π -Activation Triggered Cascade Annulation Reactions of Alkynols: Application in Construction of Ketal-lactones Related to Bioactive Natural Products

by

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Under the supervision of

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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*π -Activation Triggered Cascade Annulation Reactions of Alkynols: Application in Construction of Ketal-lactones Related to Bioactive Natural Products*" submitted by *Mr. Digambar Abasaheb Kambale* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged.

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I Mr. Digambar Abasaheb Kambale, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC15J26018 hereby undertake that, the thesis entitled π-Activation Triggered Cascade Annulation Reactions of Alkynols: Application in Construction of Ketal-lactones Related to Bioactive Natural Products has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)"*.

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Date :03/08/2021
Place : Pune

DEDICATION

With plenty of love and gratitude,

I wholeheartedly dedicate this thesis to

my respected and most loving ***'Bai & Bhau'****,*

my brother ***'Mr. Sudarshan'****,*

my better half & my life-line ***'Poonam'****,*

my lovely son ***'Parth'***

and my whole family,

all of whom made this work possible through their

endless love and support.

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Above all, I thank God Almighty for his enormous blessings. Though, many have not been mentioned, none is forgotten.

With lot of thanks

Digambar A. Kambale

Units	
°C	Degree centigrade
mg	Miligram
h	hour
Hz	Hertz
$CDCl_3$	Deuterated Chloroform
µg	Microgram
µM	Micromolar
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
nM	Nanometre
ppm	Parts per million
δ	Delta
m/z	Mass to charge ratio
Chemical Notations	
AcOH	Acetic acid
nM	Nanometre
ppm	Parts per million
$AlCl_3$	Aluminum Trichloride
AgOTf	Silver trifluoromethanesulfonate
n-Bu_2BOTf	Dibutylboryl trifluoromethanesulfonate
BH	Baylis–Hillman
n-BuLi	n-Butyl lithium
BH_3	Borane
t-BuOH	tert-Butyl alcohol
BCl_3	Boron trichloride
$BF_3.OEt_2$	Boron trifluoride etherate
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
CD_3OD	Deuterated Methanol
CrO_3	Chromium (VI) trioxide
COSY	Correlation Spectroscopy
CH_2Cl_2	Dichloromethane
$CDCl_3$	Deuterated Chloroform
CD	Circular dichroism
CBS	Corey–Bakshi–Shibata
$CeCl_3.7H_2O$	Cerium(III) chloride heptahydrate
$(CH_2O)_n$	Paraformaldehyde
$CaCO_3$	Calcium carbonate
$CuCl_2$	Copper(II) chloride
CuO	Copper oxide
CAN	ceric ammonium nitrate
$Cu(OAc)_2$	Copper acetate
$(CH_2)_2Cl_2$ (DCE)	Dichloroethane
Conc.	Concentrated
DA	Diels-Alder
DABCO	1,4-diazabicyclo[2.2. 2]octane

DMAP	4-Dimethylaminopyridine
DCC	N,N′-Dicyclohexylcarbodiimide
DMF	N, N'-Dimethylformamide
DIBAL-H	Diisobutylaluminium hydride
DMP	Dess–Martin periodinane
DDQ	2,3-Dichloro-5,6-dicyano-1,4- benzoquinone
HSQC	Heteronuclear Single Quantum Coherence
HMBC	Heteronuclear Multiple Bond Coherence
HRMS	High Resolution Mass Spectrometry
EC_{50}	Half maximal effective concentration
HSQC	Heteronuclear Single Quantum Coherence
IC_{50}	Inhibitory Concentration required for 50% inhibition
$HgCl_2$	Mercuric chloride.
$Hg(OTf)_2$	Mercury(II) trifluoromethanesulfonate
IBX	2-Iodoxybenzoic acid
$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
J	Coupling constant (in NMR)
LiHMDS	Lithium bis(trimethylsilyl)amide
LiClO	Lithium hypochlorite
LDA	Lithium diisopropylamide
MTPA	methoxytrifluoromethylphenylaceticacid
MeONHMe.HCl	N,O-Dimethylhydroxylamine hydrochloride
NOESY	Nuclear Overhausser Effect Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PPh_3AuCl	Chloro(triphenylphosphine)gold(I)
PIFA	phenyliodine(III) bis(trifluoracetate)
$Pd(OAc)_2$	Palladium acetate
PhSeCl	Phenylselenyl chloride
$i\text{-}Pr_2NEt$	N,N-Diisopropylethylamine
R_f	Retention factor
SiO_2	Silica
SAR	Structure-Activity Relationship
$Sc(OTf)_3$	Scandium triflate
$TiCl_4$	Titanium tetrachloride
TMEDA	Tetramethylethylenediamine
TLC	Thin Layer Chromatography
TMS	Trimethyl silyl
TBS	tert-butyldimethylsilyl
p-TSA	p-Toluenesulfonic acid
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TfOH	Trifluoromethane sulphonic acidδ
TFA	Trifluoro acetic acid
TfOH	Triflic acid
XRD	X-Ray Diffraction

- Independent compound and reference numbering have been used for each chapter as well as for sections of the chapters.
- All reagents and solvents were purchased from commercial suppliers and used as such without any further purification. Starting materials were obtained from commercial suppliers or prepared using known procedures.
- All the known compounds reported in literature were characterized by their NMR spectra.
- Solvents were distilled and dried following standard procedures. Petroleum ether used for column chromatography was of 60-80 °C boiling range.
- Column chromatographic separations were carried out on silica gel (100-200 or 230-400 mesh size).
- All reactions were monitored by TLC with 0.25 mm pre-coated E-Merck silica gel plates (60 F254) and TLC spots were made visible by exposing to UV light, Iodine adsorbed on silica gel or by immersion into an ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde, ninhydrin or KMnO4 followed by heating with a heat gun for ~15sec.
- NMR spectra were recorded on Bruker AV200 (200.13 MHz for 1H NMR and 50.03 MHz for 13C NMR), AV 400 (400 MHz for 1H NMR and 101 MHz for 13C NMR), Jeol-400 (400 MHz for 1H NMR and 101 MHz for 13C NMR), DRX 500 (500 MHz for 1H NMR and 126 MHz for 13C NMR) and AV 700 (700 MHz for 1H NMR and 176 MHz for 13C NMR) spectrometers.
- Chemical shifts (δ) have been expressed in ppm units relative to tetramethylsilane (TMS) as an internal standard and coupling constants (J) were measured in Hertz. The following abbreviations were used for 1H NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet and ddd = doublet of doublet of doublet.
- Optical rotations were recorded on a JASCO P-1020 polarimeter at 589 nm (sodium D-line). Specific rotations $[\alpha]^D$ are reported in deg/dm, and the concentration (c) is given in g/100 mL in the specific solvent.
- Structures and IUPAC nomenclature were generated using ChemBioDraw Ultra 14.0 software.
- High-resolution mass spectra (HRMS) (ESI) were recorded on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer.

AcSIR	**Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for award of the degree of Doctor of philosophy in Chemical Science**
Name of the Candidate	Mr. Digambar Abasaheb Kambale
Enrollment No. and Date	10CC15J26018; January 2015
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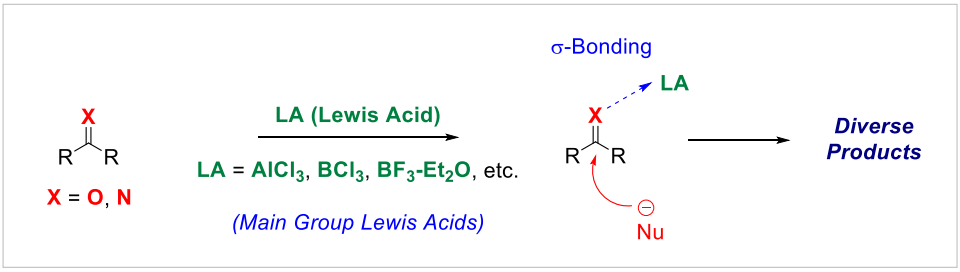
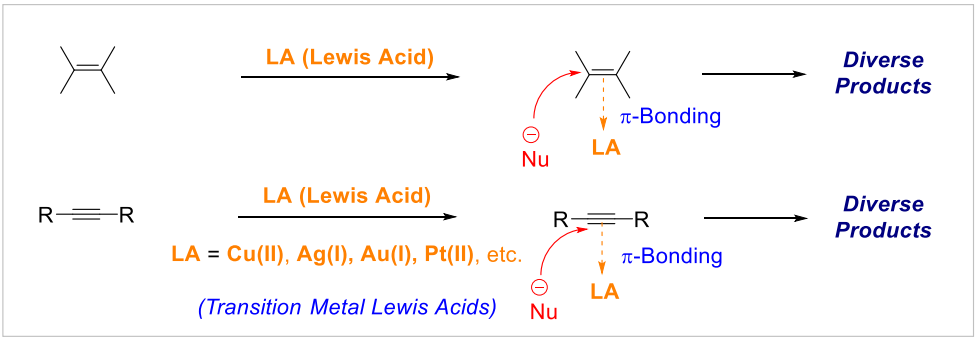
Research Supervisor	Dr. Ravindar Kontham

1. Introduction

Organic molecules containing unsaturation (aldehydes, ketones, imines, nitriles, esters, allenes, alkenes, and alkynes) form σ or π, and both complexes with diverse Lewis acids. For instance, main group element derived Lewis acids $MgCl_2$, BCl_3, BF_3-Et_2O, $AlCl_3$, $TiCl_4$, etc., form much stronger complexes with heteroatoms than carbon-carbon multiple bonds (σ-electrophilic Lewis acids)that make them versatile catalysts of the Friedel-Crafts, Diels-Alder, aldol-addition, and other electrophilic reactions. On the other hand, the salts of transition metals (Cu(I), Cu(II), Ag(I), Gold(I) and Pt(II), etc.,) can operate as bifunctional Lewis acids activating either (or both) carbon-carbon multiple (alkenes, alkynes, etc.) bonds via π-binding or (and) make theσ-complexes with heteroatoms in the same fashion as the conventional Lewis acids. Due to the affordability, accessibility from affordable precursors, and their chemical inertness toward many reagents and reaction conditions used in organic synthesis, alkenes, and alkynes attracted much interest. They led to numerous expeditious synthetic methodologies involving σ and π activating Lewis acid catalysis (mainly transitioned metal salts) (Scheme 1 and 2).[1]



Scheme 1.σ-Electrophilic activation.

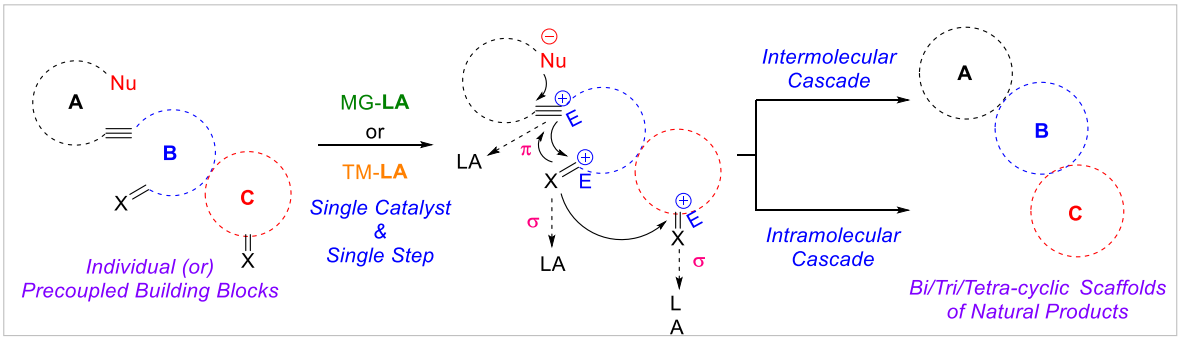


Scheme 2.π-Electrophilic activation.

Notably, alkynes (C-C triple bond containing molecules) emerged as versatile building blocks in organic synthesis due to their fascinating selective complexation patterns with transition metal derived Lewis acids, which would deliver complex natural or unnatural molecules with a prominent biological profile via intermolecular or intramolecular cascade transformations (involving alkynols, imines, and carbonyl compounds). It is well-known that transition metal salts are highly expensive and toxic to many biological systems, even with the lowest threshold concentrations. Hence there is an urgent need to identify efficient, alternative, safe and affordable catalytic systems that can exertσ and π-electrophilic catalysis (Scheme 2).

2. Statement of problem

Inspired by exciting features of alkynes, carbonyl compounds, and cascade/domino reactions (which fall under green chemistry by delivering complex organic molecules starting from simple building blocks in a single operation, which avoids massive waste generation in organic synthesis) in this thesis, we disclosed novel cascade annulation reactions of alkynols(4-pentyn-1ols and 5-hexyn-1ols) with carbonyl compounds using eco-friendly, nontoxic and affordable bismuth salts (the main group derived border-line metal salts) and TfOH (Brønsted acid) as dual activating (σ and π) catalysts for the first time. We have developed facile and efficient synthetic methodologies for the construction of α,β-unsaturated [5,5]- oxaspiro-



Scheme 3.Our approach of σ and π- (dual) activation.

lactones, α,β-unsaturated [6,5]-oxaspirolactones, and tetrahydro-oxepino-phthalides (isobenzofuranones) and [5,5]-oxaspirolactones related to biologically potent natural products (Scheme 3).

3. Objectives

a) To develop inter-and intramolecular cascade annulation reactions of alkynols(4-pentyn-1ols and 5-hexyn-1ols) with α-ketoesters viaσ and π (dual) activation catalysis to access scaffolds related to biologically active natural products.

b) The development of cost-effective, environmentally benign, and nontoxic bismuth salts (as an alternative to expensive and toxic transition metal salts) and TfOH (Brønsted acid) as efficient catalysts for these σ and π (dual) activation-induced cascade processes.

c) To device a novel synthetic methodology to access α,β-unsaturated [5,5]-oxaspirolactones via bismuth(III)-catalyzed intermolecular cascade annulation of 4-pentyn-1ols and α-ketoesters (via σ and π dual activation); and α,β-unsaturated [6,5]-oxaspirolactones through intramolecular cascade cyclization of propargylic diol-esters.

d) Development of TfOH (Brønsted acid)-catalyzed synthesis of oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [3+2]-annulation of alkynols with α-ynone-esters.

4. Methodology

This thesis is divided into four chapters.Chapter-1 deals with the introduction to alkyne chemistry, Chapter 2 comprising an introduction & previous approaches to α,β-unsaturated [5,5]-γ-spiroketal-γ-lactones, and Lewis acid-catalyzed cascade annulation of alkynols (4-pentyn-1ols) with α-ketoesters to access to γ-spiroketal-γ-lactones. In Chapter-3 provided an introduction & previous approaches to [6,5]-γ-spiroketal-γ-lactones and bismuth (III)-catalyzed cascade cyclization of propargylic diol-esters to access α,β-unsaturated [5,5]- and [6,5]-oxaspirolactones in a unified way. In Chapter-4 incorporated introduction & previous approaches to [2+2+2] and [3+2]-annulations/cycloadditions and our efforts in synthesizing oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [3+2]-annulation of alkynols with α-ynone-esters.

Chapter-1: *Introduction to alkyne chemistry*

Many higher alkynes and fine chemicals were prepared using petrochemical-based acetylene (gas, prepared by passing steam at 1500 °C through methane or reaction between calcium carbide and water) as a criticalprecursor.[2] In recent times, many advancements were disclosed to construct alkyne functionality from other building blocks, for instance, dehalogenations of dihalides, Corey-Fuchs and Ohira-Bestmann reaction of aldehydes, Sonogashira coupling reactions of aryl halides and trimethylsilyl acetylene using transition metal catalysis, and many other miscellaneous reports in the literature.[3]Alkynes possess C-C triple (one σ and two π bonds)and are inert (due to high bond energy) toward various reagents and reaction conditions used in multi-step organic synthesis. In light of their inertness towards divers reaction conditions and their selective complexation capability with metal catalysts, alkynes converted into corresponding aldehydes and ketones through Hg-mediated hydration, hyrostannylation, and hydroboration to access corresponding stannanes and boronates (used in cross-coupling reactions and hydro halogenation reactions). Recently, activation of alkynes through π–activation using Au, Ag, Pd, Pt, Cu, Ru, Rh, and Co salts as catalysts to construct different types of scaffolds via hydration, hydroalkoxylation, hydroamination, hydroarylation, etc., has emerged as one of the important fields of synthetic organic chemistry (Figure 1).[4]

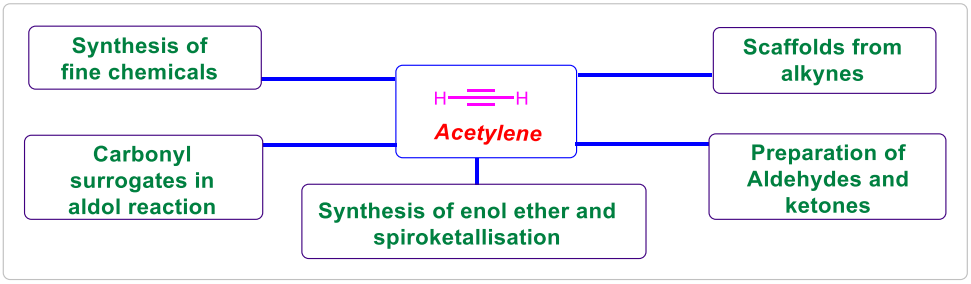


Figure 1.Diversification of acetylene into value-added chemicals.

Of all the chemistry developed using alkynes and their derivatives (through π-activation), most of them employed expensive, unsustainable, and toxic transition metal salts as catalysts. Hence, there is an urgent need to find green alternatives to perform alkyne activation-induced synthetic transformations. In light of the versatile properties of alkynes, we disclosed unprecedented dual activation (σ and π) induced cascade annulation reactions using bismuth-salts and Brønsted acid as catalysts and readily accessible alkynols (possessing hydroxyl and alkyne functionality; 4-pentyn-1ols and 5-hexyn-1ols) and carbonyl compounds as building blocks. This Chapter-I provides a brief review of the nature and chemistry of alkynes and their applications in the synthesis of diverse organic molecules.

Chapter-2: **Section-1:** *Introduction & previous approaches to [5,5]-γ-spiroketal-γ-lactones*

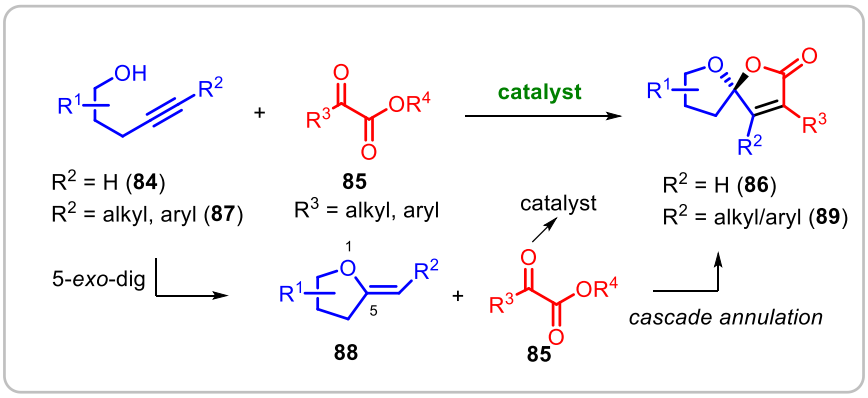
Oxaspirolactones (γ-spiroketal-γ-lactones) belong to oxaspiroketals with an ester functionality in one of the bicyclic spiro ring systems. These scaffolds are frequently found in natural products with diverse and potent biological activities. In addition, it has been demonstrated that simplified spiroacetals derived from natural products retain their biological properties. Hence, these scaffolds essentially contribute to pharmacological activities and represent privileged pharmacophores in drug discovery. In recent years, several bioactive natural products having unsaturated γ-spiroketal-γ-lactone(1,6-dioxaspiro[4.4]non-3-en-2-one; [5,5]-oxaspirolactone) appendage were isolated and have become an important sub-group of spiroketals, which include tuberostemonamide, massarinoline A, aphagrandinoidA, pyrenolide D, crassalactone D, levantenolide, papyracillicacid C, acutissimatriterpene A and many others.

In light of interesting structural features and biological activities of [5,5]-oxaspirolactones (unsaturatedγ-spiroketal-γ-lactones), a few synthetic methodologies have been disclosed in the literature. For instance, Mitsunobu's photo-oxidation of unprotected prefunctionalized furyl-alkanols give oxaspirolactones, Kitching et al. Reported from 3-butyn-1-ol via saturated oxa-spirolactone in eight steps. Recently in 2006, Shi and co-workers disclosed an expedient $SnCl_4$ (stoichiometric amount, 40 ^oC) mediated annulation of cyclopropyl-alkyl ketones and α-ketoesters, and few other miscellaneous reports. These all earlier reported methods have their limitations in using pre-functionalized starting materials, protection and deprotection sequence, stoichiometric amounts of Lewis acids, and multiple steps. Hence, the development of a new intermolecular approach for unsaturated γ-spiroketal-γ-lactones from readily available building blocks is of considerable importance from the perspective of diversity-oriented synthesis of medicinal chemistry applications and total synthesis of related bioactive natural products. As described above, this Section-1 of Chapter-2 focuses on the introduction and previous approach to unsaturatedγ-spiroketal-γ-lactones ([5,5]-oxaspirolactones), which in turn led to the development of our hypothesis to work on this subject.[5]

Chapter-2:**Section-2:***Lewis acid-catalyzed cascade annulation of alkynols with α-ketoesters: a facile access to γ-spiroketal-γ-lactones*

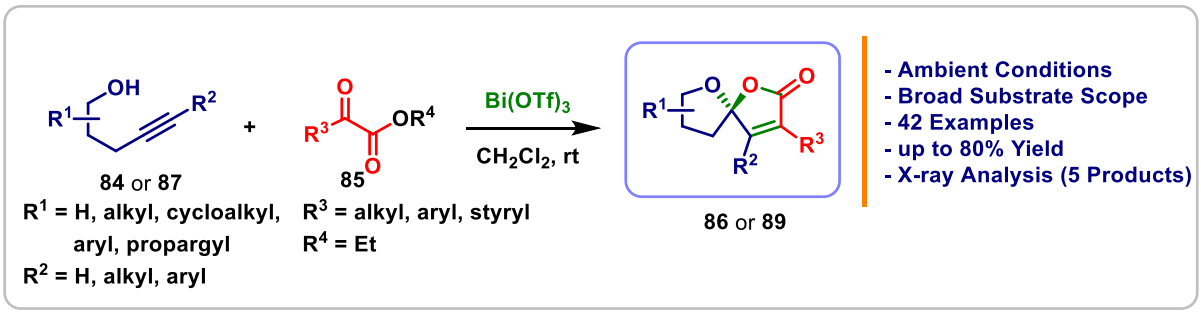
Inspired by the importance of cascade/domino reactions and as a part of research interest in Lewis acid-catalyzed (using main group border-line metal salt bismuth(III)) cascade/domino reactions involving dual activation (σ and π), herein we report a novel and efficient synthetic methodology for the construction of unsaturated γ-spiroketal-γ-lactones comprising $Bi(OTf)_3$-

catalyzed cascade annulation of alkynols (4-pentyn-1-ol derivatives) and α-ketoesters, where hydroalkoxylation of alkynol **84** and/or **87** (4-pentyn-1-ols)furnishes the exocyclic enol ether **88** via the 5-*exo*-dig mode of cyclization, which in the proximal presence of an activated α-ketoester **85** would undergo an annulation reaction to furnish the desired product **86** and/or **89** in a cascade manner (Scheme 4).



Scheme 4.Annulation of 4-pentyn-1-ols and α-ketoesters to prepare [5,5]-oxaspirolactones.

To test the above hypothesis, we have performed optimization studies using 4-pentyn-1-ols **84** (terminal alkyne containing) or **87** (internal alkyne containing) and α-ketoester **85** in combination with several alkynophilic (π-activating) catalysts (transition metal-based and other Lewis acids and also a few Brønsted acid catalysts) and found that $Bi(OTf)_3$ (anhydrous 99%, 20 mol%) in anhydrous CH_2Cl_2 at room temperature was optimal reaction condition for this annulation reaction. A total number of 42 diverse products **86** and/or **89** were prepared using terminal and internal 4-pentyn-1-ols (**84** and **87**) possessing 1°, 2° and 3° hydroxyl functionalities, and α-ketoesters having α-alkyl, vinyl, alkynyl and aryl substituents (Scheme 5). Total four products were unambiguously established using single-crystal X-ray analyses, remaining were confirmed through analogy. In addition, we also performed a couple of synthetic utility experiments on α,β-unsaturated double bond of the lactone segment of oxaspirolactones using Pd/C-hydrogenation and dihydroxylation (OSO_4, NMO) reactions.



Scheme 5. Bi(III)-catalyzed cascade annulation of 4-pentyn-1ols and α-ketoesters to access α,β-unsaturated [5,5]-oxaspirolactones.

Moreover, we provided the most probable mechanistic sequence for this π-activation triggered annulation reaction with the aid of real-time^{1}H-NMR analyses. All the synthesized γ-spiroketal-γ-lactones (**86** and **89**) were evaluated for their anticancer activity and to our delight, some compounds showed very good anti-breast cancer activity (Scheme 5).[5]

Chapter-3: **Section 1:** *Introduction & previous approaches to [6,5]-γ-spiroketal-γ-lactones*

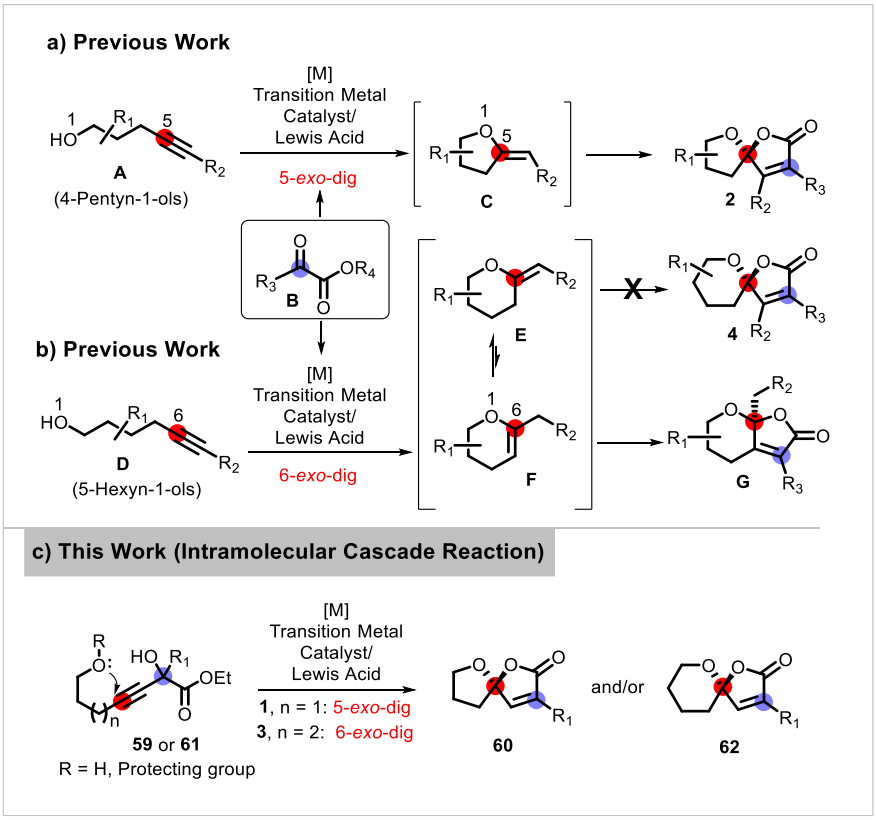
As we discussed in Chapter-2, numerous biologically active natural products contain γ-spiroketal-γ-lactone (oxaspirolactone) moiety isolated from sources of marine organisms, microbes, fungi, insects and plants. Molecular rigidity evolved from the three-dimensional skeleton and Michael acceptor nature of α,β-unsaturated lactone segment are primarily responsible for the interesting biological profile of these natural products. In light of these interesting structural features and biological profiles, there has been an increased pursuit in developing novel methodologies for the efficient construction of these scaffolds.

In general α,β-unsaturated γ-spiroketal-γ-lactones are prepared from their saturated counterparts using multiple synthetic manipulations. For instance, spirolactonization followed by halogenation and dehydro-halogenation, α-phenylselenation and oxidative elimination, and addition of halo-acrylates to lactones, are notable examples of this class. Strategies for direct construction of these scaffolds are very limited and those include, oxidative (chemical/photochemical) cascade cyclization of hydroxy-alkyl tethered furans, halocyclization of hydroxyalkyl tethered ylidene-butenolides, annulation of cyclopropyl alkyl ketones with α-ketoesters, and asymmetric multicomponent coupling of alkynols, anilines, and glyoxylic acid. This Section-1 of Chapter-3 describes various bio-active molecules possessing [6,5]-oxaspirolactone scaffold, previous synthetic approaches to access them and their merits and demerits, which in turn led to the development of our current research topic of bismuth(III)-catalyzed cascade cyclization of propargylic diol esters that provide access to diverse [6,5]-oxaspirolactones.

Chapter-3: **Section-2:***Bismuth(III)-catalyzed bis-cyclization of propargylic diol-esters: a unified strategy for the synthesis of α,β-unsaturated oxaspirolactones*

In continuation to our interest in developing cascade annulation reactions involving π-electrophilic activation of alkynols and inspired by the interesting biological profile of oxaspirolactone based natural products, previously (in Chapter-2), we have disclosed a novel cascade annulation approach for the synthesis of [5,5]-oxaspirolactones[5]in one step from 4-pentyn-1-ol **A** and α-ketoester **B** through 5-*exo*-dig mode of cyclization to give enol ether **C**

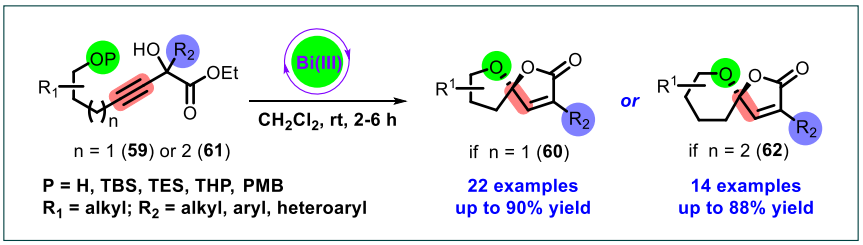
followed by annulation with **B** (entry a, Scheme 6). A similar transformation using 5-hexyn-1-ol **D** led to the formation of furo[2,3-*b*]pyran-2-one **G** instead of expected [6,5]-oxaspirolactone**4**, through initial 6-*exo*-dig cyclization to give exocyclic enol ether **E** and its inward isomerization into its thermodynamically favoured endocyclic enol ether **F** followed by annulation with α-ketoester **B** (entry b, Scheme 6). In this context, we aimed at the development of a unified strategy for the synthesis of both [5,5]- and [6,5]-oxaspirolactones (**2** and **4**). Hence, we have hypothesized that propargylic diol esters possessing 4-pentyn-1-ol or 5-hexyn-1-ol appendage (**59** or **61**) would deliver desired products **60** and **62** via initial selective alkynophilic transition metal/Lewis acid-catalyzed 5-*exo*-dig or 6-*exo*-dig cycloisomerization followed by dehydration and spiro-lactonization steps (entry c, Scheme 6).[5]



Scheme 6. Hypothesis generation for the development of a unified strategy for the synthesis of [5,5]- and [6,5]-oxaspirolactones.

To test our hypothesis, several alkynophilic catalysts (π-activating) of Bi(III), Ag(I), Au(I), Fe(II), Cu(II), In(III), Sc(II), Hg(II), Pd(III) and a few Brønsted acids were screened and found that $Bi(OTf)_3$, AgOTf and PPh_3PAuCl-AgOTf to be effective for this transformation. Among initially identified three best catalytic systems ($Bi(OTf)_3$, AgOTf and PPh_3PAuCl-AgOTf), $Bi(OTf)_3$ was chosen for this work due to its cost-effectiveness, environmentally benign nature. We prepared several propargylic diol esters **59** and/or **61** with 4-pentyn-1-ol and 5-hexyn-1-ol

appendages having 1°, 2° hydroxyl functionalitiesand subjected them to optimal reaction conditions to access various [5,5]- and [6,6]-oxaspirolactones **60** and **62** (a total number of 36 products obtained). Moreover, we have demonstrated this strategy potential using semi-protected propargylic diol esters having TBS, TES,THP, and PMB groups, which provided desired products **2** and/or**5**in good yields with equal ease (Scheme 7).



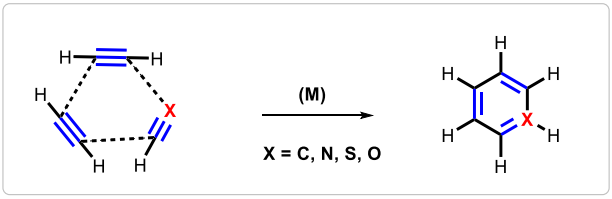
Scheme 7.Synthesis of [5,5]- and [6,6]-unsaturated oxaspirolactones from suitably functionalized propargylic diol esters.

<u>Chapter-4:</u> Section 1: *Introduction & previous approaches to [2+2+2]- and [3+2]-cycloaddition/annulation reactions*

In continuation of our research in the development of cascade annulation reaction using alkynols through π-electrophilic activation. Earlier in chapter 2 and 3, disclosed an efficient methods for the construction of [5,5]- and [6,5]-unsaturated oxaspirolactones. Construction of multi-functionalized polycyclic scaffolds related to biologically active natural products and functional materials through convergent annulation or cycloaddition strategy has been emerged as an interesting field of research due to its versatility, atom- and step-economic nature. One of these processes is the [2+2+2]-cycloaddition of alkynes for constructing functionalized arenes, which was well studied and employed in materials, medicinal, pharmaceutical and natural products chemistry. In the realm of [2+2+2]-cycloaddition of alkynes (particularly cyclo-trimerization), transition-metal-catalysis extensively explored based on Ni, Co, Pd, Cr, Rh, Fe, Zr, Nb, Ir, and other metals, where the product outcome relies heavily on the metal catalyst, substitution patterns of the substrate, in most cases vigilant workup is indispensable to avoid metal contamination due to high coordination properties of products.[11]

Due to conspicuous demand of transition metal-free, operationally simple, efficient, and cost-effective strategies, the development of a simple Brønsted acid-catalyzed [2+2+2]-cycloaddition of alkynes to construct multi-functionalized arenes is always a desirable endeavor. Despite the extensive literature on alkyne trimerization is present, only a few examples have been reported for transition metal-free processes, which include thermal

processes (temperature required is 100-600 °C), microwave irradiation (needed specialty equipment), amine-mediated cyclotrimerization of propargylic ketones, lactic-acid-induced trimerization of enaminone and intramolecular hexdehydro-Diels-Alder reaction (HDDA) of tethered ene-tetraynes. It's noteworthy to mention that an analogous construction of pyridines/pyrimidines via TfOH mediated (stoichiometric/catalytic) [2+2+2]-cycloaddition of ynamides/nitriles Maulide, Tang, Wang and Chang, and Dubovtsev and Kukushkin research groups.[12]



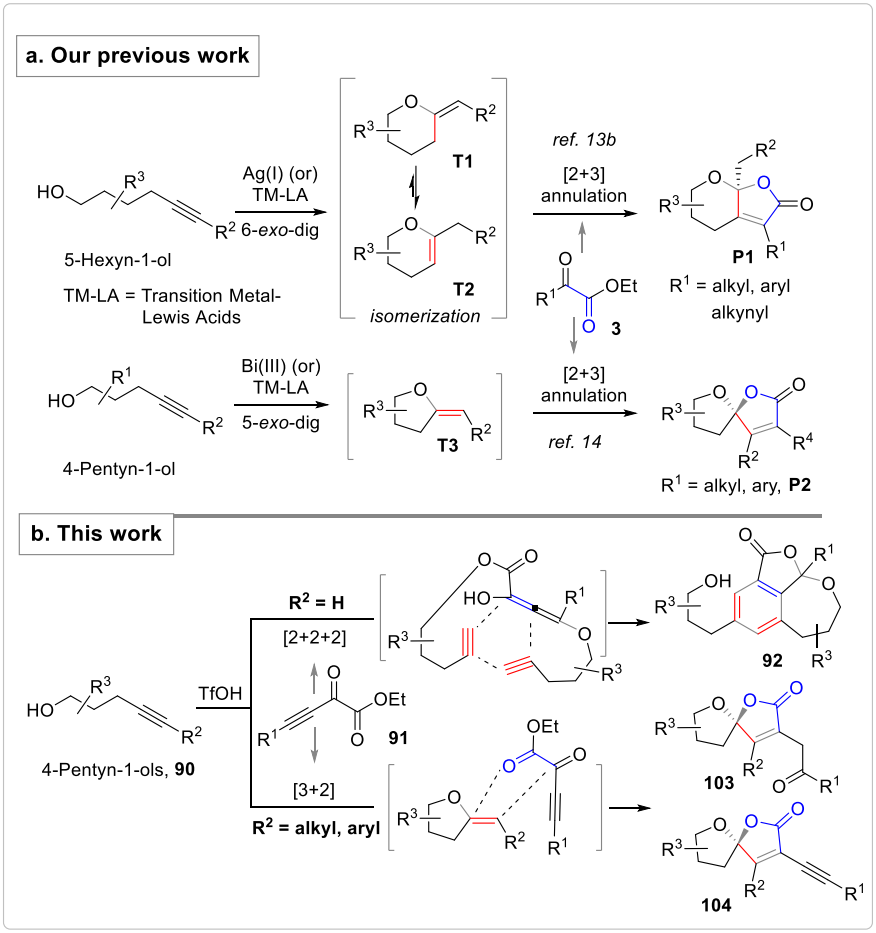
Scheme 8.Representation of [2+2+2]-cycloaddition/annulation reaction to access benzene derivatives.

Chapter 4: Section B: *Metal-free divergent synthesis of oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [2+3]-annulation of alkynols with α-ynone-esters*

To the best of our knowledge, there is no report on the TfOH-catalyzed intermolecular [2+2+2]-cycloaddition of alkynes to pro-vide tricyclic tetrahydro oxepino-phthalides, and α-aceto aryl or α-acyl [5,5]-oxaspirolactones via [3+2]-annulation involving alkynols and α-ynone-esters. Benzoxepines and phthalides (also called isobenzofuranones) are widely found in numerous bioactive natural products and pharmacologically interesting scaffolds, and phthalides are used as key intermediates in the synthesis of pharmaceuticals, natural products and heat resistant polymers. Many natural products possessing [5,5]-oxaspirolactones were isolated in recent times and known to display prominent biological profiles.

In a research program to expand the chemistry of alkynyl alcohols (alkynols) for the construction of diverse oxygen-heterocycles related to bioactive natural products, we have recently reported Ag(I) or Au(I)-Ag(I)-catalyzed [3+2]-annulation cascade reaction of 5-hexyn-1-ols with α-ketoesters and/or β-γ-unsaturated α-ketoesters to give diverse furopyranones **P1** via cyclic enol-ether **T2** (formed from alkynol via **T1**).[52b] In another investigation, Bi(III)-catalyzed annulation of 4-pentyn-1ols **90** with α-ketoesters **101** delivered α,β-unsaturated [5,5]-oxaspirolactones via the intermediacy of the enol-ether **T3** through [3+2]-annulation.[53] In these transformations alkynols undergo initial catalytic π-activation-

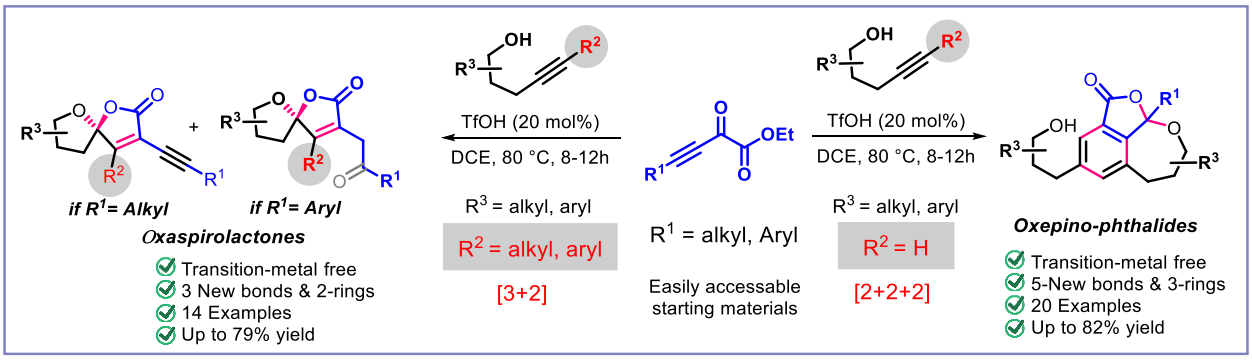
induced cycloisomerization to give respective cyclic enol ethers, which further react with activated α-ketoesters **3** and deliver annulated bicyclic scaffolds (entry a, Scheme 9). In continuation of this work, we sought to explore the reactivity of 4-pentyn-1-ols **90** with versatile synthons of **91** α-ynone-esters (possessing distinct functionalities of alkyne, ynone, carbonyl, and ester, under Lewis- and/or Brønsted acid catalysis (entry b, Scheme 9).



Scheme 9. Cascade annulation reactions of alkynols with α-ketoesters

Hence, an initial scouting reaction was performed with known 4-pentyn1-ol **90a** (possessing terminal alkyne) and α-alkynyl-α-ketoester (α-ynone-ester) **91a** under our in-house developed cycloisomerization conditions using $Bi(OTf)_3$ in CH_2Cl_2 at rt, which afforded tetrahydro-oxepino phthalide **92aa** in 62% yield along with oxaspirolactone **105aa** in 22% yield, subsequent experiment altering the solvent and temperature (DCE, 80 ^oC) did not led to any improvement in the outcome of **92aa** . After screening of other π- and σ-activating catalysts such as ($BiCl_3$, $InCl_3$, $FeCl_3$, AgOTf, AuCl, PPh_3AuCl-AgOTf, $Pd(PPh_3)_4$ and $Pd(OAc)_2$ delivered only **105aa** in 12-48% yield as we observed in our earlier investigations, whereas other catalysts (RuCl, $RhCl(PPh_3)_3$ and $NiCl_2$) known to facilitate [2+2+2]-cycloaddition failed catalyze this reaction. Gratifyingly, the reaction of **90a** (2 equiv) and **91a** (1 equiv) using 20

mol % of TfOH in DCE at 80 °C delivered exclusively **92aa** in 82% isolated yield, which was rigorously confirmed by single-crystal X-ray analysis (entry 3, Table 4.1). Further alteration of reaction parameters like molar ratios of **90a** and **91a**, Brønsted acids, catalyst loading and reaction temperatures did not led to noticeable improvement (entry 4-8, Table 4.1).[55]



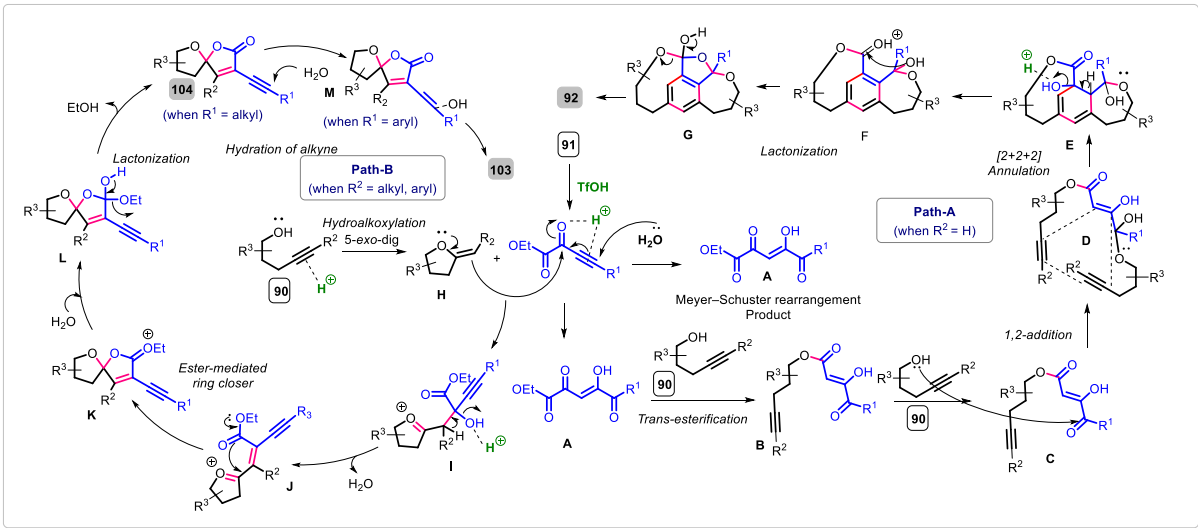
Scheme 10.[2+2+2]- and [3+2]-Annulation of 4-pentyn-1ols and α-ynone-ester

To further extend the substrate scope, 4-pentyn-1-ols possessing internal alkyne functionality 1 were examined under the optimized reaction conditions. However, a strikingly different reaction pattern was observed by providing α,β-unsaturated [5,5]-oxaspirolactones **103** and **104** with α-aceto aryl or α-alkynyl appendage respectively, depending on the nature of the substituent on the alkyne functionality of **91** (substrate with aryl substituents provided **103**, alkyl substituents gave **104** with complete regioselectivity). Optimized condition in hand, next we moved towards the synthesis of various (α-ynone-ester) and alkynols (Possessing terminal and internal). Further we have prepared 20 different oxepinophthalide and 12 different α,β-unsaturated [5,5]-oxaspirolactones **103** and **104** with α-aceto aryl or α-alkynyl [5,5]-oxaspirolactones. We have performed few control experiments to probe probable reaction mechanism and we proposed a plausible reaction mechanism.

While the precise reaction mechanism requires further investigation, plausible mechanistic pathways for forming oxepino-phthalides (Path A, Scheme 4.35) and oxaspirolactones (Path B, Scheme 4.35) based on results obtained in Scheme 4.34 and earlier reports[40-49,51,52] are presented in Scheme 4.35. The Brønsted acid-catalyzed hydration of α-ynone-ester **91** to give **A**, followed by transesterification of **A** with alkynol **90** would lead to the alkyne tethered α,γ-diketo-ester intermediate **B**. Subsequent 1,2-addition of another alkynol **90** onto the carbonyl carbon would lead to the intermediate **D**, which brings two alkynes and olefin functionalities into the proximity and facilitates the desired [2+2+2]-cycloaddition, and

furnish the tricyclic hydroxy cyclohexadiene **E**. Next, acid-mediated dehydrative aromatization of E would deliver the oxacarbenium ion intermediate **F**. Further, intramolecular transesterification leads to the orthoester intermediate **G**, which upon the strain-induced chemoselective cleavage of one of the C-O bonds leads to the tetrahydro oxepino-phthalides **92** (Path A, Scheme 11).

In contrast, the reaction of 4-pentyn-1-ols containing internal alkyne functionality **90** (R^2 = alkyl or aryl) with α-ynone-esters **91** proceeds through a [3+2]-annulation (Path B, Scheme 4.34). The TfOH-induced 5-*exo*-dig cycloisomerization of alkynol gives cyclic enol ether H**G**, which would react with activated α-ynone-ester **91** and deliver corresponding oxacarbenium ion intermediate **I** (*via* 1,2-addition). Subsequent acid-mediated dehydration to give intermediate **J**, followed by the intramolecular attack of the ester, leads to intermediate **K**. Next, the addition of *in situ* released water onto the oxacarbenium intermediate **K** furnishes hemiacetal **L**, which on the expulsion of EtOH delivers the α-alkynyl [5,5]-oxaspirolactones **104**. Interestingly, oxaspirolactone **104** possessing aryl substituents on the alkyne terminus, further undergo alkyne hydration reaction to deliver aceto-aryl [5,5]-oxaspirolactones **103** (Path B, Scheme 11).



Scheme 11. Plausible reaction mechanism.

By this method we can access complex tetrahydro-oxepino-phthalides (comprising formation of 5-new bonds and 3 rings) and regioselective α-aceto aryl or α-alkynyl [5,5]-oxaspirolactones (through 3-new bonds and 2 rings) is disclosed from readily accessible 4-pentyn-1-ols and α-ynone-esters. The oxepino-phthalides are formed through oxa-Michael/trans-esterification/[2+2+2]-anulation/intramolecular lactonization cascade, whereas the [5,5]-oxaspirolactones are obtained through 5-exo-dig-cycloisomerization/1,2-addition onto the α-ynone-ester/dehydration/lactonization (overall [3+2]-annulation) cascade.

Products were unambiguously confirmed by single-crystal X-ray analyses and analogy. These annulation reactions showed wide substrate scope. Therefore, we anticipate that this methodology will find applications in synthetic organic chemistry of bioactive natural products and medicinal chemistry.

5. Summary

1. Provided a brief review on the nature and chemistry of alkynes (particularly π-activation) and their applications in the synthesis of diverse organic molecules and connected with our hypothesis generation (Chapter-1).
2. Introduction and previous approaches for the synthesis of [5,5]-oxaspirolactonesare presented. We have disclosed a facile protocol for the synthesis of diverse α,β-unsaturated γ-spiroketal-γ-lactones ([5,5]-oxaspirolactones) employing cost-effective and environmentally friendly $Bi(OTf)_3$-catalyzed cascade annulation of alkynols (4-pentyn-1ols) with α-ketoesters via a dual (π and σ) activation process. Highlysterically demanding products, ambient reaction conditions, a cost-effective catalytic system, good yields, operational simplicity, and atom and step-economy are salient features of this strategy (Chapter-2).
3. An efficient and unified strategy for the synthesis of α,β-unsaturated [5,5]- and [6,5]-oxaspirolactones related to bioactive natural products via cascade $Bi(OTf)_3$-catalyzed cascade cyclization of propargylic diol esters is developed. Moreover, we have demonstrated the potential of this strategy using semi-protected propargylic diol esters as substrates, which provided desired products in good yields with equal ease (Chapter-3).
4. We have devised for the first time TfOH-catalyzed divergent access to complex tetrahydro-oxepino-phthalides (comprising formation of 5-new bonds and 3 rings) and regioselective α-aceto aryl or α-acyl [5,5]-oxaspirolactones (through 3-new bonds and 2 rings) is disclosed from readily accessible 4-pentyn-1-ols and α-ynone-esters. The oxepino-phthalides are formed through oxa-Michael/trans-esterification/[2+2+2]-anulation/intramolecular-lactonization cas-cade, whereas the [5,5]-oxaspirolactones are obtained through 5-exo-dig-cycloisomerization /1,2-addition onto the α-ynone-ester/dehydration/lactonization (overall [3+2]-annulation) cascade. Products were unambiguously confirmed by single-crystal X-ray analyses and analogy. These annulation reactions showed wide substrate scope under optimized reaction conditions. Therefore, we

anticipate that this methodology will find applications in synthetic organic chemistry of bioactive natural products and medicinal chemistry.

6. Future Directions

1. We have developed novel, efficient, and step-economic synthetic methodologies for the construction of α,β-unsaturated [5,5]- and [6,5]-oxaspirolactones and tricyclic oxepino-phthalides related to biologically active natural products from readily accessible alkynols (4-pentyn-1ols) and . In earlier reports, it was showed that oxaspirolactone moiety is responsible for the biological activity of related natural products and is considered a key pharmacophore. Hence, all prepared libraries of oxaspirolactones will be tested for their biological profile against diverse targets and structure-activity-relationship (SAR) studies will be performed to find lead molecules.
2. These synthetic methodologies will be employed in the total synthesis of related biologically active natural products and their analogs and SAR investigations.

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7. List of Publications and patents

List of Publications:

1. Lewis acid-catalyzed cascade annulation of alkynols with *α*-ketoesters: a facile access to *γ*-spiroketal-*γ*-lactones. **D. A. Kambale,** S. S. Thorat, M. S. Pratapure, R. G. Gonnade and R. Kontham, *Chem. Commun.* **2017**, *53*, 6641−6644.
2. Bismuth(III)-catalyzed cascade bis-cyclization of propargylic diol-esters: a unified approach for the synthesis of α,β-usaturated oxaspirolactones. **D. A. Kambale**, B. R. Borade and R. Kontham *Org. Biomol. Chem.* **2021**, *19*, 6618-6622. DOI: 10.1039/D10B00974E.
3. Metal-Free Divergent Synthesis of Oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [2+3]-Annulation of Alkynols with *α*-Ynone-esters. **D. A. Kambale**, B. R. Borade and R. Kontham (*Manuscript under preparation*).

List of Patents:

1. D. A. Kambale and R. Kontham, "SPIROKETAL- LACTONES AND PHARMA-CEUTICAL COMPOSITION CONTAINING SAME AND PROCESS OF PREPARATION THEREOF" Patent_**WO2018203346 A1**, PCT Int. Appl., 2018203346, 08 Nov **2018**.

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Chapter 1

Introduction to Alkyne Chemistry

1.1. Introduction to alkynes:

Alkynes are the class of unsaturated hydrocarbons containing C-C triple bond (two π-bonds and one σ-bond) and its empirical formula is C_nH_{2n-2}. Similar to alkenes have suffix –ene, alkynes have suffix –yne and this suffix is used when only one alkyne in the molecule. In the case of alkyne nomenclature, applies general hydrocarbon rule with suffix "yne". In physical properties point of view, alkynes are non-polar hydrocarbons, soluble in non-polar organic solvents and insoluble in water, having low melting and boiling point, the first three members (C1, C2 and C3) are gases, C4 to C8-liquids, and >C8 are solids, in general, alkynes have a higher boiling point due to higher bond energy than alkenes and alkanes. In alkynes, two adjacent carbons are bonded linearly with a bond angle of 180°, the carbon-carbon bond distance is 121 Pico meter, which is significantly shorter than alkenes (134 Pico meter) and alkanes (153 Pico meter). Hence alkynes have a strong bond with a bond strength of 839 kJ/mol, than alkenes and alkanes. However, both (pi) π-bonds are weaker than (sigma) σ-bond and can be easily broken and undergo several addition reactions on triple bonds. Moreover, alkynes are more polarizable than alkenes due to electrons present in (pi) π-bonds are loosely bonded and can be displaced. (Figure. 1.1).[1]

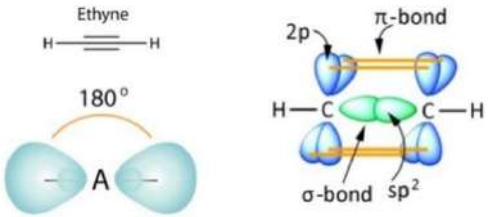
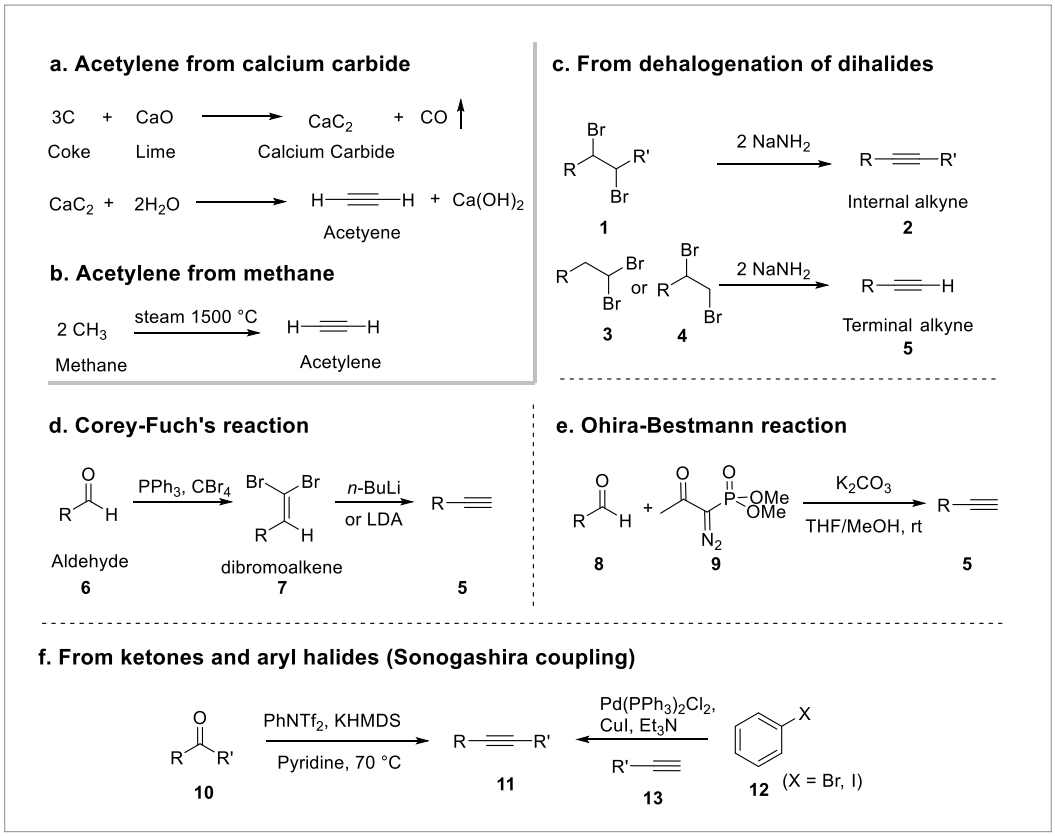


Figure 1.1.Structure and bonding of alkyne

1.2. General methods for the preparation of acetylene and higher alkynes*:*

Ethyne or another commonly called acetylene is the simplest and first member of alkynes. Generally, acetylene is widely used as a fuel and a primary building block for many valuable chemical compounds. There are several methods for preparing acetylenes, but *methane* and *calcium carbide* were used widely as sources on an industrial scale (entries a and b, Scheme 1.1). Many other (higher) alkynes can be accessed from acetylene by several chemical transformations (entries c-f). For instance, from *dehalogenation of dihalides*, *Corey-Fuchs reaction* of aldehydes,[2] *Ohira-Bestmann reaction* of aldehydes,[3,4] the reaction of *phenyl triflimide in the presence of KHMDS in pyridine*, and *Sonogashira coupling* of aryl/vinyl/allyl

halides with alkynes under transition metal catalysis (entries c-f, Scheme 1.1).[5]

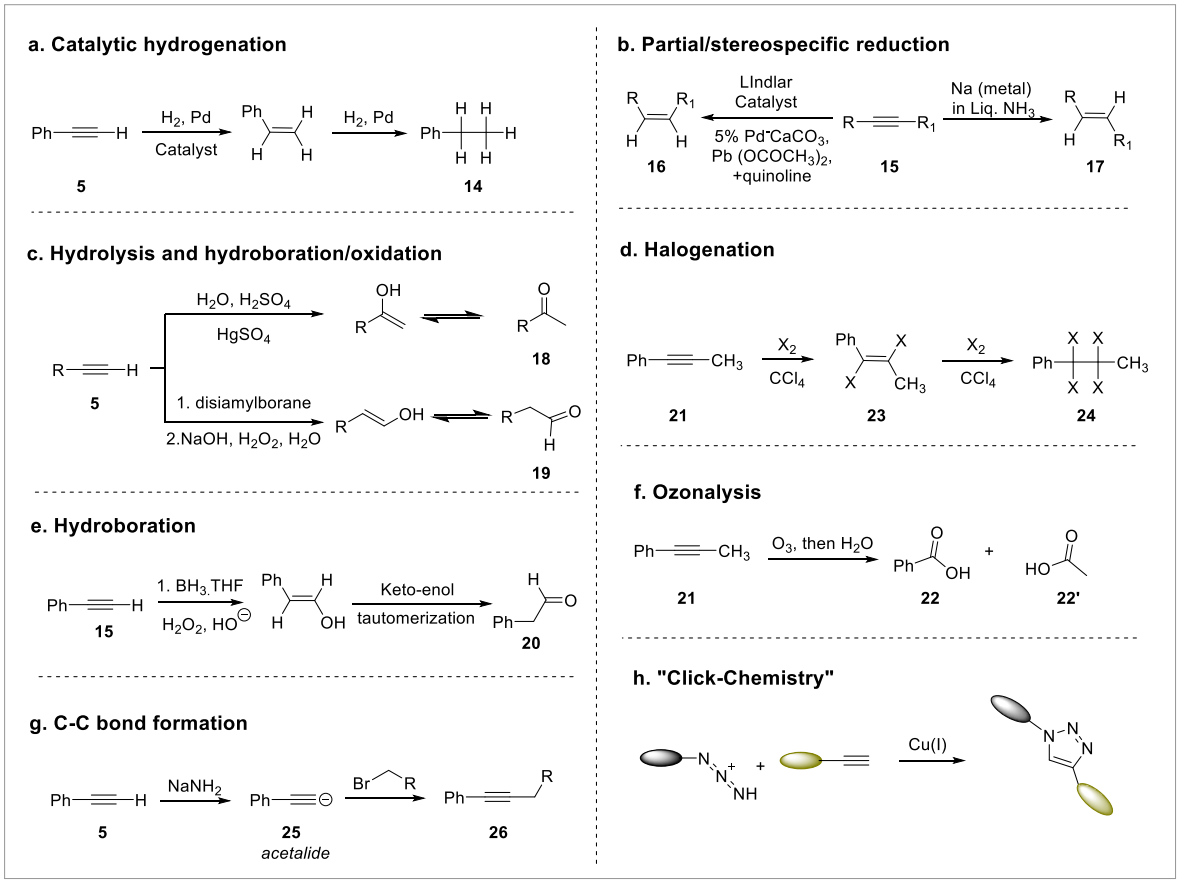


Scheme 1.1. General methods for the preparation of acetylene and higher alkynes.

1.3. General reactivity of alkynes:

As discussed in the above section, alkynes are inactive due to their high (839 kJ/mol) bond energy. However, they are well known to undergo diverse chemical transformations due to the availability of two π bonds with the aid of a suitable (alkynophilic/ π-activating) catalytic system. For example, catalytic hydrogenation reaction to give alkenes or alkanes, partial reduction to give alkenes stereospecifically, halogenation of alkynes to give di- and tetra halohydrocarbons, synthesis of aldehydes and ketones via hydration and hydroboration-followed by oxidation, ozonolysis to give corresponding carboxylic acids, hydrostannylation to give vinyl stannanes, the nucleophilic reaction of acetylenic anion on to alkyl halides and carbonyl derivatives to form diverse higher alkynes through C-C bond formation and synthesis of triazoles involving "click-chemistry" are well-established synthetic transformations of alkynes. Low reactivity/inertness of alkynes towards many reaction conditions those practiced in synthetic organic chemistry and their versatile reactivity towards specialized reaction conditions (using catalysis), alkynes emerged as versatile building blocks in chemical synthesis of diverse scaffolds, which in turn triggered the development of elegant synthetic

methodologies and catalysis involving alkynes (Scheme 1.2).



Scheme 1.2. General reactivity of alkynes.

1.4. Cycloisomerization and annulation reactions involving alkynes: Literature survey:

In light of the inherent inertness of alkynes towards numerous reagents used in organic synthesis, accessibility of novel synthetic methodologies to alkyne-containing building blocks, and the development of efficient catalytic systems to selectively functionalize alkynes (through π-activation), in recent times, extensive efforts were devoted toward the development of novel methodologies (particularly methods involving cascade cycloisomerization followed by annulation or Diels-Alder cycloaddition) to construct complex scaffolds related to medicinally important natural or unnatural molecules and functional materials.

Cycloisomerization, cycloaddition, and cascade/domino reactions are essential classes of synthetic transformations, which fall under Green Chemistry principles by delivering structurally and stereochemically complex molecules in step- and atom economic way. Alkynes tethered with alkenyl/hydroxyalkyl/aminoalkyl/aryl/heteroaryl groups emerged as versatile building blocks in constructing complex carbocycles and heterocycles employing salts/complexes of mercury, copper, silver, gold, platinum ruthenium and rhodium and a few

Brønsted acids as π-activating catalysts. Among several metal catalysts employed to activate alkynes, gold complexes work as mild and efficient Lewis acids and activate π-bonds of alkynes selectively under homogeneous conditions to provide a broad range of carbon-carbon and carbon-heteroatom bond-forming reactions.[6,7] The first example of activation of alkynes through a gold(I)-catalyst was reported by Telesin in 1998, which led to many versatile synthetic methodologies. Moreover, cobalt also used as an efficient catalyst for the Pauson-Khand ([2+2+1] annulation) reaction that is widely employed in the construction of cyclopentenones from alkynes and CO.[8]

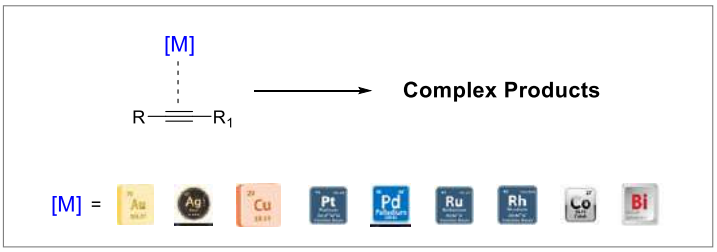
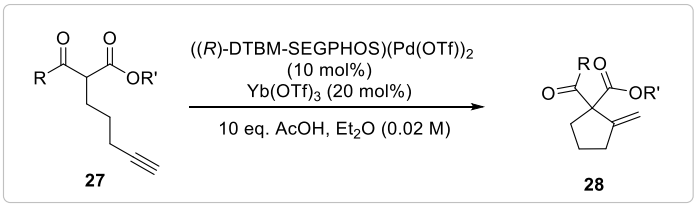


Figure 1.2. Selected metal-derived catalysts used as π-activating catalysts.

1.4.1 Conia-ene reaction:

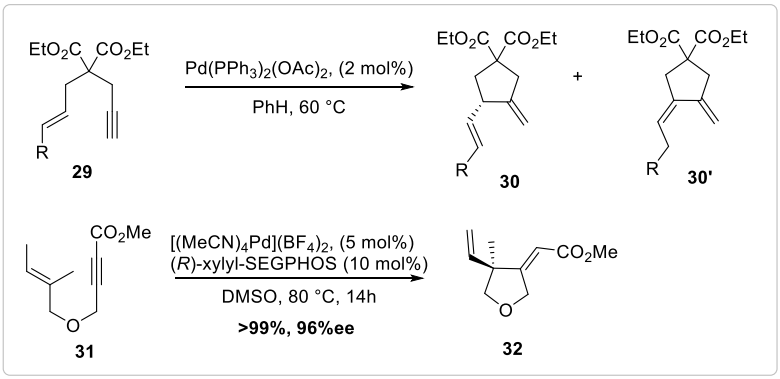
The Conia-ene reaction is an intramolecular thermal or Lewis-acid catalyzed cycloisomerization of carbonyl compounds having active methylene and alkyne/alkene groups. This reaction is a six-electron process as it occurs by forming enol and attack of enol onto the tethered alkyne/alkene in a concerted way (Scheme 1.3). In recent times, the low-temperature Conia-Ene reaction was also reported with the aid of transition metal catalysts.[9] Later, the Toste group in 2005 devised an asymmetric version of this reaction by using a bis(triflate)-palladium(II) complex with (*R*)-DTBM-SEGPHOS ligand and 10 equivalents of acetic acid and $Yb(OTf)_3$ (20 mol%) as an optimal reaction condition. By this method, one can access α-vinylated ketone products **28** from β-ketoesters **27** and alkynes with high enantioselectivities and high yields. This reaction worked smoothly with various β-ketoesters by generating palladium enolate, which attacks the alkynes activated by Lewis acid (Scheme 1.3).



Scheme 1.3. Conia-ene reaction

1.4.2 Cycloisomerisation of enyne:

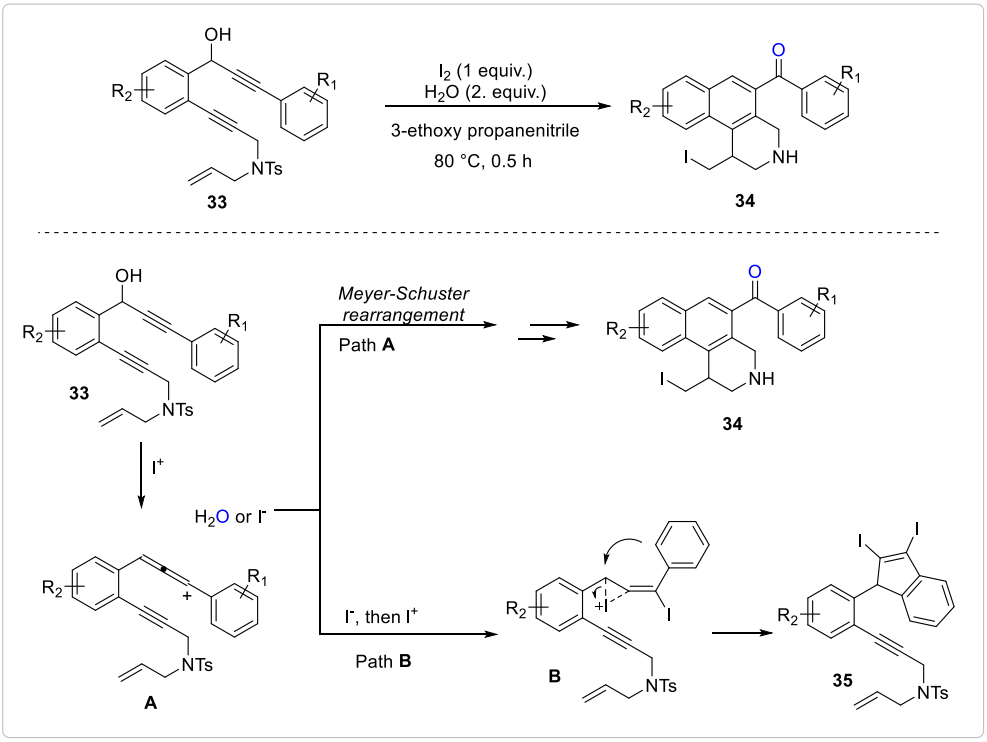
Trost and Lautens developed a palladium-mediated cycloisomerization reaction in 1985, and they found that palladium(II) salts could catalyze the cyclization of 1,6-enynes **29** to give 1,3- and 1,4-dienes **30** or **30**'.[10] Subsequently, Trost has developed an elegant approach for the stereoselective construction of substituted tetrahydrofuran **32** from 1,6-enynes **31**. Initially, they observed meager yields (less than 25%) using catalysts such as $Pd(OAc)_2$, $Pd_2(dba)_3.CHCl_3$/AcOH and $Pd_2(dba)_3.CHCl_3$/TFA. After extensive optimization with various palladium catalysts, they found appreciable yield and enantioselectivity (99% yield, 93% ee) using $Pd(TFA)_2$, (*R*)-BINAP and $[(MeCN)_4Pd](BF_4)_2$ as the catalyst precursor with (*R*)-xylyl-SEGPHOS as a ligand (Scheme 1.4).



Scheme 1.4. Cycloisomerization of Enyne

1.4.3 Cycloisomerization of dialkynes:

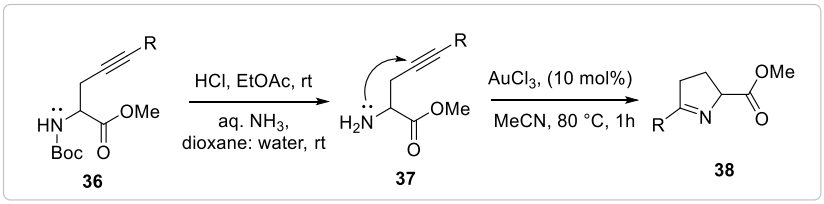
Recently in 2020, Quan's group devised an iodine-mediated cascade cycloisomerization of 1-en-6,11-diynes **33** for the synthesis of a variety of iodo-tetrahydrobenzo[*f*]isoquinoline **34** or tetrahydrophenanthrene derivatives.[11] This method has high functional group tolerance and furnished appreciable yields in very short reaction times. It is a transition metal-free and cost-effective method for the construction of iodo-tetrahydrobenzo[*f*]isoquinolines and tetrahydrophenanthrenes **35**. Two cyclic systems were achieved with one C-O, C-I, and two C-C bonds in a one-step transformation. In addition, generated iodo-products, which could be further derived through the subsequent transformations (Scheme 1.5).



Scheme 1.5. Iodine-mediated cycloisomerization of diynes

1.4.4 Cycloisomerization of amino alkyl-alkynes:

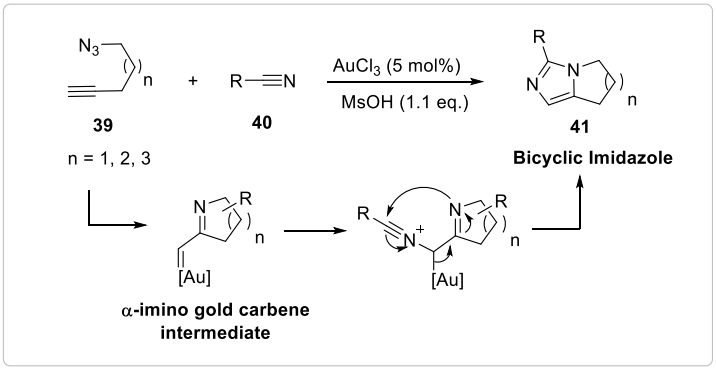
Testero's group in 2016 developed a versatile strategy of gold-catalyzed cycloisomerization of alkyne-containing amino acids, which result in C–O and C-N functionalization to deliver the alkylidene-lactones and 1-pyrrolines through 5-*exo*-dig mode of cyclization.[12] Nine different types of alkylidenelactone derivatives prepared by using this strategy from amino acids in excellent yields. In contrast, the corresponding amino esters **37** undergo gold-catalyzed intramolecular 5-*endo*-dig N-cycloisomerization to afford pyrroline carboxylate esters **38** derived from amino acids in moderate to good yields (Scheme 1.6).



Scheme 1.6. Cycloisomerization of aminoalkyl alkyne

Zhang's group in 2012 developed an efficient method for the synthesis of bicyclic imidazole **41** by [2+3]-cycloaddition reaction between nitriles **40** and azido alkynes **39**.[13] In the presence of gold catalyst, cyclic α-imino gold carbene intermediate was generated in situ via regioselective nitrene transfer from an azido group to a tethered C-C triple bond at ambient

temperature. Weakly nucleophilic nitrile, which is used as a solvent in the reaction that can react with in situ generated intermediate to provide a bicyclic imidazole in an overall bimolecular [2 + 2 + 1]-cycloaddition and in good to moderate yield. Huisgen reaction, which is another possible side reaction catalyzed by gold, was minimized using $AuCl_3$ as a catalytic system for this method (Scheme 1.7).



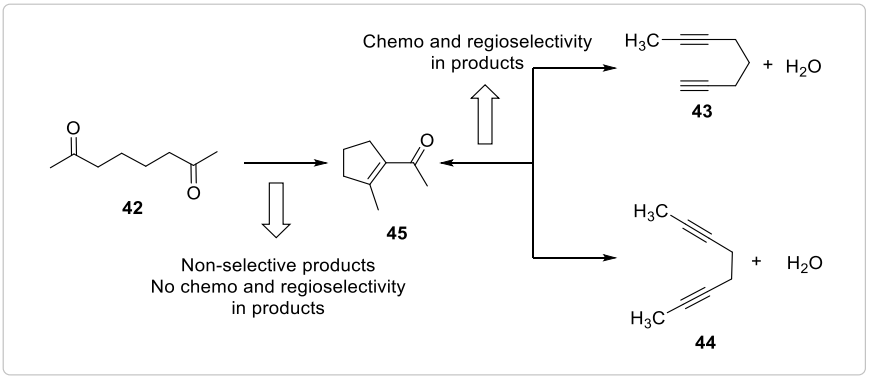
Scheme 1.7. Gold-catalyzed synthesis of bicyclic imidazoles

1.4.5 Alkynes are synthetic equivalents of carbonyl compounds in aldol condensation:

The C-C bond forming reactions are fundamental aspects of synthetic organic chemistry. In the case of carbonyl compounds such as aldol reaction is a very well-known C-C bond forming reaction and having wide applications in the total synthesis of bioactive natural products and life-saving pharmaceuticals.[14] These reactions comprise condensation of two carbonyl compounds to give a β-hydroxyl carbonyl product, which undergoes expulsion of a water molecule and delivers the α,β-unsaturated carbonyl compound.[15] Even though it is a versatile tool for C-C bond formation, there are some limitations, such as the formation of non-selective (chemo and regioselectivity) products in the case of symmetrical diketones. For example, symmetrical diketone octane-2,7-dione **42** undergo aldol condensation and gives the aldol product cyclic enone **45** along with some unwanted products. This could be due to the possibility of the formation of more than one carbanion.

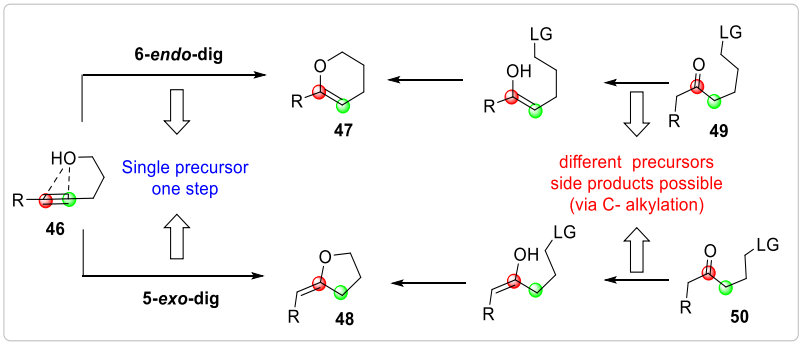
In recent times, alkynes have emerged as alternative substrates to aldehydes and ketones to access products usually obtained from aldol condensation. Suitably functionalize alkynes can be activated (through π-activation) using alkynophilic catalysts, which facilitates subsequent hydroxylation of alkynes via Markovnikov's/anti-Markovnikov's addition and forms an enol intermediate which then converts into more stable aldehyde or ketone. Tuning the catalytic system (metal and ligand) and loading can achieve the aldol product with high chemo- and regioselectivity. Therefore, alkynes serve as reliable carbonyl surrogates in various

reactions involving carbonyl compounds (Scheme 1.8).



Scheme 1.8. Alkynes as synthetic equivalents to carbonyl compounds

1.4.6 Alkynes in the synthesis of enol ethers: Traditionally, carbonyl compounds (aldehydes and/or ketones) are a fundamental class of organic molecules extensively utilized for the synthesis of various complex molecules. Carbonyl compounds can convert into their enol forms by using suitable conditions and used as nucleophiles for the construction of oxygen heterocycles (pyrans/dihydropyrans), and also was found that enol ether formation steps from carbonyl compound **49** or **50** leads to some unexpected products (for instance, C-alkylated products) and set limitations for broader applications. For example, two distinct carbonyl precursors, **49** and **50** needed for the construction of two different cyclic enol ethers **47** (six-membered, exocyclic) and **48** (5-membered, endocyclic). Whereas a single substrate containing alkyne **46** can be used as a common substrate to access **47** (through 6-*endo*-dig cyclization) and **48** (through 5-*exo*-dig cyclization) employing a suitable alkynophilic catalytic system (Scheme 1.9)**.**[16]

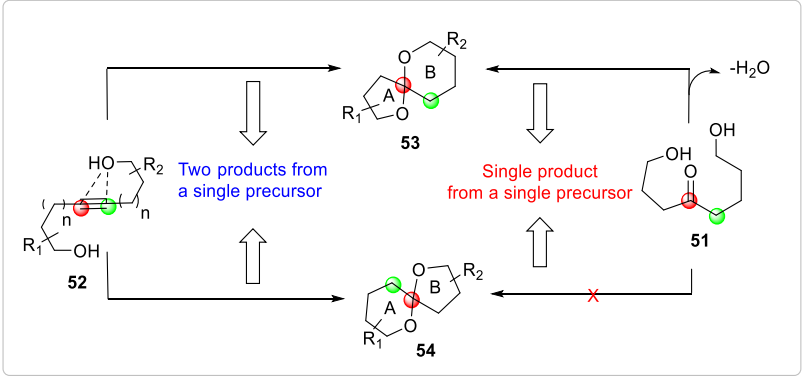


Scheme 1.9. Alkynes in the synthesis of cyclic enol ethers

1.4.7 Alkynes in spiroketalization: Spiroketals are bis-oxacyclic systems in which two rings are connected with a single carbon atom, found in numerous bioactive natural products, especially in polyketides, marine natural products, and shows a broad spectrum of potent

biological activities.[17] Usually, spiroketals are prepared through Lewis/Brønsted acid-catalyzed intramolecular dehydrative reaction of suitably functionalized keto diols.

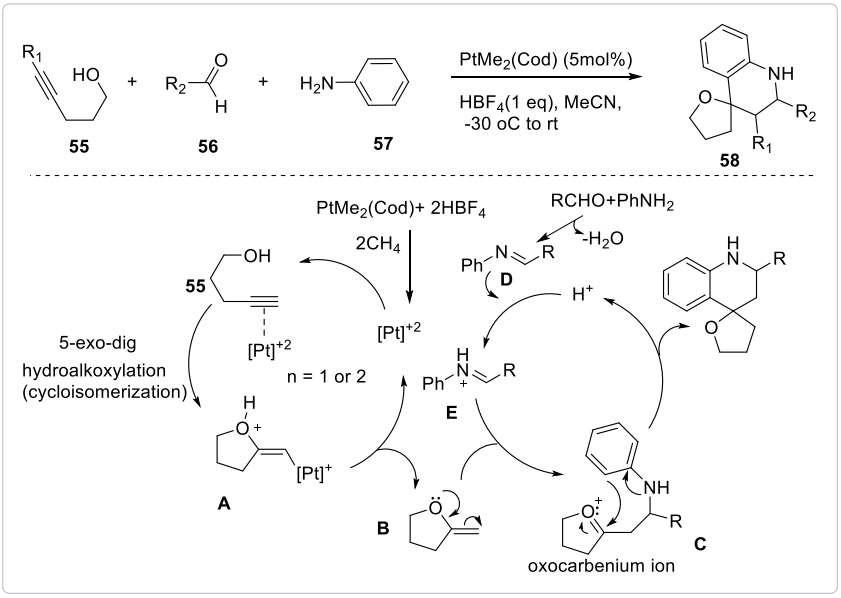
Lewis/Brønsted acid-catalyzed spiroketalization of keto diol delivers only one particular spiroketal based on tethered hydroxyalkyl groups. For example, 1,8-dihydroxyoctane-4-one **51** undergo spiroketalization by the expulsion of water and give [6,5]-spiroketal **53** only. In contrast, alkyne-diol **52** undergo spiroketalization via two different approaches, a common alkynediol precursor **52** on π-activation by using a suitable alkynophilic catalytic system undergo 5-*exo*-dig and/or 6-*endo*-dig mode cyclization through the substrate/catalyst controllable reaction conditions and would deliver either [5,6]-spiroketal **53** or [6,5]-spiroketal **54** containing spiroketals selectively (Scheme 1.10).



Scheme 1.10. Alkynes versus keto-diols in spiroketalization

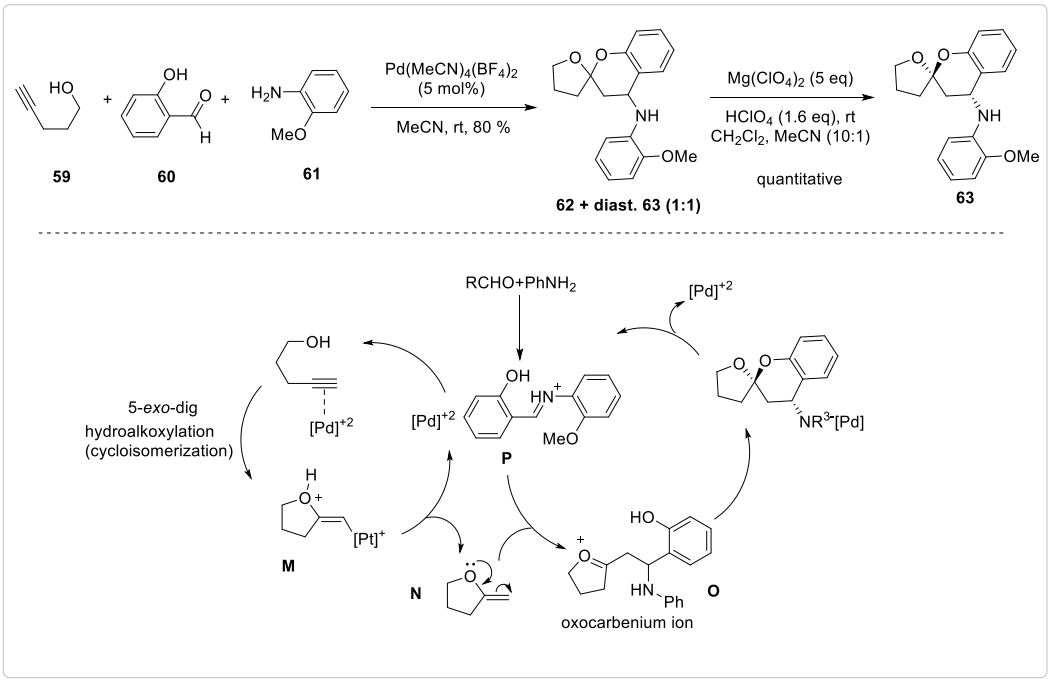
1.4.8 Cascade annulation reactions of alkynols and carbonyl compounds:

An expeditious one-pot multi-component cascade protocol encompassing Pt(II)-catalyzed synthesis of spiroquinolines from readily available alkynol (**55**), aldehydes (**56**) and anilines (**57**) was developed by Fañanás research group in 2008.[18] Pt(II)-Catalyst [$Pt(Me)_2Cod$] (5 mol%) (the cationic platinum catalyst was formed with [$Pt(Me)_2Cod$] protic acid), HBF_4(1 eq) in acetonitrile at 30 ^oC could afford various spiroquinolines ([5,5], [6,5], (**58**). This reaction proceeds through the initial C-C triple-bond activation, followed by intramolecular hydroalkoxylation of alkynol steps to give cyclic enol ether **B** via **A**, followed by the reaction of **A** with imines **E** (which are formed in situ by condensation aromatic amine **57** and aldehydes **56**) would leads to oxocarbenium ion **C,** which would undergo intramolecular Friedel-Crafts like cyclization to deliver the final product spiroquinolines (**58**) (Scheme 1.11).



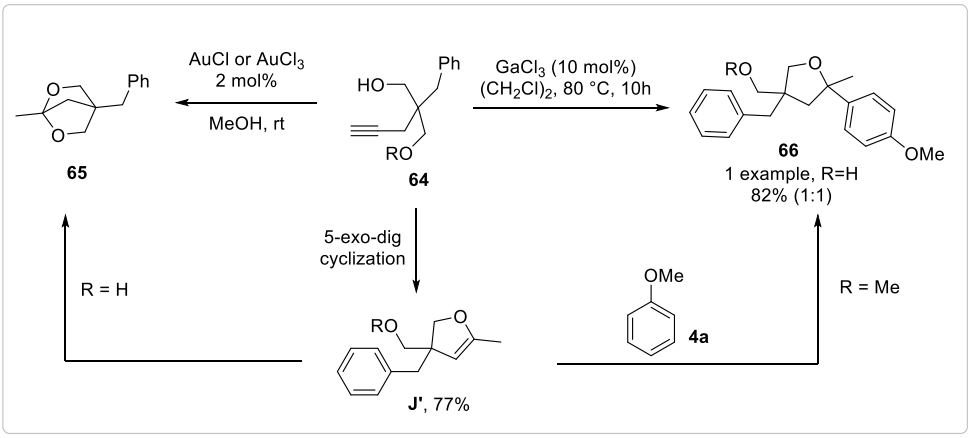
Scheme 1.11. Synthesis of spiroquinolines via one-pot multi-component cascade protocol.

Fañanás research group in 2009 reported a one-pot multi-component cascade protocol encompassing Pd(II)-catalyzed synthesis of spiroacetals from alkynol (**59**) aldehyde (**60**), and aniline (**61**).[19] The intramolecular hydroalkoxylation of alkynol catalyzed by an appropriate Pd(II)-catalyst provides the exocyclic ether **N** via **M**, which is in the presence of imine **P** (formed in situ by condensation of aldehyde and amine) would react to produce spiroacetal (**62** and **63**) as a mixture of diastereomers. This mixture was successfully converted into a more stable diastereomer **63** using $Mg(ClO_4)_2$ and $HClO_4$ in CH_2Cl_2 (Scheme 1.12).



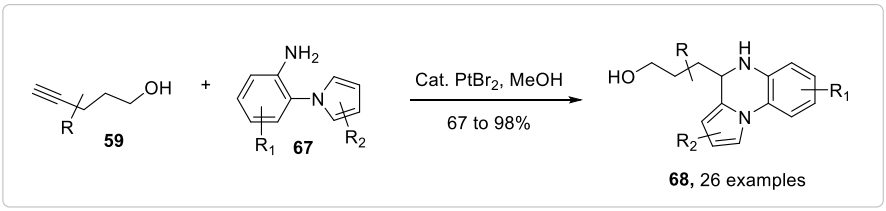
Scheme 1.12. Synthesis of amino spiroketals.

Gandon and co-workers, in 2010, successfully synthesized tetrahydrofurans from suitably constructed alkynols via Friedel-Crafts type reaction.[20] $GaCl_3$-mediated cycloisomerization of mono-protected alkyne diol (**64**) to give enol ether **J',** followed by trapping of enol ether with electron-rich arenes (anisole) delivered corresponding furans **66**. In contrast, alkyne diol (**64**, R = H) under Au(I)/Au(III) catalysis provided the bicyclic ketal **65** (Scheme 1.13).



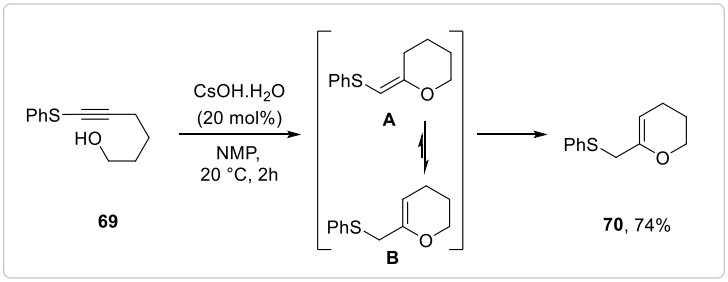
Scheme 1.13. Synthesis of tetrahydrofurans and bicyclic ketals.

Patil's research group developed an efficient method involving Markownikoff's hydroamination and hydroarylation cascade of alkynol **59** with amino-aryl pyrroles **67** by using $PtBr_2$ as a catalyst in MeOH to give substituted pyrrolo[1,2-*a*] quinoxalines and indolo[3,2-*c*] quinolines **68** in excellent yield (Scheme 1.14).[21]



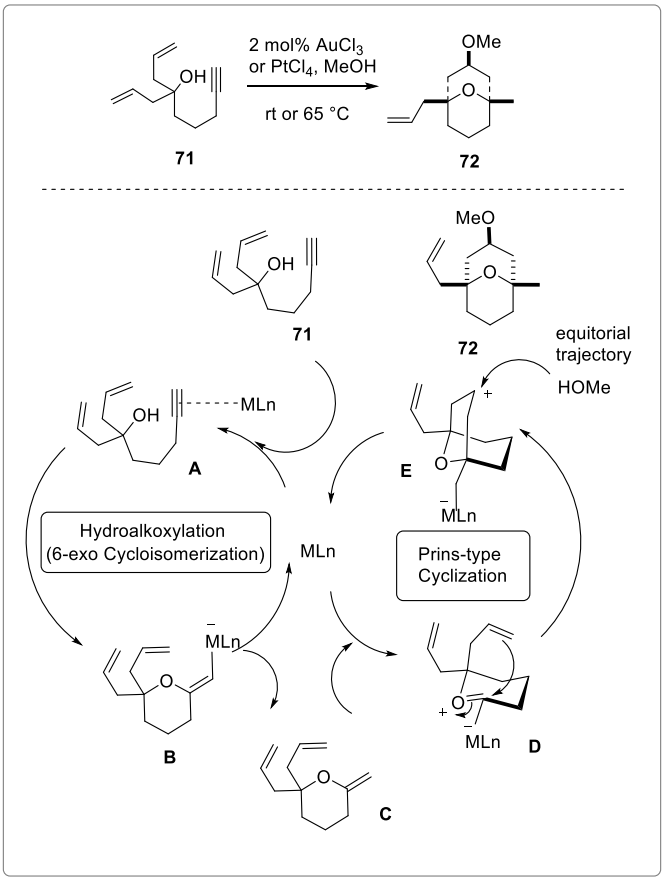
Scheme 1.14. Synthesis of substituted pyrrolo[1,2-*a*] quinoxalines and indolo[3,2-*c*] quinolines.

Paul Knochel's group in 1999 reported the catalytic amount of cesium hydroxide ($CsOH.H_2O$)-mediated intramolecular hydroalkoxylation of thiophenol-derived alkynols **69** to give corresponding enol ethers **70** and also enamines (Scheme 1.15). [22]



Scheme 1.15. Synthesis of functionalized enol ethers

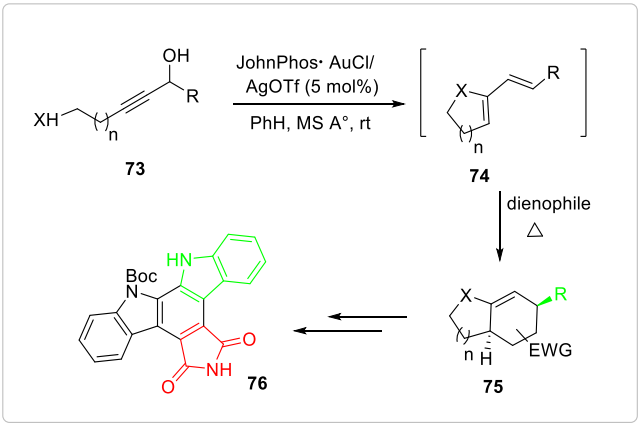
Fañanás research group devised a gold or platinum-catalyzed cascade annulation protocol for the synthesis of [3,3,1] bicyclic compounds (**72**) from suitably designed alkynols (**71**) followed by Prins-type cyclization in 2009.[23] They have performed several reactions with various alkynols and hetero-atom containing and halogen nucleophiles. By employing this method, they have synthesized enantiomerically pure [3,3,1] bicyclic compounds using a chiral-pool approach (Scheme 1.16).



Scheme 1.16. Hydroalkoxylation and Prins cyclization cascade.

Aponick's group reported in 2015 a versatile strategy for the synthesis of cyclic 2-oxodienes (**75**) from easily accessible propargylic alcohols (**73**) under a gold catalytic system.

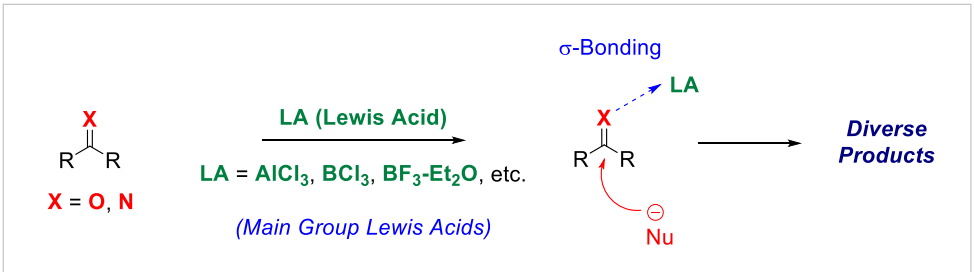
Mechanistically, the initial cycloisomerization followed by dehydration would deliver the diene 74, which subsequently undergo Diels-Alder reaction with various dienophiles to furnish the diverse bicyclic system (**75**).[24] Various substituted indole-carbazoles (**76**) were synthesized by using this method. This strategy was successfully applied for the total synthesis of arcyriaflavin A.



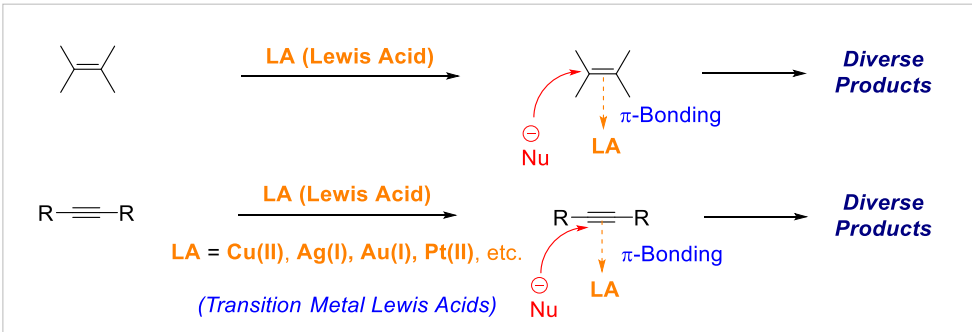
Scheme 1.17. Cycloisomerization followed by Diels-Alder cascade

1.5. σ and π–electrophilic activation and our hypothesis

As we discussed in the above sections, organic molecules containing unsaturation (aldehydes, ketones, imines, nitriles, esters, allenes, alkenes, and alkynes) form σ or π and both complexes with diverse Lewis acids. For instance, main group element derived Lewis acids $MgCl_2$, BCl_3, BF_3-Et_2O, $AlCl_3$, $TiCl_4$, etc., form much stronger complexes with heteroatoms than carbon-carbon multiple bonds (σ-electrophilic Lewis acids) that make them versatile catalysts of the Friedel-Crafts, Diels-Alder, aldol-addition, and other electrophilic reactions. On the other hand, the salts of transition metals (Cu(I), Cu(II), Ag(I), Gold(I) and Pt(II), etc.,) can operate as bifunctional Lewis acids activating either (or both) carbon-carbon multiple (alkenes, alkynes, etc.) bonds via π-binding or (and) make the σ-complexes with heteroatoms in the same fashion as the conventional Lewis acids. Due to the affordability, accessibility from affordable precursors, and their chemical inertness toward many reagents and reaction conditions used in organic synthesis, alkenes and alkynes attracted much interest. They led to numerous expeditious synthetic methodologies involving σ and π activating Lewis acid catalysis (mainly transitioned metal salts) (Scheme 1.18 and 1.19).[25]



Scheme 1.18 σ-Electrophilic activation.

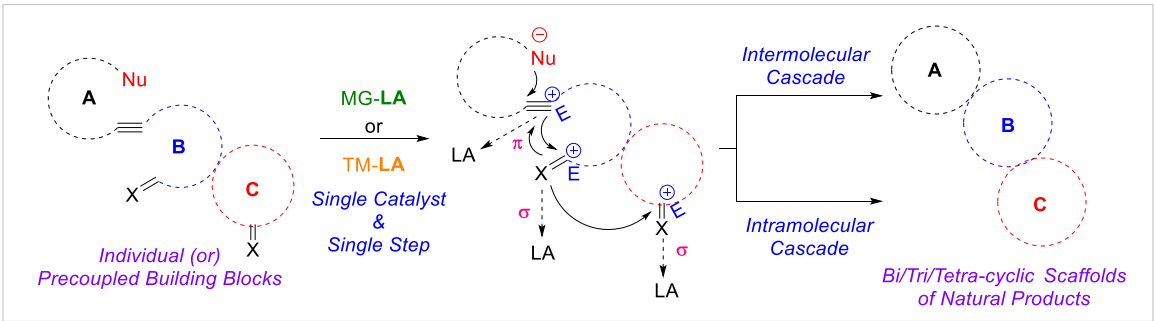


Scheme 1.19 π-Electrophilic activation.

Notably, alkynes (C-C triple bond containing molecules) emerged as versatile building blocks in organic synthesis due to their fascinating selective complexation patterns with transition metal derived Lewis acids, which would deliver complex natural or unnatural molecules with a prominent biological profile via intermolecular or intramolecular cascade transformations (involving alkynols, imines, and carbonyl compounds). It is well-known that transition metal salts are highly expensive and toxic to many biological systems, even with the lowest threshold concentrations. Hence there is an urgent need to identify efficient, alternative, safe and affordable catalytic systems that can exert σ and π-electrophilic catalysis

Bismuth is a non-transition metal (borderline main group metal) and relatively less well explored than transition metals due to its position in the periodic table. It is located next to heavy toxic metals such as mercury, thallium, and lead.[26] Bismuth is a relatively less toxic and environmentally benign catalyst than transition metals such silver, mercury, etc. Bismuth is having high hydro-compatibility than transition metals. Bismuth is also used in cosmetics, pigments, and medicines.[27] In light of these excellent features and Lewis acidity of bismuth salts, in the last four decades, very interesting organic synthetic methodologies were disclosed in the literature. In this thesis, we unveiled the dual activating nature (σ and π-activation) of bismuth(III) triflate and developed novel transformations involving intermolecular and intramolecular cascade annulation reactions involving alkynols.

Inspired by exciting features of alkynes, carbonyl compounds, and cascade/domino reactions (which fall under green chemistry by delivering complex organic molecules starting from simple building blocks in a single operation, which avoids massive waste generation in organic synthesis) in this thesis, we disclosed novel cascade annulation reactions of alkynols (4-pentyn-1ols and 5-hexyn-1ols) with carbonyl compounds using eco-friendly, non-toxic and affordable bismuth salts (the main group derived borderline metal salts) and TfOH (Brønsted acid) as dual activating (σ and π) catalysts for the first time. We have developed facile and efficient synthetic methodologies for the construction of α,β-unsaturated [5,5]-oxaspirolactones, α,β-unsaturated [6,5]-oxaspirolactones, and tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-ones (isobenzofuranones containing [5,6,7]-ring system)) related to biologically potent natural products (Scheme 1.20). In this chapter, we covered a brief introductionaboutσ-electrophilic activation, π- electrophilic activation and σ & π- (dual) activation.



Scheme 1.20 Our approach of σ and π- (dual) activation.

1.6 Conclusion:

In conclusion, this chapter provided systematic information and critical analysis through a brief literature survey, including structure, physical properties, chemical properties of alkynes, and various catalysts used for alkyne activation with the most reliable reported literature. Moreover, a brief introduction to π-electrophilic activation (alkynes, C-C triple bond), σ-electrophilic activation, and σ and π- dual activation (alkynes and carbonyl compounds) that led to the generation of our hypotheses discussed.

1.7 References:

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Chapter 2

Section A

Introduction & previous approaches to (5,5)-γ-spiroketal-γ-lactones

2.1.1 Introduction

Molecules derived from natural resources or synthesized with potent biological activity profiles attract the synthetic chemistry community to synthesize or develop new methodologies to achieve the core structure of the bioactive molecules.[1] Spiroketal and oxa-spirolactone are frequently found skeletons in many bioactive natural products and are particularly found in insect pheromones, marine organisms, polyketides derived from various resources. Oxaspirolactones are the subclass of spiroketals, in which one of the two rings contains a lactone ring system connected to common spiro carbon.[2] Oxaspirolactones are responsible for numerous biochemical or physiochemical properties due to their three-dimensional skeleton with Michael acceptor properties of α,β–unsaturated lactone functionality (Figure. 2.1).

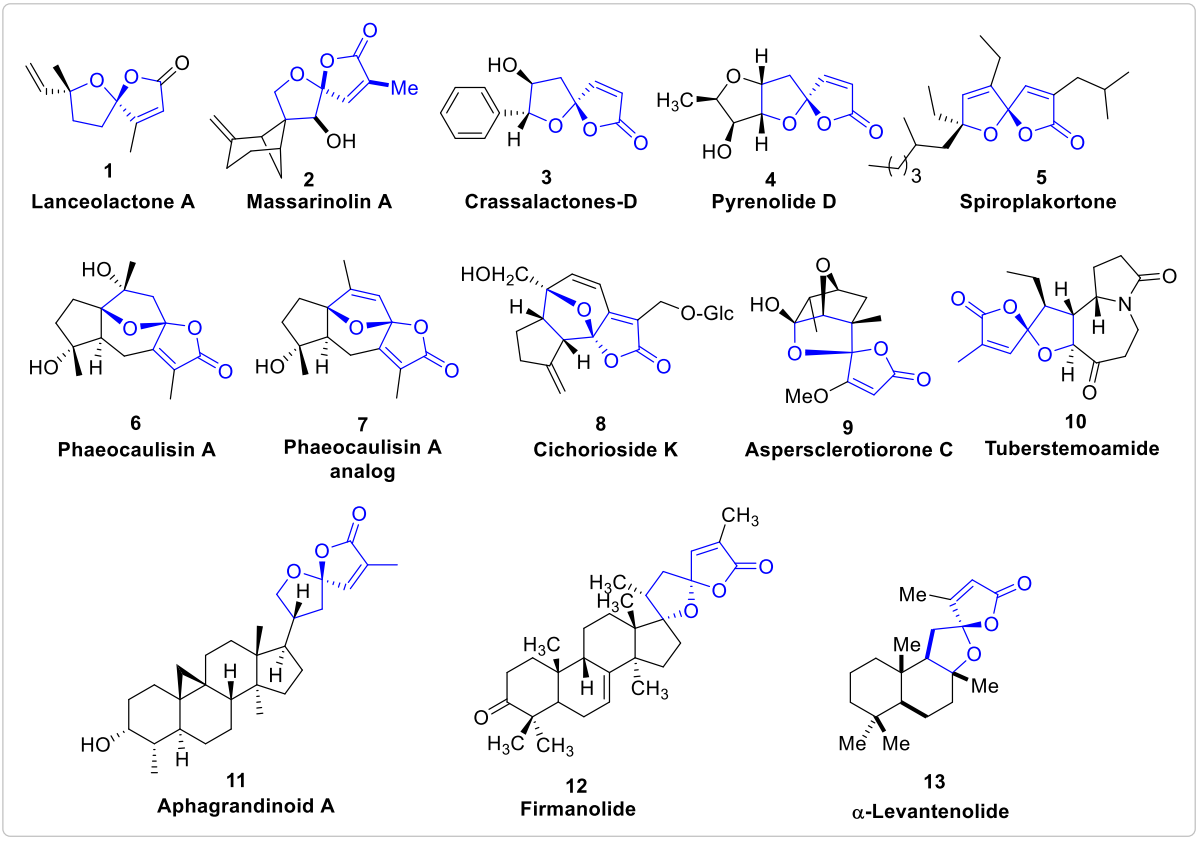


Figure. 2.1. Natural products containing oxaspirolactone core structure

Oxaspirolactones can be categorized into subcategories based on the ring system present in the molecule. Based on an intensive literature survey, it was found that [5,5]-oxaspirolactones are the largest group of oxaspirolactones among all the oxa-spirolactone containing molecules. Whereas [6,5]-oxaspirolactones are the second most abundant scaffolds found in various bioactive natural products. On the other hand, [6,6], [3,5], [4,5] and [5,6]-oxaspirolactones are

rarely found. However, some other unusual categories of oxa-spirolactones possessing [3,4], [5,4], [7,5], [4,6], and [6,7]-ring system also found in nature (Figure.2.2).

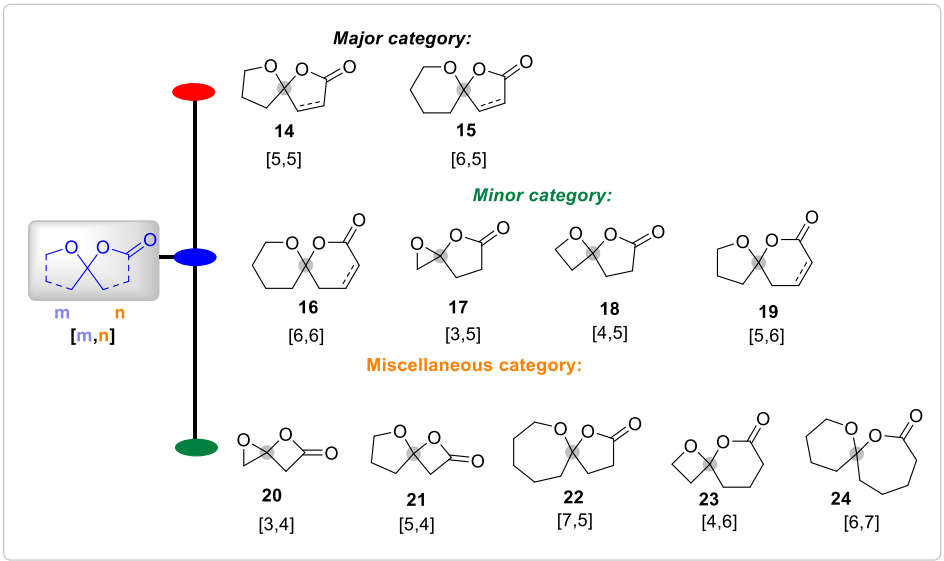


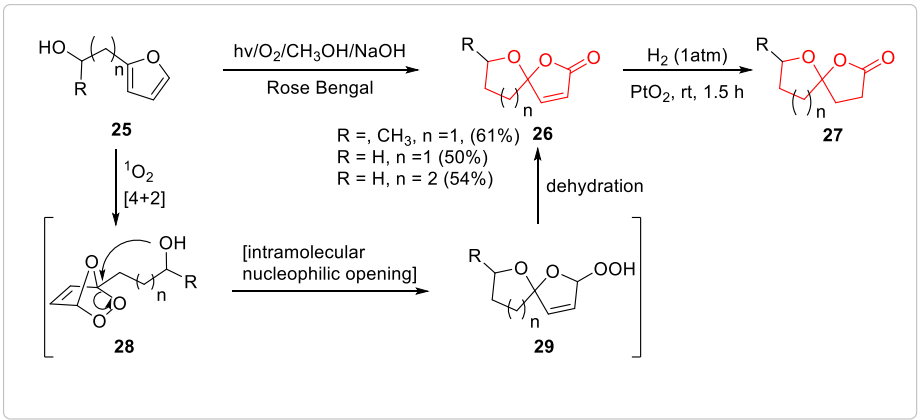
Figure. 2.2. Categories based on presence of ring system

Interestingly, Oxaspirolactones retain their biological properties even after their derivatization. Hence these scaffolds are considered privileged pharmacophores in drug discovery. This chapter mainly focused on the development of novel synthetic methodology for [5,5]-oxaspirolactones.

2.1.2 Previous Approaches:

A) Oxidation of hydroxyalkyl furan

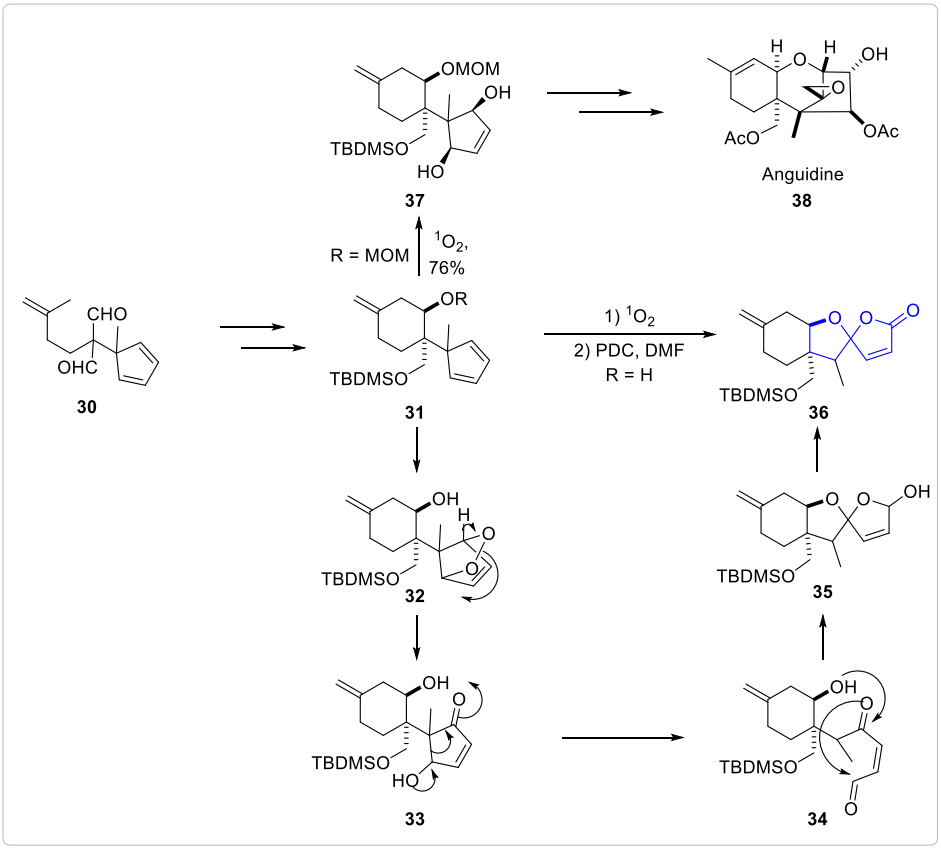
Mitsunobu and co-workers reported the photo-induced oxidation of hydroxyl furan (**25**) by using Rose Bengal as a photosensitizer in methanol under an oxygen atmosphere followed by 2 eq. of NaOH into highly complex and valuable unsaturated [5,5]-oxaspirolactones (**26**).[3] Hydroxyl furan undergo (4+2)-cycloaddition reaction of photochemically generated singlet oxygen followed by intramolecular ring-opening of hydroxyl group furnished the spiroketals (**29**) via ozonide adduct (**28**) which on dehydration delivers the unsaturated [5,5]-oxaspirolactones (**26**) in good yield. The synthesized oxaspirolactones were further converted into saturated oxa-spirolactone (**27**) by treating PtO_2 and 1.0 atmospheric hydrogen pressure at room temperature (Scheme 2.1).



Scheme 2.1. Photo-oxidation of hydroxyalkyl furan

B) Photooxidation of cyclopentadiene

Ziegler and Sobolov reported the synthesis of unsaturated [5,5]-oxaspirolactone from cyclopentadiene derivative on reaction with singlet oxygen followed by PDC mediated oxidation.[4] While working on the total synthesis of anguidine (**38**) accidentally, they could end up with unwanted unsaturated [5,5]-oxaspiroketal, which was converted into oxa-spirolactone (**36**) by PDC oxidation in DMF. Firstly, the 1,4-addition reaction furnished the endo-peroxide

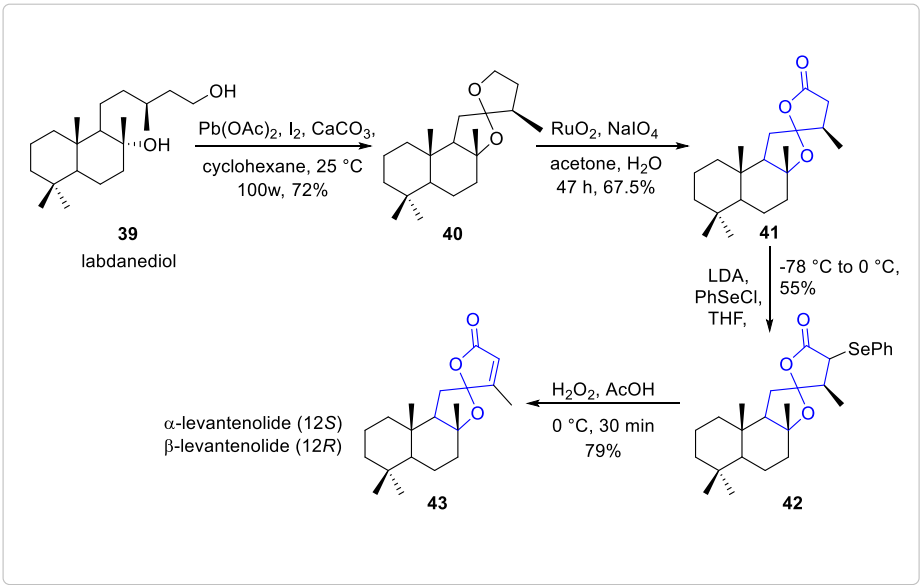


Scheme 2.2. Photooxidation of cyclopentadiene

intermediate (**32**). After ring-opening of endoperoxide gave the unprotected cyclohexanol coupled 4-hydrocyclopentenone (**33**), subsequently on retro-aldol fragmentation and spiroketalisation furnished the hydroxyl-spiroketal (**35**), After oxidation using PDC in DMF delivered the unsaturated [5,5]-oxaspirolactone (**36**) (Scheme 2.2). Whereas MOM-protected cyclohexanol delivers the cyclopentenediol (**37**), which is a key intermediate to achieve the synthesis of anguidine (Scheme 2.2).

C) Oxidation of preconstructed spiroketals

Urones and coworkers reported a synthetic protocol for the synthesis of α and β-levantenolides from naturally occurring chiral substrate labdanediol (**39**).[5] Firstly, labdanediol on oxidative spiroketalisation by using $Pb(OAc)_4$ and iodine to give **40**, further oxidation of spiroketal (**40**) to spirolactone by RuO_2-$NaIO_4$ in acetone-water mixture furnished the corresponding saturated [5,5]-oxaspirolactone (**41**) in good yield. Synthesis of α and β-levantenolides (**43**) was achieved from saturated (5,5)-oxaspirolactone (**41**) employing sequential reactions of phenylselenation followed by oxidative elimination by treatment with H_2O_2 AcOH in appreciable yield (Scheme 2.3).

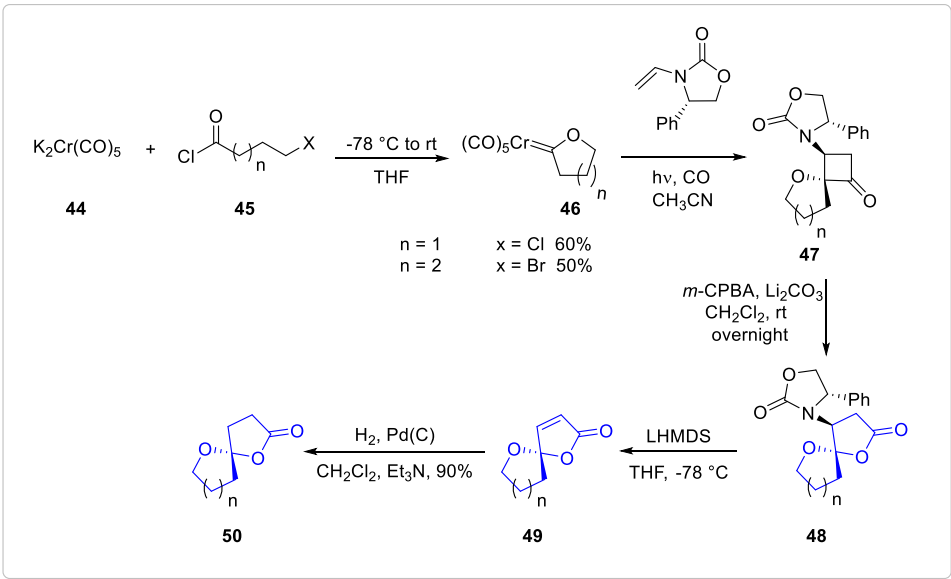


Scheme 2.3. Oxidation of preconstructed spiroketals

D) Ring expansion of spiro-cycloalkanones:

An enantioselective version for the synthesis of [5,5] and [6,5]-oxa-spirolactones reported by Hegedus and Buenoin 1998.[6] In this method, photolysis of cyclic chromium alkoxycarbene complex (**46**) with chiral ene-carbamate and CO to furnish optically pure cyclobutanone (**47**)

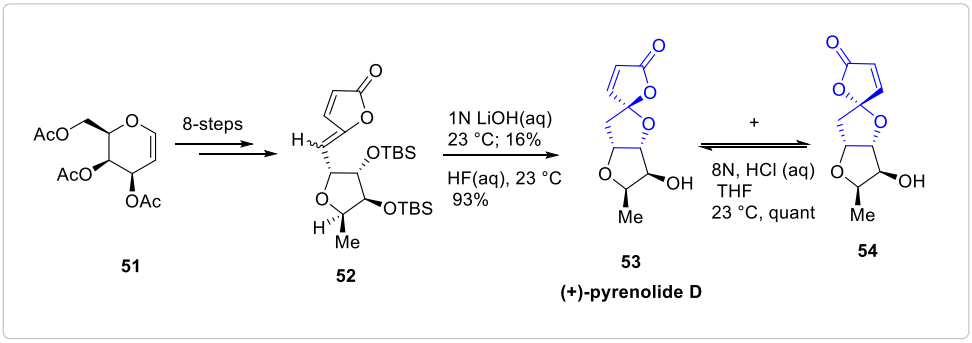
which on ring expansion by Baeyer-Villiger oxidation gave saturated oxa-spirolactone (**48**) which on base (LiHMDS) mediated expulsion of auxiliary deliver the enantiomerically pure [5,5] and [6,5]-oxa-spirolactones (**49**). Additionally, saturated [5,5] and [6,5]-oxa-spirolactones (**50**) were prepared by using Pd/C mediated hydrogenation in CH_2Cl_2 and Et_3N (Scheme 2.4).



Scheme 2.4. Ring expansion of spiro-cycloalkanones

E) From alkylidene-butenolides

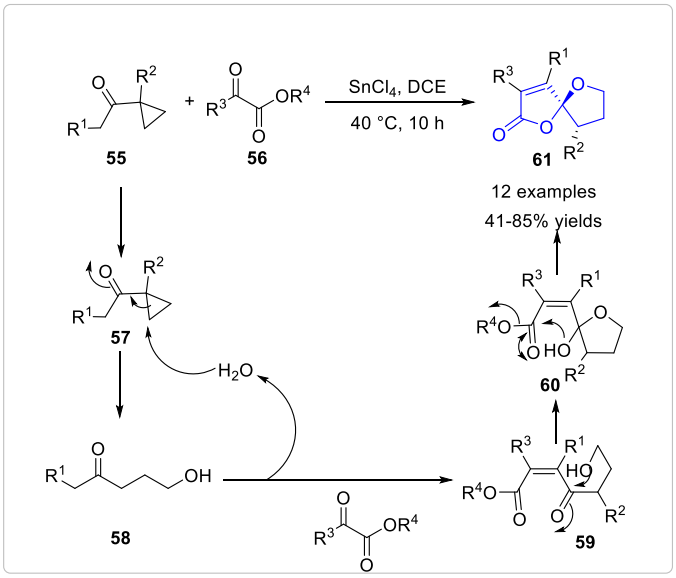
Gin group in 2001 reported the first stereoselective total synthesis of natural product (+)-pyrenolide (**53**),[7] having cytotoxic activity against several cancer cell lines. Initially, a carbohydrate-derived ylidene-butenolide (**52**) was synthesized from triacetoxy dihydropyrane (**51**) in 8 steps. Total Synthesis of (+)-pyrenolide (**53**) and its epimers was achieved in one pot and two steps sequence. Firstly, base (1.0 N LiOH aq.) mediated hydrolysis of lactone intermediate of carbohydrate derived ylidene-butenolide followed by silyl group deprotection by using HF in aqueous medium and further spirolactonization in 93% yield. The synthesis of natural diastereomers (**54**) also achieved from (+)-pyrenolide by using 8N HCl in THF in quantitative yield. (Scheme 2.5).



Scheme 2.5. Synthesis of pyrenolide D and its epimer from ylidene-butenolide.

F) Cascade annulation reactions of cyclopropyl alkyl ketones and α-ketoesters

Shi group in 2006 reported an efficient cascade annulation protocol for the synthesis of unsaturated [5,5]-oxaspirolactones (**61**) from cyclopropyl alkyl ketones (**55**) and α-ketoesters (**56**) by using Lewis acid ($SnCl_2$) in stoichiometric amount.[8] In this method a Lewis acid-mediated ring-opening of cyclopropyl by H_2O to furnish γ-hydroxy carbonyl intermediate (**58**) followed by aldol type condensation subsequent ketalization and intramolecular transesterification delivered [5,5]-oxa-spirolactone in good yield. By employing this method, diverse oxa-spirolactones (12 examples) were prepared (Scheme 2.6).

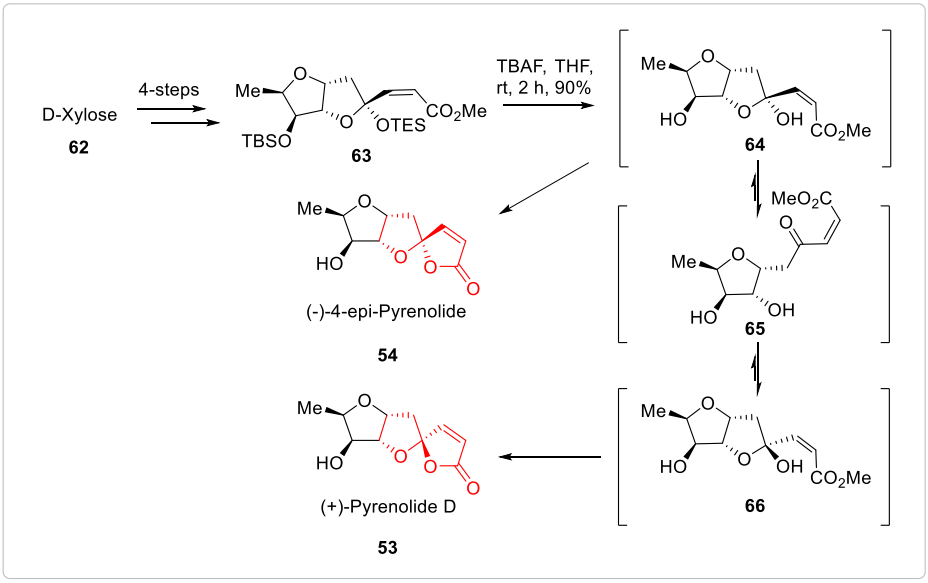


Scheme 2.6. Synthesis of [5,5]-oxaspirolactones through annulation of cyclopropyl alkyl ketones and α-ketoesters.

G) Bronsted acid-catalyzed dehydrative cyclization of keto hydroxy acid

Du group in 2013 reported the efficient synthetic approach for (−)-4-*epi*-pyrenolide (**29**) and (+)-pyrenolide D (**30**) in seven steps with 10.8% overall yield starting from chiral building

block D-xylose (**62**).[9] Initially, D-xylose (**62**) on several synthetic transformations accessed the TES-protected hemiacetal intermediate (**63**). Spirolactonization was achieved by desilylation of hemiacetal by using TBAF in THF via hemiacetal (**64**), which is in equilibrium with hydroxyl ketoester intermediate (**65**) and again it is in equilibrium with another hemiacetal intermediate (**66**). Synthesis of (–)-4-*epi*-pyrenolide (**54**) and (+)-pyrenolide D (**53**) was achieved from hemiacetal intermediates (**64**) and (**66**) respectively by intramolecular Spirolactonization. (Scheme 2.7).



Scheme 2.7. Bronsted acid-catalyzed dehydrative cyclization of keto hydroxy acid

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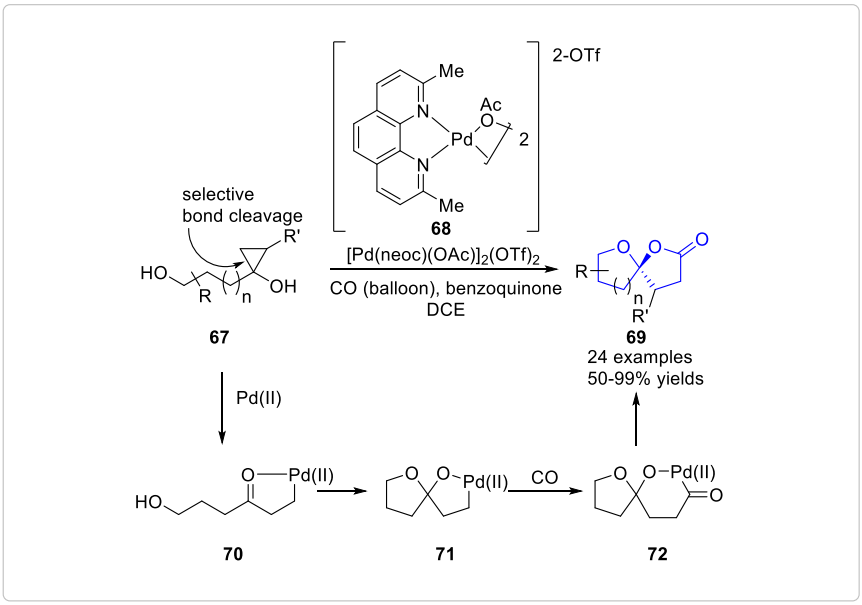
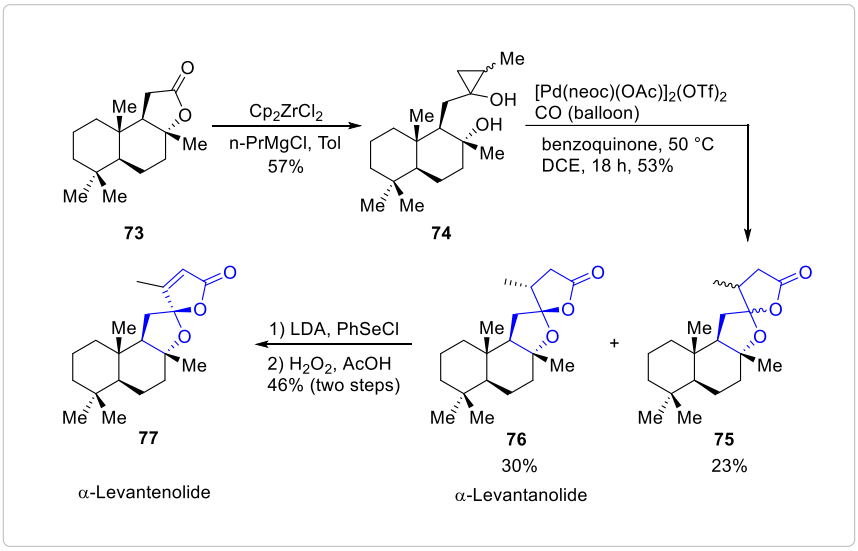
H) Carbonylative spirolactonization of hydroxyalkyl-cyclopropanols

Recently, Ming and Dai group reported a tandem approach for the synthesis of [5,5], [6,5] and [7,5]-oxspirolactones (**69**) with good to excellent yield.[10] Pd(II)-catalyzed carbonylative spirolactonization of hydro cyclopropanols (**67**) or (**74**) with CO in DCE at 50 °C for 18 h. Broad substrate scope with high functional group tolerance and scalability. By using this approach, successfully synthesized α-levantanolide (**76**), which on sequential reactions such as phenylselenation followed by treatment of H_2O_2, AcOH gave the α-levantenolide (**77**) in 2 and 4 steps using naturally occurring chiral precursor (+)-sclareolide (**73**) (Scheme 2.8 and 2.9).



Scheme 2.8. Proposed mechanism for carbonylative spirocyclization.



Scheme 2.9. Synthesis of oxa-spirolactones via carbonylative spirocyclization and its application in the synthesis of α-levantanolide and α-levantenolide.

Chapter 2

Section B

Lewis acid catalyzed cascade annulation of alkynols and α-keto esters: a facial access to γ- spiroketal-γ-lactones

2.3 Introduction

Spiroketals and oxa-spirolactones are frequently found structural units in biologically potent natural products.[11-12] In addition, it has been shown that simplified spiroacetals derived from natural products retain their biological properties. Hence, these scaffolds essentially contribute to pharmacological activities and represent privileged pharmacophores in drug discovery.[13] In recent years, several bioactive natural products with unsaturated γ-spiroketal-γ-lactone (1,6-dioxaspiro[4.4]non-3-en-2-one) appendage were isolated and have become an important sub-group of spiroketals, which include tuberostemonamide (**78**),[14] massarinoline A (**79**),[15] aphagrandinoid A (**80**),[16]pyrenolide D (**53**),[17] crassalactone D (**81**),[18] levantenolide (**82**),[19] papyracillic acid C (**83**),[19]acutissimatriterpene A , and many others (Figure 2.3).[18,19]

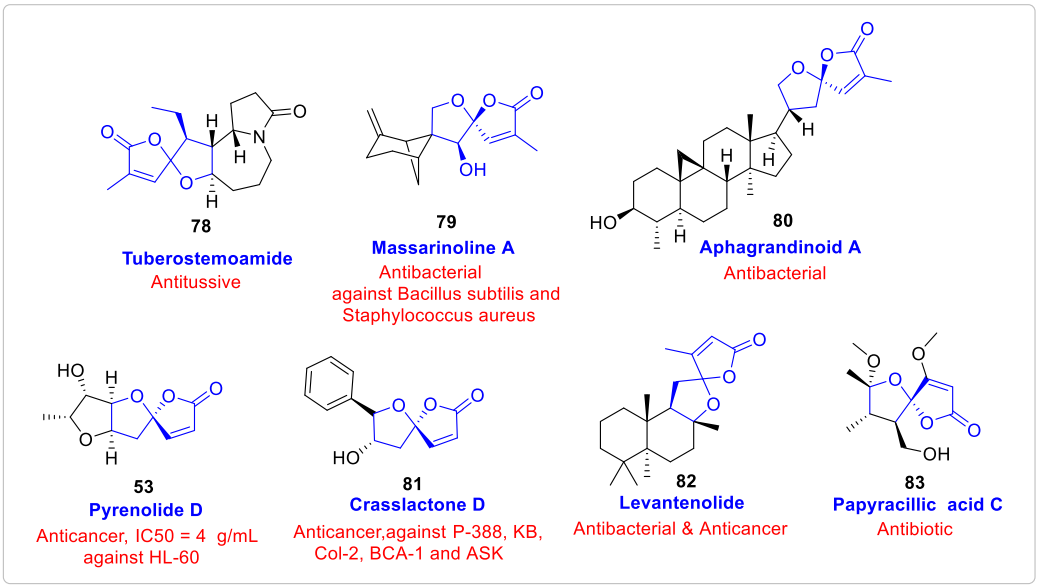


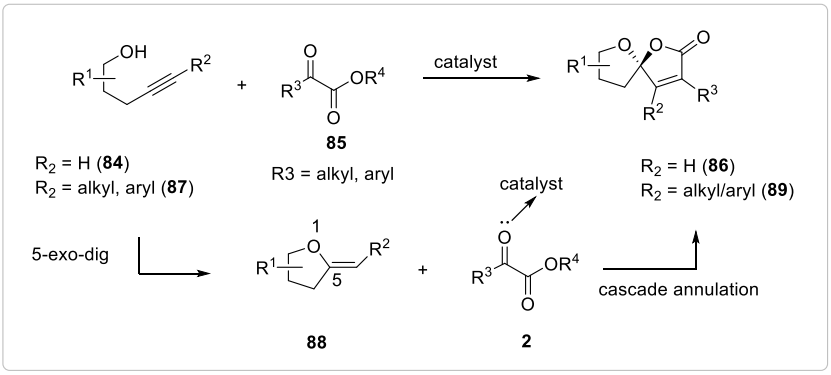
Figure. 2.3. Unsaturated γ-spiroketal-γ-lactone containing bioactive natural products

Despite their potential properties, only a few synthetic methods have been documented in the literature. For instance, Mitsunobu's protocol of photo-oxidation of unprotected pre-functionalized furyl-alkanols, which was further developed by Vassilikogiannakis*et al.*[20] and others.[21] Kitching*et al*. reported a strategy starting from 3-butyn-1-ol via saturated oxa-spirolactone in a total number of 8 steps.[22]In 2006, Shi and co-workers reported using $SnCl_4$ (stoichiometric amount, 40 ^oC) mediated annulation of cyclopropyl-alkyl ketones and α-ketoesters.[8]Few other miscellaneous reports also present in the literature.[22]

All of these approaches had limitations such as usage of pre-functionalized starting materials, protection and deprotection sequence, a stoichiometric amount of Lewis acids and multiple steps. Thus, the development of a new intermolecular approach to unsaturated γ-spiroketal-γ-lactones from easily available fragments is of considerable importance from the point of view of diversity-oriented synthesis.[23]

2.4 Hypothesis

Inspired by the emerging importance of cascade/domino reactions[24] involving alkynols[25,26] and as part of our research interest in Lewis acid-promoted cascade reactions involving alkynols,[27] we herein report a protocol for the construction of unsaturated γ-spiroketal- γ-lactones comprising $Bi(OTf)_3$catalyzed cascade annulation of alkynols (4-pentyn-1-ol derivatives) and α-ketoesters, where hydroalkoxylation of alkynol **84** and/or **87** furnish the exocyclic enol ether **88** via 5-*exo*-dig mode of cyclization, which in the proximal presence of an activated ketoester **85** would undergo an annulation reaction to furnish the desired product **86** and/or **89** in a cascade manner (Scheme 2.10).



Scheme 2.10. Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols and α-ketoesters

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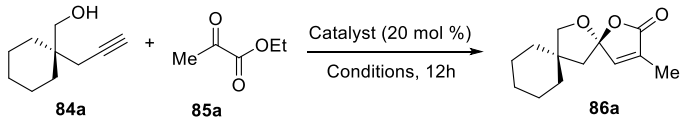
2.5 Results and discussion

To explore the feasibility of this proposed strategy, the reaction between known alkynol **84a** (1.0 eq) and ethyl pyruvate (**85a**, 1.0 eq) with commercially available $Bi(OTf)_3$ (99%, 20 mol %) in anhydrous CH_2Cl_2 at room temperature was performed (Table 1). Gratifyingly, both starting materials were completely consumed in 12 h at room temperature and gave the desired unsaturated γ -spiroketal- γ -lactone **86aa** in 80% yield (entry 1). Reaction in other solvents such as toluene, acetonitrile, and tetrahydrofuran did not improve the yield (entries 2-4).

Notably, various Lewis (entries 5-15) and Brønsted acids (entries 16-18) were also tested in this reaction, where some of them found moderately active and gave 60-70% yields. To our delight, initially identified conditions of 20 mol % $Bi(OTf)_3$ in CH_2Cl_2 at rt were found to produce the best yield of the product **86aa** (entry 1).21 Further tuning of the other parameters like molar ratios of the substrates, catalyst loading and temperature did not lead to any noticeable change in the outcome of the reaction (Table 2.1).[28]

A) Optimization of reaction conditions



84a **85a** **86a** (*racemic*)

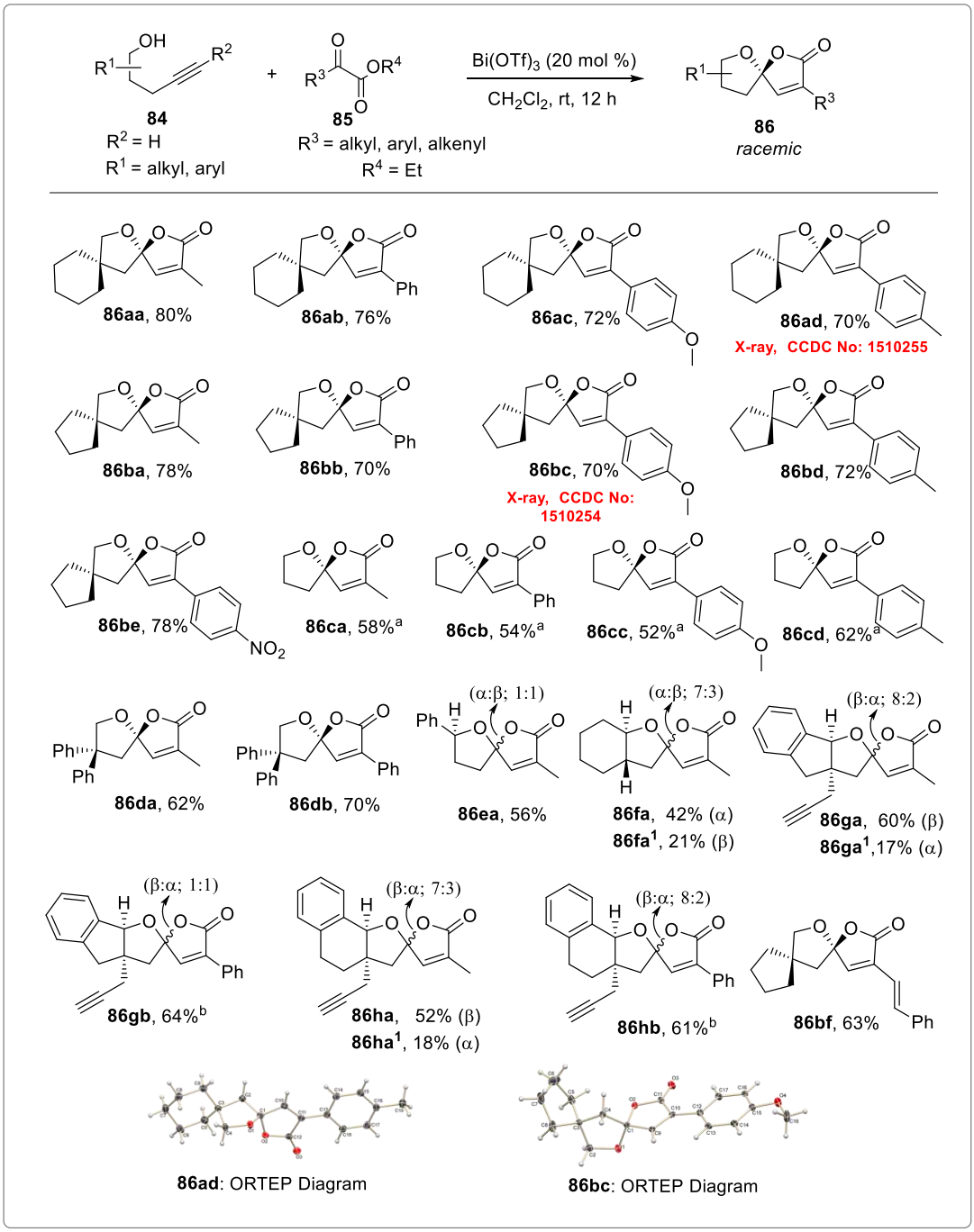
entry	catalyst	solvent	yield (%)[b]
1	$Bi(OTf)_3$	CH_2Cl_2	80
2	$Bi(OTf)_3$	toluene	70
3	$Bi(OTf)_3$	CH_3CN	64
4	$Bi(OTf)_3$	THF	65
5	$Cu(OTf)_2$	CH_2Cl_2	60
6	$Sc(OTf)_3$	CH_2Cl_2	-
7	$Fe(OTf)_2$	CH_2Cl_2	40
8	$In(OTf)_3$	CH_2Cl_2	68
9	$Hg(OTf)_2$	CH_2Cl_2	70
10	$Hg(OTf)_2$	CH_3CN	50
11	$Yb(OTf)_3$	CH_2Cl_2	-
12	$FeCl_3$	CH_3CN	50
13	$FeCl_3$	CH_2Cl_2	-
14	AgOTf	CH_2Cl_2	70
15	AgOTf	THF	60
16	PTSA	CH_3NO_2	-
17	PTSA	THF	62
18	TfOH	CH_2Cl_2	-

Table 2.1. Optimization of reaction conditions

[a]Reaction conditions unless otherwise specified: **84a** (1.0 mmol), **85a** (1.0 mmol), and catalyst (20 mol%) in the indicated solvent (anhydrous) at rt. [b]Isolated yields of **86aa**. rt = room temperature, Tf = triflate (CF_3SO_2), THF = tetrahydrofuran.

B) Scope and generality of method

Substrate scope: with substrates containing *terminal alkynes*



Scheme 2.11. Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (possessing terminal alkyne). [a]48 h (reaction time); [b] inseparable diastereomers.

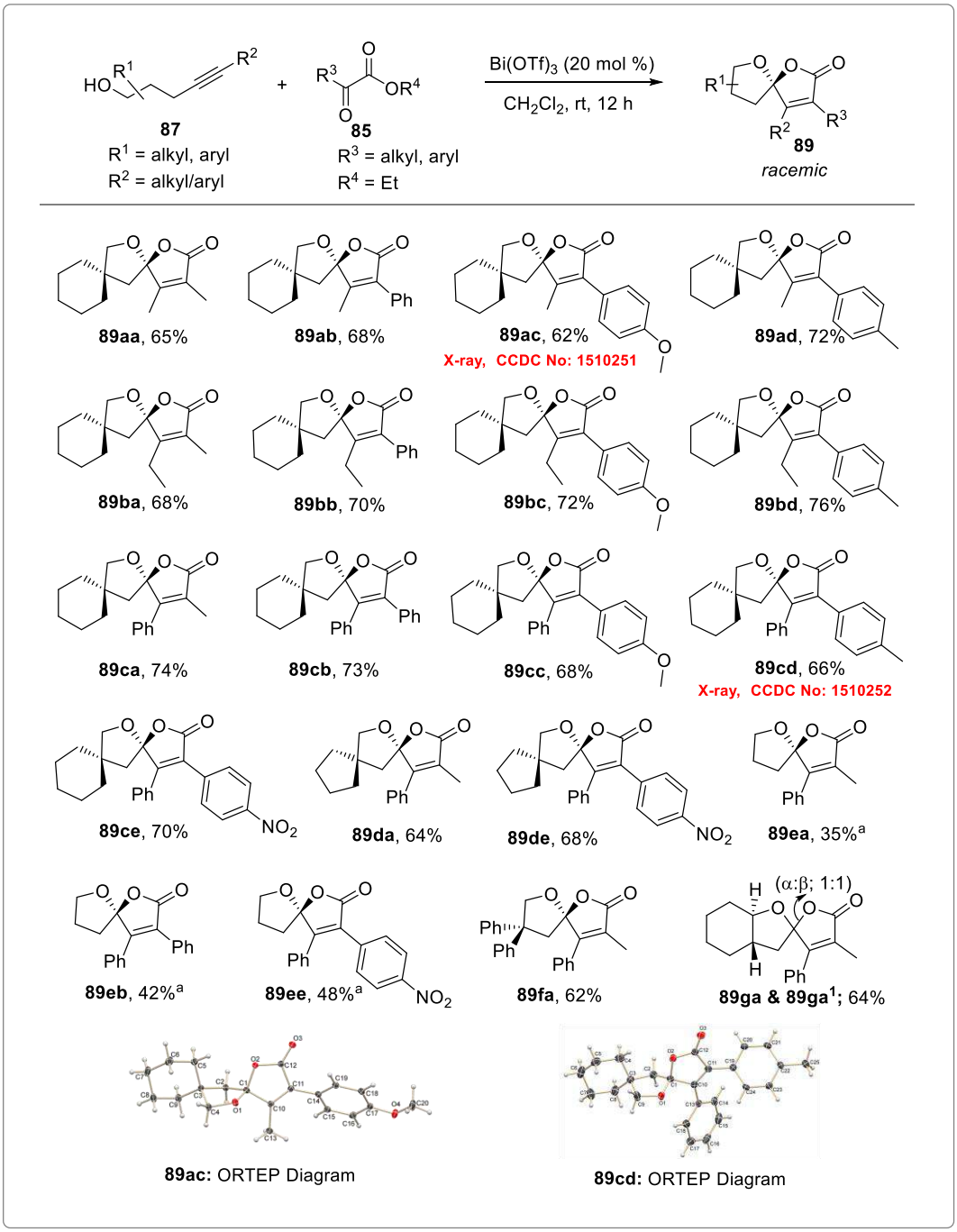
With the optimal conditions in hand, we next investigated the scope of this annulation with respect to the alkynols possessing terminal alkyne functionality and α-ketoesters (Scheme 2.11). The reaction of cyclohexane and cyclopentane fused 4-pentyn-1-ols with several alkyl and aryl α-ketoesters gave corresponding oxa-spirolactones **86aa-be** in good yields (70-80%), which clearly states that the electronic nature of the phenyl substitution of α-ketoesters has a little influence on the outcome. Unsubstituted 4-pentyn-1-ol provided desired products **86ca-cd** in moderate yields of 52-62%. 2,2-Diphenyl substituted alkynol furnished corresponding products **86da** and **86db** in 62% and 70% yield. Alkynol having benzylic-OH group was well tolerated in the reaction with ethylpyruvate and lead to the product **86ea** (dr, 1:1). trans-Cyclohexane fused alkynol possessing two alkyne functionalities gave **86fa** and **86fa**‘ (dr, 7:3). The reaction of indane-derived alkynol with ethylpyruvate gave the corresponding products **86ga** and **86ga‘** (dr, 8:2), whereas ethyl phenylglyoxylate provides **86gb** (dr, 1:1). Tetralin-fused alkynol (having two alkyne functionalities) with ethylpyruvate provided **86ha** and **86ha‘** (dr, 7:3) in good yield, whereas with ethyl phenylglyoxylate gave **86hb** (dr, 8:2). α,β-Unsaturated ketoester also proceeded smoothly and delivered the product **86bf** in a good yield of 63%. The relative stereochemistry of diastereomers was assigned based on NOE analysis. Structures of **86ad** and **86bc** were rigorously confirmed by single-crystal X-ray analysis, all other products were confirmed by analogy (Scheme 2.11).[28]

Substrate scope: with substrates containing *internal alkynes*

Taking our protocol a step further, we examined the reactivity of alkynols possessing internal alkyne functionality under standard reaction conditions. Cyclohexyl and cyclopentyl fused 4-pentyn-1-ols (with alkyl aryl substituents on alkyne termini) successfully reacted with various alkyl and aryl-α-ketoesters, and furnished highly substituted and sterically demanding γ-spiroketal-γ-lactones (**89aa-89de**) in good yields. Phenyl substituted 4-pentyn-1-ol gave products **89ea-89ee** in moderate yields. Triphenyl substituted alkynol led to the product **89fa** in 62% yield. Trans-Cyclohexane fused alkynol furnished **89ga** and **89ga’** (dr, 1:1). Products **89ac** and **89cd** were confirmed by single-crystal X-ray diffraction analysis (Scheme 2.11).[28]

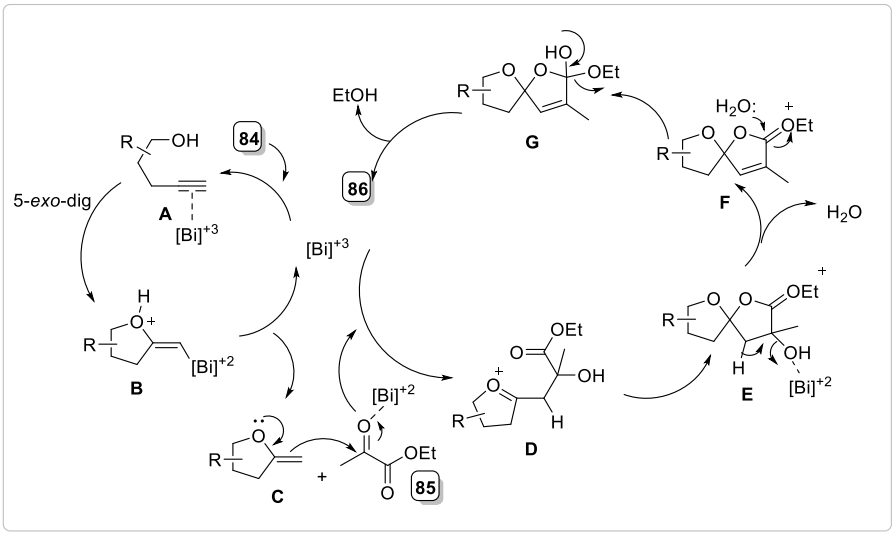
The reactivity of internal alkynols is a little slower than those of the corresponding terminal alkynols. Best yields were observed for α or β-disubstitutedalkynols as substrates than unsubstituted 4-pentyn-1-ols (**86ca**-**86cd** & **86ea**-**86ee**; Scheme 2.11 &

Scheme 2.12) can be attributed by Thorpe-Ingold effect (angle compression).[30] All the 42 examples reported in this work were noteworthy since the presence of α,β - unsaturated lactone functionality provides the platform for later product modification through reduction and oxidation (*vide infra*).



Scheme 2.12. Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (Possessing internal alkyne).[a]48 h (reaction time).

C) Plausible reaction mechanism and supporting experiments



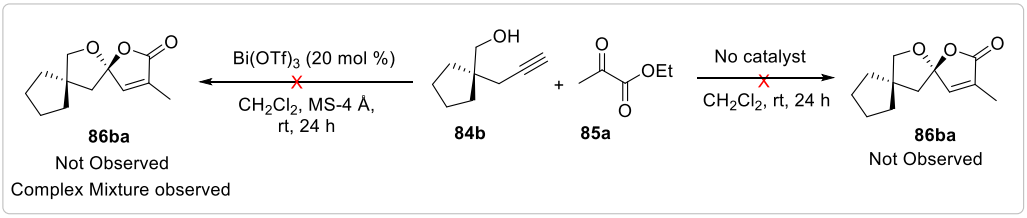
Scheme 2.13. Plausible reaction mechanism

While the precise reaction mechanism requires further studies, a plausible mechanism based on recent reports [26-29] and the results obtained in this work is proposed (Scheme 2.12). Bismuth triflate mediated hydroalkoxylation (5-*exo*-dig; π-activation) of alkynol **84** to give **B** via **A,** followed by proto-debismuthination gives the corresponding enol-ether **C**, which then reacts with the activated (σ-activation) ketone group of α-ketoester **85** to give the oxocarbenium ion intermediate **D**. Intramolecular attack of ester oxygen on to the oxocarbenium ion **D** to give **E** followed by $Bi(OTf)_3$ facilitated release of water from **E** generates the intermediate **F**. Subsequent addition of in situ generated water on to **F** gives the intermediate **G**. Next, the release of EtOH from **G** leads to the formation of unsaturated γ-spiroketal-γ-lactone **86** (Scheme 2.13).

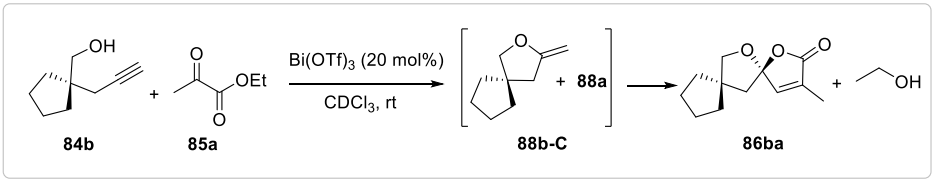
Supporting experiments

To understand this proposed mechanistic pathway, few supporting experiments were performed. The reaction of **84b** with **85a** in the absence of the catalyst failed to give the desired product (Scheme 2.14). The role of the *in situ* released water in the lactone formation step (**E→F→G**) was confirmed by carrying out the reaction in the presence of activated MS-4 Å. Formation of exocyclic-enol ether intermediate (**88b-C**) from **84b** and release of EtOH in the cascade annulation (**G→86**) were established by real-time

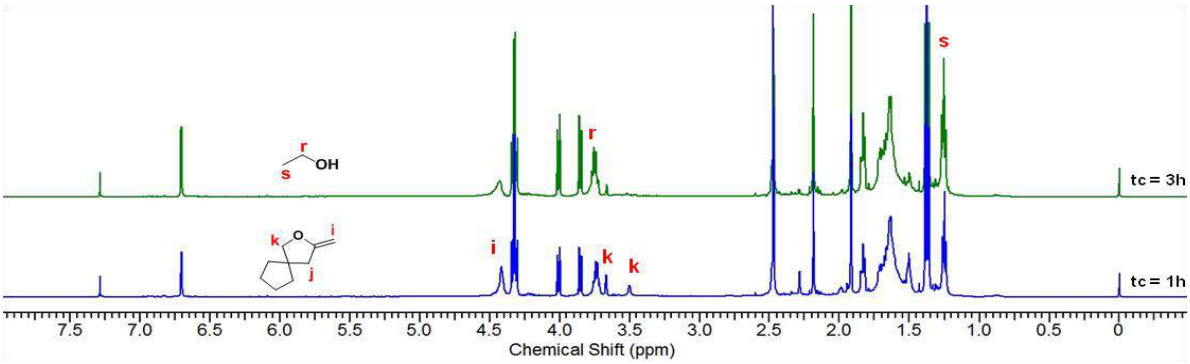
^{1}H NMR analysis (Scheme 2.15),[28] and these observations are consistent with earlier reports by Marks et al.[31] (Schemes 2.14 and 2.15).



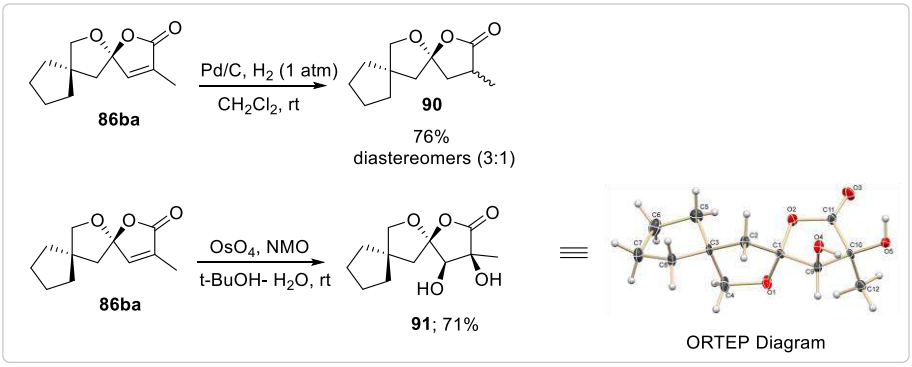
Scheme 2.14. Supporting experiments



Scheme 2.15. Real-time (^{1}H NMR) analysis



2.6 Synthetic utility of the methodology



Scheme 2.16. Synthetic utility

The synthetic utility of this method was further explored by a couple of key transformations. Reduction of unsaturated γ-spiroketal-γ-lactone **86ba** using Pd/C, H_2

(1 atm, balloon) gave the saturated product **90** in 76% yield (*dr*, 3:1). Dihydroxylation of **86ba** with OsO_4-NMO gave the corresponding diol **91** as a single diastereomer, which structure was unambiguously confirmed by single-crystal X-ray analysis (Scheme 2.16).[28]

2.7 Evolution of anti-cancer activity of unsaturated γ-spiroketal-γ-lactones

Many natural products exhibit unsaturated γ-spiroketal-γ-lactoneshows potent anticancer activities on various cancer cell lines. Various synthesized unsaturated γ-spiroketal-γ-lactone evaluated cytotoxic effect on MCF-7 breast cancer cell line were determined using MTT assay at 50µM concentration. Gratifyingly, Compound (**92**), compound (**93**) and compound (**94**) inhibit cell viability of triple negative breast cancer cell line, MDA-MB-231 with estimated IC_{50} of 31.66 µM and 19.54 at 48hrs µM respectively. Moreover, we found **C-92** and **C-93** does not affect the growth of non-cancerous L929 murine normal fibroblast cell line (Figure. 2.4).

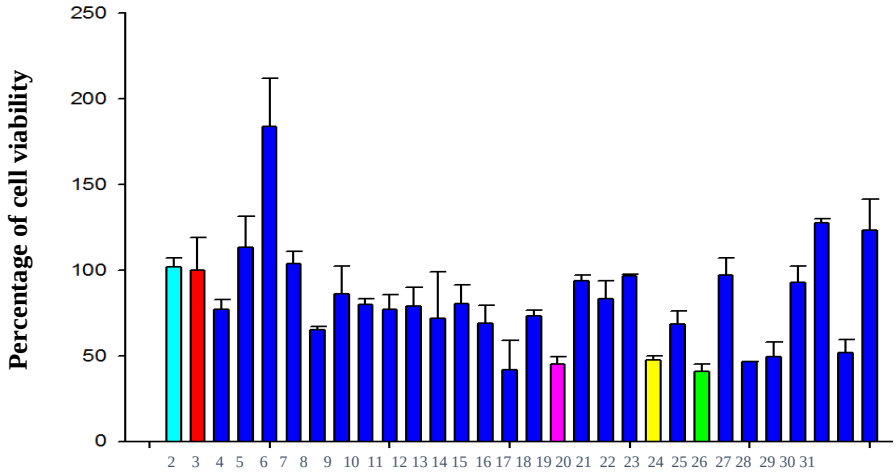


Figure. 2.4. Cytotoxic effect of lactone derivatives on MCF-7 breast cancer cell-line

Compound (**93**) also tested on MDA-MB-231 cancer cell lines and found that Compound (**93**)significantly inhibits the migration of MDA-MB-231 cells at different concentrations such as 6.25 µM, 12.5 µM and 25 µM, determined by wound closure assay (Figure. 2.5).

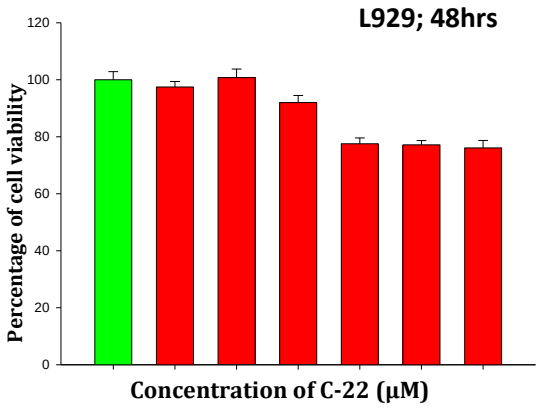


Figure. 2.5. Cytotoxic effect of C-22 on L929 Murine normal fibroblast cell line

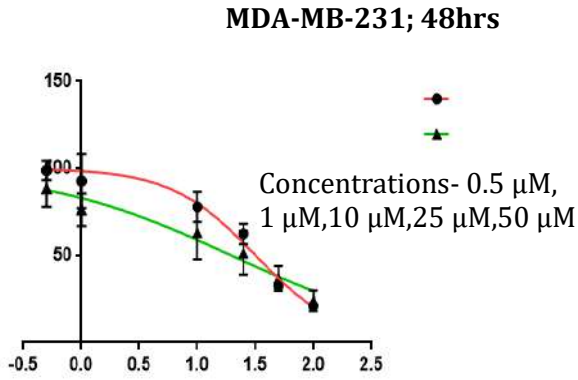


Figure. 2.6. Growth inhibitory effect of C-18 and C-22

Compound (**93**) induces cell cycle arrest by inhibiting cyclin D1 expression in MCF-7 cell line at 12.5 µM and 25 µM, determined by FACS and Immunofluorescence analysis. Compoud-18 significantly inhibits the cancer growth in 4T1 bearing mice model (breast cancer) at 50mg/Kg Bwt (Figure. 2.6).

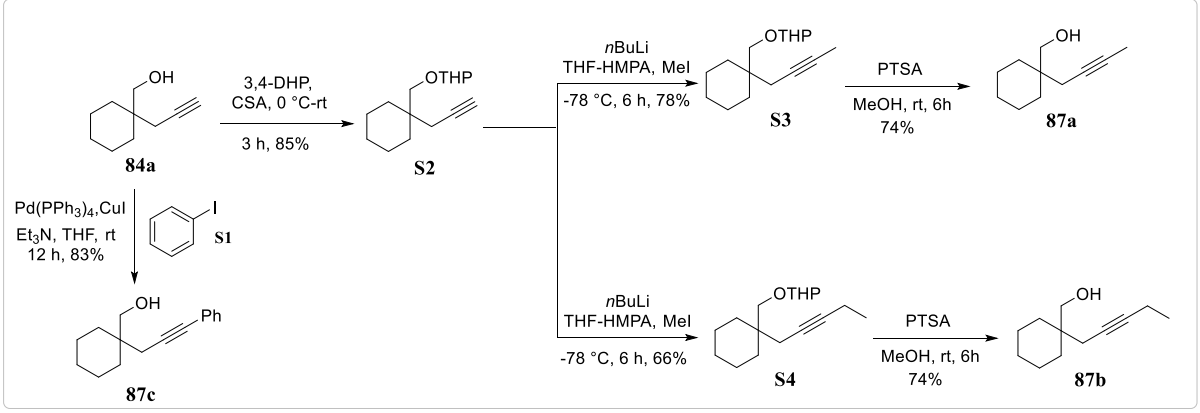
2.8 Conclusion

In conclusion, we have demonstrated a facile and efficient protocol for the synthesis of unsaturated-γ-spiroketal-γ-lactones by employing a $Bi(OTf)_3$ catalyzed cascade annulation of alkynols with α-ketoesters via a dual (π and σ) activation process. Highly sterically demanding products, ambient reaction conditions, a cost-effective catalytic system, good yields, operational simplicity, and atom and step-economy are salient features of this strategy. Synthesized unsaturated γ-spiroketal-γ–lactones were screened for aniticancer activity against various cancer cell lines and found promosing anticancer activity of Compouds 18, 22 and 24. Compound 92 and 93 shows anticancer activity against MDA-MB-231 breast cancer cell line with IC_{50} value 31.66 and 19.54 µM respectively. The application of this method in total synthesis of related biologically active natural products is currently underway in our laboratory and will be reported in due course.

2.9 Experimental procedures

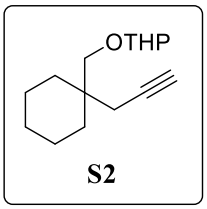
All reactions were performed under argon atmosphere with oven (80 ºC) or flame-dried glassware with septum seal. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under argon atmosphere immediately prior to use. Dichloromethane and acetonitrile were freshly distilled over calcium hydride under argon atmosphere. 30 °C corresponds to the room temperature (rt) of the laboratory when the experiments were carried out. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel.

Synthesis of alkynols:



Scheme 2.17. Synthesis of alkynols **87a, 87b** and **87c**

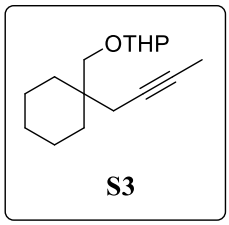
((1-(Prop-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (S2):



To a cold (0 ºC) mixture of (1-(prop-2-yn-1-yl)cyclohexyl) methanol (**84a**) (14 g, 100 mmol) and 3, 4-dihydro-2H-pyran (9.1 mL, 100 mmol) in 30 mL of anhydrous $CH_2Cl_2$was added camphor sulfonic acid(CSA, 2 g, 10 mmol). The reaction mixture was warmed slowly to rt and stirred for 3 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford((1-(prop-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (**S2**), (18.5 g, 85%) as colourless liquid.

2-((1-(But-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (S3):

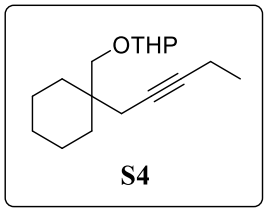
To a solution of ((1-(prop-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (**S2)** (1 g, 4.2 mmol) in anhydrous THF, *n*BuLi (1.6M in hexane, 8.1 mL, 5.1 mmol) was added at -



S3

78 °C and stirred this reaction mixture for 45 min at -78 °C under argon atmosphere.Then the solution of CH_3I (1.8 mL, 12.7 mmol) in anhydrous HMPA (1 mL) was added at same temperature and resulting reaction mixture was slowly warmed to room temperature and further stirred for 6 h.Then the reaction mixture was quenched with saturated NH_4Cl solution at 0 °Cand extracted with ethyl acetate (3x25 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Crude product was purified by silica gel chromatography (SiO_2, 2% EtOAc/hexanes) to afford 2-((1-(but-2-yn-1-yl)cyclohexyl) methanol (**S3)** (1.23 g, 78%) as a colourless liquid.

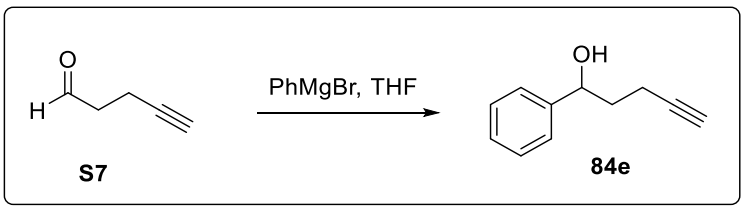
2-((1-(Pent-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (S4):



S4

To a solution of ((1-(prop-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (**S2**)(1.5 g, 6.3 mmol) in anhydrous THF, *n*BuLi (1.6M in hexane, 5 mL, 7.6 mmol) was added, and stirred this reaction mixture for 45 min at -78°C under argon atmosphere.Then the solution of EtI(1.56 mL, 1.9 mmol) in anhydrous HMPA (1 mL) was added at -78 °C and resulting reaction mixture was stirred for 6 h at rt.The reaction mixture was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate (2x25 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, crude product was purified by silica gel column chromatography (SiO_2, 10% EtOAc/hexanes) to give 2-((1-(pent-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (**S4**)(1.1g, 66%) as a colourless liquid.

1-Phenylpent-4-yn-1-ol (84e):

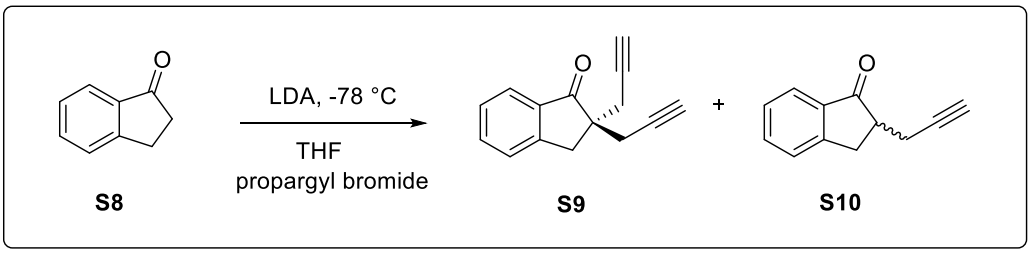


S7 **84e**

Compound **1e** was prepared using known procedure.[29]PhMgBr (1.0 M in THF, 18 mL, 1.82 mmol) was added drop wise to a solution of pent-4-ynal (**S7**) (0.5 g, 0.605 mmol) in THF (20 mL) at room temperature, the reaction mixture was stirred at rt for 2 h. Reaction was quenched by adding ice cold water (10 mL), then neutralized with 2N HCl (20 mL), extracted with EtOAc (20 mL), which was washed once with 2N HCl (20 mL) and brine solution (20

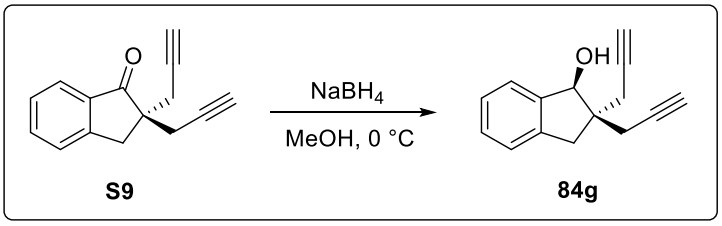
mL). Organic layer was dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure afforded the desired product 1-phenylpent-4-yn-1-ol (**84e**) (0.72 g, 70 %).

2,2-Di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (S9) and 2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (S10)



To a flame dried (100 mL) two neck round bottom flask, anhydrous THF (20 mL) was added under argon atmosphere and cooled it to 0 °C, to this diisopropylamine (0.42 mL, 4.16 mmol) followed by*n*-butyllithium (1.6 M in hexanes, 2.837 mL,) was added drop wise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added 1-indanone (**S8**) (0.5 g, 3.78mmol) in THF (20 mL) and stirred the reaction mixture at -78 °C for 30 min, then warmed to 0 °C and stirred for another 30 min. Reaction mixture was cooled back to -78 °C and propargyl bromide (80% in toluene, 0.2 mL, 3.78 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and warmed to 25 °C and stirred for overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3x25 mL), combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford 2,2-di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (**S9**)(0.2 g, 25%) and (**S10**) 2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (0.64 g, 42%).

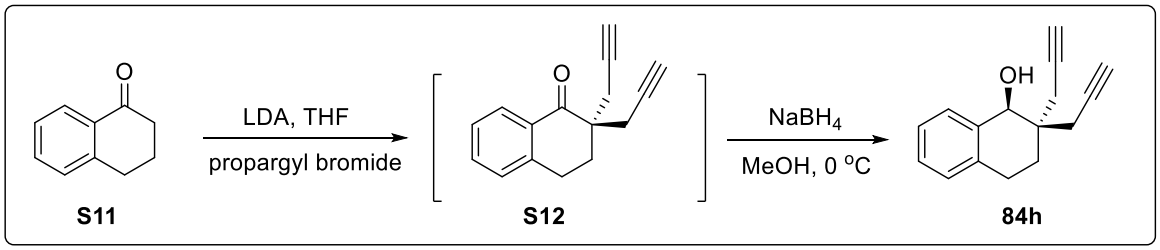
2,2-Di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-ol (84g):



To a solution of 2,2-di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (**S9**) (0.13 g 0.66 mmol) in methanol (3 mL), sodium borohydride (0.015 g, 0.4 mmol) was slowly added

at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then for 2.5 h at room temperature, after which the solvent was evaporated under reduced pressure. Aqueous NH_4Cl solution (5 mL) was added to the resulting suspension, and then extracted with EtOAc (3×5 mL). Organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 6% EtOAc/hexanes) to afford 2,2-di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-ol **(84g)**(0.12 g, 87%) as a colourless liquid.

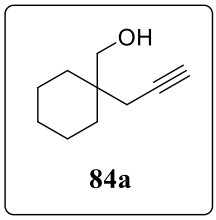
2,2-Di(prop-2-yn-1-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (84h)



To a flame dried (100 mL) two neck round bottom flask, anhydrous THF (50 mL) was added under argon atmosphere and cooled it to 0 °C, to this diisopropylamine (3.16 mL, 22.2mmol) followed by*n*-butyllithium (1.6 M in hexanes, 12.82 mL,) was added drop wise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added 1-tetralone (**S11**) (2.5 g, 17.1 mmol) in THF (10 mL) and stirred the reaction mixture at -78 °C for 30 min, then warmed to 0 °C and stirred for another 30 min. Reaction mixture was cooled back to -78 °C and propargyl bromide (80% in toluene, 1.2 mL, 17.1 mmol)was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and warmed to 25 °C and stirred for overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (4x50 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give the crude product **S12** in (1 g, 26% yield), which was subjected to next reaction without further purification.To a solution of **S12**(0.3 g, 1.35 mmol) in methanol (10 mL), sodium borohydride (0.05 g, 1.35 mmol)was slowly added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then for 2.5 h at room temperature, after which the solvent was evaporated under reduced pressure. Aqueous NH_4Cl solution (5 mL) was added to the resulting suspension, and then extracted with EtOAc (3×10 mL). Organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the

solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford 2,2-di(prop-2-yn-1-yl)-1,2,3,4-tetrahydronaphthalen-1-ol **(84h)**(0.28 g, 92%) as a solidas a colourless liquid.

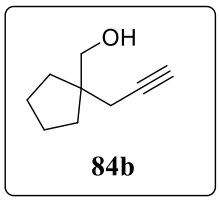
(1-(Prop-2-yn-1-yl) cyclohexyl) methanol (84a):



84a

(1-(prop-2-yn-1-yl) cyclohexyl) methanol (**84a**) was prepared using known procedure.[32]

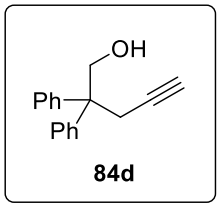
(1-(Prop-2-yn-1-yl) cyclopentyl) methanol (84b):



84b

(1-(prop-2-yn-1-yl) cyclopentyl) methanol (**84b**)was prepared using known procedure.[32]

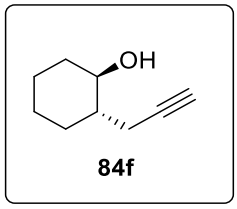
2, 2-Diphenylpent-4-yn-1-ol (84d):



84d

Compound (**1d)** was prepared using known procedure.[33]

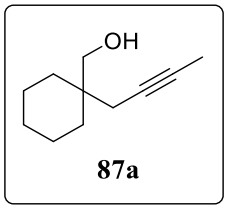
2-(Prop-2-yn-1-yl)cyclohexan-1-ol (84f):



84f

Compound **84f** was prepared using analogous literature procedure[34]

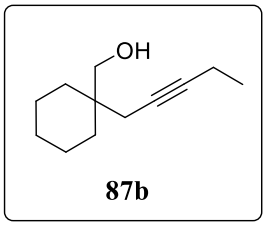
(1-(But-2-yn-1-yl) cyclohexyl) methanol (87a):



87a

To a solution of 2-((1-(but-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (**S3)** (1 g, 4 mmol) in methanol was added *p*-toluenesulfonicacid (PTSA, 0.075 g, 0.4 mmol) at 0°C and then it was slowly warmed to rt.The resulting reaction mixture was stirred for 6 h at rt, then the methanol was evaporated under reduced pressure, diluted with ethyl acetate and quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3x25 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filtered using sintered funnel, concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (SiO_2, 10% EtOAc/hexanes) to afford (1-(but-2-yn-1-yl) cyclohexyl) methanol (**87a**),(0.59 g, 74%) as a colourless liquid.

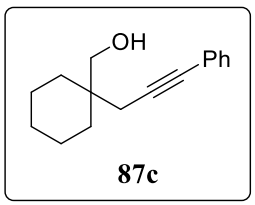
(1-(Pent-2-yn-1-yl) cyclohexyl) methanol (87b):



87b

To a solution of 2-((1-(pent-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2H-pyran (**S4**)(1.1 g, 4.16mmol)in methanol was added PTSA at0 °C and then it was warmed to room temperature, the resulting reaction mixture was stirred at rt for 6 h. Then methanol was evaporated under reduced pressure, diluted with ethyl acetate (25 mL) and washed with saturated solution of sodium bicarbonate and brine solution. The residue was dried over anhydrous sodium sulphate, filtered using sintered funnel, concentrated under reduced pressure, the crude product was purified by silica gel column chromatography (SiO_2, 10% EtOAc/hexanes) to afford(1-(pent-2-yn-1-yl) cyclohexyl) methanol **87b**(0.59g, 78%) as a colourless liquid.

(1-(3-Phenylprop-2-yn-1-yl) cyclohexyl) methanol (87c):

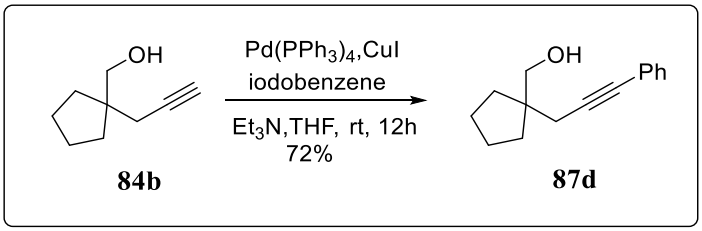


87c

(1-(3-phenylprop-2-yn-1-yl) cyclohexyl) methanol (**87c)** was prepared according to the literature.[2]$Pd(PPh_3)_4$ (0.023 g, 0.019 mmol) and CuI (0.08 g, 0.039 mmol) were added to the solution of iodobenzene (**S1**) (0.45 ml, 3.94 mmol) and (1-(prop-2-yn-1-yl) cyclohexyl) methanol (0.3 g, 1.97 mmol) (**1a)** intriethylamine (2.76 mL, 19.7 mmol) and THF (10 mL) under argon atmosphere. The reaction mixture was stirred at rt for 12 h. The mixture was filtered and the

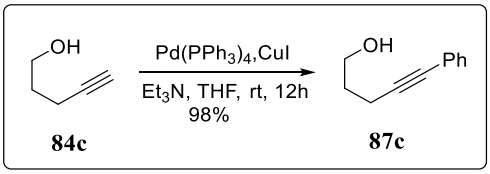
filtrate was concentrated under reduced pressure. Purified by silica gel column chromatography (10% EtOAc/hexanes) to afford the (1-(3-phenylprop-2-yn-1-yl) cyclohexyl) methanol (**87c)** as a brown oil (0.27 g, 60%).

(1-(3-Phenylprop-2-yn-1-yl)cyclopentyl)methanol (87d):



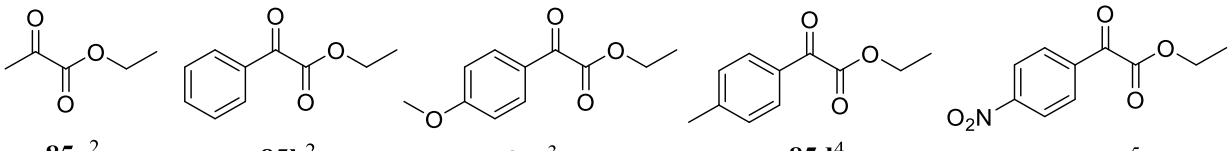
(1-(3-phenylprop-2-yn-1- cyclopentyl) methanol (**87d)** was prepared according to the literature procedure.[32]$Pd(PPh_3)_4$ (0.042 g, 0.036 mmol) and CuI (0.014 g, 0.072 mmol) were added to the solution of iodobenzene (**S1**) (0.82 mL, 7.24 mmol) and (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**84b**) (0.5 g, 3.62 mmol) in triethylamine (5 mL, 36.2 mmol) and THF (10 mL) under argon atmosphere. The reaction mixture was stirred at rt for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. Purified by silica gel column chromatography (10% EtOAc/hexanes) to afford (1-(3-phenylprop-2-yn-1-cyclopentyl) methanol (**87d)** (0.5 g, 64%) as brownish oil.

5-Phenylpent-4-yn-1-ol (87e):



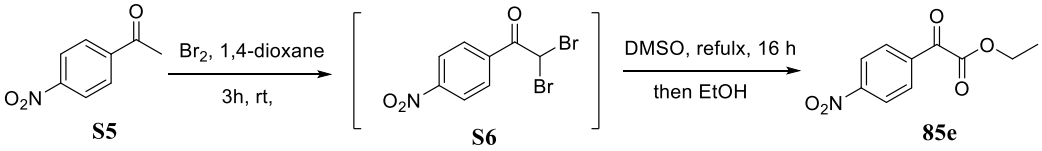
5-phenylpent-4-yn-1-ol (**87e**) was prepared according to the literature procedure.[1] $Pd(PPh_3)_4$ (0.137 g, 0.12 mmol) and CuI (0.045 g, 0.24mmol) were added to the solution of iodobenzene (**S1**) (2.7mL, 23.77 mmol) and pent-4-yn-1-ol (**84c**) (1 g, 11.89 mmol) in triethylamine (16 mL, 118.9 mmol) and anhydrous THF (15 mL) under argon atmosphere. The reaction mixture was stirred at rt for 6 h. Then the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 5-phenylpent-4-yn-1-ol (**87e**) (1.9g, 98%) brown oil.

Synthesis of α-ketoesters:[34,35,36]



85a[2] **85b**[2] **85c**[3] **85d**[4] **85e**[5]

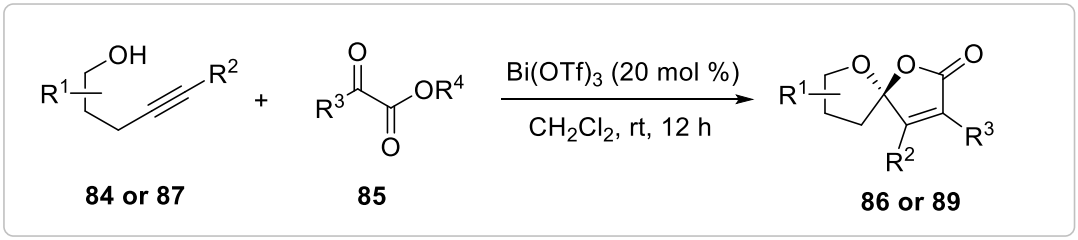
Ethyl 2-(4-nitrophenyl)-2-oxoacetate (85e)[37]:



S5 **S6** **85e**

Bromine (3.51 mL, 68mmol) was added dropwise over 20 min to anhydrous 1,4-dioxane (20 mL) at 25–30 °C under argon atmosphere and the mixture was kept under these conditions for 30 min. A solution of 1-(4-nitrophenyl)ethan-1-one(**S5**) (5 g, 34mmol) in dioxane (20 mL) was added and the mixture was stirred for another 3 h. The reaction was then quenched with ice-cold water (400 mL, 10 volumes with respect to 1,4-dioxane) and the solid was filtered off and washed with chilled hexane to give 2,2-dibromo-1-(4-nitrophenyl)ethan-1-one (**S6**), which was used in the next step without further purification. The crude **S6**was dissolved in anhydrous DMSO (60 mL) under argon. The solution was then slowly heated to 70–75 °C and stirred at this temperature for 16 h. The mixture was then cooled to rt, then EtOH (3.97 mL, 0.6 mol) was added, and the mixture was stirred for 2 h at rt. The mixture was then diluted with H_2O (100 mL) and extracted with EtOAc (4 × 30 mL). The combined organic layers were washed successively with water (3×30 mL) and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The pure product was isolated by silica gel column chromatography (12% EtOAc/hexanes) to give 3.21 g (47%) of **85e** as a yellow oil.

General Procedure for the synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols and α-ketoesters.

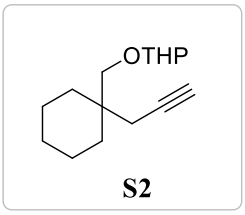


84 or 87 **85** **86 or 89**

To the alkynol **84** (0.66 mmol)/or **87** (0.66 mmol) and α-ketoester **85** (0.66 mmol) in 5 mL of anhydrous CH_2Cl_2 in a dry round bottom flask, was added $Bi(OTf)_3$ (0.13 mmol) under argon atmosphere at room temperature and stirred the reaction mixture at room temperature for mentioned reaction time. After completion of reaction (typically after 12-48 h, monitored by TLC, visualized using UV, anisaldehyde, and KMnO4 staining solutions), the reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) then extracted with CH_2Cl_2 (2x10 mL).The combined organic layers were dried over anhydrous sodium sulphate and filtered through sintered glass funnel. The residue was concentrated under reduced pressure and purified by silica gel column chromatography (100-200 mesh) to afford the corresponding unsaturated γ-spiroketal-γ-lactone **86** or **89**.

2.10 Characterization data

Compound S_2:



S2

Colorless liquid; Yield = 85%

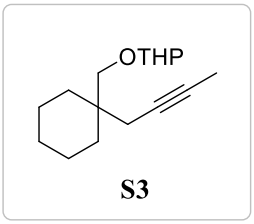
R_f = 0.6 (SiO_2, 10%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.64 - 4.57 (m, 1H), 3.96 - 3.85 (m, 1H), 3.65 (d, *J* = 9.8 Hz, 1H), 3.52 (d, *J* = 11.6 Hz, 1H), 3.21 (d, *J* = 9.2 Hz, 1H), 2.35 - 2.23 (m, 2H), 1.80 (t, *J* = 2.4 Hz, 3H), 1.84 - 1.79 (m, 1H), 1.74 -1.51 (m, 5H), 1.5 - 1.36 (m, 10H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 98.8, 82.2, 72.1, 69.9, 61.7, 36.9, 32.3, 32.1, 30.6, 26.1, 25.6, 21.6, 19.2

HRMS (ESI): *m/z* calcd for $C_{15}H_{25}O_2[M+H]^+$237.1849, found 237.1846.

Compound S_3:



S3

Colorless liquid: Yield = 78%

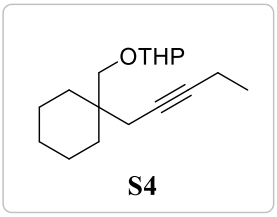
R_f = 0.4 (SiO_2, 10%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):δ 4.62 (t, *J* = 3.43 Hz, 1H), 3.94 - 3.87 (m, 1H), 3.66 (d, *J* = 9.54 Hz, 1H), 3.56 - 3.49 (m, 1H), 3.22 (d, *J* = 9.16 Hz, 1H), 2.24 - 2.2 (m, 2H), 1.8 (t, *J* = 2.67 Hz, 3H), 1.89 - 1.37 (m, 16H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 98.9, 72.3, 61.6, 37.1, 32.3, 32.1, 30.6, 26.2, 25.9, 25.6, 21.7, 19.2, 3.5

HRMS (ESI): *m/z* calcd for $C_{16}H_{27}O_2$ $[M+H]^+$251.2006, found 251.2001.

Compound S_4:



S4

Colorless liquid: Yield = 66%

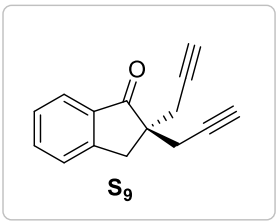
R_f = 0.45 (SiO_2, 10%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):δ 4.60 (m, 1H), 3.95 - 3.79 (m, 1H), 3.64 (d, *J* = 9.8 Hz, 1H), 3.56-3.44 (m, 1H), 3.2 (d, *J* = 9.8 Hz, 1H), 2.25 - 2.2 (m, 2H), 2.2-2.11 (m, 2 H), 1.89-1.36 (m, 16H), 1.12 (t, *J* = 7.32 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ 98.8, 83.3, 76.9, 72.3, 61.5, 37.0, 32.3, 32.1, 30.6, 26.3, 25.9, 25.6, 21.7, 19.2, 14.5, 12.5

HRMS (ESI): *m/z* calcd for $C_{17}H_{29}O_2$ $[M+H]^+$ 265.2162, found 265.2161.

Compound S_9:



S_9

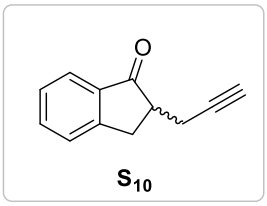
Colorless liquid: Yield = 25%

R_f = 0.6 (SiO_2, 10%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.69-7.58 (m, 1H), 7.53-7.45 (m, 1H), 7.44-7.34 (m, 1H), 3.32 (s, 2H), 2.71-2.44 (m, 4H), 1.88 (t, *J* = 2.7 Hz, 2H)

HRMS (ESI): *m/z* calcd for $C_{15}H_{12}NaO$ $[M+Na]^+$ 231.0780, found 231.0774.

Compound S_{10}:



S_{10}

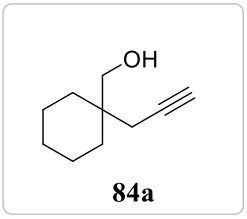
Colorless liquid: Yield = 42%

R_f = 0.59 (SiO_2, 10%EtOAc/hexanes)

^{1}HNMR ($CDCl_3$, 500MHz): δ 7.76 (d, *J* = 7.3Hz, 1H), 7.60 (t, *J* = 7.3Hz, 1H), 7.49 (d, *J* = 7.3Hz, 1H), 7.37 (t, *J* = 7.6Hz, 1H), 3.40 (dd, *J* = 17.7, 8.54Hz, 1H), 3.10 (dd, *J* = 17.1, 4.3Hz, 1H), 2.89-2.84 (m, 1H), 2.81-2.74 (m, 1H), 2.54 (ddd, *J* = 16.4, 7.9, 2.4 Hz, 1H),1.90 (t, *J* = 2.7Hz, 1H)

HRMS (ESI): *m/z* calcd for $C_{12}H_{11}O$ $[M+H]^+$171.0804, found 171.0799.

Compound 84a:



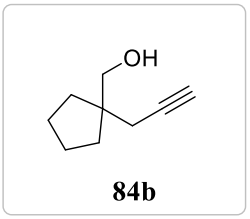
84a

Colorless oil; Yield = 79%

R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

Spectral parameters are in good accordance with the data from the literature. [1]

Compound 84b:



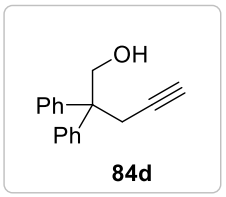
84b

Colorless liquid; Yield = 76%

R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

Spectral parameters are in good accordance with the data from the literature. [1]

Compound 84d:



84d

Solid: Yield = 82%

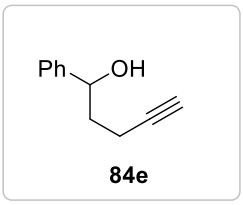
R_f= 0.6 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500MHz):δ 7.33-7.27 (m, 4H), 7.25-7.20 (m, 6H), 4.30 (s, 2H), 3.08 (d, *J* = 2.29 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H)

^{13}C NMR ($CDCl_3$, 126 MHz):δ 144. 4, 128.9, 128.02, 126.7, 81.4, 71.5, 68.3, 51.5, 27.4

HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O$ $[M+H]^+$ 237.1274, found 237.1274.

Compound 84e:



84e

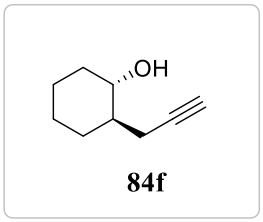
Brown liquid: Yield = 70%

R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 200 MHz):δ 7.45-7.11 (m, 5H), 4.77-4.64 (m, 1H), 2.96 (d, *J* = 3.66 Hz, 1H), 2.36-2.06 (m, 2H), 2.03-1.66 (m, 3H)

HRMS (ESI): *m/z* calcd for $C_{11}H_{13}O$ $[M+H]^+$ 161.0963, found 161.0961.

Compound 84f:



84f

Yellow oil: Yield = 71%

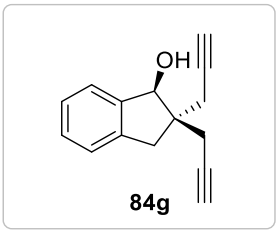
R_f= 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.38 (td, *J* = 9.9, 4.4 Hz, 1H), 2.50-2.42 (m, 1H), 2.32 (ddd, *J* = 16.8,6.9, 2.7 Hz, 1H), 2.03-1.94 (m, 3H), 1.91-1.84 (m, 1H), 1.80-1.65 (m, 2H), 1.38-1.49 (m, 1H), 1.30-1.15 (m, 4H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 83.0, 73.5, 69.7, 43.9, 35.5, 30.3, 25.4, 24.9, 21.8

HRMS (ESI): *m/z* calcd for C9H15O $[M+H]^+$ 139.1117, found 139.1114.

Compound 84g:



84g

Colorless liquid: Yield = 87%

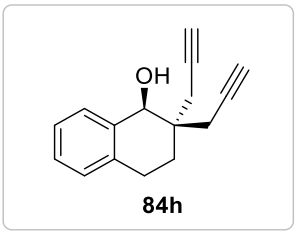
R_f= 0.4 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500MHz): δ 7.46-7.36 (m, 1H), 7.32-7.22 (m, 3H), 5.13 (s, 1H), 3.09 (d, *J*=15.9Hz, 1H), 2.92 (d, *J*=15.9Hz, 1H), 2.66 (dd, *J*=17.1, 2.4Hz, 1H), 2.62-2.52 (m, 2H), 2.44 (dd, *J*=17.1,2.4Hz, 1H), 2.28 (br.s., 1H), 2.12 (t, *J*= 2.4Hz, 1H), 2.05 (t, *J*=2.7Hz, 1H)

^{13}CNMR($CDCl_3$, 126 MHz): δ 142.8,140.5,128.6, 127.1, 125.2, 124.7, 81.9, 81.6, 80.7, 71.4, 70.6, 50.0, 40.1, 26.0, 22.1

HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O$ $[M+H]^+$ 211.1117, found 211.1119.

Compound 84h:



84h

Colorless liquid: Yield = 92%

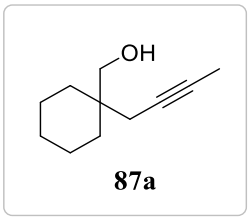
R_f= 0.35 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.40 (m, 1H), 7.26-7.20 (m, 2H), 7.17-7.11 (m, 1H), 4.68 (d, *J*=5.3Hz, 1H), 2.92-2.76 (m, 2H), 2.44 (ABq, *J*=2.2Hz, 16.7Hz, 2H), 2.43 (ABq, *J*=17.1,2.2Hz, 2H), 2.15 (d, *J*=5.7Hz, 1H), 2.09 (t, *J*=2.7Hz, 1H), 2.06 (t, *J*=2.7Hz,1H), 1.98-1.90 (m,1H), 1.90-1.83 (m,1H)

^{13}CNMR($CDCl_3$, 126 MHz): δ136.7,135.7,129.4,128.9,127.9,126.5,81.1, 80.8, 72.6, 71.0, 70.9, 39.9, 26.6, 25.4, 23.8, 23.2

HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O$ $[M+H]^+$ 225.1274, found 225.1268.

Compound 87a:



87a

Colorless liquid: Yield = 74%

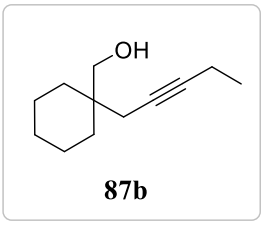
R_f= 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):δ 3.54 (s, 2 H), 2.22-2.15 (m, 2 H), 1.82 (br. s., 1H), 1.8 (t, *J* = 2.44 Hz, 3H), 1.53 - 1.32 (m, 10 H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 77.9, 76.4, 69.1, 37.7, 32.0, 26.2, 25.7, 21.6, 3.5

HRMS (ESI): *m/z* calcd for $C_{11}H_{19}O$ $[M+H]^+$ 167.2617, found 167.2619.

Compound 87b:



87b

Colorless liquid: Yield = 78%

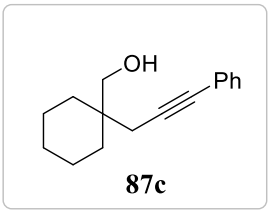
R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):δ 3.53 (s, 2H), 2.24 - 2.11 (m, 4H), 1.85 (br. s., 1H), 1.51 - 1.32 (m, 10H), 1.12 (t, *J*= 7.32 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 84.2, 76.6, 69.2, 37.6, 32.0, 26.2, 25.8, 21.6, 14.3, 12.4

HRMS (ESI): m/z calcd for $C_{12}H_{20}ONa$ $[M+H]^+$203.1406, found 203.1405.

Compound 87c:



87c

Brown oil: Yield = 60%

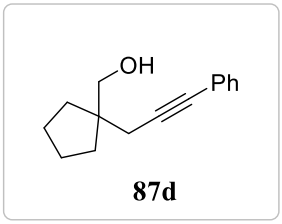
R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.36 (m, 2H),7.36-7.22 (m, 3H), 3.62 (s, 2H), 2.49 (s, 2H), 1.92 (br. s., 1H), 1.61 - 1.34 (m, 10H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 131.6, 128.2, 127.6, 123.8, 87.6, 82.8, 68.7, 38.2, 32.0, 26.2, 26.1, 21.6

HRMS (ESI): *m/z* calcd for $C_{16}H_{21}O$ $[M+H]^+$ 229.1587, found 229.1586.

Compound 87d:



87d

Brown oil: Yield = 64%

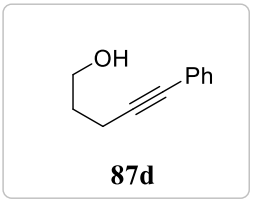
R_f= 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.34 (m, 2H), 7.32 - 7.18 (m, 3H), 3.57 (s, 2H), 2.50 (s, 2H), 1.82-1.45 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 131.6, 128.2, 127.7, 123.8, 88.5, 81.7, 69.1, 47.6, 34.3, 27.7, 25.3

HRMS (ESI): *m/z* calcd for $C_{15}H_{19}O$ $[M+H]^+$215.1430, found 215.1426.

Compound 87e:



87d

Brown oil: Yield = 98%

R_f= 0.4 (SiO_2, 20%EtOAc/hexanes)

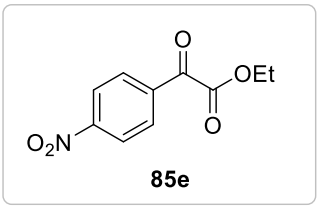
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.38 (m, 2H), 7.34-7.25 (m, 3H), 3.89-3.68 (m, 2H), 2.59-2.51 (m, 2H), 2.1 (br. s., 1H), 1.93-1.82 (m, 2H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.3, 127.7, 123.8, 89.4, 81.1, 61.7, 61.6, 31.4, 16.0

HRMS (ESI): *m/z* calcd for $C_{11}H_{13}O$ $[M+H]^+$ 161.0961, found 161.0958.

Synthesis of α-ketoesters-

Compound 85e:



85e

Yellow oil: Yield = 47%

R_f= 0.6(SiO_2, 20%EtOAc/hexanes)

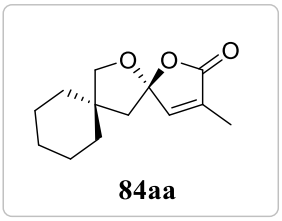
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J*=8.55 Hz, 2H), 8.21 (d, *J*= 8.55 Hz, 2H), 4.47 (q, *J*=7.32 Hz, 2H), 1.43 (t, *J*= 7.32 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 184.2, 162.3, 151.1, 137.0, 131.2, 123.9, 63.0, 14.0

HRMS (ESI): *m/z* calcd for $C_{10}H_{10}O_5N$ $[M+H]^+$ 224.0553, found 224.0549.

Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (possessing terminal alkynols)

Compound 84aa



84aa

Yellow liquid: Yield = 80%

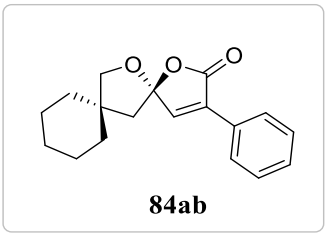
R_f = 0.6(SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$,400 MHz): δ 6.74-6.65 (m, 1H), 3.95 (d, *J* = 8.8 Hz, 1H), 3.86 (d, *J* = 8.3 Hz, 1H), 2.12 (d, *J* = 13.7 Hz, 1H), 2.01 (d, *J* = 14.2 Hz, 1H), 1.91 (d, *J* = 0.98 Hz, 3H), 1.77-1.64 (m, 2H), 1.57-1.36 (m, 8H)

^{13}C NMR ($CDCl_3$,101 MHz): δ 171.6, 145.1, 132.5, 113.2, 80.4, 47.1, 43.6, 37.4, 35.5, 25.5, 23.8, 23.7, 10.4

HRMS (ESI): *m/z* calcd for $C_{13}H_{19}O_3$ $[M+H]^+$ 223.1329, found 223.1326.

Compound 84ab:



84ab

White crystalline solid: Yield = 76%

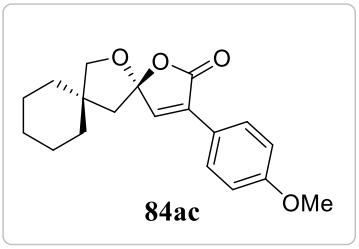
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.89-7.79 (m, 2H), 7.42 (d, *J* = 3.7 Hz, 3H), 7.18 (s, 1H), 4.03 (d, *J* = 7.9 Hz, 1H), 3.94 (d, *J* = 8.5 Hz, 1H), 2.20 (dd, *J* = 36.01, 13.4 Hz, 2H), 1.81-1.69 (m, 2H), 1.62-1.38 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.3, 143.7, 133.6, 129.7, 129.0, 128.7, 127.5, 112.4, 80.5, 47.4, 43.8, 37.4, 35.5, 25.6, 23.9, 23.8

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_3$ $[M+H]^+$285.1485, found 285.1483.

Compound 84ac:



84ac

White Solid: Yield = 72%

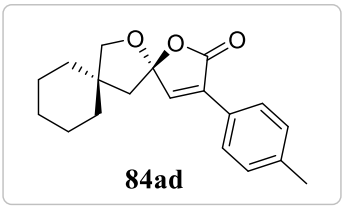
R_f= 0.75 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.05 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.01 (d, *J* = 8.3 Hz, 1H), 3.92 (d, *J* =8.3 Hz, 1H), 3.84 (s, 3H), 2.16 (dd, *J* = 38.15, 13.7 Hz, 2H), 1.77-1.69 (m, 2H), 1.59-1.40 (m, 8H).

^{13}C NMR ($CDCl_3$,101 MHz): δ 169.6, 160.7, 141.3, 132.9, 129.0, 121.5, 114.1, 112.4, 80.5, 55.3, 47.4, 43.8, 37.4, 35.5, 25.6, 23.9, 23.8

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_4$ $[M+H]^+$ 315.1591, found 315.1588.

Compound 84ad:


84ad

White Solid: Yield = 70%

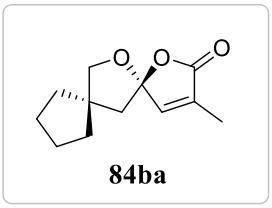
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, *J* = 8.01 Hz, 2H), 7.22 (d, *J* = 8.01 Hz, 2H), 7.12 (s, 1H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.93 (d, *J* = 8.4 Hz, 1H), 2.38 (s, 3H), 2.23 (d, *J* = 14.11 Hz, 1H), 2.13 (d, *J* = 13.73 Hz, 1H), 1.78-1.68 (m,2H), 1.61-1.31 (m, 8H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.4, 142.7, 139.9, 133.5, 129.4, 127.4, 126.1, 112.3, 80.5, 43.8, 37.4, 35.6, 25.6, 23.9, 23.8, 21.4

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_3$ $[M+H]^+$ 299.1642 found 299.1634.

Compound 84ba:


84ba

White crystalline solid: Yield = 78%

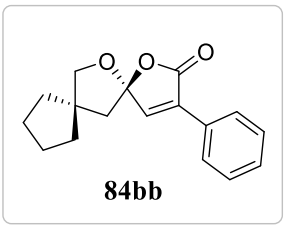
R_f = 0.6(SiO_2, 40%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.72-6.69 (m, 1H), 4.01 (d, *J* = 8.4 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 2.18 (s, 2H), 1.92 (d, *J* = 1.14 Hz, 3H), 1.86-1.81 (m, 2H), 1.74-1.58 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.6, 145.2, 132.5, 113.3, 81.1, 50.3, 47.4, 38.0, 37.2, 24.6, 24.4, 10.4

HRMS (ESI): *m/z* calcd for $C_{12}H_{17}O_3$ $[M+H]^+$ 209.1172, found 209.1171.

Compound 84bb:



White solid: Yield = 70%

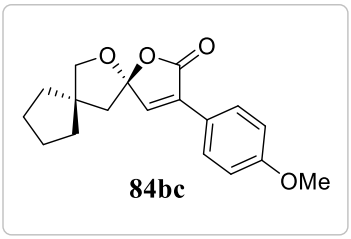
R_f= 0.6 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ7.87-7.81 (m, 2H), 7.45-7.39 (m, 3H), 7.19 (s, 1H), 4.08 (d, *J* = 8.0 Hz, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 2.31 (dd, *J* = 17.55, 13.73 Hz, 2H), 1.91-1.87 (m, 2H), 1.79-1.63 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, 143.7, 133.6, 129.7, 129.0, 128.7, 127.5, 112.4, 81.2, 50.5, 47.7, 38.0, 37.2, 24.7, 24.4

HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_3$ $[M+H]^+$ 271.1329, found 271.1328.

Compound 84bc:



White Crystalline Solid: Yield = 70%

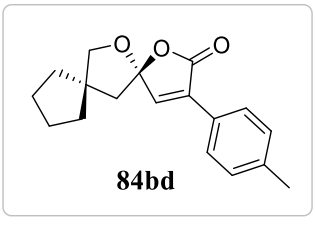
R_f= 0.6 (SiO_2, 20%EtOAc/hexanes)

1H NMR ($CDCl_3$, 500 MHz): δ 7.88-7.80 (m, 2H), 7.06 (s, 1H), 6.96-6.91 (m, 2H), 4.07 (d, *J* = 8.01 Hz, 1H), 3.91 (d, *J* = 8.01 Hz, 1H), 3.84 (s, 3H), 2.29 (dd, J = 13.35, 3.43 Hz, 2H), 1.91-1.85 (m, 2H), 1.78-1.63 (m, 6H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.6, 160.7, 141.3, 132.9, 129.0, 121.6, 114.1, 112.4, 81.2, 55.3, 50.5, 47.7, 38.1, 37.2, 29.7, 24.7, 24.4

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_4$ [M+H]+ 300.1434 found 301.1425.

Compound 84bd:



White solid: Yield = 72%

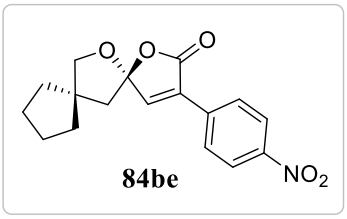
R_f= 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.13 (s, 1H), 4.07 (d, *J* = 8.5 Hz, 1H), 3.91 (d, *J* = 7.9 Hz, 1H), 2.39 (s, 3H), 2.29 (dd, *J* = 14.404, 1.22 Hz, 2H), 1.93-1.85 (m, 2H), 1.80-1.61 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.4, 142.7, 139.9, 133.4, 129.4, 127.4, 126.1, 112.4, 81.2, 50.5, 47.7, 38.0, 37.2, 24.7, 24.4, 21.4

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_3$ $[M+H]^+$ 285.1485 found 285.1476.

Compound 84be:



84be

Yellow solid: Yield = 78%

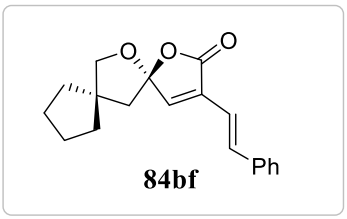
R_f = 0.75 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 9.2 Hz, 2H), 7.38 (s, 1H), 4.10 (d, *J* = 8.5 Hz, 1H), 3.94 (d, *J* = 7.9 Hz, 1H), 2.39-2.27 (m, 2H), 1.95-1.83 (m, 2H), 1.81-1.62 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.3, 148.3, 147.0, 135.0, 131.7, 128.5, 123.9, 112.6, 81.5, 50.6, 47.6, 37.9, 37.1, 24.7, 24.4

HRMS (ESI): m/z calcd for $C_{17}H_{18}O_5N$ $[M+H]^+$316.1179, found 316.1171.

Compound 84bf:



84bf

White Solid: Yield = 63%

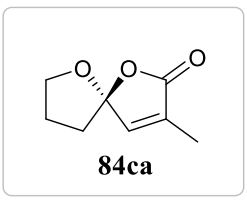
R_f= 0.6 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ7.71 (d, *J* = 16.44 Hz, 1H), 7.51 (d, *J* =7.3 Hz, 2H), 7.39-7.30 (m, 3H), 6.90 (s,1H), 6.81 (d, *J* = 14.44 Hz, 1H), 4.06 (d, *J* = 8.54 Hz, 1H), 3.9 (d, *J* = 8.54 Hz, 1H), 2.27 (s, 2H), 1.93-1.84 (m,2H), 1.52.-1.78 (m, 6H)

^{13}CNMR ($CDCl_3$, 126 MHz): δ 169.4, 143.0, 136.6, 136.2, 131.4, 128.7, 127.1, 116.1, 113.1, 81.2, 50.5, 47.8, 38.0, 37.2, 24.6, 24.4

HRMS(ESI): *m/z* calcd for $C_{19}H_{21}O_3$ $[M+H]^+$ 297.1486, found 297.1485.

Compound 84ca:



84ca

Colorless oil: Yield = 58%

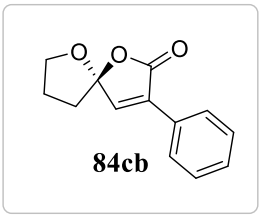
R_f= 0.45 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.73-6.70 (m, 1H), 4.65-4.19 (m, 1H), 4.10-4.03 (m, 1H), 2.34-2.23 (m, 1H), 2.22-2.06 (m, 3H), 1.93 (d, *J* = 1.91 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.4, 144.4, 133.3, 112.7, 70.3, 35.3, 24.2, 10.5

HRMS (ESI): *m/z* calcd for $C_8H_{11}O_3$ $[M+H]^+$154.0703 found 155.0699.

Compound 84cb:



Colorless liquid: Yield = 54%

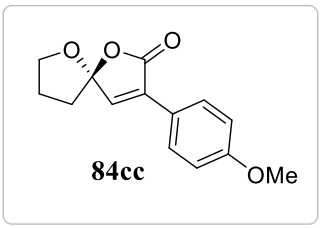
R_f = 0.45 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90-7.80 (m, 2H), 7.49-7.34 (m, 3H), 7.21 (s, 1H), 4.28 (td, *J* = 8.2, 3.7 Hz, 1H), 4.11 (q, *J* = 7.5 Hz, 1H), 2.42-2.14 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.2, 143.1, 134.3, 129.8, 129.0, 128.7, 128.2, 128.1, 127.7, 127.5, 127.3, 111.9, 70.5, 35.7, 24.3

HRMS (ESI): *m/z* calcd for $C_{13}H_{13}O_3$ $[M+H]^+$ 217.0859, found 217.0857.

Compound 84cc:



Yellow liquid: Yield = 52%

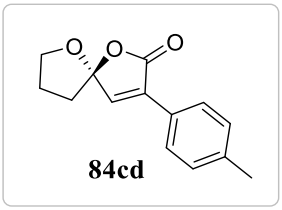
R_f= 0.4 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.31-4.24 (m, 1H), 4.15-4.08 (m, 1H), 3.83 (s, 3H), 2.38-2.12 (m, 4H)

^{13}C NMR ($CDCl_3$, 126 MHz):δ 169.5, 160.8, 140.5, 133.7, 129.0, 121.6, 114.1, 111.9, 70.4, 55.3, 35.7, 24.3

HRMS (ESI): *m/z* calcd for $C_{14}H_{15}O_4$ $[M+H]^+$ 247.0965, found 247.0964.

Compound 84cd:



Colourless oil: Yield = 62%

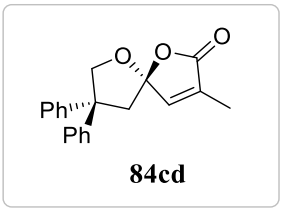
R_f= 0.6 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.15 (s, 1H), 4.33-4.25 (m, 1H), 4.17-4.08 (m, 1H), 2.38 (s, 3H), 2.43-2.12 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ169.3, 141.9, 140.0, 134.2, 129.4, 127.4, 126.2, 111.8, 70.4, 35.7, 24.3, 21.4

HRMS (ESI): m/z calcd for $C_{14}H_{15}O_3$ $[M+H]^+$ 230.1016 found 231.1009.

Compound 84da:



84cd

Brown liquid: Yield = 62%

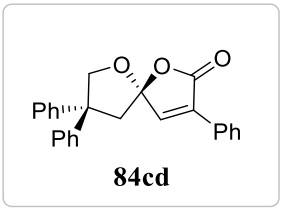
R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR (CDCl$_3$, 500 MHz) : δ 7.36-7.28 (m, 6H), 7.27-7.23 (m, 2H), 7.21-7.18 (m, 2H), 6.35 (d, *J* =1.53 Hz, 1H), 4.86 (d, *J* = 8.7 Hz, 1H), 4.49 (d, *J* = 9.1 Hz, 1H), 3.27 (d, *J* = 14.1Hz, 1H), 2.95 (d, *J* = 13.7 Hz, 1H), 1.86 (s, 3H)

^{13}CNMR(CDCl$_3$, 126 MHz): δ 171.4,145.6,145.2, 143.6, 131.7, 128.7, 128.3, 127.1, 127.0, 126.8, 112.9, 77.9, 56.3, 47.5, 10.3

HRMS (ESI): *m/z* calcd for $C_{20}H_{19}O_3$ $[M+H]^+$ 307.1329, found 307.1326.

Compound 84db:



84cd

Crystalline Solid: Yield = 70%

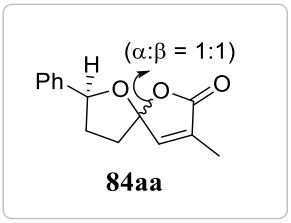
R_f = 0.6 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR(CDCl$_3$, 400 MHz): δ 7.80-7.71(m, 2H), 7.40-7.30 (m, 9H), 7.29- 7.20 (m, 4H), 6.79 (s, 1H), 4.91(d, *J* = 9.1 Hz, 1H), 4.55 (d, *J* = 9.1 Hz, 1H), 3.36 (d, *J* = 14 Hz, 1H), 3.07 (d, *J*=14 Hz, 1H)

^{13}CNMR(CDCl$_3$, 101MHz): δ 169,145.5, 143.5, 132.7, 128.8, 129.8, 128.7, 128.6, 127.5, 127.1, 126.9, 126.8, 112.1, 78.1, 56.4, 47.8

HRMS (ESI): *m/z* calcd for $C_{25}H_{21}O_3$ $[M+H]^+$ 369.1485, found 369.1469.

Compound 84ea:



84aa

Colorless liquid: Yield = 27% and 29% (dr ratio – 1:1)

R_f = 0.3 and 0.28 (SiO_2, 20% EtOAc/hexanes)

84ea-Isomer-1:

^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.52-7.22 (m, 5H), 6.89 (s, 1H), 5.45 (t, *J* = 5.72 Hz, 1H), 2.81-2.69 (m, 1H), 2.37- 2.26 (m, 2H), 2016-2.08 (m, 1H), 1.97 (s, 3H)

^{13}C NMR(CDCl$_3$, 126MHz): δ 171.4,144.3, 141.3, 133.3, 128.5, 127.8, 125.5, 112.8, 82.4, 34.4, 32.5, 10.5.

84ea-Isomer-2:

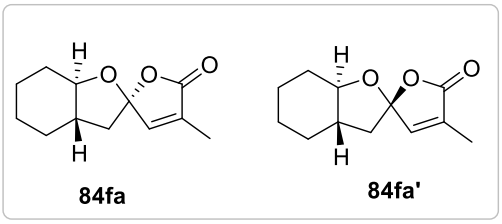
^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.52-7.22 (m, 5H), 6.79 (s, 1H), 5.21 (t, *J*=4.88 Hz, 1H), 2.57-

244 (m, 1H), 2.41- 2.21 (m, 3H), 1.97 (s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.4, 144.5, 141.0, 133.5,128.6, 128.4, 128.1, 126.3, 112.7, 85.0, 37.2, 34.1, 10.6

HRMS (ESI): *m/z* calcd for $C_{14}H_{15}O_3$ $[M+H]^+$ 231.1016, found 231.1016.

Compound 84fa and 84fa'



White solid: Yield 42% and 21%

R_f = 0.6 and 0.58 (SiO_2, 20%EtOAc/hexanes)

84fa : ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.72 (s, 1H), 3.66-3.53(m, 1H), 2.35 (dd, *J* = 13.4, 7.9Hz, 1H), 2.20-2.06 (m, 2H), 1.99-1.93 (m, 1H), 1.91 (s, 3H), 1.88 (d, *J* = 11.6Hz, 1H), 1.78 (d, *J* = 7.3Hz, 1H), 1.63-1.51 (m, 1H), 1.45-1.30 (m, 2H),1.28-1.20 (m, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.9,145.7, 131.2, 111.8, 84.7, 46.3, 39.8, 30.5, 28.5, 25.5, 24.0, 10.3

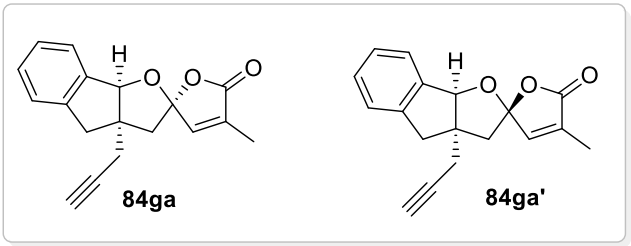
HRMS (ESI): *m/z* calcd for $C_{12}H_{17}O_3[M+H]^+$ 209.1172, found 209.1173.

84fa': ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.72 (d, *J* = 1.5Hz, 1H), 3.39 (td, *J* =10.7, 3.8Hz, 1H), 2.17-2.11 (m, 2H), 2.0 (d, *J* = 14.1Hz, 1H), 1.97-1.92 (m, 1H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.88-1.85 (m, 1H), 1.78-1.73 (m, 1H), 1.50 (qd, *J* = 11.7, 3.8 Hz, 1H),1.31-1.24 (m, 3H), 1.17 (td, *J* = 12.2, 3.4 Hz, 1H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.3, 145.9, 132.4, 111.4, 86.7, 43.7, 41.5, 31.3, 28.5, 25.5, 24.2, 10.4

HRMS (ESI): *m/z* calcdfor$C_{12}H_{17}O_3$ $[M+H]^+$ 209.1172, found 209.1174.

Compound 84ga and 84ga'



Colorless liquid: Yield 77% and 17%

R_f = 0.4 and 0.38 (SiO_2, 20% EtOAc/hexanes)

84ga : ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.25 (m, 4H), 6.56 (s, 1H), 5.59 (s, 1H), 3.30 (d, *J* = 16.5 Hz, 1H), 3.10 (d, *J* = 17.1Hz, 1H), 2.88 (AB q, *J* = 17.0, 3.0 Hz, 2H), 2.50 (d, *J* = 13.4 Hz, 1H), 2.21 (d, *J* = 14.0 Hz, 1H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.93 (d, *J* = 1.2

Hz, 3H)

^{13}C NMR($CDCl_3$, 126MHz): δ 171.2, 144.5,141.2, 140.8, 133.3, 129.4, 127.5, 125.7, 125.4, 113.2, 93.7, 81.4, 70.0, 52.6, 46.8, 43.0, 27.4, 10.5

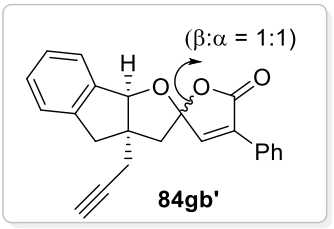
HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1172, found 281.1175.

84ga': **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.40 (d, *J* = 7.3 Hz, 1H), 7.37-7.30 (m, 1H), 7.27-7.22 (m, 2H), 6.77 (s, 1H), 5.47 (s, 1H), 3.61 (d, *J* = 16.5Hz, 1H), 3.04 (d, *J* = 16.5Hz, 1H), 2.67-2.56 (m, 2H), 2.53-2.45 (m, 1H), 2.38 (d, *J* = 13.4 Hz, 1H), 2.06 (br.s., 1H), 1.91 (s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.4, 144.6, 142.7, 139.6, 133.3, 129.6, 127.4, 126.1, 125.3, 113.9, 94.4, 80.8, 70.6, 52.6, 46.5, 43.7, 28.4, 10.4

HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1172, found 281.1175.

Compound 84gb:



White solid: Yield = 64%

R_f = 0.5 (SiO_2, 20% EtOAc/hexanes)

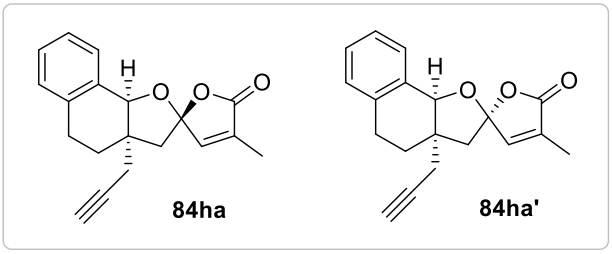
Diasterioemeric mixture of **84gb** and **84gb'**:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.74 (m, 2H), 7.45-7.12 (m, 9H), 7.02 (s,1H), 5.63 (s, 1H), 3.76-3.67 (m, 1H), 3.35-3.25 (m, 1H), 3.2-3.07 (m, 2H), 3.03-2.94 (m, 1H), 2.93-2.81 (m, 3H), 2.62-2.47 (m, 4H), 2.34-2.21 (m, 2H), 2.09-1.95 (m, 2H)

^{13}C NMR ($CDCl_3$, 101MHz) : δ 168.9, 143.1, 141.1, 140.8, 134.3, 129.9, 129.5, 128.8, 128.7, 127.6, 127.5, 127.4, 127.2, 125.8, 125.4, 125.3, 124.7, 112.4, 93.8, 81.4, 71.1, 70.2, 52.8, 50.6, 50.2, 48.8, 47.1, 43.7, 43.4, 42.9, 28.5, 27.4

HRMS (ESI): *m/z* calcd for $C_{23}H_{19}O_3$ $[M+H]^+$ 343.1329, found 343.1335.

Compound 84ha and 84ha'



Crystalline solid: Yield = 70%

R_f = 0.3 and 0.28 (SiO_2, 20% EtOAc/hexanes)

84ha: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, 7.3 Hz, 1H), 7.33-7.23 (m, 2H), 7.22-7.17 (m, 1H), 6.67 (s, 1H), 5.0 (s, 1H), 2.85-2.75 (m, 2H), 2.65-2.52 (m, 3H), 2.34 (d, *J* =

14.0 Hz, 1H), 2.07-1.97 (m, 2H), 1.97-1.87 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.5, 144.7, 137.2, 132.8, 132.3, 130.9, 128.7, 128.5, 126.7, 111.2, 83.9, 80.5, 70.8, 46.4, 43.9, 31.1, 26.6, 25.8, 10.4

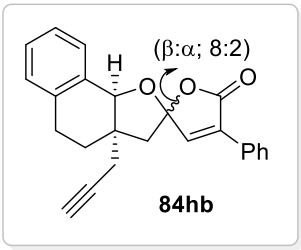
HRMS (ESI): *m/z* calcd for $C_{19}H_{19}O_3$ $[M+H]^+$ 295.1329, found 295.1318.

84ha' = ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.35 (m, 2H), 7.32-7.17 (m, 9H), 6.81 (d, *J* = 1.1Hz, 1H), 6.67 (d, *J* = 1.5Hz, 1H), 5.01 (s, 1H), 4.93 (s, 1H), 2.97-2.31 (m, 13H), 2.13-1.9 (m, 10H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.5, 171.2, 145.7, 144.7, 137.2, 136.2, 132.9, 132.6, 132.3, 132.2, 130.9, 130.7, 128.7, 128.7, 128.5, 128.5, 126.7, 126.6, 111.9, 111.2, 83.9, 83.8, 80.5, 80.3, 71.5, 70.8, 46.6, 46.4, 43.9, 43.2, 31.2, 29.7, 28.3, 26.6, 25.8, 25.5, 10.4, 10.4

HRMS (ESI): *m/z* calcd for $C_{19}H_{19}O_3$ $[M+H]^+$ 295.1329, found 295.1319.

Compound 84hb:



84hb

White Solid: Yield = 61%

R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

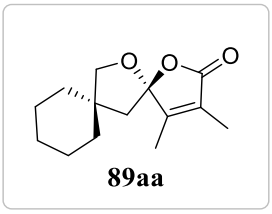
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89-7.79 (m, 2H), 7.48-7.10 (m, 12H), 5.08 (s, 1H), 3.5-2.2 (m, 12H), 2.16-1.75 (m, 5H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.2, 144.2, 143.2, 137.2, 133.8, 132.2, 131.0, 130.8, 130.1, 129.8, 129.4, 128.8, 128.7, 128.6, 127.5, 126.8, 126.6, 126.5, 126.4, 110.4, 84.0, 83.9, 80.5, 71.4, 70.9, 51.1, 46.8, 46.7, 44.1, 42.8, 40.2, 31.2, 28.2, 26.6, 26.5, 25.8, 25.3

HRMS (ESI): *m/z* calcd for $C_{24}H_{21}O_3$ $[M+H]^+$ 357.1485, found357.1473

Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (possessing internal alkynols)

Compound 89aa:



Colourless liquid: Yield = 65%

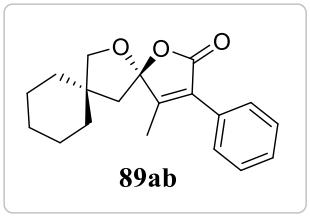
R_f = 0.7 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.95 (d, *J* = 8.8 Hz, 1H), 3.85 (d, *J* = 8.8 Hz, 1H), 2.04-1.94 (m, 2H), 1.90 (s, 3H), 1.80 (s, 3H), 1.72-1.65 (m, 2H), 1.53-1.39 (m, 8H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.7, 154.9, 126.0, 114.5, 80.6, 45.7, 43.4, 37.4, 35.6, 25.5, 23.8, 23.7, 10.5, 8.6;

HRMS (ESI): *m/z* calcd for $C_{14}H_{21}O_3$ $[M+H]^+$ 237.1485, found 237.1486.

Compound 89ab:



White solid: Yield = 68%

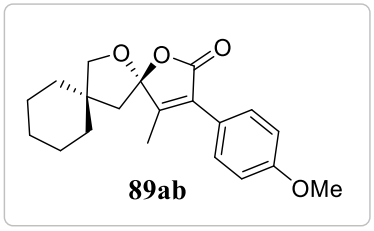
R_f = 0.5 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.34 (m, 5H), 4.06 (d, *J* = 8.5 Hz, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 2.23-2.05 (m, 2H), 2.13 (s, 3H), 1.83-1.72 (m, 2H), 1.60-1.45 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.9, 156.0, 129.6, 129.0, 128.98, 128.7, 128.5, 113.9, 80.9, 46.1, 43.7, 37.4, 35.6, 25.5, 23.9, 23.8, 11.5

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_3$ $[M+H]^+$ 299.1642, found 299.1643.

Compound 89ac:



White Crystalline solid: Yield = 62%

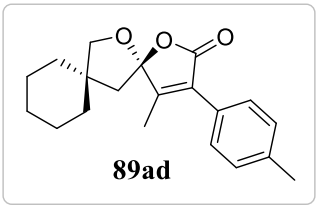
R_f = 0.45 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 4.05 (d, *J* = 7.9 Hz, 1H), 3.94 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 2.12 (s, 3H), 2.21-2.04 (m, 2H), 1.76-1.7 (m, 2H), 1.61-1.41 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.2, 159.8, 154.3, 130.4, 128.4, 122.0, 113.9, 80.8, 55.3, 46.1, 43.6, 37.4, 35.7, 25.6, 23.9, 23.8, 11.6

HRMS (ESI): m/z calcd for $C_{20}H_{25}O_4$ $[M+H]^+$ 329.1747, found 329.1739.

Compound 89ad:


89ad

White solid: Yield = 72%

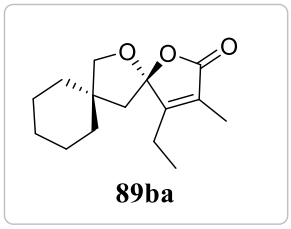
R_f = 0.45 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 4.06 (d, *J* = 8.5 Hz, 1H), 3.94 (d, *J* = 8.5 Hz, 1H), 2.40 (s, 3H), 2.12 (s, 3H), 2.21-2.05 (m, 2H), 1.81-1.72 (m, 2H), 1.56-1.34 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.0, 155.1, 138.7, 129.2, 128.9, 126.7, 113.9, 80.8, 77.2, 46.1, 43.6, 37.4, 35.7, 25.6, 23.9, 23.8, 21.4, 11.5

HRMS (ESI): *m/z* calcd for $C_{20}H_{25}O_3$ $[M+H]^+$ 313.1798, found 313.1808.

Compound 89ba:


89ba

Colourless liquid: Yield = 68%

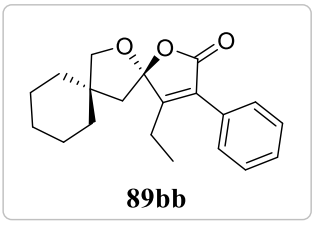
R_f = 0.45 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.96 (d, *J* = 8.5 Hz, 1H), 3.86 (d, *J* = 7.9 Hz, 1H), 2.44-2.31 (m, 1H), 2.31-2.2 (m, 1H), 2.06-1.96 (m, 2H), 1.84 (s, 3H), 1.74-1.67 (m, 2H), 1.55-1.39 (m, 8H), 1.17 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.9, 159.4, 126.0, 114.9, 80.5, 45.9, 43.3, 37.6, 35.7, 25.5, 23.9, 23.7, 18.9, 12.3, 8.6

HRMS (ESI): *m/z* calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1644.

Compound 89ba:


89bb

White Solid: Yield = 70%

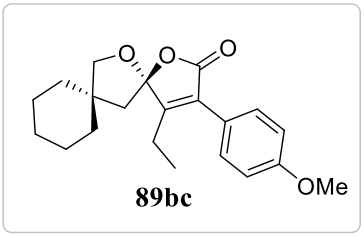
R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55-7.34 (m, 5H), 4.06 (d, *J* = 8.4 Hz, 1H), 3.95 (d, *J* = 8.4 Hz, 1H), 2.68-2.58 (m, 1H), 2.46-2.37 (m, 1H), 2.18 (s, 2H), 1.81-1.74 (m, 2H), 1.62-1.43 (m, 8H), 1.18 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.1, 160.5, 129.8, 129.4, 129.1, 128.9, 128.7, 128.4, 114.6, 80.7, 46.3, 43.5, 37.6, 35.7, 25.6, 23.9, 23.8, 19.4, 12.5

HRMS (ESI): *m/z* calcd for $C_{20}H_{25}O_3$ $[M+H]^+$ 313.1798, found 313.1797.

Compound 89bc:



89bc

Crystalline solid: Yield = 72%

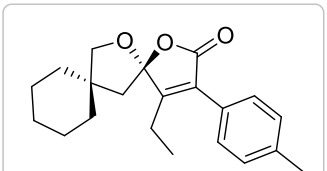
R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 4.03 (d, *J* = 8.5 Hz, 1H), 3.93 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 2.69-2.54 (m, 1H), 2.47-2.32 (m, 1H), 2.15 (s, 2H), 1.82-1.71 (m, 2H), 1.60-1.41 (m, 8H), 1.18 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.4, 159.8, 159.0, 130.2, 128.7, 122.2, 114.5, 113.9, 80.6, 55.3, 46.3, 43.4, 37.6, 35.7, 25.6, 23.9, 23.8, 19.4, 12.5

HRMS (ESI): *m/z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1904, found 343.1905.

Compound 89bd:


89bd

White solid: Yield = 76%

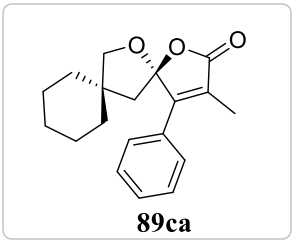
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 4.05 (d, *J* = 8.4 Hz, 1H), 3.95 (d, *J* = 8.8 Hz, 1H), 2.68-2.58 (m, 1H), 2.4 (s, 3H), 2.46-2.36 (m, 1H), 2.17 (s, 2H), 1.81-1.74 (m, 2H), 1.63-1.43 (m, 8H), 1.19 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.3, 159.8, 138.7, 129.3, 129.2, 128.8, 127.3, 126.9, 114.5, 80.6, 46.3, 43.4, 37.6, 35.8, 25.6, 23.9, 23.8, 21.3, 19.4, 12.5

HRMS (ESI): *m/z* calcd for $C_{21}H_{27}O_3$ $[M+H]^+$ 327.1955, found 327.1959.

Compound 89ca:


89ca

Colourless liquid: Yield = 74%

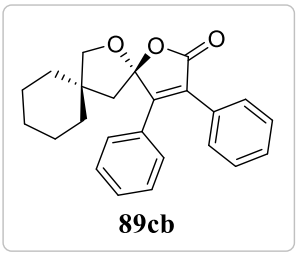
R_f = 0.6 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56-7.40 (m, 5H), 4.09 (d, *J* = 8.5 Hz, 1H), 3.94 (d, *J* = 8.5 Hz, 1H), 2.09 (d, *J* = 14.0 Hz, 1H), 2.0 (s, 3H), 1.86 (d, *J* = 14.0 Hz, 1H), 1.78-1.71 (m, 2H), 1.54-1.44 (m, 2H), 1.42-1.29 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.7, 154.8, 131.1, 129.6, 128.7, 128.4, 127.1, 115.0, 80.9, 43.3, 37.4, 35.8, 25.5, 23.9, 23.6, 9.9

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_3$ $[M+H]^+$ 299.1642, found 299.1644.

Compound 89cb:


89cb

White solid: Yield = 73%

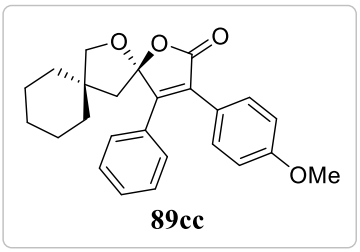
R_f = 0.5 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.34 (m, 7H), 7.34-7.29 (m, 3H), 4.15 (d, *J* = 8.4 Hz, 1H), 3.98 (d, *J* = 8.4 Hz, 1H), 2.20 (d, *J* = 13.7 Hz, 1H), 1.93 (d, *J* = 13.7 Hz, 1H), 1.84-1.76 (m, 2H), 1.56-1.48 (m, 2H), 1.44-1.31 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.8, 155.2, 131.0, 129.7, 129.5, 129.4, 128.9, 128.73, 128.71, 128.4, 114.4, 81.0, 43.4, 37.3, 35.8, 25.5, 23.9, 23.7

HRMS (ESI): *m/z* calcd for $C_{24}H_{25}O_3$ $[M+H]^+$ 361.1798, found 361.1798.

Compound 89cc:



89cc

Crystalline solid: Yield = 68%

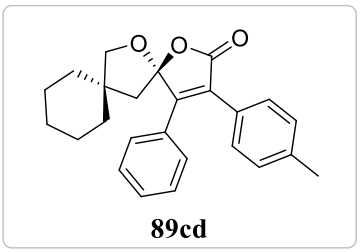
R_f = 0.45 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.33 (m, 7H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.13 (d, *J* = 8.5 Hz, 1H), 3.95 (d, *J* = 8.5 Hz, 1H), 3.81 (s, 3H), 2.17 (d, *J* = 13.4 Hz, 1H), 1.90 (d, *J* = 14.0 Hz, 1H), 1.82-1.74 (m, 2H), 1.54-1.47 (m, 2H), 1.43-1.25 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.2, 160.0, 153.5, 131.4, 130.9, 129.5, 128.7, 128.7, 128.3, 121.7, 114.4, 113.8, 80.9, 55.2, 43.4, 37.3, 35.8, 29.7, 25.5, 23.9, 23.7

HRMS (ESI): *m/z* calcd for $C_{25}H_{27}O_4$ $[M+H]^+$ 391.1904, found 391.1901.

Compound 89cd:


89cd

White solid: Yield = 66%

R_f = 0.5 (SiO_2, 20%EtOAc/hexanes)

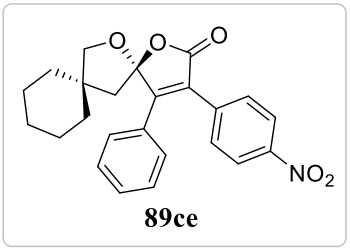
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45-7.28 (m, 7H), 7.14-7.07 (m, 2H), 4.15 (d, *J* = 8.5 Hz, 1H), 3.96 (d, *J* = 8.5 Hz, 1H), 2.34 (s, 3H), 2.18 (d, *J* = 13.4 Hz, 1H), 1.91 (d, *J* = 14.0 Hz, 1H), 1.82-1.72 (m, 2H), 1.57-1.46 (m, 2H), 1.43-1.28 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.0, 154.4, 138.9, 131.2, 129.6, 129.4, 129.1, 128.8, 128.7,

126.4, 114.4, 81.0, 46.5, 43.4, 37.3, 35.8, 25.5, 24.0, 23.7, 21.4

HRMS (ESI): *m/z* calcd for $C_{25}H_{27}O_3$ $[M+H]^+$ 375.1955, found 375.1956.

Compound 89ce:



89ce

Yellow Solid: Yield = 70%

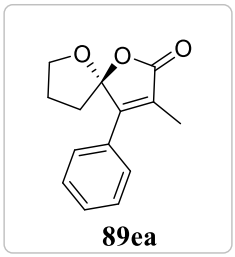
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.16 (d, *J* = 8.54 Hz, 2H), 7.61 (d, *J* = 9.16 Hz, 2H), 7.51-7.35 (m, 5H), 4.17 (d, *J* = 8.55 Hz, 1H), 3.98 (d, *J* = 8.55 Hz, 1H), 2.22 (d, *J* = 14.04 Hz, 1H), 1.93 (d, *J* = 14.04 Hz, 1H), 1.84-1.74 (m, 2H), 1.56-1.48 (m, 2H), 1.44-1.25 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.8, 158.4, 147.8, 130.6, 130.5, 129.2, 128.5, 123.5, 114.6, 81.3, 53.4, 43.6, 37.2, 35.8, 25.5, 23.9, 23.6

HRMS (ESI): *m/z* calcd for $C_{24}H_{24}O_5N$ $[M+H]^+$ 406.1649, found 406.1640.

Compound 89ea:



89ea

White solid: Yield = 35%

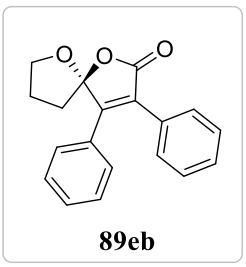
R_f = 0.45 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56-7.49 (m, 2H), 7.48-7.42 (m, 3H), 4.33 (dt, *J* = 8.5, 4.3 Hz, 1H), 4.19-4.09 (m, 1 H), 2.39-2.27 (m, 1 H), 2.19-2.10 (m, 1 H), 2.08-1.96 (m, 5H

^{13}C NMR ($CDCl_3$, 101MHz): δ 171.5, 154.3, 131.1, 129.6, 128.7, 128.3, 127.3, 114.3, 70.4, 34.9, 24.4, 9.97

HRMS (ESI): *m/z* calcd for $C_{14}H_{15}O_3$ $[M+H]^+$ 231.1016, found 231.1013.

Compound 89eb:



89eb

White solid: Yield = 42%

R_f = 0.6 (SiO_2, 20%EtOAc/hexanes)

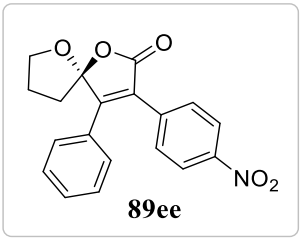
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.23 (m, 10H), 4.37 (td, *J* = 8.2, 3.7 Hz, 1H), 4.16 (m, 1H), 2.43-2.30 (m, 1H), 2.30-2.19 (m, 1H), 2.12-1.97 (m, 2H)

^{13}C NMR ($CDCl_3$,126 MHz): δ 169.7, 154.8, 131.0, 129.8, 129.5, 129.4, 129.1, 128.9, 128.8,

128.7, 128.4, 113.7, 70.7, 34.9, 24.5

HRMS (ESI): *m/z* calcd for $C_{19}H_{17}O_3$ $[M+H]^+$ 293.1172, found 293.1168.

Compound 89ee:



89ee

Solid: Yield = 48%

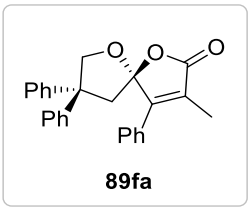
R_f = 0.45 (SiO_2, 20%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.48-7.42 (m, 1H), 7.42-7.35 (m, 4H), 4.42 (td, *J* = 8.4, 3.8 Hz, 1H), 4.21 (q, *J* = 8.0 Hz, 1H), 2.45-2.35 (m, 1H), 2.35-2.27 (m, 1H), 2.15-2.01 (m, 2H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.6, 157.9, 147.8, 136.0, 130.6, 130.5, 130.1, 129.2, 128.5, 127.1, 123.6, 113.9, 71.0, 34.9, 24.6

HRMS (ESI): *m/z* calcd for $C_{19}H_{16}O_5N$ $[M+H]^+$338.1023, found 338.1018.

Compound 89fa:



89fa

Soild: Yield = 62%

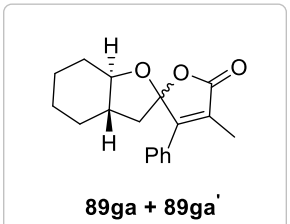
R_f = 0.5 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.24 (m, 10H), 7.20-7.12 (m, 3H), 7.1- 7.0 (m, 2H), 4.87 (d, *J* = 9.1 Hz, 1H), 4.77 (d, *J* = 9.7 Hz, 1H), 3.13 (d, *J* = 14 Hz, 1H), 2.90 (d, *J* = 14 Hz, 1H), 1.98 (s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.3, 154.8, 146.1, 144.6, 130.4, 129.5, 128.6, 128.5, 128.3, 127.7, 127.4, 126.7, 126.4, 114.6, 79.3, 55.9, 48.2, 29.7, 9.8

HRMS (ESI): *m/z* calcd for $C_{26}H_{23}O_3$ $[M+H]^+$383.1642, found 383.1642.

Compound 89ga and 89ga':



89ga + 89ga'

White solid: Yield = 64% (overall yield)

89ga: R_f = 0.60 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44-7.38 (m, 5H), 3.25 (td, *J* = 3.81, 10.3 Hz, 1H), 2.82 (dd, *J* = 3.8, 12.9 Hz, 1H), 2.12-2.02 (m, 2H),1.97 (s, 3H), 1.84-1.73 (m, 2H), 1.7-1.62 (m, 1H), 1.57-1.37 (m, 3H), 1.24-1.17 (m, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.5, 158.4, 136.0, 129.6, 129.0, 126.4, 123.3, 104.9, 78.1,

44.6, 31.7, 31.5, 31.2, 30.9, 25.2, 24.5, 8.5

HRMS (ESI) m/z calcd for $C_{18}H_{21}O_3$ $[M+H]^+$285.1486, found 285.1485.

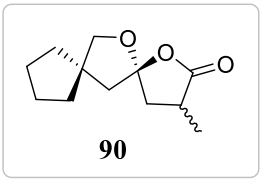
89ga':R_f = 0.53 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR($CDCl_3$, 500 MHz) δ 7.44-7.38 (m, 5H), 3.2 (td, *J* = 4.2, 10.7 1H), 2.82 (dd, *J* = 4.2, 13.35, 1H), 2.18 (s, 2H), 2.1-2.02 (m, 2H), 1.97 (s, 3H), 1.85-1.73 (m, 2H), 1.7-1.6 (m, 1H), 1.53-1.4 (m, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.5, 158.4, 136, 129.6, 129.0, 126.4, 123.3, 104.92, 78.1, 44.6, 31.7, 31.5, 31.2, 25.2, 24.5, 8.5

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_3$ $[M+H]^+$285.1487, found 285.1485.

Compound 90:



90

Crystalline solid: Yield = 76%

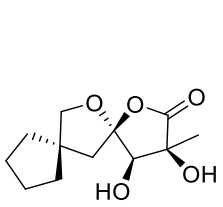
R_f = 0.65 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ (mixture of two diastereomers) 3.96-3.85 (m, 1H), 3.83 - 3.72 (m, 1H), 3.01 - 2.86 and 2.77-2.63 (m, 1H), 2.54-2.42 (m, 1H), 2.34-2.22 (m, 1H), 2.12-1.92 (m, 2H), 1.83-1.50 (m, 8H), 1.35 (minor isomer) (d, *J* = 7.32 Hz,) and 1.26 (major isomer) (d, *J* = 6.71 Hz) for 3H)

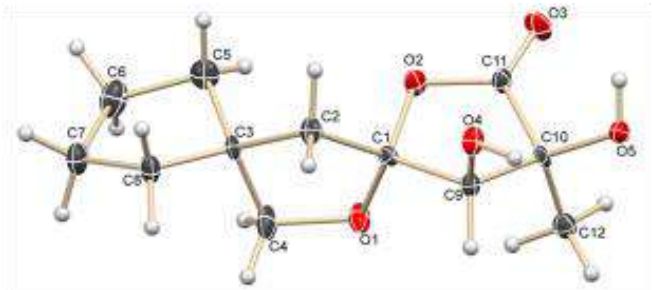
^{13}C NMR ($CDCl_3$, 101 MHz): δ (mixture of two diastereomers) 179, 115.5, 114.1, 80.4, 80.0, 49.75, 49.67, 49.63, 48.86, 41.16, 40.14, 38.58, 38.49, 37.10, 37.05, 36.01, 34.97, 24.47, 24.31, 16.55, 15.01.

HRMS (ESI): *m/z* calcd for $C_{12}H_{19}O_3$ $[M+H]^+$ 211.1329, found 211.1324.

Compound 91:



91



X-ray, CCDC No: 1510253 **ORTEP Diagram**

Crystalline solid: Yield = 71%; R_f= 0.5 (SiO_2, 50% EtOAc/hexanes

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.98 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 1H), 3.83 (d, *J* = 8.5 Hz, 1H), 3.48 (br. s., 1H), 3.25 (br. s, 1H), 2.48 (d, *J* = 14.6 Hz, 1H), 2.21 (d, *J* = 14.0 Hz, 1H), 1.64 (s, 3H), 1.84-1.54 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.9, 116.8, 81.3, 78.1, 77.2, 74.7, 48.7, 45.2, 37.8, 36.9, 24.6, 24.3, 23.0

HRMS (ESI): *m/z* calcd for $C_{12}H_{19}O_5$ $[M+H]^+$ 243.1227, found 243.1222.

2.11 References

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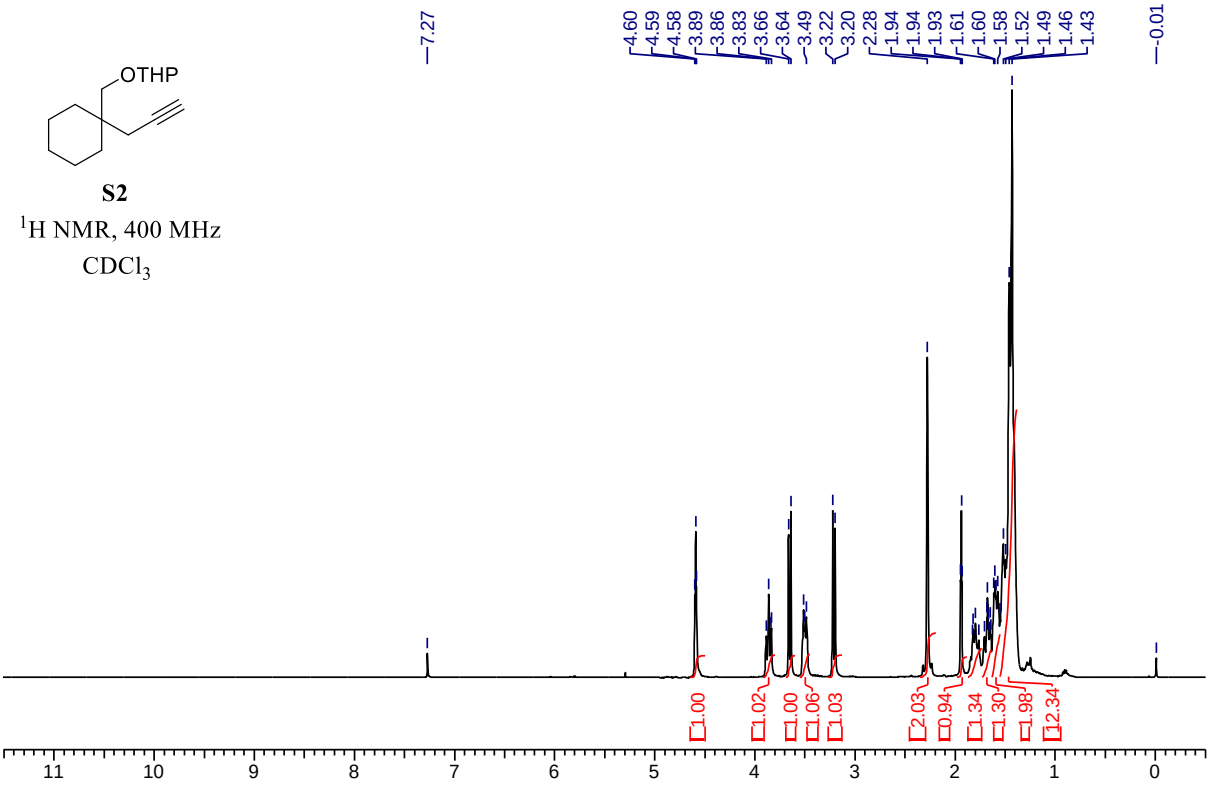
Synthesis of Alkynols:

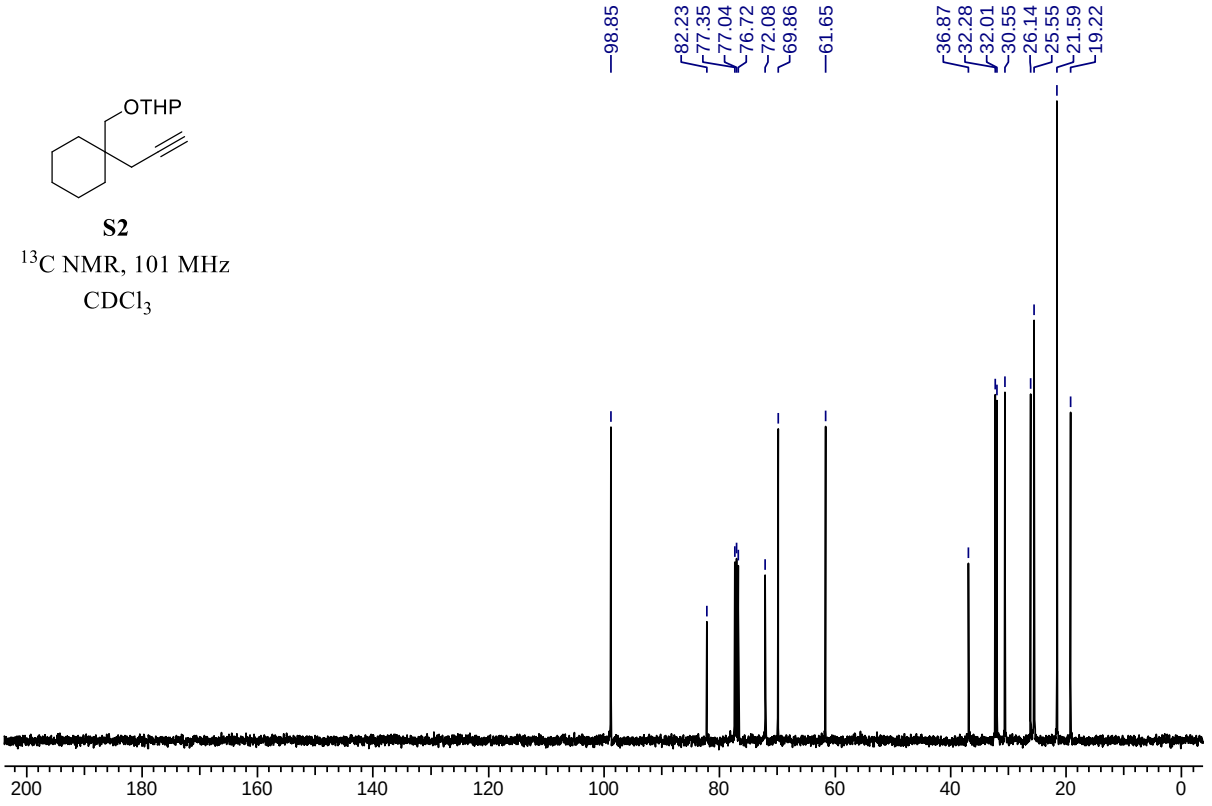
2-((1-(Prop-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (S2):



S2

^{1}H NMR, 400 MHz

$CDCl_3$

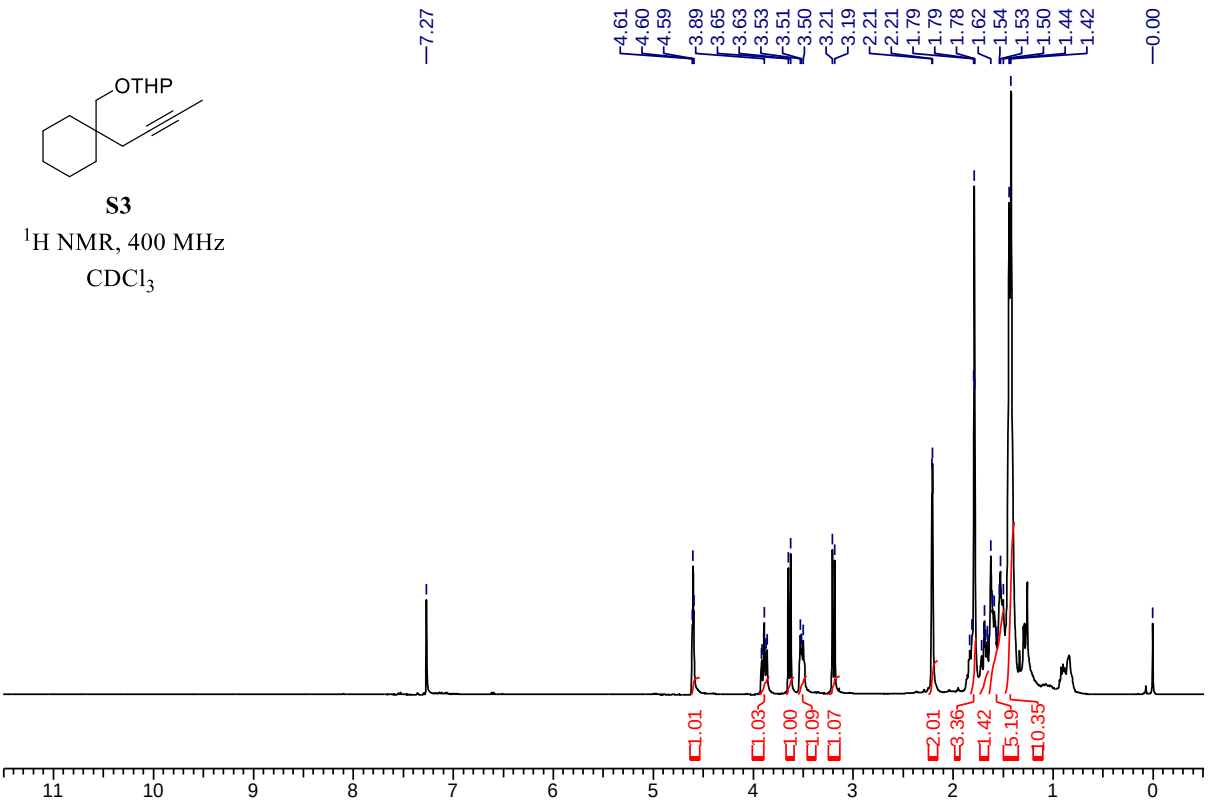


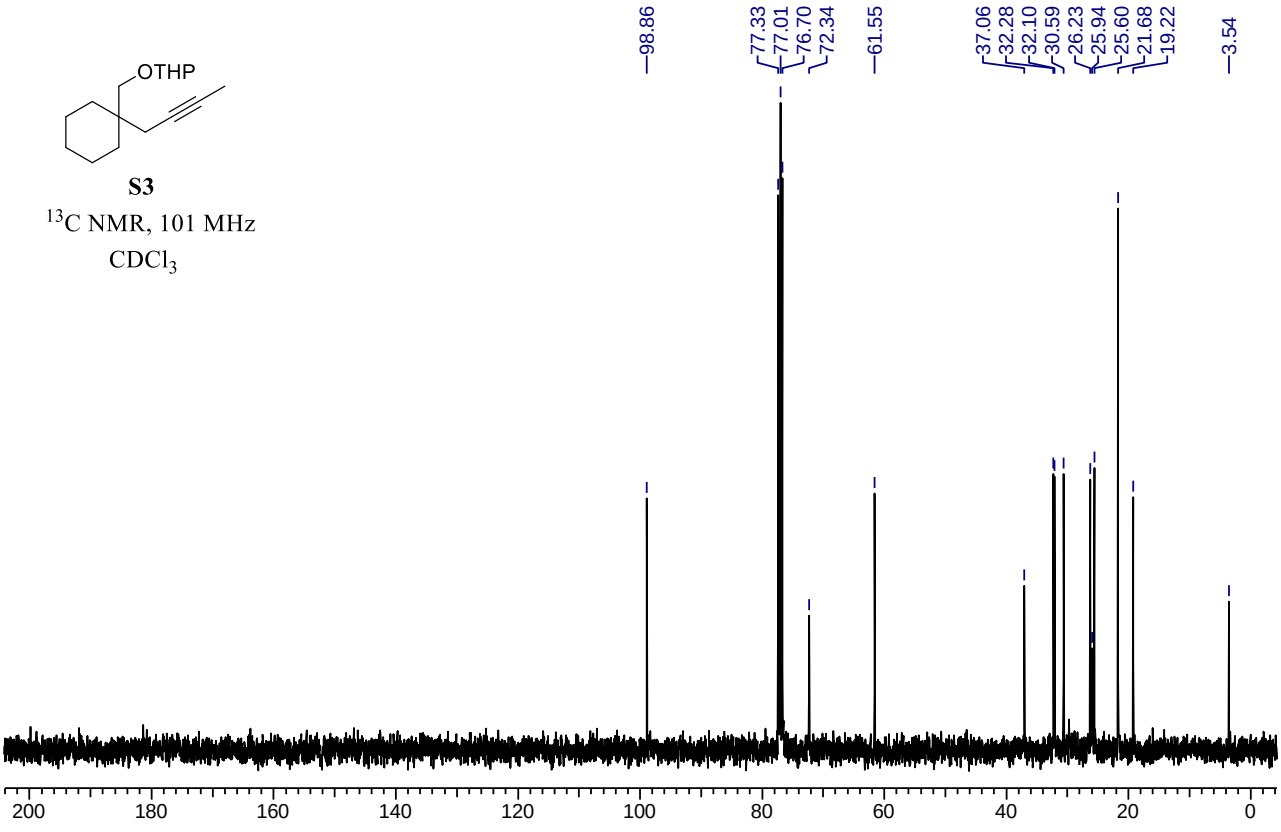
S2

^{13}C NMR, 101 MHz

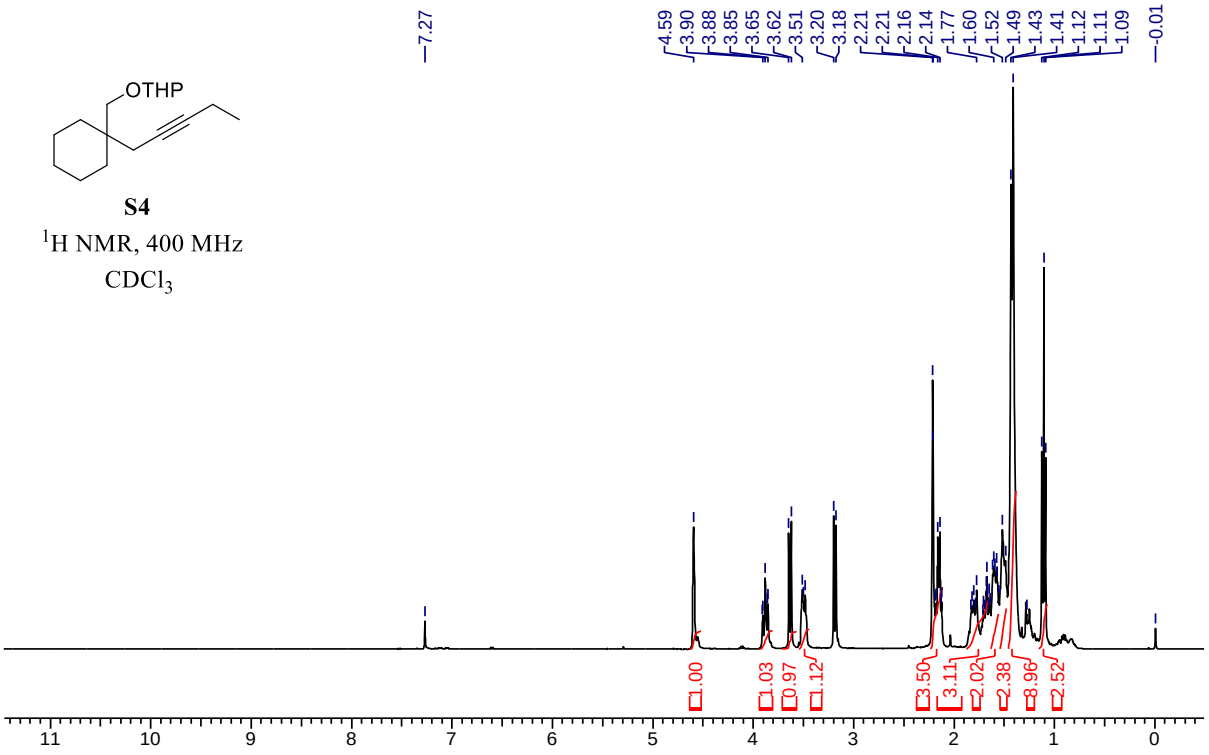
$CDCl_3$

2-((1-(But-2-yn-1-yl) cyclohexyl) methoxy) tetrahydro-2*H*-pyran (S3):





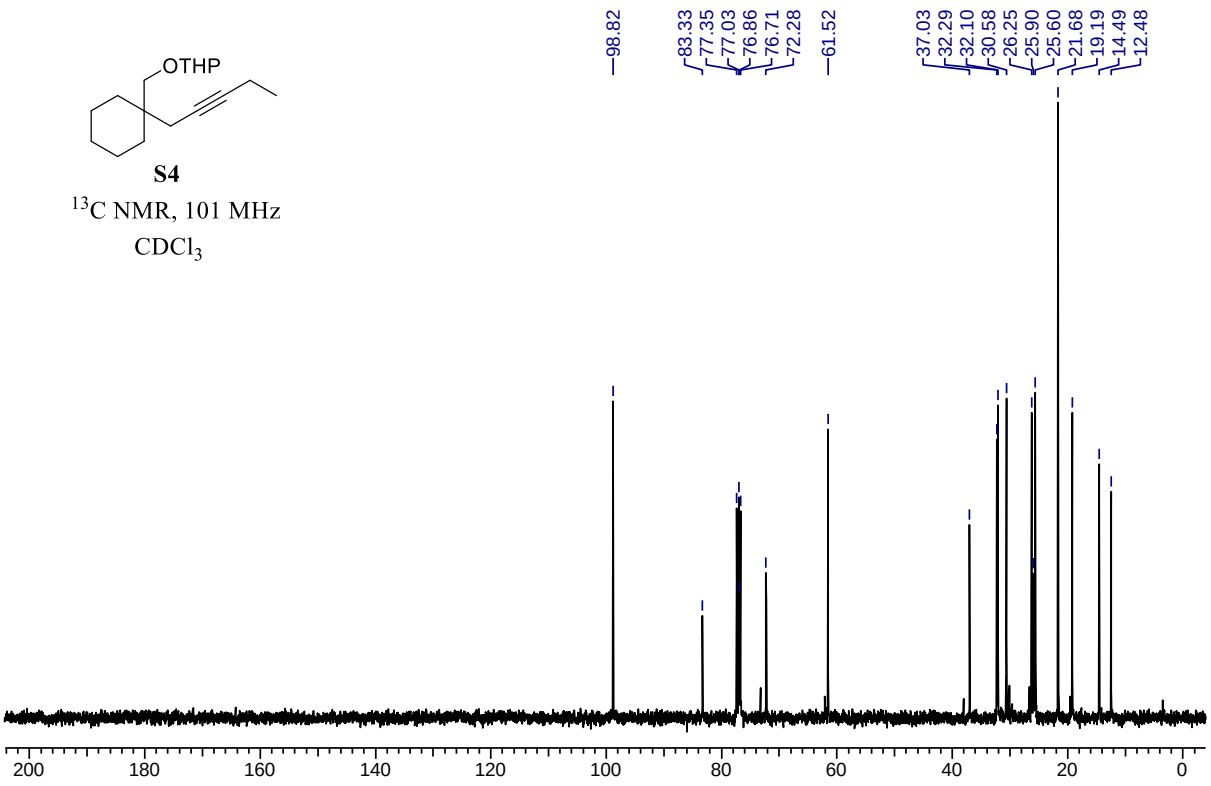
2-((1-(Pent-2-yn-1-yl)cyclohexyl)methoxy)tetrahydro-2H-pyran (S4):



S4

^{1}H NMR, 400 MHz

$CDCl_3$

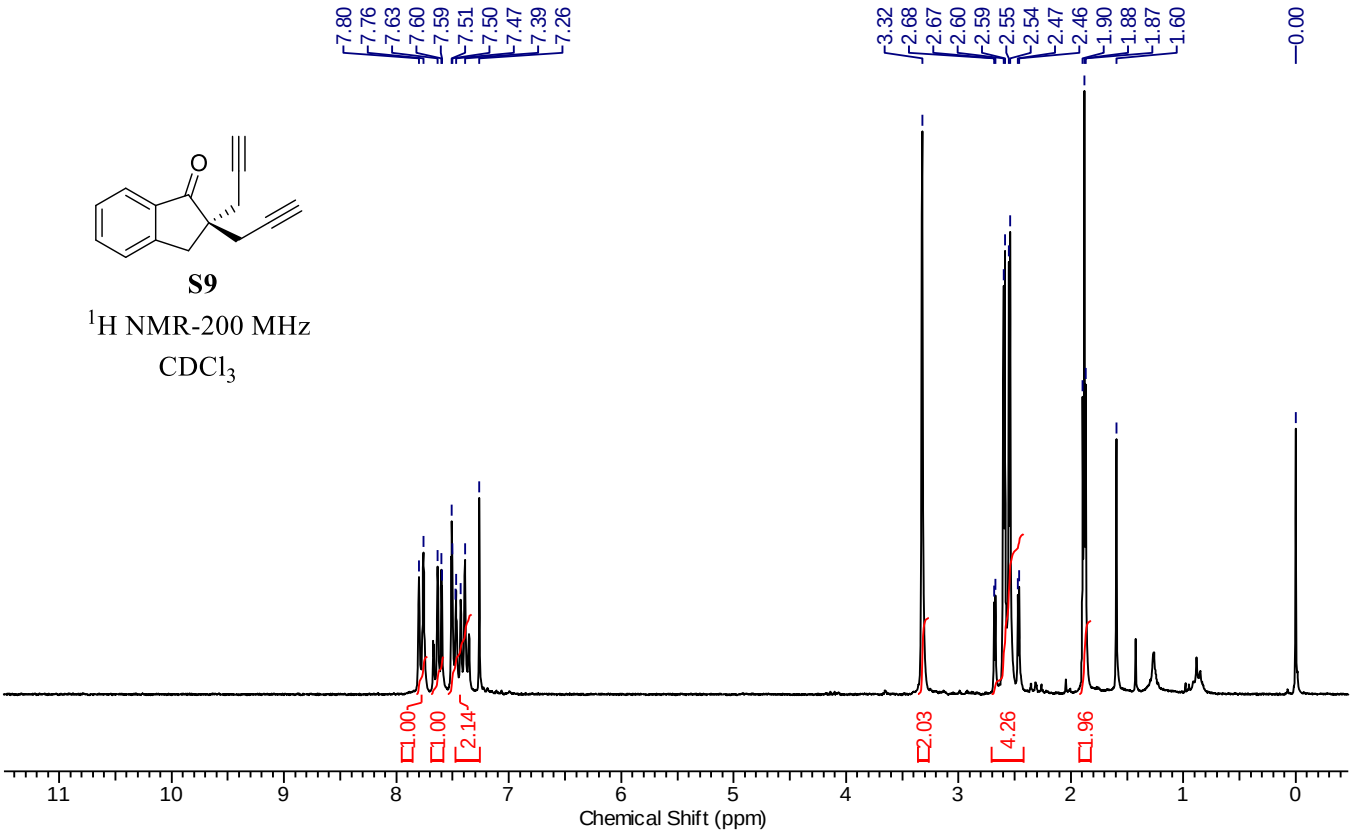


S4

^{13}C NMR, 101 MHz

$CDCl_3$

2-Di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (S9)

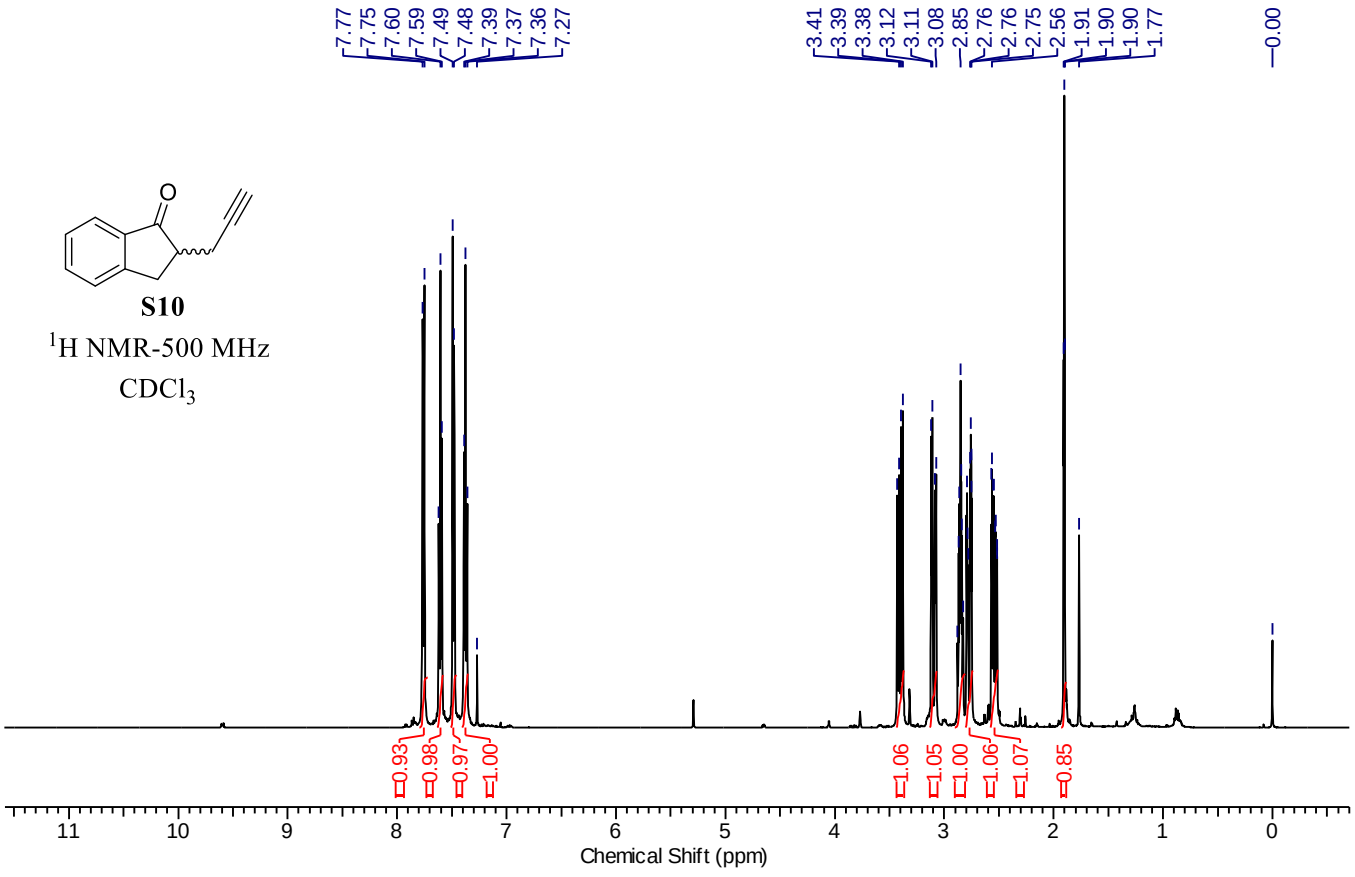


S9

^{1}H NMR-200 MHz

$CDCl_3$

2-(Prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (S10)

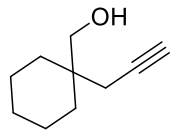


S10

^{1}H NMR-500 MHz

$CDCl_3$

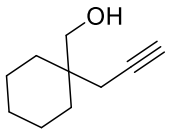
(1-(Prop-2-yn-1-yl)cyclohexyl)methanol (84a):



84a

^{1}H NMR, 400 MHz

$CDCl_3$

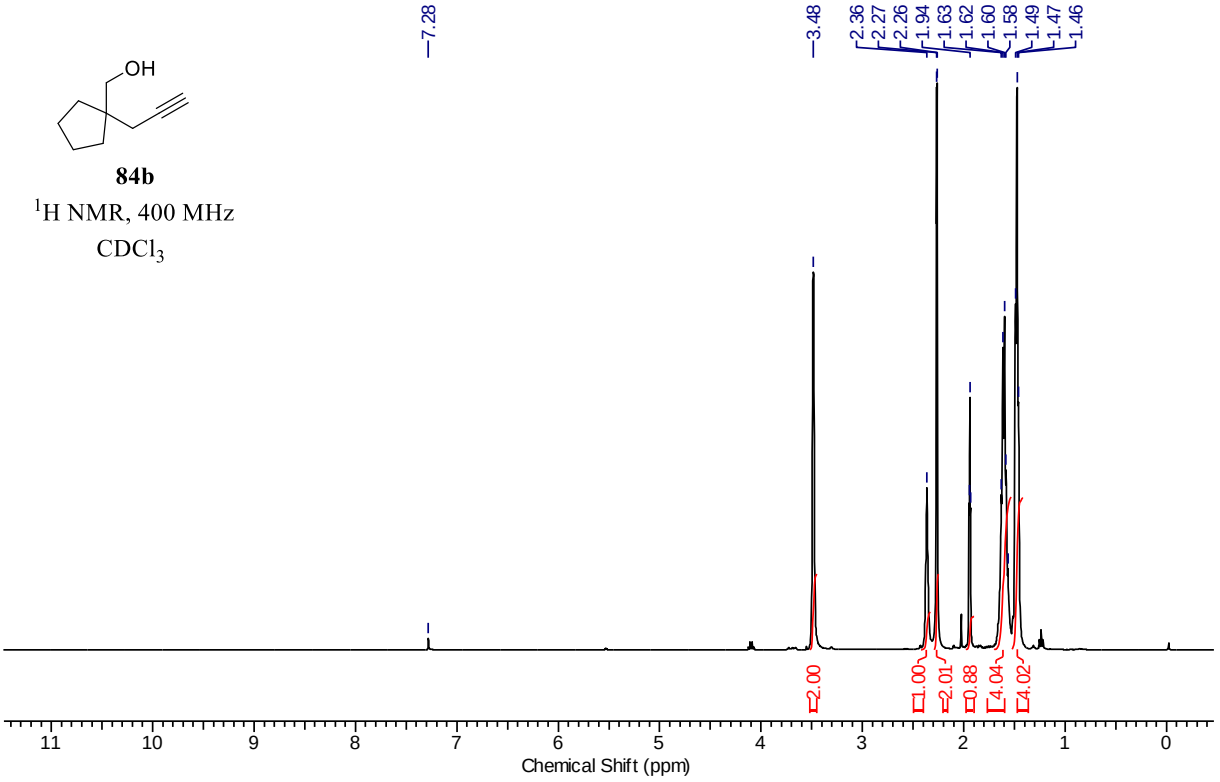


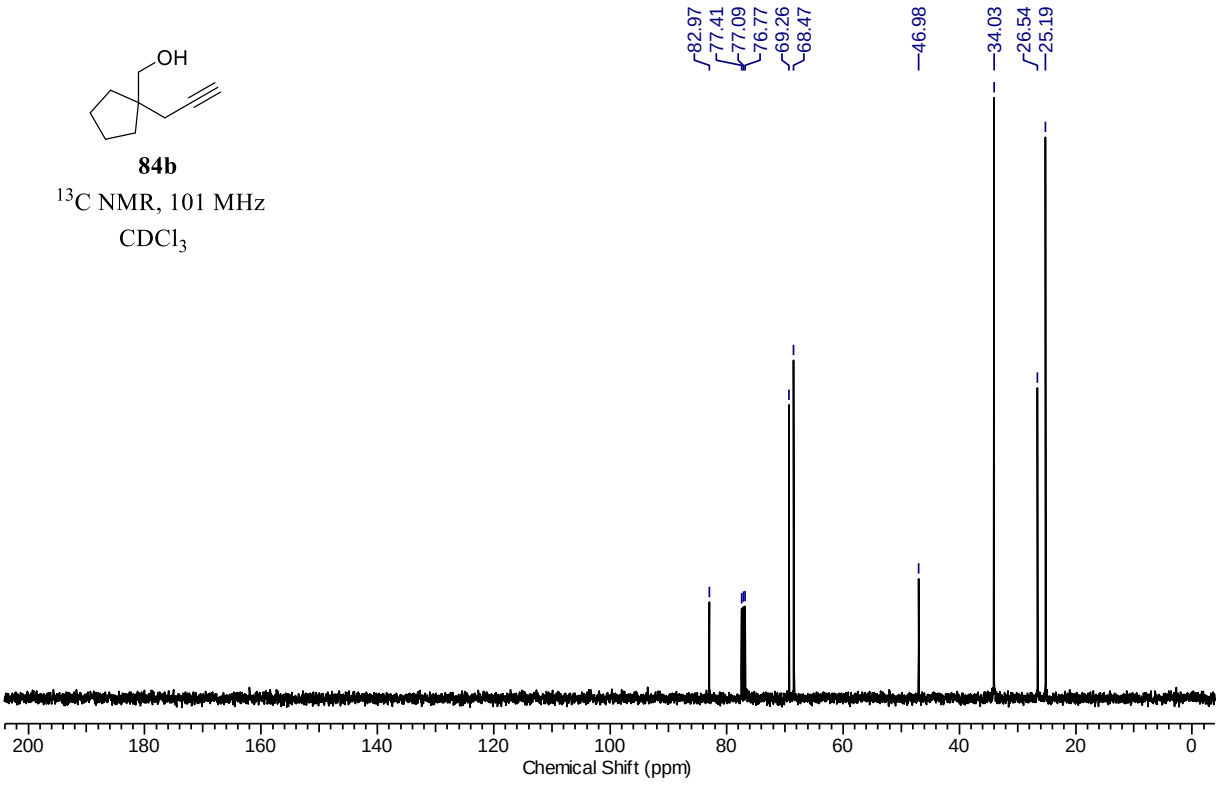
84a

^{13}C NMR, 101 MHz

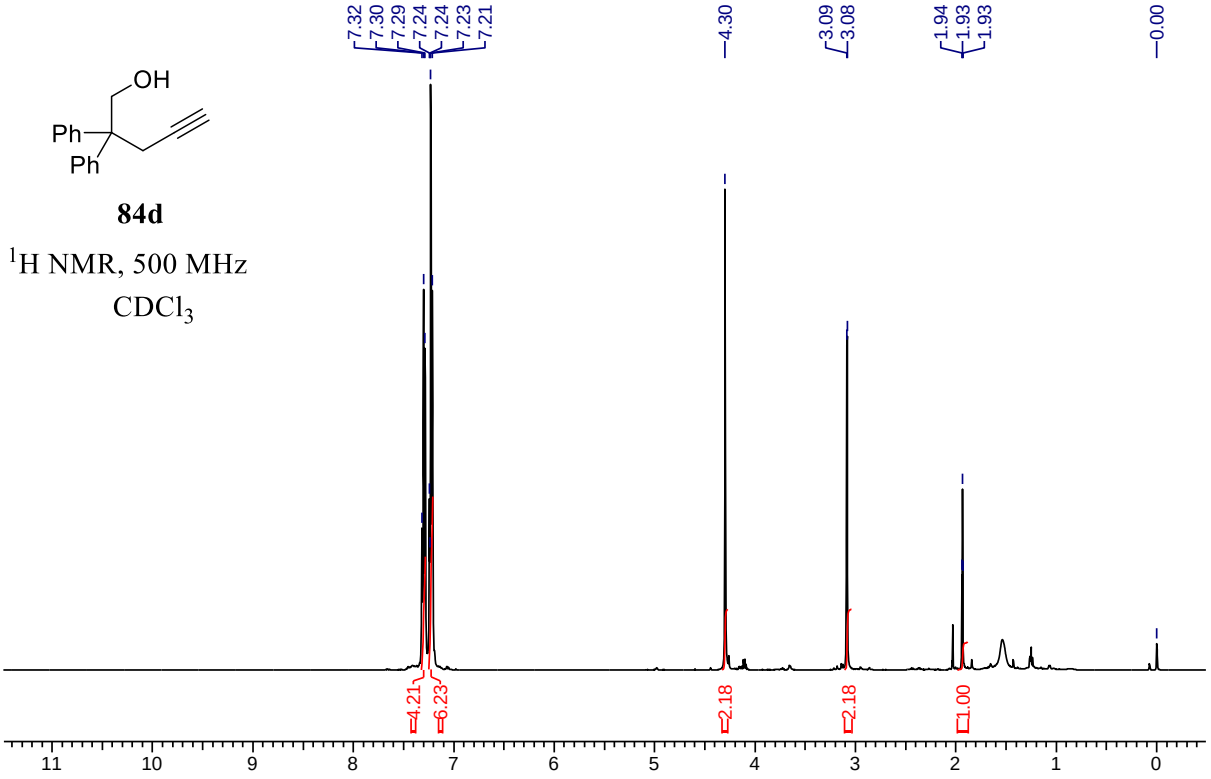
$CDCl_3$

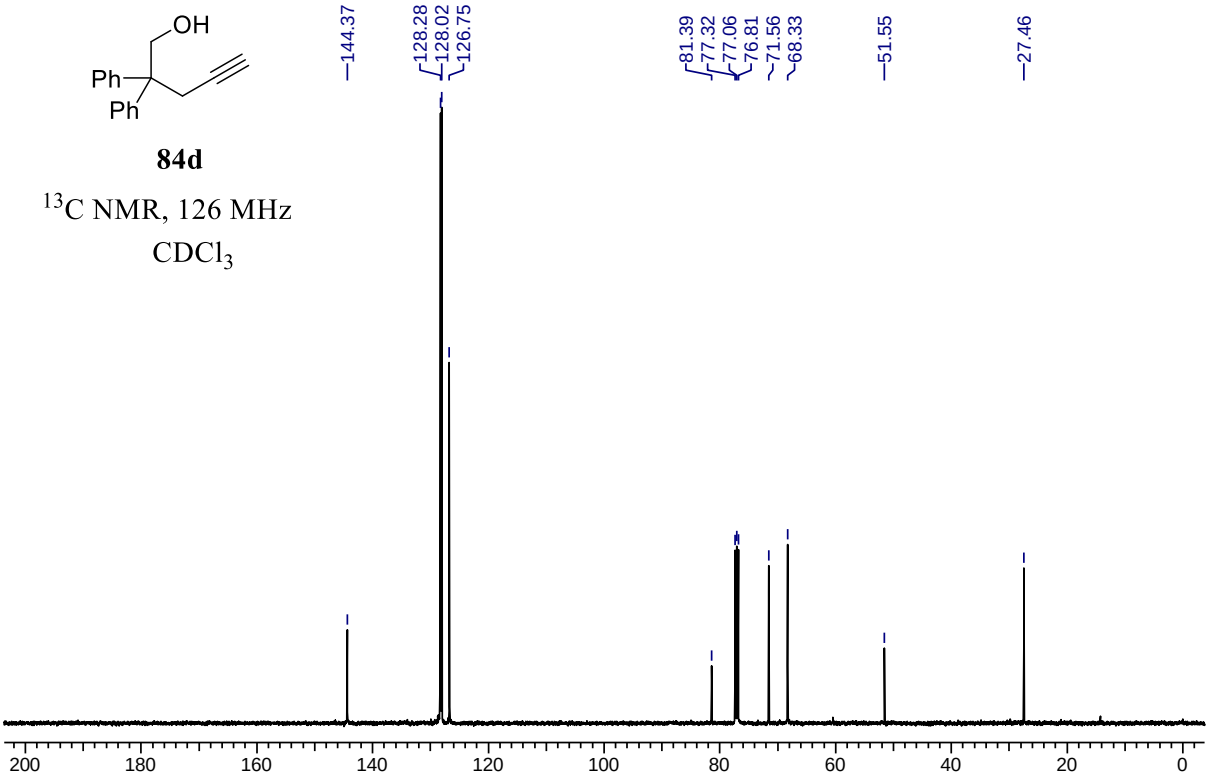
(1-(Prop-2-yn-1-yl) cyclopentyl) methanol (84b):



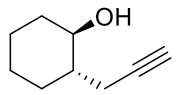


2, 2-Diphenylpent-4-yn-1-ol (84d):





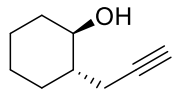
2-(Prop-2-yn-1-yl)cyclohexan-1-ol (84f):



84f

^{1}H NMR-500 MHz

$CDCl_3$

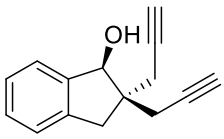


84f

^{13}C NMR-126 MHz

$CDCl_3$

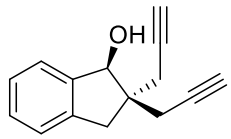
2,2-Di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-ol (84g):



84g

^{1}H NMR-500 MHz

$CDCl_3$

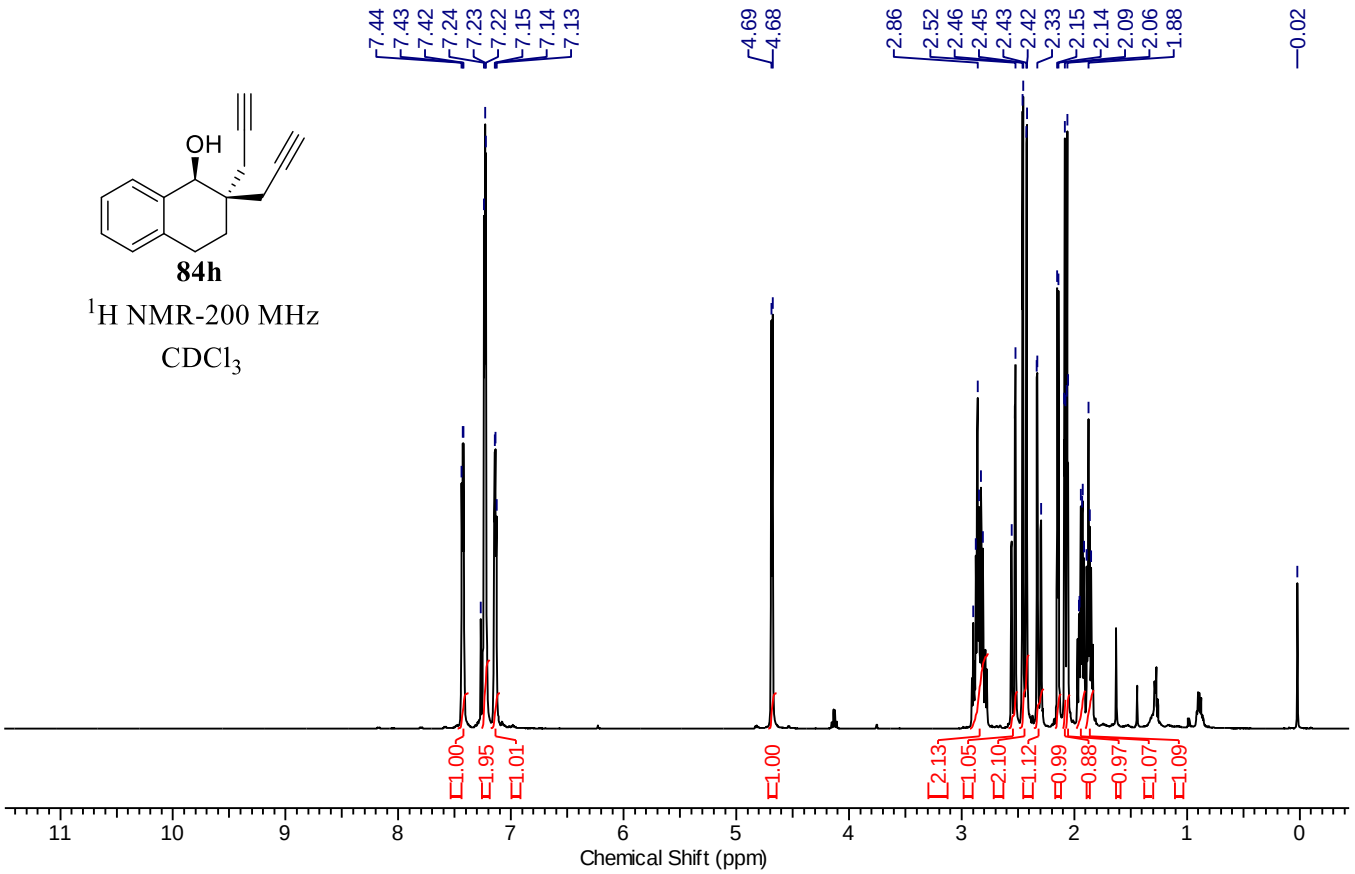


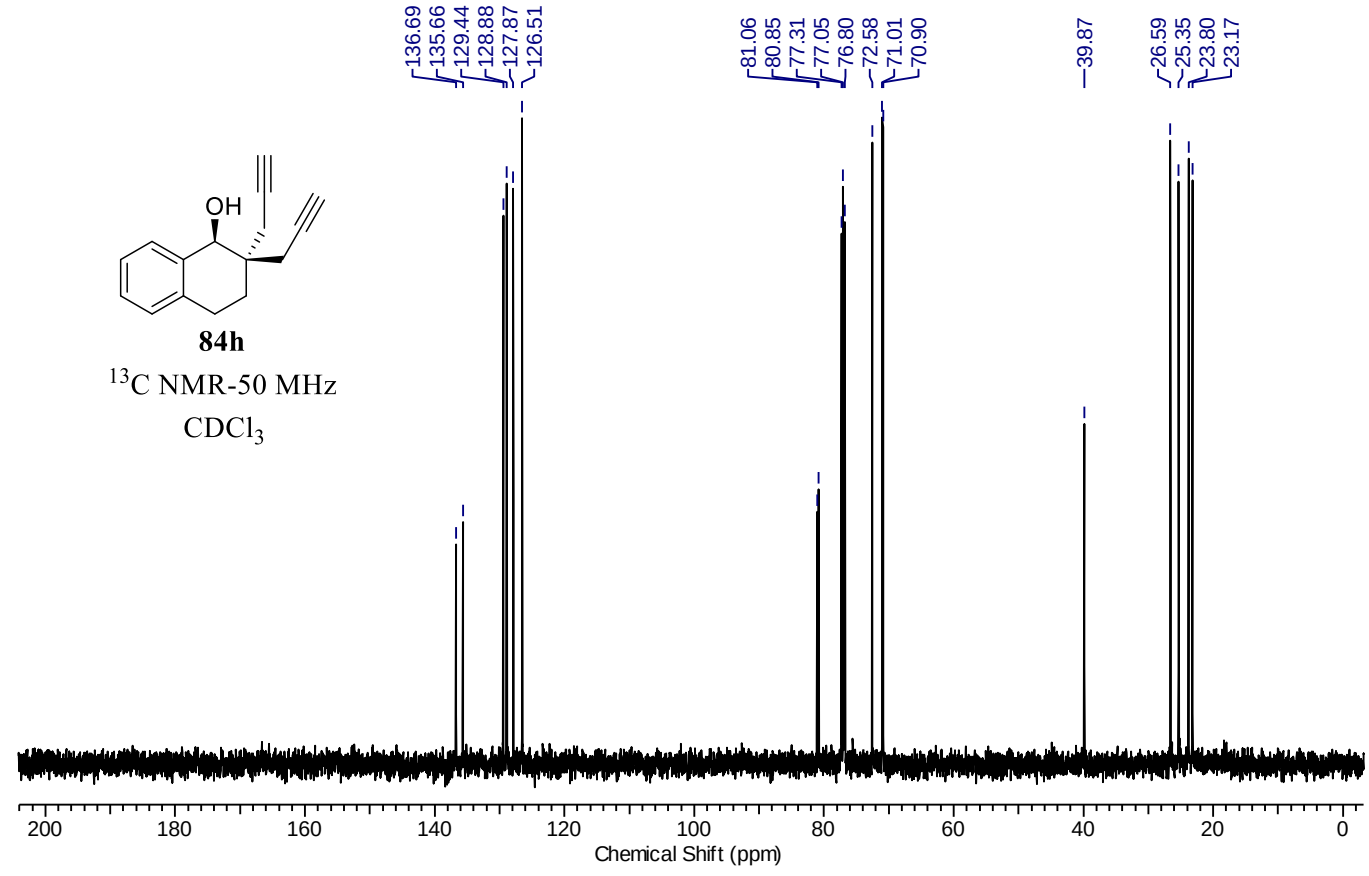
84g

^{13}C NMR-126 MHz

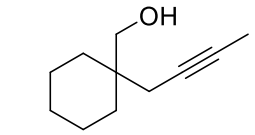
$CDCl_3$

2,2-Di(prop-2-yn-1-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (84h)





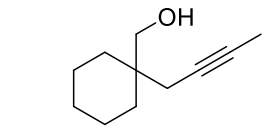
(1-(But-2-yn-1-y(1-(But-2-yn-1-yl)cyclohexyl)methanol (87a):



87a

^{1}H NMR, 400 MHz

$CDCl_3$

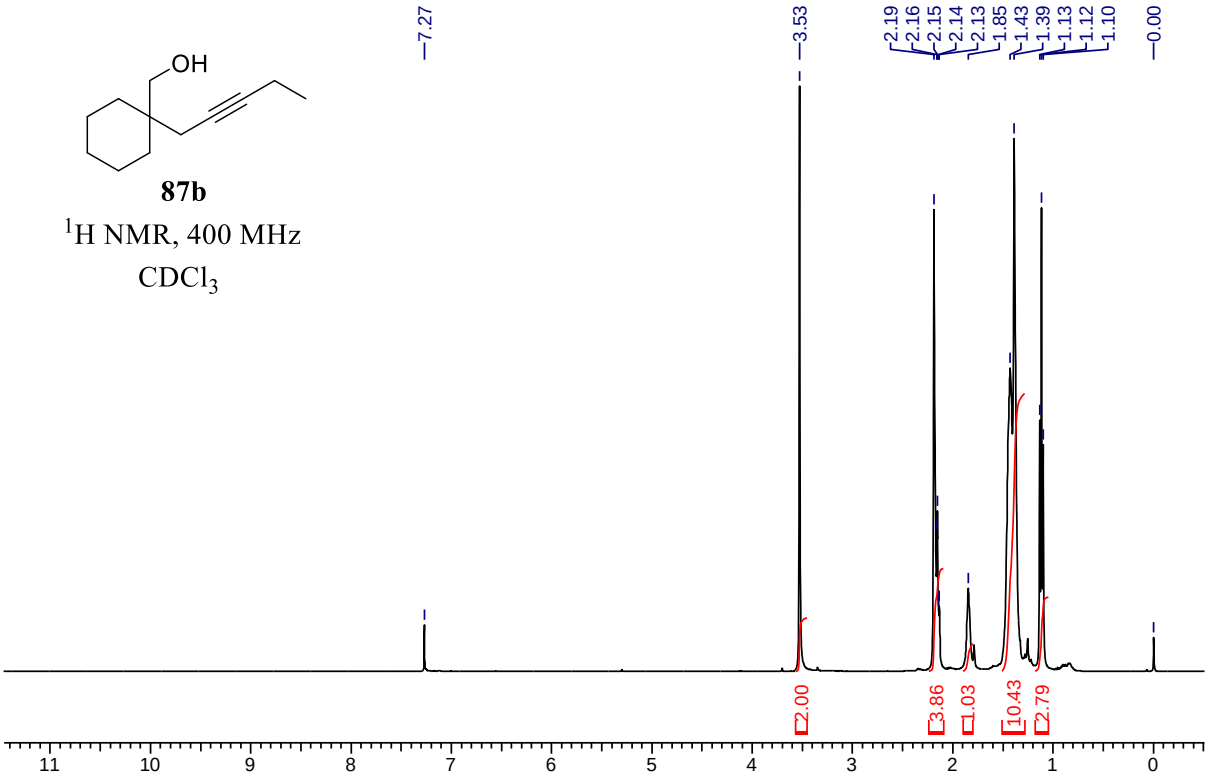


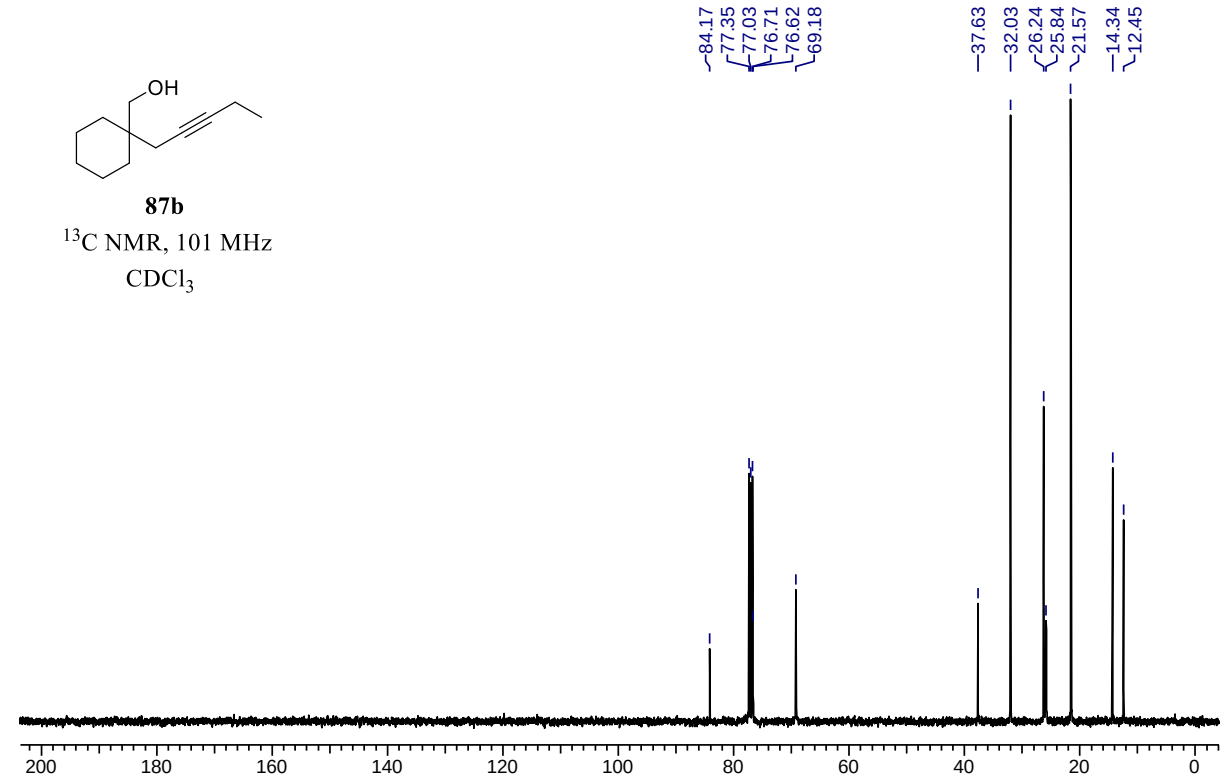
87a

^{13}C NMR, 101 MHz

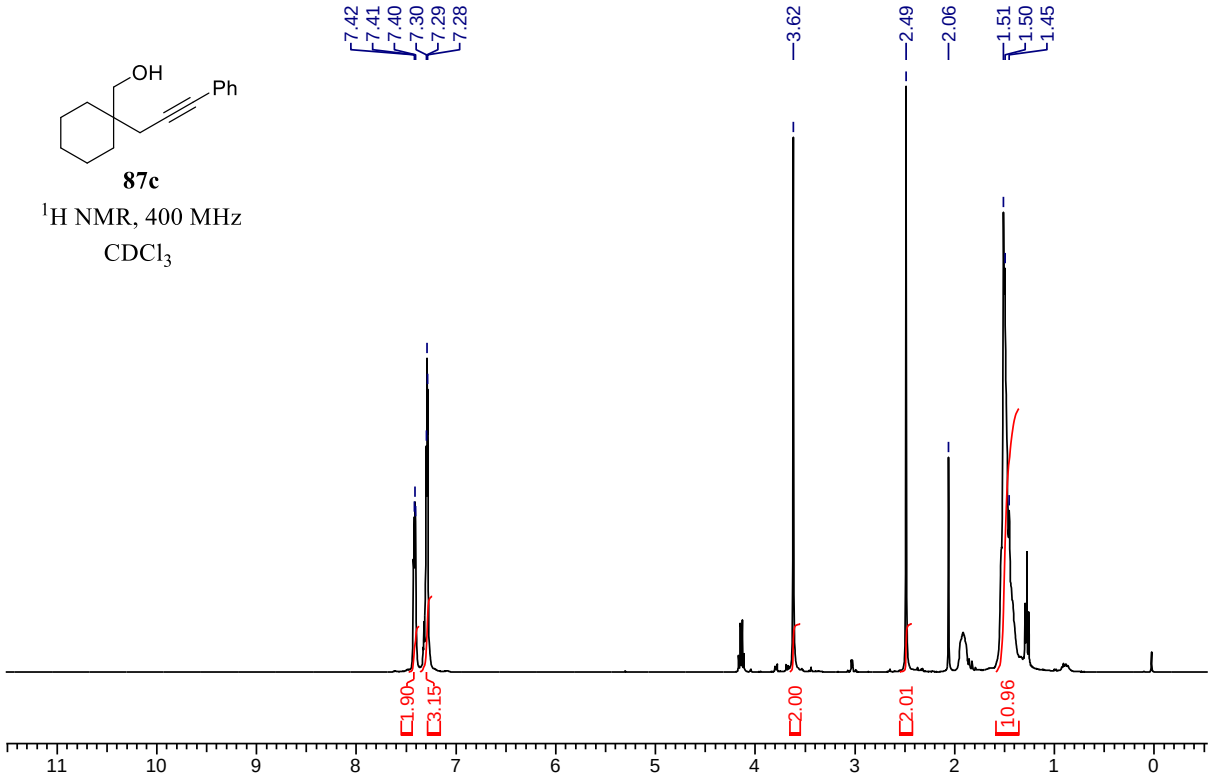
$CDCl_3$

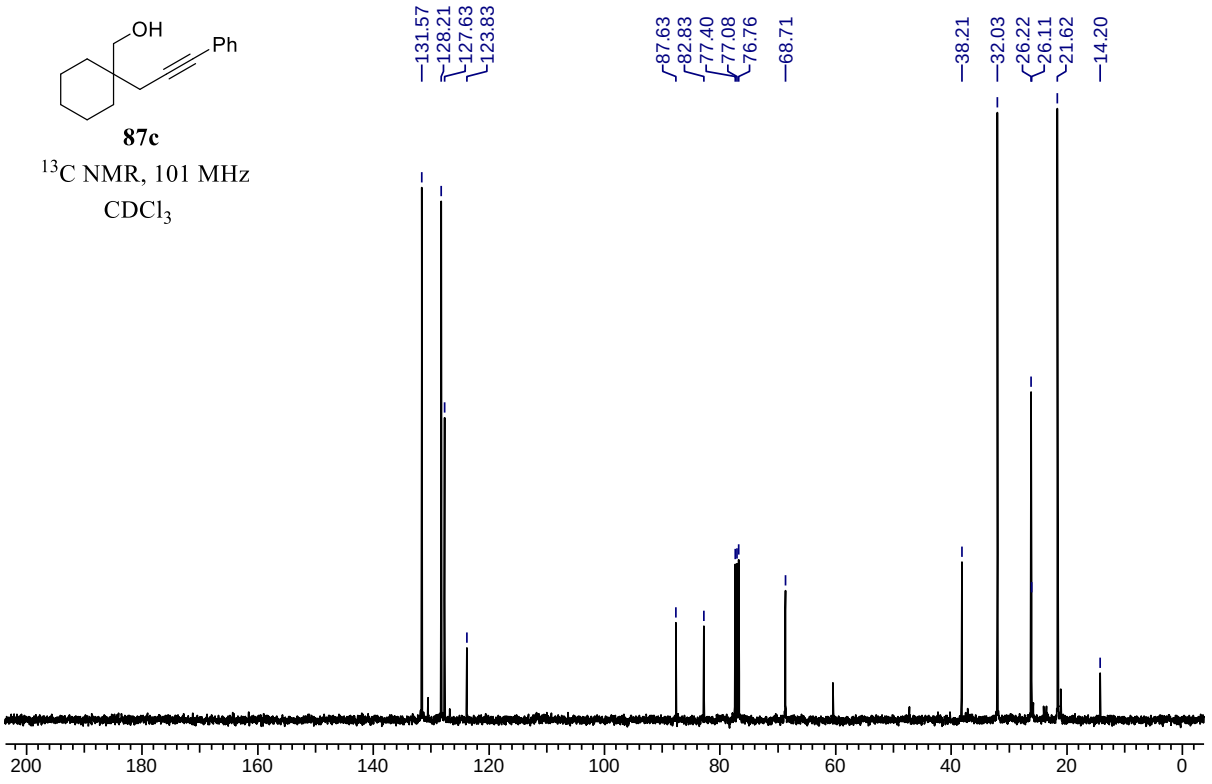
(1-(Pent-2-yn-1-yl) cyclohexyl) methanol (87b):



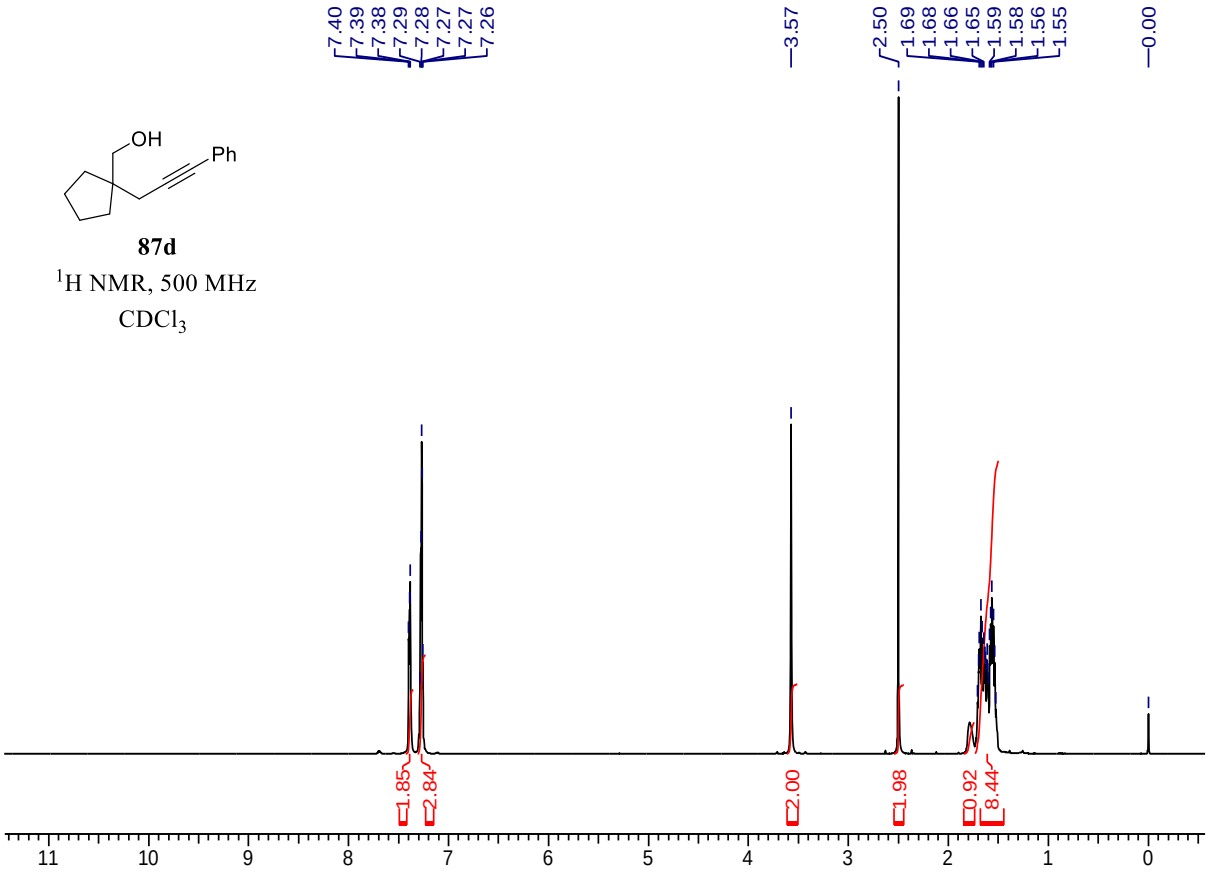


(1-(Phenylprop-2-yl)cyclohexyl)methanol (87c):





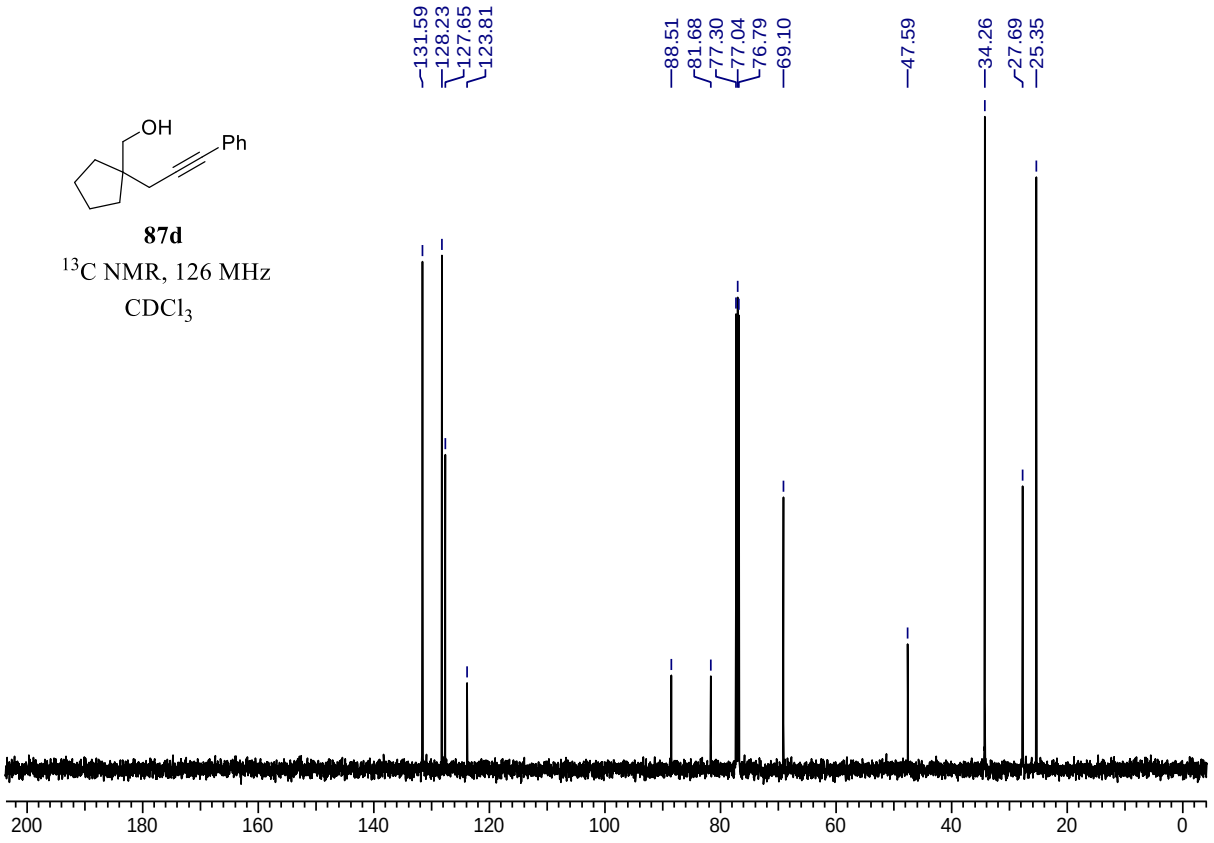
(1-(3-Phenylprop-2-yn-1-yl) cyclopentyl) methanol (87d):



87d

^{1}H NMR, 500 MHz

$CDCl_3$

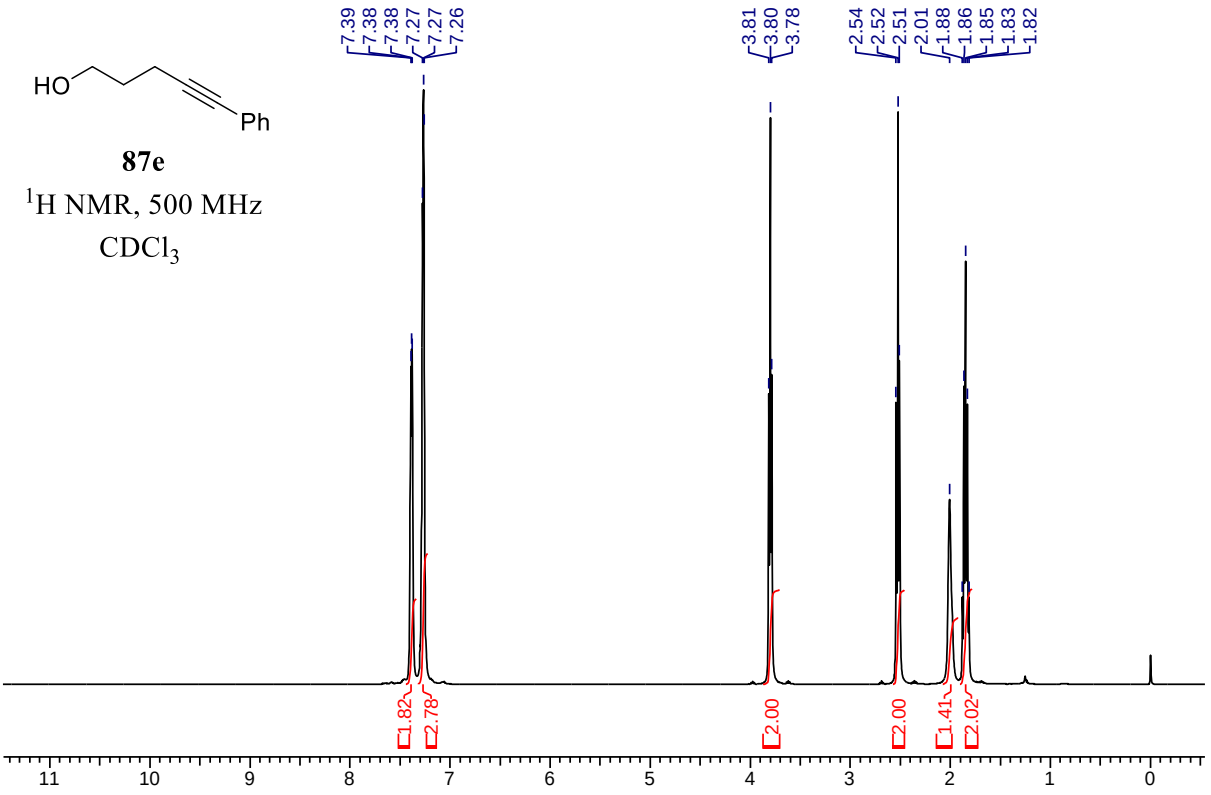


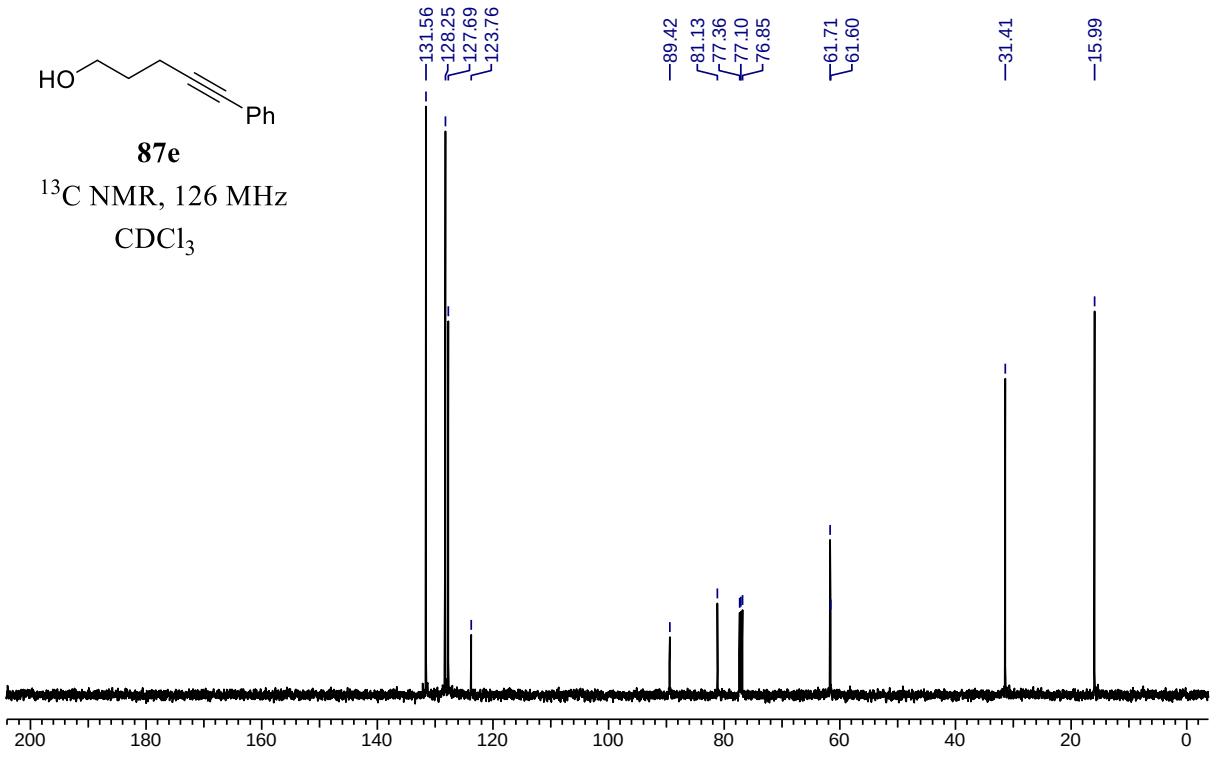
87d

^{13}C NMR, 126 MHz

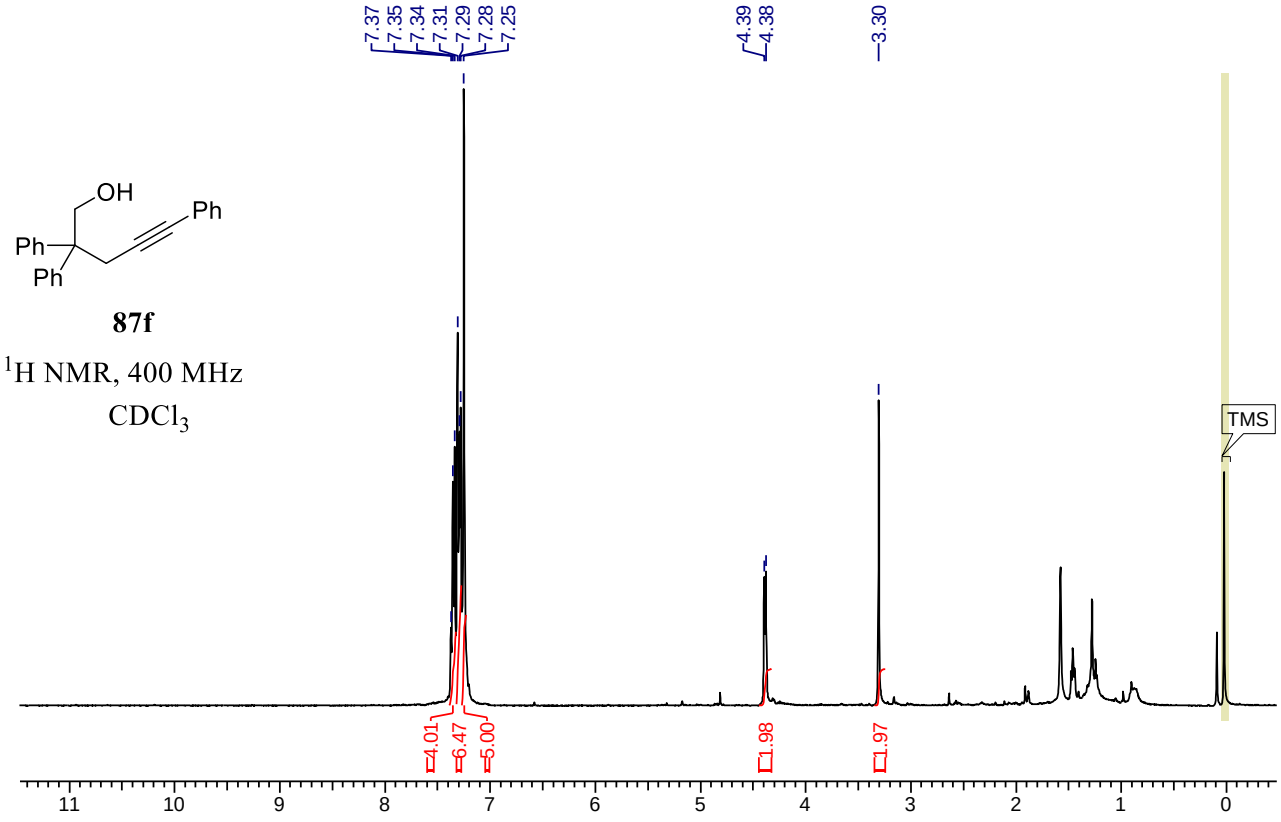
$CDCl_3$

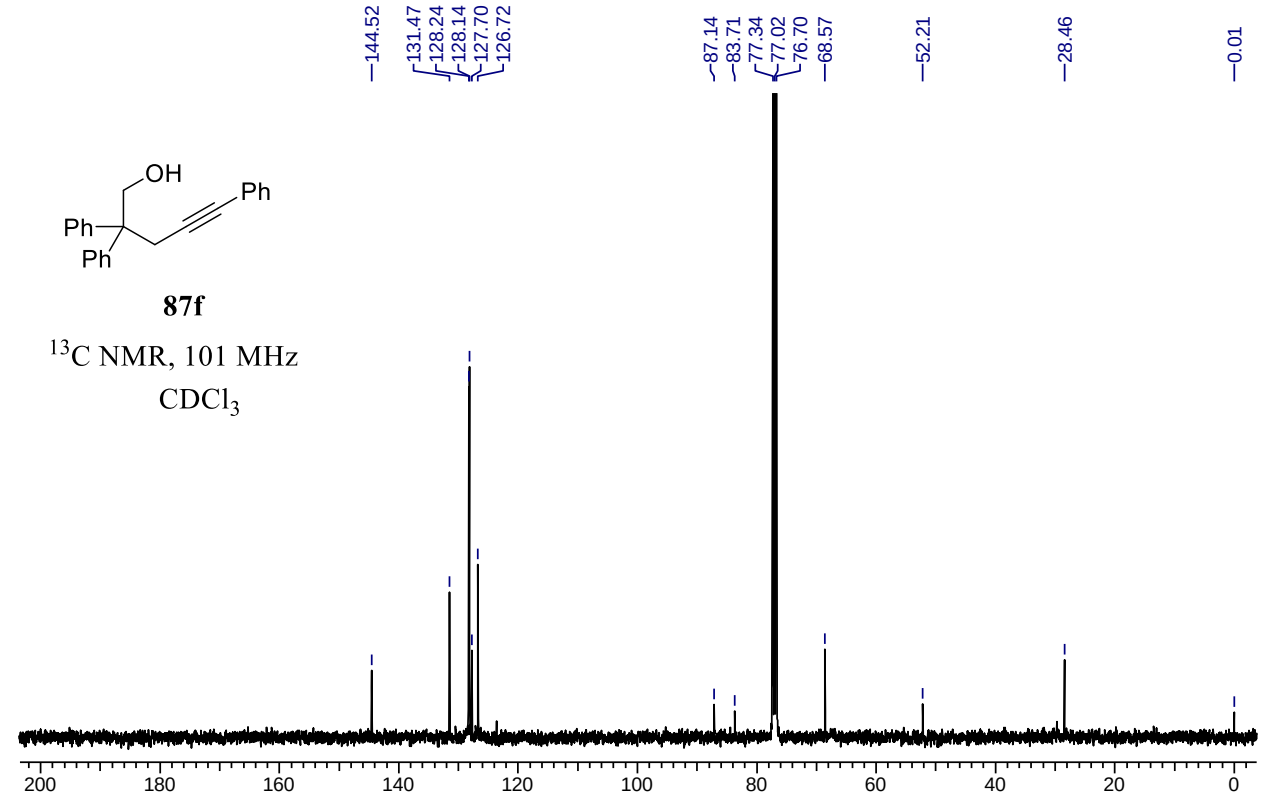
5-Phenylpent-4-yn-1-ol (87e):



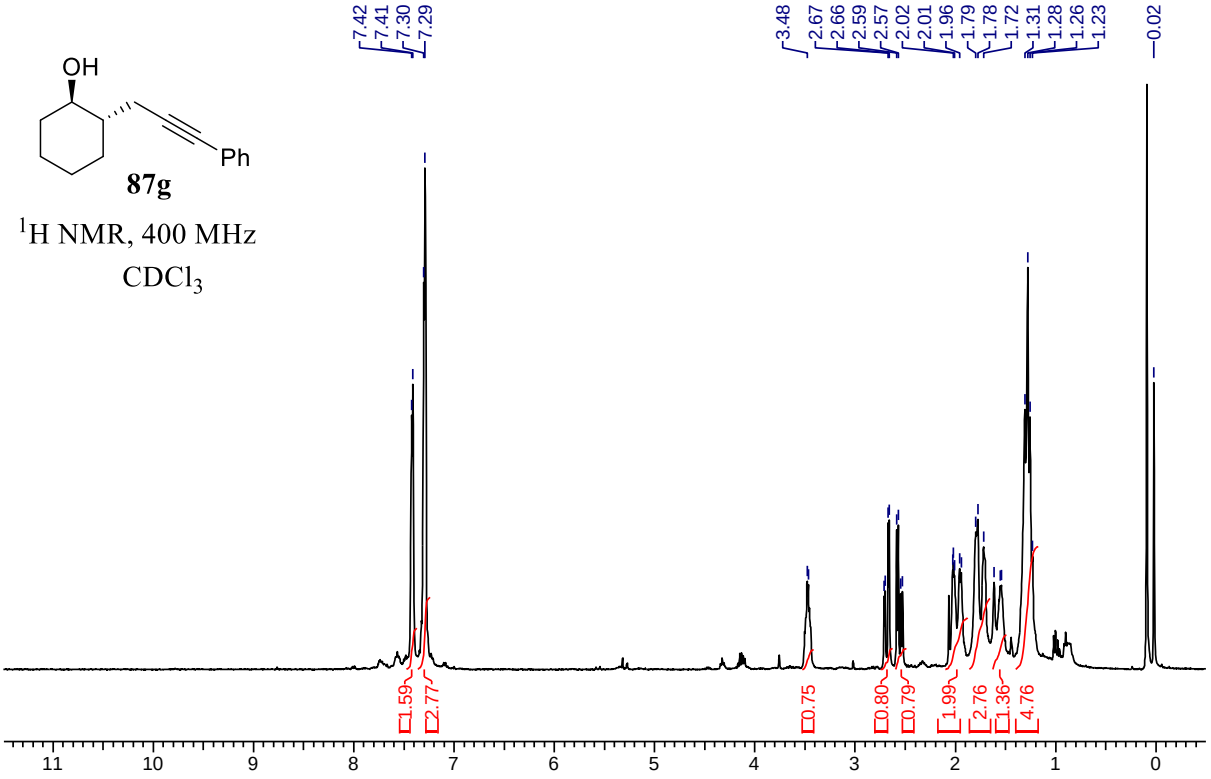


2, 2, 5-Triphenylpent-4-yn-1-ol (87f):



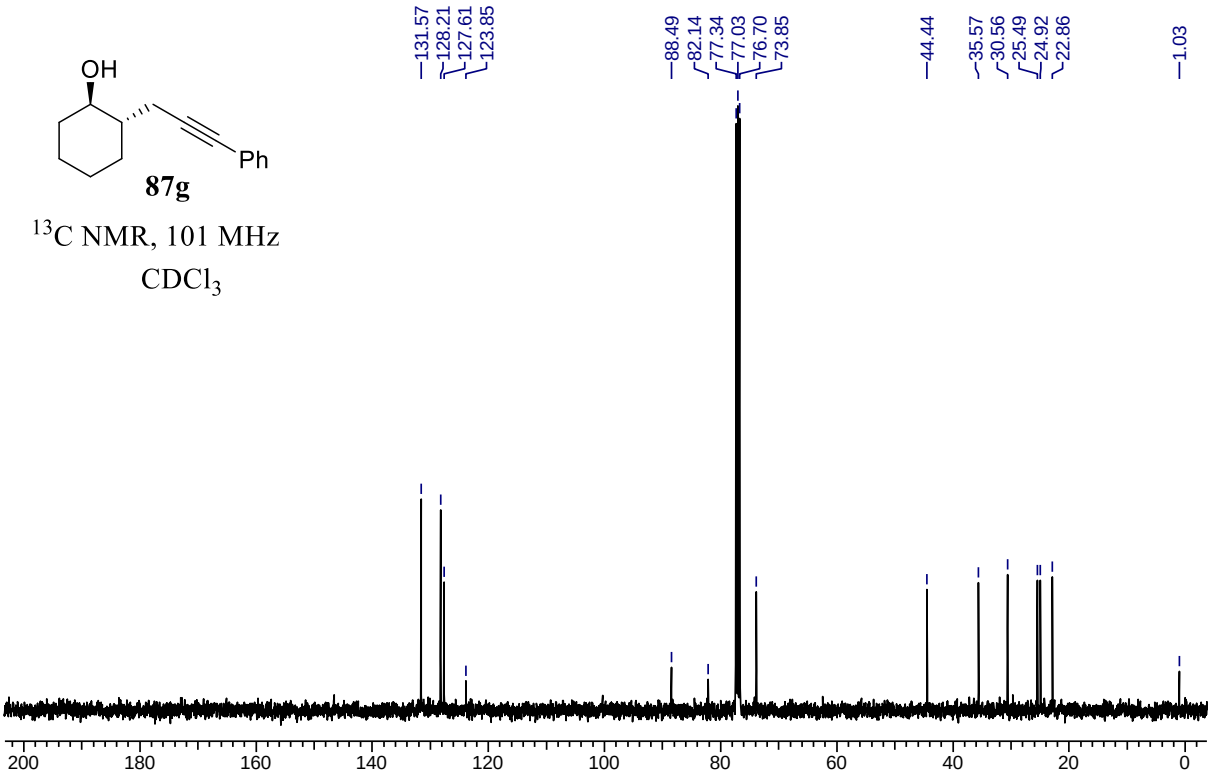


2-(3-Phenylprop-2-yn-1-yl) cyclohexan-1-ol (87g):



^{1}H NMR, 400 MHz

$CDCl_3$

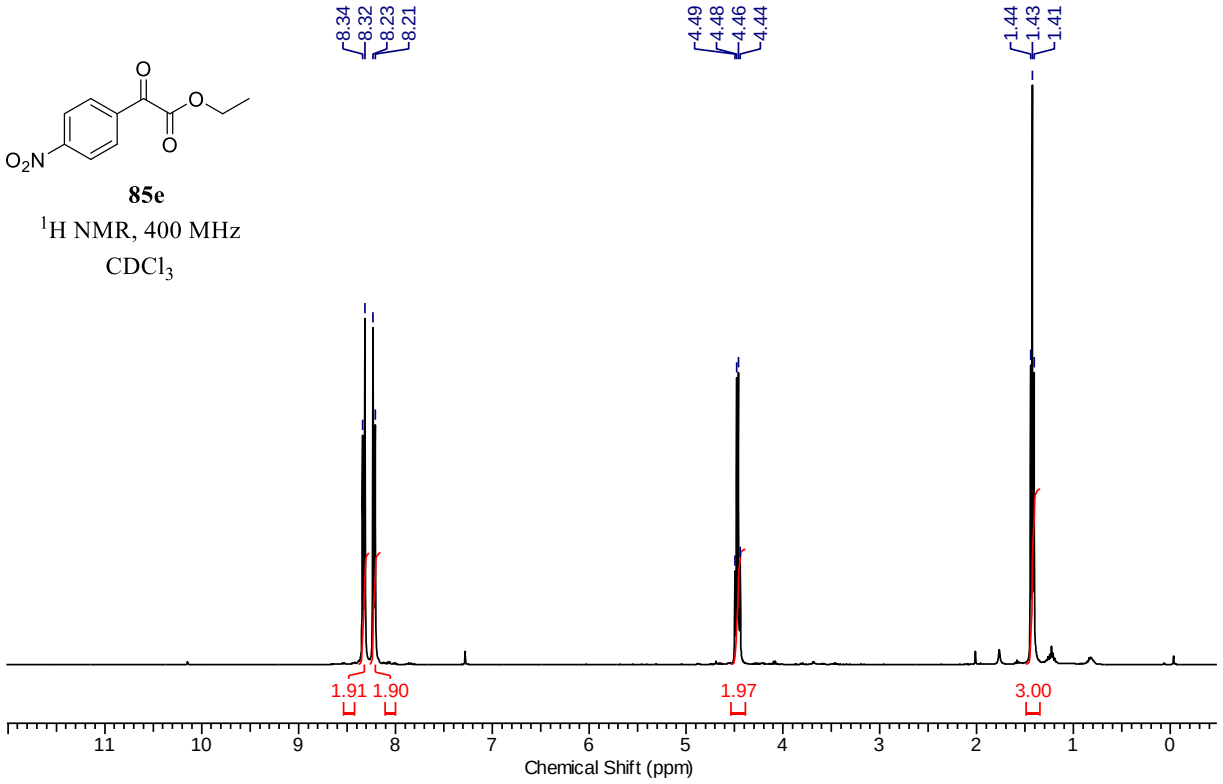


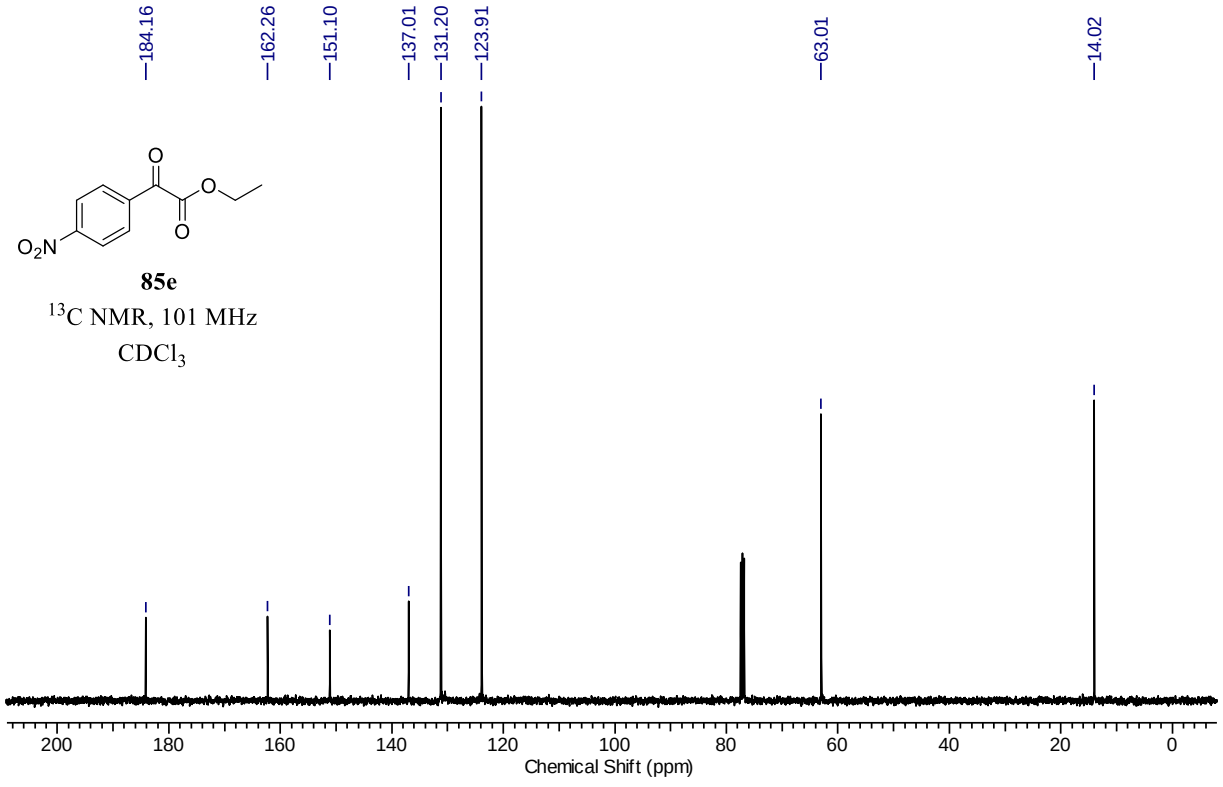
^{13}C NMR, 101 MHz

$CDCl_3$

Synthesis of α-ketoesters:

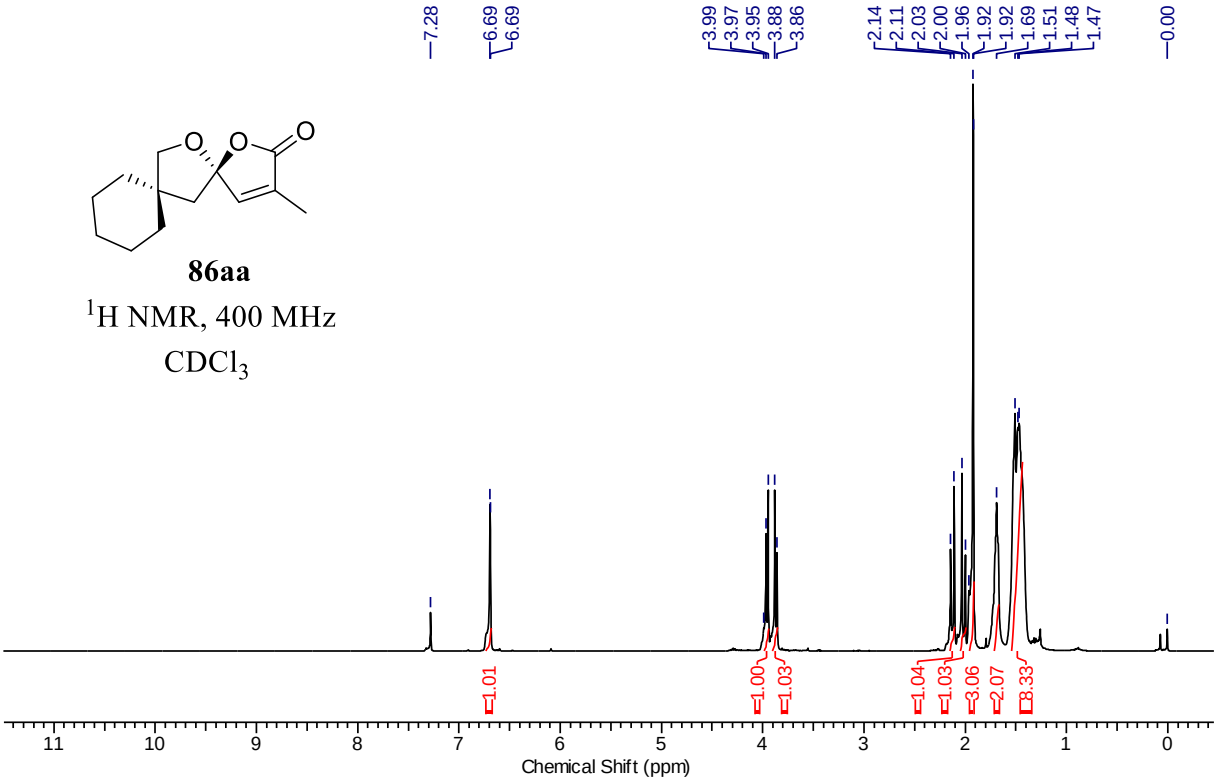
Ethyl 2-(4-nitrophenyl)-2-oxoacetate (85e):





Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (Possessing terminal alkyne)

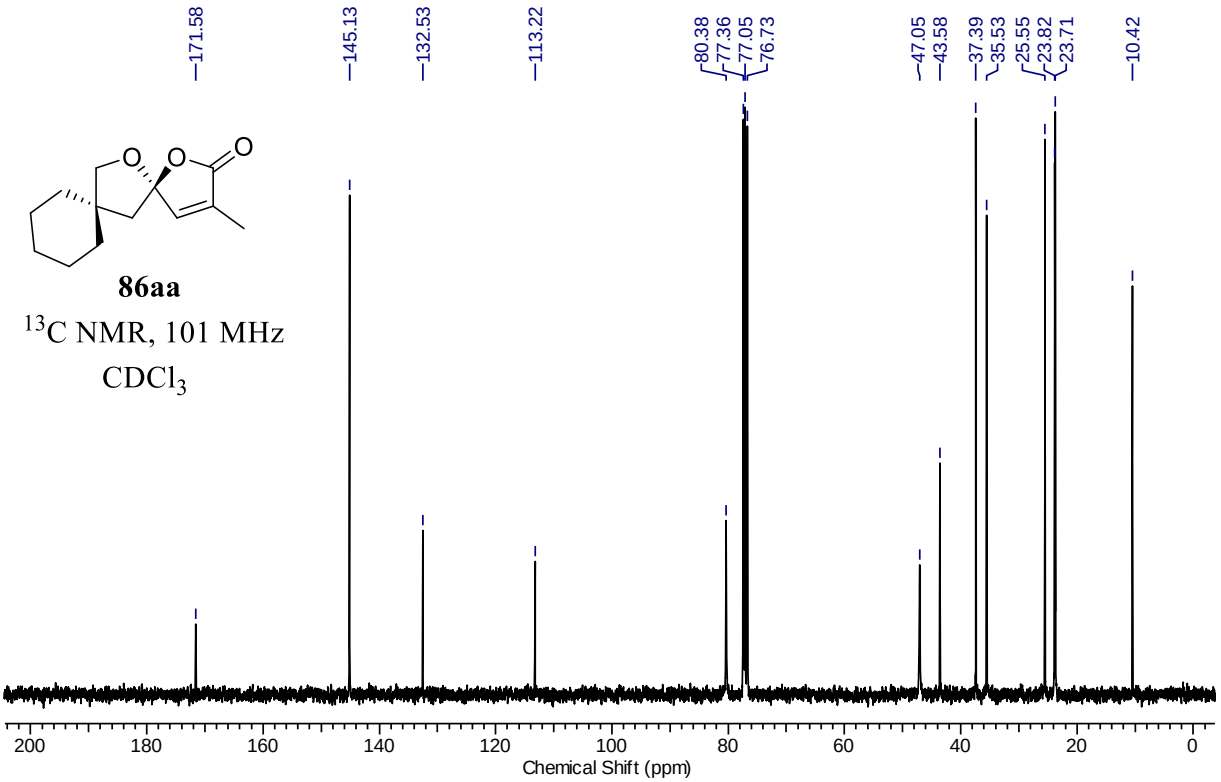
3-Methyl-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (86aa):



86aa

^{1}H NMR, 400 MHz

$CDCl_3$

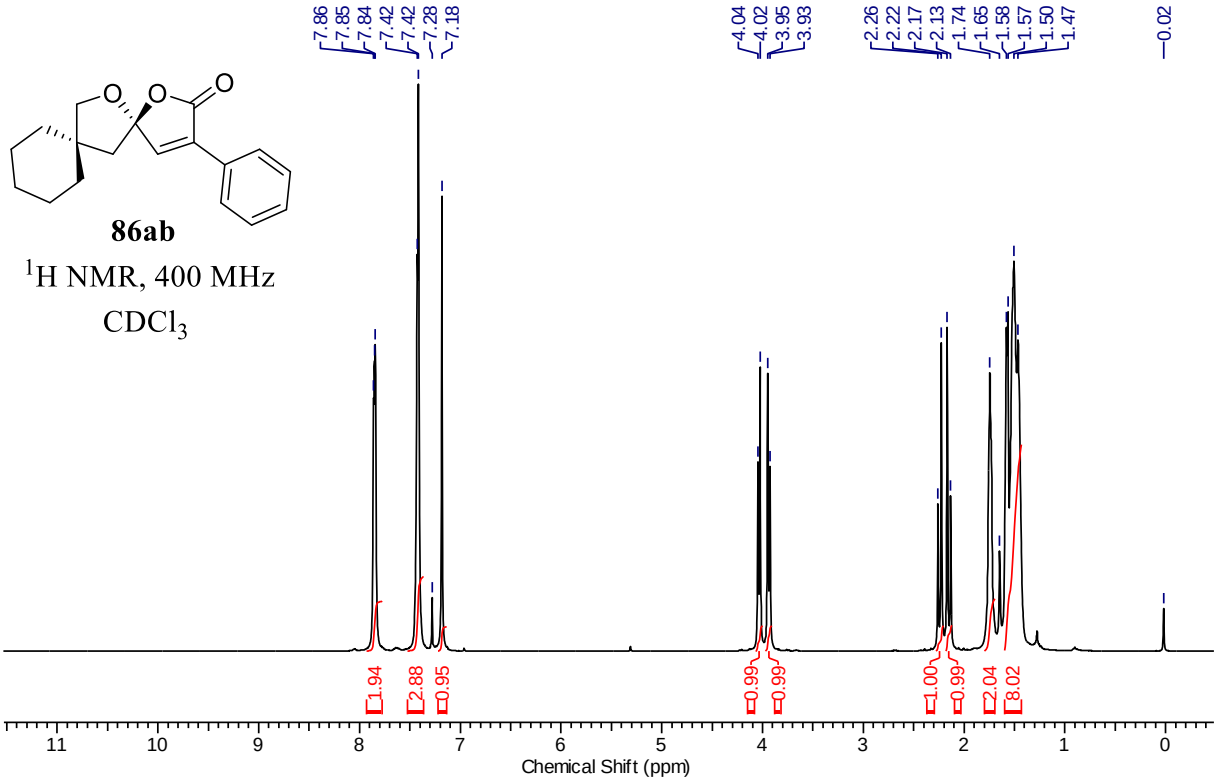


86aa

^{13}C NMR, 101 MHz

$CDCl_3$

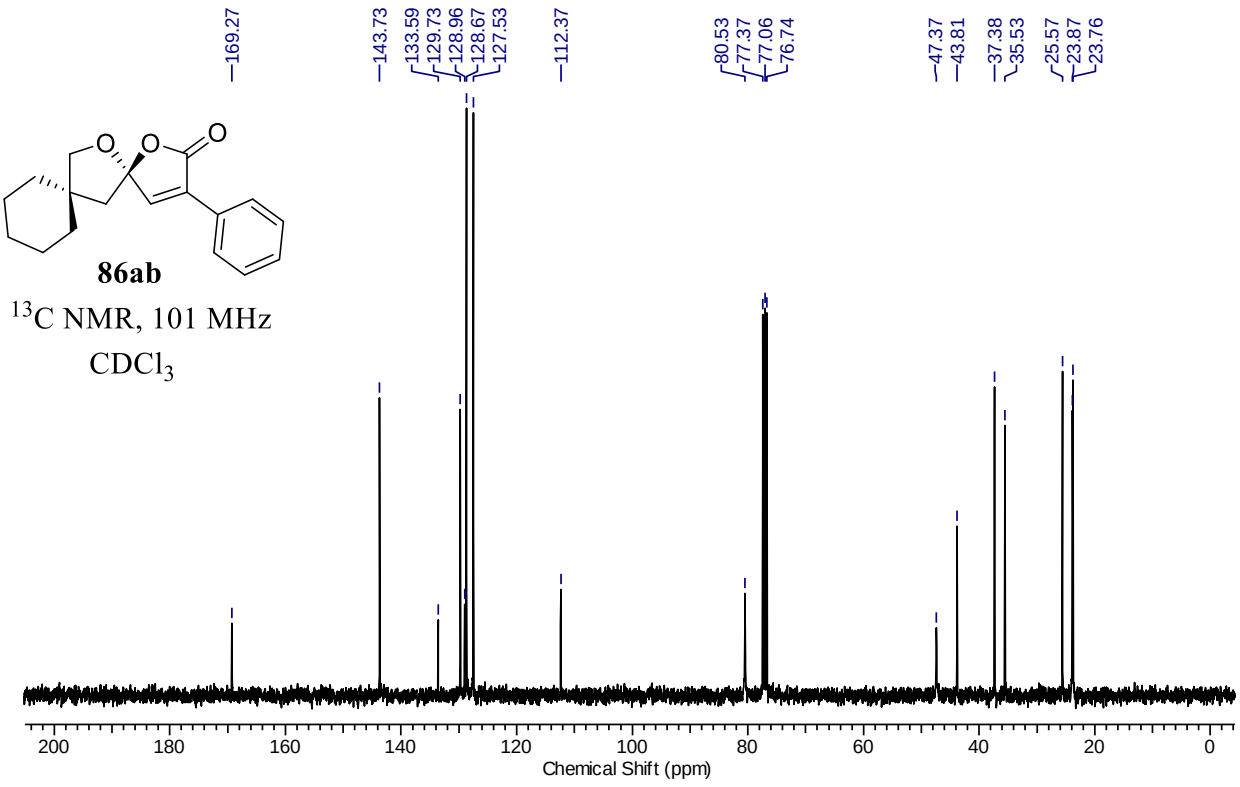
3-Phenyl-1, 14-dioxadispiro [4.4.5^7.2^5] tetradec-3-en-one (86ab):



86ab

^{1}H NMR, 400 MHz

$CDCl_3$

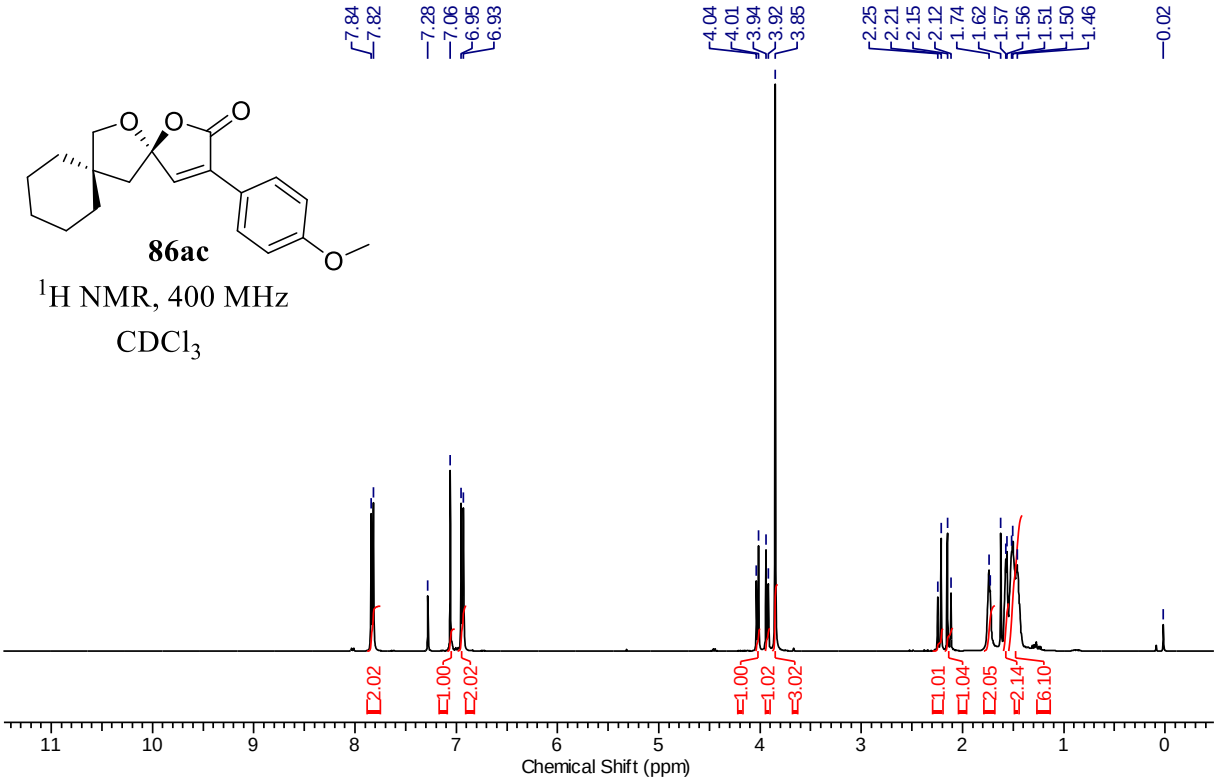


86ab

^{13}C NMR, 101 MHz

$CDCl_3$

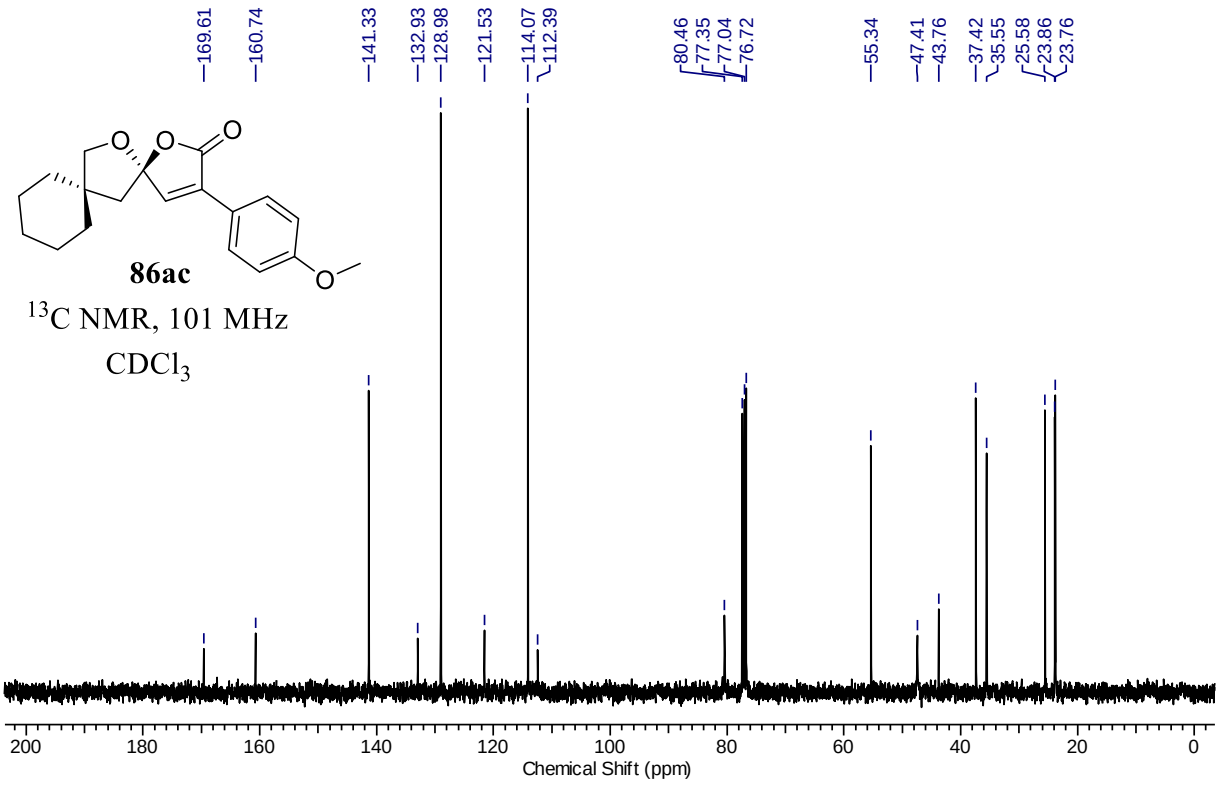
3-(4-Methoxyphenyl)-1,14-dioxadispiro[4.1.5^{7}.2^{5}]tetradec-3-en-2-one(86ac):



86ac

^{1}H NMR, 400 MHz

$CDCl_3$

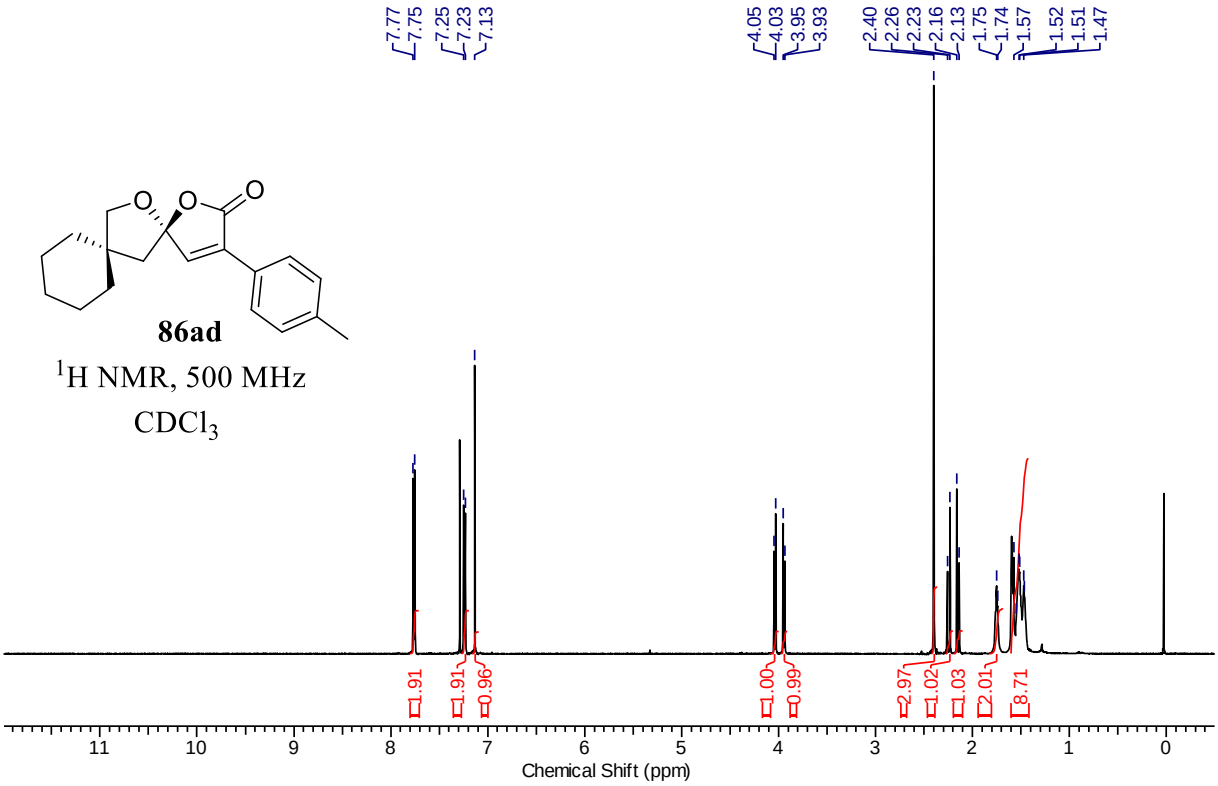


86ac

^{13}C NMR, 101 MHz

$CDCl_3$

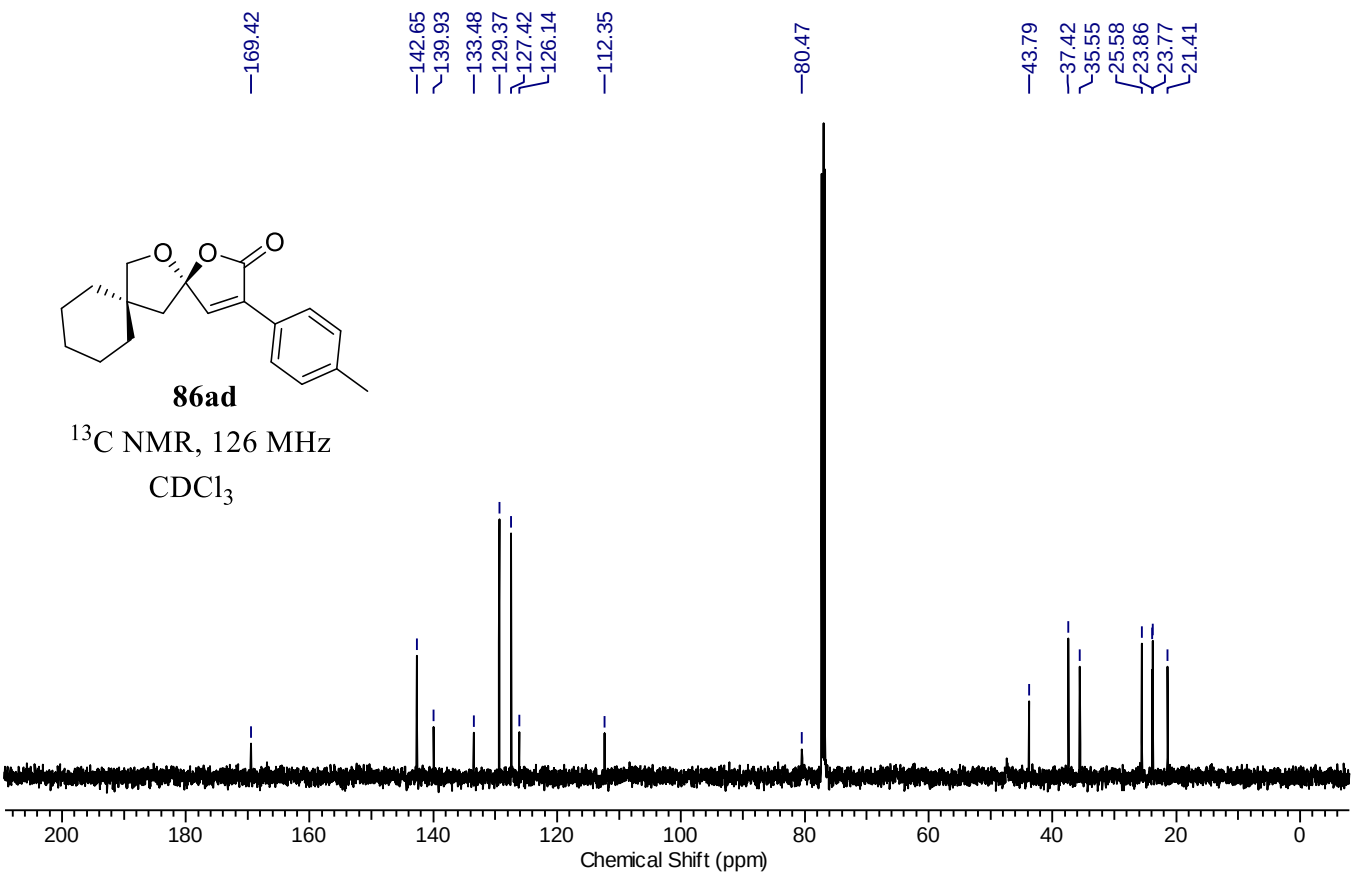
3-(*p*-Tolyl)-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (86ad):



86ad

^{1}H NMR, 500 MHz

$CDCl_3$

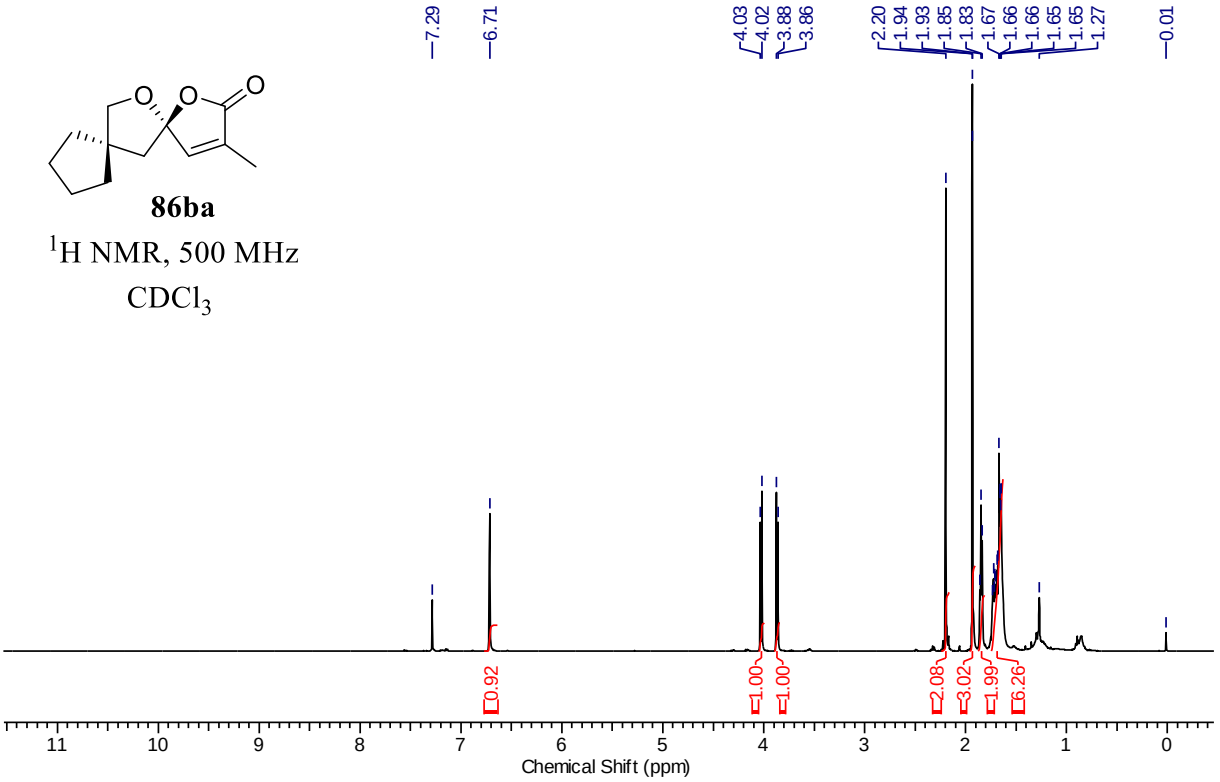


86ad

^{13}C NMR, 126 MHz

$CDCl_3$

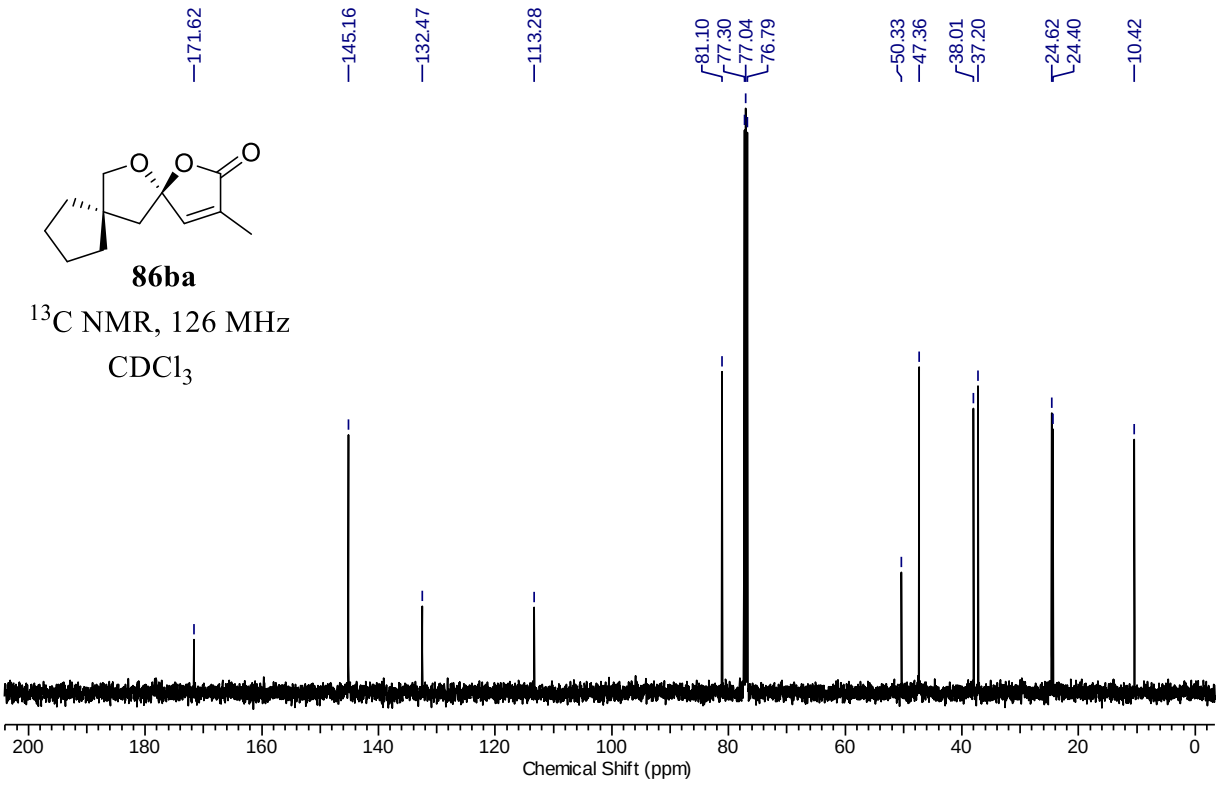
3-Methyl-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-2-one (86ba):



86ba

^{1}H NMR, 500 MHz

$CDCl_3$

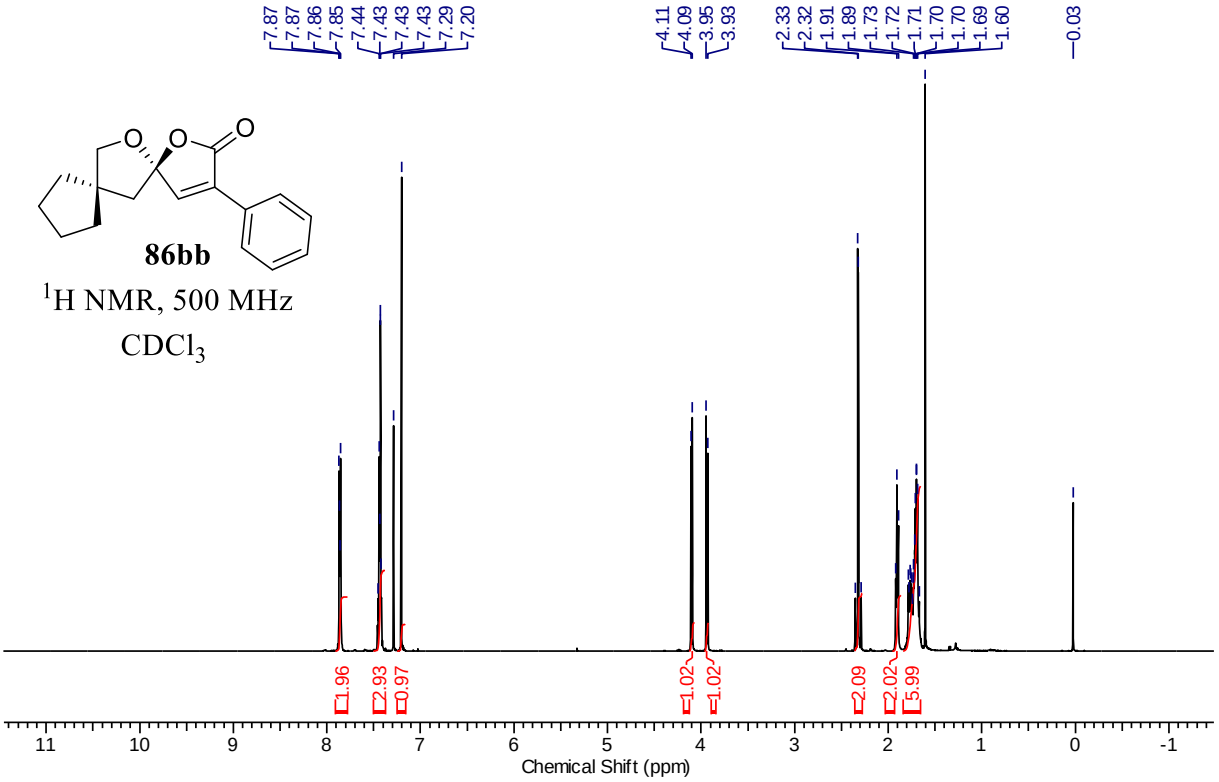


86ba

^{13}C NMR, 126 MHz

$CDCl_3$

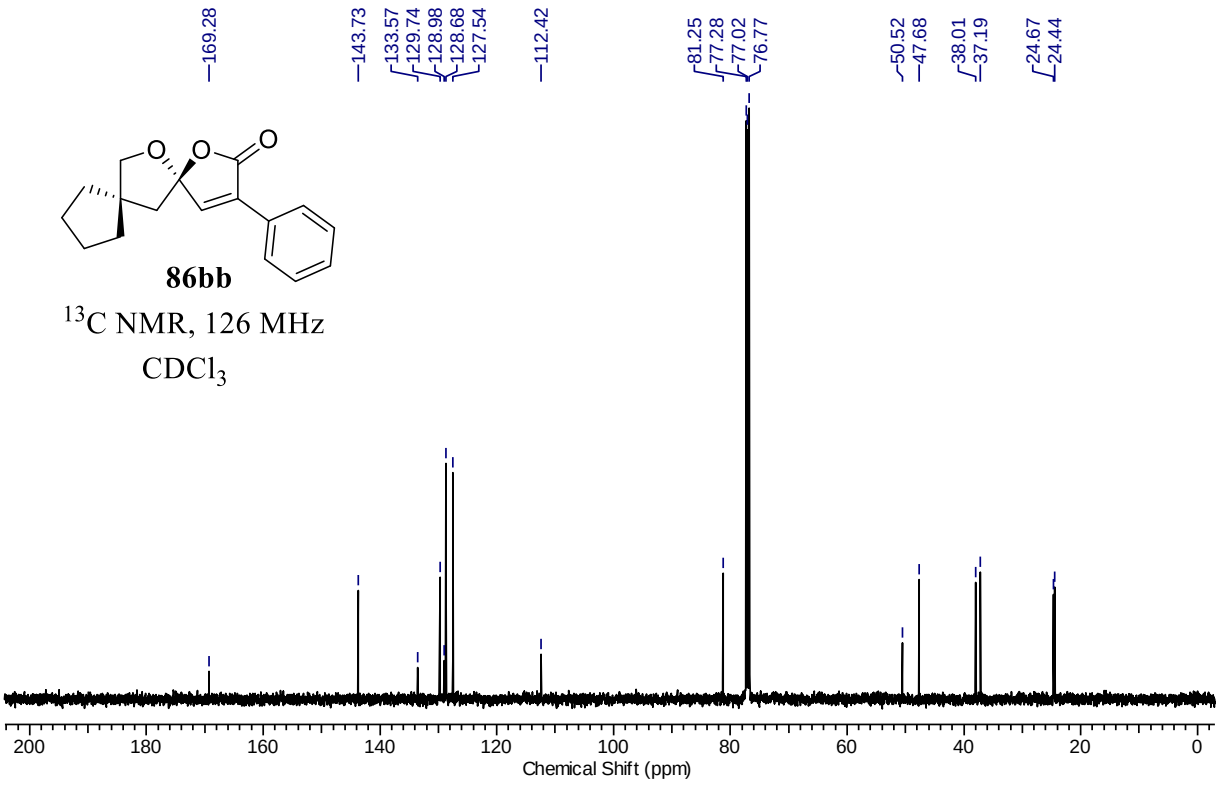
3-Phenyl-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-one(86bb):



86bb

^{1}H NMR, 500 MHz

$CDCl_3$

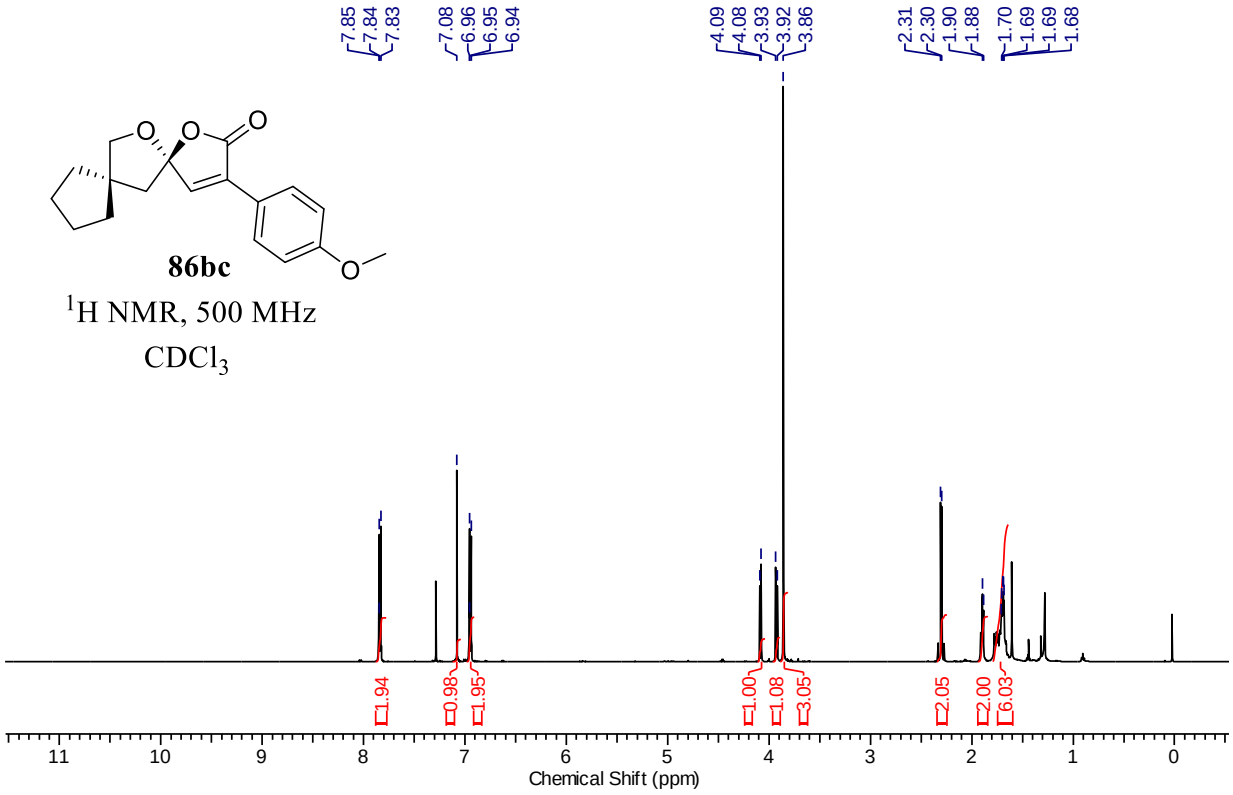


86bb

^{13}C NMR, 126 MHz

$CDCl_3$

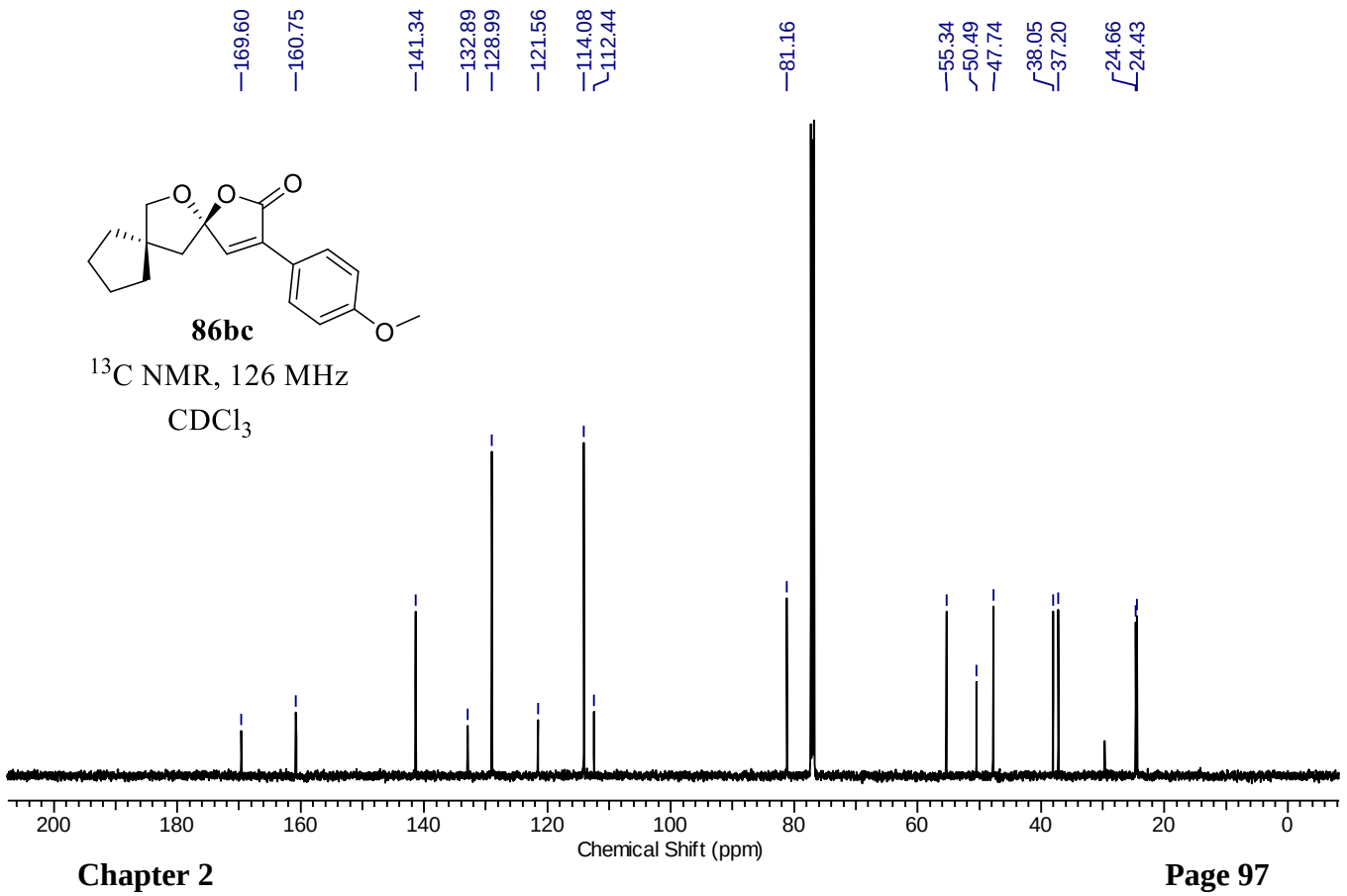
3-(4-Methoxyphenyl)-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-2-one (86bc):



86bc

^{1}H NMR, 500 MHz

$CDCl_3$

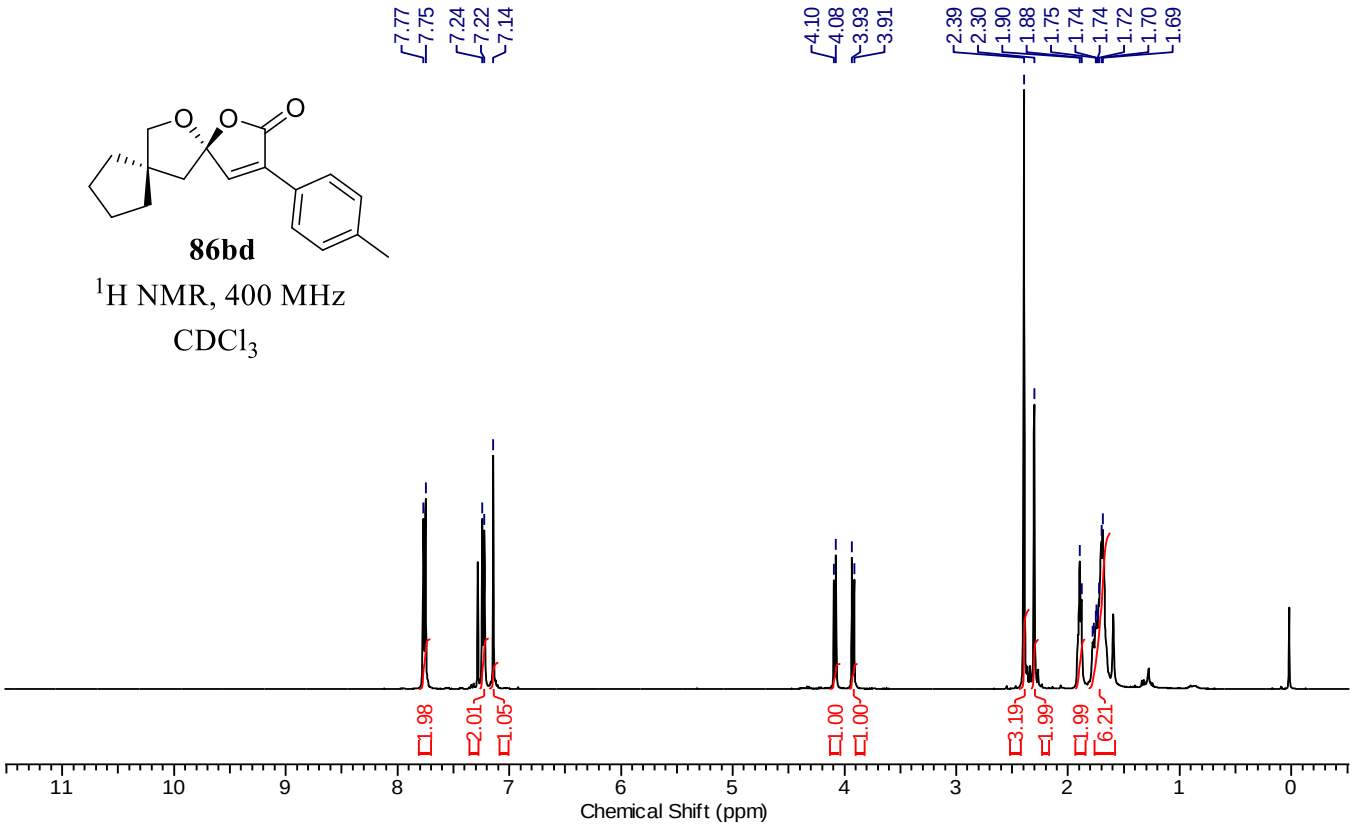


86bc

^{13}C NMR, 126 MHz

$CDCl_3$

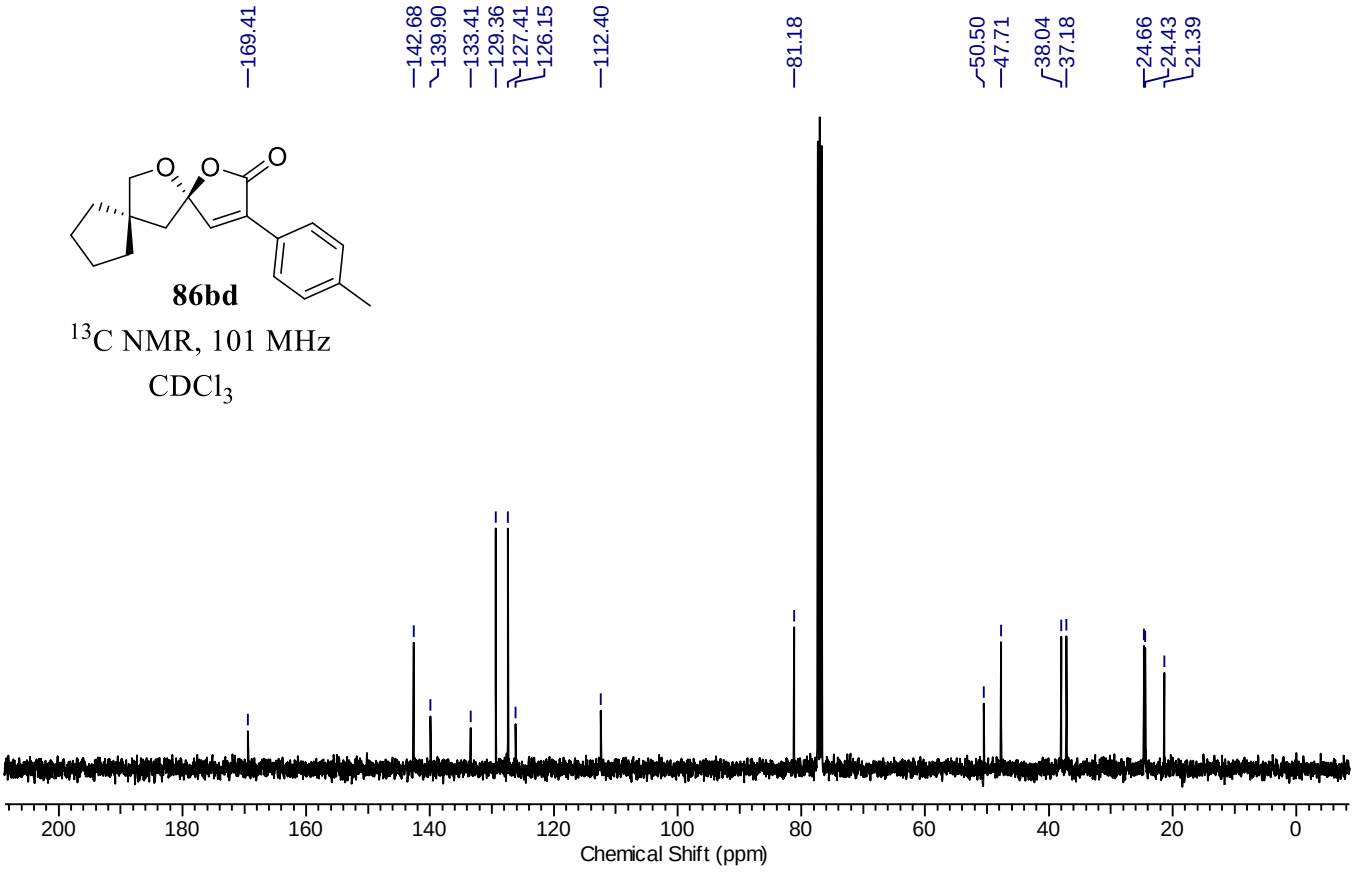
3-(*p*-Tolyl)-1,13-dioxadispiro[4.1.4^7.2^5]tridec-3-en-2-one 86bd):



86bd

^{1}H NMR, 400 MHz

$CDCl_3$

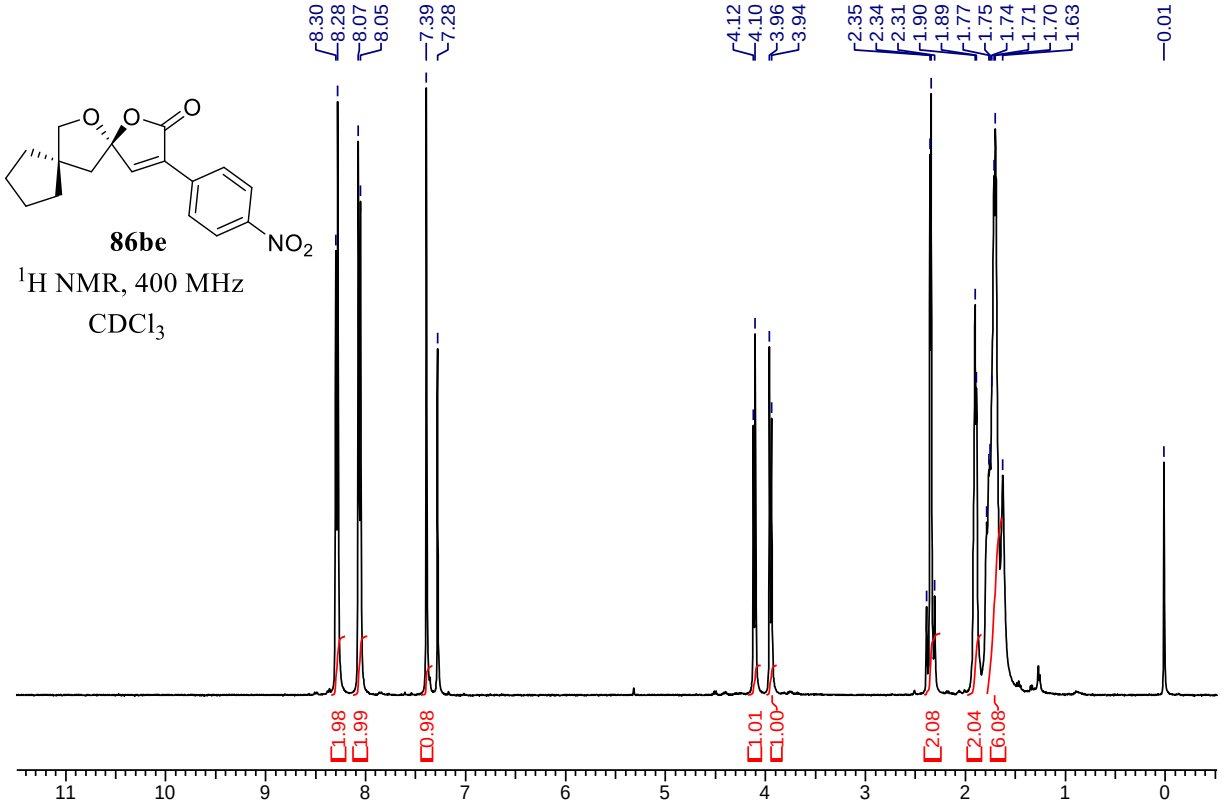


86bd

^{13}C NMR, 101 MHz

$CDCl_3$

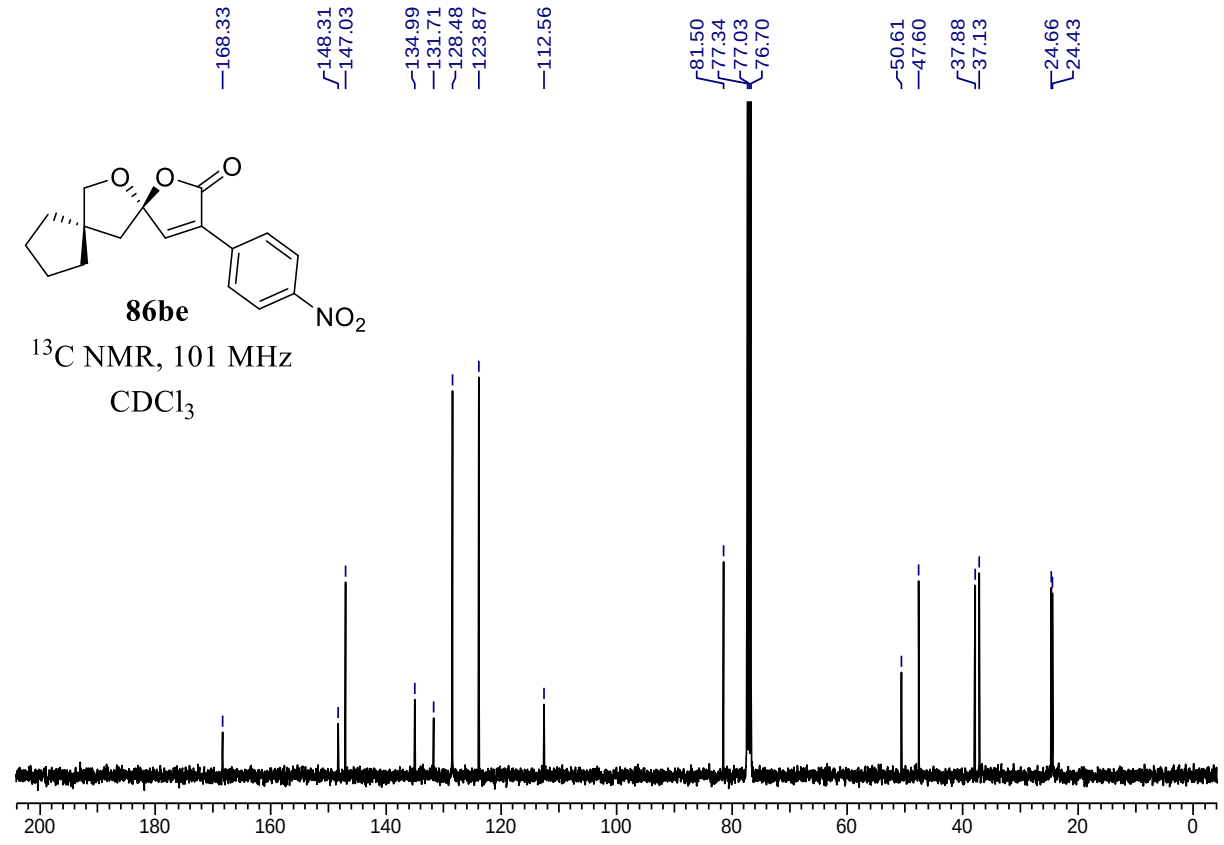
3-(4-Nitrophenyl)-1, 13-dioxadispiro [4.1.4^7.2^5] tridec-3-en-2-one (86be):



86be

^{1}H NMR, 400 MHz

$CDCl_3$

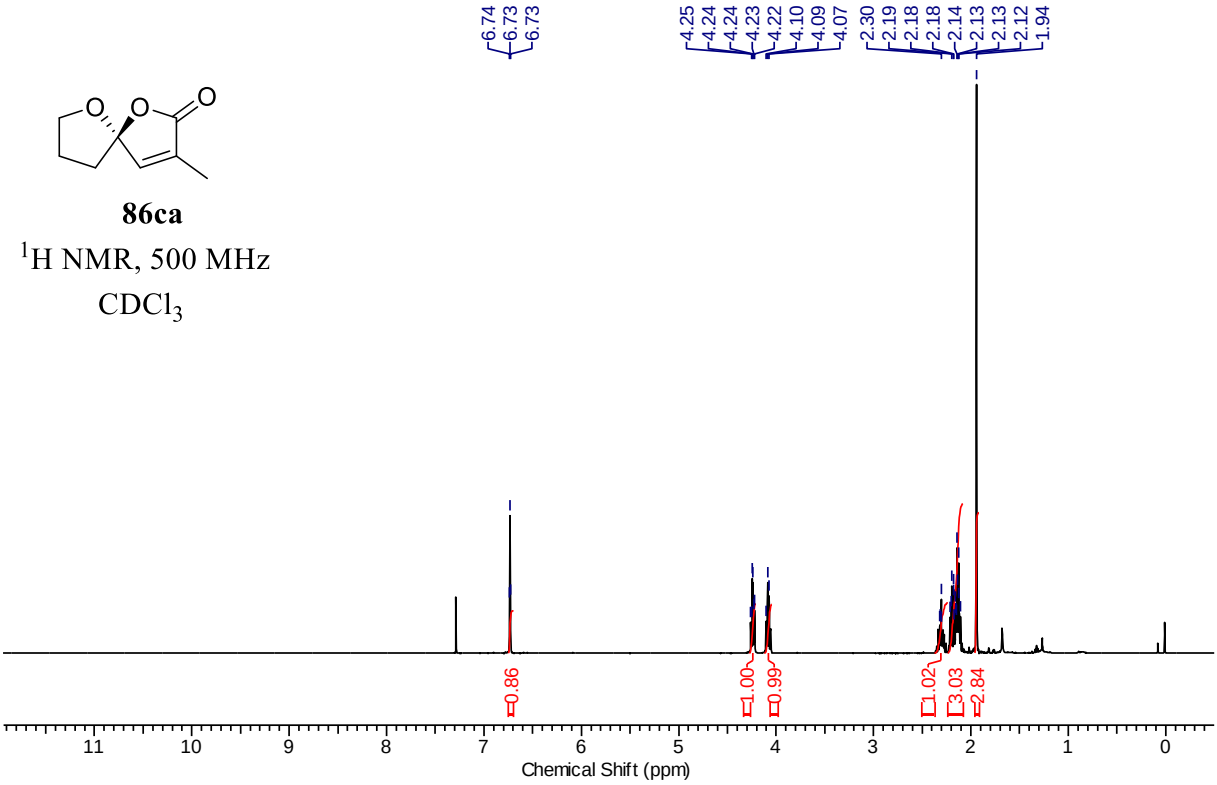


86be

^{13}C NMR, 101 MHz

$CDCl_3$

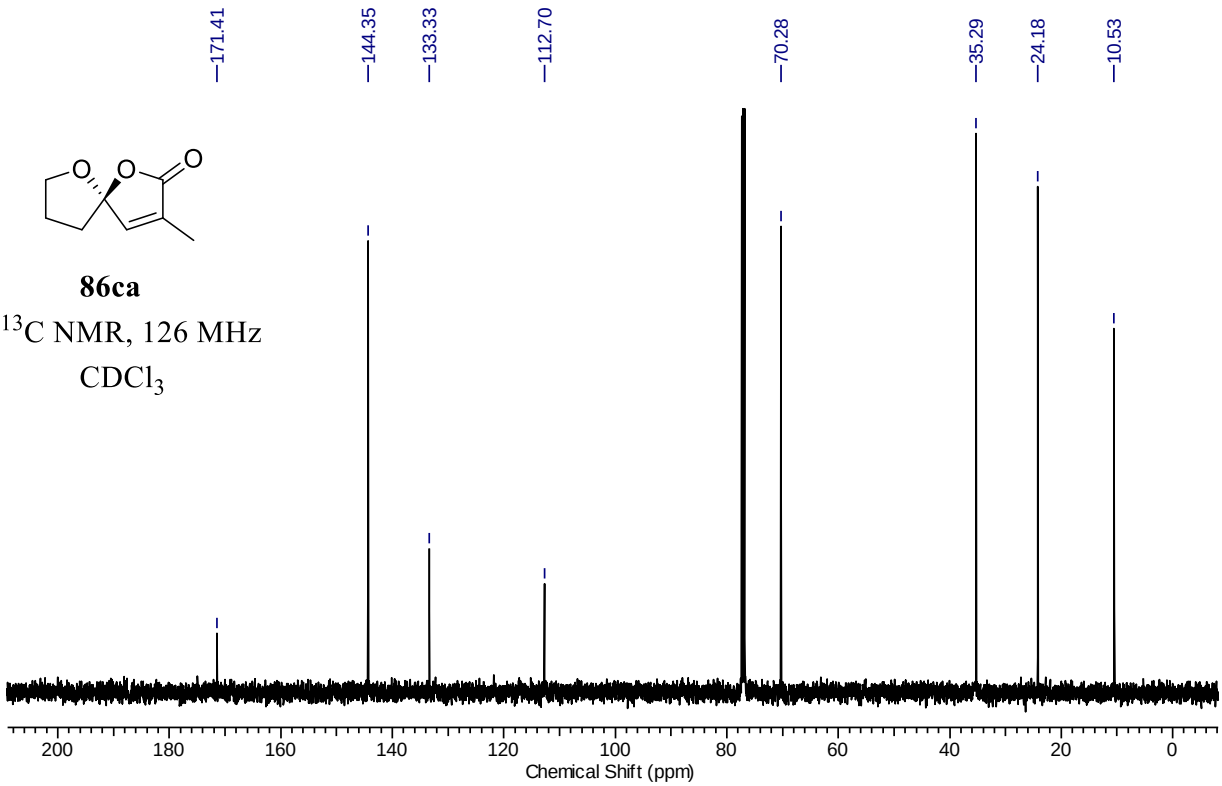
3-Methyl-1,6-dioxaspiro[4.4]non-3-en-2-one (86ca):



86ca

^{1}H NMR, 500 MHz

$CDCl_3$

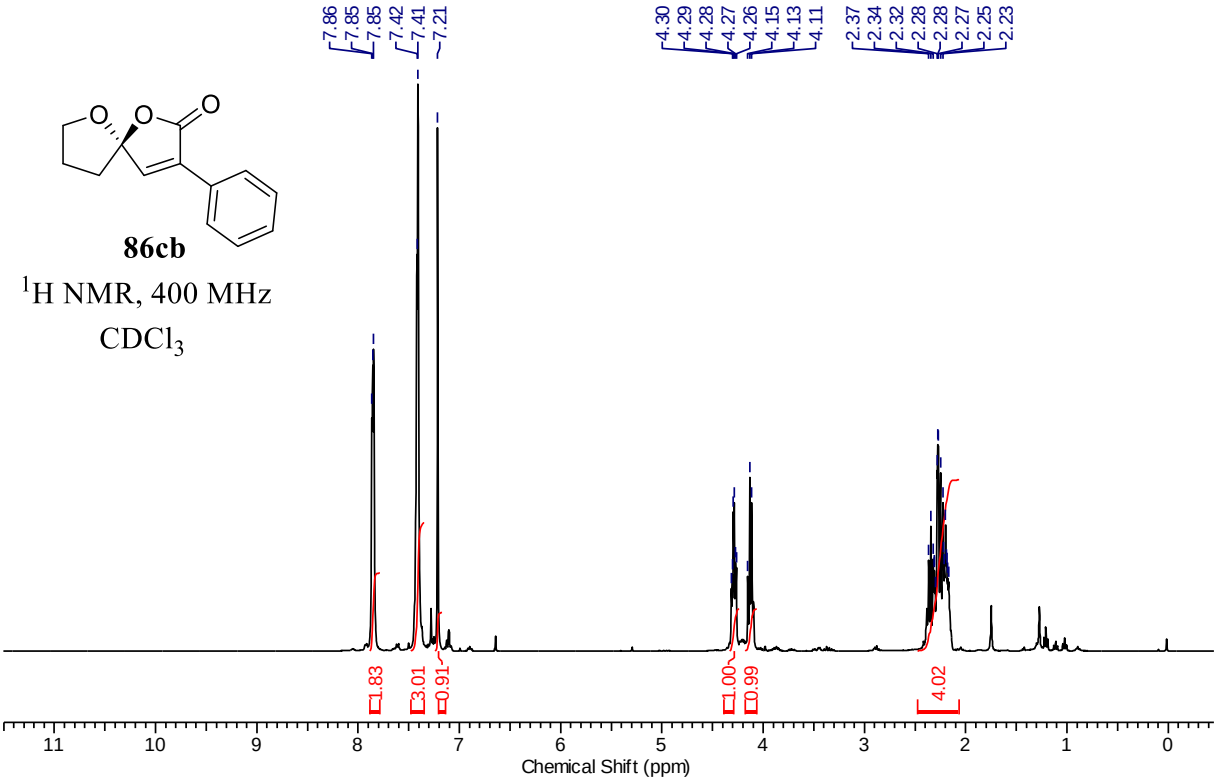


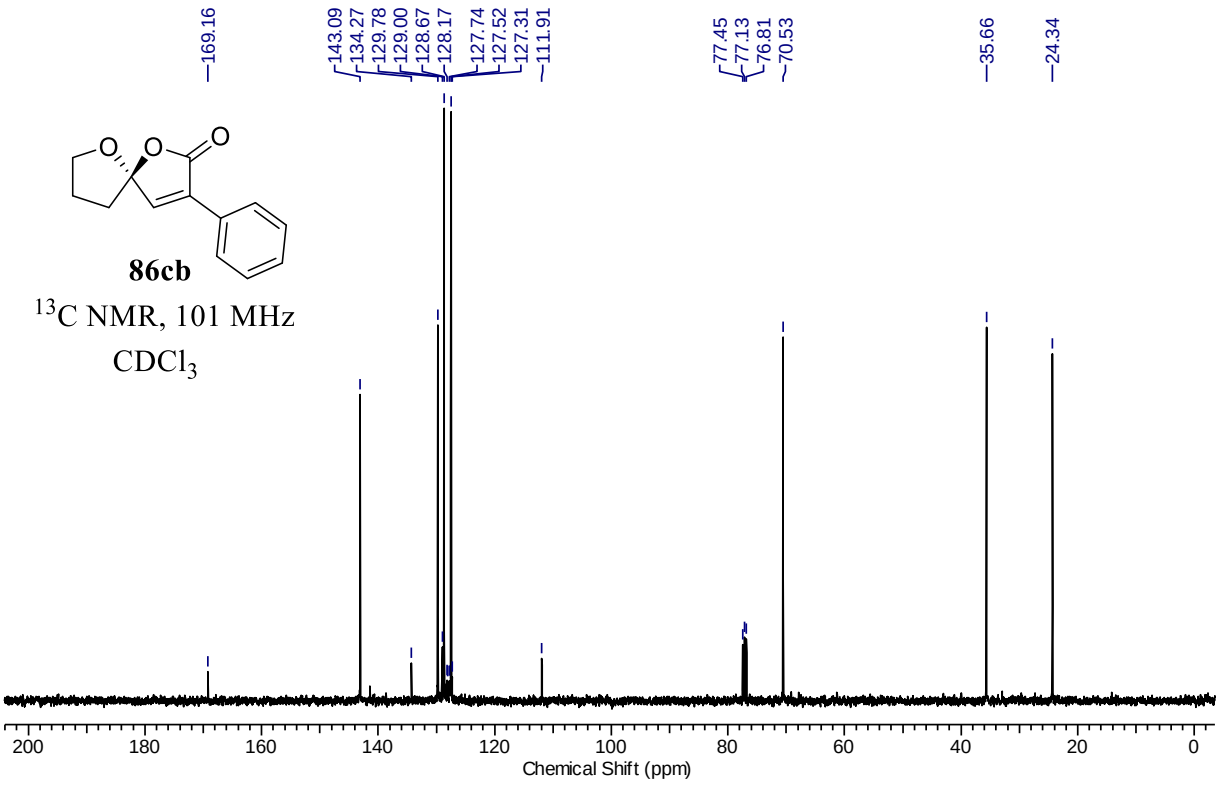
86ca

^{13}C NMR, 126 MHz

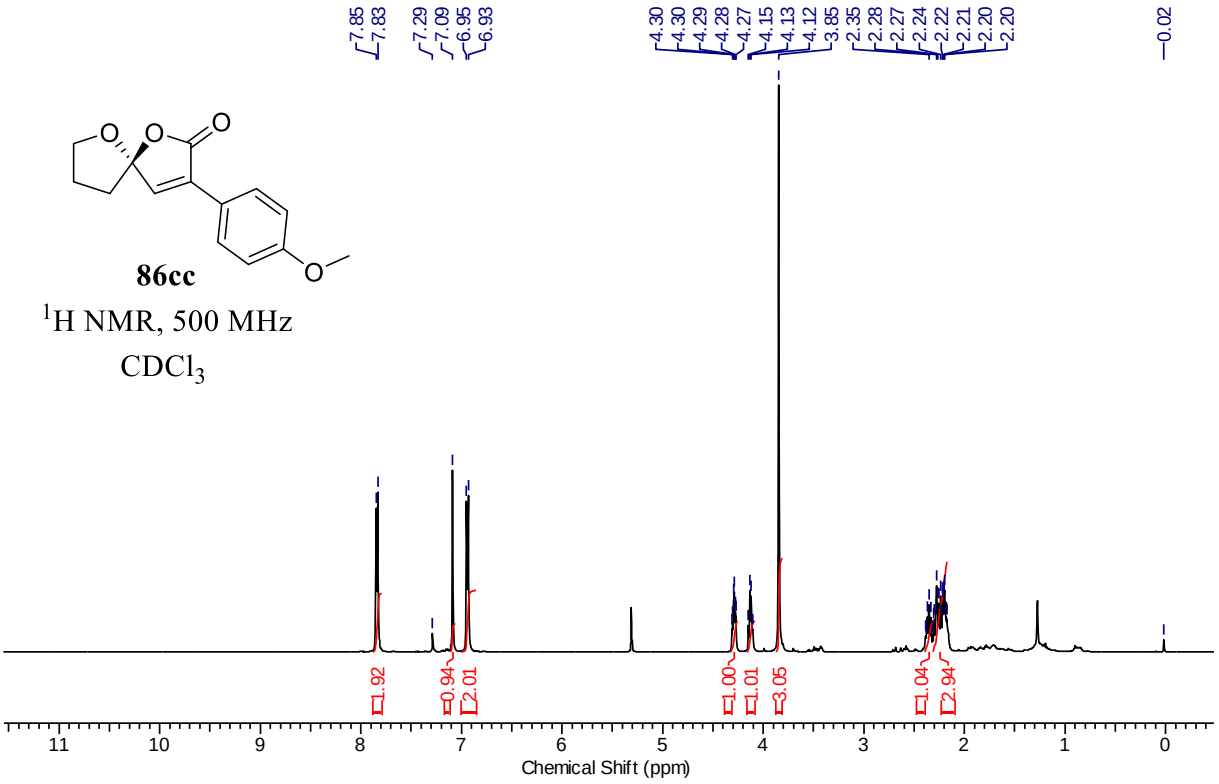
$CDCl_3$

3-Phenyl-1,6-dioxaspiro[4,4]non-3-en-2-one (86cb):





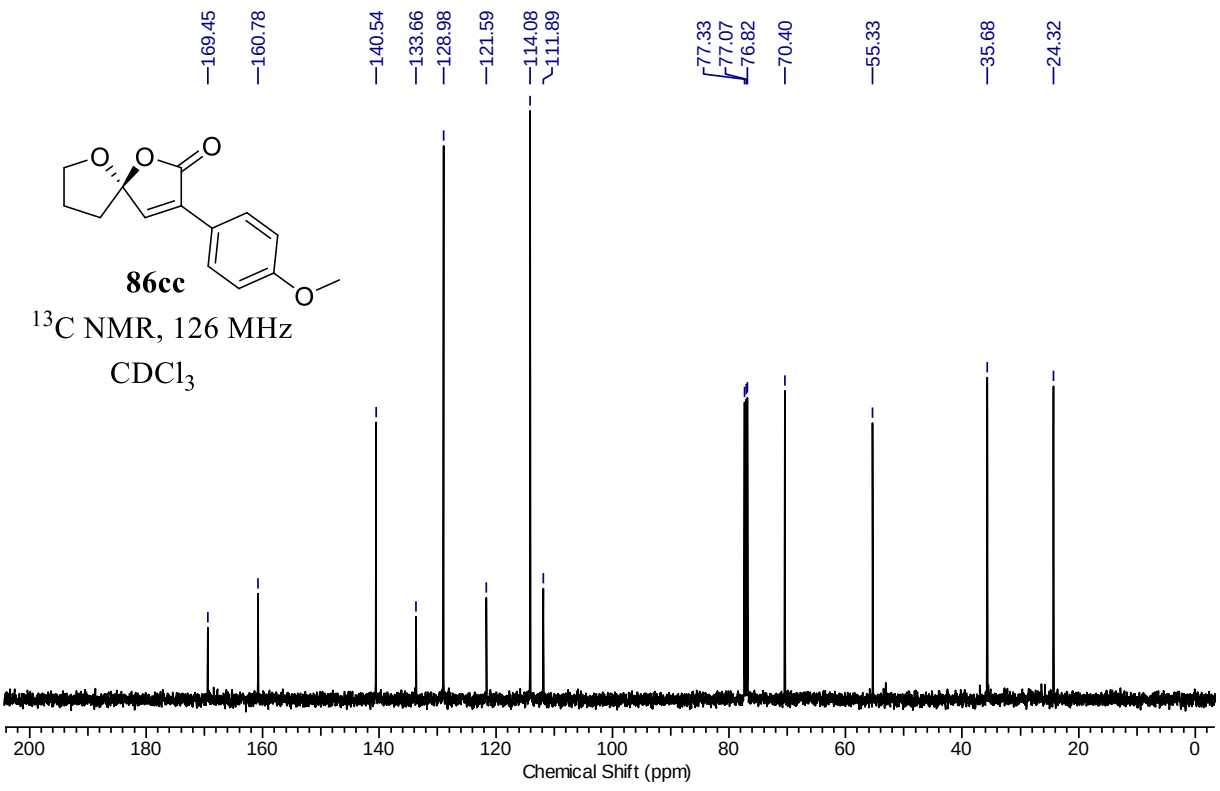
3-(4-Methoxyphenyl)-1,6-dioxaspiro[4,4]non-3-en-2-one(86cc):



86cc

^{1}H NMR, 500 MHz

$CDCl_3$

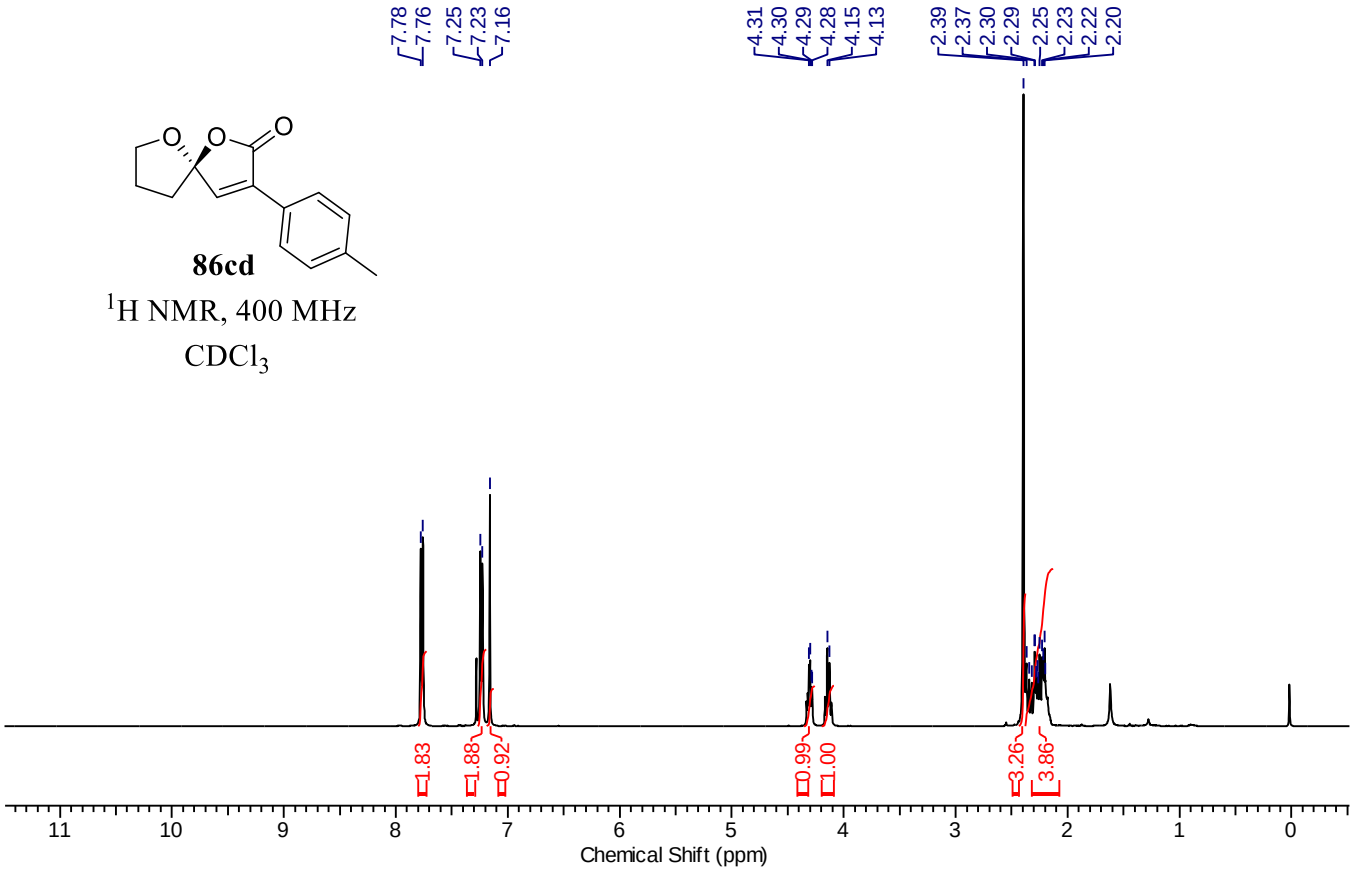


86cc

^{13}C NMR, 126 MHz

$CDCl_3$

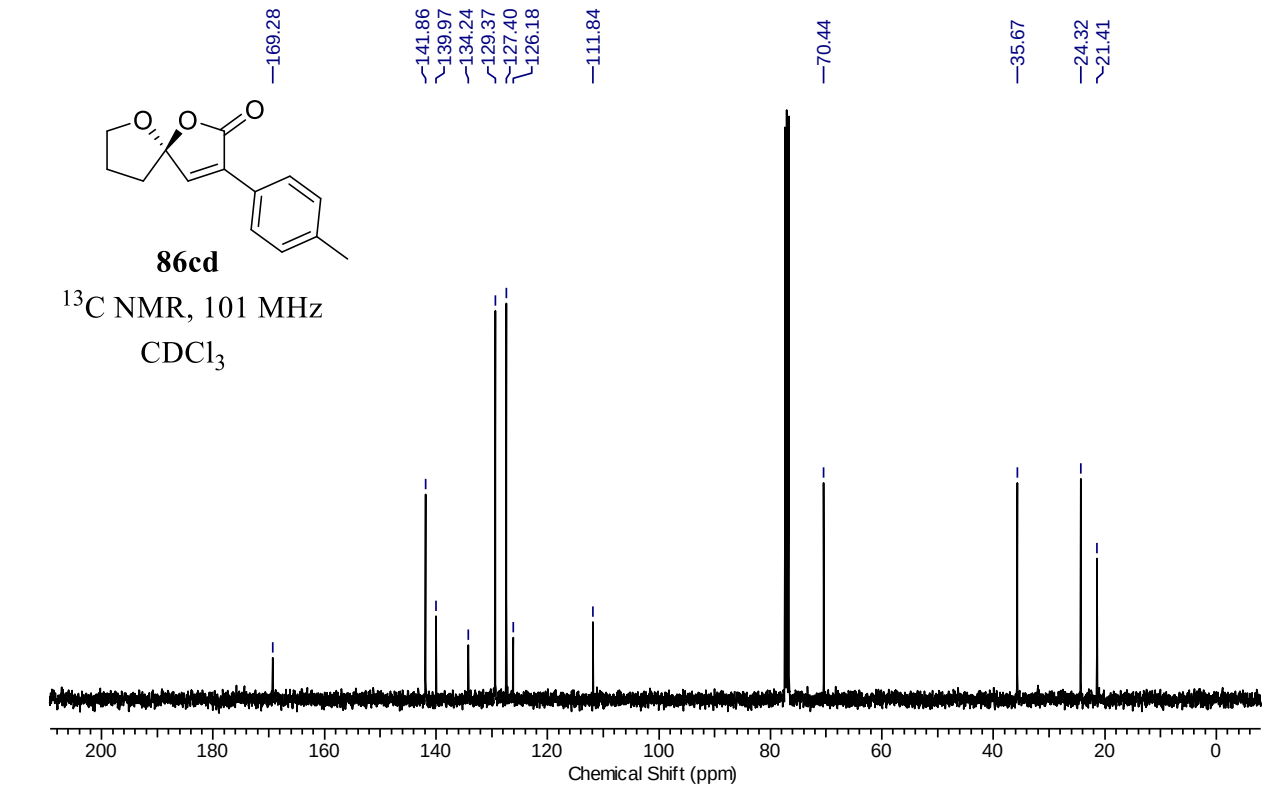
3-(*p*-Tolyl)-1,6-dioxaspiro[4.4]non-3-en-2-one (86cd):



86cd

^{1}H NMR, 400 MHz

$CDCl_3$

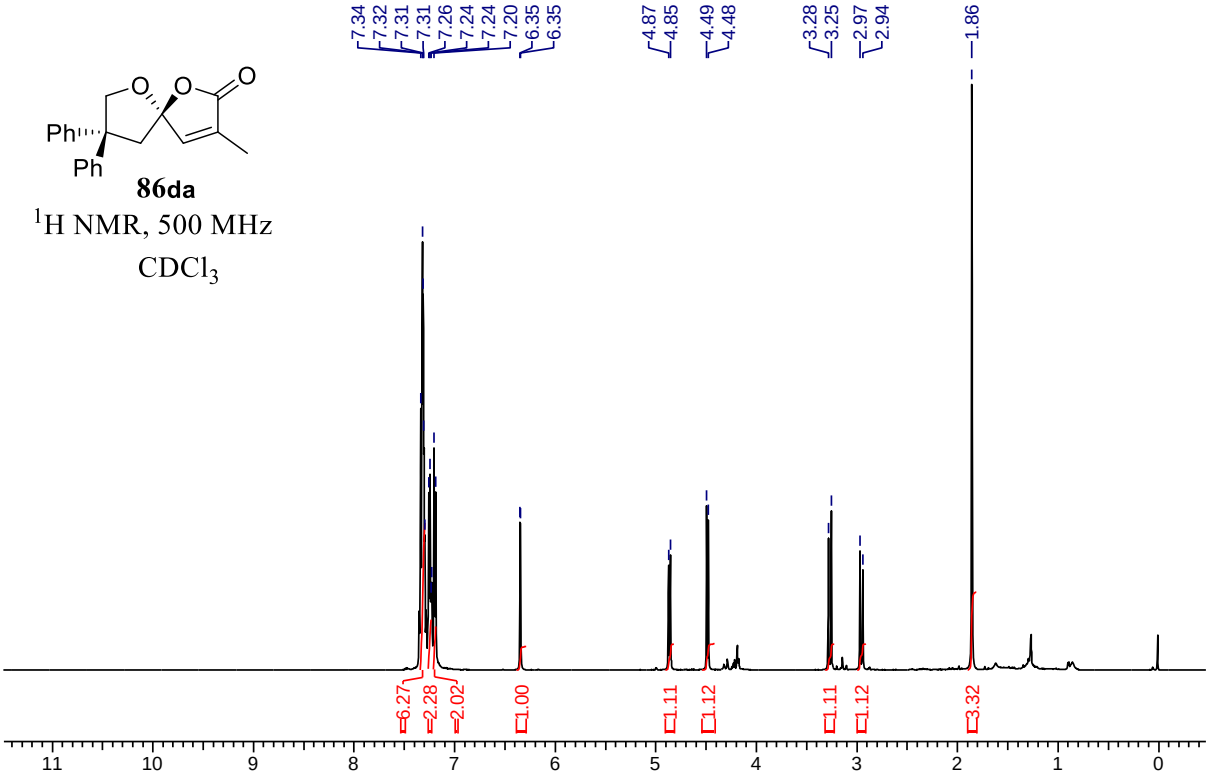


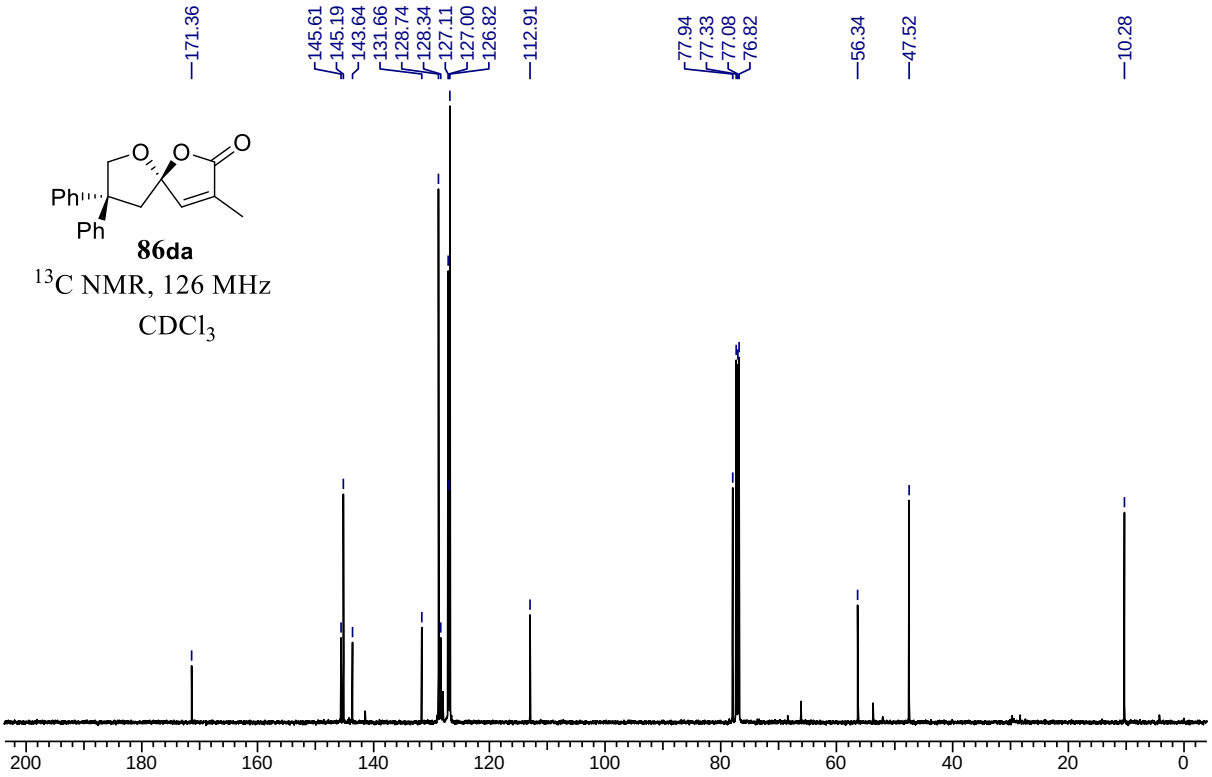
86cd

^{13}C NMR, 101 MHz

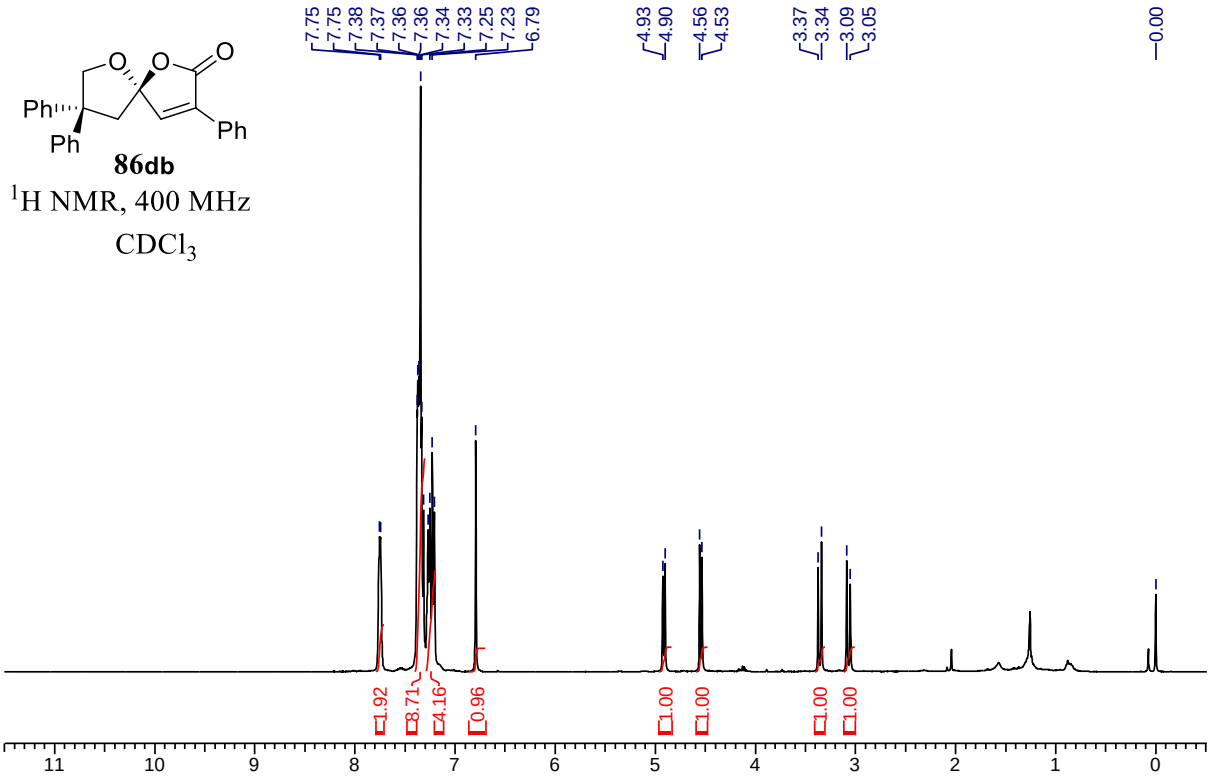
$CDCl_3$

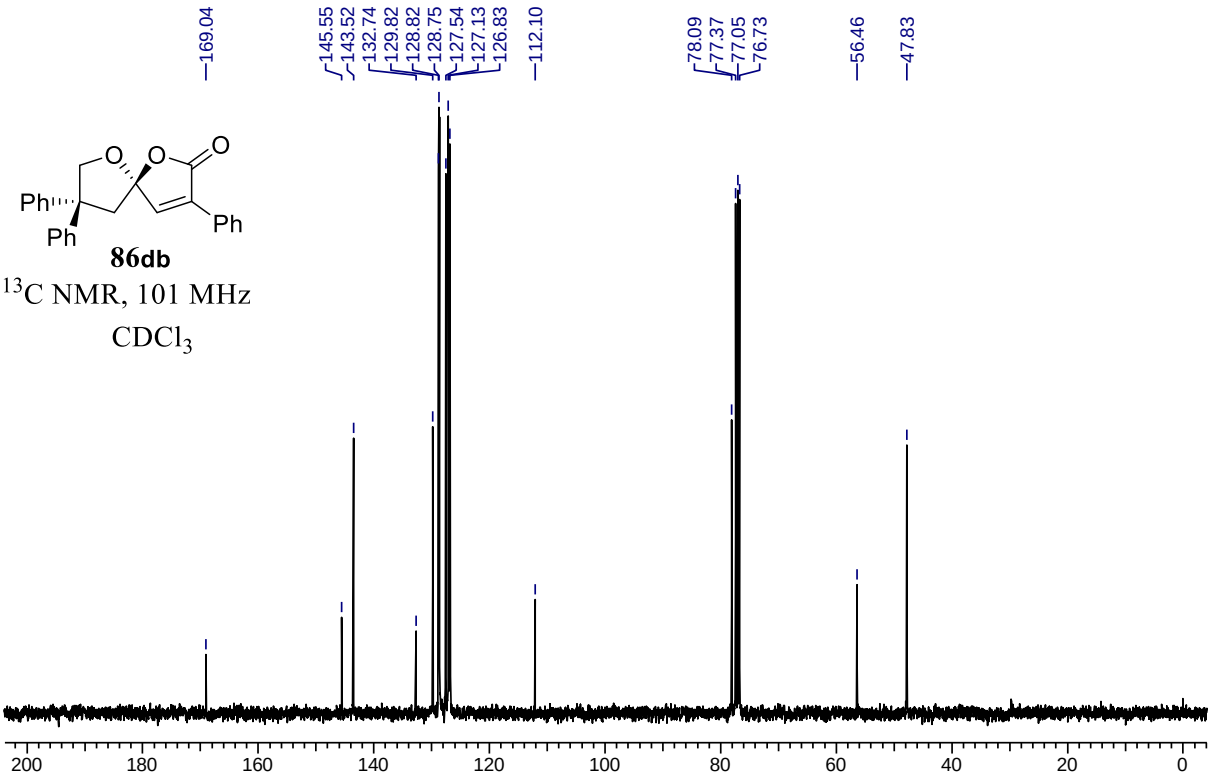
3-Methyl-8, 8-diphenyl-1, 6-dioxaspiro [4.4] non-3-en-2-one (86da):



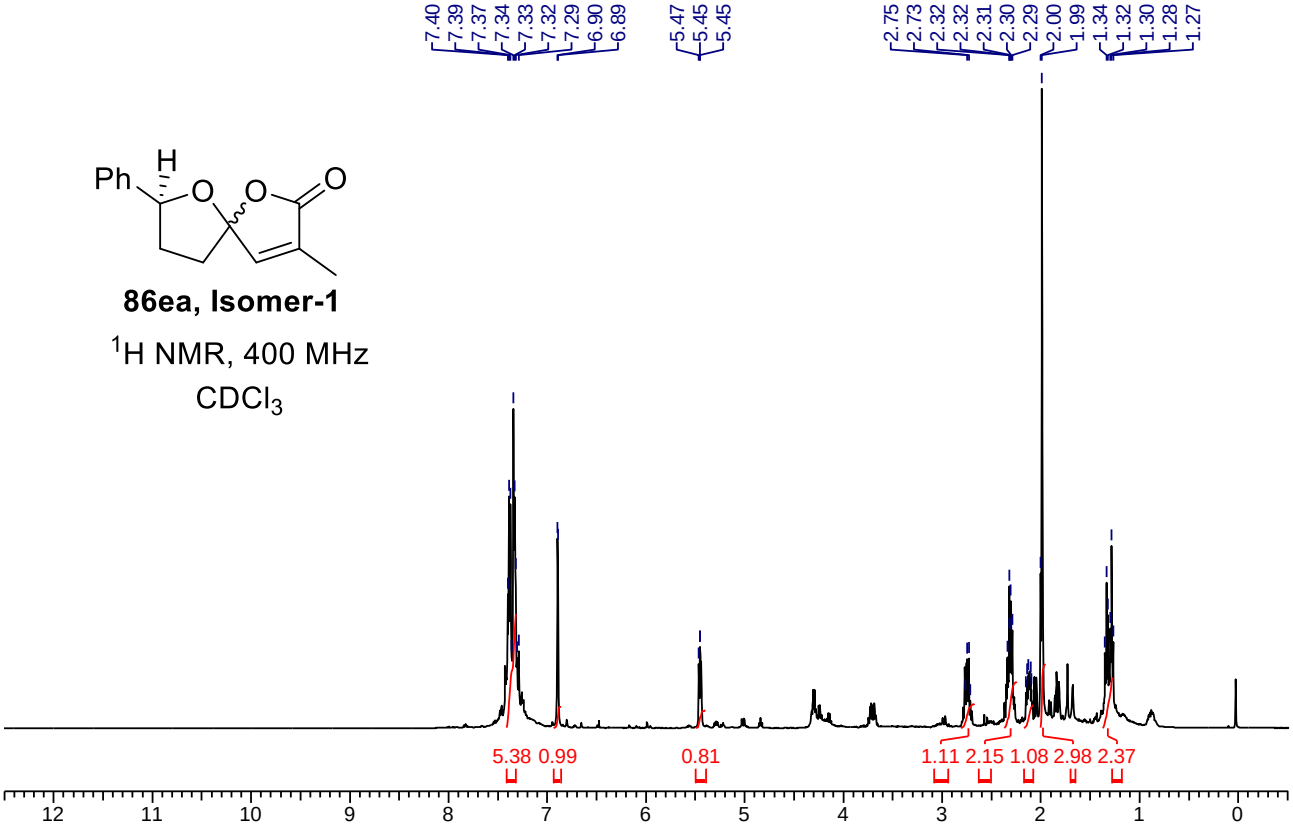


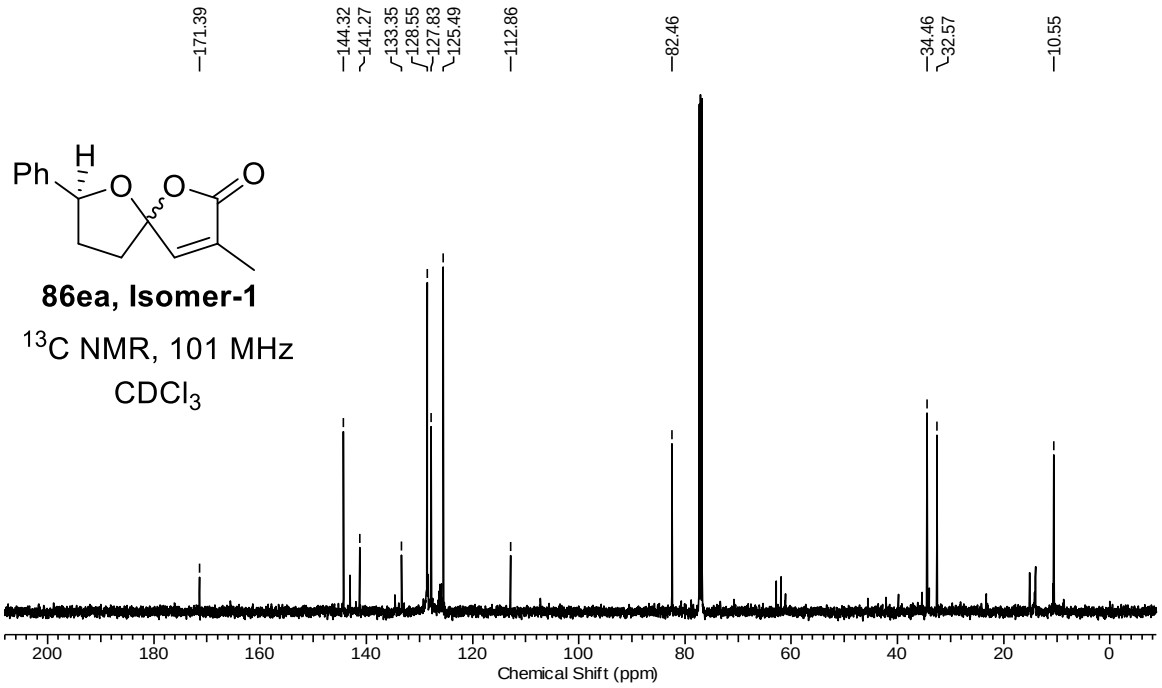
3, 8, 8-Triphenyl-1, 6-dioxaspiro [4.4] non-3-en-2-one (86db):



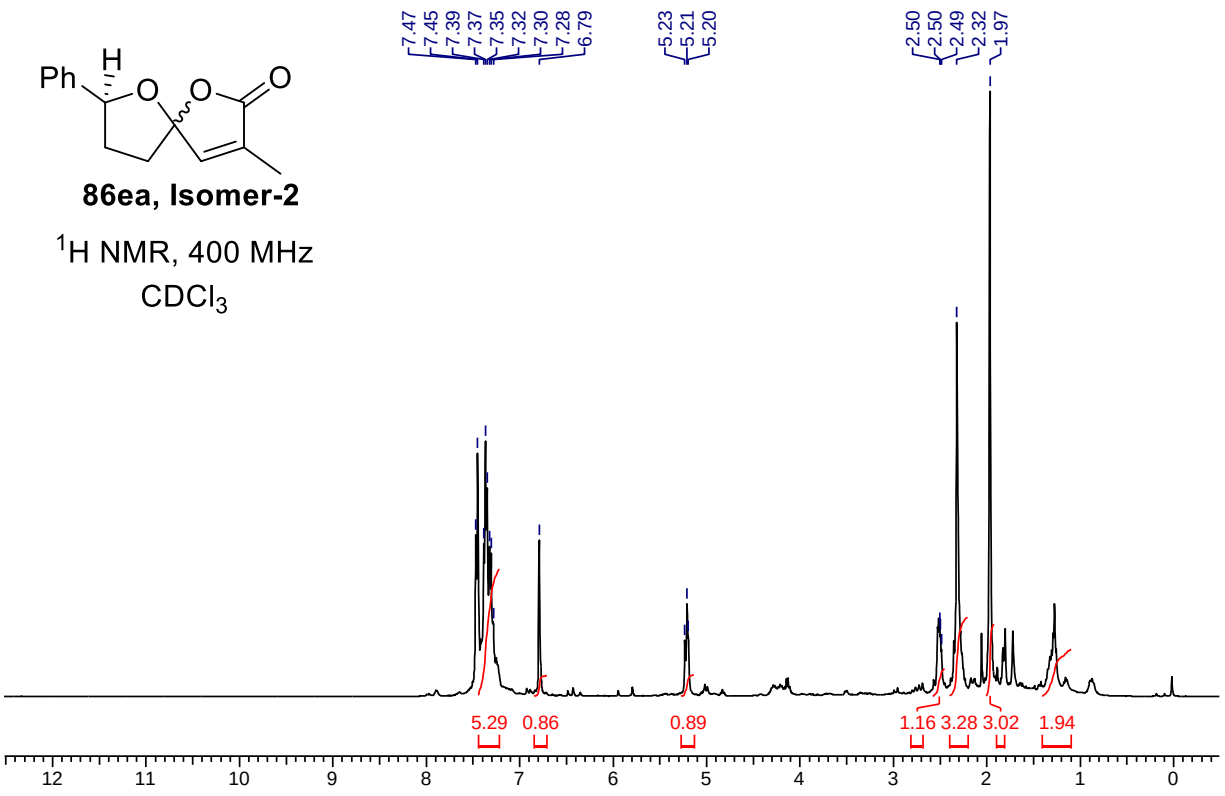


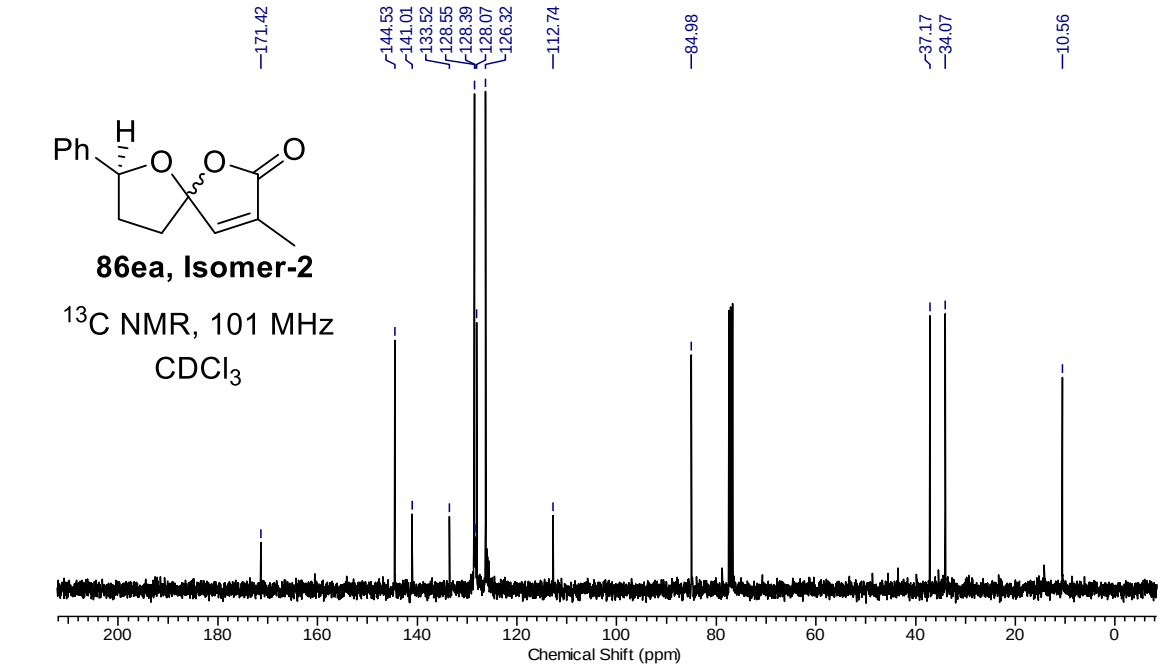
3-Methyl-7-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (86ea):



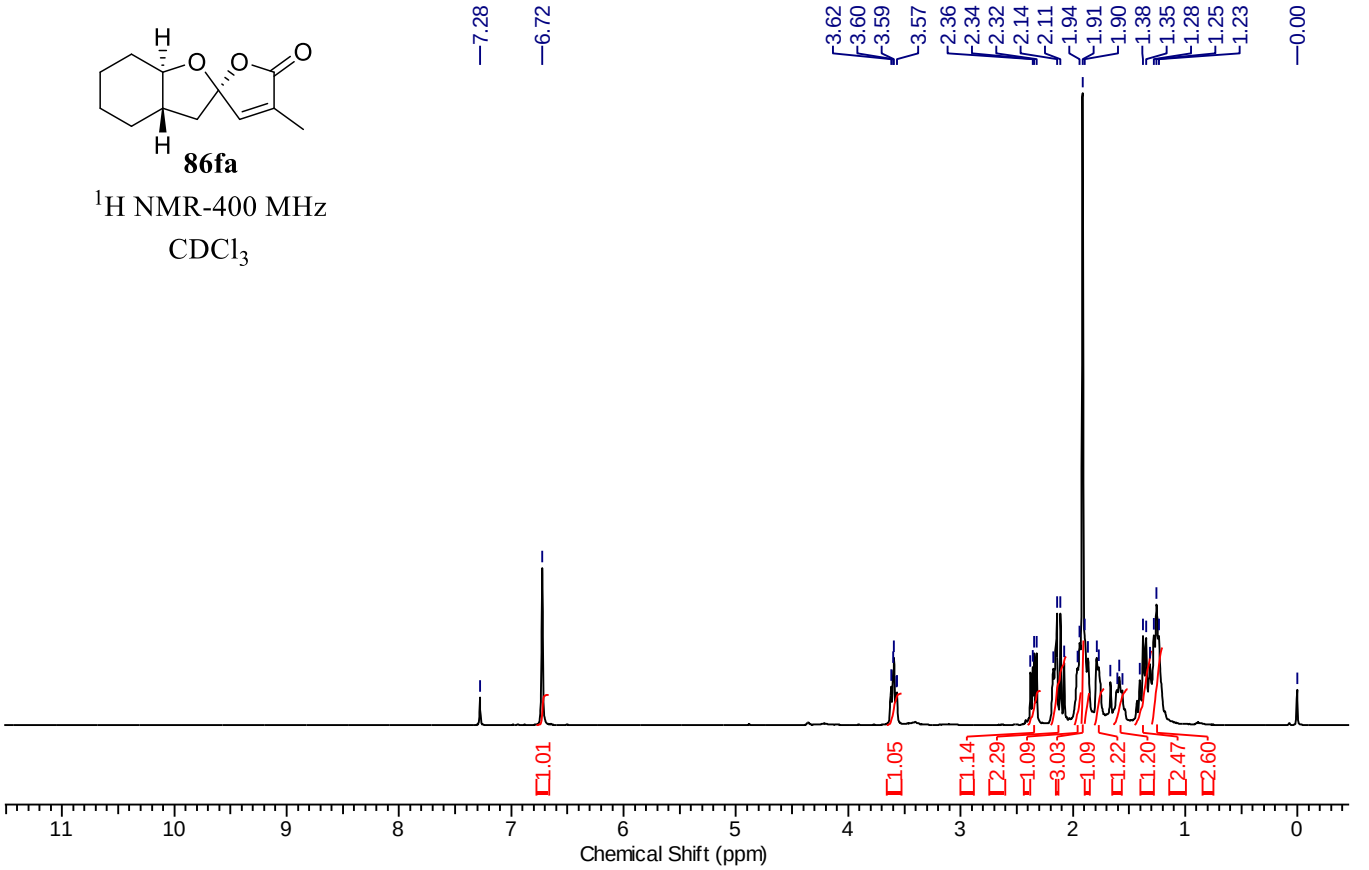


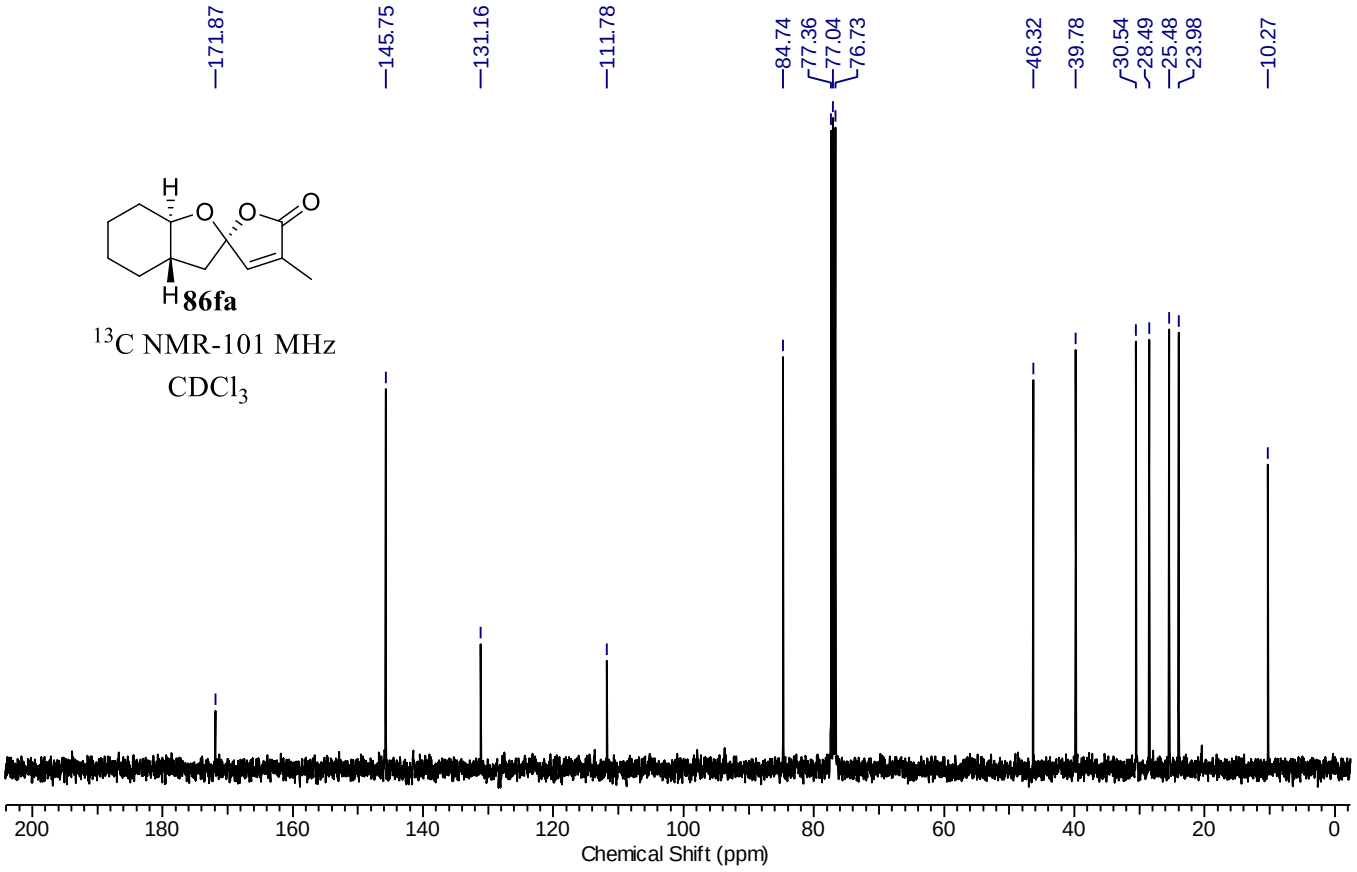
3-Methyl-7-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (86ea):



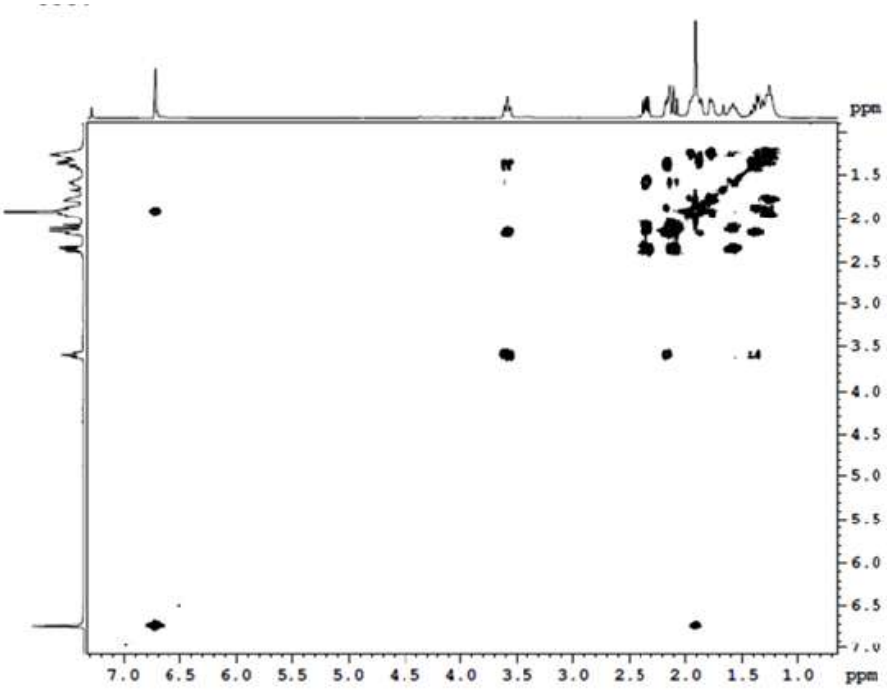


4'-Methyl-3a,4,5,6,7,7a-hexahydro-3*H*,5'*H*-spiro[benzofuran-2,2'-furan]-5'-one (86fa)

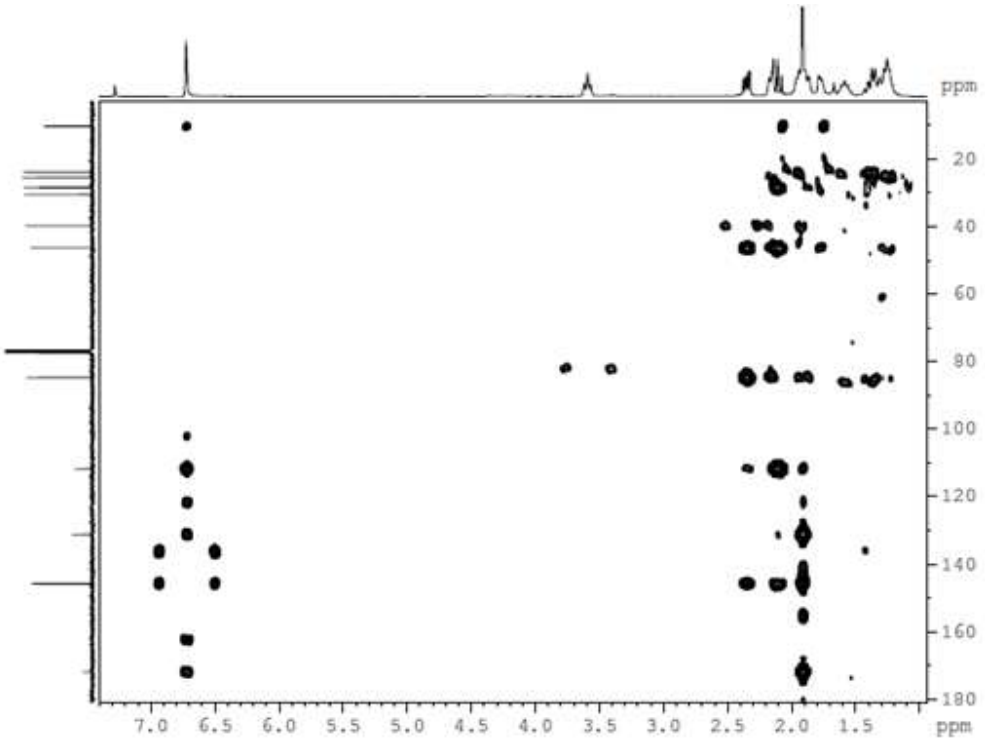




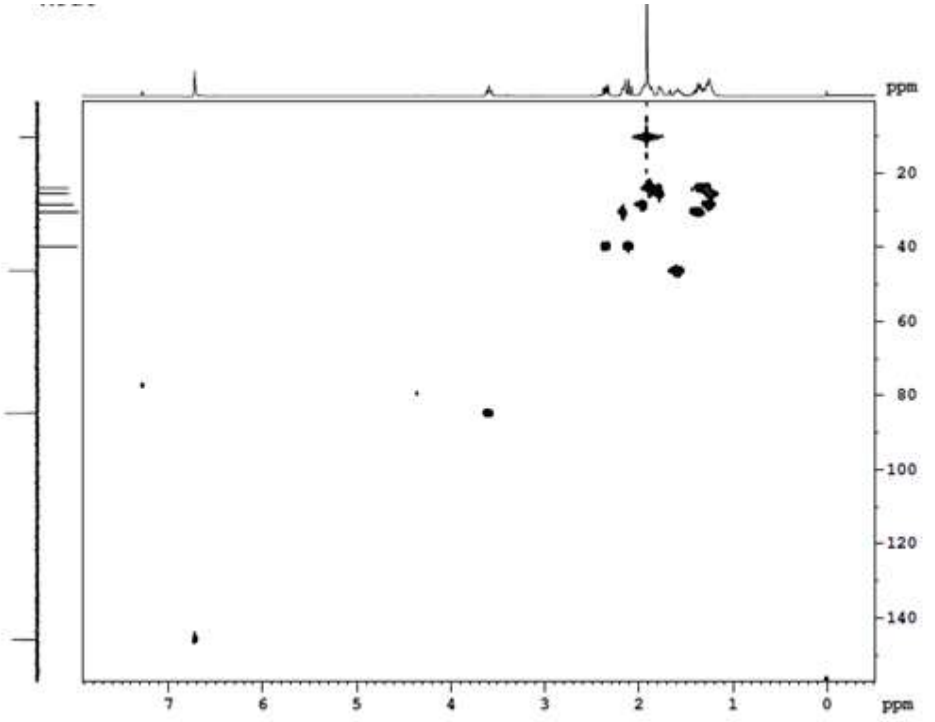
COSY: (86fa)



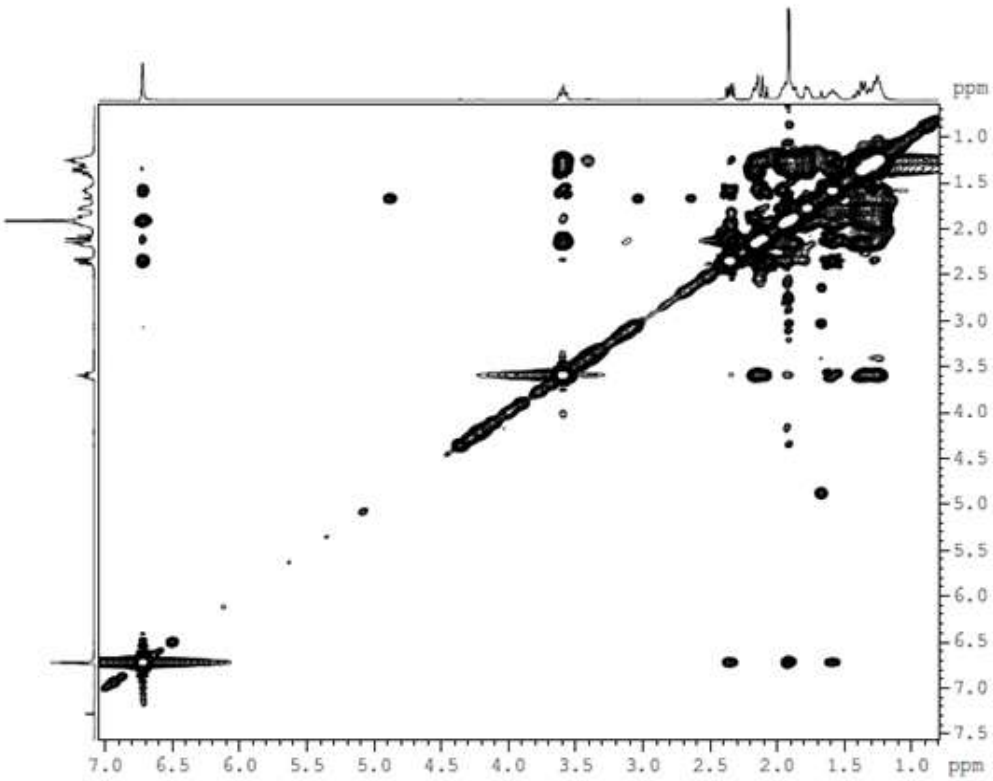
HMBC: (86fa)



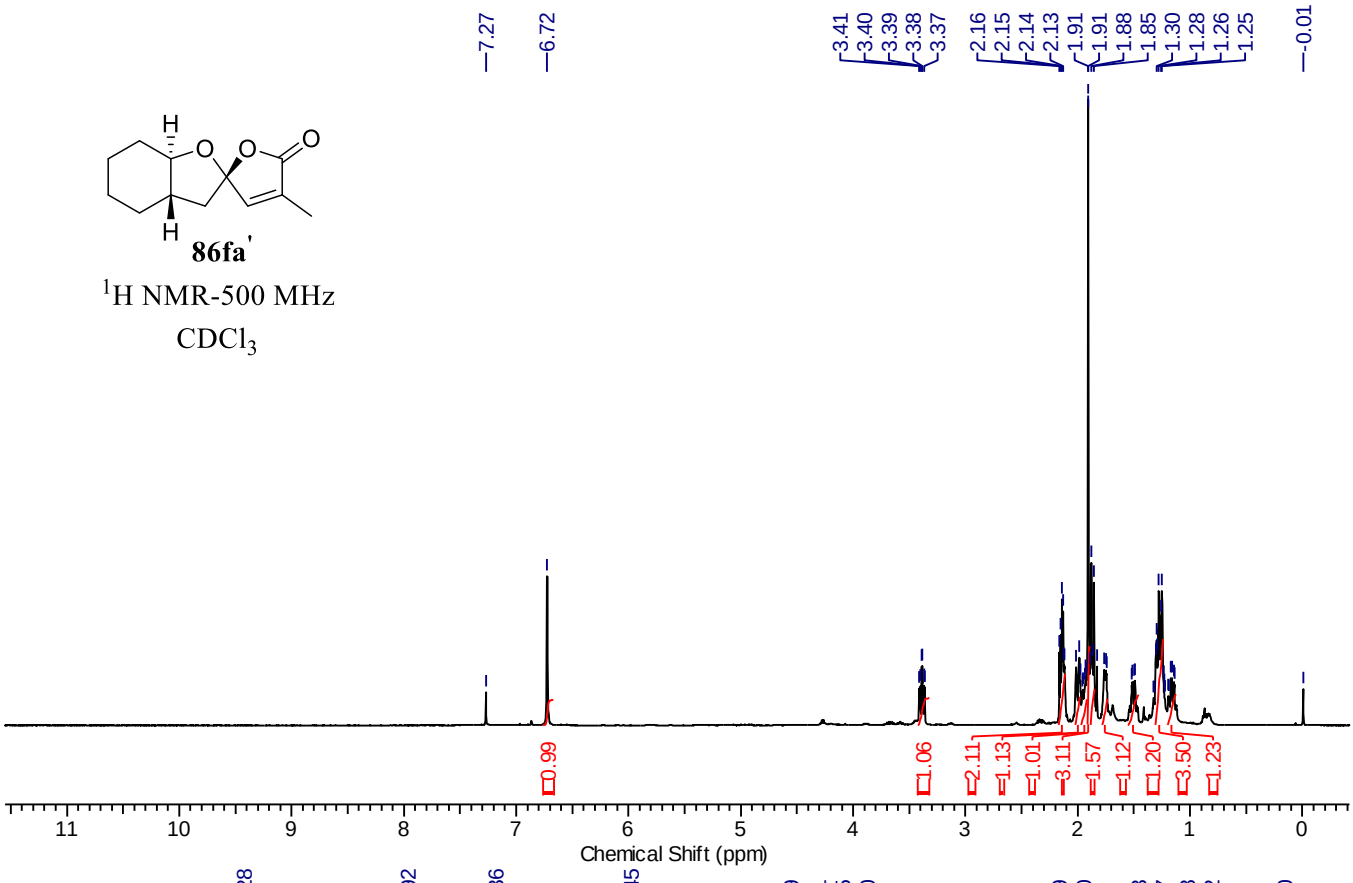
HSQC:(86fa)



NOESY:(3f)



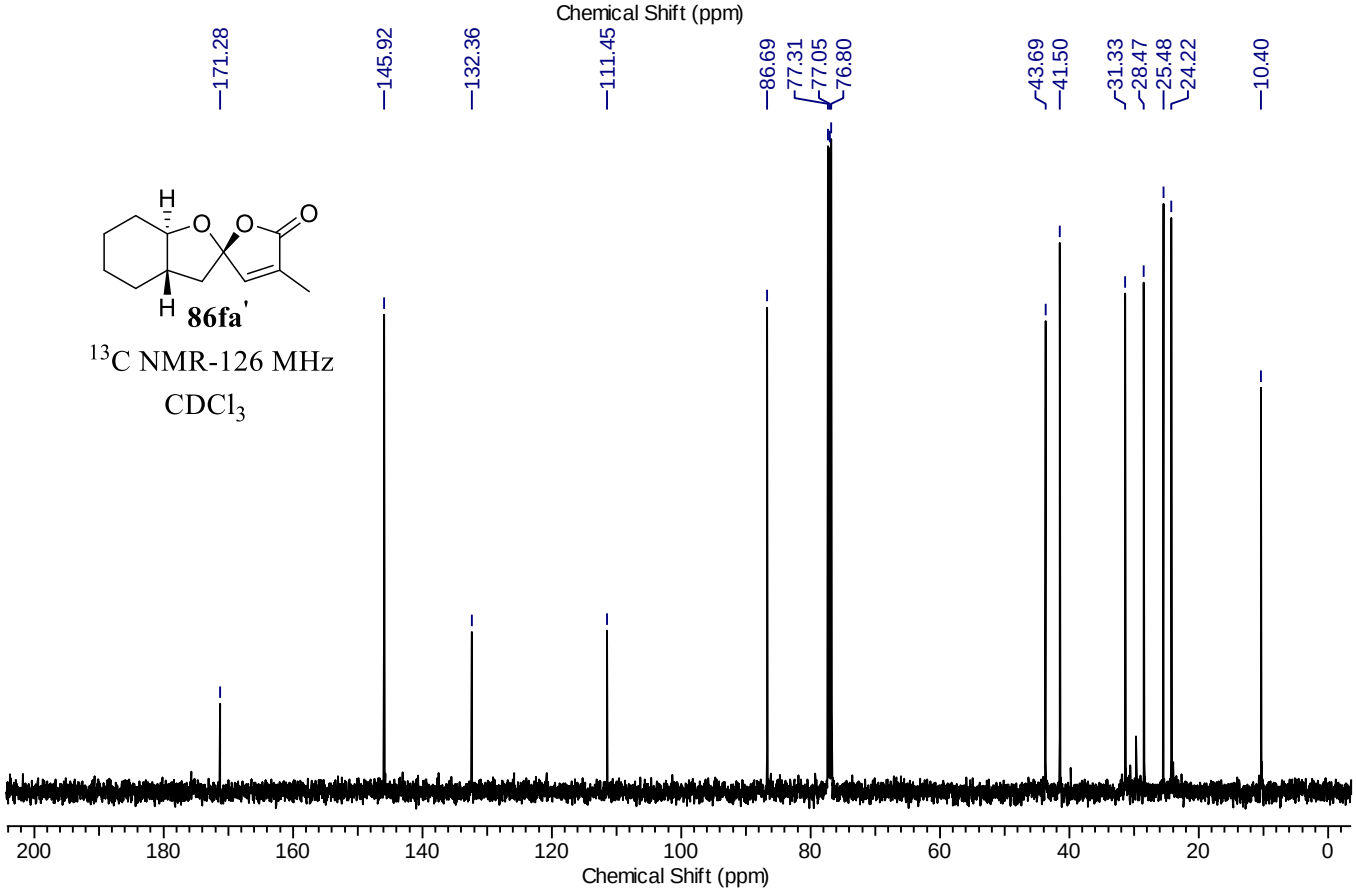
4'-Methyl-3a,4,5,6,7,7a-hexahydro-3*H*,5'*H*-spiro[benzofuran-2,2'-furan]-5'-one (86fa')



86fa'

^{1}H NMR-500 MHz

$CDCl_3$

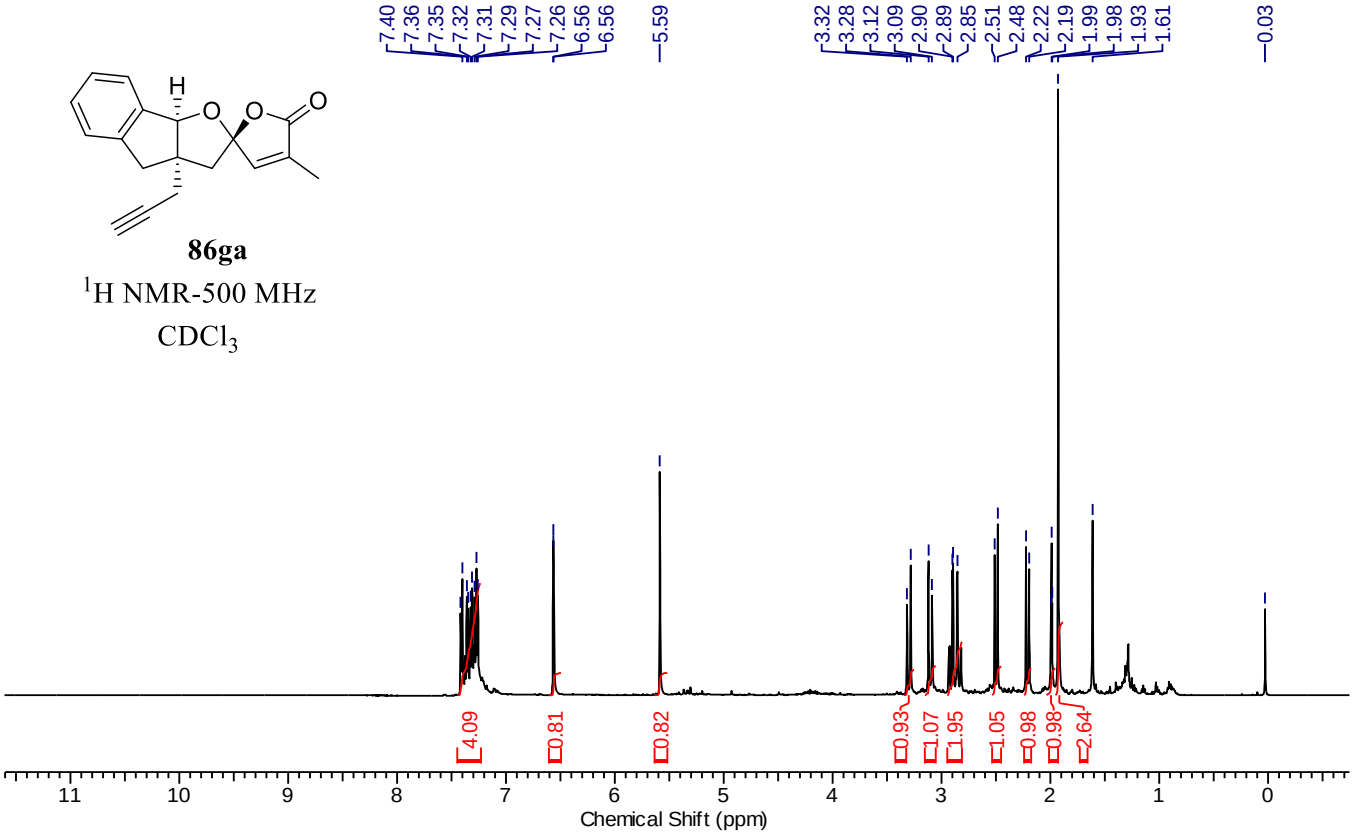


86fa'

^{13}C NMR-126 MHz

$CDCl_3$

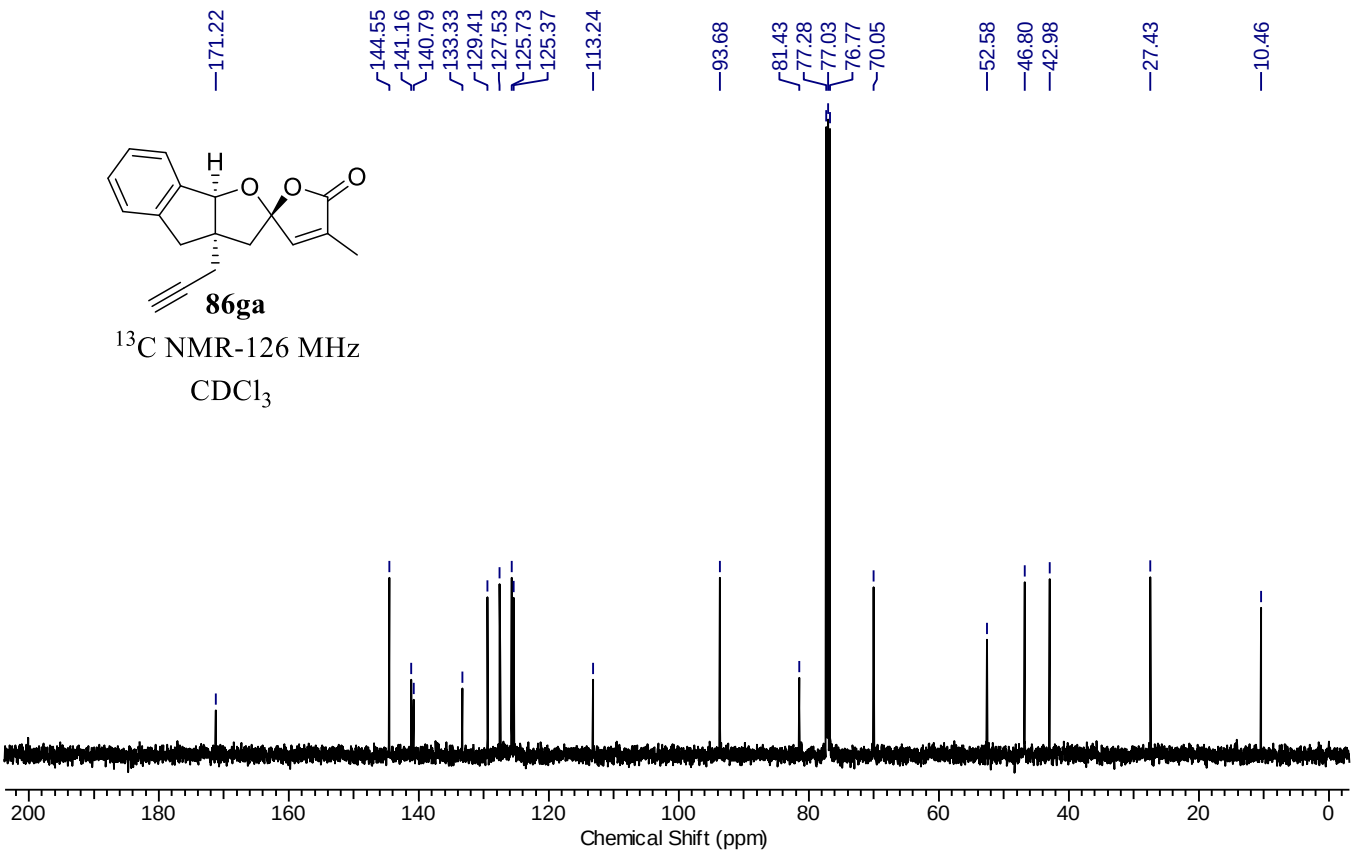
4-Methyl-3a'-(prop-2-yn-1-yl)-3',3a',4',8b'-tetrahydro-5*H*-spiro[furan-2,2'-indeno[1,2-*b*]furan]-5-one (86ga)



86ga

^{1}H NMR-500 MHz

$CDCl_3$

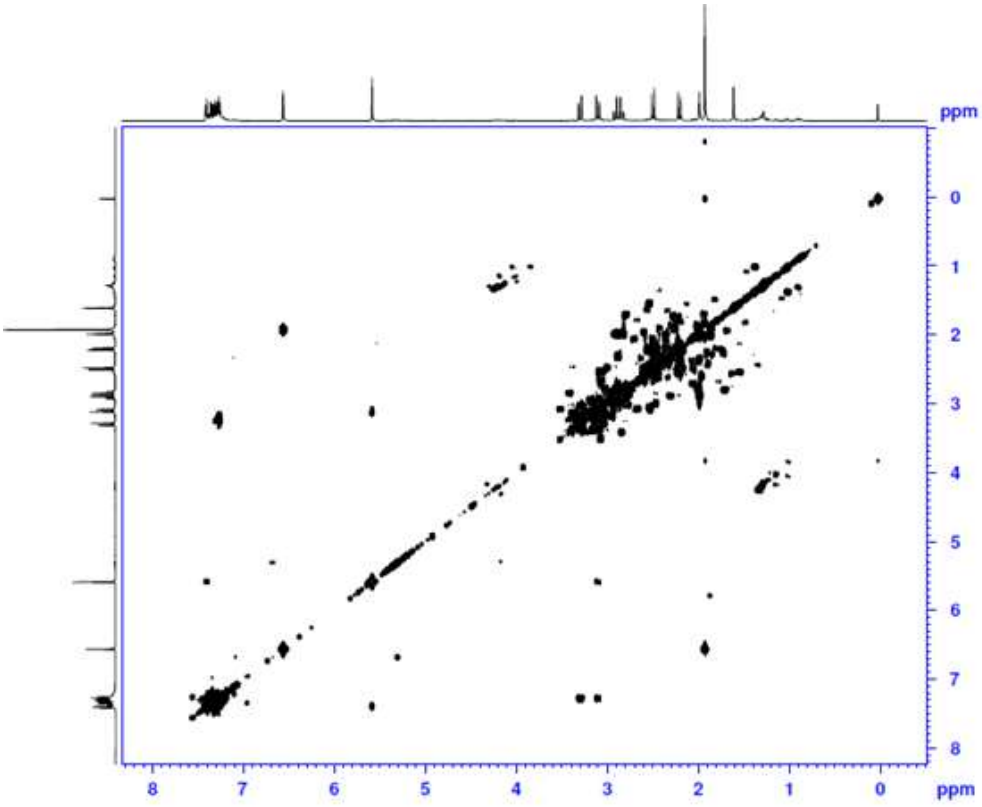


86ga

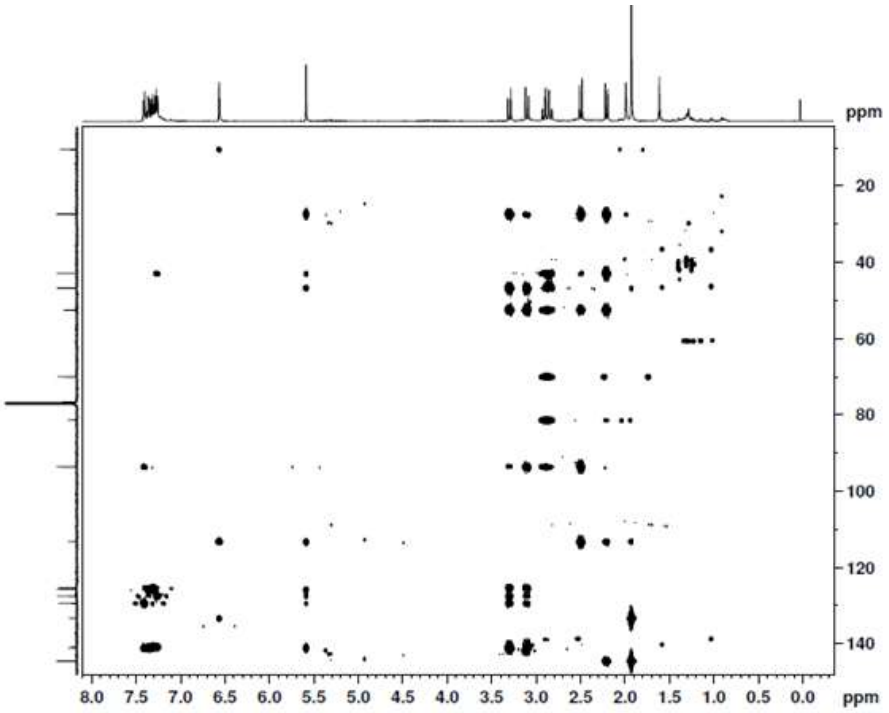
^{13}C NMR-126 MHz

$CDCl_3$

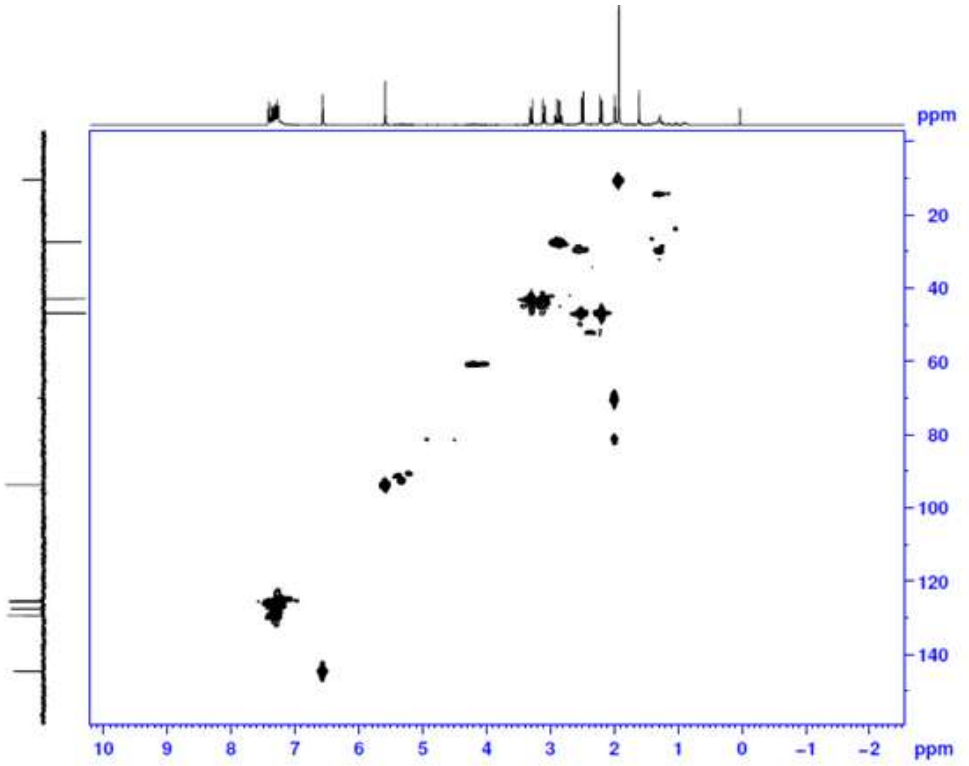
COSY:(86ga)



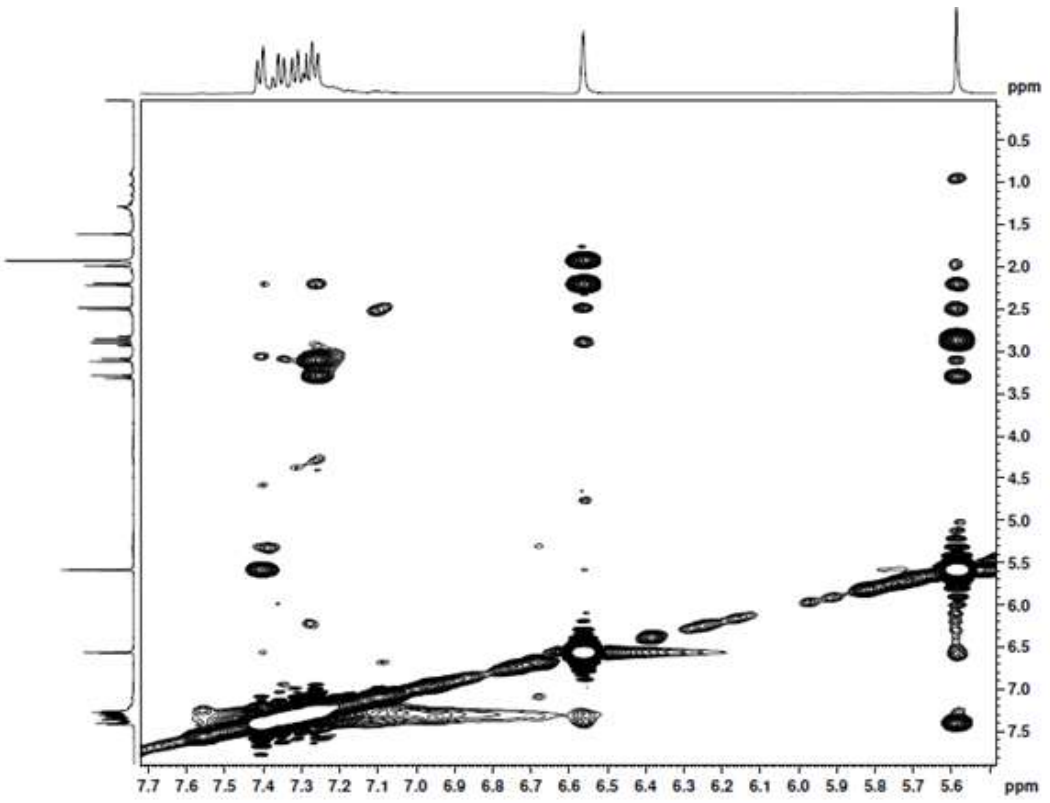
HMBC :(86ga)



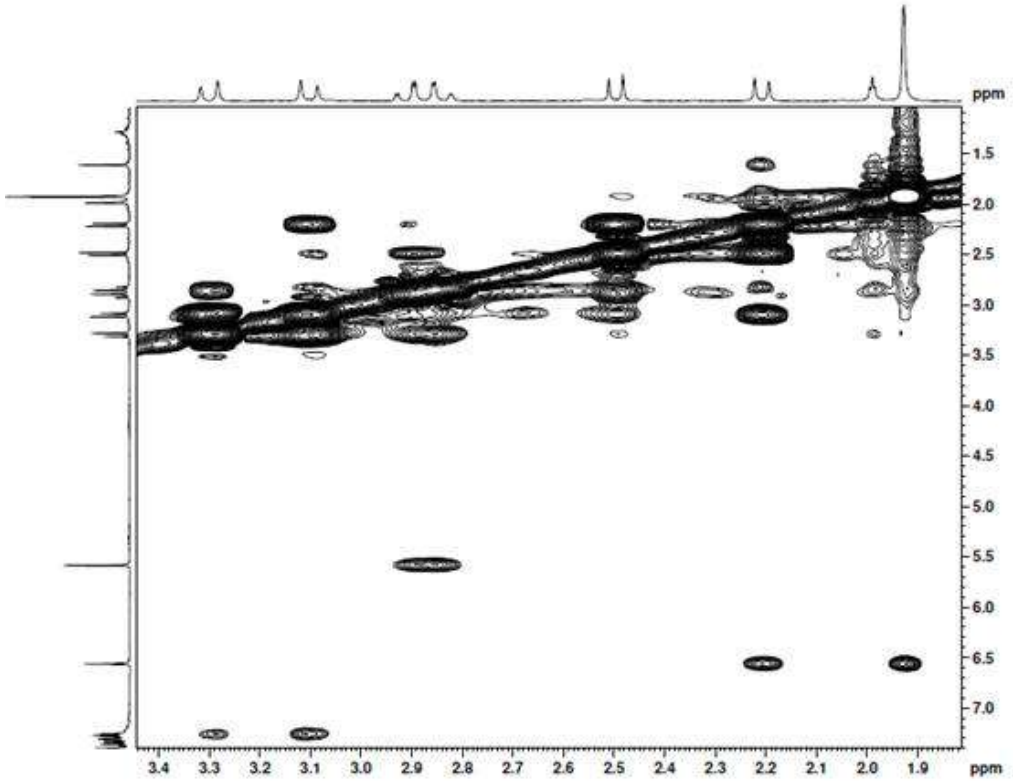
HSQC: (86ga)



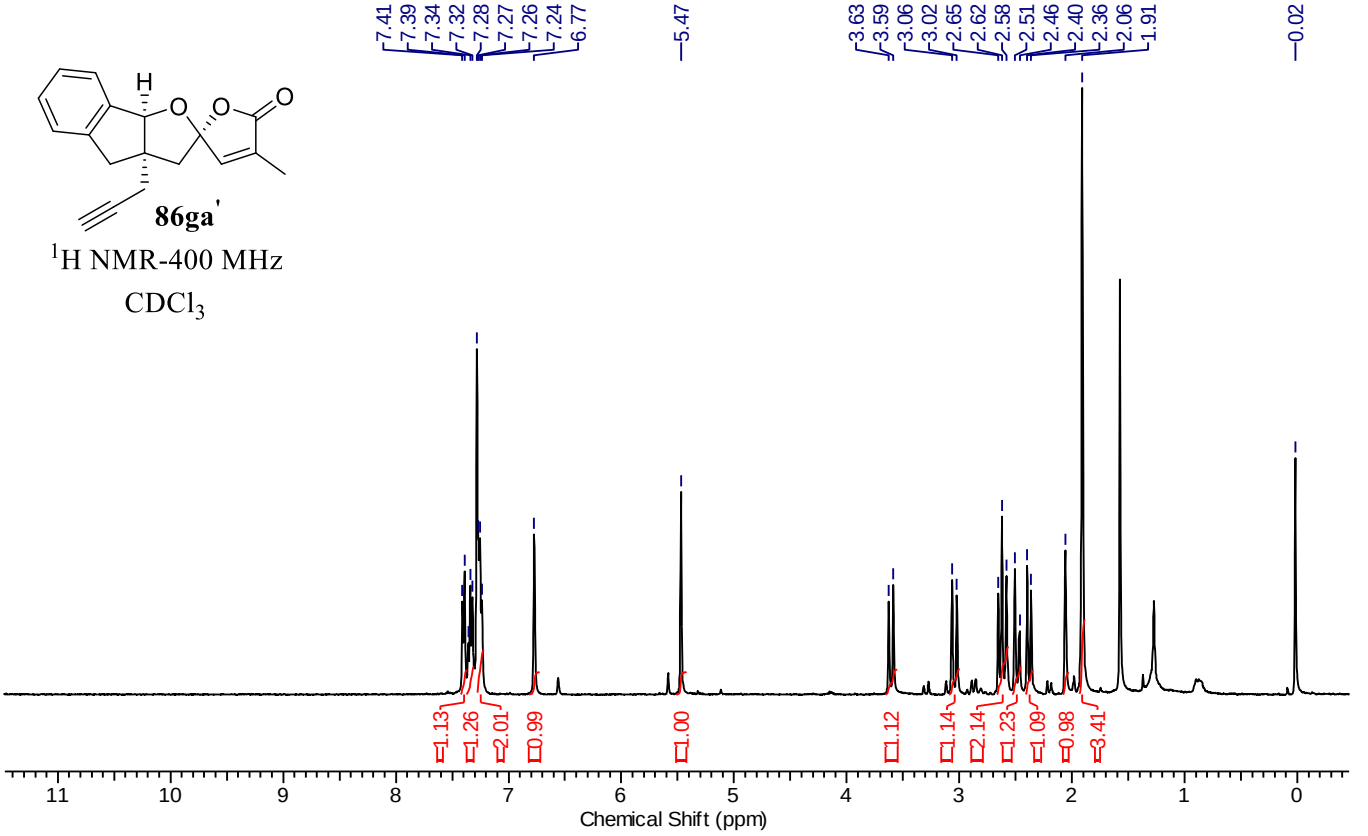
NOESY: (86ga)



NOESY: (86ga)


ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
ppm

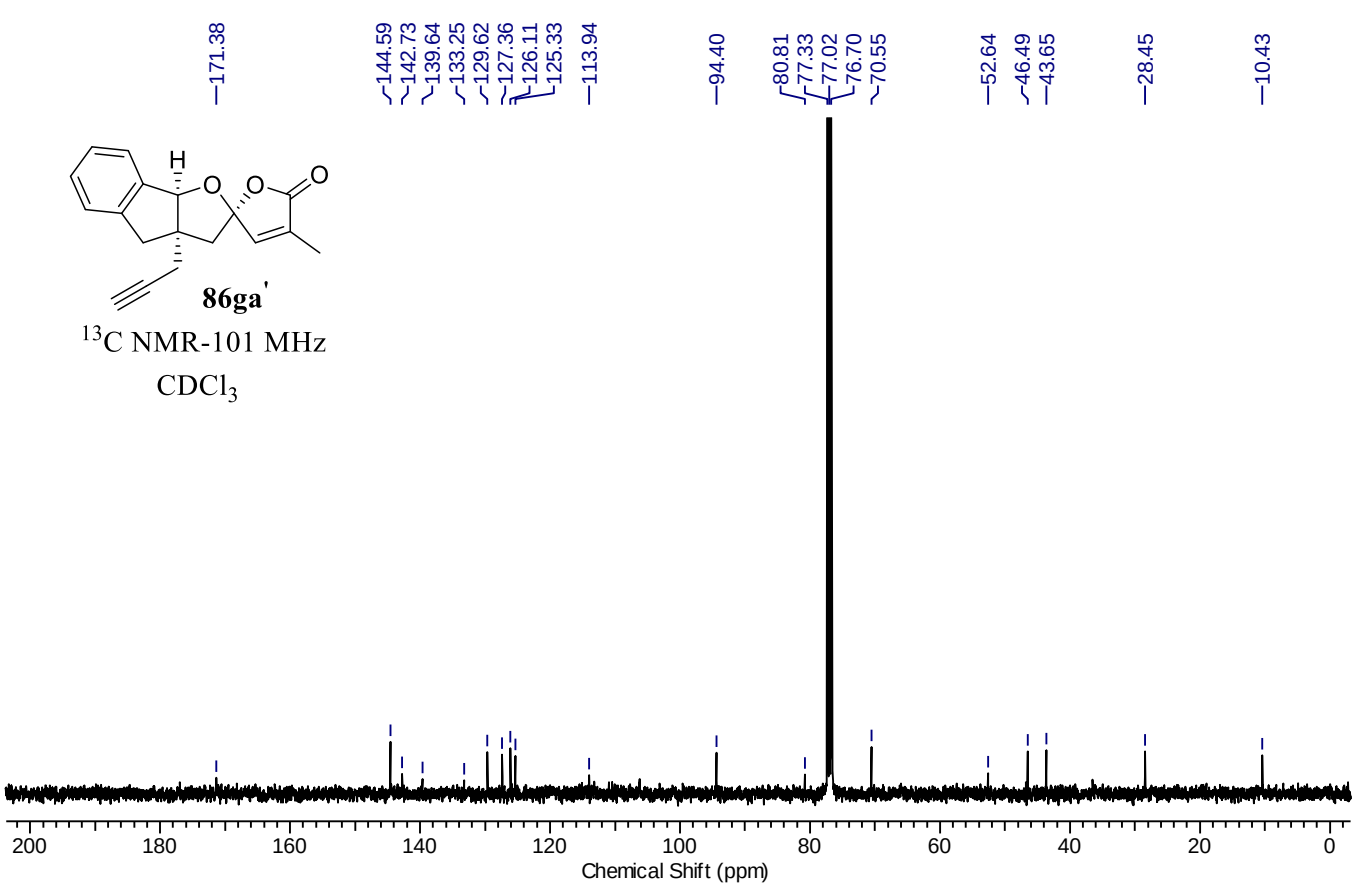
4-Methyl-3a'-(prop-2-yn-1-yl)-3',3a',4',8b'-tetrahydro-5*H*-spiro[furan-2,2'-indeno[1,2-*b*]furan]-5-one (86ga[1])



86ga'

^{1}H NMR-400 MHz

$CDCl_3$

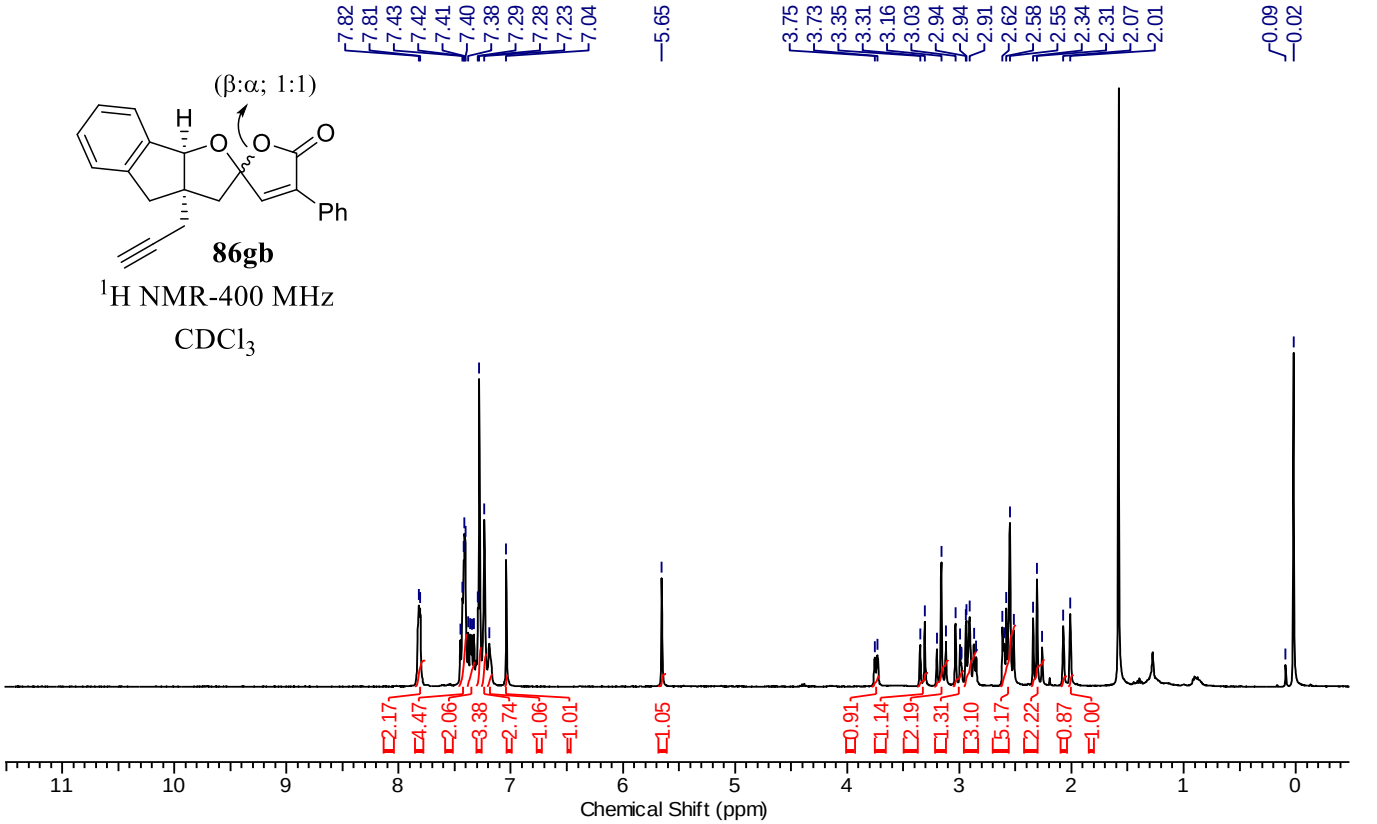


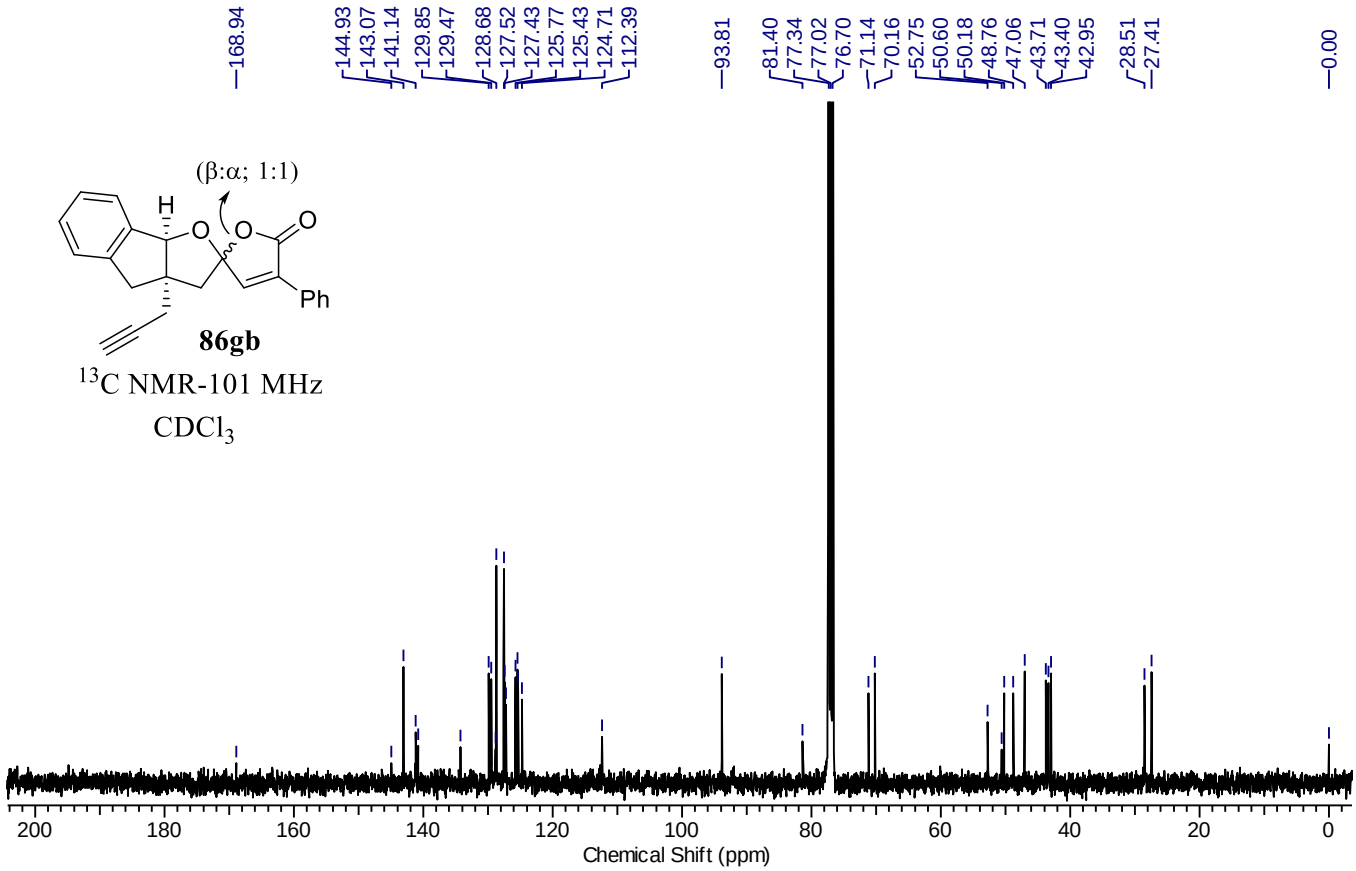
86ga'

^{13}C NMR-101 MHz

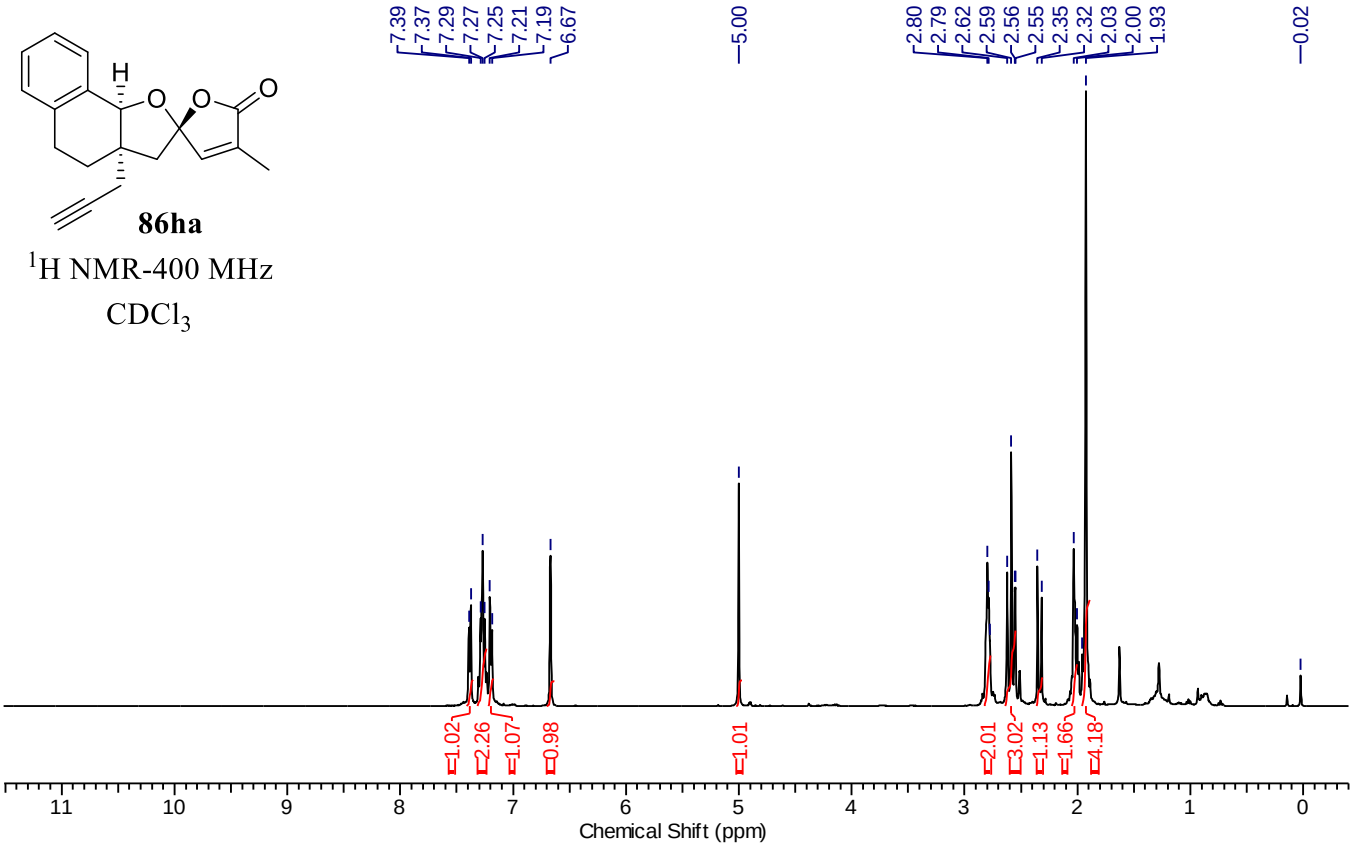
$CDCl_3$

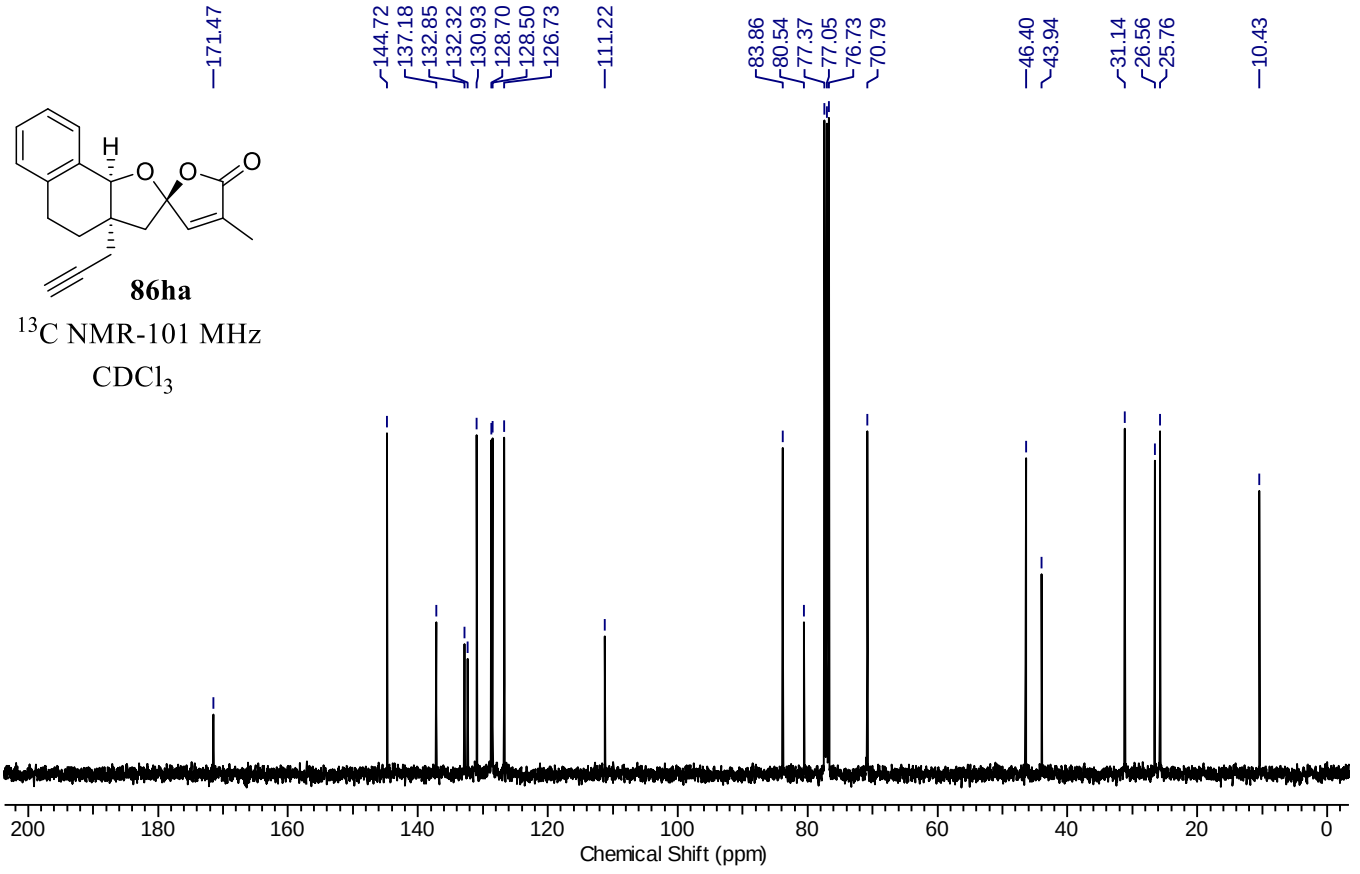
4-Phenyl-3a'-(prop-2-yn-1-yl)-3',3a',4',8b'-tetrahydro-5*H*-spiro[furan-2,2'-indeno[1,2-*b*]furan]-5-one (86gb)



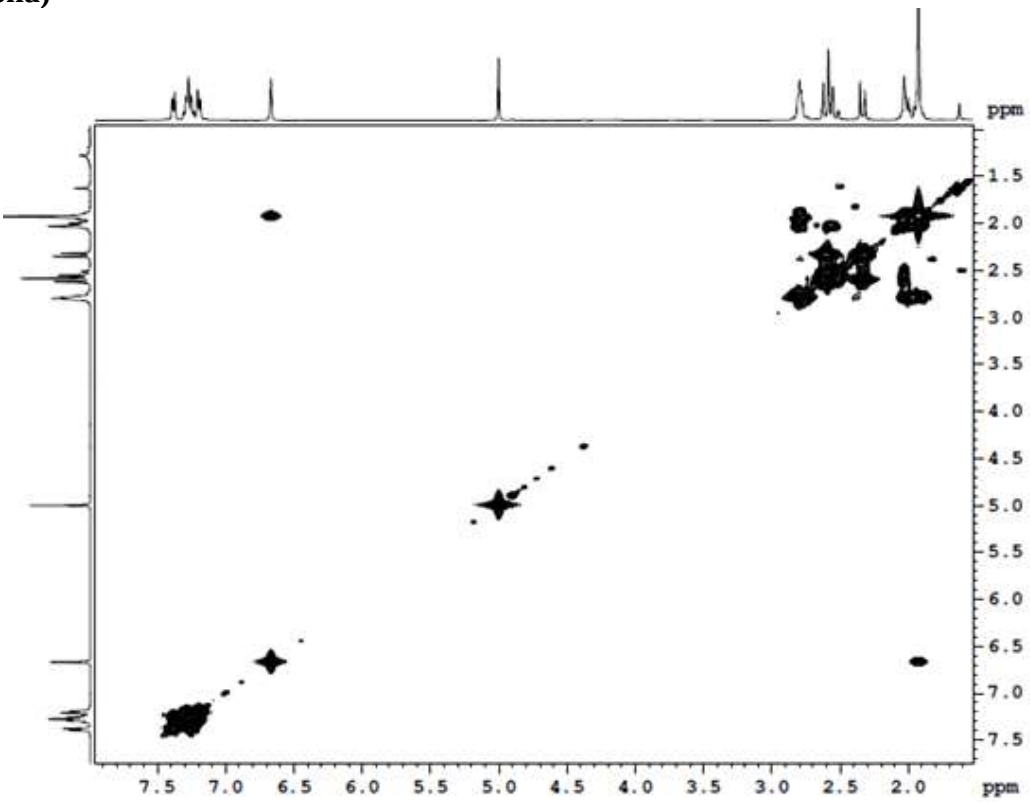


4-Methyl-3a'-(prop-2-yn-1-yl)-3a',4',5',9b'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-naphtho[1,2-*b*]furan]-5-one (86ha)

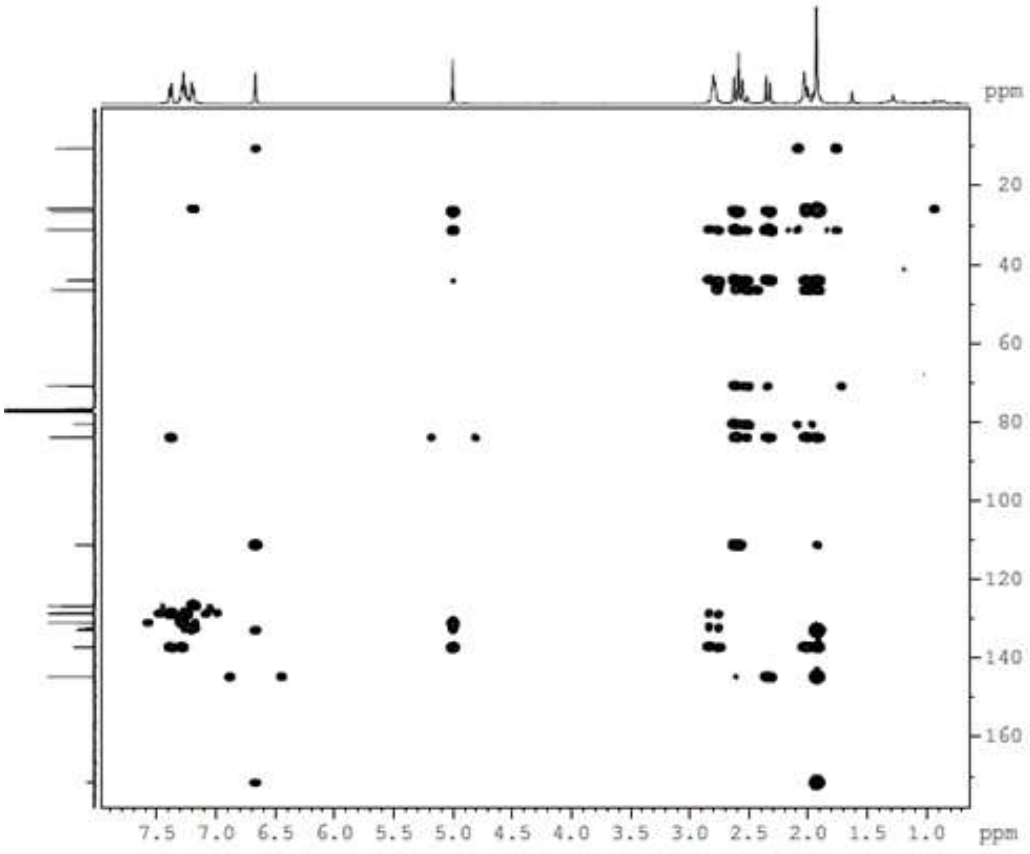




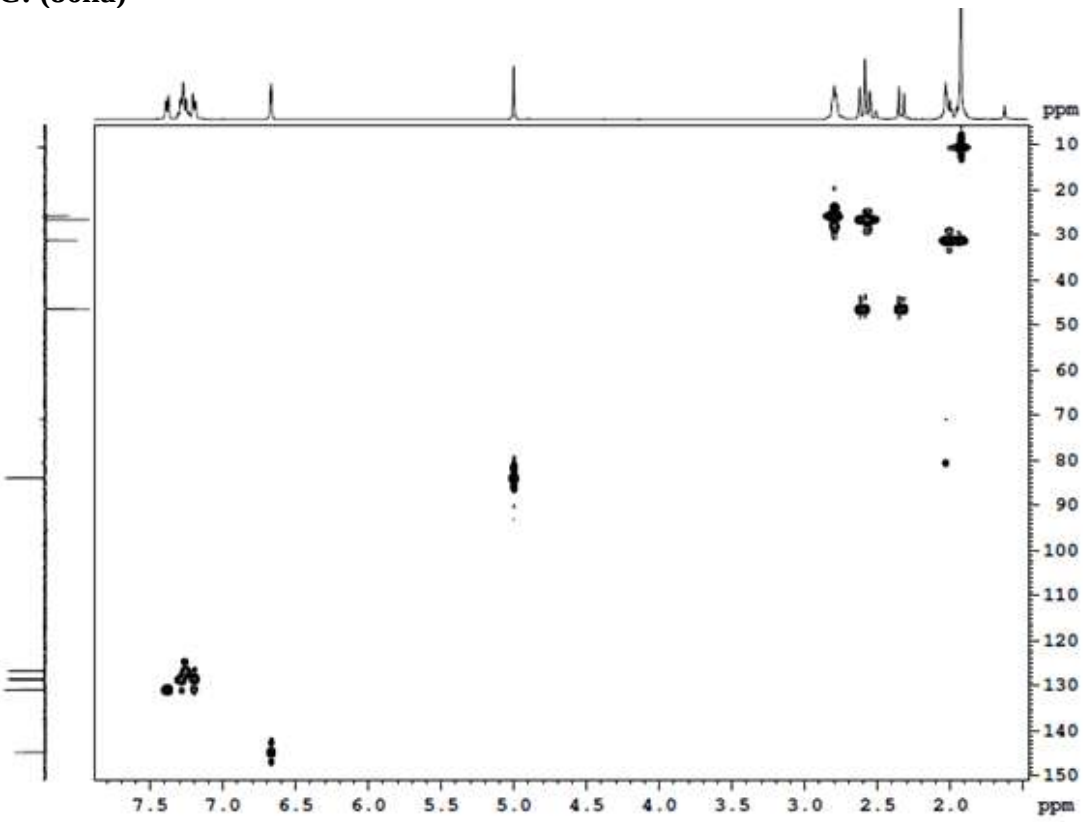
COSY: (86ha)



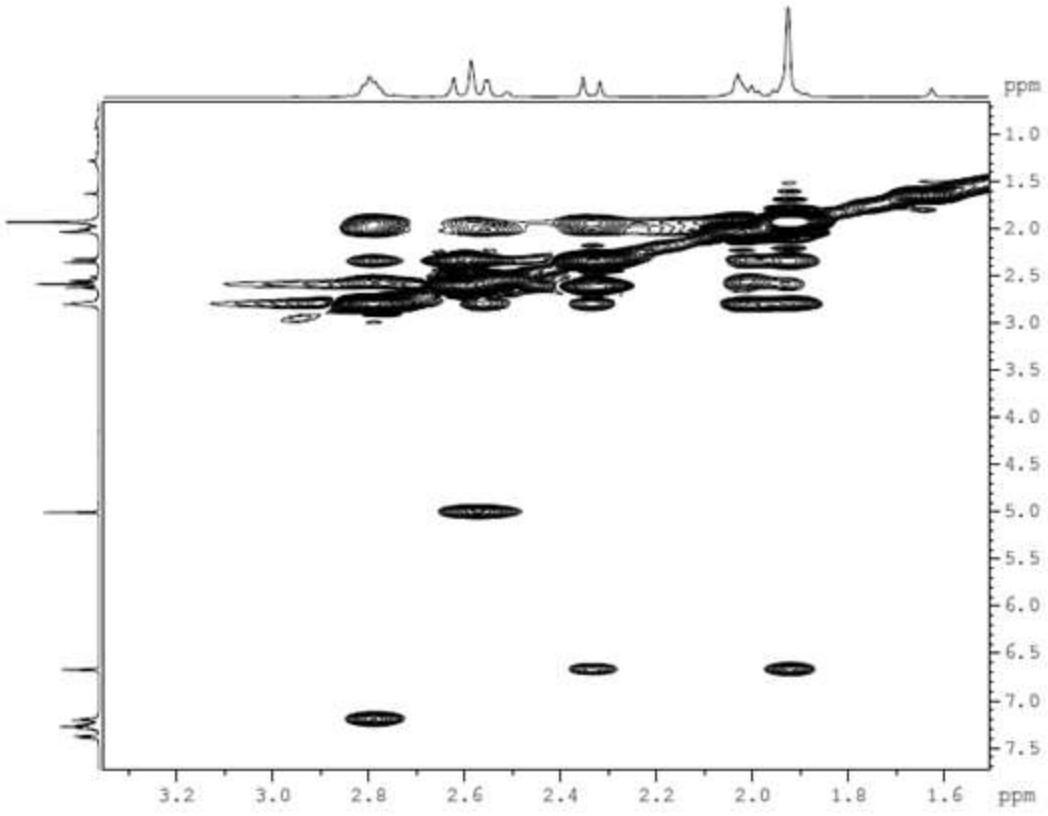
HMBC: (86ha)



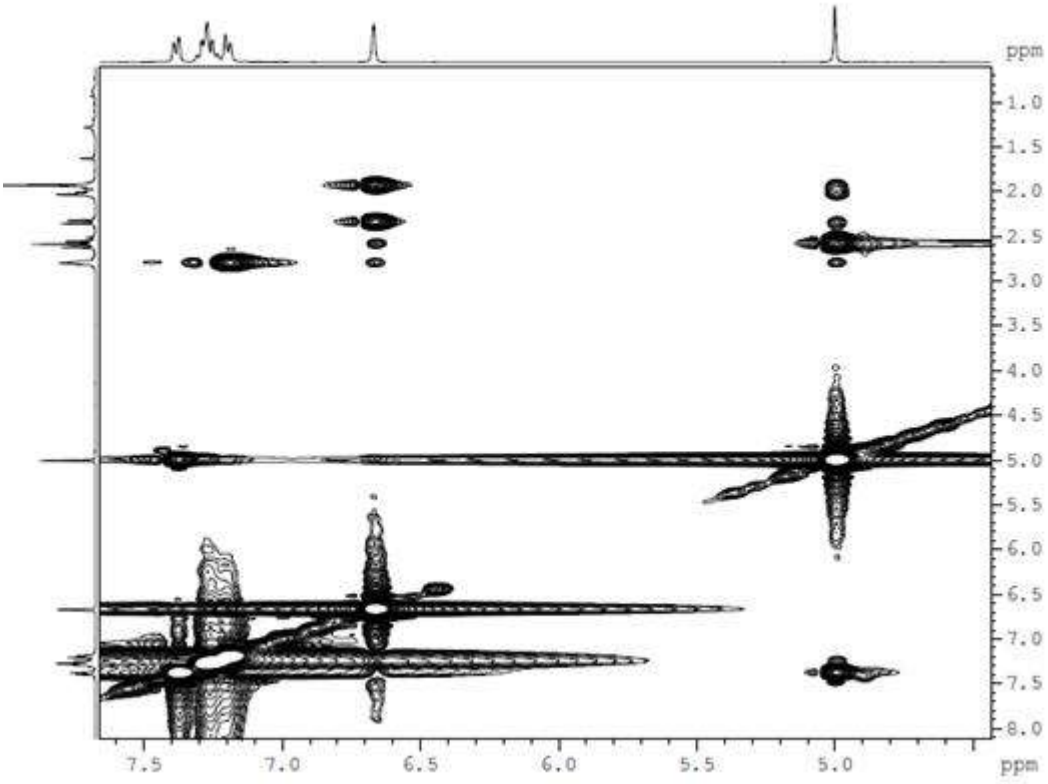
HSQC: (86ha)



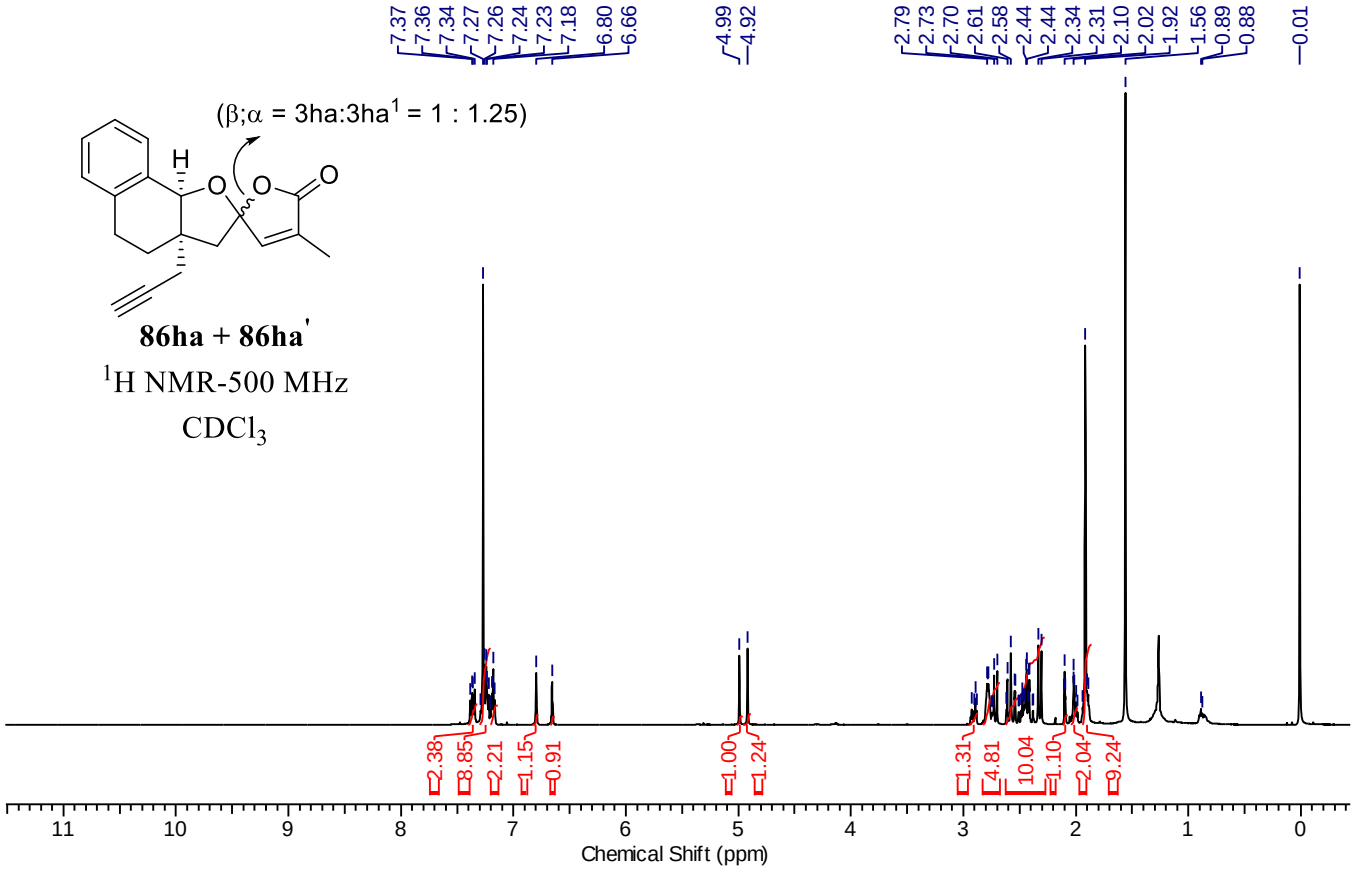
NOESY: (86ha)

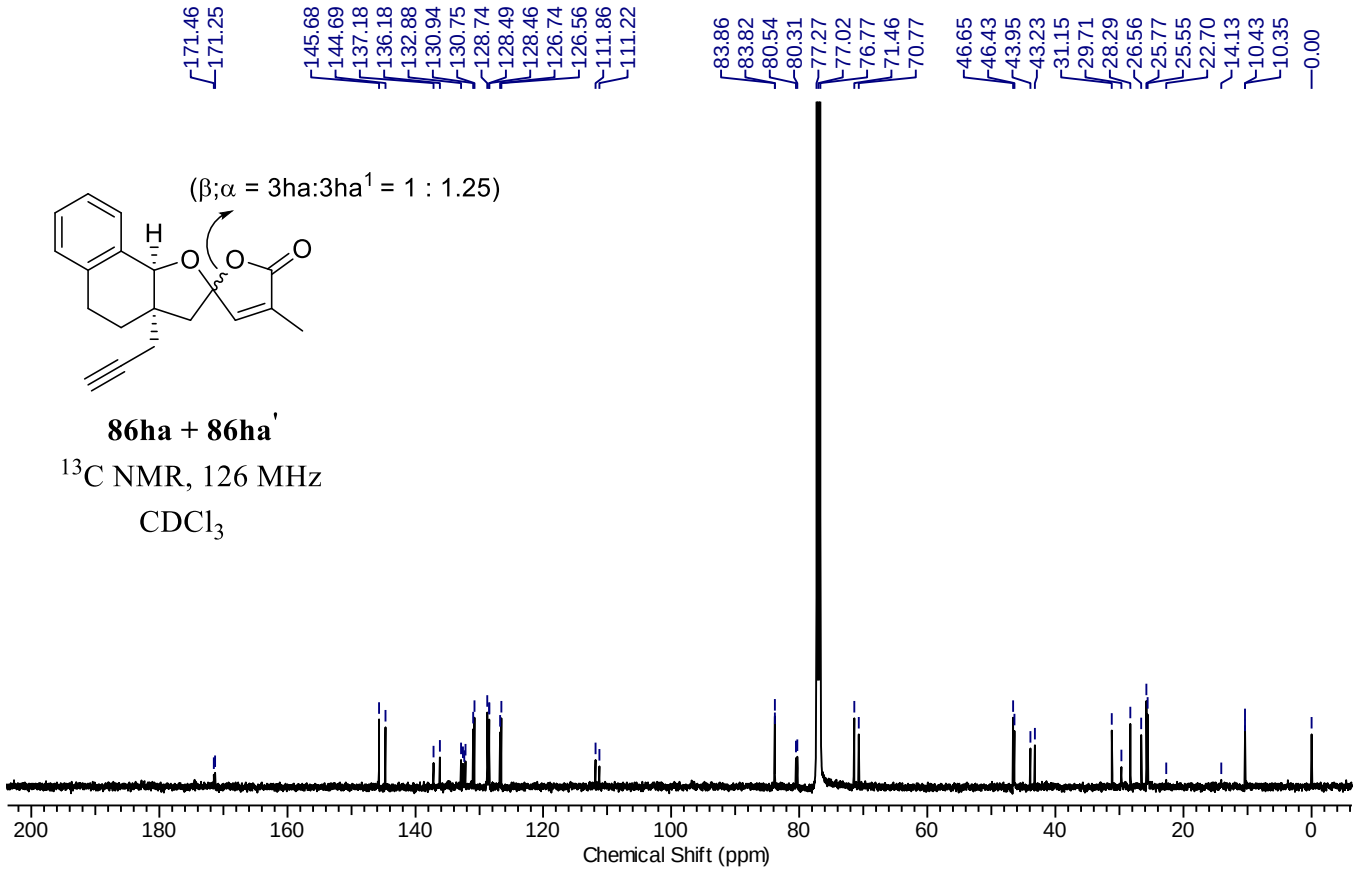


NOESY: (86ha)

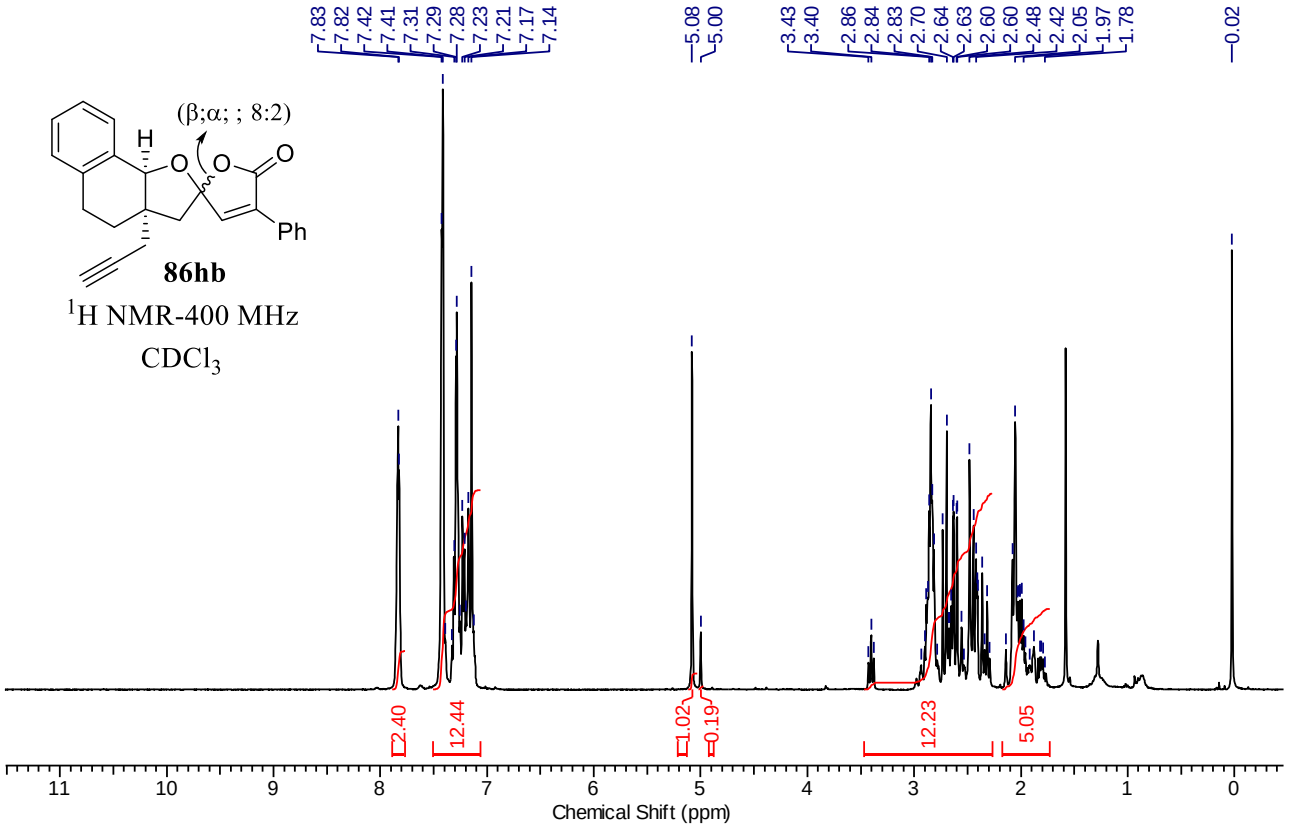


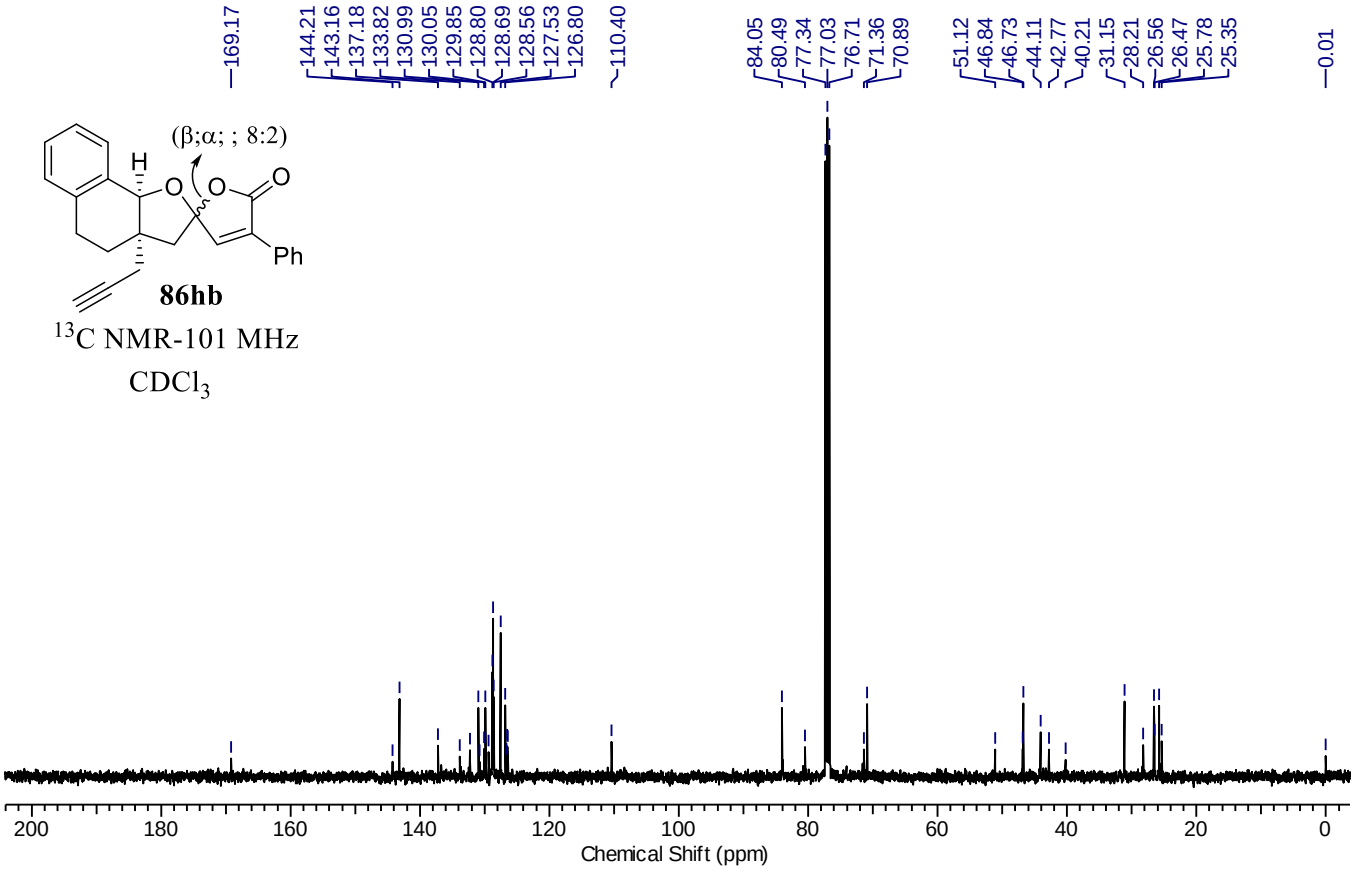
4-Methyl-3a'-(prop-2-yn-1-yl)-3a',4',5',9b'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-naphtho[1,2-*b*]furan]-5-one (86ha')



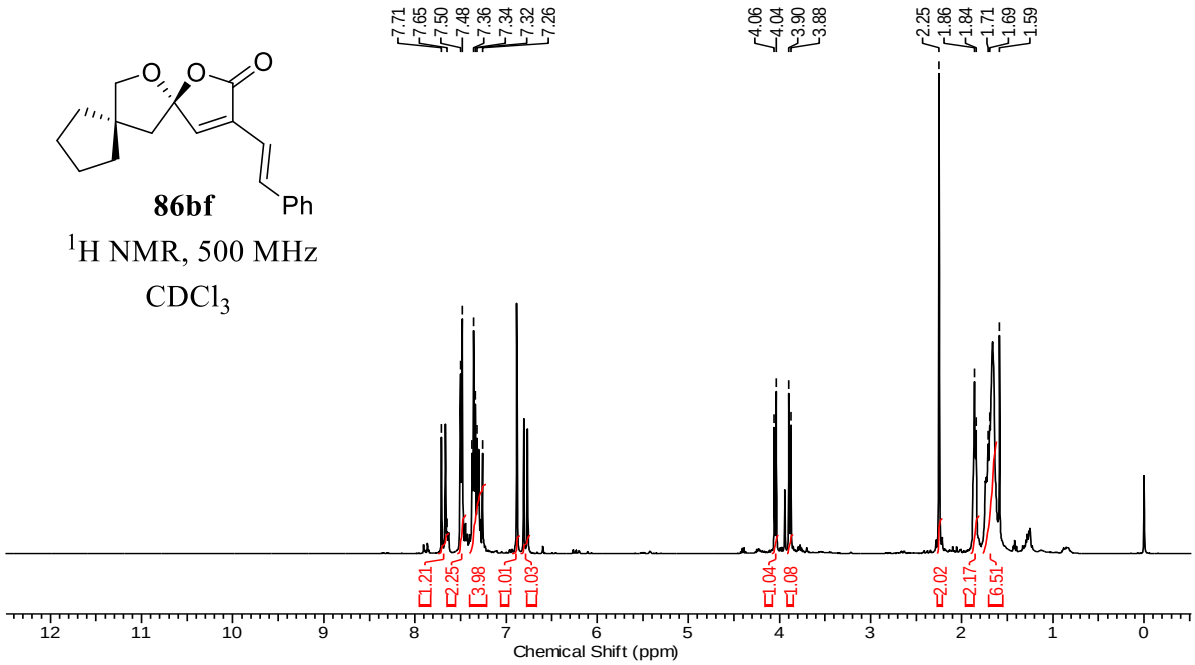


4-Phenyl-3a'-(prop-2-yn-1-yl)-3a',4',5',9b'-tetrahydro-3'*H*,5*H*-spiro[furan-2,2'-naphtho[1,2-*b*]furan]-5-one (86hb)





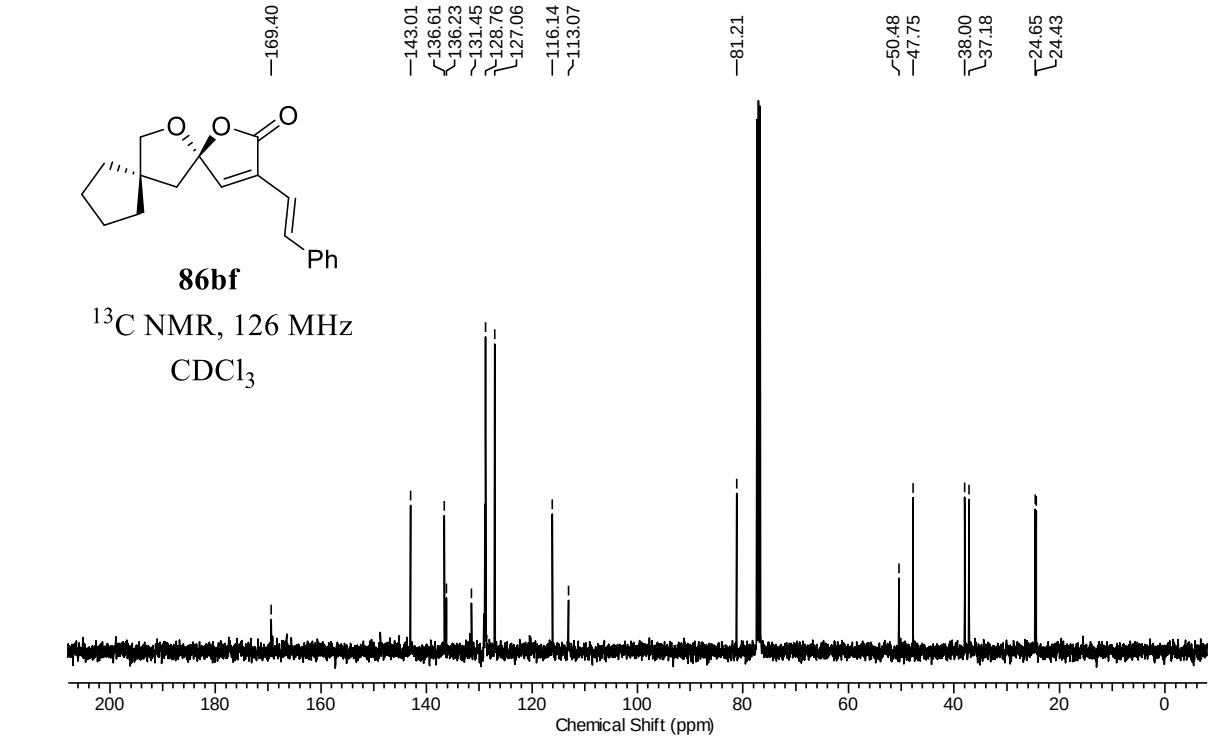
(*E*)-3-Styryl-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-2-one (86bf):



86bf

^{1}H NMR, 500 MHz

$CDCl_3$



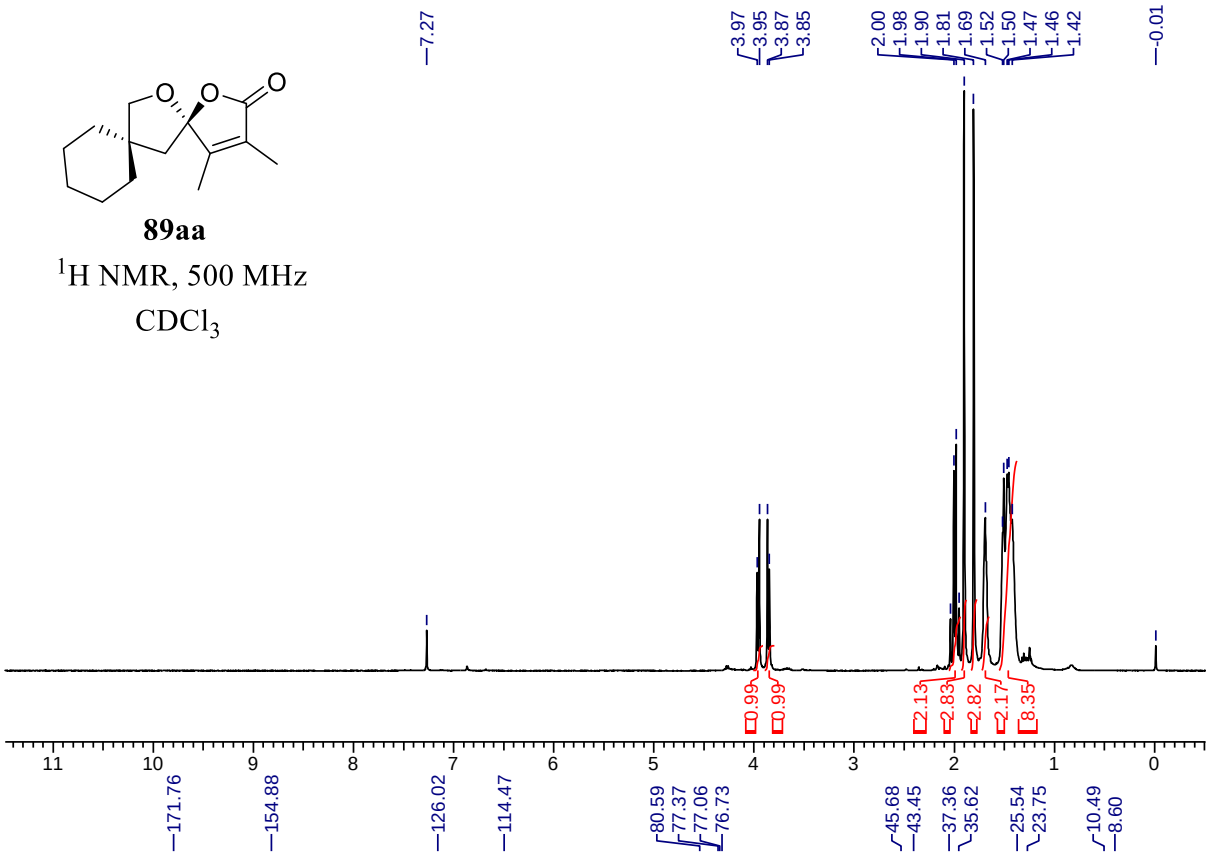
86bf

^{13}C NMR, 126 MHz

$CDCl_3$

Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (Possessing internal alkyne)

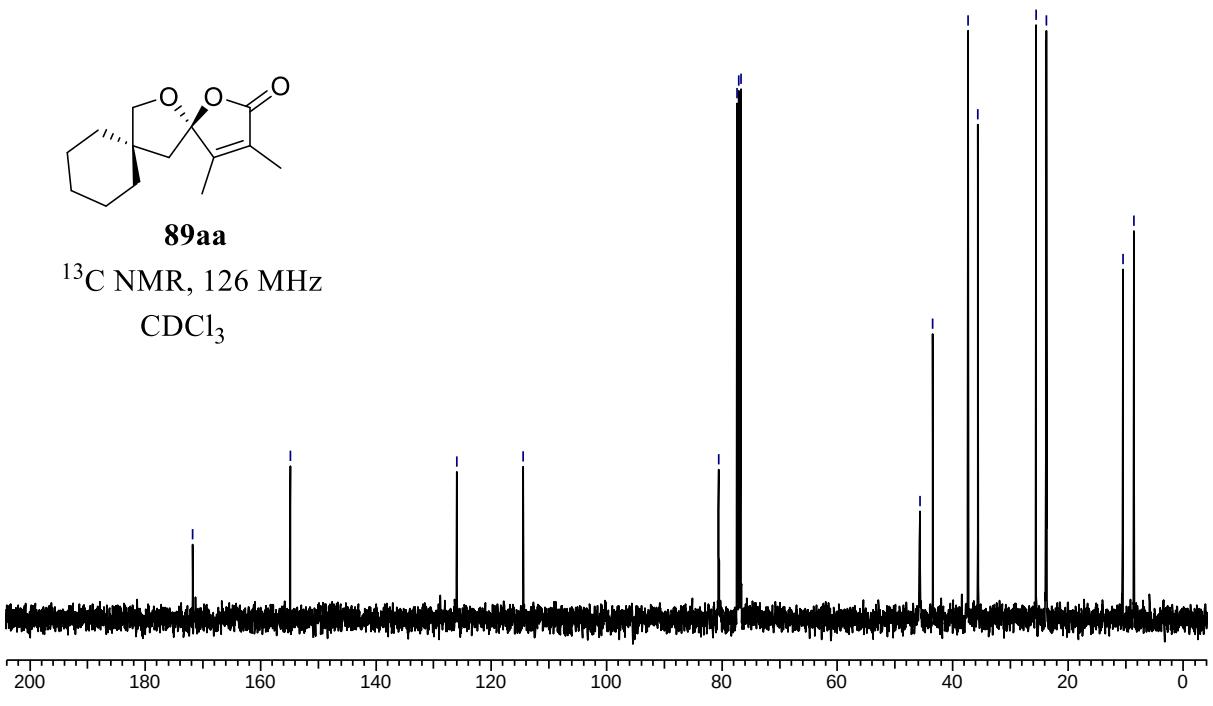
3, 4-Dimethyl-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89aa):



89aa

^{1}H NMR, 500 MHz

$CDCl_3$

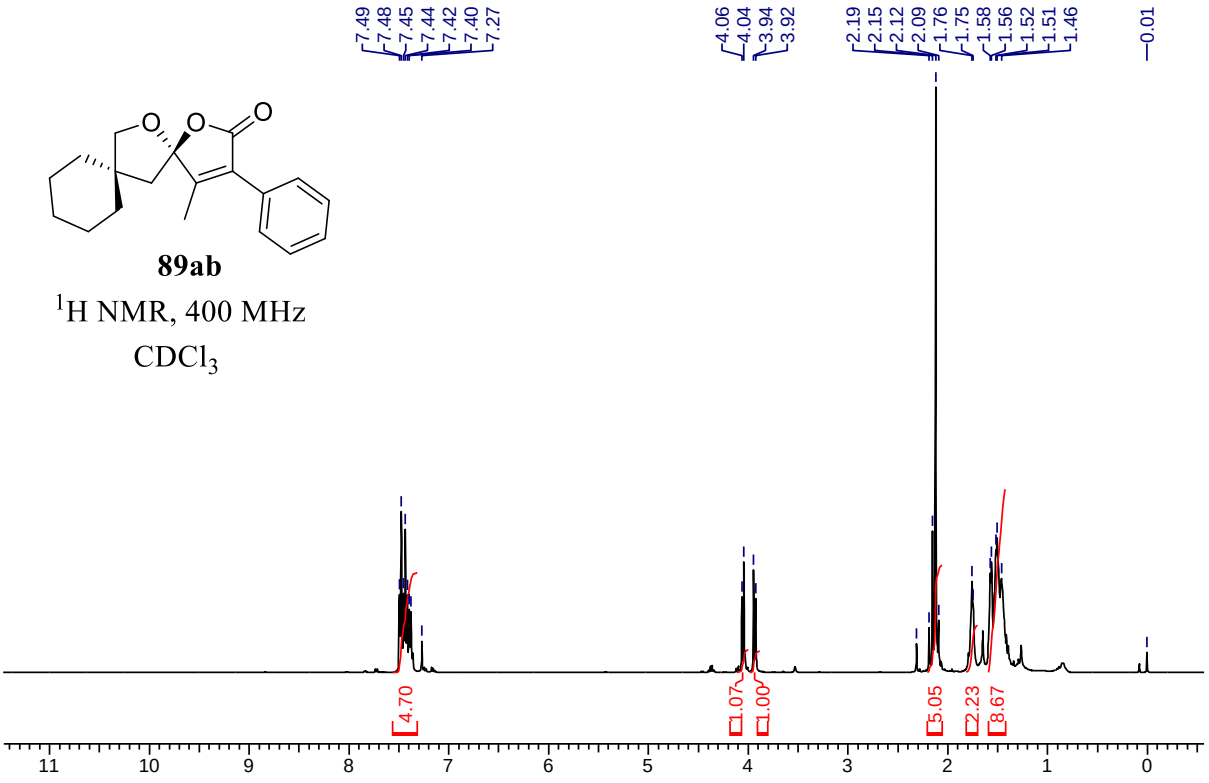


89aa

^{13}C NMR, 126 MHz

$CDCl_3$

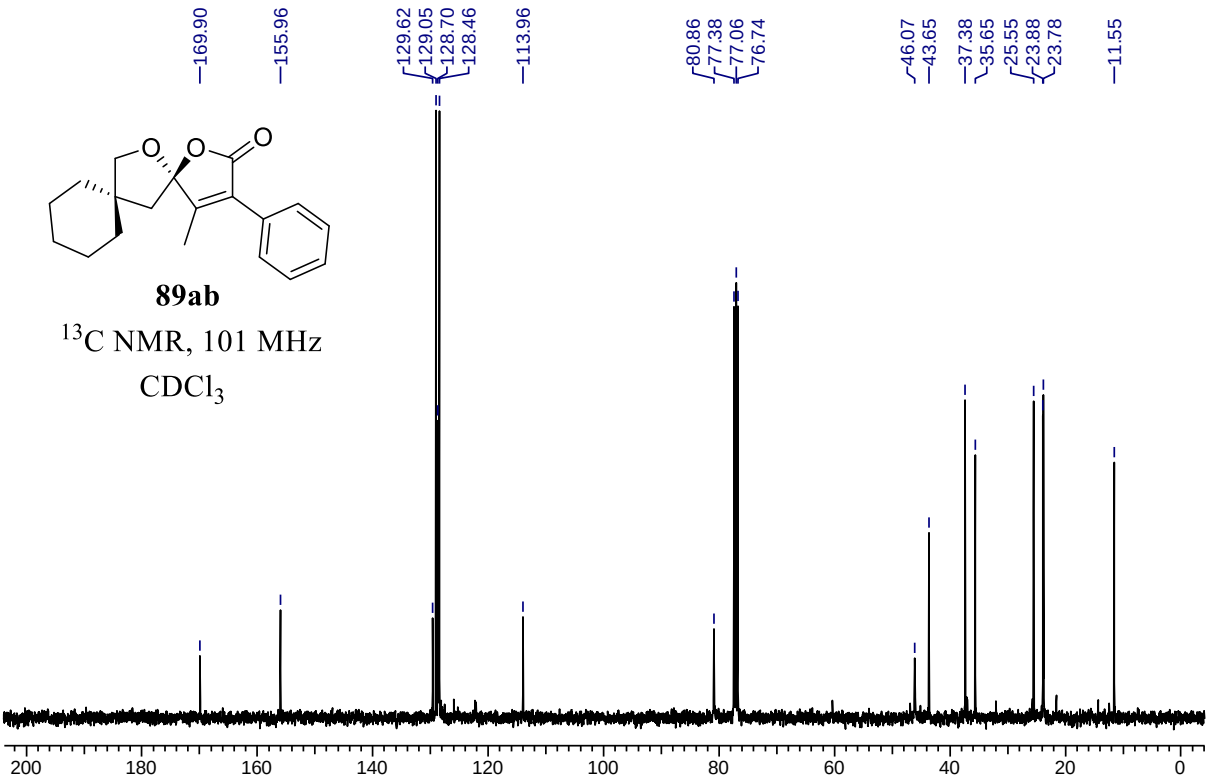
4-Methyl-3-phenyl-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89ab):



89ab

^{1}H NMR, 400 MHz

$CDCl_3$

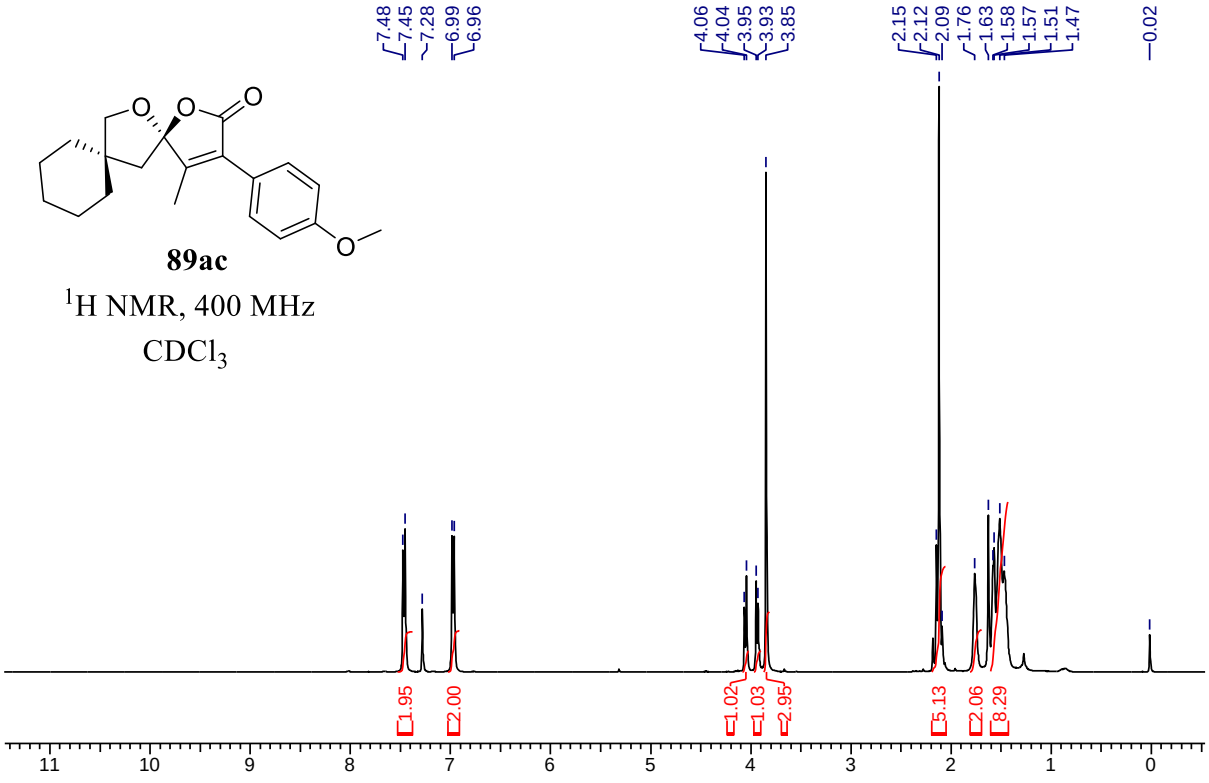


89ab

^{13}C NMR, 101 MHz

$CDCl_3$

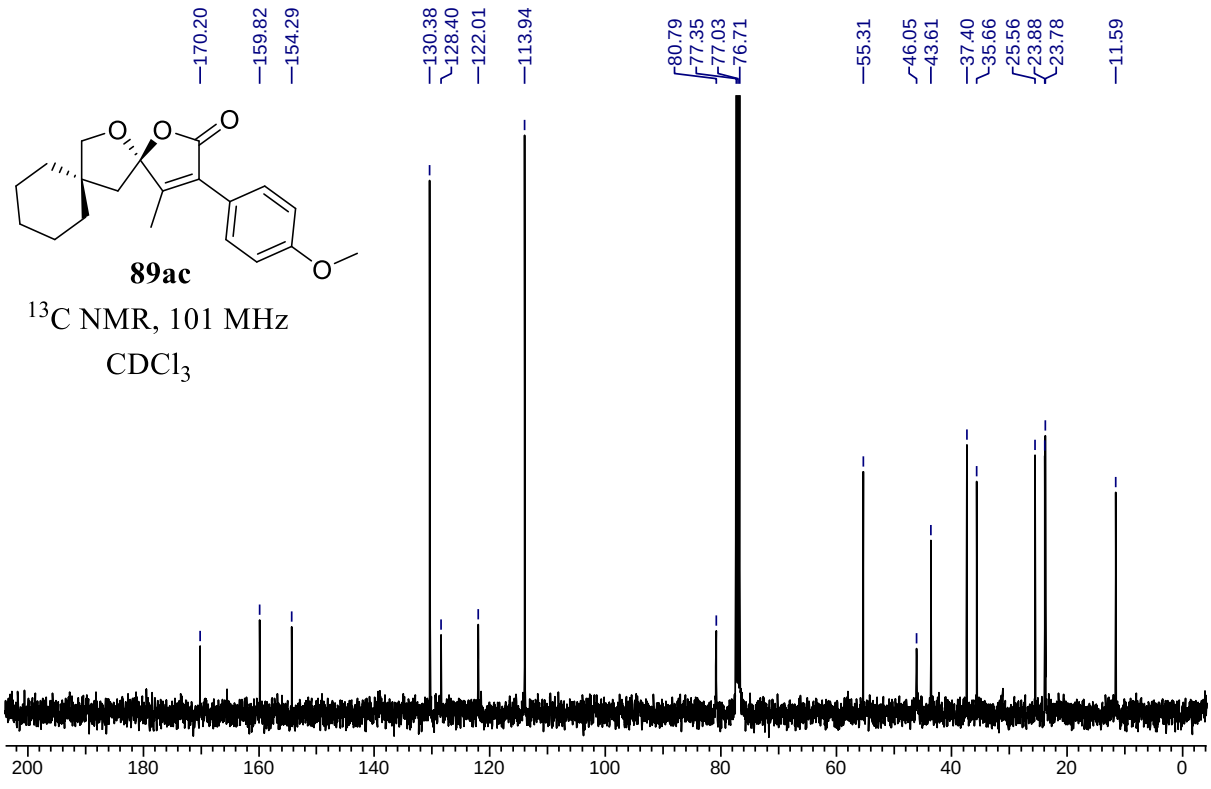
3-(4-Methoxyphenyl)-4-methyl-1, 14 dioxadispiro [4.1.5^7.2^5] tetradec -3-en-2-one (89ac):



89ac

^{1}H NMR, 400 MHz

$CDCl_3$

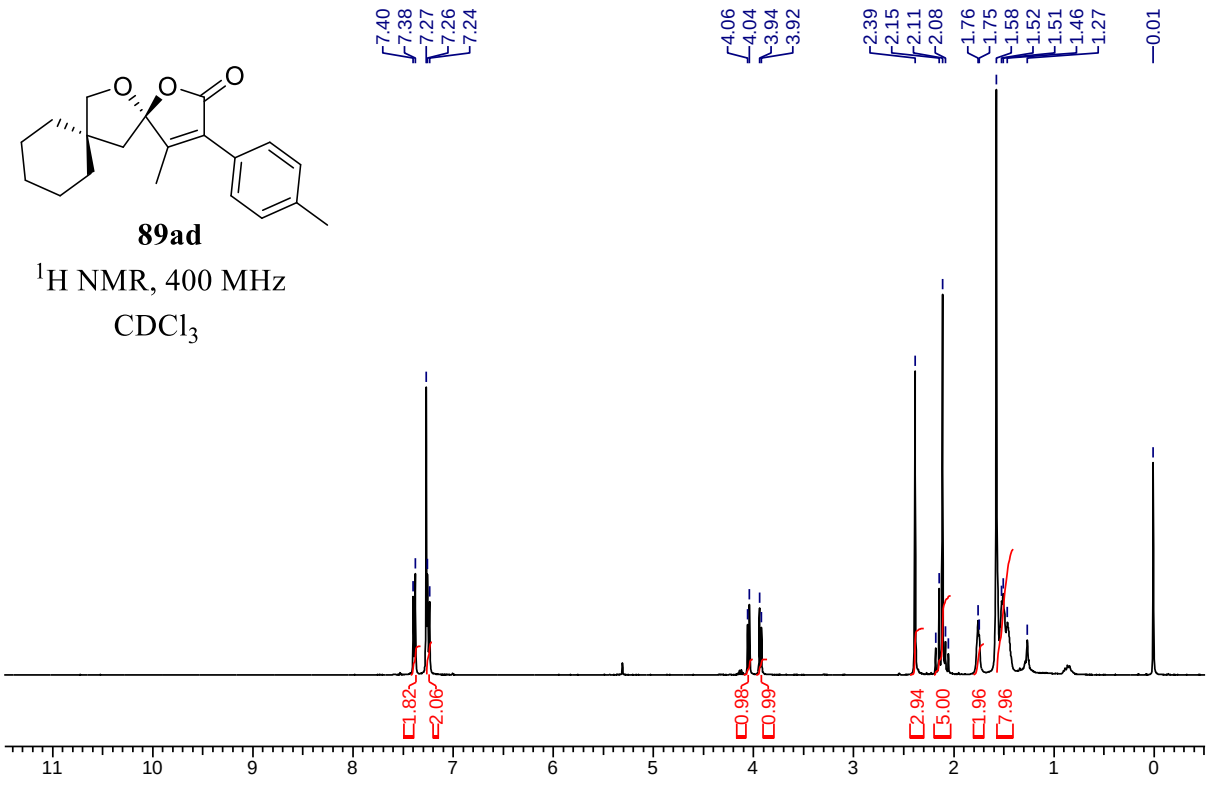


89ac

^{13}C NMR, 101 MHz

$CDCl_3$

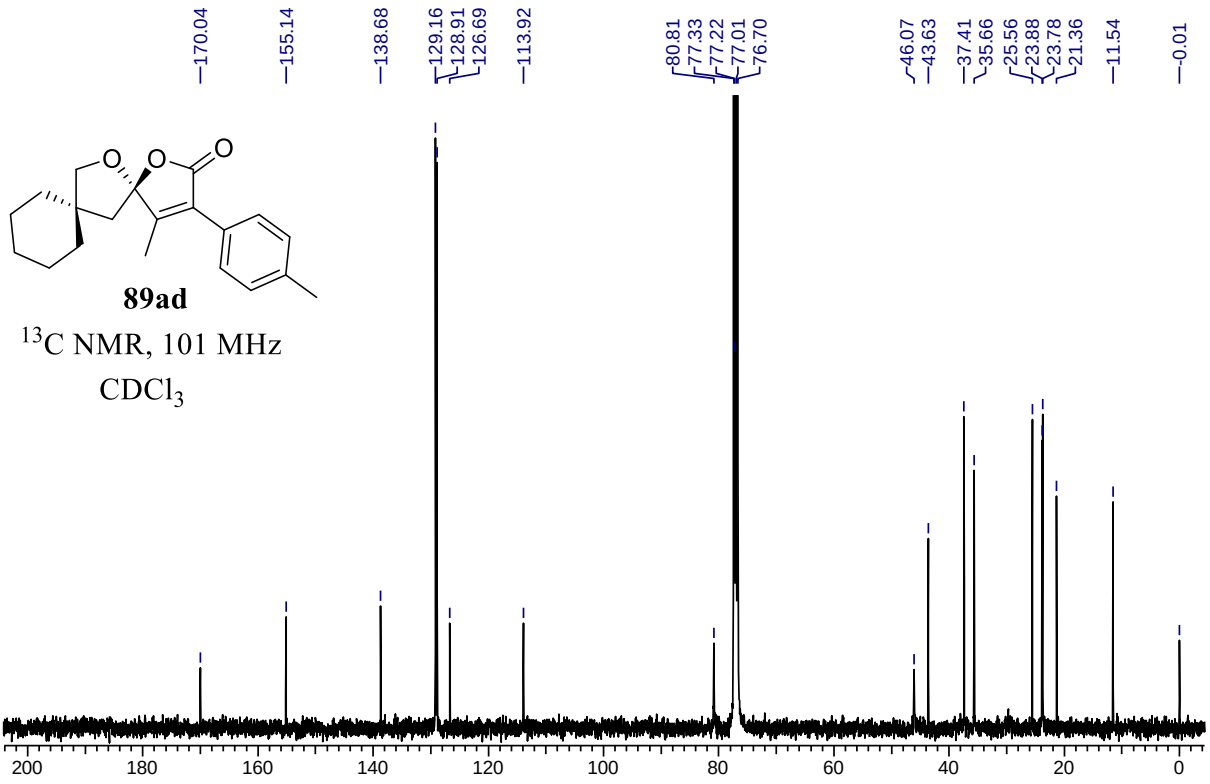
4-Methyl-3-(*p*-tolyl)-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89ad):



89ad

^{1}H NMR, 400 MHz

$CDCl_3$

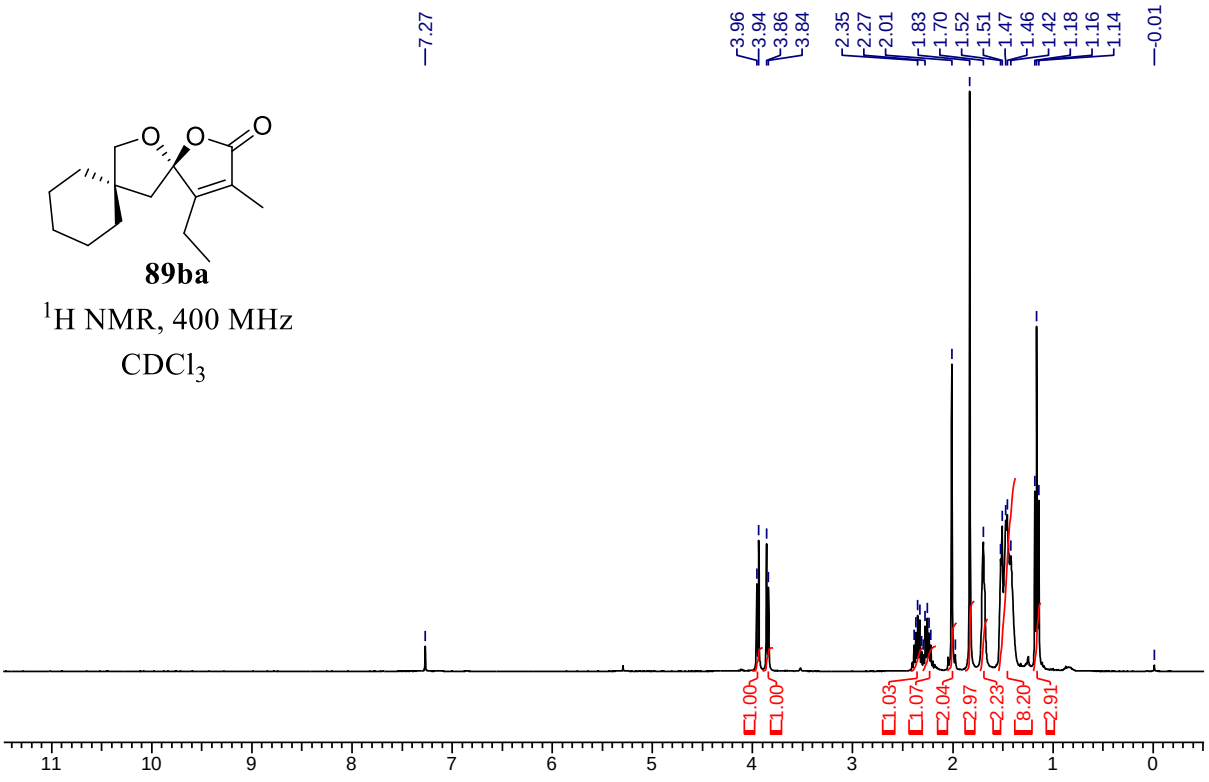


89ad

^{13}C NMR, 101 MHz

$CDCl_3$

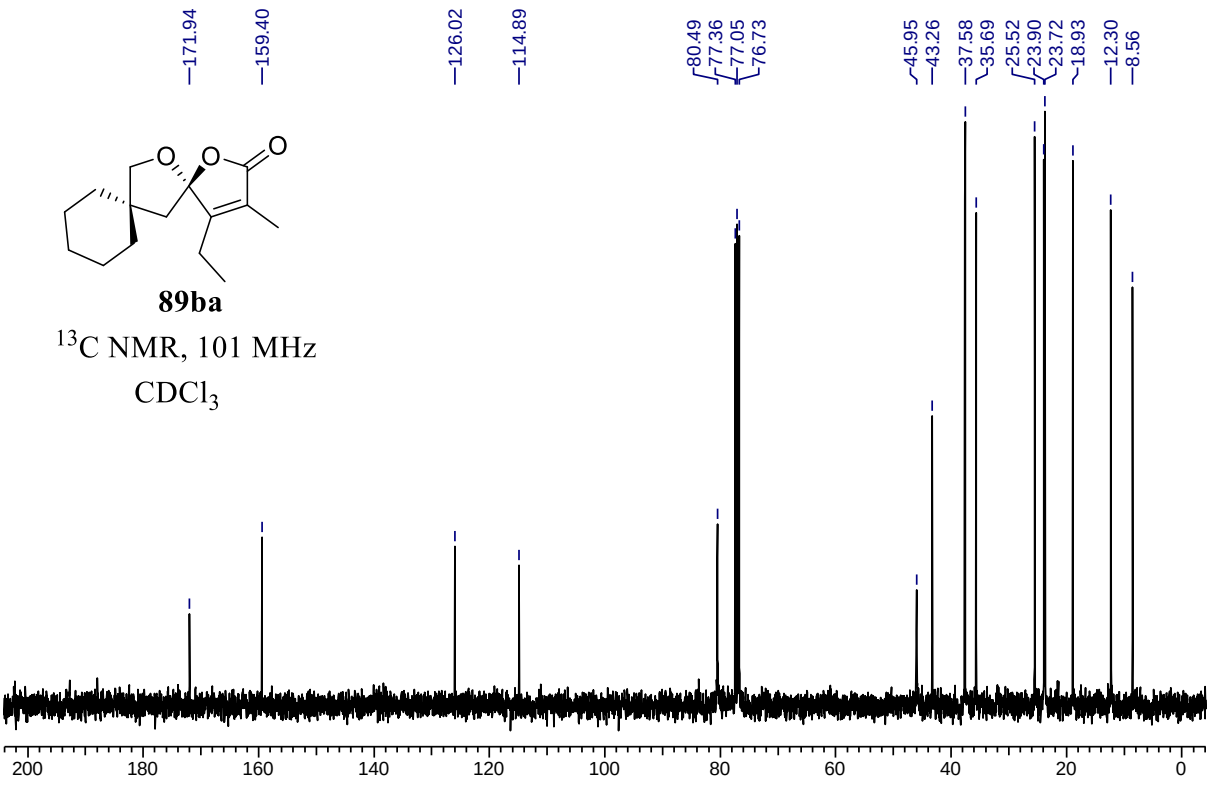
4-Ethyl-3-methyl-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89ba):



89ba

^{1}H NMR, 400 MHz

$CDCl_3$

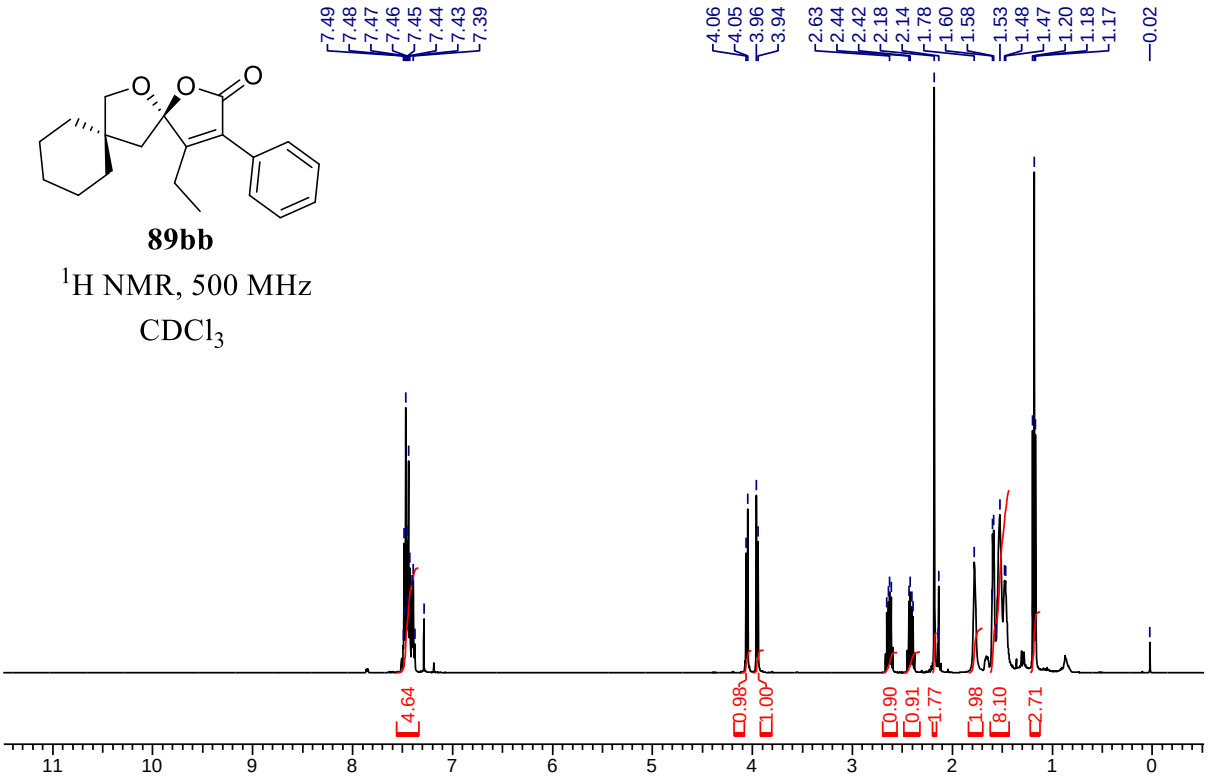


89ba

^{13}C NMR, 101 MHz

$CDCl_3$

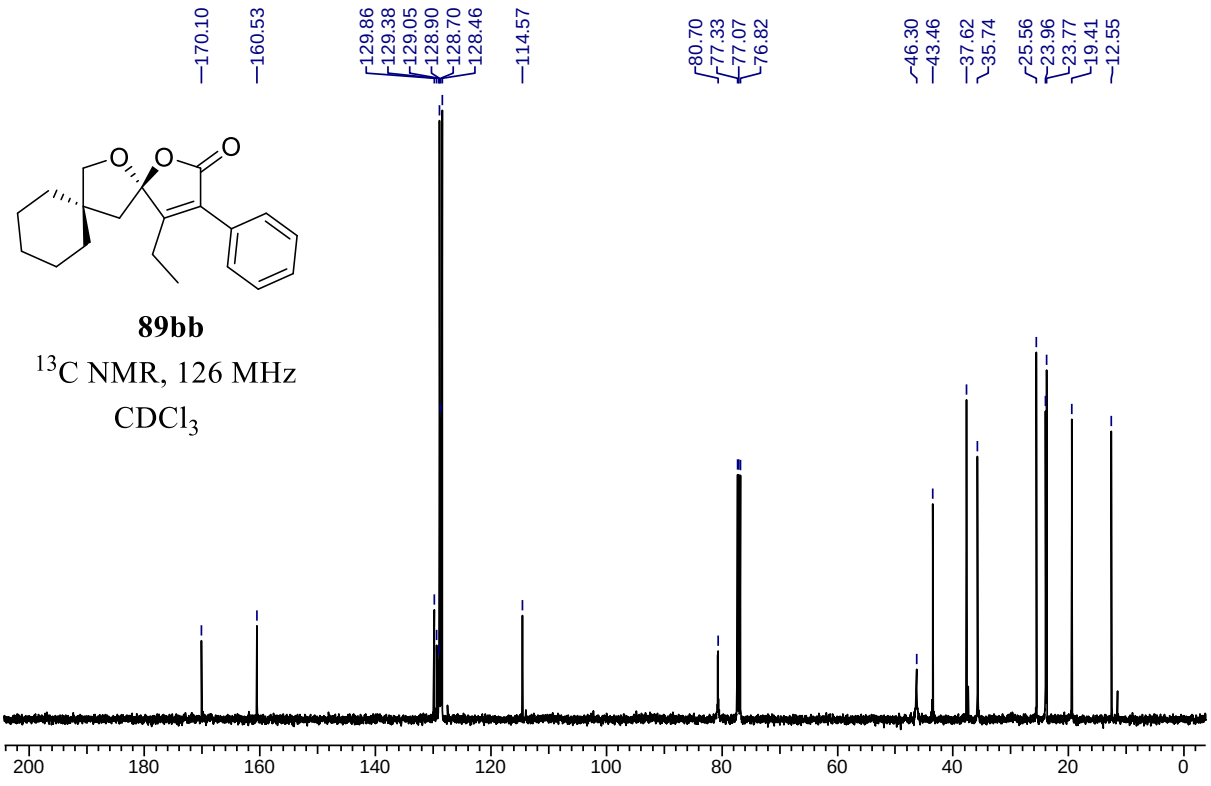
4-Ethyl-3-phenyl-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89bb):



89bb

^{1}H NMR, 500 MHz

$CDCl_3$

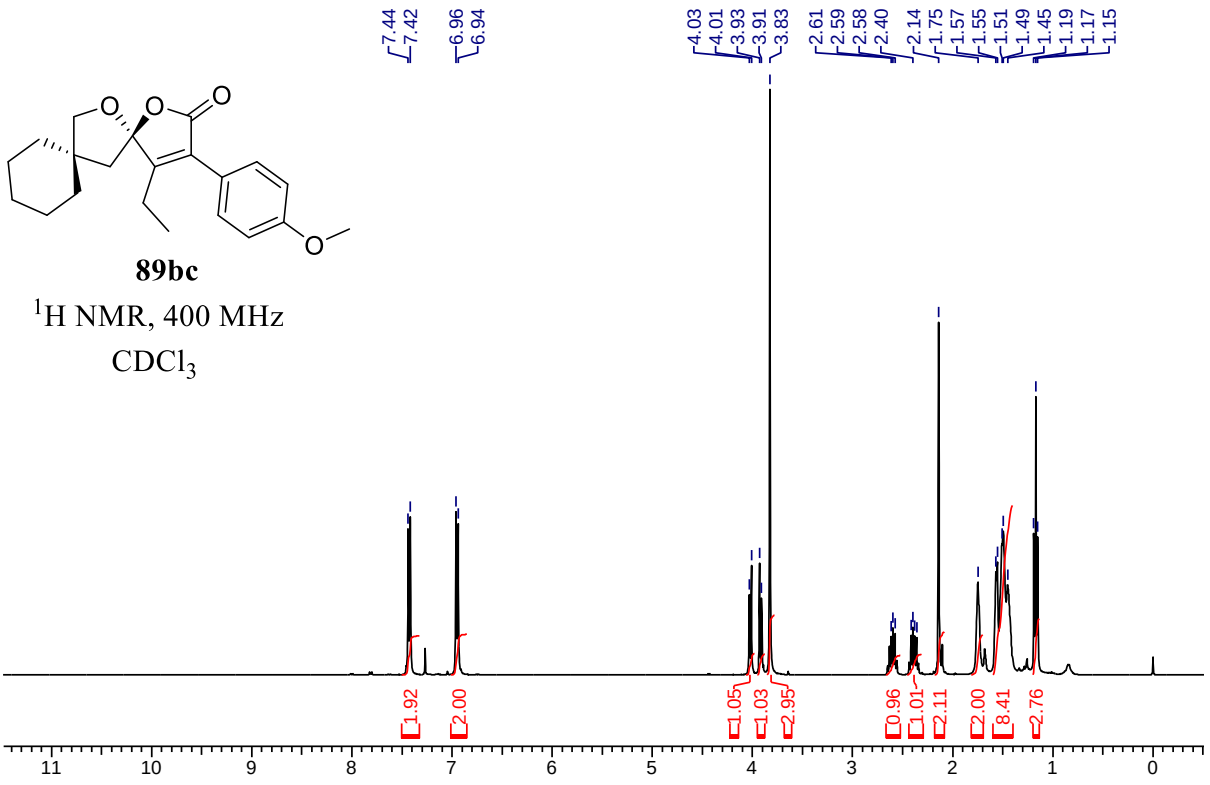


89bb

^{13}C NMR, 126 MHz

$CDCl_3$

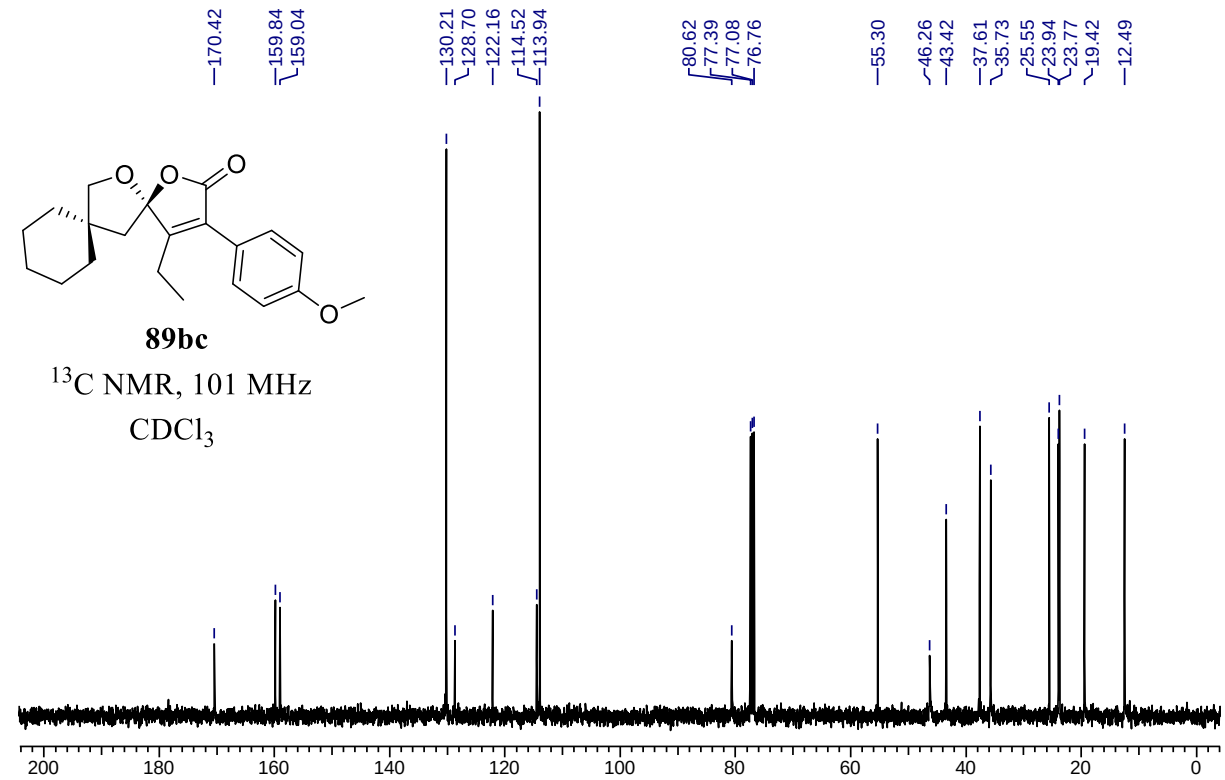
4-Ethyl-3-(4-methoxyphenyl)-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89bc):



89bc

^{1}H NMR, 400 MHz

$CDCl_3$

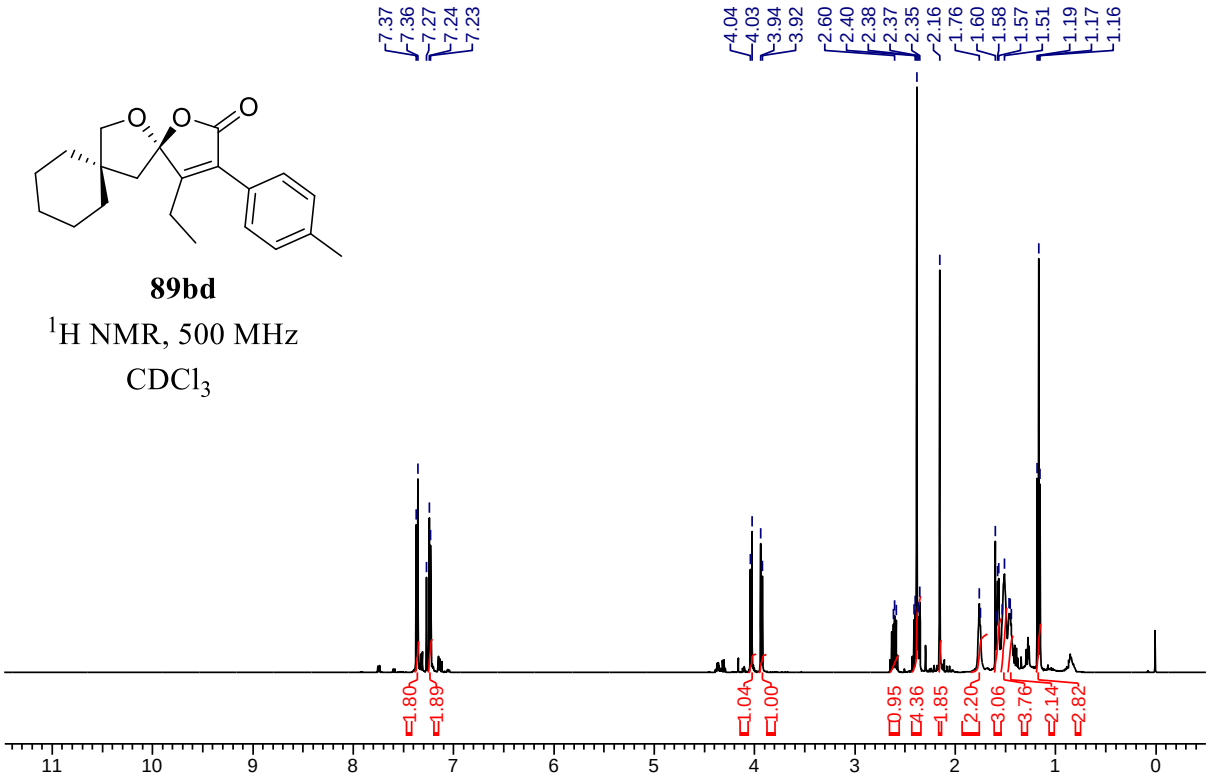


89bc

^{13}C NMR, 101 MHz

$CDCl_3$

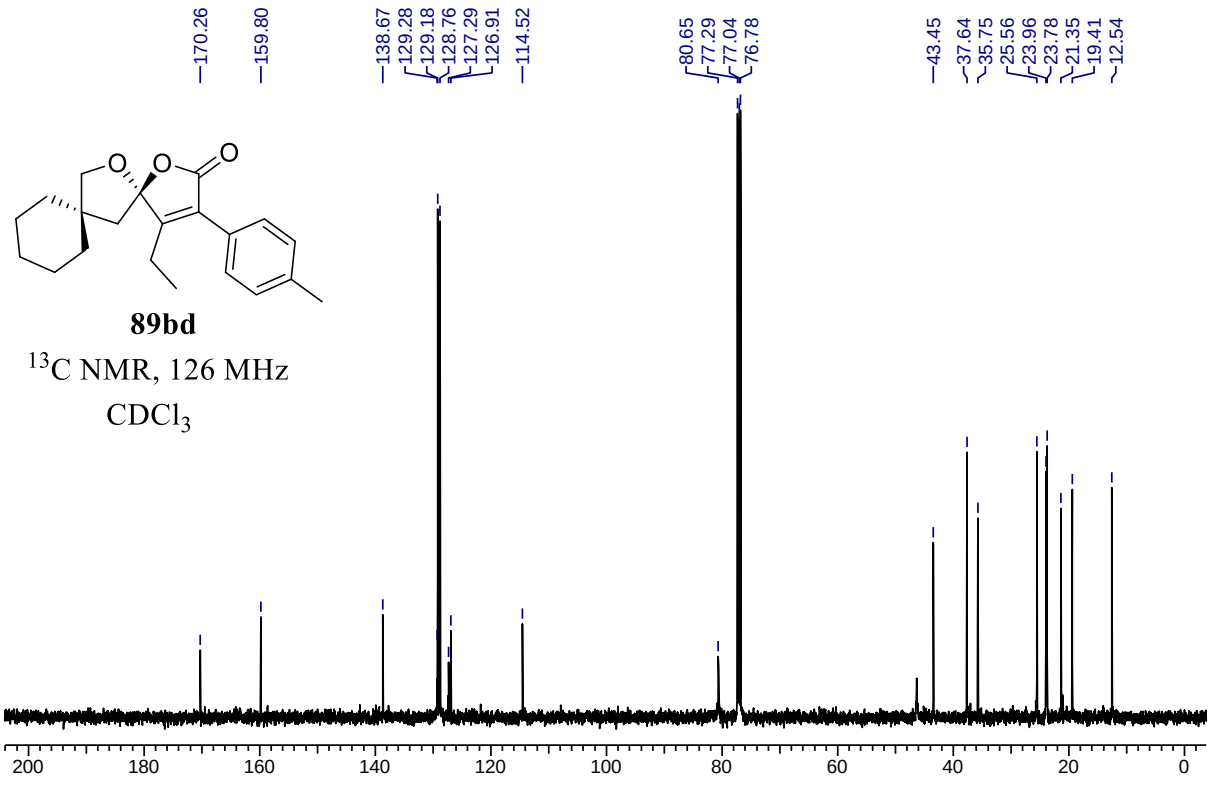
4-Ethyl-3-(*p*-tolyl)-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89bd):



89bd

^{1}H NMR, 500 MHz

$CDCl_3$

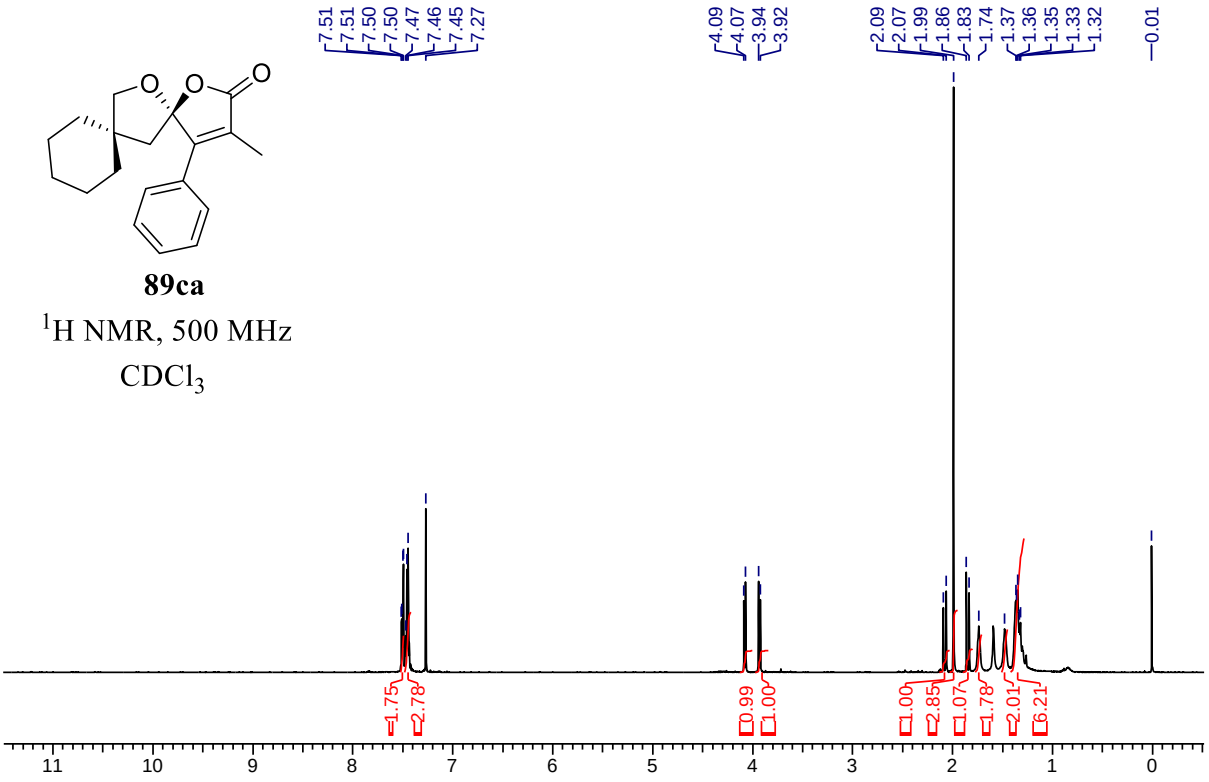


89bd

^{13}C NMR, 126 MHz

$CDCl_3$

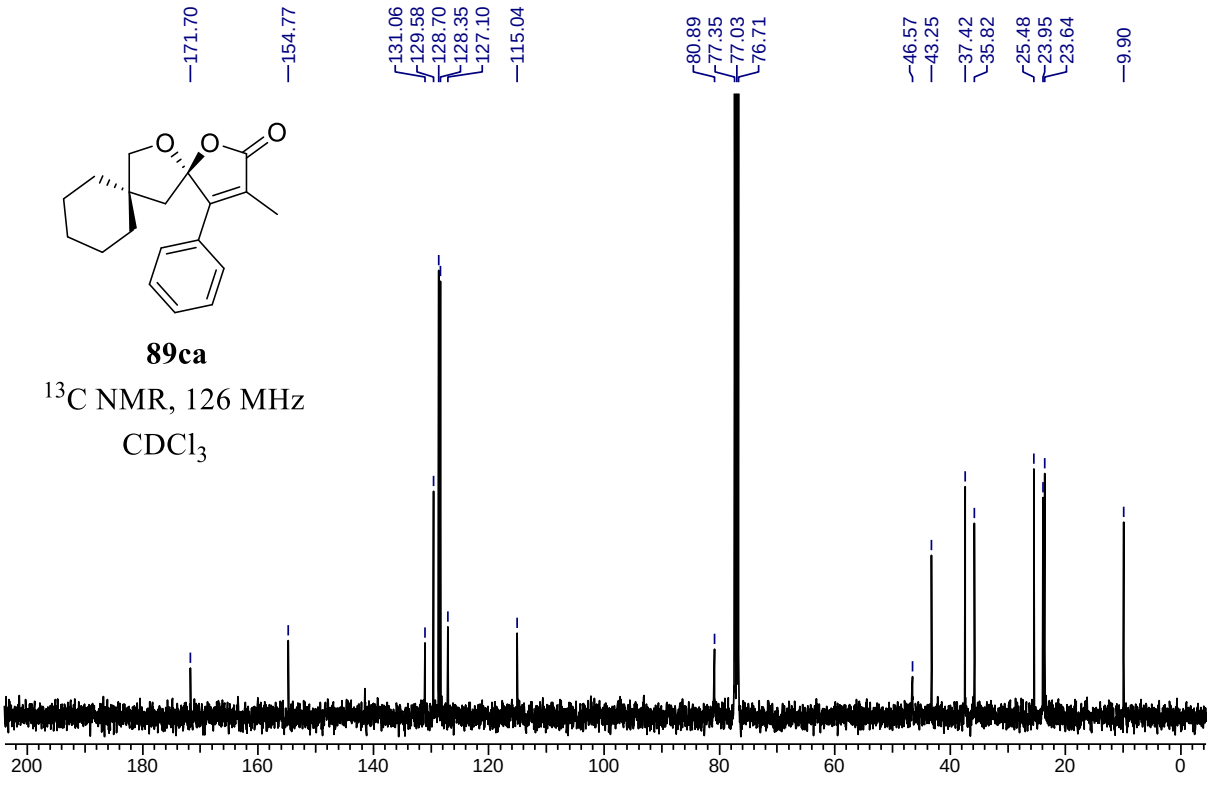
3-Methyl-4-phenyl-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (89ca):



89ca

^{1}H NMR, 500 MHz

$CDCl_3$

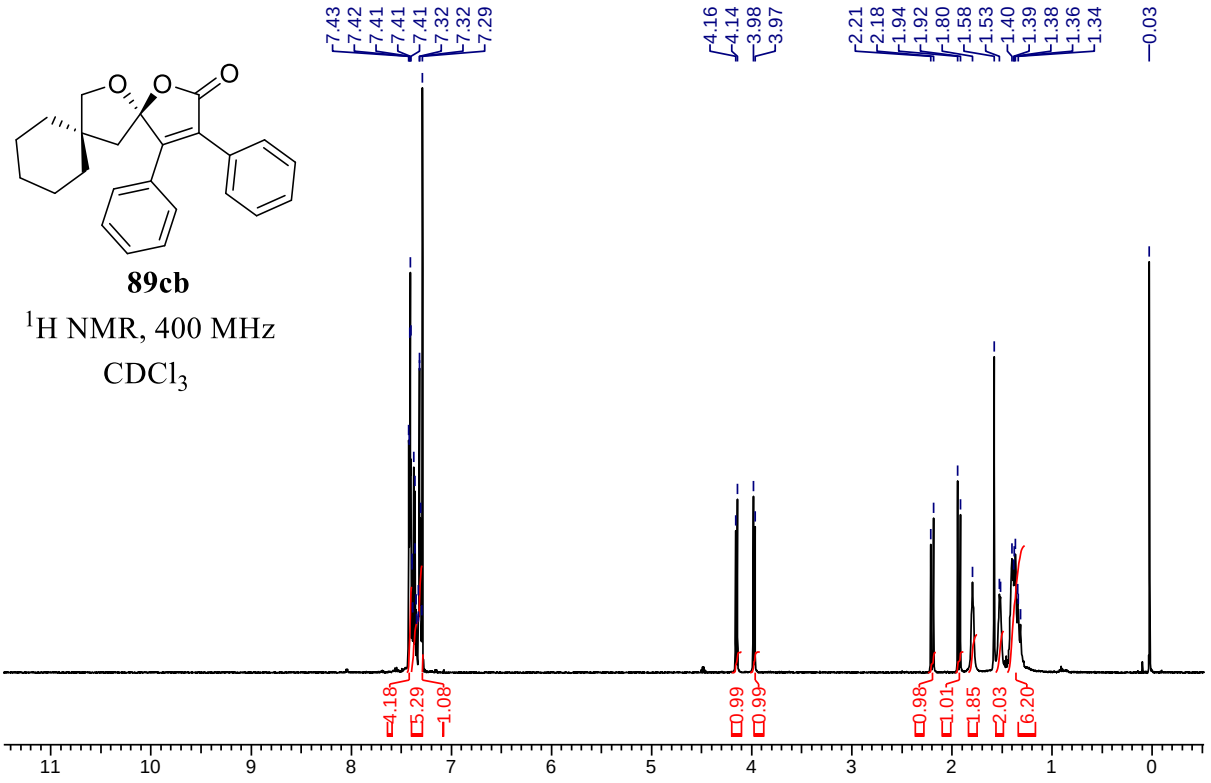


89ca

^{13}C NMR, 126 MHz

$CDCl_3$

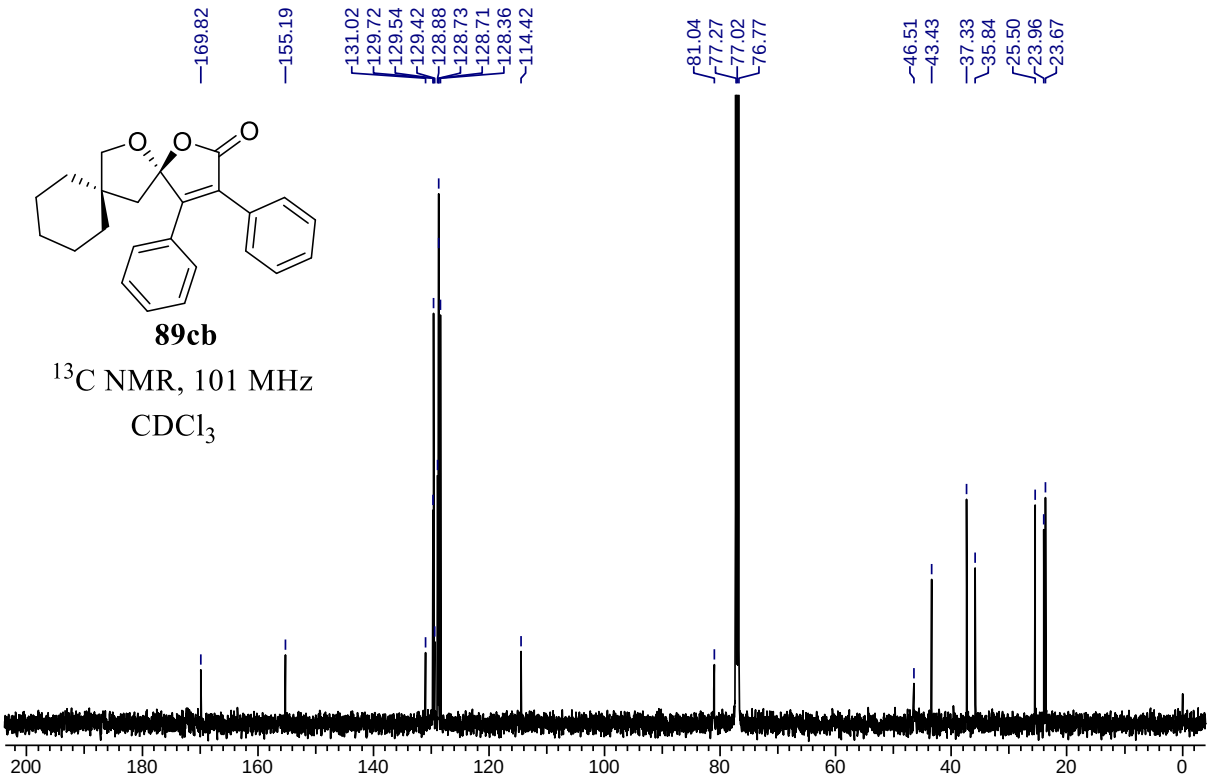
3,4-Diphenyl-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (89cb):



89cb

^{1}H NMR, 400 MHz

$CDCl_3$

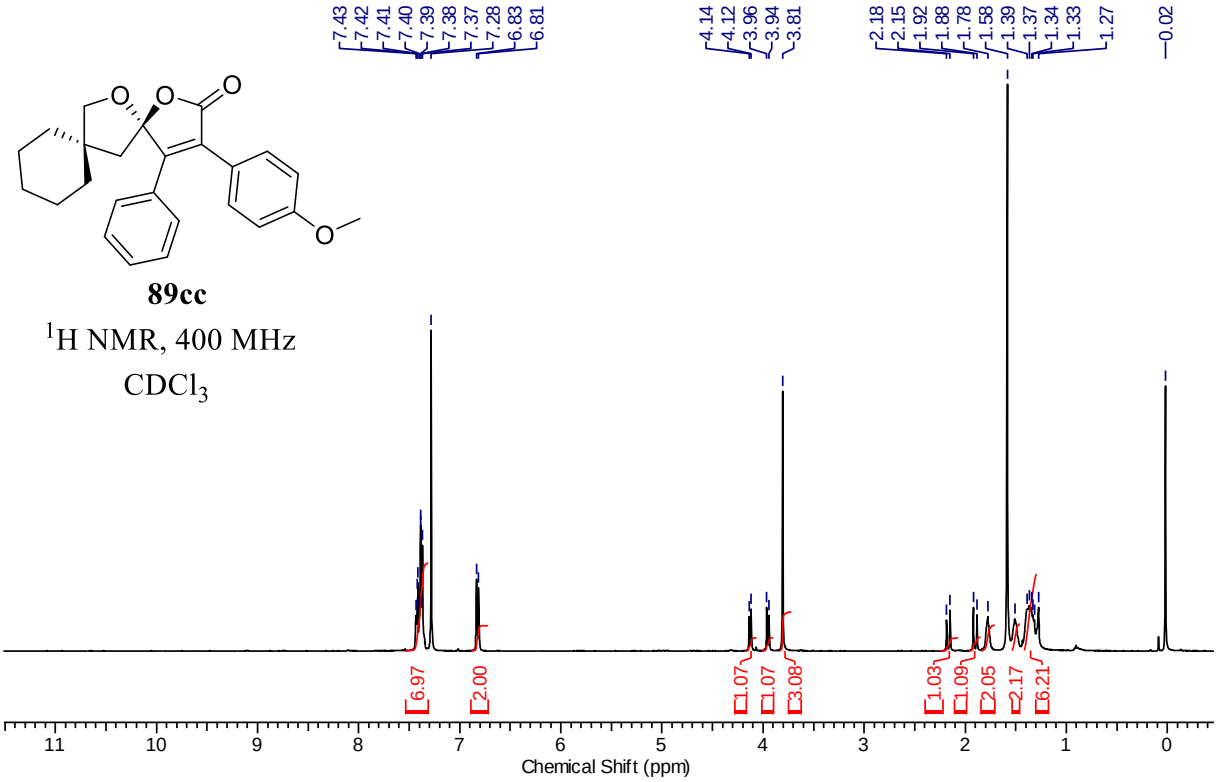


89cb

^{13}C NMR, 101 MHz

$CDCl_3$

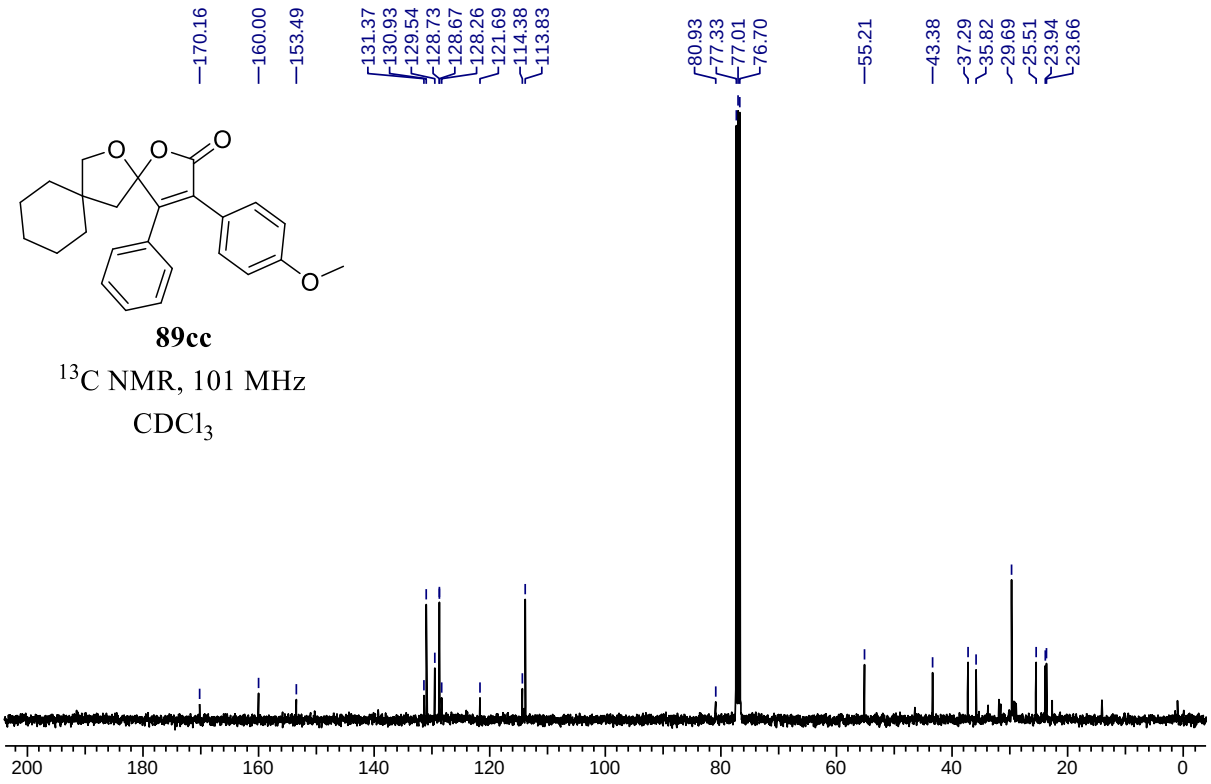
3-(4-Methoxyphenyl)-4-phenyl-1, 14-dioxadispiro [4.1.5^7.2^5] tetradec-3-en-2-one (89cc):



89cc

^{1}H NMR, 400 MHz

$CDCl_3$

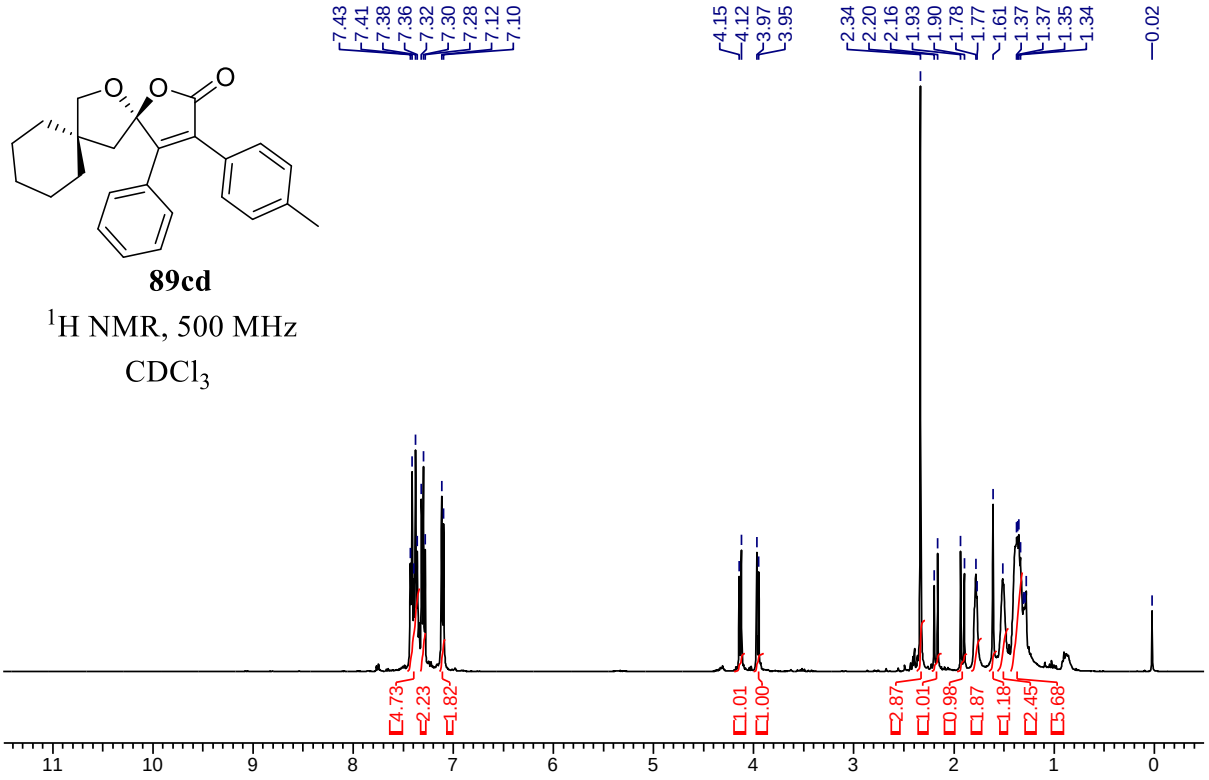


89cc

^{13}C NMR, 101 MHz

$CDCl_3$

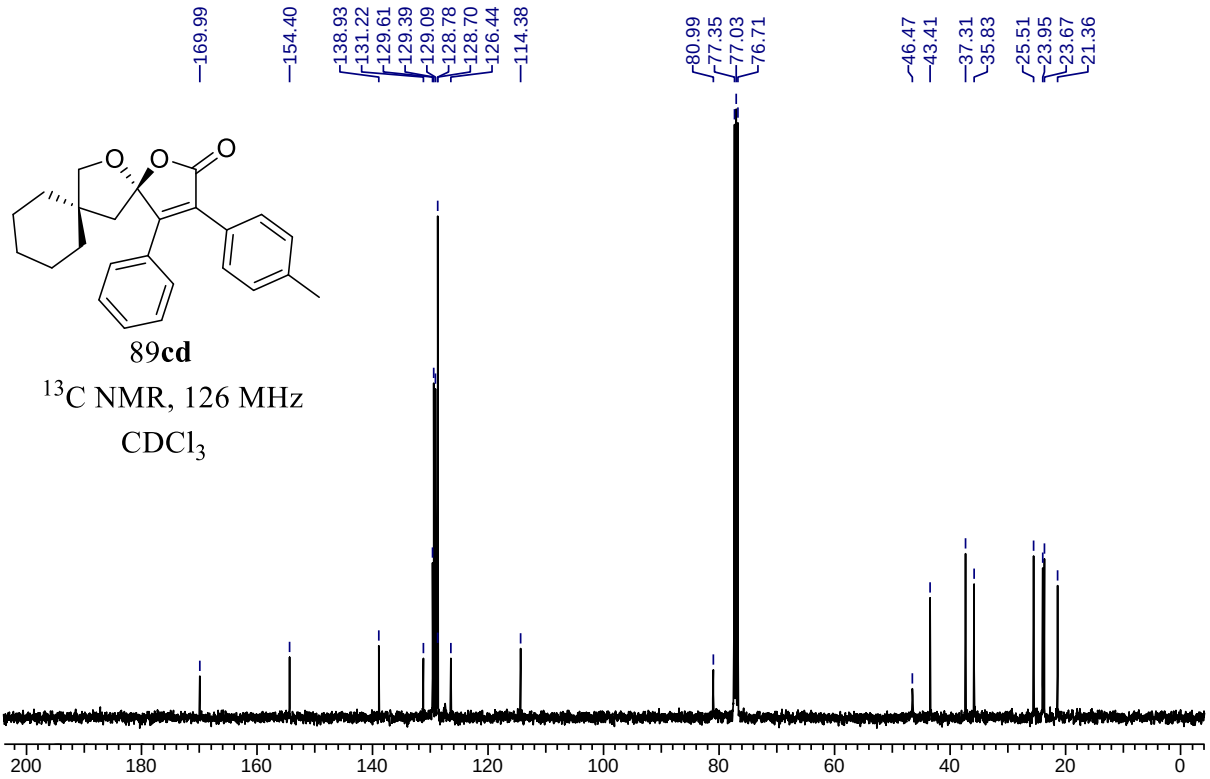
4-Phenyl-3-(*p*-tolyl)-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (89cd):



89cd

^{1}H NMR, 500 MHz

$CDCl_3$

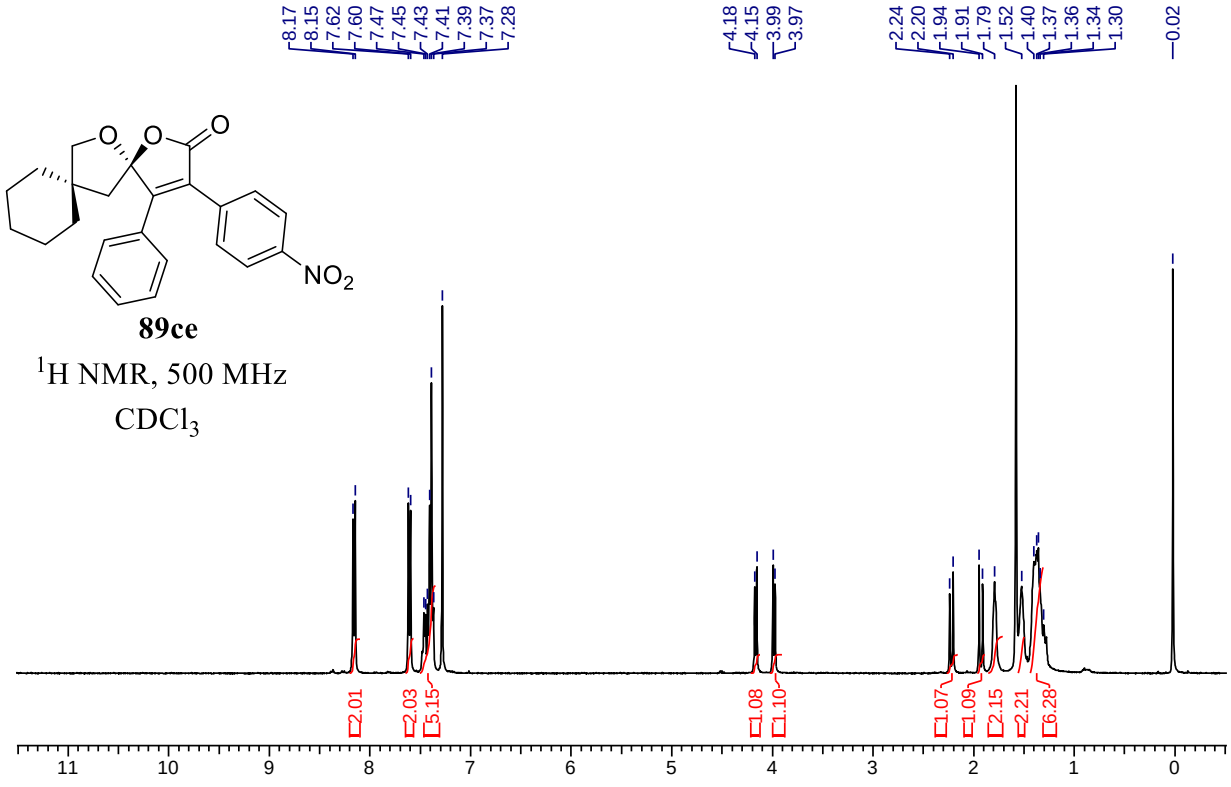


89**cd**

^{13}C NMR, 126 MHz

$CDCl_3$

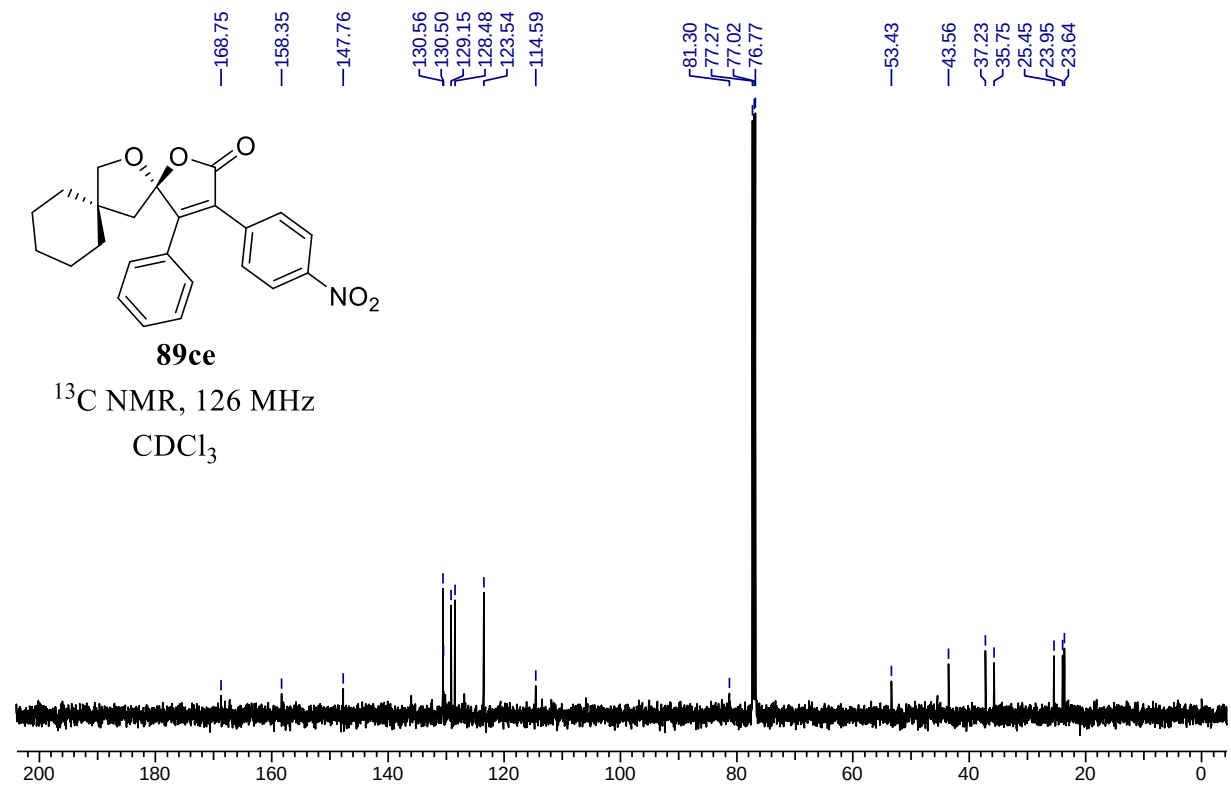
3-(4-Nitrophenyl)-4-phenyl-1,14-dioxadispiro[4.1.57.25]tetradec-3-en-2-one (89ce):



89ce

^{1}H NMR, 500 MHz

$CDCl_3$

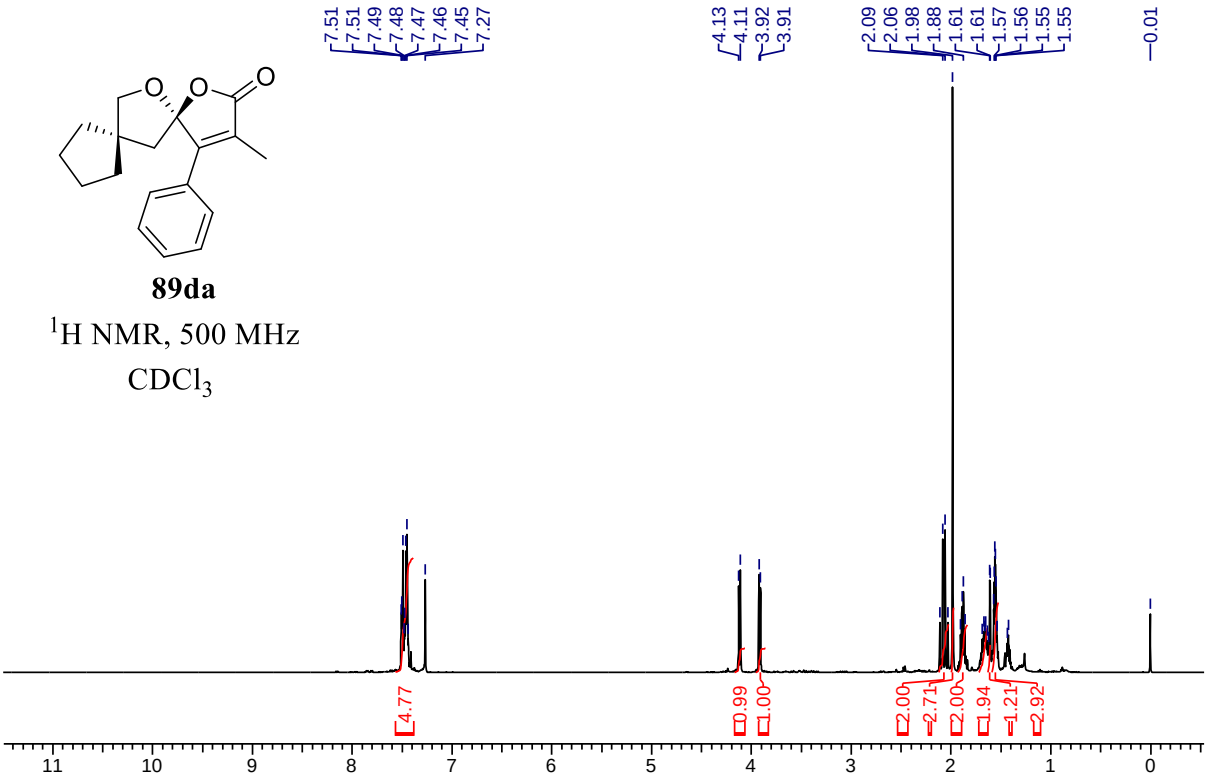


89ce

^{13}C NMR, 126 MHz

$CDCl_3$

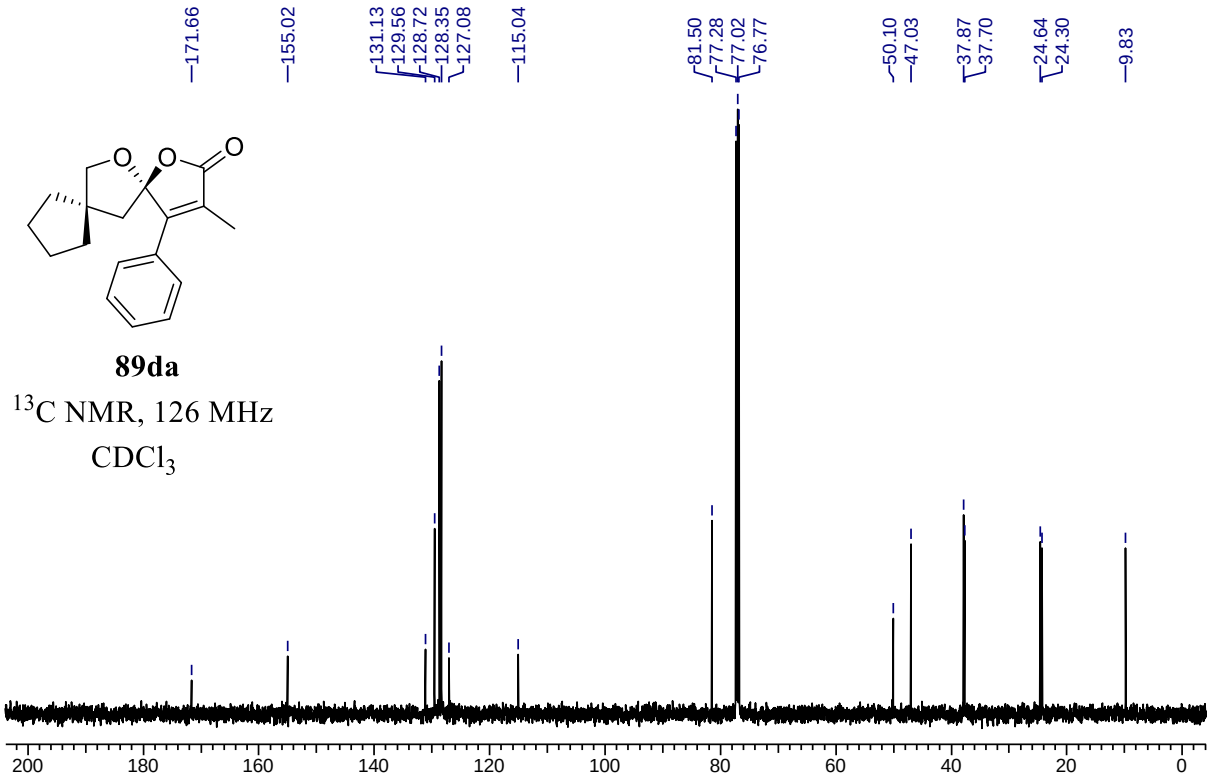
3-Methyl-4-phenyl-1, 13-dioxadispiro [4.1.4^7.2^5] tridec-3-en-2-one (89da):



89da

^{1}H NMR, 500 MHz

$CDCl_3$

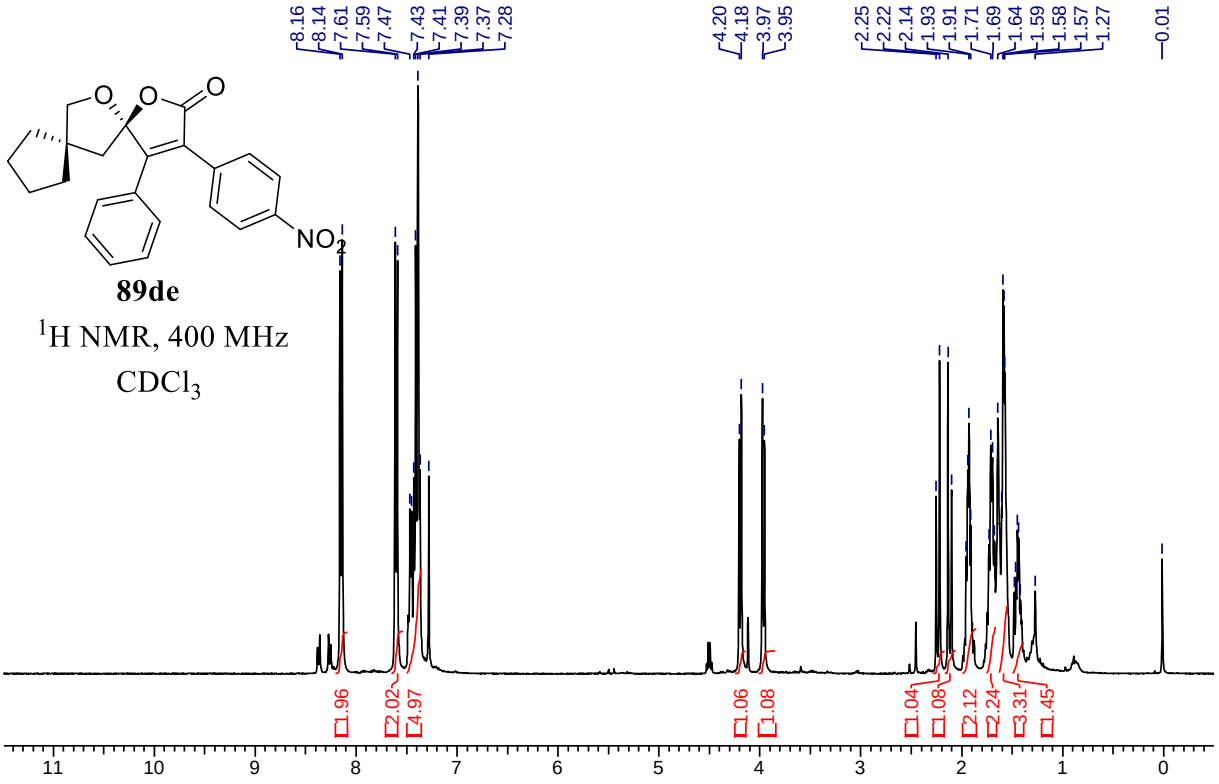


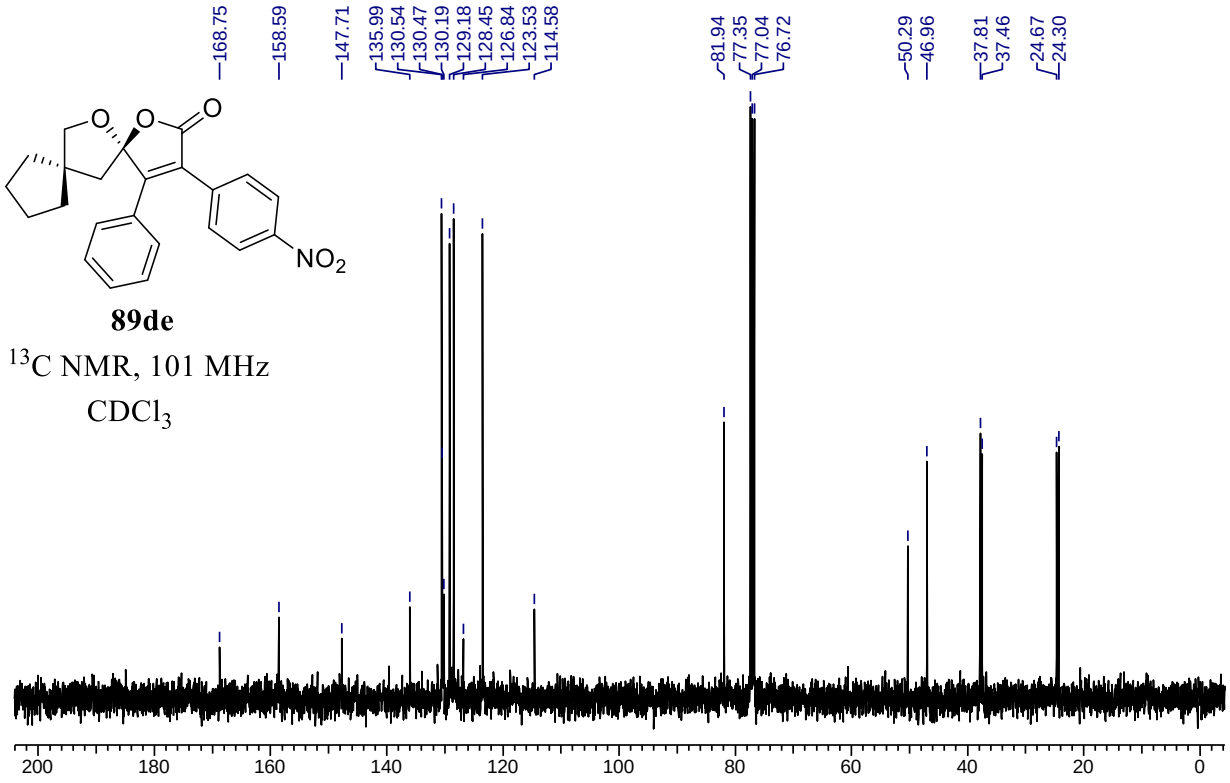
89da

^{13}C NMR, 126 MHz

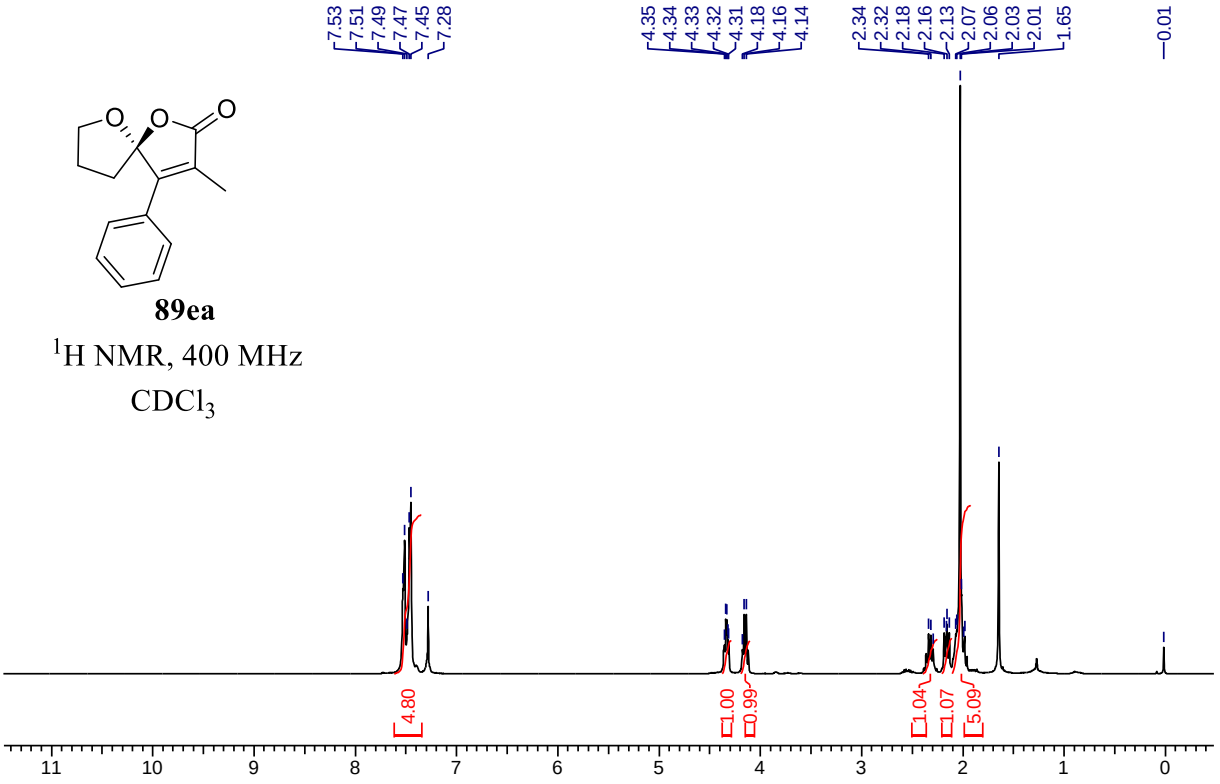
$CDCl_3$

3-(4-Nitrophenyl)-4-phenyl-1, 13-dioxadispiro [4.1.4^7.2^5] tridec-3-en-2-one (89de):





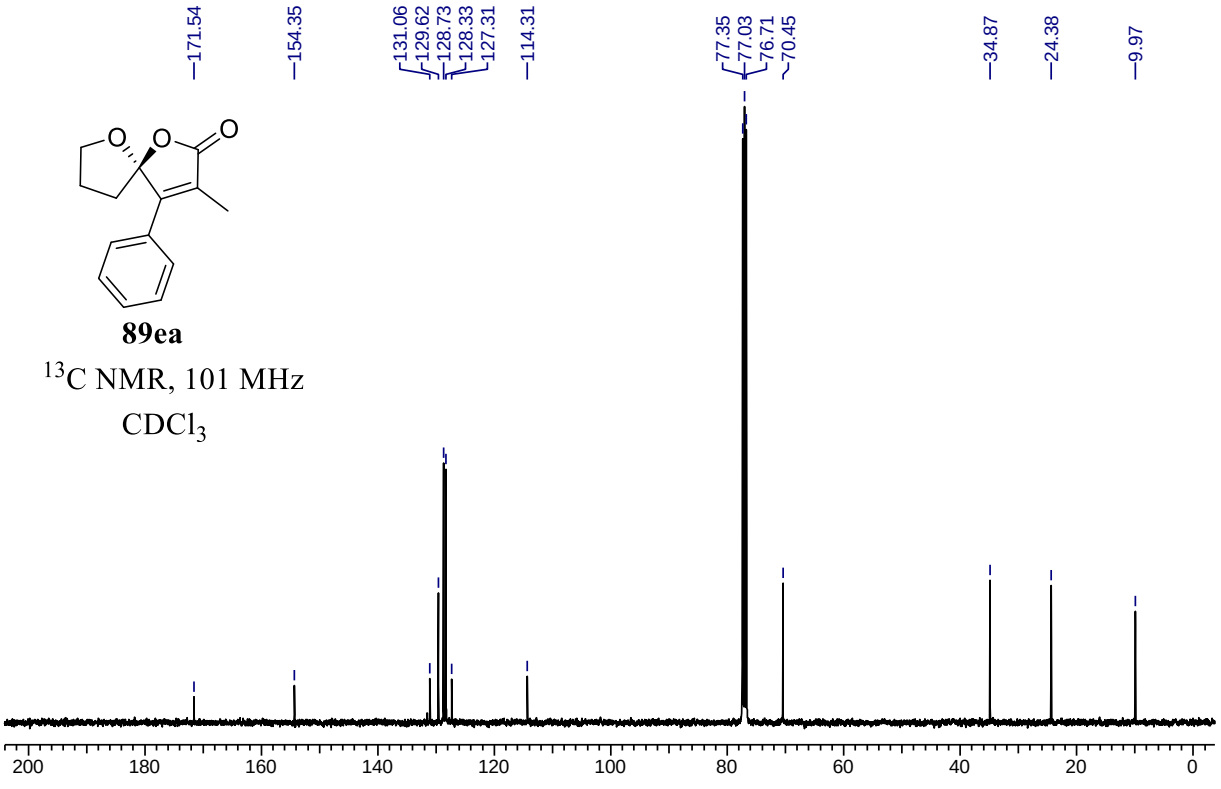
3-Methyl-4-phenyl-1, 6-dioxaspiro [4.4] non-3-en-2-one (89ea):



89ea

^{1}H NMR, 400 MHz

$CDCl_3$

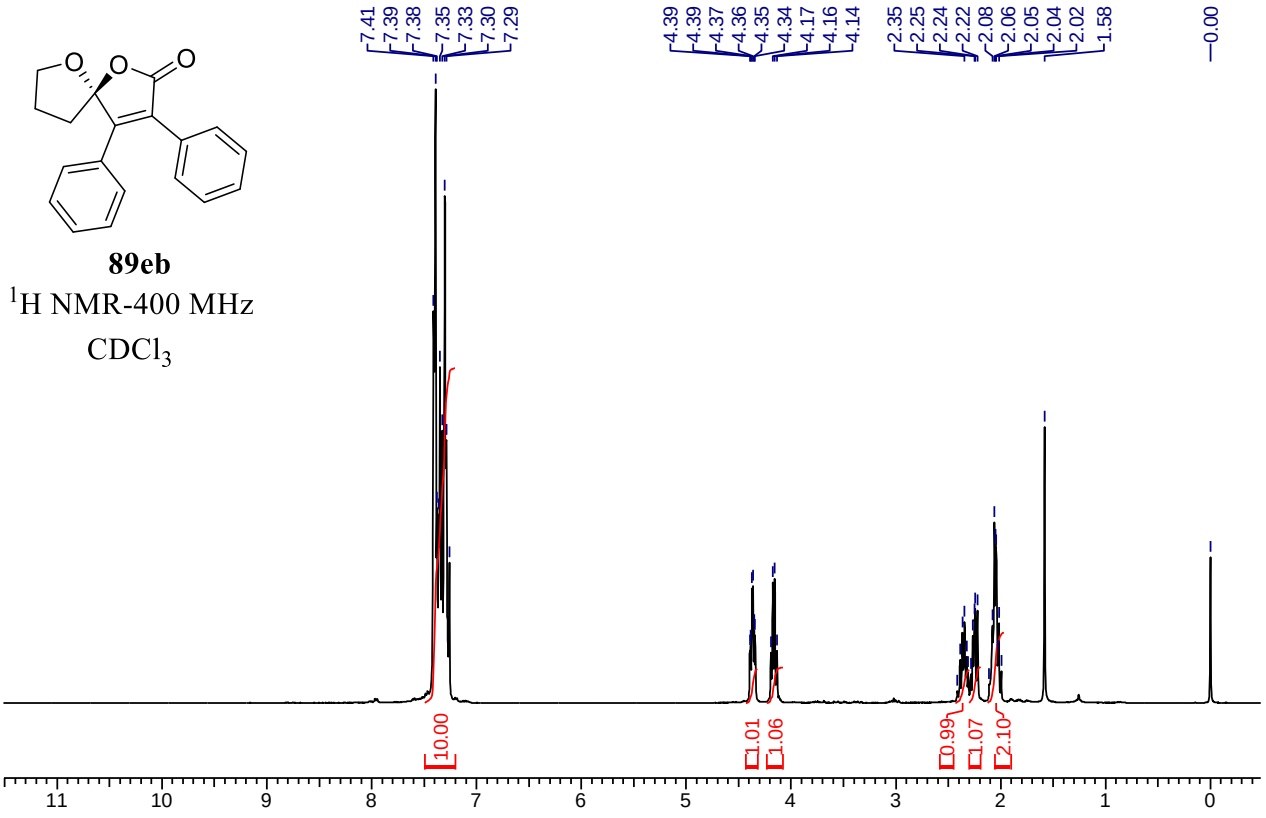


89ea

^{13}C NMR, 101 MHz

$CDCl_3$

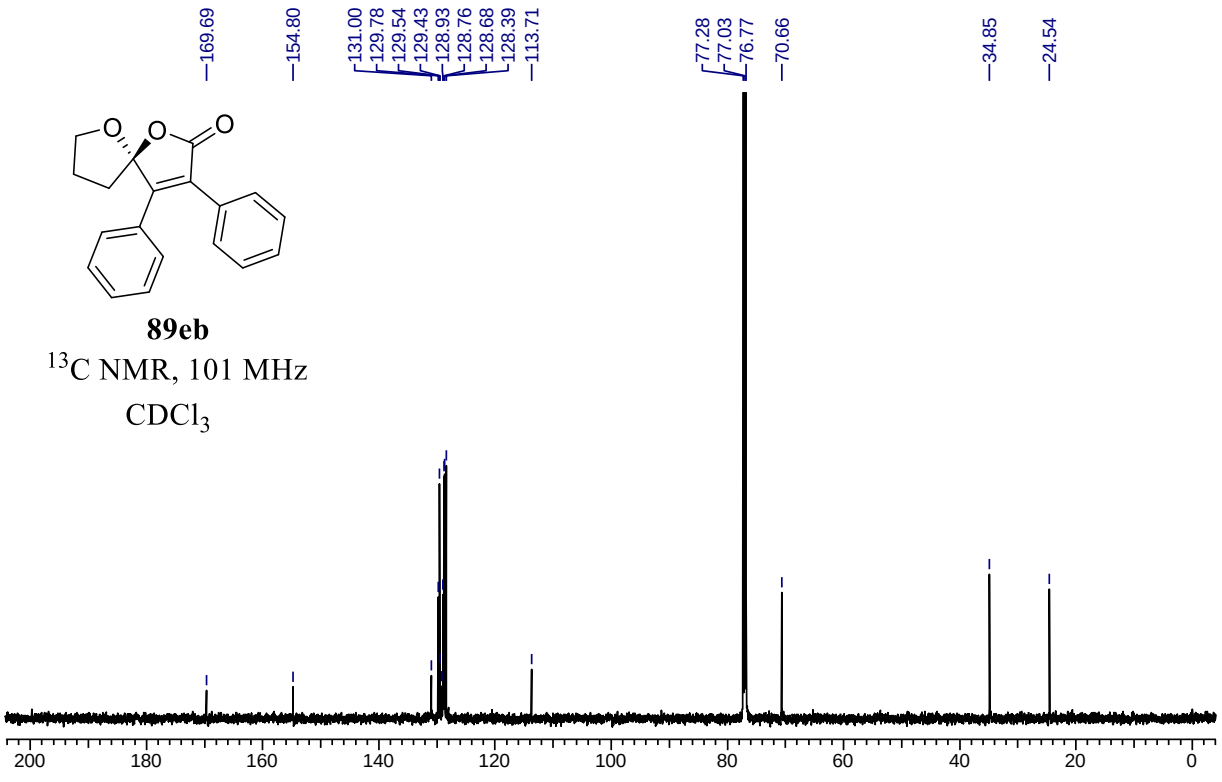
3,4-Diphenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (89eb)



89eb

^{1}H NMR-400 MHz

$CDCl_3$

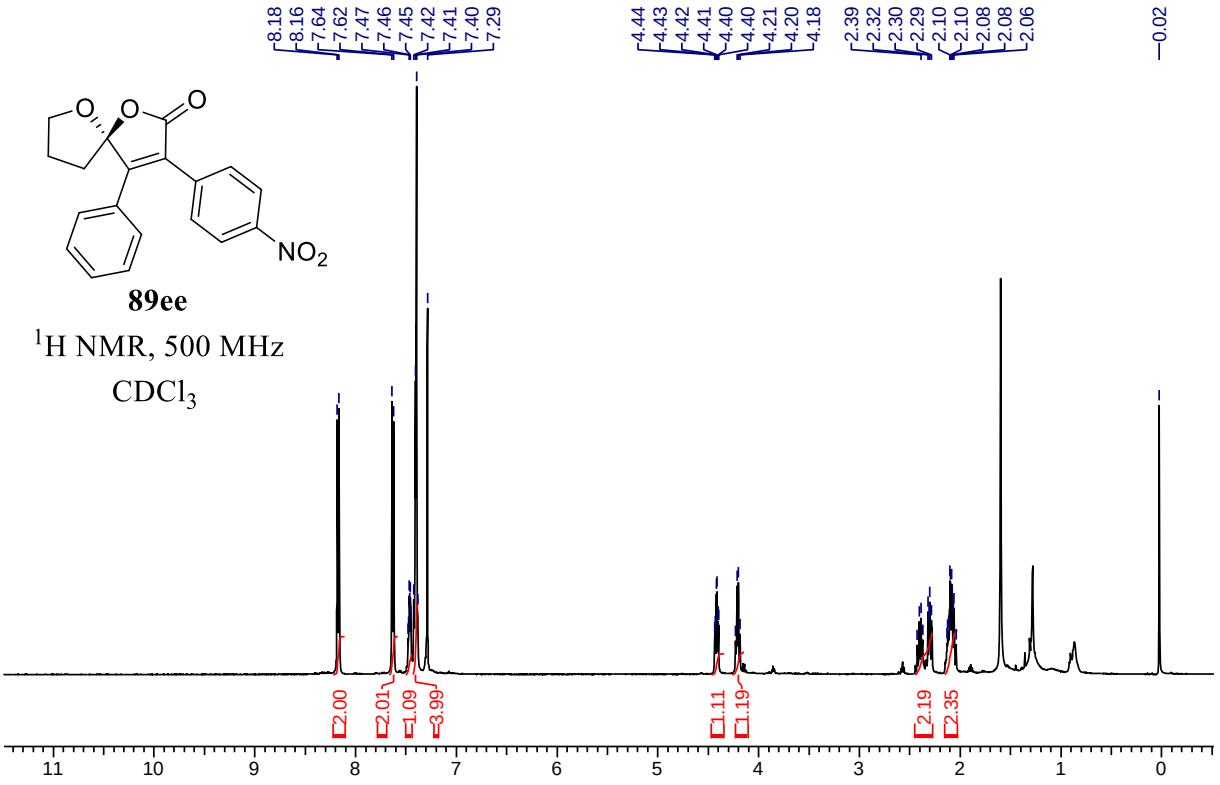


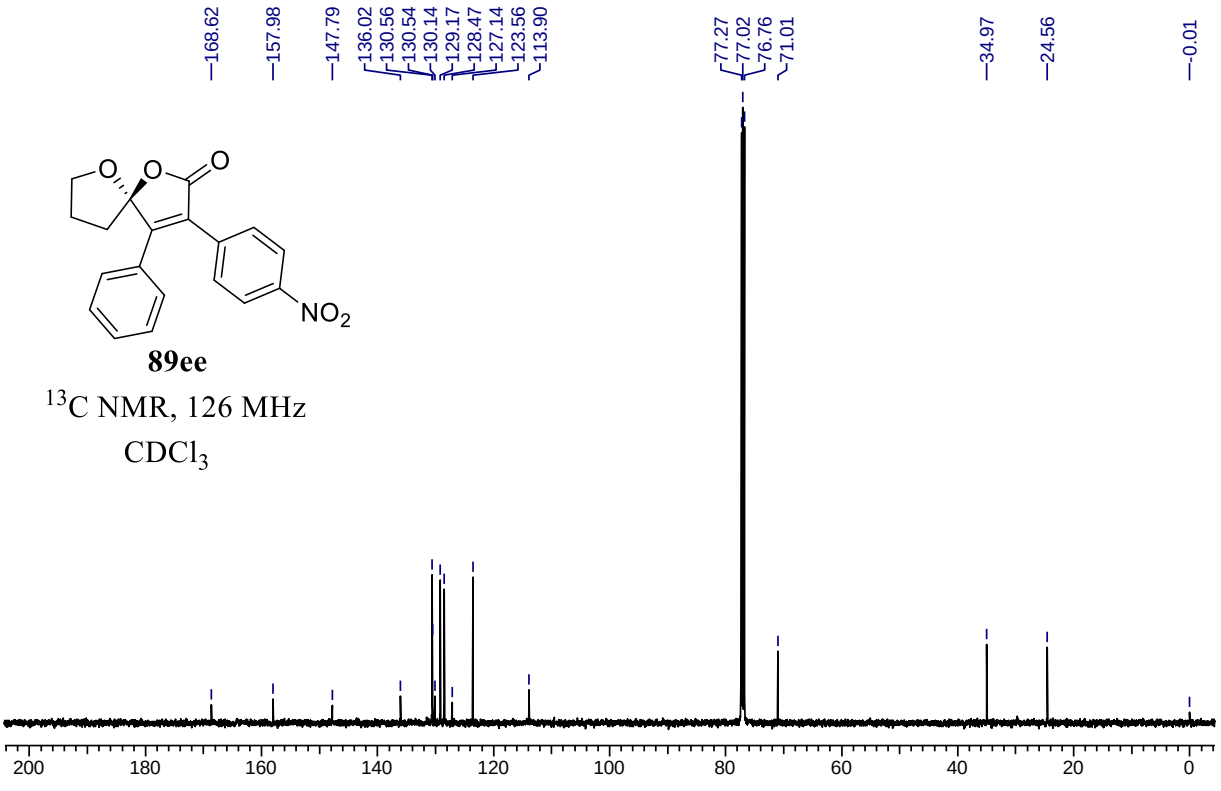
89eb

^{13}C NMR, 101 MHz

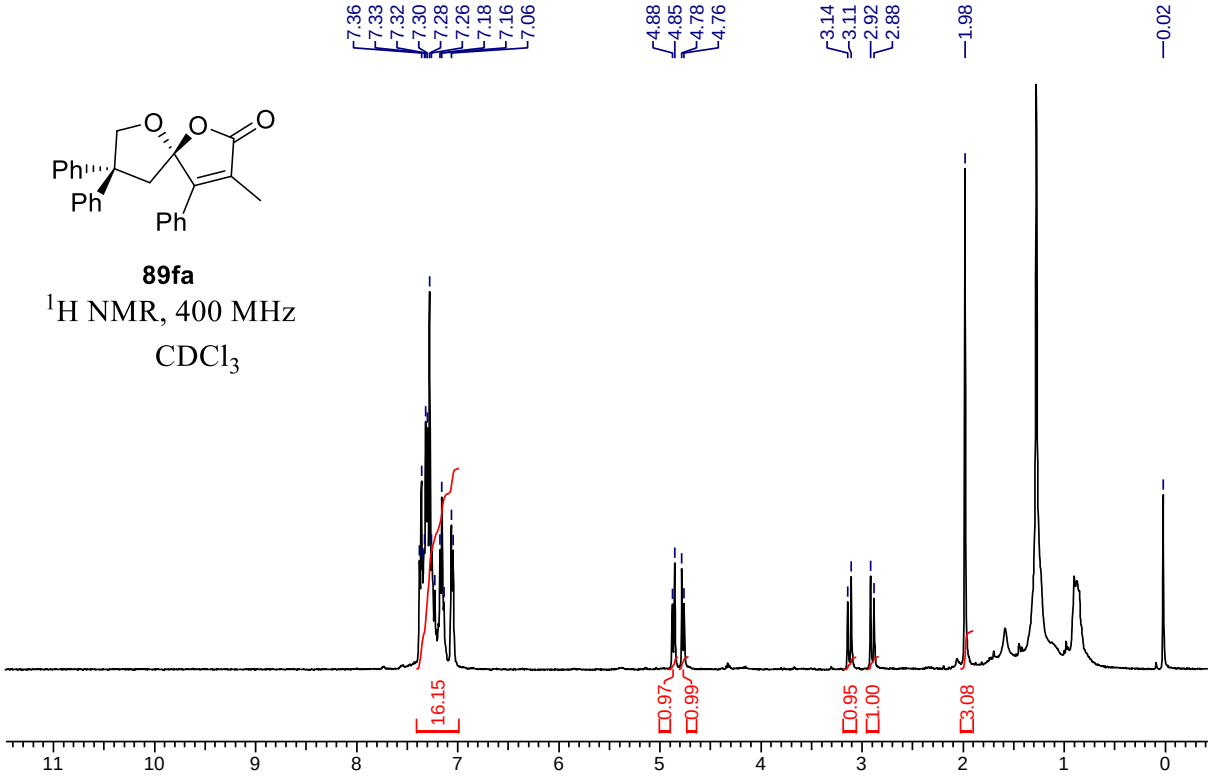
$CDCl_3$

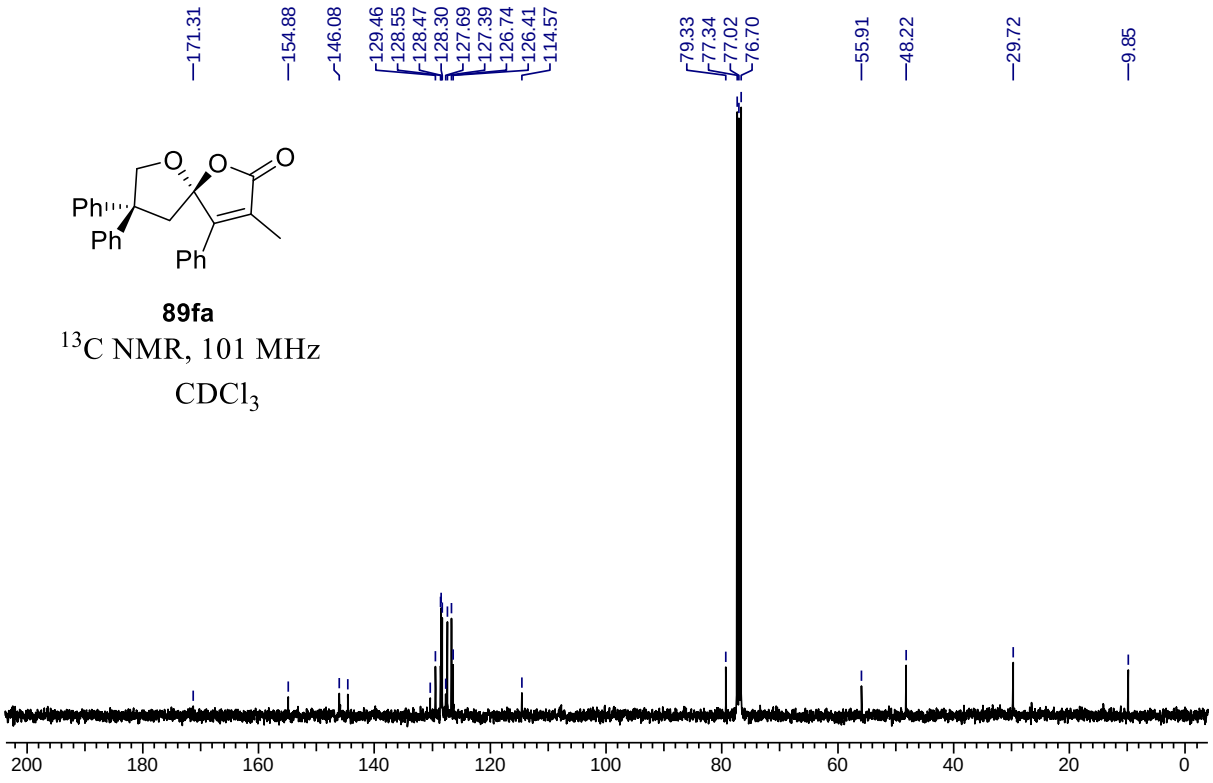
3-(4-Nitrophenyl)-4-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (89ee):



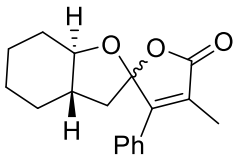


3-Methyl-4, 8, 8-triphenyl-1, 6-dioxaspiro [4.4] non-3-en-2-one (89fa):





4'-Methyl-3'-phenyl-3a, 4, 5, 6, 7, 7a-hexahydro-3*H*, 5'*H*-spiro [benzofuran-2, 2'-furan]-5'-one (89ga):



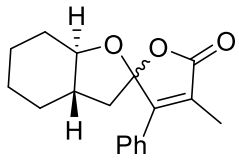
89ga

TLC: *Rf* = 0.60

(SiO_2, 20% EtOAc/hexanes);

^{1}H NMR, 500 MHz

$CDCl_3$



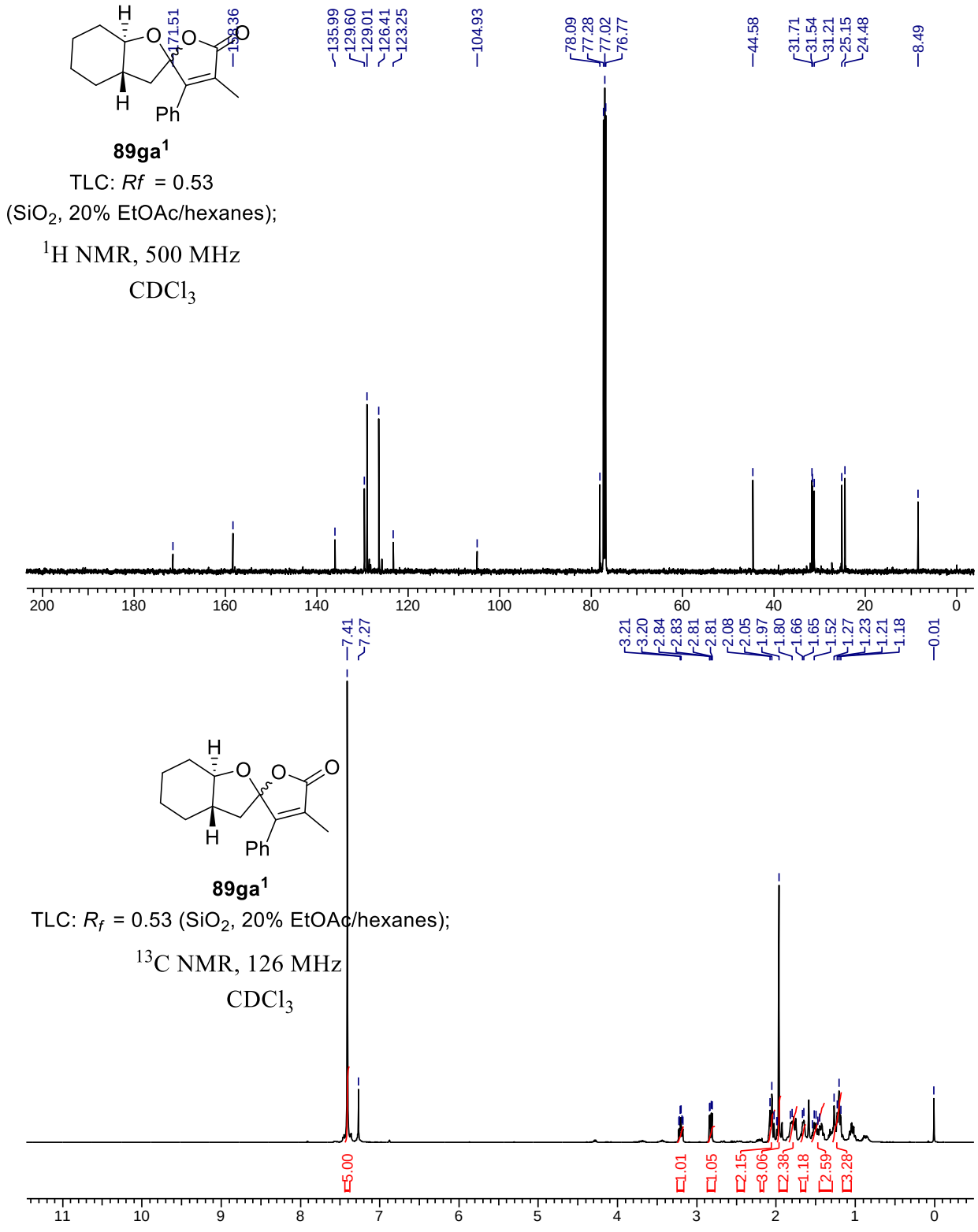
89ga

TLC: *Rf* = 0.60 (SiO_2, 20% EtOAc/hexanes);

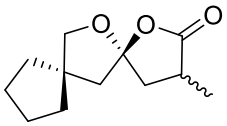
^{13}C NMR, 126 MHz

$CDCl_3$

4'-Methyl-3'-phenyl-3a, 4, 5, 6, 7, 7a-hexahydro-3*H*, 5'*H*-spiro [benzofuran-2, 2'-furan]-5'-one (89ga'):



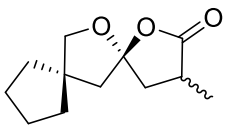
3-Methyl-1, 13-dioxadispiro [4.1.4^7.2^5] tridecan-2-one (90):



90

^{1}H NMR, 400 MHz

$CDCl_3$

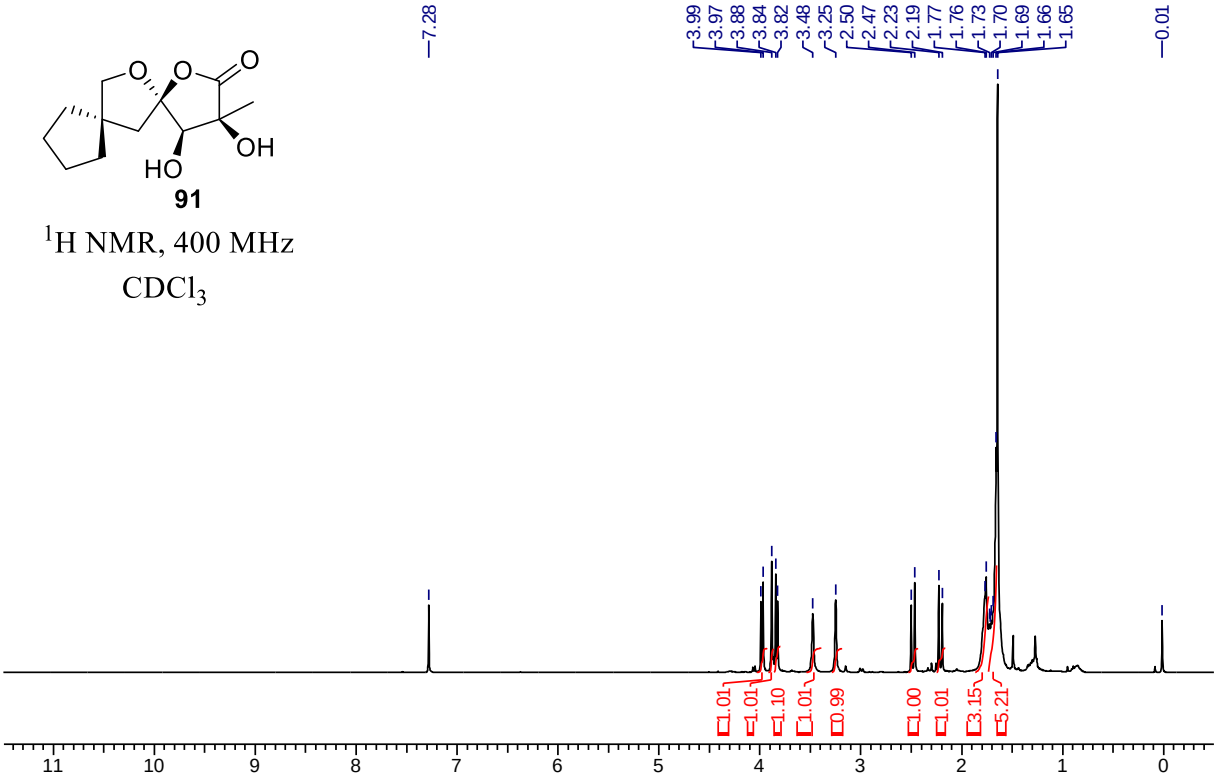


90

^{13}C NMR, 101 MHz

$CDCl_3$

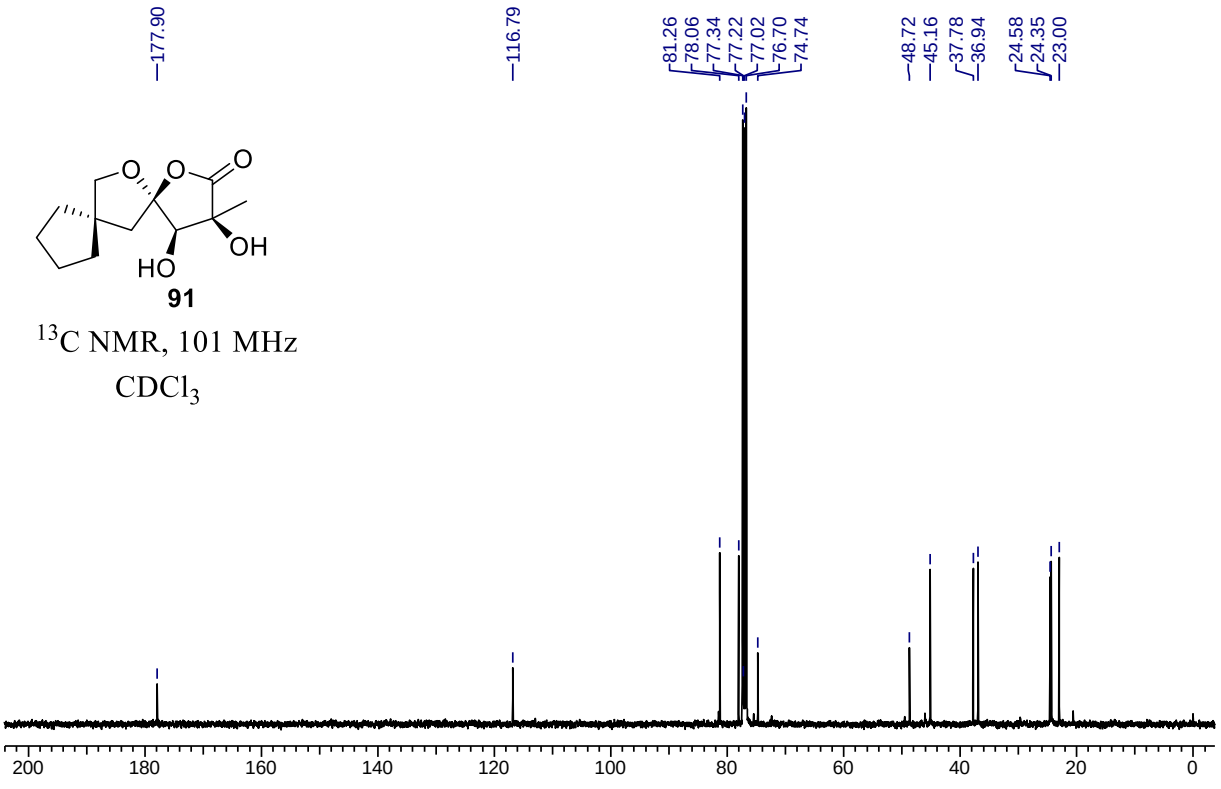
3, 4-Dihydroxy-3-methyl-1, 13-dioxadispiro [4.1.4^7.2^5] tridecan-2-one (91):



91

^{1}H NMR, 400 MHz

$CDCl_3$



91

^{13}C NMR, 101 MHz

$CDCl_3$

Chapter 3

Section A

Introduction & previous approaches to (6,5)-γ-spiroketal-γ-lactones

3.1.1 Introduction

Oxaspirolactones containing [5,5]- and [6,5]-ring systems are the major class of oxaspirolactones and found in many natural resources such as marine substances, insects, bacteria or plants, and also found in insect pheromones. Polyketide ionophore antibiotics is another major class of natural products which contains spiroketals as a main core structure. Particularly, marine natural products (spiroketals and spirolactones) attracted biologists and synthetic organic chemists due to their challenging structural features and potent bioactivities as they expose to various aquatic ecosystems. Hence they produce secondary metabolites with a unique core structure.[1]

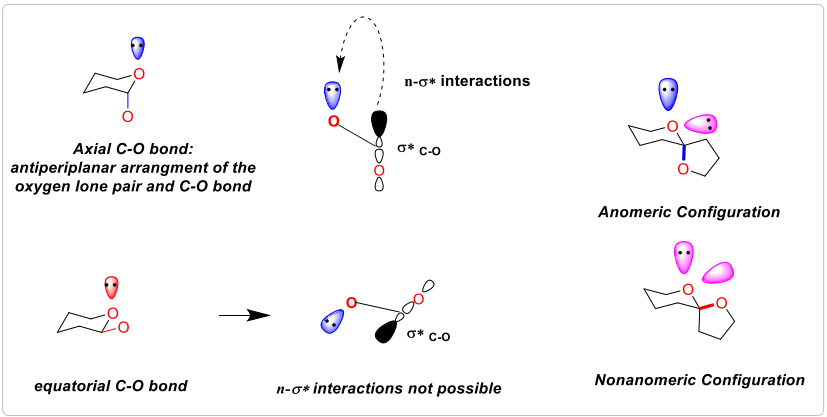


Figure. 3.1. Concept of anomeric effect and anomeric/nonanomeric configuration.

In the formation of [6,5]-spiroketals and spirolactones, the anomeric effect plays an important role in the study of conformational analysis.[2] Anomeric effect is directly related to the stability of the conformer, more the anomeric effect more stable conformation. The anomeric effect was first invented by J. T. Edward in 1955, hence it is also called as Edward-Lemieux effect. It was mainly observed in carbohydrate chemistry specifically in pyranose rings or in spiroketals possessing (6,5-oxaspirolactone). The anomeric effect is also known as stereoelectronic effect. The tendency of substitutions of heteroatoms close to another heteroatom favors in axial position instead of less hindered equatorial position in cyclohexane ring. in which the affinity of heteroatomic substituents is adjacent to a heteroatom within a cyclohexane ring in favoritism of the axial position rather than less hindered equatorial position which could be due to steric factor. This effect shows stabilizing interaction between one of the lone pairs on oxygen and the antibonding σ* orbital of the C-O bond. One of the lone pairs on the oxygen is antiperiplanar to the C-O bond.[1] Anomeric effect is mainly observed with alkoxy or acetyl group and exists in axial position. In [6,5]-spiroketals and spirolactones, two conforms are possible. The anomeric configuration bearing the axial oxygen substituent and

the nonanomeric configuration bearing the equatorial oxygen substituent as shown in Figure. 3.1. We also encountered the same effect in our synthetic [6,5]-oxaspirolactones (*vide infra*, Chapter-3, Section B).

Oxaspirolactones containing [5,5]- and [6,5] ring systems are found in highly bioactive and complex natural products such as Opaliferin (**1**) which shows cytotoxic activity against various cancer cell lines[3], paeciloketal B (**2**) shows antibiotic property[4], japonones A (**9**) and B (**10**) anti KHSV and anti-viral activity[5], lanceolactone A (**7**) shows antimicrobial activity[6] and beshanzuenone D (**8**) inhibit the NO production[7] etc. (Figure. 3.2).

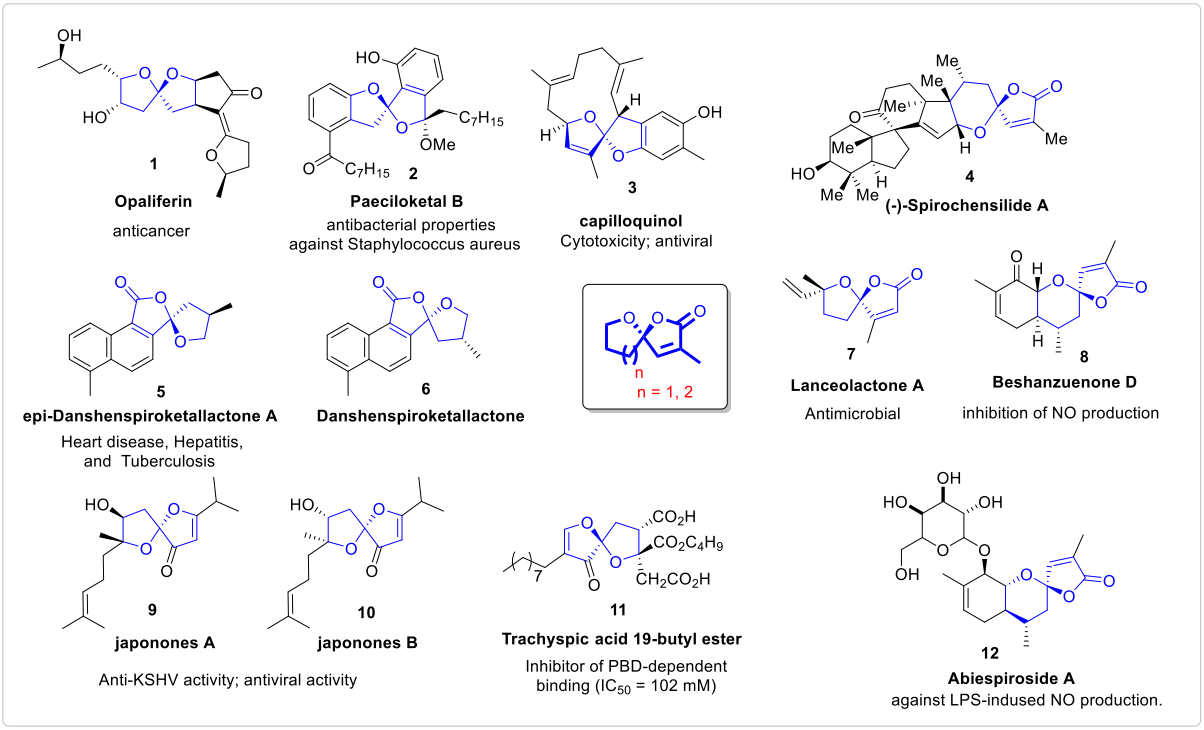
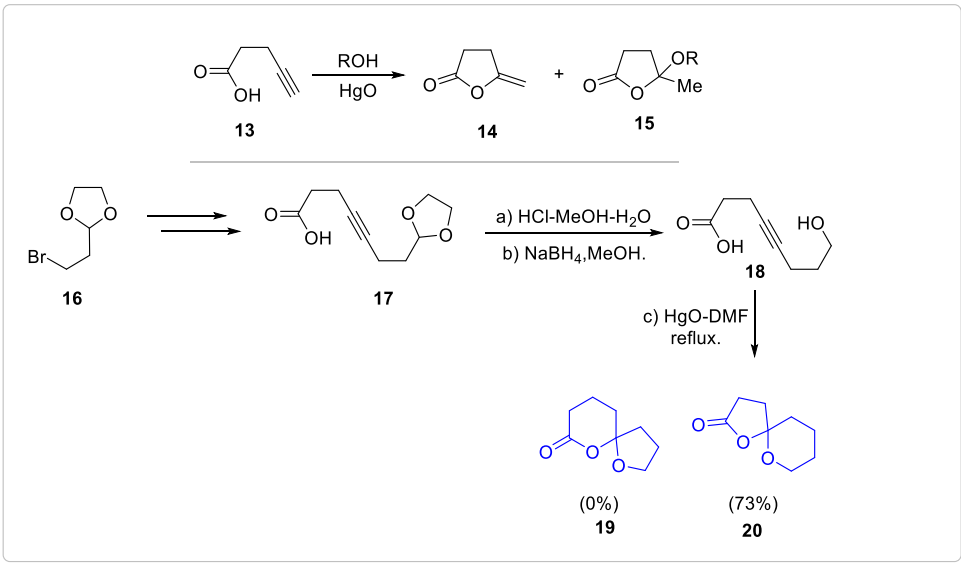


Figure. 3.2. Representative natural products containing oxaspirolactones

Owing to interesting structural features and biological profile, numerous elegant synthetic methodologies were documented in the literature to access [5,5]- and [6,5] spiroketals, and applied in the total synthesis of related natural products. In contrast, the chemistry of α,β-unsaturated [5,5]- and [6,5] oxaspirolactones was not well studied, and a very few reports were documented in the literature for the synthesis with limitations like the use of prefuctionalized starting materials which need many steps to prepare, use of the stoichiometric amount of Lewis acid and many others. Among [5,5]- and [6,5]-oxaspirolactones, very few methods are documented in the literature for the synthesis of [6,5]-oxaspirolactones. Since we provided the complete literature survey of [5,5]-oxaspirolactones in Chapter-2, herein, we mainly focused on the introduction and previous approaches for the synthesis of [6,5]-oxaspirolactones (Figure 3.2).

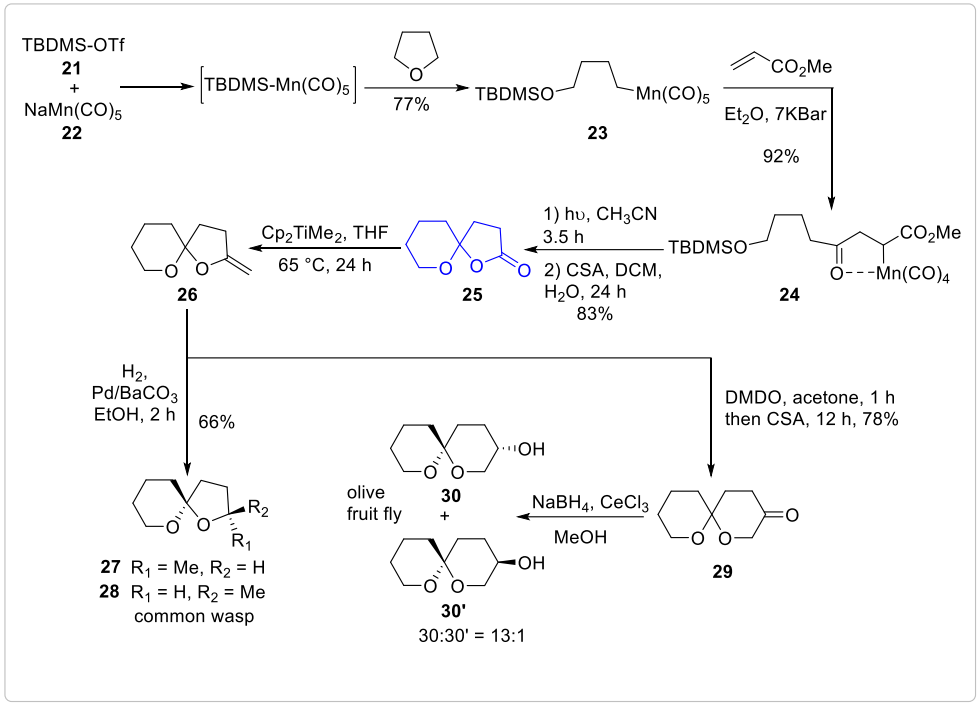
3.1.2 Previous approaches:

Yamamoto developed a strategy in 1983 for the synthesis of [6,5]-oxa-spirolactones (**19** and **20**) by cycloisomerization of alkyne carboxylic acid (**18**) to γ-methylene butyrolactones (**14**) via intramolecular hydrocarboxylation using mercury(II)oxide in aprotic solvent.[8] In this method, the hydroxyl alkyl group undergoes either intramolecular 5-*exo*-dig or 6-*endo*-dig mode of cyclization, which encouraged many synthetic chemists to further develop cascade methods. Inspired by this approach, Kitching's group reported the cycloisomerization of hydroxylalkynoic acid by using $Pd(PhCN)_2Cl_2$ via 5-*exo*-dig or 5-*endo*-dig mode of cyclization to deliver [5,5]-oxa-spirolactone which was converted into unsaturated [5,5]-oxa-spirolactone by bromination and dehydrobromonation sequence (Scheme 3.1).



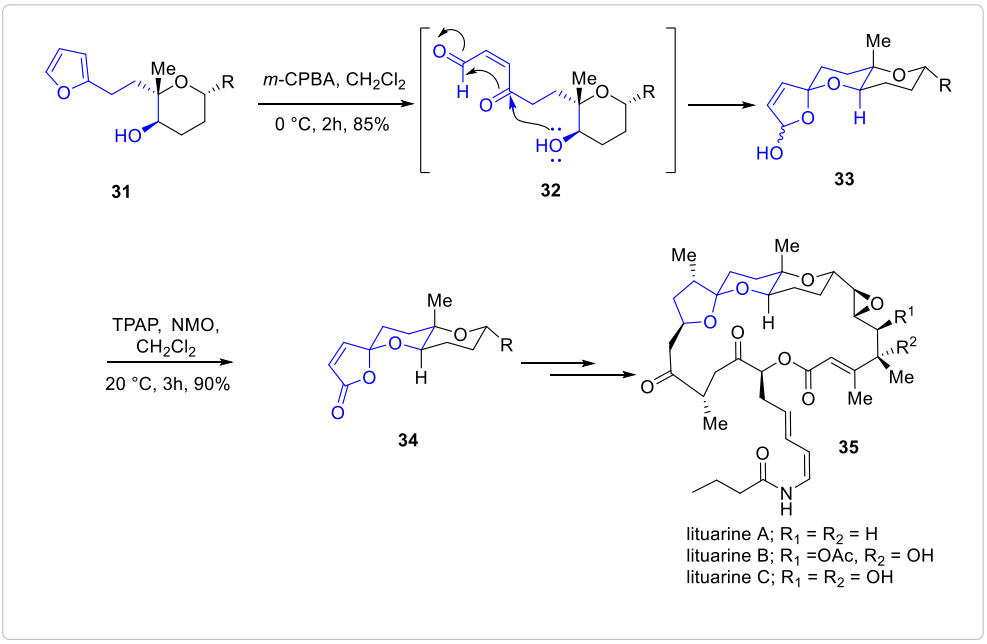
Scheme 3.1. Cycloisomerization of alkyne carboxylic acid

De Shong and Sidlerin 1991, devised a method for the synthesis of [6,5]-oxaspirolactone (**25**) using cyclic ether as key starting material.[9] Nucleophilic addition of (trialkylsilyl)manganese pentacarbonyl reagents to the cyclic ether such as tetrahydrofuran furnished the alkyl Manganese pentacarbonyl complex (**23**), followed by insertion of CO and methyl acrylate gave the intermediate (**24**). Photodemetalation and desilylation delivered the keto-hydroxy derivative which on Bronsted acid (CSA) catalyzed cyclization furnished the desired (6,5)-oxaspirolactone (**25**). Further, these [6,5]-oxaspirolactones were transformed into common wasp (**27** & **28**) and olive fruit fly (**30** & **30'**) pheromones (Scheme 3.2).



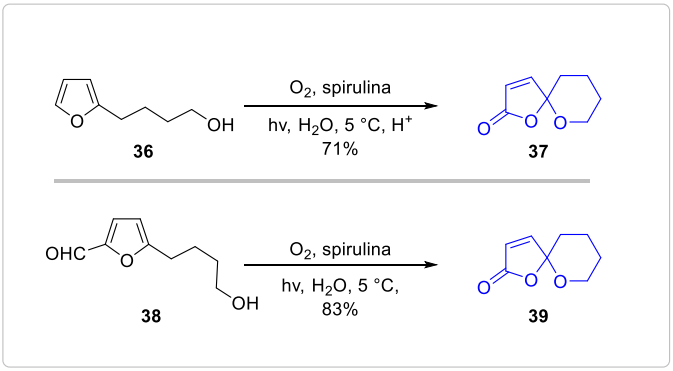
Scheme 3.2. Synthesis of (6,5)-oxaspirolactone

Robertson *et al.*, in 2004, devised a method for the synthesis of [6,5]-oxaspirolactone from tethered hydroxyl furan.[10,11] In this, *m*-CPBA mediated oxidative cyclization of hydroxyl furan (**31**) gave spiroketal (**33**), which was further oxidized by using TPAP NMO in CH_2Cl_2 to afford the desired [6,5]-oxaspirolactone (**34**) in good yields. Further, this protocol was used for the synthesis of a key intermediate of anticancer natural products lituarine (**35**) analogs (Scheme 3.3).



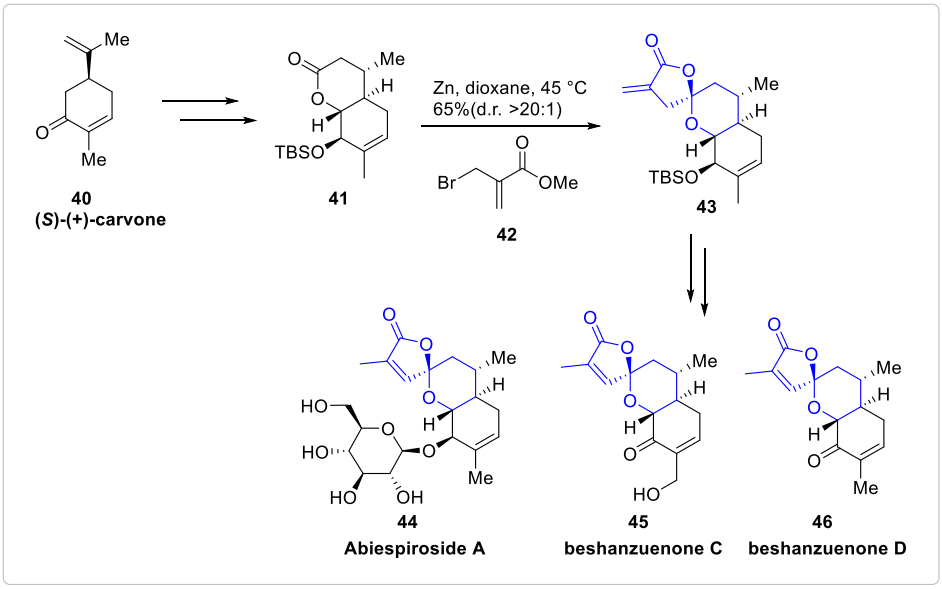
Scheme 3.3. Oxidation of hydroxyl furan

In 2012, Vassalikogiannakis group reported a green protocol for the synthesis of [6,5]-oxaspirolactones (**37** and **39**) from various substituted hydroxyalkyl furans (**36** and **38**) by using Spirulina (a nutritional supplement) as water-soluble natural photosensitizer and air, light, and water.[12] By this method, they synthesized diverse oxaspirolactones with good to excellent yields (Scheme 3.4).



Scheme 3.4. Oxidation of hydroxyalkyl furan

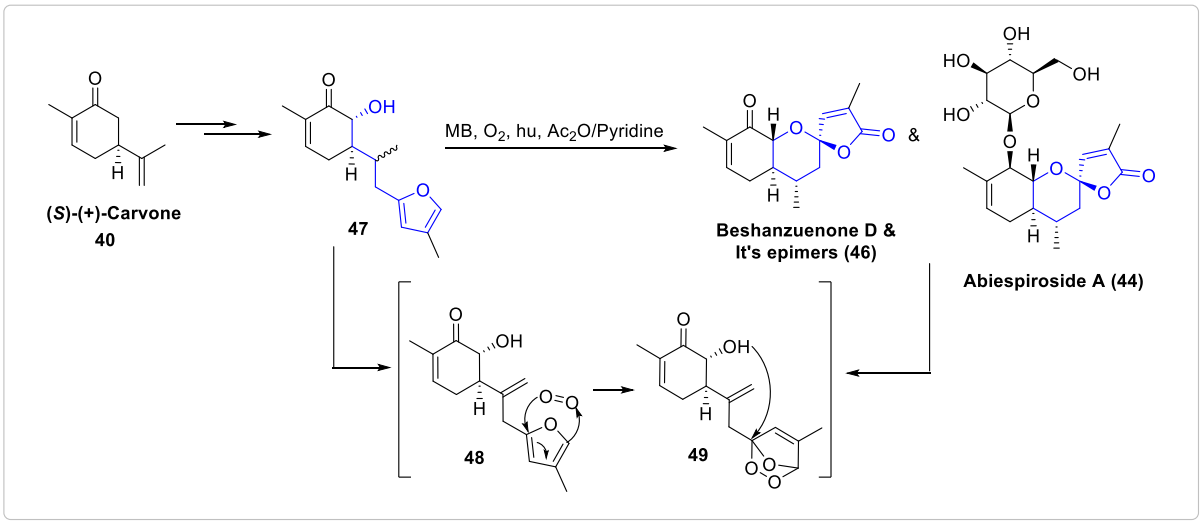
Ming and Dai group in 2018 reported the first total synthesis and biological evolution of abiespiroside A (**44**), beshanzuenone C (**45**), and beshanzuenone D (**46**) from naturally available chiral building block (*S*)-(+)-carvone (**40**).[13] The key [6,5]-oxaspirolactone (**43**) moiety was achieved from the bicyclic lactone (**41**) on treatment with in situ prepared organozinc reagent followed by spirolactonization (Scheme 3.5).



Scheme 3.5. Total synthesis of abiespiroside A (**44**), beshanzuenone C (**45**), and beshanzuenone D (**46**)

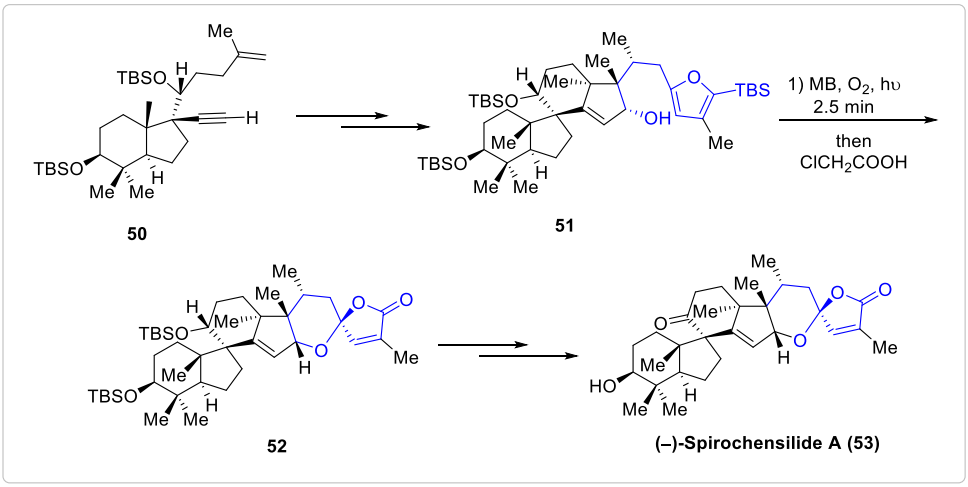
Recently, Kontham's group in 2020 reported the total synthesis of beshanzuenone D

(**46**) and its epimers and abiespiroside A (**44**).[14] They started their synthetic journey from chiral naturally available building block (*S*)-(+)-Carvone (**40**). After several interesting synthetic transformations, cyclohexanol tethered furan (**47**) was prepared and subjected to photocatalyzed oxidative (4+2)-cycloaddition reaction with molecular oxygen to access natural product beshanzuenone D (**46**) and its epimers. Further, synthesis of abiespirosideA (**44**) is also achieved by installing sugar moiety (Scheme 3.6).



Scheme 3.6. Total synthesis of beshanzuenone D and its epimers and abiespiroside A.

Recently in 2020 Zhen Yang group reported the first total synthesis of highly complex natural product (−)-spirochensilide A (**53**) in 22 steps with 2.2% overall yield. In this endeavor, the advanced intermediate bicyclic enyne **50** was subjected to Pauson-Khand reaction to install C13 quaternary chiral center and furnished substituted hydroxyl alkyl furan (**51**).



Scheme 3.7. Total synthesis of (−)-spirochensilide A

Later, Photoinduced oxidative cyclization of substituted hydroxyl alkyl furan using

methylene blue as a photosensitizer in the presence of oxygen atmosphere delivered the [6,5]-oxaspirolactone (**52**) in a good yield, which used as a precursor for the total synthesis of **53**.[15]

Chapter 3

Section B

Bismuth(III)-catalyzed bis-cyclization of propargylic diol-esters: a unified approach for the synthesis of [5,5]- and [6,5]-oxaspirolactones

3.2.1 Introduction

Numerous biologically active natural products comprise γ-spiroketal-γ-lactone (oxaspirolactone) moiety isolated from marine organisms, microbes, fungi, insects, and plants.[1,16] Among these natural oxaspirolactones, 1,6-dioxaspiro[4.4]non-3-en-2-one and 1,6-dioxaspiro[4.5]dec-3-en-2-one (alternatively referred to as [5,5]- and [6,5]-oxaspirolactones respectively) are ubiquitous with prominent biological profiles.[16a] Selected examples include crassalactone D (**53**) (anticancer, ED_{50} = 1.1 μg/mL against P-388, 3.3 μg/mL against KB, 4.0 μg/mL against Col-2, 3.2 μg/mL against BCA-1 and 3.1 μg/mL against ASK),[17] pyrenolide D (**54**)(growth-inhibitory and morphogenic activities toward fungi),[18] tuberostemoamide (**55**)(traditional Chinese medicine to treat respiratory disorders),[19]aspersclerotiorone F (**56**) (no biological activity disclosed due to isolation in a very limited amount),[20]abiespiroside A (**57**)(anticancer activity),[21] 3-O-methylabiesatrine[22] (**58**) and many others.[16a,23] Inherent molecular rigidity evolved from the three-dimensional skeleton and Michael acceptor nature of α,β-unsaturated lactone segment is primarily responsible for an interesting biological profile of these natural products. In light of these interesting structural features and biological profiles, there has been an increased pursuit in developing novel methodologies for the efficient construction of these scaffolds (Figure 3.3).[1,23]

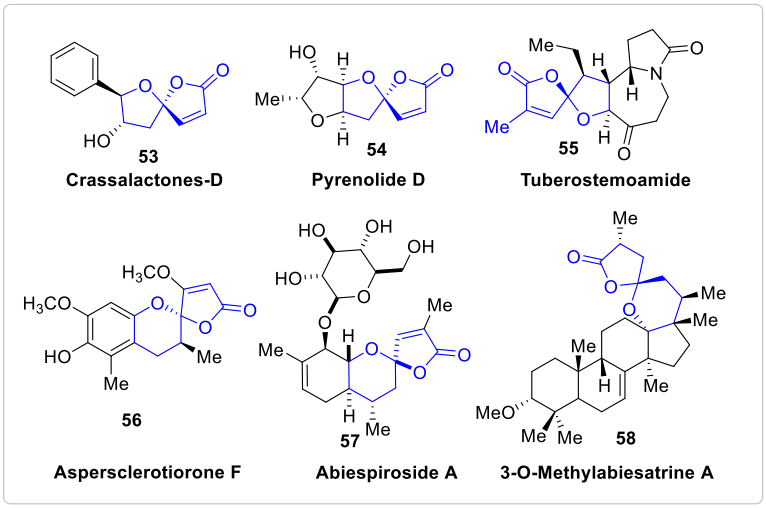


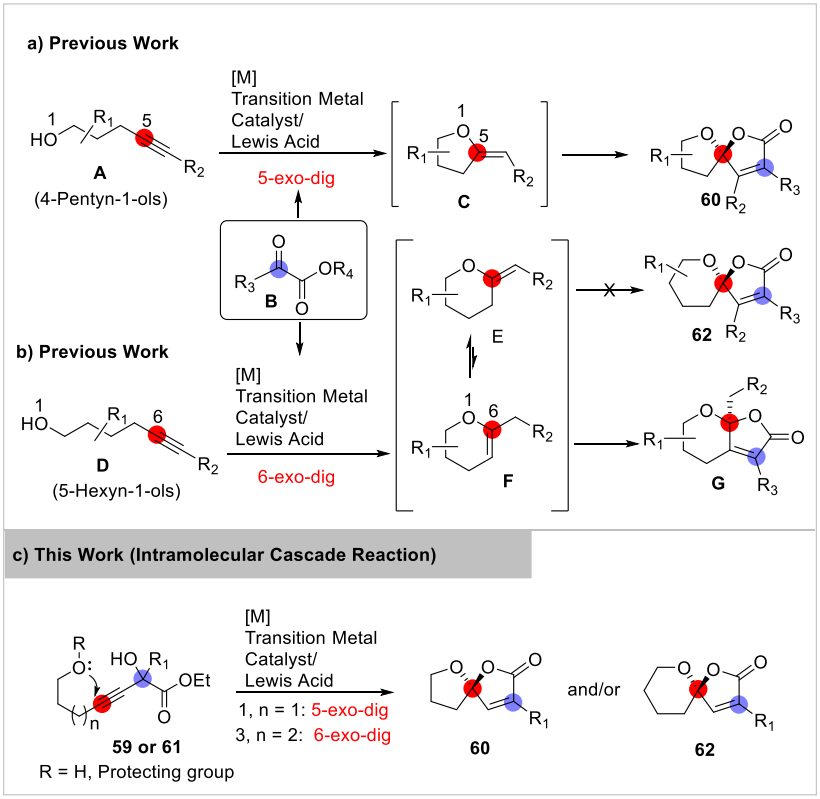
Figure. 3.3. Oxaspirolactone containing bioactive natural products

As we discussed in the earlier section (Chapter 3, Section A), traditionally α,β-unsaturated γ-spiroketal-γ-lactones are prepared from their saturated counterparts using multiple synthetic manipulations. For instance, spirolactonization followed by halogenation and dehydro-halogenation,[24] α-phenylselenation and oxidative elimination, and addition of halo-acrylates to lactones are notable examples of this class.[25] Whereas, strategies for direct construction of these scaffolds are very limited and those include, oxidative (chemical/photochemical) cascade cyclization of hydroxy-alkyl tethered

furans,[26]halocyclization of hydroxyalkyl tethered ylidene-butenolides,[27] annulations of cyclopropyl alkyl ketones with α-ketoesters,[28] and asymmetric multi-component coupling of alkynols, anilines, and glyoxylic acid.[29]

3.2.2 Hypothesis

As part of our interest in developing cascade transformations involving π-electrophilic activation of alkynols and inspired by the interesting biological profile of oxaspirolactone-derived natural products.



Scheme 3.8. Hypothesis generation based on our earlier reports

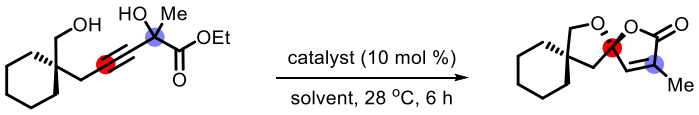
Previously, we have disclosed a novel cascade annulation approach for the synthesis of [5,5]-oxaspirolactones **60** in one step from 4-pentyn-1-ol **A** and α-ketoester **B** through 5-*exo*-dig cyclization to give enol ether **C** followed by annulation with **B** (entry a, Scheme 3.8).[30] A similar transformation using 5-hexyn-1-ol **D** led to the formation of furo[2,3-*b*]pyran-2-one **G** instead of expected [6,5]-oxaspirolactone **10**, via initial 6-*exo*-dig cyclization to give exocyclic enol ether **E** and its isomerization into its thermodynamically favored endo-cyclic

enol ether **F** followed by annulation with α-ketoester **B** (entry b, Scheme 3.8).[31] In this context, we aimed at the development of a unified strategy for the synthesis of both [5,5] and [6,5]-oxaspirolactones (**60** and **62**). Hence, we have hypothesized that propargylic diol esters possessing 4-pentyn-1-ol or 5-hexyn-1-ol appendage (**59** or **61** respectively) would deliver desired products **60** and **62** via initial selective alkynophilic transition metal/Lewis acid-catalyzed 5-*exo*-dig or 6-*exo*-dig cycloisomerization followed by dehydration and spirolactonization steps (*vide infra*) (entry c, Scheme 3.8).

3.2.3 Results and discussion

A) Optimization of reaction conditions

To investigate our hypothesis, we began by carrying out the reactions using propargylic diol ester **59a** (see Experimental Procedures section for details) as a precursor and our earlier successful alkynophilic catalytic systems[30,31] of $Bi(OTf)_3$, AgOTf and PPh_3PAuCl-AgOTf in CH_2Cl_2 at room temperature under an argon atmosphere (Table 3.1, entries 1-3). To our delight, all these reactions were provided desired [5,5]-oxaspirolactone **60a** in a good yield of 85%, 82%, and 84% respectively. Replacement of CH_2Cl_2 solvent with THF in AgOTf-catalysis gave **60a** in a low yield of 16%, which could be due to the catalyst's probable chelation with THF. Next, known other π-electrophilic catalytic systems of Au(I), Fe(II), Cu(II), In(III), Sc(II), Hg(II), and Pd(III) tested using reported solvents, where some of them found to be moderately active (Table 3.1, entries 5-15). Brønsted acids (p-TSA, TfOH) were weakly active towards this cascade reaction (Table 3.1, entries 16-18). The reaction using $Bi(OTf)_3$ in the presence of MS-4Å failed to deliver the product, which indicates the role of in situ released water in the product formation (Table 3.1, entry 19). The substrate's intactness in the absence of the catalyst showed the necessity of metal-triflate in this transformation (Table 1, entry 20). Among initially identified three best catalytic systems (Table 3.1, entries 1-3), $Bi(OTf)_3$ (anhydrous, 99%) was chosen for this work due to its cost-effectiveness, environmentally benign nature18 (Table 3.1, entry 1). Further screening of other parameters like catalyst loading, solvent, reaction time, and temperature showed insignificant improvement in the outcome (Table 3.1).



59a **60a**

entry	catalyst	solvent	yield (%)[b]
1	$Bi(OTf)_3$	CH_2Cl_2	85
2	AgOTf	CH_2Cl_2	82
3	PPh_3AuCl+AgOTf	CH_2Cl_2	84
4	AgOTf	THF	16
5	AuCl	CH_2Cl_2	36
6	$FeCl_3$	CH_2Cl_2	12
7[c]	$FeCl_3$	CH_3CN	-
8	$Cu(OTf)_2$	CH_2Cl_2	18
9	$In(OTf)_3$	CH_2Cl_2	55
10	$In(OTf)_3$	CH_3CN	51
11[c]	$Sc(OTf)_3$	CH_2Cl_2	-
12	$HgCl_2$	CH_3CN	34
13	$Hg(OTf)_2$	CH_3CN	36
14	$Hg(OTf)_2$	$CH_3CN:H_2O$	16
15[c]	$Pd(PPh_3)Cl_2$	THF	-
16[c]	*p*-TSA	CH_2Cl_2	-
17	*p*-TSA, reflux	DCE	36
18	TfOH	CH_2Cl_2	16
19[c]	$Bi(OTf)_3$, MS-4 Å	CH_2Cl_2	-
20[c]	No catalyst	CH_2Cl_2	-

[a]Reaction condition unless otherwise specified: **59a** (0.25 mmol), catalyst (10 mol %) in the indicated solvent (anhydrous, 2 mL) at rt (28 °C). [b]Isolated yield of **60a**. MS = Molecular Sieves. [c]No conversion was observed.

Table 3.1. Optimization of reaction conditions

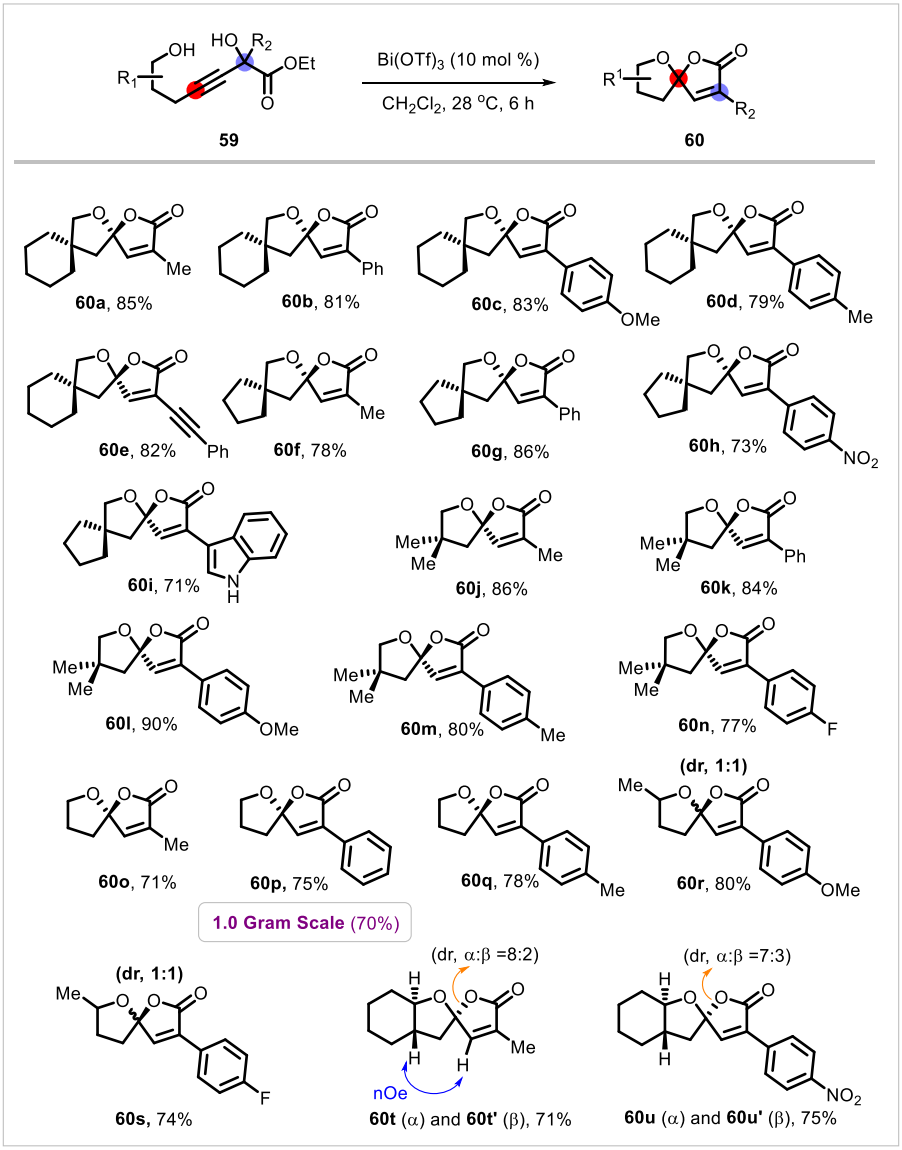
Encouraged by these results, initially, we prepared diverse propargylic diol esters (**59** or **61**) using known synthetic methods involving a single or three-step process (see Experimental Procedures section for details),[32-33] then we proceeded by examining the substrate scope for the synthesis of [5,5]-oxaspirolactones **60** (Scheme 3.9).

Substrate Scope: Scope and generality of the methodology

Synthesis of α,β-unsaturated [5,5]-oxaspirolactones 60:

The cyclohexyl derived propargylic-diol-esters having methyl, phenyl, *p*-anisyl, *p*-tolyl, and alkynyl phenyl substituents at the propargylic center were smoothly underwent reaction and furnished respective oxaspirolactones **60a-60e** in a good yield of 79-85% under

optimized conditions, without significant steric or electronic discrimination. Similarly, cyclopentyl tethered substrates with methyl, phenyl, *p*-nitrophenyl and 3-indolyl substituents provided the corresponding oxaspirolactones **60f-60i** in good yield (71-86%).



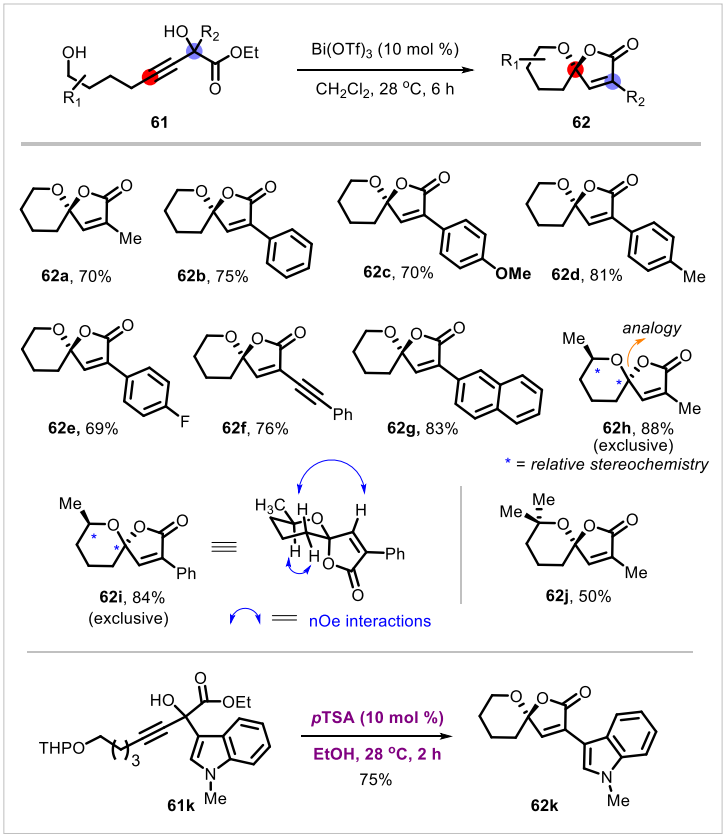
Scheme 3.9. Synthesis of [5,5]-oxaspirolactones **60** from propargylic diols esters **59**.

Gem-dimethyl substituted substrates (with methyl, phenyl, *p*-anisyl, *p*-tolyl and *p*-fluorophenyl substituents at propargylic carbon) furnished respective products **60j-60n** in 77-90% yield (Scheme 3.9).

The unsubstituted 4-pentyn-1-ol tethered substrates possessing methyl, phenyl, *p*-tolyl substituents at propargylic center were delivered corresponding products **60o-60q** in 71-78%

yield, this indicates the probable operation of Thorpe-Ingold effect in case of gem di-substituted precursors.[35] Substrates with secondary alcohol delivered corresponding oxaspirolactones **60r** and **60s** in 80% and 74% yield with 1:1 diastereomeric ratio (dr) for both products (dr was measured using ^{1}H NMR analyses). Pleasingly, cyclohexyl fused secondary alcohol-containing substrates also well-tolerated and furnished oxaspirolactones **60t**/**60t'** (dr 8:2) and **60u**/**60u'** (dr 7:3) in 71% and 75% yield (relative stereochemistry assigned based on nOe analyses)[8] (Scheme 2). The practicality of this protocol was exemplified by performing a 1.0 g scale reaction to obtain **60p** in a good yield of 70% (Scheme 3.9).

Synthesis of α,β-unsaturated [6,5]-oxaspirolactones 60:



Scheme 3.10 Synthesis of unsaturated [6,5]-oxaspirolactones **62** from propargylic diol esters **61**.

After successfully establishing the cascade process for [5,5]-oxaspirolactones **60**, we extended our study to synthesizing analogous [6,5]-oxaspirolactones **62** from diol ester **61**, and the results summarized in Scheme 3.10. Several propargylic diol esters with 1-hexynol appendage **61** were subjected to optimal reaction conditions. We were pleased to affor diverse [6,5]- oxaspirolactones **62a-62g** (possessing methyl, phenyl, *p*-anisyl, *p*-tolyl, *p*-fluorophenyl,

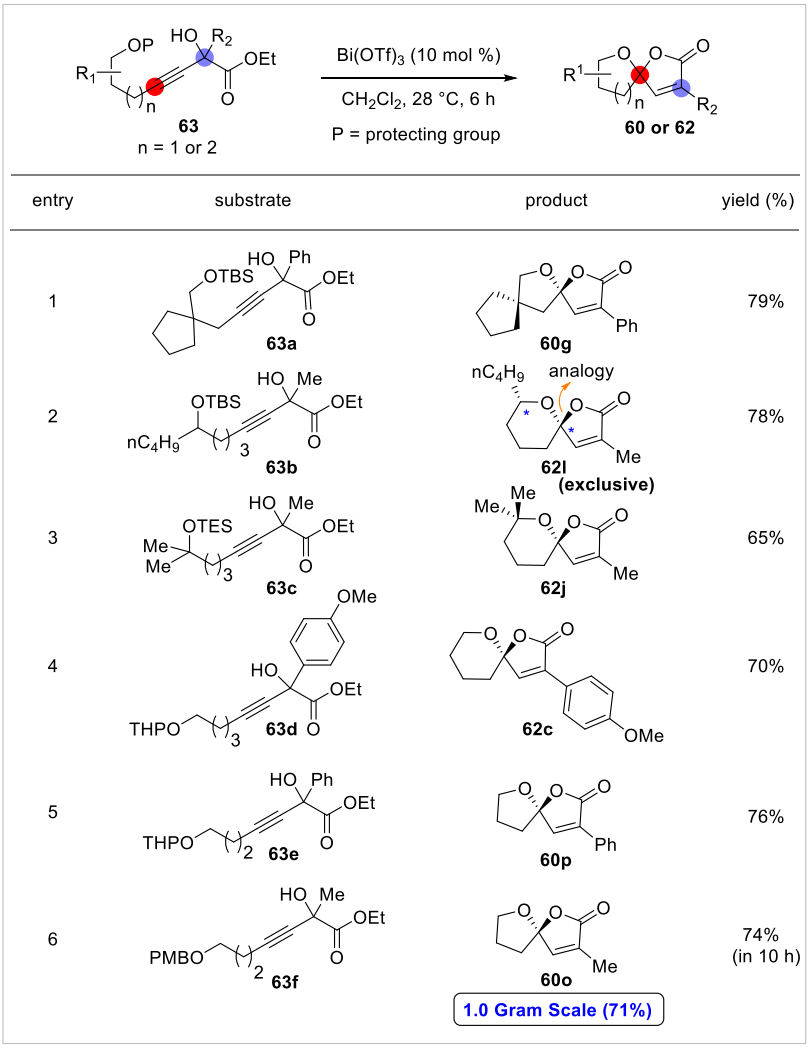
alkynyl, and 2-naphthyl substituents at α-position) in a good yield of 69-83%. Substrates with secondary hydroxyl group delivered desired oxaspirolactones **62h** and **62i** in 88% and 84% yield respectively, with exclusive diastereoselectivity.[33]The relative stereochemistry of **62i** was assigned based on nOe analysisand found that anomeric and associated effects[36] are operating here to deliver axially oriented lactone conformer **62i** as a sole product. The relative stereochemistry of **62h** was also assigned based on nOe analysis. Even, tertiary hydroxyl-containing substrate delivered corresponding oxaspirolactone **62j** in a moderate yield of 50% along with unidentified products (Scheme 3.10).

Interestingly, while preparing starting materials **61** (of Scheme 3.10), *p*-TSA-mediated THP deprotection step of indole derived alkyne diol precursor **61k** directly delivered the [6,5]-oxaspirolactone **62k** instead of free hydroxyl substrate in 75% yield in 2h, in contrast, THP deprotection of other semi-protected alkyne diols **63** (using *p*-TSA) resulted in propargylic diol esters **59** or **61** but not oxaspirolactones **60** or **62** (Scheme 3.10).[32]

-

Synthesis of (5,5) and (6,5)-oxaspirolactones from semiprotected propargylic diolesters:

Above observation (Scheme 3.10; *p*TSA-mediated conversion of **61k** into **62k**) inspired us to evaluate this cascade cyclization using semi-protected alkyne diol-esters **63** as substrates, which could avoid the extra deprotection step of this protocol's substrates synthesis (Scheme 3.11). Thus, we have prepared several protected (with TBS, TES, THP, PMB groups) substrates and subjected them to standard reaction conditions. To our delight, Mono-TBS protected diol-esters **63a** and **63b** furnished corresponding [5,5] and [6,5]-oxaspirolactones **60g** and **62l** (single diastereomer) in a good yield of 79% and 78%, without the requirement of an acid additive. Substrate **63c** having TES protection delivered **62j** in 65% yield. The THP protected propargylic diol ester **63d-63e** delivered corresponding oxaspirolactones **62c** and **60p** ingood yield. Interestingly, PMB-protected alkynol **63f** also underwent clean spirolactonization and delivered the oxaspirolactone **60o** in 74% yield in a little longer reaction time of 10 h and performed 1.0 gram scale reaction to check the practicality of our approach (Scheme 3.11).

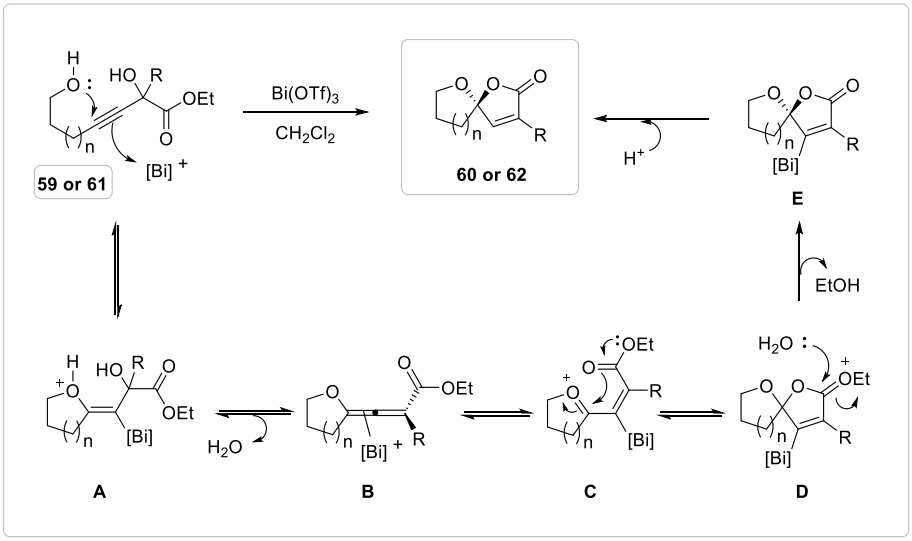


Scheme 3.11. Synthesis of [5,5]- and [6,6]-unsaturated oxaspirolactones **60** & **62** from semi-protected propargylic diol esters **63**

B) Plausible reaction mechanism

Based on our previous reports,[30,31] and others,[37] we have formulated tentative mechanistic sequence for this cascade bis-cyclization. The Lewis acid ($Bi(OTf)_3$-catalyzed π-activation of alkyne diol ester **59** or **61** would trigger the cascade process through initial oxy-functionalization of alkyne to give intermediate **A** (via 5-*exo*-dig or 6-*exo*-dig mode of ring closure), which would undergo instant dehydration to give cyclic enol ether-derived allene intermediate **B** followed by oxocarbenium species **C**. Next, **C** would undergo intramolecular nucleophilic addition of ester to provide intermediate **D**. Then, in situ released water would

attack the oxocarbenium intermediate **D** to deliver **E** via expulsion of EtOH, simultaneous proto-debismuthination of **E** would deliver the desired oxaspirolactones **60** or **62**. However, further investigations are required to establish the precise reaction mechanism (Scheme 3.12).



Scheme 3.12. Plausible reaction mechanism

3.2.4 Conclusion:

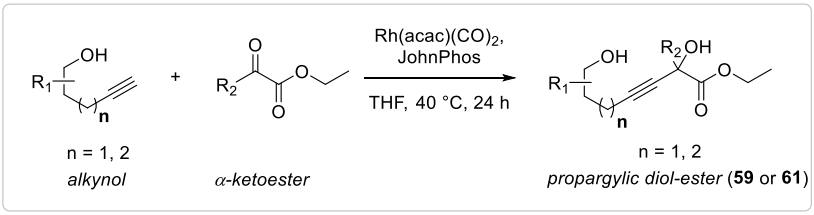
In conclusion, we have developed a unified cascade strategy for the synthesis of [5,5]- and [6,5]-oxaspirolactones possessing α,β-unsaturation. This transformation requires a simple, cost-effective, abundant, and environmentally benign $Bi(OTf)_3$ catalyst (10 mol %), ambient reaction conditions, and furnished diverse oxaspirolactones in good to excellent yields. Moreover, we have demonstrated this strategy's potential using semi-protected propargylic diol esters, which provided desired products in good yields with equal ease. Future studies will focus on utilizing this methodology in the total synthesis of biologically potent related natural products.

3.2.5 Experimetal procedures

All reactions were performed under argon atmosphere with oven (80 ºC) or flame-dried glassware with septum seal. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under argon atmosphere immediately prior to use. Dichloromethane and acetonitrile were freshly distilled over calcium hydride under argon atmosphere. 30 °C corresponds to the room temperature (rt) of the laboratory when the experiments were carried out. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel.

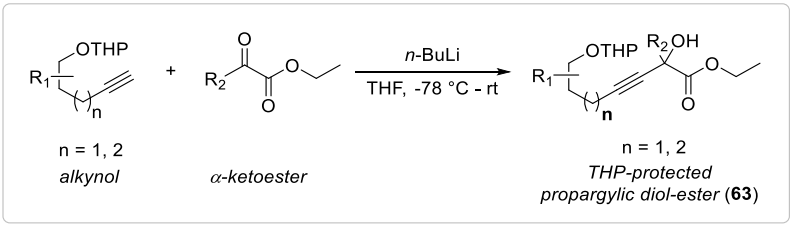
Synthesis of propargylic diol esters

***General procedure A for the synthesis of propargylic diol esters*(59 or 61):**



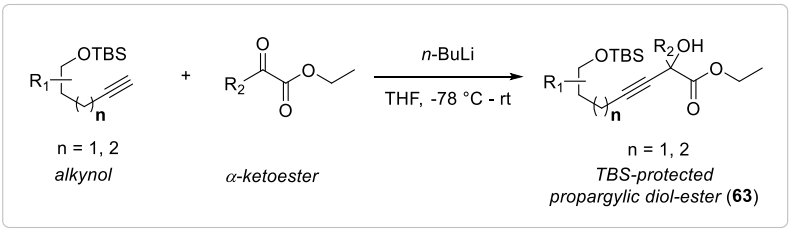
Propargylic diol esters were obtained by using known literature procedure. A solution of alkynol (1.31 mmol) and α-ketoester (3.94 mmol) in 3.0 mL of THF was added to a mixture of $Rh(acac)(CO)_2$ (0.01 g, 0.04 mmol, 3 mol%) and JohnPhos (0.035g, 0.12 mmol, 9 mol%) under argon atmosphere at room temperature, then the reaction mixture was warmed to 40 °C. After 24 h at 40 °C, the mixture was allowed to cool to room temperature, diluted and extracted with CH_2Cl_2, concentrated under reduced pressure and purified by silica gel column chromatography (using ethyl acetate/petroleum ether) to afford propargylic diol ester (**59** or **61**).

***General procedure B for the synthesis of THP- protected propargylic diol esters*(63):**



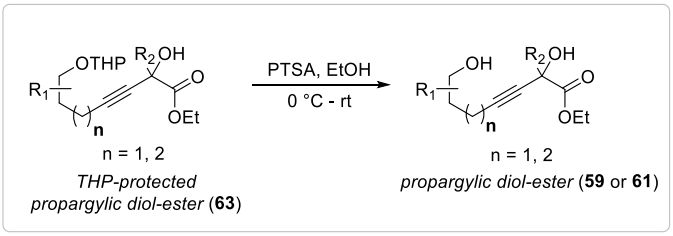
To a solution alkynol (16.9 mmol) in an anhydrous THF (30 mL) under argon atmosphere was added*n*-BuLi solution (1.6M in hexane, 25.35 mmol). The resultant mixture was stirred at -78 ºC for 45 min. Then the solution of α-ketoester (2.2 mL, 18.6 mmol) in an anhydrous THF (10 mL) was added at the same temperature and stirred the reaction mixture for 30 min. Then the reaction mixture was allowed to warm to rt and stirred until completion of reaction monitored by TLC. Reaction was quenched through the slow addition of saturated aqueous NH_4Cl solution at 0 ºC, extracted with ethyl acetate, dried over an anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification by column chromatography (SiO_2, EtOAc/hexane) afforded THP-protected propargylic diol ester (**63**).

General procedure C for the synthesis of TBS-protected propargylic diol ester (**63**):



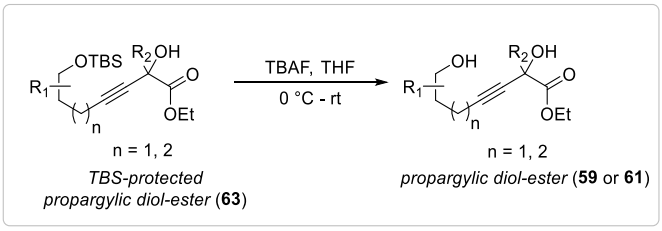
To a solution of *tert*-butyldimethyl silyl protected alkynol (1.87 mmol) in an anhydrous THF (10 mL) under argon was added*n*-BuLi(1.6 M in hexane, 2.81 mmol). The resultant mixture was stirred at -78 ºC for 45 min. Then the solution of α-ketoester in an anhydrous THFwas added at the same temperature and stirred it for 30 min. Then the reaction mixture was allowed to warm to rt and stirred till the complete conversion of starting material monitored by TLC. Reaction was quenched with saturated aqueous NH_4Cl solution at 0 ºC, warmed to rt, extracted with ethyl acetate, dried overanhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, EtOAc/hexane) afforded TBS-protected propargylic diol ester (**63).**

General procedure D for the synthesis of propargylic diol ester (59 or 61) from THP-protected propargylic diol ester (**63**):



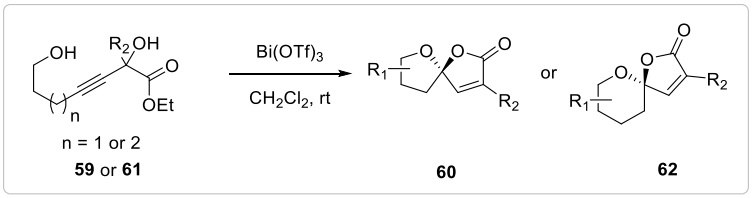
To a solution of THP-protected propargylic diol ester (8.5 mmol) in ethanol was added *p*-toluenesulfonicacid (0.85 mmol) at 0°C and then it was slowly warmed to rt.The resulting reaction mixture was stirred at rt till the complete conversion of starting material. Then the ethanol was evaporated under reduced pressure, diluted with ethyl acetate and quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3x25 mL). Combined organic layers were dried over an anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (SiO_2, EtOAc/hexanes) to afford propargylic diol ester **(59 or 61).**

General procedure E for the synthesis of propargylic diol ester from TBS-protected propargylic diol ester (**63**):



TBS-protected propargylic diol ester (**63**) (0.85 mmol) was placed in a flame-dried, two-neck, round-bottom flask under argon. To this was added an anhydrous THF (10 mL), and the mixture was cooled to 0 ºC. TBAF (1.0 M in THF, 0.94 mmol) was then added slowly at 0 ºC. The cooling bath was removed, and the system was allowed to stir at rt for 2h. After complete conversion of starting material, the reaction mixture was concentrated under reduced pressure and subjected for column chromatography (SiO_2, EtOAc/hexanes) to afford the propargylic diol ester (**59** or **61**).

General Procedure F for the synthesis of [5,5] and [6,5]-α,β-unsaturated oxaspirolactones (60 and 62) from propargylic diol esters (59 and 61):

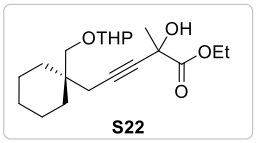


To a stirred solution of **59** or **61** (0.25 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was added $Bi(OTf)_3$ (0.025 mmol, 10 mol%) at room temperature under argon atmosphere, and the reaction mixture was stirred at rt until complete conversion monitored by TLC. The reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (2x5 mL) and combined organic layers were washed with brine solution. The combined extracts were dried over an anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (elution with EtOAc/hexanes) to afford [5,5] or [6,5]-α,β-unsaturated oxaspirolactones (**60** or **62**).

3.2.6 Characterization data

Synthesis of [5,5]- unsaturated oxa-spirolactones from propargylic diol esters:

Compound (S22):



Yellow oil: Yield = 68%

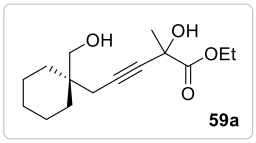
R_f= 0.3 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz):δ 4.63-4.51(m, 1H), 4.38-4.14 (m, 2H), 3.93-3.78 (m, 1H), 3.71-3.57(m 1H), 3.56-3.4(m, 2H), 3.27-3.11 (m, 1H), 2.29 (s, 2H), 1.84-1.73 (m, 2H), 1.7-1.64 (m, 4H), 1.6-1.51(m, 4H), 1.45-1.4(m, 9H), 1.32(t, *J* = 6.87Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz):δ 173.2, 98.8, 82.9, 81.7, 72.1, 67.9, 62.6, 61.6, 37.3, 32.3, 32.2, 30.5, 27.3, 26.1, 25.8, 25.5, 21.6, 19.2, 14.0

HRMS (ESI) m/z:$[M+Na]^+$ calcd for $C_{20}H_{32}O_5Na$375.2142; found 375.2135.

Compound (59a):



Colorless liquid: Yield = 66%

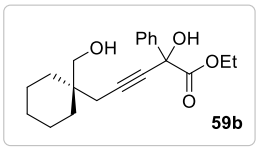
R_f= 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz):δ 4.36-4.15 (m, 2H), 3.95 (s, 1H), 3.47 (s, 2H), 2.40 (br. s, 1H), 2.24 (s, 2H), 1.63 (s, 3H), 1.47-1.25 (m, 13H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.0, 82.6, 81.9, 68.2, 68.0, 62.6, 37.9, 31.9, 27.4, 26.1, 25.2, 21.5, 14.0

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{15}H_{24}O_4Na$291.1567; found 291.1563.

Compound (59b):



Colorless liquid: Yield = 62%

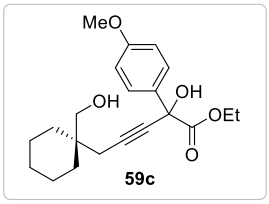
R_f = 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.59 (m, 2H), 7.42-7.27 (m, 3H), 4.35-4.08 (m, 3H), 3.57 (s, 2H), 2.39 (s, 2H), 1.51-1.38 (m, 10H), 1.27-1.18 (m, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.2, 139.8, 128.6, 128.3, 126.1, 84.9, 80.7, 72.9, 68.7, 63.4, 38.2, 32.0, 31.9, 26.1, 25.6, 25.4, 21.5, 13.9

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{20}H_{26}O_4Na$353.1721; found 353.1723.

Compound (59c):



Colorless liquid: Yield = 27% (54% brsm)

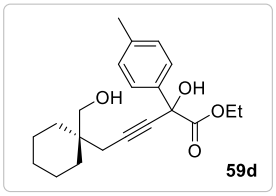
R_f= 0.2 (SiO_2, 30% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66-7.50 (m, 2H), 6.96-6.81(m, 2H), 4.38-4.08 (m, 3H), 3.81(s, 3H), 3.56 (s, 2H), 2.38 (s, 2H), 1.56-1.36 (m, 10H), 1.26-1.2 (m, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.3, 159.7, 131.9, 127.4, 113.6, 84.7, 80.8, 72.5, 68.6, 63.3, 55.3, 38.2, 32.0, 26.1, 25.5, 21.5, 13.8

HRMS (ESI) m/z:$[M+Na]^+$calcd for $C_{21}H_{28}O_5Na$ 383.1829; found 383.1829.

Compound (59d):



Colorless liquid: Yield =16% (32% brsm)

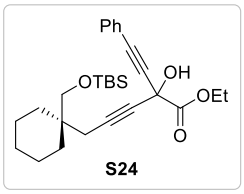
R_f= 0.2 (SiO_2, 30% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$,500 MHz): δ 7.54(d, *J* = 8.39 Hz, 2H), 7.16(d, *J* = 8.39 Hz, 2H), 4.48 (br. s, 1H), 4.34-4.09(m, 2H), 3.53 (s, 2H), 2.39-2.32 (m, 5H), 1.51-1.34(m, 10H), 1.22(t, *J* = 6.87 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.1, 138.2, 136.9, 128.9, 125.9, 84.8, 80.6, 72.8, 68.3, 63.12, 38.1, 31.9, 26.1, 25.3, 21.4, 21.0, 13.8

HRMS (ESI) m/z:$[M+Na]^+$calcd for $C_{21}H_{28}O_4Na$367.1880; found 367.1876.

Compound (S24):



Colorless liquid: Yield =49%

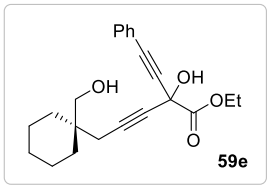
R_f= 0.6 (SiO_2, 10% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ7.72-7.62 (m, 1H), 7.5-7.44 (m, 2H), 7.35-7.31 (m, 2H), 4.44- 4.37 (m, 2H), 3.87 (br. s, 1H), 3.49-3.41(m, 2H), 2.3(s, 2H), 1.44-1.38 (m, 13H), 0.89 (s, 9H), 0.05 (s, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.2, 133.8, 132.0, 128.9, 128.8, 128.2, 121.7, 85.4, 84.2, 83.5, 78, 67.5, 63.9, 63.5, 63.3, 38.5, 31.8, 31.7, 26.2, 25.9, 21.6, 18.2, 14.0, -5.5

HRMS (ESI) m/z:$[M+Na]^+$ calcd for $C_{28}H_{40}O_4NaSi$ 491.2588; found 491.2588.

Compound (59e):



Colorless liquid:Yield = 62%

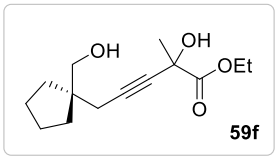
R_f= 0.40 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5-7.45 (m, 2H), 7.37-7.29 (m, 3H), 4.46-4.33 (m, 2H), 3.98 (br. s, 1H), 3.56 (s, 2H), 2.34 (s, 2H), 1.49-1.37 (m, 13H)

^{13}C NMR ($CDCl_3$,101 MHz): δ 169, 132, 129.1, 128.9, 128.3, 127.9, 121.5, 85.2, 83.8, 83.7, 78.6, 68.5, 64.1, 63.5, 38.3, 32, 26.1, 21.6, 14

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{22}H_{27}O_4$355.1904; found 355.1893.

Compound (59f):



Colorless liquid: Yield = 68%

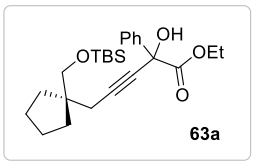
R_f=0.39 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.29 (q, *J* = 6.7 Hz, 2H), 3.53 (s, 1H), 3.48 (s, 2H), 2.3 (s, 2H), 1.82 (br. s, 1H), 1.66 (s, 3H), 1.65-1.55 (m, 4H), 1.54-1.42 (m, 4H), 1.33 (t, *J* = 6.7 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.1, 83.4, 80.9, 68.9, 67.9, 62.8, 47.3, 34.1, 27.4, 26.9, 25.2, 14

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{14}H_{23}O_4$ 255.1591, found 255.1586.

Compound (63a):



Yellowish oil: Yield = 54%

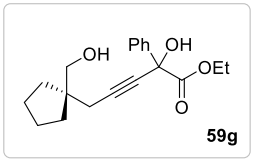
R_f = 0.5 (SiO_2, 10% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 7.32 Hz, 2H), 7.41-7.3 (m, 3H), 4.32-4.13 (m, 3H), 3.44 (s, 2H), 2.4(s, 2H), 1.68-1.48 (m, 8H), 1.22 (t, *J* = 7.32 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.3, 139.9, 128.4, 128.1, 126.3, 86.3, 78.9, 72.9, 68.3, 68.3, 47.6, 33.9, 33.9, 26.9, 25.9, 25.4, 18.2, 13.8,-5.5

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{25}H_{39}O_4Si$ 431.2612; found 431.2609.

Compound (59g):



Viscous liquid: Yield = 96%

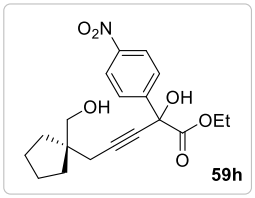
R_f= 0.3 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$,400 MHz): δ 7.7-7.62 (m, 2H), 7.41-7.3 (m, 3H), 4.34-4.24 (m, 1H), 4.23-4.12 (m, 1H), 3.54 (s, 2H), 2.42 (s, 2H), 1.71-1.5 (m, 8H), 1.23 (t, *J* = 7.32 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.1, 139.7, 128.5, 128.2, 126.1, 85.7, 79.5, 72.9, 68.9, 63.4, 47.4, 34.2, 27.1, 25.2, 13.8

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{19}H_{25}O_4$317.1747; found 317.1764.

Compound (59h):



Yellowish liquid: Yield = 14%

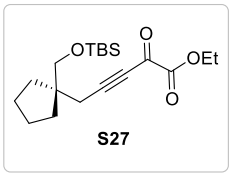
R_f = 0.4(SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.3-8.17 (m, 2H), 7.94-7.79 (m, 2H), 4.37-4.13 (m, 3H), 3.53 (s, 2H), 2.44 (s, 2H), 1.73-1.47 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.8, 147.9, 146.5, 127.5, 123.4, 86.8, 78.8, 72.4, 68.6, 63.9, 47.4, 34.3, 26.9, 25.2, 13.8

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{24}O_6N$ 362.1598; found 362.1596.

Compound (S27):



Yellowish oil: Yield = 16%

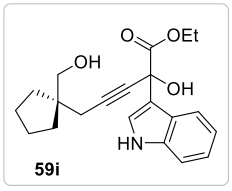
R_f = 0.5 (SiO_2, 10% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400MHz): δ 4.36 (q, *J* = 6.87 Hz, 2H), 3.42 (s, 2H), 2.58 (s, 2H), 1.67-1.51 (m, 8H), 1.38 (t, *J* = 6.87 Hz, 3H), 0.89 (s, 9H), 0.04(s, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.6, 159.2, 102.3, 80.4, 68.1, 63.0, 47.8, 34.1, 27.6, 25.8, 25.2, 18.2, 13.9, -5.5

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{19}H_{33}O_4Si$ 353.2143; found 353.2144.

Compound (59i):



Viscous liquid: Yield = 76%

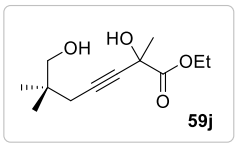
R_f= 0.3 (SiO_2, 40% EtOAc/ hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.47-7.42 (m, 1H), 7.37-7.32 (m, 1H), 7.22-7.16 (m, 1H), 7.14-7.09 (m, 1H), 4.36-4.27 (m, 1H), 4.23-4.09 (m, 2H), 3.52 (s, 2H), 2.41(s, 2H), 1.70-1.58 (m, 4H), 1.55-1.51 (m, 3H), 1.29-1.23 (m, 2H), 1.21 (t, *J* = 7.25 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.3, 136.8, 124.4, 123.9, 122.4, 120.2, 115.9, 111.3, 84.3, 79.8, 69.1, 68.9, 63.3, 47.4, 34.3, 29.7, 27.1, 25.2, 13.9

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{21}H_{25}NO_4$355.1778; found 355.1727.

Compound (59j):



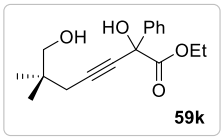
Colorless oil: Yield = 18% (30% brsm)

R_f= 0.3 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400MHz): δ 4.38-4.14 (m, 3H), 3.39(s, 2H), 2.16(s, 2H), 1.65(s, 3H), 1.32(t, *J*= 6.87 Hz, 3H), 0.95 (s, 6H)

^{13}C NMR ($CDCl_3$, 101MHz): δ 173.0, 82.7, 81.8, 70.7, 67.9, 62.7, 35.7, 28.4, 27.5, 23.7, 14.0**HRMS (ESI)** m/z: $[M+Na]^+$calcd for $C_{12}H_{20}O_4Na$ 251.1254; found 251.1249.

Compound (59k):



Yellowish oil: Yield = 9% (35% brsm)

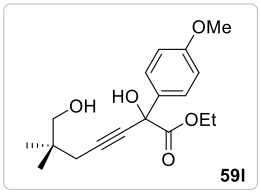
R_f = 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70-7.59(m, 2H), 7.40-7.32 (m, 3H), 4.34-4.09 (m, 3H), 3.45 (s, 2H), 2.30 (s, 2H), 1.23 (t, *J*=6.87 Hz, 3H), 1.02 (s, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.1, 139.7, 128.5, 128.2, 126.1, 85.0, 80.4, 72.9, 70.8, 63.3, 36.0, 28.6, 23.8, 13.8

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{17}H_{22}O_4Na$313.141; found 313.1404.

Compound (59l):



Colorless oil: Yield = 14% (34% brsm)

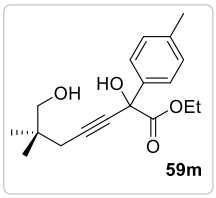
R_f= 0.3 (SiO_2, 40 % EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.5(m, 2H), 6.9-6.8 (m, 2H), 4.3-4.1(m, 3H), 3.79 (s, 3H), 3.42 (s, 2H), 2.27 (s, 2H), 1.3-1.15 (m, 3H), 0.99 (s, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz); δ 172.4, 159.8, 132.1, 127.5, 113.7, 85.0, 80.7, 72.7, 70.9, 63.3, 55.4, 38.9, 36.1, 28.7, 24.0, 14

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{18}H_{24}O_5Na$ 343.1516; found 343.1511.

Compound (59m):



Viscous liquid: Yield = 18% (37% brsm)

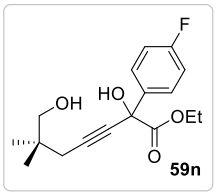
R_f= 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60-7.49 (m, 2H), 7.22-7.12 (m, 2H), 4.37-4.10 (m, 3H), 3.46 (s, 2H), 2.36 (s, 3H), 2.30 (s, 2H), 1.24 (t, *J*= 7.63 Hz, 3H), 1.02 (s, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.3, 138.4, 136.9, 129.0, 126.0, 84.8, 80.5, 72.8, 71.0, 63.4, 36.0, 29.8, 28.8, 23.9, 21.1, 13.9

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{18}H_{24}O_4Na$ 327.1567; found 327.1562.

Compound (59n):



Yellowish oil: Yield = 11% (31% brsm)

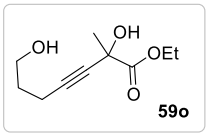
R_f = 0.3 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71-7.6 (m, 2H), 7.11-7.99 (m, 2H), 4.34-4.13(m, 3H), 3.45 (s, 2H), 2.30 (s, 2H), 1.23 (t, *J* = 6.87 Hz, 3H), 1.02 (s, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.0, 135.5, 128.1, 128.0, 115.2, 115.0, 85.2, 80.3, 72.3, 70.9, 70.7, 63.5, 36.1, 36.0, 29.7, 29.0, 28.6, 23.9, 13.9

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{17}H_{21}O_4FNa$ 331.1316; found 331.1308.

Compound (59o):



Viscous liquid: Yield = 60%

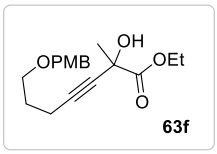
R_f= 0.4 (SiO_2, 40% EtOAc/ hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.3 (q, *J* = 6.87 Hz, 2H), 3.74 (t, *J* = 6.1 Hz, 2H), 2.35 (t, *J* = 6.87 Hz, 2H), 1.8-1.73 (m, 2H), 1.66 (s, 3H), 1.34 (t, *J* = 6.87Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.3, 84.4, 80.7, 67.9, 62.8, 61.6, 30.9, 27.4, 15.3, 14.0

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{10}H_{16}O_4Na$ 223.0941; found 223.0939.

Compound (63f):



Colorless oil: Yield = 61%

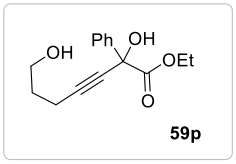
R_f= 0.5 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25(d, *J* = 9.13Hz, 2H), 6.88 (d, *J* = 8.76Hz, 2H), 4.43(s, 2H), 4.28(q,*J*= 7.13Hz, 2H), 3.8 (s, 3H), 3.51(t, *J* = 6.13Hz, 2H), 3.45 (br. s, 1H), 2.32(t, *J* = 7.13 Hz, 2H), 1.83-1.73 (m, 2H), 1.64 (s, 3H), 1.32(t, *J* = 7.13Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.1, 159.2, 130.5, 129.2, 113.8, 84.3, 80.1, 72.6, 68.4, 67.9, 62.7, 55.3, 28.5, 27.4, 15.6, 14

HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{18}H_{24}O_5Na$ 343.1516; found 343.1511.

Compound (59p):



Colorless liquid: Yield = 62%

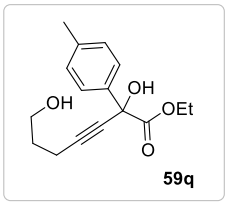
R_f= 0.5 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$,400 MHz): δ 7.5-7.4 (m, 2H), 7.36-7.26 (m, 3H), 4.58 (s, 1H), 4.38 (q, *J*=6.71Hz, 2H), 4.21 (br. s, 1H), 3.88-3.7 (m, 2H), 3.54-3.36 (m, 2H), 2.3 (t, *J*= 7.32 Hz, 2H), 1.71-1.49 (m, 8H), 1.36(t, *J*=7.32 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ168.9, 132, 129, 128.2, 121.6, 98.7, 85.5, 85.4, 83.6, 66.8, 63.9, 63.5, 62.2, 30.6, 28.8, 25.4, 24.9, 19.5, 18.6, 13.9

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{20}H_{27}O_5$347.1853, found 347.1863.

Compound (59q):



Colorless oil: Yield = 11% (27% brsm

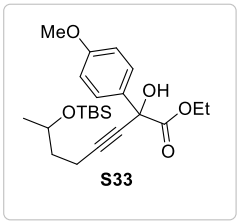
R_f= 0.4 (40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.55 (m, 2H), 7.10-7.95 (m, 2H), 4.38-4.02(m, 3H), 3.73-3.58(m, 2H), 2.64 (t,*J*=6.87Hz, 2H), 2.35 (s, 3H), 1.77-1.57(m, 2H), 1.2(t, *J*=7.33 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.4, 136.9, 129.1, 126.1, 86.4, 79.3, 76.8, 72.8, 63.5, 61.8, 31.1, 15.6, 13.9

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{16}H_{20}O_4Na$ 299.1254; found 299.1250.

Compound (S33):



Colorless liquid: Yield = 59% brms

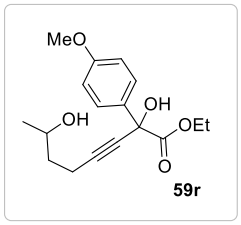
R_f = 0.3 (SiO_2, 20% EtOAc/hexanes);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, *J* = 9.1 Hz, 2H), 6.88 (d, *J* = 8.88 Hz, 2H), 4.31-4.12 (m, 3H), 4.0-3.87 (m, 1H), 3.81 (s, 3H), 2.47-2.26 (m, 2H), 1.71-1.66 (m, 2H), 1.22-1.20 (m, 3H), 1.16 (d, *J* = 6Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.4, 159.7, 132.1, 127.5, 113.5, 87.1, 78.6, 72.5, 67.2, 66.9, 64.4, 63.2, 55.3, 38.1, 30.3, 25.9, 25.3, 23.7, 18.8, 18.1, 15.3, 13.8, 13.6, -4.3, -4.8

HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{36}O_5NaSi$ 443.222; found 443.2216.

Compound (59r):



Viscous liquid: Yield = 57%brsm

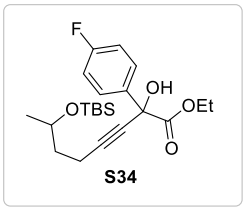
R_f = 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.63-7.5 (m, 2H), 6.95-6.8 (m, 2H), 4.34-4.13(m, 2H), 4.05-3.88 (m, 1H), 3.81 (s, 3H), 2.45 (t, *J*=6.69 Hz, 2H), 1.82(br. s, 1H), 1.78-1.64 (m, 2H), 1.3-1.2 (m, 6H)

^{13}C NMR ($CDCl_3$, 56 MHz): δ172.3, 159.8, 131.9, 127.5, 113.6, 86.6, 79.2, 72.5, 67.1, 63.3, 55.3, 37.3, 29.7, 23.4, 15.5, 13.8

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{17}H_{22}O_5Na$ 329.1359; found 329.1354.

Compound (S34):



Colorless liquid: Yield = 74% brsm

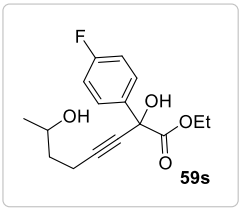
R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.57(m, 2H), 7.10-6.97(m, 2H), 4.28-4.10(m, 3H), 3.95-3.87(m, 1H), 2.41-2.34(m, 2H), 1.68-1.65(m, 1H), 1.58-1.54(m, 1H), 1.16(d, *J* = 6.10 Hz, 3H), 0.90-0.86(m, 12H), 0.06(s, 6H)

^{13}C NMR ($CDCl_3$,101 MHz): δ 172.1, 164.0, 161.6, 135.6, 128.2, 128.1, 115.1, 114.9, 87.3, 78.3, 72.3, 67.1, 38.0, 30.2, 25.8, 23.7, 18.7, 18.0, 15.3,13.5, -4.28, -4.74

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{22}H_{34}O_4FSi$ 409.2205; found 409.2203.

Compound (59s):



Viscous liquid: Yield = 57%brsm

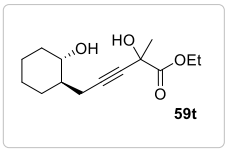
R_f= 0.4 (SiO_2. 40% EtOAc/ hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz):δ 7.69-7.57 (m, 2H), 7.1-6.96 (m, 2H), 4.35-4.17 (m, 3H), 4.02-3.86 (m 1H), 2.5-2.37 (m, 2H), 1.77-1.64 (m, 2H), 1.27-1.15 (m, 6H)

^{13}C NMR ($CDCl_3$,126 MHz): δ 171.9, 164.1, 161.6, 161.3, 135.6, 128.2, 128.1, 115.2, 115.0, 86.9, 78.9, 72.4, 67.1, 63.5, 37.2, 23.4, 15.4, 13.8

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{16}H_{19}O_4FNa$ 317.1160; found 317.1154.

Compound (59t):



Colorless liquid; Yield = 57%

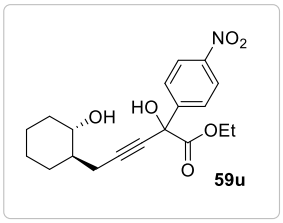
R_f=0.4 (50% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.34-4.24(m, 2H), 3.48 (br. s, 1H), 3.36-3.21(m, 1H), 2.55-2.49 (m, 1H), 2.34-2.21 (m, 1H), 2.02-1.93 (m, 1H), 1.88-1.71 (m, 2H), 1.66 (s, 3H), 1.5-1.37 (m, 1H), 1.36-1.23 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.1, 83.3, 81.4, 73.6, 68, 62.7, 44.1, 35.5, 30.4, 27.4, 25.4, 24.9, 22.06, 14.03

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{14}H_{22}O_4Na$ 277.1410; found 277.1409.

Compound (59u):



Yellowish oil: Yield =62%

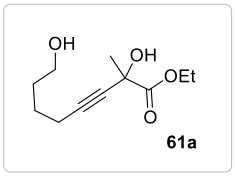
R_f = 0.4 (40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (d, *J* = 8.77 Hz, 2H), 7.88 (d, *J* = 8.39 Hz, 2H), 4.49 (br. s, 1H), 4.35-4.25 (m, 1H), 4.23-4.13 (m, 1H), 3.41-3.28 (m, 1H), 2.62 (dd, *J* = 4.20, 16.78 Hz, 1H), 2.44 (dd, *J* = 7.25, 16.78 Hz, 1H), 2.0-1.88 (m, 2H), 1.77-1.67 (m, 2H), 1.55-1.43 (m, 1H), 1.29-1.18 (m, 8H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.0, 148.0, 146.6, 127.6, 123.4, 86.8, 79.1, 73.6, 72.4, 63.9, 44.1, 35.7, 30.5, 25.4, 24.9, 22.2, 13.8

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{19}H_{23}O_6NNa$ 384.1418; found 384.1440.

Compound (61a):



Colorless liquid: Yield =52%

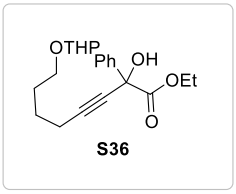
R_f= 0.2 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.29 (q, *J*= 6.87 Hz, 2H), 3.66 (t, *J*= 6.1 Hz, 2H), 2.25 (t, *J*= 6.87 Hz, 2H), 1.67-1.58 (m, 7H), 1.33 (t, *J*= 7.63 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.1, 84.5, 80.2, 67.9, 62.7, 62.2, 31.6, 27.3, 24.5, 18.4, 14.0

HRMS (ESI) m/z:$[M+Na]^+$calcd for $C_{11}H_{18}O_4Na$ 237.1097; found 237.1091.

Compound (S36):



Yellowish oil: Yield =40%

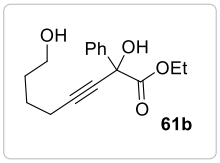
R_f = 0.3 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500MHz): δ 7.69 (d, *J*=7.63Hz, 2H), 7.4-7.26(m, 3H), 4.6(s, 1H), 4.37-4.25 (m, 2H), 4.35 (br. s, 1H), 3.82-3.76 (m, 2H), 3.55-3.39 (m, 2H), 2.3 (t, *J*=6.87 Hz, 2H), 1.89-1.49 (m, 10H), 1.22(t, *J*=6.87 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.9, 132.0, 129.0, 128.2, 121.6, 98.7, 85.5, 83.6, 66.8, 63.8, 63.5, 62.2, 30.6, 28.8, 25.4, 24.9, 19.5, 18.6, 13.9

HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{21}H_{28}O_5Na$ 383.1829; found 383.1823.

Compound (61b):



Colorless liquid: Yield = 68%

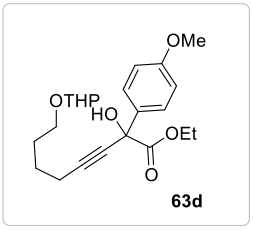
R_f= 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.62 (m, 2H), 7.40-7.28 (m, 3H), 4.35 (br. s, 1H), 4.25-4.05 (m, 2H), 3.67 (t, *J* = 6.13Hz, 2H), 2.36 (t, *J* = 6.88Hz, 2H), 1.90 (br. s, 1H), 1.71-1.66 (m, 2H), 1.6-1.5 (m, 2H), 1.29-1.17 (m, 2H), 0.84 (t, *J* = 7.25 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.2, 139.7, 128.4, 128.1, 126.1, 86.9, 78.8, 72.8, 67.0, 62.2, 31.7, 30.2, 24.6, 18.7, 18.5, 13.4

HRMS (ESI) m/z:$[M+Na]^+$ calcd for $C_{16}H_{20}O_4Na$ 299.1254; found 299.1250.

Compound (63d):



Yellowish oil: Yield = 52%

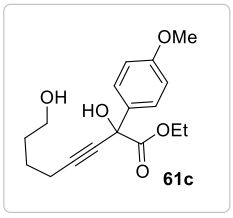
R_f = 0.5 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* = 8.77 Hz, 2H), 6.88 (d, *J* = 8.77 Hz, 2H), 4.62-4.54 (m, 1H), 4.33-4.24 (m, 1H), 4.22-4.12 (m, 2H), 3.89-3.75 (m, 5H), 3.53-3.40 (m, 2H), 2.37 (d, *J* = 6.87 Hz, 2H), 1.88-1.80 (m, 1H), 1.76-1.66 (m, 5H), 1.60-1.50 (m, 4H), 1.22 (t, *J* = 6.87 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.4, 159.7, 132.1, 127.5, 113.5, 98.8, 87, 79, 72.5, 66.9, 63.2, 62.3, 55.3, 30.7, 28.9, 25.5, 25.2, 19.6, 18.7, 13.9

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{22}H_{30}O_6Na$ 413.1935; found 413.1927.

Compound (61c):



Colorless liquid: Yield =74%

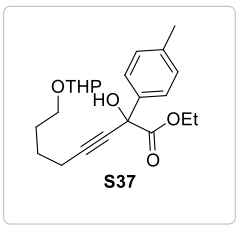
R_f= 0.4 (SiO_2, 40%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.62-7.5 (m, 2H), 6.94-6.82 (m, 2H), 4.13-4.11 (m, 3H), 3.8 (s, 3H), 3.67 (t, *J* = 6.13 Hz, 2H), 2.36 (t, *J* = 6.88 Hz, 2H), 1.78-1.6 (m, 4H), 1.21 (t, *J* = 7.13 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.3, 159.7, 132.03, 127.5, 113.6, 86.9, 79.05, 72.6, 63.2, 62.2, 55.3, 31.7, 24.6, 18.6, 13.8

HRMS (ESI) m/z:$[M+Na]^+$calcd for $C_{17}H_{22}O_5Na$ 329.1359; found 329.1354.

Compound (S37):



Yellowish oil: Yield =55%

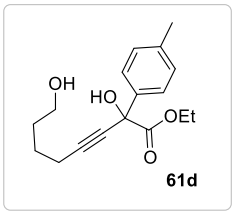
R_f = 0.3 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60-7.48 (m, 2H), 7.21-7.08 (m. 2H), 4.61-4.56 (m, 1H), 4.31-4.14 (m, 3H), 3.90-3.82 (m, 1H), 3.81-3.74 (m, 1H), 3.54-3.47 (m, 1H), 3.46-3.39 (m, 1H), 2.39-2.33 (m, 2H), 2.33 (s, 3H), 1.87-1.79 (m, 1H), 1.76-1.67 (m, 5H), 1.60-1.50 (m, 4H), 1.22 (t, *J* = 6.87Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.3, 138.2, 136.9, 128.9, 126.1, 98.7, 86.9, 78.8, 72.7, 66.8, 63.2, 62.2, 30.7, 28.9, 25.4, 25.2, 21.1, 19.5, 18.6, 13.8

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{22}H_{30}O_5Na$ 397.1985; found 397.1978.

Compound (S22):



Colorless liquid: Yield = 80%

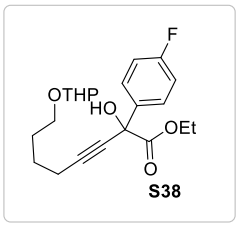
R_f= 0.4 (SiO_2, 40%EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.57 (m, 2H), 7.10-7.97 (m, 2H), 4.34-4.09 (m, 2H), 3.78 (s, 1H), 3.78-3.60 (m, 2H), 2.65 (s, 3H), 2.43-2.31 (m, 2H), 1.79-1.59 (m, 4H), 1.22 (t, *J* = 7.33 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.0, 135.5, 128.2, 128.1, 115.2, 114.9, 87.1, 78.7, 72.3, 63.4, 62.2, 31.7, 24.6, 18.6, 13.8.

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{17}H_{22}O_4Na$ 313.1410; found 313.1402.

Compound (S38):



Yellowish oil: Yield = 52%

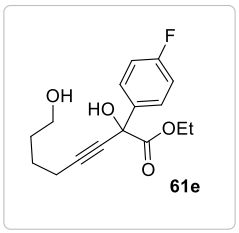
R_f = 0.3 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72-7.57(m, 2H), 7.12-6.97 (m, 2H), 4.63-4.52 (m, 1H), 4.31-4.15 (m, 3H), 3.90-3.73 (m, 2H), 3.54-3.38 (m, 2H), 2.37 (t, *J*= 6.87 Hz, 2H), 1.75-1.67 (m, 5H), 1.61-1.49 (m, 5H), 1.21(t, *J*= 7.33 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.0, 164.0, 135.6, 128.2, 128.1, 115.1, 114.9, 98.8, 87.2, 78.6, 72.3, 66.8, 63.3, 62.3, 30.7, 28.9, 25.4, 25.1, 19.5, 18.6, 13.8.

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{21}H_{27}O_5FNa$ 401.1735; found 401.1722.

Compound (61e):



Colorless liquid: Yield = 73%

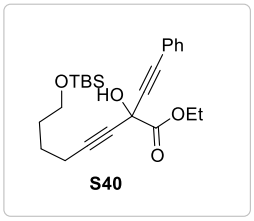
R_f= 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.56 (m, 2H), 7.11-6.97 (m, 2H), 4.39-4.08 (m, 2H), 3.8 (s, H), 3.69 (t, *J*= 5.95 Hz, 2H), 2.65 (s, 3H), 2.37 (m, 2H), 1.73-1.66 (m, 3H), 1.22 (t, *J*= 7.33 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.9, 164.03, 135.5, 128.27, 128.20, 115.17, 114.95, 87.1, 78.7, 72.3, 63.4, 62.2, 31.7, 24.6, 18.5, 13.8.

HRMS (ESI) m/z:$[M+Na]^+$calcd for $C_{16}H_{19}O_4FNa$317.1160; found 317.1152.

Compound (S22):



Yellowish oil: Yield = 49%

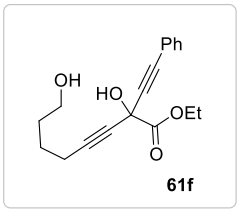
R_f = 0.7 (SiO_2, 10% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.40 (m, 2H), 7.31-7.25 (m, 3H), 4.36 (q, *J* = 7.13Hz, 2H), 3.87 (br. s, 1H), 3.62-3.55 (m, 2H), 2.29-2.22 (m, 2H), 1.60-1.55 (m, 4H), 1.34 (t, *J* = 7.13Hz, 3H), 0.84 (s, 9H), 0.0 (s, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.1, 132.0, 129.0, 128.3, 128.2, 121.7, 85.5, 85.4, 83.7, 64.0, 63.5, 61.4, 31.2, 29.7, 25.9, 25.6, 18.3, 15.2, 13.9, -5.37.

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{24}H_{35}O_4Si$ 415.2299; found 415.2294.

Compound (61f):



Colorless liquid: Yield = 66%

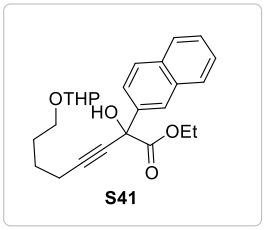
R_f= 0.4 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51-7.44 (m, 2H), 7.35-7.29 (m, 3H), 4.41 (q, *J* = 7.13Hz, 2H), 3.69 (t, *J* = 6.0Hz, 2H), 2.33 (t, *J* = 6.75Hz, 2H), 170-1.64 (m, 4H), 1.39 (t, *J* = 7.13Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.9, 132.0, 129.1, 128.23, 121.5, 85.1, 85.0, 83.7, 64.1, 63.5, 61.5, 30.6, 29.7, 15.4, 13.9

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{18}H_{21}O_4$301.1434; found 301.1421.

Compound (S41):



Yellowish oil: Yield = 45% brsm

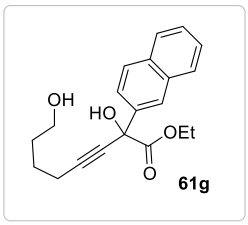
R_f= 0.4 (SiO_2, 30% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27-8.06 (m, 2H), 7.97-7.77 (m, 2H), 7.59-7.36 (m, 3H), 4.61 (s, 1H), 4.30-4.13 (m, 2H), 3.92-3.76 (m, 2H), 3.58-3.34 (m, 2H), 2.52-2.39 (t, *J*= 6.7 Hz, 2H), 1.88-1.67 (m, 6H), 1.62-1.50 (m, 4H), 1.08 (t, *J*= 7.3 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.1, 134.3, 133.9, 130.4, 130.1, 128.9, 127.2, 126.4, 125.7, 124.8, 98.9, 89.6, 78.9, 74.5, 67.0, 63.2, 62.4, 30.8, 29.1, 25.5, 25.3, 19.7, 18.9, 13.8

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{25}H_{30}O_5Na$ 433.1985; found 433.1973.

Compound (61g):



Colorless liquid: Yield =63%

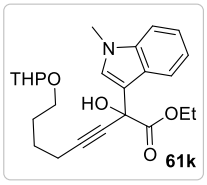
R_f= 0.3 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21-8.1 (m, 2H), 7.91-7.81 (m, 2H), 7.53-7.44 (m, 3H), 4.29-4.11 (m, 3H), 3.75-3.67 (m, 2H), 2.47-2.41 (m, 2H), 1.76-1.7 (m, 4H), 1.09(t, *J*= 7.25 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.1, 134.3, 133.9, 130.3, 130.1, 128.9, 127.1, 126.3, 125.6, 124.7, 89.4, 79.05, 74.5, 63.2, 62.3, 31.8, 24.6, 18.8, 13.7

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{20}H_{22}O_4Na$ 349.1410; found 349.1405.

Compound (61k):



Yellowish oil: Yield = 59%

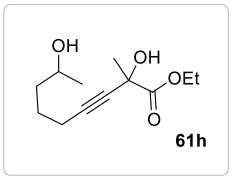
R_f =0.3 (SiO_2, 30% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.77-7.68 (m, 1H), 7.36-7.33 (m, 1H), 7.32-7.28(m, 1H), 7.25-7.20(m, 1H), 7.15-7.09(m, 1H), 4.62-4.56(m, 1H), 4.37-4.14(m, 2H), 3.91-3.84(m, 2H), 3.78(s, 3H), 3.52-3.42(m, 2H), 2.38(t, *J* = 7.0 Hz, 2H), 1.91-1.45 (m, 10H), 1.22(t, *J* = 7.13 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ172.5, 137.7, 128.5, 124.9, 121.9, 120.3, 119.6, 114.2, 109.4, 98.9, 85.6, 79.0, 69.0, 67.0, 63.2, 62.3, 32.9, 30.7, 29.0, 25.5, 25.3, 19.6, 18.7, 14.0

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{24}H_{31}O_5NNa$ 436.2094; found 436.2096.

Compound (61h):



Colorless liquid: Yield = 52%

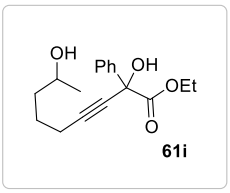
R_f= 0.2 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.28 (q, *J*=6.87 Hz, 2H), 3.87-3.763(m, 1H), 3.45(s, 1H), 2.25 (t, *J*=6.87 Hz, 2H), 1.53(s, 3H), 1.6-1.43(m, 4H), 1.33 (t, *J*=7.63 Hz, 3H), 1.17(d, *J* = 6.87 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz):δ 173.2, 84.7, 80.3, 68.0, 67.7, 62.8, 38.3, 27.5, 24.6, 23.7, 18.7, 14.1

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{12}H_{20}O_4Na$ 251.1254; found 251.1245.

Compound (61i):



Colorless liquid: Yield = 22% (54% brsm)

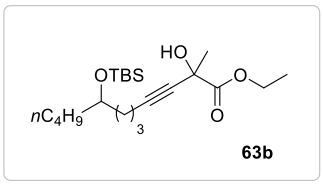
R_f= 0.2 (SiO_2, 40% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.58 (m, 2H), 7.41-7.3 (m, 3H), 4.33-4.08 (m, 3H), 3.89-3.80 (m, 1H), 2.4-2.32 (m, 2H), 1.78-1.48 (m, 4H), 1.29-1.16 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ 172.3, 139.8, 128.5, 128.2, 126.2, 87.0, 78.9, 72.9, 67.6, 67.06, 63.3, 38.3, 30.3, 24.6, 23.6, 18.8, 18.7, 13.8, 13.5

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{17}H_{22}O_4Na$ 313.1410; found 313.1404.

Compound (63b):



Yellowish oil: Yield = 60%

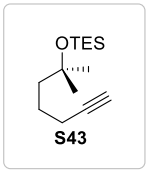
R_f= 0.4 (SiO_2, 10% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.28(q, *J* = 6.87 Hz, 2H), 3.67-3.55 (m, 1H), 2.25-2.16 (m, 2H), 1.64 (s, 3H), 1.56-1.39 (m, 7H), 1.35-1.24(m, 7H), 0.87 (s, 12H), 0.03 (s, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ 173.1, 84.8, 79.9, 71.7, 67.8, 6.6, 36.7, 36.0, 30.4, 27.4, 27.3, 25.8, 24.05, 22.8, 18.8, 18.06, 14.06, 13.9, -4.5;

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{21}H_{40}O_4NaSi$ 407.2588; found 407.2580.

Compound (S43):



Yellow oil: Yield = 56%

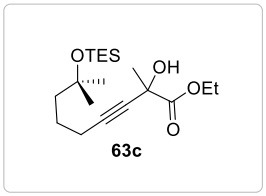
R_f= 0.8 (SiO_2, 10% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):δ 2.22-2.15 (m, 2H), 1.96-1.91 (m, 1H), 1.62-1.49 (m, 4H), 1.21 (s, 6H), 0.96-0.92 (m, 9H), 0.61-0.54 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ 84.8, 73.1, 68.1, 44.2, 29.9, 23.6, 18.9, 7.1, 6.8, 6.4

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{14}H_{29}OSi$ 241.1982; found 241.1983.

Compound (63c):



Yellowish oil: Yield =73%

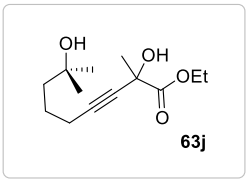
R_f= 0.5 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):δ 4.30 (q, *J* = 7.13 Hz, 2H), 3.42(s, 1H), 2.20(d,*J* = 6.88 Hz, 2H), 1.66 (s, 3H), 1.59-1.47 (m, 4H), 1.34 (t, *J* = 7.13 Hz, 3H), 1.20 (s, 6H), 0.94 (t. *J* = 8.0 Hz, 9H), 0.57 (q, *J* = 7.75 Hz, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ173.2, 85.1, 79.9, 73.1, 67.9, 62.7, 44.2, 29.9, 27.3, 23.4, 19.1, 14.0, 7.12, 6.7

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{19}H_{36}O_4NaSi$ 379.2275; found 379.2270.

Compound (63j):



Colorless liquid: Yield =66%

R_f = 0.7 (SiO_2, 20% EtOAc/hexanes)

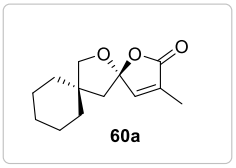
^{1}H NMR ($CDCl_3$, 400 MHz):δ 4.3(q, *J*= 7.13Hz, 2H), 2.23(t, *J* = 6.63 Hz, 2H), 1.66 (s, 3H), 1.62-1.52 (m, 4H), 1.34 (t, *J* = 7.13Hz, 3H), 1.22 (s, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.1, 84.7, 80.2, 76.7, 70.8, 67.9, 62.7, 42.9, 29.3, 27.4, 23.4, 19.1, 14.04

HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{13}H_{22}O_4Na$ 265.1410; found 265.1411.

Synthesis of [5,5] - Unsaturated Oxa-spirolctones from Propargylic Diol Esters:

Compound (60aa):



Colorless liquid: Yield = 85%

R_f = 0.7 (SiO_2, 20% EtOAc/hexanes)

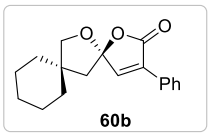
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.69-6.67(m, 1H), 3.95(d, *J* = 8.39 Hz, 1H), 3.86 (d, *J* = 8.39 Hz, 1H), 2.12 (d, *J* = 14.5 Hz, 1H), 2.01 (d, *J* = 14.5 Hz, 1H), 1.91 (s, 3H), 1.72-1.64 (m, 2H), 1.53-1.38 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.6, 145.1, 132.5, 113.2, 80.4, 47.1, 43.6, 37.4, 35.5, 25.6, 23.8, 23.7, 10.4.

FTIR (cm^{-1}) 2928, 2857, 1767, 1669, 1447, 1329, 1123, 1008, 972, 870, 763;

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{13}H_{19}O_3$223.1329; found 223.1333.

Compound (60b):



White solid: Yield = 81%

R_f = 0.7 (SiO_2, 20% EtOAc/hexanes)

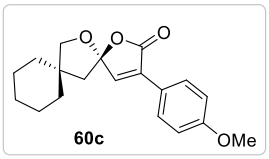
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.75 (m, 2H), 7.5-7.37 (m, 3H), 7.17 (s, 1H), 4.04(d, *J*= 8.46 Hz, 1H), 3.93 (d, *J*=8.46 Hz, 1H), 2.24 (d, *J*= 13.89 Hz, 1H), 2.13(d, *J*= 13.77 Hz, 1H), 1.81-1.68 (m, 2H), 1.64-1.39 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.3, 143.7, 133.6, 129.7, 129, 128.7, 127.5, 112.4, 80.5, 47.4, 43.8, 37.4, 35.5, 25.6, 23.9, 23.8.

FTIR (cm^{-1}) 3023, 2928, 2858, 1761, 1647, 1451, 1216, 1123, 1037, 944, 847, 762, 671.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{21}O_3$285.1485; found 285.1483.

Compound (60c):



White solid: Yield = 83%

R_f= 0.6 (SiO_2, 20% EtOAc/hexanes)

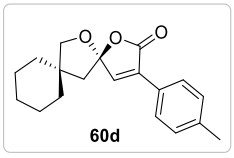
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.75 (m, 2H), 7.06 (s, 1H), 7.04-6.92 (m, 2H), 4.04 (d, *J*= 8.46 Hz, 1H), 3.93 (d, *J*=8.46 Hz, 1H), 3.86 (s, 3H), 2.24 (d, *J*=13.89 Hz, 1H), 2.13(d, *J*= 13.77 Hz, 1H), 1.81-1.68 (m, 2H), 1.64-1.39 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.6, 160.7, 141.3, 132.9, 129.0, 121.5, 114.1, 112.4, 80.5, 55.4, 47.4, 43.8, 37.4, 35.6, 25.6, 23.87, 23.76

FTIR (cm^{-1}) 3022, 2927, 2856, 1761, 1610, 1512, 1455, 1252, 1216, 1171, 1124, 1033, 909, 838, 761, 666

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{19}H_{23}O_4$315.1591; found 315.1582.

Compound (60d):



White solid: Yield = 79%

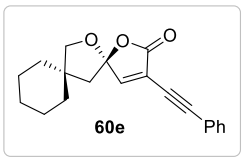
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.70 (m, 2H), 7.23-7.18 (m, 2H), 7.11 (s, 1H), 4.0 (d, *J*= 8.46 Hz, 1H), 3.91 (d, *J*=8.46 Hz, 1H), 2.36 (s, 3H), 2.21 (d, *J*= 13.89 Hz, 1H), 2.12 (d, *J*= 13.77 Hz, 1H), 1.74-1.69 (m, 2H), 1.56-1.42 (m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.4, 142.6, 139.8, 133.3, 129.3, 127.3, 126.0, 112.3, 80.4, 47.3, 43.7, 37.3, 35.5, 25.5, 23.8, 23.7, 21.3

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{19}H_{23}O_3$ 299.1642; found 299.1643.

Compound (60e):



Viscous liquid: Yield = 82%

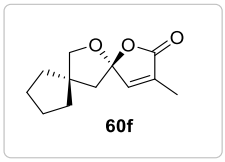
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57-7.52(m, 2H), 7.4-7.34(m, 3H), 7.14-7.09(m, 1H), 4.01(d, *J*= 8.39Hz, 1H), 3.92(d, *J* = 8.39Hz, 1H), 2.21(d, *J* = 13.73Hz, 1H), 2.1(d, *J* = 13.73Hz, 1H), 1.73-1.68(m, 2H), 1.53-1.44(m, 8H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.3, 150.4, 133.8, 132.1, 129.6, 128.4, 121.5, 120.1, 113.8, 97.9, 80.8, 78.1, 43.8, 37.3, 35.5, 25.5, 23.9, 23.7

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_3$ 309.1485; found 309.1483.

Compound (S22):



White solid: Yield = 78%

R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

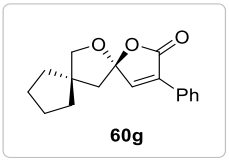
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.71(s, 1H), 4.01(d, *J* = 8.4 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 2.18 (s, 2H), 1.92 (s, 3H), 1.86-1.81 (m, 2H), 1.7-1.58 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.6, 145.1, 132.5, 113.3, 81.1, 50.3, 47.4, 38.01, 37.2, 24.6, 24.4, 10.4

FTIR (cm^{-1}) 3020, 2931, 2866, 1764, 1659, 1447, 1397, 1330, 1222, 1115, 1006, 758, 672

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{12}H_{17}O_3$209.1172; found 209.1176.

Compound (60g):



White solid: Yield = 86 %

R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

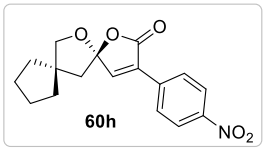
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88-7.8 (m, 2H), 7.46-7.37 (m, 3H), 7.19 (s, 1H), 4.08 (d, *J* = 8.1 Hz, 1H), 3.92 (d, *J* = 8.39 Hz, 1H), 2.4-2.2 (m, 2.37-2.25 (m, 2H), 1.93-1.84 (m, 2H), 1.79-1.62 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, 143.7, 133.6, 129.7, 129.0, 128.7, 127.6, 112.4, 81.3, 50.5, 47.7, 38.01, 37.2, 24.7, 24.4

FTIR (cm^{-1}) 3023, 2955, 2403, 1763, 1647, 1439, 1334, 1216, 1116, 1034, 942, 852, 760, 669.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{19}O_3$271.1329; found 271.1333.

Compound (60h):



Yellowish solid: Yield = 73%

R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

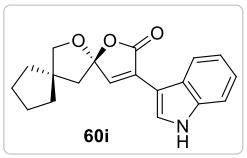
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 9.2 Hz, 2H), 7.39 (s, 1H), 4.11(d, *J* = 8.5 Hz, 1H), 3.94 (d, *J* = 7.9 Hz, 1H), 2.39-2.27 (m, 2H), 1.95-1.83 (m, 2H), 1.81-1.62 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.3, 148.3, 147.0, 135.0, 131.7, 128.5, 123.9, 112.6, 81.5, 50.6, 47.6, 37.9, 37.1, 24.6, 24.4

FTIR (cm^{-1}) 3023, 2949, 1756, 1650, 1521, 1350, 1215, 1350, 1215, 1118, 1047, 760

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{17}H_{18}O_5N$ 316.1179; found 316.1187.

Compound (60i):



Yellowish solid: Yield =71%

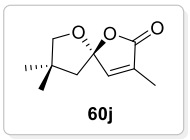
R_f = 0.3 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ δ8.5(br. s, 1H), 8.32-8.21 (m, 1H), 7.85-7.73 (m, 1H), 7.50-7.40 (m, 1H), 7.3-7.2 (m, 2H), 7.18 (s, 1H), 4.09 (d, *J* = 8.39Hz, 1H), 3.93(d, *J* = 7.63Hz, 1H), 2.34 (dd, *J* = 12.97, 2.29Hz, 2H), 1.94-1.84 (m, 2H), 1.8-1.65 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.8, 136.4, 136.2, 128.0, 127.2, 125.6, 123.0, 121.1, 119.7, 114.0, 111.8, 105.9, 81.1, 64.5, 50.4, 48.0, 38.2, 37.3, 24.7, 24.4.

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{19}H_{20}O_3N$310.1438; found 310.1438.

Compound (60j):



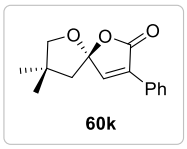
Viscous liquid: Yield = 86%

TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.63 (s, 1H), 3.8 (d, *J*=8.39Hz, 1H), 3.66(d, *J*=8.39Hz, 1H), 1.99(s, 2H), 1.81(s, 3H), 1.18(s, 3H), 1.09(s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.3, 145.2, 131.8, 113.4, 81.8, 48.8, 39.3, 27.5, 25.9, 10.1**HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{10}H_{15}O_3$183.1016; found 183.1015.

Compound (60k):



White solid: Yield = 84%

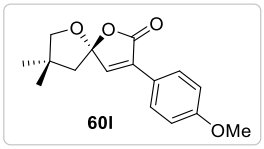
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86-7.77 (m, 2H), 7.43-7.33(m, 3H), 7.16 (s, 1H), 3.96 (d, *J*=8.39Hz, 1H), 3.8(d, *J*=8.39Hz, 1H), 2.19(s, 2H), 1.31(s, 3H), 1.22 (s, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.2, 143.8, 133.3, 129.7, 128.9, 128.6, 127.5, 112.7, 82.2, 49.4, 39.7, 27.8, 26.1

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{15}H_{17}O_3$ 245.1172; found 245.1172.

Compound (60l):



White solid: Yield = 89%

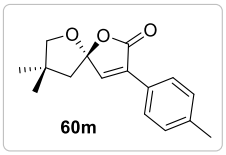
TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89-7.76 (m, 2H), 7.06 (s, 1H), 6.97-6.85 (m, 2H), 3.97 (d, *J*= 8.24 Hz, 1H), 3.84 (s, 3H), 3.81 (d, *J*= 8.24 Hz, 1H), 2.23- 2.14 (m, 2H), 1.32 (s, 3H), 1.23 (s, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.5, 160.7, 141.4, 132.7, 128.9, 121.4, 114.0, 112.7, 82.1, 55.3, 49.5, 39.7, 27.9, 26.2

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{16}H_{19}O_4$275.1278; found 275.1274.

Compound (60m):



White solid: Yield =80%

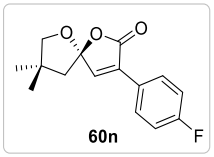
R_f= 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.69 (m, 2H), 7.2-7.15(m, 2H), 7.11 (s, 1H), 3.93(d, *J*=8.39 Hz, 1H), 3.78(d, *J*=8.39Hz, 1H), 2.34(s, 3H), 2.15(s, 2H), 1.29(s, 3H), 1.19 (s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.3, 142.8, 139.7, 132.9, 129.2, 127.2, 125.9, 112.6, 82.0, 49.2, 39.6, 27.6, 26.0, 21.2

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{16}H_{19}O_3$259.1329; found 259.1328.

Compound (60n):



White solid: Yield = 77%

R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

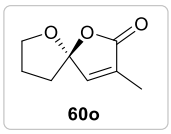
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92-7.77 (m, 2H), 7.16-7.05 (m, 3H), 3.98 (d, *J*= 8.39 Hz, 1H), 3.82 (d, *J*= 8.39 Hz, 1H), 2.20 (s, 2H), 1.33 (s, 3H), 1.23 (s, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.1, 164.7, 162.3, 143.3, 132.3, 129.6, 129.5, 125.0, 115.9, 115.6, 112.7, 82.2, 49.4, 39.7, 27.8, 26.1

^{19}F NMR ($CDCl_3$, 376 MHz): δ 110.4.

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{15}H_{16}FO_3$ 263.1078; found 263.1082.

Compound (60c):



Yellowish oil: Yield = 71 %

R_f = 0.3 (SiO_2, 20% EtOAc/hexanes)

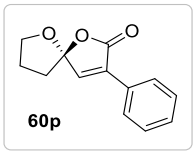
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.74-6.67 (m, 1H), 4.24-4.17 (m, 1H), 4.08-4.01(m, 1H), 2.35-2.08 (m, 4H), 1.91 (s, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.3, 144.3, 133.2, 112.6, 70.2, 35.2, 24.1, 10.4

FTIR (cm^{-1}) 3023, 2928, 2404, 1729, 1655, 1452, 1263, 1216, 1050, 844, 760, 670

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_8H_{11}O_3$155.0703; found 155.1313.

Compound (60p):



Yellow oil: Yield = 75%

R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

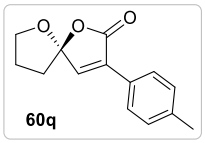
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89-7.79 (m, 2H), 7.44-7.39 (m, 3H), 7.20 (s, 1H), 4.34-4.24 (m, 1H), 4.17-4.07(m, 1H), 2.40-2.11 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.1, 143.0, 134.3, 129.7, 128.9, 128.6, 127.4, 111.8, 70.5, 35.6, 24.2

FTIR (cm^{-1}) 3074, 2976, 2899, 1762, 1643, 1590, 1491, 1449, 1340, 1231, 1175, 1094, 1017, 955, 932, 876, 756, 695, 658

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{13}H_{13}O_3$217.0859; found 217.0864.

Compound (60q):



Yellow solid: Yield = 78%

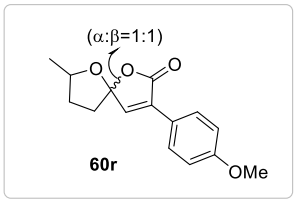
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75(d, J = 8.13Hz, 2H), 7.22(d, J = 8Hz, 2H), 7.15 (s, 1H), 4.33-4.24 (m, 1H), 4.16-4.07 (m, 1H), 2.38 (s, 3H), 2.36-2.15 (m, 4H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, 141.9, 140, 134.2, 129.4, 127.4, 126.2, 111.8, 70.4, 35.7, 24.3, 21.4

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{14}H_{15}O_3$231.1016; found 231.1019.

Compound (60r):



60r

Inseparable mixture of diastereomers (*dr*, 1:1): Yield =80%

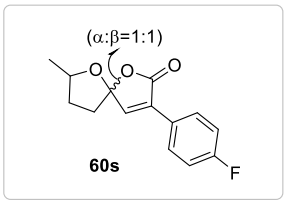
^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.86-7.7 (m,, 2H), 7.06 (d, *J* = 14.38 Hz, 1H), 6.96-6.89 (m, 2H), 4.67-4.53 (m, 0.44H), 4.5-4.39(m, 0.47H), 3.84 (s, 3H), 2.49-2.22 (m, 3H), 2.05-1.7 (m, 1H), 1.43 (d, *J* = 6.13 Hz, 1.5H), 1.33(d, *J* = 6.25 Hz, 1.5H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 169.6, 160.7, 140.9, 140.8, 133.7, 133.4, 129.0, 121.7, 121.6, 114.1, 112.0, 111.9, 79.7, 78.1, 55.3, 37.3, 35, 32.2, 31.4, 22, 21.2

FTIR (cm^{-1}) 3020, 2926, 2856, 1759, 1008, 1511, 1456, 1378, 1337, 1222, 1178, 1101, 939, 837, 758, 668

HRMS (ESI) m/z:[M+H]$^+$calcd for $C_{15}H_{17}O_4$261.1121; found 261.1125.

Compound (60s):



60s

Inseparable mixture of diastereomers (*dr*, 1:1): Yield = 74%

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.91-7.79 (m, 2H), 7.17-7.06 (m, 3H), 4.66-4.55 (m, 0.42H), 4.5-4.4 (m, 0.41H), 2.58-2.21 (m, 3H), 2.08-1.86 (m, 1H), 1.81-1.7(m, 0.58H), 1.43 (d, *J* = 6.13 Hz, 1.44H), 1.33 (d, *J* = 6.25 Hz, 1.56H)

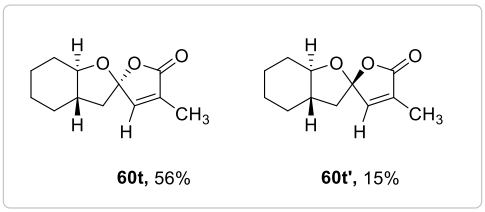
^{13}C NMR (CDCl$_3$, 101 MHz): δ 169.2, 164.8, 142.9, 142.8, 133.3, 133.0, 129.6, 129.5, 125.2, 115.9, 115.7, 112.0, 111.9, 79.9, 78.3, 43.9, 37.3, 35.0, 32.1, 31.4,22.0, 21.1.

^{19}F NMR (CDCl$_3$, 376 MHz): δ 110.4.

HRMS (ESI) m/z:[M+Na]$^+$ calcd for $C_{14}H_{13}O_3FNa$271.0741; found 271.0739.

Compound (60t & 60t'):

Two separable diastereomers (**60**t and **60t'**) in 8:2 ratio (0.023 g, 56% and 0.006 g, 15 %) : white solid.



60t, 56% **60t'**, 15%

R_f= 0.6 (SiO_2, 20% EtOAc/hexanes).

Relative stereochemistry was assigned based on NOE analysis.

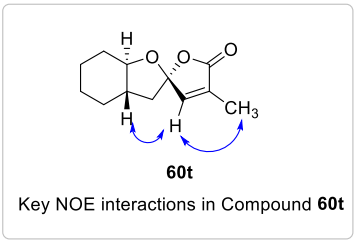
Major diastereomer (**60t**): **^{1}H NMR (CDCl$_3$, 400 MHz):**δ6.72 (s, 1H), 3.66-3.53 (m, 1H), 2.35 (dd, *J*= 13.4, 7.9 Hz, 1H), 2.2-2.06 (m, 2H), 1.99-1.8 (m, 5H), 1.81-1.74 (m, 1H), 1.62-1.53

(m, 1H), 1.43-1.21 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ171.9, 145.8, 131.2, 111.8, 84.7, 46.3, 39.8, 30.5, 28.5, 25.5, 24.0, 10.3

FTIR (cm^{-1}) 3017, 2940, 2841, 1759, 1643, 1456, 1216, 1023, 927, 846, 760, 668

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{12}H_{17}O_3$209.1172; found 209.1176.



60t

Key NOE interactions in Compound **60t**

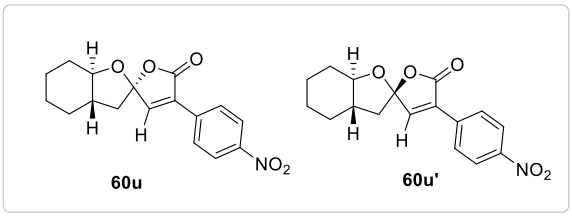
Minor diastereomer (**60t'**): **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 6.71(s, 1H), 3.39 (td, *J*= 10.7, 3.8 Hz, 1H), 2.17-2.11 (m, 2H), 2.1-1.94 (m, 1H), 1.93-1.8 (m, 5H), 1.78-1.69 (m, 1H), 1.57-1.42 (m, 1H), 1.4.-1.21 (m, 3H), 1.19-1.08 (m, 1H)

^{13}C NMR ($CDCl_3$, 126 MHz):δ171.3, 145.9, 132.3, 111.4, 86.7, 43.7, 41.5, 31.3, 28.5, 25.5, 24.2, 10.4

FTIR (cm^{-1}) 2926, 2858, 1767, 1662, 1454, 1375, 1312, 1253, 1158, 1113, 1056, 973, 928, 863, 759

HRMS (ESI) m/z:$[M+H]^+$ calcd for $C_{12}H_{17}O_3$209.1172; found 209.1176.

Compound (60u & 60u'):



60u **60u'**

Two separable diastereomers (**60u** and **60u'**) in 7:3 ratio (yield: 0.023 g, 52% and 0.01g, 23% isolated yield): White solid.

R_f= 0.6 (SiO_2, 20% EtOAc/hexanes)

Major diastereomer(60u): **^{1}H NMR ($CDCl_3$, 400 MHz):**δ 8.32-8.22 (m, 2H), 8.09-7.97 7.38 (s, 1H), 3.69 (td, *J* = 3.75, 10.63 Hz, 1H), 2.50 (dd, *J* = 7.5, 13.63Hz 1H), 2.28-2.17 (m, 2H), 2.04-1.88(m, 2H), 1.85-1.76 (m, 1H), 1.74-1.61 (m, 1H), 1.49-1.28 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.6, 148.3, 147.4, 135.0, 130.6, 128.5, 123.9, 111.1, 85.3,

46.5, 40.1, 30.6, 28.5, 25.4, 24.0

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{17}H_{18}O_5N$316.1179; found 316.1187.

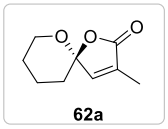
Minor diastereomer (60u'): **^{1}H NMR ($CDCl_3$, 400 MHz):**δ 8.34-8.21 (m, 2H), 8.10-7.98 (m, 2H), 7.42 (s, 1H), 3.55-3.40 (m, 1H), 2.36-2.25 (m, 1H), 2.24-2.15 (m, 1H), 2.11-1.98 (m, 3H), 1.97-1.88 (m, 1H), 1.85-1.76 (m, 1H), 1.62-1.54 (m, 1H), 1.37-1.21 (m, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ 168.1, 148.3, 147.9, 135.0, 131.7, 128.4, 123.9, 110.8, 87.3, 43.8, 41.8, 31.3, 28.5, 24.4, 24.2

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{17}H_{18}O_5N$ 316.1179; found 316.1178.

Synthesis of [6,5] -Unsaturated Oxa-spirolactones from Propargylic Diol Esters:

Compound (62a):


62a

Colorless liquid: Yield =70%

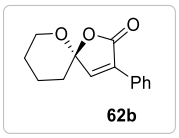
R_f= 0.2 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81-6.67(m, 1H), 4.02 (td, *J* = 3.81, 11.4Hz, 1H), 3.95-3.84 (m, 1H), 2-1.93 (m, 1H), 1.91 (s, 3H), 1.87-1.79 (m, 2H), 1.73-1.66 (m, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz):δ 171.9, 147.2, 131.9, 104.8, 65.0, 32.3, 24.1, 19.1, 10.5

HRMS (ESI) m/z:$[M+H]^+$ calcd for $C_9H_{13}O_3$169.1459; found 169.0869.

Compound (62b):



62b

Viscous liquid: Yield = 75%

R_f = 0.40 (SiO_2, 20% EtOAc/hexanes)

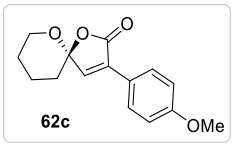
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90-7.77 (m, 2H), 7.47-7.35 (m, 3H), 7.22 (s, 1H), 4.09 (td, *J* = 3.05, 11.44 Hz, 1H), 4.0-3.90 (m, 1H), 2.05-1.69 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.6, 145.6, 133.2, 129.7, 129.1, 128.7, 127.5, 104.0, 65.0, 32.5, 24.1, 19.1

FTIR (cm^{-1}) 3074, 3022, 2946, 1760, 1645, 1484, 1448, 1367, 1305, 1261, 1222, 1112, 1051, 1006, 947, 927, 850, 754, 691

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{14}H_{15}O_3$231.1016; found 231.1019.

Compound (62c):



Viscous liquid: Yield = 70%

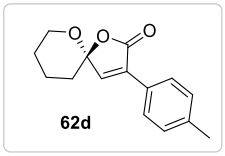
R_f = 0.40 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81(d, *J*= 9.16 Hz, 2H), 7.11 (s, 1H), 6.93 (d, *J*= 9.16 Hz, 2H), 4.08 (td, *J*= 3.21, 11.45 Hz, 1H), 3.97-3.91 (m, 1H), 3.84 (s, 3H), 2.05-1.73 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.9, 160.7, 143.3, 132.4, 128.9, 121.6, 114.0, 103.9, 65.0, 55.3, 32.5, 24.1, 19.1

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{15}H_{17}O_4$261.1121; found 261.1125.

Compound (62d):



Viscous liquid: Yield = 81%

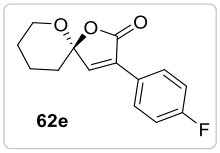
R_f = 0.40 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.68, (m, 2H), 7.22-7.17 (m, 2H), 7.15(s, 1H), 4.06 (td, *J*= 3.81, 11.44 Hz, 1H), 3.96-3.89 (m, 1H), 2.35 (s, 3H), 2.05-1.62 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.7, 144.6, 139.8, 132.8, 129.3, 127.3, 126.1, 103.9, 64.9, 32.4, 24.1, 21.3, 19.1

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{15}H_{17}O_3$245.1172; found 245.1170.

Compound (62e):



Viscous liquid: Yield = 69%

R_f = 0.40 (SiO_2, 20% EtOAc/hexanes)

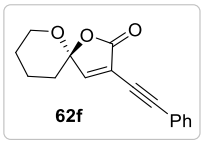
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.74 (m, 2H), 7.18 (s, 1H), 7.14-7.05 (m, 2H), 4.08 (td, *J* = 3.66, 11.45 Hz, 1H), 4.01-3.88 (m, 1H), 2.09-1.71 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.5, 163.7 (*J* = 250.24 Hz), 145.1 (*J* = 2.29 Hz), 132.1, 129.5 (*J* = 8.39 Hz), 125.2, 115.8 (*J* = 21.36 Hz), 104.0, 65.0, 32.4, 24.1, 19.1

19F NMR ($CDCl_3$, 376 MHz): δ 110.5.

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{14}H_{14}O_3F$ 249.0921; found 249. 0919.

Compound (62f):



Viscous liquid: Yield = 76%

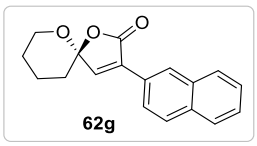
R_f = 0.40 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59-7.50 (m, 2H), 7.41-7.33 (m, 3H), 7.16 (s, 1H), 4.29 (td, *J*= 3.81, 8.39 Hz, 1H), 4.16-4.08 (m, 1H), 2.39-2.14 (m, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.2, 149.6, 132.1, 129.6, 128.4, 121.5, 120.8, 113.3, 97.9, 78.1, 70.8, 35.8, 31.9, 24.2, 22.7, 14.1

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{16}H_{15}O_3$255.1016; found 255.1006.

Compound (62g):



White solid: Yield = 83%

R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

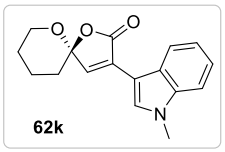
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89-7.81(m, 3H), 7.58-7.51(m, 1H), 7.5-7.37(m, 3H), 7.2(s, 1H), 4.17-4.02(m, 1H), 4.01-3.87(m, 1H), 2.06-1.66(m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.2, 150.4, 133.7, 133.6, 129.8, 128.7, 127.8, 126.8, 126.1, 125.1, 124.5, 104.8, 65.1, 32.6, 24.2, 19.1

FTIR (cm^{-1}) 3019, 2944, 1764, 1650, 1592, 1508, 1448, 1367, 1298, 1225, 1130, 1051, 998, 921, 862, 760, 664

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{18}H_{17}O_3$281.1172; found 281.1178.

Compound (62k):



Viscous liquid: Yield = 75%

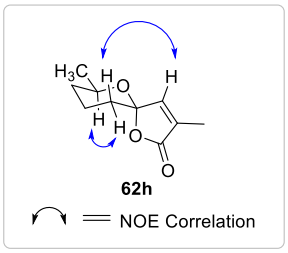
R_f = 0.40 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17(s, 1H), 7.8 (d, *J* = 8.1 Hz, 1H), 7.4 (d, *J* = 8.37 Hz, 1H), 7.36-7.31(m, 1H), 7.3-7.24(m, 1H),7.2 (s, 1H), 4.18-4.08 (m, 1H), 4.03-3.96 (m, 1H), 3.86 (s, 3H), 2.1-1.98 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.69 (m, 2H

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.2, 137.8, 131.6, 126.3, 122.6, 120.8, 119.8, 110.0, 105.4, 65.1, 33.2, 33.02, 24.3, 19.4

HRMS (ESI) m/z:$[M+H]^+$ calcd for $C_{17}H_{18}O_3N$284.1281; found 284.1281.

Compound (62h):



Colorless liquid: Yield =88%

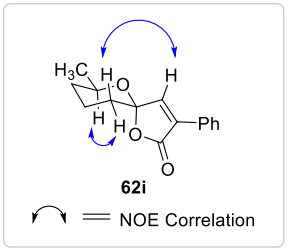
R_f= 0.6 (SiO_2, 20% EtOAc/hexanes

^{1}H NMR ($CDCl_3$, 500 MHz):δ 6.76 (q, *J* = 1.63 Hz, 1H), 4.15-4.06 (m, 1H), 2.09-1.94 (m, 1H), 1.92 (d, *J* = 1.63 Hz, 3H), 1.85-1.78 (m, 1H), 1.77-1.68 (m, 3H), 1.22 (d, *J* = 6.13 Hz, 1H), 1.19(d, *J* = 6.25 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.1, 147.5, 131.9, 105.4, 70.9, 31.8, 31.6, 29.7, 25.4, 21.7, 19.4, 10.5

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{10}H_{15}O_3$183.1016; found 183.1015.

Compound (62i):



Colorless liquid: Yield =84%

R_f= 0.6 (SiO_2, 20% EtOAc/hexanes)

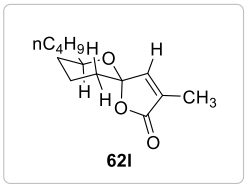
Relative stereochemistry was assigned based on NOE analysis.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 - 7.81 (m, 2H), 7.44 - 7.38 (m, 3H), 7.23 (s, 1H), 4.21 - 4.13 (m, 1H), 2.08 - 1.99 (m, 1H), 1.90 - 1.82 (m, 2H), 1.80 - 1.74 (m, 2H), 1.42 - 1.33 (m, 1H), 1.22 (d, *J*= 6.49 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.6, 145.8, 132.9, 129.6, 129.1, 128.6, 127.4, 104.5, 70.9, 32.0, 31.5, 21.7, 19.4

HRMS (ESI) m/z:$[M+H]^+$calcd for $C_{15}H_{17}O_3$245.1172; found 275.1174.

Compound (62l):



Colorless liquid: Yield =78%

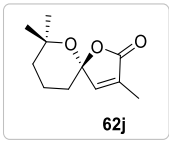
R_f = 0.6 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.75 (q, *J* = 1.63 Hz, 1H), 3.99-3.87 (m, 1H), 2.01-1.92 (m, 1H), 1.91(d, *J* = 1.63 Hz, 3H), 1.85-1.67 (m, 4H), 1.41-1.18 (m, 7H), 0.91-0.85 (m, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.2, 147.6, 131.7, 105.5, 74.7, 35.7, 32.2, 29.7, 27.3, 22.7, 19.5, 14.0, 10.5

HRMS (ESI) m/z:$[M+Na]^+$calcd for $C_{13}H_{20}O_3Na$ 247.1305; found 247.1304.

Compound (62j):



Colorless liquid: Yield =50%

R_f = 0.7 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.72-6.69 (m, 1H), 1.90 (s, 3H), 1.72-1.68 (m, 3H), 1.39-1.38 (m, 3H), 1.25 (m, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.2, 148.3, 131.7, 105.6, 75.4, 35.1, 32.1, 31.8, 26.4, 16.1, 10.5

HRMS (ESI) m/z: $[M+H]^+$calcd for $C_{11}H_{16}O_3$197.1172; found 197.1172.

3.2.8 References

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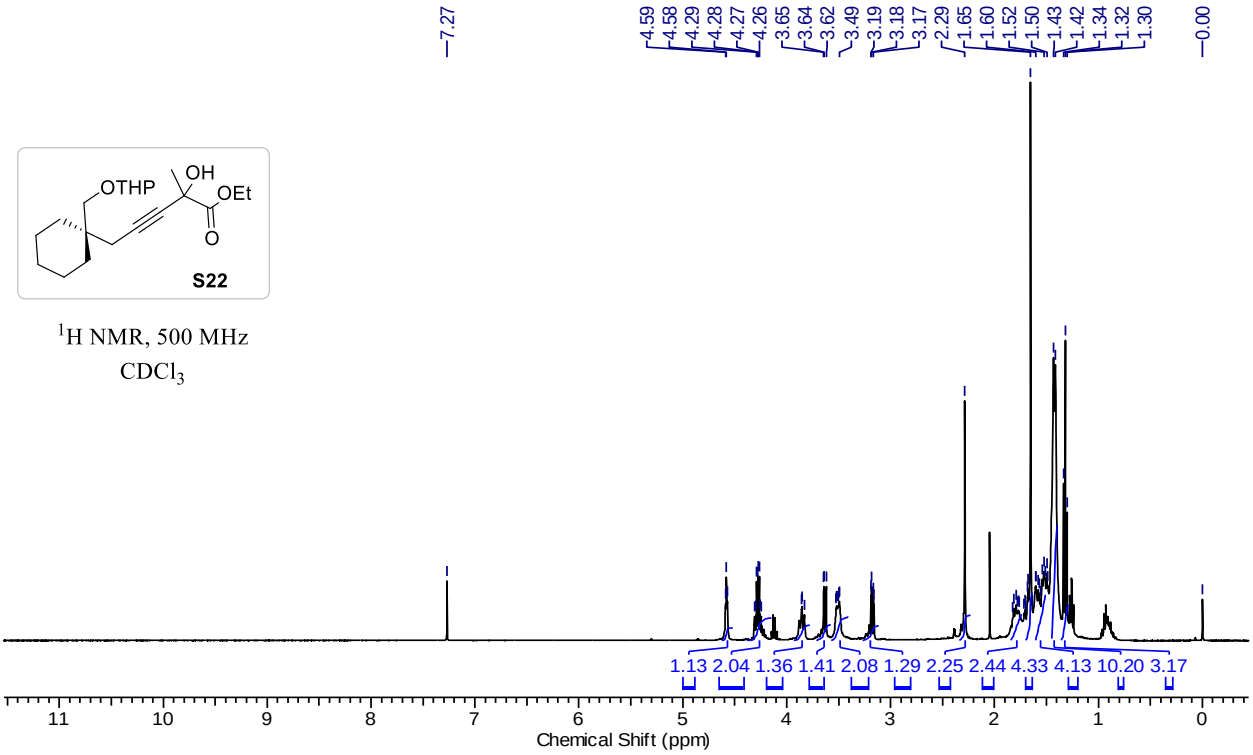
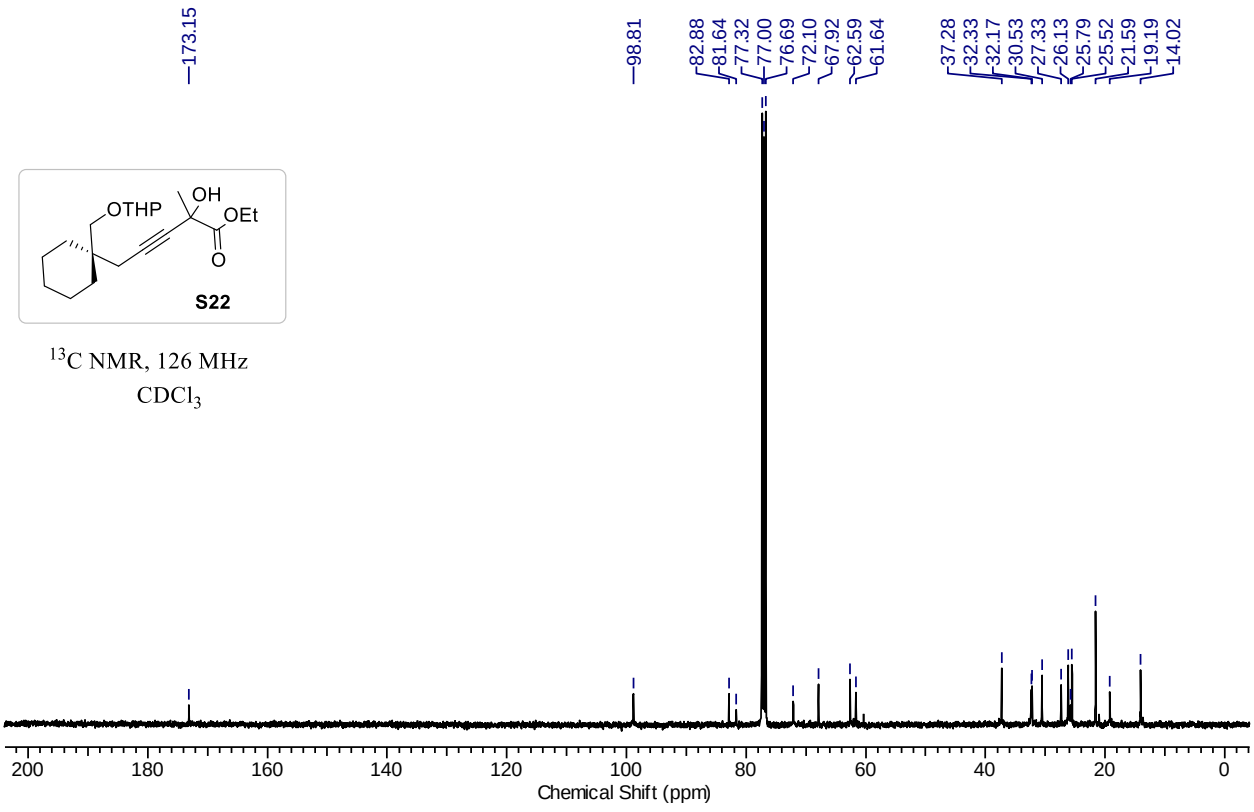
Ethyl 2-hydroxy-2-methyl-5-(1-(((tetrahydro-2*H*-pyran-2-yl) oxy) methyl) cyclohexyl) pent-3-ynoate (S22):

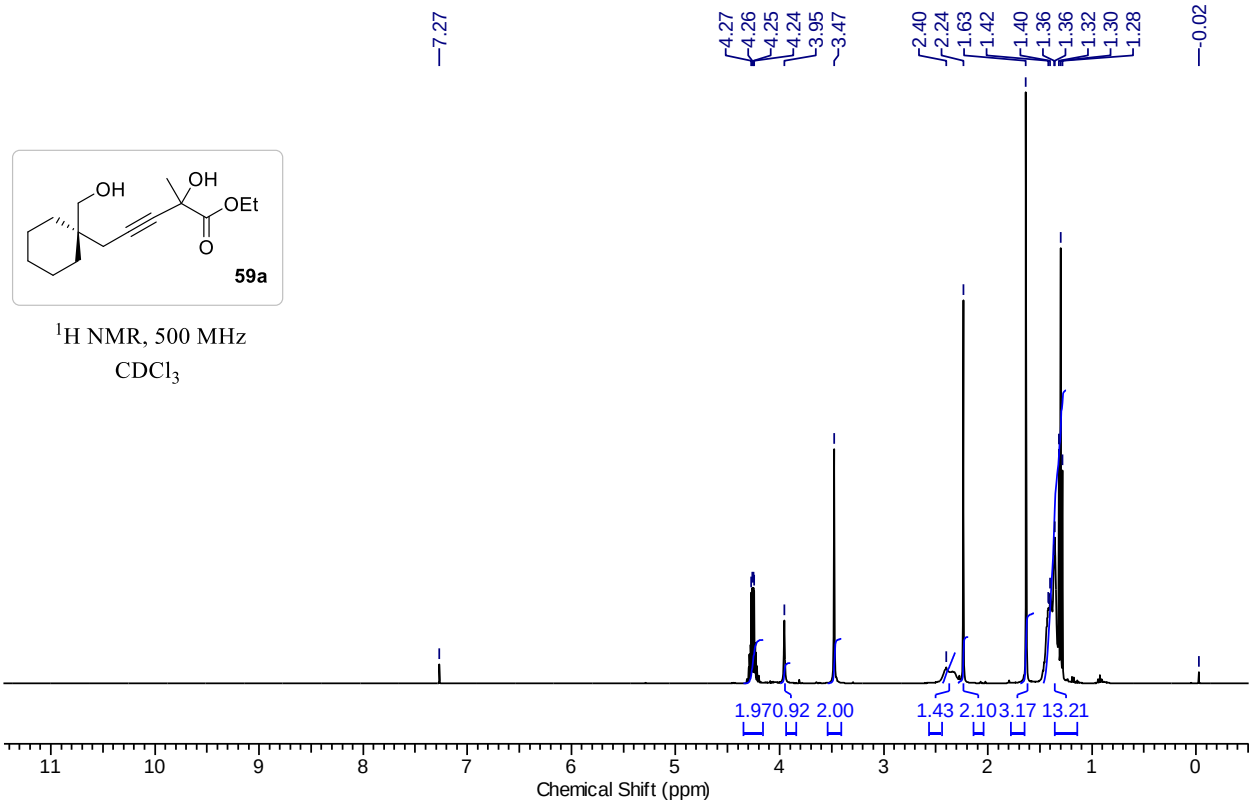


^{1}H NMR, 500 MHz
$CDCl_3$

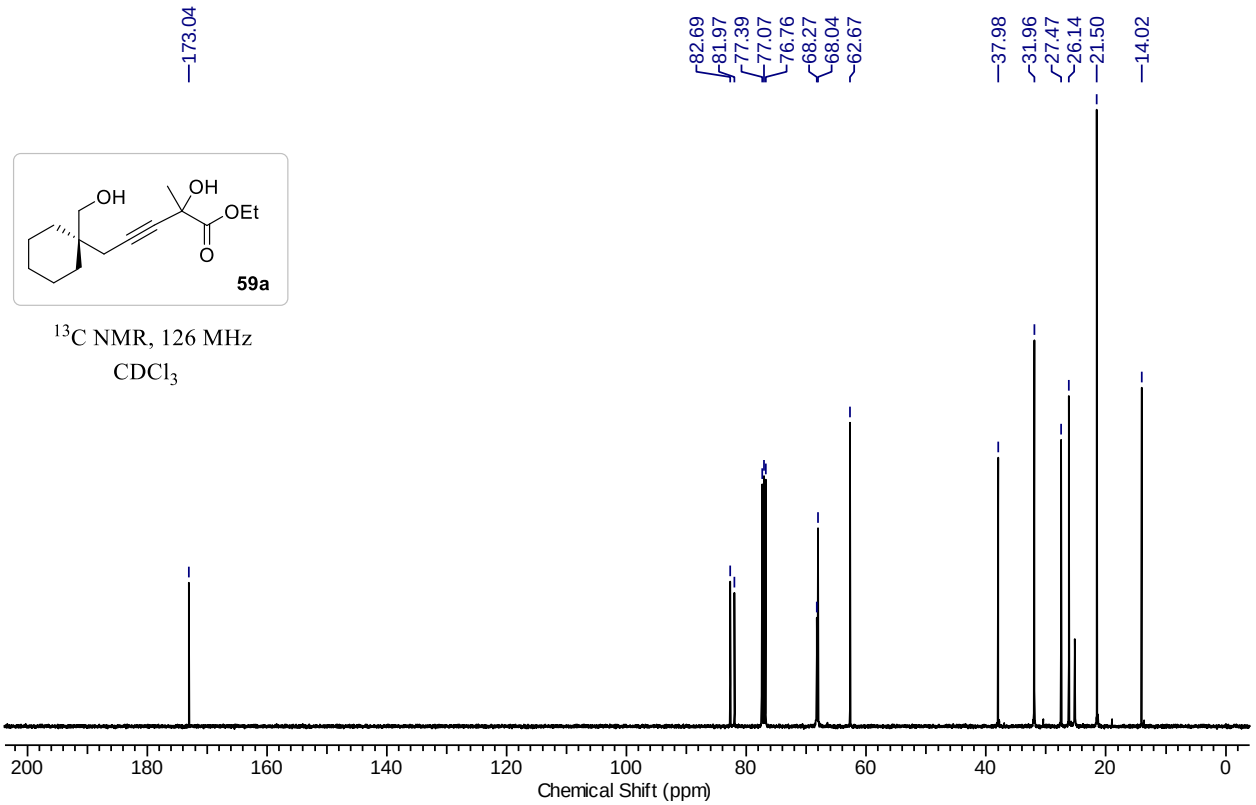


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclohexyl)-2-methylpent-3-ynoate (59a):

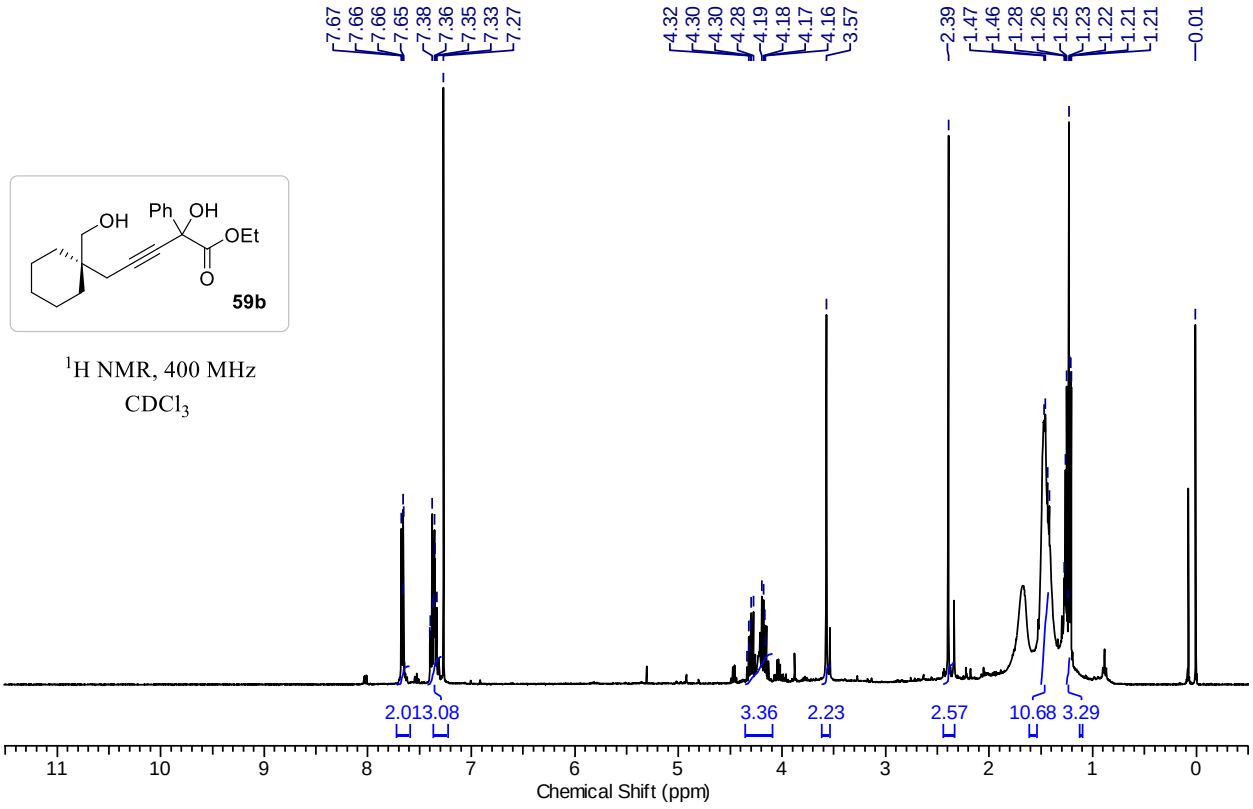


^{1}H NMR, 500 MHz
$CDCl_3$

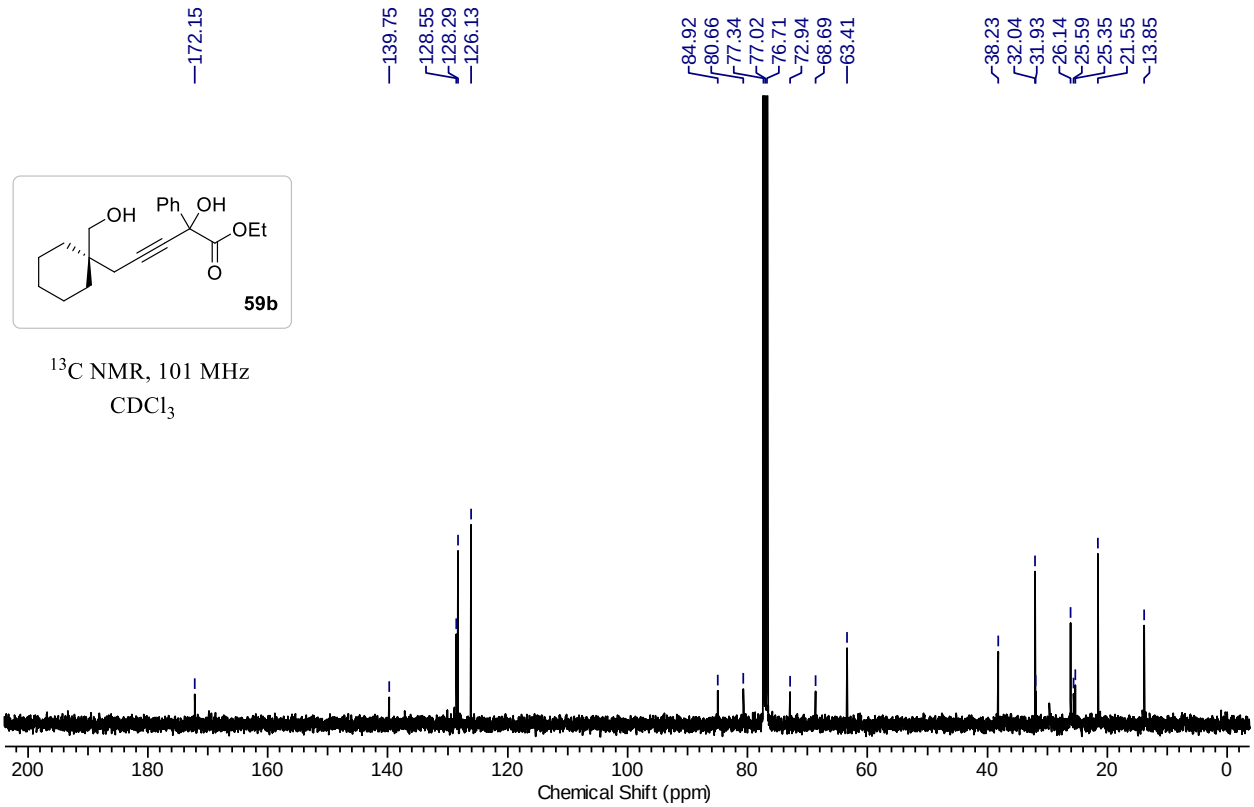


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclohexyl)-2-phenylpent-3-ynoate (59b):

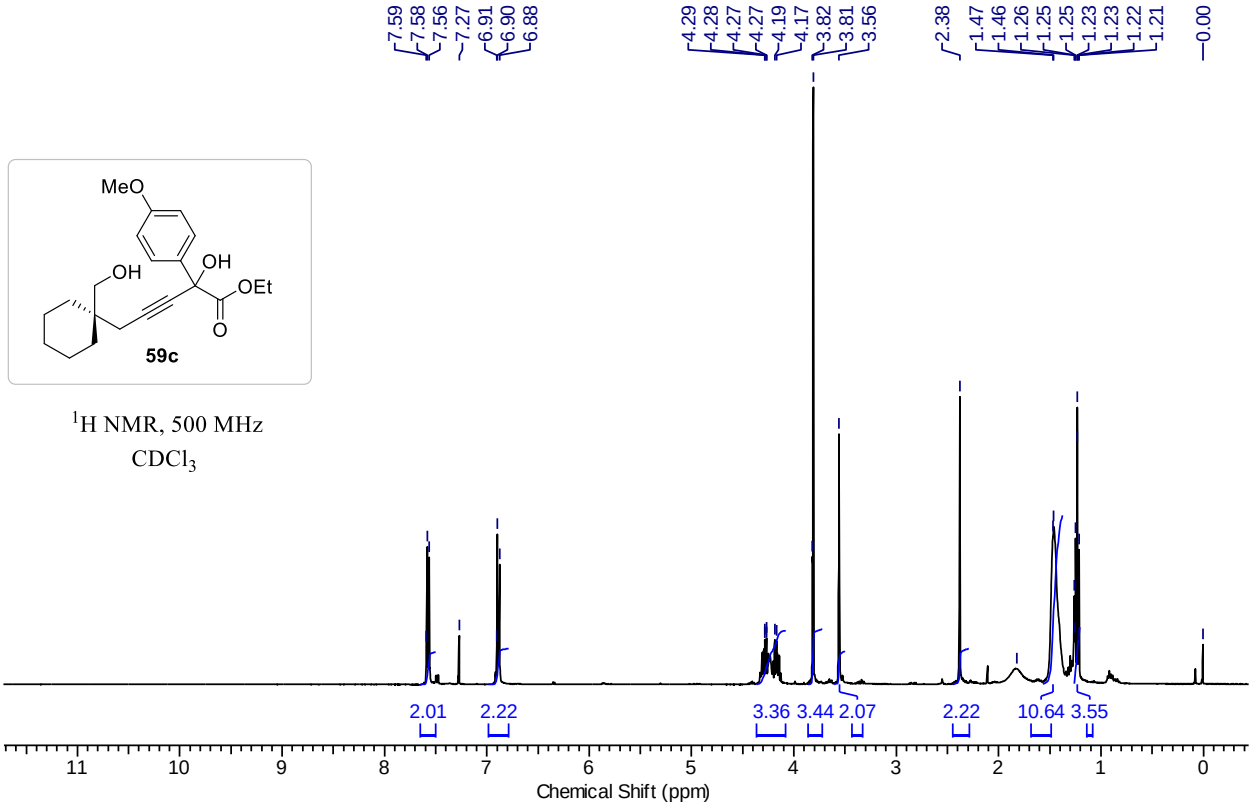


^{1}H NMR, 400 MHz
$CDCl_3$

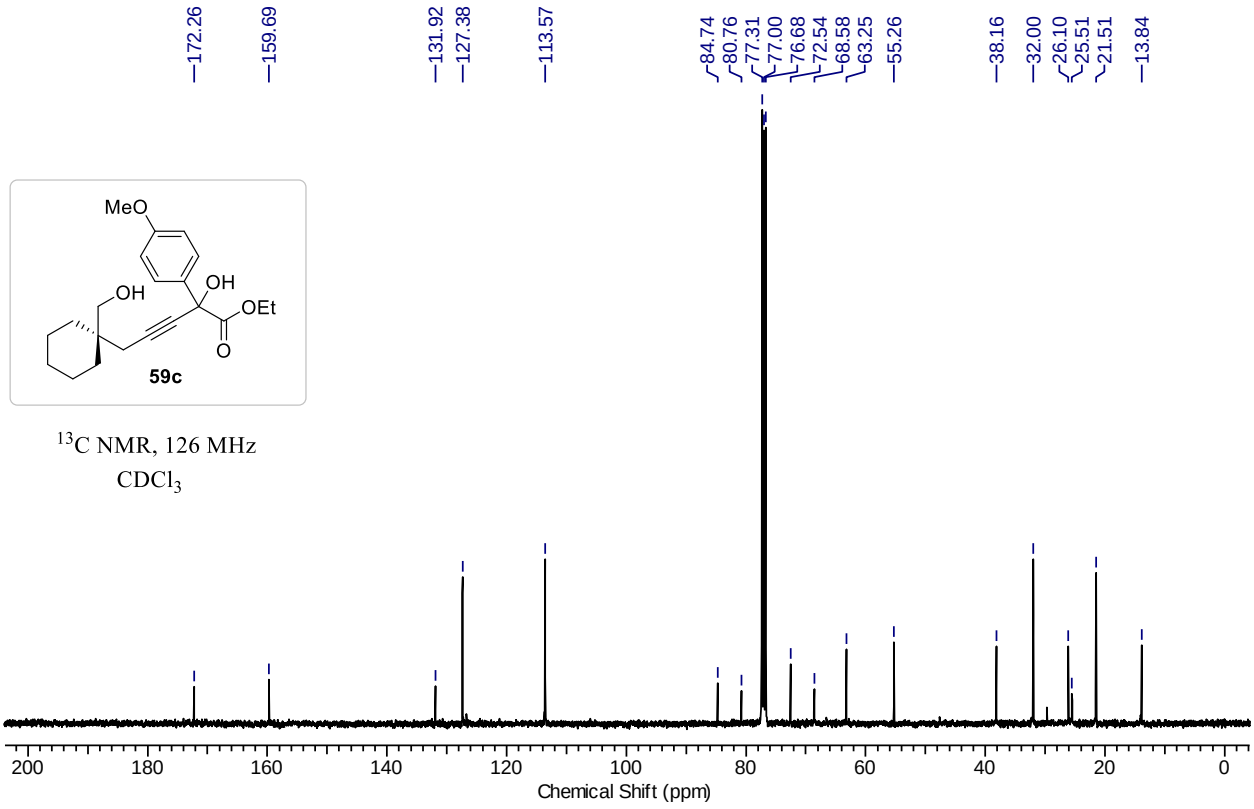


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclohexyl)-2-(4-methoxyphenyl)pent-3-ynoate (59c):

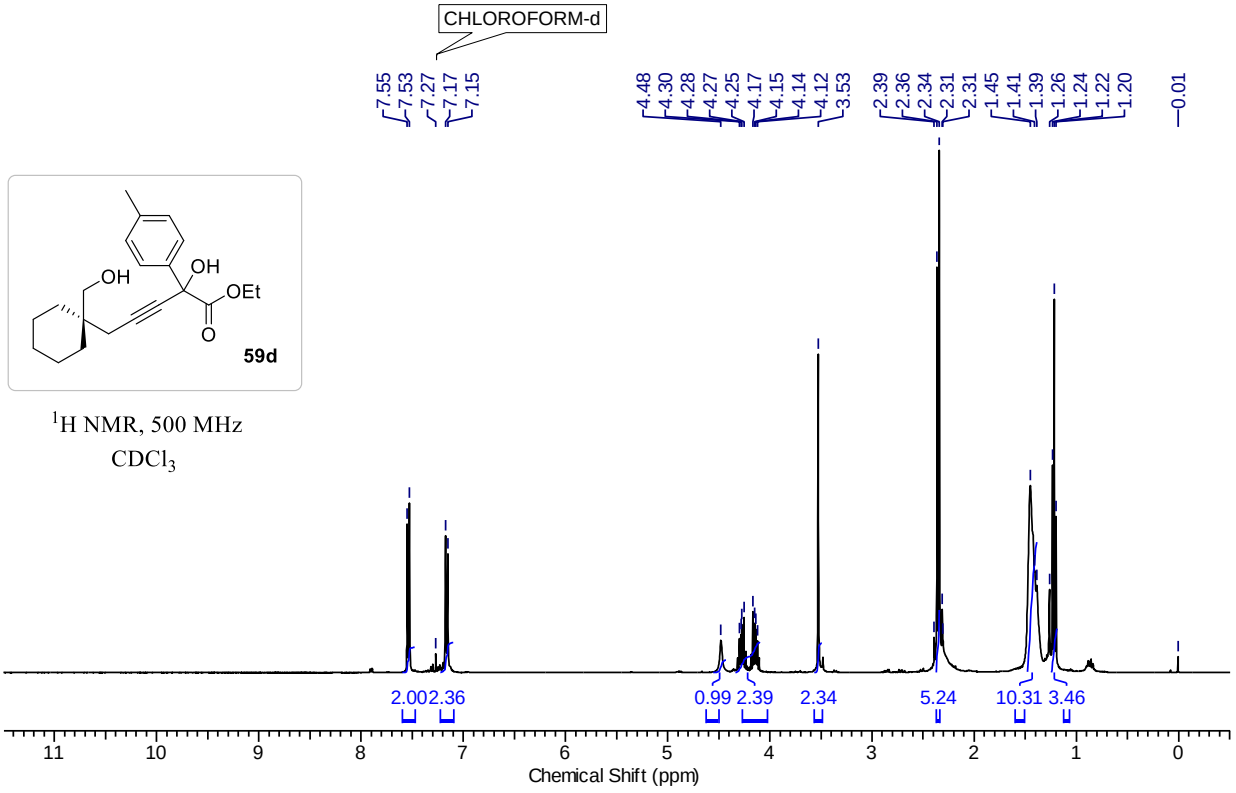


^{1}H NMR, 500 MHz
$CDCl_3$

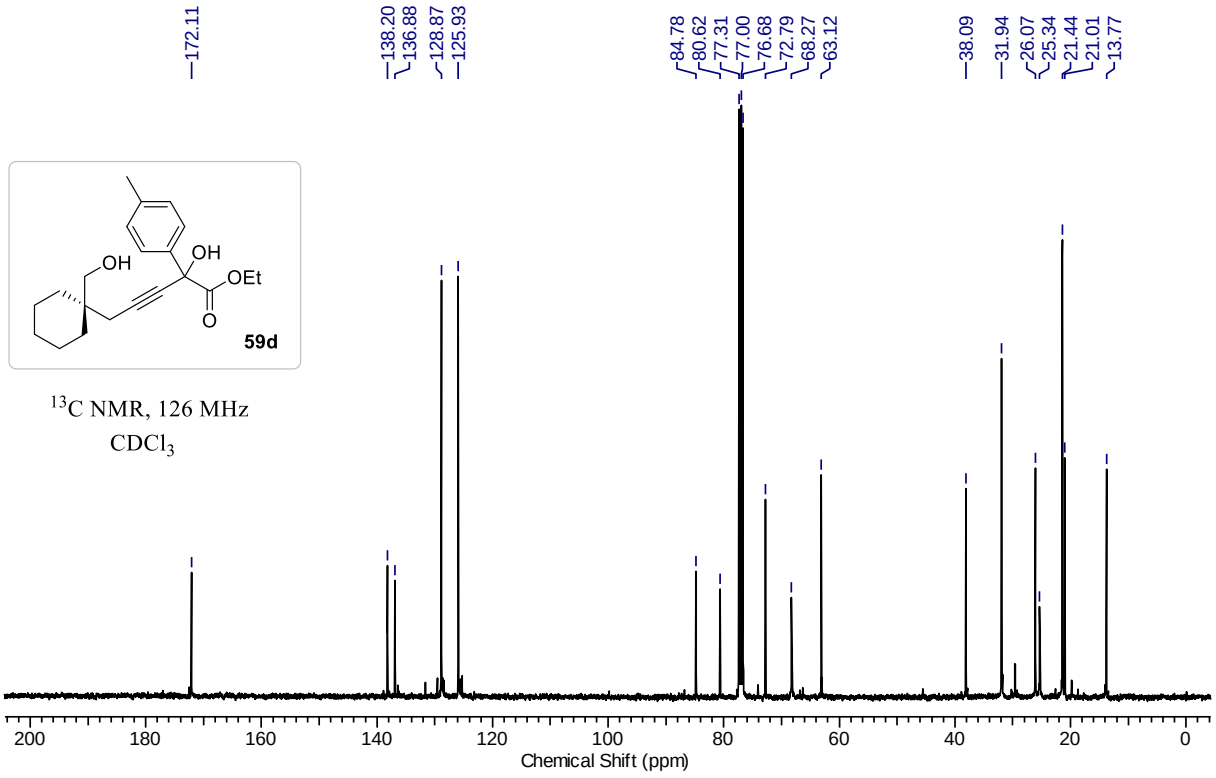


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclohexyl)-2-(*p*-tolyl)pent-3-ynoate (59d):

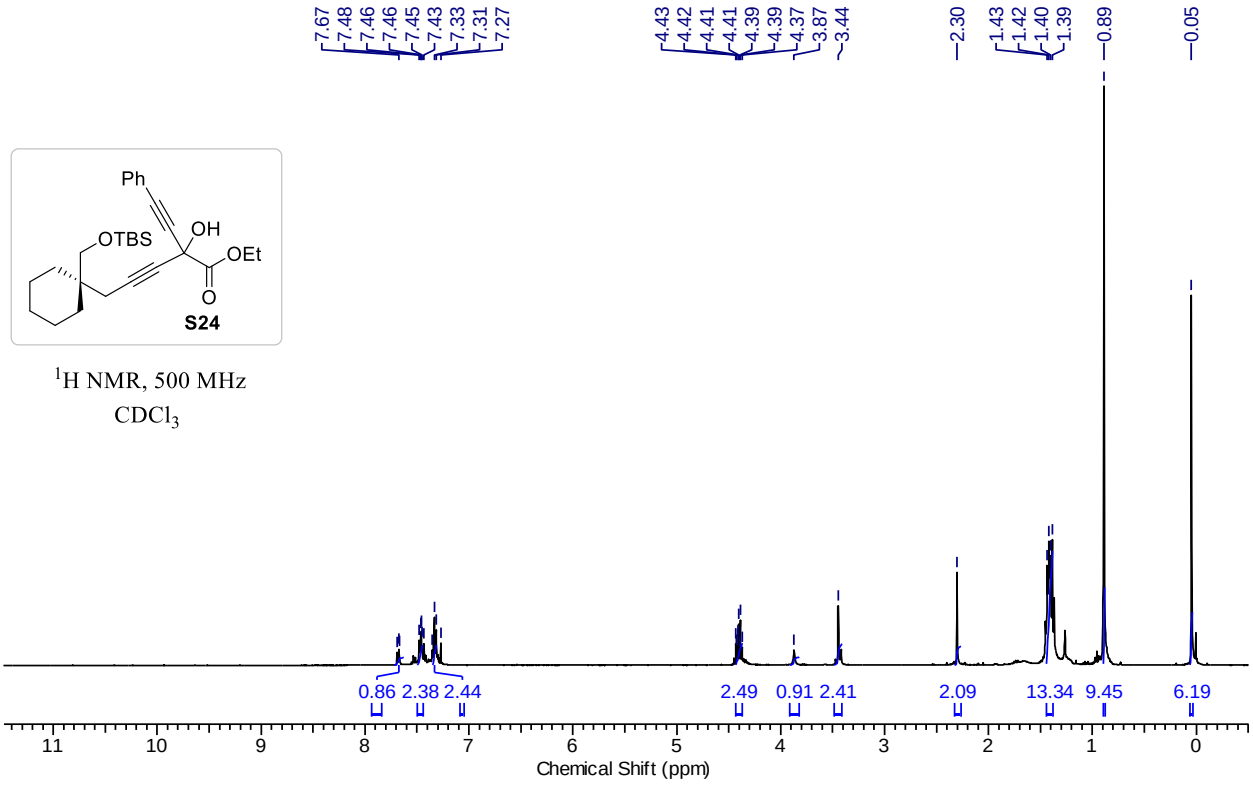


^{1}H NMR, 500 MHz
$CDCl_3$

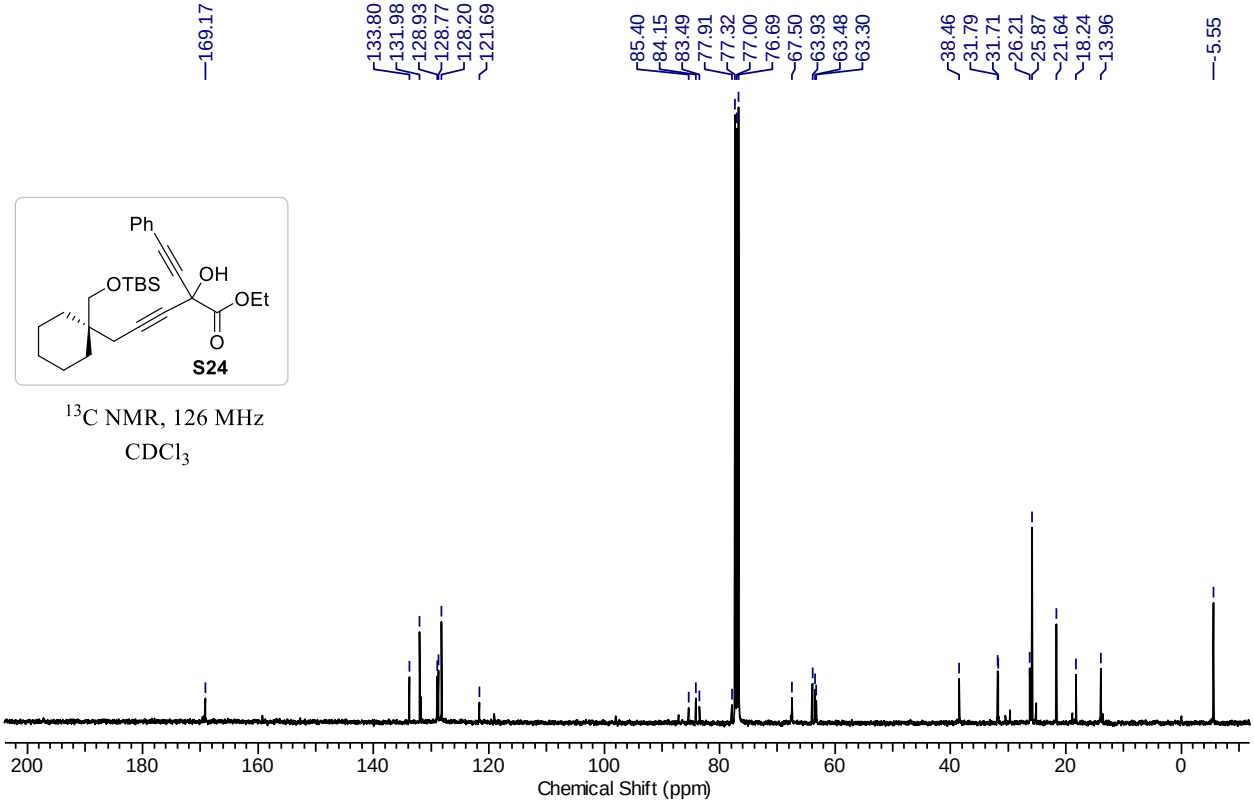


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 5-(1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohexyl)-2-hydroxy-2-(phenylethynyl) pent-3-ynoate (S24):

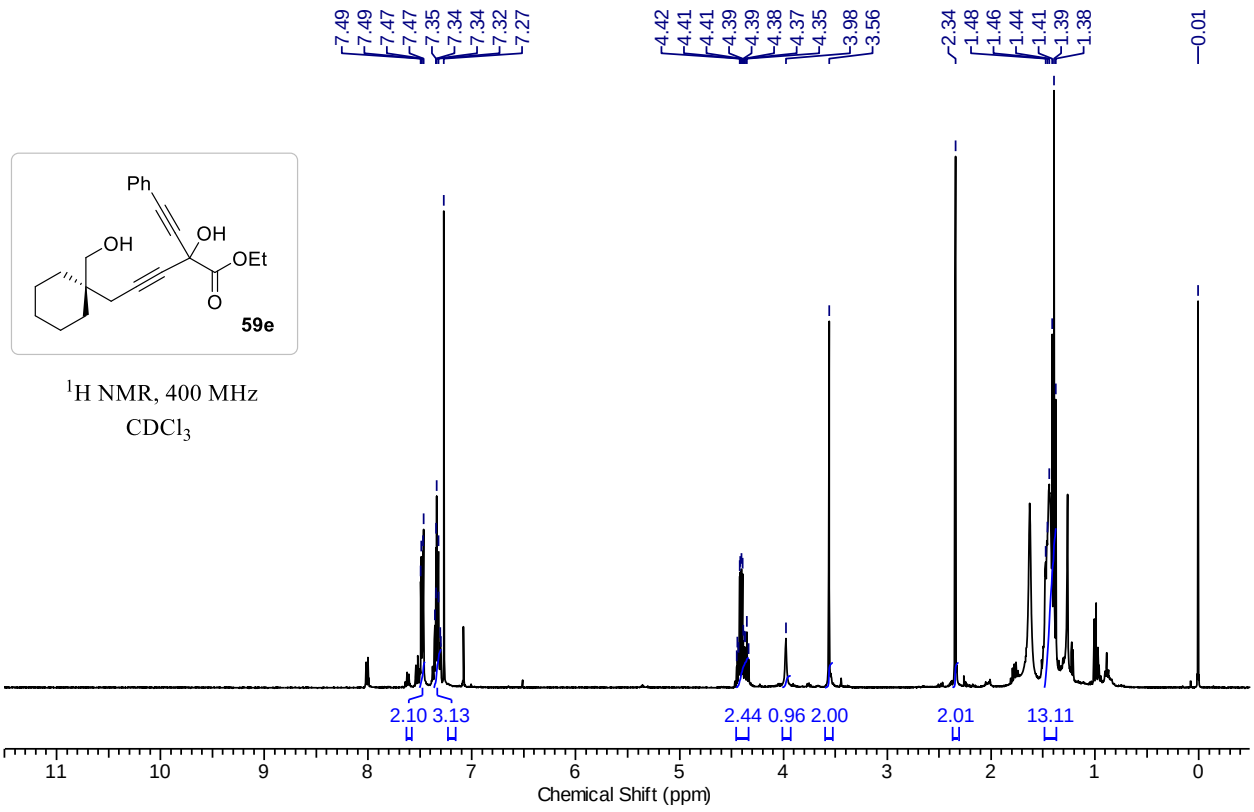


^{1}H NMR, 500 MHz
$CDCl_3$

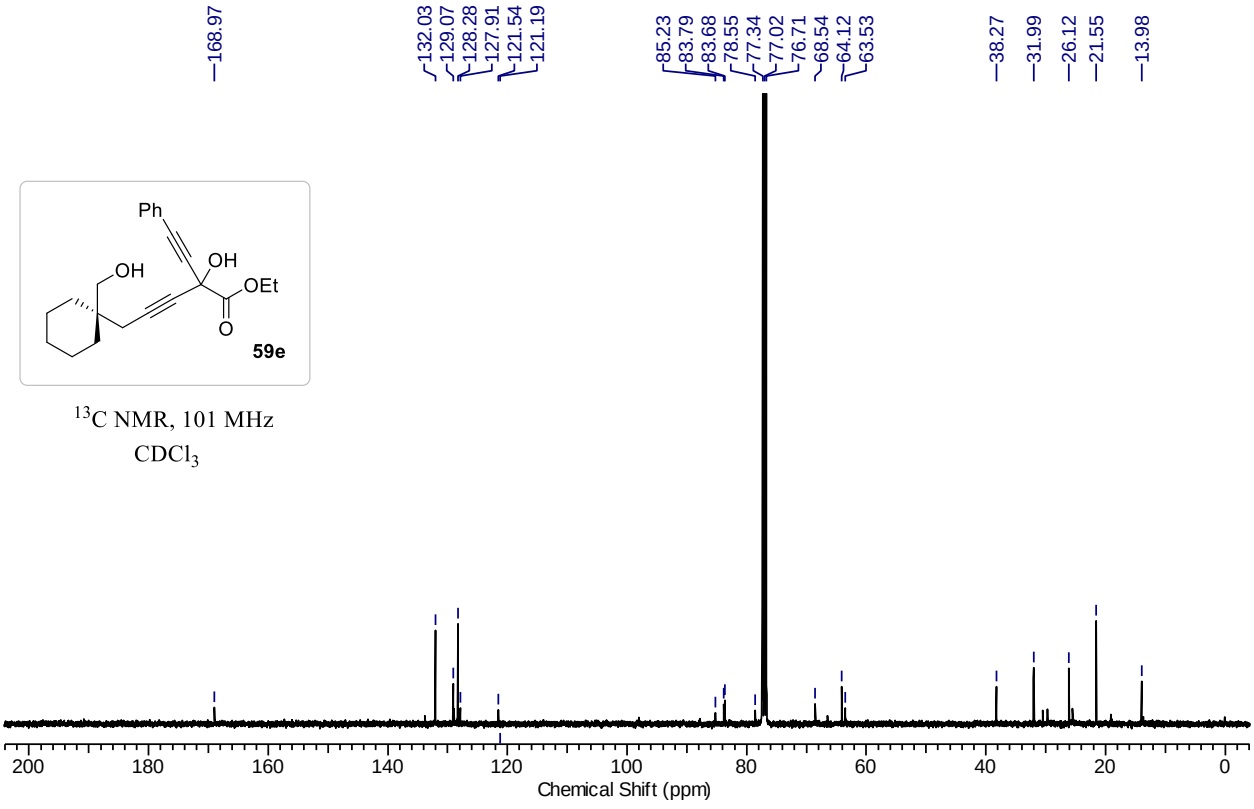


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclohexyl)-2-(phenylethynyl)pent-3-ynoate (59e):

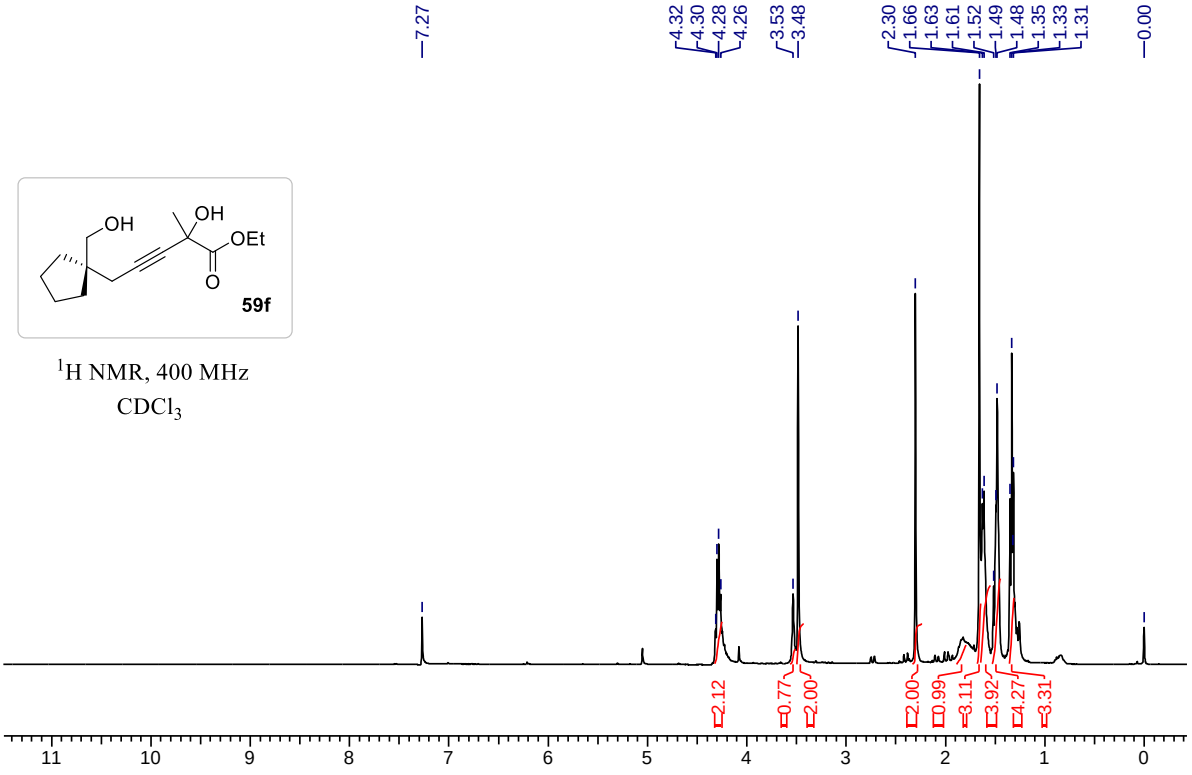


^{1}H NMR, 400 MHz
$CDCl_3$

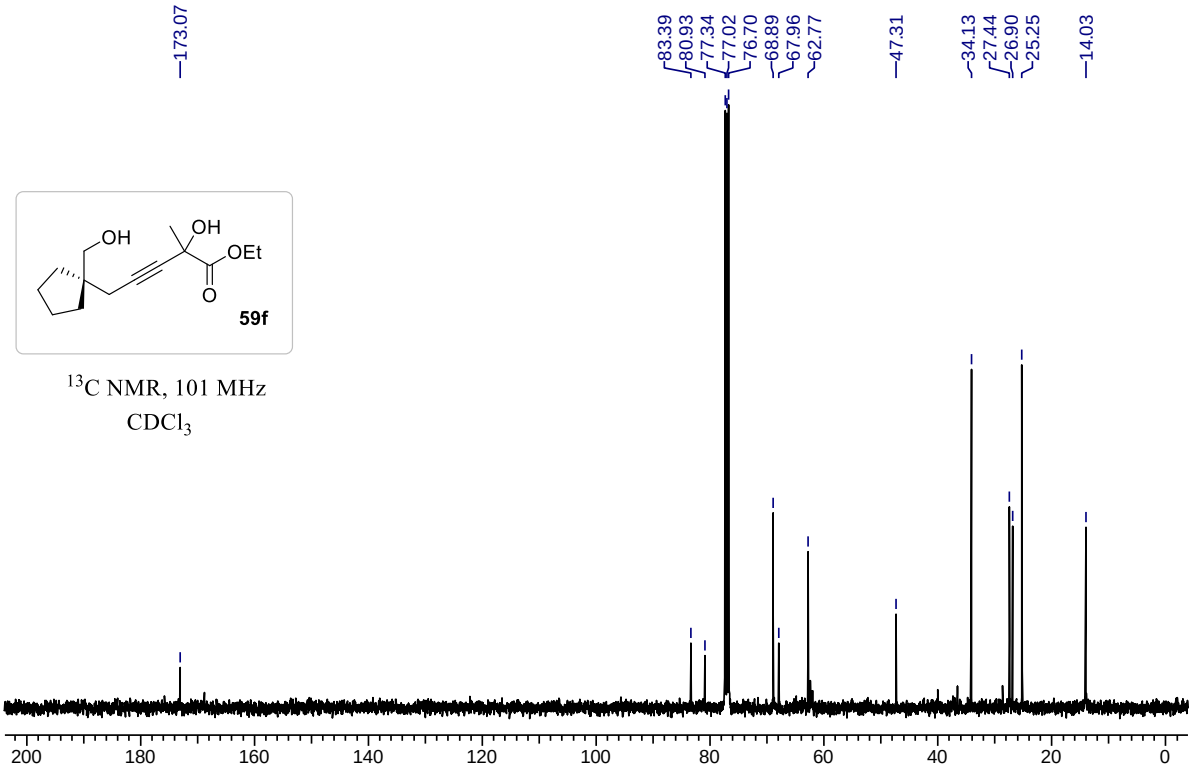


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclopentyl)-2-methylpent-3-ynoate (59f):

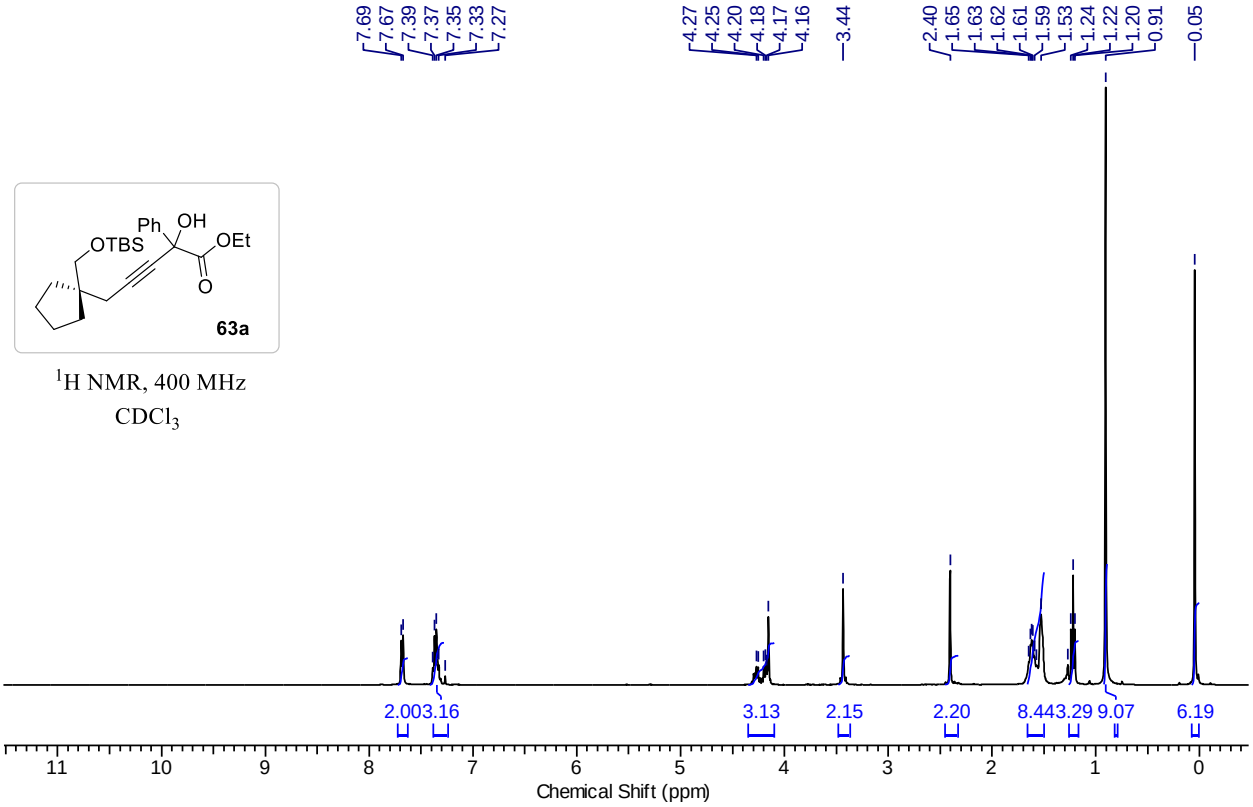


^{1}H NMR, 400 MHz
$CDCl_3$

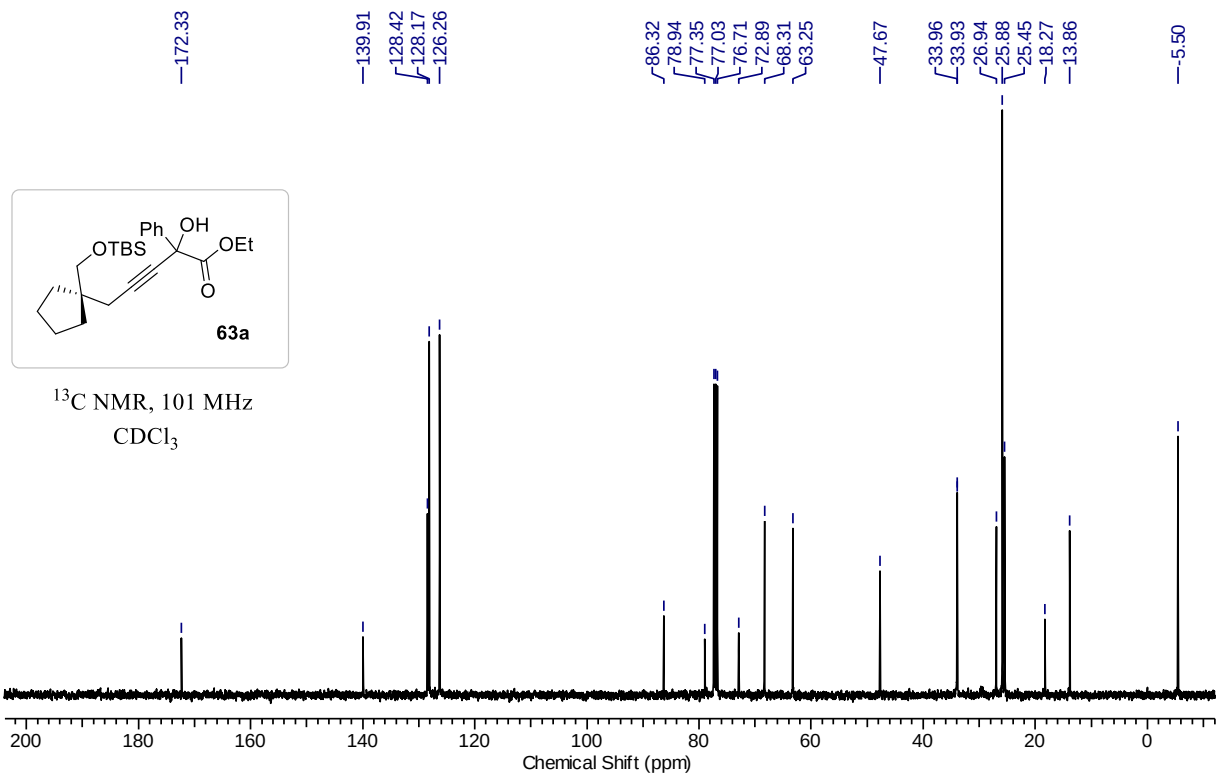


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 5-(1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopentyl)-2-hydroxy-2-phenylpent-3-ynoate (63a):

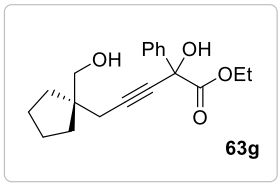


^{1}H NMR, 400 MHz
$CDCl_3$

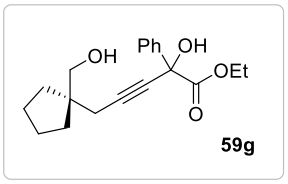


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclopentyl)-2-phenylpent-3-ynoate (59g):

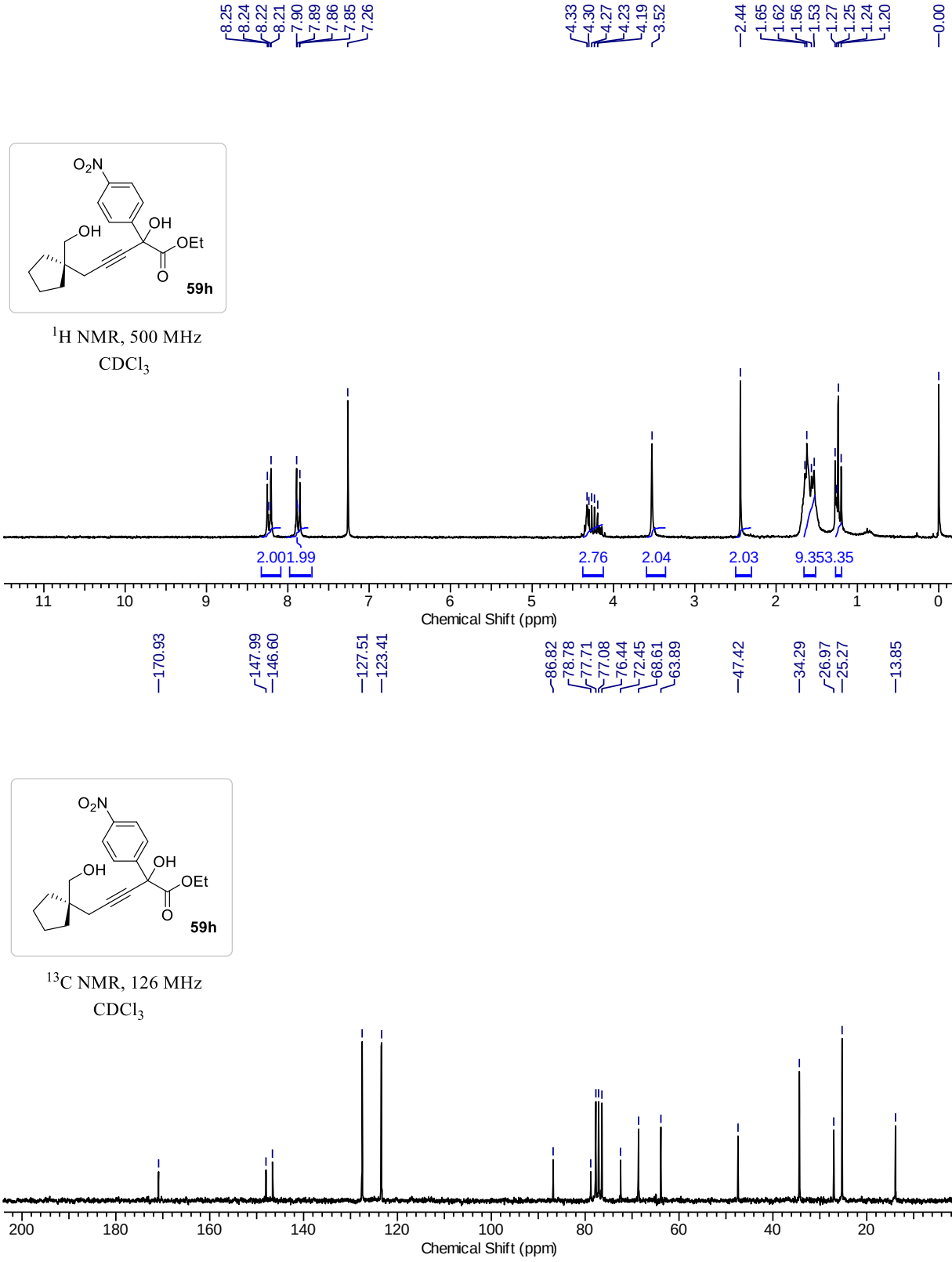


^{1}H NMR, 400 MHz
$CDCl_3$

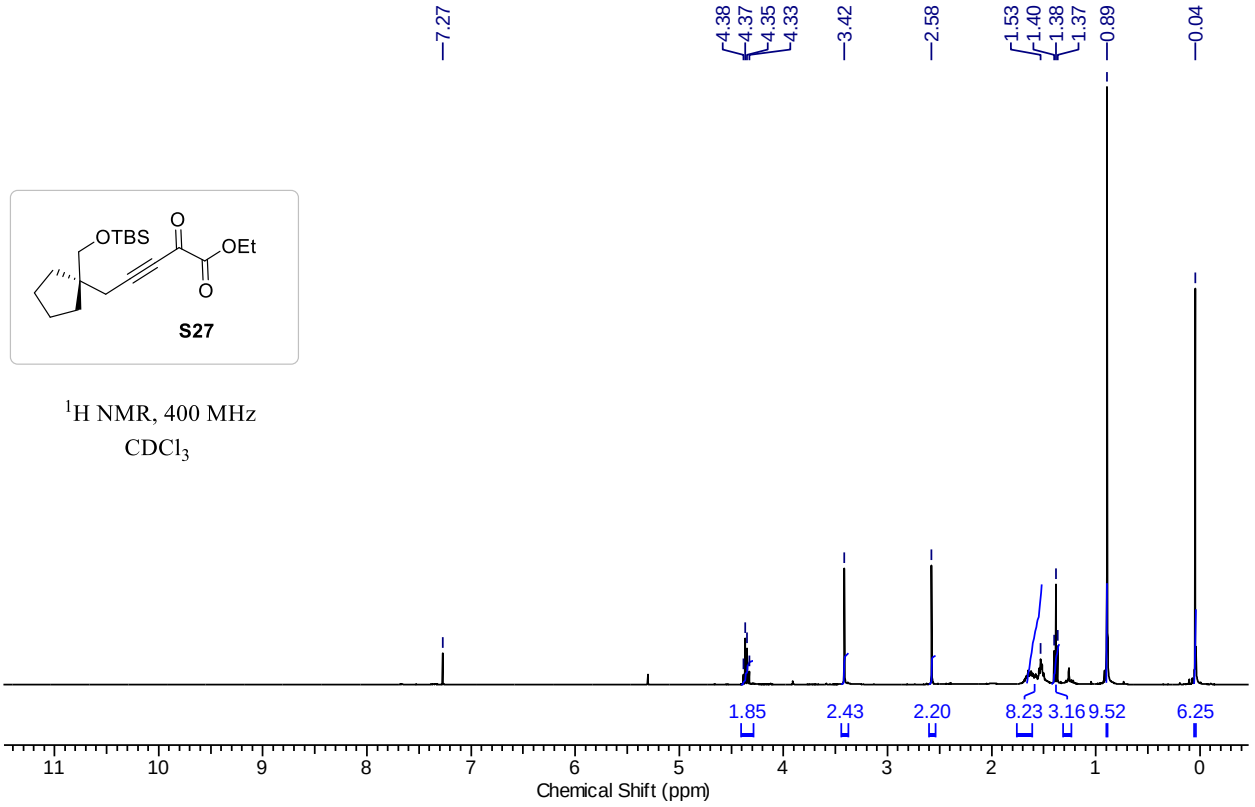


^{13}C NMR, 101 MHz
$CDCl_3$

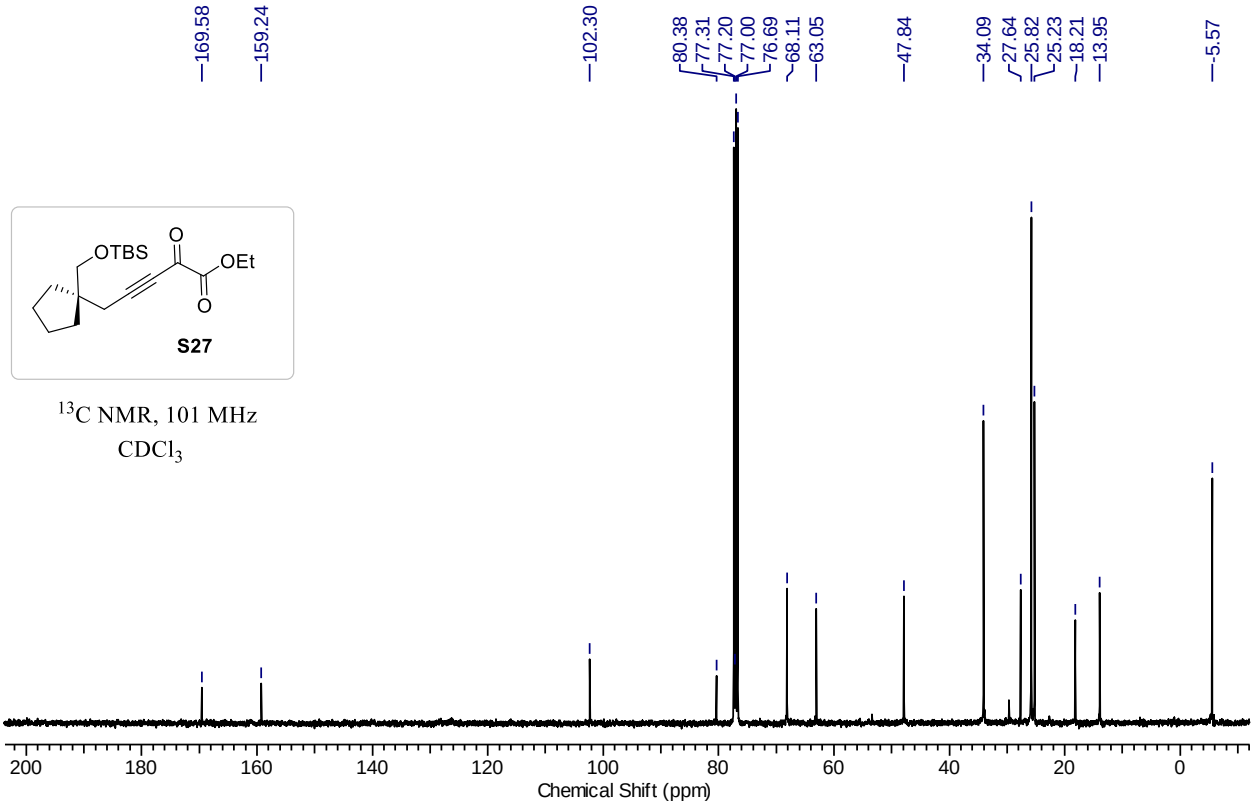
Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclopentyl)-2-(4-nitrophenyl)pent-3-ynoate(59h):



Ethyl 5-(1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopentyl)-2-oxopent-3-ynoate(S27):

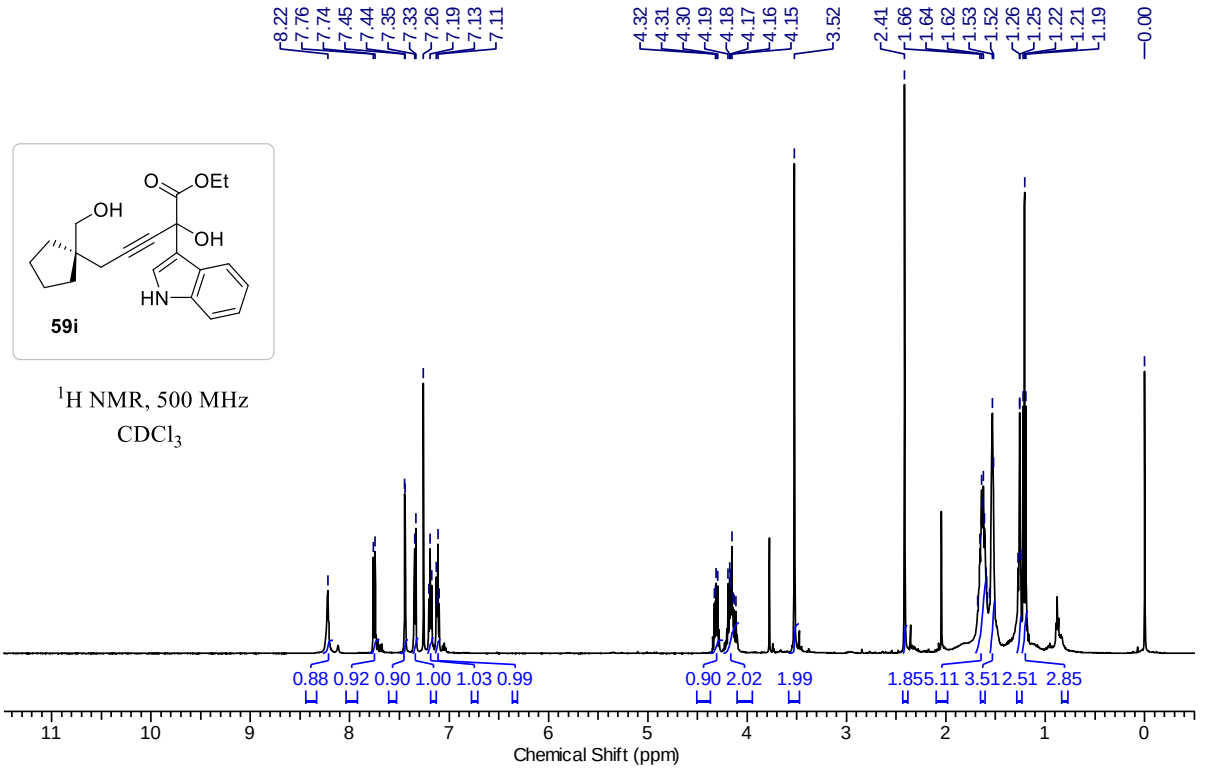


^{1}H NMR, 400 MHz
$CDCl_3$

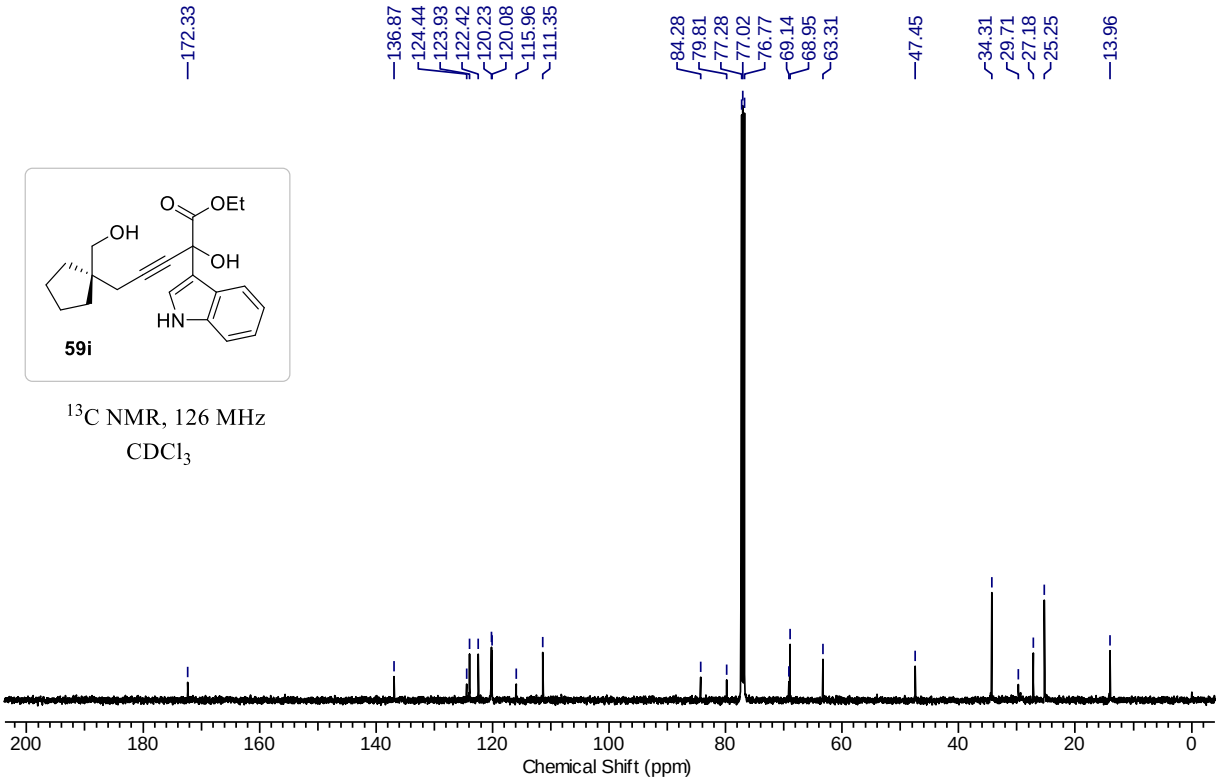


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(1-(hydroxymethyl)cyclopentyl)-2-(1*H*-indol-3-yl)pent-3-ynoate (59i):

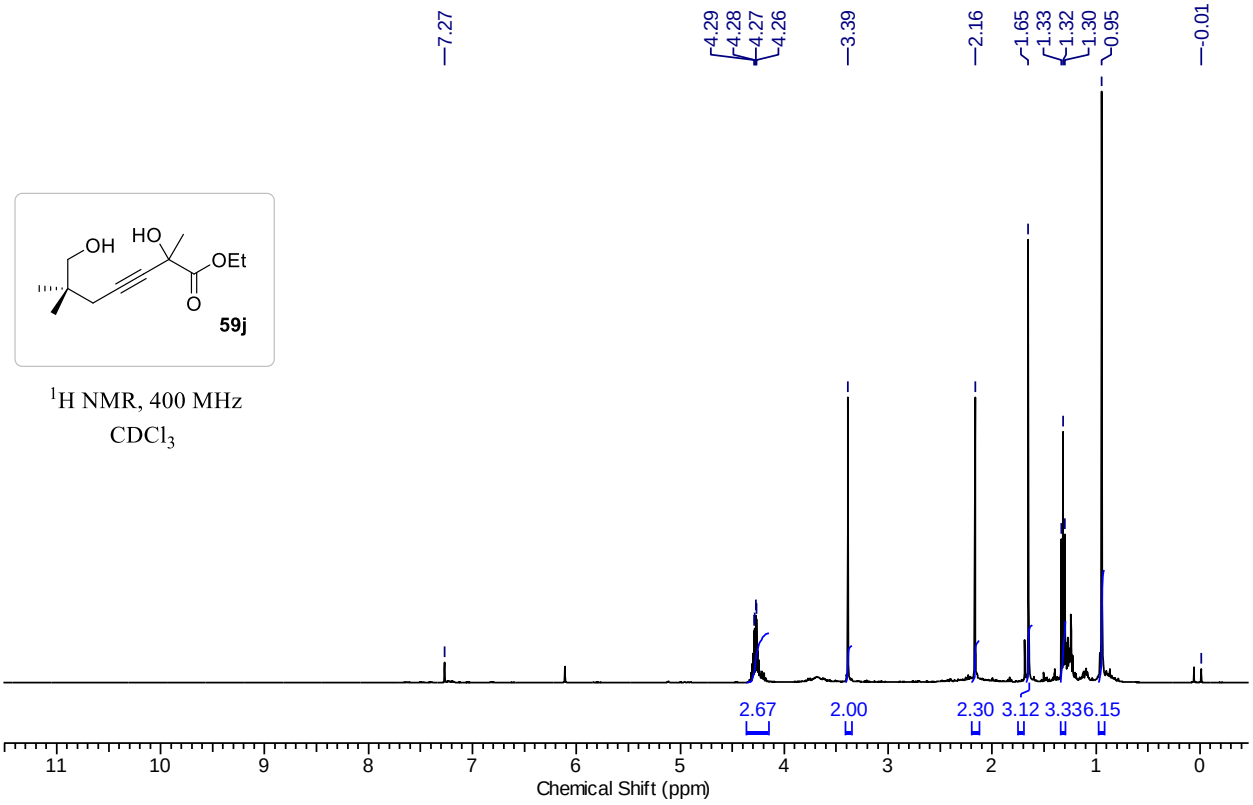


^{1}H NMR, 500 MHz
$CDCl_3$

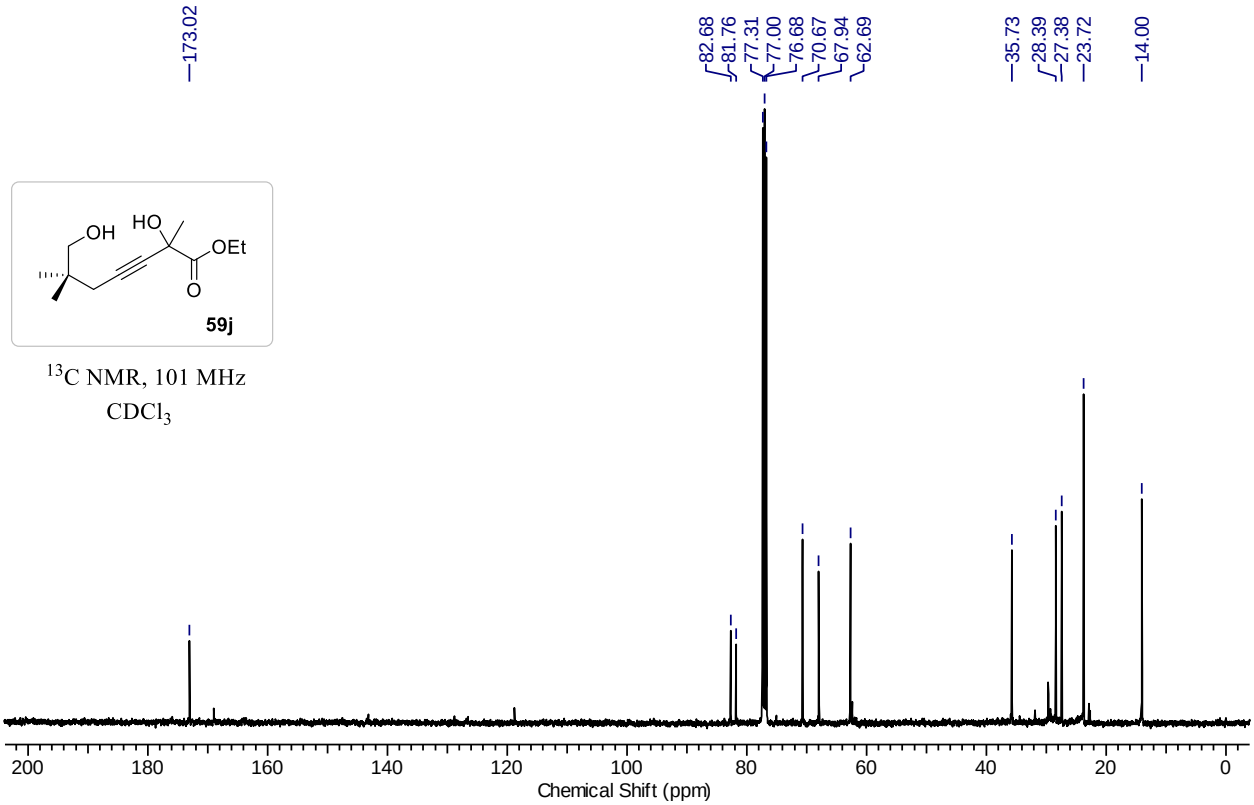


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2,7-dihydroxy-2,6,6-trimethylhept-3-ynoate(59j):

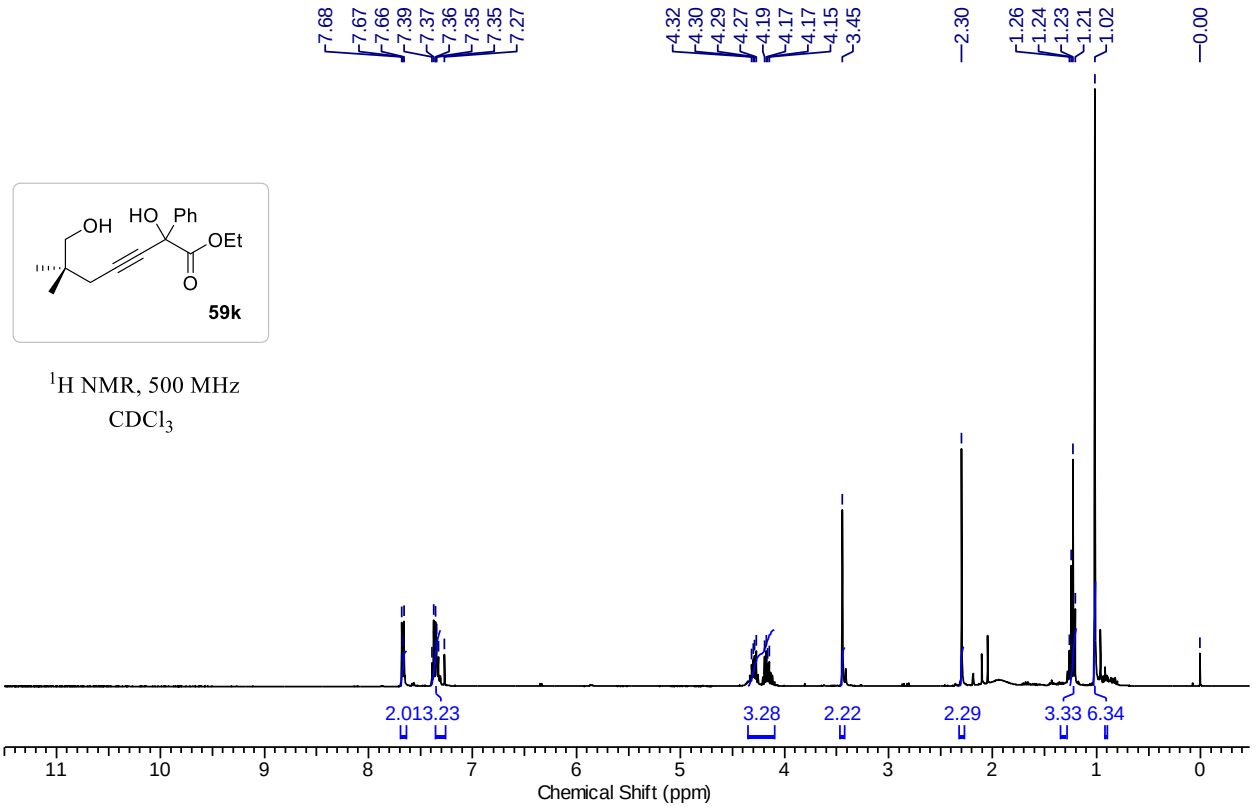


^{1}H NMR, 400 MHz
$CDCl_3$

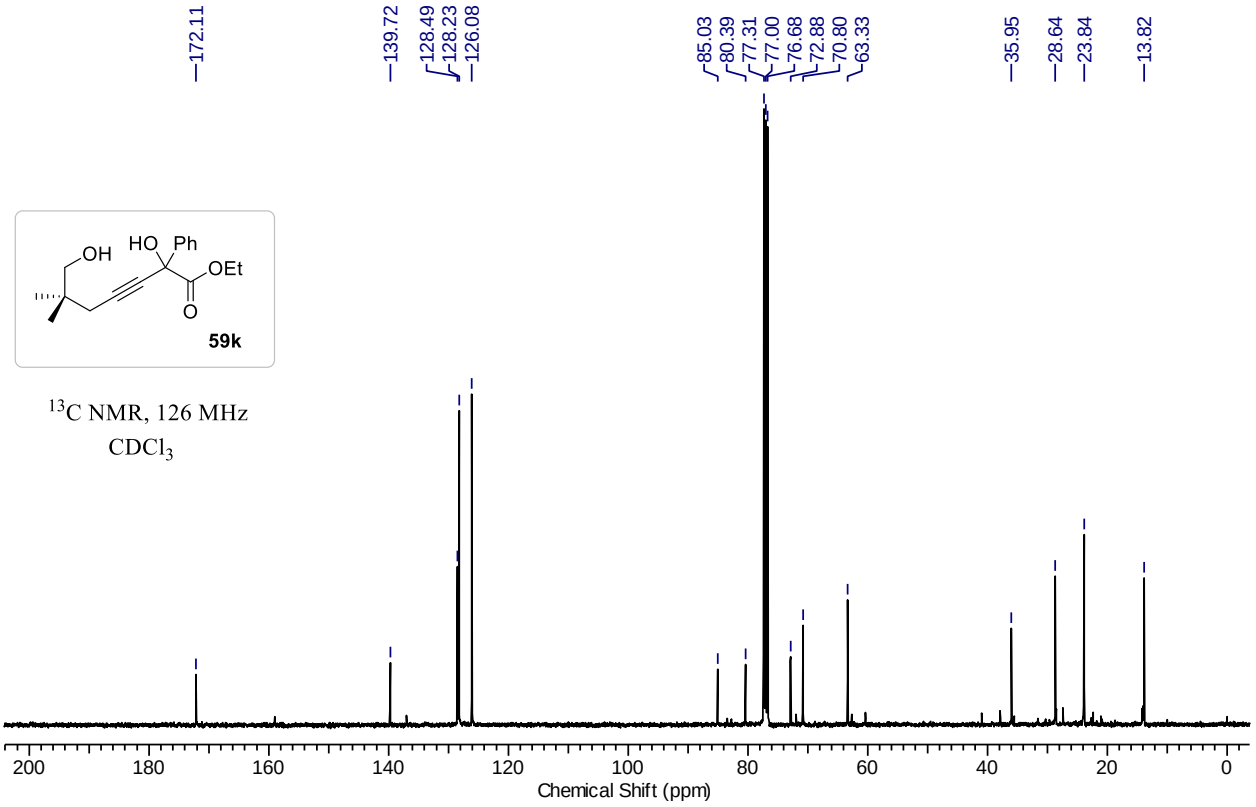


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2,7-dihydroxy-6,6-dimethyl-2-phenylhept-3-ynoate(59k):

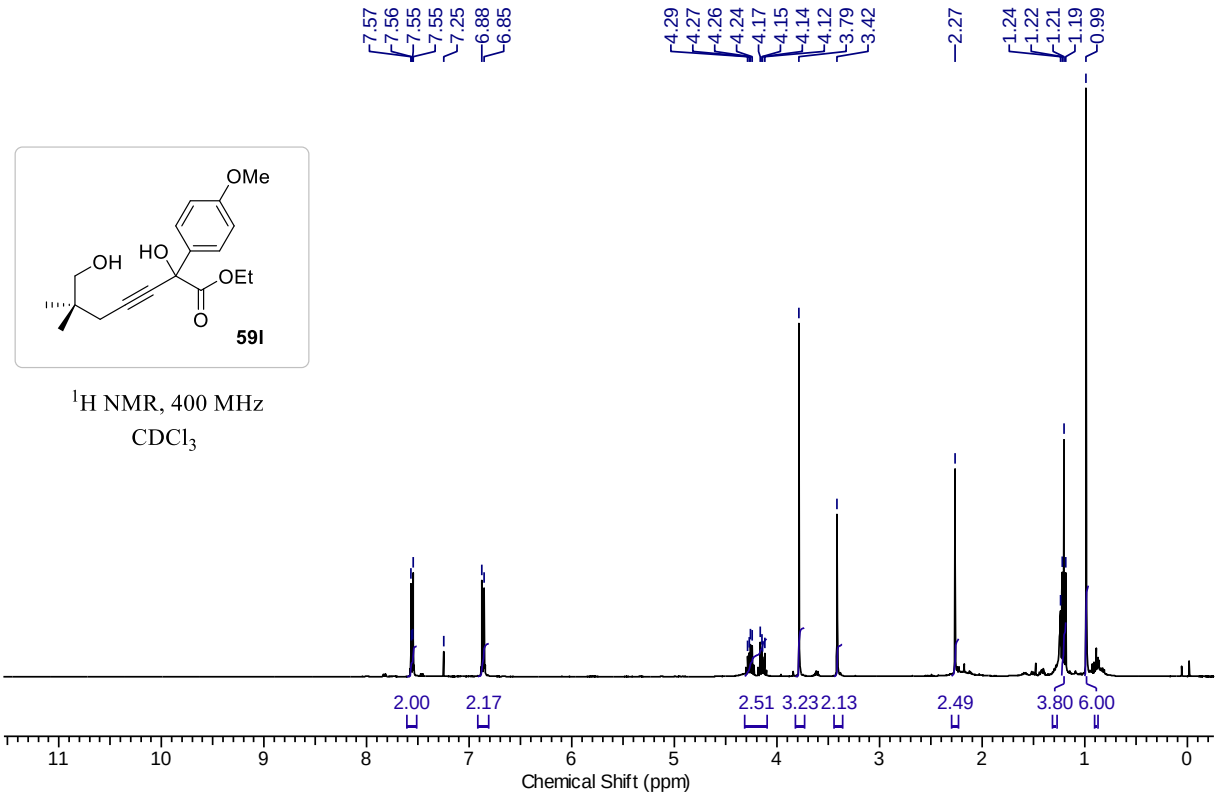


^{1}H NMR, 500 MHz
$CDCl_3$

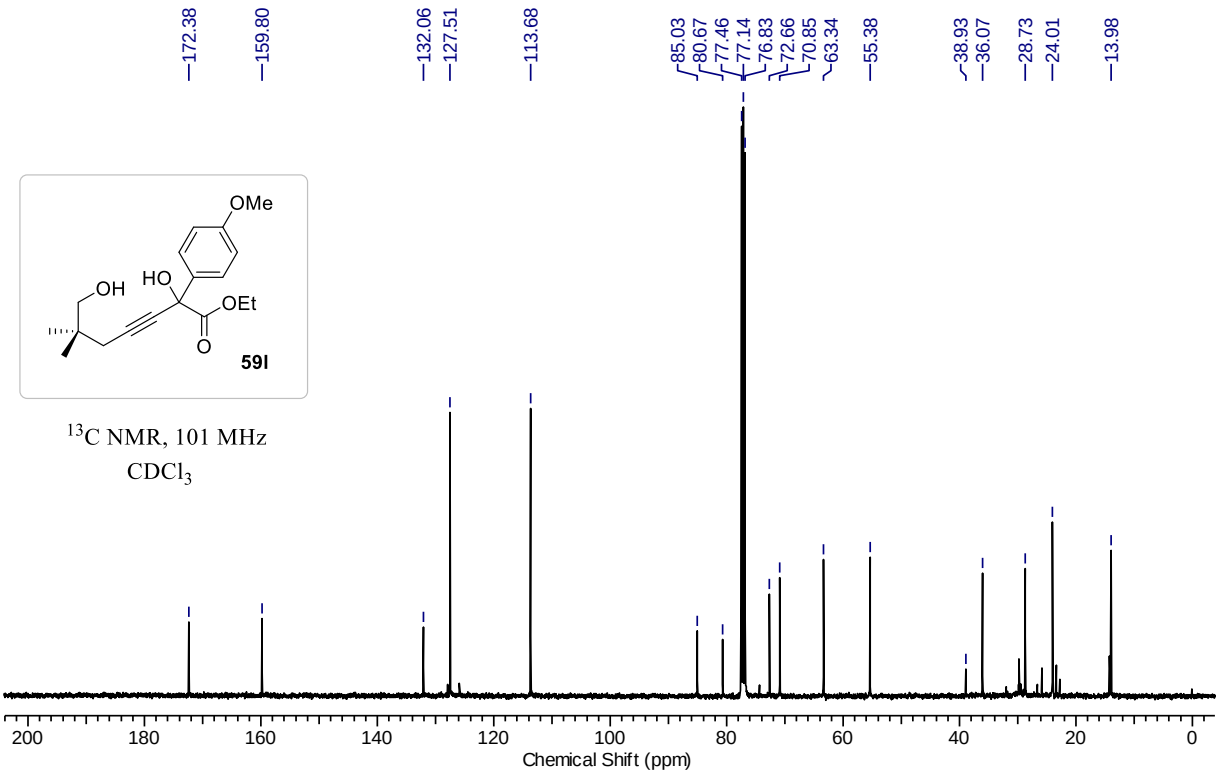


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2,7-dihydroxy-2-(4-methoxyphenyl)-6,6-dimethylhept-3-ynoate(59l):

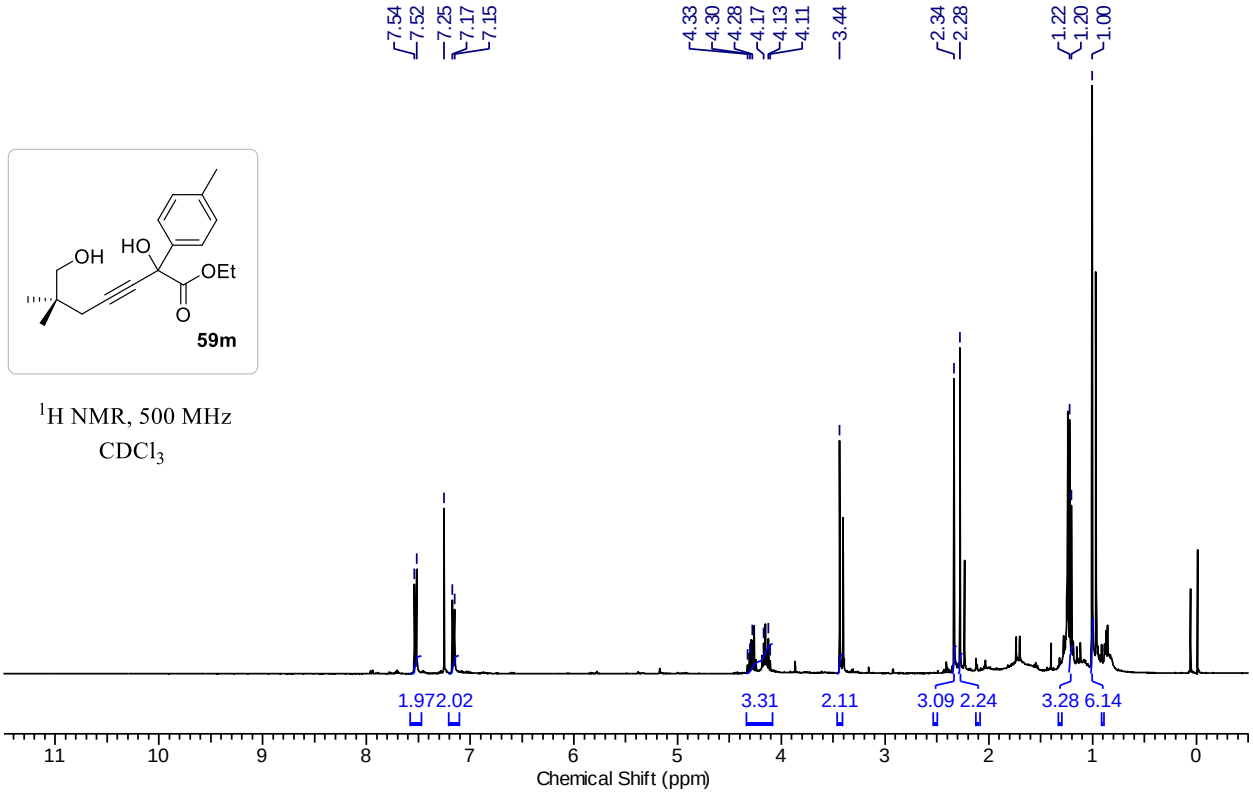


^{1}H NMR, 400 MHz
$CDCl_3$

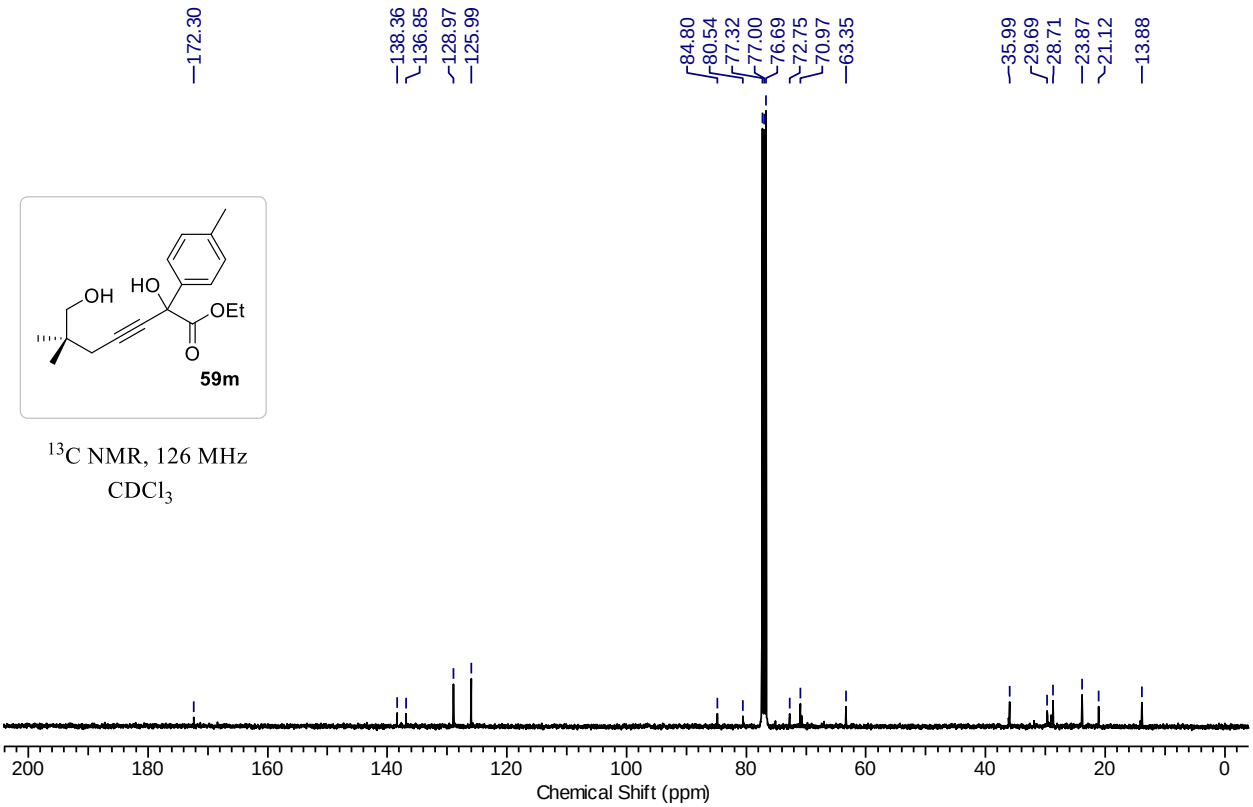


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2,7-dihydroxy-6,6-dimethyl-2-(*p*-tolyl)hept-3-ynoate(59m):

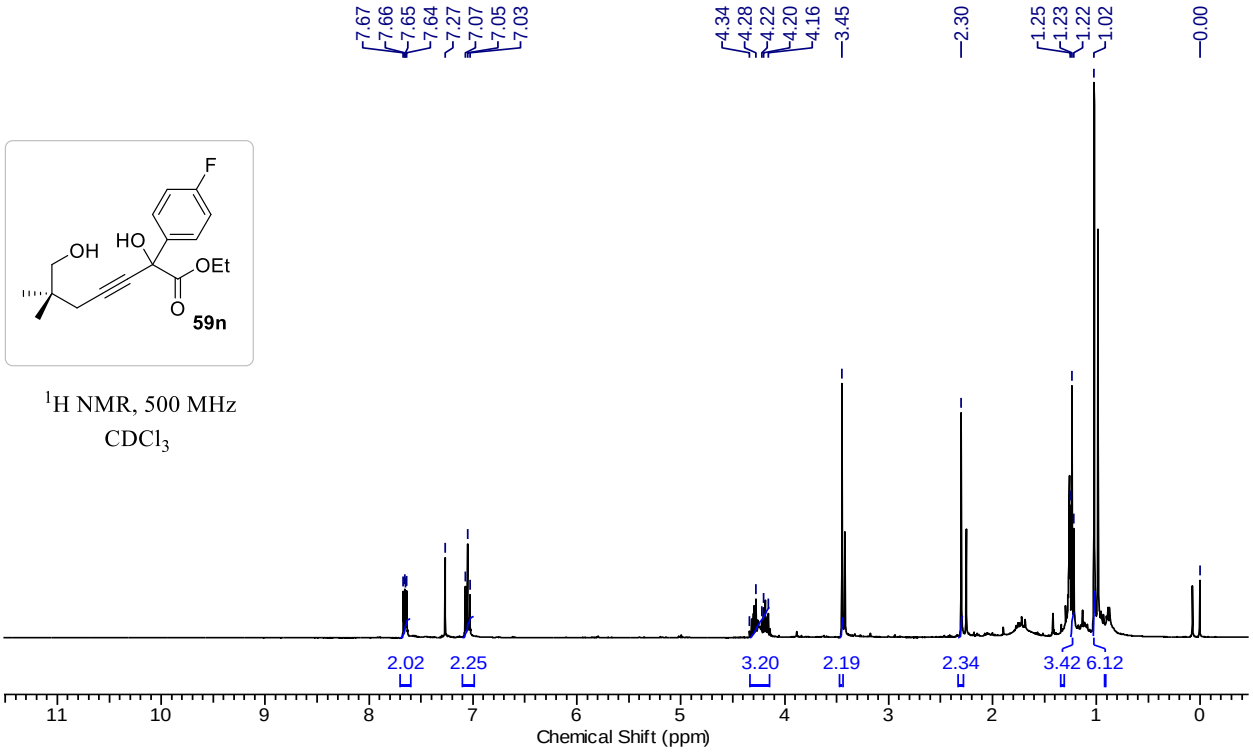


^{1}H NMR, 500 MHz
$CDCl_3$

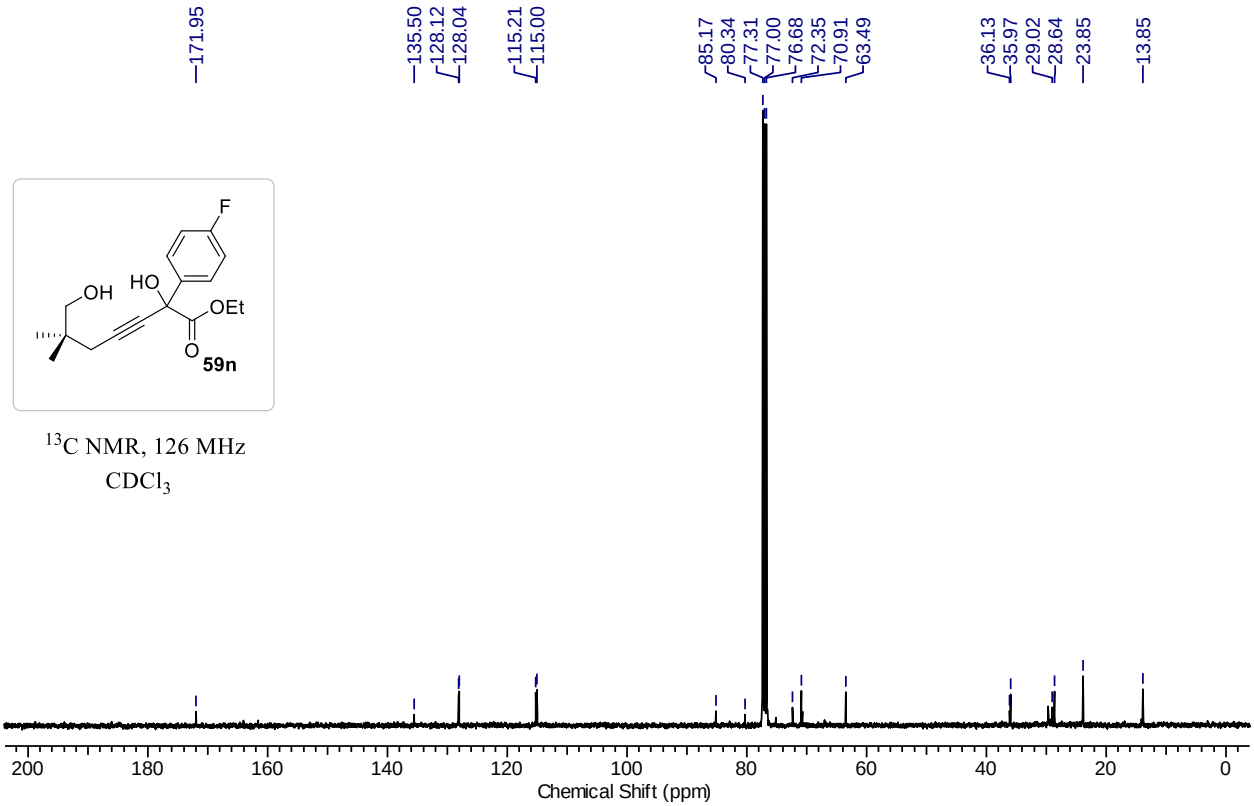


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2-(4-fluorophenyl)-2,7-dihydroxy-6,6-dimethylhept-3-ynoate (59n):

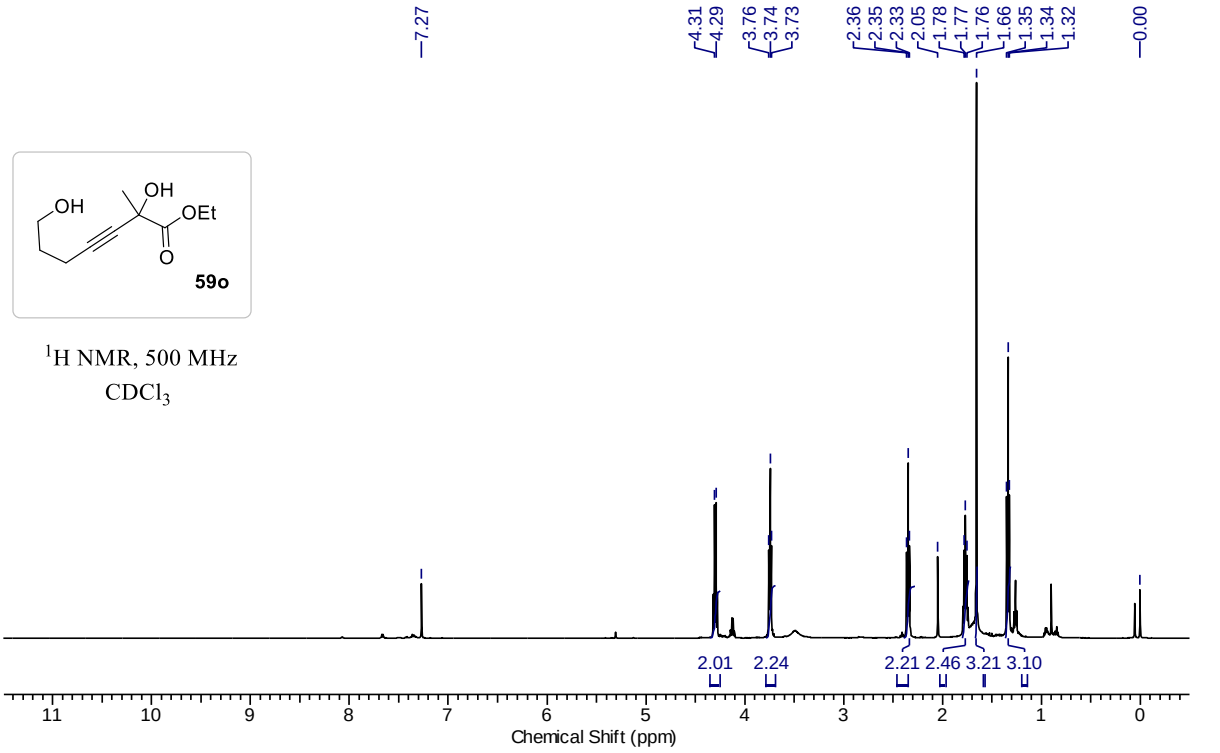


^{1}H NMR, 500 MHz
$CDCl_3$

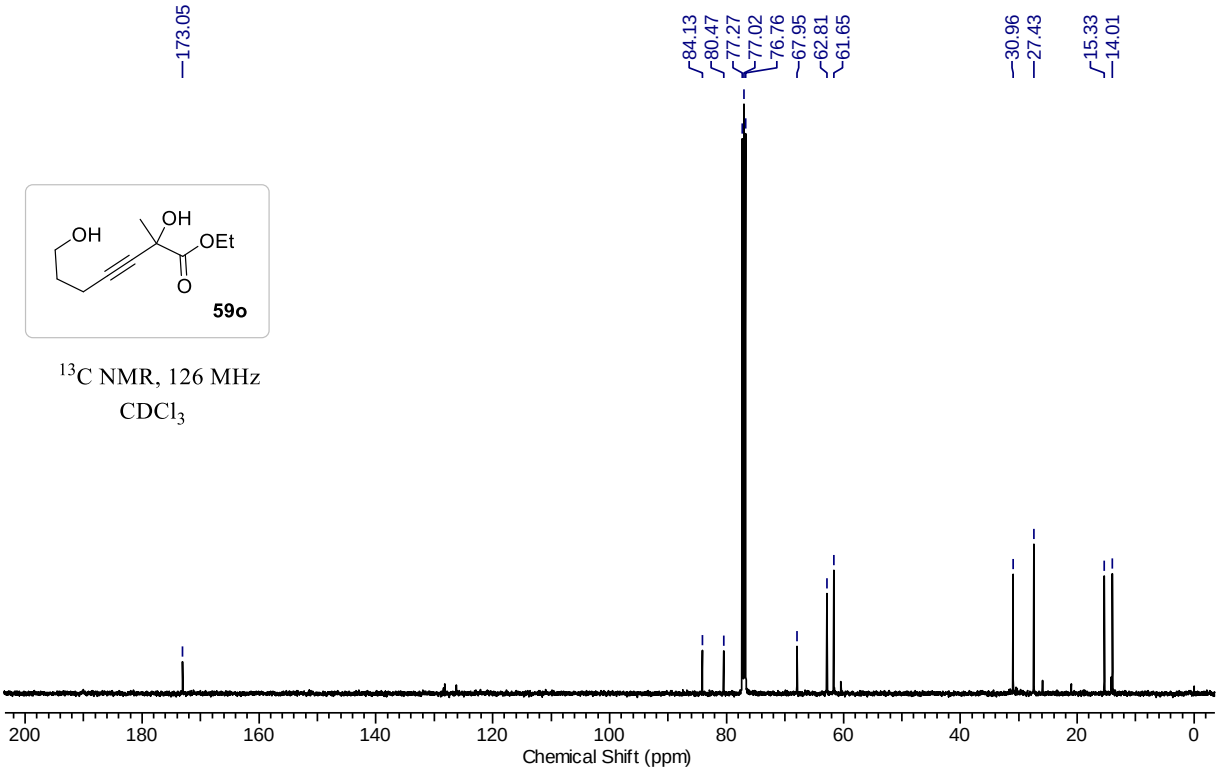


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2,7-dihydroxy-2-methylhept-3-ynoate (59o):

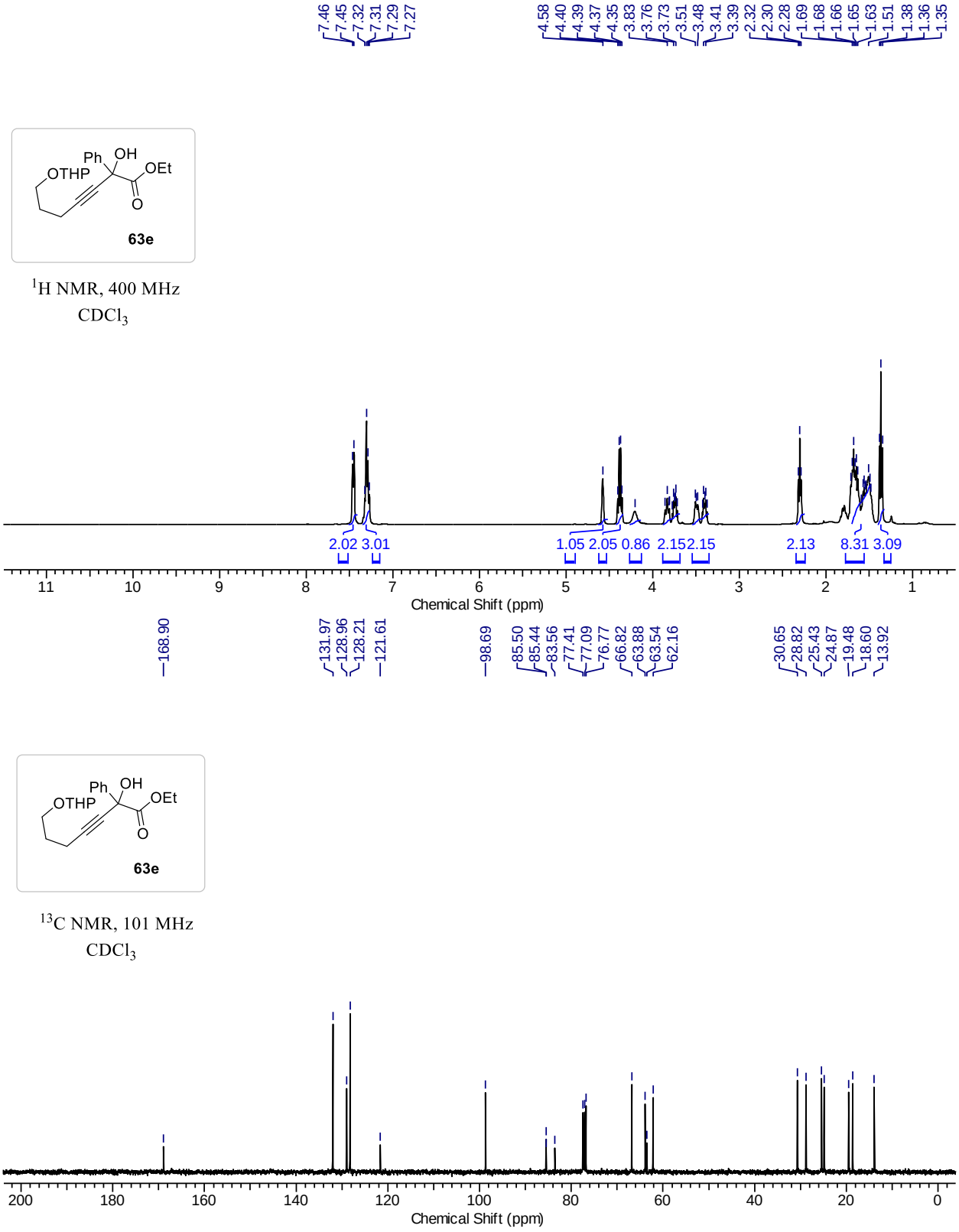


^{1}H NMR, 500 MHz
$CDCl_3$

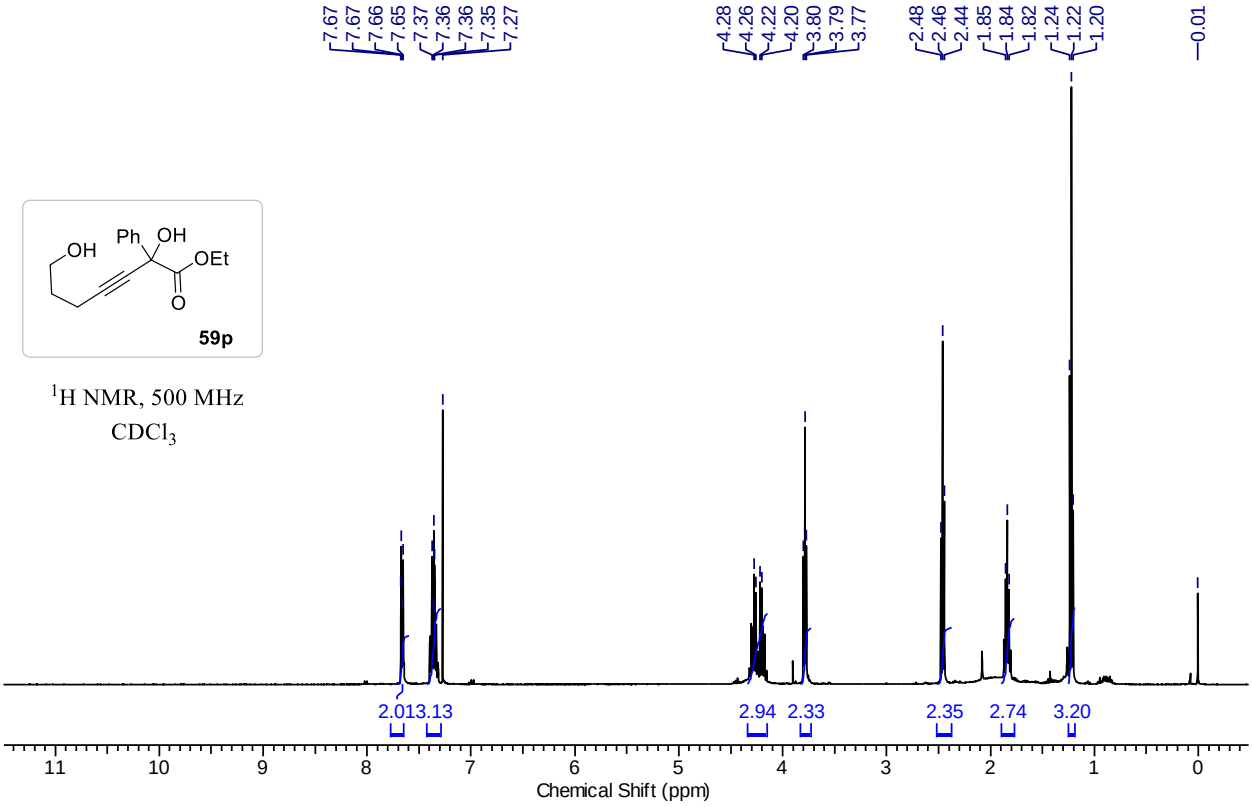


^{13}C NMR, 126 MHz
$CDCl_3$

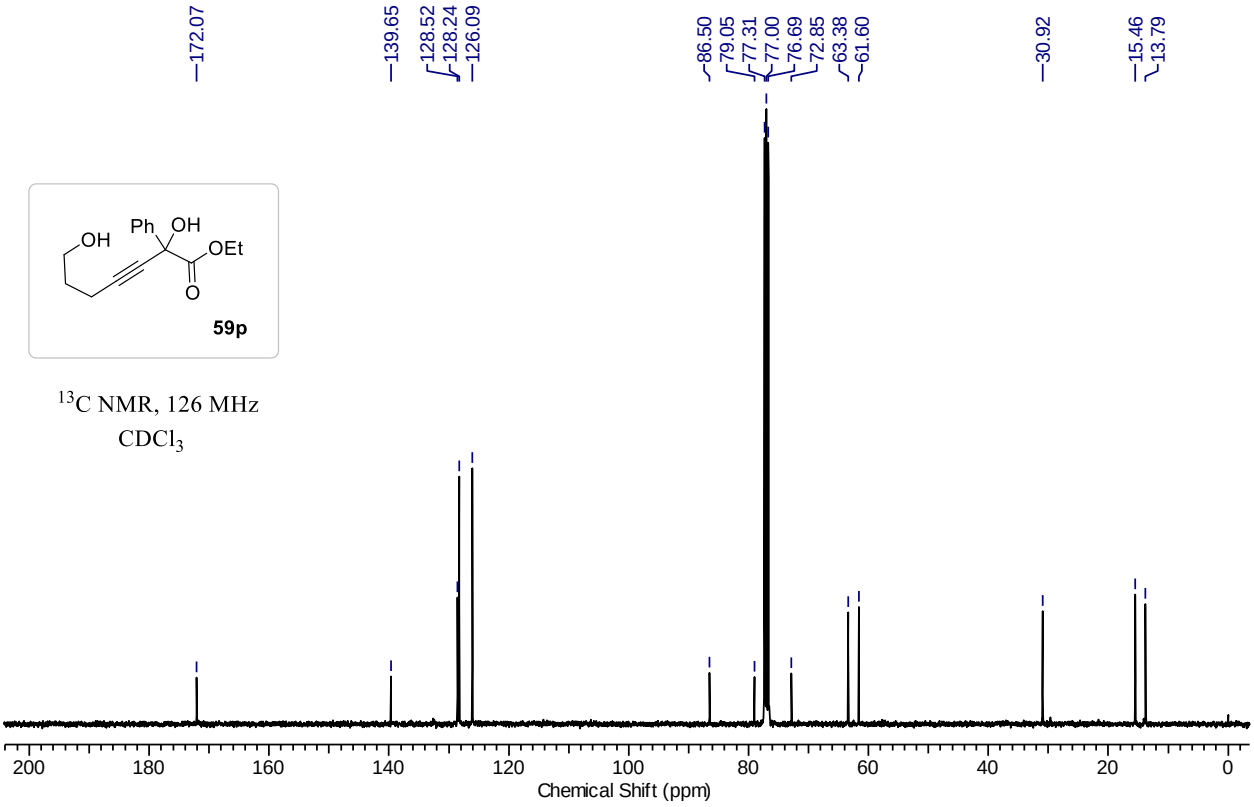
Ethyl 2-hydroxy-2-phenyl-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-3-ynoate (59e):



Ethyl 2,7-dihydroxy-2-phenylhept-3-ynoate(59p):

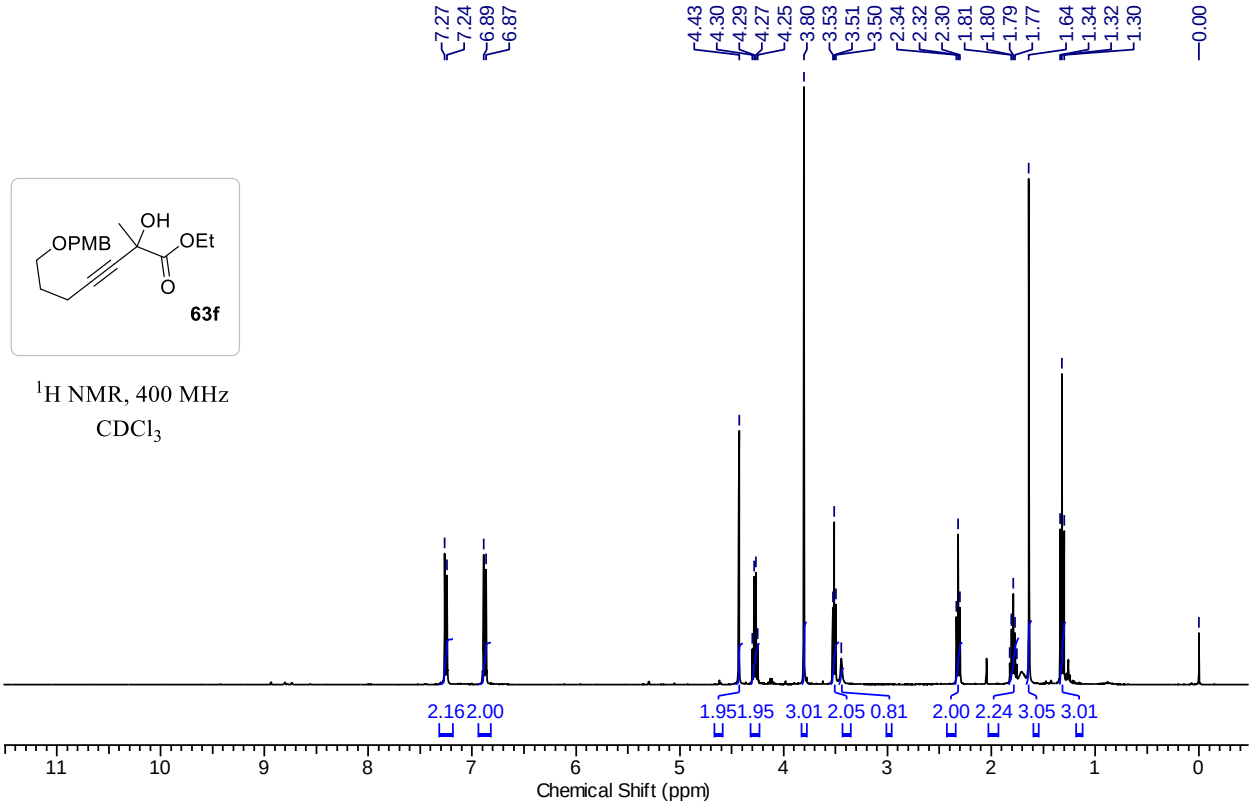


^{1}H NMR, 500 MHz
$CDCl_3$

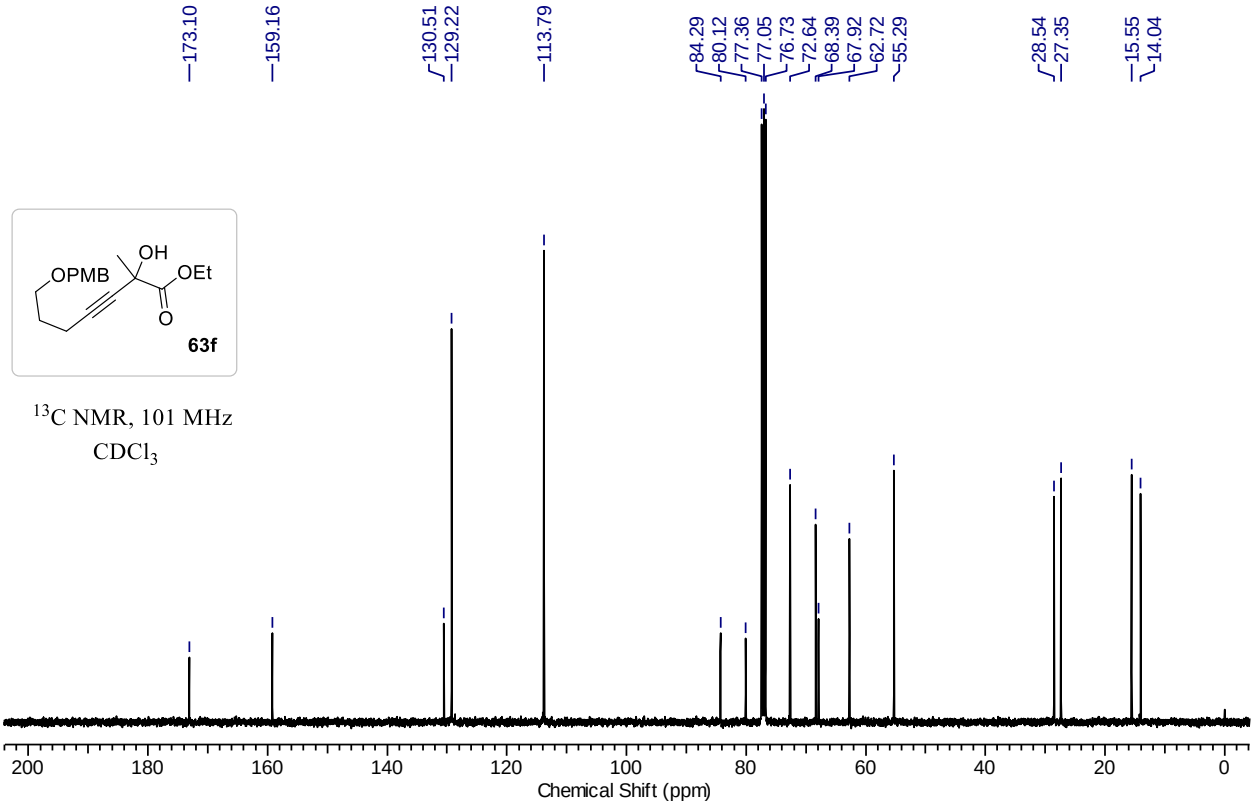


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-7-((4-methoxybenzyl)oxy)-2-methylhept-3-ynoate (63f):

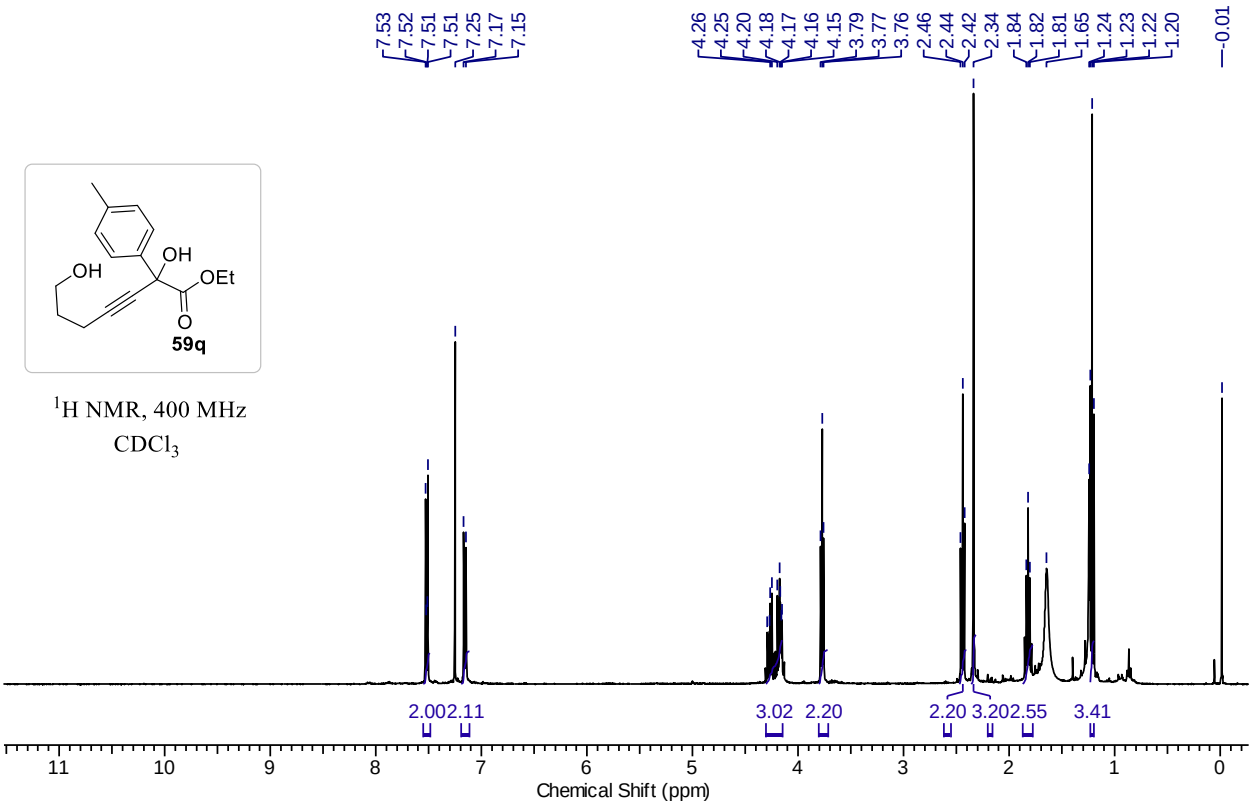


^{1}H NMR, 400 MHz
$CDCl_3$

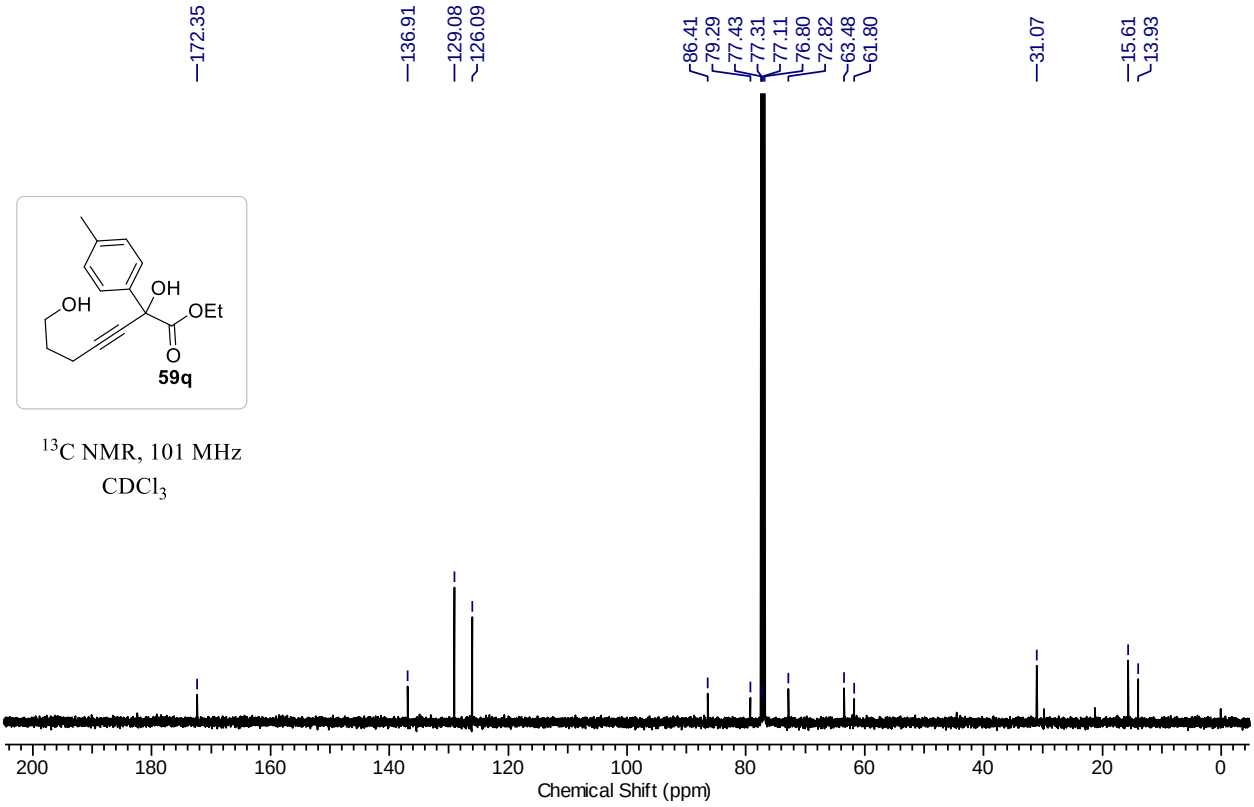


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2,7-dihydroxy-2-(*p*-tolyl)hept-3-ynoate (63q):

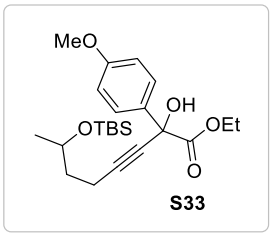


^{1}H NMR, 400 MHz
$CDCl_3$

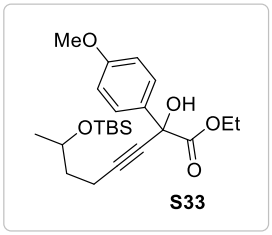


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl7-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-(4-methoxyphenyl)oct-3-ynoate (S33):

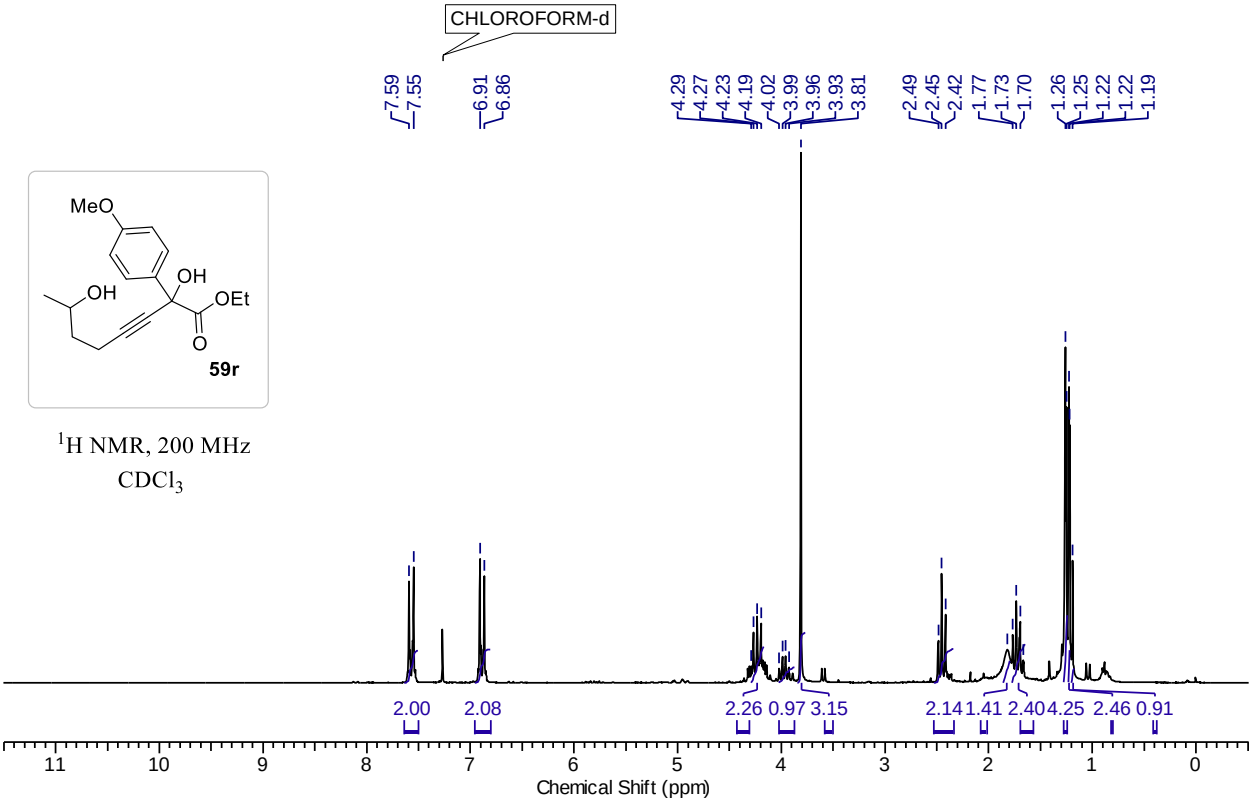


^{1}H NMR, 400 MHz
$CDCl_3$

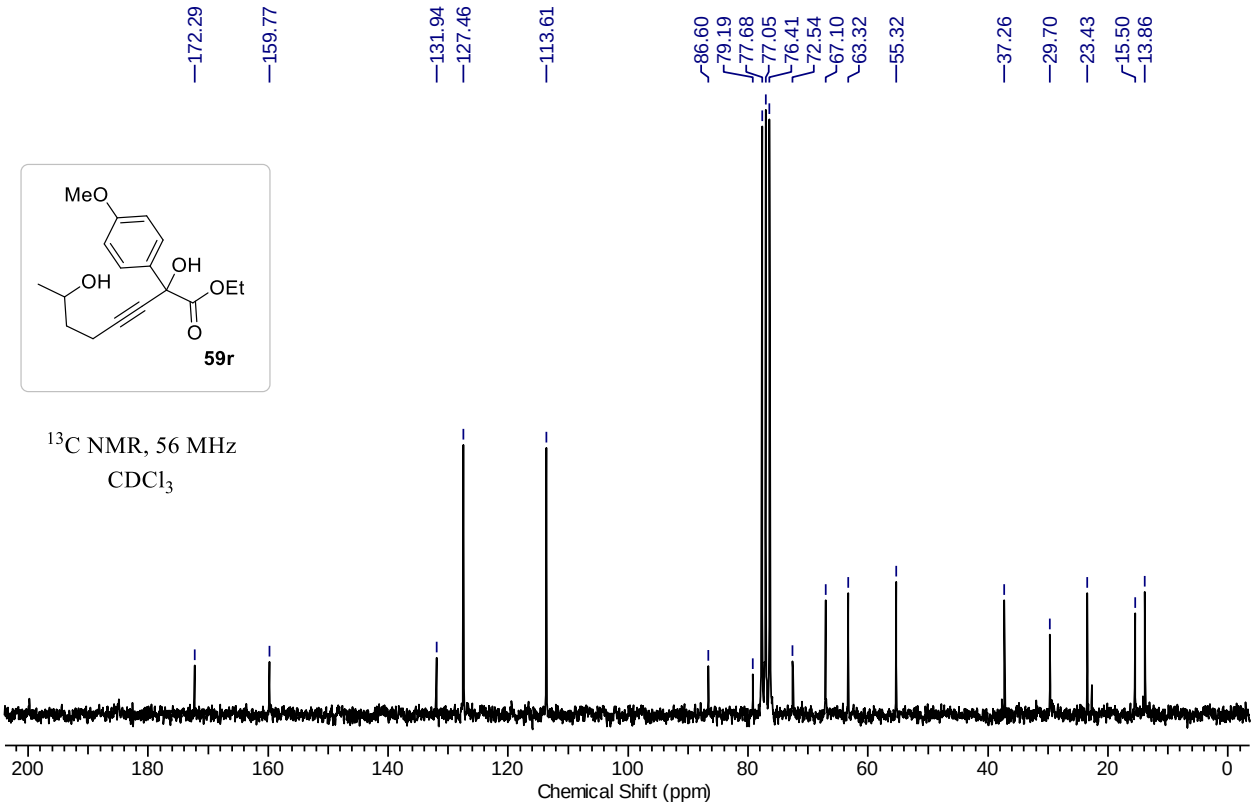


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2,7-dihydroxy-2-(4-methoxyphenyl)oct-3-ynoate (59r):

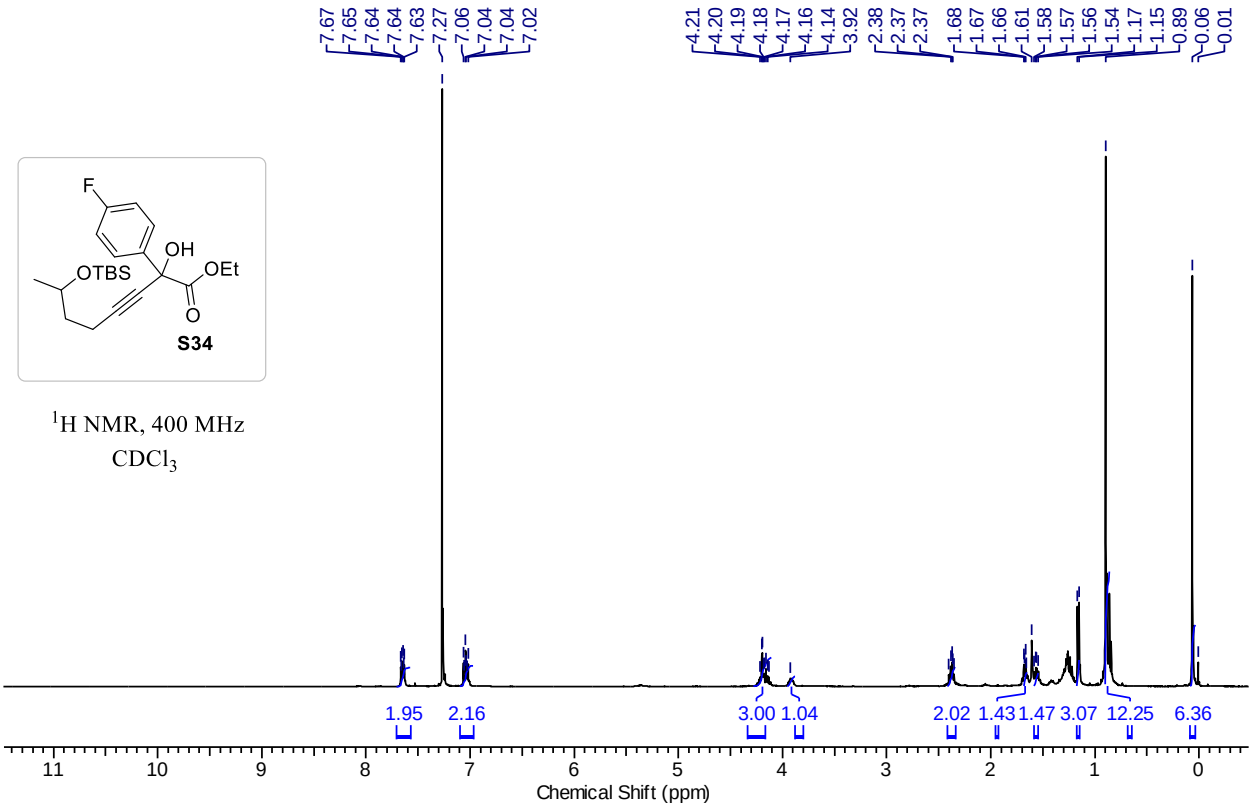


^{1}H NMR, 200 MHz
$CDCl_3$

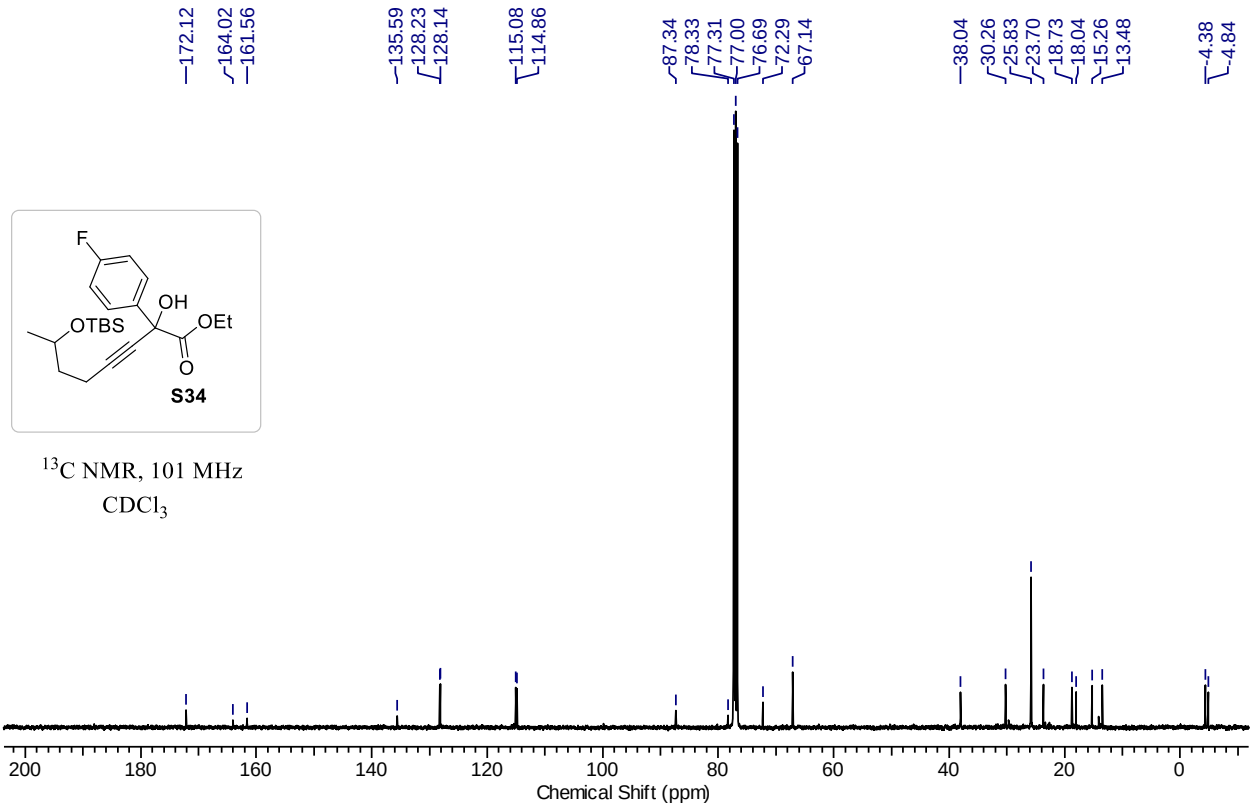


^{13}C NMR, 56 MHz
$CDCl_3$

Ethyl 7-((*tert*-butyldimethylsilyl)oxy)-2-(4-fluorophenyl)-2-hydroxyoct-3-ynoate(S34):

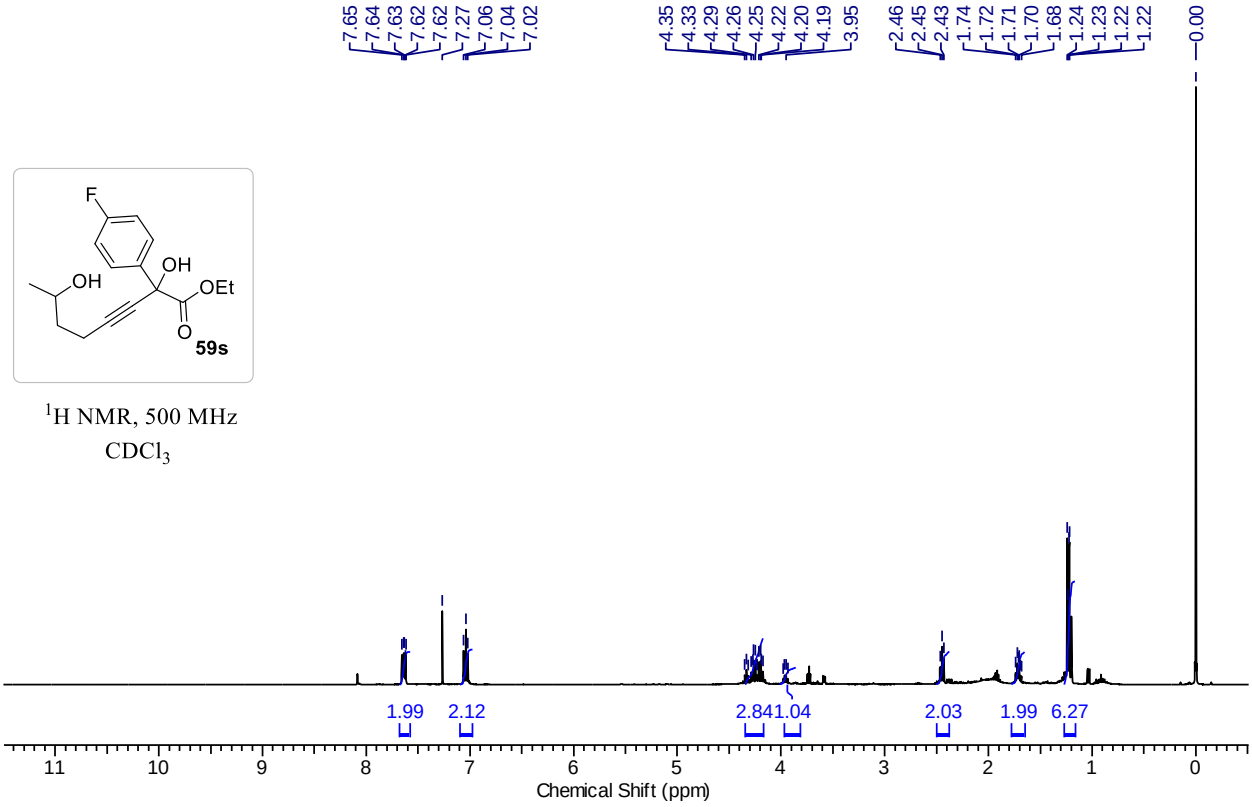


^{1}H NMR, 400 MHz
$CDCl_3$

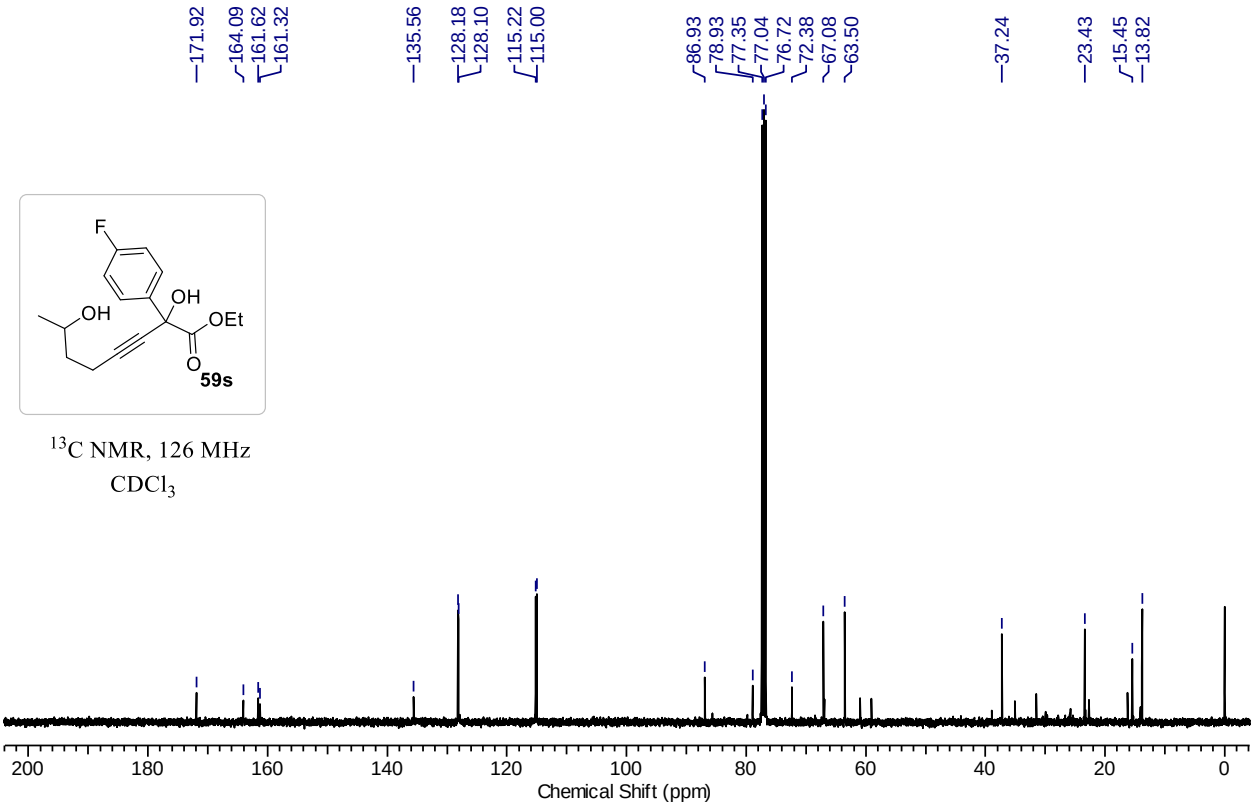


^{13}C NMR, 101 MHz
$CDCl_3$

Ethyl 2-(4-fluorophenyl)-2,7-dihydroxyoct-3-ynoate(59s):

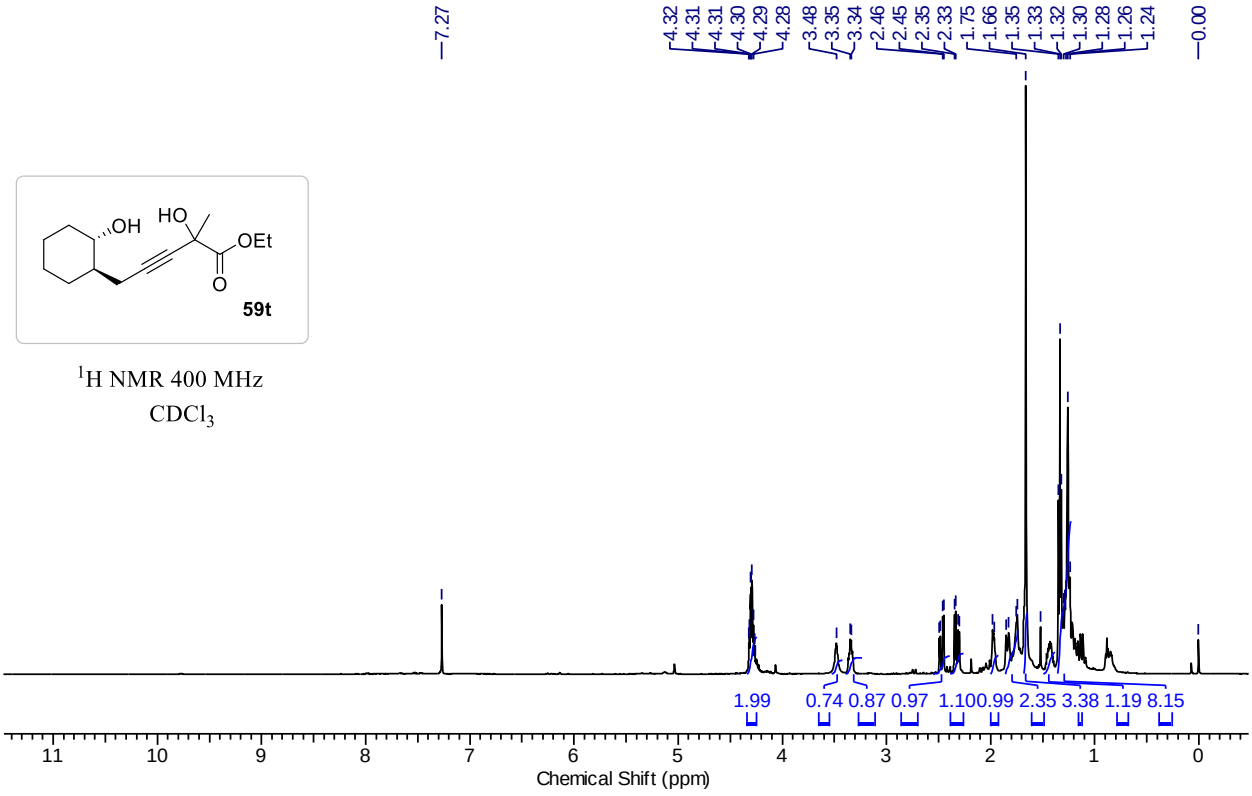


^{1}H NMR, 500 MHz
$CDCl_3$

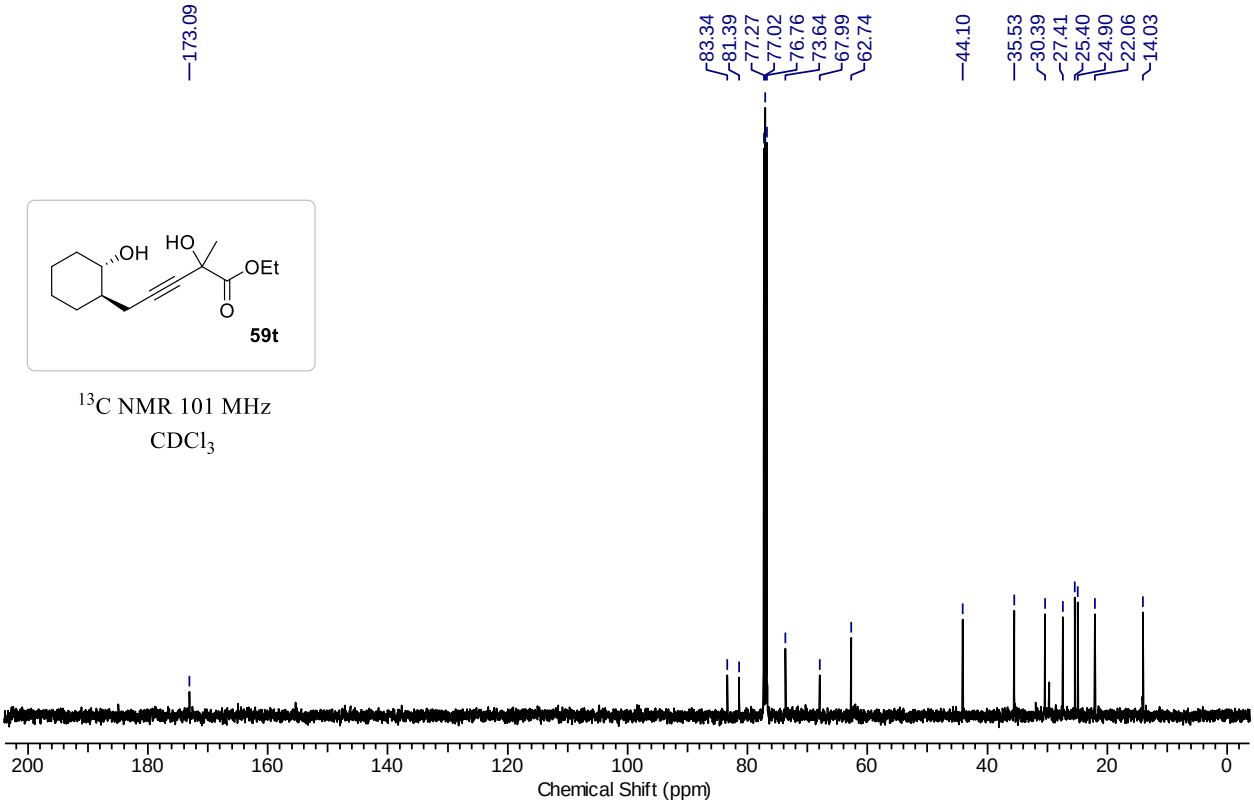


^{13}C NMR, 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-5-(2-hydroxycyclohexyl)-2-methylpent-3-ynoate (59t):

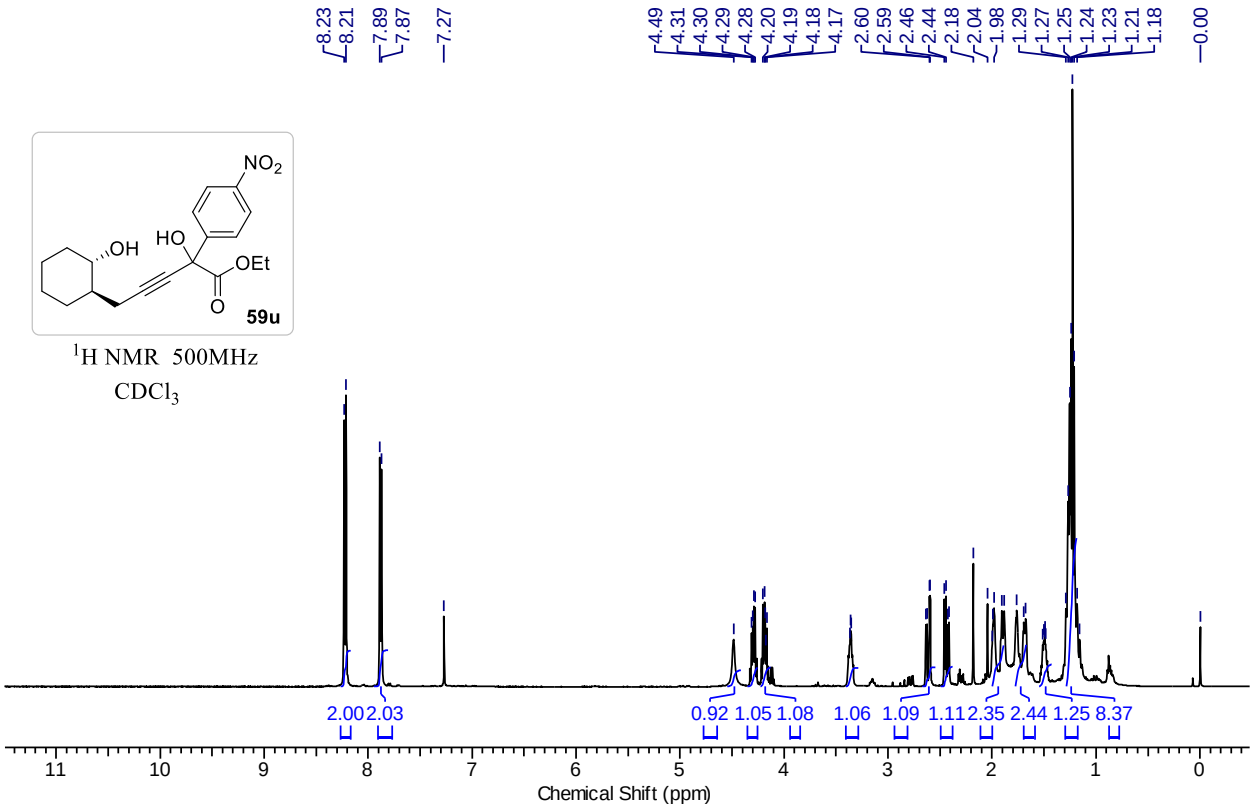


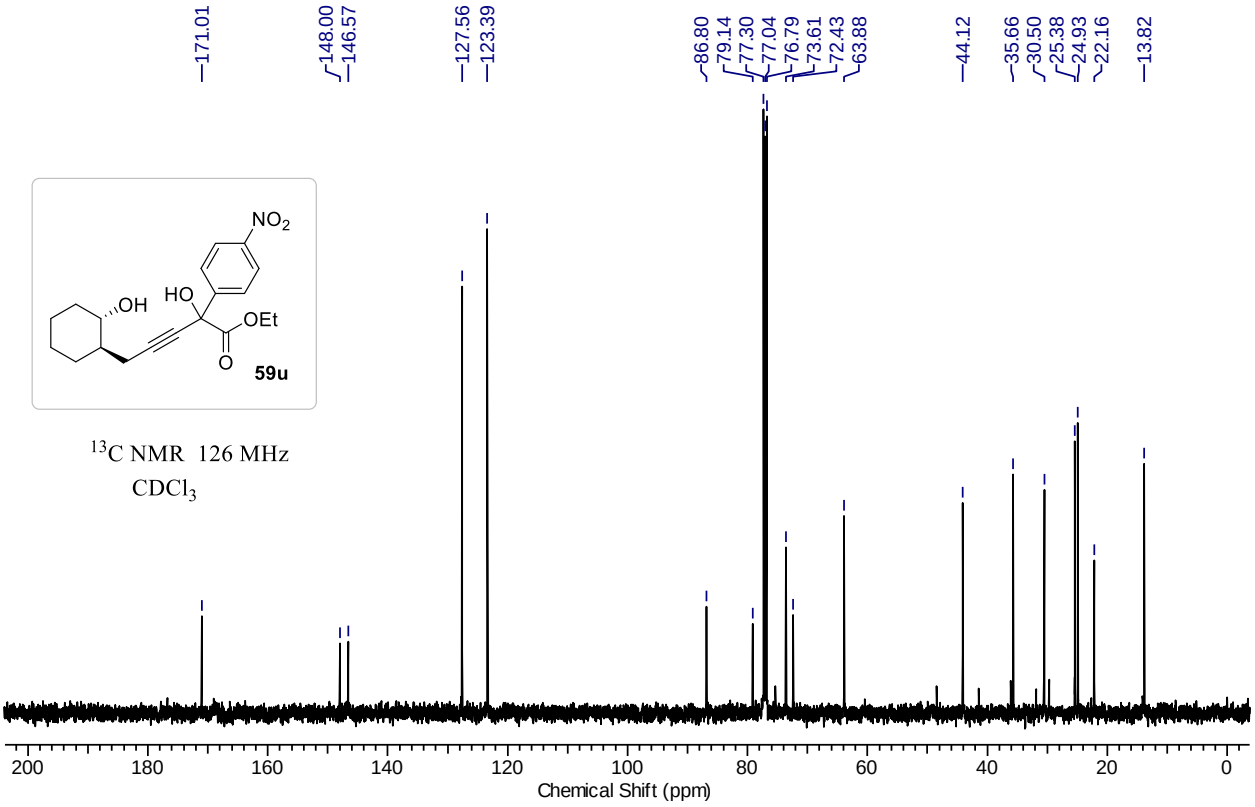
^{1}H NMR 400 MHz
$CDCl_3$



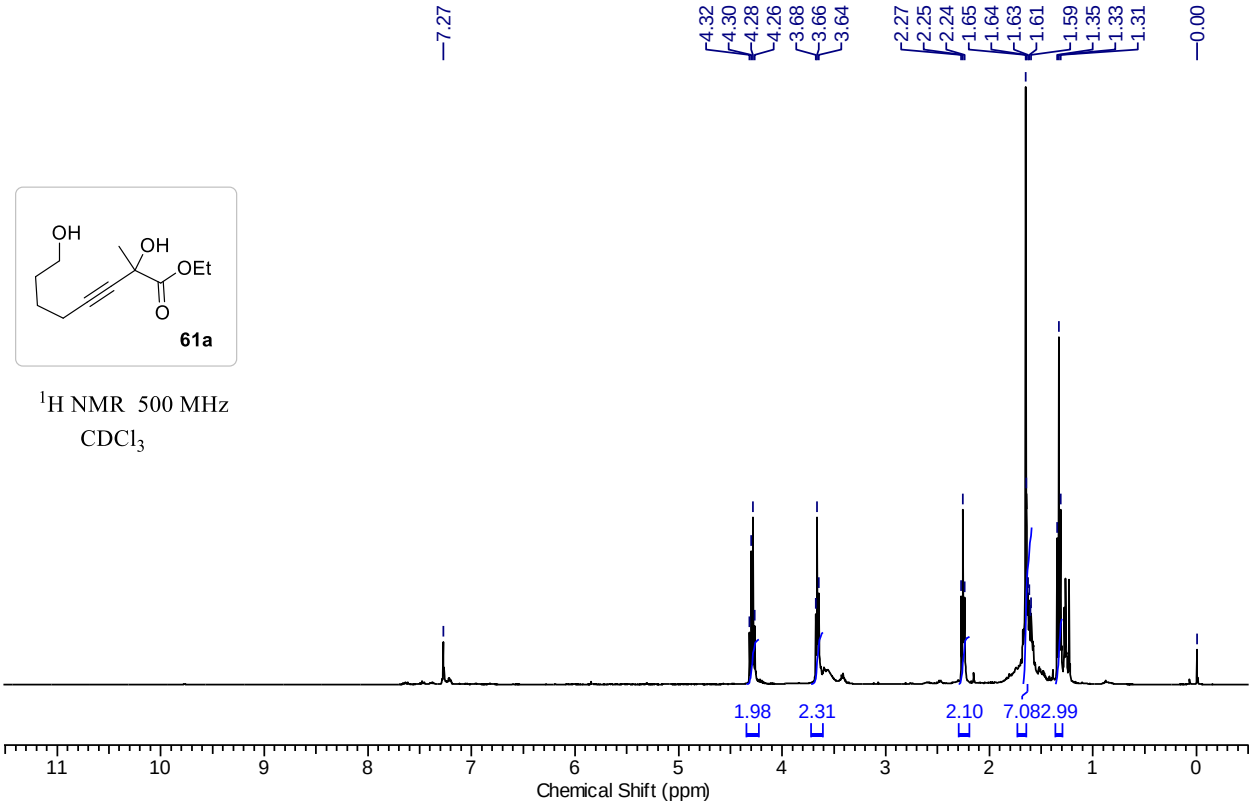
^{13}C NMR 101 MHz
$CDCl_3$

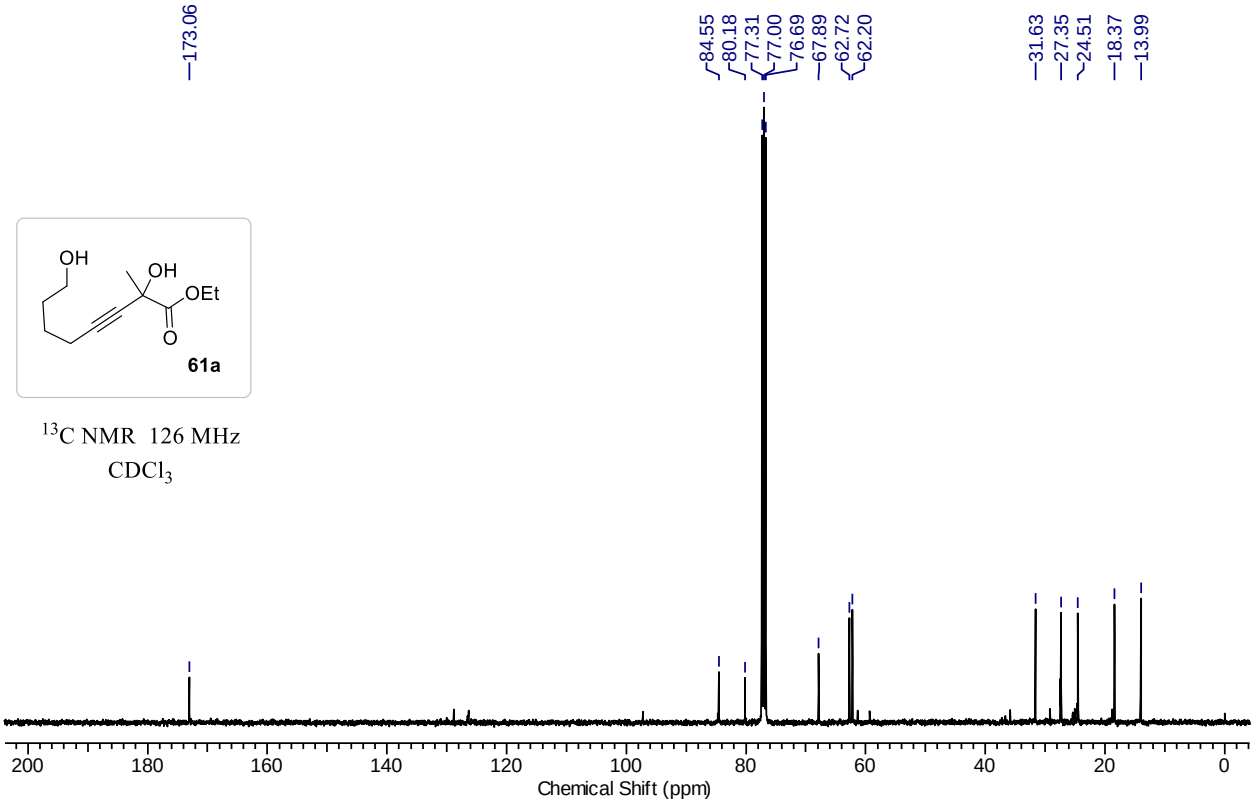
Ethyl 2-hydroxy-5-(2-hydroxycyclohexyl)-2-(4-nitrophenyl) pent-3-ynoate (59u):



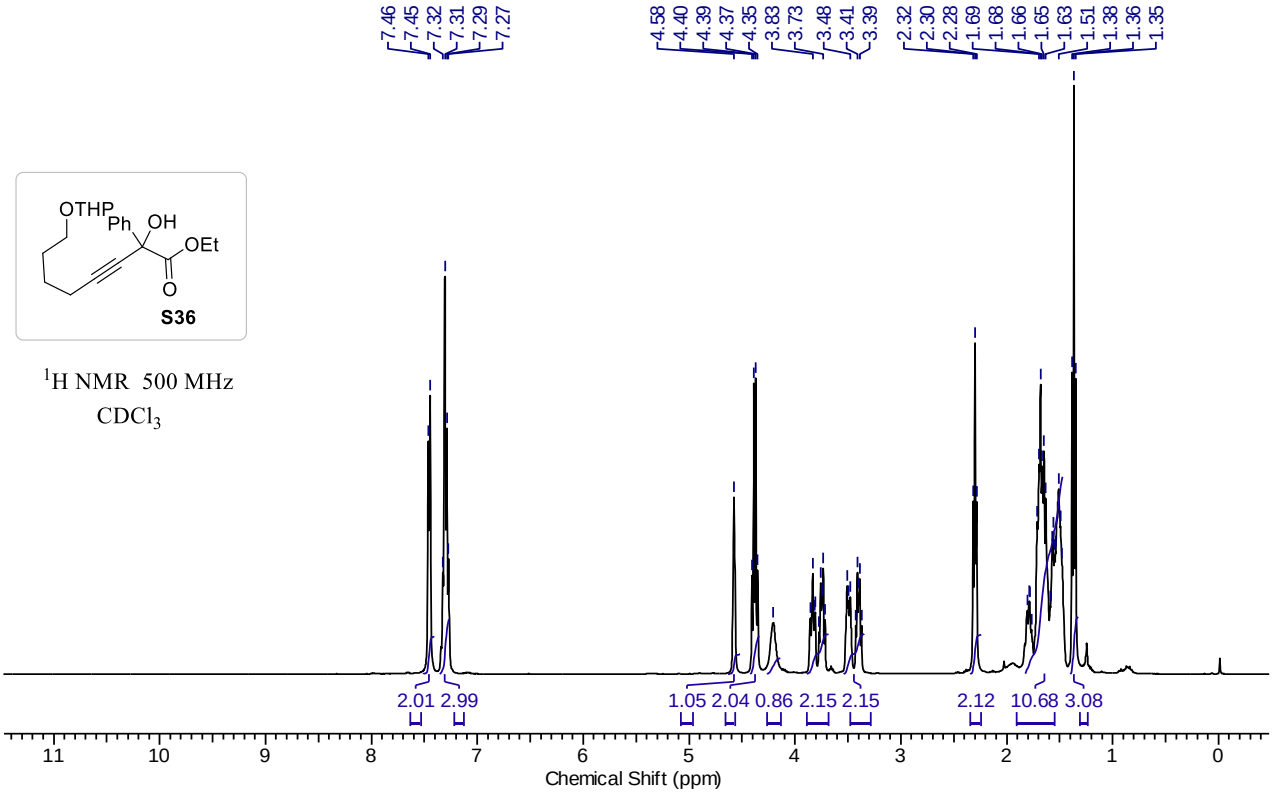


Ethyl 2, 8-dihydroxy-2-methyloct-3-ynoate (61a):

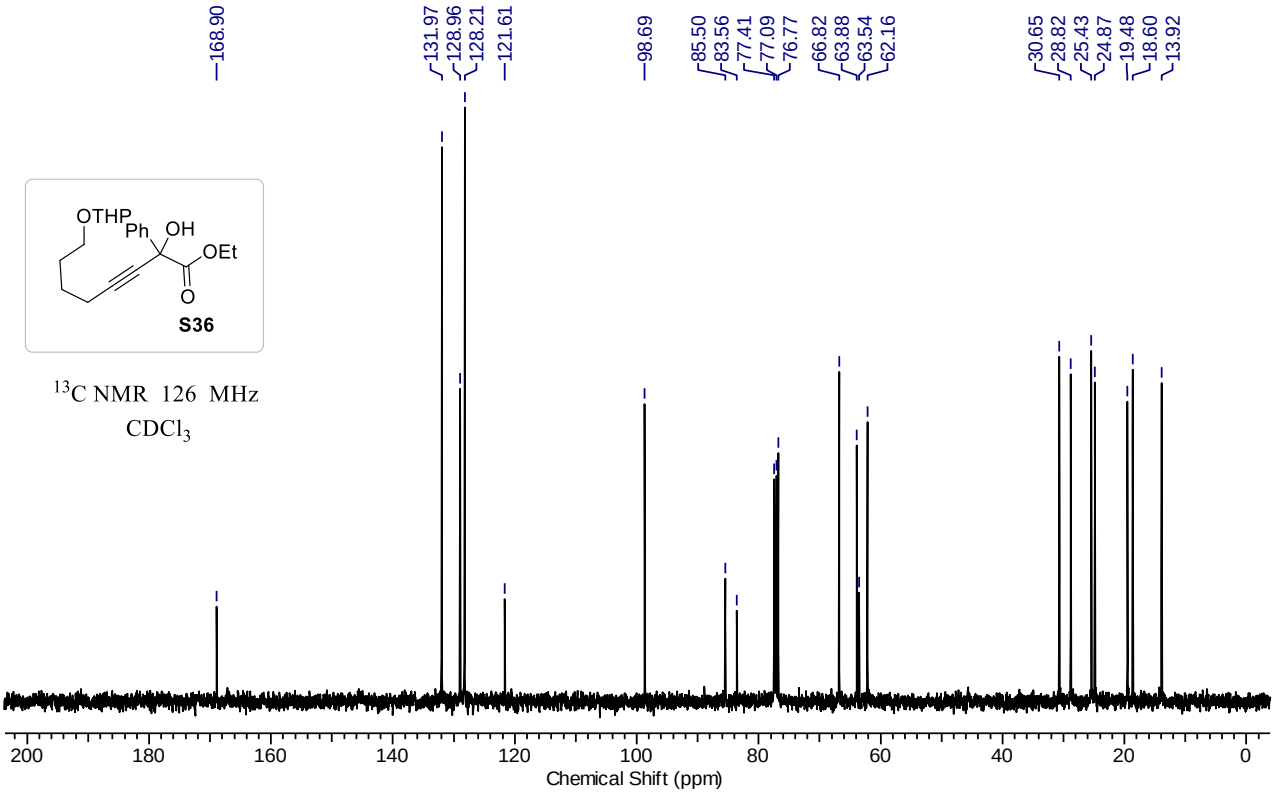




Ethyl 2-hydroxy-2-phenyl-8-((tetrahydro-2*H*-pyran-2-yl) oxy) oct-3-ynoate (S36):

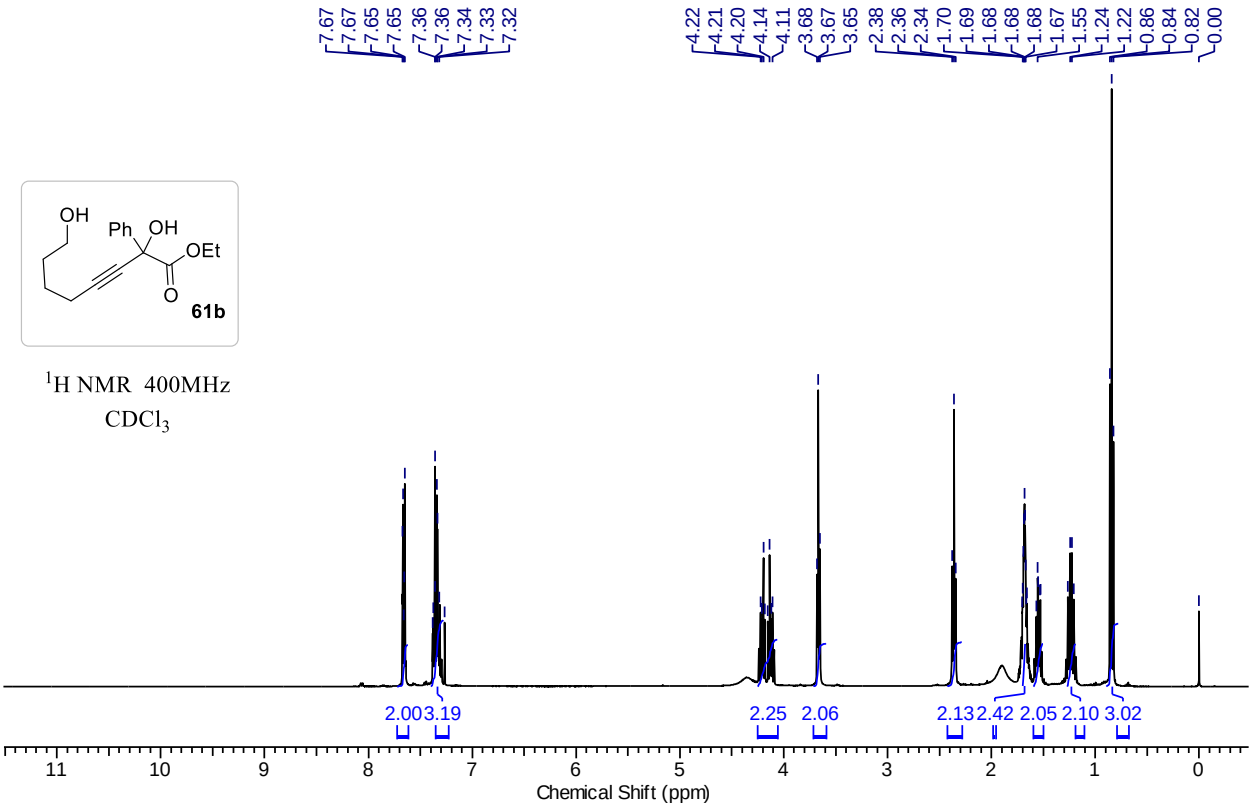


^{1}H NMR 500 MHz
$CDCl_3$

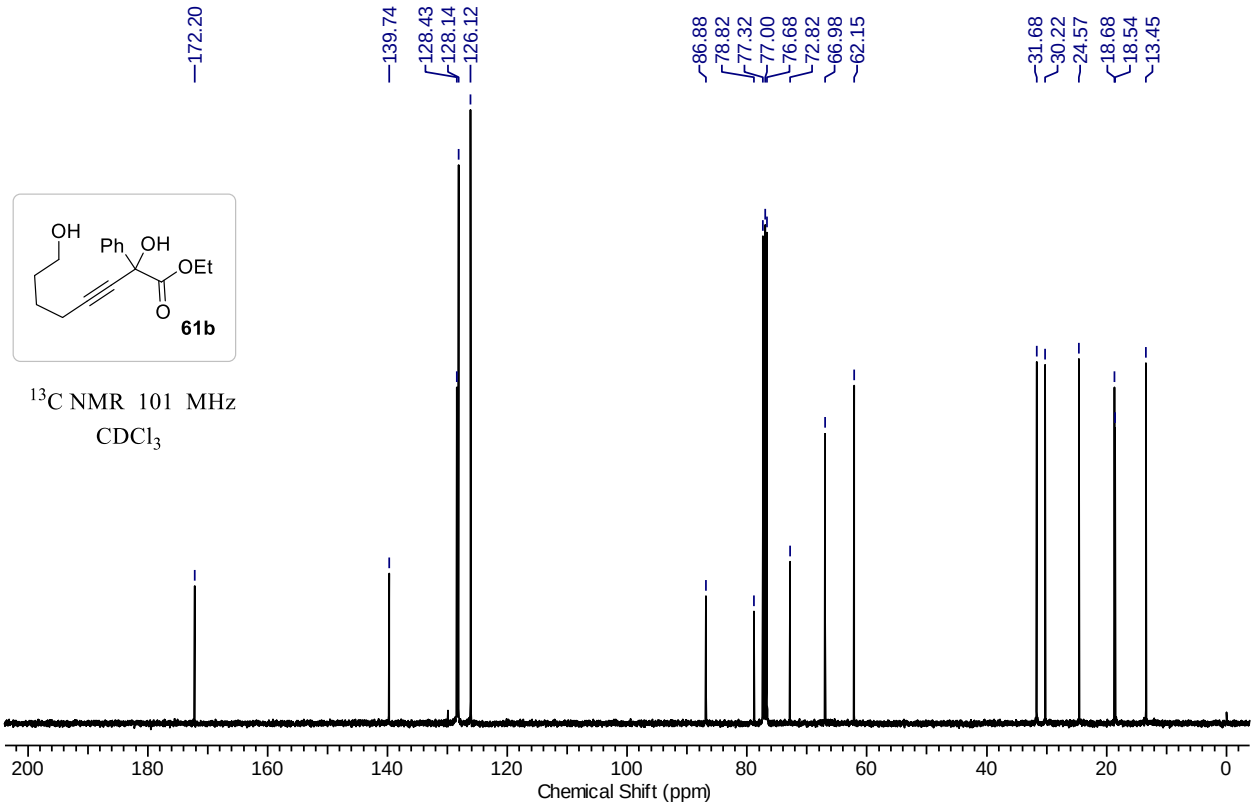


^{13}C NMR 126 MHz
$CDCl_3$

Ethyl 2,8-dihydroxy-2-phenyloct-3-ynoate (61b):

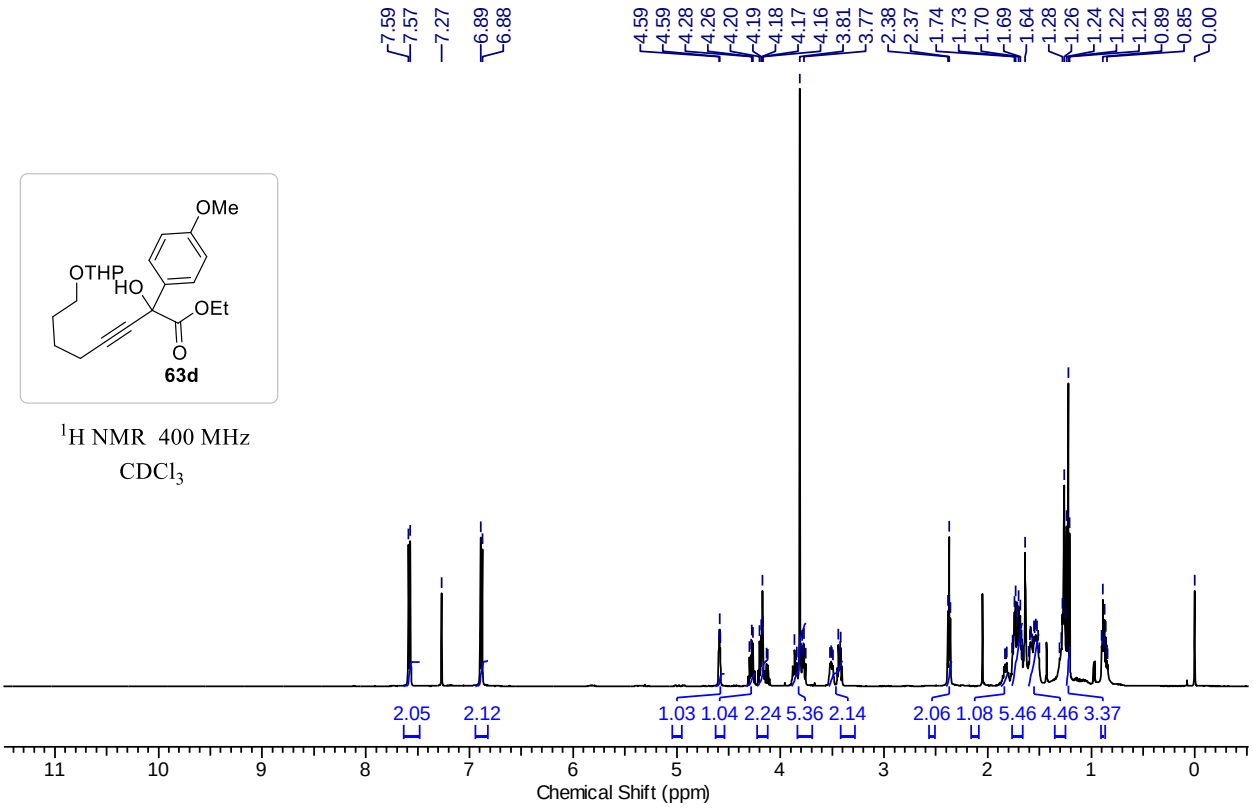


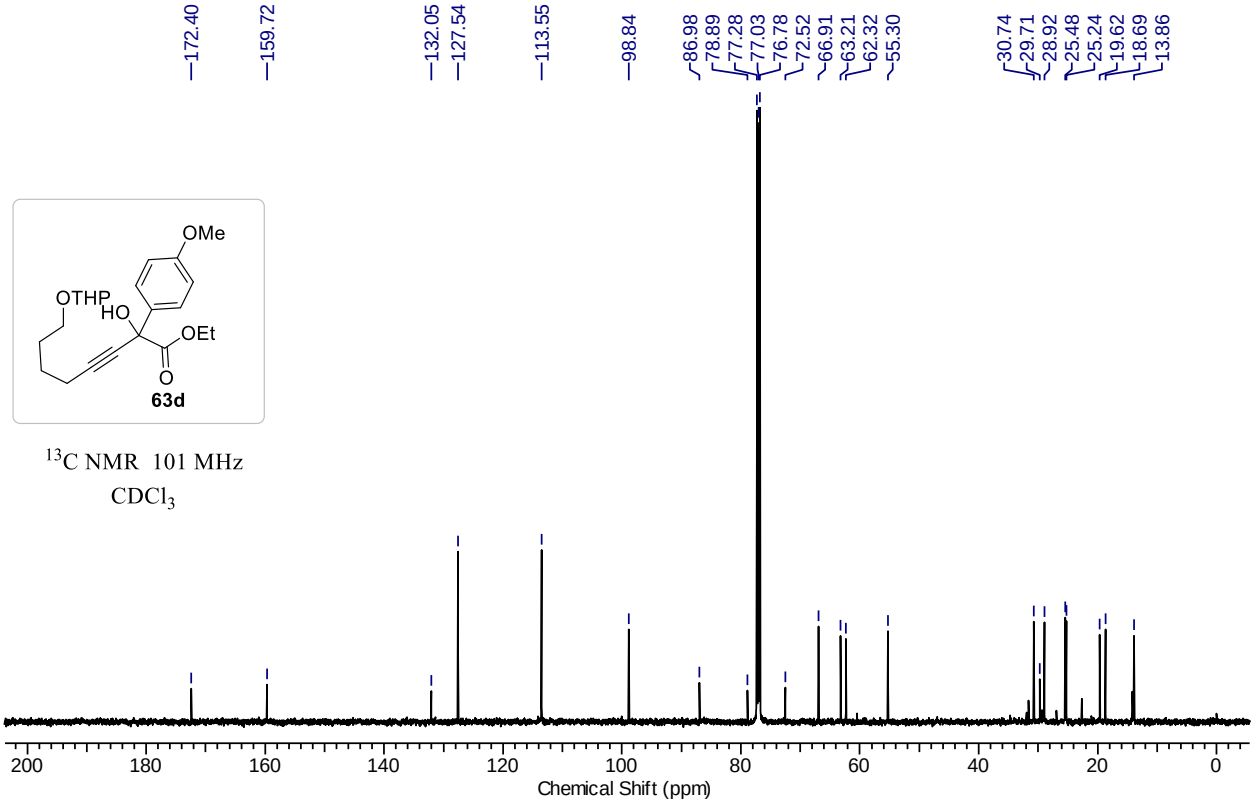
^{1}H NMR 400MHz
$CDCl_3$



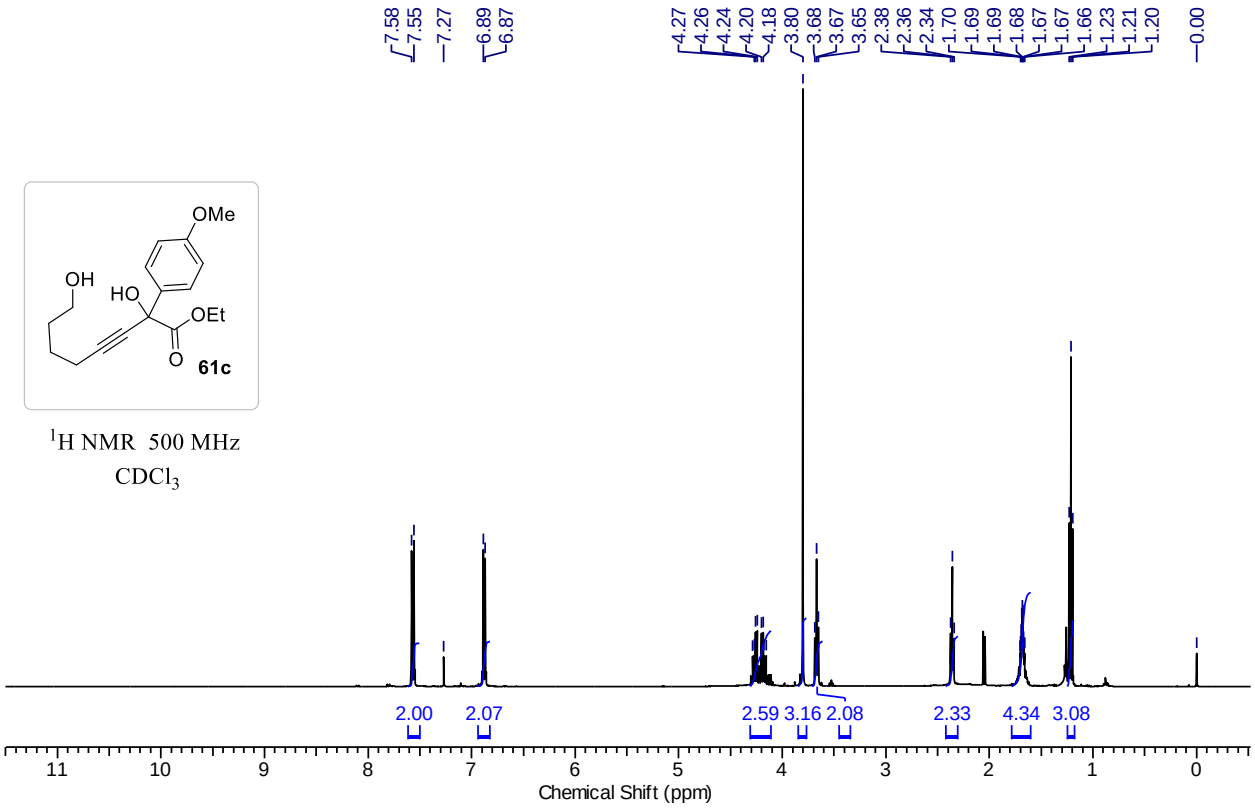
^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 2-hydroxy-2-(4-methoxyphenyl)-8-((tetrahydro-2*H*-pyran-2-yl)oxy)oct-3-ynoate (63d):

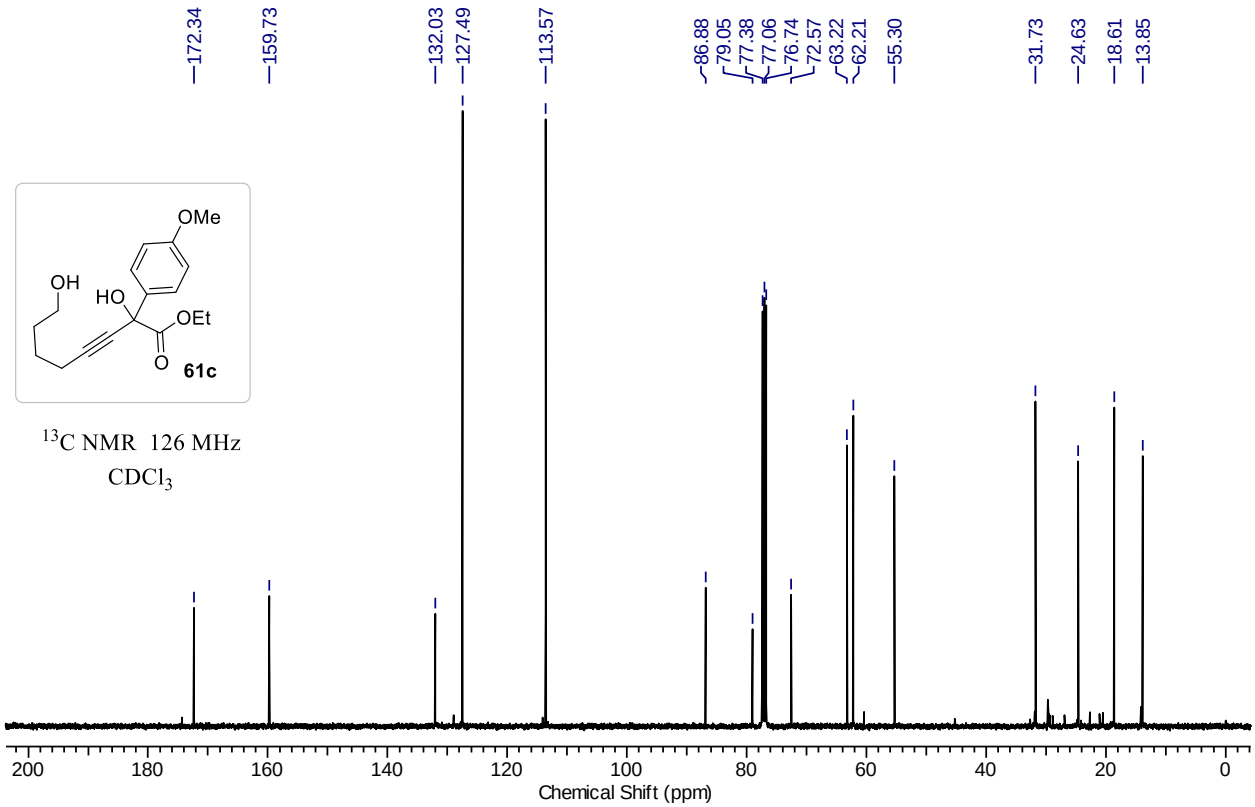




Ethyl 2,8-dihydroxy-2-(4-methoxyphenyl)oct-3-ynoate (61c):

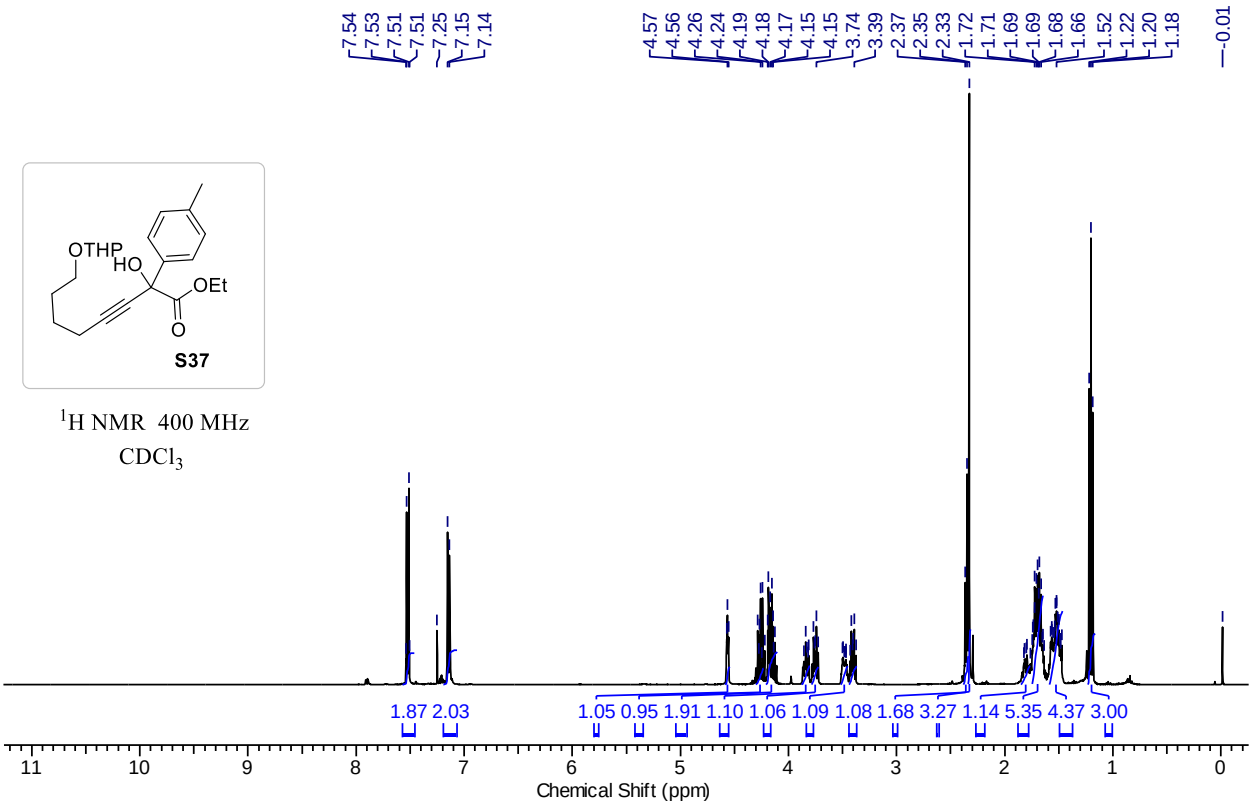


^{1}H NMR 500 MHz
$CDCl_3$

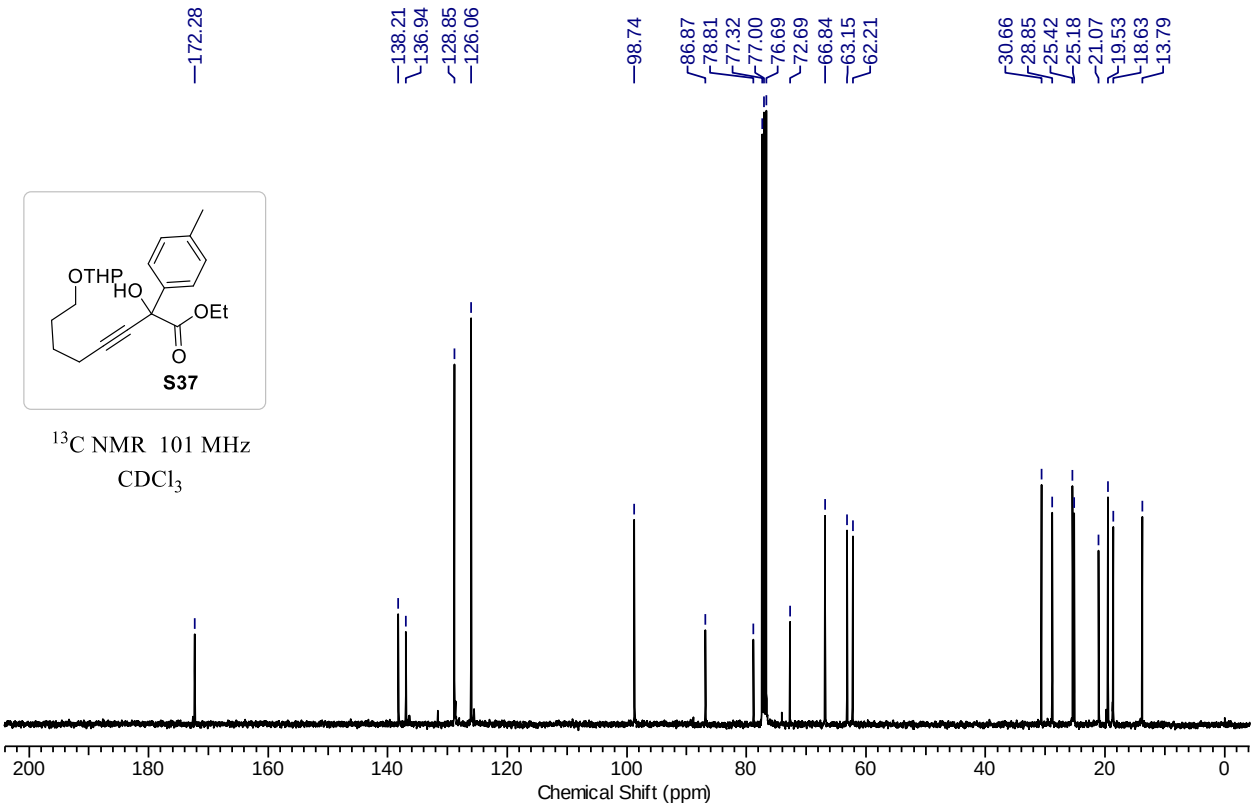


^{13}C NMR 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-8-((tetrahydro-2*H*-pyran-2-yl)oxy)-2-(*p*-tolyl)oct-3-ynoate (S37):

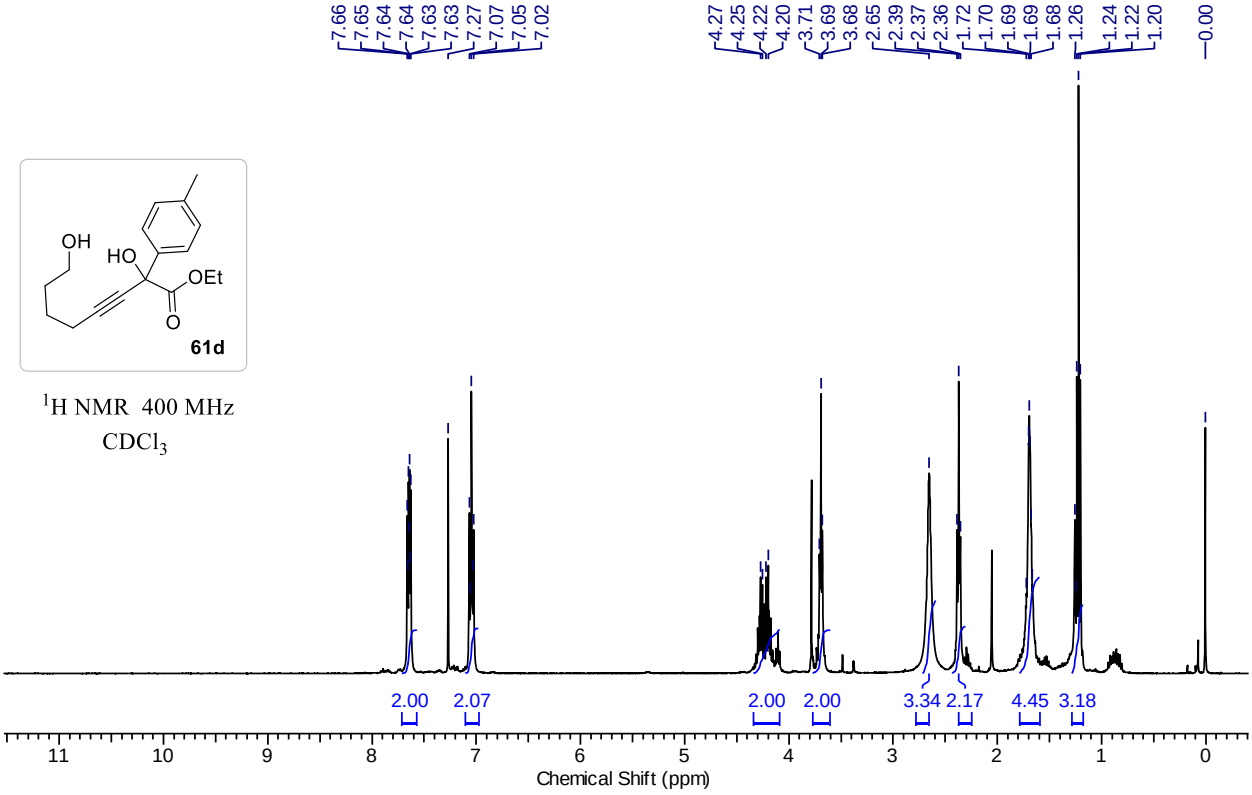


^{1}H NMR 400 MHz
$CDCl_3$

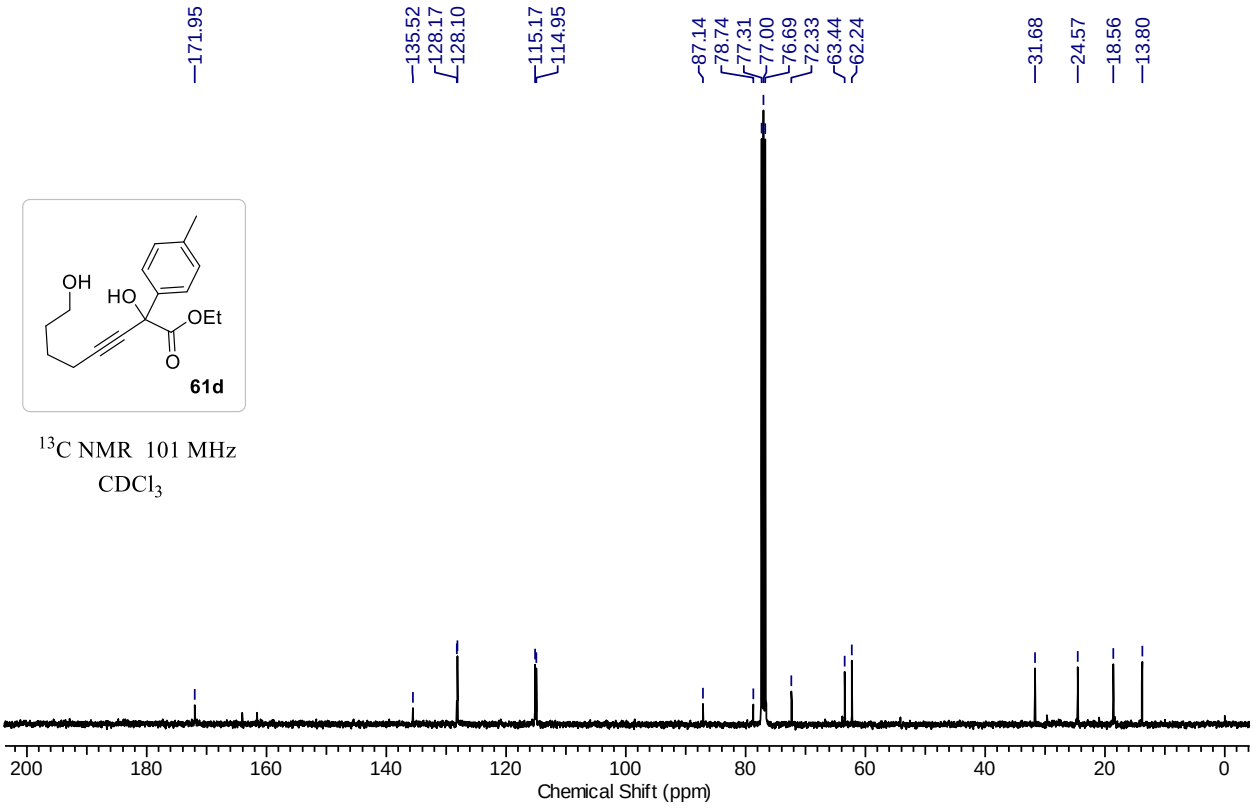


^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 2,8-dihydroxy-2-(*p*-tolyl)oct-3-ynoate (61d):

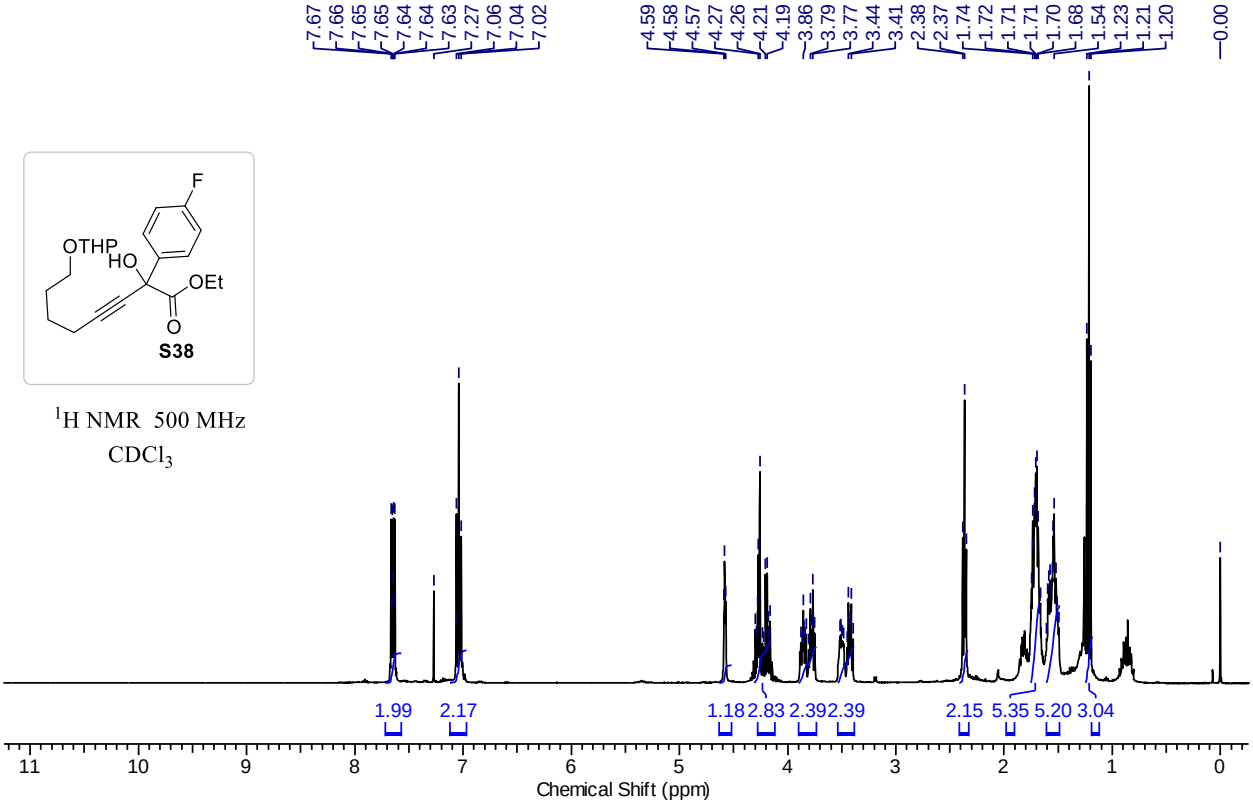


^{1}H NMR 400 MHz
$CDCl_3$

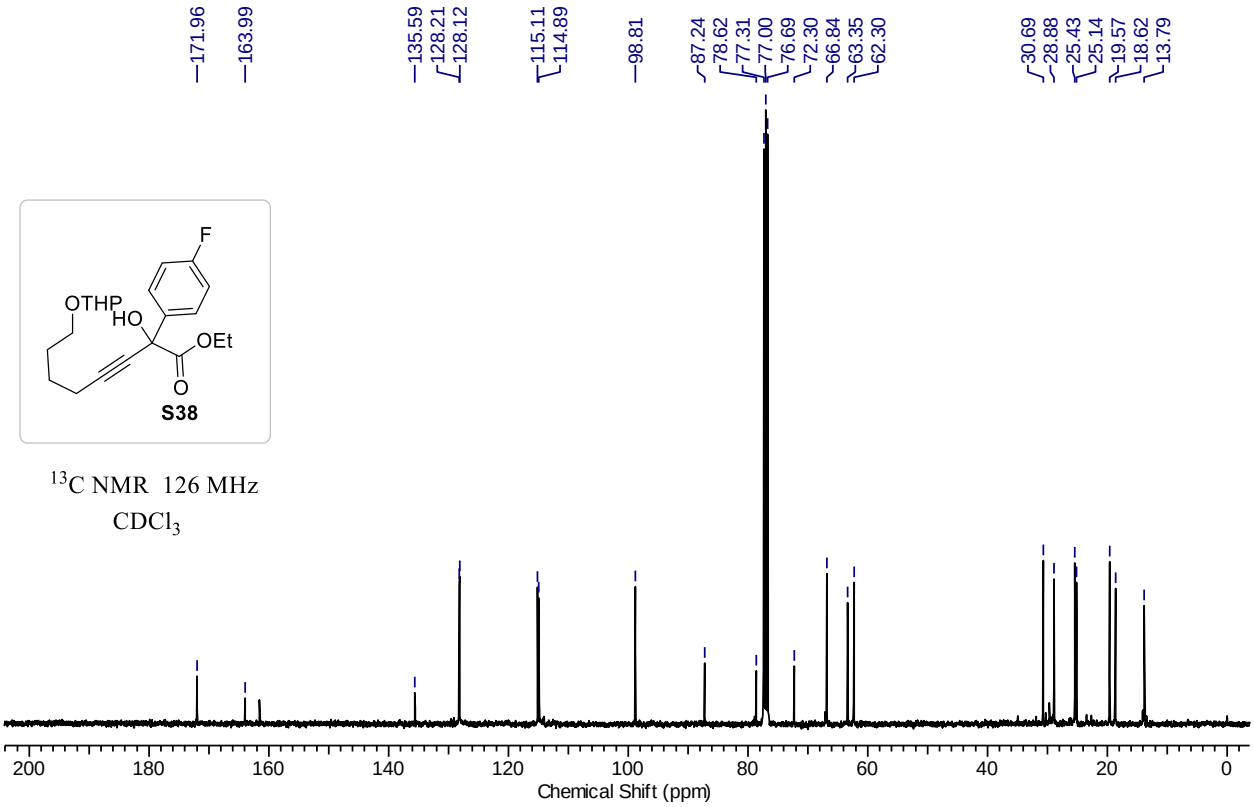


^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 2-(4-fluorophenyl)-2-hydroxy-8-((tetrahydro-2*H*-pyran-2-yl)oxy)oct-3-ynoate (S38):

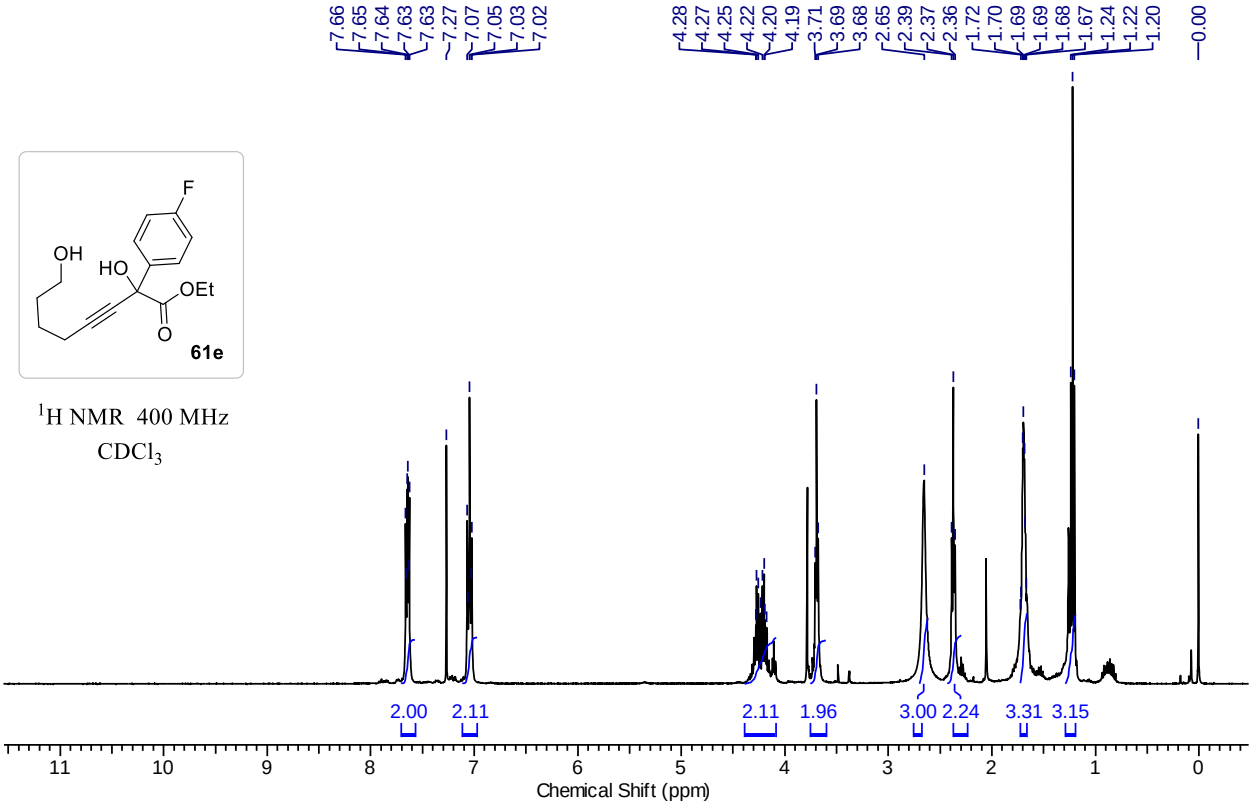


^{1}H NMR 500 MHz
$CDCl_3$

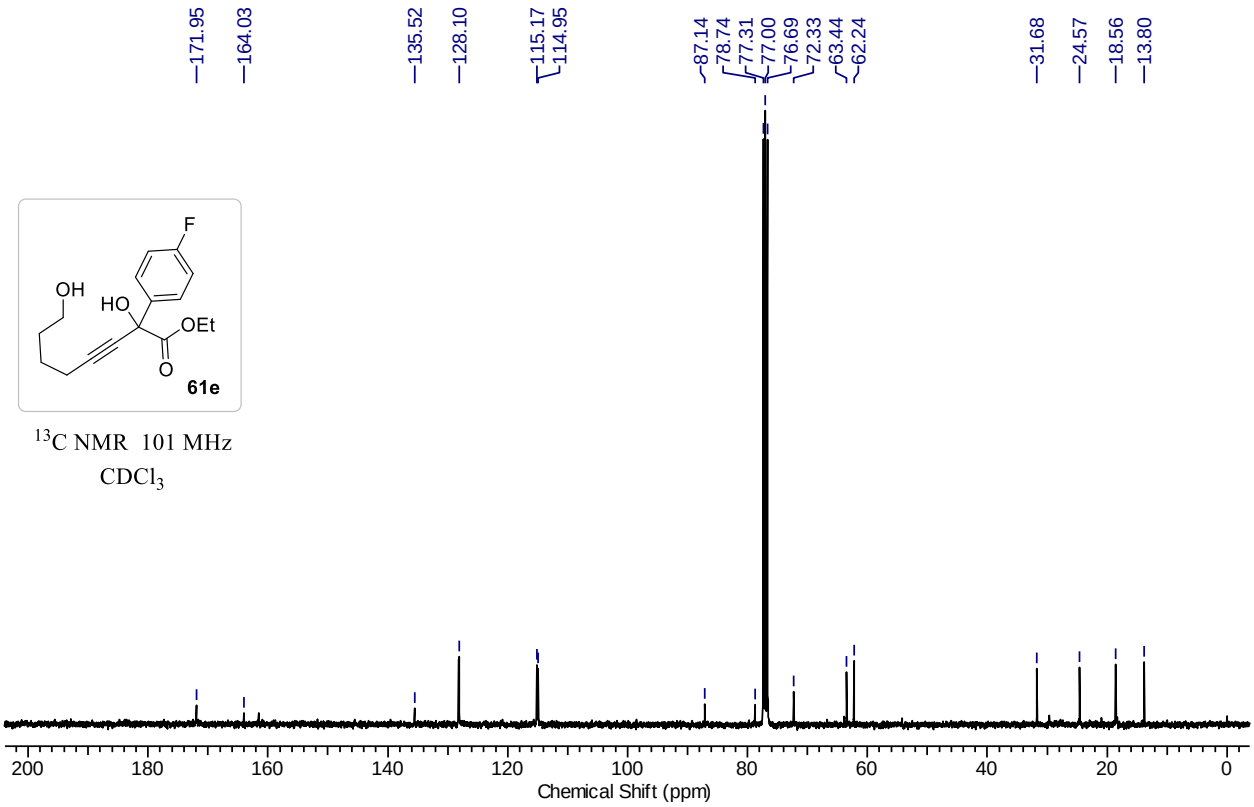


^{13}C NMR 126 MHz
$CDCl_3$

Ethyl 2-(4-fluorophenyl)-2,8-dihydroxyoct-3-ynoate (61e):

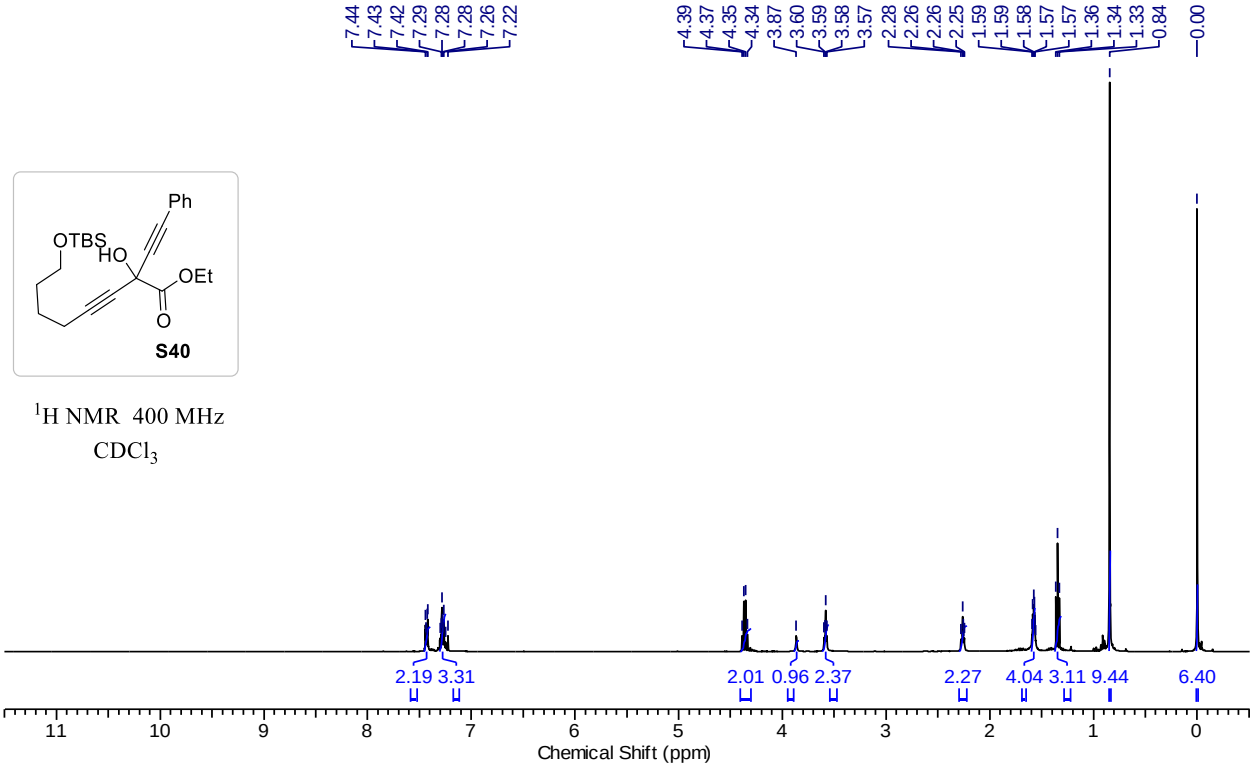


^{1}H NMR 400 MHz
$CDCl_3$

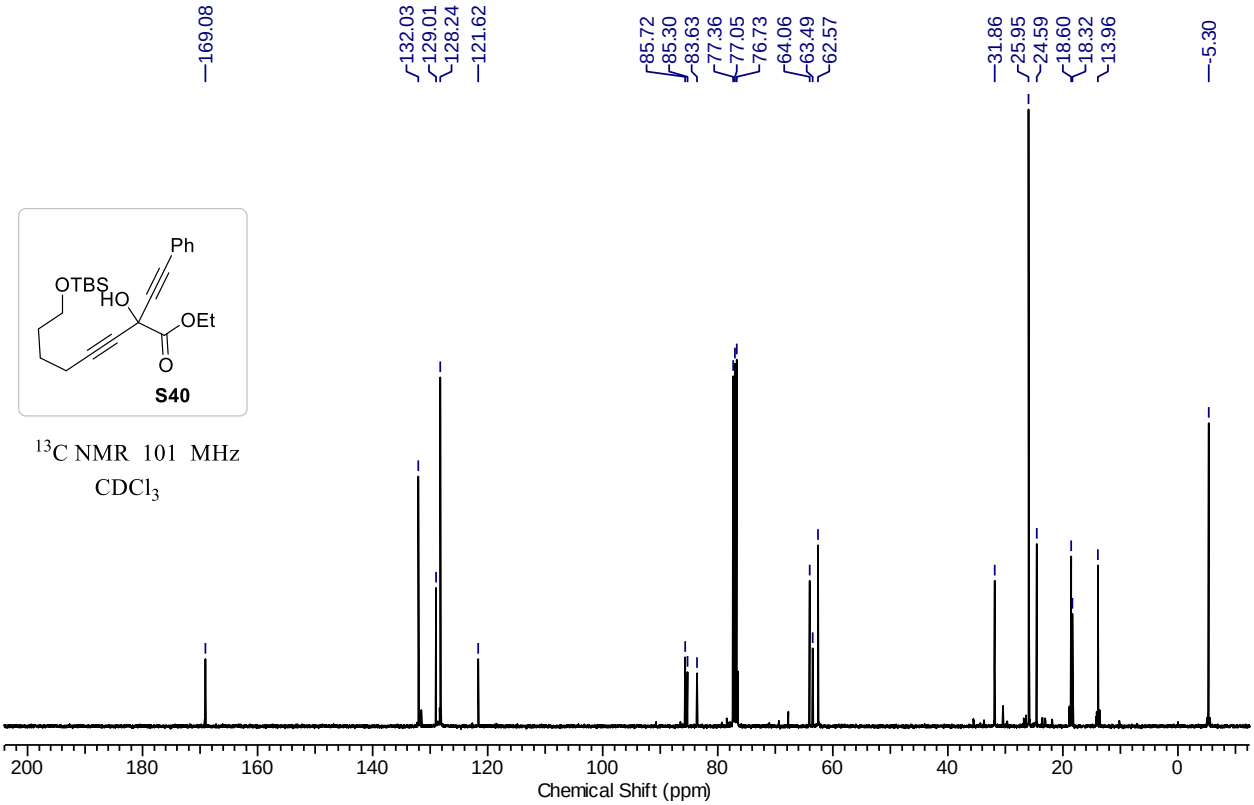


^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 8-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-(phenylethynyl)oct-3-ynoate (S40):

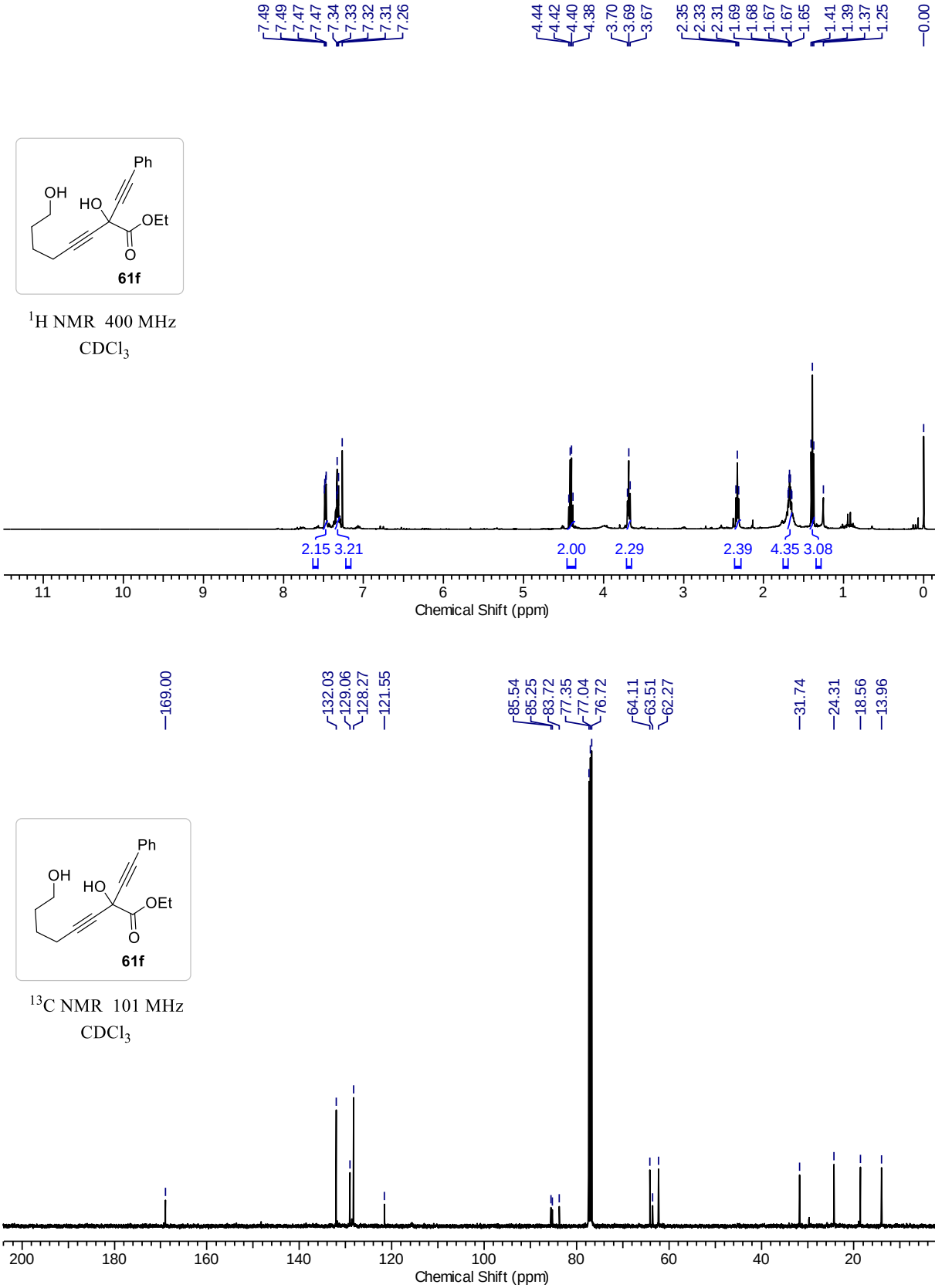


^{1}H NMR 400 MHz
$CDCl_3$

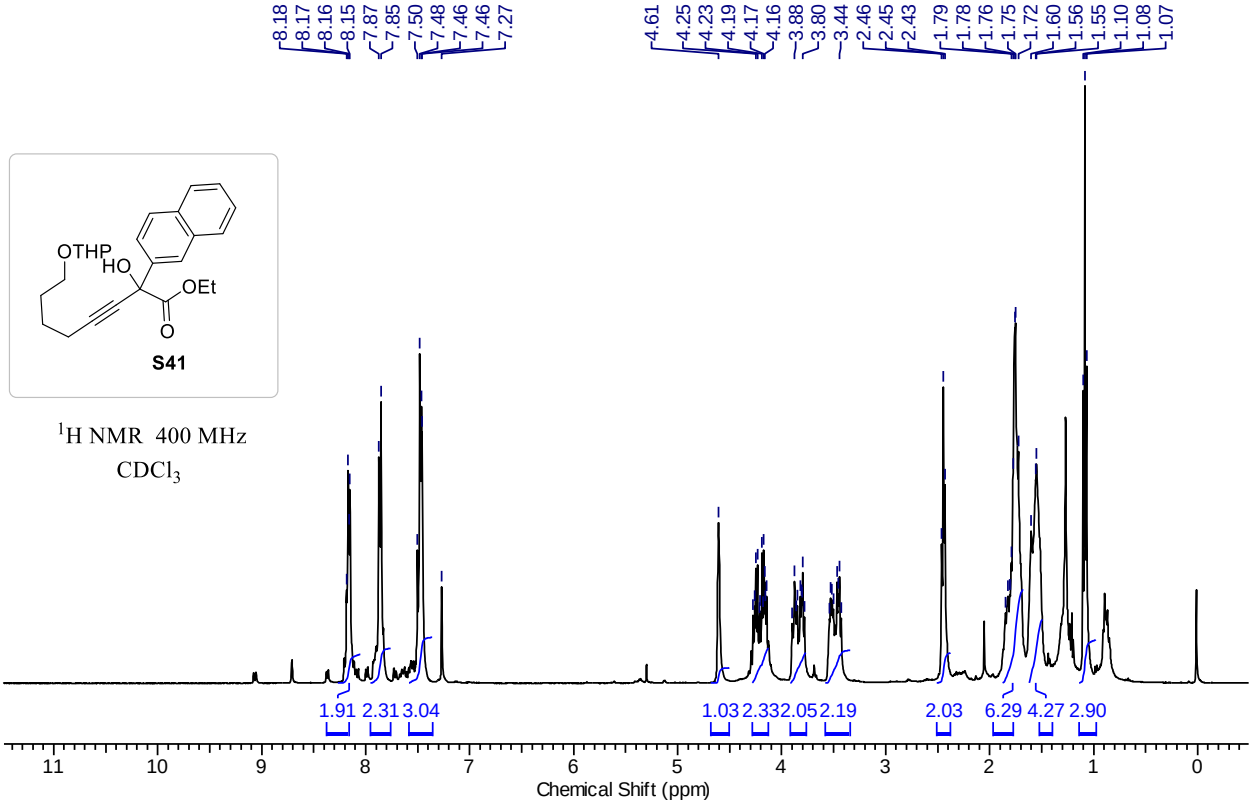


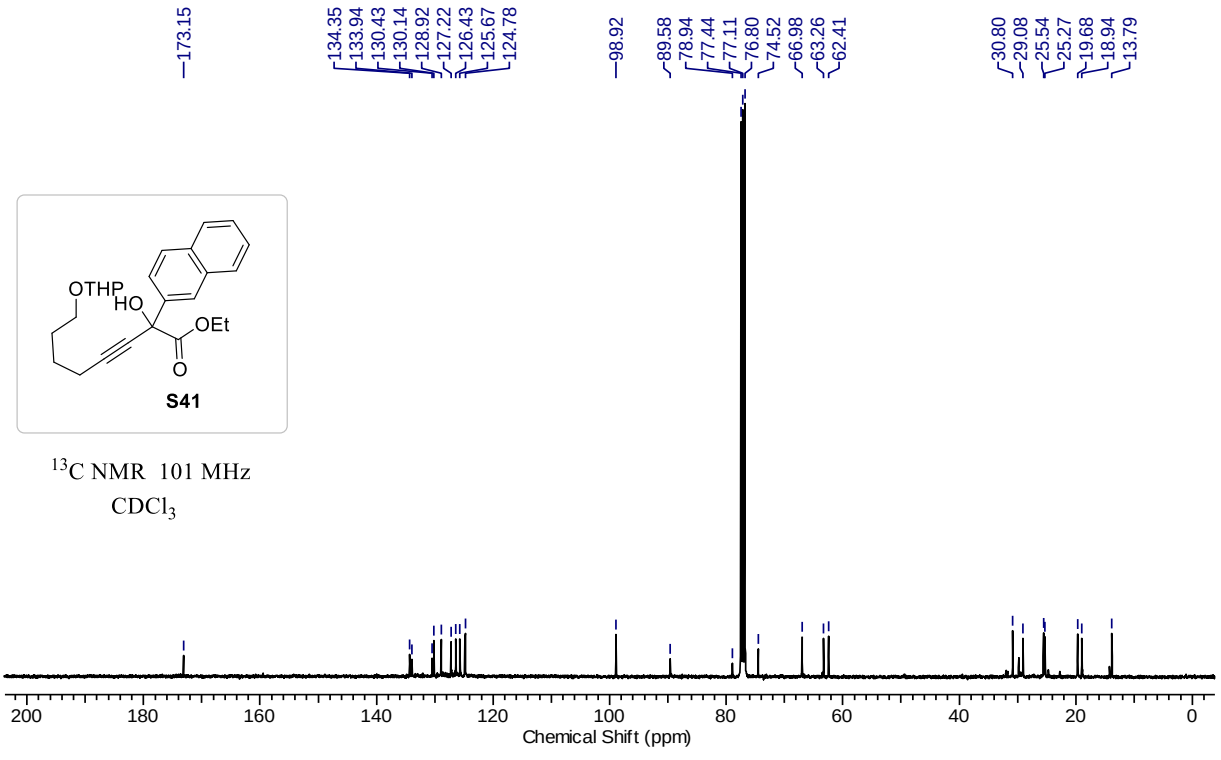
^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 2,8-dihydroxy-2-(phenylethynyl)oct-3-ynoate (61f):

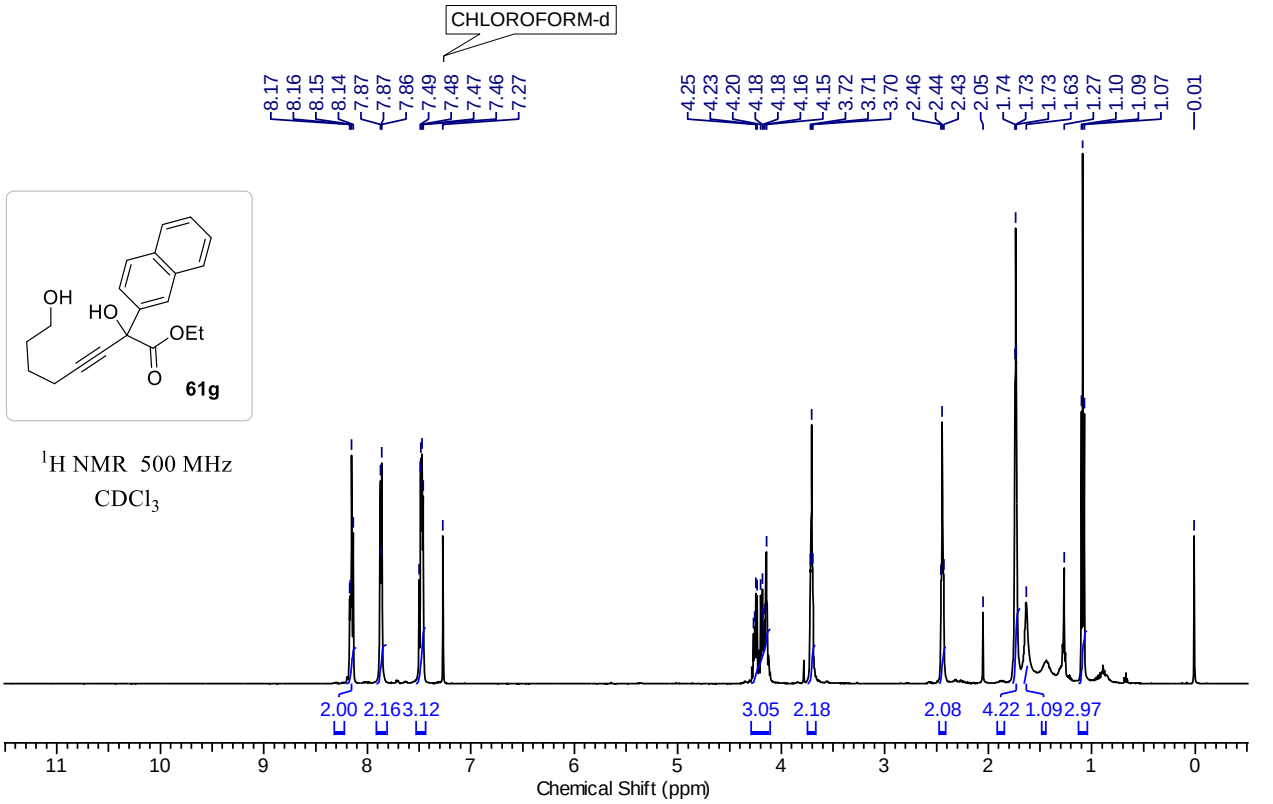


Ethyl2-hydroxy-2-(naphthalen-2-yl)-8-((tetrahydro-2*H*-pyran-2-yl) oxy) oct-3-ynoate (S41):

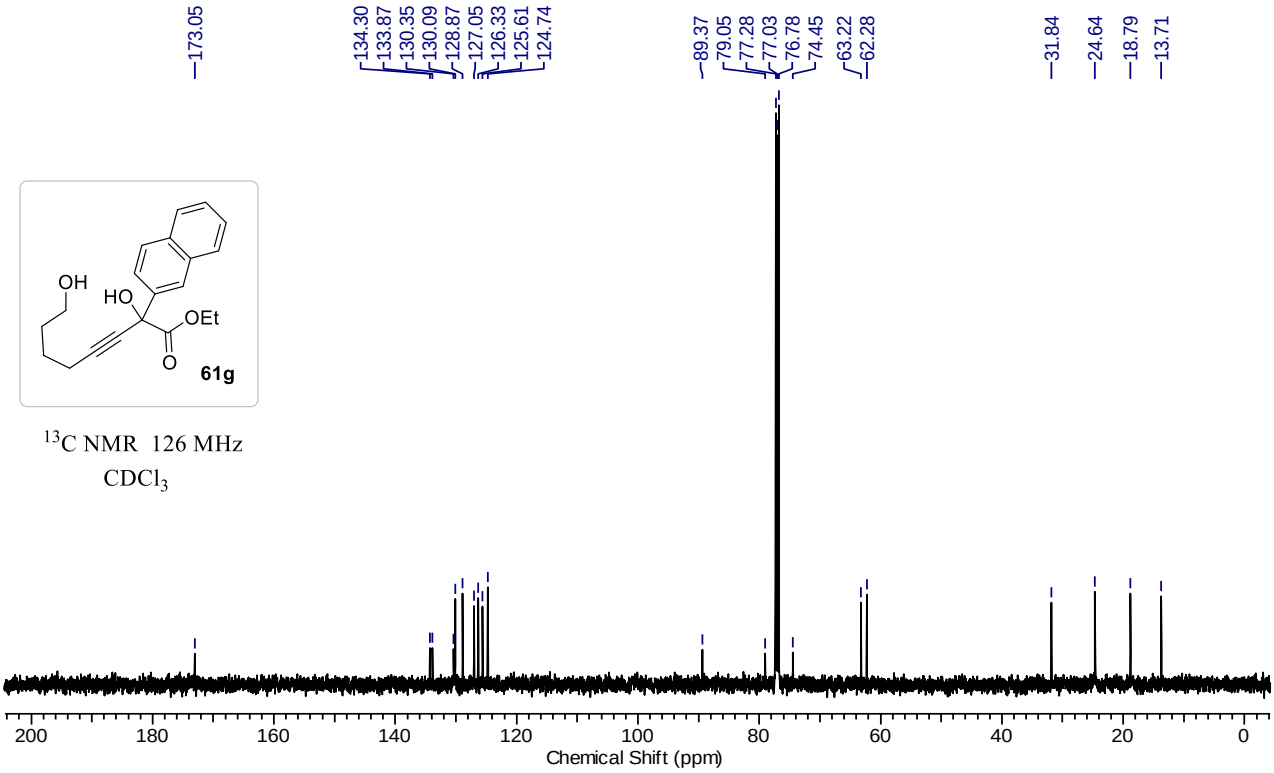




Ethyl 2, 8-dihydroxy-2-(naphthalen-2-yl) oct-3-ynoate (61g):

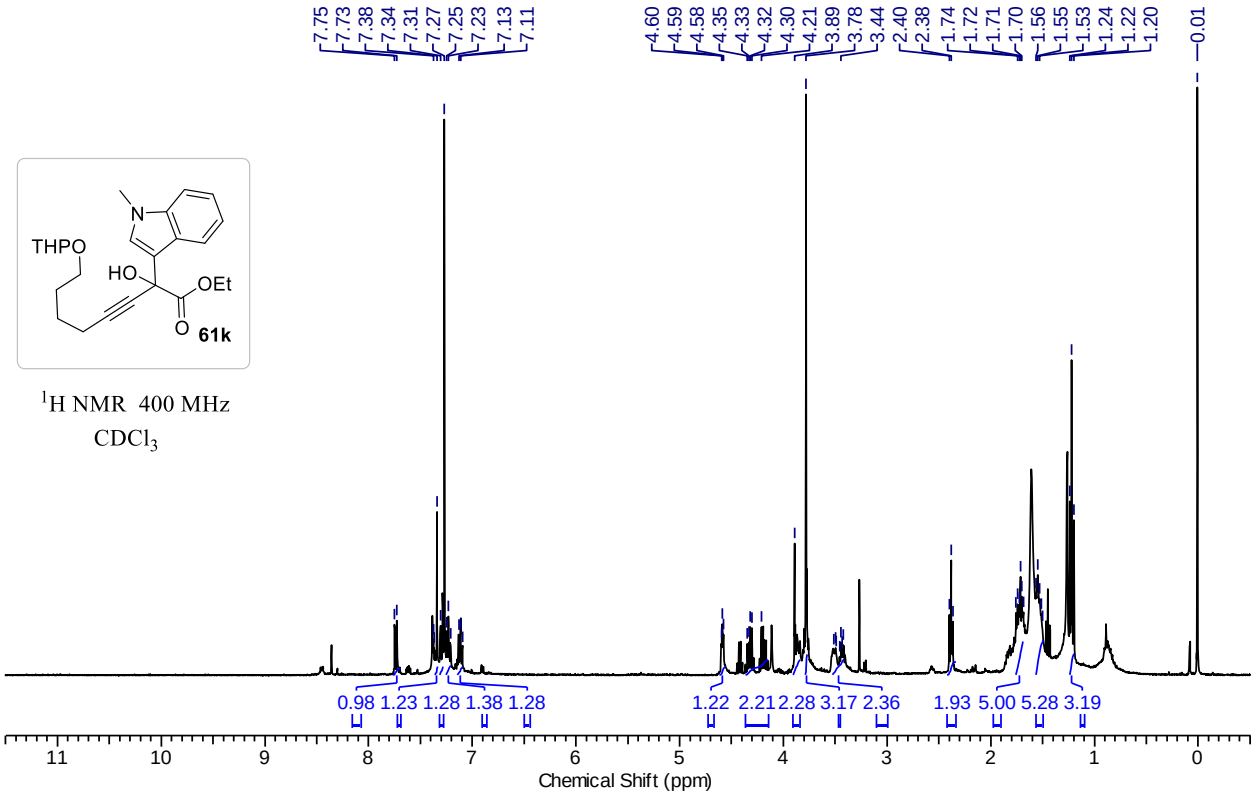


^{1}H NMR 500 MHz
$CDCl_3$

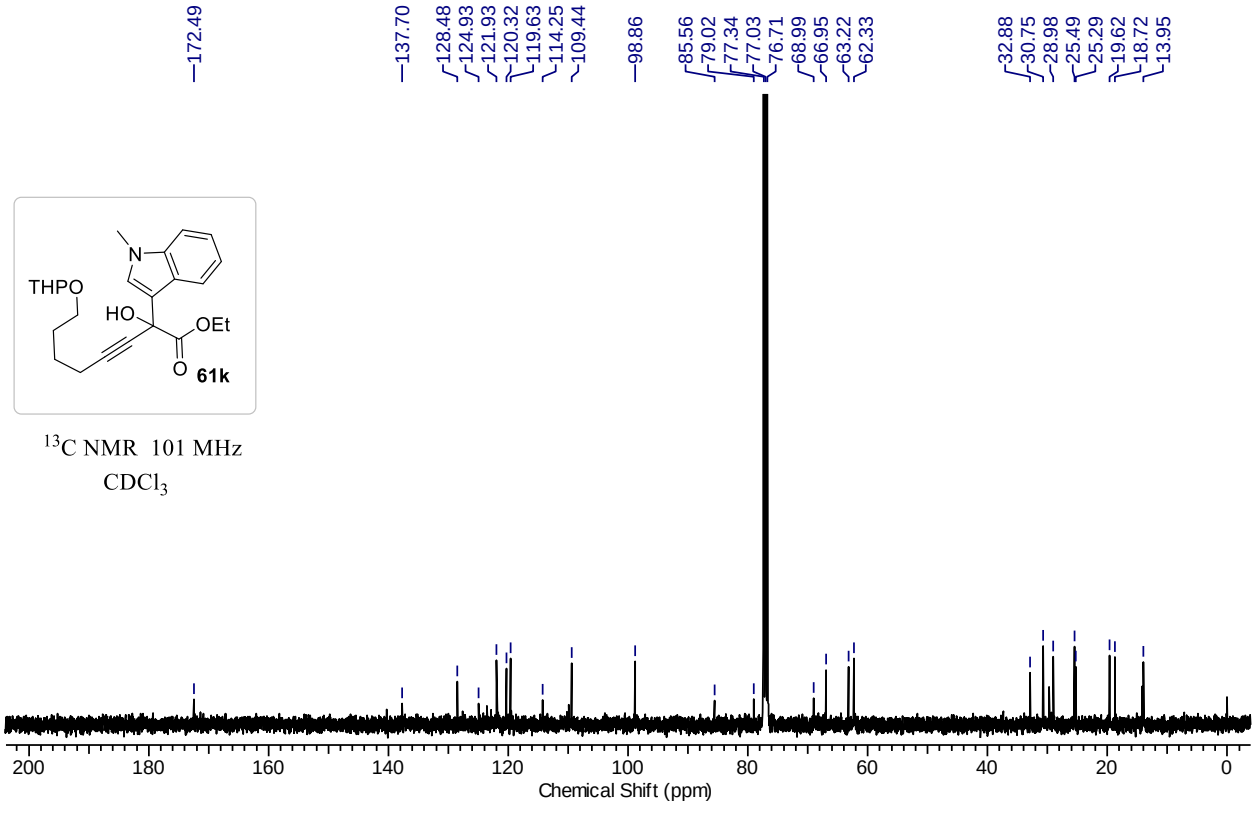


^{13}C NMR 126 MHz
$CDCl_3$

Ethyl 2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)-8-((tetrahydro-2*H*-pyran-2-yl)oxy)oct-3-ynoate (61k):

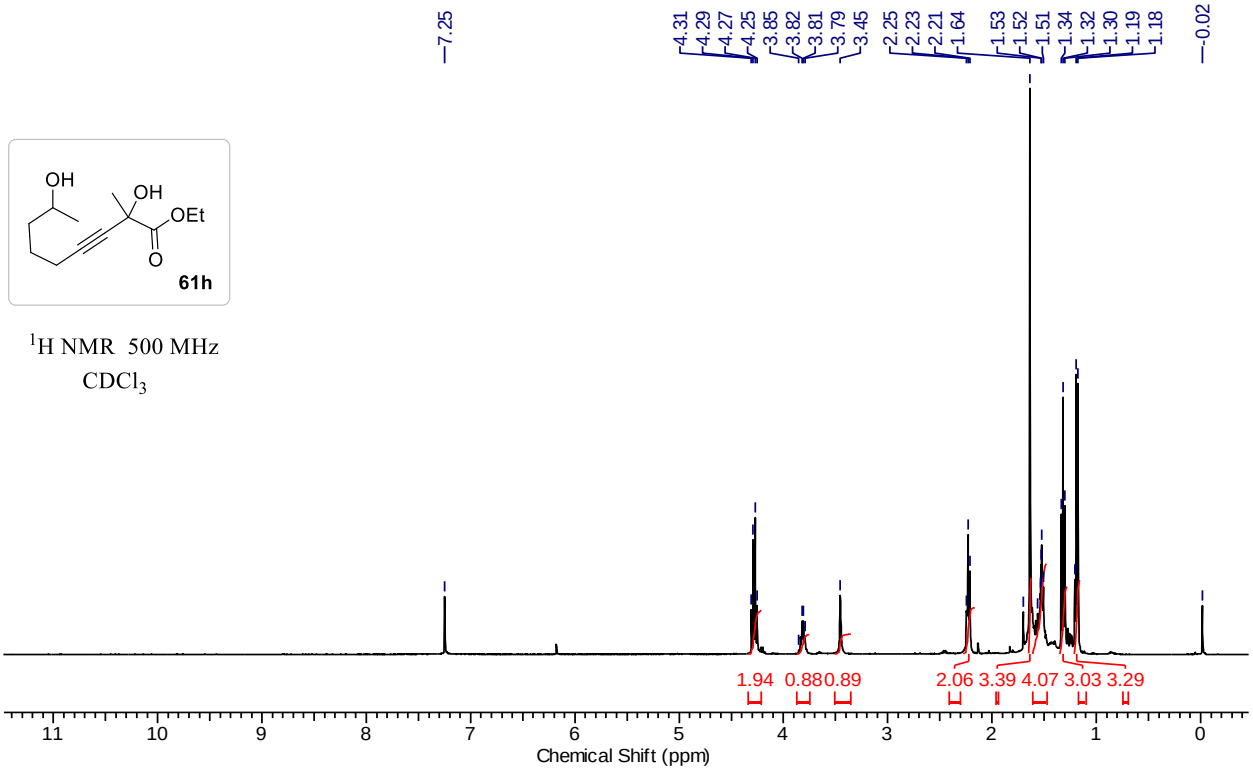


^{1}H NMR 400 MHz
$CDCl_3$

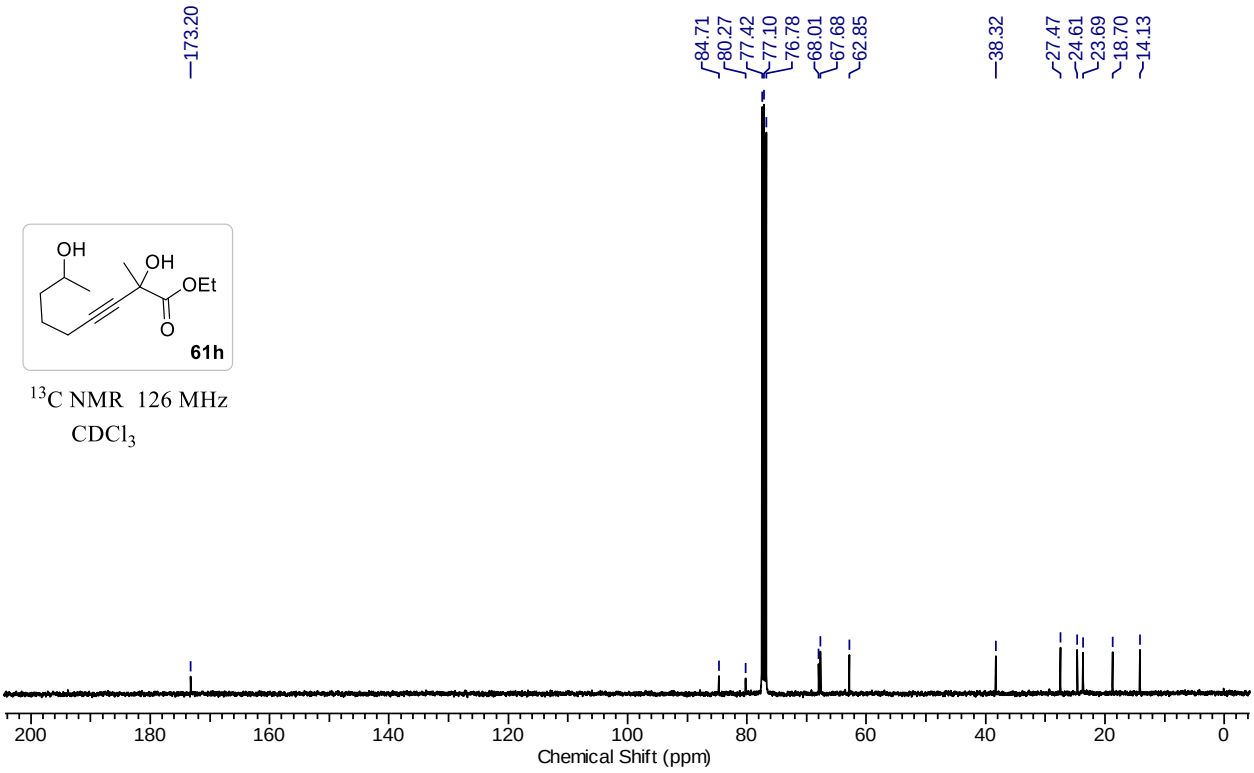


^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 2,8-dihydroxy-2-methylnon-3-ynoate (61h):

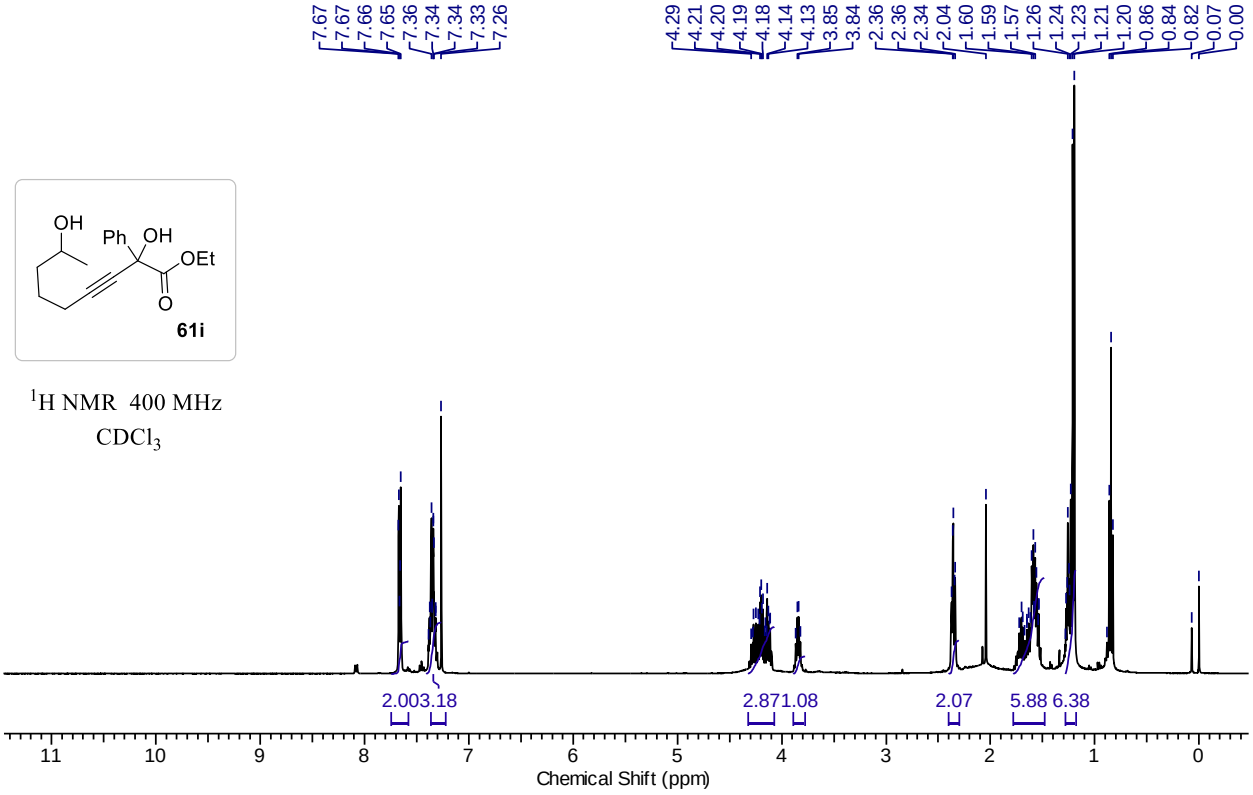


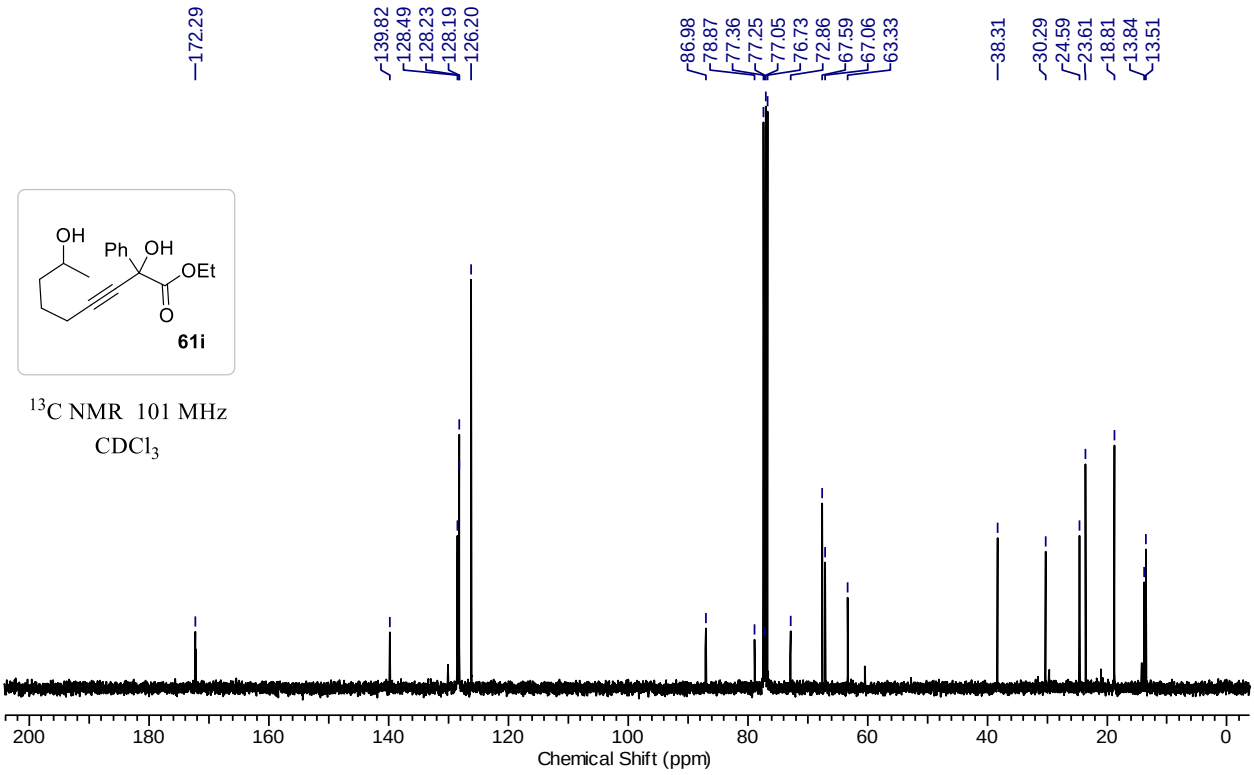
^{1}H NMR 500 MHz
$CDCl_3$



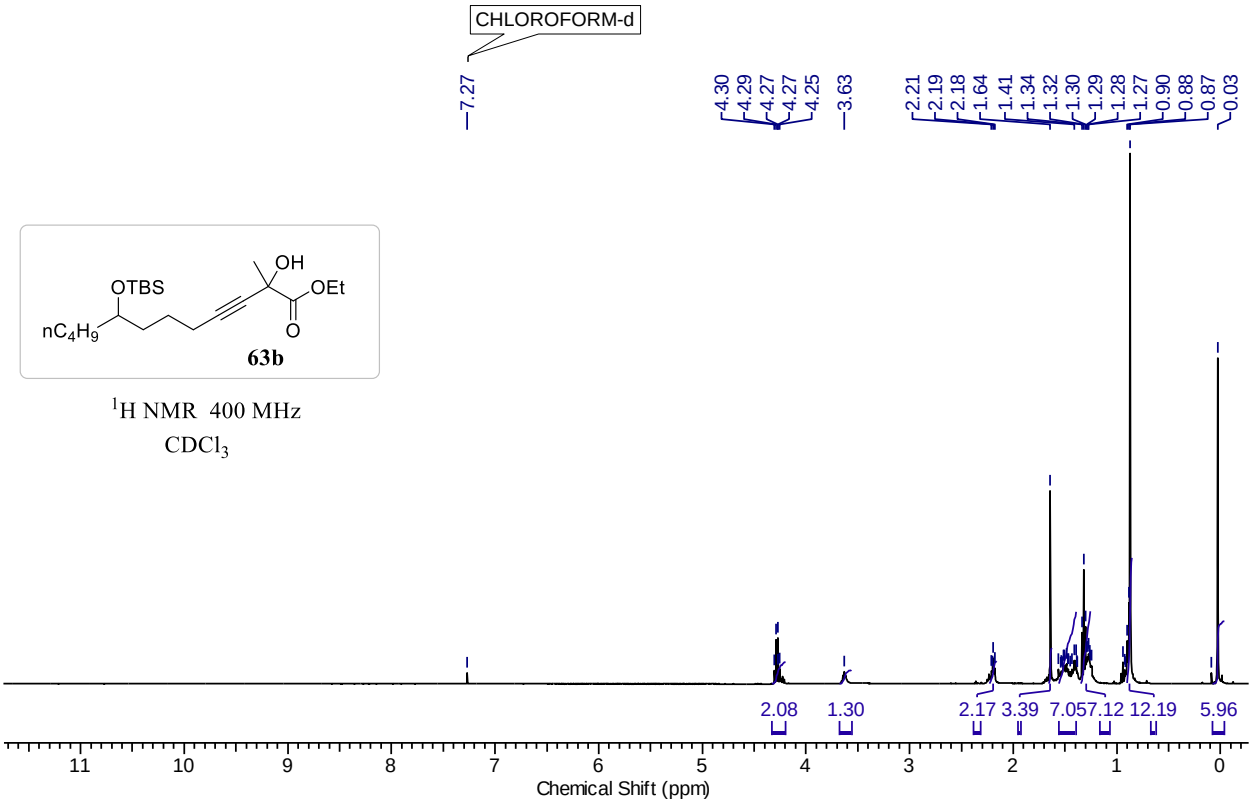
^{13}C NMR 126 MHz
$CDCl_3$

Ethyl 2,8-dihydroxy-2-phenylnon-3-ynoate (61i):

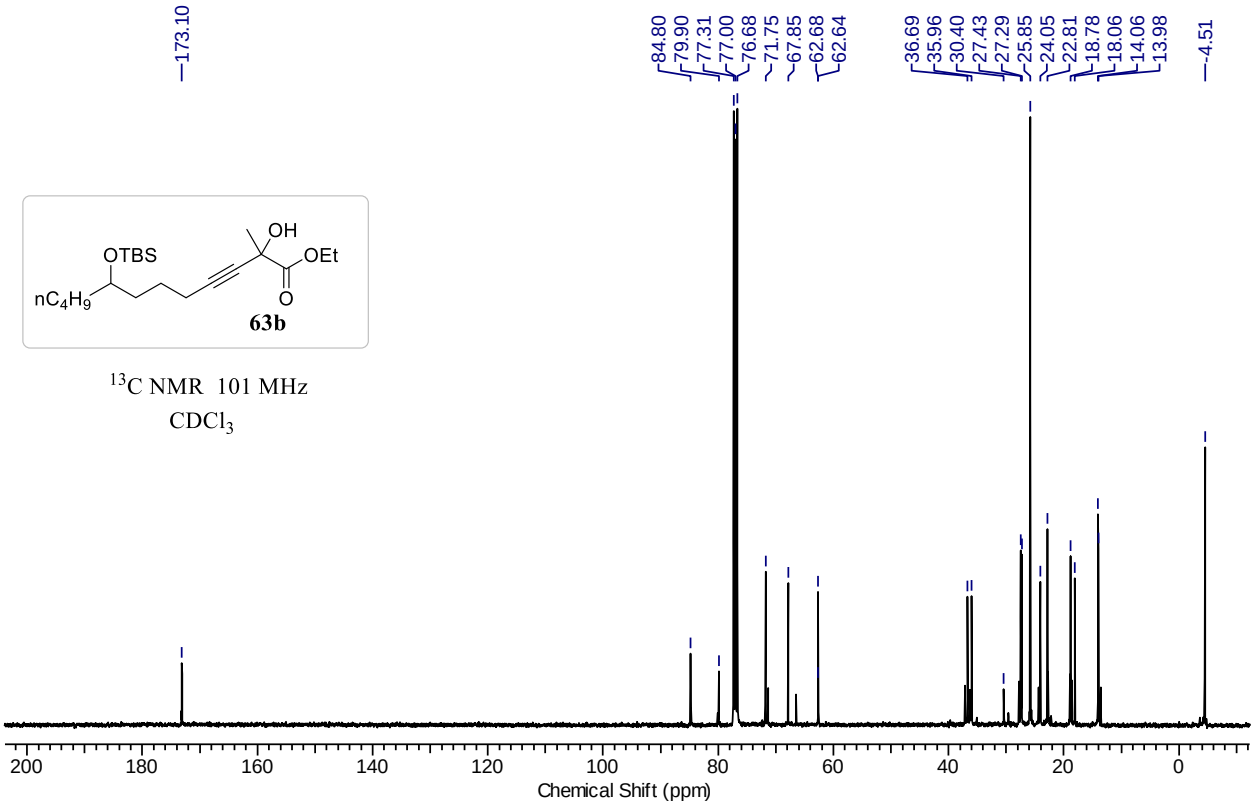




Ethyl 8-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methyldodec-3-ynoate(63b):

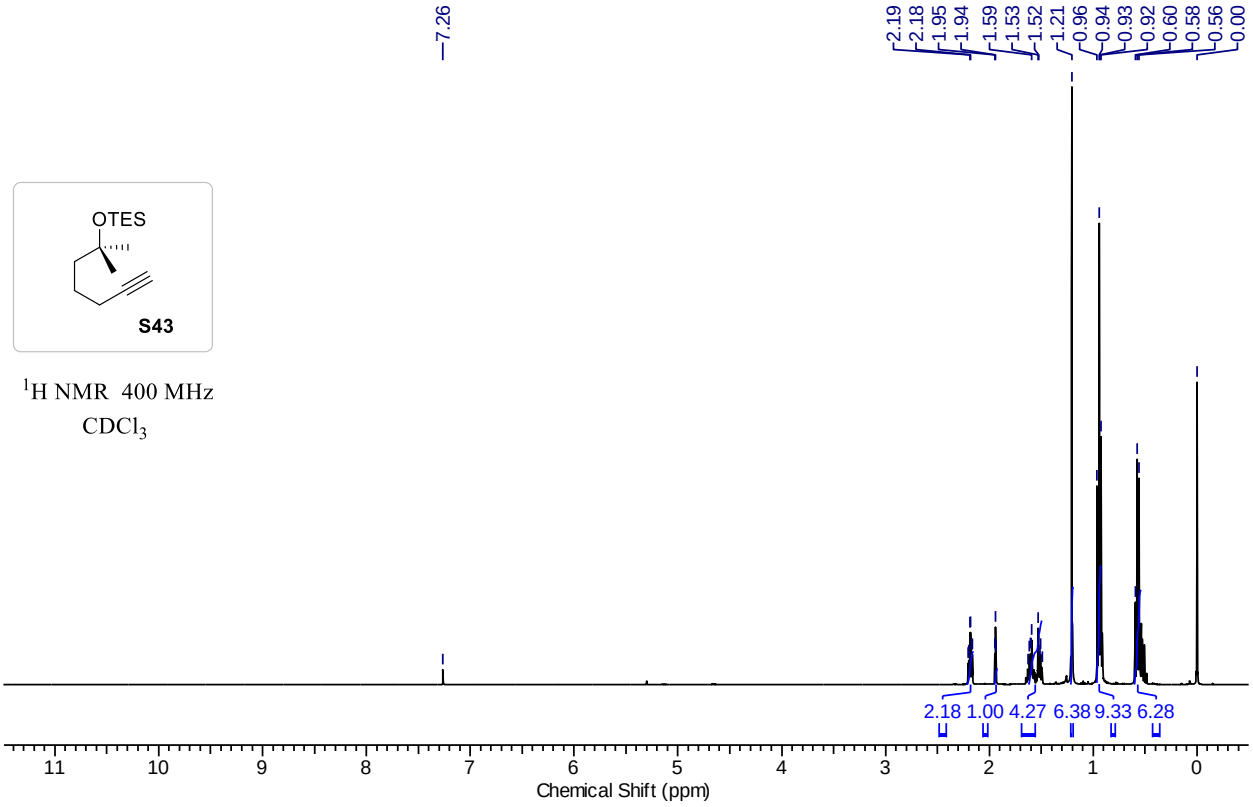


^{1}H NMR 400 MHz
$CDCl_3$

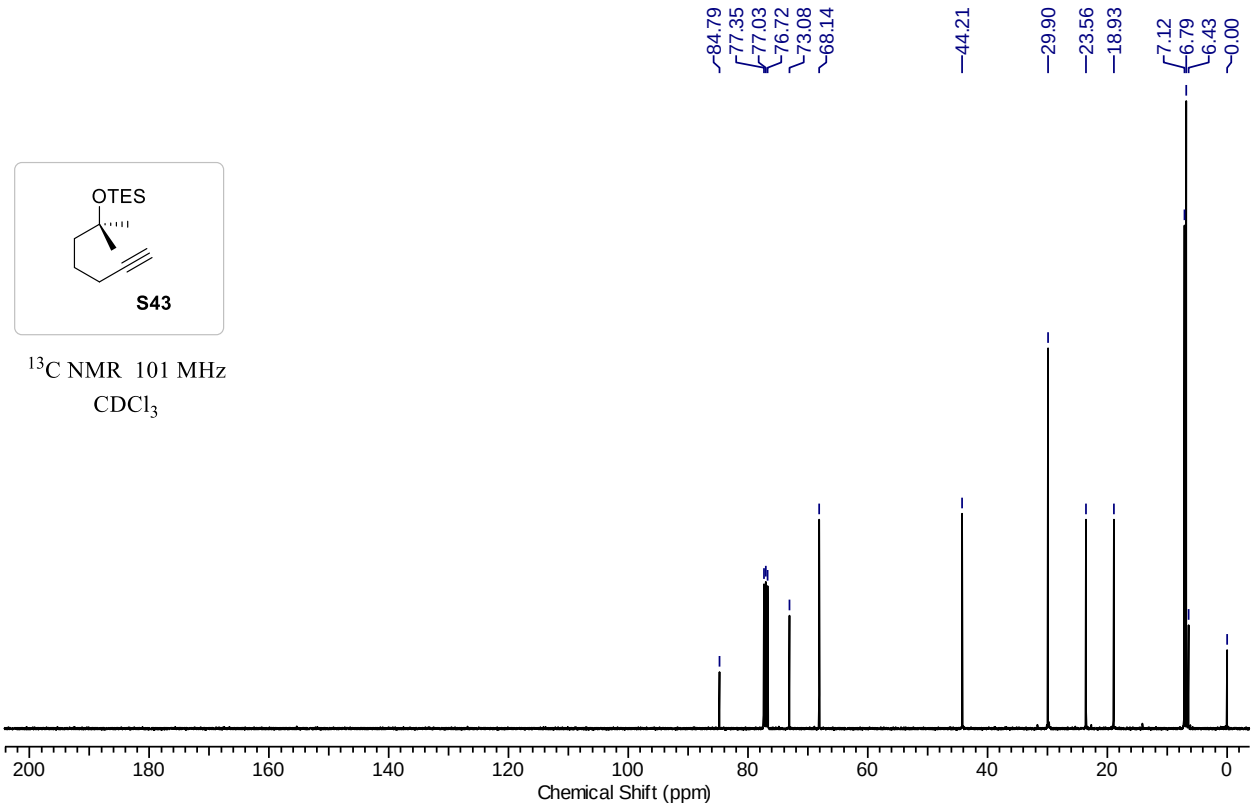


^{13}C NMR 101 MHz
$CDCl_3$

Triethyl((2-methylhept-6-yn-2-yl)oxy)silane (S43):

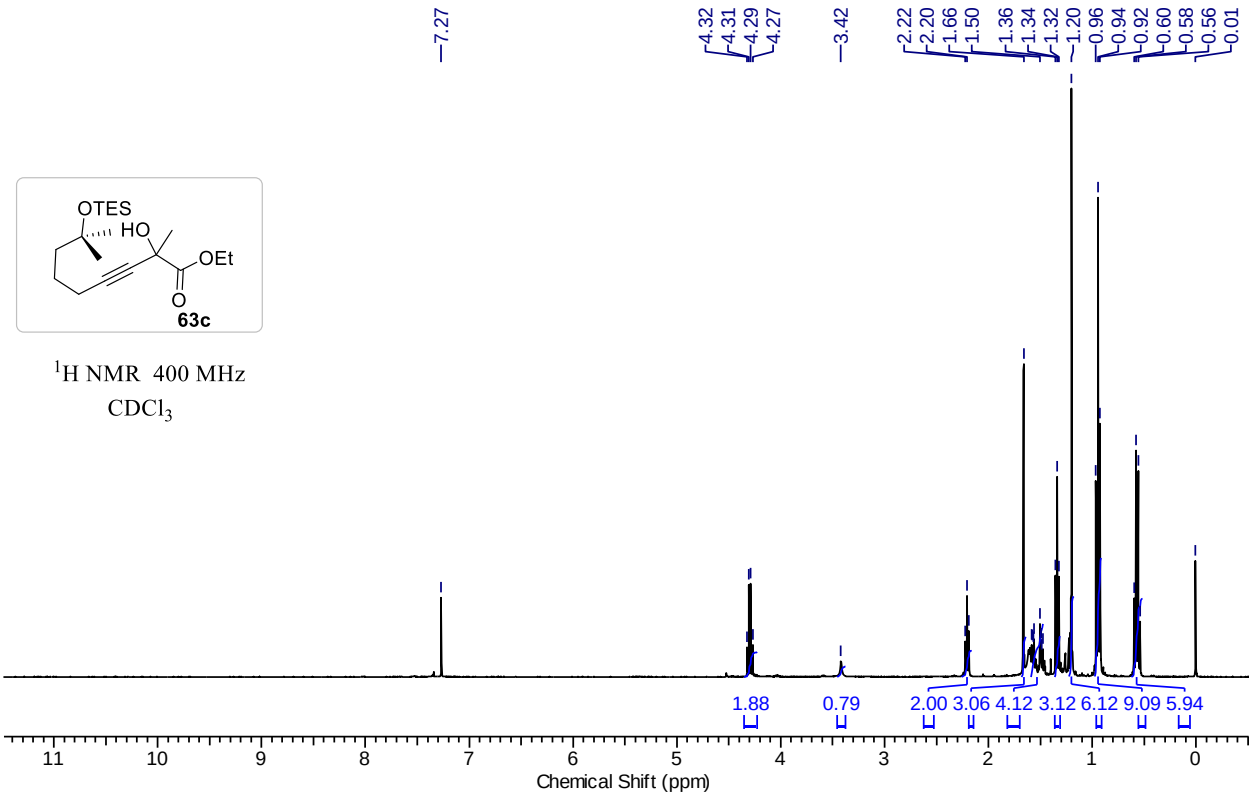


^{1}H NMR 400 MHz
$CDCl_3$

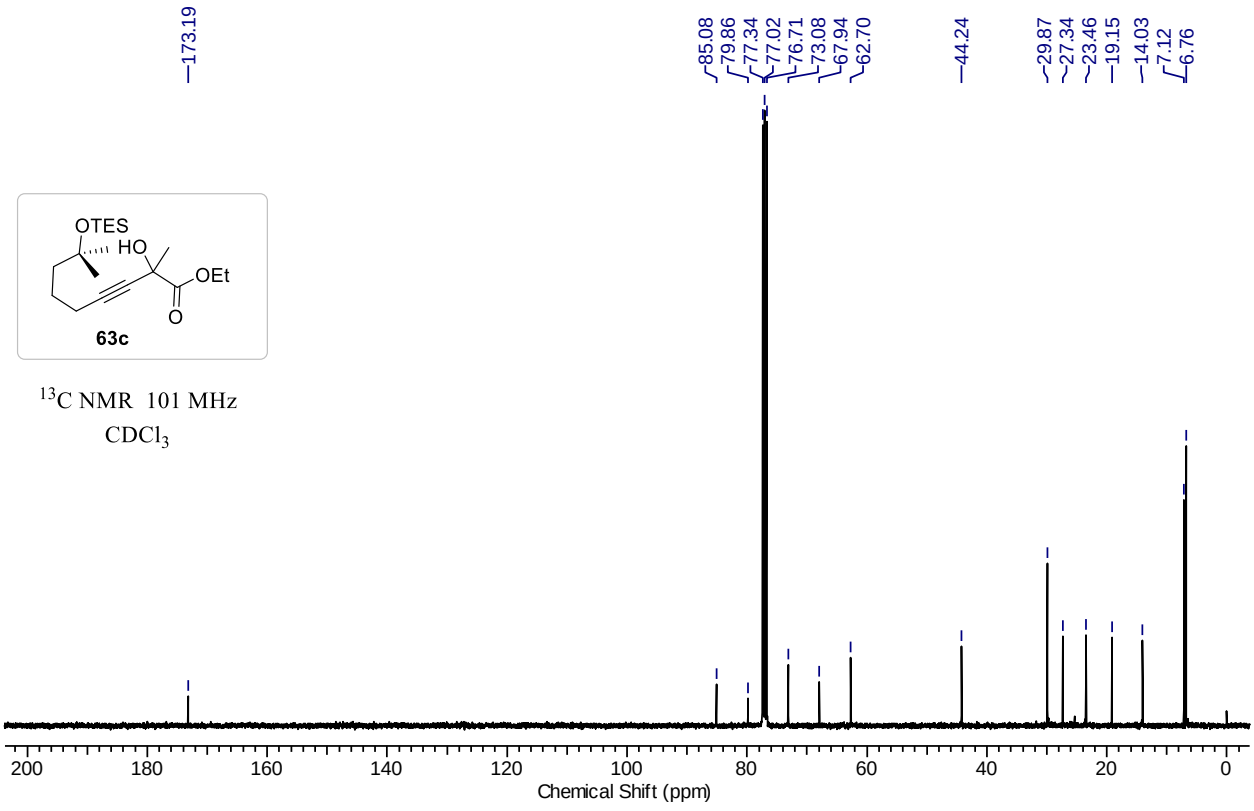


^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 2-hydroxy-2,8-dimethyl-8-((triethylsilyl)oxy)non-3-ynoate (63c):

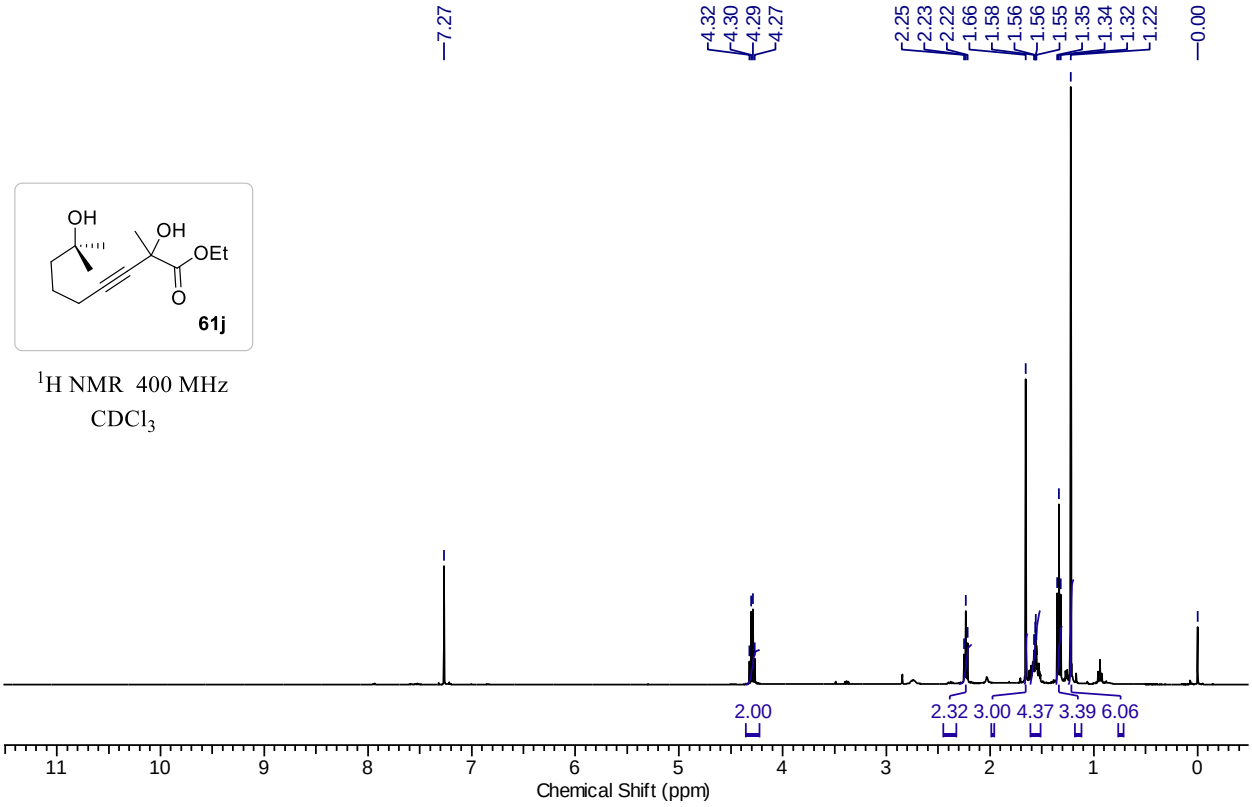


^{1}H NMR 400 MHz
$CDCl_3$

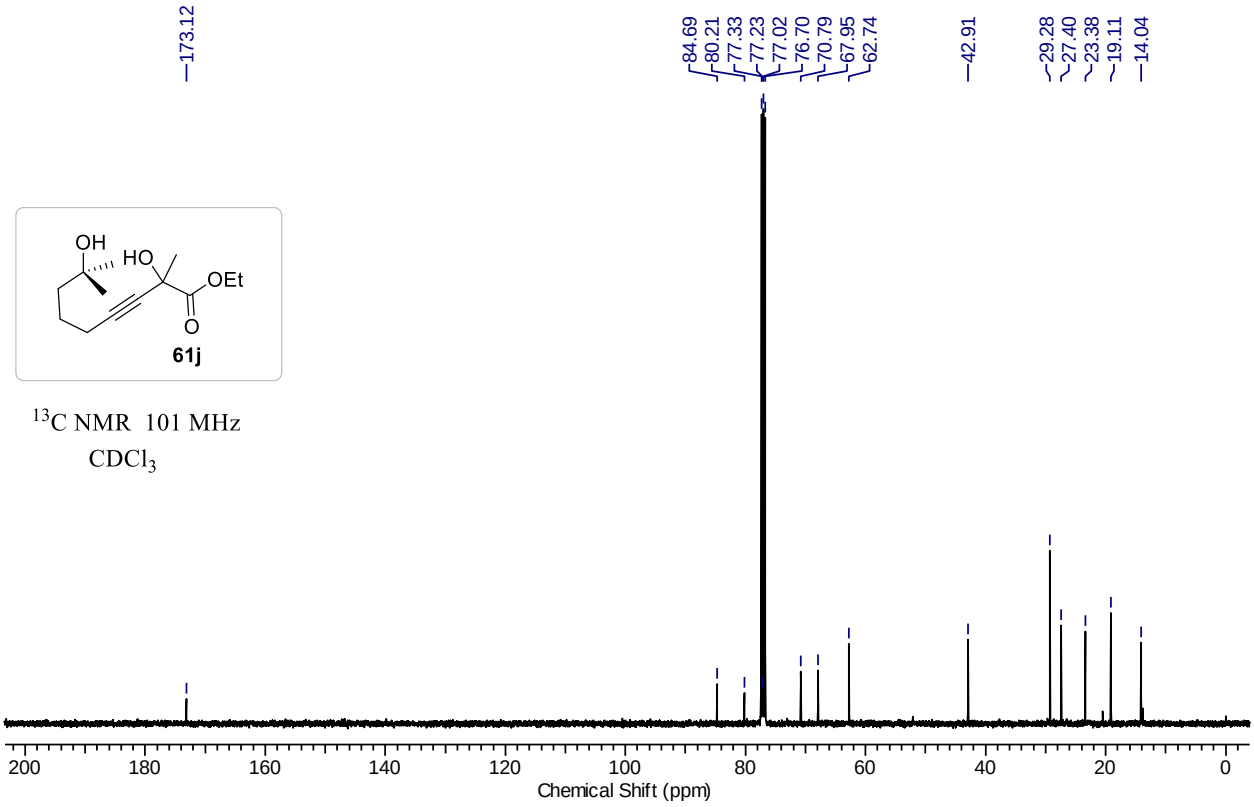


^{13}C NMR 101 MHz
$CDCl_3$

Ethyl 2,8-dihydroxy-2,8-dimethylnon-3-ynoate (61j):

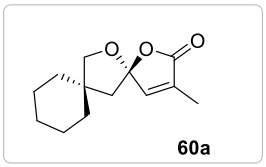


^{1}H NMR 400 MHz
$CDCl_3$

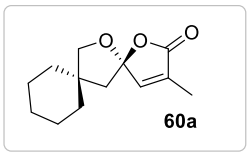


^{13}C NMR 101 MHz
$CDCl_3$

3-Methyl-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (60a):

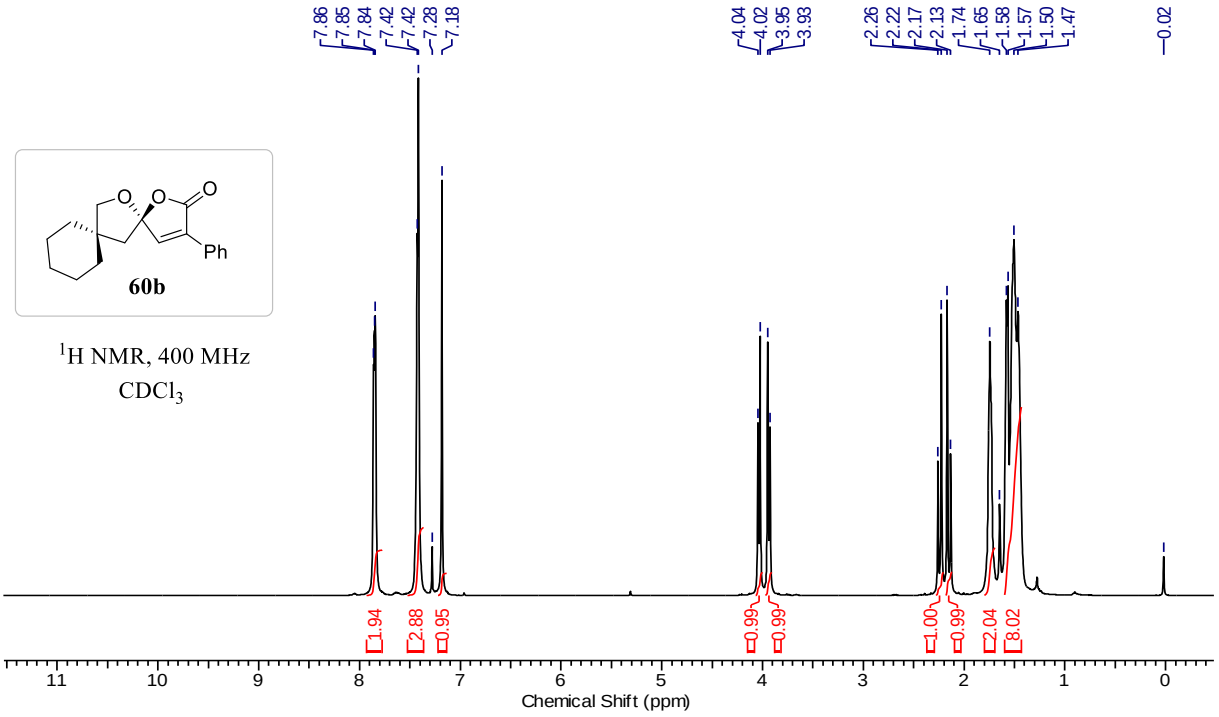


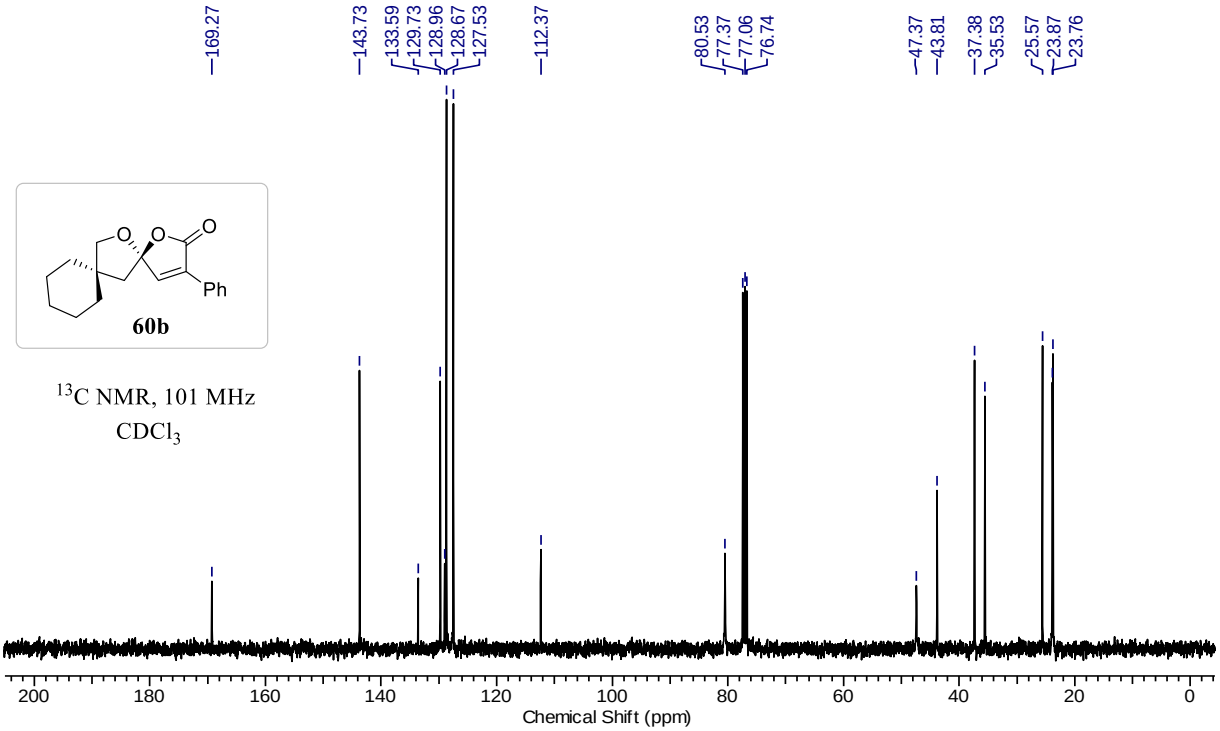
^{1}H NMR, 400 MHz
$CDCl_3$



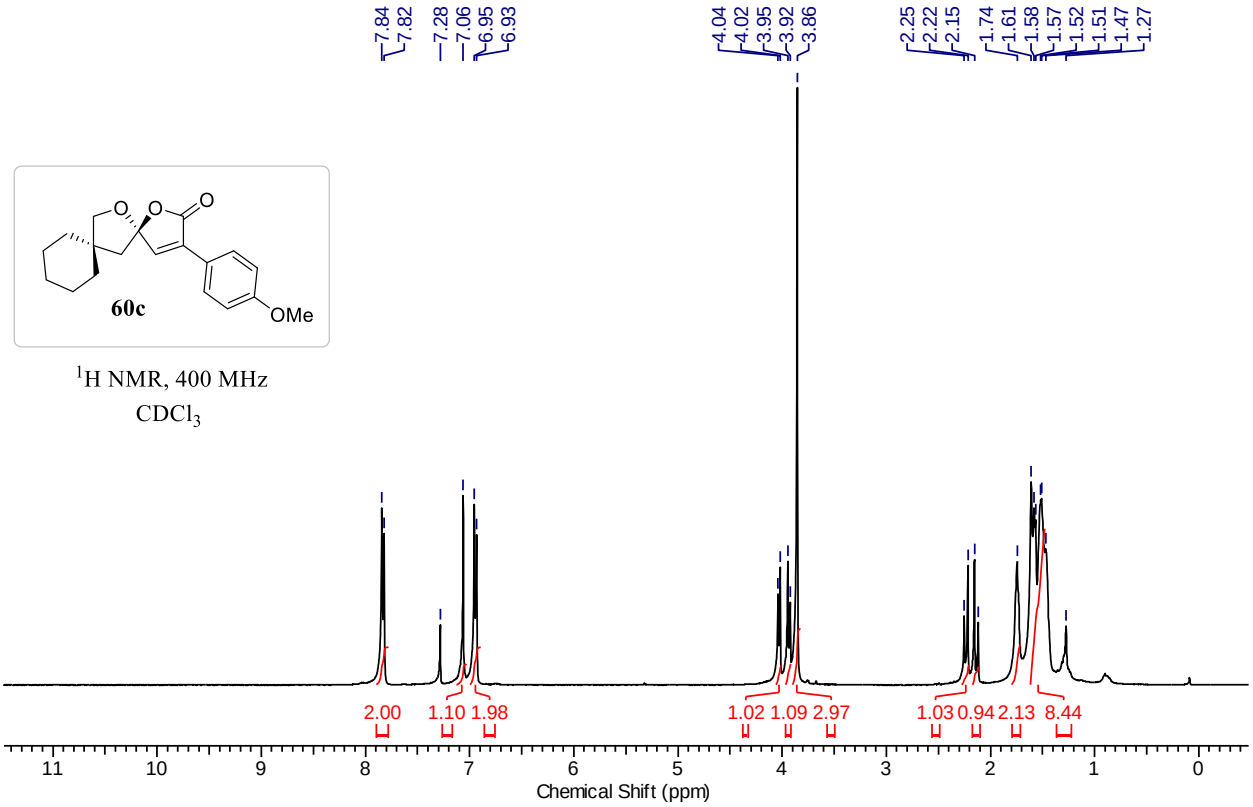
^{13}C NMR, 101 MHz
$CDCl_3$

3-Phenyl-1, 14-dioxadispiro [4.4.5^7.2^5] tetradec-3-en-one (60b):

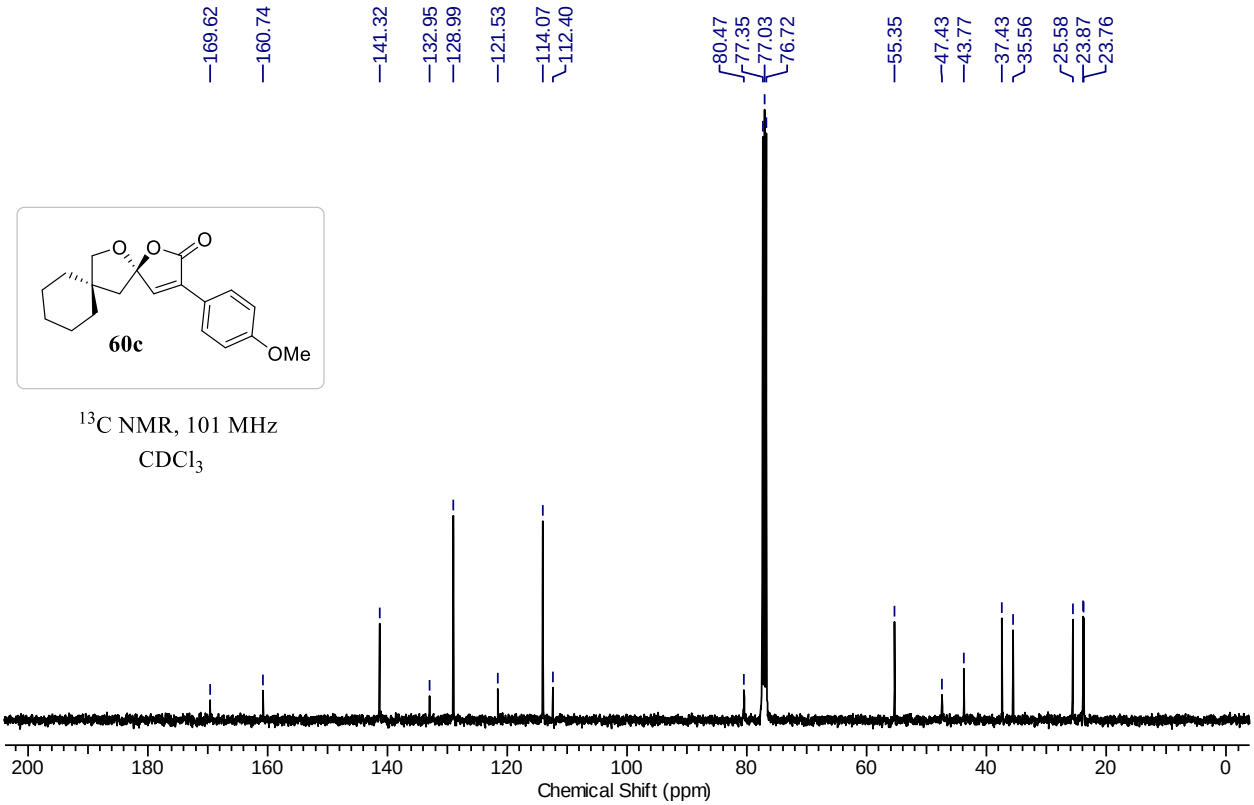




3-(4-Methoxyphenyl)-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (60c):

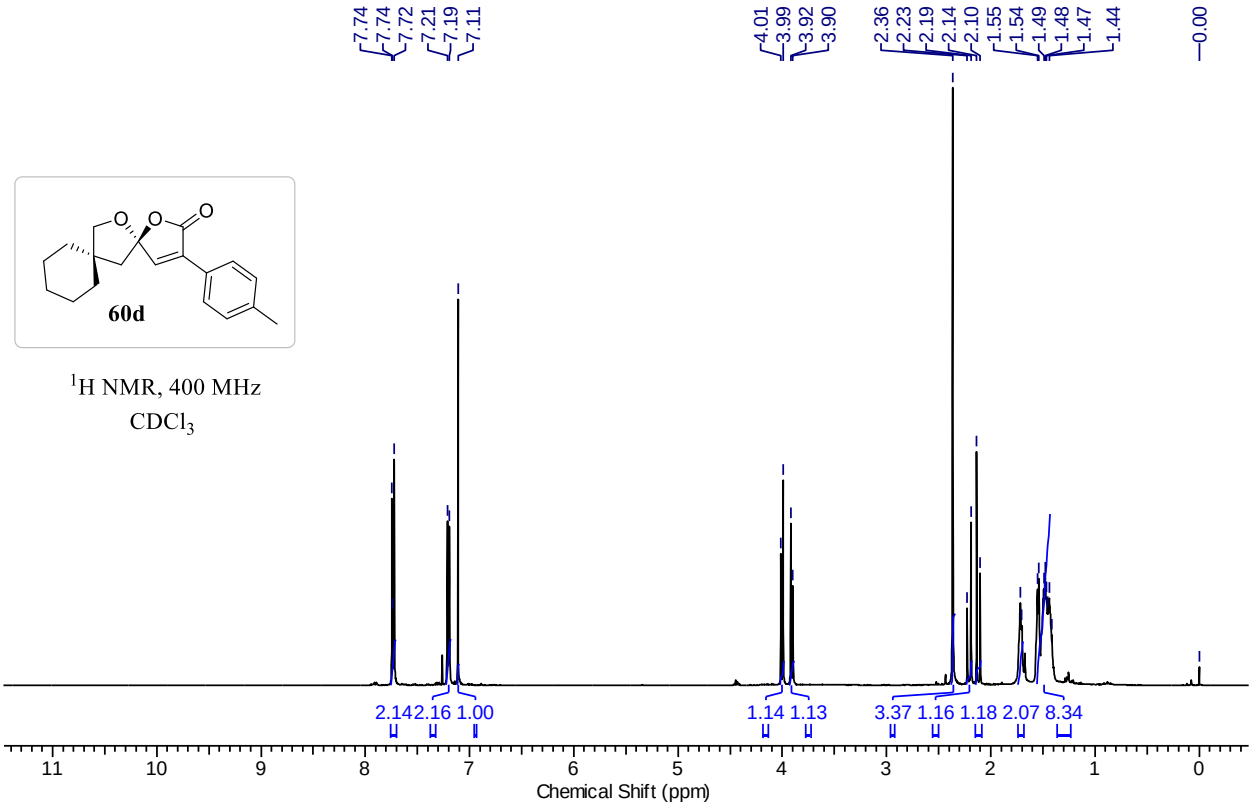


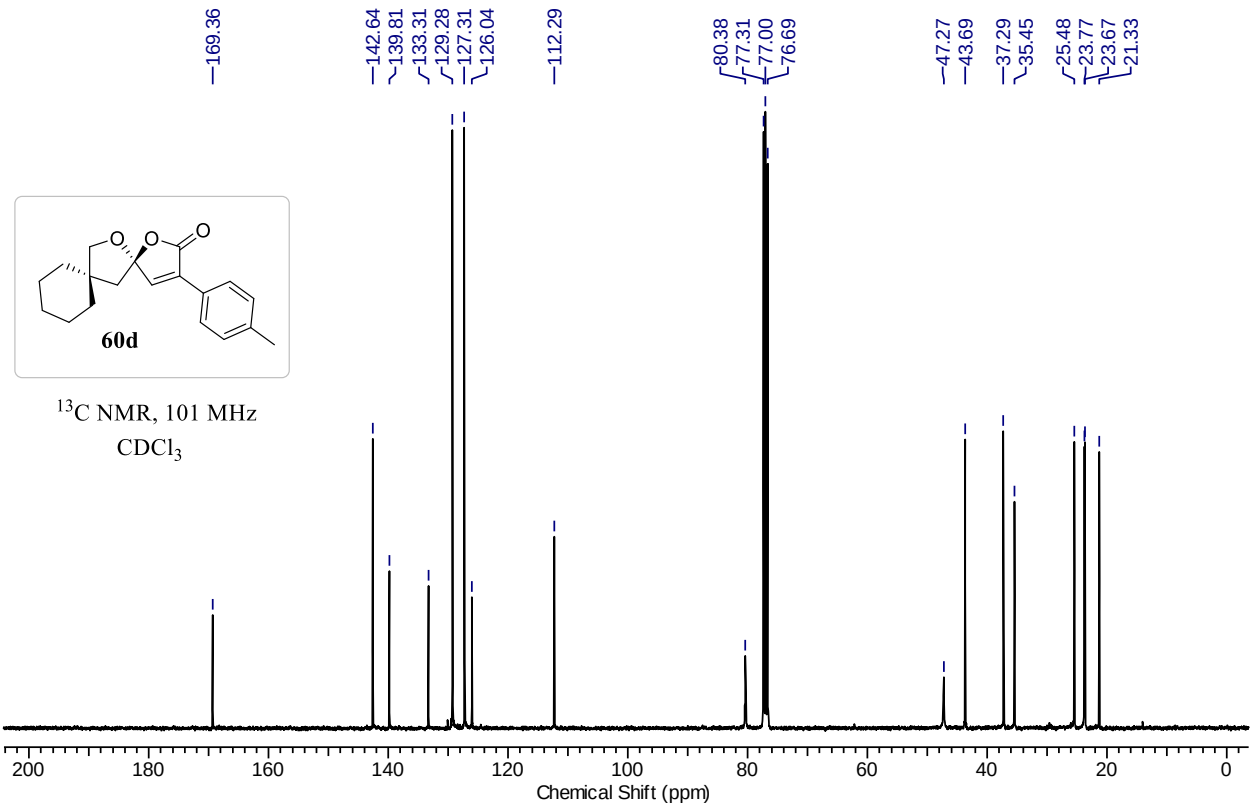
^{1}H NMR, 400 MHz
$CDCl_3$



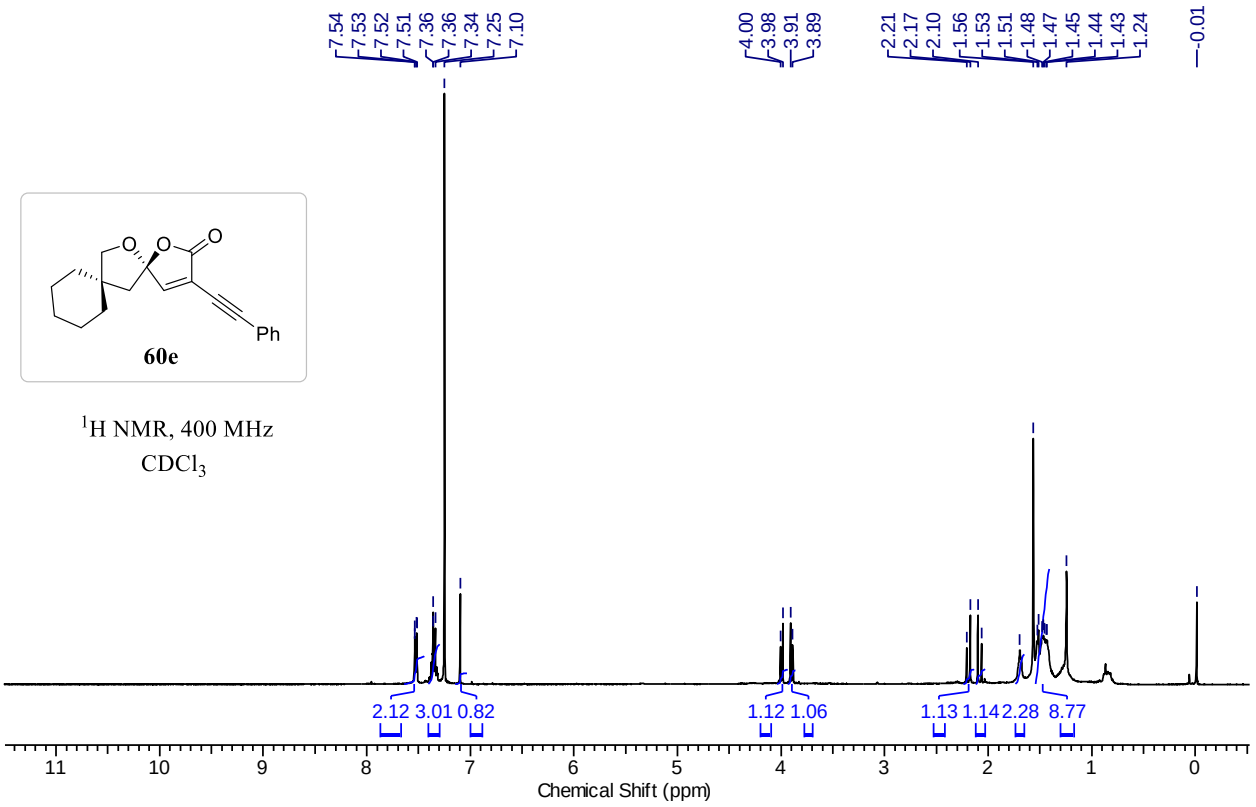
^{13}C NMR, 101 MHz
$CDCl_3$

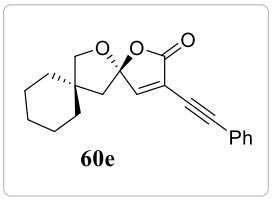
3-(*p*-Tolyl)-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (60d):





3-(Phenylethynyl)-1,14-dioxadispiro[4.1.5^{7}.2^{5}]tetradec-3-en-2-one (60e):





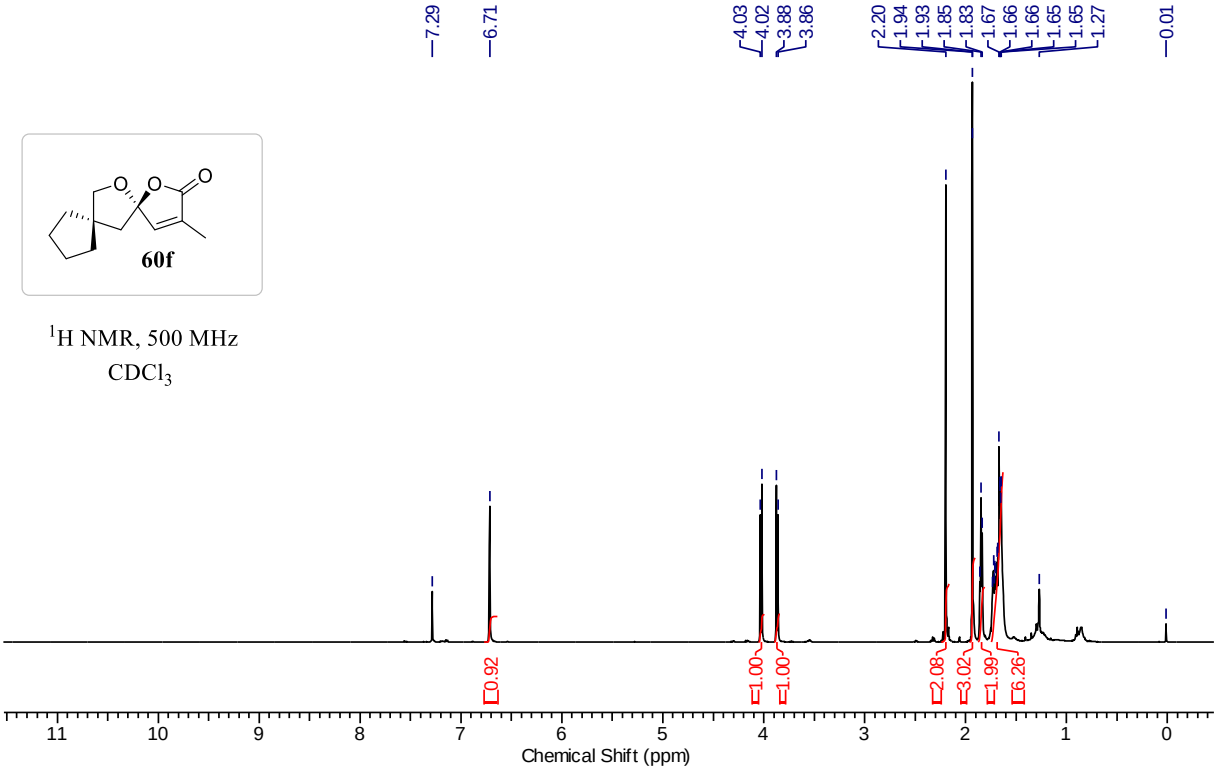
60e

^{1}H NMR, 400 MHz
$CDCl_3$

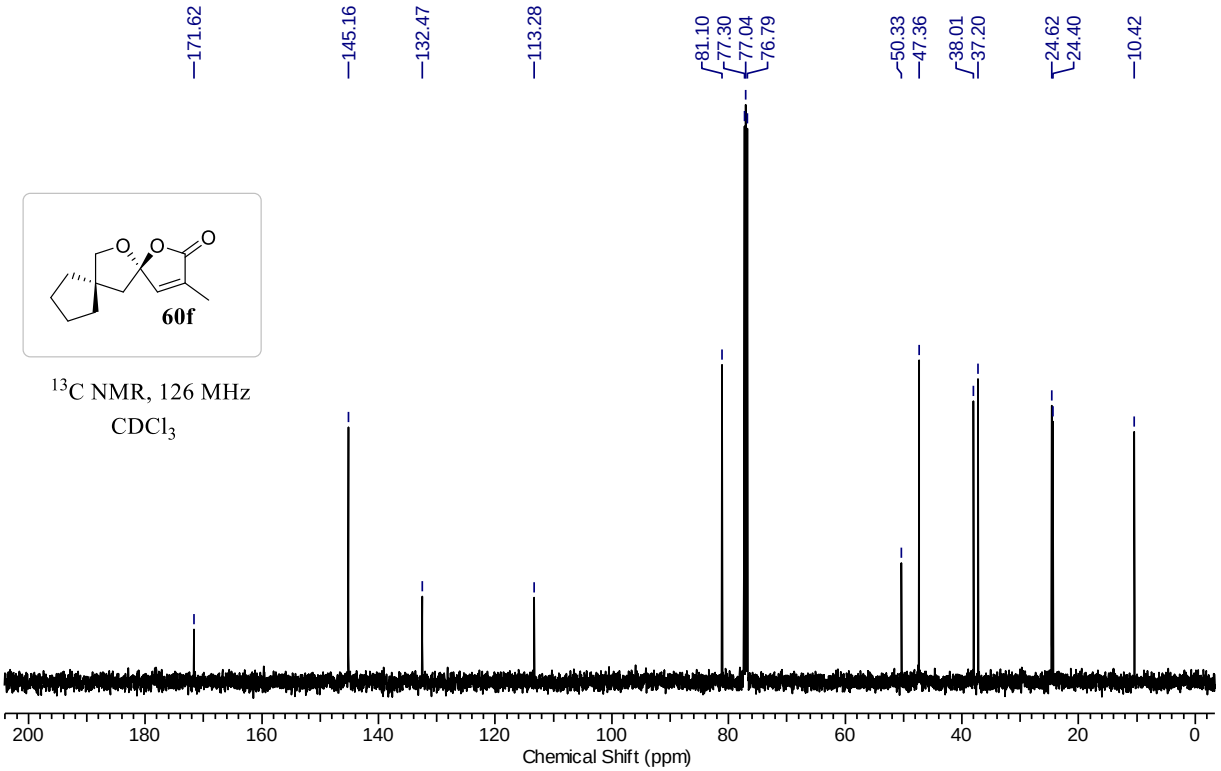
60e

^{13}C NMR, 101 MHz
$CDCl_3$

3-Methyl-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-2-one (60f):

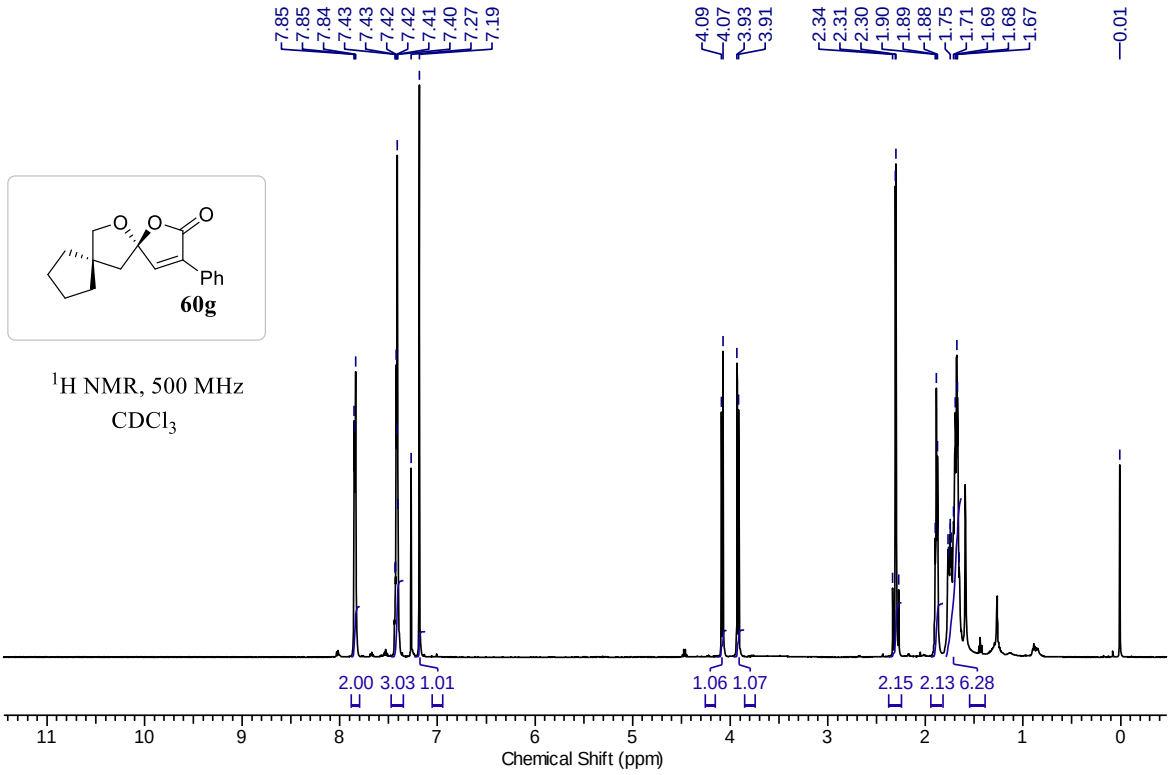


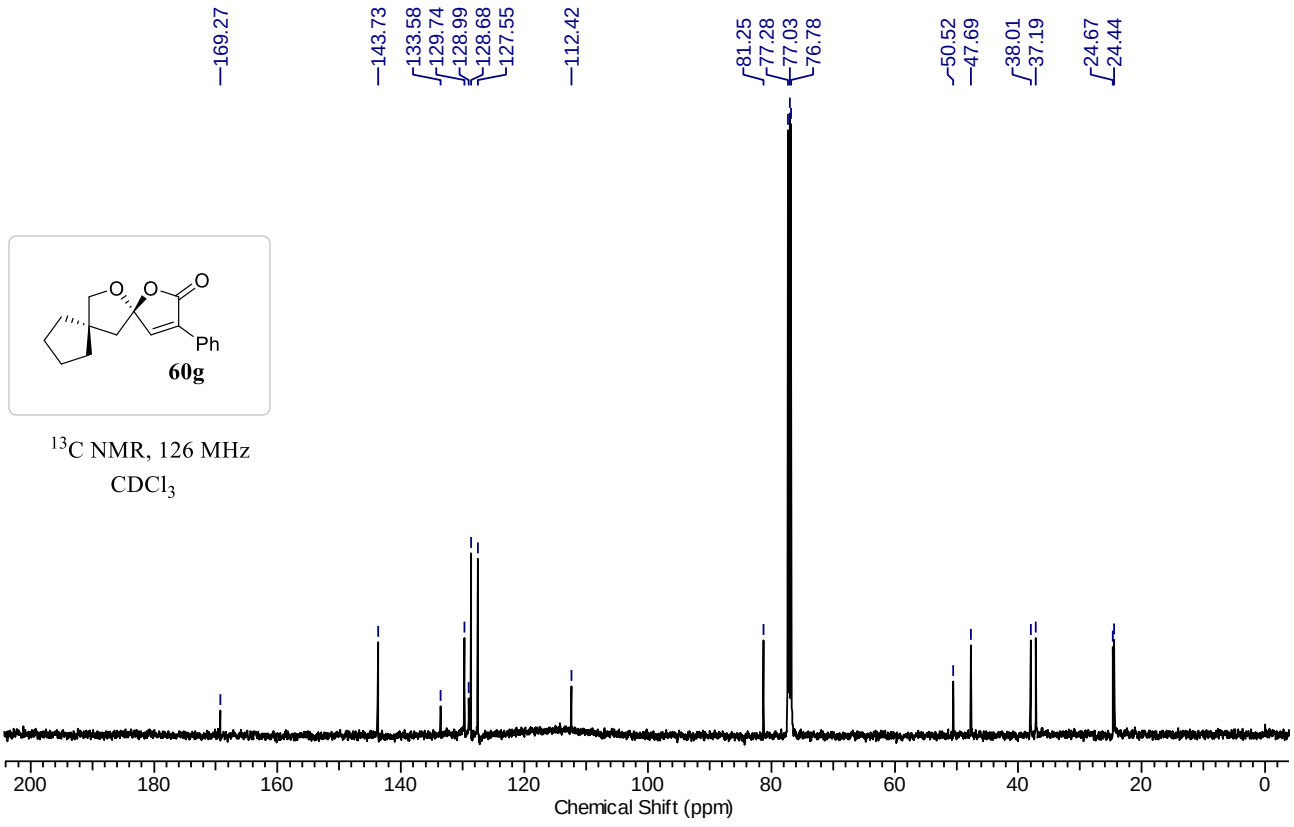
^{1}H NMR, 500 MHz
$CDCl_3$



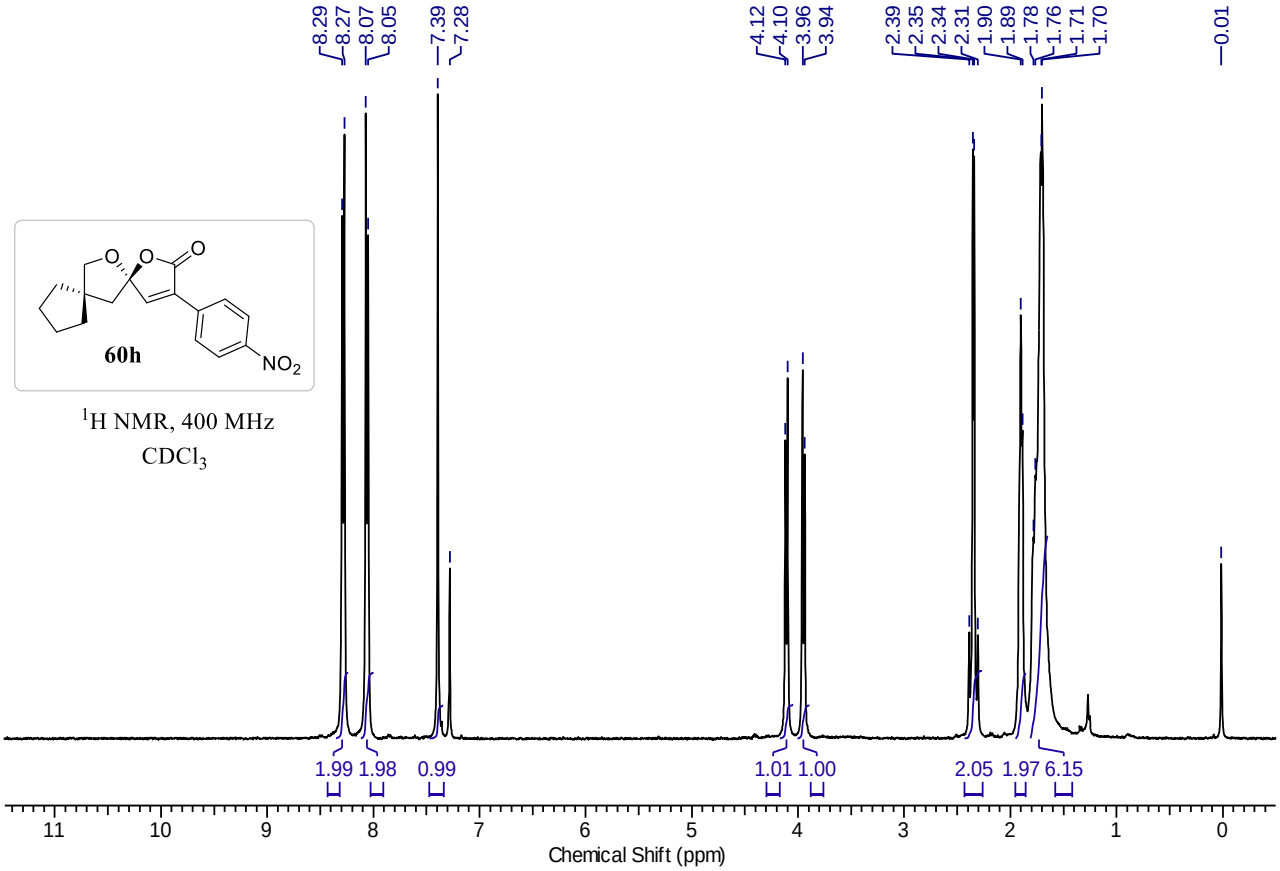
^{13}C NMR, 126 MHz
$CDCl_3$

3-Phenyl-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-2-one (60g) :

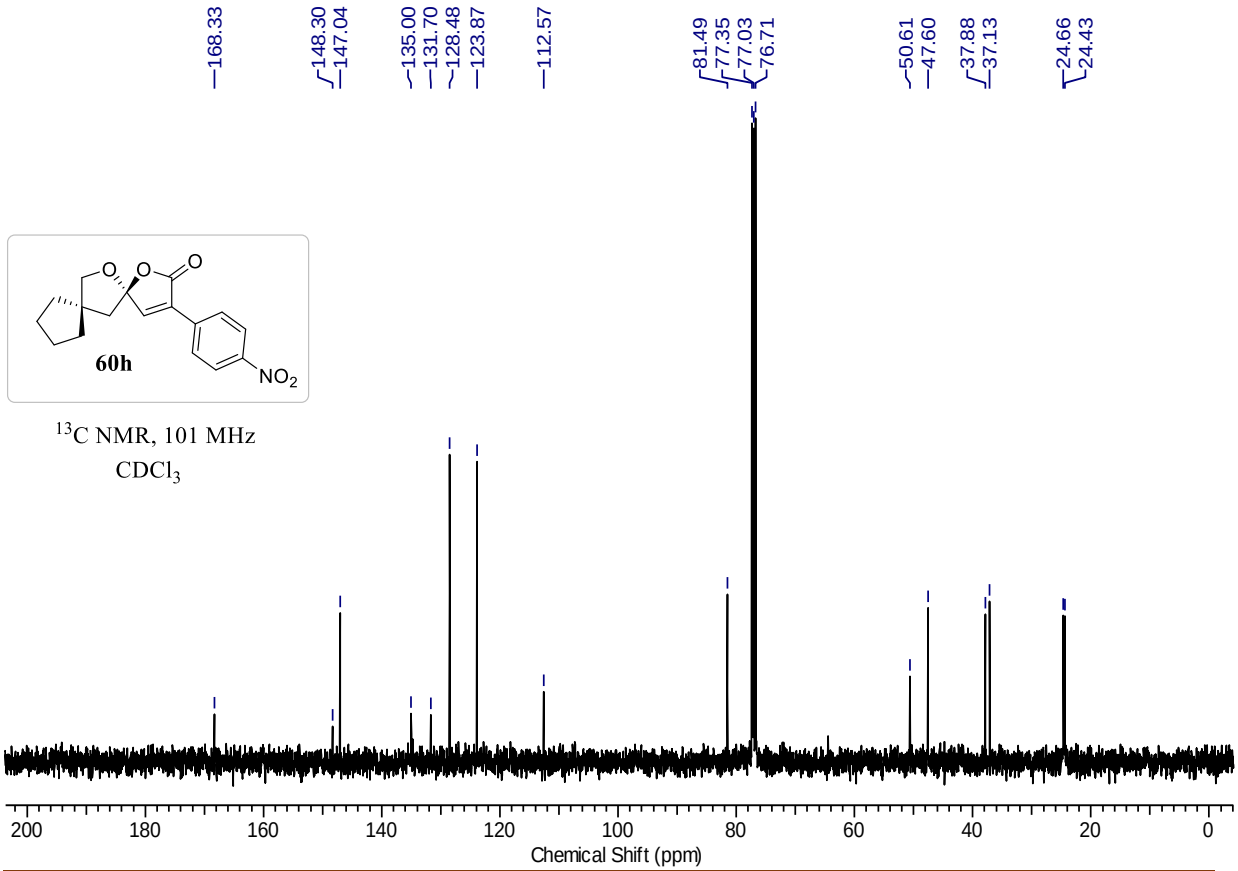




3-(4-Nitrophenyl)-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-2-one (60h):

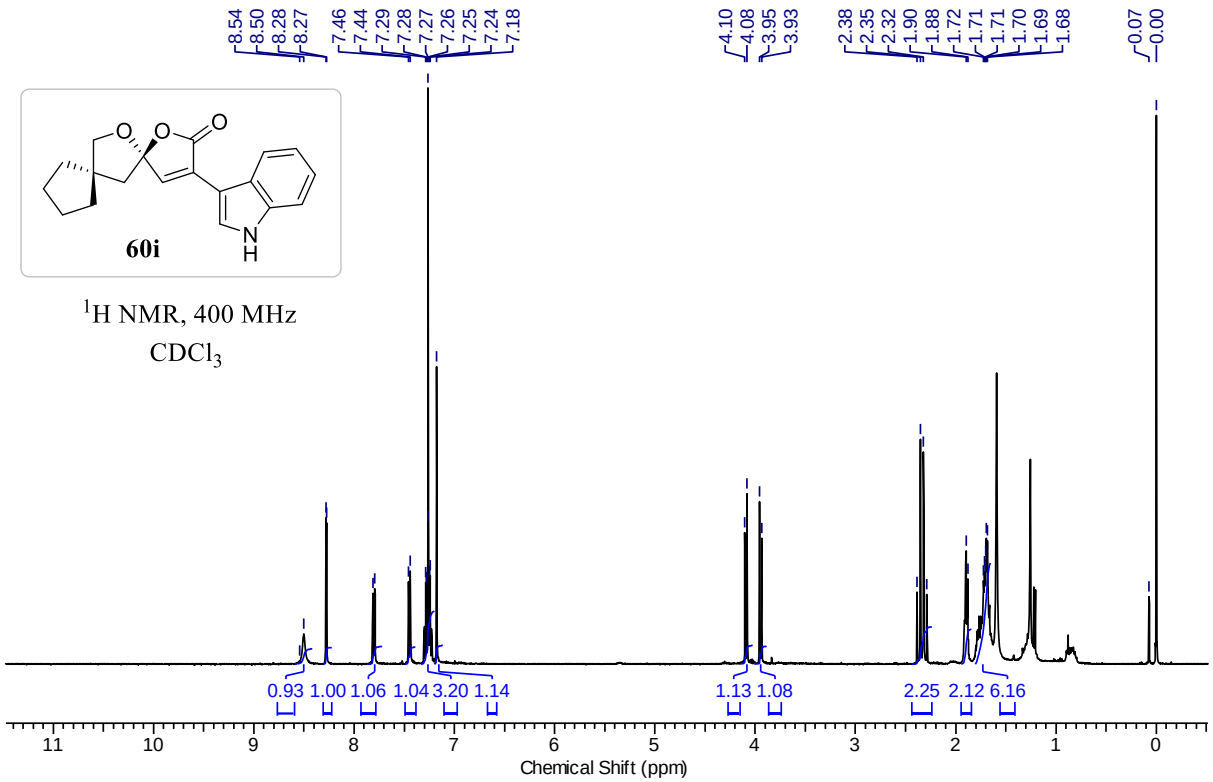


^{1}H NMR, 400 MHz
$CDCl_3$

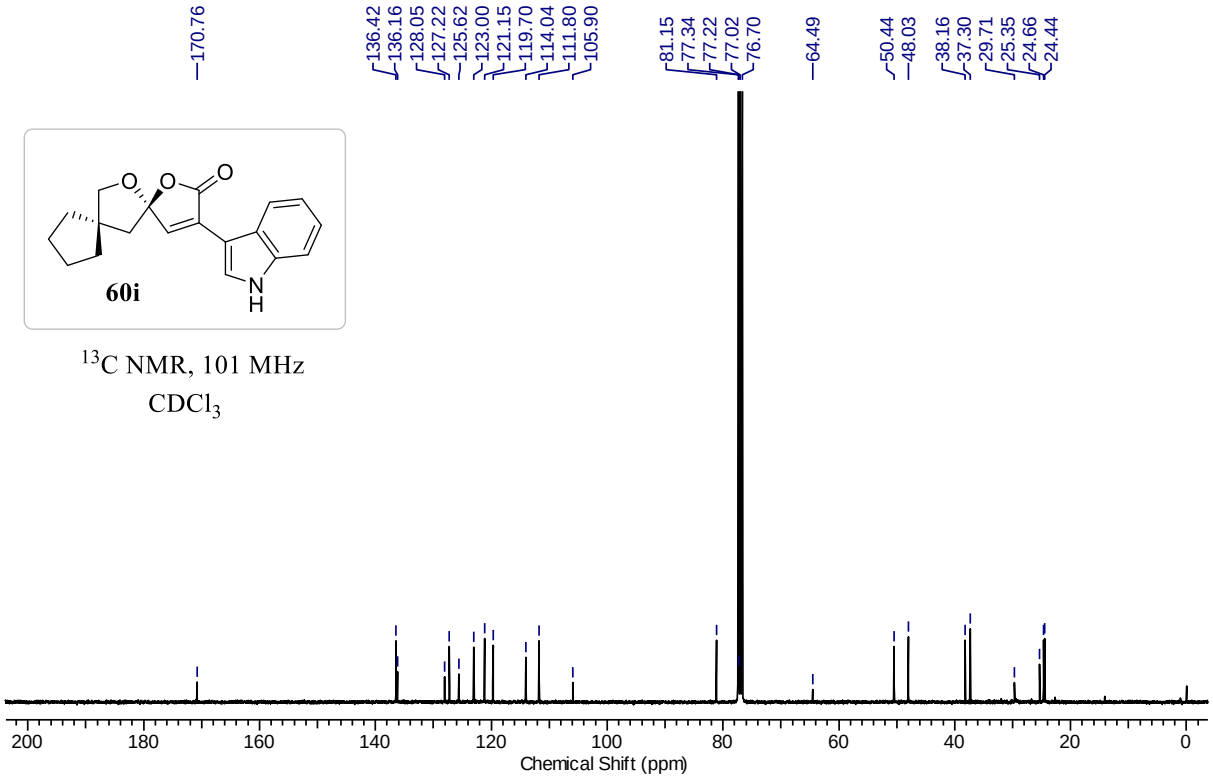


^{13}C NMR, 101 MHz
$CDCl_3$

3-(1*H*-indol-3-yl)-1,13-dioxadispiro[4.1.4^{7}.2^{5}]tridec-3-en-2-one (60i):

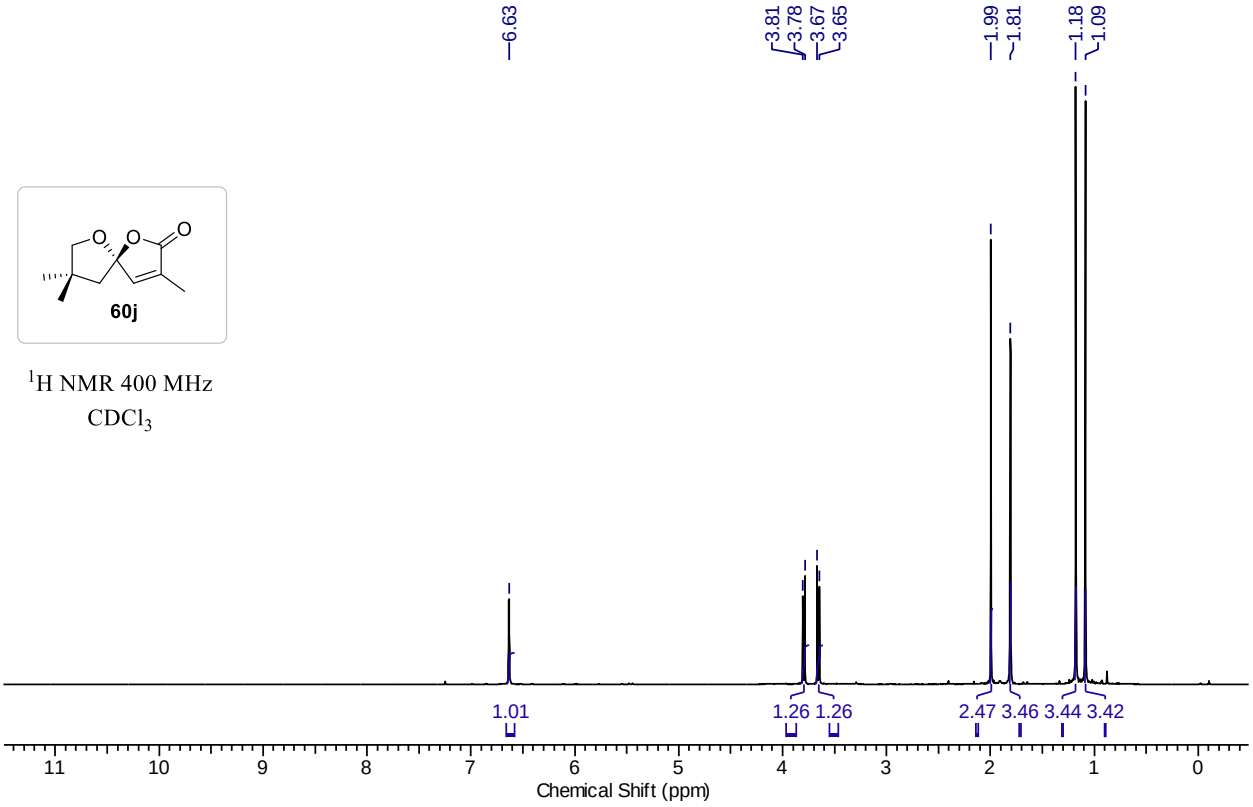


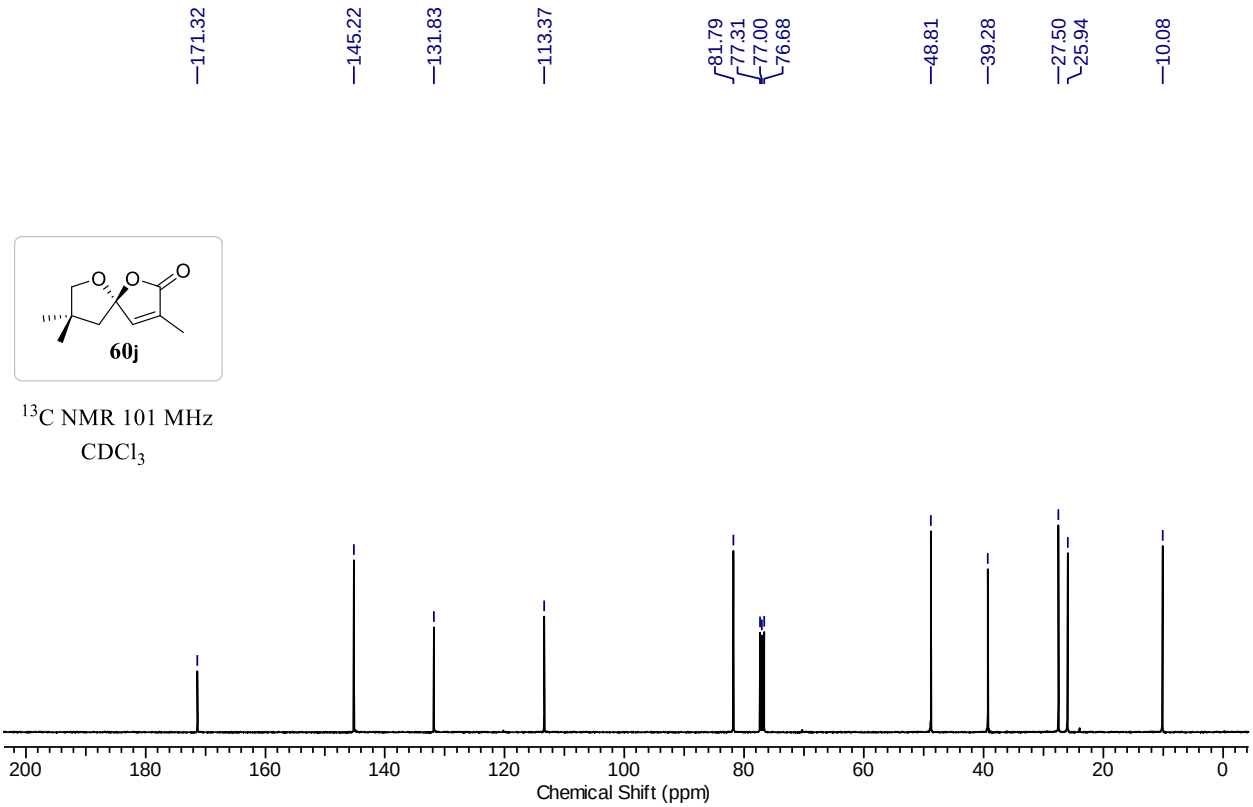
^{1}H NMR, 400 MHz
$CDCl_3$



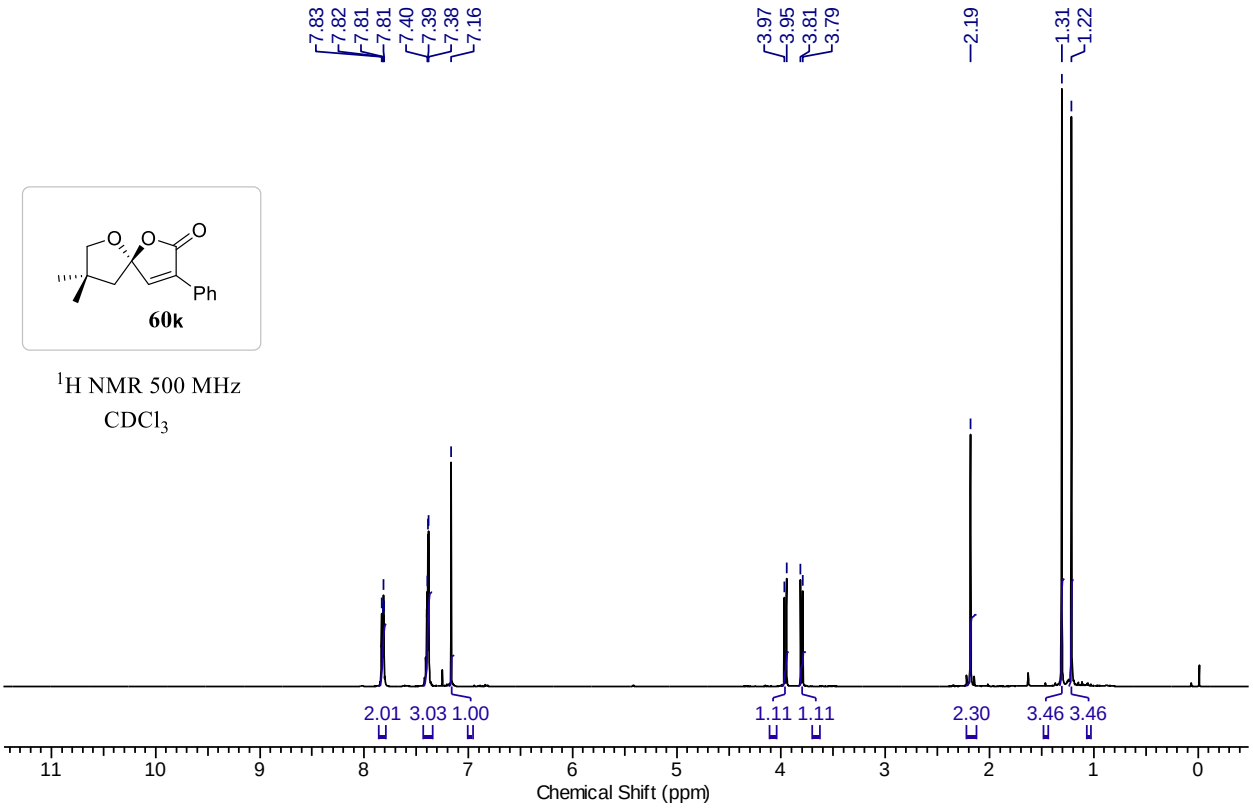
^{13}C NMR, 101 MHz
$CDCl_3$

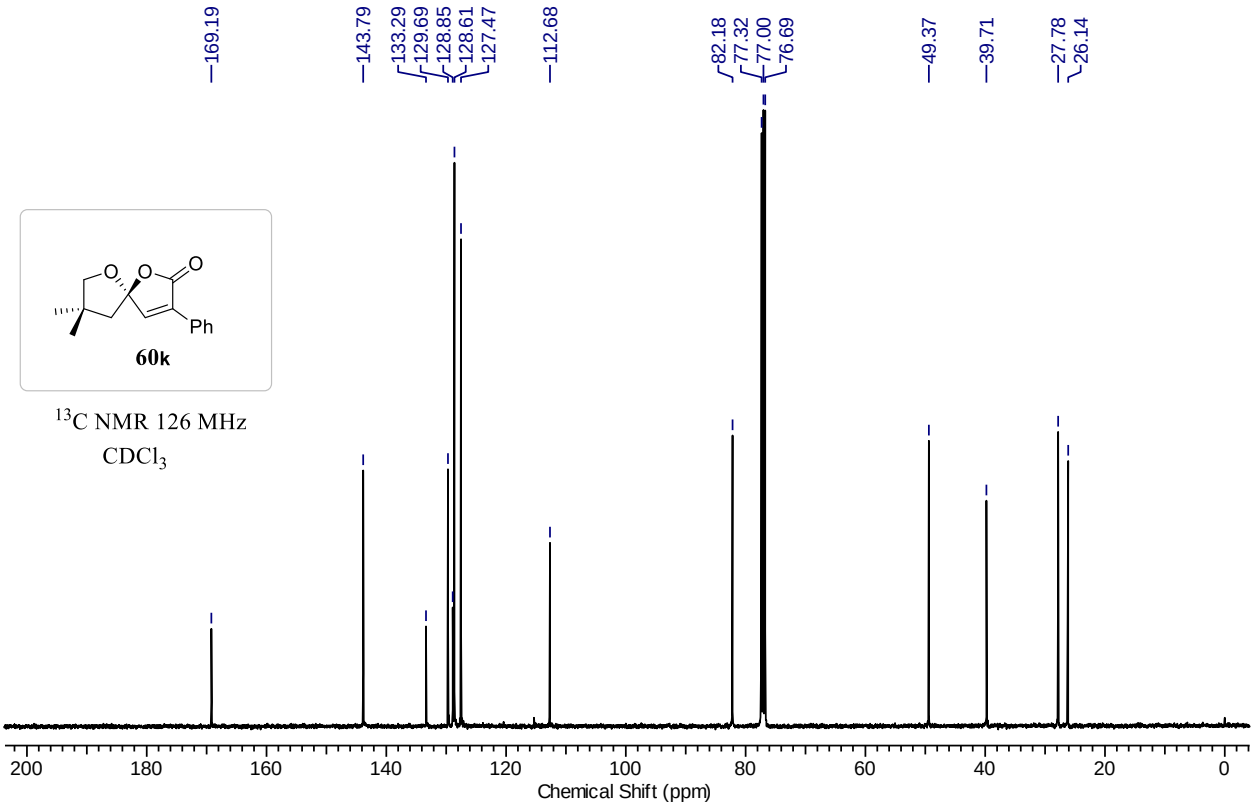
3,8,8-Trimethyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60j):



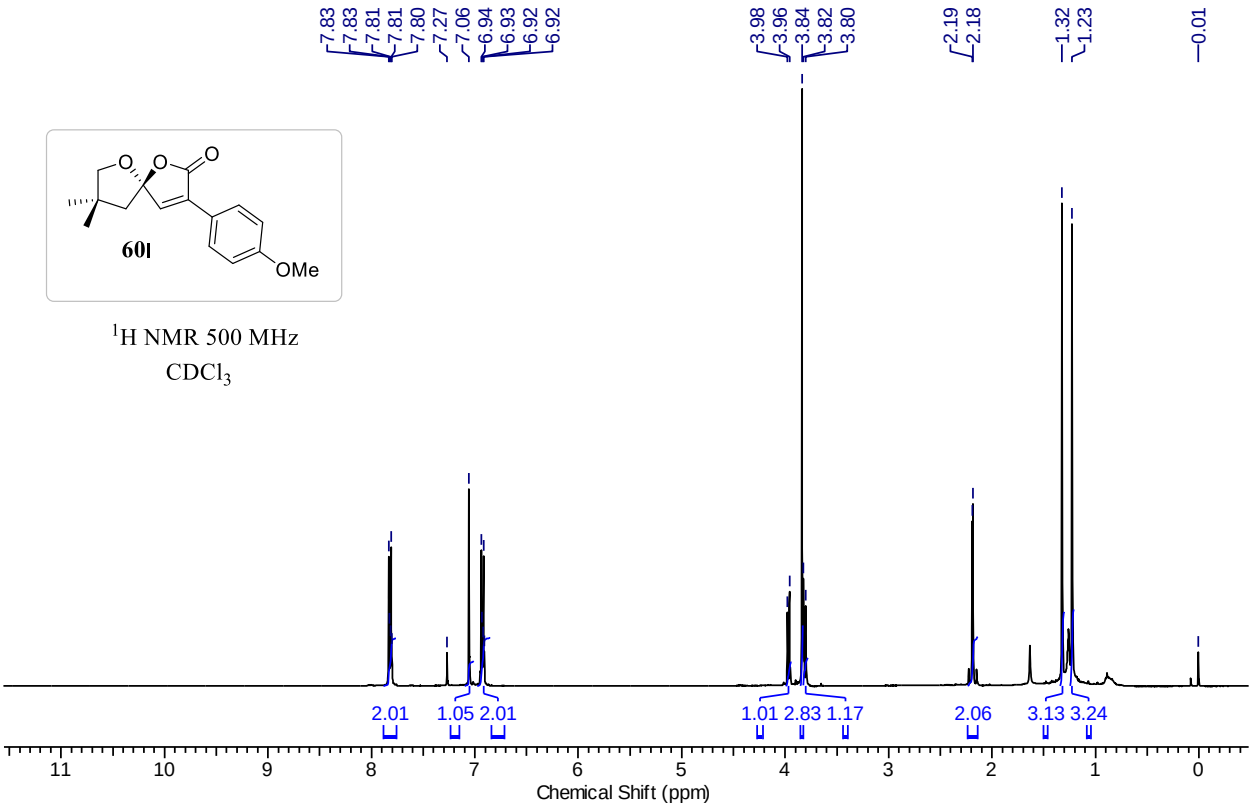


8,8-Dimethyl-3-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60k):

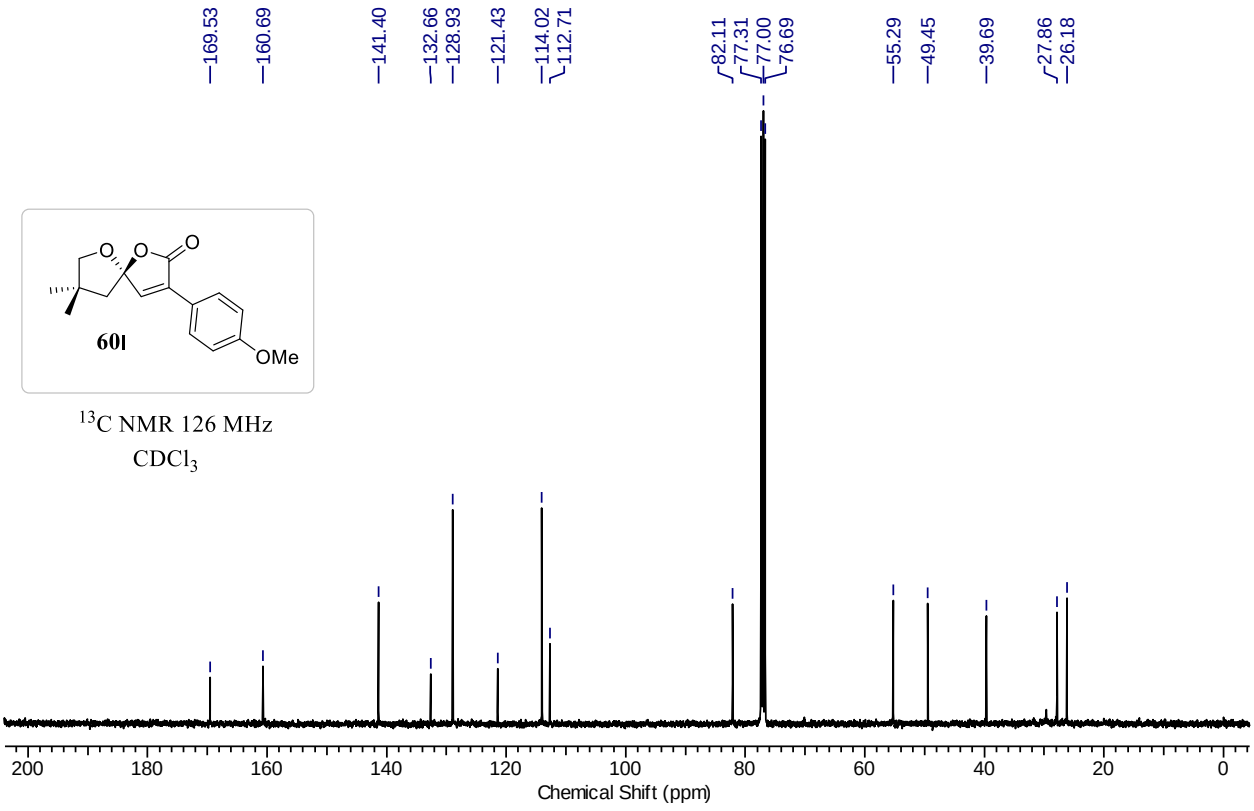




3-(4-Methoxyphenyl)-8,8-dimethyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60l):

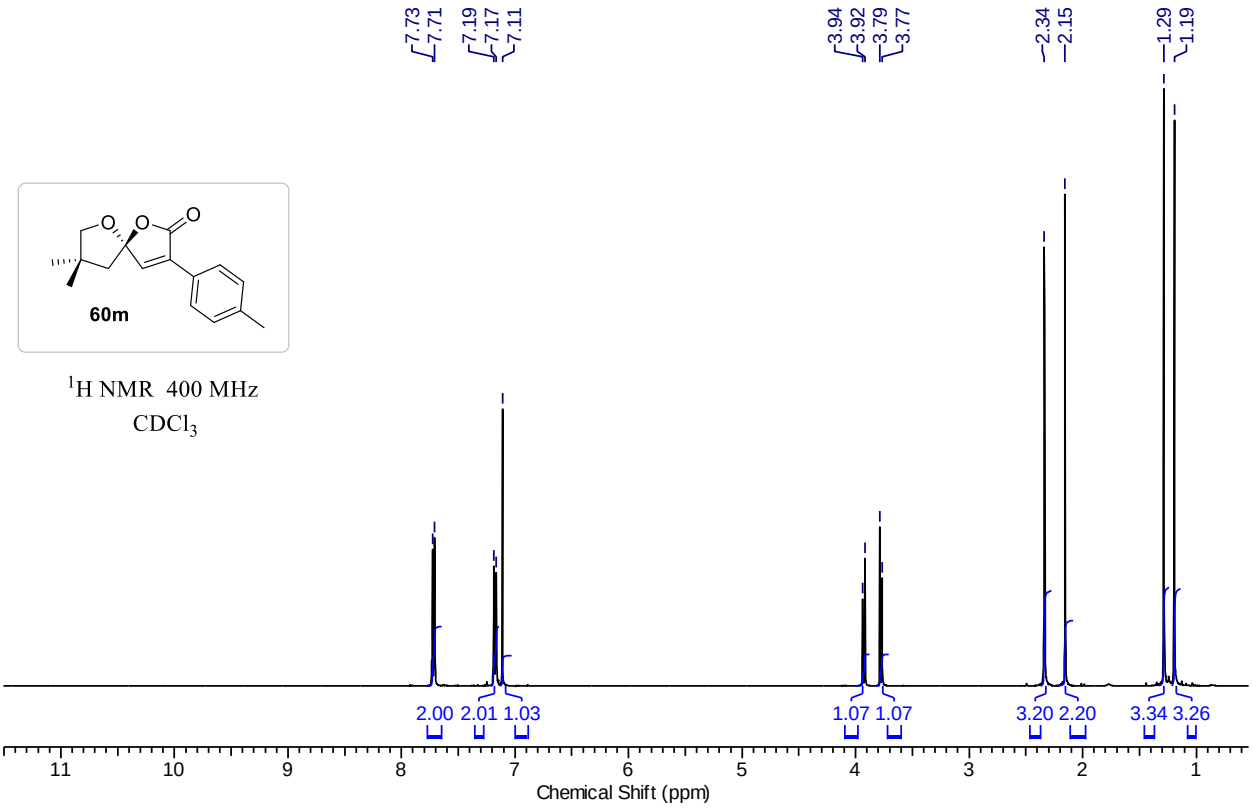


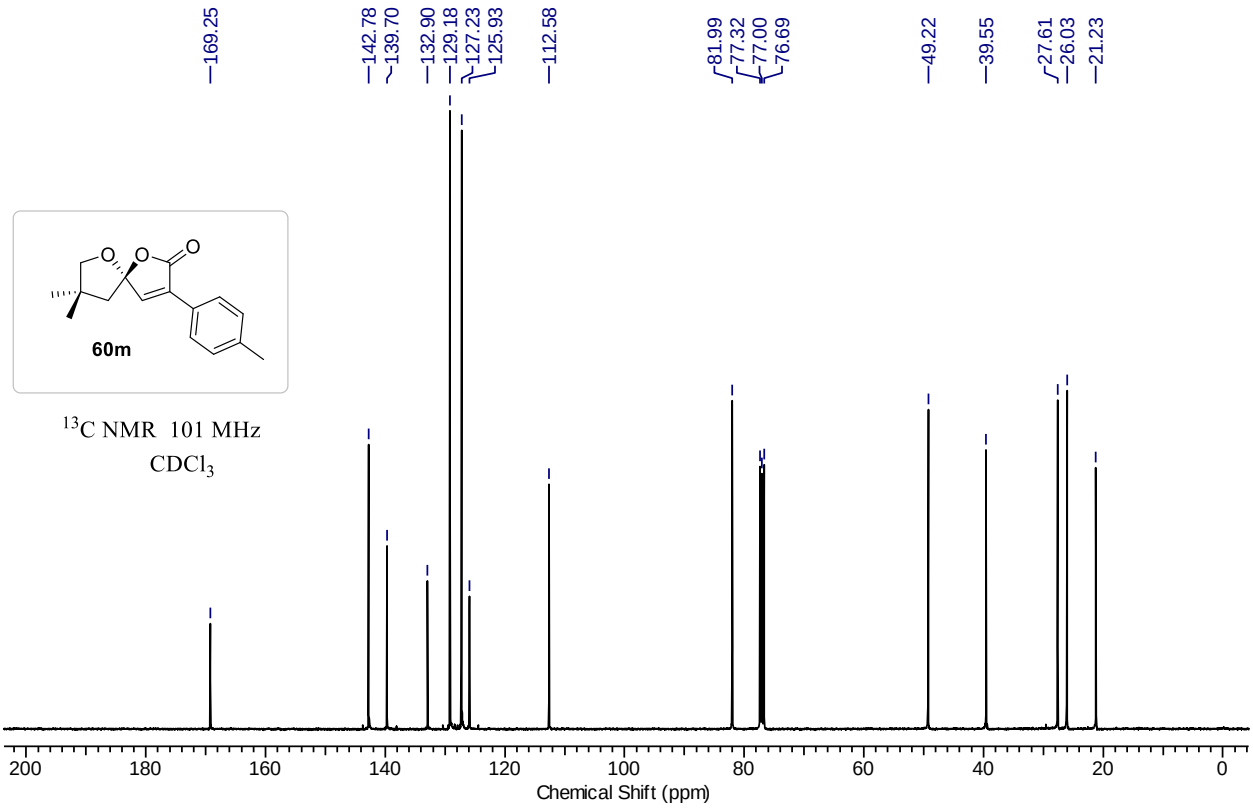
^{1}H NMR 500 MHz
$CDCl_3$



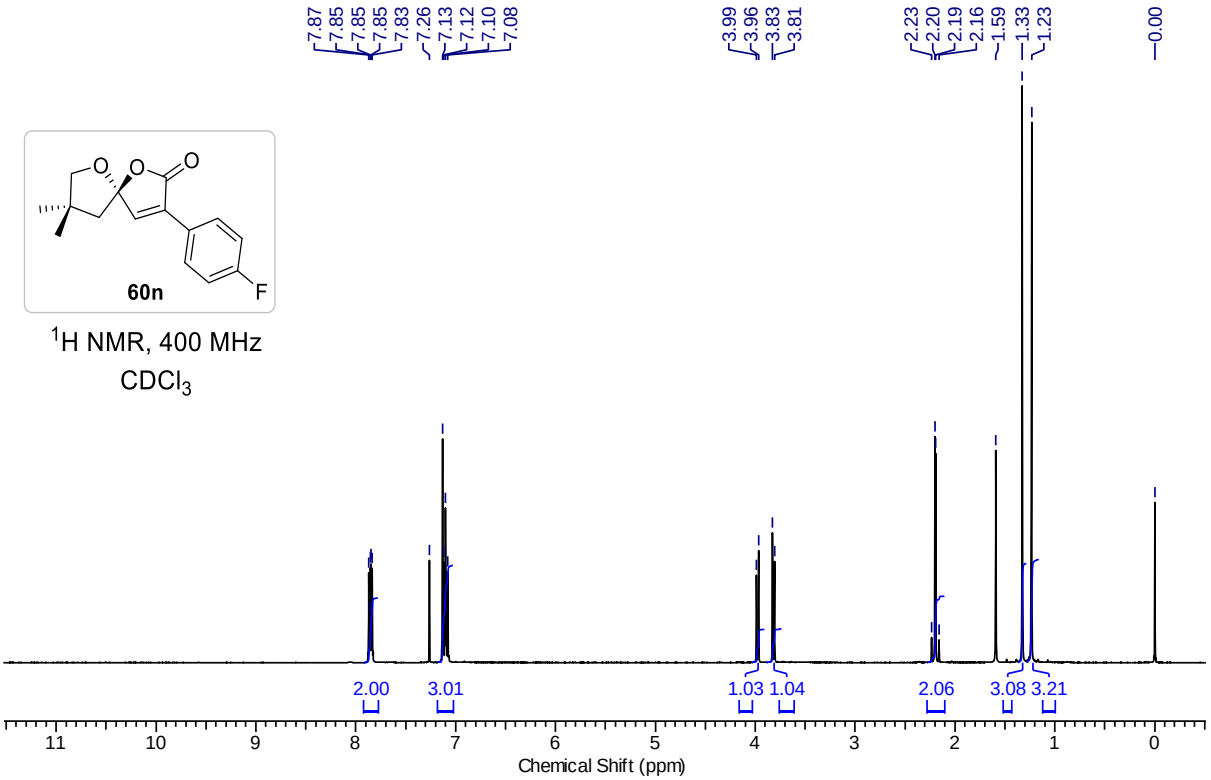
^{13}C NMR 126 MHz
$CDCl_3$

8,8-Dimethyl-3-(*p*-tolyl)-1,6-dioxaspiro[4.4]non-3-en-2-one (60m):

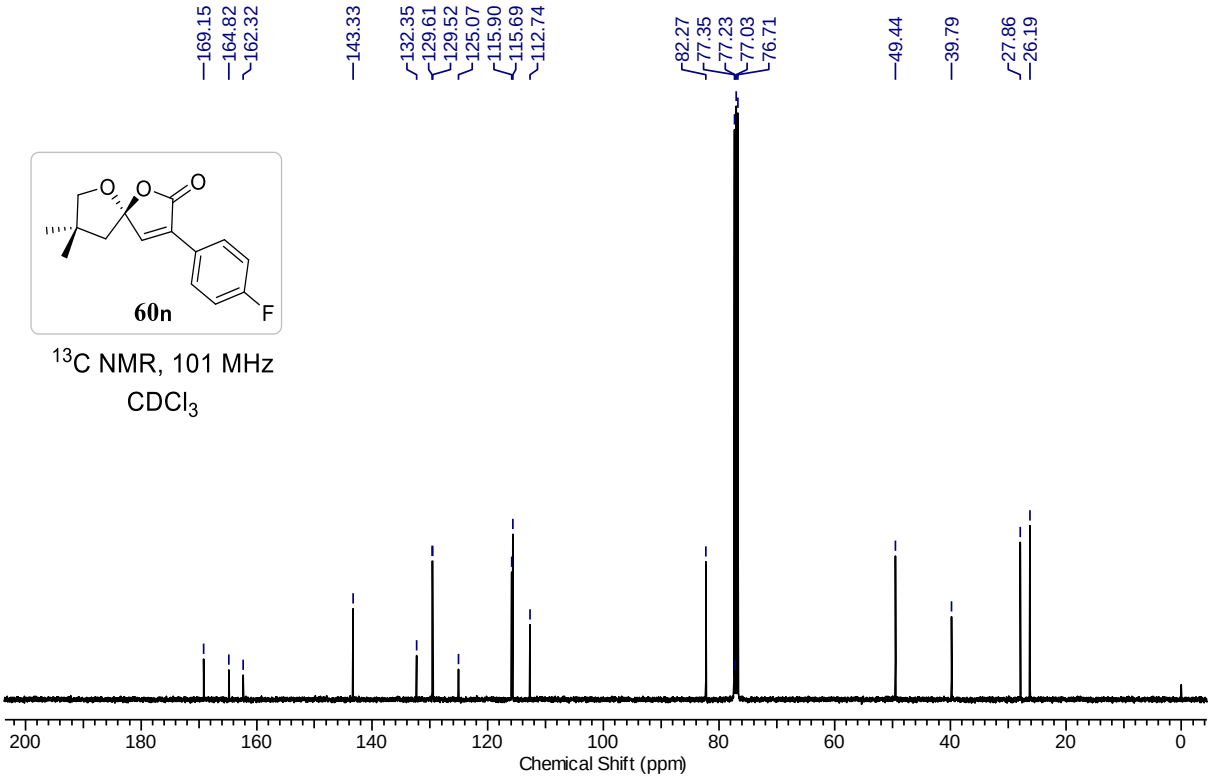




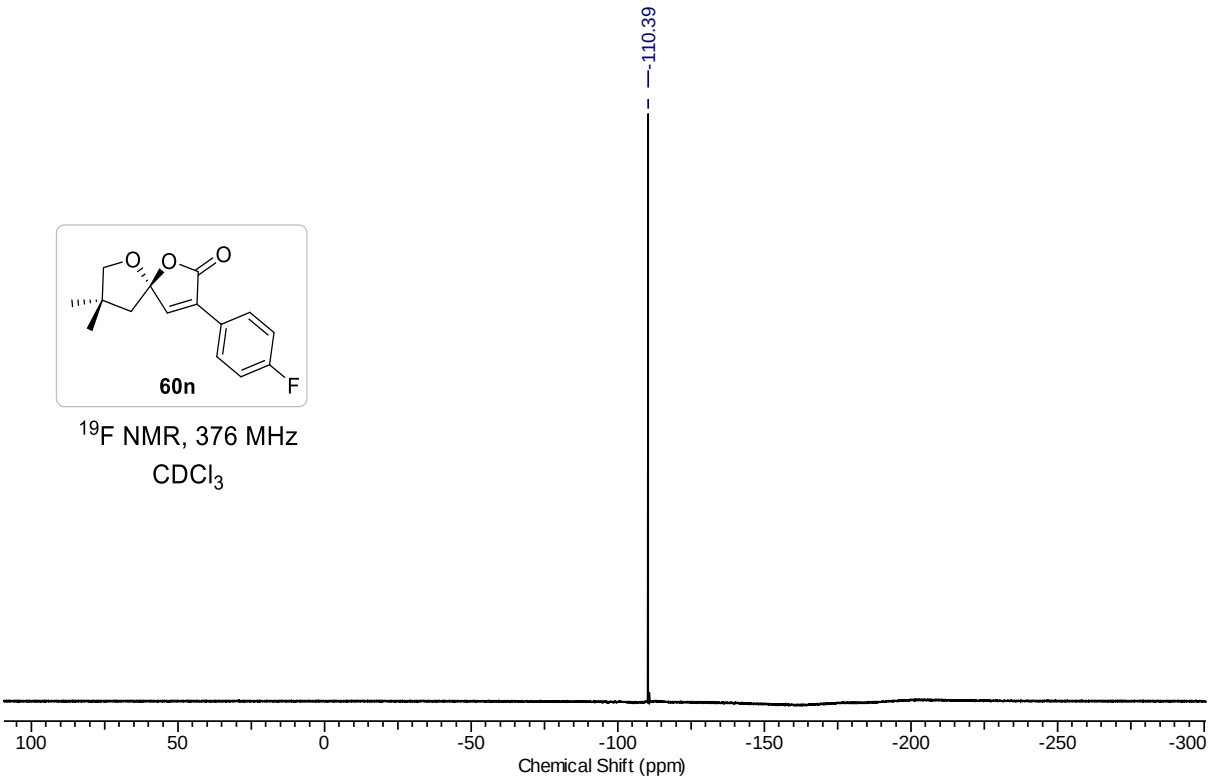
3-(4-Fluorophenyl)-8,8-dimethyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60n):



^{1}H NMR, 400 MHz
$CDCl_3$

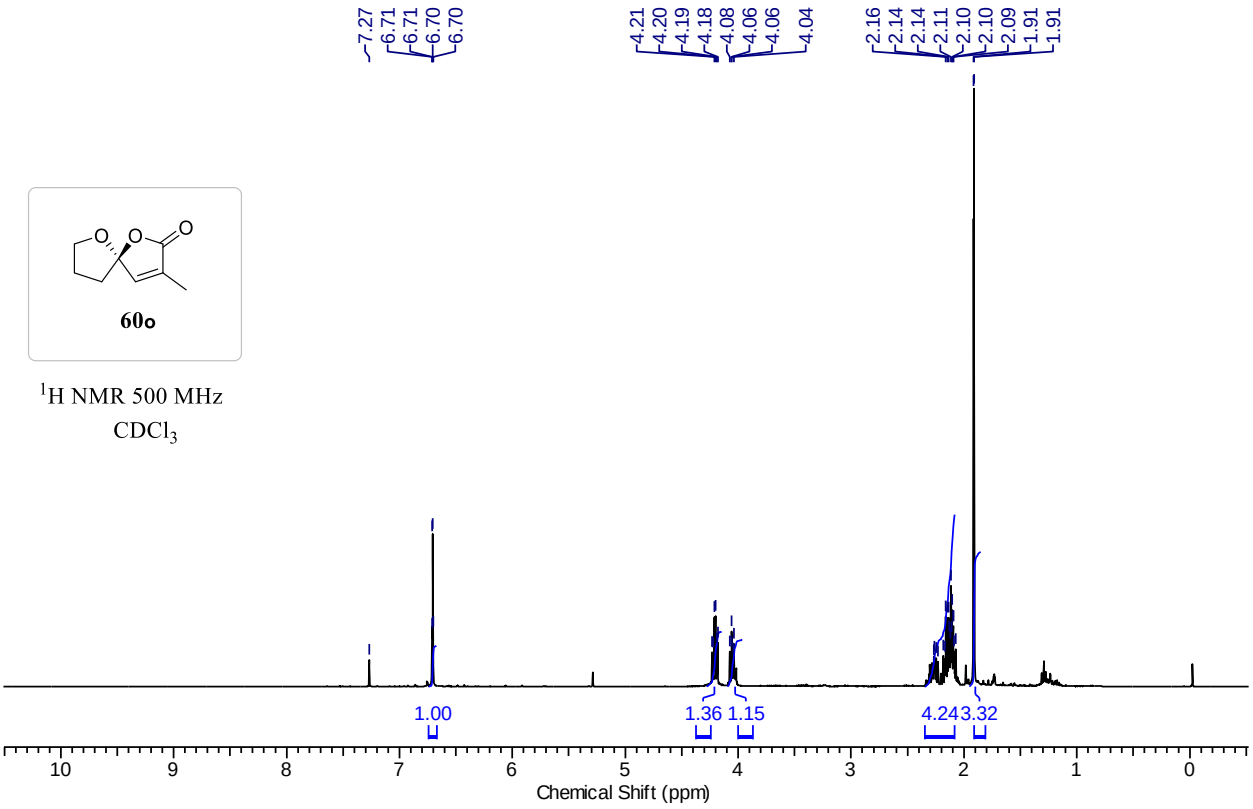


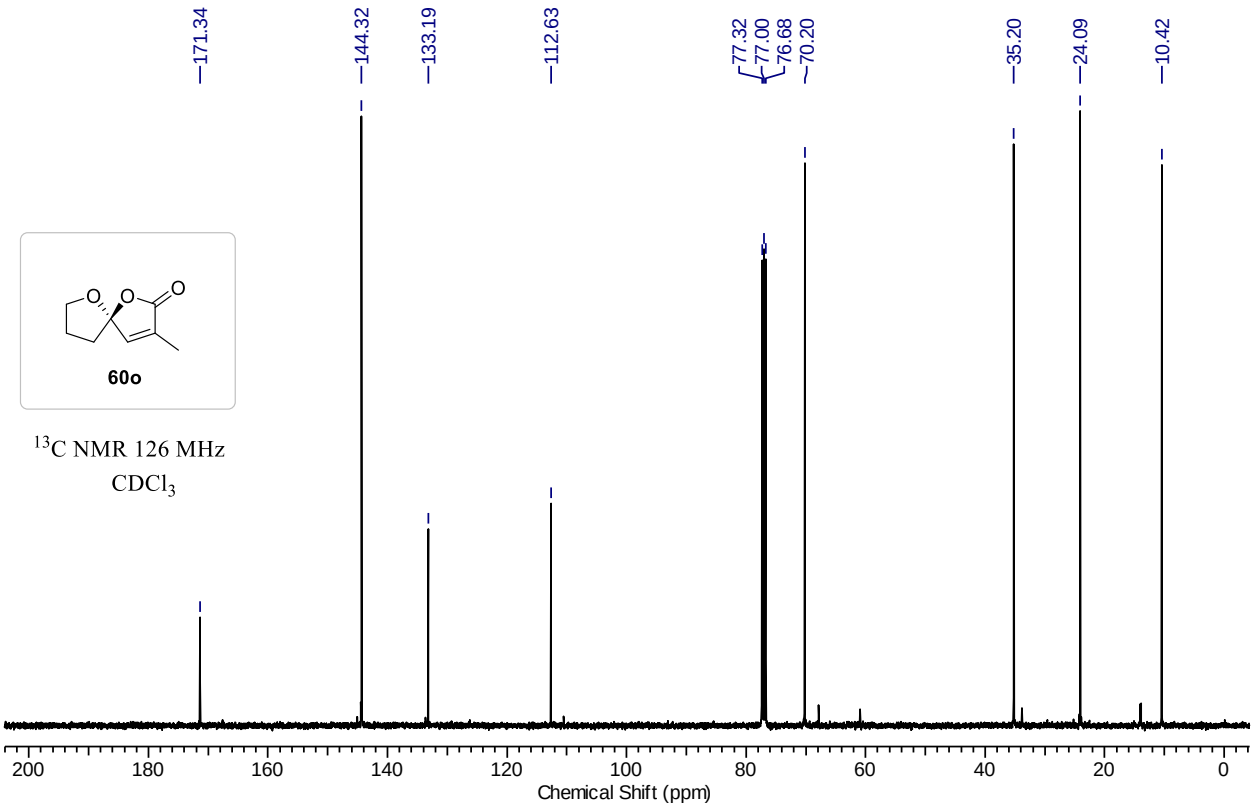
^{13}C NMR, 101 MHz
$CDCl_3$



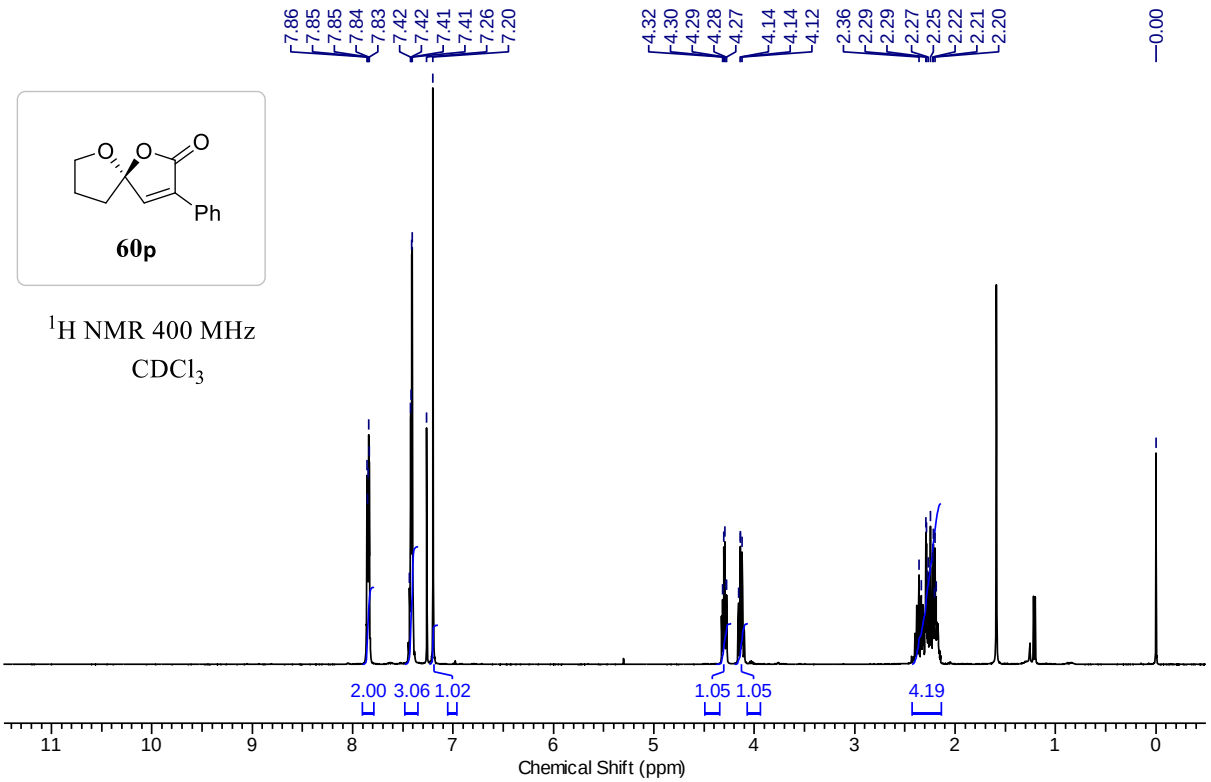
^{19}F NMR, 376 MHz
$CDCl_3$

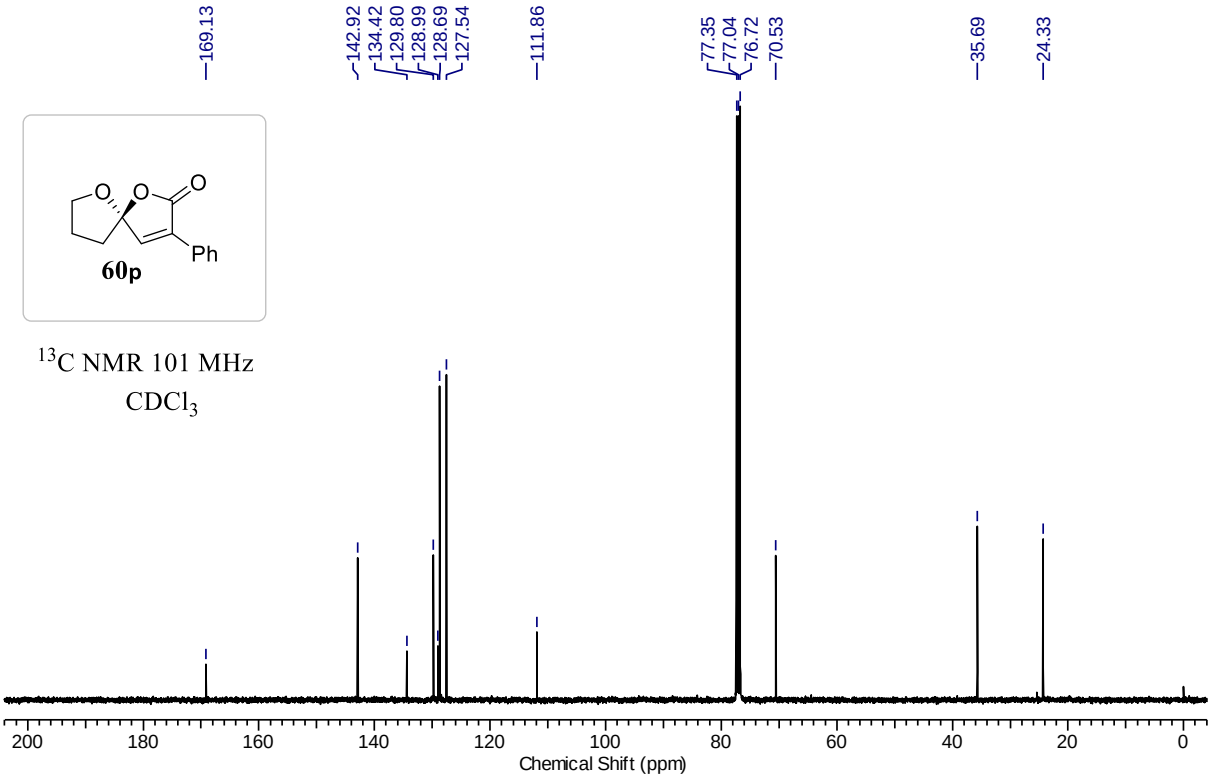
3-Methyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60o):



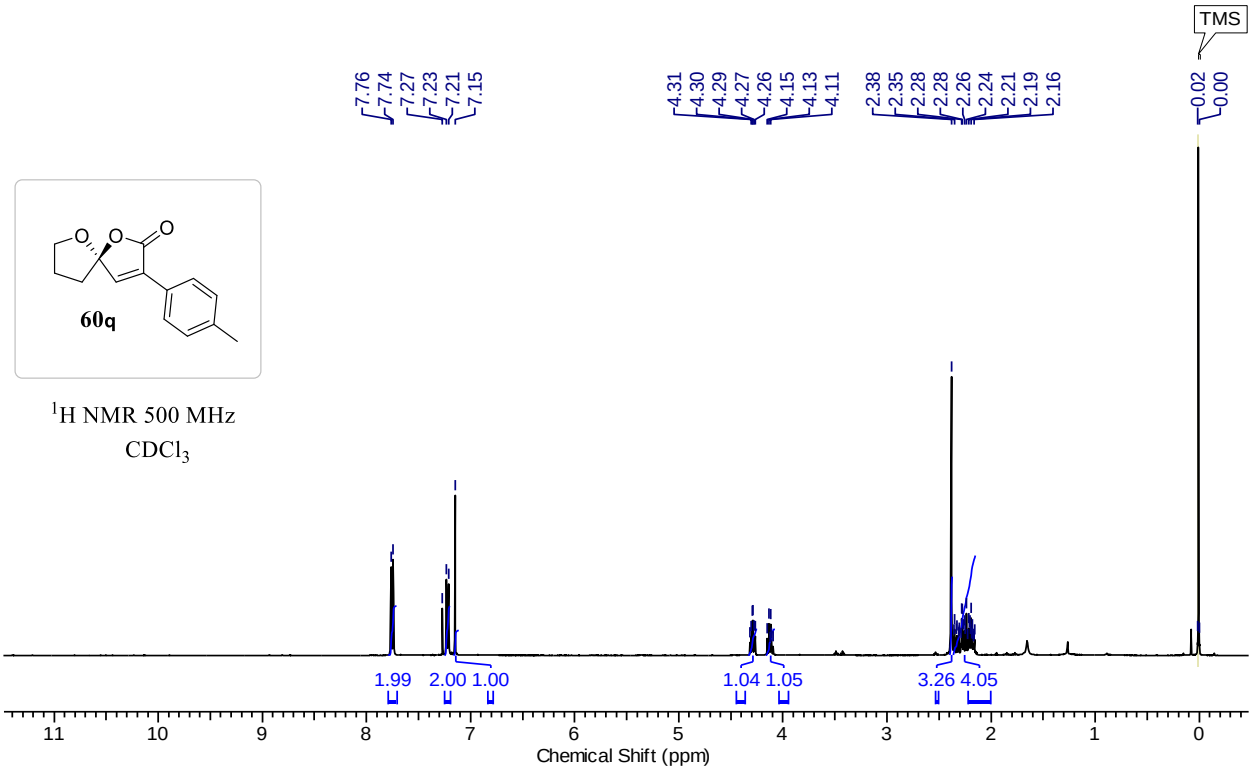


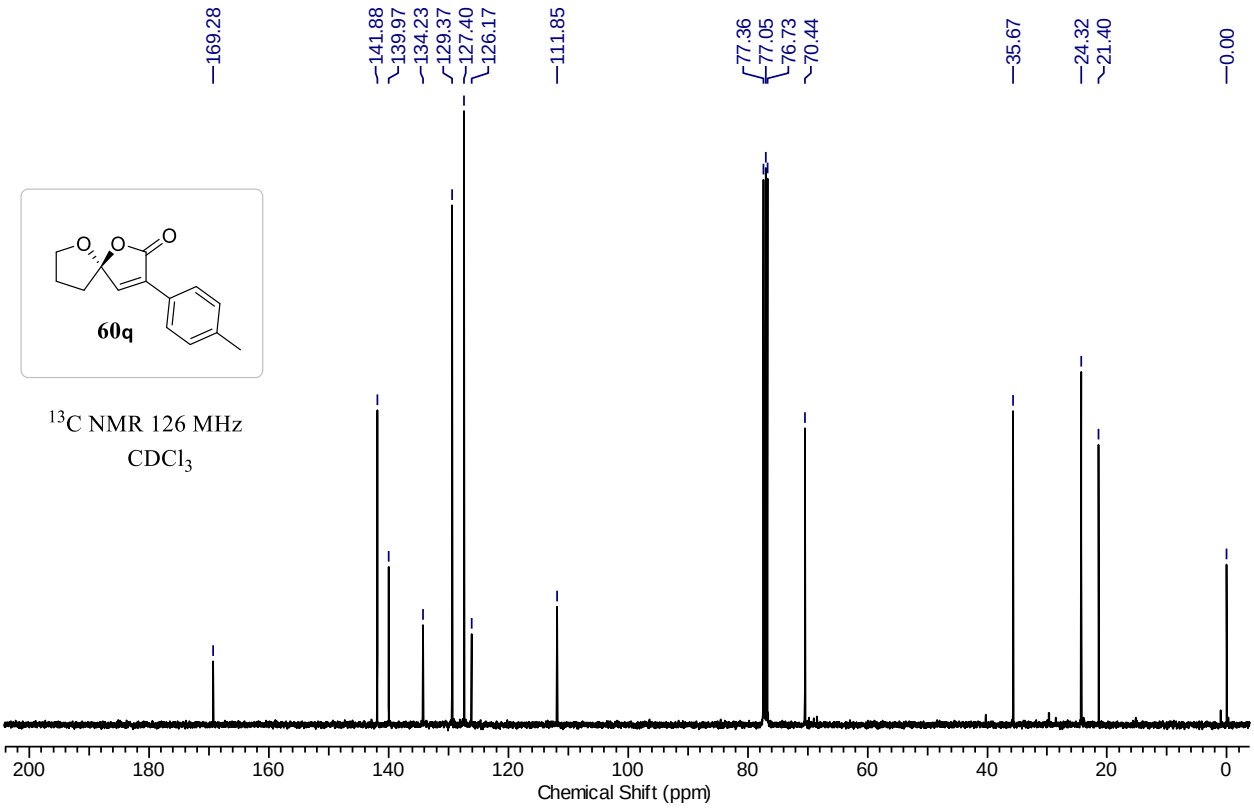
3-Phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60p):



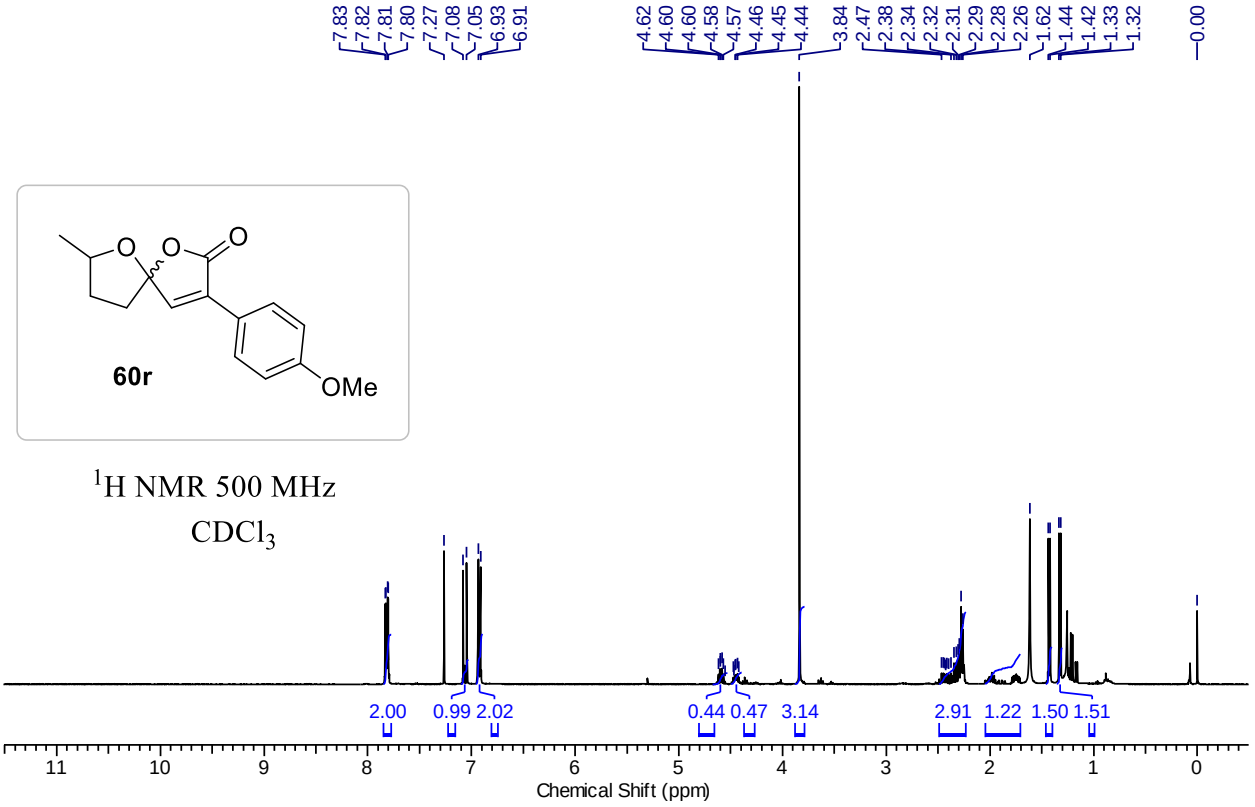


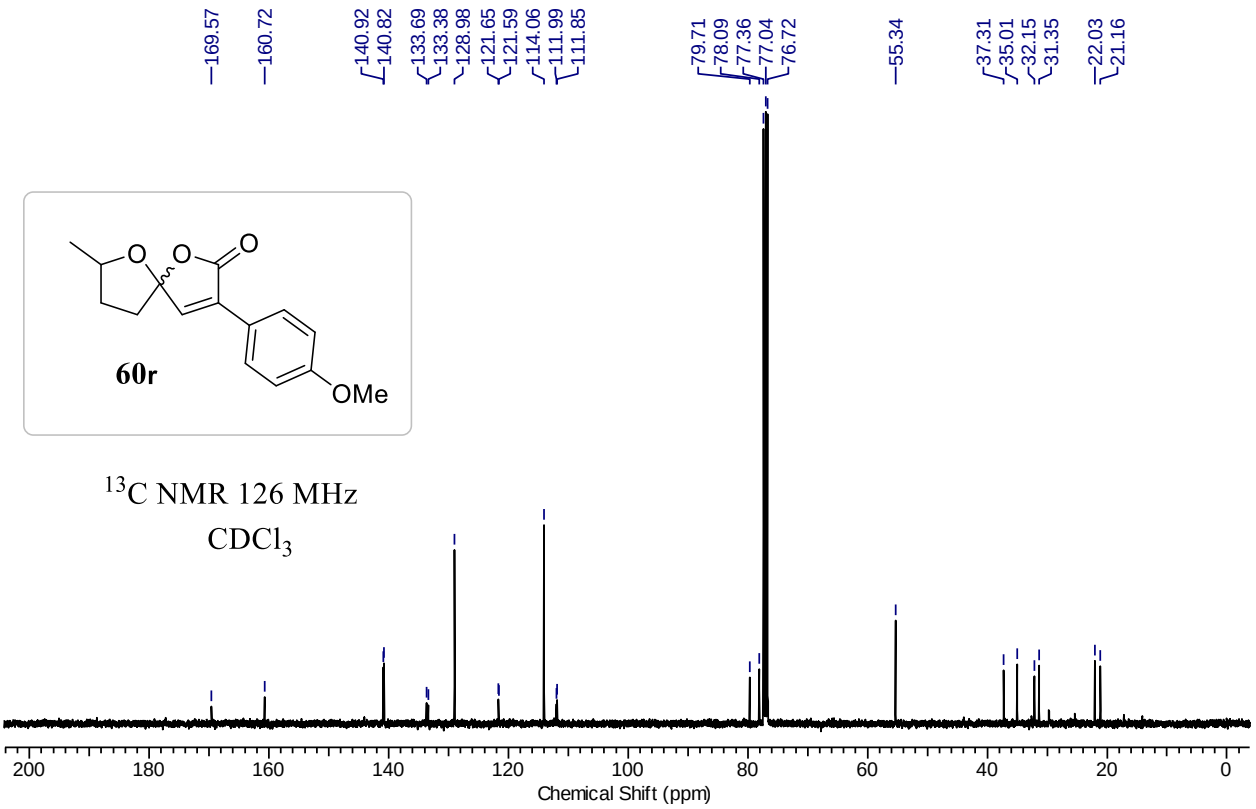
3-(*p*-Tolyl)-1,6-dioxaspiro[4.4]non-3-en-2-one (60q):



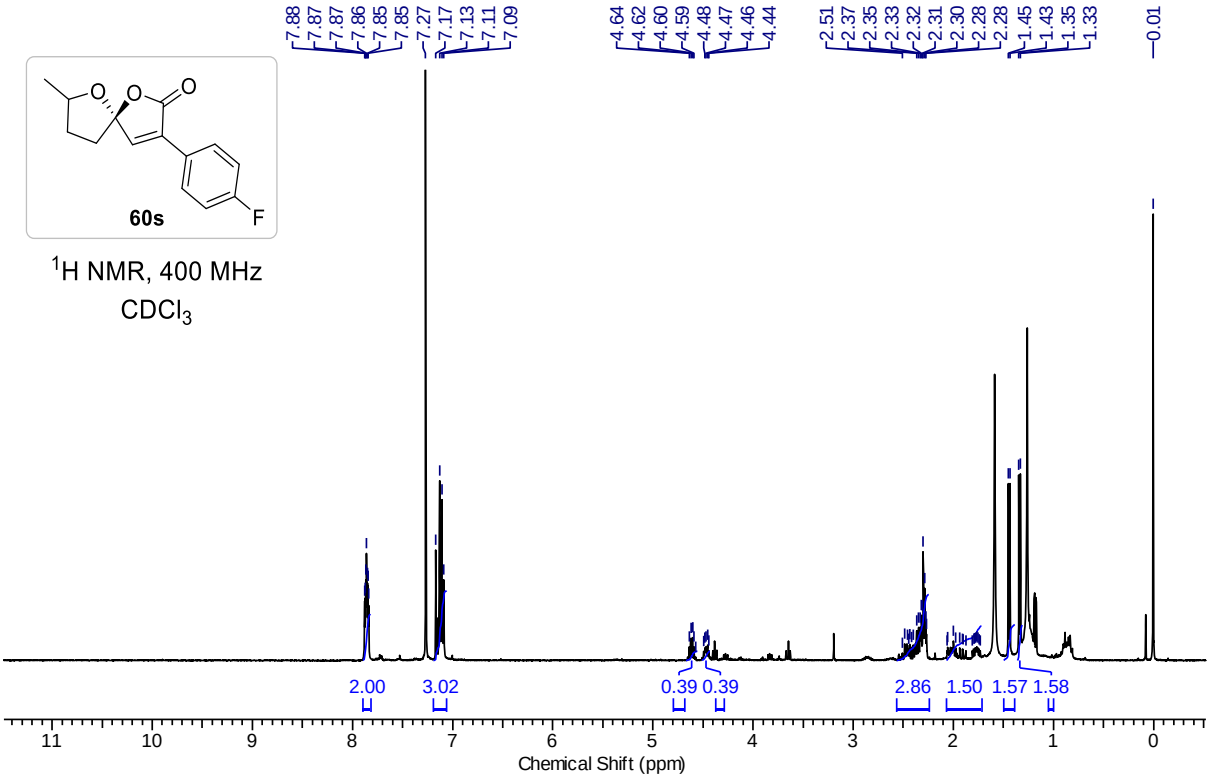


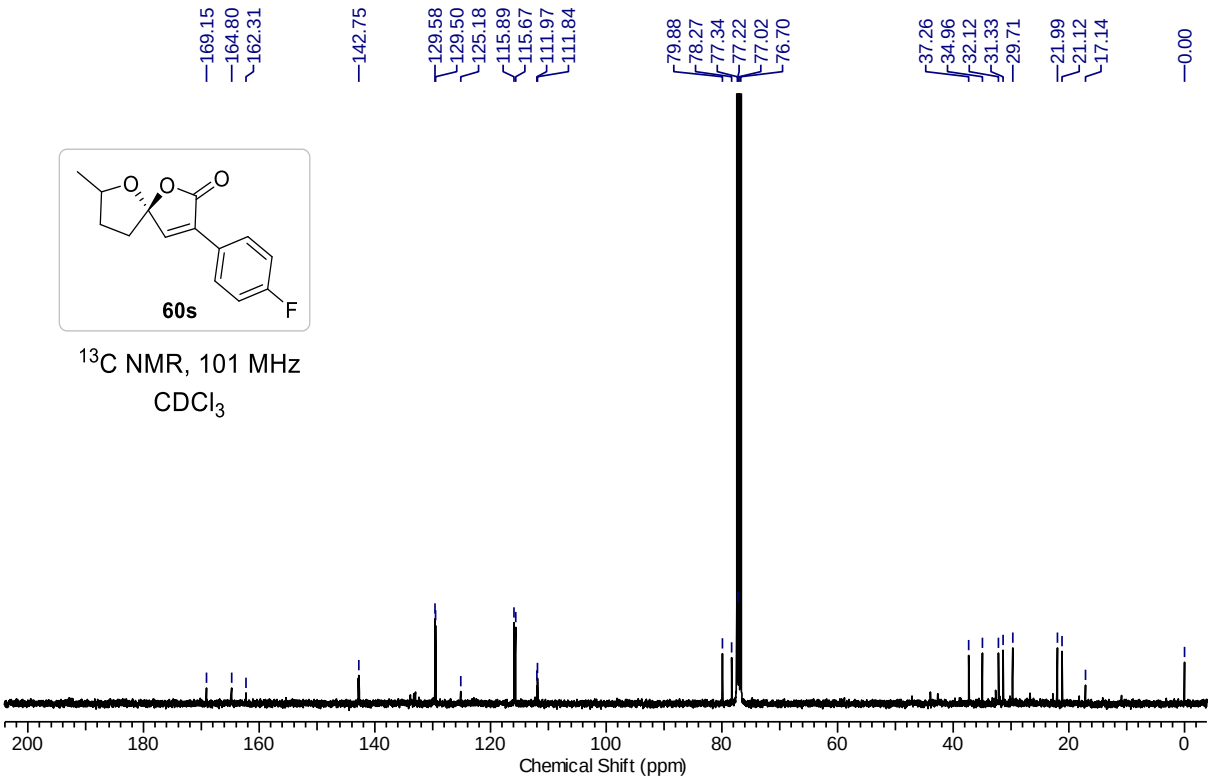
3-(4-Methoxyphenyl)-7-methyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60r):

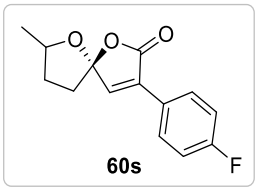




3-(4-fluorophenyl)-7-methyl-1,6-dioxaspiro[4.4]non-3-en-2-one (60s):





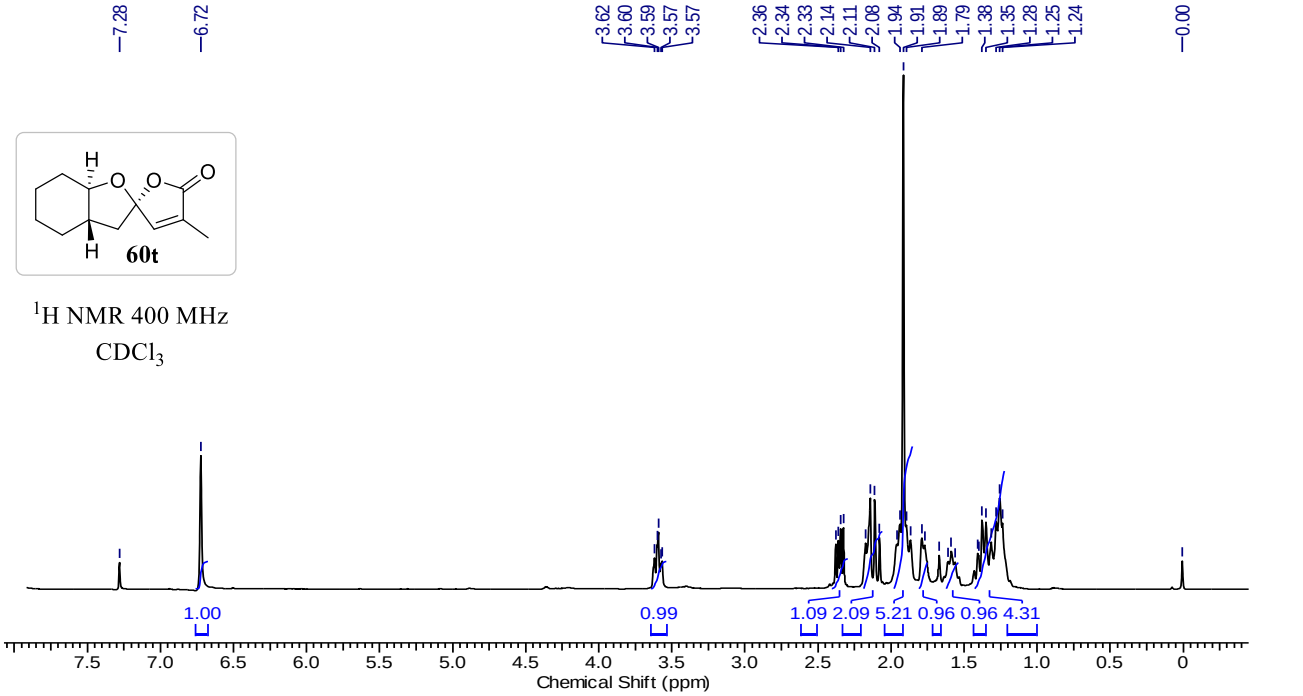


60s

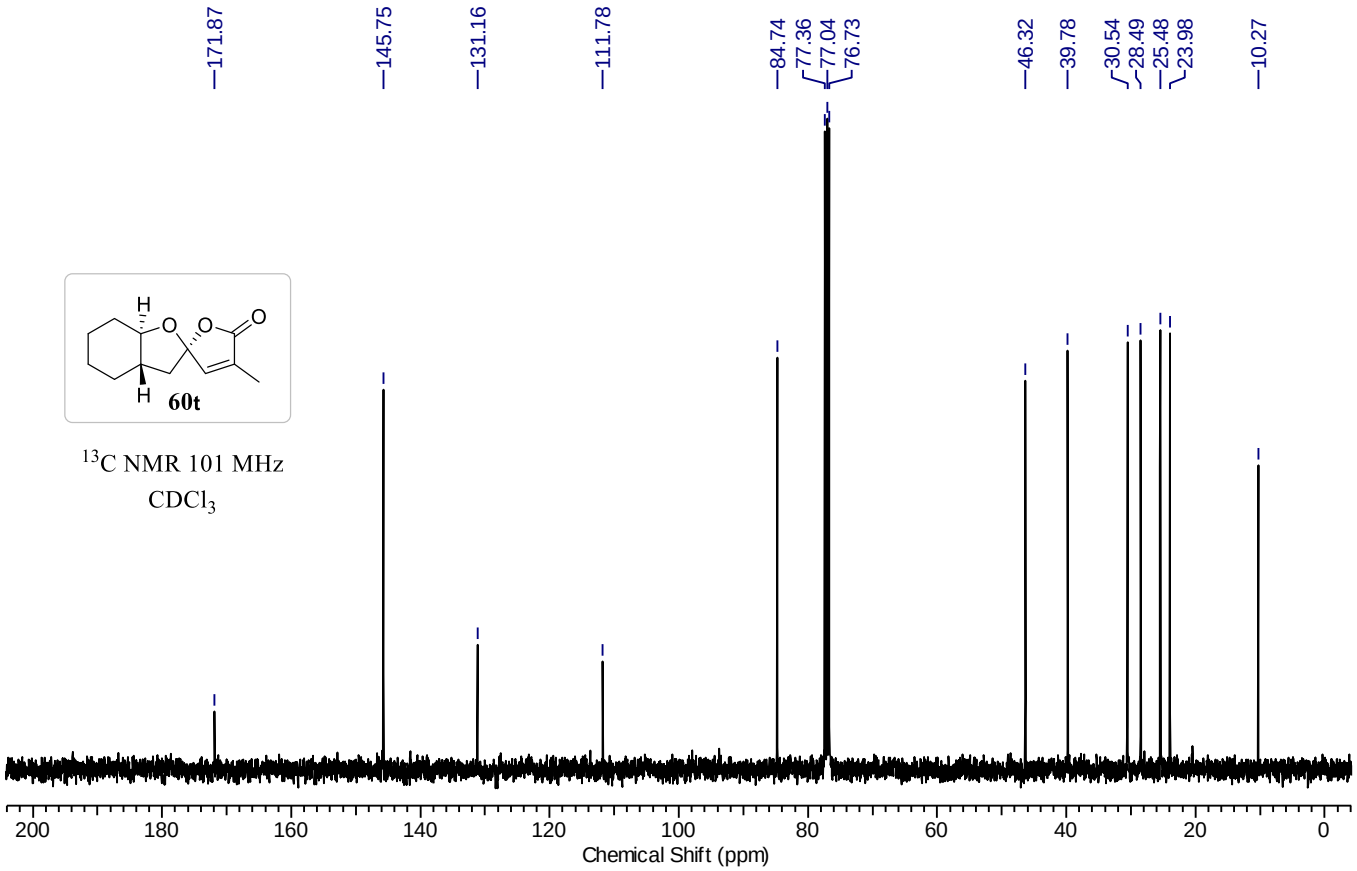
^{19}F NMR, 376 MHz

$CDCl_3$

4'-Methyl-3a,4,5,6,7,7a-hexahydro-3H,5'*H*-spiro[benzofuran-2,2'-furan]-5'-one (60t):

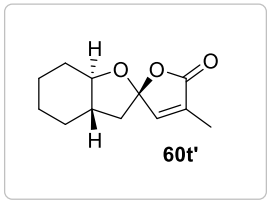


^{1}H NMR 400 MHz
$CDCl_3$

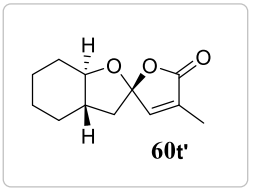


^{13}C NMR 101 MHz
$CDCl_3$

4'-Methyl-3a,4,5,6,7,7a-hexahydro-3H,5'*H*-spiro[benzofuran-2,2'-furan]-5'-one (60t'):

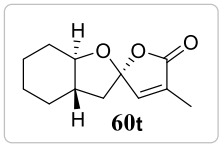


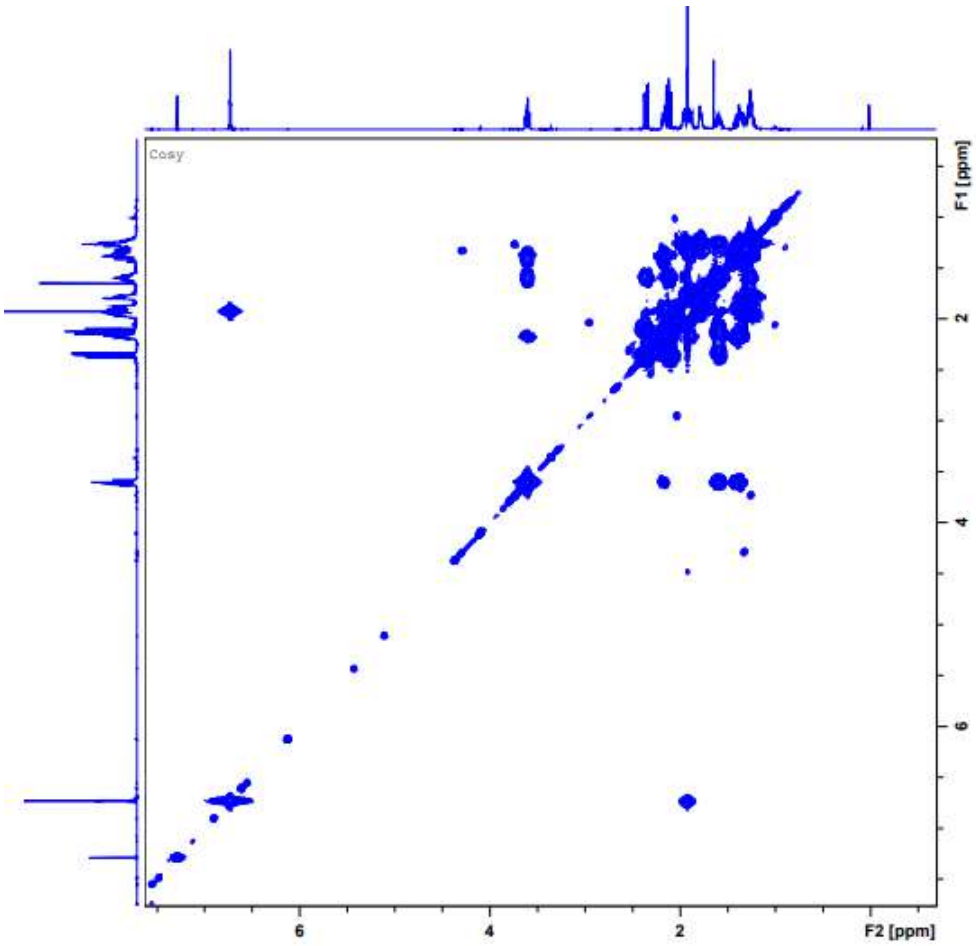
^{1}H NMR 500 MHz
$CDCl_3$



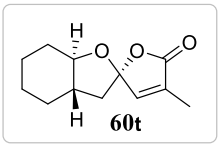
^{13}C NMR 126 MHz
$CDCl_3$

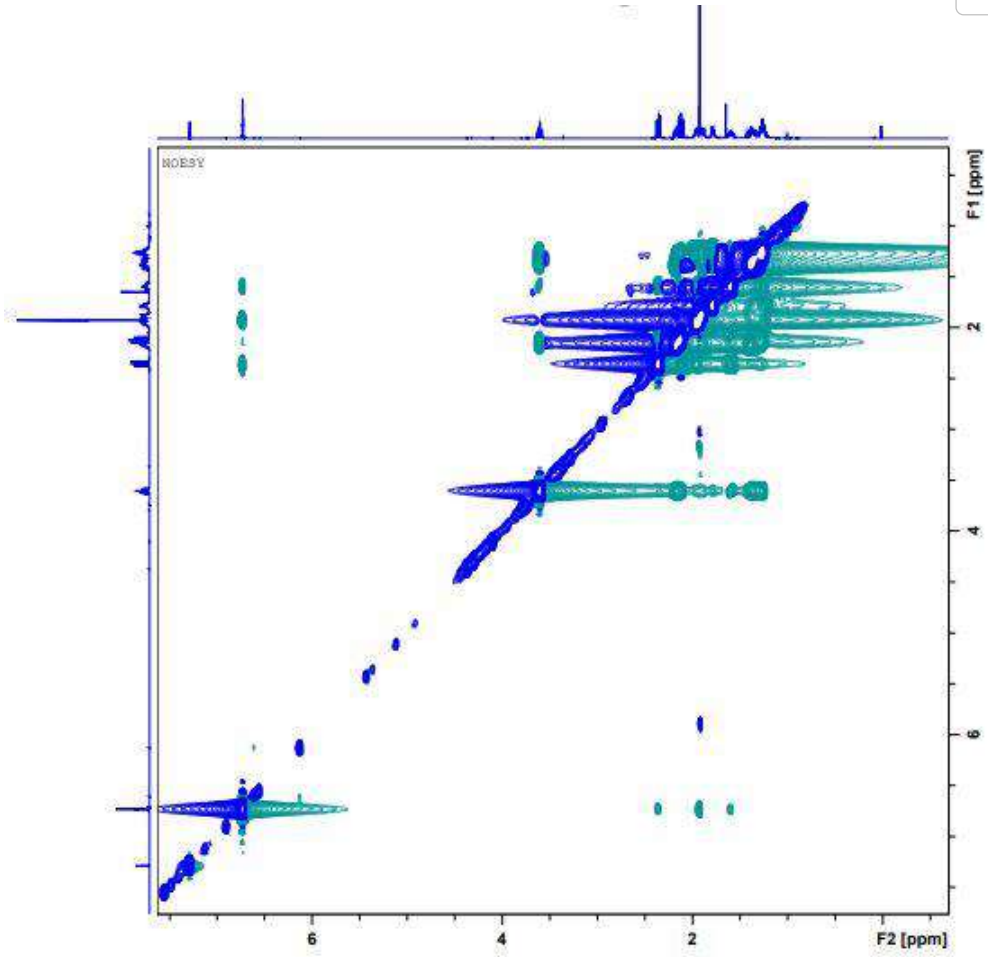
COSY: (60t)



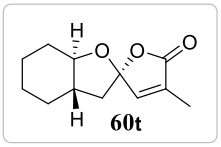


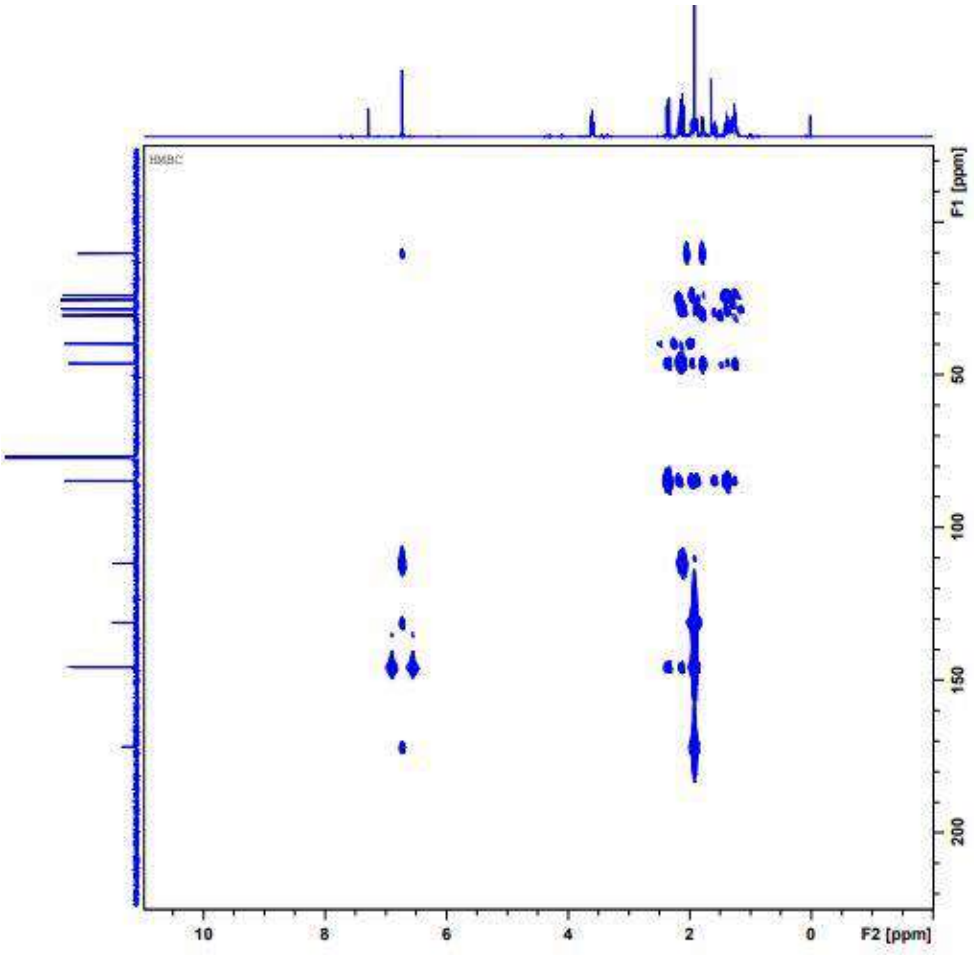
NOESY: (60t)



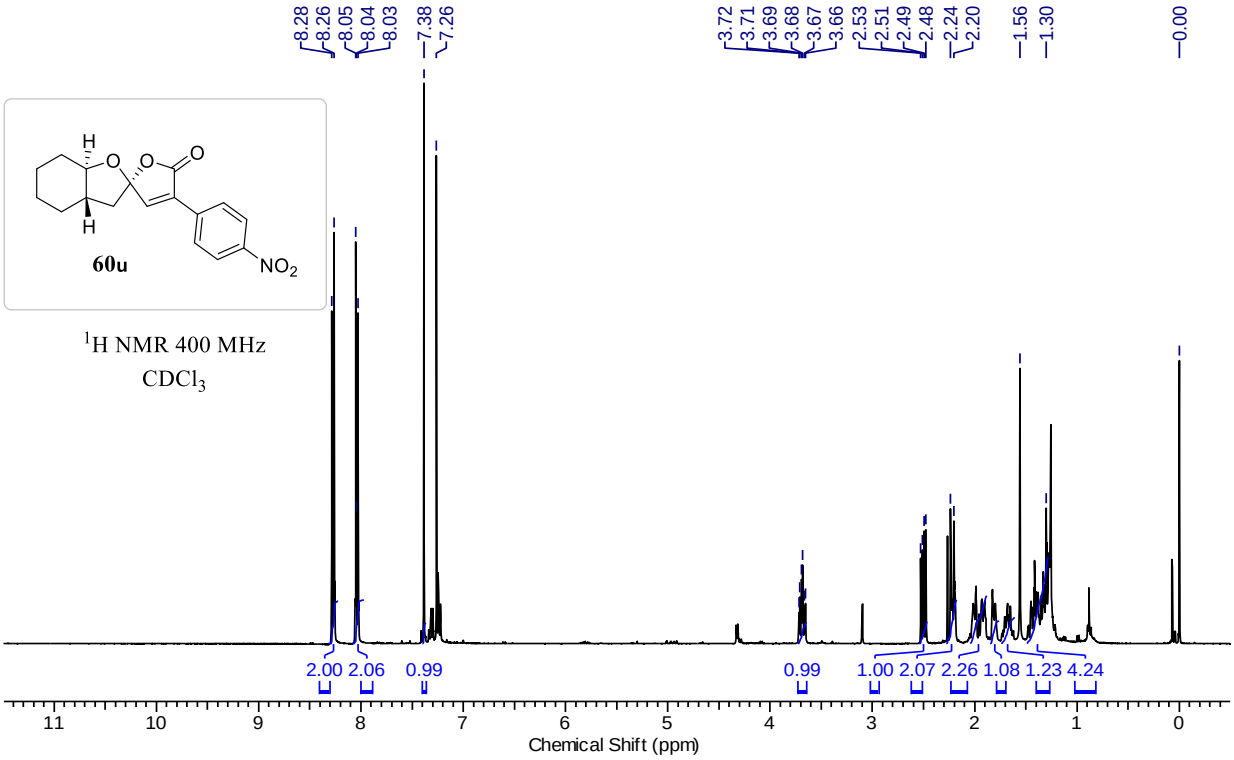


HMBC: (60t)

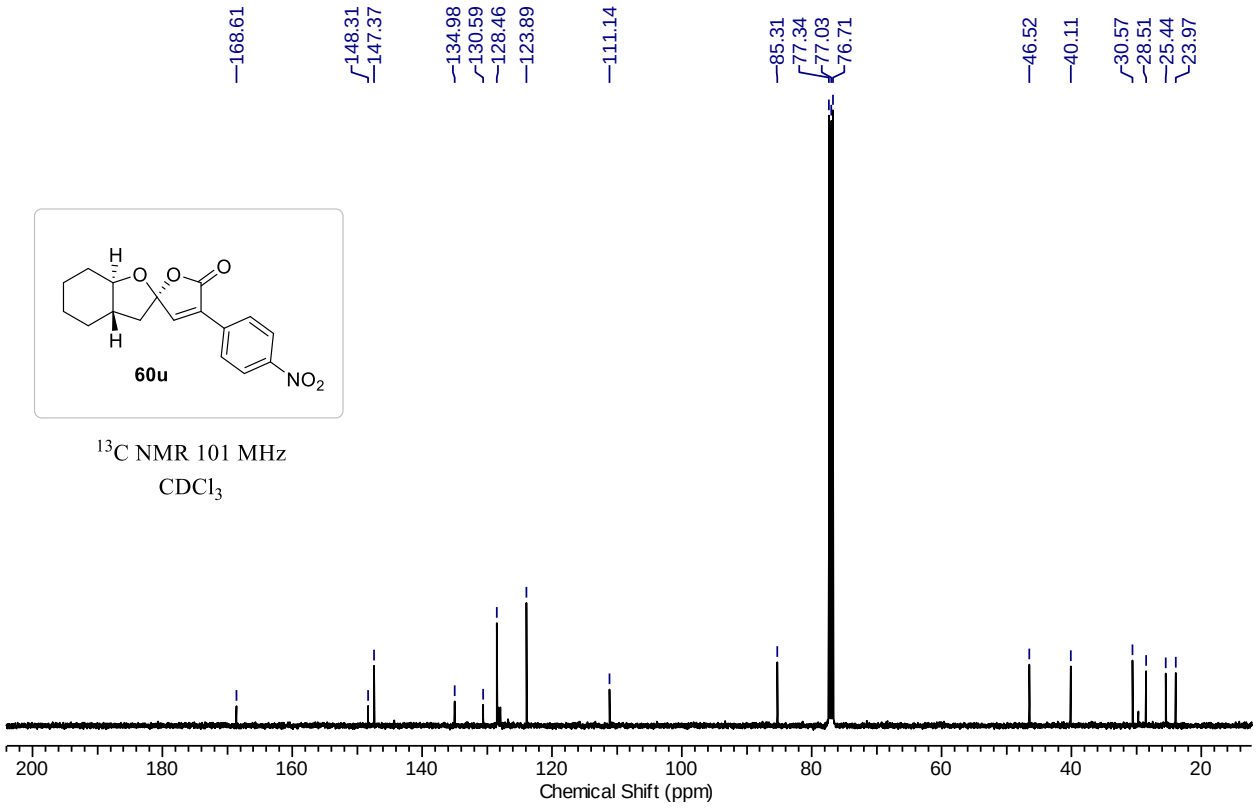




4'-(4-Nitrophenyl)-3a,4,5,6,7,7a-hexahydro-3H,5'*H*-spiro[benzofuran-2,2'-furan]-5'-one (60u):

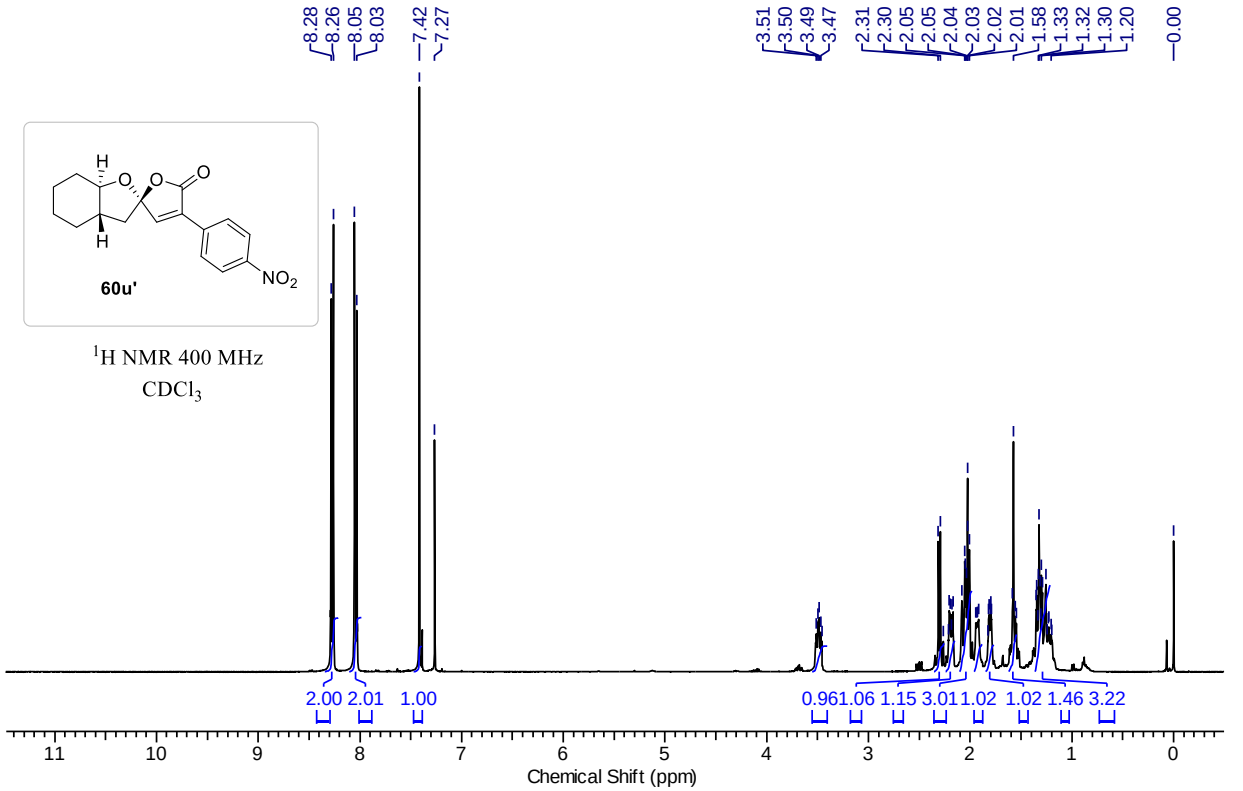


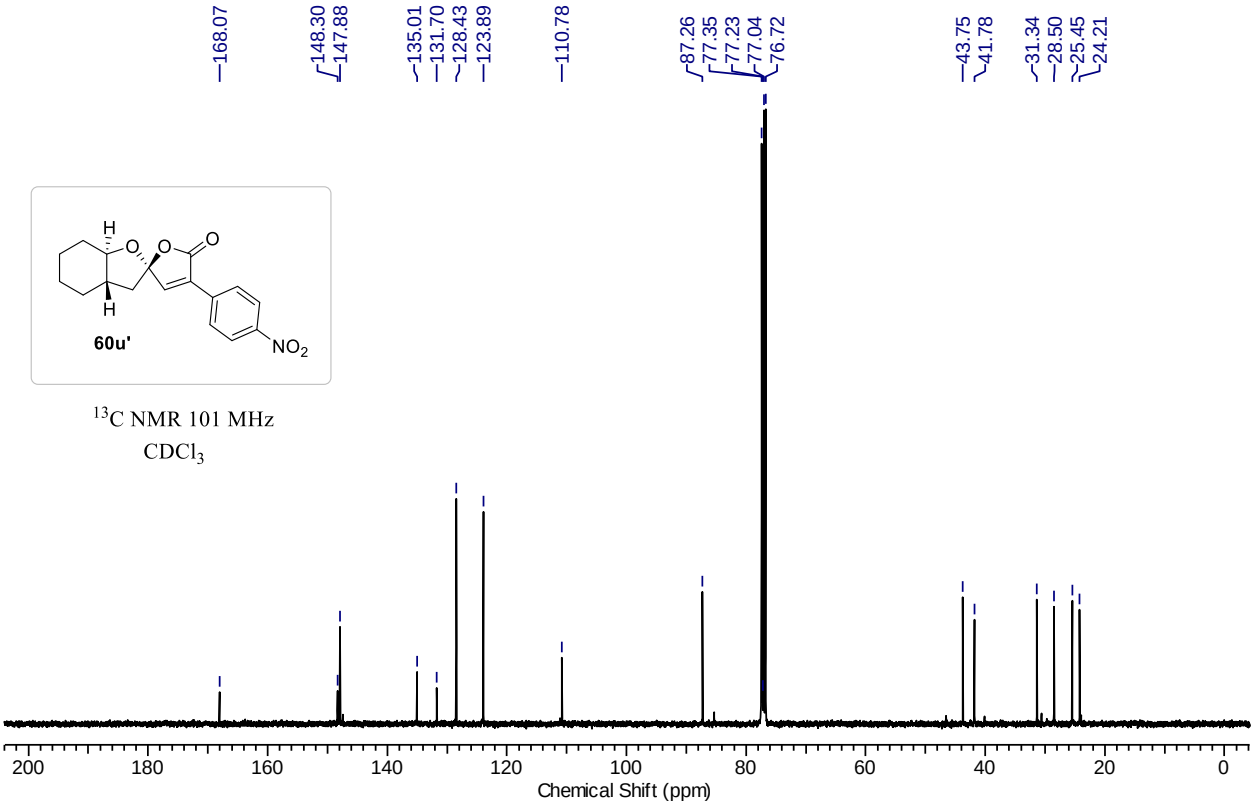
^{1}H NMR 400 MHz
$CDCl_3$



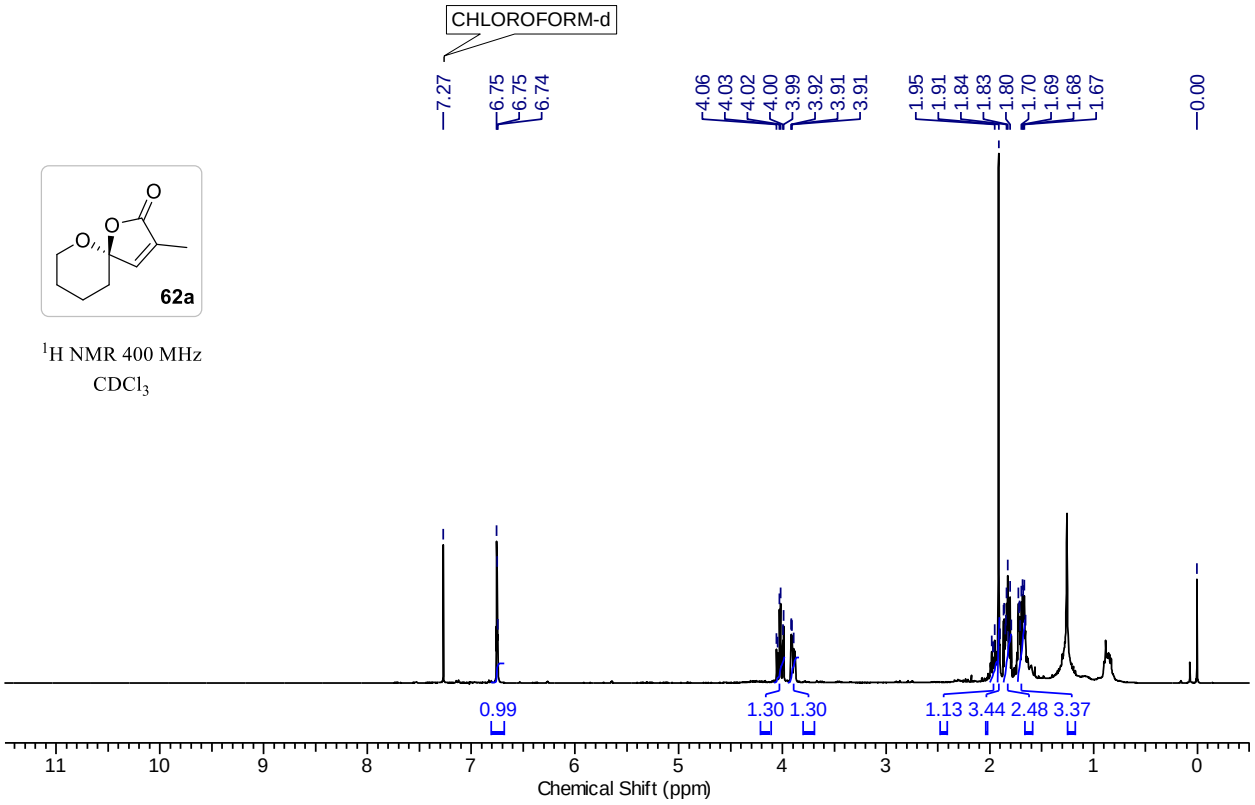
^{13}C NMR 101 MHz
$CDCl_3$

4'-(4-Nitrophenyl)-3a,4,5,6,7,7a-hexahydro-3*H*,5'*H*-spiro[benzofuran-2,2'-furan]-5'-one (60u'):

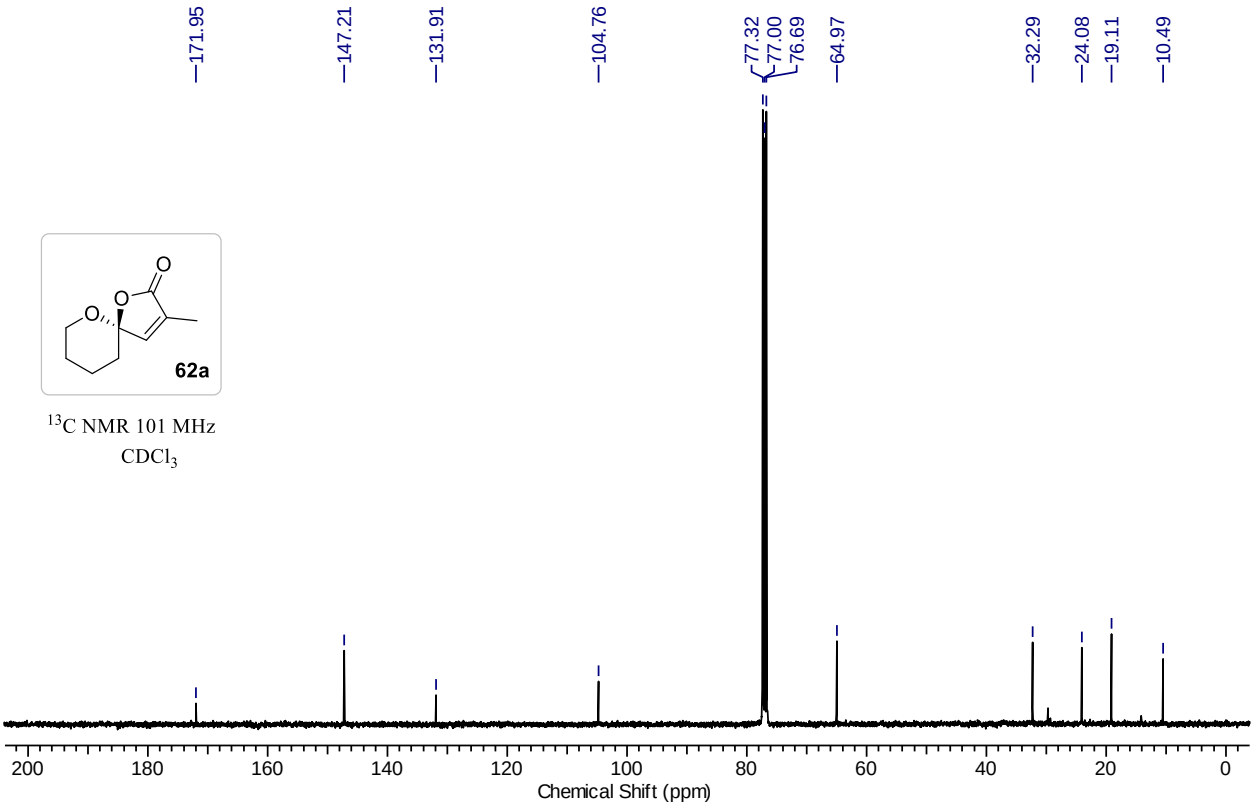




3-Methyl-1,6-dioxaspiro[4.5]dec-3-en-2-one (62a):

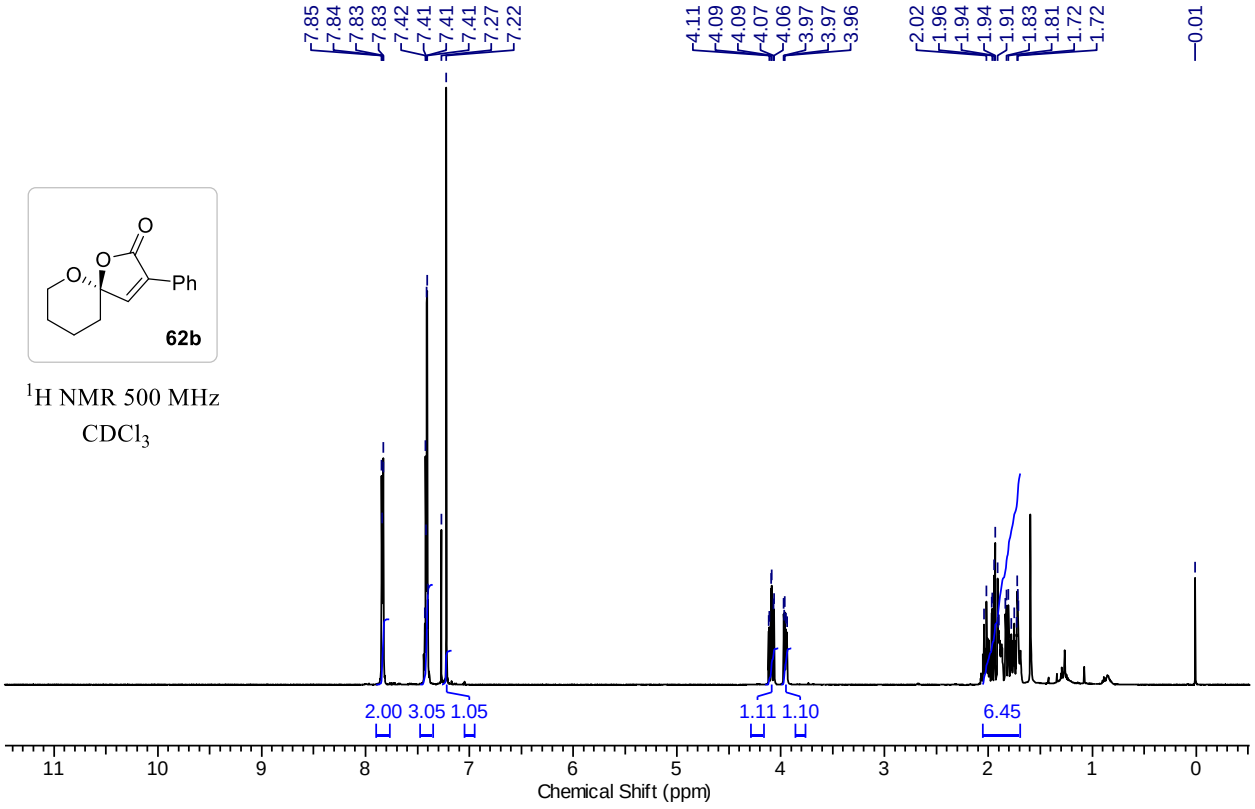


^{1}H NMR 400 MHz
$CDCl_3$

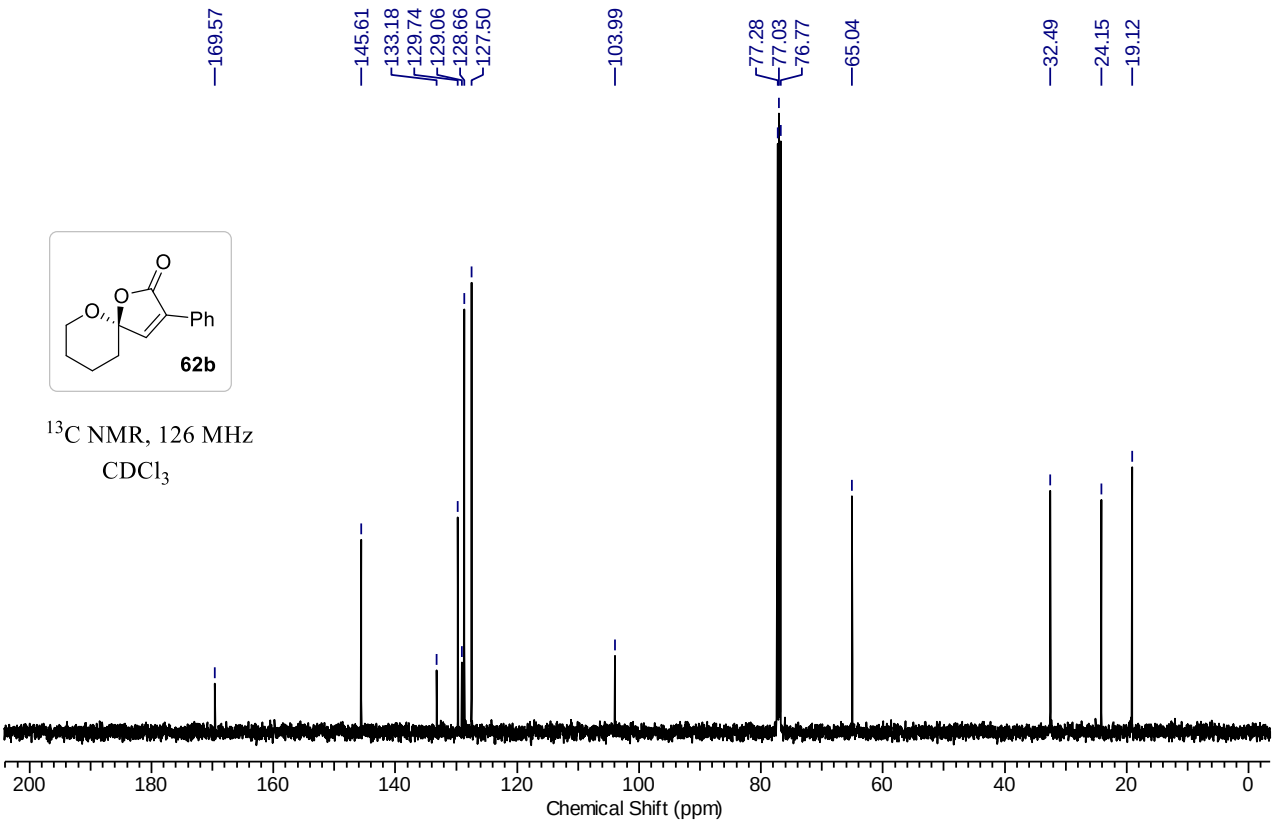


^{13}C NMR 101 MHz
$CDCl_3$

3-Phenyl-1,6-dioxaspiro[4.5]dec-3-en-2-one (62b):

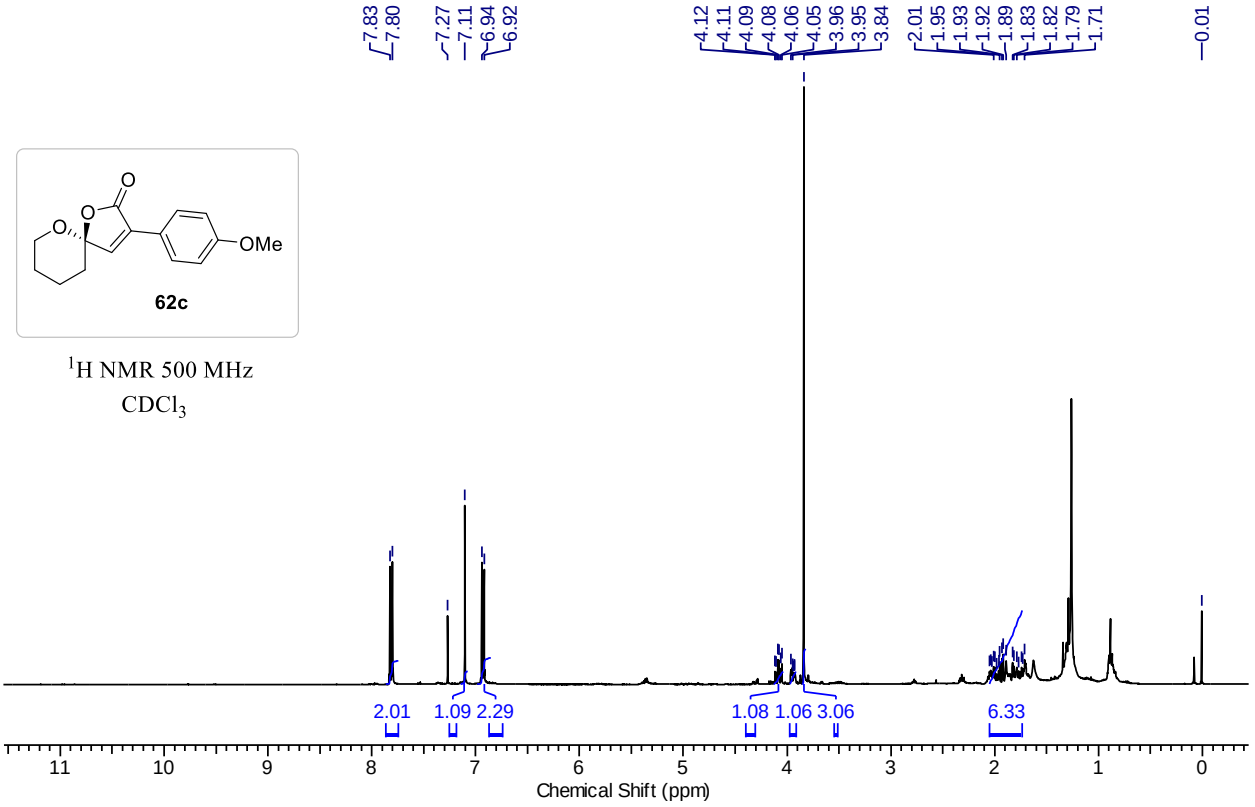


^{1}H NMR 500 MHz
$CDCl_3$

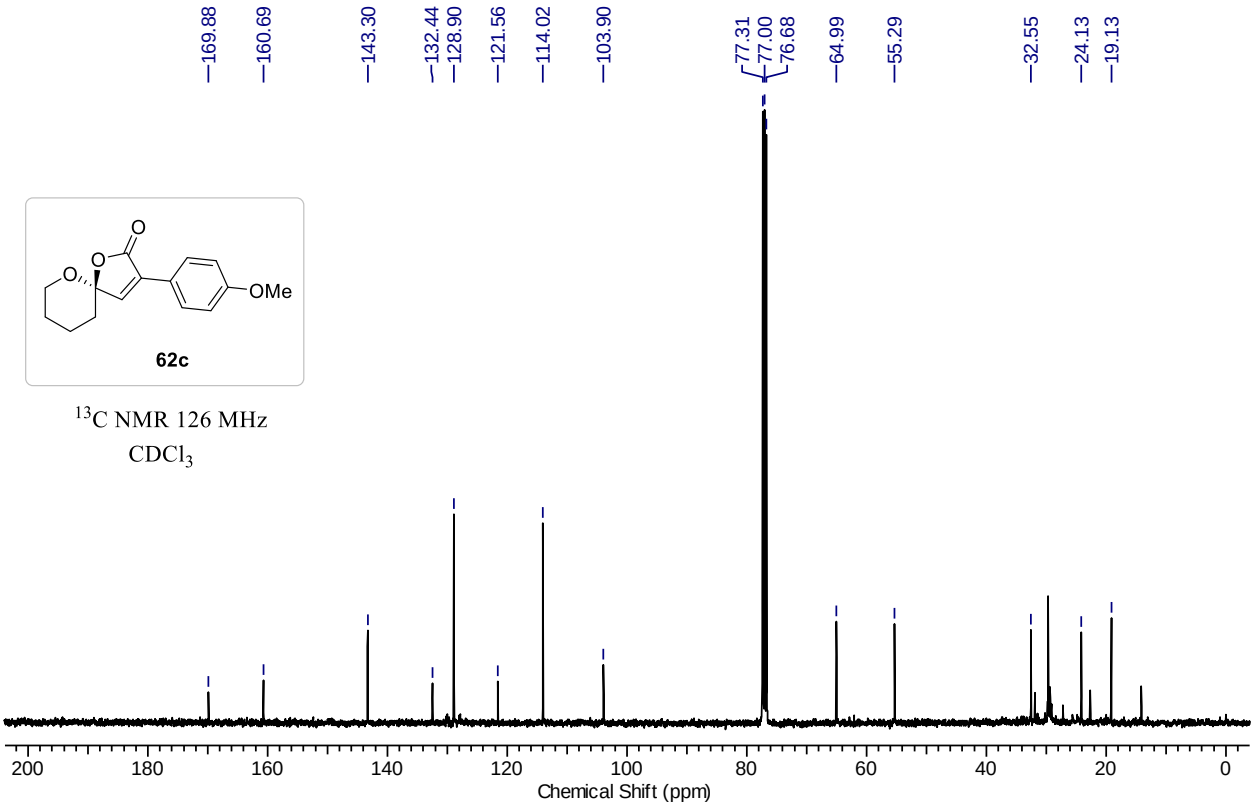


^{13}C NMR, 126 MHz
$CDCl_3$

3-(4-Methoxyphenyl)-1,6-dioxaspiro[4.5]dec-3-en-2-one (62c):

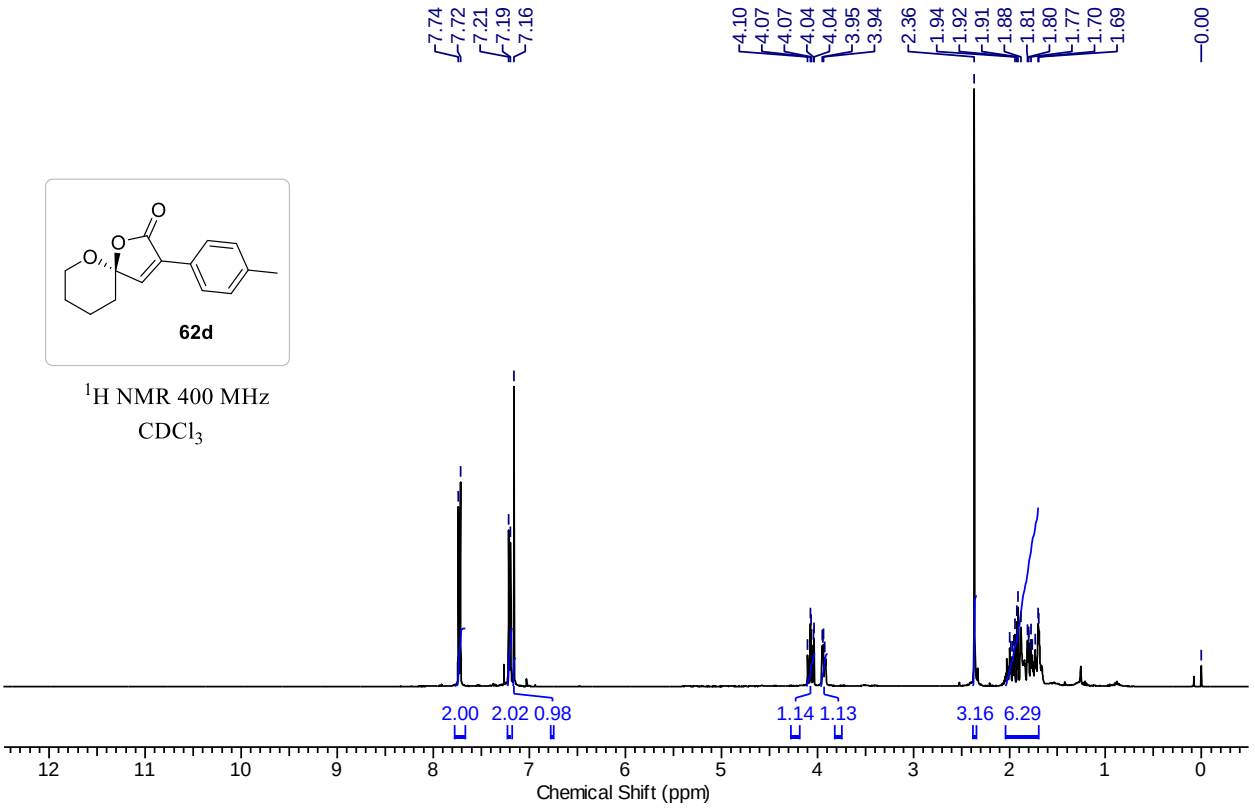


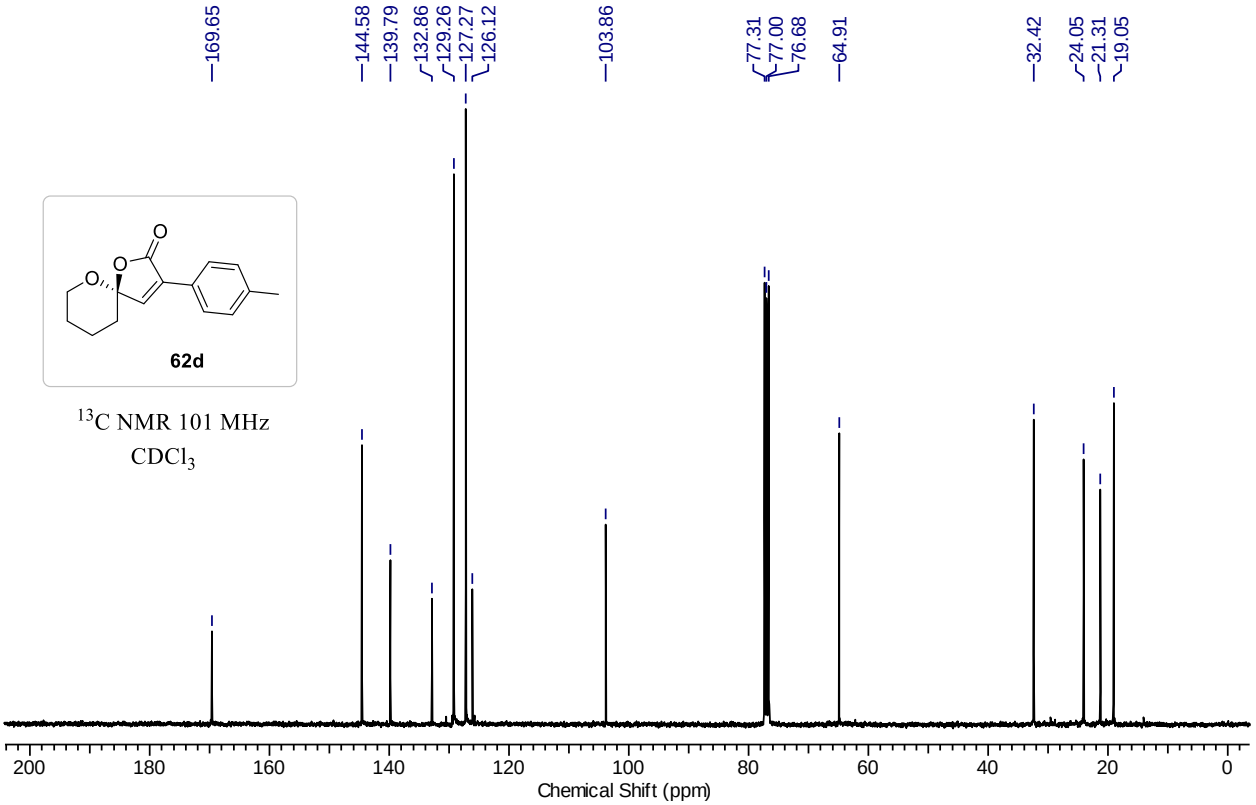
^{1}H NMR 500 MHz
$CDCl_3$



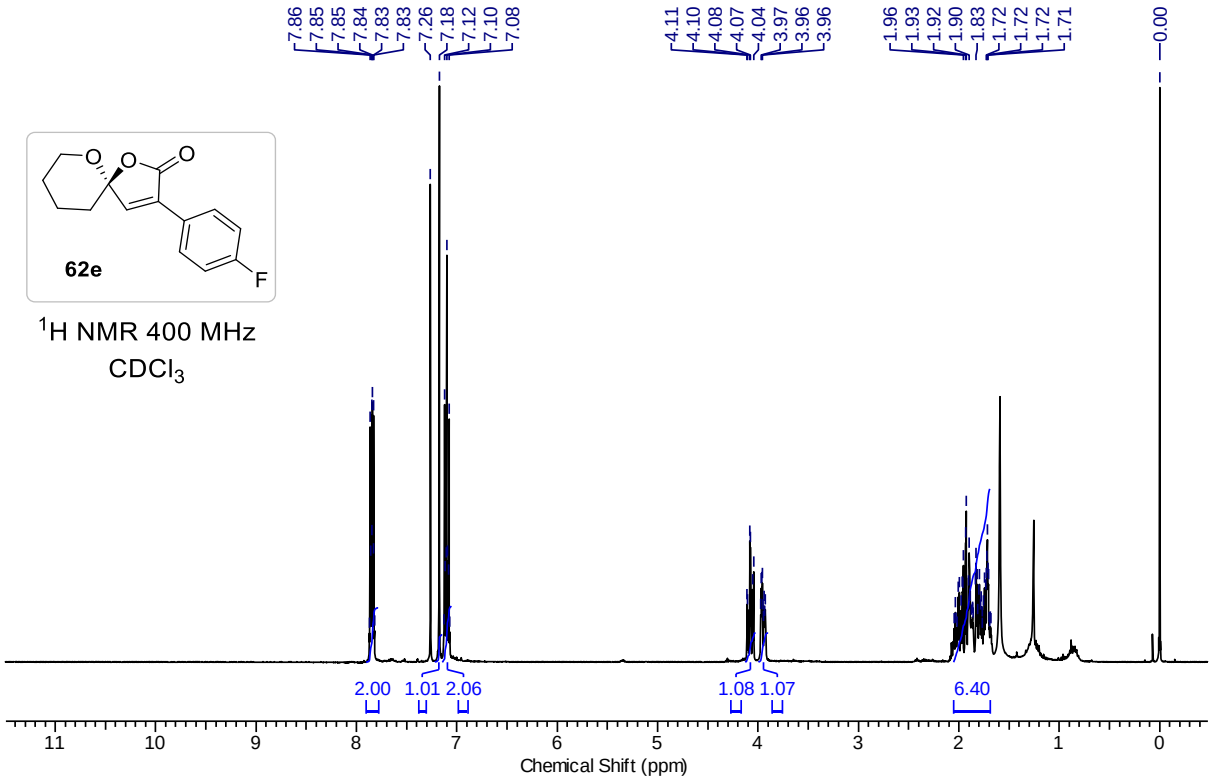
^{13}C NMR 126 MHz
$CDCl_3$

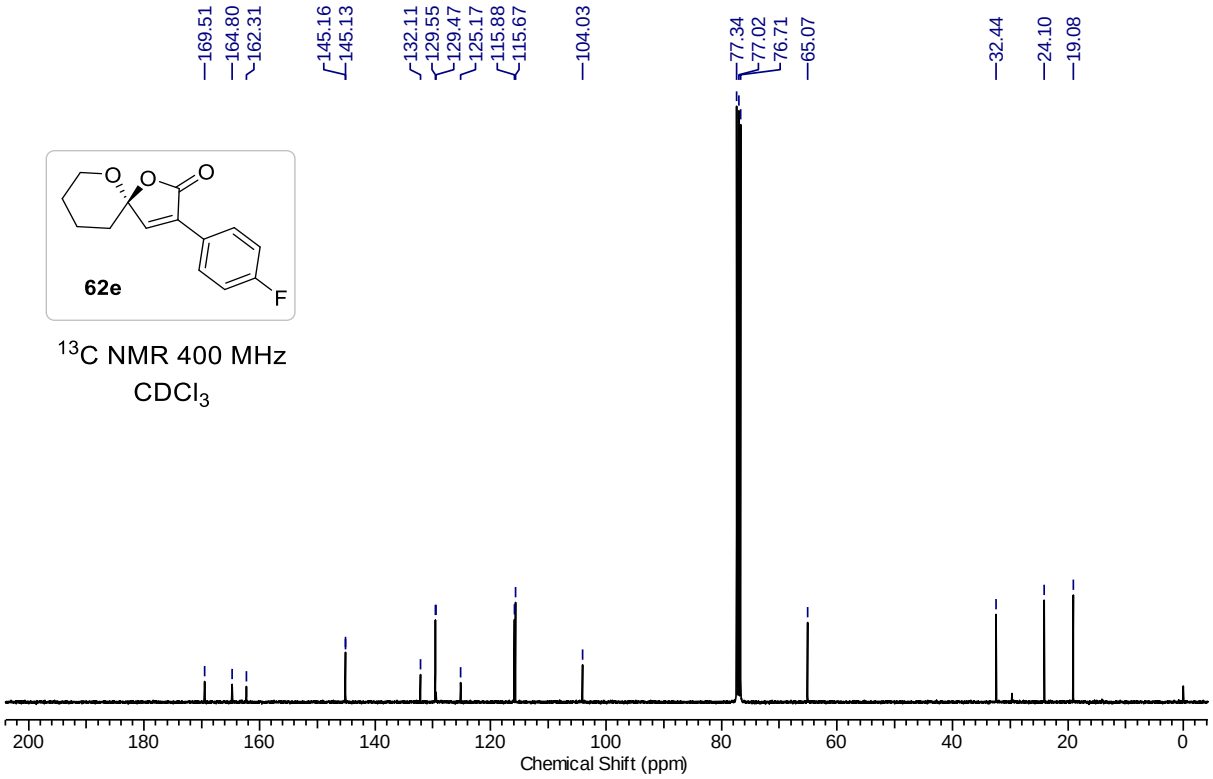
3-(*p*-Tolyl)-1,6-dioxaspiro[4.5]dec-3-en-2-one (62d):

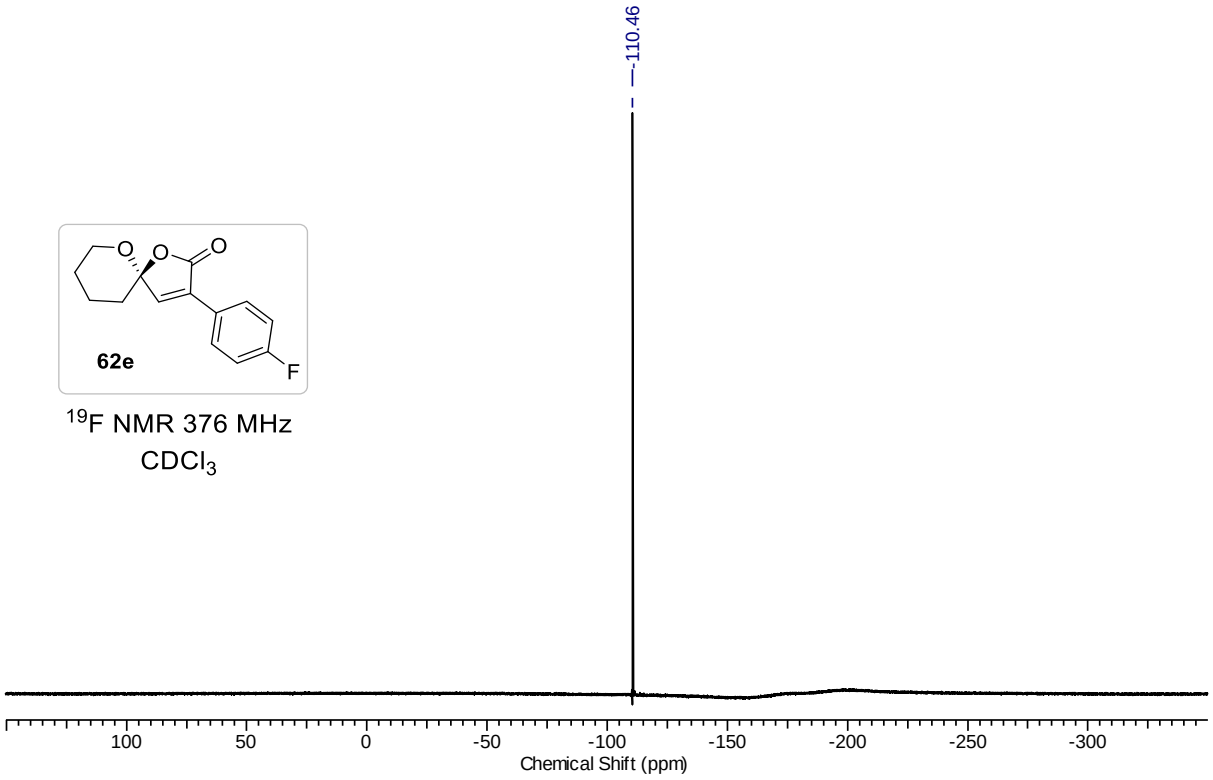




3-(4-fluorophenyl)-1,6-dioxaspiro[4.5]dec-3-en-2-one (62e):



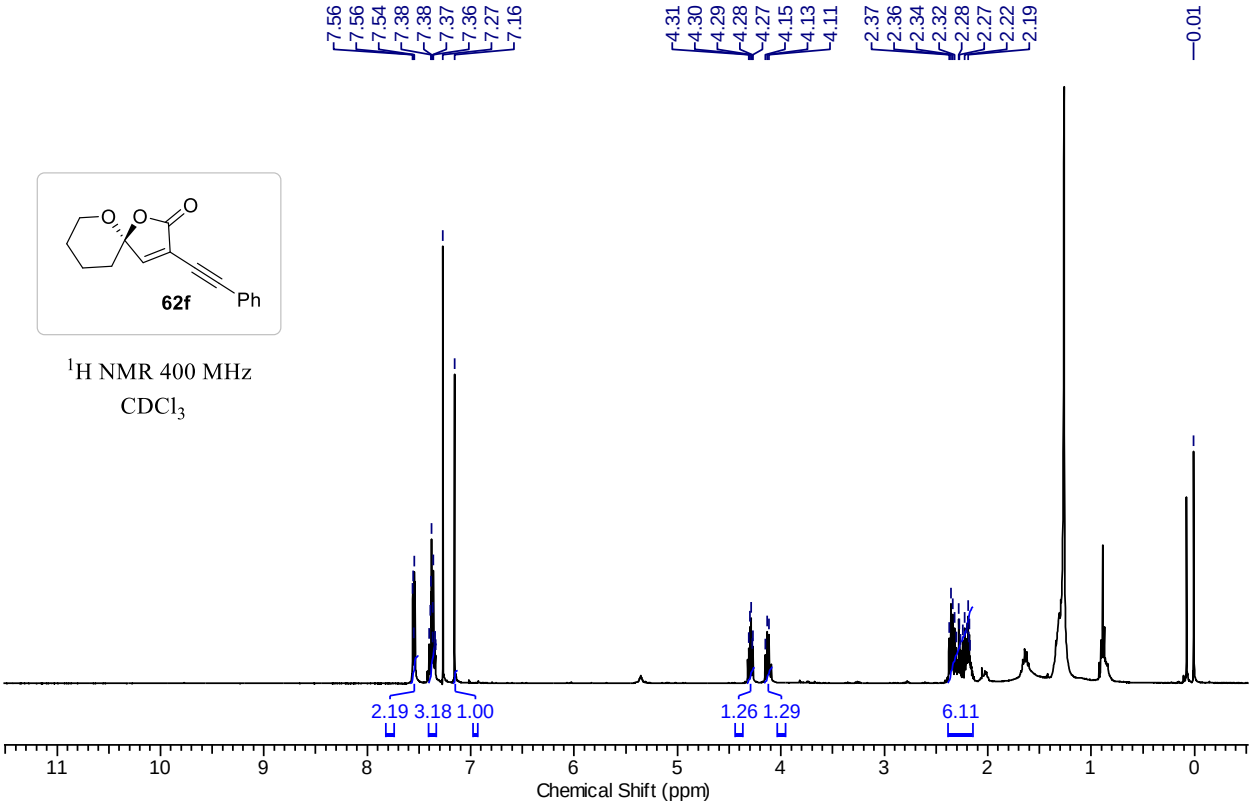




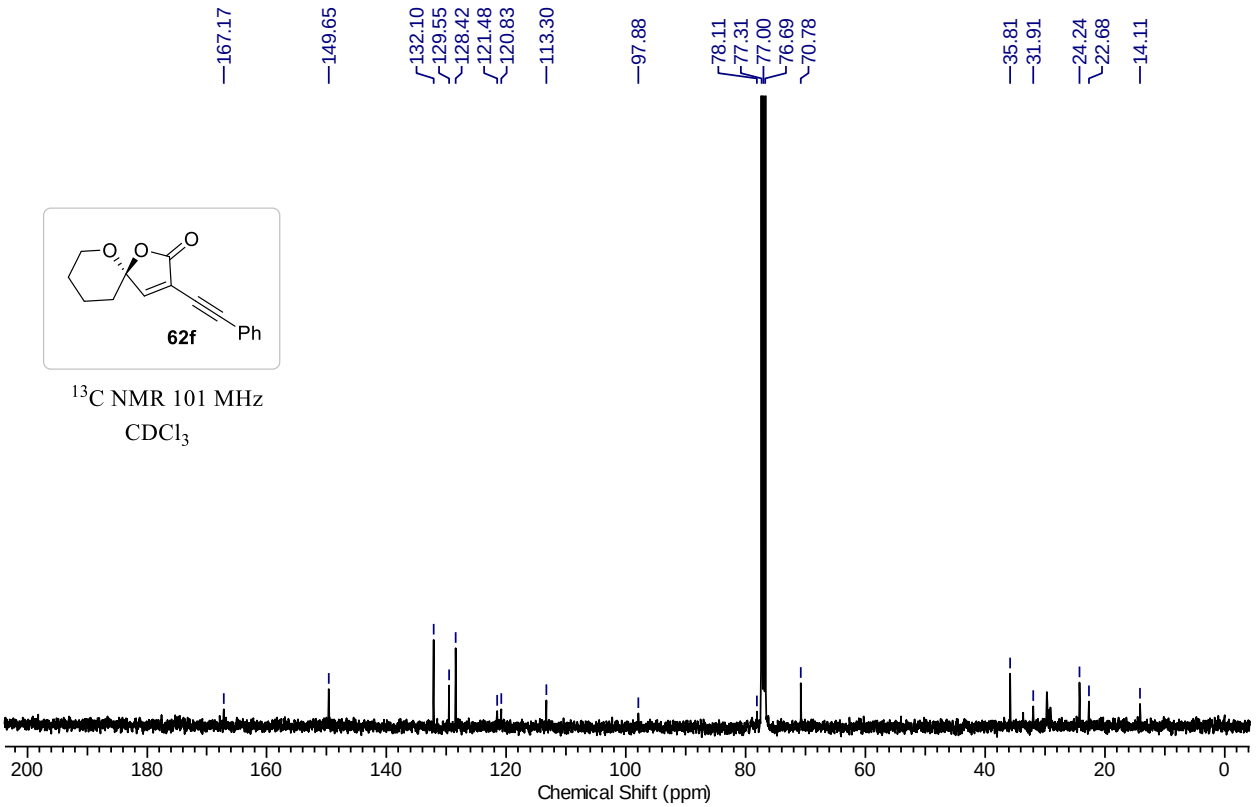
^{19}F NMR 376 MHz

$CDCl_3$

3-(Phenylethynyl)-1,6-dioxaspiro[4.5]dec-3-en-2-one (62f):

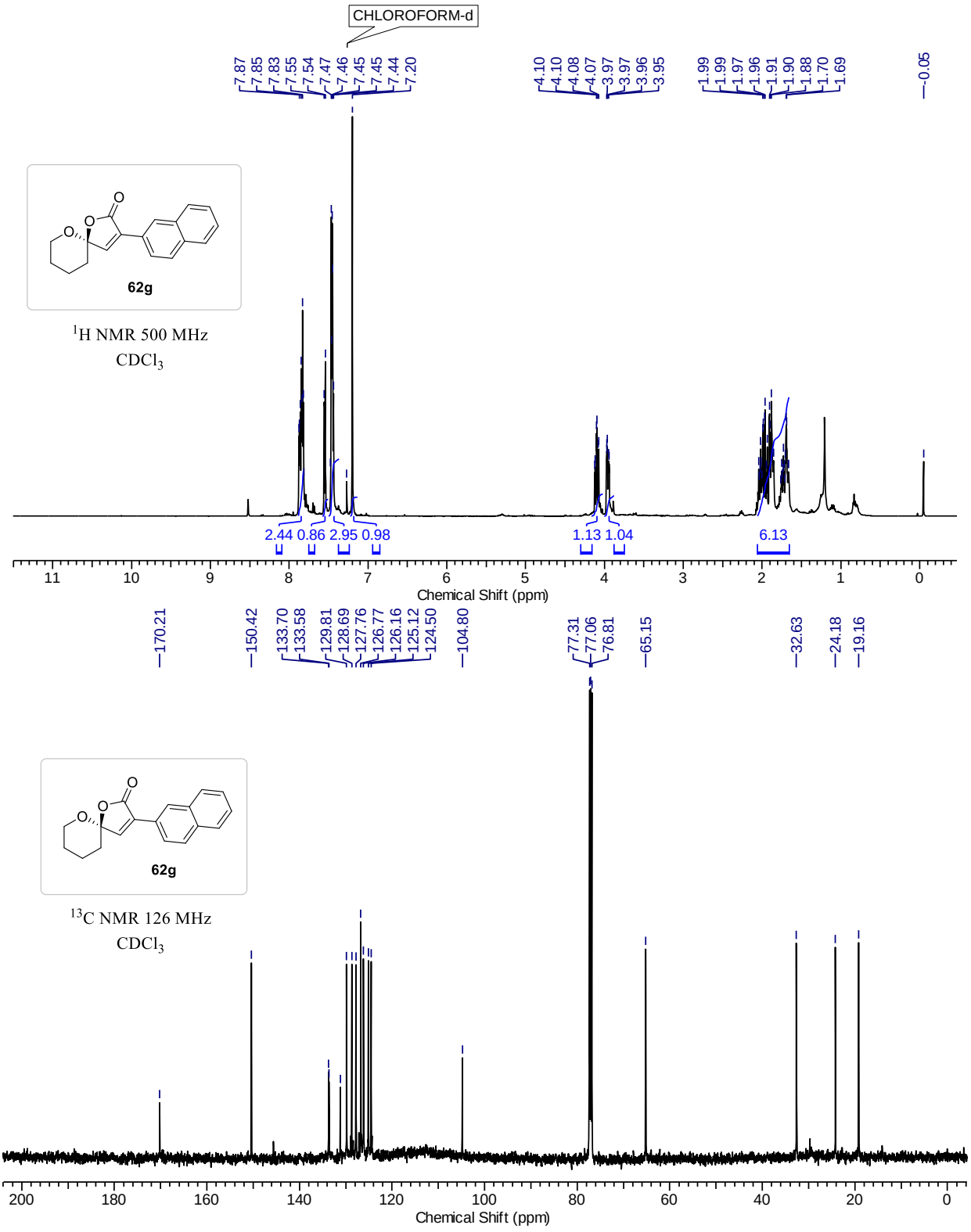


^{1}H NMR 400 MHz
$CDCl_3$

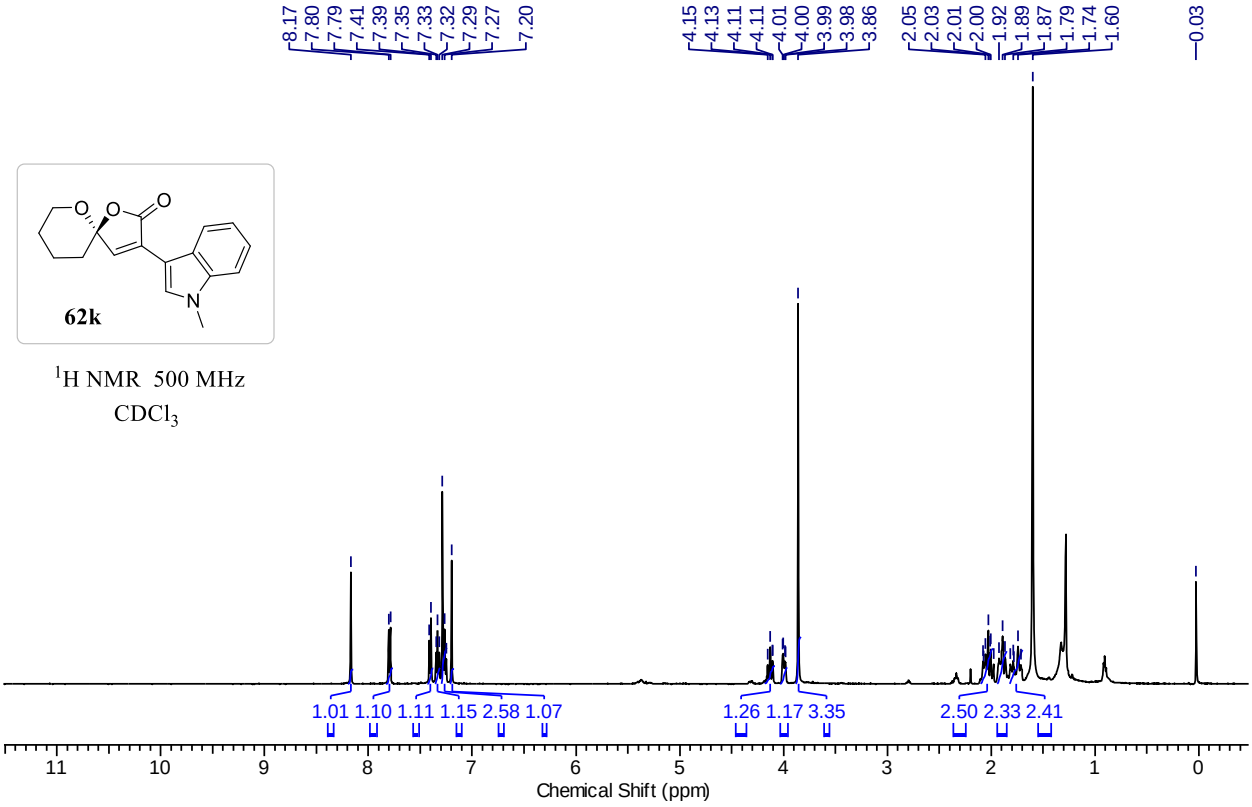


^{13}C NMR 101 MHz
$CDCl_3$

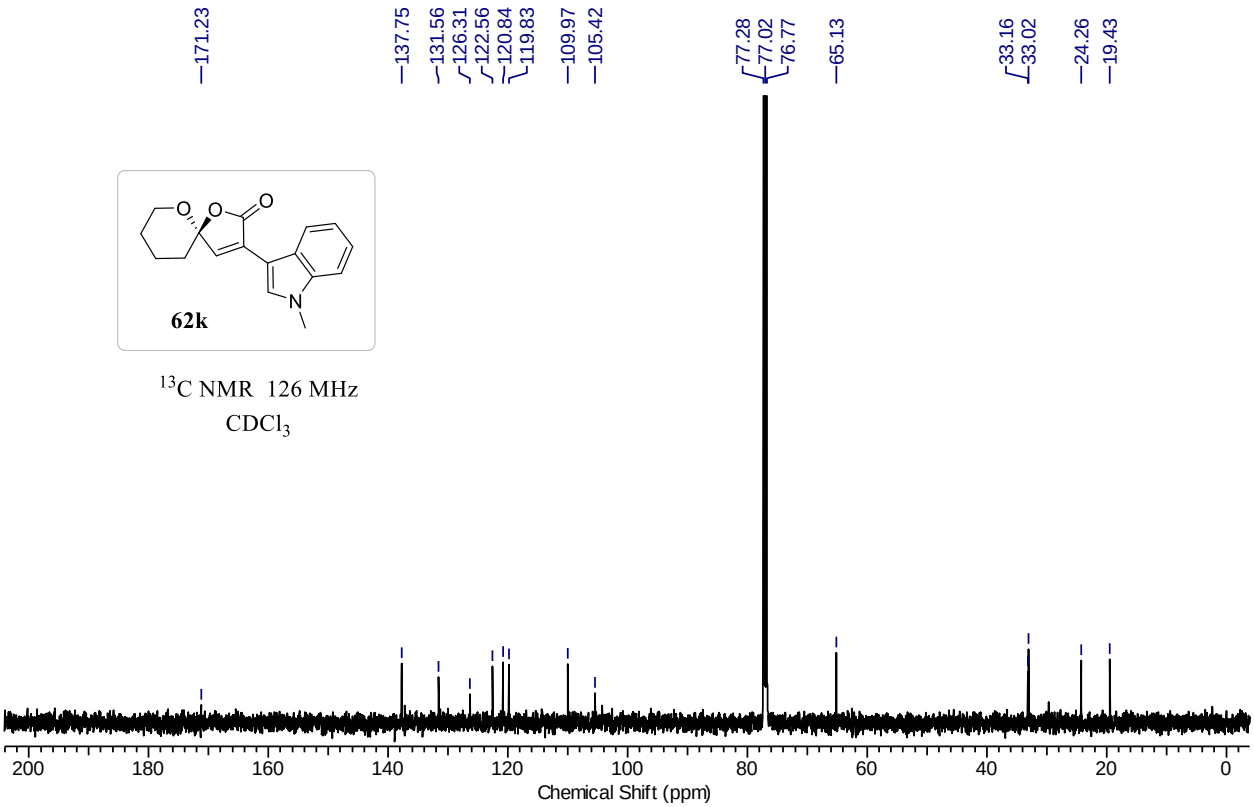
3-(Naphthalen-2-yl)-1,6-dioxaspiro[4.5]dec-3-en-2-one (62g):



3-(1-Methyl-1*H*-indol-3-yl)-1,6-dioxaspiro[4.5]dec-3-en-2-one (62k):

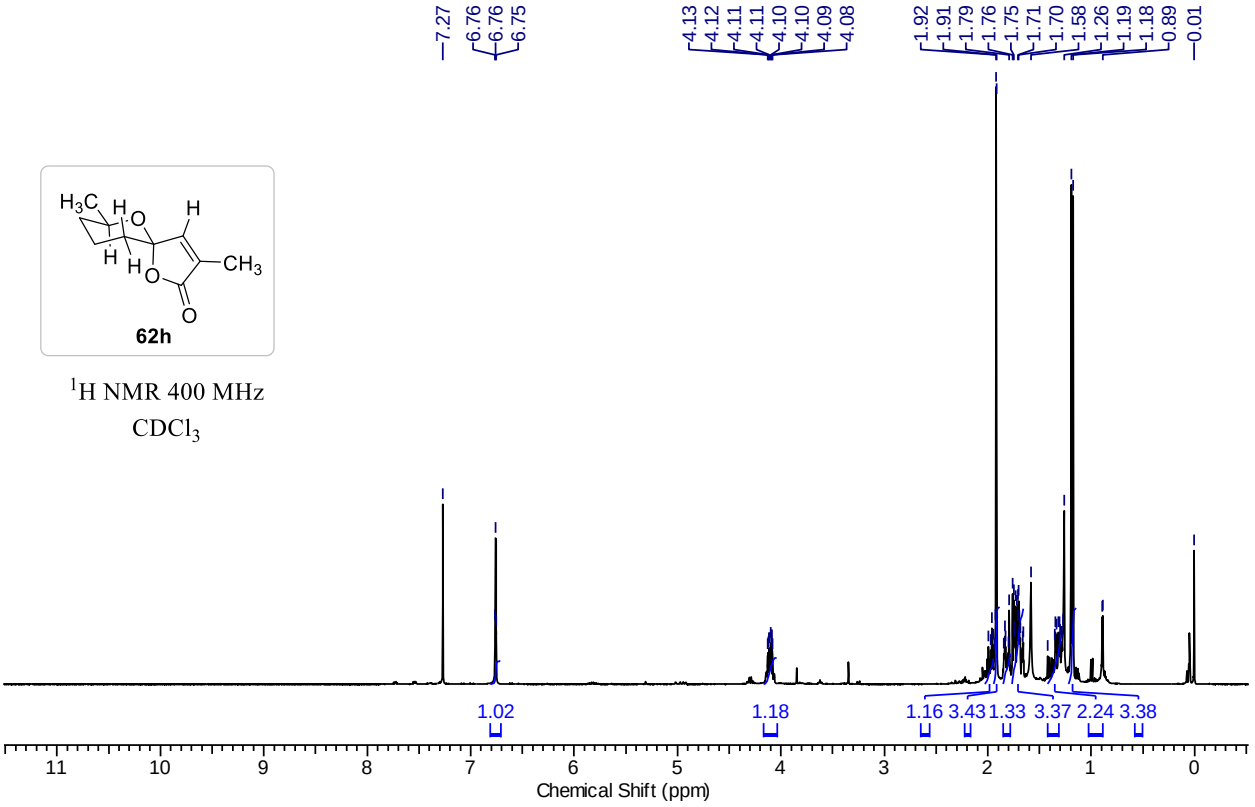


^{1}H NMR 500 MHz
$CDCl_3$

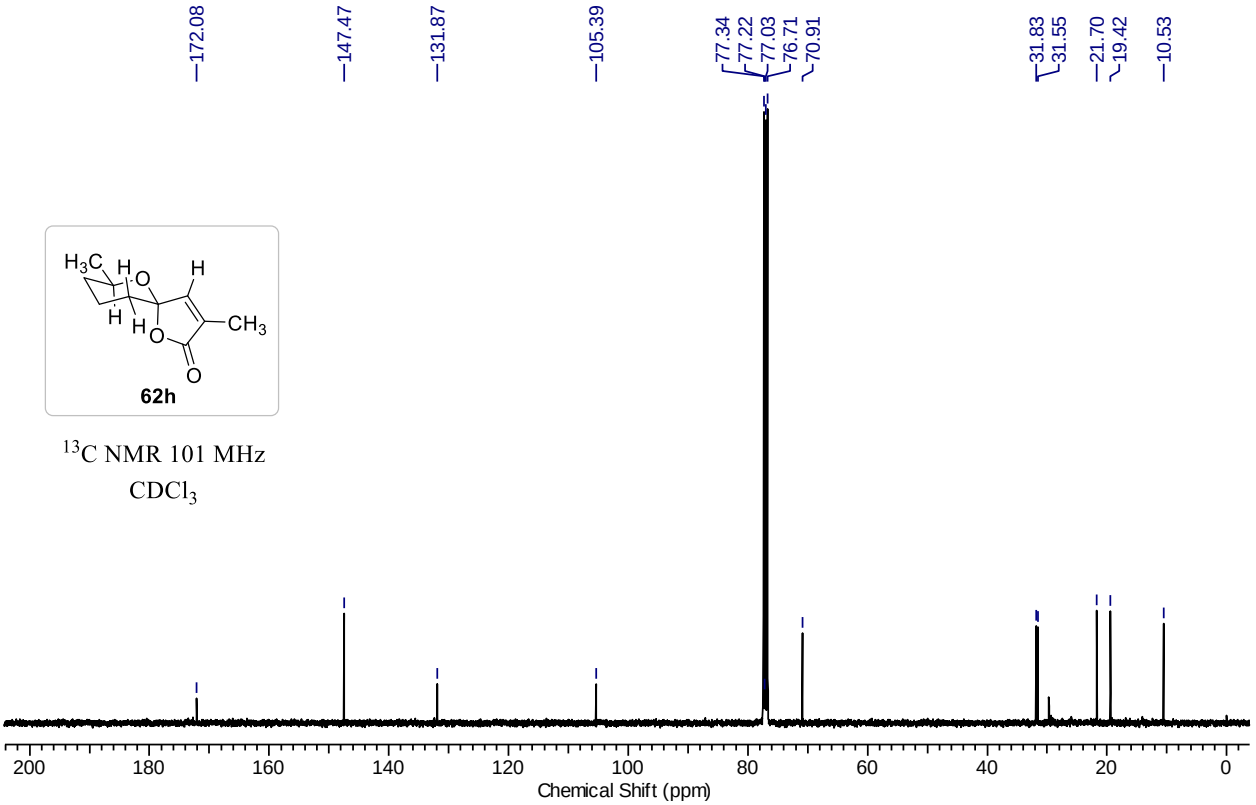


^{13}C NMR 126 MHz
$CDCl_3$

3,7-Dimethyl-1,6-dioxaspiro[4.5]dec-3-en-2-one (62h):

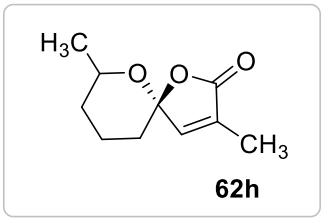


^{1}H NMR 400 MHz
$CDCl_3$



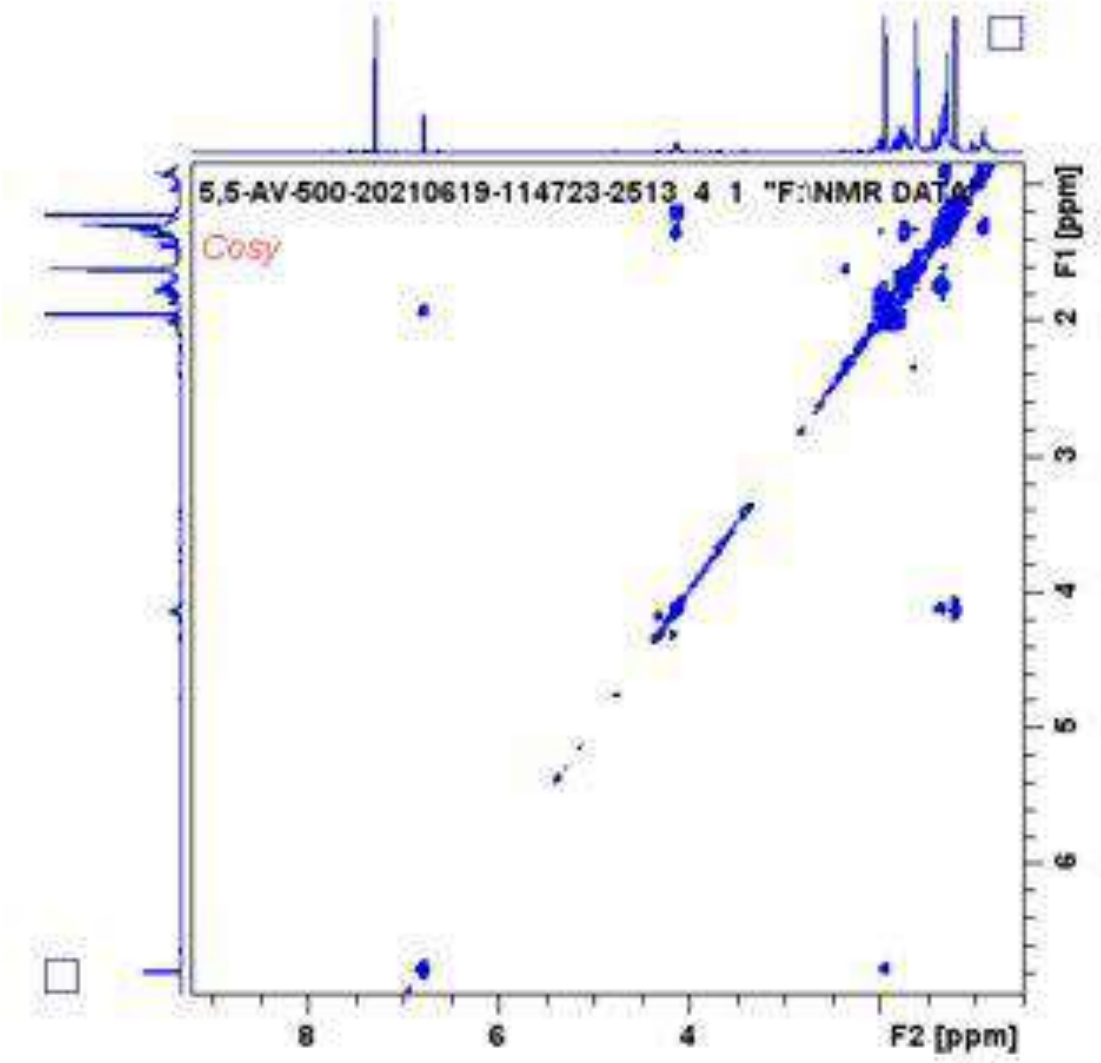
^{13}C NMR 101 MHz
$CDCl_3$

2D NMR analysis of 62h:

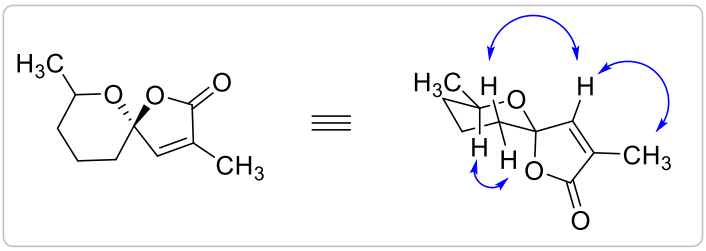


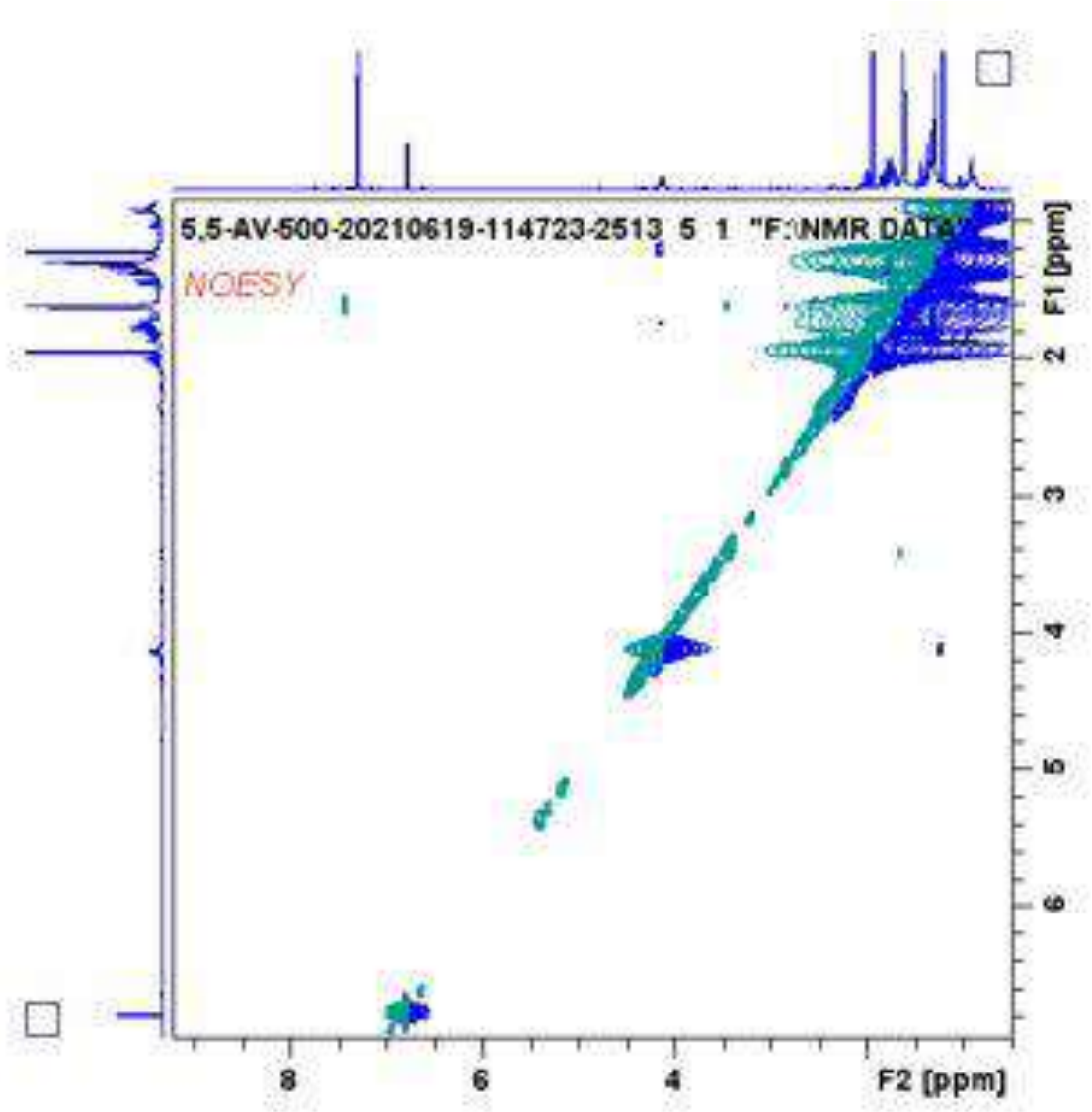
62h

COSY: (62h)

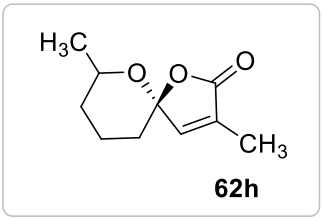


NOESY: (62h)

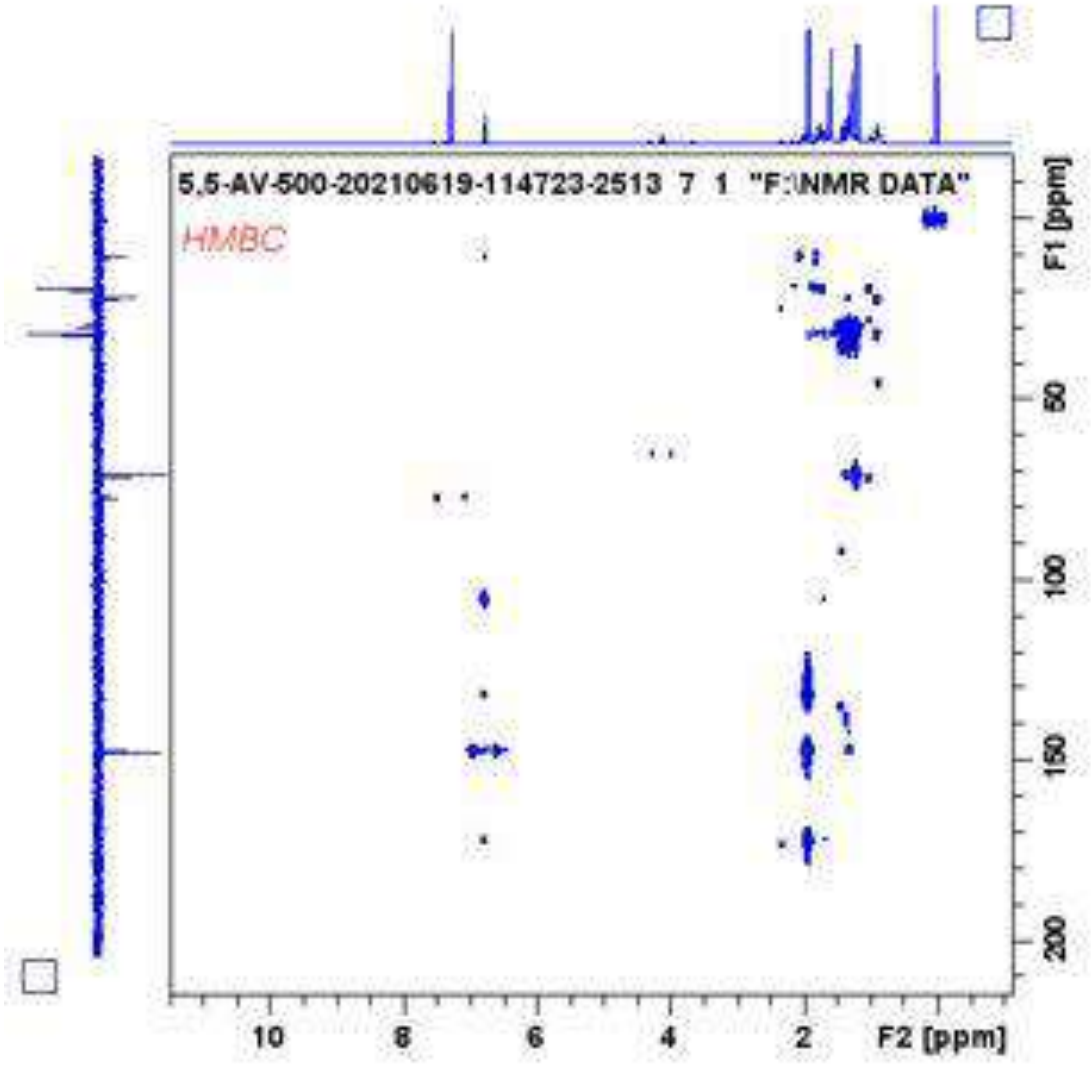

H3C
O
O
O
CH3
H3C
H
O
H
H
H
O
CH3
O


5.5-AV-500-20210619-114723-2513 5 1 "F:\NMR DATA
NOESY
F1 [ppm]
2
3
4
5
6
8
6
4
F2 [ppm]

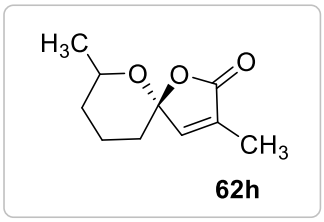
HMBC: (62h)


H3C
O
O
O
CH3

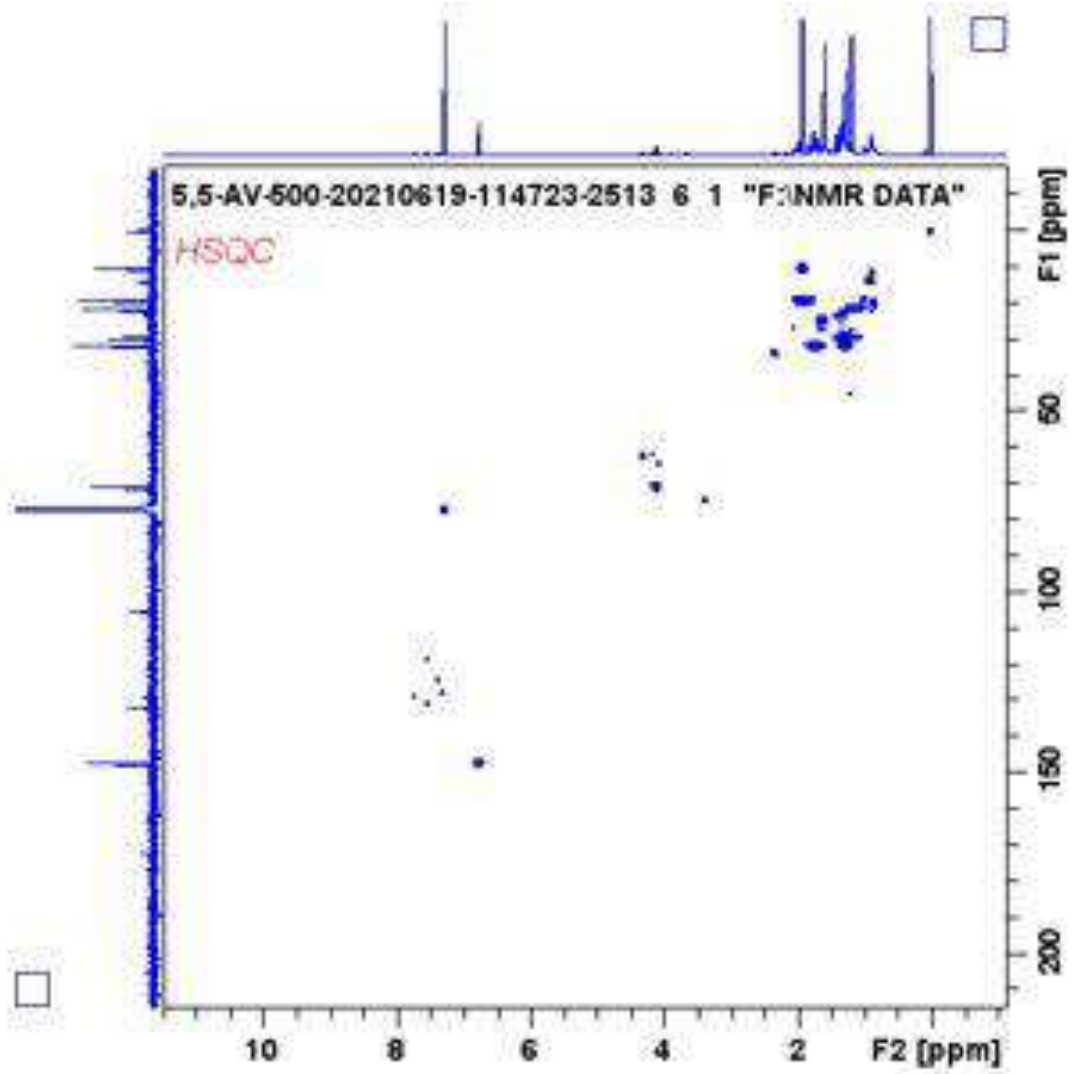
62h


5.5-AV-500-20210619-114723-2513 7 1 "F:\NMR DATA"
HMBC
F1 [ppm]
50
100
150
200
10
8
6
4
2
F2 [ppm]

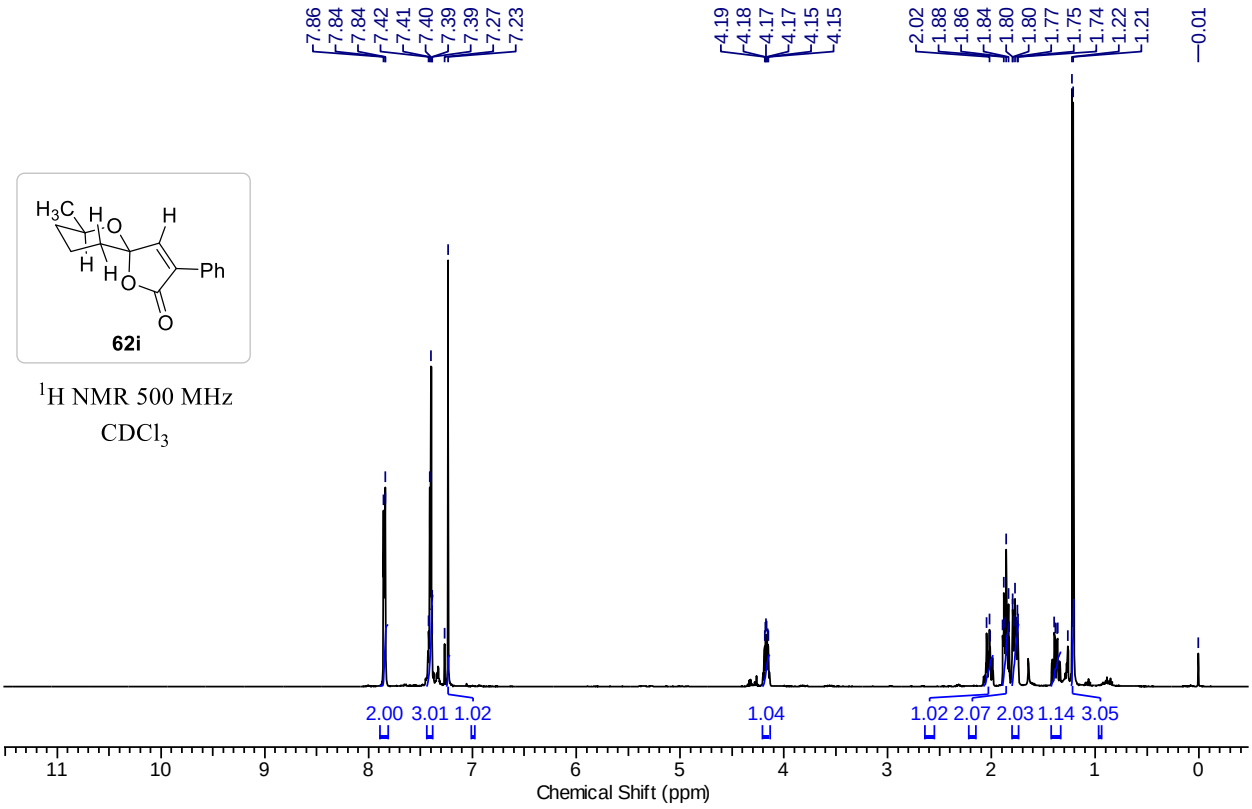
HSQC: (62h)


H3C
O
O
O
CH3

62h

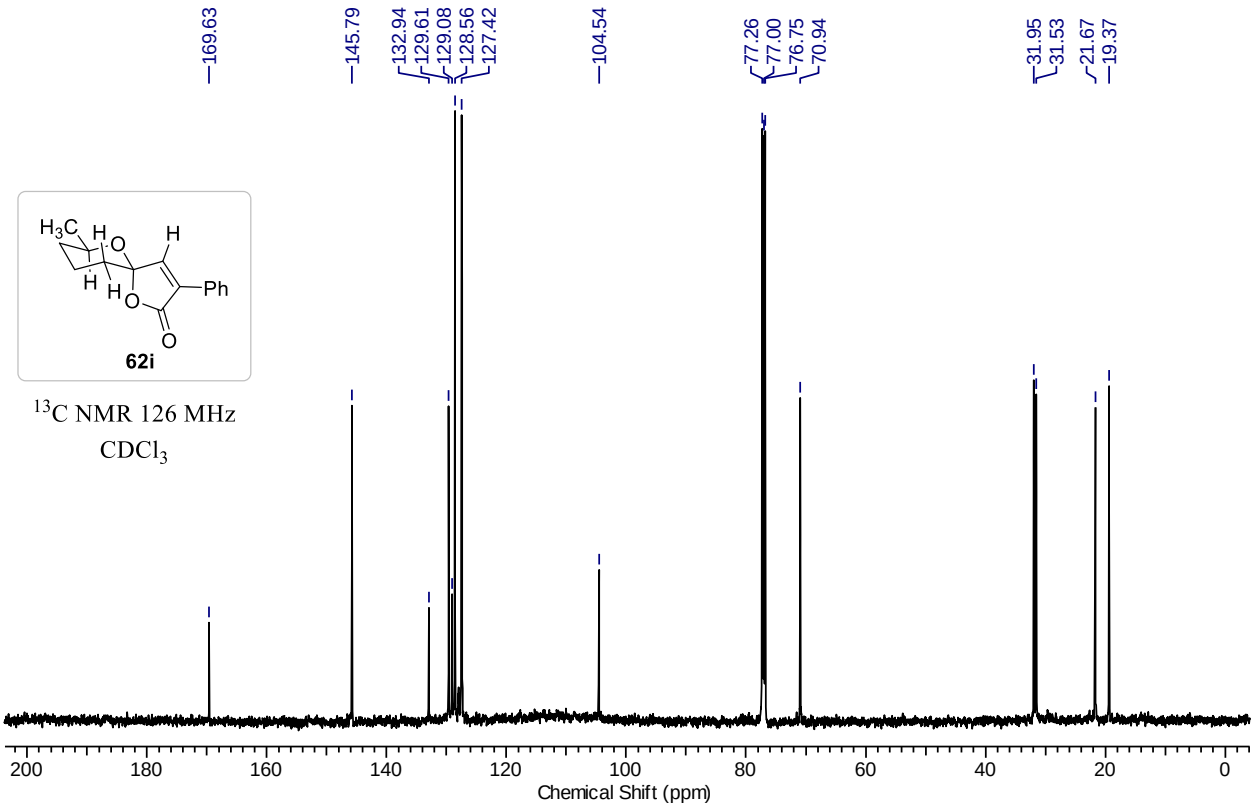

5,5-AV-500-20210619-114723-2513 6 1 "F:\NMR DATA"
HSQC
F1 [ppm]
50
100
150
200
10
8
6
4
2
F2 [ppm]

7-Methyl-3-phenyl-1,6-dioxaspiro[4.5]dec-3-en-2-one (62i):



62i

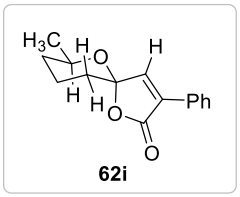
^{1}H NMR 500 MHz
$CDCl_3$

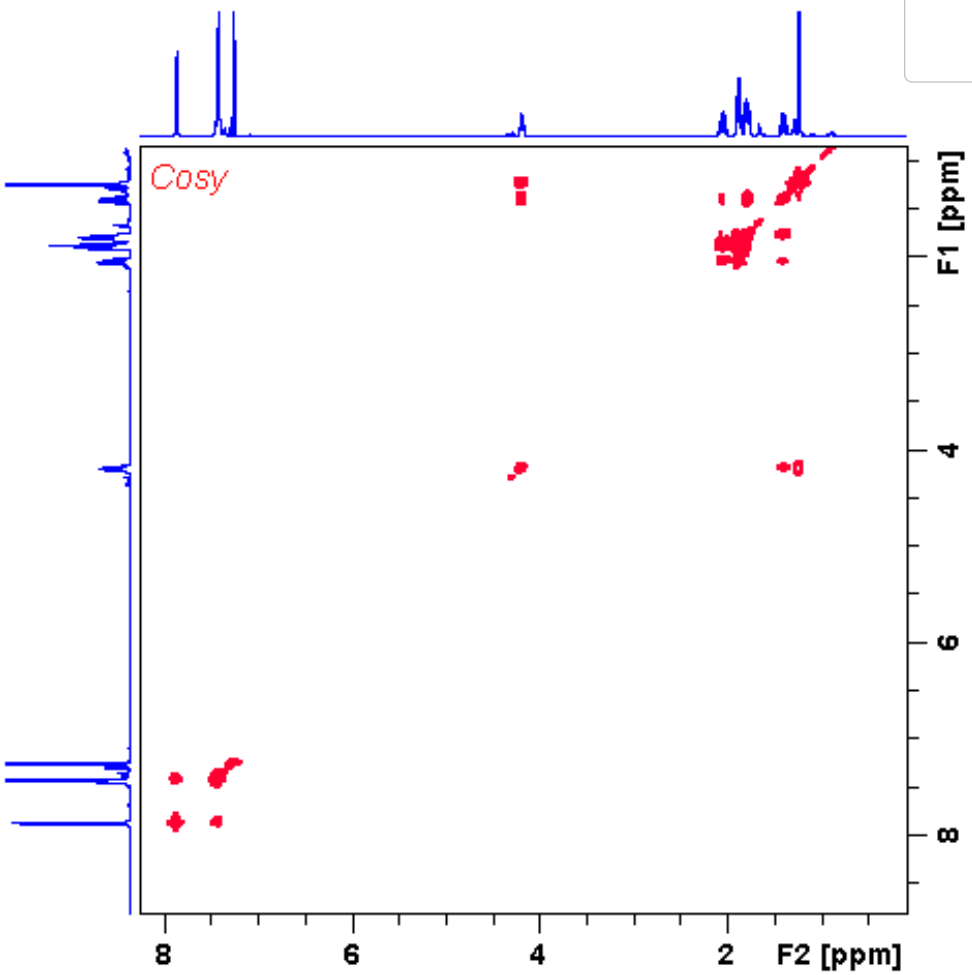


62i

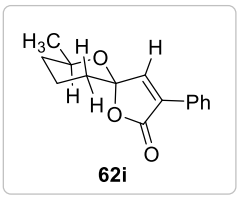
^{13}C NMR 126 MHz
$CDCl_3$

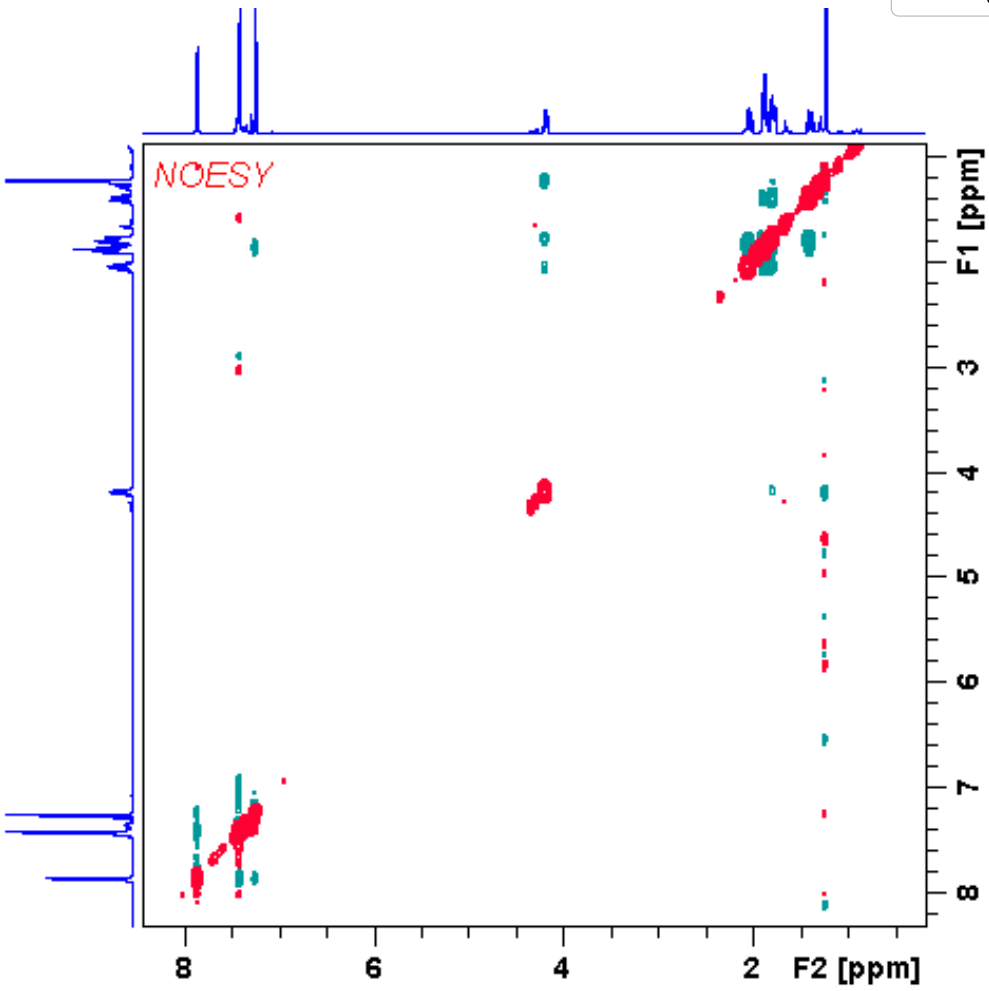
COSY: (62i)



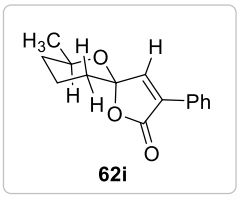


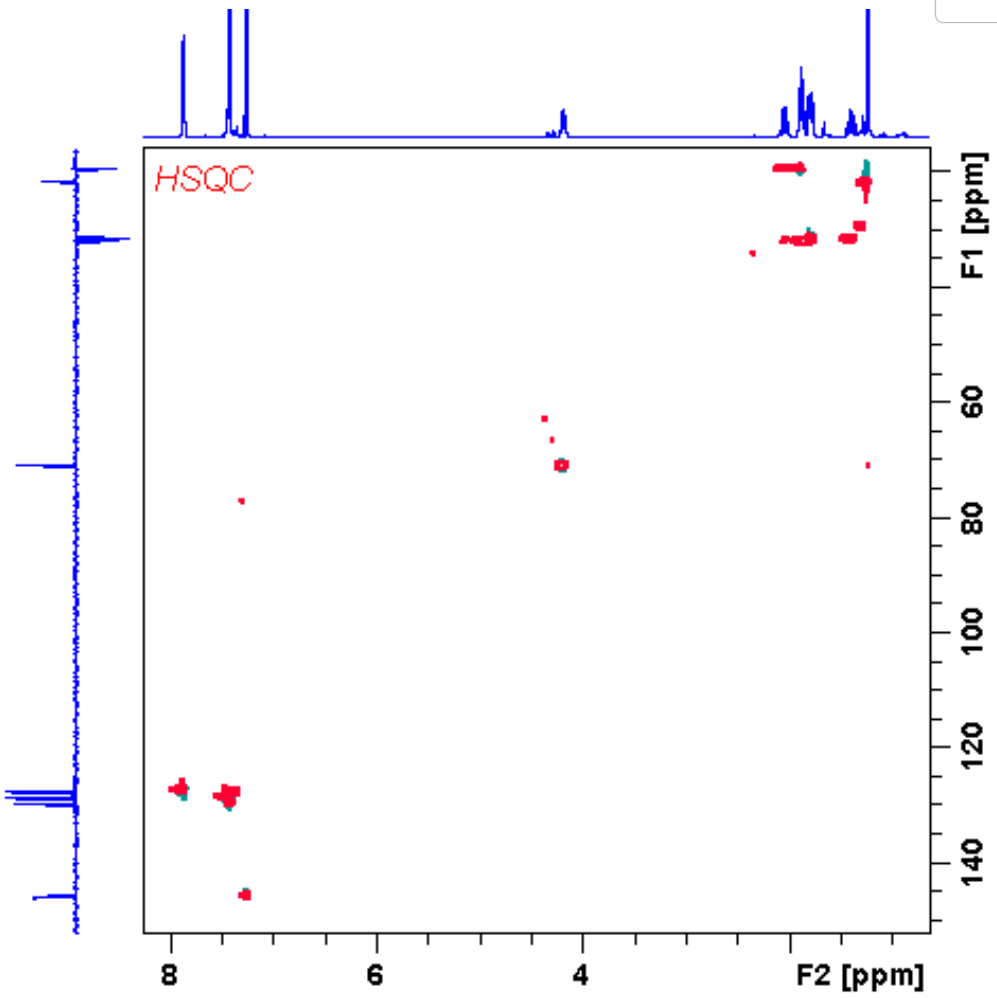
NOESY: (62i)



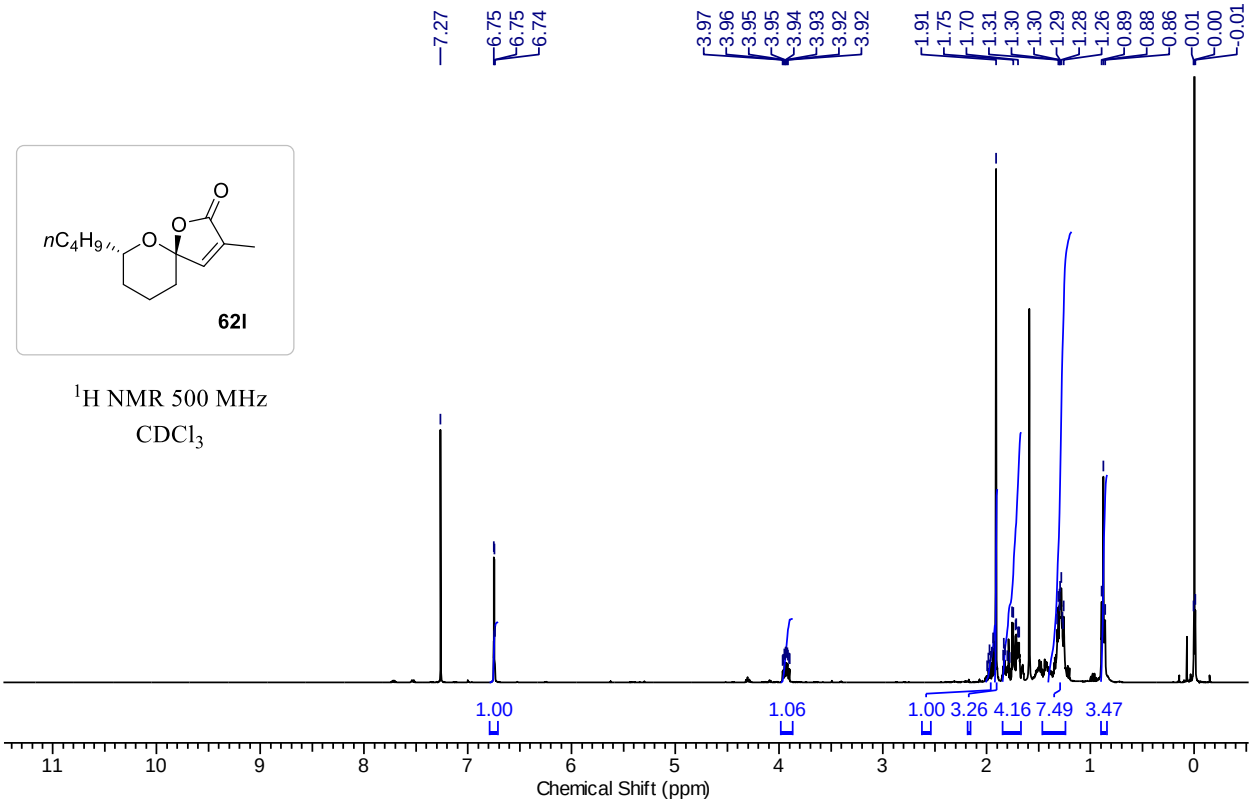


HSQC: (62i)

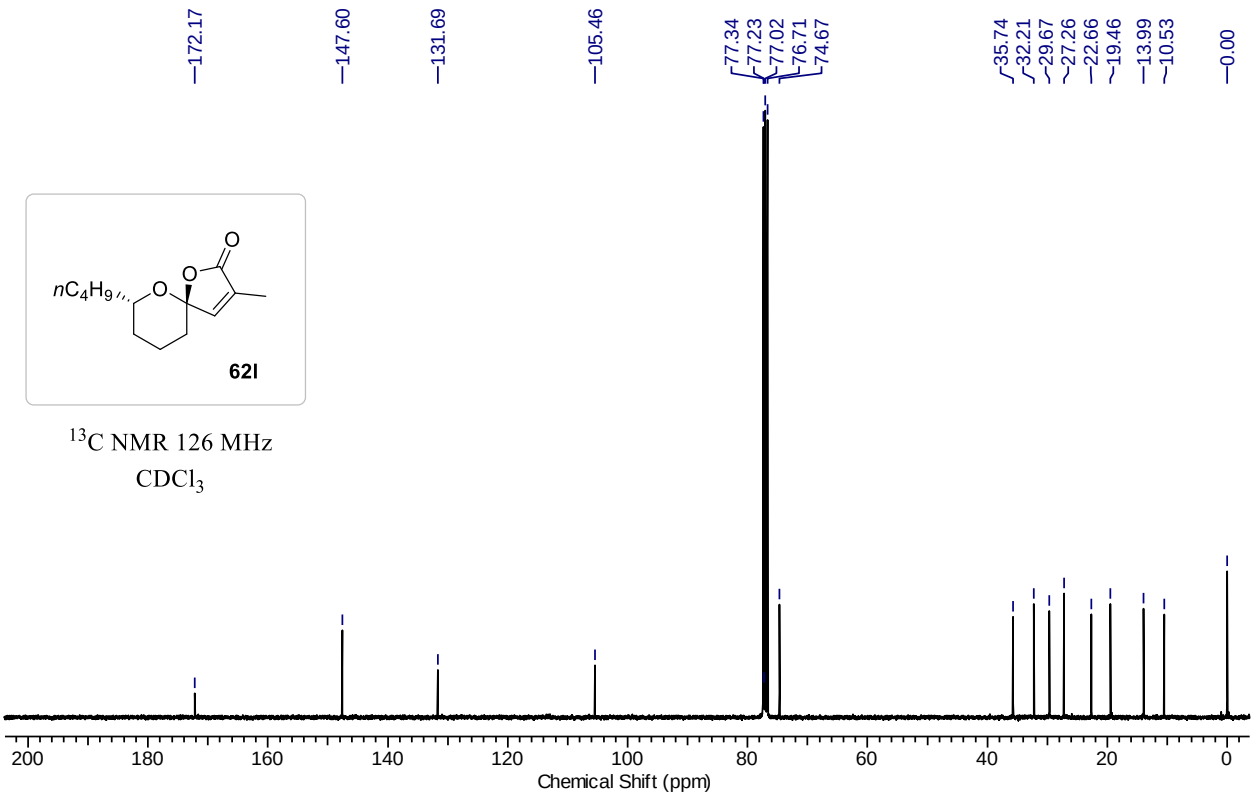




7-Butyl-3-methyl-1,6-dioxaspiro[4.5]dec-3-en-2-one (62l):

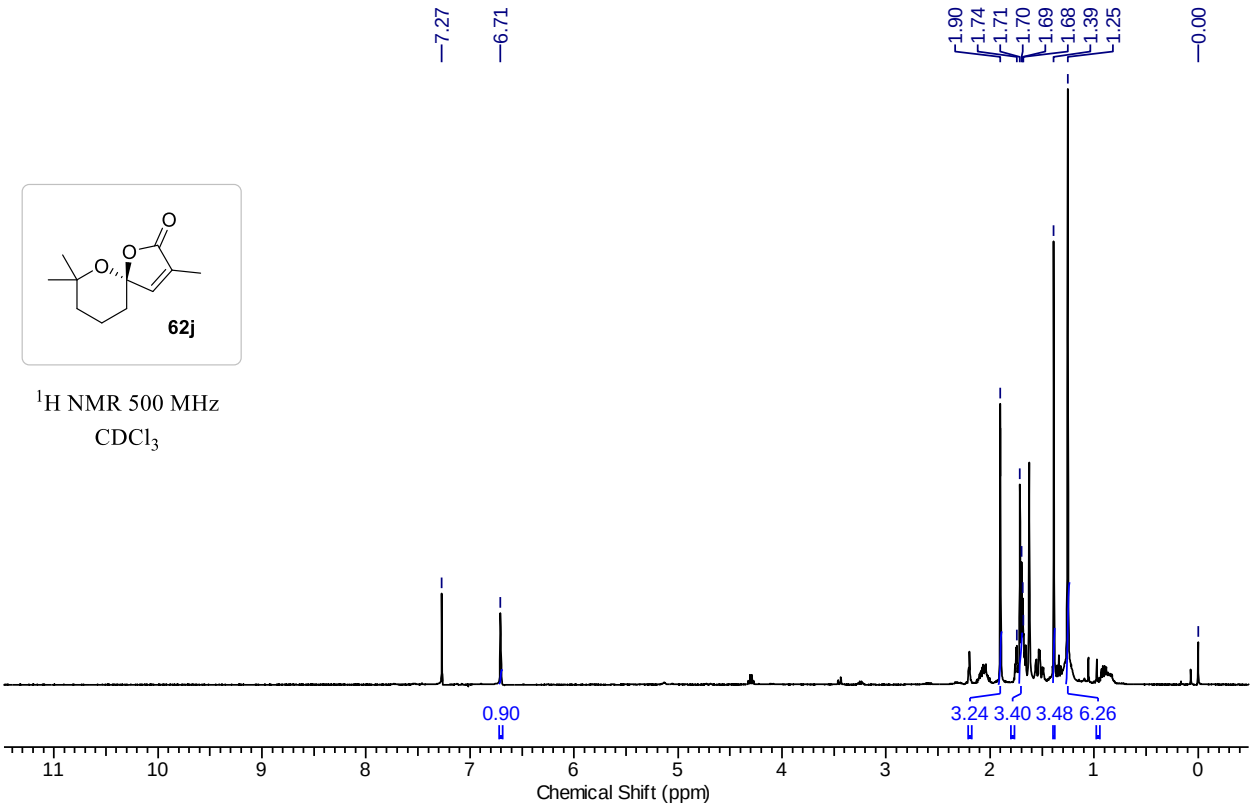


^{1}H NMR 500 MHz
$CDCl_3$

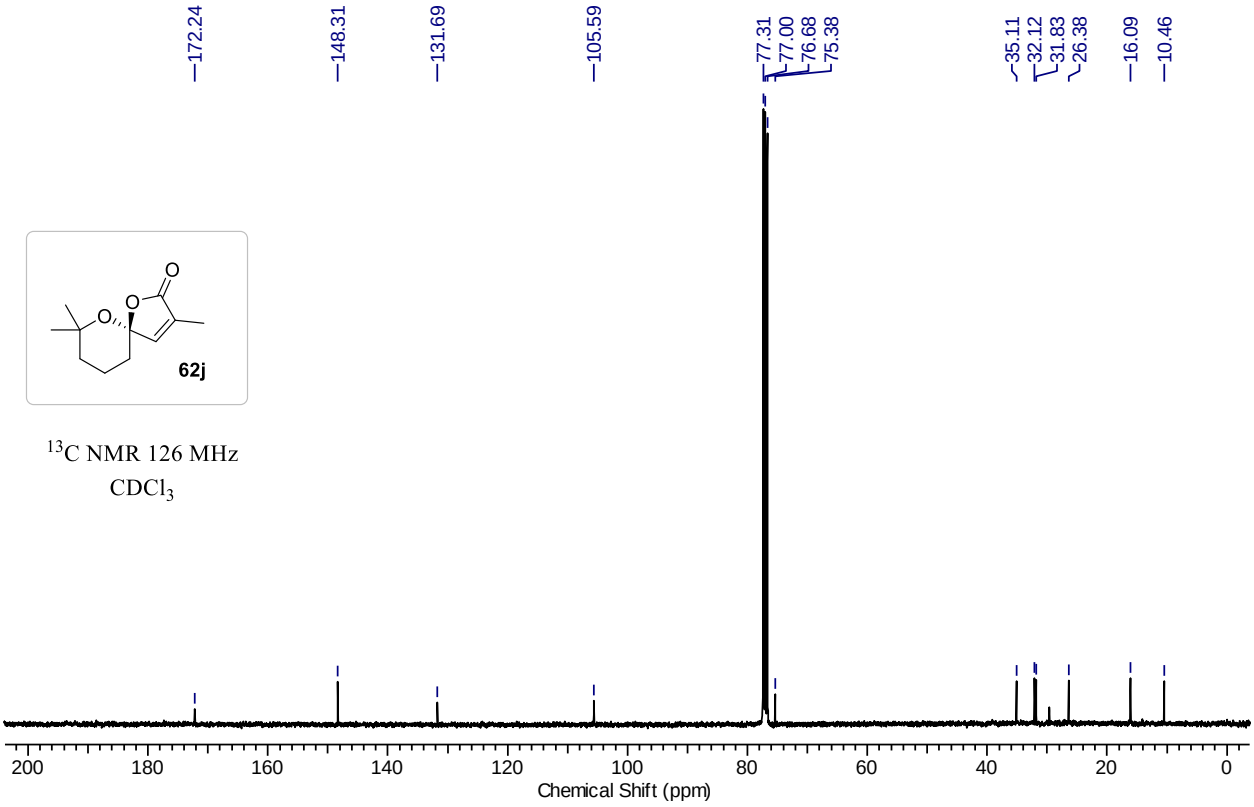


^{13}C NMR 126 MHz
$CDCl_3$

3,7,7-Trimethyl-1,6-dioxaspiro[4.5]dec-3-en-2-one (62j):



^{1}H NMR 500 MHz
$CDCl_3$



^{13}C NMR 126 MHz
$CDCl_3$

Chapter 4

Section A

Introduction & previous approaches to [2+2+2] and [3+2]-annulation reactions involving alkynes

4.1 [2+2+2]-Cycloaddition/annulation involving alkynes: Introduction

The construction of structurally complex molecules from simple starting materials through convergent annulation/cycloaddition reactions is an important aspect of organic synthesis due to quick access to complex scaffolds, step- and atom economic nature. Among numerous cycloaddition reactions reported to date [2+2+2]-cycloaddition/annulation reaction is one of the important tools for synthesizing various multi-functionalized 6-membered carbo- or heterocycles, for instance, arenes, pyridines, isobenzofuranones, and many other polycyclic heterocycles which involves different types of unsaturated functional groups. Moreover, these reactions generally possess high functional groups tolerance, for example, alkynes, alkenes, arynes, allenes, nitriles, imines, aldehydes, ketones, isocyanates, and many others.[1a]

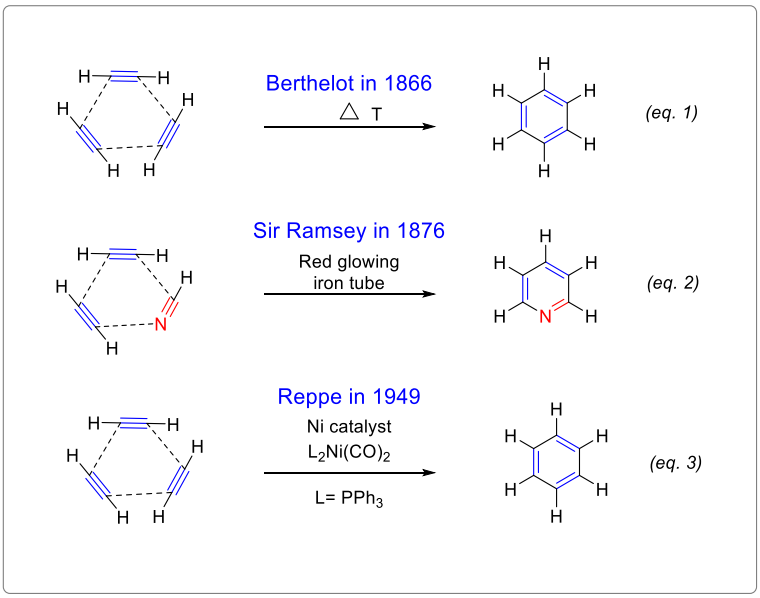


Figure. 4.1. Origin of [2+2+2]-cycloaddition reactions involving alkynes.

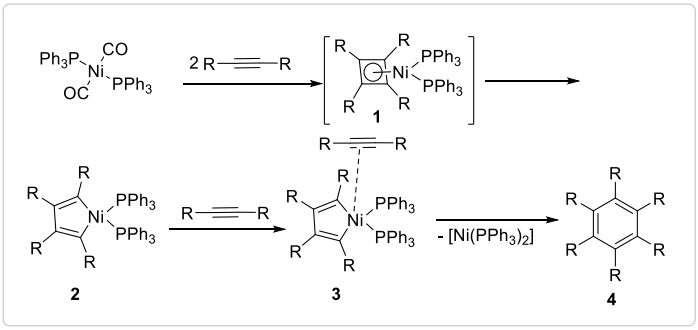
The actual journey of [2+2+2]-cycloaddition reaction started 150 years ago by Berthelot in 1866, who performed the metal-free thermal (400 °C) cyclotrimerization of acetylene and observed the formation of benzene[1bc] (eq. 1). In contrast, Sir Ramsey in 1876, used heterogeneous catalysis, using a red glowing iron tube with acetylene and HCN to furnish the pyridine as a product (eq. 2). Later, Reppe, in 1949, first time performed the reaction of acetylenes using nickel catalyst ($Ni(CO)_2(PPh_3)_2$). Further, he developed it as a versatile tool for the synthesis of structurally complex molecules (eq. 3) (Figure 4.1).[2] This very interesting finding by Reppe led to the development of diverse transition metal-catalyzed [2+2+2]-cycloaddition reactions involving transition metals such as Pd, Ru, Rd, Co, Ni, Ir, Ti, Nb etc, and were successfully employed in the construction of complex

scaffolds related to bioactive natural products, pharmaceutically interesting molecules, and functional materials. In the context of our investigations in this thesis, herein we provide a brief literature survey of transition metal-catalyzed and transition metal-free [2+2+2]-cycloaddition reactions of alkynes those utilized in the construction of substituted benzenes, N-heterocycles (pyridine derivatives) and oxygen heterocycles particularly isobenzofurans and isobenzofuranones (also called phthalides) (Figure 4.1).

4.2 Previous approaches:

4.2.1 Synthesis of substituted benzenes: through transition-metal catalysis

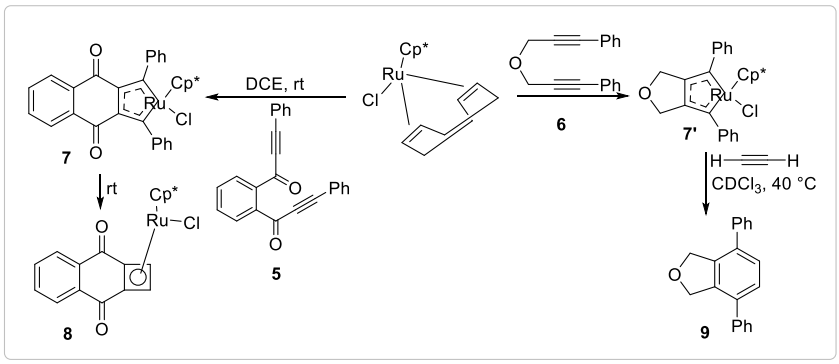
There are numerous methods reported in the literature for the synthesis of highly complex natural products or synthesized derivatives containing substituted benzene rings. Among all [2+2+2] cycloaddition or cycloisomerization reaction of alkynes is an efficient strategy, which was reported extensively using Ru, Rh, Ni, Co, Fe, Ir, and many other transition metal-based catalytic systems. As we discussed above, the first [2+2+2] cycloaddition or cyclotrimerization of alkyne was disclosed by Reppe and Schweckendiek in 1948,[3a] Later in 1962, Kennerly et al. investigated a $[Ni(CO)_2(PPh_3)_2]$ catalyzed cyclotrimerization and linear polymerization of acetylenes and also studied the effect of various factors such solvent, temperature. Further, they proposed a reaction mechanism based on a deuterium labeling experiment in which first alkynes coordination was followed by oxidative addition to the C-H bond. Whereas in the case of hexa-substituted benzene synthesis from disubstituted acetylene, firstly, two acetylene molecules with nickel complex would deliver a 5-membered planner complex **2**, upon further co-ordination of another acetylene molecule deliver hexa-substituted aromatic ring system **3** (Scheme 4.1).[3b]



Scheme 4.1.Cyclotrimerization of disubstituted alkynes under nickel catalysis

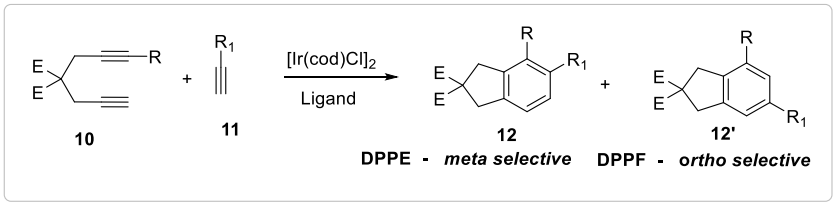
After intensive study of Yamamoto's group in the field of cycloaddition reactions using ruthenium catalysts, several theoretical and experimental investigations of [2+2+2]-

cycloaddition reaction of 1,2-bis(propiolyl)benzenes were carried out. When diynes **5** are substituted with phenyl at the terminal end, the reactions did not proceed with diphenyl acetylene or acetylene.[4] Whereas oxygen-tethered diyne **6** with phenyl substitutions at the terminal end was exposed to cycloaddition reaction using a stoichiometric amount of ruthenium complex to give the ruthenacyclopentatriene **7** and **7'**, which was then heated at 40 °C with acetylene to access terphenyl **9** derivative with moderate (37%) yield (Scheme 4.2).



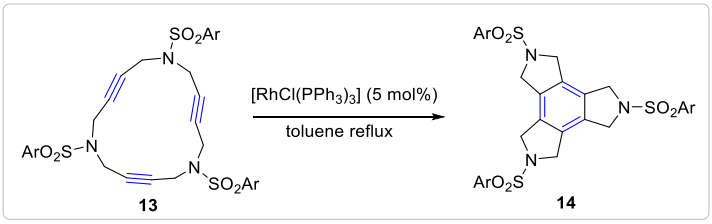
Scheme 4.2. [2+2+2]-Cycloaddition of diynes with alkynes using ruthenium complexes.

While working on the cyclotrimerization of acetylenes and alkynes possessing electron-withdrawing group for the formation of acetylene complex with iridium catalyst [$IrH(CO)(PPh_3)_3$] was observed by Baddley and Tupper,[5a] which was previously reported by Ibers and Kirchner in 1973.[5b] Inspired by these investigations, various developments made in iridium catalyzed [2+2+2]-Cycloaddition (cyclotrimerization) of alkynes by different research groups.[5c,g] Recently in 2006, Takeuchi reported the synthesis of polysubstituted benzene derivatives with good to excellent yield using $[Ir(cod)Cl]_2$/DPPE as a catalytic system from the reaction of α,ω-diynes **10** with terminal or internal alkynes. This approach could tolerate a wide range of functional groups such as alcohols, amines, alkene, ether, halogen and nitriles to furnish desired polysubstituted benzene derivatives **12** amd **12'** in appreciable yield. The reaction of 1,6-octadiyne derivatives with terminal alkyne delivered the ortho and meta products. The regioselectivity of the product depends on the use of ligand for that transformation. The regioselectivity of the products is controlled by the choice of ligand. Ligand DPPE gave meta selective, whereas DPPF the ortho-substituted product respectively with good yield[5h] (Scheme 4.3).



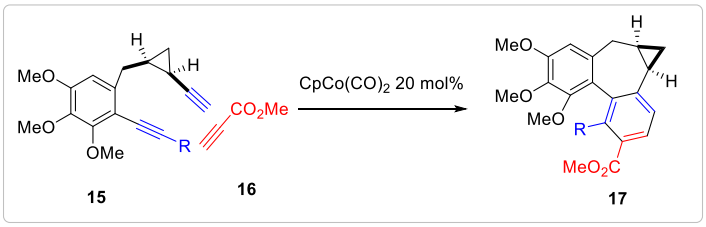
Scheme 4.3. Ir-catalyzed [2+2+2] cycloaddition of diynes with alkynes

Witulski group in 1999 used Wilkinson catalyst ($RhCl(PPh_3)_3$) first time for the cyclotrimerization of alkynes.[6] Later Yamamoto group also developed various [2+2+2]-cycloaddition strategies using Wilkinson catalyst[4] Further Roglans group in 2009, devised a method for cycloisomerization of azamacrocycles **13** of polyacetylenes using 5 mol % of Wilkinson catalyst to obtain aza-heterocycle **14** (Scheme 4.4).[7]



Scheme 4.4. Rh-catalyzed intramolecular [2+2+2]-cycloaddition

Vollhardt group and many others developed cobalt-catalyzed [2+2+2]-cycloaddition reactions of alkynes to construct diverse substituted carbocyclic and heterocyclic compounds.[8a] Recently, in 2016, the Ramana group developed cobalt-catalyzed cyclotrimerization of diyne **15** and methyl propiolate **16** and successfully employed this approach for the synthesis of cyclopropyl allocolchicinoid **17** and its analogous (Scheme 4.5).[8b]



Scheme 4.5. Synthesis of cyclopropyl allocolchicinoid and its analogous

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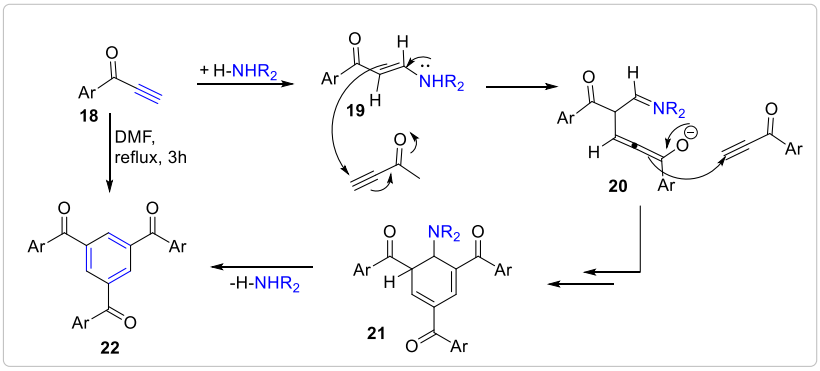
4.2.2 Synthesis of substituted benzenes: through transition-metal free approaches

The above list of transition metal (Ni, Ru, Ir) catalyzed [2+2+2]-cycloaddition reactions is not exhaustive; there are numerous methods also reported in the literature using diverse catalytic systems. In these reactions, the product outcome relies heavily on the metal catalyst, substitution patterns of the substrate. In most cases, a vigilant workup is indispensable to avoid toxic metal contamination due to the high coordination properties of products. Transition metal-free approaches are always desirable owing to their economics, sustainability, and non-toxic nature. In light of this emerging importance of transition metal-free reactions, in recent times, several efforts were devoted to developing novel [2+2+2]-

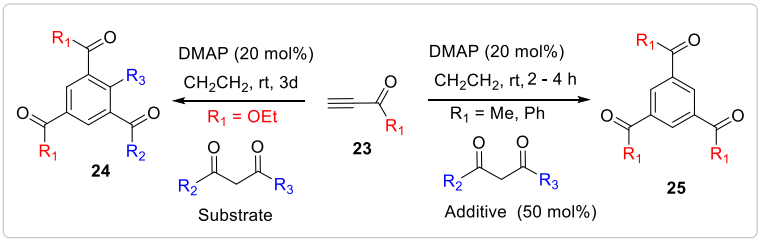
cycloaddition reactions of alkynes. Herein we present a few representative examples of this class (organocatalytic, thermal, microwave-assisted).[9]

For instance, Balasubramanian and Venkataramani et al. in 1980 reported the cyclotrimerization reactions of aromatic alkynyl ketones **18**, refluxed in DMF (*N*, *N*–dimethylformamide) to obtain 1,3,5-triaroylbenzenes with up to 80% yield.[10] Similarly, they tried other solvents such as toluene, xylene, and o-dichlorobenzene but obtained unreacted starting material. The reaction proceeds via nucleophilic addition of amine onto alkynyl ketone to furnish the enamine-ketone **19**, which on a further attack of another mole of alkynyl ketone delivers the allene intermediate **20**. Next, the allene-derived enolate would react with another molecule of ynone and gives the cyclohexadiene **21**, which on deamination of secondary amine furnishes the 1,3,5-triaroylbenzenes **22** (Scheme 4.6).



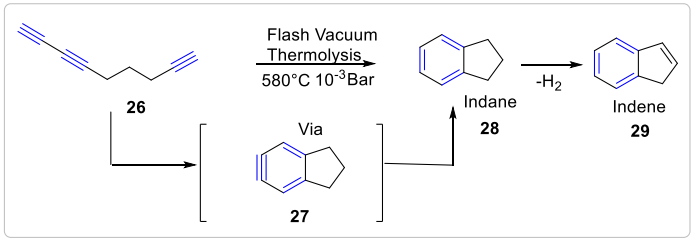
Scheme 4.6. Transition metal-free [2+2+2]-cyclotrimerization of alkynyl ketones using amine.

Further, several modified versions of this work were reported by different groups.[10] Xue et al. reported the cyclization reactions of alkynyl ketones **23** with 1,3-diketones in the presence of DMAP (20 mol%) as a catalyst, which gave 1,3,5-trisubstituted benzene **24** and **25** ring system with good to excellent (>90%) yield at room temperature.[11] In this reaction 1,3-diketone serves as a co-catalyst because it does activation during conjugate addition. DMAP plays an important role as a catalyst or accesses diverse benzene derivatives in this reaction. Substituents present on the 1,3-diketones play a crucial role in reactivity and selectivity due to their electronic and steric effects in product formation (Scheme 4.7).



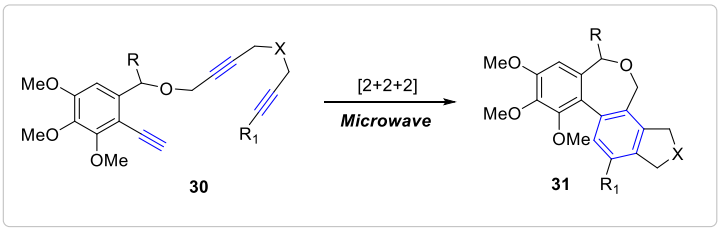
Scheme 4.7. Transition metal-free trimerization of alkynyl ketones using DMAP and 1,3-diketones.

In general, the construction of benzene ring by cycloisomerization of alkynes is little difficult due to large activation barrier. Johnson group in 1997, designed an efficient method of uncatalyzed cyclotrimerization of alkynes to deliver indene/indane **29**/**28** either via aryne **27** or 1,4-diradical intermediates which depends upon the connectivity of alkynes.[12]. Later the same group in 1999, discovered the synthesis of indane from triyne **26** (1,3,8-nonatriyne) by flash thermolysis at very high temperature (580 °C), which was further converted into indene by dehydrogenation step (Scheme 4.8).



Scheme 4.8. Intramolecular [2+2+2]-cycloaddition through flash thermolysis.

Microwave-assisted reactions play an important role in synthetic chemistry and are widely employed due to their shorter reaction times, good yields, and selectivity.[13a,13b] Taking advantage of microwave-assisted transformations, recently in 2009, Normans et. al. reported a challenging intramolecular [2+2+2]-cycloaddition reaction of triyne **30** for the construction of highly complex 6/7/5/6 tetracyclic scaffolds **31** possessing a seven-membered via formation of three new rings in a single operation (Scheme 4.9).[13]

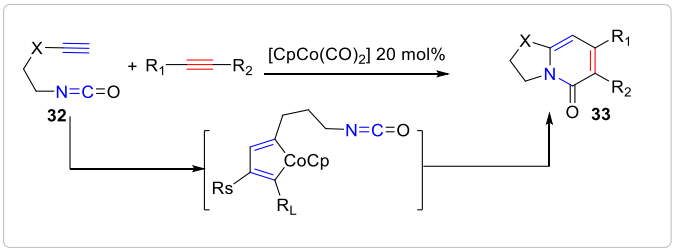


Scheme 4.9. Microwave-assisted intramolecular [2+2+2]-cycloaddition reaction of triynes.

4.2.3 Synthesis of pyridines (*N*-heterocycles): through transition-metal catalysis

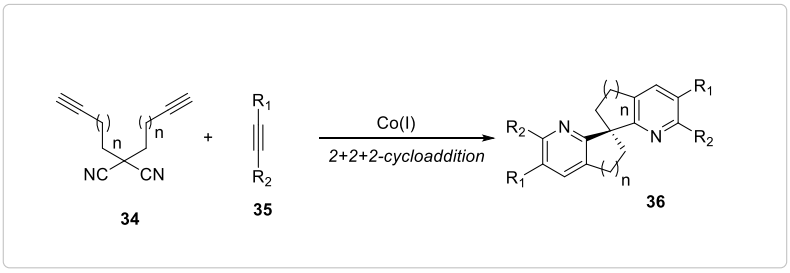
[2+2+2]-cycloaddition reactions are not only useful for the construction of carbocyclic compounds (benzenoids) but various heterocyclic compounds as well. After Ramsey's protocol using the heterogeneous catalyst to synthesize pyridines, other transition metal-catalyzed cyclotrimerization reactions were also developed. Vollhardt's group in 1984, reported cobalt catalyzed [2+2+2]-cycloaddition reactions of 5-isocyanato-pentynes **32** and

one mole of alkyne for the synthesis of pyridine-2-one **33** and this method was applied for the synthesis of antitumor alkaloid camptothecin.[14] Further, they have also studied the regioselectivity of this reaction and found that the large group will go alpha to cobalt center (Scheme 4.10).



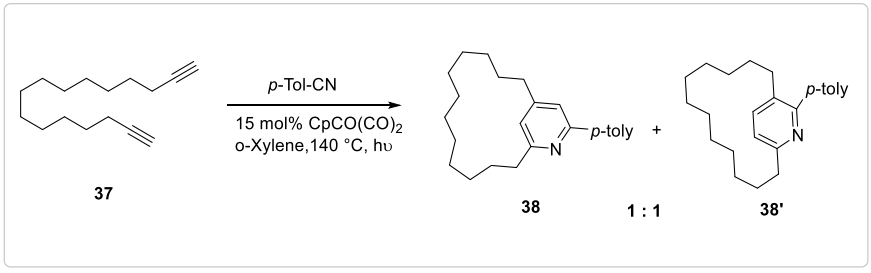
Scheme 4.10. Synthesis of pyridine-2-one through cobalt catalysis.

Carlos's group, in 1999, reported an efficient and versatile tool for the synthesis of unprecedented C2 symmetric ligand spiropyridines **36** in moderate to good yield. A one-step reaction in which acyclic bis-alkyno-nitrile **34** reacts with alkynes **35** using Co(I) catalyst to construct a highly complex architecture. By this method, they have achieved the first synthesis of the interesting 7,7′- and 8,8′-spiropyridines from acyclic precursors in a cascade manner (Scheme 4.11). [15]



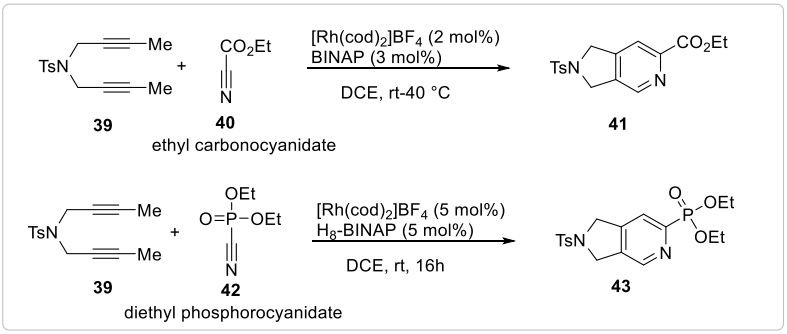
Scheme 4.11. Synthesis of spiropyridines through Co(I)-catalyzed [2+2+2]-cycloaddition.

Maryanoff and co-workers reported in 2001, a cobalt catalyzed the synthesis of macrocyclization of diynes **37** and nitriles or diynes containing nitrile with alkynes to prepare macrocycles containing pyridines **38**.[16] This method is a complementary method of ring-closing metathesis (RCM) to achieve such types of heterocycles (Scheme 4.12).



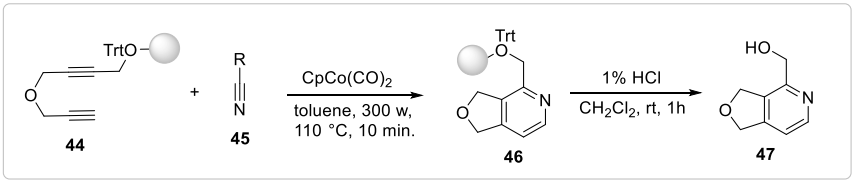
Scheme 4.12. Cobalt-catalyzed synthesis of macrocycle containing pyridine.

Tanaka et. al. in 2006 reported the synthesis of pyridines by [2+2+2]-cycloaddition reaction with propargylic amines and nitriles. They treated diyne **39** (propargylic amine) with ethyl cyanoformate **40** using $[Rh(cod)_2]BF_4$/BINAP as a catalyst to deliver the 2,3- dihydro-1*H*-pyrrolo[3,4-*c*]pyridines **41** in good to excellent yield.[17] Later same group reported the synthesis substituted pyridines using the same diynes (Scheme 4.13).



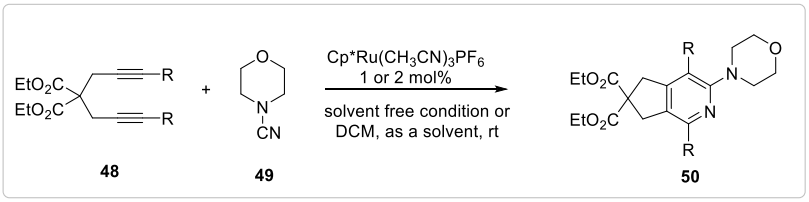
Scheme 4.13. Synthesis of pyridines from propargylic amine and nitriles

Dieters group in 2007 reported the microwave-assisted synthesis of pyridines **47**, pyridones, and imino-pyridines from oxygen inserted diyne **44** and nitriles **45**.[18] By using this strategy, different substrates can deliver the pyridines in high yield, excellent purity, and chemo and regioselectivity. In this approach, they used $CpCo(CO)_2$ as a catalyst and did not require an inert reaction condition (Scheme 4.14).



Scheme 4.14. Co-catalyzed, microwave-assisted synthesis of pyridine.

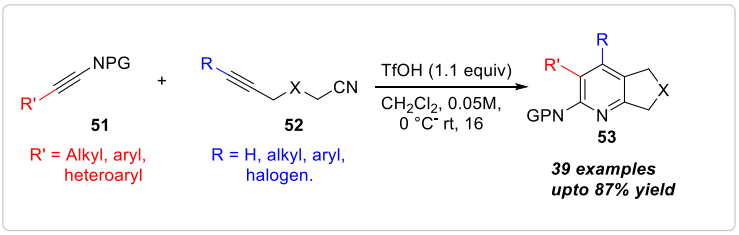
A mild and efficient approach for the synthesis of 2-amino pyridines **50** by Ru-catalyzed [2+2+2]-cycloaddition of α,ω-diynes **48** with cyanamides **49** under ambient reaction condition. This is a highly regioselective process with good to excellent yields. Reaction with unsymmetrical diynes provided corresponding 2-aminopyridines. This transformation requires $Cp^*Ru(CH_3CN)_3PF_6$ as a catalyst, a commercially available catalyst without ligand and additives (Scheme 4.15).[19]



Scheme 4.15. Synthesis of 2-amino pyridines by Ru-catalyzed [2+2+2]-cycloaddition.

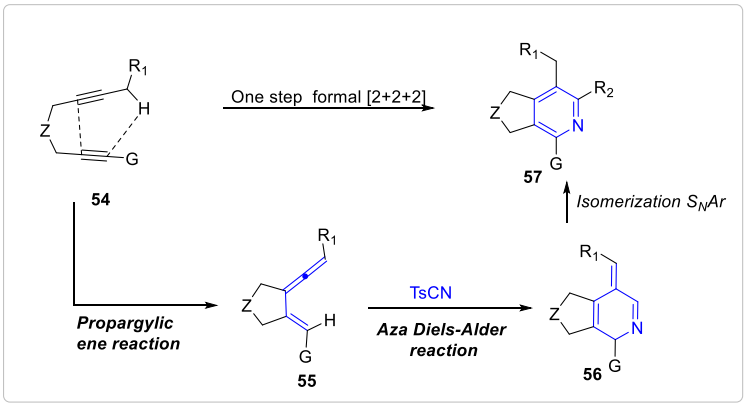
4.2.4 Synthesis of pyridines (*N*-heterocycles): through transition-metal free approaches

Maulide's group in 2016 reported a Brønsted acid-catalyzed an intermolecular cycloaddition reaction of alkynes **51** and nitriles **52** for the synthesis of substituted pyridines **53** via formal [2+2+2]-cycloaddition under mild reaction condition.[20] They have performed [2+2+2]-cycloaddition reaction of various alkynes containing a heteroatom such as nitrogen, sulfur with several nitriles possessing alkynes with aryl, alkyl and halogen functionality using 1.1 equivalent TfOH under mild (-78 °C-rt) reaction condition (Scheme 4.16).



Scheme 4.16. TfOH-mediated synthesis of pyridines from alkynes and nitriles.

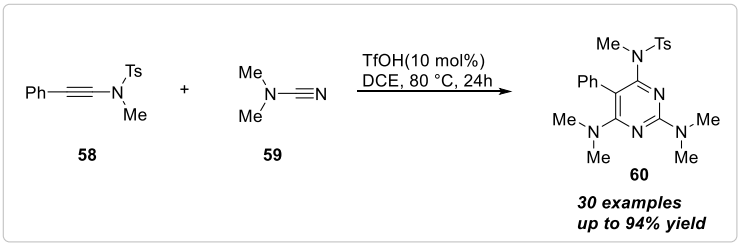
Danheiser's group in 2018 devised a bimolecular formal [2+2+2]-cycloaddition for the synthesis of a polysubstituted pyridine ring system **57**. This method is an efficient metal-free approach and involves base (DBU) mediated propargylic ene reaction of diyne **54** to form a vinylallenes **55**, subsequent intermolecular cycloaddition reaction with TsCN leads to substituted pyridines **57**. The synthesized 2-sulfonylpyridine serves as a versatile intermediate that undergoes substitution reactions with various oxygen or carbon nucleophiles (Scheme 4.17).[21]



Scheme 4.17. Synthesis of pyridines by transition metal-free [2+2+2]-cycloaddition.

Recently in 2021, Kukushkin's group reported the catalytic (TfOH 10 mol%) Brønsted acid-catalyzed regioselctive [2+2+2]-cycloaddition reactions of 2 moles of cyanamides **58** and one mole of ynamides **59** to achieve 2,4,6-triaminopyrimidines with appreciable yield. By using this approach they have prepared a wide range of 2,4,6-

triaminopyrimidines derivatives **60** (30 examples) (Scheme 4.18).



Scheme 4.18. TfOH catalyzed synthesis of 2,4,6-triaminopyrimidines

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4.3 Isobenzofuranones (phthalides): Introduction and previous approaches involving [2+2+2]-cycloaddition of alkynes

According to the recent statistical data, more than 75% of modern low-molecular-weight drugs used in medicine contain heterocycles (particularly N, O, or S). The incorporation of a heterocyclic moiety into a molecule provides a useful means for the alteration of key drug properties of solubility, lipophilicity, polarity, and H-bonding potential, which results in the optimization of the ADME and toxicology properties. Moreover, many heterocyclic lead compounds were isolated from natural sources as well, and their structures were subsequently simplified or modified to expand the drug-like chemical space. After N-heterocycles, O-heterocycles are the second most common category that appears as the FDA-approved drugs' structural components. Njardarson et al.'s analysis of the database of drugs (in 2017) disclosed that approximately 27% of unique approved small molecules and 15% of all approved drugs of 311 pharmaceuticals belong to O-heterocycles (consisting particularly pyranoses, furanoses, macrolactones, morpholines, and dioxolanes). Besides, O-heterocycle-derived scaffolds were ubiquitous in numerous bioactive natural products, including vitamins, hormones, antibiotics, sugars, etc. However, their importance in drug discovery has not been deservedly perceived, and they were often deserted in favor of N-heterocycles, which could be primarily due to the accessibility of a plethora of well-established synthetic methodologies and possible mimicking of physiological chemical entities by N-heterocycles. Among diverse readily accessible O-heterocycles in the chemical space, especially cyclic ethers and lactones have been fruitfully utilized as bioisosteres of amide (peptide) bonds in the design, discovery. The oxygen atom of these cyclic ethers/esters can form H-bonds (like peptides) by enhancing the binding affinity of the drug with receptors of respective enzymes.

Isobenzofuranones are often called phthalides, belong to the class of oxygen heterocycles, in which γ-butyrolactone moiety is fused with a benzene ring. These scaffolds

became fascinating synthetic targets owing to their frequent presence in many bioactive natural products, and their utilization as key intermediates in the synthesis of diverse chemicals, active pharmaceutical ingredients, heat resistant polymers, functionalized naphthalenes, naphthacenes, and anthracene based natural products. Isobenzofuranone containing natural or synthetic products shows a wide range of bioactivities such as antibacterial, antiviral, and antihypertensive activity.[23b] Herein we present a few representative examples for isobenzofuranone (phthalides) containing natural products, stachybotrylactone acetate[24a] **61**, taiwanin C[24b] **64**, phomoarcherins A,[24c] **63** djalonensin[24d] **65**, (+)-bicuculline[24d] **62** (active against circulatory disorders and heart diseases). *n*-Butylphthalide (NBP) **66** is currently marketed as an antiplatelet drug for ischemia-cerebralapoplexy[23a] containing isobenzofuranone as a core structure. (Figure 4.2).

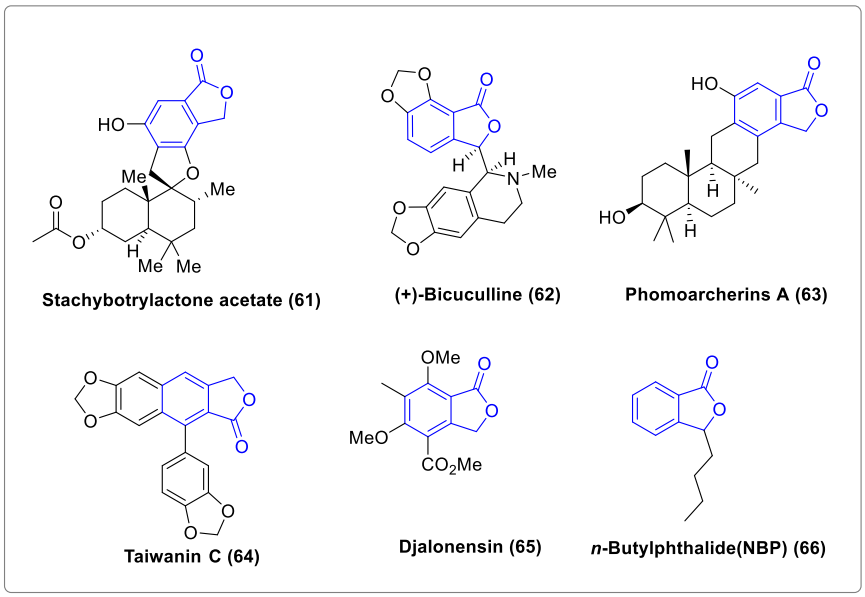
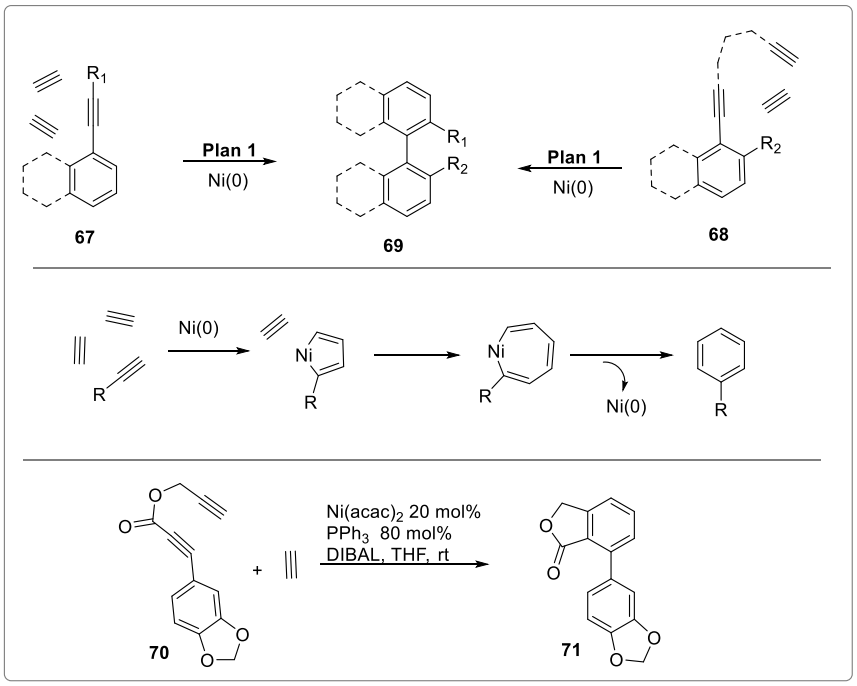


Figure. 4.2. Bioactive natural products containing isobenzofuranone skeleton.

After an extensive literature survey, we found that isobenzofuranones (phthalides) were primarily synthesized from substituted arenes (possessing preconstructed benzene ring) via a sequence of transformations, for instance, cyclocarbonylation of ortho-halobenzyl alcohol,[25] oxidation of phthalyl alcohol,[26] Cannizzaro-type lactonization of dialdehyde,[27] reductions of phthalic anhydride,[28] oxidative annulations of ortho-methyl benzoic acid.[29] In recent times, elegant synthetic approaches comprising transition metal-catalyzed [2+2+2] cycloaddition of pre-functionalized alkynes were disclosed in the literature, and some representative examples were presented in the below Section 4.1.6.

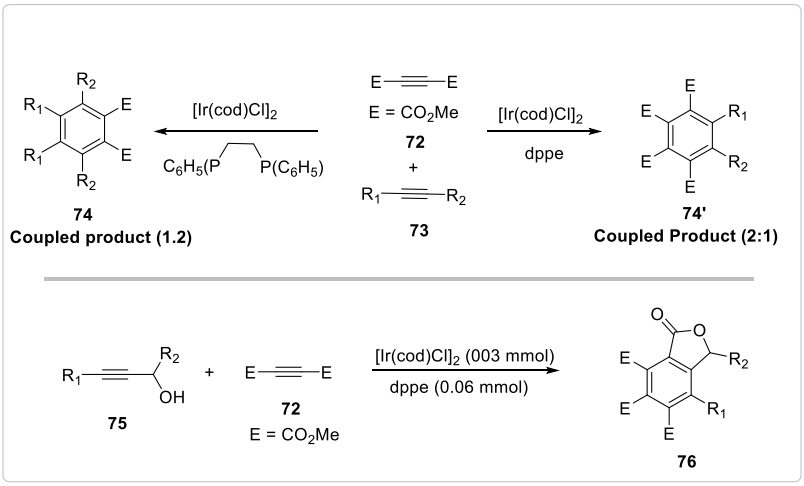
4.3.1 Synthesis of isobenzofuranones (phthalides): through transition metal-catalyzed [2+2+2]-cycloaddition

Mori's group, in 1999, reported the synthesis of biaryls **69** through nickel-catalyzed [2+2+2]-cycloadditions reaction of alkynes. They planned to synthesis biaryl in two ways. In the first route, substituted phenylacetylene **67** reacted with two equivalents of acetylene, whereas in the second route α,ω-diyne **68** having a phenyl group was treated with one equivalent of acetylene under Ni(0)-catalysis. This method was successfully extended for the synthesis of isobenzofuranones (Scheme 4.19).[30]



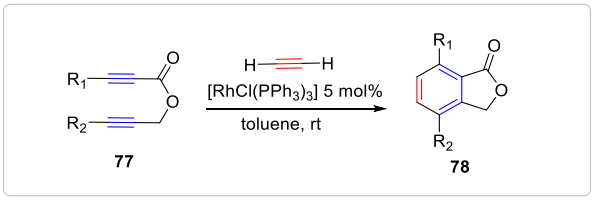
Scheme 4.19. Ni(0)-catalyzed [2+2+2]-cycloaddition to access biaryls and isobenzofuranones

Yoshihiko's group in 2003, devised a strategy for the synthesis of aryl systems by cross-coupling of dimethyl acetylenedicarboxylate (DMAD) **72** with acetylene **73**. It is a highly selective cross-coupling reaction using $[Ir(cod)Cl]_2$ as a catalyst. They made the very important observation that the reaction between dimethyl acetylenedicarboxylate (DMAD) with acetylene using dppe as a ligand gave coupled products **74**' in 2:1 ratio (R_1 and R_2 ortho vs. para), whereas using bis(diphenylphosphino)ethane as a ligand delivered in coupled products **74** in 1:2 ratio. Using this approach, they have also synthesized the isobenzofuranones **76** by the reaction of dimethyl acetylenedicarboxylate (DMAD) **72** with propargylic alcohol under optimized reaction conditions in good yield (Scheme 4.20).[31]



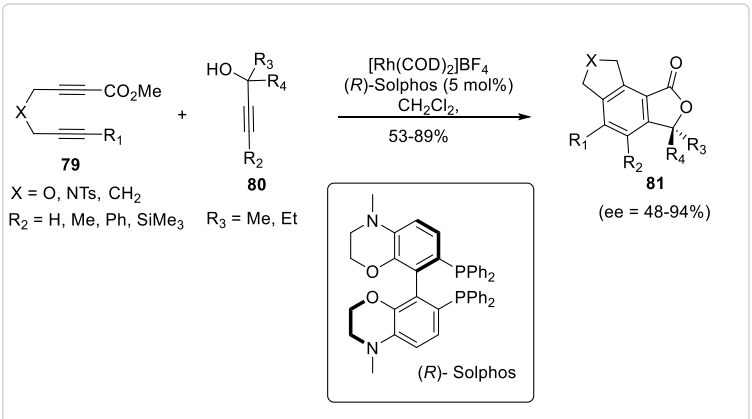
Scheme 4.20. Ir-catalyzed [2+2+2]-cycloadditions of DMAD and alkynes.

Witulski group in 2004 reported a versatile approach for the synthesis of substituted phthalides **78** from tethered diyne **77** esters and acetylene by using Wilkinson catalyst (Scheme 4.21).[32]



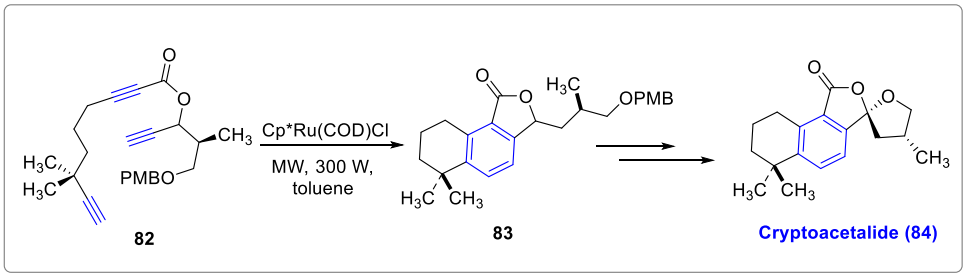
Scheme 4.21. [2+2+2]-Cycloaddition of diyne-ester with acetylenes.

Later Tanaka et al., in 2007, devised an enantioselective version for the synthesis of optically active phthalides **81** with up to 89% yield and 94% ee.[33] In this method Rh(I)-mediated intermolecular cycloaddition of 1,6-diyne **79** (tethered with an ester functionality) and *ter*-propargylic alcohols **80** in the presence of chiral phosphoric acid furnished phthalides **81** (Scheme 4.22).



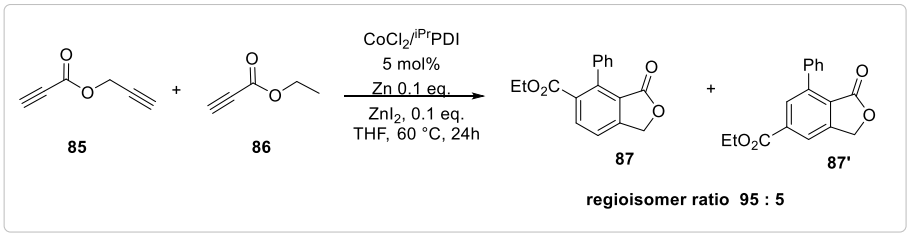
Scheme 4.22. Asymmetric [2+2+2]-cycloaddition of diyne-ester with propargylic alcohols.

Deiter's group in 2010 reported the first total synthesis of cryptoacetalide **84** a tetracyclic terpene in 12 steps using intramolecular [2+2+2]-cycloaddition as a key step. Cp*RuCl(COD) catalyzed reaction of triyene **82** under microwave irradiation furnished the tricyclic phthalide **83** in 90% yield. Next, DDQ-mediated PMB deprotection followed by photo-induced irradiation (200 W Xe/Hg lamp) in presence of iodine and iodobenzene diacetate delivered the inseparable mixture of cryptoacetalide **84** and *epi*-cryptoacetalide in a 2:1 ratio (Scheme 4.23).[34]



Scheme 4.23. Total synthesis of cryptoacetalide via intramolecular [2+2+2]-cycloaddition.

Recently in 2020, Savela's group reported a cobalt-catalyzed intermolecular approach for the synthesis of isobenzofuranones **87** and **87'** through [2+2+2]-cycloaddition of ester or amide tethered 1,6-diynes **85** with ethyl propiolate derivatives[35] **86**. They have screened several ligands and observed the formation of regioisomers. Among them, ^{iPr}PDI found the best ligand with an isomeric ratio of 95:5 in THF. This reaction proceeds via a five-membered cobalt complex followed by [4+2]-cycloaddition of cobalt complex with ethyl propiolate derivatives to furnish isobenzofuranone (Scheme 4.24).

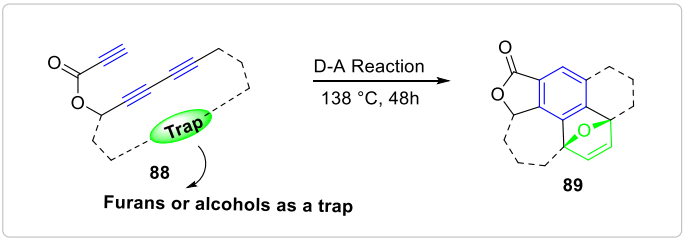


Scheme 4.24. Cobalt-catalyzed synthesis of isobenzofuranones (phthalides).

4.3.2 Synthesis of isobenzofuranones (phthalides): through transition metal-free [2+2+2]-cycloaddition

The transition metal-free [2+2+2]-cycloaddition reactions involving alkynes are very limited, there is only one report disclosed by Hoye's group in 2018 via hexadehydro Diels-Alder (HDDA) reaction of triynes **88**, which would result in an aryne reactive intermediate

and trapped in situ with tethered furans or alcohols.[36] Using this method, prepared a few polycyclic isobenzofuranones **89** (Scheme 4.25).



Scheme 4.25. Synthesis of substituted isobenzofuranones by HDDA reaction

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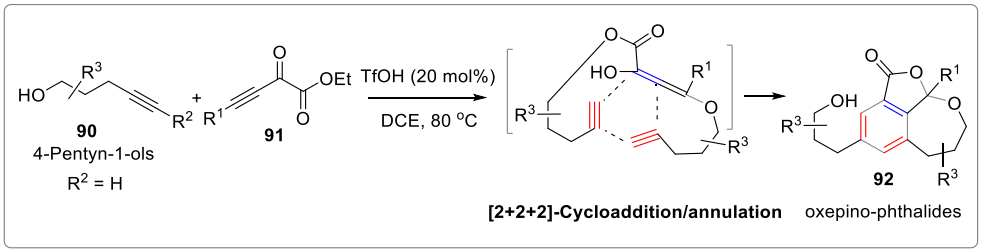
4.3.3 Our hypothesis for the synthesis of tetrahydro oxepino-phthalides (isobenzofuranones) through Brønsted acid-catalyzed [2+2+2]-cycloaddition.

After the above extensive literature survey, we found no report on a simple Brønsted acid-catalyzed [2+2+2]-cycloaddition/annulation reaction of alkynes to prepare multi-functionalized arenes and isobenzofuranones. Due to the atom-economic nature, cost-effectiveness and sustainability, the development of transition metal-free cycloaddition reactions gaining utmost importance in recent times. In light of the very interesting profile of (as discussed in above Sections 4.1 and 4.2) isobenzofuranones (phthalides), [2+2+2]-cycloaddition reactions, and our ongoing interest in expanding the chemistry of alkynyl alcohols (alkynols) for the synthesis of diverse oxygen heterocycles related to bioactive natural products, we devised a novel synthetic protocol for the construction of isobenzofuranone-derived oxepines from readily accessible simple building blocks of 4-pentyn-1ols (possessing terminal alkyne) and α-ynone-esters under TfOH-catalysis for the first time, which we incorporated into this Chapter-IV of the thesis (vide infra). Based on the outcome of our investigations and reported literature, we have postulated a plausible reaction mechanism for this transformation. The reaction of 4-pentyl-1ol with α-ynone-ester would deliver the corresponding allenol with concomitant transesterification, and participates in intramolecular [2+2+2]-annulation reaction to deliver desired oxepino-phthalides (Scheme 4.26).

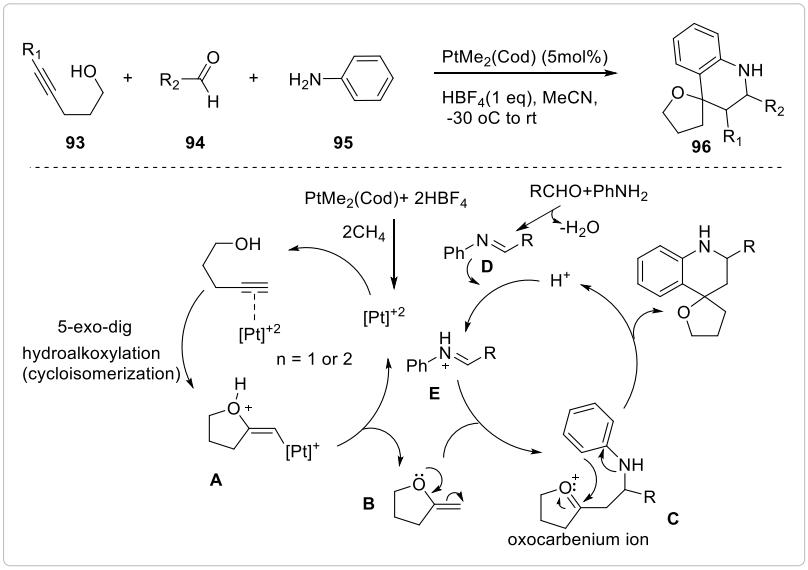


Scheme 4.26. **Present work**: [2+2+2]-annulation of 4-pentyn-1ols with α-ynone-esters.

4.4 Introduction and previous approaches to [3+2]-annulation reactions involving alkynols

As discussed in Section A of Chapter-I, alkynols (hydroxyl-containing alkynes) can be used as versatile synthons in synthetic organic chemistry. Particularly, 4-pentyn-1ols and 5-hexyn-1ols undergo cycloisomerization reaction to generate respective end- or exocyclic enol ethers, which works as nucleophiles (acyl anion equivalents) and participate in reactions with diverse electrophiles, and also interesting annulation reactions. In recent times a couple of [3+2] and [4+2]-annulation reactions involving alkynols were reported in the literature, which is presented herein.

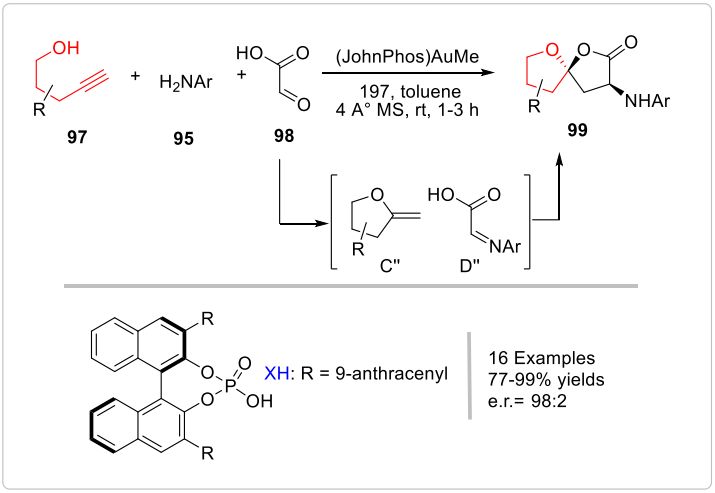
A one-pot multi-component cascade protocol encompassing Pt(II)-catalyzed synthesis of spiroquinolines **96** from readily available alkynol **93**, aldehydes **94** and anilines **95** were developed by Fañanás research group in 2008. Pt(II)-Catalyst [$Pt(Me)_2Cod$] (5 mol%) (the cationic platinum catalyst was formed with [$Pt(Me)_2Cod$] protic acid), HBF_4(1 eq) in acetonitrile at 30 ^oC could afford various [5,5]- and [6,5]-spiroquinolines **96** through a [3+2]-annulation pathway. This reaction proceeds through the initial C-C triple-bond activation, followed by intramolecular hydroalkoxylation of alkynol steps to give cyclic enol ether **B** via **A**, followed by the reaction of **A** with imines **E** (which are formed in situ by condensation aromatic amine **95** and aldehydes **94**) would lead to oxocarbenium ion **C**, which would undergo intramolecular Friedel-Crafts like cyclization to deliver the final product spiroquinolines[37] **96** (Scheme 4.27).



Scheme 4.27. Synthesis of spiroquinolines via one-pot multi-component [3+2]-annulation.

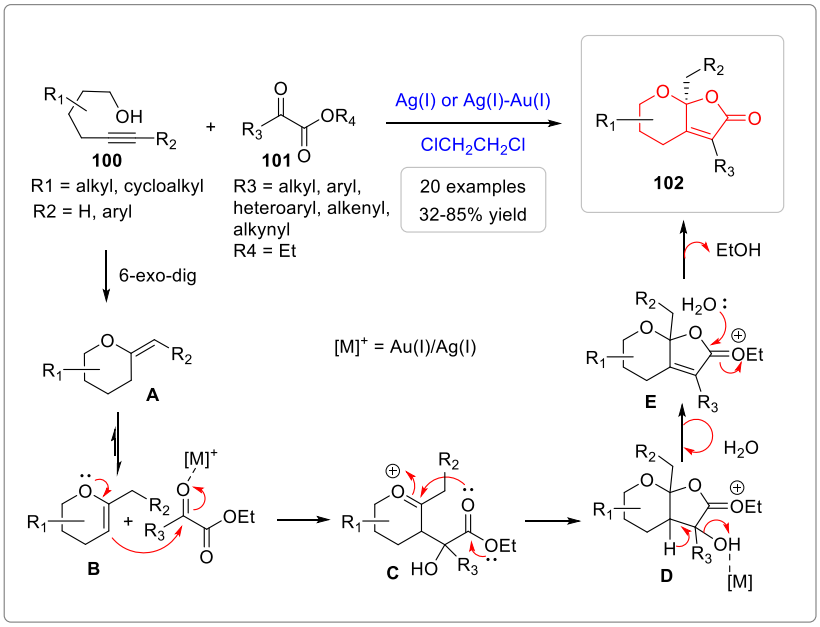
The first catalytic enantioselective synthesis of [5,5]-oxa-spirolactones **99** possessing

α-amino functionality was reported by Rodriguez and Fañanás in 2013 through a gold phosphate catalyzed one-pot three-component coupling of alkynols **97**, anilines **95** and glyoxylic acid[38] **98**. The combination of (JohnPhos)AuMe and (*R*)-BINOL-derived phosphoric acid, which would in situ generate the cationic gold phosphate complex and can catalyze the cycloisomerization of alkynol **97** to get the exocyclic enol-ether intermediate **A** and its formal asymmetric [3+2]-cycloaddition with in situ generated imine **B** (from glyoxylic acid and anilines) cascade deliver the desired oxaspirolactones **99**. This highly straightforward and robust protocol delivered diverse [5,5] and [6,5]-oxa-spirolactones possessing α-N-aryl substitution in excellent isolated yields (77-99%) and enantioselectivity (up to 98:2 *er*). The absolute configuration of products was rigorously confirmed by single-crystal X-ray analysis and analogy (Scheme 4.28).



Scheme 4.28. Synthesis of oxaspirolactones through enantioselective multicomponent reaction.

Recently, in 2018, our group reported a facile protocol for the synthesis of furo[2,3-b]pyran-2-ones via Ag(I) or Ag(I)-Au(I)-catalyzed cascade [3+2]-annulation of hexyn-1-ols and α-ketoesters using π & σ activation (dual activation) strategy. This cascade reaction proceeds through Ag(I)-mediated hydroalkoxylation of alkynols via 6-exo-dig cyclization (π-activation) to form exocyclic enol ether which undergoes isomerization into a more favored endo enol ether intermediate. Nucleophilic addition of enol ether onto the preactivated (σ-activation) ketoester, followed subsequent cascade steps lead to the formation of furo-pyranones. This method was found to be highly efficient with good substrate scope (20 examples) and isolated yields (32-85%) (Scheme 4.29).



Scheme 4.29. Synthesis of furo[2,3-*b*]pyranones through cascade [3+2]-annulation of alkynols and α-ketoesters

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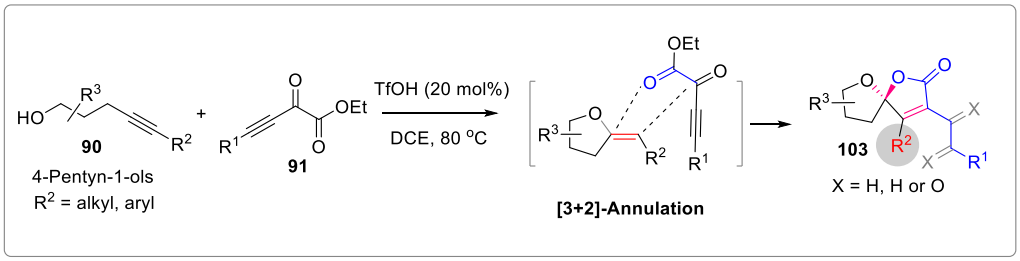
4.4.1 Our hypothesis for the synthesis of [5,5]-oxaspirolactones through Brønsted acid-catalyzed [3+2]-annulation involving alkynols.

In the last two decades, alkynes were emerged as versatile synthons in synthetic organic chemistry and led to the discovery of novel synthetic methodologies. 4-Pentyn-1-ols and 5-hexyn-1-ols are known to generate cyclic enol-ethers possessing exo- or endo-cyclic double bond which is equivalent to acyl anion. Moreover, these cyclic enol-ethers possessing the nature of nucleophile and electrophile by generating oxa-carbenium ions. These enol ether active intermediates readily participate in [3+2]- and/or [4+2]-annulation reactions with diverse building blocks under dual activating (σ and π) transition metal catalysis, Au, Pd, Pt were known to facilitate this reaction. Aiming at developing eco-friendly and cost-effective catalytic annulation reactions, our group recently disclosed a novel synthetic methodology for the construction of [5,5]-oxaspirolactones through Bi(III)-catalyzed cascade [3+2]-annulation of 4-pentyn-1-ols and α-ketoesters (see Chapter-1).

In continuation to this work, we were curious to verify the reactivity of 4-pentyn-1-ols (possessing internal alkyne) with α-alkynyl α-ketoesters (α-ynone-esters) under Brønsted acid catalysis. To our delight, after extensive screening of diverse dual activating (σ and π) catalytic systems, we found that simple TfOH (Brønsted acid) was able to catalyze the reaction and delivered corresponding α-aceto aryl or α-acyl [5,5]-oxaspirolactones with

concomitant hydration of tethered alkyne functionality with complete regioselectivity (complete details of our results incorporated in Section B of this Chapter 4) (Scheme 4.30).



Scheme 4.30. Present work: [3+2]-Annulation of 4-pentyn-1ols with α-ynone-esters.

THE END

Chapter 4

Section B

Present work

Metal-free divergent synthesis of oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [3+2]-annulation of alkynols with α-ynone-esters

Present work:

4.5Introduction:

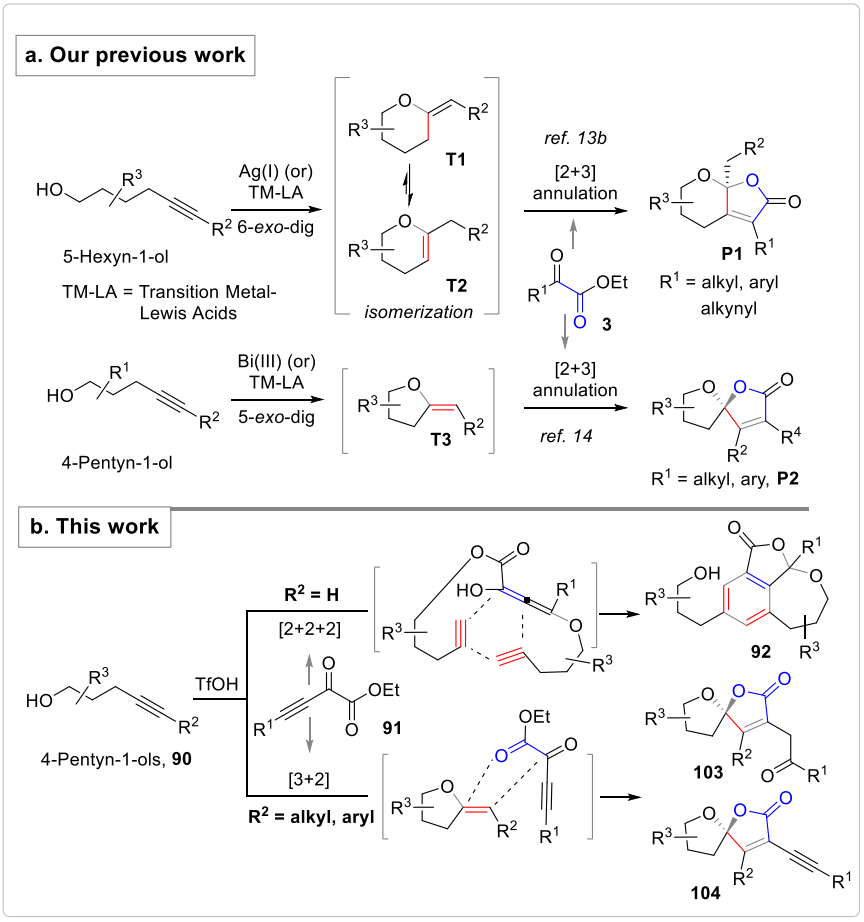
Construction of multi-functionalized polycyclic scaffolds related to biologically active natural products and functional materials through convergent annulation or cycloaddition strategy has been emerged as an interesting field of research due to its versatility, atom- and step-economic nature. One of these processes is the [2+2+2]-cycloaddition of alkynes for constructing functionalized arenes, which was well studied and employed in materials, medicinal, pharmaceutical, and natural products chemistry. In the realm of [2+2+2]-cycloaddition of alkynes (particularly cyclo-trimerization), transition-metal-catalysis extensively explored based on Ni, Co, Pd, Cr, Rh, Fe, Zr, Nb, Ir, and other metals, where the product outcome relies heavily on the metal catalyst, substitution patterns of the substrate, in most cases vigilant workup is indispensable to avoid metal contamination due to high coordination properties of products.[40]

Due to conspicuous demand for transition metal-free, operationally simple, efficient, and cost-effective strategies, the development of a simple Brønsted acid-catalyzed [2+2+2]-cycloaddition of alkynes to construct multi-functionalized arenes is always a desirable endeavor. Despite the extensive literature on alkyne trimerization is present, only a few examples have been reported for transition met-al-free processes,[41] which include thermal processes (temperature required is 100-600 °C),[42] microwave irradiation (needed specialty equipment),[43]amine-mediated cyclotrimerization of propargylic ketones,[44] lactic-acid-induced trimerization of enaminone[45]and intramolecular hexdehydro-Diels-Alder reaction (HDDA) of tethered ene-tetraynes.[46] It's noteworthy to mention that an analogous construction of pyridines/pyrimidines via TfOH mediated (stoichiometric/catalytic) [2+2+2]-cycloaddition of ynamides/nitriles Maulide,[47] Tang,[48] Wang and Chang,[49] and Dubovtsev and Kukushkin research groups.[50]

To the best of our knowledge, there is no report on the TfOH-catalyzed intermolecular [2+2+2]-cycloaddition of alkynes to pro-vide tricyclic tetrahydrooxepino-phthalides, and α-aceto aryl or α-acyl [5,5]-oxaspirolactones via [3+2]-annulation involving alkynols and α-ynone-esters. Benzoxepines[51a-b] and phthalides[51c] (also called isobenzofuranones) are widely found in numerous bioactive natural products and pharmacologically interesting scaffolds and phthalides are used as key intermediates in the synthesis of pharmaceuticals, natural products, and heat resistant polymers. Many natural products possessing [5,5]-oxaspirolactones were

isolated in recent times and known to display prominent biological profiles.[52a,53]

4.6Hypothesis:



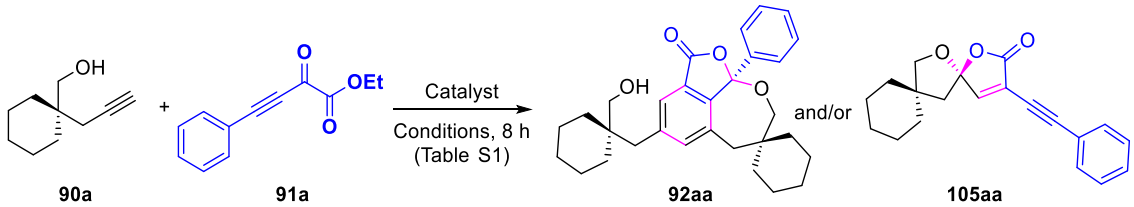
Scheme 4.31. Cascade annulation reactions of alkynols with α-ketoesters

In a research program to expand the chemistry of alkynyl alcohols (alkynols) for the construction of diverse oxygen-heterocycles related to bioactive natural products, we have recently reported Ag(I) or Au(I)-Ag(I)-catalyzed [3+2]-annulation cascade reaction of 5-hexyn-1-ols with α-ketoesters and/or β-γ-unsaturated α-ketoesters to give diverse furopyranones**P1** via cyclic enol-ether **T2** (formed from alkynol via **T1**).[52b] In another investigation, Bi(III)-catalyzed annulation of 4-pentyn-1ols**90** with α-ketoesters**101** delivered α,β-unsaturated [5,5]-oxaspirolactones via the intermediacy of the enol-ether **T3** through [3+2]-annulation.[53]In these transformations alkynols undergo initial catalytic πactivation-induced cycloisomerization to give respective cyclic enol ethers, which further react with activated α-ketoesters and deliver annulated bicyclic scaffolds (entry a, Scheme 4.6).

4.7 Result and discussion:

4.7.1 Optimisation of reaction condition:

Table 4.1. Reaction optimization[a]



entry	catalyst	solvent, temp	% yield of **3aa**[b]	% yield of **4aa**[b]
1	$Bi(OTf)_3$	CH_2Cl_2, rt	62	22
2	$Bi(OTf)_3$	DCE , 80 °C	71	19
3	$BiCl_3$	CH_2Cl_2, rt	-	48
4	$BiCl_3$	CH_3CN, rt	-	31
5	$InCl_3$	CH_2Cl_2, rt	-	10
6[c]	$FeCl_3$	CH_2Cl_2, rt	-	-
7[c]	AgOTf	CH_2Cl_2, rt	-	13
8[c]	AuCl	CH_3CN, rt	-	-
9	PPh_3AuCl and AgOTf	CH_3CN, rt	-	12
10[c]	$Pd(PPh_3)_4$	CH_3CN, rt	-	-
11[c]	$Pd(OAc)_2$	CH_3CN, rt	-	-
12[c]	RuCl	CH_2Cl_2, rt	-	-
13[c]	$RhCl(PPh_3)_3$	CH_2Cl_2, rt	-	-
14[c]	$RhCl(PPh_3)_3$	EtOH, rt	-	-
15[c]	$NiCl_2.6H_2O$	CH_3CN, rt	-	-
16[c]	TfOH	CH_2Cl_2, rt	-	-
17[c]	TfOH	DCE, rt	-	-
18	**TfOH**	**DCE, 80 °C**	**82**	-
19	TfOH (10 mol %)	DCE, 80 °C	76	-
20	TfOH (5 mol %)	DCE, 80 °C	60	-
21[d]	TfOH	DCE, 80 °C	42	-
22	TfOH	toluene, 80 °C	67	-
23[c]	MsOH	DCE, 80 °C	-	-
24	*p*-TsOH	DCE, 80 °C	48	-
25[c]	PPTS	DCE, 80 °C	-	-
26[c]	AcOH	DCE, 80 °C	-	-
27[c]	TFA	DCE, 80 °C	-	-

[a]Reaction conditions unless otherwise specified: **90a** (0.43 mmol), **91a** (0.21 mmol), catalyst (20 mol %) in the indicated solvent (anhydrous, 5 mL) in 8 h. [b]Isolated yields of**92aa** and **93aa**.[c]No conversion was observed. [d]**90a** (0.21 mmol), **91a** (0.21 mmol), catalyst (20 mol %) were used, in which **90a** was completely reacted and **91a** was recovered.

Hence, an initial scouting reaction was performed with known 4-pentyn1-ol **90a** (possessing terminal alkyne) and α-alkynyl-α-ketoester (α-ynone-ester) **91a** under our in-

house developed cycloisomerization conditions using $Bi(OTf)_3$ in CH_2Cl_2 at rt, which afforded

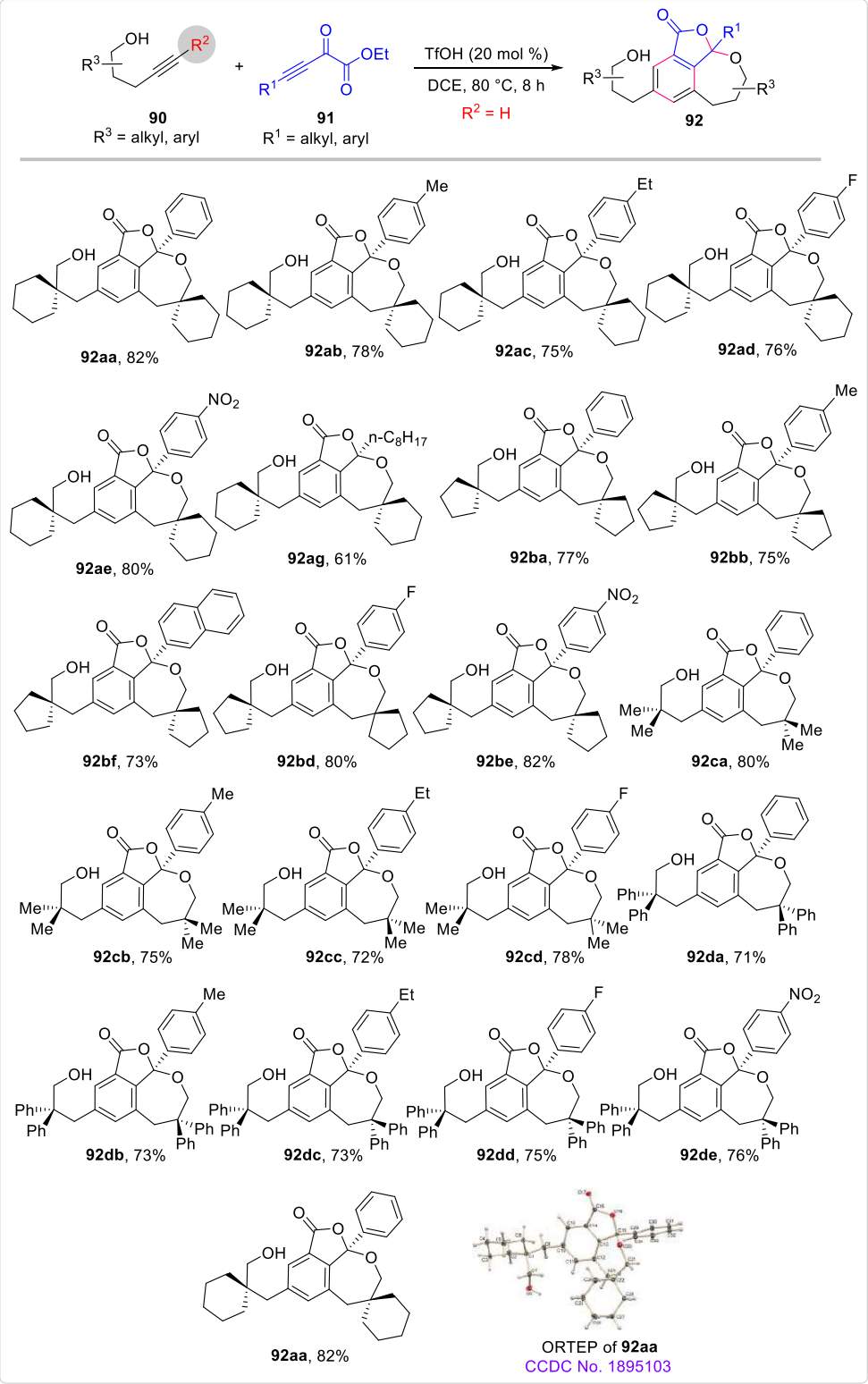
tetrahydro-oxepinophthalide**92aa** in 62% yield along with oxaspirolactone**105aa** in 22% yield, subsequent experiment altering the solvent and temperature (DCE, 80 ^oC) did not led to any improvement in the outcome of **92aa** (entries 1 and 2, Table 4.1). Next, the screening of other π- and σ-activating catalysts ($BiCl_3$, $InCl_3$, $FeCl_3$, AgOTf, AuCl, PPh_3AuCl-AgOTf, $Pd(PPh_3)_4$ and $Pd(OAc)_2$ delivered only **105aa** in 12-48% yield as we observed in our earlier investigations[53] (see Table 4.1), [54,55] whereas other catalysts (RuCl, $RhCl(PPh_3)_3$ and $NiCl_2$) known to facilitate [2+2+2]-cycloaddition[40] failed to catalyze this reaction (see Table 4.1). Gratifyingly, the reaction of **90a** (2 equiv) and **91a** (1 equiv) using 20 mol % of TfOH in DCE at 80 ^oC delivered exclusively**92aa** in 82% isolated yield, which was rigorously confirmed by single-crystal X-ray analysis (entry 3, Table 4.1). Further alteration of reaction parameters like molar ratios of **90a** and **91a**, Brønsted acids, catalyst loading and reaction temperatures did not lead to noticeable improvement (entry 4-8, Table 4.1).[55]

4.7.2 Scope and generality of method:

With optimal reaction conditions in hand, we set out to investigate the scope of the current reaction concerning 4-pentyn-1-ols (possessing internal alkyne) **90** and α-ynone-esters **91**. The reactions of cyclohexane- and cyclopentane-derived 4-pentyn-1-ols with several α-ynone-esters possessing phenyl, *p*-tolyl, *p*-ethyl, *p*-flouro, *p*-nitro and naphthyl substituents cleanly furnished corresponding oxepino-phthalides**92aa-92ae**/**92ba-be** in good yields (73-82%). Similarly, annulation of geminal dimethyl and diphenyl substituted 4-pentyn-1-ols with various α-ynone-esters delivered respective oxepino-phthalides**92ca-92de** in very good yields (71-80%). The germinal dimethyl and diphenyl substituted 4-pentynols delivered the desired products in good yields. This could be attributed to the operation of the Thorpe-Ingold effect[56] (angle compression effect, which facilitates the ring-closure step of the process).

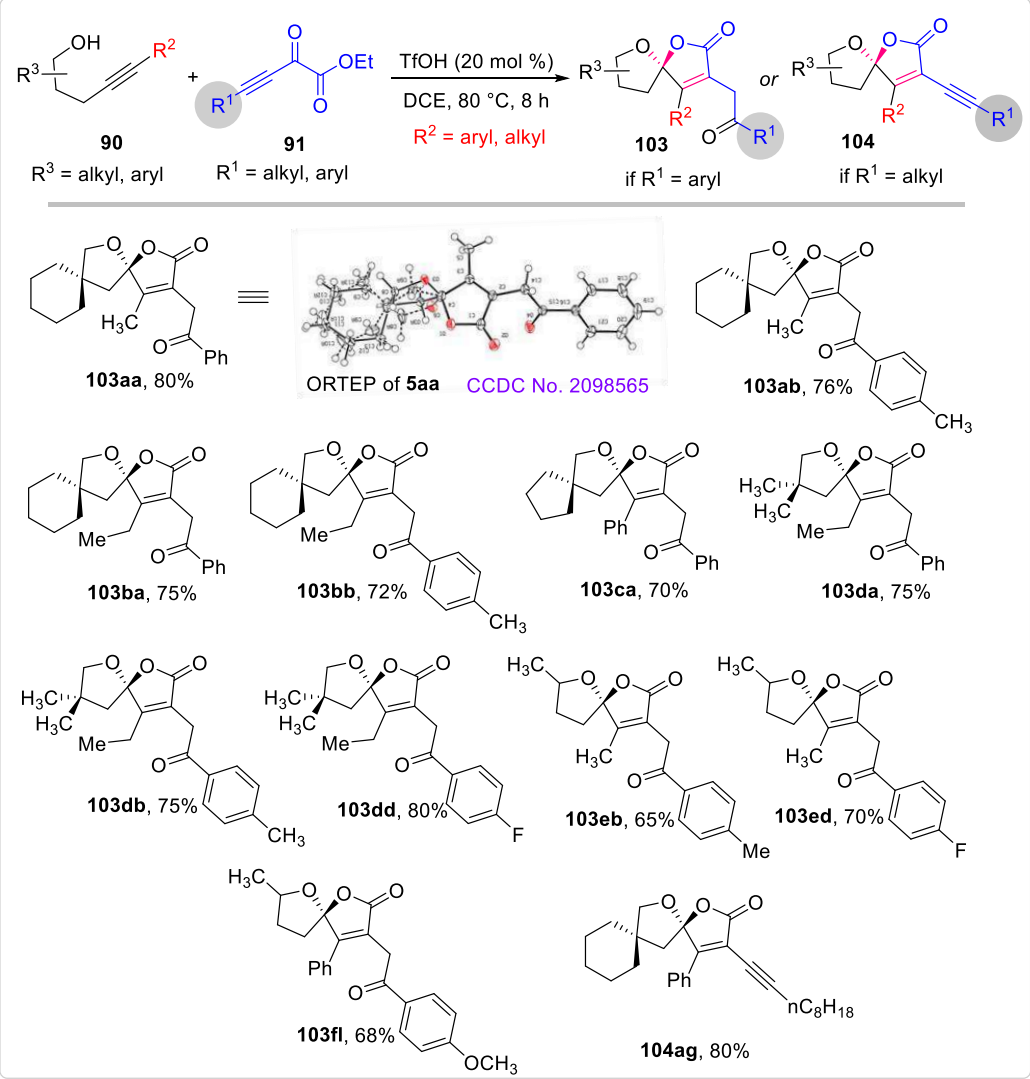
Next, we examined the reactivity of alkyl-substituted ynone-ester **91g**, which was also found to be a very good substrate and delivered corresponding product **3ag** in good yield. The electronic nature of substituents of α-ynone-esters **91** was found to have no significant influence on this annulation reaction (Scheme 4.32).

A) Synthesis of tetrahydro-oxepino-phthalides (92):



Scheme 4.32. Synthesis of tetrahydro-oxepino-phthalides 92[a,b]

B) Synthesis of [5,5]-oxaspirolactones (103 and 104):



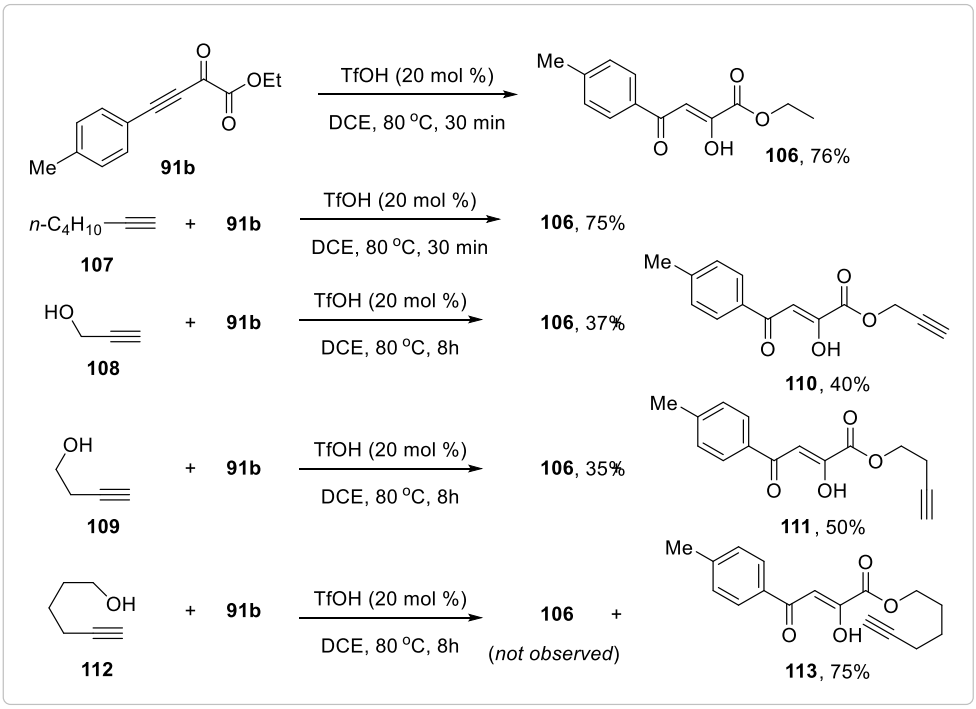
Scheme 4.33. Synthesis of [5,5]-oxaspirolactones **103** and **104**[a,b,c]

[a]see the Supporting Information (SI) for the synthesis of starting materials **90** and **91**.[b]Reaction conditions unless otherwise specified: **90** (0.49 mmol) and**91** (0.49 mmol) used, [b]Isolated yield provided

To further extend the substrate scope, 4-pentyn-1-ols possessing internal alkyne functionality **90** were examined under the optimized reaction conditions. However, a strikingly different reaction pattern was observed by providing α,β-unsaturated [5,5]-oxaspirolactones **104** and **103** with α-alkynyl or α-aceto appendage respectively, depending on the nature of the substituent on the alkyne functionality of **91** (substrate with aryl substituents provided **103**, alkyl substituents gave **104** with complete regioselectivity. The reaction between methyl-substituted alkynol and phenyl- *p*-tolyl derived ynone-esters

delivered corresponding oxaspirolactones **103aa** and **103ab** in 80 and 76% yield respectively. Varying the substituent of the alkyne moiety of **90** (R^2 of **90**, ethyl, phenyl) and ynone-ester **91** (R^1 of **91**, phenyl, *p*-tolyl, *p*-fluorophenyl, *p*-anisyl) were well tolerated and produced **103ba**, **103bb**, **103ca**,**103da-db**,**103dd**,**103eb**,**103ed** and **103fh**. In contrast, ynone-esters **91** having alkyl substituents (R^1) furnished α-alkynyl oxaspirolactones (Scheme 4.33). The structure of **103aa** was unambiguously confirmed by single-crystal X-ray analysis. The remaining products were confirmed based on analogy.

4.7.3 A) Supporting experiments for the mechanism

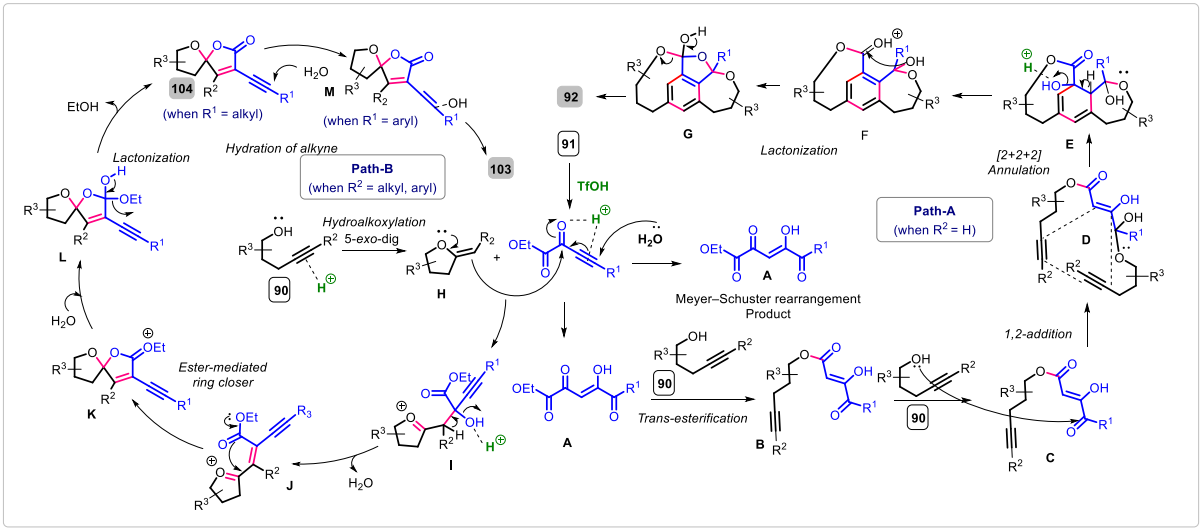


Scheme 4.34. Supporting experiments for the mechanism

Next, we examined the reaction profile of other alkynes/alkynols under optimized reaction conditions, which provides insight to postulate a reliable mechanistic sequence. The reaction of α-ynone-ester **91b** under optimized reaction conditions delivered the α,γ-diketo-ester **106** good (76%) yield. The reaction of 1-hexyne **107** with α-ynone-ester **91b** delivered enol form of α–γ-diketo-ester **106**, in which alkyne **107** was completely intact. Propargylic alcohol **108** and homopropargylic alcohol **109** delivered α–γ-diketo-ester **106** along with trans-esterified allenols **110** and **111** respectively, and did not lead to annulation products. Interestingly, 5-hexyn-1ol **112** reacted well with α-ynone-ester **91b** and delivered the trans-

esterified α–γ-diketo-ester **113** exclusively. These results implicitly suggest the role of α,γ-diketo-ester-derived transesterification intermediate in the catalytic cycle of [2+2+2]-annulation reaction (*vide infra*) (Scheme 4.34).

B) Plausible reaction mechanism



Scheme 4.35. Plausible reaction mechanism

While the precise reaction mechanism requires further investigation, plausible mechanistic pathways for forming oxepino-phthalides (Path A, Scheme 4.35) and oxaspirolactones (Path B, Scheme 4.35) based on results obtained in Scheme 4.34 and earlier reports[40-49,51,52] are presented in Scheme 4.35. The Brønsted acid-catalyzed hydration of α-ynone-ester **91** to give **A**, followed by transesterification of **A** with alkynol **90** would lead to the alkyne tethered α,γ-diketo-ester intermediate **B**. Subsequent 1,2-addition of another alkynol **90** onto the carbonyl carbon would lead to the intermediate **D**, which brings two alkynes and olefin functionalities into the proximity and facilitates the desired [2+2+2]-cycloaddition, and furnish the tricyclic hydroxy cyclohexadiene **E**. Next, acid-mediated dehydrative aromatization of E would deliver the oxacarbenium ion intermediate **F**. Further, intramolecular transesterification leads to the orthoester intermediate **G**, which upon the strain-induced chemoselective cleavage of one of the C-O bonds leads to the tetrahydro oxepino-phthalides **92** (Path A, Scheme 4.35).

In contrast, the reaction of 4-pentyn-1-ols containing internal alkyne functionality **90** (R^2 = alkyl or aryl) with α-ynone-esters **91** proceeds through a [3+2]-annulation (Path B, Scheme 4.34). The TfOH-induced 5-*exo*-dig cycloisomerization of alkynol gives cyclic enol

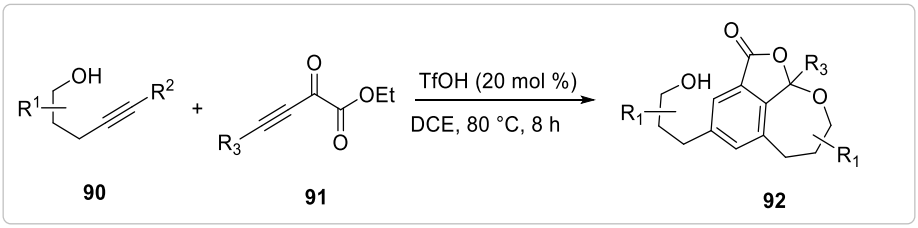
ether H**G**, which would react with activated α-ynone-ester **91** and deliver corresponding oxacarbenium ion intermediate **I** (*via* 1,2-addition). Subsequent acid-mediated dehydration to give intermediate **J**, followed by the intramolecular attack of the ester, leads to intermediate **K**. Next, the addition of *in situ* released water onto the oxacarbenium intermediate **K** furnishes hemiacetal **L**, which on the expulsion of EtOH delivers the α-alkynyl [5,5]-oxaspirolactones **104**. Interestingly, oxaspirolactone **104** possessing aryl substituents on the alkyne terminus, further undergo alkyne hydration reaction to deliver aceto-aryl [5,5]-oxaspirolactones **103** (Path B, Scheme 4.35).

4.8 Conclusion:

In conclusion, the first TfOH-catalyzed divergent access to complex tetrahydro-oxepino-phthalides (comprising formation of 5-new bonds and 3 rings) and regioselective α-aceto-aryl or α-alkynyl [5,5]-oxaspirolactones (through 3-new bonds and 2 rings) is disclosed from readily accessible 4-pentyn-1-ols and α-ynone-esters. The oxepino-phthalides are formed through oxa-Michael/trans-esterification/[2+2+2]-annulation/intramolecular-lactonization cascade, whereas the [5,5]-oxaspirolactones are obtained through 5-*exo*-dig-cycloisomerization /1,2-addition onto the α-ynone-ester/dehydration/lactonization (overall [2+3]-annulation) cascade. Single-crystal X-ray analyses and analogy unambiguously confirmed products. These annulation reactions showed wide substrate scope and were also found to be well reproducible on a gram-scale under optimized reaction conditions. Therefore, we anticipate this methodology will find applications in synthetic organic chemistry of bioactive natural products and medicinal chemistry.

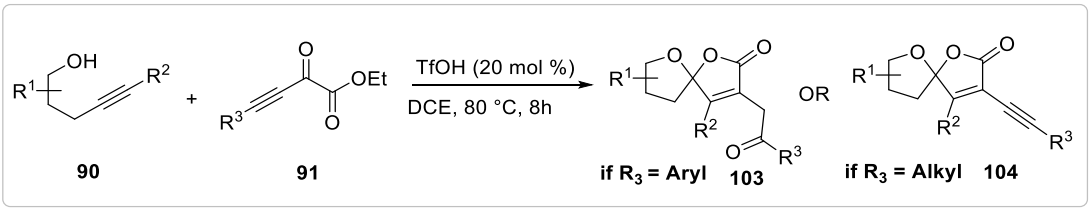
4.9 Experimental procedure:

A) General procedures for the synthesis of tetrahydro oxepino-phthalides



Alkynol **(90) (**0.99 mmol) and α-alkynyl α-ketoester (α-ynone-ester) **91**(0.49 mmol) were taken into a single neck round bottom flask, then dissolved in 5 mL of anhydrous $ClCH_2CH_2Cl$.To that TfOH(0.099 mmol) was added under argon atmosphere at room temperature (rt). The resulting reaction mixture was heated at 80 °C for respective reaction times. After completing the reaction (typically after 8h, monitored by TLC, visualized using UV, anisaldehyde staining solutions) the reaction was quenched with saturated aqueous $NaHCO_3$solution, then extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered through sintered glass funnel. The filtrate was concentrated under reduced pressure and purified using silica-gel column chromatography (100-200 mesh) to afford the corresponding tetrahydro oxepino-phthalides **92**.

B) General procedure for the synthesis of [5,5]-oxaspirolactones.



Alkynol **90 (**0.49 mmol)and α-alkynyl α-ketoester **91**(0.49 mmol) were taken into a single neck round bottom flask, then dissolved in 5 mL of anhydrous $ClCH_2CH_2Cl$. To that TfOH (0.099 mmol) was added under argon atmosphere at room temperature (rt). The resulting reaction mixture was heated at 80 °C for respective reaction times. After completing the reaction (typically after 8h – 12h, monitored by TLC & visualized using UV, anisaldehyde staining solutions) the reaction was quenched with saturated aqueous-$NaHCO_3$solution, then extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered through sintered glass funnel. The filtrate was concentrated under reduced pressure and purified using silica-gel column chromatography (100-200 mesh) to

afford the corresponding [5,5]-oxaspirolactone**103** or **104**.

Synthesis of alkynols (90) and α-alkynyl α-ketoesters (91)

All the alkynols and α-alkynyl α-ketoesters were synthesized using known literature reports (entries A-C, Figure 4.3).

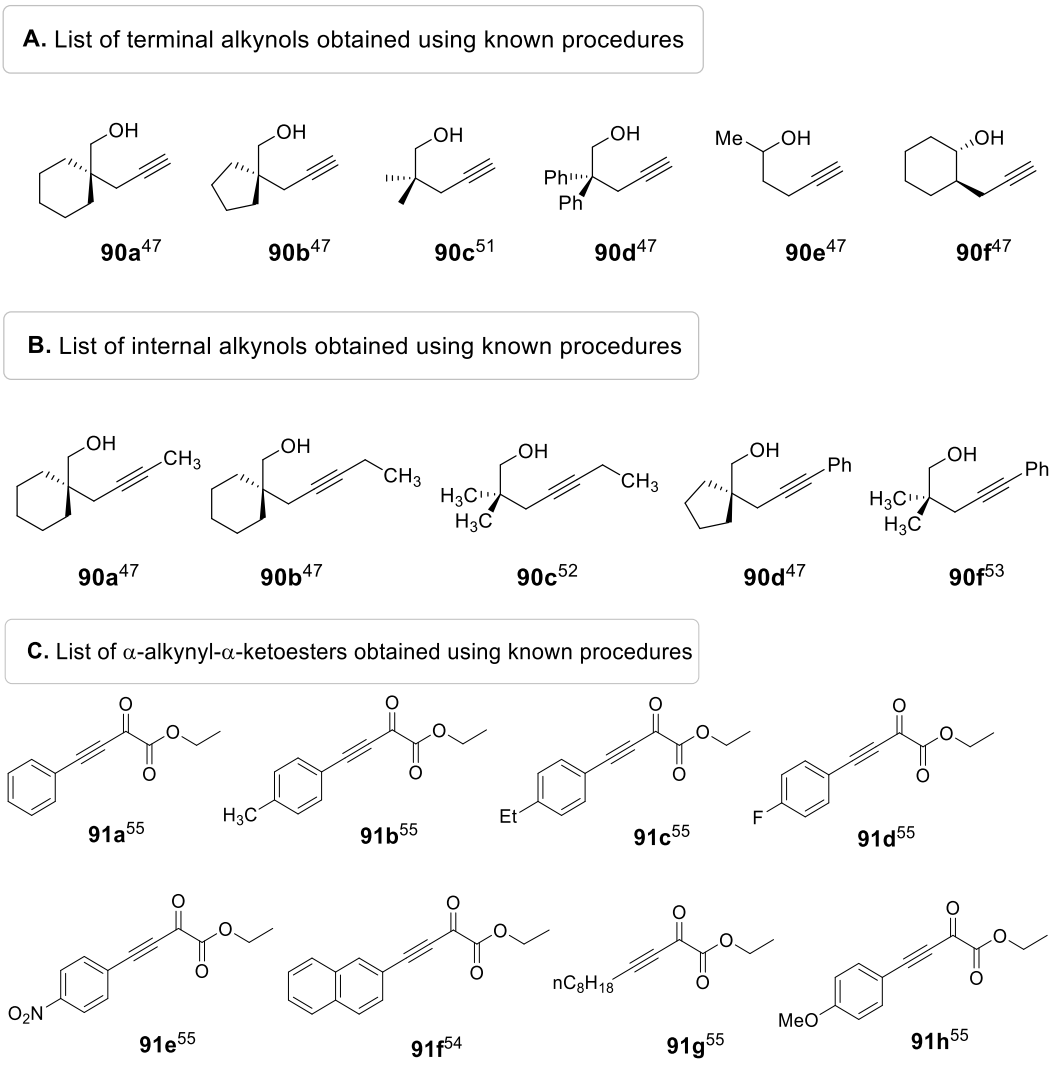
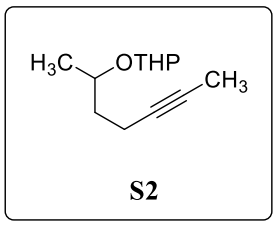


Figure 4.3.Structural details of building blocks

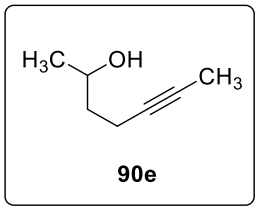
2-(Hept-5-yn-2-yloxy) tetrahydro-2*H*-pyran (S2):



S2

To a solution of 2-((2,2-dimethylpent-4-yn-1-yl)oxy)tetrahydro-2H-pyran[56] (**S1)** (1 g, 5.48 mmol) in anhydrous THF, *n*BuLi (2.5 M in hexane, 5.48 mL, 8.2 mmol) was added at -78 ^{o}C and stirred this reaction mixture for 45 min at -78 ^{o}C under argon atmosphere. Then the solution of CH_3I (0.51 mL, 8.2 mmol) in anhydrous HMPA (1 mL) was added at same temperature and resulting reaction mixture was slowly warmed to room temperature and further stirred for 6 h. Then the reaction mixture was quenched with saturated NH_4Cl solution at 0 ^{o}C and extracted with ethyl acetate (3x25 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Crude product was purified by silica gel chromatography (SiO_2, 2% EtOAc/hexanes) to afford 2-(hept-5-yn-2-yloxy) tetrahydro-2*H*-pyran (S2) (1.43 g, 80%) as a colourless liquid.^{1}H NMR ($CDCl_3$, 400MHz): δ 4.74-4.69 (m, 0.5H), 4.66-4.61 (m, 0.5H), 3.96-3.77 (m, 2H), 3.51-3.42 (m, 1H), 2.29-2.20 (m, 0.5H), 2.18-2.11 (m, 0.5H), 1.86 -1.77 (m, 1H), 1.77-1.72 (m, 3H), 1.71-1.60 (m, 2H), 1.59-1.45 (m, 4H), 1.21 (d, *J* = 6.3 Hz, 1.58H), 1.09 (d, *J* = 6.1 Hz, 1.3H); ^{13}C NMR ($CDCl_3$, 101MHz): δ 99.2, 94.9, 78.9, 78.7, 75.5, 75.3, 73.1, 69.4, 62.7, 61.9, 36.7, 36.0, 31.0, 31.0, 25.5, 25.4, 21.5, 19.9, 19.3, 18.8, 15.3, 14.8, 3.4; HRMS (ESI):*m/z* calcd for $C_{12}H_{20}O_2$ $[M+Na]^+$ 219.1356 found 219.1356.

Hept-5-yn-2-ol (90e):

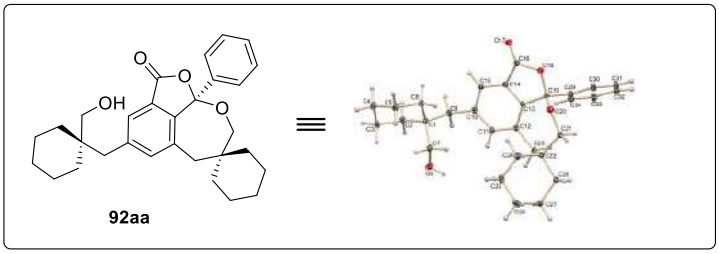


90e

To a solution of 2-(hept-5-yn-2-yloxy) tetrahydro-2*H*-pyran (S2) (1 g, 5 mmol) in methanol was added CSA (0.118 g, 0.5 mmol) at 0 °C and then it was slowly warmed to rt. The resulting reaction mixture was stirred for 6h at rt, and then the methanol was evaporated under reduced pressure, diluted with ethyl acetate and quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3x25 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filtered using a sintered funnel, concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (SiO_2, 10% EtOAc/hexanes) to afford hept-5-yn-2-ol (**90e**) (0.59 g, 85%) as a colorless liquid.^{1}H NMR ($CDCl_3$, 400MHz): δ 4.01-3.85 (m, 1H), 2.31-2.17 (m, 2H), 1.79-1.75 (m, 3H), 1.6-1.54 (m, 2H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101MHz,): δ 78.6, 76.2, 67.3, 37.7, 23.3, 15.4, 3.4; HRMS (ESI): *m/z* calcd for $C_7H_{13}O$ $[M+H]^+$113.0961 found 113.0962.

4.10 Characterization of Data

Compound 92aa:



White solid; Yield = 82%

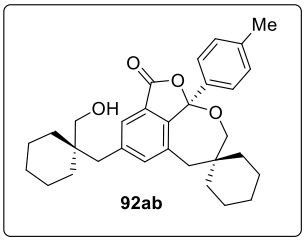
TLC: R_f =0.3 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$,500 MHz): δ 7.64 (s, 1H), 7.43-7.34 (m, 5H), 7.31 (s, 1H), 3.62 (d, *J* = 12.59 Hz, 1H), 3.57-3.49 (m, 1H) 3.33 (s, 2H), 3.04-2.91 (m, 1H), 2.84 (q, *J* = 12.97 Hz, 2H), 2.43 (d, *J* = 13.73 Hz, 1H), 1.86-1.30 (m, 21H).

^{13}C NMR ($CDCl_3$,126 MHz): δ 168.3, 144.8, 143.3, 136.3, 135.4, 129.5, 128.6, 127.1, 126.8, 124.8, 74.8, 67.1, 48.5, 41.8, 37.9, 34.2, 34.0, 33.3, 29.7, 24.5.

HRMS (ESI):*m/z*calcd for $C_{30}H_{37}O_4$ $[M+H]^+$ 461.2686, found 461.2687.

Compound 92ab:



White solid; Yield = 78%

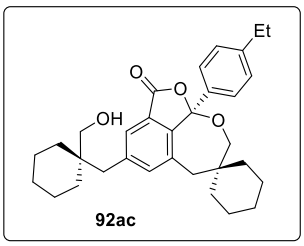
TLC: R_f = 0.2 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$,400 MHz): δ 7.6 (s, 1H), 7.31-7.22(m, 3H), 7.21-7.11(m, 2H), 3.69-3.56(m, 1H), 3.32(s, 2H), 2.80(s, 2H), 2.70-2.61(m, 2H), 2.35(s, 2H), 1.66-1.20(m, 23H).

^{13}C NMR ($CDCl_3$,101 MHz): δ 168.4, 145.0, 142.4, 139.5, 136.8, 136.7, 134.5, 129.6, 129.3, 128.1, 127.1, 126.6, 125.0, 66.5, 41.1, 38.6, 32.5, 32.3, 31.6, 31.1, 28.6, 26.3, 26.1, 22.7, 21.6, 21.4, 21.2, 21.0, 15.3, 14.1.

HRMS (ESI):*m/z* calcd for $C_{31}H_{39}O_4$ $[M+H]^+$ 475.2843, found 475.2856.

Compound 92ac:



White solid; Yield = 75%

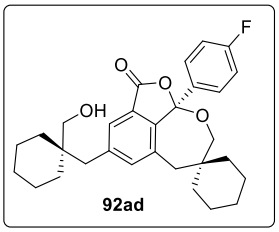
TLC: R_f = 0.2 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$,400 MHz): δ 7.70-7.48 (m, 1H), 7.4-7.3 (m, 3H), 7.3-7.05(m, 2H), 3.68-3.48 (m, 1H), 3.31 (s, 2H), 2.78 (s, 2H), 2.8-2.5 (m, 3H), 2.33 (s, 2H), 1.62-1.08 (m, 22H), 1.0-0.82 (m, 2H).

^{13}C NMR ($CDCl_3$,101 MHz): δ 168.6, 145.9, 145.0, 142.5, 136.9, 134.6, 129.4, 128.2,

127.1, 126.7, 125.1, 66.5, 41.2, 38.7, 32.5, 32.3, 31.7, 28.6, 26.4, 26.1, 22.7, 21.7, 21.5, 21.3, 15.4. **HRMS (ESI):** *m/z* calcd for $C_{32}H_{41}O_4$ $[M+H]^+$ 489.2999, found 489.3003.

Compound 92ad:



92ad

White solid; Yield = 76%

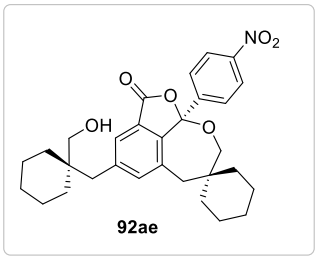
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz):δ7.67-7.57 (m, 1H), 7.43-7.28 (m, 3H), 7.13-6.96 (m, 2H), 3.67-3.52 (m, 1H), 3.33 (s, 2H), 2.81 (s, 2H), 2.73-2.55 (m, 2H), 1.65-1.54 (m, 3H), 1.53-142(m, 9H), 1.38-1.30 (m, 7H), 1.02-0.88 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz):δ168.2, 164.2, 162.2, 144.4, 142.8, 136.9, 134.4, 128.6, 127.1, 125.2, 115.7, 115.5, 66.4, 41.2, 38.7, 35.8, 32.5, 32.3, 31.9, 31.0, 29.7, 26.3, 26.0, 25.8, 21.6, 21.4, 21.0.

HRMS (ESI):*m/z* calcd for $C_{30}H_{36}O_4F$ $[M+H]^+$ 479.2592 found 479.2596.

Compound 92ae:



92ae

White crystalline solid; Yield =80%

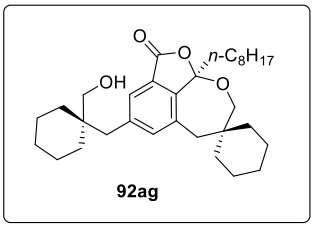
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz):δ 8.22 (d, *J* = 19.13 Hz, 2H), 7.66 (s, 1H), 7.57 (d, *J* = 8.76 Hz, 2H), 7.31 (s, 1H), 3.71-3.58 (m, 1H), 3.32 (s, 2H), 2.82 (s, 2H), 2.75-2.60 (m, 1H), 2.58-2.46 (m, 1H), 1.54-1.25(m, 19H), 0.99-0.92 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.9, 148.4, 137.0, 127.6, 127.1, 125.6, 123.9, 66.4, 41.2, 38.7, 32.5, 32.3, 31.0, 26.3, 26.0, 21.6, 21.4, 21.1.

HRMS (ESI):*m/z* calcd for $C_{30}H_{36}O_6N$ $[M+H]^+$ 506.2537 found 506.2544.

Compound 92ag:



92ag

White solid; Yield = 61%

TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

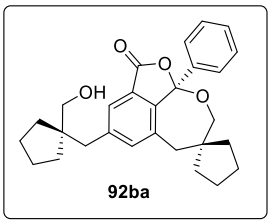
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (s, 1H), 7.19 (s, 1H), 3.63-3.48 (m, 1H), 3.3 (s, 2H), 2.86 (d, *J* = 13.88 Hz, 1H), 2.76 (s, 2H), 2.71-2.64 (m, 1H), 2.34-2.22 (m, 2H), 2.01-1.90 (m, 1H), 1.64-1.2

(m, 34H), 0.9-0.82 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.8, 142.2, 136.2, 133.4, 125.0, 66.5, 38.6, 32.5, 31.8, 29.5, 29.3, 29.1, 26.3, 26.1, 22.6, 21.6, 21.5, 14.1.

HRMS (ESI):*m/z* calcd for $C_{32}H_{48}O_4$ $[M+Na]^+$ 519.3445, found 519.3442.

Compound 92ba:



White crystalline solid; Yield = 77%

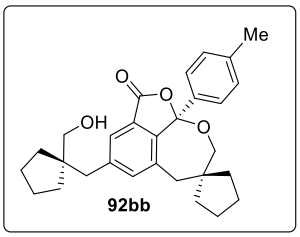
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 500 MHz):δ7.66 (s, 1H), 7.44-7.34 (m, 5H), 7.33 (s, 1H), 3.64 (d, *J* =12.59 Hz, 1H), 3.5(br. s., 1H), 3.35 (s, 2H), 3.05-2.91 (m, 1H), 2.85 (q, *J* = 13.35 Hz, 2H), 2.46 (d, *J* = 14.11 Hz), 1.71-1.44 (m, 19H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.3, 144.8, 143.3, 136.4, 129.5, 128.7, 127.1, 126.9, 124.9, 67.2, 48.6, 41.8, 38.0, 34.2, 34.1, 33.3, 24.5.

HRMS (ESI):*m/z* calcd for $C_{28}H_{33}O_4$$[M+H]^+$ 433.2373 found 433.2374.

Compound 92bb:



White crystalline solid; Yield = 75%

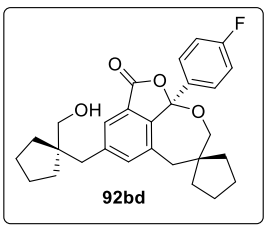
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.58 (m, 1H), 7.32-7.27 (m, 1H), 7.26-7.21 (m, 2H), 7.19-7.13 (m, 2H), 3.62 (d, *J* = 12.76 Hz, 1H), 3.46 (br. s. 1H), 3.32 (s, 2H), 3.04-2.91 (m, 1H), 2.88-2.73 (m, 2H), 2.47-2.38 (m, 1H), 2.36 (s, 3H), 1.70-1.43 (m, 16)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.0, 148.3, 147.4, 129.3, 127.1, 126.8, 124.8, 67.2, 48.5, 41.8, 37.9, 34.2, 34.1, 33.3, 31.6, 24.5, 22.7, 21.3, 18.4, 14.1.

HRMS (ESI):*m/z* calcd for $C_{29}H_{35}O_4$ $[M+H]^+$ 447.2530 found 447.2526.

Compound 92bd:



White crystalline solid; Yield = 80%

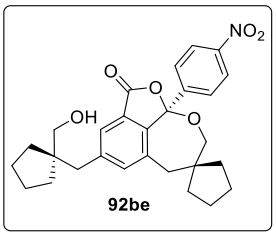
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.48 (m, 2H), 7.40-7.28 (m, 2H), 7.05 (t, *J* = 8.63 Hz, 2H), 3.63-3.52 (m, 1H), 3.32 (s, 2H), 2.85 (q, *J* = 13.13 Hz, 2H), 2.53-2.38 (m, 1H), 1.78-1.42 (m, 17H), 1.31-1.22 (m, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ167.7, 164.5, 162.1, 144.5, 143.6, 136.4, 132.4, 131.5, 130.9, 128.8, 127.1, 125.0, 115.8, 115.5, 71.8, 67.2, 48.6, 41.8, 38.0, 34.5, 34.2, 34.1, 33.3, 30.6, 29.7, 27.7, 24.5, 24.3, 22.7, 19.2, 14.1, 13.7

HRMS (ESI):*m/z* calcd for $C_{28}H_{32}O_4F$ $[M+H]^+$ 451.2279 found 451.2290.

Compound 92be:



White crystalline solid; Yield = 82%

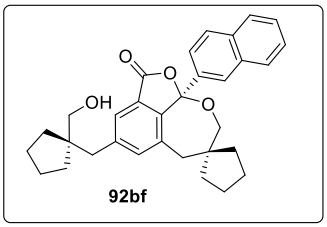
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88 (m, 2H), 7.81-7.89 (m, 1H), 7.63-7.50 (m, 2H), 7.40-7.32 (m, 1H), 3.61-3.50 (m, 1H), 3.42-3.36 (m, 2H), 2.92-279 (m, 2H), 2.47 (d, *J* = 14.13 Hz, 1H), 2.15-2.06 (m, 1H), 1.73-1.42 (m, 16H);

^{13}C NMR ($CDCl_3$, 101 MHz): δ167.8, 148.5, 144.4, 143.5, 136.5, 135.4, 132.4, 130.9, 128.9, 127.8, 127.0, 125.3, 123.9, 74.8, 71.8, 67.1, 60.4, 58.5, 48.6, 41.8, 38.1, 34.2, 34.1, 27.7, 24.5, 24.4, 19.2, 18.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{31}O_6N$ $[M+Na]^+$ 500.2044 found 500.2045.

Compound 92bf:



White Solid; Yield = 73%

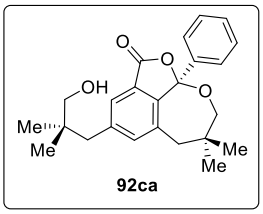
TLC: R_f= 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.91-7.83 (m, 2H), 7.79-7.72 (m, 1H), 7.68-7.60 (m, 2H), 7.55-7.47 (m, 2H), 7.39-7.32 (m, 1H), 3.73-3.60 (m, 1H), 3.41-3.28 (m, 2H), 3.10-2.95 (m, 1H), 2.93-2.77 (m, 2H), 1.75-1.47 (m, 16H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.7, 148.3, 147.4, 145.5, 133.7, 132.7, 128.9, 128.5, 127.7, 127.3, 127.0, 126.5, 126.5, 125.0, 124.1, 67.2, 48.6, 41.8, 34.2, 34.1, 33.3, 31.9, 31.6, 24.5, 22.7, 14.1.

HRMS (ESI): *m/z* calcd for $C_{32}H_{35}O_4$ $[M+H]^+$ 483.2530 found 483.2538.

Compound 92ca:



White solid: Yield = 80%

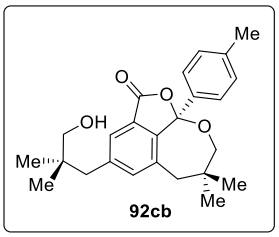
TLC: R_f= 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (s, 1H), 7.45-7.30 (m, 5H), 7.23 (s, 1H), 3.55 (d, *J* = 12.76 Hz, 1H), 3.33 (s, 2H), 2.93-2.81 (m, 1H), 2.73 (q, *J* = 13.01 Hz, 2H), 2.38-2.26 (m, 1H), 1.74-1.58 (m, 2H), 1.30-1.23 (m, 2H), 1.10-0.99 (m, 2H), 0.95-0.88 (m, 6H), 0.66 (s, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.2, 144.6, 144.5, 142.8, 136.7, 129.5, 128.6, 127.2, 126.6, 125.1, 70.6, 44.1, 36.5, 27.7, 24.0, 23.9, 23.1.

HRMS (ESI): *m/z* calcd for $C_{24}H_{29}O_4$ $[M+H]^+$ 381.2060 found 381.2067.

Compound 92cb:



White crystalline solid: Yield = 75%

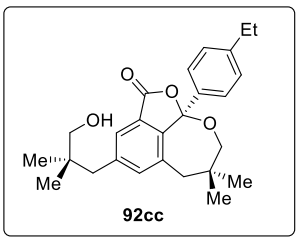
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (s, 1H), 7.29-7.14 (m, 5H), 3.60-3.47 (m, 1H), 3.33 (s, 2H), 2.95-2.81 (m, 1H), 2.73 (q, *J* = 13.01 Hz, 2H), 2.47-2.39 (m, 1H), 2.36 (s, 3H), 2.34-2.26 (m, 1H), 1.32-1.22 (m, 2H), 1.09-1.98 (m, 2H), 0.95-0.78 (m, 6H), 0.65 (s, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.3, 144.8, 142.6, 139.5, 136.5, 129.6, 129.3, 128.1, 127.2, 126.6, 125.0, 97.9, 70.6, 62.6, 58.5, 44.1, 36.5, 27.7, 24.0, 23.9, 23.1, 21.2, 18.4.

HRMS (ESI): *m/z* calcd for $C_{25}H_{31}O_4$ $[M+H]^+$ 395.2217 found 395.2228.

Compound 92cc:



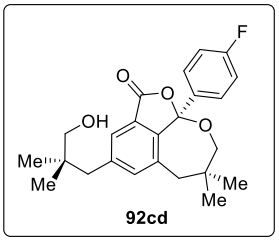
White solid: Yield = 72%

TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (s, 1H), 7.39-7.31 (m, 2H), 7.16 (s, 1H), 7.09-7.03 (m, 2H), 3.98 (s, 0.5H), 3.80 (s, 2H), 3.54-3.50 (m, 1H), 2.88-2.77 (m, 2H), 2.73 (s, 2H), 2.34-2.28 (m, 1H), 2.14 (s, 3H), 1.28-1.23 (m, 2H), 1.08-1.01 (m, 4H), 0.95 (s, 6H), 0.65 (m, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.0, 167.9, 164.5, 162.0, 158.0, 144.5, 142.2, 136.5, 128.6, 127.3, 125.2, 115.8, 115.6, 73.5, 71.4, 63.2, 44.8, 44.6, 35.3, 35.1, 27.7, 24.3, 24.2, 23.0, 21.0, 14.0.

Compound 92cd:



92cd

White crystalline solid; Yield =78%

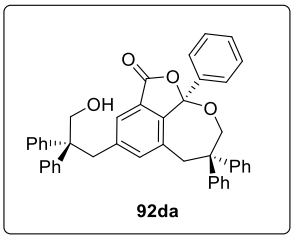
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 7.26-7.11 (m, 5H), 3.60-3.47(m, 1H), 3.32(s, 2H), 2.95-2.81 (m, 1H), 2.27 (q, *J* = 13.01Hz, 2H), 2.43-2.25 (m, 4H), 2.36-2.35 (s, 2H)1.77 (br.s, 1H), 1.30-1.20 (m, 2H), 0.93-0.86 (m, 6H), 0.67-0.62 (m, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.4, 144.8, 142.7, 139.5, 136.6, 129.3, 127.1, 126.6, 125.0, 70.5, 60.4, 58.5, 44.1, 36.6, 36.5, 27.7, 24.7, 24.0, 23.9, 23.1, 21.2, 18.4, 14.1.

HRMS (ESI): *m/z* calcd for $C_{24}H_{28}O_4F$ $[M+H]^+$ 399.1966 found 399.1958.

Compound 92da:



92da

White crystalline solid; Yield = 71%

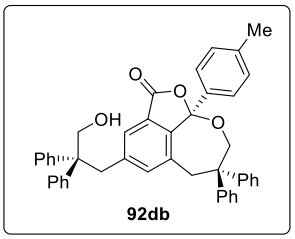
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-6.88 (m, 25H), 4.61-4.29 (m, 1H), 4.21-3.99 (m, 1H), 3.94-3.64 (m, 3H), 3.64-3.51 (m, 1H), 3.44 (d, *J* = 14.13 Hz, 1H), 3.23-3.02 (m, 1H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.3, 148.4, 146.4, 145.1, 144.6, 144.0, 141.2, 137.7, 129.9, 128.9, 128.5, 128.3, 128.2, 128.1, 127.5, 126.9, 126.9, 65.9, 53.1, 41.1, 31.6, 22.7.

HRMS (ESI): *m/z* calcd for $C_{44}H_{36}O_4$ $[M+Na]^+$ 651.2606 found 651.2520.

Compound 92db:



92db

White solid; Yield = 73%

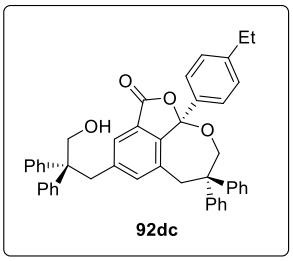
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-6.91 (m, 24H), 6.57-6.33 (m, 2H), 4.46 (br. s, 1H), 4.26-3.96 (m, 1H), 3.91-3.66 (m, 3H), 3.64-3.50 (m, 1H), 3.43 (d, *J* = 14.13 Hz, 1H), 3.24-3.05 (m, 1H), 2.36 (s, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.4, 146.4, 145.1, 144.8, 144.1, 141.0, 139.9, 137.7, 129.6, 128.5, 128.4, 128.1, 127.5, 126.9, 126.8, 126.3, 125.4, 65.9, 53.0, 41.1, 21.3.

HRMS (ESI): *m/z* calcd for $C_{45}H_{38}O_4$ $[M+Na]^+$ 665.2662 found 643.2770.

Compound 92dc:



White solid: Yield = 73%

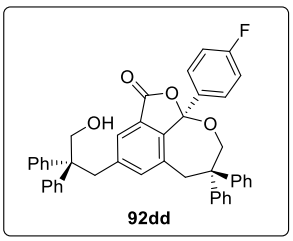
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-6.91 (m, 24H), 6.62-6.30 (m, 2H), 4.16-4.65 (m, 4H), 3.61-3.06 (m, 3H), 2.44 (s, 1H), 2.42-2.37(m, 1H), 2.36 (s, 2H), 1.60-1.54 (m, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.4, 145.1, 144.1, 129.7, 129.6, 128.5, 128.4, 128.1, 127.5, 126.9, 126.8, 125.4, 97.9, 65.9, 62.6, 53.1, 41.1, 21.8, 21.3, 14.1.

HRMS (ESI): *m/z* calcd for $C_{46}H_{41}O_4$ $[M+H]^+$ 657.2999 found 657.3008.

Compound 92dd:



White crystalline solid: Yield = 75%

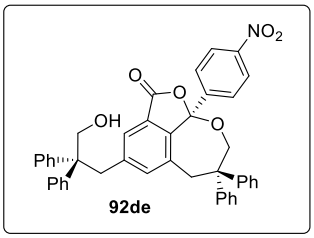
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-6.98 (m, 24H), 6.58-6.39 (m, 2H), 4.44 (br. s. 1H), 4.20-3.91 (m, 1H), 3.88-3.69 (m, 3H), 3.65-3.50 (m, 1H), 3.46 (d, *J* = 14.13 Hz, 1H), 3.24-3.07 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.1, 164.7, 162.2, 146.2, 145.0, 144.3, 144.0, 143.9, 141.4, 137.8, 128.9, 128.5, 128.4, 128.2, 128.0, 127.4, 125.9, 125.6, 116.1, 115.8, 65.9, 53.0, 41.1.

HRMS (ESI): *m/z* calcd for $C_{44}H_{35}O_4F$ $[M+Na]^+$ 669.2412 found 669.2416.

Compound 92de:



White solid; Yield = 76%

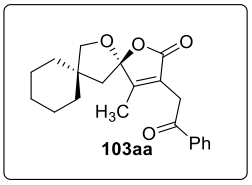
TLC: R_f = 0.3 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23-8.16 (m, 1H), 7.60-7.39 (m, 2H), 7.37-7.08 (m, 19H), 7.0-6.76 (m, 2H), 6.38-6.45 (m, 2H), 4.10-3.91 (m, 1H), 3.84-3.67 (m, 2H), 3.65-3.47 (m, 2H); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 166.8, 155.1, 149.7, 148.6, 144.9, 144.0, 143.7, 143.4, 138.0, 133.7, 132.4, 128.8, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.4, 127.0, 126.9, 126.5, 126.0, 124.1, 65.9, 53.0, 41.2.

HRMS (ESI): *m/z* calcd for $C_{44}H_{36}O_6N$ $[M+H]^+$ 674.2537 found 674.2540.

Synthesis of [5,5]-oxaspirolactone:

Compound 103aa:



White crystalline solid; Yield = 80%

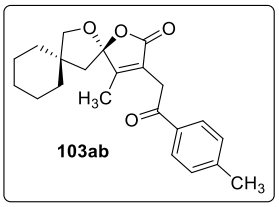
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07-7.96 (m, 2H), 7.64-7.54 (m, 1H), 7.53-7.42 (m, 2H), 4.06 (d, *J* = 16.88 Hz, 1H), 4.0 (d, *J* = 8.50 Hz, 1H), 3.89 (d, *J* = 8.38 Hz, 1H), 3.84 (d, *J* = 16.26 Hz, 1H), 2.13 (d, J = 1H), 2.05(d, *J* = Hz, 1H), 1.96 (s, 3H), 1.76-1.67 (m, 2H), 1.56-1.41 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.4, 170.8, 159.5, 136.1, 133.6, 128.8, 128.5, 123.7, 114.9, 80.9, 45.9, 43.5, 37.4, 35.6, 33.4, 25.6, 23.8, 23.7, 11.2.

HRMS (ESI): *m/z* calcd for $C_{21}H_{25}O_4$ $[M+H]^+$ 341.1747 found 341.1757.

Compound 103ab:



White crystalline solid; Yield = 76%

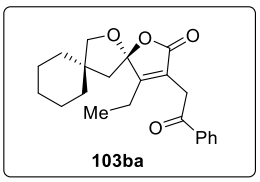
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J = 8.25Hz, 2H), 7.27(d, J = 7.38 Hz, 2H), 4.04 (d, J = 16.88Hz, 1H), 4.0(d, J = 8.38 Hz, 1H), 3.89 (d, J = 8.50 Hz, 1H), 3.81 (d, J = 16.38Hz, 1H), 2.42 (s, 3H), 2.09 (dd, J = 13.88, 30.64 Hz, 2H), 1.95 (s, 1H), 1.75-1.67 (m, 2H), 1.54-1.43 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.0, 170.9, 159.4, 144.5, 133.6, 129.4, 128.6, 123.8, 114.8,43.5, 37.4, 35.6, 33.3, 25.5, 23.8, 23.7, 21.7, 11.2.

HRMS (ESI): *m/z* calcd for $C_{22}H_{26}O_4$ $[M+Na]^+$ 377.1723 found 377.1719.

Compound 103ba:



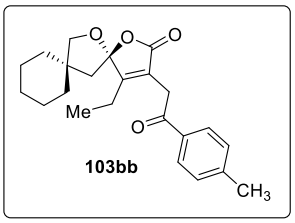
White solid: Yield = 75%

TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59-7.45 (m, 2H), 7.43-7.28 (m, 3H), 4.01 (d, *J* = 8.50 Hz, 1H), 3.89 (d, *J* = 8.50 Hz, 1H), 2.64-2.53 (m, 1H), 2.51-2.39 (m, 1H), 2.09 (q, *J* = 13.88 Hz, 2H), 1.74-1.69 (m, 2H), 1.55-1.42 (m, 8H), 1.36 (t, *J* = 7.63 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.9, 167.7, 131.9, 129.2, 128.4, 122.0, 115.2, 98.8, 81.0, 78.3, 43.5, 37.5, 35.6, 25.5, 23.9, 23.7, 20.7, 19.2, 11.8

Compound 103bb:



White solid; Yield =72%

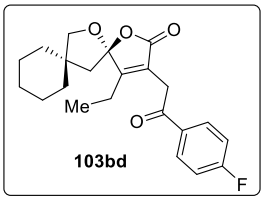
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.86 (m, 2H), 7.31-7.21 (m, 2H), 4.06-3.96 (m, 2H), 3.92-3.84(m, 2H), 2.48-2.42(m, 1H), 2.41(s, 3H), 2.36-2.24 (m, 1H), 2.11 (q, *J* = 13.88 Hz, 2H), 1.74.1.66 (m, 2H), 1.55-1.40 (m, 8H), 1.14 (t, *J* = 7.63 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.1, 171.1, 163.3, 144.4, 133.7, 129.4, 128.5, 123.9, 115.3, 80.8, 46.2, 43.3, 37.6, 35.7, 33.4, 25.5, 23.9, 23.7, 21.7, 19.4, 12.1.

HRMS (ESI): *m/z* calcd for $C_{23}H_{29}O_4$ $[M+H]^+$ 369.2060 found 389.2061.

Compound 103bd:



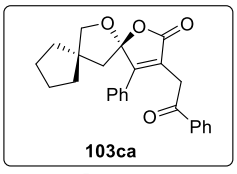
White solid: Yield = 74%

TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12-7.96 (m, 2H), 7.22-7.04 (m, 2H), 4.05-3.96 (m, 2H), 3.92.3.84 (m, 2H), 2.49-2.37 (m, 1H), 2.36-2.24 (m, 1H), 2.11 (q, *J* = 13.76Hz, 2H), 1.75-1.68 (m, 2H), 1.56-1.43 (m, 8H), 1.15 (t, *J* = 7.63 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 193.1, 171.0, 167.3, 164.7, 163.6, 132.6, 132.1, 123.6, 116.0, 115.8, 115.4, 80.1, 46.2, 43.4, 37.6, 35.7, 35.1, 33.4, 25.5, 23.9, 23.7, 22.8, 19.4, 12.1.

Compound 103ca:



White solid; Yield = 70%

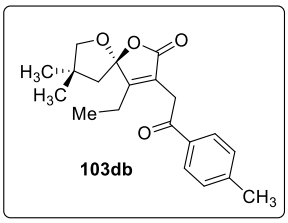
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-7.93 (m, 2H), 7.62-7.39 (m, 8H), 4.21 (d, *J* = 17.26 Hz, 1H), 4.14 (d, *J* = 8.13Hz, 1H), , 3.92 (d, *J* = 8.13Hz, 1H), 3.84 (d, *J* = 17.39Hz, 1H), 2.27 (d, *J* = 13.51Hz, 1H), 2.10 (d, *J* = 13.63Hz, 1H), 1.90 (t, *J* = 7.13Hz, 2H), 1.71-1.67 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.2, 170.6, 158.9, 136.2, 133.6, 130.6, 130.0, 128.9, 128.8, 128.7, 128.3, 128.0, 127.9, 125.4, 115.5, 81.7, 78.5, 50.1, 47.2, 41.3 37.7, 37.5, 36.8, 34.6, 24.7, 24.2.

HRMS (ESI): *m/z* calcd for $C_{25}H_{25}O_4$ $[M+H]^+$ 389.1749 found 389.1747

Compound 103cb:



White solid; Yield = 75%

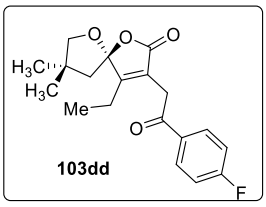
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 8.25 Hz, 2H), 7.27 (d, *J* = 8Hz, 2H), 4.02 (d, *J* = 16.88Hz, 1H), 3.95 (d, *J* = 8.25Hz, 1H), 3.88 (d, *J* = 16.88 Hz, 1H), 3.79 (d, *J* = 8.25Hz, 1H), 2.49-2.42(m, 1H), 2.41(s, 3H), 2.36-2.23 (m, 1H), 2.17 (m, 1H), 2.09 (m,1H), 1.32(s, 3H), 1.21(s, 3H), 1.15 (t, *J* = 7.75Hz, 3H);

^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.1, 171.0, 163.3, 144.4, 133.6, 129.3, 128.5, 123.8, 115.7, 82.5, 48.4, 39.1, 33.3, 28.0, 26.5, 21.6, 19.3, 12.0.

HRMS (ESI): *m/z* calcd for $C_{20}H_{25}O_4[M+H]^+$ 329.1747 found 329.1745.

Compound 103cd:



White solid: Yield = 80%

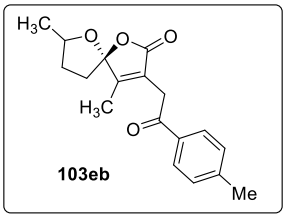
TLC: R_f = 0.4 (SiO_2, 20% EtOAc /hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-7.96 (m, 2H), 7.24-7.01 (m, 2H), 4.01 (d, *J* = 16.76 Hz, 1H), 3.96 (d, *J* = 8.25 Hz, 1H), 3.88 (d, *J* = 16.76 Hz, 1H), 3.80 (d, *J* = 8.25 Hz, 1H), 2.51-2.38 (m, 1H), 2.37-2.25(m, 1H), 2.13 (dd, J = 13.76, 31.89 Hz, 2H) 1.33 (s, 3H), 1.22 (s, 3H), 1.16 (t, *J* = 7.63Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 193.0, 171.0, 167.3, 164.7, 163.7, 132.5, 131.1, 123.5, 116.0, 115.8, 82.6, 48.4, 39.2, 33.4, 28.1, 26.6, 19.4, 12.1.

HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_4F$ $[M+H]^+$ 333.1797 found 333.1501.

Compound 103fb:



Colorless liquid; Yield = 65%

TLC: R_f = 0.4 ($Si0_2$, 20% EtOAc/Hexanes)

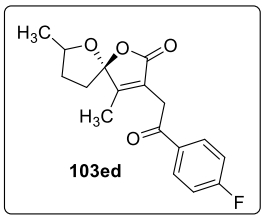
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, *J* = 8.13Hz, 2H), 7.27(d, *J* = 8Hz, 2H), 4.63-4.50 (m, 0.5H), 4.45-4.38 (m, 0.5H), 4.07-4.0 (m, 1H), 3.84-3.78 (m, 1H), 2.42(m, 3H), 2.37-2.05 (m, 4H), 1.95 (d, *J* = 3.75Hz, 3H), 1.40 (d, *J* = 6.13Hz, 1.5H), 1.29(d, *J* = 6.25Hz, 1.5H);

^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.1, 170.9, 159.4, 159.3, 144.5, 133.6, 130.9, 129.4,

128.8, 128.6, 124.1, 123.8, 114.4, 114.2, 80.2, 78.1, 35.7, 33.6, 33.3, 32.2, 31.7, 22.0, 21.7, 21.0, 19.2, 11.2, 11.1.

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_4$ $[M+Na]^+$ 301.1434 found 301.1431.

Compound 103fd:



Colorless liquid; Yield = 70%

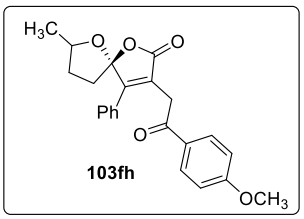
TLC: R_f = 0.4 ($Si0_2$, 20% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11-8.0 (m, 2H), 7.21-7.08 (m, 2H), 4.65-4.48 (m, 0.5H), 4.47-4.39 (m, 0.5H), 4.02 (d, *J* = 16.51Hz, 1H), 3.81 (d, *J* = 16.63 Hz, 2H), 2.53-2.08 (m, 4H), 1.97 (s, 3H), 1.41 (d, *J* = 6.13 Hz, 1.61H), 1.30 (d, *J* = 6.25 Hz, 1.62 H);

^{13}C NMR ($CDCl_3$, 101 MHz): δ 193.0, 170.8, 167.3, 164.8, 159.7, 159.6, 132.5, 131.3, 131.2, 123.7, 123.4, 116.0, 115.8, 114.5, 114.3, 80.3, 78.2, 35.7, 33.6, 33.3, 32.2, 31.7, 22.0, 21.0, 11.2, 11.1.

HRMS (ESI): *m/z* calcd for $C_{17}H_{18}O_4F$ $[M+Na]^+$ 305.1184 found 305.1178 .

Compound 103fh:



Colorless liquid; Yield = 68%

TLC: R_f = 0.4 (Si02, 20% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02-7.86 (m, 2H), 7.61-7.50 (m, 2H), 3.40-3.30 (m, 3H), 7.0-6.87 (m, 2H), 4.73-4.54 (m, 0.5H), 4.49-4.40 (0.61H), 3.88 (s, 3H), 3.84-3.75 (m, 1H), 2.50-2.23 (m, 2H), 2.20-1.99 (m, 2H), 1.48 (d, *J* = 6Hz, 1.5H), 1.34 (d, J = 6.13 Hz);

^{13}C NMR ($CDCl_3$, 101 MHz): δ 193.7, 170.7, 163.9, 158.2, 130.7, 129.9, 129.3, 128.8, 128.7, 128.1, 128.0, 113.9, 80.4, 78.5, 55.6, 36.7, 34.5, 34.2, 32.2, 31.5, 21.9, 21.0.

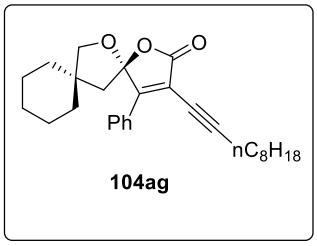
HRMS (ESI): *m/z* calcd for $C_{23}H_{23}O_5$ $[M+Na]^+$ 379.1540 found 379.1536.

Compound 104ag:

Colorless liquid; Yield = 80%

TLC: R_f = 0.4 ($Si0_2$, 20% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-7.93 (m, 2H), 7.51-7.43 (m, 3H), 4.14 (d, *J* = 8.63 Hz, 1H), 4.06 (d, *J* = 8.63 Hz, 1H), 2.55-2.41 (m, 2H), 2.12 (d, *J* = 13.76 Hz, 1H), 2.01 (d, *J* =

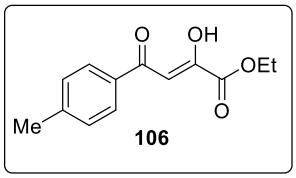


104ag

2.01 Hz, 1H), 1.82-1.69 (m, 2H), 1.66-1.56 (m, 5H), 1.55-1.35 (m, 11H), 1.33-1.23 (m, 10 H), 0.88 (t, *J* = 6.75 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.0, 157.2, 130.8, 130.2, 128.6, 128.3, 115.3, 114.1, 102.6, 71.7, 443.3, 38.1, 36.1, 31.8, 29.2, 29.1, 28.9, 28.2, 25.4, 24.1, 23.6, 22.7, 20.0, 14.1.

Compound 106:



106

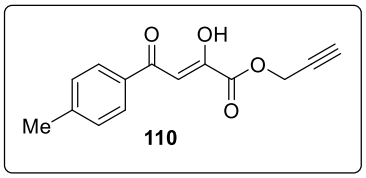
Colorless liquid;Yield: 76%

TLC: R_f = 0.6 ($Si0_2$, 20% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 15.32 (b. s. 1 H) 7.89 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.05 (s, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.43 (s, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ 190.8, 169.2, 162.3, 145.0, 132.3, 129.6, 128.0, 97.9, 77.3, 76.7, 62.5, 21.8, 14.1.

Compound 110:



110

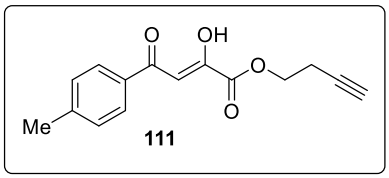
Colorless liquid; Yield: 40%

TLC: R_f= 0.5 ($Si0_2$, 20% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ15.25 (br. s. 1 H), 7.91 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.09 (s, 1 H), 4.93 (d, *J* = 2.5 Hz, 2 H), 2.57 (t, *J* = 2.4 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ 191.0, 167.7, 161.6, 145.2, 132.2, 129.7, 128.1, 98.4, 77.3, 77.0, 76.7, 76.1, 53.6, 21.8.

Compound 111:



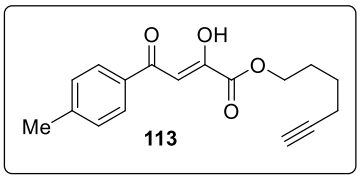
111

Colorless liquid; Yield: 50%

TLC: R_f = 0.5 ($Si0_2$, 20% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 400MHz): δ 15.35 (br.s., 1 H), 7.93 - 7.85 (m, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.08 (s, 1 H), 4.43 (td, *J* = 7.0, 14.2 Hz, 2 H), 2.69 (dq, *J* = 2.7, 6.9 Hz, 2 H), 2.50 - 2.35 (m, 3 H), 2.11 - 1.98 (m, 1 H)

Compound 113:



113

Colorless liquid; Yield: 75%

TLC: R_f = 0.6 ($Si0_2$, 20% EtOAc/Hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 15.38 (br. s., 1 H), 7.90 (d, *J* = 8.3 Hz, 2 H), 7.31 (d,*J* = 8.0, 2H), 7.05 (s, 1 H), 4.44-4.27 (m, 2 H), 2.44 (s, 3 H), 2.35-2.20(m, 2H), 2.0-1.84 (m, 3H), 1.72-1.63 (m, 2H), 1.45-1.35 (m, 1H).

^{13}C NMR ($CDCl_3$, 101MHz): δ 190.8, 169.0, 162.4, 145.0, 132.3, 129.6, 128.0, 97.9, 83.6, 69.0, 66.0, 27.4, 24.8, 21.8, 18.1.

4.11 References:

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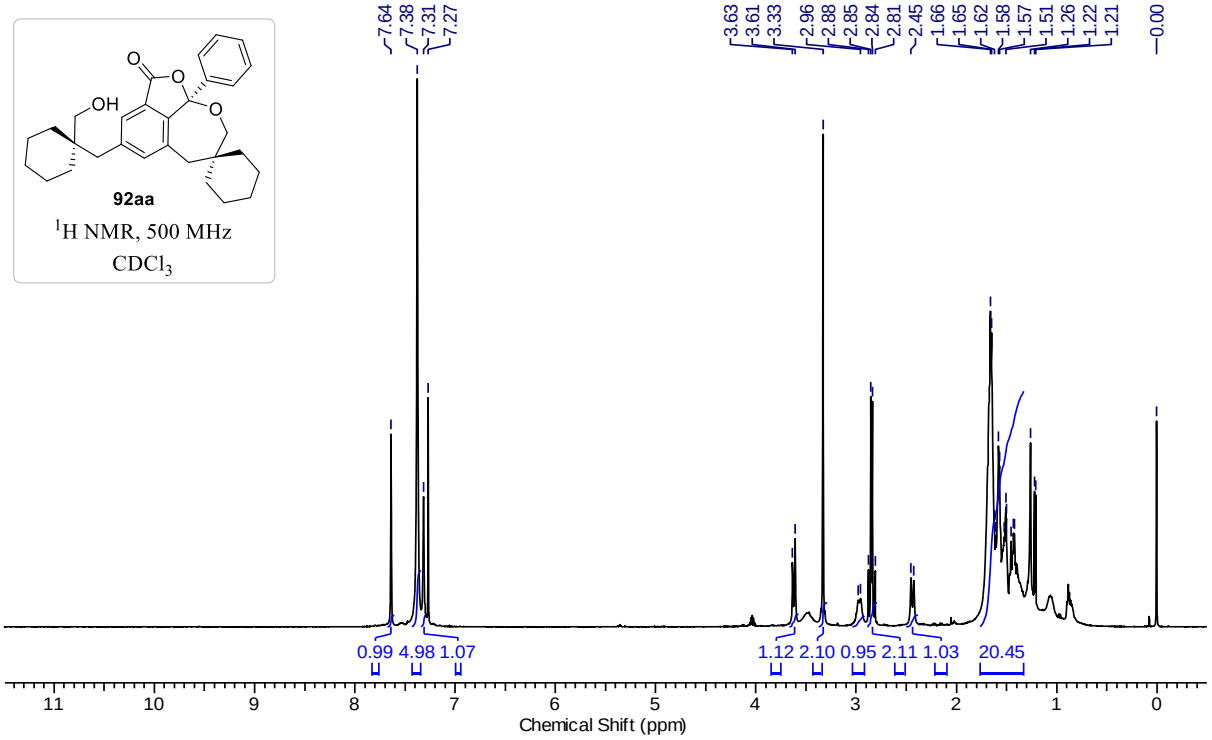
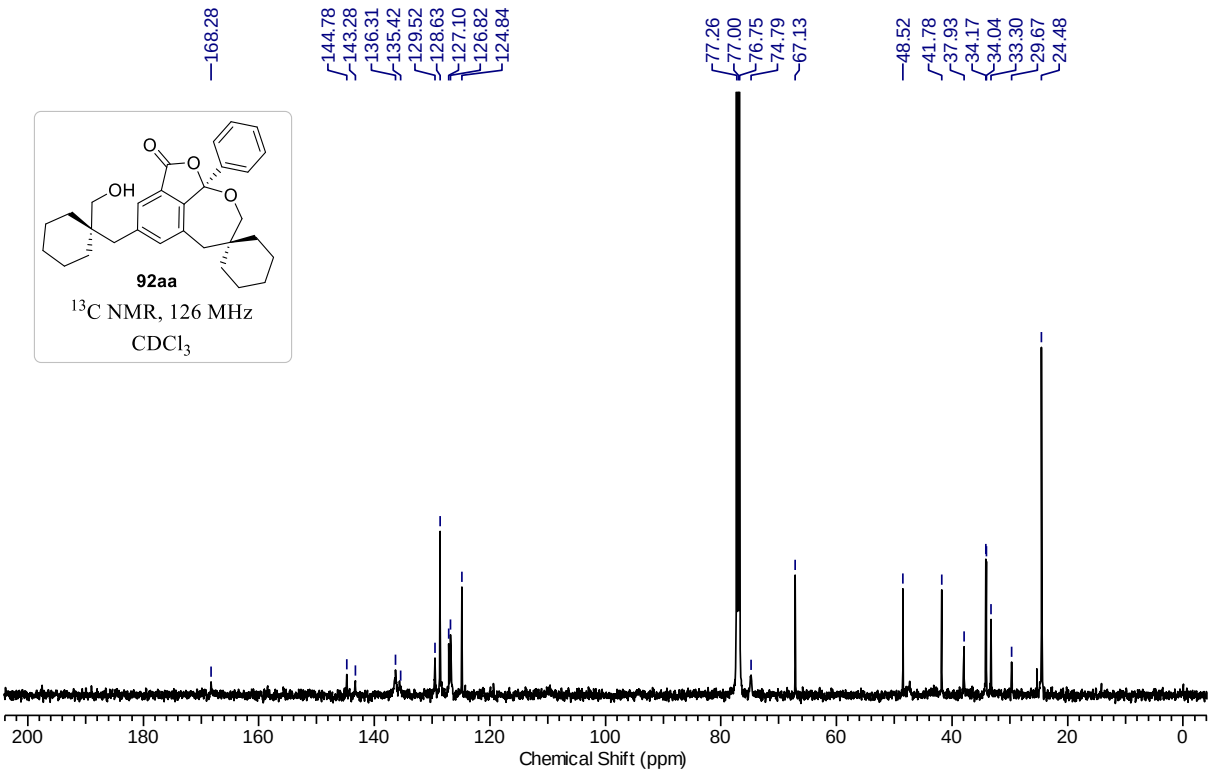
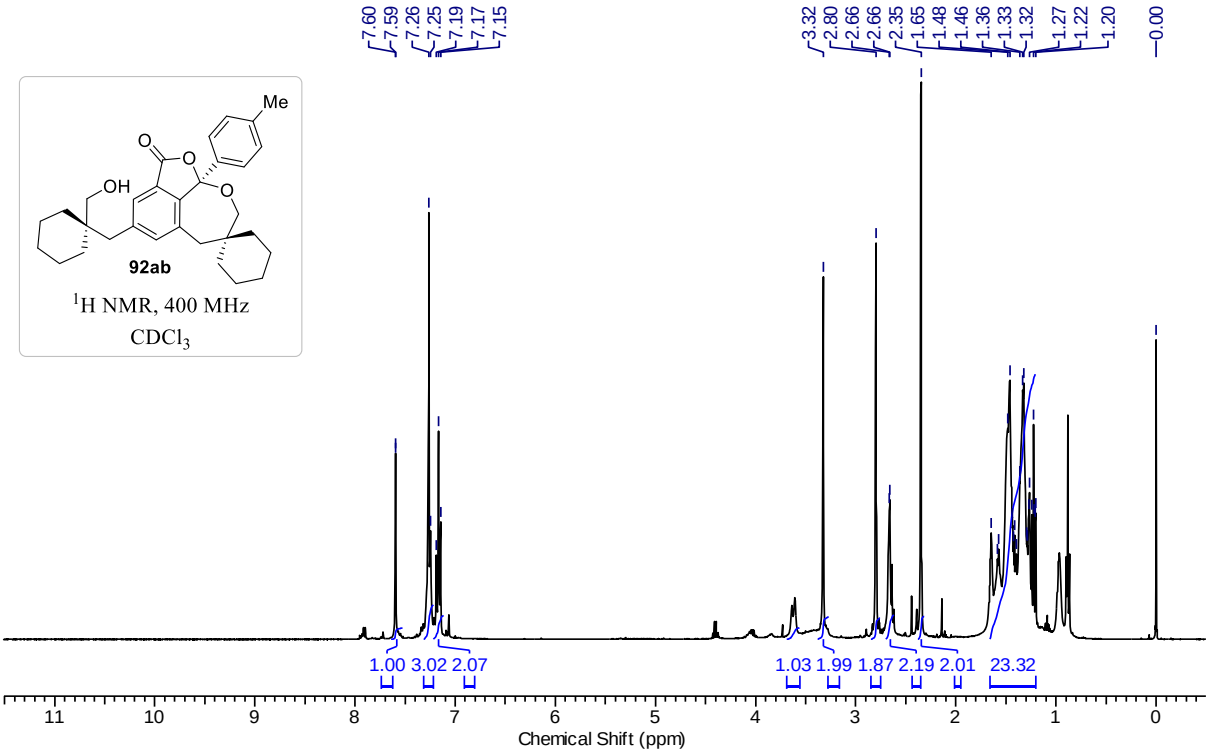
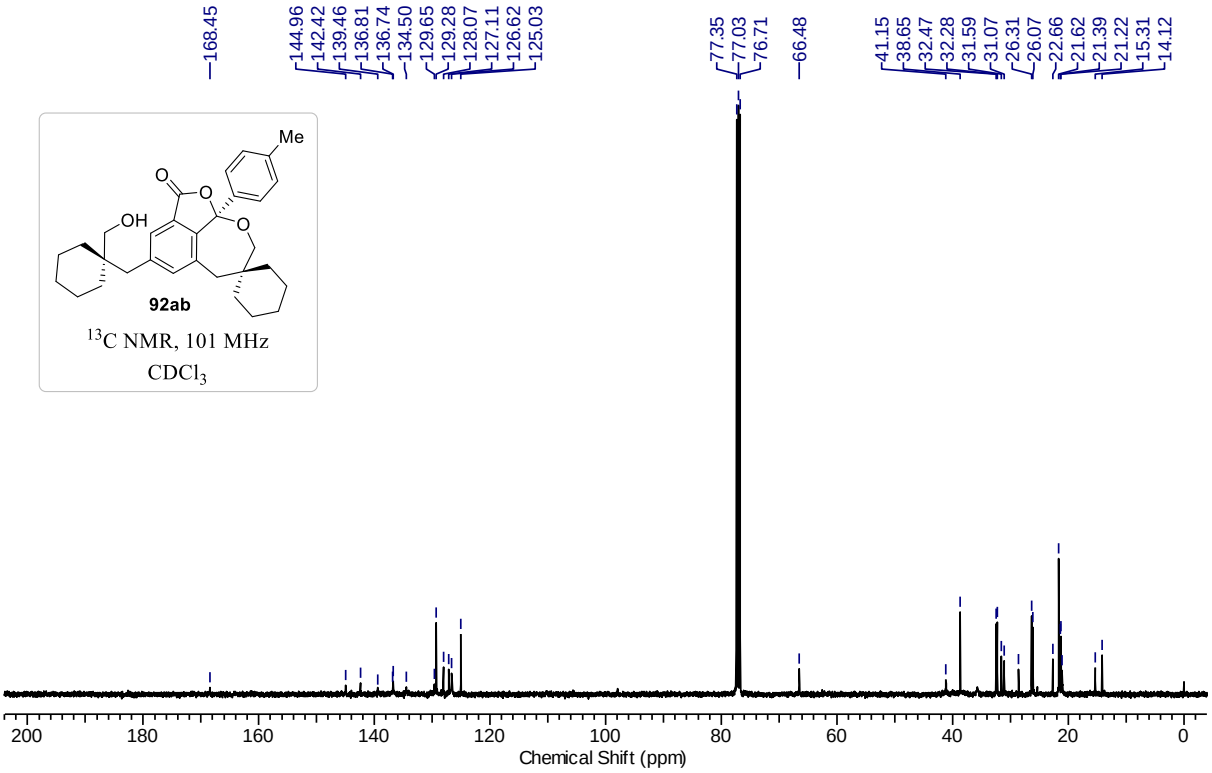
4'-((1-(hydroxymethyl)cyclohexyl)methyl)-9*a*'-phenyl-6',9*a*'-dihydro-2'*H*,8'*H*-spiro[cyclohexane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92aa):



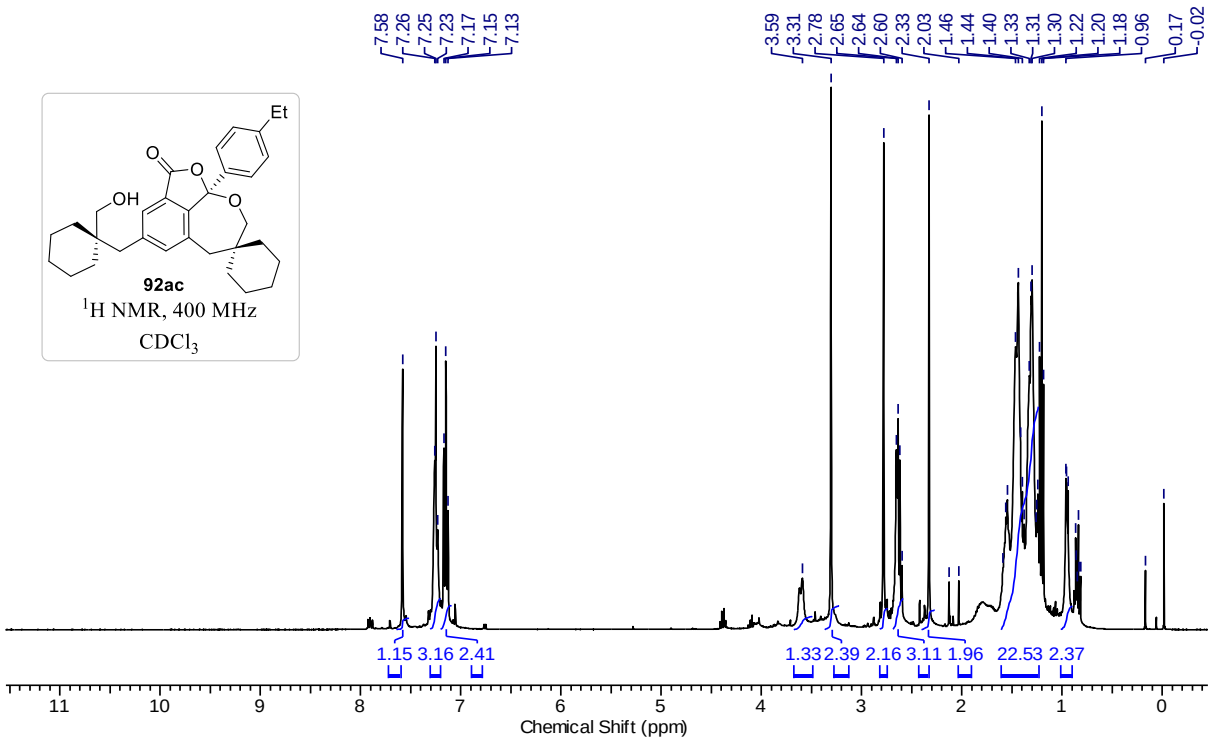


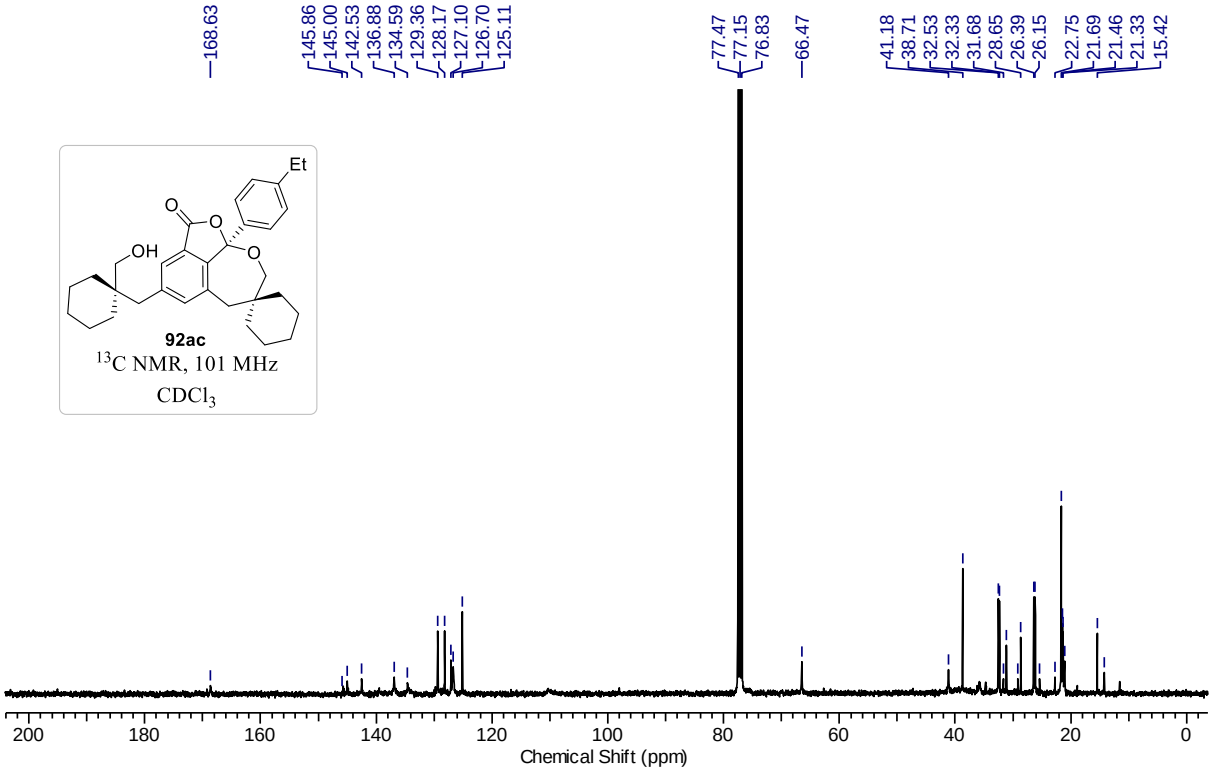
4'-((1-(hydroxymethyl)cyclohexyl)methyl)-9*a*'-(*p*-tolyl)-6',9*a*'-dihydro-2'*H*,8'*H*-spiro[cyclohexane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92ab):



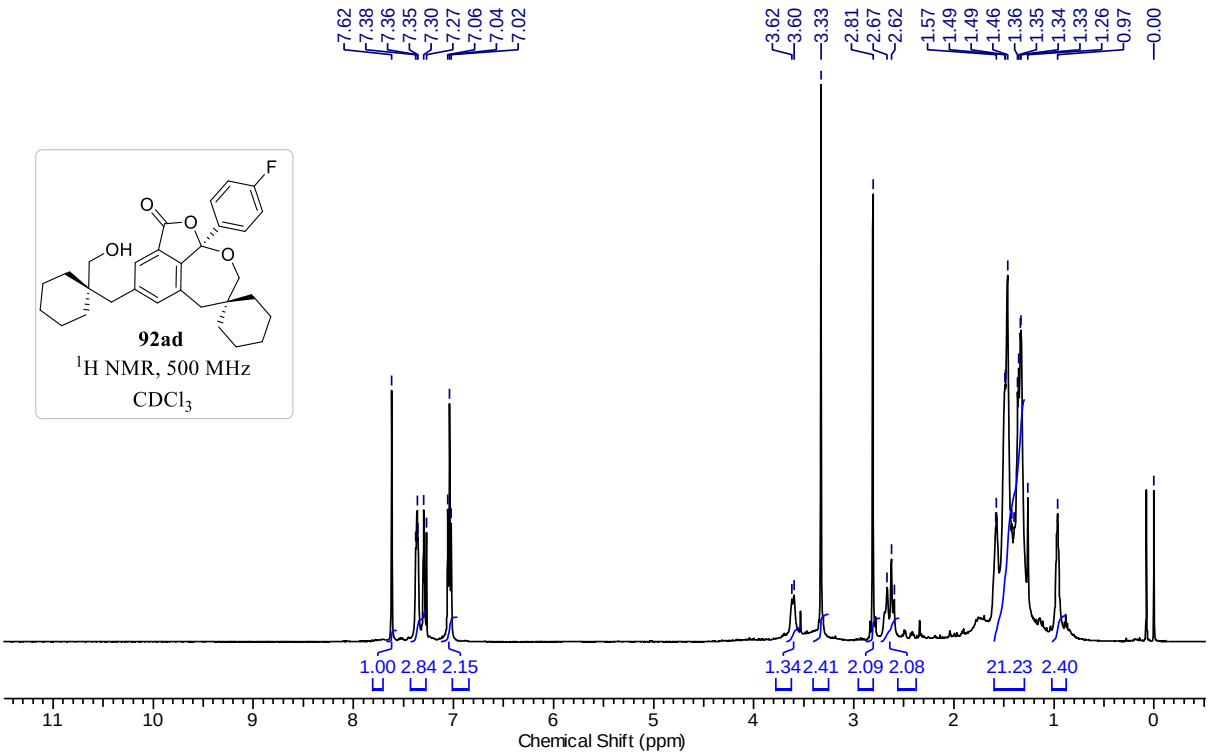


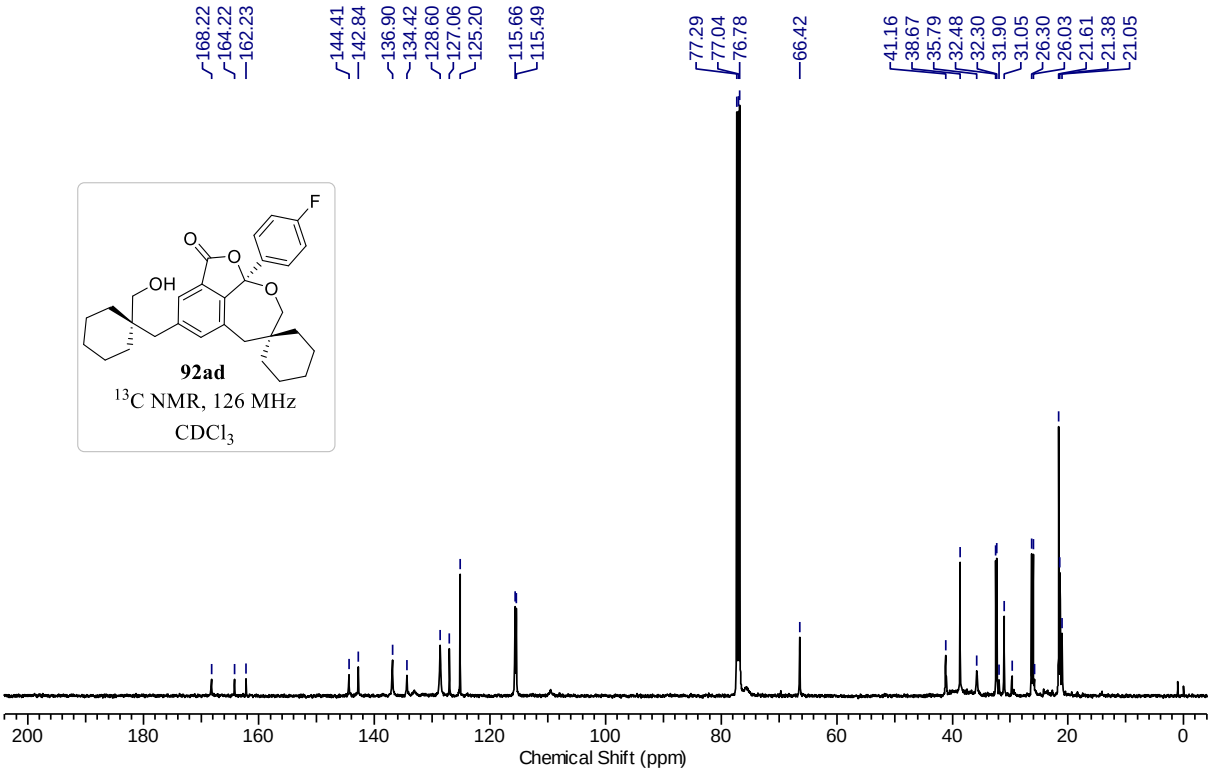
9*a*'-(4-ethylphenyl)-4'-((1-(hydroxymethyl)cyclohexyl)methyl)-6',9*a*'-dihydro-2'*H*,8'*H*-spiro[cyclohexane-1,7'-oxepino[2,3,4-cd]isobenzofuran]-2'-one (92ac):



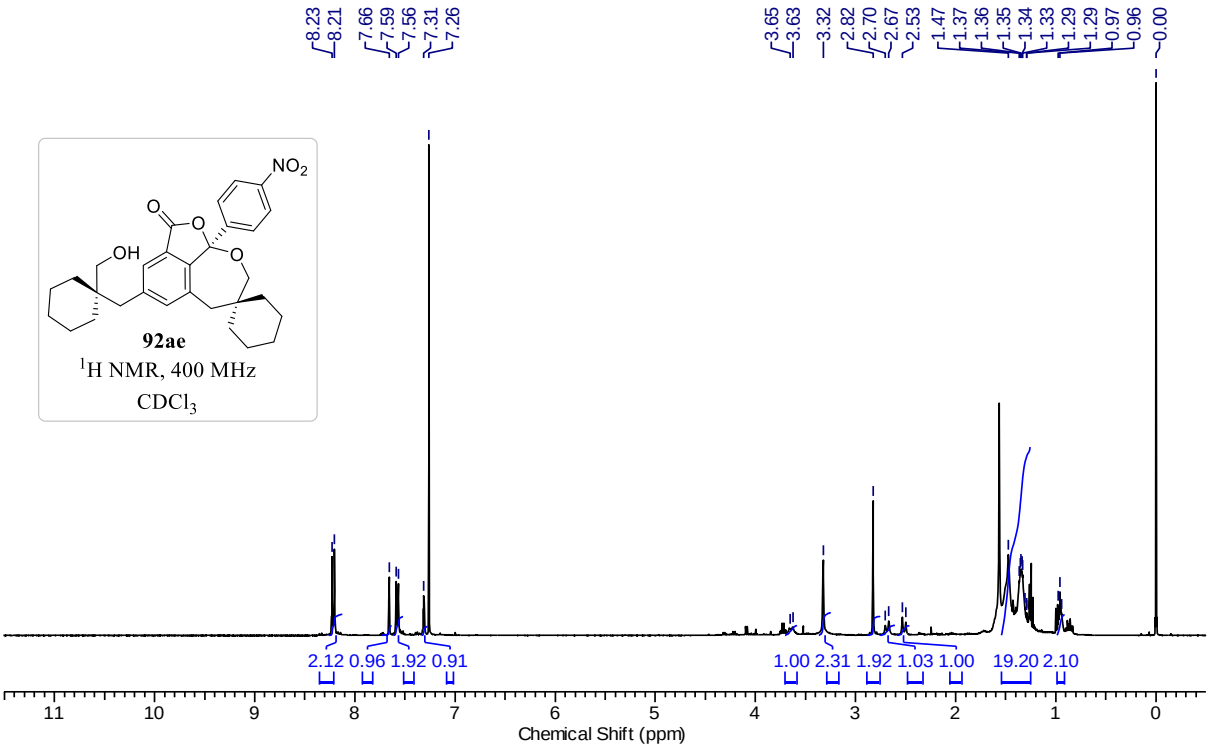


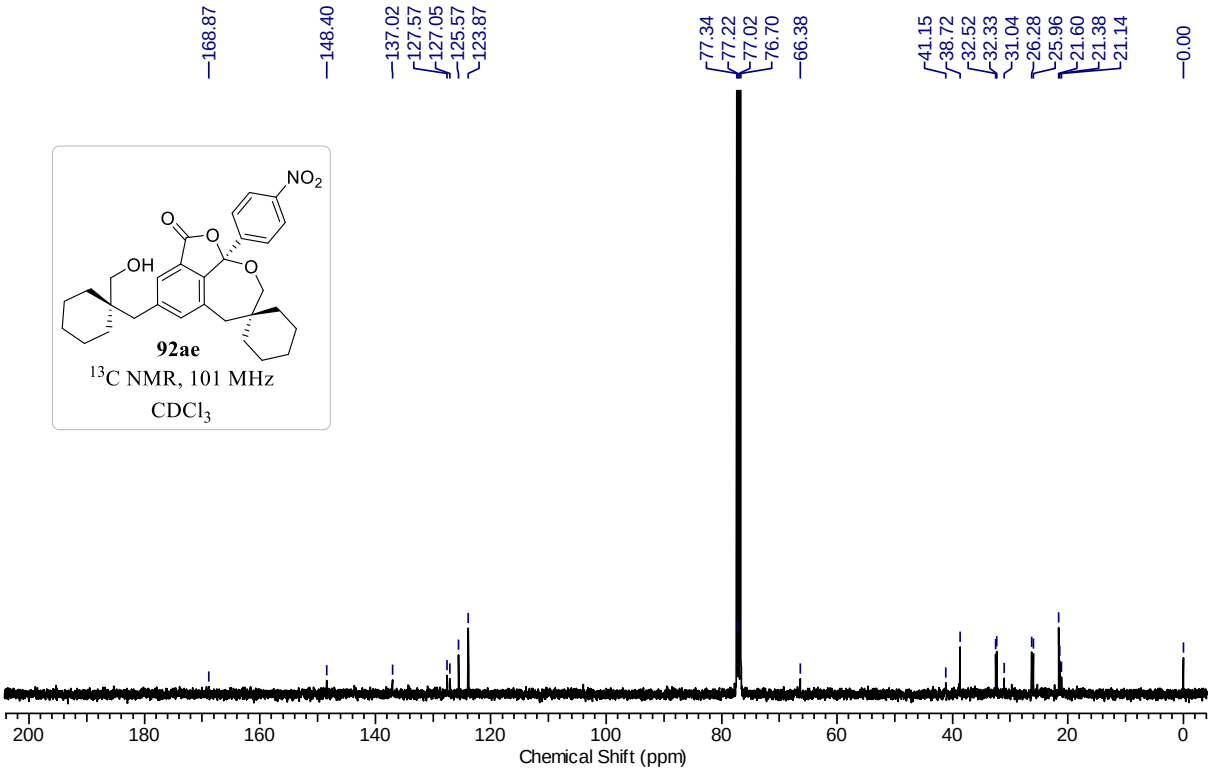
9*a*'-(4-fluorophenyl)-4'-((1-(hydroxymethyl)cyclohexyl)methyl)-6',9*a*'-dihydro-2'*H*,8'*H*-spiro[cyclohexane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92ad)



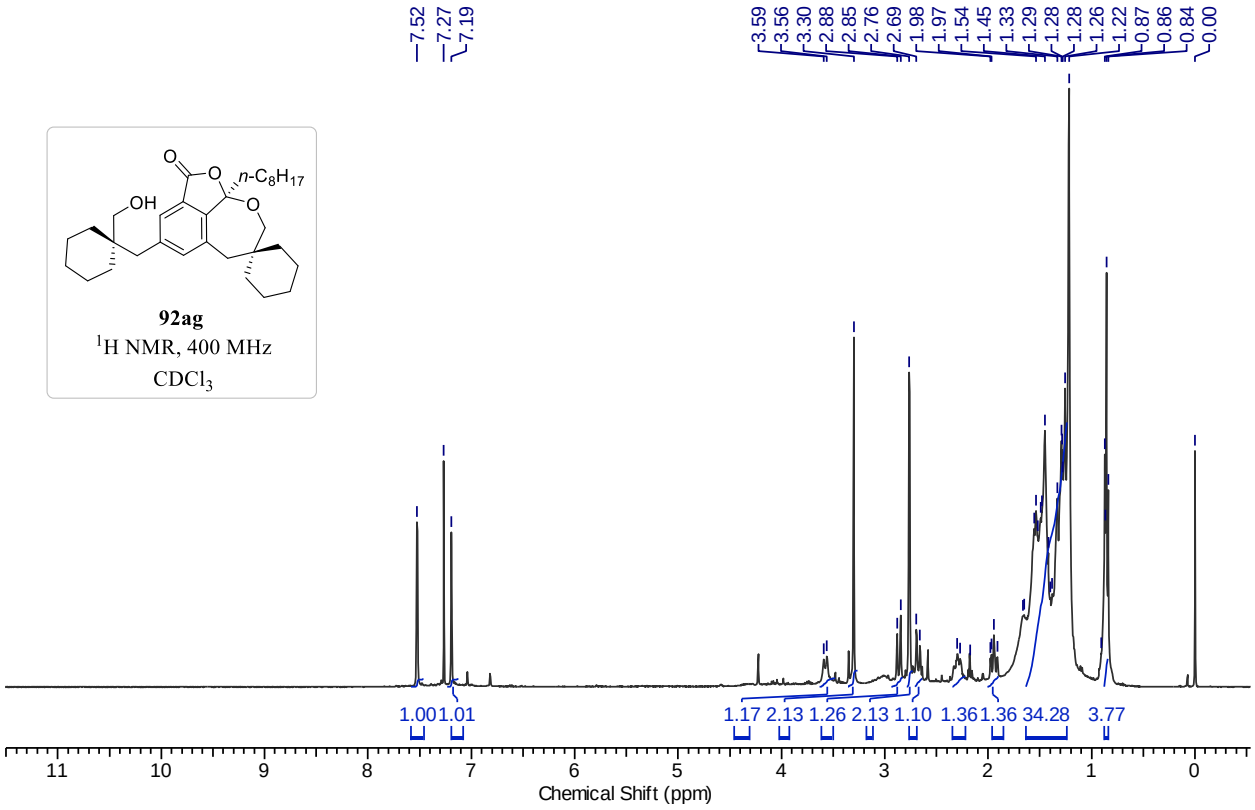


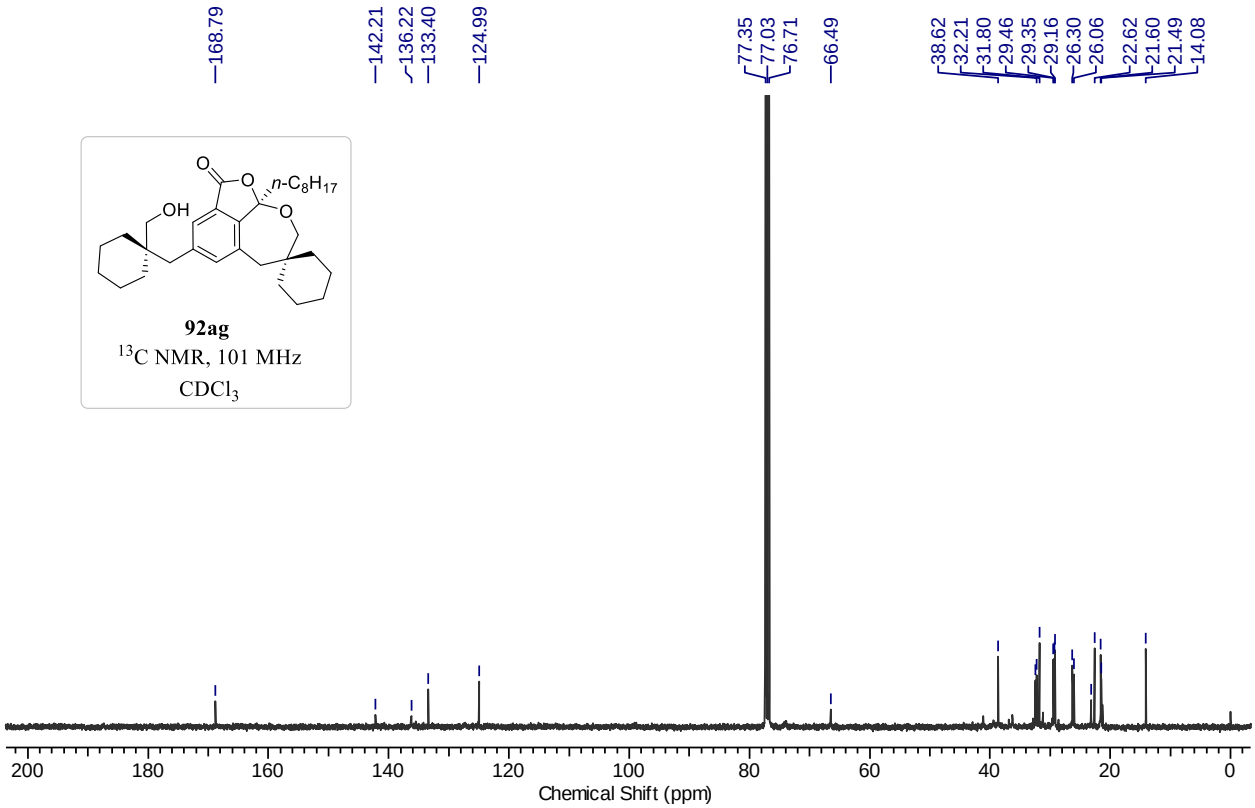
4'-((1-(hydroxymethyl)cyclohexyl)methyl)-9*a*'-(4-nitrophenyl)-6',9*a*'-dihydro-2'*H*,8'*H*-spiro[cyclohexane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92ae)



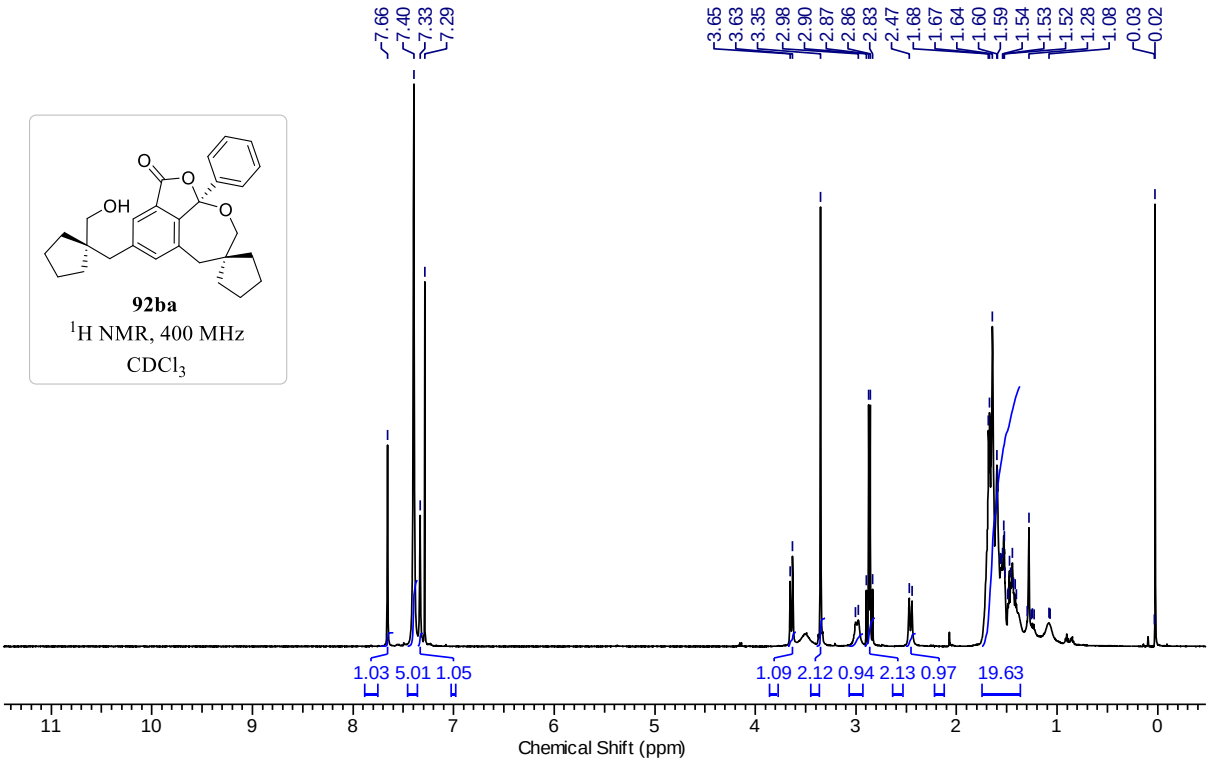


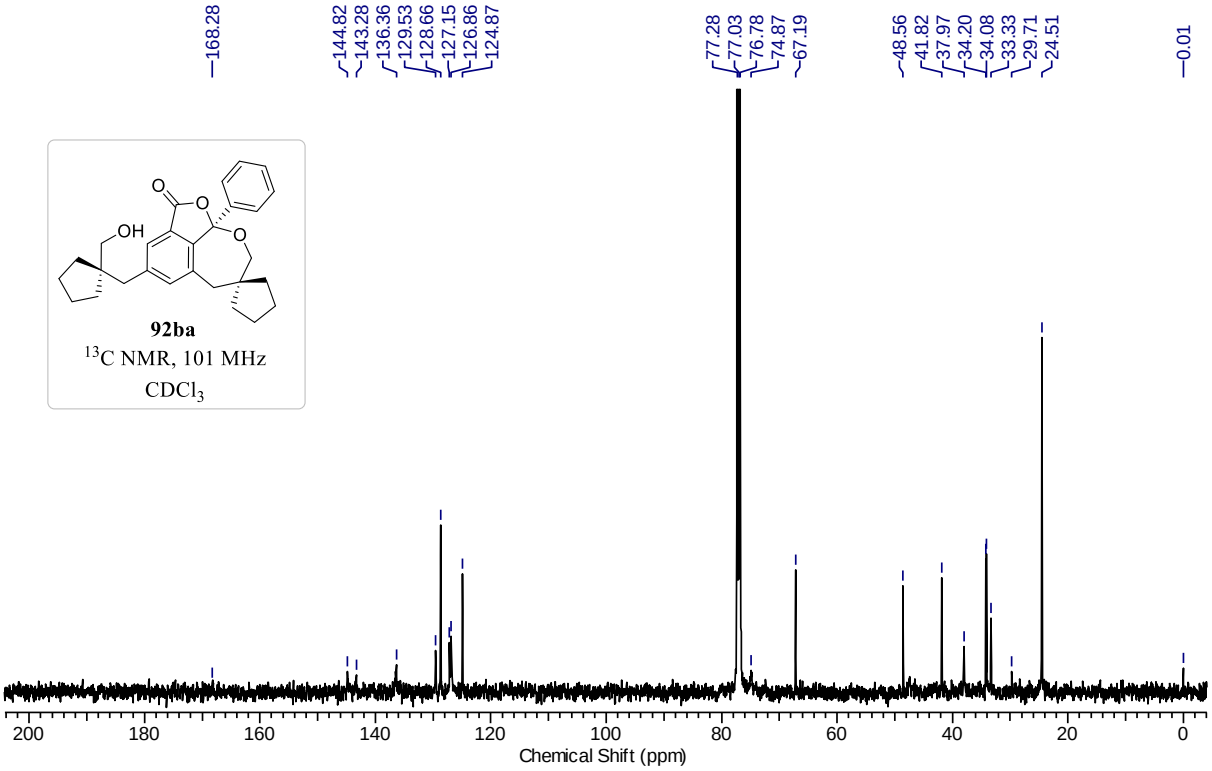
4'-((1-(hydroxymethyl)cyclohexyl)methyl)-9a'-octyl-6',9a'-dihydro-2'H,8'H-spiro [cyclohexane-1,7'-oxepino[2,3,4-cd]isobenzofuran]-2'-one (92ag):



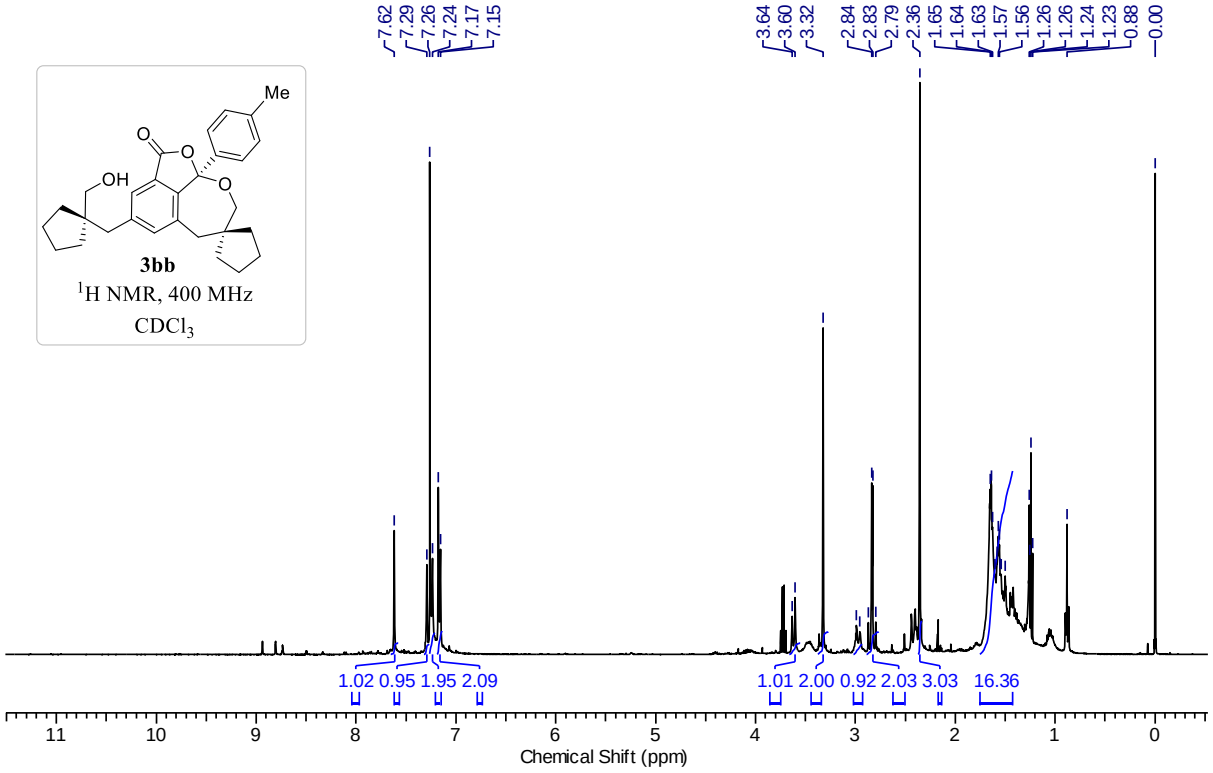


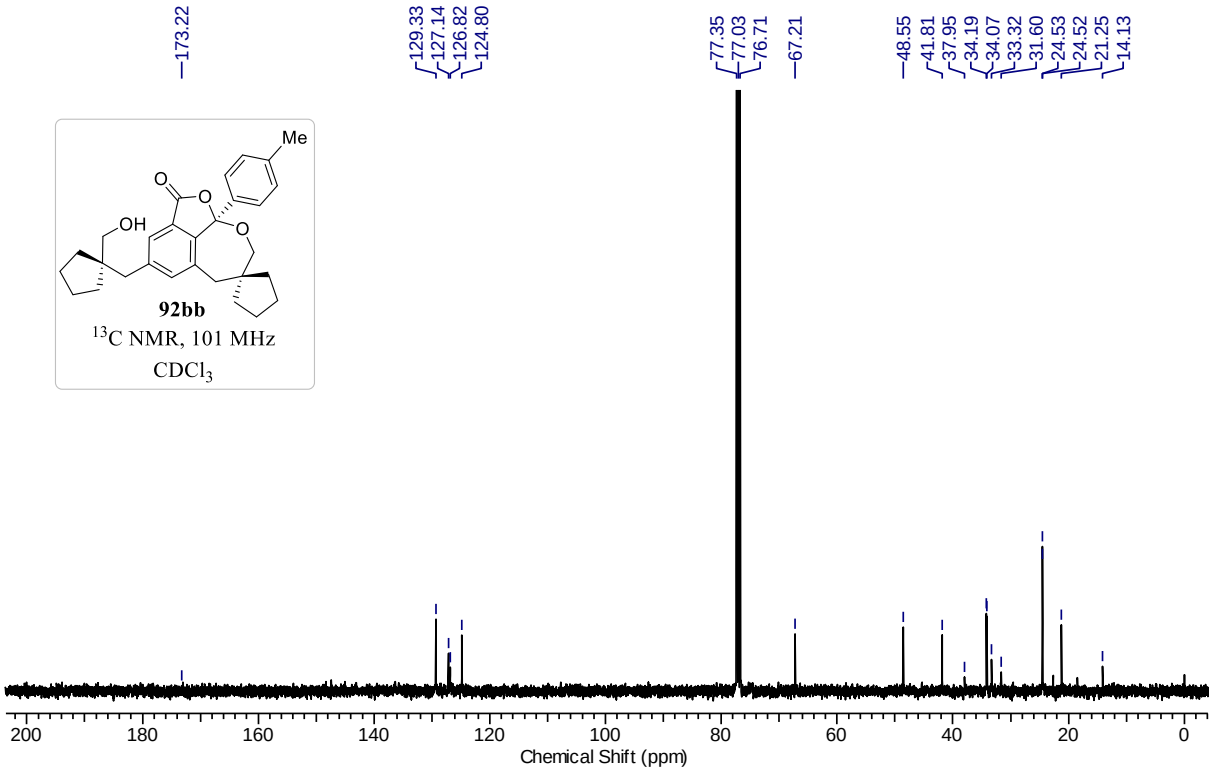
4'-((1-(hydroxymethyl)cyclopentyl)methyl)-9*a*'-phenyl-6',9*a*'-dihydro-2'*H*,8'*H*-spiro[cyclopentane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92ba)



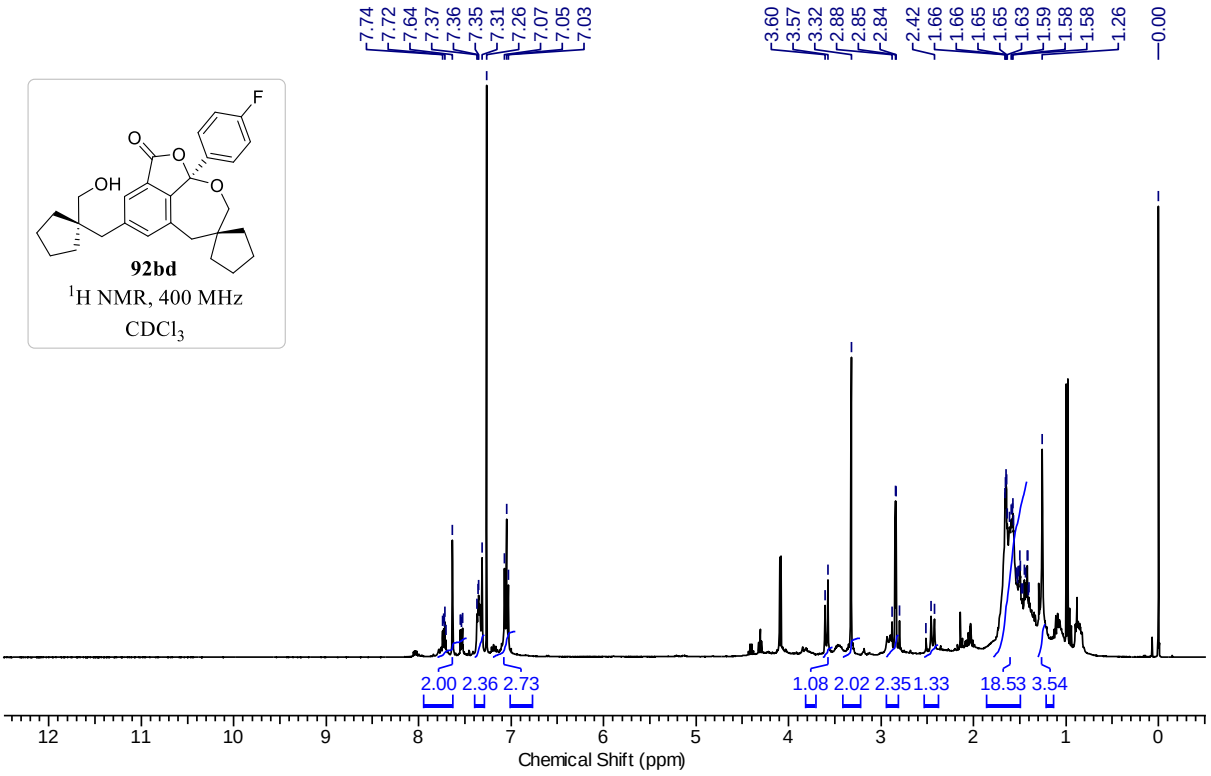


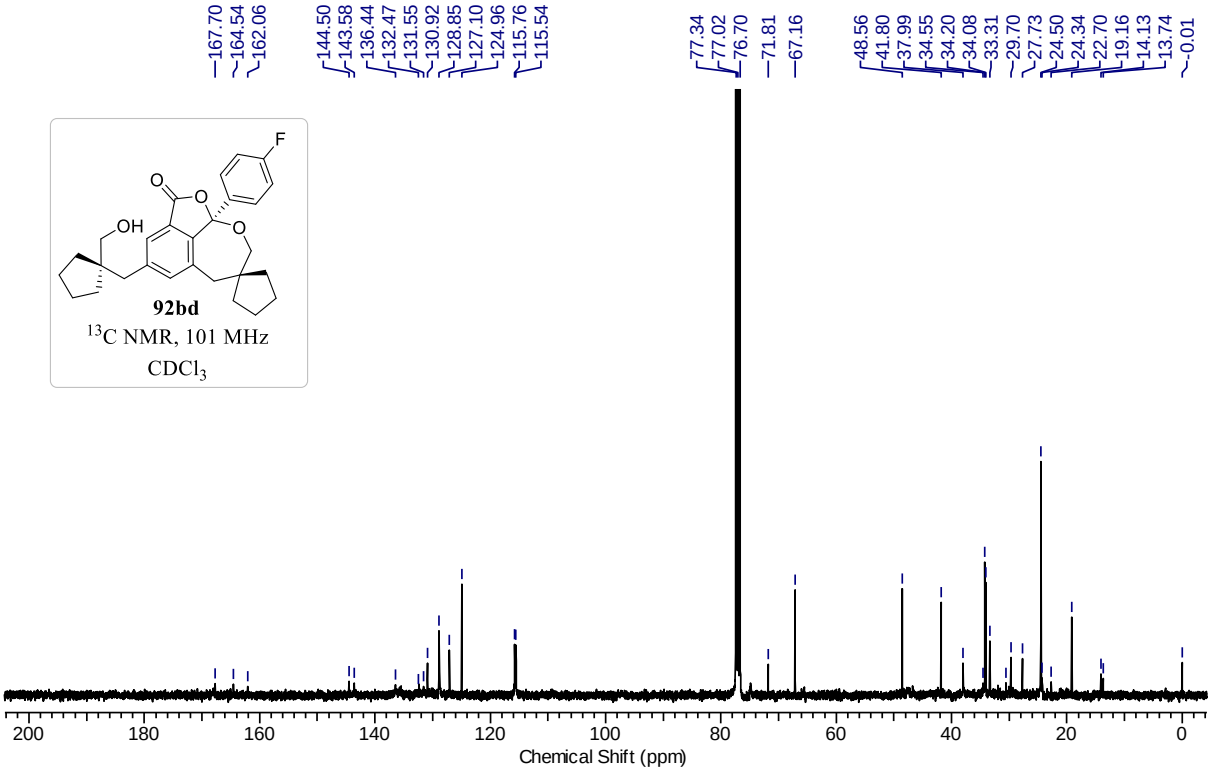
4'-((1-(hydroxymethyl)cyclopentyl)methyl)-9a'-(*p*-tolyl)-6',9a'-dihydro-2'H,8'H-spiro[cyclopentane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92bb):



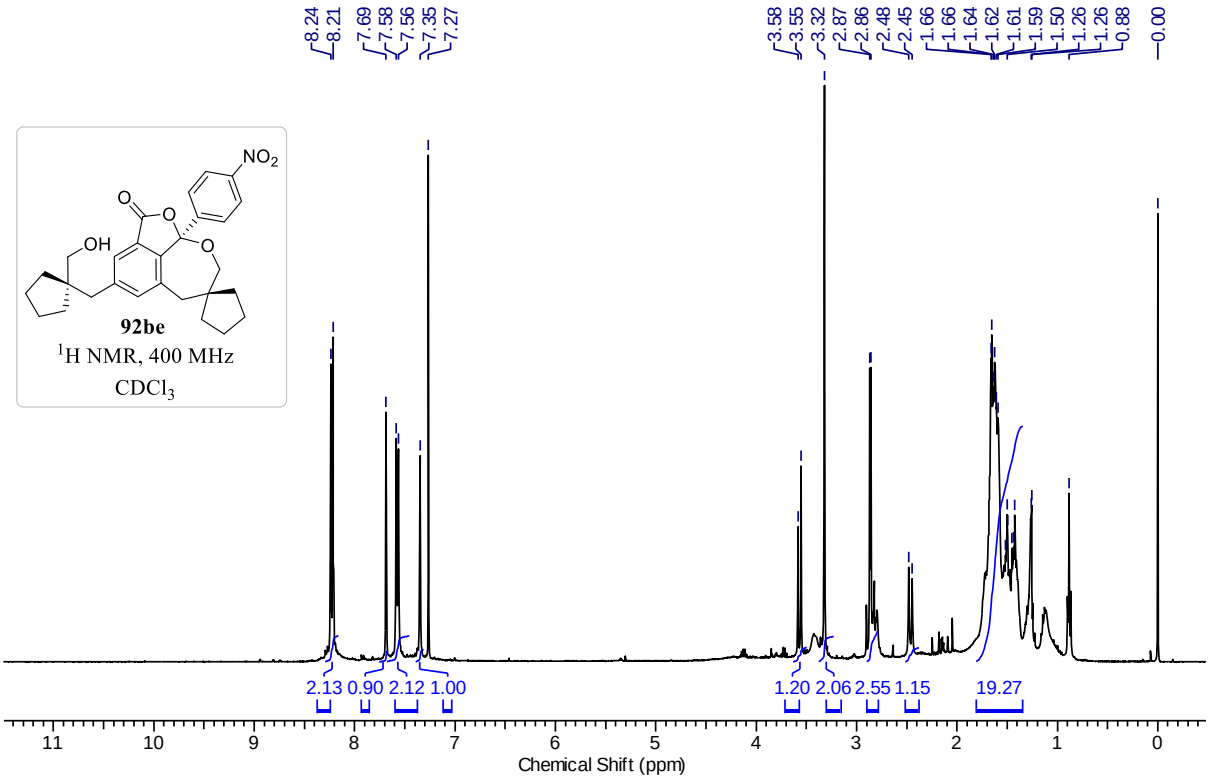


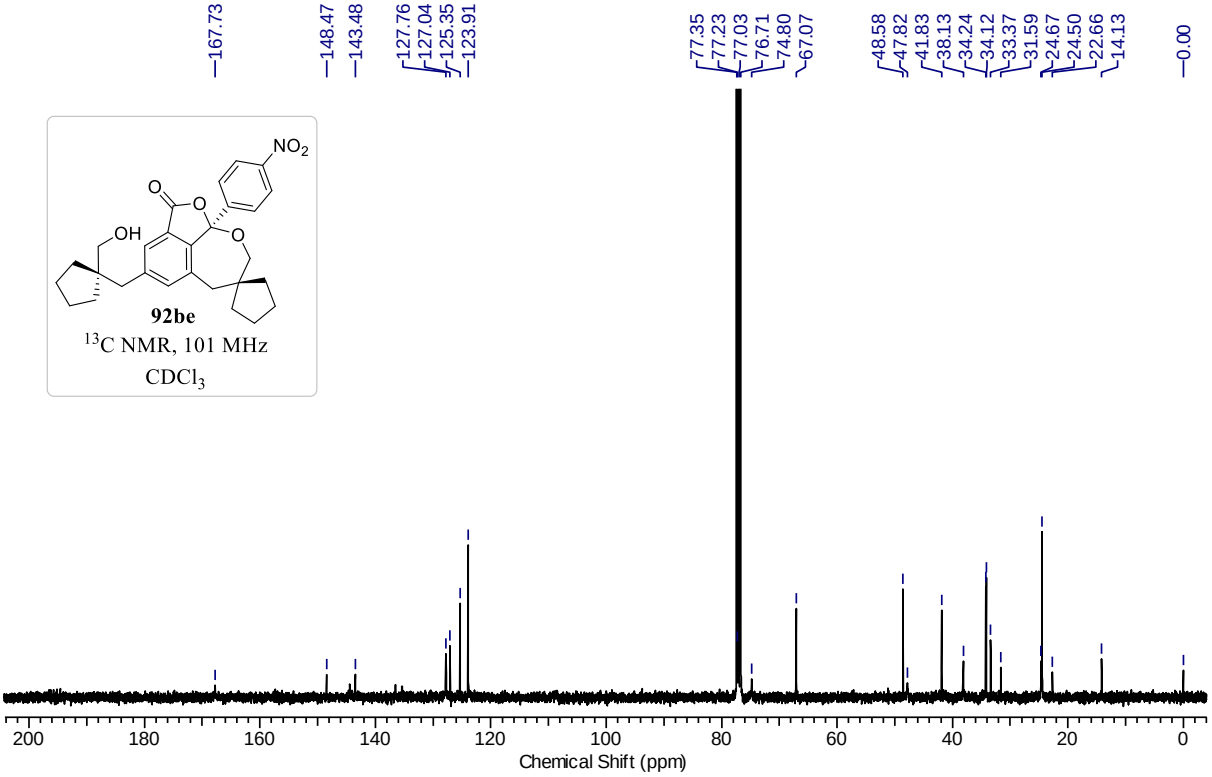
9*a*'-(4-fluorophenyl)-4'-((1-(hydroxymethyl)cyclopentyl)methyl)-6',9*a*'-dihydro-2'*H*,8'*H*-spiro[cyclopentane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92bd)



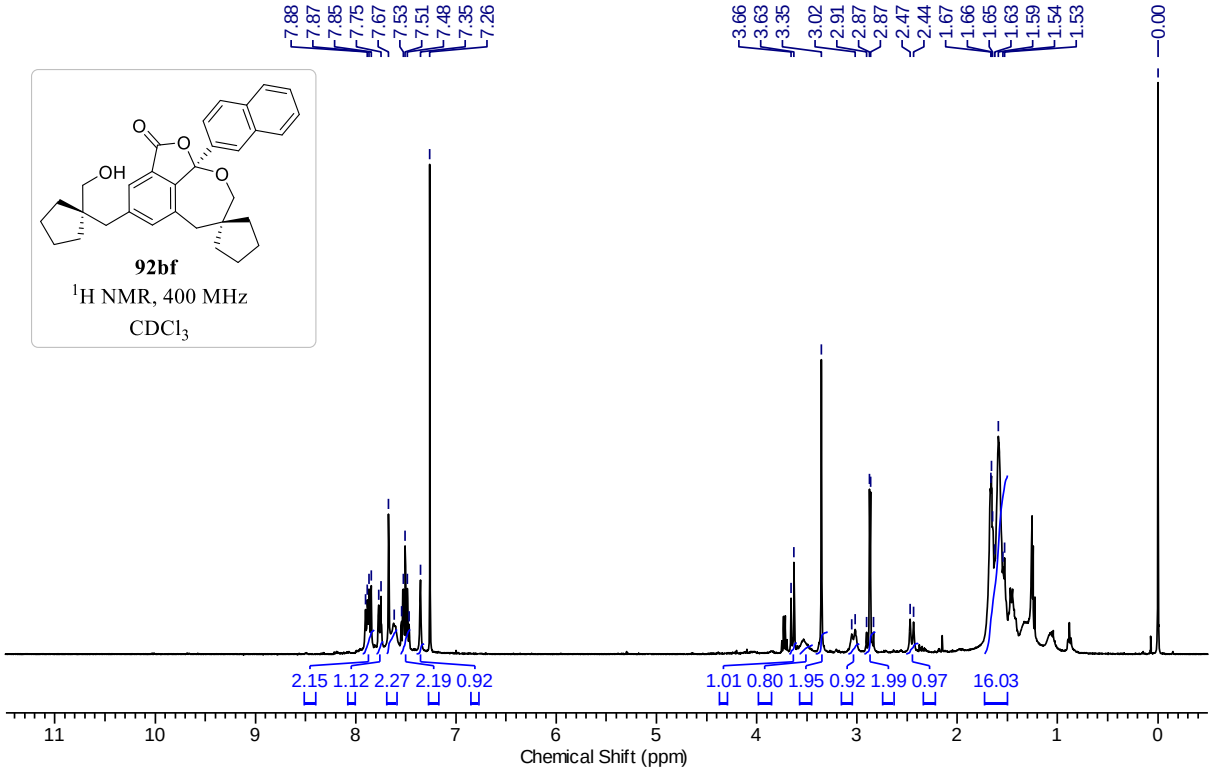


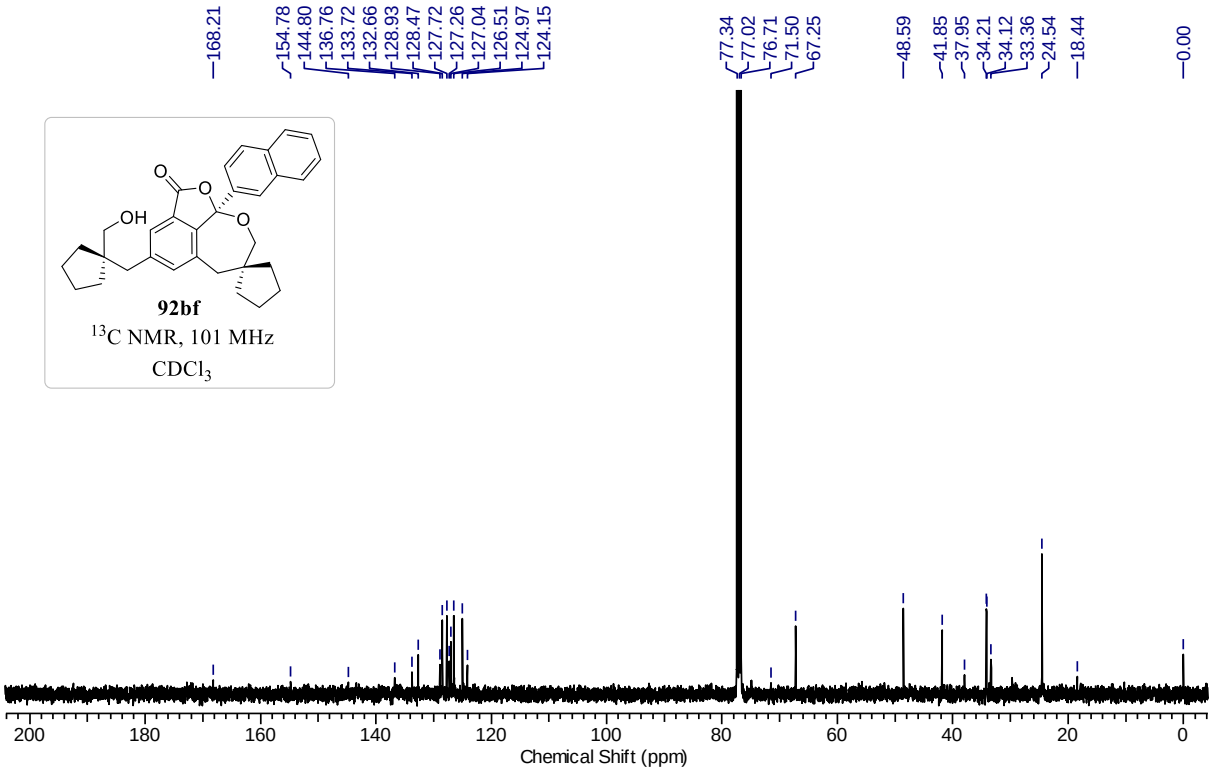
4'-((1-(hydroxymethyl)cyclopentyl)methyl)-9a'-(4-nitrophenyl)-6',9a'-dihydro-2'H,8'H-spiro[cyclopentane-1,7'-oxepino[2,3,4-*cd*]isobenzofuran]-2'-one (92be):



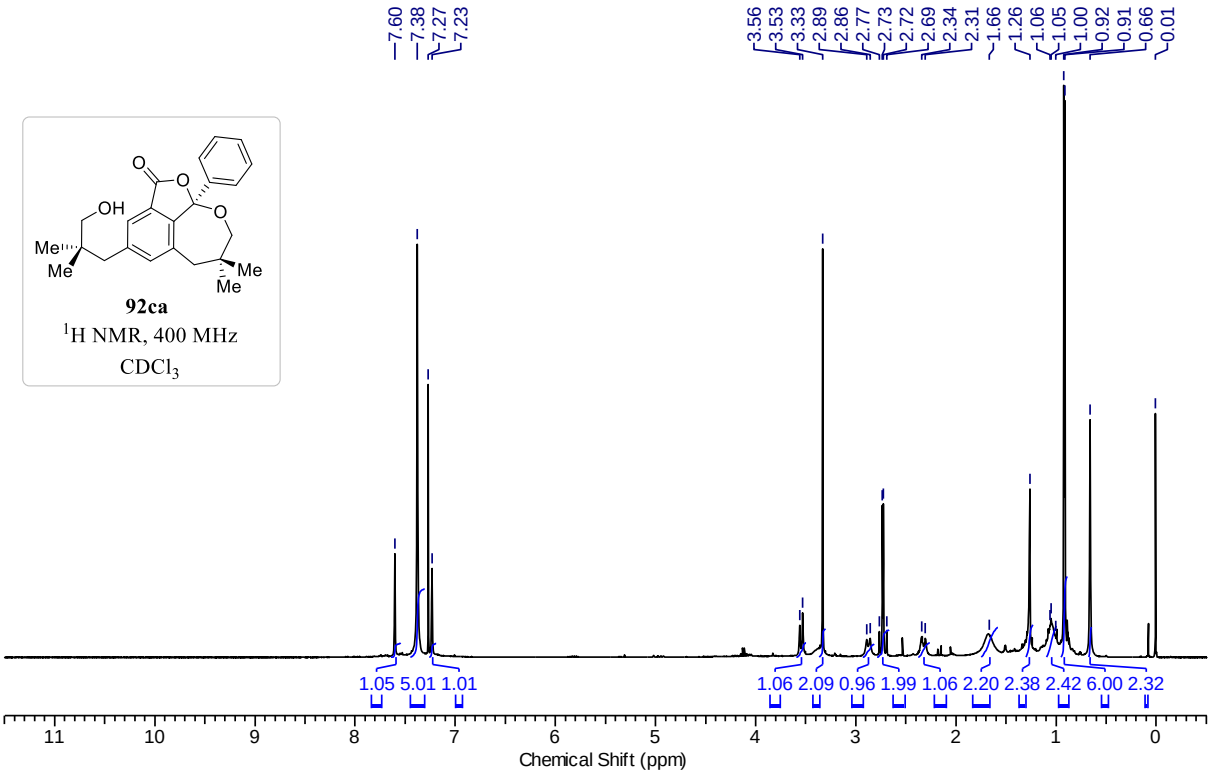


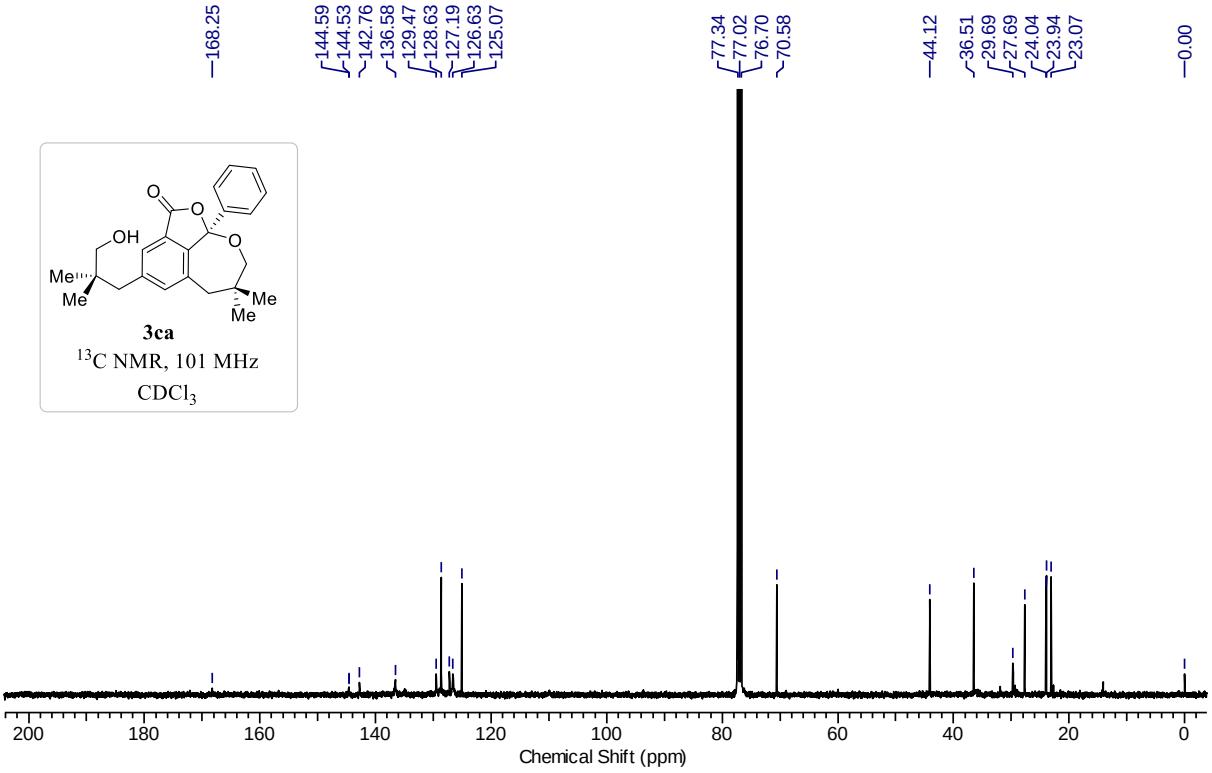
4'-((1-(hydroxymethyl)cyclopentyl)methyl)-9a'-(naphthalen-2-yl)-6',9a'-dihydro-2'H,8'H-spiro[cyclopentane-1,7'-oxepino[2,3,4-cd]isobenzofuran]-2'-one (92bf):



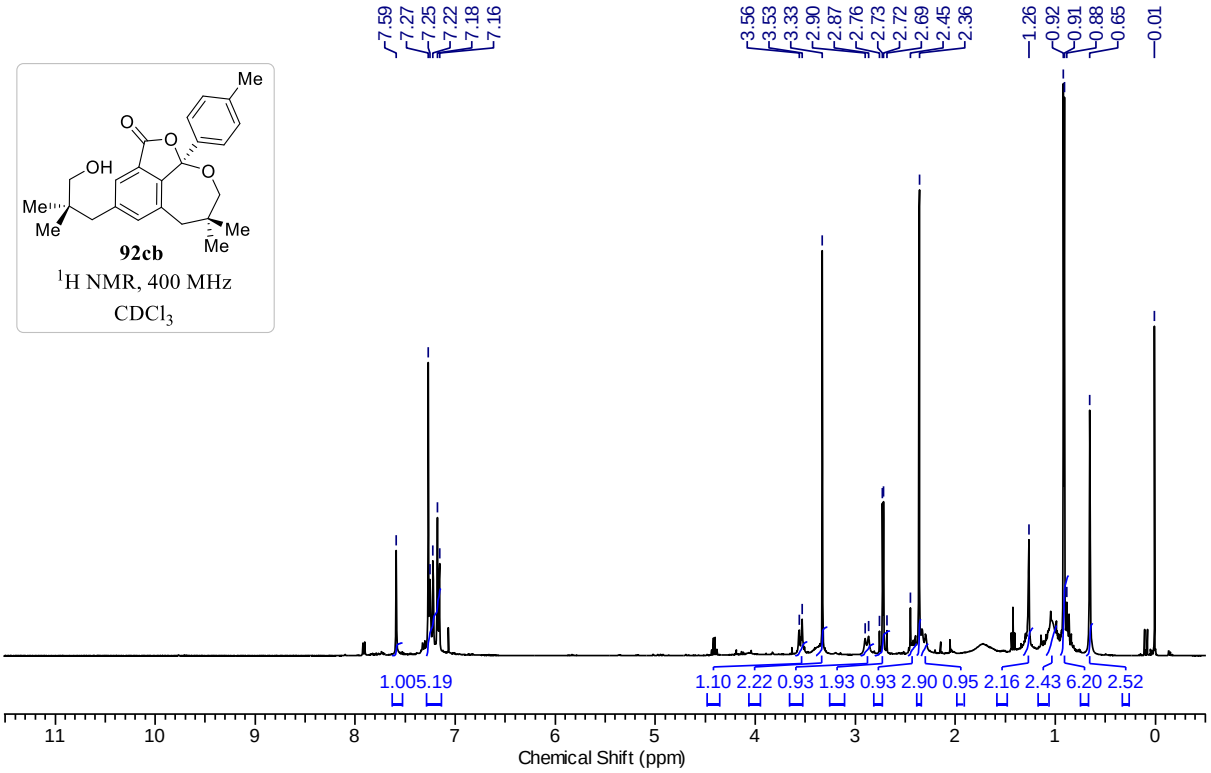


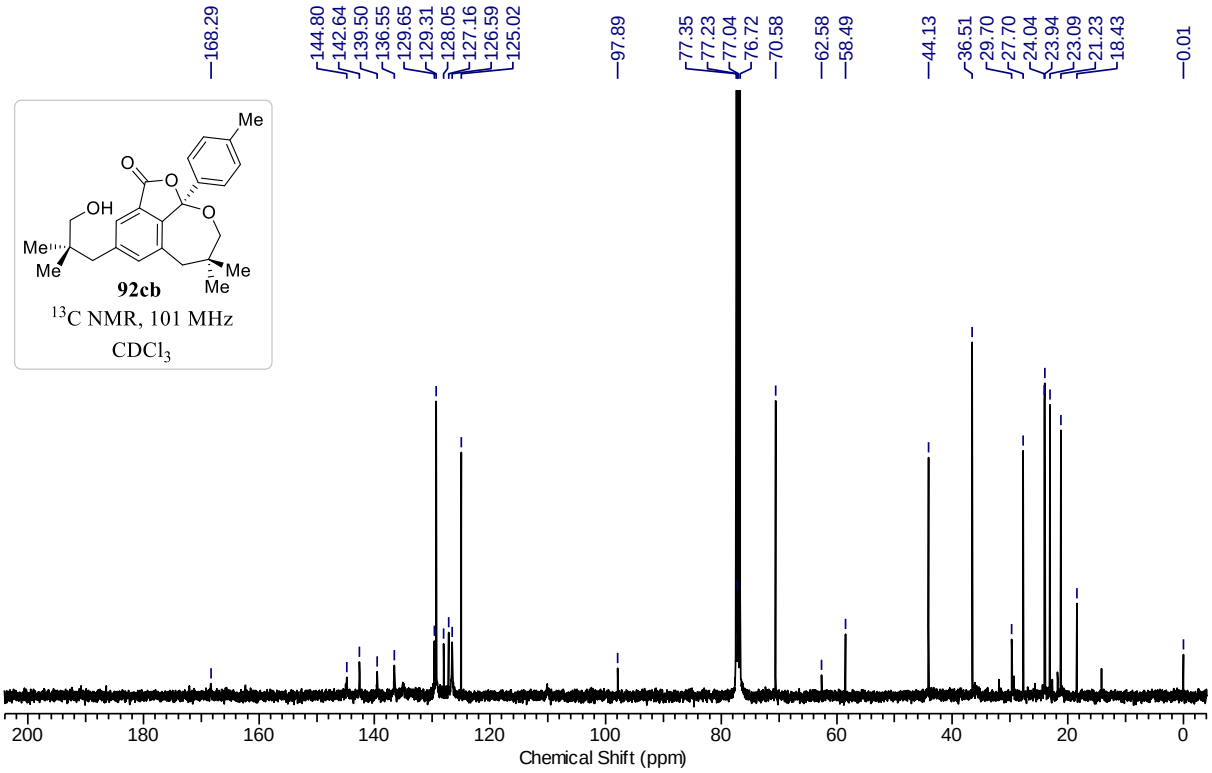
4-(3-hydroxy-2,2-dimethylpropyl)-7,7-dimethyl-9*a*-phenyl-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92ca)



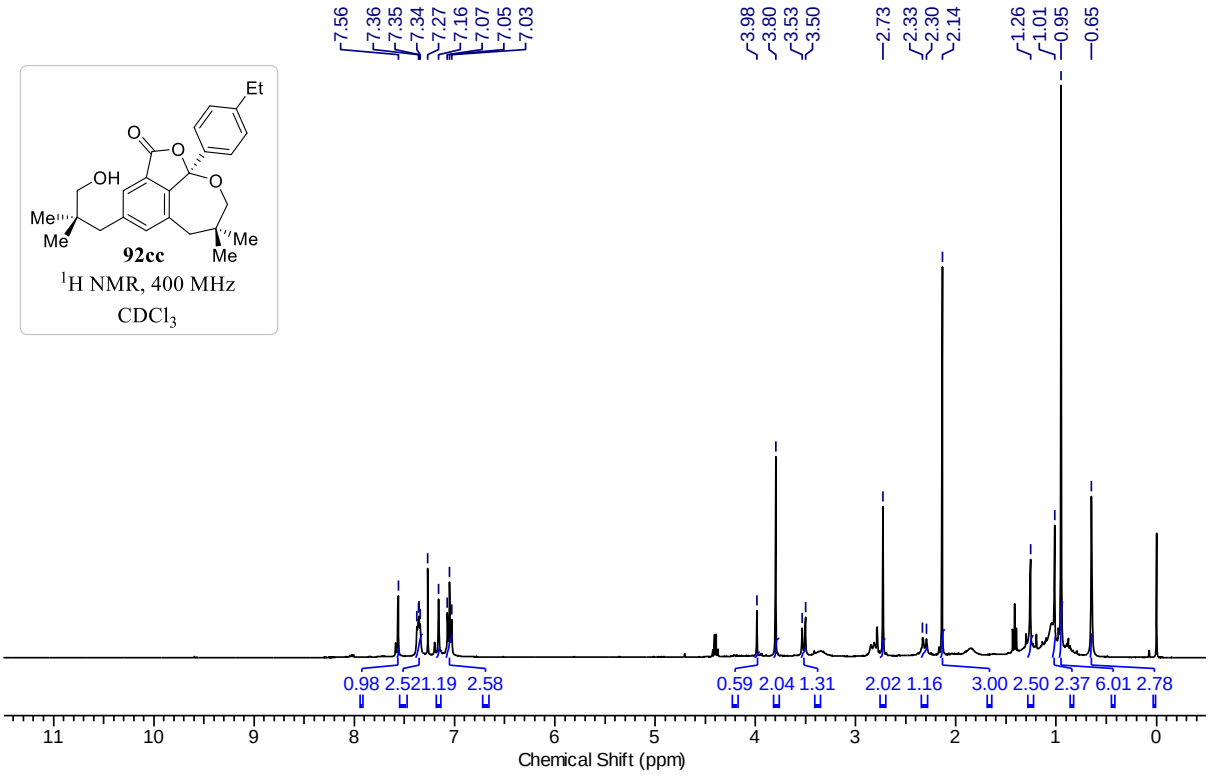


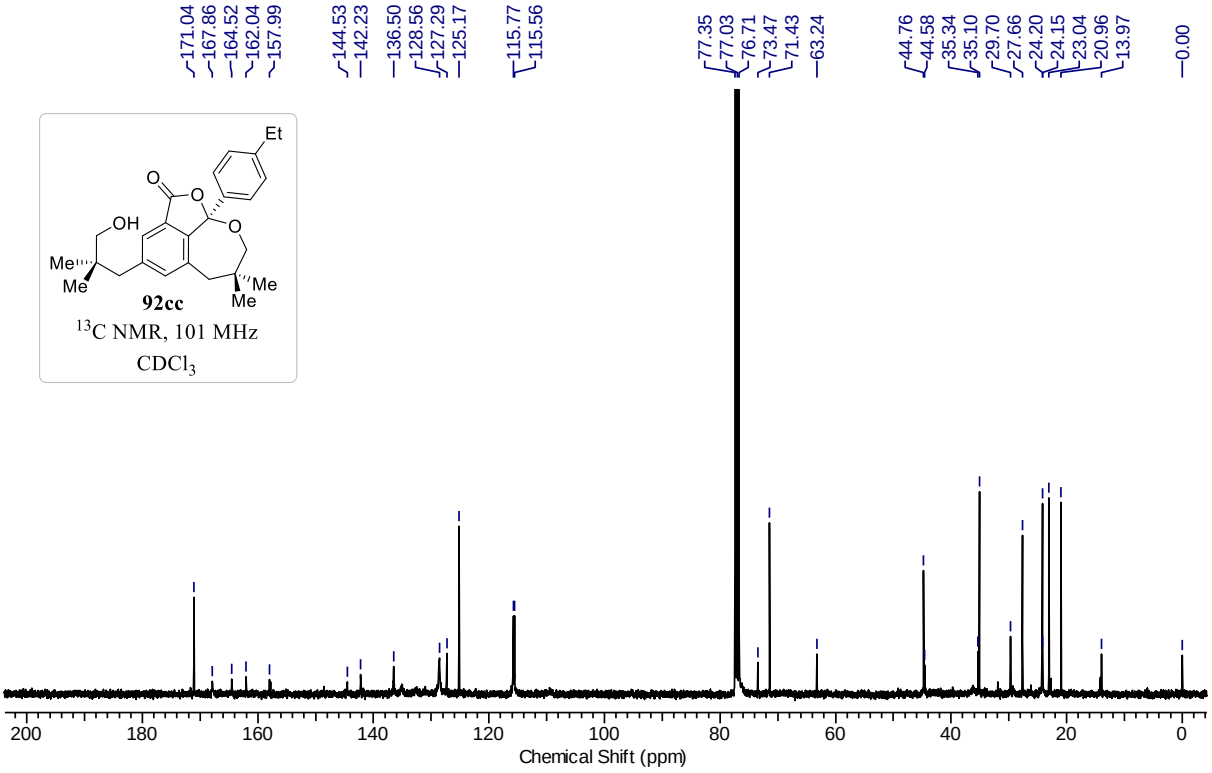
4-(3-hydroxy-2,2-dimethylpropyl)-7,7-dimethyl-9*a*-(*p*-tolyl)-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92cb)



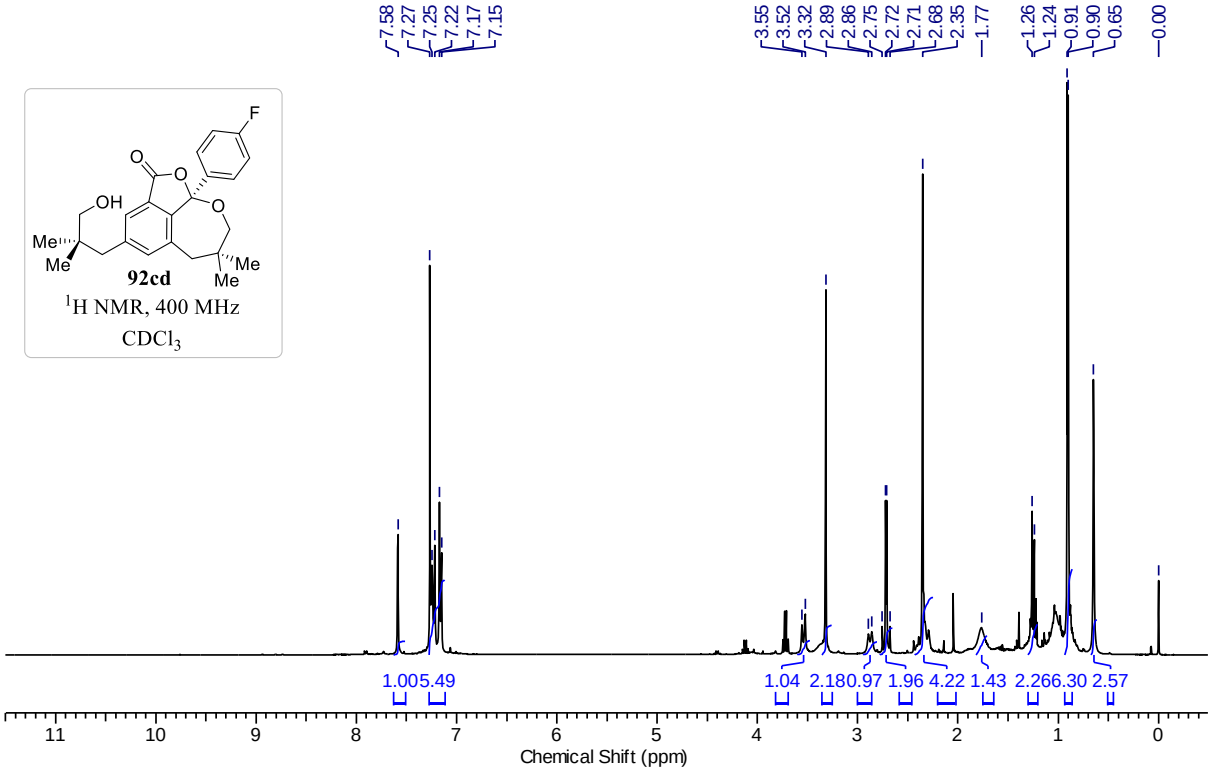


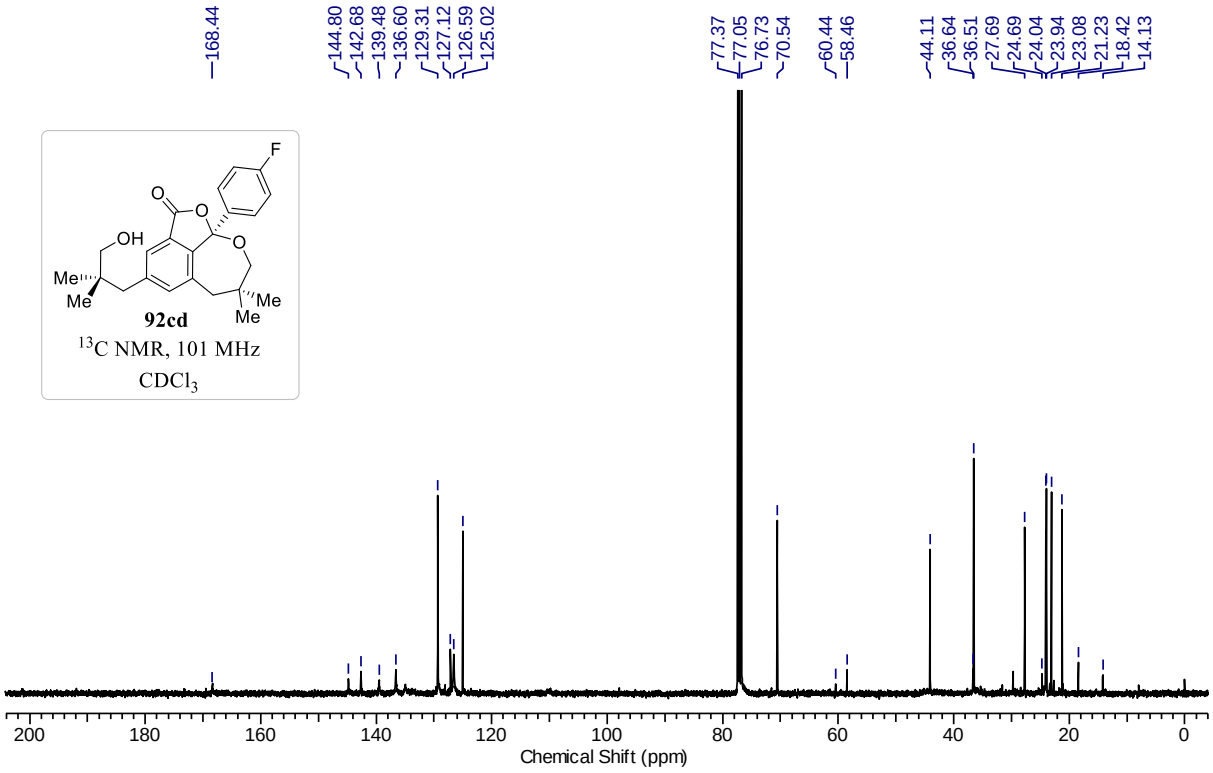
9*a*-(4-ethylphenyl)-4-(3-hydroxy-2,2-dimethylpropyl)-7,7-dimethyl-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92cc)



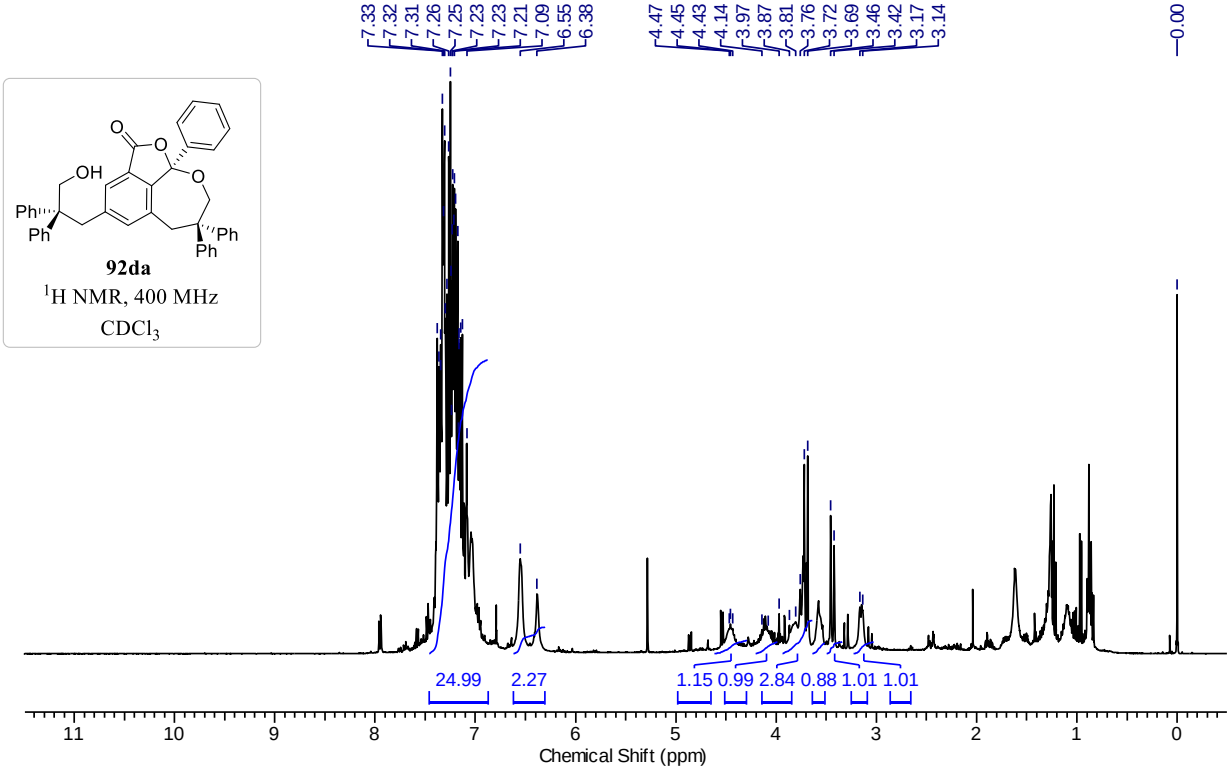


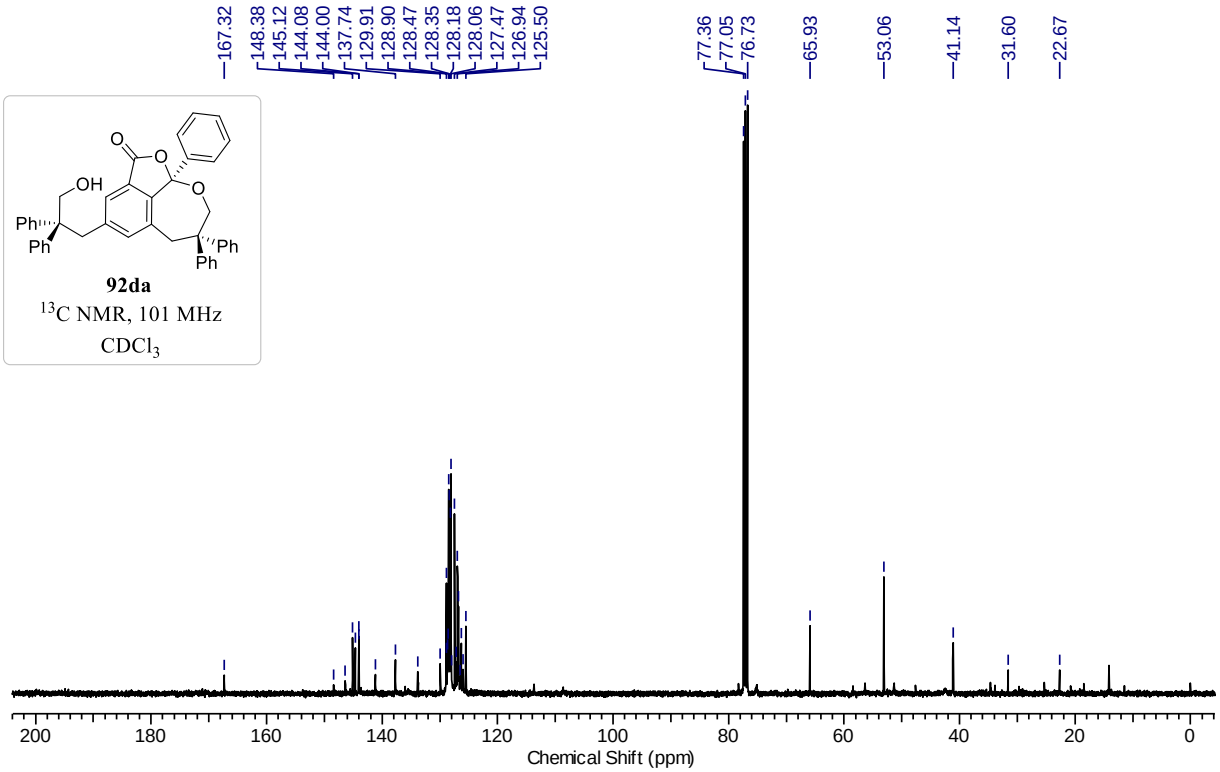
9*a*-(4-fluorophenyl)-4-(3-hydroxy-2,2-dimethylpropyl)-7,7-dimethyl-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92cd)



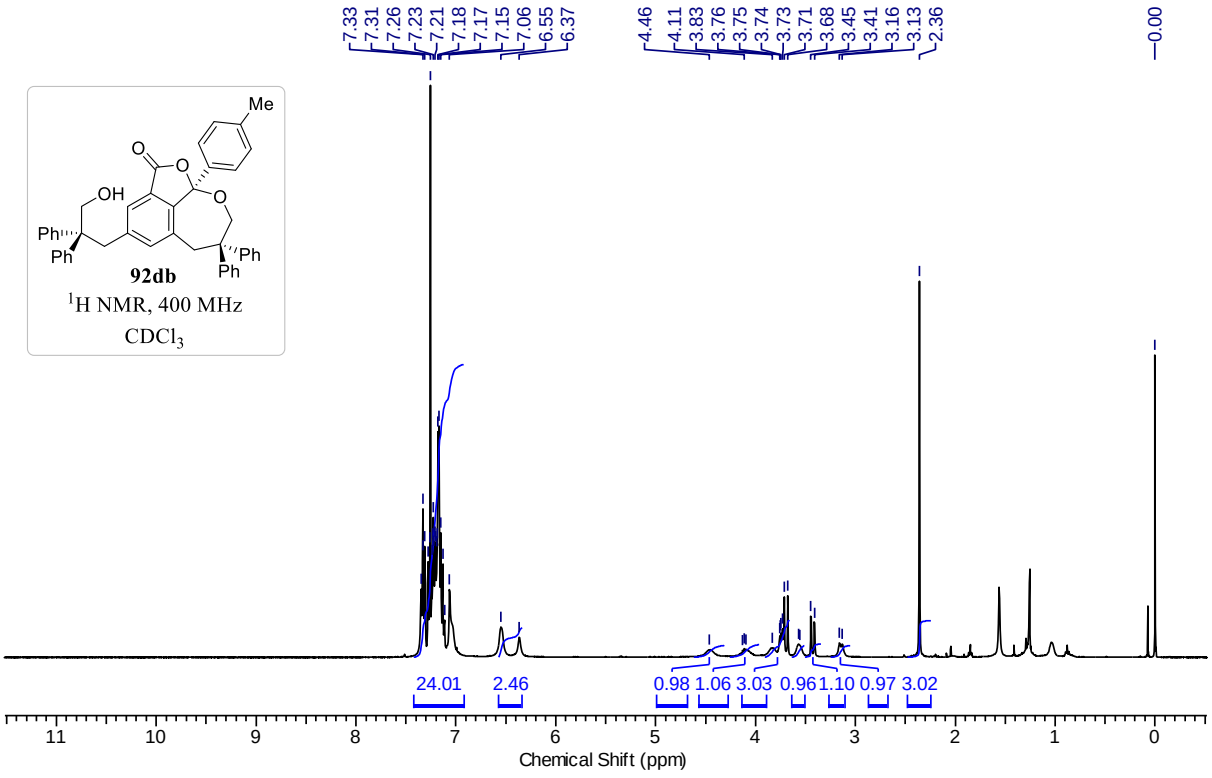


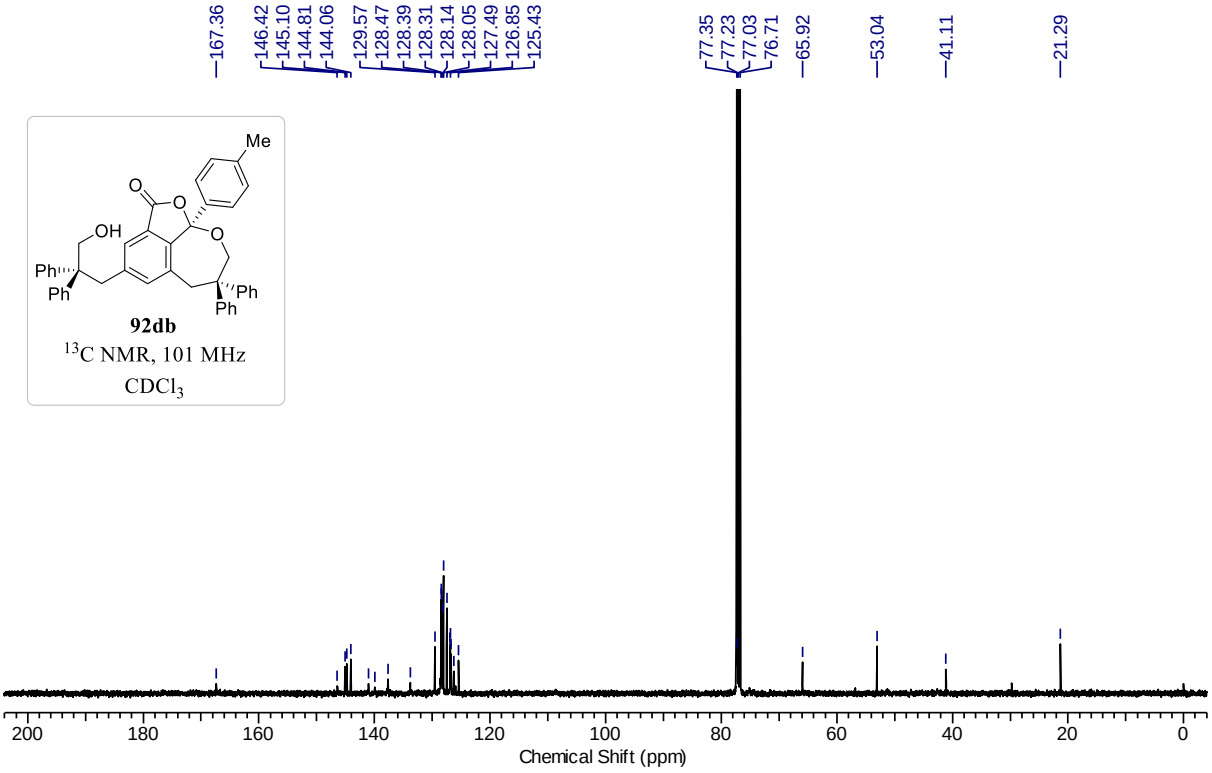
4-(3-hydroxy-2,2-diphenylpropyl)-7,7,9*a*-triphenyl-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-cd]isobenzofuran-2-one (92da)



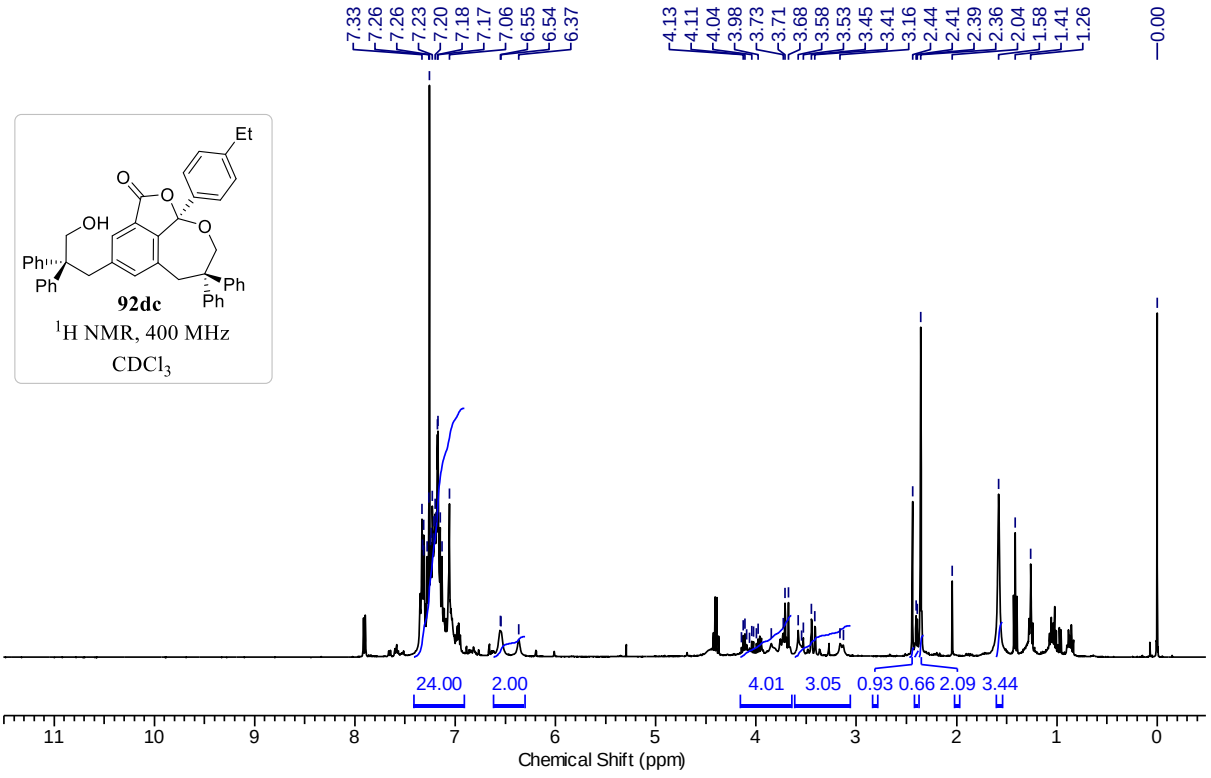


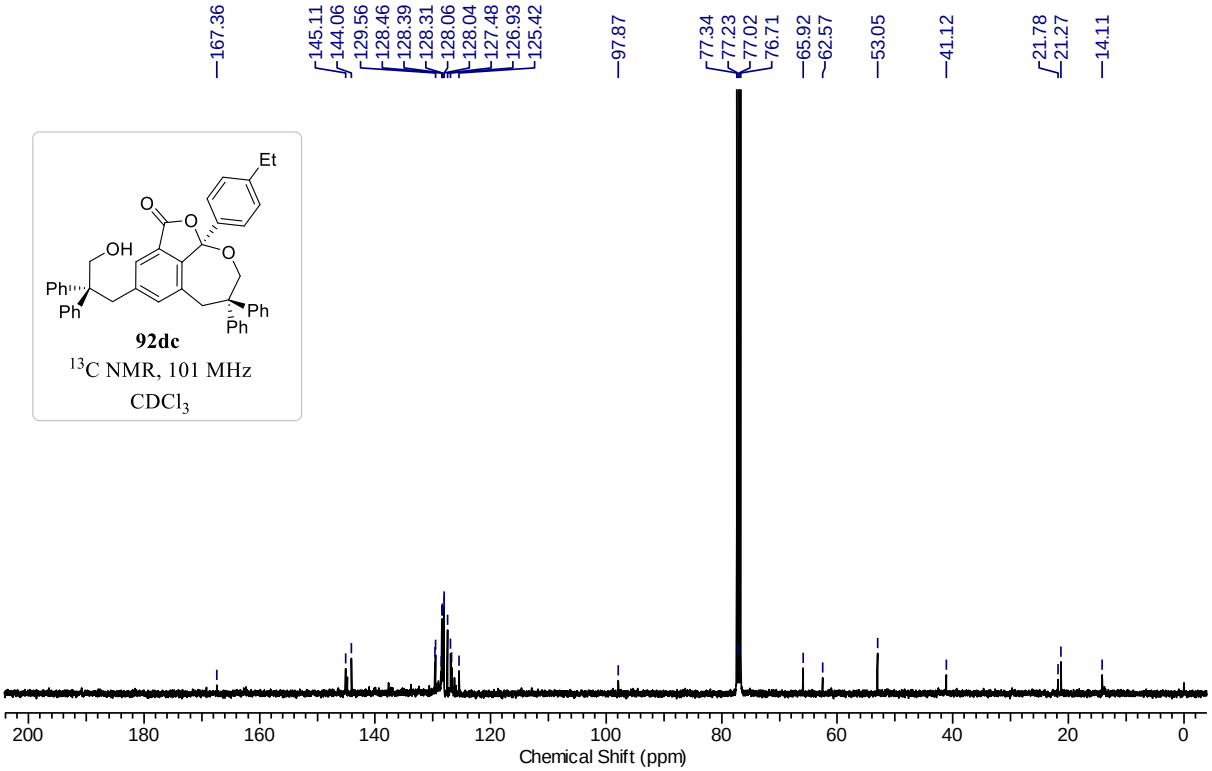
4-(3-hydroxy-2,2-diphenylpropyl)-7,7-diphenyl-9*a*-(*p*-tolyl)-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92db)



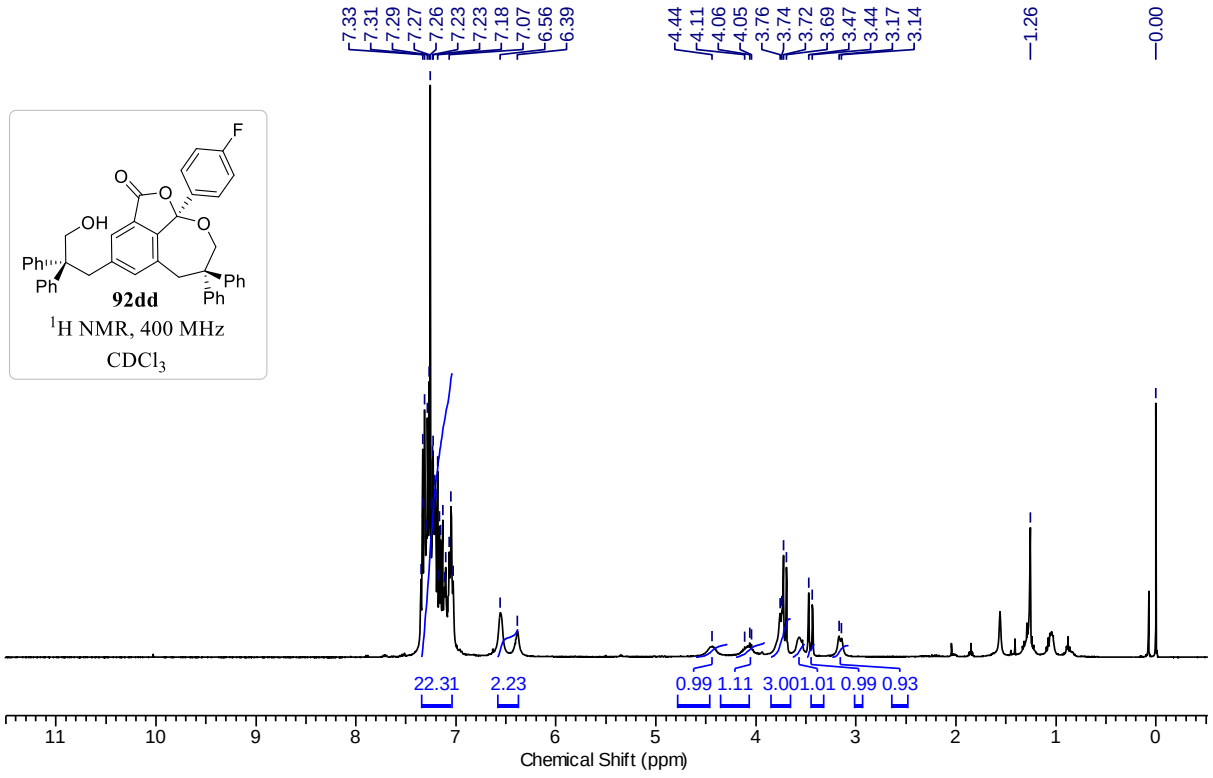


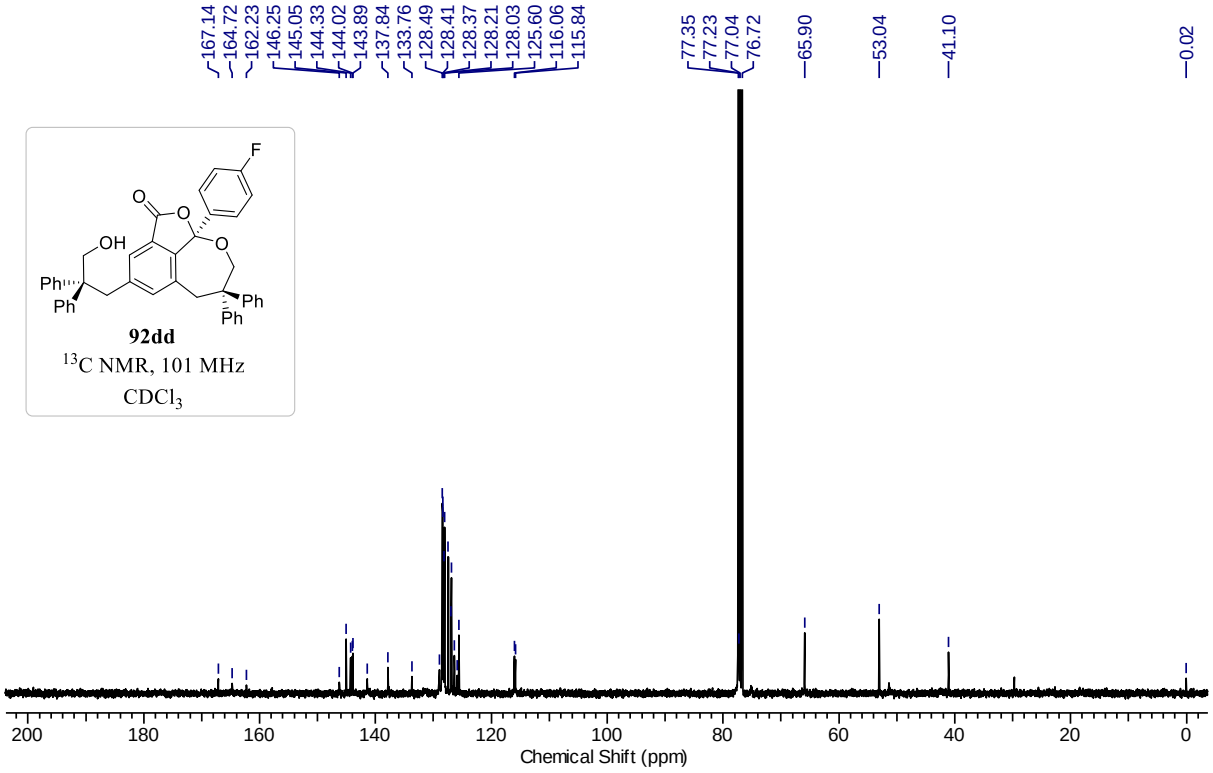
9*a*-(4-ethylphenyl)-4-(3-hydroxy-2,2-diphenylpropyl)-7,7-diphenyl-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92dc)



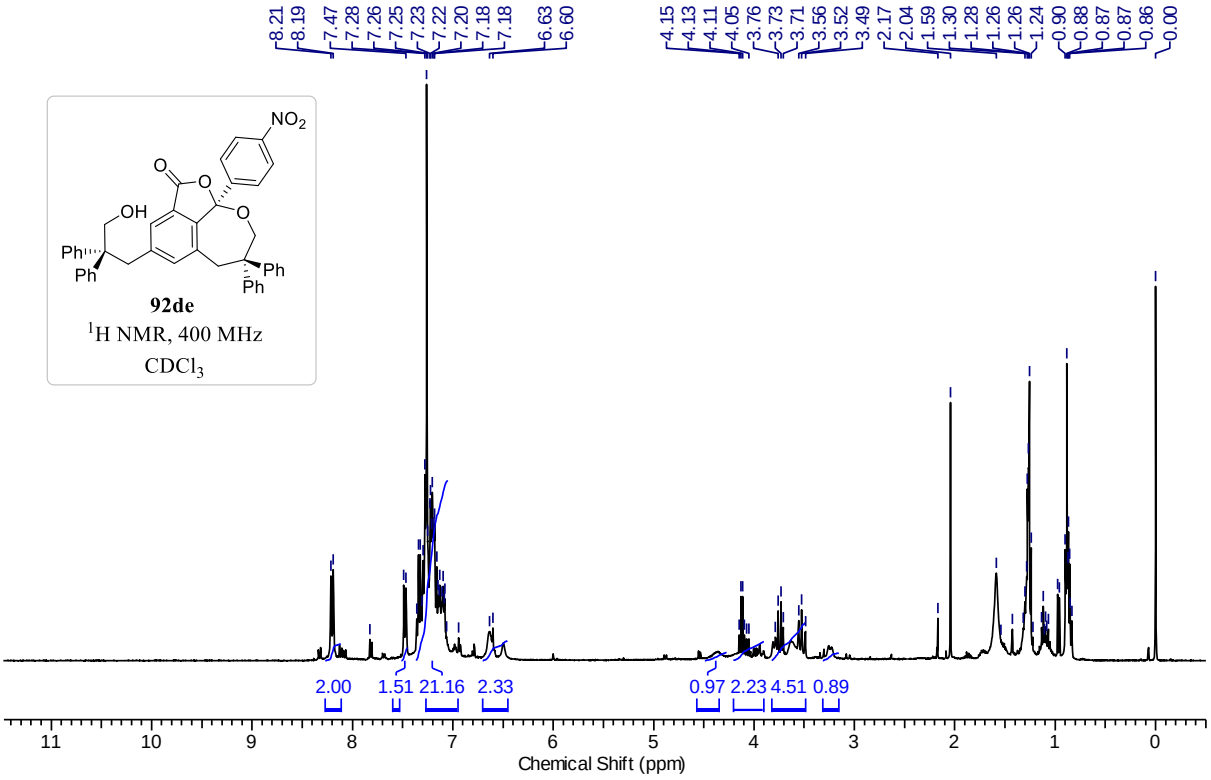


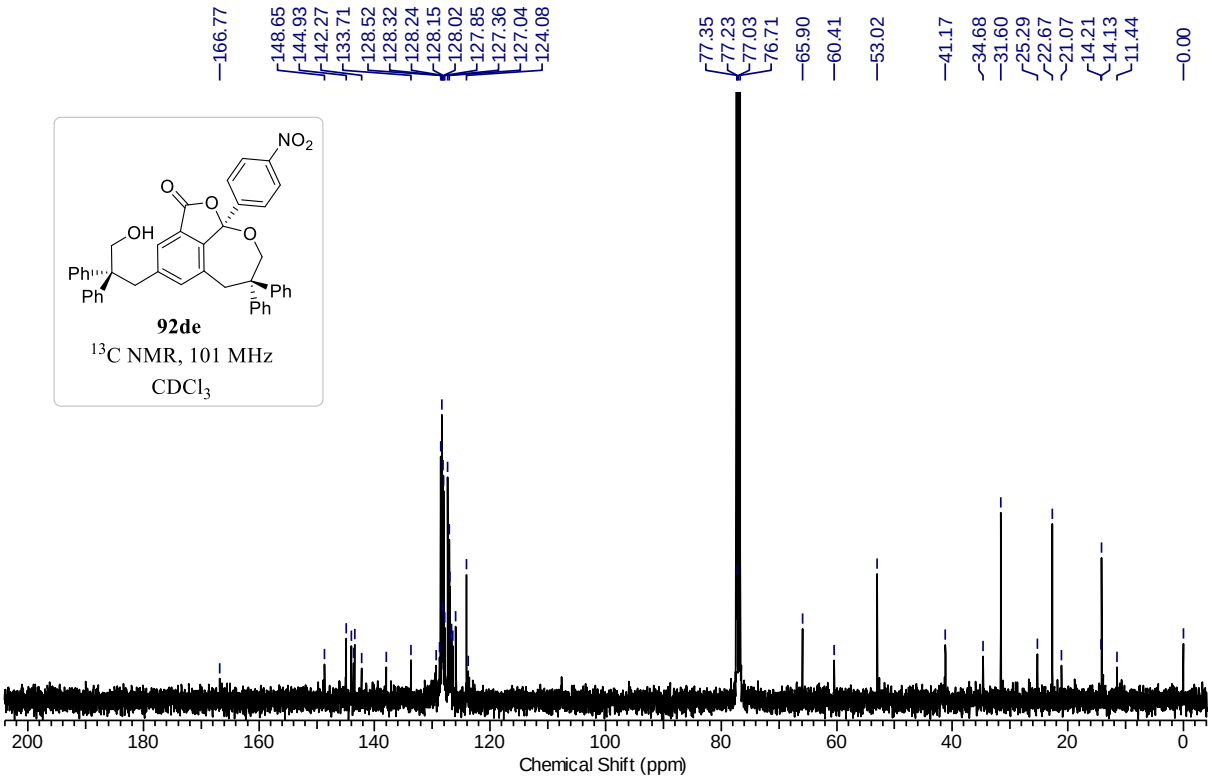
9*a*-(4-fluorophenyl)-4-(3-hydroxy-2,2-diphenylpropyl)-7,7-diphenyl-6,7,8,9*a*-tetrahydro-2*H*-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92dd)





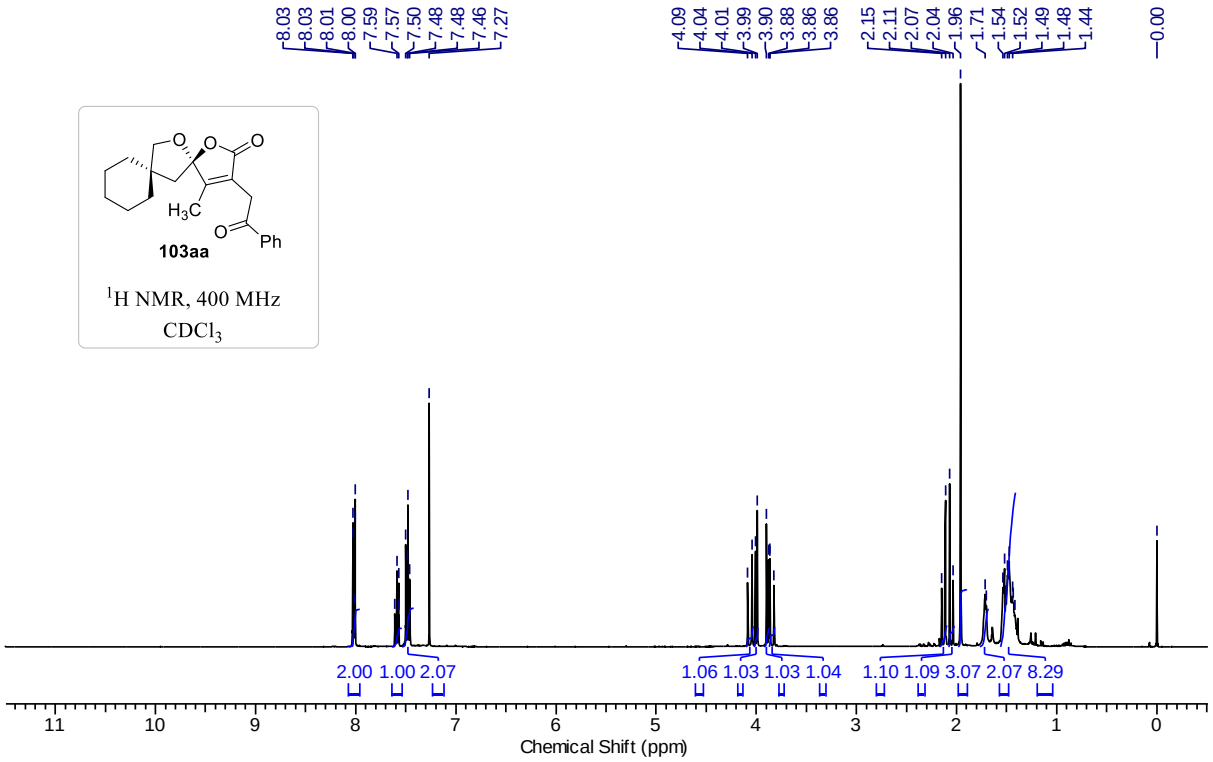
4-(3-hydroxy-2,2-diphenylpropyl)-9a-(4-nitrophenyl)-7,7-diphenyl-6,7,8,9a-tetrahydro-2H-oxepino[2,3,4-*cd*]isobenzofuran-2-one (92de):

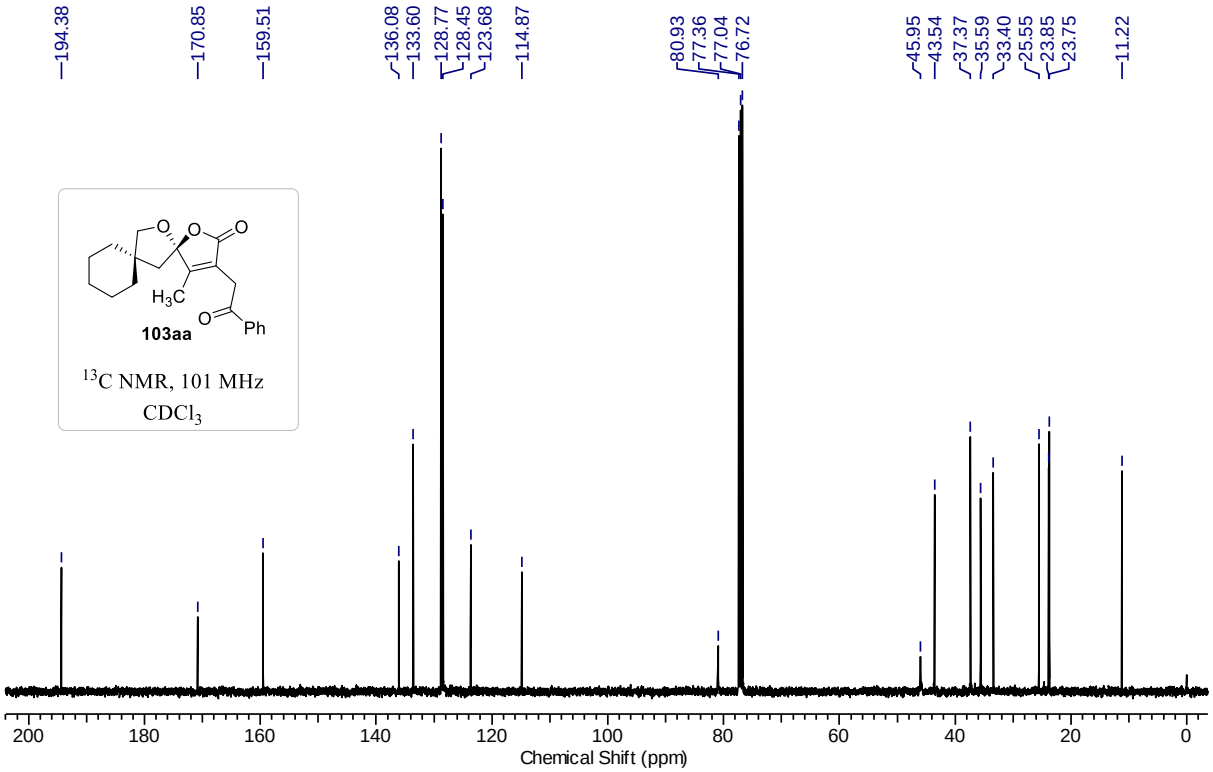




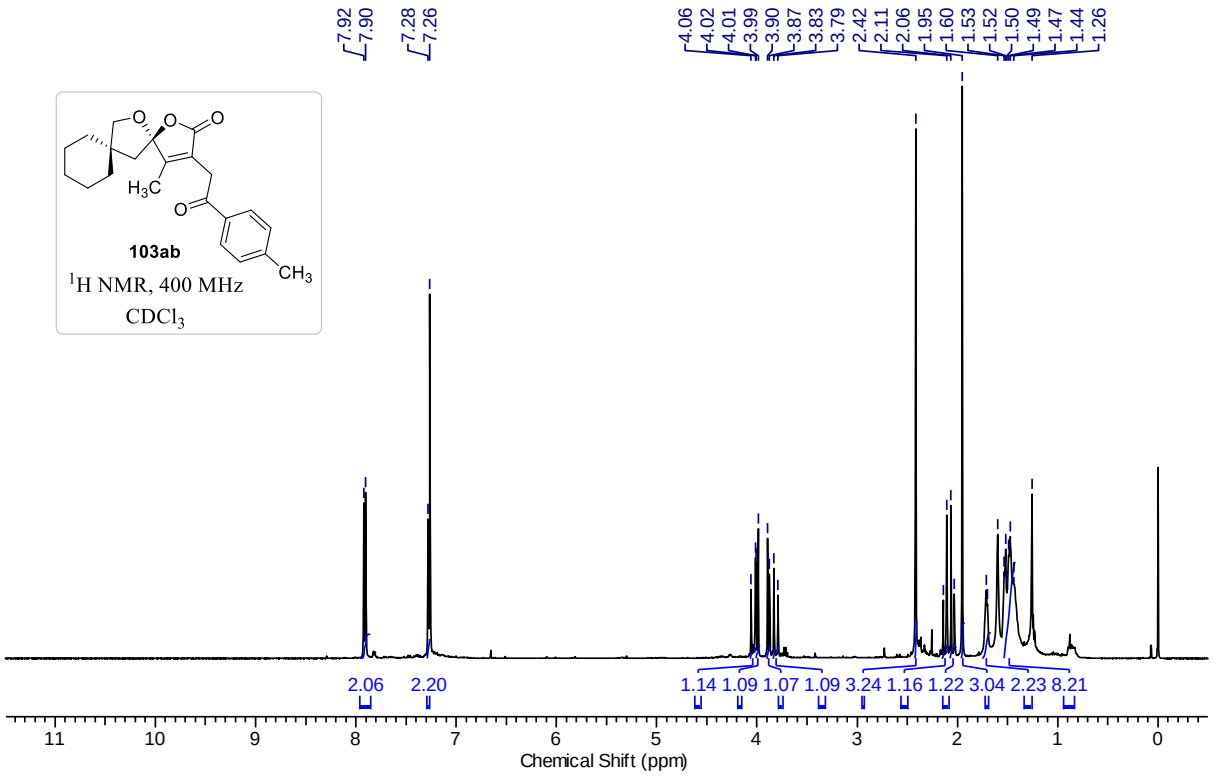
Synthesis of [5,5]-oxaspirolactone:

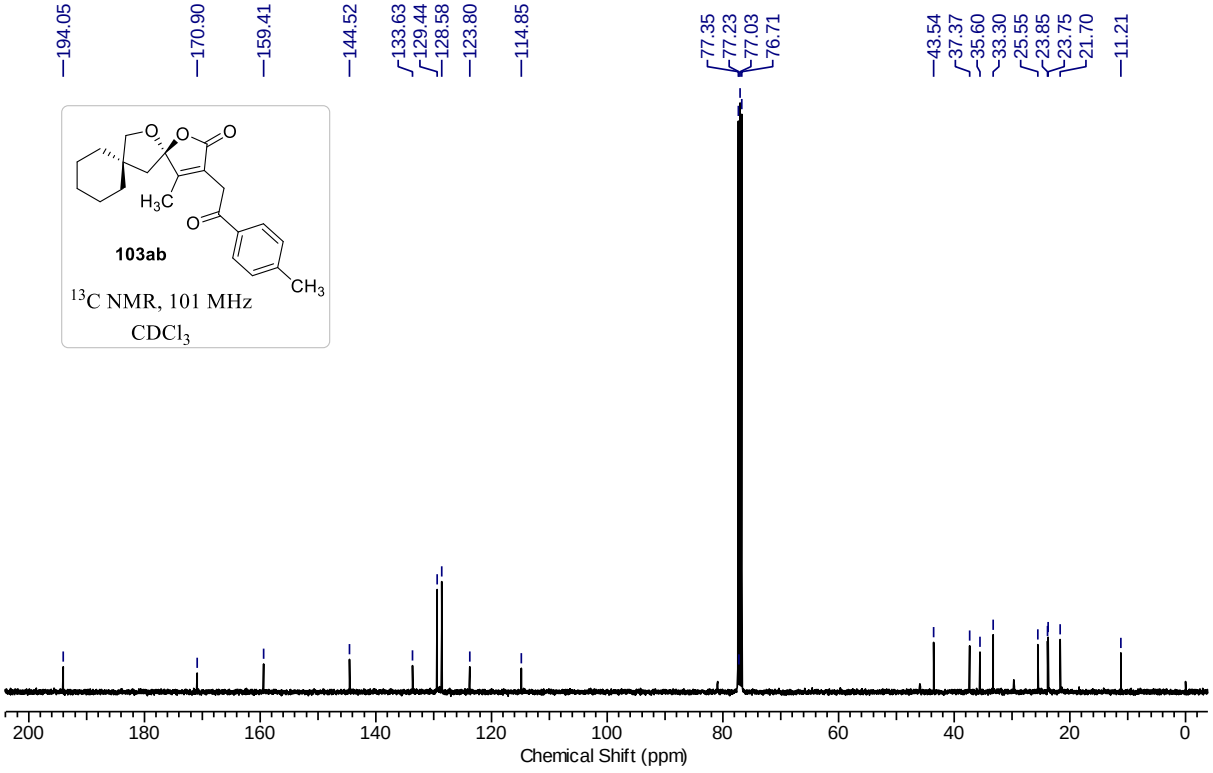
4-Methyl-3-(2-phenylacetyl)-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (103aa):



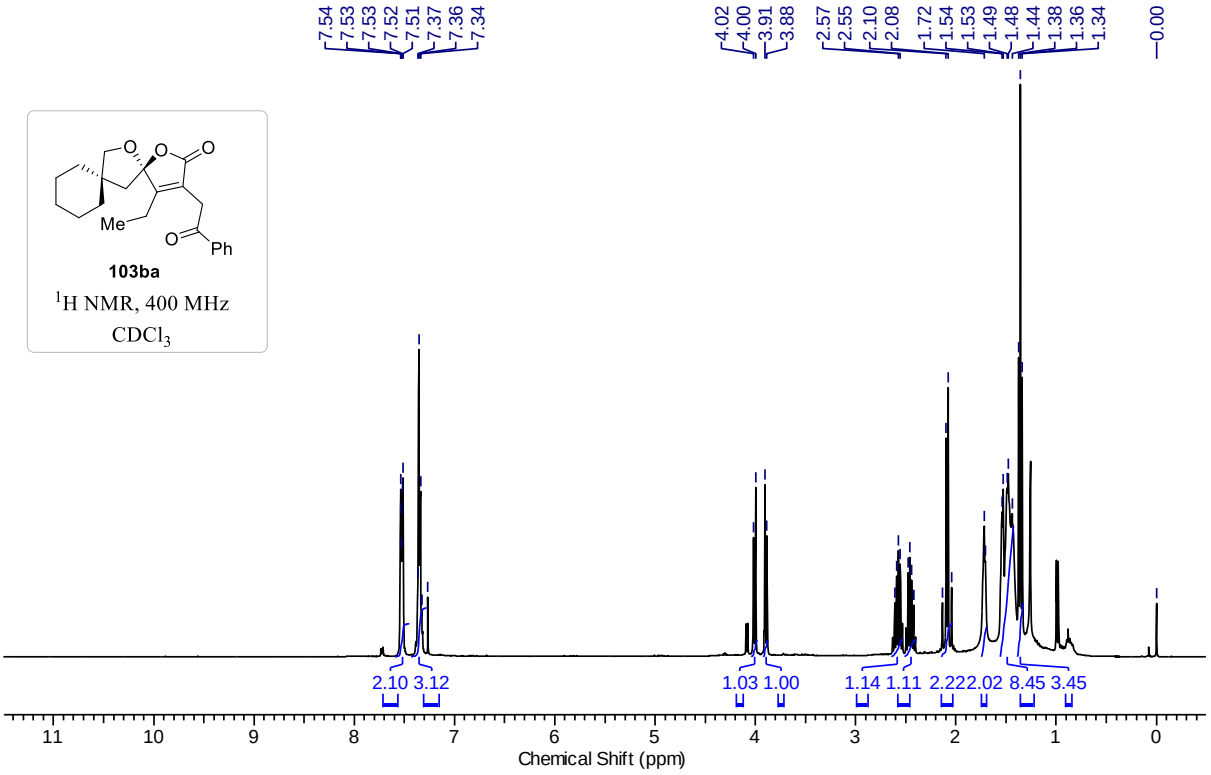


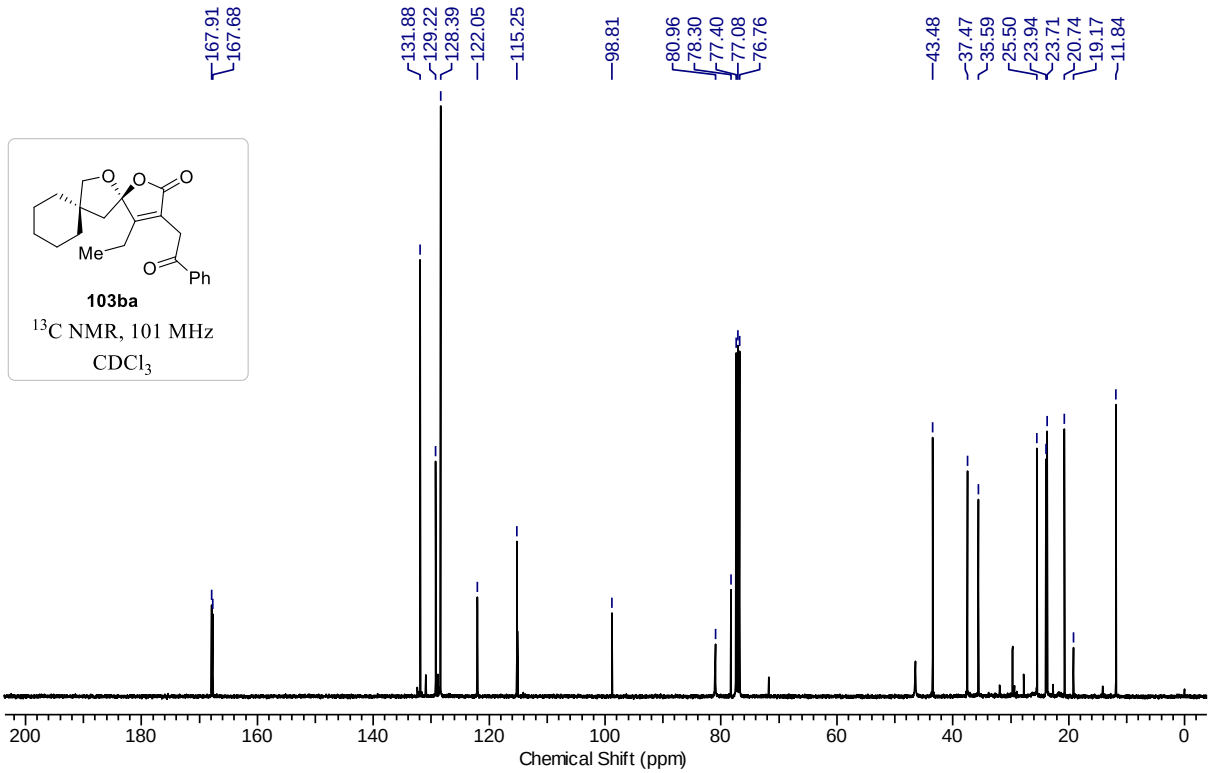
4-Methyl-3-(2-(*p*-tolyl)acetyl)-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (103ab):



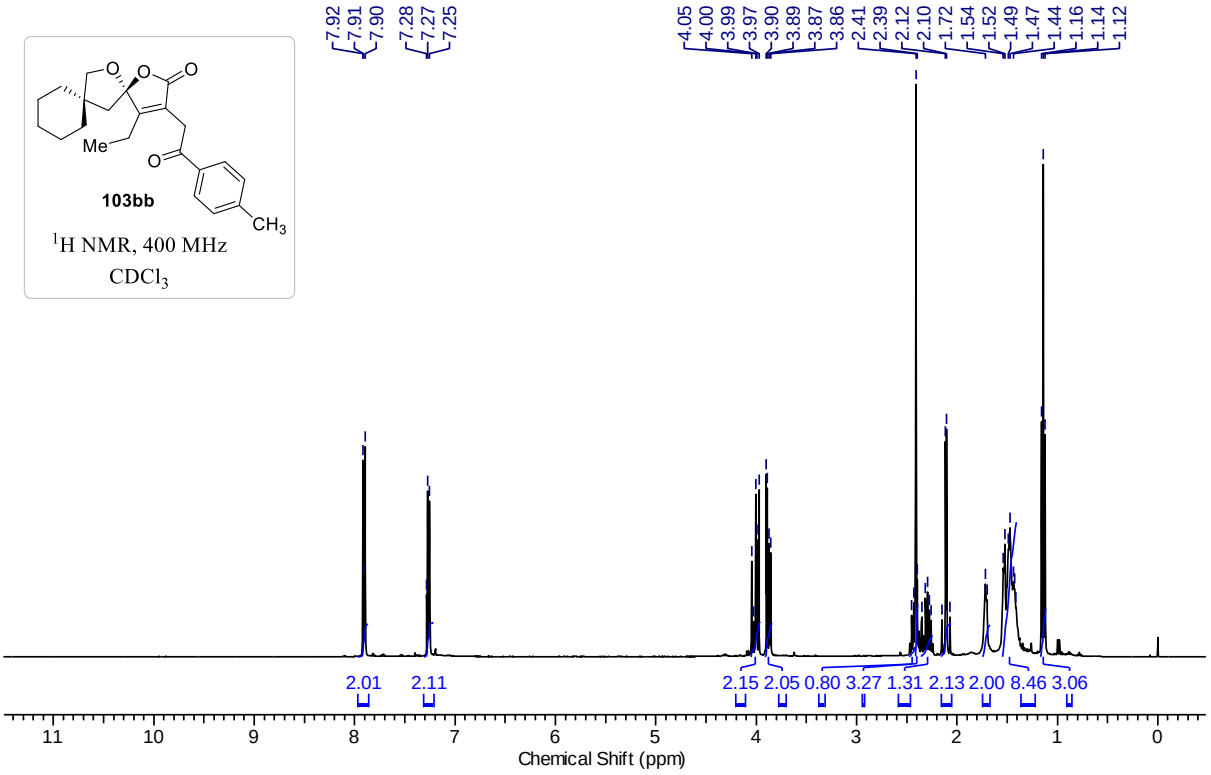


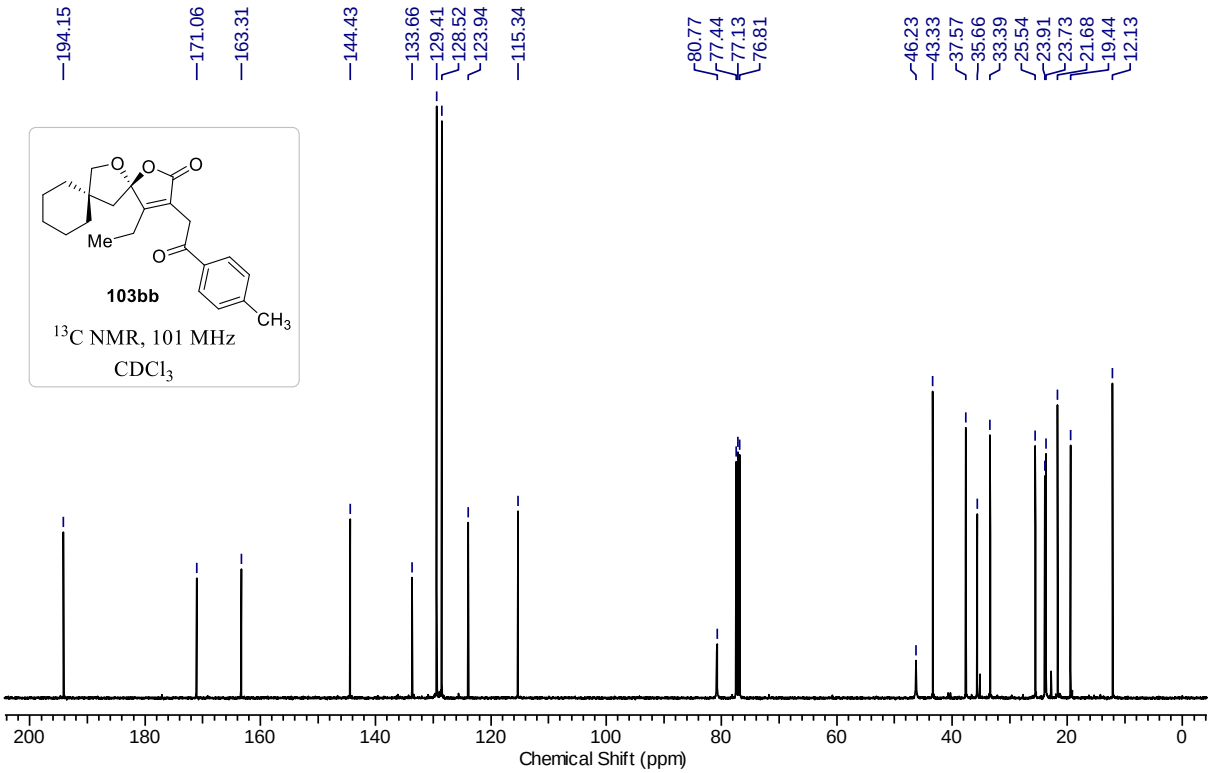
4-Ethyl-3-(2-phenylacetyl)-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (103ba)



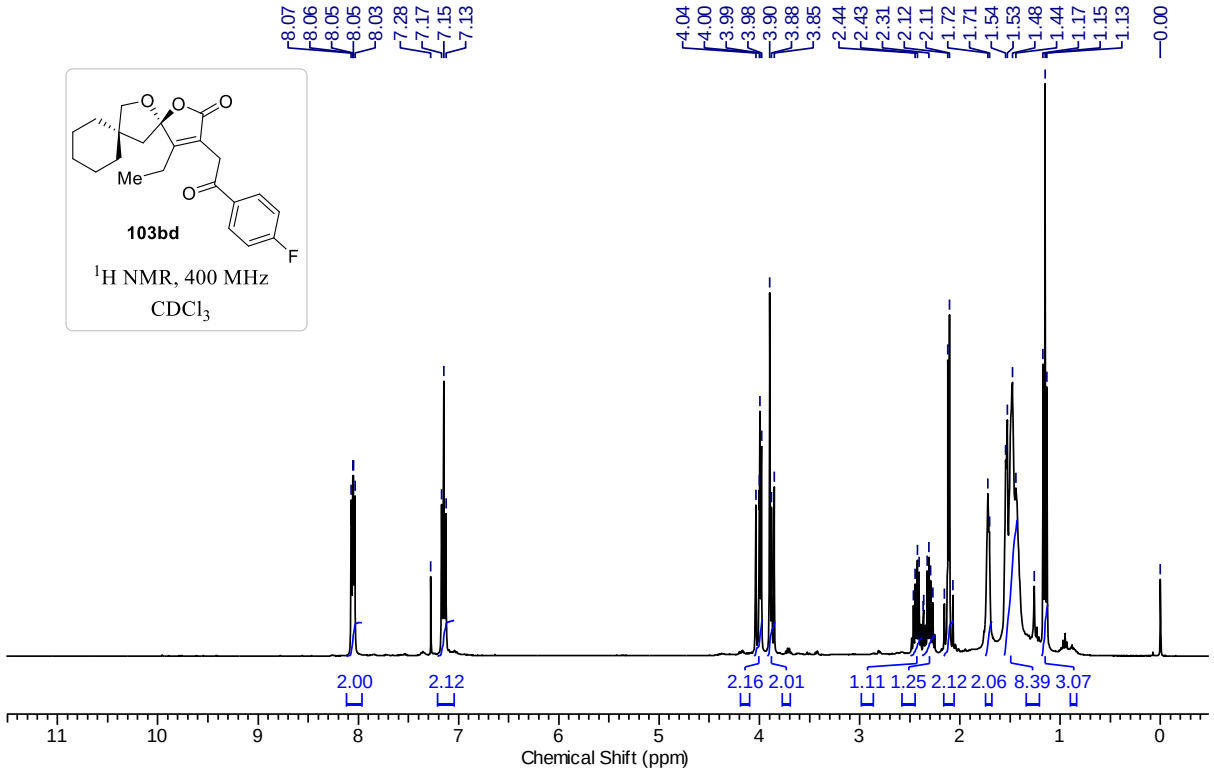


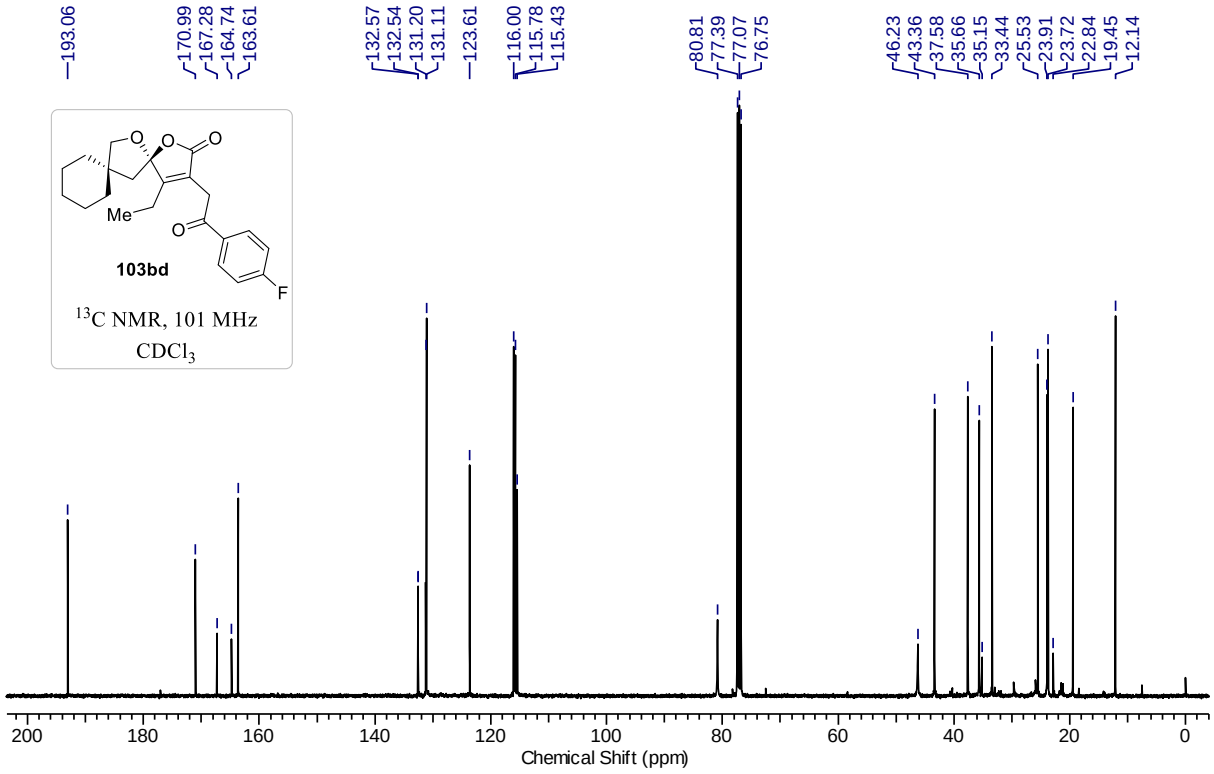
4-Ethyl-3-(2-(*p*-tolyl)acetyl)-1,14-dioxadispiro[4.1.5^7.2^5]tetradec-3-en-2-one (103 bb):



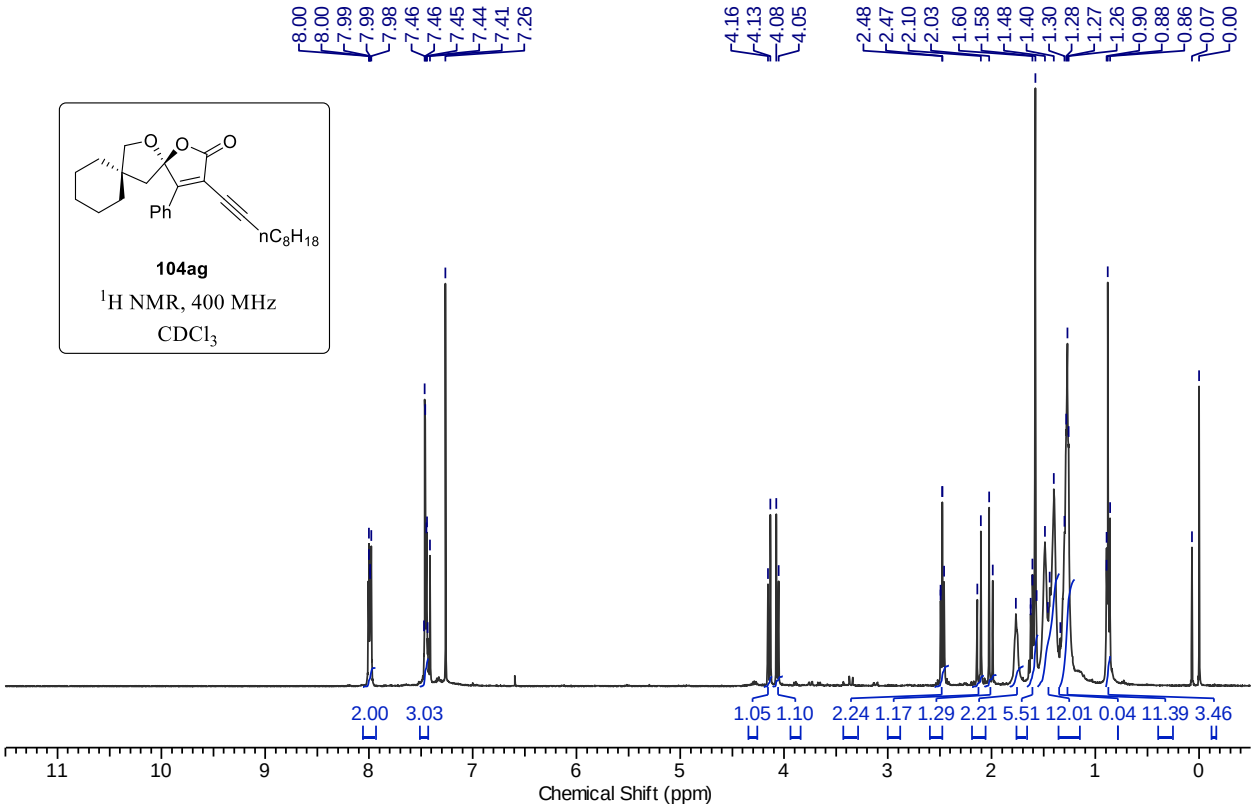


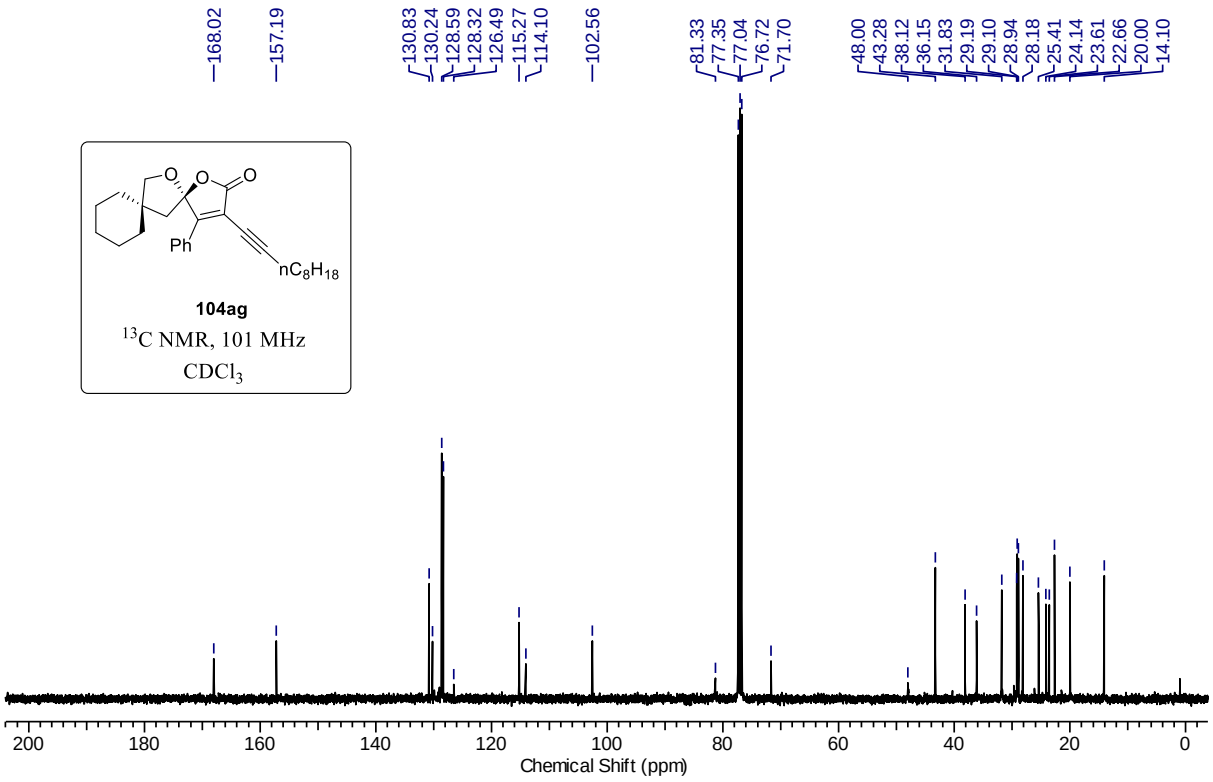
4-Ethyl-3-(2-(4-fluorophenyl)acetyl)-1,14-dioxadispiro[4.1.5^{7}.2^{5}]tetradec-3-en-2-one (103 bd):



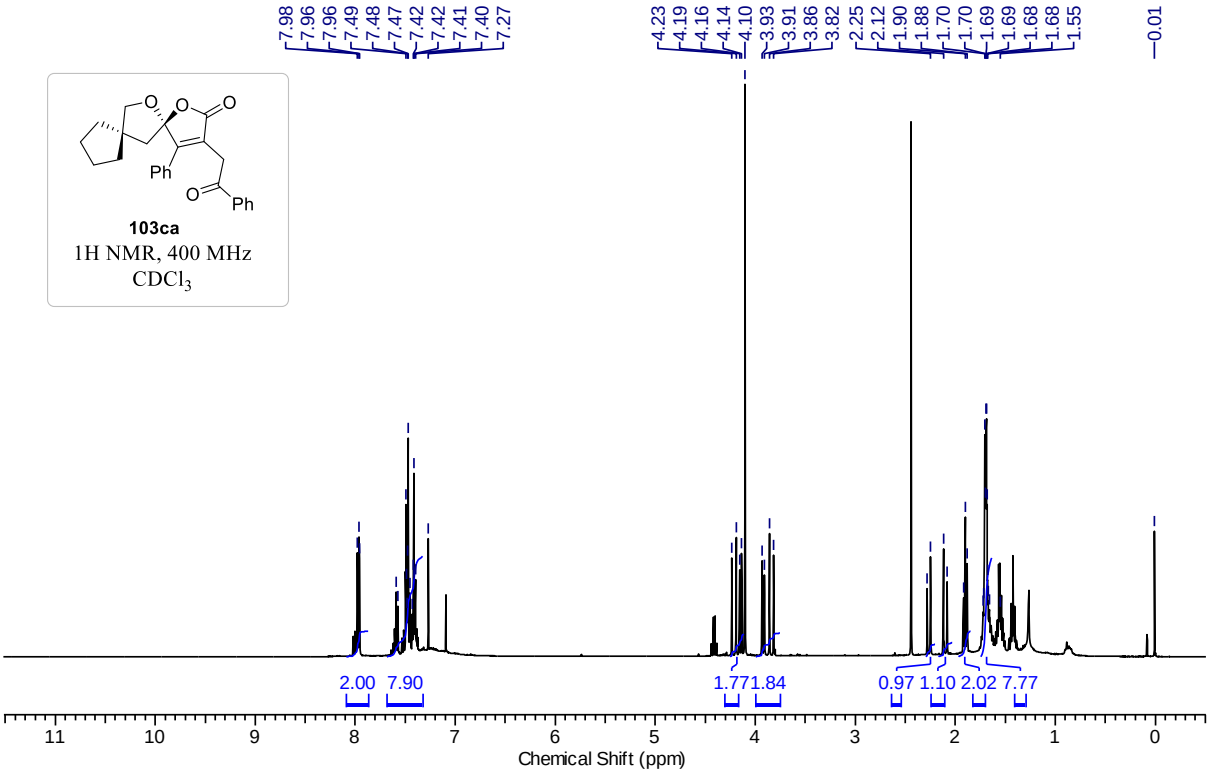


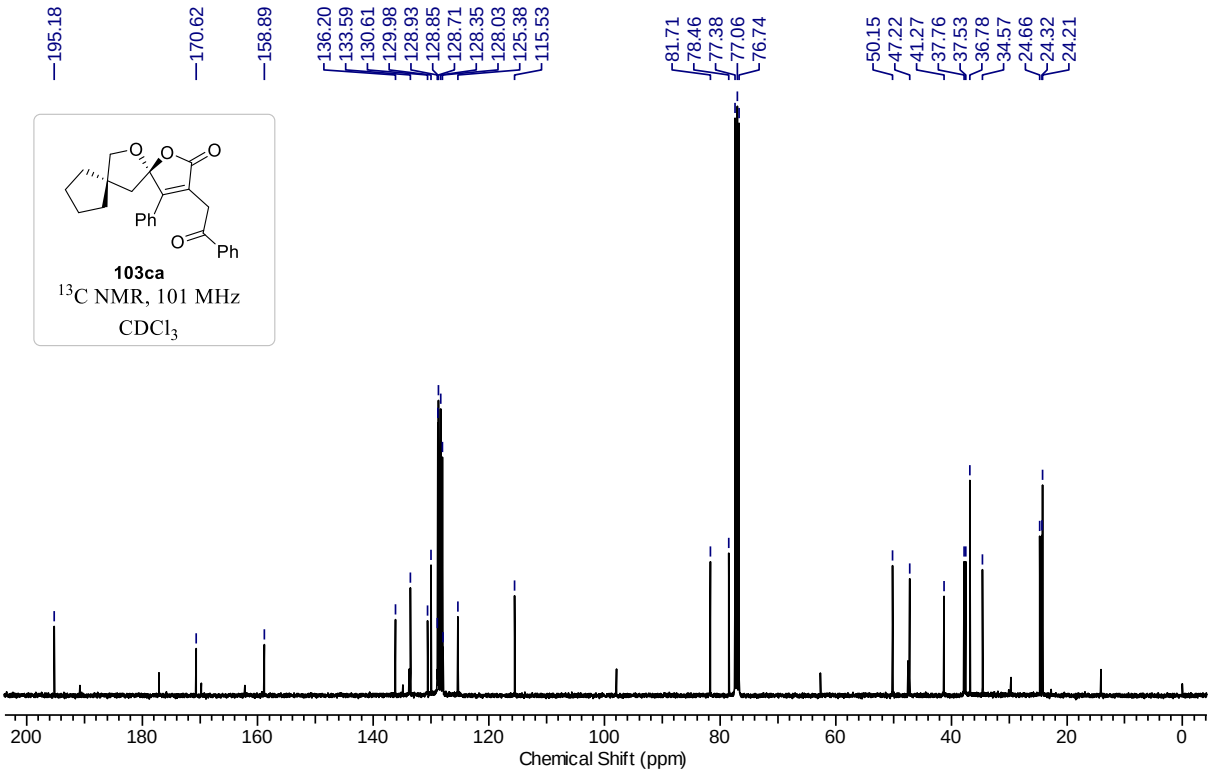
3-Decanoyl-4-phenyl-1,14-dioxadispiro[4.1.57.25]tetradec-3-en-2-one (104gg):



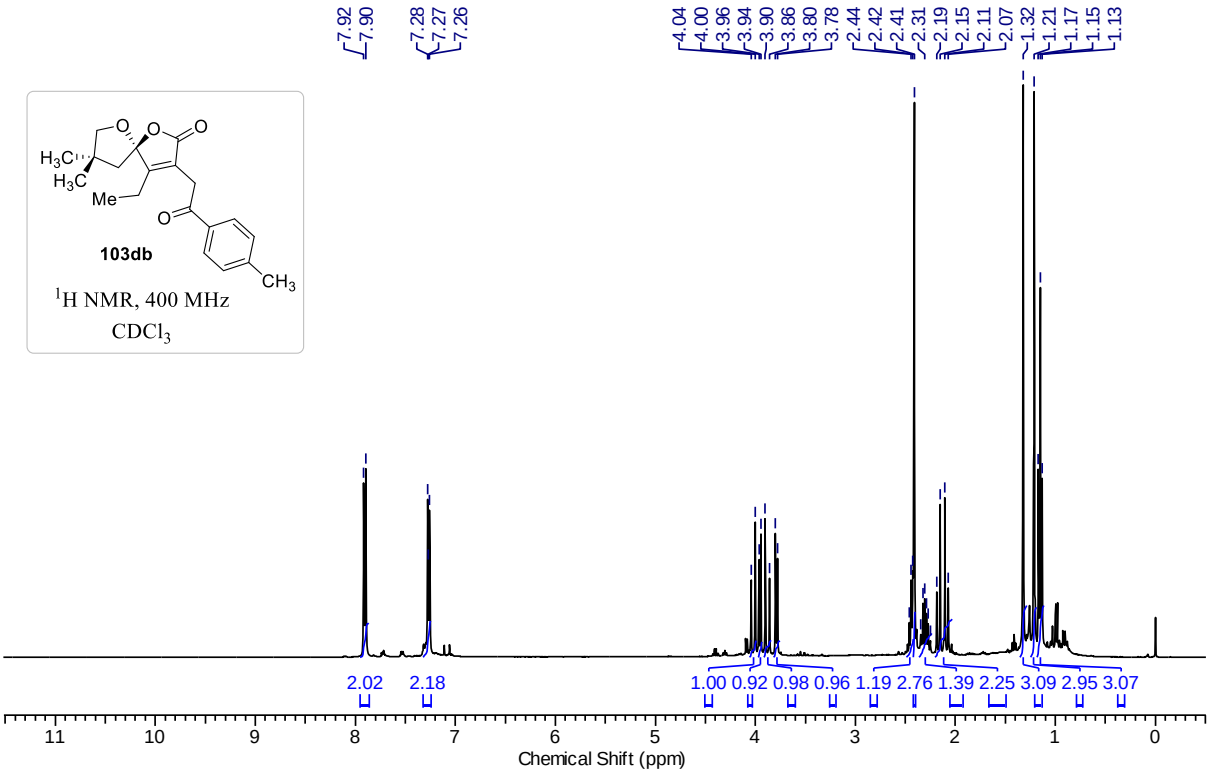


4-phenyl-3-(2-phenylacetyl)-1,13-dioxadispiro[4.1.4^7.2^5]tridec-3-en-2-one (103ca):





4-Ethyl-8,8-dimethyl-3-(2-(*p*-tolyl)acetyl)-1,6-dioxaspiro[4.4]non-3-en-2-one (103db):


7.92
7.90
7.28
7.27
7.26
4.04
4.00
3.96
3.94
3.90
3.86
3.80
3.78
2.44
2.42
2.41
2.31
2.19
2.15
2.11
2.07
1.32
1.21
1.17
1.15
1.13
103db
^{1}H NMR, 400 MHz
$CDCl_3$
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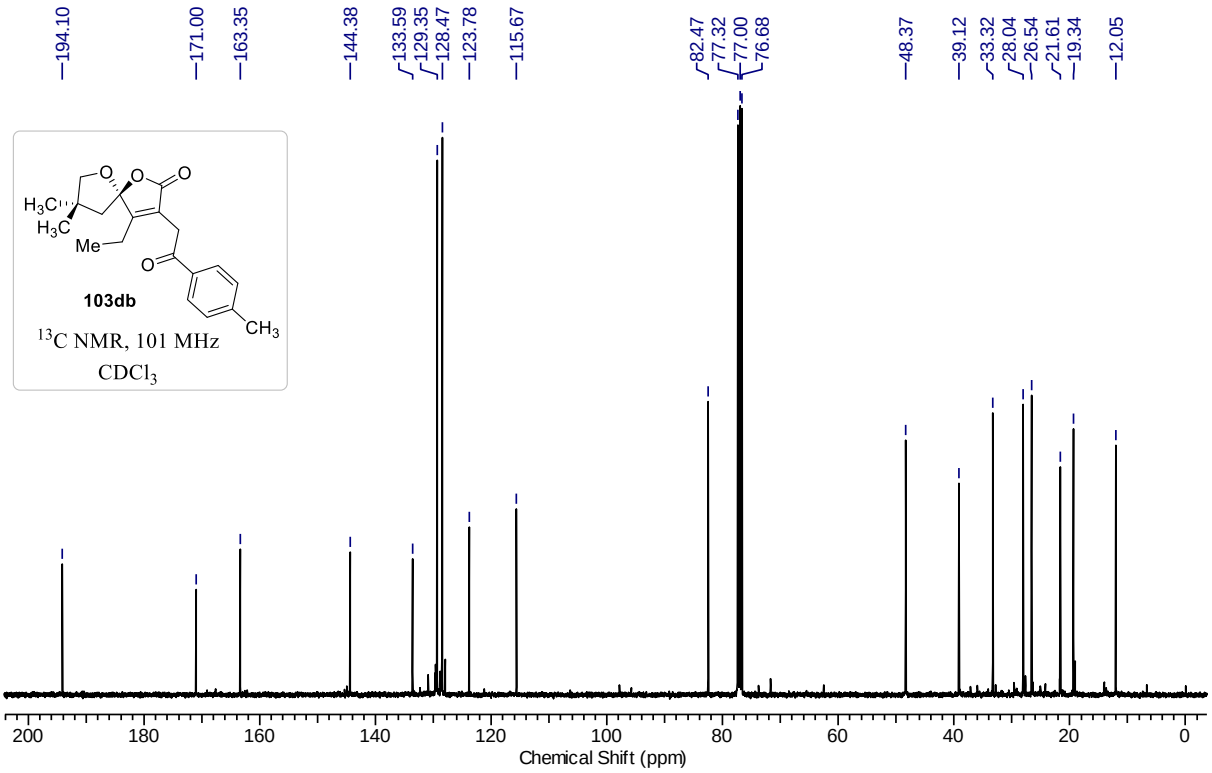
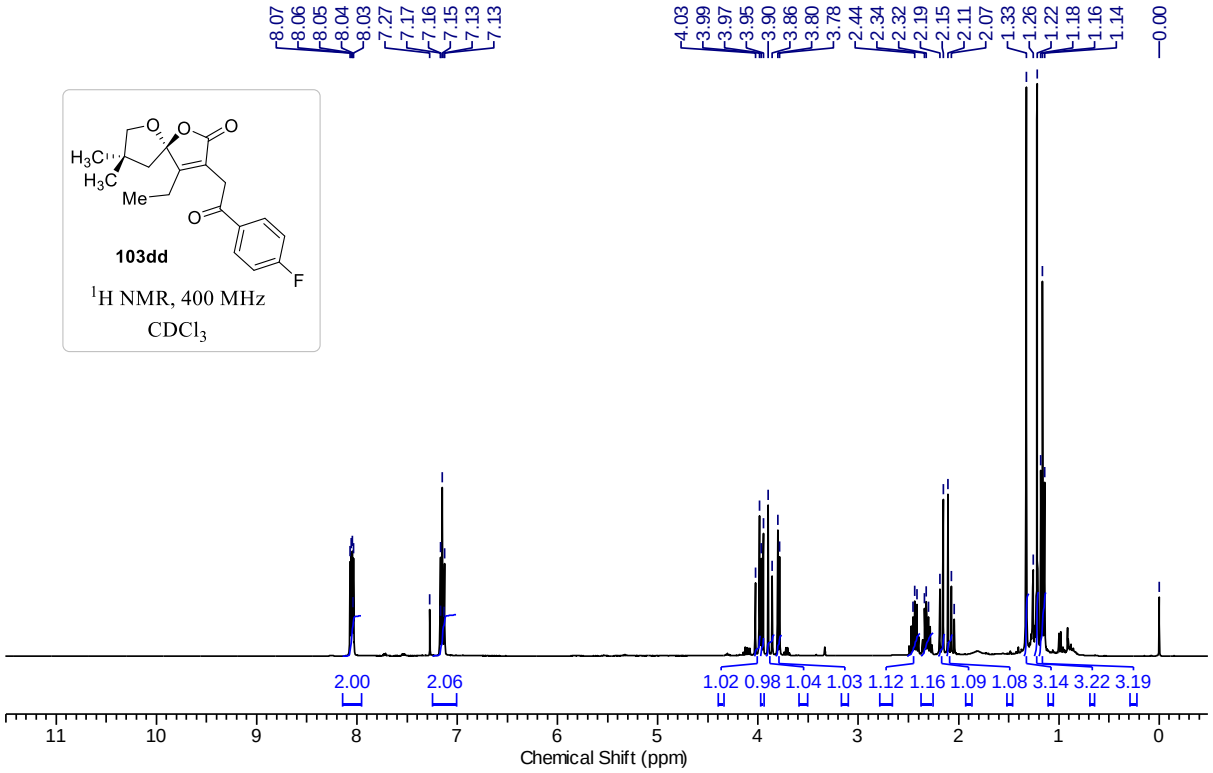
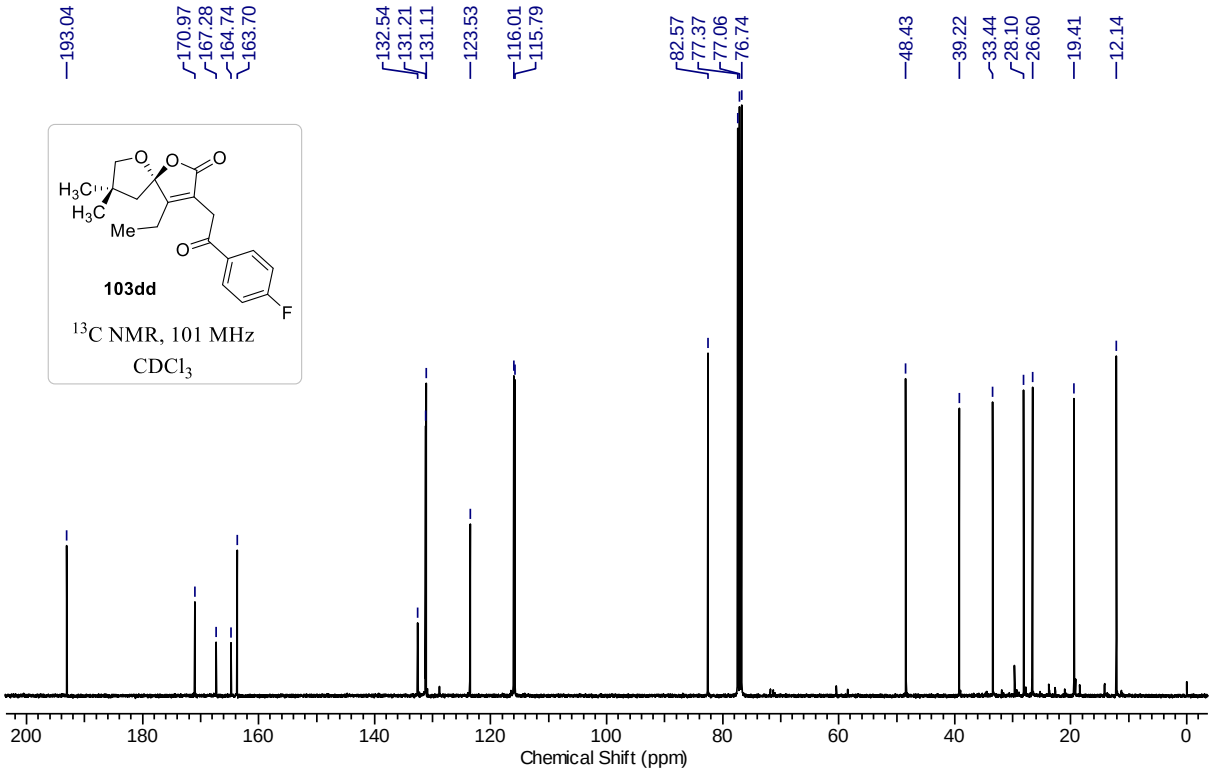
2.18
1.00 0.92 0.98 0.96 1.19 2.76 1.39 2.25 3.09 2.95 3.07
Chemical Shift (ppm)

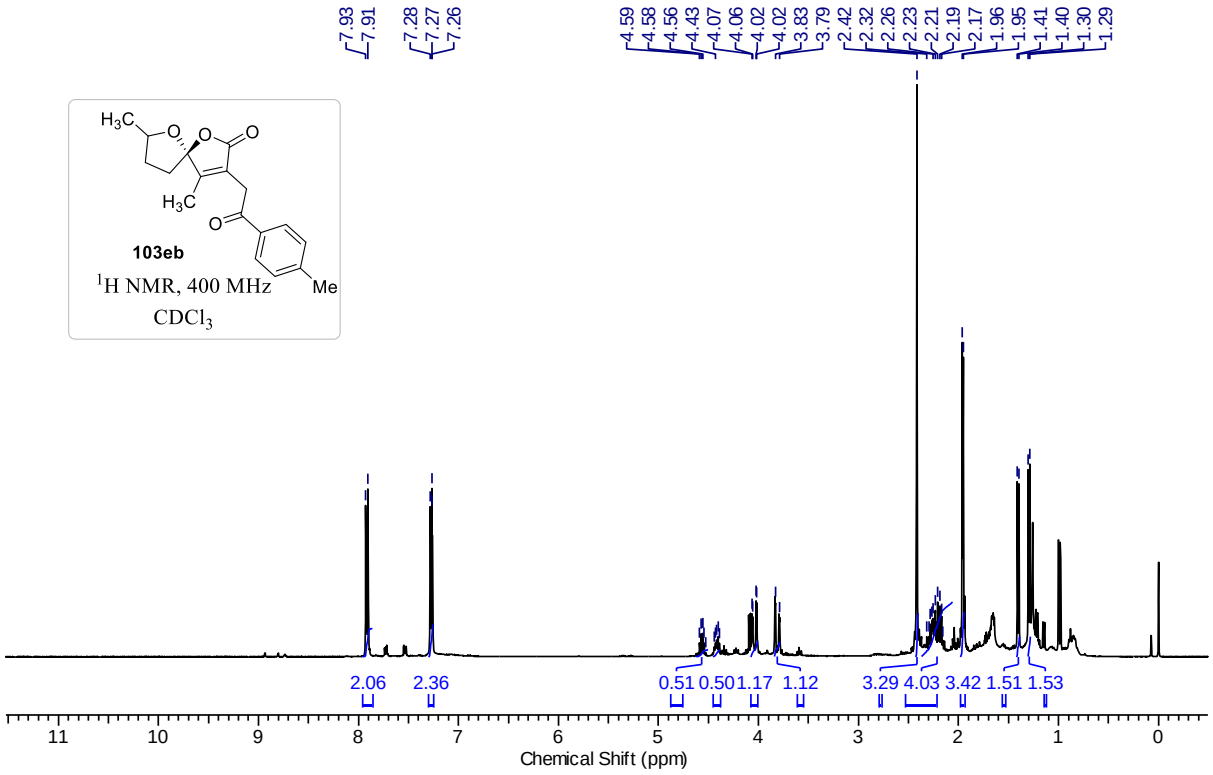

194.10
171.00
163.35
144.38
133.59
129.35
128.47
123.78
115.67
82.47
77.32
77.00
76.68
48.37
39.12
33.32
28.04
26.54
21.61
19.34
12.05
103db
^{13}C NMR, 101 MHz
$CDCl_3$
Chemical Shift (ppm)

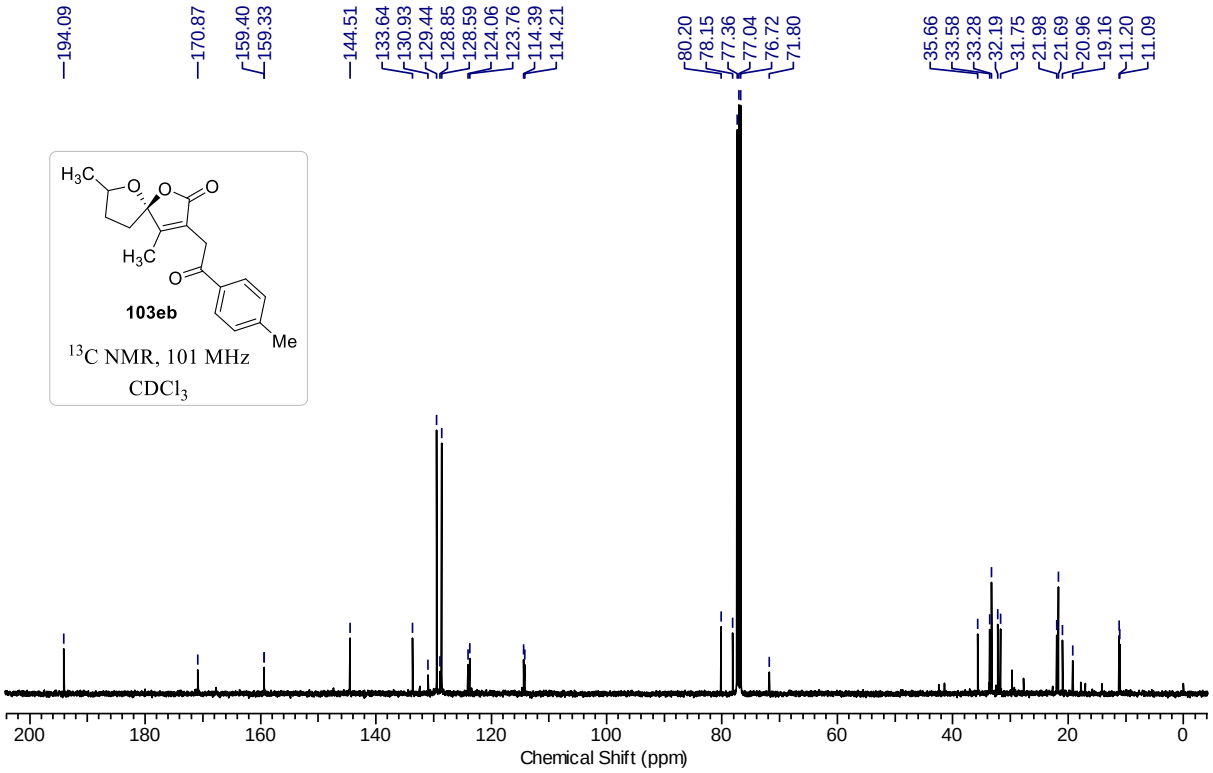
4-Ethyl-3-(2-(4-fluorophenyl)acetyl)-8,8-dimethyl-1,6-dioxaspiro[4.4]non-3-en-2-one (103 dd):



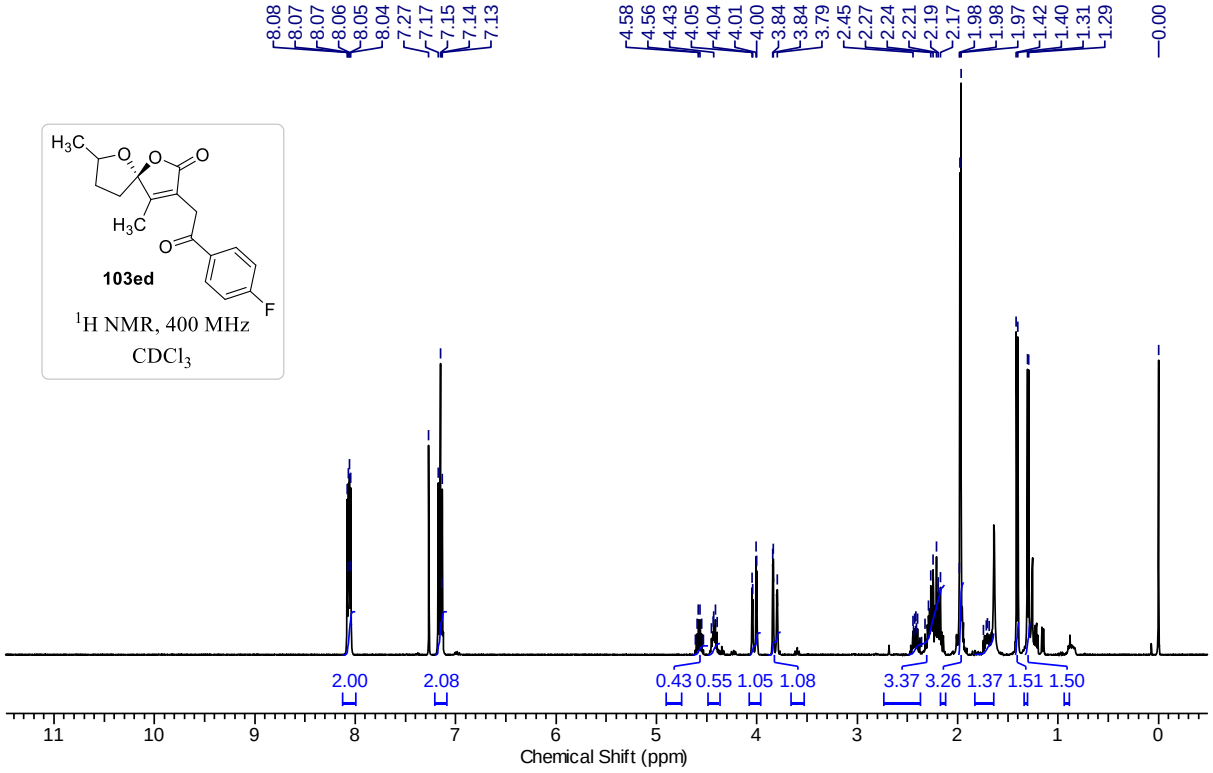


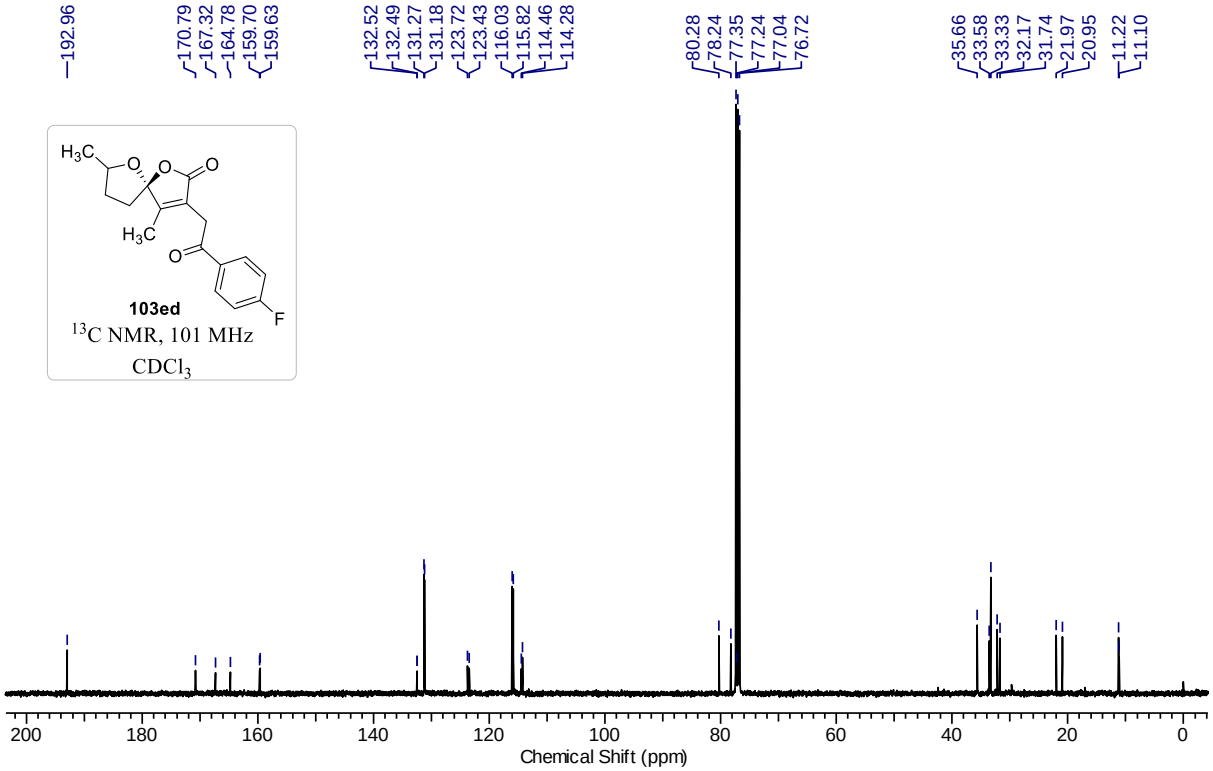
4,7-Dimethyl-3-(2-(*p*-tolyl)acetyl)-1,6-dioxaspiro[4.4]non-3-en-2-one (103eb):



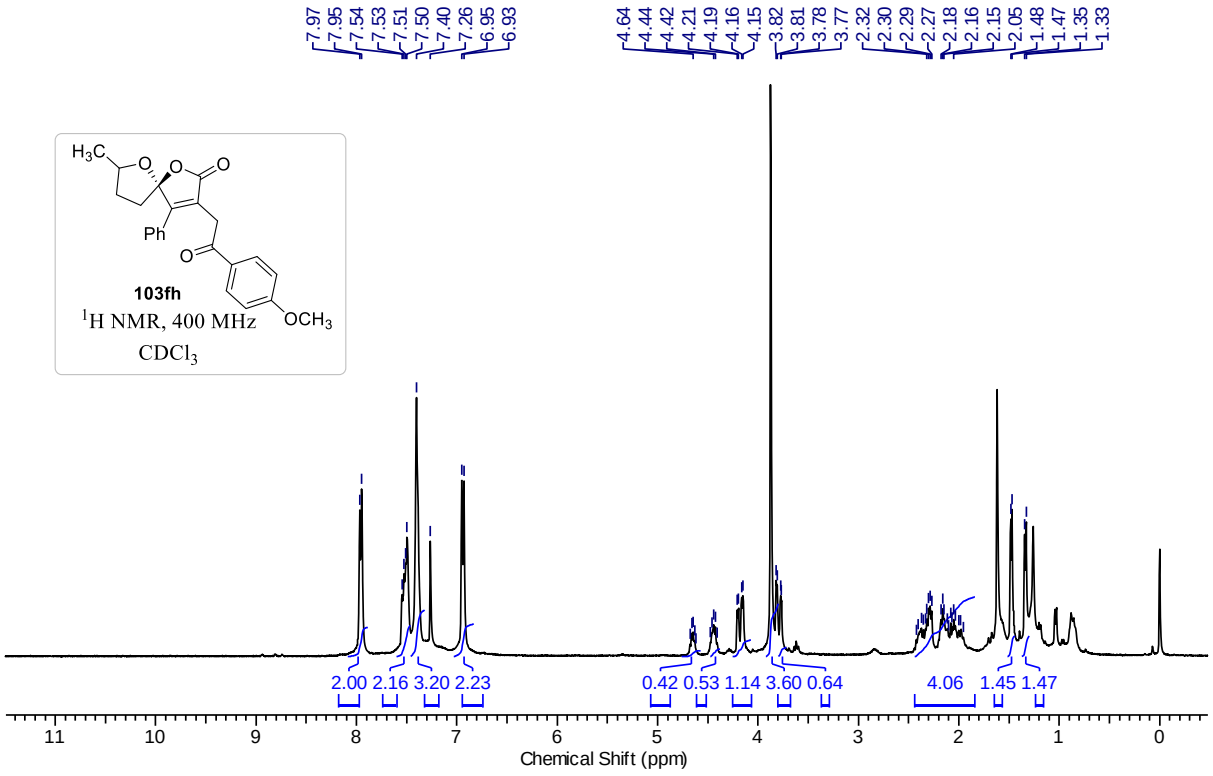


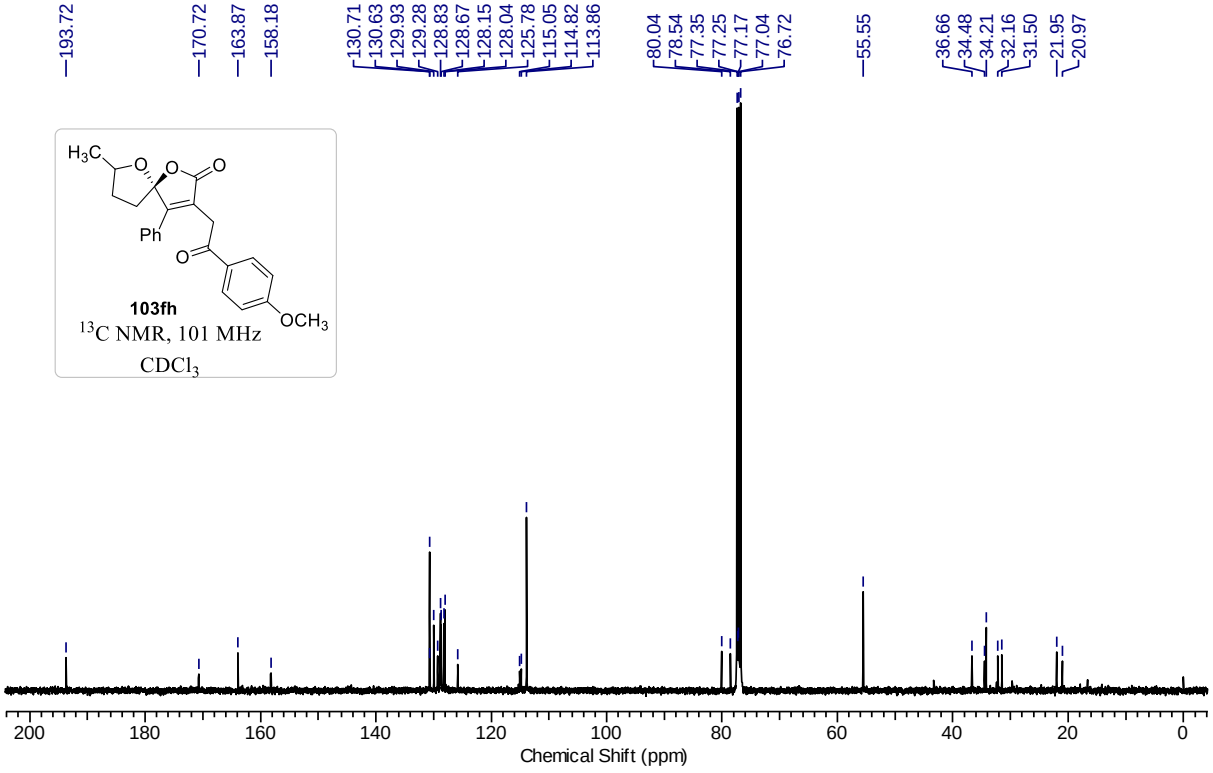
3-(2-(4-Fluorophenyl)acetyl)-4,7-dimethyl-1,6-dioxaspiro[4.4]non-3-en-2-one (103ed):





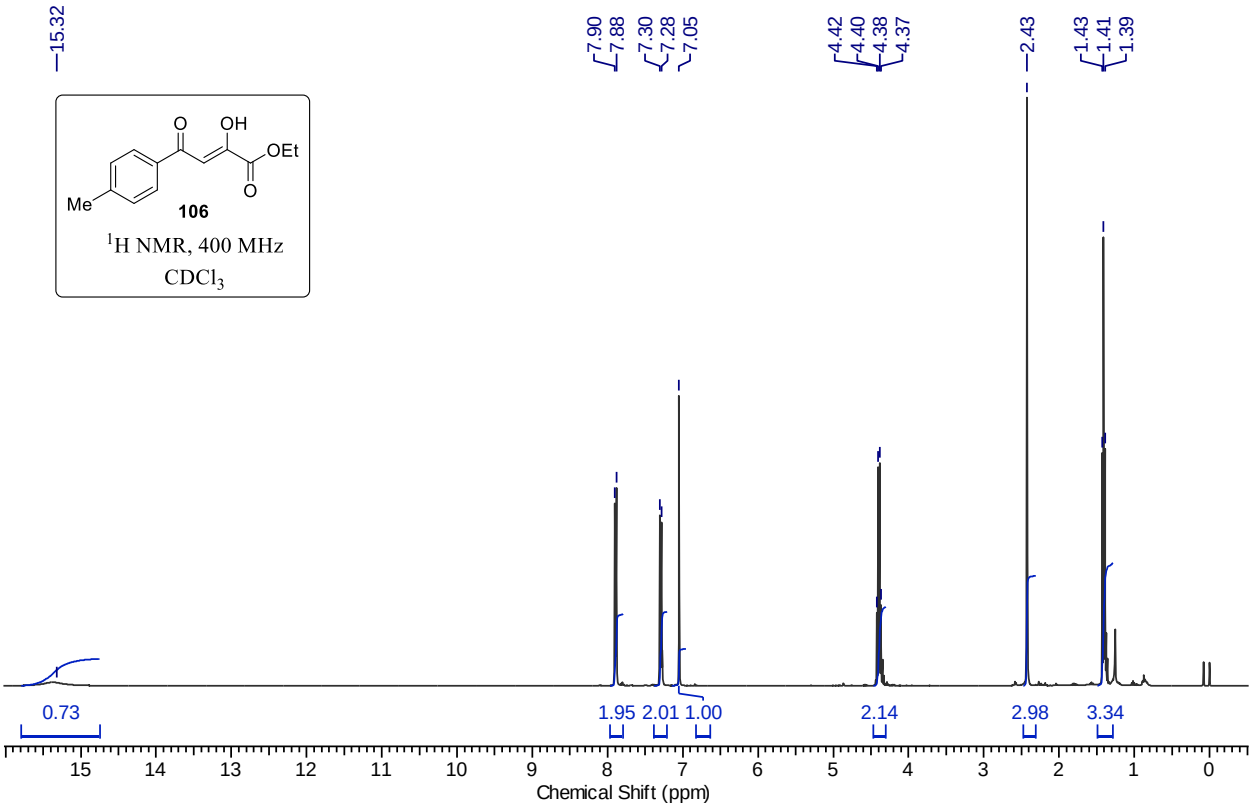
3-(2-(4-methoxyphenyl)acetyl)-7-methyl-4-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (103fh)

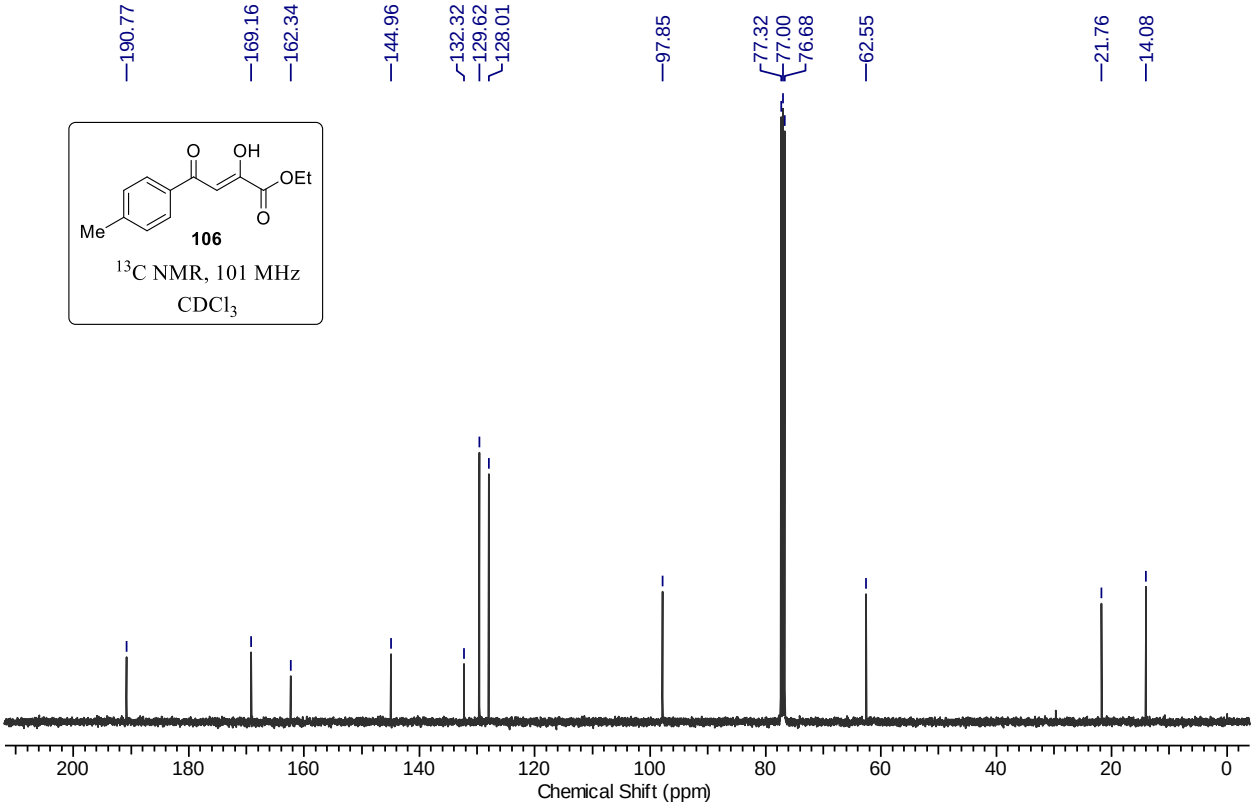


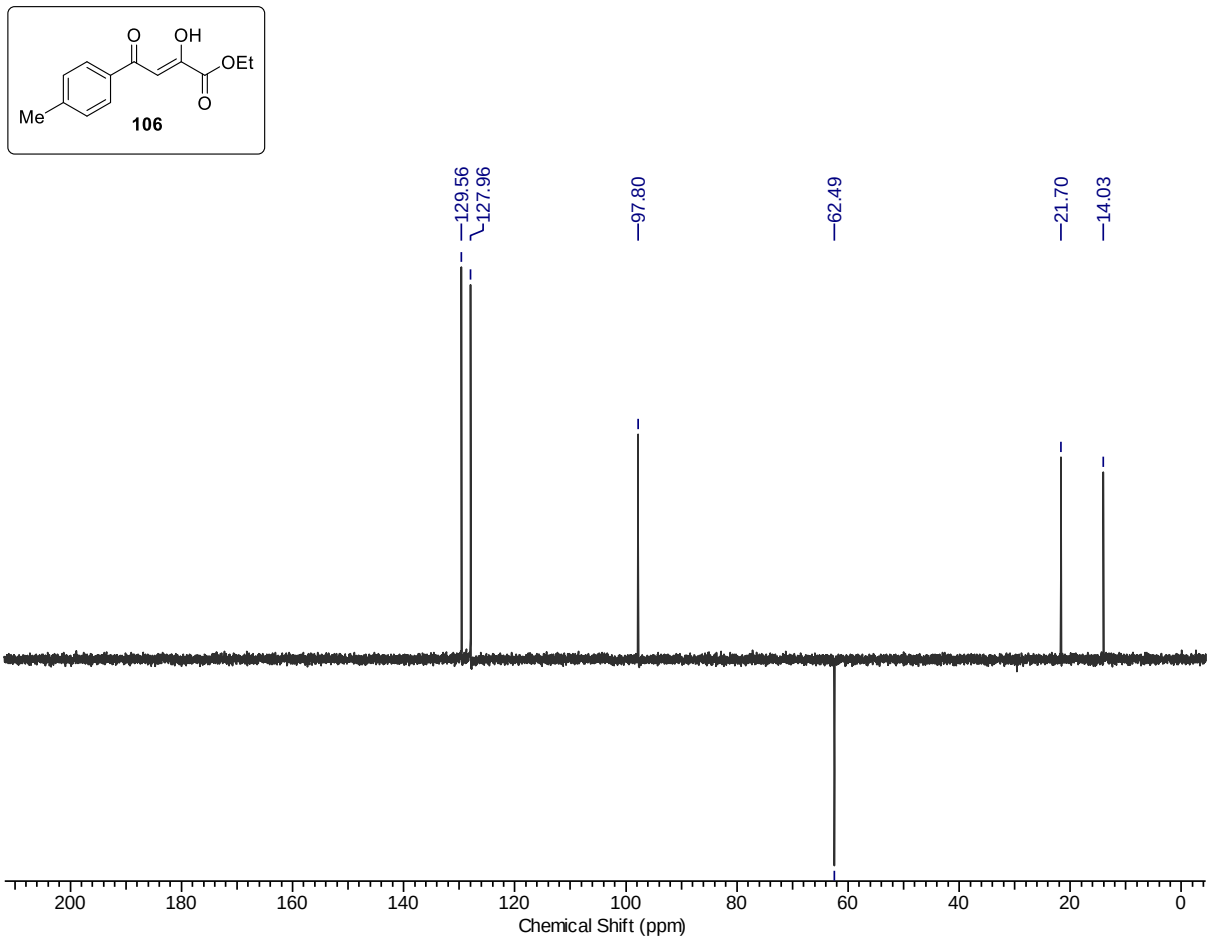


Supporting experiments for the mechanism:

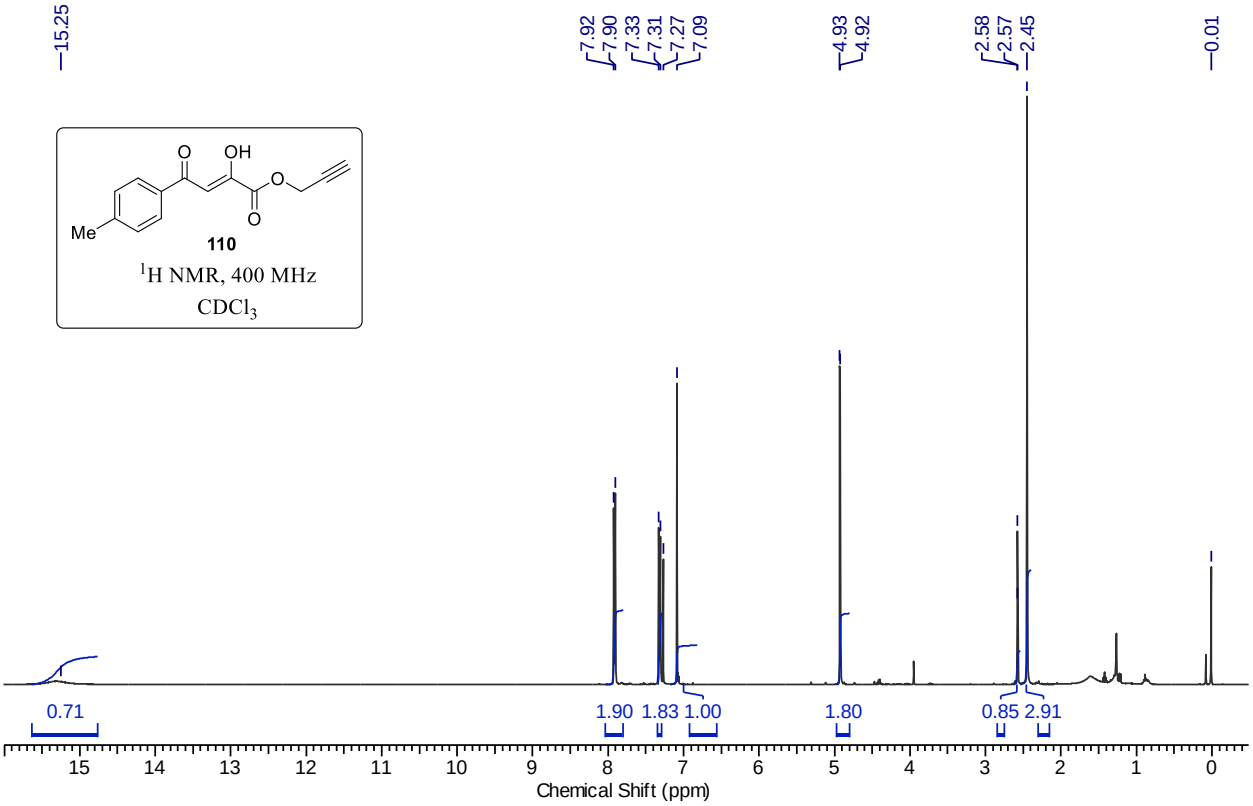
Ethyl 2-hydroxy-4-(*p*-tolyl)buta-2,3-dienoate (106) :

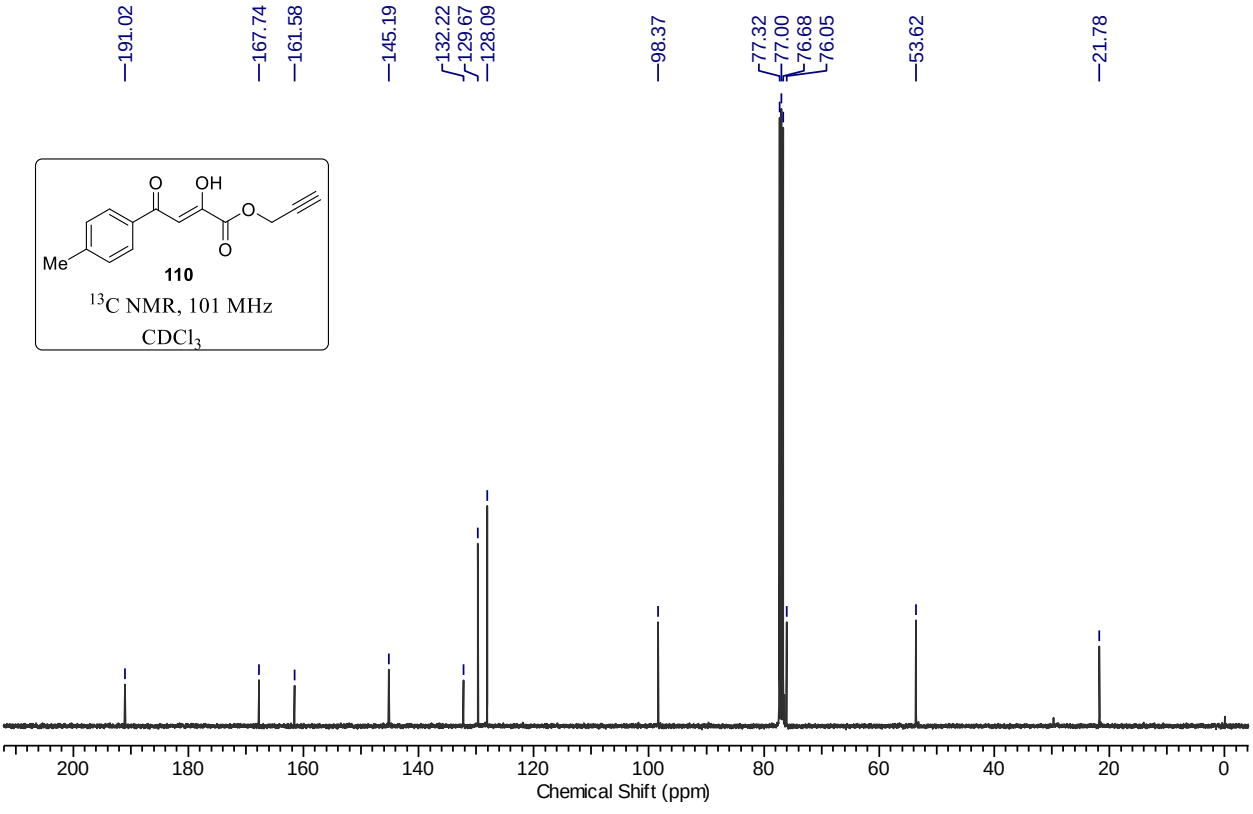


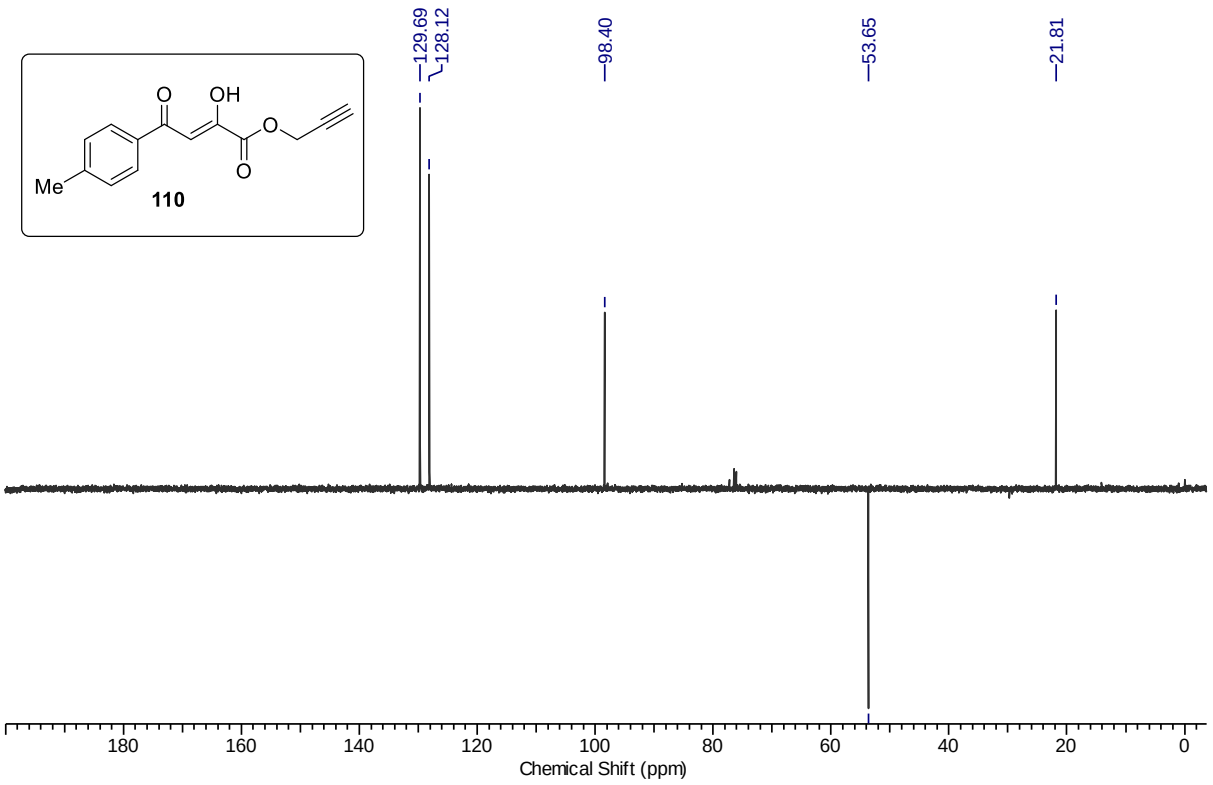




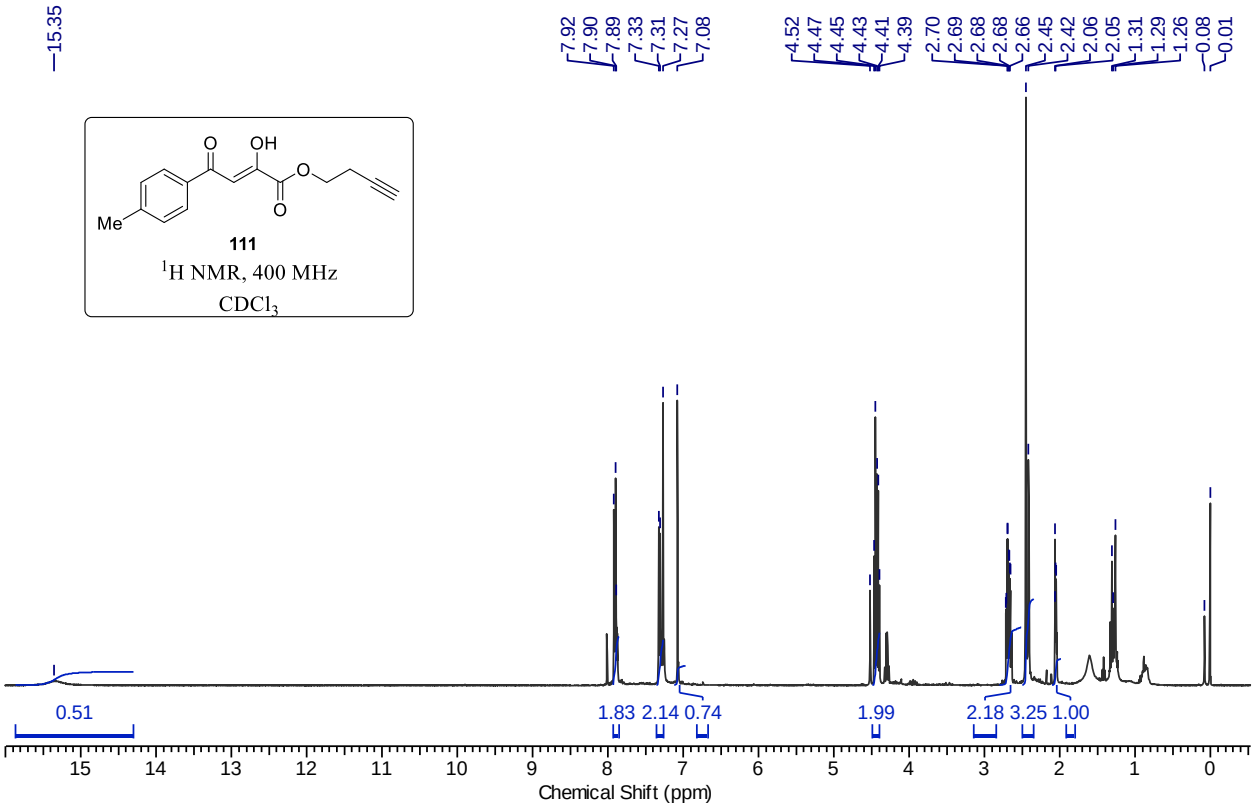
Prop-2-yn-1-yl 2-hydroxy-4-(*p*-tolyl)buta-2,3-dienoate (110):


15.25
7.92
7.90
7.33
7.31
7.27
7.09
4.93
4.92
2.58
2.57
2.45
0.01
O
OH
O
O
Me
110
^{1}H NMR, 400 MHz
$CDCl_3$
0.71
1.90
1.83
1.00
1.80
0.85
2.91
Chemical Shift (ppm)

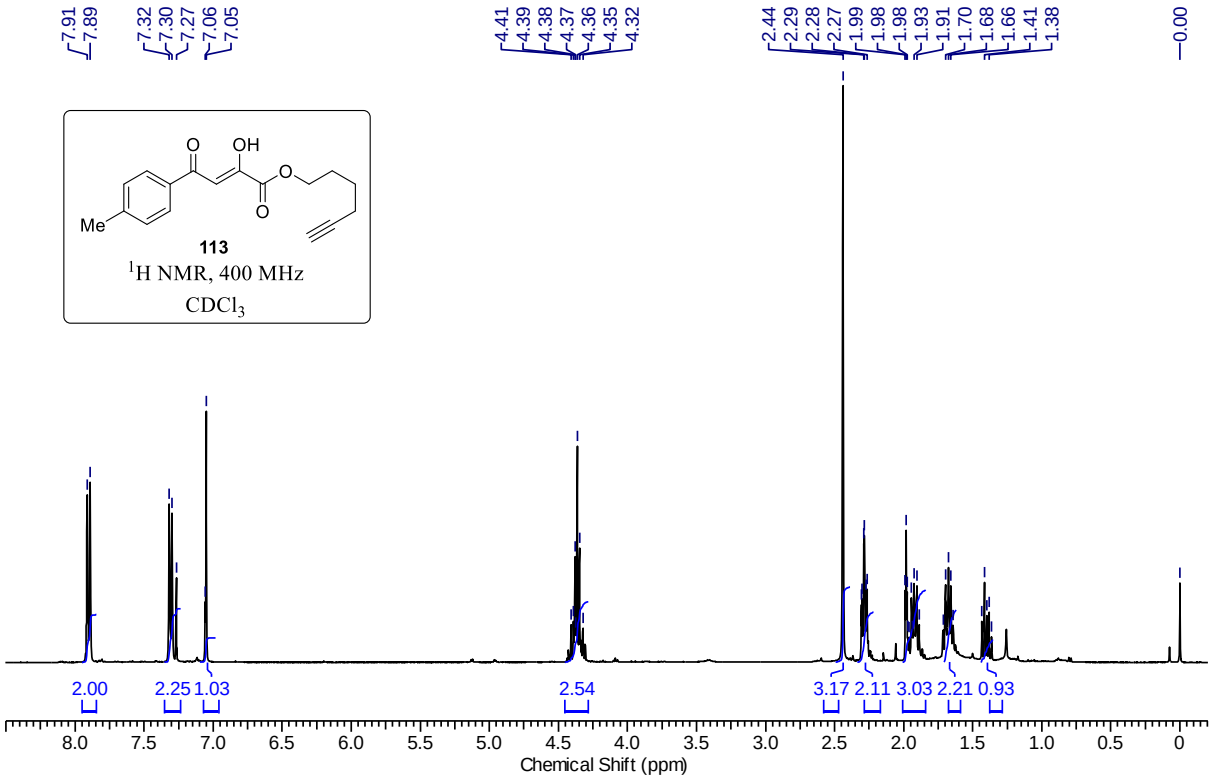

191.02
167.74
161.58
145.19
132.22
129.67
128.09
98.37
77.32
77.00
76.68
76.05
53.62
21.78
O
OH
O
O
Me
110
^{13}C NMR, 101 MHz
$CDCl_3$
Chemical Shift (ppm)

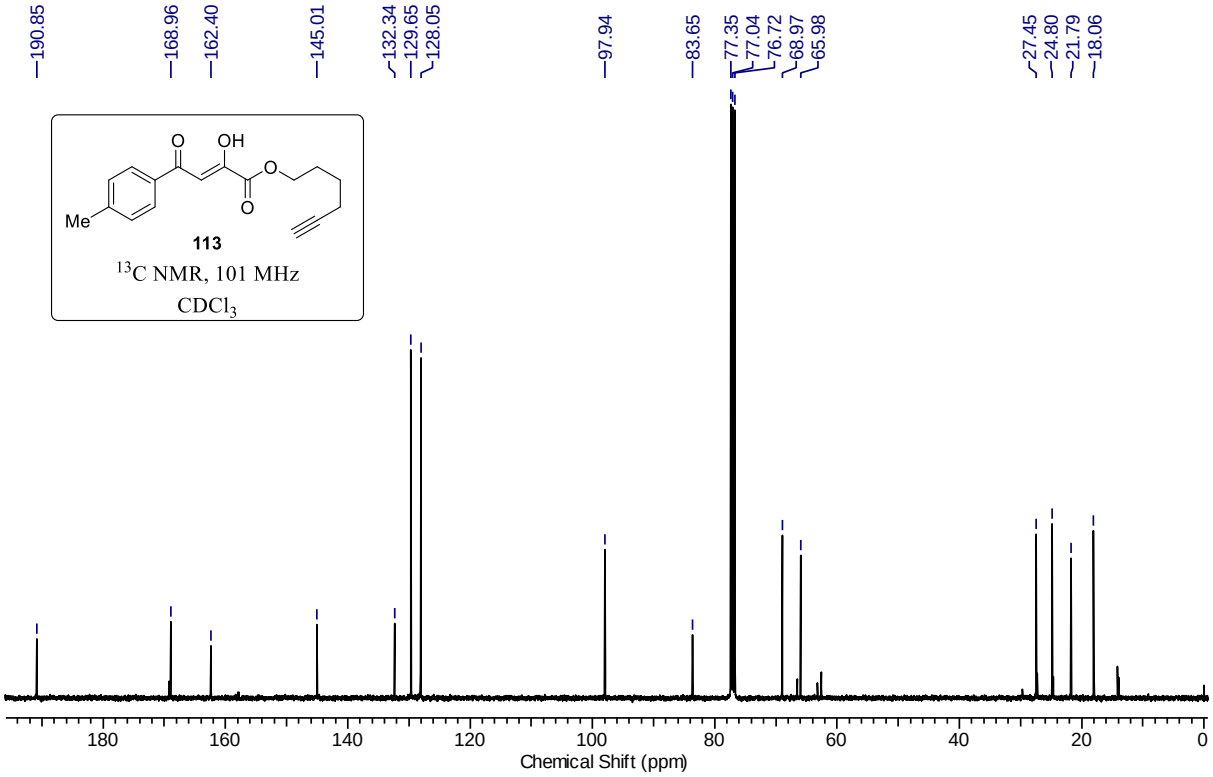


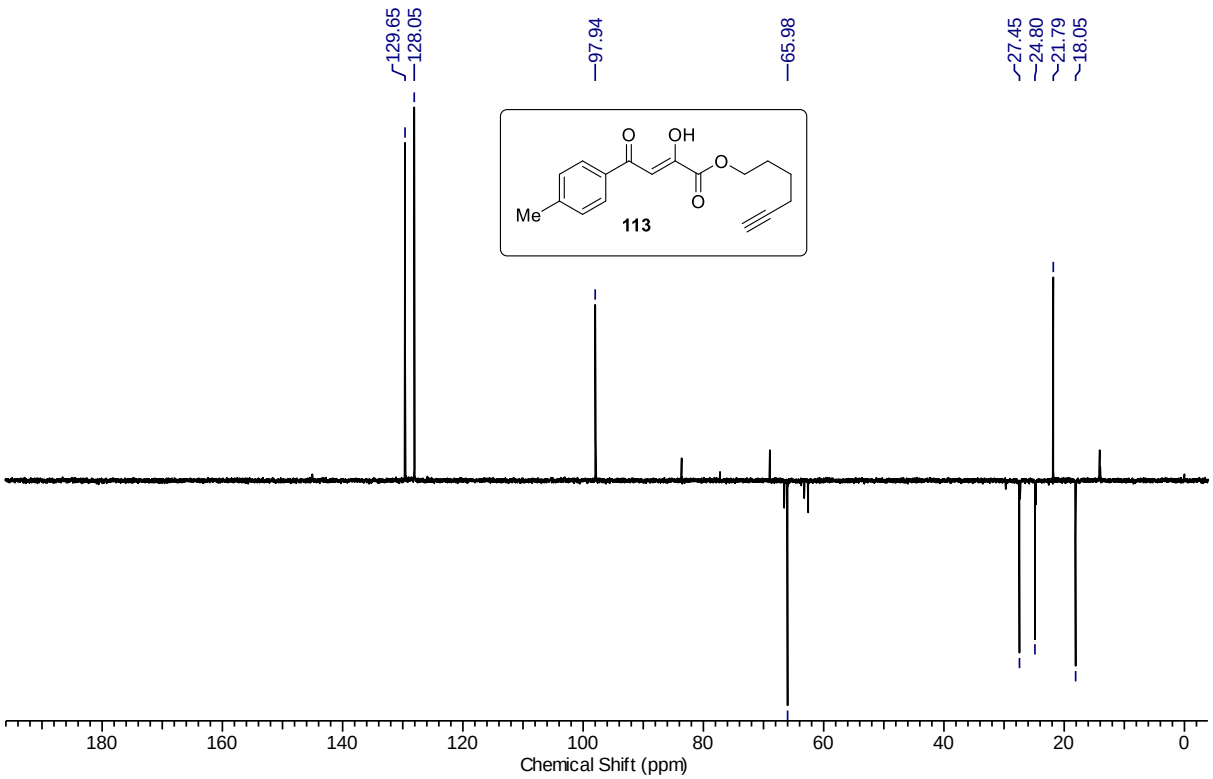
But-3-yn-1-yl 2-hydroxy-4-(*p*-tolyl)buta-2,3-dienoate (111):



Hex-5-yn-1-yl 2-hydroxy-4-(*p*-tolyl)buta-2,3-dienoate (113):






129.65
128.05
97.94
65.98
27.45
24.80
21.79
18.05
O
OH
O
O
Me
113
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

ABSTRACT

Name of the Student: Digambar A. Kambale **Registration No.:** 10CC15J26018

Faculty of Study: Chemical Science **Year of Submission:** 2021

AcSIR academic centre/CSIR Lab: **Name of the Supervisor:** Dr. Ravindar Kontham

CSIR-National Chemical Laboratory, Pune

Title of the thesis: π -Activation Triggered Cascade Annulation Reactions of Alkynols: Application in Construction of Ketal-lactones Related to Bioactive Natural Products

Alkynes (C-C triple bond containing molecules) emerged as versatile building blocks in organic synthesis due to their fascinating selective complexation patterns with transition metal derived Lewis acids, which would deliver complex natural or unnatural molecules with a prominent biological profile via intermolecular or intramolecular cascade transformations (involving alkynols, imines, and carbonyl compounds). It is well-known that transition metal salts are highly expensive and toxic to many biological systems, even with the lowest threshold concentrations. Hence there is an urgent need to identify efficient, alternative, safe and affordable catalytic systems that can exert σ and π-electrophilic catalysis.

Inspired by exciting features of alkynes, carbonyl compounds, and cascade/domino reactions (which fall under green chemistry by delivering complex organic molecules starting from simple building blocks in a single operation, which avoids massive waste generation in organic synthesis) in this thesis, we disclosed novel cascade annulation reactions of alkynols (4-pentyn-1ols and 5-hexyn-1ols) with carbonyl compounds using eco-friendly, nontoxic and affordable bismuth salts (the main group derived border-line metal salts) and TfOH (Brønsted acid) as dual activating (σ and π) catalysts for the first time.

This thesis divided into four chapters, Chapter-1 deals with the introduction to alkyne chemistry, Chapter 2 comprising an introduction & previous approaches to α,β-unsaturated [5,5]-γ-spiroketal-γ-lactones and Lewis acid-catalyzed cascade annulation of alkynols (4-pentyn-1ols) with α-ketoesters to access to γ-spiroketal-γ-lactones. In Chapter-3 provided an introduction & previous approaches to [6,5]-γ-spiroketal-γ-lactones and bismuth(III)-catalyzed bis-cyclization of propargylic diol-esters to access α,β-unsaturated [5,5]- and [6,5]-oxaspirolactones in a unified way. In Chapter-4, incorporated introduction & previous approaches to [2+2+2]-annulations/cycloadditions and our efforts in synthesizing metal-free divergent synthesis of oxepino-phthalides and [5,5]-oxaspirolactones by [2+2+2]- and [3+2]-annulation of alkynols with α-Ynone-esters.

List of Publications Emanating from the Thesis Work

1. Lewis acid-catalyzed cascade annulation of alkynols with α-ketoesters: a facile access to γ-spiroketal-γ-lactones. **D. A**. **Kambale,** S. S. Thorat, M. S. Pratapure, R. G. Gonnade and R. Kontham, *Chem. Commun.* **2017**, *53*, 6641−6644.
2. Bismuth(III)-catalyzed bis-cyclization of propargylic diol-esters: a unified approach for the synthesis of [5,5]- and [6,5]-oxaspirolactones. **D. A**. **Kambale**, B. R. Borade and R. Kontham (*Org. Biomol. Chem.* **2021**, *19*, 6618-6622; doi.org/10.1039/D1OB00974E).
3. Metal-Free Divergent Synthesis of Oxepino-phthalides and [5,5]-oxaspirolactones through [2+2+2]- and [2+3]-Annulation of Alkynols with α-Ynone-esters. **D. A**. **Kambale**, B. R. Borade and R. Kontham (*Manuscript under preparation*).

List of Patents Emanating from the Thesis Work

1. D. A. Kambale and R. Kontham, "SPIROKETAL- LACTONES AND PHARMA CEUTICAL COMPOSITION CONTAINING SAME AND PROCESS OF PREPARATION THEREOF" Patent No. **WO2018203346A1**, 8 Nov. 2018

List of Posters Presented with Details

1. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2018**)

   Title: *Lewis acid catalyzed cascade annulation of alkynols with α-ketoesters: a facile access to γ-spiroketal-γ-lactones.*

   Abstract: A novel Lewis acid catalyzed intermolecular cascade annulation of alkynols with α-ketoesters has been developed. This simple and efficient cascade annulation proceeds through a 5-*exo*-dig cyclization of alkynols followed by annulation with α-ketoester to provide a wide variety of unsaturated γ-spiroketal-γ-lactones (1,6-dioxaspiro[4.4]non-3-en-2-ones) related to many natural products..

   ---

2. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2021**)

   Title: *Synthesis of tetrahydro-2H-oxepino[2,3,4-cd]isobenzofuran-2-one through [2+2+2]-annulations of alkynols and α-alkynylα-ketoesters* **.**

   Abstract: Herein we disclose a cascade annulation strategy for the synthesis of tetrahydro-2*H*-oxepino[2,3,4-*cd*] isobenzofuran-2-one from alkynols and α-alkynyl α-ketoester. This simple and efficient method proceeds through initially oxa-Machael addition on to the α-alkynyl α-ketoester subsequently formal (2+2+2)- cycloaddition followed by intramolecular lactonization furnishes the desired of tetrahydro-2*H*-oxepino[2,3,4-*cd*] isobenzofuran-2-one. In this method used 20 mol% of TfOH as transition metal free, cost effective catalytic system. $Bi(OTf)_3$ (20 mol%) was also found to be a reliable catalyst for this transformation. Facile reaction

conditions, simple Bronsted acid catalysis, broad substrate scope and good yields are salient features of this method

List of Conference Attended with Details

International Conference on Nature Inspired Initiatives in Chemical Trends Organic synthesis (2016).

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, 53, 6641

Received 11th May 2017,
Accepted 30th May 2017

DOI: 10.1039/c7cc03668j

rsc.li/chemcomm

Lewis acid catalyzed cascade annulation of alkynols with α-ketoesters: a facile access to γ-spiroketal-γ-lactones†

Digambar A. Kambale,[ab] Sagar S. Thorat,[ab] Madhukar S. Pratapure,[ab] Rajesh G. Gonnade[bc] and Ravindar Kontham*[ab]

A novel Lewis acid catalyzed intermolecular cascade annulation of alkynols with α-ketoesters has been developed. This simple and efficient cascade annulation proceeds through a 5-*exo*-dig cyclization of alkynols followed by annulation with α-ketoester to provide a wide variety of unsaturated γ-spiroketal-γ-lactones (1,6-dioxaspiro[4.4]non-3-en-2-ones) related to many natural products.

Spiroketals and oxa-spirolactones are frequently found structural units in biologically potent natural products.[1,2] In addition, it has been shown that simplified spiroacetals derived from natural products retain their biological properties. Hence, these scaffolds essentially contribute to pharmacological activities and represent privileged pharmacophores in drug discovery.[3] In the recent years, several bioactive natural products with unsaturated γ-spiroketal-γ-lactone (1,6-dioxaspiro[4.4]non-3-en-2-one) appendage were isolated and have become an important sub-group of spiroketals, which include tuberostemonamide,[4] massarinoline A,[5] aphagrandinoid A,[6] pyrenolide D,[7] crassalactone D,[8] levantenolide,[9] papyracillic acid C,[9] acutissimatriterpene A and many others (Fig. 1).[8,10]

Despite their potential properties, only a few synthetic methods have been documented in the literature, for instance, Mitsunobu's protocol of photo-oxidation of unprotected pre-functionalized furyl-alkanols, which was further developed by Vassilikogiannakis *et al.*[11] and others.[12] Kitching *et al.* reported a strategy starting from 3-butyn-1-ol *via* saturated oxa-spirolactone in a total number of 8 steps.[13] In 2006, Shi and co-workers reported $SnCl_4$ (stoichiometric amount, 40 °C) mediated annulation of cyclopropyl-alkyl ketones and α-ketoesters.[14] Few other miscellaneous reports also present in the literature.[15] All of these approaches have limitations such as the use of prefunctionalized starting materials, the protection and deprotection sequence, stoichiometric amounts of Lewis acids and multiple steps. Thus, the development of a new intermolecular approach to unsaturated γ-spiroketal-γ-lactones from easily available fragments is of considerable importance from the point of view of diversity-oriented synthesis.[15]

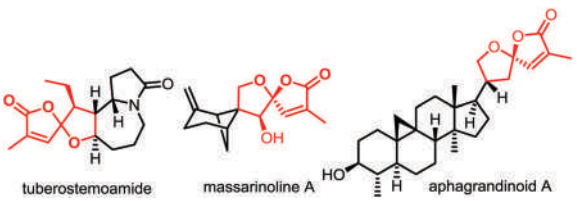


Fig. 1 Unsaturated γ-spiroketal-γ-lactone containing bioactive natural products.

Inspired by the emerging importance of cascade/domino reactions[16] involving alkynols[17,18] and as part of our research interest in Lewis acid-promoted cascade reactions involving alkynols,[19] we herein report a protocol for the construction of unsaturated γ-spiroketal-γ-lactones comprising $Bi(OTf)_3$ catalyzed cascade annulation of alkynols (4-pentyn-1-ol derivatives) and α-ketoesters, where hydroalkoxylation of alkynol **1** and/or **4** furnishes the exocyclic enol ether **5** *via* the 5-*exo*-dig mode of cyclization, which in the proximal presence of an activated α-ketoester **2** would undergo an annulation reaction to furnish the desired product **3** and/or **6** in a cascade manner (Scheme 1).

To explore the feasibility of this proposed strategy, the reaction between known alkynol **1a** (1.0 eq.) and ethylpyruvate (**2a**, 1.0 eq.) with commercially available $Bi(OTf)_3$ (99%, 20 mol%) in anhydrous CH_2Cl_2 at room temperature was performed (Table 1). Gratifyingly, both starting materials were completely consumed in 12 h at room temperature and gave the desired unsaturated γ-spiroketal-γ-lactone **3aa** in 80% yield (entry 1). The reaction in other solvents such as toluene, acetonitrile and tetrahydrofuran did not result in any improvement in the yield (entries 2–4). Notably, various Lewis (entries 5–15) and

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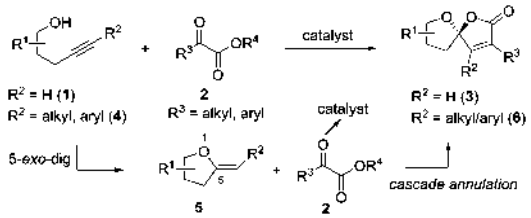
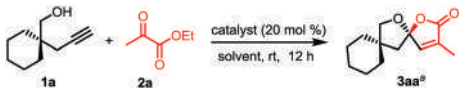
† Electronic supplementary information (ESI) available. CCDC 1510251–1510255. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc03668j



Scheme 1 Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols and α-ketoesters.

Table 1 Optimization of the reaction conditions

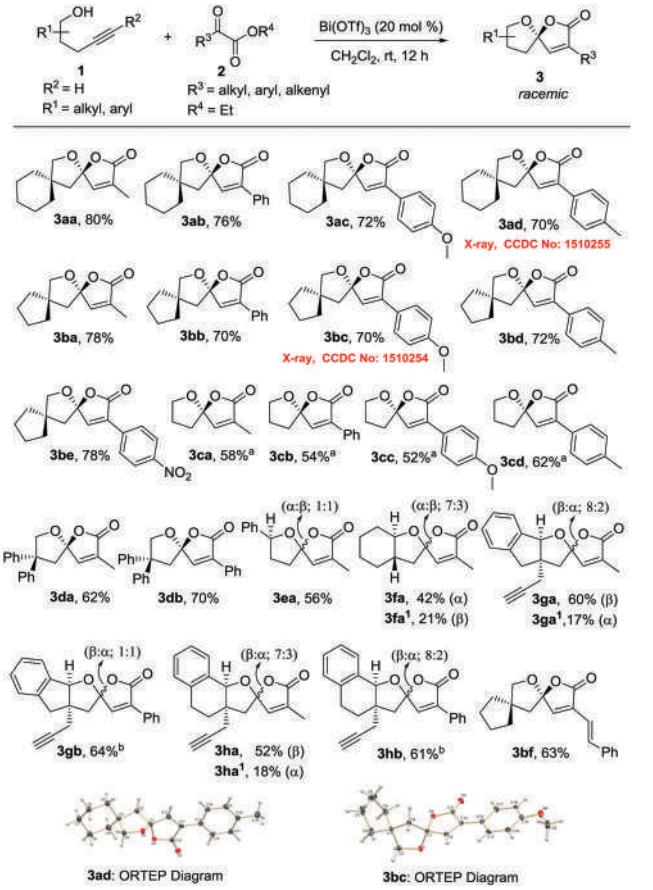


Entry	Catalyst	Solvent	Yield[b] (%)
1	$Bi(OTf)_3$	CH_2Cl_2	80
2	$Bi(OTf)_3$	Toluene	70
3	$Bi(OTf)_3$	CH_3CN	64
4	$Bi(OTf)_3$	THF	65
5	$Cu(OTf)_2$	CH_2Cl_2	60
6	$Sc(OTf)_3$	CH_2Cl_2	—
7	$Fe(OTf)_2$	CH_2Cl_2	40
8	$In(OTf)_3$	CH_2Cl_2	68
9	$Hg(OTf)_2$	CH_2Cl_2	70
10	$Hg(OTf)_2$	CH_3CN	50
11	$Yb(OTf)_3$	CH_2Cl_2	—
12	$FeCl_3$	CH_3CN	50
13	$FeCl_3$	CH_2Cl_2	—
14	AgOTf	CH_2Cl_2	70
15	AgOTf	THF	60
16	PTSA	CH_3NO_2	—
17	PTSA	THF	62
18	TfOH	CH_2Cl_2	—

[a] Reaction conditions unless otherwise specified: **1a** (1.0 mmol), **2a** (1.0 mmol), and catalyst (20 mol%) in the indicated solvent (anhydrous) at rt. [b] Isolated yields of **3aa**. rt = room temperature, Tf = triflate (CF_3SO_2), THF = tetrahydrofuran.

Brønsted acids (entries 16–18) were also tested in this reaction, where some of them found to be moderately active and gave 60–70% yields. To our delight, the initially identified conditions of 20 mol% $Bi(OTf)_3$ in CH_2Cl_2 at rt were found to produce the best yield of the product **3aa** (entry 1).[21] Further tuning of the other parameters like molar ratios of the substrates, catalyst loading and temperature did not lead to any noticeable change in the outcome of the reaction (Table 1).[20]

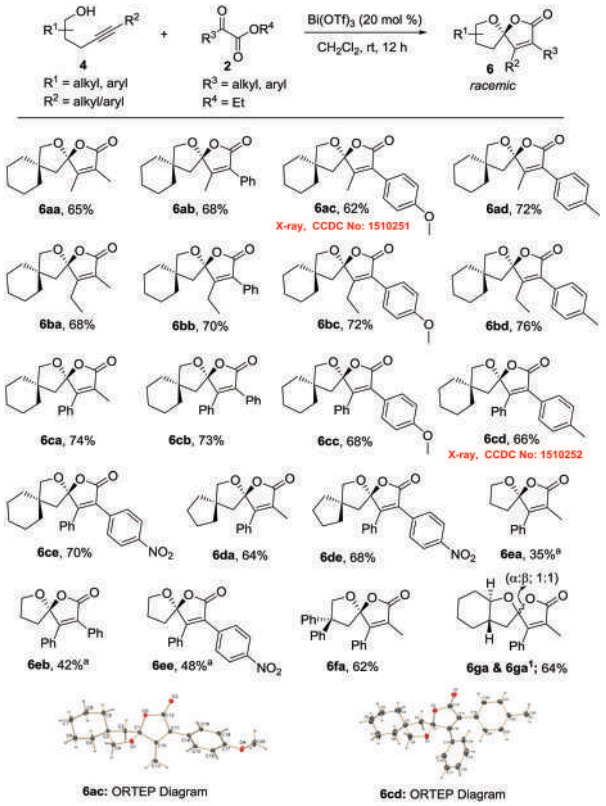
With the optimal conditions in hand, we next investigated the scope of this annulation with respect to the alkynols possessing terminal alkyne functionality and α-ketoesters (Scheme 2). The reaction of cyclohexane and cyclopentane fused 4-pentyn-1-ols with several alkyl and aryl α-ketoesters gave the corresponding oxa-spirolactones **3aa–be** in good yields (70–80%), which clearly states that the electronic nature of the phenyl substitution of α-ketoesters has little influence on the outcome. Unsubstituted 4-pentyn-1-ol provided the desired products **3ca–cd** in moderate yields of 52–62%. 2,2-Diphenyl substituted alkynol furnished the corresponding products **3da** and **3db** in 62% and 70% yields, respectively. Alkynol having a benzylic-OH group was well



Scheme 2 Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (possessing terminal alkyne). [a]48 h (reaction time); [b]inseparable diastereomers.

tolerated in the reaction with ethylpyruvate and led to the product **3ea** (dr, 1 : 1). *trans*-Cyclohexane fused alkynol gave **3fa** and **3fa¹** (dr, 7 : 3). The reaction of indane-derived alkynol (possessing two alkyne functionalities) with ethylpyruvate gave the corresponding products **3ga** and **3ga¹** (dr, 8 : 2), whereas with ethyl phenylglyoxylate gave **3gb** (dr, 1 : 1). The reaction of tetralin-fused alkynol (having two alkyne functionalities) with ethylpyruvate provided **3ha** and **3ha¹** (dr, 7 : 3) in good yields, whereas with ethyl phenylglyoxylate gave **3hb** (dr, 8 : 2). α,β-Unsaturated ketoester also proceeded smoothly and delivered the product **3bf** in good yield of 63%. The relative stereochemistry of diastereomers was assigned based on NOE analysis. The structures of **3ad** and **3bc** were rigorously confirmed by single crystal X-ray analysis, and all other products were confirmed by analogy (Scheme 2).[20]

Taking our protocol a step further, we examined the reactivity of alkynols possessing an internal alkyne functionality under standard reaction conditions. Cyclohexyl and cyclopentyl fused 4-pentyn-1-ols (with alkyl or aryl substituents on alkyne termini) successfully reacted with various alkyl and aryl-α-ketoesters and furnished highly substituted and sterically demanding γ-spiroketal-γ-lactones (**6aa–6de**) in good yields. Phenyl substituted 4-pentyn-1-ol gave products **6ea–6ee** in moderate yields. Triphenyl substituted alkynol led to the product **6fa** in 62% yield.

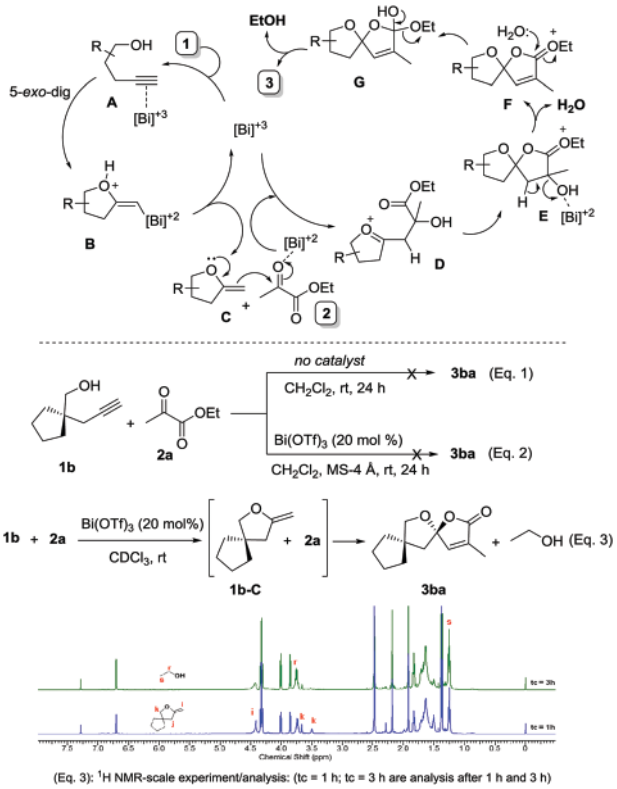


Scheme 3 Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (possessing internal alkyne functionality). [a]48 h (reaction time).

trans-Cyclohexane fused alkynol furnished **6ga** and **6ga[1]** (dr, 1 : 1). Products **6ac** and **6cd** were confirmed by single crystal X-ray diffraction analysis (Scheme 3).[20]

The reactivity of internal alkynols is little slower than those of the corresponding terminal alkynols. Best yields were observed for α- or β-disubstituted alkynols as substrates compared to those of unsubstituted 4-pentyn-1-ols (**3ca–3cd** & **6ea–6ee**; Schemes 2 and 3), which can be attributed to the Thorpe–Ingold effect (angle compression).[22] All the 42 examples reported in this work were noteworthy, since the presence of the α,β-unsaturated lactone functionality provides a platform for later product modification through reduction and oxidation (*vide infra*).

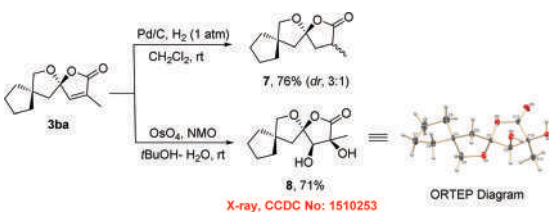
While the precise reaction mechanism requires further studies, a plausible mechanism based on recent reports[18–21] and the results obtained in this work is proposed (Scheme 4). The bismuth triflate mediated hydroalkoxylation (5-*exo*-dig; π-activation) of alkynol **1** gives **B** *via* **A**, followed by proto-debismuthination giving the corresponding enol-ether **C**, which then reacts with the activated (σ-activation) ketone group of α-ketoester **2** to give the oxocarbenium ion intermediate **D**. The intramolecular attack of the ester oxygen onto the oxocarbenium ion **D** gives **E**, followed by a $Bi(OTf)_3$ facilitated release of water from **E** generating the intermediate **F**. The subsequent addition of the *in situ* generated water on to **F** gives the intermediate **G**. Next, the release of EtOH from **G** leads to the formation of unsaturated γ-spiroketal-γ-lactone **3**.



Scheme 4 Postulated reaction mechanism and supporting experiments.

To understand this proposed mechanistic pathway, a few supporting experiments were performed (Scheme 4). The reaction of **1b** with **2a** in the absence of the catalyst failed to give the desired product (eqn (1)). The role of the *in situ* released water in the lactone formation step (**E** → **F** → **G**) was confirmed by carrying out the reaction in the presence of activated MS-4 Å (eqn (2)). The formation of the exocyclic-enol ether intermediate (**1b-C**) from **1b** and the release of EtOH in the cascade annulation (**G** → **3**) were established by real-time ^1H NMR analysis (eqn (3)) (Scheme 4),[20] and these observations are consistent with earlier reports by Marks *et al.*[23]

The synthetic utility of this method was further explored *via* a couple of key transformations. The reduction of unsaturated γ-spiroketal-γ-lactone **3ba** using Pd/C and H_2 (1 atm, balloon) gave the saturated product **7** in 76% yield (dr, 3 : 1). The dihydroxylation of **3ba** with OsO_4-NMO gave the corresponding diol **8** as a single diastereomer, the structure of which was unambiguously confirmed by single crystal X-ray analysis (Scheme 5).[20]



Scheme 5 Synthetic utility.

In summary, a simple access for the synthesis of diverse unsaturated γ-spiroketal-γ-lactones has been developed by employing a $Bi(OTf)_3$ catalyzed cascade annulation of alkynols with α-ketoesters *via* a dual (π and σ) activation process. Highly sterically demanding products, ambient reaction conditions, a cost-effective catalytic system, good yields, operational simplicity, and atom and step-economy are salient features of this strategy. The application of this method in total synthesis of related biologically active natural products is currently underway in our laboratory and will be reported in due course.

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Bismuth(III)-catalyzed bis-cyclization of propargylic diol-esters: a unified approach for the synthesis of [5,5]- and [6,5]-oxaspirolactones†

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Herein we disclose an unprecedented intramolecular cascade strategy for the construction of α,β-unsaturated [5,5]- and [6,5]-oxaspirolactones that capitalizes on the π-electrophilic Lewis acid-catalyzed 5-*exo-dig* or 6-*exo-dig* mode of cyclization of propargylic diol esters, followed by dehydration and spirolactonization steps. Moreover, semi-protected substrates also delivered the respective oxaspirolactones with the same ease and in appreciable yields under optimal reaction conditions.

Numerous biologically active natural products possess the γ-spiroketal-γ-lactone (oxaspirolactone) moiety isolated from marine organisms, microbes, fungi, insects and plants.[1] Among these natural oxaspirolactones, 1,6-dioxaspiro[4.4]non-3-en-2-one and 1,6-dioxaspiro[4.5]dec-3-en-2-one (alternatively referred to as [5,5]- and [6,5]-oxaspirolactones, respectively) are ubiquitous with prominent biological profiles.[1a] Selected examples include crassalactone D (anticancer, ED_{50} = 1.1 μg mL^{-1} against P-388, 3.3 μg mL^{-1} against KB, 4.0 μg mL^{-1} against Col-2, 3.2 μg mL^{-1} against BCA-1 and 3.1 μg mL^{-1} against ASK),[2] pyrenolide D (growth-inhibitory and morphogenic activities toward fungi),[3] tuberostemoamide (traditional Chinese medicine to treat respiratory disorders),[4] aspersclerotiorone F (no biological activity disclosed due to isolation in a very limited amount),[5] abiespiroside A (anticancer activity),[6] 3-*O*-methylabiesatrine[7] and many others.[1a,8] The inherent molecular rigidity evolved from the three-dimensional skeleton and the Michael acceptor nature of α,β-unsaturated lactone segments is primarily responsible for the interesting biological profile of these natural products. In light of their interesting structural features and biological profile, increasing efforts have been made toward the development of novel methodologies for the efficient construction of these scaffolds (Fig. S1†).[1,8]

Traditionally, α,β-unsaturated γ-spiroketal-γ-lactones are prepared from their saturated counterparts using multiple synthetic manipulations. For instance, spirolactonization followed by halogenation and dehydro-halogenation,[9] α-phenylselenation and oxidative elimination, and addition of halo-acrylates to lactones are notable examples of these manipulations,[10] whereas, strategies for the direct construction of these scaffolds are very limited and include the oxidative (chemical/photochemical) cascade cyclization of hydroxy-alkyl tethered furans,[11] halocyclization of hydroxyalkyl tethered ylidene-butenolides,[12] annulation of cyclopropyl alkyl ketones with α-ketoesters,[13] and asymmetric multi-component coupling of alkynols, anilines, and glyoxylic acid.[14]

As part of our interest in the development of cascade transformations involving the π-electrophilic activation of alkynols and inspired by the interesting biological profile of oxaspirolactone-based natural products, previously, we had disclosed a novel cascade annulation approach for the synthesis of [5,5]-oxaspirolactones **2** in one step from 4-pentyn-1-ol **A** and α-ketoester **B** through 5-*exo-dig* cyclization to obtain enol ether **C** followed by annulation with **B** (entry a, Scheme 1).[15] A similar transformation using 5-hexyn-1-ol **D** led to the formation of furo[2,3-*b*]pyran-2-one **G** instead of the expected [6,5]-oxaspirolactone **4**, *via* the initial 6-*exo-dig* cyclization to afford exocyclic enol ether **E** and its isomerization into its thermodynamically favored *endo*-cyclic enol ether **F** followed by annulation with α-ketoester **B** (entry b, Scheme 1).[16] In this context, we aimed at the development of a unified strategy for the synthesis of both [5,5]- and [6,5]-oxaspirolactones (**2** and **4**). Accordingly, we have hypothesized that propargylic diol esters possessing a 4-pentyn-1-ol or 5-hexyn-1-ol appendage (**1** or **3** respectively) would deliver the desired products **2** and **4** *via* an initial selective alkynophilic transition metal/Lewis acid-catalyzed 5-*exo-dig* or 6-*exo-dig* cycloisomerization followed by dehydration and spirolactonization steps (*vide infra*) (entry c, Scheme 1).

We began investigating our hypothesis by carrying out the reactions using propargylic diol ester[17] **1a** (see the ESI† for details)[8] as a precursor and our earlier successful alkynophilic

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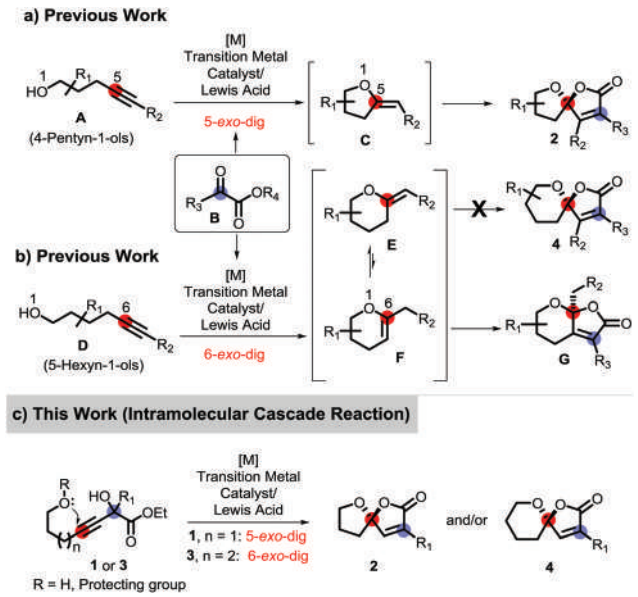
†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ob00974e

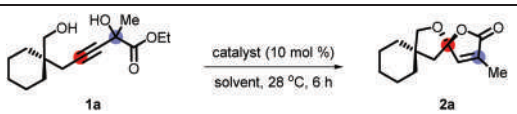


Scheme 1 Hypothesis generation based on our earlier work.

catalytic systems,[15,16] namely, $Bi(OTf)_3$, AgOTf and PPh_3PAuCl-AgOTf in CH_2Cl_2, at room temperature under an argon atmosphere (Table 1, entries 1–3). To our delight, all these reactions provided the desired [5,5]-oxaspirolactone **2a** in a good yield of 85%, 82%, and 84%, respectively. The replacement of the CH_2Cl_2 solvent with THF in AgOTf-catalysis gave **2a** in a low yield of 16%, which could be due to the catalyst's probable chelation with THF (Table S1,† entry 4).[8] Next, other known π-electrophilic catalytic systems of Au(I), Fe(II), Cu(II), In(III), Sc(II), Hg(II), and Pd(III) were tested using the reported solvents, and some of them were found to be moderately active (Table S1,† entries 5–15).[8] Brønsted acids (*p*-TSA, TfOH) were weakly active towards this cascade reaction (Table S1,† entries 16–18).[8] The reaction using $Bi(OTf)_3$ in the presence of MS-4 Å failed to deliver the product, which indicates the role of *in situ* released water in product formation (*vide infra*) (Table 1, entry 4). The substrate's intactness in the absence of the catalyst showed the necessity of the metal-triflate in this transformation (Table 1, entry 5). Among the initially identified three best catalytic systems (Table 1, entries 1–3), $Bi(OTf)_3$ (anhydrous, 99%) was chosen for this work due to its cost-effectiveness and environmentally benign nature[18] (Table 1, entry 1). Further screening of other parameters such as catalyst loading, solvent, reaction time, and temperature showed an insignificant improvement in the outcome (Table 1).

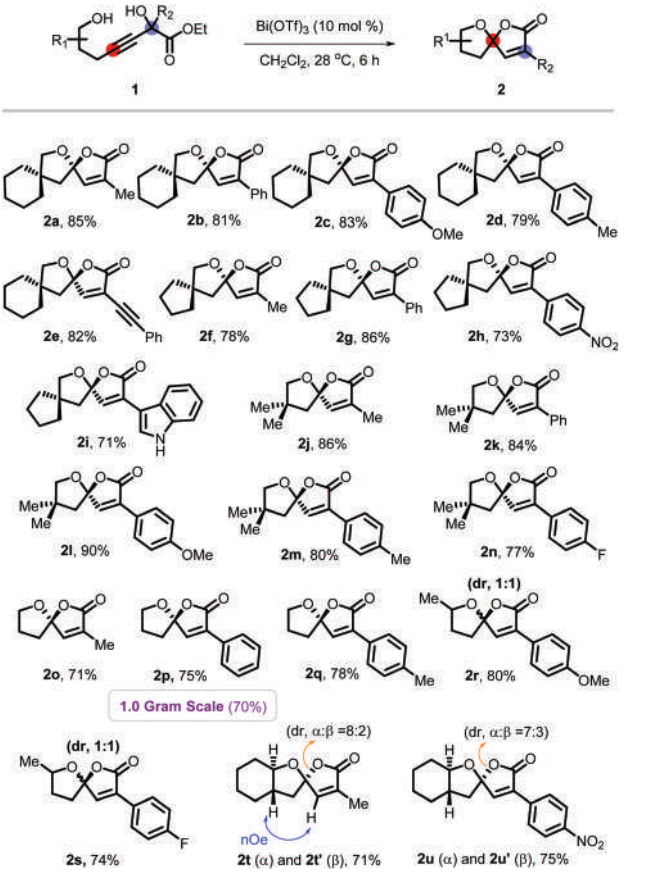
Encouraged by these results, initially, we prepared diverse propargylic diol esters (**1** or **3**) using known synthetic methods involving a single or three-step process (see the ESI† for details);[8,17] then we proceeded by examining the substrate scope for the synthesis of [5,5]-oxaspirolactones **2** (Scheme 2). The cyclohexyl derived propargylic-diol-esters having methyl, phenyl, *p*-anisyl, *p*-tolyl, and alkynyl phenyl substituents at the propargylic center smoothly underwent the reaction and afforded the respective oxaspirolactones **2a–2e** in good yields of 79–85% under the optimized conditions, without significant steric or electronic discrimination. Similarly, the cyclopentyl tethered substrates with methyl, phenyl, *p*-nitrophenyl and 3-indolyl substituents provided the corresponding oxaspirolactones **2f–2i** in good yields (71–86%). Gem-dimethyl substituted substrates (with methyl, phenyl, *p*-anisyl, *p*-tolyl and *p*-fluorophenyl substituents at the propargylic carbon) furnished the

Table 1 Reaction optimization[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	$Bi(OTf)_3$	CH_2Cl_2	85
2	AgOTf	CH_2Cl_2	82
3	PPh_3AuCl-AgOTf (1 : 1)	CH_2Cl_2	84
4[c]	$Bi(OTf)_3$, MS-4 Å	CH_2Cl_2	—
5[c]	No catalyst	CH_2Cl_2	—

[a] Reaction conditions unless otherwise specified: **1a** (0.25 mmol), and catalyst (10 mol%) in the indicated solvent (anhydrous, 2 mL) at rt (28 °C). [b] Isolated yield of **2a**. MS = molecular sieves. [c] No conversion was observed.



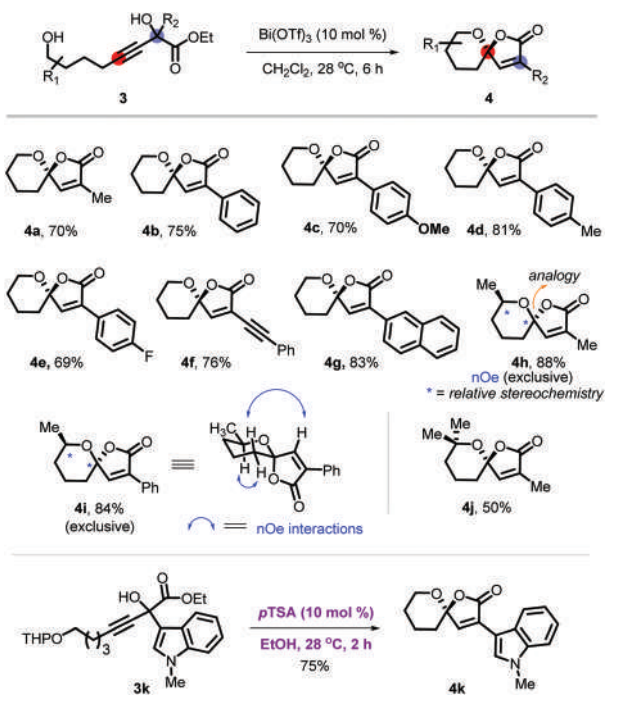
Scheme 2 Synthesis of unsaturated [5,5]-oxaspirolactones **2** from propargylic diol esters **1**.

respective products **2j–2n** in 77–90% yields. The unsubstituted 4-pentyn-1-ol tethered substrates possessing methyl, phenyl, and *p*-tolyl substituents at the propargylic center delivered the corresponding products **2o–2q** in 71–78% yields, and this indicates the probable influence of the Thorpe–Ingold effect in the case of the *gem* di-substituted precursors.[19] Substrates with the secondary alcohol delivered the corresponding oxaspirolactones **2r** and **2s** in 80% and 74% yields with a 1 : 1 diastereomeric ratio (dr) for both products (dr was measured using ^{1}H NMR analyses). Pleasingly, cyclohexyl fused secondary alcohol-containing substrates also tolerated the reaction well and furnished oxaspirolactones **2t**/**2t′** (dr 8 : 2) and **2u**/**2u′** (dr 7 : 3) in 71% and 75% yields (relative stereochemistry assigned based on nOe analyses)[8] (Scheme 2).

After successfully establishing the cascade process for [5,5]-oxaspirolactones **2**, we extended our study to synthesizing the analogous [6,5]-oxaspirolactones **4** from diol ester **3**, and the results are shown in Scheme 3. Several propargylic diol esters with the 1-hexynol appendage **3** were subjected to the optimal reaction conditions. We were pleased to obtain diverse [6,5]-oxaspirolactones **4a–4g** (possessing methyl, phenyl, *p*-anisyl, *p*-tolyl, *p*-fluorophenyl, alkynyl, and 2-naphthyl substituents at the α-position) in good yields of 69–83%. Substrates with the secondary hydroxyl group delivered the desired oxaspirolactones **4h** and **4i** in 88% and 84% yields, respectively, with exclusive diastereoselectivity.[8] The relative stereochemistry of **4h** and **4i** was assigned based on NOE analysis[8] and it was found that anomeric and associated effects[20] operated here to deliver the axially oriented lactone conformer **4i** as a sole product. Even the tertiary hydroxyl-containing substrate delivered the corresponding oxaspirolactone **4j** in a moderate yield of 50% along with unidentified products (Scheme 3).

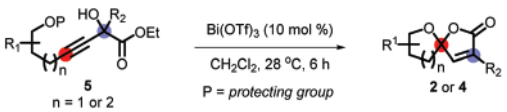
Interestingly, while preparing the starting materials **3** (of Scheme 3), the *p*TSA-mediated THP deprotection step of the indole derived alkyne diol precursor **3k** directly delivered the [6,5]-oxaspirolactone **4k** instead of the free hydroxyl substrate in 75% yield in 2 h; in contrast, the THP deprotection of the other semi-protected alkyne diols **5** (using *p*TSA) resulted in the propargylic diol esters **1** or **3** but not oxaspirolactones **2** or **4** (Scheme 3).[8]

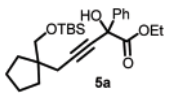
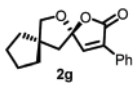
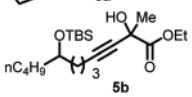
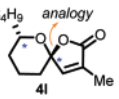
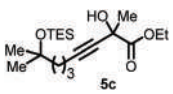
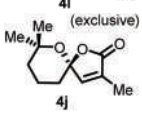
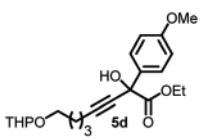
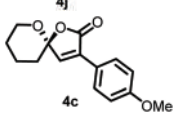
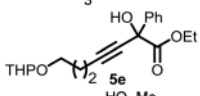
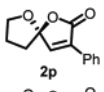
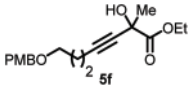
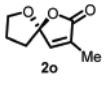
This observation inspired us to evaluate the cascade cyclization of the semi-protected alkyne diol-esters **5**, which could avoid the extra deprotection step of this protocol's substrate synthesis (Table 2). Thus, we prepared several protected (with TBS, TES, THP, and PMB groups) substrates and subjected them to the standard reaction conditions. To our delight, the mono-TBS protected diol-esters **5a** and **5b** furnished the corresponding [5,5] and [6,5]-oxaspirolactones **2g** and **4l** (single diastereomer) in good yields of 79% and 78%, respectively, without the requirement of an acid additive. Substrate **5c** having TES protection delivered **4j** in 65% yield. The THP protected propargylic diol ester **5d–5e** delivered the corresponding oxaspirolactones **4c** and **2p** in good yields. Interestingly, the PMB-protected alkynol **5f** also underwent clean spirolactonization and delivered the oxaspirolactone **2o** in 74% yield in a little longer reaction time of 10 h (Table 2). The practicality of

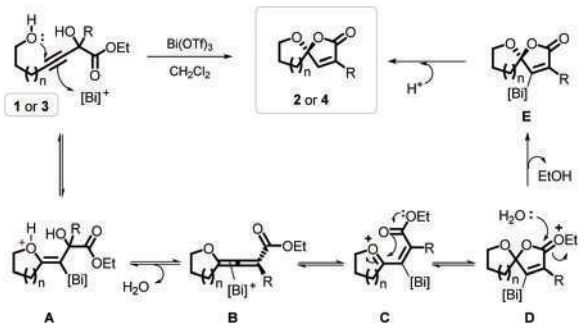


Scheme 3 Synthesis of unsaturated [6,5]-oxaspirolactones **4** from propargylic diol esters **3**.

Table 2 Synthesis of unsaturated [5,5]- and [6,5]-oxaspirolactones from semi-protected propargylic diol esters



Entry	Substrate	Product	Yield (%)
1			79%
2			78%
3			65%
4			70%
5			76%
6			74% (in 10 h)



Scheme 4 Plausible reaction mechanism.

this protocol was exemplified by performing a 1.0 g scale reaction to obtain **2p** (Scheme 2) and **2o** (Table 2) in a good yield of 70% and 71%, respectively.

Based on our previous reports,[15,16] and those of others,[21] we have formulated the tentative mechanistic sequence for this cascade cyclization. The Lewis acid ($Bi(OTf)_3$)-catalyzed π-activation of the alkyne diol ester **1** or **3** would trigger the cascade process through the initial oxy-functionalization of the alkyne to give intermediate **A** (*via* the 5-*exo-dig* or 6-*exo-dig* mode of ring closure), which would undergo instant dehydration to give the cyclic enol ether-derived allene intermediate **B** followed by the oxocarbenium species **C**. Next, **C** would undergo intramolecular nucleophilic addition of the ester to provide intermediate **D**. Then, *in situ* released water would attack the oxocarbenium intermediate **D** to deliver **E** *via* the expulsion of EtOH, simultaneously undergoing proto-debismuthination to provide the desired oxaspirolactones **2** or **4**. However, further investigations are required to establish the precise reaction mechanism (Scheme 4).

In summary, we have developed a unified cascade strategy for the synthesis of [5,5]- and [6,5]-oxaspirolactones with α,β-unsaturation. This transformation requires a simple, cost-effective, abundant, and environmentally benign $Bi(OTf)_3$ catalyst (10 mol%) and ambient reaction conditions, and furnishes diverse oxaspirolactones in good to excellent yields. Moreover, we have demonstrated this strategy's potential using semi-protected propargylic diol esters, which provided the desired products in good yields with equal ease. Future studies will focus on utilizing this methodology in the total synthesis of biologically potent related natural products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Erratum