Stony Brook University

Synthesis of Novel Fused Tropones and Colchicinoids Through Rh(I)-Catalyzed [2+2+2+1] Cycloaddition of Triynes with Carbon Monoxide

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Abstract of the Dissertation

Synthesis of Novel Fused Tropones and Colchicinoids Through Rh(I)-Catalyzed [2+2+2+1] Cycloaddition of Triynes with Carbon Monoxide

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Natural products and their metabolites isolated from diverse natural origins have been an extraordinary starting place for the research of active pharmaceuticals, agrochemicals and other applications. Core structures of those natural products serve as templates to obtain more potent and selective agents through systematic structure-activity relationship (SAR) studies. A unique feature of natural products is that they often contain complex fused-ring skeletons. However, the traditional synthetic methodologies to access these fused-ring skeletons were not efficient in the ease of synthesis and with atom economy. Therefore, the need to develop more efficient synthetic methods that provide access to fused-ring skeletons is essential. Transition metal-catalyzed cycloaddition reactions have proven to be one of the most efficient methods for natural products synthesis as well as constructing "natural product-like" and "drug-like" skeletons in highly selective manner as well as with high atom economy.

As part of ongoing studies in the Ojima laboratory on the transition metal-catalyzed carbocyclizations and higher-order cycloaddition reactions, the Rh(I)-catalyzed [2+2+2+1] cycloaddition of triynes was investigated. The reaction of triynes in the presence of $[Rh(CO)_2Cl]_2$ and CO (2 atm) gave novel 5-7-*n* fused tricyclic products. In addition, with carefully design of the triyne substrates, novel colchicinoids can be prepared in short steps. The reaction variables as well as the mechanisms for the formation of these fused ring products are presented.

Dedicated to my late grandparents
and
my family

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LIST OF ABBREVIATIONS

Ac	-	acetyl
atm	-	atmosphere
BINAP	-	2,2'-bis(diphenylphosphino)-1-1'-binapthyl
BINOL	-	1,1´-Bi-2-naphthol
Boc	-	*tert*-butyl carbonate
Bu	-	butyl
bp	-	boiling point
bs	-	broad singlet
bt	-	broad triplet
CAMP	-	methylcyclohexyl-o-anisylphosphine
COD	-	1,5-cyclooctadiene
CO	-	carbon monoxide
d	-	doublet
DCE	-	1,2-dichloroethane
DCM	-	dichloromethane
DIAD	-	diisopropyl azodicarboxylate
DIOP	-	(+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dd	-	doublet of doublets
DEA	-	diethylamine
DMAP	-	4-dimethylaminopyridine
DMF	-	dimethylformamide
dppp	-	diphenylphosphino propane
DuPHOS	-	(+)-1,2-Bis[(2S,5S)-2,5-dimethylphospholano]benzene
ee	-	enantiomeric excess
ESI	-	electrospray ionization
Et	-	ethyl
Et_2O	-	ethyl ether
EtOAc	-	ethyl acetate
FIA	-	flow-injection analysis (direct injection mass analysis)
g	-	gram
GC- MS	-	gas chromatography mass spectrometry
h	-	hour
HPLC	-	high performance liquid chromatography
HR-MS	-	high resolution mass spectrometry
Hz	-	hertz
IR	-	infrared spectroscopy
K	-	Kelvin
kcal	-	kilo calorie
L	-	liter
LC-MS	-	liquid chromatography mass spectrometry
LiHMDS	-	lithium hexamethyldisilizane
M	-	multiplet
MeCN	-	acetonitrile
MeOH	-	methanol

mmol	-	millimole
mol	-	mole
M	-	molarity
mg	-	milligram
MHz	-	mega hertz
mL	-	milliliter
m.p.	-	melting point
MS	-	mass spectrometry
Ms	-	mesylate
MW	-	molecular weight
µW	-	microwave
NMR	-	nuclear magnetic resonance
NP	-	natural product
Ph	-	phenyl
ppm	-	parts per million
q	-	quartet
rt	-	room temperature
s	-	singlet
SAR	-	structure activity relationship
t	-	triplet
t-Bu	-	*tert*-butyl
TEA	-	triethylamine
Tf	-	triflate
TFA	-	trifluroacetic acid
TFE	-	2,2,2-trifluoroethanol
THF	-	tetrahydrofuran
THP	-	tetrahydropyranyl
TMSCl	-	trimethylsilyl chloride
TLC	-	thin layer chromatography
TMS	-	trimethylsilyl
Ts	-	tosylate
p-TSA	-	*p*-toluenesulfonic acid

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Chapter 1

Carbonylative carbocyclization and cycloaddition reactions

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§ 1.1. Introduction

Carbon-carbon bond formation is perhaps the most fundamental and useful transformation in synthetic organic chemistry, yet remains a challenging goal for many organic chemists. Among the reaction classes, cycloaddition represents a convenient way to prepare various carbocyclic and heterocyclic systems from relatively simple starting materials.[1] The "classical" cycloaddition reactions, such as Diels-Alder reaction, thermal cycloadditions, and photochemical cycloadditions, require either the presence of polarized or "activated" functional groups in the starting materials or otherwise harsh reaction conditions to facilitate the transformations

Over the past few decades, researchers have directed attention towards the fertile and growing field of metal-catalyzed cycloaddition reactions. Metal-catalyzed cycloaddition reactions provide both high atom economy as well as high selectivities (chemo-, regio-, and enantio-) in product formation based on the metal species and reaction conditions.[2] Complexation of the metal to unactivated olefins, acetylene, and other unsaturated precursors greatly alter their reactivities, and thus open a new door for the development of novel cycloaddition reactions. Using metal-catalyzed cycloaddition reactions, many highly complex polycyclic systems, which may be virtually inaccessible through classical pericyclic reactions or other carbon-carbon bond formation, have been constructed from thoughtfully designed starting materials under mild conditions in a single step.[2a]

Several reviews have been published on transition metal-mediated cycloaddition[3] and carbocyclization reactions.[4] Metal-assisted cycloaddition reactions[5] and their applications to medium-sized ring syntheses[6] have also been reviewed. Among the reaction types in catalytic cyclization processes, the carbocyclizations of enynes, dienes, diynes, enediynes, trienes, triynes, and their hetero-atom analogues are extremely important and useful reactions for the syntheses of a variety of carbocyclic and heterocyclic compounds.[2a, 7] The term "carbocyclization" has been used to describe an annulation process involving carbon-carbon bond formation via carbometallation, a process that is fundamentally different from radical cyclization as well as thermal and photochemical cycloaddition.[8] When the carbocyclization process incorporates carbon monoxide, the process is categorized as carbonylative carbocyclization and provides efficient routes to cyclic and fused ketones.

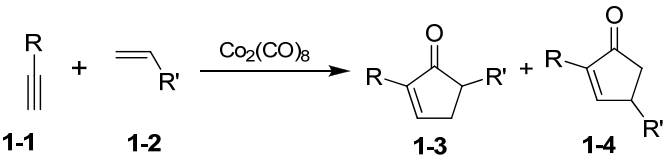
Mechanistic studies of various transition metal catalyzed carbocyclization and cycloaddition reactions have been carried out over the years and the versatilities of intermediate species have also been exploited.[7a, 9] Thus, over the past decade, a variety of otherwise forbidden or difficult to achieve reactions have been realized including [5+2+1],[10] [4+2+2],[11] and other higher-order cycloadditions.[7a, 8, 12]

This chapter provides a brief overview of carbonylative cycloaddition as well as higher order cycloaddition from recent literature. Additionally, novel silicon-initiated carbocyclization (SiCaC), carbonylative carbobicyclization (CO-SiCaB), and carbonylative carbotricyclization (CO-SiCaT) reactions as well as higher-order [2+2+2+1] cycloaddition reactions pioneered in Ojima's laboratory are also discussed.

§ 1.2. Carbonylative Cycloaddition and Higher-Order Cycloaddition

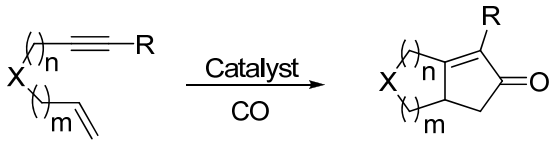
§ 1.2.1. Carbonylative Cycloaddition

In 1973, Pauson and Khand reported the preparation of cyclopentenones **1-3** and **1-4** from the three-component transition metal-catalyzed [2+2+1] cycloaddition of alkyne **1-1**, alkene **1-2**, and carbon monoxide in the presence of a stoichiometric amount of $Co_2(CO)_8$ (**Scheme 1-1**).[13] This reaction is attractive for organic synthesis because a wide variety of functionalities such as esters, ethers, tertiary amines, amides, and alcohols, are well tolerated under the given reaction conditions.



Scheme 1-1: Intermolecular Pauson-Khand reaction.

In 1981, Schore introduced the first examples of the intramolecular Pauson-Khand reaction (**Scheme 1-2**)[14] resolving the regioselectivity issues observed in the intermolecular Pauson-Khand reaction. The addition of a tether that linked the alkene and alkyne moieties, resulted in a bicyclic product from an acyclic substrate. Since bicyclic skeletons can be constructed in a single step, this intramolecular Pauson-Khand reaction has been utilized in the key step of the total synthesis of natural products.[15]



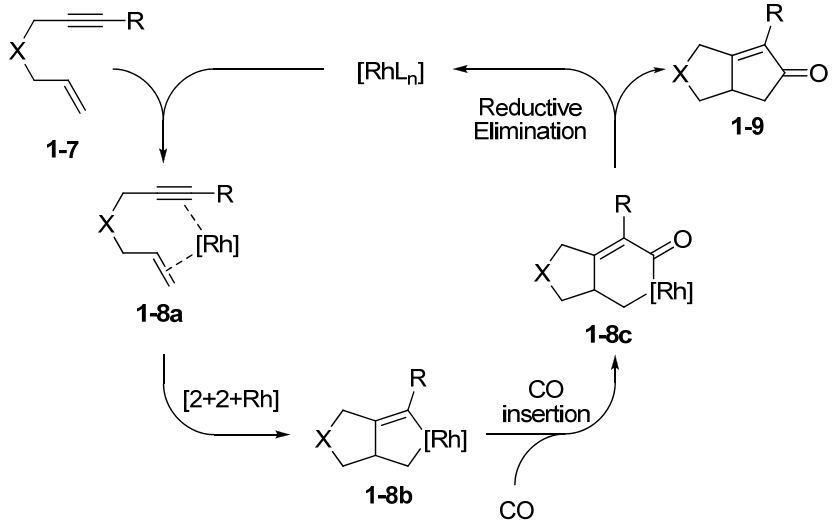
1-5 **1-6**

X = O, NR, CH_2, $C(CO_2R)$; R = SiR_3, alkyl, Ar

Catalyst = Co, Rh, Ti, Zr, Ir, Ru

Scheme 1-2: Intramolecular Pauson-Khand reaction.

Following the discovery of this reaction, numerous improvements have been reported including reaction temperature reduction, use of other transition metals, and the use of catalytic amounts of metal species.[16] In the 1990's, cobalt, titanium, ruthenium, and rhodium complexes were reported to serve as catalysts in the catalytic Pauson-Khand reaction.[16a, 17] A proposed mechanism for the PK reaction of 1,6-enynes **1-7** catalyzed by Rh is outlined in **Scheme 1-3**.[18]

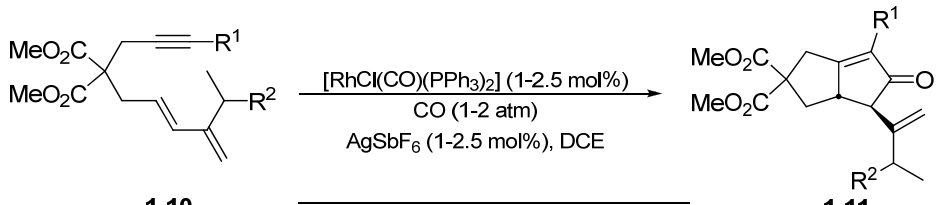


Scheme 1-3: Proposed mechanism of the PK reaction catalyzed by Rh-complex.

The reaction starts with coordination of the enyne **1-7** to the active Rh catalyst, giving intermediate **1-8a**. Intermediate **1-8a** undergoes [2+2+Rh] cycloaddition giving 5-5 rhodacyclopentene **1-8b**. Carbon monoxide (CO) coordination to the metal center followed by migratory insertion into the Rh-C bond gives 5-6 rhodacyclohexenone **1-8c. R**eductive elimination yields the PK reaction product bicyclo[3.3.0]octenone **1-9**.

In the efforts to expand the scope of Pauson-Khand type reaction (PKTR), researchers have been exploring various carbon components in Rh-catalyzed PKTR. Wender and coworkers have reported diene-alkyne PKTR (**Scheme 1-4**).[19] Using $[RhCl(CO)(PPh_3)_2]$ (1-2.5 mol%), $AgSbF_6$ (1-2.5 mol%) in dichloroethane under CO (1-2 atm), a series of dienynes **1-10** were

converted to the corresponding alkenyl cyclopentenones **1-11** in good to excellent yields and as a single diastereomer.

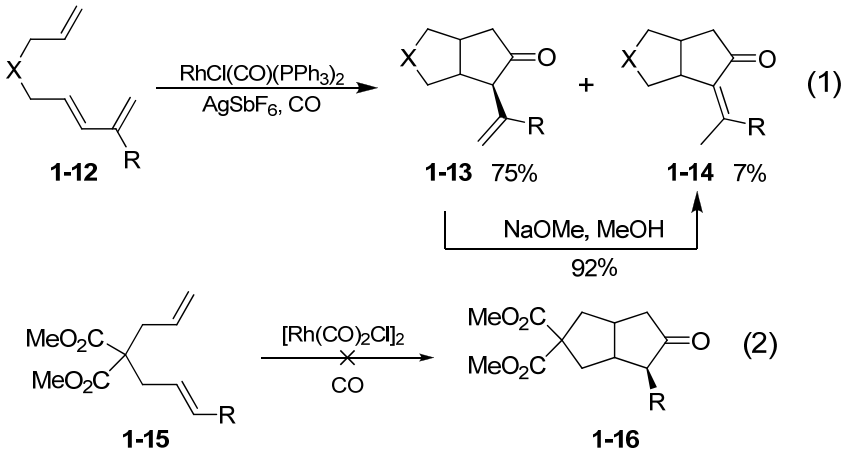


1-10 **1-11**

Entry	R^1	R^2	Yield (%)
1	Me	Me	89
2	TMS	Me	85
3	H	Me	43
4	H	H	42
5	Me	H	86

Scheme 1-4: The PKR of dieneynes **1-10**

Wender and coworkers also reported diene-alkene PKTR (**Scheme 1-5, Eq. 1**).[20] The triene substrate **1-12** has been studied in great detail in the intramolecular Diels-Alder reactions for the construction of six-membered rings.[21] However, the alkene-alkene PKTR was *not* known. Bis-alkenes **1-15** were employed in a control reaction using similar conditions for the PKTR; but, no reaction took place, regardless of functional groups (**Scheme 1-5, Eq. 2**). The result demonstrated that the dienyl moiety in substrate 1-12 is essential for the reactivity observed in this series of substrates.

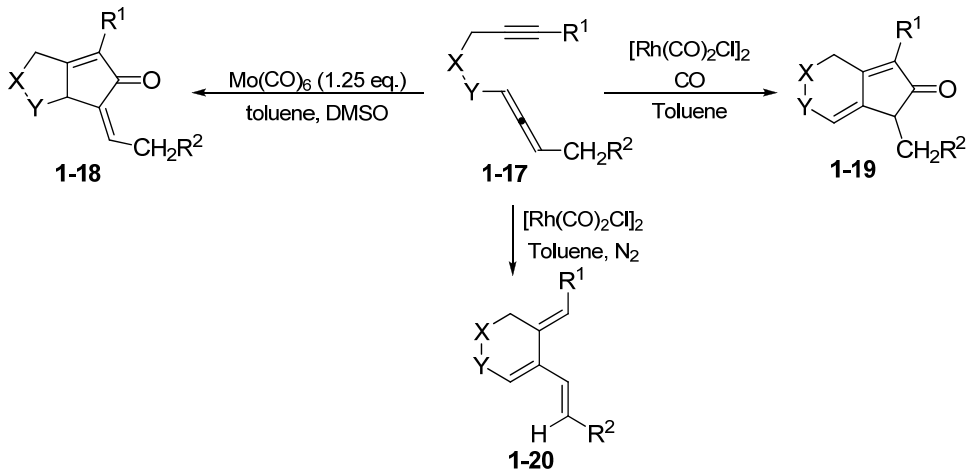


Scheme 1-5: Rh-catalyzed diene-alkene PKR.

Diene-ene **1-12**, treated with Rh catalyst and $AgSbF_6$ additive under CO atmosphere gave product **1-13** and **1-14** in a combined yield of 82%. A control experiment has shown that product

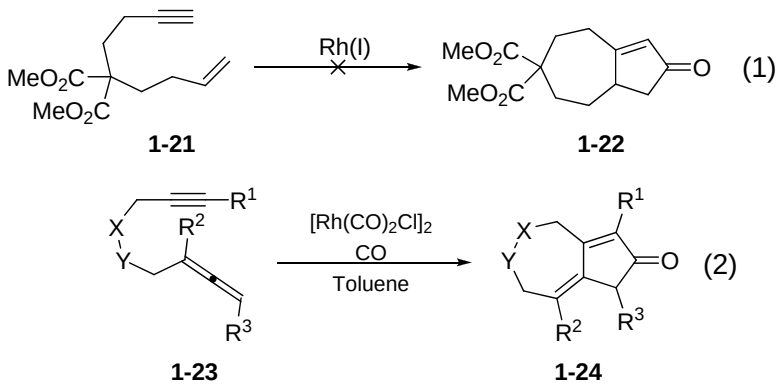
1-14 was formed exclusively from the isomerization of the double bond of **1-13**. It should be noted that the substituents on the diene moiety played an important role in this reaction. While substitutions on the 2-position of the diene was well-tolerated, substitutions on the 1- or 3-positions were shown to be detrimental to the reaction.

Transformations of allenyne **1-17** by transition metals gave different carbocycles and heterocycles depending on reaction conditions (**Scheme 1-6**).[22] Molybdenum-catalyzed PKTR of allenyne **1-17** gave **1-18**, in which the proximal double bond of allenyne **1-17** selectively reacted with the metal center to give the [3.3.0] bicyclic **1-18.** In the Rh-catalyzed PKTR of **1-17**, the distal double bond reacted with the Rh catalyst to give the complimentary regioselective product [4.3.0] bicyclic **1-19.** In the absence of carbon monoxide, allenyne **1-17** undergoes an Alder Ene reaction with the proximal double bond to form the cross-conjugated trienes **1-20**.



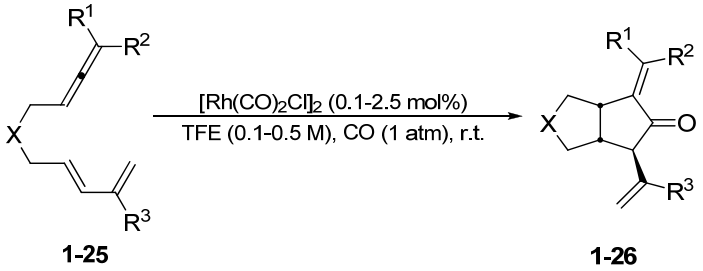
Scheme 1-6: transition metal-catalyzed transformation of allenyne **1-17**.

Allenic PKTR is attractive in the construction of larger bicyclic [*m*.3.0] ring systems (*m*>4). One particular ring system of interest is the bicyclic [5.3.0] ring skeleton, which exists in broad ranges of natural products. Despite the successful constructions of [3.3.0] and [4.3.0] bicyclics from Rh-catalyzed PKR of enynes, construction of [5.3.0] bicyclics **1-22** from enyne **1-21** has proven to be challenging (**Scheme 1-7, Eq. 1**).[23] The major breakthrough in the construction of [5.3.0] bicyclics **1-24** was accomplished independently by Brummond and Mukai using allenic PKTR (**Scheme 1-7, Eq. 2**).[23-24]



Scheme 1-7: Formation of bicyclo[5.3.0]ring system.

Previously, Wender reported a Rh-catalyzed alkene-diene PKTR[20], in which a diene moiety was found to be essential for the reaction. Similar results were obtained when the same concept was applied to the allenic PKTR (**Scheme 1-8**).[25]



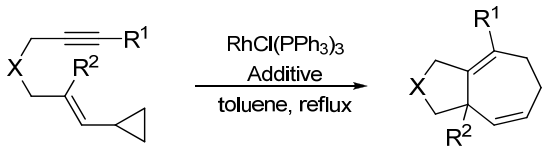
Entry	X	R^1	R^2	R^3	Yield (%)
1	NTs	Me	Me	Me	97
2	$C(CO_2Me)_2$	Me	Me	*i*-Pr	92
3	O	Me	Me	H	97
4	NTs	H	Me	*i*-Pr	39

Scheme 1-8: Rh- catalyzed allene-diene PKR.

It should be noted that the substitution at the terminal carbon of allene played a key role in reaction dynamic. Di-substituted allene substrates afforded products in high yield under various reaction conditions. Mono-substituted allene substrates gave diastereomeric products due to axially chirality in the allene. Terminally unsubstituted allene substrates required higher reaction temperature and higher CO pressure for the reaction to proceed. The desired products were obtained in low yield along with the [4+2] products. Addition of acid has been shown to enhance the reaction rate without reduction in yield.

§ 1.2.2. Higher-Order Cycloaddition

The development of rhodium catalyzed [5+2] cycloadditions of vinylcyclopropanes (VCP) with a variety of 2π components was reported by Wender.[26] In 1995, the first example of transition metal catalyzed [5+2] Cycloaddition of VCP and alkynes was reported (**Scheme 1-9**).[26d] Various tethered alkyne-VCP underwent Rh-catalyzed [5+2] cycloaddition, affording good (but the yields are in the 80s) yields irrespective of the steric and electronic properties of the R^1 group. Products with quaternary centers are also obtained in high yields.



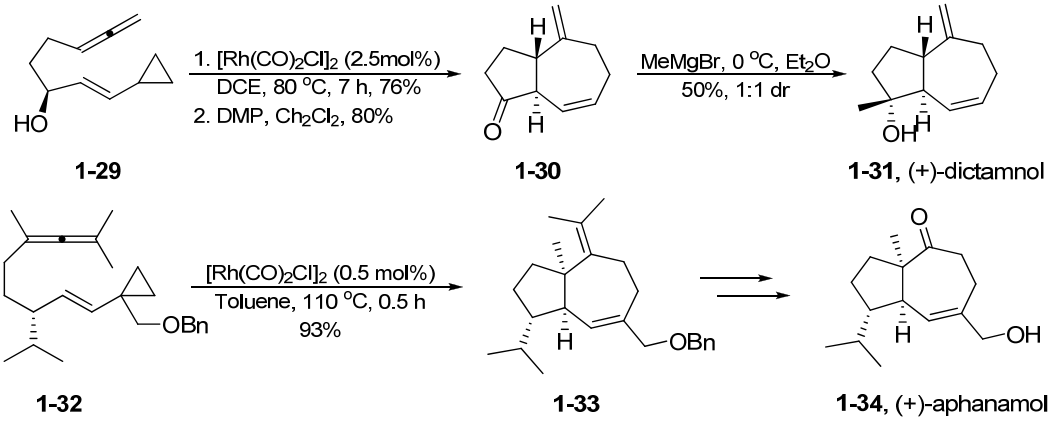
1-27 **1-28**

Conditions	X	R^1	R^2	Time (h)	Yield (%)
A	$C(CO_2Me)_2$	Me	H	0.3	83
B	O	Me	H	1.5	88
B	O	TMS	H	3.5	83
B	O	Ph	H	1.5	80
B	O	CO_2Me	H	1.3	74
C	$C(CO_2Me)_2$	Me	Me	0.5	82

Condition A: $RhCl(PPh_3)_3$ (0.5 mol%), AgOTf (0.5 mol%)
Condition B: $RhCl(PPh_3)_3$ (10 mol%)
Condition C: $RhCl(PPh_3)_3$ (10 mol%), AgOTf (10 mol%)

Scheme 1-9: Rh-catalyzed alkyne-VCP [5+2] cycloaddition.

In addition to the tethered alkyne-VCP [5+2] cycloaddition, [5+2] cycloaddition of tethered allene-VCP[26b] have also been achieved. Intramolecular allene-VCP [5+2] cycloaddition served as the key step in the syntheses of (+)-dictamnol and (+)-aphanamol I (**Scheme 1-10**).[26a, 26e]

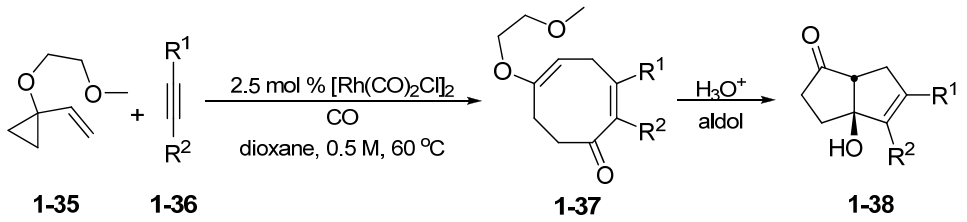


1-29 **1-30** **1-31**, (+)-dictamnol

1-32 **1-33** **1-34**, (+)-aphanamol

Scheme 1-10: Rh-catalyzed alkyne-VCP [5+2] cycloaddition.

A three component [5+2+1] cycloaddition of VCP **1-35**, alkynes **1-36** and carbon monoxide using $[Rh(CO)_2Cl]_2$ as catalyst was reported by Wender and coworkers.[10] The process initially leads to an eight-membered ring **1-37.** Upon hydrolytic workup, bicyclo [3.3.0] octenone products **1-38** formed through transannular closure of the eight-membered ring intermediate in good to excellent yields (**Scheme 1-11**).

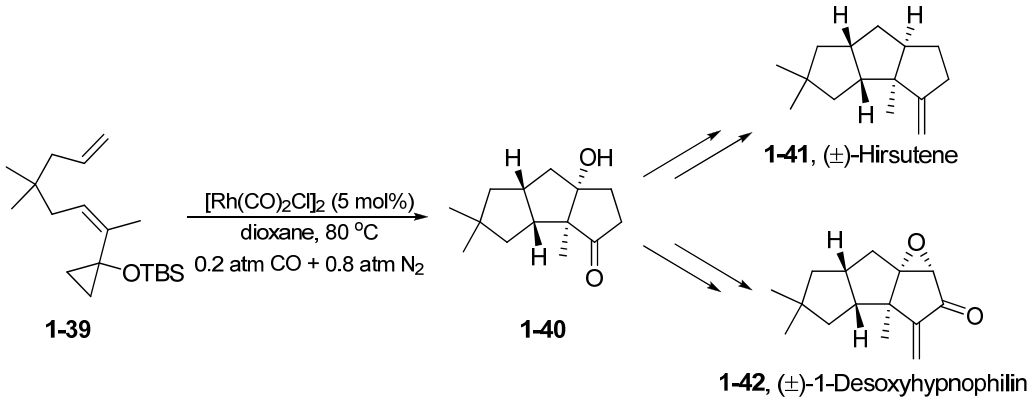


1-35 **1-36** **1-37** **1-38**

Entry	R^1	R^2	CO (atm)	**1-38** Yield (%)
1	$COCH_3$	Et	2	97
2	$COCH_3$	TMS	1	54
3	$COCH_3$	Ph	1	88
4	$CONH_2$	Ph	1	96
5	CHO	Ph	2	69
6	CO_2Et	Ph	1	79
7	CO_2Et	TMS	1	67
8	CO_2Et	Me	1	85
9	CO_2Me	CO_2Me	1	48

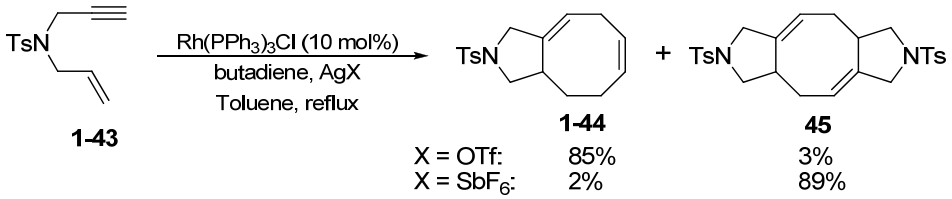
Scheme 1-11: Intermolecular [5+2+1] cycloaddition of VCP **1-35** with alkynes **1-36**.

After the intermolecular tandem [5+2+1] cycloaddition /aldol reaction was discovered, an intramolecular version was used in the key step to obtain a common intermediate **1-40** enroute to the total synthesis of both (±)-Hirsutene **1-41** and (±)-1- Desoxyhypnophilin **1-42** (**Scheme 1-12**).[27] The linear triquinanes (±)-Hirsutene **1-41** and (±)-1- Desoxyhypnophilin **1-42** have displayed promising antibiotic and antitumor activities.[28] These compounds possess novel architecture characterized by *cis-anti-cis* fused cyclopentane skeleton. The reaction of (*Z*)-siloxy-ene-VCP **1-39** gave a single diastereomer of the tricyclic product **1-40** with the desired *cis-anti-cis* configuration.



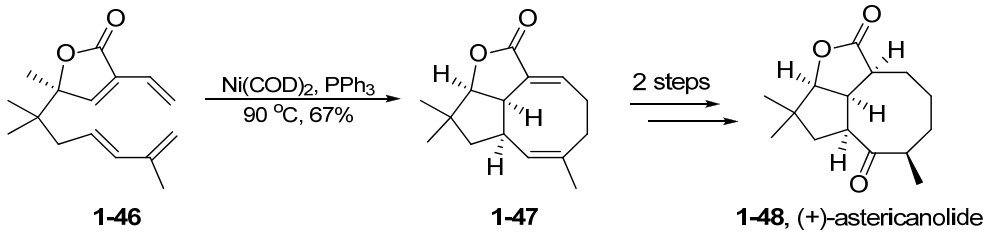
Scheme 1-12: Total synthesis of (+/-)-Hirsutene **1-41** and (+/-)-Desoxyhypnophilin **1-42** via [5+2+1] cycloaddition of ene-vinylcylopropane **1-39**.

In the effort to construct eight-member ring systems, Evans *et. al.* have done extensive work on [4+2+2] cycloadditions.[11] During the course of their studies, they found that the counterions of the silver additive played a key role in the product selection. When silver triflate was employed in the reaction, [4+2+2] cycloaddition between the enyne **1-43** and butadiene was greatly favored. In contrast, when silver hexafluoroantimonate was employed, the homodimer of enyne **1-43** resulting from [2+2+2+2] cycloaddition was formed as the major product (**Scheme 1-13**).



Scheme 1-13: Rh-catalyzed [4+2+2] cycloaddition of enyne **1-43** with butadiene.

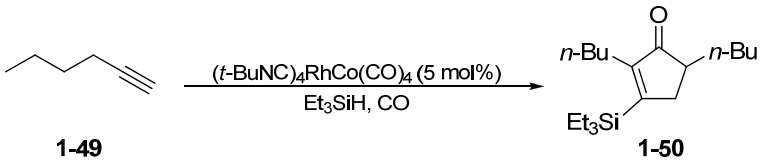
An efficient Ni catalyzed intramolecular [4+4] cycloaddition of bis-diene **1-46** for the construction of eight-membered ring was developed and applied to a short total synthesis of (+)-astericanolide **1-48** (**Scheme 1-14**).[29]



Scheme 1-14: Ni-catalyzed [4+4] cycloaddition of bis-diene **1-46**.

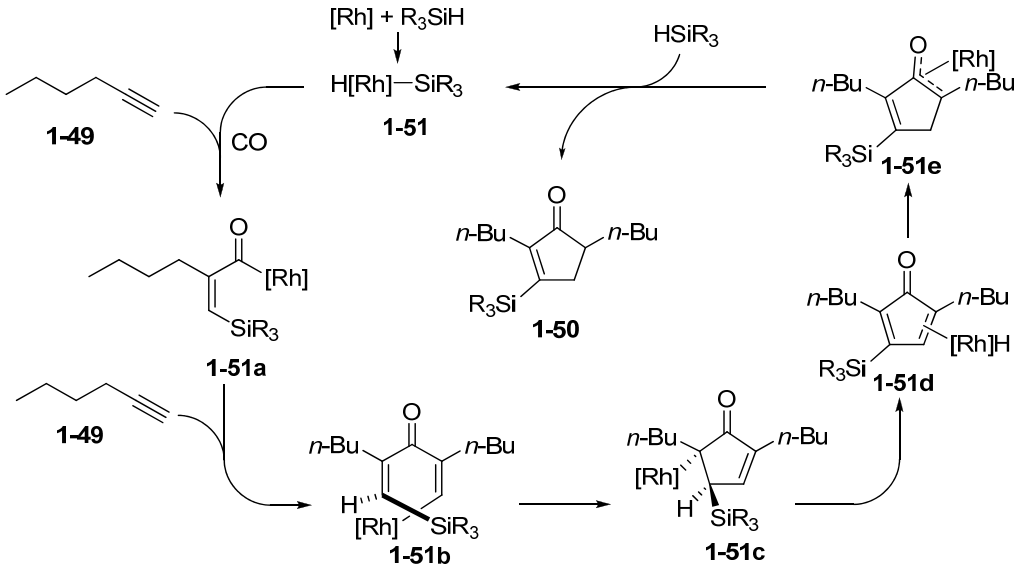
§ 1.3. Silylcarbocyclizations and Carbonylative Silylcarbocyclizations

The Rh-catalyzed carbonylative silylcarbocyclization (CO-SiCaC) reaction of 1-hexeyne **1-49** gave silylcyclopentenone **1-50** (**Scheme 1-15**). Compound **1-50** was isolated as a minor product during studies of the silylformylation of 1-hexyne **1-49** with dimethylphenylsilane catalyzed by $Co_2Rh_2(CO)_{12}$.[30] Under optimized conditions using Et_3SiH and (t-BuNC)$_4$RhCo(CO)$_4$ as the catalyst at 60 ^oC, **1-50** was isolated in 54% yield.[30b]



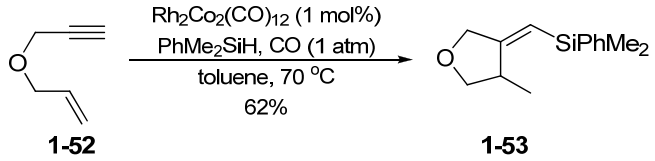
Scheme 1-15: Synthesis of silylcyclopentenone **1-50** *via* CO-SiCaC reaction

The mechanism was proposed by Ojima and coworkers for this intermolecular CO-SiCaC reaction (**Scheme 1-16**).[30b] β-silylacryloyl-[Rh] complex **1-51a** was formed during the silylformylation process. Intermolecular trapping of the β-silylacryloyl-[Rh] complex **1-51a** by a second molecule of 1-hexyne **1-49** gives intermediate **1-51b**. Subsequent carbocyclization gives intermediate **1-51c**. Syn-β-hydride elimination forms cyclopentadienone-[Rh]-H complex **1-51d**. Highly regioselective hydrometallation of the olefin moiety at the least sterically congested site gives intermediate **1-51e**. Silane-promoted reductive elimination of rhodium affords **1-50** and regenerates the active catalyst.



Scheme 1-16: Proposed mechanism for the formation of silylcyclopentenone **1-50**.

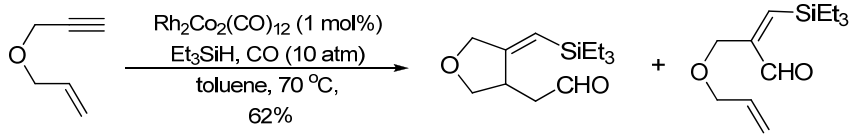
Based on the observation of silylcyclopentenone **1-50** product and the analysis of the proposed mechanism, it was postulated that β-silylethenyl-[Rh] intermediate **1-51a** (**Scheme 1-16**) could be trapped by an unsaturated moiety in an intramolecular fashion. Thus, the intramolecular version of the CO-SiCaC and silylcarbocyclization (SiCaC) reactions were investigated using 1,6-eneynes.[30b] For example, the reaction of allyl propargyl ether **1-52** with $PhMe_2SiH$ catalyzed by $Rh_2Co_2(CO)_{12}$ (1 mol%) gave 3-(silylmethylene)-4-methylhydrofuran **1-53** in 62% yield (**Scheme 1-17**). This result clearly supports the observation that the β-silylethenyl-[Rh] species **1-51a** (**Scheme 1-16**) could be efficiently trapped in an intramolecular fashion by an olefin moiety.



1-52 **1-53**

Scheme 1-17: SiCaC reaction of 1,6-eneyne **1-52**.

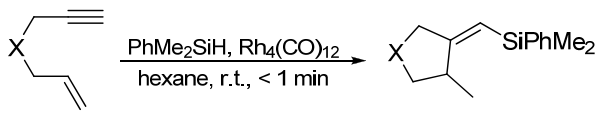
When the reaction of **1-52** was carried out under 10 atm of CO using Et_3SiH, the CO-SiCaC reaction took place to give the corresponding aldehyde **1-54** as a minor product (15-20 %) together with the silylformylation product **1-55** (70-75 %) (**Scheme 1-18**).[30b] In this case, the higher CO pressure favored the carbonylated products.



1-52 **1-54** (10-15%) **1-55** (70-75%)

Scheme 1-18: CO-SiCaC reaction of 1,6-eneyne **1-52**.

Thus the Ojima group has investigated the SiCaC reaction of enynes in detail, and has applied it to a wide range of substrates. Rhodium carbonyl clusters, such as $Rh_4(CO)_{12}$, and bimetallic clusters such as $Rh_2Co_2(CO)_{12}$ have been found to be very effective catalysts in promoting this transformation. The reaction of 1,6-enynes **1-56** with $PhMe_2SiH$ catalyzed by $Rh_4(CO)_{12}$ was complete within 1 minute at room temperature, and gave the corresponding silylmethylene-2-methylcyclopentanes **1-57** in good to excellent yields (**Scheme 1-19**). [31]

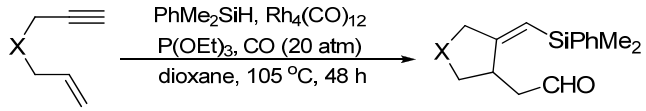


1-56 **1-57**

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

Scheme 1-19: SiCaC reaction of 1,6-eneynes **1-56**.

When the reaction of **1-56** catalyzed by $Rh_4(CO)_{12}$/ $P(OEt)_3$ was carried out under 20 atm of CO, the CO-SiCaC reaction took place almost exclusively and gave **1-58** in good to excellent yields (**Scheme 1-20**).[31] A variety of substrates were shown to be effective in the Rh-catalyzed SiCaC and CO-SiCaC reactions and thus provide efficient methods for the construction of synthetically useful substituted *exo*-methylene-cyclopentane and pyrrolidine products.



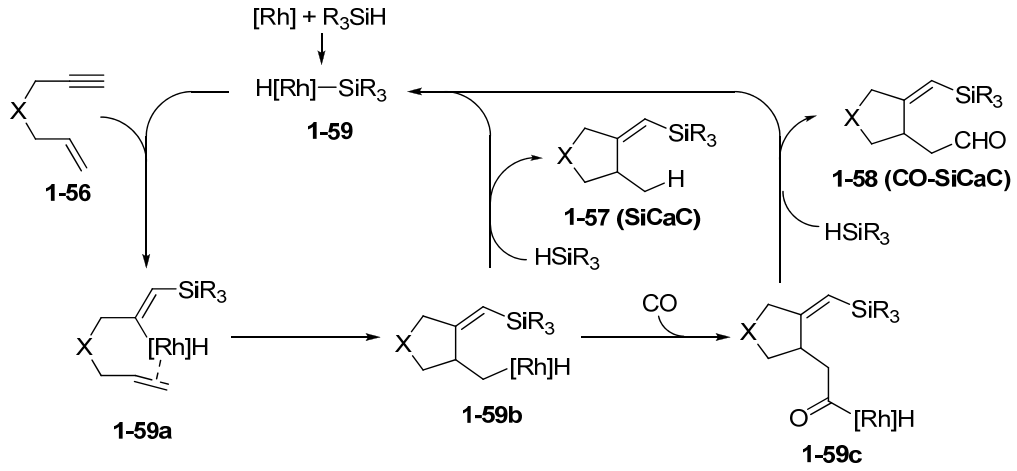
1-56 **1-58**

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

Scheme 1-20: CO-SiCaC reaction of 1,6-eneynes **1-56**.

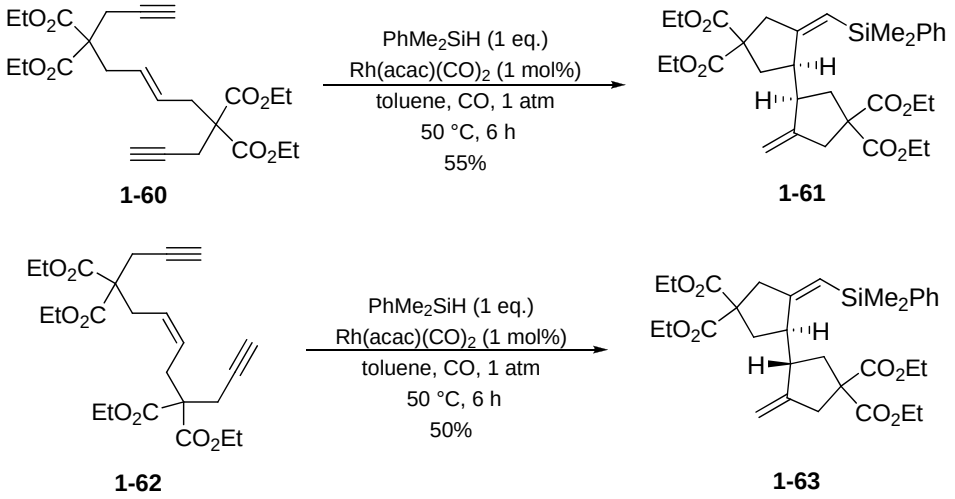
The proposed mechanism for the SiCaC and CO-SiCaC reactions of 1,6-eneynes **1-56** is illustrated in **Scheme 1-21**. The reaction begins with the formation of the active R_3Si-[Rh]H catalytic complex **1-59**, followed by regioselective insertion of the acetylene moiety of eneyne **1-56** to the Si-Rh bond to generate *β*-silylvinyl-[Rh] complex **1-59a**. Coordination of the olefin moiety of **1-59a**, followed by intramolecular carbometallation, leads to the formation of intermediate **1-59b**. At this point, the pathways can diverge to the formation of SiCaC **1-57** and CO-SiCaC **1-58** products. At low pressure of CO, hydrosilane-promoted reductive elimination occurs to give SiCaC product **1-57** and regenerates silyl-[Rh] complex **1-59**. At high CO pressure, coordination to the metal center followed by migratory insertion of CO into the alkyl-

[Rh] bond of **1-59b** leads to the formation of acyl-[Rh] complex **1-59c**. Hydrosilane-promoted reductive elimination affords CO-SiCaC product **1-58** and regenerates the active catalyst species **1-59**. Though a CO atmosphere is not essential for the formation of the SiCaC product, the CO atmosphere appears to stabilize the active [Rh] catalyst species, especially when Rh and Rh-Co carbonyl clusters are used for a prolonged period of time.



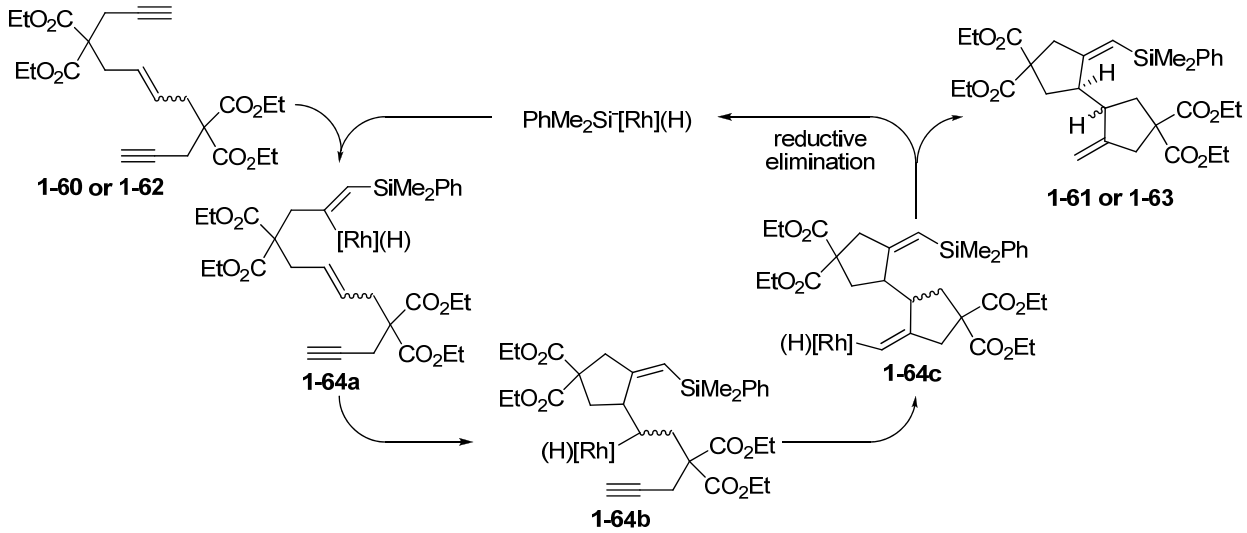
Scheme 1-21: Proposed SiCaC and CO-SiCaC mechanisms

Based on the results of the SiCaC study on 1,6-eneynes, Ojima and coworkers postulated that the alkyl-[Rh](H) intermediate **1-59b** (**Scheme 1-21**), could be further trapped by an appropriately placed unsaturated moiety. The resulting cascade carbocyclization would provide polycyclic frameworks from relatively simple starting materials. The hypothesis was confirmed when (6*E*)-dodec-6-ene-1,11-diyne **1-60** reacted with $PhMe_2SiH$, catalyzed by $Rh(acac)(CO)_2$ at 50 ^oC and atmospheric pressure of CO afforded (*R*,*R*)-bis(*exo*-methylenecyclopentyl) **1-61** in 55% isolated yield (**Scheme 1-22**).[7a] In a similar manner, the reaction of (6*Z*)-dodec-6-ene-1,11-diyne **1-62** gave (*S*,*R*)-bis(*exo*-methylenecyclopentyl) **1-63** in 50% isolated yield (**Scheme 1-22**). These cascade reactions proceeded stereospecifically according to the double bond geometry.[7a]



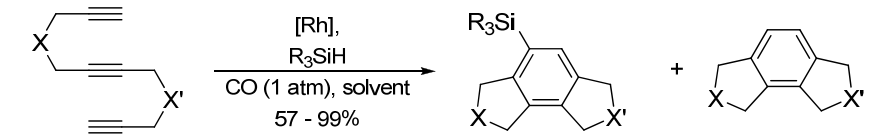
Scheme 1-22: SiCaC of dodec-6-ene-1,11-diynes **1-60** and **1-62**.

The proposed mechanism for the SiCaC reaction is depicted in **Scheme 1-23**. The reaction begins with the insertion of the alkyne moiety of **1-60** or **1-62** into the Si-[Rh] bond of the active Si-[Rh]H catalytic complex to give intermediate **1-64a** which then undergoes the first carbometallation to form intermediate **1-64b**. Then, the alkyl-[Rh](H) of intermediate **1-64b** is trapped by the second acetylene moiety to form the vinyl-[Rh](H) intermediate **1-64c**. Reductive elimination gives **1-61** or **1-63**. Although the third carbometallation of the vinylsilane moiety with the vinyl-[Rh] species of **1-64c** to form the corresponding fused tricyclic skeleton was conceptually possible, such a cyclization was not observed. This result may well be attributable to the rotational freedom about the bond connecting the two cyclopentyl units.[7a]



Scheme 1-23: Proposed mechanism for SiCaC of dodec-6-ene-1,11-diynes **1-60** and **1-62**.

It was anticipated that confining the rotational freedom about the bond of intermediate **1-64c** (**Scheme 1-23**) by introducing a carbon-carbon double bond would generate a rigid framework that would facilitate the subsequent carbometallation which would then lead to a third carbocyclization. Such prospects led to the investigation of the cascade SiCaC reaction of dodec-1,6,11-triynes **1-65**. A novel silicon-initiated cascade carbotricyclization (SiCaT) of triynes **1-65** catalyzed by rhodium complexes giving the corresponding fused tricyclic benzene derivatives **1-66** and **1-67** in good to excellent yields was reported (**Scheme 1-24**).[32] The SiCaT reaction is applicable to 1,7,12- and 1,7,13-triynes, affording 6-6-5 and 6-6-6 fused tricyclic benzene derivatives, respectively.

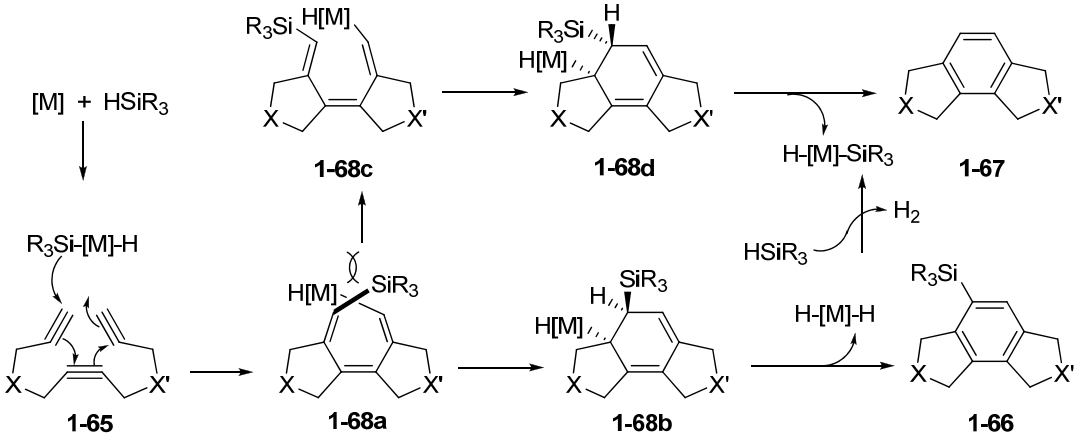


1-65
X, X' = O, N, and CR_2

1-66 **1-67**

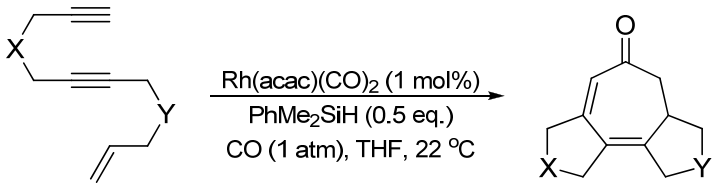
Scheme 1-24: SiCaT of 1,6,11-triynes **1-65**.

A proposed mechanism for the SiCaT reaction using the 1,6,11-triyne system is illustrated in **Scheme 1-25**. Similar to the proposed mechanism of SiCaC of dodec-6-ene-1,11-diynes **1-60** and **1-62,** the reaction proceeds through the insertion of one of the terminal alkynes of **1-65** into the active Si-[Rh]H complex generating an ethenyl-[Rh] intermediate which is followed by the second and third alkyne insertions to form intermediate **1-68a**. Subsequent carbocyclization followed by *syn-β*-hydride elimination gives the silylbenzene product **1-66**. Alternatively, ethenyl-[Rh] intermediate **1-68a** is isomerized to the thermodynamically more favorable intermediate **1-68c** *via* a zwitterionic carbene species, i.e., the "Ojima-Crabtree isomerization mechanism".[33] Subsequent carbocyclization gives **1-68d**. In this intermediate, the Rh and the C-4 hydrogen are *trans* to each other, precluding *syn-β*-hydride elimination. Instead, *β*-silyl elimination takes place to give non-silylated benzene product **1-67**.



Scheme 1-25: Proposed mechanism for SiCaT of 1,6,11-triynes **1-65**.

When an olefin is at the terminal position of an enediyne system, carbonylative carbotricyclization (CO-SiCaT) reaction takes place, incorporating CO into the product.[34] As **Scheme 1-26** shows, the reaction of dodec-11-ene-1,6-diynes **1-69** catalyzed by $Rh(acac)(CO)_2$ under an atmospheric pressure of CO gave the corresponding cyclopenta[*e*]azulenes **1-70** in good to excellent yields (**Scheme 1-26**).



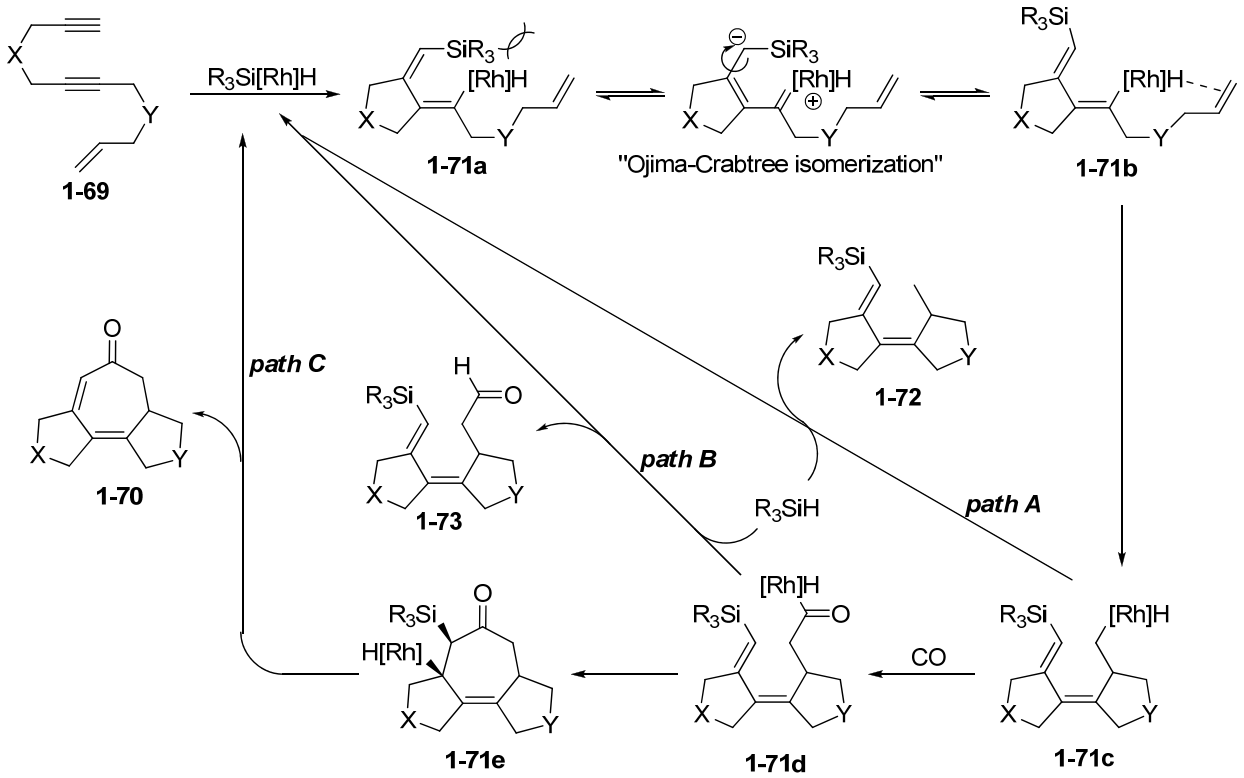
1-69 **1-70**

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

Scheme 1-26: CO-SiCaT of dodec-11-ene-1,6-diynes **1-69**.

A proposed mechanism for the CO-SiCaT reaction is illustrated in **Scheme 1-27**.[34] The reaction begins with the insertion of the terminal alkyne moiety of **1-69** into the Si-Rh bond of the active R_3Si-[Rh]H catalytic complex. Carbocyclization then occurs to give (*Z*)-dienyl-

[Rh](H) intermediate **1-71a**. Because of the steric hindrance between the vinylsilane and the vinyl-[Rh] moieties, **1-71a** isomerizes to **1-71b** through the "Ojima-Crabtree isomerization mechanism". Subsequent carbocyclization gives common intermediate **1-71c**. Silane promoted reductive elimination of **1-71c** should give **1-72** (**path A**). The CO insertion to **1-71c** gives acyl-[Rh](H) intermediate **1-71d** and silane promoted reductive elimination of **1-71d** should yield aldehyde **1-73** (**path B**). Carbocyclization of **1-70d** gives tricyclic intermediate **1-71e** that has the silicon and the [Rh] moieties in *syn* positions (**path C**). Subsequent *syn*-*β*-silyl elimination takes place to afford the fused 5-7-5 tricyclic product **1-70** and regenerates the active catalyst species, R_3Si- [Rh](H).



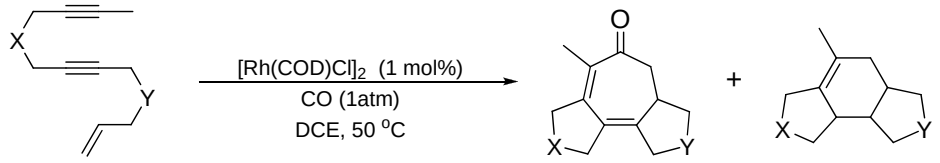
Scheme 1-27: Proposed mechanism for CO-SiCaT of dodec-11-ene-1,6-diynes **1-69**.

When one or more equivalent of hydrosilane is used, silane promoted reductive elimination is accelerated so that products **1-72** (***path A***) and **1-73 (*path B*)** are obtained besides **1-70**. This is because the hydrosilane promoted reductive elimination pathways (***path A*** and ***B***) are bimolecular processes. As such, the presence of stoichiometric or excess amount of hydrosilane and high reaction concentration leads to products **1-72** and **1-73**. It is worthy to note that cyclopenta[*e*]azulene **1-70** is exclusively formed under optimized conditions using a catalytic amount of hydrosilane and high dilution conditions (***path C***). The reactions of

enediynes substituted at the terminal position did not yield the carbonylated products but rather the 5-6-5 tricyclic products.[34b]

§ 1.4. Rh(I)-Catalyzed [2+2+2+1] Cycloaddition

During the studies on the scope and limitations of the CO-SiCaT reaction, it was found that in *the absence of hydrosilane*, 1-substituted endiynes **1-74** also afforded carbonylative tricyclization products **1-75** in good to excellent yields, accompanied by a small amount of non-carbonylated product **1-76** (**Scheme 1-28**).[34b, 35]



1-74 **1-75** **1-76**

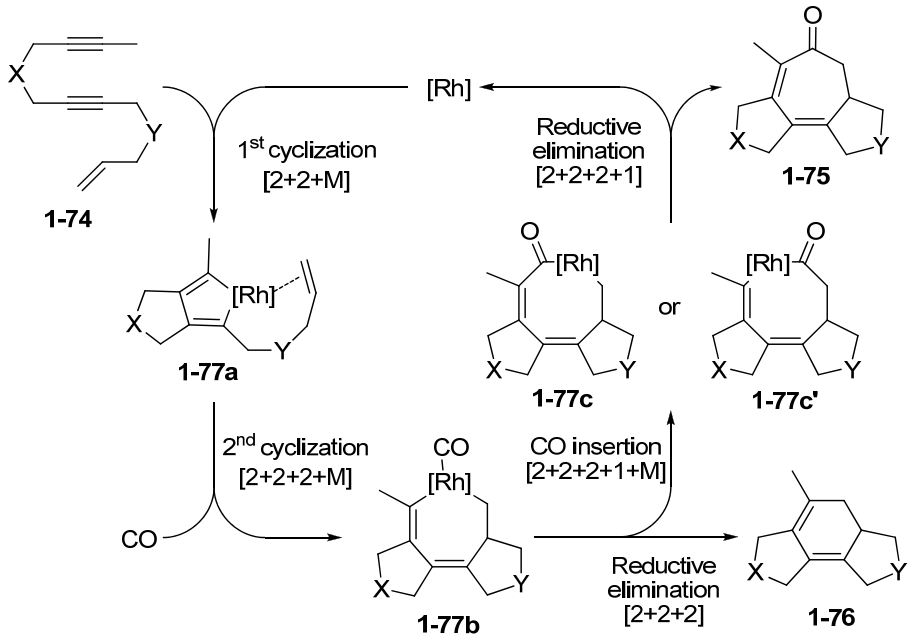
Entry	X	Y	**1-75** Yield (%)
1	$C(CO_2Et)_2$	$C(CO_2Et)_2$	88
2	O	O	53
3	O	$C(CO_2Et)_2$	79
4	NTs	NTs	84
5	$C(CO_2Et)_2$	NTs	69
6	NTs	$C(CO_2Et)_2$	88
7	$C(CO_2Et)_2$	NBoc	70
8	$C(CH_2OMe)_2$	$C(CH_2OMe)_2$	92
9	$C(CH_2OBn)_2$	$C(CH_2OBn)_2$	91
10	$C(CH_2OAc)_2$	$C(CH_2OAc)_2$	82

Scheme 1-28: Rh-catalyzed [2+2+2+1] cycloaddition of enediyne **1-74**.

Even though this novel Rh-catalyzed [2+2+2+1] cycloaddition of endiyne and CO provides similar products to that of the CO-SiCaT reaction, the mechanistic pathways are very different. CO-SiCaT reaction is a stepwise process of carbocyclizations,[34a] while the Rh-catalyzed [2+2+2+1] cycloaddition is believed to proceed *via* a series of metallacycle formations (**Scheme 1-29**).[34b, 35]

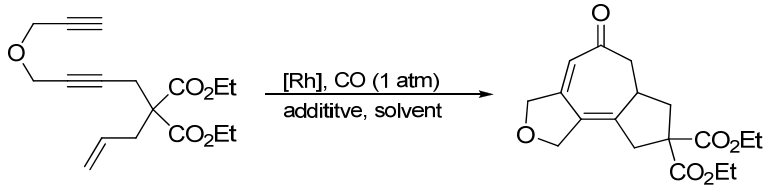
In the proposed mechanism (**Scheme 1-29**), the Rh catalyst selectively coordinates to the diyne moiety of **1-74** and cyclization forms the metallacycle **1-77a**, sequential alkene insertion with CO coordination gives the metallacycle **1-77b**. From metallacycle **1-77b**, migratory insertion of CO to the Rh-C bond gives metallacycle **1-77c** or **1-77c'** and subsequent reductive

elimination of Rh affords cycloadduct **1-75**. Reductive elimination of Rh from metallacycle **1-77b** prior to CO insertion gives [2+2+2] cycloadduct **1-76 (Scheme 1-29)**.



Scheme 1-29: Proposed mechanism for Rh-catalyzed [2+2+2+1] cycloaddition of enediyne **1-74.**

Interestingly, the reaction of un-substituted dodec-11-ene-1,6-diyne **1-78** under the optimized [2+2+2+1] cycloaddition conditions proceeded very slowly (3 days) to give the tricyclic adduct **1-79** only in 51% yield (**Scheme 1-30, entry 2**).[34b] In contrast, the CO-SiCaT of enediyne **1-78** gave **1-79** in 91% isolated yield within 24 h (**Scheme 1-30, entry 1**).[34b] Thus, the two carbonylative cyclization processes are complimentary with respect to substrate type.

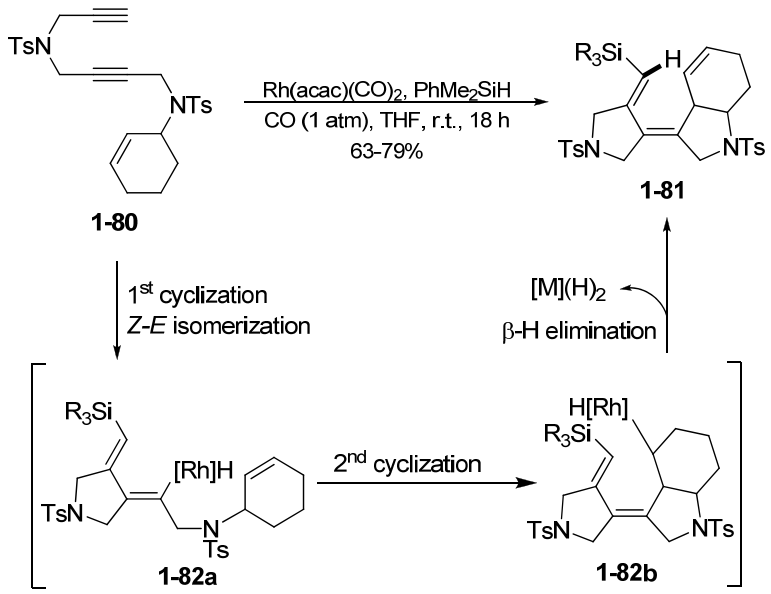


Entry	Additive	[Rh]	Slovent	Yield (%)
1	Me_2PhSiH	$Rh(acac)(CO)_2$	THF	91
2	--	$[Rh(COD)Cl]_2$	DCE	51

Scheme 1-30: CO-SiCaT and [2+2+2+1] cycloaddition of dodec-11-ene-1,6-diyne **1-78**.

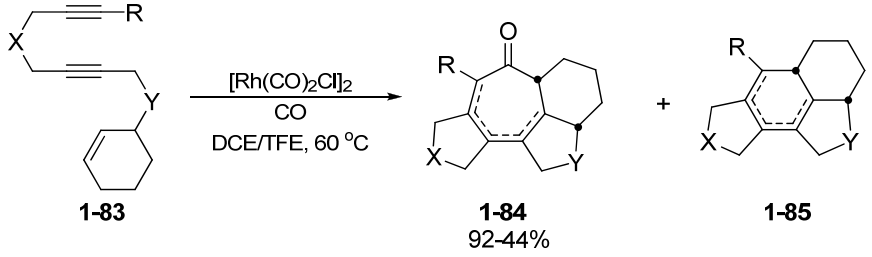
The treatment of cyclohexene-diyne **1-80** under carbonylative silylcarbotricylizaton (CO-SiCaT) conditions afforded *bis* pyrrolidine-triene **1-81** in good yield.[34b] The observed product **1-81** was correctly predicted based on a possible β-hydride elimination pathway of the key

intermediate **1-82b** (**Scheme 1-31**).[34b] The formation of product **1-81** without the observation of the 5-7-6-5 fused tetracyclic product indicates that the β-hydride elimination pathway is much faster than CO insertion under the reaction conditions.



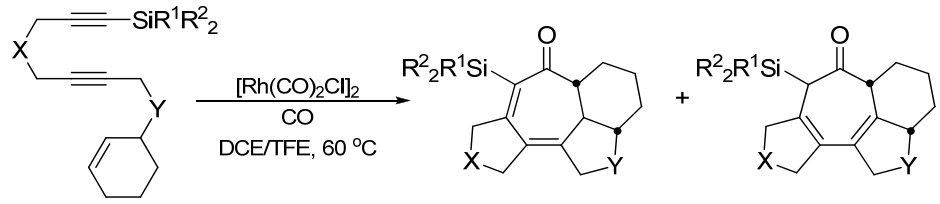
Scheme 1-31: Carbonylative silylcarbotricylizaton of cyclohexene-diyne **1-80**.

Alternatively, terminal alkyne substituted cyclohexene-diynes **1-83** were subjected to previously developed [2+2+2+1] cycloaddition conditions[34b, 35] to form the 5-7-6-5 fused tetracyclics **1-84** in good to excellent yield with almost exclusive selectivity (**Scheme 1-32**).[36] During reaction optimization, it was found that trifluoroethanol (TFE) as solvent additive was essential for the high product selectivity as well as for higher product yield. When the terminal alkyne was substituted with methyl group, many substrates gave exclusive formation of 5-7-6-5 fused tetracyclics; in some cases small amounts of 5-6-6-5 fused tetracyclic product were observed. However, the phenyl substituted substrate gave, the 5-7-6-5 and 5-6-6-5 fused tetracyclic products in 1 to 1 ratio.



Scheme 1-32: Formation of 5-7-6-5 fused tetracyclic from Rh-catalyzed [2+2+2+1] cycloaddition of cyclohexene-diyne **1-83**.

Extremely interesting results were obtained when silyl substituted cyclohexene-diynes were employed in the [2+2+2+1] cycloaddition. The product selectivity was exclusive toward 5-7-6-5 fused tetracyclic. However, analysis of the crude products indicated a 1:1 mixture of two isomers. Further analysis revealed that one of the isomers was the anticipated product **1-87**, while the other was its diene-shifted regioisomer **1-88** (**Scheme1-33**).



1-86 **1-87** **1-88**

Scheme 1-33: Formation of 5-7-6-5 fused tetracyclic regioisomers from Rh-catalyzed [2+2+2+1] cycloaddition of cyclohexene-diyne **1-86**.

The CO-SiCaT and Rh(I)-catalyzed [2+2+2+1] cycloaddition of enediyne derivatives, pioneered in Ojima's laboratory, provide a straight-forward and complimentary method to fused polycyclics. The products are also clearly amenable to further functionalization. These methods offer broad access to other fused products. As part of ongoing studies on the development of the novel higher-order cycloaddition process, the [2+2+2+1] cycloaddition of triynes which provided the fused tropone products were investigated. The details of these studies are presented in the subsequent chapters.

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Chapter 2

Rhodium-Catalyzed [2+2+2+1] Cycloaddition of Triynes

Table of Content

§2.1. Introduction

2,4,6-Cycloheptatrien-1-one (**2-1**), also known as tropone or cycloheptatrienylium oxide (**Figure 2-1**),[1] is a non-benzenoid aromatic compound that can be found in various biologically active molecules. The aromatic property arises from the polarizable carbonyl group that in an extreme case a full positive charge on the carbon atom, which is delocalized with the 6-π electrons.

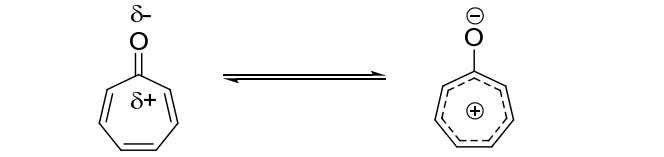
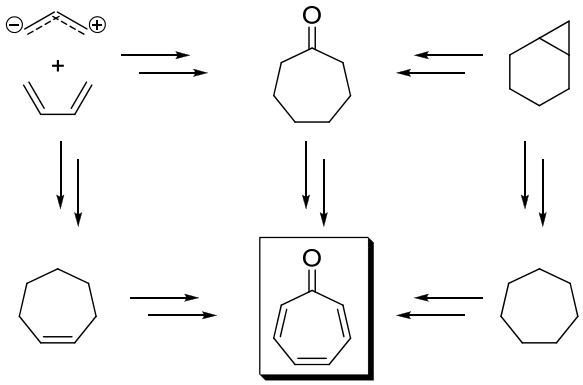


Figure 2-1: Structure of tropone.

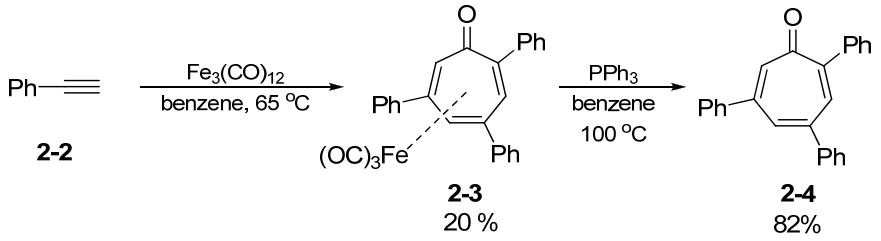
The structure of tropone is deceptively simple and there are many synthetic protocols for the synthesis of tropone. However, there are no straightforward or relatively simple reported methods to obtain tropone and its derivatives.[2] The common feature of many syntheses is the construction of the seven-membered ring followed by elaborate modifications.[2] One major route to seven-membered rings is through [4+3] type cyclization. The other major route is through [4.1.0] bicyclic ring expansion to seven-membered rings (**Scheme 2-1**).



Scheme 2-1: Synthetic protocol for the synthesis of tropone.

Since the discovery of tropone, only one direct synthesis of tropone has been reported. In 1959, Hübel and Braye reported the formation of iron-complexed tropone **2-3** from the reaction of phenylacetylene (**2-2**) and iron-carbonyl clusters (**Scheme 2-2**).[3] In the presence of either $Fe_2(CO)_9$ or $Fe_3(CO)_{12}$, phenylacetylene reacted thermally to give $Fe(CO)_3$-complexed tropones **2-3** in 20% yield. Decomplexation to free tropone **2-4** can be achieved in high yield.[4] Even

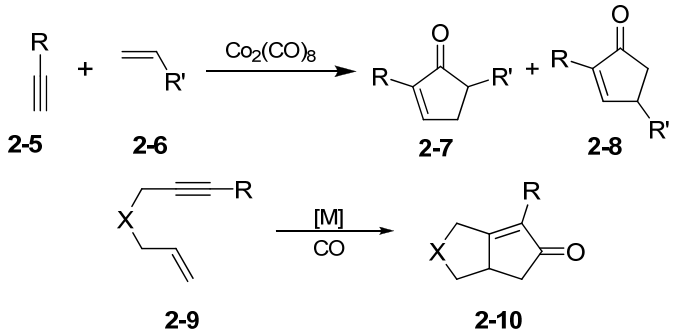
though this is the first direct synthesis of a tropone, it is impractical as a useful synthetic route with such low yields.



Scheme 2-2: Direct synthesis of tropone from phenylacetylene **(2-2).**

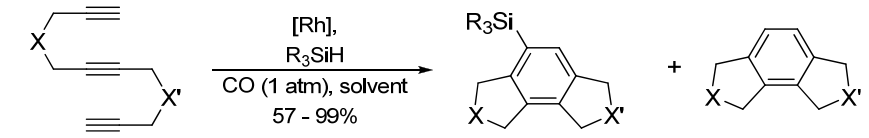
Cyclizations of unsaturated molecules are intensively studied reactions since they can potentially afford a variety of substituted heterocyclic and polycyclic compounds of paramount importance in chemical industry and pharmaceutical research. The simplest example is the one-step formation of benzene by acetylene trimerization. In 1866, Berthelot discovered the formation of benzene in low yields by high temperature treatment of acetylene.[5] In 1949, Reppe reported that homogeneous nickel complexes can be employed for the preparative cyclization of acetylene to benzene.[6] This key observation led to enormous expansion of varieties of transition-metal catalyzed cyclotrimerization of alkynes.[7]

In 1973, Pauson and Khand reported the preparation of cyclopentenones **2-7** and **2-8** from the three-component transition metal-catalyzed [2+2+1] cycloaddition of alkyne **2-5**, alkene **2-6**, and carbon monoxide in the presence of a stoichiometric amount of $Co_2(CO)_8$ (**Scheme 2-3**).[8] Since the discovery of the Pauson-Khand reaction, many great improvements have been made: (1) intramolecular fashion resolving regioselectivity issues;[9] (2) employing catalytic amount of various metal species;[10] (3) variety of unsaturated moieties have been exploited.[11] Ultimately, the Pauson-Khand reaction opened a new door for carbonylative cycloadditions.



Scheme 2-3: Inter- and intramolecular Pauson-Khand reaction.

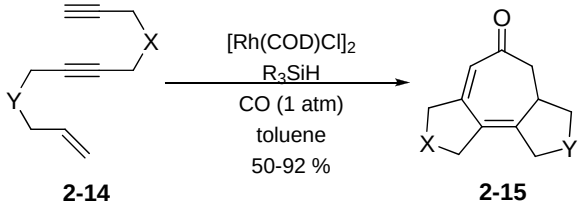
In 1999, a novel silicon-initiated cascade carbotricyclization (SiCaT) of triynes **2-11** catalyzed by homogenous rhodium catalysts was reported by Ojima's Laboratory (**Scheme 2-4**).[12] Under the optimized conditions, silylated or non-silylated annulated-benzene derivatives **2-12** and **2-13** can be selectively obtained.



2-11 X, X' = O, N, and CR_2 **2-12** **2-13**

Scheme 2-4: SiCaT of 1,6,11-triynes **2-11.**

In 2000, Ojima's laboratory found that using enediynes **2-14** as substrates in the same catalytic system resulted in carbonyl insertion to form 5-7-5 fused ring systems **2-15** (**Scheme 2-5**).[13] This was the first example of Silicon-Initiated Carbonylative Carbotricyclization (CO-SiCaT) leading to the construction of the 5-7-5 fused ring systems in high yields, and it can be described as a formal [2+2+2+1] cycloaddition.

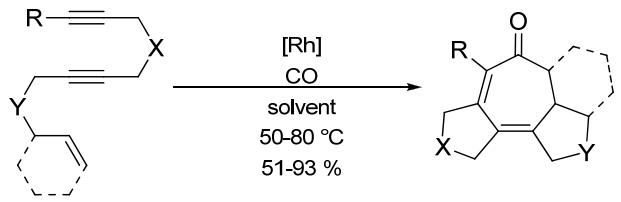


2-14 **2-15**

X, Y=esters, ethers, O, NR'

Scheme 2-5: Rh-catalyzed Carbonylative Carbotricyclization (CO-SiCaT) of enediyne **2-14.**

During the study of substrates scopes and limitations, it was found that the CO-SiCaT did not proceed well when terminal-substituted alkyne substrates **2-16** were employed. However, it was also found that the 5-7-5[13b, 14] and 5-7-6-5[15] fused ring systems **2-17** could be achieved by Rh-catalyzed [2+2+2+1] cycloadditions in the absence of hydrosilane when substrates with terminal-substituted alkynes were employed (**Scheme 2-6**). Even though similar fused ring products were obtained, the Rh-catalyzed [2+2+2+1] cycloaddition went through fundamentally different catalytic mechanism than that of CO-SiCaT.

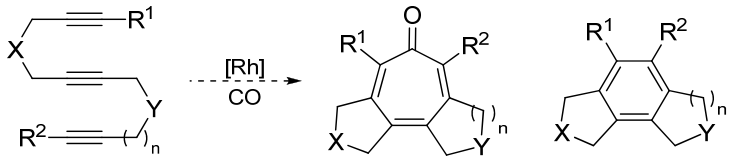


2-16 **2-17**

R= TMS. alkyl; X, Y=esters, ethers, O, NR'

Scheme 2-6: Rh-catalyzed [2+2+2+1] cycloaddition of enediyne **2-16.**

The success in the Rh-catalyzed [2+2+2+1] cycloaddition of enediynes has directed our attention toward the Rh-catalyzed [2+2+2+1] cycloaddition of triynes **2-18** in the formation of tropone **2-19** (**Scheme 2-7**). To our surprise, even though cycloaddition of alkynes under CO atmosphere conceptually can lead to the formation of tropone derivatives, this area has not been explored, and thus it is utmost importance that we survey this uncharted territory.



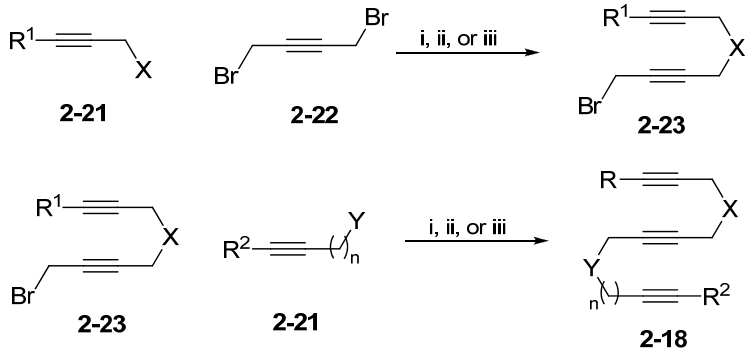
2-18 **2-19** **2-20**

Scheme 2-7: Rh-catalyzed [2+2+2+1] cycloaddition of triynes **2-18.**

§2.2. Results and Discussions

§2.2.1. Triyne Substrate Synthesis

Triynes were synthesized following the general synthetic protocol in **scheme 2-8**. The First alkyne **2-21** component was coupled with 1,4-dibromobutyne **2-22** under basic conditions to give the diynebromide **2-23**, followed by the installment of the third alkyne component to furnish various triynes **2-18** in good to excellent yields.

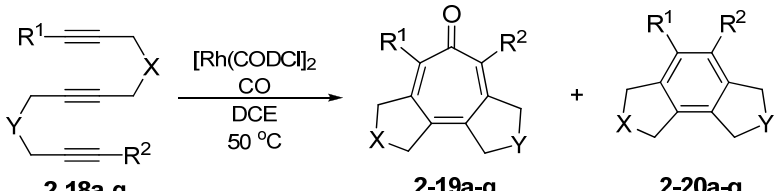


(i)NaH, THF, rt; (ii)NaH, DMF, rt; (iii)K_2CO_3, MeCN, reflux.

Scheme 2-8: Generic synthetic protocol of triynes **2-18.**

§2.2.2. Rh-Catalyzed Cycloaddition of Triynes for the Formation of 5-7-5 and 5-6-5 Fused-Ring Systems

Employing 2,7,12-triynes **2-18a-g** as substrates under previously established Rh-catalyzed [2+2+2+1] cycloaddition conditions of enediynes, we successfully obtain both the carbonylative product (tropone) **2-19a-g** and the arene product **2-20a-g** (**Scheme 2-9**).



R^1, R^2 = Me, H, TMS

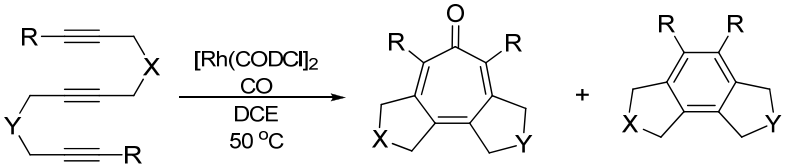
X, Y = $C(CO_2Et)_2$, NTs, O

Scheme 2-9: Formation of 5-7-5 fused tropone through Rh-catalyzed [2+2+2+1] cycloaddition of 2,7,12-triynes.

A summary of the cycloaddition results is outlined in **table 2-1**. Entries 1-6 are the results of using various 2,7,12-triyne substrates **2-18a-f**. Under the standard reaction conditions, all substrates reached complete conversion, with tropone product as minor product up to 30 % yield.

Nitrogen tethered triyne **2-18d** (entry 4) formed an insoluble precipitate which could not be analyzed. In contrast, terminally unsubstituted triyne **2-18f** (entry 6) only afforded arene product. Under dilute conditions, we hoped that increasing the concentration of CO to the triyne would increase tropone product; however, no improvement in the tropone product ratio was observed, and reaction rate was slower as expected. Increasing CO pressure (400 psi) did not increase the tropone product ratio (entry 8). In fact, the high pressure reaction inhibited the production of tropone, and after 12 h of reaction only 30 % conversion to arene product was achieved. It is believed that the high pressure of CO saturated the catalyst coordination sites and thus inhibited alkyne coordination.

Table 2-1: Rh-catalyzed tricyclization.



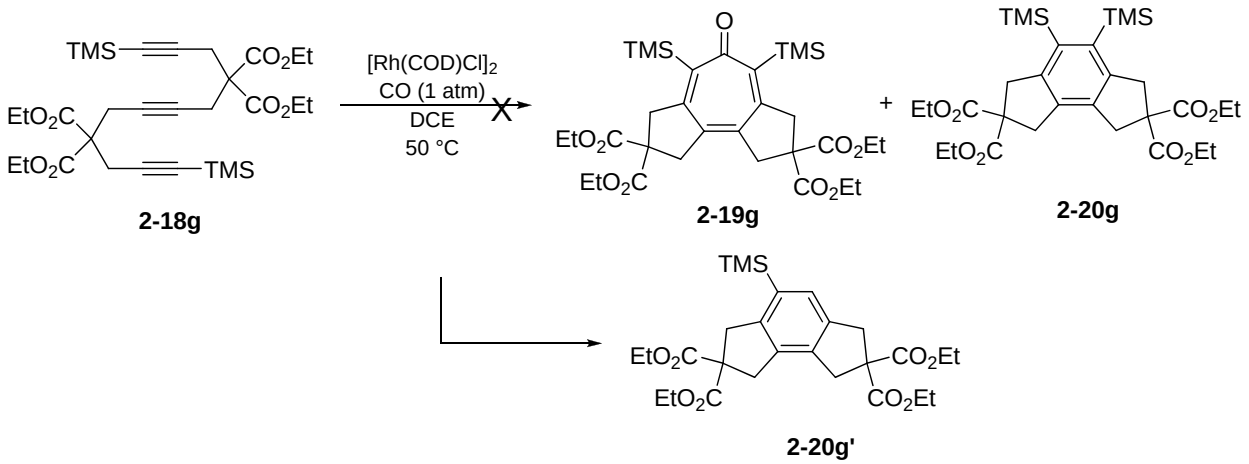
2-18a-f **2-19a-f** **2-20a-f**

Entry	Triyne	X, Y	R	Solvent	Conc. [M]	Temp °C	Time	CO pressure	Conversion* (**2-19**, **2-20**) %
1	**2-18a**	X=Y=C(CO_2Et)$_2$	Me	DCE	0.1	50	16 h	ambient	100 (20, 80)
2	**2-18b**	X=Y=O	Me	DCE	0.1	50	16 h	ambient	100 (30, 70)
3	**2-18c**	X=NTs, Y=C(CO_2Et)$_2$	Me	DCE	0.1	50	16 h	ambient	100 (18, 82)
4	**2-18d**	X=Y=NTs	Me	DCE	0.1	50	16 h	ambient	100 (n/a)
5	**2-18e**	X=O, Y=C(CO_2Et)$_2$	Me	DCE	0.1	50	16 h	ambient	100 (19, 81)
6	**2-18f**	X=Y=C(CO_2Et)$_2$	H	DCE	0.1	50	16 h	ambient	100 (0, 100)
7	**2-18a**	X=Y=C(CO_2Et)$_2$	Me	DCE	0.01	50	16 h	ambient	62 (14, 86)
8	**2-18e**	X=O, Y=C(CO_2Et)$_2$	Me	DCE	0.1	60	12 h	400 psi	30 (0, 100)

*Conversion and product ratio determined by ^{1}H NMR

Comparison of entry 1 and entry 6 from table 2-1 revealed that the substituents on the terminal acetylenes played a key role in the product selectivity. Tropone **2-19a** was obtained in 20% yield when terminal acetylenes were substituted with methyl group; On the other hand, arene product **2-20f** was obtained exclusively when the terminal substituents were hydrogen. . It was hypothesized that larger substituents at the terminal acetylene may give higher ratio of

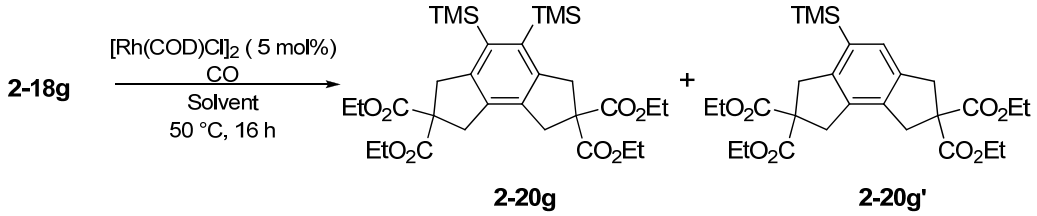
tropone due to steric hindrance between bulkier substituents. To test this hypothesis, triyne **2-18g** with trimethylsilyl group as terminal substituents was prepared for the cycloaddition. In an interesting turn of events, not only was the tropone **2-19g** not observed; the expected arene product **2-20g** was not observed as well. Instead, a mono-desilylated arene product **2-20g'** was obtained (**Scheme 2-10**).



2-18g **2-19g** **2-20g** **2-20g'**

Scheme 2-10: Formation of mono-desilylated arene product 2-20g' from triyne **2-18g** cycloaddition.

It was speculated that the trace content of water or HCl in the dichloroethane solvent (DCE) may have caused the desilylation. In comparison, when THF and toluene were used as the solvents, the yield of expected product **2-20g** was greatly increased in the case of toluene which demonstrated that hydroscopic property of the solvent can influence the desilylation.



2-20g **2-20g'**

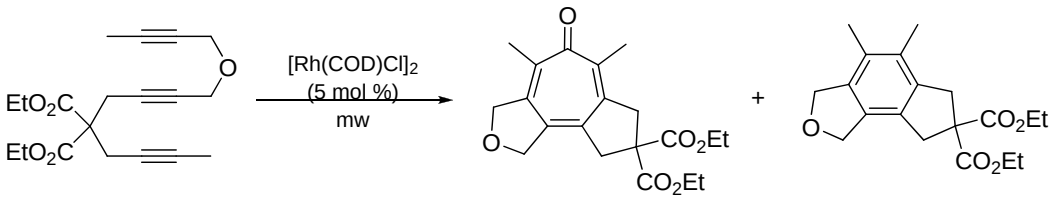
Entry	Solvent	**2-20g: 2-20g**(%)*
1	DCE	5:95
2	THF	15:85
3	Toluene	75:25

*determined by ^{1}H NMR

Scheme 2-11: Solvent effect on desilylation.

This Rh-catalyzed tricyclization was found to proceed well in microwave-assisted reactions. With sufficient heating, the reaction could reach 100 % conversion in 10 min. The conditions and results of microwave-assisted reaction using CEM Discover microwave reactor are shown in **table 2-2**.

Table 2-2: Microwave-assisted Rh-catalyzed tricyclization of triyne **2-18e.**



2-18e **2-19e** **2-20e**

Entry	Solvent	Conc. [M]	CO Sources	Temp (^{o}C)	Conversion* (%)	**2-19e**:**2-20e** (%)*
1	DCE	0.1	CO (20 psi)	50 -> 80	~10 -> 100	17.0:83.0
2	DCE	0.1	CO (20 psi)	80	100	17.6:82.4
3	DCE	0.1	CO (20 psi), $Mo(CO)_6$ (5 eq.)	80	100	16.6;83.4
4	Toluene	0.1	$Mo(CO)_6$ (5 eq.)	110	100	12.5:87.5
5	Toluene	0.1	$Mo(CO)_6$ (10 eq.)	110	100	15.0:85.0

CEM Discover

Temp:	50 ^{o}C	80 ^{o}C	110 ^{o}C
Power:	100 W	125 W	200 W
Time:	10 min	10 min	10 min

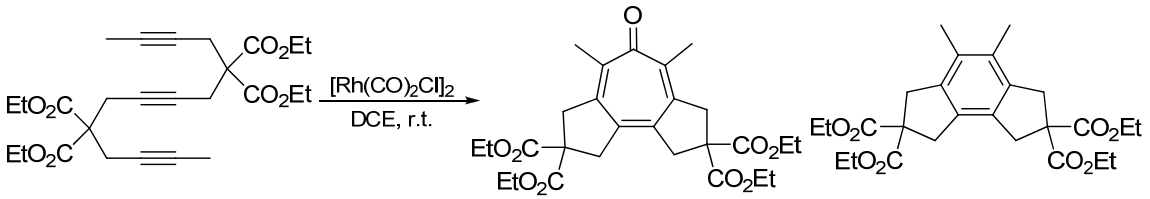
* Conversion and products ratio were determined by ^{1}H NMR

Triyne **2-18e** was the first heated to 50 ^{o}C, the same as the traditional oil bath heating temperature. It was found that the reaction only had about 10 % conversion, and thus it was put back for further heating (entry 1). After 10 min at 80 ^{o}C the reaction reached 100 % conversion to give tropone product in 17 % by NMR. $Mo(CO)_6$ was used as an alternative CO source(entries 3-5). Even though $Mo(CO)_6$ gave less carbonylative product, it demonstrated that an alternate CO source can be used when introduction of CO gas is impractical.

In a control experiment in which $[Rh(CO)_2Cl]_2$ was employed as the catalyst, triyne **2-18a** readily underwent cycloaddition to give both tropone **2-19a** and arene product **2-20a** under nitrogen atmosphere (**Table 2-3**, entry 1). This result suggested that the CO source for the tropone product came from the catalyst. We hoped that by replenishing CO in the reaction system, better product selectivity would be obtained; however, no reaction took place under CO atmosphere. When the reaction atmosphere changed from carbon monoxide to nitrogen,

cycloaddition took place and reached full conversion within 10 min (entry 2). Such observation suggested that for this particular catalyst system, CO gas would fully occupy the coordination site on the metal center and thus prevent the cycloaddition from taking place.

Table 2-3: Control experiment employing $[Rh(CO)_2Cl]_2$.



2-18a **2-19a** **2-20a**

Entry	Conditions	[Rh] (mol%)	Conversion (%)	**2-19a**:**2-20a** (%)*
1	N_2 (1 atm), 2 h	5	100	13:68
2	1) CO (1 atm), 2.5 h 2) N_2 (1 atm), 10 min	5	100	17:64
3	N_2 (1 atm), 10 min	25	100	0:100
4	N_2 (1 atm), 10 min	50	100	0:100

*determined by ^{1}H NMR

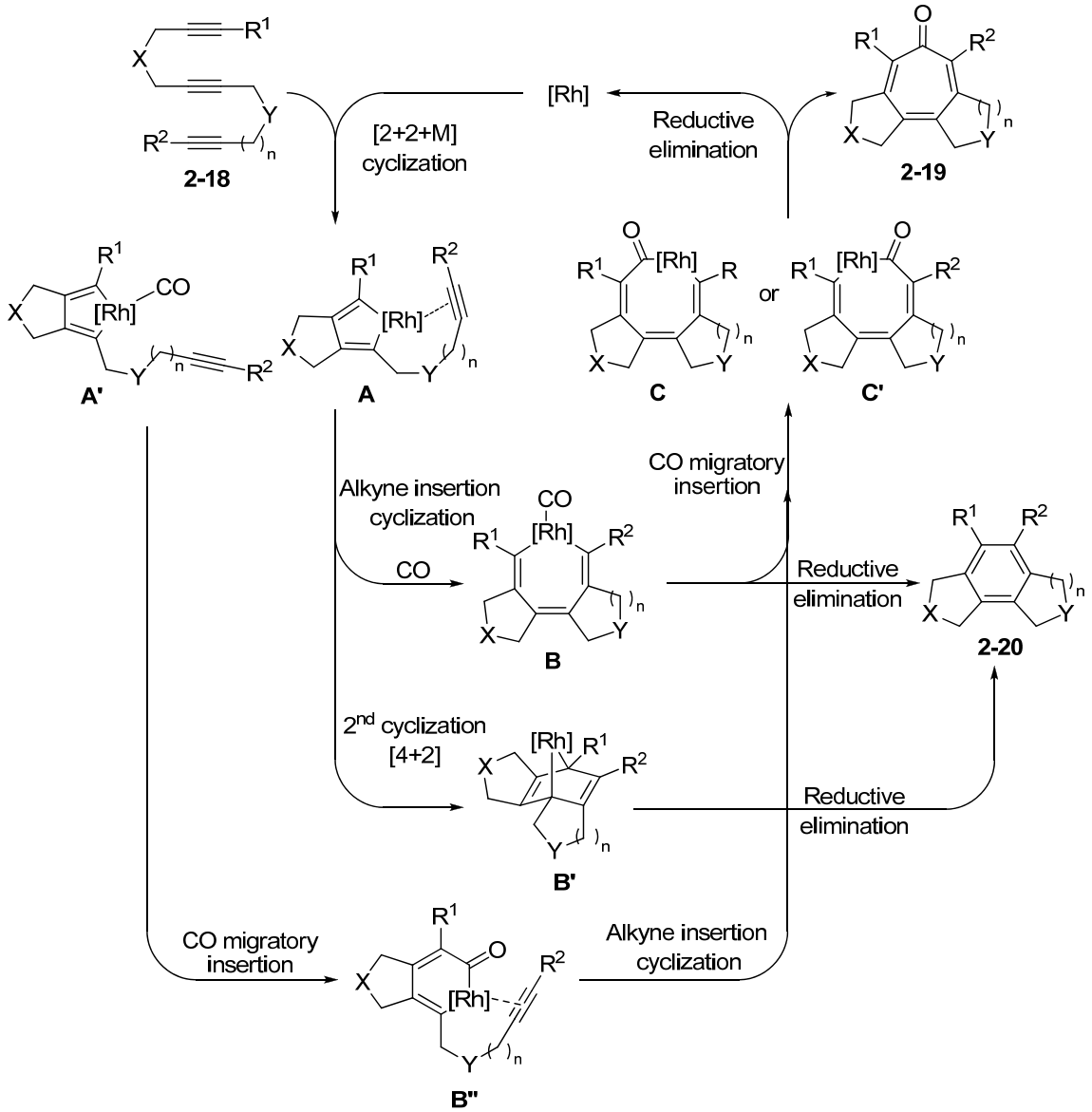
Since the CO source came exclusively from the catalyst, we hoped that increasing the amount of catalyst would increase the tropone formation. By using 25 mol% of the catalyst, which provide stoichiometric amount of CO, complete conversion was achieved within 10 min. But unlike the catalytic Rh-catalyzed reaction in which tropone was observed (entries 1 and 2), in sub-stoichiometric Rh-catalyzed reaction only arene product **2-20a** was afforded as the exclusive product (**Table 2-3**, entry 4).

§2.2.3. Proposed Mechanisms

The proposed mechanism for the [2+2+2+1] cycloaddition of triyne is depicted in **Scheme 2-12**. Initially, a couple of ligand-alkyne substitutions occur; subsequently, the two alkyne ligands generate metallacyclopentadiene **A** or **A'** through oxidative coupling. The coordination of a third alkyne then takes place followed by alkyne insertion to yield a planar aromatic metallacycloheptatriene **B**. Subsequent reductive elimination takes place generating arene **2-20** and regenerates the catalyst (so-called Schore's mechanism[7d]). Alternatively,

intramolecular [4+2] Diels-Alder cycloaddition to form a 7-metallanorbornadiene complex **B'** has been proposed, which can undergo reductive elimination to form the arene **2-20**.[16]

Under carbon monoxide atmosphere, migratory insertion of CO takes place from metallacycloheptatriene **B** which leads to metallacyclooctatrienone **C** or **C'**. Subsequent reductive elimination takes place generating tropone **2-19** and the catalyst. On the other hand, if migratory insertion of CO takes place from metallacyclopentadiene **A'** it will lead to the formation of metallacyclohexadienone **B''**, reductive elimination at this stage is highly unlikely to take place as it will result in an antiaromatic cyclopentadienone. Alkyne coordination and insertion to B" and subsequent reductive elimination will also generate the tropone product **2-19**.



Scheme 2-12: Proposed mechanism of triyne cycloaddition.

Based on the proposed mechanism outlined above, it was speculated that, when metallacyclopentadiene **A** was formed from 2,7,12-triynes **2-18a-g**, the third alkyne moiety may already be in the vicinity of the metal center, which favors the formation of metallacycloheptatriene **B** or 7-metallanorbornadiene complex **B'** leading to formation of arene product. We hypothesized that adding more degree of freedom to the alkyne moiety by extending the tether length, may facilitate early migratory insertion of CO forming metallacyclohexadienone **B''** and thus improve the production of tropone product **2-19.**

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§2.2.4. Rh-Catalyzed Cycloaddition of Triynes for the Formation of 5-7-6 and 5-6-6 Fused-Ring Systems

To test this hypothesis, 2,7,13-triyne **2-18h** and 3,9,15-triyne **2-18i** were synthesized (**Figure 2-2**). Triyne **2-18h** has a 3-atom tether between two alkynes and a 4-atom tether on the other side; triyne **2-18i** has 4-atom tether on both sides. If the hypothesis is correct, this longer tether should slow down the alkyne coordination and allow increased carbonyl incorporation, and thus leading to increased tropone product.

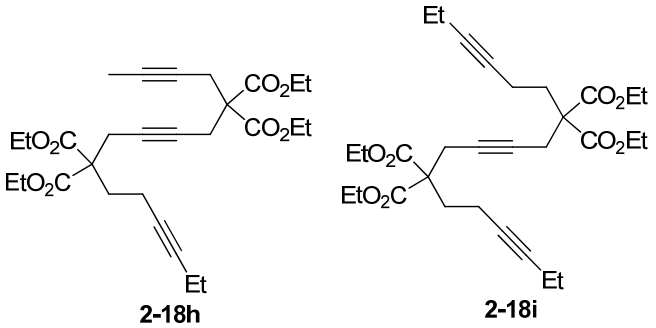
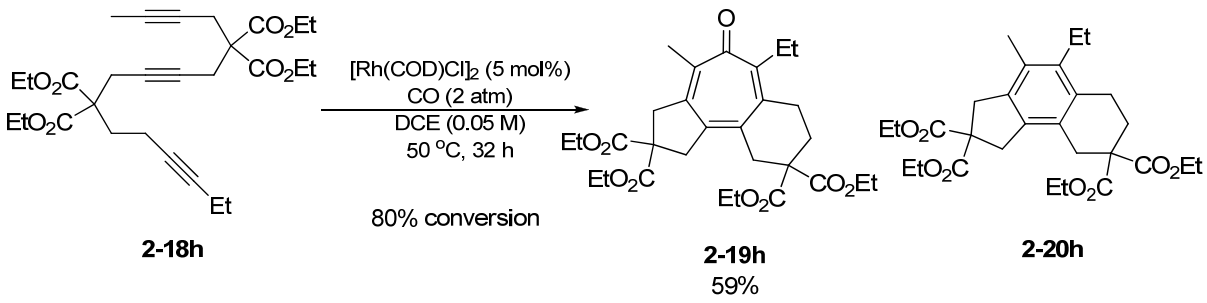


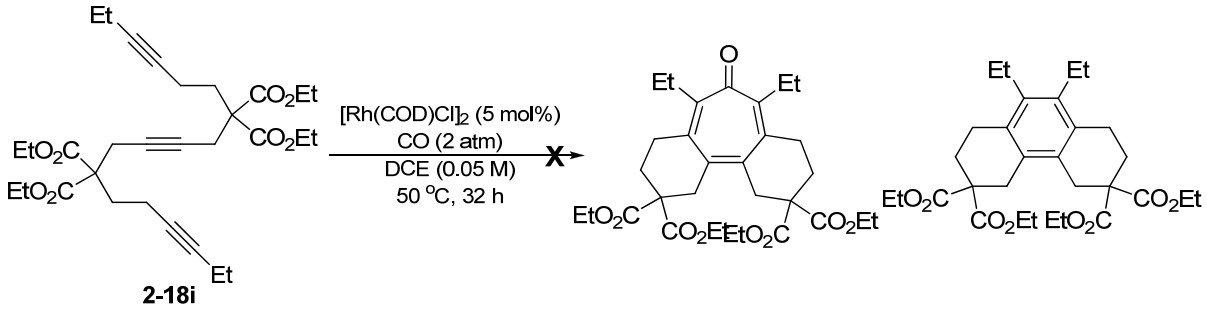
Figure 2-2: 2,7,13-Triyne 2-18h and 3,9,15-triyne **2-18i.**

When triyne **2-18h** was subjected to carbonylative cycloaddition conditions, the reaction did not reach full conversion after 32 h (**Scheme 2-13**). Nevertheless, carbonylated product **2-19h** was indeed the major product in 59% isolated yield. The arene product **2-20h** co-eluted with the unreacted starting material and could not be separated.



Scheme 2-13: Cycloaddition of triyne **2-18h.**

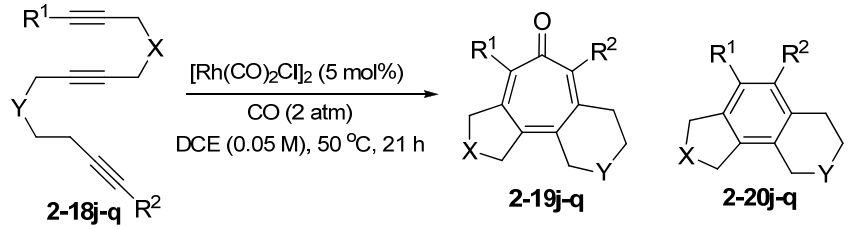
Triyne **2-18i** was also subjected to carbonylative cycloaddition (**Scheme 2-14**). However, after 32 h no reaction took place. Even when a more active catalyst $[Rh(CO)_2Cl]_2$ was employed, triyne **2-18i** still did not undergo the cycloaddition. It is likely that the 4-carbon tethers severely slow down the alkynes coordination to the metal center and prohibited the formation of metallacycles.



Scheme 2-14: Cycloaddition of triyne **2-18i.**

Based on this exciting result, a series of new triyne substrates **2-18j-p** were synthesized and subjected to the cycloaddition conditions, the results are summarized in **table 2-4**. Previously, employing $[Rh(COD)Cl]_2$ as catalyst, the reaction could not reach full conversion after 32 h. A more active $[Rh(CO)_2Cl]_2$ catalyst was used instead, and most of the substrates could reach full conversion after 21 h.

Table 2-4: Cycloaddition summary of triyne **2-18j-p.**



2-18j-q **2-19j-q** **2-20j-q**

Entry	Triyne	X	Y	R^1	R^2	conversion (%)	**2-19:2-20**
1	**2-18j**	$C(CO_2Et)_2$	$C(CO_2Et)_2$	Ph	Me	90	2:1[a,b]
2	**2-18k**	$C(CO_2Et)_2$	$C(CO_2Et)_2$	Me	Me	100	1:1[b]
3	**2-18l**	NTs	$C(CO_2Et)_2$	Me	Me	100	1:1.2[c]
4	**2-18m**	NTs	$C(CO_2Et)_2$	Ph	Me	100	1:1[c]
5	**2-18n**	$C(CO_2Et)_2$	NTs	Ph	Me	100	2.4:1[b]
6	**2-18o**	$C(CO_2Et)_2$	NTs	Me	Ph	100	1:4.3[c]
7	**2-18p**	NTs	NTs	$AcOCH_2$	Me	100	1.6:1[d]
8	**2-18q**	O	NTs	Me	Me	100	2:1[a,b]

[a] reaction time 16 h; [b] isolated products ratio; [c] HPLC ratio @ 220nm; [d] ^{1}H NMR ratio

In many cases tropones are the major product or at least in 1:1 ratio to the arene products. It appears that phenyl substitution at R^1 position enhances the product selectivity in favor of tropone products compared to the methyl analogues (entries 1 and 2; entries 3 and 4). Interestingly, in comparing triyne **2-18m** and **2-18n** (entries 4 and 5), in which X and Y substitution pattern were switched, the product selectivity further improved to 2.4:1 in favor of tropone for substrate 2-18n (entry 5). In contrast, triyne **2-18n** and **2-18o** (entries 5 and 6) in which substitution patterns are opposite in R^1 and R^2 groups, the product selectivity dramatically changed in favor of arene product.

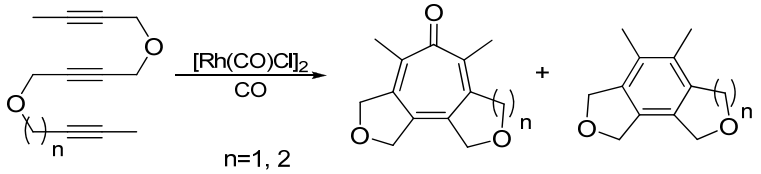
§2.2.5. Computation Study of Rh-catalyzed Cycloaddition of Triynes

In recent decades, transition metal-catalyzed cycloaddition reactions have received a lot of attention for the development of complex carbon and heteroatom skeletons. Various types of reactions have been discovered with the main focus of the work being dedicated to the development of the substrate scopes, reaction conditions, and product selectivities. In contrast,

the understanding of the reactions from the theoretical point of view has been very limited. In the past, the reaction pathways for transition metal-catalyzed cycloaddition reactions were largely based on guess and speculations with no way to be validated. One major reason was that computation power was very expensive and limited, and the computation method at the time was not a reliable resource to provide trustworthy calculations involving metal system. In recent years, great efforts have been committed to the development of calculation methods suitable for transition metal systems due to the fact that transition metals and their complexes have played a key role in modern chemistry.[17]

The main difficulty associated with the calculation of transition metal containing systems is the degeneracy from the electrons that partially occupy the *d* orbitals.[18] Density functional theory (DFT) is a widely used computation method to tackle large transition metal-containing systems and has shown great promise as an *ab initio* method over the Hartree-Fock (HF) method.[18-19] Recently, Montero-Campill *et al.* reported a theoretical study of the mechanism for [2+2+2+1] cycloaddition of enediyne systems.[20] In their work, they employed DFT calculation using 6-31+G** + LANAL2DZ mixed basis set which utilizes the Los Alamos effective core potential on the transition metal, while Pople-type basis set is utilized on all other atoms. According to their results, the multistep reaction mechanism pathway is in agreement with the previously proposed mechanism by Ojima and coworkers.[13b, 14]

In this work, computation studies of reaction pathways of novel Rh(I)-catalyzed [2+2+2+1] cycloaddition of triynes are presented (**Scheme 2-15**). Calculations were done with density functional theory (DFT) employing functional B3LYP. B3LYP[21] combines the three-coefficient dependent hybrid functional for the exchange energy proposed by Becke (B3) with the correlation functional proposed by Lee, Yang, and Parr (LYP). LACVP** basis set (combined 6-31G** basis set for C, O, H, and Cl atoms, and the effective core potential LANL2DZ[22] basis set for the Rh atom) was used. Each of the stationary points was characterized as minimum or transition state by the vibrational frequency analysis. All calculations were carried out with Spartan08[23] program.



Scheme 2-15: General [2+2+2+1] reaction of triynes studied in this work.

Late CO insertion reaction pathway for 5-7-6 fused-ring system in Gas Phase.

$[Rh(CO)_2Cl]_2$ dimer was chosen as the catalyst in the calculations. The $[Rh(CO)_2Cl]_2$ dimer was found to be in equilibrium with two monomeric units, and the rhodium atom bonded to two ligands (CO and Cl) is the active species.[24] **Figures 2-3** shows the proposed intermediates and the transition states, and the calculated energy profiles for the [2+2+2+1] cycloaddition in the gas phase catalyzed by rhodium.

Considering the triple bonds as ligands, two of these bonds parallel to each other and coordinated to the Rh metal center would give the starting complex **A (Figure 2-3)**. Through the transition state **B** intermediate **C** is obtained, which is a 5-5 fused-bicyclic metallocycle. The third triple bond then coordinates to the metal center to give intermediate **D1**. From intermediate **D1** there is additional CO coordination to the Rh atom. The metal adopts an octahedral geometry to form the intermediate **E1**. The metallacycle expands from 5- to 7-membered ring through transition state **F1**. The rhodium complex of **F1** has an octahedral geometry with $20e^-$. This unfavorable electronic state is overcome in **G1**, where the metal center has coordination of 5 and adapts a pseudopyramidal geometry with $18e^-$, which satisfies the $18e^-$ electron rule. From intermediate **G1** there are two possible outcomes. It can undergo reductive elimination through **G1_E** to form the arene product **G1_EP**.

Alternatively, In the transition state **H1**, one of the CO ligands inserts into the main ring between the rhodium and the carbon next to the metal forming a new 5-8-5 metallacycle **I**. Through the transition state **J**, the two carbons bonded to the rhodium center form a new bond and the rhodium complex is eliminated to give **K**, where the rhodium is coordinated by the oxygen atom from the cycloheptatrienone.

Transition state **B** is the highest electronic energy point of this reaction pathway (+3.45 kcal/mol). From the diagram it is clear that transition states **F1**, **H1,** and **J** are very energetically expensive in relation to the intermediates **E1, G1**, and **I** (over 8-20 kcal/mol in terms of electronic energy and 3-20 kcal/mol in free energy). It is remarkable that from **D1** to **K** there is an energy difference about 90 kcal/mol between the electronic energy and the free energy. This is due to the CO insertion which influences the entropy factor of the free energy.

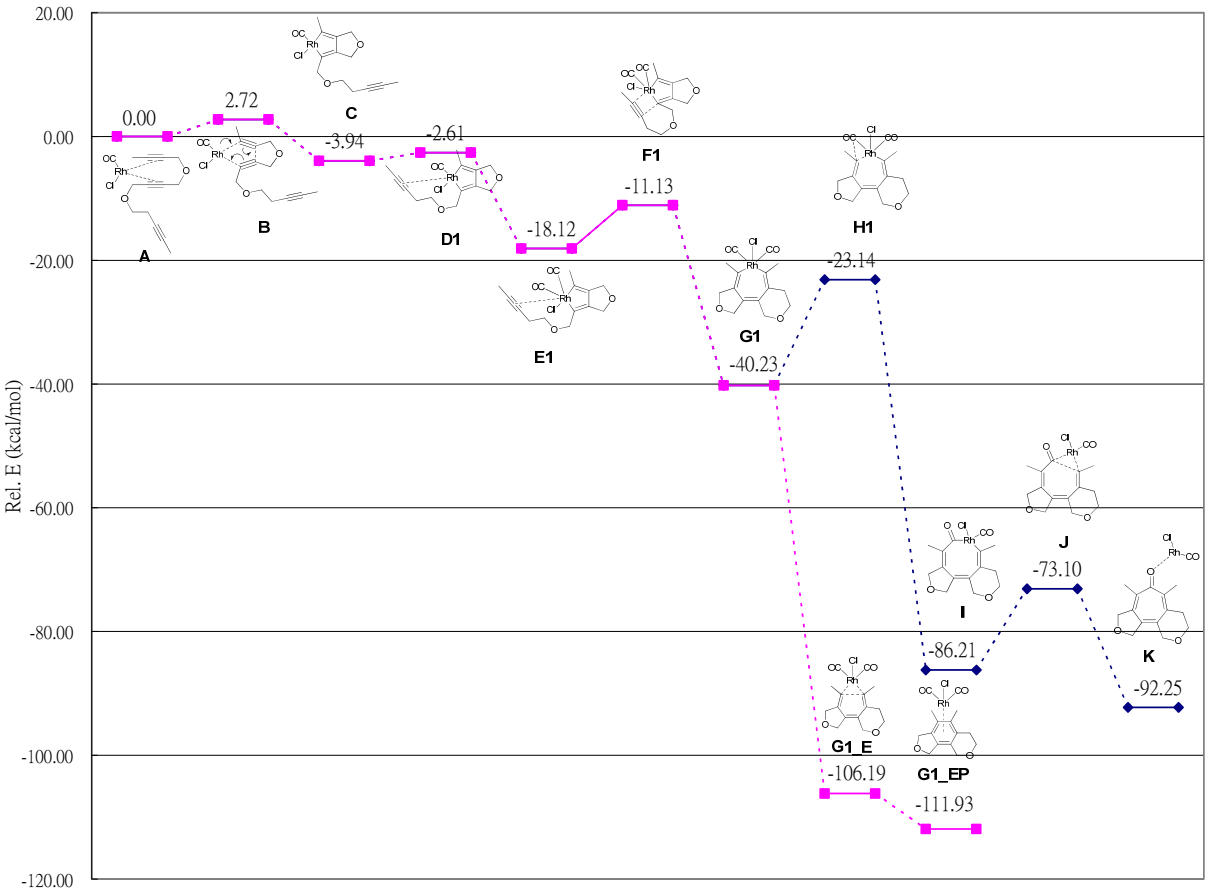


Figure 2-3: Relative energies with zero-point energy included (kcal/mol) for the 5-7-6 fused-ring late CO insertion reaction pathway at 298.15 K in the gas phase at the B3LYP/6-31G**+LANL2DZ level.

Early CO insertion reaction pathway for 5-7-6 fused-ring system in Gas Phase.

Alternative reaction pathway involving early CO insertion was also proposed (see **Scheme 2-12**). The proposed intermediates and the transition states, and the calculated energy profiles are depicted in **Figure 2-4**. From the common intermediate metallacyclopentadiene **C**, additional CO coordination leads to intermediate **D2**. In the transition state **E2**, one of the CO ligands inserts into the main ring between the rhodium and the carbon next to the metal forming a new metallacyclhexadienone **F2**. The third triple bond then coordinates to the metal center to give intermediate **G2**. Metallacycle expands from 6- to 8-memebered ring through transition state **H2** leading to 5-8-5 metallacycle **I**. Reductive elimination through transition state **J** would give **K** where the rhodium is coordinated by the oxygen atom from the cycloheptatrienone.

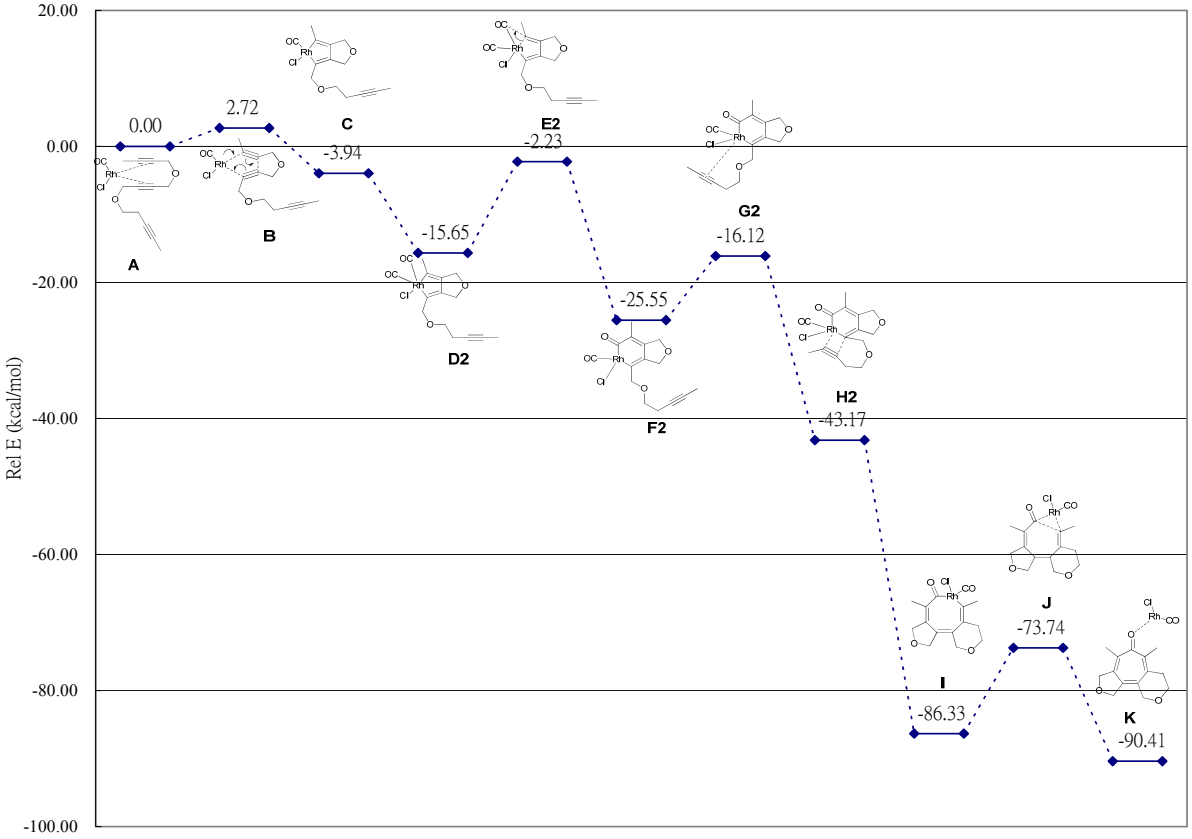


Figure 2-4: Relative energies with zero-point energy included (kcal/mol) for the5-7-6 fused-ring early CO insertion reaction pathway at 298.15 K in the gas phase at the B3LYP/6-31G**+LANL2DZ level.

In comparing these two reaction pathways, the CO insertion is the rate determining step in both pathways. However, in the late CO insertion pathway (**Figure 2-3**), the activation energy for CO insertion is calculated to be more than 17 kcal/mol; in contrast, the activation energy for CO insertion in the early CO insertion pathway (**Figure 2-4**) was less than 14 kcal/mol. It is clear that early CO insertion is favored. In addition, in the late CO insertion pathway (**Figure 2-3**), reductive elimination from intermediate **G1** to **G1_E** was greatly exothermic, which makes the transition state **H1** for the CO insertion highly unfavorable. Another important aspect of comparison between these two reaction pathways is the endothermic processes involved. Between the common intermediate **C** and intermediate **I**, in the late CO insertion pathway, there are a total of 3 endothermic process to be overcome (**D1**, **F1**, and **H1**), but in the early CO insertion pathway there are only 2 endothermic process to be overcome (**E2** and **G2**). The overall energies required to overcome the endothermic processes are less in the case of early CO

insertion. Therefore, once the first endothermic process is overcame under elevated temperature conditions, early CO insertion may compete with the late CO insertion becoming the major process to afford more carbonylated product.

Late CO insertion reaction pathway for 5-7-5 fused-ring system in Gas Phase.

The proposed intermediates, the transition states, and the calculated energy profiles for the late CO insertion pathway for the 5-7-5 fused-ring system are depicted in **Figure 2-5**. Unlike 5-7-6 fused-ring system, the initial [2+2+Rh] cycloaddition process leading to intermediate **B** is a highly exothermic process; the energy released is enough to enable the formation of intermediate **C**. From intermediate **C**, alkyne coordination (**D1**) and insertion (**F1**) leading to intermediate **G1** were also exothermic. Once the CO insertion (**H1**) was overcame which leads to intermediate **I**, reductive elimination through **J** ultimately gives the product **K**.

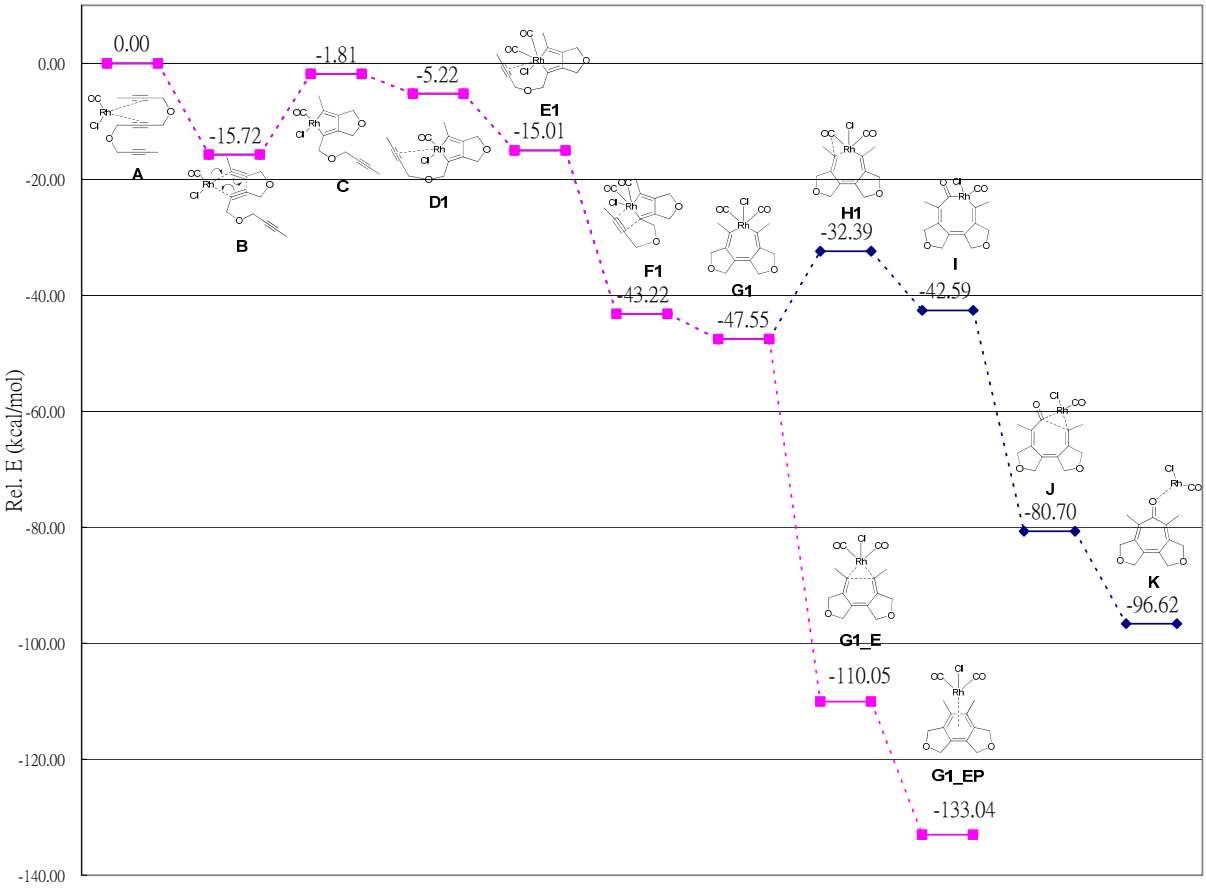


Figure 2-5: Relative energies with zero-point energy included (kcal/mol) for the 5-7-5 fused-ring late CO insertion reaction pathway at 298.15 K in the gas phase at the B3LYP/6-31G**+LANL2DZ level.

Early CO insertion reaction pathway for 5-7-5 fused-ring system in Gas Phase.

The proposed intermediates, the transition states, and the calculated energy profiles for the early CO insertion pathway for the 5-7-5 fused-ring system are depicted in **Figure 2-6**. From the intermediate **C**, additional CO coordination leads to intermediate **D2**. CO insertion through transition state **E2** gives the metallacyclhexadienone **F2**. Alkyne coordination and insertion leads to intermediate **I**, and eventually forms the product **K**.

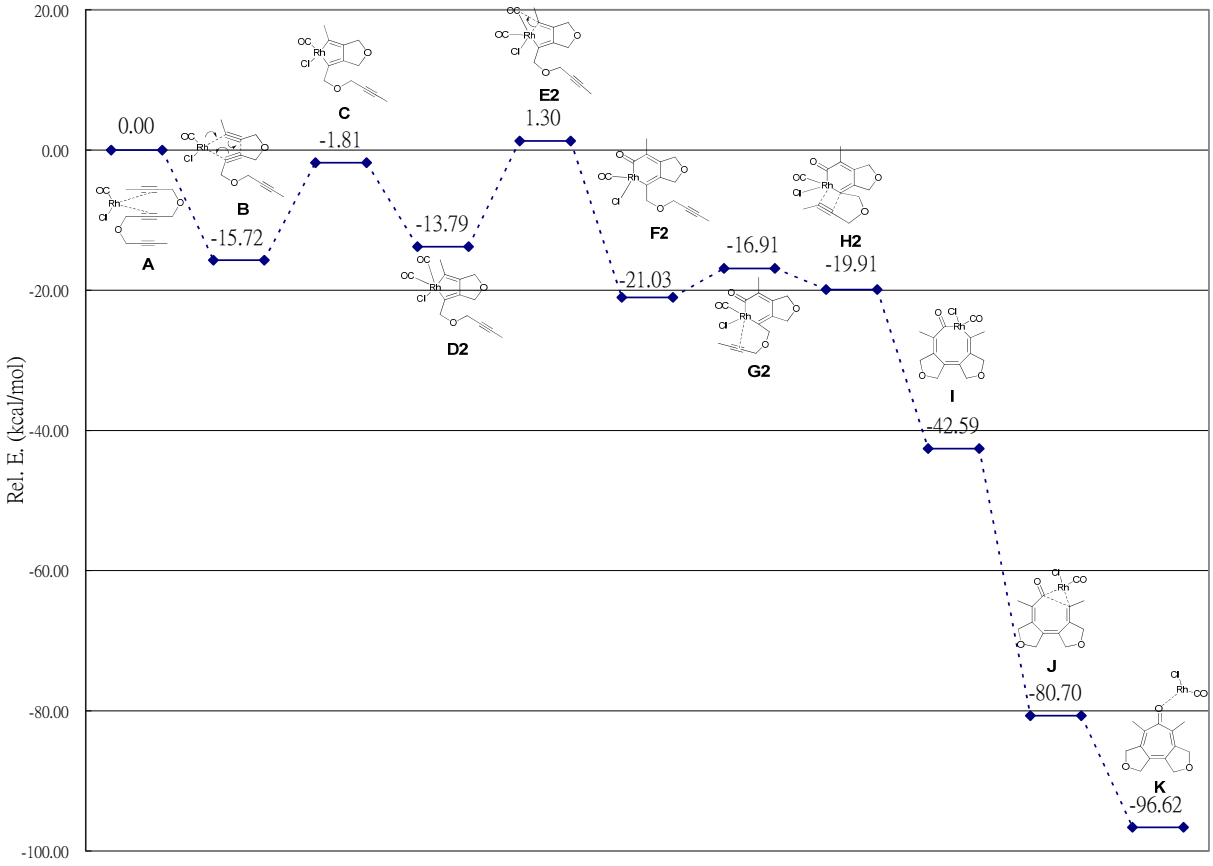


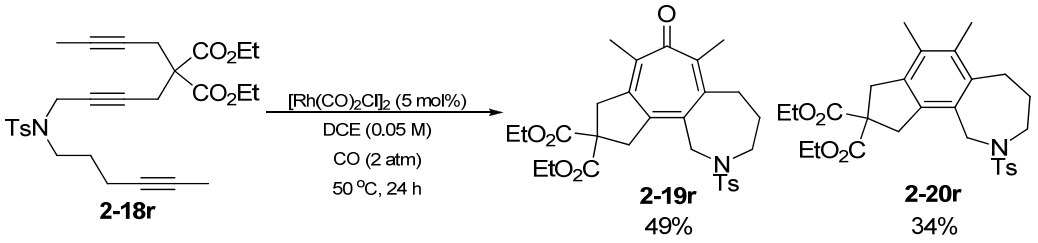
Figure 2-6: Relative energies with zero-point energy included (kcal/mol) for the 5-7-5 fused-ring early CO insertion reaction pathway at 298.15 K in the gas phase at the B3LYP/6-31G**+LANL2DZ level.

The calculated exothermic nature of this 5-7-5 fused-ring formation with $[Rh(CO)_2Cl]_2$ catalyst is in agreement with the experimental results (**Section 2.2.2**). In comparing the energy profiles between the two pathways for the 5-7-5 fused-ring formation, the early alkyne coordination/insertion is greatly favored over the early CO insertion. Similar to the 5-7-6 fused ring formation, late CO insertion pathway is greatly favored the formation of arene product. The

transition state for the early CO insertion was the highest energy point in the pathway over the starting complex, which is less likely to happen, and thus greatly reduce the formation of carbonylated product.

§2.2.6. Rh-Catalyzed Cycloaddition of Triynes for the Formation of 5-7-7 and 5-6-7 Fused-Ring Systems

Previous results supported our hypothesis that extending the tether length between the triynes can enhance the product selectivity towards the tropone product. It is therefore logical to further extend the atom tether to test if the carbonylated product can be further increased. Triyne **2-18r** with a 5-atom tether on one side was synthesized and subjected to the cycloaddition conditions (**Scheme 2-16**). Giving that longer tether may retard the reaction rate, longer reaction time was allowed. After 24 h, the reaction reached full conversion and was confirmed by both TLC and HPLC. Under the standard HPLC conditions the product ratio at 254 nm was 15:1 in favor of tropone, but at 220 nm the ratio was only 1.5:1 (**Figure 2-7**). After both products were isolated, the isolated product ratio was in agreement with the product ratio at 220 nm wavelength.



Scheme 2-16: Cycloaddition of triyne **2-18r.**

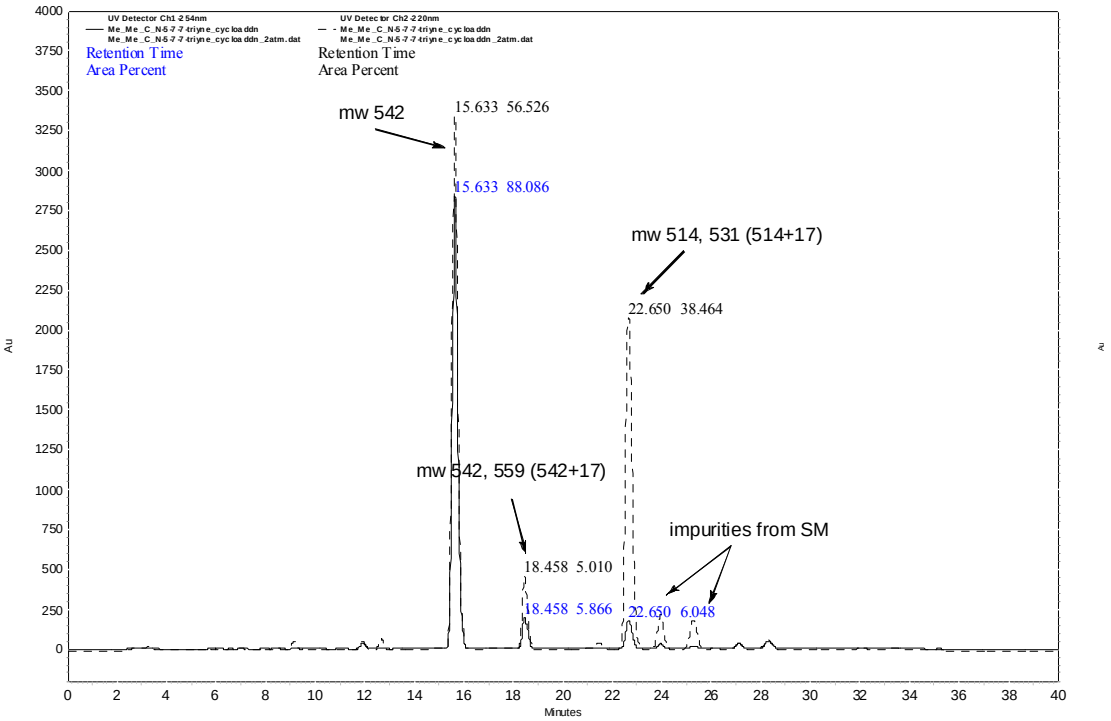
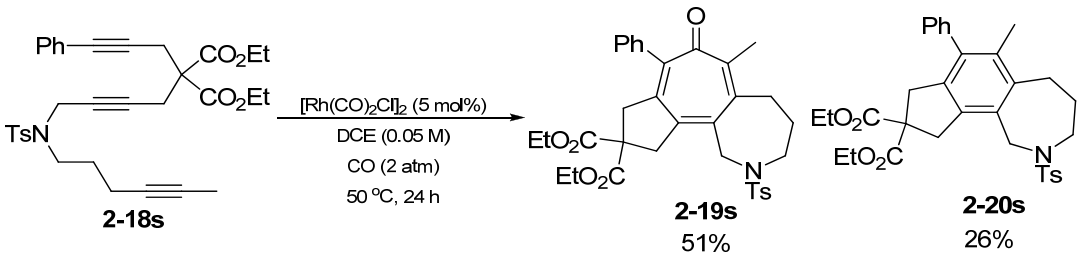


Figure 2-7: HPLC trace of cycloaddition crude of triyne **2-18r.**

When 1-phenyl substituted triyne **2-18s** was subjected to the reaction conditions, the product selectivity was slightly improved to 2:1 (**Scheme 2-17**). Even though the product ratio did not further increase with the longer tether, the formation of both 5-7-7 and 5-6-7 fuse-ring systems is a very encouraging result considering the fact that direct formation of 7-7 fused-ring was not known in the literature.



Scheme 2-17: Cycloaddition of triyne **2-18s.**

§2.3. Conclusions

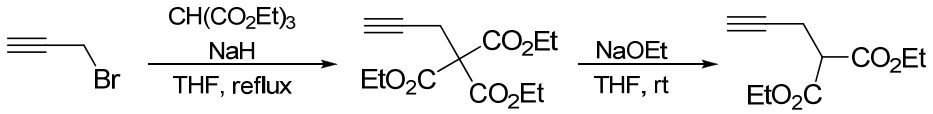
In continuing studies on the Rh(I)-catalyzed higher order cycloaddition reaction, triyne derivatives were synthesized and found to afford the desired 5-7-*n* (*n* = 5, 6, 7) fused tropone products in moderate to good yields. Mechanistic pathways are proposed for each of the observed products. Based on the analysis of the mechanism, improvement on product selectivity was achieved. This methodology provides direct access to 7-7 fused tropones which is desired for the synthesis of colchicines. Application of [2+2+2+1] cycloaddition towards the synthesis of novel colchicinoids will be discussed in the subsequent chapter.

§2.4. Experimental Section

General Information:

All chemicals were obtained from either Sigma-Aldrich or Acros Organics and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under nitrogen and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents and using Fisher silica gel (particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[25] Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with Shimadzu FTIR-84005 spectrophotometer.

Diethyl propargylmalonate (2-21a)[26]



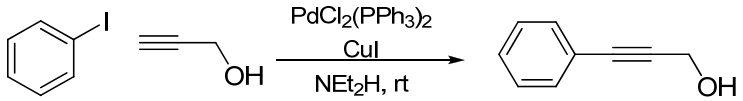
2-21a

To a suspension of NaH (2.48 g, 60% dispersion in mineral oil, 62.0 mmol) in THF (115 mL) under N_2 atmosphere, was added a solution of triethyl methanetricarboxylate (12.0 g, 51.7 mmol) in THF (10 mL) dropwise with stirring at room temperature. The reaction mixture was stirred at room temperature for 1 h. To the reaction mixture was added a solution of propargyl bromide (7.68 g, 80 wt% solution in toluene, 51.7 mmol) dropwise with stirring at room temperature. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with DCM and filtered through celite. The solvents were removed under reduced pressure.

The resulted crude was added dropwise to the suspension of sodium ethoxide (4.22 g, 62.0 mmol) in THF (150 mL) at 0 ^{o}C. The reaction was allowed to warm to room temperature slowly

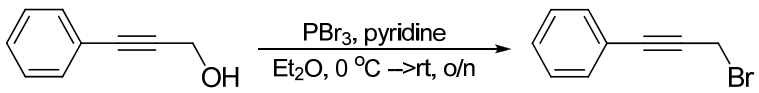
and stirred overnight. The reaction was quenched with 6 M HCl solution and the solvent was removed under reduced pressure. The resulted oil was dissolved in Et_2O, and washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 5%) to afford diethyl propargylmalonate as yellow liquid (9.25 g, 90% for 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 6 H, *J* = 7.2 Hz), 2.01 (t, 1 H, *J* = 2.7 Hz), 2.78 (d*d, 2 H, *J* = 2.7 Hz * 7.8 Hz), 3.56 (t, 1 H, *J* = 7.9 Hz), 4.23 (q, 4 H, *J* = 7.2 Hz). All data are in agreement with those reported in the literature.[26]

3-Phenylprop-2-yn-1-ol[27]



To a solution of $PdCl_2(PPh_3)_2$ (0.35 g, 0.50 mmol) and CuI (0.28 g, 1.50 mmol) in diethylamine (DEA) (52 mL, 0.50 mol) was added iodobenzene (3.36 mL, 30 mmol), and the reaction was stirred for 30 min. Propargyl alcohol (1.40 g, 25.0 mmol) was added dropwise to the reaction mixture, and the reaction was allowed to stir at room temperature overnight. The resulted reaction mixture was diluted with Et_2O and the organic layer was washed with saturated NH_4Cl solution, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 15%) to afford 3-phenylprop-2-yn-1-ol as pale yellow oil (3.30 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50 (s, 2 H), 7.32 (m, 3 H), 7.44 (m, 2 H). All data are in agreement with those reported in the literature.[27]

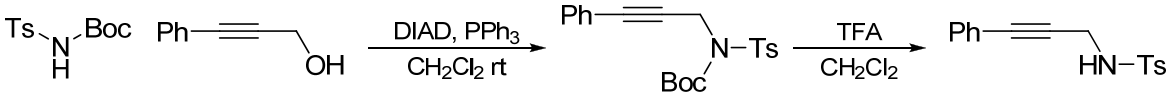
3-Phenylpropargylbromide[28]



To a solution of 3-Phenylprop-2-yn-1-ol (2.00 g, 15.1 mmol) and pyridine (0.12 mL, 1.51 mmol) in Et_2O (40 mL) at 0 °C, was added dropwise a solution of PBr_3 (0.71 mL, 7.57 mmol) in Et_2O (10 mL). The resultant reaction mixture was stirred under nitrogen for 19 h at room temperature. Water was then added followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The

crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 5%) to afford 3-phenylpropargylbromide as pale yellow oil (2.22 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (s, 2 H), 7.33 (m, 3 H), 7.45 (m, 2 H). All data are in agreement with those reported in the literature.[28]

_N_-(3-Phenylpropargyl)-_N_-(4-methylbenzenesulfonyl)amine (2-21b)[29]

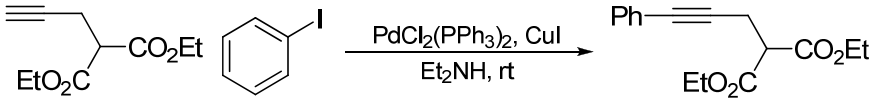


2-21b

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylbenzenesulfonyl)amine (5.13 g, 18.9 mmol) and triphenylphosphine (5.46 g, 20.8 mmol) in DCM (75 mL) was added diisopropyl azodicarboxylate (4.21 g, 20.8 mmol) dropwise at room temperature, and the reaction was stirred for 30 min. 3-Phenylprop-2-yn-1-ol (2.50 g, 18.9 mmol) was added to the reaction mixture, and the reaction was stirred overnight. The solvent was removed under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford *N*-(*tert*-butoxycarbonyl)-*N*-(3-phenylpropargyl)-*N*-(4-methylbenzenesulfonyl)amine as pale yellow oil (6.57 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 9 H), 2.42 (s, 3 H), 4.85 (s, 2 H), 7.33 (m , 7 H), 7.97 (d, 2 H, J = 8.1 Hz).

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(3-phenylpropargyl)-*N*-(4-methylbenzenesulfonyl)amine (6.57 g, 17.0 mmol) in DCM (100 mL) was added trifluoroacetic acid (10 mL) dropwise, and the reaction was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give *N*-(3-phenylpropargyl)-*N*-(4-methylbenzenesulfonyl)amine **(2-21b)** as pale yellow solid (4.71 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3 H), 4.08 (d, 2 H, J = 6.3 Hz), 4.58 (bt, 1 H), 7.13 (m , 2 H), 7.27 (m , 5 H), 7.81 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.43, 33.78, 83.18, 84.72. 122.02, 127.48, 128.13, 128.50, 129.68, 131.52, 136.85, 143.73. All data are in agreement with those reported in the literature.[29]

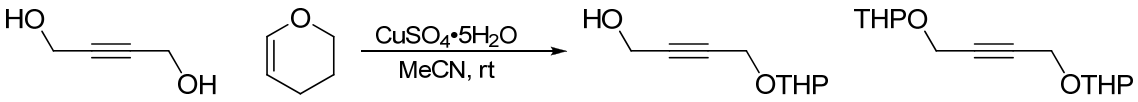
Diethyl 3-phenylpropargylmalonate (2-21c)[30]



2-21a **2-21c**

To a solution of $PdCl_2(PPh_3)_2$ (0.17 g, 0.25 mmol) and CuI (0.09 g, 0.50 mmol) in diethylamine (DEA) (26.1 mL, 252 mmol) was added iodobenzene (1.41 mL, 12.6 mmol), and the reaction was stirred for 30 min. Diethyl propargylmalonate **(2-21a)** (2.50 g, 12.6 mmol) was added dropwise to the reaction mixture, and the reaction was allowed to stirred at room temperature overnight. The resulted reaction mixture was diluted with Et_2O and the organic layer was washed with saturated NH_4Cl solution, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford diethyl 3-phenylpropargylmalonate **(2-21c)** as pale yellow oil (2.99 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 6 H, *J* = 7.8 Hz), 3.00 (d, 2 H, *J* = 7.8 Hz), 3.65 (t, 1 H, *J* = 7.8 Hz), 4.24 (q, 4 H, *J* = 7.8 Hz), 7.27 (m , 3 H), 7.37 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.08, 19.43, 51.49, 61.73, 82.42, 85.44, 123.22, 127.95, 128.18, 131.62, 168.06. All data are in agreement with those reported in the literature.[30]

***O*-Tetrahydro-2*H*-pyranylbut-2-yn-1,4-diol**[31]

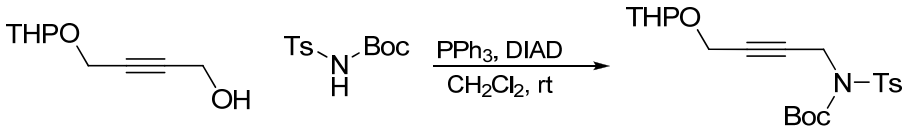


To a mixture of 2-butyn-1,4-diol (9.00 g, 0.10 mol) and copper (II) sulfate pentahydrate (5.22 g, 0.02 mol) in MeCN (200 mL) was added 3,4-dihydro-2*H*-pyran (10.5 mL, 0.11 mol) dropwise *via* syringe pump over 1 h period and the reaction was stirred overnight. The reaction mixture was dilute with DCM and filtered through celite, and the solvents were removed under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to afford *O*-tetrahydro-2*H*-pyranylbut-2-yn-1,4-diol as pale yellow oil (11.7 g, 62 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52–1.86 (m, 7 H), 3.50–3.57 (m, 1 H), 3.80–3.88 (m, 1 H), 4.22–4.38 (m, 4 H), 4.80 (t, 1 H, *J* = 3.2 Hz). All data are in agreement with those reported in the literature.[31b]

1,4-Bis(tetrahydro-2*H*-pyran-2-yloxy)but-2-yne was afforded as light yellow oil (5.80 g, 22%): ^{1}H NMR (300 MHz, $CDCl_3$): δ1.46–1.79 (m, 12 H), 3.43–3.48 (m, 2 H), 3.73–3.79 (m, 2

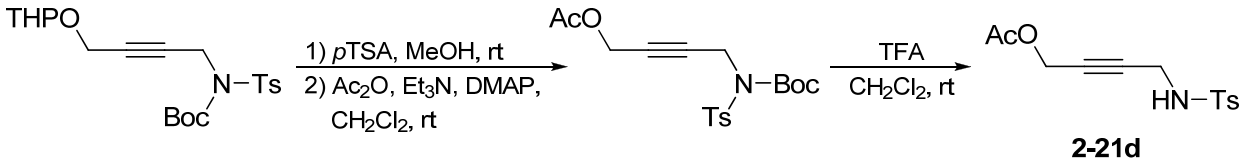
H), 4.19 (d, , 1 H, J = 17.6 Hz), 4.22 (d, , 2 H, J = 12.4 Hz), 4.27 (d, , 1 H, J = 14.2 Hz), 4.74 (t, 2 H, J = 3.4 Hz). All data are in agreement with those reported in the literature.[32]

_N_-(_tert_-Butoxycarbonyl)-_N_-[4-(tetrahydro-2_H_-pyran-2-yloxy)but-2-ynyl]-_N_-(4-methylbenzenesulfonyl)amine



To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylbenzenesulfonyl)amine (4.78 g, 17.6 mmol) and triphenylphosphine (5.09 g, 19.4 mmol) in DCM (50 mL) was added diisopropyl azodicarboxylate (4.92 g, 19.4 mmol) dropwise at room temperature, and the reaction was stirred for 30 min. *O*-tetrahydro-2*H*-pyranylbut-2-yn-1,4-diol (3.00 g, 17.6 mmol) was added to the reaction mixture, and the reaction was stirred overnight. The solvent was removed under reduced pressure and the crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 15%) to afford *N*-(*tert*-butoxycarbonyl)-*N*-[4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-ynyl]-*N*-(4-methylbenzenesulfonyl)amine as pale yellow oil (6.91 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9 H), 1.52–1.86 (m, 7 H), 2.44 (s, 3 H), 3.51 (m, 1 H), 3.82 (m, 2 H), 4.28 (q, 2 H, J = 1.8 Hz), 4.67 (t, 2 H, J =1.8 Hz), 4.81 (t, 1 H, J = 3.3 Hz), 7.30 (d, 2 H, J = 8.1 Hz), 7.91 (d, 2 H, J = 8.1 Hz).

_N_-[4-(Acetoxy)but-2-ynyl]-_N_-(4-methylbenzenesulfonyl)amine (2-21d)

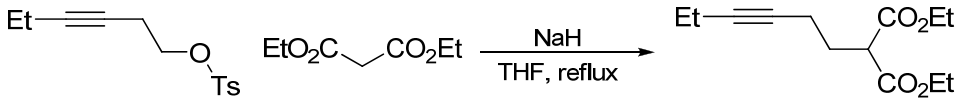


To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-[4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-ynyl]-*N*-(4-methylbenzenesulfonyl)amine (2.00 g, 4.72 mmol) in MeOH (45 mL) was added a solution of *p*-tolylsulfonic acid (8.98 mg, 0.04 mmol) in MeOH (5 mL). The reaction was stirred and monitored by TLC until starting material disappeared. The reaction was quenched with addition of saturated $NaHCO_3$ solution, followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude (1.60 g) was carried to next step without further purification.

A solution of crude alcohol (1.60 g, 4.72 mmol) in DCM (50 ml) was added triethylamine (1.99 ml, 14.17 mmol) and DMAP (0.05 g, 0.47 mmol). Acetic anhydride (0.89 ml, 9.45 mmol) was added drop-wise, and the reaction was stirred and monitored by TLC until starting material disappeared. The reaction was quenched with addition of 1 M HCl solution, followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford *N*-(*tert*-butoxycarbonyl)-*N*-[4-(acetoxy)but-2-ynyl]-*N*-(4-methylbenzenesulfonyl)amine as pale yellow oil (1.58 g, 88% for 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9 H), 2.10 (s, 3 H), 2.45 (s, 3 H), 4.67 (t, 2 H, *J* = 2.1 Hz), 4.70 (t, 2 H, *J* =2.1 Hz), 7.32 (d, 2 H, *J* = 8.4 Hz), 7.91 (d, 2 H, *J* = 8.4 Hz).

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-[4-(acetoxy)but-2-ynyl]-*N*-(4-methylbenzenesulfonyl)amine (1.58 g, 4.14 mmol) in DCM (100 mL) was added trifluoroacetic acid (5 mL, 64.9 mmol) and the reaction was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to give *N*-[4-(acetoxy)but-2-ynyl]-*N*-(4-methylbenzenesulfonyl)amine **(2-21d)** as light yellow oil (1.10 g, 95%): ^{1}NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3 H), 2.43 (s, 3 H), 3.87 (t*d, 2 H, *J* = 1.8*6.0 Hz), 4.44 (t, 2 H, *J* = 1.8 Hz), 4.60 (t, 1 H, *J* = 6.0 Hz), 7.31 (d, 2 H, *J* = 8.1 Hz), 7.76 (d, 2 H, *J* = 8.1 Hz).

Diethyl 2-(hex-3-ynyl)malonate (2-21e)[33]

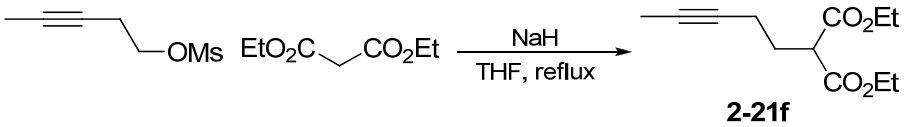


2-21e

To a suspension of NaH (0.23 g, 60 wt% in mineral oil, 5.9 mmol) in THF(40 mL) was added diethyl malonate (2.4 g, 15 mmol) dropwise, and the reaction was stirred for 30 min. A solution of hex-3-ynyl tosylate[34] (1.5 g, 5.9 mmol) in THF (10 mL) was added to the reaction mixture dropwise and the reaction was stirred at room temperature overnight. The reaction was quenched with addition of water, and followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0%

→ 10%) to afford diethyl 2-(hex-3-ynyl)malonate **(2-21e)** as pale yellow oil (0.70 g, 49 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, 3 H, *J* = 7.5 Hz), 1.27 (t, 6 H, *J* = 7.2 Hz), 2.03-2.2.30 (m, 6 H), 3.56 (t, 1 H, *J* = 7.5 Hz), 4.20 (q, 4 H, *J* = 7.2 Hz). Hex-3-ynyl tosylate was recovered from column (0.69 g, 46%). All data are in agreement with those reported in the literature. [33]

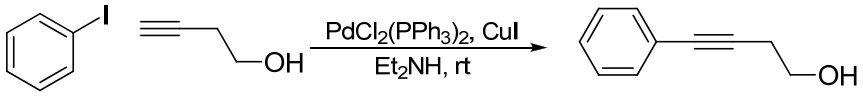
Diethyl 2-(pent-3-ynyl)malonate (2-21f)[33]



2-21f

To a suspension of NaH (0.71 g, 60 wt% in mineral oil, 17.8 mmol) in THF(40 mL) was added diethyl malonate (4.8 g, 30 mmol) dropwise, and the reaction was stirred for 30 min. A solution of 3-pentynyl mesylate[35] (1.9 g, 12 mmol) in THF (20 mL) was added to the reaction mixture dropwise and the reaction was stirred at room temperature for overnight. The reaction was quenched with addition of water, and followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford diethyl 2-(pent-3-ynyl)malonate **(2-21f)** as pale yellow oil (1.64 g, 61 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ1.27 (t, 6 H, *J* = 7.2 Hz), 1.77 (t, 3 H, *J* = 2.4Hz), 2.05 (m, 2 H), 2.22 (m, 2 H), 3.55 (t, 1 H, *J* = 7.5 Hz), 4.19 (q, 4 H, *J* = 7.2 Hz)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.44, 14.04, 16.70, 27.93, 50.75, 61.38, 169.19. All data are in agreement with those reported in the literature.[33]

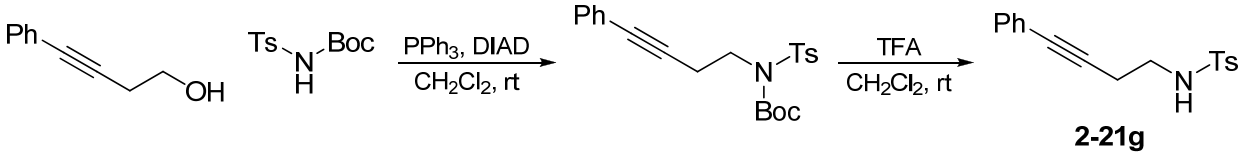
4-Phenylbut-3-yn-1-ol[36]



To a solution of $PdCl_2(PPh_3)_2$ (0.90 g, 1.28 mmol) and CuI (0.49 g, 2.6 mmol) in diethylamine (DEA) (20 mL) was added iodobenzene (8.7 g, 43 mmol), and the reaction was stirred for 30 min. 3-Butyn-1-ol (3.0 g, 43 mmol) was added dropwise to the reaction mixture, and the reaction was allowed to stir at room temperature overnight. The resulted reaction mixture was diluted with Et_2O and the organic layer was washed with saturated NH_4Cl solution, 1 M HCl solution, saturated $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and concentrated

under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 10% → 25%) to afford 4-phenylbut-3-yn-1-ol as light yellow oil (5.96 g, 95%); ^{1}H NMR (300 MHz, $CDCl_3$): δ1.90 (bs, 1H), 2.73 (t, 2 H, *J* = 6.3 Hz), 3.85 (t, 2 H, *J* = 6.3 Hz), 7.30-7.48 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.07, 61.42, 82.73, 86.57, 123.59, 128.17, 128.49, 131.91. All data are in agreement with those reported in the literature.[36]

_N_-(4-Phenylbut-3-ynyl)-_N_-(4-methylbenzenesulfonyl)amine (2-21g)[37]

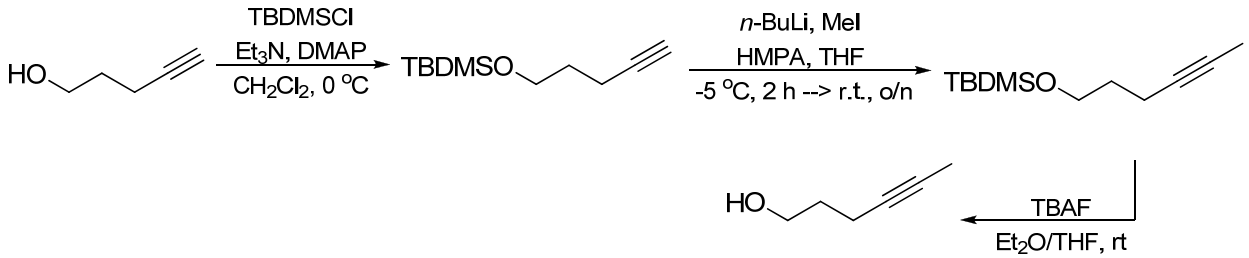


2-21g

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylbenzenesulfonyl)amine (3.71 g, 13.7 mmol) and triphenylphosphine (3.77 g, 14.4 mmol) in DCM (50 mL) was added diisopropyl azodicarboxylate (2.91 g, 14.4 mmol) drop-wise, and the reaction was stirred for 30 min. 4-phenylbut-3-yn-1-ol (2.00 g, 13.7 mmol) was added to the reaction mixture and the reaction was stirred overnight. Solvent was removed under reduced pressure, and the crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 5%) to give *N*-(*tert*-butoxycarbonyl)-*N*-(4-phenylbut-3-ynyl)-*N*-(4-methylbenzenesulfonyl)amine as off-white solid (4.53 g, 83%): mp. 96-97 ^{o}C; ^{1}NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9 H), 2.43 (s, 3 H), 2.88 (t, 2 H, *J* = 7.2 Hz), 4.08 (t, 2 H, *J* = 7.2 Hz), 7.26-7.38 (m, 7 H), 7.84 (d, 2 H, *J* = 8.4 Hz).

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-Phenylbut-3-ynyl)-*N*-(4-methylbenzenesulfonyl)amine (4.53 g, 11.4 mmol) in DCM (100 mL) was added trifluoroacetic acid (10 mL, 38.9 mmol) and the reaction was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution. The organic layer was separated and dried over Mg SO_4. The solvent was removed under reduced pressure and the crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to give *N*-(4-phenylbut-3-ynyl)-*N*-(4-methylbenzenesulfonyl)amine **(2-21g)** as colorless oil (3.27 g, 96%): ^{1}NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.57 (t, 2 H, *J* = 6.3 Hz), 3.19 (q, 2 H, *J* = 6.3 Hz), 4.80 (bt, 1 H, *J* = 6.3 Hz), 7.26-7.37 (m, 7 H), 7.84 (m, 2 H). All data are in agreement with those reported in the literature.[37]

4-Hexyn-1-ol[38]



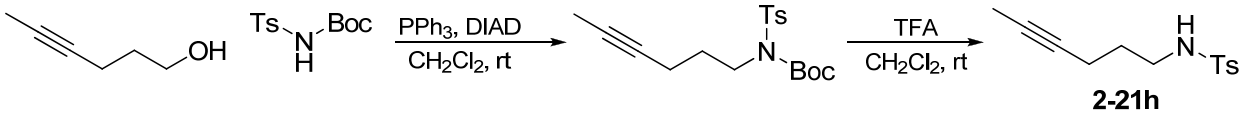
To a solution of 4-pentyn-1-ol (6.00 g, 71.3 mmol) in DCM (200 mL) was added sequentially a solution of TBDMSCl (11.0 g, 72.8 mmol) in DCM (40 mL), a solution of DMAP (0.09 g, 0.72 mmol) in DCM (10 mL), and TEA (11.03 mL, 78.0 mmol) under nitrogen at 0 °C. The reaction was allowed to stir overnight. The reaction was quenched with addition of water and followed by extraction with DCM. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by vacuum distillation (82-84 °C/15 mmHg)to give 4-pentynyl tert-butyldimethylsilyl ether as colorless liquid (12.92 g, 91%)%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.72 (m, 2 H), 1.93 (t, 1 H, *J* = 2.7 Hz), 2.67 (m, 2 H), 3.70 (t, 2 H, *J* = 6.0 Hz). All data are in agreement with those reported in the literature.[38a]

4-Pentynyl tert-butyldimethylsilyl ether (6.19 g, 31.2 mmol) was dissolved in THF (30 mL) and the solution was cooled to -5 °C. *n*-BuLi (2.5 M in hexanes, 13.73 mL, 34.3 mmol) was added dropwise to the solution, and it was allowed to stirred for 2 h. A solution of MeI (5.76 g, 40.6 mmol) in HMPA (15 mL, 86 mmol) was added to the reaction, and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 5%) to give 4-hexynyl tert-butyldimethylsilyl ether as colorless liquid (6.31 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.67 (m, 2 H), 1.77 (t, 1 H, *J* = 2.4 Hz), 2.20 (m, 2 H), 3.68 (t, 2 H, *J* = 6.0 Hz).

4-Hexynyl tert-butyldimethylsilyl ether (6.30 g, 29.7 mmol) was dissolved in Et_2O (150 mL) and THF (50 mL). TBAF (1.0 M in THF, 35.6 mL, 35.6 mmol) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine and

dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 20%) to give 4-hexyny-1-ol as colorless liquid (1.44 g, 49%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (t, 1 H, *J* = 6.0 Hz), 1.57 (m, 5 H), 2.25 (m, 2 H), 3.75 (q, 2 H, *J* = 6.0 Hz). All data are in agreement with those reported in the literature.[38b]

_N_-(Hex-4-ynyl)-_N_-(4-Methylbenzenesulfonyl)amine (2-21h)[39]

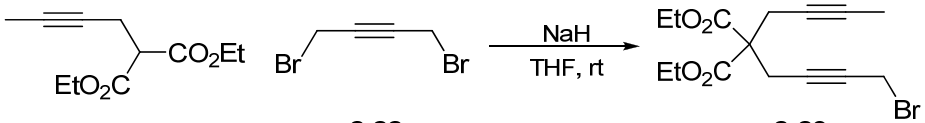


2-21h

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylbenzenesulfonyl)amine (1.4 g, 5.1 mmol) and triphenylphosphine (1.4 g, 5.4 mmol) in DCM (50 mL) was added diisopropyl azodicarboxylate (1.1 g, 5.4 mmol) drop-wise, and the reaction was stirred for 30 min. 4-hexyn-1-ol (0.50 g, 5.1 mmol) was added to the reaction mixture and the reaction was stirred overnight. The solvent was removed under reduced pressure, and the crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 5%) to give *N*-(*tert*-butoxycarbonyl)-*N*-(hex-4-ynyl)-*N*-(4-methylbenzenesulfonyl)amine as colorless oil (1.54 g, 86%):^{1}NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9 H), 1.77 (t, 3 H, *J* = 2.4 Hz), 1.93 (m, 2 H), 2.21 (m, 2 H), 2.44 (s, 3 H), 3.89 (m, 2 H), 7.30 (d, 2 H, *J* = 7.8 Hz), 7.78 (d, 2 H, *J* = 7.8 Hz).

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(hex-4-ynyl)-*N*-(4-methylbenzenesulfonyl)amine (1.5 g, 4.4 mmol) in DCM (100 mL) was added trifluoroacetic acid (2.0 mL, 39 mmol) and the reaction was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to give *N*-(hex-4-ynyl)-*N*-(4-methylbenzenesulfonyl)amine **(2-21h)** as colorless oil (1.07 g, 97%): ^{1}NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 2 H), 1.73 (t, 3 H, *J* = 2.7 Hz), 2.13 (m, 2 H), 2.43 (s, 3 H), 3.06 (m, 2 H), 4.59 (bt, 1 H), 7.31 (d, 2 H, *J* = 8.1 Hz), 7.75 (d, 2 H, *J* = 8.1 Hz). All data are in agreement with those reported in the literature.[39]

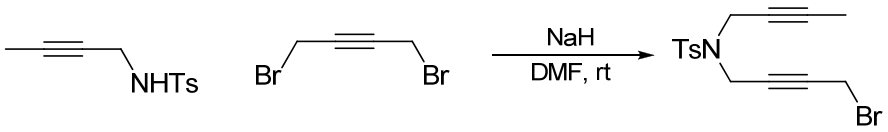
1-Bromo-5,5-di(carbethoxy)-nona-2,7-diyne (2-23a)[13b, 14]



2-22 **2-23a**

Diethyl 2-(but-2-ynyl)malonate[40] (5.0 g, 24 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 1.00 g, 23.6 mmol) in 80 mL of THF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of 1,4-dibromobut-2-yne **(2-22)** (15 g, 71 mmol) in 100 mL of THF *via* cannula over 2.5 h. The mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield yellow oil. The excess dibromobutyne was recovered by distillation (100 ^oC/4 mmHg). The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give product 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(2-23a)** as yellow oil (6.88 g, 85%); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 6 H, J = 7.2 Hz), 1.75 (t, 2 H, J = 2.7 Hz), 2.88 (q, 2 H, J = 2.7 Hz), 3.02 (t, 2 H, J = 2.1 Hz), 3.87 (t, 2 H, J = 2.1 Hz), 4.25 (q, 4 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.45, 14.02, 14.69, 22.74, 22.99, 56.70, 61.69, 61.87, 72.94, 78.20, 79.14, 82.23, 168.86. All data are in agreement with those reported in the literature.[13b, 14]

1-Bromo-5-(4-methylbenzenesulfonyl)-5-azanona-2,7-diyne (2-23b)[13b, 14]

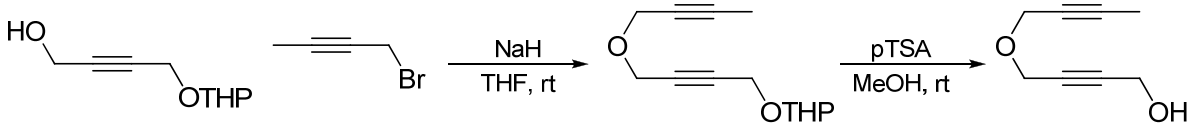


2-22 **2-23b**

N-(But-2-ynyl)-*N*-(4-methylbenzenesulfonyl)amine[13b] (0.50 g, 2.2 mmol) in 5 mL of DMF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.11 g, 2.7 mmol) in 5 mL of DMF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of 1,4-dibromobut-2-yne **(2-22)** (1.5 g, 7.1 mmol) in 5 mL of DMF *via* cannula and the resulting mixture stirred at room temperature for 18 h. The mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield yellow oil. The excess dibromobutyne was recovered by distillation (100 ^oC/4 mmHg). The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0% → 15%) to give 1-bromo-5-(4-

methylbenzenesulfonyl)-5-azanona-2,7-diyne **(2-23b)** as viscous yellow oil (490 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (t, 3 H, *J* = 2.4 Hz), 2.43 (s, 3 H), 3.72 (t, 2 H, *J* = 2.1 Hz), 4.06 (q, 2 H, *J* = 2.4 Hz), 4.21 (d, 2 H, *J* = 2.1 Hz), 7.32 (d, 2 H, *J* = 8.4 Hz), 7.72 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.38, 13.69, 21.51, 36.49, 36.96, 71.33, 79.63, 80.43, 82.02, 127.89, 129.42, 135.30, 143.72. All data are in agreement with those reported in the literature. [13b, 14]

5-Oxanona-2,7-diyn-1-ol[41]

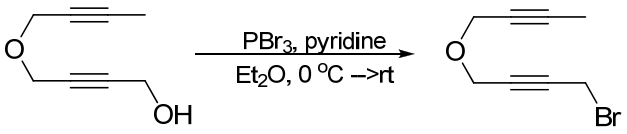


To a suspension of NaH (1.17 g, 60 wt% in mineral oil, 29.3 mmol) in THF(30 mL) was added a solution of *O*-tetrahydro-2*H*-pyranylbut-2-yn-1,4-diol (3.84 g, 22.6 mmol) in THF (15 mL) dropwise, and the reaction was stirred for 30 min. A solution of 2-butynylbromide (3.00 g, 22.6 mmol) in THF (15 mL) was added to the reaction mixture dropwise. The reaction was stirred at room temperature overnight. The reaction was quenched with addition of water, and followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford *O*-tetrahydro-2*H*-pyranyl-5-oxa-nona-2,7-diyn-1-ol as pale yellow oil (4.46 g, 89 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ1.52–1.86 (m, 7 H), 1.85 (t, 3 H, *J* = 2.4 Hz), 3.49–3.57 (m, 1 H), 3.80–3.88 (m, 1 H), 4.19 (m, 2 H), 4.27–4.32 (m, 3 H), 4.80 (t, 3 H, *J* = 3.3 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.56, 19.01, 25.32, 30.21, 54.24, 56.63, 57.13, 61.98, 74.31, 81.34, 82.68, 83.08, 96.83.

To a solution of *O*-tetrahydro-2*H*-pyranyl-5-oxa-nona-2,7-diyn-1-ol (4.46 g, 20.1 mmol) in MeOH (120 mL) was added a solution of *p*-tolylsulfonic acid (0.69 g, 4.01 mmol) in MeOH (5 mL) and the reaction was stirred overnight at room temperature. The reaction was quenched with addition of saturated $NaHCO_3$ solution, followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to afford 5-oxanona-2,7-diyn-1-ol as pale yellow oil (2.39 g, 86 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (t, 3 H, *J* = 2.4 Hz), 4.20 (q, 2 H, *J* = 2.4 Hz), 4.27 (t, 2 H, *J* = 2.4 Hz), 4.31 (t, 2

H, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.53, 50.97, 56.50, 57.17, 74.15, 81.09, 83.23, 84.92. All data are in agreement with those reported in the literature.[41]

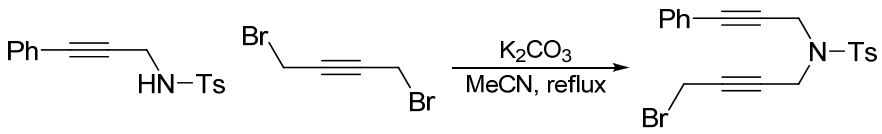
1-Bromo-5-oxanona-2,7-diyne (2-23c)[41]



2-23c

To a solution of 5-oxanona-2,7-diyn-1-ol (2.39 g, 17.3 mmol) and pyridine (0.15 mL, 1.73 mmol) in Et_2O (30 mL) at 0 °C, was added dropwise a solution of PBr_3 (0.81 mL, 8.6 mmol) in Et_2O (10 mL). The resultant reaction mixture was stirred under nitrogen for 19 h at room temperature. Water was then added followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford 1-bromo-5-oxanona-2,7-diyne **(2-23c)** as colorless oil (2.850 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$): δ1.85 (t, 3 H, J = 2.4 Hz), 3.95 (q, 2 H, J = 2.4 Hz), 4.18 (t, 2 H, J = 2.4 Hz), 4.29 (t, 2 H, J = 2.4 Hz). All data are in agreement with those reported in the literature.[41]

1-Bromo-5-(4-methylbenzenesulfonyl)-8-phenyl-5-azaocta-2,7-diyne (2-23d)

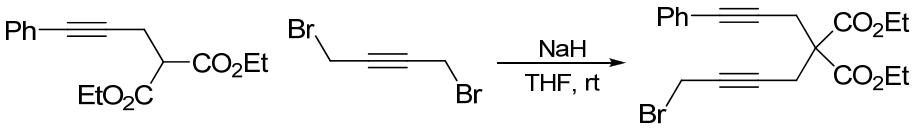


2-21b **2-22** **2-23d**

To a solution of *N*-(3-phenylpropargyl)-*N*-(4-methylbenzenesulfonyl)amine **(2-21b)** (2.0 g, 7.0 mmol) in MeCN (50 mL) was added K_2CO_3 (2.9 g, 21 mmol), and the mixture was heated to 60 °C for 15 min. 1,4-Dibromobut-2-yne **(2-22)** (5.9 g, 28 mmol) was added to the reaction mixture in one portion, and the reaction was heated to 90 °C overnight. The resulted reaction mixture was dilute with DCM and filtered through celite. The solvents were removed under reduced pressure. The excess dibromobutyne was recovered by distillation (100 °C/4 mmHg). The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 15%) to afford 1-bromo-5-(4-methylbenzenesulfonyl)-8-phenyl-5-azaocta-2,7-diyne **(2-23d)** as yellow oil (2.247 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 3.75 (t, 2 H, J = 2.4 Hz), 4.27 (t, 2 H, J = 2.4 Hz), 4.36 (s, 2 H), 7.28 (m , 7 H), 7.76 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 13.70, 21.50, 36.91, 37.45, 79.59, 80.70, 81.33, 85.92, 122.09, 127.92, 128.17, 128.56, 129.63, 131.55, 131.63, 143.94.

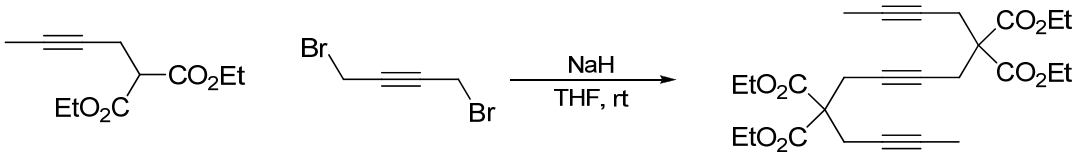
1-Bromo-5,5-di(carbethoxy)-8-phenylocta-2,7-diyne (2-23e)



2-21c **2-22** **2-23e**

To a suspension of NaH (0.44 g, 60 wt% in mineral oil, 10.9 mmol) in THF(60 mL) was added 1,4-dibromobut-2-yne **(2-22)** (7.7 g, 37 mmol) dropwise at 0 ^oC. A solution of diethyl 3-phenylpropargylmalonate **(2-21c)** (2.5 g, 9.1 mmol) in THF (10 mL) was added to the reaction mixture dropwise. The reaction was stirred at room temperature overnight. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The excess dibromobutyne was recovered by distillation (100 ^oC/4 mmHg). The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford 1-bromo-5,5-di(carbethoxy)- 8-phenylocta-2,7-diyne **(2-23e)** as light yellow oil (3.10 g, 84%): ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 6 H, J = 7.2 Hz), 3.10(t, 2 H, J = 2.4 Hz), 3.17 (s, 2 H), 3.88 (t, 2 H, J = 2.4 Hz), 4.25 (q, 4 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ14.08, 14.64, 23.24, 23.65, 56.81, 62.06, 78.45, 82.09, 83.76, 83.85, 123.04, 128.05 128.19, 131.65, 168.71.

5,5,10,10-Tetra(carbethoxy)tetradeca-2,7,12-triyne (2-18a)

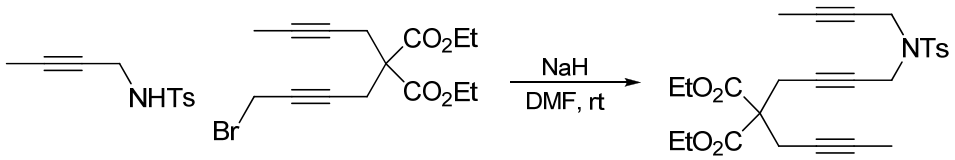


2-22 **2-18a**

To a suspension of NaH (0.30 g, 7.5 mmol) in THF (20 mL), was added a solution of diethyl 2-(but-2-ynyl)malonate[13b] (1.5 g, 7.1 mmol) in THF (10 mL). The reaction mixture was stirred under N_2 atmosphere at room temperature for 1 h. To the reaction mixture was added a solution of 1,4-dibromobut-2-yne **(2-22)** (0.76 g, 3.6 mmol) in THF (20 mL) dropwise with stirring at room temperature and the reaction mixture was stirred at room temperature for 16 h.

The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford 5,5,10,10-tetra(carbethoxy)tetradeca-2,7,12-triyne **(2-18a)** as light yellow oil (1.37 g, 81%): TLC (SiO_2, hexanes:EtOAc = 9:1, R_f = 0.30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 12 H, *J* = 7.2 Hz), 1.74 (t, 6 H, *J* = 2.4 Hz), 2.85 (q, 4 H, *J* = 2.4 Hz), 2.90 (s, 4 H), 4.20 (q, 4 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.4, 14.0, 22.8, 56.8, 61.7, 73.3, 77.7, 78.7, 169.0; 133.9; IR (neat, cm^{-1}): 2981 (w), 2922 (w), 2908 (w), 2237 (w), 1735 (s), 1465 (w), 1444 (w), 1429 (w), 1388 (w), 1367 (w), 1326 (m), 1290 (m), 1207 (s), 1193 (s), 1095 (w), 1070 (m), 1051 (m), 1012 (w), 860 (w); HRMS (ES) m/z calcd for $C_{26}H_{35}O_8$ $(M + H)^+$: 475.2332, found 475.2341 (Δ 1.9 ppm)

5-(4-Methylbenzenesulfonyl)-10,10-di(carbethoxy)-5-azatetradeca-2,7,12-triyne (2-18c)

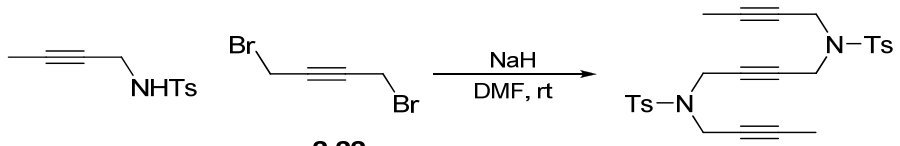


2-23a **2-18c**

To a suspension of NaH (0.14 g, 3.4 mmol) in DMF (10mL), was added a solution of *N*-(but-2-ynyl)-*N*-(4-methylbenzenesulfonyl)amine[13b] (0.61 g, 2.7 mmol) in DMF (10 mL) dropwise with stirring at room temperature. The reaction mixture was stirred under Nitrogen atmosphere at room temperature for 1 h. To the reaction mixture was added a solution of 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(2-23a)** (0.93 g, 2.7 mmol) in DMF (5 mL) dropwise with stirring at room temperature and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 20%) to afford 5-(4-methylbenzenesulfonyl)-10,10-di(carbethoxy)-5-azatetradeca-2,7,12-triyne **(2-18c)** as light yellow oil (1.02 g, 77%): TLC (SiO_2, hexanes:EtOAc = 9:1, R_f = 0.10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 6 H, *J* = 7.2 Hz), 1.63 (t, 3 H, *J* = 2.4 Hz), 1.75 (t, 3 H, *J* = 2.4 Hz), 2.43 (s, 3 H), 2.72 (q, 2 H, *J* = 2.4 Hz), 2.82 (t, 2 H, *J* = 2.1 Hz), 4.04 (q, 2 H, *J* = 2.4 Hz), 4.07 (t, 2 H, *J* = 2.1 Hz), 4.18 (q, 4 H, *J* = 7.2 Hz); 7.30 (d, 2 H, *J* = 8.1

Hz), 7.69 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.3, 3.5, 14.0, 21.5, 22.8, 22.9, 36.5, 56.6, 61.8, 71.5, 73.0, 75.8, 79.0, 80.5, 81.7, 127.9, 129.4, 135.5, 143.5, 168.9; IR (neat, cm^{-1}): 2982 (m), 2920 (w), 2854 (w), 2237 (w), 1735 (s), 1596 (w), 1443 (m), 1427 (m), 1350 (s), 1327 (m), 1292 (m), 1196 (s), 1165 (s), 1095 (s), 1053 (m), 1018 (w), 906 (m), 860 (w), 813 (w), 748 (m), 660 (m). HRMS (ES) m/z calcd for $C_{26}H_{31}NO_6S$ $(M + H)^+$: 486.1950, found 486.1937 (Δ 2.7 ppm).

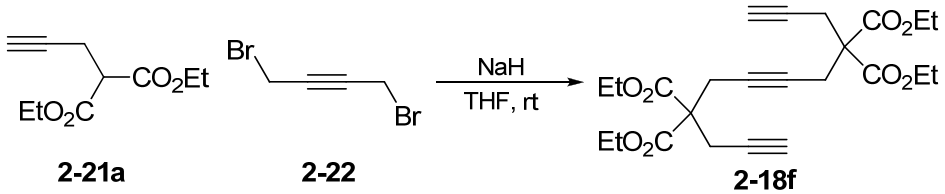
5,10-Di(4-methylbenzenesulfonyl)- 5,10-diazatetradeca-2,7,12-triyne (2-18d)



2-22 **2-18d**

To a suspension of NaH (0.45 g, 11.3 mmol) in DMF (15 mL), was added a solution of *N*-(but-2-ynyl)-*N*-(4-methylbenzenesulfonyl)amine[13b] (2.0 g, 9.0 mmol) in DMF (15 mL). The reaction mixture was stirred under N_2 atmosphere at room temperature for 1 h. To the reaction mixture was added a solution of 1,4-dibromobut-2-yne **(2-22)** (0.95 g, 4.5 mmol) in DMF (10 mL) dropwise with stirring at room temperature and. the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 25%) to afford 5,10-di(4-methylbenzenesulfonyl)- 5,10-diazatetradeca-2,7,12-triyne **(2-18d)** as light yellow oil (1.737 g, 78 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (t, 6 H, J = 2.4 Hz), 2.43 (s, 6 H), 3.93 (q, 4 H, J = 2.4 Hz), 3.99 (s, 4 H), 7.30 (m, 4 H), 7.67 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.4, 21.5, 36.3, 36.7, 71.3, 78.3, 81.9, 127.9, 129.4, 135.4, 143.8; IR (neat, cm^{-1}): 3032 (w), 2974 (w), 2920 (w), 2851 (w), 2237 (w), 1597 (m), 1493 (w), 1439 (m), 1350 (s), 1331 (s), 1292 (w), 1254 (w), 1161 (s), 1092 (s), 1068 (w), 1018 (w), 953 (w), 903 (s), 802 (m), 744 (s), 660 (s) ; HRMS (ES) m/z calcd for $C_{26}H_{28}N_2O_4S_2$ $(M + H)^+$:497.1569, found 497.1572 (Δ 0.3 ppm).

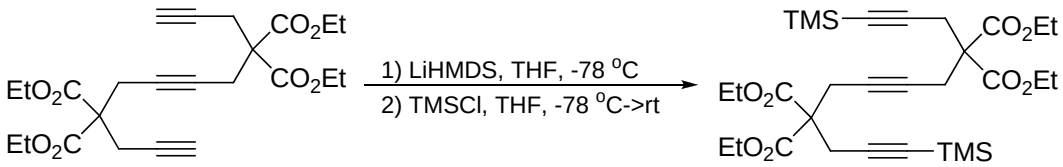
4,4,9,9-Tetra(carbethoxy)dodeca-1,6,11-triyne (2-18f) [13b]



2-21a **2-22** **2-18f**

To a suspension of NaH (0.20 g, 5.0 mmol) in THF (20 mL), was added a solution of diethyl propargylmalonate **(2-21a)** (0.91 g, 4.6 mmol) in THF (10 mL) dropwise with stirring at room temperature. The reaction mixture was stirred under N_2 atmosphere at room temperature for 1 h. To the reaction mixture was added a solution of 1,4-dibromobut-2-yne **(2-22)** (0.49 g, 2.3 mmol) in THF (10 mL) dropwise with stirring at room temperature. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. The drying agent was removed by vacuum filtration and the solution was concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford 4,4,9,9-tetra(carbethoxy)dodeca-1,6,11-triyne **(2-18f)** as colorless oil (1.79 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 12 H, J = 7.2 Hz), 1.99 (t, 2 H, J = 2.7 Hz), 2.93 (m, 8 H), 4.21 (q, 8 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.4, 22.7, 56.4, 62.0, 71.4, 77.7, 78.7, 168.7. All data are in agreement with those reported in the literature.[13b]

1,12-Bis(trimethylsilyl)-4,4,9,9-tetra(carbethoxy)dodeca-1,6,11-triyne (2-18g)

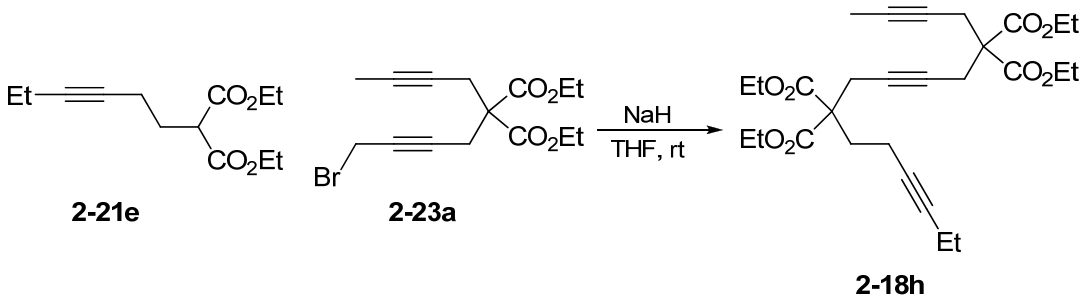


2-18f **2-18g**

To a solution of 4,4,9,9-tetra(carbethoxy)dodeca-1,6,11-triyne **(2-18f)** (0.80 g, 1.8 mmol) in THF (20 mL) at -78 °C under N_2 was added LiHMDS (1.0 M in THF, 4.48 mL, 4.48 mmol) dropwise. The resulting solution was stirred for 2 h at this temperature before a solution of TMSCl (0.78 g, 7.2 mmol) in THF (5 mL) was added. The reaction mixture was stirred for an additional 3 h at -78 °C before being allowed to warm up to 0 °C. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were

washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford 1,12-bis(trimethylsilyl)-4,4,9,9-tetra(carbethoxy)dodeca-1,6,11-triyne **(2-18g)** as light yellow oil (1.06 g, 99 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 18 H), 1.25 (t, 12 H, *J* = 7.2 Hz), 2.91 (s, 4 H), 2.94 (s, 4 H), 4.20 (q, 8 H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.14, 14.20, 22.96, 24.00, 56.89, 62.04, 77.92, 88.21, 101.38, 168.91; IR (neat, cm^{-1}): 2962 (s), 2939 (s), 2901 (s), 2179 (s), 1739 (s), 1465 (w), 1444 (w), 1427 (w), 1388 (w), 1365 (w), 1323 (m), 1288 (s), 1249 (s), 1195 (s), 1095 (w), 1053 (m), 1033 (m); HRMS (ES) m/z calcd for $C_{30}H46O_8Si_2$ $(M + H)^+$: 591.2810, found 591.2804 (Δ 1.0 ppm)

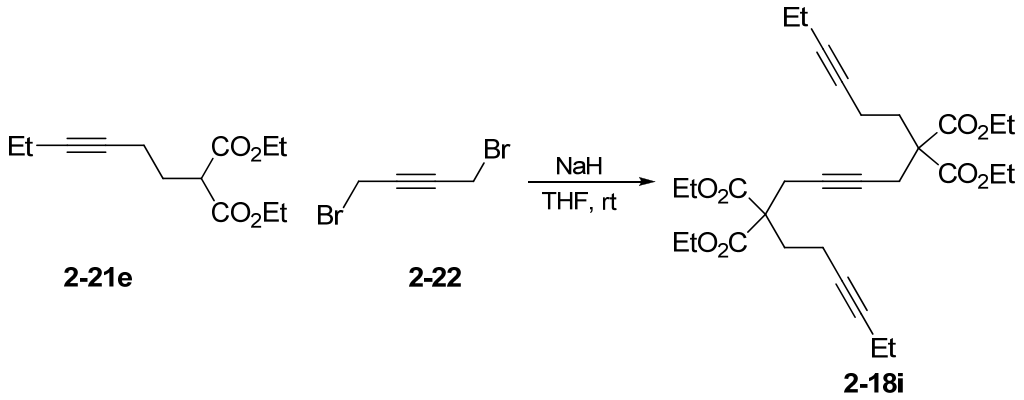
5,5,10,10-Tetra(carbethoxy)hexadeca-2,7,13-triyne (2-18h)



To a suspension of NaH (0.05 g, 60 wt% in mineral oil, 1.3 mmol) in THF (10 mL) was added a solution of diethyl 2-(hex-3-ynyl)malonate **(2-21e)** (0.25 g, 1.0 mmol) in THF (3 mL) dropwise and the reaction was stirred for 30 min. A solution of 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(2-23a)** (0.36 g, 1.0 mmol) in THF (2 mL) was added to the reaction mixture dropwise. The reaction was stirred at room temperature overnight. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford 5,5,10,10-tetra(carbethoxy)hexadeca-2,7,13-triyne **(2-18h)** as pale yellow oil (0.451 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, 3 H. *J* = 7.2 Hz), 1.25 (t, 6 H, *J* = 7.2 Hz), 1.74 (t, 3 H. *J* = 2.7 Hz), 2.08-2.2.30 (m, 6 H), 2.79 (t, 2 H. *J* = 2.4 Hz), 2.86 (q, 2 H. *J* = 2.7 Hz), 2.91 (t, 2 H. *J* = 2.4 Hz), 4.20 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.45, 12.38, 13.97, 14.00, 14.09, 22.75, 22.79, 22.98, 31.32, 56.42, 56.74, 61.53, 61.70, 73.21, 77.58, 77.77, 77.94, 78.76, 82.15,

169.03, 169.91; HRMS (ES) m/z calcd for $C_{28}H_{39}O_8$ $(M + H)^+$: 503.2645, found 503.2644 (Δ 0.2 ppm).

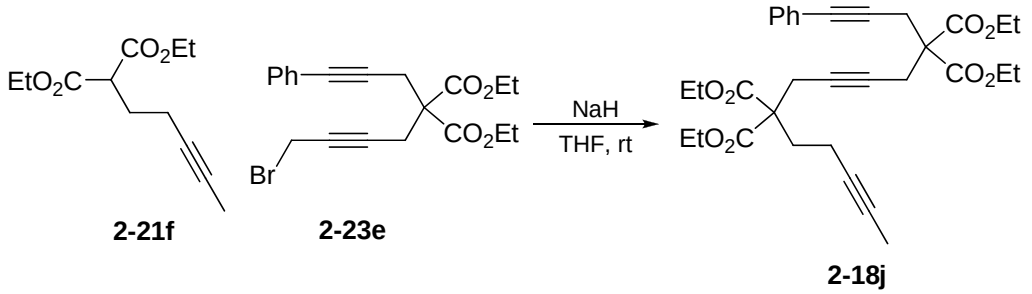
7,7,12,12-Tetra(carbethoxy)octadeca-3,9,15-triyne (2-18i)



2-21e **2-22** **2-18i**

To a suspension of NaH (0.08 g, 60 wt% in mineral oil, 2.00 mmol) in THF (15 mL) under N_2 atmosphere, was added a solution of diethyl 2-(hex-3-ynyl)malonate **(2-21e)** (0.41 g, 1.7 mmol) in THF (5 mL). The reaction mixture was stirred under N_2 atmosphere at room temperature for 30 min. To the reaction mixture was added a solution of 1,4-dibromobut-2-yne **(2-22)** (0.18 g, 0.83 mmol) in THF (5 mL) dropwise with stirring at room temperature and. the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford 7,7,12,12-tetra(carbethoxy)octadeca-3,9,15-triyne **(2-18i)** as light yellow solid (0.18 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, 6 H, *J* = 7.2 Hz), 1.25 (t, 12 H, *J* = 7.2 Hz), 2.08-2.2.30 (m, 12 H), 2.79 (s, 4 H), 4.19 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.40, 13.99, 14.10, 22.98, 31.35, 56.41, 61.54, 77.66, 77.92, 82.18, 169.91; HRMS (ES) m/z calcd for $C_{30}H_{43}O_8$ $(M + H)^+$: 531.2958, found 531.2953 (Δ 0.9 ppm).

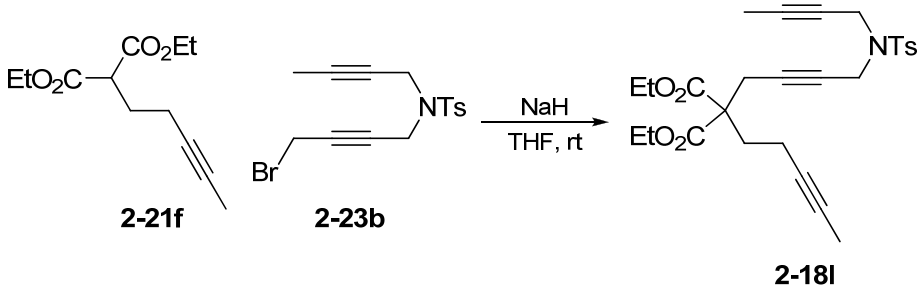
1-Phenyl-4,4,9,9-tetra(carbethoxy)tetradeca-1,6,12-triyne (2-18j)



2-21f **2-23e** **2-18j**

A solution of diethyl 2-(pent-3-ynyl)malonate **(2-21f)** (0.56 g, 2.47 mmol) in THF (5 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 0.12 g, 3.0 mmol) in THF (20 mL) under nitrogen and the resulting mixture was stirred for 30 min at room temperature. A solution of 1-bromo-5,5-di(carbethoxy)-8-phenylocta-2,7-diyne **(2-23e)** (1.0 g, 2.5 mmol) in THF (5 mL) was then added dropwise and the reaction mixture was stirred at room temperature overnight. Water was added followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to give 1-phenyl-4,4,9,9-tetra(carbethoxy)tetradeca-1,6,12-triyne **(2-18j)** as colorless oil (1.20 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (m, 12 H), 1.74 (t, 3 H, *J* = 2.4 Hz), 2.11 (m, 2 H), 2.25 (t, 2 H, *J* = 2.4 Hz), 2.80 (t, 2 H, *J* = 2.4 Hz), 2.99 (t, 2 H, *J* = 2.4 Hz),3.15 (s, 2 H) , 4.21 (m, 8 H), 7.25-7.38 (m, 5 H)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.44, 13.98, 14.04, 22.96, 23.41, 31.27, 56.39, 56.81, 61.56, 61.87, 76.13, 77.64, 77.73, 77.84, 83.46, 84.20, 123.24, 127.89, 128.14, 131.65, 168.84, 169.91; HRMS (ES) m/z calcd for $C_{32}H_{39}O_8$ $(M + H)^+$: 551.2645, found 551.2648 (Δ 0.5 ppm).

5-(4-Methylbenzenesulfonyl)-10,10-di(carbethoxy)-5-azapentadeca-2,7,13-triyne (2-18l)

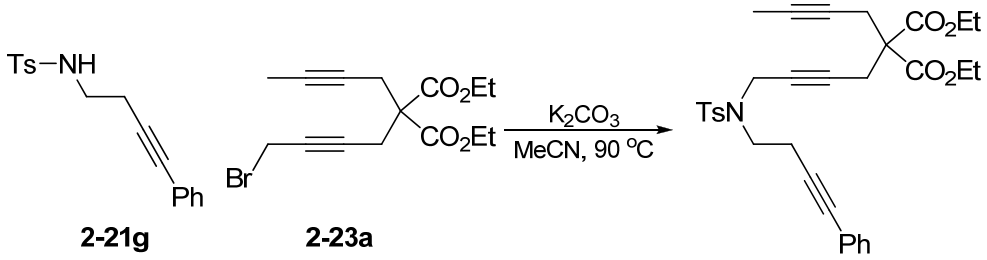


2-21f **2-23b** **2-18l**

To a suspension of NaH (0.11 g, 2.65 mmol) in THF (10 mL) was added a solution of diethyl 2-(pent-3-ynyl)malonate **(2-21f)** (0.50 g, 2.2 mmol) in THF (5 mL) dropwise with stirring

at room temperature, and the reaction mixture was stirred at room temperature for 1 h. To the reaction mixture was added a solution of 1-bromo-5-tosyl-5-azanona-2,7-diyne **(2-23b)** (0.78 g, 2.21 mmol) in THF (10 mL) dropwise with stirring at room temperature and. the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 15%) to afford 5-(4-Methylbenzenesulfonyl)-10,10-di(carbethoxy)-5-azatetradeca-2,7,13-triyne **(2-18l)** as light yellow oil (0.814 g, 74%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 6 H, *J* = 7.2 Hz), 1.64 (t, 3 H, *J* = 2.4 Hz), 1.75 (t, 3 H, *J* = 2.4 Hz), 2.04 (m, 2 H). 2.14 (m, 2 H), 2.43 (s, 3 H), 2.69 (t, 2 H, *J* = 2.4 Hz), 4.07 (m,4 H), 4.18 (q, 4 H, *J* = 7.2 Hz); 7.30 (d, 2 H, *J* = 8.1 Hz), 7.69 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.57, 14.16, 14.21, 21.67, 21.73, 23.19, 31.60, 36.70, 36.77, 56.46, 61.86, 71.65, 76.09, 76.52, 77.80, 80.60, 81.91, 128.12, 129.56, 135.75, 143.76, 169.98; HRMS (ES) m/z calcd for $C_{27}H_{33}NO_6S$ $(M + H)^+$: 500.2107, found 500.2106 (Δ 0.2 ppm).

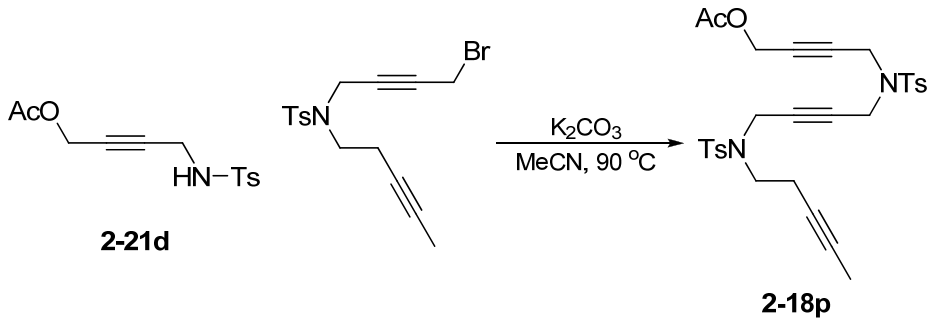
1-Phenyl-5-(4-Methylbenzenesulfonyl)-10,10-di(carbethoxy)-5-azatetradeca-1,7,12-triyne (2-18o)



To a suspension of K_2CO_3 (0.69 g, 5.0 mmol) in MeCN (15 mL) was added a solution of *N*-(4-phenylbut-3-ynyl)-*N*-(4-methylbenzenesulfonyl)amine **(2-21g)** (0.50 g, 1. 7 mmol) in MeCN (5 mL) and a solution of 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(2-23a)** (0.57 g, 1.7 mmol) in MeCN (10 mL). The reaction was heated to 90 °C overnight. The reaction mixture was diluted with DCM and filtered through celite, and the filtrate was concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 15%) to give 1-phenyl-5-(4-Methylbenzenesulfonyl)-10,10-di(carbethoxy)-5-azatetradeca-1,7,12-triyne **(2-18o)** as light yellow oil (0.87 g, 93 %): ^{1}NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 6 H,

J = 7.2 Hz), 1.74 (t, 3 H, *J* = 2.7 Hz), 2.43 (s, 3 H), 2.64 (q, 2 H, *J* = 2.4 Hz), 2.70 (t, 2 H, *J* = 6.6 Hz), 2.79 (t, 2 H, *J* = 2.1 Hz), 3.40 (t, 2 H, *J* = 6.6 Hz), 4.09 (t, 2 H, *J* = 2.1 Hz), 4.13-4.22 (m, 6 H), 7.26-7.39 (m, 7 H), 7.74 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.75, 14.21, 20.10, 21.79, 22.94, 23.12, 37.78, 45.59, 56.72, 62.00, 73.22, 76.33, 79.22, 80.93, 82.52, 86.56, 123.59, 127.68, 127.76, 128.44, 129.88, 131.81, 136.41, 143.75, 169.07; HRMS (ES) m/z calcd for $C_{32}H_{36}NO_6S$ $(M + H)^+$: 562.2263, found 562.2265 (Δ 0.4 ppm).

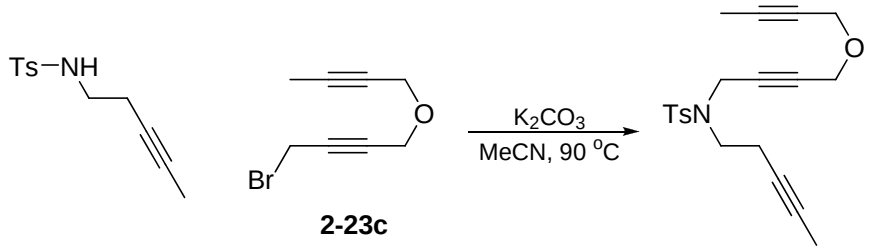
1-Acetoxy-5,10-bis(4-methylbenzenesulfonyl)-5,10-diazapentadeca-2,7,13-triyne (2-18p)



2-21d **2-18p**

To a suspension of K_2CO_3 (0.49 g, 3.6 mmol) in MeCN (10 mL) was added a solution of *N*-[4-(acetoxy)but-2-ynyl]-*N*-(4-methylbenzenesulfonyl)amine **(2-21d)** (0.50 g, 1.8 mmol) in MeCN (5 mL) and a solution of 1-bromo-5-tosyl-5-azadeca-2,8-diyne (0.66 g, 1.8 mmol) in MeCN (5 mL). The reaction was heated to 90 °C overnight. The reaction mixture was diluted with DCM, filtered through celite and the filtrate was concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 15%) to give 1-acetoxy-5,10-bis(4-methylbenzenesulfonyl)-5,10-diazapentadeca-2,7,13-triyne **(2-18p)** as light yellow oil (0.94 g, 93 %): ^{1}NMR (300 MHz, $CDCl_3$) δ 1.75 (t, 3 H, *J* = 2.7 Hz), 2.07 (s, 3 H), 2.35 (m, 2 H), 2.43 (s, 3 H), 2.44 (s, 3 H),3.19 (t, 2 H, *J* = 7.8 Hz), 3.92 (t, 2 H, *J* = 1.8 Hz), 3.95 (t, 2 H, *J* = 1.8 Hz), 4.05 (t, 2 H, *J* = 1.8 Hz), 4.47 (t, 2 H, *J* = 1.8 Hz), 7.29-7.32 (m, 4 H), 7.62-7.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ3.61, 19.32, 20.79, 21.70, 21.75, 36.60, 37.44, 46.15, 52.01, 75.58, 78.00, 78.22, 79.21, 79.26, 80.10, 127.71, 127.77, 128.00, 128.06, 129.80, 135.44, 136.22, 143.99, 144.26, 170.19; HRMS (ES) m/z calcd for $C_{29}H_{33}N_2O_6S_2$ $(M + H)^+$: 569.1780, found 569.1777 (Δ 0.5 ppm).

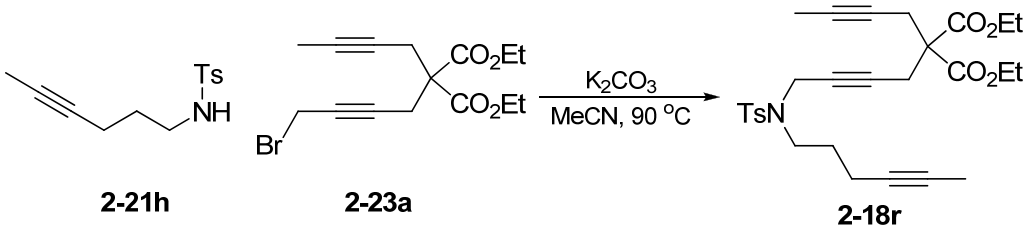
10-(4-Methylbenzenesulfonyl)-5-oxa-10-azapentadeca-2,7,13-triyne (2-18q)



2-23c **2-18q**

To a suspension of K_2CO_3 (1.6 g, 12 mmol) in MeCN (20 mL) was added a solution of *N*-(pent-4-ynyl)-*N*-(4-methylbenzenesulfonyl)amine (0.94 g, 4.0 mmol) in MeCN (5 mL) and a solution of 1-bromo-5-oxanona-2,7-diyne **(2-23c)** (0.80 g, 4.0 mmol) in MeCN (5 mL). The reaction was heated to 90 °C overnight. The reaction mixture was diluted with DCM, filtered through celite and the filtrate was concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 20%) to give 10-(4-methylbenzenesulfonyl)-5-oxa-10-azapentadeca-2,7,13-triyne **(2-18q)** as light yellow oil (1.39 g, 98 %): ^{1}NMR (300 MHz, $CDCl_3$) δ 1.75 (t, 3 H, *J* = 2.4 Hz), 1.85 (t, 3 H, *J* = 2.4 Hz), 2.42 (m, 5 H), 3.30 (t, 2 H, *J* = 7.5 Hz), 3.96 (q, 2 H, *J* = 2.4 Hz), 3.99 (t, 2 H, *J* = 2.4 Hz), 4.22 (t, 2 H, *J* = 2.4 Hz), 7.29 (d, 2 H, *J* = 7.8 Hz), 7.71 (d, 2 H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.88, 19.40, 21.78, 37.64, 46.13, 56.48, 57.23, 74.38, 75.68, 77.91, 79.84, 81.18, 83.35, 127.82, 129.67, 136.29, 143.73; HRMS (ES) m/z calcd for $C_{20}H_{24}NO_3S$ $(M + H)^+$: 358.1477, found 358.1476 (Δ 0.3 ppm).

7-(4-Methylbenzenesulfonyl)-12,12-di(carbethoxy)-7-azahexadeca-2,9,14-triyne (2-18r)

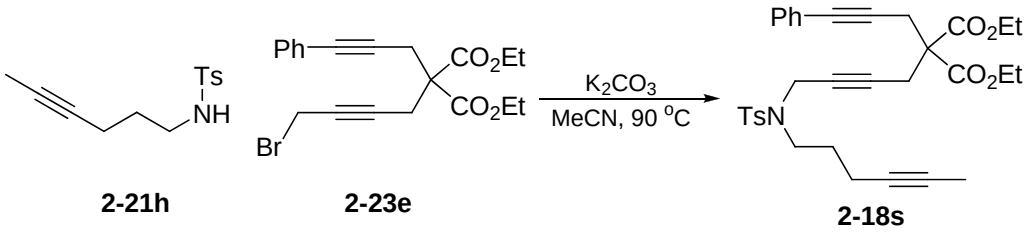


2-21h **2-23a** **2-18r**

To a suspension of K_2CO_3 (0.83 g, 6.0 mmol) in MeCN (15 mL) was added a solution of *N*-(hex-4-ynyl)-*N*-(4-methylbenzenesulfonyl)amine **(2-21h)** (0.50 g, 2.0 mmol) in MeCN (5 mL) and a solution of 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(2-23a)** (0.68 g, 2.0 mmol) in MeCN (5 mL). The reaction was heated to 90 °C overnight. The reaction mixture was diluted with DCM, filtered through celite, and the filtrate was concentrated under reduced pressure. The

crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give 7-(4-methylbenzenesulfonyl)-12,12-di(carbethoxy)-7-azahexadeca-2,9,14-triyne **(2-18r)** as light yellow oil (0.91 g, 89 %): ^{1}NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 6 H, *J* = 7.2 Hz), 1.66-1.78 (m, 8 H), 2.17 (m, 2 H), 2.44 (s, 3 H), 2.62 (q, 2 H, *J* = 2.4 Hz), 2.73 (t, 2 H, *J* = 2.1 Hz), 3.20 (t, 2 H, *J* = 7.2 Hz), 4.09 (t, 2 H, *J* = 2.1 Hz), 4.14 (m, 4 H), 7.30 (d, 2 H, *J* = 7.8 Hz), 7.78 (d, 2 H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.63, 14.17, 14.22, 16.24, 21.76, 22.86, 23.03, 27.44, 37.09, 45.72, 56.67, 61.97, 73.20, 76.17, 76.45, 78.07, 79.10, 80.59, 127.84, 129.71, 136.25, 143.55, 169.03; HRMS (ES) m/z calcd for $C_{28}H_{36}NO_6S$ $(M + H)^+$: 514.2263, found 514.2257 (Δ 1.2 ppm).

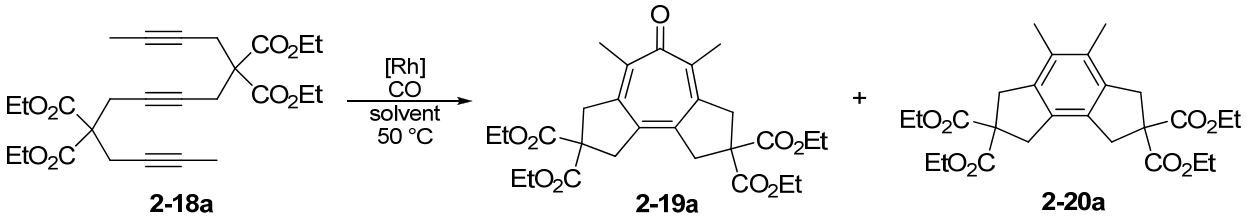
1-Phenyl-9-(4-Methylbenzenesulfonyl)-4,4-di(carbethoxy)-9-azapentadeca-1,6,13-triyne (2-18s)



2-21h **2-23e** **2-18s**

To a suspension of K_2CO_3 (0.66 g, 4.8 mmol) in MeCN (5 mL) was added a solution of *N*-(hex-4-ynyl)-*N*-(4-methylbenzenesulfonyl)amine **(2-21h)** (0.40 g, 1.59 mmol) in MeCN (5 mL) and a solution of 1-bromo-5,5-di(carbethoxy)- 8-phenylocta-2,7-diyne **(2-23e)** (0.65 g, 1.6 mmol) in MeCN (5 mL). The reaction was heated to 90 °C for overnight. The reaction mixture was diluted with DCM and filtered through celite, and the solution was concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 15%) to give 1-phenyl-9-(4-Methylbenzenesulfonyl)-4,4-di(carbethoxy)-9-azapentadeca-1,6,13-triyne **(2-18s)** as light yellow oil (0.653 g, 71 %): ^{1}NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 6 H, *J* = 7.2 Hz), 1.70-1.78 (m, 5 H), 2.17 (m, 2 H), 2.35 (s, 3 H), 2.80 (t, 2 H, *J* = 1.8 Hz), 2.90 (s, 2 H), 3.22 (t, 2 H, *J* = 7.2 Hz), 4.11 (t, 2 H, *J* = 1.8 Hz), 4.14 (m, 4 H), 7.30 (m, 5 H), 7.70 (d, 2 H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.61, 14.25, 16.29, 21.72, 23.07, 23.64, 27.48, 37.11, 45.76, 56.75, 62.20, 76.46, 76.51, 78.09, 80.45, 83.90, 84.08, 123.26, 127.79, 127.86, 128.48, 129.69, 129.75, 131.82, 136.25, 143.63, 168.87; HRMS (ES) m/z calcd for $C_{33}H_{38}NO_6S$ $(M + H)^+$: 576.2420, found 576.2423 (Δ 0.5 ppm).

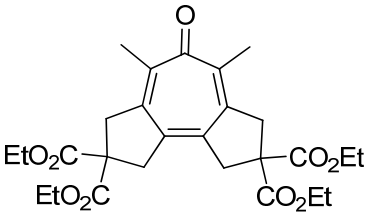
General Procedures of rhodium-catalyzed [2+2+2+1] cycloaddition of triynes



2-18a **2-19a** **2-20a**

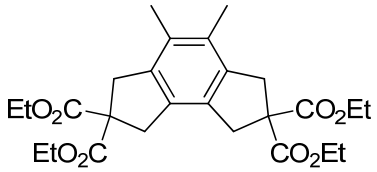
A typical procedure is described here for the reaction of triyne **2-18a**. All other reactions were ran following the same procedure unless otherwise noted. Triyne **2-18a** (100 mg, 0.211 mmol) was introduced to a Schlenck tube, followed by $Cl(CH_2)_2Cl$ (2.11 mL) under nitrogen atmosphere, and then CO was bubbled into the solution at room temperature (**Caution!! Must be done in a well ventilated hood**). After 15 min, $[Rh(COD)Cl]_2$ (5.2 mg, 0.0105 mmol, 5 mol%) was added under CO and the resulting mixture was stirred at room temperature for an additional 5 min. Then, the reaction mixture was heated to 50 ^oC with stirring and kept for 16 h under CO (ambient pressure, bubbled into the solution). The reaction mixture was cooled to room temperature and all volatiles were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:EtOAc = 25:1 to 9:1 to 1.5:1) affording **2-19a** and **2-20a.**

4,6-Dimethyl-2,2,8,8,tetra(carbethoxy)-1,3,7,8-tetrahydro-5-oxo-cyclopenta[*e*]azulene (2-19a)



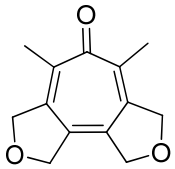
Yellow solid; m.p.78-81 °C; TLC (SiO_2, hexanes: EtOAc = 4:1, R_f = 0.10); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 12 H, *J* = 7.2 Hz), 2.23 (s, 6 H), 3.42 (s, 4 H), 3.53 (s, 4 H), 4.21 (q, 8 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.1, 29.7, 42.3, 43.2, 57.5, 62.1, 138.8, 141.7, 146.6, 170.8, 184.4; IR (neat, cm^{-1}): 2980 (m), 2926 (m), 2853 (w), 1732 (s), 1566 (m), 1466 (w), 1445 (w), 1420 (w), 1388 (w), 1367 (m), 1290 (m), 1252 (s), 1200 (m), 1175 (m), 1163 (m), 1076 (m), 989 (w), 860 (w); LR-MS *m/z* calcd for $C_{27}H_{34}O_9$ (M^+) 502.5, found (M+ 1): 503.1; HRMS (ES) m/z calcd for $C_{27}H_{35}O_9$ $(M + H)^+$: 503.2281, found 503.2271 (Δ 2.0 ppm).

4,5-Dimethyl-2,2,7,7-tetra(carbethoxy)-1,3,6,8-tetrahydro-*as*-indacene (2-20a)



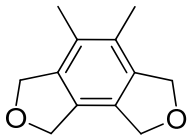
White solid; m.p.96-98 °C; TLC (SiO_2, hexanes: EtOAc = 4:1, R_f = 0.44); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 12 H, *J* = 7.2 Hz), 2.13 (s, 6 H), 3.49 (s, 4 H), 3.50 (s, 4 H), 4.20 (q, 8 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 15.7, 39.1, 40.0, 60.0, 61.6, 130.6, 132.2, 138.1, 171.9; IR (neat, cm^{-1}): 2980 (m), 2935 (m),2906 (m), 2872 (w), 1732 (s), 1464 (w), 1387 (w), 1365 (m), 1298(s), 1277(s), 1250 (s), 1186 (s), 1157 (s), 1095 (s), 1060 (s), 1016 (w), 860 (w); LR-MS *m/z* calcd for $C_{26}H_{34}O_8$ (M^+) 474.5, found (M+ 1): 475.2; HRMS (ES) m/z calcd for $C_{26}H_{35}O_8$ $(M + H)^+$: 475.2332, found 475.2338 (Δ 1.3 ppm).

4,6-Dimethyl-1,3,7,8-tetrahydro-5-oxo-2,8-dioxa-cyclopenta[*e*]azulene (2-19b)



Yellow solid; turn brown at ~ 200 °C m.p. 229-231 °C; TLC (SiO_2, hexanes: EtOAc = 9:1, R_f = 0.06); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 6 H), 4.85 (s, 4 H), 5.02 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 73.6, 75.0, 135.0, 140.0, 146.2, 182.9; IR (neat, cm^{-1}): 2921 (w), 2850 (w), 1557 (s), 1541 (s), 1466 (m), 1448 (m), 1375 (m), 1325 (w), 1269 (w), 1170 (m), 1105 (m), 1085 (m), 1057 (s), 933 (s), 752 (m); LR-MS *m/z* calcd for $C_{13}H_{14}O_3$ (M^+) 218.3, found (M+ 1): 219.0; HRMS (ES) m/z calcd for $C_{13}H_{15}O_3$ $(M + H)^+$: 219.1021, found 219.1013 (Δ 3.7 ppm).

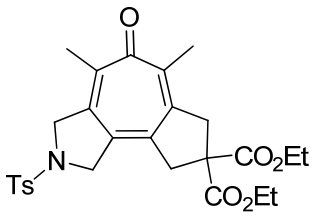
4,5-Dimethyl-1,3,6,8-tetrahydro-2,7-dioxa-*as*-indacene (2-20b)



Yellow solid; turn brown at ~ 200 °C m.p. 212-214 °C; TLC (SiO_2, hexanes: EtOAc = 9:1, R_f = 0.20); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 6 H), 5.04 (s, 4 H), 5.09 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 72.9, 73.4, 128.6, 128.8, 138.2; IR (neat, cm^{-1}): 2918 (w), 2848 (m), 1458 (w), 1350 (w), 1303 (m), 1078 (w), 1041 (s), 904 (s), 750 (m); LR-MS *m/z* calcd for $C_{12}H_{14}O_2$

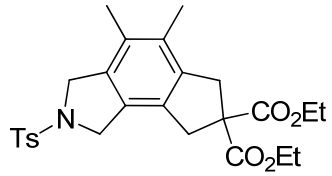
(M^+) 190.2, found (M+ 1): 191.0; HRMS (ES) m/z calcd for $C_{13}H_{15}O_2$ $(M + H)^+$: 191.1072, found 191.1066 (Δ 3.1 ppm).

4,6-Dimethyl-8,8-di(carbethoxy)-1,3,7,8-tetrahydro-2-(4-Methylbenzenesulfonyl)-5-oxo-2-aza-cyclopenta[*e*]azulene (2-19c)



Yellow solid; m.p. 82-85 °C; TLC (SiO_2, hexanes: EtOAc = 4:1, R_f = 0.12); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 6 H, *J* = 7.2 Hz), 2.11 (s, 3 H), 2.22 (s, 3 H), 2.42 (s, 3 H), 3.29 (s, 2 H), 3.50 (s, 2 H), 4.21 (q, 4 H, *J* = 7.2 Hz), 4.29 (s, 2 H), 4.46 (s, 2 H), 7. 35 (d, 2 H, *J* = 8.1 Hz), 7.76 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 18.4, 19.2, 21.5, 41.6, 43.1, 54.6, 55.3, 57.6, 62.2, 127.7, 130.0, 132.7, 134.3, 138.4, 140.7, 142.4, 143.0, 144.3, 146.7, 170.5, 183.6; IR (neat, cm^{-1}): 2978 (m), 2923 (m), 2854 (w), 1732 (s), 1597 (w), 1570 (m), 1447 (w), 1366 (m), 1350 (m), 1288 (m), 1254 (s), 1165 (s), 1072 (m), 1053 9m), 1018 (w), 860 (w), 814 (w), 667 (s); LR-MS *m/z* calcd for $C_{27}H_{31}NO_7S$ (M^+) 513.6, found (M+ 1) 514.0; HRMS (ES) m/z calcd for $C_{27}H_{32}NO_7S$ $(M + H)^+$: 514.1899, found 514.1897 (Δ 0.4 ppm).

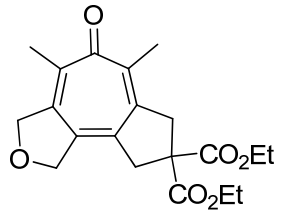
4,5-Dimethyl-7,7-di(carbethoxy)-1,3,6,8-tetrahydro-2-(4-Methylbenzenesulfonyl)-2-aza-*as*-indacene (2-20c)



White solid; turn brown at ~ 138 °C m.p. 144-146 °C; TLC (SiO_2, hexanes: EtOAc = 4:1, R_f = 0.24); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 6 H, *J* = 7.2 Hz), 2.06 (s, 3 H), 2.12 (s, 3 H), 2.40 (s, 3 H), 3.40 (s, 2 H), 3.48 (s, 2 H), 4.19 (q, 4 H, *J* = 7.2 Hz), 4.52 (bs, 4 H), 7. 31 (d, 2 H, *J* = 8.1 Hz), 7.77 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 15.6, 21.5, 38.8, 39.8, 53.0, 53.6, 60.0, 61.8, 127.5, 128.5, 129.5, 129.8, 131.0, 131.7, 133.9, 134.5, 139.2, 143.6, 171.5; IR (neat, cm^{-1}): 2978 (m), 2923 (m), 2854 (w), 1732 (s), 1596 (w), 1450 (w), 1346 (m), 1281 (m),

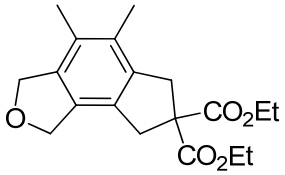
1250 (s), 1190 (m), 1165 (s), 1099 (m), 1065 (m), 1018 (w), 860 (w), 817 (w), 736 (w), 667 (s); LR-MS *m/z* calcd for $C_{26}H_{31}NO_6S$ (M^+) 485.6, found (M + 1*)*: 486.1; HRMS (ES) m/z calcd for $C_{26}H_{32}NO_6S$ $(M + H)^+$: 486.1950, found 486.1947 (Δ 0.6 ppm).

4,6-Dimethyl-8,8-di(carbethoxy)-1,3,7,8-tetrahydro-5-oxo-2-oxa-cyclopenta[*e*]azulene (2-19e)



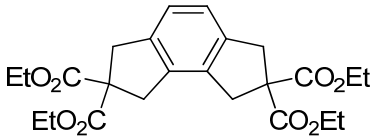
Yellow solid; m.p. 64-66 °C; TLC (SiO_2, hexanes: EtOAc = 9:1, R_f = 0.04); ^{1}H NMR (300 MHz, $CDCl_3$): δ1.26 (t, 6 H, *J* = 7.2 Hz), 2.12 (s, 3 H), 2.27 (s, 3 H), 3.30 (s, 2 H), 3.55 (s, 2 H), 4.22 (q, 4 H, *J* = 7.2 Hz), 4.93 (s, 2 H), 5.01 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 17.9, 19.2, 41.1, 43.0, 57.9, 62.2, 74.8, 75.4, 136.4, 137.4, 139.0, 142.8, 145.6, 147.2, 170.6, 183.5; IR (neat, cm^{-1}): 2982 (m), 2924 (s), 2851 (m), 1732 (s), 1678 (w), 1566 (m), 1535 (w), 1447 (m), 1369 (m), 1296 (m), 1254 (s), 1196 (m), 1161 (m), 1068 (m), 1018 (w), 941 (w), 860 (w). ; HRMS (ES) m/z calcd for $C_{20}H_{25}O_6$ $(M + H)^+$: 361.1651, found 361.1644 (Δ 1.9 ppm).

4,5-Dimethyl-7,7-di(carbethoxy)-1,3,6,8-tetrahydro-2-oxa-*as*-indacene (2-20e)



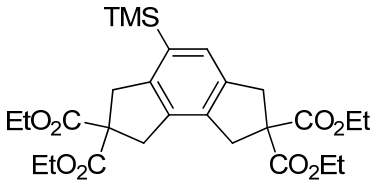
Yellow solid; m.p. 86-88 °C; TLC (SiO_2, hexanes: EtOAc = 9:1, R_f = 0.30); ^{1}H NMR (300 MHz, $CDCl_3$): δ1.26 (t, 6 H, *J* = 7.2 Hz), 2.10 (s, 3 H), 2.18 (s, 3 H), 3.46 (s, 2 H), 3.53 (s, 2 H), 4.21 (q, 4 H, *J* = 7.2 Hz), 5.05 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 15.4, 15.8, 39.0, 39.7, 60.2, 61.7, 73.1, 73.6, 128.1, 129.7, 131.0, 131.3, 137.6, 138.8, 171.7; IR (neat, cm^{-1}): 2978 (m), 2935 (m), 2905 (m), 2854 (m), 1732 (s), 1458 (m), 1447 (m), 1366 (m), 1277 (s), 1250 (s), 1188 (s), 1157 (s), 1095 (s), 1049 (w), 1014 (w), 906 (w), 860 (w) ; HRMS (ES) m/z calcd for $C_{19}H_{25}O_5$ $(M + H)^+$: 333.1702, found 333.1696 (Δ 1.8 ppm).

2,2,7,7-Tetra(carbethoxy)-1,3,6,8-tetrahydro-*as*-indacene (2-20f)



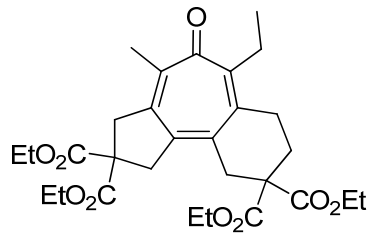
White solid; m.p. 74-75 °C; TLC (SiO_2, hexanes: EtOAc = 9:1, R_f = 0.28); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 12 H, *J* = 7.2 Hz), 3.50 (s, 4 H), 3.55 (s, 4 H), 4.20 (q, 8 H, *J* = 7.2 Hz), 7.00 (s, 2 H); LR-MS *m/z* calcd for $C_{24}H_{30}O_8$ (M^+) 446.5, found (M+ 1): 447.1. The data were consistent with literature values.[12]

4-Trimethylsilyl-2,2,7,7-tetra(carbethoxy)-1,3,6,8-tetrahydro-*as*-indacene (2-20g')



White solid; m.p. 83-85 °C; TLC (SiO_2, hexanes: EtOAc = 9:1, R_f = 0.30); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.28 (s, 9 H), 1.25 (t, 12 H, *J* = 7.2 Hz), 3.48 and 3.50 (s and s, 4 H), 3.56 and 3.59 (s and s, 4 H), 4.20 (q, 8 H, *J* = 7.2 Hz), 7.15 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.8, 14.0, 38.3, 39.1, 40.4, 41.3, 60.2, 60.7, 61.7, 128.2, 133.7, 135.1, 136.9, 138.3, 144.2, 171.6, 171.7; IR (neat, cm^{-1}): 2982 (s), 2959 (m), 2874 (m), 1732 (s), 1447 (m), 1427 (m), 1389 (m), 1366 (m), 1249 (s), 1188 (s), 1157 (s), 1095 (m), 1068 (s), 1045 (m), 1011 (m), 968 (w), 872 (s), 837 (s), 756 (m); LR-MS *m/z* calcd for $C_{27}H_{38}O_8Si$ (M^+) 518.7, found (M+ 1): 519.2; HRMS (ES) m/z calcd for $C_{27}H_{39}O_8Si$ $(M + H)^+$: 519.2414, found 519.2407 (Δ 1.3 ppm).

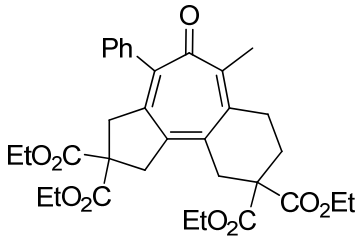
4-Methyl-6-ethyl-2,2,9,9,tetra(carbethoxy)-1,3,7,8,9-pentahydro-5-oxo-benzo[*e*]azulene (2-19h)



Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, 3 H, *J* = 7.5 Hz), 1.25 (m, 12 H), 2.18 (s, 3 H), 2.23 (t, 2 H, *J* = 6.3 Hz), 2.71 (m, 4 H), 3.05 (s, 2 H), 3.43 (s, 2 H), 3.63 (s, 2 H), 4.20 (m,

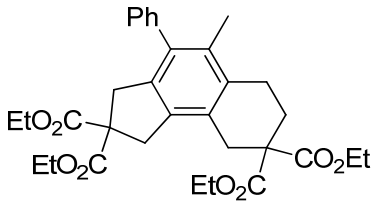
8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 14.22, 18.82, 25.72, 27.70, 28.51, 35.68, 42.12, 42.38, 53.77, 56.94, 61.95, 62.17, 135.08, 140.22, 141.07, 143.73, 144.64, 146.81, 171.22, 171.71, 188.48; LR-MS *m/z* calcd for $C_{27}H_{34}O_9$ (M^+) 530.6, found (M+ 1): 530

4-Phenyl-6-methyl-2,2,9,9-tetra(carbethoxy)-1,3,7,8,9-pentahydro-5-oxo-benzo[*e*]azulene (2-19j)



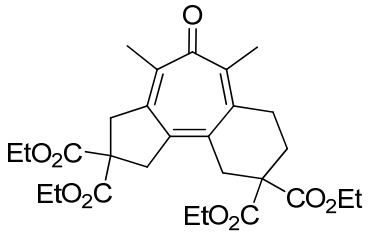
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (m, 12 H), 2.20 (s, 3 H), 2.26 (t, 2 H, *J* = 6.3 Hz), 2.71 (t, 2 H, *J* = 6.3 Hz), 3.08 (s, 2 H), 3.13 (s, 2 H), 3.60 (s, 2 H), 4.18 (m, 8 H), 7.24-7.40 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.90, 13.98, 18.47, 27.77, 28.18, 35.80, 41.73, 42.98, 53.47, 57.08, 61.75, 61.83, 127.40, 128.03, 129.10, 135.82, 138.81, 14.046, 141.61, 142.76, 143.01, 144.93, 170.71, 171.27, 187.14.

4-Phenyl-5-methyl-2,2,8,8-tetra(carbethoxy)-3,6,7,8,9-pentahydro-1*H*-cyclopenta[*a*]naphthalene (2-20j)



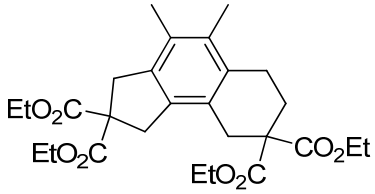
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (m, 12 H), 1.92 (s, 3 H), 2.36 (t, 2 H, *J* = 6.6 Hz), 2.68 (t, 2 H, *J* = 6.6 Hz), 3.18 (s, 2 H), 3.27 (s, 2 H), 3.57 (s, 2 H), 4.18 (m, 8 H), 7.16-7.19 (m, 2 H), 7.31-7.43 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.98, 14.02, 16.32, 24.37, 28.05, 32.59, 39.35, 40.47, 52.96, 59.72, 61.44, 61.56, 126.61, 128.25, 128.38, 129.23, 132.08, 132.64, 135.35, 136.11, 136.18, 140.52, 171.41, 171.75.

4,6-Dimethyl-2,2,9,9-tetra(carbethoxy)-1,3,7,8,9-pentahydro-5-oxo-benzo[*e*]azulene (2-19k)



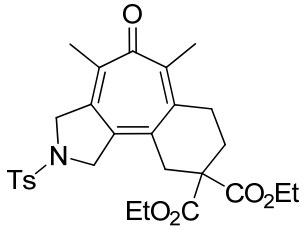
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21-1.28 (m, 14H), 2.19-2.23 (m, 8H), 2.69 (t, 2H, *J* = 6.6 Hz), 3.04 (s, 2H), 3.45 (s, 2H), 3.61 (s, 2H), 4.15-4.24 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.97, 18.61, 18.68, 27.83, 28.36, 35.84, 41.98, 42.20, 53.42, 56.71, 61.70, 61.94, 134.58, 139.61, 140.84, 141.12, 143.1, 144.66, 170.95, 171.30, 188.19.

4,5-Dimethyl-2,2,8,8-tetra(carbethoxy)-3,6,7,8,9-pentahydro-1*H*-cyclopenta[*a*]naphthalene (2-20k)



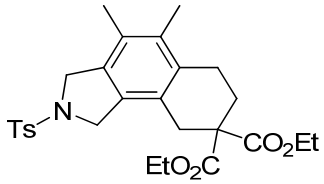
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21-1.28 (m, 12 H), 2.07 (s, 3 H), 2.15 (s, 3 H), 2.31 (t, 2 H, *J*= 6.6 Hz), 2.67 (t, 2 H, *J* = 6.6 Hz), 3.11 (s, 2 H), 3.53 (s, 2 H), 3.54 (s, 2 H), 4.14-4.24 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.01, 14.7, 16.29, 24.44, 28.17, 32.51, 39.3, 40.16, 52.92, 59.44, 61.36, 61.62, 126.55, 129.56, 131.62, 133.18, 135.19, 136.37, 171.40, 171.92.

4,6-Dimethyl-9,9-di(carbethoxy)-2-(4-methylbenzenesulfonyl)-1,3,7,8,9-pentahydro-5-oxo-2-aza-benzo[*e*]azulene (2-19l)



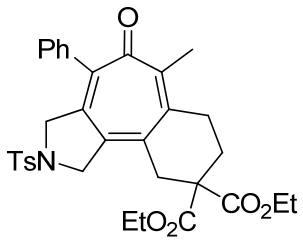
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 6 H, *J* = 7.2 Hz), 2.08 (s, 3 H), 2.07 (m, 5 H), 2.41 (s, 3 H), 2.69 (t, 2 H, *J*= 6.6 Hz), 2.88 (s, 2 H), , 4.19 (q, 4 H, *J* = 7.2 Hz), 4.40 (s, 2 H), 4.61 (s, 2 H), 7.33 (d, 2 H, *J* = 8.1 Hz), 7.78 (d, 2 H, *J* = 8.1 Hz).

4,5-Dimethyl-8,8-di(carbethoxy)-2-(4-methylbenzenesulfonyl)-3,6,7,8,9-pentahydro-2-aza-1*H*-cyclopenta[*a*]naphthalene (2-20l)



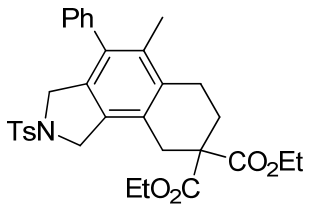
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, 6 H, *J* = 7.2 Hz), 2.05 (s, 3 H), 2.07 (s, 3 H), 2.30 (t, 2 H, *J* = 6.6 Hz), 2.40 (s, 3 H), 2.65 (t, 2 H, *J* = 6.6 Hz), 2.98 (s, 2 H), 4.16 (q, 4 H, *J* = 7.2 Hz), 4.57 (s, 4 H), 7.31 (d, 2 H, *J* = 8.1 Hz), 7.77 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.21, 14.84, 16.39, 21.66, 24.55, 28.19, 32.37, 52.84, 53.61, 54.17, 61.76, 125.85, 127.71, 128.64, 130.03, 131.71, 132.81, 132.98, 134.06, 134.48, 143.76, 171.31; HRMS (ES) m/z calcd for $C_{27}H_{34}NO_6S$ $(M + H)^+$: 500.2107, found 500.2105 (Δ 0.4 ppm).

4-Phenyl-6-methyl-9,9-di(carbethoxy)-2-(4-methylbenzenesulfonyl)-1,3,7,8,9-pentahydro-5-oxo-2-aza-benzo[*e*]azulene (2-19m)



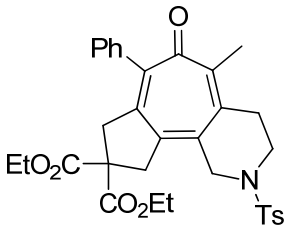
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 6 H, *J* = 7.2 Hz), 2.18 (s, 3 H), 2.25 (t, 2 H, *J* = 6.3 Hz), 2.42 (s, 3 H), 2.70 (t, 2 H, *J* = 6.3 Hz), 2.91 (s, 2 H), 4.09 (s, 2 H), 4.22 (q, 4 H, *J* = 7.2 Hz), 4.61 (s, 2 H), 7.15-7.18 (m, 2 H), 7.29-7.41 (m, 5 H), 7.60-7.61 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.03, 18.70, 21.54, 27.74, 28.07, 35.49, 53.26, 54.55, 55.09, 62.01, 127.71, 128.26, 128.33, 12.73, 129.86, 132.80, 135.59, 136.56, 137.11, 140.49, 140.54, 142.29, 144.05, 144.28, 171.01, 186.41; HRMS (ES) m/z calcd for $C_{33}H_{36}NO_7S$ $(M + H)^+$: 590.2212, found 590.2208 (Δ 0.7 ppm).

4-Phenyl-5-methyl-8,8-di(carbethoxy)-2-(4-methylbenzenesulfonyl)-3,6,7,8,9-pentahydro-2-aza-1*H*-cyclopenta[*a*]naphthalene (2-20m)



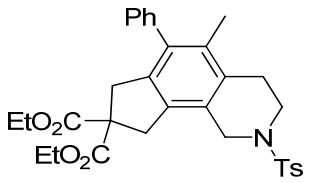
Light yellow oil;[1]H NMR (300 MHz, $CDCl_3$): δ1.25 (t, 6 H, *J* = 7.2 Hz), 1.90 (s, 3 H), 2.35 (t, 2 H, *J* = 6.9 Hz), 2.40 (s, 3 H), 2.66 (t, 2 H, *J* = 6.9 Hz), 3.05 (s, 2 H), , 4.19 (q, 4 H, *J* = 7.2 Hz), 4.29 (s, 2 H), 4.59 (s, 2 H), 7.05-7.09 (m, 2 H), 7.28-7.42 (m, 5 H), 7.66-7.72 (m, 2 H); [13]C NMR (100 MHz, $CDCl_3$) δ 13.98, 16.12, 21.41, 24.24, 27.84, 29.62, 32.19, 52.63, 53.27, 54.01, 61.59, 127.19, 127.30, 127.44, 128.52, 128.67, 129.74, 131.65, 132.50, 133.08, 133.77, 134.95, 139.23, 143.47, 171.05; HRMS (ES) m/z calcd for $C_{32}H_{36}NO_6S$ $(M + H)^+$: 562.2263, found 562.2265 (Δ 0.4 ppm).

4-Phenyl-6-methyl-2,2-di(carbethoxy)-9-(4-methylbenzenesulfonyl)-1**,3,7,8,9-pentahydro-5-oxo-9-aza-benzo[*e*]azulene (2-19n)**



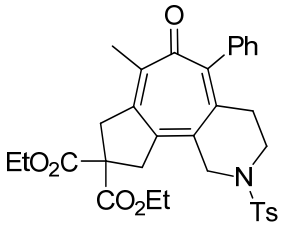
Light yellow oil; [1]H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, 6 H, *J* = 7.2 Hz), 2.04 (s, 2 H), 2.10 (s, 3 H), 2.43 (s, 3 H), 2.77 (t, 2 H, *J* = 6.3 Hz), 3.12 (s, 2 H), 3.38-3.42 (m, 4 H), 4.17 (q, 4 H, *J* = 7.2 Hz), 7.22-7.25 (m, 2 H), 7.28-7.42 (m, 5 H), 7.65-7.69 (m, 2 H); [13]C NMR (100 MHz, $CDCl_3$) δ 14.27, 18.83, 21.86, 30.51, 41.08, 43.10, 43.56, 48.72, 57.65, 62.39, 127.87, 128.03, 128.40, 129.45, 130.12, 133.81, 134.04, 138.45, 138.55, 139.23, 142.29, 144.1, 144.58, 144.72, 170.79, 187.07.

4-Phenyl-5-methyl-2,2-di(carbethoxy)-8-(4-methylbenzenesulfonyl)-3,6,7,8,9-pentahydro-8-aza-1*H*-cyclopenta[*a*]naphthalene (2-20n)



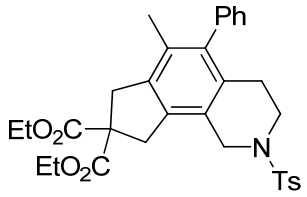
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, 6 H, *J* = 7.2 Hz), 1.91 (s, 3 H), 2.44 (s, 3 H), 2.81 (t, 2 H, *J* = 5.7 Hz), 3.24 (s, 2 H), 3.37 (t, 2 H, *J* = 5.7 Hz), 3.45 (s, 2 H), 4.13 (s, 2 H), 4.16 (q, 4 H, *J* = 7.2 Hz), 7.10-7.14 (m, 2 H), 7.26-7.43 (m, 5 H), 7.74-7.76 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.98, 16.12, 21.51, 27.36, 38.59, 40.20, 43.69, 46.06, 59.84, 61.75, 126.61, 126.90, 127.83, 128.41, 129.02, 129.70, 130.76, 133.00, 133.56, 136.84, 137.02, 140.00, 143.9, 171.53.

4-Methyl-6-phenyl-2,2-di(carbethoxy)-9-(4-methylbenzenesulfonyl)-1,3,7,8,9-pentahydro-5-oxo-9-aza-benzo[*e*]azulene (2-19o)



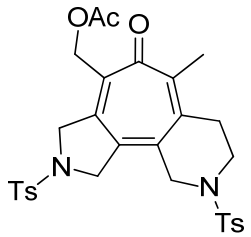
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, 6 H, *J* = 7.2 Hz), 2.16 (s, 3 H), 2.38 (m, 5 H), 3.26 (t, 2 H, *J* = 6.6 Hz), 3.49 (s, 2 H), 3.51 (s, 2 H), 4.27 (m, 6 H), 6.92-6.95 (m, 2 H), 7.20-7.38 (m, 5 H), 7.58-7.60 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.23, 18.91, 21.69, 30.97, 41.58, 42.43, 43.64, 47.68, 57.08, 62.50, 127.49, 127.57, 128.57, 128.87, 129.93, 133.97, 134.21, 139.88, 140.05, 141.04, 143.47, 144.37, 144.80, 146.13, 170.89, 186.13; HRMS (ES) m/z calcd for $C_{33}H_{36}NO_7S$ $(M + H)^+$: 590.2212, found 590.2208 (Δ 0.7 ppm).

4-Methyl-5-phenyl-2,2-di(carbethoxy)-8-(4-methylbenzenesulfonyl)-3,6,7,8,9-pentahydro-8-aza-1*H*-cyclopenta[*a*]naphthalene (2-20o)



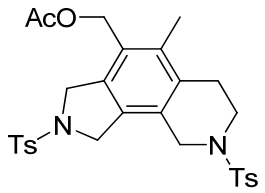
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, 6 H, *J* = 7.2 Hz), 1.88(s, 3 H), 2.42 (m, 5 H), 3.18 (t, 2 H, *J* = 5.7 Hz), 3.48 (s, 2 H), 3.54 (s, 2 H), 4.14 (s, 2 H), 4.23 (t, 4 H, *J* = 7.2 Hz), 6.98-7.02 (m, 2 H), 7.30-7.42 (m, 5 H), 7.65-7.72 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.23, 17.16, 21.68, 28.52, 38.95, 39.99, 43.92, 46.03, 59.75, 62.09, 125.02, 127.09, 127.95, 128.73, 129.37, 129.88, 130.35, 130.38, 133.35, 135.38, 137.42, 140.12, 140.74, 143.82, 171.92; HRMS (ES) m/z calcd for $C_{32}H_{36}NO_6S$ $(M + H)^+$: 562.2263, found 562.2266 (Δ 0.5 ppm).

4-Acetoxymethyl-6-methyl-2,9-di(4-methylbenzenesulfonyl)-1,3,7,8,9-pentahydro-5-oxo-2,9-diaza-benzo[*e*]azulene (2-19p)



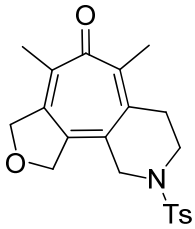
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02(s, 3 H), 2.14 (s, 3 H), 2.42 (s, 3 H), 2.43 (s, 3 H), 2.30 (t, 2 H, *J* = 6.3 Hz), 3.30 (t, 2 H, *J* = 6.3 Hz), 3.90 (s, 2 H), 4.32 (s, 2 H), 4.46 (s, 2 H), 4.93 (s, 2 H), 7.28-7.36 (m, 4 H), 7.61-7.79 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.57, 21.54, 21.95, 30.31, 45.72, 46.51, 52.11, 54.12, 62.66, 126.19, 126.43, 127.79, 128.12, 29.59, 130.13, 130.76, 131.96, 132.55, 133.68, 134.84, 136.96, 143.87, 144.11, 170.62, 186.77.

4-Acetoxymethyl-5-methyl-2,8-di(4-methylbenzenesulfonyl)-3,6,7,8,9-pentahydro-2,8-diaza-1*H*-cyclopenta[*a*]naphthalene (2-20p)



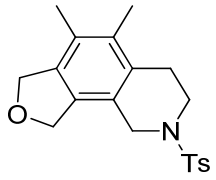
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02(s, 3 H), 2.16 (s, 3 H), 2.41 (s, 3 H), 2.44 (s, 3 H), 2.30 (t, 2 H, *J* = 5.7 Hz), 3.30 (t, 2 H, *J* = 5.7 Hz), 3.94 (s, 2 H), 4.44 (s, 2 H), 4.67 (s, 2 H), 4.98 (s, 2 H), 7.32-7.38 (m, 4 H), 7.69-7.80 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.66, 20.92, 21.74, 27.53, 43.68, 45.82, 52.49, 53.29, 61.66, 127.19, 127.43, 127.79, 128.00, 130.09, 130.15, 130.84, 132.43, 132.76, 133.72, 134.84, 136.41, 144.11, 144.27, 170.80; HRMS (ES) m/z calcd for $C_{29}H_{33}N_2O_6S_2$ $(M + H)^+$: 569.1780, found 569.1780 (Δ 0.0 ppm).

4,6-Dimethyl-9-(4-methylbenzenesulfonyl)-1**,3,7,8,9-pentahydro-5-oxo-2-oxa-9-aza-benzo[*e*]azulene (2-19q)**



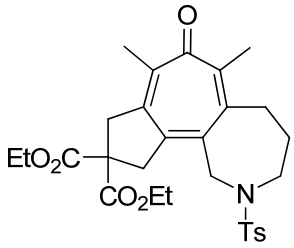
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3 H), 2.22 (s, 3 H), 2.41 (s, 3 H), 2.84 (t, 2 H, *J* = 6.3 Hz), 3.36 (t, 2 H, *J* = 6.3 Hz), 3.92 (s, 2 H), 4.92 (s, 2 H), 4.94 (s, 2 H), 7.30 (d, 2 H, *J* = 8.1 Hz), 7.65 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.87, 19.11, 21.75, 31.03, 43.36, 47.67, 74.23, 74.95, 127.78, 130.06, 130.75, 133.38, 138.73, 138.85, 139.59, 143.82, 144.48, 144.60, 186.13; HRMS (ES) m/z calcd for $C_{21}H_{24}NO_4S$ $(M + H)^+$: 386.1426, found 386.1427 (Δ 0.3 ppm).

4,5-Dimethyl-8-(4-methylbenzenesulfonyl)-3,6,7,8,9-pentahydro-2-oxa-8-aza-1*H*-cyclopenta[*a*]naphthalene (2-20q)



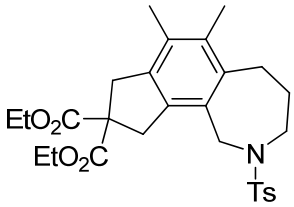
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3 H), 2.12 (s, 3 H), 2.43 (s, 3 H), 2.83 (t, 2 H, *J* = 5.7 Hz), 3.35 (t, 2 H, *J* = 5.7 Hz), 4.01 (s, 2 H), 5.00 (s, 2 H), 5.07 (s, 2 H), 7.33 (d, 2 H, *J* = 8.1 Hz), 7.72 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.62, 16.69, 21.72, 27.61, 44.03, 45.90, 73.08, 73.97, 122.94, 128.00, 128.18, 129.96, 130.89, 132.72, 133.25, 134.18, 136.48, 143.99; HRMS (ES) m/z calcd for $C_{20}H_{24}NO_3S$ $(M + H)^+$: 358.1477, found 358.1478 (Δ 0.3 ppm).

10,10-Di(carbethoxy)-6,8-dimethyl-7-oxo-2-(4-methylbenzenesulfonyl)-2,3,4,5,9,11-hexahydro-1*H*-azuleno[4,5-*c*]azepine (2-19r)



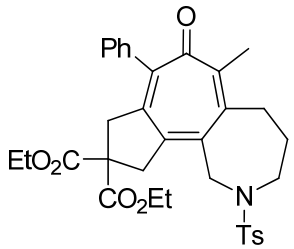
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.62 (m, 2 H), 1.97 (s, 3 H), 2.14 (s, 3 H), 2.37 (s, 3 H), 2.61 (m, 2 H), 3.38 (s, 2 H), 3.57 (t, 2 H, *J* = 5.7 Hz), 3.62 (s, 2 H), 4.20 (q, 4 H, *J* = 7.2 Hz), 4.48 (s, 2 H), 7.07 (d, 2 H, *J* = 8.1 Hz), 7.76 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15, 17.96, 18.78, 21.58, 26.55, 33.07, 41.38, 41.84, 50.61, 52.29, 57.09, 62.24, 126.81, 129.76, 136.71, 136.78, 140.07, 140.11, 141.89, 143.74, 144.37, 145.69, 171.01, 189.41; HRMS (ES) m/z calcd for $C_{29}H_{36}NO_7S$ $(M + H)^+$: 542.2212, found 542.2215 (Δ 0.6 ppm).

6,7-Dimethyl-9,9-di(carbethoxy)-2-(4-methylbenzenesulfonyl)-2,3,4,5,8,10-hexahydroindeno[4,5-*c*]azepine (2-20r)



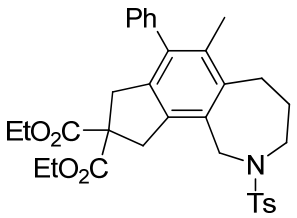
Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 6 H, *J* = 7.2 Hz), 1.62 (m, 2 H), 2.11 (s, 3 H), 2.18 (s, 3 H), 2.90 (s, 3 H), 2.80 (m, 2 H), 3.46 (t, 2 H, *J* = 5.7 Hz), 3.55 (s, 2 H), 3.75 (s, 2 H), 4.20 (q, 4 H, *J* = 7.2 Hz), 4.36 (s, 2 H), 7.19 (d, 2 H, *J* = 8.4 Hz), 7.52 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.20, 15.76, 17.29, 21.66, 26.88, 28.71, 39.61, 40.49, 49.39, 51.35, 59.61, 61.92; HRMS (ES) m/z calcd for $C_{28}H_{36}NO_6S$ $(M + H)^+$: 514.2263, found 514.2260 (Δ 0.6 ppm).

10,10-Di(carbethoxy)-6-methyl-8-phenyl-7-oxo-2-(4-methylbenzenesulfonyl)-2,3,4,5,9,11-hexahydro-1*H*-azuleno[4,5-*c*]azepine (2-19s)



Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 6 H, *J* = 7.2 Hz), 1.67 (m, 2 H), 1.94 (s, 3 H), 2.40 (s, 3 H), 2.65 (m, 2 H), 3.09 (s, 2 H), 3.64 (t, 2 H, *J* = 5.7 Hz), 3.68 (s, 2 H), 4.18 (q, 4 H, *J* = 7.2 Hz), 4.54 (s, 2 H), 7.13 (d, 2 H, *J* = 7.8 Hz),7.26-7.42 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.17, 17.85, 21.70, 26.66, 33.04, 41.13, 42.80, 50.94, 52.13, 57.42, 62.17, 126.85, 127.84, 128.28, 129.38, 129.87, 136.88, 137.86, 138.55, 139.65, 142.11, 143.70, 143.93, 144.55, 145.19, 170.89, 188.152; HRMS (ES) m/z calcd for $C_{34}H_{38}NO_7S$ $(M + H)^+$: 604.2369, found 604.2368 (Δ 0.2 ppm).

6-Methyl-7-phenyl-9,9-di(carbethoxy)-2-(4-methylbenzenesulfonyl)-2,3,4,5,8,10-hexahydroindeno[4,5-*c*]azepine (2-20s)



Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, 6 H, *J* = 7.2 Hz), 1.66 (m, 2 H), 1.93 (s, 3 H), 2.40 (s, 3 H), 2.84 (m, 2 H), 3.25 (s, 2 H), 3.54 (t, 2 H, *J* = 5.7 Hz), 3.82 (s, 2 H), 4.16 (q, 4 H, *J* = 7.2 Hz), 4.44 (s, 2 H), 7.15-7.24 (m, 4 H), 7.27-7.55 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.20, 17.32, 21.70, 26.63, 28.98, 39.64, 40.79, 49.40, 51.76, 59.93, 61.89, 127.03, 127.40, 128.65, 129.19, 129.67, 132.07, 132.49, 136.28, 136.82, 137.21, 138.66, 139.45, 140.99, 143.14, 171.94; HRMS (ES) m/z calcd for $C_{33}H_{38}NO_6S$ $(M + H)^+$: 576.2420, found 576.2424 (Δ 0.7 ppm).

§2.5. References

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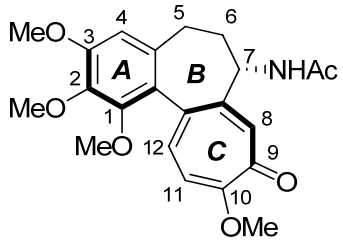
Chapter 3

Formation of Novel Colchicinoids through Rh-Catalyzed [2+2+2+1] Cycloaddition of Triynes

Table of Content

§ 3.1. Introduction

Colchicine (**Figure 3-1**), a toxic natural product, is one of the main alkaloids isolated from meadow saffron (*Colchicum autumnale* L.). It was first isolated by Pelletier and Caventou in 1820.[1] The correct structure of colchicine eluded scientists for more than a century. Major progress of structure elucidation was made by Dewar in 1945, who assumed that ring C was a cycloheptatrienolone with aromatic character.[2] The correct structure of colchicine was confirmed by X-ray crystal-structure analysis in 1952.[3]

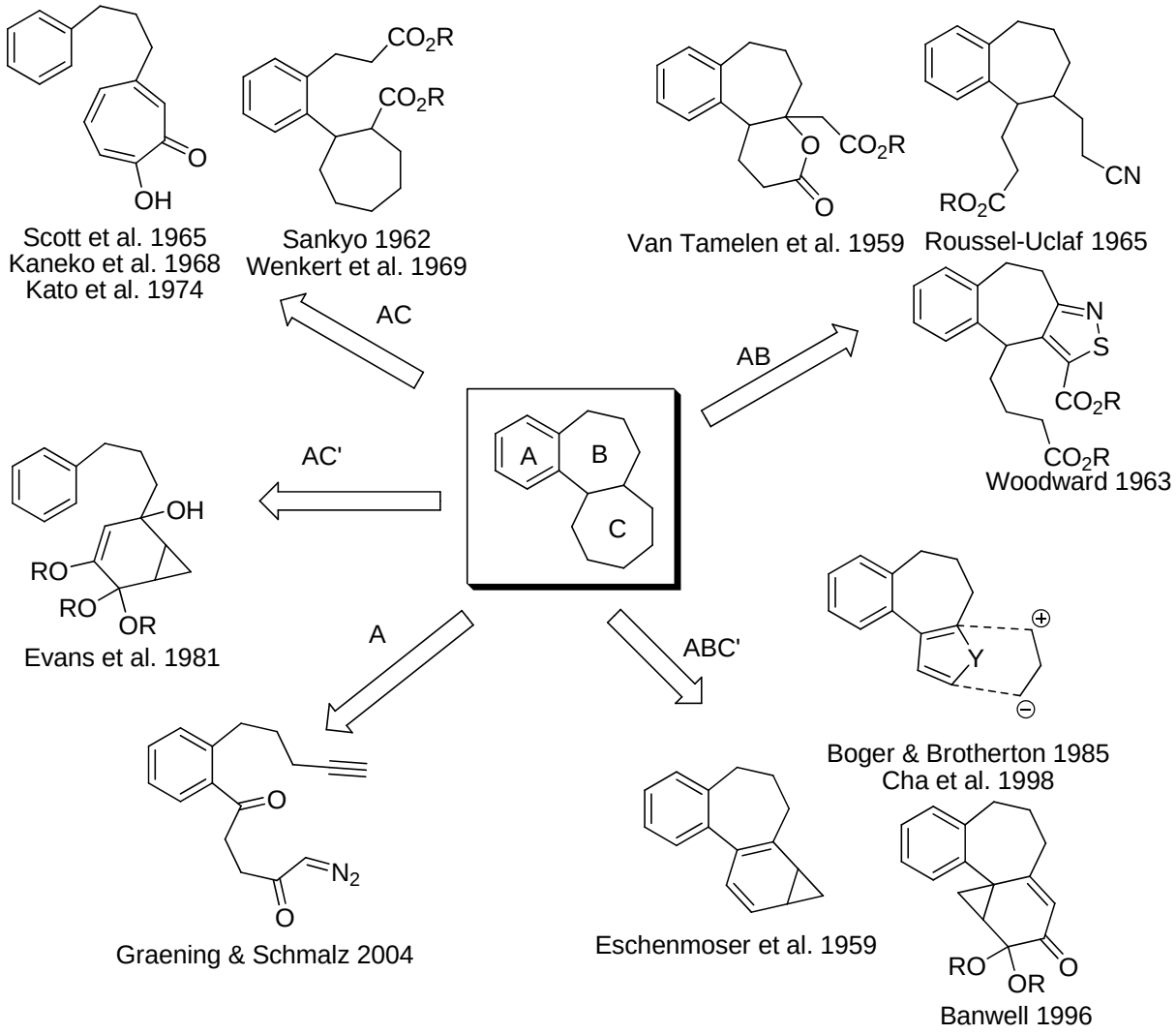


(-)-(a*R,7S*)-*Colchicine*

Figure 3-1: Structure of Colchicine.

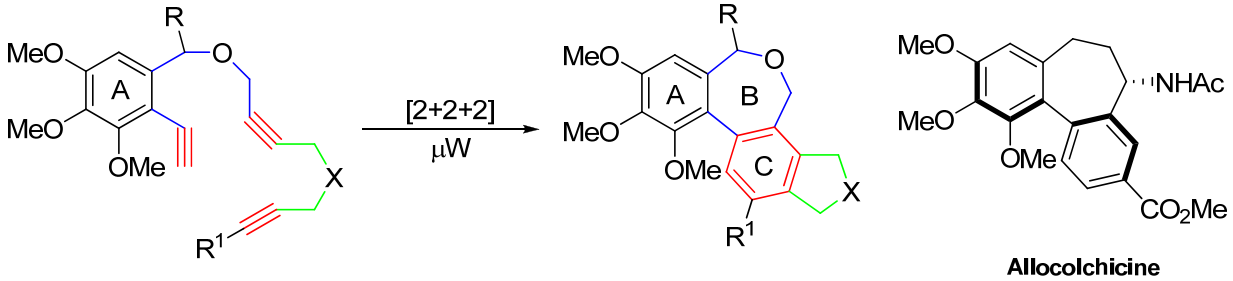
Colchicine is one of the oldest known drugs and has been used for more than 2000 years in the treatment of acute gout, and remarkably, it's still being used for this purpose despite dosing issues concerning its toxicity.[1] It is also prescribed for its cathartic and emetic effects. Colchicine can also act as an antimitotic agent by binding to tubulin. It disrupts the tubulin/microtubule equilibrium in such a manner that mitosis is arrested in metaphase.[4] Therefore, this compound can be used to selectively damage rapidly proliferating cancer cells.[5]

Since the confirmation of the structure of colchicine in 1952, this deceptively simple structure has been an important target molecule in natural product synthesis over the past six decades. A considerable number of very distinct synthetic approaches have been reported (Scheme **3-1**).[1] However, the search for more efficient routes to colchicine and its analogues still remains a challenging goal, especially with respect to the construction of the unique 7-7 annulated tropolone substructure (ring B and C).[6]



Scheme 3-1: Retrosynthetic classification of colchicine syntheses.

In 2009, Nicolaus *et al.* reported a 6-oxa-allocolchicinoids synthesis based on a [2+2+2] cycloaddition approach (**Scheme 3-2**).[7] This approach opens a short and efficient route towards a variety of novel allocolchinoids, some of which exhibited apoptosis-inducing activities.



Scheme 3-2: A [2+2+2] Cycloaddition approach toward 6-oxa-allocolchicinoids

The successful examples from [2+2+2+1] cycloaddition in the formation of 5-7-7 fused tropones have prompted us to investigate the possibility of [2+2+2+1] cycloaddition approach towards the synthesis of novel colchicinoids (**Figure 3-2**).

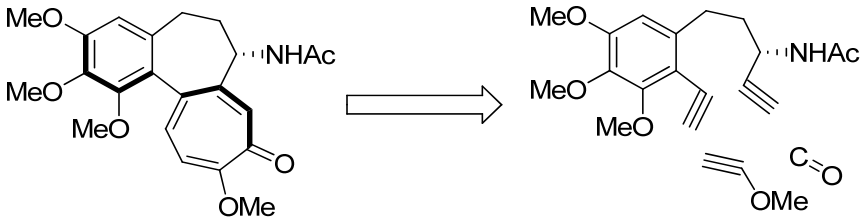
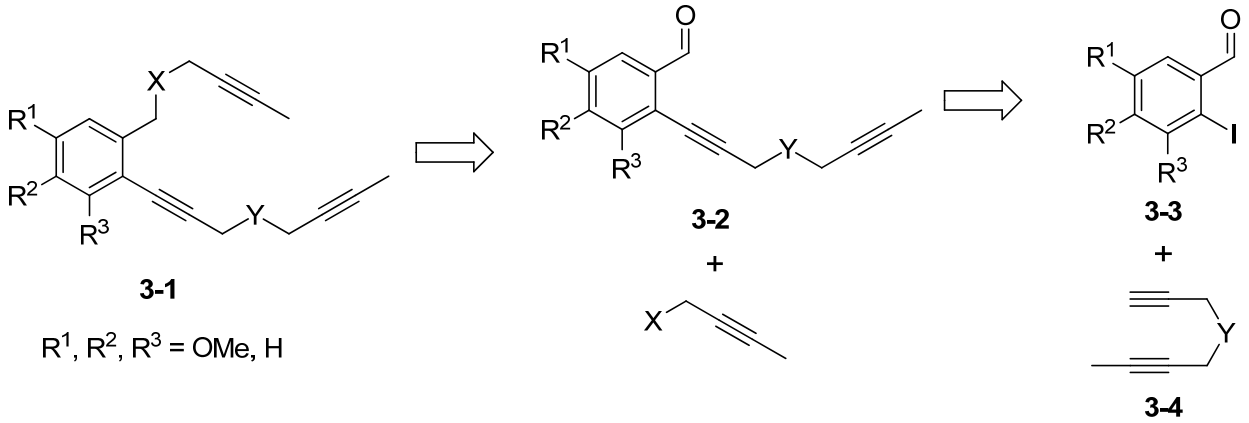


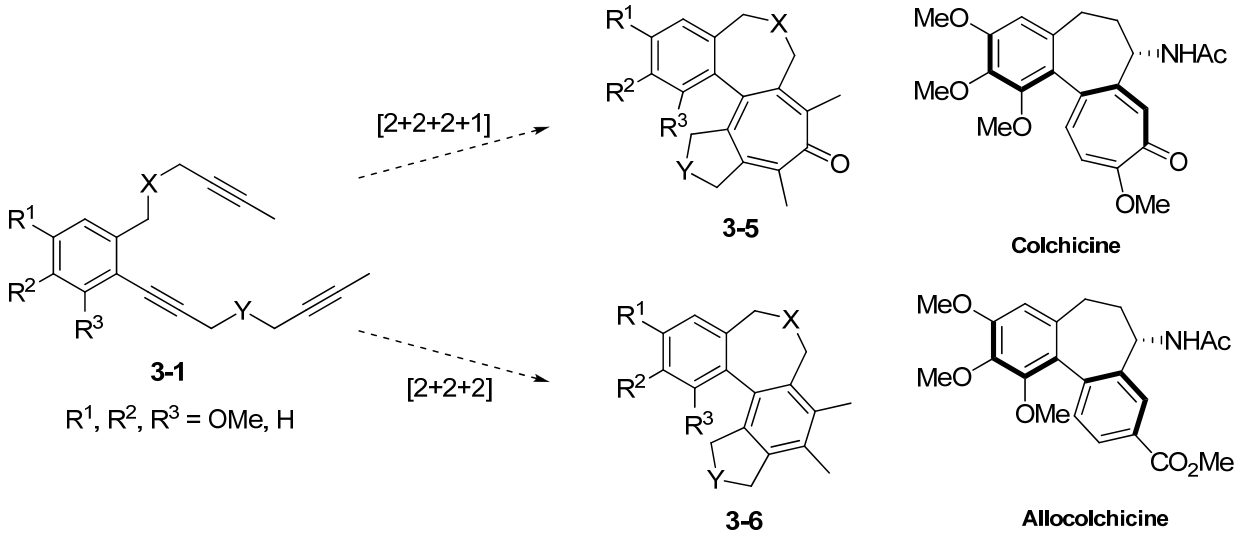
Figure 3-2: Retrosynthetic analysis of colchicines based on [2+2+2+1] cycloaddition approach.

Retrosynthesis of the designed triyne **3-1** reveals that starting from iodobenzaldehyde **3-3**, diyne moiety **3-4** could be installed through Sonogashira coupling. Modification of aldehyde group of **3-2** would allow the installation of the other alkyne component and thus furnish the desired triyne substrates **3-1** (**Scheme 3-3**).



Scheme 3-3: Retrosynthetic analysis of the design triyne substrates.

The designed triyne substrates **3-1** are expected to undergo [2+2+2+1] cycloaddition to afford 6-7-7-5 fused tetracyclics **3-5**, which possess the desired 6-7-7 fused tropone core structure of colchicine. When the triynes undergo [2+2+2] cycloadditions, 6-7-6-5 fused tetracyclics **3-6** which resemble allocolchicine are expected (**Scheme 3-4**).

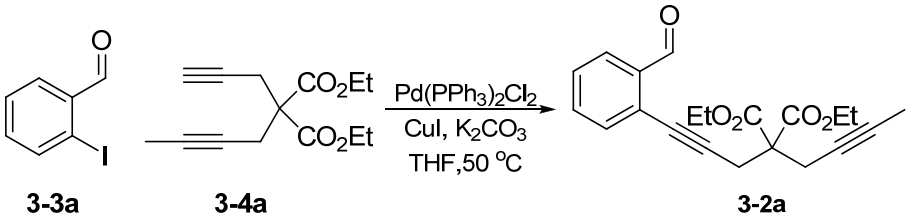


Scheme 3-4: Tetracyclics formation from cycloadditions of triyne **3-1.**

§ 3.2. Results and Discussions

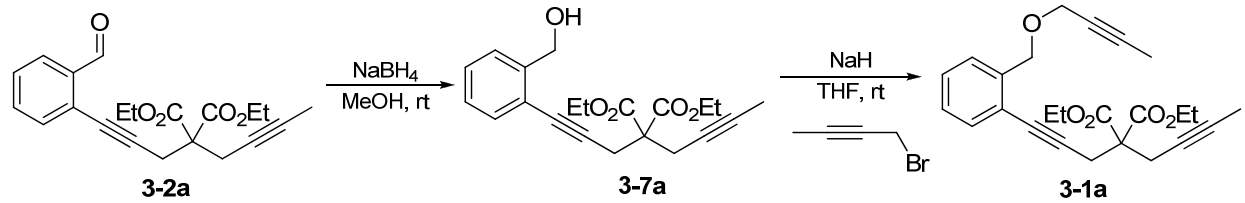
§ 3.2.1. Substrate Synthesis

The Sonogashira coupling reaction between the diyne **3-4a** and iodobenzaldehyde **3-3a** was carried out following the procedure reported by Yeom *et al* [8] to give the desired diyne-aldehyde **3-2a** in good yields (**Scheme 3-5**).

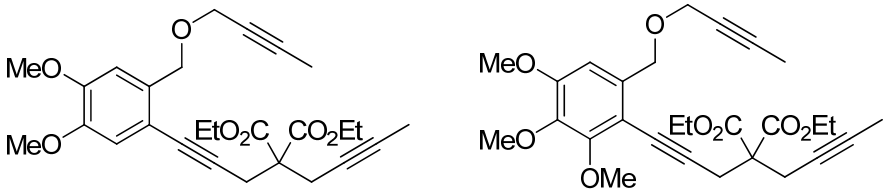


Scheme 3-5: Installation of diyne **3-4a** through Sonogashira coupling.

The diyne-aldehyde **3-2a** was then reduced to diyne-alcohol **3-7a**, followed by alkylation to give the desired triyne **3-1a** (**Scheme 3-6**). Triyne **3-1b** and **3-1c** were synthesized in a similar fashion (**Figure 3-3**).



Scheme 3-6: Synthesis of triyne **3-1a.**



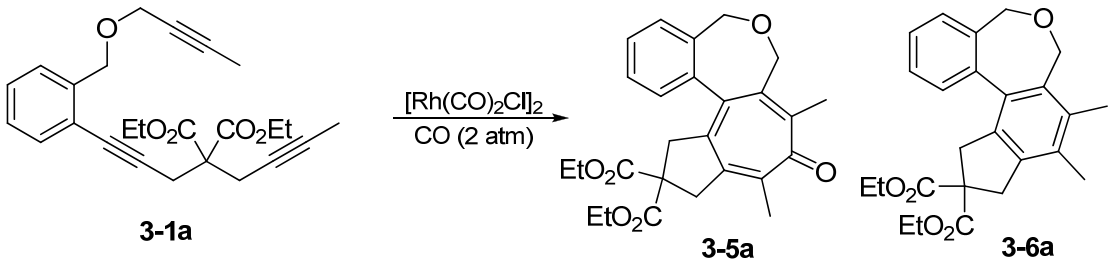
3-1b **3-1c**

Figure 3-3: Synthesized triyne **3-1b** and **3-1c.**

§ 3.2.2. Reaction Condition Optimization

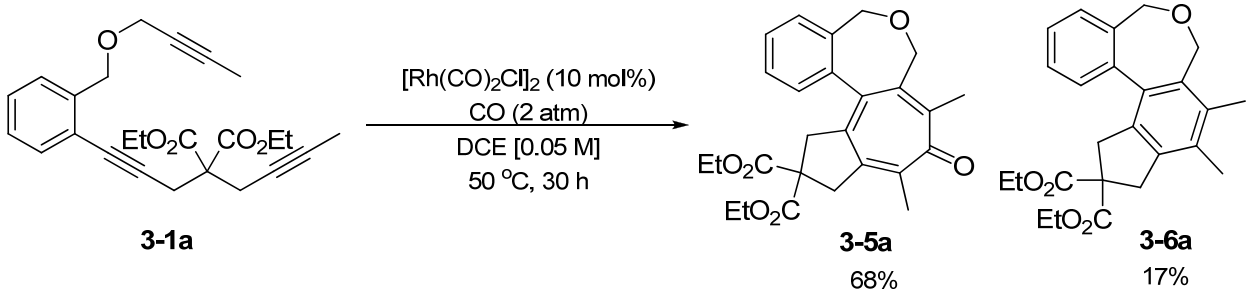
Triyne **3-1a** was used to optimize the reaction conditions; the results are summarized in **Table 3-1**. The initial trial using typical reaction conditions ($[Rh(CO)_2Cl]_2$ 5 mol%, DCE [0.05 M], 50 ^oC, 18 h) only afforded moderate conversion. However, the product selectivity greatly favored the carbonylated tetracyclic product (entry1). With extended reaction time, excellent conversion was achieved (entry 2). Under more concentrated reaction condition, the conversion was low as well as the product selectivity; these observations are likely to be caused by the lower CO concentration in the reaction system (entry 3). TFE as the solvent was detrimental to the product selectivity (entry 4). When toluene was used as solvent, and the temperature was increased to 80 ^oC, 96% conversion was obtained in 24 h, but with slight decrease in product selectivity (entry 6). The best reaction condition found so far entails using 10 mol% of the catalyst, 2 atm of CO in DCE at 50 ^oC, which gave good conversion and the best product selectivity in 24 h (entry 7).

Table 3-1: Reaction condition optimization using triyne **3-1a**.



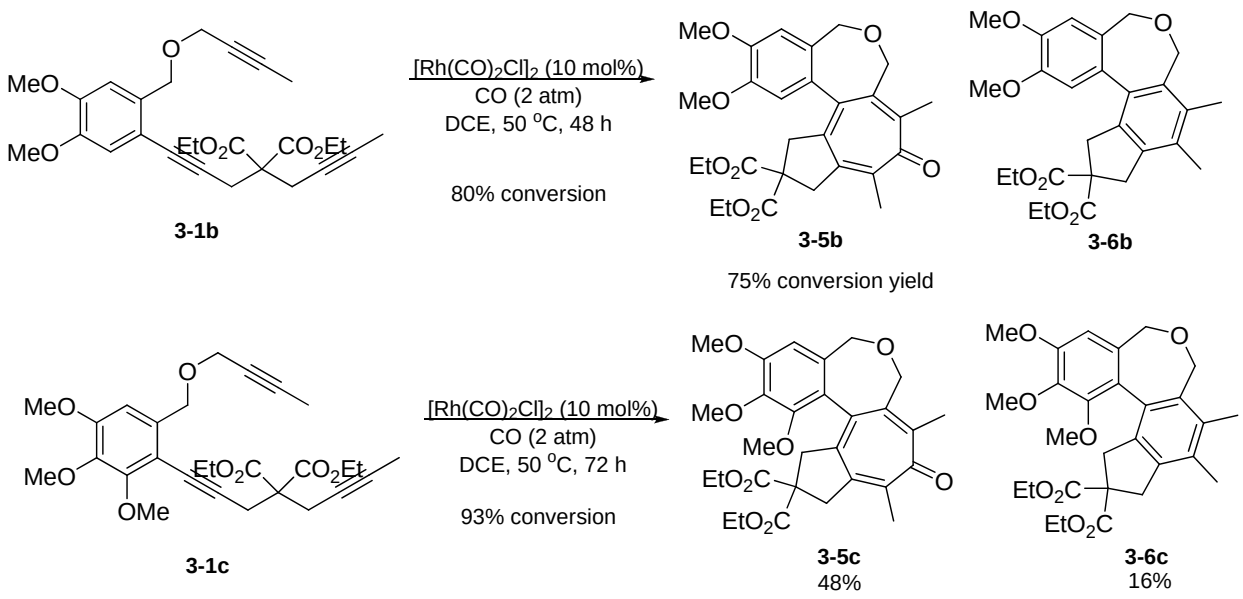
Entry	substrate quantity	Conc.	Catalyst Loading	Temp. (°C)	Solvent	Time	conversion	product ratio @ 220nm
1	25 mg	0.05 M	5 mol%	50	DCE	18 h	60-70%	5.3:1
2	25 mg	0.05 M	5 mol%	50	DCE	40 h	96-97%	4.3:1
3	100 mg	0.1 M	5 mol%	50	DCE	48 h	86-89%	4.7:1
4	25 mg	0.05 M	5 mol%	50	TFE	24 h	60%	1.5:1
5	15 mg	0.05 M	5 mol%	50–>80	$CDCl_3$	45 min 30min	60% 100%	1:3
6	20 mg	0.05 M	5 mol%	80	Toluene	24 h	96%	4.2:1
7	20 mg	0.05 M	10 mol%	50	DCE	24 h	90%	8:1

Triyne 3-1a was subjected to the optimized reaction conditions, and the product **3-5a** and **3-6a** were isolated (**Scheme 3-7**).



Scheme 3-7: Cycloaddition of triyne **3-1a** under optimized condition.

Similarly, triyne **3-1b** and **3-1c** were also subjected to the optimized reaction conditions found so far (**Scheme 3-7**). The reaction rate was slower than that of **3-1a** for both substrates. Surprisingly, triyne **3-1b** only afforded carbonylated tetracyclic product **3-5b** in 75% conversion yield, with no trace of non-carbonylated tetracyclic product **3-6b**. Triyne **3-1c** required much longer reaction time to reach good conversion with moderate product selectivity.



Scheme 3-8: Cycloaddition of triyne **3-1b** and **3-1c**.

During the spectral analysis, **3-5c** was found to be a mixture of 2 compounds in a ratio of 3:1 favoring the expected compound. The unknown compound was also found to be a carbonylated tetracyclic product. However, a more down-field carbonyl shift at 199.5 ppm in the ^{13}CNMR and the lack of absorption at the higher wavelength in the UV spectra indicate a non-conjugated system. More careful structure elucidation of the unknown product is needed.

§ 3.3. Conclusions

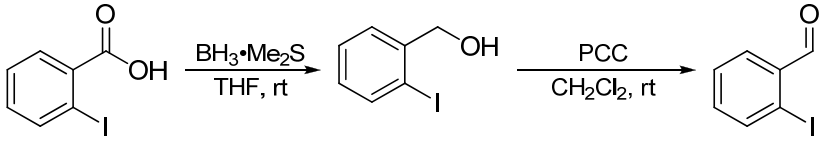
Continuing with the studies on the Rh(I)-catalyzed higher order cycloaddition of triynes, [2+2+2+1] triyne cycloaddition methodology has been applied to the formation of novel colchicinoids. The designed triyne derivatives were synthesized and subjected to the carbonylative cycloaddition and were found to afford the desired 5-7-*n*-5 fused tropone products in good yields. Studies of substrate scopes and limitations are actively under way.

§ 3.4. Experimental Section

General Information:

All chemicals were obtained from either Sigma-Aldrich or Acros Organics and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under nitrogen and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash chromatography was performed with the indicated solvents and using Fisher silica gel (particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[9] Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with Shimadzu FTIR-84005 spectrophotometer. Low-Resolution Mass Spectrometry was performed on Agilent 1100LC/MSD-VL (Flow Injection Analysis).

2-Iodobenzaldehyde (3-3a)[10]



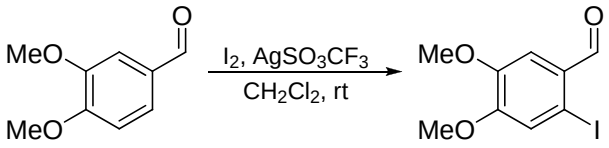
3-3a

2-Iodobenzoic acid (6.00 g, 24.2 mmol) in THF (100 mL) was added $BH_3 \cdot Me_2S$ solution (2 M in THF, 25 mL) slowly, and the reaction was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with addition of water, and the solvent was removed under reduced pressure. The crude reaction mixture was extracted with Et_2O, and the combined organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure to afford 2-iodobenzyl alcohol as light yellow oil. The crude was pure enough to carry forward into the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 2 H), 7.00 (dt, 1 H, J = 1.5, 7.8 Hz), 7.37 (dt, 1 H, J = 1.5, 7.8 Hz), 7.46 (dd, 1

H, *J* = 1.5, 7.8 Hz), 7.82 (dd, 1 H, *J* = 1.5, 7.8 Hz). All data are in agreement with those reported in the literature.[10a]

To a suspension of pyridinium chlorochromate (15.6 g, 72.6 mmol) in DCM (80 mL) was added dropwise a solution of 2-iodobenzyl alcohol (5.60 g, 24.2 mmol) in DCM (20 mL). The reaction was stirred overnight at room temperature under nitrogen atmosphere. The crude reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give 2-iodobenzaldehyde **(3-3a)** as a light yellow solid (4.923 g, 88% for 2 steps.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.50 (m, 2 H), 7.87-7.97 (m, 2 H), 10.07 (d, 1 H, *J* = 0.9 Hz). All data are in agreement with those reported in the literature.[10b]

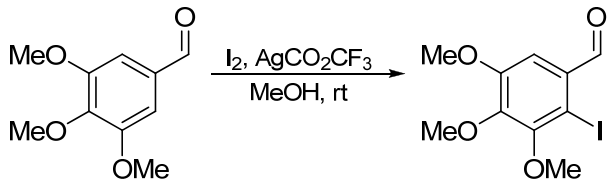
2-Iodo-4,5-dimethoxybenzaldehyde (3-3b)[11]



3-3b

To a solution of 3,4-dimethoxybenzaldehyde (1.00 g, 7.24 mmol) in DCM (70 mL) was added silver trifluoromethanesulfonate (1.86 g, 7.24 mmol). A solution of iodine (2.02 g, 7.92 mmol) in DCM (30 mL) was added dropwise to the reaction mixture, and the reaction was stirred overnight at room temperature under nitrogen atmosphere. The crude reaction mixture was filtered through celite, and the excess iodine was quenched with saturated Na_2SO_3 solution, and the organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The resulted yellow solid was tritrated with cold Et_2O to give 2-iodo-4,5-dimethoxybenzaldehyde **(3-3b)** as an off-white solid (1.69 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 3.96 (s, 3 H), 7.31 (s, 1 H), 7.42 (s, 1 H), 9.87 (s, 1 H). All data are in agreement with those reported in the literature.[11]

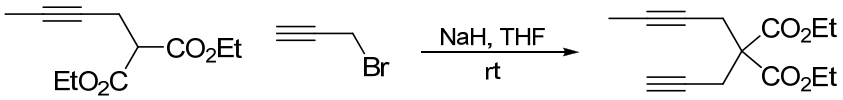
2-Iodo-3,4,5-trimethoxybenzaldehyde (3-3c)[7]



3-3c

To a solution of 3,4,5-trimethoxybenzaldehyde (2.00 g, 10.2 mmol) in MeOH (70 mL) was added silver trifluoroacetate (2.48 g, 11.2 mmol). A solution of iodine (2.59 g, 10.2 mmol) in MeOH (30 mL) was added dropwise to the reaction mixture, and the reaction was stirred overnight at room temperature under nitrogen atmosphere. The crude reaction mixture was filtered through celite, and the excess iodine was quenched with saturated Na_2SO_3 solution, and the organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 15%) to give 2-iodo-3,4,5-trimethoxybenzaldehyde **(3-3c)** as an off-white solid (3.11 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 3.92 (s, 3 H), 3.97 (s, 3 H), 7.35 (s, 1 H), 10.05 (s, 1 H). All data are in agreement with those reported in the literature.[7]

Diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (3-4a)

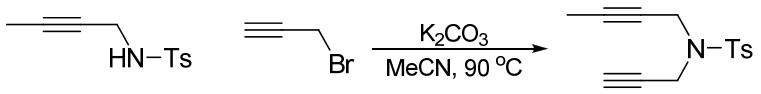


3-4a

To a suspension of sodium hydride (0.68 g, 17.0 mmol, 60 wt% in mineral oil) in THF (50 mL) was added dropwise a solution of diethyl 2-(but-2-ynyl)malonate[12] (3.00 g, 14.1 mmol) in THF(25 mL). The reaction was stirred for additional 30 min after gas evolution stopped. A solution of propargyl bromide (2.52 g, 17.0 mmol, 80 wt% in toluene) was added dropwise to the reaction. The reaction was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with addition of water. The excess solvent was removed under reduced pressure, and the crude was extracted with Et_2O. The combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate **(3-4a)** as light yellow oil (3.007 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 6 H, J = 7.2 Hz), 1.75 (t,3 H, J = 2.4 Hz), 2.01 (t, 1 H, J = 2.7 Hz), 2.92

(q, 2 H, *J* = 2.4 Hz), 2.96 (d, 2 H, *J* = 2.7 Hz), 4.21 (q, 4 H, *J* = 7.2 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.42, 13.97, 22.49, 22.83, 56.58, 61.61, 61.82, 71.34, 72.94, 78.74, 79.04, 168.91.

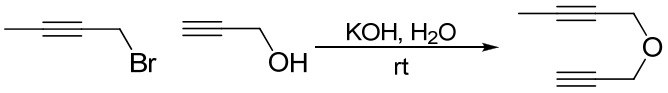
_N_-(But-2-ynyl)-_N_-(prop-2-ynyl)-_N_-(4-methylphenylsulfonyl)amine (3-4b)[13]



3-4b

To a solution of *N*-(but-2-ynyl)-*N*-(4-methylphenylsulfonyl)amine[12] (3.00 g, 13.4 mmol) in MeCN (70 mL) was added K_2CO_3 (5.57 g, 40.3 mmol), and propargyl bromide (2.39 g, 16.1 mmol, 80 wt% in toluene). The reaction mixture was stirred overnight at 90 °C under nitrogen atmosphere. The reaction was filtered through celite, and the filtrate was concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 15%) to give *N*-(but-2-ynyl)-*N*-(prop-2-ynyl)-*N*-(4-methylphenylsulfonyl)amine **(3-4b)** as a light yellow oil (3.232 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (t, 3 H, *J* = 2.7 Hz), 2.13 (t, 1 H, *J* = 2.4 Hz), 2.42 (s, 3 H), 4.09 (q, 2 H, *J* = 2.7 Hz), 4.13 (d, 2 H, *J* = 2.4 Hz), 7.29 (d, 2 H, *J* = 8.4 Hz), 7.71 (d, 2 H, *J* = 8.4 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.34, 2149, 36.09, 36.68, 71.28, 73.64, 76.53, 81.93, 127.92, 129.35, 135.37, 143.67. All data are in agreement with those reported in the literature.[13]

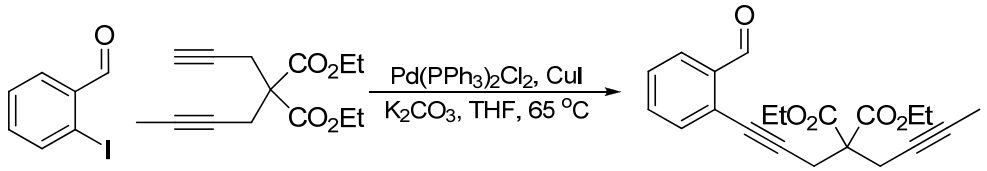
1-(Prop-2-ynyloxy)but-2-yne (3-4c)[14]



3-4c

To a solution of potassium hydroxide (3.75 g, 66.9 mmol) in water (25 mL) was added propargyl alcohol (3.00 g, 53.5 mmol) and 1-bromobut-2-yne (7.12 g, 53.5 mmol). The reaction mixture was stirred rapidly overnight at room temperature under nitrogen atmosphere. The mixture was extracted with Et_2O. The combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by vacuum distillation (72-78 °C/15 mmHg) to give 1-(prop-2-ynyloxy)but-2-yne **(3-4c)** as a colorless oil (4.56g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ1.86 (t, 3 H, *J* = 2.7 Hz), 2.43 (t, 1 H, *J* = 2.4 Hz), 4.21 (q, 2 H, *J* = 2.7 Hz), 4.24 (d, 2 H, *J* = 2.4 Hz). All data are in agreement with those reported in the literature.[14]

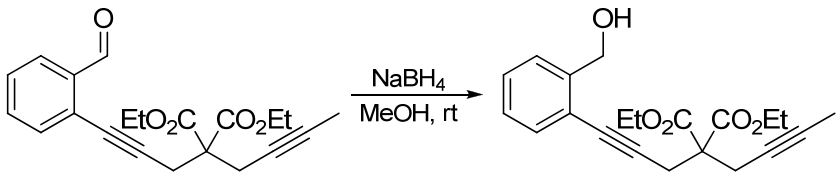
Diethyl 2-(but-2-ynyl)-2-(3-(2-formylphenyl)prop-2-ynyl)malonate (3-2a)



3-3a **3-4a** **3-2a**

To a mixture of $Pd(PPh_3)_2Cl_2$ (0.06g, 0.08mmol), CuI (0.03 g, 0.172 mmol), and K_2CO_3 (1.78 g, 12.9 mmol) in THF (30 mL) was added 2-iodobenzaldehyde **(3-3a)** (1.00 g, 4.31 mmol) and a solution of diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate **(3-4a)** (1.61 g, 6.46 mmol) in THF (10 mL). The reaction mixture was stirred overnight at 50 ^oC under nitrogen atmosphere. The reaction was filtered through celite, and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 15%) to give Diethyl 2-(but-2-ynyl)-2-(3-(2-formylphenyl)prop-2-ynyl)malonate **(3-2a)** as a light yellow oil (1.44g, 94%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 6 H, *J* = 7.2 Hz), 1.77 (t,3 H, *J* = 2.4 Hz), 2.97 (q, 2 H, *J* = 2.4 Hz), 3.27 (s, 2 H), 4.24 (q, 4 H, *J* = 7.2 Hz), 7.38-7.55 (m, 3 H), 7.87-7.90 (m, 1 H), 10.45 (d, 1 H, *J* = 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.72, 14.28, 23.55, 24.04, 57.06, 62.21, 73.10, 79.41, 79.63, 92.20, 127.06, 127.21, 128.62, 133.79, 133.86, 136.40, 169.21, 192.05.

Diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)phenyl)prop-2-ynyl)malonate (3-7a)

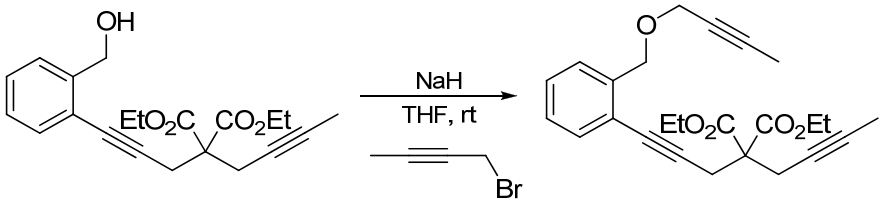


3-2a **3-7a**

To a solution of diethyl 2-(but-2-ynyl)-2-(3-(2-formylphenyl)prop-2-ynyl)malonate **(3-2a)** (1.44 g, 4.06 mmol) in MeOH (65 mL) was added sodium borohydride (0.30 g, 8.12 mmol) in one portion, and the reaction was stirred for 1 h until gas evolution stopped. The reaction was quenched with addition of 1 M HCl solution, and the solvent was removed under reduced pressure. The crude reaction mixture was extracted with Et_2O. The combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 10% → 25%) to give diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)phenyl)prop-2-ynyl)malonate **(3-7a)** as light

yellow oil (1.130 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.77 (t,3 H, *J* = 2.4 Hz), 2.97 (q, 2 H, *J* = 2.4 Hz), 3.22 (s, 2 H), 4.24 (q, 4 H, *J* = 7.2 Hz), 4.73 (s, 2 H), 7.19-7.41 (m, 4H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.70, 14.25, 23.51, 24.07, 57.15, 62.21, 64.23 , 73.15, 79.53, 81.46, 89.22, 121.90, 127.64, 128.00, 128.62, 132.67,142.87, 169.56.

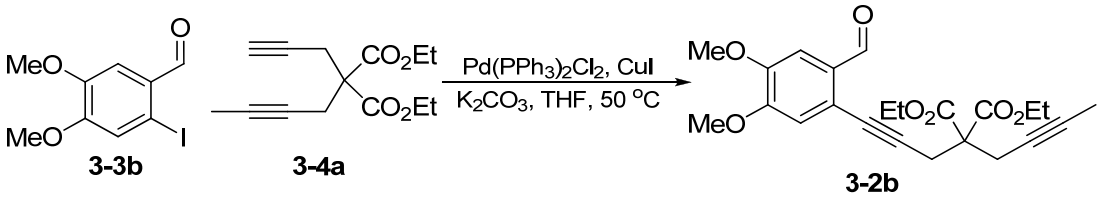
Diethyl 2-(but-2-ynyl)-2-(3-(2-((but-2-ynyloxy)methyl)phenyl)prop-2-ynyl)malonate (3-1a)



3-7a **3-1a**

To a suspension of sodium hydride (0.19 g, 4.8 mmol, 60 wt% in mineral oil) in THF (30 mL) was added a solution of diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)phenyl)prop-2-ynyl)malonate **(3-7a)** (1.14 g, 3.21 mmol) in THF (10 mL). The reaction was stirred for additional 30 min after gas evolution stopped. 1-bromobut-2-yne (0.85 g, 6.4 mmol) was added dropwise to the reaction. The reaction was stirred overnight at room temperature. The reaction was quenched with addition of water. The solvent was removed under reduced pressure, and the crude reaction mixture was extracted with Et_2O. The combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 15%) to give diethyl 2-(but-2-ynyl)-2-(3-(2-((but-2-ynyloxy)methyl)phenyl)prop-2-ynyl)malonate **(3-1a)** as a light yellow oil (0.505 g, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.77 (t,3 H, *J* = 2.4 Hz), 1.88 (t,3 H, *J* = 2.4 Hz), 2.98 (q, 2 H, *J* = 2.4 Hz), 3.23 (s, 2 H), 4.19-4.27 (m, 6 H), 4.68 (s, 2 H), 7.16-7.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.72, 3.87, 14.29, 23.35, 23.94, 57.17, 58.57, 62.06, 69.91, 73.39, 75.46, 79.31, 81.27, 82.78, 89.16, 121.98, 127.38, 127.68, 128.39, 132.45, 139.85, 169.33; HRMS (ES) m/z calcd for $C_{25}H_{29}O_5$ $(M + H)^+$: 409.2015, found 409.2018 (Δ 0.7 ppm).

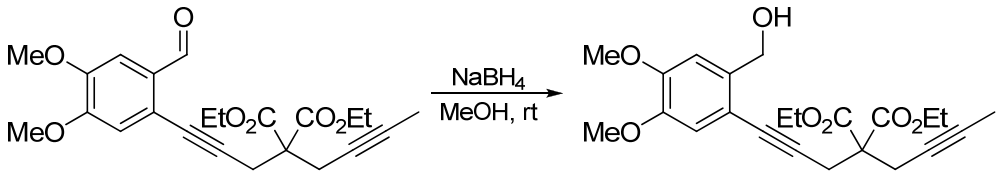
Diethyl 2-(but-2-ynyl)-2-(3-(2-formyl-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (3-2b)



3-3b **3-4a** **3-2b**

To a mixture of $Pd(PPh_3)_2Cl_2$ (0.04 g, 0.068mmol), CuI (0.02 g, 0.13 mmol), and K_2CO_3 (1.42 g, 10.3 mmol) in THF (30 mL) was added 2-iodo-4,5-dimethoxy benzaldehyde **(3-3b)** (1.00 g, 4.31 mmol) and a solution of diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate **(3-4a)** (1.286 g, 5.14 mmol) in THF (10 mL). The reaction mixture was stirred overnight at 50 ^oC under nitrogen atmosphere. The reaction was filtered through celite, and the solution was concentrated under reduced pressure. The crude reaction mixture was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 25%) to give diethyl 2-(but-2-ynyl)-2-(3-(2-formyl-4,5-dimethoxyphenyl)prop-2-ynyl)malonate **(3-2b)** as light yellow oil (1.28 g, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.77 (t,3 H, *J* = 2.4 Hz), 2.97 (q, 2 H, *J* = 2.4 Hz), 3.25 (s, 2 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 4.24 (q, 4 H, *J* = 7.2 Hz), 6.90 (s, 1 H), 7.36 (s, 1 H), 10.28 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ3.72, 14.26, 23.50, 24.06, 56.14, 56.26, 57.20, 62.20, 73.21, 79.51, 81.48, 87.48, 111.47, 113.90, 115.07, 131.49, 148.20, 149.50, 169.61, 191.09

Diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (3-7b)

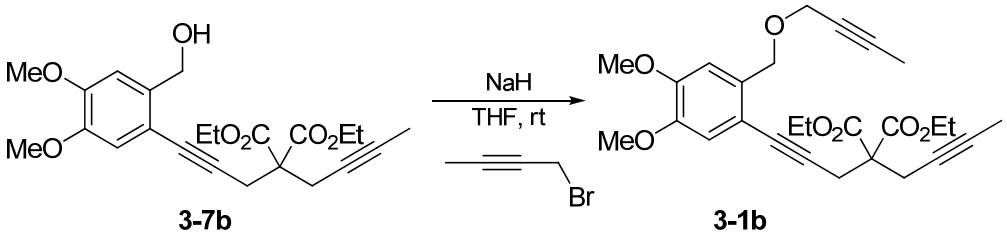


3-2b **3-7b**

To a solution of diethyl 2-(but-2-ynyl)-2-(3-(2-formyl-4,5-dimethoxyphenyl)prop-2-ynyl)malonate **(3-2b)** (1.28 g, 3.08 mmol) in MeOH (80 mL) was added sodium borohydride (0.22 g, 6.16 mmol) in one portion, and the reaction was stirred for 1 h until gas evolution stopped. The reaction was quenched with addition of 1 M HCl solution, and the solvent was removed under reduced pressure. The crude reaction mixture was extracted with Et_2O. The combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by flashed chromatography

(silica gel, EtOAc/Hexanes = 10% → 40%) to give diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate **(3-7b)** as a light yellow oil (1.02 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.77 (t,3 H, *J* = 2.4 Hz), 2.97 (q, 2 H, *J* = 2.4 Hz), 3.20 (s, 2 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 4.25 (q, 4 H, *J* = 7.2 Hz), 4.67 (s, 2 H), 6.89 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.72, 14.26, 23.50, 24.06, 56.14, 56.26, 57.20, 62.20, 64.01, 73.21, 79.51, 81.48, 87.48, 111.47, 113.90, 115.07, 136.49, 148.20, 149.50, 169.61.

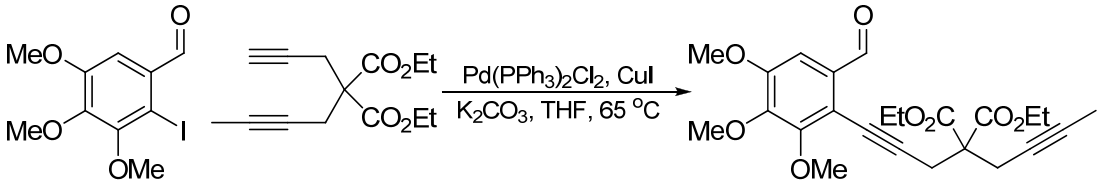
Diethyl 2-(but-2-ynyl)-2-[3-(2-(but-2-ynyloxy)methyl)]-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (3-1b)



3-7b **3-1b**

To a suspension of sodium hydride (0.15 g, 3.9 mmol, 60 wt% in mineral oil) in THF (20 mL) was added a solution of diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate **(3-7b)** (1.09 g, 2.62 mmol) in THF (10 mL). The reaction was stirred for additional 30 min after gas evolution stopped. 1-bromobut-2-yne (0.69 g, 5.2 mmol) was added dropwise to the reaction. The reaction was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with addition of water. The excess solvent was removed under reduced pressure, and the crude was extracted with Et_2O. The combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 25%) to give diethyl 2-(but-2-ynyl)-2-(3-(2-((but-2-ynyloxy)methyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate **(3-1b)** as a light yellow oil (0.393 g, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.77 (t, 3 H, *J* = 2.4 Hz), 1.88 (t, 3 H, *J* = 2.4 Hz), 2.98 (q, 2 H, *J* = 2.4 Hz), 3.21 (s, 2 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 4.18 (q, 2 H, *J* = 2.4 Hz), 4.21 (q, 4 H, *J* = 7.2 Hz), 4.62 (s, 2 H), 6.84 (s, 1 H), 6.95 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.723, 3.88, 14.30, 23.37, 23.94, 56.16, 56.22, 57.19, 58.39, 62.05, 69.82, 73.43, 75.53, 79.31, 81.30, 82.74, 87.40, 110.97, 114.17, 114.75, 133.26, 148.10, 149.55, 169.37; HRMS (ES) m/z calcd for $C_{27}H_{32}NaO_7$ $(M + Na)^+$: 491.2046, found 491.2047 (Δ 0.2 ppm).

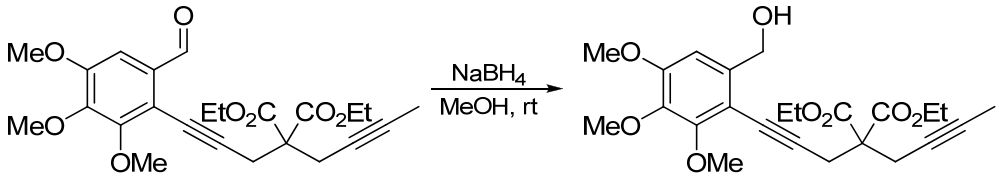
Diethyl 2-(but-2-ynyl)-2-(3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate (3-2c)



3-3c **3-4a** **3-2c**

To a suspension of $Pd(PPh_3)_2Cl_2$ (0.04 g, 0.063 mmol), CuI (0.02 g, 0.126 mmol), and K_2CO_3 (1.29 g, 9.30 mmol) in THF (30 mL) was added 2-iodo-3,4,5-trimethoxy benzaldehyde **(3-3c)** (1.00 g, 3.10 mmol) and a solution of diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate **(3-4a)** (1.17 g, 4.65 mmol) in THF (10 mL). The reaction mixture was stirred overnight at 65 ^oC under nitrogen atmosphere. The reaction was filtered through celite and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 5% → 25%) to give diethyl 2-(but-2-ynyl)-2-(3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate **(3-2c)** as a light yellow oil (0.978 g, 71%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.77 (t,3 H, *J* = 2.4 Hz), 2.99 (q, 2 H, *J* = 2.4 Hz), 3.30 (s, 2 H), 3.91 (s, 3 H), 3.93 (s, 3 H), 3.95 (s, 3 H), 4.23 (q, 4 H, *J* = 7.2 Hz), 7.21 (s, 1 H), 10.33 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.71, 14.26, 23.50, 24.26, 56.41, 57.04, 61.38, 61.63, 62.16, 73.20, 74.84, 79.50, 94.77, 105.23, 116.02, 132.45, 147.81, 153.97, 155.17, 169.24, 191.06.

Diethyl 2-(but-2-ynyl)-2-(3-(6-(hydroxymethyl)-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate (3-7c)

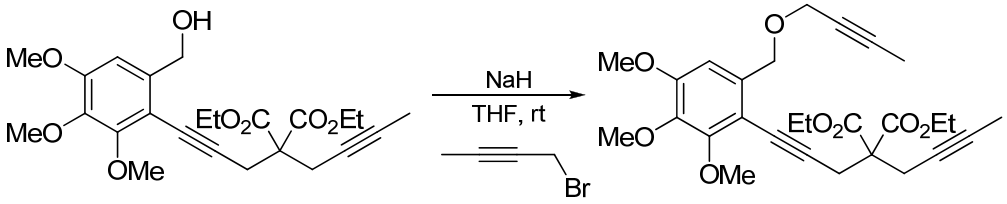


3-2c **3-7c**

To a solution of diethyl 2-(but-2-ynyl)-2-(3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate **(3-2c)** (0.98 g, 2.20 mmol) in MeOH (80 mL) was added sodium borohydride (0.17 g, 4.4 mmol) in one portion, and the reaction was stirred for 1 h until gas evolution stopped. The reaction was quenched with addition of 1 M HCl solution, and the excess solvent was removed under reduced pressure. The crude reaction mixture was extracted with Et_2O. The

combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 10% → 40%) to give diethyl 2-(but-2-ynyl)-2-(3-(6-(hydroxymethyl)-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate **(3-7c)** as a light yellow oil (0.868 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ1.26 (t, 6 H, *J* = 7.2 Hz), 1.77 (t,3 H, *J* = 2.4 Hz), 2.97 (q, 2 H, *J* = 2.4 Hz), 3.20 (s, 2 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 3.94 (s, 3 H),, 4.25 (q, 4 H, *J* = 7.2 Hz), 4.61 (s, 2 H), 6.79 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.71, 14.24, 23.51, 24.34, 56.27, 57.16, 61.28, 61.46, 62.18, 64.23, 73.23, 79.45, 91.77, 107.46, 109.05, 139.54, 141.58, 153.88, 155.37, 169.63.

Diethyl 2-(but-2-ynyl)-2-(3-(6-((but-2-ynyloxy)methyl)-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate (3-1c)

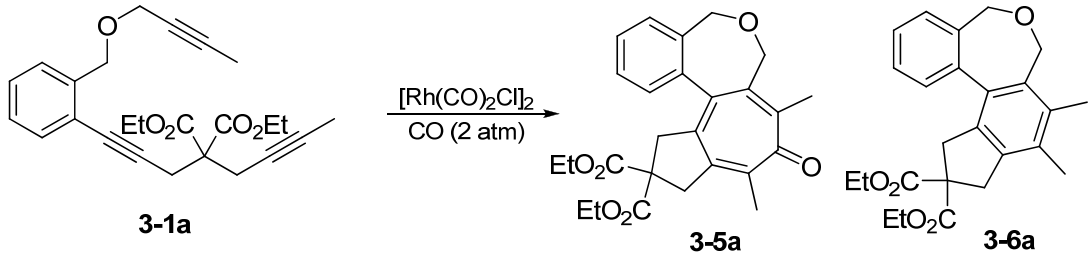


3-7c **3-1c**

To a suspension of sodium hydride (0.12 g, 3.0 mmol, 60 wt% in mineral oil) in THF (15 mL) was added a solution of diethyl 2-(but-2-ynyl)-2-(3-(6-(hydroxymethyl)-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate **(3-7c)** (0.88 g, 2.0 mmol) in THF (10 mL). The reaction was stirred for additional 30 min after gas evolution stopped. 1-Bromobut-2-yne (0.52 g, 3.9 mmol) was added dropwise to the reaction. The reaction was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with addition of water. The excess solvent was removed under reduced pressure, and the crude was extracted with Et_2O. The combined organic layers was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by flashed chromatography (silica gel, EtOAc/Hexanes = 0% → 25%) to give diethyl 2-(but-2-ynyl)-2-(3-(6-((but-2-ynyloxy)methyl)-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate **(3-1c)** as light yellow oil (0.347 g, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.76 (t, 3 H, *J* = 2.4 Hz), 1.88 (t, 3 H, *J* = 2.4 Hz), 3.00 (q, 2 H, *J* = 2.4 Hz), 3.27 (s, 2 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.90 (s, 3 H), 4.20-4.28 (m, 6 H), 4.61 (s, 2 H), 6.79 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.71. 3.87, 14.27, 23.32, 24.19, 6.27, 27.15, 587, 61.27, 61.43, 62.01, 69.87,73.47, 75.42, 79.21, 82.86, 91.79,

106.77, 109.22, 136.57, 141.40, 153.88, 155.04, 169.37; HRMS (ES) m/z calcd for $C_{28}H_{35}O_8$ $(M + H)^+$: 499.2332, found 499.2334 (Δ 0.4 ppm).

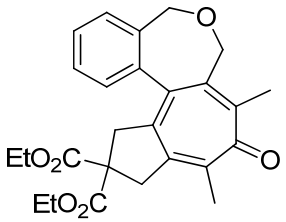
Rhodium-catalyzed [2+2+2+1] cycloaddition of triynes



3-1a **3-5a** **3-6a**

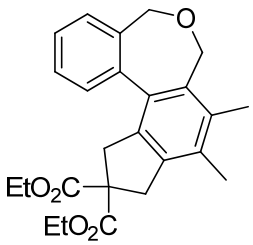
Triyne **3-1a** (100 mg, 0.24 mmol) was introduced to a 10 mL round-bottomed flask, followed by $Cl(CH_2)_2Cl$ (4.8 mL) and $[Rh(CO)_2Cl]_2$ (9.3 mg, 0.024 mmol, 10 mol%). The reaction vessel was placed in autoclave; the autoclave was purged with CO 3 times and pressurized to 2 atm (**Caution!! must be done in a well-ventilated fume hood**). The autoclave was placed in 50 ^oC oil bath for 24 h. After the reaction, all volatiles were removed from the reaction mixture under reduced pressure and the crude product was purified by flash chromatography on silica gel EtOAc/Hexanes = 10% → 30%) affording **3-5a** and **3-6a**. Other substrates were run with similar procedure unless stated otherwise.

8,8-Di(carbethoxy)-4,6-dimethyl-5-oxo-2,3,7,9-tetrahydro-1*H*-azuleno[5,4-*c*]benzo[*e*]oxepine (3-5a)



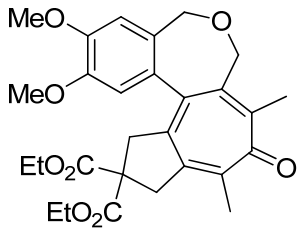
^1H NMR (300 MHz, $CDCl_3$) δ 1.12-1.35 (m, 6 H), 2.26(s, 3H), 2.37 (s, 3 H), 2.94 (bs, 1 H), 3.37 (bs, 1 H), 3.49 (s, 2 H), 3.88 (bs, 1 H), 4.02-4.26 (m, 4 H), 4.55 (s, 2 H), 4.70 (bs, 1 H), 7.11-7.16 (m, 1 H), 7.31-7.43 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.13, 18.59, 19.79, 42.36, 44.82, 57.96, 62.13, 65.28, 68.11, 128.75, 128.95, 129.05, 129.23, 132.70, 138.07, 140.01, 140.29, 141.17, 142.01, 142.06, 145.68, 170.80, 190.85; LR-MS *m/z* calcd for $C_{26}H_{28}O_6$ (M^+) 436.5, found (M+ 1): 437.1; HRMS (ES) m/z calcd for $C_{26}H_{29}O_6$ $(M + H)^+$: 437.1964, found 437.1966 (Δ 0.5 ppm).

11,11-Di(carbethoxy)-8,9-dimethyl-7,10,11,12-tetrahydro-5*H*-benzo[*e*]indeno[5,4-*c*]oxepine (3-6a)



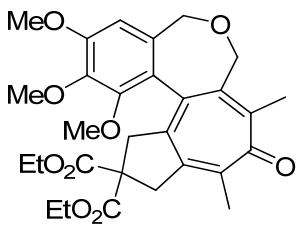
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3 H, *J* = 7.2 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz), 2.29 (s, 3 H), 2.38 (s, 3 H), 3.32 (d, 1 H, *J* = 16.5 Hz), 3.57 (d, 1 H, *J* = 16.2 Hz), 3.71 (d, 1 H, *J* = 16.5 Hz), 3.83 (d, 1 H, *J* = 11.7 Hz), 4.02-4.30 (m, 6 H), 4.45 (d, 1 H, *J* = 11.1 Hz), 4.82 (d, 1 H, *J* = 11.7 Hz), 7.36-7.57 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15, 14.31, 15.71, 17.14, 40.49, 40.74, 60.10, 61.87, 62.02, 62.88, 67.51, 128.09, 128.21, 128.34, 129.71, 132.67, 132.71, 134.31, 134.46, 134.82, 135.37, 140.03, 140.25, 171.79, 172.08; LR-MS *m/z* calcd for $C_{25}H_{28}O_5$ (M^+) 408.5, found (M+ 1): 409.2; HRMS (ES) m/z calcd for $C_{25}H_{29}O_5$ $(M + H)^+$: 409.2015, found 409.2015 (Δ 0.0 ppm).

8,8-Di(carbethoxy)-4,6-dimethyl-11,12-dimethoxy-5-oxo-2,3,7,9-tetrahydro-1*H*-azuleno[5,4-*c*]benzo[*e*]oxepine (3-5b)



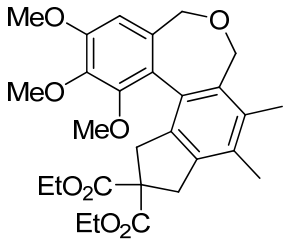
^{1}H NMR (300 MHz, $CDCl_3$) δ1.16-1.24(m, 6 H), 2.25(s, 3H), 2.37 (s, 3 H), 3.00 (bs, 1 H), 3.40 (bs, 1 H), 3.50 (s, 2 H), 3.86 (s, 3 H), 3.87 (bs, 1 H), 3.95 (s, 3 H), 4.10-4.30 (m, 4 H), 4.48 (s, 2 H), 4.70 (bs, 1 H), 6.67 (s, 1 H), 6.87 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15, 18.60, 19.89, 19.92, 42.47, 44.91, 56.22, 56.25, 56.38, 57.93, 62.14, 65.38, 67.95, 111.93, 112.24, 125.42, 134.24, 138.54, 140.19, 140.21, 141.10, 142.33, 145.71, 148.91, 149.31, 170.82, 190.56; HRMS (ES) m/z calcd for $C_{28}H_{33}O_8$ $(M + H)^+$: 497.2175, found 497.2171 (Δ 0.8 ppm).

8,8-Di(carbethoxy)-4,6-dimethyl-10,11,12-trimethoxy-5-oxo-2,3,7,9-tetrahydro-1*H*-azuleno[5,4-*c*]benzo[*e*]oxepine (3-6b)



^{1}H NMR (300 MHz, $CDCl_3$): see appendix page273; ^{13}C NMR (100 MHz, $CDCl_3$) δ14.09, 14.16, 18.53, 20.06, 42.51, 43.86, 56.29, 57.63, 61.44, 61.51, 61.95, 62.05, 68.12, 108.15, 127.64, 128.17, 135.05, 137.78, 140.35, 142.06, 142.52, 143.21, 145.74, 150.93, 153.94, 170.71, 171.25, 190.68; HRMS (ES) m/z calcd for $C_{29}H_{35}O_9$ $(M + H)^+$: 527.2881, found 527.2885 (Δ 0.8 ppm).

1,2,3-Trimethoxy-11,11-di(carbethoxy)-8,9-dimethyl-7,10,11,12-tetrahydro-5*H*-benzo[*e*]indeno[5,4-*c*]oxepine (3-6c)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3 H, *J* = 7.2 Hz), 1.28 (t, 3 H, *J* = 7.2 Hz), 2.28 (s, 3 H), 2.36 (s, 3 H), 3.22 (d, 1 H, *J* = 17.1 Hz), 3.47, (s, 3 H), 3.51 (d, 1 H, *J* = 16.5 Hz), 3.71 (d, 1 H, *J* = 16.5 Hz), 3.86 (d, 2 H, *J* = 6 Hz), 3.91-3.96 (m, 8 H), 4.7-4.33 (m, 5 H), 4.84 (d, 1 H, *J* = 11.7 Hz), 6.72 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.25, 15.66, 17.15, 40.59, 40.94, 56.30, 59.81, 61.00, 61.67, 61.76, 63.16, 67.56, 108.43, 125.84, 131.14, 131.48, 132.14, 132.35, 133.38, 136.59, 139.46, 142.54, 150.83, 153.23, 172.22, 172.25; HRMS (ES) m/z calcd for $C_{28}H_{35}O_8$ $(M + H)^+$: 499.2332, found 499.2328 (Δ 0.8 ppm).

§ 3.5. References

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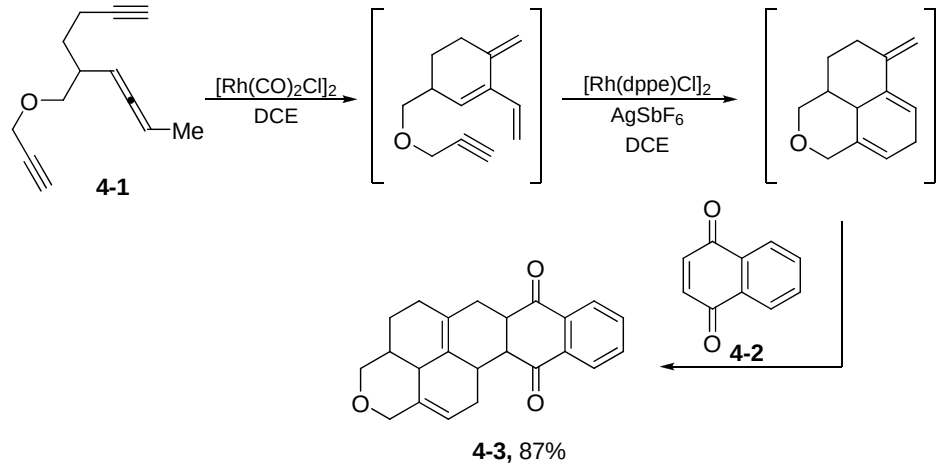
Chapter 4

Rhodium-Catalyzed [2+2+2+1] Cycloaddition of Allenediynes

Table of Content

§4.1. Introduction

Polycyclic frameworks are ubiquitous in nature. For several decades, researchers have tried to find efficient ways to synthesize polycyclics that mimic natural products.[1] Based on the Stork-Eschenmoser hypothesis of polyene cyclization,[2] construction of polycyclic compounds from linear unsaturated precursors has drawn a lot of attention in the synthetic community.[1b, 3] Transition-metal-catalyzed carbocyclization reaction is one of the most important carbon skeleton-forming reactions. Using relatively simple but appropriately designed precursors, complex polycyclic molecules which cannot be obtained with classical pericyclic reactions or other classical carbon-carbon bond forming reactions can be synthesized under mild conditions in few steps using transition metal catalyzed carbocyclization reactions.[4] Mechanistic studies of various transition metal catalyzed carbocyclization reactions are well established and the versatilities of metal catalyst species have also been exploited.[3] Recently, Brummond *et. al*. demonstrated a rapid synthesis of polycyclic framework **4-3** from one-pot tandem Rh-catalyzed Alder-ene/Diels-Alder/Diels-Alder reactions using allene and alkyne as building blocks (**Scheme 4-1**).[5]

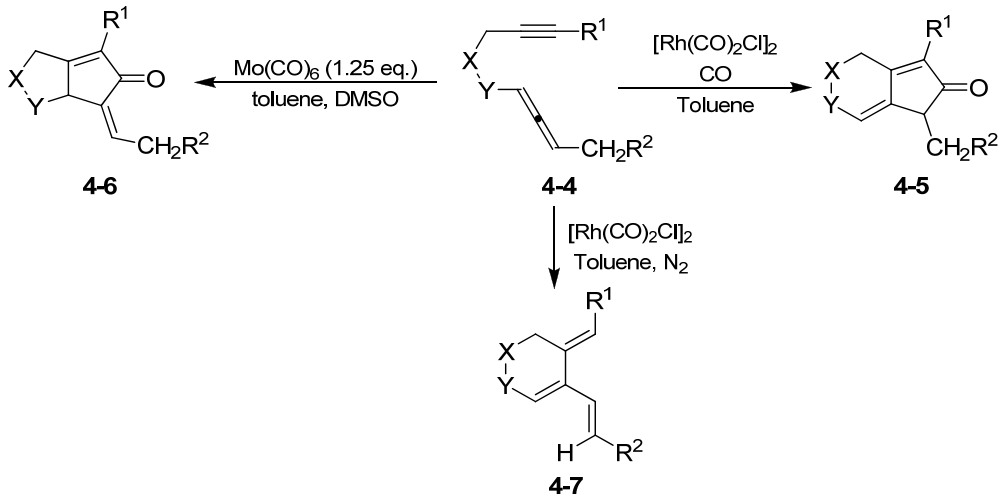


Scheme 4-1: Rapid polycyclic construction from tandem Rh-catalyzed Alder-ene/Diels-Alder/Diels-Alder reactions of allene-diyne **4-1.**

Allene is an important versatile building block in organic synthesis and in transition metal-catalyzed carbon-carbon bond forming reactions.[6] The major challenge in the use of allenes in synthesis is the selectivity between the two reactive orthogonal double bonds.[7] The most utilized strategy is the use of functional groups on the carbon atom next to the allene moiety to control the selectivity by both geometrical restriction and electronic differentiation of

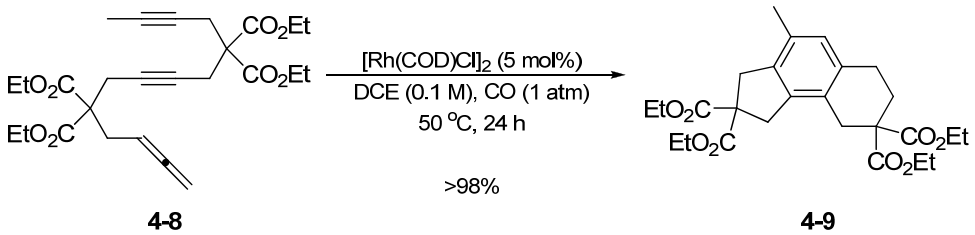
the orthogonal double bonds of the allene. [7] However, in recent developments of transition metal-catalyzed transformation of allenes, the selectivity can solely depend on the metal species used in the transformation.[8]

Transformations of allenyne **4-4** by transition metals can be diversified into different carbocycles depending on reaction conditions **(Scheme 4-2)**.[9] Pauson-Khand type reaction (PKTR) of allenyne **4-4** gave complimentary regioselective products depending on the metal used in the reaction. In the rhodium catalyzed PKTR, the catalyst reacted with distal double bond to give the [4.3.0] bicyclic product **4-5**; whereas a molybdenum catalyst reacted with proximal double bond to give the [3.3.0] bicyclic product **4-6**. In the absence of carbon monoxide, allenyne **4-4** underwent Rh-catalyzed Alder-Ene reaction with the distal double bond to form the cross-conjugated trienes **4-7**.



Scheme 4-2: Diverse carbocycles formation of allenyne **4-4.**

In 2005, Ojima reported the first example of cycloaddition of allenediyne **4-8** under the standard reaction conditions of [2+2+2+1] cycloaddition of enediynes. However, only [2+2+2] cycloadduct **4-9** was afforded as exclusive product (**Scheme 4-3**).[10]



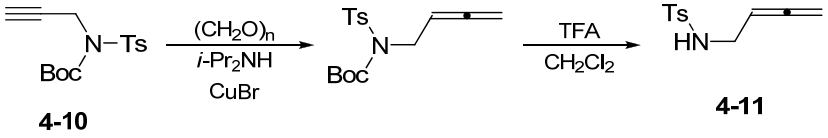
Scheme 4-3: Formation of fused benzene **4-9** from Rh-catalyzed [2+2+2] cycloaddition of allenediyne **4-8.**

Intrigued by these findings, we set out to develop a highly efficient synthetic route to the 5-7-6 tricyclic skeleton *via* a single step process from allenediynes. An advantage of this approach is that from simple and readily accessible starting materials, a variety of richly functionalized polycyclics with modifiable functional groups can be obtained in a few steps. As part of our ongoing investigations into Rh(I)-catalyzed higher-order cycloadditon of enediyne derivatives, we applied the previously developed [2+2+2+1] cycloaddition process to allenediyne substrates. We found that allenediynes would undergo several reaction pathways and result in different products. Possible mechanisms of each reaction pathway are proposed based on products formation.

§4.2. Results and Discussions

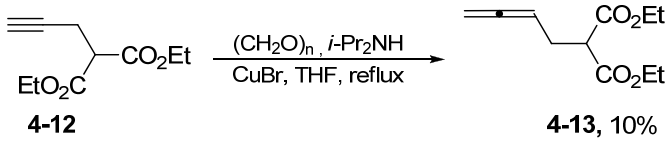
§4.2.1. Allenes and Substrates Syntheses

During the literature search for allene component synthesis, it was found that the Boc-protected *N*-(propargyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-10)** can be readily converted to Boc-protected *N*-(allenyl)-*N*-(4-methylbenzenesulfonyl)amine using the Crabbé Reaction. After trifluoroacetic acid mediated deprotection of Boc, *N*-(buta-2,3-dienyl)-*N*-(4-Methylbenzenesulfonyl)amine **(4-11)** was obtained in good yield (**Scheme 4-4**).[11]



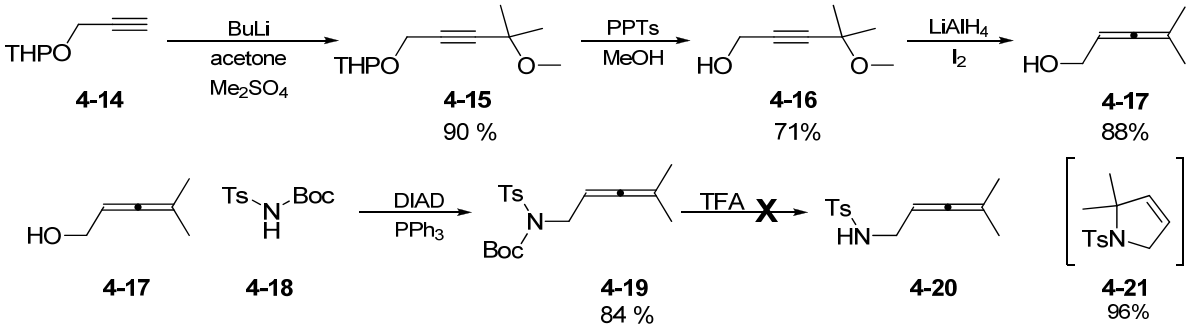
Scheme 4-4: One-step formation of allene **4-11** from propargylic amine **4-10** Through the Crabbé Reaction**.**

However, applying the Crabbé reaction to convert diethyl propargylmalonate **(4-12)** to the desired diethyl 2-(buta-2,4-dienyl)malonate **(4-13)** gave extremely low yield (**Scheme 4-5**). Thus, a more practical method to obtain allenylmalonate **4-13** still needs to be investigated.[10]



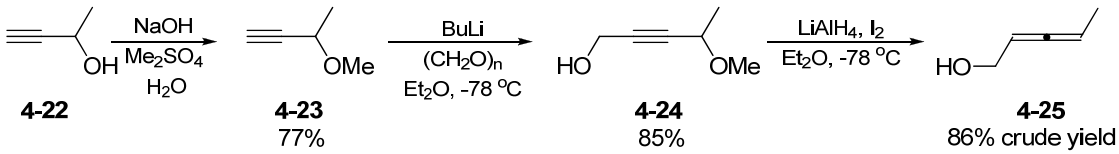
Scheme 4-5: One-step formation of allenemalonate **4-13** from propargylmalonate **4-12** through the Crabbé Reaction**.**

In a paper described by Keck, various substituted allene alcohols could be synthesized in good yields (**scheme 4-6).**[12] From the tetrahydro-*2H*-pyran propargyl ether **(4-14)**, alkylation and THP deprotection gave alcohol **4-16** in good yield. LAH reduction of the alkyne with iodine (I_2) gave the desired allene alcohol **4-17** in good yield. The dimethyl substituted allene alcohol 4-17 was then subjected to Mitsunobu reaction to form the Boc-protected tosylamine **4-18** in good yield. However, the TFA mediated deprotection of Boc, did not give the desired allenylamine **4-20**, instead the dihydropyrrolidine product **4-21** was obtained. Formation of dihydropyrolidine **4-21** is believed to proceed through electrophile-induced aminocyclization in an 5-*endo-trig* manner under highly acidic condition.[13]



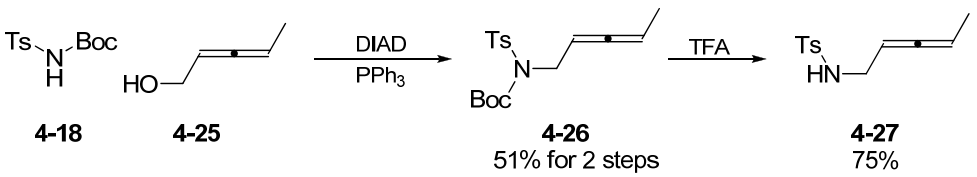
Scheme 4-6: Formation of disubstituted allenes.

The major downside of this particular procedure is the use of tetrahydro-*2H*-pyran propargyl ether **(4-14)**; it shows poor atom economy, because of the large protecting group. Since the key step to obtain allenic alcohol is the LAH/I_2 reduction of methoxypentynol **4-16**, it is crucial to obtain the methoxypentynol through other means. Thus, commercially available 4-butyn-2-ol **4-22** was first methylated to obtain 2-methyoxy-4-butyne **(4-23) (Scheme 4-7)**. 2-Methyoxy-3-butyne **(4-23)** was then treated with base and paraformaldehyde to obtain the desired methoxypentynol **4-24**. LAH/I_2 reduction of methoxypentynol **4-24** gave the monomethyl substituted allenic alcohol **4-25** in good yield. Since the 3-butyn-2-ol **(4-22)** was a racemic mixture, the monomethyl substituted allenic alcohol **4-25** was also a racemic mixture (**Scheme 4-7**).



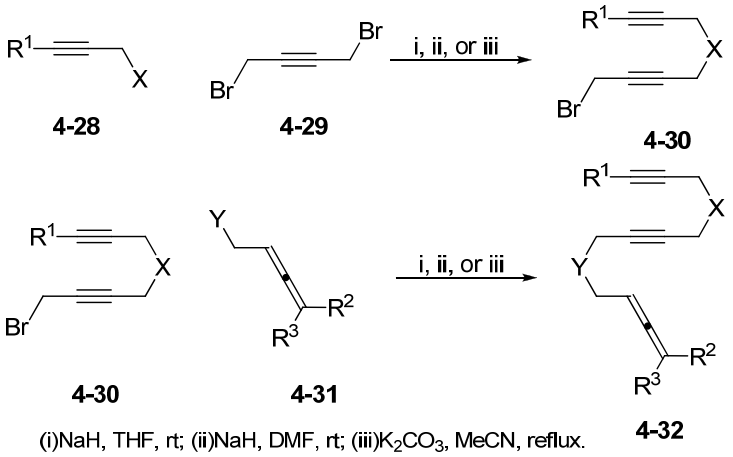
Scheme 4-7: Formation of monosubstituted allenic alcohol **4-25.**

The mono-methyl substituted allenic alcohol **4-25** was then subjected to Mitsunobu reaction and TFA deproctection to form the allenylamine **4-27** in good yield (**scheme 4-8**).



Scheme 4-8: Synthesis of mono-substituted allenylamine **4-27.**

After the allene components were successfully obtained, allenediynes were synthesized following the general synthetic protocol outlined in **Scheme 4-9**. First, the alkyne component was coupled with 1,4-dibromobutyne under basic conditions to give the bromodiyne **4-30**, followed by the installment of the allene component **4-31** to furnish various allenediynes **4-32** (F**igure 4-1**) in good to excellent yields.



Scheme 4-9: Synthesis of allenediyne substrates**.**

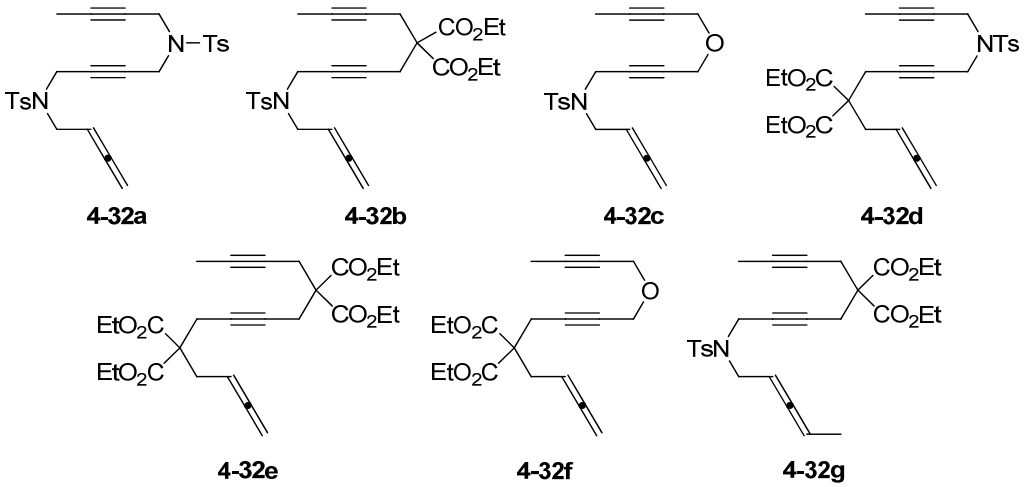


Figure 4-1: Synthesized allenediyne substrates **4-32a-g.**

§4.2.2. Cycloaddition of Allenediynes

The allenediyne **4-32a** was initially tested in the carbonylative cycloaddition reaction. The reaction was carried out in an autoclave for 20 h ($[Rh(CO)_2Cl]_2$ 5 mol%, CO (2 atm), 50 ^oC). Crude TLC showed two major spots, and low-resolution mass spectrometry (FIA) indicated the carbonylated product to be the major product. The HPLC trace of the crude mixture showed three major peaks (**Figure 4-2**). After product isolation by column chromatography, and characterization, the non-carbonylated product **4-33a** corresponds to the peak at 20.5 min (**Figure 4-2**). The ^1H NMR spectra of product **4-33a** indicated the presence of an aromatic hydrogen. It is believed that the aromatic product arose from the double bond isomerization of the expected triene product. The mechanism will be discussed in the subsequent section. The isolated material of carbonylative product corresponds to both peaks at 15.0 min and 17.4 min (**Figure 4-2**); LC-MS confirmed both peaks to be carbonylative products. The complex nature of ^1H NMR spectra also indicated the carbonylative product was a mixture. Although the expected product **4-34a** can be identified through ^1H NMR spectral analysis, the structure of co-eluted carbonylated isomer could not be confirmed at this point.

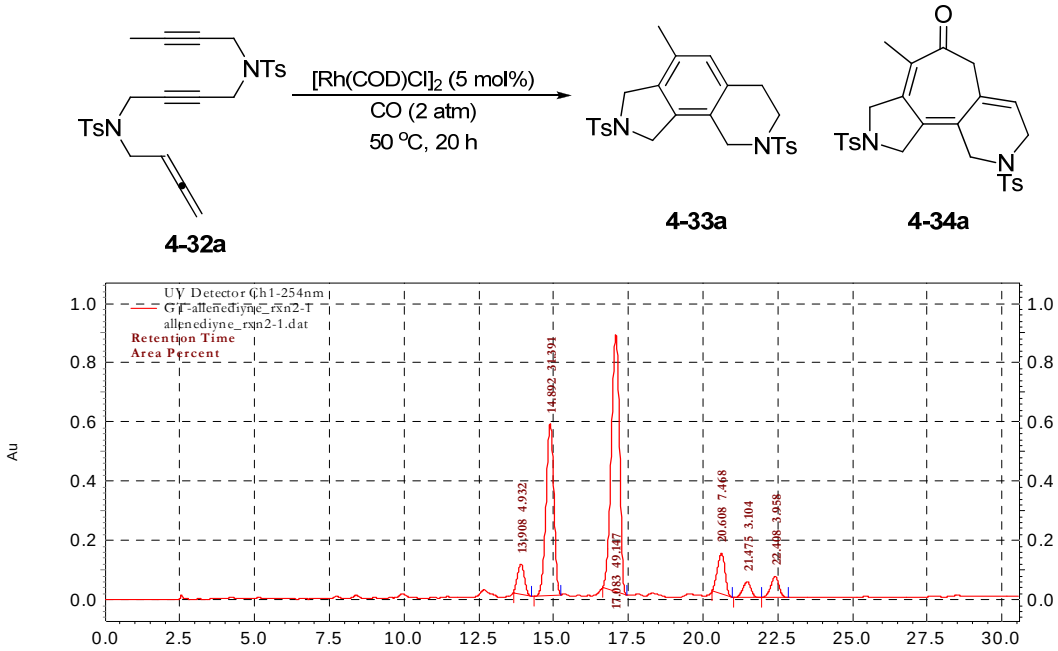
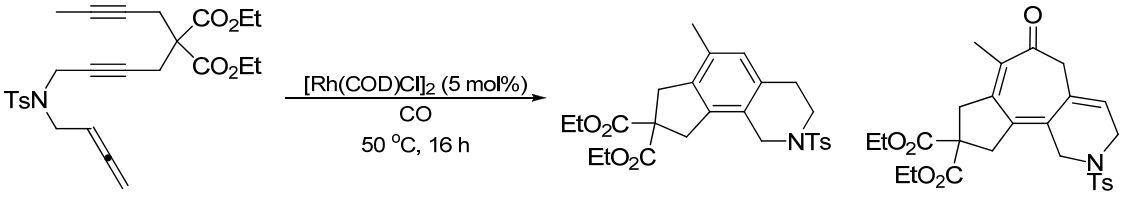


Figure 4-2: HPLC trace of reaction crude of allenediyne **4-32a**.

Allenediyne **4-32b** was used in condition optimizations, and the results were summarized in **table 4-1**. Under 1 atm of CO the 5-6-6 fused-ring product was the predominant product with

minor amount of carbonylated product (entry 1). With increase of CO pressure carbonylative products became the major product (entries 2 and 3). However, the increase of the product selectivities was not substantial. The product selectivities decreased as the dilution factor increased (entries 4 and 5). Similar phenomenon was observed for the carbonylated product isomers formation. The attempt to isolate and characterize carbonylated isomers was unsuccessful as the carbonylated isomers co-eluted as a single spot.

Table 4-1: Optimization of [2+2+2+1] cycloaddition of **4-32b** with CO.



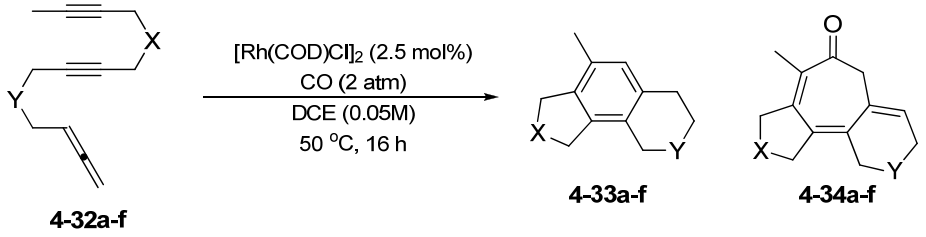
4-32b **4-33b** **4-34b**

Entry	pressure (atm)	concentration (M)	Products Ratio **4-33b**:**4-34b***	Carbonylative isomer products ratio
1	1	0.1	4.5:1	
2	5	0.1	1:3.7	1.8:1
3	10	0.1	1:5.2	2:1
4	2	0.05	1:3.4	1.4:1
5	2	0.025	1:2.8	1.3:1

* HPLC: Curosil column, 0.75 mL/min, gradient: 45% –>75% acetonitrile

Six allenediynes were subjected to the best reaction conditions found so far (**Table 4-1**, entry 4), and the results were summarized in **Table 4-2**. The conversion and the product ratio were determined by HPLC (Phenomex Curosil, 45→85% MeCN/H_2O, 0.75 mL/min). Amine tethered allene substrates (**4-32a-c**) all gave carbonylated products as the major products, and the carbonylated product isomers ratio ranged from 1.3:1 to 3:1. However, these products co-eluted together and could not be separated by column chromatography. Malonate tethered allene substrates (**4-32d-f**) gave better product distribution, however, the ratio of the carbonylated product isomers could not be determined, because the peaks overlapped even under the best HPLC conditions. In the case of allenediyne **4-32e**, the non-carbonylated product **4-33e** was the major product. Allenediyne **4-32f** gave the highest carbonylated product **4-34f** selectivity of ~13:1.

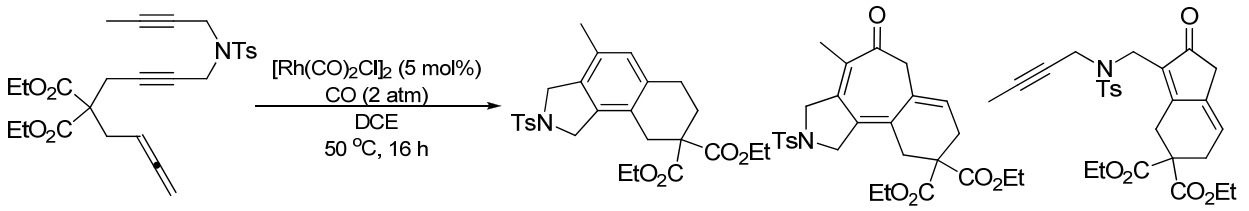
Table 4-2: Formation of 5-6-6 tricyclics **4-33a-f** and 5-7-6 tricyclics **4-34a-f** through [2+2+2+1] cycloaddition of **4-32a-f** with CO.



4-32a-f **4-33a-f** **4-34a-f**

Allenediyne	X	Y	Conversion	products ratio **4-33:4-34**	Carbonylative isomer products ratio
4-32a	NTs	NTs	100 %	1:1.6	1:1.6
4-32b	$C(CO_2Et)_2$	NTs	100 %	1:2.9	1:1.3
4-32c	O	NTs	100 %	1:4.3	1:3
4-32d	NTs	$C(CO_2Et)_2$	100 %	1:6.6	n/a
4-32e	$C(CO_2Et)_2$	$C(CO_2Et)_2$	100 %	1.2:1	n/a
4-32f	O	$C(CO_2Et)_2$	100 %	1:12.7	n/a

In the reaction employing allenediyne **4-32d**, even though HPLC failed to separate the carbonylated isomers, TLC showed two overlapping spots at the polarity corresponding to carbonylated product. There were 3 products isolated and identified. Other than the expected [2+2+2] cycloadduct **4-33d** and [2+2+2+1] cycloadduct **4-34d,** the third product was identified as the carbonylated 5-6 fused-ring product **4-35d** from the [2+2+1] cycloaddition (**scheme 4-10**). After careful comparison of spectral data of the crude NMR between the cycloaddition of different allenediyne substrates, it was confirmed that [2+2+1] cycloadduct was present in all cases.

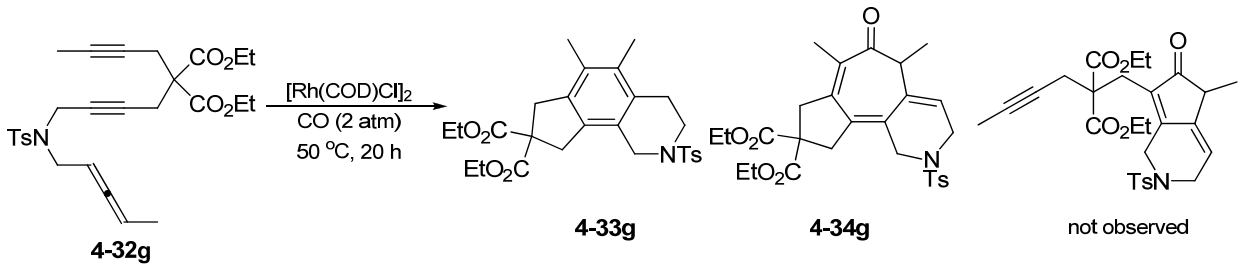


4-32d **4-33d** **4-34d** **4-35d**

Scheme 4-10: Product isolation and identification of cycloaddition of allenediyne **4-32d**.

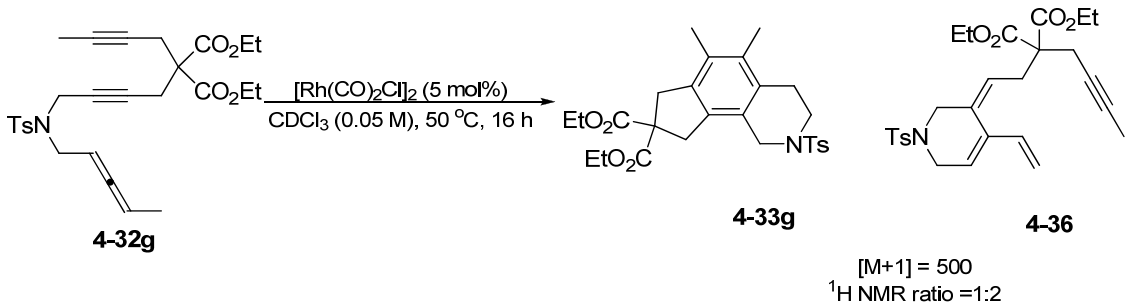
In addition to the previously proposed mechanism for enediyne substrates,[10, 14] the observation of [2+2+1] cycloadduct suggested the reaction may also start at the allene side.

Based on this observation, we hypothesized that substitution at the terminal carbon of the allene may alter the reactivity of the allene and thus it may help to bias the product distribution. Allenediyne **4-32g** with mono-methyl substitution at the terminal carbon of the allene was synthesized and subjected to the cycloaddition. Two spots were observed on the crude TLC; after isolation of the products by column chromatography, the major spot was found to be the non-carbonylated product **4-33g**, and the 5-7-6 fused-ring product **4-34g** was obtained in minute quantity. The previously observed [2+2+1] cycloadduct was not observed (**Scheme 4-11**). During the NMR analysis of the isolated non-carbonylated product; however, it was found that the product was a mixture of two compounds.



Scheme 4-11: Cycloaddition of mono-methyl substituted allenediyne **4-32g.**

In order to confirm the structures of the mixture, the allenediyne was subjected to [2+2+2] cycloaddition conditions in hopes of obtaining the pure benzene product. However, similar results were observed. LC-MS showed that both compounds in the mixture have the same molecular weight. After spectra elucidation, it was found that one of the products was the expected 5-6-6 tricyclic product **4-33g**, and the other product in the mixture was the cycloisomerization product **4-36** (**Scheme 4-12**).



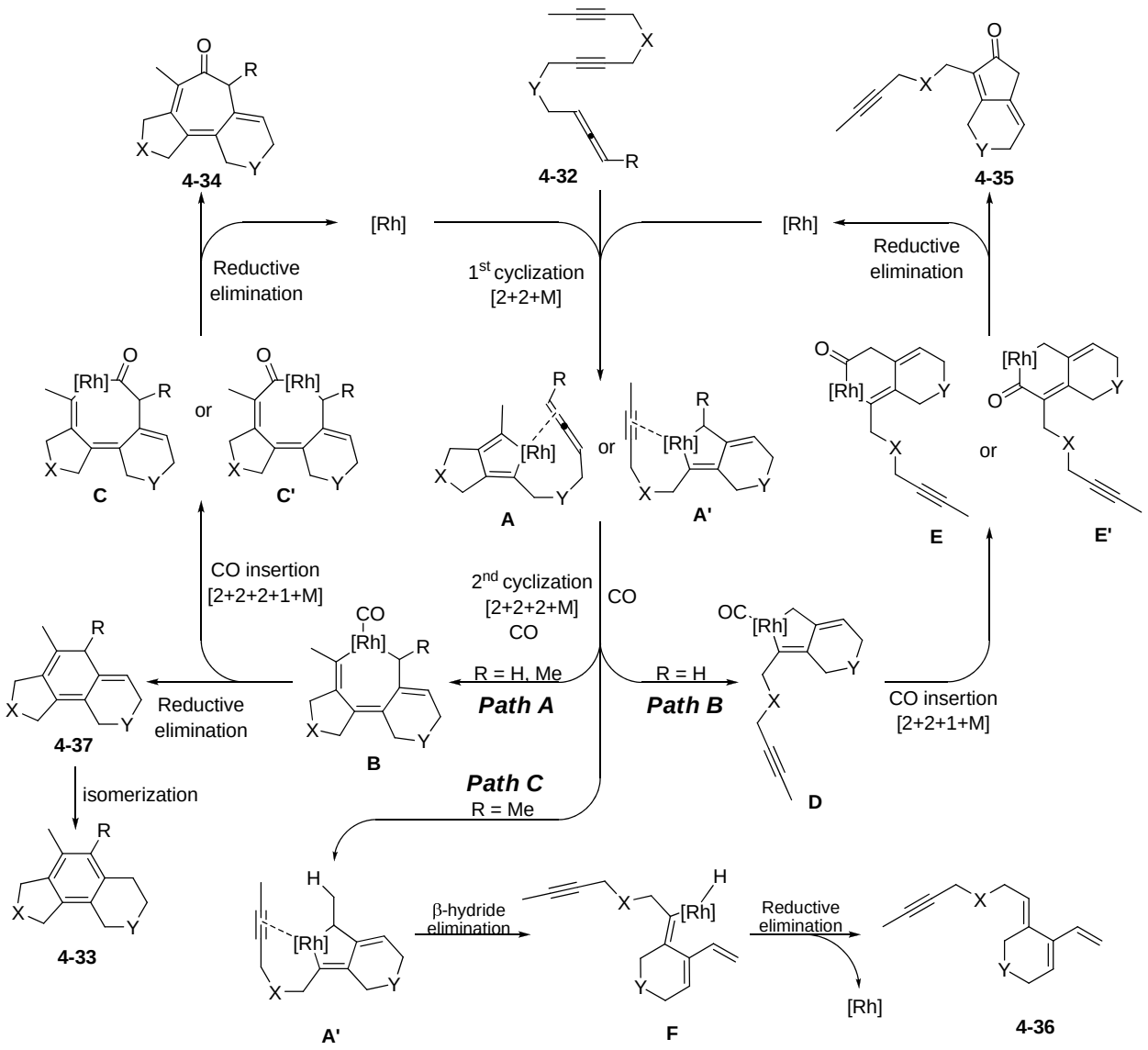
Scheme 4-12: Rh-caralyzed [2+2+2] cycloaddition of allenediyne **4-32g**.

§4.2.3. Proposed Mechanisms

Based on the observed products from the cycloaddition of allenediynes **4-32**, mechanistic pathways that account for the observed products are outlined in **Scheme 4-13.** From the previously proposed reaction pathway **4A**,[10, 14] rhodium oxidatively inserts into the diynes to form the intermediate **A**. However, formation of intermediate **A'** through Rh insertion to allene-alkyne must also to be considered based on the observation of products **4-35** and **4-36**. From intermediate **A** or **A',** the insertion of the remaining unsaturated component would lead to intermediate **B**. Reductive elimination from intermediate **B** in theory should give the triene product **4-37**. However, based on the spectral analysis of the product, only aromatic product **4-33** was observed which is presumably formed from double bond isomerization to aromatize the ring.

In reaction pathway **4B**, 5-6 fused bicyclic product **4-35** arose from intermediate **A'**. CO coordination to Rh takes place to form intermediate **D**. Migratory insertion of CO leads to intermediate **E** or **E'** followed by reductive elimination of Rh to give 5-6 fused bicyclic product **4-35**.

The mechanism for formation of cycloisomerization product **4-36** observed for the methyl substituted allenediyne cycloaddition is also proposed (pathway **4C**). The first cyclization between the distal allene double bond, alkyne, and the rhodium metal leads to the intermediate **A'**, Due to the presence of *β*-hydrogen at the allenic methyl group, *β*-hydride elimination takes place to form intermediate **F** followed by reductive elimination and thus resulting in cycloisomerization product **4-36**. Because the β-hydride elimination took place in a much faster rate than the carbonyl insertion, [2+2+1] cycloaddition was completely inhibited.



Scheme 4-13: Proposed mechanisms of Rh-catalyzed cycloaddition of allenediyne.

§4.3. Conclusions

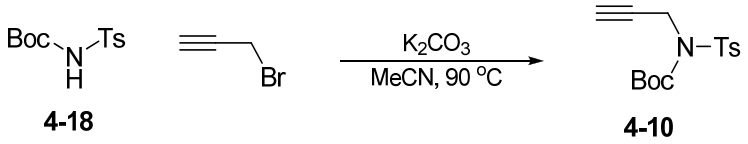
In summary, preliminary results from the [2+2+2+1] cycloaddition of allenediynes with carbon monoxide was described. The reactions of allenediynes proceeded through competitive cycloaddition reaction pathways forming diverse products. When the terminal carbon of the allene moiety was unsubstituted, carbonylative cycloaddition pathways (path **A** and **B**) were highly favored, however, there was little bias between path **A** and **B**. When there was a methyl substitution at the terminal carbon of the allene, cycloisomerization became the predominant reaction pathway. Further studies on the scope and application as well as mechanistic studies of this unique process are underway.

§3.4. Experimental Section

General Information:

All chemicals were obtained from either Sigma-Aldrich or Acros Organics and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under nitrogen and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). All reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates. Flash column chromatography was performed with the indicated solvents and using Fisher silica gel (particle size 170-400 Mesh). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[15]

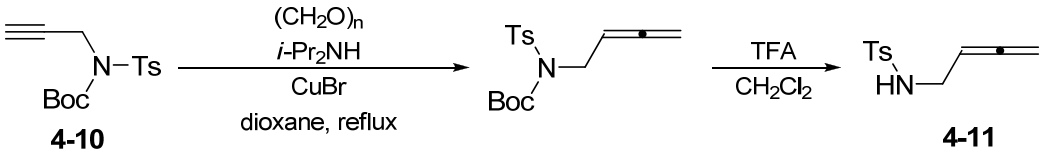
***N*-(*tert*-Butoxycarbonyl)-*N*-(propargyl)-*N*-(4-methylbenzenesulfonyl)amine (4-10)**



4-18 **4-10**

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-18)** (15.0 g, 55.3 mmol) in MeCN (200 mL) was added K_2CO_3 (22.9 g, 0.166 mol), and the mixture was heated to 60 °C for 15 min. Propargyl bromide (8.64 g, 80 wt% solution in toluene, 55.3 mmol) was added to the reaction mixture, and the reaction was heated to 90 °C overnight. The reaction mixture was diluted with methylene chloride and filtered through celite. The solvents were removed under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 10%) to afford *N*-(*tert*-butoxycarbonyl)-*N*-(propargyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-10)** as white prism (16.3 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9 H), 2.33 (t, 3 H, J = 2.7 Hz), 2.45 (s, 3 H), 4.63 (d, 2 H, J = 2.7 Hz), 7.31 (d , 2 H, J = 8.7 Hz), 7.90 (d, 2 H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 27.7, 35.6, 72.0, 78.4, 84.9, 128.1, 128.2, 136.5, 144.4, 150.0. All data are in agreement with those reported in the literature.[16]

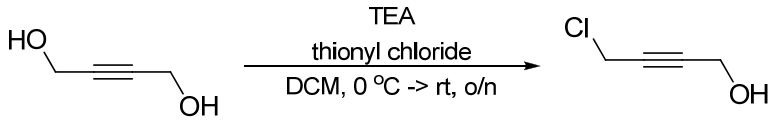
***N*-(Buta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine (4-11)**



To a suspension of paraformaldehyde (0.91 g, 30.4 mmol) and CuBr (1.09 g, 7.60 mmol) in dioxane (50 mL) was added *N*-(*tert*-butoxycarbonyl)-*N*-(propargyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-10)** (4.70 g, 15.2 mmol) and the reaction mixture was heated to 100 ^{o}C for 30 min. Diisopropylamine (4.26 mL, 30.4 mmol) was added to the reaction mixture dropwise. The reaction mixture was then heated at reflux overnight. The reaction mixture was diluted with ethyl ether (200 mL) and filtered through celite. The solvents were removed under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5%) to afford *N*-(*tert*-butoxycarbonyl)-*N*-(buta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine as pale yellow oil (3.583 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9 H), 2.44 (s, 3 H), 4.46 (m, 2 H), 4.79 (m, 2 H), 5.29 (m, 1 H), 7.33 (d , 2 H, J = 8.4 Hz), 7.90 (d, 2 H, J = 8.4 Hz).

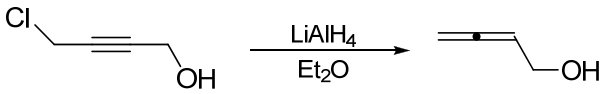
N-(*tert*-butoxycarbonyl)-*N*-(buta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine (3.583 g, 11.1 mmol) was dissolved in DCM (100 mL), and TFA (5 mL) was added dropwise. The reaction was stirred at room temperature for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to afford *N*-(buta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-11)** as pale yellow oil (2.350 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ2.44 (s, 3 H), 3.60 (m, 2 H), 4.45 (bs, 1 H), 4.77 (m, 2 H), 5.07 (m, 1 H), 7.31 (d , 2 H, J = 8.1 Hz), 7.75 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.51, 41.40, 78.05, 87.15, 127.18, 129.69, 137.03, 143.51, 207.99. All data are in agreement with those reported in the literature.[11b]

4-Chloro-2-butyn-1-ol



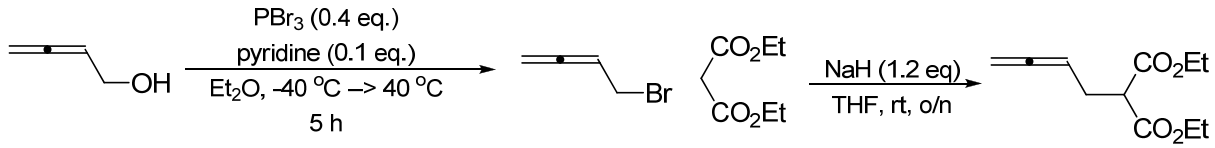
Butyn-1,4-diol (15 g, 0.17 mol) was dissolved in triethylamine (24 mL, 0.17 mol) under nitrogen. After butynediol was dissolved, DCM (50 mL) was added to the solution, and the solution was cooled to 5 °C. Thionyl chloride (13 mL, 0.17 mol) was added slowly to the solution *via* syringe pump over 1 h period. The reaction was stirred for additional 1 h at 5 °C, then the ice bath was removed and the reaction was stirred at room temperature overnight. *tert*-butylmethyl ether(200 mL) was added to the reaction, and then filtered through celite to removed the precipitate. The precipitate cake was washed with additional ether. The filtrate was concentrated under reduced pressure. The resulting brown oil was distilled under reduced pressure (bp: 60-63 °C, 3 torr; lit.[17] 80 °C, 5mmHg) to give colorless liquid (13.2 g, 72%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (t, 2 H, J = 1.8 Hz), 4.33 (t, 2 H, J = 1.8 Hz). All data are in agreement with those reported in the literature.[17-18]

2,3-Butadien-1-ol



A solution of 4-chlorobut-2-yn-1-ol (6.06 g, 58.0 mmol) in Et_2O (30 mL) was added to a suspension of $LiAlH_4$ (3.36 g, 89.0 mmol) in Et_2O (70 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 1 h before water was added. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Distillation (bp128-130 °C, lit.[19] 126-128 °C) afforded but-3,4-dien-1-ol1 as colorless oil (0.928 g, 23 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (br, 1 H), 4.15 (m, 2 H), 4.86 (m, 2 H), 5.35 (m, 1 H). All data are in agreement with those reported in the literature.[10]

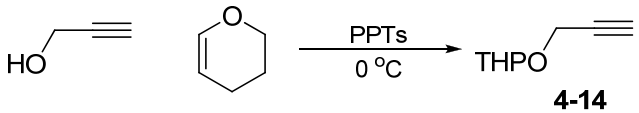
Diethyl 2-(buta-2,3-dienyl)malonate



To a solution of 2,3-butadien-1-ol (1.515 g, 21.6 mmol) and pyridine (0.174 mL) in Et_2O (40 mL) at -20 °C was added PBr_3 (0.813 mL, 8.65 mmol) over a 15 min. period. The resulting reaction mixture was stirred for 2 h at -20 °C, warmed to room temperature over a period of 3 h before being heated to 40 °C and stirred for an additional 30 minutes. The obtained orange solution was then poured into a brine solution and extracted with Et_2O. The organic layers were dried over Na_2SO_4, filtrated and concentrated under reduced pressure affording 4-bromobut-1,2-diene, which was used without purification.

To a suspension of NaH (60% dispersion in mineral oil, 1.038 g, 25.9 mmol) in THF (50 mL) under nitrogen was added diethyl malonate (8.66 g, 54.1 mmol). The reaction mixture was warmed up to room temperature and stirred for 30 min. A solution of 4-bromobut-1,2-diene (2.88 g, 21.62 mmol) in THF (10 mL) was then added dropwise and the resultant mixture stirred for an additional 18 h at room temperature. Water was then added and the organic phase was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford diethyl 2-(buta-2,3-dienyl)malonate as colorless oil (2.916 g, 64 % for 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 6 H, *J* = 7.2 Hz), 2.59 (m, 2 H), 3.47 (t, 1 H, *J* = 7.8 Hz), 4.20 (m, 4 H), 4.72 (m, 2 H), 5.14 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.08, 27.42, 51.58, 61.44, 76.2, 86.76, 168.87, 210.10. All data are in agreement with those reported in the literature.[10]

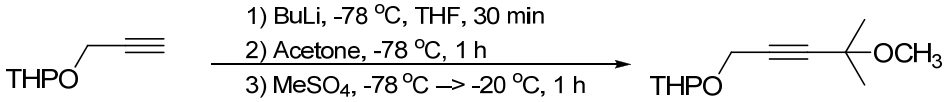
2-(Prop-2-ynyloxy)tetrahydro-2*H*-pyran (4-14)



4-14

In a 50 mL round-bottomed flask was added propargyl alcohol (7.0 g, 130 mmol) and pyridium *p*-toluenesulfonate (0.5 g, 1.99 mmol) to give a clear solution. The solution was cooled to 0 °C. 3,4-dihydro-2*H*-pyran (10.50 g, 125 mmol) was added to the solution dropwise and the reaction was allowed to warm to room temperature gradually and stirred overnight. The reaction mixture was diluted with Et_2O, and the solution was washed with water, saturated $NaHCO_3$ solution, brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran **(4-14)** as colorless liquid (17.50 g, 100%). The resulted material was pure enough for further reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.90 (m, 6 H), 2.41 (t, 1 H, J = 2.4 Hz), 3.50-3.57 (m, 1 H), 3.80-3.87 (m, 1 H), 4.19-4.33 (m, 2 H), 4.82 (t, 1 H, J = 3.0 Hz). All data are in agreement with those reported in the literature.[20]

2-(4-Methoxy-4-methylpent-2-ynyloxy)tetrahydro-2*H*-pyran (4-15)

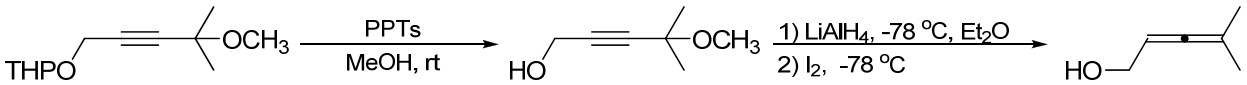


4-14 **4-15**

A solution of 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran (10.00 g, 71.3 mmol) in THF (10 mL) was added to a solution of *n*-butyllithium (2.2 M in cyclohexanes, 40.5 mL, 89 mmol) in THF (150 mL) at -78 °C under nitrogen and the resulting mixture was stirred for 15 min. Acetone (7.86 mL, 107 mmol) was added dropwise *via* syringe, and the reaction was stirred for 30 min. Dimethyl sulfate (20.45 mL, 214 mmol) was added dropwise *via* syringe, and the reaction was stirred for 2 h. Hexamethylphosphoramide (20 mL, 115 mmol) was added to the reaction, and the cold bath was removed. The reaction was stirred at room temperature for additional 1 h. The solvent was removed under reduced pressure, and the crude was diluted with Et_2O and washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 5%) to give 2-(4-methoxy-4-methylpent-2-ynyloxy)tetrahydro-2*H*-pyran **(4-15)** as colorless oil (13.63 g, 90 %):^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 6 H), 1.50-1.80 (m, 6 H),

3.35 (s, 3 H), 3.49-3.56 (m, 1 H), 3.80-3.88 (m, 1 H), 4.25-4.36 (m, 2 H), 4.82 (t, 1 H, J = 3.0 Hz).

4-Methylpenta-2,3-dien-1-ol (4-17)

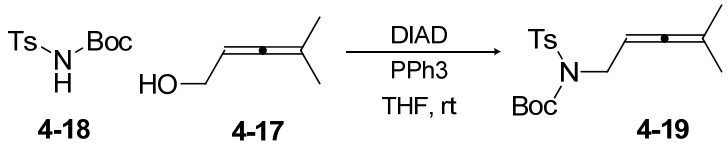


4-15 **4-16** **4-17**

To a solution of 2-(4-methoxy-4-methylpent-2-ynyloxy)tetrahydro-2*H*-pyran **(4-15)** (13.63 g, 64.2 mmol) in MeOH (150 mL) was added pyridium *p*-toluenesulfonate (1.614 g, 6.42 mmol) and the reaction was stirred for 4 h. The reaction was quenched with addition of saturated $NaHCO_3$ solution. Methanol was removed under reduced pressure and the resulted crude was diluted with Et_2O. The solution was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 25%) to give 4-methoxy-4-methylpent-2-yn-1-ol **(4-16)** as colorless oil (5.843 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 6 H), 1.66 (bs, 1 H), 3.35 (s, 3 H), 4.31 (s, 2 H).

To a suspension of $LiAlH_4$ (3.55 g, 94 mmol) in ethyl ether (300 mL) was added 4-methoxy-4-methylpent-2-yn-1-ol **(4-16)** (3. 00 g, 23.41 mmol) dropwise at 0 °C. The reaction was cooled to -78 °C, and iodine (17.82 g, 70.2 mmol) was added in one portion and the reaction was stirred at -78 °C for 2 h. The reaction was quenched with saturated Roschelle salt solution (20 mL), followed by addition of saturated $Na_2S_2O_3$ solution. The reaction was extracted with Et_2O, and the organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 4-methylpenta-2,3-dien-1-ol **(4-17)** as light yellow oil (2.013 g, 88% crude yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (bs, 1 H), 1.72 (s, 3 H), 1.73 (s, 3 H), 4.07 (d, 2 H, J = 5.4 Hz), 5.19 (m, 1 H). All data are in agreement with those reported in the literature.[21]

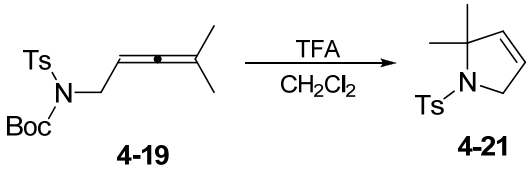
***N*-(*tert*-Butoxycarbonyl)-*N*-(4-methylpenta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine (4-19)**



4-18 **4-17** **4-19**

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-18)** (2.76 g, 10.2 mmol) and triphenylphosphine (3.21 g, 12.2 mmol) in DCM (30 mL) was added diisopropyl azodicarboxylate (2.47 g, 12.2 mmol) drop-wise, and the reaction was stirred for 30 min. 4-Methylpenta-2,3-dien-1-ol **(4-17)** (1.00 g, 10.2 mmol) was added to the reaction mixture and the reaction was stirred overnight. The solvent was removed under reduced pressure, and the crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylpenta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-19)** as colorless oil (3.012 g, 84 %):^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9 H), 1.72 (s, 3 H), 1.73 (s, 3 H), 2.42 (s, 3 H), 4.19 (d, 2 H, *J* = 5.4 Hz), 5.12 (m, 1 H), 7.33 (d, 2 H, *J* = 8.1 Hz), 7.80 (d, 2 H, *J* = 8.1 Hz).

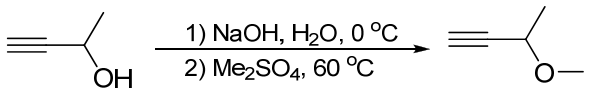
2,2-Dimethyl-*N*-(4-Methylbenzenesulfonyl)-2,5-dihydro-1*H*-pyrrole (4-21)



4-19 **4-21**

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylpenta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-19)** (3.01 g, 8.57 mmol) in DCM (100 mL) was added TFA (5 mL, 64.9 mmol) and the reaction was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to give 2,2-dimethyl-*N*-(4-Methylbenzenesulfonyl)-2,5-dihydro-1*H*-pyrrole **(4-21)** as colorless oil (2.078 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, 3 H, *J* = 1.2 Hz), 1.77 (d, 3 H, *J* = 1.2 Hz), 2.46 (s, 3 H), 3.59 (m, 1 H), 4.16 (m, 1 H), 5.20 (m, 2 H), 7.36 (d, 2 H, *J* = 8.1Hz), 7.94 (d, 2 H, *J* = 8.1Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.48, 21.67, 25.75, 50.31, 58.53, 119.52, 128.29, 129.85, 143.54, 145.65, 151.76.

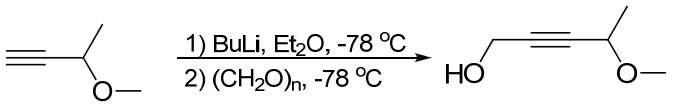
3-Methoxybut-1-yne (4-23)



4-22 **4-23**

To a solution of sodium hydroxide (22.26 g, 0.57 mol) in water (30 mL) was added 3-butyn-2-ol **(4-22)** (30.00 g, 0.43 mol) at 0 °C and the reaction was stirred for 1 h. Dimethyl sulfate (49.1 mL, 0.514 mol) was added to the reaction mixture dropwise, and then the reaction was heated to 60 °C for 2 h. The product was distilled at 62-64 °C (lit.,[22] bp = 62-68 °C) to give 3-methoxybut-1-yne **(4-23)** as colorless liquid (27.70 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 3 H, *J* = 6.6 Hz), 2.42 (d, 1 H, *J* = 2.1 Hz), 3.41 (s, 3 H), 4.06 (dq, 1 H, *J* = 2.1, 6.6 Hz). All data are in agreement with those reported in the literature.[22]

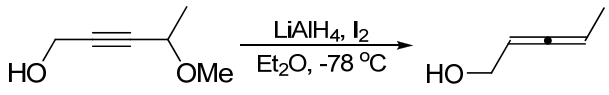
4-Methoxypent-2-yn-1-ol (4-24)



4-23 **4-24**

To a solution of *n*-butyllithium (28.5 mL, 2.5 M in Hexanes, 71.3 mmol) in Et_2O (100 mL) was added 3-methoxybut-1-yne **(4-23)** (5.00 g, 59.4 mmol) dropwise at -78 °C and the reaction was stirred at -78 °C for 1 h. Paraformaldehyde (3.57 g, 119 mmol) was added to the reaction solution in small portions. The reaction was stirred at -78 °C for additional 2 h, and the cold bath was removed and the reaction was warm to room temperature and stirred overnight. The reaction was quenched with 6 N HCl solution. The organic layer was washed with water, saturated $NaHCO_3$ solution, brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by vacuum distillation (100 – 103 °C/18 mmHg) to give 4-methoxypent-2yn-1-ol **(4-24)** as light yellow liquid (5.763g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 3 H, *J* = 6.6 Hz), 3.40 (s, 3 H), 4.06 (t*q, 1 H, *J* = 1.8*6.6 Hz), 4.31 (d, 2 H, *J* = 1.8 Hz). All data are in agreement with those reported in the literature.[23]

Penta-2,3-dien-1-ol (4-25)

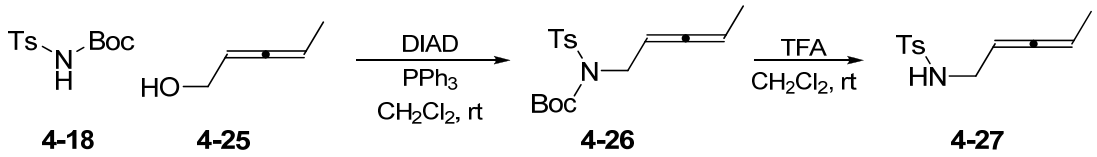


4-24 **4-25**

To a suspension of $LiAlH_4$ (2.13 g, 56.1 mmol) in Et_2O (100 mL) was added 4-methoxypent-2-yn-1-ol **(4-24)** (1.60 g, 14.25mmol) dropwise at 0 °C. The reaction was cooled to -78 °C, and iodine (10.67 g, 42.1 mmol) was added in one portion and the reaction was stirred at

-78 °C for 2 h. The reaction was quenched with saturated Roschelle salt solution, followed by addition of saturated $Na_2S_2O_3$ solution. The mixture was extracted with Et_2O, and the organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give penta-2,3-dien-1-ol **(4-25)** as light yellow oil (1.012 g, 86% crude yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (m, 3 H), 4.11 (m, 2 H), 5.28 (m, 2 H). All data are in agreement with those reported in the literature.[24]

***N*-(Penta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine (4-27)**

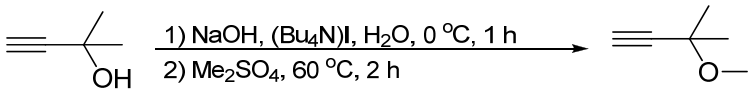


4-18 **4-25** **4-26** **4-27**

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-18)** (3.80 g, 14.0 mmol) and triphenylphosphine (4.41 g, 16.8 mmol) in DCM (30 mL) was added diisopropyl azodicarboxylate (3.40 g, 16.8 mmol) dropwise, and the reaction was stirred for 30 min. Penta-2,3-dien-1-ol **(4-25)** (1.00 g, 10.2 mmol) was added to the reaction mixture and the reaction was stirred overnight. The solvent was removed under reduced pressure, and the crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give *N*-(*tert*-butoxycarbonyl)-*N*-(penta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-26)** as colorless oil (2.422 g, 51% for 2 steps):^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9 H), 1.64 (m, 3 H), 2.44 (s, 3 H), 4.42 (m, 2 H), 5.21 (m, 2 H), 7.30 (d, 2 H, J = 8.1 Hz), 7.82 (d, 2 H, J = 8.1 Hz).

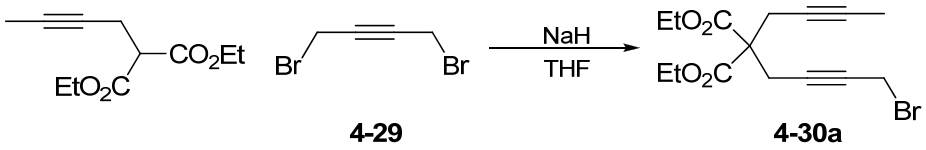
To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(Penta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-26)** (2.422 g, 7.18 mmol) in DCM (100 mL) was added TFA (3 mL, 38.9 mmol) and the reaction was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to give *N*-(penta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-27)** as colorless oil (1.27 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (m, 3 H), 2.43 (s, 3 H), 3.54 (m, 2 H), 4.48 (bs, 1 H), 5.00 (m, 1 H), 5.17 (m, 1 H), 7.30 (m, 2 H), 7.75 (m, 2 H). All data are in agreement with those reported in the literature.[25]

3-Methoxy-3-methylbut-1-yne



To a 12 M solution of sodium hydroxide (37.2 mL, 0.446 mol) and tetrabutylamonium iodide (0.549 g, 1.49 mmol) was added 2-methyl-3-butyn-2-ol (25.00 g, 0.297 mol) at 0 °C and the reaction was stirred for 1 h. Dimethyl sulfate (31.2 mL, 0.327 mol) was added to the reaction mixture dropwise, and then the reaction was heated at 60 °C for 2 h. The product was distilled at 79-82 °C (lit.,[26] bp = 80-82 °C) to give 3-methoxy-3-methylbut-1-yne as colorless liquid (23.07g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 6 H), 2.42 (s, 1 H), 3.41 (s, 3 H), 3.37 (s, 3 H). All data are in agreement with those reported in the literature.[27]

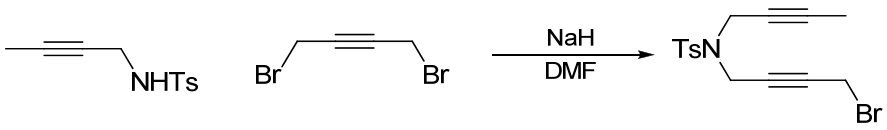
1-Bromo-5,5-di(carbethoxy)-nona-2,7-diyne (4-30a)



4-29 **4-30a**

Diethyl 2-(but-2-ynyl)malonate[28] (5.0 g, 24 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 1.00 g, 23.6 mmol) in 80 mL of THF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of 1,4-dibromobut-2-yne (**4-29)** (15.0 g, 70.7 mmol) in 100 mL of THF *via* cannula over 2.5 h. The mixture was then stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield yellow oil. The excess dibromobutyne was recovered by distillation (100 °C/4 mmHg). The residue was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give product 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(4-30a)** as yellow oil (6.88 g, 85%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 6H, J = 7.2 Hz), 1.75 (t, 2H, J = 2.7 Hz), 2.88 (q, 2H, J = 2.7 Hz), 3.02 (t, 2H, J = 2.1 Hz), 3.87 (t, 2H, J = 2.1 Hz), 4.25 (q, 4H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.45, 14.02, 14.69, 22.74, 22.99, 56.70, 61.69, 61.87, 72.94, 78.20, 79.14, 82.23, 168.86. All data are in agreement with those reported in the literature.[10, 14]

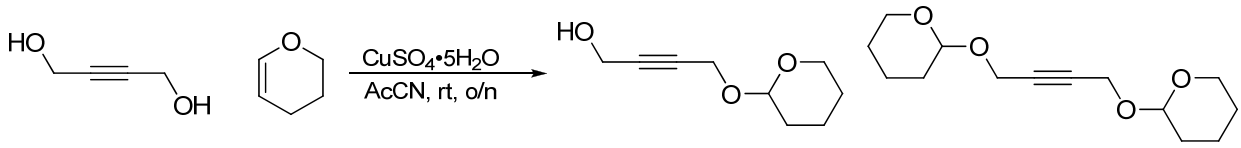
1-Bromo-5-(4-methylbenzenesulfonyl)-5-azanona-2,7-diyne (4-30b)



4-29 **4-30b**

N-(But-2-ynyl)-*N*-(4-methylbenzenesulfonyl)amine (500 mg, 2.24 mmol) in 5 mL of DMF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 107 mg, 2.69 mmol) in 5 mL of DMF. The resulting mixture was stirred for 1 h at room temperature. The mixture was then transferred to a solution of 1,4-dibromobut-2-yne **(4-29)** (1.50 g, 7.07 mmol) in 5 mL of DMF *via* cannula and the resulting mixture stirred at room temperature for 18 h. The mixture was diluted with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield yellow oil. The excess dibromobutyne was recovered by distillation (100 ^oC/4 mmHg). The residue was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give 1-bromo-5-(4-methylbenzenesulfonyl)-5-azanona-2,7-diyne **(4-30b)** as viscous yellow oil (490 mg, 62%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (t, 3 H, *J* = 2.4 Hz), 2.43 (s, 3 H), 3.72 (t, 2 H, *J* = 2.1 Hz), 4.06 (q, 2 H, *J* = 2.4 Hz), 4.21 (d, 2 H, *J* = 2.1 Hz), 7.32 (d, 2 H, *J* = 8.4 Hz), 7.72 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.38, 13.69, 21.51, 36.49, 36.96, 71.33, 79.63, 80.43, 82.02, 127.89, 129.42, 135.30, 143.72. All data are in agreement with those reported in the literature.[10, 14]

***O*-Tetrahydro-2*H*-pyranylbut-2-yn-1,4-diol[29]**

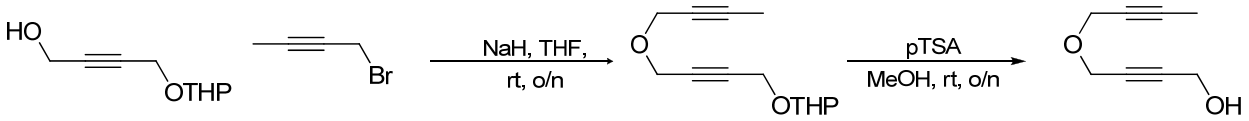


To a mixture of 2-butyn-1,4-diol (9.00 g, 0.105 mol) and copper (II) sulfate pentahydrate (5.22 g, 0.021 mol) in MeCN (200 mL) was added 3,4-dihydro-2*H*-pyran (10.49 mL, 0.115 mol) dropwise *via* syringe pump over 1 h period. The reaction was stirred overnight. The reaction mixture was dilute with DCM and filtered through celite to remove copper sulfate, and the solvents were removed under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to afford *O*-tetrahydro-2*H*-

pyranylbut-2-yn-1,4-diol as pale yellow oil (11.69 g, 62 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52–1.86 (m, 7 H), 3.50–3.57 (m, 1 H), 3.80–3.88 (m, 1 H), 4.22–4.38 (m, 4 H), 4.80 (t, 1 H, *J* = 3.2 Hz). All data are in agreement with those reported in the literature.[29b]

1,4-Bis(tetrahydro-2H-pyran-2-yloxy)but-2-yne was afforded as light yellow oil (5.80 g, 22%): ^{1}H NMR (300 MHz, $CDCl_3$): δ1.46–1.79 (m, 12 H), 3.43–3.48 (m, 2 H), 3.73–3.79 (m, 2 H), 4.19 (d, , 1 H, *J* = 17.6 Hz), 4.22 (d, , 2 H, *J* = 12.4 Hz), 4.27 (d, , 1 H, *J* = 14.2 Hz), 4.74 (t, 2 H, *J* = 3.4 Hz). All data are in agreement with those reported in the literature.[30]

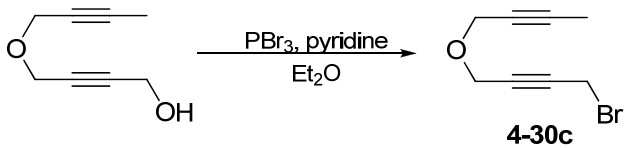
5-Oxanona-2,7-diyn-1-ol



To a suspension of NaH (1.173 g, 60 wt% in mineral oil, 29.3 mmol) in THF(30 mL) was added a solution of *O*-tetrahydro-2*H*-pyranylbut-2-yn-1,4-diol (3.84 g, 22.6 mmol)in THF (15 mL) dropwise, and the reaction was stirred for 30 min. 2-Butynylbromide (3.00 g, 22.6 mmol) in THF (15 mL) was added to the reaction mixture dropwise. The reaction was stirred at room temperature overnight. The reaction was quenched with addition of water, and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford *O*-tetrahydro-2*H*-pyranyl-5-oxa-nona-2,7-diyn-1-ol as pale yellow oil (4.46 g, 89 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ1.52–1.86 (m, 7 H), 1.85 (t, 3 H, *J* = 2.4 Hz), 3.49–3.57 (m, 1 H), 3.80–3.88 (m, 1 H), 4.19 (m, 2 H), 4.27–4.32 (m, 3 H), 4.80 (t, 3 H, *J* = 3.3 Hz).

To a solution of *O*-tetrahydro-2*H*-pyranyl-5-oxa-nona-2,7-diyn-1-ol (4.46 g, 20.1 mmol) in MeOH (20 mL) was added a solution of *p*-tolylsulfonic acid (0.691 g, 4.01 mmol) in MeOH (5 mL). The reaction was stirred overnight at room temperature. The reaction was quenched with addition of water, and extracted with Et_2O. The combined organic layers were washed with water brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 20%) to afford 5-oxanona-2,7-diyn-1-ol as pale yellow oil (2.39 g, 86 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (t, 3 H, *J* = 2.4 Hz), 4.20 (q, 2 H, *J* = 2.4 Hz), 4.27 (t, 2 H, *J* = 2.4 Hz), 4.31 (t, 2 H, *J* = 2.4 Hz). All data are in agreement with those reported in the literature.[31]

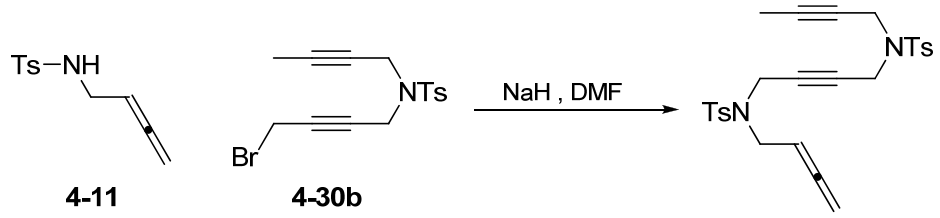
1-Bromo-5-oxanona-2,7-diyne (4-30c)



4-30c

To a solution of 5-oxanona-2,7-diyn-1-ol (2.39 g, 17.3 mmol) and pyridine (0.15 mL, 1.73 mmol) in Et_2O (30 mL) at 0 °C, was added dropwise a solution of PBr_3 (0.814 mL, 8.63 mmol) in Et_2O (10 mL). The resultant reaction mixture was stirred under nitrogen for 19 h at room temperature. Water was then added followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford 1-bromo-5-oxanona-2,7-diyne **(4-30c)** as colorless oil (2.850 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$): δ1.85 (t, 3 H, *J* = 2.4 Hz), 3.95 (q, 2 H, *J* = 2.4 Hz), 4.18 (t, 2 H, *J* = 2.4 Hz), 4.29 (t, 2 H, *J* = 2.4 Hz). All data are in agreement with those reported in the literature.[31]

5,10-Bis(4-Methylbenzenesulfonyl)-5, 10-diazatetradeca-1,2-dien-7,12-diyne (4-32a)

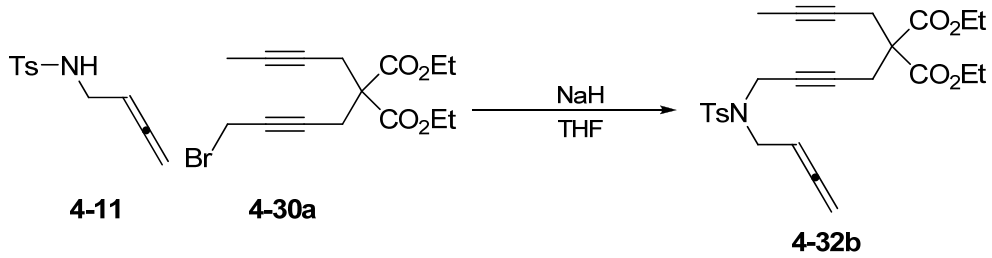


4-11 **4-30b** **4-32a**

To a suspension of NaH (0.07 g, 60% dispersion in mineral oil, 1.8 mmol) in DMF (5 mL) under nitrogen was added a solution of *N*-(buta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-11)** (0.32 g, 1.4 mmol) in DMF (5 mL). The reaction mixture was stirred for 30 min. A solution of 1-bromo-5-(4-methylbenzenesulfonyl)-5-azanona-2,7-diyne (0.50 g, 1.4 mmol) in DMF (5 mL) was then added dropwise, and the resultant mixture stirred for an additional 18 h at room temperature. Water was then added and the organic phase was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford 5,10-bis(4-methylbenzenesulfonyl)-5, 10-diazatetradeca-1,2-dien-7,12-diyne **(4-32a)** as yellow oil (0.63 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (t, 3 H, *J* = 2.4 Hz), 2.42 (s, 3H), 2.44 (s, 3H), 3.76(m, 2 H), 3.86 (q, 2 H, *J* = 2.4

Hz), 3.89 (t, 2 H, J = 1.8 Hz), 4.03 (t, 2 H, J = 1.8 Hz), 4.76 (m, 2 H), 4.98 (m, 1 H), 7.30 (m, 4 H), 7.65 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.33, 21.51, 21.54, 36.04, 36.16, 36.57, 45.68, 71.20, 76.42, 78.23, 78.37, 81.86, 85.37, 127.56, 127.85, 129.38, 129.59, 135.39, 136.06, 143.73, 143.78, 209.72; HRMS (ES) m/z calcd for $C_{26}H_{29}N_2O_4S_2$ $(M + H)^+$: 497.1569, found 497.1573 (Δ 0.8 ppm).

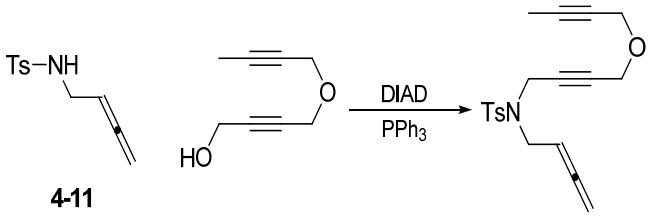
5-(4-Methylbenzenesulfonyl)-10,10-di(carbethoxy)-5-azatetradeca-1,2-dien-7,12-diyne (4-32b)



4-11 **4-30a** **4-32b**

To a suspension of NaH (0.07 g, 60 wt% in mineral oil, 1.8 mmol) in DMF (5 mL) was added a solution of *N*-(buta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-11)** (0.32 g, 1.4 mmol) in DMF (5 mL) dropwise. 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(4-30a)** (0.48 g, 1.4 mmol) in DMF (5 mL) was added to the reaction mixture dropwise. The reaction was stirred at room temperature overnight. The reaction was quenched with addition of water, followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to afford 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(4-32b)** as pale yellow oil (0.596 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, 6 H, J = 7.2 Hz), 1.74 (t, 3 H. J = 2.7 Hz), 2.43 (s, 3 H), 2.66 (q, 2 H. J = 2.7 Hz), 2.75 (t, 2 H. J = 2.7 Hz), 3.83 (td, 2 H, J = 2.7 Hz, 7.2 Hz), 4.10 (t, 2 H. J = 2.7 Hz), 4.16 (m, 4 H), 4.77 (td, 2 H, J = 2.7 Hz, 6.6 Hz), 5.01 (p, 1 H, J = 6.6 Hz), 7.31 (d, 2 H. J = 7.8 Hz), 7.70 (d, 2 H. J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.45, 13.99, 21.52, 22.64, 22.83, 36.18, 45.33, 56.44, 61.76, 73.02, 75.85, 76.63, 78.86, 80.35, 85.49, 127.53, 129.53, 129.62, 136.36, 143.43, 168.83, 209.68; HRMS (ES) m/z calcd for $C_{26}H_{32}NO_6S$ $(M + H)^+$: 486.1950, found 486.1950 (Δ 0.0 ppm).

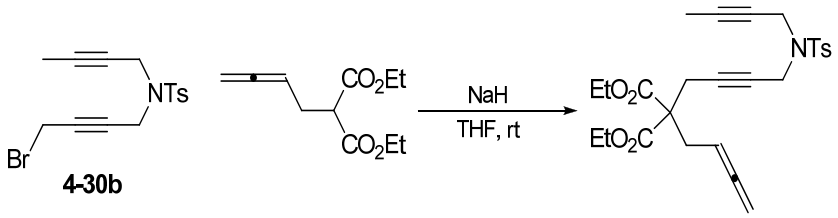
5-(4-Methylbenzenesulfonyl)-5-aza-10-oxatetradeca-1,2-dien-7,12-diyne (4-32c)



4-11 **4-32c**

To a solution of triphenylphosphine (1.04 g, 3.98 mmol) in THF (20 mL) was added diisopropyl azodicarboxylate (3.40 g, 3.98 mmol) dropwise, and the reaction was stirred until precipitation formed. A solution of *N*-(buta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-11)** (0.81 g, 3.6 mmol) in THF (5 mL) was added to reaction mixture and stirred for 1 h, and then a solution of 5-oxanona-2,7-diyn-1-ol (0.50 g, 3.62 mmol) in THF (5 mL) was added to the reaction mixture and the reaction was stirred overnight. The solvent was removed under reduced pressure, and the crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 0% → 10%) to give 5-(4-Methylbenzenesulfonyl)-5-aza-10-oxatetradeca-1,2-dien-7,12-diyne **(4-32c)** as light yellow oil (0.834 g, 67%):^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (t, 3 H, *J* = 2.7 Hz), 2.43 (s, 3 H), 3.86 (td, 2 H, *J* = 2.7 Hz, 7.2 Hz), 3.98 (m, 4 H), 4.18 (t, 2 H, *J* = 1.8 Hz), 4.77 (td, 2 H, *J* = 2.7 Hz, 6.6 Hz), 5.04 (p, 1 H, *J* = 6.6 Hz), 7.28 (d, 2 H. *J* = 7.8 Hz), 7.72 (d, 2 H. *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.76, 21.70, 36.45, 46.00, 56.48, 57.17, 74.43, 79.59, 81.18, 83.29, 85.58, 85.76, 127.95, 129.74, 136.41, 143.77, 210.02; HRMS (ES) m/z calcd for $C_{19}H_{22}NO_3S$ $(M + H)^+$: 344.1320, found 344.1320 (Δ 0.0 ppm).

10-(4-Methylbenzenesulfonyl)-5,5-di(carbethoxy)-10-azatetradeca-1,2-dien-7,12-diyne (4-32d)

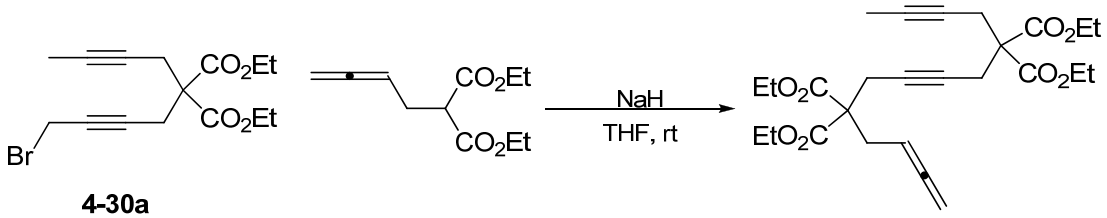


4-30b **4-32d**

A solution of diethyl 2-(buta-2,3-dienyl)malonate (0.25 g, 1.2 mmol) in THF (2 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 57 mg, 1.8 mmol) in THF (10 mL)

under nitrogen and the resulting mixture was stirred for 30 min at room temperature. A solution of 1-bromo-5-(4-methylbenzenesulfonyl)-5-azanona-2,7-diyne **(4-30b)** (0.42 g, 1.2 mmol) in THF (2 mL) was then added dropwise and the reaction mixture was stirred at room temperature overnight. Water was added followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford 10-(4-Methylbenzenesulfonyl)-5,5-di(carbethoxy)-10-azatetradeca-1,2-dien-7,12-diyne **(4-32d)** as light yellow oil (421 mg, 74%):^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 6 H, *J* = 7.2 Hz), 1.63 (t, 3 H, *J* = 2.4 Hz), 2.42 (s, 3H), 2.60 (td, 2 H, *J* = 2.4 Hz, 5.4 Hz), 2.72 (t, 2 H, *J* = 2.4 Hz), 4.04-4.07 (m, 4 H), 4.19 (q, 4 H, *J* = 7.2 Hz), 4.65 (td, 2 H, *J* = 2.4 Hz, 6.4 Hz), 4.85 (m, 1 H), 7.30 (d , 2 H, *J* = 7.8 Hz), 7.71 (d, 2 H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.55, 14.22, 21.71, 23.02, 31.81, 36.67, 36.72, 57.17, 61.87, 71.64, 74.91, 76.05, 80.69, 81.89, 84.04, 128.10, 129.58, 135.75, 143.75, 169.73; HRMS (ES) m/z calcd for $C_{26}H_{32}NO_6S$ $(M + H)^+$: 486.1950, found 486.1950 (Δ 0.0 ppm).

5,5,10,10-Tetra(carbethoxy)-tetradeca-1,2-dien-7,12-diyne (4-32e)

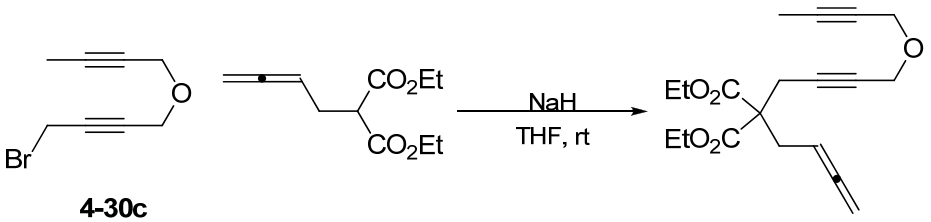


4-30a **4-32e**

A solution of diethyl 2-(buta-2,3-dienyl)malonate (0.25 g, 1.2 mmol) in THF (2 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 57 mg, 1.75 mmol) in THF (10 mL) under nitrogen and the resulting mixture was stirred for 30 min at room temperature. A solution of 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(4-30a)** (0.40 g, 1.2 mmol) in THF (2 mL) was then added dropwise and the reaction mixture was stirred at room temperature overnight. Water was added followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford 5,5,10,10-tetra(carbethoxy)-tetradeca-1,2-dien-7,12-diyne **(4-32e)** as light yellow oil (454 mg, 81%):^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (m, 12 H), 1.74 (t, 3 H, *J* = 2.4 Hz), 2.71 (td, 2 H, *J* = 2.4 Hz,

8.0 Hz), 2.79 (t, 2 H, *J* = 2.4 Hz), 2.85 (q, 2 H, *J* = 2.4 Hz), 2.90 (t, 2 H, *J* = 2.4 Hz), 4.19 (m, 8 H), 4.66 (td, 2 H, *J* = 2.4 Hz, 6.4 Hz), 4.93 (m, 1 H) ; HRMS (ES) m/z calcd for $C_{26}H_{35}O_8$ $(M + H)^+$: 475.2332, found 475.2334 (Δ 0.4 ppm). The data was consistent with literature values.[10]

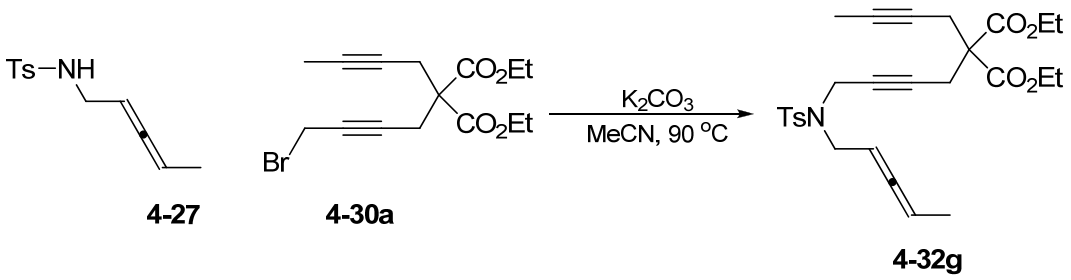
5,5-Di(carbethoxy)-10-oxatetradeca-1,2-dien-7,12-diyne (4-32f)



4-30c **4-32f**

A solution of diethyl 2-(buta-2,3-dienyl)malonate (0.30 g, 1.4 mmol) in THF (2 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 68 mg, 1.70 mmol) in THF (10 mL) under nitrogen and the resulting mixture was stirred for 30 min at room temperature. A solution of 1-bromo-5-oxanona-2,7-diyne **(4-30c)** (0.28 g, 1.4 mmol) in THF (1 mL) was then added dropwise and the reaction mixture was stirred at room temperature overnight. Water was added followed by extraction with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to afford 5,5-di(carbethoxy)-10-oxatetradeca-1,2-dien-7,12-diyne **(4-32f)** as colorless oil (353 mg, 75%):^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6 H, *J* = 7.2 Hz), 1.85 (t, 3 H, *J* = 2.4 Hz), 2.75 (td, 2 H, *J* = 2.4 Hz, 8.1 Hz), 2.89 (t, 2 H, *J* = 2.4 Hz), 4.15-4.24 (m, 8 H), 4.67 (td, 2 H, *J* = 2.4 Hz, 6.6 Hz), 4.96 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.79, 14.24, 23.18, 31.92, 56.81, 56.98, 57.32, 61.88, 74.60, 74.93, 78.73, 81.81, 83.20, 84.08, 169.87, 210.36; HRMS (ES) m/z calcd for $C_{19}H_{25}O_5$ $(M + H)^+$: 333.1702, found 333.1699 (Δ 0.9 ppm).

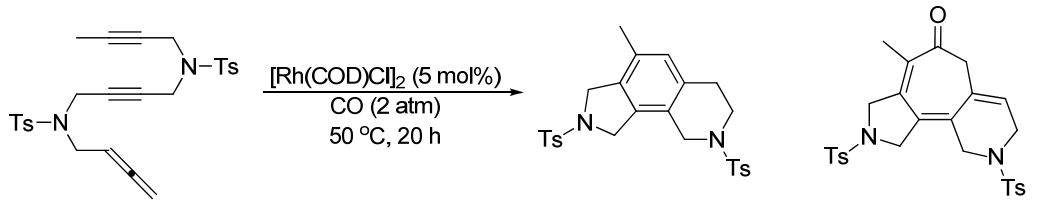
6-(4-Methylbenzenesulfonyl)-11,11-di(carbethoxy)-6-azapentadeca-2,3-dien-8,13-diyne (4-32g)



4-27 **4-30a** **4-32g**

To a suspension of K_2CO_3 (0.70 g, 5.1 mmol) in CH_3CN (20 mL) was added the solution of *N*-(penta-2,3-dienyl)-*N*-(4-methylbenzenesulfonyl)amine **(4-27)** (0.40 g, 1.7 mmol) in MeCN (5 mL) and a solution of 1-bromo-5,5-di(carbethoxy)-nona-2,7-diyne **(4-30a)** (0.58 g, 1.7 mmol) in MeCN (5 mL). The reaction was heated at 90 °C overnight. The reaction mixture was diluted with DCM and filtered through celite. The filtrate was concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 5% → 10%) to give 6-(4-methylbenzenesulfonyl)-11,11-di(carbethoxy)-6-azapentadeca-2,3-dien-8,13-diyne **(4-32g)** as light yellow oil (0.583 g, 70 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 6 H, *J* = 7.2 Hz), 1.65 (m, 3 H), 1.74 (t, 3 H, *J* = 2.4 Hz), 2.44 (s, 3 H), 2.66 (q, 2 H, *J* = 2.4 Hz), 3.78 (m, 2 H), 4.10-4.20 (m, 6 H), 4.93 (m , 1 H), 5.16 (m, 1 H), 7.30 (m, 2 H), 7.70 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.70, 14.20, 14.24, 21.71, 21.77, 22.89, 23.02, 36.21, 46.06, 56.71, 61.99, 73.28, 76.18, 79.06, 80.44, 85.65, 87.58, 127.80, 129.76, 136.74, 143.59, 169.08, 206.67; HRMS (ES) m/z calcd for $C_{27}H_{34}NO_6S$ $(M + H)^+$: 500.2107, found 500.2103 (Δ 0.8 ppm).

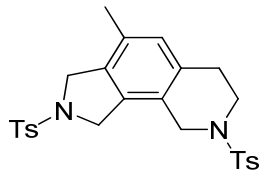
[2+2+2+1] Cycloaddition of allenediyne



General Procedure: To a solution of allenediyne (50 mg, 0.103 mmol) in DCE (1.030 mL, 0.1 M) was added $[Rh(CO)_2Cl]_2$ (2.0 mg, 5 mol%). The reaction vessel was placed in autoclave; the autoclave was purged with CO three times and pressurized to 2 atm (**Caution!! Must be done in a well ventilated hood**). The autoclave was placed in 50 °C oil bath for 16 h. The autoclave was allowed to cool to room temperature and the gas vented. The solution was

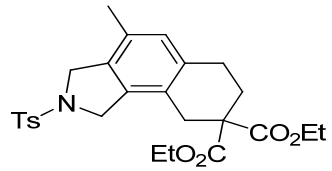
concentrated under reduced pressure and the resulting crude was purified by flash column chromatography (silica gel, EtOAc/Hexanes = 10% → 30%).

4-Methyl-2,3,6,7,8,9-hexahydro-2,8-ditosyl-2,8-diaza-1*H*-cyclopenta[*a*]naphthalene (4-33a)



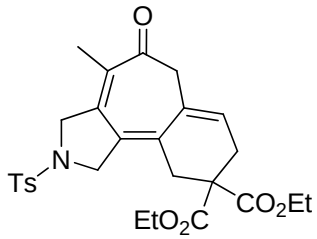
yellow oil (18 mg, 36%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3 H), 2.42 (s, 3 H), 2.44 (s, 3 H), 2.87 (t, 2 H, *J* = 5.7 Hz), 3.28 (t, 2 H, *J* = 5.7 Hz), 3.95 (s, 2 H), 4.44 (s, 2 H), 4.50 (s, 2 H), 6.78 (s,1 H), 7. 33 (m, 4 H), 7.75 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.53, 21.70, 29.02, 29.92, 43.73, 45.32, 52.66, 53.14, 124.04, 127.82, 127.91, 129.39, 130.15, 131.09, 132.88, 133.13, 133.58, 133.99, 144.04, 144.12; HRMS (ES) m/z calcd for $C_{26}H_{29}N_2O_4S_2$ $(M + H)^+$: 497.1569, found 497.1567 (Δ 0.4 ppm).

4-Methyl-8,8-di(carbethoxy)-2,3,6,7,8,9-hexahydro-2-tosyl-2-aza-1*H*-cyclopenta[*a*]naphthalene (4-33d)



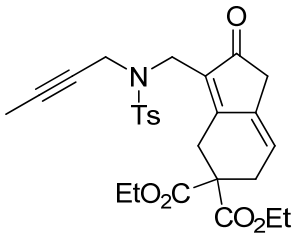
yellow oil; TLC (SiO_2, hexanes: EtOAc = 3:2, R_f = 0.72); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 6 H, *J* = 7.2 Hz), 2.11 (s, 3 H), 2.26 (t, 2 H, *J* = 6.6 Hz), 2.41 (s, 3 H), 2.72 (t, 2 H, *J* = 6.6 Hz), 2.96 (s, 2 H), 4.17 (q, 4 H, *J* = 7.2 Hz), 4.53 (s, 2 H), 4.55 (s, 2 H), 6.75 (s,1 H), 7. 31 (d, 2 H, *J* = 8.4 Hz), 7.78 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.22, 14.28, 21.66, 25.80, 28.05, 30.36, 31.75, 53.53, 54.17, 61.82, 125.99, 127.82, 129.88, 130.02, 130.20, 132.99, 134.61, 134.69, 143.81, 171.31; HRMS (ES) m/z calcd for $C_{26}H_{32}NO_6S$ $(M + H)^+$: 486.1950, found 486.1949 (Δ 0.2 ppm).

4-Methyl-9,9-di(carbethoxy)-1,2,3,5,6,8,9,10-octahydro-2-tosyl-5-oxo-2-aza-benzo[*e*]azulene (4-34d)



yellow oil; TLC (SiO_2, hexanes: EtOAc = 3:2, R_f = 0.52); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, 6 H, *J* = 7.2 Hz), 1.79 (s, 3 H), 2.43 (s, 3 H), 2.73 (bd, 2 H, *J* = 4.2 Hz), 2.81 (s, 2 H), 3.32 (bd, 2 H, *J* = 1.2 Hz), 4.13(m, 6 H), 4.23 (s, 2 H), 5.85 (bt, 1 H), 6.75 (s,1 H), 7. 35 (d, 2 H, *J* = 8.1 Hz), 7.76 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.19, 15.63, 21.77, 32.15, 34.61, 49.93, 53.86, 54.16, 54.9, 62.15, 128.17, 120.91, 120.94, 130.12, 131.03, 132.75, 133.03, 133.14, 143.50, 144.37, 170.29, 194.41; HRMS (ES) m/z calcd for $C_{27}H_{33}NO_7S$ $(M + H)^+$: 514.1899, found 514.1891 (Δ 1.6 ppm).

3-[(*N*-(But-2-ynyl)-4-methylbenzenesulfonamido)methyl]-5,5-di(carbethoxy)-2-oxo-4,6-dihydro-1*H*-indene (4-35d)



yellow oil; TLC (SiO_2, hexanes: EtOAc = 3:2, R_f = 0.42); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 6 H, *J* = 7.2 Hz), 1.53 (t, 3 H, *J* = 2.4 Hz), 2.43 (s, 3 H), 2.89 (m, 4 H), 3.38 (s, 2 H), 4.01 (q, 2 H, *J* = 2.4 Hz), 4.06 (s, 2 H), 4.17 (q, 2 H, *J* = 7.2 Hz), 5.93 (t, 1 H, *J* = 4.2 Hz), 7. 30 (d, 2 H, *J* = 8.1 Hz), 7.75 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.51, 14.17, 21.71, 30.47, 31.10, 38.07, 38.35, 39.77, 54.34, 62.18, 72.10, 82.18, 122.56, 128.26, 129.51, 134.57, 134.99, 135.70, 143.61, 164.56, 170.45, 203.61; HRMS (ES) m/z calcd for $C_{27}H_{33}NO_7S$ $(M + H)^+$: 514.1899, found 514.1908 (Δ 1.8 ppm).

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Chapter 5

Synthesis of Biphenols for Monodentate Phosphorus Ligands

Table of Content

§ 5.1. Introduction

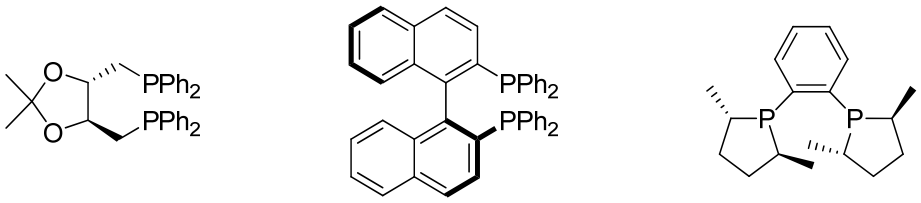
Exponential growth of research in asymmetric catalysis was not started until the 1960's. In 1961, Natta successfully polymerized benzofurane using $AlCl_3$/phenylalanine catalyst to obtain an optically active polymer.[1] Outside of polymer chemistry, the first example of organometallic asymmetric catalysis was described by Nozaki, Noyori *et al*. in 1966.[2] They used chiral salen-copper complex catalyst in cyclopropanation of an alkene. In the same year, Wilkinson established homogeneous hydrogenation of alkenes with $[RhCl(PPh_3)_3]$.[3] The landmark of asymmetric catalysis was set by Knowles and Hornor in 1968 by modifying Wilkinson's homogeneous hydrogenation catalyst with a chiral monodentate phosphine **5-1**.[4] Even though the enantioselectivity was only 15%, this work demonstrated that an achiral catalyst can be transformed into a chiral catalyst through ligand exchange using chiral ligands. After the optimization of the phosphine ligand system, using methylcycohexyl-*o*-anisylphosphine (CAMP) **5-2,** Knowles was able to obtain 88% enantiomeric excess. This was the first reported catalytic reaction in which an enzyme-like selectivity could be obtained with a man-made catalyst.

5-1 **CAMP, 5-2**

Figure 5-1: Chiral monodentate phosphine ligands.

In the early 1970's, Kagan used the bidentate phosphorus ligand *R,R*-DIOP **5-3** for asymmetric hydrogenation of olefins to obtain high enantiopurity.[5] The most significant of Kagan's work was that it had demonstrated that the chirality of a chiral catalyst did not need to be on the chelating atoms to obtain good results. Two of the biggest breakthroughs in organometallic asymmetric catalysis were published in 1980s. Katsuki and Sharpless introduced *asymmetric epoxidation* of allylic alcohols using diethyl tartrate-titanium complex catalyst.[6] Noyori described the application of *asymmetric hydrogenation* using BINAP-rhodium complexes.[7] These methods are now routine reactions in synthesis because of their broad scope of application and high enantiomeric-excess (ee) of the products. In 2001, the Nobel Prize in Chemistry was awarded to Knowles, Noyori, and Sharpless in recognition of their works in chirally-catalyzed hydrogenation and oxidation.

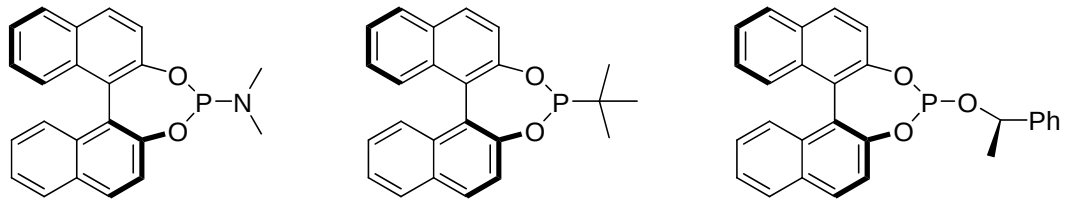
Discovery of effective chiral catalysts is the most fundamental aspect in the development of asymmetric synthesis. Rather than developing a super-catalyst for all organic reactions, it is more feasible to develop catalyst libraries capable of fine-tuning to a specific target reaction. Chiral Lewis Acids are well-known catalysts in many organic reactions.[8] Combinations of chiral ligands with metals are widely developed in catalysis of organic reactions. Among them, phosphorus ligands have been heavily studied. Although chiral monophosphines[4b] were the first ligands applied in asymmetric hydrogenation, this area was dominated by chiral bidentate ligands for several decades. Enormous efforts were put into the development of bidentate ligands such as DIOP **5-3**,[5] BINAP **5-4**,[7] and DuPHOS **5-5**,[9] but only a few of these ligands are commercially available.



(*S,S*)-DIOP **5-3** (*S*)-BINAP **5-4** (*S,S*)-DuPHOS **5-5**

Figure 5-2: Chiral bidentate Phosphine ligands.

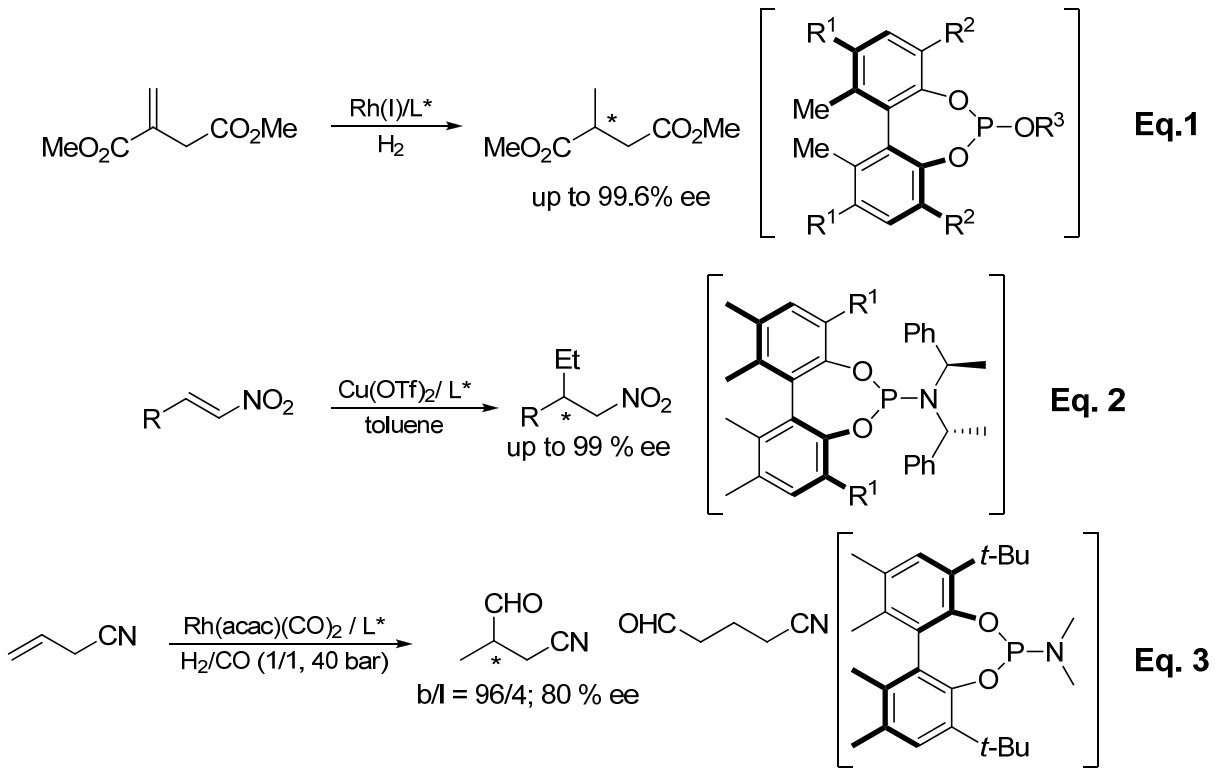
The major drawback of these bidentate ligands is that they are often hard to synthesize, thus making them more expensive. In addition, bidentate ligands are difficult to fine-tune, accordingly some of the attention has turned to monodentate ligands. In 2000, it was demonstrated simultaneously by Reetz and Feringa that a monodentate ligand family based on the BINOL back bone such as phosphoramidite (MonoPhos) **5-6**, phosphonite **5-7**, and phosphite **5-8** were effective catalysts in the hydrogenation of methyl-2-acetamido acrylate with ee's up to 99%.[10] These ligands gave comparable or even better results than the previous bidentate ligands. The facile synthesis with good fine-tuning capability and lower cost make these monodentate ligands ideal for asymmetric catalysis.



MonoPhos, **5-6** Phosphonite, **5-7** Phosphite, **5-8**

Figure 5-3: Binol-based monodentate phosphorus ligands.

In Ojima's Laboratory, new classes of monodentate phosphorous ligands based on the biphenol backbone have been developed.[11] These biphenol-based monodentate phosphorus ligands possess three modifiable substituents including the 6 and 6' positions, 5 and 5' positions and 3 and 3' positions. Together, these modifiable substituents provide the fine-tuning capability for these ligands. It has been found that the 6 and 6'-dimethyl groups make the biphenol more configurationally stable due to the steric-induced restricted rotation.[11] The 5 and 5' positions of the biphenol can be modified for recovery and recycling of the catalysts.[12] Recently, Ojima *et al*. developed 5 and 5' fluorinated biphenol ligands for Rh-catalyzed hydroformylation of alkenes in supercritical CO_2 and fluorous solvents.[12a] These catalysts can be used in biphasic catalysis for easy recovery. Hultzsch *et al*. have developed polymer supported biphenol-based catalysts for olefin metathesis.[12b, 13] The chiral biphenol was linked to the polymer support through 5 and 5' linkage. Recovery of the catalyst can be done with simple filtration. The 3 and 3' substituents of the biphenol play a very critical role in enantioselectivity. The phosphite and phosphoramidite groups also play a role in enantioselectivity. It has been demonstrated that these biphenol-based phosphite **5-9** and phosphoramidites **5-10** ligands can be readily synthesized and applied to various catalytic asymmetric transformations.[11, 14] The phosphite ligands have shown excellent enantioselectivity in the Rh-catalyzed hydrogenation of dimethyl itaconate with ee up to 99.6% (**Scheme 5-1, Euqation 1**).[11] The phosphoramidite ligands have been successfully applied to Cu-catalyzed conjugate addition of diethylzinc to nitroalkenes (**Scheme 5-1, Euqation 2**) and Rh-catalyzed hydroformylation of allyl cyanides (**Scheme 5-1, Euqation 3**).[14a, 14b] These excellent results have led us to develop and expand the biphenol-based monodentate phosphorus ligand libraries.



Scheme 5-1: Applications of biphenol-based Phosphorus ligands in asymmetric reactions.

The purpose of this project was to synthesize biphenols for development of monodentate phosphorus ligand library. Monodentate phosphorus ligands (phosphites **5-9**, phosphoramidites **5-10** and phosphonites **5-11** - only *S*-isomers are shown) are prepared from enantiopure axially chiral biphenols, where substituents R^1, R^2, and R^3 can be modified to provide tuning capability for catalytic activity and enantioselectivity.

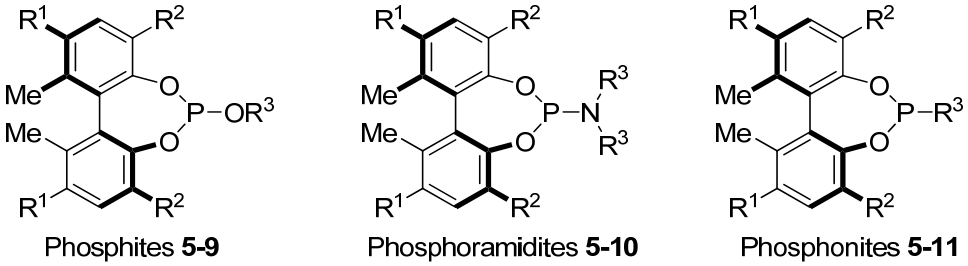
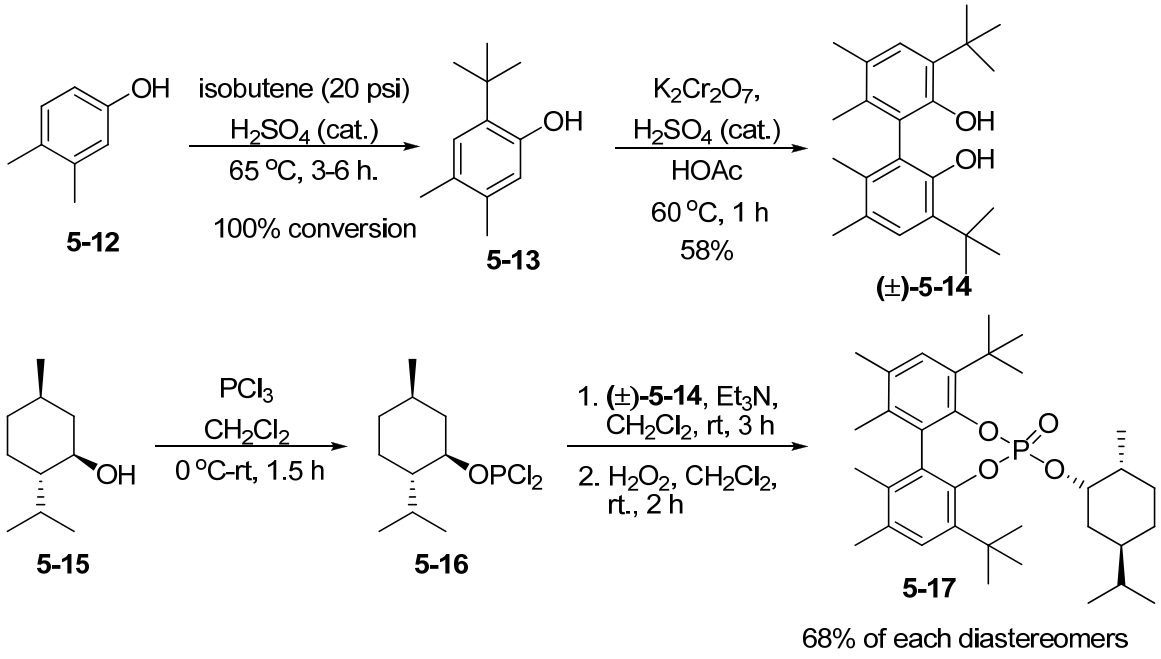


Figure 5-4: Biphenol-based monodentate phosphorus ligand library.

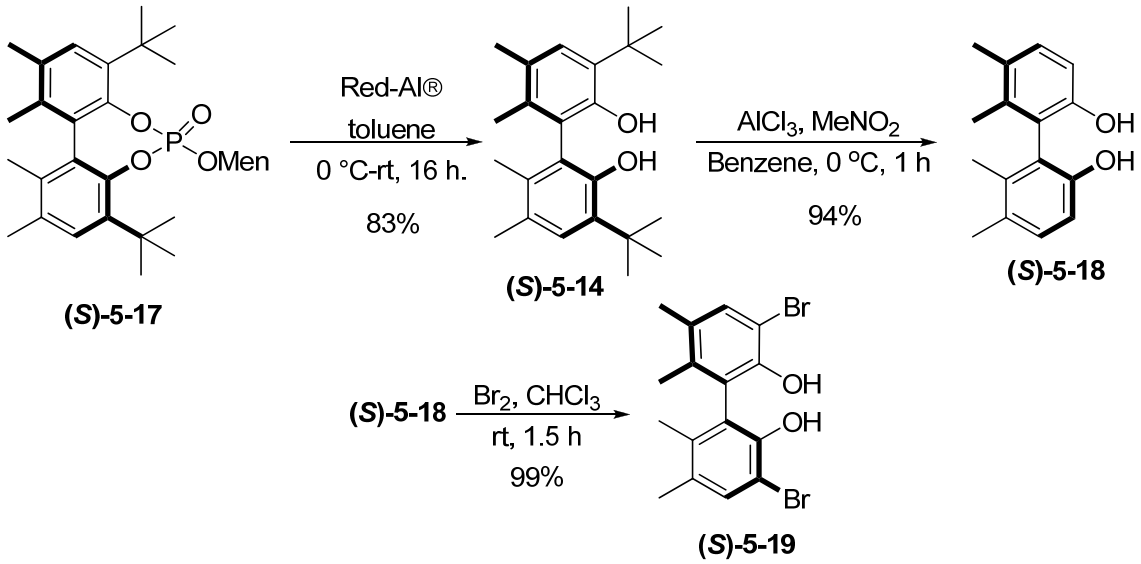
§ 5.2. Results and Discussions

The synthesis of the chiral 3,3'-di-*tert*-butylbiphenol began with electrophilic aromatic substitution of 3,4-dimethylphenol **(5-12)** under 2-methylpropene pressure to give 2-*tert*-butyl 4,5-dimethylphenol **(5-13)** (**Scheme 5-2**). Homocoupling of phenol **5-13** was accomplished using Jones' reagent to give racemic biphenol **5-14**. The racemic biphenol **5-14** was resolved by diastereomeric resolution using menthol as chiral auxiliary. Treatment of biphenol **5-14** with menthyl dichlorophosphite **(5-16)**, and subsequent oxidation with hydrogen peroxide, gave the desired diastereomeric menthol phosphates **5-17**.



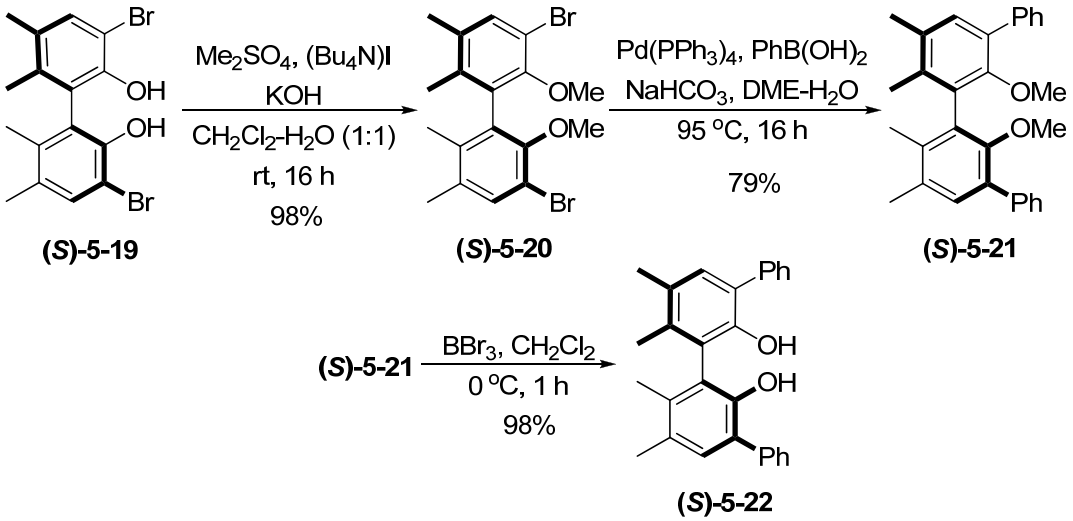
Scheme 5-2: Synthesis and chemo-resolution of the 3,3'-di-*tert*-butylbiphenol **5-17**

From the isolated diastereomer **(*S*)-5-17**, the menthol was removed by Red-Al® reduction to give enantiopure 3,3' di-*tert*-butylbiphenol **(*S*)-5-14**. The *tert*-butyl groups were removed by acyl transfer reaction using $AlCl_3$ and nitromethane to give 3,3'-dihydrobiphenol **(*S*)-5-18**. The 3,3'-dibromobiphenol **(*S*)-5-19** was obtained from bromination of 3,3'-dihydrobiphenol **(*S*)-5-18** (**Scheme 5-3**).



Scheme 5-3: Syntheses of biphenol derivatives

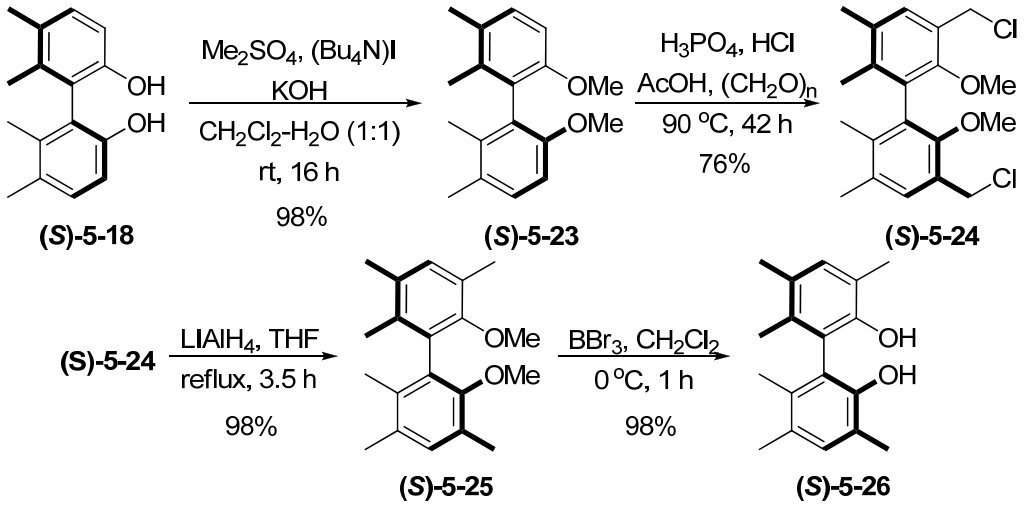
The hydroxyl groups of 3,3'-dibromobiphenol **(*S*)-5-19** were protected as the methyl ethers using Me_2SO_4. The protected biphenyl **(*S*)-5-20** was subjected to Suzuki coupling with phenylboronic acid, follow by deprotection of the methoxy groups using BBr_3 to give the 3,3'-diphenylbiphenol **(*S*)-5-22** in good overall yield (**Scheme 5-4**).



Scheme 5-4: Synthesis of 3,3'-diphenylbiphenol

Protection of the hydroxyl groups of 3,3'-dihydrobiphenol **(*S*)-5-18** using Me_2SO_4 gave the protected biphenol **(*S*)-5-23** in excellent yield. The chloromethylation of 3 and 3' positions was achieved by reacting biphenol **(*S*)-5-23** with paraformaldehyde under acidic condition. The chloromethyl groups were reduced to methyl groups using $LiAlH_4$, followed by deprotection of

the methoxy groups using BBr_3 to give the 3,3'-dimethylbiphenol **(*S*)-5-26** in excellent overall yield (**Scheme 5-5**).



Scheme 5-5: Synthesis of 3,3'-dimethylbiphenol

§ 5.3. Conclusions

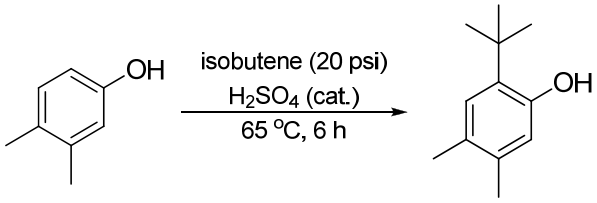
The broad applications of biphenol-based phosphorous ligands in catalytic asymmetric reactions prompted us to synthesize the enantiopure biphenols in large quantities. The efficient synthetic route was reproduced and both (*R*)- and (*S*)-enantiomers of various bephenols were successfully obtained.

§ 5.4. Experimental Section

General Information:

All chemical were obtained from either Sigma-Aldrich or Acros Organics and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under nitrogen and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). ^{1}H, ^{13}C and ^{31}P data were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[15] Melting points were measured on Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on Perkin-Elmer Model 241 polarimeter. GC/MS was performed on Agilent 6890GC/5973 Mass Selective Detector.

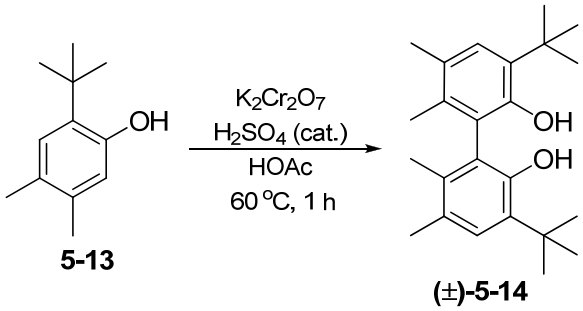
2-*tert*-Butyl-4,5-dimethylphenol (5-13)



5-12 **5-13**

The reaction vessel was a 300 mL autoclave with a glass lining fitted with a magnetic stirring bar. 3,4-dimethylphenol **(5-12)** (100 g, 0.82 mol) and concentrated sulfuric acid (1.0 mL) were charged into the reaction vessel. The autoclave was pressurized with isobutene (20 psi) and heated to 65 °C with stirring for 6 hours. The autoclave was opened and the brownish oil crude product was analyzed by GC-MS. The crude product **5-13** was used in next step without purification. GC-MS: 100% conversion, M.W.: 178 *m/z*

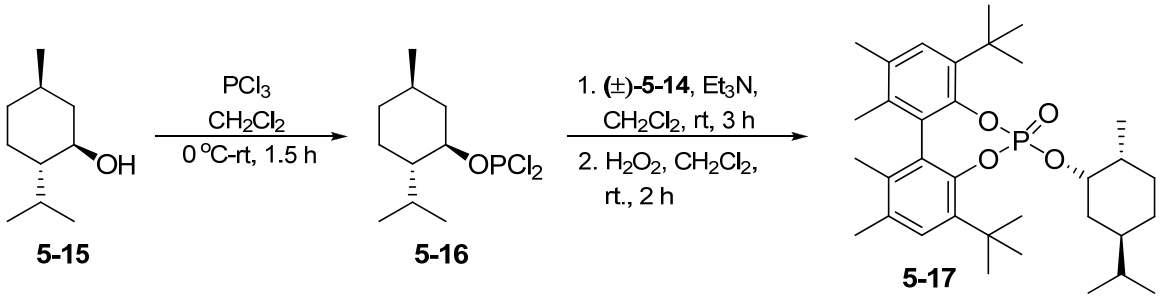
3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols ((±)-5-14)



5-13 **(±)-5-14**

Potassium dichromate (75 g, 0.3 mol) was dissolved in sulfuric acid (150 mL) and water (400 mL). The potassium dichromate solution was carefully added to an acetic acid (650 mL) solution of 4,5-dimethyl-2-*tert*-butylphenol **(5-13)**. Reaction was exothermic, color changed to dark green and white precipitation was observed. The reaction was stirred for 30 minutes at 60 ^{o}C, and then cooled to room temperature. The solid was isolated via filtration and washed with water and MeOH. The remaining solid was stirred with MeOH at 0 ^{o}C for 15 min. and then isolated by filtration. The solid was dried *in vacuo* to give pure diol **(±)-5-14** as off-white solid (83.55 g, 58%); mp:162-163 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 18 H), 1.82 (s, 6 H), 2.26 (s, 6 H), 4.80 (s, 2 H), 7.13 (s, 2 H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 20.0, 34.5, 120.1, 128.0, 128.7, 133.4, 134.1, 150.4. All data are in agreement with those reported in the literature.[16]

Preparation and resolution of (*S*)-5-17 and (*R*)-5-17

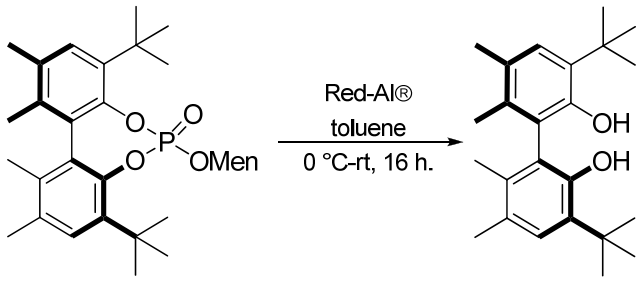


5-15 **5-16** **5-17**

A solution of (*1R, 2S, 5R*)-(-)-menthol **5-15** (23.34 g, 0.15 mol) in DCM (100 mL) was slowly added to a solution of phosphorus trichloride (1.5 eq., 20 mL, 0.23 mol) in DCM (100 mL) over a period of 30 minutes at 0 ^{o}C. After the addition of menthol solution was completed, the ice bath was removed and the mixture was stirred at room temperature for 1 hour. The solvent and volatiles were removed under vacuum to afford menthyl chlorophosphine **5-16**. The compound

5-16 was dissolved in DCM (150 mL) and to this solution, triethylamine (3 eq., 63.0 mL, 0.45 mol) and **(±)-5-14** (52.89 g, 0.15 mol) in DCM (300 mL) was added over 30 min. The reaction was stirred for an additional 2 h. The solution was filtered and H_2O_2 (35%, 143 mL) was added very slowly with stirring. The biphasic mixture was stirred rapidly for 2 h. The organic layer was separated and washed with water and brine, and then dried over $MgSO_4$. The solution was filtered and concentrated by rotary evaporation to afford a solid. The solid was dried under vacuum to afford **(±)-5-17**. The diastereomeric mixture of phosphates was dissolved in minimum amount of hot acetic acid and allowed to cool to room temperature over 24 h. The crystals were isolated by filtration and washed with cold acetic acid. The solid was dried *in vacuo* to give **(*S*)-5-17**. A second recrystallization from hot acetic acid afforded pure **(*S*)-5-17** as fiber-like crystals. The mother liquor was concentrated *in vacuo* to give a solid enriched with **(*R*)-5-17**. Crude **(*R*)-5-17** was crystallized from hot MeOH. And the solution was cooled to 0 ^oC. The solid was isolated by filtration and recrystallized from hot MeOH to give **(*R*)-5-17** as granulated crystals. **(*S*)-5-17** (28.03 g, 68%); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.34. **(*R*)-5-17** (28.35 g, 69%); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.84.

(*S*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols ((*S*)-5-14)



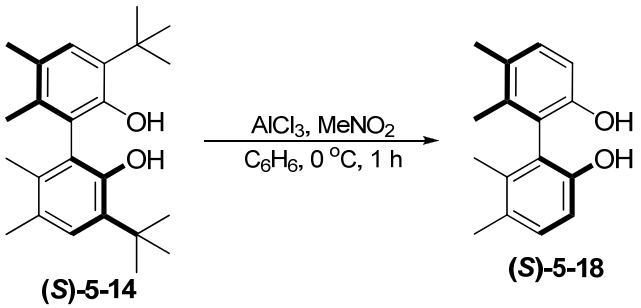
(*S*)-5-17 **(*S*)-5-14**

Resolved **(*S*)-5-17** (28.0 g, 50.5 mmol) was dissolved in toluene (200 mL) in a 2 L round bottom flask fitted with a 100 mL capacity addition funnel. Red-Al® (40 mL, 70% wt. in toluene) was added to the addition funnel and then added dropwise at 0 ^oC to the phosphate solution. The reaction was stirred at room temperature for 16 h and then quenched with water and bleach. The mixture was diluted with Et_2O, and organic layer was separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with sodium hypochlorite and brine, and then dried over $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed under reduced pressure to afford the solid. The menthol was removed by repeatly

washing with cold MeOH until the minty odor vanished. The resolved **(*S*)-5-14** was collected by filtration and dried under vacuum. The optical purity of **(*S*)-5-14** was characterized by ^{31}P NMR. **(*S*)-5-14** granulated white crystals (14.87 g, 83%); mp: 162-163 ^{o}C; ^{31}P NMR. (121 MHz, $CDCl_3$): no signal observed. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 18H), 1.85 (s, 6H), 2.28 (s, 6H), 4.83 (s, 2H), 7.16 (s, 2H). All data are in agreement with those reported in the literature.[16]

The synthesis of **(*R*)-5-14** from **(*R*)-5-17** followed the same procedure. **(*R*)-5-14** granulated white crystals (23.81 g, 87%); mp: 161-163 ^{o}C; ^{31}P NMR. (121 MHz, $CDCl_3$): no signal observed. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 18H), 1.83 (s, 6H), 2.26 (s, 6H), 4.81 (s, 2H), 7.13 (s, 2H). All data are in agreement with those reported in the literature.[16]

(*S*)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diols ((*S*)-5-18)

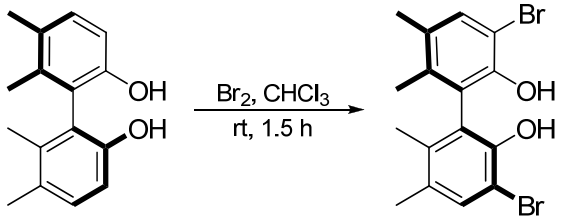


To a solution of **(*S*)-5-14** (5.29 g, 15.0 mmol) in benzene (80 mL) at 0 ^{o}C, a solution of $AlCl_3$ (3.42 g, 25.6 mmol) in benzene (20 mL) and nitromethane (25 mL) was added dropwise by addition funnel over 30 min. The reaction mixture was stirred at 0 ^{o}C for 30 min. The reaction was quenched by addition of water. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solution was concentrated under reduced pressure to give the crude product, which was recrystallized from hexane-DCM solution to afford **(*S*)-5-18** as white fiber-like crystals (3.40 g, 94%); mp: 200.0-201.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 6H), 2.26 (s, 6H), 4.52 (s, 2H), 6.82 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 19.9, 112.7, 120.2, 129.3, 131.4, 136.9, 151.8. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-18** from **(*R*)-5-14** followed the same procedure. **(*R*)-5-18** white fiber-like crystals (3.24 g, 89%); mp: 199.0-200.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 6H), 2.26 (s, 6 H), 4.52 (s, 2 H), 6.82 (d, 2 H, *J* = 8.1 Hz), 7.13 (d,2 H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 20.0, 112.7, 120.3, 129.4, 131.4, 137.0 151.9. All data are in agreement

with those reported in the literature.[11]

(*S*)-3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols ((*S*)-5-19)

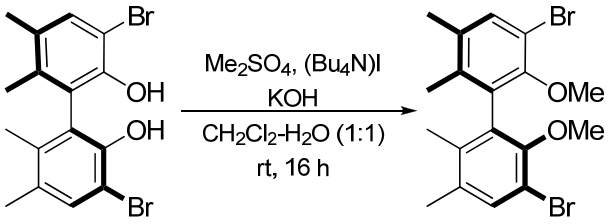


(*S*)-5-18 **(*S*)-5-19**

To a solution of **(*S*)-5-18** (1.30 g, 5.37 mmol) in $CHCl_3$ (50 mL), a solution of Br_2 (0.80 mL, 5.0 mmol) in $CHCl_3$ (10 mL) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of saturated Na_2SO_3 solution. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with water and brine, and then dried over Na_2SO_4. The solution was concentrated under reduced pressure to afford **(*S*)-5-19** as white solid (2.13 g, 99%); mp 171.0-172.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.86 (s, 6 H), 2.26 (s, 6 H), 5.11 (s, 2 H), 7.35 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 20.0, 106.9, 123.7, 130.8, 133.0, 136.8, 148.0. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-19** from **(*R*)-5-18** followed the same procedure. **(*R*)-5-19** white solid (2.150 g, 99%); mp: 169.0-170.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.86 (s, 6 H), 2.25 (s, 6 H), 5.11 (s, 2 H), 7.35 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 20.0, 106.9, 123.7, 130.8, 133.0, 136.8, 148.0. All data are in agreement with those reported in the literature.[11]

(*S*)-3,3'-Dibromo-2,2'-dimethoxy-5,5',6,6'-tetramethylbiphenyl ((*S*)-5-20)



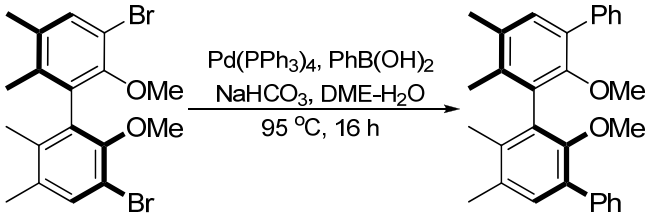
(*S*)-5-19 **(*S*)-5-20**

To a biphasic mixture of **(*S*)-5-19** (1.0 g, 2.5 mmol), $(Bu_4N)I$ (0.099 g, 0.027 mmol), and KOH (0.431 g, 7.68 mmol) in 50 mL of DCM-H_2O (1:1), dimethyl sulfate (0.7 mL, 7.5 mmol)

was added all at once. The biphasic mixture was stirred at room temperature overnight. The organic layer was separated, and the aqueous layer was extracted with DCM. The organic layers were combined and washed with brine and dried over Na_2SO_4. The solution was concentrated under vacuum and titrated with MeOH to afford **(*S*)-5-20** as whit solid. (1.051 g, 98%); mp: 150.0-151.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 6 H), 2.26 (s, 6 H), 3.50 (s, 6 H), 7.39 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 20.0, 60.4, 113.8, 133.2, 133.6, 134.2, 113.60, 152.7. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-20** from **(*R*)-5-19** followed the same procedure. **(*R*)-5-20** white solid. (1.067 g, 99%); mp: 149.0-150.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 6 H), 2.26 (s, 6 H), 3.50 (s, 6 H), 7.39 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 20.0, 60.4, 113.8, 133.2, 133.6, 134.2, 113.60, 152.7. All data are in agreement with those reported in the literature.[11]

(*S*)-2,2'-Dimethoxy-5,5',6,6'-tetramethyl-3,3'-diphenylbiphenyl ((*S*)-5-21)



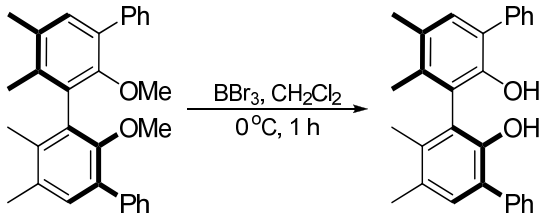
(*S*)-5-20 **(*S*)-5-21**

A suspension of **(*S*)-5-20** (1.00 g, 2.34 mmol) and $Pd(PPh_3)_4$ (135 mg, 0.12 mmol) in 25 mL of DME was stirred at room temperature for 30 min. To this suspension solutions of $PhB(OH)_2$ (630 mg, 5.17 mmol) in DME (10 mL) and $NaHCO_3$ (1.18 g, 14.04 mmol) in 15 mL of water was added. The mixture was stirred and refluxed at 95 ^oC for 16 h. The reaction mixture was allowed to cool to room temperature and diluted with Et_2O. The organic layer was separated and washed with brine, and then dried over Na_2SO_4. The solution was concentrated under reduced pressure, and the crude product was purified with column chromatography on silica gel with eluent of hexane-EtOAc (20:1) to afford **(*S*)-5-21** as white solid (0.777 g, 79%); mp: 56.0-57.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 6 H), 2.33 (s, 6 H), 3.19 (s, 6 H), 7.18 (s, 2 H), 7.27-7.34 (m, 2 H), 7.36-7.43 (m, 4 H), 7.60-7.64 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 20.4, 60.4, 126.9, 128.4, 129.3, 131.5, 131.6, 132.2, 132.6, 135.7, 139.5, 153.5. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-21** from **(*R*)-5-20** followed the same procedure. **(*R*)-5-21** white solid

(0.904 g, 92%); mp: 56.5-58.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 6 H), 2.33 (s, 6 H), 3.19 (s, 6 H), 7.18 (s, 2 H), 7.27-7.34 (m, 2 H), 7.36-7.43 (m, 4 H), 7.60-7.64 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 20.4, 60.4, 126.9, 128.4, 129.3, 131.5, 131.6, 132.2, 132.6, 135.7, 139.5, 153.5. All data are in agreement with those reported in the literature.[11]

(*S*)- -5,5',6,6'-Tetramethyl-3,3'-diphenylbiphenyl-2,2'-diol ((*S*)-5-22)

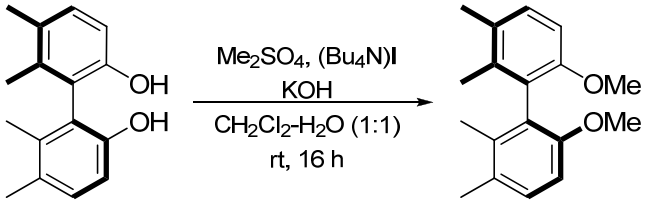


(*S*)-5-21 **(*S*)-5-22**

To a stirring solution of **(*S*)-5-21** (0.78 g, 1.84 mmol) in DCM (15 mL) at 0 °C, BBr_3 solution (4.50 mL, 1 M in DCM) was added dropwise. The reaction was stirred at 0 °C for 1 h. The reaction was quenched by addition of water (40 mL). The aqueous layer was extracted with DCM. The organic layers were combined and washed with brine, and then dried over Na_2SO_4. The solution was concentrated under reduced pressure to afford **(*S*)-5-22** as off-white solid (0.715 g, 98%); mp: 153.0-154.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99 (s, 6 H), 2.32 (s, 6 H), 4.88 (s, 2 H), 7.23 (s, 2 H), 7.28-7.36 (m, 2 H), 7.38-7.46 (m, 4 H), 7.56-7.62 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 19.8, 121.6, 125.6, 126.3, 127.1, 128.4, 129.2, 132.1, 136.4, 137.9, 148.4. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-22** from **(*R*)-5-21** followed the same procedure. **(*R*)-5-22** as off-white solid (0.831 g, 98%); mp: 152.5-153.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99 (s, 6 H), 2.32 (s, 6 H), 4.88 (s, 2 H), 7.23 (s, 2 H), 7.28-7.36 (m, 2 H), 7.38-7.46 (m, 4 H), 7.56-7.62 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 19.8, 121.6, 125.6, 126.3, 127.1, 128.4, 129.2, 132.1, 136.4, 137.9, 148.4. All data are in agreement with those reported in the literature.[11]

(*S*)-6,6'-Dimethoxy-2,2',3,3'-tetramethylbiphenyl ((*S*)-5-23)

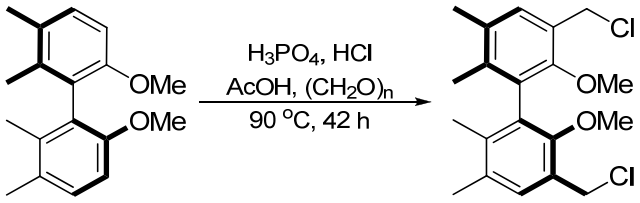


(*S*)-5-18 **(*S*)-5-23**

To a biphasic mixture of **(*S*)-5-18** (2.00 g, 9.25 mmol), $(Bu_4N)I$ (0.273 g, 0.74 mmol), and KOH (1.28 g, 22.7 mmol) in DCM-H_2O (1:1) (60 mL), dimethyl sulfate (2.30 mL, 24.55 mmol) was added. The biphasic mixture was stirred overnight under room temperature. The organic layer was separated, and the aqueous layer was extracted with DCM. The organic layers were combined and washed with water, NH_4OH, and brine, and dried over $MgSO_4$. The solution was concentrated under reduced pressure to give **(*S*)-5-23** as off-white solid (2.199 g,98%); mp: 112.0-113.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 6 H), 2.26 (s, 6 H), 3.66 (s, 6 H), 6.74 (d, 2 H, J = 8.4 Hz), 7.11 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 20.0, 55.9, 108.1, 126.8, 128.5, 128.9, 136.4, 155.2. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-23** from **(*R*)-5-18** followed the same procedure. **(*R*)-5-23** off-white solid (2.216 g,98%); mp: 110.0-112.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 6H), 2.26 (s, 6 H), 3.66 (s, 6 H), 6.74 (d, 2 H, J = 8.4 Hz), 7.11 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 20.0, 55.9, 108.1, 126.8, 128.5, 128.9, 136.4, 155.2. All data are in agreement with those reported in the literature.[11]

(*S*)-3,3'-Bis(chloromethyl)-2,2'-dimethoxy-5,5',6,6'-tetramethylbiphenyl ((*S*)-5-24)



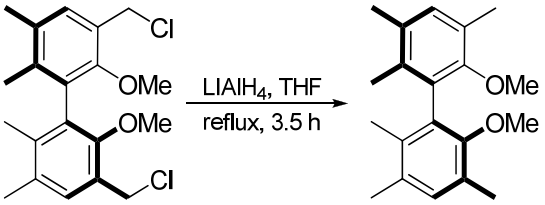
(*S*)-5-23 **(*S*)-5-24**

To the solution of **(*S*)-5-23** (1.00 g, 3.71 mmol) in 85% H_3PO_4 (15 mL), concentrated HCl (15 mL), and AcOH (15 mL), paraformaldehyde (3.50 g). The reaction mixture was heated to 90 ^oC and stirred for 42 h. The solution was allowed to cool to room temperature and extracted with

benzene. The combined organic layers were washed with water, saturated Na_2CO_3 solution, and brine, and then dried over $MgSO_4$. The solution was concentrated under vacuum to afford crude. The crude was purified with column chromatography on silica gel with eluent of hexane-EtOAc (20:1) to give **(*S*)-5-24** as white solid (1.035 g, 76%); mp: 104.5-106.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.93 (s, 6 H), 2.30 (s, 6 H), 3.37 (s, 6 H), 4.57 (d, 2 H, J = 11.1 Hz), 4.80 (d, 2 H, J = 10.8 Hz), 7.25 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 20.2, 41.7, 60.9, 127.9, 128.2, 131.2, 131.4, 132.7, 137.4, 154.0. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-24** from **(*R*)-5-23** followed the same procedure. **(*R*)-5-24** white solid (2.731 g, 92%); mp: 104.-105.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.93 (s, 6 H), 2.30 (s, 6 H), 3.37 (s, 6 H), 4.57 (d, 2 H, J = 11.1 Hz), 4.80 (d, 2 H, J = 10.8 Hz), 7.25 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 20.2, 41.7, 60.9, 127.9, 128.2, 131.2, 131.4, 132.7, 137.4, 154.0. All data are in agreement with those reported in the literature.[11]

(*S*)-2,2'-Dimethoxy-3,3',5,5',6,6'-hexamethylbiphenyl ((*S*)-5-25)



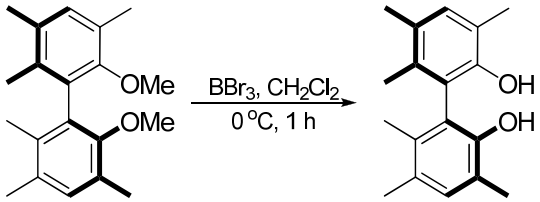
(*S*)-5-24 **(*S*)-5-25**

To a stirring suspension of $LiAlH_4$ (0.72 g, 19.0 mmol) in THF (10 mL), the solution of **(*S*)-5-24** (1.45 g, 3.94 mmol) in THF (15 mL) was added dropwise. The reaction mixture was refluxed for 3.5 hours and then cooled to 0 ^oC. The reaction was quenched with dropwise addition of THF/water (3:1, 6 mL). The mixture was extracted with Et_2O. The combined organic layers were washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure to afford crude product. The crude was purified with column chromatography on silica gel with eluent of hexane-EtOAc (20:1) to give **(*S*)-5-25** as white solid (1.146 g, 98%); mp: 73.0-74.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 6 H), 2.25 (s, 6 H), 2.28 (s, 6 H), 3.33 (s, 6 H), 7.00 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1, 16.6, 20.1, 59.5, 127.4, 131.3, 131.5, 131.7, 133.4, 154.1. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-25** from **(*R*)-5-24** followed the same procedure. **(*R*)-5-25** white solid (0.1.926 g, 95%); mp: 74.0-75.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 6 H), 2.25 (s, 6 H),

2.28 (s, 6 H), 3.33 (s, 6 H), 7.00 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1, 16.6, 20.1, 59.5, 127.4, 131.3, 131.5, 131.7, 133.4, 154.1. All data are in agreement with those reported in the literature.[11]

(*S*)-3,3',5,5',6,6'-Hexamethylbiphenyl-2,2'-diol ((*S*)-5-26)



(*S*)-5-25 **(*S*)-5-26**

To a stirring solution of **(*S*)-5-25** (1.11 g, 3.72 mmol) in DCM (15 mL) at 0 °C, BBr_3 solution (4.5 mL, 1 M in DCM) was added dropwise. The solution was stirred at 0 °C for 1 hour. The reaction was quenched by slow addition of water (40 mL). The aqueous layer was extracted with DCM. The organic layers were combined and washed with water and brine, and then dried over $MgSO_4$. The solution was concentrated under vacuum to afford **(*S*)-5-26** (0.986 g, 98%); mp: 136.0-138.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 6 H), 2.23 (s, 12 H), 4.53 (s, 2 H), 7.00 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8, 16.2, 19.7, 119.9, 121.3, 128.4, 132.6, 133.8, 149.8. All data are in agreement with those reported in the literature.[11]

The synthesis of **(*R*)-5-26** from **(*R*)-5-25** followed the same procedure. **(*R*)-5-26** (1.656 g, 97%); mp: 136.0-137.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 6 H), 2.23 (s, 12 H), 4.53 (s, 2 H), 7.00 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8, 16.2, 19.7, 119.9, 121.3, 128.4, 132.6, 133.8, 149.8. All data are in agreement with those reported in the literature.[11]

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Chapter 1

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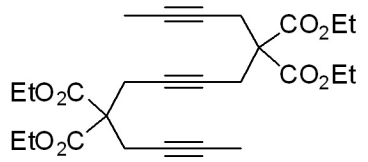
APPENDIX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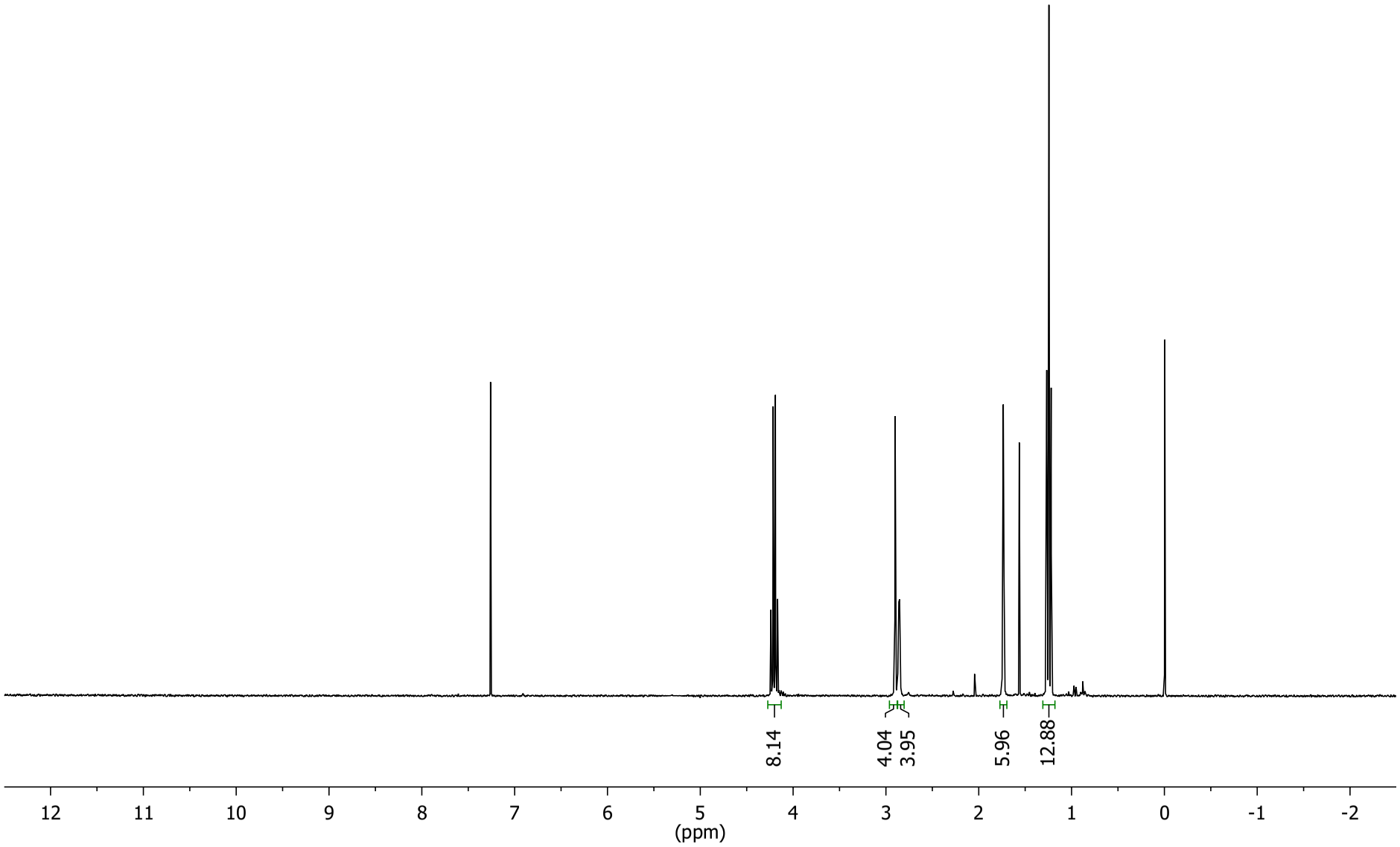
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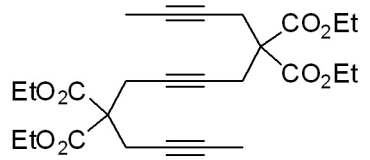
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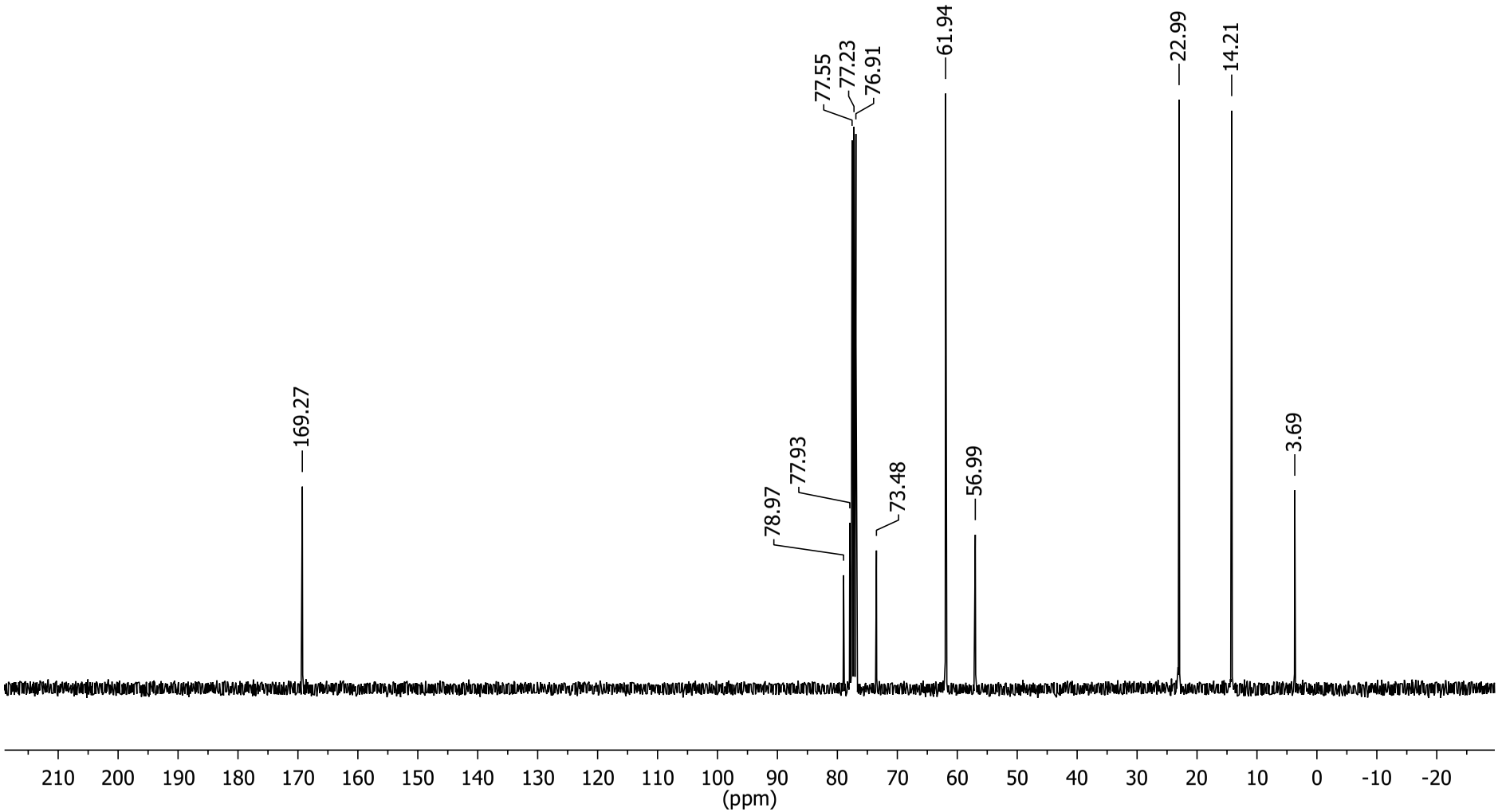
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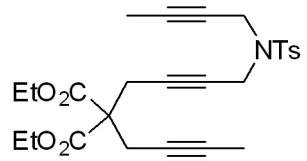
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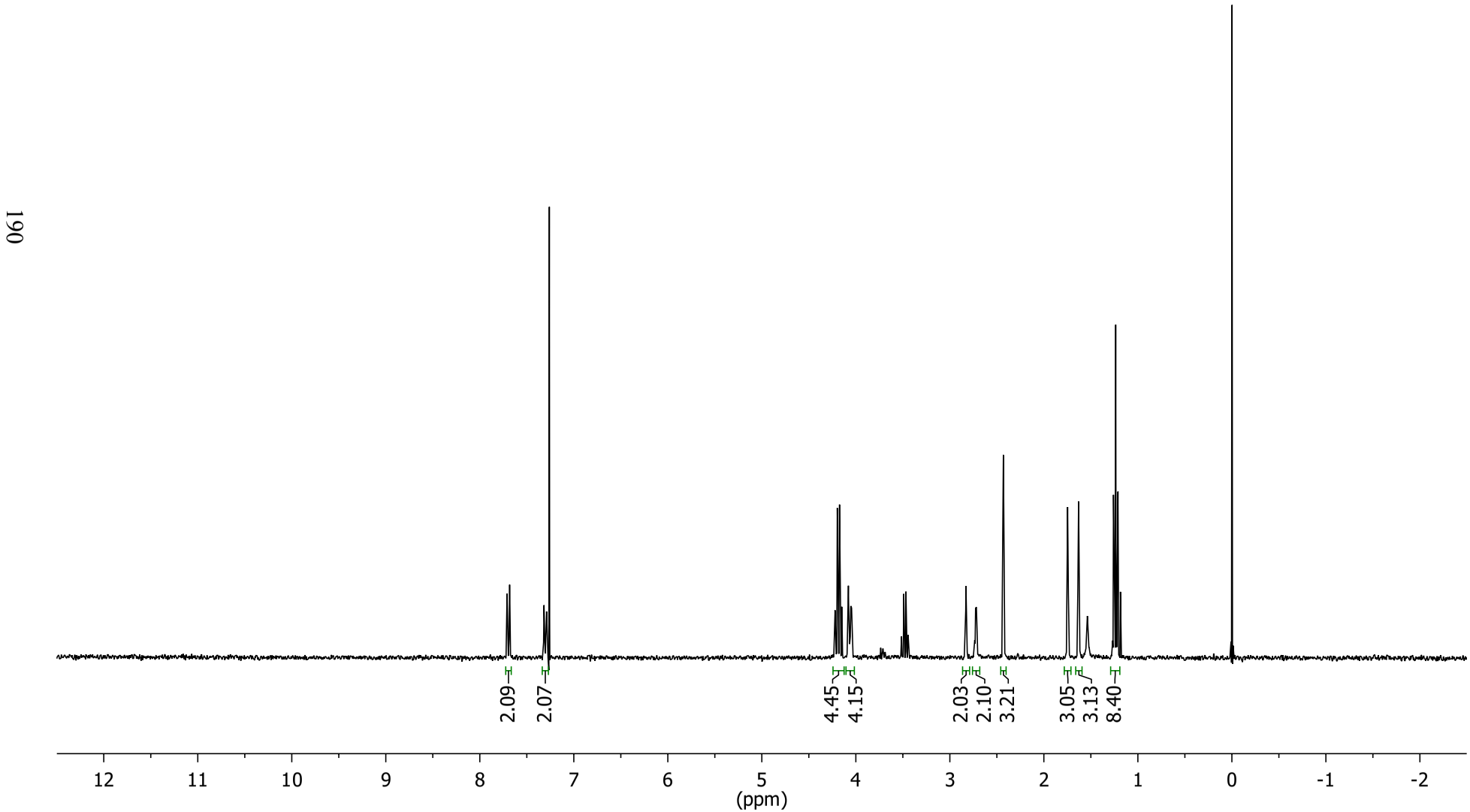
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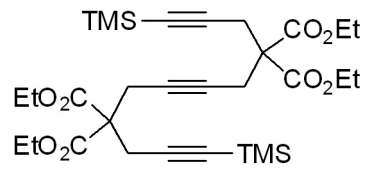
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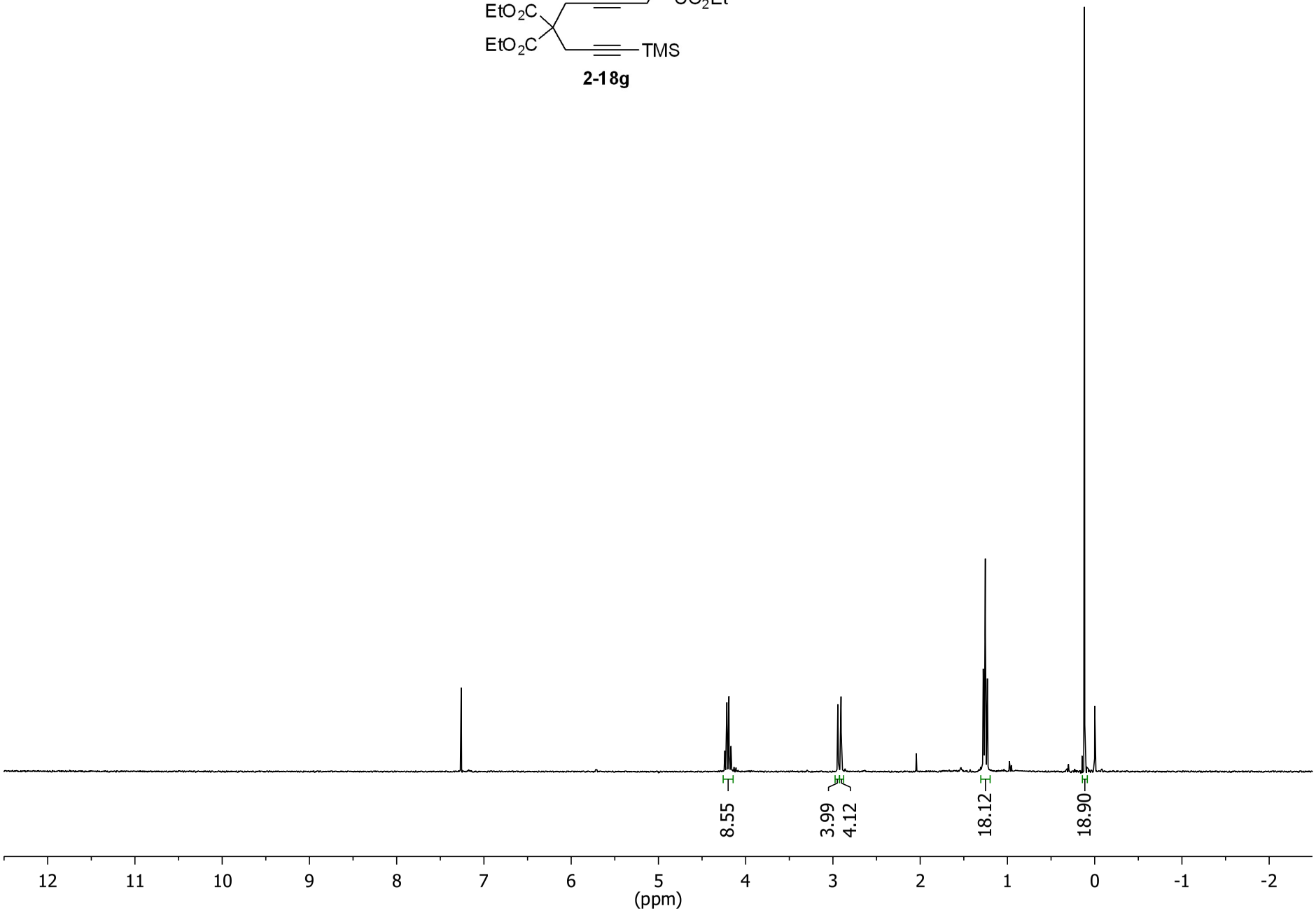
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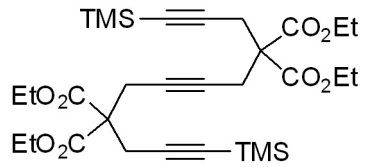
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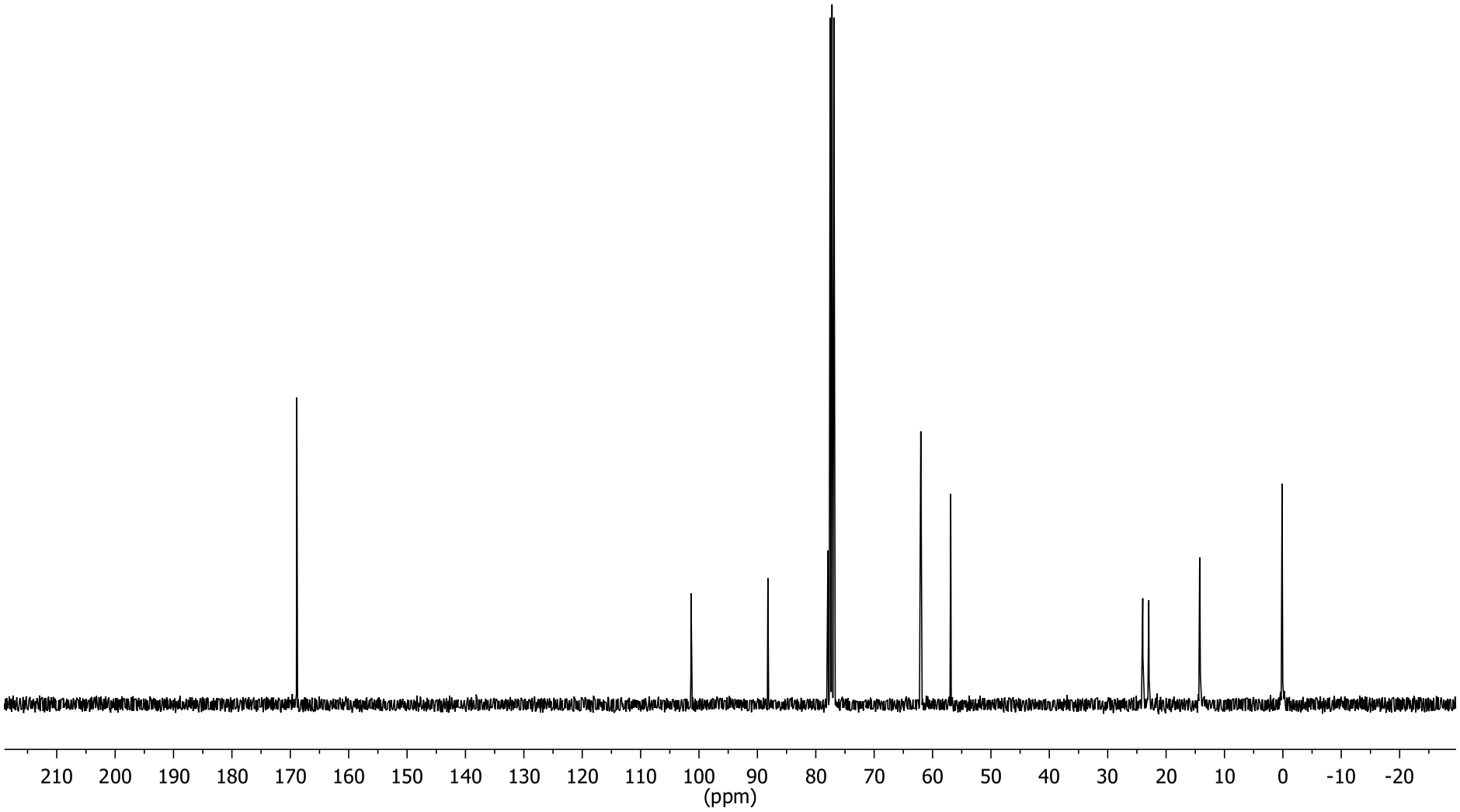
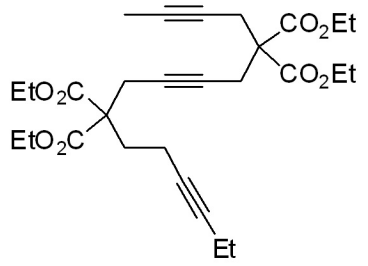
TMS

2-18g

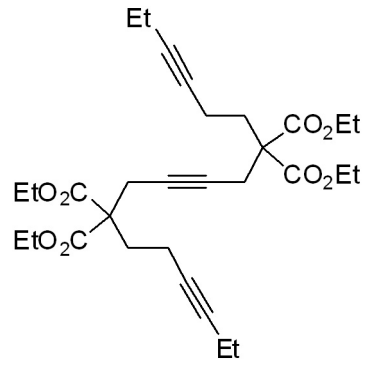

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)


CO2Et
CO2Et
EtO2C
EtO2C
Et

2-18h

7.69
1.83
1.87
1.89
5.72
3.00
11.91
2.94
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

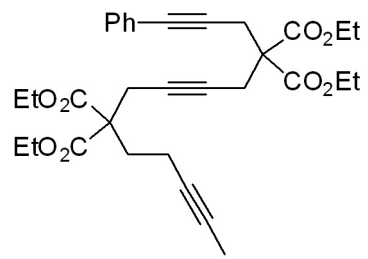
3.451
12.383
13.969
14.000
14.091
22.749
22.787
22.984
31.324
56.420
56.738
61.527
61.701
73.206
76.681
77.000
77.319
77.584
77.774
77.941
78.761
82.153
169.027
169.907
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2Et
CO2Et
EtO2C
EtO2C
Et
2-18h


Et
CO2Et
CO2Et
EtO2C
EtO2C
Et

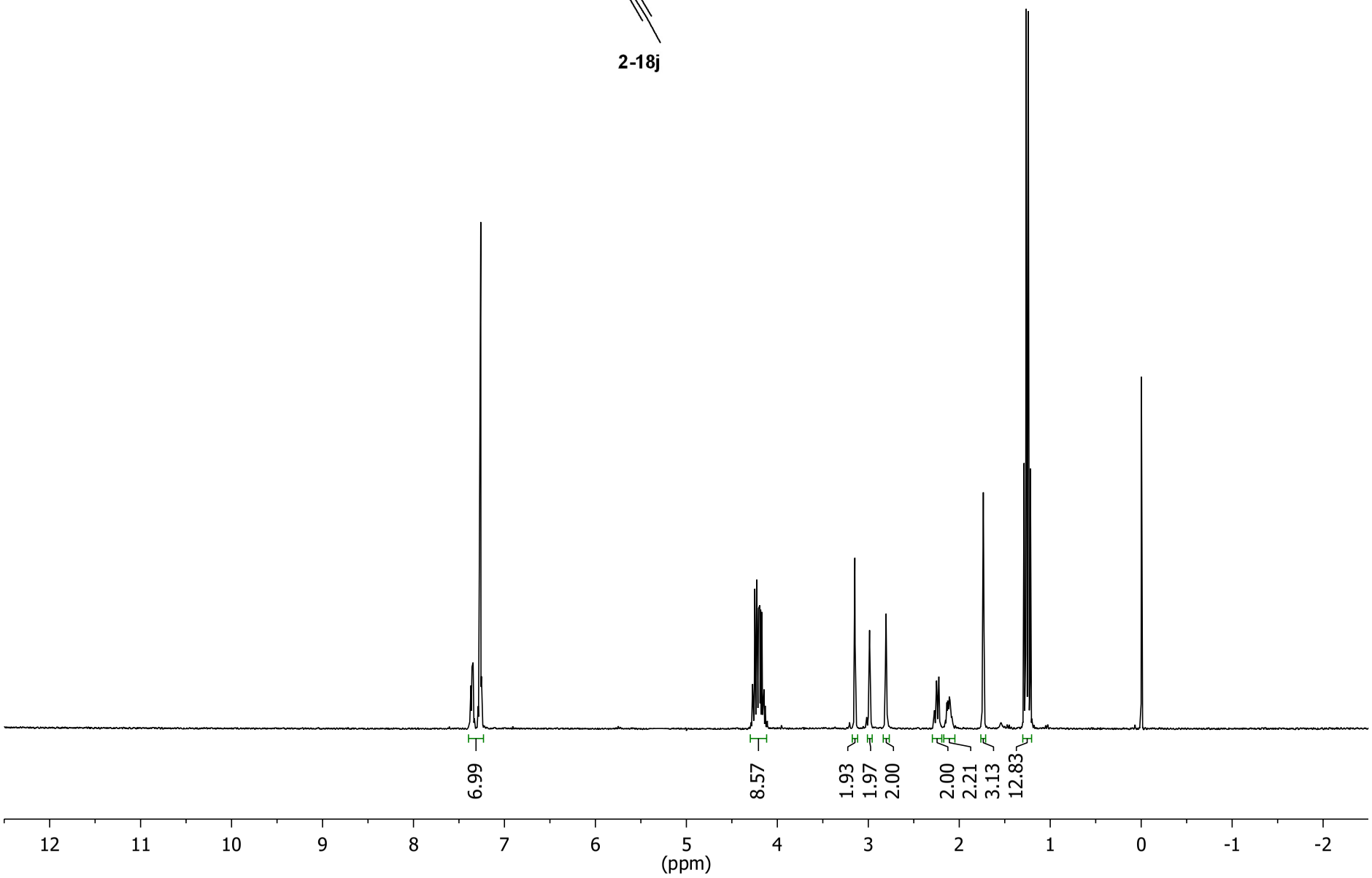
2-18i

8.21
4.00
12.39
13.86
6.76
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

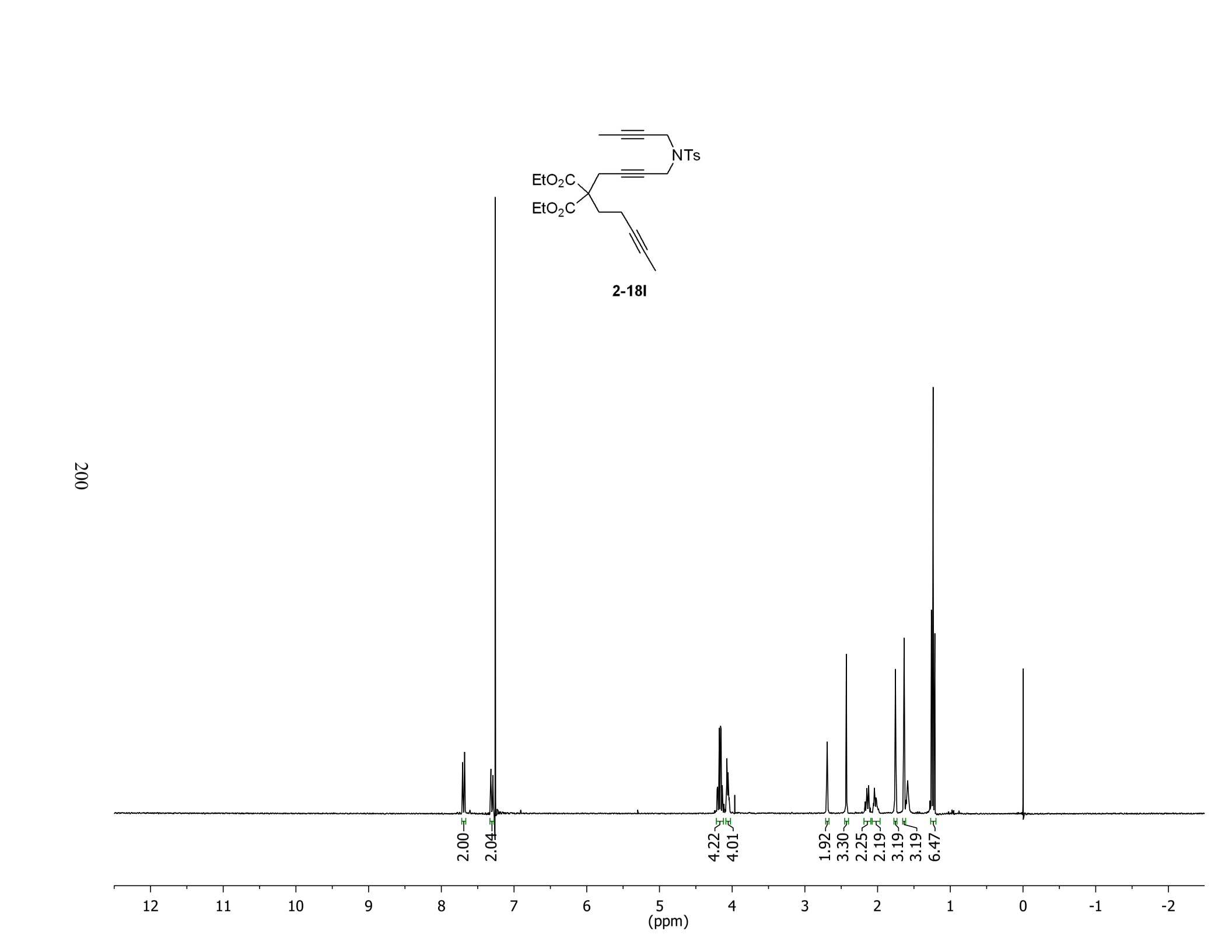
12.398
13.992
14.098
22.984
31.347
56.412
61.542
76.681
77.000
77.319
77.660
77.918
82.183
169.907
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2Et
CO2Et
Et
Et
EtO2C
EtO2C
2-18i


Ph
CO2Et
CO2Et
EtO2C
EtO2C

2-18j


6.99
8.57
1.93
1.97
2.00
2.00
2.21
3.13
12.83
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

170.14
169.07
131.88
128.37
128.13
123.47
84.43
78.08
77.97
77.88
76.37
62.11
61.80
57.05
56.63
31.51
23.65
23.21
14.28
14.22
3.69
77.55
77.23
76.91
Ph
CO2Et
CO2Et
EtO2C
EtO2C
2-18j
(ppm)


NTs
EtO2C
EtO2C
2-18l
200
2.00
2.04
4.22
4.01
1.92
3.30
2.25
2.19
3.19
3.19
6.47
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

169.96
143.74
135.73
129.53
128.14
81.91
80.59
77.79
76.52
76.08
71.64
61.86
56.45
36.76
36.70
31.60
23.19
21.66
14.20
14.16
3.57
77.54
77.22
76.90
NTs
EtO2C
EtO2C
2-18l
(ppm)

2-18o

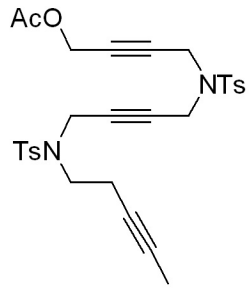
202

2.00 7.06 6.15 2.04 1.70 2.29 1.96 2.59 2.79 5.77

12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

(ppm)

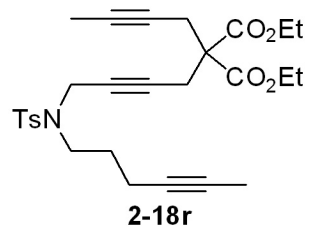
169.05
143.74
136.40
131.79
129.80
128.43
127.75
123.58
86.56
80.92
79.21
77.54
77.22
76.91
76.32
73.21
62.04
61.97
56.71
45.58
37.78
23.11
20.10
14.24
14.19
(ppm)
CO2Et
CO2Et
TsN
Ph
2-18o


AcO
NTs
TsN

2-18p

4.00
4.16
1.87
2.04
1.94
1.90
1.94
6.32
2.15
3.05
3.02
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

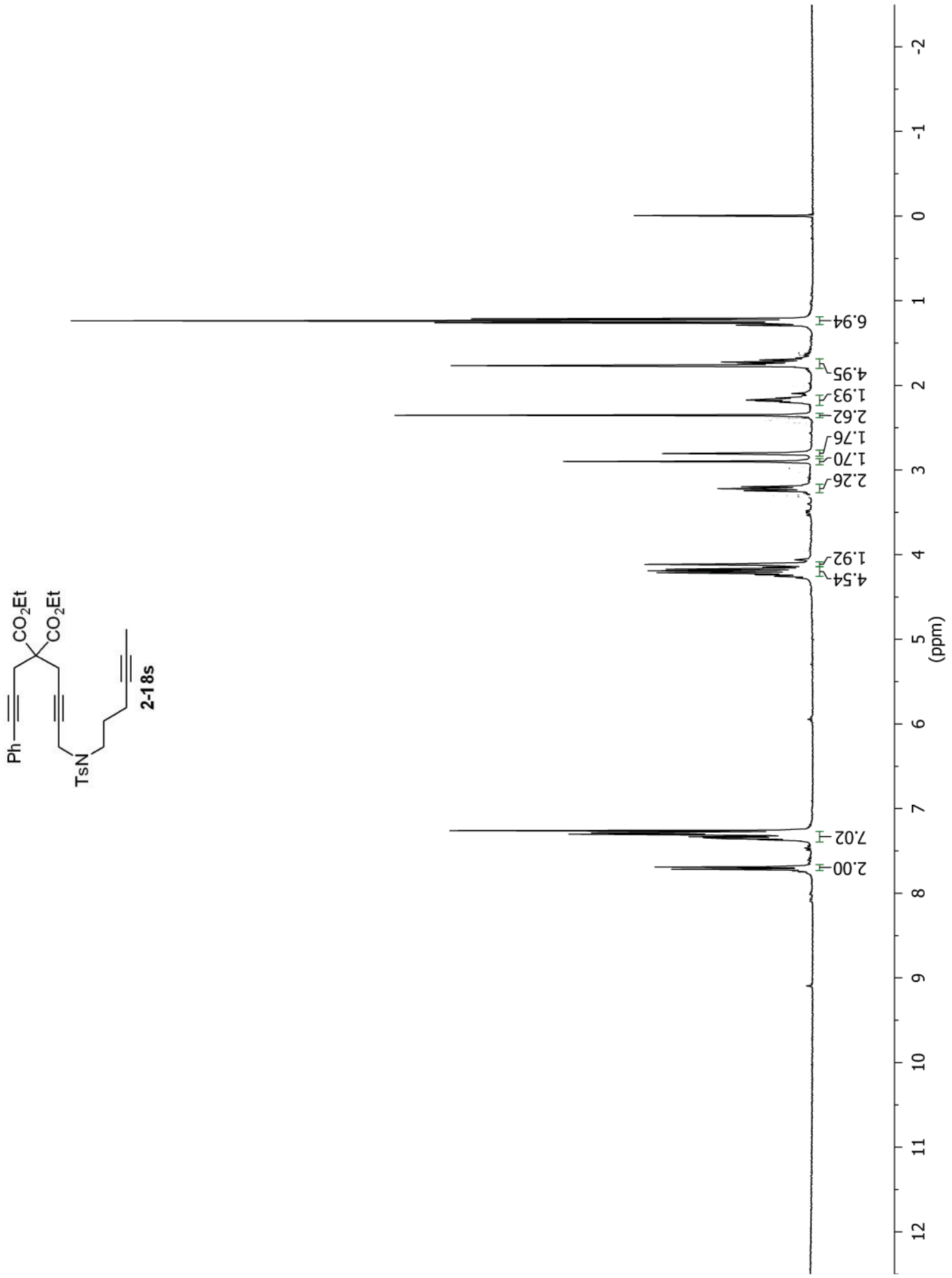
170.17
144.25
143.98
136.21
135.42
129.78
127.99
127.69
80.09
79.25
79.21
78.21
77.99
75.57
52.00
46.15
37.43
36.60
21.76
21.70
19.32
(ppm)
AcO
TsN
NTs
2-18p


CO2Et
CO2Et
TsN

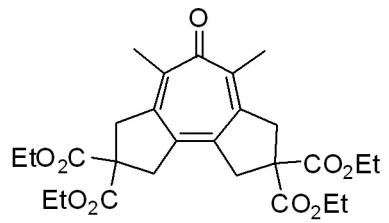
2-18r

2.00
1.88
3.95
1.97
1.95
1.69
1.65
2.44
1.79
8.09
6.12
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

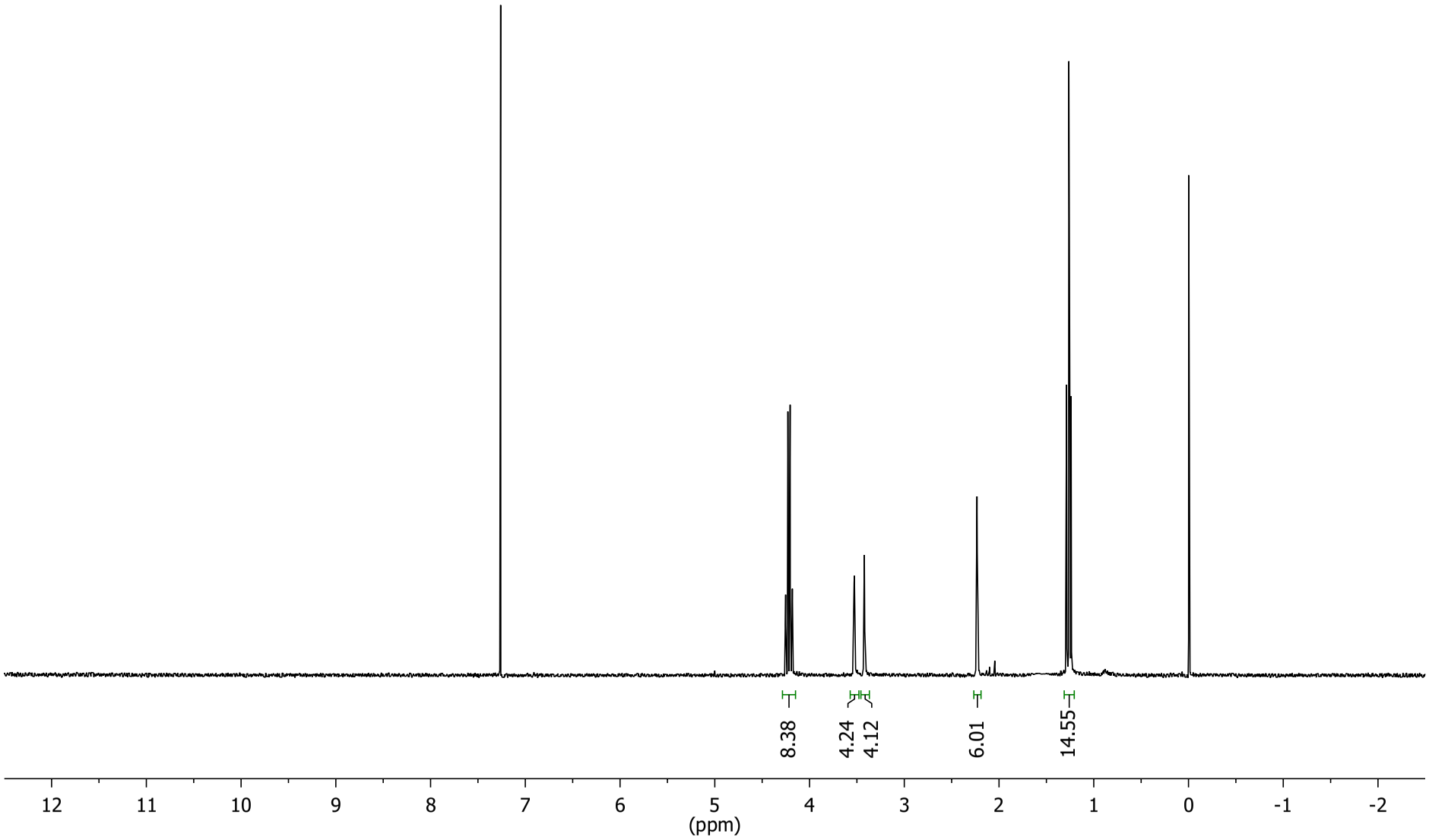
169.01
143.53
136.24
129.70
127.82
127.74
80.58
78.07
77.54
77.22
76.90
76.44
76.17
73.20
61.96
56.67
45.72
37.09
23.02
22.85
16.24
14.22
14.17
3.56
(ppm)
CO2Et
CO2Et
TsN
2-18r

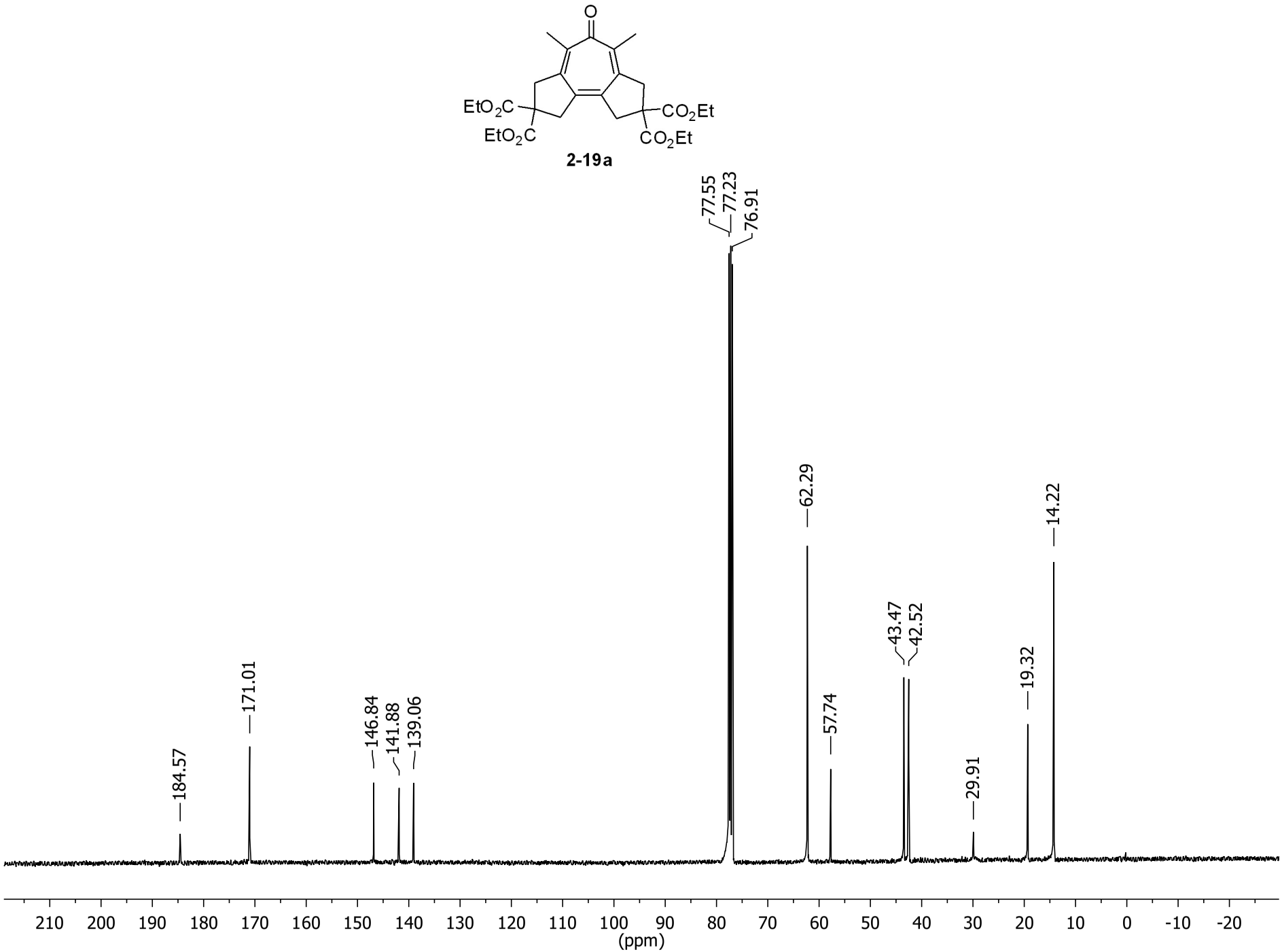

Ph
CO2Et
CO2Et
TsN
2-18s
6.94
4.95
1.93
2.62
1.76
1.70
2.26
1.92
4.54
7.02
2.00
(ppm)

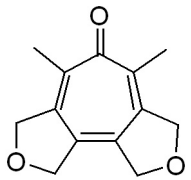
168.86
143.62
136.23
131.81
129.74
129.68
128.47
127.85
127.78
123.25
84.07
83.90
80.44
78.08
77.54
77.23
76.91
76.51
62.23
62.17
56.74
45.76
37.11
27.48
23.64
23.07
21.71
16.28
14.29
14.24
(ppm)
Ph
CO2Et
CO2Et
TsN
2-18s


O
EtO2C
EtO2C
CO2Et
CO2Et

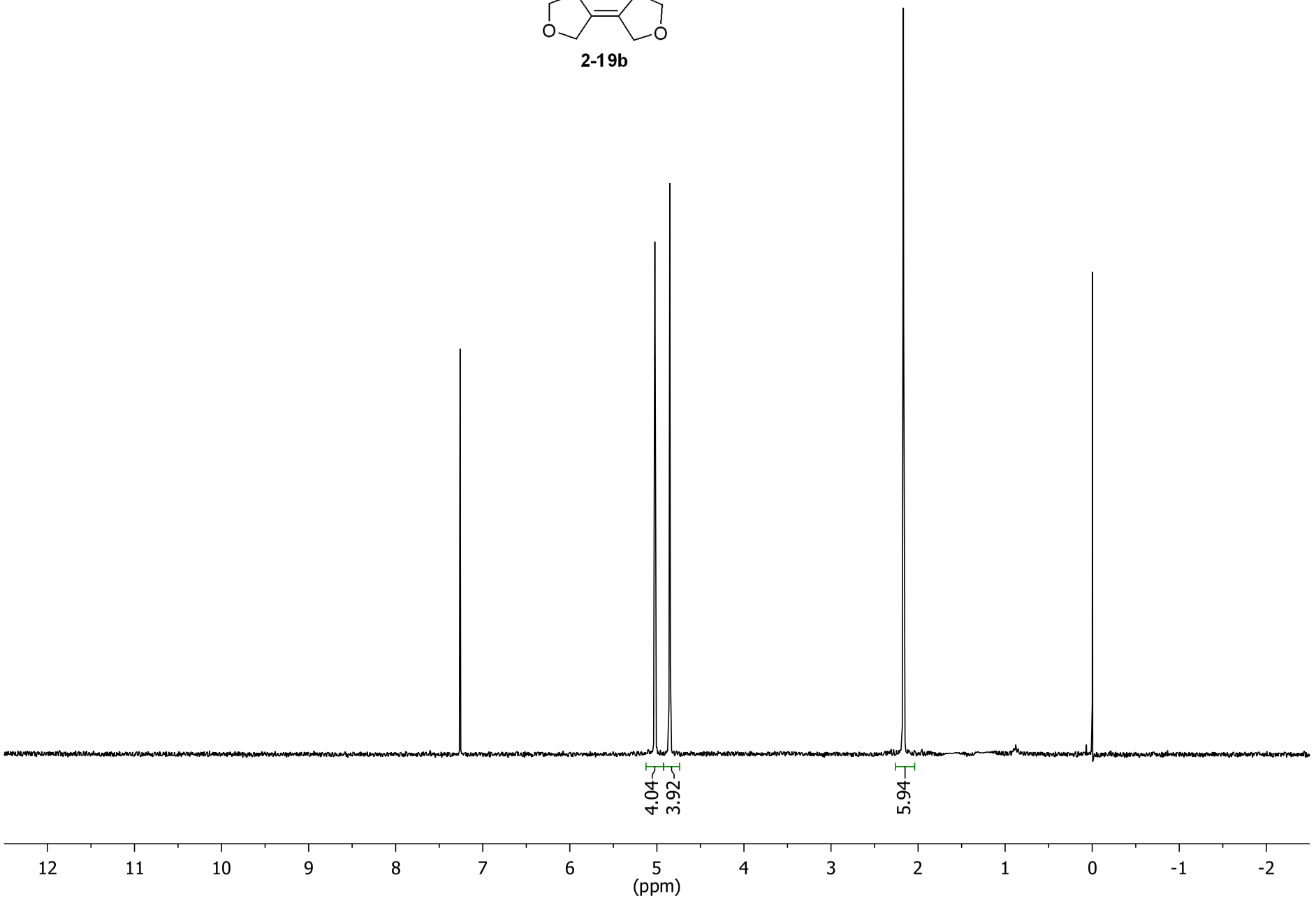
2-19a


8.38
4.24
4.12
6.01
14.55
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

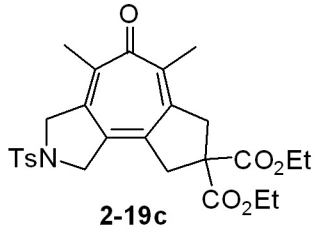

O
EtO2C
EtO2C
CO2Et
CO2Et
2-19a
77.55
77.23
76.91
62.29
57.74
43.47
42.52
29.91
19.32
14.22
184.57
171.01
146.84
141.88
139.06
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)



2-19b



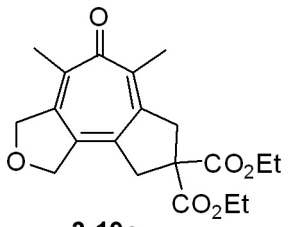
2-19b


O
TsN
CO2Et
CO2Et

2-19c

2.00
2.00
1.96
1.96
4.21
2.03
1.95
3.15
3.12
3.20
9.22
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

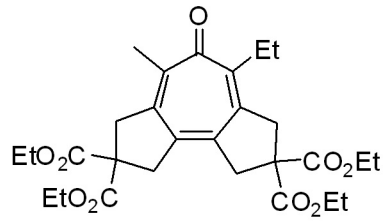
77.55
77.23
76.91
62.47
57.80
55.52
54.86
43.30
41.83
29.91
21.77
19.46
18.65
14.21
183.81
170.70
146.93
144.50
143.21
142.61
140.94
138.63
134.53
132.97
130.24
127.90
CO2Et
CO2Et
O
TsN
2-19c
(ppm)



2-19e

183.77
170.84
147.47
145.82
143.00
139.25
137.61
136.67
77.55
77.23
76.91
75.66
75.00
62.41
58.13
43.27
41.31
29.92
19.48
18.17
14.22
(ppm)
CO2Et
CO2Et
O
O

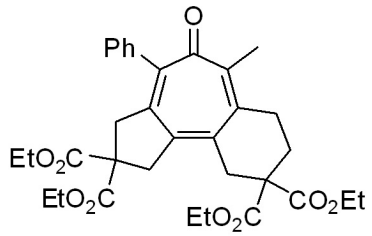
2-19e


O
Et
EtO2C
EtO2C
CO2Et
CO2Et

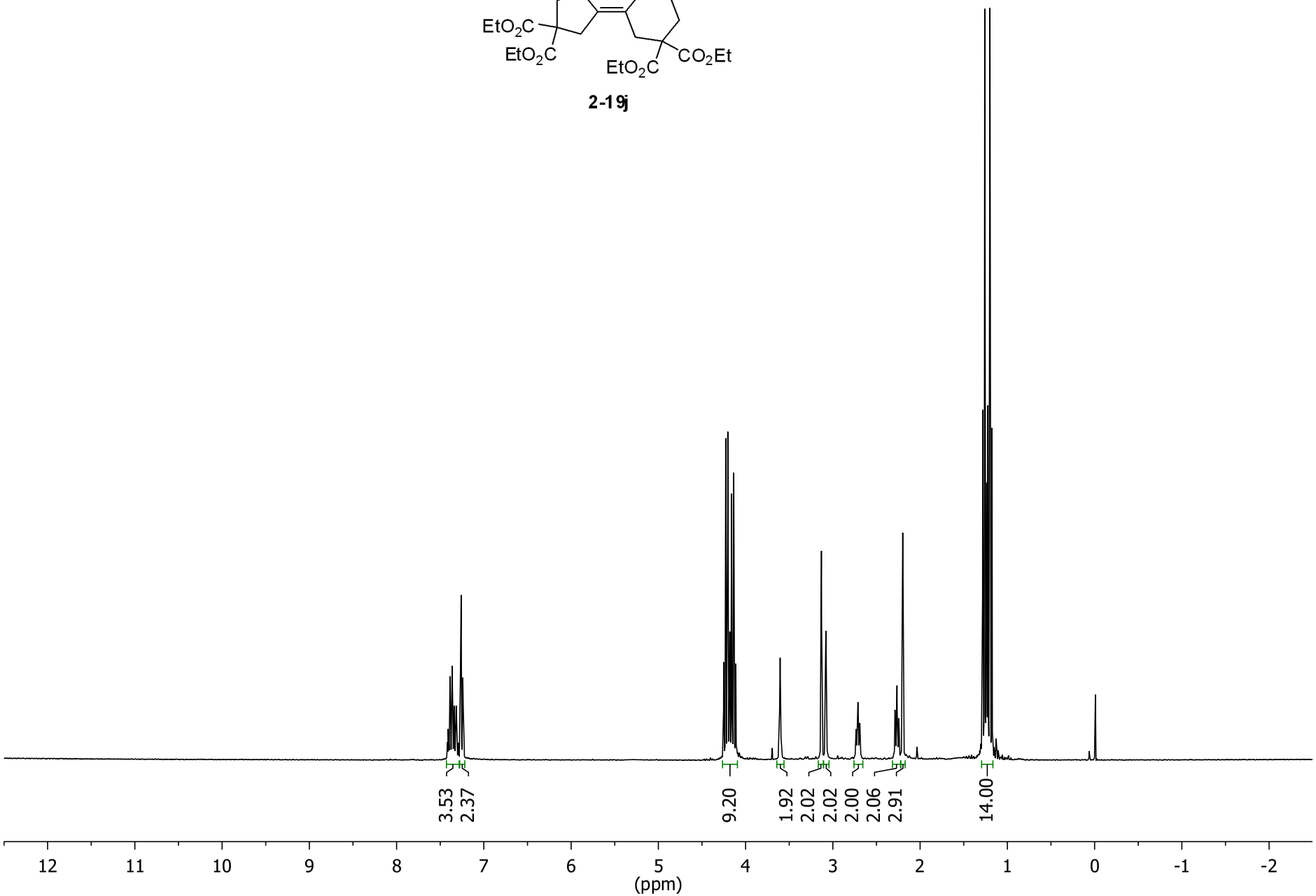
2-19h

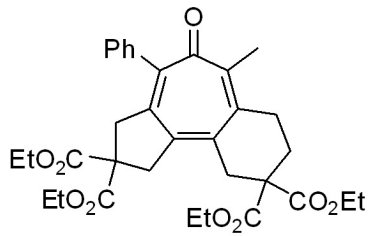
8.00
1.93
1.98
1.92
3.94
2.08
2.94
13.42
3.14
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

77.55
76.91
62.17
61.96
56.94
53.77
42.38
42.12
35.69
28.52
27.70
25.72
18.82
14.23
14.16
188.47
171.70
171.21
146.80
144.63
143.73
141.06
140.22
135.07
Et
O
CO2Et
CO2Et
EtO2C
EtO2C
2-19h
(ppm)

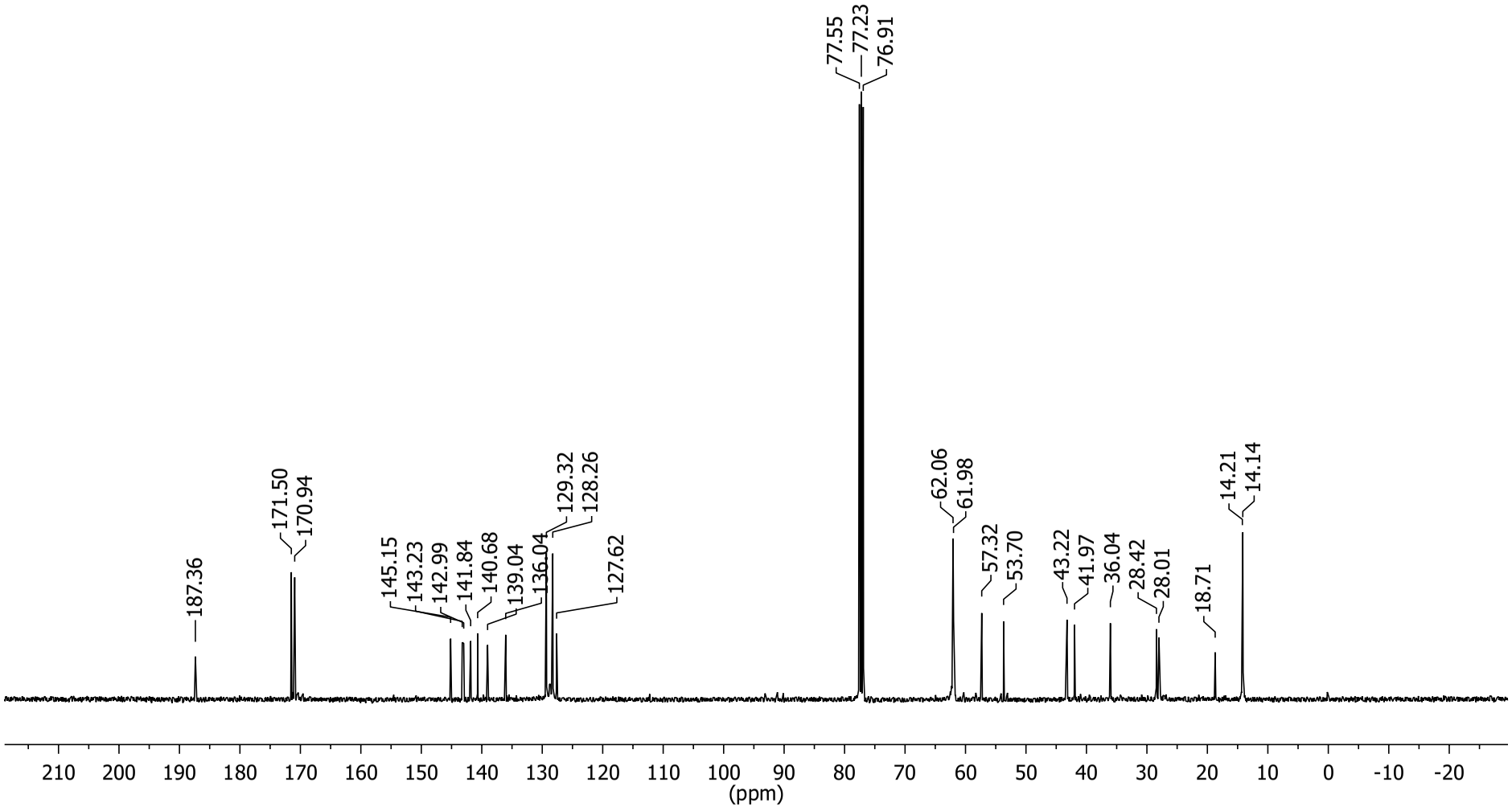

O
Ph
EtO2C
EtO2C
EtO2C
CO2Et

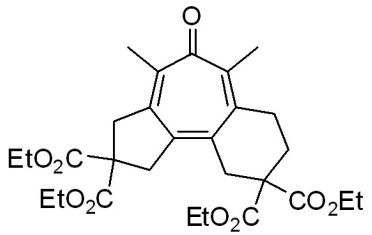
2-19j


3.53
2.37
9.20
1.92
2.02
2.02
2.00
2.06
2.91
14.00
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)


O
Ph
EtO2C
EtO2C
EtO2C
CO2Et

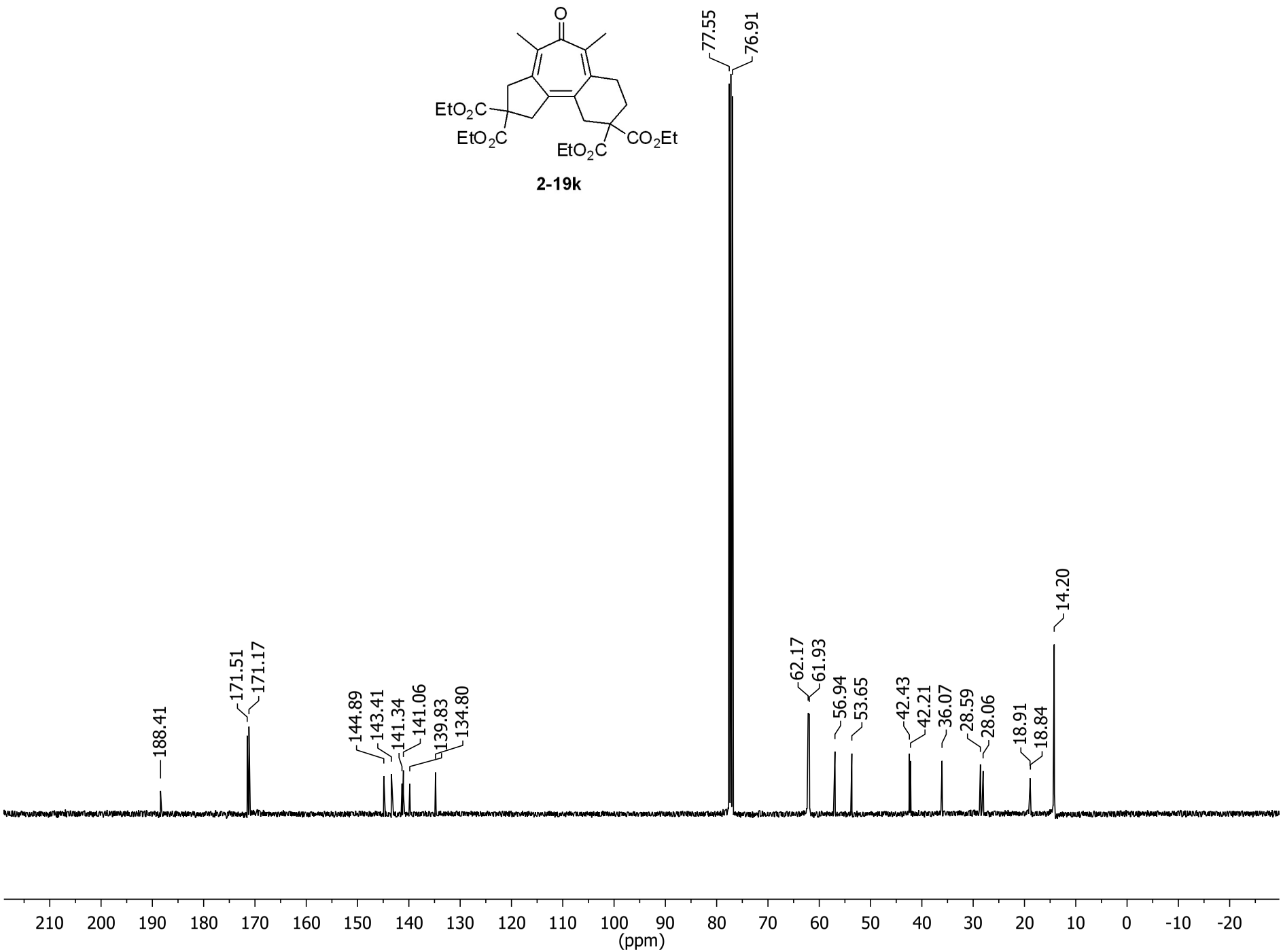
2-19j

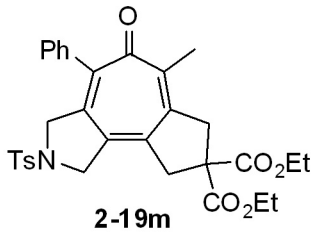

187.36
171.50
170.94
145.15
143.23
142.99
141.84
140.68
139.04
136.04
129.32
128.26
127.62
77.55
77.23
76.91
62.06
61.98
57.32
53.70
43.22
41.97
36.04
28.42
28.01
18.71
14.21
14.14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)


O
EtO2C
EtO2C
EtO2C
CO2Et

2-19k

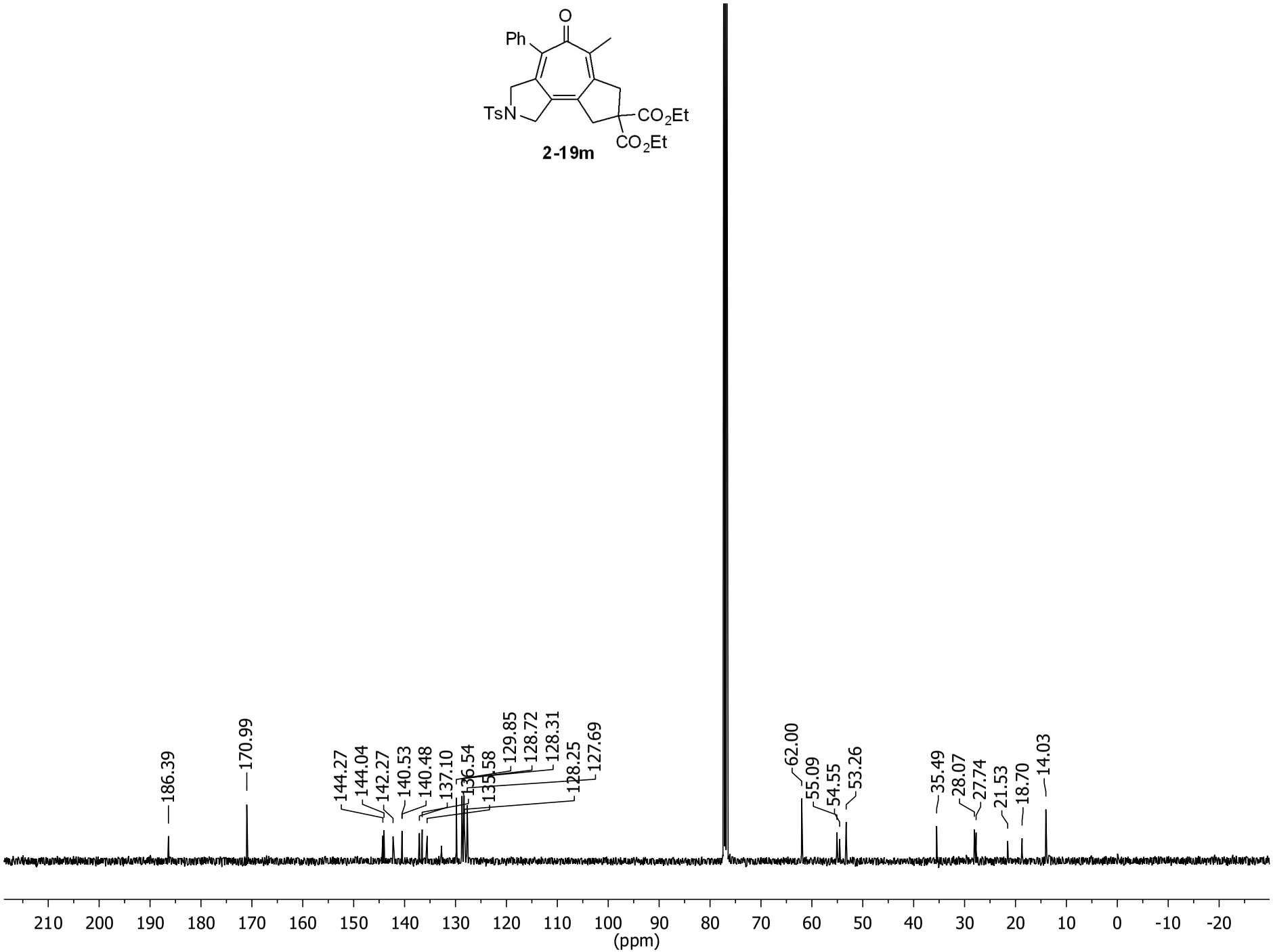
9.20
1.90
2.00
1.98
2.08
8.08
15.06
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

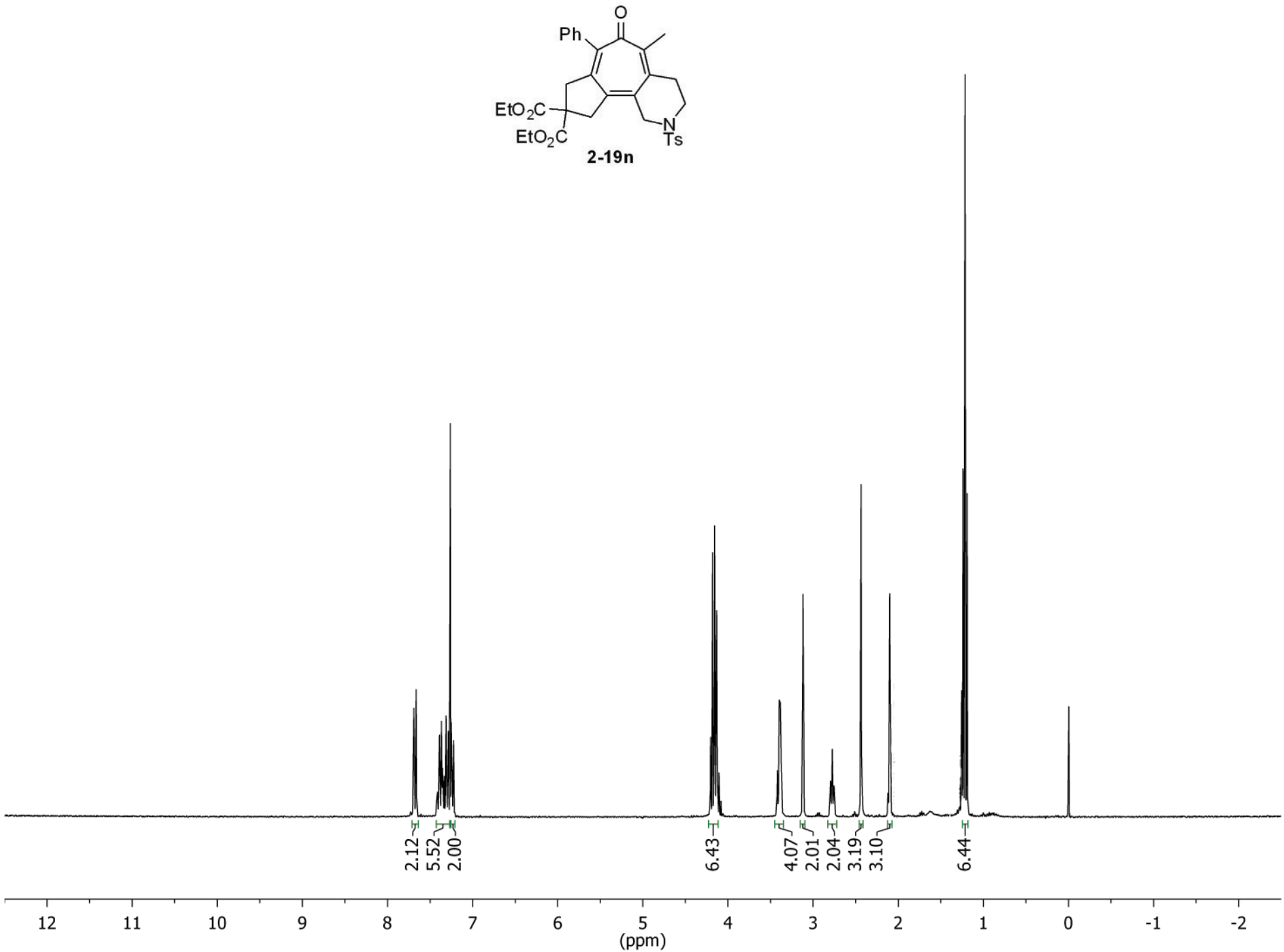

O
EtO2C
EtO2C
EtO2C
CO2Et
2-19k
77.55
76.91
188.41
171.51
171.17
144.89
143.41
141.34
141.06
139.83
134.80
62.17
61.93
56.94
53.65
42.43
42.21
36.07
28.59
28.06
18.91
18.84
14.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)


O
Ph
TsN
CO2Et
CO2Et

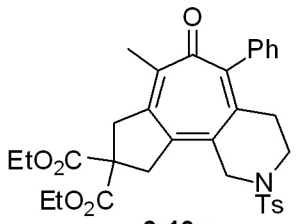
2-19m

1.00
2.60
1.00
0.98
1.00
2.08
0.97
1.00
1.49
1.11
1.51
3.47
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)


O
Ph
TsN
CO2Et
CO2Et
2-19m
186.39
170.99
144.27
144.04
142.27
140.53
140.48
137.10
136.54
135.58
129.85
128.72
128.31
128.25
127.69
62.00
55.09
54.55
53.26
35.49
28.07
27.74
21.53
18.70
14.03
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)


O
Ph
EtO2C
EtO2C
N
Ts
2-19n
2.12
5.52
2.00
6.43
4.07
2.01
2.04
3.19
3.10
6.44
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

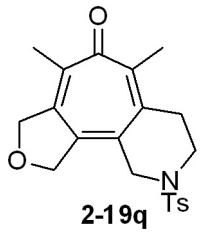
14.19
18.75
21.79
30.42
41.00
43.02
43.48
48.64
57.57
62.30
76.91
77.55
127.78
127.94
128.30
129.36
130.03
133.93
138.38
138.46
139.13
142.19
144.41
144.48
144.61
170.69
186.97
(ppm)
Ts
N
O
Ph
EtO2C
EtO2C
2-19n


O
Ph
EtO2C
EtO2C
N
Ts

2-19o

2.00
3.17
2.06
1.96
6.10
3.97
2.02
5.28
3.12
6.69
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

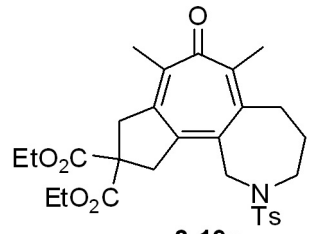
186.11
170.87
146.11
144.78
144.35
143.46
141.02
140.04
139.86
133.96
129.91
128.86
128.55
127.56
127.47
77.54
77.22
76.90
62.49
57.07
43.64
42.42
41.58
30.97
21.69
18.91
14.23
(ppm)
Ph
N
Ts
O
EtO2C
EtO2C
2-19o


O
O
N
Ts

2-19q

2.00
2.10
1.83
1.95
1.90
1.94
2.04
3.51
2.89
2.94
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

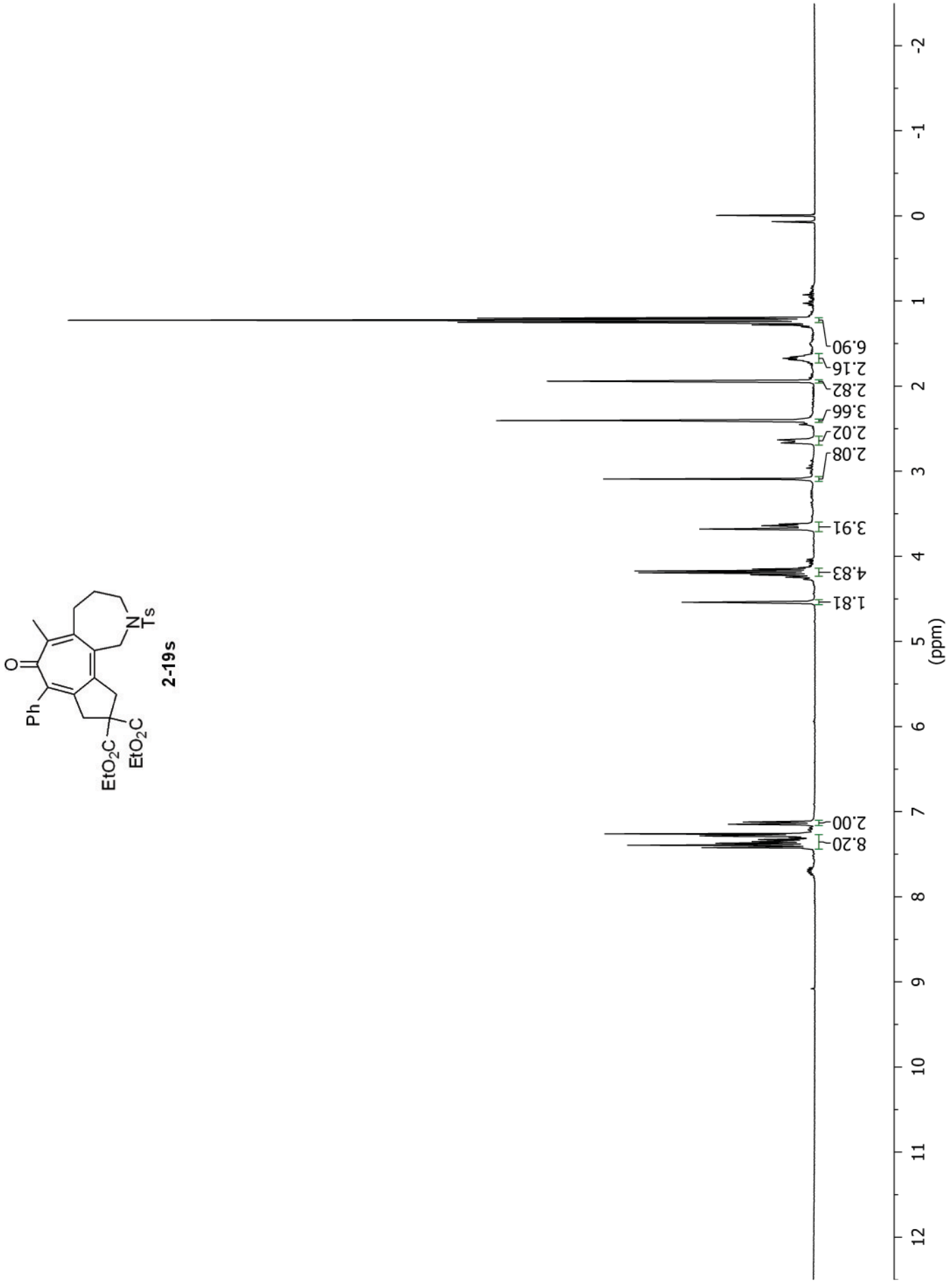
186.11
144.59
144.47
143.81
139.57
138.84
138.71
133.36
130.74
130.05
127.77
77.54
77.23
76.91
74.95
74.22
47.66
43.36
31.03
21.74
19.11
17.90
(ppm)
2-19q


O
EtO2C
EtO2C
N
Ts

2-19r

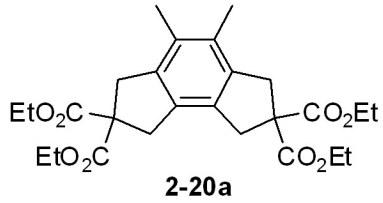
2.12
1.95
1.88
4.37
1.87
1.99
2.00
1.97
3.09
3.00
2.95
2.18
7.04
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

189.39
170.99
145.67
144.36
143.73
141.88
140.10
140.06
136.76
136.70
129.75
126.79
77.54
77.22
76.90
62.24
57.08
52.28
50.60
41.84
41.38
33.07
26.54
21.60
21.56
18.81
18.77
18.00
17.95
14.18
14.15
(ppm)
EtO2C
EtO2C
O
N
Ts
2-19r

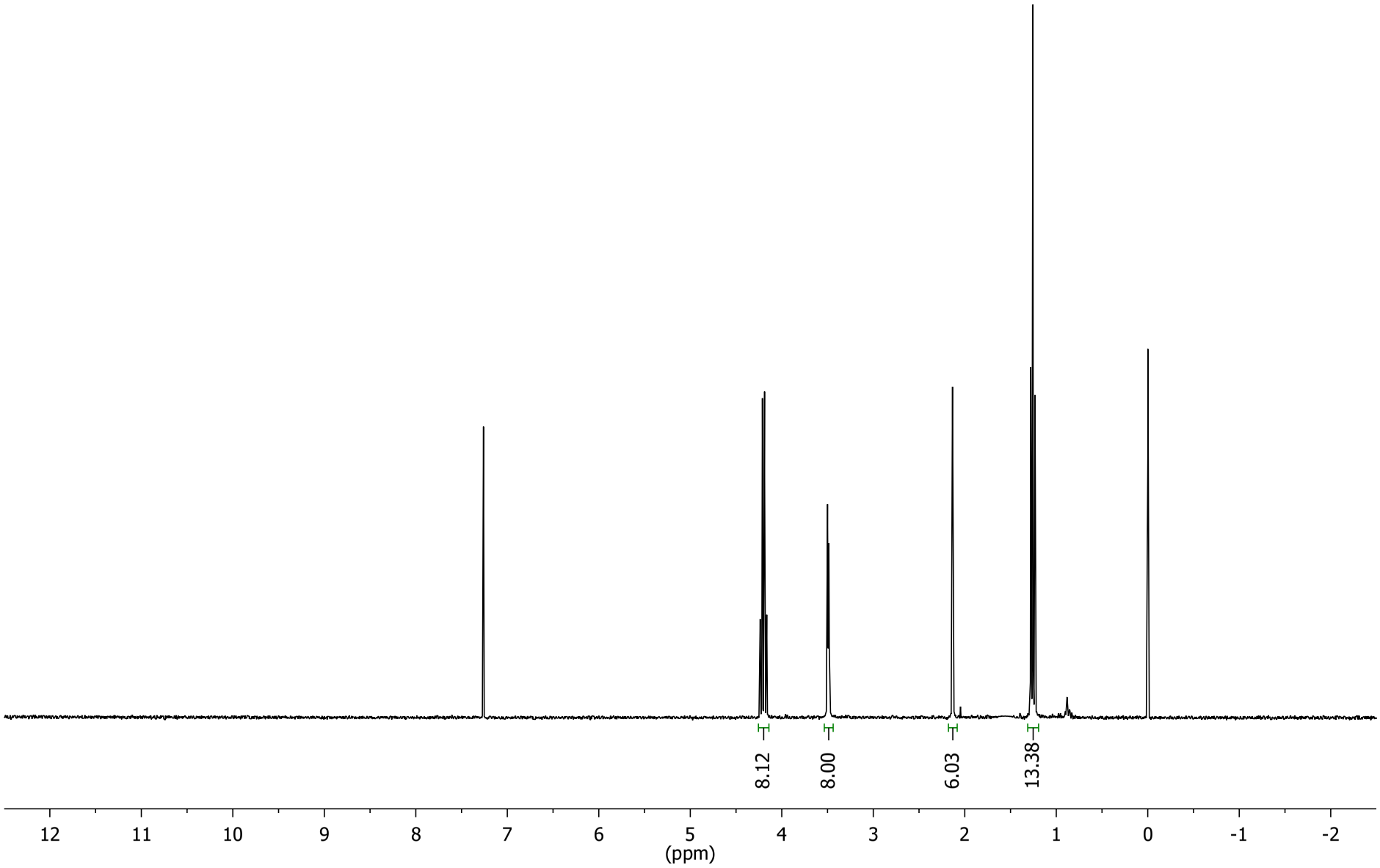

6.90
2.16
2.82
3.66
2.02
2.08
3.91
4.83
1.81
2.00
8.20
(ppm)
Ph
EtO2C
EtO2C
Ts
N
O

2-19s

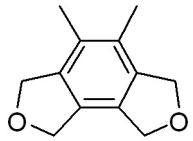
14.17
14.20
21.70
21.73
26.67
33.05
41.14
42.81
50.94
52.13
57.43
62.18
62.35
76.91
77.23
77.55
126.85
128.27
129.38
129.87
136.88
137.86
138.55
139.65
142.10
143.70
143.93
144.54
145.19
170.89
188.14
(ppm)
2-19s


EtO2C
CO2Et
EtO2C
CO2Et

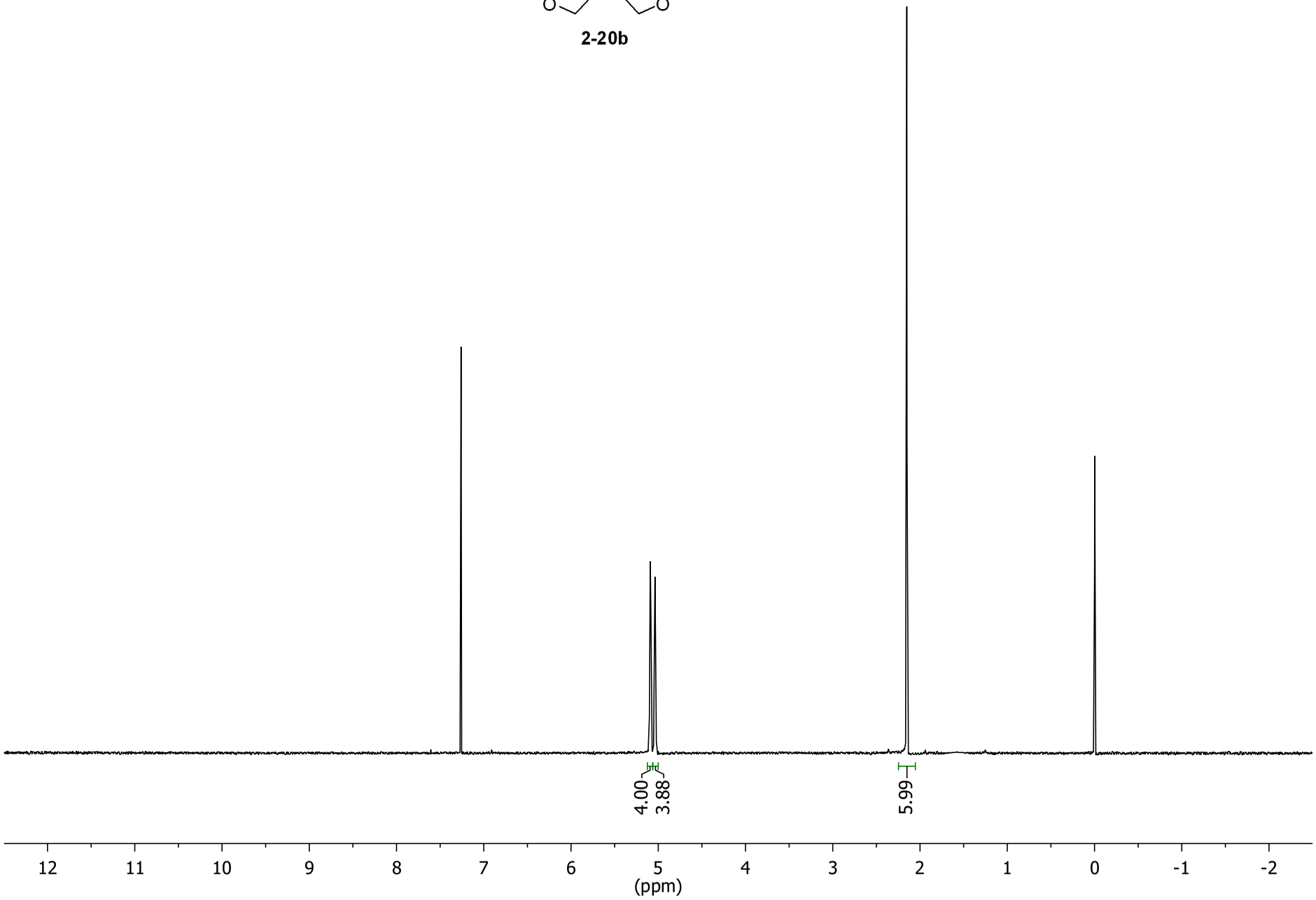
2-20a


8.12
8.00
6.03
13.38
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

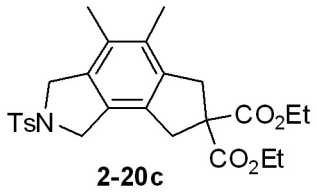
172.09
138.38
132.43
130.79
77.55
77.23
76.91
61.89
60.22
40.23
39.34
15.96
14.25
(ppm)
CO2Et
CO2Et
EtO2C
EtO2C
2-20a



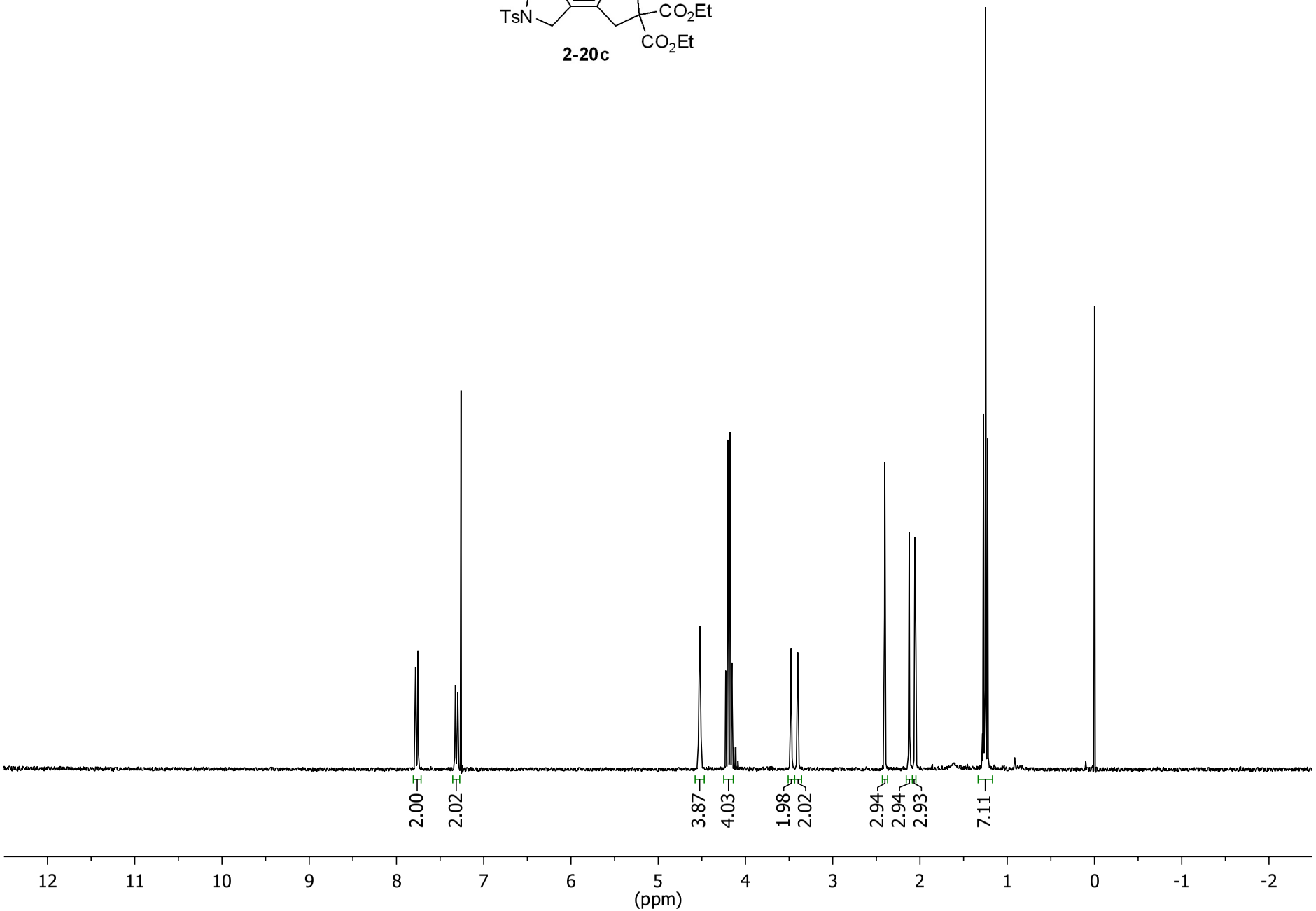
2-20b



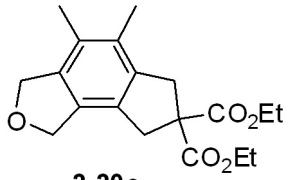
15.68
73.13
73.58
76.91
77.23
77.55
128.82
129.07
138.42
2-20b
(ppm)


TsN
CO2Et
CO2Et

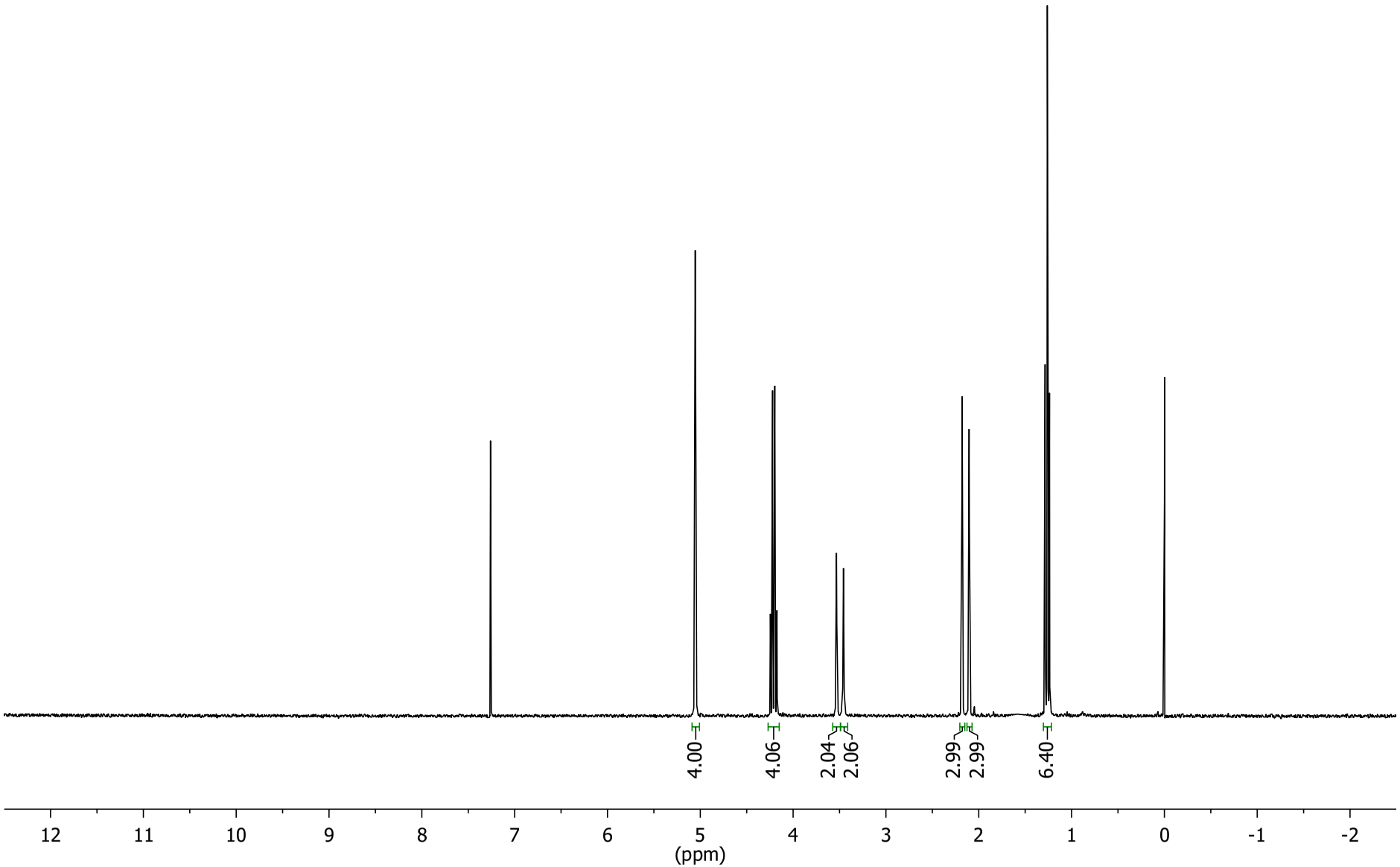
2-20c


2.00
2.02
3.87
4.03
1.98
2.02
2.94
2.94
2.93
7.11
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

171.76
143.78
139.46
134.68
134.09
131.87
131.23
130.03
129.69
128.72
127.76
77.55
77.23
76.91
62.04
60.22
53.83
53.21
40.02
39.01
21.70
15.80
14.23
(ppm)
TsN
CO2Et
CO2Et
2-20c


O
CO2Et
CO2Et

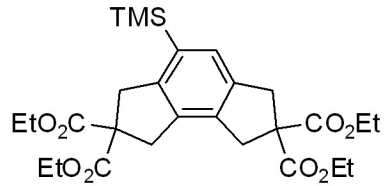
2-20e


4.00
4.06
2.04
2.06
2.99
2.99
6.40
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

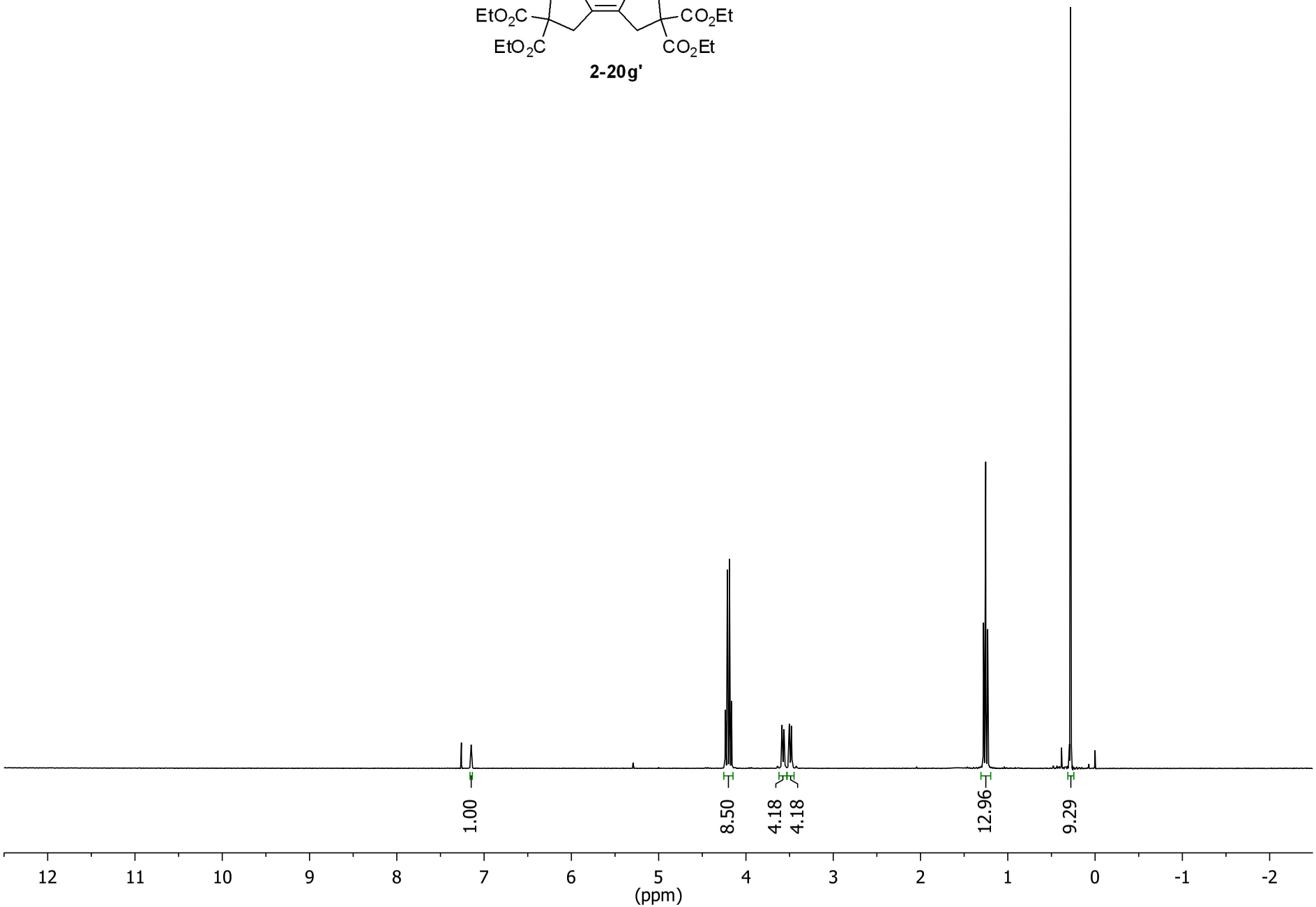
171.93
139.01
137.82
131.57
131.29
129.89
128.33
77.55
77.23
76.91
73.84
73.37
61.98
60.45
39.98
39.21
16.03
15.66
14.25
(ppm)

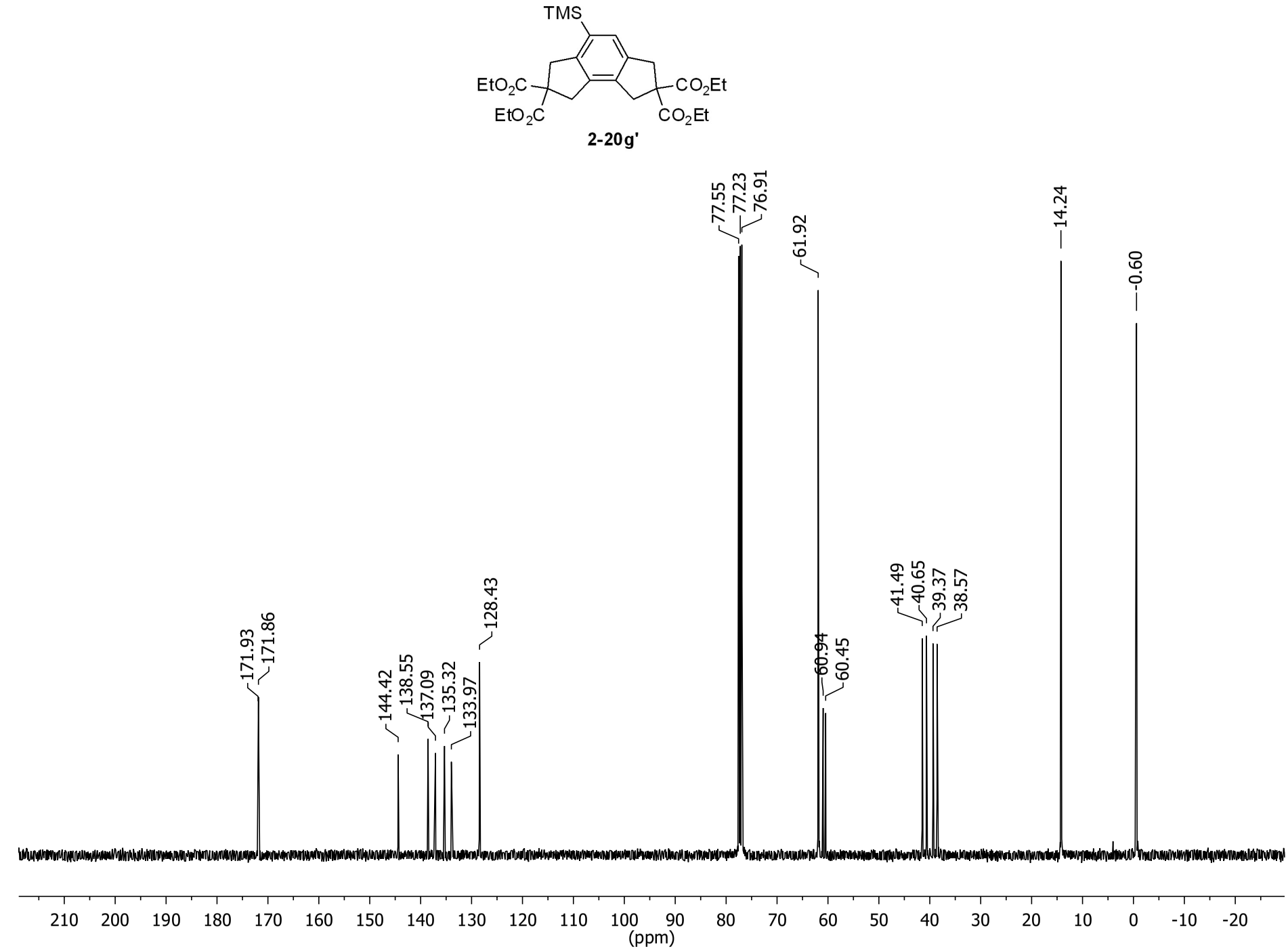
CO2Et
CO2Et
O

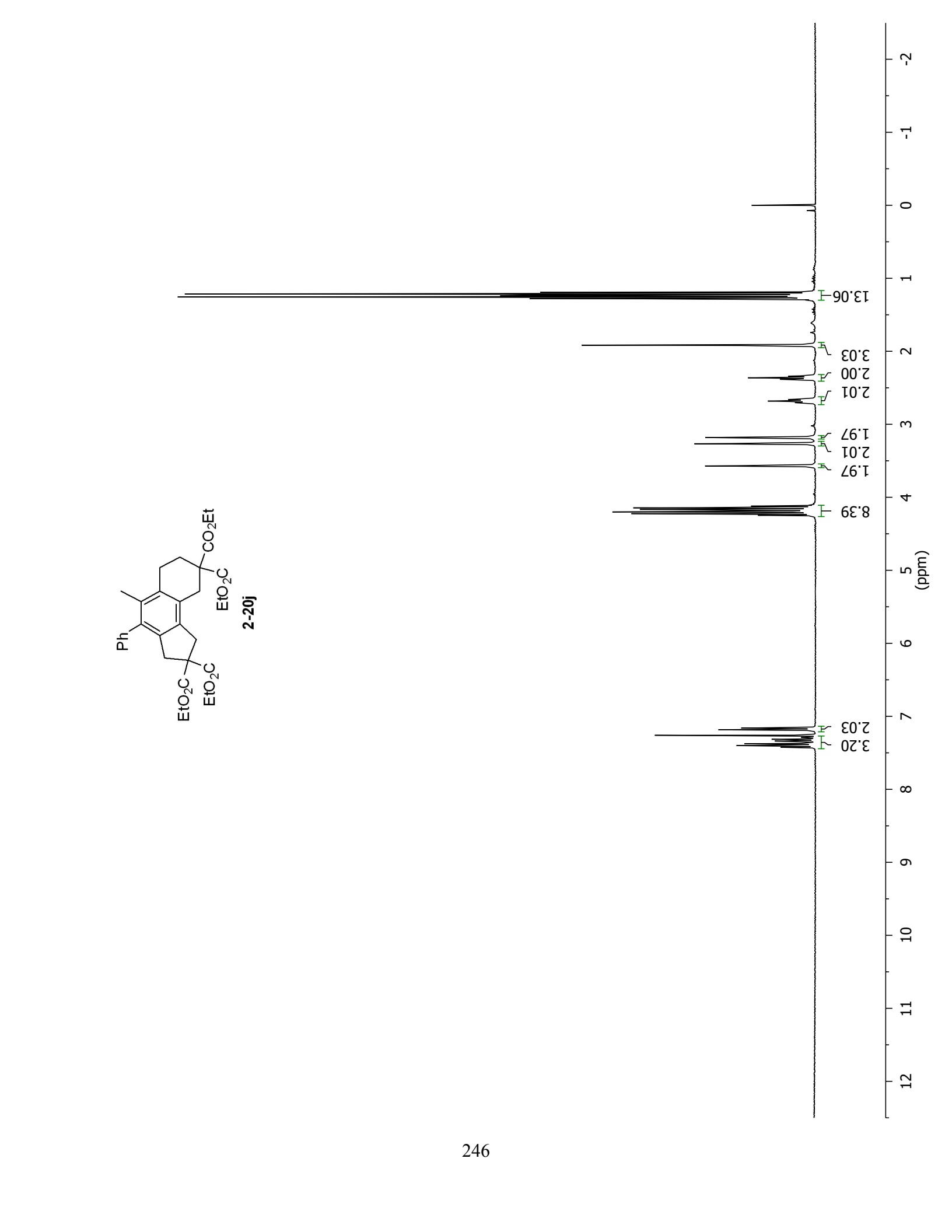
2-20e


TMS
EtO2C
CO2Et
EtO2C
CO2Et

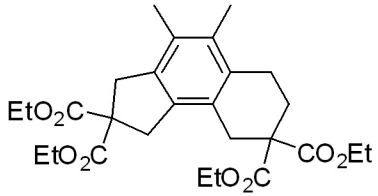
2-20g'


1.00
8.50
4.18
4.18
12.96
9.29
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

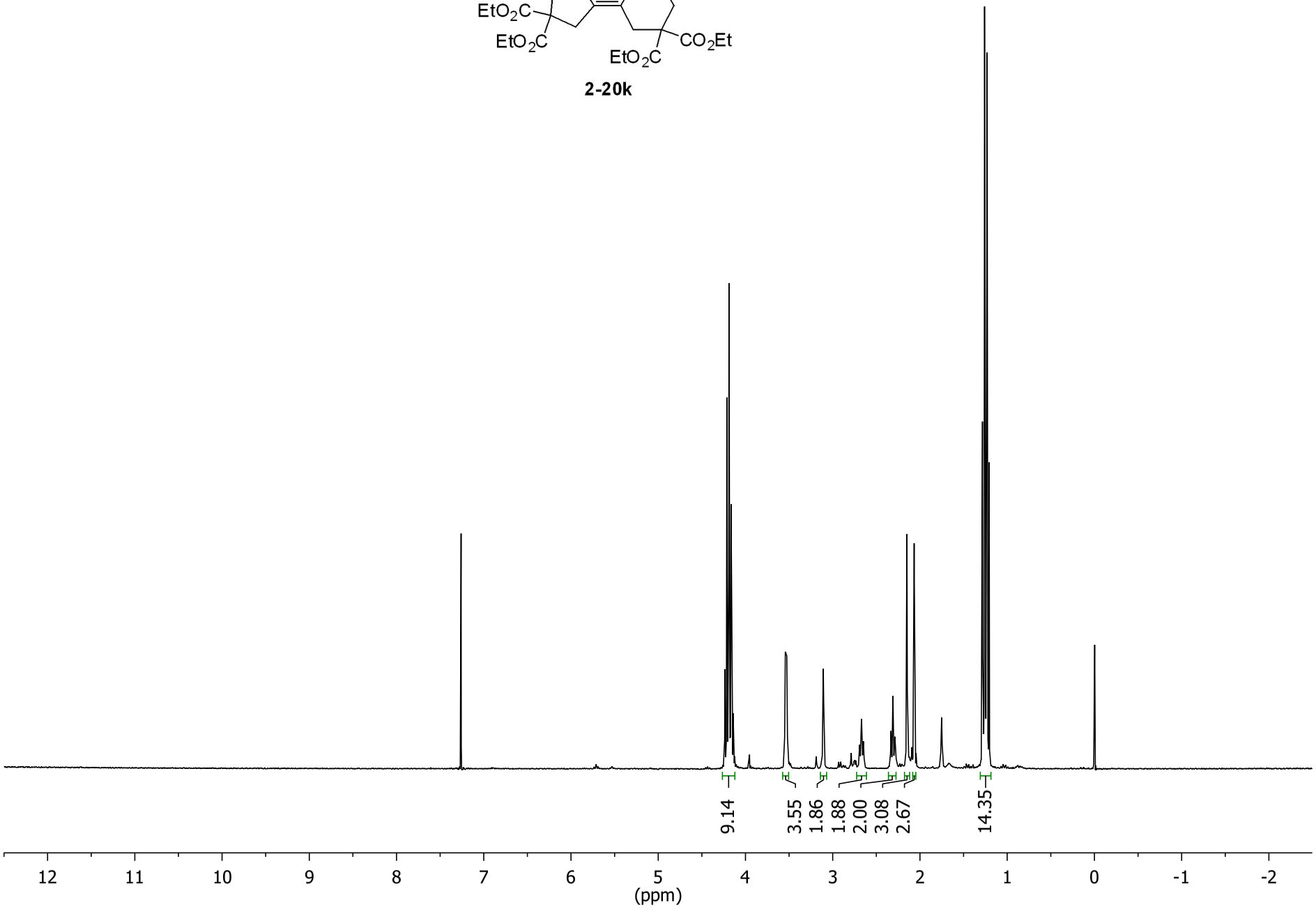

TMS
EtO2C
CO2Et
EtO2C
CO2Et
2-20g'
77.55
77.23
76.91
61.92
14.24
-0.60
171.93
171.86
144.42
138.55
137.09
135.32
133.97
128.43
60.94
60.45
41.49
40.65
39.37
38.57
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)


Ph
CO2Et
EtO2C
EtO2C
EtO2C
2-20j
13.06
3.03
2.00
2.01
1.97
2.01
1.97
8.39
2.03
3.20
(ppm)

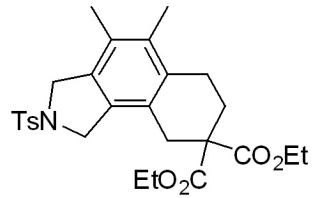
171.98
171.64
140.75
136.41
136.34
135.58
132.87
132.31
129.47
128.61
128.48
126.84
77.55
77.23
76.91
61.80
61.68
59.96
53.19
40.71
39.59
32.83
28.30
24.61
16.56
14.26
14.22
Ph
EtO2C
EtO2C
EtO2C
CO2Et
2-20j
(ppm)


EtO2C
EtO2C
EtO2C
CO2Et

2-20k


9.14
3.55
1.86
1.88
2.00
3.08
2.67
14.35
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

172.14
171.62
136.59
135.42
133.40
131.84
129.78
126.78
77.55
77.23
76.91
61.85
61.59
61.76
59.67
53.16
40.39
39.60
32.75
28.40
24.68
16.53
14.99
14.24
CO2Et
EtO2C
EtO2C
EtO2C
2-20k
(ppm)

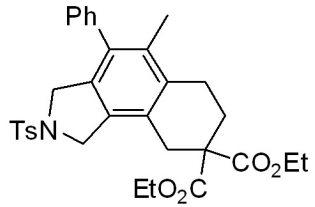

TsN
CO2Et
EtO2C

2-20l

250

2.00
2.07
3.77
4.29
1.87
2.05
3.25
2.43
6.09
7.42
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

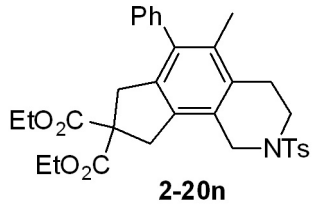
171.29
143.75
134.47
134.05
132.97
132.79
131.70
130.02
128.63
127.70
125.84
77.54
77.22
76.91
61.76
54.16
53.61
52.84
32.36
28.19
24.54
21.65
16.39
14.84
14.24
14.21
TsN
EtO2C
CO2Et
2-20l
(ppm)


Ph
TsN
CO2Et
EtO2C

2-20m

2.05
5.21
2.08
2.00
4.17
2.11
2.04
2.07
3.15
2.15
3.11
6.74
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

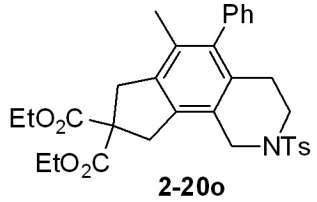
171.28
143.69
139.45
135.17
134.00
133.30
132.73
131.88
129.96
128.90
128.75
127.67
127.53
127.42
77.55
77.23
76.91
61.82
54.24
53.51
52.86
32.43
29.86
28.07
24.47
21.64
16.35
14.22
(ppm)
Ph
TsN
EtO2C
CO2Et
2-20m


Ph
EtO2C
EtO2C
NTs

2-20n

2.05
5.63
2.21
6.60
2.00
2.07
2.06
2.00
3.26
3.09
7.55
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

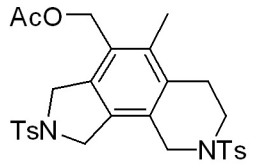
171.75
143.91
140.23
137.24
137.07
133.78
133.23
130.99
129.93
129.24
128.64
128.06
127.12
126.84
77.55
77.23
76.91
61.98
60.06
46.30
43.93
40.44
38.83
27.60
21.75
16.37
14.21
(ppm)
Ph
NTs
EtO2C
EtO2C
2-20n


Ph
EtO2C
EtO2C
NTs

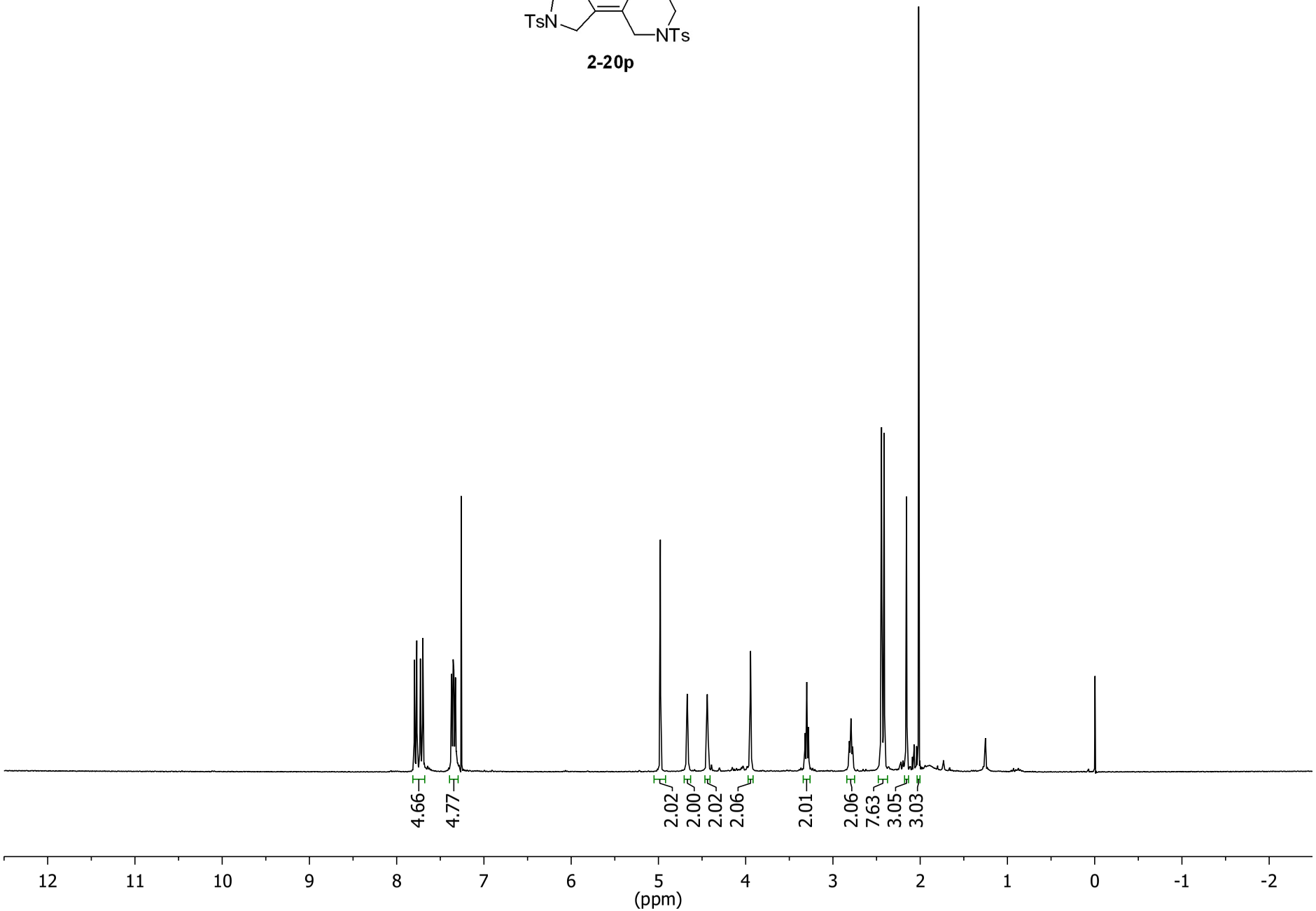
2-20o

2.00
5.22
1.98
4.17
1.98
1.98
1.98
1.95
5.12
3.00
6.33
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

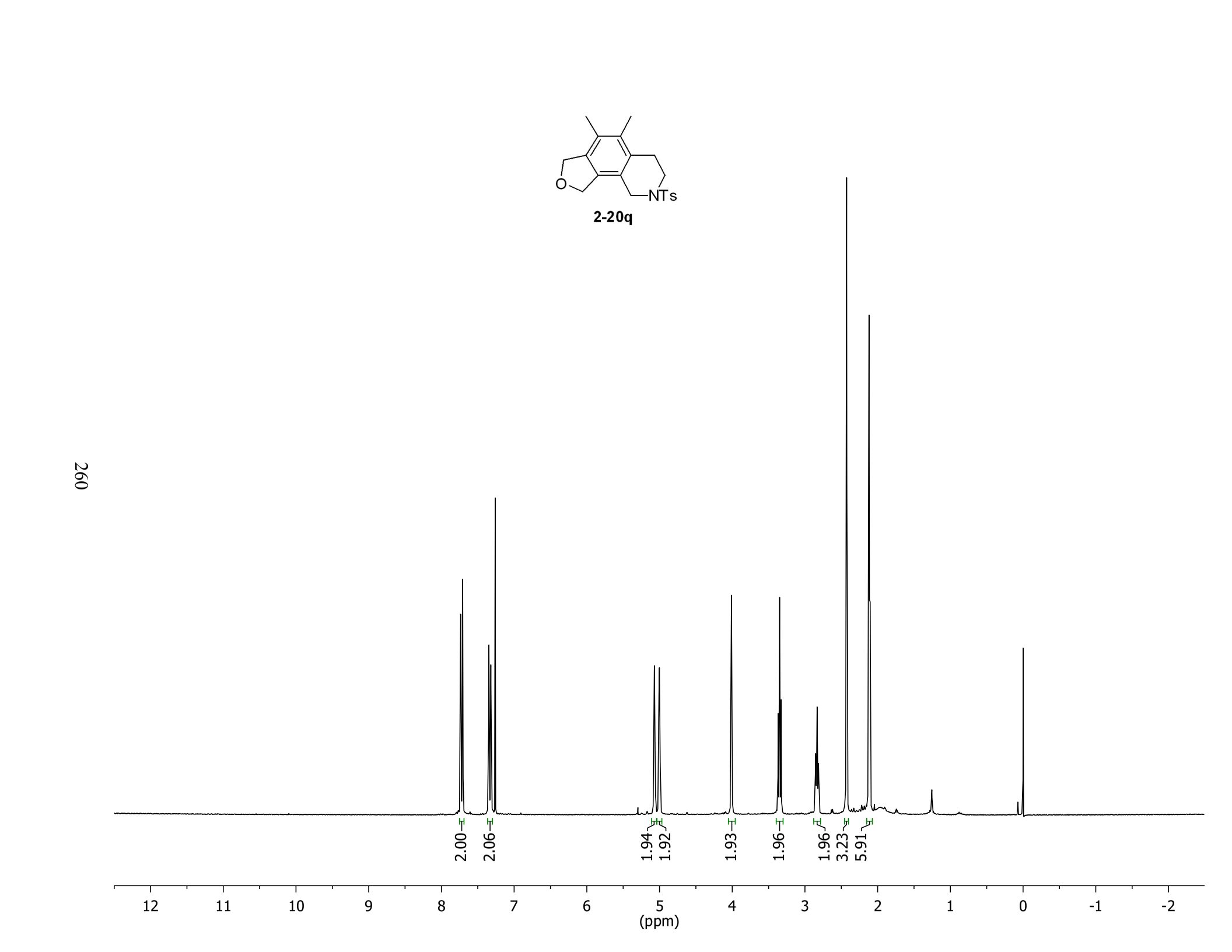
171.90
143.80
140.72
140.11
137.40
135.37
133.34
130.37
130.34
129.87
129.36
128.71
127.94
125.01
77.54
77.22
76.91
62.09
59.74
46.03
43.91
39.98
38.94
28.51
21.70
21.67
17.20
17.16
14.25
14.23
Ph
NTs
EtO2C
EtO2C
2-20o
(ppm)


AcO
TsN
NTs

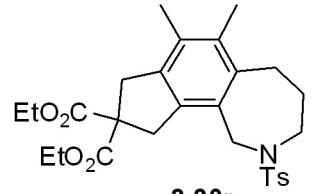
2-20p


4.66
4.77
2.02
2.00
2.02
2.06
2.01
2.06
7.63
3.05
3.03
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

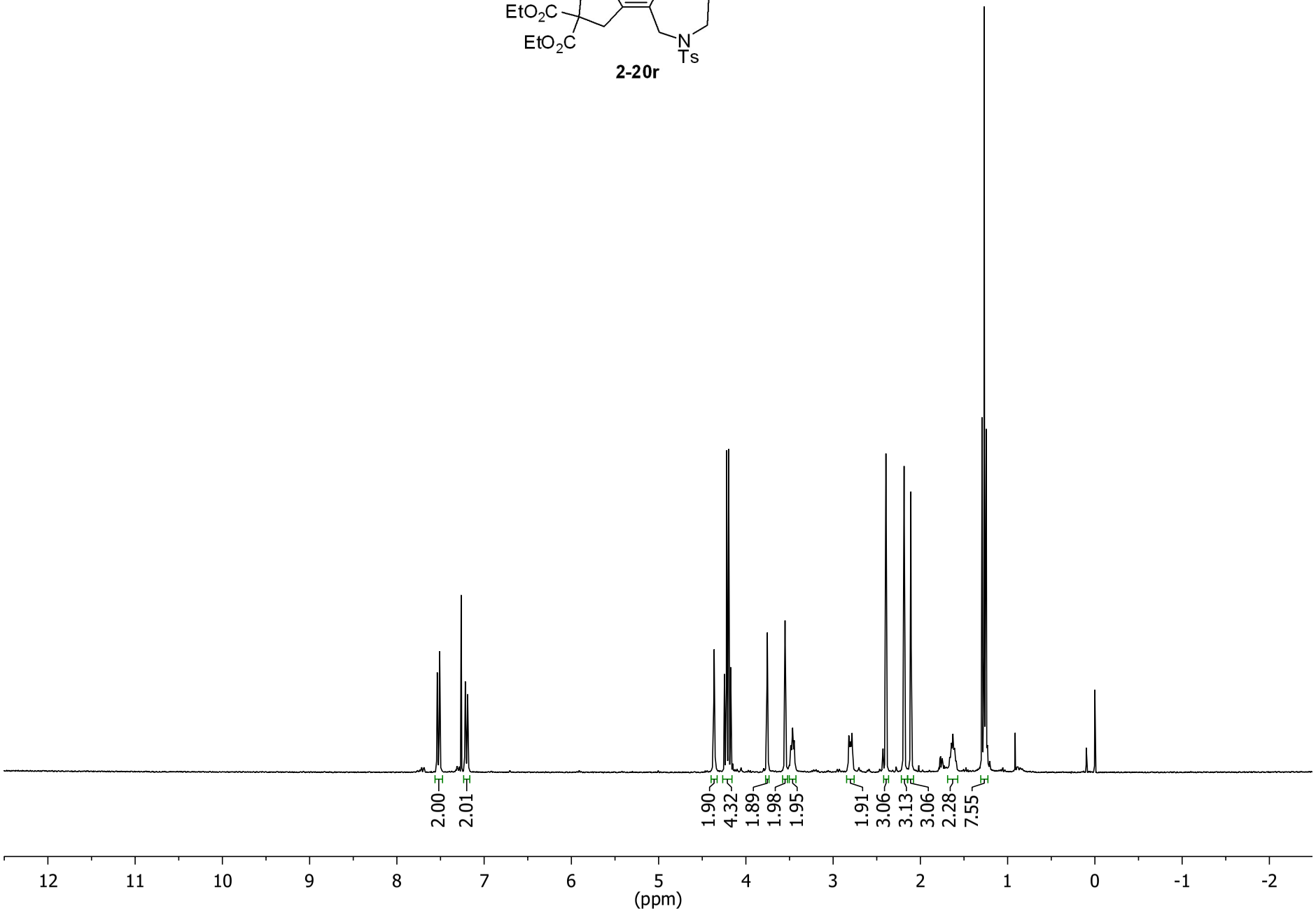
170.78
144.26
144.09
136.39
134.83
132.74
132.42
130.83
130.14
130.07
127.98
127.78
127.41
127.18
77.54
77.23
76.91
61.65
53.28
52.49
45.82
43.68
27.52
21.74
20.92
14.66
AcO
TsN
NTs
2-20p
(ppm)


O
NTs
2-20q
260
2.00
2.06
1.94
1.92
1.93
1.96
1.96
3.23
5.91
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

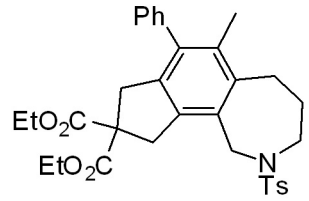
143.98
136.47
134.16
133.23
132.70
130.88
129.94
128.17
127.98
122.93
77.54
77.23
76.91
73.96
73.07
45.90
44.03
27.60
21.72
16.69
14.62
NTs
O
2-20q
(ppm)


EtO2C
EtO2C
N
Ts

2-20r


2.00
2.01
1.90
4.32
1.89
1.98
1.95
1.91
3.06
3.13
3.06
2.28
7.55
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

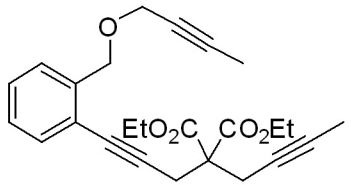
172.08
143.04
138.97
137.20
136.74
136.06
133.03
132.09
130.13
129.57
127.34
77.54
77.22
76.90
61.91
59.61
51.34
49.39
40.49
39.61
28.72
26.88
21.65
14.25
14.20
(ppm)
2-20r


Ph
EtO2C
EtO2C
N
Ts

2-20s

2.00
3.18
2.14
2.05
1.93
4.59
1.95
2.00
2.04
2.00
3.41
3.11
2.38
6.81
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

171.92
143.13
140.98
139.44
138.65
137.20
136.80
136.27
132.48
132.06
129.66
129.18
128.64
127.38
61.88
59.92
51.75
49.40
40.79
39.64
28.98
26.63
21.70
17.36
14.21
14.19
(ppm)
Ph
EtO2C
EtO2C
N
Ts
2-20s



3-1a

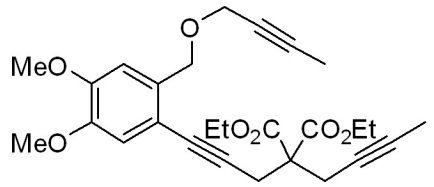
266

1.08
1.13
0.91
0.95
2.00
6.25
1.91
1.98
3.02
2.99
6.34

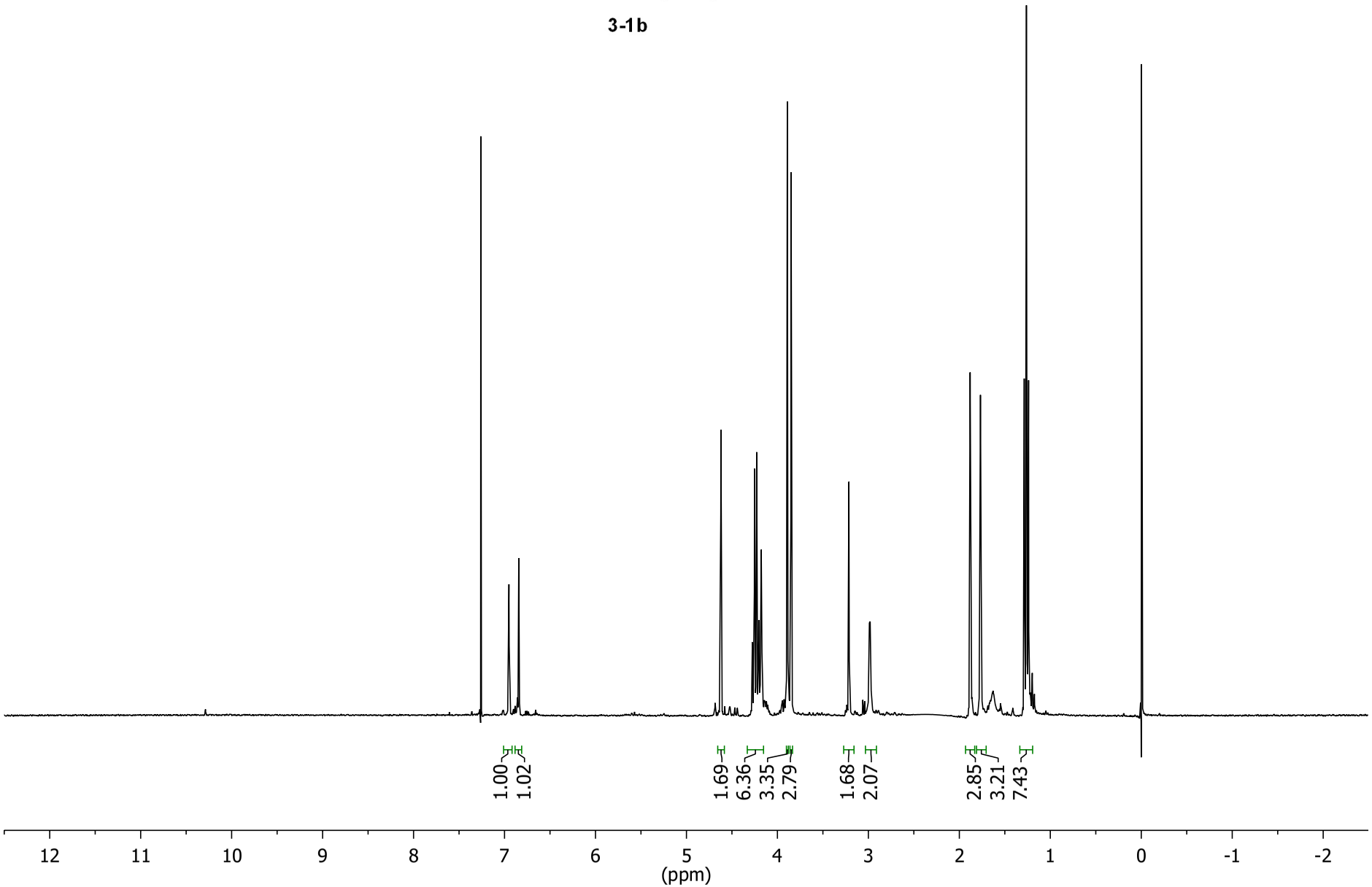
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

(ppm)

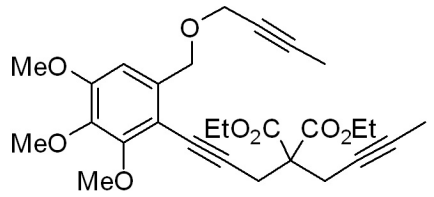
3.72
3.88
14.30
23.36
23.94
57.17
58.57
62.06
62.22
69.92
73.39
75.46
76.98
77.48
79.31
81.27
82.78
89.16
121.98
127.37
127.67
128.39
132.45
139.84
169.32
(ppm)
EtO2C
CO2Et
3-1a


MeO
MeO
O
EtO2C
CO2Et

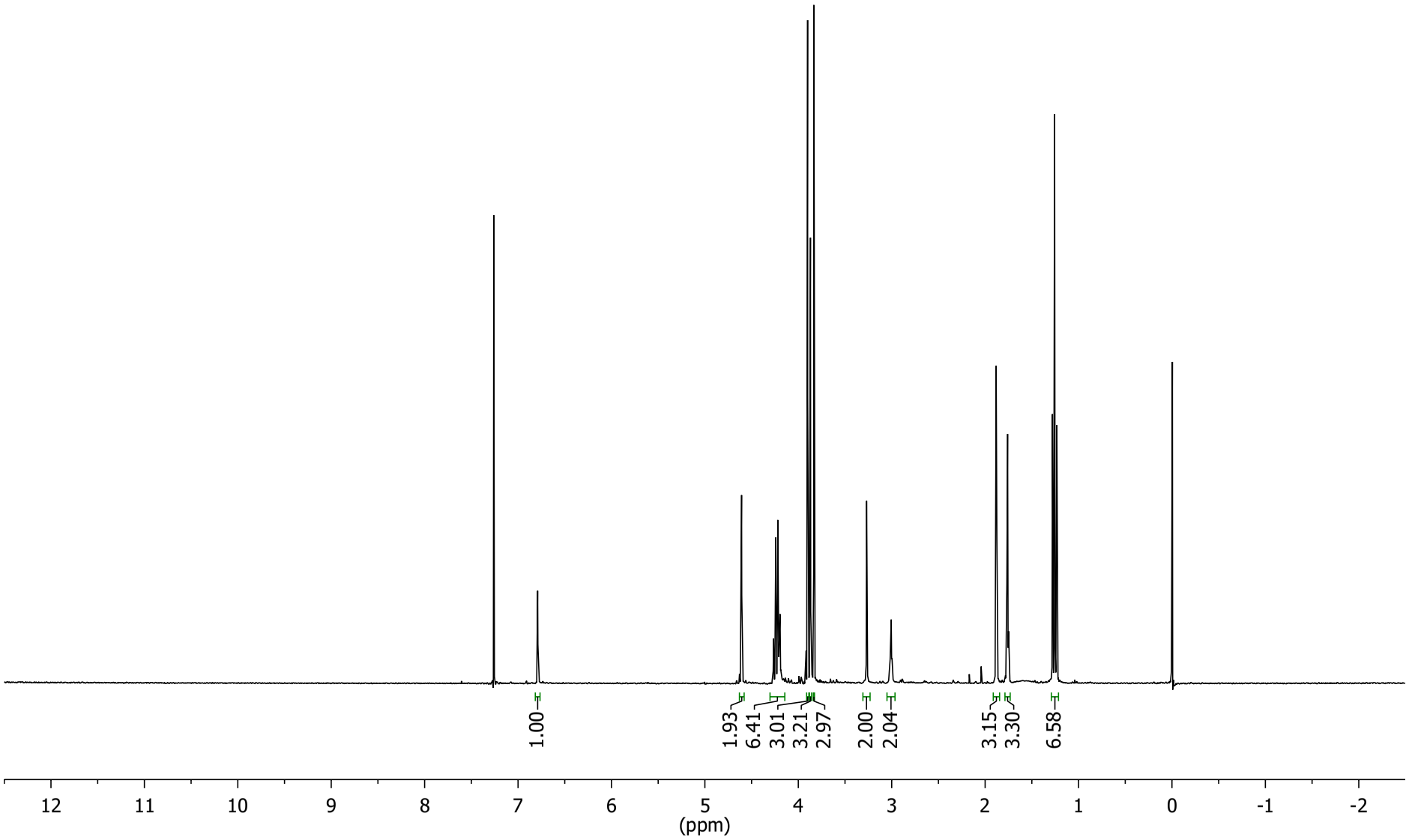
3-1b


1.00
1.02
1.69
6.36
3.35
2.79
1.68
2.07
2.85
3.21
7.43
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

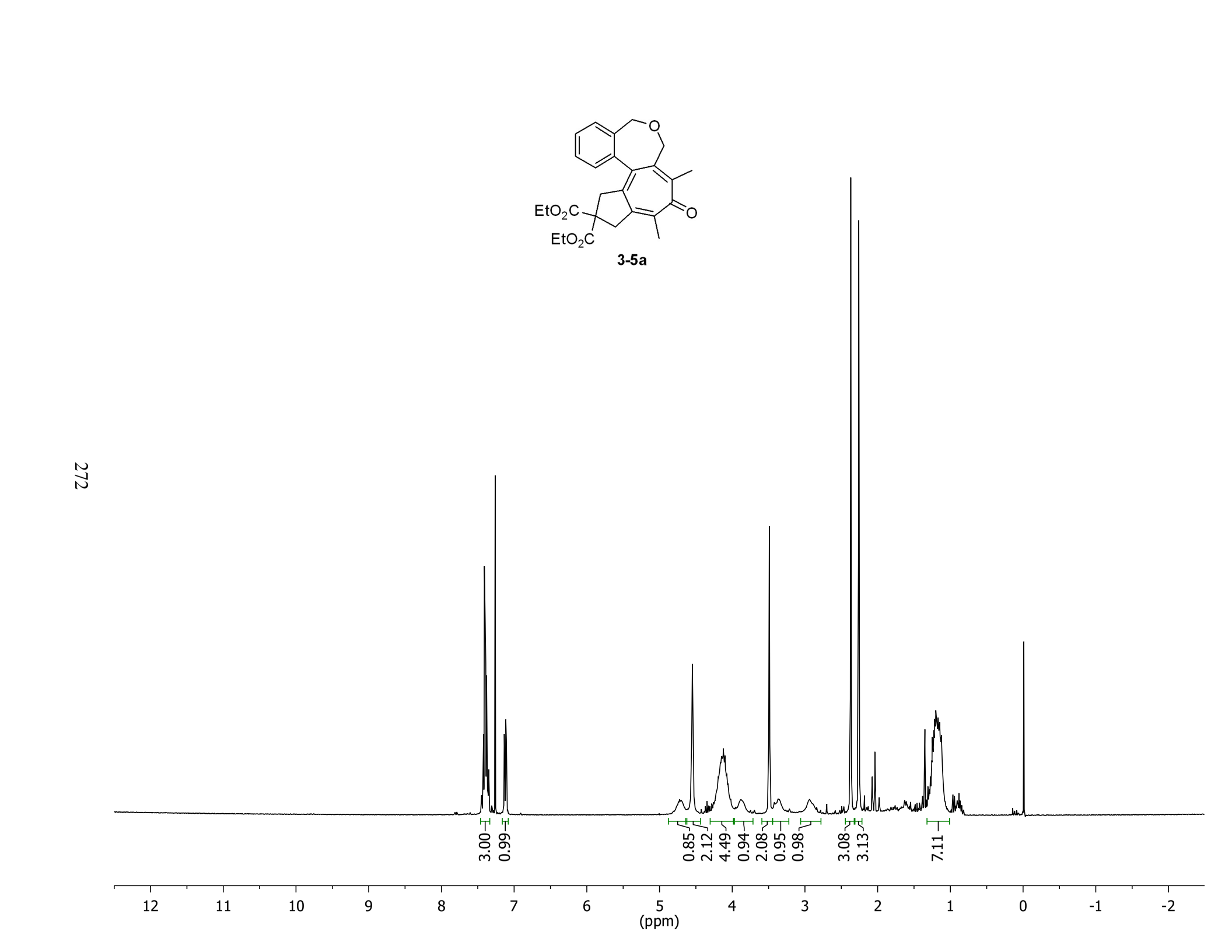
3.73
3.88
14.30
23.37
23.94
56.15
56.21
57.18
58.38
62.04
69.81
73.42
75.52
76.97
77.48
79.30
81.30
87.39
110.96
114.16
114.74
133.24
148.08
149.54
169.35
MeO
MeO
O
EtO2C
CO2Et
3-1b
(ppm)


MeO
MeO
MeO
O
EtO2C
CO2Et

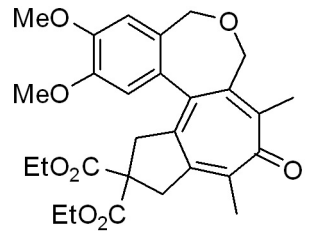
3-1c


1.00
1.93
6.41
3.01
3.21
2.97
2.00
2.04
3.15
3.30
6.58
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

3.71
3.87
14.27
23.32
24.19
56.27
57.14
58.66
61.26
61.42
62.00
69.86
73.46
76.97
77.47
91.78
106.76
109.21
136.56
141.38
153.86
155.02
169.35
MeO
MeO
MeO
O
EtO2C
CO2Et
3-1c
(ppm)


O
EtO2C
EtO2C
O
3-5a
272
3.00
0.99
0.85
2.12
4.49
0.94
2.08
0.95
0.98
3.08
3.13
7.11
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

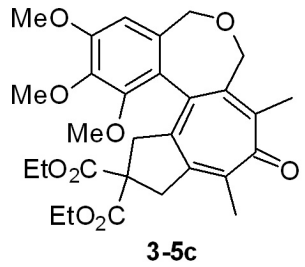
190.83
170.78
145.66
142.04
141.99
141.15
140.27
140.00
138.06
132.68
129.21
129.04
128.94
128.74
77.48
77.22
76.97
68.11
65.27
62.12
57.95
44.81
42.35
19.79
18.59
14.13
(ppm)
EtO2C
EtO2C
3-5a


MeO
MeO
O
EtO2C
EtO2C
O

3-5b

1.00
0.98
1.11
2.28
6.13
4.54
4.53
3.47
1.30
3.57
3.47
8.45
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

77.54
77.23
76.91
67.94
62.13
57.93
56.37
56.24
44.93
42.47
19.89
18.60
14.13
112.23
111.92
125.41
138.53
140.17
140.20
141.08
142.32
145.69
148.90
170.80
190.54
MeO
MeO
EtO2C
EtO2C
O
O
3-5b
(ppm)

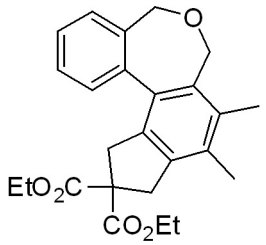

MeO
MeO
MeO
EtO2C
EtO2C
O
O

3-5c

+ unknown

1.00
0.29
1.44
2.94
3.16
3.29
1.06
1.09
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

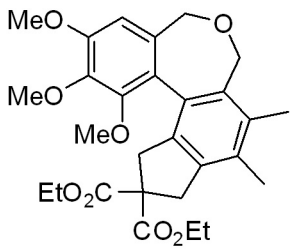
199.53
190.66
171.70
171.26
171.23
170.69
153.92
150.91
145.73
143.20
142.04
140.34
137.76
135.03
128.15
127.63
110.02
108.14
68.12
62.05
61.94
61.50
61.43
57.63
56.29
43.86
42.51
40.47
38.71
20.05
18.53
14.16
14.09
(ppm)
+ unknown
MeO
MeO
MeO
EtO2C
EtO2C
O
O
3-5c


O
EtO2C
CO2Et

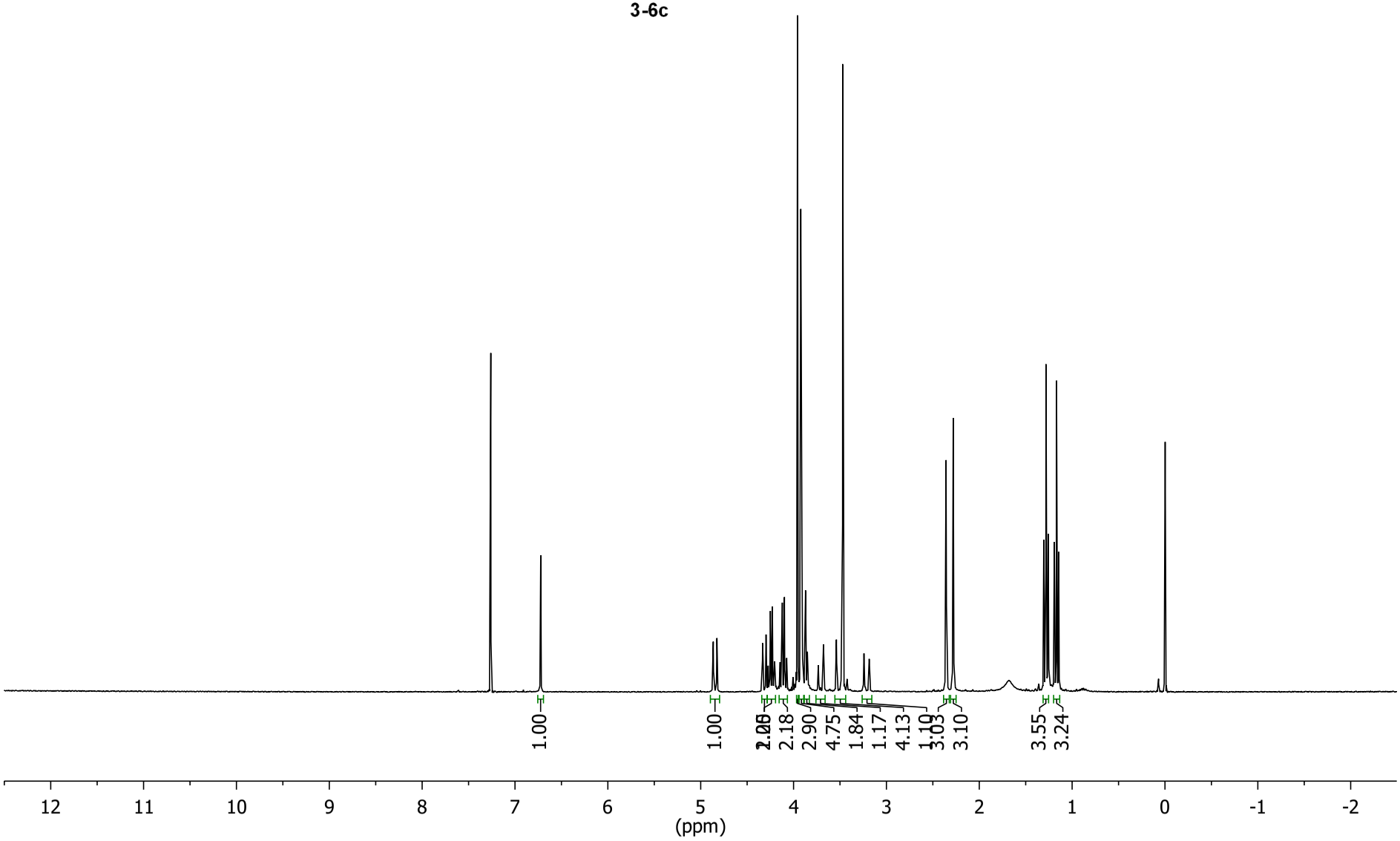
3-6a

1.00
3.23
0.97
1.00
6.97
1.05
1.04
1.10
1.06
2.97
3.11
3.82
3.26
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

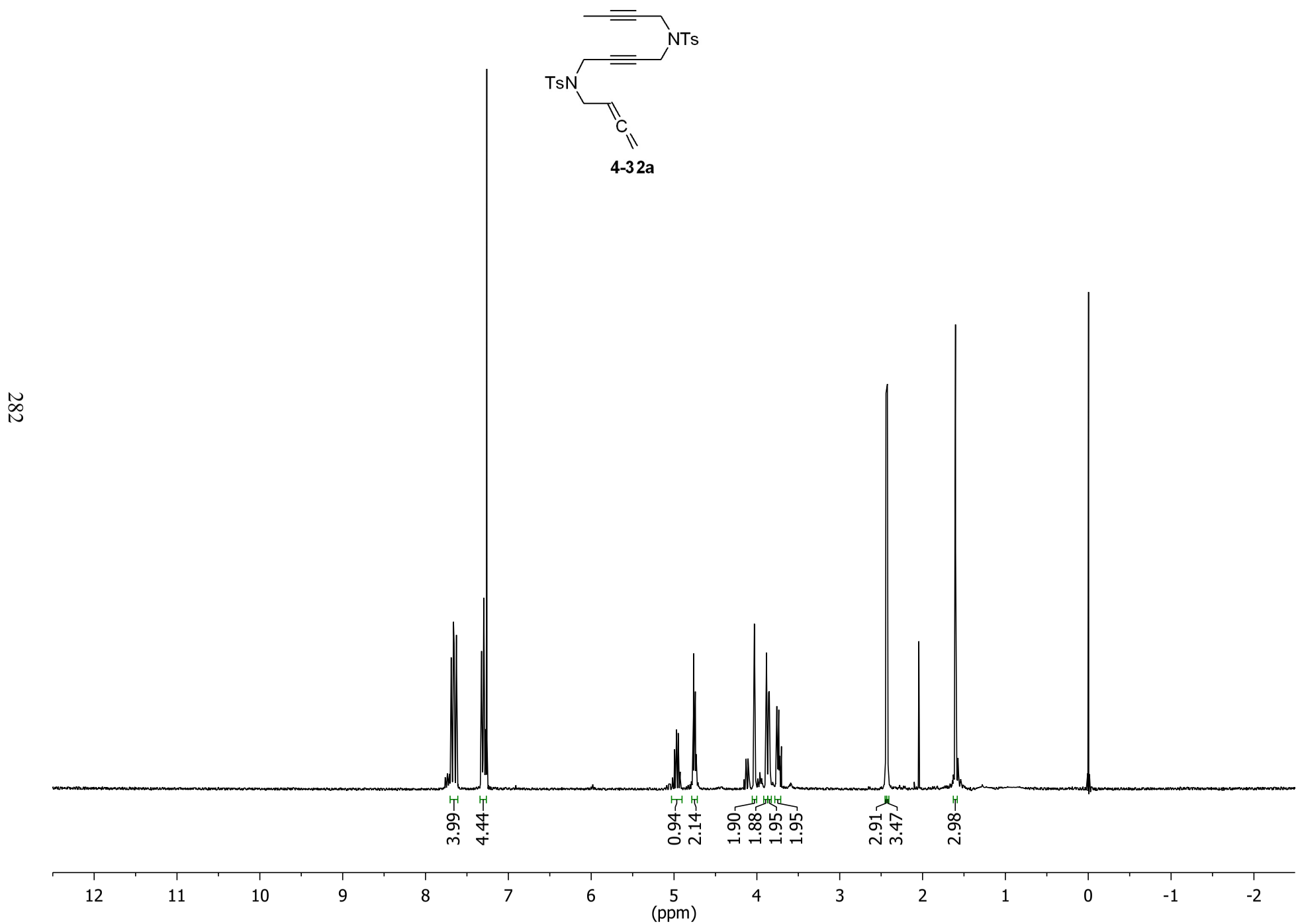
14.31
40.49
40.74
60.09
61.87
62.01
76.90
77.22
77.54
128.07
128.20
128.33
129.70
132.66
132.70
134.30
134.44
134.81
135.36
140.01
140.23
171.78
172.06
(ppm)
EtO2C
CO2Et
3-6a


MeO
MeO
MeO
O
EtO2C
CO2Et

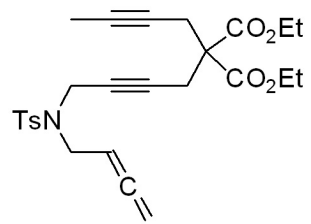
3-6c


1.00
1.00
2.18
2.90
4.75
1.84
1.17
4.13
3.10
3.55
3.24
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

14.245
15.664
17.151
40.585
40.941
56.301
59.807
60.998
61.673
61.757
63.161
67.555
76.911
77.230
77.549
108.434
125.843
131.139
131.481
132.141
132.354
133.378
136.588
139.456
142.537
150.832
153.230
172.216
172.254
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
MeO
MeO
EtO2C
CO2Et
3-6c


NTs
TsN
C
4-32a
3.99
4.44
0.94
2.14
1.90
1.88
1.95
1.95
2.91
3.47
2.98
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

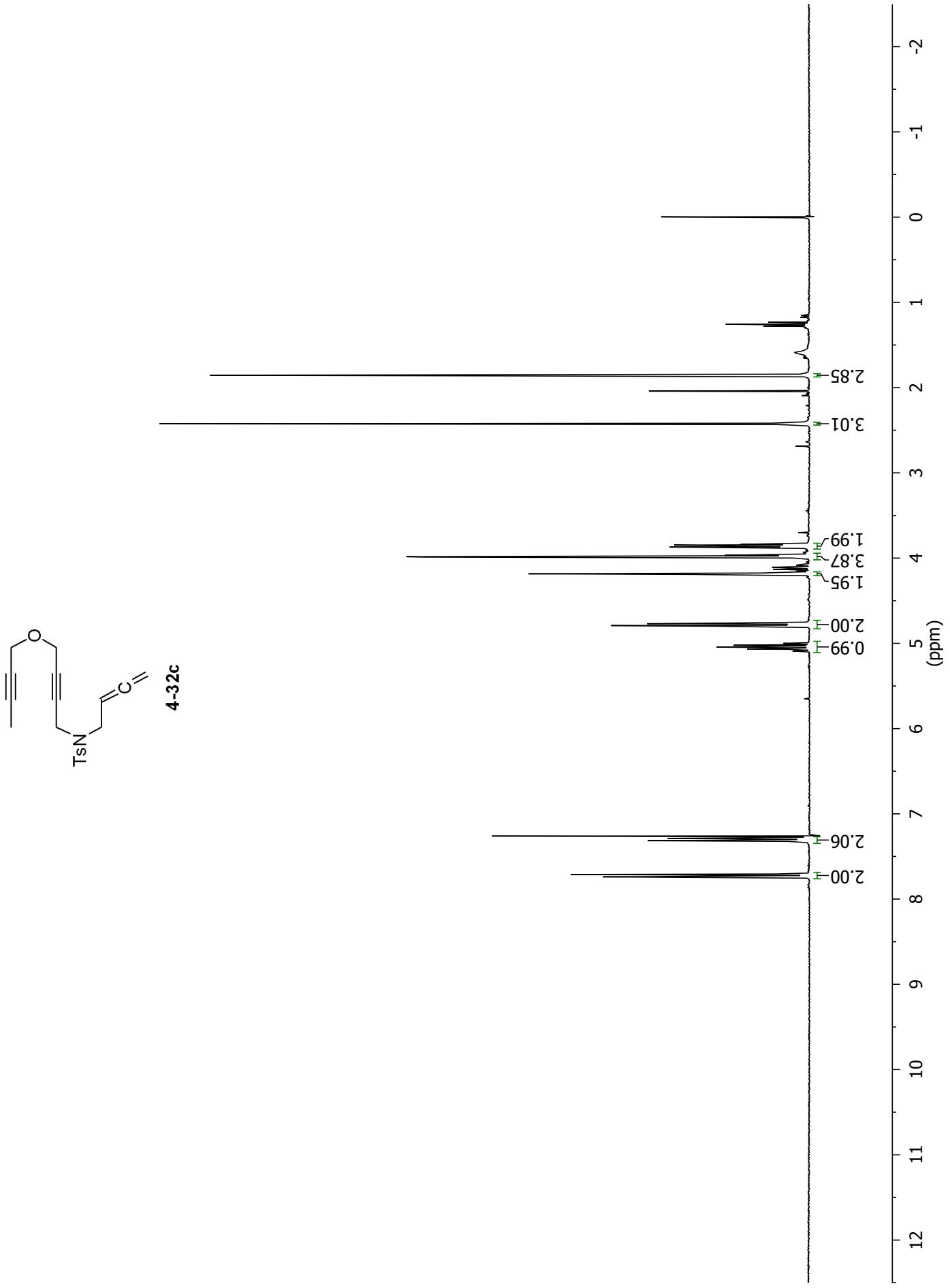
209.70
143.76
143.72
136.05
135.38
129.58
129.36
127.84
127.54
85.36
81.85
78.37
78.22
76.41
71.19
45.68
36.57
36.03
21.53
21.50
3.33
(ppm)
NTs
TsN
C
4-32a


CO2Et
CO2Et
TsN

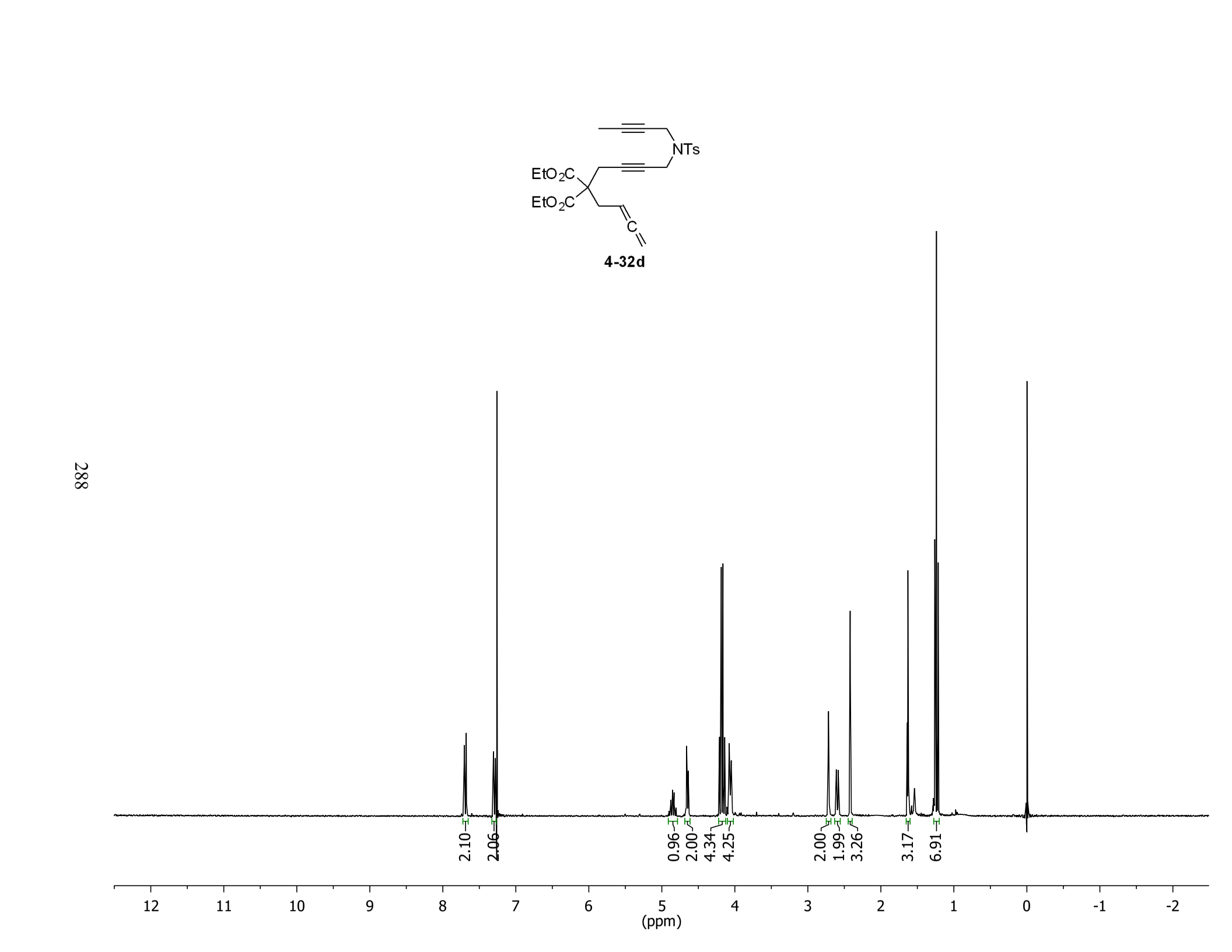
4-32b

2.00
1.99
0.92
1.92
6.18
2.01
1.85
1.84
2.99
3.45
6.11
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

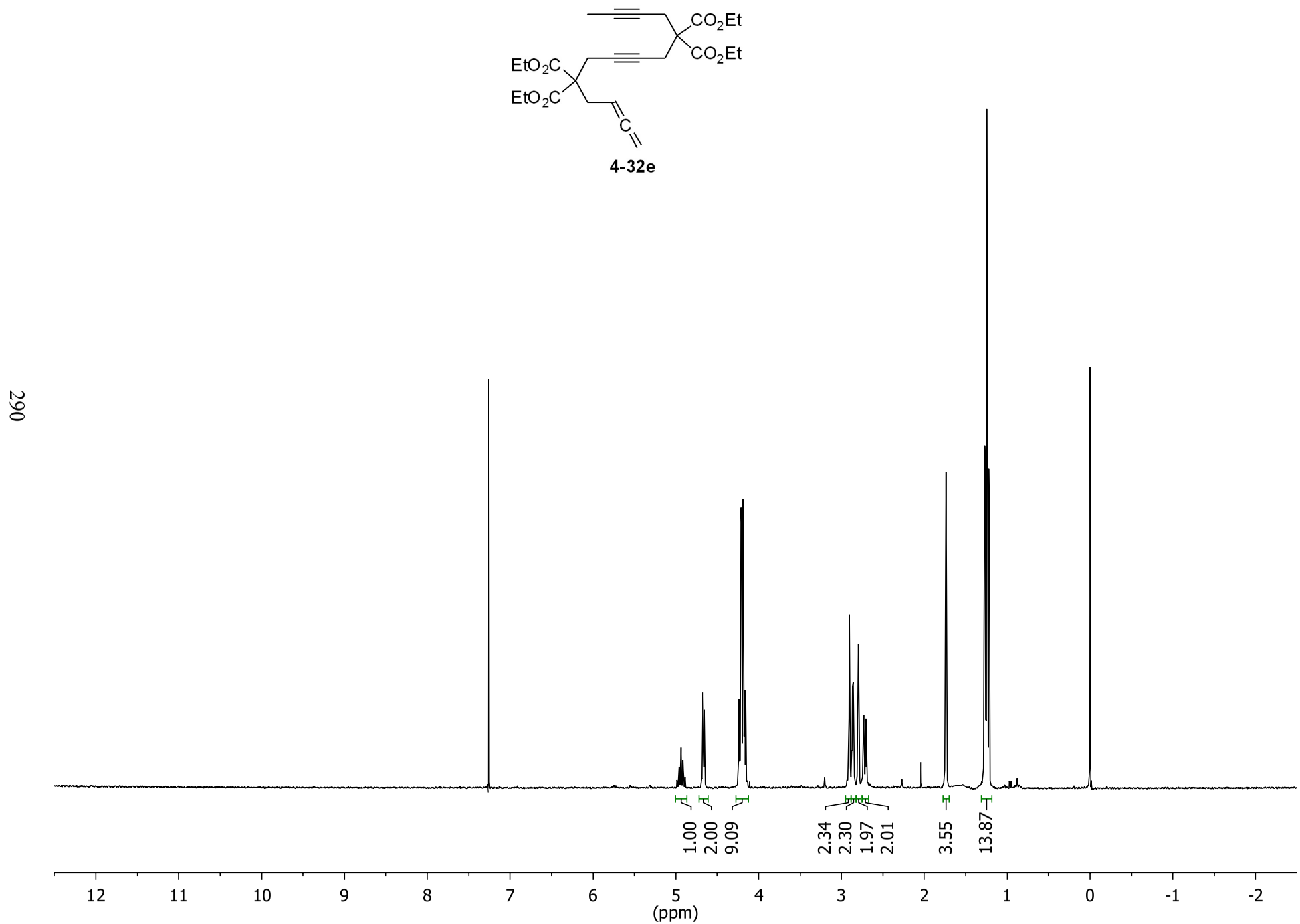
209.90
169.06
143.66
136.59
129.85
129.75
127.75
85.72
80.58
79.09
77.55
77.23
76.91
76.59
76.08
73.24
62.00
56.68
45.57
36.41
23.06
22.88
21.76
14.23
3.69
(ppm)
CO2Et
CO2Et
TsN
4-32b

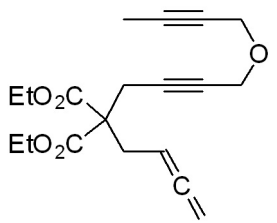

O
TsN
4-32c
2.85
3.01
1.99
3.87
1.95
2.00
0.99
2.06
2.00
(ppm)

210.00
143.76
136.40
129.73
129.68
127.94
127.87
85.67
83.28
81.17
79.59
76.66
74.42
57.16
56.48
45.99
36.45
21.76
21.69
3.82
(ppm)
TsN
O
4-32c


NTs
EtO2C
EtO2C
4-32d
288
2.10
2.06
0.96
2.00
4.34
4.25
2.00
1.99
3.26
3.17
6.91
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

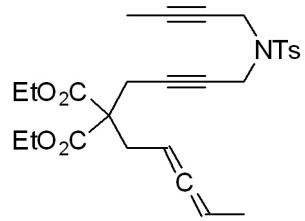
210.25
169.73
143.76
135.75
129.59
128.11
84.05
81.89
80.70
77.55
77.23
76.91
76.06
74.92
71.65
61.88
57.19
36.74
36.68
31.82
23.04
21.73
14.24
3.57
(ppm)
NTs
EtO2C
EtO2C
4-32d


CO2Et
CO2Et
EtO2C
EtO2C
C
4-32e
290
1.00
2.00
9.09
2.34
2.30
1.97
2.01
3.55
13.87
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

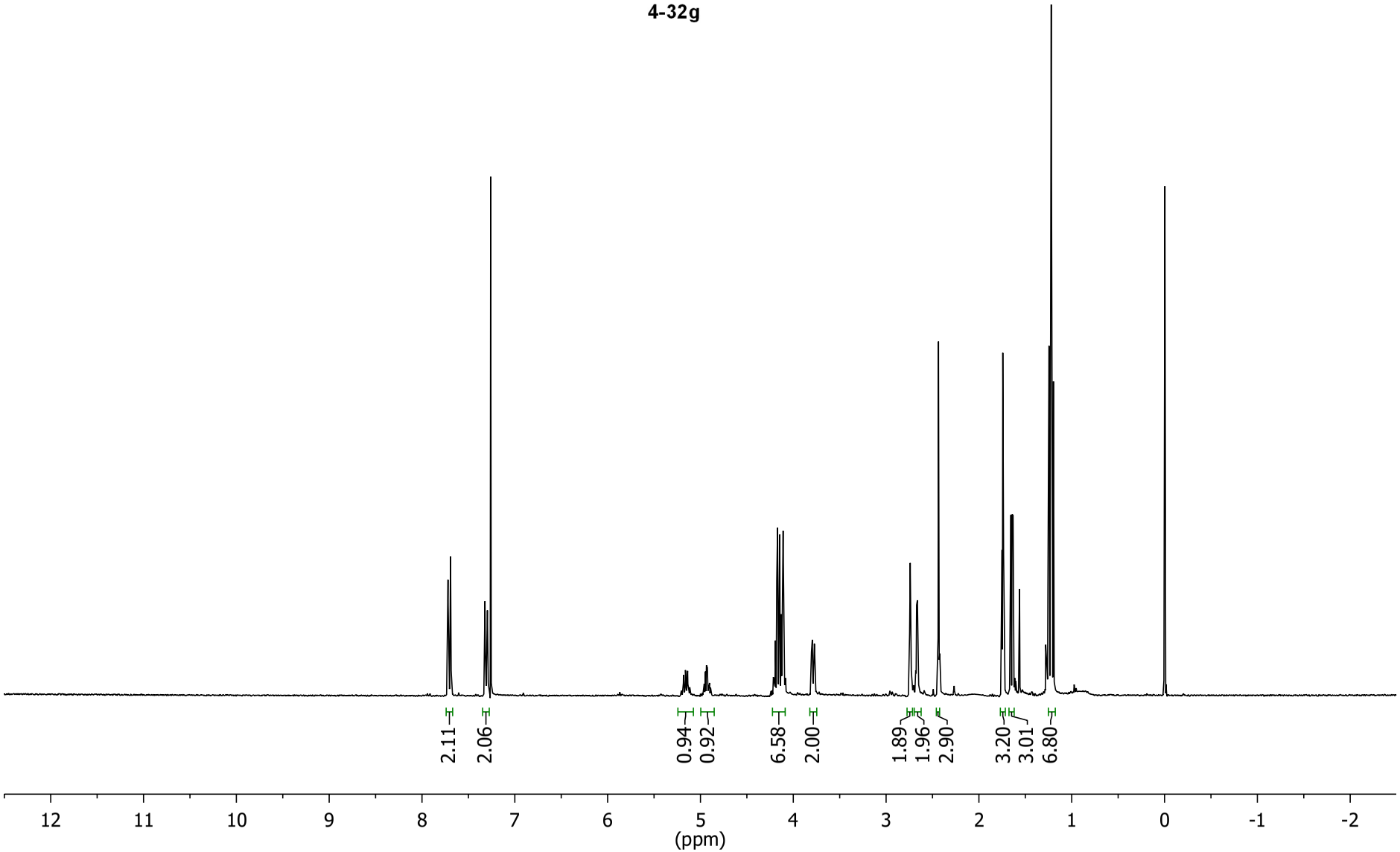


4-32f

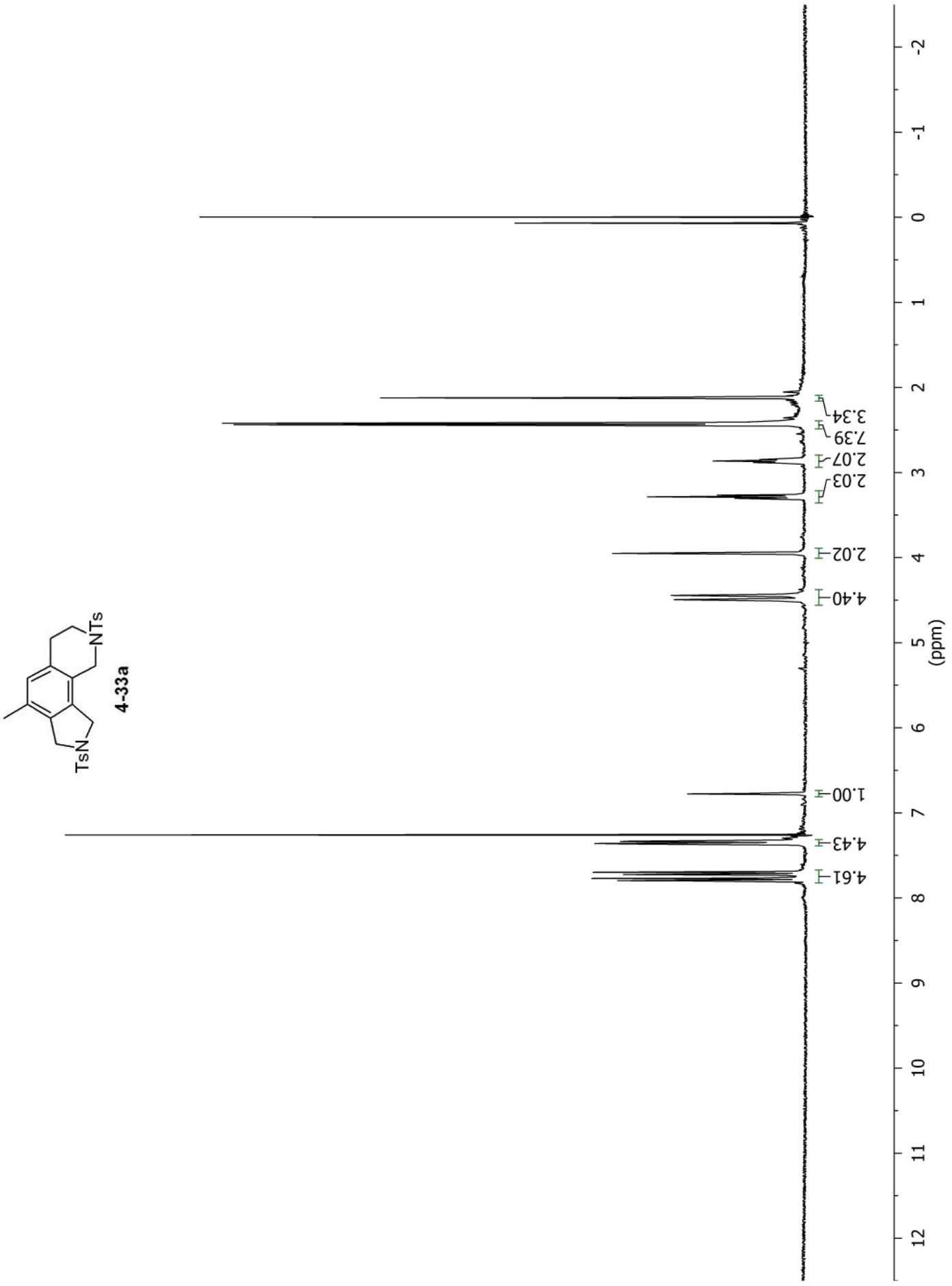
210.34
169.86
84.07
83.12
81.80
78.72
77.54
76.90
74.93
74.59
62.29
61.88
57.31
56.98
56.81
32.20
31.91
23.52
23.18
14.24
3.78
EtO2C
EtO2C
4-32f
(ppm)


NTs
EtO2C
EtO2C
C

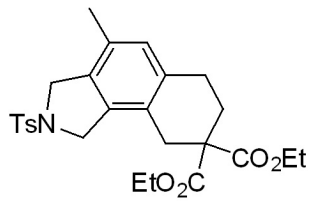
4-32g


2.11
2.06
0.94
0.92
6.58
2.00
1.89
1.96
2.90
3.20
3.01
6.80
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

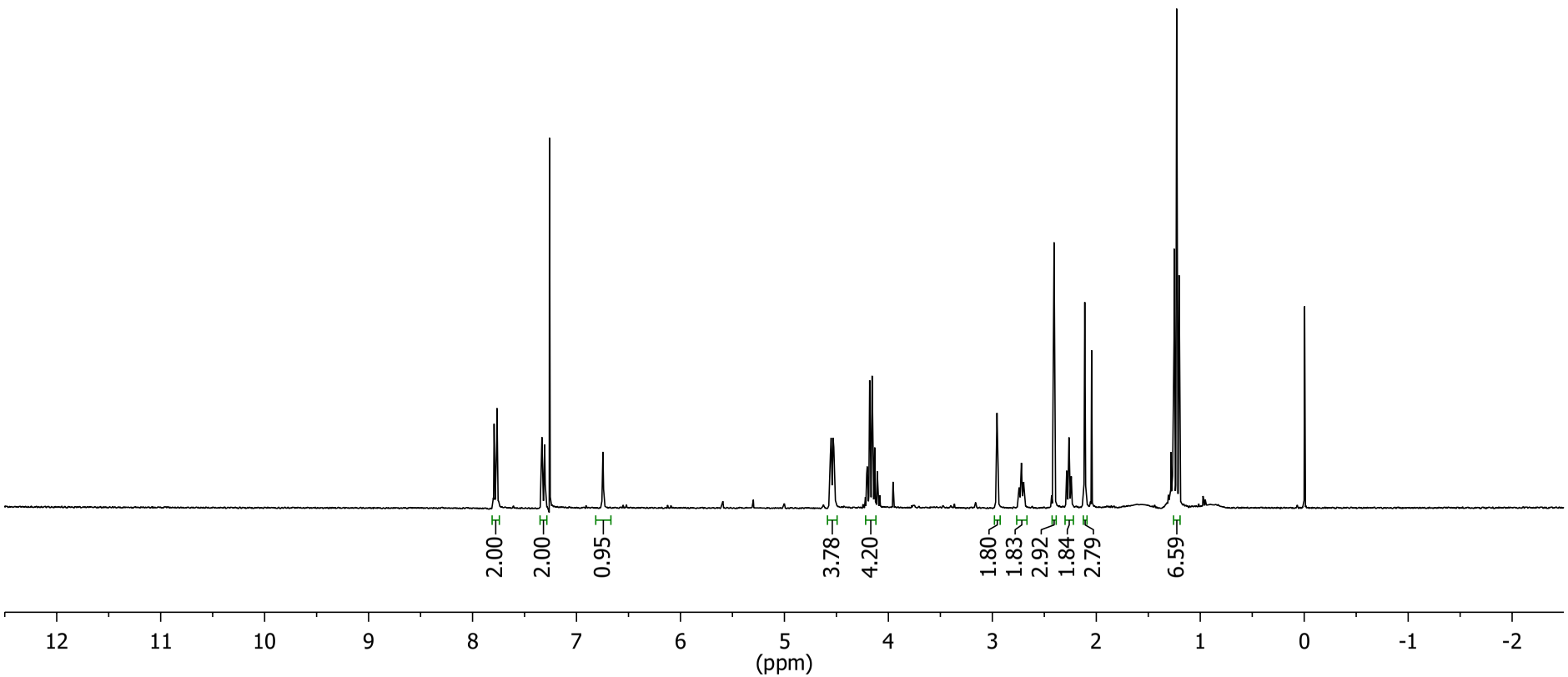
206.65
169.06
143.57
136.73
129.75
127.78
80.43
79.05
77.54
77.22
76.90
76.16
73.27
61.98
56.71
46.06
36.21
23.02
22.89
14.24
14.19
3.69
NTs
EtO2C
EtO2C
4-32g
(ppm)


NTs
TsN
4-33a
4.40
2.02
2.03
2.07
7.39
3.34
1.00
4.43
4.61
(ppm)

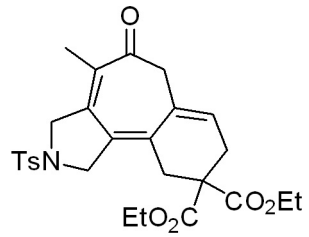
144.13
144.05
133.11
132.86
131.08
130.17
130.06
129.37
127.94
127.78
124.01
77.55
77.23
76.91
53.13
52.66
45.32
43.73
29.01
21.75
18.49
NTs
TsN
4-33a
(ppm)


TsN
CO2Et
EtO2C

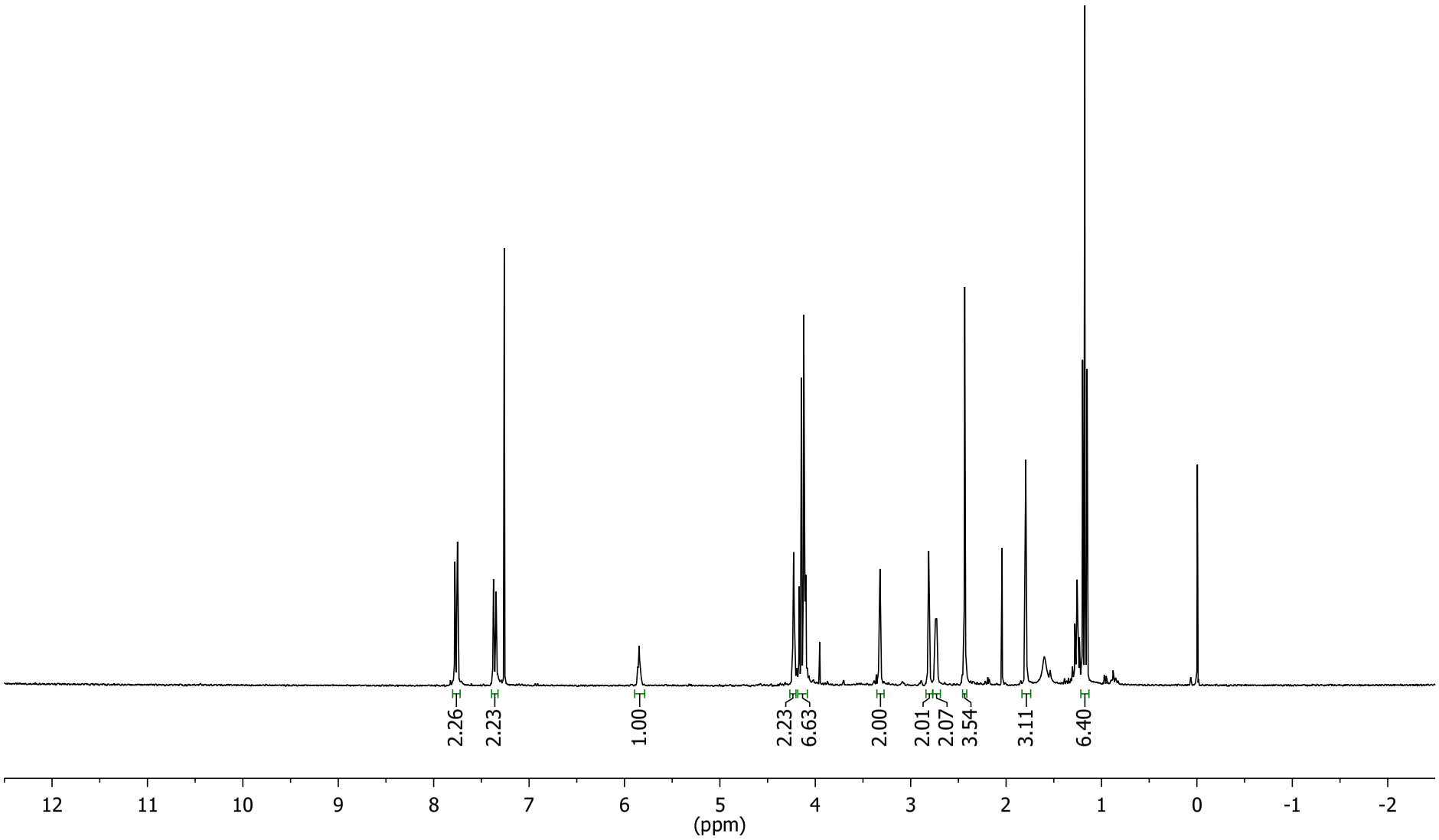
4-33d


2.00
2.00
0.95
3.78
4.20
1.80
1.83
2.92
1.84
2.79
6.59
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

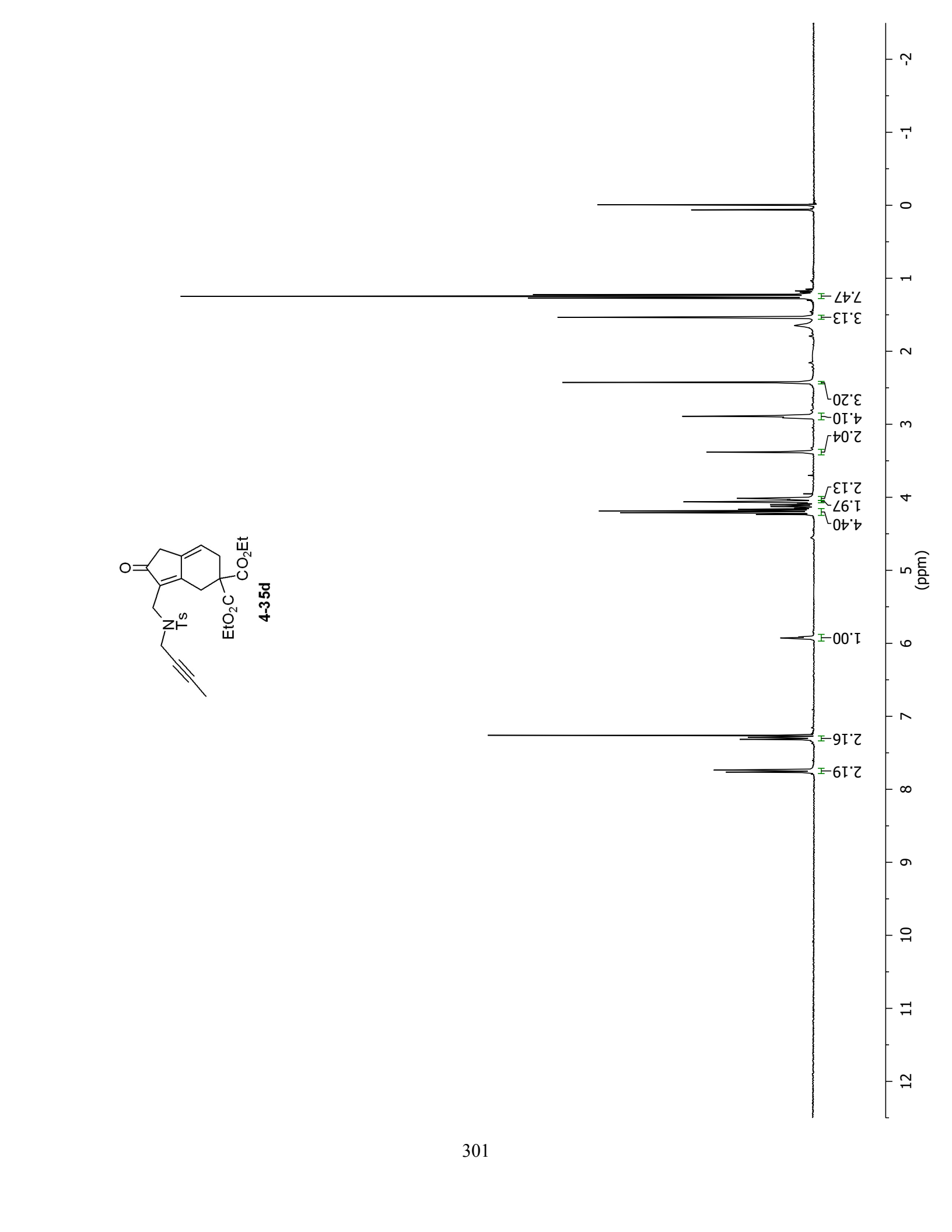
171.30
143.80
134.68
134.60
132.98
130.18
130.01
129.28
127.80
125.98
61.81
53.52
31.75
28.04
25.80
14.22
(ppm)
TsN
CO2Et
EtO2C
4-33d


O
TsN
EtO2C
CO2Et

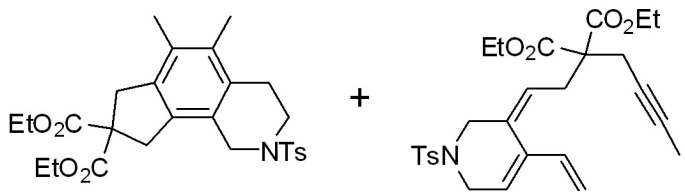
4-34d


2.26
2.23
1.00
2.23
6.63
2.00
2.01
2.07
3.54
3.11
6.40
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)

194.39
170.28
144.36
143.49
133.12
133.02
132.74
131.02
130.11
129.93
129.90
128.16
77.55
77.23
76.91
62.15
54.93
54.15
53.86
49.92
34.60
32.15
21.77
15.63
14.19
(ppm)
TsN
O
EtO2C
CO2Et
4-34d


O
N
Ts
EtO2C
CO2Et
4-35d
7.47
3.13
3.20
4.10
2.04
2.13
1.97
4.40
1.00
2.16
2.19
(ppm)

O
CO2Et
EtO2C
N
Ts
4-35d
203.59
170.43
164.54
143.60
135.69
134.98
134.55
129.49
128.25
122.55
82.16
77.52
77.21
76.89
72.09
62.15
54.34
39.77
38.35
38.07
31.10
30.47
21.70
14.17
3.51
(ppm)


EtO2C
EtO2C
NTs
+
CO2Et
EtO2C
TsN

1.00
1.09
1.08
1.10
1.03
1.17
2.11
2.26
1.05
1.14
1.13
1.30
2.44
1.57
0.73
1.50
3.67
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
(ppm)