ENANTIO-PURE SYNTHESIS OF ENYNE EPOXIDES AND THEIR IRON-CATALYZED S_N2" REACTIONS WITH GRIGNARD REAGENTS

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ABSTRACT

ENANTIO-PURE SYNTHESIS OF ENYNE EPOXIDES AND THEIR IRON-CATALYZED S_N2" REACTIONS WITH GRIGNARD REAGENTS

The use of transition-metal catalysts in synthetic chemistry has gained a lot of significance in the last decade, by virtue of their selectivity wheather regio-isomerically, or enantiomerically, or both. Besides their superior selectivity, these reactions have also been considered as atom economic and environmental-friendly. Iron-catalyzed reactions gained undeniable attention in regard to their low toxicity and presence in enzymatic reactions. Thus, use of iron catalysts in synthesis of biologically important and intermediary chemicals bear great significance.

Allene motifs, which exist in vast number of naturally occurring compounds are important intermediates in synthesis of bio-active materials due to their versatile reactivity and instrict chirality. The first transition metal-mediated sythesis of allenes was accomplished by 1,3-substitution reaction of propargylic acetates with stoichiometric amounts of organocuprates (Rona *et al.,* 1968). Later on, Fürstner and co-workers have established a technique that, allows the use of catalytic amounts of iron complexes for the reaction of Grignard reagents with propargylic oxiranes which yields α-allenol compounds with different modes of addition (Fürstner *et al*., 2003).

In addition to significant developments in this field, our group has established iron-promoted reactions of enyne acetates and oxiranes with Grignard reagents, producing functionalized vinyl allene structures (Taç *et al*., 2017).

In that study, reactions that proceeded regioselectively in 1,5-substitution (S_N2'') manner yielded vinyl allenes in good to high yields. However, stereoselectivity of the method was not sufficiently satisfactory.

Nevertheless, we disclose herein that the corresponding iron-catalyzed reactions of enyne oxiranes with an endocyclic alkenyl moiety are highly stereoselective; vinyl allene products could be obtained in high diastereomeric ratios by this method. Moreover, the ability to synthesize oxirane substrates in high enantiomeric purity allowed the production of the desired enantiopure vinyl allenes.

ÖZET

ENANTİYO SAF ENIN EPOKSİTLERIN SENTEZİ VE GRIGNARD REAKTİFLERİ İLE DEMİR KATALİZLİ S_N2" TEPKİMELERİ

Sentetik kimya alanında geçiş metal katalizli tepkimeler, geçtiğimiz on yıldan bu yana, gerek yüksek enantiyomerik gerek ise yüksek regio seçimliliklerinden ötürü, gittikçe daha önemli bir sentetik yöntem olmaktadır. Yüksek seçimliliklerinin yanı sıra bu reaksiyonlar çevre dostu ve atom ekonomik olarak nitelendirilmektedir. Düşük toksisiteleri ve enzimatik reaksiyonlarda bulunmaları nedeniyle, demir katalizli tepkimeler yadsınamaz ölçüde ilgi görmektedir. Bu nedenlerden dolayı, biyolojik öneme sahip kimyasalların ve ara kimyasalların demir katalizli sentezi büyük değer taşımaktadır. Çok sayıda doğal bileşikte bulunan allen motiflerin, çok yönlü reaktiflikleri ve doğal kiraliteleri nedeniyle bir çok biyo-aktif maddelerin sentezinde oldukça önemli ara yapılardır.

İlk metal-destekli allen sentezi, propargilik asetatların stokiyometrik miktarlarda organobakır reaktifleri ile 1,3-sübstitüsyon reaksiyonu sonucu gerçekleşmiştir (Rona *vd.,* 1968). Daha sonraları, Fürstner ve çalışma arkadaşları, katalitik miktardaki demir komplekslerinin Grignard bileşikleri ile proparjilik oksiranlar kullanılarak, α-allenol yapılarını seçimli olarak ve yüksek verimler ile elde etmişlerdir (Fürstner *vd.,* 2003).

Bu alandaki önemli çalışmalara ek olarak, grubumuz tarafından enin asetat ve oksiran yapılarının Grignard reaktifleri ile demir katalizli katılma tepkimeleri geliştirilmiştir. Ancak geliştiren bu metotda asiklik enin oksiran yapıların demir katalizli Grignard reaktifleri ile katılma reaksiyonları yüksek verimde fakat maalesef düşük stereo seçimlilik ile hedeflenen ürünleri vermiştir (Taç *vd.,* 2017).

Ancak, yukarıda bahsedilen asiklik enin oksiran yapıları yerine başlangıç reaktifi olarak endosiklik alkenil yapısı içeren bir enin oksiran ile aynı reaksiyon gerçekleştirildiğinde, yukarıdaki sonucun aksine tepkimeler yüksek stereo seçimlilikte gerçekleşerek vinil allenler yüksek diastereo seçimli olarak elde edilmiştir. Enin oksiranların enantiyo saf olarak sentezlenebilmesi elde edilen vinil allenlerin de enantiyo saf olarak üretilmesini sağlamıştır.

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ABBREVIATIONS

Bu	n-butyl
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DIPA	Diissopropylamine
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin periodinane
EtOAc	Ethyl acetate
GC	Gas chromotography
h	Hour
i-Pr	Isopropyl
m-CPBA	meta-Chloroperoxybenzoic acid
mg	Miligrams
min.	Minute
mL	Mililiter
mmol	Milimoles
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
ON	Overnight
Ph	Phenyl
Pyr	Pyridine
RT	Room temperature
SPS	Solvent Purification System
TBSCl	Tert-butyldimethylsillyl chloride
TEPA	Triethylphosphonoacetate
THF	Tetrahydrofuran
TLC	Thin Layer Chromotography

CHAPTER 1

INTRODUCTION

Allenes are extensive tool for organic synthesis that characterized by two cumulated carbon-carbon double bonds that aligned 90^{o} with respect to each end. Structurely, allenes bear an axial chirality that could be transfered. Besides chirality, their distinctive reactivity enables them to be potential intermediates for various important transformations. Numerous allene structures could be encountered in various natural products, hence it claims vital biological activity.

Various transition metals have been involved for the synthesis of allenes which include Cu, Rh, Pd, and Fe as the most common ones accompanied by scope of substrates ranging from dihalocyclopropanes, dihalides and functionalized propargylic compounds. While abundant examples of synthetic routes present to synthesize allene structures, they were mainly generated by S_N2'-type (1,3-substitution) reactions.

One of the significant example done by Artok group involves S_N2"-type (1,5-substitution) of reaction of enyne acetates or oxiranes with Grignard reagents catalyzed by iron complexes that leads to the formation of vinyl allenes. It was noticed that acyclic derivatives of enyne oxiranes had low stereoselectivity while endo-cyclic counterpart showed remarkable stereoselectivity (Taç *et al*., 2017).

Having this information in hand, this study has aimed at to produce enantio-selective synthesis of vinyl allene structures from enantiomerically enriched endo-cyclic enyne oxiranes. The reaction proceeds with 1,5-substitution pattern in *anti* mode of addition to produce vinyl allenes with high diastereomeric ratios up to *100:0.*

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CHAPTER 2

LITERATURE WORKS

2.1. Metal-Catalyzed S_N2'- Type Reaction of Propargyl Compounds

In the last decade, leading works have been carried out by Ma, Krause, Alcaide and Almendros research groups. However, the first use of organometallic reagents in synthesis of allenes was achieved by Rona *et al.,* (1968) (Figure 2.1). Propargyl acetates were subjected to react with stoichiometric amounts of organocuprates to facilitate 1,3-substitution reaction that would create an allene structure. Subsequently this method was further exploited for the synthesis of allenes.

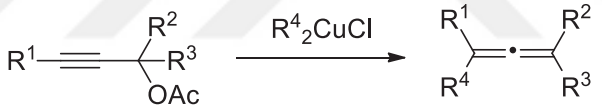


Figure 2. 1 S_N2'-Reaction of propargyl acetates with stoichiometric amount of organocuprates
(Source: Rona *et al*., 1968 ; 1969)

Propargyl oxiranes are important in conjugate addition reactions to form allenes with a reactive hydroxyl group, which are referred to as so allenols. Examples of first utilization of propargylic oxiranes in presence of organometals were examined by de Montellano *et al.,* (1973). The reaction yielded the desired alkylated allene products along with the reduced form of the α-allenol structure as the side-product. The stereo-selectivity of this technique was not clearly demonstrated (Figure 2.2).

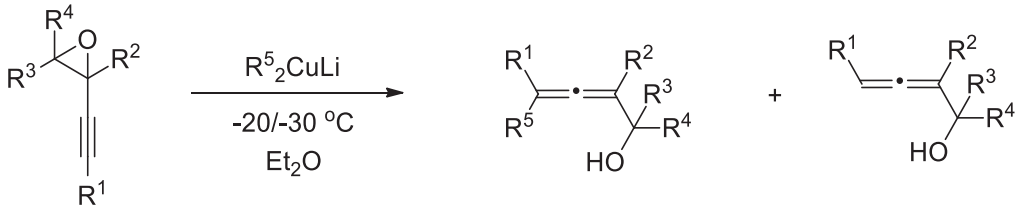


Figure 2. 2 Reaction of propargyl epoxides with stoichiometric amounts of dialkyllithium cuprate
(Source : de Montellano *et al.,* 1973)

An enantiomerically enriched form of the starting propargyl oxiranes was used by Oehlschlager and Czyzewska (1983). Propargyl epoxide with terminal alkynyl moiety was reacted with organocuprates in presence Me_2S. The reaction proceeded with *anti*-S_N2' fashion to yield enantioenriched α-allenol structures (Figure 2.3).

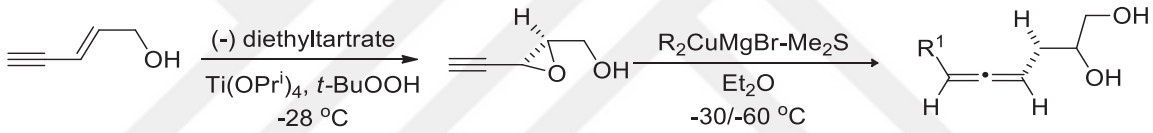


Figure 2. 3 Enantioenriched reaction of terminal enyne oxiranes with organocuprates
(Source: Oehlschlager and Czyzewska, 1983).

First catalytic version of the methodology was proposed by Alexakis' group (1989; 1991). Progargylic oxiranes were subjected to react with Grignard reagents in presence of copper(I) bromide catalyst. It was found that, diastereoselectivity of the reaction was dependent on additives (Figure 2.4).

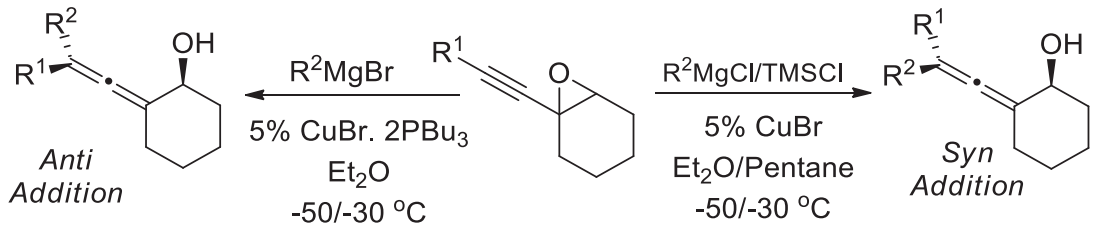


Figure 2. 4 Reaction of propargylic oxiranes with Grignard reagents in presence of CuBr catalyst
(Source: Alexakis *et al.,* 1989; 1991)

Later on Fürstner and coworkers (2003) proved that the reaction of propargylic oxiranes with Grignard reagents in the presence of iron catalyst effectively yield the desired α−allenol structures. The selectivity of the reaction was strongly depended on the solvent and the temperature of the reaction medium.

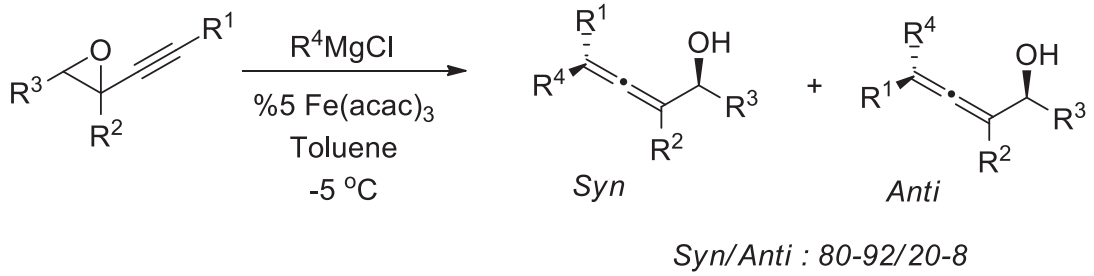


Figure 2. 5 Iron catalyzed reaction of propargylic oxiranes with Grignard reagents
(Source : Fürstner *et al*., 2003)

Stereoselective reaction of propargyl oxiranes with arylboronic acids was asserted by Murakami and his group (Miura *et al.,* 2007). The reaction was catalyzed by a rhodium complex to yield arylated allenols with *syn* mode of addition.

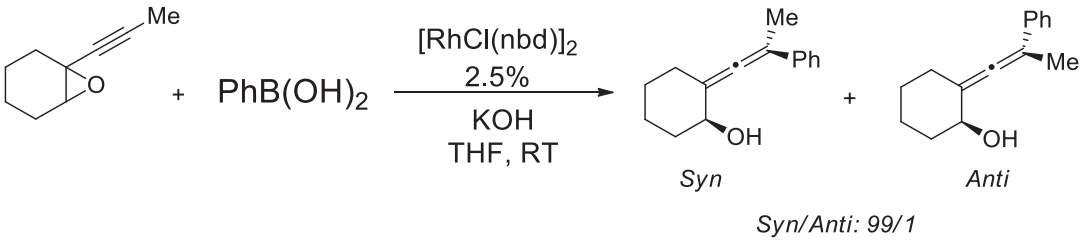


Figure 2. 6 Rhodium catalyzed reaction of propargylic oxiranes with arylboronic acids
(Source: Miura *et al.,* 2007)

2.2 Metal-Catalysed S_N2'-Type Reactions of Allyl Epoxide

There are some example of S_N2 addition of Grignard reagent instead of S_N2' type. The reaction proceeded by direct addition to the epoxide ring rather then coordinating to the allylic moiety (Hyoung *et al.,* 2008) (Figure 2.7).

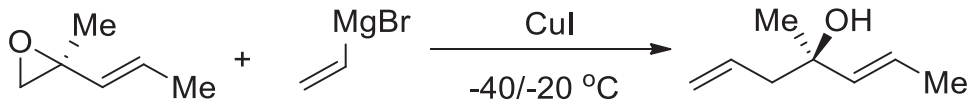


Figure 2. 7 Reactions of allyl epoxides with Grignard Reagents in S_N2' fashion (Source: Hyoung *et al.,* 2008)

Later on, a method was discovered by Millet and Alexakis to allow cyclic allyl epoxides to react in S_N2' mode. Copper(I) was used as catalyst and chiral ferrocene as the ligand, which enables kinetic resolution of the product with high stereoselectivity (Figure 2.8).

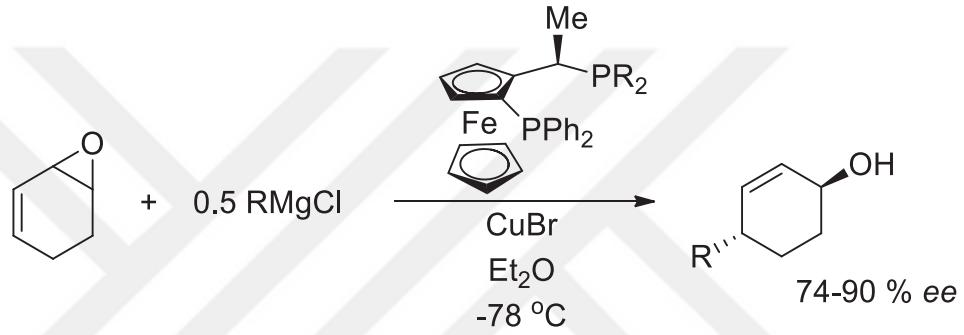


Figure 2. 8 Reaction of allyl epoxide with Grignard reagents in presence of a copper(I) catalyst and ferrocenyl ligand leading to kinetic resolution (Source: Millet and Alexakis *et al.,* 2007)

2.3. Substitution Reactions of 2,4- Enyne Reagents in Presence of Metal Catalyst

An S_N2'' type method was displayed on 1-chloro-2-en-4-yne compound first by Goré and Dulcere. Regardless of the Grignard reagent and additive used reactions were concluded with mixture of isomers (Goré and Dulcere, 1972; 1981) (Figure 2.9).

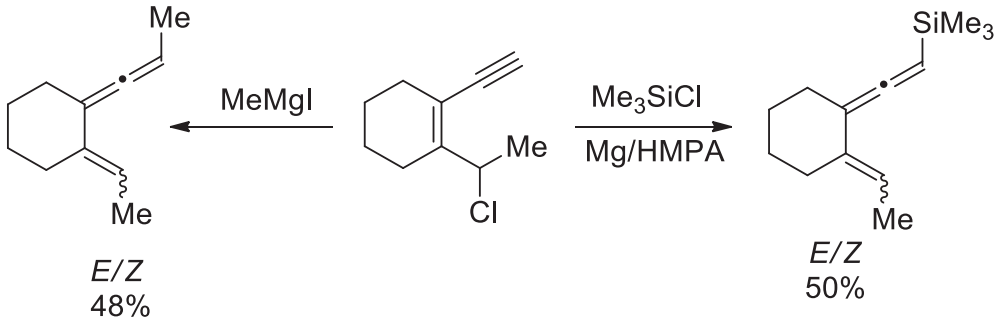


Figure 2. 9 Catalyst free reaction of 2,4-enyne compound withmethylmagnesium iodide or trimethylsilylmagnesium chloride (Source: Goré and Dulcere; 1972, 1981)

Another method was presented by Krause and Purpura which reacts 2,4-enyne acetates with organolithium cuprates to yield vinyl allene products as a mixture of E/Z isomers through 1,5-substitution reaction (Purpura and Krause, 1999; Krause and Purpura, 2000) (Figure 2.10).

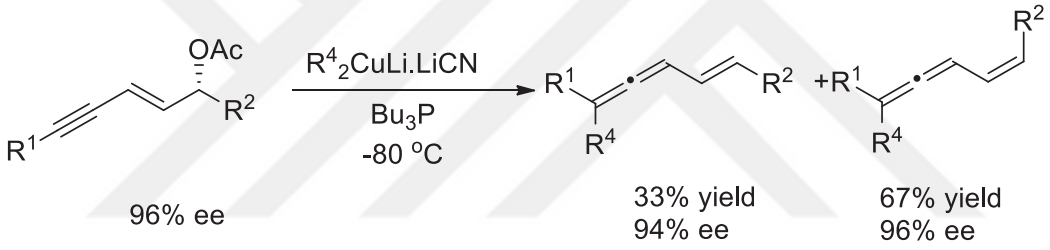


Figure 2. 10 S_N2'' reaction of enyne acetates with organolithium cuprates (Source: Krause and Purpura, 2000)

The reaction was also performed on *E*-enyne oxiranes with stoichiometric amounts of Me_2CuLi/LiI or *t*-$Bu_2CuLi/LiCN$ which yielded vinyl allene products as a *E/Z* mixture but the use of methylcuprate as the nucleophile caused the reductive formation of a vinyl allene product (Figure 2.11).

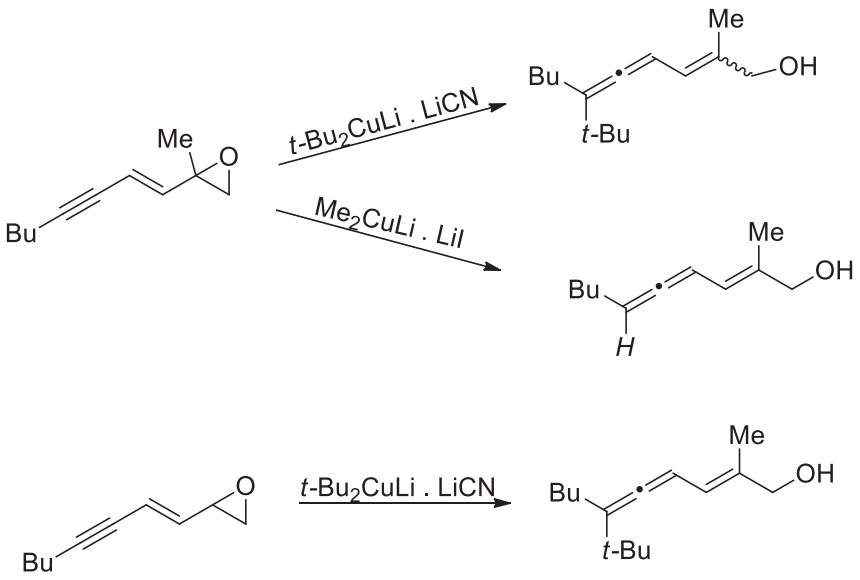


Figure 2. 11 Reaction of E-enyne oxiranes with organolithium cuprates (Source: Krause and Purpura, 2000)

Another example of 1,5-substitution reaction was performed by our group using enyne carbonates as substrates with aryl boronic acids over palladium and rhodium catalysts. Both *Z*- and *E*- configured substrates were determined to be amendable reagents for the Pd-catalyzed method, whereas only the *Z*- configured form could be applicable for the Rh-catalyzed counterpart (Üçüncü *et al.,* 2011) (Figure 2.12).

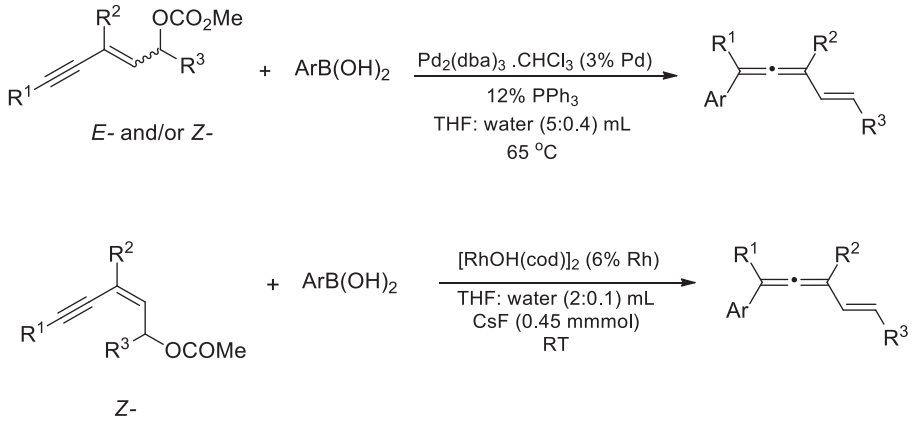


Figure 2. 12 Coupling reactions of enyne acetates and carbonates with organoboronic acids in presence of palladium and rhodium catalyst (Source: Üçüncü *et al.,* 2011)

Enantio-enriched (*Z*)-2,4-enyne carbonates were also subjected to the alkoxy carbonylation reactions under established conditions, yet the product was recovered as a racemic mixture. If the conditions are tuned carefully, the stereoselectivity of the reaction could be improved and almost complete centre-to-axial chirality transfer could be achieved (Akpınar *et al.,* 2011, Karagöz *et al.,* 2014) (Figure 2.13).

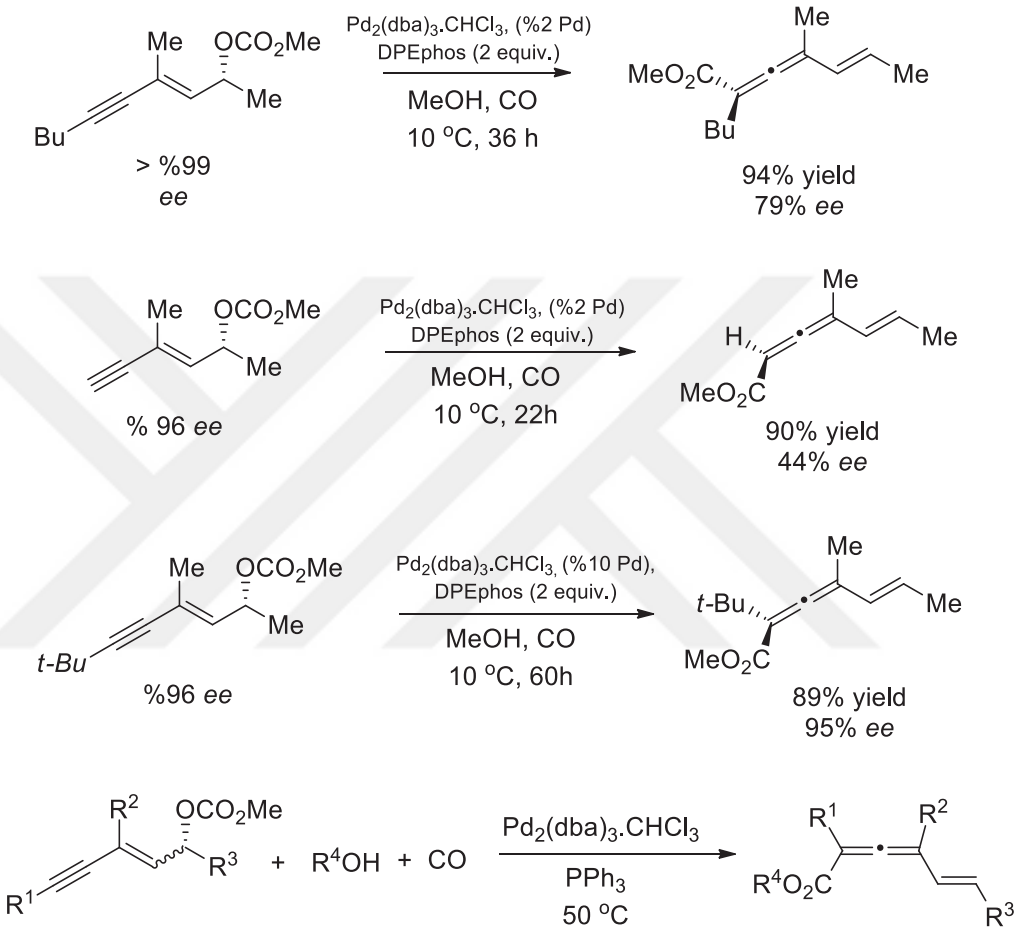


Figure 2. 13 Palladium-catalysed alkoxycarbonylation of (*E)* and *(Z*)-2,4-enyne carbonates
(Source: Akpınar *et al.,* 2011, Karagöz *et al.,* 2014)

A variation of this technique was proposed by our group which involves highly stereoselective alkoxycarbonylation of enyne oxiranes via palladium catalysis (Kuş *et al.,* 2013) (Figure 2.14).

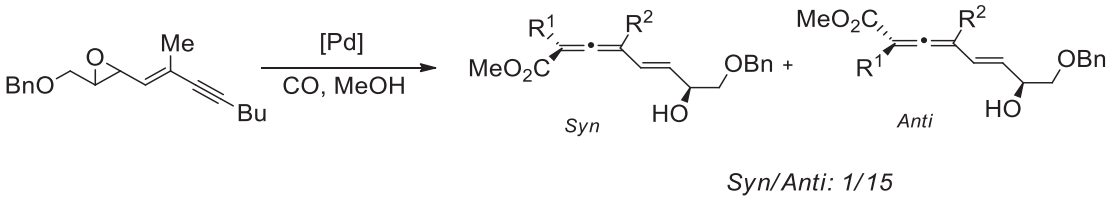


Figure 2. 14 Stereo-selective alkoxycarbonylation of enyne oxiranes via palladium catalysis
(Source: Kuş *et al.,* 2013)

Unlike the other examples, Li and Alexakis (2012) found that Cu(I) catalyzed reactions of conjugated enyne halides with Grignard reagents proceeded through 1,3-S_N2' pathway (Figure 2.15).

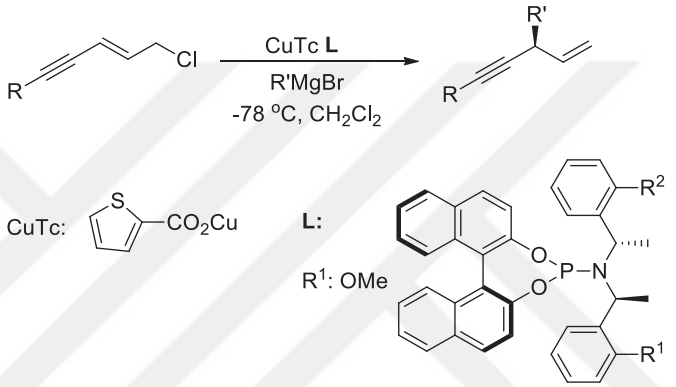


Figure 2. 15 Reactions of enyne chloride with Grignard reagents in presence of Cu(I) catalyst
(Source: Li and Alexakis, 2012)

2.4. Vinyl allenes as Reactive Compounds

So far, hundreds of allene compounds were extracted from natural sources most of which are enantiomerically pure and bio-active compounds (Krause and Hoffman-Rödar, 2004a; 2004b).

Besides their unique chirality and bio-activity, allenes have been useful intermediates in synthesis of complex structures due to their reamarkable reactivities. For instance, their reactivity toward the Diels-Alder reactions are always carried out with high yields and stereo-selectivities (Figure 2.16) (Spino *et al.,* 1998).

Having biased tendency towards the *s-cis* conformation and ability to transfer their axial chirality made them significantly important in asymmetric synthesis of cyclic products (Reich *et al.,* 1988; Koop *et al.,* 1996; Gibbs *et al.,* 1989; Bond,1990).

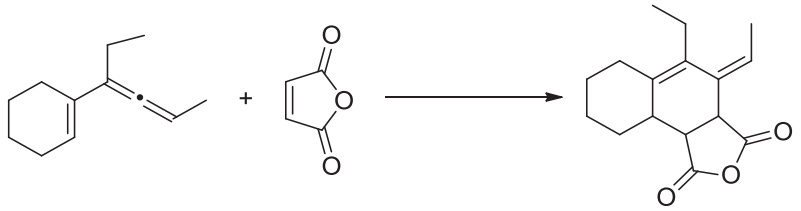


Figure 2. 16 Highly reactive and stereoselective Diels-Alder reaction
(Source:Spino *et al.,* 1998)

A fungal metabolite, Sterpurene was synthesized enantiopurely by Gibbs *et al.,* (1989) and also racemically from intramolecular Diels Alder reaction (Krause *et al.,* 1993) (Figure 2.17).

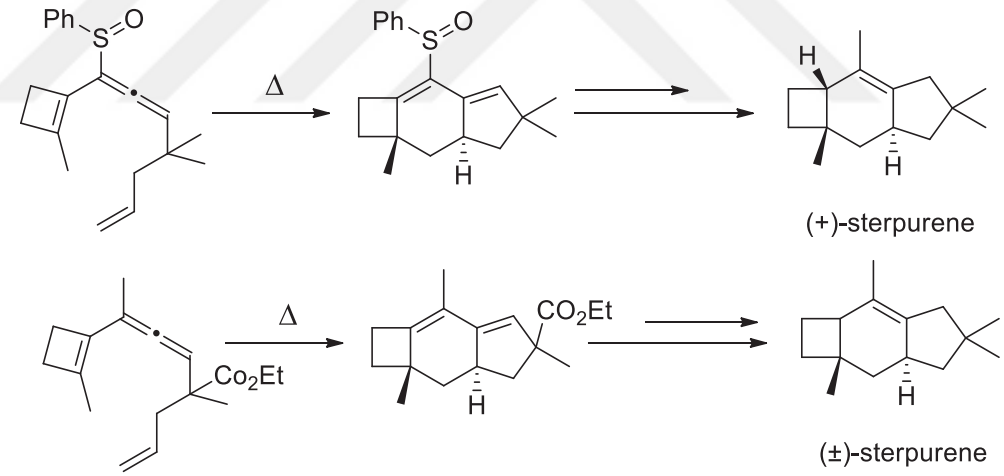


Figure 2. 17 Synthesis of sterpurene over vinyl allene structure by intramoleculer Diels Alder reaction
(Source: Gibbs *et al.*, 1989; Krause *et al.,* 1993)

Moreover, biogenetical structure called espreamicin A was synthesized by intramolecular Diels Alder reaction of vinyl allenes (Schrieber and Kiessling, 1988) (Figure 2.18).

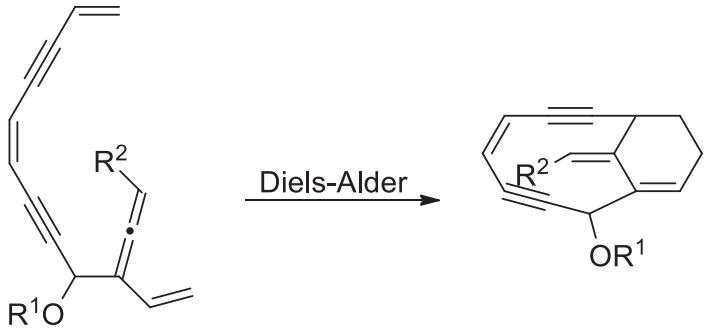


Figure 2. 18 Synthesis of esparmicin A through a intramolecular Diels Alder reaction of vinyl allene structure
(Source: Schreiber and Kiessling, 1988).

Reaction of vinyl allenes with terminal alkynes in presence of Rh(I) catalyst yielded tri-substituted benzenes (Murakami *et al.,* 1988) (Figure 2.19).

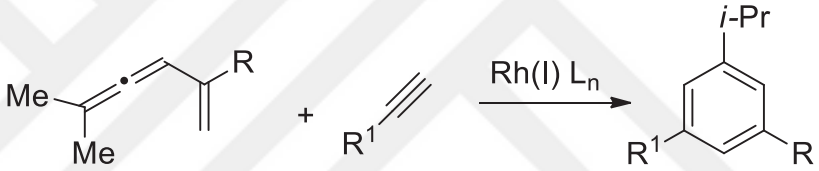


Figure 2. 19 Intermolecular cyclization of vinyl allenes and terminal alkynes in presence of Rh(I) catalyst
(Source: Murakami *et al.,* 1988)

Furthermore, Murakami showed that Pauson-Khand type of reactions were also possible with vinyl allenes in presence of Rh(I) catalyst (Murakami *et al.,* 1999a; 1999b) (Figure 2.20).

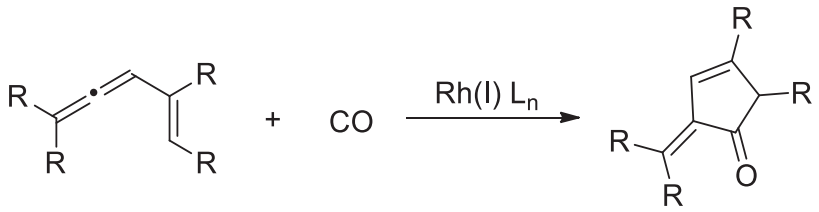


Figure 2. 20 Pauson-Khand type reaction of vinyl allenes
(Source: Murakami, *et al.,* 1999a; 1999b)

A polycyclic structure could be synthesized stereoselectively from an en-vinyl allene motif through gold-catalysed cycloisomerisation process (Gandon *et al.,* 2008; Lemiere *et al.,* 2009) (Figure 2.21).

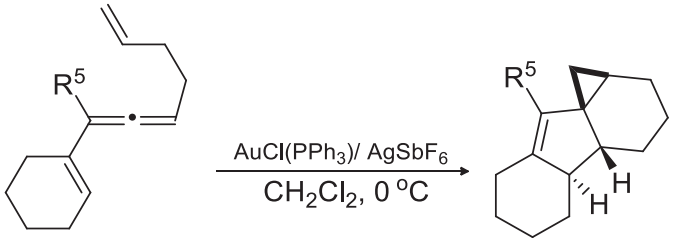


Figure 2. 21 Cycloisomerisation reaction of an en-vinyl allene structure in the presence of a gold catalyst
(Source: Gandon *et al.,* 2008; Lemiere *et al.,* 2009)

CHAPTER 3

EXPERIMENTAL STUDY

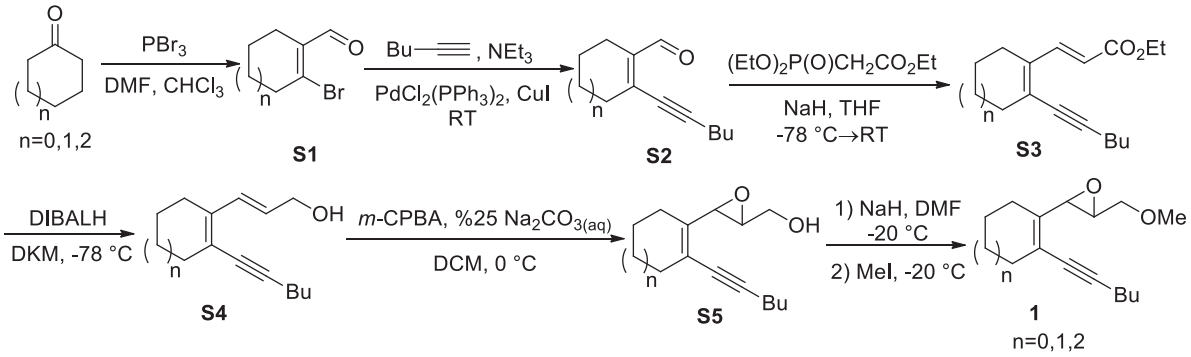
3.1. General Procedure

Dimethylformamide (DMF) used was dried at a solvent purification system (SPS, MBRAUN 800), dichloromethane (DCM) and chloroform ($CHCl_3$) were dried over 3Å molecular sieve that was preactivated by heating at 400 ^oC for 24 hour and cooled under argon gas prior to use. Tetrahydrofuran (THF) which was used in sytheses was distilled from benzophenone-ketyl under nitrogen atmosphere. Pure samples were analysed by: GC-MS (Thermo/ISQ) equipped with Thermo TR-5MS (30 m, 0.25 mm ID) column; nuclear magnetic resonance (NMR) spectra were acquired on Varian Vnmr*J* 400 spectrometer using $CDCl_3$ as NMR solvent unless otherwise stated.

3.2. Synthesis of Substrates

Syntheses of all intermediates were performed under N_2 or Ar gas atmosphere unless otherwise stated. but THF that was used in catalytic reactions was freshly distilled from $LiAlH_4$ under ultra high purity (6 grade- 99.9999%) argon gas atmosphere which was passed thorough KOH and P_2O_5 filled glass tube. All materials were purified using silica gel (60-200 mesh) column chromatography technique using hexane/EtOAc as mobile phase. It must be noted that enyne oxirane substrates must be purified with NEt_3 deactivated silica gel in order to prevent decomposition.

3.2.1. Synthesis of 1a,1b,1c



To the mixture of DMF (12 mL, 153 mmol) and chloroform (80 mL) which was cooled to 0 °C, PBr_3 (14 mL, 138 mmol) was added dropwise and stirred at this temperature for 1 hour. To this mixture cycloalkanone (60 mmol) was added dropwise and the whole mixture was refluxed for overnight. Upon completion, the reaction was terminated with ice-water mixture and carefully neutralized with $NaHCO_3$. Organic phase was separated and aqueous phase was washed with DCM, then the extract was dried over Na_2SO_4, filtered, and concentraded under reduced pressure. The crude product was purified by silica gel column chromatograpy to obtain **S1** as pale yellow oil (hexane/EtOAc; yield: n=0, 67%; n=1, 72%; n=2, 74%) (Vilsmeier and Haack, 1927).

In a degassed Et_3N (50 mL), **S1** (25 mmol), $PdCl_2(PPh_3)_2$ (2 mol% Pd, 355 mg, 0.5 mmol) and CuI (2 mol%, 95 mg, 0.5 mmol) were added and stirred at room temperature for 10 minutes. To this mixture, 1-hexyne (3.5 mL, 30 mmol) was slowly added. The mixture was magnetically stirred at RT under inert gas. The reaction was monitored with gas chromatography. After depletion of the reactant, the reaction was terminated with addition of saturated NH_4Cl solution and extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was then purified by column chromatography to yield endo-cyclic enyne aldehyde **S2** as pale yellow oil (hexane/EtOAC; yield: n=0, 88%; n=1, 91%; n=2, 90%) (Sonogashira, 1975).

To a suspension of dry THF (50 mL) and NaH (528 mg, 22 mmol) cooled down to 0 °C, triethyl phosphonoacetate (4.8 mL, 24 mmol) was added dropwise and stirred at room temperature for 1 hour. After that, **S2** (3.8 g, 20 mmol) dissolved in 10 mL THF was added dropwise into this mixture at -78 °C. The mixture was stirred at this

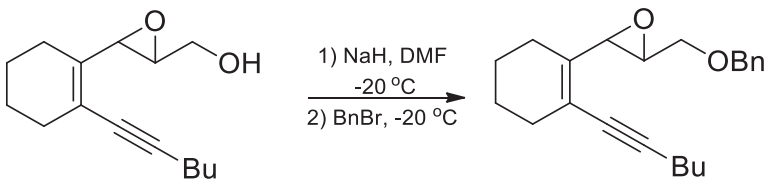
temperature for 1 h and then brought to RT. The reaction was monitored by gas chromatography technique. Upon completion, the reaction was terminated with saturated NH_4Cl solution, extracted with Et_2O, and dried with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purified via silica gel column chromatography to yield **S3** as colourless oil (hexane/EtOAc; n=0, 77%; n=1, 82%; n=2, 82%) (Wadsworth and Emmons, 1961).

To the solution of **S3** (10 mmol) and dry DCM (60 mL) cooled to -78 ^oC, diisopropyl aluminum hydride (DIBALH) (3 equiv, 30 mL, 1.0 M in DCM) was added dropwise and stirred at this temperature. The reaction was monitored by TLC and upon completion, the mixture was quenched with saturated Rochelle's Salt (sodium-potassium tartarate) solution. The quenched mixture was stirred for 3 hours at room temperature. The organic phase was separated and the inorganic phase was washed with DCM. The combined organic phases were dried with Na_2SO_4, filtered, and evaporated under reduced pressure.The crude mixture was purified by column chromatography with silica gel to obtain **S4** as colorless oil (hexane/EtOAC; yield: n=0, 81%; n=1, 89%; n=2, 82%) (Kuş *et al.,* 2015).

To the mixture of dienynol **S4** (2 mmol) and 30 mL DCM at 0 ^oC, 12 mL of 25% Na_2CO_3 aqueous solution was added. The mixture was re-cooled to 0 ^oC and *m*-CPBA (762 mg, 3.4 mmol, ≤77%) was added. The reaction was monitored by TLC and upon completion, the mixture was diluted with water, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by NEt_3-deactivated silica gel column chromatography and enyne oxirane **S5** was obtained as pale yellow oil (hexane/EtOAc; yield: n=0, 27%; n=1, 83%; n=2, 55%) (Kuş *et al.,* 2015).

The compound **S5** (1 mmol) was added dropwise to the mixture of DMF (2 mL) and NaH (26.4 mg, 1.1 mmol) under Argon atmosphere at -20 ^oC. After stirring this mixture 0.5 hour at same temperature, MeI (75 µL, 1.2 mmol) was added and stirred additional 1 h. The reaction was monitored by TLC and terminated with 10 mL water-methanol mixture (1:1). The methyl-substituted structure **1** was purified by NEt_3-deactivated silica gel column chromatography as pale yellow oil (hexane/EtOAc; **1a**, n=0, 91%; **1b**, n=1, 88%; **1c**, n=2, 82%).

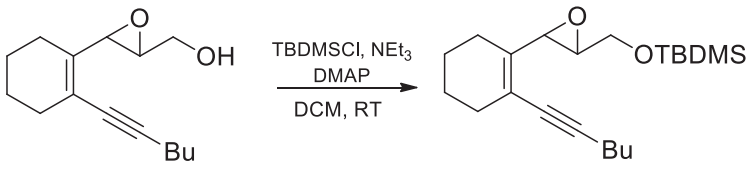
3.2.2. Synthesis of 1d



S5 **1d**

Compound **S5** (1 mmol) in 1 mL of DMF (1 mmol) was added dropwise to the of DMF (2 mL) solution of NaH (26.4 mg, 1.1 mmol) under argon atmosphere at -20 °C. After stirring this mixture for 0.5 hour at the same temperature, BnBr (143 μL, 1.2 mmol) was added and stirred for additional 1 hour. The reaction was monitored by TLC and terminated by 10 mL of water-methanol mixture (1:1). The benzyl-substituted structure **1d** was purified by NEt_3-deactivated silica gel column chromatography as pale yellow oil (hexane/EtOAc; 81%).

3.2.3. Synthesis of 1e

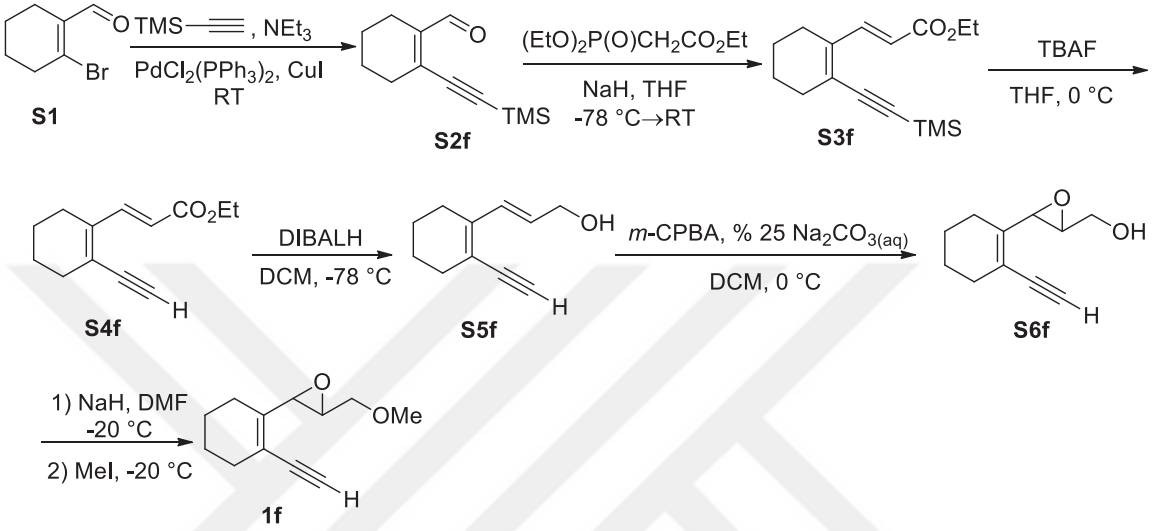


S5 **1e**

S5 (234 mg, 1 mmol) was dissolved in 15 mL DCM under nitrogen atmosphere. To this solution, subsequently, was added; *tert*-butyldimethylsilyl chloride (TBDMSCl, 1.2 equivalent, 181 mg, 1.2 mmol), Et_3N (1.25 equiv, 0.2mL, 1.25 mmol), and catalytic amounts of 4-dimethylaminopyridine (DMAP; 12.5 mg, 0.1 mmol), respectively, and stirred for 24 hour. The reaction was monitored by TLC, extracted with DCM, dried over Na_2SO_4, and filtered. The silyl-substitued compound **1e** was purified by NEt_3-

deactivated silica gel column chromatography method (pale yellow oil, hexane/EtOAc, 87%) (Kuş *et al.,* 2015).

3.2.4. Synthesis of 1f



S1 (10 mmol), $PdCl_2(PPh_3)_2$ (2% mol Pd, 142 mg, 0.2 mmol), and CuI (2% mol Cu, 38 mg, 0.2 mmol) were added in degassed Et_3N (50 mL) and stirred at RT for 10 minutes. To this mixture, trimethylsilyl acetylene (1.7 mL, 12 mmol) was slowly added. The reaction was carried on for 1h and monitored by GC. After depletion of the reactant, the reaction was terminated by the addition of saturated NH_4Cl solution and extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was then purified by column chromatography to yield endo-cyclic enyne aldehyde **S2f** as pale yellow oil (hexane/EtOAC; 92%) (Sonogashira, 1975).

Previous step was repeated to gather sufficient amount of substrate. To a suspension of dry THF (25 mL) and NaH (243 mg, 10 mmol) cooled down to 0 ^oC , triethyl phosphonoacetate (2.2 mL, 11.1 mmol) was added dropwise and mixed at room temperature for 1 hour. After that, **S2f** (1.9 g, 9.2 mmol) was dissolved in 5 mL of THF was added dropwise into this mixture at -78 ^oC. The mixture was stirred at this temperature for 1h and then brought to RT. The reaction was monitored by GC. Upon

completion, the reaction was terminated with saturated NH_4Cl solution, extracted with Et_2O, and dried with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography to yield **S3f** as colourless oil (hexane/EtOAc; 81%) (Wadsworth and Emmons, 1961).

To a solution of **S3f** (828 mg, 3mmol) in 10 mL of dry THF at 0 ^oC, (TBAF, 1.3 equiv, 3.9 mL, 3.9 mmol, 1 M in THF) was added dropwise and stirred for 1 hour. The reaction was monitored with TLC and terminated with saturated ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried with Na_2SO_4, filtered, and concentraded under reduced pressure. The crude product was purified with NEt_3-deactivated by silica gel colum chromatography to yield **S4f** product as pale yellow oil (hexane/EtOAc; 92%).

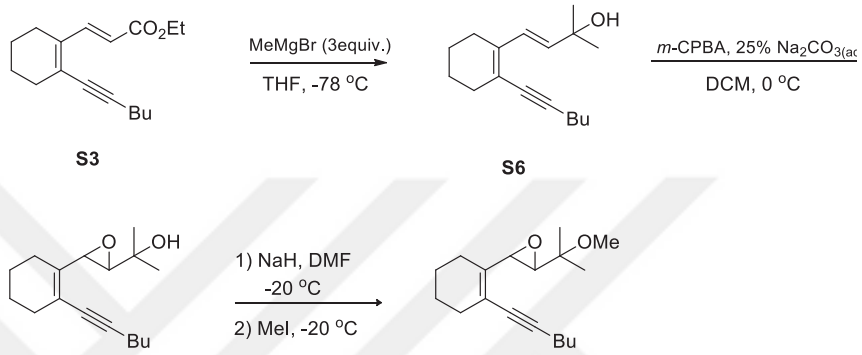
To the solution of **S4f** (2 mmol) in dry DCM (15 mL) cooled down to -78 ^oC, DIBALH (3 equiv, 6 mL, 1.0 M in DCM) was added dropwise and stirred at this temperature. The reaction was monitored with TLC and upon completion, the mixture was quenched with saturated Rochelle's Salt (sodium-potassium tartarate) solution. The quenched mixture was stirred for 3 hours at RT. The organic phase was separated and the aqueous phase was extracted with DCM. The combined organic phases were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography to obtain **S5f** (colourless oil; hexane/EtOAC; 88%).

Previous step was repeated to gather sufficient amount of substrate. To the solution of dienynol **S5f** (2mmol) in 30 mL of DCM at 0 ^oC, 12 mL 25% Na_2CO_3 solution was added. The mixture was re-cooled to 0 ^oC and *m*-CPBA (762 mg, 3.4 mmol, ≤77%) was added. The reaction was monitored by TLC and upon completion, the mixture was diluted with water, extracted by DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by NEt_3 treated silica gel column chromatography to obtain enyne oxirane **S6f** as pale yellow oil (hexane/EtOAc; 53%).

Previous step was repeated to gather sufficient amount of substrate. The compound **S6f** (1 mmol) was added dropwise to the mixture of DMF (2 mL) and NaH (26.4 mg, 1.1 mmol) under Argon atmosphere at -20 ^oC. After stirring this mixture for 0.5 hour at the same temperature, MeI (75 μL, 1.2 mmol) was added and stirred for

additional 1h. The reaction was monitored by TLC and terminated with the addition of 10 mL of water-methanol mixture (1:1). The methyl substituted structure **1f** has purified by NEt_3-deactivated silica gel (pale yellow oil; hexane/EtOAc; 88%).

3.2.4. Synthesis of 1g



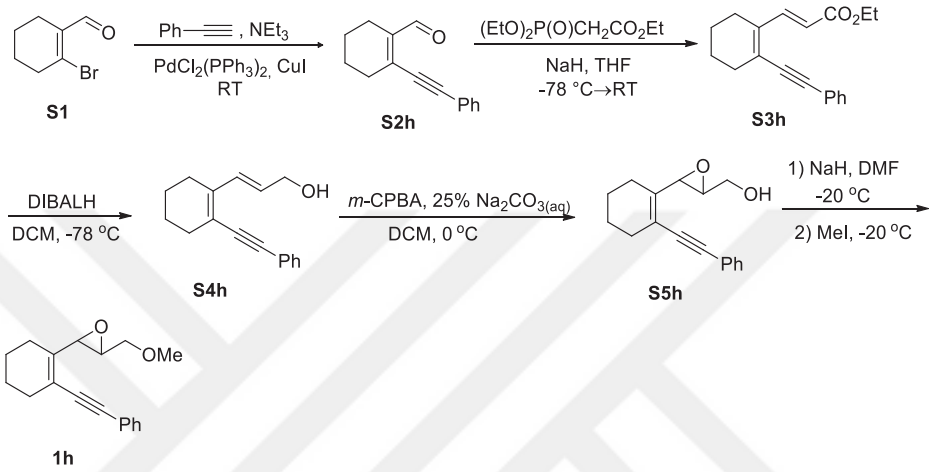
To the solution of **S3** (10 mmol) in 40 mL of dry THF cooled down to -78 °C, MeMgBr (3 equiv, 30 mmol, 10 mL, 3 M in THF) was added dropwise. The reaction progress was monitored by TLC and terminated with the addition of saturated NH_4Cl solution. Organic phases were separated and aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The crude material was purified by silica gel column chromatography to obtain product **S6** as yellow oil (hexane/EtOAc; 87%).

To the mixture of dienynol **S6** (2 mmol) in 30mL of DCM at 0 °C, 12 mL of 25% Na_2CO_3 solution was added. The mixture was re-cooled to 0 °C and *m*-CPBA (762 mg, 3.4 mmol, ≤77%) was added. The reaction was monitored by TLC and upon completion, the mixture was diluted with water, extracted by DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by NEt_3-deactivated silica gel column chromatography to obtain enyne oxirane **S7** as pale yellow oil (hexane/EtOAc; 47%).

Previous step was repeated to gather sufficient amount of substrate. The compound **S7** (1 mmol) was added dropwise to the mixture of DMF (2 mL) and NaH (26.4 mg, 1.1 mmol) under Argon atmosphere at -20 °C. After stirring this mixture for 0.5 hour at the same temperature, MeI (75 μL , 1.2 mmol) was added and stirred further

for additional 1h. The reaction was monitored by TLC and terminated with 10 mL of water-methanol mixture (1:1). Methyl substituted structure **1g** was purified by NEt_3-deactivated silica gel (pale yellow oil; hexane/EtOAc; 80%).

3.2.5. Synthesis of 1h



In a degassed Et_3N (50 mL), **S1** (25 mmol), $PdCl_2(PPh_3)_2$ (2 mol% Pd, 355 mg, 0.5 mmol) and CuI (2 mo%l Cu, 95 mg, 0.5 mmol) were added and stirred at room temperature for 10 minutes. To this mixture phenyl acetylene (3.3 mL, 30 mmol) was slowly added. The mixture was magnetically stirred at RT under intert gas. The reaction was monitored with GC.After depletion of the reactant, the reaction was terminated with the addition of saturated NH_4Cl solution and extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was then purified by column chromatography to yield endo-cyclic enyne aldehyde **S2h** as yellow-green oil (hexane/EtOAC; 67%).

Previous step was repeated to gather sufficient amount of substrate. To a suspension of dry THF (50 mL) and NaH (528 mg, 22 mmol) cooled down to 0 °C, triethyl phosphonoacetate (4.8 mL, 24 mmol) was added dropwise and stirred at room temperature for 1h. Then, **S2h** (20 mmol). Dissolved in 10mL of THF was added dropwise into the mixture at -78 °C. The mixture was stirred at this temperature for 1h and then brought to RT. The reaction was monitored by GC. Upon completion, the reaction was terminated with saturated NH_4Cl solution, extracted with Et_2O, and dried

with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography to yield **S3h** as yellow-green-oil (hexane/EtOAc; 82%) (Wadsworth and Emmons, 1961).

To the solution of **S3h** (10 mmol) in dry DCM (60 mL) cooled down to -78 ^oC, DIBALH (3 equiv, 30 mL, 1.0 M in DCM) was added dropwise and stirred at this temperature. The reaction was monitored by TLC and upon completion, the mixture was quenched with saturated Rochelle's salt (sodium-potassium tartarate) solution. The quenched mixture was stirred for 3 hours at room temperature. The organic phase was separated and the aqueous phase was extracted with DCM. The combined organic phases were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography to obtain **S4h** as greenish oil (hexane/EtOAC; 81%).

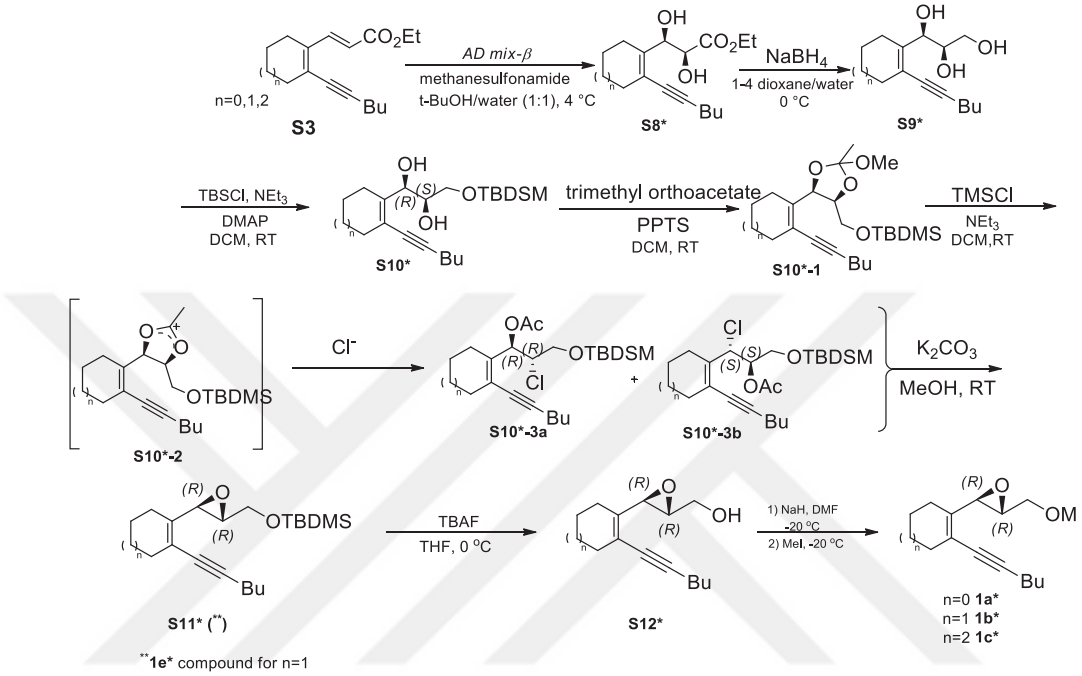
To the solution of dienynol **S4h** (2 mmol) in 30. mL DCM at 0 ^oC, 12 mL of 25% Na_2CO_3 solution was added. The mixture was re-cooled to 0 ^oC and *m*-CPBA (762 mg, 3.4 mmol, ≤77%) was added. The reaction was monitored by TLC and upon completion, the mixture was diluted with water, extracted by DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by NEt_3-deactivated silica gel column chromatography to yield enyne oxirane **S5h** as pale yellow oil (hexane/EtOAc; 75%).

The compound **S5h** (1 mmol) was added dropwise to the mixture of DMF (2 mL) and NaH (26.4 mg, 1.1 mmol) under argon atmosphere at -20 ^oC. After stirring this mixture for 0.5 hour at the same temperature, MeI (75 μL; 1.2 mmol) was added and stirred for additional hour. The reaction was monitored by TLC and terminated with 10 mL of water-methanol mixture (1:1). The methyl substituted structure **1h**, purified by NEt_3-deactivated silica gel column chromatography (pale yellow oil; hexane/EtOAc; 89%).

3.2.6 Synthesis of 1a*,1b*,1c*,1e*

To a mixture of 80 mL water/*t*-BuOH (1:1) mixture at room temperature, 9.2 g *AD mix-β* and methanesulfonamide (760 mg, 8 mmol) were added and stirred until the solution becomes clearer (*approx. 15 minutes*, *upon addition of AD mix-β, the mixture*

becomes diphasic heterogeneous red mixture yet after some stirring it becomes clearer pale red solution). Afterwards, the mixture was cooled to 0 °C, and **S3** (8mmol) was added to the mixture. The reaction medium was kept dark and temperature was held at 4 °C.



When the reaction was complete (around 3-10 days) as judged by TLC analyses, 12 g of $Na_2S_2O_3$ was added and the mixture was stirred for 1h at RT. The reaction medium was diluted with water, extracted with EtOAc, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography to yield **S8*** compound (white solid, hexane/EtOAc, yield: n=0, 55%; n=1, 78%; n=2, 75%) (Sharpless *et al.,* 1992).

The compound **S8*** (4 mmol) was dissolved in 1,4-dioxane/water (40 mL, 1:1) mixture, cooled down to 0 °C and $NaBH_4$ (3 equiv, 454 mg, 12 mmol) was added in portions to the mixture. The mixture was stirred at this temperature until the depletion of **S8*** as judged by TLC. The completed reaction was terminated with 0.1 M HCl, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield **S9*** as white paste (hexane/EtOAc; n=0, 80%; n=1, 95%; n=2, 87%).

To the solution of **S9*** (3.8 mmol), in DCM (15 mL) was added TBDMSCl (1.2 equiv, 689 mg, 4.56 mmol), NEt_3 (1,25 equiv, 0.7 mL, 4.75 mmol) and catalytic amount of 4-dimethylaminopyridine (DMAP, 25 mg, 0.2 mmol) and stirred at room temperature for 24 hours. The reaction was monitored by TLC and upon completion the reaction mixture was diluted with water, extracted with DCM, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The silylated product **S10*** was purified by column chromatography (yellow oil; hexane/EtOAc; n=0, 70%; n=1, 81%; n=2, 77%).

The diol compound **S10*** (0.2 mmol) was dissolved in dry DCM (1 mL) under argon atmosphere and subsequently, 0.5 mg PPTS (pyridinium *p*-toluene sulfonate), trimethyl orthoacetate (1.2 equiv; 32 μL; 0.24 mmol) added. The reaction progress was monitored by TLC and following the complete conversion of the reagent, the reaction flask was evaporated at room temperature under reduced pressure. The crude mixture was further evaporated by vacuum pump for 5 minutes to completely remove volatile compounds that are by-products of this reaction. In the sequel, 1 mL dry DCM was added into the flask, then NEt_3 (2 μL, 10% mmol), trimethylsilyl chloride (1.2 equiv; 31 μL; 0.24 mmol) were added succesively. The progress of the reaction was monitored by TLC and upon depletion of the reactant, the reaction flask was evaporated under reduced pressure at room temperature. As the last step of this one-pot synthesis, the crude product was taken under argon atmosphere and charged with 1 mL of dry MeOH. To this mixture was added K_2CO_3 (4 equiv; 110 mg; 0.8 mmol) and the mixture was stirred at room temperature until the reactant was consumed. The reaction was terminated with water, extracted with DCM, dried by Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by NEt_3-treated silica gel column chromatography to yield *trans*-configured **S11*** compound (**1e*** compound for n=1) as pale yellow oil (hexane/EtOAc; *yield of three-steps combined*; n=0, 47%; n=1, 63%; n=2, 56%) (Kolb and Sharpless 1992).

Previous step was repeated to gather sufficient amount of substrate. To a solution **S11*** (0.2 mmol) in 10 mL dry THF at 0 ºC, TBAF (1.3 equiv, 0.26 mL, 0.26 mmol, 1 M in THF) was added dropwise and stirred 1 hour. The reaction was monitored by TLC and terminated with saturated ammonium chloride solution. The organic phase was separated and aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and concentraded under reduced pressure. The

crude product was purified by NEt3-deactivated silica gel colum chromatography to yield **S12*** product as pale yellow oil (hexane/EtOAc; n=0, 87%; n=1, 92%; n=2, 91%).

Previous step was repeated to gather sufficient amount of substrate. The compound **S12*** (1 mmol) was added dropwise to the mixture of DMF (2 mL) and NaH (26.4 mg, 1.1 mmol) under Argon atmosphere at -20 ^{o}C. After stirring this mixture for 0.5 hour at same temperature, MeI (75 μL, 1.2 mmol) was added and mixed for additional hour. The reaction was monitored by TLC and terminated with 10 mL of water/methanol (1:1) mixture. The structure **1*** was purified by NEt_3-treated silica gel column chromatography (pale yellow oil; hexane/EtOAc; **1a***, n=0, 91%; **1b***, n=1, 88%; **1c***, n=2, 82%).

3.2.7 Synthesis of 1d*

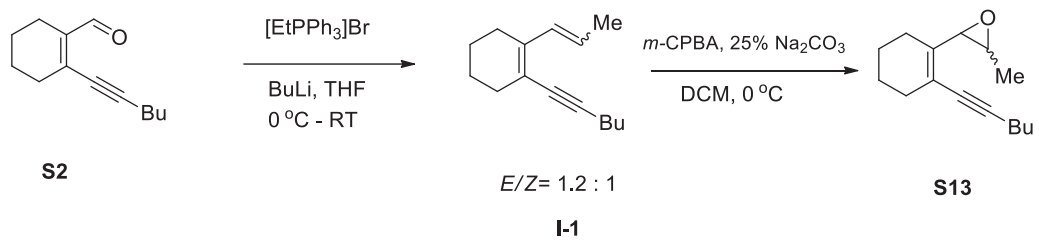
S12* **1d***

The compound **S12*** (1 mmol) was added dropwise to the mixture of DMF (2mL) and NaH (26.4 mg, 1.1 mmol) under argon atmosphere at -20 ^{o}C. After stirring this mixture for 0.5 hour at the same temperature, BnBr (1.2 mmol) was added and stirred for additional 1 hour. The reaction was monitored by TLC and terminated with 10 mL water-methanol mixture (1:1). The structure **1d*** was purified by NEt_3-deactivated silica gel column chromatography (pale-yellow oil; hexane/EtOAc; 93%).

3.3. Intermediate Substrates and Reagents Used en Route To Synthesize Enantioenriched Epoxides

In search of a method to sythesize enantiomerically-enriched epoxide, a number of methods were tested. Those applications are described below.

3.3.1. Synthesis of intermediate I-1 and S13



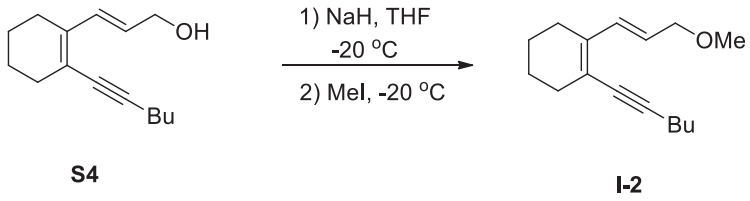
S2 *E*/*Z*= 1.2 : 1 **I-1** **S13**

At 0 °C, BuLi (2.8 mL, 7 mmol, 2.5 M in hexane) was added dropwise to the solution of the Wittig reagent Et(PPh_3)Br (2.23 g, 6 mmol) in dry THF (25 mL) and stirred at the same temperature for 1 hour. Then, **S2** (950 mg, 5 mmol) was added dropwise and the mixture was warmed up to RT. Subsequent to the completion, as judged by TLC analysis, the reaction was terminated with saturated NH_4Cl solution, extracted with Et_2O, dried by Na_2SO_4, and evaporated under reduced pressure. The nixture was purified by column chromatography to obtain **I-1** as pale yellow oil (hexane/EtOAC; 87%; *E/Z*= 1.2:1). The separation of the *E/Z* mixture could be possible by column chromatography over neutral alumina supported $AgNO_3$ (hexane/EtOAc; **EI-1**; 480 mg; 2.37 mmol; **ZI-1**, 399 mg; 1.98 mmol). The column material was prepared as follows;

A suspension of $AgNO_3$ (125 g) and neutral alumina (500 g) in 380 mL of ultrapure water was stirred vigorously and then its water content was removed using rotary evaporator at 100 °C, followed by powerful vacuum pump evaporation at 130 °C.

To the soluion of the dienynol (*E)*-**I-1** or (*Z*)-**I-1** (2 mmol) and 30 mL DCM at 0 °C, 12 mL of 25% Na_2CO_3 solution was added. The mixture was re-cooled to 0 °C and *m*-CPBA (762 mg, 3.4 mmol, ≤77%) was added. The reaction was monitored by TLC and upon completion, the mixture was diluted with water, extracted by DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by NEt_3-treated silica gel column chromatography to yield enyne oxirane **S13** as pale yellow oil; hexane/EtOAc; yield: 47% for (*E*)**I-1**, 49% for (*Z*)**I-1**) (Cameron, 2010).

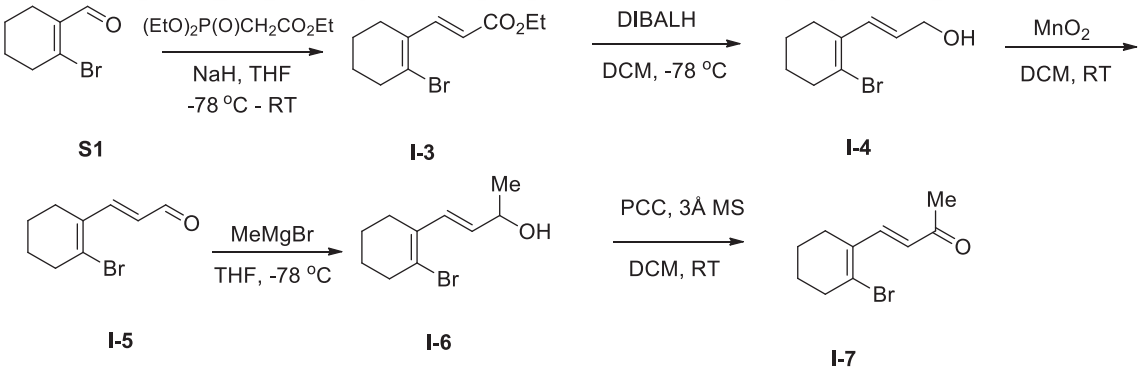
3.3.2. Synthesis of the intermediate I-2



S4 **I-2**

The compound **S4** (1 mmol) was added dropwise to the mixture of THF (5 mL) and NaH (26.4 mg, 1.1 mmol) under N_2 atmosphere at -20 °C. After stirring this mixture 0.5 hour at the same temperature, MeI (1.2 mmol) was added and stirred for additional 1 hour. The reaction was monitored by TLC and terminated with 10 mL water/methanol mixture (1:1). The dienyne structure **I-2** was purified by silica gel column chromatography (pale yellow oil; hexane/EtOAc; 93%) (Kuş *et al.,* 2015).

3.3.3. Synthesis of vinyl bromide derivatives



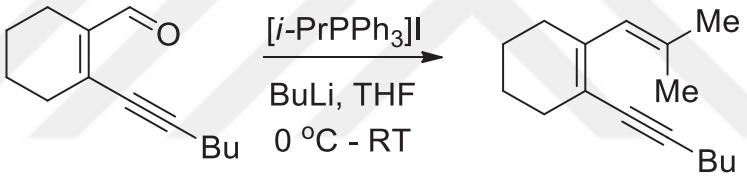
S1 **I-3** **I-4**

I-5 **I-6** **I-7**

On the basis of the aforementioned method, **S1** reagent obtained using Vilsmeier-Haack reagent (1.89 g, 10 mmol) was subjected to Horner-Wadsworth-Emmons (HWE) reaction (**I-3**, 81%) followed by reduction with DIBAL-H (**I-4**, 87%). Allyl alcohol **I-4** (5 mmol) was added to the mixture of 50 mL dry DCM and activated MnO_2 (20 equiv, 1.47 g, 100 mmol) and stirred at room temperature for 5 hours. Upon completion, the solution was filtered by celite/SiO_2 combination and evaporated under reduced pressure. The crude mixture containing **I-5** was dissolved in 30 mL dry THF

and brought to -78 °C. MeMgBr (6 mmol, 2 mL, 3.0 M in THF) was added to the reaction flask dropwise and then stirred for 1 h and the process was monitored by TLC. After completion, the reaction was terminated with saturated NH_4Cl solution, extraced with Et_2O, and dried over Na_2SO_4. The concentrated compound was purified by column chromatography (**I-6**; hexane/EtOAc; 87%). Powdered and activated (heated at 200 °C) molecular sieve 3Å (5 g) was added into the dry DCM (30 mL) solution of **I-6** (693 mg, 3 mmol) at RT and under N_2 atmosphere. PCC (1.94 g, 9 mmol), was added in portions to the mixture over 20 minutes and stirred for 3 hours. At the end of the reaction, the mixture was filtered by celite/glasswool/SiO_2 combination using hexane/Et_2O as the mobile phase. The fitrate obtained was evaporated under reduced pressure and purified by column chromatography (**I-7**; hexane/Et_2O; 82%) (Kuş *et al.,* 2015; Wu *et al.,* 2013).

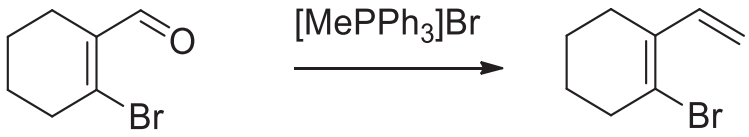
3.3.4. Synthesis of the intermediate I-8



S2 **I-8**

Isopropyl iodide (5.44 g, 32 mmol) and triphenylphosphine (9.96 g, 38 mmol) were added to a teflon-covered steel reactor and mixed for 5 hours at 100 °C. The crude material was used in the Wittig reaction without further purification (Smith,1980). The aldehyde (**S2**, 950 mg, 5 mmol) was treated with [*i*-$PrPPh_3$]I (2.6 g, 6 mmol) in the presence of BuLi (1.5 equiv) in dry THF (120 mL) following the procedures described above (**I-8**; pale yellow oil; hexane; 81%) (Kuş *et al.,* 2015).

3.3.5. Synthesis of the intermediate I-9

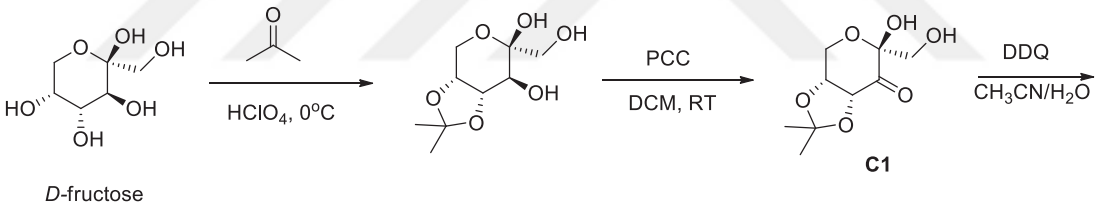


S1 **I-9**

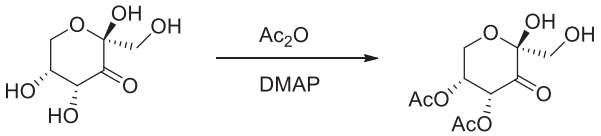
From the compound **S1** (950 mg, 5 mmol), **I-9** compound was synthesized using [$MePPh_3$]Br (2.2 g, 6 mmol) as the Witting reagent under the conditions as described for the synthesis of **I-1** (colorless oil; pentane; 83%) (Kuş *et al.,* 2015).

3.3.6. Synthesis of Shi-catalysts

Shi-catalysts **C1** and **C2** were synthesized by following procedures starting from *D*-fructose as described below;



D-fructose **C1**



C2

To a flask containing acetone (740 mL) was added *D*-fructose (36.84 g, 204.7 mmol) and dimetoxypropane (14.8 mL, 120 mmol) successively, and chilled to 0 °C. Then perchloric acid (8.6 mL, 70%) was added dropwise and stirred at this temperature for 6 hours. The pH of the mixture was set to 7-8 by ammonium hydroxide solution and the crude mixture was evaporated and then the solid residue was crystalized by hexane/DCM (4:1) mixture (white powder, 51%, M.P.: 116-119 °C). The acetylated *D*-fructose (5.2 g, 20 mmol) was dissolved in dry DCM (100 mL) under N_2 atmosphere and to this solution was added, molecular sieves (3Å) (activated under vacuum at 200

ºC). Subsequently, to this suspension was added PCC (11.64 g, 54 mmol) in portions in 15 minutes and stirred 3 hours. The mixture was filtered over celite, concentrated under reduced pressure, and purified by column chromatography using SiO_2 as the stationary phase (white-crystaline, hexane/Et_2O, 88%). The ketone **C1** obtained was recrystalized by hexane/DCM (M.P: 102-105 ºC, $[\alpha]^{25}_D$: -125º, c= 1.0; $CHCl_3$) (Wu *et al.,* 2013). The solution of acetonitrile/water (90 mL, 9:1) and **C1** (5.8 g, 26.7 mmol) was charged with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.6 g, 2.6 mmol), and stirred at room temperature for 7 hours. Later on, the crude mixture was evaporated under reduced pressure, then 80 mL EtOAc was added, dried by Na_2SO_4, and filtered. The solvent was evaporated and the residue was purified by silica gel column chromatography (white solid; hexane/EtOAc; 71%). The diol (3.5 g, 16.1 mmol) collected from the previous step was dissolved in DCM (150 mL) under N_2 atmosphere and cooled down to 0 ºC. Ac_2O (4.6 mL, 48.7 mmol) was added dropwise over 20 minutes. The solution was warmed to room temperature was stirred for 16 hours and filtered over short silica gel column to purify by silica gel column chromatography to yield **C2** as colorless syrup (hexane/EtOAc; 74%) (Wu *et al.,* 2002).

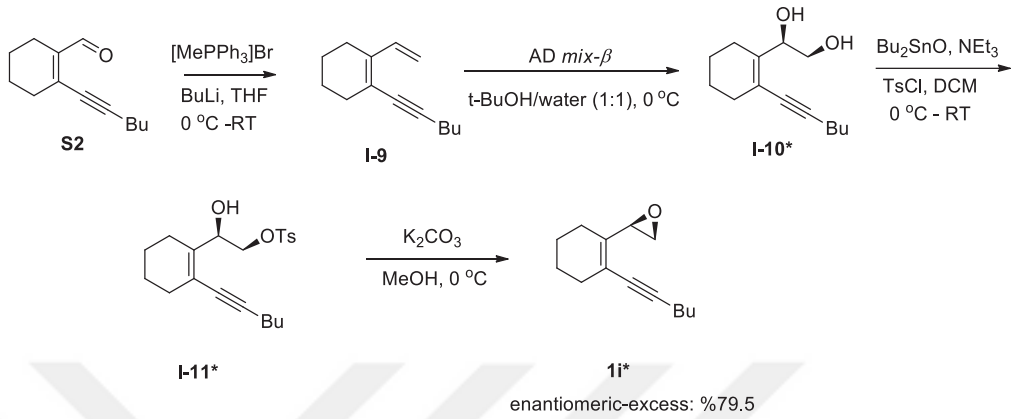
3.3.7. Sythesis of the organocatalyst C3

C3

Commercially available α,α–Diphenyl-L-prolynol (253 mg, 1 mmol) was dissolved in dry DCM (5 mL) under N_2 atmosphere at 0 ºC. Then, imidazole (3 equiv, 204 mg, 3 mmol) and TMSCl (2.5 equiv, 0.32 mL, 2.5 mmol) were added succesively and stirred for 16 hours at room temperature. At the end of the process, 6.5 mL of methyl *tert*-butylether (MTBE) was added to the mixture and the precipitate obtained was filtered, washed with 5 mL of water and 5 mLof brine, dried over Na_2SO_4, and

evaporated under reduced pressure to produce **C3** as yellow oil (%82) (Murar *et al.,* 2014).

3.3.8. Multiple step synthesis of an enantio-enriched terminal epoxide

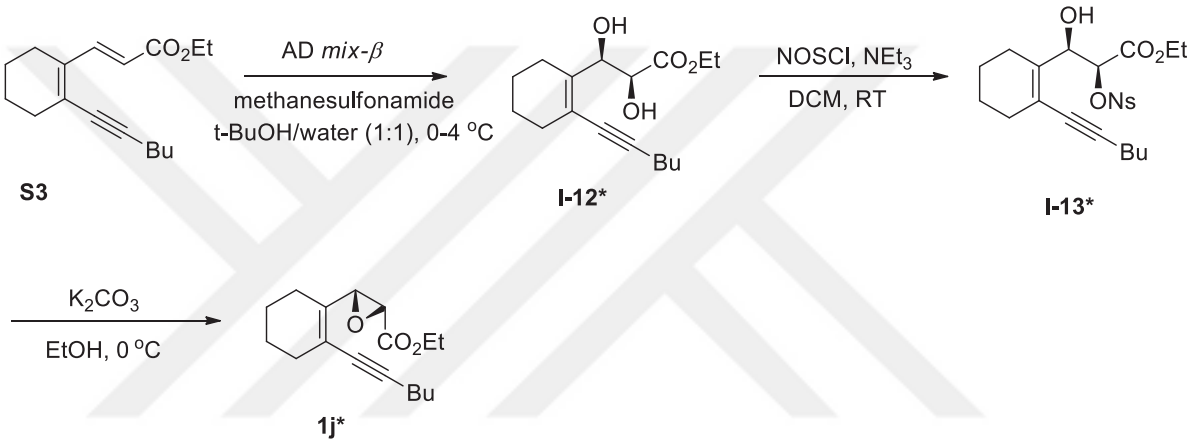


Indirect synthesis of enantiomerically-enriched epoxide was started from Wittig reaction of **S2** (2 mmol) to yield **I-9** (1.6 mmol) with the technique stated above. Following this, 10 mL of water/*t*-BuOH (1:1) mixture was charged with 1.4 g of AD *mix-β* and the mixture was stirred until it appears clear (approx. 10 minutes). Then this flask was cooled down to 0 ºC and **I-9** (188 mg, 1 mmol) was added to the reaction mixture. The reaction flask was stored at 0-4 º C and monitored by TLC until depletion of the reactant (10 days approx.). Upon completion, 1.5 g of $Na_2S_2O_3$ was added and allowed to warm to room temperature and stirred additional 1 hour. The reaction was diluted with water, extracted with EtOAc, dried by Na_2SO_4, filtered, evaporated under reduced pressure, and purified by silica gel column chromatography, which yield diol **I-10*** as white solid (hexane/EtOAc; 94%) (Sharpless *et al.,* 1992).

Under N_2 atmosphere, **I-10*** (202 mg, 0.91 mmol) was dissolved in 5 mL dry DCM and cooled down to 0 ºC. To this solution, NEt_3 (1.25 equiv, 0.16 mL. 1.14 mmol), Bu_2SnO (1.25 equiv, 5.5 mg, 1.14 mmol) and TsCl (1.0 equiv, 174 mg, 0.91 mmol) were sequentially added and the mixture was stirred at the same temperature for 0.5 h. The mixture was then warmed to RT and stirred further for 1 h. The reaction was terminated with the addition of water, extracted with EtOAc, dried by Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography and thus the compound **I-11*** was obtained as yellow oil (hexane/EtOAc, 94%). The epoxidation

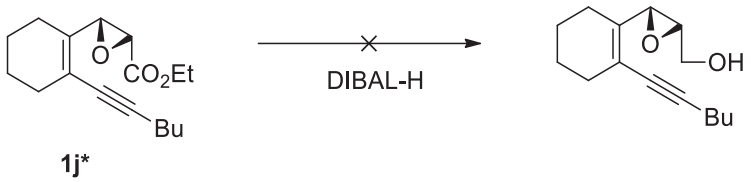
process was carried out by stirring 5 mL of methanol solution of **I-11*** in the presence of K_2CO_3 (2.6 equiv, 306 mg, 2.21 mmol) at 0 ^oC. At the end of the reaction, the mixture was diluted with water, extracted by Et_2O, dried over Na_2SO_4, and filtered. The concentrated mixture was purified by NEt_3-deactivated silica gel column chromatography to obtain **1i*** as colorless oil (hexane/EtOAc; 82%; 79.5% ee) (Karnekanti *et al.,* 2015).

3.3.9. Synthesis of 1j* and 1k*



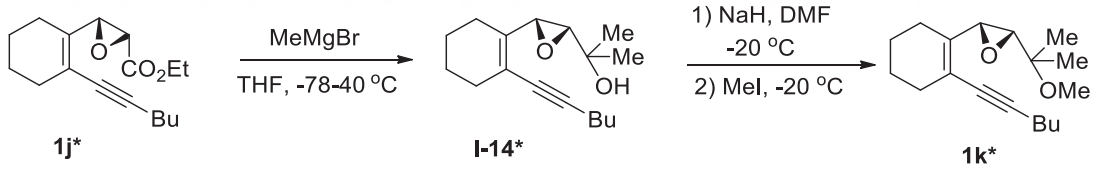
The asymmetric dihydroxylation method was applied to the **S3** (10 mmol), using same the procedure described for the preparation of **S8*** (**I-12***, white solid; hexane/EtOAc; 64%). Under N_2 atmosphere, **I-12*** (1.47 g, 5 mmol), was dissolved in dry DCM (10 mL). Into this solution, NEt_3 (1.25 equiv, 0.9 mL, 6.25 mmol), NsCl (1.2 equiv., 1.33 g, 6 mmol) were added and the mixture was stirred 1 hour. Then, the reaction medium was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to obtain **I-13*** as pale-yellow oil (hexane/EtOAc; 97%). For epoxidation, **I-13*** (1.44 g, 3 mmol) was dissolved in 15 mL EtOH, and cooled to 0 ^oC. K_2CO_3 (3 equiv, 1.24 g, 9 mmol) was added to the mixture and stirred 3 hours. Upon completion 20 mL water was added to the reaction mixture and then extracted with Et_2O, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by NEt_3-deactivated silica gel column chromatography to obtain **1j*** as

colorless oil (hexane/EtOAc, 87%) (Shemet *et al.,* 2015). However, the reduction of **1j*** by DIBAL-H was proceeded unsuccesfuly, which led to a complex mixture



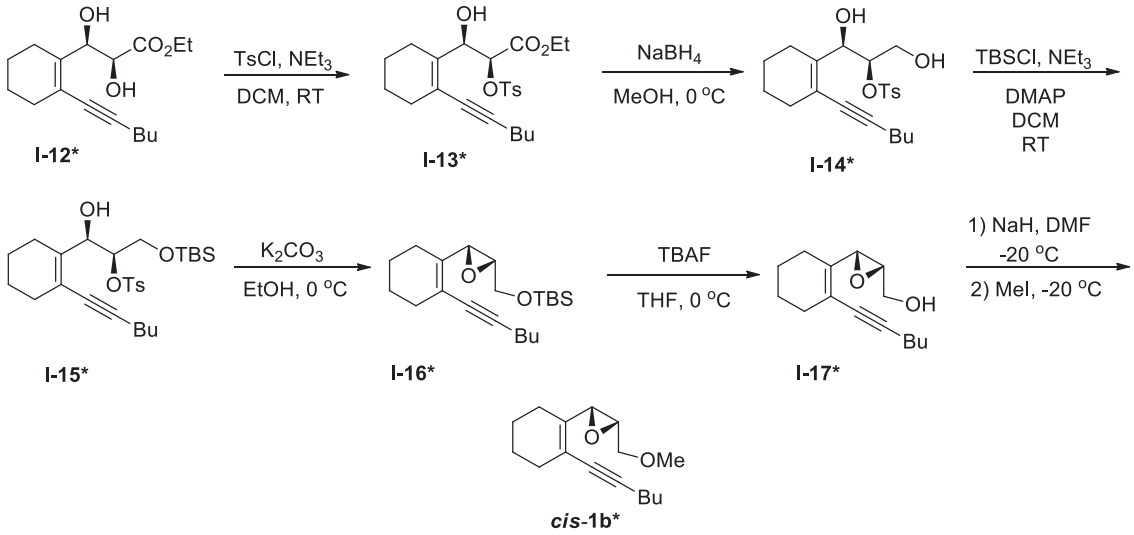
1j*

Instead of reduction of **1j***, its ester group was attempted to transfom to a *tert*-alcohol functionality by a Grignard reagent. The compound **1j*** (552 mg, 2 mmol) was dissolved in 20 mL dry THF and cooled down to -78 ^{o}C. MeMgBr (6 mmol, 2 mL, 3.0 in THF) was added dropwise into this solution and stirred for 1 hour. Then the reaction medium was brought to -40 ^{o}C and monitored by TLC. Upon depletion of the reactant, saturated NH_4Cl solution was added. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to obtain **I-14*** as yellow oil (hexane/EtOAc; 72%).



1j* **I-14*** **1k***

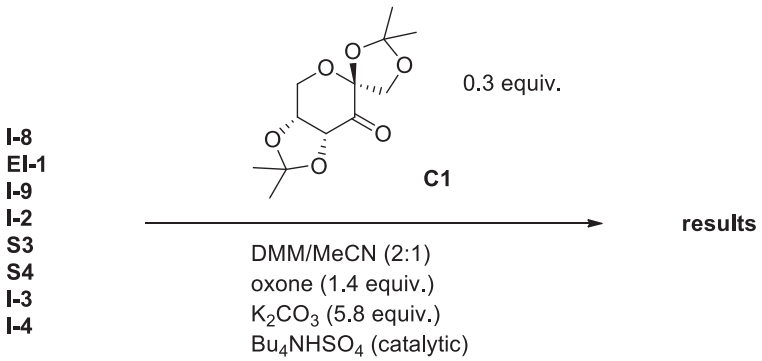
3.3.10 Synthesis of *cis*-1b*



I-12* **I-13*** **I-14*** **I-15*** **I-16*** **I-17*** ***cis*-1b***

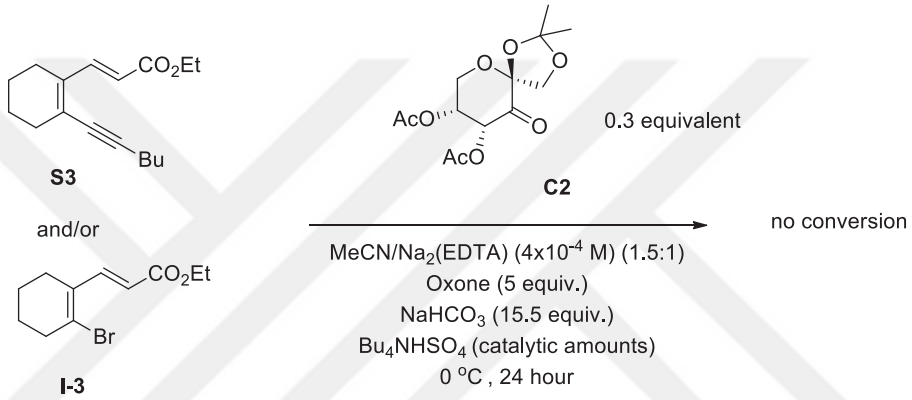
The hydroxyl group α to ester group was tosylated using the same procedure performed for the reaction of **I-13*** with NsCl as described above for **I-12*** (5mmol, 94%). To a 20 mL MeOH solution of **I-13*** (4 mmol), $NaBH_4$ (3 equiv, 454 mg, 12 mmol) was added in portions at 0 ^oC and stirred until the completion, as judged by TLC. The reaction was terminated with 0.1 M HCl solution, extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified over silica gel column chromatography to yield **I-14*** as white paste (hexane/EtOAC; 95%). Under an inert gas atmosphere, **I-14*** (3.8 mmol) was dissolved in dry DCM (15 mL) and subsequently, TBDMSCl (1.2 equiv, 689 mg, 4.56 mmol), NEt_3 (1.25 equiv, 0.7 mL, 4.75 mmol), and catalytic amounts of 4-dimethylaminopyridine (DMAP, 25 mg, 0.2 mmol) were added and the reaction mixture was stirred for 24 hours. The reaction was terminated with water, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The sillylated product **I-15*** was purified by silica gel column chromatography (pale yellow oil; hexane/EtOAc; 87%). The epoxidation of the compound **I-15*** (3.3 mmol) was perforned following the procedure as that of **1j*** (**I-16***; pale yellow oil; hexane/EtOAc; 83%). To a dry THF (10 mL) solution of **I-16*** (2 mmol) was added TBAF (1.3 equiv, 2.6 mL, 2.6 mmol, 1 M in THF) dropwise at 0 ^oC under nitrogen atmosphere. The mixture was stirred for 1 hour and then the reaction was terminated with water, extracted with Et_2O, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Thus the compound **I-17*** was isolated by NEt_3-deactivated silica gel column chromatography (pale yellow oil; hexane/EtOAc; 92%) (Hayashi *et al.,* 2005). The methylation of the alcohol group was performed as described for the synthesis of **1b** (colorless oil; hexane/EtOAc; 86%).

3.3.11. Shi-asymmetric epoxidation method



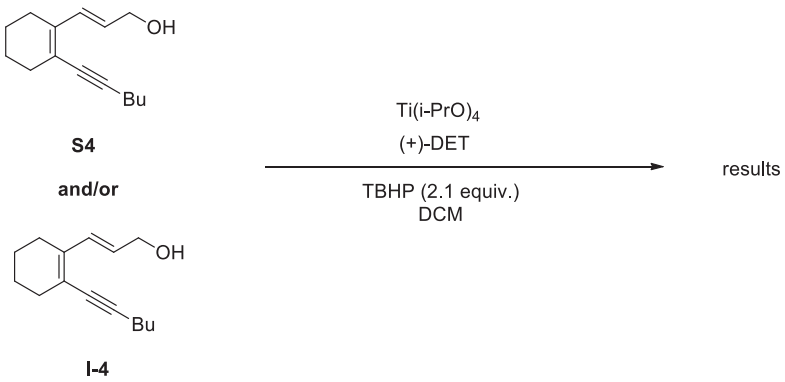
The substrate (1 equiv) (**Table 4.3.**) and **C1** (0.3 equiv) dissolved in dimethoxymethane and acetonitrile mixture (DMM/MeCN, 2:1, 12 mL/mmol) and

Bu_4NHSO_4 was added in catalytic amounts (0.05 equiv.). To this mixture buffer solution (described in **Table 4.3.**) was added and the solution was cooled down to tempereature designated in **Table 4.3**. Oxone ($KHSO_5$, 1.4 equiv) dissolved in water (4 mL/mmol) and K_2CO_3 (5.8 equiv) dissolved in 4 mL $Na_2(EDTA)$ ($4x10^{-4}$M/ mmol) were added simultaneously to the reaction medium over designated time with syringe pump (described in **Table 4.3.**). As soon as addition ended, pentane water mixture was added to quench reaction. Organic phases were separated and aqueous phase was extracted with pentane, dried over Na_2SO_4, filtered and evaporated under reduced pressure to be further purified by silica gel column chromatography (**Table 4.3**.**)** (Wang and Shi, 1998; Frohn and Shi, 2000; Burke and Shi, 2006).



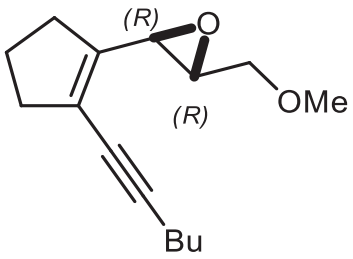
Selected substrate **S3** or **I-3** was dissolved in MeCN (5 mL/mmol), cooled down to 0 ^oC and subsequently, $Na_2(EDTA)$ ($4x10^{-4}$ M) (5 mL/mmol), catalytic amounts of Bu_4NHSO_4 were added. In a separate flask, oxone (5 equiv) and $NaHCO_3$ (15.5 equiv) were ground and mixed throughly and then added to the reaction flask in portions untill PH exceeds 7. Later on, **C2** (0.3 equiv) in MeCN (2.5 mL/mmol) was added to the reaction medium. Remaining oxone/$NaHCO_3$ mixture was added to the reaction over 4.5 hour period. Upon completion of the addition, the reaction was stirred for 7.5 hour at 0 ^oC and stirred 12 hours at room temperature. The reaction was terminated by the addition of water. Extraction of the aqueous phase was done by EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure (Wu *et al.,* 2002).

3.3.12. Sharpless Asymmetric Epoxidation Method

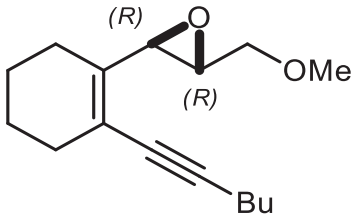


Moleculer sieve 4Å (250 mg/mmol), powdered and activated at 300 ^{o}C under vacuum was added in DCM (7 mL/mmol) and the suspention was cooled down to -20 ^{o}C. Subsequently with amounts indicated in Table 4.4, Ti(*i*-PrO)$_4$ and tartrate derivatives were added into the reaction flask, stirred for 20 minute, and adjusted to an indicated temperatures. The reactant was dissolved in DCM (2 mL/mmol) and added to the reaction flask in 30 minutes. Later on, an amount of TBHP (2.1 equiv, 3.8 M in toluene) as designated in Table 4.4 was added to the reaction medium dropwise and the reaction was monitored by TLC (Katsuki and Sharpless, 1980; Hanson and Shaprless, 1986).

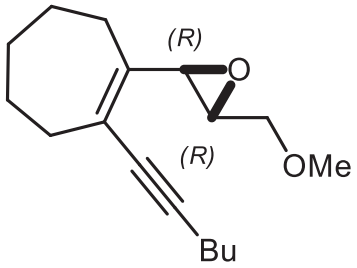
3.4. Characterization of Substrates



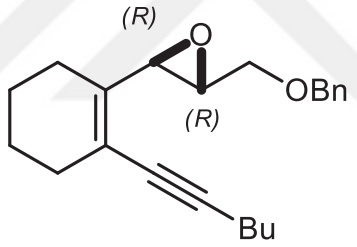
1a*: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77 (d, *J* = 2.1 Hz, 1H), 3.71 (dd, *J* = 11.8, 2.6 Hz, 1H), 3.39 (s, 3H), 3.42 – 3.36 (m, 1H), 3.23 (dt, *J* = 6.3, 3.1 Hz, 1H), 2.46 (t, *J* = 7.6 Hz, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.11 – 2.06 (m, 2H), 1.89 – 1.76 (m, 2H), 1.57 – 1.34 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.4, 126.2, 96.4, 75.8, 72.8, 59.2, 56.4, 53.0, 37.7, 30.8, 30.6, 22.0, 21.9, 19.3, 13.6. Specific Rotation: $[\alpha]^{28}_{D}$ = 1.302 (c=3.07 in $CHCl_3$) ; HPLC: OJ-H, hexane/IPA = 99.0:1.0, 1 mL/min, 254 nm, RT_1= 10.80 (major), RT_2= 15.93 (minor), ee% : 99.0.



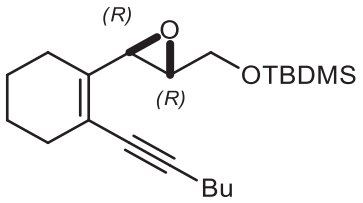
1b*: 1b: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 - 7.26 (m, 5H), 3.88 (d, *J* = 2.2 Hz, 1H), 3.69 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.45 – 3.31 (m,1H), 3.40 (s, 3H), 3.12 (dt, *J* = 5.4, 2.7 Hz, 1H), 2.34 (t, *J* = 6.8 Hz, 2H), 2.23 – 2.11 (m, 2H), 2.08 – 1.88 (m, 2H), 1.72 – 1.34 (m, 8H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.3, 121.7, 94.2, 79.5, 73.1, 59.2, 56.2, 55.2, 30.9, 30.8, 22.4, 22.2, 21.9, 21.7, 19.2, 13.6. Specific Rotation: $[\alpha]^{24}_{\Delta}$ = 10.3 (c=1.165 in $CHCl_3$) ; HPLC: OJ-H, hexane, 1 mL/min, 254 nm, RT_1= 8.564 (major), RT_2= 11.752 (minor), ee% : 97.3.



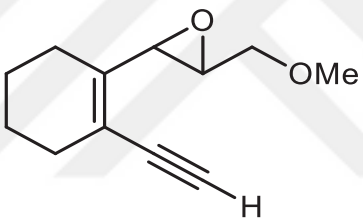
1c*: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.96 (d, *J* = 2.3 Hz, 1H), 3.74 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.39 (s, 3H), 3.40 – 3.35 (m, 1H), 3.01 (dt, *J* = 5.8, 2.6 Hz, 1H), 2.43 – 2.28 (m, 2H), 2.33 (t, *J* = 6.9 Hz, 2H), 1.97 – 1.82 (m, 2H), 1.76 – 1.65 (m, 2H), 1.56 – 1.35 (m, 8H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.7, 127.0, 95.0, 80.7, 72.8, 59.1, 55.8, 55.1, 35.7, 32.5, 30.9, 26.2, 26.1, 25.2, 21.9, 19.3, 13.6. Specific Rotation: $[\alpha]^{28}_D$= -11.428 (c=2.45 in $CHCl_3$) ; HPLC: OJ-H, hexane/IPA= 99:1, 1 mL/min, 254 nm, RT_1= 7.94 (major), RT_2= 11.30 (minor), ee% : 97.1.



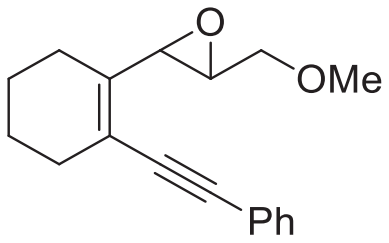
1d*: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 4.59 (q, *J* = 12.0 Hz, 2H), 4.01 (d, *J* = 2.2 Hz, 1H), 3.81 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.47 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.24 (dt, *J* = 5.9, 2.6 Hz, 1H), 2.31 (t, *J* = 6.9 Hz, 2H), 2.22 – 2.09 (m, 2H), 1.98 – 1.90 (m, 2H), 1.73 – 1.34 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9, 137.3, 128.4, 127.7, 127.7, 121.8, 94.3, 79.5, 73.2, 70.7, 56.4, 55.4, 30.9, 30.9, 22.4, 22.2, 21.9, 21.7, 19.2, 13.6. Specific Rotation: $[\alpha]^{24}_D$ = -0.97 (c=4.11 in $CHCl_3$) ; HPLC: OJ-H, hexane/IPA= 99.0:1.0, 1 mL/min, 254 nm, RT_1= 6.29 (major), RT_2= 7.69 (minor), ee% : 94.6.



1e*: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.99 (d, *J* = 1.8 Hz, 1H), 3.87 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.64 (ddd, *J* = 11.9, 4.7, 0.8 Hz, 1H), 3.12 – 3.08 (m, 1H), 2.29 (t, *J* = 6.9 Hz, 2H), 2.18 – 2.07 (m, 2H), 2.03 – 1.86 (m, 2H), 1.71 – 1.32 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 121.4, 94.0, 79.5, 63.5, 56.9, 56.2, 30.9, 30.9, 25.8, 22.4, 22.2, 21.9, 21.7, 19.2, 18.3, 13.6, -5.3, -5.4. Specific Rotation: $[\alpha]^{24}_{D}$= 11 (c=0.22 in $CHCl_3$) HPLC: OD-3, hexane, 1 mL/min, 254nm, RT_1= 7.025 (major) , RT_2=15.177 (minor), ee% : 94.6.



1f: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.96 (d, *J* = 1.3 Hz, 1H), 3.71 (ddd, *J* = 11.5, 2.9, 0.9 Hz, 1H), 3.39 (s, 3H), 3.40 – 3.35 (m, 1H), 3.19 (dt, *J* = 6.3, 3.1 Hz, 1H), 3.13 (s, 1H), 2.23 – 2.14 (m, 2H), 2.06 – 1.93 (m, 2H), 1.76 – 1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.1, 120.1, 82.6, 81.1, 72.9, 59.2, 55.9, 55.3, 30.3, 22.5, 22.0, 21.4.

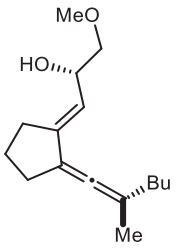


1h: ^{1}H NMR (400 MHz, $CDCl_3$-d) δ: 7.46 – 7.37 (m, 2H), 7.36 – 7.24 (m, 3H), 4.09 (d, *J* = 2.3 Hz, 1H), 3.76 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.52 – 3.39 (m, 2H), 3.42 (s, 3H), 3.34 – 3.22 (m, 1H), 2.30 (s, 3H), 2.12 – 2.01 (m, 2H), 1.85 – 1.54 (m, 3H), 1.42 (s, 0H), 1.28 (s, 1H), 0.89 (s, 1H), 0.92 – 0.81 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ: 139.5, 131.3, 128.3, 128.1, 123.5, 121.1, 93.3, 88.3, 72.9, 59.2, 56.3, 55.5, 30. 22.7, 22.2, 21.6.

3.5. General Method for Iron-Mediated Reactions of Enyne Oxiranes

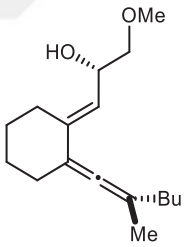
All the glassware used in the reaction were kept at oven for 24 hour at 120 ^{o}C then cooled under argon atmosphere prior to use. THF was distilled over $LiAlH_4$ under ultra high purity argon (6 grade- 99.9999%), which was passed thorough KOH and P_2O_5 filled glass tube. The catalyst, $Fe(acac)_3$ was taken into a Schlenk that held under 6 grade argon balloon and 2 mL dry THF was added. Subsequent to stirring of the mixture for 1 minute at room temperature, the schlenk was cooled down to -50 $^{\circ}$C, the Grignard reagent (3 equiv, MeMgBr, 3 M in THF) was added to the reaction mixture dropwise, and then stirred for 15 minutes. The enyne oxirane reagent (0.1 mmol in 1 mL dry THF) was added into the reaction medium via a syringe pump over 30 minutes. When the addition of the Grignard solution completed, the reaction was further continued. Following the completion of the reaction as judged by TLC, the reaction was terminated with saturated NH_4Cl solution, extracted with Et_2O, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (pale yellow oil, hexane/EtOAc). The enantiomeric-excess was analyzed by HPLC using a suitable chiral columns and diastereometric ratios were determined by NMR technique using C_6D_6 as the solvent (Table 1,2).

3.6. Characterization of products



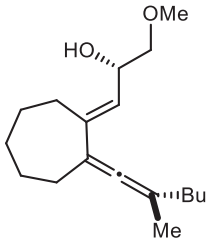
2aa*

2aa*: ^{1}H NMR (400 MHz, C_6D_6) δ 5.83 (dt, *J* = 8.2, 2.4 Hz, 1H), 4.54 (td, *J* = 8.0, 4.1 Hz, 1H), 3.18 – 3.08 (m, 2H), 2.98 (s, 3H, minor), 2.96 (s, 3H, major), 2.38 (t, *J* = 7.2 Hz, 2H), 2.33 – 2.22 (m, 1H), 2.11 (dtd, *J* = 10.2, 7.7, 2.6 Hz, 1H), 1.91 (td, *J* = 7.2, 2.2 Hz, 2H), 1.64 (s, 3H, major), 1.63 (s, 3H, minor), 1.51 – 1.21 (m, 7H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ: 195.4, 142.6, 119.8, 105.7, 103.8, 76.4, 69.3, 58.2, 34.2, 31.6, 30.0, 29.8, 24.9, 22.4, 18.8, 13.8. MS (EI, m/z): 250 (<5, M^+), 205 (98), 187 (46), 145 (80), 131 (53), 117 (58), 105 (77), 91 (98), 79 (63), 57 (45), 45 (47). Specific Rotation: $[\alpha]^{28}_D$ = -46.511 (c= 0.301 in $CHCl_3$). HPLC: AS-H, hexane, 1 mL/min, 254 nm, RT_1= 24.05(major) RT_2=24.54 (minor), ee% : 99.67.



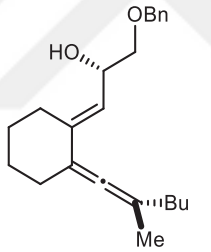
2ba*

2ba*: ^{1}H NMR (400 MHz, C_6D_6) δ: 5.74 (d, *J* = 8.0 Hz, 1H), 4.67 – 4.57 (m, 1H), 3.18 – 3.10 (m, 2H), 2.99 (s, 3H, minor), 2.98 (s, 3H, major), 2.37 – 2.22 (m, 4H), 2.22 – 2.10 (m, 1H), 2.00 – 1.81 (m, 2H), 1.65 (s, 3H, major), 1.64 (s, 3H, minor), 1.55 – 1.23 (m, 8H), 0.86 (t, *J* = 7.3 Hz, 3H, major), 0.85 (t, *J* = 7.3 Hz, 3H, minor). ^{13}C NMR (100 MHz, C_6D_6) δ: 197.7, 139.6, 123.7, 104.8, 98.6, 76.6, 67.0, 58.2, 34.0, 31.9, 29.8, 28.7, 26.2, 25.8, 22.3, 19.2, 13.9. , MS(EI m/z): 264.2 (37.31, M^+), 219.1 (36), 201.2 (26.30), 177.2 (14.85), 163.1 (29.37), 159.1 (17.87), 145.1(51.69), 133.1 (92.06), 131 (54), 119 (45), 105 (100), 91 (88), 77 (39) 57 (21), HRMS (m/z ,$(M+H)^+$) : 265.21621 (calculated) , 265.21401 (found). Specific rotation: $[\alpha]^{24}_D$= -38.23 (c=1,21 $CHCl_3$), HPLC: IC, hexane/IPA= 95:5, 1 mL/min, 254 nm, RT_1= 6.14 (major) , RT_2= 6.55 (minor), ee% : 97.3.



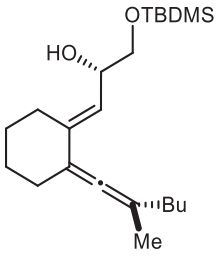
2ca*

2ca: ^{1}H NMR (400 MHz, C_6D_6) δ 5.83 (d, *J* = 8.1 Hz, 1H), 4.61 (td, *J* = 8.1, 4.0 Hz, 1H), 3.28 – 3.06 (m, 2H), 2.97 (s, 3H, minor), 2.96 (s, 3H, major), 2.31 – 2.18 (m, 4H), 1.90 (tq, *J* = 14.8, 7.3 Hz, 2H), 1.64 (s, 3H, major), 1.62 (s, 3H, minor), 1.59 – 1.16 (m, 11H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ: 199.8, 142.7, 124.6, 108.2, 99.1, 76.7, 67.5, 58.2, 34.0, 33.0, 31.4, 30.2, 29.8, 29.7, 29.2, 22.4, 18.9, 13.8., MS (EI m/z): 278.3 (<5, M^+), 147 (6), 133 (6), 117 (12), 105 (9), 91 (31), 79 (14), 67 (9), 55 (21), 45 (100). HRMS (m/z,$(M+H)^+$: 279.23186 (calculated) , 279.23272 (found). Specific Rotation: $[\alpha]^{19}_D$= -47.61 (c= 2.16 $CHCl_3$), HPLC: OD-3, hexane/IPA: 99.5:0.5, 1 mL/min, 254 nm, RT_1= 11.60 (major), RT_2= 12.73 (minor), ee% : 99.6.



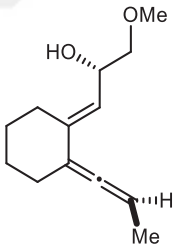
2da*

2da*: ^{1}H NMR (400 MHz, C_6D_6) δ 7.18 – 7.02 (m, 5H), 5.76 (d, *J* = 8.1 Hz, 1H), 4.65 (td, *J* = 7.8, 4.1 Hz, 1H), 4.21 (s, 2H, minor), 4.20 (s, 2H, major), 3.32 – 3.21 (m, 2H), 2.30 – 2.21 (m, 4H), 2.14 – 2.06 (m, 1H), 1.96 – 1.82 (m, 2H), 1.63 (s, 3H, major), 1.62 (s, 3H, minor), 1.53 – 1.16 (m, 8H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ:197.7, 139.6, 138.4, 128.2, 127.4, 123.7, 104.8, 98.6, 74.3, 72.9, 67.2, 34.0, 31.9, 29.8, 28.7, 26.1, 25.7, 22.3, 19.3, 13.9. HRMS (ESI) $C_{23}H_{33}O_2$ $(M + H)^+$: 363.2295 (calculated), 363.2280 (measured). MS(EI m/z): 340.2 (6.42, M^+), 219 (15), 203 (8), 189 (13), 175.1 (8), 161 (11), 149 (10), 133 (19), 119 (20), 105 (30), 91 (100), 77 (14) Specific Rotation: $[\alpha]^{24}_D$= -28,10 (c= 1.21 $CHCl_3$); HPLC: IC, hexane/IPA= 95:5, 1 mL/min, 254 nm, RT_1= 6.12 (minor) , RT_2= 6.55 (major), ee% : 97.5.



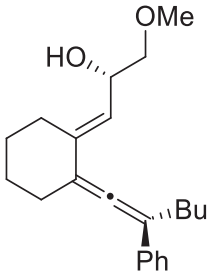
2ea*

2ea*: ^{1}H NMR (400 MHz, C_6D_6) δ 5.76 (d, *J* = 8.1 Hz, 1H, major), 5.74 (d, *J* = 7.6 Hz, 1H, minor), 4.56 – 4.49 (m, 1H), 3.56 – 3.49 (m, 2H, minor), 3.52 – 3.42 (m, 2H, major), 2.40 – 2.21 (m, 4H), 2.14 – 2.02 (m, 1H), 1.98 – 1.83 (m, 2H), 1.65 (s, 3H, major), 1.63 (s, 3H, minor),1.51 – 1.25 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.85 (s, 9H), -0.06 (s, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ: 197.7 (major), 197.6 (minor), 139.6 (major), 139.5 (minor), 124.0 (minor), 123.9 (major), 105.0 (minor), 104.9 (major), 98.6 (major), 98.4 (minor), 68.8 (minor), 68.7 (major), 67.3, 34.1 (major), 34.0 (minor), 31.9 (major), 31.9 (minor), 29.8 (major), 29.7 (minor), 28.8, 26.2 (minor), 26.1 (major), 25.8 (major), 25.8 (minor), 25.7, 22.3 (major), 22.2 (minor), 19.4 (major), 19.2 (minor), 18.1, 13.9, -5.7, -5.6. MS(EI m/z): 364.4 (<5, M^+), 291 (26), 203 (20), 157 (30), 145 (16), 131 (23), 177 (27), 105 (19), 101 (29), 91 (40), 77.0 (17), 75 (100), 59 (26) Specific Rotation: $[\alpha]^{24}_{D}$=32.84 (c= 0.02 0,28 $CHCl_3$) .



2fa

2fa: ^{1}H NMR (400 MHz, C_6D_6) δ: 5.72 (d, *J* = 8.1 Hz, 1H), 5.10 – 5.03 (m, 1H), 4.64 – 4.56 (m, 1H), 3.15 – 3.06 (m, 2H), 2.96 (s, 3H), 2.33 – 2.17 (m, 4H), 2.13 – 2.01 (m, 1H), 1.51 (d, *J* = 7.0 Hz, 3H), 1.47 – 1.39 (m, 2H), 1.36 – 1.22 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ: 201.3, 138.6, 124.3, 104.9, 85.0, 76.5, 66.9, 58.2, 31.4, 28.4, 25.8, 25.6, 14.6. MS(EI m/z): 208 (9), 175 (5), 163 (100), 145 (36), 121 (32), 117 (31), 105 (29), 91 (62), 79 (33) 77 (34), 55 (38).



1ha

2bb: ^{1}H NMR (400 MHz, C_6D_6-d6) δ: 7.48 – 7.41 (m, 2H), 7.15 (s, 1H), 7.04 (td, *J* = 7.8, 7.3, 6.0 Hz, 1H), 4.81 (d, *J* = 9.5 Hz, 1H), 4.45 – 4.36 (m, 1H), 3.37 (dd, *J* = 9.5, 2.6 Hz, 1H), 3.20 (dd, *J* = 9.4, 6.6 Hz, 1H), 2.93 (d, *J* = 0.8 Hz, 4H), 2.37 (d, *J* = 17.5 Hz, 3H), 2.30 – 2.19 (m, 3H), 2.17 (s, 1H), 1.99 (d, *J* = 17.9 Hz, 2H), 1.50 – 1.43 (m, 1H), 1.46 – 1.38 (m, 1H), 1.41 – 1.30 (m, 9H), 1.30 – 1.23 (m, 7H), 0.88 (d, *J* = 6.5 Hz, 2H), 0.82 (t, *J* = 7.1 Hz, 3H), 0.26 (s, 1H). ^{13}C NMR (400 MHz, C_6D_6-d6) .. MS (EI m/z): 326 (28, M^+), 252 (20), 251 (54), 209 (21), 196 (23), 195 (100), 181 (24), 167 (50), 165 (30), 141 (24), 129 (14), 115 (15), 91 (39), 67 (16).

CHAPTER 4

RESULT AND DISCUSSION

From the work done by Artok's group, it has been proved that reaction of acyclic enyne epoxides with Grignard reagents in presence of iron catalyst produced vinyl allene structures in high yields. Yet, this method showed low stereo-electivity producing only low diastereomeric ratios (Figure 4.1) (Taç *et al.,* 2017).

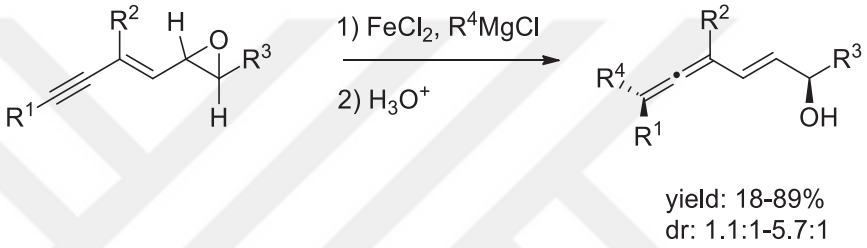


Figure 4. 1 Iron catalyzed reaction of acyclic enyne epoxides with Grignard reagents
(Source: Taç *et al.,* 2017).

Although acyclic conjugates yielded with low diastereomeric ratios, endocyclic derivative (**1b**) showed remarkable stereoselectivity. (Figure 4.2)

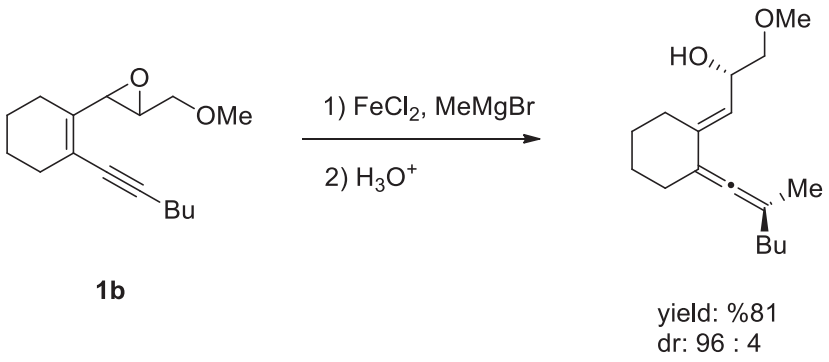


Figure 4. 2 Iron catalyzed reaction of acyclic enyne epoxides with Grignard reagents
(Source: Taç *et al.,* 2017).

High diastereoselectivity in this reaction means that chirality bound to the epoxide ring has been transfered to the allenyl moiety in the product with great success, which led us to think about that, the method might be suitable to synthesize

enantiomerically enriched exo-cylic vinyl allenes with a hydroxyl group on the allylic position. This was the ambition that has driven us to undertake this study.

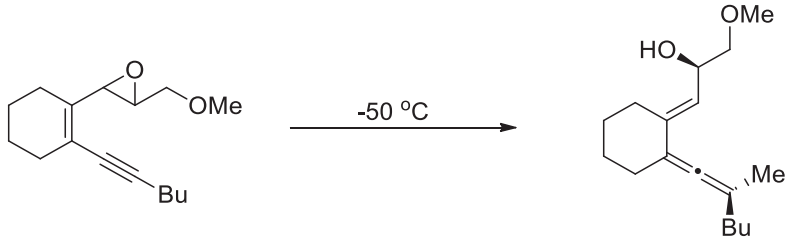
Studies began with optimization work; initially optimum conditions used in the previous work was applied for endo-cyclic enyne epoxide substrate **1b** (Figure 4.3.). Two methods were applied for the optimisation, (Table 4.1.):

Method A: Grignard reagent was added first to the dry THF solution of the catalyst and stirred for 10 minutes. Then, with the help of a syringe pump, the reactant was added in 1 mL solvent over a designated time.

Method B: Reactant was added in 1 mL solvent first and stirred 1 minute. Then with the help of a syringe pump Grignard reagent was added in 1 mL solvent over a designated time.

We observed that halogen atom on the Grignard reagent did not effected the outcome of the reaction (Table 4.1., Entries 1 and 2). Reproducible results were obtained consequent to the use of $Fe(acac)_3$ with Method A, but only when THF was distilled over $LiAlH_4$ and used fresh (Table 4.1., Entry 3-5). When the same conditions were applied with $FeCl_2$ (Table 4.1., Entry 8), non-reproducible results were observed. Surveying the literature, it was understood that reactions performed with different brands of $FeCl_2$ could show different performances (Buchwald and Bolm, 2009; Perry *et al.,* 2012). Besides, the hygroscopic nature of $FeCl_2$ could affect the catalytic cycle by coordination of water molecules as a ligand to the metal complex. Hence $Fe(acac)_3$ has been the choice of catalys in our studies.

Table 4. 1 Optimisation studies



1b (0.1 mmol)

No.	Fe complex (%20)	MeMgX (3 equiv.)	Experimental Method	Addition Time (min.)	Solvent (3mL)	Yields[a] (%)
1	$FeCl_2$	MeMgBr	B	30	THF	Complex
2	$FeCl_2$	MeMgCl	B	30	THF	Complex
3[b]	$Fe(acac)_3$	MeMgBr	A	30	THF	Complex
4[c]	$Fe(acac)_3$	MeMgBr	A	30	THF	Complex
5	$Fe(acac)_3$	MeMgBr	A	30	THF	84 (83)[e]
6	$Fe(acac)_3$	MeMgBr	B	30	THF	Complex
7	$Fe(acac)_3$	MeMgCl	A	30	THF	65[d]
8	$FeCl_2$	MeMgBr	A	30	THF	90 (86)[e]
9	$FeCl_2$	MeMgCl	A	30	THF	86 (84)[e]
10	$Fe(acac)_3$	MeMgBr	A	30	Et_2O	Complex
11	$Fe(acac)_3$	MeMgBr	B	30	Et_2O	Complex
12	$Fe(acac)_3$	MeMgBr	A	30	Toluene	Complex
13	$Fe(acac)_3$	MeMgBr	B	30	Toluene	Complex
14	$Fe(acac)_3$	MeMgBr	A	30	Hexane	Complex
15	$Fe(acac)_3$	MeMgBr	A	30	DME	Complex

[a] Determined by ^1H NMR as benzaldehyde internal standart.

[b] THF,used from SPS.

[c] THF, dried over benzophenone/ketyl radical.

[d] The reactant presence was determined by TLC, the reaction was brought to completion by further addition of catalyst.

[e] isolated yield; dr= 94.5: 6.5

.

Upon achieving optimized results, a method to synthesize enantio-enriched epoxide was searched. Few techniques are known in the literature that enables asymmetric epoxidation in a single step, some of the important works were;

1. Jacobsen-Katsuki Epoxidation: Asymmetric epoxidation of cis disubstitued olefins in presence of a Salen-like catalyst. This method works only for cis olefins and not practicle for conjugated molecules (Zhang *et al.,* 1990).
2. Corey-Chaykovsky Reaction: Epoxidation of carbonyl compounds in the presence of sulfonium ylides. (Corey and Chaykovsky, 1965)
3. Organocatalytic Asymmetric Epoxidation : An asymmetric epoxidation method for α,β–unsaturated aldehydes using phase transfer, peptide-type, chiral amine and imine catalysts (Marigo *et al.,* 2005).
4. Sharpless Asymmetric Epoxidation : Allows asymmetric epoxidation of allylic alcohols using titanium and chiral dialkyltartrate compounds (Katsuki and Sharpless, 1980).
5. Shi-Asymmetric Epoxidation: Cyclic ketone compounds derived from *D*- or *L*-fructose can be used as catalysts in asymmetric epoxidation of alkyl substitued olefins (Shi, 1996).

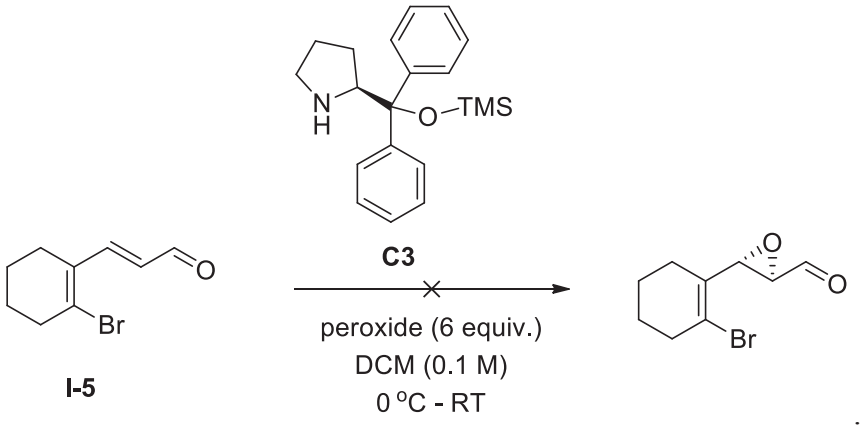
Due to their large substrate scope, milder reaction conditions,and single step reaction, Sharpless and Shi Asymmetric Epoxidation methods are favorable techniques among chemist. There are undoubtly also a number of alternative methods in the literature. The following as a such example tested in this study

Information gathered from the literature stated that α,β-unsaturated carbonyl compounds were susceptible to asymmetric epoxidation by a organocatalyst which can be synthesized from commercially available α,α–Diphenyl-L-prolynol (**C3**) compound (Figure 4.4.) (Table 4.2.) (Murar *et al.,,* 2014).

As an intermediate to endocyclic enyne oxirane molecule **I-5** was subjected to epoxidation over **C3** catalyst using different peroxides in different amount. Unfortunately, all our effords failed to yield the desired epoxide structure and instead resulted in a complex mixture (Table 4.2.).

Next our efforts directed to the application of Shi-Asymmetric Epoxidation technique over a number of substrates (Figure 4.3.) using Shi catalysts **C1** and **C2 (**Figure 4.4.).

Table 4. 2 Organocatalytic Asymmetric Epoxidation reactions



	C3 (%)	Peroxide
1	10	H_2O_2
2	20	H_2O_2
3	20	TBHP
4[a]	20	TBHP
5[b]	20	TBHP
6	20	UHP
7[a,c]	100	TBHP

[a] Reaction carried out at -20 °C

[b] Reaction carried out with I-7 compound

[c] TBHP added over 2 hours

UHP: Urea hydrogenperoxide complex

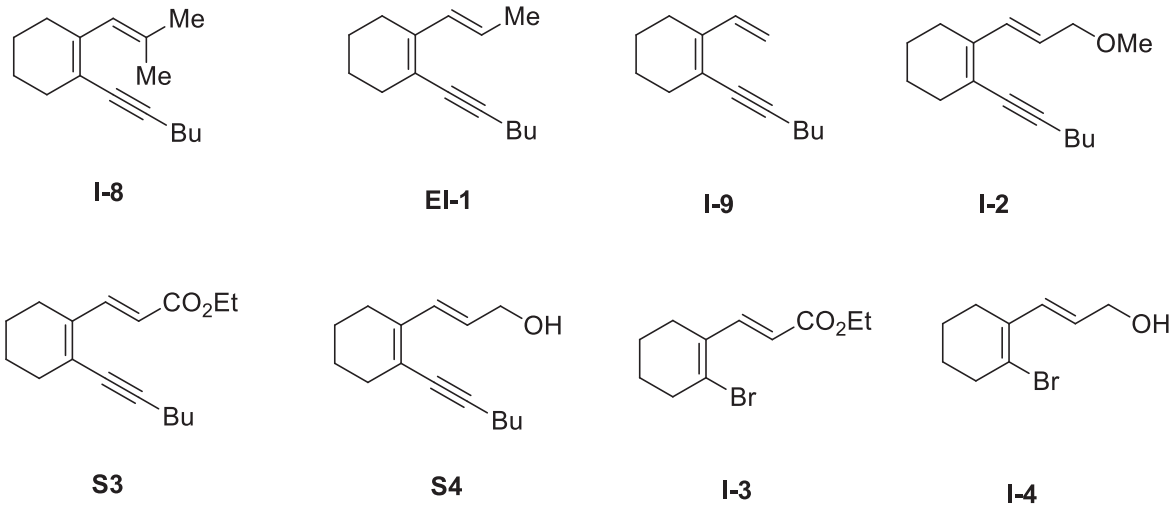


Figure 4. 3 Substrate scope of Shi-Asymmetric Epoxidation reactions

With the use of **C1** catalyst, whether a carbonate or borax buffer is used, in most cases either reactant was recovered as it is or resulted in undesired product formation or complex mixture (Table 4.3.). Only in one case was the desired epoxide product could be recovered, however in a low yield (27%) and enantioselectivity (7.5 ee%).

C2 catalyst which has been reported to be suitable asymmetric catalyst for α,β–unsaturated esters (Wu *et al.,* 2002) was also tested. Unfortunately it was completely ineffective for our substrates **S3** and **I-3** Figure 4.4.

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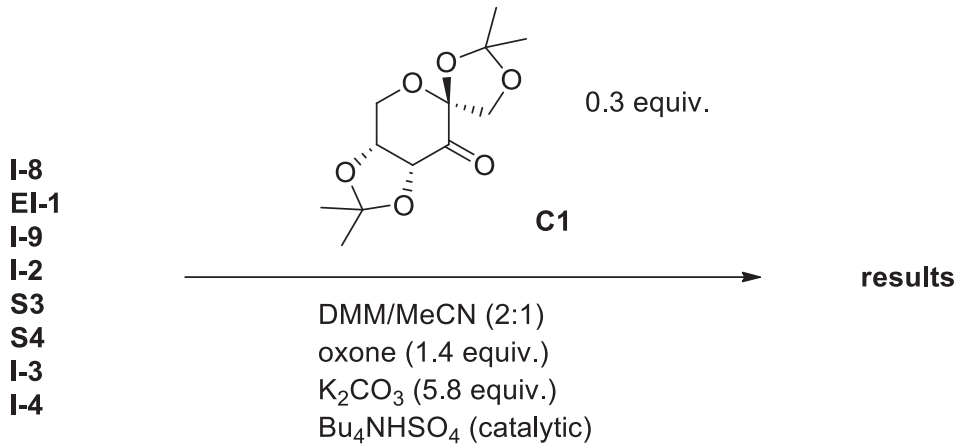
C2 catalyst which has been reported to be suitable asymmetric catalyst for α,β–unsaturated esters (Wu *et al.,* 2002) was also tested. Unfortunately it was completely ineffective for our substrates **S3** and **I-3** Figure 4.4.

It has been know that the Sharpless Asymmetric Epoxidation (Katsuki and Sharpless, 1980) method is a prominent method for asymmetric epoxidation of allylic alcohols which proceeds through coordination of allylic alcohol to the catalyst (Katsuki and Sharpless, 1986). However, this coordination may be disrupted by the presence of other electron-rich groups such as a double bond. This undesired stituations could be avoided by use of lower amounts of catalyst and ligand or by adding molecular sieves (Katsuki and Sharpless, 1986)

Table 4. 3 Shi-Asymmetric Epoxidation Experiments



No	Reactant	Buffer Solution	Temperature (°C)	Addition time (hours)	Result
1	**I-8**	K_2CO_3/AcOH solution	-10	3	reactant+product+side product
2[a]	**EI-1**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	-10	1,5	reactant+product+side product
3	**S10**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	-10	7	reactant+product+side product
4	**I-8**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	-15	16	reactant
5	**I-8**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	0	4	reactant+complex
6[b]	**I-8**	K_2CO_3/AcOH solution	-10	4	reactant+product+side product
7[c]	**EI-1**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	-10	1,5	reactant+product (% 7.5 ee)
8	**I-9**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	0	3	reactant+complex
9	**I-2**	K_2CO_3/AcOH solution	-10	5	reactant
10	**I-2**	K_2CO_3/AcOH solution	0	5	reactant
11	**I-2**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	0	5	reactant
12	**S3**	K_2CO_3/AcOH solution	-10	5	reactant
13[d]	**S3**	K_2CO_3/AcOH solution	0	3	reactant
14	**S4**	K_2CO_3/AcOH solution	-10	3	reactant+complex
15	**S4**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	-10	3	reactant+complex
16	**I-3**	K_2CO_3/AcOH solution	0	4	reactant
17	**I-4**	K_2CO_3/AcOH solution	-10	3	reactant
18	**I-4**	0,05 M Borax,in 4×10^{-4} M Na_2EDTA	-10	3	reactant
19	**I-4**	K_2CO_3/AcOH solution	0	3	reactant

[a] ^{1}H-NMR determination of reactant:product:impurities = 3:1:0.9

[b] 1.6 equiv. oxone, 6.7 equiv. K_2CO_3 and DMM/DME (3:1) were used.

[c] 35% conversion, 27% yield, 7.5% e.e, 63% of reactant recovered.

[d] 2 equivalent oxone was used.

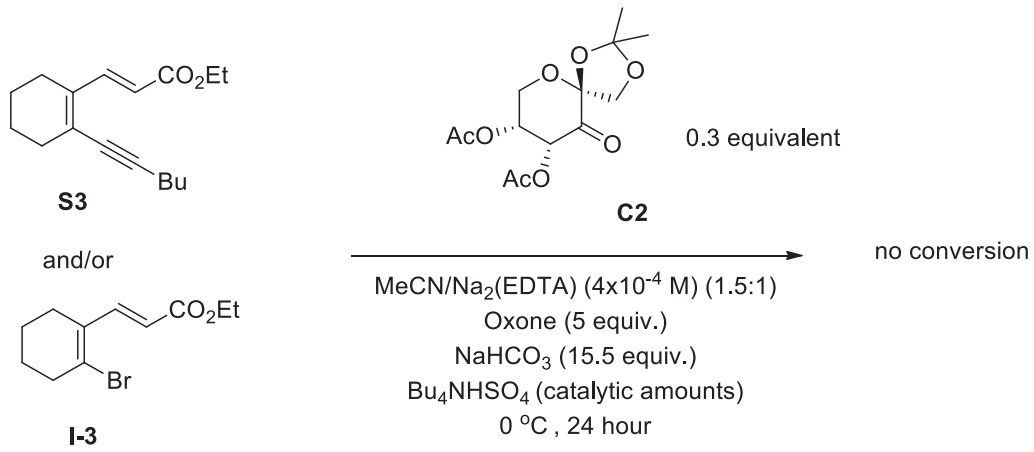
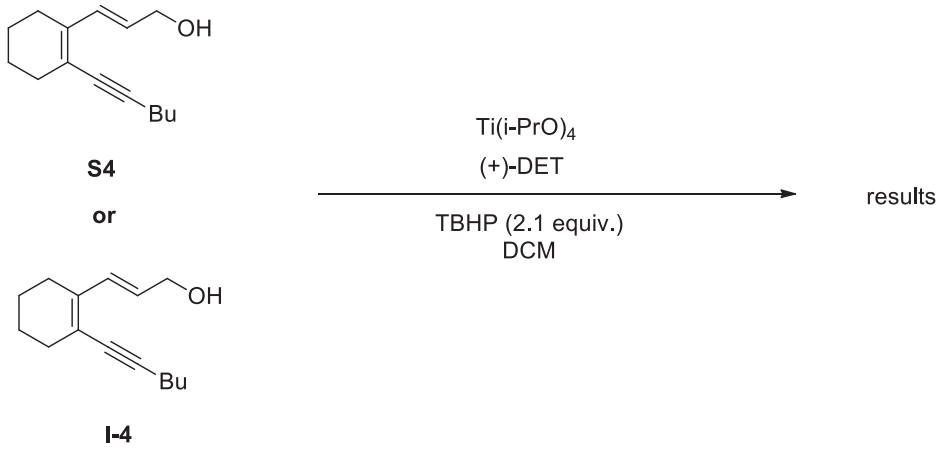


Figure 4. 4 Shi-Asymmetric Epoxidation with α,β– unsaturated esters in the presence of **C2** ketone

Unfortunately, synthesized allylic alcohols **S4** and **I-4** having conjugated π-bonds and inherent rigidity due to the cyclic structure prevented the formation of epoxides (Table 4.4.). Despite the use of molecular sieves, adjusting the quantity of catalyst and ligand and various temperatures no trace of epoxide formation was detected.

Having realized that direct epoxidatin would not be achievable by so far available methods, we turned our attention to indirect routes. Finally, we were able to accomplish the synthesis of enyne epoxides with high ees via Sharpless asymmetric dihydroxylation (Sharpless *et al.*, 1992) of dienyne esters followed by steps as shown in Chapter 3.

Table 4. 4 Sharpless-Asymmetric Epoxidation experiments



No	Reactant	Ti(O-*i* Pr)$_4$(%)	Tartrate (%)	Time (hours) /T (°C)	Results
1	**S4**	5	(+)-DET, 6	1/0	Complex
2	**S4**	5	(+)-DET, 6	1/-20	Complex
3	**S4**	14	(+)-DET, 16	1). 1/-30 °C; 2). ON[a]/Df[b]	Complex
4	**S4**	14	(+)-DET, 16	3/-30	Complex
5	**S4**	50	(+)-DET, 60	1). 1/-30 °C; 2). ON[a]/Df[b]	Complex
6	**S4**	5	(+)-DET, 6	1/-50	Complex
7	**S4**	100	(+)-DET, 100	1/-50	Complex
8	**S4**	5	(+)-DIPT, 6	1/-50	Complex
9	**S4**	5	(+)-DIPT, 6	1/-50	Complex
10	**S4**	14	(+)-DET, 16	20/-80	Reactant+ Complex
11	**S4**	10	(+)-DET, 12	5/-80	Reactant+ Complex
12	**S4**	10	(+)-DET, 12	10/-80	Reactant+ Complex
13	**S4**	10	(+)-DIPT, 12	10/-80	Reactant+ Complex
14	**I-4**	5	(+)-DET, 6	3/-20	Complex
15	**I-4**	5	(+)-DIPT, 6	3/-20	Complex
16	**I-4**	5	(+)-DET, 6	3/-20	Complex
17	**I-4**	5	(+)-DET, 6	5/50	Reactant+ Complex

[a] Overnight

[b] Deep-Freezer

.

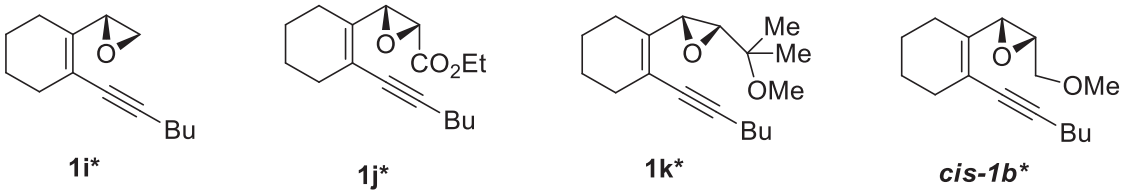


Figure 4. 5 Enantioenriched epoxides

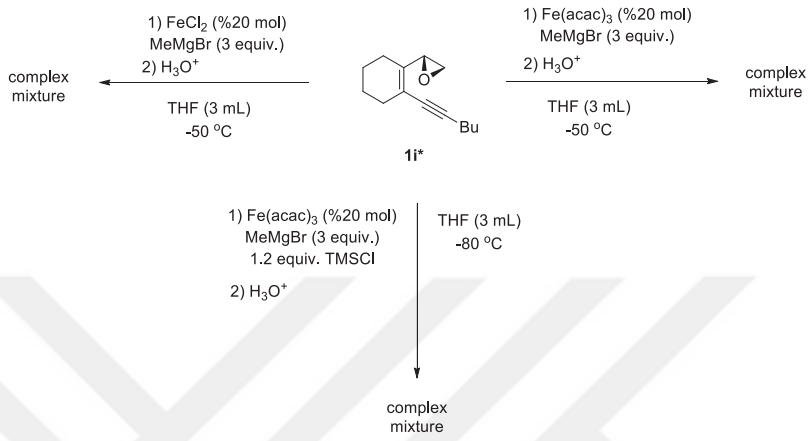


Figure 4. 6 Iron catalyzed reactions of **1i*** with Grignard reagents

The reaction of **1i*** under optimal conditions resulted with complex mixture. Some variation of experimental conditions made no difference. The major product type detected appears to be due to the direct substitution of the one of epoxide carbon with the Grignard reagent.

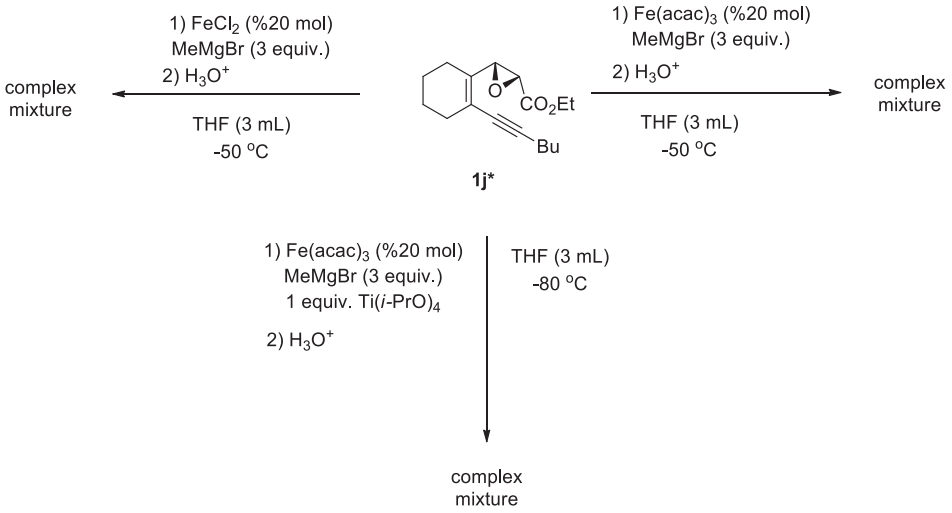


Figure 4. 7 Iron-catalyzed reactions of **1j*** with Grignard reagents

Although it was long-shot to expect ester-functionalized epoxide to react with Grignard reagents in a desired manner, we still performed a couple of experiments to test it. All experiments were resulted with inseparable complex mixtures. Possibly, Grignard reagents attacked to carbonyl carbon of the ester group rather than complexing with Fe complex or resulted with direct addition to the epoxide ring. Even if we could not reduce the ester group, we were able to functionalize it with the addition of two methyl groups by Grignard reagent.

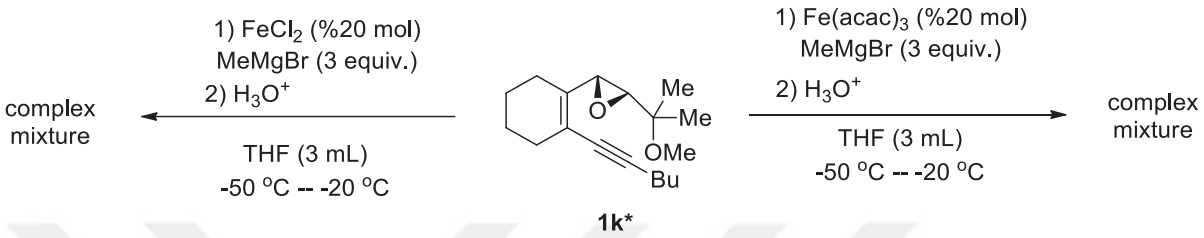


Figure 4. 8 Iron-catalyzed reactions of **1k*** with Grignard reagents

Compound **1k*** was reacted with Fe complexes in order to obtain vinyl allenes. However, as our thoughts, the crowded nature of the epoxide moiety could be blocking the approach of Fe complex with Grignard reagents. In line with this consideration, all experiments fail to donate the desired product. Gathering the results from past and present experiments, we planned to synthesize an epoxide molecule with *cis*-configuration that has less bulky substitutent on the oxirane moiety, ***cis*-1b***.

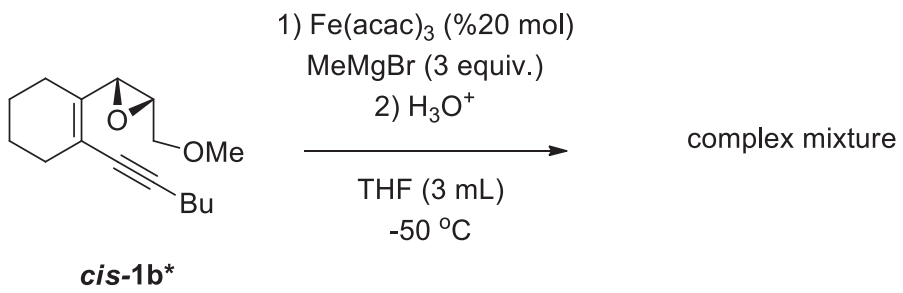


Figure 4. 9 Iron-catalyzed reactions of ***cis*-1b*** with Grignard reagents

Under the optimized conditions, ***cis*-1b*** also failed to yield the desired alkylated allene product. We understood that this experiment is only suitable for ***trans***-configured enyne epoxide but not for ***cis***- analogue. To understand the reason behind this, MM2 energy minimization of structures were done. Structures at minimum energy level showed that ***cis***- configured sturcture was sterically hindered for the approach of organoiron complex (Figure 4.11.). Therefore, studies continued with ***trans***- configured enyne epoxides.

The substrate scope of the method was investigated over *trans*-endocylic enyne oxiranes with different functionalities and ring sizes. Firstly, the effect of protecting group on the pendant oxygen functionality was evaluated. As observed, relatively lower yields could be attained with voluminous groups (Table 4.5., Entry 1-3, **1b***, **1d***, **1e***).

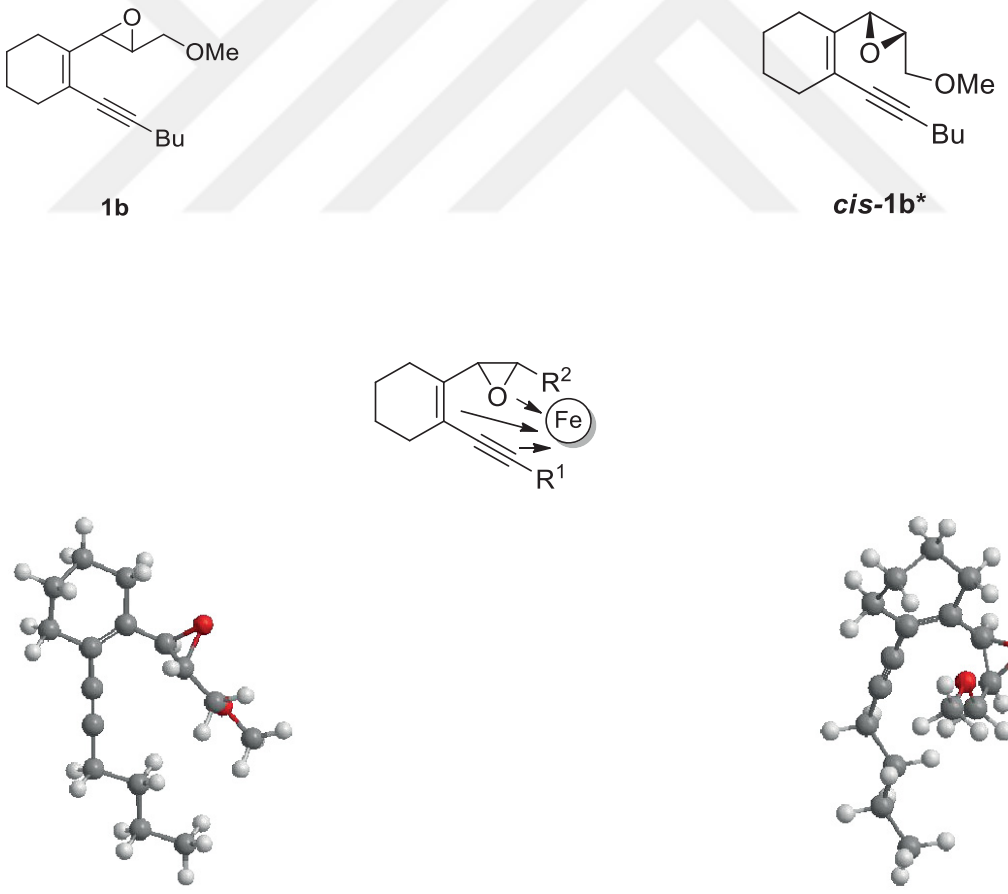
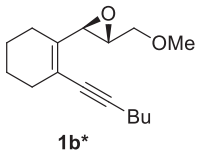
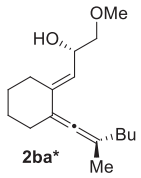
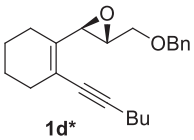
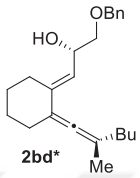
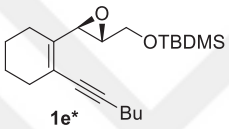
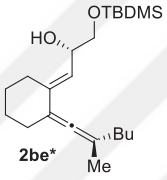
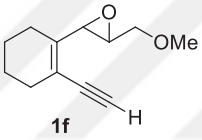
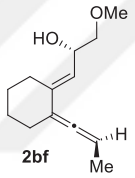
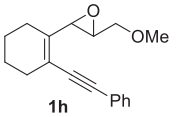
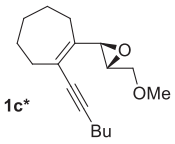
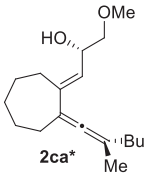
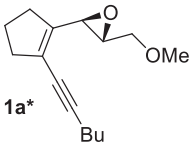
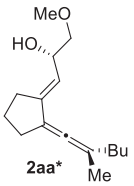


Figure 4. 10 3D structures of ***cis***- and ***trans***- configured enyne epoxide compounds

Table 4. 5 Iron-catalysed reactions of endocyclic trans enyne epoxides with Gringnard Reagents

Name	Structure of Reactant	Time (min)	Product	Yield (%)	Enantiomeric Excess (%)	Diastereomeric Ratio [a]
1	 **1b***	30	 **2ba***	81	97.3	96:4
2	 **1d***	240	 **2bd***	72	97.5	95:5
3	 **1e***	50	 **2be***	67	N.D	71:29
4	 **1f**	30	 **2bf**	66	-	100:0
5	 **1h**	30	No Data	No Data	No data	No Data
6	 **1c***	30	 **2ca***	71	99.6	92:8
7	 **1a***	30	 **2aa***	75	95.7	90:10

N.D= Not Determined

[a] Determined by ^{1}HNMR

Moreover, while benzoxyl derivative showed great stereoselectivity, the silylated counterpart yielded the corresponding product with low diastereoselectivity

(Table 4.5., Entries 2-3, **1d***, **1e***) and, in fact, on contrary to the general trend, minor diastereomeric form being produced by other substrates was the main form with this reagent, indicating that sterical factors arisen from pendant oxygen influences the stereoselectivity of the process.

The group on the alkynl moiety was also varied. Terminal alkyne substrate proceeded with complete stereoselectivity, however, providing the corresponding vinyl allene product in a moderate yield, which indicated that sterically less hindered alkynyl moiety allows the formation of more stereoselective products (Table 4.5. Entry 4, **1f**). However, the reaction of the **1h** having a phenyl substituent on the alkynl group proceeded with the formation of direct addition product as well as a reductive product. (Table 4.5., Entry 5).

A reaction was also performed with **1b** and PhMgBr. Eventhough the reactant did not consume completely, the phenyl substituted allene could be recovered in 35% yield. Two possible estimation could be derived from these inferior results, the phenyl-substitued enyne oxirane could be sterically hindered for organoiron complex to approach, hence, instead of allene, a reductive alcohol product could be formed. Second, it is known that iron metal tends to form ferrocenyl complexes easily (Pauson and Kealy, 1951; Pauson, 2001). During the catalytic cycle, the reactant and the iron compound could form a complex that halts the reaction from proceeding over the desired path way. In the case of PhMgBr, some of the reactant was converted to the desired product, before the deactivation of the reaction medium.

Later on, effect of ring size was investigated. It is evident that five and seven-membered rings are also applicable for the method; good yield of vinyl allene products could be obtained with the corresponding substrates. However, it must be noted that the product with five-member ring is relatively unstable, thus, special care (e.g., storage temperature, atmosphere) should be taken while handling it (Table 4.5., Entries 6-7, **1c***, **1a***).

To determine the exact structure and stereomeric mode NOE study was performed. As desribed by Sharpless, asymmetric dihydroxylation reaction and following workup should yield epoxide structure with *R,R* stereo-configuration (Figure

4.12.) (Sharpless *et al.*, 1992; Kolb and Sharpless, 1992). Although we have this information, type of addition (*-anti*, *-syn*) could differ the configuration of final product.

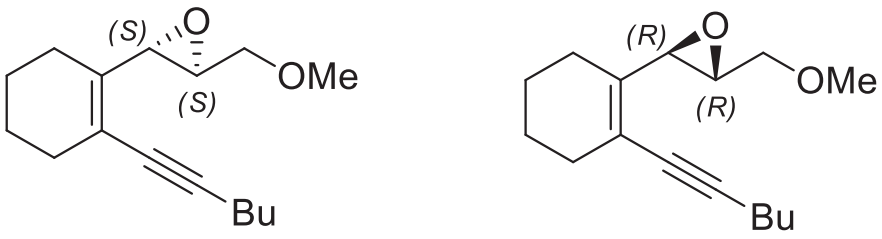


Figure 4. 11 Enantiomers of enyne epoxide

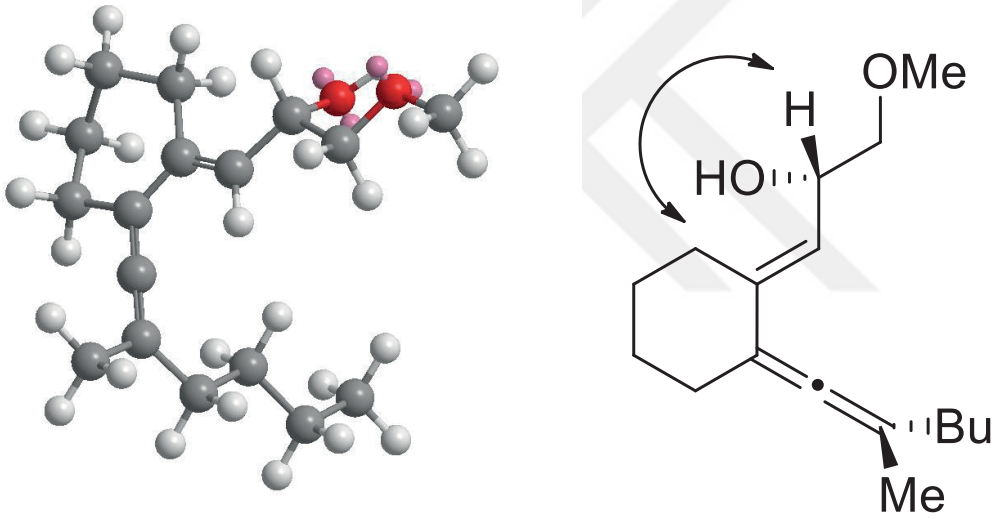


Figure 4. 12 Structure of Allene Compound

Results of NOE analysis showed that, allylic hydrogen interacts with two hydrogen of the ring which is only possible when double bond has ***E-*** configuration while the allene configuration was determined by information supplied by Lowe (1965) (Figure 4.13.).

Proposed mechanism is initiated by transmetallation of iron with Grignard reagent. Conformational orientation the epoxide ring appears to be key factor for the stereoselectivity of the process, so that existing configuration of the coupling products dictates the involment of the less congested confirmer, in which terminal substituent on the epoxide ring is most distance from alkynyl moiety as specified in Figure 4.14. By

doing so, the alkenyl and/or alkynyl moieties could be more accessible by the iron complex.

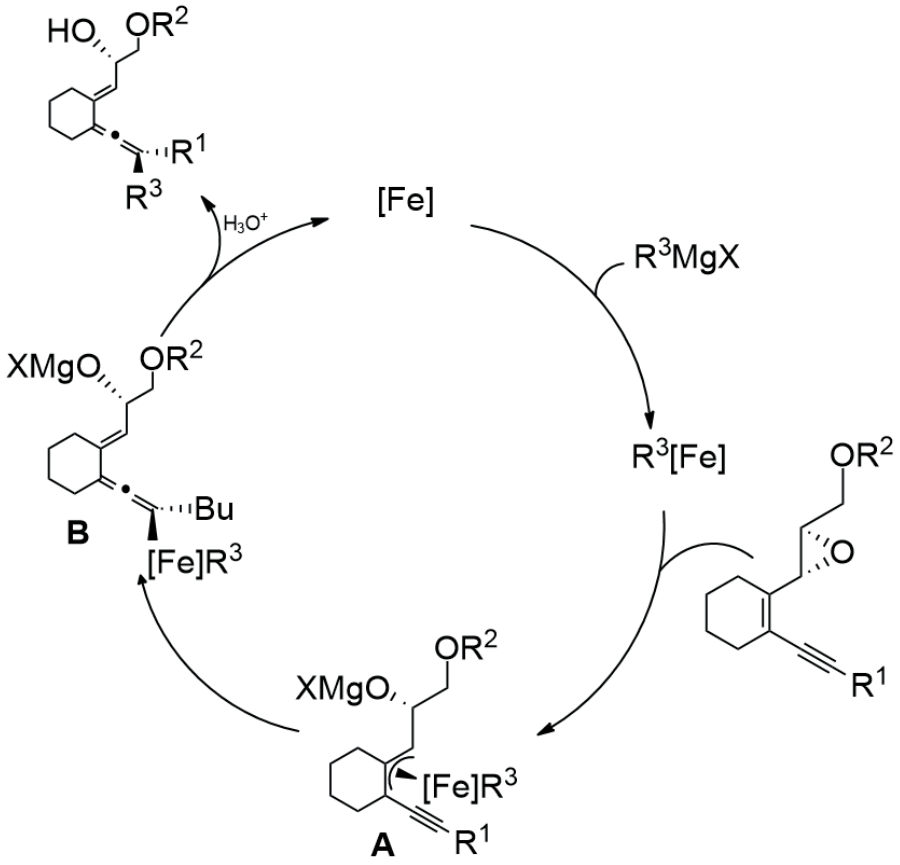


Figure 4. 13 Proposed reaction mechanism

Subsequent oxidative addition to the epoxide ring may form π-allyliron complex that opens the epoxide ring. Afterwards, the organoiron complex migrates to alkynl group and rearrangement of π electrons forms vinyl allene structure. Finally, reductive elimination of organoiron and protonation yields desired allene and regenerates the catalyst to its native state. From the predicted mechanism, we could understand the results of reactions clearly. As the R^2 group increases in size, approach of the iron complex could be difficult. Similar situation could happen to occur when R^1 substitued with –Ph, because of high conjugation and possible delocalization of electrons through alkynl and vinylic moieties (Table 4.5., Entry 5). On contrary, exceptional diastereo-selectivity of terminal alkyne substrate could be related to the ease of approach and coordination to iron complex. (Table 4.5., Entry 4).

CHAPTER 5

CONCLUSION

Endo-cyclic enyne oxiranes showed exceptional stereoselectivity toward the reaction of Grignard reagent in presence of iron catalyst with respect to acyclic analogues. Synthesis of enantio-enriched oxiranes and high center to axial chirality transfer enables us to produce targeted vinyl allene structures with almost one definite structure.

Synthesis of enantio-enriched oxirane was achieved by Sharpless asymmetric Dihydroxylation and asymmetric transformation of 1,2-diols to epoxide methods with epoxides having >%95 enantiomeric excess.

Reactions mainly proceeded with 1,5-substitution(S_N2'') in anti-mode with respect to leaving group. The relative configuration of the epoxide ring determines the stereoselectivity of the process. The product had a chirality center at hydroxyl carbon as (*S*) and allene moiety as (*R*) configuration.

REFERENCES

Akpınar, G. E., Kuş, M., Üçüncü, M., Karakuş, E., Artok, L., Palladium-Catalyzed Alkoxycarbonylation of (Z)-2-En-4-yn Carbonates Leading to 2,3,5-Trienoates, Org. Lett.,13, 748-51, (2011).

Alexakıs, A., Marek, I., Manganey, P., Normant, J. F., Diastereoselective Synthesis of α-Allenic Alcohols from Propargylic Epoxides., Tetrahedron Lett., 30, 2387–90, (1989).

Alexakıs, A., Marek, I., Manganey, P., Normant, J. F., Diastereoselective Syn or Anti Opening of Propargylic Epoxides. Synthesis of α-Allenic Alcohols., Tetrahedron, 47, 1677-96, (1991).

Alexakıs, A., Stereochemical aspects on the formation of chiral allenes from propargylic ethers and epoxides., Pure Appl. Chem., 64, 387-92, (1992).

Beerbower, A. 1983. "The HSAB Principle and Extended Solubility Theory", Inorganica Chimica Acta, 75, 193-97

Bekele, T., Brunette, S. R., Lıpton, M. A., Synthesis and Cycloaromatization of a Cyclic Enyne−Allene Prodrug., J. Org. Chem., 68, 8471-9, (2003).

Bond, D., An ab Initio Study of Vinyl allene Conformations, J. Org. Chem., 55, 661-5, (1990).

Bouda, H., Borredon, M.E., Delmas, M., Gaset, A. 1987. "Aldehydes and Ketones Epoxidation with Trimethylsulfonium Bromide in a Slightly Hydrated Solid-Liquid Medium", Synthetic Comm., 17, 503-13.

Buchwald, S.L., Bolm, C. 2009. "On the Role of Metal Contaminants in Catalyses with $FeCl_3$", Angew. Chem. Int. Ed., 48, 5586-87.

Burke C.P., Shı, Y. 2006. “Regio- and Enantioselective Epoxidation of Dienes by a Chiral Dioxirane: Synthesis of Optically Active Vinyl cis-Epoxides”, Angew. Chem. Int. Ed., 45, 4475-78

Cameron, G.M. 2010. “Synthesis, Characterization, and Effects of Silver Impregnated Alumina On Escherichia Coli as a Model For Antimicrobial Control of Gram-Negative Bacteria” Master’s Degree Thesis, The Faculty of Biological Science, Clark Atlanta University, Atlanta, USA.

Corey, E.J., Chaykovsky, M., “Dimethyloxosulfonium Methylide and Dimethylsulfonium Methylide Formation and Application to Organic Synthesis”, J. Am. Chem. Soc., 87:6, 1965.

de Montellano, P. R. O., Synthesis of Allenic Alcohols, J.C.S. Chem. Commun., 709-10, (1973).

Dulcere, J. P., Goré, J., Roumestant, M. L. Bull. Soc. Chim. Fr., 1119, (1974)

Dulcere, J. P., Grımaldı, J., Santellı, M., Synthesis of Silyl-Substituted Vinyl allenes, Tetrahedron Lett., 22, 3179-80, (1981).

Falcıola, C. A., Alexakıs, F. A., Copper-Catalyzed Asymmetric Allylic Alkylation, Eur. J. Org. Chem., 3765–80, (2008).

Fang, Z., Lıao, P. C., Yang Y. L., Yang, F. L., Chen, Y. L., Lam, Y., Hua, Y. F., Wu, S. H., Synthesis and Biological Evaluation of Polyenylpyrrole Derivatives as Anticancer Agents Acting through Caspases-Dependent Apoptosis, J. Med. Chem., 53, 7967–78, (2010)

Franck-Neumann, M., Martına, D. Neff, D., Amplification of chirality by transition metal coordination: synthesis of chiral allenes and allene manganese complexes of high enantiomeric purity. Synthesis of methyl (R, E) -(−) -(2,4,5-tetradecatrienoate (pheromone of Acanthoscelides obtectus (say)), Tetrahedron: Asymmetry, 9, 697–708, (1998).

Frohn, M., Shı, Y. 2000. “Chiral Ketone-Catalyzed Asymmetric Epoxidation Of Olefins”, Synthesis, 14, 1979-00.

Fujı, N., Nakaı, K., Habashıta, H., Yoshızawa, H., Ibuka, T., Garrıdo, F., Mann, A., Chounan, Y., Yamamoto, Y. 1993. “SN2’ Selective Alkylation of Allylic Chlorides and Mesylates with RZnX Reagents Generated from Grignard Reagents, Zinc chloride, Lithium chloride, and Cu(II)-Salts”, Tetrahedron Lett., 26, 4227-30.

Fürstner, A., Méndez, M., Iron-Catalyzed Cross-Coupling Reactions: Efficient Synthesis of 2,3-Allenol Derivatives, Angew. Chem. Int. Ed., 42, 5355 –7, (2003).

Gandon, V., Lemıère, G., Hours, A., Fensterbank, L., Malacrıa, M., The Role of Bent Acyclic Allene Gold Complexes in Axis-to-Center Chirality Transfers, Angew. Chem. Int. Ed., 47, 7534–8, (2008).

Gibbs, R. A., Bartels, K., Lee, R. W. K. Lee, Okamura, W. H., An Enantioselective Central-Axial-Central Chiral Element Transfer Process Leading to a Concise Synthesis of (+)-Sterpurene: Intramolecular Diels-Alder Reactions of Vinyl allene Sulfoxides., J. Am. Chem. Soc., 111, 3717-25, (1989).

Goré, J., Dulcere, J. P., New Synthesis of Vinyl allenes., J. Chem. Soc., Chem. Commun. 866-7, (1972).

Hanson R.M., Sharpless, K.B. 1986. “Procedure for the Catalytic Asymmetric Epoxidation of Allylic Alcohols in the Presence of Molecular Sieves”, J. Org. Chem., 51, 1922-25.

Hatano, M., Ito, O., Suzukı, S., Ishıhara K. 2010. “Zinc(II)-Catalyzed Addition of Grignard Reagents to Ketones”, J. Org. Chem., 75, 5008-16

Hayashı, Y., Shojı, M., Mukaıyama, T., Gotoh, H., Yamaguchı, S., Nakata, M., Kakeya, H., Osada H. 2005. “First Asymmetric Total Synthesis of Synerazol, an Antifungal Antibiotic, and Determination of Its Absolute Stereochemistry”, J. Org. Chem., 70, 5643-54

Hıll, J.G., Rossıter, B.E., Sharpless K.B. 1983. “Anhydrous tert-Butyl Hydroperoxide in Toluene:The Preferred Reagent for Applications Requiring Dry TBHP”, J. Org. Chem., 48, 3607-08.

Hoffmann-Röder A., Krause N., Synthesis and Properties of Allenic Natural Products and Pharmaceuticals., Angew. Chem. Int. Ed., 43, 1196-216, (2004).

Hyoung, C. K., Sung, H. K.; Youn, J.-H., Synthesis of L-cladinose using enantioselective desymmetrization., Synlett, 2526–8, (2008).

Karnekanti, R., Hanumaıah M., Sharma, G.V.M. 2015. “Stereoselective Total Synthesis of (+)-Anamarine and 8-epi-(–)-Anamarine from D-Mannitol”, Synthesis, 47, 2997–08.

Katsuki, T., Sharpless, K.B. 1980. “The First Practical Method for Asymmetric Epoxidation”, J. Am. Chem. Soc., 102, 5974-76.

Kolb H.C., Sharpless K. B. 1992 “A Simplified Procedure for the Stereospecific Transformation of 1,2-Diols into Epoxides”, Tetrahedron, 48, 10515-30.

Koop, U., Handke, G., Krause N., Synthesis of Vinyl allenes by Conjugate 1,6-, l,S-, 1,lO- and lJ2-AdditionReactions of Organocuprates with Acetylenic Michael Acceptors and Their Use as Dienes in Intermolecular Diels-Alder Reactions, Liebigs Ann.,1487- 99, (1996).

Krasovskiy A., Knochel P. 2004. “A LiCl-Mediated Br/Mg Exchange Reaction for the Preparation of Functionalized Aryl- and Heteroarylmagnesium Compounds from Organic Bromides”, Angew. Chem. Int. Ed., 43, 3333-36.

Krasovskıy, A., Kopp, F., Knochel P. 2006. “Soluble Lanthanide Salts ($LnCl_3$•2LiCl) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds”, Angew. Chem. Int. Ed., 45, 497-00

Krause N., Hoffmann-Röder A., Modern Allene Chemistry; Krause N.; Hashmi, A. S. K., Eds., Wiley-VCH: Weinheim, 2004b; V. 2, p. 997.

Krause N., Hoffmann-Röder A., Synthesis of allenes with organometallic reagents., Tetrahedron, 60, 11671–11694, (2004a).

Krause, N., Purpura, M., "Remote Stereocontrol" in Organocopper Chemistry: Highly Enantioselective Synthesis of Vinyl allenes by 1,5-Substitution of Enyne Acetates., Angew. Chem. Int. Ed., 39, 4355-6, (2000).

Krause, N., Synthesis of (±)-Sterpurene and Hydroxylated Derivatives by 1,6-Addition of Organocuprates to Acceptor-Substituted Enynes., Liebigs Ann. Chem., 521-5, (1993).

Kropp, P. J., Mcneely, S. A., Davıs, R. D., Photochemistry of Alkyl Halides. 10. Vinyl Halides and Vinylidene Dihalides, J. Am. Chem. Soc., 10, 6907-15, (1983).

Kurzawa, T., Harms, K., Koert, U. 2018. "Stereoselective Synthesis of the Benzodihydropentalene Core of the Fijiolides", Org. Lett., 20, 1388-91

Kuş, M., Artok, L., AygüN, M. 2015. "Palladium-Catalyzed Alkoxycarbonylation of Conjugated Enyne Oxiranes: A Diastereoselective Method for the Synthesis of 7-Hydroxy-2,3,5-trienoates", J. Org. Chem., 80, 5494−06.

Lee, J. H., Toste, F.D., Gold(I)-Catalyzed Synthesis of Functionalized Cyclopentadienes, Angew. Chem. Int. Ed., 46, 912-4, (2007).

Lemière, G., Gandon, V., Carıou, K., Hours, A., Fukuyama, T., Dhımane, A.-L., Fensterbank, L., Malacrıa, M., Generation and Trapping of Cyclopentenylidene Gold Species: Four Pathways to Polycyclic Compounds., J. Am. Chem. Soc., 131, 2993–3006, (2009).

Li, H., Alexakıs, A., Enyne Chlorides: Substrates for Copper-Catalyzed Asymmetric Allylic Alkylation., Angew. Chem. Int. Ed., 51, 1055–8, (2012).

Lowe, G., “The Absolute Configuration of Allenes” Chemical Communications, Number 17, Page 411, (1965).

Ma, S., Pd-Catalyzed Coupling Reactions Involving Propargylic/Allenylic Species., Eur. J. Org. Chem., 1175-83, (2004).

Marigo, M., Franzen, J., Poulsen, T.B., Zhuang, W., Jørgensen K.A. 2005. “Asymmetric Organocatalytic Epoxidation of α,β -Unsaturated Aldehydes with Hydrogen Peroxide”, J. Am. Chem. Soc., 127, 6964-65.

Millet, R., Alexakis, A., Copper-Catalyzed Kinetic Resolution of 1,3-Cyclohexadiene Monoepoxide with Grignard Reagents, Synlett, 435–8, (2007).

Mıura, T., Shimada, M., Ku, S.-Y., Tamaı, T., Murakami, M., Stereoselective Synthesis of α-Allenols by Rhodium-Catalyzed Reaction of Alkynyl Oxiranes with Arylboronic Acids., Angew. Chem. Int. Ed., 46, 7101–3, (2007).

Murakami, M., Itami, K., Ito, Y., Catalytic Asymmetric [4 + 1] Cycloaddition Of Vinyl Allenes With Carbon Monoxide: Reversal Of The Induced Chirality By The Choice Of Metal., J. Am. Chem. Soc., 121, 4130-5, (1999b).

Murakami, M., Itami, K., Ito, Y., Coordination Modes And Catalytic Carbonylative [4 + 1] Cycloaddition Of Vinyl Allenes, Organometallics, 18, 1326-36, (1999a).

Murakami, M., Ubukata, M., Itami, K., Ito, Y., Rhodium-Catalyzed Intermolecular [4+2] Cycloaddition Of Unactivated Substrates., Angew. Chem. Int. Ed., 37, 2248-50, (1998).

Murar, C.E., Thuaud F., Bode, J.W., “Kaha Ligations That Form Aspartyl Aldehyde Residues As Synthetic Handles For Protein Modification And Purification”, J. Am. Chem. Soc., 136, 18140−48, (2014).

Oehlschlager, A. C., Czywska, E., Chiral Epoxides As Precursors Of Chiral Allenes., Tetrahedron Lett., 24, 5587-90, (1983).

Ogasawara, M., Nagano, T., Hayashı, T., A New Route To Methyl (R,E)-(-)-Tetradeca-2,4,5-Trienoate (Pheromone Of Acanthoscelides Obtectus) Utilizing A Palladium-Catalyzed Asymmetric Allene Formation Reaction., J. Org. Chem., 70, 5764-67, (2005).

Orfanopoulos, M., Smonou, I., Foote, C. S., Intermediates in the Ene Reactions of Singlet Oxygen and N-Phenyl-1,2,4-triazoline-3,5-dione with Olefins, J. Am. Chem. Soc., 112, 3607-14, (1990).

Pauson, P.L., "Ferrocene-how it all began", Journal of Organometallic Chemistry, Volumes 637-639, Pages 3-6, (2001).

Pauson, P.L., Kealy, T.J., "A New Type of Organo-Iron Compound", Nature 168, 1039-1040, (1951).

Perry, M.C., Gıllett, A.N., Law T.C. 2012. "An Unprecedented Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Grignard Reagents with Non-Activated Aryl Chlorides", Tetrahedron Letters 53, 4436-39.

Picha, J., Vanek, V., Budesinsky, M., Mladkova, J., Garrow, T.A., Jıracek, J. 2013. "The Development of a New Class of Inhibitors for Betainehomocysteine S-methyltransferase", Eur. J. of Med. Chem., 65, 256-75

Purpura, M., Krause, N., Regio- and Stereoselective Synthesis of Vinyl allenes by 1,5-(SN'')-Substitution of Enyne Acetates and Oxiranes with Organocuprates., Eur. J. Org. Chem., 267-75, (1999).

Purpura, M., Krause, N., Regio- and Stereoselective Synthesis of Vinyl allenes by 1,5-(SN'')-Substitution of Enyne Acetates and Oxiranes with Organocuprates, Eur. J. Org. Chem., 267-75, (1999).

Reich, H. C., Eisenhart, E. K., Whipple, W. L., Kelly, M. J., Stereochemistry of Vinyl allene Cycloadditions., J. Am. Chem. Soc., 110, 6432-42, (1988).

Rona, P., Crabbé, P., A Novel Allene Synthesis., J. Am. Chem. Soc., 90, 4733–4, (1968).

Rona, P., Crabbé, P., A Novel Synthesis of Substituted Allenes., J. Am. Chem. Soc., 91, 3289–92, (1969).

Satoh, T., Hanaki, N., Kuramochi, Y., Inoue, Y., Hosoya, K., Sakaı, K., A new Method for Synthesis of Allenes, Including an Optically Active Form, from Aldehydes and Alkenyl Aryl Sulfoxides by Sulfoxide-Metal Exchange as the Key Reaction and an Application to a Total Synthesis of Male Bean Weevil Sex Attractant., Tetrahedron, 58, 2533–49, (2002).

Schmittel, M., Steffen, J.-P., Maywald, M., Engels, B., Helten, H., Musch, P., Ring size effects in the C2–C6 biradical cyclisation of enyne–allenes and the relevance for neocarzinostatin, J. Chem. Soc., Perkin Trans. 2, 1331-9, (2001)

Schreiber, S. L., Kiessling, L. L., Synthesis of the Bicyclic Core of the Esperamicin/Calichemicin Class of Antitumor Agents., J. Am. Chem. Soc., 110, 631-3, (1988).

Sharpless, K.B., Amberg, W., Bennani, Y.L., Crispıno, G.A., Hartung, J., Jeong, K.-S., Kwong, H.-L., Morıkawa, K., Wang, Z.-M., Xu, D., Zhang X.-L. 1992. "The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement", J. Org. Chem., 57, 2768-71

Shemet, A., Sarlah, D., Carreira, E.M., "Stereochemical Studies of Opening of Chloro Vinyl Epoxides: Cyclic Chloronium Ions as Intermediates", Org. Lett., 17, 1878-1881, 2015.

Shi, L., Chen, L., Chen, R., Chen L. 2010. "Synthesis of Deuterium-Labelled Fosamprenavir Calcium", J. Label Compd. Radiopharm, 53, 147-51.

Shi, Y., "An Efficient Asymmetric Epoxidation Method for trans-olefins mediated by a Fructose-Derived Ketone". J. Am. Chem. Soc. 118 (40): 9806–9807, (1996).

Shing, T.K.M., Tai, V.W.-F., Tam E.K.W. 1994. “Practical and Rapid Vicinal Hydroxylation of Alkenes by Catalytic Ruthenium Tetraoxide”, Angew. Chem. Int. Ed., 33, 2312-13

Sonogashira, K., Tohda, Y., Hagihara, N., “A Convenient Synthesis of Acetylenes : Catalytic Substitutions of Acetylenic Hydrogen With Bromoalkenes, Iodoarenes, and Bromopyridines”, Tetrahedron Letters, No. 50, pp. 4467-4470, (1975).

Spino, C., Pesant, M., Dory, Y., “A New Look at the Diels-Alder Transition State”, Angew. Chem. Int. Ed., 37, No.23, 1998.

Taç, D., Aytaç, İ.A., Karatavuk, A.O., Kuş, M., Ziyanak, F., Artok L. 2017. “Iron-Promoted 1,5-Substitution (SN2’’) Reactions of Enyne Acetates and Oxiranes with Grignard Reagents”, Asian J. Org. Chem., 6, 1415-20.

Touchard, F.P., Capelle, N., Mercier M. 2005. “Efficient and Scalable Protocol for the Z-Selective Synthesis of Unsaturated Esters by Horner-Wadsworth-Emmons Olefination”, Adv. Synth. Catal., 347, 707-11

Urabe, H., Suzuki, K., Sato, F., Intramolecular Cyclization of 2,7- or 2,8-Bis-unsaturated Esters Mediated by (η2-Propene) Ti(O-i-Pr)2. Facile Construction of Mono- and Bicyclic Skeletons with Stereoselective Introduction of a Side Chain. A Synthesis of d-Sabinene., J. Am. Chem. Soc., 119, 10014-27, (1997).

Üçüncü, M., Karakuş, E., Kuş, M., Akpinar, G. E., Aksin-Artok, Ö., Krause, N., Artok, L., Rhodium- and Palladium-Catalyzed 1,5-Substitution Reactions of 2-En-4-yne Acetates and Carbonates with Organoboronic Acids, J. Org. Chem., 76, 5959-71, (2011).

Vilsmeier, A., Haack, A., ‘’Über die Einwirkung von Halogenphosphor auf Alkyl-formanilide. Eine neue Methode zur Darstellung sekundärer und tertiärer p-Alkylamino-benzaldehyde’’. Berichte der deutschen chemischen Gesellschaft (A and B Series), Volume 60, Issue-1, (1927).

Waddell, M. K., Bekele, T., Lipton, M. A., Ring Size and Substituent Effects in Oxyanion-Promoted Cyclizations of Enyne-allenes: Observation of a Myers−Saito Cycloaromatization at Cryogenic Temperature, J. Org. Chem., 71, 8372-7, (2006).

Wadsworth, W.S, Emmons, W.D, '' The Utility of Phosphonate Carbanions in Olefin Synthesis''. J. Am. Chem. So. 83, 7, 1733-1738, (1961).

Wang, C., Tobrman, T., Xu, Z., Negishi, E., Highly Regio- and Stereoselective Synthesis of (*Z*)-Trisubstituted Alkenes via Propyne Bromoboration and Tandem Pd-Catalyzed Cross-Coupling, Org. Lett., 11, 4092–5, (2009).

Wei, Z., Loebach, J.L., Wilson, S.R., Jacobsen, E.N., "Enantioselective Epoxidation of Unfuncionalized Olefins Catalyzed by (Salen)manganese Complexes", J. Am. Chem. Soc., Vol. 112, No. 7, 1990.

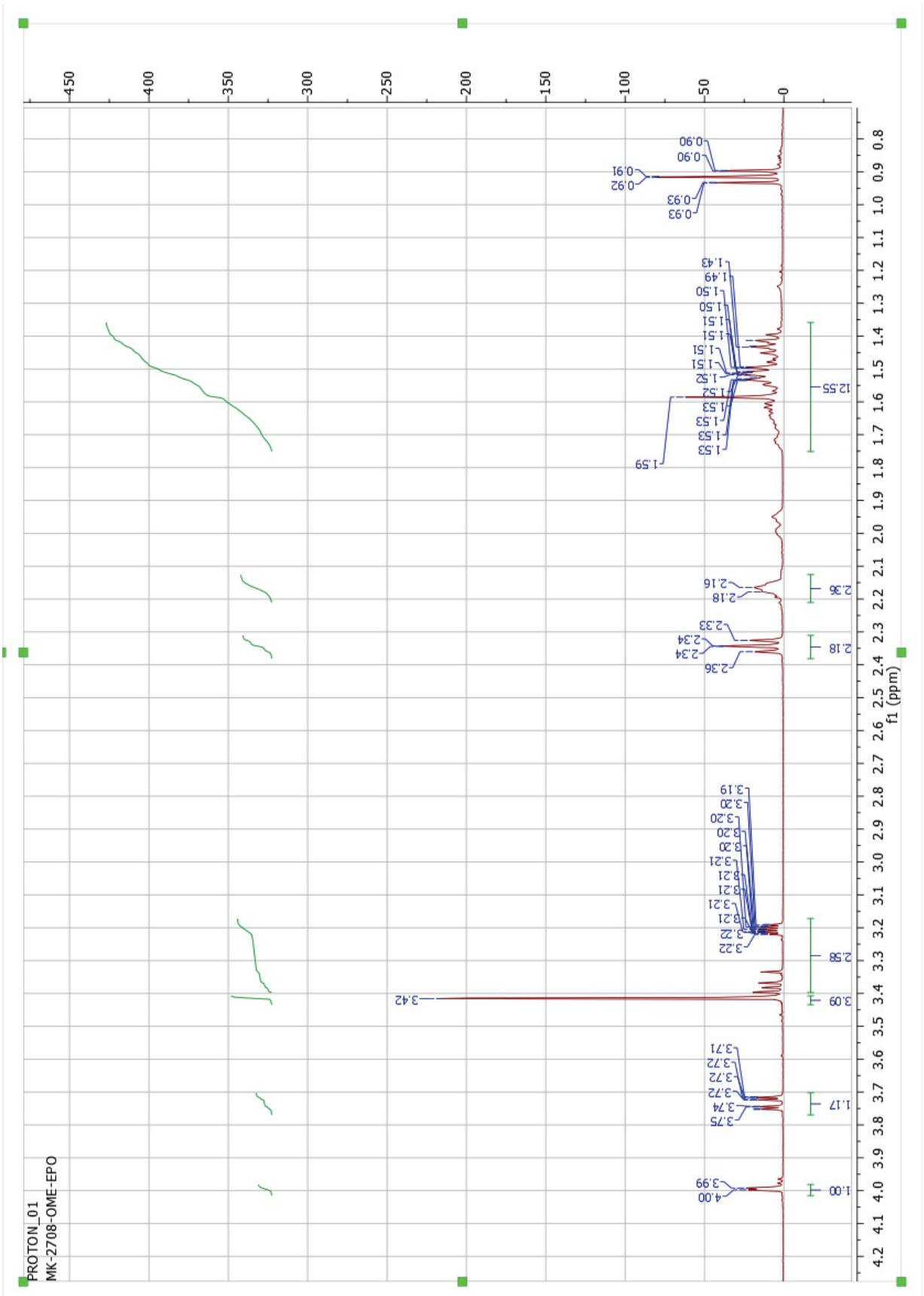
Wu, H.Y., Chang, C.-W., Chein R.-J. 2013. "Enantioselective Synthesis of (Thiolan-2-yl)diphenylmethanol and Its Application in Asymmetric, Catalytic Sulfur Ylide-Mediated Epoxidation", J. Org. Chem., 78, 5788−93.

Wu, H.Y., She, X. Shi, Y. 2002. "Highly Enantioselective Epoxidation of α,β-Unsaturated Esters by Chiral Dioxirane", J. Am. Chem. Soc., 124, 8792-93.

APPENCIES

APPENDIX A

^{1}H NMR AND ^{13}CNMR SPECTRUMS OF REACTANTS AND PRODUCT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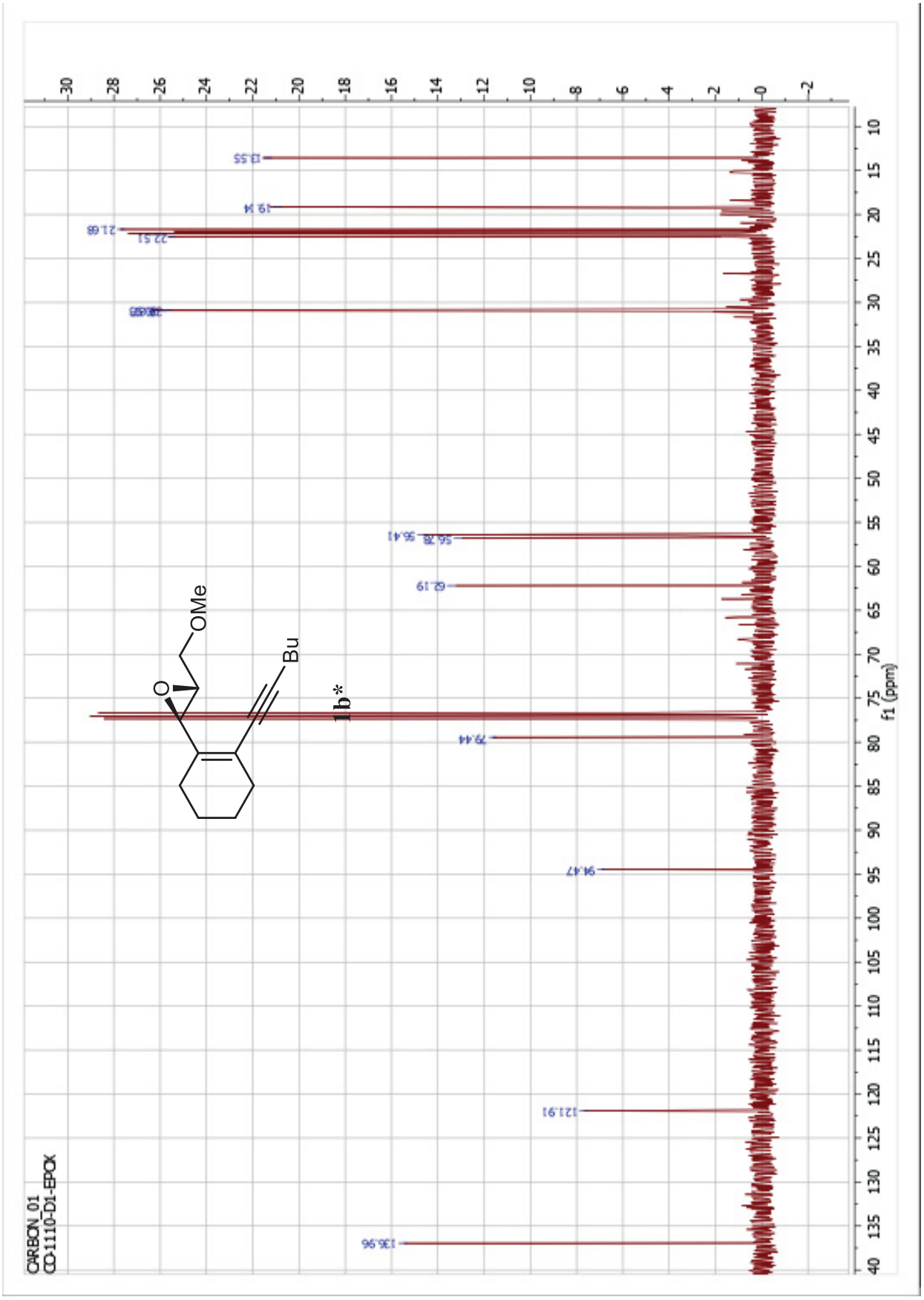
f1 (ppm)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O
1b*
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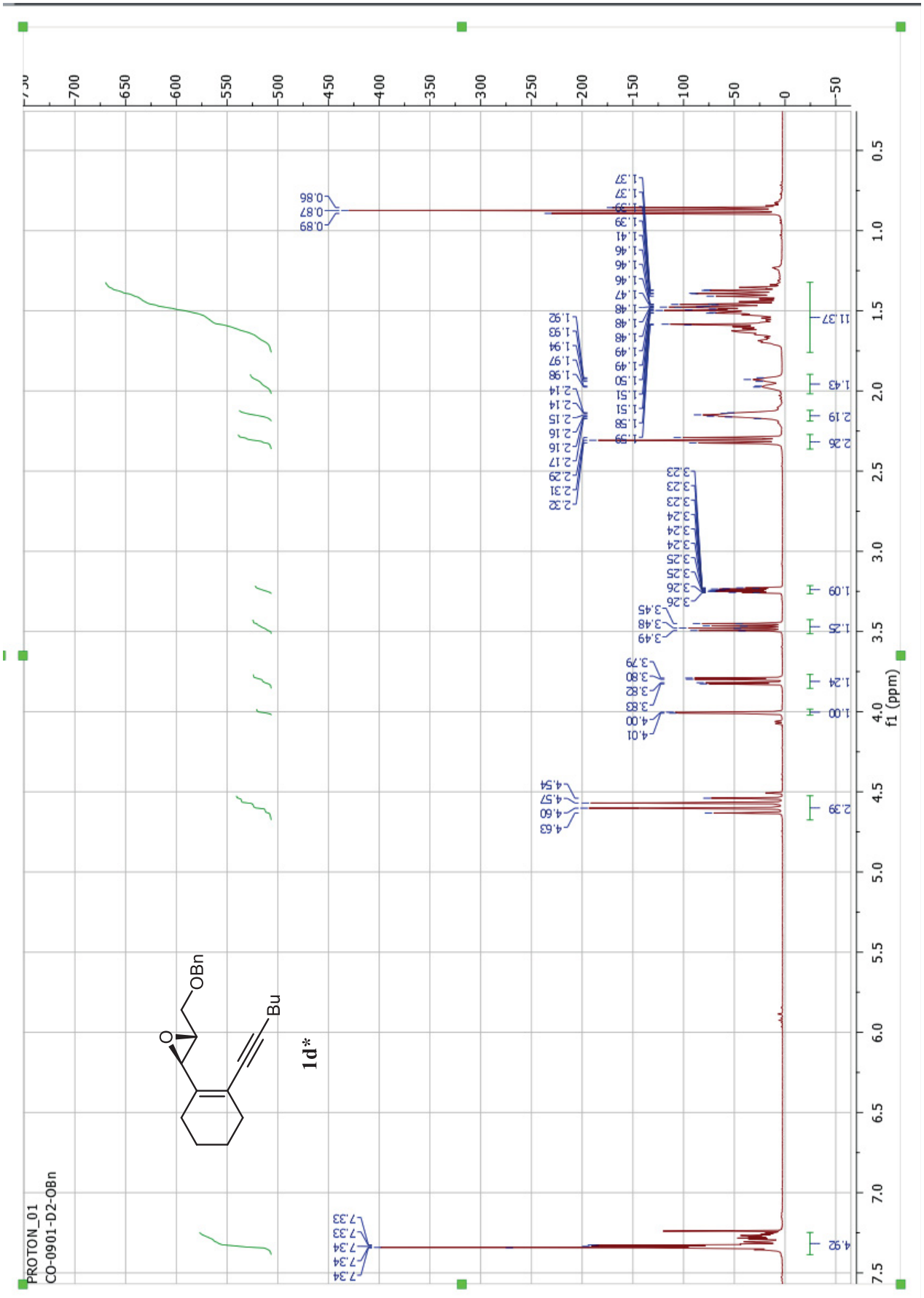
136.96
f1 (ppm)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1d*
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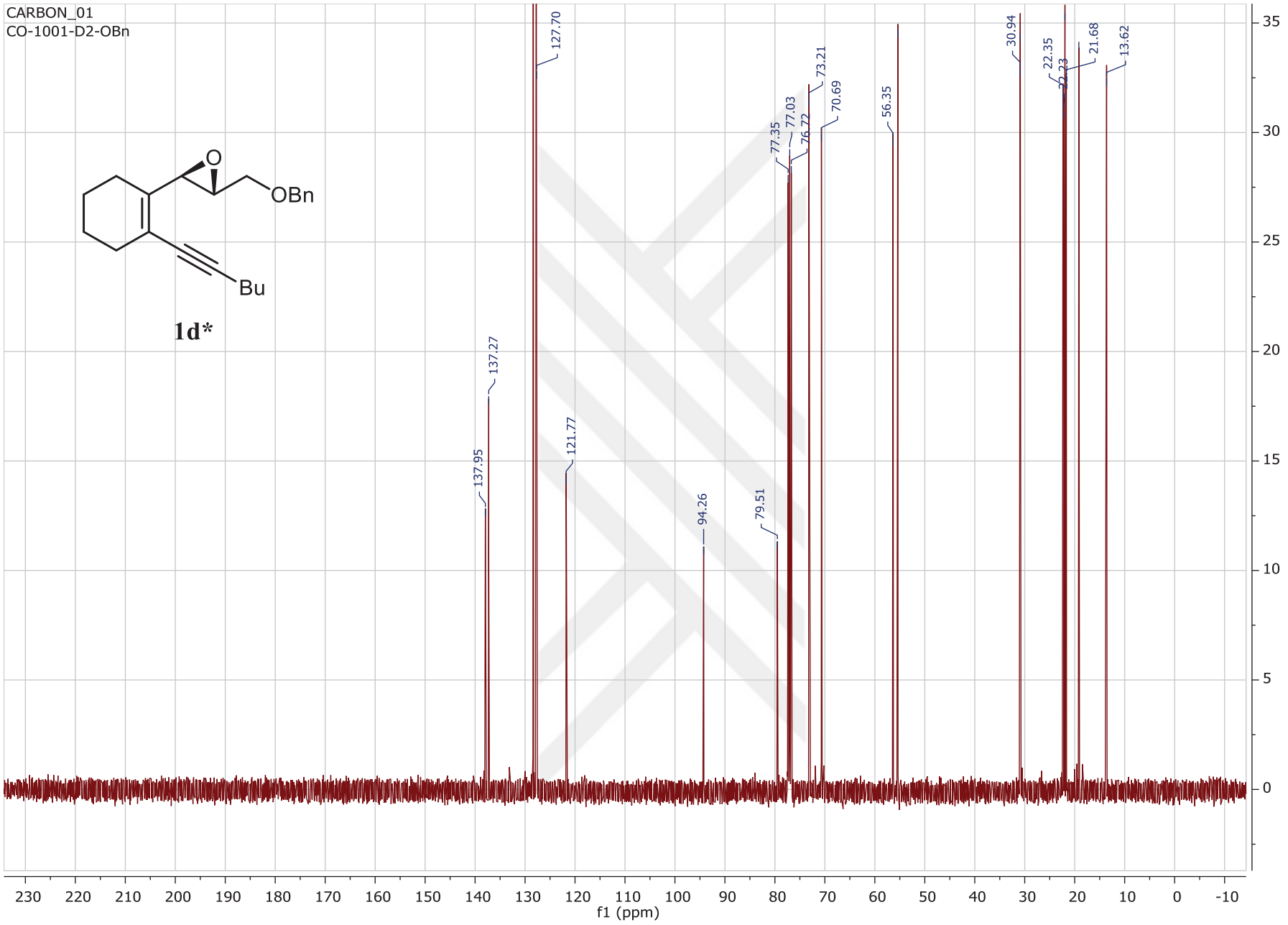
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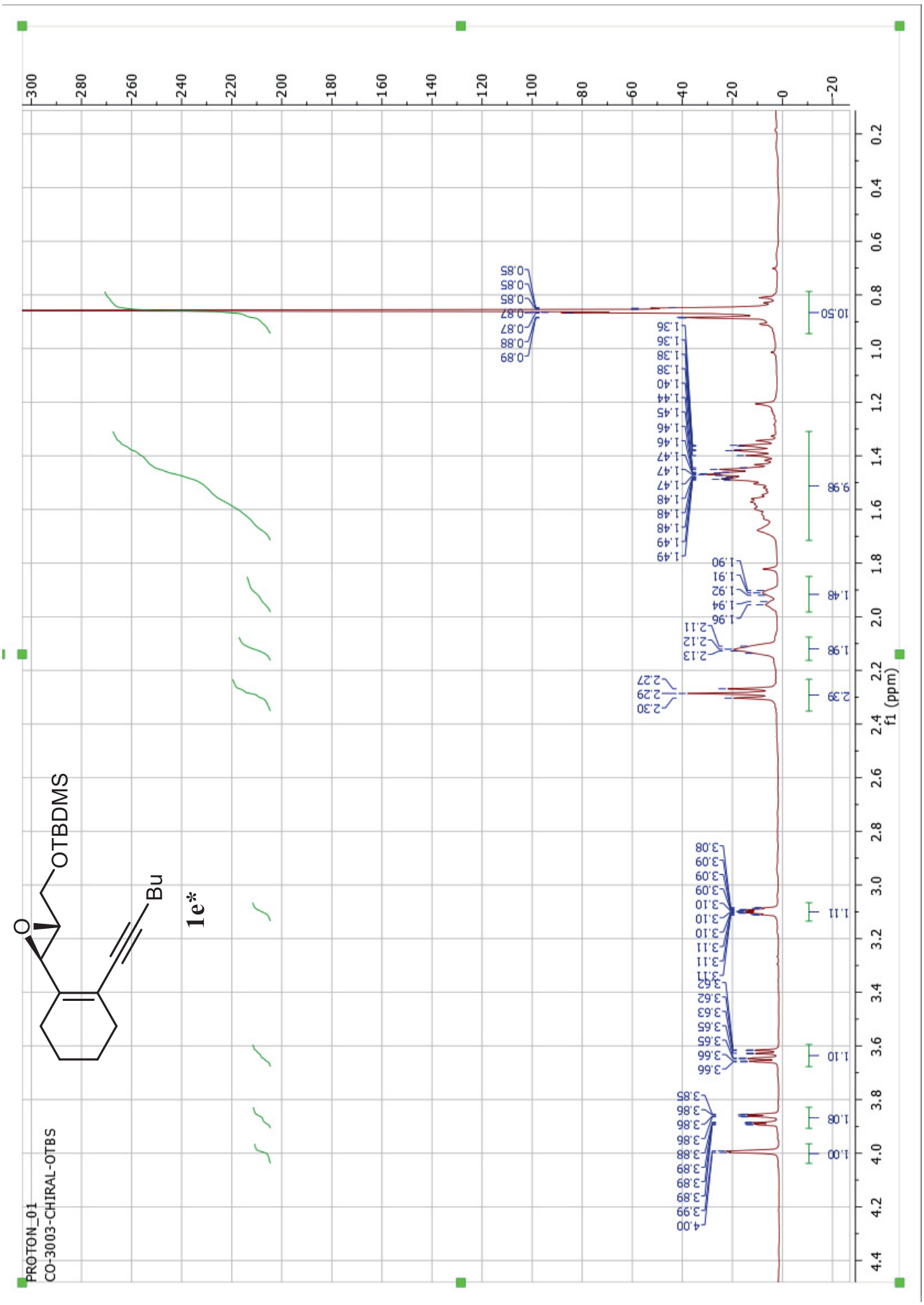
f1 (ppm)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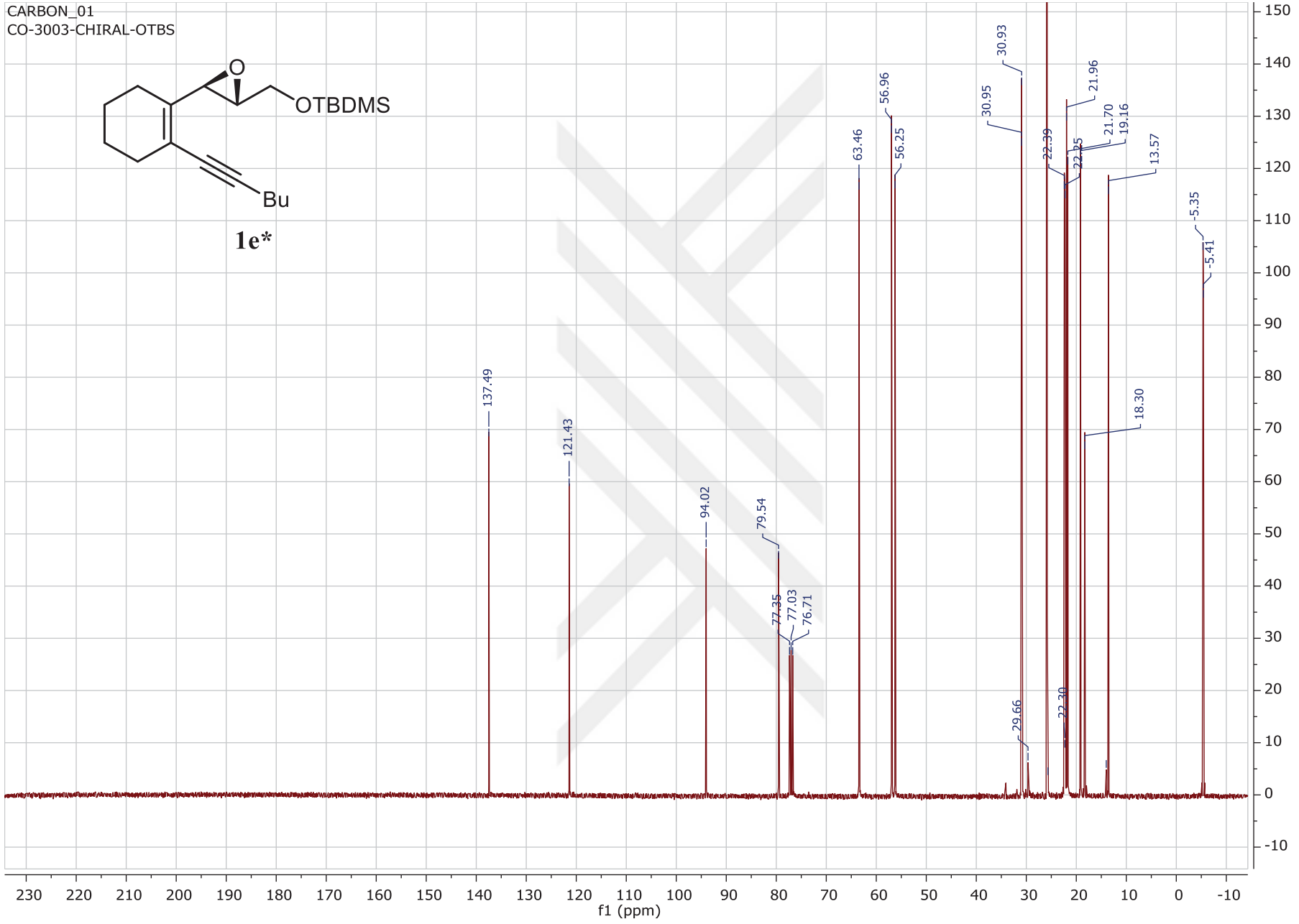
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76.71
63.46
56.96
56.25
30.95
30.93
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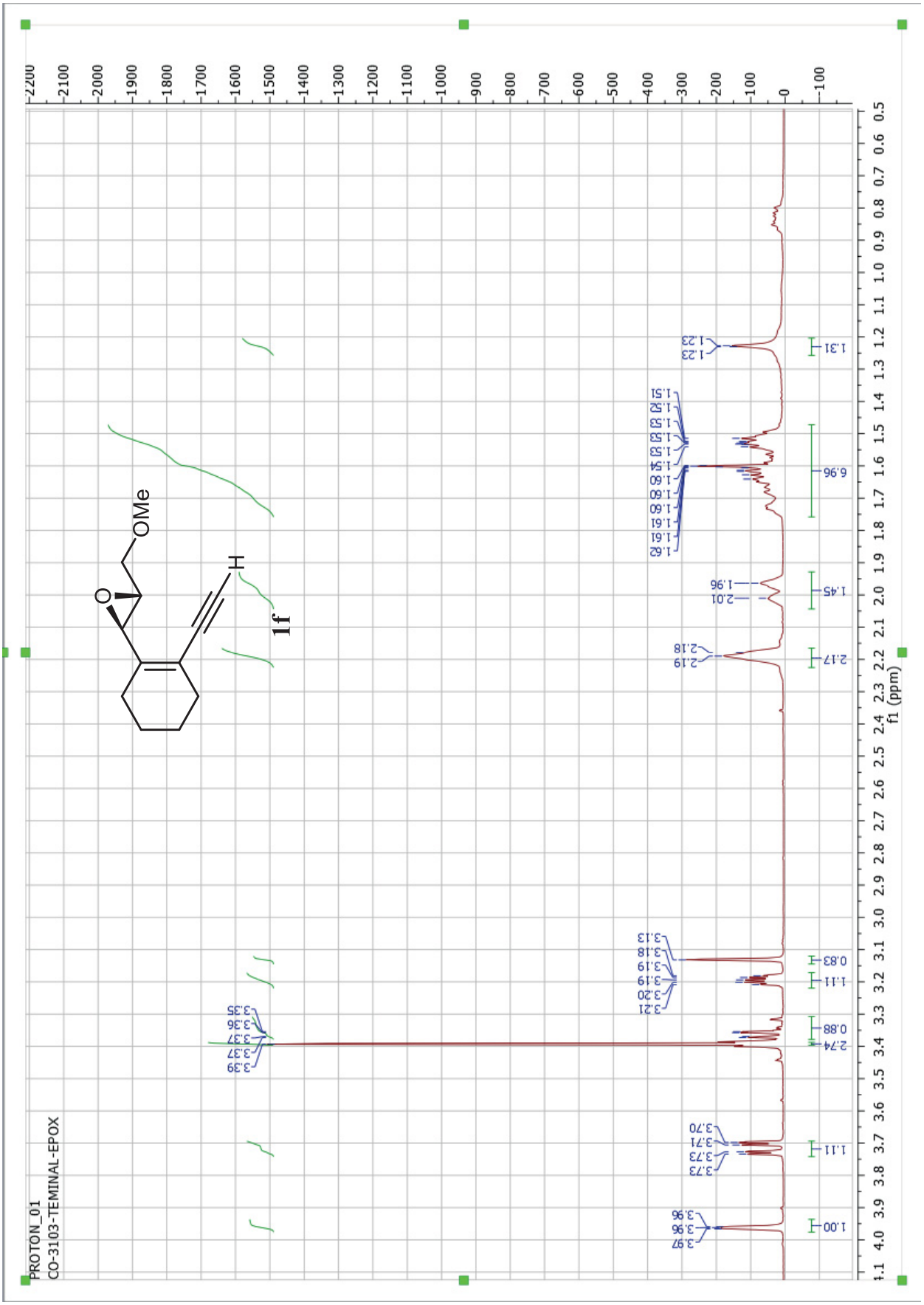
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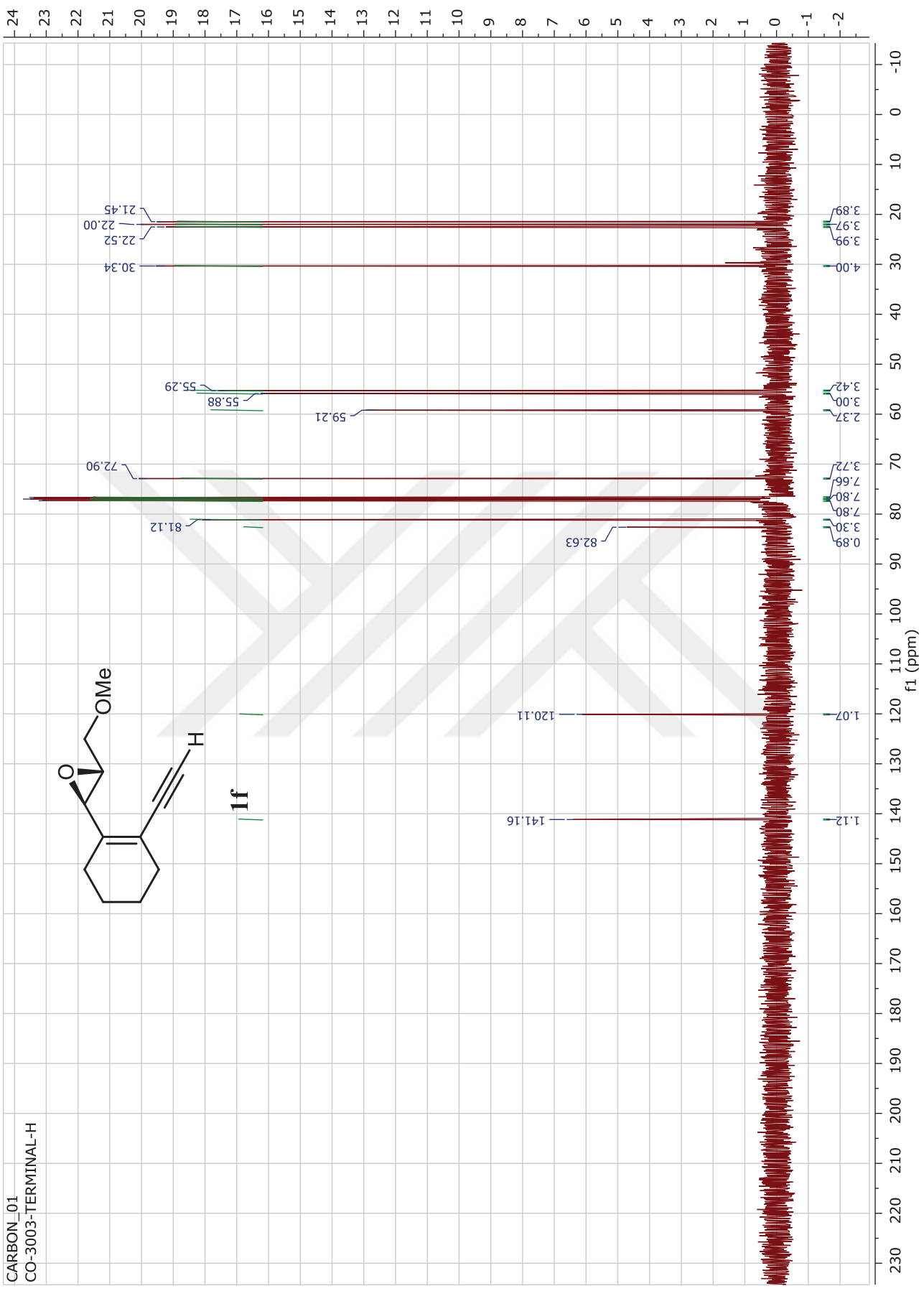
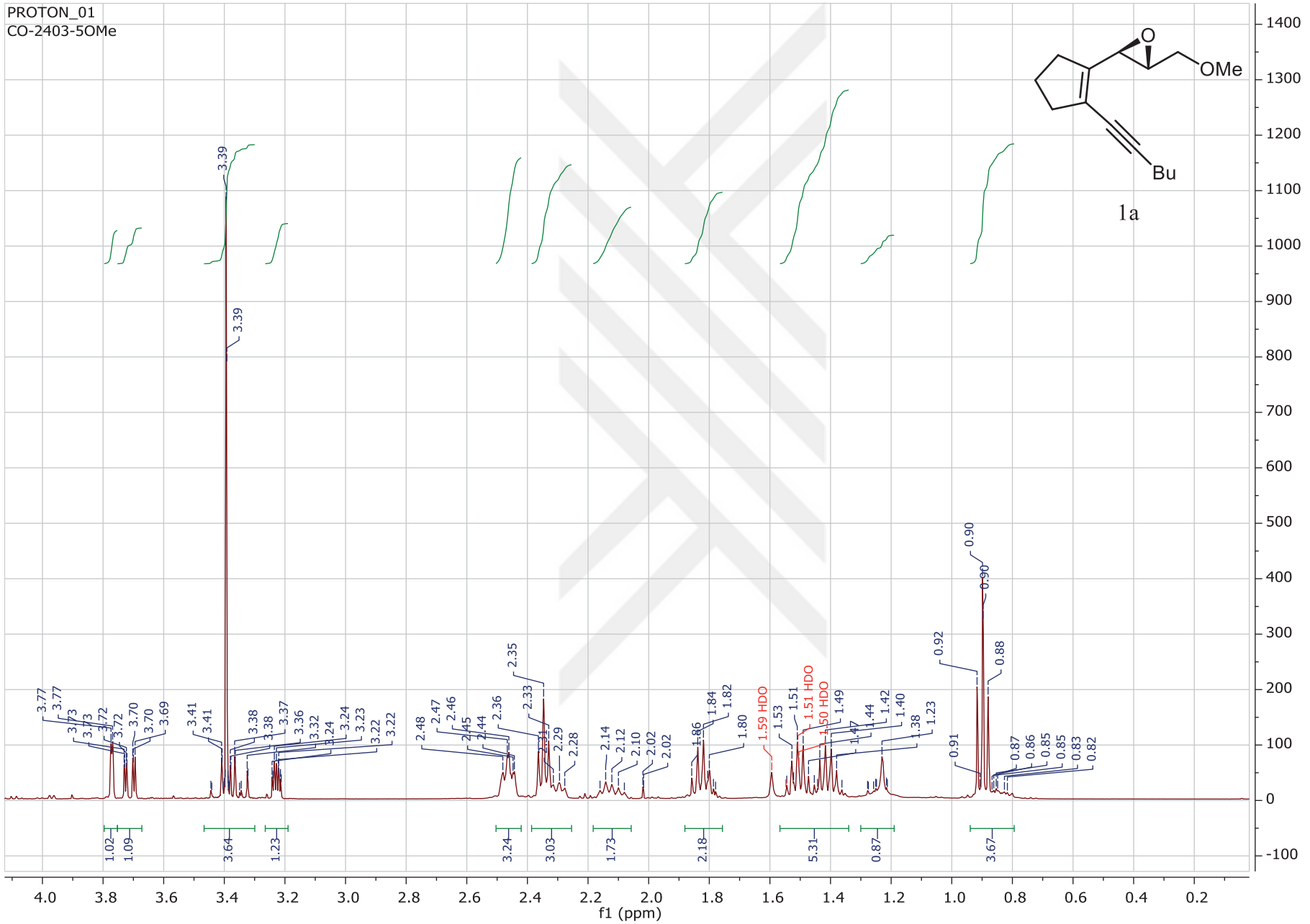
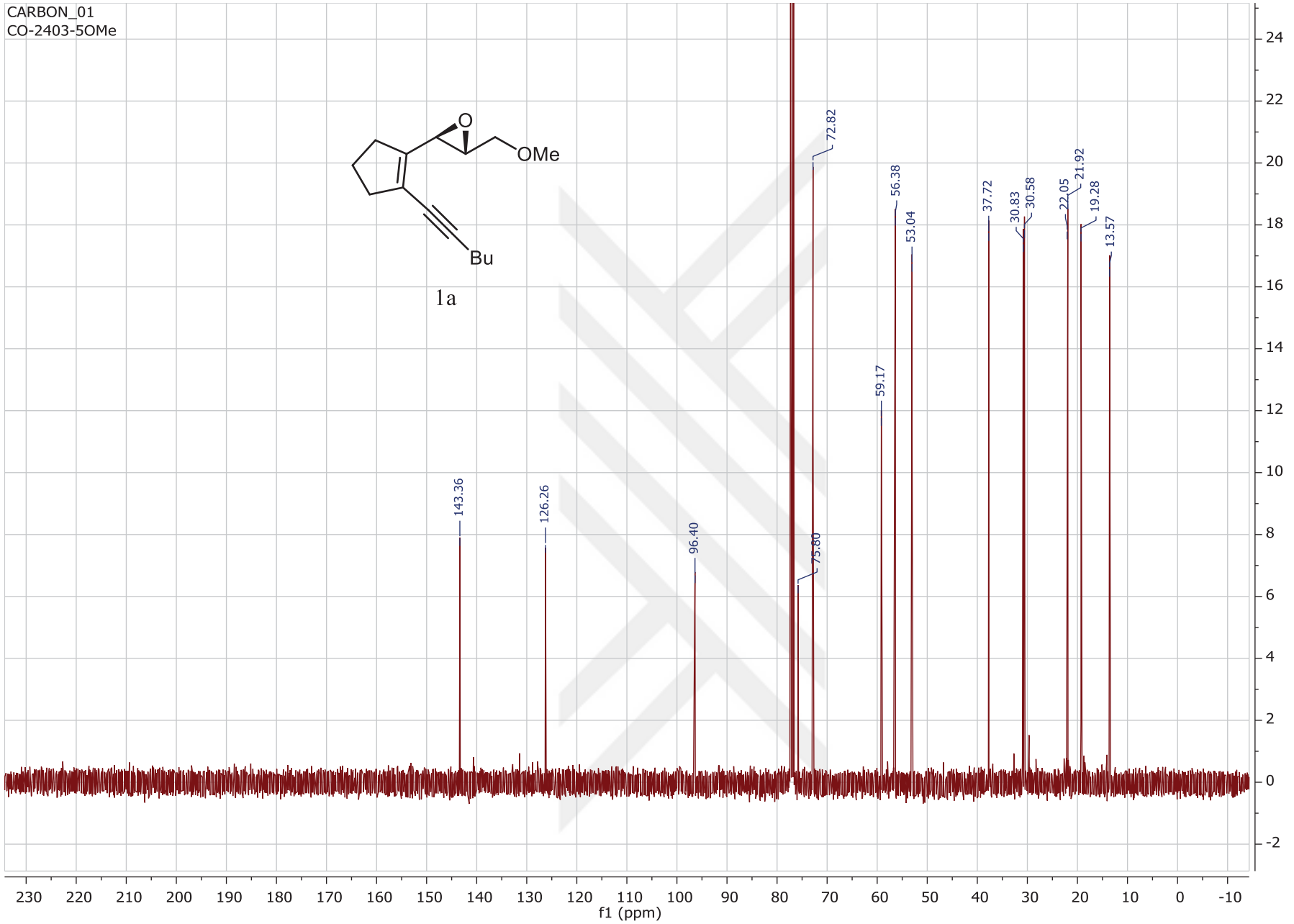
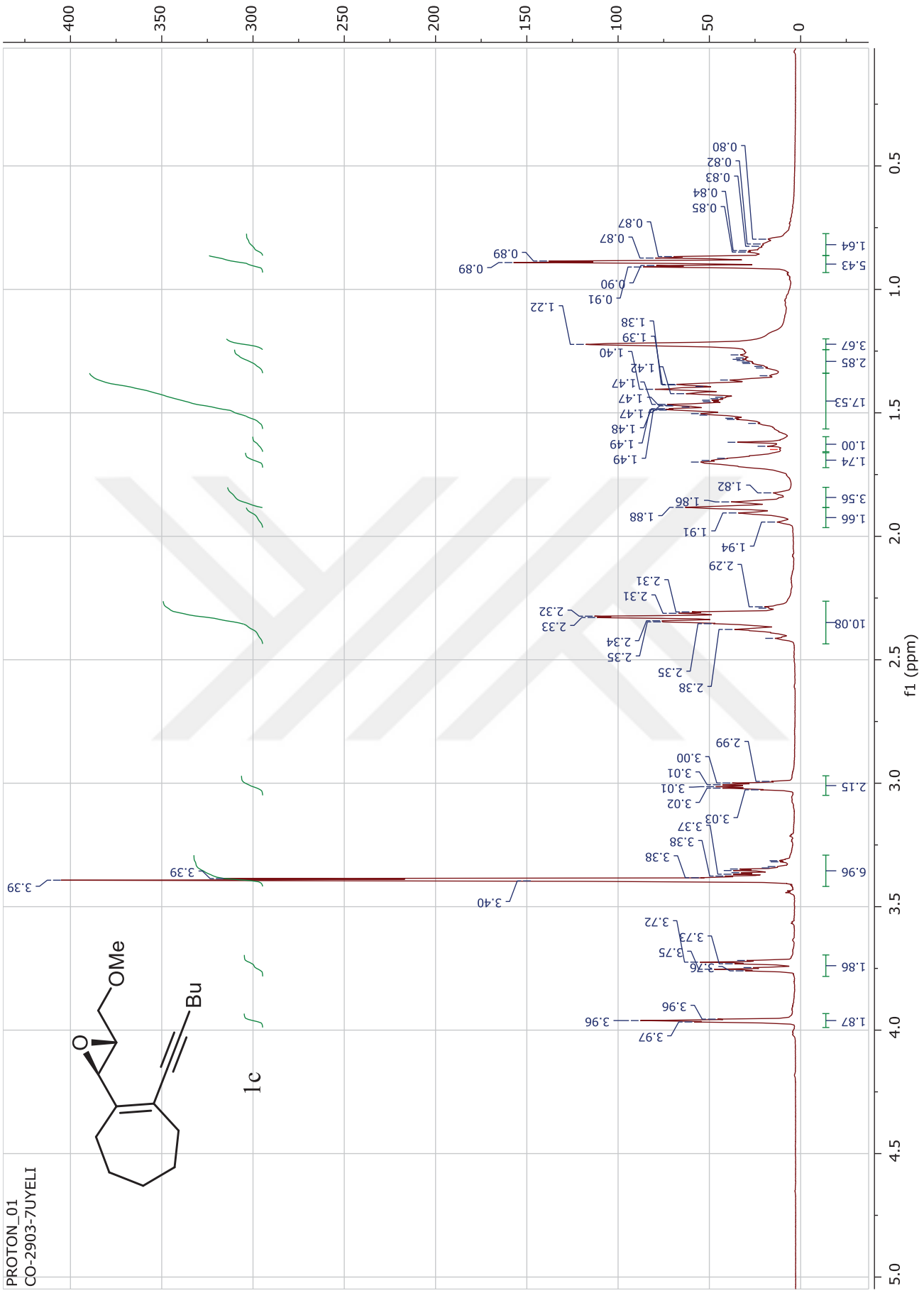
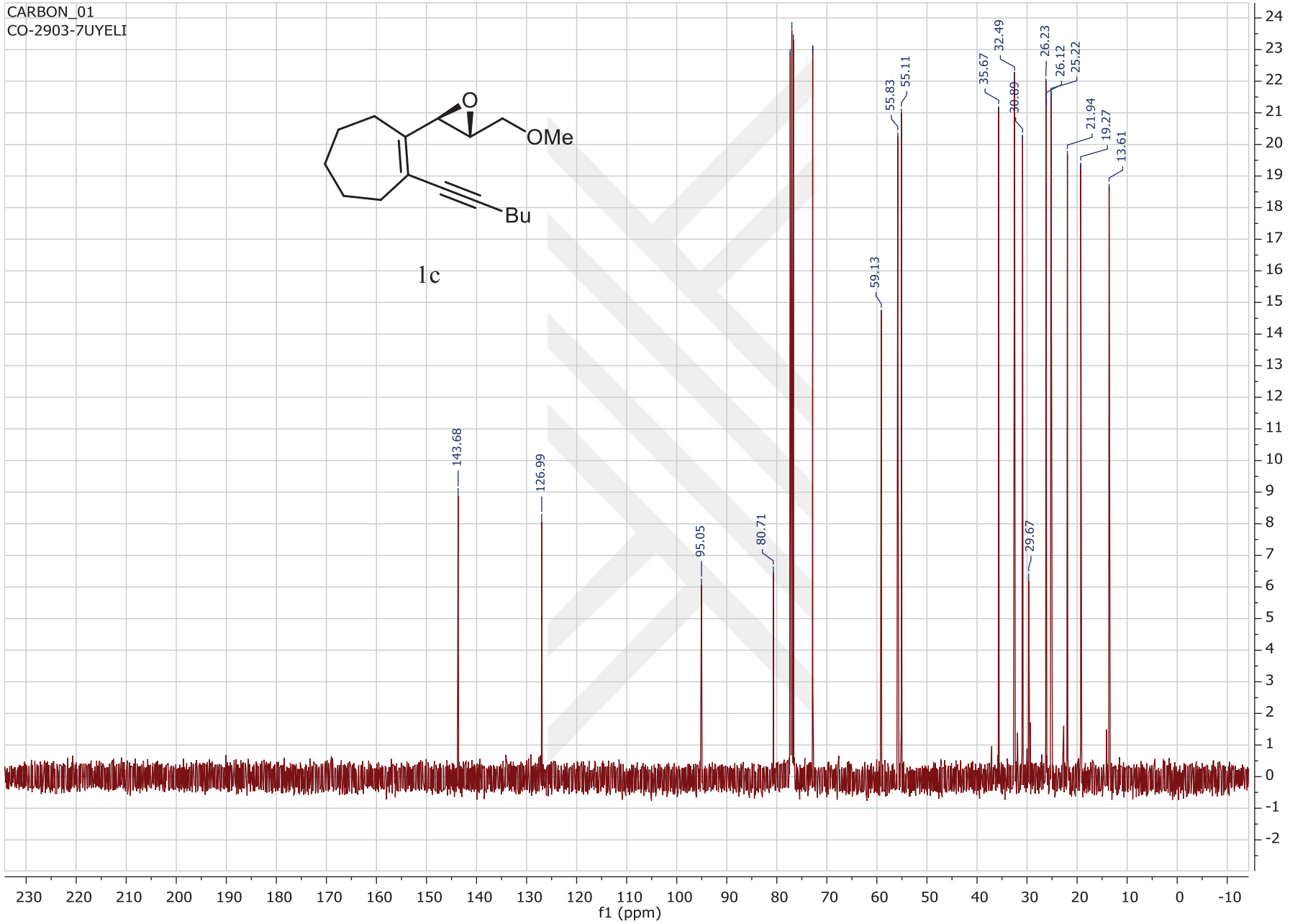
1f
f1 (ppm)

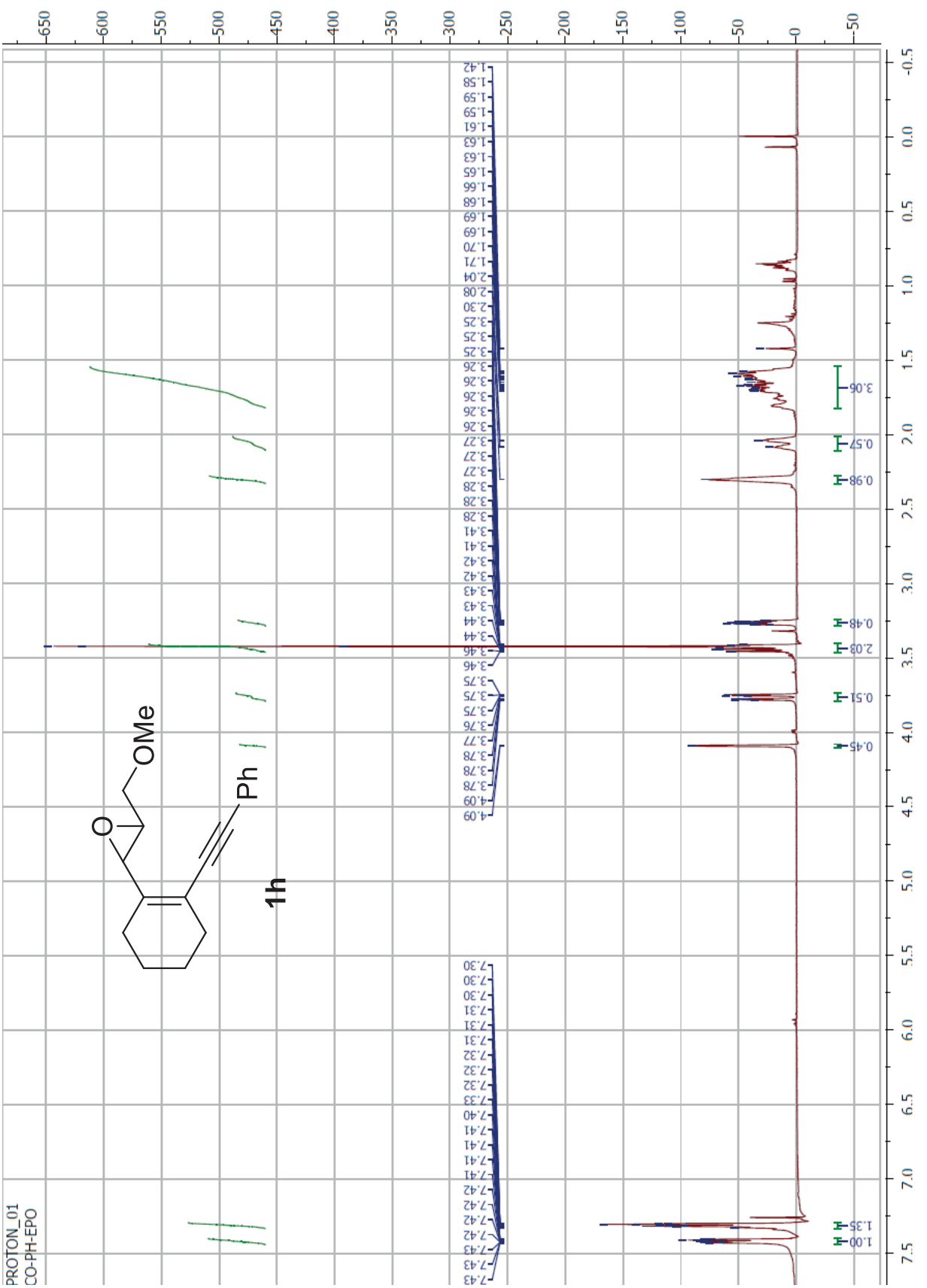

CARBON_01
CO-3003-TERMINAL-H
1f
OMe
O
H
f1 (ppm)
21.45
22.00
22.52
30.34
55.29
55.88
59.21
72.90
81.12
82.63
120.11
141.16
3.89
3.97
3.99
4.00
3.42
3.00
2.37
3.72
7.66
7.80
7.80
3.30
0.89
1.07
1.12

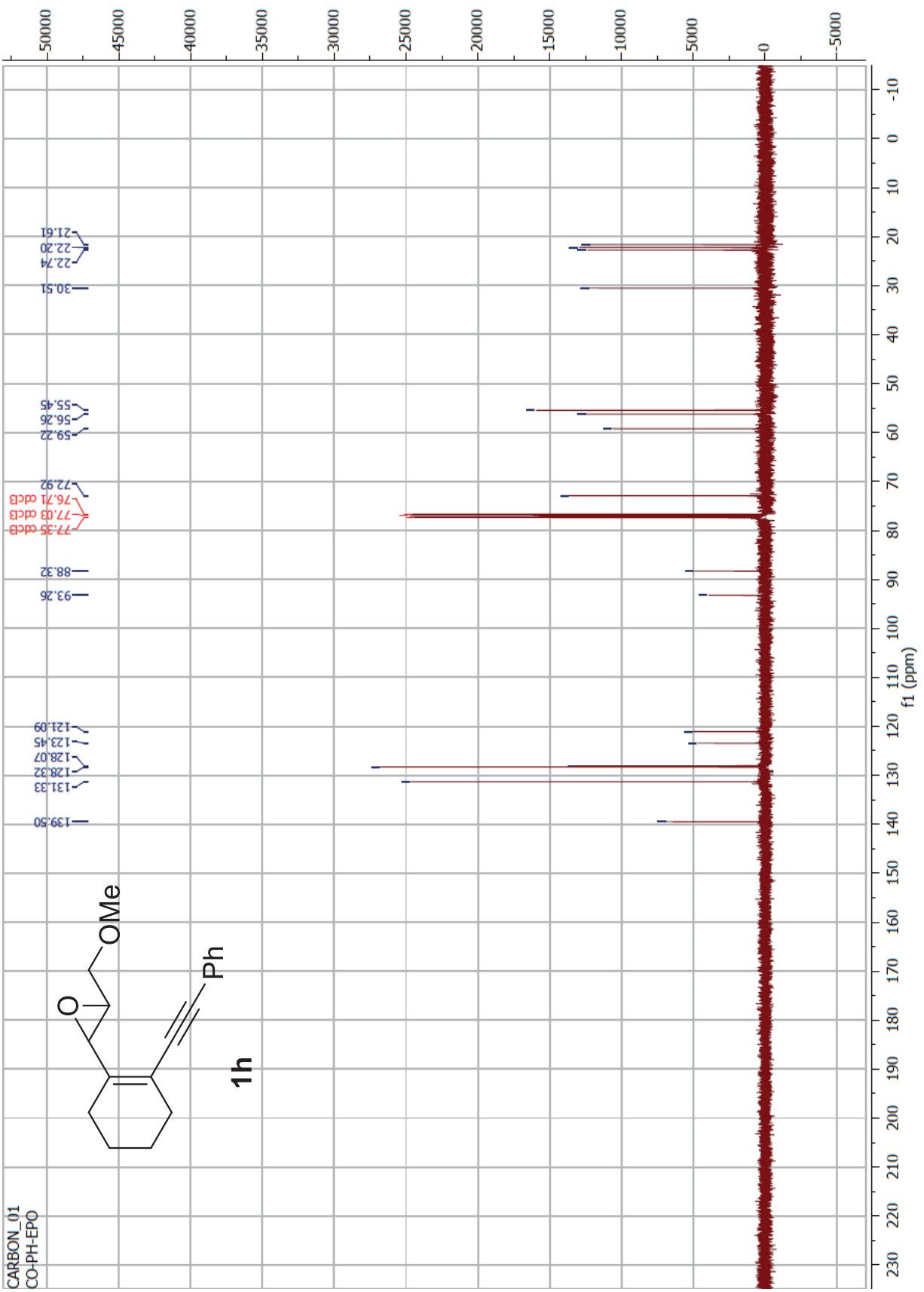

PROTON_01
CO-2403-5OMe
OMe
Bu
1a
f1 (ppm)

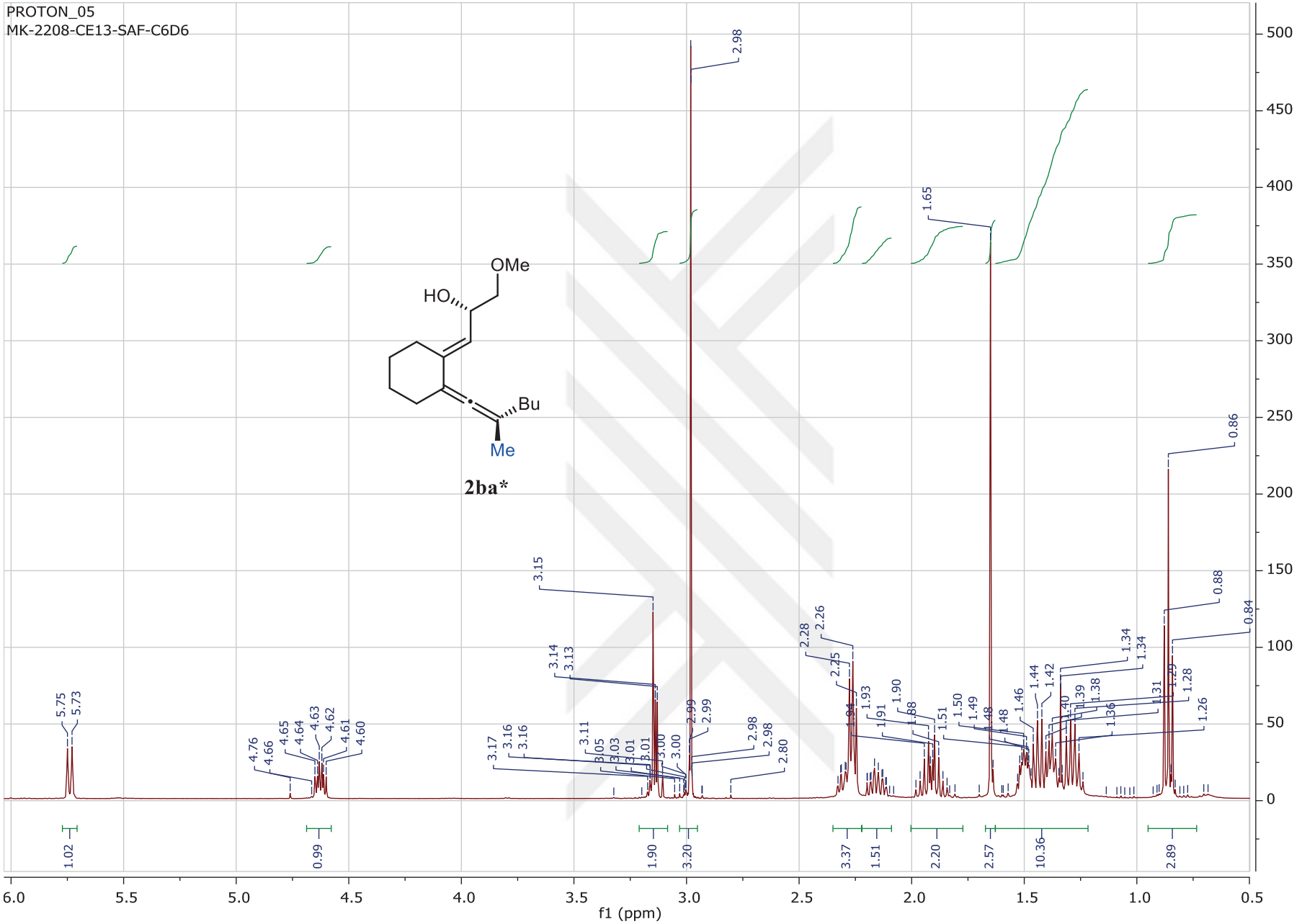

CARBON_01
CO-2403-5OMe
O
OMe
Bu
1a
143.36
126.26
96.40
75.80
72.82
59.17
56.38
53.04
37.72
30.83
30.58
22.05
21.92
19.28
13.57
f1 (ppm)

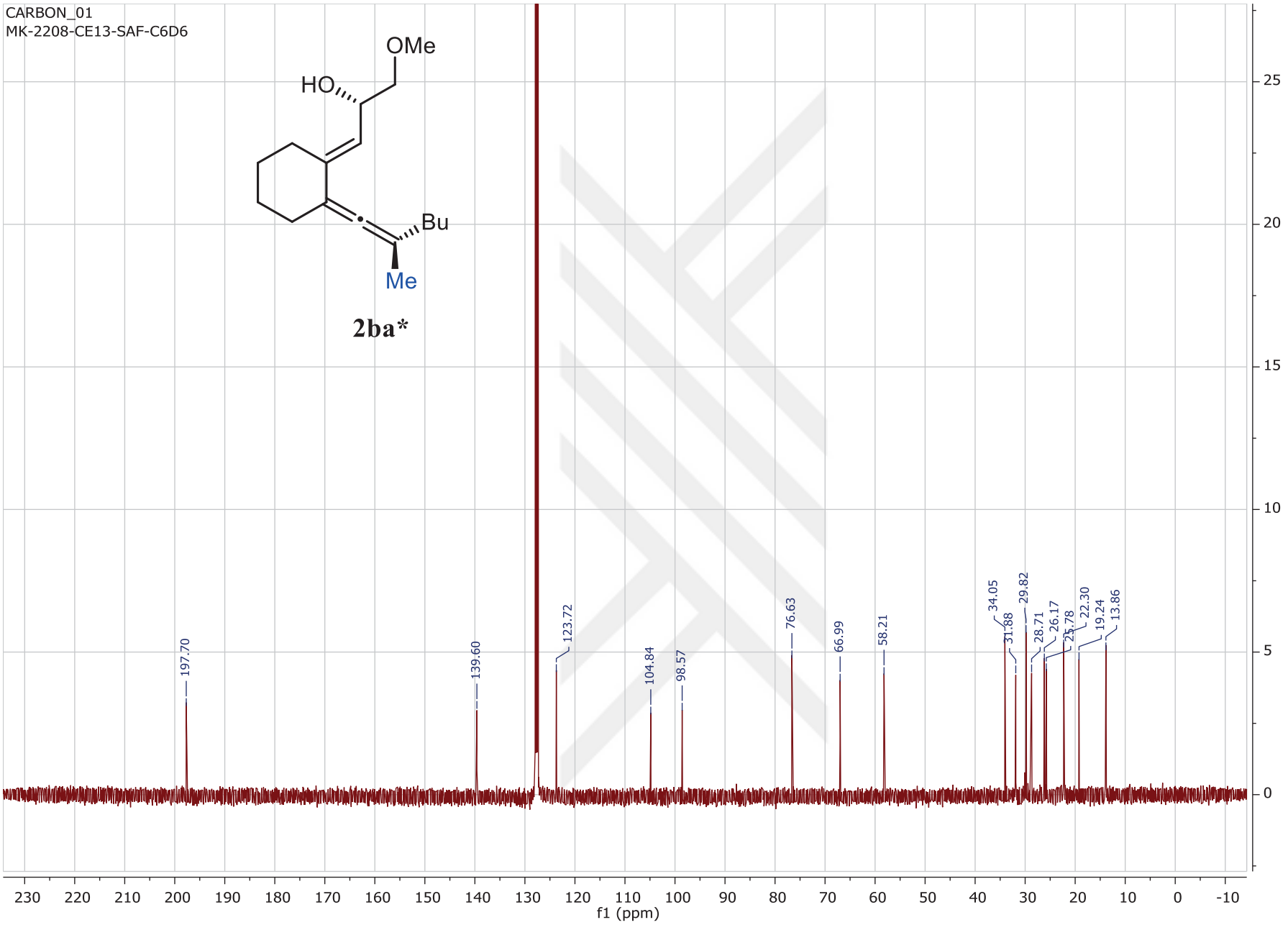

PROTON_01
CO-2903-7UYELI
1c
OMe
Bu
O
f1 (ppm)

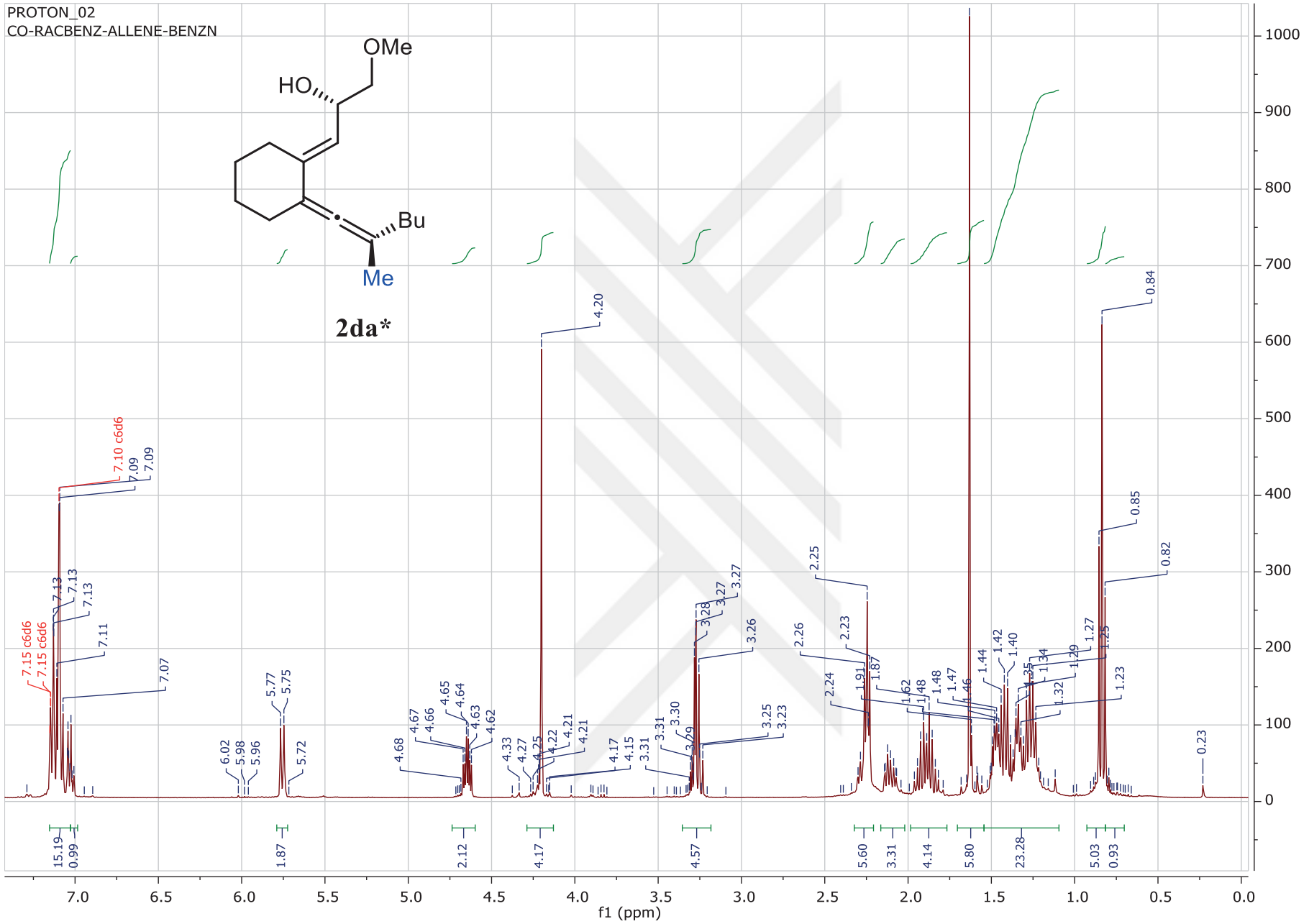

CARBON_01
CO-2903-7UYELI
O
OMe
Bu
1c
143.68
126.99
95.05
80.71
59.13
55.83
55.11
35.67
32.49
30.89
29.67
26.23
26.12
25.22
21.94
19.27
13.61
f1 (ppm)

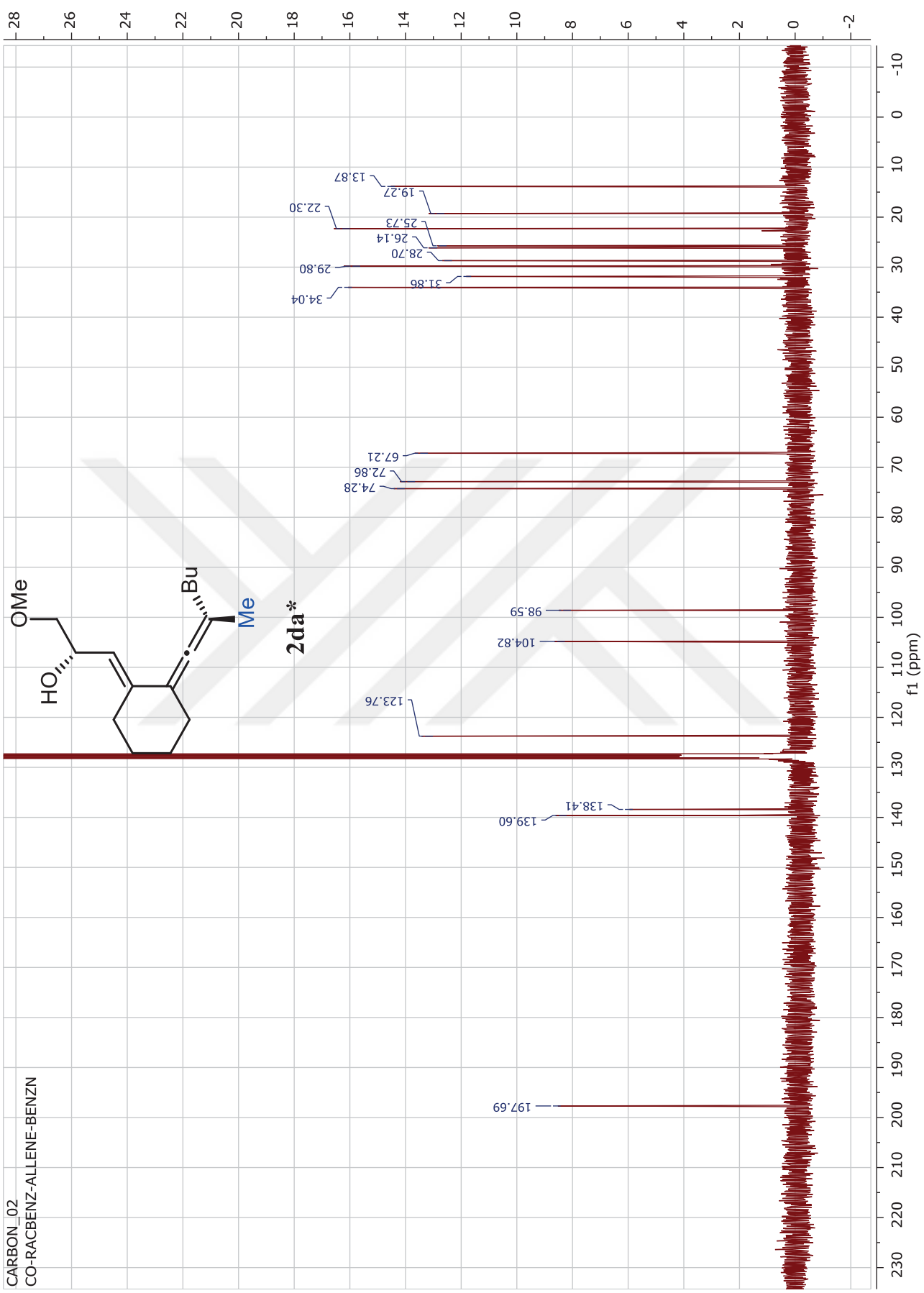

PROTON_01
CO-PH-EPO
OMe
Ph
O
1h

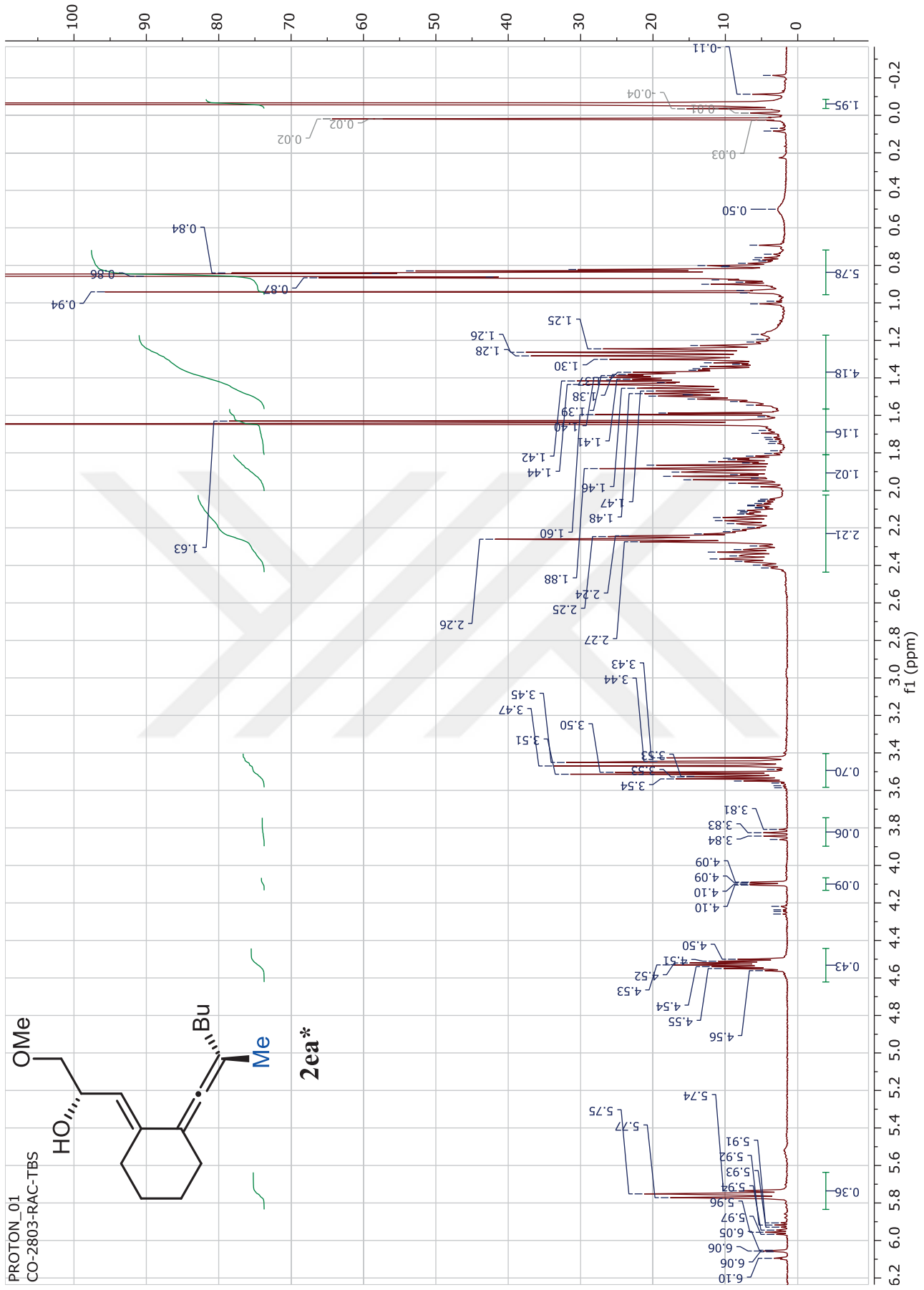

CARBON_01
CO-PH-EPO
1h
OMe
O
Ph
139.50
131.33
128.32
128.07
123.45
121.09
93.26
88.32
77.35 cdcl3
77.03 cdcl3
76.71 cdcl3
72.92
59.22
56.26
55.45
30.51
22.74
22.20
21.61
f1 (ppm)

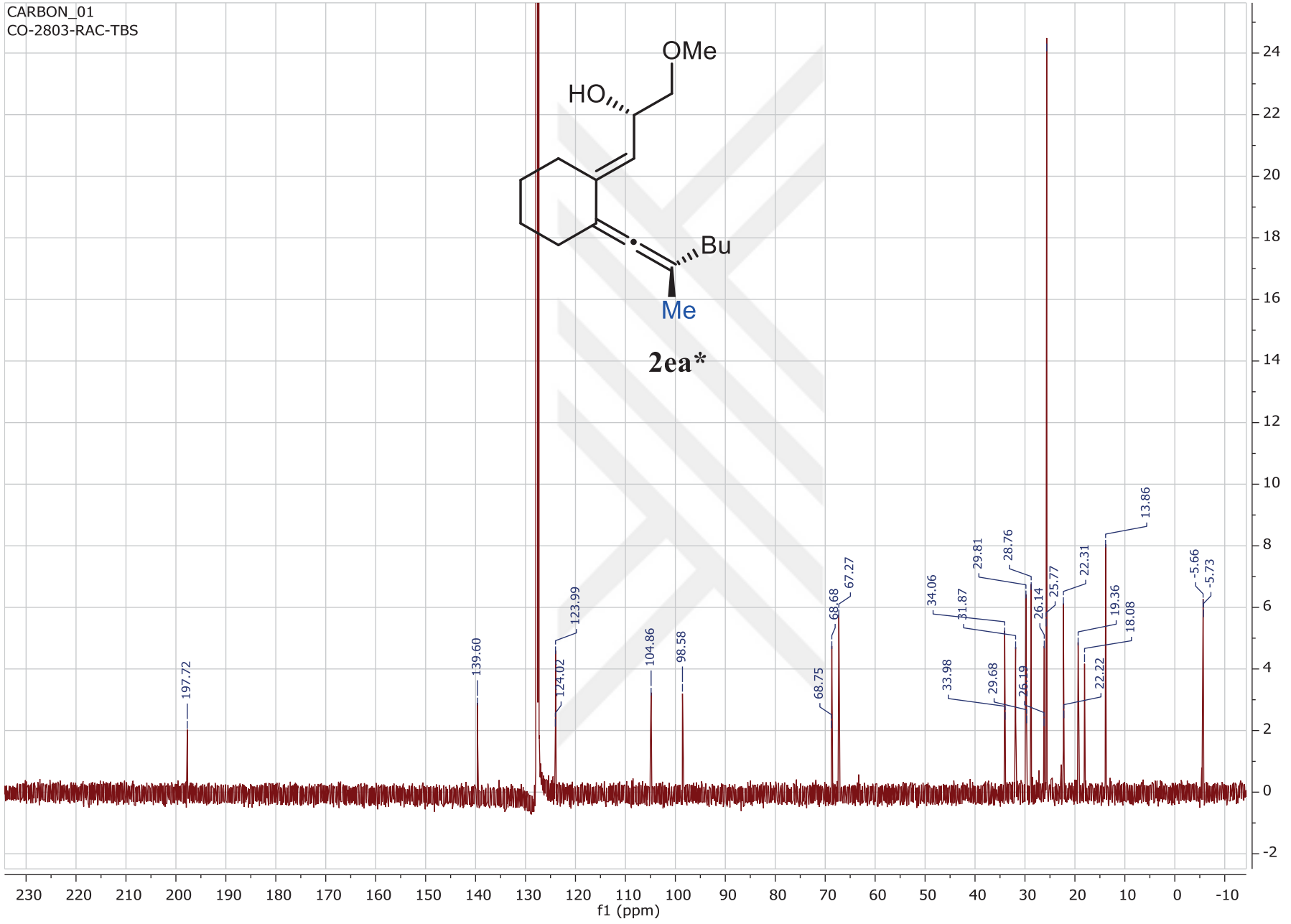

PROTON_05
MK-2208-CE13-SAF-C6D6
OMe
HO
Bu
Me
2ba*
f1 (ppm)

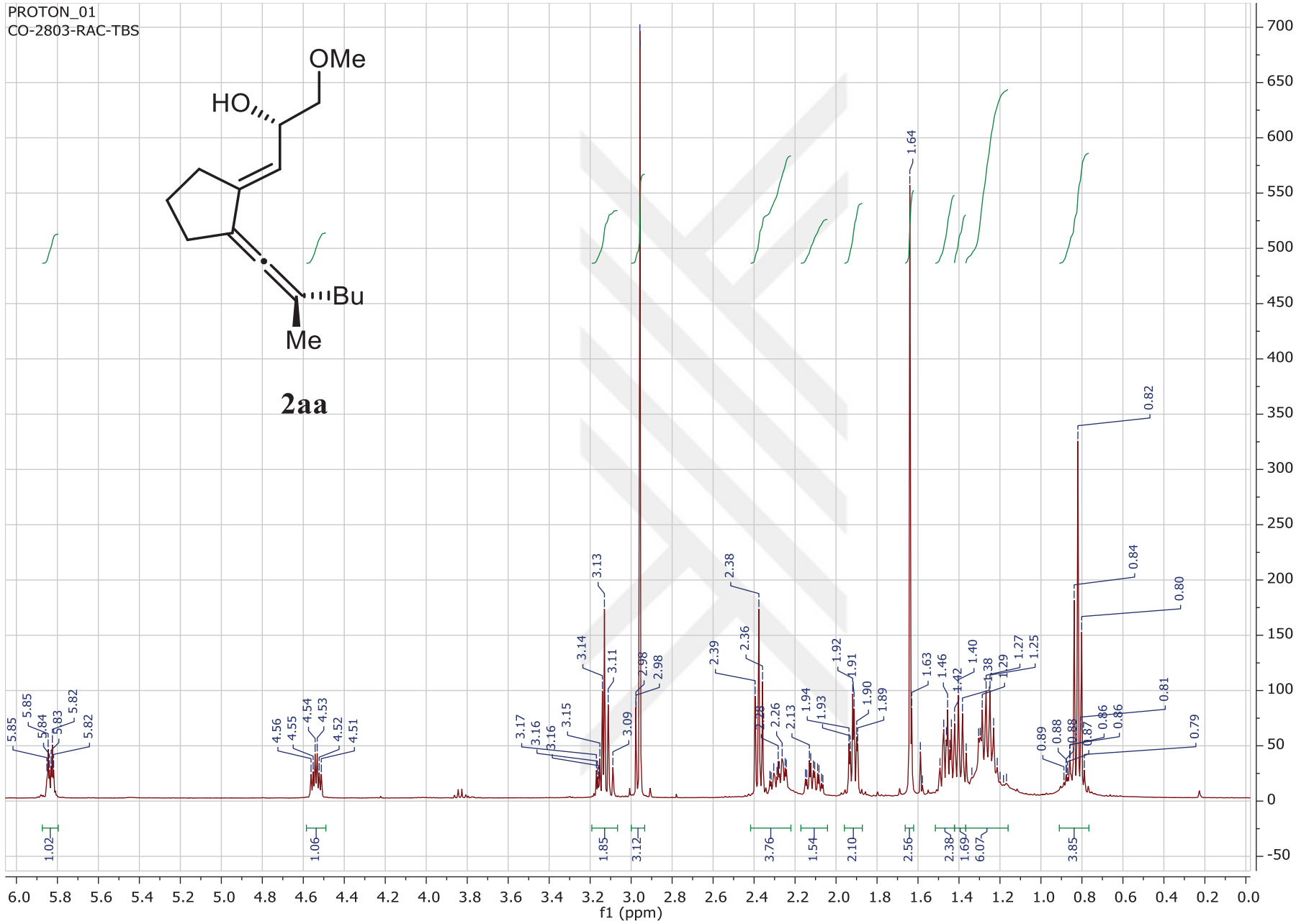

CARBON_01
MK-2208-CE13-SAF-C6D6
OMe
HO
Bu
Me
2ba*
197.70
139.60
123.72
104.84
98.57
76.63
66.99
58.21
34.05
31.88
29.82
28.71
26.17
25.78
22.30
19.24
13.86
f1 (ppm)

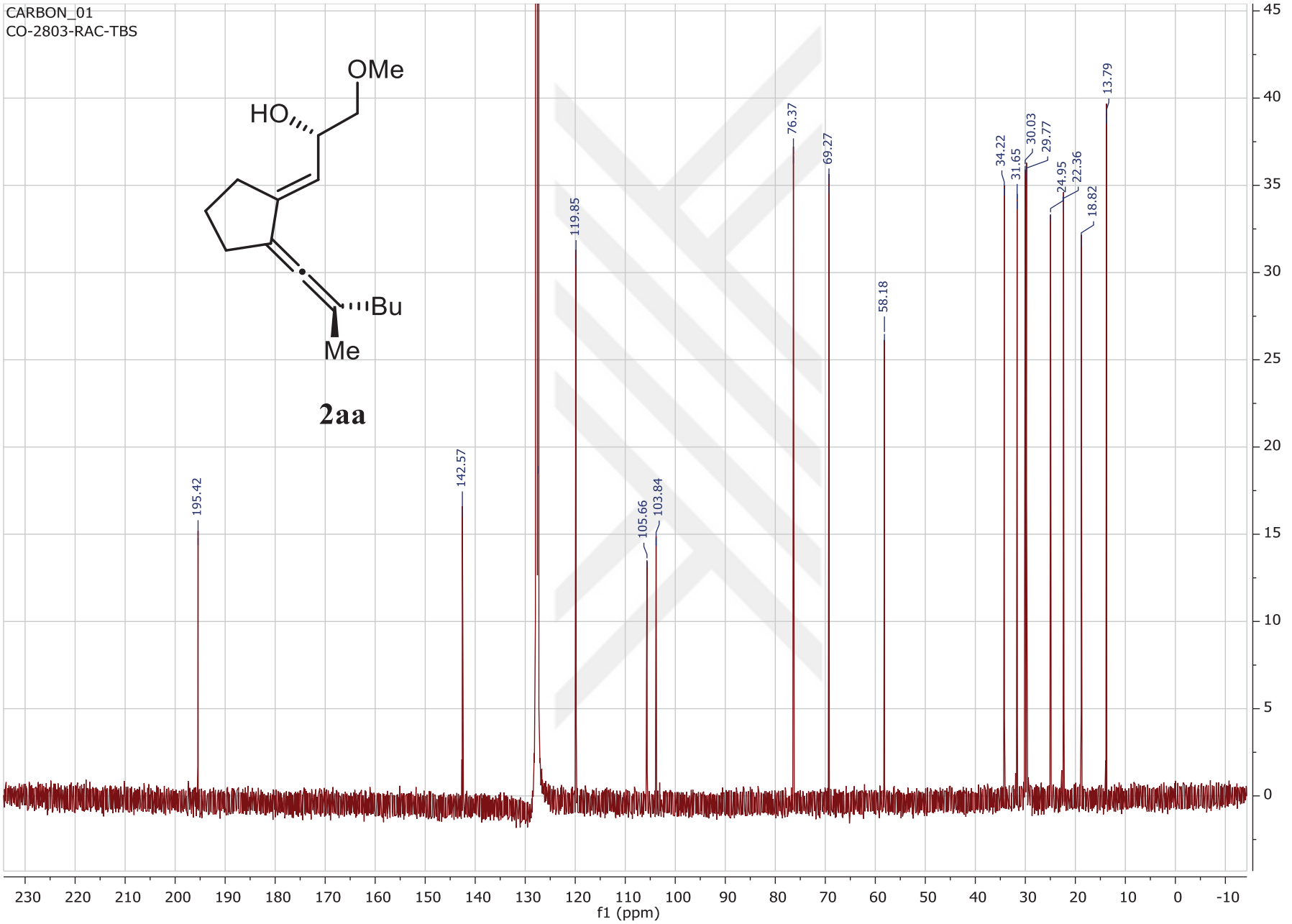

PROTON_02
CO-RACBENZ-ALLENE-BENZN
OMe
HO
Bu
Me
2da*
f1 (ppm)

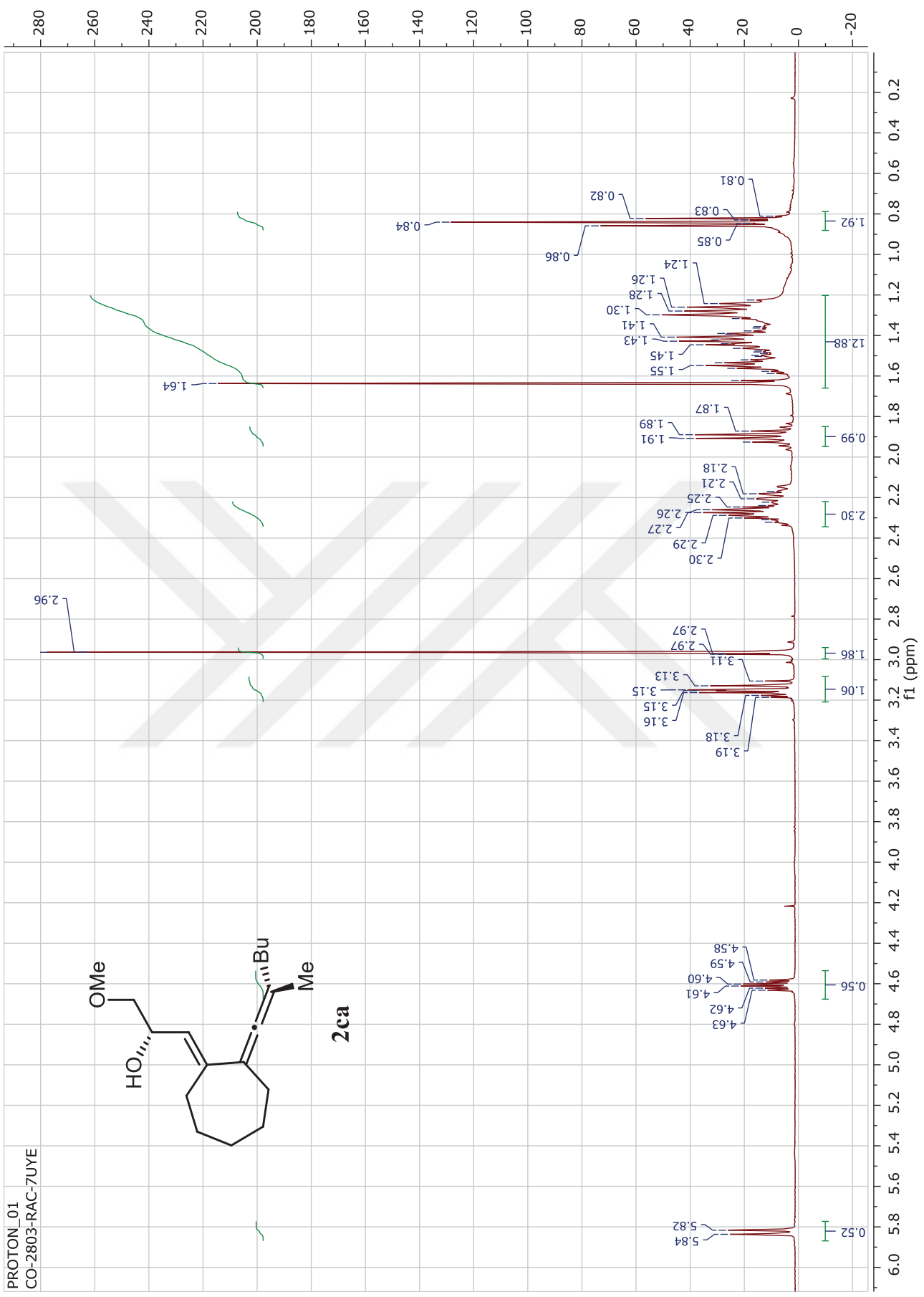

CARBON_02
CO-RACBENZ-ALLENE-BENZN
2da*
OMe
HO
Bu
Me
197.69
139.60
138.41
123.76
104.82
98.59
74.28
72.86
67.21
34.04
31.86
29.80
28.70
26.14
25.73
22.30
19.27
13.87
f1 (ppm)

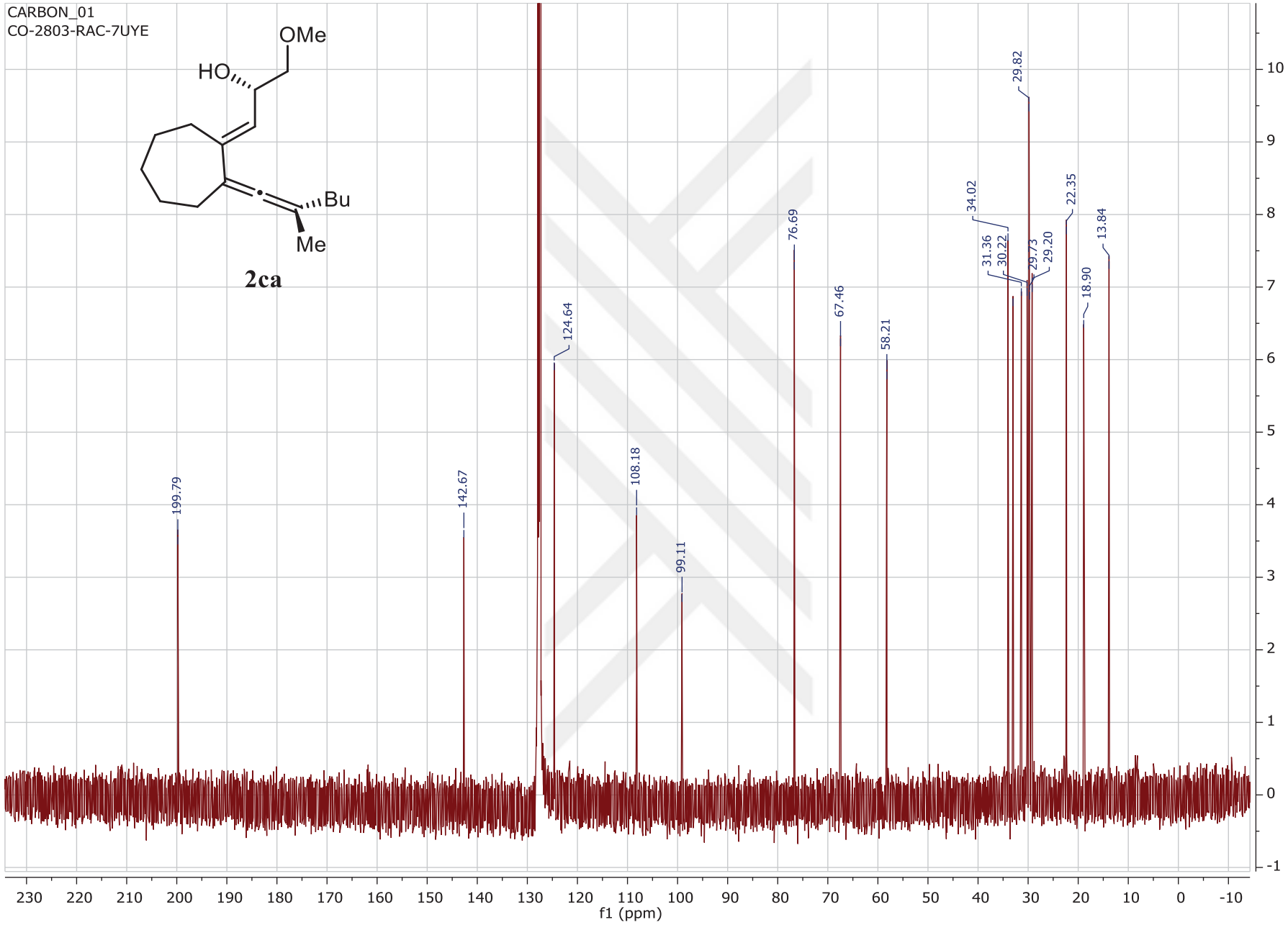

PROTON_01
CO-2803-RAC-TBS
OMe
HO
Bu
Me
2ea*
f1 (ppm)


CARBON_01
CO-2803-RAC-TBS
OMe
HO
Bu
Me
2ea*
197.72
139.60
124.02
123.99
104.86
98.58
68.75
68.68
67.27
34.06
33.98
31.87
29.81
29.68
28.76
26.19
26.14
25.77
22.31
22.22
19.36
18.08
13.86
-5.66
-5.73
f1 (ppm)


PROTON_01
CO-2803-RAC-TBS
OMe
HO
Bu
Me
2aa
f1 (ppm)


CARBON_01
CO-2803-RAC-TBS
OMe
HO
Bu
Me
2aa
195.42
142.57
119.85
105.66
103.84
76.37
69.27
58.18
34.22
31.65
30.03
29.77
24.95
22.36
18.82
13.79
f1 (ppm)


PROTON_01
CO-2803-RAC-7UYE
OMe
HO
Bu
Me
2ca
f1 (ppm)


CARBON_01
CO-2803-RAC-7UYE
OMe
HO
Bu
Me
2ca
199.79
142.67
124.64
108.18
99.11
76.69
67.46
58.21
34.02
31.36
30.22
29.82
29.73
29.20
22.35
18.90
13.84
f1 (ppm)

MK-7UYE-NOE

Sample Name	MK-7UYE-NOE	Pulse sequence	NOESY1D	Temperature	25
Date collected	2019-04-10	Solvent	cdcl3	Spectrometer	vnmrj.iyte.edu.tr-vnmrs400
				Study owner	vnmr1
				Operator	vnmr1

MK-7UYE-NOE

ACQUISITION

sw	6410.3
at	2.556
np	32768
fb	4000
bs	32
ss	2
d1	1.000
nt	64
ct	64

TRANSMITTER

tn	H1
sfrq	399.914
tof	399.9
tpwr	62
pw	15.000

NOESY

pwx1	0.500
[illegible]	[illegible]
gzlvlmix	1500.000
[illegible]	sech180

DPFGSE

[illegible]	MK-7UYE-NOE_NOESY1D_002
[illegible]	8
[illegible]	107153.6
gzlvlA	932
gtA	0.001000
[illegible]	MK-7UYE-NOE_NOESY1D_002
[illegible]	8
[illegible]	107153.6
gzlvlB	1398
gtB	0.001000
gstabAB	0.000500

GRADIENT

gzlvlC	-233
gt1	0.001000
gstab	0.000500
nsgrd	1392
hsqc	0.002000

PRESATURATION

satmode	n
wet	n

DECOUPLER

dn	C13
dm	nnn

SAMPLE

date	Apr 10 2019
solvent	cdcl3
file	/home/vnmr1/vnmrsys/data/MK-7UYE-NOE_20190410_01/NOESY1D_02

SPECIAL

temp	not used
[illegible]	60
[illegible]	2d
pw90	15.000

FLAGS

sspul	y
il	n
in	n
dp	y
hs	nn

PROCESSING

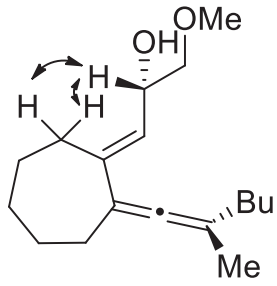
fn	not used

DISPLAY

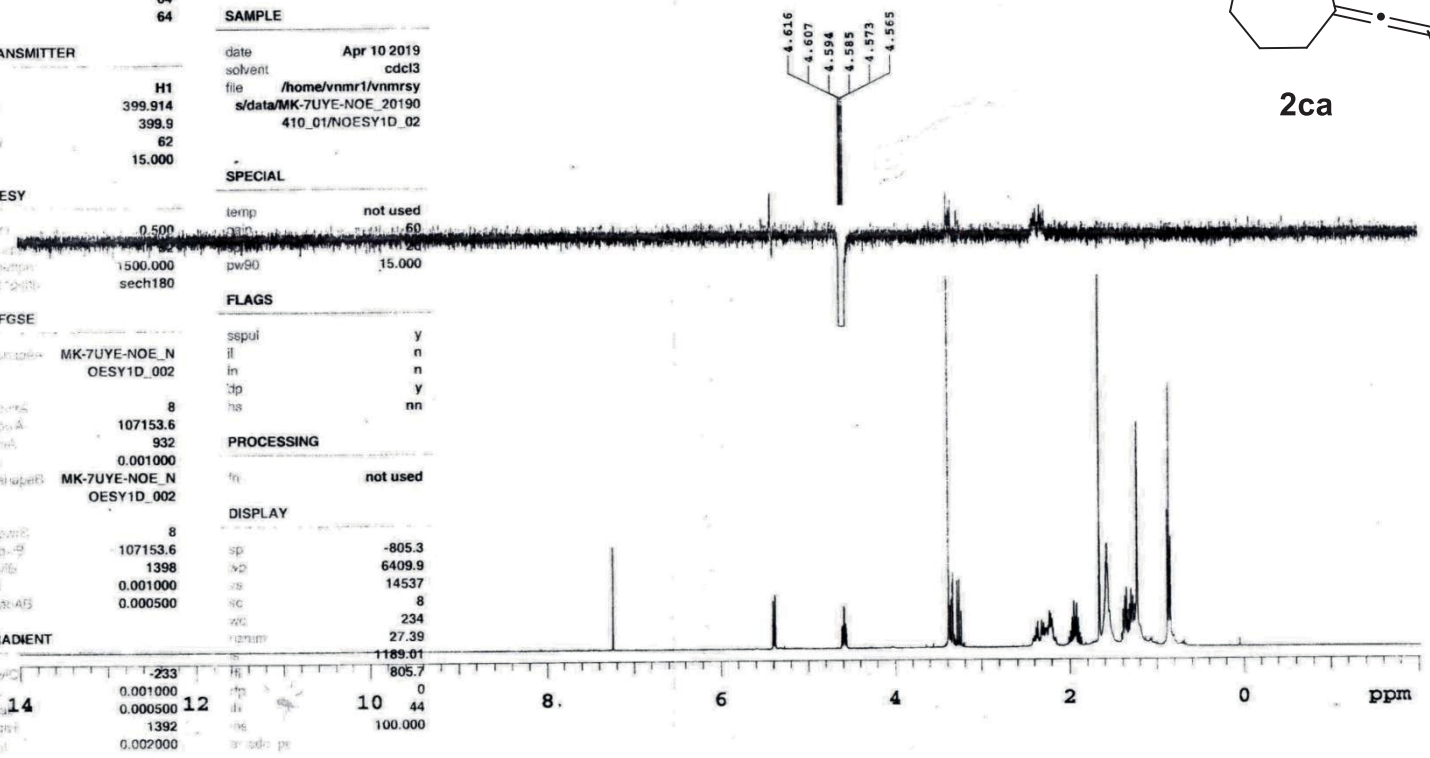
sp	-805.3
wp	6409.9
rs	14537
lc	8
wc	234
rfldrm	27.39
rfl	1189.01
rfp	805.7
th	0
dl	44
ins	100.000
arraydim	[illegible]

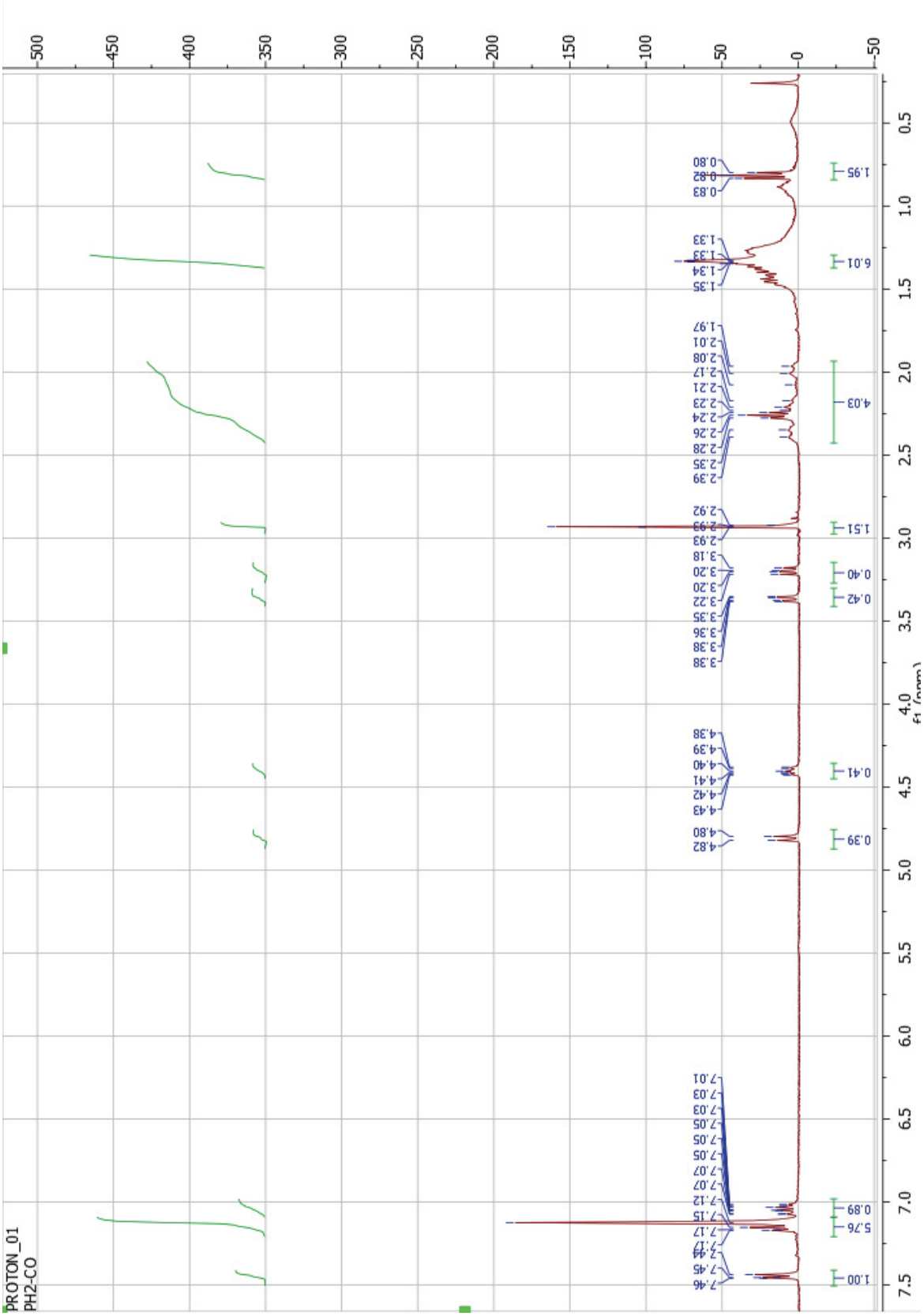
PEAK FREQUENCIES

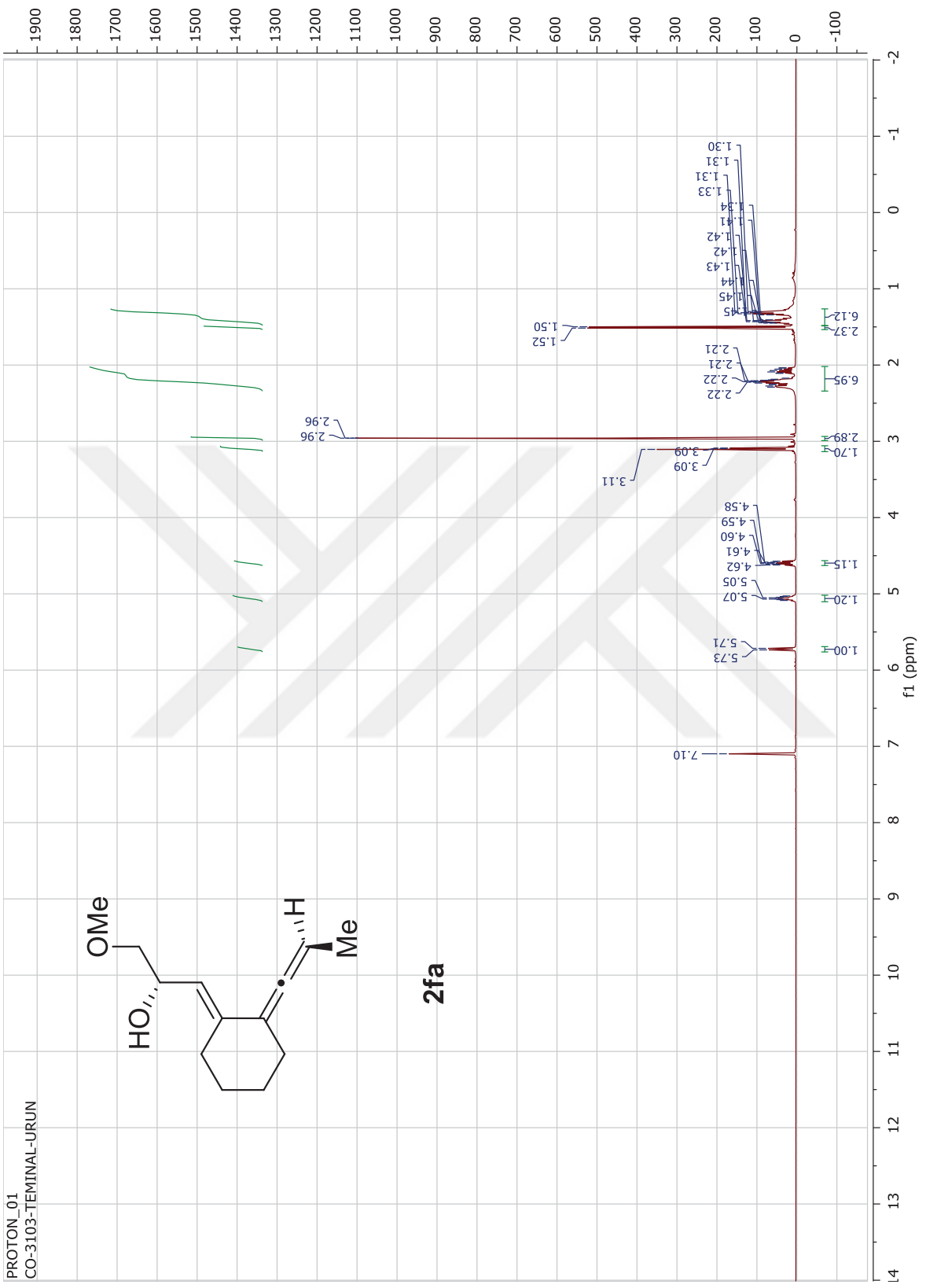
index	freq(ppm)	Intensity
1	4.61559	-148.556
2	4.60679	-145.447
3	4.59407	-297.34
4	4.58526	-277.454
5	4.57255	-162.913
6	4.56472	-145.475

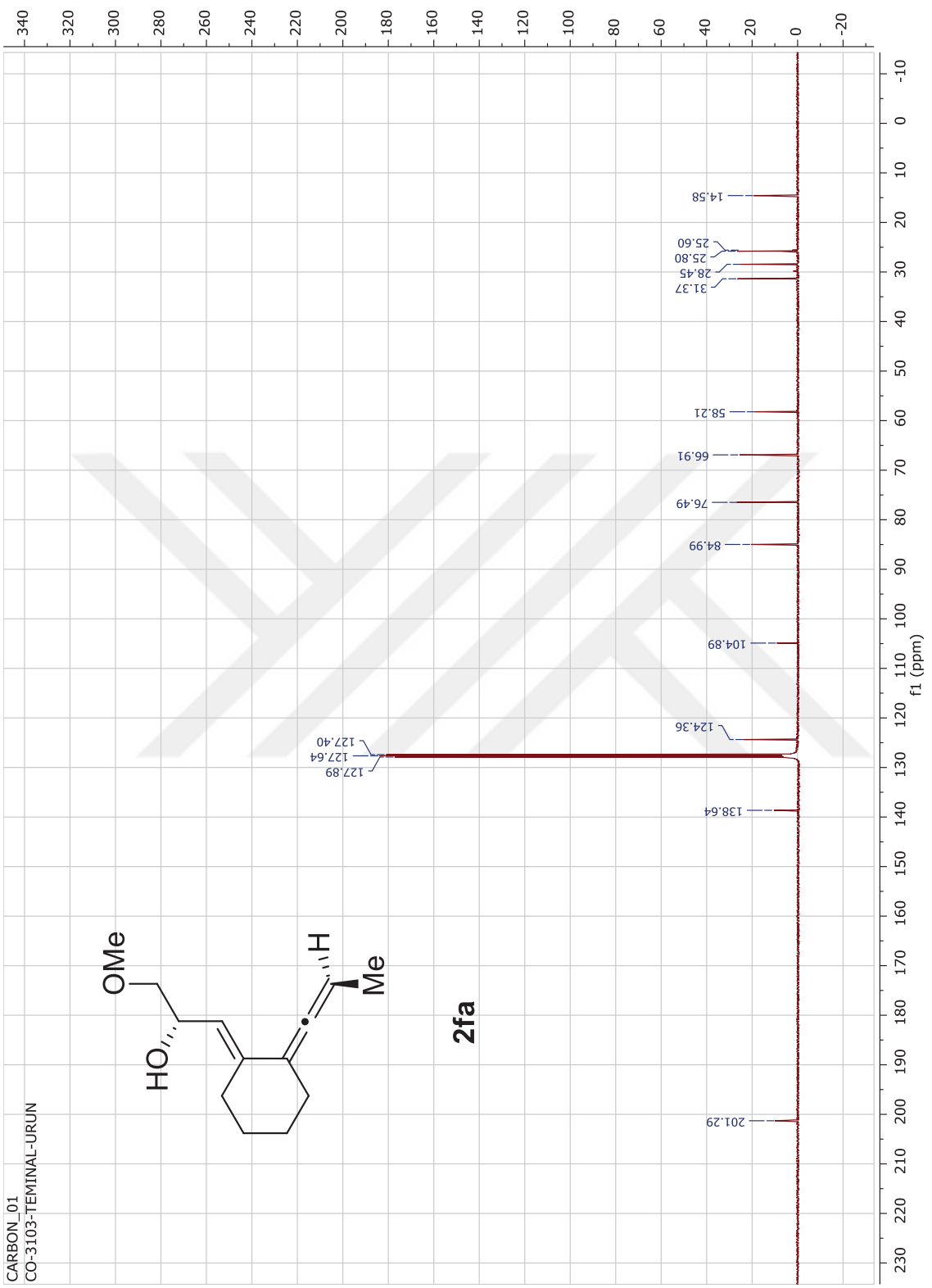


2ca




PROTON_01
PH2-CO
f1 (ppm)


PROTON_01
CO-3103-TEMINAL-URUN
OMe
HO
H
Me
2fa
f1 (ppm)


CARBON_01
CO-3103-TEMINAL-URUN
OMe
HO
H
Me
2fa
14.58
25.60
25.80
28.45
31.37
58.21
66.91
76.49
84.99
104.89
124.36
127.40
127.64
127.89
138.64
201.29
f1 (ppm)

MK-6UYE-TEMINAL-NOE

Sample Name	**MK-6UYE-TEMINAL-NOE**	Pulse sequence	**NOESY1D**	Temperature	**25**	Study owner	**vnmr1**
Date collected	**2019-04-10**	Solvent	**cdcl3**	Spectrometer	**vnmrj.lyte.edu.tr-vnmrs400**	Operator	**vnmr1**

MK-6UYE-TEMINAL-NOE

ACQUISITION

sw	6410.3
at	2.556
np	32768
fb	4000
bs	32
ss	2
d1	1.000
nt	64
ct	64

TRANSMITTER

tn	H1
sfrq	399.914
tof	399.9
tpwr	62
pw	15.000

NOESY

mixN	0.500
sweepw	1500.000
sweepshp	sech180

DPFGSE

selshapeA	MK-6UYE-TEMIN AL-NOE_NOESY1D_002
selpwrA	7
selpwA	125874.1
gzlvlA	932
gtA	0.001000
selshapeB	MK-6UYE-TEMIN AL-NOE_NOESY1D_002
selpwrB	7
selpwB	125874.1
gzlvlB	1398
gtB	0.001000
gstabAB	0.000500

GRADIENT

gzlvlC	-233
gtC	0.001000
gstab	0.000500
nsgrad	1392
tsgt	0.002000

PRESATURATION

satmode	n
wet	n

DECOUPLER

dn	C13
dm	nnn

SAMPLE

date	Apr 10 2019
solvent	cdcl3
file	/home/vnmr1/vnmrsys/data/MK-6UYE-TEMINAL-NOE_20190410_01/NOESY1D_02

SPECIAL

satpwr	not used
satdur	600
spin	20
pw90	15.000

FLAGS

sspul	y
lll	n
mj	n
dp	y
hs	nn

PROCESSING

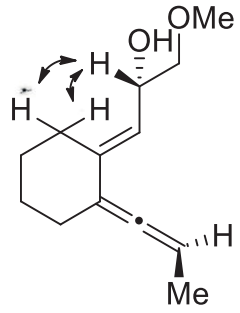
ft	not used

DISPLAY

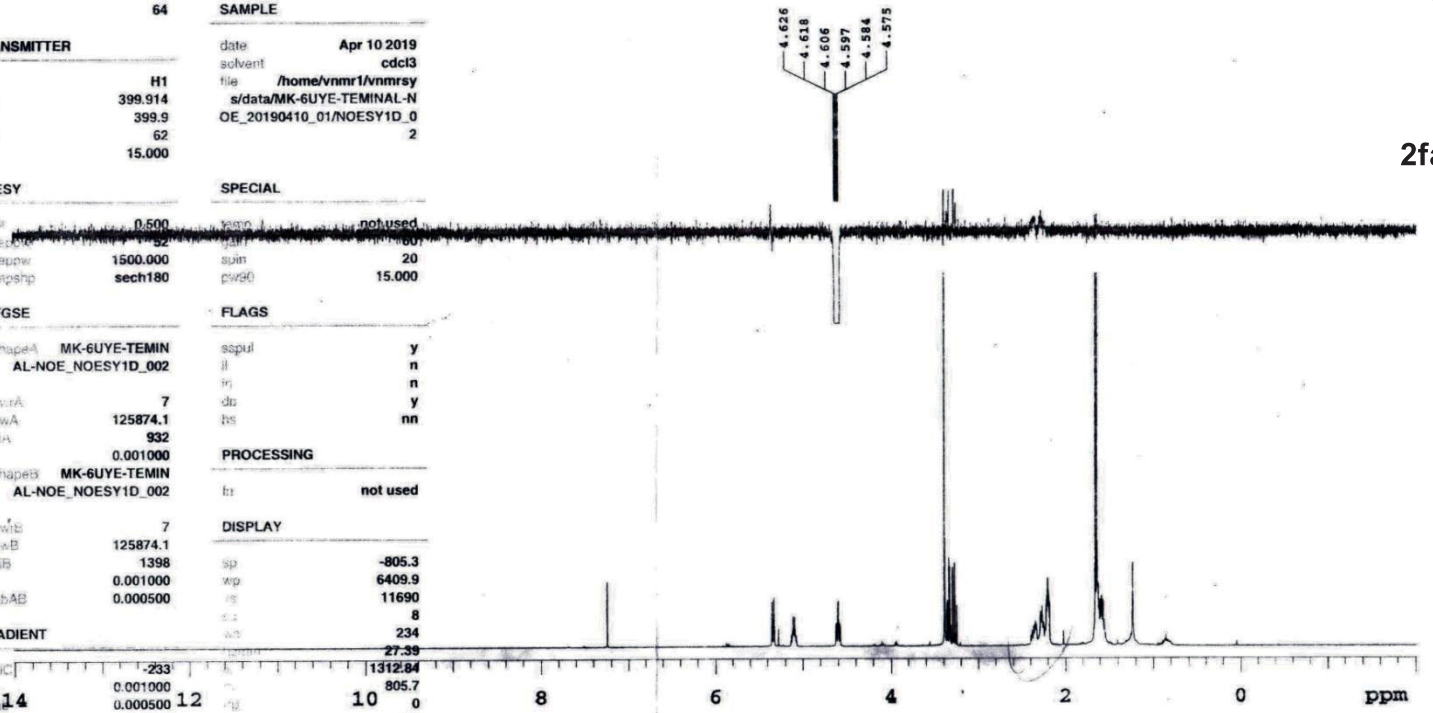
sp	-805.3
wp	6409.9
rfl	11690
rfp	8
vs	234
sdp	27.39
th	1312.84
cr	805.7
rfl	0
rfp	44
vs	100.000

PEAK FREQUENCIES

index	freq(ppm)	intensity
1	4.62635	-150.392
2	4.61853	-148.164
3	4.60581	-285.469
4	4.597	-297.289
5	4.58429	-158.379
6	4.57548	-146.144

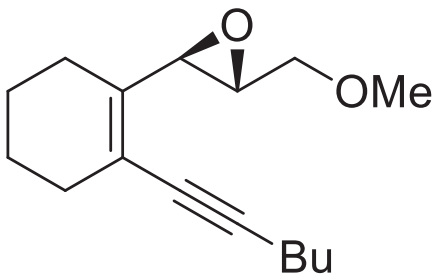


2fa

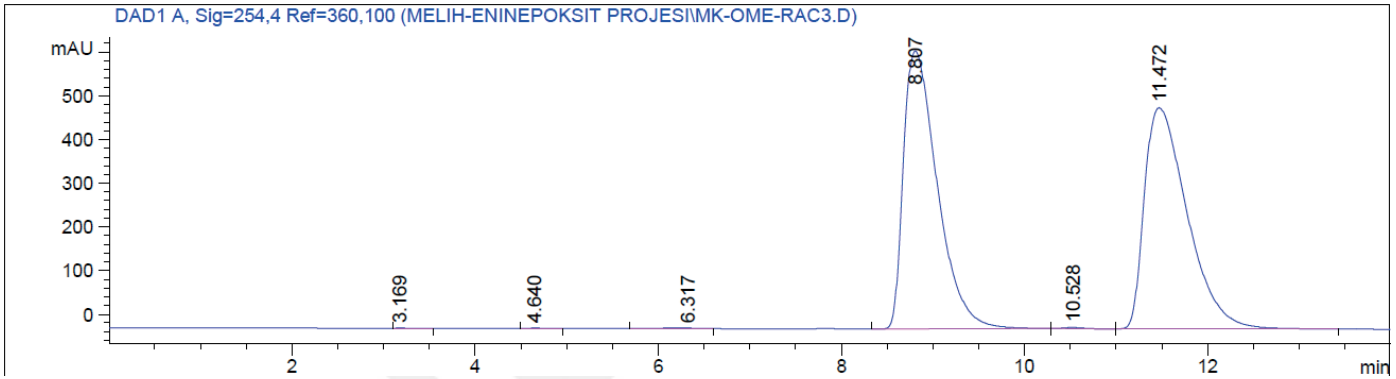


APPENDIX B

HPLC CHROMATOGRAM OF REACTANTS AND PRODUCTS

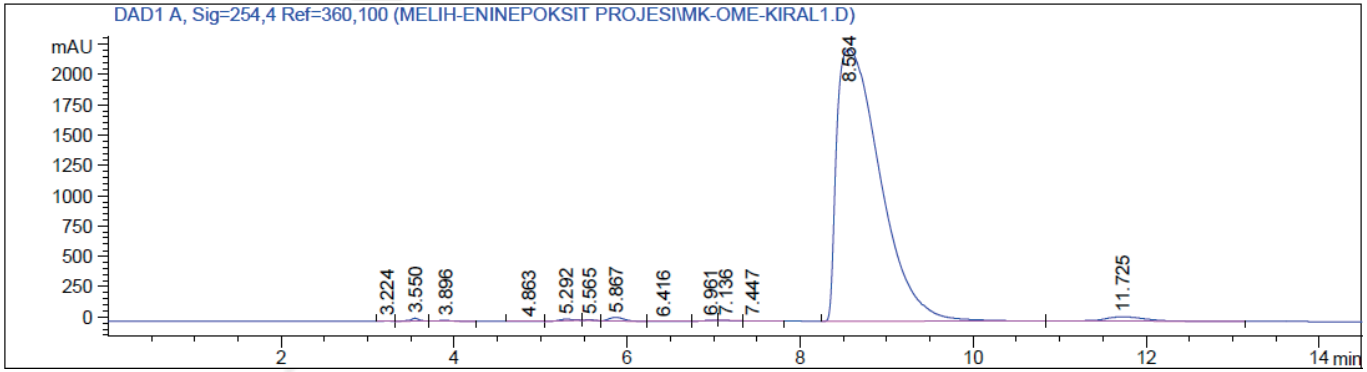


1b*

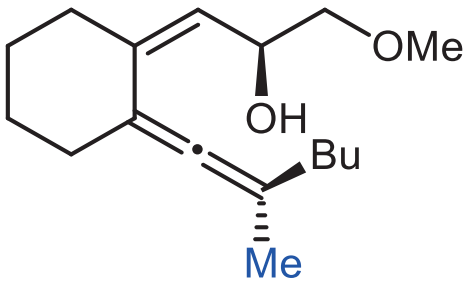


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

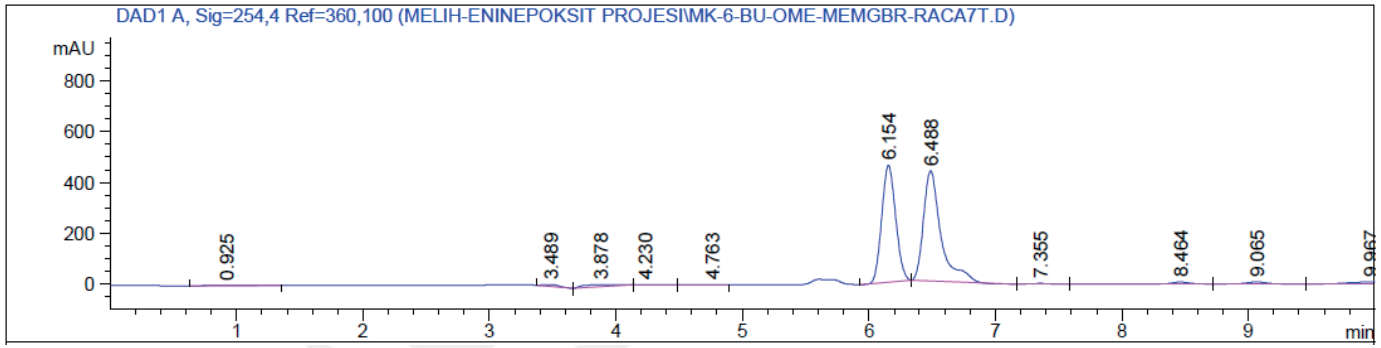
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.169	BB	0.1127	8.48479	1.04491	0.0257
2	4.640	BB	0.1159	10.31591	1.18090	0.0313
3	6.317	BB	0.3182	35.58523	1.40150	0.1078
4	8.807	BB	0.3985	1.64015e4	636.80432	49.6856
5	10.528	BB	0.2082	45.95225	3.07794	0.1392
6	11.472	BB	0.5060	1.65088e4	506.87787	50.0105



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
7	5.867	BB	0.1737	327.75211	29.47809	0.4086
8	6.416	BB	0.2382	24.39105	1.35394	0.0304
9	6.961	BB	0.1754	28.08810	2.69983	0.0350
10	7.136	BB	0.1406	10.51071	1.24382	0.0131
11	7.447	BB	0.1609	23.50158	2.09528	0.0293
12	8.564	BB	0.5443	7.80767e4	2241.77539	97.3320
13	11.725	BB	0.5060	1326.45508	37.92677	1.6536

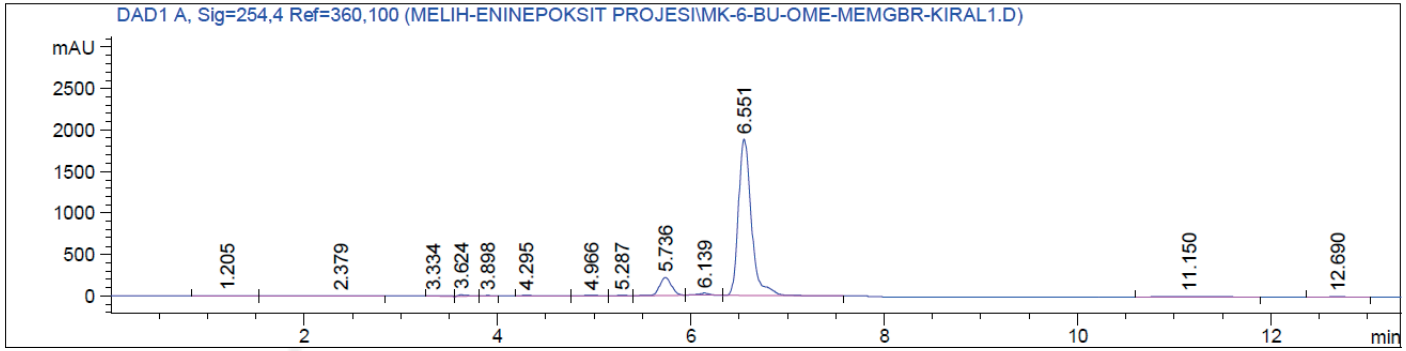


2ba*

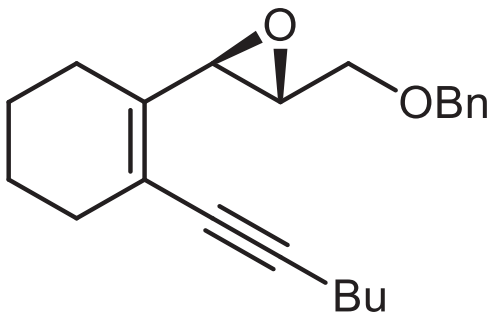


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

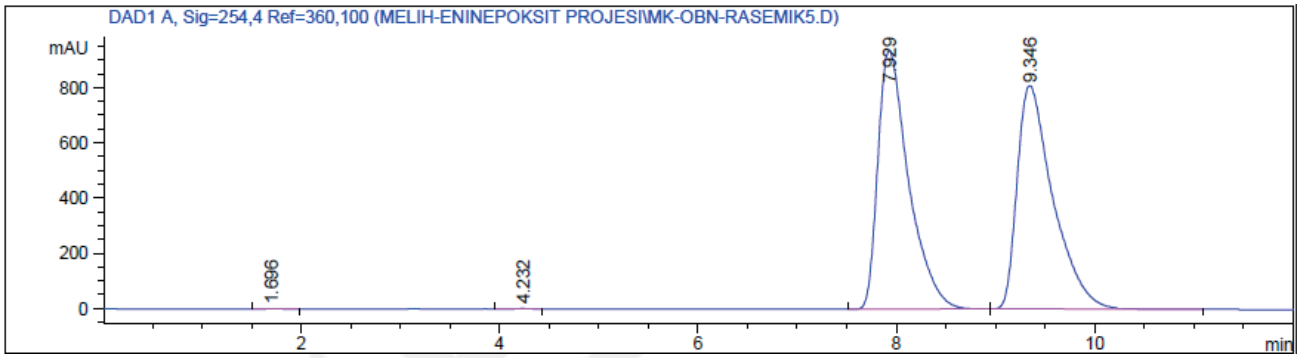
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.925	BB	0.2579	30.90809	1.73465	0.3716
2	3.489	BB	0.1142	53.10096	6.86707	0.6385
3	3.878	BB	0.2403	155.73882	8.17191	1.8726
4	4.230	BB	0.0970	13.08581	1.98172	0.1573
5	4.763	BB	0.1258	9.83148	1.14982	0.1182
6	6.154	BB	0.1191	3519.30811	460.87115	42.3167
7	6.488	BB	0.1425	4181.66846	433.74808	50.2810
8	7.355	BB	0.1425	32.97863	3.54489	0.3965
9	8.464	BB	0.1603	81.63943	7.91824	0.9816
10	9.065	BB	0.1921	103.19314	8.12701	1.2408
11	9.967	BBA	0.2649	135.14688	8.50461	1.6250



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.192	BB	0.2198	28.58387	1.94161	0.7027
2	3.645	BB	0.1006	16.00357	2.15626	0.3934
3	3.890	BB	0.0819	10.30227	1.88079	0.2533
4	4.909	BB	0.1198	18.33145	2.23156	0.4507
5	5.733	BB	0.1328	92.64079	11.16535	2.2776
6	6.143	BB	0.1184	43.10600	5.68895	1.0598
7	6.551	BB	0.1422	3747.19727	403.98325	92.1249
8	7.711	BB	0.1683	15.05546	1.32787	0.3701
9	11.149	BB	0.4388	96.29561	3.33538	2.3674



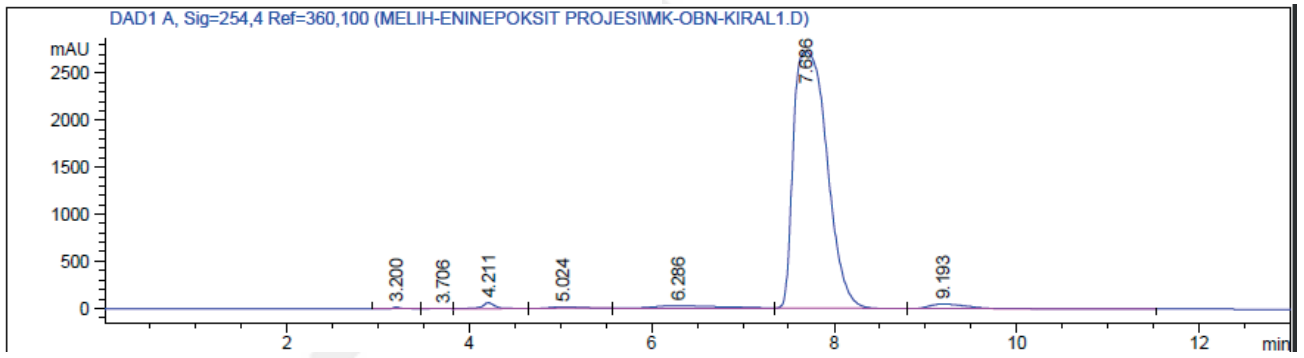
1d*



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

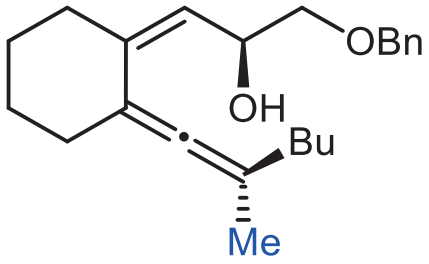
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.696	BB	0.1280	9.02195	1.01255	0.0222
2	4.232	BB	0.1160	20.60006	2.66900	0.0508
3	7.929	BB	0.3239	2.02143e4	936.24335	49.8517
4	9.346	BB	0.3729	2.03049e4	808.67627	50.0752

Totals : 4.05489e4 1748.60117

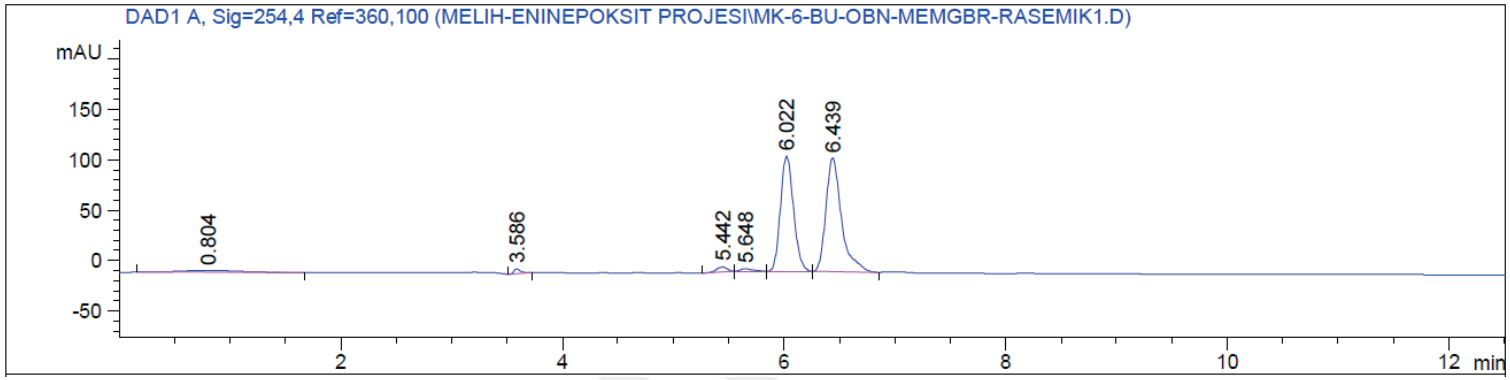


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.200	BB	0.0969	136.26230	20.66701	0.1859
2	3.706	BB	0.1328	24.35265	2.61020	0.0332
3	4.211	BB	0.1468	639.22711	62.79219	0.8722
4	5.024	BB	0.3651	403.26935	16.62055	0.5502
5	6.286	BB	0.6821	1234.17419	25.61537	1.6840
6	7.686	BB	0.4093	6.93492e4	2720.95630	94.6248

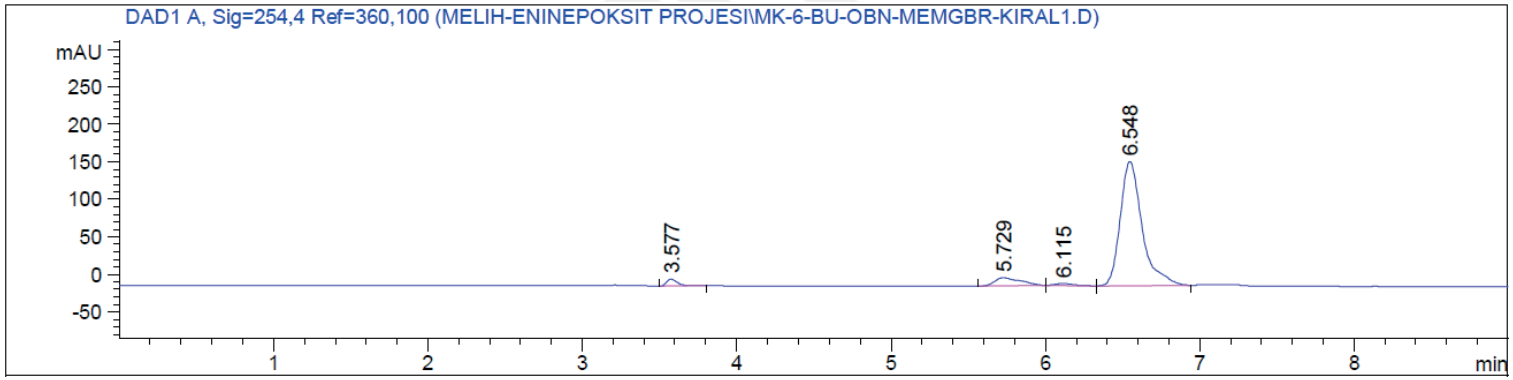


2da*

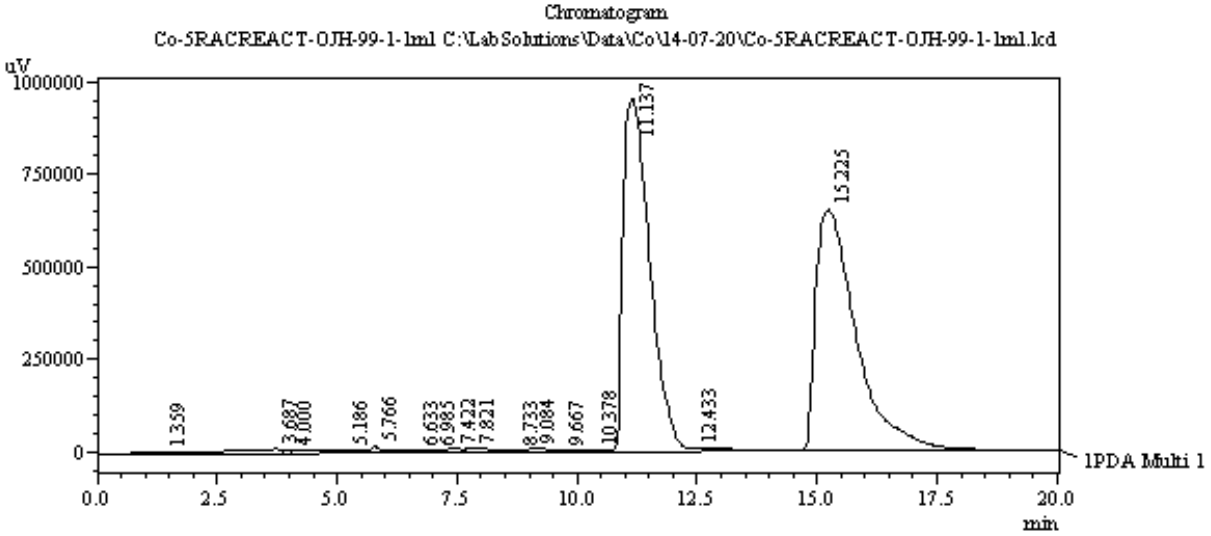


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.804	BB	0.4486	69.60711	1.86876	3.1961
2	3.586	BB	0.0673	20.77296	4.72650	0.9538
3	5.442	BB	0.1073	32.40594	4.89406	1.4880
4	5.648	BB	0.1182	21.88641	2.76844	1.0049
5	6.022	BB	0.1274	933.46814	114.20604	42.8612
6	6.439	BB	0.1482	1099.74768	112.34391	50.4961



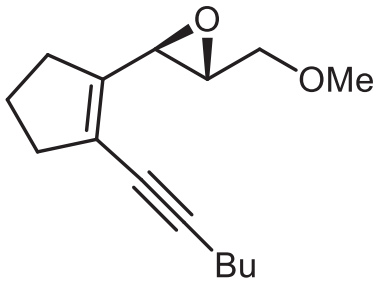
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.578	BB	0.0706	11.04220	2.44730	3.1100
2	6.548	BB	0.1492	344.01422	34.83768	96.8900



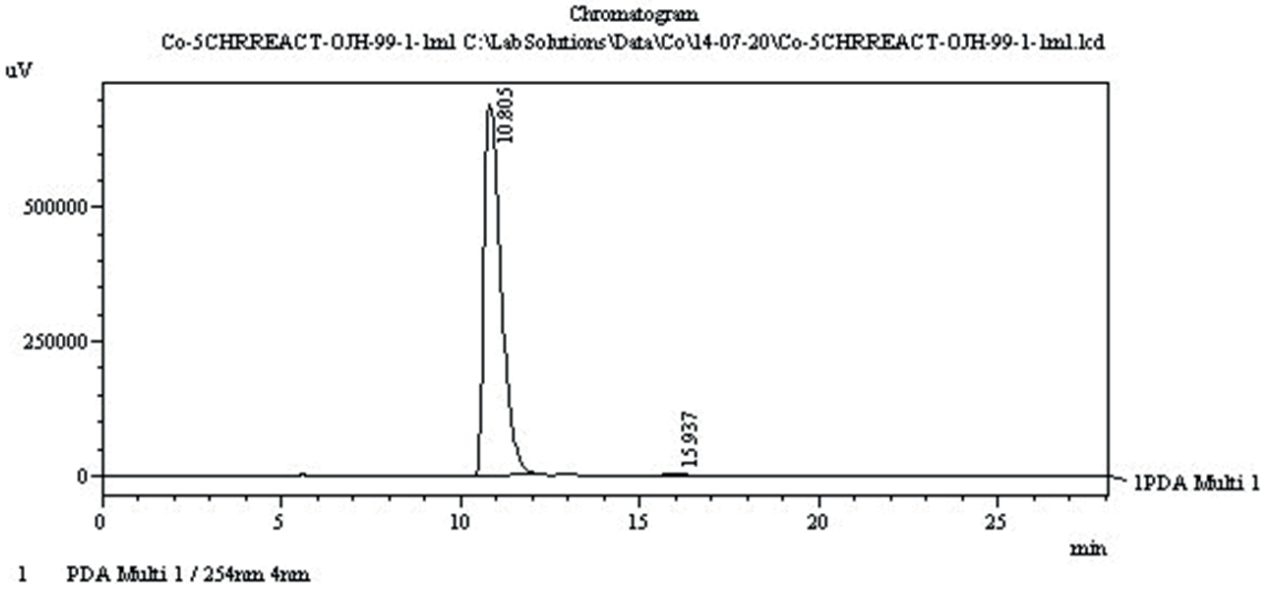
Quantitative Results

PDA

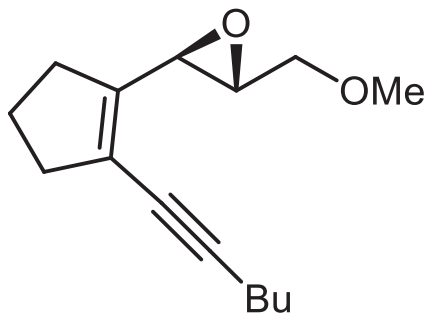
ID#	Name	Ret. Time	Area %
1	1	11.137	46.504
2	2	15.225	47.615



1a



1 PDA Multi 1 / 254nm 4nm

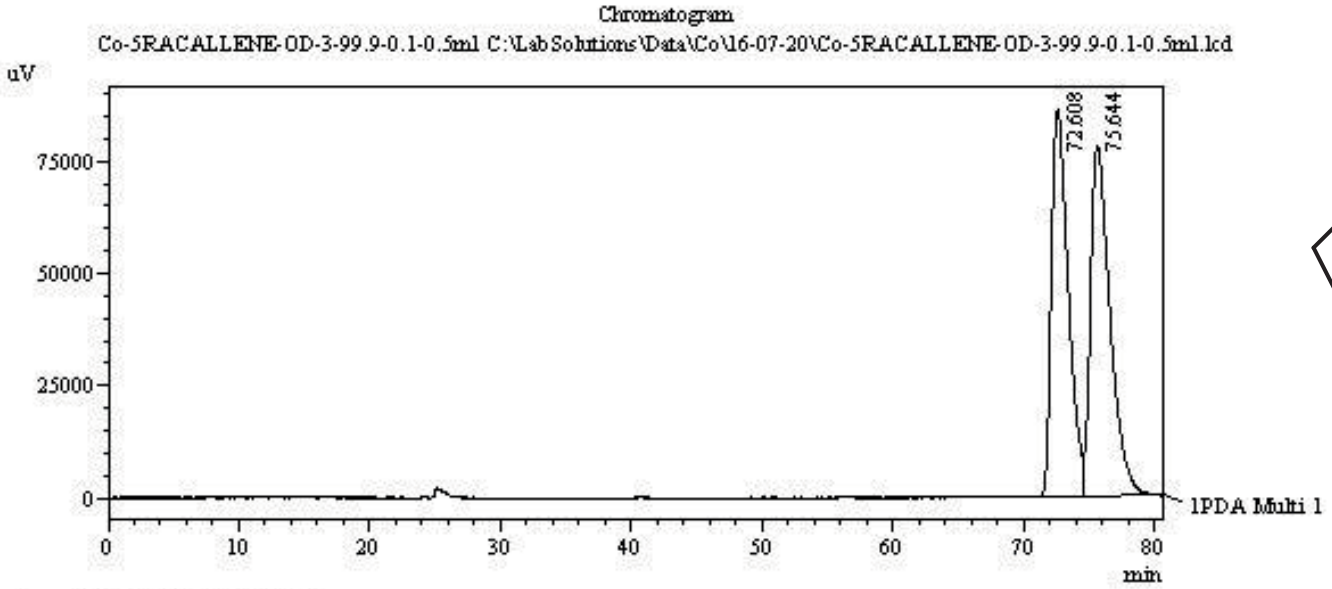


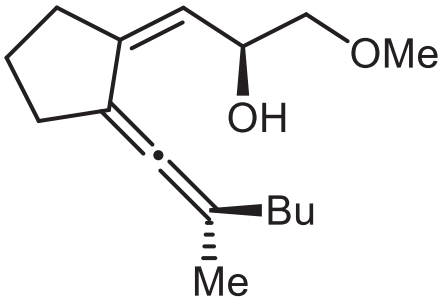
1a

Quantitative Results

PDA

ID#	Name	Ret. Time	Area %
1	1st	10.805	99.305
2	2nd	15.937	0.695



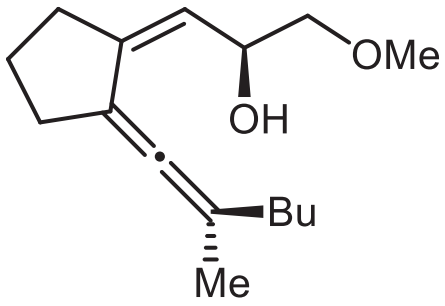


2aa

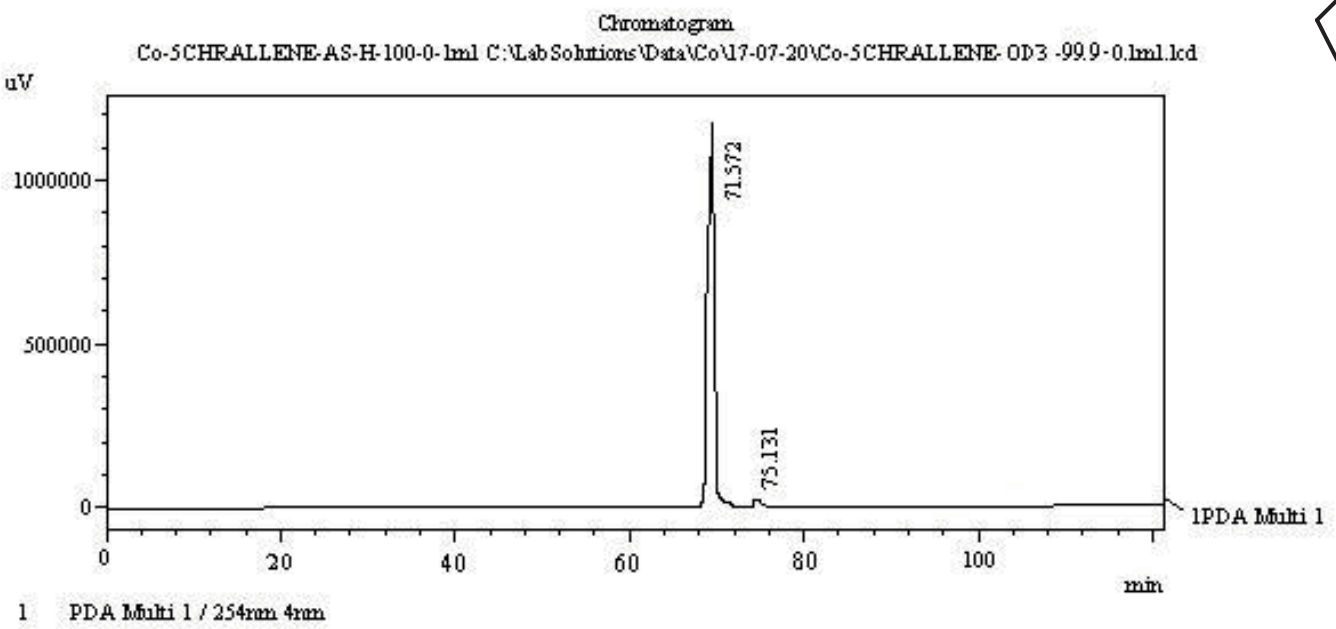
Quantitative Results

PDA

ID#	Name	Ret. Time	Area %
1	1	72.608	48.747
2	2	75.644	51.253



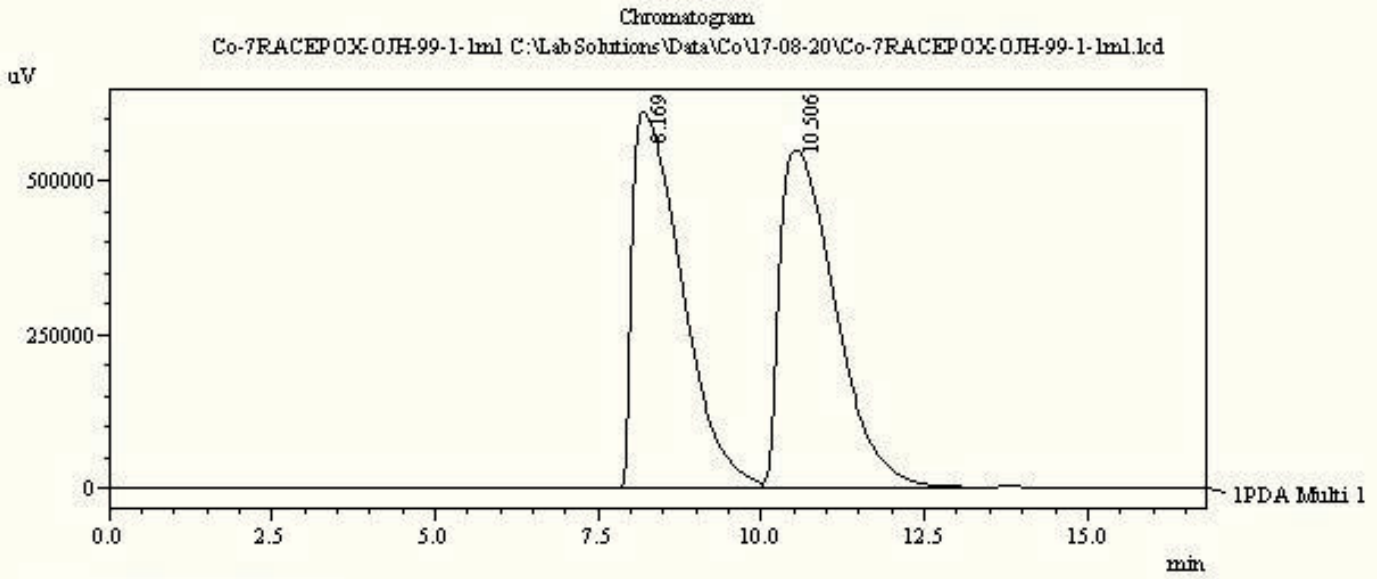
2aa



Quantitative Results

PDA

ID#	Name	Ret. Time	Area %
1	1	71.572	99.675
2	2	75.131	0.325

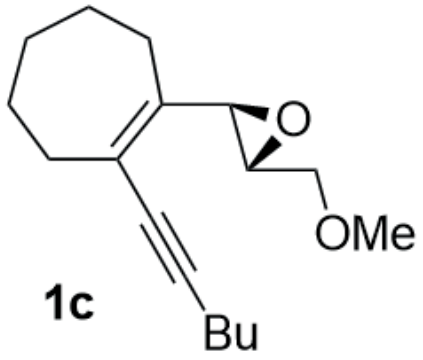


1 PDA Multi 1 / 254nm 4nm

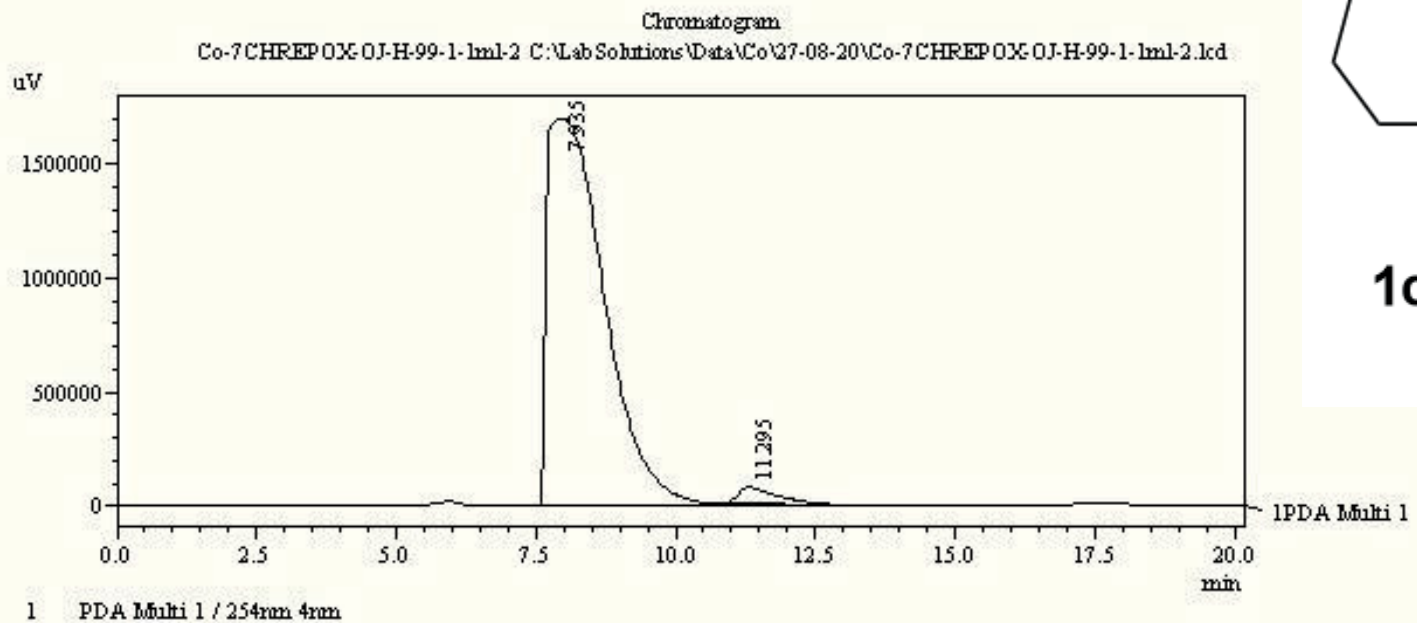
Quantitative Results

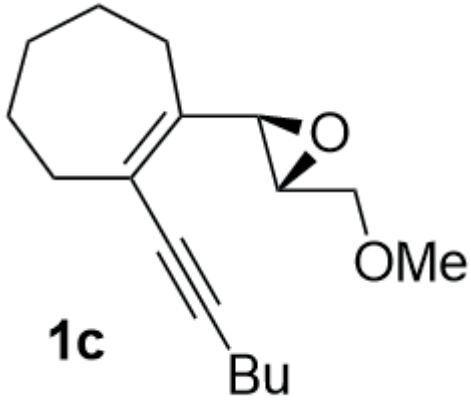
PDA

ID#	Name	Ret. Time	Area %
1	1	8.169	49.790
2	2	10.506	50.210



1c

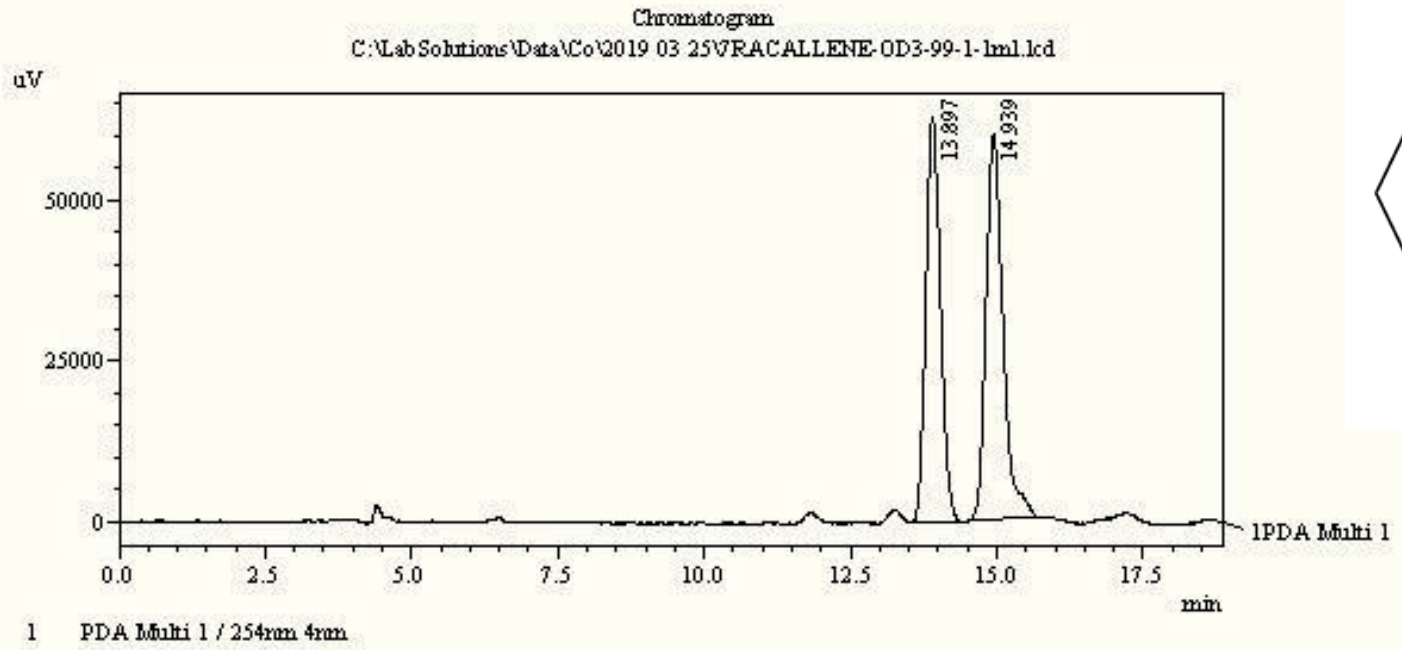


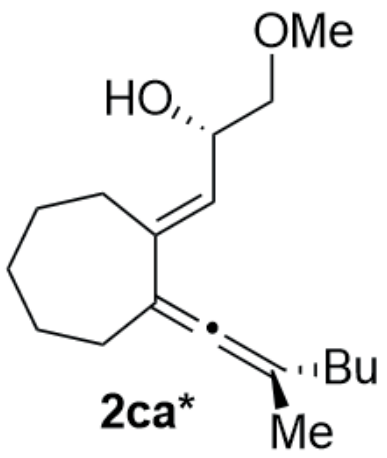


Quantitative Results

PDA

ID#	Name	Ret. Time	Area %
1	1	7.935	97.077
2	2	11.295	2.923

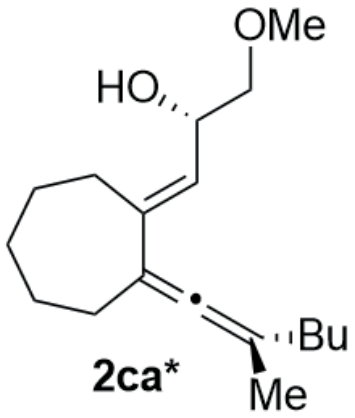




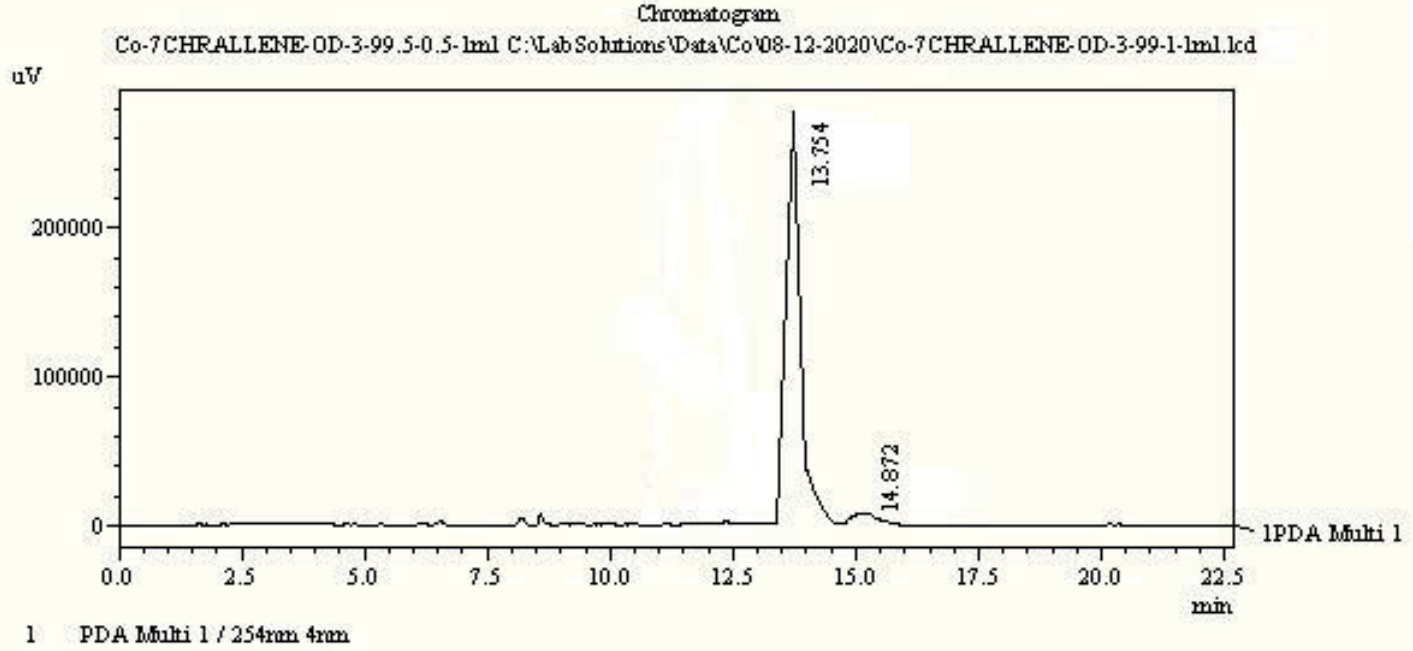
Quantitative Results

PDA

ID#	Name	Ret. Time	Area %
1	1	13.897	47.364
2	2	14.939	52.636



2ca*



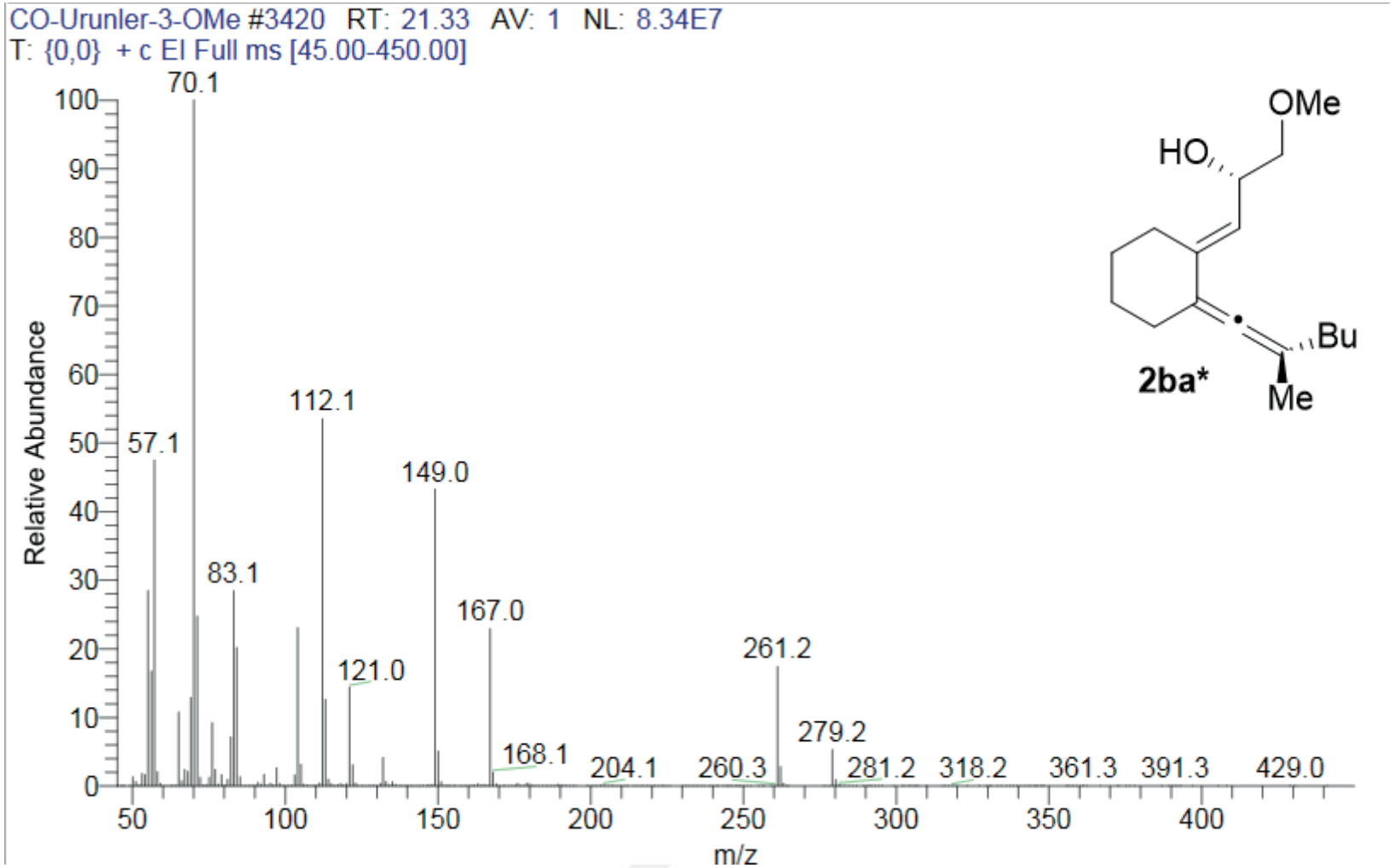
Quantitative Results

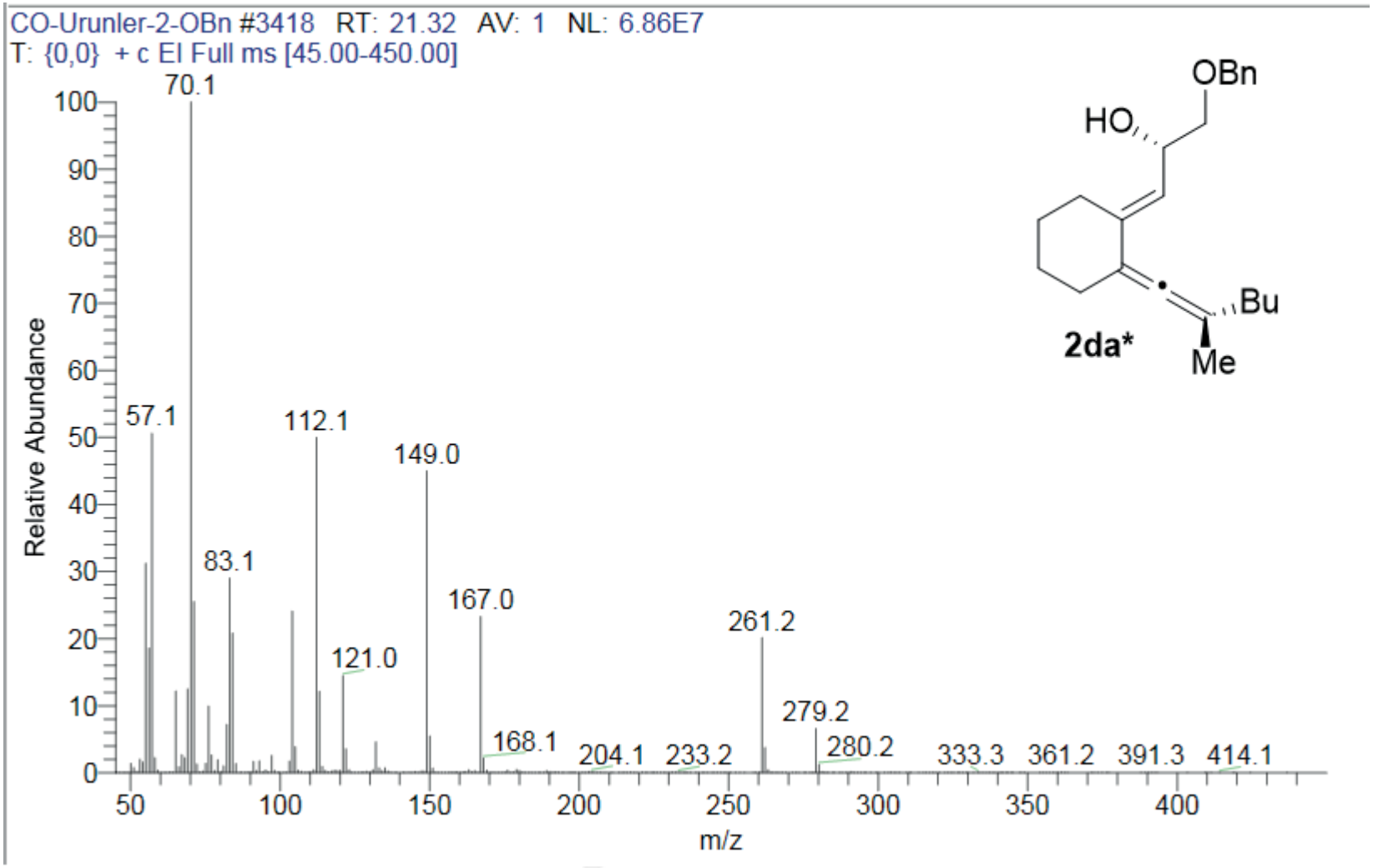
PDA

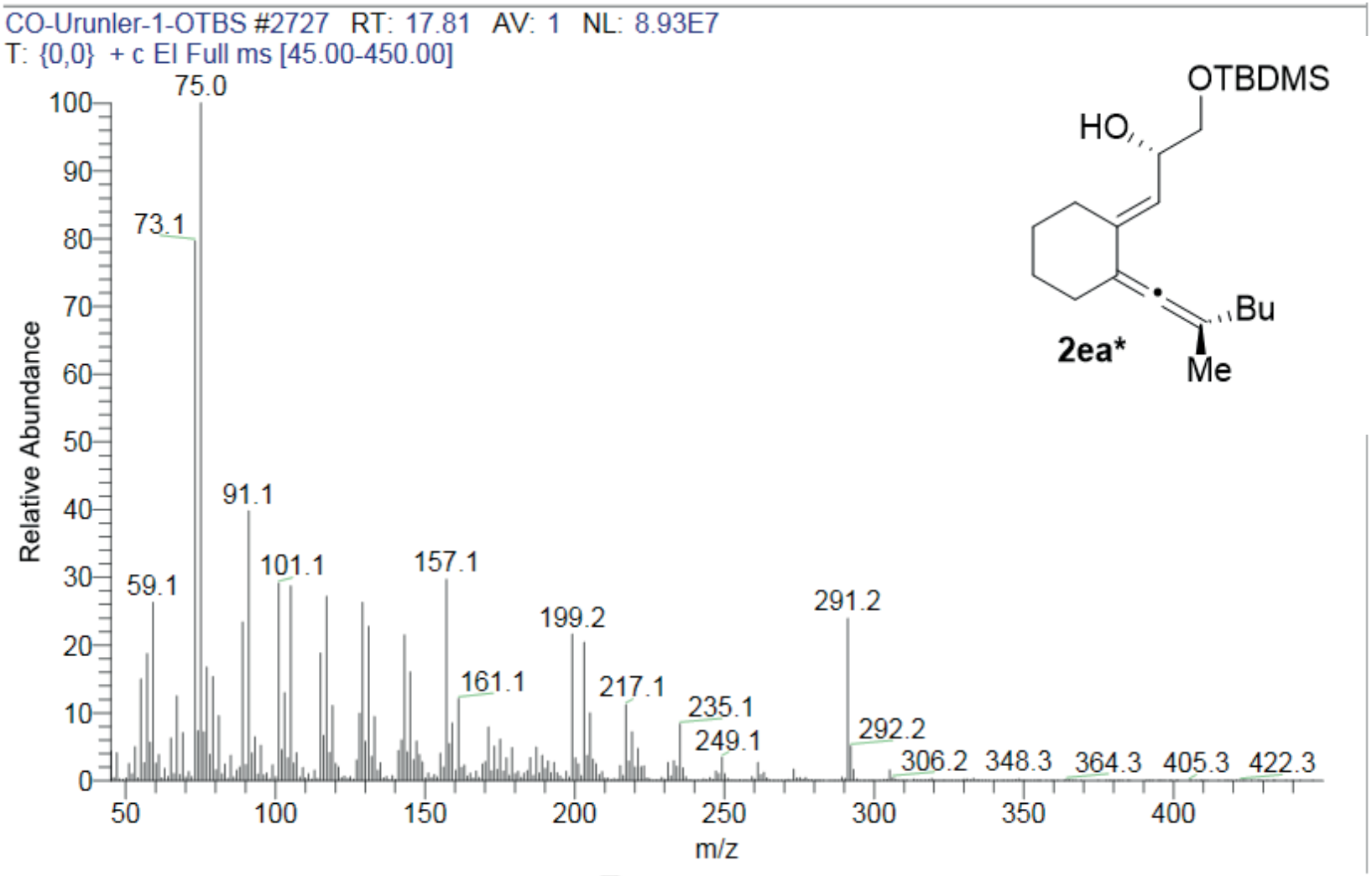
ID#	Name	Ret. Time	Area %
1	1	13.754	4.214
2	2	14.872	95.786

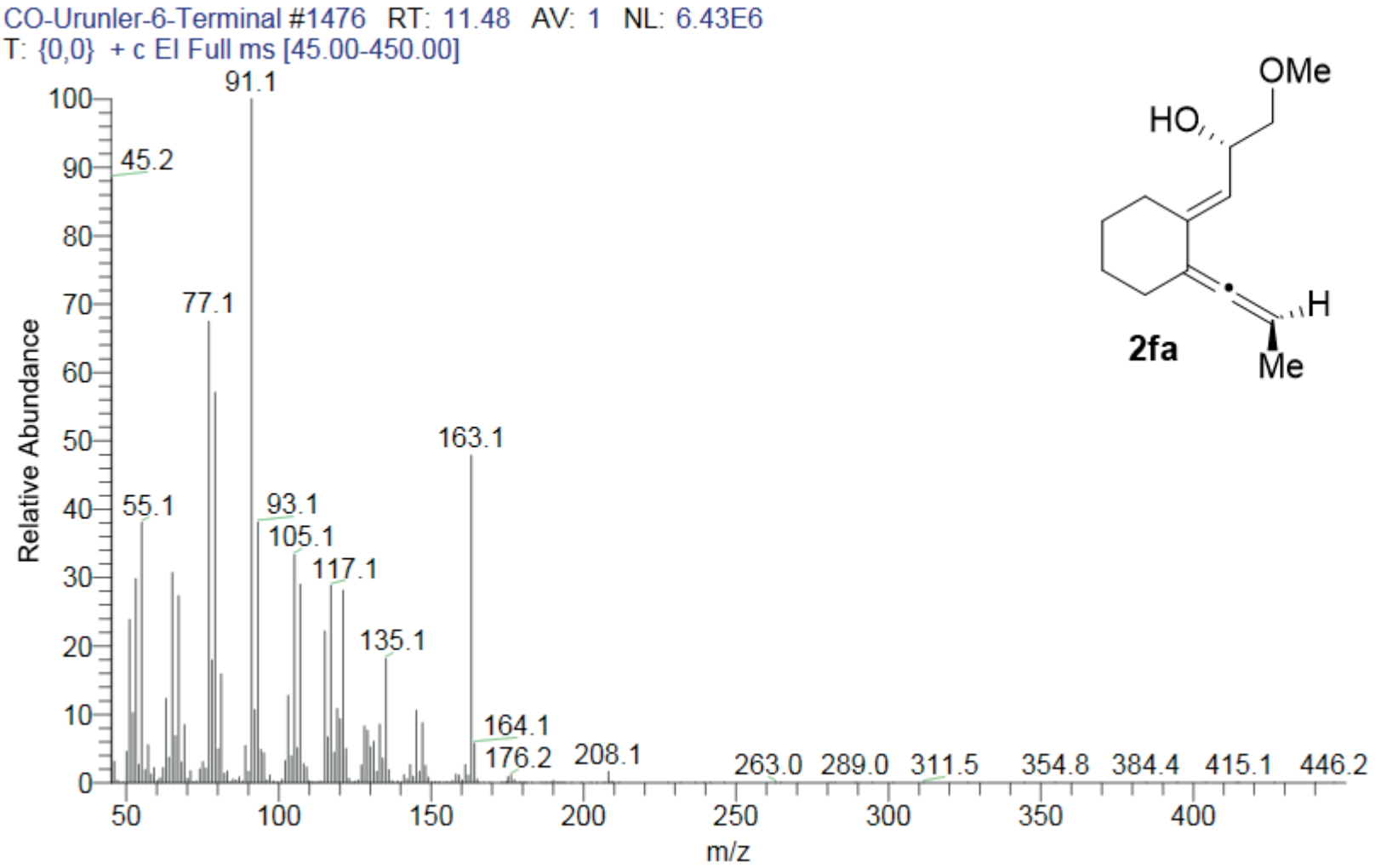
APPENDIX C

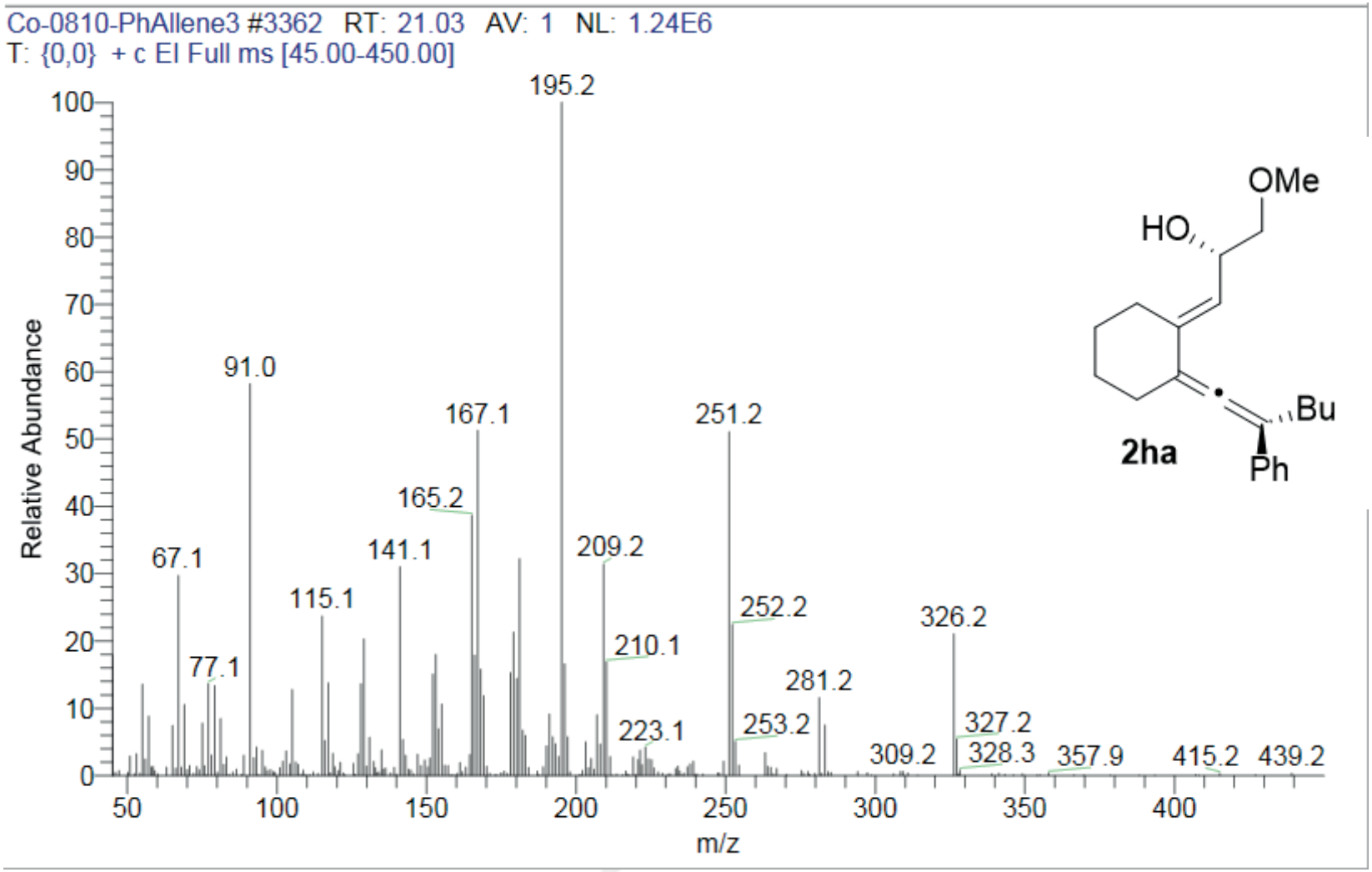
MASS SPECTRA OF THE PRODUCTS

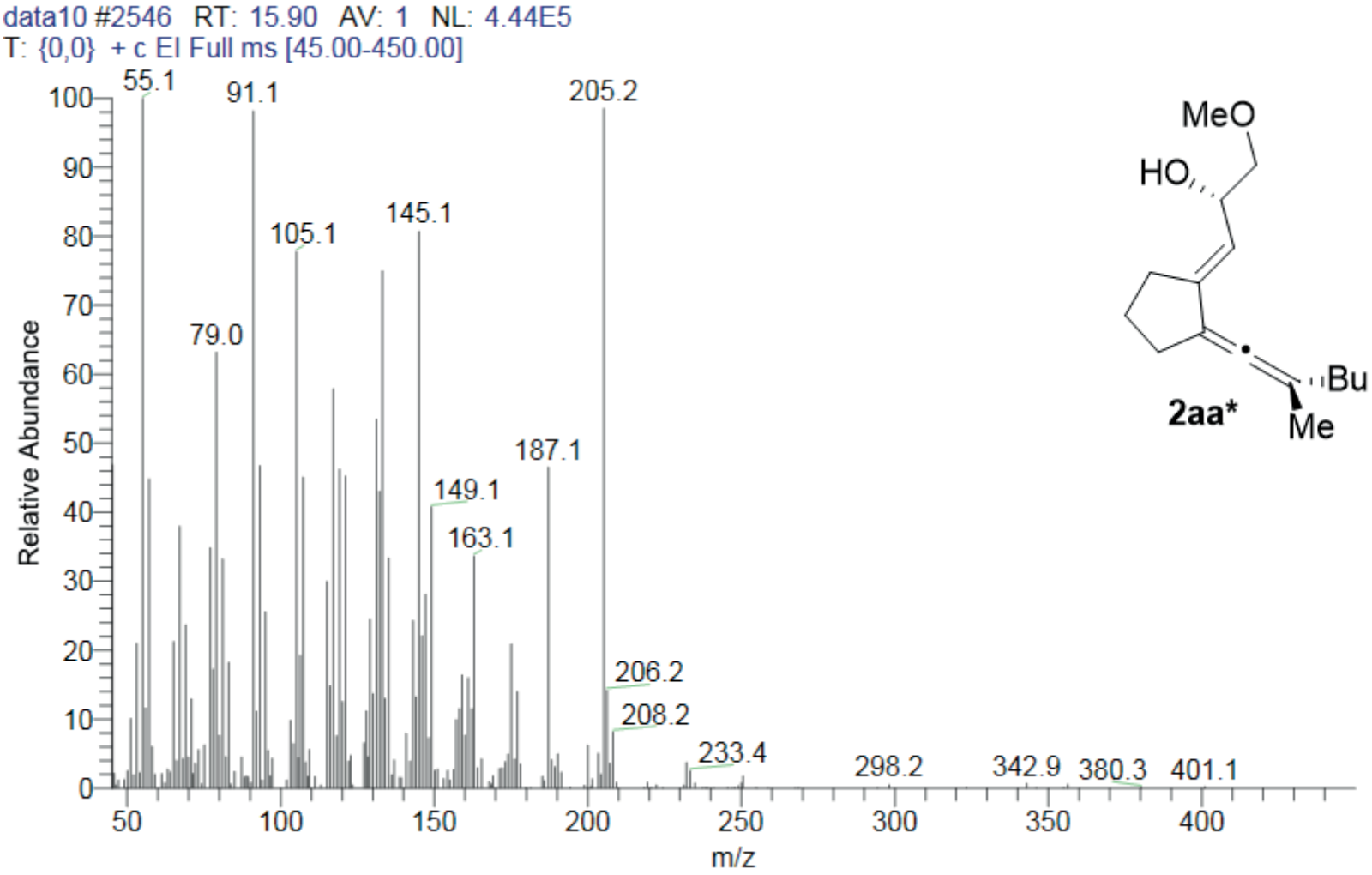

CO-Urunler-3-OMe #3420 RT: 21.33 AV: 1 NL: 8.34E7
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
70.1
57.1
112.1
149.0
83.1
167.0
121.0
261.2
279.2
168.1
204.1
260.3
281.2
318.2
361.3
391.3
429.0
OMe
HO
Bu
Me
2ba*

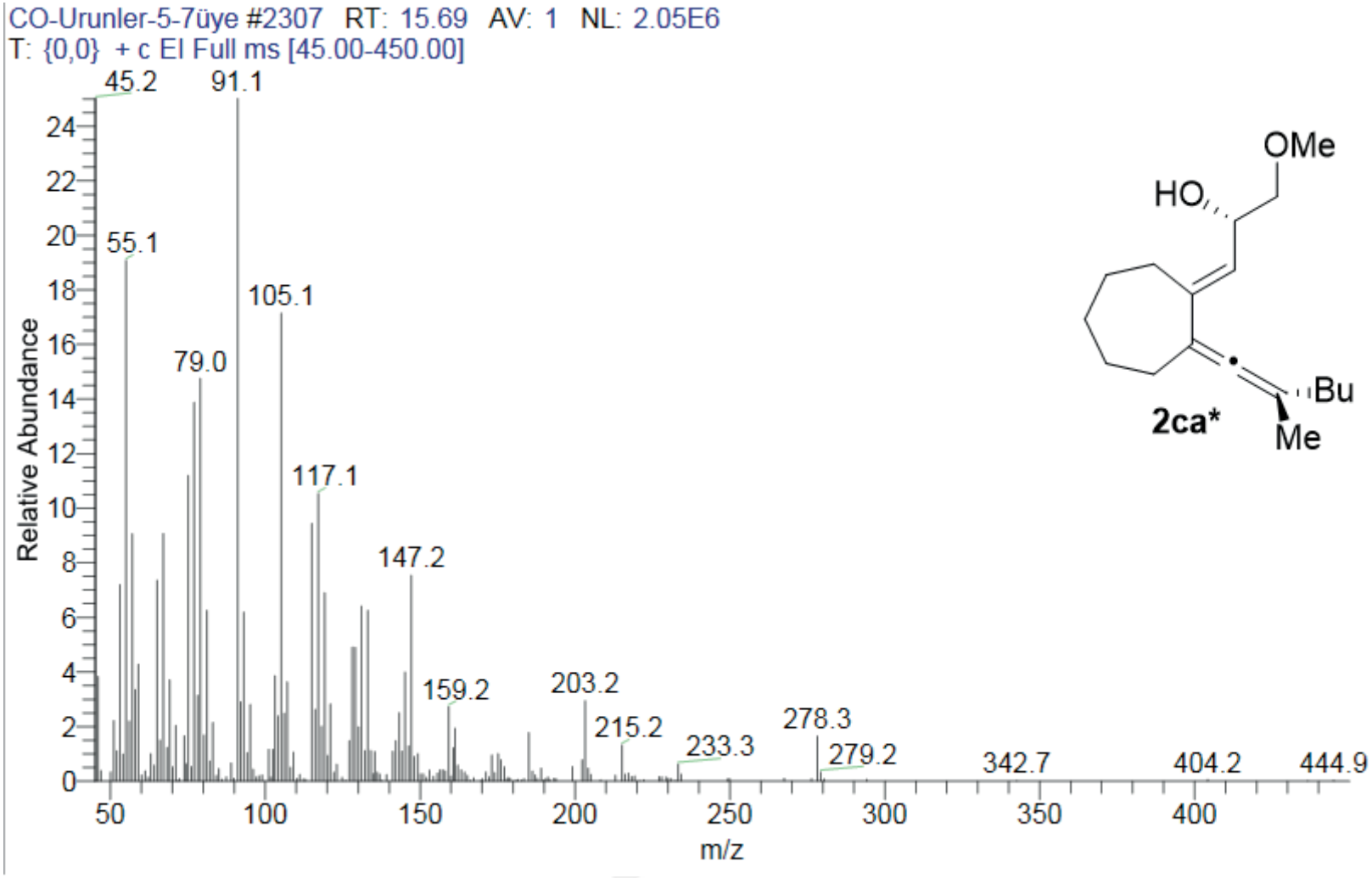

CO-Urunler-2-OBn #3418 RT: 21.32 AV: 1 NL: 6.86E7
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
70.1
57.1
112.1
149.0
83.1
167.0
261.2
121.0
279.2
168.1
204.1
233.2
280.2
333.3
361.2
391.3
414.1
OBn
HO
Bu
Me
2da*

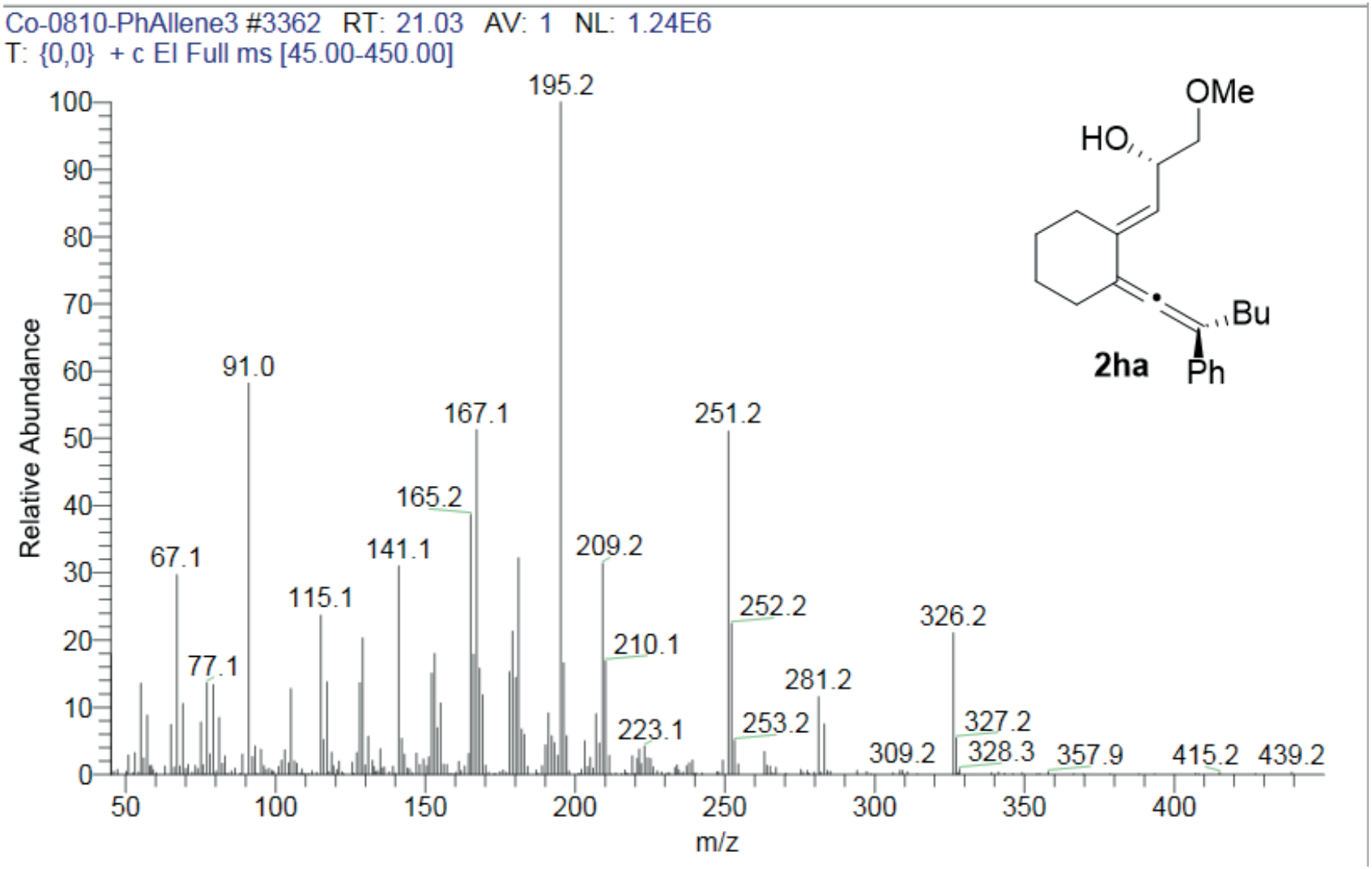

CO-Urunler-1-OTBS #2727 RT: 17.81 AV: 1 NL: 8.93E7
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
75.0
73.1
91.1
101.1
59.1
157.1
161.1
199.2
217.1
235.1
249.1
291.2
292.2
306.2
348.3
364.3
405.3
422.3
OTBDMS
HO
Bu
Me
2ea*


CO-Urunler-6-Terminal #1476 RT: 11.48 AV: 1 NL: 6.43E6
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
91.1
45.2
77.1
163.1
55.1
93.1
105.1
117.1
135.1
164.1
176.2
208.1
263.0
289.0
311.5
354.8
384.4
415.1
446.2
OMe
HO
H
Me
2fa


Co-0810-PhAllene3 #3362 RT: 21.03 AV: 1 NL: 1.24E6
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
195.2
91.0
167.1
251.2
165.2
209.2
67.1
141.1
115.1
252.2
326.2
210.1
77.1
281.2
223.1
253.2
327.2
309.2
328.3
357.9
415.2
439.2
OMe
HO
Bu
Ph
2ha


data10 #2546 RT: 15.90 AV: 1 NL: 4.44E5
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
55.1
91.1
205.2
105.1
145.1
79.0
187.1
149.1
163.1
206.2
208.2
233.4
298.2
342.9
380.3
401.1
MeO
HO
Bu
Me
2aa*


CO-Urunler-5-7üye #2307 RT: 15.69 AV: 1 NL: 2.05E6
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
45.2
91.1
55.1
105.1
79.0
117.1
147.2
159.2
203.2
215.2
233.3
278.3
279.2
342.7
404.2
444.9
OMe
HO
Bu
Me
2ca*


Co-0810-PhAllene3 #3362 RT: 21.03 AV: 1 NL: 1.24E6
T: {0,0} + c EI Full ms [45.00-450.00]
Relative Abundance
m/z
195.2
91.0
167.1
251.2
165.2
209.2
67.1
141.1
115.1
252.2
326.2
210.1
77.1
281.2
223.1
253.2
327.2
309.2
328.3
357.9
415.2
439.2
OMe
HO
Bu
Ph
2ha