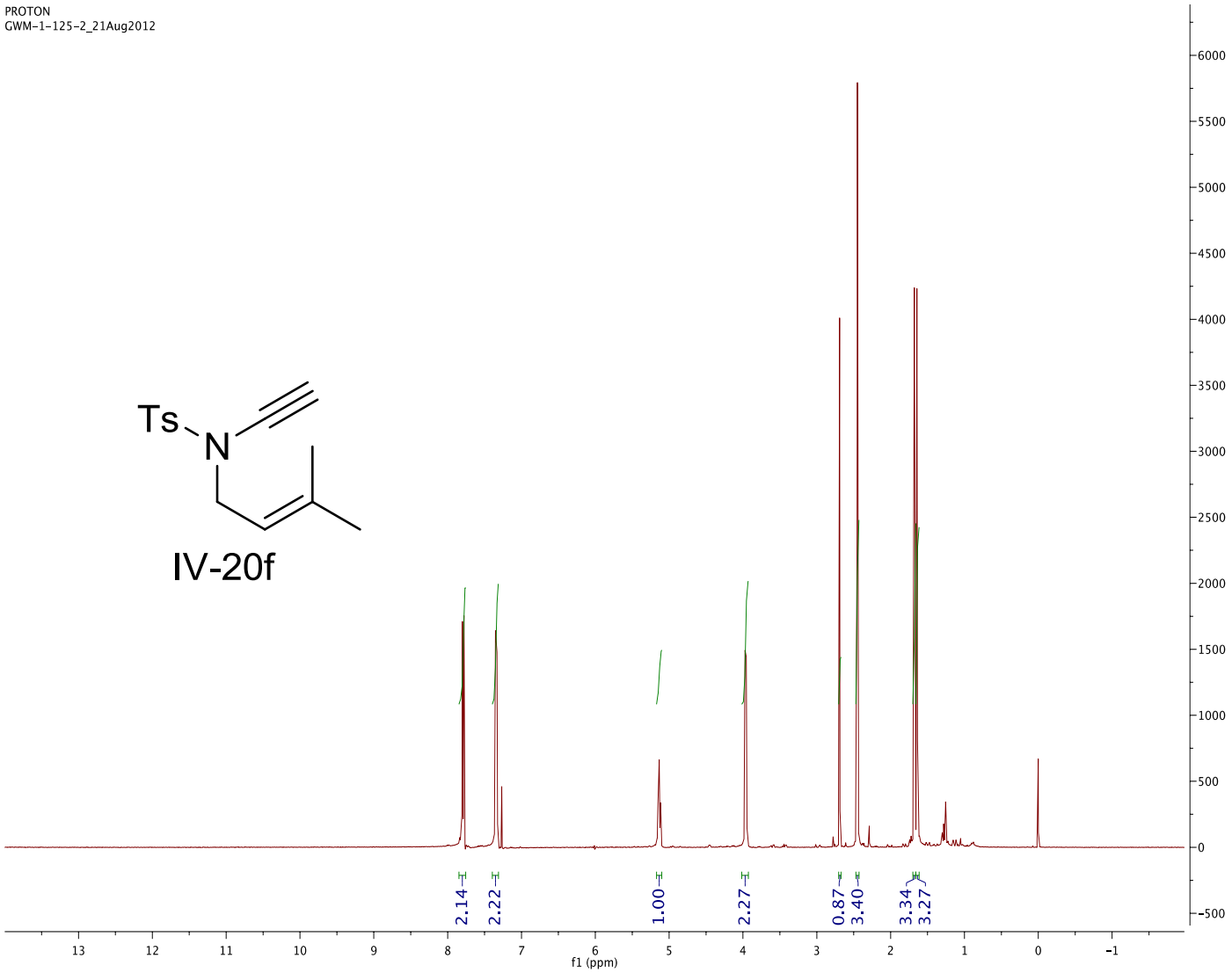


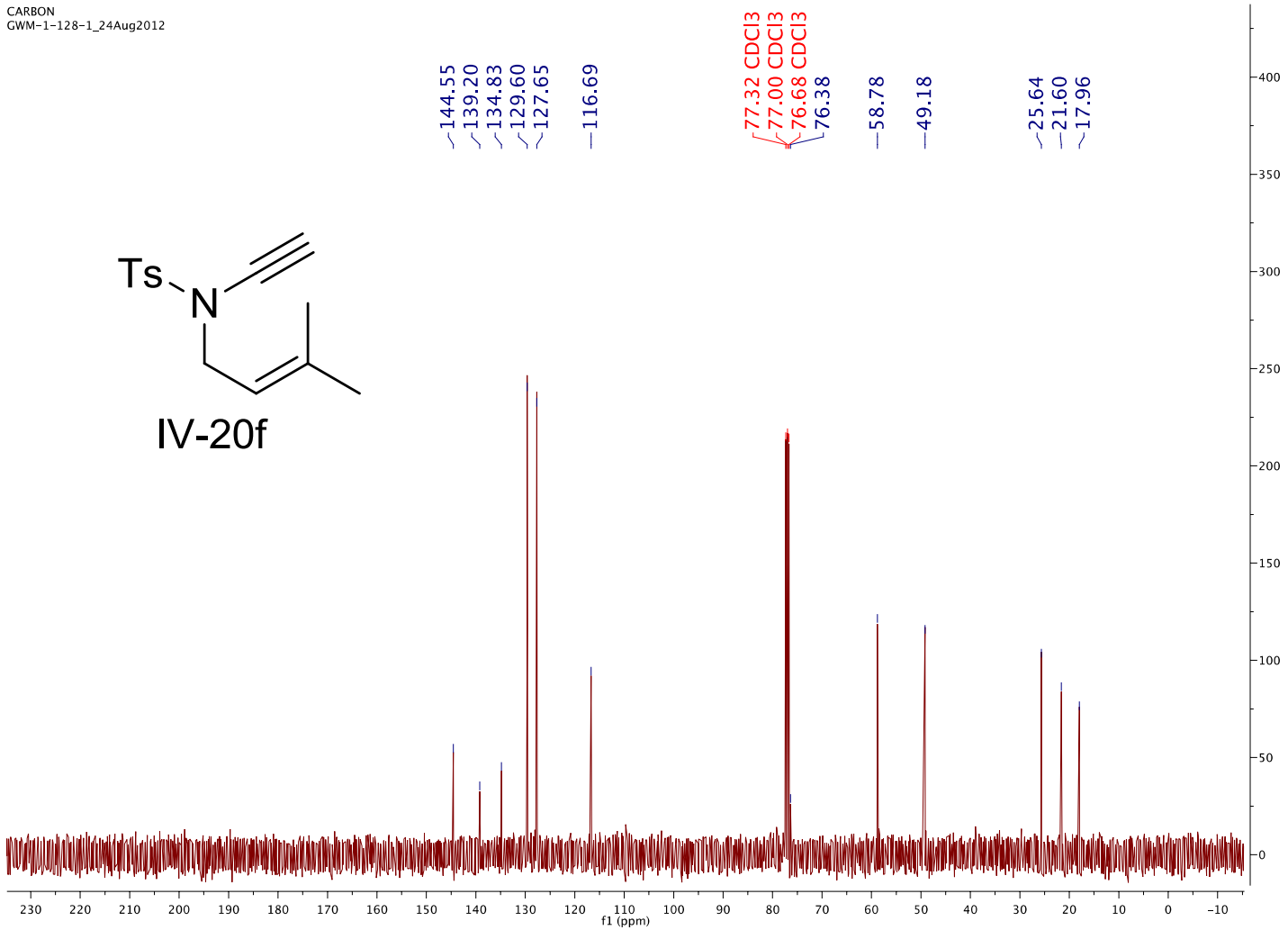

IV-20m

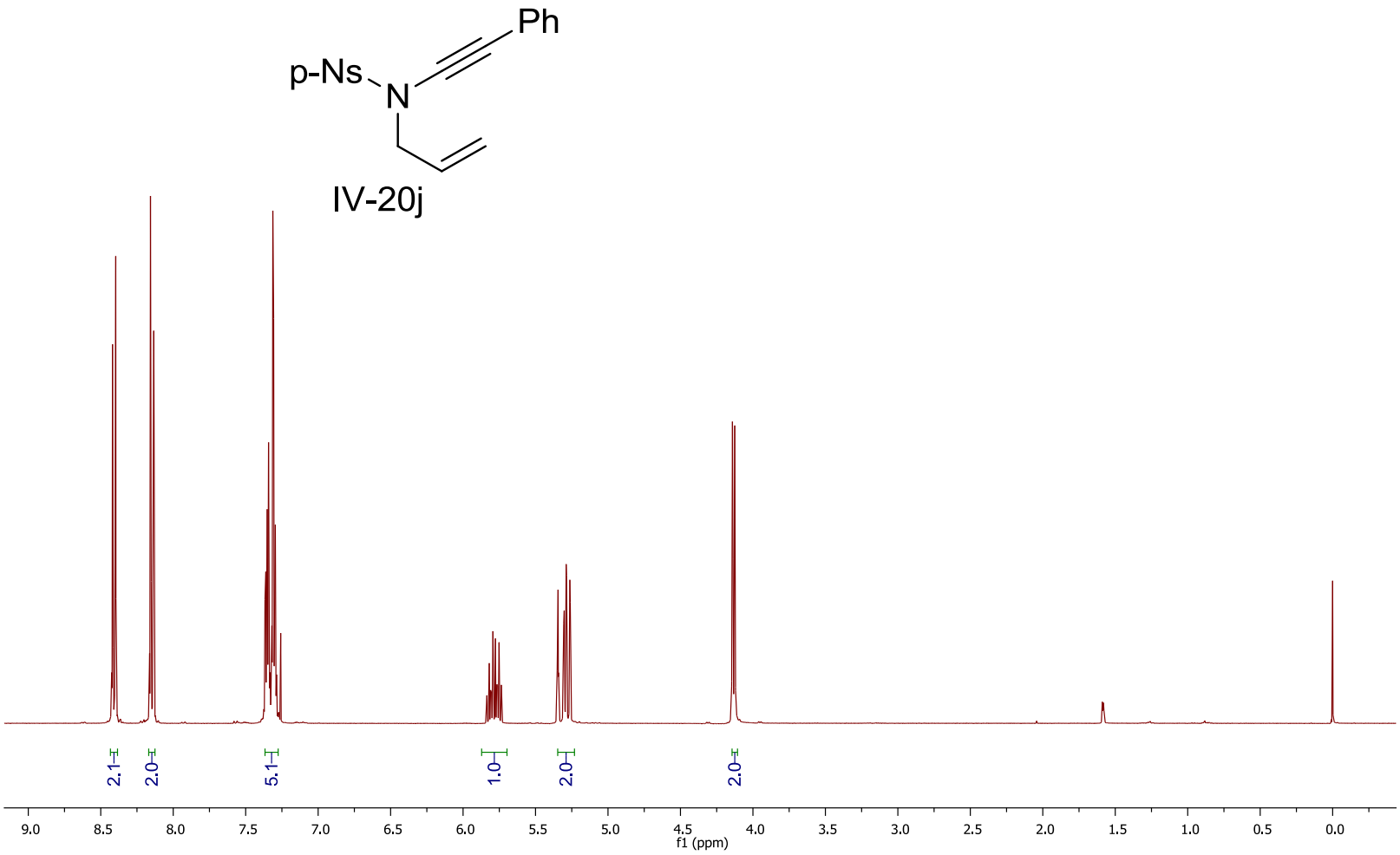


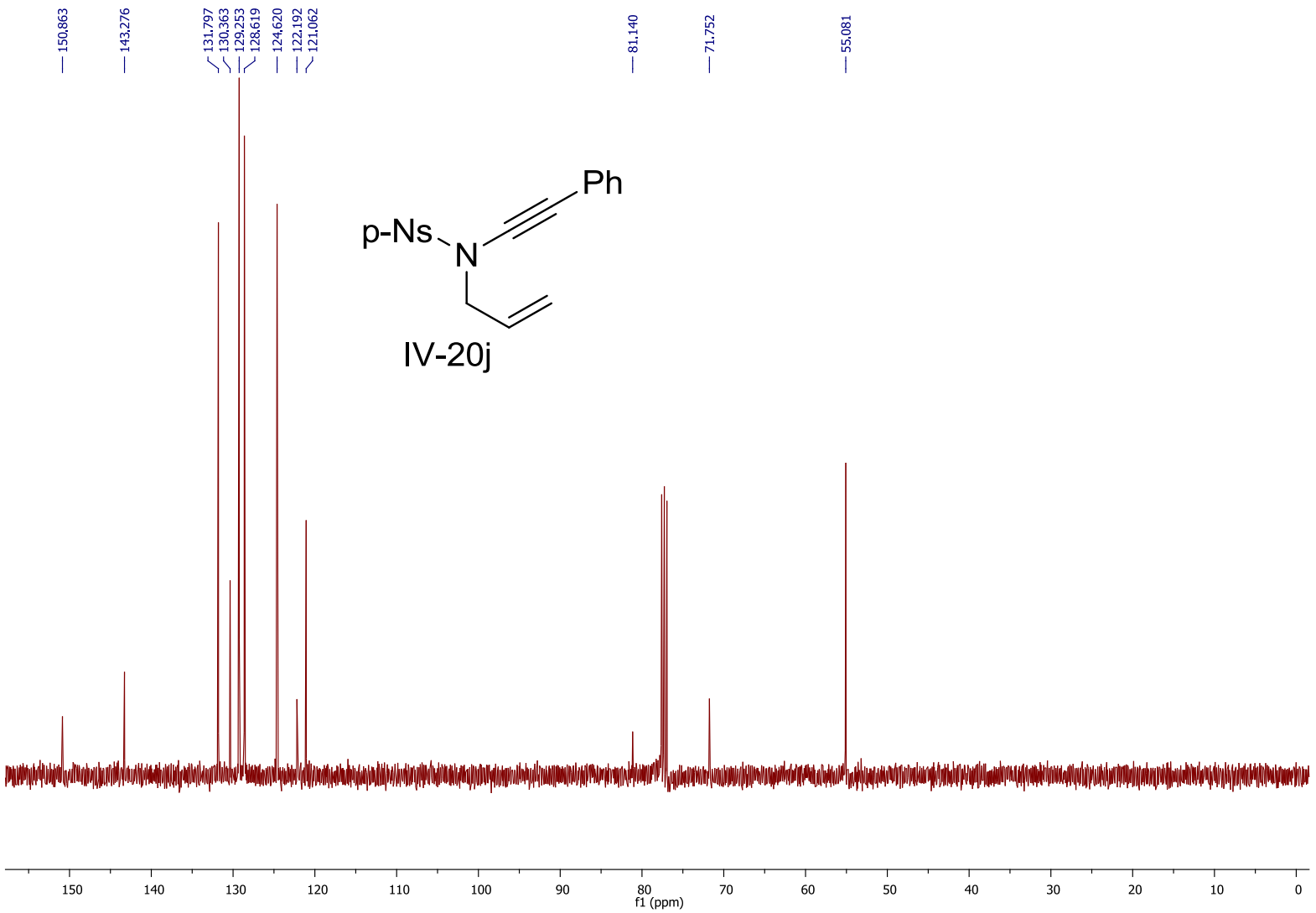

CARBON
144.35
141.54
134.67
131.16
129.57
128.42
128.24
127.65
125.78
119.59
77.32
77.00
76.68
73.50
69.91
54.20
34.52
30.44
21.54
17.80
Ts
N
Ph
IV-20m
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

PROTON
GWM-1-125-2_21Aug2012

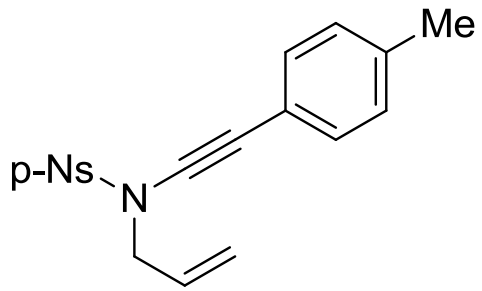



CARBON
GWM-1-128-1_24Aug2012
144.55
139.20
134.83
129.60
127.65
116.69
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
76.38
58.78
49.18
25.64
21.60
17.96
Ts
N
IV-20f
f1 (ppm)

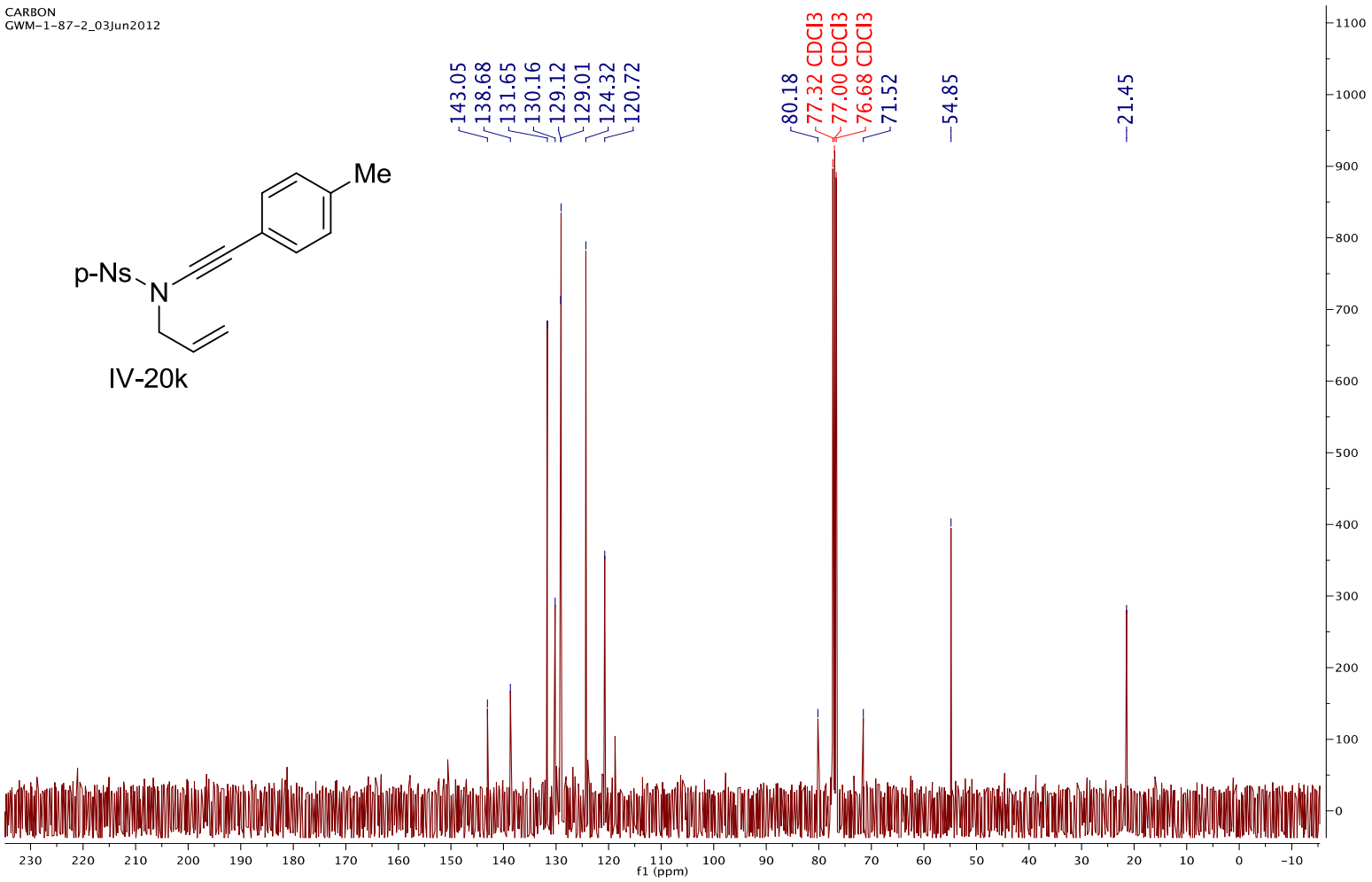

Ph
p-Ns
N
IV-20j
2.1
2.0
5.1
1.0
2.0
2.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

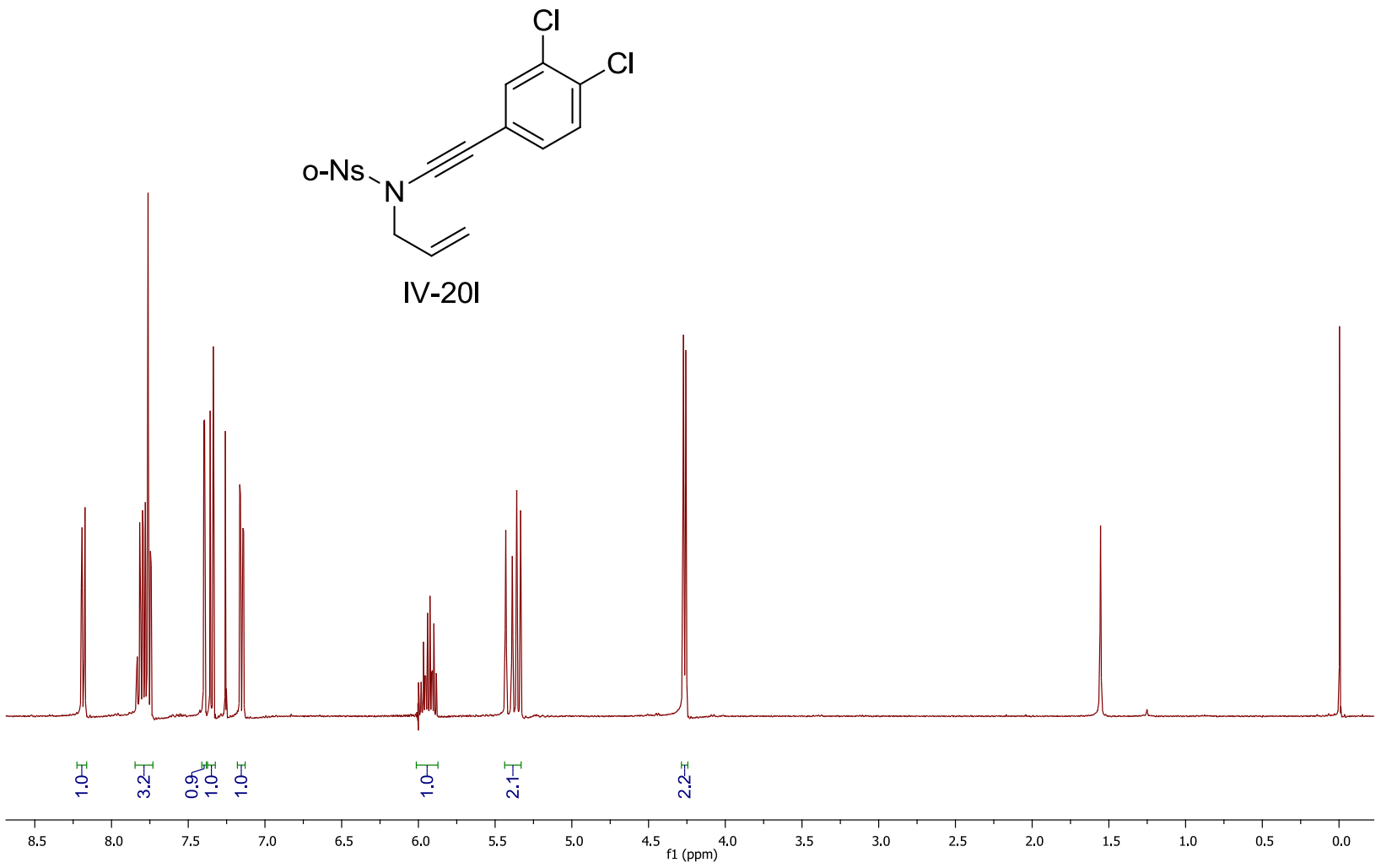

150.863
143.276
131.797
130.363
129.253
128.619
124.620
122.192
121.062
81.140
71.752
55.081
Ph
p-Ns
N
IV-20j
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

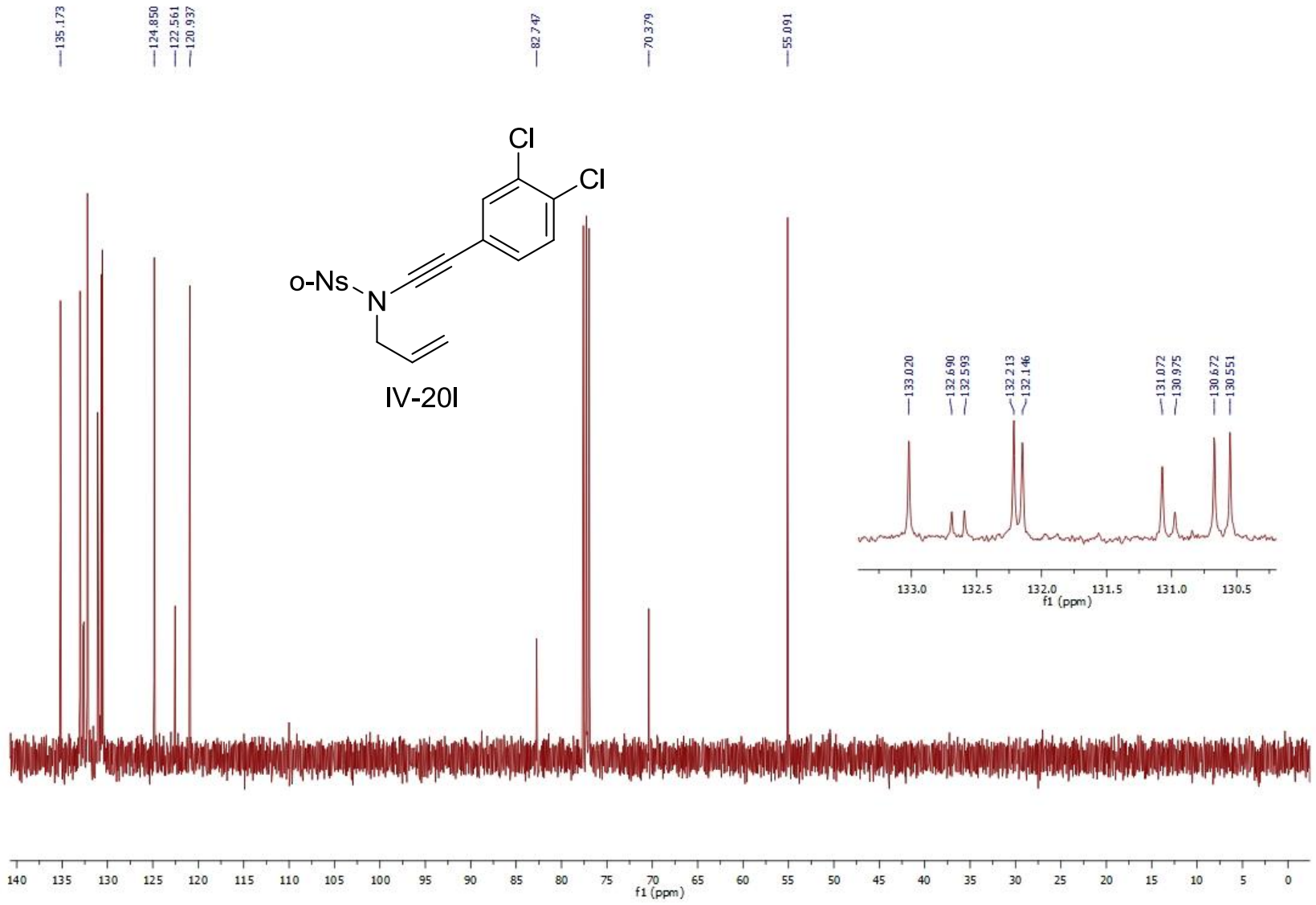
PROTON
GWM-1-87-2_03Jun2012

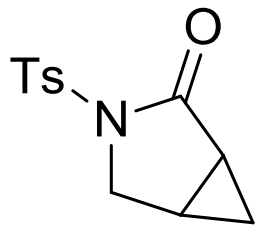



IV-20k

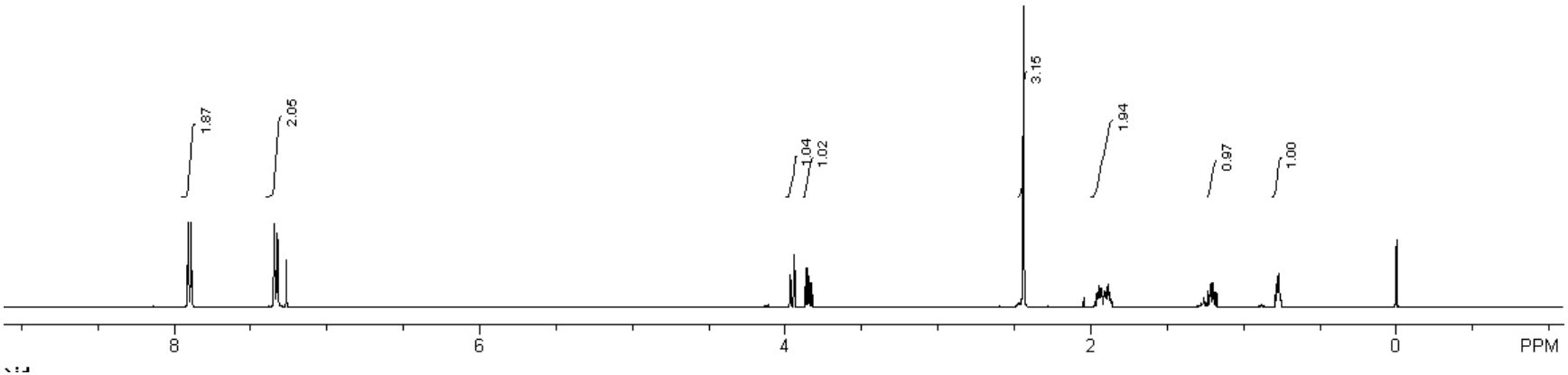

CARBON
GWM-1-87-2_03Jun2012
143.05
138.68
131.65
130.16
129.12
129.01
124.32
120.72
80.18
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
71.52
54.85
21.45
Me
p-Ns
N
IV-20k
f1 (ppm)

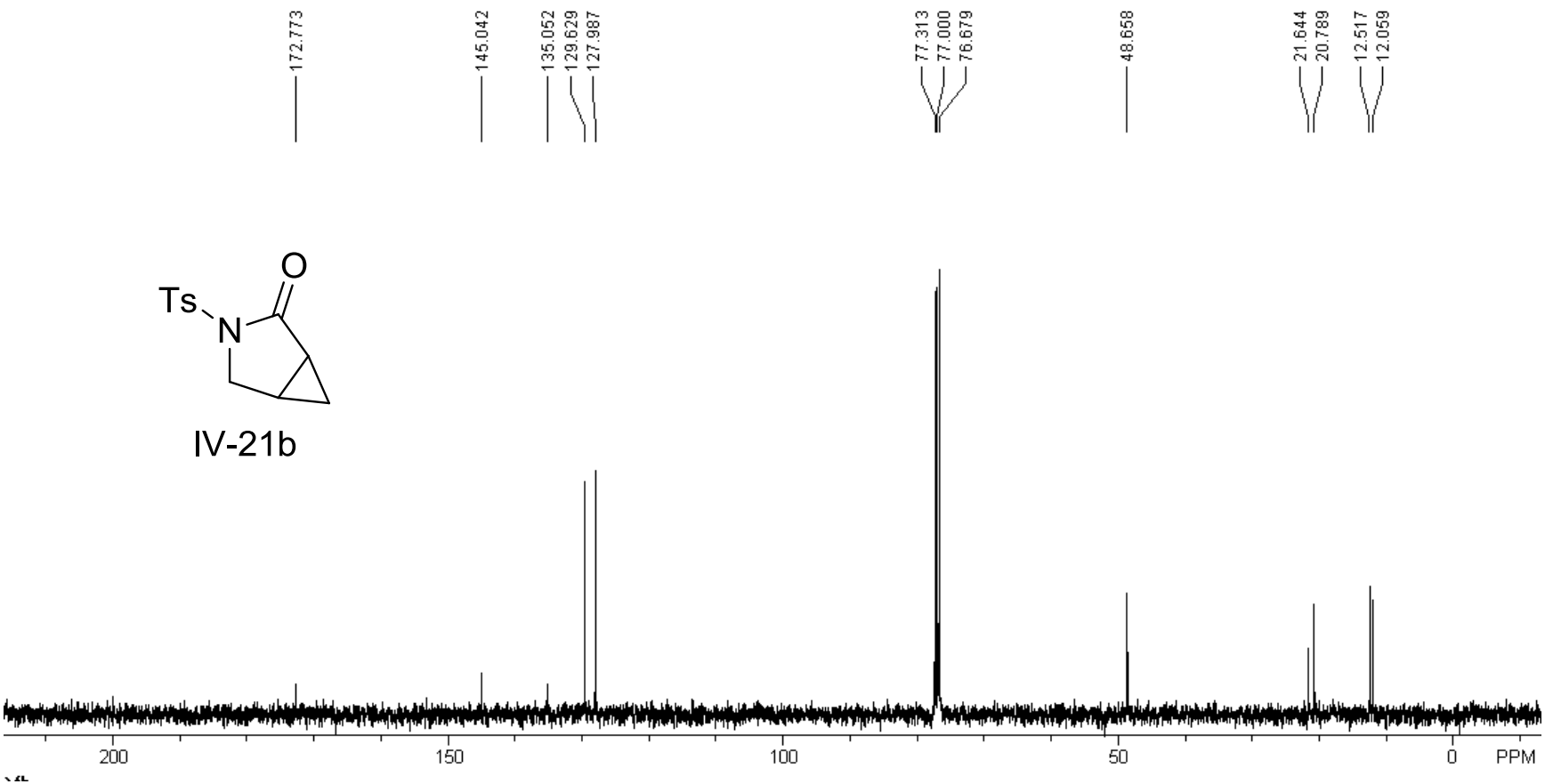

Cl
Cl
o-Ns
N
IV-20l
1.0
3.2
0.9
1.0
1.0
1.0
2.1
2.2
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


135.173
124.850
122.561
120.937
82.747
70.379
55.091
Cl
Cl
o-Ns
N
IV-20l
133.020
132.690
132.593
132.213
132.146
131.072
130.975
130.672
130.551
133.0
132.5
132.0
131.5
131.0
130.5
f1 (ppm)
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)

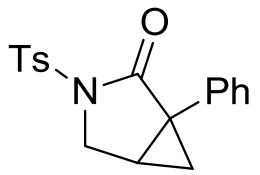



IV-21b

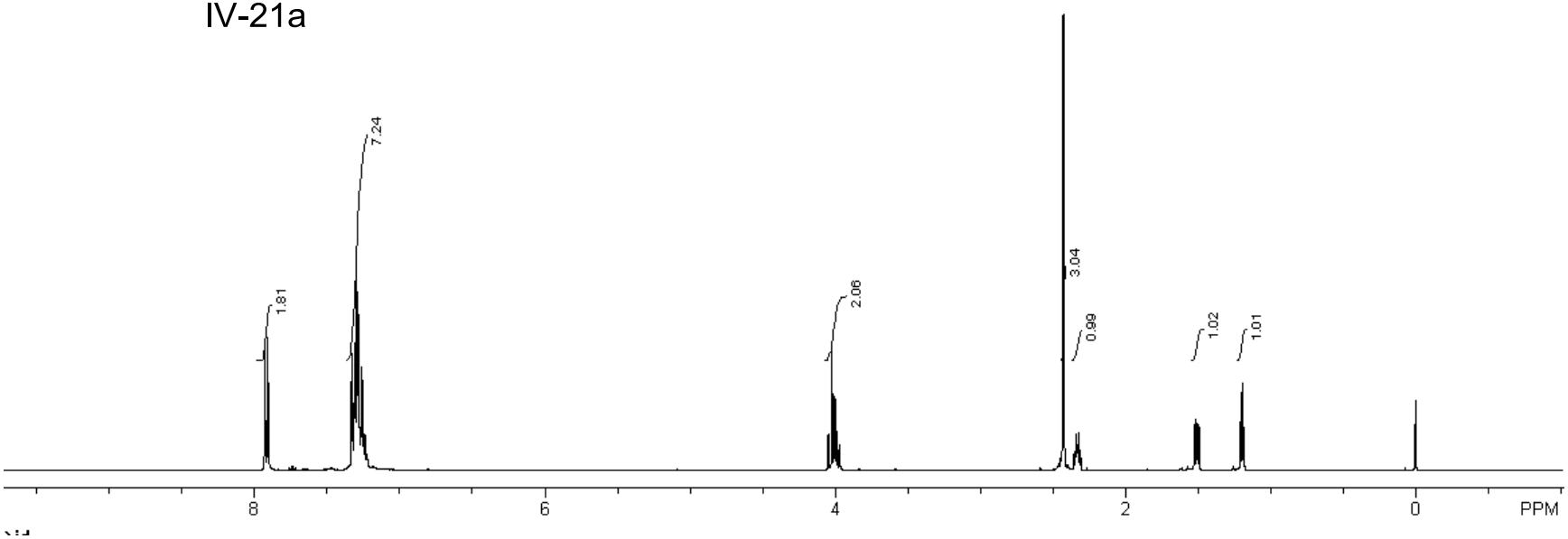


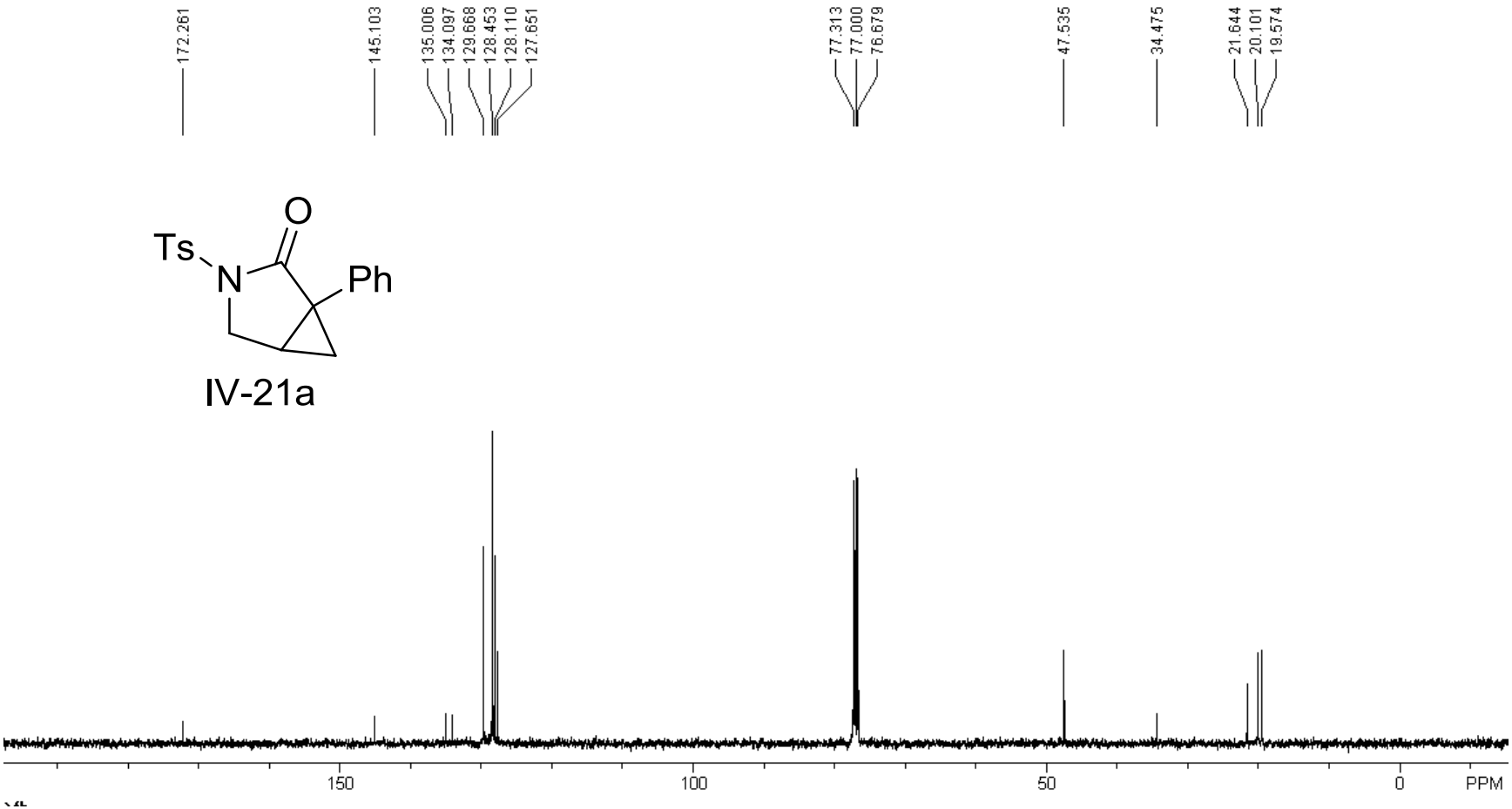

172.773
145.042
135.052
129.629
127.987
77.313
77.000
76.679
48.658
21.644
20.789
12.517
12.059
Ts
N
O
200
150
100
50
0
PPM

IV-21b

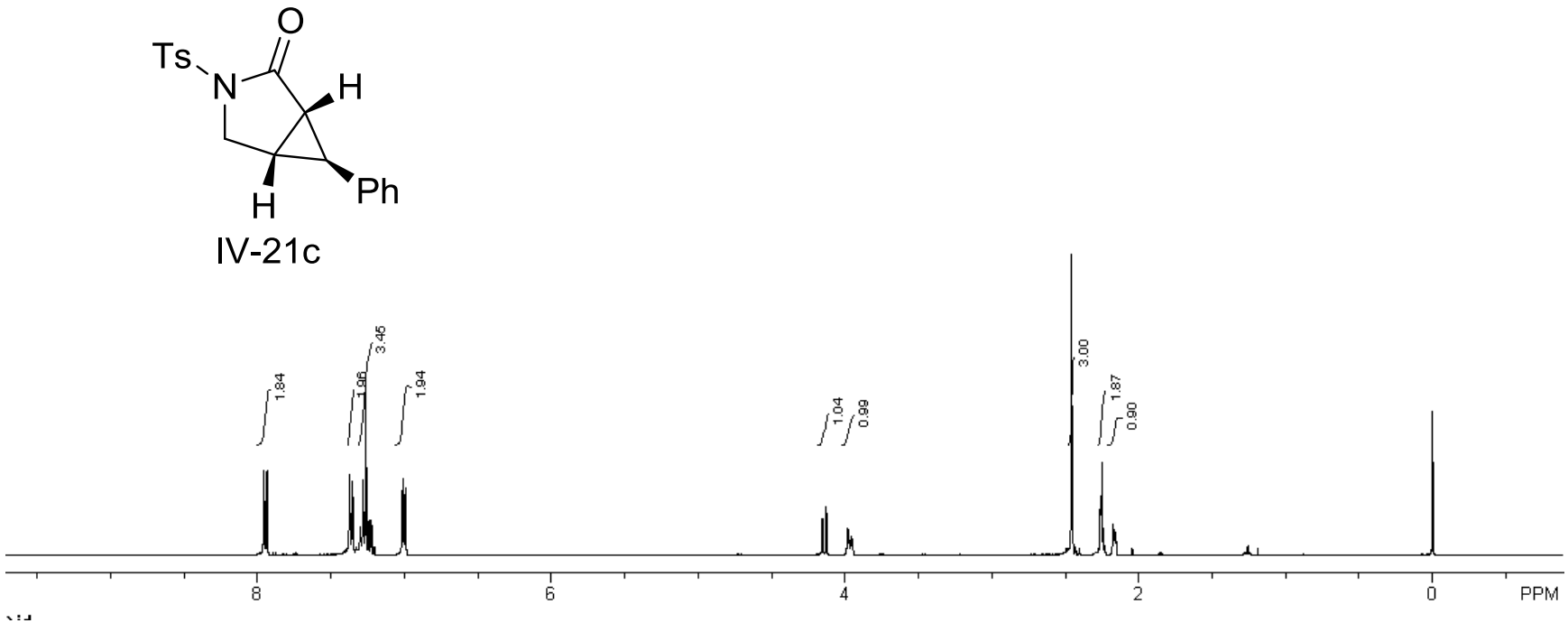


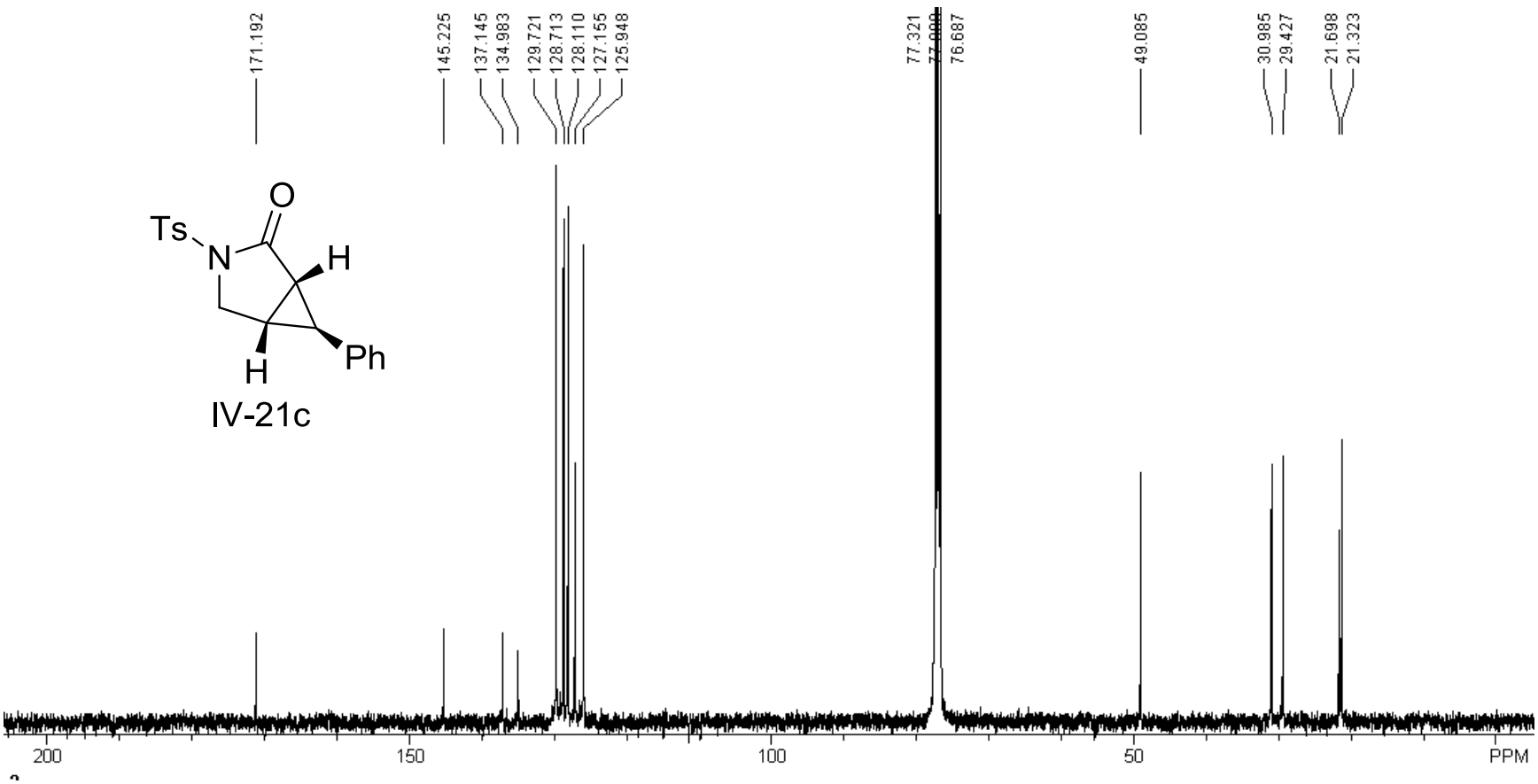

IV-21a



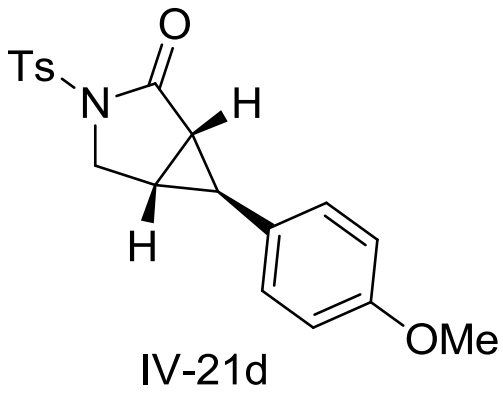

172.261
145.103
135.006
134.097
129.668
128.453
128.110
127.651
77.313
77.000
76.679
47.535
34.475
21.644
20.101
19.574
O
Ts
N
Ph
150
100
50
0
PPM

IV-21a

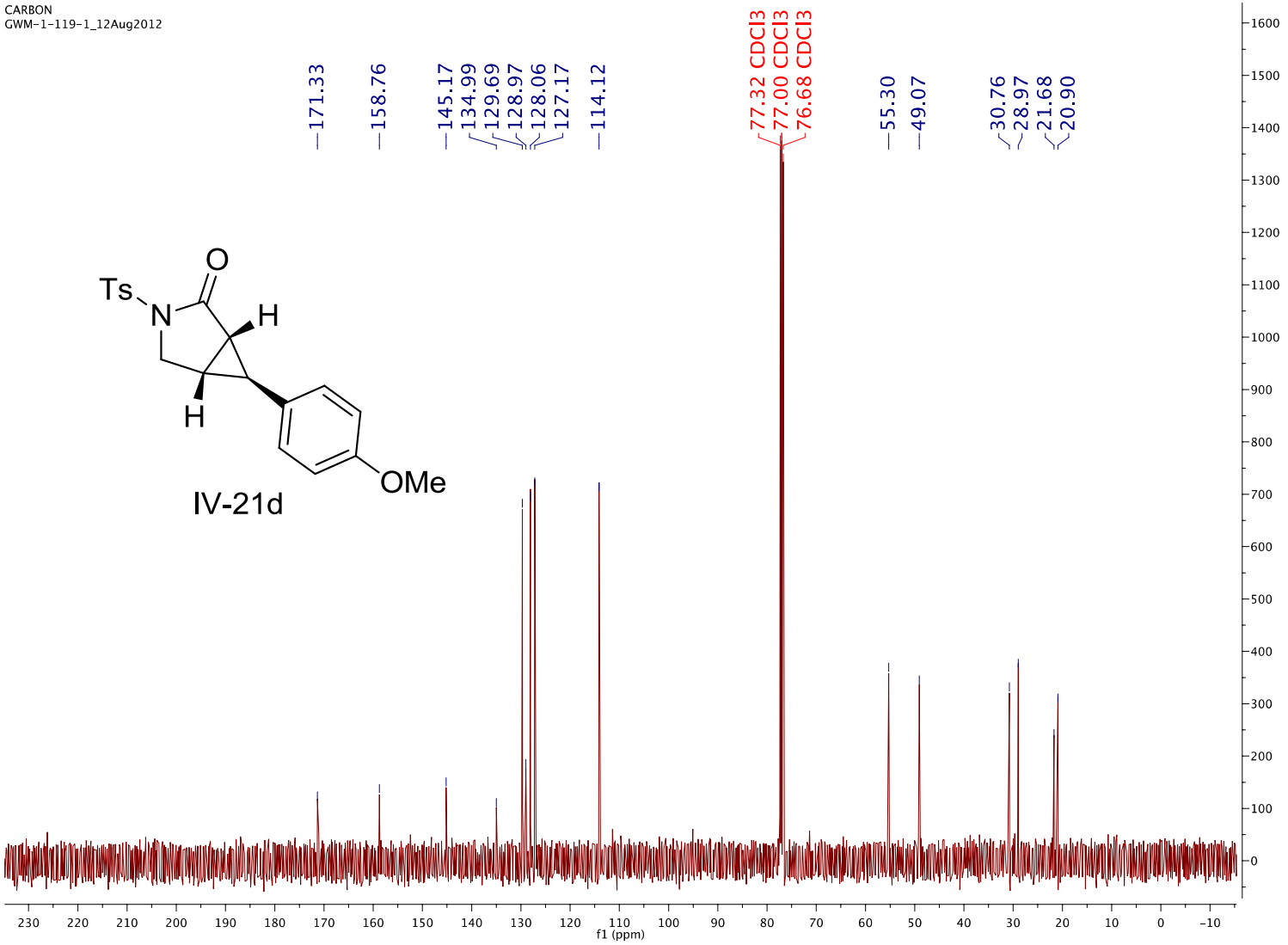

O
Ts
N
H
H
Ph
IV-21c
1.84
1.96
3.45
1.94
1.04
0.99
3.00
1.87
0.90
8
6
4
2
0
PPM

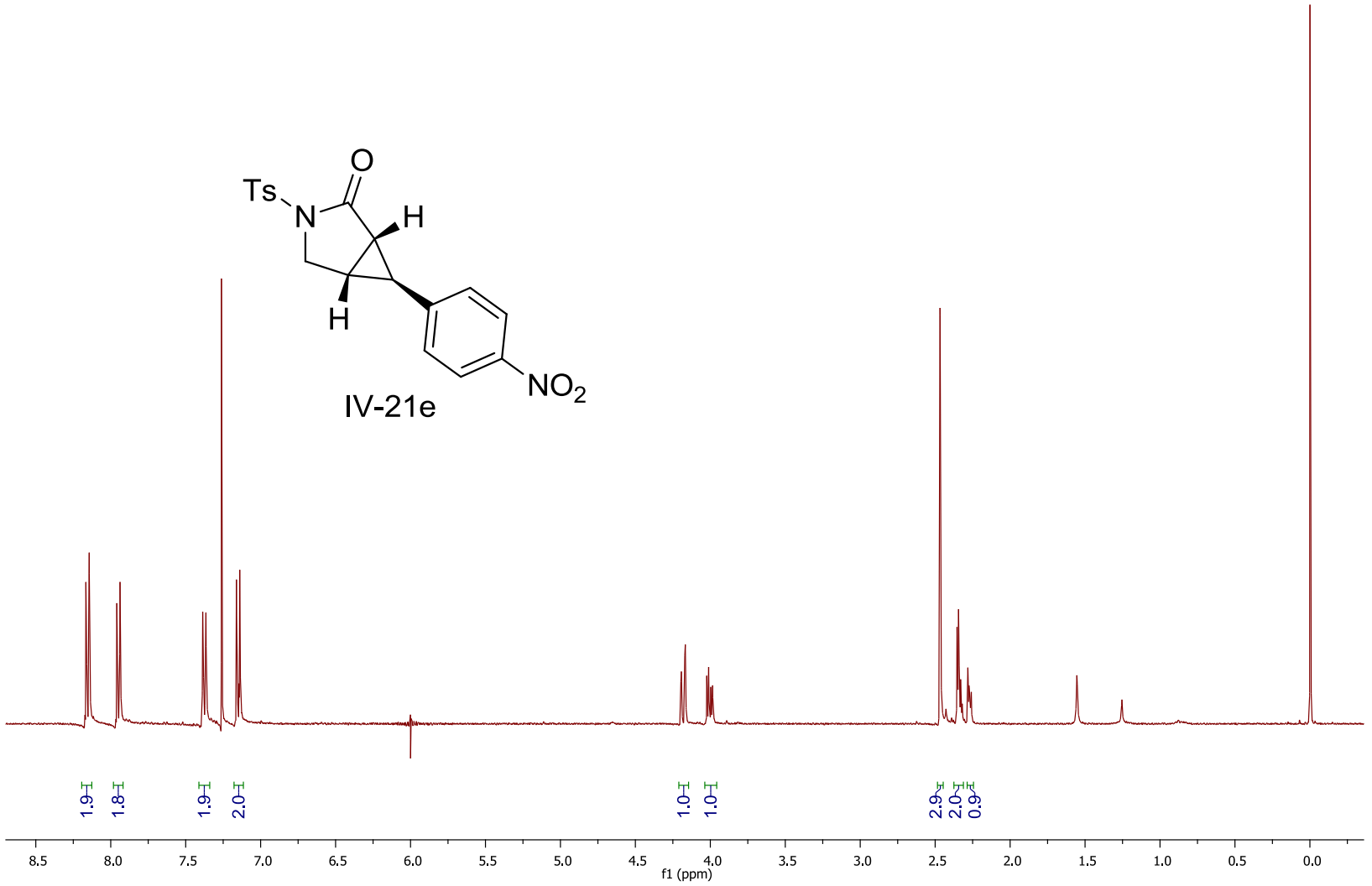

171.192
145.225
137.145
134.983
129.721
128.713
128.110
127.155
125.948
77.321
77.000
76.687
49.085
30.985
29.427
21.698
21.323
O
Ts
N
H
H
Ph
IV-21c
200
150
100
50
PPM

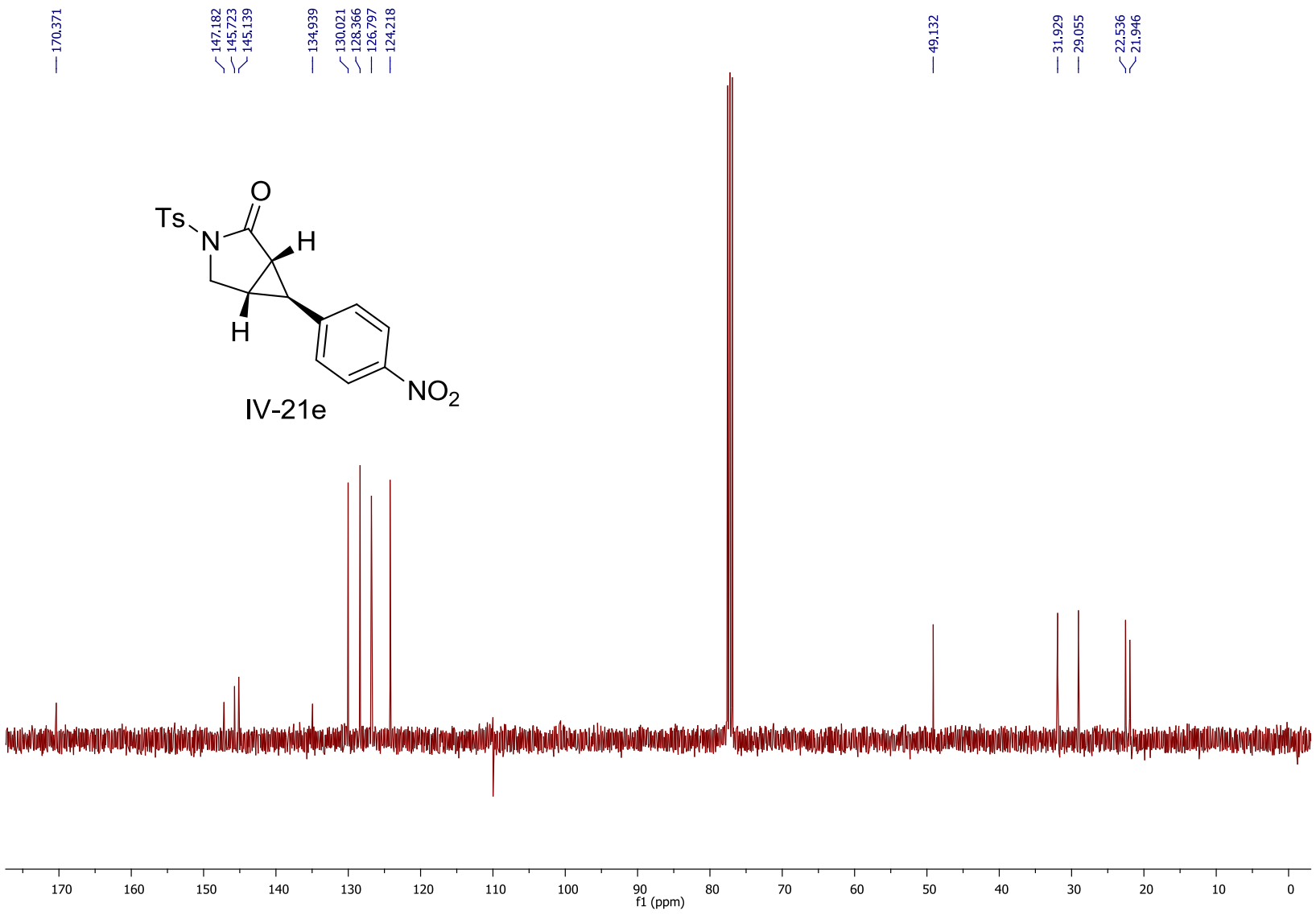
PROTON
GWM-1-119-1_12Aug2012



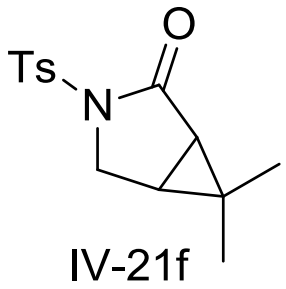

IV-21d


CARBON
GWM-1-119-1_12Aug2012
171.33
158.76
145.17
134.99
129.69
128.97
128.06
127.17
114.12
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
55.30
49.07
30.76
28.97
21.68
20.90
Ts
N
O
H
H
OMe
IV-21d
f1 (ppm)

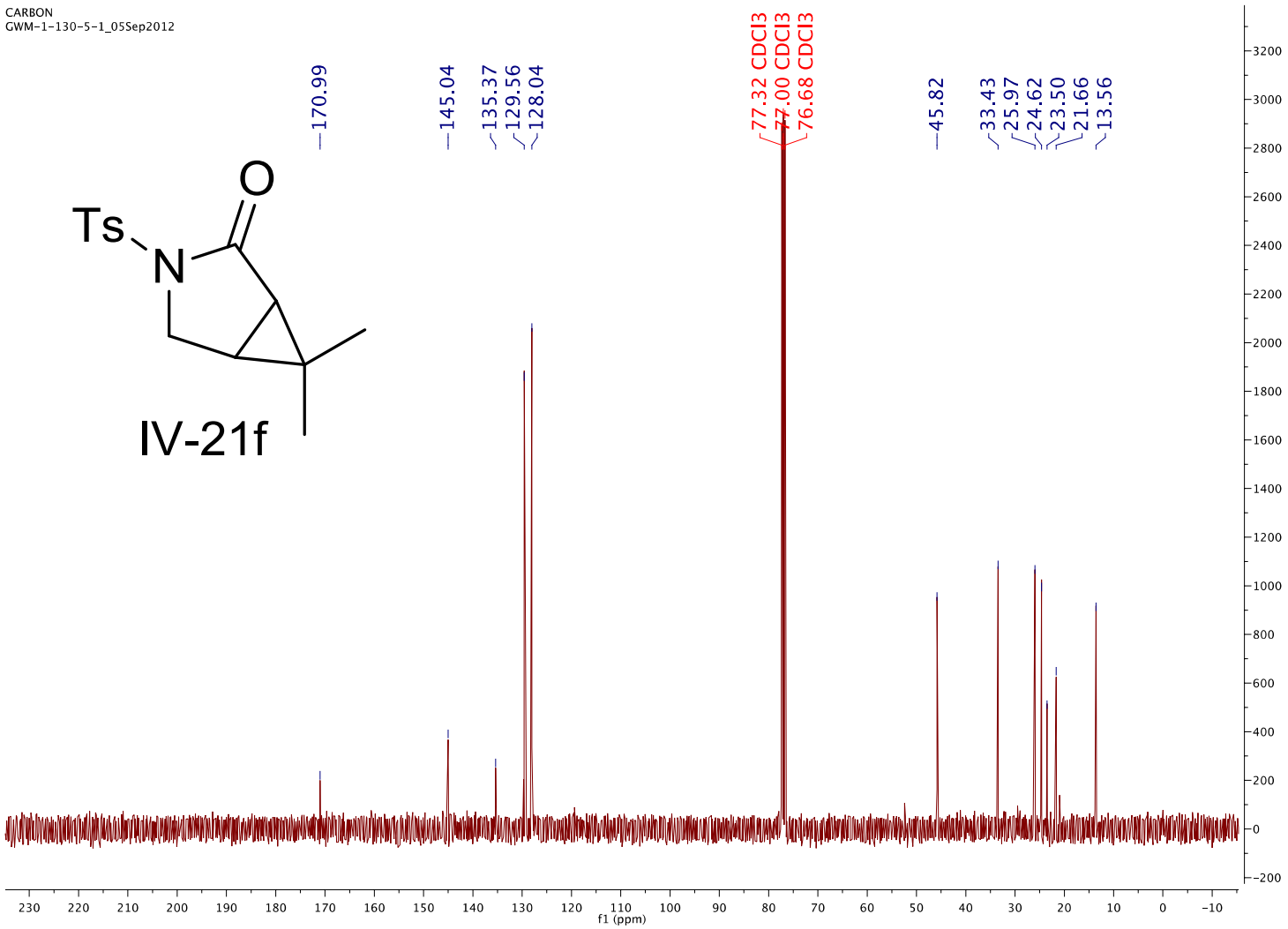

O
Ts
N
H
H
NO2
IV-21e
1.9
1.8
1.9
2.0
1.0
1.0
2.9
2.0
0.9
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

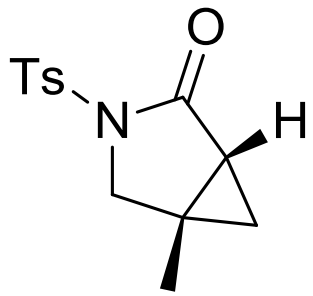

170.371
147.182
145.723
145.139
134.939
130.021
128.366
126.797
124.218
49.132
31.929
29.055
22.536
21.946
Ts
N
O
H
H
NO2
IV-21e
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

PROTON
gwm-1-130-6-4_07Sep2012

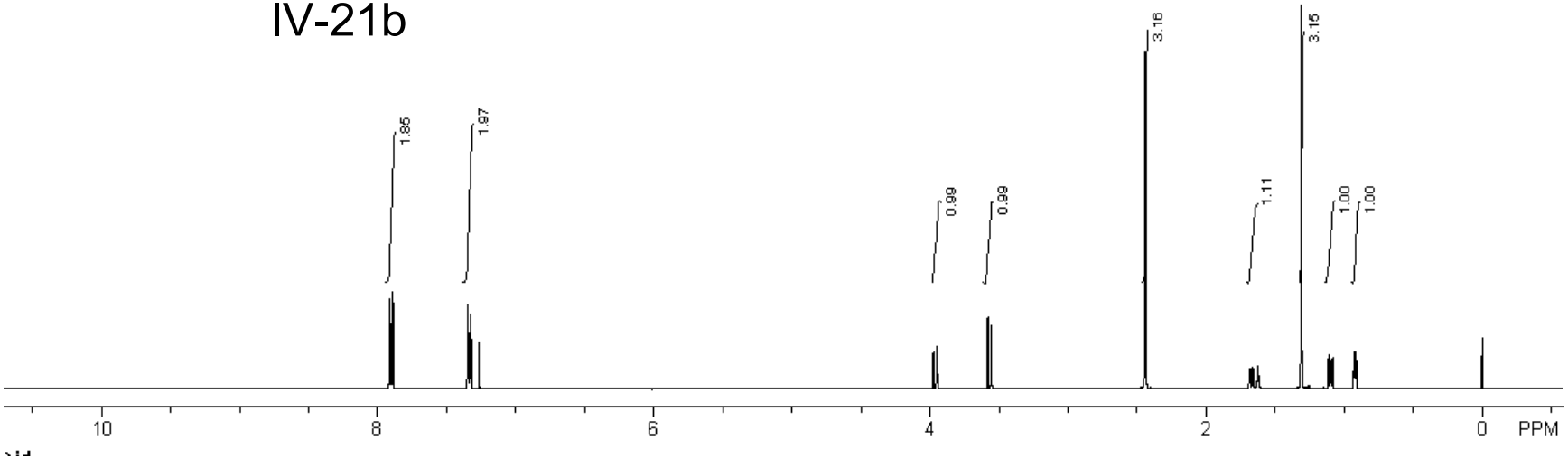


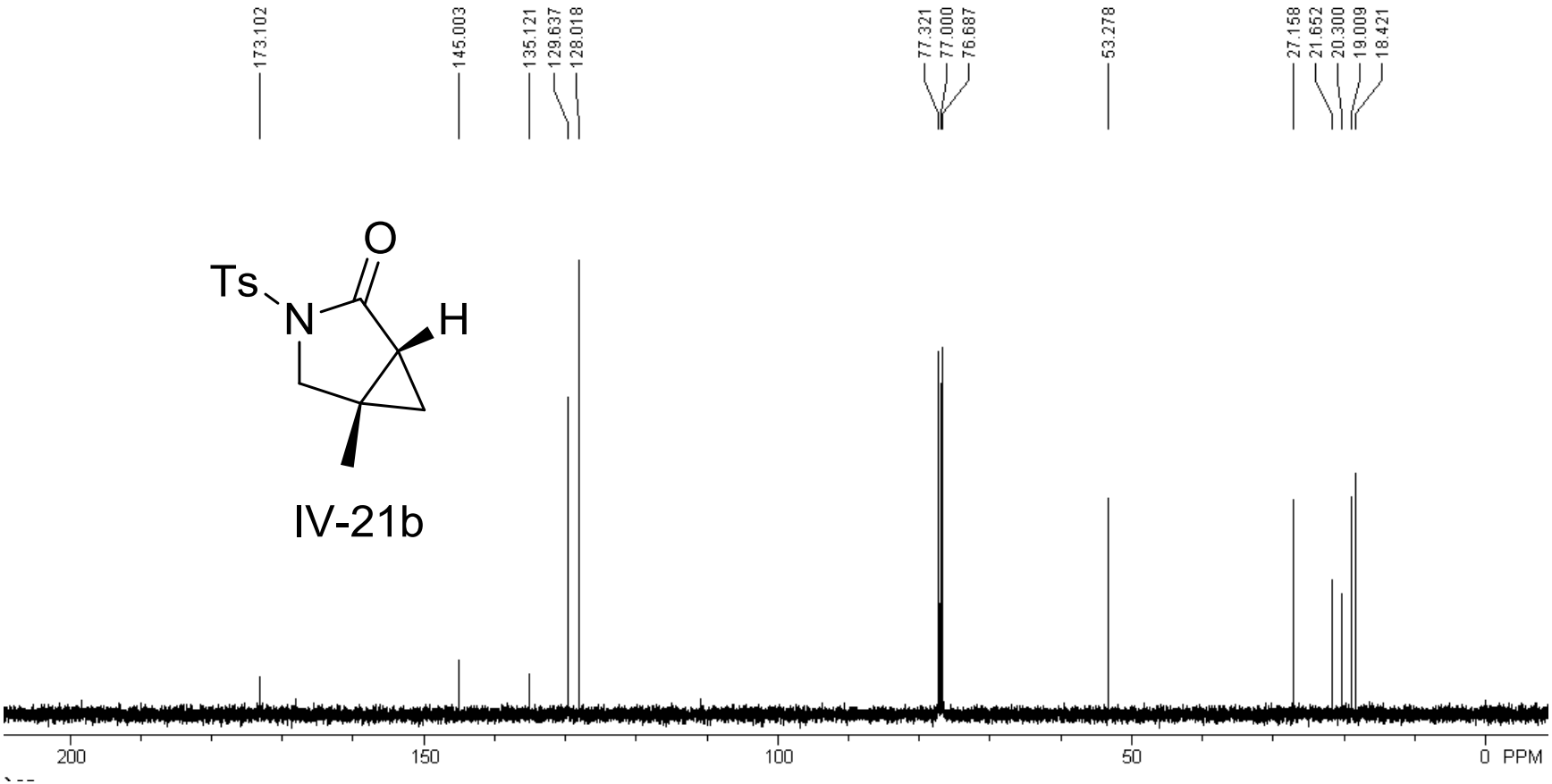

IV-21f

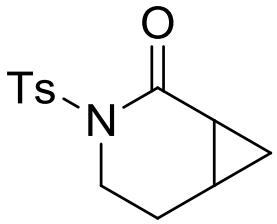

CARBON
GWM-1-130-5-1_05Sep2012
170.99
145.04
135.37
129.56
128.04
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
45.82
33.43
25.97
24.62
23.50
21.66
13.56
Ts
N
O
IV-21f
f1 (ppm)



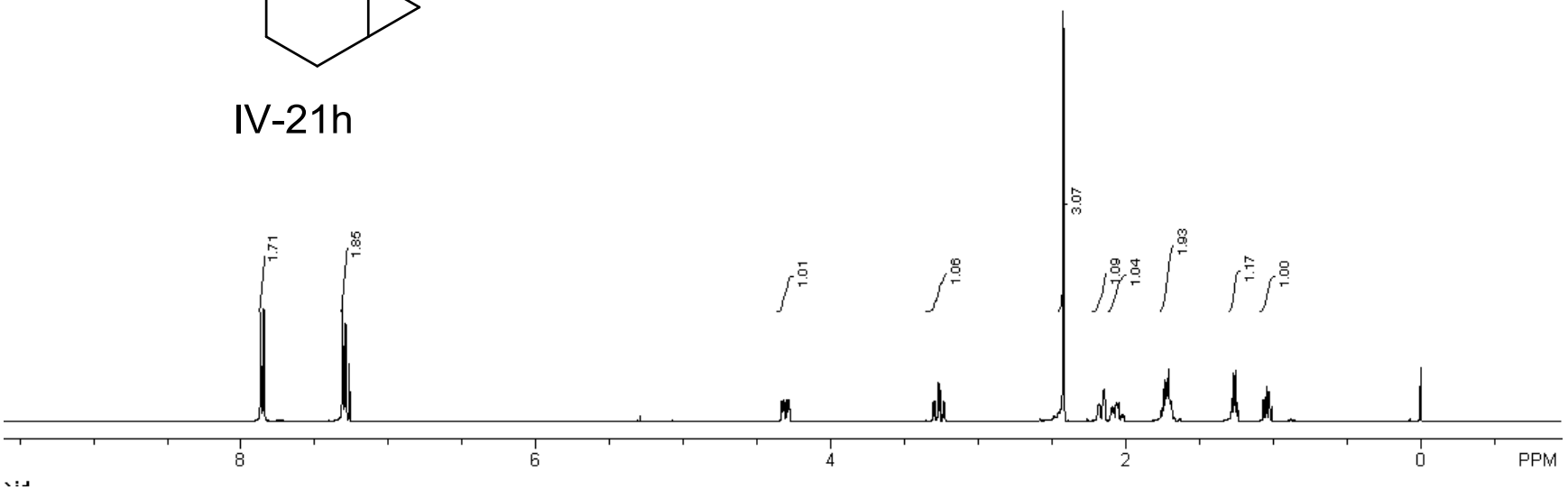

IV-21b

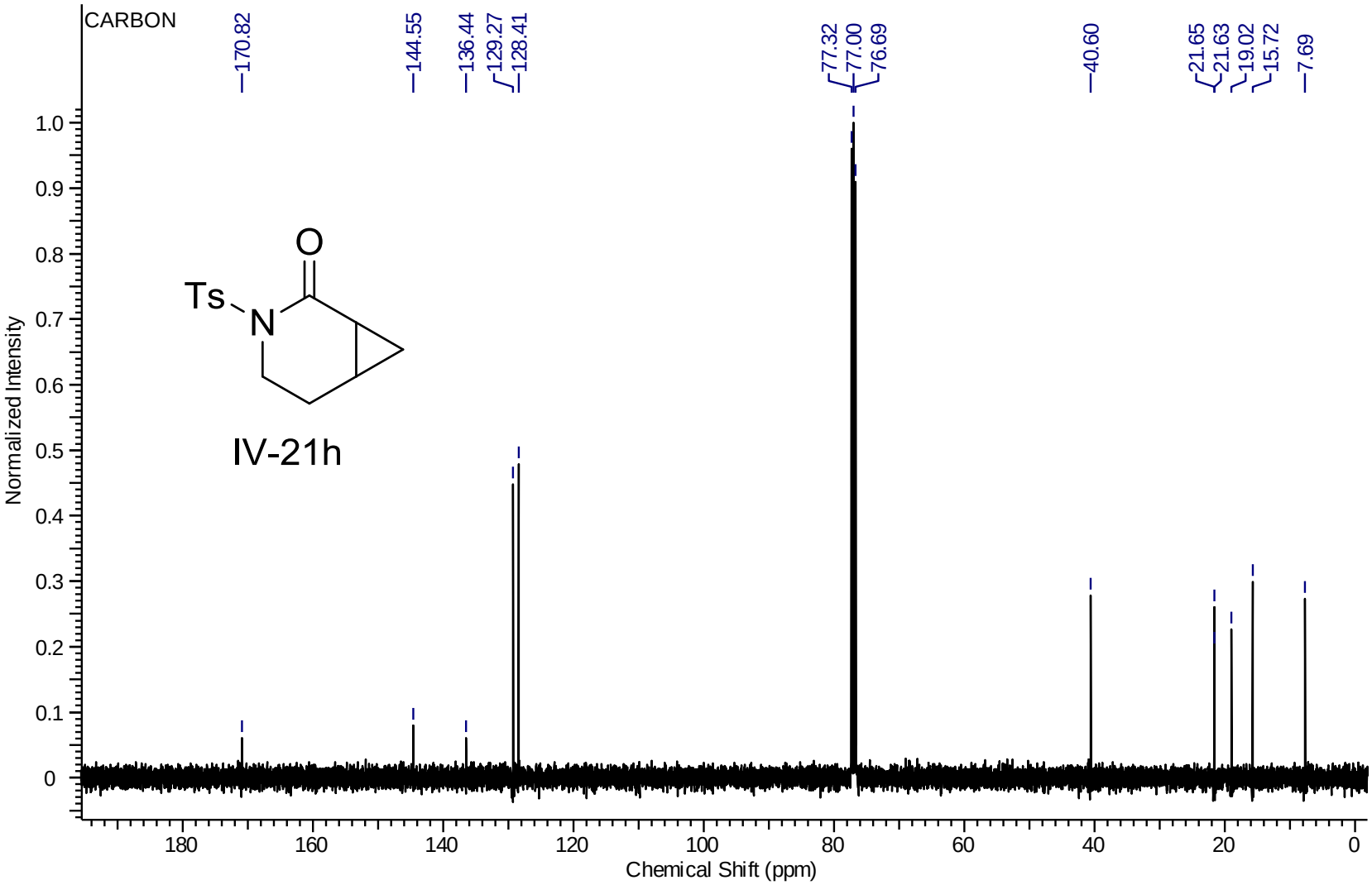


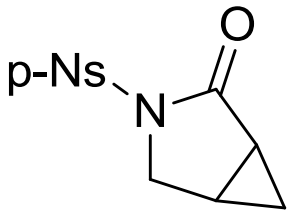

173.102
145.003
135.121
129.637
128.018
77.321
77.000
76.687
53.278
27.158
21.652
20.300
19.009
18.421
O
Ts
N
H
IV-21b
200
150
100
50
0 PPM



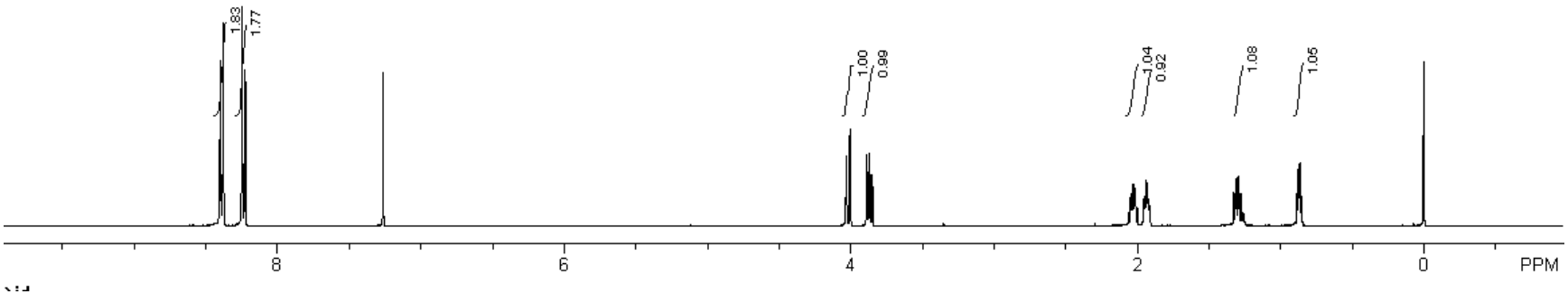

IV-21h

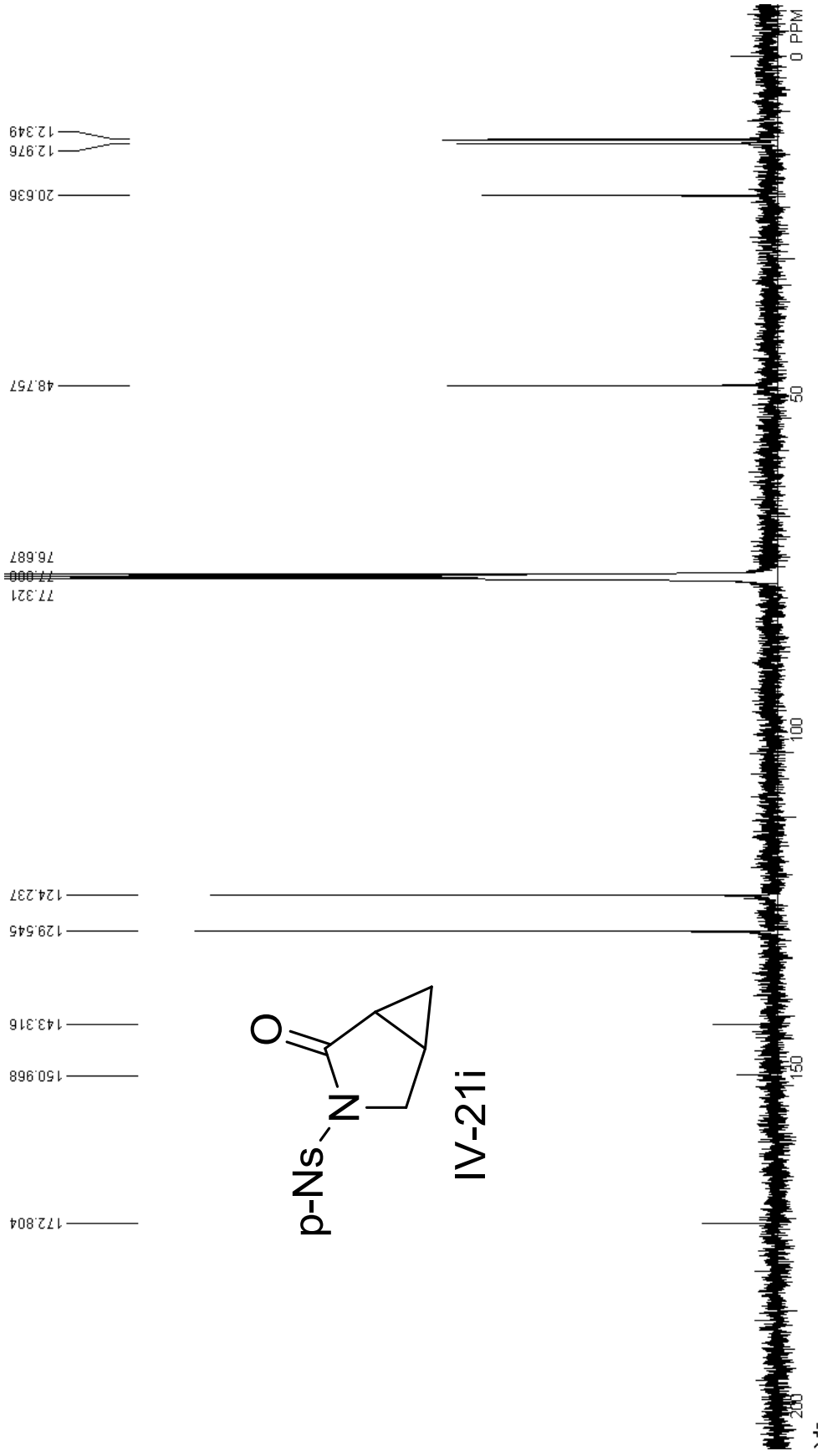


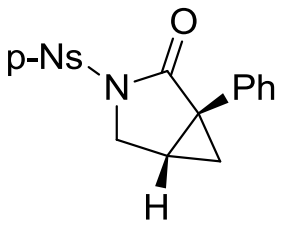

CARBON
170.82
144.55
136.44
129.27
128.41
77.32
77.00
76.69
40.60
21.65
21.63
19.02
15.72
7.69
Ts
N
O
IV-21h
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



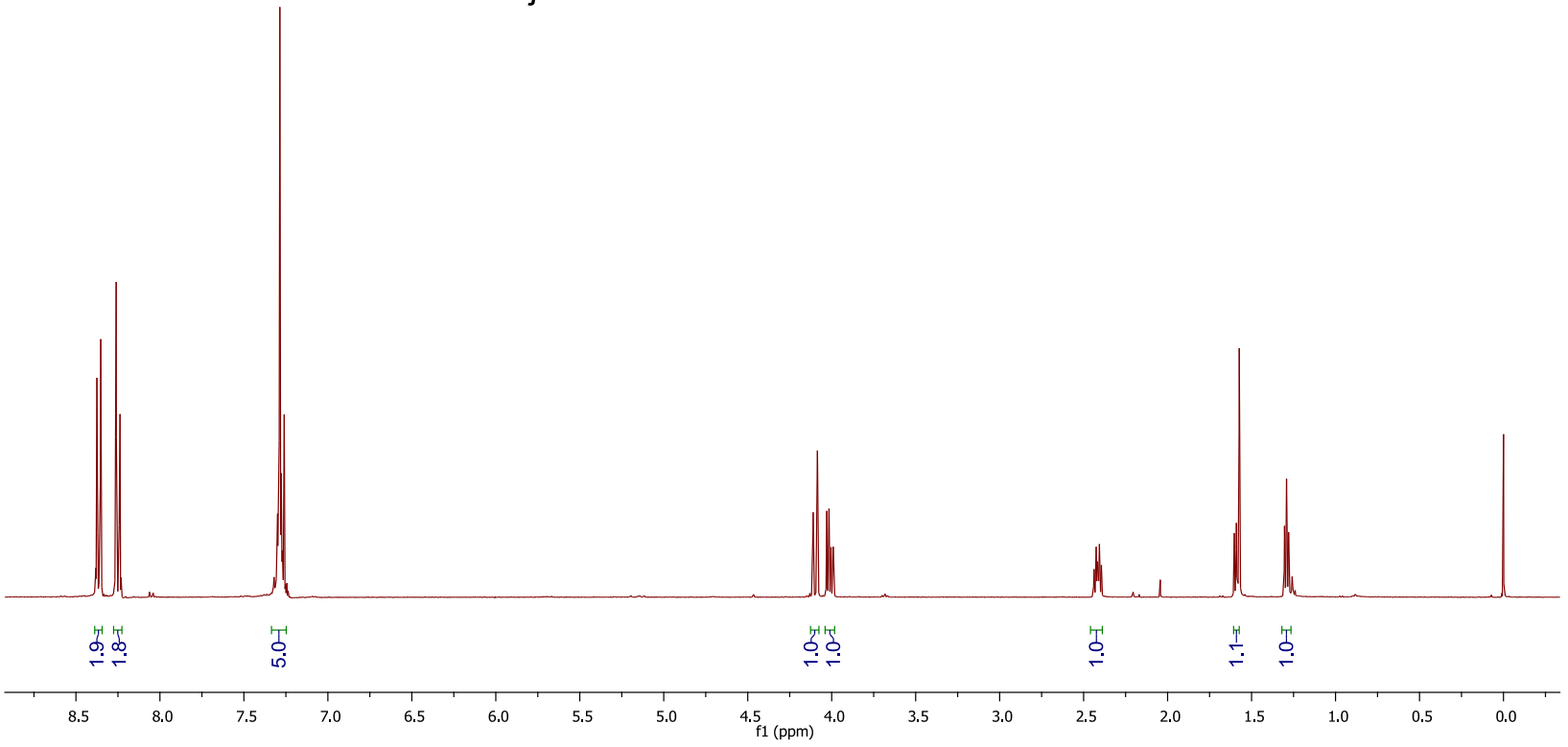

IV-21i

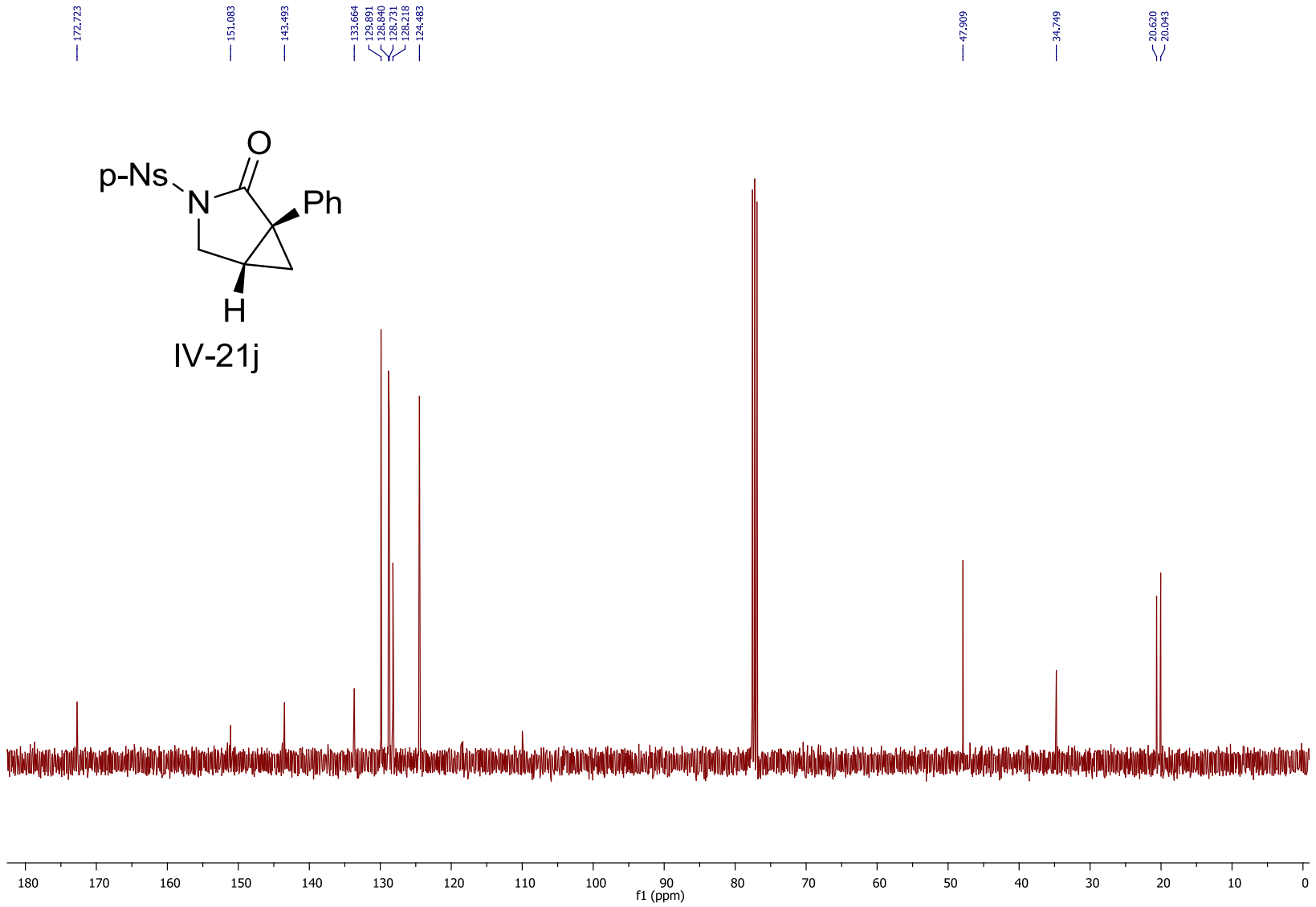



172.804
150.968
143.316
129.545
124.237
77.321
76.687
48.757
20.636
12.976
12.349
p-Ns
N
O
IV-21i
0 PPM
50
100
150
200

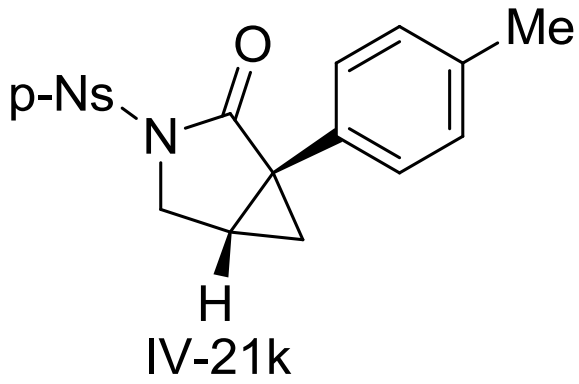

p-Ns
N
O
Ph
H

IV-21j

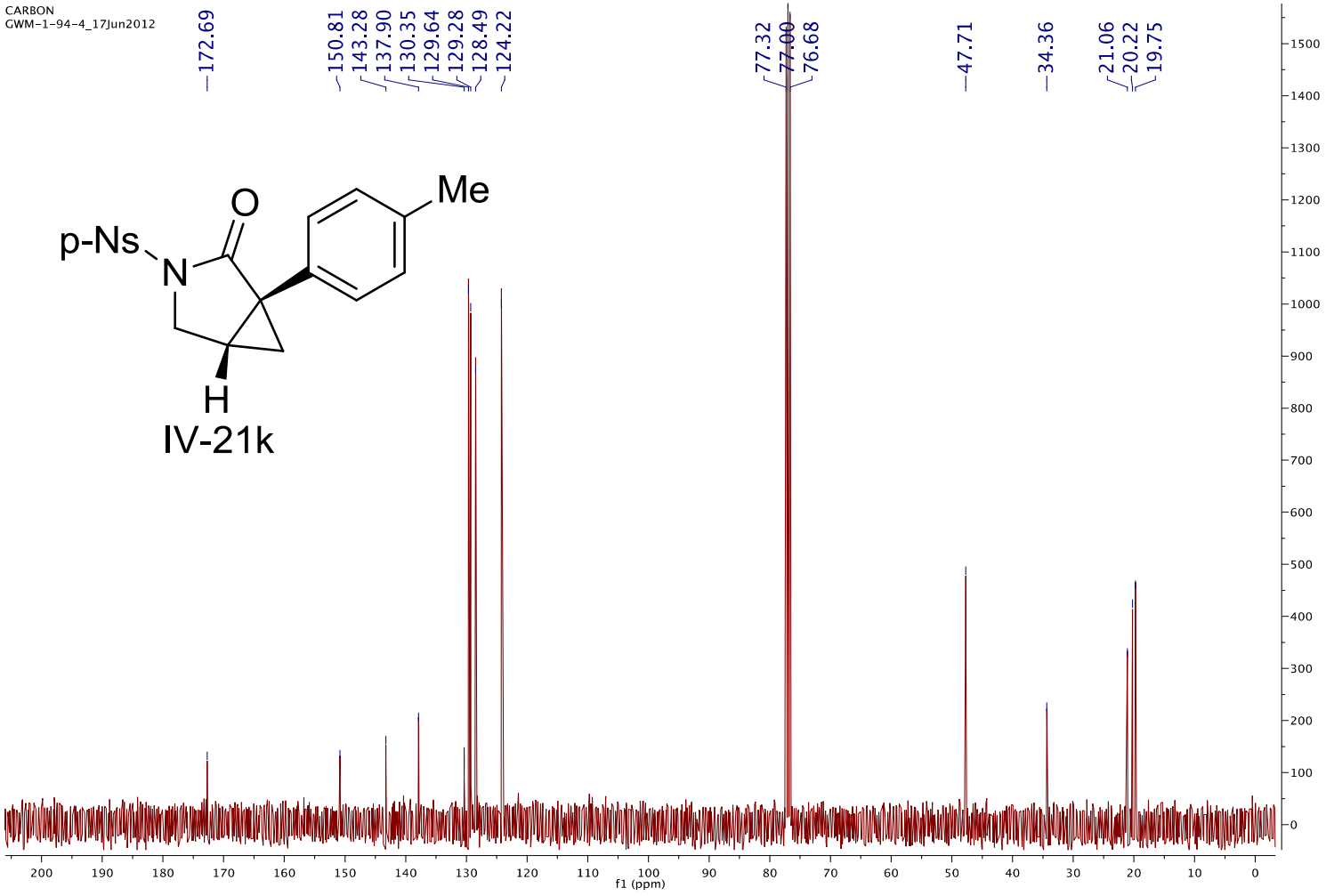

1.9
1.8
5.0
1.0
1.0
1.0
1.1
1.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

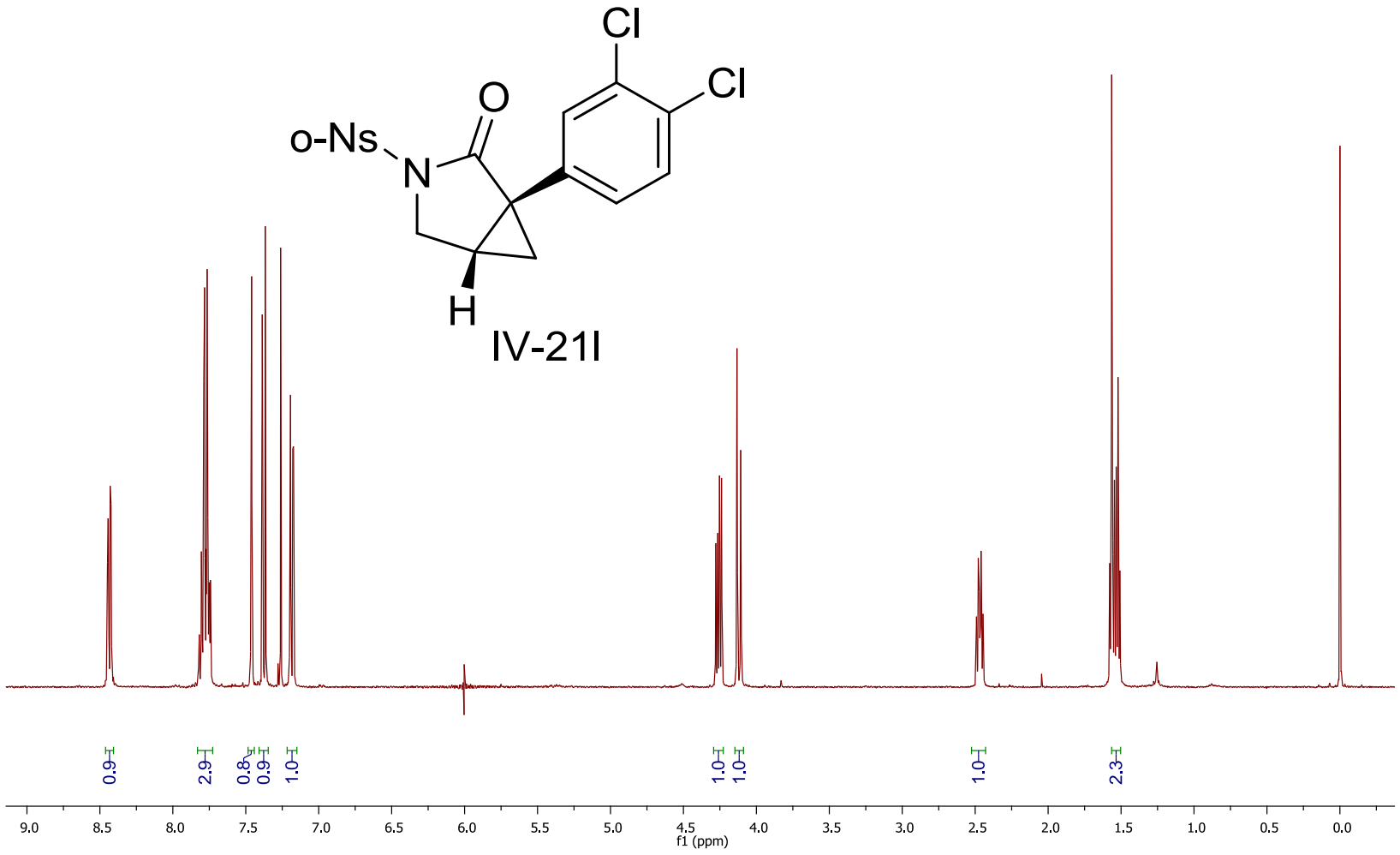

172.723
151.083
143.493
133.664
129.891
128.840
128.731
128.218
124.483
47.909
34.749
20.620
20.043
p-Ns
N
O
Ph
H
IV-21j
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

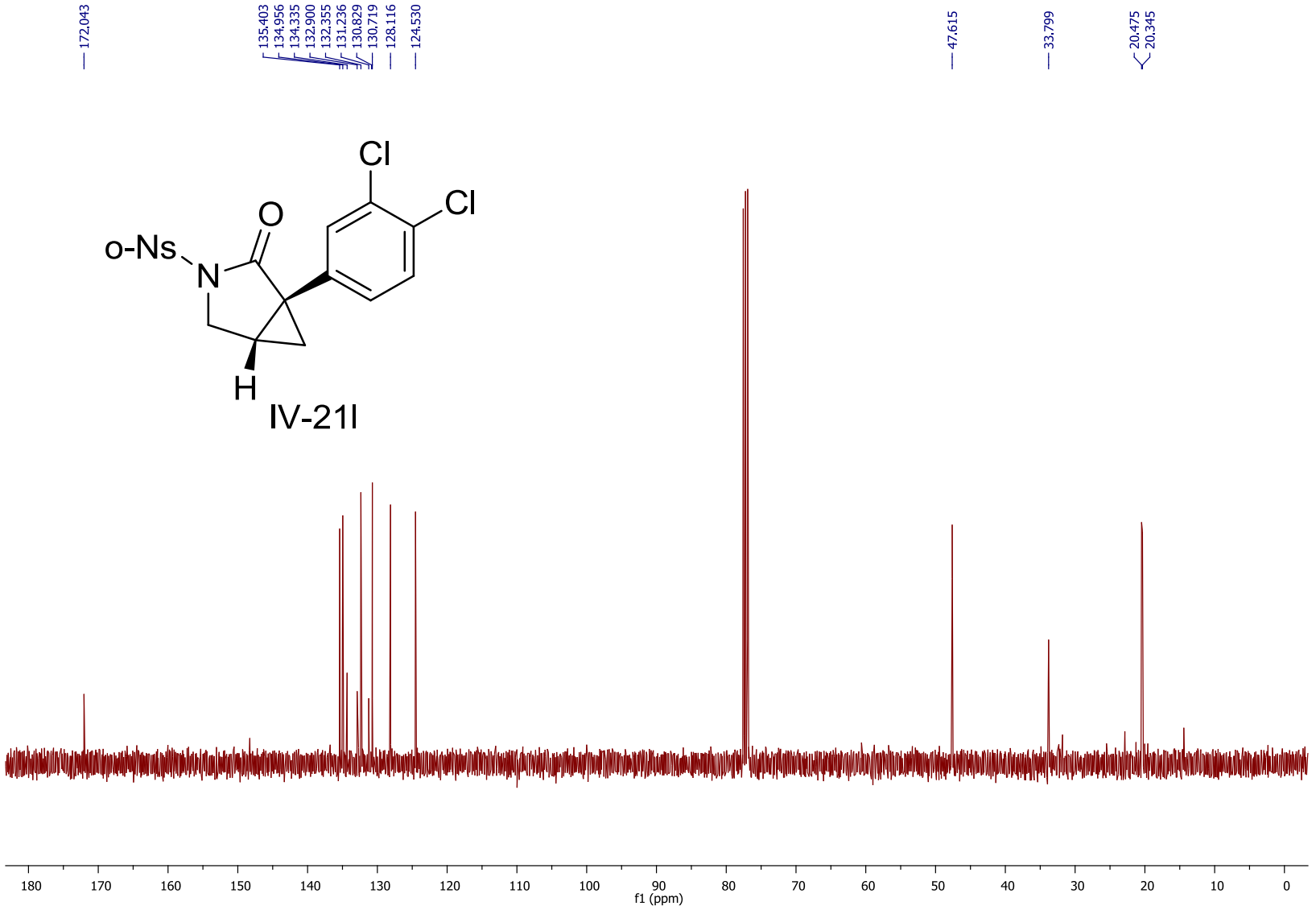
PROTON
GWM-1-94-4_17Jun2012

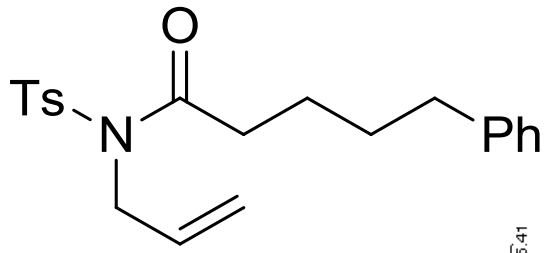



IV-21k

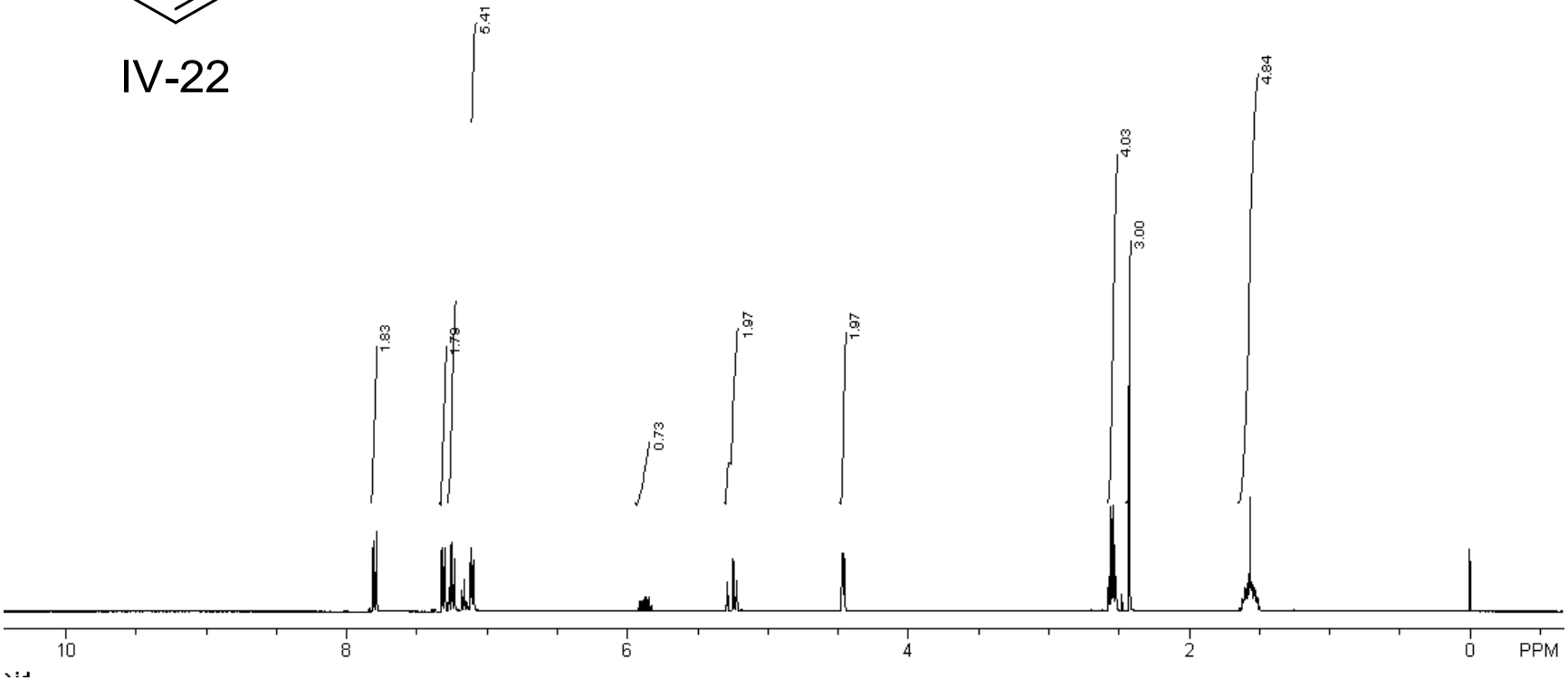

CARBON
GWM-1-94-4_17Jun2012
172.69
150.81
143.28
137.90
130.35
129.64
129.28
128.49
124.22
77.32
77.00
76.68
47.71
34.36
21.06
20.22
19.75
p-Ns
N
O
Me
H
IV-21k
f1 (ppm)

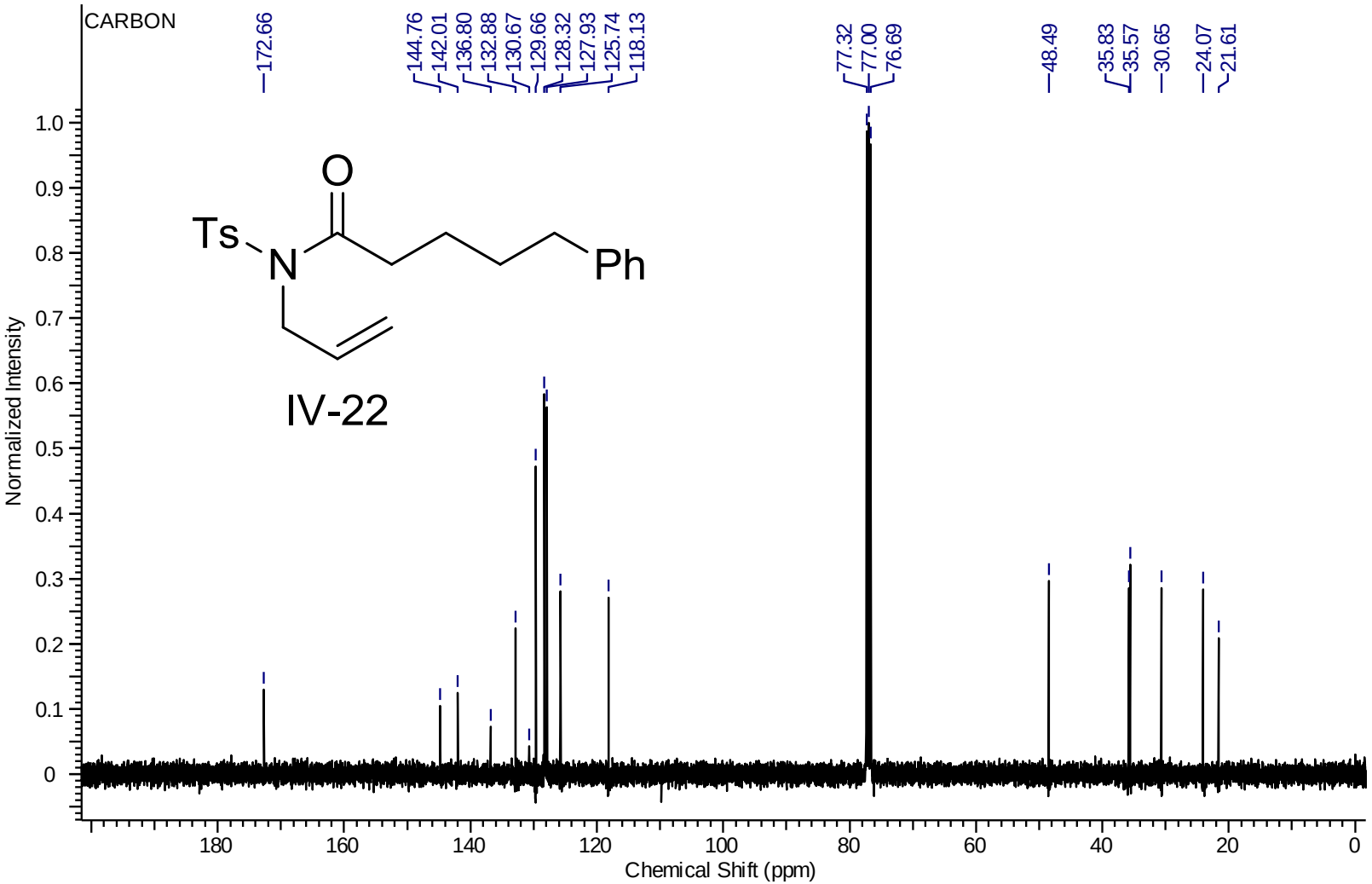

Cl
Cl
O
o-Ns
N
H
IV-21l
0.9
2.9
0.8
0.9
1.0
1.0
1.0
1.0
2.3
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

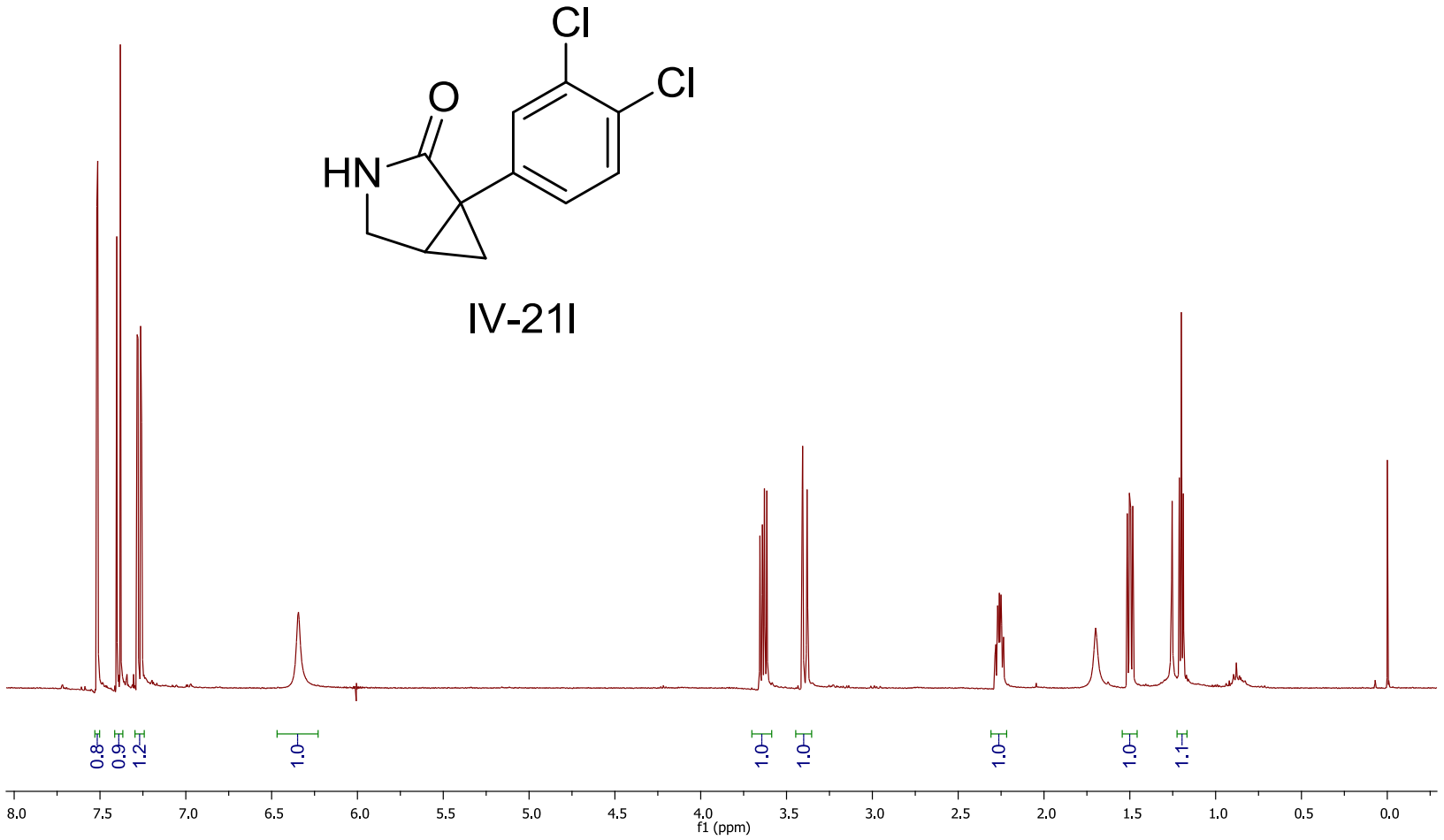

172.043
135.403
134.956
134.335
132.900
132.355
131.236
130.829
130.719
128.116
124.530
47.615
33.799
20.475
20.345
Cl
Cl
O
o-Ns
N
H
IV-21l
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

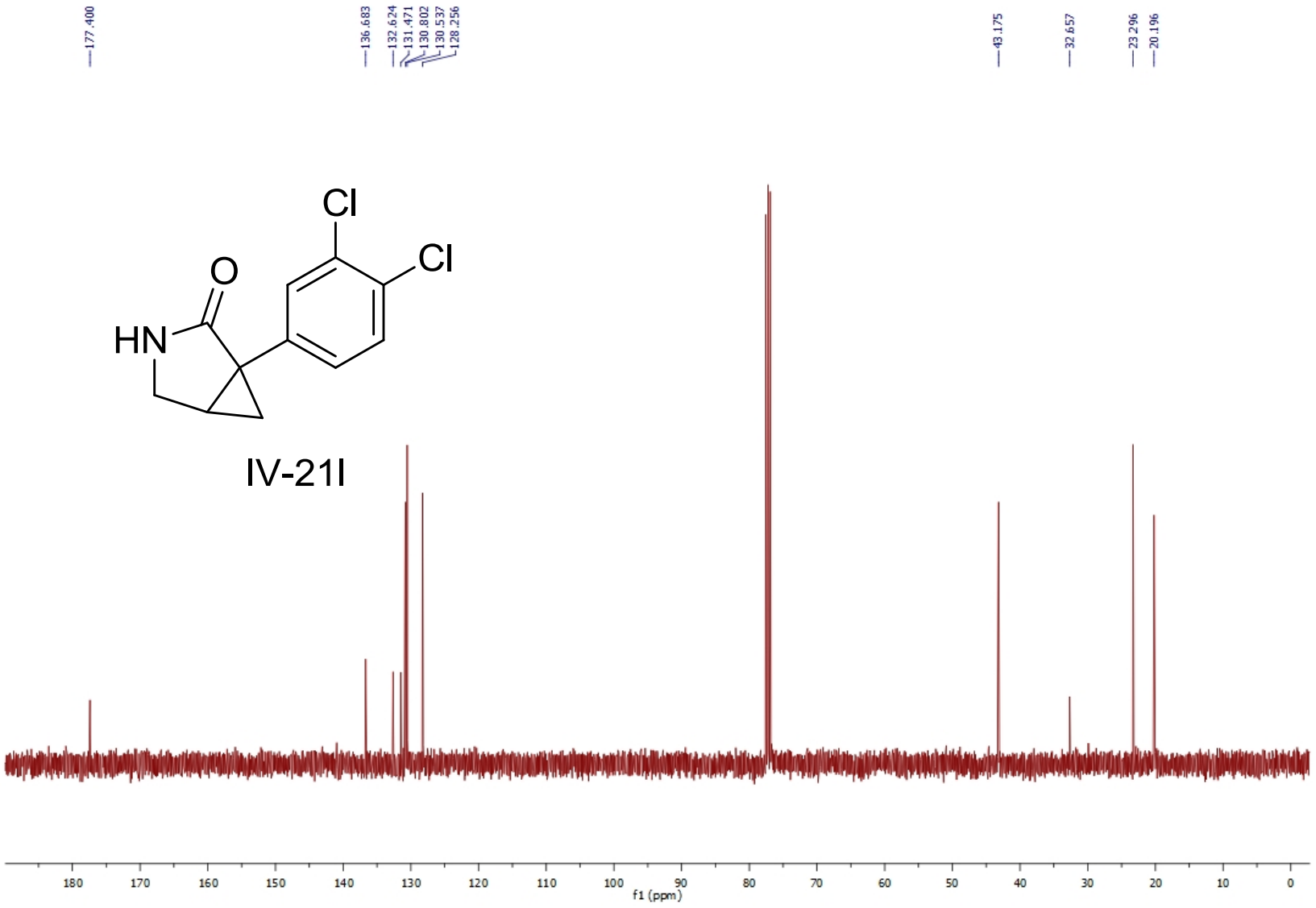



IV-22




CARBON
172.66
144.76
142.01
136.80
132.88
130.67
129.66
128.32
127.93
125.74
118.13
77.32
77.00
76.69
48.49
35.83
35.57
30.65
24.07
21.61
O
Ts
N
Ph
IV-22
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


Cl
Cl
O
HN
IV-21I
0.8
0.9
1.2
1.0
1.0
1.0
1.0
1.0
1.1
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)


177.400
136.683
132.624
131.471
130.802
130.537
128.256
43.175
32.657
23.296
20.196
Cl
Cl
O
HN
IV-21I
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)