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Los Angeles

Transition Metal-Mediated Synthesis and Functionalization of Macrocycles

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Philosophy

in Chemistry

by

Sedef Karabiyikoglu

2015

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2015

ABSTRACT OF THE DISSERTATION

Transition Metal-Mediated Synthesis and Functionalization of Macrocycles

by

Sedef Karabiyikoglu

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2015

Professor Craig A. Merlic, Chair

Transition metal-mediated synthesis and functionalization of macrocycles were investigated. A novel synthetic strategy was discovered to build macrocyclic enynes; *vic*-dibromo tetrasubstituted alkenes were utilized as highly effective protected alkyne groups in selective ene-ene ring closing metathesis reactions of (*E*)-dibromotrienes. Macrocyclic enynes with varied sizes and functionality were synthesized in excellent yields by facile Zn-promoted deprotection of (*E*)-dibromodiene rings. The new strategy circumvented high catalyst loadings and reaction condition restrictions; thus, was proven superior to traditional alkyne protection methods employing dicobalt octacarbonyl complexations. Cyclic enynes were obtained in a more step-economic and efficient manner compared to classical S_N2 ring closing processes. The reactivity and utility of enyne rings were showcased by platinum(II)-catalyzed transannular cyclopropanations.

The first dicobalt hexacarbonyl-promoted transannular [4+2] cycloaddition reactions were demonstrated. Optimized cycloadditions for macrocyclic dicobalt-dienyne complexes afforded target tricyclic scaffolds in a more effective manner than thermal transannular Diels-Alder reactions of metal-free dienyne rings. Further, dicobalt hexacarbonyl complexes of unactivated dienophiles underwent intermolecular room temperature-[4+2] cycloadditions with unactivated dienes leading to products that are inaccessible by thermal Diels-Alder reactions. Cycloaddition reactions of complexes were highly selective; [4+2] reaction adducts were obtained stereospecifically and competing Pauson-Khand reactions were not detected.

Functionalizations of enyne macrocycles through intermolecular and transannular reactions of their corresponding dicobalt complexes were studied. Novel complex polycycles were prepared by intramolecular and intermolecular [2+2+2], [2+2+1+1], [2+2+1] cycloadditions. The chemoselectivity of dicobalt-promoted cycloadditions was altered by varying the promoter and solvents utilized. The first transannular Pauson-Khand reaction was discovered. The novel synthetic method was optimized and structural requirements for reaction substrates were investigated.

This dissertation of Sedef Karabiyikoglu is approved.

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ABBREVIATIONS

o	Degree
*	Star
~	Approximately
α	Alpha
β	Beta
μ	Micro
π	Pi
σ	Sigma
acac	Acetylacetonate
Ac	Acetyl
AIBN	Azobisisobutyronitrile
ATR	Attenuated total reflection
aq	Aqueous
Ar	Any aryl
atm	Atmosphere
b	Broadened
BHT	2,6-Di- <i>tert</i> -butyl-4-methylphenol
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
Bu	Butyl
C	Celsius
CAN	Cerium ammonium nitrate
cm ⁻¹	Reciprocal centimeters
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet

DA	Diels-Alder
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylamino pyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,3-Bis(diphenylphosphino)ferrocene
<i>dr</i>	Diastereomeric excess
<i>E</i>	Entgegen
<i>ee</i>	Enantiomeric excess
equiv	Equivalents
Et ₂ O	Diethyl Ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
FT	Fourier Transform
g	Gram
<i>Gem</i>	Geminal
Grubbs I	Grubbs' first generation catalyst
Grubbs II	Grubbs' second generation catalyst
Grubbs III	Hoveyda-Grubbs' second generation catalyst
h	Hour
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectroscopy

hν	Light
Hz	Hertz
kcal	Kilocalorie
<i>i</i>	Iso
IR	Infrared
L	Ligand
LAH	Lithium aluminum hydride
m	Milli
<i>m</i>	meta
M	Molar
Me	Methyl
MeOH	Methanol
MHz	Megahertz
mol	Mole
mmol	Millimole
MPM	4-Methoxybenzyl
Ms	Mesyl
M.S.	Molecular sieves
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
NMR	Nuclear magnetic resonance
<i>o</i>	Ortho
p	Pentet
<i>p</i>	Para
Pa	Pascal
Ph	Phenyl
pin	Pinacol
Piv	Pivaloyl

PK	Pauson-Khand
ppm	Parts per million
PPTS	Pyridinium para-toluenesulfonate
Pr	Propyl
q	Quartet
R	Any alkyl group
<i>R</i>	Rectus
RCM	Ring closing metathesis
rt	Room temperature
s	Singlet
<i>S</i>	Sinister
sext	Sextet
t	Triplet
TADA	Transannular Diels-Alder
TAPK	Transannular Pauson-Khand
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
Tf	Triflate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMTU	1,1,3,3-Tetramethylthiourea
Troc	2,2,2-Trichloroethyl
Ts	Tosyl
UV	Ultraviolet

<i>Vic</i>	Vicinal
Vis	Visible
W	Watt
Z	Zusammen

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PUBLICATIONS AND PRESENTATIONS

Karabiyikoglu, S.; Merlic, C. A. “*tert*-Butyldimethylsilanol” *e-EROS Encyclopedia of Reagents for Organic Synthesis* **2014**.

Merlic, C. A.; Karabiyikoglu, S. “Intermolecular and Transannular Cyclization Reactions of Macrocyclic Dicobalt Hexacarbonyl-Alkyne Complexes,” *248th National Meeting of American Chemical Society*, San Francisco, CA, USA; August **2014**.

Karabiyikoglu, S.; Kelgokmen, Y.; Zora, M. “Facile Synthesis of Iodopyridines from *N*-Propargylic β -Enaminones via Iodine-mediated Electrophilic Cyclization,” *Tetrahedron* **2015**, *71*, 4324.

Karabiyikoglu, S.; Merlic, C. A. “Transannular [4 + 2] Cycloaddition Reactions of Cobalt-Complexed Macrocyclic Dienynes,” *Organic Letters* **2015**, *17*, 4086.

He, C.; Chen, T.; Patel, A.; Karabiyikoglu, S.; Merlic, C. A.; Houk, K. “Distortion, Tether, and Entropy Effects on Transannular Diels–Alder Cycloaddition Reactions of 10 to 18-Membered Rings,” *Journal of the American Chemical Society* **2015** (Submitted Manuscript).

Karabiyikoglu, S.; Iafe, R. G.; Merlic, C. A. “Ring Closing Metathesis with Vicinal Dibromoalkenes as Protected Alkynes: A Synthetic Approach to Macrocyclic Enynes,” *Organic Letters* **2015** (Submitted Manuscript).

Karabiyikoglu, S.; Merlic, C. A. “Intermolecular and Transannular Cyclization Reactions of Macrocyclic Dicobalt Hexacarbonyl-Alkyne Complexes,” (Manuscript in Preparation).

Chapter 1

Metal-Mediated Transannular Reactions: A Review

1.1. Introduction

A wide range of natural products and/or biologically active molecules exist as polycyclic structures, so generating efficient synthetic plans to access these complex scaffolds is particularly important.^{1,2} There are three main topological approaches for the preparation of polycyclic molecules; I) intermolecular cycloadditions with at least one cyclic reaction partner, II) intramolecular reactions in which a side chain reacts with another functionality located on the ring or another active side chain tethered on the ring and III) transannular reactions (Figure 1.1).¹ In a *transannular* (etymology: latin prefix *trans* – across or through, latin root *anno* – year or circle of the sun or latin *annular* – adjectival form of latin *annulus* – little ring) reaction a polycyclic molecule is constructed by an intramolecular bond formation in an existing cyclic structure.³

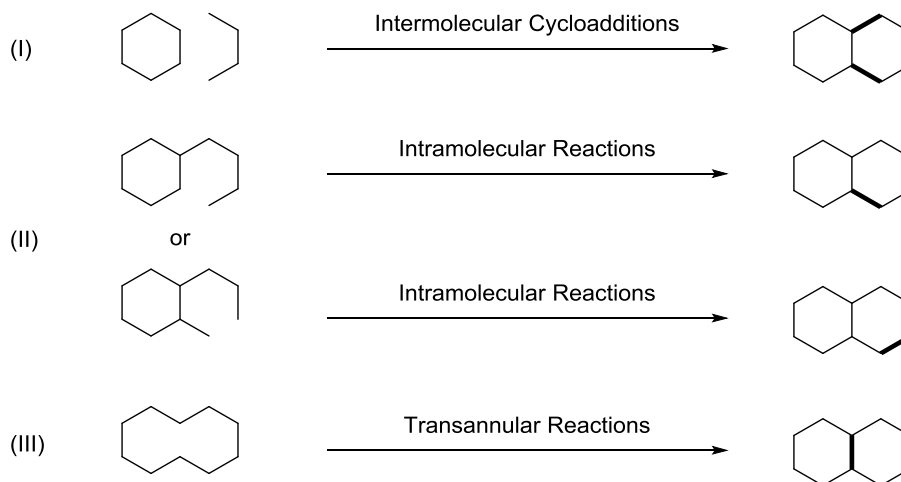


Figure 1.1. Topological classification of synthetic approaches for the preparation of polycyclic molecules

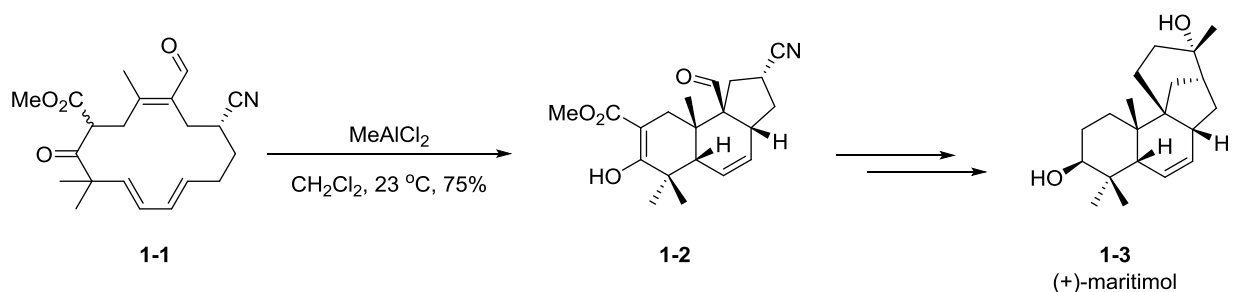
Due to challenges in the preparation of macrocyclic substrates, transannular transformations are underdeveloped compared to other polycycle synthesis methods (Figure 1.1). However, recent studies established that transannular reactions are highly efficient and reliable synthetic tools to access complex structures.^{1,4} This is especially true in asymmetric synthesis of polycycles containing multiple chiral centers where transannular reactions can provide high stereochemical control stemming from the conformational constraints imparted by locating the functional units of macrocyclic substrates in close proximity.^{1,5} Moreover, transannulations are highly step and atom economical strategies as conversions of monocyclic structures to fused polycyclic systems are achieved in a single step.⁶

Over the years researchers employed many well-established reactions in a transannular fashion and thrived preparing natural products, pharmaceuticals, and other interesting compounds through simple protocols. The range of transannular reactions investigated include aldol condensations,⁷ radical cyclizations,⁸ Michael reactions⁹ to 1,3-dipolar cycloadditions.¹⁰ The main goal of transannular syntheses is to solve more than one synthetic problem in less than one or two operations while maintaining high overall yields. This can only be achieved with a transannular synthetic plan exhibiting high stereo- and regiochemical control. In this sense, when faced with obstacles in the course of such synthetic protocols, chemists have utilized metals - mainly transition metals- to increase the potency and stereoselectivity of reactions. This review chapter aims to present those transannular reactions that employed metals. For simplicity, acid/base-promoted transannular reactions in which alkali metal cations Li^+ , Na^+ and K^+ stabilize the anionic intermediates, were excluded.

1.2. Metal-Mediated Transannular Cycloaddition Reactions

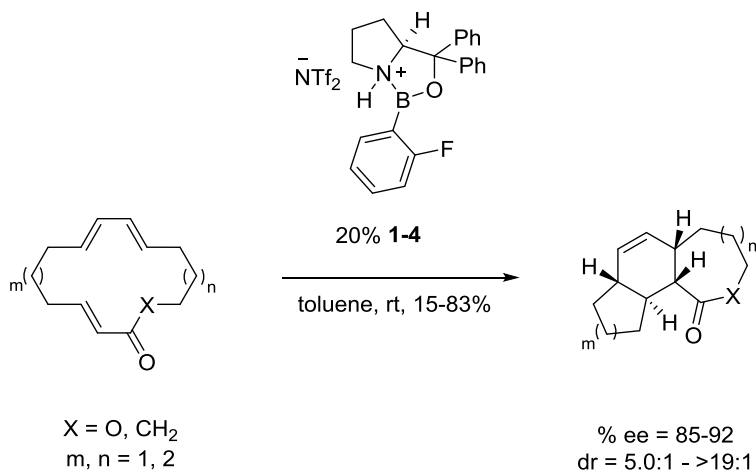
A number of different transannular cycloadditions leading to complex fused ring structures have been demonstrated. Although there is great potential for cycloadditions like 1,3-dipolar and [2+2] reactions to appear in effective transannular processes, the literature reports only a small number of examples.^{10,11} On the other hand, the great majority of transannular reactions described in the literature are [4+2] cycloadditions, i.e. transannular Diels-Alder (TADA) reactions.¹ The all-encompassing efficiency of Diels-Alder reactions,¹² in terms of scope, atom economy and versatility, is exhibited in most applications of transannular transformations.^{1,13} While proximity-induced^{6,14} and thermal¹⁵ TADA reactions are well studied, reports on metal-mediated versions of the reaction are rare. In fact, the first transition metal-promoted transannular [4+2] cycloaddition reaction was explored by the Merlic research group and this reaction is discussed in detail in the following chapters. In other examples of metal-mediated TADA reactions metalloids were utilized as Lewis acids to lower the activation barriers and/or modulate the stereoselectivity of reactions.

Asymmetric synthesis of the diterpenoid (+)-maritimidol,¹⁶ (**1-3**), used in Carribean folk medicine for the treatment of venereal diseases, was studied by the Deslonchamps research group. For this investigation a series of macrocyclic systems were prepared and in order to improve reaction stereoselectivity, Lewis acids such as MeAlCl₂, Me₂AlCl and SnCl₄ were tested. The Lewis acid catalysts increased the TADA reactivity at low temperatures and in turn provided higher stereocontrol.¹⁷ After optimization, the macrocyclic triene **1-1** underwent Lewis acid catalyzed *endo*-diastereoselective TADA reaction affording the (+)-*maritimidol* precursor tricyclic **1-2** in 75% yield as a single diastereoisomer (Scheme 1.1).¹⁸



Scheme 1.1. Synthesis of (+)-maritimidol via a Lewis acid-catalyzed TADA reaction

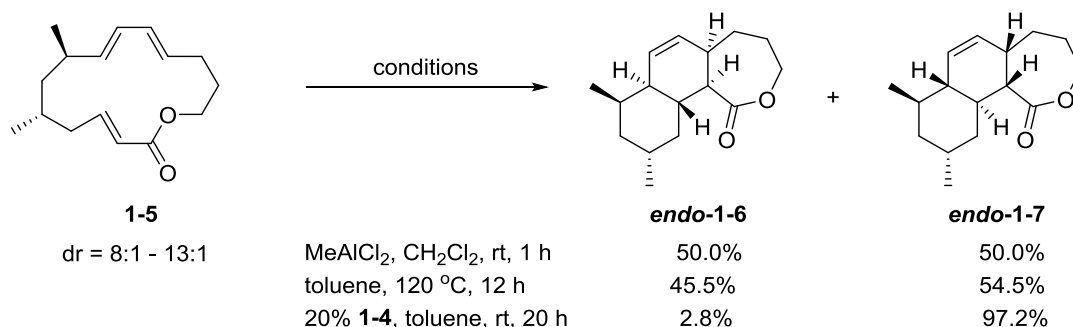
The Jacobsen group demonstrated the first enantioselective TADA reaction utilizing triflimide activated chiral oxazaborolidine Lewis acid **1-4** as the catalyst.¹⁹ This methodology provided a wide scope of tricyclic products in high enantiomeric excesses (Scheme 1.2).



Scheme 1.2. Chiral Lewis acid-catalyzed enantioselective TADA reactions

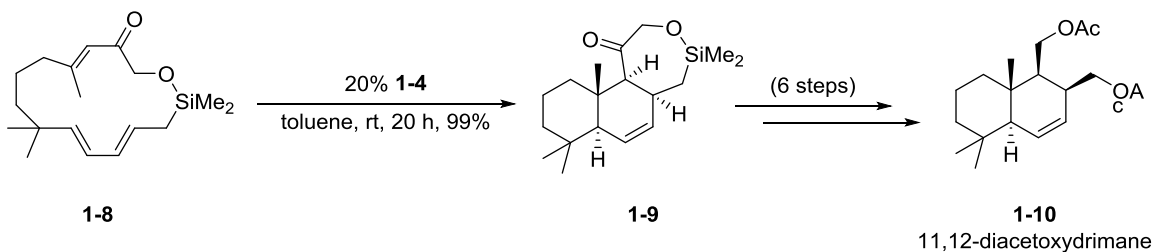
Impressively, it was possible with this method to adjust the stereochemical outcomes of similar TADA reactions of specific macrocycles and alter the inherent diastereoselectivity. This catalyst-controlled diastereoselectivity was illustrated by control reactions of unbiased macrocycle **1-5** (Scheme 1.3). While the achiral Lewis acid-catalyzed or thermal TADA

reactions of **1-5** proceeded with poor selectivity, chiral catalyst **1-4** dramatically favored formation of the *endo-1-6* diastereomer (Scheme 1.3).¹⁹



Scheme 1.3. Catalyst-controlled diastereoselectivity in TADA reactions of cyclic triene **1-5**

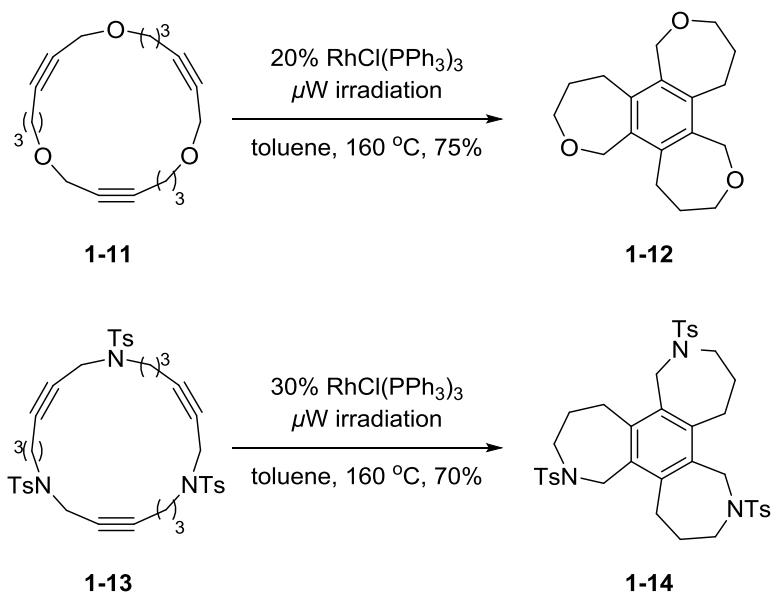
Jacobsen utilized this highly versatile enantioselective TADA reaction as the key step in the total synthesis of sesquiterpene 11,12-diacetoxydrimane (**1-10**).¹⁹ Macrocyclic lactone **1-8** with an all-*trans* triene arrangement, underwent *endo*-selective TADA reaction smoothly forming tricyclic compound **1-9** as a single diastereoisomer in quantitative yield. The synthesis of **1-10** was completed in 6 further steps (Scheme 1.4).¹⁹



Scheme 1.4. Synthesis of 11,12-diacetoxydrimane by the Jacobsen group

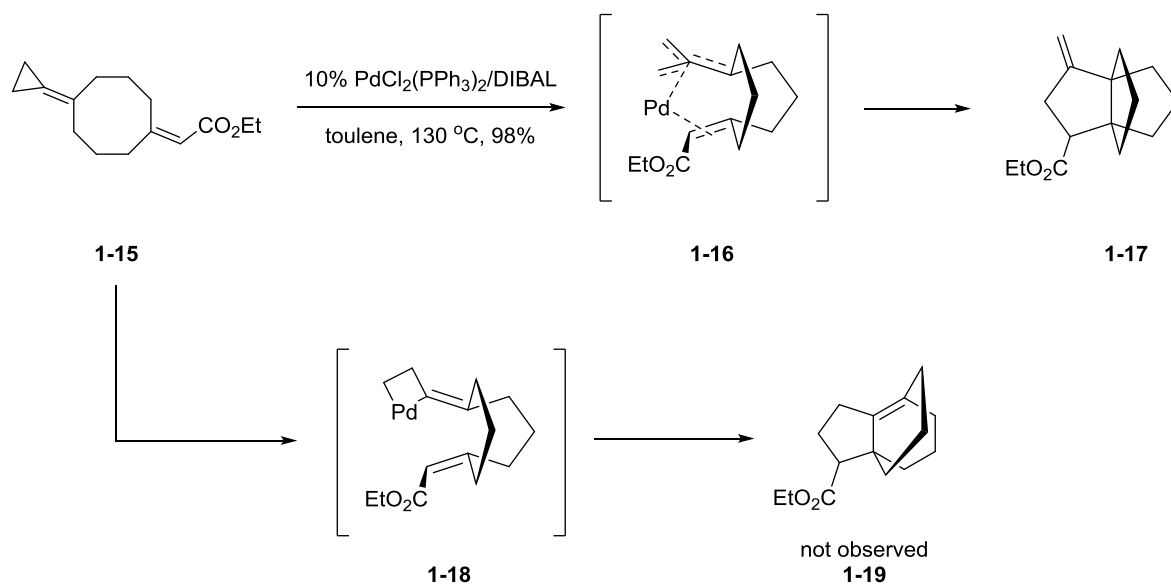
Martin and co-workers demonstrated an interesting metal-mediated transannular cycloaddition reaction.²⁰ *C*₃-symmetric tetracycles that were determined to be quite suitable for molecular recognition were prepared through transannular [2+2+2] cycloadditions. The reactions

were performed under microwave irradiation in the presence of Wilkinson's catalyst and benzocyclotrimers **1-12** and **1-14** were synthesized in 75% and 70% yield, from macrocyclic triynes **1-11** and **1-13**, respectively (Scheme 1.5).



Scheme 1.5. Rh-catalyzed transannular [2+2+2] cycloaddition reactions

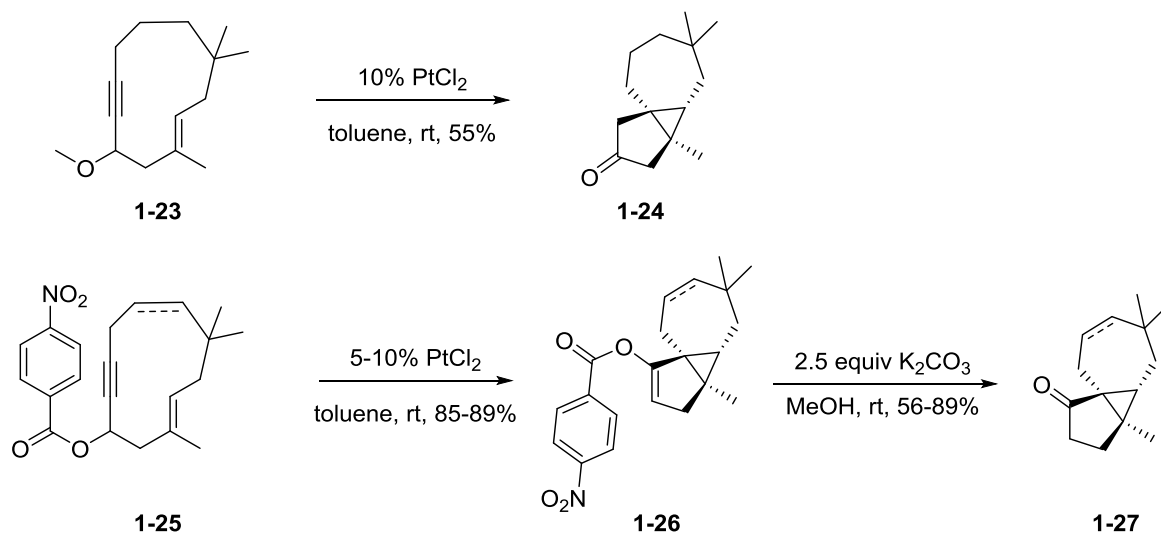
An impressive *exocyclic* transannular ring closure of olefinic methylenecyclopropanes (**1-15**) leading to [3.3.3]propellanes (**1-17**) was discovered by Nakamura and co-workers (Scheme 1.6).²¹ These transannular cycloadditions were unusually effective with the utilization of group 10 metal catalysts Ni(cod)₂, Ni(acac)₂ or PdCl₂(PPh₃)₂.²¹ The reaction mechanism involves cleavage of the sp³C-sp³C bond of the cyclopropane followed by formation of trimethylenemethane-like intermediate **1-16** which is stabilized by transannular interactions with the metal (Scheme 1.6). These transannular interactions led to a unique regioselectivity that was not observed in similar intermolecular reactions of methylenecyclopropane substrates since in the latter case cyclopropane sp³C-sp²C bond cleavage by the metal catalyst was preferred (Scheme 1.6).^{21,22}



Scheme 1.6. Synthesis of [3.3.3]propellanes through metal-catalyzed transannular cycloadditions

1.3. Metal-Mediated Transannular Cyclopropanations

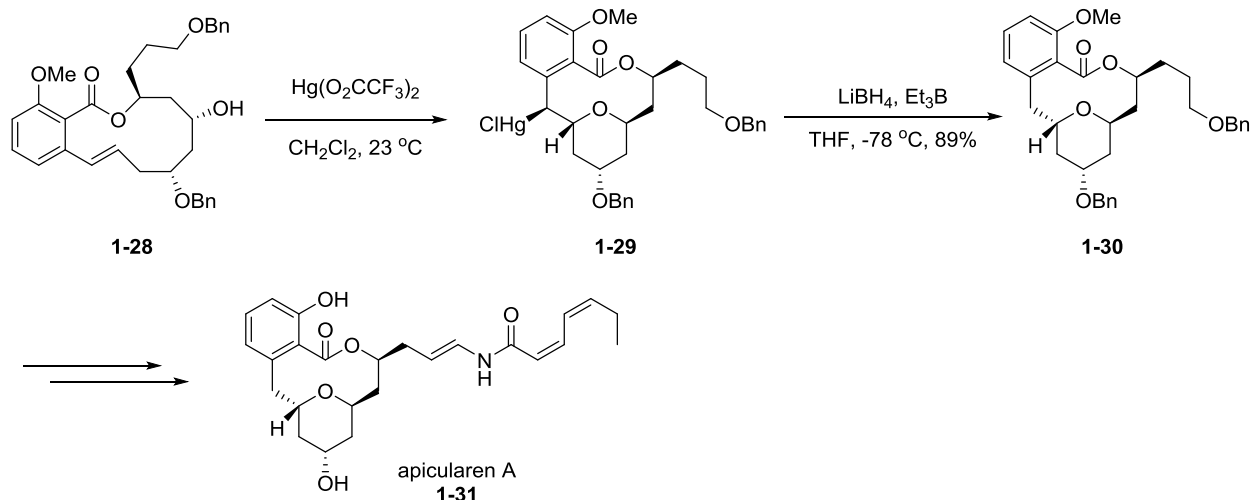
Over the years various metal-mediated cyclopropanation reactions have been explored²³ and there are a few examples of these reactions implemented in a transannular manner. The Sampson group investigated cyclopropanation of 11-membered macrocyclic lactones via transannular metal-stabilized carbene addition reactions.²⁴ A series of intramolecular and transannular model reactions employing palladium, rhodium and copper catalysts were tested. The results showed that while electron-deficient macrocycles failed to undergo any transannular reactions, macrocyclic α -diazo lactone **1-21** with an electron-rich methoxy-substituted alkene unit undergoes successful transannular cyclopropanation under Cu(acac)₂ catalysis affording the target cyclooctane product **1-22** in only modest yield (Scheme 1.7).



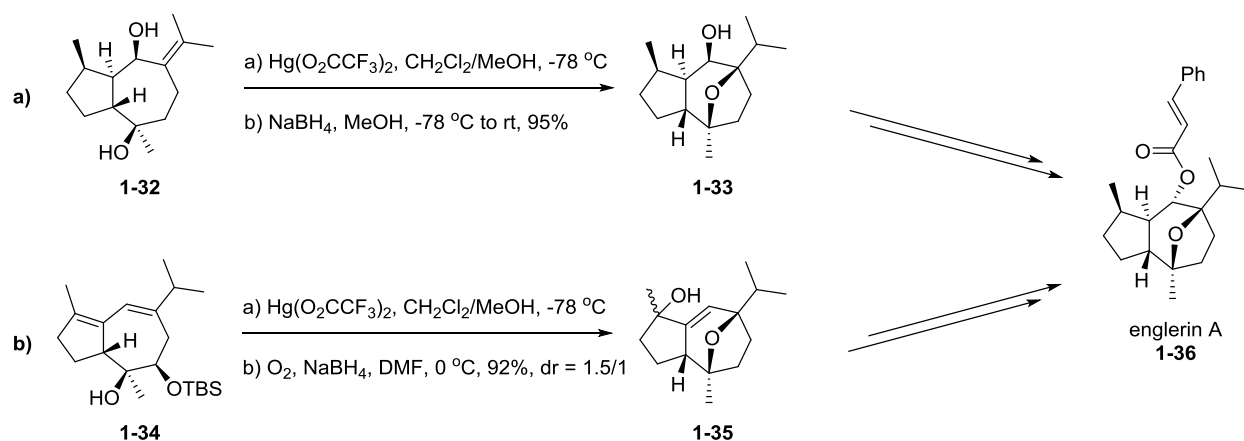
Scheme 1.8. Pt-catalyzed transannular cyclopropanations developed by Malacria and co-workers

1.4. Metal-Mediated Transannular Hydroalkoxylations

A total synthesis of apicularen A (**1-31**), a cytostatic antitumor agent, was developed by the Maier research group.²⁹ The key transformation in this synthesis was a highly stereo- and regioselective, mercuric trifluoroacetate-promoted transannular etherification of macrolactone **1-28** building the pyran ring of *apicularen A* (Scheme 1.9). Remarkably, the unwanted retrocyclization of intermediate **1-29** was suppressed by simply changing the solvent from CH_2Cl_2 to THF and performing the reduction with LiBH_4 in the presence of Et_3B . It should be noted that use of a metal promoter in the pyran formation step was crucial as the same transannular transformation failed completely when macrocycle **1-28** was treated with the common hydroalkoxylation reagent *N*-(phenylseleno)phthalimide.³⁰ Later, this transannular oxymercuration-demercuration methodology was successfully incorporated into the synthesis of the sesquiterpene englerin A (**1-36**) by the Maier³¹ and Parker³² research groups (Schemes 1.10a and 1.10b).



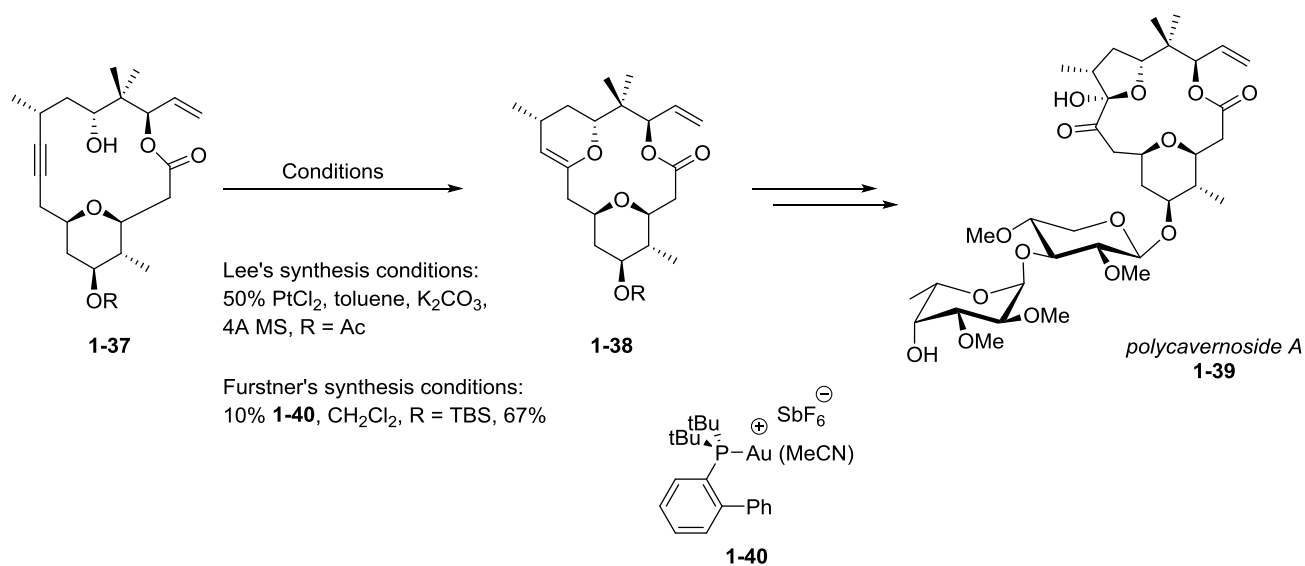
Scheme 1.9. Hg-mediated transannular hydroalkoxylation in apicularen A synthesis



Scheme 1.10. Hg-mediated transannular hydroalkoxylation in englerin A synthesis a) by the Maier group and b) by the Parker group

Over the years the Furstner group elegantly investigated carbophilic activations of alkynes with π -acidic metal catalysts and demonstrated elegant syntheses of a large library of natural products.^{4a} An important component of the research was dedicated to different applications of transannular hydroalkoxylation of alkynes under Pt or Au catalysis. Polycavernoside A (**1-39**) is a potent marine toxin that is the cause of fatal food poisonings resulting from ingestion of the red

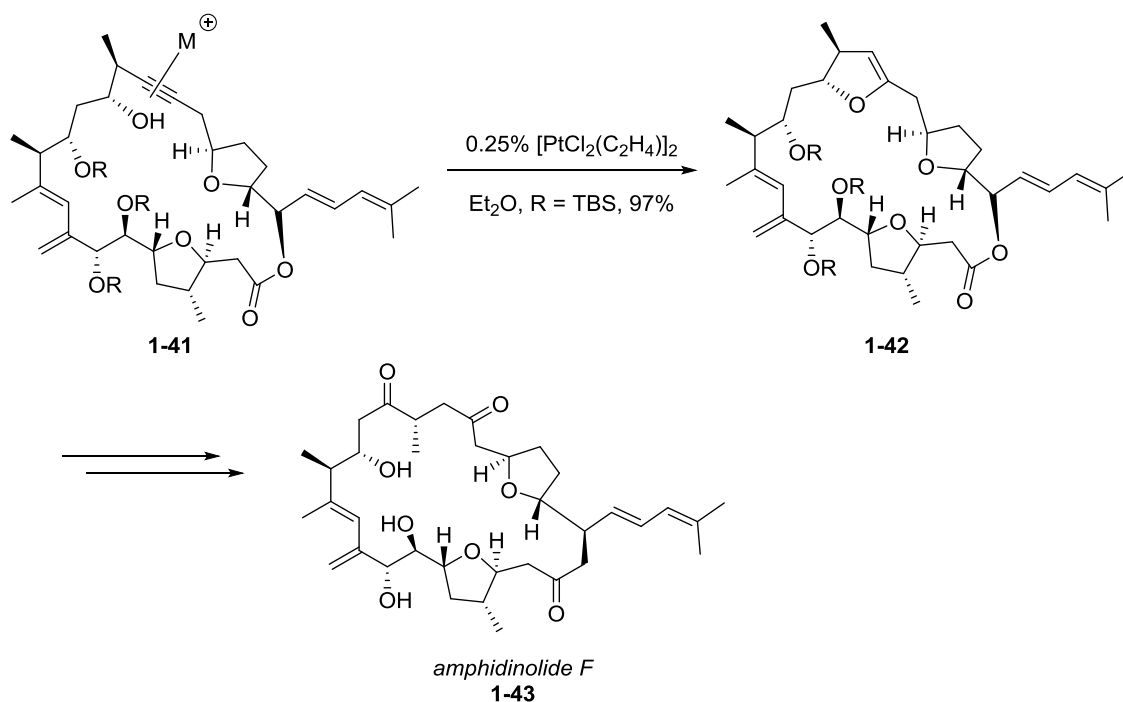
Alga *Gracilaria edulis* in the Philippines.³³ Previously a number of different syntheses of polycavernoside A were reported,³⁴ but only recently the Lee³⁵ and Furstner³⁶ groups used a transannular transformation as the basis for the synthesis and obtained the target through a relatively step-economic protocol. In Lee's synthesis an alkyne transannular hydroalkoxylation was performed with half-stoichiometric PtCl₂ under a CO atmosphere to provide the cyclic enol ether **1-38** (Scheme 1.11). The Furstner group preferred a bulky gold complex (**1-40**) to catalyze the transannular hydroalkoxylation of macrocyclic alkyne **1-37** (Scheme 1.11) and by doing so suppressed the undesired Overman-type [3,3] sigmatropic rearrangement of the allylic ester unit, which could have been easily catalyzed by Pt(II).³⁷



Scheme 1.11. Pt- and Au-catalyzed transannular hydroalkoxylation in polycavernoside A syntheses by the Lee and Furstner groups

A transannular hydroalkoxylation was also utilized in the synthesis of the marine natural product amphidinolide F (**1-43**) by Furstner and co-workers.³⁸ The key structural aspect in this synthesis was a trans alignment of the unprotected alcohol in macrocycle **1-41** with the alkyne

unit and the π -acidic metal coordinated to that alkyne unit in order to ensure a highly regioselective transannular 5-*endo* cyclization. As expected, **1-41** underwent a quantitative transannular addition forming macrocyclic enol ether **1-42** with just a trace amount of $[\text{PtCl}_2(\text{C}_2\text{H}_4)]_2$ (Scheme 1.12). Impressively, transannular nucleophile-alkyne-metal alignment prevented **1-41** from undergoing a competing 4-*exo*-dig pathway.

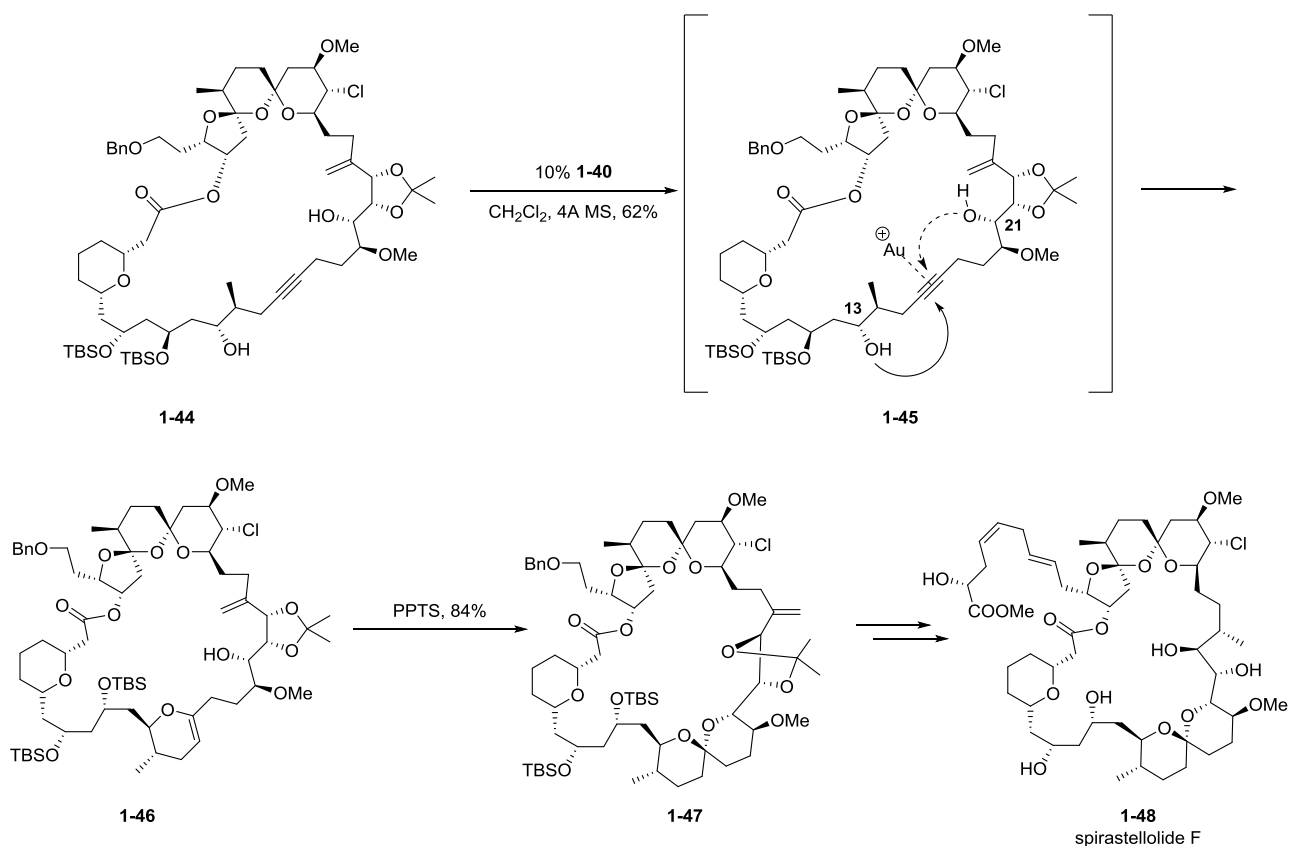


Scheme 1.12. Pt-catalyzed transannular hydroalkoxylation in a synthesis of amphidinolide

F

Spirastrellolide F (**1-48**) is a potent phosphatase inhibitor possessing a backbone with 21 stereogenic centers. The Furstner group completed a challenging synthesis of this complex molecule through a gold-catalyzed stepwise transannular spiroacetalization.³⁹ The key spiro-transformation starts with a transannular 6-*endo*-dig hydroalkoxylation catalyzed by **1-40** (Scheme 1.13). Smaller gold catalysts resulted the formation of the incorrect regioisomer via a 5-

exo-dig addition process. However, bulky complex **1-40** prevented transannular attack of the crowded hydroxyl group at C21, instead favoring formation of the desired regioisomer **1-46** through transannular attack of the hydroxyl group at C13. The required spiroketal **1-47** was formed as a single isomer via treatment of **1-46** with catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) (Scheme 1.13).

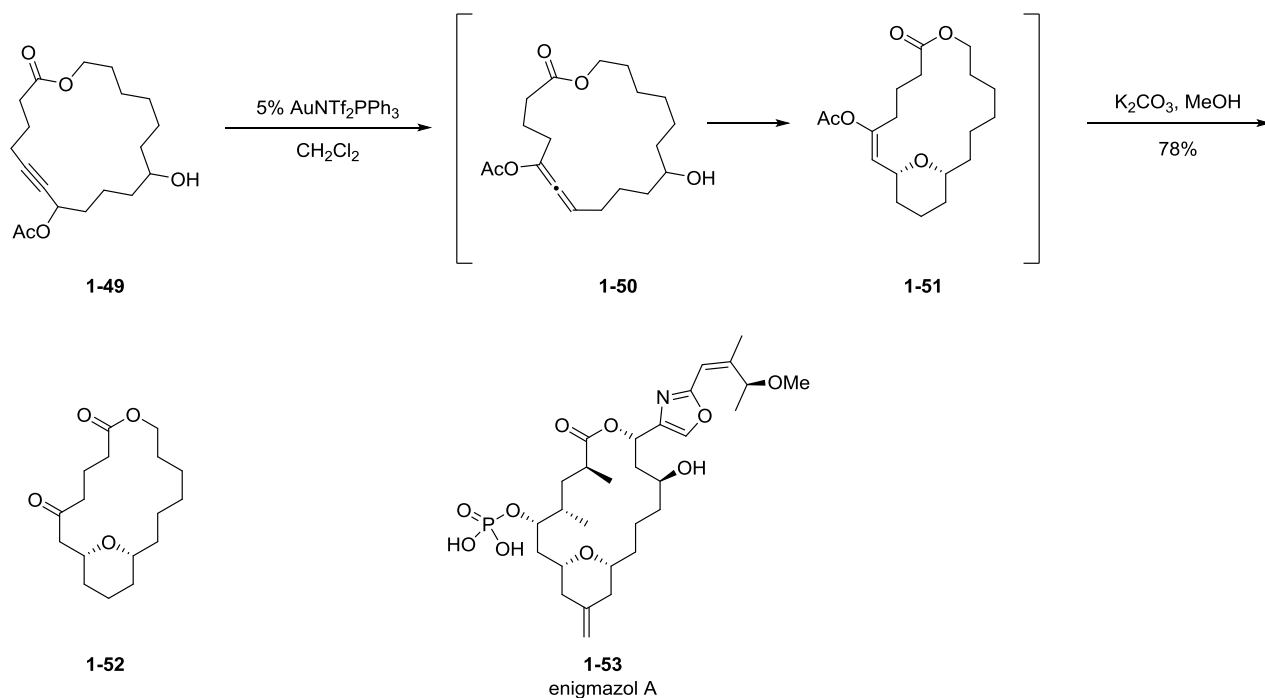


Scheme 1.13. Au-catalyzed transannular hydroalkoxylation in a synthesis of spirastrellolide

F

Transannular hydroalkoxylation can be performed with different π -systems. The π -acidic catalyst $\text{AuNTf}_2\text{PPh}_3$ played an indirect role in the transannular hydroxylation of **1-49** affording **1-52**, the core structure of enigmazole A (**1-53**).⁴⁰ The gold catalyst promoted the

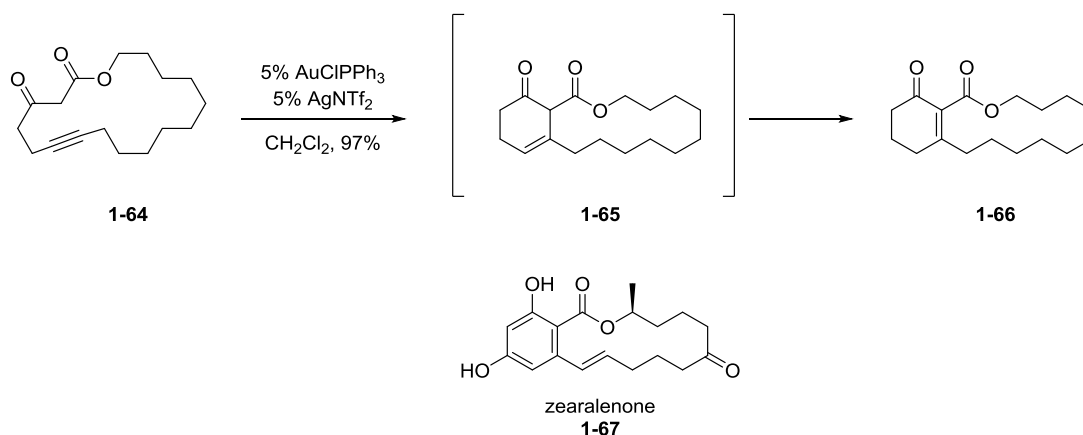
rearrangement⁴¹ of macrocyclic alkyne **1-49** to allenyl acetate **1-50** and subsequent transannular hydroxyl attack formed macrocycle **1-51** which was converted to target product **1-52** via hydrolytic work-up (Scheme 1.14).⁴²



Scheme 1.14. Au-promoted transannular hydroalkoxylation of macrocyclic allene **1-50**

It is noteworthy that transannular hydroalkoxylation can be performed with substrates that do not bear any nucleophilic hydroxyl groups. Various natural product core structures were prepared by altering the transannular reactivity and by choosing the proper π -acidic catalyst. An example is the synthesis of macrocycle **1-57**⁴² that maps onto the core scaffolds of furanocembranoids *pukalide* (**1-58**), *deoxy-pukalide* (**1-59**) and *iopholide* (**1-60**).⁴³ Treatment of macrocyclic β -ketoester **1-54** with a catalytic amount of AuCl_3 in refluxing MeOH led to transannular attack of the enol oxygen in complex **1-55** and formed the intermediate **1-56** (Scheme 1.15). Through rearrangement of intermediate **1-56** into the more stable furan unit,

Although it doesn't serve as an example for hydroalkoxylation, one transannular transformation that should be mentioned in the context of this section is the synthesis of cyclic enone **1-66** that constitutes the core of resorcylic acid macrolide zearalenone (**1-67**). Furstner and co-workers demonstrated that macrocyclic alkyne **1-64** participated in a transannular Conia-ene cyclization⁴⁵ under π -acidic AuClPPh₃ catalysis.⁴² It is believed that transannular 6-*endo* addition of β -ketoester across the alkyne forms the intermediate **1-65** which rapidly rearranges to more stable enone **1-66** (Scheme 1.17).⁴²

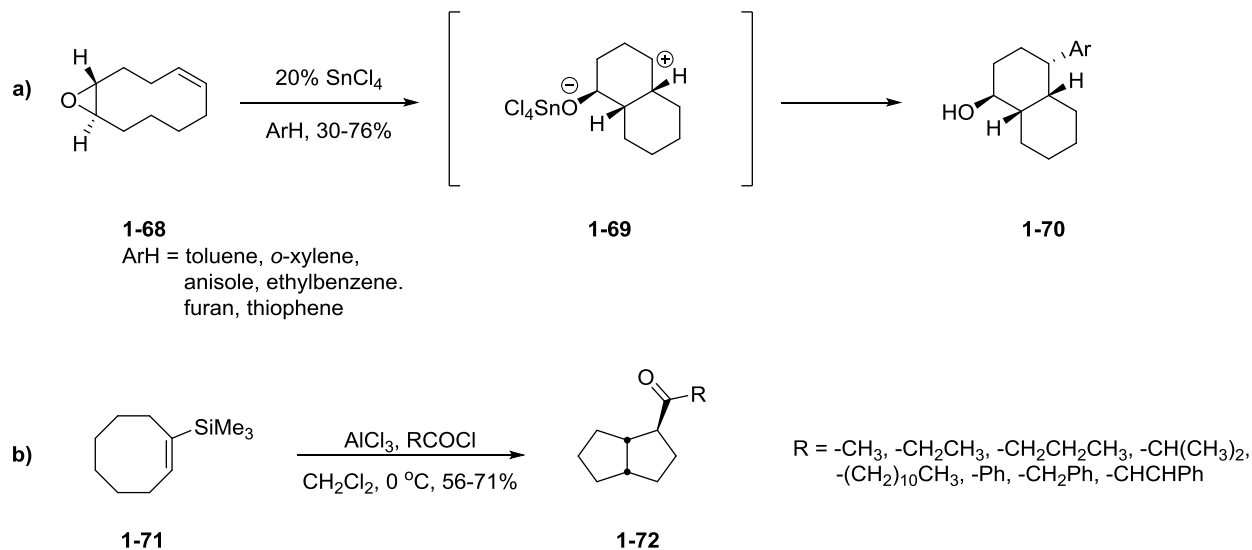


Scheme 1.17. Au-catalyzed transannular Conia-ene cyclization in the synthesis of zearalenone core framework 1-66

1.5. Metal-Mediated Transannular Cation-Olefin, Michael and Friedel-Crafts Reactions

One of the earliest examples of metal-mediated transannular reactions was demonstrated by Taylor and co-workers. *trans*-5,6-Epoxy-*cis*-cyclodecene (**1-68**) underwent a transannular cation-olefin reaction with catalytic amounts of SnCl₄ in various solvents that acted as cation traps (Scheme 1.18a).⁴⁶ Remarkably, in these reactions four stereogenic centers were formed selectively via single transannular ring closure. Later a related methodology was utilized by Nagendrappa to synthesize *exo-cis*-bicyclo[3.3.0]-2-octyl ketones (**1-72**).⁴⁷

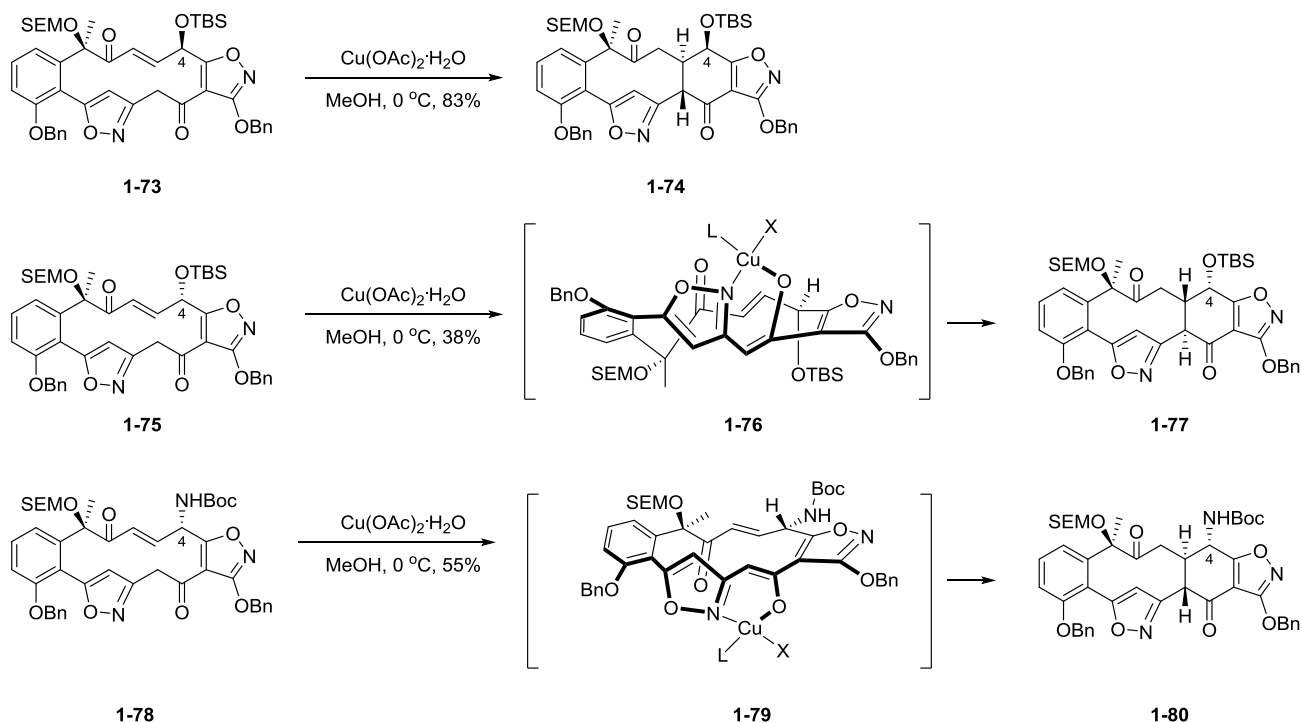
Trimethylsilylcyclooctene **1-71** went through AlCl_3 -promoted transannular cyclizations in the presence of various acyl chlorides (Scheme 1.18b).



Scheme 1.18. Sn- and Al-mediated transannular cation-olefin cyclizations

Transannular conjugate additions of nucleophiles to electron-poor olefins were successfully incorporated in a number of syntheses and several of these transannular Michael reactions utilized metals. An efficient application of a metal-mediated transannular Michael addition was exhibited by the Evans group.⁴⁸ Three tetracycline antibiotic core structures (**1-74**, **1-77** and **1-80**) were built via transannular Michael additions (Scheme 1.19). 14-Membered macrocycles **1-73**, **1-75** and **1-78** underwent transannular transformations smoothly in the presence of copper(II) acetate; deprotonations by the soft base acetate led to the formation of copper(II) enolates (**1-76** and **1-79**) and the subsequent transannular additions were completely diastereoselective. It was evident that the stereochemical outcomes were fully dictated by the chiral center at C4. Merely changing the silyloxy substituent at this position to an NHBoc group caused a reversal in the reactive face selection. The reason for this reversal was suggested to be NHBoc group interacting

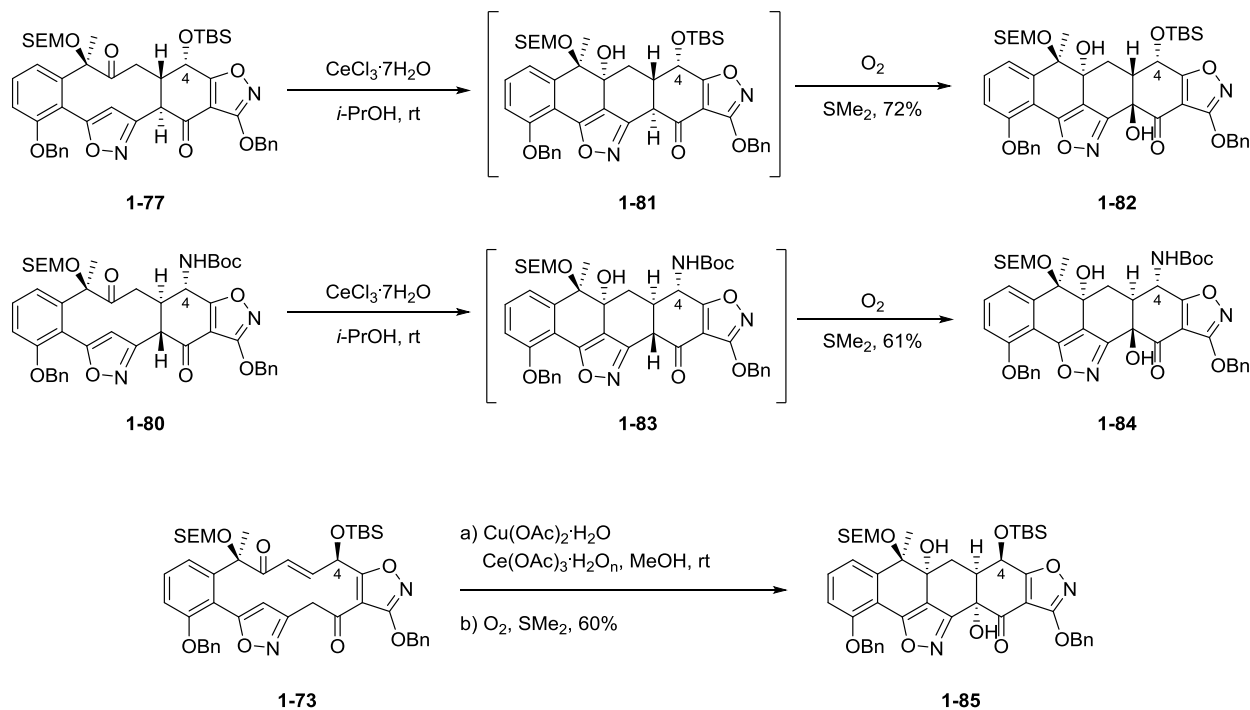
with the oxygen atom of the neighboring isoxazole ring and favoring a certain conformer of macrocyclic complex **1-79**. However, the reasoning behind the preferred axial position of OTBS group in **1-76** could not be explained.⁴⁸



Scheme 1.19. Cu-promoted transannular Michael reactions in the synthesis of core structures of tetracycline antibiotics

Evans and co-workers prepared an additional class of tetracycline core structures through sequential transannular cyclizations (Scheme 1.20). In the presence of the Lewis acid CeCl_3 macrocycles **1-77** and **1-80**, previously synthesized by transannular Michael reactions (Scheme 1.19), underwent diastereoselective transannular Friedel-Crafts reactions and the target hexacyclic core structures **1-82** and **1-84** were obtained after in situ oxidations of **1-81** and **1-83**, respectively (Scheme 1.20). Moreover, an impressive diastereoselective one pot transformation comprising a transannular Michael/ transannular Friedel-Crafts/oxidation reaction sequence

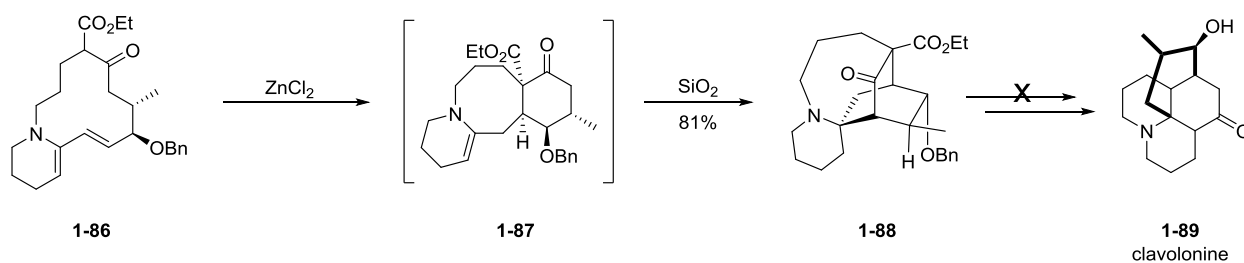
occurred when macrocycle **1-73** was treated with both $\text{Cu}(\text{OAc})_2$ and $\text{Ce}(\text{OAc})_3$ resulting in the formation of polycycle **1-85** in a 60% overall yield.⁴⁸



Scheme 1.20. Transannular Friedel-Crafts and Cu-promoted transannular

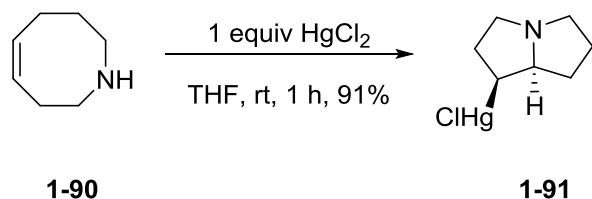
Michael/Friedel-Crafts reactions in the synthesis of tetracycline antibiotic core structures

The Evans group demonstrated yet another successful metal-mediated transannular Michael reaction during their attempts to synthesize the polycyclic alkaloid *clavolonine* (**1-89**).⁴⁹ In the presence of the Lewis acid ZnCl_2 enamine macrocycle **1-86** went through a stereoselective transannular Michael addition. The resultant tricycle **1-87** was unstable and was converted to the tetracyclic ketoester **1-88** via a spontaneous intramolecular Mannich cyclization upon exposure to silica gel or alumina (Scheme 1.21). Unfortunately molecule **1-88** was not suitable for the total synthesis of the target natural product and the research group devised an alternative synthetic approach to access clavolonine.⁴⁹



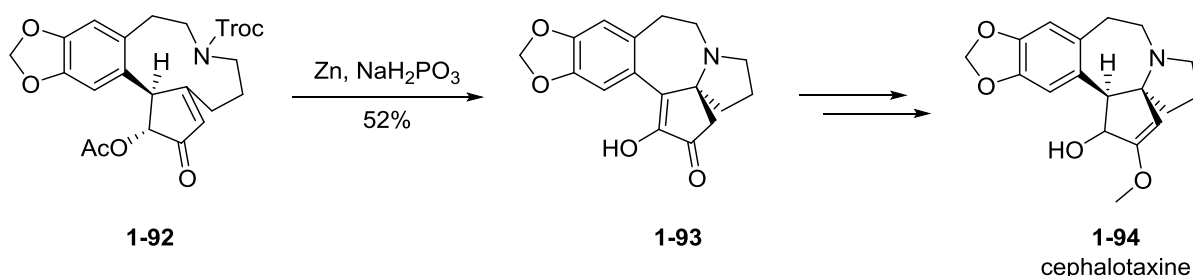
Scheme 1.21. Zn-promoted transannular Michael reaction

One of the most common methods to access azabicyclic structures is transannular ring contractions of monocycles possessing *N*-protected nucleophiles.^{4b} Transition metals, especially palladium, were used in these transformations to deprotect the final *N*-protonated products without affecting the transannular step,⁵⁰ but, more importantly, metals were used as activators in transannular aza-Michael addition versions of these reactions. Sawicki and Wilson studied the mechanism of transannular cyclizations in eight-membered rings with secondary amines.⁵¹ This early study showed that 1-aza-4-cyclooctene (**1-90**) when treated with HgCl_2 transannularly cyclized to pyrrolizidine **1-91** in excellent yield (Scheme 1.22). It was suggested that HgCl_2 (and other soft electrophiles) approached the double bond from the less hindered face and formed an onium ion. Subsequently, nitrogen nucleophile addition to this ion in a transannular fashion yielded only the product with *trans* geometry. The study also pointed out the importance of using a metal with low affinity towards nitrogen since transition metals like Pd shut down the transannular cyclization path by coordinating to the olefin and nitrogen simultaneously.⁵¹



Scheme 1.22. Hg-promoted transannular aza-Michael reaction

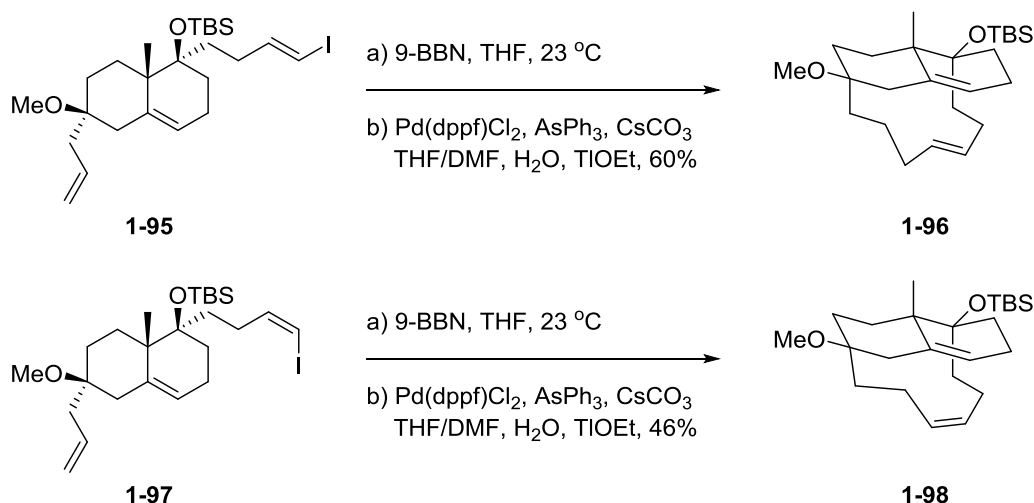
Li and co-workers employed a transannular aza-Michael reaction in the racemic synthesis of the alkaloid cephalotaxine (**1-94**).⁵² The Michael system (**1-92**) with an exocyclic olefin was activated by Zn-promoted reduction. Selective N-Troc bond cleavage initiated the transannular diastereoselective formation of **1-93** (Scheme 1.23).



Scheme 1.23. Zn-initiated transannular aza-Michael reaction in the synthesis of cephalotaxine

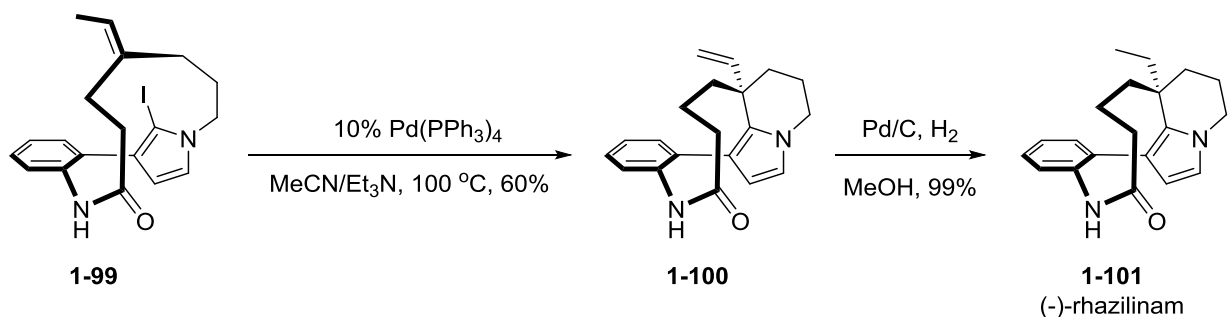
1.6. Metal-Mediated Transannular Coupling Reactions

Surprisingly, examples of coupling reactions that were performed in a transannular fashion are quite rare in the literature. In fact transannular macrocyclizations by intramolecular *B*-alkyl Suzuki reactions described by Danishefsky in 2000,⁵³ are the first reported transannular cross-coupling reactions. In this study, tandem regioselective terminal olefin hydroborations with 9-BBN and transannular Pd(0)-catalyzed Suzuki couplings formed macrocycles (**1-96** and **1-98**) in one pot maintaining high control over olefin geometry (Scheme 1.24). In terms of reactivity and stereochemical control these reactions were proven superior to ring closing metathesis reactions. For instance macrocycle, **1-96** could not be synthesized by the latter approach from iodide free derivative of **1-95**.⁵³



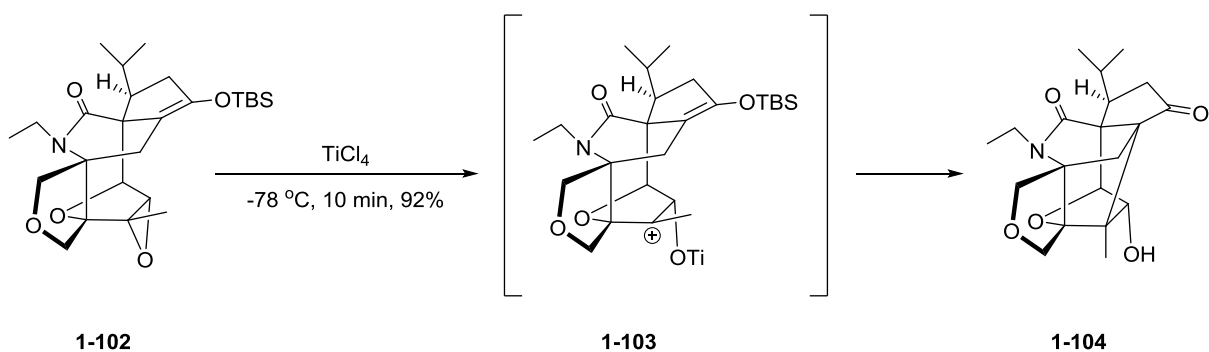
Scheme 1.24. Transannular macrocyclizations via intramolecular *B*-alkyl Suzuki cross-coupling reactions

One elegantly executed example of a transannular cross-coupling reaction was investigated as the key step in the total synthesis of rhazilinam,⁵⁴ a natural product that mimics the cellular activity of taxol.⁵⁵ Planar chiral **1-99** went through enantiospecific transannular Heck coupling under Pd(0) catalysis building the otherwise challenging to access framework **1-100** (Scheme 1.25). A subsequent quantitative hydrogenation step concluded the synthesis of the natural isomer of (-)-rhazilinam (**1-101**). The transannular Heck reaction was quite versatile; the unnatural isomer (+)-rhazilinam was also prepared successfully by the same methodology from the other enantiomer of **1-99**.



Scheme 1.25. Transannular Heck coupling in the synthesis of (-)-rhazilinam

A fascinating transannular ring formation reaction that generates the 5-5-5-5 fused ring system of the *crinipellin* family with the correct absolute stereochemistry was investigated by the Sieburth research group (Scheme 1.26).⁵⁶ Although this transformation was not a formal coupling reaction, the net outcome was construction of a new C-C bond. When molecule **1-102** was treated with TiCl_4 an epoxide opening produced a tertiary carbocation susceptible to transannular nucleophilic attack. As a result, complex cage structure **1-104** was built with complete stereocontrol. It should be noted that a number of other methods were tried to access **1-104**; however, none of the trials were successful.⁵⁶



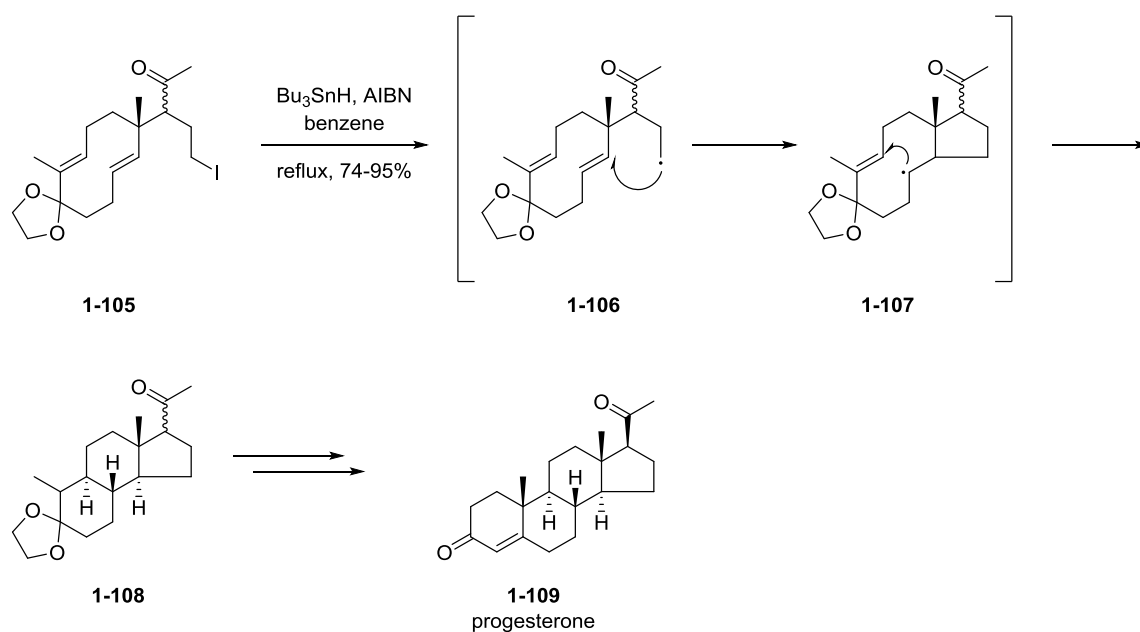
Scheme 1.26. Ti-promoted transannular C-C bond formation

1.7. Metal-Mediated Free-Radical Transannular Cyclizations

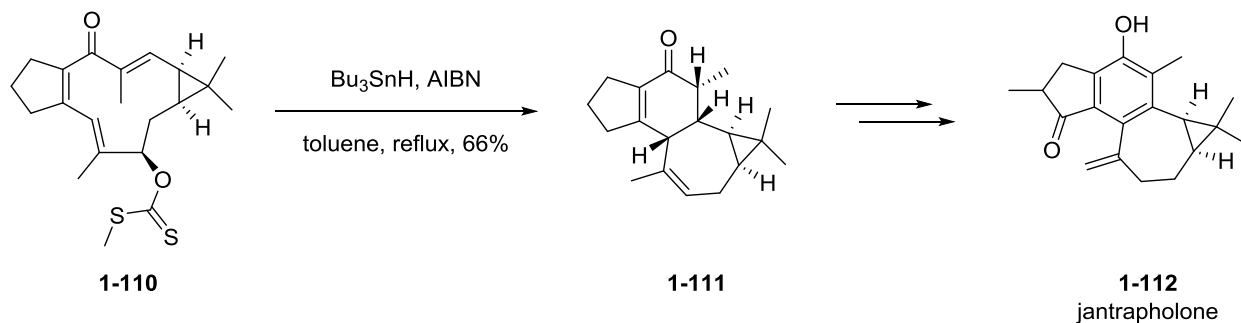
Reactive intermediates taking part in transannular reactions are not limited to carbocations, carbanions and carbenes. Free-radical transannular cyclizations have also attracted considerable attention since the first examples were reported in 1964 by Dowbenko⁵⁷ and Friedman.⁵⁸ These reactions have now become common strategies in polycyclic natural product synthesis.⁵⁹ When metal-free radical initiators failed to trigger cyclizations, tin,⁶⁰ titanium⁶¹ and copper⁶² reagents were used to assist the desired transannular reactions. Selected examples that were explored as part of biologically active molecule syntheses are discussed in this section.

Takashi and co-workers reported an efficient synthesis of the steroid BCD-ring system (**1-108**) of *progesterone* (**1-109**), using a transannular radical cyclization as the key step.^{60d} The synthesis started with radical formation on the molecule tether upon treatment with tributyl hydride and the intramolecular attack of this radical onto the main ring initiated the transannular cyclization (Scheme 1.27). The stereochemistry of resultant polycycle was determined by X-ray crystallography and computational studies.

The Yamamura research group implemented a transannular radical cyclization strategy to the synthesis of the jantrapholone (**1-112**) core framework.^{60g} Xanthate **1-110** underwent transannular cyclization in the presence of Bu_3SnH and AIBN constructing a 5-6-7-3 fused ring system (**1-111**) stereoselectively (Scheme 1.28).



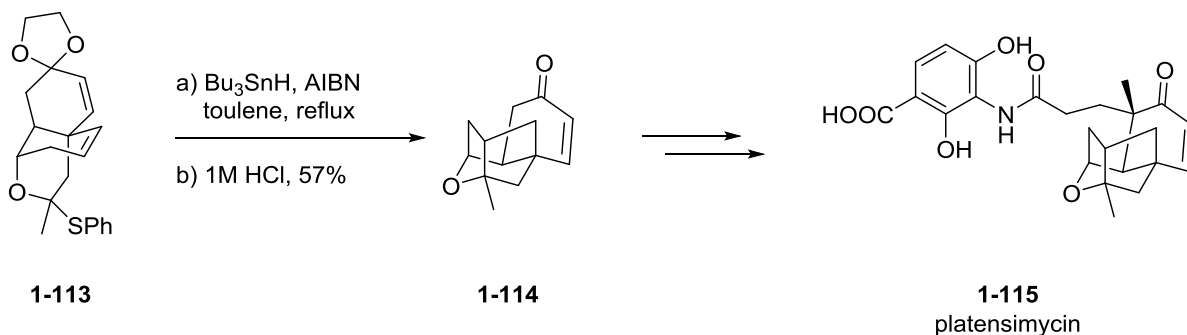
Scheme 1.27. Sn-promoted transannular radical cyclizations in the synthesis of progesterone BCD-ring systems



Scheme 1.28. Sn-promoted transannular radical cyclization in the synthesis of jantrapholone core framework 1-111

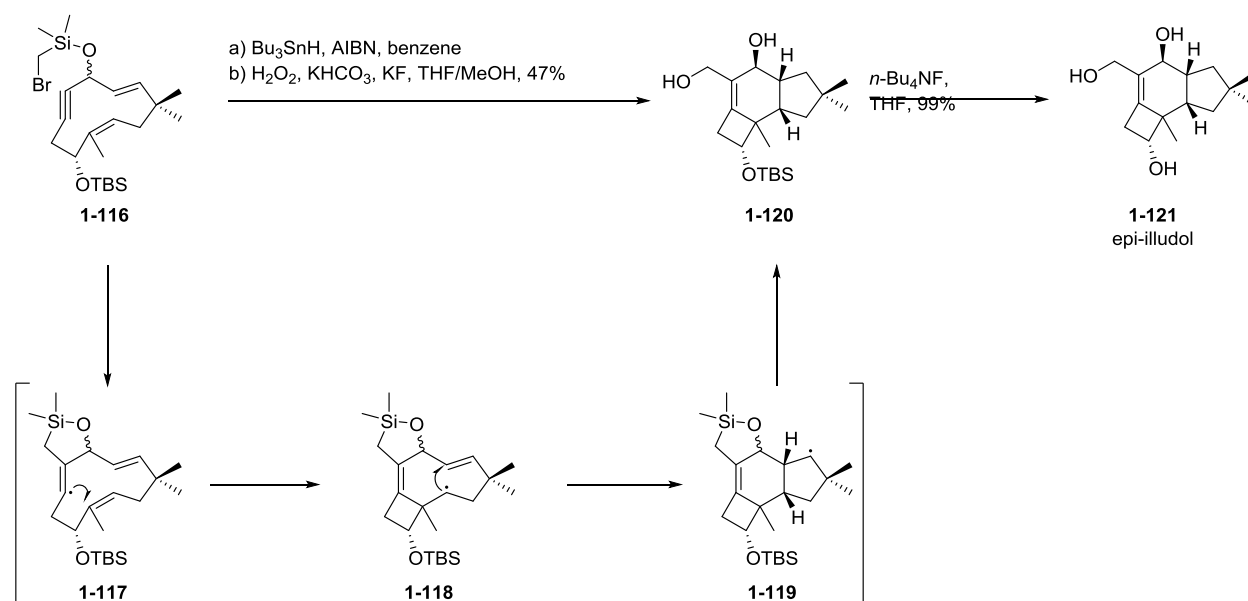
The caged core structure of *platensimycin* (**1-115**) was synthesized stereoselectively by Matsuo and co-workers using a transannular radical cyclization of monothioacetal with Bu_3SnH and AIBN as one of the key steps in the synthesis (Scheme 1.29).⁶⁰ⁱ Tributyltin hydride was crucial for the synthesis of the cage structure **1-114** as the transannular cyclization of

monothioacetal **1-113** failed completely in the presence of the hydrogen atom sources tris(trimethylsilyl)silane and triphenyltin hydride.⁶⁰ⁱ



Scheme 1.29. Sn-promoted transannular radical cyclization in the synthesis of the platensimycin caged core structure

A number of synthetic protocols to access the sesquiterpene epi-illudol (**1-121**) were investigated,⁶³ but the first diastereoselective total synthesis was achieved through a cascade of transannular radical cyclizations.^{60g} The Malacria group showed that upon treatment with tributyltin hydride 11-membered dienyne **1-116** went through transannular cyclizations assembling the tricyclic strained skeleton of epi-illudol stereoselectively (Scheme 1.30). In this sense transannular radical cyclization method was proven to be superior even to Vollhardt's one-step intramolecular [2+2+2] cycloaddition method.^{63c}



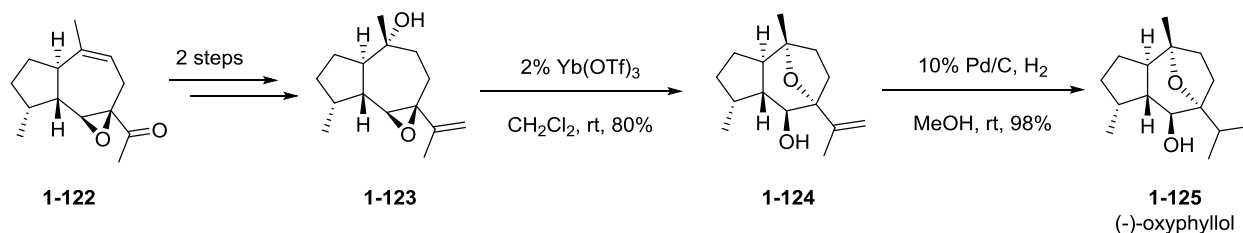
Scheme 1.30. Sn-promoted transannular radical cyclizations in the synthesis of epi-illudol

1.8. Metal-Mediated Transannular Ring Opening/Ring Closing Cascade Reactions

Transannular ring opening reactions are not as common as their ring closing counterparts; however, several research groups efficiently incorporated ring closing/ring opening cascade reaction strategies into the synthesis of several natural products. This section covers those examples that involve ring openings triggered by transannular nucleophilic addition followed or accompanied by transannular cyclizations.

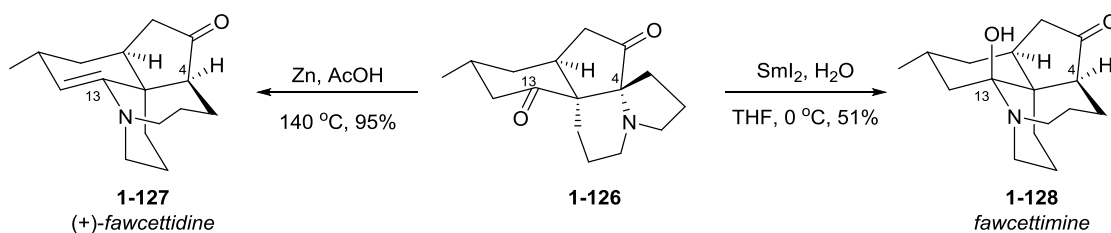
The Metz group prepared the guaiane sesquiterpene (–)-oxyphyllol (**1-125**) in an enantioselective manner from the epoxy enone **1-122** that already served as an intermediate for the total synthesis of (–)-englerin A.⁶⁴ Precursor **1-122** was easily converted to **1-123** via alkene hydroxylation followed by a Wittig reaction, but attempts to cyclize **1-123** through transannular epoxide opening/ring closing cascade reactions in acidic medium failed leading to decomposition. However, catalytic amounts of ytterbium triflate achieved the formation of

oxygen-bridged bicyclic hydroazulene **1-124** and hydrogenation completed the synthesis of **1-125** (Scheme 1.31). It should be noted that Taylor's transannular Friedel-Crafts cyclization (Scheme 1.18a) can be included in the same category as this transannular cascade strategy.



Scheme 1.31. Yb-catalyzed transannular epoxide opening/ring closing cascade reactions in the synthesis of (-)-oxyphyllol

Lei and co-workers prepared *fawcettidine* and *fawcettimine*-type *lycopodium* alkaloids (**1-127** and **1-128**) via transannular ring opening/ring closing cascade reactions (Scheme 1.32).⁶⁵ The reductive transannular cleavage of the C4-N bond of **1-126** occurred in the presence of zinc and the subsequent transannular C13-N bond formation afforded (+)-*fawcettidine* (**1-127**) in excellent yield. Moreover, the regioselectivity of the reaction was altered by simply switching the metal promoter. Treatment of **1-126** with SmI_2 achieved transannular cascade C4-N bond cleavage and C13-N bond formation with selective reduction of carbonyl group on C13. This transformation generated *fawcettimine* **1-128** stereoselectively (Scheme 1.32).



Scheme 1.32. Zn- and Sm-promoted transannular ring opening/ring closing cascade reactions

1.9. Summary and Outlook

Metal-catalyzed and -promoted transannular reactions reported in the literature so far are reviewed in this chapter. The reactions covered include cycloadditions, cyclopropanations, hydroalkoxylations, Friedel-Crafts reactions, Michael and aza-Michael reactions, coupling reactions, free-radical cyclizations and ring opening/closing cascade reactions. The showcased metal-mediated transannular reactions were utilized as powerful methodological approaches for remarkably stereoselective syntheses of polycycles, many of which are precursors to natural products and pharmaceuticals. Various investigated transannular reactions also provide a strong basis for future chemical methodology discoveries. In comparison to general transannular reactions that underwent impressive advancements during the last years, metal-mediated counterparts are still underdeveloped, but this review illustrated that new exciting progress focusing on a wider range of reactions and new applications should be expected in this area in the immediate future. Valuable contributions to metal-mediated transannular chemistry made by Merlic research group are discussed in detail in the upcoming chapters.

1.10. References

1. Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2014**, *70*, 9461.
2. Baeriswyl, V.; Heinis, C. *ChemMedChem* **2013**, *8*, 377.
3. Muller, P. *Pure Appl. Chem.* **2009**, *66*, 1077.
4. a) Furstner, A. *Acc. Chem. Res.* **2014**, *47*, 925. b) Rizzo, A.; Harutyunyan, S. R. *Org. Biomol. Chem.* **2014**, *12*, 6570. c) Jiong, Y.; Haoran, X. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; Wiley: New York, NY, 2013; Vol. 1; Part 2, pp 551-579; d) Clarke, P. A.; Reeder, A. T.; Winn, J. *Synthesis* **2009**, 691.
5. a) Campbell, E. L.; Skepper, C. K.; Sankar, K.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2013**, *15*, 5306. b) Vasamsetty, L.; Khan, F. A.; Mehta, G. *Tetrahedron Lett.* **2014**, *55*, 7068. c) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 2722. d) Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818.
6. Iafe, R. G.; Kuo, L. J.; Hochstatter, D. G.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2013**, *15*, 582.
7. For examples of transannular aldol reactions, see: a) Inoue, M.; Sato, T.; Hiramama, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4843. b) Evans, D. A.; Rimpin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816. c) Lee, A. S.; Liao, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2014**, *136*, 13442. d) Catino, A. J.; Sherlock, A.; Shieh, P.; Wzorek, J. S.; Evans, D. A. *Org. Lett.* **2013**, *15*, 3330. e) Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737.
8. For examples of transannular radical cyclizations, see: a) Friedman, L. *J. Am. Chem. Soc.* **1964**, *86*, 1885. b) Nicolaou, K. C.; McGarry, D. G.; Somers, p. K.; Veale, C. A.; Furst,

- J. Am. Chem. Soc.* **1987**, *109*, 2504. c) Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825. d) Zhu, C.; Liu, Z.; Chen, G.; Zhang, K.; Ding, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 879.
- 9.** For examples of transannular Michael reactions, see: a) Snider, B. B.; Zhou, *J. Org. Lett.* **2006**, *8*, 1283. b) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968. c) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron* **2011**, *67*, 5054.
- 10.** For examples of transannular 1,3-dipolar cycloadditions, see: 31. a) Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 6401; b) Tang, B.; Bray, C. D.; Pattenden, G. *Org. Biomol. Chem.* **2009**, *7*, 4448. c) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901. d) Franklin, A. I.; Bensa, D.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 1901.
- 11.** White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665.
- 12.** a) Yiang, X.; Wang, R. *Chem. Rev.* **2013**, *113*, 5515; b) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902; c) Hayashi, Y. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: New York, NY, 2002; p 5; d) Taschner, M. J. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, CT, 1989; Vol. 1, pp 1-101; (s) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
- 13.** Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4743.
- 14.** a) Diedrich, M. K.; Klarner, F. –G.; Beno, B. R.; Houk, K. N.; Senderowitz, H.; Still, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 10255. b) Krenske, E. H.; Perry, E. W.; Jerome, S. V.; Maimone, T. J.; Baran, P. S.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3016.

15. For examples of thermal TADA reactions, see: a) Shing, T. K. M.; Yang, J. *J. Org. Chem.* **1995**, *60*, 5785. b) Soucy, P.; L'Heureux, A.; Toro, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 9983. c) Toro, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 6847. d) Phoenix, S.; Reddy, M. S.; Deslongchamps, P. *J. Am. Chem. Soc.* **2008**, *130*, 13989. Also see references 5c and 5d.
16. Hufford, C. D.; Guerrero, R. D.; Doorenbos, N. J. *J. Pharm. Sci.* **1976**, *95*, 778.
17. Toro, A.; Lemelin, C.-A.; Preville, P.; Belanger, G.; Deslongchamps, P. *Tetrahedron* **1999**, *55*, 4655.
18. Toro, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526.
19. Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736.
20. Carrillo, R.; Martin, T.; Loopez-Rodriguez, M.; Crisoostomo, F.P. *Org. Lett.* **2013**, *16*, 552.
21. a) Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112. b) Yamago, S.; Nakamura, E. *Tetrahedron* **1989**, *45*, 3081.
22. a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. b) Binger, P. *Angew. Chem. Int. Ed.* **1972**, *11*, 309.
23. For reviews, see: a) Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* **2015**, *48*, 1021. b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979. c) Zhang, L.; Sun, J.; Kozmina, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. d) Mendez, M.; Mamane, V.; Furstner, A. *Chemtracts-Org. Chem.* **2003**, *16*, 397. e) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215.
24. Dudones, J. D.; Sampson, P. *Tetrahedron* **2000**, *56*, 9555.

25. Blaszykowski, C.; Harrak, Y.; Goncualves, M. H.; Cloarec, J. M.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771.
26. For examples of diastereoselective Pt-catalyzed cyclopropanations, see: a) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104. b) Furtsner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. c) Furtsner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2001**, *123*, 11863. For theoretical studies on selectivity in Pt-catalyzed cyclopropanation of 1,6-enynes, see: a) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *J. Org. Chem.* **2004**, *69*, 8018. b) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics* **2005**, *24*, 3172.
27. Hayashi, K.-I.; Asano, K.-I.; Tanaka, M.; Takaoka, D.; Nozaki, H. *Phytochemistry* **1998**, *48*, 461.
28. Warmers, U.; Konig, W. A. *Phytochemistry* **1999**, *52*, 1519.
29. Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821.
30. Kuhnert, S. M.; Maier, M. E.; *Org. Lett.* **2002**, *4*, 643.
31. Ushakov, D. B.; Navickas, V.; Strobele, M.; Maichle-Mossmer, C.; Sasse, F.; Maier, M. *E. Org. Lett.* **2011**, *13*, 2090.
32. Lee, J.; Parker, K. A. *Org. Lett.* **2012**, *14*, 2682.
33. Yotsu-Yamashita, M.; Yasumoto, T.; Yamada, S.; Bajarias, F. F. A.; Formeloza, M. A.; Romero, M. L.; Fukuyo, Y. *Chem. Res. Toxicol.* **2004**, *17*, 1265.
34. For selected examples, see: a) Fujiwara, K.; Murai, A. *J. Am. Chem. Soc.* **1998**, *120*, 10770. b) Paquette, L. A.; Barriault, L.; Pissarnitski, D. *J. Am. Chem. Soc.* **1999**, *121*, 4542. c) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagorny, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593.

35. Woo, S. K.; Lee, E. *J. Am. Chem. Soc.* **2010**, *132*, 4564.
36. Brewitz, L.; Llaveria, J.; Yada, A.; Furstner, A. *Chem. Eur. J.* **2013**, *19*, 4532.
37. Overman, L. E. *Angew. Chem. Int. Ed.* **1984**, *23*, 579.
38. Valot, G.; Regens, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Furstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9534.
39. Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Furstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8739.
40. a) Oku, N.; Takada, K.; Fuller, W. R.; Wilson, J. A.; Peach, M. L.; Pannell, L. K.; McMahon, J. B.; Gustafson, K. R. *J. Am. Chem. Soc.* **2010**, *132*, 10278. b) Skepper, C. K.; Quach, T.; Molinski, T. F.; *J. Am. Chem. Soc.* **2010**, *132*, 10286.
41. a) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149. b) Cadierno, V.; Crochet, P.; Garcia-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015.
42. Persich, P.; Llaveria, J.; Lhermet, R.; de Haro, T.; Stade, R.; Kondoh, A.; Furstner, A. *Chem. Eur. J.* **2013**, *19*, 13047.
43. Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298.
44. Smith, A. B.; Chen, S. S. -Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 10935.
45. a) Furstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. c) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168. d) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486.
46. Taylor, S. K.; Lilley, G. L.; Lilley, K. J.; McCoy, P. A. *J. Org. Chem.* **1981**, *46*, 2709.
47. Bandodakar, B. S.; Nagendrappa, G. *Tetrahedron Lett.* **1989**, *30*, 7461.

48. Wzorek, J. S.; Knopfel, T. F.; Sapountzis, I.; Evans, D. A. *Org. Lett.* **2012**, *14*, 5840.
49. Evans, D. A.; Scheerer, J. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 6038.
50. For examples, see: a) Cakmak, M.; Mayer, P.; Trauner, D. *Nat. Chem.* **2011**, *3*, 543. b) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2013**, *11*, 3187.
51. Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 288.
52. Li, W. –D. Z.; Duo, W. –G.; Zhuang, C. –H. *Org. Lett.* **2011**, *13*, 3538.
53. Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695.
54. Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224.
55. David, B.; Sevenet, T.; Morgat, M.; Guenard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317.
56. Chen, P.; Carroll, P. J.; Sieburth, S. M. *Org. Lett.* **2010**, *12*, 4510.
57. Dowbenko, R. *Tetrahedron* **1964**, *20*, 1843.
58. Friedman, L. *J. Am. Chem. Soc.* **1964**, *86*, 1885.
59. Handa, S.; Pattenden, G. *Contemp. Org. Synth.* **1997**, 196.
60. a) Porter, N. A.; Chang, V. H. –T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554. b) Colclough, D.; White, J. B.; Smith, W. B.; Chu, Y. *J. Org. Chem.* **1993**, *58*, 6303. c) Jones, P.; Li, W. –S.; Pattenden, G.; Thomson, N. M. *Tetrahedron Lett.* **1997**, *52*, 9069. d) Tomida, S.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 2363. e) Aissa, C.; Dhimane, A. –L.; Malacria, M. *Synlett* **2000**, 1585. f) Nagano, H.; Tada, A.; Isobe, Y.; Yajima, T. *Synlett* **2000**, 1193. g) Matsuura, T.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **2001**, *42*, 4163. h) Dhimane, A. –L.; Aissa, C.; Malacria, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3284. i) Matsuo, J.; Takeuchi, K.; Ishibashi, H. *Org. Lett.* **2008**,

- 10, 4049. j) Elliott, M. R.; Dhimane, A. –L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427.
- 61.** a) Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, P.; Sanchez, E. M.; Arteaga, J. F.; Piedra, M. *Eur. J. Org. Chem.* **2006**, 3434. b) Cuerva, J. M.; Campana, A. G.; Justicia, J.; Rosales, A.; Oller-Lopez, J. L.; Robles, R.; Cardenas, D. J.; Bunuel, E.; Oltra, J. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 5522.
- 62.** Nishiyama, K.; Hata, K.; Sato, T. *Tetrahedron* **1975**, *31*, 239.
- 63.** a) Matsumoto, T.; Miyano, K.; Kagawa, S.; Yu, S.; Ogawa, J.; Ichibara, A. *Tetrahedron Lett.* **1975**, *16*, 3521. b) Semmelhack, M. F.; Tomoda, S.; Nagaoka, H.; Boettger, S. D.; Hurst, K. M. *J. Am. Chem. Soc.* **1980**, *102*, 7567. c) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381.
- 64.** Zahel, M.; Metz, P. *Beilstein J. Org. Chem.* **2013**, *9*, 2028.
- 65.** Li, H.; Wang, X.; Lei, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 491.

Chapter 2

Synthesis of Cyclic Enynes by Ring Closing Metathesis Using Vicinal Dibromoalkenes as Protected Alkynes

2.1. Introduction

Macrocycles and polycycles, as also showcased in chapter 1, constitute a vast array of biologically active molecules; they exist in numerous natural products, pharmaceuticals and are widely used in industrial chemistry.¹ Among these complex molecules cyclic enynes occupy an important spot in synthetic chemistry that arose with interest in annulene structures in the 1960s.² Their significance is even more important now as many biologically active natural products with cyclic enyne units were discovered over the years.³ Enyne rings map on to the core structures of very potent antitumor antibiotics like neocarzinostatin **2-1**,⁴ kedarcidin,⁵ C-1027 chromophore,⁶ maduropeptin **2-2**,⁷ N199A2 chromophore,⁸ esperamicin-A₁,⁹ calicheamicin- γ_1 ⁹ and alkaloids¹⁰ like njaoamine *G* and *H* **2-3** (Figure 2.1). Cyclic enynes were also used as precursors in the synthesis of natural molecules like the diterpene (+)-epoxydictymene,^{11a} curcosone family,^{11b} macrolide aigialomycin D,^{11c} ecklonialactone family^{11d} and penarolide sulfate A₁.^{11e} In addition, cyclic enynes were explored as substrates in transannular reactions like cyclopropanations (section 1.3, scheme 1.8),^{12a} hydroalkoxylations (section 1.4, scheme 1.12 and 1.13),^{12b,c} and free-radical cyclizations (section 1.7, scheme 1.30).^{12d} All these discoveries stimulated investigations on the construction of enyne rings.

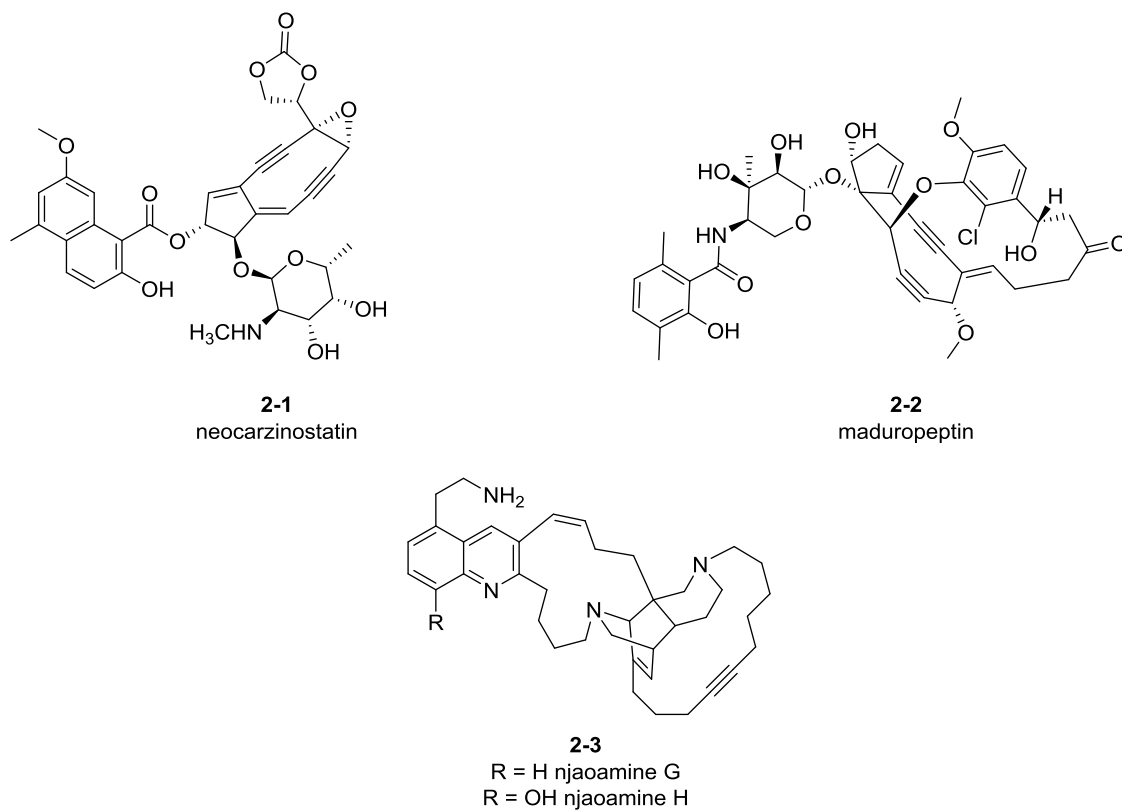
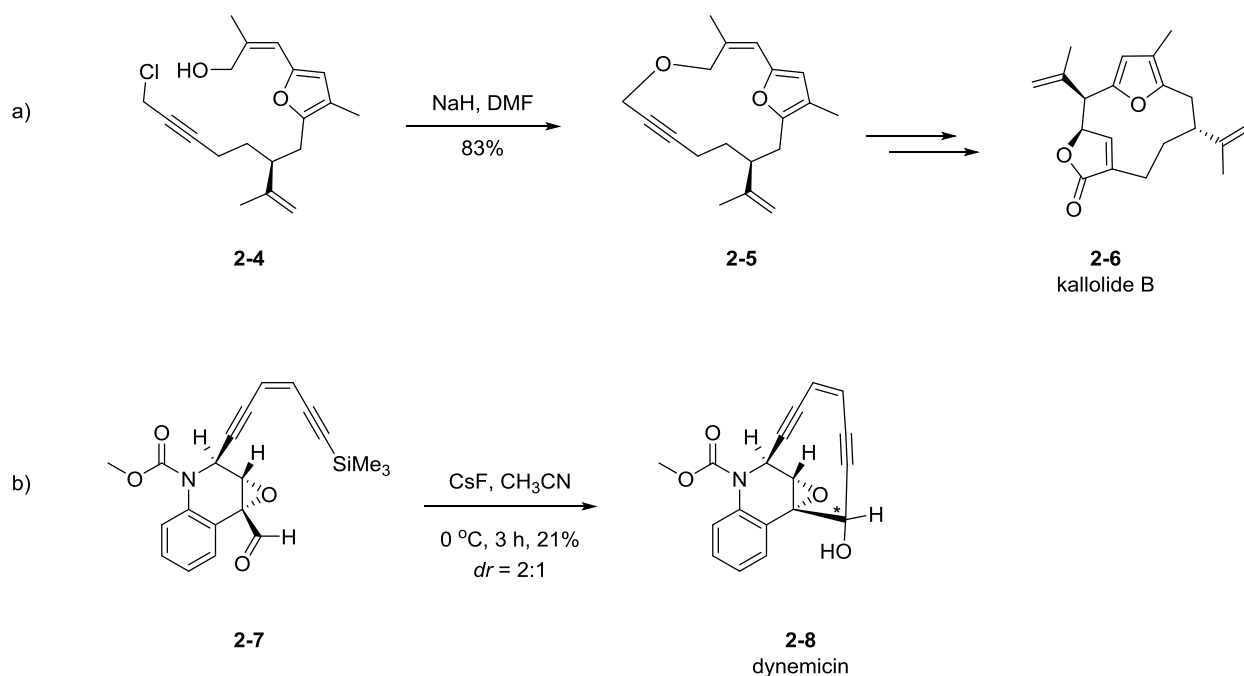


Figure 2.1. Examples of natural products with cyclic enyne cores

2.1.1. Synthesis of Cyclic Enynes

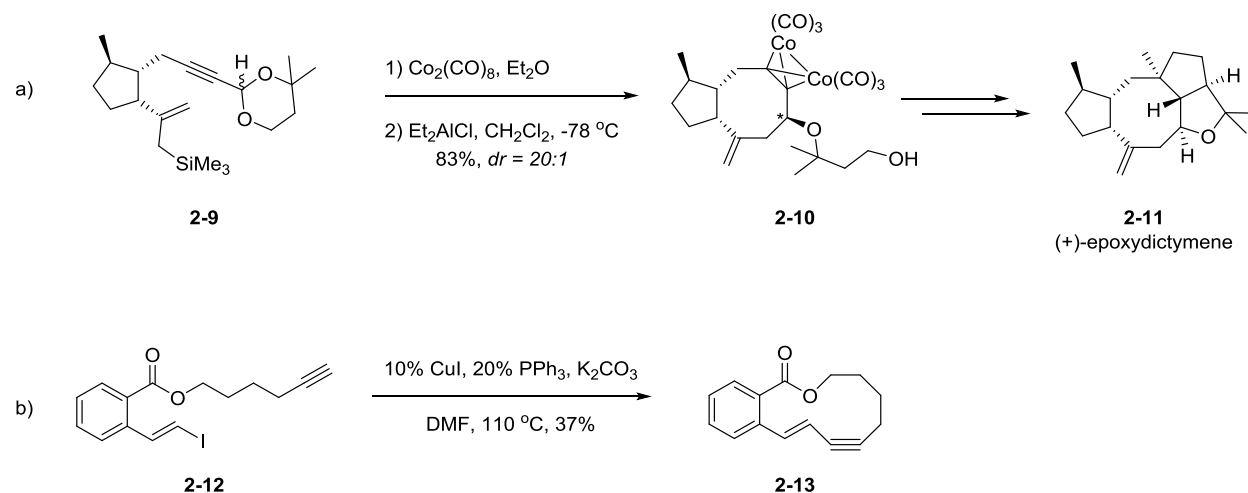
Traditionally, cyclic enynes are prepared through various cyclization reactions of functionalized acyclic enynes. The most common method is the intramolecular S_N2 reactions of acyclic substrates with chain ends differentiated into nucleophilic and electrophilic functional groups.¹³ Enyne ring formation step in the total synthesis of kallolide-B (**2-6**)^{13b} is one of the many examples of this strategy (Scheme 2.1a). Intramolecular condensation reactions have frequently been used in cyclic enyne syntheses.¹⁴ For instance, Wender and co-workers utilized a CsF-promoted intramolecular aldehyde condensation to synthesize the core cyclic enyne unit of dynemicin (**2-8**), a potent tumor cell line inhibitor (Scheme 2.1b).^{14g}



Scheme 2.1. Examples of cyclic enyne synthesis: a) by intramolecular S_N2 reaction and b) by intramolecular condensation reaction

Transition metals have been applied in a number of intramolecular reactions to synthesize enyne rings. One approach is to perform an intramolecular version of the Nicholas reaction,¹⁵ an organic reaction in which a dicobalt octacarbonyl-stabilized propargylic cation is trapped with a nucleophile.^{11a,16} The Magnus group successfully applied this methodology to the synthesis of enediyne antitumor agents esperamicin, calicheamicin, dynemicin and neocarzinostatin.^{16b} The Schreiber group investigated the tandem use of this cobalt-mediated reaction in the synthesis of (+)-epoxydictymene (2-11).^{11a} Acyclic enyne 2-9 was converted into dicobalt hexacarbonyl complexed cyclic enyne 2-10 in two steps and the synthesis was carried on without decomplexation of the dicobalt unit (Scheme 2.2a). Another approach utilizing transition metals is to close an enyne ring by an intramolecular coupling reaction. Over the years various cyclic enynes were prepared via intramolecular pinacol coupling,¹⁷ and Pd-¹⁸ and Cu-catalyzed¹⁹

intramolecular cross-coupling reactions. For example, a series 12-membered cyclic enyne lactones were prepared via modified Sonogashira coupling reactions (Castro-Stephens coupling)²⁰ under CuI catalysis in modest yields (Scheme 2.2b).^{19a}

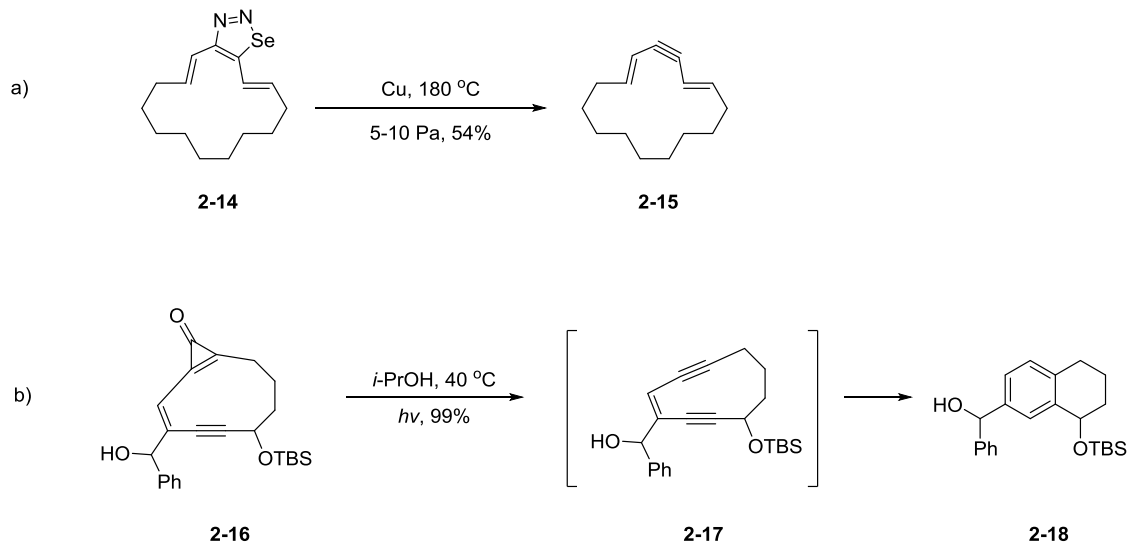


Scheme 2.2. Examples of cyclic enyne synthesis by a) intramolecular Nicholas reaction and b) intramolecular coupling reaction

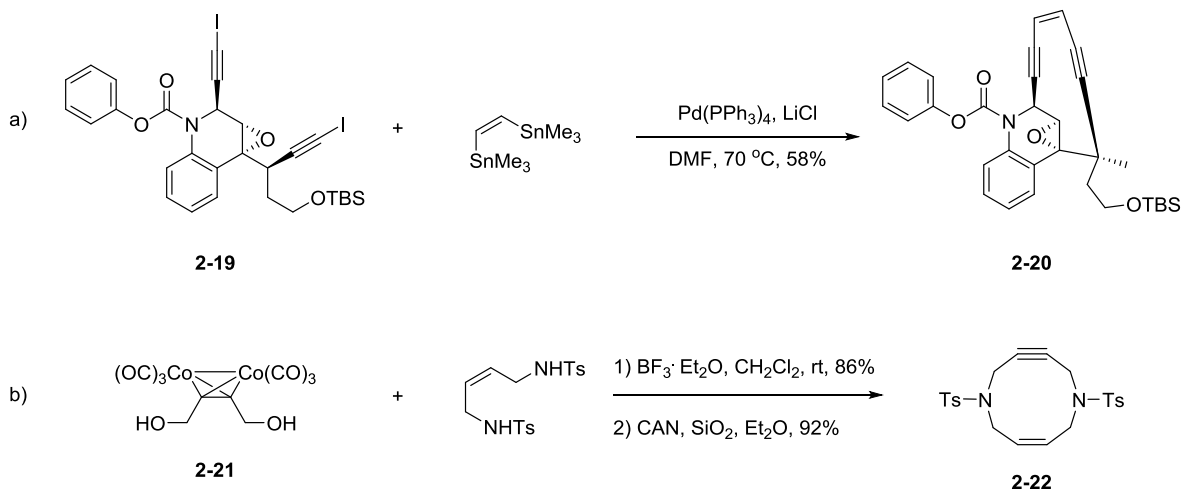
Several cyclic enyne synthesis methods involved intramolecular cyclization reactions followed by introduction of alkyne or alkene units into already formed fused polyring systems through cycloelimination reactions.^{21,11e} Applications of these methods, however, have decreased in number over time as the final cycloelimination reactions usually require harsh conditions. Two rather efficient and recent examples of this approach are the thermal fragmentation of 1,2,3-selenadiazole **2-14** (Scheme 2.3a)^{21b} and the photochemical decarbonylation of cyclopropenone **2-16** leading to formation of reactive enediyne **2-17** (Scheme 2.3b).^{21c}

Although they are not as efficient or common as intramolecular reactions, several intermolecular methods were investigated to prepare cyclic enynes. A few reported examples

include intermolecular palladium²² or copper²³ catalyzed double coupling reactions (Scheme 2.4a) and intermolecular double Nicholas reactions (Scheme 2.4b).²⁴



Scheme 2.3. Examples of cyclic enyne synthesis by cycloelimination reactions on already formed unsaturated ring systems



Scheme 2.4. Examples of cyclic enyne synthesis by a) intermolecular double coupling reaction and b) intermolecular double Nicholas reaction

The above mentioned cyclic enyne synthetic strategies (section 2.1.1) generally suffer from tedious substrate preparations, low yields and limited product scope. Constructing acyclic substrates with the chain ends possessing differentiated functionality adds extra steps to the synthetic protocols. Moreover, these substrates usually contain heavy halides or pseudo halides as leaving groups which are removed in the ring formation step and this does not serve well for the overall mass/atom economy. More often than not the final cyclization steps provide low yields which do not match the time and material spent on the preparation of the reaction substrates. In addition, these cyclic enyne syntheses are not quite generic. They are generally effective in the formation of medium sized rings with endocyclic conjugated enyne or, as several showcased examples illustrated, conjugated enediyne units. Therefore, considering the importance of cyclic enynes, it is necessary to develop more efficient and general methods.

2.1.2 Synthesis of Cyclic Enynes by Ring Closing Metathesis Reactions

Employing mild reaction conditions and high functional group tolerance ring closing metathesis (RCM) is one of the most powerful tools in organic synthesis.²⁵ In order to minimize the problems inherent with the previously mentioned cyclic enyne synthetic approaches, ene-ene RCM reactions of acyclic dienynes or yne-yne RCM reactions of acyclic enediynes can be considered as an alternative synthetic approach. However, the major obstacle is that RCM reactions lack chemoselectivity and ene-yne metathesis is preferred whenever an ene-ene or yne-yne vs ene-yne reactivity competition exists.²⁶ Experimental and theoretical studies showed that dienynes do not prefer the “ene-then-ene” pathway which leads to cyclic enyne products but instead follow the “ene-then-yne” or “yne-then-ene” pathways forming bicyclic products (Figure 2.2).²⁷ This preference can be explained for substrates with 3- or 4-atom side chains connecting the alkyne and alkene units that the initially formed metal carbene is located in close proximity

with the alkyne thus favoring the insertion.²⁷ Moreover, “ene-then-yne” and “yne-then-ene” pathways are thermodynamically more favored since they produce conjugated intermediates leading to conjugated bicyclic products that are more stable than cyclic enynes.^{27c}

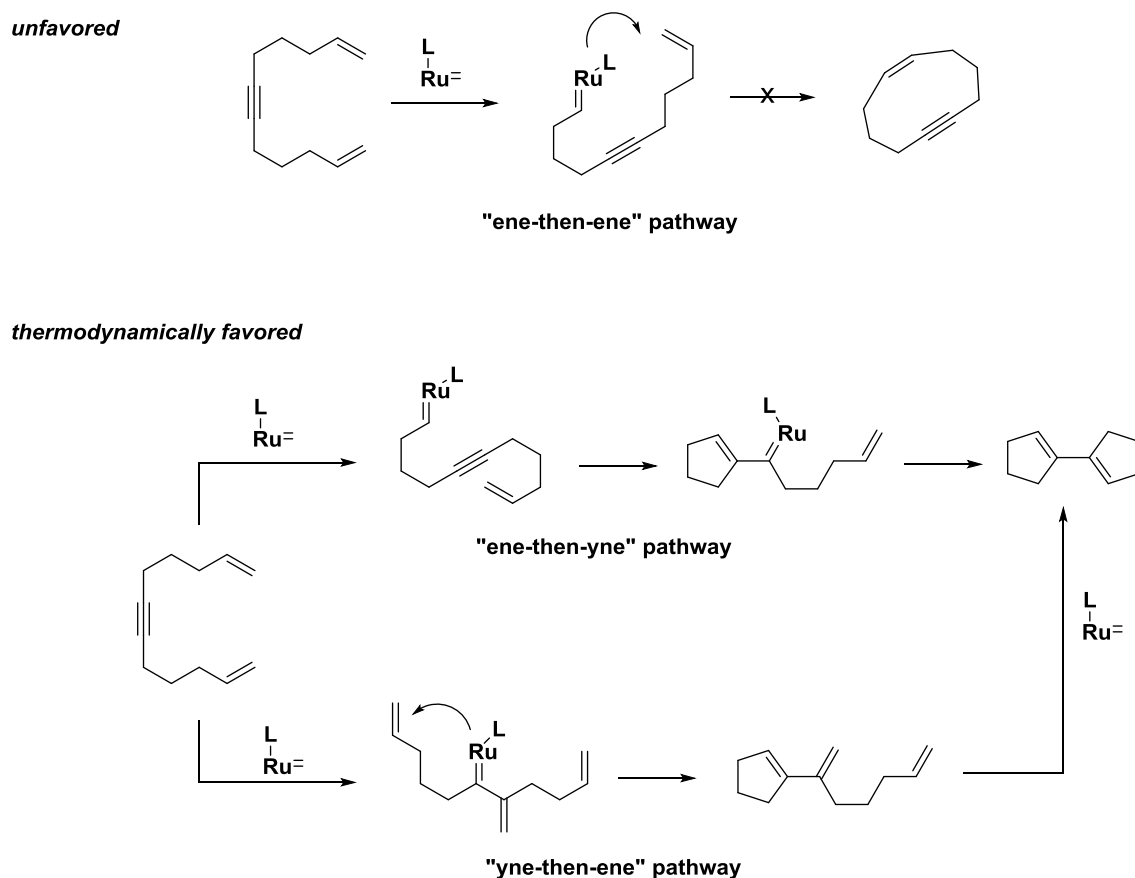
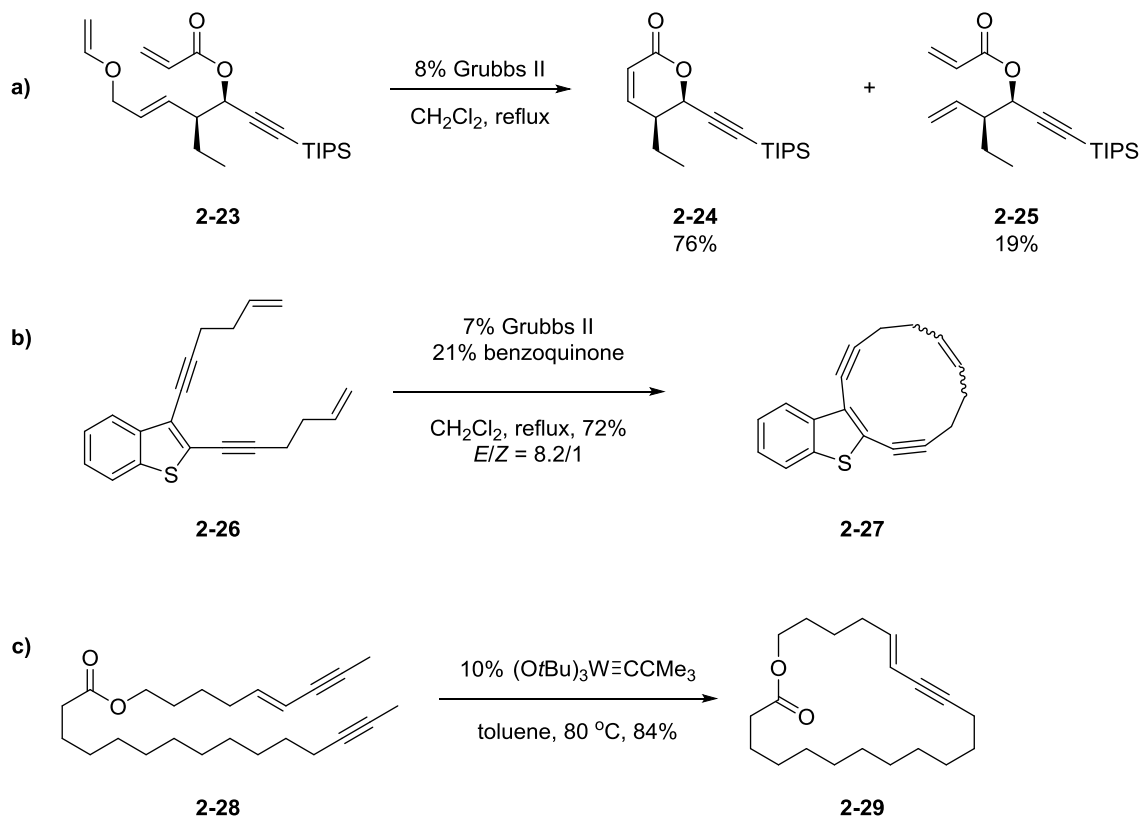


Figure 2.2. Mechanisms of ene-ene RCM and ene-yne RCM reactions of dienynes

A few exceptions to this chemoselectivity were observed when the alkyne is sterically hindered by bulky silyl groups blocking the ene-yne insertion path²⁸ (Scheme 2.5a)^{28b} or the alkyne is too strained to undergo ring closing ene-yne metathesis²⁹ (Scheme 2.5b).^{29a} In addition, the Fürstner group showed that ring closing yne-yne metathesis can be favored over ene-yne metathesis and cyclic enynes can be synthesized only when specialized Schrock alkylidyne complexes are used together with conjugated enediyne substrates^{11d,30} (Scheme 2.5c).³⁰ These

yne-yne RCM reactions did not occur in the presence of classical Grubbs catalysts and instead produced mixtures of oligomers.



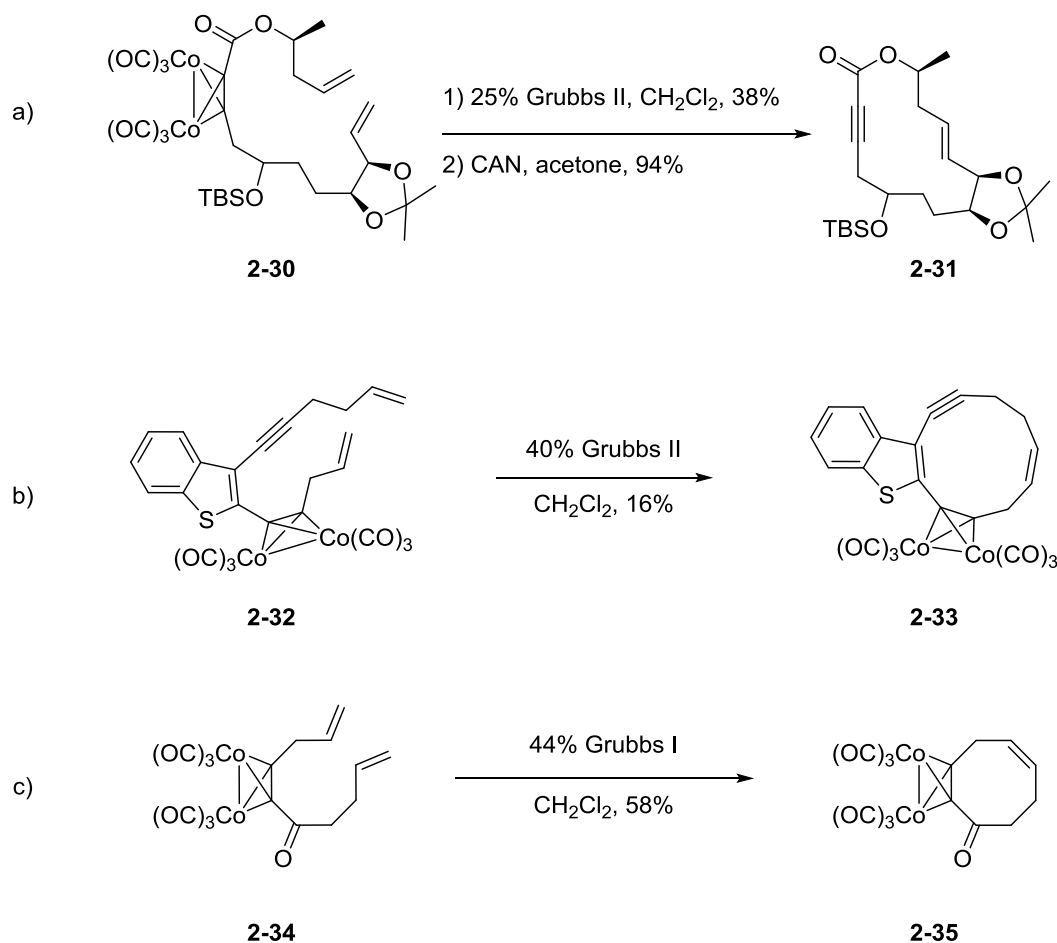
Scheme 2.5. Examples of exceptional cases to ene-yne RCM reaction selectivity

2.2. Results and Discussion

2.2.1. Dicobalt Hexacarbonyl Complexes as Protected Alkynes in RCM Reactions

Our main objective was to build a library of enyne rings that could serve as substrates for various transannular reactions and we wanted to utilize the versatile metathesis method to access the desired cyclic enynes. However, as outlined in section 2.1.2, an efficient, general ene-ene metathesis reaction with acyclic dienyne requires that the alkyne units must be protected. Previously, dicobalt hexacarbonyl complexes were used as protected alkynes in RCM

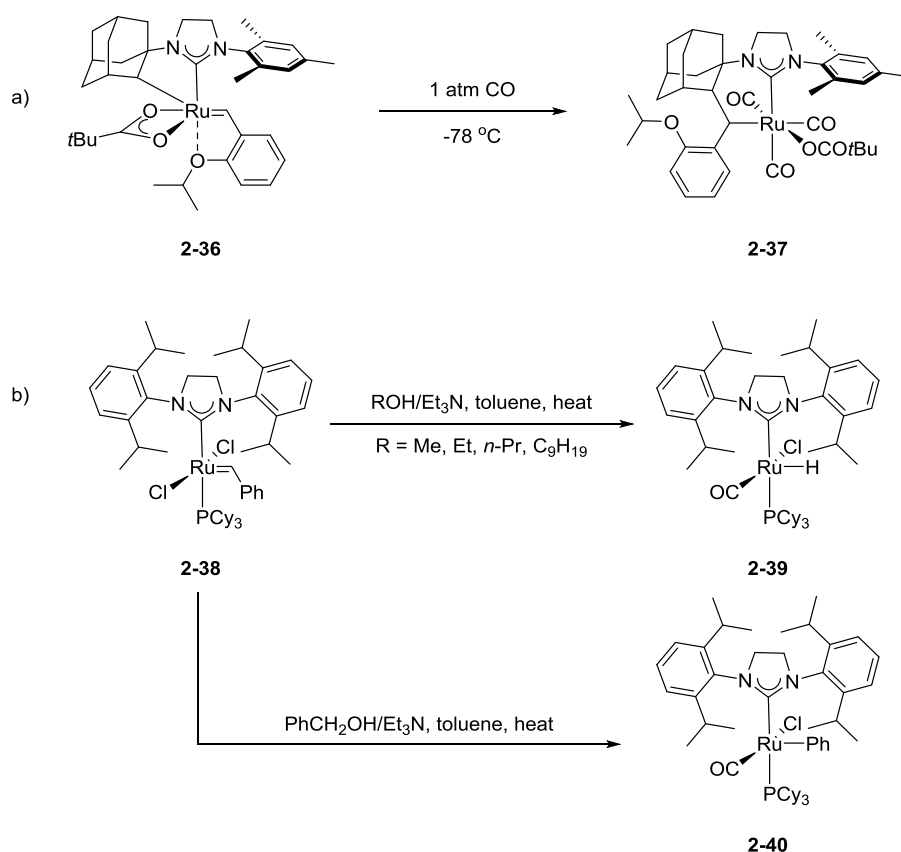
reactions.^{11c,26a-c,29b,31} In these examples, dicobalt hexacarbonyl-alkyne complexes did not go through carbene insertions into alkynes allowing ene-ene RCM reactions to occur and in some cases the alkene-like geometries of dicobalt complexes enhanced the metathesis reactions by releasing ring strain in the final cyclic products or by pushing the alkene tethers of diyne substrate close to each other (Scheme 2.6a,^{11c} 2.6b,^{29b} 2.6c^{31c}).



Scheme 2.6. Examples of ene-ene RCM reactions with dicobalt hexacarbonyl-alkyne complexes

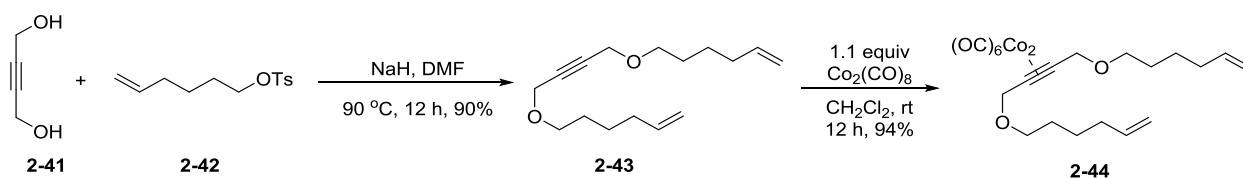
However, in syntheses using dicobalt hexacarbonyl complexes as protected alkynes, various side reactions, high catalyst loadings and poor yields should be expected. Most RCM reactions

require heat^{25a} and dicobalt complexed dienyne can readily undergo thermal Pauson-Khand reactions forming cyclopentenones.^{26c,31e,32} The main cause of high catalyst loadings and low yields, on the other hand, is the release of π -acidic CO when dicobalt hexacarbonyl complexes are subjected to even small amounts of heat. The released CO rapidly coordinates to the metal center of the metathesis catalyst. Due to a competition in π -back bonding, the pre-catalyst loses its ability to stabilize the alkylidene and in turn produces metathesis inactive metal complexes³³ (Scheme 2.7a).^{33e} Moreover, it was reported that when primary alcohols are used to quench metathesis reactions in the presence of bases, alcoholysis generates CO molecules that act as the main quencher rather than the alkoxy or alcohol molecules^{33e-i} (Scheme 2.7b).^{33h}



Scheme 2.7. Deactivation of metathesis catalysts with CO

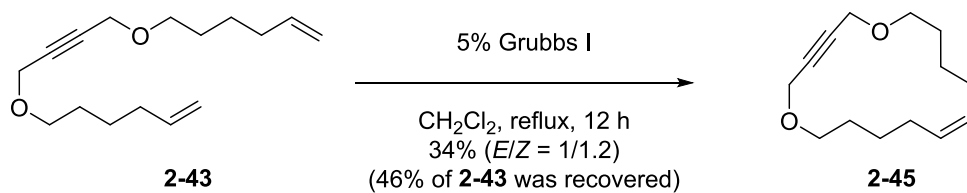
The destructive effects of CO molecules on metathesis catalysts were also demonstrated experimentally during our studies. Acyclic dienyne **2-43** was synthesized by NaH-promoted nucleophilic substitution reaction of commercially available but-2-yne-1,4-diol (**2-41**) with *p*-methylbenzenesulfonate **2-42** and the dicobalt hexacarbonyl complex **2-44** was obtained in high yield through complexation of dienyne **2-43** with dicobalt octacarbonyl (Scheme 2.8).



Scheme 2.8. Synthesis of dienyne 2-43 and dicobalt complex 2-44

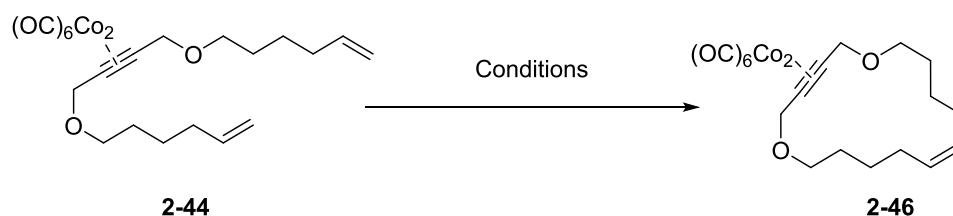
Dienyne **2-43** was subjected to RCM reaction conditions. In the presence of 5% Grubbs' 1st generation catalyst (Grubbs I), cyclic enyne **2-45** was formed in a mere 34% yield as a mixture of *E* and *Z* isomers³⁴ together with unidentifiable metathesis side products and unreacted starting material with 46% recovery (Scheme 2.9). Then complex **2-44** was tested for RCM reaction to synthesize dicobalt hexacarbonyl-enyne ring **2-46**, but the trials were even less successful than the RCM reaction of “unprotected” dienyne **2-43** (Table 2.1). Experimental conditions that afforded cyclic enyne **2-45** did not produce any dicobalt-complexed RCM product (Table 2.1 entry 4), toluene was not the proper choice of solvent (Table 2.1 entry 2) and the more reactive³⁵ Grubbs' 2nd generation catalyst (Grubbs II) was completely ineffective (Table 2.1 entry 3). We achieved to synthesis of **2-46** by performing the RCM reactions at lower temperatures in order to decrease the amount of CO generated and increased the catalyst loadings (Table 2.1 entries 1, 5 and 6). However, the reaction yields were very low since lowering the temperature also decreased the metathesis reaction initiation rates significantly.^{25a} These experimental results

showed that development of an alternative alkyne protection method for metathesis reactions is essential.



Scheme 2.9. Synthesis of cyclic enyne **2-45** via RCM reaction of “unprotected” dienyne **2-43**

Table 2.1. Synthesis of cyclic enyne complex **2-46**

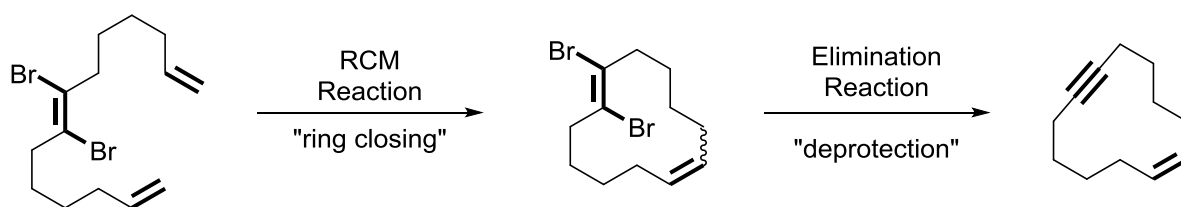


Entry	Temperature (°C)	Catalyst	Catalyst (%)	Time (h)	Solvent	Yield (%) ^a
1	25	Grubbs I	2	12	CH ₂ Cl ₂	12
2	25	Grubbs I	5	12	toluene	0
3	25	Grubbs II	5	12	CH ₂ Cl ₂	0
4	40	Grubbs I	5	24	CH ₂ Cl ₂	0
5	25	Grubbs I	15	24	CH ₂ Cl ₂	14
6	0	Grubbs I	10	72	CH ₂ Cl ₂	13

^aThe yields were determined by ¹H-NMR. Only Z isomer was observed.

alkenes since their metathesis reactions create quaternary Cs located α to the metal centers in the metallacyclobutene intermediates.^{25a}

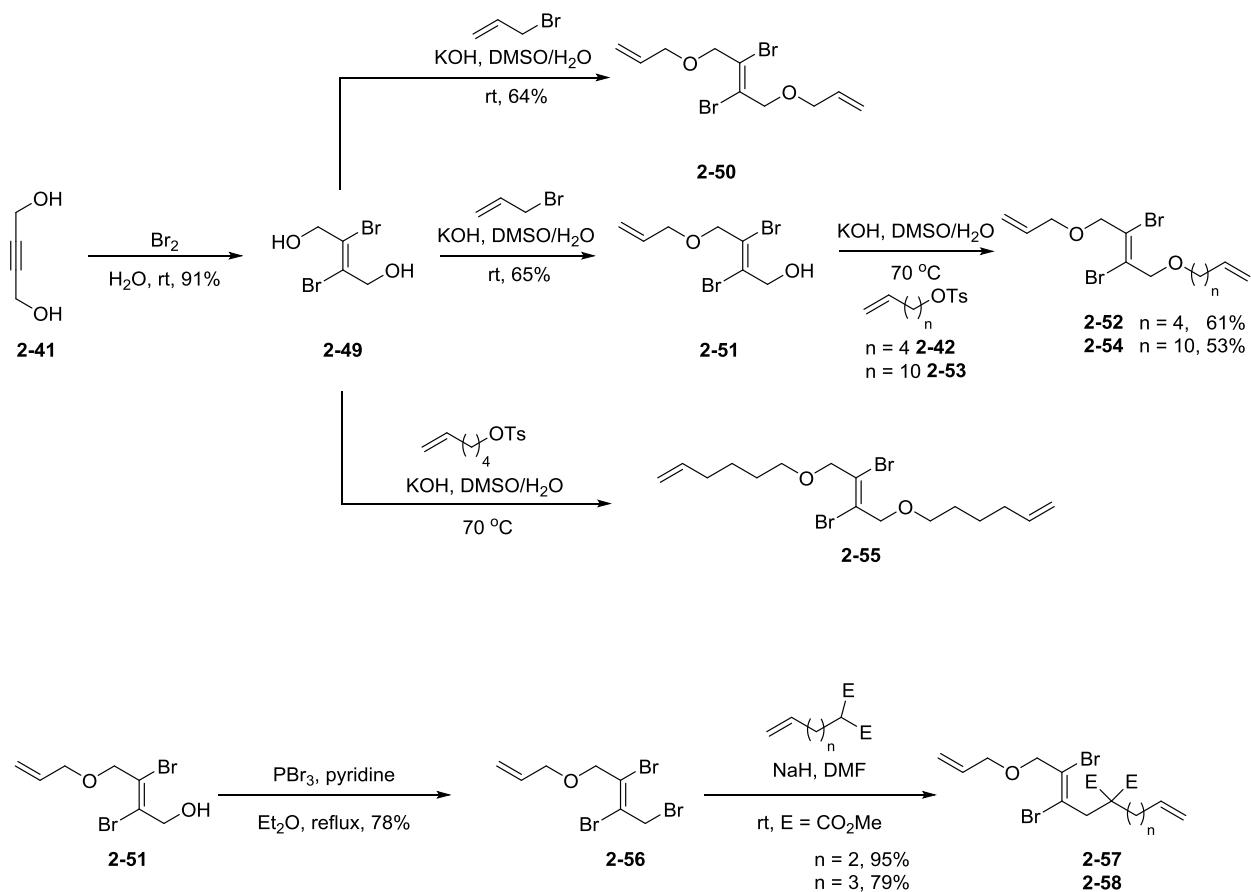
We decided to utilize this lack of reactivity of tetra-substituted alkenes as the basis for a new alkyne protection strategy (Scheme 2.11). We proposed that converting the alkyne units of dienyne into tetra-substituted *vic*-dibromoalkenes would make them inert in metathesis reactions and ene-ene RCM would be preferred. The resultant cyclic dienes would be easily “deprotected” via elimination reactions providing the desired cyclic enynes. To our knowledge, since its discovery in late 1800s, alkyne bromination has been employed as a protection method in only two cases; acetylenediamide synthesis³⁸ and acetylenedicarboxylic acid ester synthesis.³⁹ In this regard, our strategy would provide a unique and interesting modern entry to this synthetic methodology.

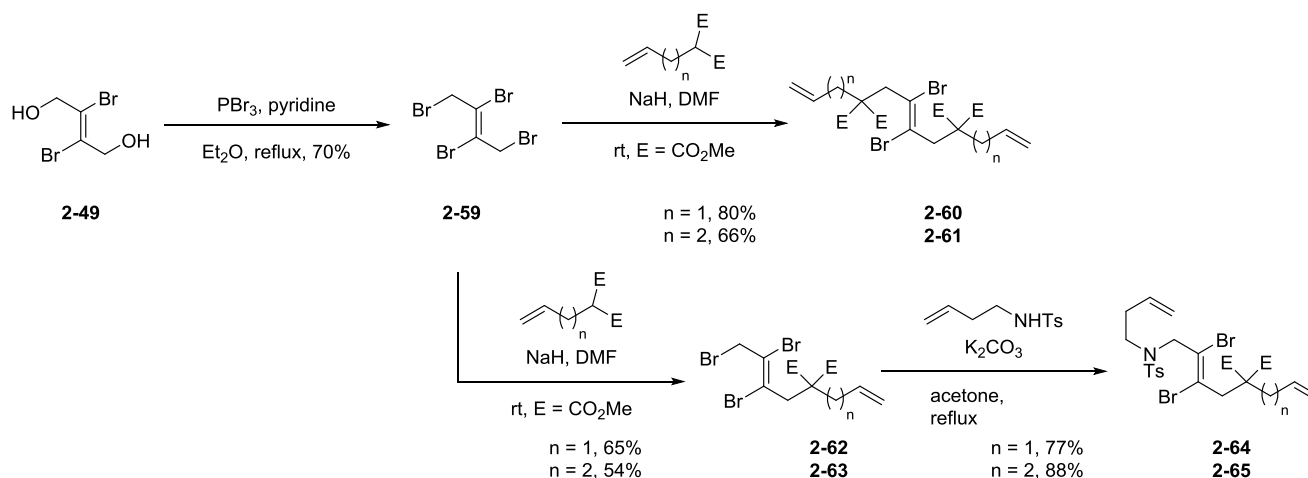


Scheme 2.11. A new synthetic strategy to access cyclic enynes

A library of novel RCM reaction substrates was prepared by simple base-promoted substitution reactions and fully characterized (Scheme 2.12, the details are enclosed in the experimental section). Synthon (*E*)-2,3-dibromobut-2-ene-1,4-diol **2-49** was synthesized by bromination of commercially available diol **2-41** and easily purified through extraction. Diol **2-49** was then subjected to allyl bromide and a number of *p*-methylbenzyl sulfonates in the presence of KOH to synthesize diether RCM substrates **2-50**, **2-52**, **2-54** and **2-55**. Interestingly, synthesis of these diether substrates failed when the diol **2-49** was treated with hydride bases

which lead to decomposition. Monoether substrates **2-57** and **2-58** were prepared in good yields through the reactions of tribromodiene **2-56** with dimethyl malonate derivatives. Further bromination of **2-49** provided tetrabromo synthon **2-59** (Scheme 2.12). NaH- and K_2CO_3 -promoted substitution reactions of **2-59** afforded all-carbon triene substrates **2-60**, **2-61** and sulfonamide containing triene substrates **2-64**, **2-65**, respectively.

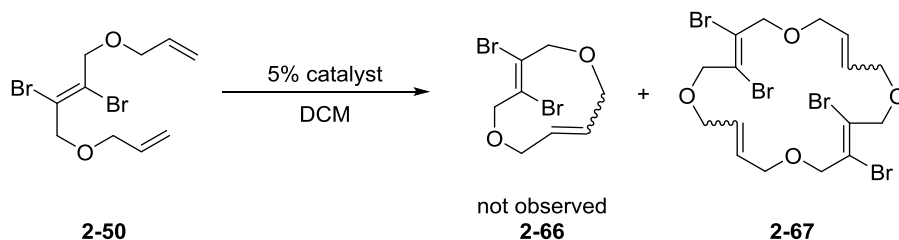




Scheme 2.12. Synthesis of RCM reaction substrates

The triene **2-50** was subjected to various RCM conditions to synthesize the 10-membered diene ring **2-66** (Table 2.2). Room temperature RCM reactions with Grubbs I and Grubbs II catalysts were not effective and mixtures of oligomers were obtained together with unreacted starting material (Table 2.2 entries 1 and 2). Being polyethers these oligomers were highly polar and they could not be readily isolated. However, the room temperature experiment with Grubbs I did afford the less polar **2-67** in 10% yield as the major oligomer. Based on high resolution mass spectroscopy results and NMR spectra **2-67** was predicted to be the 20-membered tetraene ring in the form of a mixture of *ZZ*, *EE*, *EZ* isomers in an unidentifiable ratio. This structure is the RCM product of the dimer which formed via intermolecular metathesis of two **2-50** molecules. Lowering the concentration of **2-50** decreased the amount of oligomers formed through further intermolecular metathesis reactions and increased the yield of **2-67** by favoring the intramolecular reaction of the dimer of **2-50** (Table 2.2 entry 3 vs 6). The metathesis reactivity of **2-50** was increased with higher temperatures and longer reaction times, but the desired 10-membered ring **2-66** did not form.

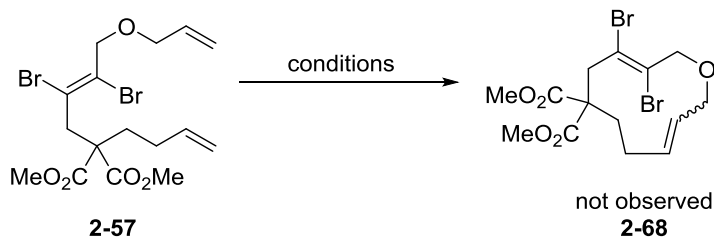
Table 2.2. Attempted synthesis of 10-membered cyclic diene 2-66 by a RCM reaction



Entry	Temperature (°C)	Catalyst	Concentration of 2-50 (M)	Time (h)	Recovered 2-50 (%)	Yield of 2-67 (%) ^a
1	25	Grubbs I	0.005	4	13	10
2	25	Grubbs II	0.005	4	34	0
3	40	Grubbs I	0.005	12	0	30
4	40	Grubbs II	0.005	6	0	0
5	40	Grubbs I	0.002	6	75	0
6	40	Grubbs I	0.002	12	0	50

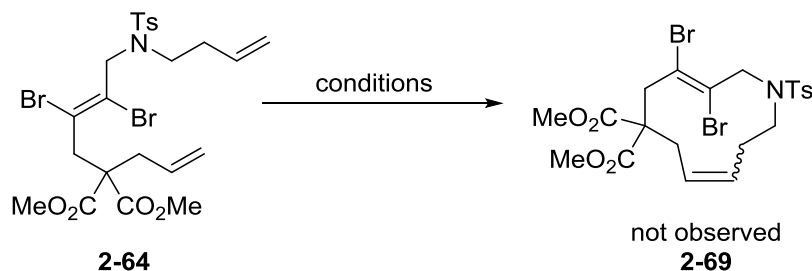
^aThe yields are of isolated products.

Considering formation of 20-membered dimer RCM product **2-67**, the cause of the failed RCM reactions seemed to be the high ring strain in the target 10-membered molecule **2-66** rather than the existence of *vic*-dibromoalkene units. Possibly due to the same reason the synthesis of 11-membered monoether diene ring **2-68** from substrate **2-57** could not be achieved even under heated reaction conditions with reactive catalysts (Scheme 2.13). High dilution or dropwise addition of **2-57** could not block the oligomerization pathways. Likewise 11-membered sulfonamide containing diene ring **2-69** was also not observed after various RCM reaction conditions were applied on substrate **2-64** (Scheme 2.14).



5% Grubbs I, DCM (0.002M), reflux, 16 h (only a mixture of oligomers was formed)
 10% Grubbs II, DCM (0.004M), **2-57** was added dropwise over 5 h, reflux (76% of **2-57** was recovered)
 10% Grubbs II, DCM (0.004M), **2-57** was added dropwise over 12 h, reflux (only a mixture of oligomers was formed)
 5% Grubbs I, DCM (0.001M), reflux, 12 h (10% of **2-57** was recovered)

Scheme 2.13. Attempted synthesis of 11-membered cyclic diene **2-68** by a RCM reaction



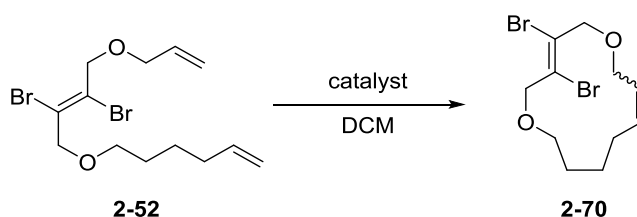
5% Grubbs I, DCM (0.002M), reflux, 20 h (76% of **2-64** was recovered)
 10% Grubbs I, DCE (0.004M), reflux, 18 h (75% of **2-64** was recovered)
 5% Grubbs II, DCM (0.002M), reflux, 12 h (only a mixture of oligomers was formed)

Scheme 2.14. Attempted synthesis of 11-membered cyclic diene **2-69** via a RCM reaction

To avoid oligomerization products we switched to larger rings, so triene **2-52** was tested to synthesize the 13-membered ring **2-70** (Table 2.3). At room temperature with Grubbs I catalyst the target ring was formed in 30% yield with a 8/1 ratio of *E/Z* isomers (Table 2.3 entry 1) but this experiment was not efficient as the catalyst loading was too high (20%). A trial with the more reactive Grubbs II catalyst failed to form **2-70** and instead gave a mixture of decomposition products (Table 2.3 entry 2). Contrary to dicobalt hexacarbonyl complexes, our alkyne protection group was expected to be tolerant to heat so we tested the RCM reaction of **2-52** in refluxing DCM and the reaction successfully afforded **2-70** in 69% yield as a 2.5/1 mixture of *E/Z* isomers (Table 2.3 entry 3). This showed that in addition to avoiding catalyst decomposition, another

advantage of using heat-tolerant protecting groups in RCM reactions was to be able to compensate for the decrease in initiation rate caused by the high dilution of substrate. In refluxing DCM, Hoveyda-Grubbs' 2nd generation catalyst (Grubbs III) was ineffective (Table 2.3 entry 4) while Grubbs II catalyst was too active and produced an unidentifiable mixture of metathesis products (Table 2.3 entry 5).

Table 2.3. Synthesis of cyclic diene 2-70 via RCM reaction



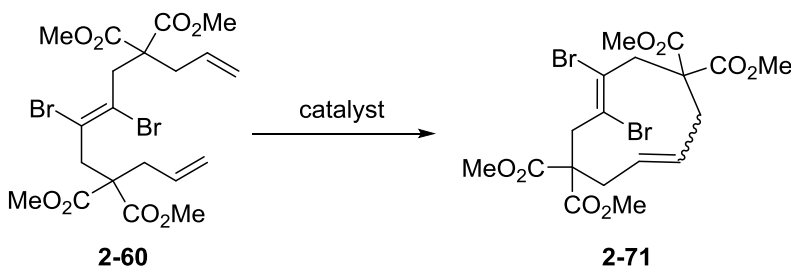
Entry	Temperature (°C)	Catalyst	Catalyst (%)	Time (h)	Concentration of 2-52	Yield (%) ^a (E/Z)
1	25	Grubbs I	20	12	0.005	30 (8/1)
2	25	Grubbs II	5	12	0.005	0
3	40	Grubbs I	5	12	0.002	69 (2.5/1)
4	40	Grubbs III	5	12	0.002	10 (1/0)
5	40	Grubbs II	5	12	0.002	0

^aThe yields are of isolated products.

All-carbon rings are known to have less strain compared to their heteroatom bearing analogs as C-C σ -bonds (~154 pm) are longer than C-O (~143 pm) and C-N σ -bonds (~147 pm).^{24b} As a result, although the rings **2-66**, **2-68** and **2-69** were failed to form, we tested the ability of all-carbon 10-membered ring **2-71** to be prepared (Table 2.4). In contrast with diether substrate **2-**

50, all-carbon triene **2-60** was quite resistant to oligomerization, but it also exhibited low activity in RCM reactions. Optimum reaction conditions from studies on the synthesis of **2-70** (Table 2.3 entry 3) afforded only a trace amount of **2-71** and 90% of the starting molecule was recovered (Table 2.4 entry 1). Higher temperatures and longer reaction times did not improve the yield dramatically (Table 2.4 entry 2, 78% of **2-60** was recovered). In order to increase the metathesis reaction rate both substrate concentration and catalyst loadings were increased (Table 2.4 entries 4-6. For entry 5; 68% of **2-60** was recovered). Fortunately, under these conditions with more reactive Grubbs II catalyst, ring **2-71** was obtained in a 90% yield as a 1/5 mixture of *E/Z* isomers (Table 2.4 entry 6).

Table 2.4. Synthesis of 10-membered cyclic diene 2-71 via a RCM reaction



Entry	Temperature (°C)	Catalyst	Catalyst (%)	Time (h)	Solvent	Yield (%) ^a (<i>E/Z</i>)
1^b	40	Grubbs I	5	12	CH ₂ Cl ₂	2 (1/0)
2^b	85	Grubbs I	5	36	DCE	9 (1.7/1)
3^b	40	Grubbs II	5	12	CH ₂ Cl ₂	50 (1/5.3)
4^c	40	Grubbs I	10	36	CH ₂ Cl ₂	54 (1.7/1)
5^c	85	Grubbs I	10	36	DCE	2 (1/0)
6^c	40	Grubbs II	10	12	CH ₂ Cl ₂	90 (1/5)

^aThe yields are of isolated products. ^bConcentration of **2-60** was 0.002M. ^cConcentration of **2-60** was 0.004M.

We applied these optimized RCM reaction conditions (Table 2.3 entry 3, table 2.4 entry 6 for **2-71**) to various dibromotriene substrates and obtained diene macrocycles that served as cyclic enyne precursors in good to high yields (Figure 2.3). The reaction scope involves all carbon diene rings (**2-71**, **2-72**), a cyclic monoether (**2-74**), cyclic diethers (**2-70**, **2-75**, **2-76**) and a cyclic sulfonamide (**2-73**). Tetrasubstituted *vic*-dibromoalkenes thus served as excellent protected alkyne groups since the cyclization yields were high and each reaction went smoothly providing only the ene-ene RCM product. The methodology was not limited to formation of medium rings. 19-membered **2-76** and 16-membered **2-75** were synthesized successfully in 65% and 87% yields respectively (Figure 2.3).

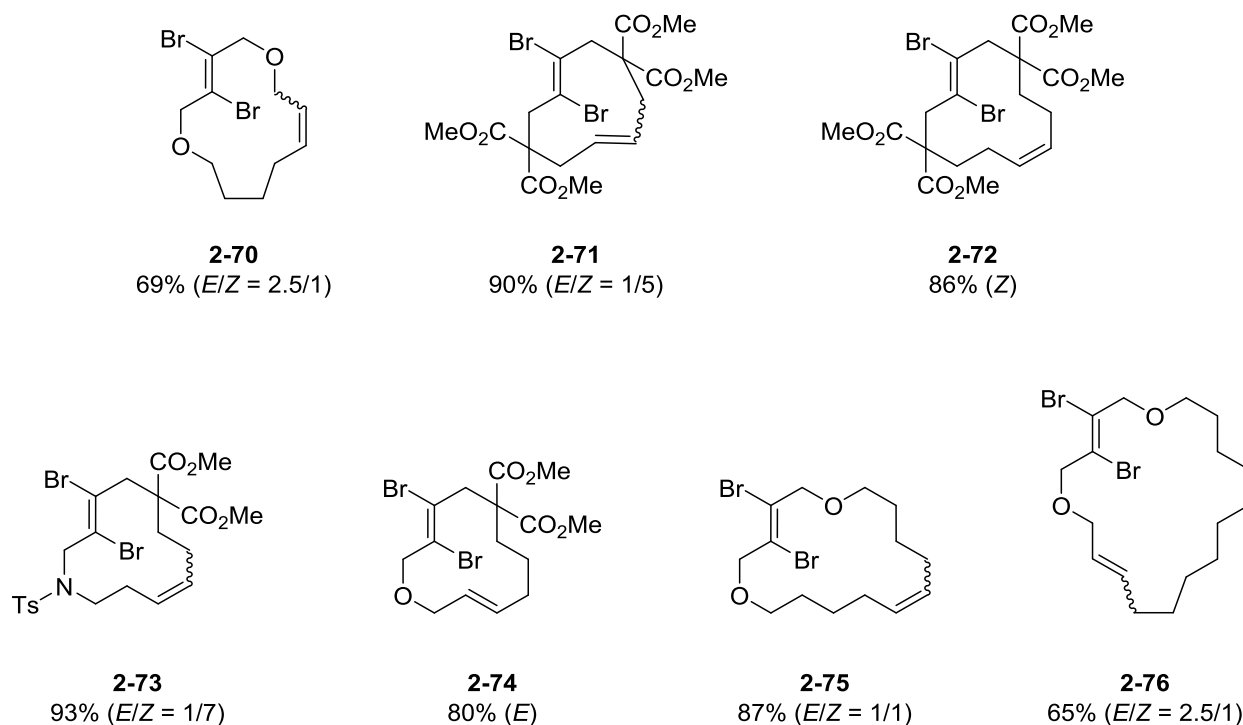
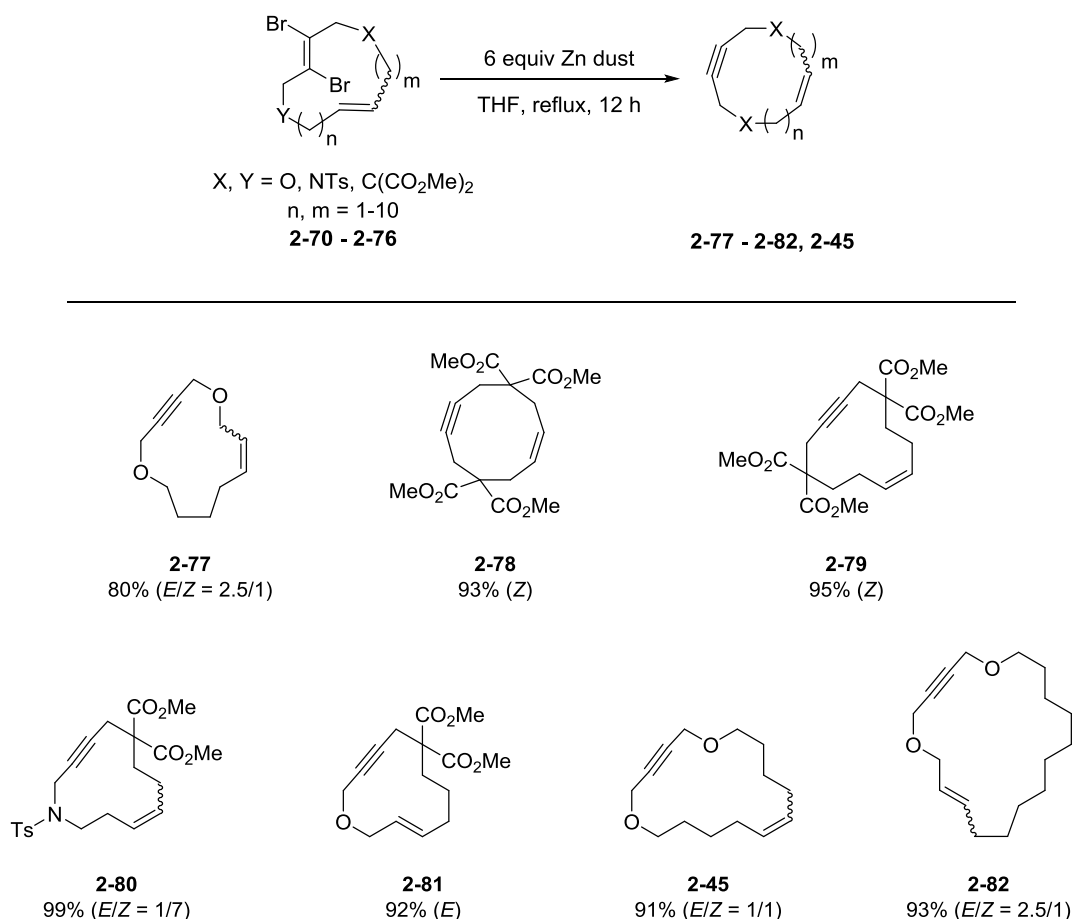


Figure 2.3. Protected cyclic enynes synthesized by RCM reactions

Although the *Z*-geometry is favored for the formation of small and medium alkene rings, stereoselective synthesis of large rings by metathesis is challenging. Recently, detailed investigations on the preparation and applications of stereoselective macrocyclic RCM catalysts were conducted by the Grubbs⁴⁰ and Hoveyda⁴¹ research groups. Studies showed that traditional metathesis catalysts (e.g. Grubbs I, Grubbs II and Grubbs III) lack kinetic selectivity and the corresponding *E/Z* ratios are determined by the relative stabilities of the macrocyclic isomers. Therefore; the stereochemical outcome is affected by the ring size and/or substitution patterns.^{40,41} RCM reactions of dibromotrienes also exhibited similar behavior. While formation of symmetric 16-membered **2-75** showed no stereoselectivity, smaller ring 13-membered **2-70** and larger ring 19-membered **2-76** were formed with the same *E/Z* ratio (2.5/1). Moreover, we observed a pronounced allylic chalcogen effect⁴² in macrocyclic RCM reactions. Under the same conditions 12-membered all-carbon ring **2-72** and 12-membered monoether ring **2-74** were synthesized as single isomers, but with complete reversal of stereochemistry. In fact, metathesis substrates with allyl ether tethers (**2-52**, **2-53** and **2-58**) gave the *E* macrocyclic isomers as the single or major isomer (Figure 2.3).

The ¹H NMR spectra of rings **2-70** – **2-75** exhibited unexpected diastereotopicity for protons α and β to the dibromoalkene units. This was attributed to rigidity imposed by the bromine atoms restricting rotations leading to favored conformations with the geminal methylene protons and esters located in different environments. Such behavior was not exhibited by the larger and less strained 19-membered ring **2-76**. The *Z*-isomer of **2-71** was particularly interesting with regard to the diastereotopicity. The ¹H NMR displayed two distinct sets of multiplets for the vinyl protons, suggesting it exists as a mixture of two conformers with planar chirality and interconversion between the enantiomeric conformers is slow on the NMR time scale.

The next step was to deprotect macrocyclic dienes (Figure 2.3 **2-70** – **2-76**) to access enyne rings. To our delight, inexpensive and easy to handle Zn dust promoted deprotection and the target cyclic enynes were formed in excellent yields (Scheme 2.15). Conveniently, the stereoisomeric distributions were not affected during the deprotection reactions and the *E/Z* ratios of macrocyclic isomers were maintained.



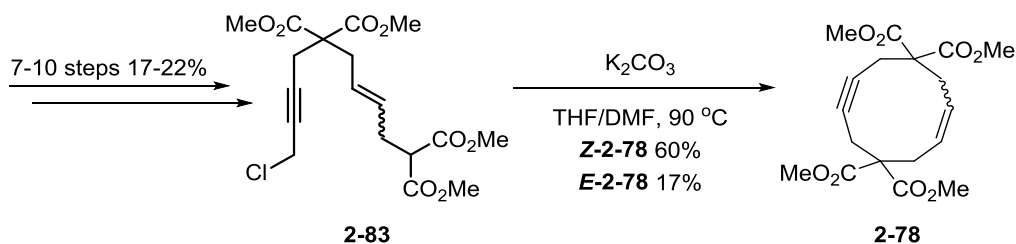
Scheme 2.15. Synthesis of cyclic enynes by Zn-promoted deprotection reactions

As previously mentioned, enyne rings with allyl and homoallyl moieties cannot be synthesized by RCM of unprotected acyclic dienynes since the ene-yne RCM reactions are preferred. Our new synthetic strategy, on the other hand, allows efficient access to those cyclic

enynes. In addition, our method has proven superior to alkyne protection through $\text{Co}_2(\text{CO})_8$ complexation. Macrocyclic **2-45** and its dicobalt-complexed counterpart **2-46** were formed in poor yields by RCM reactions of acyclic enynes **2-43** and **2-44** respectively (**2-45** was formed in 34% yield, **2-46** was formed in 14% yield, Scheme 2.9 and Table 2.1) while the new metathesis protocol provided **2-45** with a 79% overall yield (Figure 2.3 and Scheme 2.15).

The synthesis of 10-membered cyclic alkynes is challenging. Deslongchamps prepared enyne **2-78** as a mixture of the monomer and the dimer via an intramolecular nucleophilic substitution reaction.^{13d} This base-promoted intramolecular substitution method formed the *Z* isomer of **2-78** in a 60% yield and the more strained, less stable isomer *E* in a mere 17% yield from the *Z* and *E* acyclic enynes, respectively (Scheme 2.16). Synthesis of cyclic enyne **2-78** was also somewhat problematic via the elimination method. Diene **2-71** required harsher reaction conditions for the completion of the deprotection process. After testing several conditions (details are reported in the experimental section) we determined that when a THF solution of **2-71** was heated in a sealed tube at 60 °C for 4 days complete consumption of **2-71** occurred. As a result of this deprotection reaction only more stable *Z* isomer of **2-78** was isolated in a 93% yield (total product yield was 78%) and the less stable *E* isomer was not detected. Our approach to the challenging synthesis of this 10-membered enyne was proven to be more versatile than Deslongchamps's intramolecular substitution approach. While RCM substrate **2-60** was prepared in 3 steps and 1 column chromatography purification in a 51% overall yield (Scheme 2.12), intramolecular substitution reaction substrate **Z-2-83** was prepared in 7 steps and 6 column chromatography purifications in a 17% overall yield and **E-2-83** was prepared in 10 steps and 8 column chromatography purifications in a 22% overall yield.^{13d} In addition, our RCM strategy afforded **Z-2-78** in a total of 5 steps with a 36% overall yield while Deslongchamps's method

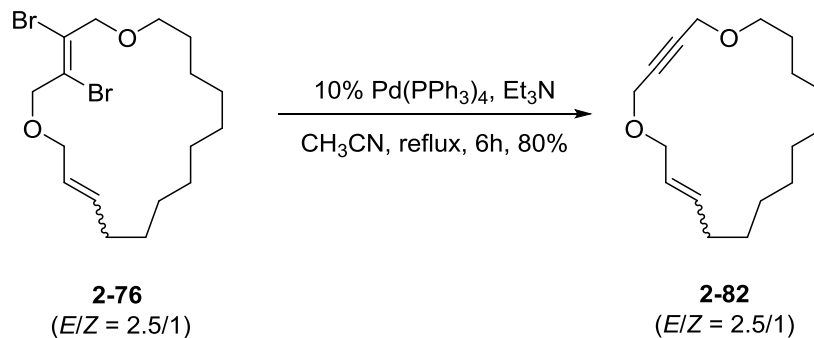
required an 8-step synthesis of the same molecule with a 10% overall yield. This is a simple example of the advantages achieved by metathesis reactions in ring closing transformations which avoid the synthesis of substrates with the chain ends functionally differentiated.



Scheme 2.16. Synthesis of *E*- and *Z*-2-78 reported by Deslongchamps

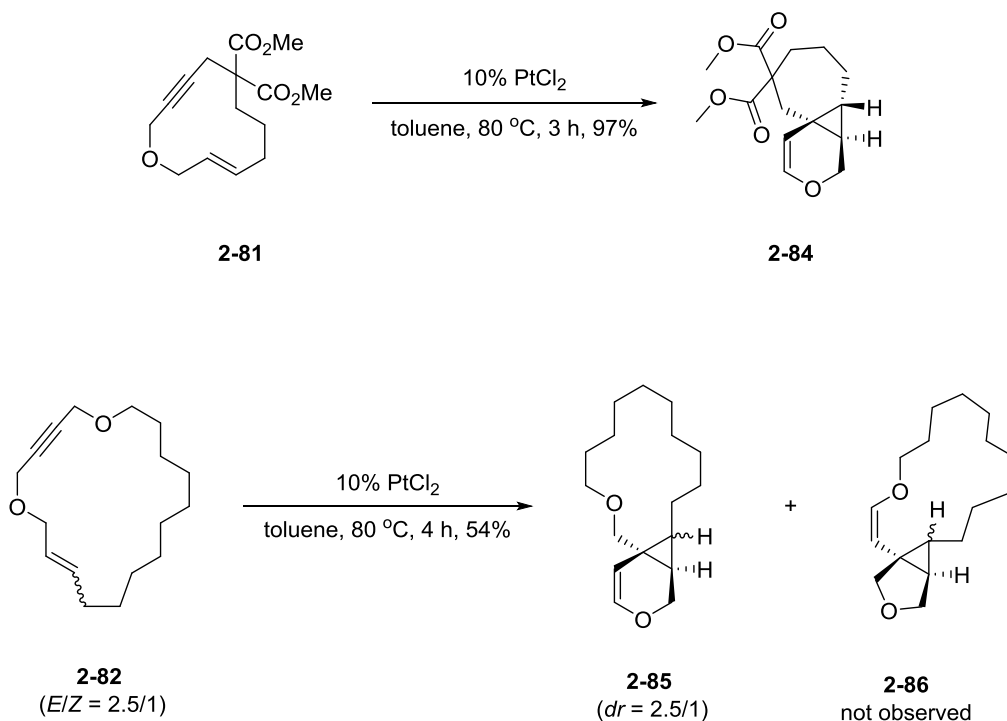
2.2.3. Transannular Reactions

As discussed in detail in Chapter 1, there is a wide range of fascinating transannular reactions in which macrocycles can participate. One of those transformations is transannular coupling reactions (Chapter 1 section 1.6). In order to demonstrate the utility of the macrocycles prepared through RCM reactions, a possible transannular Heck coupling⁴³ of diene **2-76** was tested (Scheme 2.17). Unfortunately Pd(0) was more suited to promote elimination of vicinal bromides as enyne **2-82** was obtained in 80% yield and no coupling product was detected.



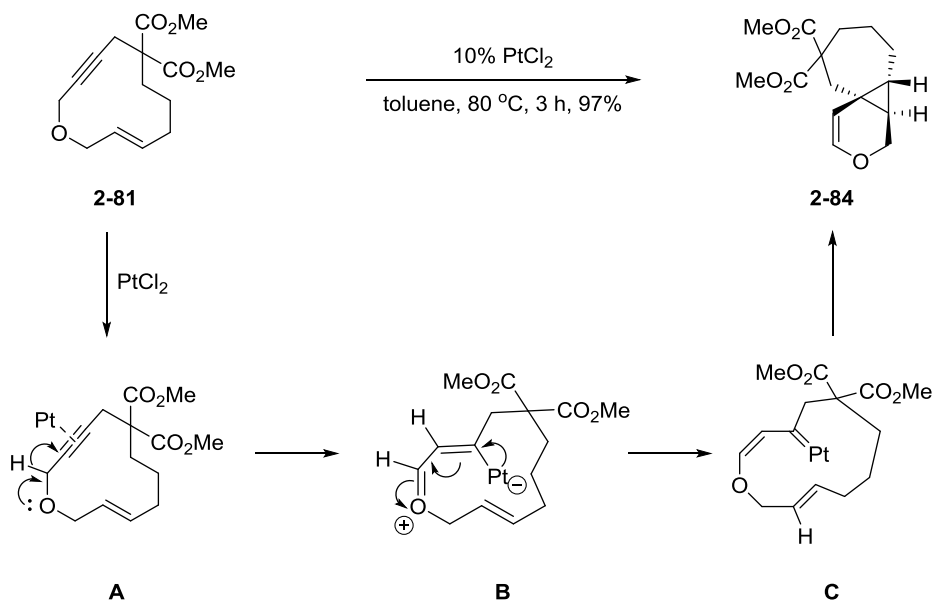
Scheme 2.17. Attempted transannular Heck coupling of 2-76

Among the macrocycles taking part in polycycle syntheses through transannular reactions the enyne sub-class is one of the most widely used (Chapter 1 sections 1.4, 1.7 and 1.8)¹² so we shifted our focus to testing the transannular reactions of our synthesized novel enyne rings. Platinum-catalyzed intramolecular cyclopropanations of acyclic allyl propargyl ethers^{44,45} has extensively been investigated. In addition, this organometallic reaction was applied in a transannular fashion using 1,5-enyne rings with exocyclic alkoxy substituents at the propargylic positions by the Malacria research group (Chapter 1 scheme 1.8).^{12a} Inspired by these reported examples we subjected macrocycles **2-81** and **2-82** to Pt(II)-catalyzed, ligand-free, cyclopropanation reactions and tricyclic enol ethers **2-84** and **2-85** were successfully synthesized in good yields (Scheme 2.18).



Scheme 2.18. Pt-catalyzed transannular cyclopropanations of **2-81** and **2-82**

Detailed experimental^{12a,44,45} and theoretical⁴⁶ studies revealed that Pt-catalyzed cyclopropanations are regio- and diastereoselective. We observed similar selectivities in the synthesis of **2-84** and **2-85**. Inferring from previous investigations we propose the reaction mechanism illustrated in Scheme 2.19. Transannular cycloisomerization involves an initial 1,2-hydride shift in the enyne-Pt complex **A** leading to allylic platinacarbene **C** through oxonium intermediate **B**. Stereospecific cyclopropanation^{44,45,46} of carbene **C** affords the polycycle **2-84**. Formation of the vinyl carbene is facilitated by delocalization of lone pair electrons from the β -heteroatom.^{12a,45f,g,46} As expected, Pt-catalyzed reaction of *E*-enyne **2-81** produced a single diastereomer **2-84** and the heteroatom effect dictated the regioselectivity. The stereoisomeric ratio of **2-82** was preserved in the cycloisomerization due to the stereospecific cyclopropanation step (formation of product from intermediate **C** in Scheme 2.19) and NMR spectra of polycycle **2-85** confirmed that formation of the 3,4-dihydropyran ring was preferred over formation of the tetrahydrofuran moiety (Scheme 2.18 structure **2.86**).



Scheme 2.19. Proposed mechanism of Pt-catalyzed transannular cyclopropanations

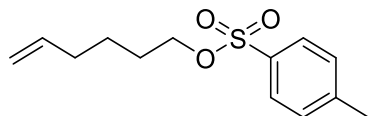
2.3. Conclusions

In conclusion, a new strategy to access macrocyclic enynes was developed. A variety of RCM reaction substrates with dibromoalkene units was prepared by simple base-promoted substitution reactions under mild conditions. *Vic*-dibromo tetrasubstituted alkenes served as excellent protected alkyne groups and (*E*)-dibromotrienes selectively went through successful ene-ene RCM reactions leading to diene rings. Novel macrocyclic enynes with various ring sizes and substitution patterns were prepared in excellent yields by facile Zn-promoted deprotection reactions. Several advantages brought about by utilizing this metathesis methodology were demonstrated. In comparison to classical S_N2 ring closing processes, cyclic enynes were obtained in a more step-economic and efficient manner by avoiding introduction of differentiated chain-end functionality into the substrates. This alkyne protection tactic employed for RCM reactions was proven superior to traditional alkyne protection methods such as by Co₂(CO)₆ complexation. Ene-ene RCM reactions in the presence of *vic*-dibromo tetrasubstituted alkenes tolerated high temperatures, various functional groups and did not demand high catalyst loadings. The utility of macrocyclic enynes was illustrated by highly stereo- and regioselective Pt(II)-catalyzed transannular cyclopropanations. We believe our new approach to cyclic enyne synthesis provides a modern and versatile entry to both alkyne protection chemistry and ring closing metathesis applications.

2.4. Experimental

General Procedures

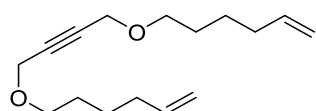
All commercial compounds were used as received unless otherwise stated. DCM and Et₃N were purified by distillation over CaH₂. THF, Et₂O and toluene were distilled prior to use from sodium-benzophenone ketyl. All reactions were carried out in flame-dried glassware under a N₂ atmosphere, unless otherwise stated. Metathesis catalysts (Materia Inc.) were stored in a glovebox and used as received. Column chromatography was performed using silica gel (Davisil, 40-63 micron) and reagent grade solvents without deactivation, unless noted. NMR spectra were recorded on a Bruker ARX-400 instrument and calibrated to the solvent signal (CDCl₃ δ = 7.26 ppm for ¹H NMR, δ = 77.0 ppm for ¹³C NMR, C₆D₆ δ = 7.16 ppm for ¹H NMR, δ = 128.0 ppm for ¹³C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), or b (broadened). IR spectra were recorded on a Jasco FTIR-4100 spectrophotometer with an ATR attachment and selected signals are reported in cm⁻¹. Mass spectra were recorded on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE Direct Analysis in Real Time (DART) ion source.



Hex-5-en-1-yl 4-methylbenzenesulfonate (2-42)

TsCl (5.2 g, 27.5 mmol) was added portionwise to a stirred and ice-cooled solution of hex-5-en-1-ol (3 mL, 25 mmol), DMAP (0.06 g, 0.50 mmol) and Et₃N (4.5 mL, 32.5 mmol) in DCM (55 mL). The mixture was stirred for 1 h at 0 °C and 12 h at room temperature. After completion, the reaction solution was diluted with DCM, washed with brine and dried over MgSO₄. The solution was filtered through silica gel and concentrated *in vacuo* to give 6.25 g (98% yield) of the known⁴⁷ colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.78 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.71 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 4.98-4.92 (m, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 2.03-1.97 (m, 2H), 1.68-1.61 (m, 2H), 1.44-1.37 (m, 2H).



1,4-bis(hex-5-en-1-yloxy)but-2-yne (2-43)

A flame-dried flask was charged with NaH (314 mg, 7.86 mmol, 60% w/w dispersion in mineral oil) and dry DMF (5 mL) under a N₂ atmosphere. The suspension was cooled to 0 °C and a solution of but-2-yne-1,4-diol (0.23 g, 2.62 mmol) in dry DMF (5 mL) was added dropwise. The mixture was stirred for 45 min at 0 °C prior to the addition of **2-42** (2.0 g, 7.86 mmol) in 3 mL dry DMF. The reaction solution was allowed to stir at 90 °C overnight. Upon completion, water was added and the crude mixture was extracted with DCM. The combined organic layers

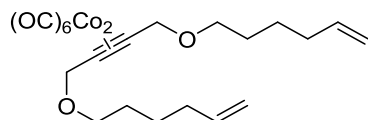
were washed with water, brine, and dried over MgSO₄. Solvent was removed *in vacuo*. Chromatography with 9:1 hexanes:EtOAc afforded 0.59 g (90% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.80 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 2H), 5.00 (bdd, *J* = 17.0, 1.8 Hz, 2H), 4.94 (bdd, *J* = 10.4, 0.8 Hz, 2H), 4.17 (s, 4H), 3.50 (t, *J* = 6.5, 4H), 2.07 (bq, *J* = 7.2 Hz, 4H), 1.64-1.57 (m, 4H), 1.40-1.42 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 138.5, 114.4, 82.2, 69.9, 58.2, 33.4, 28.8, 25.3;

IR (neat ATR): 3324, 2930, 2855, 1640, 1541, 1438, 1348, 1118, 1103, 1084, 992, 908;

HRMS (DART): calcd [M-H]⁺ 251.20056, found 251.19978.



[(Co₂(CO)₆)-(μ-η², η²-HC=C(CH₂)₄OCH₂C≡CCH₂O(CH₂)₄C=CH)] (2-44)

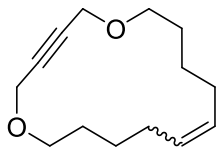
To a solution of **2-43** (0.58 g, 2.32 mmol) in DCM (30 mL) Co₂(CO)₈ (0.87 g, 2.55 mmol) was added. The mixture was stirred at room temperature for 12 h. The solvent was removed *in vacuo*. Chromatography with 15:1 hexanes/EtOAc afforded 1.17 g (94% yield) of a red oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.85-5.75 (m, 2H), 5.00 (d, *J* = 17.2 Hz, 2H), 4.94 (d, *J* = 10.0 Hz, 2H), 4.61 (s, 4H), 3.59 (t, *J* = 6.0 Hz, 4H), 2.07 (bq, *J* = 6.8 Hz, 4H), 1.63 (bp, *J* = 7.0 Hz, 4H), 1.48 (bp, *J* = 7.0 Hz, 4H);

¹³C NMR (100 MHz, C₆D₆, ppm) δ: 199.8 (CO), 138.5, 114.4, 92.8 (Co-C≡C-Co), 70.73, 70.63, 33.4, 29.1, 25.3;

IR (neat ATR): 2940, 2861, 2092, 2049, 2007, 1644, 1435, 1338, 1100, 992, 909;

HRMS (DART): calcd $[M-O(CH_2)_4C=CH]^+$ 436.94763, found 436.94687.



Synthesis of 1,6-dioxacyclohexadec-11-en-3-yne (2-45) via Metathesis of 2-43

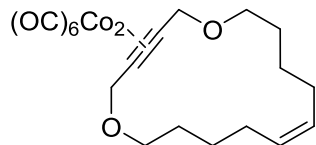
2-43 (0.106 g, 0.423 mmol) was reacted with Grubbs' 1st generation catalyst (17 mg, 0.05 mmol) in DCM at 40 °C for 12 h and chromatography with 9:1 hexanes/EtOAc afforded 32 mg of a colorless oil (34% NMR yield, *E/Z* ratio 1/1.2). After chromatography 14 mg of the *Z* isomer was isolated together with 49 mg of 1,4-bis(hex-5-en-1-yloxy)but-2-yne (46% recovery) as one fraction and a mixture of *E* and *Z* isomers (18 mg *E/Z* = 4/1) as another fraction. The reaction also formed a mixture of unidentifiable possible oligomeric metathesis products.

¹H NMR (400 MHz, CDCl₃, ppm) δ : (*E*) 5.48-5.42 (m, 2H), 4.17 (s, 4H), 3.56 (t, *J* = 7.2 Hz, 4H), 2.08-2.04 (m, 4H), 1.67 (p, *J* = 7.2 Hz, 4H), 1.53-1.44 (m, 4H); (*Z*) 5.40-5.30 (m, 2H), 4.18 (s, 4H), 3.60 (t, *J* = 6.4 Hz, 4H), 2.16-2.10 (m, 4H), 1.66 (p, *J* = 6.2 Hz, 4H), 1.53-1.44 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : (*E*) 130.6, 82.6, 70.3, 58.08, 31.6, 28.3, 24.9; (*Z*) 129.8, 82.5, 68.2, 58.1, 27.7, 25.5, 25.3;

IR (neat ATR): 2929, 2854, 1442, 1348, 1267, 1102, 970;

HRMS (DART): calcd $[M+H]^+$ 223.16926, found 223.16897.



Complex 2-46

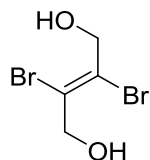
A flame-dried round bottom flask was charged with Grubbs' 1st generation catalyst (34 mg, 0.04 mmol) under N₂. A solution of starting **2-45** (1.16 g, 2.06 mmol) in dry DCM (200 mL) was added into the flask and the resultant solution was stirred overnight at room temperature. The solvent was removed *in vacuo* and the product was isolated as a mixture with unreacted starting material after column chromatography with 20:1 Petroleum ether/Et₂O. Yield was determined by ¹H NMR (130 mg, 12%). After a second column chromatography fractions containing only product were combined and concentrated for characterization.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.42 (bt, *J* = 4.4 Hz, 2H), 4.70 (s, 4H), 3.64 (t, *J* = 6.0 Hz, 4H), 2.06 (bq, *J* = 6.4 Hz, 4H), 1.64 (bp, *J* = 6.2 Hz, 4H), 1.51-1.46 (m, 4H);

¹³C NMR (100 MHz, C₆D₆, ppm) δ: 129.9, 93.2 (Co-C≡C-Co), 71.1, 70.1, 28.5, 26.29, 25.98;

IR (neat ATR): 2937, 2857, 2092, 2050, 2017, 1609, 1431, 1342, 1099, 842

HRMS (DART): calcd [M+H]⁺ 509.00514, found 509.00306.



(E)-2,3-dibromobut-2-ene-1,4-diol (2-49)

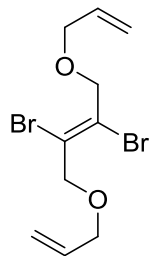
But-2-yne-1,4-diol (2.30 g, 26.54 mmol) was dissolved in water (50 mL) and cooled to 0 °C. Bromine (1.8 mL, 35.03 mmol) was added dropwise. The resultant light yellow solution was stirred at 0 °C for 30 min and for an additional 90 min at room temperature. The reaction was quenched with a small amount of saturated Na₂S₂O₃ solution and neutralized by addition of 1 M NaOH. After extraction with ethyl acetate the combined organic layers were dried over MgSO₄, filtered through silica gel and the solvent was evaporated *in vacuo*. Removal of the solvent under vacuum afforded 5.94 g (91% yield) of the known⁴⁸ white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 4.54 (s, 4H), 2.00 (bs, 2H);

¹H NMR (400 MHz, (CD₃)₂SO, ppm) δ: 5.48 (t, *J* = 6.0 Hz, 2H), 4.28 (d, *J* = 6.0 Hz, 4H);

¹³C NMR (100 MHz, (CD₃)₂SO, ppm) δ: 123.2, 65.8;

IR (neat ATR): 3226, 1440, 1361, 1245 1061, 1010, 999.



(E)-1,4-bis(allyloxy)-2,3-dibromobut-2-ene (2-50)

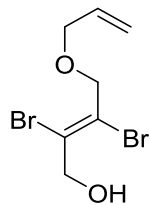
2-49 (3.0 g, 12.2 mmol) was dissolved in a H₂O/DMSO mixture (5 mL/20 mL) and cooled to 0 °C. Potassium hydroxide (1.70 g, 30.5 mmol) was added prior to dropwise addition of allyl bromide (2.6 mL, 30.5 mmol). The solution was warmed to room temperature and stirred for 16 h. The reaction mixture was diluted with water and extracted with DCM. The organic extracts were washed with brine, dried over MgSO₄ and the solvent was removed *in vacuo*. Column chromatography with 9:1 petroleum ether/Et₂O afforded 2.5 g (64% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 5.94 (ddt, $J = 17.4, 10.2, 5.8$ Hz, 2H), 5.33 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 2H), 5.23 (ddt, $J = 10.4, 1.6, 1.2$ Hz, 2H), 4.46 (s, 4H), 4.01 (ddd, $J = 5.8, 1.4, 1.4$ Hz, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 133.9, 121.8, 117.8, 73.1, 70.9;

IR (neat ATR): 2919, 2855, 1439, 1349, 1270, 1085, 991, 923;

HRMS (DART): calcd [M+H]⁺ 326.94128, found 326.93997.



(E)-4-(allyloxy)-2,3-dibromobut-2-en-1-ol (2-51)

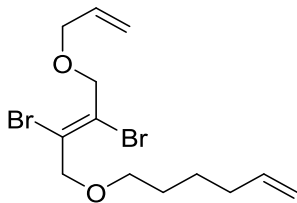
2-49 (0.42 g, 1.72 mmol) was dissolved in a H₂O/DMSO mixture (1 mL/2 mL) and cooled to 0 °C. Potassium hydroxide (0.97 g, 1.72 mmol) was added prior to dropwise addition of allyl bromide (0.10 mL, 0.69 mmol). The solution was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with water and extracted with DCM. The organic extracts were washed with brine, dried over MgSO₄ and the solvent was removed *in vacuo*. Column chromatography with 3:1 hexanes/EtOAc afforded 0.13 g (65% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 5.93 (ddt, $J = 17.2, 10.4, 5.6$ Hz, 1H), 5.33 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H), 5.23 (ddt, $J = 10.4, 1.6, 1.2$ Hz, 1H), 4.56 (s, 2H), 4.43 (s, 2H), 4.02 (ddd, $J = 5.8, 1.4, 1.4$ Hz, 2H), 2.01 (bs, 1H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 133.8, 123.9, 120.1, 117.9, 73.1, 70.9, 67.2;

IR (neat ATR): 3338, 2915, 2858, 1440, 1351, 1245, 1080, 1063, 1008, 926;

HRMS (DART): calcd [M+H]⁺ 286.90998, found 286.90898.



(E)-6-((4-(allyloxy)-2,3-dibromobut-2-en-1-yl)oxy)hex-1-ene (2-52)

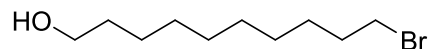
2-51 (0.73 g, 2.56 mmol) was dissolved in a H₂O/DMSO mixture (5 mL/20 mL) and cooled to 0 °C. Potassium hydroxide (0.20 g, 3.34 mmol) was added prior to addition of **2-42** (2.0 g, 7.70 mmol). The solution was heated to 70 °C and stirred for 5 h. The reaction mixture was diluted with water and extracted with DCM. Organic extracts were washed with brine, dried over MgSO₄ and the solvent was removed *in vacuo*. Column chromatography with 9:1 hexanes/EtOAc afforded 0.57 g (61% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.33 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.23 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1H), 5.00 (ddt, *J* = 17.2, 2.0, 1.6 Hz, 1H), 4.95 (ddt, *J* = 10.0, 2.0, 1.2 Hz, 1H), 4.47 (s, 2H), 4.45 (s, 2H), 4.01 (ddd, *J* = 5.8, 1.4, 1.4 Hz, 2H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.11-2.05 (m, 2H), 1.66-1.59 (m, 2H), 1.52-1.44 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 138.5, 133.9, 122.2, 121.5, 117.8, 114.5, 73.8, 73.1, 70.9, 69.9, 33.4, 28.9, 25.3;

IR (neat ATR): 2922, 2855, 1648, 1590, 1540, 1341, 1287, 1162, 1120, 1080, 918;

HRMS (DART): calcd [M+H]⁺ 368.98823, found 368.98757.

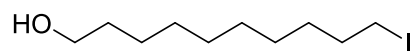


10-bromodecan-1-ol

Concentrated HBr (1.2 mL, 6.88 mmol, 48% w/w (9 M) in H₂O) was added to a mixture of decane-1,10-diol (1.0 g, 5.74 mmol) in toluene (15 mL). The resultant biphasic mixture was refluxed for 48 h. After completion the reaction mixture was diluted with ether and the layers were separated. The organic phase was washed with 1 M NaOH and brine, dried over MgSO₄ and the solvent was removed *in vacuo*. Chromatography with 1:1 hexanes/Et₂O gave 1.1 g (82% yield) of the known⁴⁹ colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 3.64 (t, *J* = 6.8 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 1.85 (p, *J* = 7.2 Hz, 2H), 1.59-1.52 (m, 2H), 1.43-1.25 (m, 12H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 62.9, 33.9, 32.72, 32.68, 29.6, 29.25, 29.24, 28.36, 28.0, 25.6.

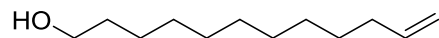


10-iododecan-1-ol

Sodium iodide (2.5 g, 16.40 mmol) was added to a solution of 10-bromodecan-1-ol (1.1 g, 4.68 mmol) in dry acetone (25 mL) and the solution was refluxed overnight. The reaction mixture was diluted with H₂O and extracted with EtOAc. The combined organic layers were washed with 1% Na₂S₂O₃ solution and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 4:1 hexanes/Et₂O afforded 1.26 g (95% yield) of the known⁵⁰ white solid.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 3.64 (t, $J = 6.8$ Hz, 2H), 3.18 (t, $J = 7.2$ Hz, 2H), 1.81 (p, $J = 7.2$ Hz, 2H), 1.59-1.52 (m, 2H), 1.39-1.29 (m, 12H);

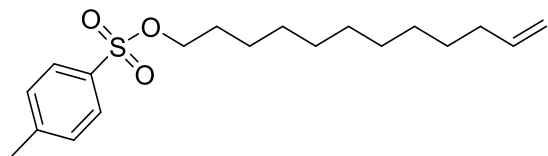
^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 62.9, 33.4, 32.7, 30.4, 29.37, 29.26, 29.22, 28.4, 25.6, 7.2.



Dodec-11-en-1-ol

CuI (0.4 g, 2.11 mmol) was added into a flame-dried flask and flashed with N_2 . Anhydrous THF (5 mL) was added and the suspension was cooled to -40 °C. Vinylmagnesium bromide (6.3 mL, 6.33 mmol, 1 M) was added and the reaction was stirred for 15 min at -40 °C. Then, HMPA (0.7 mL, 4.22 mmol), triethyl phosphite (0.7 mL, 4.22 mmol), and 10-iododecan-1-ol (0.6 g, 2.11 mmol, dissolved in 5 mL THF) were added consecutively and the mixture was stirred for 1 h at -40 °C and for 2 h at room temperature. Saturated NH_4Cl was added to quench the reaction and the crude product was extracted with EtOAc, washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Chromatography with 1:1 hexanes/ Et_2O afforded 0.375 g (96% yield) of the known⁵¹ colorless oil.

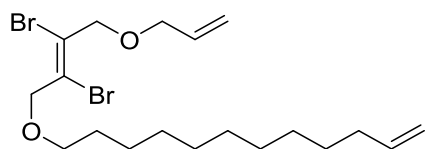
^1H NMR (400 MHz, CDCl_3 , ppm) δ : 5.81 (ddt, $J = 17.0, 10.2, 6.8$ Hz, 1H), 4.99 (ddt, $J = 17.0, 2.2, 1.6$ Hz, 1H), 4.92 (ddt, $J = 10.2, 2.2, 1.2$ Hz, 1H), 3.63 (t, $J = 6.6$ Hz, 2H), 2.06-2.00 (m, 2H), 1.60-1.53 (m, 2H), 1.41-1.28 (m, 14H).



Dodec-11-en-1-yl 4-methylbenzenesulfonate (2-53)

TsCl (0.45 g, 2.37 mmol) was added portionwise to a stirred and ice-cooled solution of dodec-11-en-1-ol (0.36 g, 1.97 mmol), DMAP (5 mg, 0.04 mmol) and Et₃N (0.6 mL, 3.95 mmol) in DCM (15 mL). The mixture was stirred for 1 h at 0 °C and 8 h at room temperature. After completion, the reaction solution was diluted with DCM, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 4:1 hexanes/EtOAc gave 0.57 g (85% yield) of the known⁵² colorless crystalline solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.81 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 4.98 (ddt, *J* = 17.0, 2.2, 1.6 Hz, 1H), 4.92 (ddt, *J* = 10.0, 2.0, 1.2 Hz, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 2.44 (s, 3H), 2.06-2.00 (m, 2H), 1.66-1.59 (m, 2H), 1.38-1.21 (m, 14H).



(*E*)-12-((4-(allyloxy)-2,3-dibromobut-2-en-1-yl)oxy)dodec-1-ene (2-54)

2-51 (1.16 g, 4.04 mmol) was dissolved in a H₂O/DMSO mixture (8 mL/32 mL) and cooled to 0 °C. Potassium hydroxide (0.3 g, 5.05 mmol) was added prior to addition of **2-53** (0.57 g, 1.68 mmol). The solution was heated to 70 °C and stirred for 16 h. The reaction mixture was diluted with water and extracted with DCM. The organic extracts were washed with brine, dried

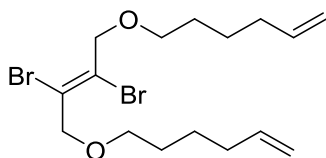
over MgSO₄ and the solvent was removed *in vacuo*. Column chromatography with 9:1 hexanes/EtOAc afforded 0.40 g (53% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.81 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.33 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.23 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1H), 4.98 (ddt, *J* = 17.0, 2.2, 1.6 Hz, 1H), 4.92 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.47 (s, 2H), 4.45 (s, 2H), 4.01 (ddd, *J* = 5.8, 1.4, 1.4 Hz, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.06-2.00 (m, 2H), 1.63-1.57 (m, 2H), 1.36-1.27 (m, 14H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 139.1, 133.9, 122.3, 121.5, 117.8, 114.0, 73.8, 73.2, 70.8, 70.2, 33.7, 29.51, 29.45, 29.43, 29.37, 29.32, 29.0, 28.8, 26.0;

IR (neat ATR): 2924, 2854, 1644, 1465, 1264, 1104, 992, 910;

HRMS (DART): calcd [M+H]⁺ 453.08214, found 453.08115.



(E)-6-((2,3-dibromo-4-(hex-5-en-1-yloxy)but-2-en-1-yl)oxy)hex-1-ene (2-55)

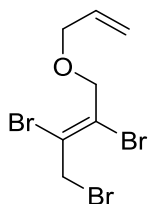
2-49 (0.97 g, 3.93 mmol) was dissolved in a H₂O/DMSO mixture (2 mL/8 mL) and cooled to 0 °C. Potassium hydroxide (0.44 g, 7.86 mmol) was added prior to addition of **2-42** (2.50 g, 9.83 mmol). The solution was heated to 70 °C and stirred for 5 h. The reaction mixture was diluted with water and extracted with DCM. The organic extracts were washed with brine, dried over MgSO₄ and the solvent was removed *in vacuo*. Column chromatography with 9:1 hexanes/EtOAc afforded 0.64 g (40% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.80 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 2H), 5.01 (ddt, *J* = 17.2, 2.0, 1.6 Hz, 2H), 4.95 (ddt, *J* = 10.0, 2.0, 1.2 Hz, 2H), 4.45 (s, 4H), 3.45 (t, *J* = 6.4 Hz, 4H), 2.11-2.05 (m, 4H), 1.66-1.59 (m, 4H), 1.52-1.44 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 138.5, 122.0, 114.4, 73.9, 69.8, 33.3, 28.9, 25.3;

IR (neat ATR): 2933, 2858, 1640, 1105, 993, 908;

HRMS (DART): calcd [M+H]⁺ 411.03519, found 411.03375.



(E)-1-(allyloxy)-2,3,4-tribromobut-2-ene (2-56)

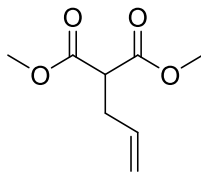
Phosphorus tribromide (0.1 mL, 1.63 mmol) was slowly added to a solution of **2-51** (0.82 g, 2.90 mmol) and pyridine (0.04 mL, 0.52 mmol) in Et₂O (4 mL) at 0 °C. The solution was stirred at 0 °C for 30 min then refluxed for 4 h. After cooling, the reaction was quenched with water and the aqueous layer was extracted with ether. The combined organic extracts were washed with saturated NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with petroleum ether afforded 0.79 g (78% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.93 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.33 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.24 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1H), 4.48 (s, 2H), 4.41 (s, 2H), 4.00 (ddd, *J* = 5.8, 1.4, 1.4 Hz, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 133.8, 124.2, 119.2, 118.1, 73.2, 71.1, 37.3;

IR (neat ATR): 3076, 2981, 2916, 2856, 1645, 1511, 1423, 1214, 1101, 988, 927, 873;

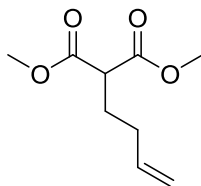
HRMS (DART): calcd $[M+H]^+$ 346.82763, found 346.82592.



Dimethyl 2-allylmalonate

Dimethyl malonate (1.0 mL, 8.74 mmol) was added dropwise to a suspension of NaH (350 mg, 8.74 mmol, 60% w/w dispersion in mineral oil) in THF (30 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then 3-bromoprop-1-ene (0.6 mL, 7.30 mmol) was added slowly. The reaction mixture was refluxed overnight and was then quenched with H₂O. The heterogeneous mixture was diluted with ether and the organic layer was washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 4:1 petroleum ether/Et₂O gave 0.70 g (57% yield) of the known⁵³ colorless oil.

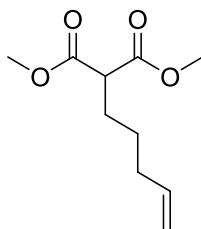
¹H NMR (400 MHz, CDCl₃, ppm) δ : 5.76 (ddt, $J = 17.0, 10.2, 6.8$ Hz, 1H), 5.12 (ddt, $J = 17.2, 1.6, 1.4$ Hz, 1H), 5.06 (dd, $J = 10.4, 1.2$ Hz, 1H), 3.73 (s, 6H), 3.46 (t, $J = 7.6$ Hz, 1H), 2.67-2.63 (m, 2H).



Dimethyl 2-(but-3-en-1-yl)malonate

Dimethyl malonate (2.0 mL, 17.73 mmol) was added dropwise to a suspension of NaH (710 mg, 17.73 mmol, 60% w/w dispersion in mineral oil) in THF (50 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then tetrabutylammonium iodide (TBAI) (1.6 g, 4.43 mmol) and 4-bromobut-1-ene (1.5 mL, 14.78 mmol) were added. The reaction mixture was refluxed overnight and then quenched with H₂O. The heterogeneous mixture was diluted with ether and the organic layer was washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 9:1 hexanes/EtOAc gave 1.9 g (70% yield) of the known⁵³ colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 5.75 (ddt, $J = 16.8, 10.4, 6.6$ Hz, 1H), 5.06-4.99 (m, 2H), 3.73 (s, 6H), 3.39 (t, $J = 7.4$ Hz, 1H), 2.12-2.06 (m, 2H), 2.04-1.98 (m, 2H).

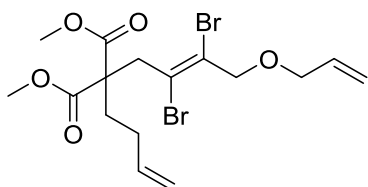


Dimethyl 2-(pent-4-en-1-yl)malonate

Dimethyl malonate (1.2 mL, 10.13 mmol) was added dropwise to a suspension of NaH (400 mg, 10.13 mmol, 60% w/w dispersion in mineral oil) in DMF (20 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then 5-bromopent-1-ene (1 mL, 8.44 mmol) was added

slowly. The reaction mixture was allowed to stir overnight at room temperature and then diluted with H₂O. The crude product was extracted with Et₂O and the combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 4:1 petroleum ether/Et₂O gave 0.93 g (55% yield) of known⁵³ colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.77 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.01 (ddt, *J* = 17.0, 1.8, 1.6 Hz, 1H), 4.96 (ddt, *J* = 10.2, 1.8, 1.2 Hz, 1H), 3.73 (s, 6H), 3.36 (t, *J* = 7.6 Hz, 1H), 2.11-2.05 (m, 2H), 1.94-1.88 (m, 2H), 1.45-1.37 (m, 2H).



Dimethyl (*E*)-2-(4-(allyloxy)-2,3-dibromobut-2-en-1-yl)-2-(but-3-en-1-yl)malonate (2-57)

A solution of dimethyl 2-(but-3-en-1-yl)malonate (256 mg, 1.37 mmol) in DMF (2 mL) was added dropwise to a suspension of NaH (55 mg, 1.37 mmol, 60% w/w dispersion in mineral oil) in DMF (3 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then **2-56** (400 mg, 1.45 mmol, in 5 mL DMF) was added slowly. The reaction mixture was allowed to stir for 24 h at room temperature and was then quenched with H₂O. The crude product was extracted with Et₂O and the combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 4:1 petroleum ether/Et₂O gave 494 mg (95% yield) of a colorless oil.

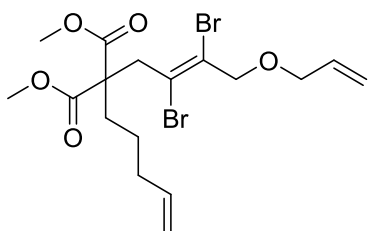
¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.92 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.83-5.71 (m, 1H), 5.32 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.21 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1H), 5.04 (bdd, *J* = 17.0,

1.2 Hz, 1H), 4.97 (bdd, $J = 10.0, 1.6$ Hz, 1H), 4.44 (s, 2H), 3.97 (ddd, $J = 6.0, 1.6, 1.2$ Hz, 2H), 3.75 (s, 6H), 3.59 (s, 2H), 2.06 (bs, 2H), 2.05 (bs, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 170.9, 137.2, 134.0, 123.3, 119.2, 117.9, 115.2, 73.5, 70.7, 56.8, 52.7, 42.8, 31.2, 28.8;

IR (neat ATR): 2951, 1732, 1433, 1274, 1198, 1073, 915, 867;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 454.98863, found 454.98575.



Dimethyl (*E*)-2-(4-(allyloxy)-2,3-dibromobut-2-en-1-yl)-2-(pent-4-en-1-yl)malonate (**2-58**)

A solution of dimethyl 2-(pent-4-en-1-yl)malonate (0.52 g, 2.61 mmol) in DMF (3 mL) was added dropwise to a suspension of NaH (105 mg, 2.61 mmol, 60% w/w dispersion in mineral oil) in DMF (7 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then **2-56** (0.76 g, 2.18 mmol, in 10 mL DMF) was added slowly. The reaction mixture was allowed to stir for 24 h at room temperature and was then quenched with H_2O . The crude product was extracted with Et_2O and combined organic layers were washed with water and brine, dried over MgSO_4 and concentrated *in vacuo*. Chromatography with 4:1 petroleum ether/ Et_2O gave 0.80 g (79% yield) of a colorless oil.

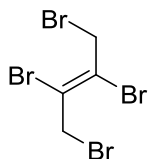
^1H NMR (500 MHz, CDCl_3 , ppm) δ : 5.91 (ddt, $J = 17.2, 10.2, 5.5$ Hz, 1H), 5.76 (ddt, $J = 17.0, 10.0, 6.7$ Hz, 1H), 5.32 (ddt, $J = 17.2, 1.5, 1.5$ Hz, 1H), 5.21 (ddt, $J = 10.5, 1.5, 1.5$ Hz, 1H), 4.99

(ddt, $J = 17.0, 2.0, 1.5$ Hz, 1H), 4.95-4.93 (m, 1H), 4.43 (s, 2H), 3.97 (ddd, $J = 5.5, 1.5, 1.5$ Hz, 2H), 3.74 (s, 6H), 3.56 (s, 2H), 2.07-2.03 (m, 2H), 1.96-1.93 (m, 2H), 1.39-1.33 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 171.0, 137.9, 134.0, 123.2, 119.3, 117.9, 115.0, 73.5, 70.7, 57.1, 52.7, 42.8, 33.7, 31.6, 23.9;

IR (neat ATR): 2951, 2857, 1732, 1434, 1232, 1197, 1180, 1085, 993, 915;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 469.00428, found 469.00341.



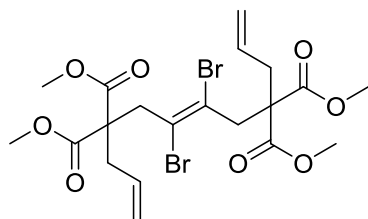
(E)-1,2,3,4-tetrabromobut-2-ene (2-59)

Phosphorus tribromide (0.6 mL, 6.50 mmol) was slowly added to a solution of **2-49** (2 g, 8.13 mmol) and pyridine (0.1 mL, 1.46 mmol) in Et_2O (10 mL) at 0 °C. The solution was stirred at 0 °C for 30 min then refluxed for 4 h. After cooling, the reaction was quenched with water and the aqueous layer was extracted with ether. The combined organic extracts were washed with saturated NaHCO_3 and brine, and dried over MgSO_4 . The solution was passed through a silica gel plug and concentrated *in vacuo* affording 2.07 g (70% yield) of the known⁵⁴ white solid.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 4.34 (s, 4H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 121.1, 36.9;

IR (neat ATR): 1417, 1210, 1162, 1082, 894;



Tetramethyl (*E*)-6,7-dibromododeca-1,6,11-triene-4,4,9,9-tetracarboxylate (2-60)

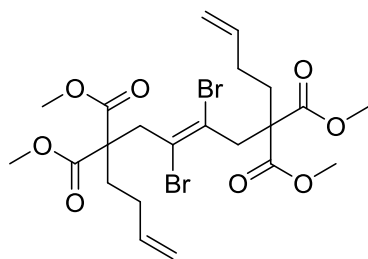
A solution of dimethyl 2-allylmalonate (0.46 g, 2.69 mmol) in DMF (3 mL) was added dropwise to a suspension of NaH (135 mg, 3.36 mmol, 60% w/w dispersion in mineral oil) in DMF (10 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then **2-59** (0.5 g, 1.35 mmol) was added slowly. The reaction mixture was allowed to stir for 24 h at room temperature and was then quenched with H₂O. The crude product was extracted with Et₂O and the combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 4:1 petroleum ether/Et₂O gave 0.59 g (80% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.83 (ddt, *J* = 16.8, 10.0, 7.4 Hz, 2H), 5.13-5.07 (m, 4H), 3.72 (s, 12 H), 3.58 (s, 4H), 2.70 (bd, *J* = 7.2 Hz, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 170.4, 132.5, 120.2, 119.1, 57.6, 52.5, 43.1, 36.7;

IR (neat ATR): 2947, 1734, 1429, 1285, 1194, 1157, 1052, 937, 850;

HRMS (DART): calcd [M+H]⁺ 555.00467, found 555.00370.



Tetramethyl (*E*)-7,8-dibromotetradeca-1,7,13-triene-5,5,10,10-tetracarboxylate (2-61)

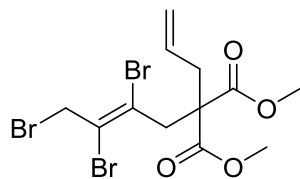
A solution of dimethyl 2-(but-3-en-1-yl)malonate (0.40 g, 2.15 mmol) in DMF (3 mL) was added dropwise to a suspension of NaH (86 mg, 2.15 mmol, 60% w/w dispersion in mineral oil) in DMF (7 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then **2-59** (0.35 g, 0.93 mmol) was added slowly. The reaction mixture was allowed to stir for 24 hr at room temperature and was then quenched with H₂O. The crude product was extracted with Et₂O and the combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 4:1 hexanes/DCM gave 0.36 g (66% yield) of a white solid.

¹H NMR (400 MHz, C₆D₆, ppm) δ: 5.79 (ddt, *J* = 17.0, 10.2, 6.4 Hz, 2H), 5.10 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 2H), 4.94 (ddt, *J* = 10.2, 1.8, 1.2 Hz, 2H), 3.70 (s, 4H), 3.29 (s, 12H), 2.32-2.28 (m, 4H), 2.20-2.14 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 170.8, 137.1, 120.2, 115.2, 56.8, 52.6, 43.1, 30.9, 28.8;

IR (neat ATR): 2927, 1723, 1434, 1292, 1248, 1200, 1107, 1046, 914, 876;

HRMS (DART): calcd [M+H]⁺ 583.03597, found 583.03448.



Dimethyl (E)-2-allyl-2-(2,3,4-tribromobut-2-en-1-yl)malonate (2-62)

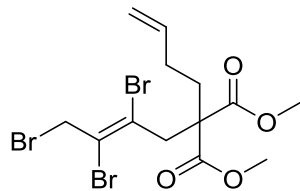
A solution of dimethyl 2-allylmalonate (0.42 g, 2.42 mmol) in DMF (4 mL) was added dropwise to a suspension of NaH (126 mg, 3.16 mmol, 60% w/w dispersion in mineral oil) in DMF (10 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then **2-59** (1.2 g, 3.16 mmol) was added slowly. The reaction mixture was allowed to stir overnight at room temperature and was then quenched with H₂O. The crude product was extracted with Et₂O and the combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 9:1 petroleum ether/Et₂O gave 0.73 g (65% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.79 (ddt, *J* = 17.0, 10.2, 7.2 Hz, 1H), 5.14-5.08 (m, 2H), 4.45 (s, 2H), 3.73 (s, 6H), 3.51 (s, 2H), 2.71 (bd, *J* = 7.2 Hz, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 170.2, 132.2, 121.6, 120.3, 119.5, 57.7, 52.6, 42.7, 37.7, 37.0;

IR (neat ATR): 2954, 1729, 1433, 1290, 1201, 914, 875;

HRMS (DART): calcd [M+H]⁺ 462.85728, found 462.85641.



Dimethyl (*E*)-2-(but-3-en-1-yl)-2-(2,3,4-tribromobut-2-en-1-yl)malonate (2-63)

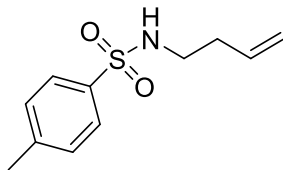
A solution of dimethyl 2-(but-3-en-1-yl)malonate (0.35 g, 1.86 mmol) in DMF (3 mL) was added dropwise to a suspension of NaH (100 mg, 2.42 mmol, 60% w/w dispersion in mineral oil) in DMF (10 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then **2-59** (0.90 g, 2.42 mmol) was added slowly. The reaction mixture was allowed to stir for overnight at room temperature and was then quenched with H₂O. The crude product was extracted with Et₂O and combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography with 9:1 petroleum ether/Et₂O gave 0.47 g (54% yield) of a colorless oil.

¹H NMR (400 MHz, C₆D₆, ppm) δ: 5.69 (ddt, *J* = 17.0, 10.2, 6.4 Hz, 1H), 5.03 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 4.89 (ddt, *J* = 10.4, 1.6, 1.4 Hz, 1H), 3.84 (s, 2H), 3.51 (s, 2H), 3.27 (s, 6H), 2.25-2.21 (m, 2H), 2.14-2.07 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 170.6, 136.9, 121.7, 120.4, 115.2, 57.0, 52.7, 42.7, 37.7, 31.2, 28.7;

IR (neat ATR): 2921, 2847, 1732, 1515, 1457, 1439, 1281, 1242, 1225, 1177, 1040, 1000, 804;

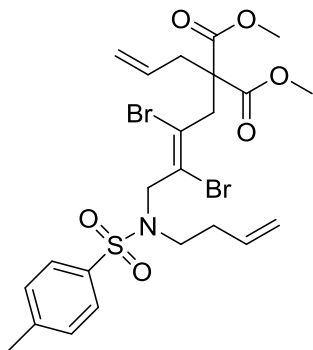
HRMS (DART): calcd [M+H]⁺ 476.87293, found 476.87076.



***N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide**

4-bromobut-1-ene (1.1 mL, 9.85 mmol) added into a suspension of K_2CO_3 (2.47 g, 17.9 mmol) and tosylamide (1.53 g, 8.95 mmol) in acetone (9 mL). The reaction was refluxed overnight. After quenching with saturated NH_4Cl , the crude product was extracted with Et_2O , washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography with 4:1 hexanes/ $EtOAc$ afforded 1.12 g (59% yield) of the known⁵⁵ colorless oil.

1H NMR (400 MHz, $CDCl_3$, ppm) δ : 7.73 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 5.66-5.56 (m, 1H), 5.05-4.99 (m, 2H), 4.59 (bt, $J = 5.2$ Hz, 1H), 3.02-2.97 (m, 2H), 2.41 (s, 3H), 2.21-2.16 (m, 2H).



Dimethyl (*E*)-2-allyl-2-(2,3-dibromo-4-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)but-2-en-1-yl)malonate (2-64)

A solution of dimethyl **2-62** (0.63 g, 1.36 mmol) in acetone (6 mL) added into a suspension of K_2CO_3 (342 mg, 2.47 mmol) and *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (280 mg, 1.24

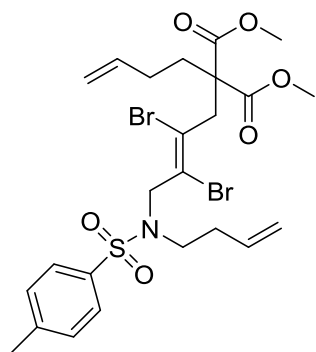
mmol) in acetone (6 mL). The reaction was refluxed for 24 h. After quenching with saturated NH_4Cl , the crude product was extracted with DCM, washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Chromatography with 3:1 petroleum ether/ Et_2O afforded 574 mg (77% yield) of a white solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 7.71 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 5.88-5.77 (m, 1H), 5.65 (ddt, $J = 17.2, 10.0, 6.8$ Hz, 1H), 5.12-4.98 (m, 4H), 4.41 (s, 2H), 3.72 (s, 6H), 3.57 (s, 2H), 3.19-3.15 (m, 2H), 2.68 (d, $J = 7.2$ Hz, 2H), 2.42 (s, 3H), 2.30-2.25 (m, 2H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3 , ppm) δ : 170.3, 143.4, 137.0, 134.3, 132.3, 129.5, 127.3, 122.3, 119.48, 119.30, 117.1, 57.5, 54.6, 52.6, 47.0, 43.1, 36.8, 32.4, 21.4;

IR (neat ATR): 3272, 3076, 1730, 1651, 1544, 1431, 1216, 1202, 1159, 927;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 608.01346, found 608.01244.



(E)-dimethyl-2-(but-3-en-1-yl)-2-(2,3-dibromo-4-(N-(but-3-en-1-yl)-4-methylphenyl sulfonamido)but-2-en-1-yl)malonate (2-65)

A solution of dimethyl **2-63** (0.44 g, 0.93 mmol) in acetone (5 mL) added into a suspension of K_2CO_3 (233 mg, 1.68 mmol) and *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (190 mg, 0.84 mmol) in acetone (5 mL). The reaction was refluxed for 24 h. After quenching with

saturated NH_4Cl , the crude product was extracted with DCM, washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Chromatography with 4:1 hexanes/EtOAc afforded 458 mg (88% yield) of a white solid.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.71 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 5.77-5.68 (m, 1H), 5.63 (ddt, $J = 17.0, 10.2, 6.8$ Hz, 1H), 5.04-4.93 (m, 4H), 4.41 (s, 2H), 3.73 (s, 6H), 3.55 (s, 2H), 3.17-3.14 (m, 2H), 2.42 (s, 3H), 2.28-2.22 (m, 2H), 2.00 (bs, 4H);

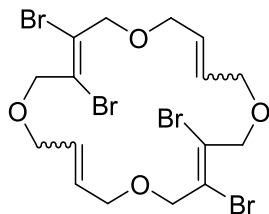
^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 170.6, 143.4, 137.00, 136.94, 134.3, 129.5, 127.3, 122.3, 119.5, 117.1, 115.2, 56.7, 54.6, 52.6, 46.9, 43.0, 32.3, 31.1, 28.7, 21.4;

IR (neat ATR): 3076, 2962, 2930, 1730, 1452, 1431, 1341, 1280, 1200, 1159, 1088, 925, 912, 745, 664;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 622.02911, found 622.02847.

General procedure for ring closing metathesis reactions:

A flame-dried round bottom flask equipped with a reflux condenser was charged with Grubbs' 1st generation catalyst (0.05 equiv) under N_2 . The metathesis reaction substrate dissolved in dry DCM (0.002 M) was added to the flask and the resultant solution was refluxed overnight. After completion the solvent was removed *in vacuo* and the product was purified by column chromatography.



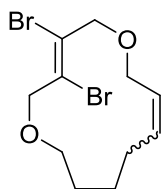
(3E,13E)-3,4,13,14-tetrabromo-1,6,11,16-tetraoxacycloicosa-3,8,13,18-tetraene (2-67)

According to the *General procedure*, **2-50** (0.13 g, 0.398 mmol) was reacted with catalyst (16 mg, 0.020 mmol) and chromatography with 4:1 petroleum ether/Et₂O afforded 59 mg of a white solid (50% yield as stereoisomeric mixture).

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.93-5.76 (m, 4H), 4.48-4.44 (m, 8H), 4.07-4.05 (m, 8H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 130.2, 129.9, 129.3, 122.6, 122.35, 122.28, 121.7, 74.0, 73.32, 73.23, 71.0, 70.4, 65.23, 65.12;

HRMS (DART): calcd [M+H]⁺ 596.81269, found 596.81086.



(3E)-3,4-dibromo-1,6-dioxacyclotrideca-3,8-diene (2-70)

According to the *General procedure*, **2-52** (0.20 g, 0.543 mmol) was reacted with catalyst (22 mg, 0.027 mmol) and chromatography with 14:1 hexanes/EtOAc afforded 127 mg of a colorless oil (69% yield, *E/Z* ratio 2.5/1).

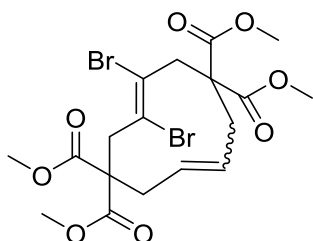
¹H NMR (400 MHz, CDCl₃, ppm) δ: (*E*) 5.74 (dddd, *J* = 15.0, 9.6, 4.6, 1.2 Hz, 1H), 5.67-5.62 (m, 1H), 4.75 (d, *J* = 14.2 Hz, 1H), 4.69 (d, *J* = 13.7 Hz, 1H), 4.45-4.40 (m, 1H), 4.23 (dd, *J* =

14.4, 2.4 Hz, 1H), 4.13 (dd, $J = 13.6, 2.4$ Hz, 1H), 3.83 (dd, $J = 13.6, 9.6$ Hz, 1H), 3.67-3.55 (m, 2H), 2.27-2.20 (m, 1H), 1.84-1.75 (m, 1H), 1.69-1.44 (m, 4H); (**Z**) 5.63-5.53 (m, 2H), 4.88 (d, $J = 14.3$ Hz, 1H), 4.84 (d, $J = 13.6$ Hz, 1H), 4.33 (dd, $J = 12.4, 8.0$ Hz, 1H), 4.12-4.06 (m, 2H), 4.03 (bdd, $J = 12.4, 5.6$ Hz, 1H), 3.81-3.76 (m, 1H), 3.48-3.42 (m, 1H), 2.14-2.05 (m, 1H), 1.95-1.86 (m, 1H), 1.69-1.44 (m, 4H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : (**E**) 133.6, 128.1, 124.5, 121.4, 75.6, 74.8, 74.5, 70.5, 31.4, 29.3, 23.0; (**Z**) 134.2, 125.0, 123.5, 122.5, 74.6, 71.5, 67.5, 63.1, 28.5, 25.4, 23.8;

IR (neat ATR): 2916, 2858, 1734, 1647, 1541, 1445, 1287, 1125, 1078, 1050, 970, 904;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 340.95693, found 340.95596.



Tetramethyl (**3E**)-3,4-dibromocyclodeca-3,8-diene-1,1,6,6-tetracarboxylate (**2-71**)

According to the *General procedure*, **2-60** (0.283 g, 0.510 mmol, 0.004 M in 128 mL DCM) was reacted with Grubbs' 2nd generation catalyst (43 mg, 0.051 mmol) and chromatography with 3:2 hexanes/ Et_2O afforded 240 mg of colorless crystals (90% yield, *E/Z* ratio 1/5).

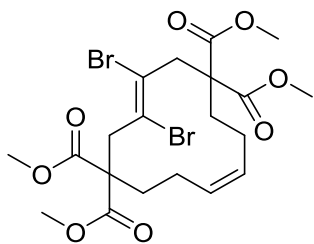
^1H NMR (400 MHz, CDCl_3 , ppm) δ : (**E**) 6.14-6.05 (m, 2H), 4.38 (d, $J = 14.9$ Hz, 2H), 3.80 (s, 6H), 3.71 (s, 6H), 3.12 (d, $J = 14.8$ Hz, 2H), 3.06 (d, $J = 13.2$ Hz, 2H), 2.47 (ddd, $J = 13.2, 7.2, 3.2$ Hz, 2H); (**Z**) 5.90-5.83 (m, 1H), 5.28-5.21 (m, 1H), 4.18 (d, $J = 15.3$ Hz, 1H), 4.05 (d, $J =$

14.6 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.42 (ddd, $J = 14.4, 2.2, 1.0$ Hz, 1H), 3.27-3.17 (m, 2H), 2.90 (dd, $J = 14.8, 12.4$ Hz, 1H), 2.60 (bt, $J = 14.8$ Hz, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : (*E*) 170.8, 170.6, 126.7, 122.0, 53.17, 52.8, 52.62, 43.5, 38.5; (*Z*) 171.6, 171.5, 170.3, 169.8, 130.4, 125.0, 122.5, 118.7, 55.6, 53.7, 53.3, 53.2, 53.09, 52.69, 43.8, 41.8, 31.7, 30.3;

IR (neat ATR): 2955, 1728, 1428, 1218, 1175, 1059, 855;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 526.97337, found 526.97216.



Tetramethyl (*3E,9Z*)-3,4-dibromocyclododeca-3,9-diene-1,1,6,6-tetracarboxylate (**2-72**)

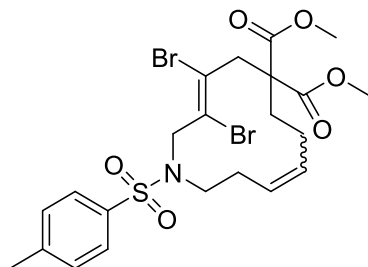
According to the *General procedure*, **2-61** (0.195 g, 0.334 mmol) was reacted with catalyst (14 mg, 0.017 mmol) and chromatography with 4:1 hexanes/EtOAc afforded 160 mg of a white solid (86% yield).

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 5.58 (bt, $J = 5.1$ Hz, 2H), 4.18 (d, $J = 15.4$ Hz, 2H), 3.77 (s, 6H), 3.74 (s, 6H), 3.33 (d, $J = 15.4$ Hz, 2H), 2.12 (td, $J = 14.4, 5.1$ Hz, 2H), 2.03-1.88 (m, 4H), 1.75-1.65 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 171.4, 170.6, 130.0, 121.3, 56.9, 53.07, 52.90, 41.4, 32.1, 21.9;

IR (neat ATR): 2914, 2850, 2836, 1721, 1648, 1541, 1426, 1375, 1215, 1183;

HRMS (DART): calcd $[M+H]^+$ 555.00467, found 555.00302.



Dimethyl (3E)-3,4-dibromo-1-tosylazacyclododeca-3,9-diene-6,6-dicarboxylate (2-73)

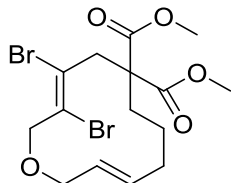
According to the *General procedure*, **2-65** (0.203 g, 0.326 mmol) was reacted with catalyst (14 mg, 0.016 mmol) and chromatography with 4:1 hexanes/EtOAc afforded 180 mg of a white solid (93% yield, *E/Z* ratio 1/7).

¹H NMR (400 MHz, CDCl₃, ppm) δ : (*E*) 7.68 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.63-5.51 (m, 2H), 4.24-4.14 (m, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.62 (ddd, *J* = 14.8, 5.2, 2.4 Hz, 1H), 3.20 (bd, *J* = 16.4, 1H), 2.60-2.53 (m, 1H), 2.44-2.34 (m, 2H), 2.34 (s, 3H), 2.20-2.11 (m, 2H), 1.61-1.45 (m, 2H); (*Z*) 7.70 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.54 (ddd, *J* = 10.8, 10.8, 4.4 Hz, 1H), 5.45 (ddd, *J* = 10.4, 10.4, 6.4 Hz, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 13.6 Hz, 1H), 4.20 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.75 (bs, 6H), 3.44 (ddd, *J* = 14.4, 12.0, 7.2 Hz, 1H), 3.32 (dd, *J* = 16.0, 2.4 Hz, 1H), 2.68 (ddd, *J* = 23.2, 11.2, 2.4 Hz, 1H), 2.44-2.34 (m, 2H), 2.43 (s, 3H), 2.20-2.11 (m, 2H), 1.61-1.45 (m, 2H)

¹³C NMR (100 MHz, CDCl₃, ppm) δ : (*Z*) 171.4, 169.8, 143.5, 135.4, 132.3, 129.7, 127.2, 126.1, 123.2, 120.2, 57.5, 56.6, 53.2, 53.0, 48.3, 41.0, 32.7, 29.4, 22.3, 21.4 (signals for the *E* isomer were not observed in the ¹³C NMR spectrum due to the minute amount in the product mixture);

IR (neat ATR): 2951, 2922, 2851, 1749, 1597, 1436, 1303, 1266, 1164, 927;

HRMS (DART): calcd $[M+H]^+$ 593.99781, found 593.99607.



Dimethyl (3E,10E)-3,4-dibromooxacyclododeca-3,10-diene-6,6-dicarboxylate (2-74)

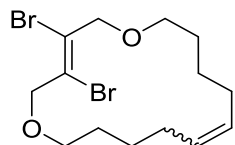
According to the *General procedure*, dimethyl **2-58** (0.185 g, 0.395 mmol) was reacted with catalyst (16 mg, 0.0197 mmol) and chromatography with 4:1 petroleum ether/Et₂O afforded 140 mg of a white solid (80% yield).

¹H NMR (400 MHz, C₆D₆, ppm) δ : 5.69 (dt, $J = 15.6, 7.2$ Hz, 1H), 5.56 (ddd, $J = 15.4, 8.4, 3.6$ Hz, 1H), 4.49 (d, $J = 3.2$ Hz, 1H), 4.45 (d, $J = 4.4$ Hz, 1H), 4.19 (dd, $J = 13.2, 2.4$ Hz, 1H), 3.89 (dd, $J = 14.4, 2.8$ Hz, 1H), 3.43 (dd, $J = 13.4, 8.6$ Hz, 1H), 3.39 (s, 3H), 3.26 (dd, $J = 16.0, 2.4$ Hz, 1H), 3.20 (s, 3H), 2.40-2.32 (m, 1H), 1.91 (d, $J = 12.4$ Hz, 1H), 1.88 (d, $J = 13.2$ Hz, 1H), 1.48-1.41 (m, 1H), 1.30 (q, $J = 12.4$ Hz, 1H), 1.25-1.18 (m, 1H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 172.0, 170.3, 133.1, 129.4, 125.9, 117.7, 75.6, 74.4, 56.2, 52.9, 40.6, 29.2, 28.5, 23.5;

IR (neat ATR): 2954, 2925, 2857, 1732, 1455, 1432, 1294, 1265, 1240, 1207, 1172, 1056, 974;

HRMS (DART): calcd $[M+H]^+$ 440.97298, found 440.97067.



(3E)-3,4-dibromo-1,6-dioxacyclohexadeca-3,11-diene (2-75)

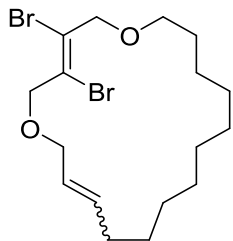
According to the *General procedure*, **2-55** (0.20 g, 0.487 mmol) was reacted with catalyst (20 mg, 0.024 mmol) and chromatography with 14:1 hexanes/EtOAc afforded 162 mg of a colorless oil (87% yield, *E/Z* ratio 1/1).

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.45-5.38 (m, 2H), 5.37-5.31 (m, 2H), 4.84 (d, *J* = 12.5 Hz, 2H), 4.81 (d, *J* = 11.7 Hz, 2H), 4.14 (d, *J* = 12.5 Hz, 4H), 3.57-3.49 (m, 8H), 2.14-2.01 (m, 8H), 1.69-1.62 (m, 8H), 1.60-1.51 (m, 4H), 1.48-1.37 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 130.4, 129.8, 122.8, 122.7, 74.6, 74.4, 70.9, 68.7, 31.8, 28.8, 27.8, 25.8, 25.3, 24.7;

IR (neat ATR): 3002, 2969, 2938, 2859, 2359, 2341, 1439, 1365, 1229, 1216, 1124, 1093, 1073, 1010, 970, 913;

HRMS (DART): calcd [M+H]⁺ 383.00389, found 383.00198.



(3E)-3,4-dibromo-1,6-dioxacyclonadeca-3,8-diene (2-76)

According to the *General procedure*, **2-54** (0.15 g, 0.332 mmol) was reacted with catalyst (14 mg, 0.017 mmol) and chromatography with 14:1 petroleum ether/Et₂O afforded 92 mg of a colorless oil (65% yield, *E/Z* ratio 2.5/1).

¹H NMR (400 MHz, CDCl₃, ppm) δ: (*E*) 5.74 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.63-5.54 (m, 1H), 4.47 (s, 2H), 4.44 (s, 2H), 3.99 (dd, *J* = 6.4, 0.8 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.13-2.06 (m, 2H), 1.67-1.56 (m, 2H), 1.45-1.37 (m, 4H), 1.29 (bs, 10 H); (*Z*) 5.63-5.54 (m, 2H), 4.50 (s, 2H), 4.47 (s, 2H), 4.04 (bs, *J* = 5.2 Hz, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.13-2.06 (m, 2H), 1.67-1.56 (m, 2H), 1.45-1.37 (m, 4H), 1.29 (bs, 10 H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: (*E*) 136.3, 125.8, 122.51, 122.1, 74.15, 72.3, 70.4, 69.7, 31.3, 29.1, 28.2, 27.97, 27.93, 27.6, 27.5, 27.2, 25.4; (*Z*) 134.4, 125.3, 122.49, 122.3, 74.0, 73.3, 69.4, 65.1, 28.6, 28.1, 27.94, 27.7, 27.4, 26.9, 26.6, 25.2 (1 C peak overlaps);

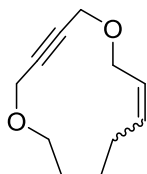
IR (neat ATR): 2924, 2854, 1454, 1264, 1096, 970;

HRMS (DART): calcd [M+H]⁺ 425.05084, found 425.04955.

General procedure for deprotection:

A flame-dried flask equipped with a reflux condenser was charged with Zn dust (6 equiv) and flushed with N₂. A solution of substrate (0.02 M) in THF was added into the flask and refluxed

overnight. After completion the resultant reaction suspension was diluted with EtOAc, filtered through celite and the solvent was removed *in vacuo*. The product was purified by column chromatography.



1,6-dioxacyclotridec-8-en-3-yne (2-77)

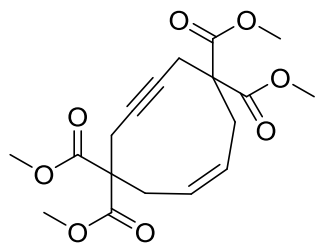
According to the *General procedure*, **2-70** (135 mg, 0.397 mmol) was reacted with Zn dust (156 mg, 2.38 mmol) and chromatography with 14:1 hexanes/EtOAc afforded 57 mg of a colorless oil (80% yield, *E/Z* ratio 2.5/1).

¹H NMR (400 MHz, CDCl₃, ppm) δ : (*E*) 5.76 (dt, *J* = 15.2, 6.0 Hz, 1H), 5.67 (dt, *J* = 15.6, 6.8 Hz, 1H), 4.17 (bt, *J* = 1.6 Hz, 2H), 4.13 (bt, *J* = 1.4 Hz, 2H), 4.09 (d, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 7.0 Hz, 2H), 2.10 (bddd, *J* = 12.0, 6.6, 0.8 Hz, 2H), 1.74 (p, *J* = 6.8 Hz, 2H), 1.62-1.49 (m, 2H); (*Z*) 5.79-5.70 (m, 1H), 5.50-5.44 (m, 1H), 4.59 (d, *J* = 7.6 Hz, 2H), 4.21 (bt, *J* = 1.6 Hz, 2H), 4.13 (bt, *J* = 1.4 Hz, 2H), 3.67 (t, *J* = 5.4 Hz, 2H), 2.19 (dd, *J* = 15.7, 8.0 Hz, 2H), 1.62-1.49 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : (*E*) 133.4, 128.9, 84.2, 83.0, 73.9, 69.3, 58.9, 58.4, 31.1, 28.3, 23.1; (*Z*) 136.0, 124.5, 84.3, 81.7, 68.3, 62.4, 58.7, 55.5, 28.7, 26.0, 24.9;

IR (neat ATR): 2927, 2851, 1446, 1350, 1240, 1207, 1094, 1079, 971, 898;

HRMS (DART): calcd [M+H]⁺ 181.12231, found 181.12197.



Tetramethyl (Z)-cyclodec-3-en-8-yne-1,1,6,6-tetracarboxylate (2-78)

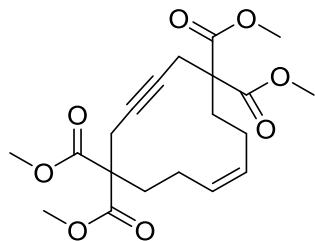
According to the *General procedure*, **2-71** (168 mg, 0.319 mmol) was reacted with Zn dust (125 mg, 1.915 mmol) at 60°C for 4 days in a sealed vial and chromatography with 3:1 hexanes/EtOAc followed by recrystallization from pentane afforded 91 mg of the known^{13d} white solid (pure *Z* isomer 93% yield, total reaction yield 78%). The *E* isomer was not observed.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.45 (t, *J* = 5.2 Hz, 2H), 3.73 (s, 12 H), 3.08 (bs, 2H), 2.95-2.45 (m, 6H).

Table 2.5. Conditions tested for deprotection of 2-71

Entry	Promoter (equiv)	Solvent	Temperature (°C)	Time (h)	Yield (%)	Isomer Ratio (<i>E/Z</i>)
1^a	Zn (6)	THF	66	12	53	1/18
2	Zn (6)	1,4-dioxane	101	72	-	-
3	Pd(PPh ₃) ₄ (0.10)	MeCN	82	96	-	-
4	Zn (6)	THF	60	96	78	0/1

^a47% of starting material was recovered.



Tetramethyl (Z)-cyclododec-9-en-3-yne-1,1,6,6-tetracarboxylate (2-79)

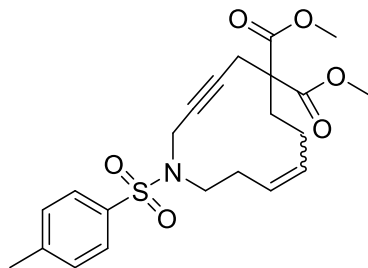
According to the *General procedure*, **2-72** (132 mg, 0.238 mmol) was reacted with Zn dust (93 mg, 1.43 mmol) and chromatography with 4:1 hexanes/EtOAc afforded 90 mg of a white solid (95% yield).

¹H NMR (400 MHz, C₆D₆, ppm) δ : 5.56-5.48 (m, 2H), 3.19 (s, 12H), 3.01 (s, 4H), 2.41-2.37 (m, 4H), 2.21-2.24 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 170.8, 129.9, 78.4, 55.6, 52.6, 33.5, 23.5, 21.8;

IR (neat ATR): 2956, 2929, 2852, 1728, 1446, 1432, 1268, 1210, 1103, 1083, 1067;

HRMS (DART): calcd [M+H]⁺ 395.17004, found 395.16877.



Dimethyl 1-tosylazacyclododec-9-en-3-yne-6,6-dicarboxylate (2-80)

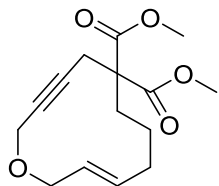
According to the *General procedure*, **2-73** (157 mg, 0.264 mmol) was reacted with Zn dust (104 mg, 1.58 mmol) and chromatography with 3:1 hexanes/EtOAc afforded 114 mg of a white solid (99% yield, *E/Z* ratio 1/7).

¹H NMR (400 MHz, CDCl₃, ppm) δ: (*E*) 7.67 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 5.61-5.50 (m, 2H), 3.79 (t, *J* = 1.6 Hz, 2H), 3.72 (s, 6H), 3.18-3.15 (m, 2H), 2.83 (t, *J* = 1.7 Hz, 2H), 2.45-2.40 (m, 2H), 2.42 (s, 3H), 2.05-1.93 (m, 4H); (*Z*) 7.65 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 5.65 (dt, *J* = 10.8, 7.6 Hz, 1H), 5.46 (dt, *J* = 10.8, 8.4 Hz, 1H), 3.92 (t, *J* = 1.6 Hz, 2H), 3.71 (s, 6H), 3.09-3.05 (m, 2H), 2.98 (t, *J* = 1.8 Hz, 2H), 2.56 (dt, *J* = 8.4, 8.4 Hz, 2H), 2.42 (s, 3H), 2.05-1.93 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: (*Z*) 170.5, 143.6, 135.2, 131.2, 129.8, 127.5, 127.2, 80.7, 77.4, 55.5, 52.9, 49.4, 40.1, 33.9, 29.1, 22.8, 21.5 (2C) (signals at 21.50 ppm and 20.75 ppm can be observed when the ¹³C NMR spectrum was taken in C₆D₆) (signals for the *E* isomer were not observed in the ¹³C NMR spectrum due to the minute amount in the product mixture);

IR (neat ATR): 2954, 2926, 2857, 1731, 1597, 1435, 1339, 1272, 1159, 1089, 1068, 927;

HRMS (DART): calcd [M+H]⁺ 434.16318, found 434.16176.



Dimethyl (*E*)-oxacyclododec-10-en-3-yne-6,6-dicarboxylate (2-81)

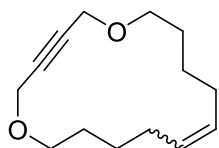
According to the *General procedure*, **2-74** (114 mg, 0.259 mmol) was reacted with Zn dust (102 mg, 1.55 mmol) and chromatography with 4:1 hexanes/EtOAc afforded 67 mg of a white solid (92% yield).

¹H NMR (400 MHz, C₆D₆, ppm) δ : 5.59 (dt, $J = 15.6, 6.4$ Hz, 1H), 5.44 (dt, $J = 15.6, 7.2$ Hz, 1H), 3.87 (t, $J = 2.2$ Hz, 2H), 3.81 (d, $J = 6.4$ Hz, 2H), 3.23 (s, 6H), 3.07 (t, $J = 2.2$ Hz, 2H), 2.38-2.34 (m, 2H), 1.72 (td, $J = 6.4, 5.2$ Hz, 2H), 1.20-1.13 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 170.9, 133.1, 130.5, 82.5, 81.3, 74.3, 59.6, 55.6, 52.7, 29.2, 29.1, 22.5, 22.3;

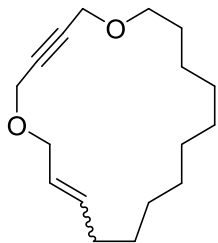
IR (neat ATR): 2950, 2930, 2856, 1728, 1450, 1430, 1297, 1267, 1241, 1202, 1176, 1052;

HRMS (DART): calcd [M]⁺ 280.13053, found 280.12918.



1,6-dioxacyclohexadec-11-en-3-yne (2-45)

According to the *General procedure*, **2-75** (110 mg, 0.288 mmol) was reacted with Zn dust (113 mg, 1.72 mmol) and chromatography with 9:1 hexanes/EtOAc afforded 58 mg of a colorless oil (91% yield, *E/Z* ratio 1/1). For spectral data refer to page 68.



1,6-dioxacyclononadec-8-en-3-yne (2-82)

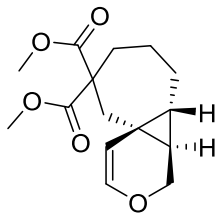
According to the *General procedure*, **2-76** (156 mg, 0.367 mmol) was reacted with Zn dust (144 mg, 2.21 mmol) and chromatography with 9:1 petroleum ether/Et₂O afforded 90 mg of a colorless oil (93% yield, *E/Z* ratio 2.5/1).

¹H NMR (400 MHz, CDCl₃, ppm) δ: (*E*) 5.72 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.64-5.48 (m, 1H), 4.18 (t, *J* = 1.6 Hz, 2H), 4.16 (t, *J* = 1.6 Hz, 2H), 4.05 (dd, *J* = 6.4, 0.8 Hz, 2H), 3.55 (t, *J* = 6.6 Hz, 2H), 2.13-2.07 (m, 2H), 1.62 (p, *J* = 6.8 Hz, 2H), 1.45-1.36 (m, 4H), 1.30 (bs, 10H); (*Z*) 5.64-5.48 (m, 2H), 4.20 (t, *J* = 1.6 Hz, 2H), 4.18 (t, *J* = 1.6 Hz, 2H), 4.15-4.13 (m, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.13-2.07 (m, 2H), 1.63 (p, *J* = 6.4 Hz, 2H), 1.45-1.36 (m, 4H), 1.30 (bs, 10H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: (*E*) 136.1, 125.8, 82.76, 82.09, 69.92, 69.89, 58.29, 56.1, 31.2, 28.9, 28.1, 27.98, 27.87, 27.5, 27.3, 26.9, 25.4; (*Z*) 134.5, 125.3, 82.66, 82.03, 69.5, 64.9, 58.23, 57.2, 28.5, 28.3, 27.92, 27.84, 27.7, 27.2, 27.0, 26.7, 25.2;

IR (neat ATR): 2926, 2853, 1454, 1343, 1260, 1096, 970;

HRMS (DART): calcd [M+H]⁺ 265.21621, found 265.21568.



Dimethyl-(4aR,4bR,9aS)-4,4a,4b,5,6,7-hexahydrocyclohepta[2,3]cyclopropa[1,2-c]pyran-8,8(9H)-dicarboxylate (2-84)

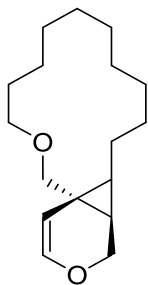
A flame-dried flask was charged with PtCl₂ (6 mg, 0.0214 mmol), **2-81** (60 mg, 0.214 mmol) and toluene (11 mL). The suspension was heated at 80 °C and the reaction was monitored by TLC. After the complete consumption of starting eneyne (3 h), the solvent was removed *in vacuo* and chromatography with 4:1 hexanes/EtOAc afforded 58 mg of a colorless oil (97% yield).

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.99 (d, *J* = 6.1 Hz, 1H), 5.04 (d, *J* = 6.1 Hz, 1H), 4.06 (dd, *J* = 10.4, 1.2 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.66 (dd, *J* = 10.4 (no overlap with the peak at 3.67 was observed when ¹H NMR was taken in C₆D₆), 2.2 Hz, 1H), 2.57 (d, *J* = 15.6 Hz, 1H), 2.42 (ddd, *J* = 14.2, 9.8, 4.0 Hz, 1H), 2.09 (ddd, *J* = 14.5, 9.4, 5.2 Hz, 1H), 1.98 (d, *J* = 15.6 Hz, 1H), 1.94-1.80 (m, 1H), 1.75 (ddd, *J* = 14.0, 7.0, 3.8 Hz, 1H), 1.57 (tt, *J* = 14.4, 4.4 Hz, 1H), 1.21 (dt, *J* = 11.2, 5.6 Hz, 1H), 1.10-1.09 (m, 1H), 1.06-0.95 (m, 1H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 173.0, 172.6, 140.1, 109.9, 61.6, 56.9, 52.6, 52.3, 37.8, 34.1, 33.1, 29.1, 27.9, 23.7, 16.5;

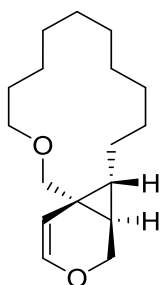
IR (neat ATR): 2992, 2952, 2861, 1729, 1637, 1456, 1433, 1244, 1209, 1171, 1040, 1018, 956;

HRMS (DART): calcd [M+H]⁺ 281.13707, found 281.13707.



4,5,6,7,8,9,10,11,12,12a,12b,13-dodecahydro-1H,3H-pyrano[4',3':1,3]cyclopropa[1,2-c][1]oxacyclotetradecine (2-85)

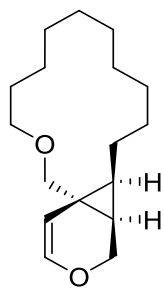
A flame-dried flask was charged with PtCl_2 (7 mg, 0.0246 mmol), **2-82** (65 mg, 0.246 mmol, *E/Z* ratio = 2.5/1) and toluene (10 mL). The suspension was heated at 80 °C and the reaction was monitored by TLC. After the complete consumption of starting eneyne (4 h), the solvent was removed *in vacuo* and chromatography with 9:1 hexanes/EtOAc afforded 35 mg of a colorless oil (54% yield with stereoisomer ratio 2.5/1).



(Major isomer)

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 6.13 (d, $J = 6.0$ Hz, 1H), 5.40 (d, $J = 6.0$ Hz, 1H), 4.08 (dd, $J = 10.4$ Hz, 0.8 Hz, 1H), 3.67 (dd, $J = 10.4, 2.0$ Hz, 1H), 3.54 (d, $J = 9.6$ Hz, 1H), 3.53-3.33 (m, 2H), 3.15 (d, $J = 9.6$ Hz, 1H), 1.71-1.14 (m, 18H), 1.06-1.04 (m, 1H), 1.0-0.99 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 140.28, 108.8, 71.5, 69.0, 61.3, 31.0, 28.5, 27.9, 27.48, 27.40, 26.9, 26.6, 25.6, 25.2, 23.9, 22.9, 20.5;



(Minor isomer)

¹H NMR (400 MHz, CDCl₃, ppm) δ : 6.25 (d, $J = 6.2$ Hz, 1H), 5.11 (d, $J = 6.2$ Hz, 1H), 4.01-3.95 (m, 2H), 3.75 (d, $J = 9.6$ Hz, 1H), 3.53-3.33 (m, 2H), 2.81 (d, $J = 9.3$ Hz, 1H), 1.71-1.14 (m, 20H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 140.39, 101.3, 78.3, 71.8, 60.4, 31.4, 29.7, 29.6, 27.51, 27.2, 26.7, 26.3, 25.8, 25.4, 22.3, 20.0, 19.0;

For mixture of isomers;

IR (neat ATR): 2921, 2855, 1636, 1458, 1361, 1260, 1239, 1106, 1091, 1082, 1066, 1055, 853;

HRMS (DART): calcd [M+H]⁺ 265.21621, found 265.21512.

2.5. References and Notes

1. a) Bhat, A.; Roberts, L. R.; Dwyer, J. J. *Eur. J. Med. Chem.* **2015**, *94*, 471. b) Giordanetto, F.; Kihlberg, J. *J. Med. Chem.* **2013**, *57*, 278. c) Chatterjee, B.; Smritilekha, B.; Mondal, D. *Tetrahedron: Asymmetry* **2014**, *25*, 1. d) Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2014**, *70*, 9461. e) Baeriswyl, V.; Heinis, C. *ChemMedChem* **2013**, *8*, 377.
2. Untch, K. G.; Wysocki, D. C. *J. Am. Chem. Soc.* **1966**, *88*, 2608. b) Sondheimer, F.; Wolovsky, R.; Garratt, P. J.; Calder, I. C. *J. Am. Chem. Soc.* **1966**, *88*, 2610. c) Sondheimer, F.; Pilling, G. M. *J. Am. Chem. Soc.* **1971**, *93*, 1970.
3. a) Hopf, H. Compounds with All-Carbon Functions: Polyynes, Arynes, Enynes, and Alkynes. In *Methods of Molecular Transformations*; Houben-Weyl Vol. 43; Science of Synthesis: Stuttgart, 2008; pp 289-339. b) Wang, D.; Gao, S. *Org. Chem. Front.* **2014**, *1*, 556.
4. Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331.
5. a) Leet, J. E.; Schroeder, D. R.; Hofstead, S. J.; Golik, J.; Colson, K. L.; Huang, S.; Klohr, S. E.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 7946. b) Leet, J. E.; Schroeder, D. R.; Langley, D. R.; Colson, K. L.; Huang, S.; Klohr, S. E.; Lee, M. S.; Golik, J.; Hofstead, S. J.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8432. c) Kawata, S.; Ashizawa, S.; Hiramata, M. *J. Am. Chem. Soc.* **1997**, *119*, 12012.
6. a) Iida, K.; Ishii, T.; Hiramata, M. *Tetrahedron Lett.* **1993**, *34*, 4079. b) Yoshida, K.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett.* **1993**, *34*, 2637. c) Iida,

- K.; Fukuda, S.; Tanaka, T.; Imajo, S.; Ishiguro, M.; Yoshida, K.; Otani, T.; Hirama, M. *Tetrahedron Lett.* **1996**, *37*, 4997.
7. Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Zein, N.; Langley, D. R.; Lee, M. S.; Matson, J. A.; Doyle, T. W. *J. Am. Chem. Soc.* **1994**, *116*, 9351.
8. a) Ando, T.; Ishii, M.; Kajiura, T.; Kameyama, T.; Miwa, K.; Sugiura, Y. *Tetrahedron Lett.* **1998**, *39*, 6495. b) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887. c) Kobayashi, S.; Ashizawa, S.; Takahashi, Y.; Sugiura, Y.; Nagaoka, M.; Lear, M. J. Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 11294.
9. Dai, W. M. *Curr. Med. Chem.* **2003**, *10*, 2265.
10. Kashman, Y.; Bishara, A.; Aknin, M. *Mar. Drugs* **2010**, *8*, 2810.
11. a) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353. b) Burlison, J. A.; Gray, J. M.; Young, D. G. *J. Tetrahedron Lett.* **2001**, *42*, 5363. c) Geng, X.; Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413. d) Hickmann, V.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11042. e) Banfi, L.; Guanti, G.; Basso, A. *Eur. J. Org. Chem.* **2000**, 939.
12. a) Blaszykowski, C.; Harrak, Y.; Goncalves, M. H.; Cloarec, J. M.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771. b) Valot, G.; Regens, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9534. c) Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8739. d) Matsuura, T.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **2001**, *42*, 4163.

- 13.** For examples of enyne ring synthesis via intramolecular S_N2 reactions, see: a) Wender, P. A.; McKinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369. b) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729. c) Takashi, T.; Tanaka, H.; Hirai, Y.; Doi, T.; Yamada, H.; Shiraki, T.; Sugiura, Y. *Angew. Chem. Int. Ed.* **1993**, *32*, 1657. d) Deslongchamps, P.; Lamothe, S.; Lin, H. S. *Can. J. Chem.* **1987**, *65*, 1298.
- 14.** For examples of enyne ring synthesis via intramolecular condensation reactions, see: a) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. b) Toshima, K.; Yanagawa, K.; Ohta, K.; Kano, T.; Nakata, M. *Tetrahedron Lett.* **1994**, *35*, 1573. c) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. d) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. e) Crevisy, C.; Beau, J. M. *Tetrahedron Lett.* **1991**, *32*, 3171. f) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. g) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. h) Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. *Chem. Lett.* **1991**, 1271. i) Wehlage, T.; Krebs, A.; Link, T. *Tetrahedron Lett.* **1990**, *31*, 6625.
- 15.** a) Nicholas, K.M. *J. Organomet. Chem.* **1972**, *21*, 44. b) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, 4163.
- 16.** For examples of enyne ring synthesis via intramolecular Nicholas reaction, see: a) Magnus, P.; Annoura, H.; Harling, J. *J. Org. Chem.* **1990**, *55*, 1709. b) Magnus, P. *Tetrahedron* **1994**, *50*, 1397. c) Maier, M. E.; Langenbacher, D. *Synlett* **1994**, 713. d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. e) Green, J. R. *Chem. Commun.* **1998**, 1751. f) Patel, M. M.; Green, J. R. *Chem. Commun.* **1999**, 509.

17. For examples, see: a) Nicolaou, K. C.; Sorensen, E. J.; Discordia, R.; Hwang, C. K.; Minto, R. E.; Bharucha, K. N.; Bergman, R. G. *Angew. Chem. Int. Ed.* **1992**, *31*, 1044. b) Ferri, F.; Bruckner, R.; Herges, R. *New J. Chem.* **1998**, *22*, 531.
18. For examples, see: a) Hirama, M.; Fujiwara, K. Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120. b) Dai, W. M.; Wu, A. *Tetrahedron Lett.* **2001**, *42*, 81.
19. For examples, see: Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487. b) Anthony, J.; Boldi, A. M.; Boudon, C.; Gisselbrecht, J. P.; Gross, M.; Seiler, P.; Knobler, C. B.; Diederich, F. *Helv. Chim. Acta* **1995**, *78*, 797. c) Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381.
20. Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.
21. For examples, see: a) Meier, H.; Echter, T.; Petersen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 942. b) Meier, H.; Bissinger, H. J.; Vierengel, A. *Tetrahedron Lett.* **2010**, *51*, 1952. c) Poloukhine, A.; Popik, A. A. *J. Org. Chem.* **2005**, 1297. d) Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909. e) Wender, P. A.; Tebbe, M. J. *Tetrahedron Lett.* **1991**, *32*, 4863.
22. a) Shair, M.D.; Yoon, T. Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755. b) Riva, R.; Banfi, L.; Basso, A.; Gandolfo, V.; Guanti, G. *Eur. J. Org. Chem.* **2010**, 2768.
23. a) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 385. b) Ohkita, M.; Ando, K.; Suzuki, T.; Tsuji, T. *J. Org. Chem.* **2000**, *65*, 4385.
24. a) Diaz, D. D.; Cenal, J. P.; Martin, V. S. *Molbank*, **2008**, M562. b) Ni, R.; Mitsuda, N.; Kashiwagi, T.; Igawa, K.; Tomooka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1190.

25. a) Grela, K. *Ed. Olefin Metathesis: Theory and Practice*; John Wiley & Sons: Hoboken, 2014. b) Dragutan, V.; Dragutan, I. *Platinum Metals Rev.* **2011**, *55*, 33.
26. a) Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 3206. b) Ono, K.; Nagata, T.; Nishida, A. *Synlett* **2003**, 1207. c) Rosillo, M.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Org. Biomol. Chem.* **2003**, *1*, 1450. d) Bressy, C.; Vors, J. P.; Hillebrand, S.; Arseniyadis, S. Cossy, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 10137. e) Kang, B.; Kim, D. H.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041. f) Fukumoto, H.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 2731. g) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020.
27. a) Maifeld, S. V.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118. b) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509. c) Clavier, H.; Correa, A.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2009**, *15*, 10244.
28. a) Kim, S. H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073. b) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Tetrahedron* **2010**, *66*, 6358.
29. a) Danilkina, N.; Nieger, M.; Selivanov, S.; Brase, S.; Balova, I. *Eur. J. Org. Chem.* **2012**, 5660. b) Danilkina, N. A.; Lyapunova, A. G.; Khlebnikov, A. F.; Starova, G. L.; Brase, S.; Balova, I. A. *J. Org. Chem.* **2015**, *80*, 5546.
30. Lacombe, F.; Radkowski, K.; Seidel, G.; Fürstner, A. *Tetrahedron* **2004**, *60*, 7315.
31. a) Green, J. R. *Synlett* **2001**, 353. b) Burlison, J. A.; Gray, J. M.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 5363. c) Young, D. G. J.; Burlison, J. A.; Peters, U. *J. Org. Chem.* **2003**, *68*, 3494. d) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.*

- 2004**, 43, 2020. e) Rosillo, M.; Arnaiz, E.; Abdi, D.; Blanco-Urgoiti, J.; Dominguez, G.; Perez-Castells, J. *Eur. J. Org. Chem.* **2008**, 3917.
- 32.** Sugihara, T.; Yamaguchi, M. *Synlett* **1998**, 1384.
- 33.** a) Poater, A.; Ragone, F.; Correa, A.; Cavallo, L. *J. Am. Chem. Soc.* **2009**, 131, 9000. b) Galan, B. R.; Gembicky, M.; Dominiak, P. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, 127, 15702. c) Galan, B. R.; Pitak, M.; Gembicky, M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2009**, 131, 6822. d) Herbert, M. B.; Lan, Y.; Keitz, B. K.; Liu, P.; Endo, K.; Day, M. W.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, 134, 7861. e) Nelson, D. J.; Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. *Chem. Commun.* **2014**, 50, 10355. f) Manzini, S.; Poater, A.; Nelson, D. J.; Cavallo, L.; Slawin, A. M. Z.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2014**, 53, 8995. g) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, 22, 1089. h) Banti, D.; Mol, J. C. *J. Organomet. Chem.* **2004**, 689, 3113. i) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827.
- 34.** Stereoisomers of symmetric cyclic dienes and enynes can be determined by ^{13}C NMR. Carbon atoms α to the disubstituted alkene moiety in the *Z* isomers resonate more upfield than the corresponding carbon atoms in the *E* isomers. Moreover, α -Cs in macrocyclic *Z* isomers resonate 5-6 ppm more upfield than the corresponding Cs in RCM substrates. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy: High-Resolution Methods and Applications in Organic Chemistry and Biochemistry*; Verlag Chemie: Weinheim, Germany, 1987.
- 35.** Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, 128, 15960.
- 36.** Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, 17, 2484.
- 37.** Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Zillers, J. W. *J. Am. Chem. Soc.* **1995**, 117, 5503.

38. Schulte, K. E.; Coen, K. *Chim. Ther.* **1970**, *5*, 72.
39. a) Charlton, J. L.; Chee, G. *Tetrahedron Lett.* **1994**, *35*, 6243. b) Charlton, J. L.; Chee, G.; McColeman, H. *Can. J. Chem.* **1995**, *73*, 1454. c) Hashmi, A. S. K.; Grundl, M. A.; Nass, A. R.; Naumann, F.; Bats, J. W.; Bolte, M. *Eur. J. Org. Chem.* **2001**, 4705.
40. Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94.
41. a) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88. b) Zhang, H.; Yu, E. C.; Torker, S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493.
42. a) Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, *6*, 1219. b) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378. c) Moulins, J. R.; Burnell, D. J. *Tetrahedron Lett.* **2011**, *52*, 3992.
43. Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224.
44. Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567.
45. For examples of selective Pt-catalyzed cyclopropanations, see : a) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2001**, *123*, 11863. c) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104. d) Mendez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. e) Anjum, S.; Marco-Contelles, J. *Tetrahedron* **2005**, *61*, 4793. f) Newcomb, E. T.; Ferreira, E. M. *Org. Lett.* **2013**, *15*, 1772. g) Stevenson, S. M.; Newcomb, E. T.; Ferreira, E. M. *Chem. Commun.* **2014**, *50*, 5239. For a review, see: Zhang, L.; Sun, J.; Kozmina, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.

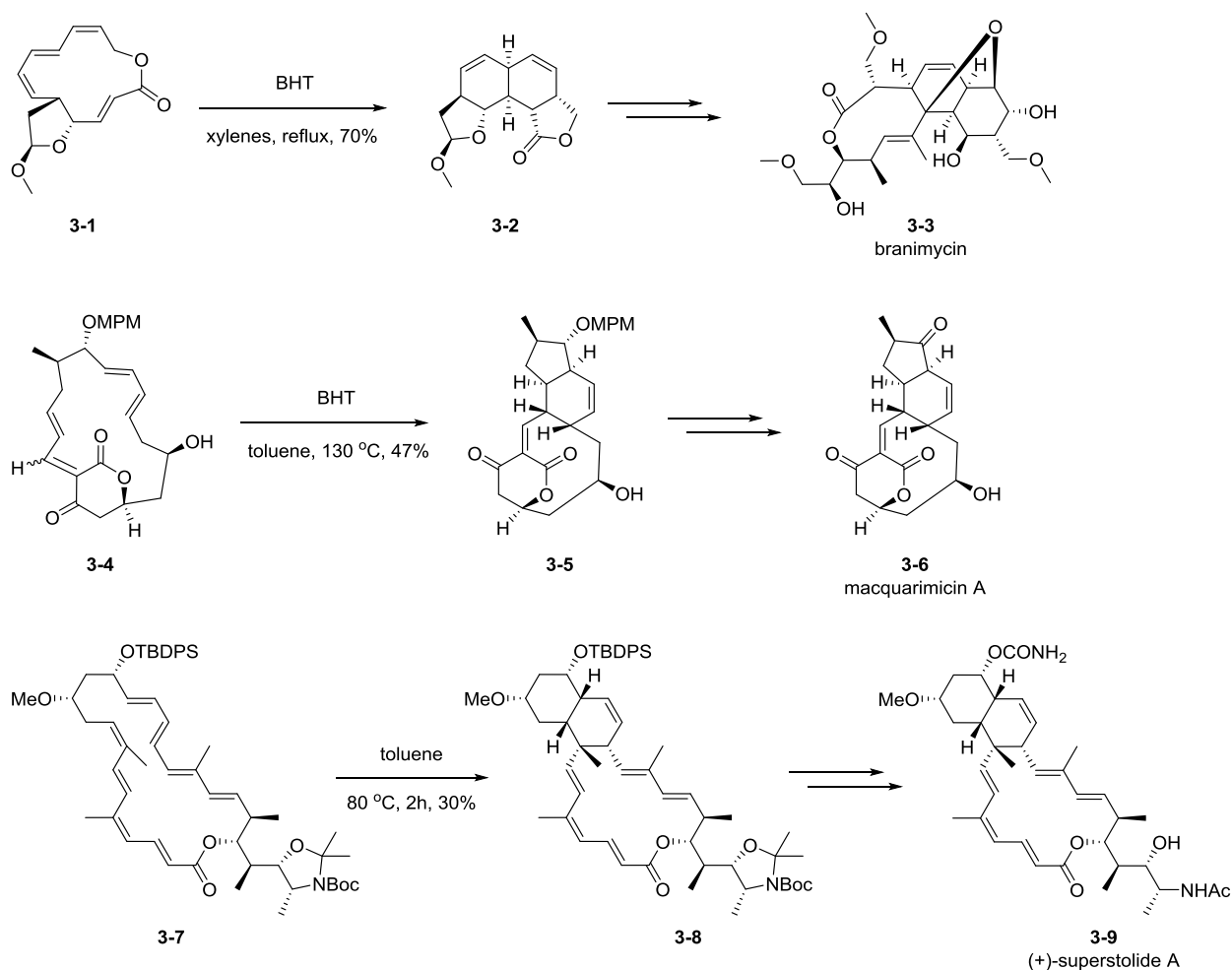
- 46.** For theoretical studies on selectivity in Pt-catalyzed cyclopropanation of 1,6-enynes, see:
- a) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *J. Org. Chem.* **2004**, *69*, 8018.
 - b) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics* **2005**, *24*, 3172.
 - c) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics* **2005**, *24*, 3182.
 - d) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345.
 - e) Marco-Contelles, J.; Soriano, E. *J. Mol. Struct.* **2006**, *761*, 45.
- Mori, K. *Eur. J. Org. Chem.* **2005**, 2040.
- 47.** Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267.
- 48.** Kang, S. K.; Kim, W. S.; Moon, B. H. *Synthesis* **1985**, 1161.
- 49.** Mori, K. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 2727.
- 50.** Berube, M.; Laplante, Y.; Poirier, D. *Chem. Med.* **2006**, *2*, 329.
- 51.** Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232.
- 52.** Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405.
- 53.** Valette, A. *Ann. Chim.* **1948**, *3*, 644.
- 54.** Belmessieri, D.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2013**, *15*, 3472.

Chapter 3

Transannular [4+2] Cycloaddition Reactions of Dicobalt-Complexed Macrocyclic Dienynes

3.1. Introduction

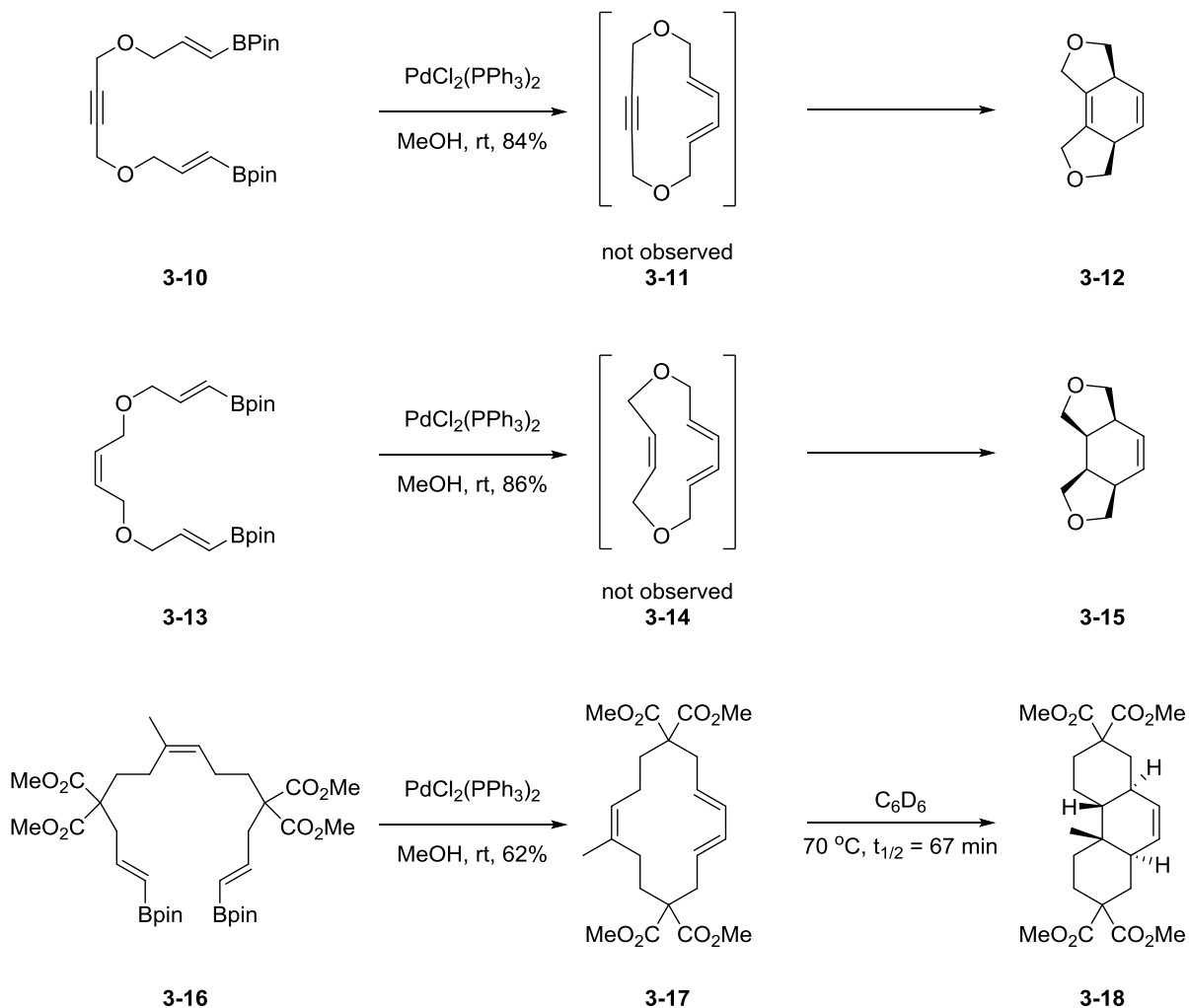
The Diels-Alder reaction plays a crucial role in synthetic chemistry as one of the most powerful transformations since its discovery in the 1920s.¹ This highly versatile reaction is used in the construction of complex organic compounds without scope or functional group limitations and with high atom economy.² The transannular version of the Diels-Alder reaction has been employed as an effective synthetic tool for building complex polycyclic scaffolds and provides the most sophisticated examples of transannular reactions.³ Transannular Diels-Alder (TADA) reactions exhibit unique stereoselective behavior resulting from the combination of conformational restrictions the macrocyclic substrates possess along with endo-/exo-selectivity and stereospecificity inherent to Diels-Alder reactions.^{3a} The high levels of stereochemical control delivered by TADA reactions also allow the prediction of facial selectivity in processes with macrocyclic substrates holding pre-installed stereogenic centers.^{3a,4} These valuable synthetic and stereochemical features led to frequent employment of TADA reactions in the total synthesis of important natural products and pharmaceuticals.⁵ The preparation of the antibiotic metabolite branimycin (**3-3**),⁶ the neutral sphingomyelinase (N-SMase) inhibitor macquarimicin A (**3-6**)⁷ and the cytotoxic macrolide (+)-superstolide A (**3-9**)^{4a} are selected examples of the widespread application of TADA reactions in natural product synthesis (Scheme 3.1). A fascinating fact is that the first Diels-Alderase enzyme purified and characterized plays a key role in the biosynthesis of spinosyn A, is actually a catalyst for a TADA reaction.⁸



Scheme 3.1. Examples of TADA reactions in natural product syntheses

Remarkably, TADA reactions make it possible to build polycyclic structures under mild conditions and at room temperature⁹ through placement of diene and dienophiles in close proximity.¹⁰ For example the Merlic research group reported palladium(II)-catalyzed oxidative couplings of bis(vinylboronate esters) as a highly effective preparation of triene and dienyne macrocycles (Scheme 3.2).¹¹ Some of the investigated macrocyclizations formed reactive strained cyclic intermediates (**3-11** and **3-14** in Scheme 3.2) that readily underwent proximity-induced TADA reactions at room temperature (Scheme 3.2).¹² This study not only provided a

mild and facile entry to macrocycle synthesis, but also opened up a new avenue suggesting TADA reactivity can be modulated through alteration of substrate structures.



Scheme 3.2. Previous work by the Merlic research group on TADA reactions

In order to gain a deeper insight on the effects of substrate structures on proximity-induced TADA reactions we collaborated with the Houk research group and conducted a comparative study using experimental and computational investigations. Macrocyclic dienynes with various ring sizes were prepared and distortion, tether length and entropy effects on their TADA reactions were tested.

Although TADA reactions have been widely investigated, involvement of metals in these transformations to promote or catalyze them remains poorly established. In this regard, the only reported examples employing metals are TADA reactions promoted by metalloids Lewis acids in the synthesis of (+)-maritamol investigated by the Deslongchamps group (Chapter 1 Scheme 1.1)¹³ and enantioselective TADA reactions investigated by the Jacobsen group (Chapter 1 Scheme 1.2).¹⁴ Transition metal catalyzed or promoted TADA reactions, on the other hand, were unknown.

Over the years dicobalt-alkyne complexes have been shown to have a wide range of applications in synthetic chemistry. In addition to operating as protected alkynes¹⁵ and stabilized propargyl cations,¹⁶ dicobalt hexacarbonyl-alkyne complexes participate in several important cycloaddition reactions.¹⁷ In particular, the [2+2+1] cycloaddition leading to cyclopentenones, known as the Pauson-Khand reaction (PKR), is the most frequently studied.¹⁸ Nevertheless, studies on other cycloaddition reactions of alkyne- $\{\text{Co}_2(\text{CO})_6\}$ complexes, especially the [4+2] reaction, are rare. Although being an understudied topic, we postulated that [4+2] cycloaddition reactions of dicobalt complexes would provide structures inaccessible via metal-free Diels-Alder reactions and would present a unique entry to both organocobalt and macrocycle chemistry. The details of our investigations on the first transannular [4+2] cycloadditions of macrocyclic alkyne- $\{\text{Co}_2(\text{CO})_6\}$ complexes and the advantages of this transformations over metal-free TADA reactions are discussed in this chapter.

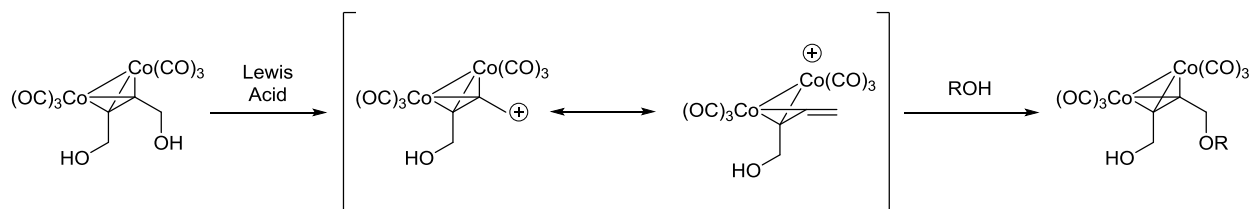
3.2. Results and Discussion

Previous studies conducted in our laboratories on Pd(II)-catalyzed synthesis of macrocycles revealed that strained 12-membered cyclic trienes and dienynes (e.g. **3-11** and **3-14** in Scheme 3.2) are unisolable and they in situ form tricyclic polycycles through room temperature-TADA reactions. On the other hand, all-carbon 14-membered triene **3-17** was less strained and more stable than the 12-membered diether analogues; therefore, it did not go through rapid room temperature-TADA reaction. Tricycle **3-18** was obtained through thermal a TADA reaction of **3-17** and the half-life of reaction was determined as 67 minutes at 70 °C (Scheme 3.2).^{12a} In accordance with these results, computational investigations revealed that 12-membered macrocycles are enthalpically the most favorable structures.^{12b} Moreover, heteroatoms and alkynyl units contract the 12-membered cyclic substrates increasing the TADA reactivity. The TADA activation barrier of diyne **3-11** was computed to be 12.6 kcal/mol while triene **3-14** was found to have an activation barrier of 15.7 kcal/mol under the same conditions.^{12b} As expected, TADA reaction activation energy of larger ring **3-17** was experimentally determined as 26.1 kcal/mol which was in good agreement with the computed range of 23-28 kcal/mol thus explaining the lack of reactivity of the 14-membered ring at room temperature.^{12b}

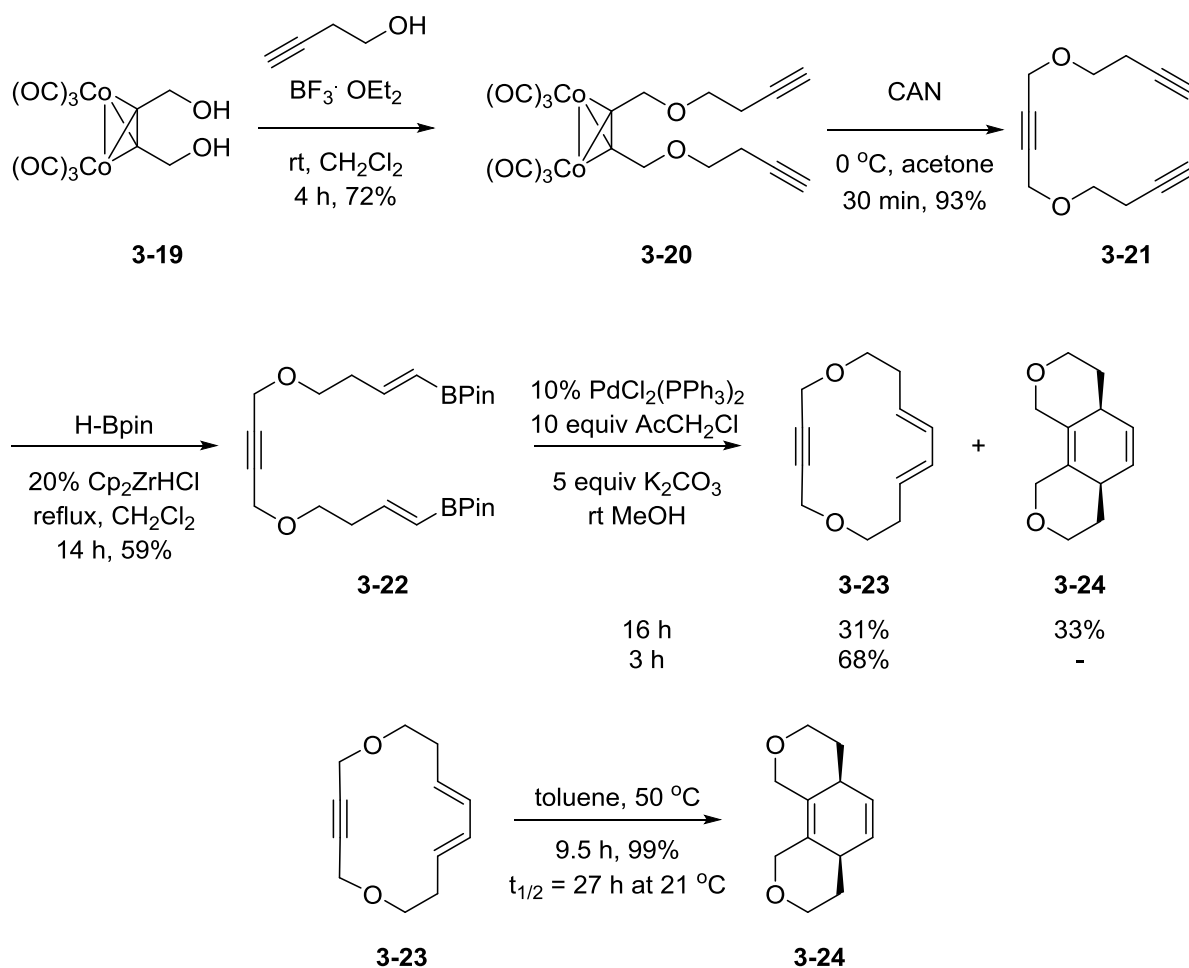
To explore further the effects of heteroatoms on alkynyl dienophiles on the TADA reactivities of dienynes we needed to synthesize 14-membered ring **3-23** (Scheme 3.4). However, trials to prepare triyne **3-21** via classical S_N2 reactions with various nucleophiles and electrophiles failed. This was most likely due to the tendency of homopropargyl electrophiles to undergo elimination reactions in the presence of bases and the low reactivity of but-3-yn-1-olate when used as nucleophile. Therefore, we subjected dicobalt-complexed diol **3-19** to a double Nicholas reaction (for the mechanism, see Scheme 3.3).^{16,19} The Lewis acid BF₃ activated formation of propargyl

cations that are stabilized by cobalt. Nucleophilic reaction with homopropargyl alcohol afforded complex **3-20** in 72% yield (Scheme 3.4)

The resultant complex **3-20** was easily converted to target triyne **3-21** by high-yielding $\text{Ce}(\text{NO}_3)_6(\text{NH}_4)_2$ (CAN) oxidation/decomplexation (Scheme 3.4). Selective bis-hydroboration catalyzed by Schwartz's reagent²⁰ resulted in bis(vinylboronate ester) **3-22**. Macrocyclic **3-23** was observed to be slightly more reactive than 14-membered **3-17**, but not as reactive as 12-membered dienyne or trienes like **3-11** and **3-14**. A 16-hour Pd(II)-catalyzed macrocyclization reaction of **3-22** formed macrocycle **3-23** in a 31% yield and TADA reaction tricycle **3-24** in a 33% yield indicating the facility of the room temperature, proximity-induced TADA reaction of the 14-membered dienyne. Decreasing the macrocyclization reaction time to 3 hours afforded **3-23** in a 68% yield as the sole isolable product. TADA reaction of isolated **3-23** at 21 °C was monitored by ¹H-NMR spectroscopy and the reaction half-life was determined to be 27 hours at this temperature (details are presented in the experimental section). On the other hand, thermal TADA reaction of **3-23** was complete in 9.5 hours at 50 °C. The experimental TADA activation barrier was determined to be 27.0 kcal/mol which was in good agreement with the computed value of 28.0 kcal/mol.^{12b}



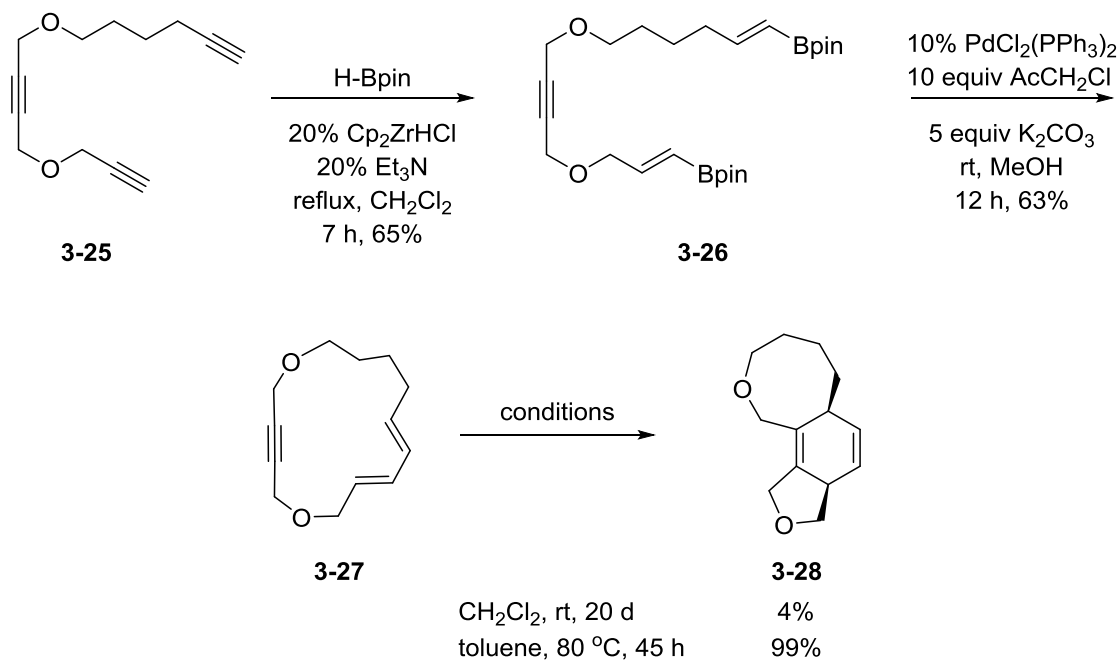
Scheme 3.3. General mechanism of the Nicholas reaction



Scheme 3.4. Preparation and TADA reaction of dienyne 3-23

We then gravitated towards TADA reactions of larger dienyne rings to investigate the effects of different tether lengths and, in turn, ring sizes on reactivity. Hydroboration of triyne **3-25** produced bis(vinylboronate ester) **3-26** in good yield and Pd(II)-catalyzed coupling reaction of **3-26** formed macrocycle **3-27** in 63% yield (Scheme 3.5). The 15-membered cyclic dienyne was considerably less reactive than 14-membered dienyne **3-23** as the overnight room temperature macrocyclization of **3-27** did not yield any of the expected TADA product. In fact, stirring **3-27** at room temperature for 20 days produced tricyclic TADA product **3-28** in a mere 4% yield. A thermal TADA reaction was more effective as **3-28** was formed quantitatively upon heating **3-27**

at 80 °C for 45 hours (Scheme 3.5). However, this thermal reaction of **3-27** was not as facile as the reactions of 14-membered macrocycles **3-17** or **3-23**. These results were anticipated as in the 15-membered macrocycle it is more conformationally challenging for diene and dienophile units to approach each other and the TADA product tricyclic **3-28** contains a fused medium sized ring (8-membered) that is relatively more difficult to access with respect to five- and six-membered counterparts.



Scheme 3.5. Preparation and TADA reaction of dienyne 3-27

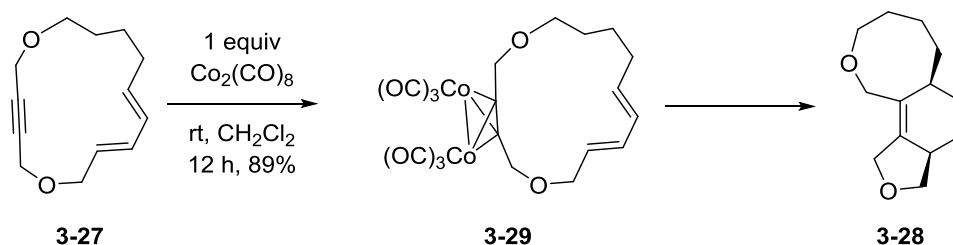
It was evident that as the macrocycle size increases the TADA reactivity decreases, thus we aimed to discover alternative transannular [4+2] cycloaddition routes for unreactive TADA substrates. Although studies on [4+2] cycloaddition reactions of alkyne- $\{\text{Co}_2(\text{CO})_6\}$ complexes were scarce, there were a few reported examples that encouraged us to explore novel dicobalt-promoted transannular [4+2] cycloadditions of macrocyclic dienynes. Pauson and Khand reported intermolecular tandem Diels-Alder/[2+2+1] reactions of a few terminal dicobalt

hexacarbonyl-complexed alkynes with 1,3-cyclohexadiene in 1978.²¹ However, none of the in situ formed Diels-Alder products could be isolated as they rapidly underwent Pauson-Khand ([2+2+1] cycloaddition) reactions affording cyclopentenones. The Iwasawa and Zhang research groups demonstrated 30 years later intermolecular Diels-Alder reactions with dicobalt complexes of otherwise inaccessible strained and reactive cyclic alkynes.²² During these investigations it was unclear whether the [4+2] reaction was indeed activated by the presence of the metal rather than simply heat since the dicobalt-free dienophiles such as cycloheptyne were unstable and could not be prepared for control reactions.

Dicobalt hexacarbonyl complex **3-29** was synthesized in 89% yield under mild conditions by complexation of **3-28** with $\{\text{Co}_2(\text{CO})_8\}$ and tested for transannular [4+2] reactions (Table 3.1). We did not observe TADA product **3-28** even after stirring complex **3-29** for 7 days at room temperature (Table 3.1 entry 1). The rate determining step of a Pauson-Khand reaction (PKR) is de-coordination of a CO ligand to provide an open coordination site for an incoming alkene. To facilitate this mechanistic step, various promoters are commonly employed to either oxidize CO to CO_2 or to weakly coordinate to the metal center.²³ We proposed that promoters might also activate transannular [4+2] cycloaddition reactions activating the coordination of the diene to the dienophile complex unit. Promoter/solvent systems commonly used for PKR substrates with propargylic units were thus selected for screening.²⁴ DMSO/THF and TMTU/toluene systems were ineffective at room temperature (Table 3.1 entries 2 and 3), but experiments at 80 °C produced the desired TADA product in 74 and 99% yields, respectively (Table 3.1 entries 4 and 5). The reaction times indicated that the dicobalt-promoted TADA reaction was considerably more facile than the cobalt-free TADA reaction; while the TADA reaction of metal-free macrocycle **3-27** was complete in 45 hours, tricycle **3-28** was obtained in quantitative yield from

complex **3-29** in only 12 hours at the same temperature (Table 3.1 entry 5 vs Scheme 3.5). An impressive result was obtained when the cycloaddition reaction was performed with a stronger promoter. Although metal-free dienyne ring **3-27** was unreactive in a TADA reaction at room temperature (Scheme 3.5), complex **3-29** formed product **3-28** in 80% yield in just 30 minutes when treated with NMO (Table 3.1 entry 6). Increasing the reaction time to 4 hours for complete consumption of the complex increased the yield to 90% (Table 3.1 entry 7). Acetonitrile solvent, which was the choice of promoter/solvent in previously reported cycloaddition reactions of dicobalt complexes,²² did not affect the product yield, but dramatically slowed the reaction (Table 3.1 entry 8).

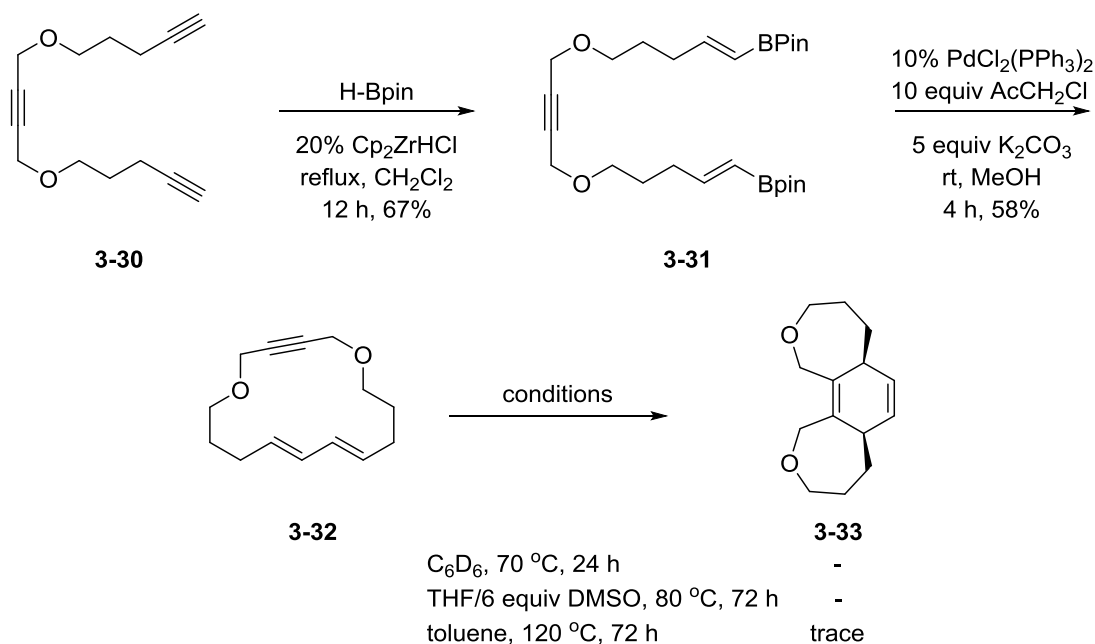
Table 3.1. Preparation and transannular [4+2] reactions of complex 3-29



Entry	Temperature (°C)	Promoter ^a	Promoter equiv	Time (h)	Solvent	Yield (%) ^b
1	25	-	-	168	CH ₂ Cl ₂	0
2	25	DMSO	6	120	THF	0
3	25	TMTU	0.6	72	toluene	0
4	80	DMSO	6	18	THF	74
5	80	TMTU	0.6	12	toluene	99
6	25	NMO	6	0.5	CH ₂ Cl ₂	80
7	25	NMO	6	4	CH ₂ Cl ₂	90

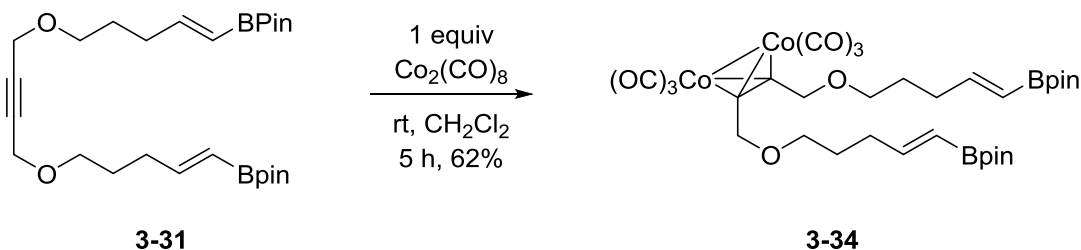
^aDMSO = Dimethyl sulfoxide NMO = *N*-methylmorpholine-*N*-oxide TMTU = 1,1,3,3-tetramethylthiourea ^bYields are of isolated products. For entries 1-4 unreacted starting material was recovered as dicobalt complex **3-29** and/or decomplexed diyne **3-27**.

After observing dramatic [4+2] reactivity changes by merely installing a single additional atom on to substrate rings, we decided to test even larger macrocycles to elucidate the general trend. 16-membered dienyne ring **3-32** was prepared via hydroboration of **3-30** followed by Pd(II)-catalyzed macrocyclization and then subjected to transannular [4+2] reaction conditions (Scheme 3.6). Metal-free TADA reaction of **3-32** was not effective as tricyclic compound **3-33** was not formed even after heating **3-32** at 70 °C for 24 hours or at 80 °C for 72 hours. When macrocycle **3-32** was heated in toluene at 120 °C for 72 hours only a trace amount of product was observed by TLC. Clearly, this larger system no longer benefits from a proximity effect and lacking diene or dienophile activating groups, no TADA reactions were observed.

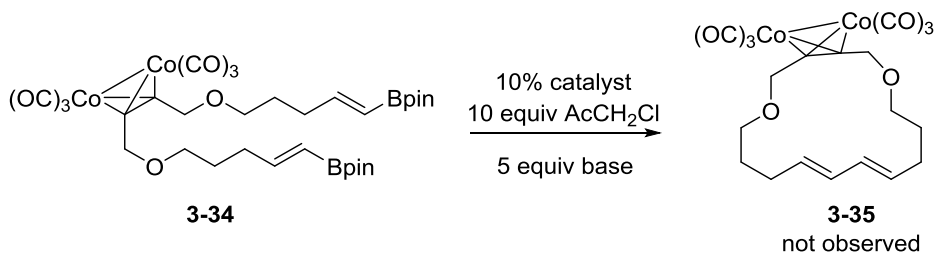


Scheme 3.6. Preparation and attempted metal-free TADA reaction of dienyne 3-32

Proximity-induced, metal-free TADA reaction of macrocyclic dienyne **3-32** failed, but we postulated that the dicobalt complexed ring could undergo successful transannular [4+2] cycloaddition considering the reactivity improvement detected in the reactions of 15-membered macrocycle **3-27**. Initially, we attempted to prepare dicobalt hexacarbonyl complexed macrocycle **3-35** through Pd(II)-catalyzed coupling reaction of complex **3-34** (Table 3.2) in order to benefit from the pseudo *cis* alkene structure of {Co₂(CO)₆}-alkyne unit that could release the strain in the product ring and force the vinylboronate ester coupling partners in close proximity during macrocyclization. **3-34** was synthesized in 62% yield by complexation of bis(vinylboronate ester) **3-31** (Scheme 3.7). Several intramolecular coupling reaction conditions, including the conditions that produced macrocycle **3-32** successfully (Scheme 3.6), were tested but unfortunately target complex **3-35** did not form (Table 3.2). Each trial led to a mixture of unreacted starting material and unidentifiable decomposition products. This could be caused by deactivation of palladium catalyst through CO coordination or unwanted CO insertion reactions.²⁵ A coupling reaction was performed at 0 °C to inhibit the release of CO from the substrate complex but nevertheless **3-35** was not detected (Table 3.2 entry 6).



Scheme 3.7. Preparation of complex 3-34

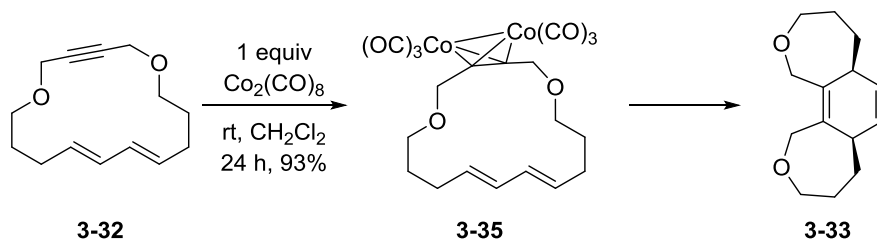
Table 3.2. Attempted synthesis of complex 3-35 by Pd(II)-catalyzed macrocyclization

Entry	Temperature (°C)	Catalyst	Time (h)	Solvent	Base
1	25	PdCl ₂ (PPh ₃) ₂	24	MeOH	K ₂ CO ₃
2	25	PdCl ₂ (PPh ₃) ₂	12	DMF	K ₂ CO ₃
3	25	PdCl ₂ (PPh ₃) ₂	12	DMF	CsF
4	25	PdCl ₂ (PPh ₃) ₂	19	THF	CsF
5	25	PdCl ₂	48	DMF	CsF
6	0	PdCl ₂ (PPh ₃) ₂	12	MeOH	K ₂ CO ₃

We used the previous strategy to prepare dicobalt complex **3-35** and the complexation reaction of **3-32** with {Co₂(CO)₈} afforded the target macrocyclic complex in 93% yield (Table 3.3). Transannular [4+2] cycloaddition reaction conditions were applied on **3-35** and to our delight tricyclic product **3-33**; despite being inaccessible through metal-free thermal TADA reactions, formed in satisfactory yields (Table 3.3). Dicobalt-promoted reactions were highly dependent on the promoter/solvent composition. The previously most active promoter NMO was ineffective at room temperature or at 80 °C (Table 3.3 entries 1 and 2). When heat was used as the sole promoter product yields were low (Table 3.3 entries 3 and 4). While toluene/TMTU was found to provide a quantitative conversion of 15-membered cycle **3-27** to tricycle **3-28** (Table

3.1 entry 5), it failed to promote formation of tricycle **3-33**. Higher yields were achieved when benzene was used as the solvent partner to TMTU (Table 3.3 entry 6). Finally, product **3-33** was successfully synthesized in an 86% yield with a THF/DMSO system (Table 3.3 entry 7).

Table 3.3. Preparation and transannular [4+2] reactions of complex 3-35



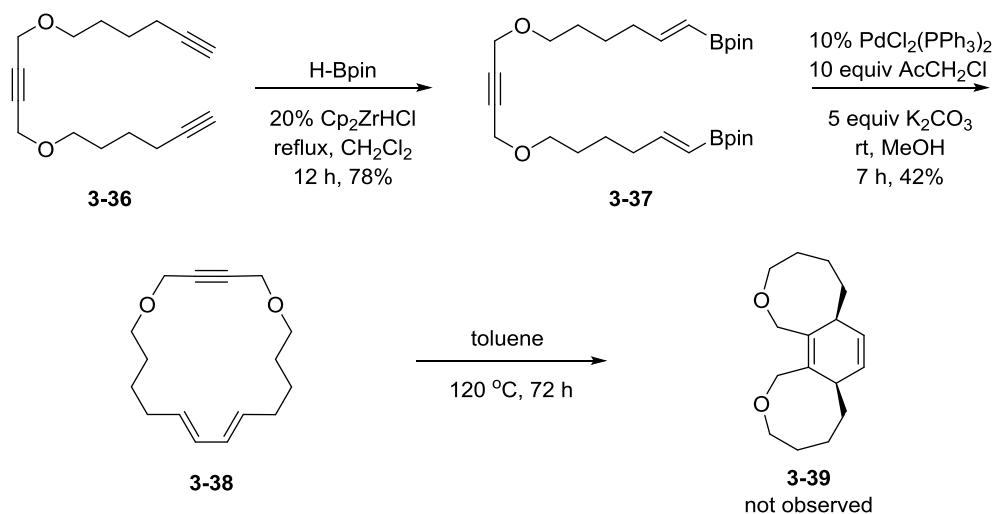
Entry	Temperature (°C)	Promoter	Promoter equiv	Time (h)	Solvent ^a	Yield (%) ^b
1	25	NMO	6	48	CH ₂ Cl ₂	14
2	80	NMO	6	48	DCE	17
3	80 - 100	-	-	96	toluene	21
4	140	-	-	17	(n-Bu) ₂ O	25
5	100	TMTU	0.6	24	toluene	-
6	70	TMTU	2	12	benzene	51
7	80	DMSO	6	18	THF	86

^aDCE = 1,2-dichloroethane. ^bYields are of isolated products. For entry 1 unreacted starting material was recovered as complex **3-35** and decomplexed dienyne **3-32**. For entries 2-6 recovered **3-35** and **3-32** were detected together with unidentifiable decomposition products.

Tricyclic products **3-28** and **3-33** were obtained from the cobalt-promoted reactions as single diastereomers and they were predicted to have *cis* stereochemistry. ¹H NMR analysis determined that thermal metal-free TADA reaction of dienyne **3-27** and transannular [4+2] cycloaddition

reaction of complex **3-29** formed the same diastereomer. Thus, the stereochemistry of tricyclic products **3-28** and **3-33** from cobalt-promoted reactions were assigned as *cis*.

We next turned to a transannular cycloaddition reaction of an even larger dienyne ring. 18-membered macrocycle **3-38** was synthesized from bis(vinylboronate ester) **3-37** in 42% yield by Pd(II)-catalyzed macrocyclization (Scheme 3.8). Like dienyne **3-32**, macrocycle **3-38** failed to undergo a thermal TADA reaction; after heating at 120 °C for 72 hours, no desired tricycle **3-39** was formed. These outcomes correspond well with results of theoretical studies. The TADA reaction activation energy was calculated to be 37.9 kcal/mol for 16-membered **3-32**, a value 10 units higher than the TADA activation barrier of 14-membered **3-23** (28.0 kcal/mol). The barrier was calculated to be even higher at 41.6 kcal/mol for 18-membered **3-38**.^{12b}

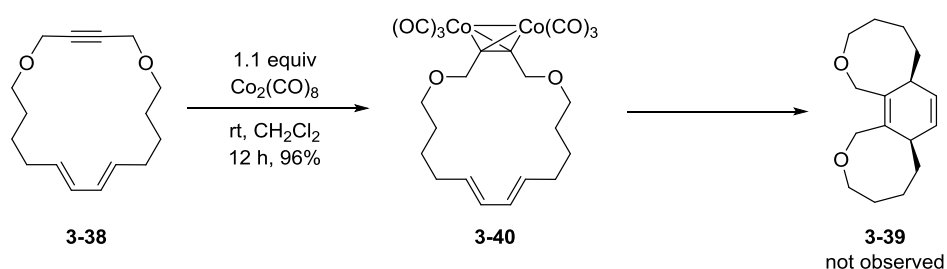


Scheme 3.8. Preparation and attempted TADA reaction of dienyne 3-38

Dicobalt hexacarbonyl complex **3-40** was prepared by a complexation reaction of **3-38** with Co₂(CO)₈ and subjected to test experiments for transannular [4+2] reaction with various promoters (Table 3.4). Even at high temperatures with extensive reaction times (1-14 days), no product formation was detected. These experiments resulted in mixtures of unreacted complex **3-**

40 along with unidentifiable decomposition products (Table 3.4 entries 1-5). On the other hand, when reactive the promoter NMO was utilized together with solvent/promoter MeCN to facilitate the reaction, dicobalt-free macrocycle **3-38** was recovered quantitatively after 5 hours (Table 3.4 entry 6). The lack of reactivity may be due to steric interference by the extended methylene chains and thus the increased distortion energy.

Table 3.4. Preparation and attempted transannular [4+2] reactions of complex 3-40

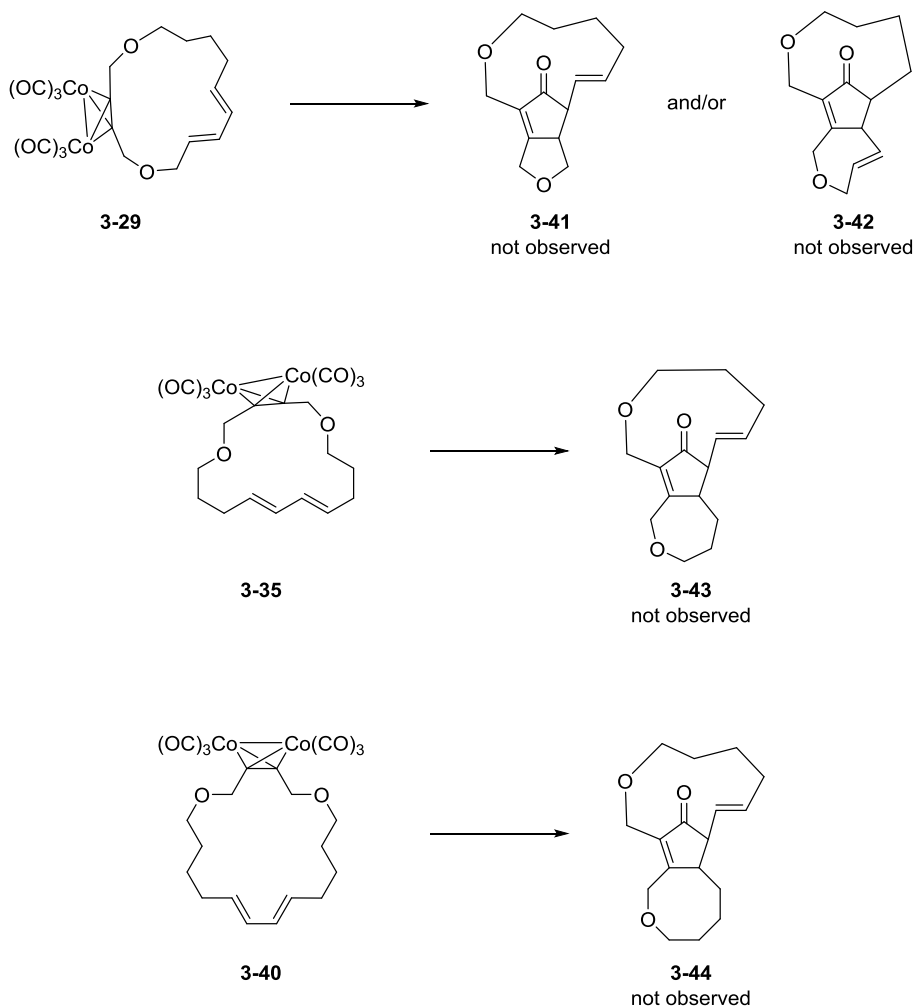


Entry	Temperature (°C)	Promoter	Promoter equiv	Time (d)	Solvent
1	60	TMTU	0.6	14	toluene
2	90	TMTU	0.6	3	toluene
3	110	TMTU	1.2	1	toluene
4	70	DMSO	6	1	toluene
5	90	DMSO	6	5	toluene
6	70	NMO	6	5 h	MeCN

Metal-free TADA reaction product **3-24**, dicobalt-promoted transannular [4+2] cycloaddition products **3-28** and **3-33** are polycycles with 1,4-cyclohexadiene moieties, thus aromatization might be anticipated especially at high temperatures in the presence of oxidants. However, aromatization products derived from **3-24** and **3-33** were not observed. The aromatized form of

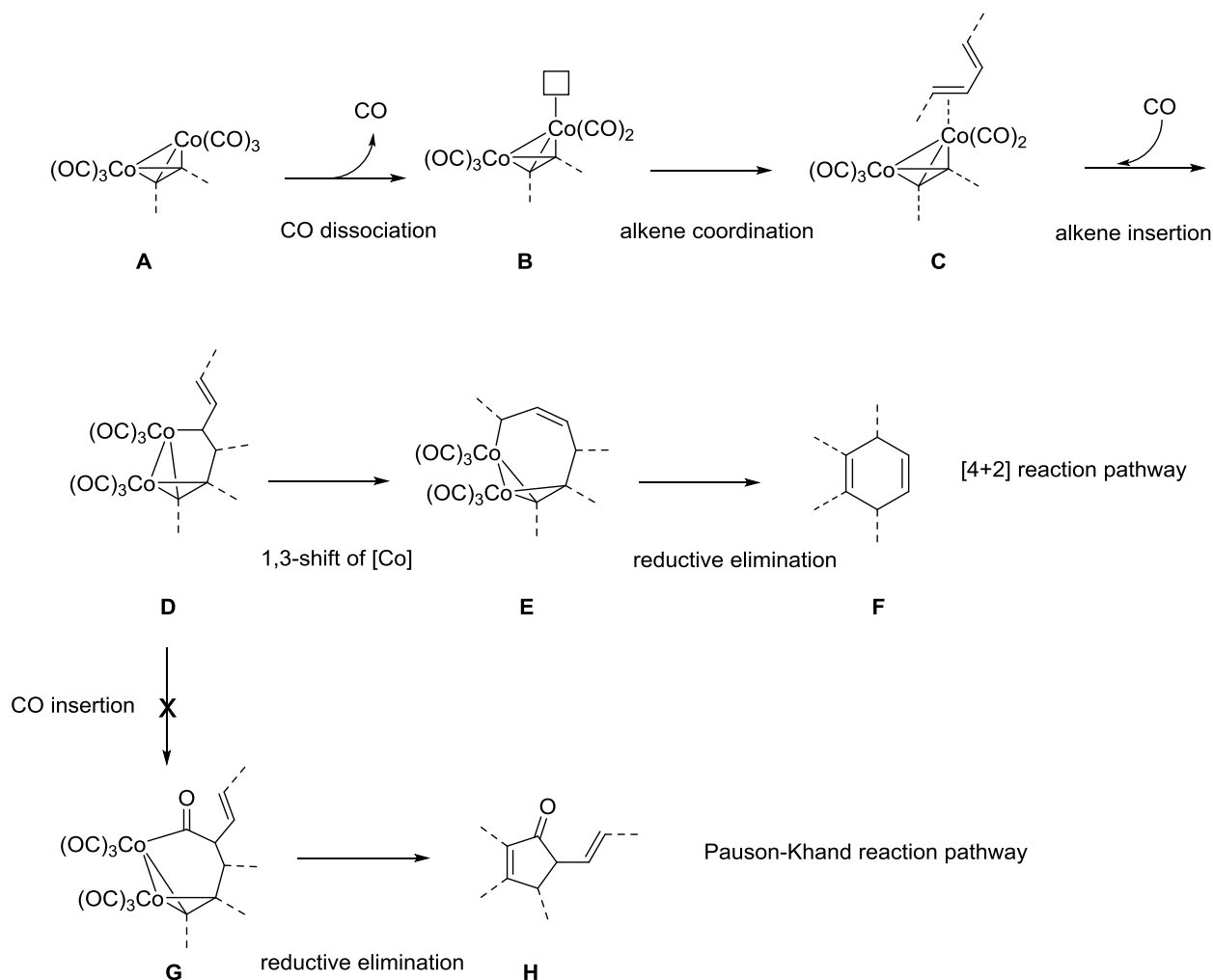
3-28 was detected by ^1H NMR only in trials involving cobalt and oxidizing promoters together with heat. Fortunately, since it is possible to synthesize **3-28** at room temperature (Table 3.1 entries 6-8), aromatization can be avoided.

One reason for the limited number of dicobalt-promoted [4+2] cycloaddition examples reported in the literature is the high propensity for Pauson Khand reactions to occur. $\{\text{Co}_2(\text{CO})_6\}$ -alkyne complexes are known to readily undergo intermolecular PKR with dienes.^{21,26} Moreover, it was shown that an intramolecular PKR pathway is preferred over dicobalt-promoted intramolecular [4+2] cycloaddition reactions when acyclic dienyne dicobalt complexes were treated with promoters.²⁷ In our studies, transannular [4+2] cycloaddition reactions of dicobalt complexes showed impressive selectivity and none of the possible transannular PKR products **3-41**, **3-42**, **3-43** or **3-44** were detected (Scheme 3.9).



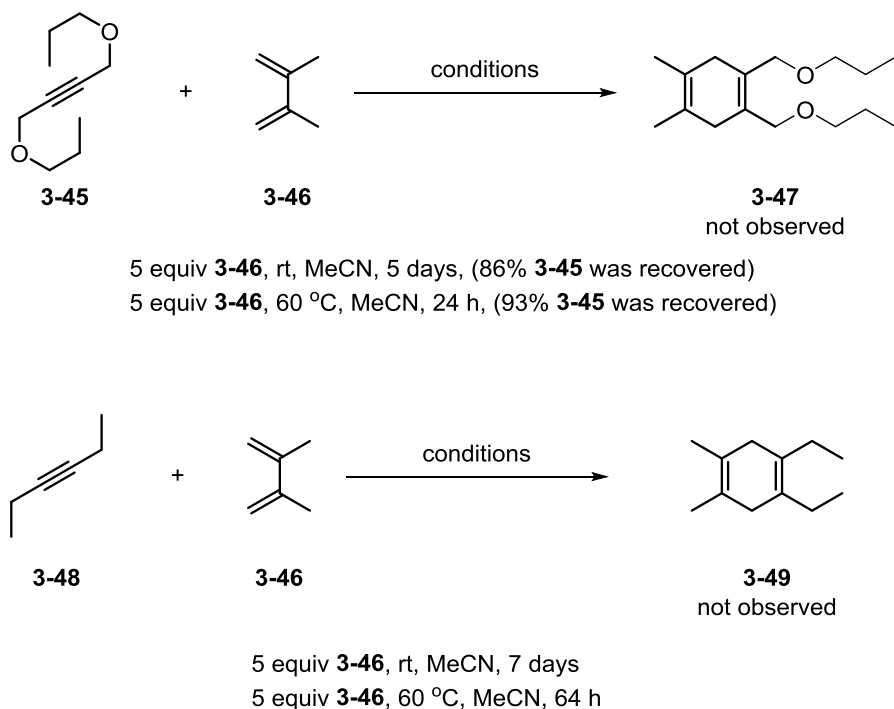
Scheme 3.9. Possible transannular Pauson-Khand reaction products

This selectivity may be due to conformational effects and a tendency for the intermediate cobaltocycle **D** that results from alkene insertion into the dicobalt-alkyne moiety to undergo a 1,3-shift (Scheme 3.10) and subsequent reductive elimination faster than CO insertion/reductive elimination path (i.e. Pauson-Khand reaction path in Scheme 3.10).^{22a} Failed attempts to perform [4+2] cycloaddition reactions with catalytic amounts of $\{\text{Co}_2(\text{CO})_8\}$ (details are discussed in Chapter 4) imply that metal-activated classical concerted Diels-Alder type reactions²⁸ are not likely to occur. This in turn strengthens the possibility of the proposed stepwise mechanism.



Scheme 3.10. Proposed general mechanism of dicobalt-promoted [4+2] cycloadditions

Finally, we tested intermolecular versions of dicobalt-promoted [4+2] cycloadditions. For these control reactions we selected dienes and dienophiles that are not activated with electron-donating or electron-withdrawing components similar to our TADA reaction substrates. Diels – Alder reactivities of dienophiles 1,4-dipropoxybut-2-yne (**3-45**) and 3-hexyne (**3-48**) were tested with 2,3-dimethylbuta-1,3-diene (**3-46**). Expected Diels-Alder adducts **3-47** and **3-49** were not formed at room temperature and thermal Diels-Alder reactions similarly did not occur (Scheme 3.11).

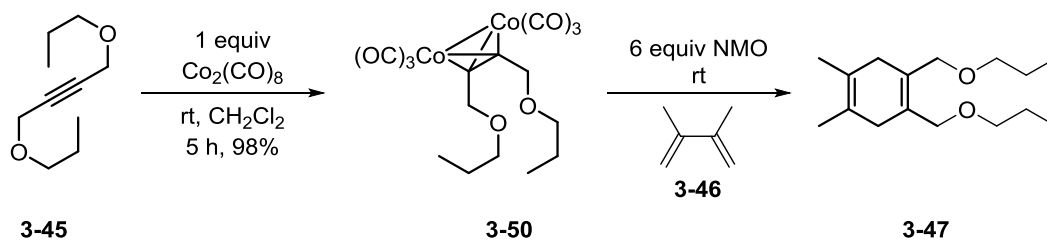


Scheme 3.11. Attempted metal-free intermolecular Diels-Alder reactions of dienophiles 3-45 and 3-48 with 2,3-dimethylbuta-1,3-diene (3-46)

Dicobalt hexacarbonyl complex **3-50** was prepared and tested for an intermolecular [4+2] cycloaddition (Table 3.5). Remarkably, the dicobalt complexed version of otherwise Diels-Alder inactive alkyne **3-45** formed product **3-47** at room temperature in the presence of NMO. Acetonitrile was found to be a better solvent choice for the reaction (Table 3.5 entry 1 vs entry 2). Following previous reports,²² the equivalents of diene and the concentration of dienophile **3-50** were increased which led to formation of product in a high yield (Table 3.5 entry 3). However, use of 30 equivalents of diene was considered as a setback in terms of reaction generality and efficiency, but use of stoichiometric amounts of diene decreased the yield considerably (Table 3.5 entry 4). We proposed that NMO-assisted CO decooordination is quite facile and that decomposition of the alkyne complex through multiple CO decoordinations occurs faster than coordination of the alkene to the metal center. Fortunately, slow addition of a

NMO/acetonitrile solution into the reaction and a small increase in diene equivalence afforded [4+2] product in satisfactory yields (Table 3.5 entries 6-8).

Table 3.5. Preparation and intermolecular [4+2] reaction of complex 3-50

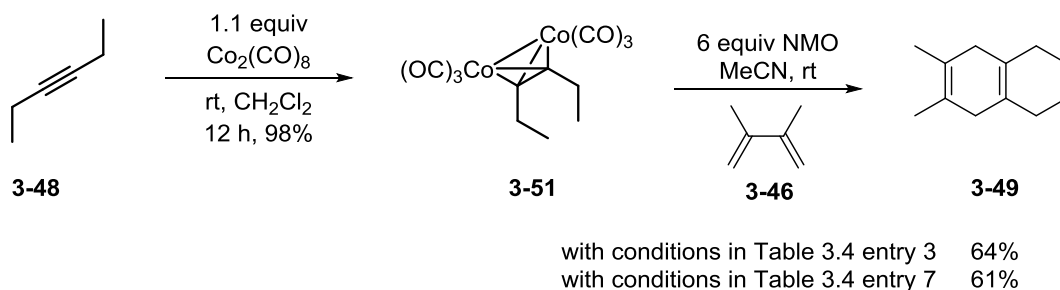


Entry	Concentration of 3-50 (M)	Equivalent of 3-46	Time (h)	Solvent	Yield (%)
1	0.1	10	12	CH ₂ Cl ₂	30
2	0.1	10	24	MeCN	60
3	0.2	30	12	MeCN	84
4	0.2	1	24	MeCN	41
5	1.0	5	24	MeCN	62
6 ^a	0.2	5	24	MeCN	63
7 ^b	0.2	5	24	MeCN	70
8 ^c	0.2	5	24	MeCN	67

^aA solution of NMO was added dropwise over 1 hour. ^bA solution of NMO was added dropwise over 5 hours. ^cA solution of NMO was added dropwise over 14 hours.

Complex **3-51** was also reactive and [4+2] adduct **3-49** was obtained in a 64% yield at room temperature by using 30 equivalents of diene and the mild promoter MeCN as the solvent. Slow addition of NMO avoided high loadings of **3-46** and afforded adduct **3-49** successfully in a 61% yield (Scheme 3.12). To our delight like the transannular analogues, the intermolecular [4+2]

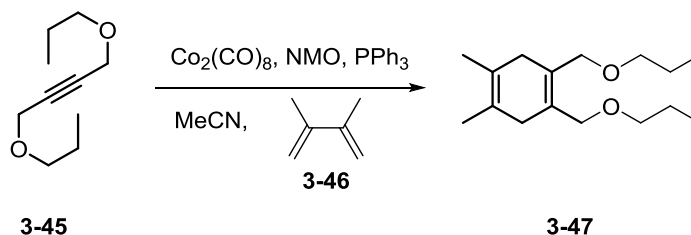
reactions were chemoselective; a competing Pauson-Khand reaction was not observed from **3-50** and only a trace was detected from **3-51**. These results suggest that dicobalt-promoted [4+2] cycloaddition reactions may be more feasible than previously thought and deserve further exploration.



Scheme 3.12. Preparation and intermolecular [4+2] reaction of complex **3-51**

Intermolecular [4+2] reactions of alkyne **3-45** with catalytic amounts of $\{\text{Co}_2(\text{CO})_8\}$ were also tested (Table 3.6). The reactions were not effective; in acetonitrile with the reactive promoter NMO only trace amounts of product were detected (Table 3.6 entries 1-3). As suggested in the reaction mechanism (Scheme 3.10) regeneration of a dicobalt hexacarbonyl-alkyne complex may be necessary. Therefore, a catalytic reaction was tested under 1 atm of CO in the presence of the mild promoter DMSO since NMO was suspected to decompose the catalyst rapidly before alkyne-dicobalt complexation occurs (Table 3.6 entry 4). However, no product was observed. Finally, triphenyl phosphine was tested as a substitute ligand for CO (Table 3.6 entries 5 and 6), but $\{\text{Co}_2(\text{CO})_{6-n}(\text{PPh}_3)_n\}$ -alkyne complexes were likely to be less stable and more difficult to access compared to all carbonyl complexes, so the [4+2]-product could not be obtained through these trials. Bisphosphino ligands can be tested in the future as potentially more effective alternatives.

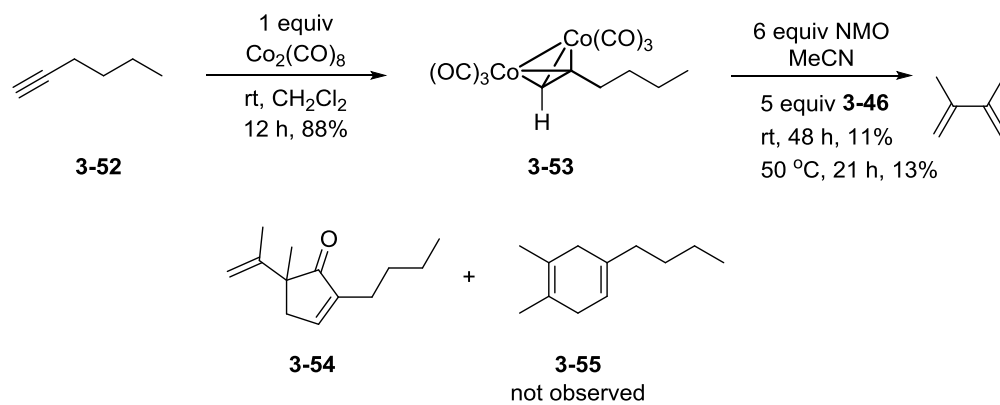
Table 3.6. Attempted catalytic intermolecular [4+2] reaction of 3-45



Entry	Concentration of 3-45 (M)	Equivalent of 3-46	Equivalents of $\text{Co}_2(\text{CO})_8/\text{NMO}/\text{PPh}_3$	Temperature ($^\circ\text{C}$)	Yield (%)
1	2	1	0.1/0.1/-	25	trace
2	2	1	0.1/1/-	25	trace
3	0.5	1	0.1/1/-	40	8
4 ^a	0.2	5	0.1/-/-	25	0
5	0.5	1	0.1/-/1	25	0
6	1	4	0.1/0.1/0.2	25	0

^a6 equiv DMSO was used. Reaction was carried under 1 atm CO.

In order to investigate the reactivity of terminal alkyne-dicobalt complexes we prepared complex **3-53** and subjected it to our optimized conditions. Complex **3-53** was highly resistant to cycloadditions. Even under thermal [4+2] reaction conditions, after 21 hours TLC studies showed complex **3-53** as the major component in the medium. Interestingly, the test experiments yielded only small amounts of Pauson-Khand product **3-54** as the sole isolated product (Scheme 3.13, structure was determined by $^1\text{H-NMR}$). It was clear that dicobalt hexacarbonyl complexes of terminal alkynes have different reactivities than internal analogues and demand alternative approaches for further investigations.



Scheme 3.13. Preparation and attempted intermolecular [4+2] reaction of complex 3-53

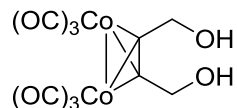
3.3. Conclusions

In conclusion, we demonstrated the first transannular [4+2] cycloaddition reactions of dicobalt hexacarbonyl alkyne complexes. In addition, the examples presented are the first transition metal-mediated transannular [4+2]/Diels-Alder reactions. Substrates with 14-, 15-, 16-, and 18-membered cyclic dienynes were efficiently synthesized via versatile Pd(II)-catalyzed macrocyclizations of the corresponding bis(vinylboronate esters). Proximity-induced, thermal TADA reactions of the macrocyclic dienynes were tested and a direct correlation between ring size and TADA reactivity was detected. In a cyclic diyne as the bridge tethers connecting the diene and dienophile units get longer, the tendency of the molecule to go through a TADA reaction decreases. Experimental outcomes were in good agreement with the results of theoretical studies. Dicobalt-promoted transannular reactions were significantly more effective than the metal-free analogues and the transannular [4+2] cycloaddition product from a 16-membered diyne was only accessible by dicobalt-mediated reactions. Cycloadditions of dicobalt hexacarbonyl complexes were highly selective; the tricyclic products were obtained as single diastereomers and competing Pauson-Khand reactions were not observed. Intermolecular control reactions confirmed the ability to force unactivated dienes and dienophiles to participate room temperature-[4+2] cycloaddition reactions selectively avoiding the Pauson-Khand reaction pathway. Overall, this project provided valuable contributions to an almost untouched research area of organocobalt chemistry and a novel, versatile method to prepare polycyclic structures under mild conditions.

3.4. Experimental

General Procedures

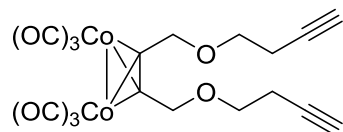
All commercial compounds were used as received unless stated otherwise. Dicobalt octacarbonyl was purchased from Strem Chemicals, Inc. as a solid, stabilized with 1–5 % hexane and was stored at 0 °C. DCM and Et₃N were purified by distillation over CaH₂. THF, Et₂O and toluene were distilled prior to use from sodium-benzophenone ketyl. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere, unless stated otherwise. Column chromatography was performed using silica gel (Davisil, 40-63 micron) and reagent grade solvents without deactivation, unless noted. NMR spectra were recorded on a Bruker ARX-400 instrument and calibrated to the solvent signal (CDCl₃ δ = 7.26 ppm for ¹H NMR, δ = 77.0 ppm for ¹³C NMR, C₆D₆ δ = 7.16 ppm for ¹H NMR, δ = 128.0 ppm for ¹³C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sextet (sext), m (multiplet), or b (broadened). IR spectra were recorded on a Jasco FTIR-4100 spectrophotometer with an ATR attachment and selected signals are reported in cm⁻¹. Mass spectra were recorded on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE Direct Analysis in Real Time (DART) ion source.



$[(\text{Co}_2(\text{CO})_6)-(\mu-\eta^2, \eta^2\text{-HOCH}_2\text{C}\equiv\text{CCH}_2\text{OH})]$ (3-19)

To a solution of but-2-yne-1,4-diol (0.50 g, 5.81 mmol) in DCM (25 mL) $\text{Co}_2(\text{CO})_8$ (2.20 g, 6.39 mmol) was added. The mixture was stirred at rt for 12 h and solvent was removed *in vacuo*. Chromatography with 1:1 hexanes/ Et_2O afforded 2.14 g (99% yield) of the known²⁹ red crystals.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 4.87 (s, 4H), 2.70 (bs, 2H).



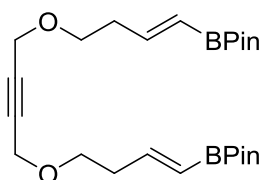
$[(\text{Co}_2(\text{CO})_6)-(\mu-\eta^2, \eta^2\text{-HC}\equiv\text{C}(\text{CH}_2)_2\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{O}(\text{CH}_2)_2\text{C}\equiv\text{CH})]$ (3-20)

A flame dried round bottom flask was charged with **3-19** (0.46 g, 1.24 mmol) in dry DCM (12 mL) under N_2 atmosphere. The solution was cooled to 0 °C and $\text{BF}_3\cdot\text{OEt}_2$ (0.30 mL, 2.48 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min before 3-butyn-1-ol (1 mL, 12.40 mmol) was added dropwise. The reaction mixture was allowed to stir for 1 h at 0 °C and for 4 h at rt. The solution was diluted with DCM, washed with saturated NaHCO_3 solution and brine, and dried over MgSO_4 . Chromatography with 9:1 petroleum ether/ Et_2O afforded 0.425 g (72% yield) of a red oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 4.70 (s, 4H), 3.74 (t, $J = 7$ Hz, 4H), 2.51 (td, $J = 7.0, 2.8$ Hz, 4H), 1.97 (t, $J = 2.8$ Hz, 2H);

General Procedure 1: Preparation of bis(vinylboronate esters)

A dry two neck round bottom flask equipped with a reflux condenser was charged with Cp_2ZrHCl (0.20 equiv) under a N_2 atmosphere. A solution of triyne (1 equiv) in dry DCM was added at $0\text{ }^\circ\text{C}$ forming a suspension with the Cp_2ZrHCl . Pinacolborane (4 - 4.5 equiv) was added dropwise to this suspension. The resultant solution was stirred at $0\text{ }^\circ\text{C}$ for 30 min and was refluxed for overnight. The reaction was quenched with water, diluted with DCM and washed with brine. After drying with MgSO_4 the solvent was removed *in vacuo*. Chromatography with 4:1 petroleum ether/ Et_2O afforded the product.



1,4-bis((E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyloxy)but-2-yne (3-22)

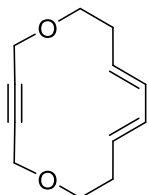
According to the *General Procedure 1* Cp_2ZrHCl (0.054 g, 0.21 mmol) reacted with **3-21** (0.2 g, 1.05 mmol) and pinacolborane (0.70 mL, 4.73 mmol) to afford 0.276 g (59% yield) of a colorless oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 6.61 (dt, $J = 18.0, 6.4$ Hz, 2H), 5.52 (dt, $J = 18.0, 1.6$ Hz, 2H), 4.18 (s, 4H), 3.60 (t, $J = 6.6$ Hz, 4H), 2.46 (tdd, $J = 6.6, 6.4, 1.6$ Hz, 4H), 1.25 (s, 24H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 150.1, 83.1, 82.3, 68.6, 58.3, 35.8, 24.8 (boron substituted vinyl carbons absent);

IR (neat ATR): 2977, 2931, 2857, 1639, 1441, 1389, 1357, 1318, 1142, 1102, 1084, 997, 970, 849;

HRMS (DART): calcd $[M+H]^+$ 447.30838, found 447.30665.



(9E, 11E)-1,6-dioxacyclotetradeca-9,11-diene-3-yne (3-23)

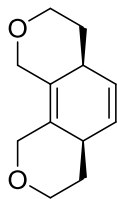
A flame dried round bottom flask was charged with $\text{PdCl}_2(\text{PPh}_3)_2$ (0.02 g, 0.029 mmol) and flashed with N_2 . Methanol (145 mL), **3-22** (0.129 g, 0.29 mmol), chloroacetone (0.23 mL, 2.89 mmol) and aqueous K_2CO_3 (2 M, 0.7 mL, 1.45 mmol) were added and the mixture was allowed to stir at rt. The reaction was monitored via TLC and after 3 h all starting material was consumed. The reaction solvent was removed *in vacuo* and chromatography with 4:1 petroleum ether/ Et_2O afforded 0.038 g (68% yield) of a white solid.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 6.24-6.19 (m, 2H), 5.75-5.65 (m, 2H), 4.11 (s, 4H), 3.60 (t, $J = 5.4$ Hz, 4H), 2.25 (dt, 7.2, 5.6 Hz, 4H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 134.3, 128.4, 82.6, 71.8, 60.2, 33.5;

IR (neat ATR): 2940, 2918, 2873, 1431, 1351, 1254, 1123, 1095, 1066, 993, 967;

HRMS (DART): calcd $[M+H]^+$ 193.12231, found 193.12174.



(cis)-1,3,4,4a,6a,7,8,10-octahydropyrano[4,3-*h*]isochromene (3-24)

A flame dried round bottom flask was charged with **3-23** (12 mg, 0.0624 mmol) and toluene (2 mL). The solution was heated at 50 °C for 9.5 h. TLC and NMR showed complete conversion and removal of solvent *in vacuo* gave a quantitative yield of the colorless liquid TADA product.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.50 (s, 2H), 4.68 (d, *J* = 12.8 Hz, 2H), 4.02 (ddd, *J* = 11.4, 4.4, 0.8 Hz, 2H), 3.62-3.56 (m, 4H), 2.80-2.77 (m, 2H), 1.78 (ddt, *J* = 13.2, 3.6, 2.0 Hz, 2H), 1.63 (dd, *J* = 12.0, 4.4 Hz, 1H), 1.57 (dd, *J* = 12.0, 4.4 Hz, 1H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 127.70, 127.67, 68.2, 66.1, 36.4, 35.7;

IR (neat ATR): 2965, 2937, 2916, 2838, 2359, 1138, 1098, 1077, 941, 861, 775;

HRMS (DART): calcd [M+H]⁺ 193.12231, found 193.12182

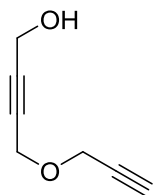
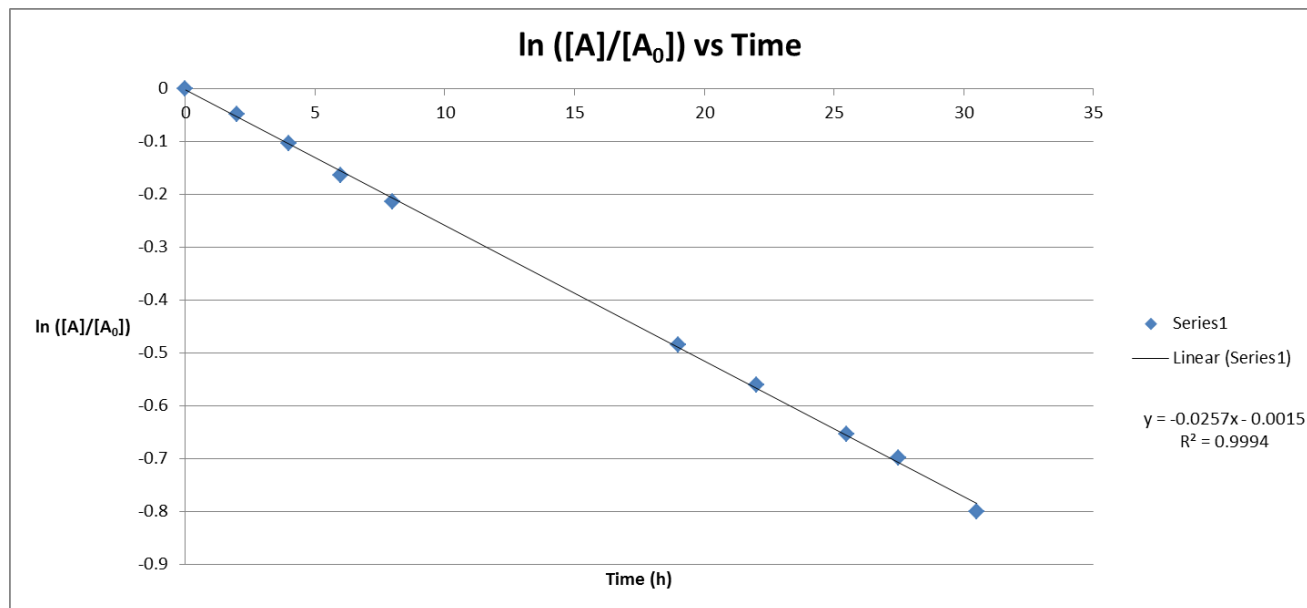
NMR conversion study

Compound **3-23** was dissolved in CDCl₃, deoxygenated with N₂ and placed in an NMR tube. The tube was kept in a mineral oil bath with a stabilized temperature of 21 °C and a ¹H NMR spectrum was taken each time period shown below in Table 3.6 to monitor conversion of **3-23** to TADA product **3-24**. From ln ([A]/[A₀]) vs time plot the slope was found to be -0.0257 h⁻¹ and the t_{1/2} was calculated to be 26.97 h (27 h).

Table 3.7. Conversion of 3-23 to TADA product 3-24

Entry	Time (h)	SM/TADA	SM (A) %	TADA %	Ln([A]/[A ₀])
1.	0	1/0.01	99.00	1.00	0
2.	2	1/0.06	94.34	5.66	-0.0482
3.	4	1/0.12	89.28	10.72	-0.1033
4.	6	1/0.19	84.03	15.97	-0.1639
5.	8	1/0.25	80.00	20.00	-0.2131
6.	19	1/0.64	60.97	39.03	-0.4847
7.	22	1/0.77	56.50	43.50	-0.5609
8.	25.5	1/0.94	51.55	48.45	-0.6527
9.	27.5	1/1.03	49.26	50.74	-0.6980
10.	30.5	1/1.18	45.87	54.13	-0.7993

Ln ([A]/[A₀]) vs Time Plot



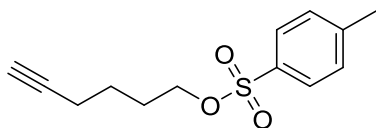
4-(prop-2-yn-1-yloxy)but-2-yn-1-ol

To a suspension of KOH (11.60 g, 206.75 mmol) in DMSO (100 mL) were added propargyl bromide (4.50 mL, 41.25 mmol, 80% w/v in toluene) and but-2-yne-1,4-diol (17.5 g, 206.75 mmol). The mixture was then stirred for 2 h, poured into water, and extracted with DCM. The aqueous phase was then acidified with aqueous HCl (6 M) and further extracted with DCM. The combined organic phases were reduced in volume, washed with water, dried with MgSO₄, and concentrated *in vacuo*. Chromatography with 3:1 hexanes/EtOAc afforded 3.097 g (60% yield) of the known³⁰ colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 4.32 (s, 2H), 4.30 (s, 2H), 4.25 (d, *J* = 2.4 Hz, 2H), 2.45 (t, *J* = 2.4 Hz, 1H), 1.77 (bs, 1H).

General Procedure 2: Preparation of 4-methylbenzenesulfonates

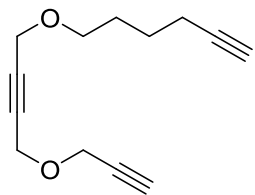
TsCl (1.1 equiv) was added portionwise to a stirred and ice-cooled solution of an alcohol (1.0 equiv), DMAP (0.01 equiv) and Et₃N (1.3 equiv) in DCM. The mixture was stirred for 1 h at 0 °C and then at rt. Upon completion, the reaction solution was diluted with DCM, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography with 4:1 Hexanes/EtOAc.



Hex-5-yn-1-yl 4-methylbenzenesulfonate

According to the *General Procedure 2*, TsCl (10.80 g, 56.64 mmol) was reacted with hex-5-yn-1-ol (6.4 mL, 51.50 mmol), DMAP (63 mg, 0.515 mmol) and Et₃N (9.3 mL, 66.95 mmol) in DCM. Chromatography with 4:1 hexanes/EtOAc gave 12.08 g (93% yield) of the known³¹ colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 2.15 (td, *J* = 6.8, 2.4 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.80-1.73 (m, 2H), 1.60-1.51 (m, 2H).



6-((4-(prop-2-yn-1-yloxy)but-2-yn-1-yl)oxy)hex-1-yne (3-25)

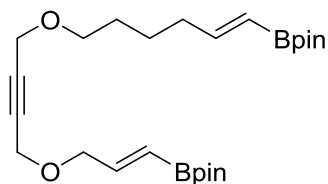
A flame dried flask was charged with NaH (157 mg, 3.92 mmol, 60% w/w dispersion in mineral oil) and dry DMF (4 mL) under a N₂ atmosphere. The suspension was cooled to 0 °C and a solution of 4-(prop-2-yn-1-yloxy)but-2-yn-1-ol (374 mg, 3.01 mmol) in dry DMF (4 mL) was added dropwise. The mixture was stirred for 45 min at 0 °C prior to the addition of hex-5-yn-1-yl 4-methylbenzenesulfonate (760 mg, 3.01 mmol). The reaction solution was allowed to stir at 85 °C overnight. Upon completion, water was added and the crude mixture was extracted with DCM. The combined organic layers were washed with water, brine and dried over MgSO₄. Solvent was removed *in vacuo*. Chromatography with 4:1 hexanes/EtOAc afforded 496 mg (81% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 4.30 (t, *J* = 1.4 Hz, 2H), 4.25 (d, *J* = 2.4 Hz, 2H), 4.17 (t, *J* = 1.8 Hz, 2H), 3.52 (t, *J* = 6.2, 2H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.22 (td, *J* = 7.0, 2.8 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.75-1.68 (m, 2H), 1.65-1.57 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 84.1, 83.2, 81.1, 78.8, 75.0, 69.4, 68.5, 58.1, 56.7, 56.4, 28.4, 25.0, 18.1;

IR (neat ATR): 3234, 2947, 1432, 1253, 1206, 1066, 1046, 966;

HRMS (DART): calcd [M+H]⁺ 205.12231, found 205.12120.



4,4,5,5-tetramethyl-2-((*E*)-6-((4-(((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyloxy)but-2-yn-1-yl)oxy)hex-1-en-1-yl)-1,3,2-dioxaborolane (3-26)

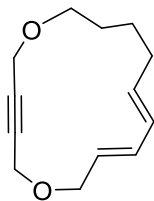
Following *General Procedure 1* the product was obtained in a 48% yield, so the procedure was modified; Cp₂ZrHCl (0.24 g, 0.92 mmol) reacted with **3-25** (0.94 g, 4.60 mmol), pinacolborane (3.0 mL, 20.71 mmol) and Et₃N (0.13 ml, 0.92 mmol). The reaction was refluxed for 7 h and afforded 1.38 g (65% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.65-6.57 (m, 2H), 5.70 (dt, *J* = 18.0, 1.6 Hz, 1H), 5.42 (dt, *J* = 18.0 Hz, 1.6 Hz, 1H), 4.19 (t, *J* = 1.6 Hz, 2H), 4.15 (t, *J* = 1.6 Hz, 2H), 4.12 (dd, *J* = 4.8, 1.6 Hz, 2H), 3.47 (t, *J* = 6.4 Hz, 2H), 2.20-2.14 (m, 2H), 1.63-1.56 (m, 2H), 1.52-1.45 (m, 2H), 1.258 (s, 12H), 1.254 (s, 12H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 154.1, 148.2, 83.3, 82.9, 82.6, 81.9, 71.1, 69.9, 58.2, 57.7, 35.4, 29.0, 24.78, 24.76, 24.71 (boron substituted vinyl carbons absent);

IR (neat ATR): 2978, 2934, 2865, 1639, 1350, 1320, 1142, 1121, 997, 970, 848;

HRMS (DART): calcd [M+H]⁺ 461.32403, found 461.32247.



(8E,10E)-1,6-dioxacyclopentadeca-8,10-dien-3-yne (3-27)

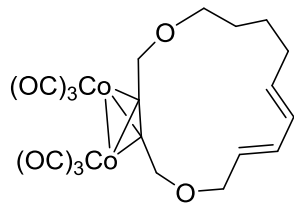
A flame dried round bottom flask was charged with PdCl₂(PPh₃)₂ (45 mg, 0.064 mmol) and flushed with N₂. Methanol (320 mL), **3-26** (0.294 g, 0.64 mmol), chloroacetone (0.50 mL, 6.38 mmol) and aqueous K₂CO₃ (2 M, 1.6 mL, 3.19 mmol) were added and the mixture was allowed to stir at rt overnight. Methanol was removed *in vacuo* and chromatography with 4:1 petroleum ether/Et₂O afforded 83 mg (63% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.30 (dd, *J* = 15.2, 10.0 Hz, 1H), 6.15 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.86 (dt, *J* = 15.2, 7.2 Hz, 1H), 5.77 (dt, *J* = 15.2, 7.6 Hz, 1H), 4.16 (t, *J* = 1.6 Hz, 2H), 4.13, (t, *J* = 1.8 Hz, 2H), 4.09 (dd, *J* = 7.2, 0.4 Hz, 2H), 3.49 (t, *J* = 8.0 Hz, 2H), 2.18 (td, *J* = 6.4, 5.6 Hz, 2H), 1.69-1.63 (m, 2H), 1.51-1.45 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 135.2, 134.8, 130.2, 127.6, 84.8, 82.5, 74.1, 69.0, 58.6, 57.9, 33.7, 28.9, 22.4;

IR (neat ATR): 2934, 2857, 1648, 1540, 1357, 1121, 1087, 1041, 997;

HRMS (DART): calcd [M+H]⁺ 207.13796, found 207.13718.



Complex 3-29

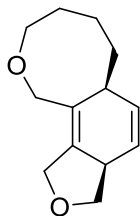
To a solution of **3-27** (102 mg, 0.495 mmol) in DCM (10 mL) $\text{Co}_2(\text{CO})_8$ (170 mg, 0.495 mmol) was added. The mixture was stirred at rt overnight. The solvent was removed *in vacuo*. Chromatography with 19:1 hexanes/EtOAc afforded 217 mg (89% yield) of a red oil.

$^1\text{H NMR}$ (400 MHz, C_6D_6 , ppm) δ : 5.92-5.77 (m, 2H), 5.44-5.32 (m, 2H), 4.32 (s, 2H), 4.25 (s, 2H), 3.74 (bd, $J = 7.2$ Hz, 2H), 3.15 (t, $J = 7.2$ Hz, 2H), 1.84-1.79 (m, 2H), 1.42-1.38 (m, 2H), 1.12 (bs, 2H);

$^{13}\text{C NMR}$ (100 MHz, C_6D_6 , ppm) δ : 199.8 (CO), 135.9, 134.5, 131.2, 126.4, 93.8 (Co-C \equiv C-Co), 92.9 (Co-C \equiv C-Co), 70.95, 70.93, 70.0, 67.5, 31.5, 26.5, 22.9;

IR (neat ATR): 3016, 2937, 2857, 2091, 2048, 2004, 1615, 1448, 1353, 1088, 1065, 993;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 492.97384, found 492.97159.



(cis)-1,3a,5a,6,7,8,9,11-octahydro-3H-oxocino[3,4-e]isobenzofuran (3-28)

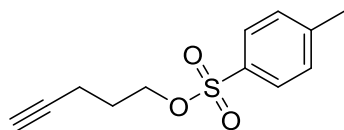
A flame dried round bottom flask was charged with complex **3-29** (75 mg, 0.152 mmol) in DCM (5 mL). NMO (107 mg, 0.914 mmol) dissolved in 3 mL DCM was added slowly. The solution was stirred at rt and monitored by TLC. After the complete consumption of starting material (4 h) the reaction mixture was filtered through short silica plug to remove a purple precipitate. Removal of solvent *in vacuo* afforded 28 mg (90% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 5.77 (bdt, $J = 9.6$ Hz, 1.6, 1H), 5.57 (bd, $J = 10.0$ Hz, 1H), 4.51 (d, $J = 12.8$ Hz, 1H), 4.39 (bd, $J = 12.8$ Hz, 1H), 4.19 (t, $J = 7.2$ Hz, 1H), 4.09 (bs, 2H), 3.86-3.80 (m, 1H), 3.41 (ddd, $J = 11.2, 8.8, 2.8$ Hz, 1H), 3.28 (dd, $J = 10.8, 7.2$ Hz, 1H), 3.16-3.06 (m, 2H), 2.51-2.44 (m, 1H), 1.77-1.70 (m, 1H), 1.66-1.56 (m, 2H), 1.52-1.36 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 137.4, 134.6, 127.4, 121.8, 71.4, 69.3, 68.7, 67.9, 41.0, 38.3, 30.9, 28.9, 22.6;

IR (neat ATR): 3020, 2928, 2852, 1068, 1029, 901, 815, 703;

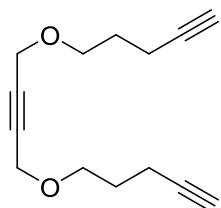
HRMS (DART): calcd [M+H]⁺ 207.13796, found 207.13717.



Pent-4-yn-1-yl 4-methylbenzenesulfonate

According to *General Procedure 2*, TsCl (3.0 g, 15.7 mmol) was reacted with pent-4-yn-1-ol (1.3 mL, 14.27 mmol), DMAP (17 mg, 0.143 mmol) and Et₃N (2.6 mL, 18.55 mmol) in DCM. Chromatography with 4:1 hexanes/EtOAc gave 3.04 g (90% yield) of the known³² colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 4.14 (t, J = 6.0 Hz, 2H), 2.44 (s, 3H), 2.25 (td, J = 6.8, 2.8 Hz, 2H), 1.88 (t, J = 2.8 Hz, 1H), 1.87-1.82 (m, 2H).



1,4-bis(pent-4-ynyloxy)but-2-yne (3-30)

A flame dried flask was charged with NaH (584 mg, 14.6 mmol, 60% w/w dispersion in mineral oil) and dry DMF (10 mL) under a N₂ atmosphere. The suspension was cooled to 0 °C and a solution of but-2-yne-1,4-diol (0.42 g, 4.87 mmol) in dry DMF (10 mL) was added dropwise. The mixture was stirred for 45 min at 0 °C prior to the addition of pent-4-yn-1-yl 4-methylbenzenesulfonate (2.9 g, 12.2 mmol in 5 mL dry DMF). The reaction solution was allowed to stir at 90 °C overnight. Upon completion, water was added and the crude mixture was extracted with DCM. The combined organic layers were washed with water, brine, and dried

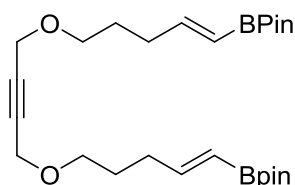
over MgSO₄. Solvent was removed *in vacuo*. Chromatography with 9:1 hexanes/EtOAc afforded 0.72 g (68% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 4.14 (s, 4H), 3.56 (t, *J* = 6.2 Hz, 4H), 2.25 (td, *J* = 7.2, 2.8 Hz, 4H), 1.92 (t, *J* = 2.8 Hz, 2H), 1.80-1.73 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 83.7, 82.3, 68.6, 68.3, 58.4, 28.4, 15.2;

IR (neat ATR): 3289, 2944, 2884, 1435, 1304, 1250, 1103, 1075;

HRMS (DART): calcd [M-H]⁺ 217.12231, found 217.12217.



1,4-bis((*E*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enyloxy)but-2-yne (3-31)

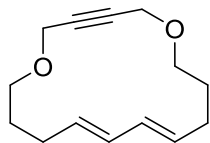
According to *General Procedure 1* Cp₂ZrHCl (0.22 g, 0.84 mmol) reacted with **3-30** (0.92 g, 4.21 mmol) and pinacolborane (2.5 mL, 16.86 mmol) to afford 1.34 g (67% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.61 (dt, *J* = 18.0, 6.4 Hz, 2H), 5.44 (dt, *J* = 18.0, 1.4 Hz, 2H), 4.16 (s, 4H), 3.49 (t, *J* = 6.4 Hz, 4H), 2.25-2.19 (m, 4H), 1.75-1.68 (m, 4H), 1.26 (s, 24H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 153.5, 83.0, 82.3, 69.5, 58.3, 32.2, 28.0, 24.8 (boron substituted vinyl carbons absent);

IR (neat ATR): 2916, 2852, 1638, 1443, 1349, 1139, 1102, 1074, 987, 959, 895, 742;

HRMS (DART): calcd $[M+H]^+$ 475.33968, found 475.33886.



(10E, 12E)-1,6-dioxacyclohexadeca-10,12-diene-3-yne (3-32)

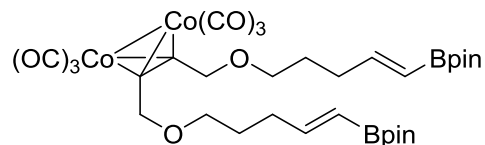
A flame dried round bottom flask was charged with $\text{PdCl}_2(\text{PPh}_3)_2$ (0.07 g, 0.098 mmol) and flushed with N_2 . Methanol (500 mL), **3-31** (0.465 g, 0.98 mmol), chloroacetone (0.80 mL, 9.80 mmol) and aqueous K_2CO_3 (2 M, 2.5 mL, 4.9 mmol) were added and the mixture was allowed to stir at rt for 4 h. Methanol was removed *in vacuo* and chromatography with 4:1 petroleum ether/ Et_2O afforded 0.125 g (58% yield) of a white solid.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 6.08-6.01 (m, 2H), 5.59-5.48 (m, 2H), 4.10 (s, 4H), 3.49 (t, $J = 6.2$ Hz, 4H), 2.21-2.16 (m, 4H), 1.73-1.67 (m, 4H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 131.5, 130.7, 82.2, 68.4, 57.9, 29.5, 27.8,

IR (neat ATR): 3014, 2911, 2849, 2360, 1667, 1344, 1133, 1098, 1084, 989, 957;

HRMS (DART): calcd $[M+H]^+$ 221.15361, found 221.15314.

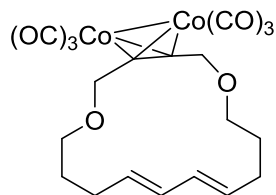


Complex 3-34

To a solution of **3-31** (700 mg, 1.476 mmol) in DCM (5 mL) $\text{Co}_2(\text{CO})_8$ (420 mg, 1.230 mmol) was added. The mixture was stirred for 5h at rt. The solvent was removed *in vacuo*. Chromatography with 9:1 hexanes/EtOAc afforded 580 mg (62% yield) of a red oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 6.63 (dt, $J = 17.6, 6.4$ Hz, 2H), 5.45 (d, $J = 18.0$ Hz, 2H), 4.59 (s, 4H), 3.59 (t, $J = 6.4$ Hz, 4H), 2.27-2.22 (m, 4H), 1.77-1.70 (m, 4H), 1.26 (s, 24H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3 , ppm) δ : 200.2 (CO), 153.7, 117.2 (Co-C \equiv C-Co), 83.0, 70.9, 70.4, 32.2, 28.3, 24.7 (boron substituted vinyl carbons absent).



Complex 3-35

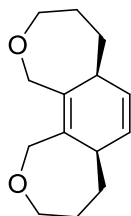
To a solution of **3-32** (125 mg, 0.567 mmol) in DCM (15 mL) $\text{Co}_2(\text{CO})_8$ (194 mg, 0.567 mmol) was added. The mixture was stirred at rt for 24 h. The solvent was removed *in vacuo*. Chromatography with 19:1 hexanes/EtOAc afforded 265 mg (93% yield) of a red oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 6.09-6.02 (m, 2H), 5.61-5.54 (m, 2H), 4.61 (s, 4H), 3.57 (t, $J = 5.4$ Hz, 4H), 2.18 (td, $J = 6.8, 5.2$ Hz, 4H), 1.78-1.73 (m, 4H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 131.9, 131.5, 92.9 (Co-C \equiv C-Co), 71.5, 70.3, 30.4, 29.3
(CO peak was not observed);

IR (neat ATR): 3020, 2942, 2848, 2090, 2049, 1997, 1627, 1441, 1346, 1095, 988;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 506.98949, found 506.98830.



(cis)-1,3,4,5,7a,8,9,10,12-decahydrobenzo[2,1-c:3,4-c']bis(oxepine) (3-33)

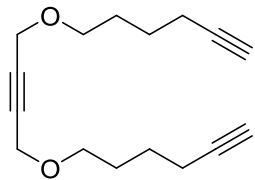
A flame dried two necked round bottom flask equipped with a reflux condenser was charged with complex **3-35** (130 mg, 0.257 mmol) in THF (30 mL). DMSO (0.10 mL, 1.54 mmol) was added and the solution was refluxed for 18 h. The solvent was removed *in vacuo*. Chromatography with 4:1 hexanes/EtOAc afforded 57 mg (86% yield) of a colorless oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 5.71(dd, $J = 2.8, 1.2$ Hz, 2H), 4.31 (d, $J = 14.0$ Hz, 2H), 4.11 (d, $J = 14.4$ Hz, 2H), 4.03 (dtd, $J = 12.2, 3.4, 1.6$ Hz, 2H), 3.21 (td, $J = 11.8, 2.0$ Hz, 2H), 2.95 (d, $J = 10$ Hz, 2H), 1.94-1.89 (m, 2H), 1.78-1.60 (m, 4H), 1.16-1.06 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 133.9, 129.9, 71.2, 70.0, 38.0, 37.7, 30.3;

IR (neat ATR): 3022, 2914, 2863, 2053, 1132, 1100, 1070, 895, 740;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 221.15361, found 221.15300.



1,4-bis(hex-5-ynoxy)but-2-yne (3-36)

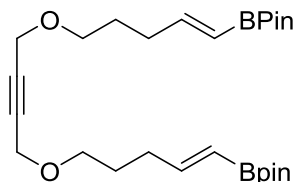
A flame dried flask was charged with NaH (648 mg, 16.25 mmol, 60% w/w dispersion in mineral oil) and dry DMF (20 mL) under N₂ atmosphere. The suspension was cooled to 0 °C and a solution of but-2-yne-1,4-diol (467 mg, 5.42 mmol) in dry DMF (10 mL) was added dropwise. The mixture was stirred for 45 min at 0 °C prior to the addition of hex-5-yn-1-yl 4-methylbenzenesulfonate (4.10 g, 16.25 mmol in 5 mL dry DMF). The reaction solution was allowed to stir at 90 °C for 36 h. Upon completion, water was added and the crude mixture was extracted with DCM. The combined organic layers were washed with water, brine, and dried over MgSO₄. Solvent was removed *in vacuo*. Chromatography with 4:1 hexanes/EtOAc afforded 1.16 g (87% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 4.17 (s, 4H), 3.52 (t, *J* = 6.4 Hz, 4H), 2.22 (td, *J* = 7.0, 2.8 Hz, 4H), 1.94 (t, *J* = 2.8 Hz, 2H), 1.75-1.67 (m, 4H), 1.65-1.57 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 84.1, 82.2, 69.3, 68.3, 58.2, 28.4, 25.0, 18.0;

IR (neat ATR): 3292, 2939, 2862, 1350, 1137, 1105, 1082, 906;

HRMS (DART): calcd [M+H]⁺ 247.16926, found 247.16907.



1,4-bis((*E*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enyloxy)but-2-yne (3-37)

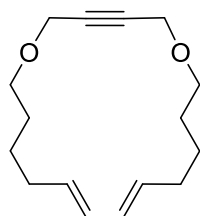
According to *General Procedure 1* Cp_2ZrHCl (0.22 g, 0.84 mmol) reacted with **3-36** (0.92 g, 4.21 mmol) and pinacolborane (2.5 mL, 16.86 mmol) to afford 1.34 g (67% yield) of a colorless oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 6.61 (dt, $J = 18.0, 6.4$ Hz, 2H), 5.44 (dt, $J = 18.0, 1.4$ Hz, 2H), 4.16 (s, 4H), 3.49 (t, $J = 6.4$ Hz, 4H), 2.25-2.19 (m, 4H), 1.75-1.68 (m, 4H), 1.26 (s, 24H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3 , ppm) δ : 153.5, 83.0, 82.3, 69.5, 58.3, 32.2, 28.0, 24.8 (boron substituted vinyl carbons absent);

IR (neat ATR): 2916, 2852, 1638, 1443, 1349, 1139, 1102, 1074, 987, 959, 895, 742;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 475.33968, found 475.33886.



(11*E*, 13*E*)-1,6-dioxacyclooctadeca-11,13-diene-3-yne (3-38)

A flame dried round bottom flask was charged with $\text{PdCl}_2(\text{PPh}_3)_2$ (56 mg, 0.079 mmol) and flushed with N_2 . Methanol (600 mL), **3-37** (0.396 g, 0.79 mmol), chloroacetone (0.60 mL, 7.90 mmol) and aqueous K_2CO_3 (2 M, 2.0 mL, 3.90 mmol) were subsequently added and the mixture

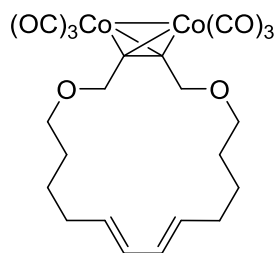
was allowed to stir at rt for 7 h. Methanol was removed *in vacuo* and chromatography with 4:1 petroleum ether/Et₂O afforded 82 mg (42% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.10-6.03 (m, 2H), 5.61-5.51 (m, 2H), 4.16 (s, 4H), 3.50 (t, *J* = 7.2 Hz, 4H), 2.13 (dt, *J* = 6.4, 5.6 Hz, 4H), 1.66 (tt, *J* = 6.8, 6.0 Hz, 4H) 1.56-1.50 (m, 4H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 132.0, 131.0, 82.2, 70.1, 57.9, 31.8, 28.5, 24.2;

IR (neat ATR): 3012, 2931, 2855, 2359, 1443, 1350, 1267, 1207, 1121, 1099, 990, 740;

HRMS (DART): calcd [M+H]⁺ 249.18491, found 249.18450.



Complex 3-40

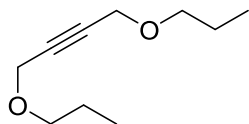
To a solution of **3-38** (60 mg, 0.242 mmol) in DCM (10 mL) Co₂(CO)₈ (91 mg, 0.265 mmol) was added. The mixture was stirred at rt overnight. The solvent was removed *in vacuo*. Chromatography with 19:1 hexanes/EtOAc afforded 124 mg (96% yield) of a red oil.

¹H NMR (400 MHz, C₆D₆, ppm) δ: 5.99-5.92 (m, 2H), 5.44-5.37 (m, 2H), 4.36 (s, 4H), 3.27 (t, *J* = 6.6 Hz, 4H), 1.88 (td, *J* = 6.8, 5.2 Hz, 4H), 1.44 (p, *J* = 6.8 Hz, 4H), 1.30-1.24 (m, 4H);

¹³C NMR (100 MHz, C₆D₆, ppm) δ: 199.8 (CO), 131.7, 131.5, 93.5 (Co-C≡C-Co), 70.6, 70.0, 31.3, 27.5, 23.9;

IR (neat ATR): 3012, 2934, 2859, 2092, 2048, 2003, 1615, 1443, 1350, 1096, 989;

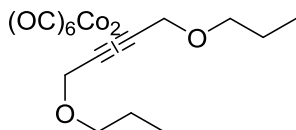
HRMS (DART): calcd $[M+H]^+$ 535.02079, found 535.01808.



1,4-dipropoxybut-2-yne (3-45)

But-2-yne-1,4-diol (1.07 g, 12.5 mmol) was dissolved in H₂O/DMSO mixture (5 mL/20 mL) and cooled to 0 °C. Potassium hydroxide (1.75 g, 31.2 mmol) was added prior to dropwise addition of 1-bromopropane (2.5 mL, 27.5 mmol). The solution was warmed to rt and stirred for 48 h. The reaction mixture was diluted with water, extracted with diethyl ether. Organic extracts were washed with brine, dried over MgSO₄ and filtered through a short silica plug. Removal of solvent *in vacuo* afforded 1.67 g (78% yield) of the known³³ colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 4.18 (s, 4H), 3.46 (t, $J = 6.8$ Hz, 4H), 1.66-1.57 (m, 4H), 0.93 (t, $J = 7.4$ Hz, 6H).



Complex 3-50

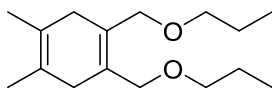
To a solution of **3-45** (493 mg, 2.89 mmol) in DCM (15 mL) Co₂(CO)₈ (1.0 g, 2.89 mmol) was added. The mixture was stirred at rt for 5 h. The solvent was removed *in vacuo*. Chromatography with 19:1 hexanes/EtOAc afforded 1.30 g (98% yield) of a red oil.

¹H NMR (400 MHz, C₆D₆, ppm) δ : 4.31 (s, 4H), 3.21 (t, $J = 6.1$ Hz, 4 H), 1.46 (bsxt, $J = 6.8$ Hz, 4H), 0.84 (t, $J = 7.2$ Hz, 6H);

¹³C NMR (100 MHz, C₆D₆, ppm) δ: 199.7 (CO), 92.8 (Co-C≡C-Co), 72.5, 70.5, 22.9, 10.3;

IR (neat ATR): 2965, 2938, 2878, 2093, 2049, 2007, 1464, 1337, 1096;

HRMS (DART): calcd [M-OCH₂CH₂CH₃]⁺ 396.91633, found 396.91446.



1,2-dimethyl-4,5-bis(propoxymethyl)cyclohexa-1,4-diene (3-47)

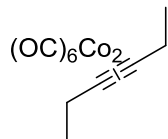
A flame dried round bottom flask was charged with **3-50** (274 mg, 0.60 mmol) and 2,3-dimethylbuta-1,3-diene (0.3 mL, 3.00 mmol). A solution of NMO (422 mg, 3.60 mmol) in MeCN (3 mL) was added dropwise over 5 h and the resultant reaction solution was stirred for 24 h at rt. Solvent was removed and flash chromatography with 9:1 hexanes/EtOAc afforded 104 mg (70% yield) of a colorless oil.

¹H NMR (400 MHz, C₆D₆, ppm) δ: 3.95 (s, 4H), 3.20 (t, *J* = 6.4 Hz, 4H), 2.76 (s, 4H), 1.55-1.46 (m, 10H), 0.85 (t, *J* = 7.4 Hz, 6H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 130.3, 122.7, 71.8, 69.2, 36.3, 22.9, 18.0, 10.6;

IR (neat ATR): 2961, 2931, 2857, 1609, 1456, 1351, 1089, 1036, 957;

HRMS (DART): calcd [M+H]⁺ 253.21621, found 253.21546.

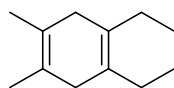


Complex 3-51

To a solution of 3-hexyne (0.5 mL, 4.40 mmol) in DCM (10 mL) $Co_2(CO)_8$ (1.7 g, 4.84 mmol) was added. The mixture was stirred at rt overnight. The solvent was removed *in vacuo*. Chromatography with 19:1 hexanes/EtOAc afforded 1.59 g (98% yield) of the known³⁴ red oil.

1H NMR (400 MHz, $CDCl_3$, ppm) δ : 2.87 (bs, 4H), 1.29 (bs, 6H);

^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ : 200.6 (CO), 101.5 (Co-C \equiv C-Co), 27.0, 15.5;



1,2-diethyl-4,5-dimethylcyclohexa-1,4-diene (3-49)

A flame dried round bottom flask was charged with **3-51** (92 mg, 0.25 mmol) and 2,3-dimethylbuta-1,3-diene (0.14 mL, 1.25 mmol). A solution of NMO (176 mg, 1.50 mmol) in MeCN (1.2 mL) was added dropwise over 5 h and the resultant reaction solution was stirred for 24 h at rt. Solvent was removed and flash chromatography with petroleum ether afforded 25 mg (60% yield) of a colorless oil. During the work-up processes some aromatization occurred as 1H -NMR showed 9% aromatized product with a signals at 6.93 ppm (s, 2H), 2.21 (s, 6H), 2.15-2.10 (m, 4H), 1.20 (t, $J = 7.4$ Hz, 8H). Trace amounts of possible Pauson-Khand reaction products were detected in 1H -NMR as evidenced by weak signals at 6.00 (s), 5.63 (s), 5.33 (t, $J = 7.2$ Hz),

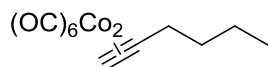
5.22 (t, $J = 7.4$ Hz), 5.05 (s), 4.96 (s), 2.61 (d, $J = 7.2$ Hz), 1.94 (dt, $J = 8.4, 0.8$ Hz), 1.86-1.85 (m), 1.05-0.92 (m or multiple singlets) ppm.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 2.57 (s, 4H), 2.05 (q, $J = 7.4$ Hz, 4H), 1.64 (s, 6H), 0.98 (t, $J = 7.4$ Hz, 6H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3 , ppm) δ : 129.0, 123.4, 37.2, 24.9, 18.0, 13.2;

IR (neat ATR): 2963, 2932, 2869, 2050, 2024, 1616, 1456, 1373, 887;

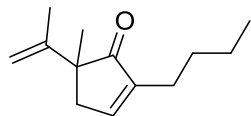
HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 165.16378, found 165.16353.



Complex 3-53

Hex-1-yne (0.3 mL, 2.66 mmol), dicobalt octacarbonyl (900 mg, 2.66 mmol) and DCM (10 mL) were added into a round bottom flask. The mixture was stirred at room temperature under N_2 overnight. Solvent was removed *in vacuo* and the crude product was passed through a short silica plug with hexanes affording 866 mg (88% yield) of known³⁵ red oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 6.00 (s, 1H), 2.85 (t, $J = 7.2$ Hz, 2H), 1.64-1.57 (m, 2H), 1.51-1.42 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H).



2-butyl-5-methyl-5-(prop-1-en-2-yl)cyclopent-2-en-1-one (3-54)

A flame dried round bottom flask was charged with **3-53** (146 mg, 0.39 mmol) and 2,3-dimethylbuta-1,3-diene (0.23 mL, 1.98 mmol). A solution of NMO (280 mg, 2.38 mmol) in MeCN (2 mL) was added dropwise over 5 h and the resultant reaction solution was stirred overnight at 50 °C. Solvent was removed and flash chromatography with 19:1 hexanes/EtOAc afforded 10 mg (13% yield) of a white solid.

¹H NMR (400 MHz, C₆D₆, ppm) δ : 6.53-6.51 (m, 1H), 4.89 (bd, $J = 0.4$ Hz, 1H), 4.82 (dq, $J = 1.6, 1.6$ Hz, 1H), 2.27 (ddd, $J = 18.6, 4.7, 2.0$ Hz, 1H), 2.18-2.05 (m, 2H), 1.83 (ddt, $J = 18.8, 2.8, 2.0$ Hz, 1H), 1.49 (dd, $J = 1.2, 0.8$ Hz, 3H), 1.42-1.26 (m, 2H), 1.16 (sext, $J = 7.4$ Hz, 2H), 1.11 (s, 3H), 0.78 (t, $J = 7.4$ Hz, 3H);

¹³C NMR (100 MHz, C₆D₆, ppm) δ : 209.5, 153.1, 146.0, 144.5, 110.9, 51.7, 41.5, 29.9, 24.8, 22.36, 22.26, 19.3, 13.6;

IR (neat ATR): 2963, 2933, 2872, 1704, 1637, 1451, 1379, 1007, 890;

HRMS (DART): calcd [M+H]⁺ 193.15869, found 193.15829.

3.5. References

1. Diels, O.; Alder, K. *Justus Liebigs Annalen der Chemie* **1928**, 460, 98.
2. a) Yiang, X.; Wang, R. *Chem. Rev.* **2013**, 113, 5515. b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, 41, 1668. c) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, 42, 902. d) Ooi, T.; Maruoka, K. In *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, NY, 1999; Vol. 3, pp 1237-1254. e) Boger, D. L. *Tetrahedron* **1983**, 39, 2869.
3. a) Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, 57, 4243. b) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, 105, 4779. c) Singh, R.; Panda, G. *Tetrahedron* **2013**, 69, 2853.
4. a) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, 130, 2722. b) Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, 73, 1818.
5. a) Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2014**, 70, 9461. b) Campbell, E. L.; Skepper, C. K.; Sankar, K.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2013**, 15, 5306. c) Vasamsetty, L.; Khan, F. A.; Mehta, G. *Tetrahedron Lett.* **2014**, 55, 7068.
6. a) Felzmann, W.; Arion, V. B.; Mieusset, J.-L.; Mulzer, J. *Org. Lett.* **2006**, 8, 3849. b) Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev, V. S. *Chem. Eur. J.* **2006**, 12, 5992.
7. Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2004**, 126, 11254.

8. a) Kim, H. J.; Ruszczycky, M. W.; Choi, S.; Liu, Y.; Liu, H. *Nature* **2011**, *473*, 109. b) Townsend, C. A. *ChemBioChem* **2011**, *12*, 2267.
9. a) Iafe, R. G.; Kuo, L. J.; Hochstatter, D. G.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2013**, *15*, 582. b) Xu, Y.-C.; Cantin, M.; Deslongchamps, P. *Can. J. Chem.* **1990**, *68*, 2137. c) Berube, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5255.
10. a) Diedrich, M. K.; Klarner, F. -G.; Beno, B. R.; Houk, K. N.; Senderowitz, H.; Still, W. *C. J. Am. Chem. Soc.* **1997**, *119*, 10255. b) Krenske, E. H.; Perry, E. W.; Jerome, S. V.; Maimone, T. J.; Baran, P. S.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3016.
11. Iafe, R. G.; Chan, D. G.; Kuo, J. L.; Boon, B. A.; Faizi, D. J.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2012**, *14*, 4282.
12. a) Iafe, R. G.; Kuo, L. J.; Hochstatter, D. G.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2013**, *15*, 582. b) He, C. Q.; Chen, T.; Patel, A.; Karabiyikoglu, S.; Merlic, C. A.; Houk, K. N. Distortion, Tether, and Entropy Effects on Transannular Diels–Alder Cycloaddition Reactions of 10–18-Membered Rings. Submitted to *Journal of the American Chemical Society*
13. a) Toro, A.; Lemelin, C.-A.; Preville, P.; Belanger, G.; Deslongchamps, P. *Tetrahedron* **1999**, *55*, 4655. b) Toro, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526.
14. Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736.
15. Gobbo, P.; Romagnoli, T.; Barbon, S. M.; Price, J. T. Keir, J.; Gilroy, J. B.; Workentin, M. S. *Chem. Commun.* **2015**, *51*, 6647.
16. Amin, J.; Motevalli, M.; Richards, C. J. *J. Organomet. Chem.* **2015**, *776*, 43.

17. a) Omae, I. *Appl. Organometal. Chem.* **2007**, *21*, 318. b) Taylor, C. J. S.; Ward, B. D. *New J. Chem.* **2008**, *32*, 1850.
18. a) Kerr, W. J. The Pauson-Khand Reaction – an Introduction. In *The Pauson-Khand Reaction Scope, Variations and Applications*; Torres, R. R., Eds.; Wiley & Sons: Chichester, 2012; pp 1-17. b) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Domínguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32.
19. Nicholas, K. M.; Pettit, R. *Tetrahedron* **1971**, *37*, 3475. For examples of double Nicholas reaction, see: a) Diaz, D.; Martin, T.; Martin, V. S. *Org. Lett.* **2001**, *3*, 3289. b) Diaz, D. D.; Cenal, J. P.; Martin, V. S. *Molbank* **2008**, 562. c) Ni, R.; Mitsuda, N.; Kashiwagi, T.; Igawa, K.; Tomooka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1190.
20. a) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127. b) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777.
21. Khand, I. U.; Pauson, P. L.; Habib, J. A. M. *J. Chem. Research (S)* **1978**, 346.
22. a) Iwasawa, N.; Ooi, I.; Inaba, K.; Takaya, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7534. b) Zhang, J.; Xing, S.; Ren, J.; Jiang, S.; Wang, Z. *Org. Lett.* **2015**, *17*, 218.
23. Cambeiro, X. C.; Pericas, M. A. The Mechanism of the Pauson-Khand Reaction: Hypothesis, Experimental Facts, and Theoretical Investigations In *The Pauson-Khand Reaction Scope, Variations and Applications*; Torres, R. R., Eds.; Wiley & Sons: Chichester, 2012; pp 23-49.
24. a) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593. b) Ishaq, S.; Porter, M. J. *Synth. Commun.* **2006**, 547. c) Turlington, M.; Yue, Y. Yu, X.; Pu, L. *J. Org. Chem.* **2010**, *75*, 6941. d) Chung, Y. K.; Lee, B. Y. *Organometallics* **1993**, *12*, 220.

25. Iwasawa, N.; Satoh, H. *J. Am. Chem. Soc.* **1999**, *121*, 7951.
26. Becheanu, A.; Bell, T.; Laschat, S.; Baro, A.; Frey, W.; Steinke, N.; Fischer, P. Z. *Naturforsch.* **2006**, 589.
27. a) Park, K. H.; Choi, S. Y.; Kim, S. Y., Chung, Y. K. *Synlett* **2006**, 527. b) Odedra, A.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 567.
28. a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. b) Wei, K.; Li, W.; Koike, K.; Nikaido, T. *Org. Lett.* **2005**, *7*, 2833. c) Morschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952. d) Horie, H.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2012**, *48*, 3866. e) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359.
29. a) Gruselle, M.; Malezieux, B.; Vaissermann, J. *Organometallics* **1998**, *17*, 2337. b) Arrais, A.; Boccaleri, E.; Sappa, E.; Secco, A. *J. Sol-Gel Sci. Technol.* **2006**, *38*, 283.
30. Banti, D.; Groaz, E.; North, M. *Tetrahedron* **2004**, *60*, 8043.
31. Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M. Davies, J. E.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494.
32. Berna, J.; Crowley, J. D.; Goldup, S. M.; Hanni, K. D.; Lee, A.; Leigh, D. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5709.
33. Barbot, F.; Dauphin, B.; Miginiac, P. *Synthesis* **1985**, 768.
34. Happ, B.; Bartik, T.; Zucchi, C.; Rossi, M. C.; Ghelfi, F.; Palyi, G.; Varadi, G.; Szalontai, G.; Horvath, I. T.; Chiesi-Villa, A.; Guastini, C. *Organometallics* **1995**, *14*, 809.
35. Asano, K.; Uesugi, Y.; Yoshida, J. *Org. Lett.* **2013**, *15*, 2398.

Intermolecular and Transannular Cycloadditions of Macrocyclic $\{\text{Co}_2(\text{CO})_6\}$ -Alkyne Complexes

4.1. Introduction

Organocobalt compounds have been pivotal in chemistry and taken part in a wide range of scientific¹ and industrial² applications. Cobalt has a high propensity to form octahedral structures and sandwich molecules with ligands containing C, O and N atoms. Mono- and dicobalt complexes have a high affinity to interact with carbonyl groups, C-C and C-N π -bonds. These features led to cobalt-mediated transformations that benefit from π -bond reactivity^{1c} like cycloadditions, alkyne protections, C-H activations, reductive couplings, addition reactions, carbocyclizations, cross-coupling reactions, enyne couplings and transformations in which cobalt constitutes the core of vitamin B₁₂-type catalysts.^{1b}

Among various cobalt complexes, dicobalt octacarbonyl $\{\text{Co}_2(\text{CO})_8\}$, discovered by Mond and Cowap in 1910,³ is the most widely utilized.^{1,4} The complex is commercially available, easy to handle (no glovebox is required) and requires no further pre-experiment purifications.⁴ The complex has high functional group tolerance, forms stable acetylenic dicobalt hexacarbonyl molecules with many different alkynes through simple, high yielding-experiments at ambient temperatures with common solvents.⁴

Reactions of dicobalt hexacarbonyl complexes can be segregated into three major groups. In Nicholas reactions⁵ dicobalt stabilized propargyl cations or radicals readily react with various nucleophiles (also see chapter 3 section 3.2). Dicobalt carbonyl complexation is used to protect alkynes⁶ (also see chapter 2 section 2.2.1) and through bond angle modifications this complexation decreases the bond order in the host organic molecule from three to a pseudo two thus placing the substituents in more favorable positions for cyclization reactions and by the

same distortion effect decreasing strain in cyclic organic compounds.⁷ Finally, $\{\text{Co}_2(\text{CO})_6\}$ -alkyne complexes took place in many important cycloaddition reactions among which the [2+2+1] cycloaddition known as the Pauson-Khand Reaction (PKR)⁸ is the most frequently studied.^{1,4}

Participation of dicobalt octacarbonyl in macrocycle chemistry is rather limited compared to the massive number of examples with small and medium cyclic $\{\text{Co}_2(\text{CO})_6\}$ -alkyne complexes. Several macrocycle syntheses employing the Nicholas reaction were illustrated in literature.⁹ A number of studies reported on dicobalt hexacarbonyl complexed macrocyclic alkynes, diynes and triynes investigating the reactivity change in these macrocycles caused by the distortion effects of $\{\text{Co}_2(\text{CO})_8\}$ complexation.¹⁰ However, potential cycloadditions and transannular reactions of macrocyclic complexes have been overlooked. In that sense our $\{\text{Co}_2(\text{CO})_6\}$ -mediated transannular [4+2] reactions (Chapter 3) represent the first examples. We extended our investigations to other synthetic applications and discovered novel transannular and intermolecular [2+2+1] reactions, intermolecular [2+2+2] cycloaddition reactions and intermolecular [2+2+1+1] cycloaddition reactions of macrocyclic dicobalt hexacarbonyl complexes with the key controlling factor being choice of reaction promoter.

4.2. Results and Discussion

4.2.1. Intermolecular [2+2+2] Cycloadditions

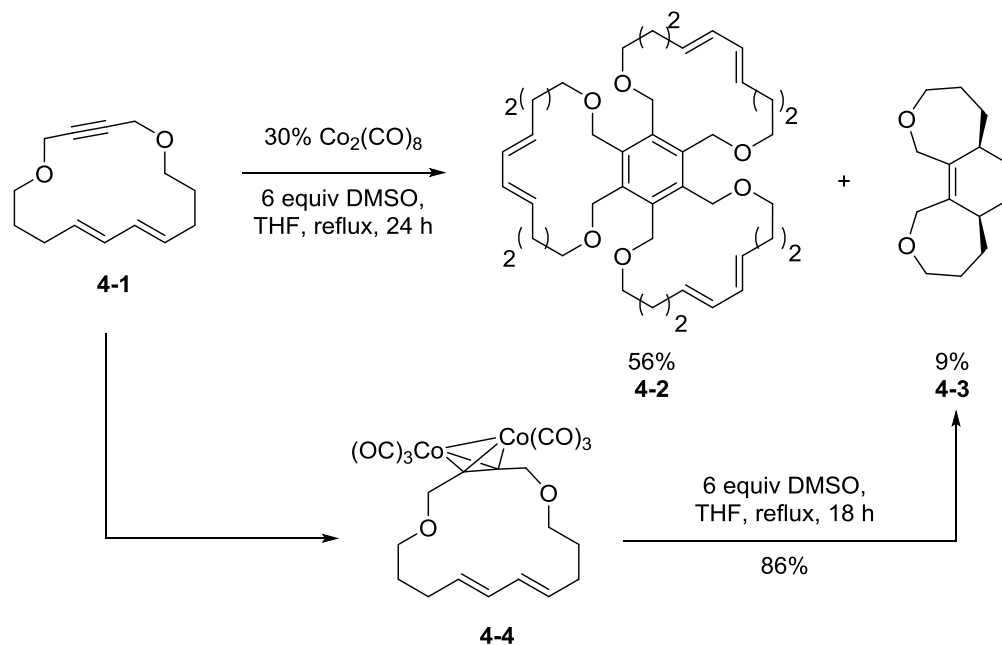
[2+2+2] cycloadditions, or generally called cyclotrimerisations, have been studied in detail and well understood since evidence of these transformations was first spotted by Berthelot in 1866.¹¹ Over the years this trivial reaction has been used to efficiently prepare benzene, cyclohexadiene and cyclohexene derivatives along with heterocycles.¹² As elaborate studies continued more advanced applications of [2+2+2] cycloadditions were discovered: reactions

were performed stereoselectively,¹³ applied on medium and large rings with multiple double and triple bonds in transannular fashion^{9e,14} and widely incorporated in polymer chemistry.¹⁵ Many metals can catalyze [2+2+2] reactions, but group 9 metals, especially cobalt, were found to be best suited for the task.¹² Although most of the [2+2+2] cycloaddition examples were established with cyclopentadienyl cobalt complexes,^{12c,d} the carbonyl complex {Co₂(CO)₈} was employed in a considerable number of syntheses. In fact one of the earliest examples of a [2+2+2] cycloaddition reaction was cyclotrimerisation of cyclooctyne catalyzed by {Co₂(CO)₈}.¹⁶ Dicobalt octacarbonyl-mediated cyclotrimerisations were used in sugar chemistry to form water soluble trimannosides with protein cross-linker properties,¹⁷ in functionalization of organometallic alkynes in order to enhance electrochemical properties of substrates,¹⁸ in cluster formations with acetylenic heterocycles,¹⁹ in construction of bulky polycyclic systems with extended aromaticities,²⁰ in intramolecular functionalizations of dicobalt-stabilized triynes²¹ and in tandem organic syntheses.²² However, to the best of our knowledge intermolecular cyclotrimerisation of macrocyclic {Co₂(CO)₆}-alkyne complexes has yet to be reported.

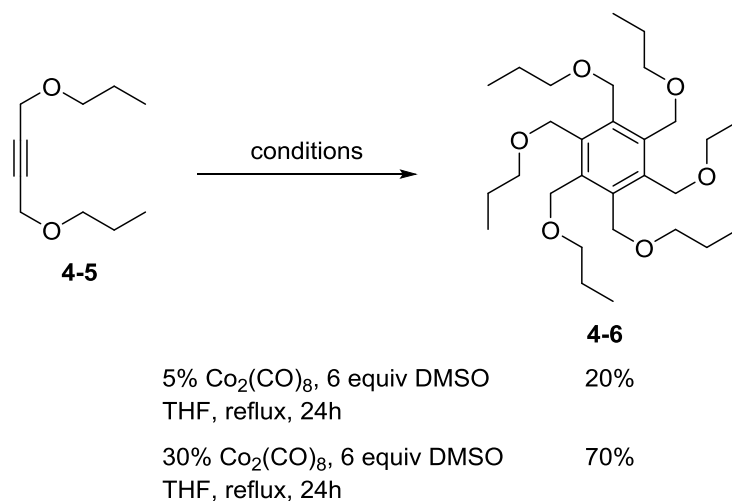
We investigated dicobalt hexacarbonyl-promoted [4+2] cycloaddition reactions (Chapter 3). Dicobalt complex of 16-membered dienyne **4-1** was found to go through a transannular [4+2] reaction in the presence of DMSO as the promoter in refluxing THF forming the polycyclic product **4-3** (Scheme 4.1). During our attempts to perform this reaction catalytically, we observed instead an intermolecular [2+2+2] cycloaddition reaction of macrocyclic dienyne **4-1**. Trimer **4-2** was synthesized in 56% yield along with a small amount of the transannular [4+2] reaction product **4-3** (Scheme 4.1).

In order to test the generality of this transformation we subjected model alkyne **4-5** to [2+2+2] cycloaddition reaction conditions (Scheme 4.2). Cyclotrimerisation was only modestly

catalytic, with high substrate concentrations (0.5M) and 5 mol % catalyst the target benzene product **4-6** was obtained in 20% yield. Trimer **4-6** was synthesized in 70% yield when $\{\text{Co}_2(\text{CO})_8\}$ was used in 30 mol %.

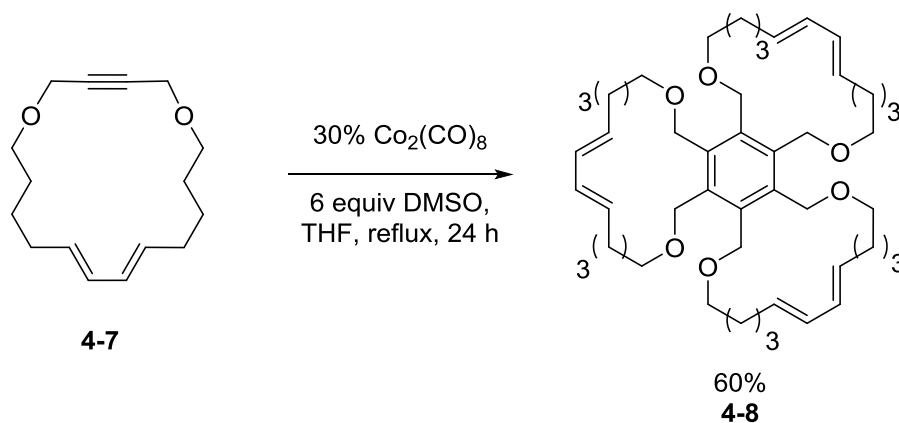


Scheme 4.1. Intermolecular [2+2+2] cycloaddition vs transannular [4+2] cycloaddition of macrocyclic dienyne 4-1



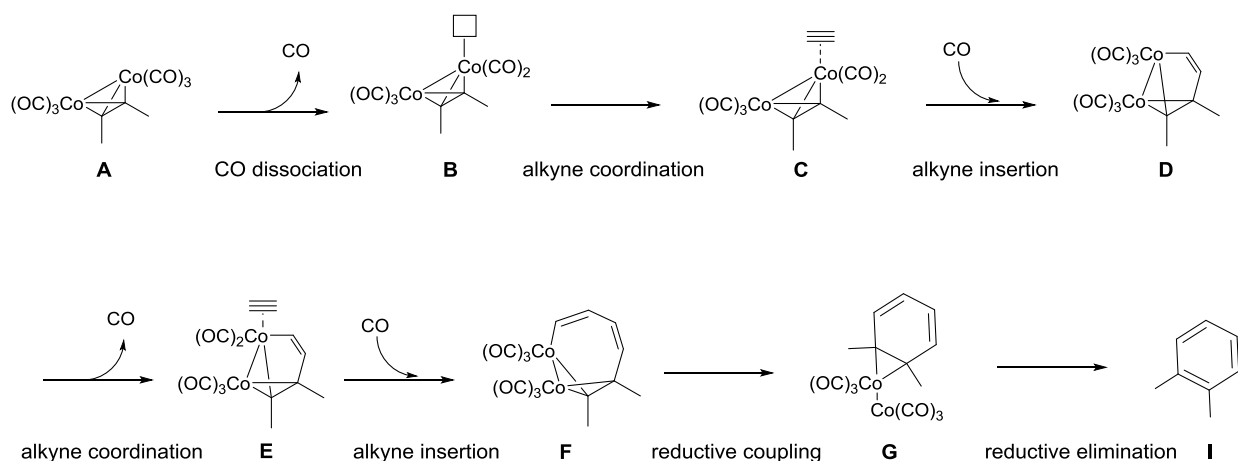
Scheme 4.2. Intermolecular [2+2+2] cycloaddition of model alkyne 4-5

Since intermolecular [2+2+2] cycloaddition reactions are important in the synthesis of dendrimeric structures,^{12,15,17,18} formation of a benzene fused with three macrocyclic substituents is particularly interesting. Therefore, we tested 18-membered dienyne **4-7** in the cyclotrimerisation reaction and successfully obtained benzene derivative **4-8** in 60% yield as the sole cycloaddition product (Scheme 4.3).



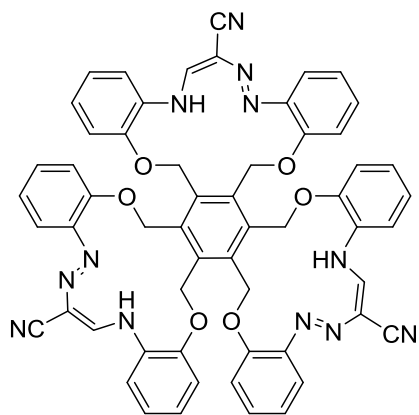
Scheme 4.3. Intermolecular [2+2+2] cycloaddition of macrocyclic dienyne **4-7**

Detailed studies on the mechanism of dicobalt hexacarbonyl-promoted alkyne cyclotrimerisation have been reported^{23,24} and a general schematic is depicted in Scheme 4.4. The mechanism is initiated with alkyne coordination and subsequent insertion of a metal-free alkyne into a Co-C bond forming cobaltocycle **D**. Experimental studies showed stabilization of complex **D** through formation of various cyclopentadienyl dicobalt “flyover” complexes that favor coordination and insertion of a second alkyne leading to cobaltocycle **F**.^{18b,24} Consecutive reductive coupling and reductive elimination steps produce the final benzene product. It was shown that this mechanistic cycle can work with catalytic amounts of $\{\text{Co}_2(\text{CO})_8\}$ when the reaction is performed under high pressures of CO ($\sim 30 \text{ atm}$)²² and/or high temperatures.^{12c,d}



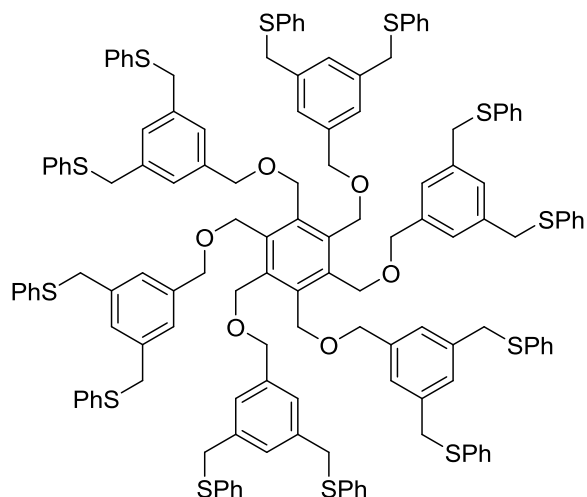
Scheme 4.4. General mechanism of $\{\text{Co}_2(\text{CO})_8\}$ -promoted [2+2+2] cycloaddition

Our preliminary results were particularly exciting as the products synthesized belong to an important class of organic molecules (Scheme 4.5). Benzene derivatives with hexa- (CH_2OR) substituents have proven quite useful in various chemical applications.²⁵ The key hexa-substituted benzene pattern is found in sugar clusters with protein cross-linker properties,¹⁷ in crown ethers (or hexa-hosts for inclusion complexes),²⁶ in active ligands for transition metal catalysts,²⁷ in dendrimers used in production of scratch-free, self-standing cross-linked transparent films,²⁸ in biodegradable polymers²⁹ and in metal-organic frameworks (MOFs).³⁰ The novel intermolecular [2+2+2] cycloaddition products prepared in the course of our project could thus be investigated in the future as potential substrates for these applications.



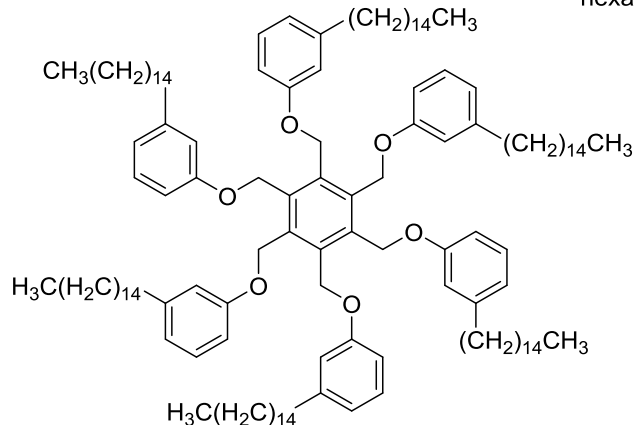
4-9^{26b}

tris(crown formazan)



4-10^{27a}

hexapincer ligand



4-11²⁸

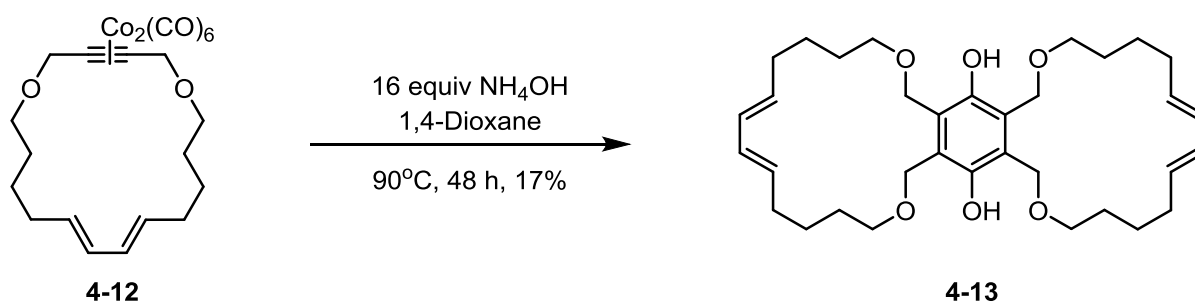
host polymer for
metal nanoparticles

Scheme 4.5. Examples of chemically important molecules with structural resemblance to products 4-2, 4-5 and 4-8

4.2.2. Intermolecular [2+2+1+1] Cycloadditions

During our investigations on cycloaddition reactions of dicobalt hexacarbonyl-alkyne complexes various promoters were scanned in order to facilitate the CO de-coordination step in the reactions. The choice of promoter/solvent system was determined to be crucial as different

systems altered the reaction chemoselectivities observed. The 18-membered dienyne dicobalt complex **4-12** lacked reactivity in transannular [4+2] and [2+2+1] cycloadditions even when the most common Pauson-Khand reaction promoters were used (Chapter 3). Therefore, we decided to test the complex under more stringent conditions. Amines, acting as hard ligands, were shown to possess labilizing effects in $\{\text{Co}_2(\text{CO})_8\}$ -mediated Pauson-Khand reactions at high temperatures.³¹ Complex **4-12** was heated in 1,4-dioxane in the presence of co-solvent/promoter aqueous ammonium hydroxide, but neither the tricyclic transannular [4+2] cycloaddition product nor transannular the Pauson-Khand reaction product was observed. Unexpectedly intermolecular [2+2+1+1] cycloaddition adduct **4-13** was isolated in 17% as the sole product (Scheme 4.6).

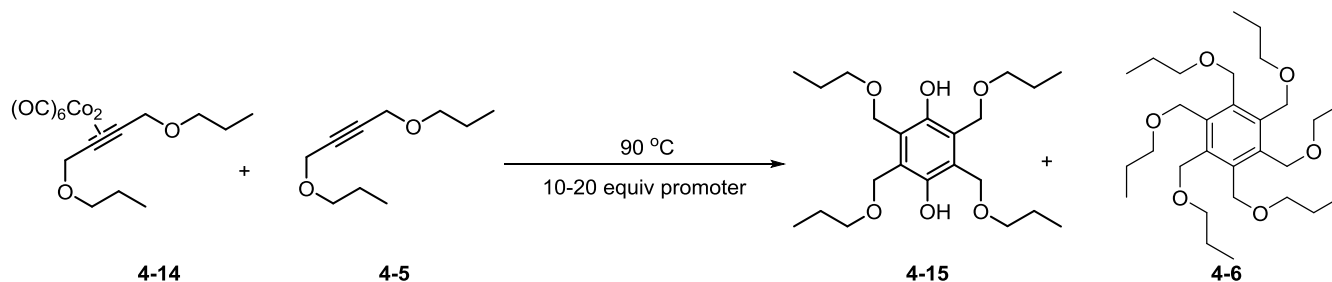


Scheme 4.6. Intermolecular [2+2+1+1] cycloaddition of macrocyclic complex 4-12

Although the starting material was mostly lost through decomposition and the synthesis was not very efficient, this was an interesting outcome not just due to the importance of hydroquinone derivatives,³² but also the scarcity of hydroquinone or quinone syntheses mediated by cobalt-carbonyl complexes.³³ The reported examples of participation of $\{\text{Co}_2(\text{CO})_8\}$ in hydroquinone/quinone synthesis are limited to dicobalt octacarbonyl-promoted intramolecular *rearrangement* of 1-(1,2-propadienyl)cyclopropanols to 1,4-hydroquinones³⁴ and synthesis of η^4 -quinone cobalt complexes.³⁵ Therefore, there have been no reports of $\{\text{Co}_2(\text{CO})_8\}$ directly promoting hydroquinone synthesis via cycloaddition. However, it is likely that the

4-6 (Table 4.1, entries 2 and 3). Likewise, THF was best suited for the [2+2+2] cycloaddition reaction and benzene product **4-6** was obtained in 56% yield while **4-15** was not detected in the reaction solution (Table 4.1, entry 4). We added metal free alkyne **4-5** in the [2+2+1+1] test reactions to increase the yield of **4-15**, but these trials favored formation of the [2+2+2] adduct instead. Benzene derivative **4-6** was obtained in 23% yield when 1,4-dioxane was used as the solvent and in 69% yield in the presence of THF (Table 4.1, entries 5 and 6) while **4-15** was not detected in either case.

Table 4.1. Intermolecular [2+2+1+1] cycloaddition of complex 4-14

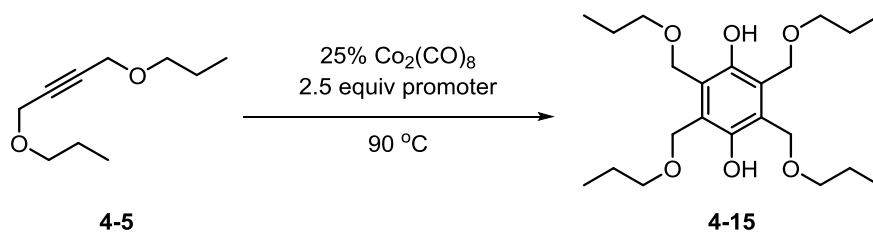


Entry	Promoter	Equiv of 4-5 ^a	Time (h)	Solvent	Yield of 4-15 (%)
1	NH ₄ OH	-	36	1,4-dioxane	26
2	Et ₃ N	-	72	1,4-dioxane	-
3 ^b	NH ₄ OH	-	14	MeCN	-
4 ^{c,b}	NH ₄ OH	-	14	THF	-
5 ^d	NH ₄ OH	1	40	1,4-dioxane	-
6 ^{e,b}	NH ₄ OH	1	14	THF	-

^a1 equiv with respect to complex **4-14**. ^bComplete consumption of starting molecules was observed. ^c56% **4-6** was isolated. ^d23% **4-6** was isolated. ^e69% **4-6** was isolated.

The intermolecular [2+2+1+1] cycloaddition reaction of alkyne **4-5** was tested in the presence of catalytic amounts of $\{\text{Co}_2(\text{CO})_8\}$ (Table 4.2). DMSO as co-promoter/solvent and 1-methylpiperidine as promoter were both ineffective (Table 4.2, entries 1 and 2). Incorporation of Et_3N as promoter (Table 4.2, entry 3) and NH_4OH as the sole solvent yielded trace amounts of **4-15** that was only detectable by TLC (Table 4.2, entry 4). A 1,4-dioxane/ NH_4OH solvent/promoter system was effective and produced hydroquinone **4-15** in a modest 21% yield (Table 4.2, entry 5). This result is particularly promising as it shows there is a minute efficiency difference between the catalytic transformation and hydroquinone synthesis by the reaction of dicobalt complex (Table 4.1, entry 1). These results might be improved under the stringent conditions suggested by previously reported investigations (Scheme 4.7) if the design of an industrial process is targeted.

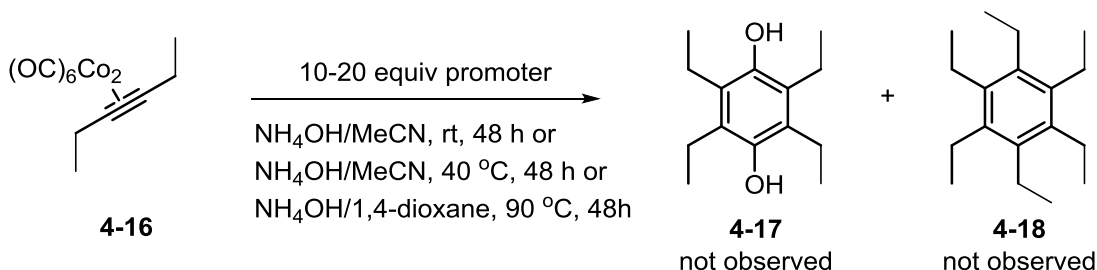
Table 4.2. $\{\text{Co}_2(\text{CO})_8\}$ -catalyzed intermolecular [2+2+1+1] cycloaddition of alkyne 4-5



Entry	Promoter	Time (h)	Solvent	Yield (%)
1 ^{a,b}	NH_4OH	12	1,4-dioxane/DMSO	-
2 ^c	1-methylpiperine	12	1,4-dioxane	-
3 ^b	Et_3N	72	1,4-dioxane	trace
4 ^c	NH_4OH	24	-	trace
5 ^c	NH_4OH	17	1,4-dioxane	21

^a1,4-dioxane and DMSO were used in a 1:1 ratio. ^bTLC showed unreacted **4-5** and complex **4-14** as the major products which were not isolated. ^cTLC showed [2+2+2] cycloaddition adduct as the major product.

It was suspected that the existence of propargylic ether units in substrates **4-5**, **4-12** and **4-14** would be problematic and could be the cause of the poor product yields, so 3-hexyne complex **4-16** was tested under these [2+2+1+1] reaction conditions. Unfortunately, TLC studies showed that starting material was inert and hydroquinone **4-17** or the [2+2+2] cycloaddition adduct **4-18** were not observed in the course of trial experiments (Scheme 4.8).

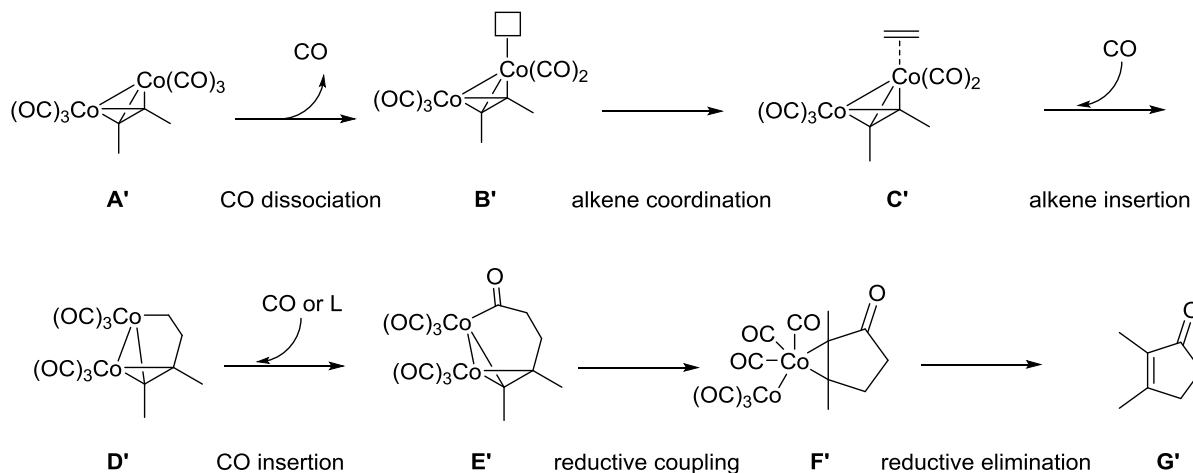


Scheme 4.8. Attempted intermolecular [2+2+1+1] cycloaddition of complex 4-16

4.2.3. Pauson-Khand Reactions of Dicobalt Hexacarbonyl-Alkyne Complexes

The Pauson-Khand reaction (PKR), discovered by Ihsan Ulhan Khand and Peter Ludwig Pauson in the early 1970's,⁸ is a dicobalt octacarbonyl-promoted [2+2+1] cycloaddition of an alkyne, an alkene and a carbon monoxide (for the general mechanism, see scheme 4.9).³⁹ The Pauson-Khand reaction has evolved and been improved tremendously over the years.⁴⁰ The reaction was shown to tolerate a wide range of functional groups, the scope was extended to substrates different than alkenes,⁴¹ the reaction was performed catalytically⁴² and promoted by various metal complexes other than $\{Co_2(CO)_8\}$.⁴³ In addition, complete stereochemical control over the reaction was achieved.⁴⁴ Due to its high versatility this cycloaddition reaction is now accepted as one of the most powerful synthetic tools and the most efficient method to prepare

cyclopentenone derivatives. Countless Pauson-Khand transformations have been applied in total synthesis of significant natural products and biologically active molecules.⁴⁵

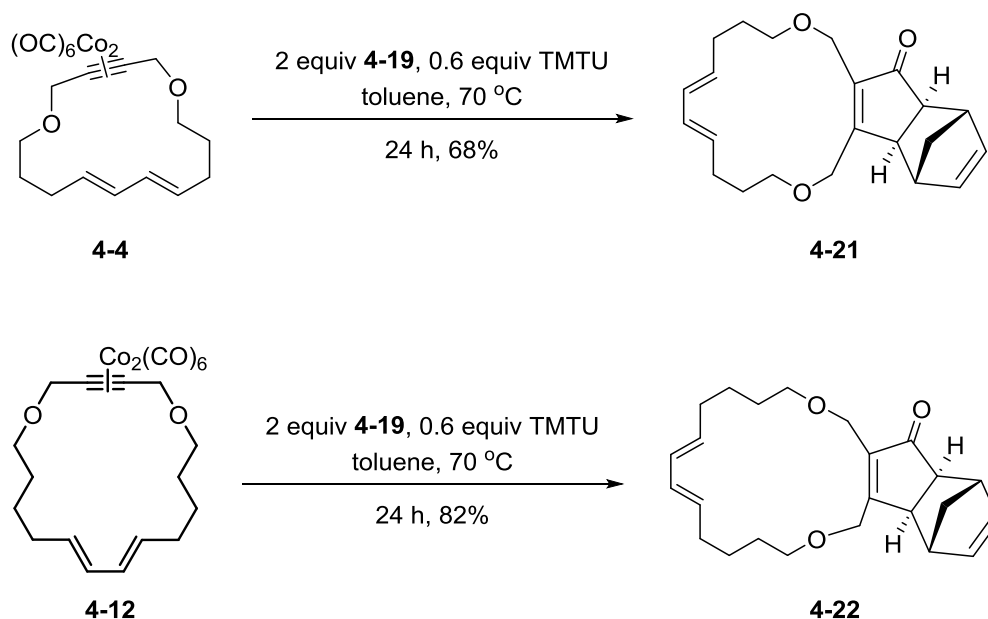


Scheme 4.9. Mechanism of Pauson-Khand reaction

Surprisingly, the transannular version of this well studied reaction was unknown. It was previously illustrated that dicobalt hexacarbonyl complexes of macrocyclic dienyne undergo transannular [4+2] cycloaddition and no transannular Pauson-Khand (TAPK) reaction products were observed (Chapter 3). Our goal was to investigate the possibility to alter the reactivity/chemoselectivity of macrocyclic complexes and achieve the first TAPK reaction.

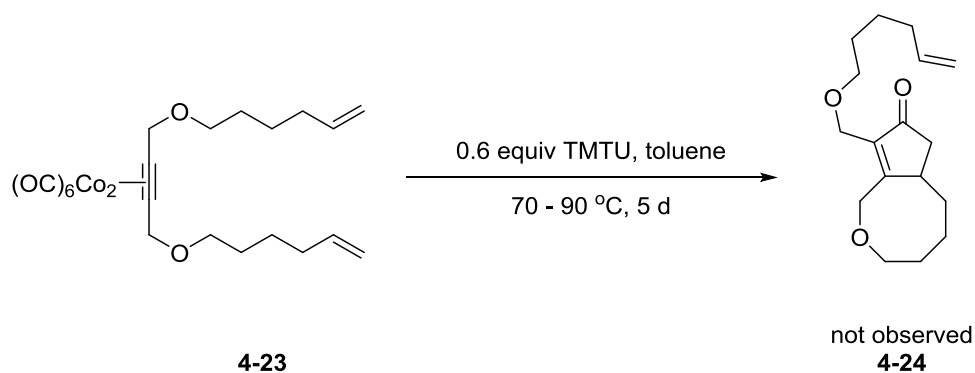
First we tested the reactivity of the alkyne units in the structures. Occasionally, propargylic ethers were shown to be problematic in Pauson-Khand reactions leading to undesired rearrangements, ionizations and hydrogenolyses,⁴⁶ so model alkyne complex **4-14** and norbornadiene (**4-19**) were subjected to various intermolecular PK reaction conditions (Table 4.3). Heat as the sole reaction promoter was ineffective and 64% of the starting material was recovered (Table 4.3, entry 1). In previous studies amine and sulfide promoters with 1,2-dichloroethane (DCE) solvent were used to overcome the problems caused by propargylic

Macrocyclic complexes **4-4** and **4-12** were tested under the optimized intermolecular PK reaction conditions with norbornadiene. To our delight, the complexes were quite active and novel PK reaction products **4-21** and **4-22** were obtained in 68 and 82% yields respectively (Scheme 4.10). It is noteworthy that the molecules preferred to follow an *intermolecular* reaction path over *intramolecular* [4+2] (see Chapter 3, Tables 3.3 and 3.4) or [2+2+1] reaction paths.



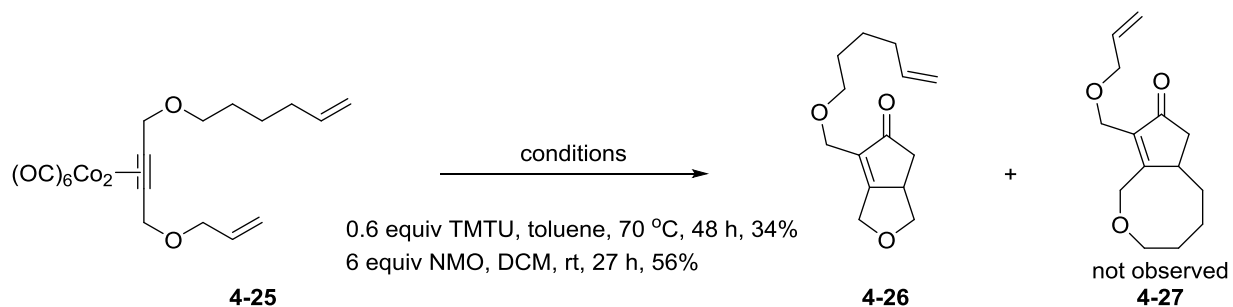
Scheme 4.10. Intermolecular PK reactions of complexes 4-4 and 4-12

Since the alkyne units in the macrocyclic complexes were shown to be active in PK reactions, the effect of chain length on possible TAPK reactions of macrocyclic dienynes was tested. Model acyclic dienyne complex **4-23** was heated at 70 °C in the presence of the promoter TMTU and the experiment was monitored by TLC. Over 4 days no change in reaction solution was observed. The temperature was increased to 90 °C; however, in 24 hours **4-23** decomposed into a complex mixture of inseparable and unidentifiable molecules and the expected intramolecular PK reaction product **4-24** could not be isolated or detected (Scheme 4.11).



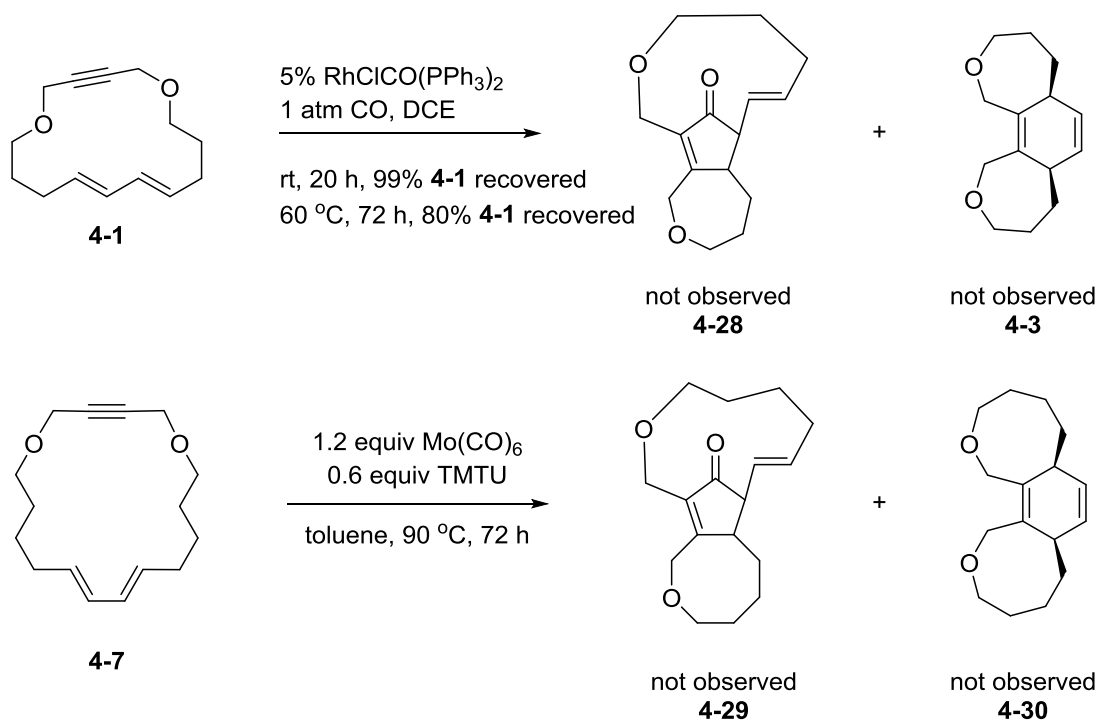
Scheme 4.11. Attempted intramolecular PK reaction of complex 4-23

The length of the tether connecting $\{Co_2(CO)_6\}$ -alkyne and alkene units is crucial in intramolecular PK reactions. Although complex **4-23** failed to go through an intramolecular PK reaction, unsymmetrical acyclic dienyne complex **4-25** afforded novel cyclopentenone product **4-26** in 34 and 56% yields in the presence of promoters TMTU and NMO respectively (Scheme 4.12). The regioisomer **4-27** that would be formed through the reaction of $\{Co_2(CO)_6\}$ -alkyne with the alkene unit separated by the longer chain, was not observed. Unfortunately the transannular version of this intramolecular PK reaction was not possible since under the conditions that formed **4-26** (Schem 4.12), 15-membered unsymmetrical macrocyclic dienyne complex **3-29** underwent a high yielding transannular [4+2] cycloaddition without forming TAPK products (see Chapter 3, table 3.1).



Scheme 4.12. Intramolecular PK reaction of complex 4-25

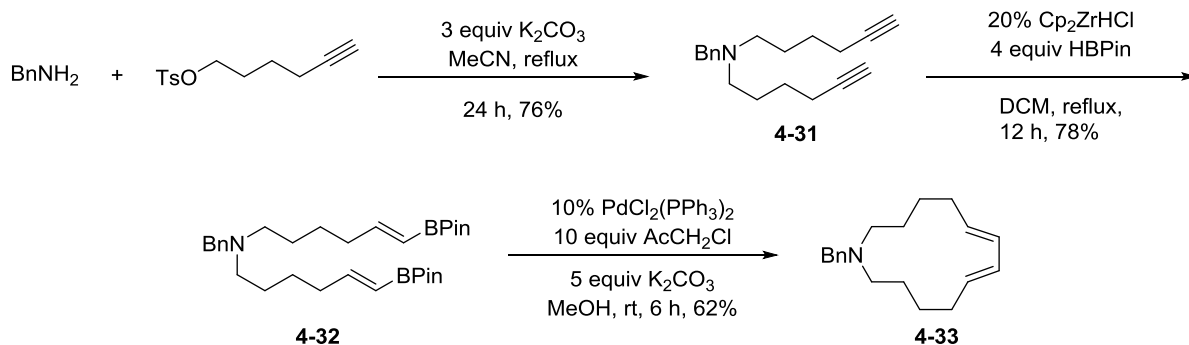
Previous reports in the literature show that Pauson-Khand reactions of dicobalt hexacarbonyl-alkyne complexes with dienes are more challenging than the reactions with simple alkenes^{46,48} and often different metal carbonyl complexes were utilized.^{43,49} We tested cyclic dienyne **4-1** with the catalyst $RhClCO(PPh_3)_2$ under 1 atm CO pressure for a TAPK reaction, but no transannular [2+2+1] (**4-28** and **4-29**) or [4+2] (**4-3** and **4-30**) products were observed either at room temperature or at 60 °C (Scheme 4.13). After the reactions 99% and 80% of starting cyclic dienyne **4-1** were recovered, respectively. These results also reconfirmed the results on TADA reactions presented in Chapter 3. 18-membered macrocyclic dienyne **4-7** was heated with $Mo(CO)_6$ in the presence of TMTU, however, starting material did not undergo any transformations (Scheme 4.13)



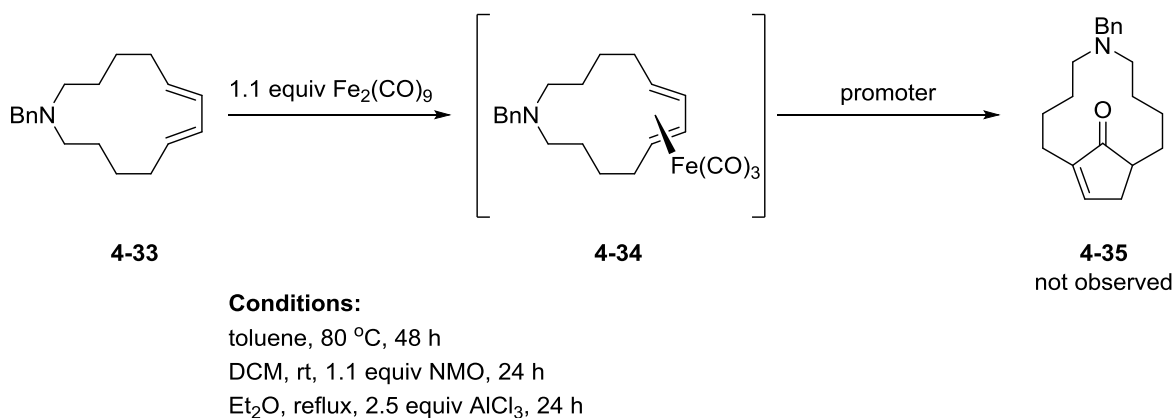
Scheme 4.13. Attempted Rh- and Mo-mediated TAPK reactions of dienynes **4-1** and **4-7**

Since cyclic dienynes had exhibited no transannular Pauson-Khand reactivity, we gravitated towards different macrocyclic substrates. There have been examples of iron carbonyl complexes promoting Pauson-Khand reactions of dienes with alkynes.⁵⁰ We proposed that these transformations could be performed in a transannular fashion with macrocyclic dienes. Diyne **4-31** was prepared from benzylamine and subjected to our standard hydroboration conditions (Scheme 4.14). Bis(vinyl boronate ester) **4-32** was synthesized in 78% yield and successfully transformed into cyclic diene **4-33** under our optimized Pd(II)-catalyzed macrocyclization conditions.⁵¹ 13-membered macrocycle **4-33** was subjected to previously reported Pauson-Khand reaction conditions^{50,52} in the presence of Fe₂(CO)₉ (Scheme 4.15). Heat, NMO and Lewis acid AlCl₃ were tested as promoters to activate the PK reaction of in situ formed Fe(CO)₃-diene

complex **4-34**. The expected TAPK reaction product **4-35** was not detected most likely due to steric constraints.



Scheme 4.14. Preparation of macrocyclic diene 4-33

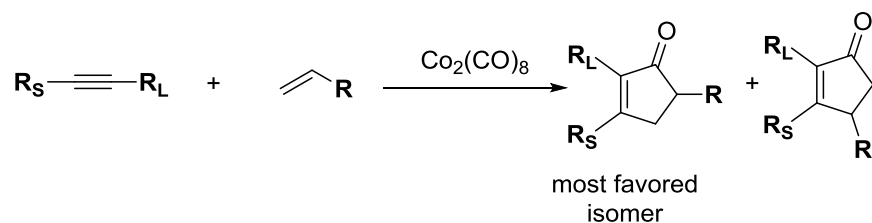


Scheme 4.15. Attempted Fe₂(CO)₉-promoted TAPK reaction of diene 4-33

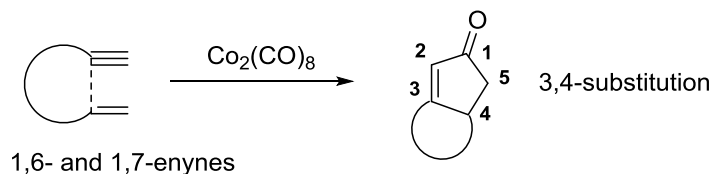
Finally, we decided to test the transannular Pauson-Khand reactivity of macrocyclic enynes which are easily accessible by our RCM strategy (Chapter 2). *Intramolecular* Pauson-Khand reactions of enynes show a distinct regioselectivity compared to the *intermolecular* counterparts.^{39,46} Enynes with short tethers form 3,4-substituted bicyclopentenones locating the bulky substituents β to the carbonyl group, whereas in the products of intermolecular PK

reactions sterically demanding groups are found α to the carbonyl groups (Scheme 4.16). 1,6- and 1,7-enynes are known to exhibit the former regioselectivity in intramolecular PK reactions.

Regioselectivity in Intermolecular PK Reactions



Regioselectivity in Intramolecular PK Reactions

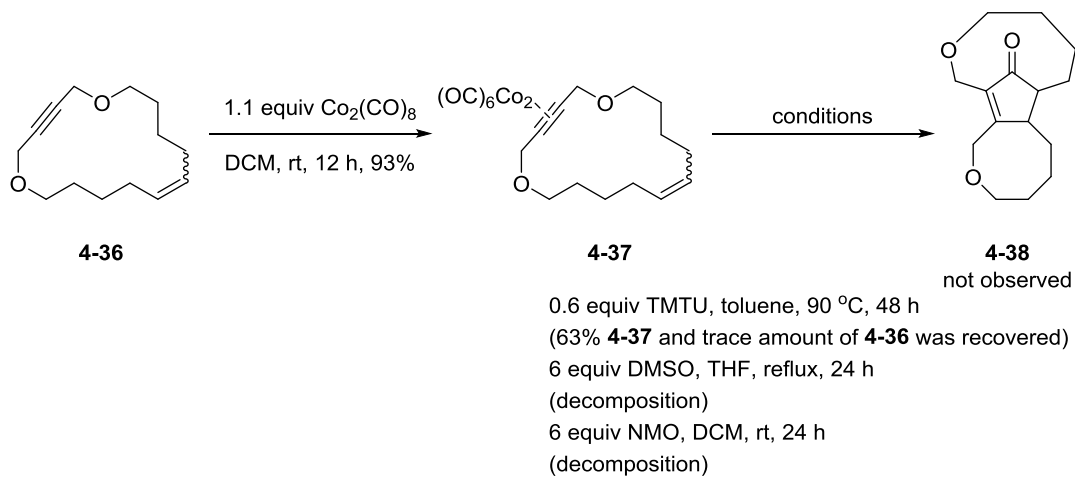


Scheme 4.16. Regioselectivity in $\{\text{Co}_2(\text{CO})_8\}$ -promoted PK reactions

On the other hand, it is extremely challenging to perform intramolecular PK reactions of enynes with long tethers and synthesize medium sized rings fused with cyclopentenones (Scheme 4.11 and 4.12). There are very few examples of bicyclopentenone molecules with 3,4-substitution pattern formed, with poor yields, through intramolecular PK of dicobalt hexacarbonyl enyne complexes with the reactive sites 5 or more atoms apart.⁵³

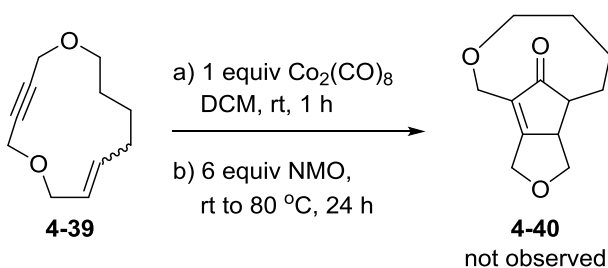
The reactivity, regioselectivity and stereoselectivity of a cycloaddition reaction can be altered by performing the reaction in a transannular fashion so even though formation of bicycles **4-24** and **4-27** failed, we tested the TAPK reactivity of 16-membered cyclic $\{\text{Co}_2(\text{CO})_6\}$ -enyne complex **4-37** (Scheme 4.17). The complex was unreactive in TMTU/toluene system as 63% of **4-37** together with a trace amount of **4-36** was recovered after heating the reaction solution at 90

°C for two days. DMSO/THF and NMO/DCM promoter/solvent systems were too harsh and the experiments resulted in decomposition of the starting complex. The target TAPK product **4-38** was not detected.



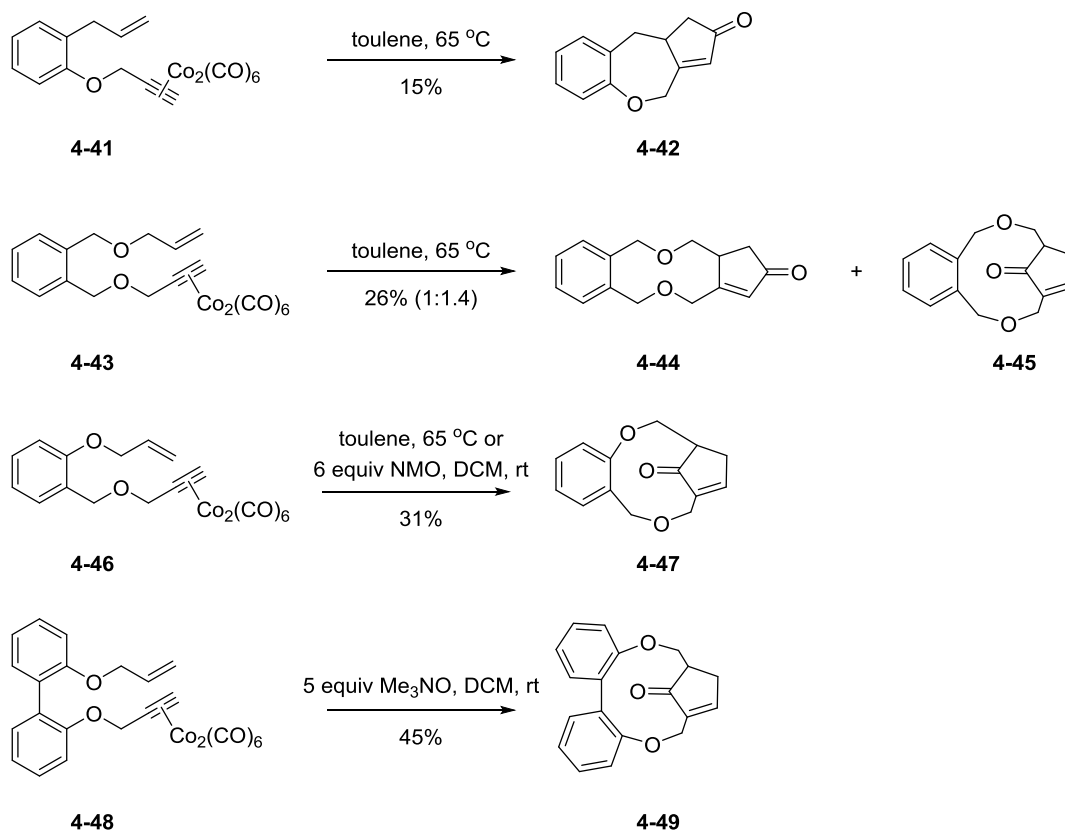
Scheme 4.17. Preparation and attempted TAPK reaction of complex **4-37**

A macrocycle with a 1,6- or 1,7-enyne unit was expected to favor the 3,4-substitution product thus cyclic enyne **4-39** was subjected to a quick, small scale TAPK test reaction (Scheme 4.18). The dicobalt hexacarbonyl complex was prepared in situ and following complete conversion of the enyne the promoter NMO was added. The reaction solution was heated with a gradual temperature increase and monitored by TLC. After 24 hours complete decomposition of the substrate occurred and TAPK reaction adduct **4-40** was not detected by NMR spectroscopy.



Scheme 4.18. Attempted TAPK reaction of enyne **4-39**

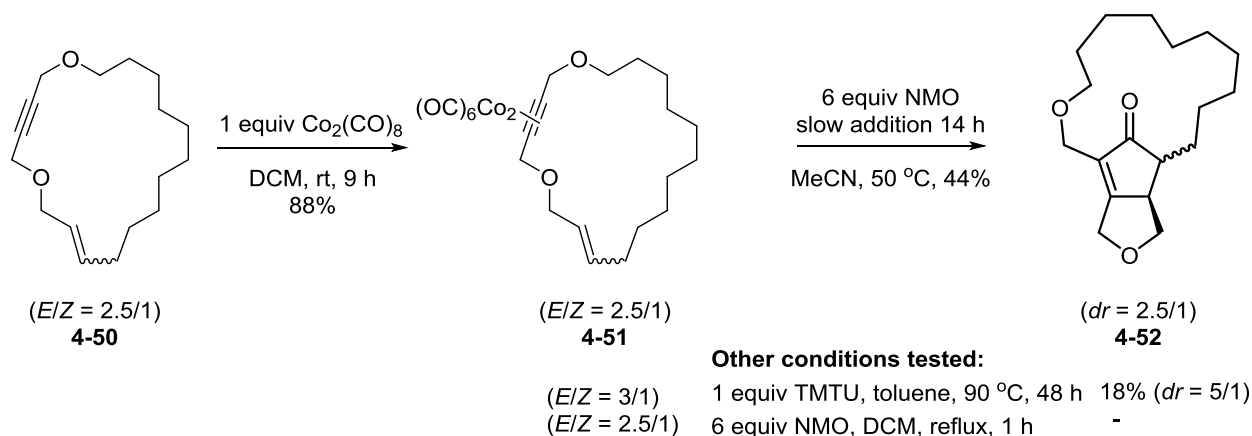
The Krafft research group took a different approach to synthesis of medium rings via the Pauson-Khand reaction and embedded rigid aromatic rings into long tethers of enynes in order to decrease conformational mobility and favor 3,4-substitution.⁵⁴ A large library of 1,8-, 1,9-, 1,10-, and 1,11-enynes were prepared and subjected to various $\{\text{Co}_2(\text{CO})_8\}$ -promoted intramolecular PK reaction conditions (Scheme 4.19). Restrains in conformational flexibility did not solve the 3,4-substitution path problem and only a few medium ring products (**4-42**, **4-44**) were synthesized in poor yields. Interestingly, the Krafft group detected the first 2,5-substituted bicyclic PK reaction products (**4-45**, **4-47**, **4-49**). Various substrates with different tether lengths were tested, but only some of the 1,10- and 1,11-enynes were found to be reactive.⁵⁴ Reaction conditions were not general and optimization experiments were done for each substrate.



Scheme 4.19. Intramolecular PK reactions of long tethered enynes by the Krafft group

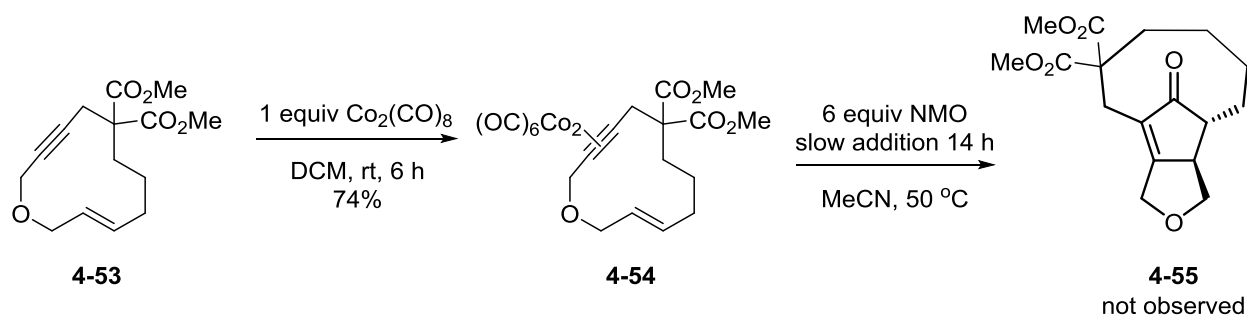
The results of the above mentioned experiments were particularly crucial to our study. It was evident that there are several structural restrictions in building transannular Pauson-Khand reaction substrates. The cyclic substrate should have one short chain connecting the alkyne to the alkene so that 3,4-substitution can be achieved forming the fused bicyclic moiety of the TAPK reaction product. Moreover, the substrate should have one long chain allowing formation of the 2,5-substituted (bridged) bicyclic unit.

Macrocyclic enyne complex **4-51** was prepared in high yield via reaction of 19-membered enyne **4-50** (synthesized by our RCM methodology, Chapter 2) with $\{\text{Co}_2(\text{CO})_8\}$ (Scheme 4-20). To our delight the complex afforded the desired TAPK reaction product **4-52** in 18% yield by mild heating in the presence of TMTU. In order to improve the product yield, **4-51** was tested in a NMO/DCM system at room temperature. After 17 hours only unreacted starting material and decomplexed macrocyclic enyne was detected. A small scale test reaction was performed with NMO in refluxing MeCN. The reaction was quite fast; after 1 hour a 1:1 mixture of decomplexed starting material and TAPK reaction product was obtained. The NMO/MeCN combination was more productive and improved the conversion; however, the cycloaddition was not as fast or faster than the decomplexation side reaction. Thus we applied the technique used in intermolecular [4+2] cycloadditions to overcome a similar obstacle (Chapter 3). Thus, a solution of NMO in MeCN was added dropwise over 14 hours at 50 °C and tricycle **4-52**, the first TAPK reaction product, was synthesized in 44% yield (Scheme 4-20). The transannular Pauson-Khand reaction was stereospecific like intramolecular Pauson-Khand reactions⁴⁴ as **4-52** was obtained with same diastereoisomeric ratio as macrocyclic enyne complex **4-51**.



Scheme 4.20. First transannular Pauson-Khand reaction

Previously, the beneficial effects of all-carbon chains as a structural constraint in cyclization reactions was established (Chapter 2 and Chapter 3). Macrocyclic enyne **4-53** with an all-carbon 1,8-enyne unit was subjected to TAPK reaction conditions following the synthesis of dicobalt hexacarbonyl complex **4-54** (Scheme 4.21). However, the tether length was not adequate for a successful 2,5-substitution and decomplexed cyclic enyne was recovered quantitatively. Synthesis of different macrocyclic enynes are currently under investigation.



Scheme 4.21. Attempted transannular Pauson-Khand reaction of enyne 4-53

4.3. Conclusions

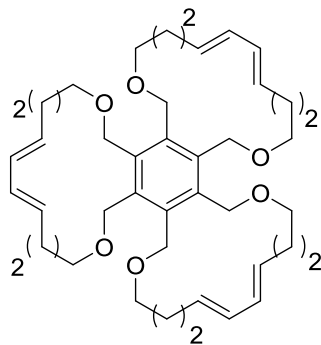
In conclusion macrocycle functionalizations through dicobalt hexacarbonyl-promoted cycloadditions were investigated. The complexes were easily synthesized by reactions of dicobalt octacarbonyl with macrocycles prepared by versatile palladium(II)-catalyzed oxidative coupling reactions or ring closing metathesis reactions. The cyclization processes uncovered encompass intermolecular [2+2+2], [2+2+1+1], [2+2+1] reactions of macrocyclic dienes and the first transannular Pauson-Khand reactions of macrocyclic enynes. In all the discovered cycloadditions the key issue was the choice of reaction promoter/solvent system. Chemoselectivity in the cycloadditions was modulated by simple alterations of reagents used. The structural requirements for transannular Pauson-Khand cyclization substrates were explored and reaction conditions were optimized. A novel tricyclic cyclopentenone was synthesized under optimized TAPK reaction conditions in a stereospecific manner. We believe our studies provide compelling evidence for the overlooked utility of macrocycles in transition metal chemistry and the reactions investigated can be utilized in preparations of chemically and industrially valuable molecules.

4.4. Experimental

General Procedures

All commercial compounds were used as received unless stated otherwise. Dicobalt octacarbonyl was purchased from Strem Chemicals, Inc. as a solid, stabilized with 1–5 % hexane and was stored at 0 °C. Metathesis catalysts (Materia Inc.) were stored in a glovebox and used as received. DCM and Et₃N were purified by distillation over CaH₂. THF, Et₂O and toluene were distilled prior to use from sodium-benzophenone ketyl. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere, unless stated otherwise. Column chromatography was performed using silica gel (Davisil, 40-63 micron) and reagent grade solvents without deactivation, unless noted. NMR spectra were recorded on a Bruker ARX-400 instrument and calibrated to the solvent signal (CDCl₃ δ = 7.26 ppm for ¹H NMR, δ = 77.0 ppm for ¹³C NMR, C₆D₆ δ = 7.16 ppm for ¹H NMR, δ = 128.0 ppm for ¹³C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sextet (sext), m (multiplet), or b (broadened). IR spectra were recorded on a Jasco FTIR-4100 spectrophotometer with an ATR attachment and selected peaks are reported in cm⁻¹. Mass spectra were recorded on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE Direct Analysis in Real Time (DART) ion source.

For synthesis protocols and characterization information of hex-5-en-1-yl 4-methylbenzenesulfonate, **4-23**, **4-36**, **4-37**, **4-39**, **4-50**, **4-53**, see Chapter 2, section 2.4; for hex-5-yn-1-yl 4-methylbenzenesulfonate, **4-1**, **4-3**, **4-4**, **4-5**, **4-7**, **4-12**, **4-14**, **4-16**, see Chapter 3, section 3.4.



(6E,8E,20E,22E,34E,36E)-

1,3,4,5,10,11,12,14,15,17,18,19,24,25,26,28,29,31,32,33,38,39,40,42-tetracosahydrobenzo[1,2-c:3,4-c':5,6-c'']tri[1,6]dioxacyclohexadecine (4-2)

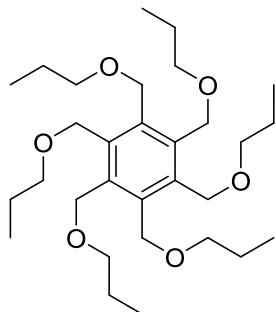
4-1 (158 mg, 0.72 mmol) was dissolved in THF (14 mL). Dicobalt octacarbonyl (74 mg, 0.21 mmol) and DMSO (0.3 mL, 4.30 mmol) were added and the solution was refluxed for 24 h. Solvent was removed *in vacuo* and column chromatography with 4:1 hexanes/EtOAc afforded 88 mg (56% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.23-6.16 (m, 6H), 5.65-5.55 (m, 6H), 4.57 (s, 12 H), 3.45 (t, *J* = 4.8 Hz, 12H), 2.22 (td, *J* = 6.8, 6.0 Hz, 12 H), 1.67-1.61 (m, 12H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 138.1, 132.0, 130.8, 69.4, 66.9, 30.9, 28.6;

IR (neat ATR): 2908, 2851, 1107, 1085, 983;

HRMS (DART): calcd [M+H]⁺ 661.44627, found 661.44470.



1,2,3,4,5,6-hexakis(propoxymethyl)benzene (4-6)

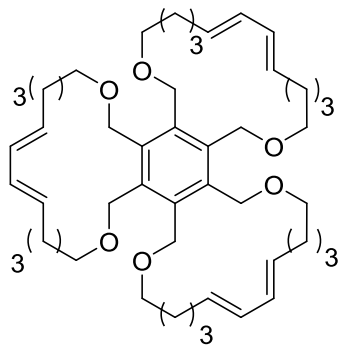
4-5 (126 mg, 0.74 mmol) was dissolved in THF (15 mL). Dicobalt octacarbonyl (76 mg, 0.22 mmol) and DMSO (0.3 mL, 4.44 mmol) were added and the solution was refluxed for 24 h. Solvent was removed *in vacuo* and column chromatography with 4:1 hexanes/EtOAc afforded 88 mg (70% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 4.63 (s, 12H), 3.46 (t, $J = 6.6$ Hz, 12H), 1.60 (sext, $J = 7.0$ Hz, 12H), 0.92 (t, $J = 7.4$ Hz, 18H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 137.7, 72.4, 66.2, 22.9, 10.6;

IR (neat ATR): 2962, 2936, 2873, 1353, 1087, 908, 728;

HRMS (DART): calcd [M+H]⁺ 511.39932, found 511.39808.



(5E,7E,17E,19E,29E,31E)-1,3,4,9,10,12,13,15,16,21,22,24,25,27,28,33,34,36-octadecahydrobenzo[1,2-c:3,4-c':5,6-c'']tri[1,6]dioxacyclotetradecine (4-8)

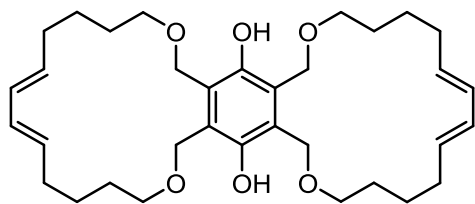
4-7 (43 mg, 0.17 mmol) was dissolved in THF (4 mL). Dicobalt octacarbonyl (18 mg, 0.05 mmol) and DMSO (0.07 mL, 1.04 mmol) were added and the solution was refluxed for 24 h. Solvent was removed *in vacuo* and column chromatography with 6:1 hexanes/EtOAc afforded 26 mg (60% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.11-6.04 (m, 6H), 5.54-5.47 (m, 6H), 4.47 (s, 12H), 3.48 (t, *J* = 8.0 Hz, 12H), 2.15 (td, *J* = 7.2, 4.4 Hz, 12H), 1.66-1.59 (m, 12H), 1.49-1.42 (m, 12H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 137.7, 132.4, 131.3, 71.1, 66.0, 33.0, 28.3, 23.8;

IR (neat ATR): 2927, 2857, 1443, 1356, 1081, 989, 907, 727;

HRMS (DART): calcd [M+H]⁺ 745.54017, found 745.53687.



(7E,9E,24E,26E)-3,4,5,6,11,12,13,14,18,20,21,22,23,28,29,30,31,33-octadecahydro-1H,16H-benzo[1,2-c:4,5-c']di[1,6]dioxacyclooctadecine-17,34-diol (4-13)

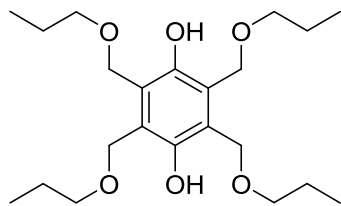
In a round bottom flask complex **4-12** (145 mg, 0.27 mmol), NH₄OH (2.2 mL, 2 M) and dioxane (6 mL) were mixed. The reaction solution was heated at 90 °C for 48 h. The reaction mixture was diluted with ether, filtered through celite and then through MgSO₄. Column chromatography with 9:1 hexanes/EtOAc afforded 13 mg (17% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 8.30 (s, 2H), 6.08-6.01 (m, 4H), 5.55-5.47 (m, 4H), 4.59 (s, 8H), 3.48 (t, *J* = 7.4 Hz, 8H), 2.13 (td, *J* = 7.0, 4.8 Hz, 8H), 1.66-1.59 (m, 8H), 1.51-1.44 (m, 8H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 148.3, 132.2, 131.5, 122.5, 69.8, 65.5, 32.0, 27.6, 23.6;

IR (neat ATR): 3361, 2922, 2857, 1691, 1541, 1432, 1375, 1267, 1089, 1035, 985;

HRMS (DART): calcd [M+H]⁺ 555.36802, found 555.36545.



2,3,5,6-tetrakis(propoxymethyl)benzene-1,4-diol (4-15)

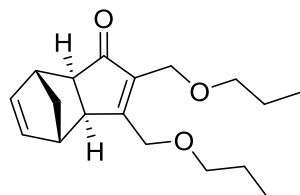
In a round bottom flask complex **4-14** (280 mg, 0.61 mmol), NH_4OH (1.7 mL, 4 M) and dioxane (5 mL) were mixed. The reaction solution was heated at 90 °C for 36 h. The reaction mixture was diluted with ether, filtered through celite and then through MgSO_4 . Column chromatography with 9:1 petroleum ether/ Et_2O afforded 32 mg (26% yield) of a white solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 8.11 (s, 2H), 4.71 (s, 8H), 3.45 (t, $J = 6.6$ Hz, 8H), 1.66-1.57 (m, 8H), 0.91 (t, $J = 7.4$ Hz, 12H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3 , ppm) δ : 148.4, 122.8, 72.0, 65.7, 22.8, 10.6;

IR (neat ATR): 3748, 1558, 1540, 1363, 1215, 1077;

HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 398.26629, found 398.26503.



2,3-bis(propoxymethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (4-20)

A flame dried round bottom flask was charged with TMTU (52 mg, 0.39 mmol) and flushed with N_2 . A solution of complex **4-14** (300 mg, 0.65 mmol) in toluene (10 mL) and norbornadiene (0.13 mL, 1.31 mmol) was added. The reaction solution was stirred at 70 °C for 12 h. Solvent

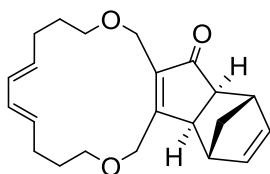
was removed *in vacuo* and column chromatography with 4:1 hexanes/EtOAc afforded 106 mg (56% yield) of a colorless oil.

¹H NMR (400 MHz, C₆D₆, ppm) δ: 5.99 (dd, *J* = 5.6, 3.2 Hz, 1H), 5.86 (dd, *J* = 5.6, 2.8 Hz, 1H), 4.33 (d, *J* = 15.2 Hz, 1H), 4.16 (dd, *J* = 15.2, 0.8 Hz, 1H), 4.15 (d, *J* = 12.0 Hz, 1H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.17 (t, *J* = 6.6 Hz, 2H), 3.13 (ddt, *J* = 19.6, 9.2, 6.4 Hz, 2H), 2.91 (bs, 1H), 2.74 (bs, 1H), 2.73 (d, *J* = 5.2 Hz, 1H), 2.14 (d, *J* = 5.2 Hz, 1H), 1.50-1.36 (m, 4H), 1.26-1.21 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 208.1, 174.9, 140.9, 138.4, 137.1, 73.0, 72.5, 67.3, 61.5, 52.3, 48.7, 43.6, 42.6, 41.3, 22.80, 22.76, 10.51, 10.50;

IR (neat ATR): 2964, 2938, 2874, 1698, 1100, 693;

HRMS (DART): calcd [M+H]⁺ 291.19547, found 291.19484.



(6*E*,8*E*)-1,3,4,5,10,11,12,14,14*b*,15,18,18*a*-dodecahydro-19*H*-15,18-methanoindeno[1,2*c*][1,6]dioxacyclohexadecin-19-one (4-21)

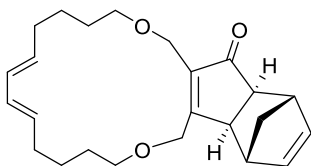
A flame dried round bottom flask was charged with TMTU (26 mg, 0.19 mmol) and flushed with N₂. A solution of complex **4-4** (166 mg, 0.33 mmol) in toluene (6 mL) and norbornadiene (0.10 mL, 0.65 mmol) was added. The reaction solution was stirred at 70 °C for 24 h. Solvent was removed *in vacuo* and column chromatography with 4:1 hexanes/EtOAc afforded 76 mg (68% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.32 (dd, *J* = 5.6, 2.8, 1H), 6.20 (dd, *J* = 5.6, 2.8 Hz, 1H), 6.02 (dd, *J* = 14.6, 6.6 Hz, 1H), 5.93 (dd, *J* = 14.4, 6.4 Hz, 1H), 5.62-5.47 (m, 2H), 4.36 (d, *J* = 15.2 Hz, 1H), 4.31 (d, *J* = 15.2 Hz, 1H), 3.90 (s, 2H), 3.54 (ddd, *J* = 9.8, 6.0, 3.8 Hz, 1H), 3.49-3.38 (m, 3H), 3.01 (bs, 1H), 2.94 (bs, 1H), 2.90 (d, *J* = 5.2 Hz, 1H), 2.31 (d, *J* = 5.2 Hz, 1H), 2.28-2.09 (m, 4H), 1.76-1.66 (m, 4H), 1.40 (dt, *J* = 9.2, 1.2 Hz, 1H), 1.24 (bd, *J* = 9.2 Hz, 1H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 208.3, 175.9, 139.7, 138.6, 137.0, 133.0, 131.9, 129.9, 129.3, 71.7, 70.1, 67.9, 60.7, 52.2, 48.7, 43.7, 42.7, 41.1, 31.9, 30.6, 28.5 (2 C signals overlap);

IR (neat ATR): 2916, 2868, 1692, 1095, 985, 911, 727;

HRMS (DART): calcd [M+H]⁺ 341.21112, found 341.21017.



(7E,9E)-1,3,4,5,6,11,12,13,14,16,16b,17,20,20a-tetradecahydro-21H-17,20-methanoindeno[1,2-c][1,6]dioxacyclooctadecin-21-one (4-22)

A flame dried round bottom flask was charged with TMTU (17 mg, 0.13 mmol) and flushed with N₂. A solution of complex **4-12** (115 mg, 0.22 mmol) in toluene (5 mL) and norbornadiene (0.04 mL, 0.43 mmol) was added. The reaction solution was stirred at 70 °C for 24 h. Solvent was removed *in vacuo* and column chromatography with 4:1 hexanes/EtOAc afforded 65 mg (82% yield) of a colorless oil.

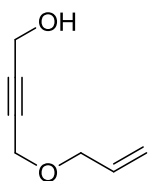
¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.30 (dd, *J* = 5.4, 3.0, 1H), 6.19 (dd, *J* = 5.4, 3.0 Hz, 1H), 6.05 (dd, *J* = 14.4, 10.4 Hz, 1H), 5.98 (dd, *J* = 14.4, 10.4 Hz, 1H), 5.55-5.44 (m, 2H), 4.46 (d, *J* =

16 Hz, 1H), 4.32 (d, $J = 15.6$ Hz, 1H), 4.08 (dd, $J = 18.8, 12.4$ Hz, 2H), 3.50 (td, $J = 7.2, 2.4$ Hz, 2H), 3.30 (t, $J = 7.2$ Hz, 2H), 2.94-2.91 (m, 3H), 2.29 (d, $J = 5.2$ Hz, 1H), 2.21-2.03 (m, 4H), 1.66-1.60 (m, 2H), 1.58-1.47 (m, 4H), 1.45-1.40 (m, 2H), 1.38 (bd, $J = 9.2$ Hz, 1H), 1.21 (bd, $J = 9.2$ Hz, 1H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 208.1, 175.6, 140.1, 138.6, 137.1, 132.6, 131.8, 131.5, 131.3, 70.3, 70.1, 66.7, 61.9, 52.3, 48.8, 43.7, 42.8, 41.3, 32.0, 31.3, 27.42, 27.32, 24.1, 23.5;

IR (neat ATR): 2937, 2861, 1690, 1637, 1372, 1107, 990, 913, 731;

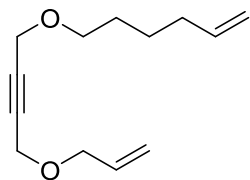
HRMS (DART): calcd $[\text{M}+\text{H}]^+$ 369.24242, found 369.24141.



4-(allyloxy)but-2-yn-1-ol

To a suspension of KOH (2.30 g, 41.3 mmol) in DMSO (20 mL) were added allyl bromide (1.4 mL, 16.2 mmol) and but-2-yne-1,4-diol (3.5 g, 41.3 mmol). The mixture was then stirred for 1 h, poured into water, and extracted with ether. The aqueous phase was then acidified with aqueous HCl (6 M) and further extracted with ether. The combined organic phases were reduced in volume, washed with water, dried with MgSO_4 , and concentrated *in vacuo*. Chromatography with 3:1 hexanes/ Et_2O afforded 1.15 g (57% yield) of a known⁵⁵ colorless oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 5.90 (ddt, $J = 17.2, 10.4, 5.6$ Hz, 1H), 5.31 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H), 5.22 (ddt, $J = 10.4, 1.6, 1.2$ Hz, 1H), 4.32-4.30 (m, 2H), 4.19 (t, $J = 1.6$ Hz, 2H), 4.05 (dt, $J = 5.6, 1.2$ Hz, 2H), 1.74 (bt, $J = 5.6$ Hz, 1H).



6-((4-(allyloxy)but-2-yn-1-yl)oxy)hex-1-ene

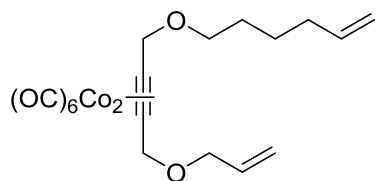
A flame dried flask was charged with NaH (261 mg, 6.53 mmol, 60% w/w dispersion in mineral oil) and dry DMF (6 mL) under N₂ atmosphere. The suspension was cooled to 0 °C and a solution of 4-(allyloxy)but-2-yn-1-ol (343 mg, 2.72 mmol) in dry DMF (6 mL) was added dropwise. The mixture was stirred for 45 min at 0 °C prior to the addition of hex-5-en-1-yl 4-methylbenzenesulfonate (830 mg, 3.26 mmol). The reaction solution was allowed to stir at room temperature for 24 h. Upon completion, water was added and the crude mixture was extracted with DCM. The combined organic layers were washed with water, brine, and dried over MgSO₄. Solvent was removed *in vacuo*. Chromatography with 9:1 hexanes/EtOAc afforded 520 mg (92% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.90 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.79 (ddt, *J* = 17.0, 10.4, 6.8 Hz, 1H), 5.29 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.21 (ddt, *J* = 10.4, 1.2, 1.2 Hz, 1H), 4.99 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 4.94 (ddt, *J* = 10.0, 1.2, 1.2 Hz, 1H), 4.19-4.16 (m, 4H), 4.05 (dt, *J* = 5.6, 1.2 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.09-2.04 (m, 2H), 1.64-1.56 (m, 2H), 1.49-1.41 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 138.6, 133.9, 117.8, 114.5, 82.6, 81.9, 70.6, 70.0, 58.2, 57.4, 33.4, 28.9, 25.4;

IR (neat ATR): 2937, 2857, 1439, 1349, 1117, 1080, 992, 909;

HRMS (DART): calcd $[M+H]^+$ 209.15361, found 209.15374.



Complex 4-25

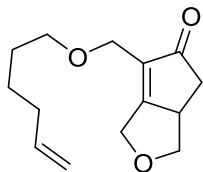
To a solution of 6-((4-(allyloxy)but-2-yn-1-yl)oxy)hex-1-ene (156 mg, 0.75 mmol) in DCM (10 mL) $\text{Co}_2(\text{CO})_8$ (282 mg, 0.82 mmol) was added. The mixture was stirred at room temperature for 3 h. The solvent was removed *in vacuo*. Chromatography with hexanes afforded 323 mg (87% yield) of red oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 5.93 (ddt, $J = 17.2, 10.8, 5.4$ Hz, 1H), 5.80 (ddt, $J = 17.0, 10.2, 6.6$ Hz, 1H), 5.35-5.30 (m, 1H), 5.20 (dd, $J = 10.4, 1.2$ Hz, 1H), 5.00 (dd, $J = 17.2, 1.6$ Hz, 1H), 4.94 (bd, $J = 10.4$ Hz, 1H), 4.65 (s, 2H), 4.62 (s, 2H), 4.15 (bd, $J = 5.2$ Hz, 2H), 3.60 (t, $J = 6.4$ Hz, 2H), 2.10-2.05 (m, 2H), 1.66-1.59 (m, 2H), 1.52-1.45 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 138.7, 134.3, 116.8, 114.4, 71.6, 70.99, 70.95, 70.2, 67.9, 33.5, 29.2, 25.3 (cobalt coordinated alkyne carbons absent and CO signal was not observed);

IR (neat ATR): 3016, 2969, 2942, 2093, 2049, 1997, 1439, 1365, 1228, 1216, 1091, 910;

HRMS (DART): calcd $[M-\text{OCH}_2\text{CH}=\text{CH}_2]^+$ 436.94763, found 436.94797, calcd $[M-\text{O}(\text{CH}_2)_4\text{CH}=\text{CH}_2]$ 394.90068, found 394.90097.



6-((hex-5-en-1-yloxy)methyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (4-26)

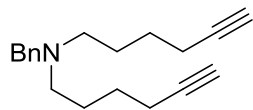
A flame dried round bottom flask was charged with NMO (388 mg, 2.89 mmol) and flushed with N₂. A solution of complex **4-25** (238 mg, 0.48 mmol) in DCM (10 mL) was added and the resultant solution was stirred at room temperature for 27 h. DCM was removed *in vacuo* and column chromatography with 4:1 hexanes/EtOAc afforded 64 mg (56% yield) of a colorless oil.

¹H NMR (400 MHz, C₆D₆, ppm) δ : 5.66 (ddt, $J = 17.0, 10.2, 6.8$ Hz, 1H), 4.98-4.89 (m, 2H), 4.48 (d, $J = 16.4$ Hz, 1H), 4.41 (dd, $J = 16.4, 1.6$ Hz, 1H), 4.07 (ddt, $J = 14.4, 2.8, 2.0$ Hz, 1H), 4.01 (dtd, $J = 14.4, 2.4, 1.4$ Hz, 1H), 3.71 (t, $J = 7.8$ Hz, 1H), 3.06 (t, $J = 6.2$ Hz, 2H), 2.58 (dd, $J = 11.2, 8.0$ Hz, 1H), 2.42-2.37 (m, 1H), 2.05 (ddd, $J = 17.6, 6.4, 0.4$ Hz, 1H), 1.89-1.83 (m, 2H), 1.50 (dd, $J = 17.4, 3.8$ Hz, 1H), 1.37-1.30 (m, 2H), 1.29-1.21 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 207.1, 178.6, 138.4, 133.8, 114.5, 71.37, 71.20, 65.5, 64.7, 44.0, 39.0, 33.3, 28.9, 25.2;

IR (neat ATR): 2934, 2857, 1710, 1680, 1374, 1272, 1121, 1024, 911, 887, 732;

HRMS (DART): calcd [M+H]⁺ 237.14852, found 237.14890.

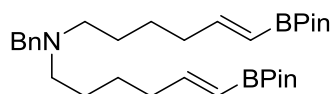


***N*-benzyl-*N*-(hex-5-yn-1-yl)hex-5-yn-1-amine (4-31)**

In a flame-dried round bottom flask benzylamine (0.5 mL, 4.57 mmol), potassium carbonate (2.0 g, 13.73 mmol) and hex-5-yn-1-yl 4-methylbenzenesulfonate (2.3 g, 9.15 mmol) were mixed with dry acetonitrile (15 mL). The resultant suspension was refluxed for 24 h. Upon completion the reaction mixture was filter through celite and the solvent was removed *in vacuo*. Column chromatography with 4:1 hexanes/EtOAc (small amount of Et₃N was added) afforded 930 mg (76% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.32-7.27 (m, 4H), 7.24-7.20 (m, 1H), 3.53 (s, 2H), 2.41 (t, *J* = 6.8 Hz, 4H), 2.15 (td, *J* = 6.8, 2.8 Hz, 4H), 1.93 (t, *J* = 2.6 Hz, 2H), 1.61-1.48 (m, 8H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 127.8, 128.0, 126.60, 126.57, 84.4, 68.1, 58.5, 52.9, 26.13, 26.01, 18.1.



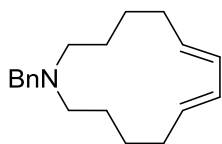
***(E)*-*N*-benzyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-((*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)hex-5-en-1-amine (4-32)**

A dry two neck-round bottom flask equipped with a reflux condenser was charged with Cp₂ZrHCl (70 mg, 0.27 mmol) under a N₂ atmosphere. A solution of **4-31** (366 mg, 1.37 mmol) in dry DCM was added into the flask at 0 °C and formed a suspension with Cp₂ZrHCl. Pinacolborane (0.8 mL, 5.47 mmol) was added dropwise to this suspension. The resultant

solution was stirred at 0 °C for 30 min and was refluxed for overnight. The reaction was quenched with water, diluted with DCM and washed with brine. After drying with MgSO₄ the solvent was removed *in vacuo*. Chromatography with 4:1 hexanes/EtOAc (small amount of Et₃N was added) afforded 560 mg (78% yield) of a colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.29-7.28 (m, 4H), 7.23-7.20 (m, 1H), 6.60 (dt, *J* = 18.0, 6.4 Hz, 2H), 5.40 (dt, *J* = 18.0, 1.4 Hz, 2H), 3.51 (s, 2H), 2.37 (t, *J* = 7.0 Hz, 4H), 2.14-2.06 (m, 4H), 1.46-1.34 (m, 8H), 1.26 (s, 24H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 154.4, 128.68 (2 C signals overlap), 127.97 (2 C signals overlap), 82.8, 58.5, 53.4, 35.6, 26.5, 25.9, 24.6 (boron substituted vinyl carbons absent).

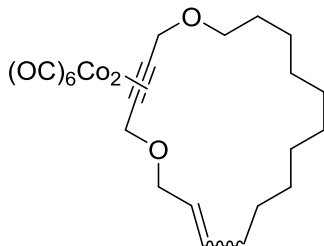


(6*E*,8*E*)-1-benzylazacyclotrideca-6,8-diene (4-33)

A flame dried round bottom flask was charged with PdCl₂(PPh₃)₂ (154 mg, 0.22 mmol) and flushed with N₂. Methanol (550 mL), **4-32** (1.15 g, 2.20 mmol), chloroacetone (1.8 mL, 22.0 mmol) and aqueous K₂CO₃ (2 M, 5.5 mL, 10.98 mmol) were subsequently added and the mixture was allowed to stir at room temperature for 6 h. Methanol was removed *in vacuo* and chromatography with 3:2 hexanes/EtOAc (small amount of Et₃N was added) afforded 366 mg (62% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.34-7.28 (m, 4H), 7.24-7.20 (m, 1H), 6.12-6.05 (m, 2H), 5.43-5.32 (m, 2H), 3.59 (s, 2H), 2.36-2.29 (m, 4H), 2.10-2.05 (m, 4H), 1.42-1.35 (m, 4H), 1.26-1.20 (m, 4H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 140.9, 132.0, 130.3, 128.5, 127.9, 126.4, 58.4, 52.5, 33.6, 23.3, 22.8.



Complex 4-51

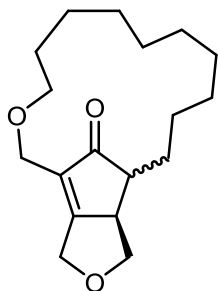
To a solution of **4-50** (132 mg, 0.50 mmol) in DCM (10 mL) $\text{Co}_2(\text{CO})_8$ (171 mg, 0.50 mmol) was added. The mixture was stirred at room temperature for 9 h. The solvent was removed *in vacuo*. Chromatography with 19:1 petroleum ether/ Et_2O afforded 242 mg (88% yield, *E/Z* = 2.5/1) of a red oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : (*E*) 5.71-5.51 (m, 2H), 4.64 (s, 2H), 4.61 (s, 2H), 4.14 (d, J = 5.6 Hz, 2H), 3.58 (t, J = 5.8 Hz, 2H), 2.08 (bd, J = 6.0 Hz, 2H), 1.59-1.55 (m, 2H), 1.40-1.28 (m, 14H), (*Z*) 5.71-5.51 (m, 2H), 4.67 (s, 2H), 4.64 (s, 2H), 4.23 (d, J = 6.0 Hz, 2H), 3.58 (t, J = 5.8 Hz, 2H), 2.08 (bd, J = 6.0 Hz, 2H), 1.59-1.55 (m, 2H), 1.40-1.28 (m, 14H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : (*E*) 199.5 (CO), 193.2 (CO), 135.1, 126.8, 94.23 (Co-C \equiv C-Co), 94.22 (Co-C \equiv C-Co), 71.33, 71.29, 71.0, 68.8, 31.6, 28.9, 27.9, 27.48, 27.39, 27.13, 27.09, 27.04, 24.7, (*Z*) 199.5 (CO), 193.2 (CO), 133.9, 126.3, 94.26 (Co-C \equiv C-Co), 94.19 (Co-C \equiv C-Co), 71.6, 70.9, 69.8, 66.4, 29.0, 28.3, 27.66, 27.59, 27.57, 27.26, 27.1 (2 C signals overlap), 26.9, 25.0;

IR (neat ATR): 2928, 2857, 2092, 2049, 2013, 1622, 1460, 1348, 1095, 971;

HRMS (DART): calcd $[M+H]^+$ 551.05209, found 551.05013.



4-52

A flame-dried flask was charged with **4-51** (115 mg, 0.21 mmol) and acetonitrile (20 mL). The solution was heated to 50 °C and NMO (147 mg, 1.25 mmol in 10 mL MeCN) was added dropwise over 14 h. Upon completion, the reaction was cooled to room temperature, solvent was removed *in vacuo* and chromatography with 1:1 hexanes/Et₂O afforded 27 mg (44% yield) of a colorless oil.

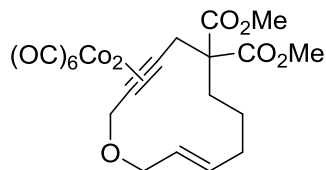
¹H NMR (400 MHz, CDCl₃, ppm) δ : (**Major**) 4.70 (d, J = 16.4 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 4.34 (dd, J = 14.0, 14.0 Hz, 1H), 4.24 (d, J = 12.8 Hz, 1H), 4.04 (d, J = 12.8 Hz, 1H), 3.50-3.44 (m, 1H), 3.42-3.36 (m, 1H), 3.24-3.18 (m, 2H), 2.26 (bt, J = 2.6 Hz, 1H), 2.19-2.11 (m, 1H), 1.76-1.64 (m, 1H), 1.65-1.50 (m, 2H), 1.47-1.14 (m, 14H), (**Minor**) 4.66 (d, J = 16.8 Hz, 1H), 4.60 (d, J = 16.4 Hz, 1H), 4.19 (dt, J = 11.6, 0.8 Hz, 1H), 4.15 (dd, J = 8.4, 8.4 Hz, 1H), 3.96 (d, J = 11.6 Hz, 1H), 3.56 (dd, J = 11.2, 8.4 Hz, 1H), 3.50-3.44 (m, 1H), 3.36-3.18 (m, 2H), 2.72-2.67 (m, 1H), 1.76-1.64 (m, 2H), 1.47-1.14 (m, 16H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : (**Major**) 209.7, 180.2, 133.9, 71.4, 69.5, 64.9, 61.4, 49.2, 47.5, 28.1, 27.7, 27.3, 26.7, 26.6, 26.4, 26.0, 25.61, 24.5, (**Minor**) 210.4, 177.4, 130.9, 70.7,

67.3, 65.3, 61.8, 49.7, 47.7, 28.7, 27.8, 27.6, 26.9, 25.59, 25.2, 24.2, 23.7 (1 C signal overlaps around 27.0 ppm);

IR (neat ATR): 2925, 2855, 1712, 1676, 1094, 1025, 986, 889, 733;

HRMS (DART): calcd $[M+H]^+$ 293.21112, found 293.21005.



Complex 4-54

To a solution of **4-53** (95 mg, 0.34 mmol) in DCM (7 mL) Co₂(CO)₈ (116 mg, 0.34 mmol) was added. The mixture was stirred at room temperature for 6 h. The solvent was removed *in vacuo*. Chromatography with 9:1 petroleum ether/Et₂O afforded 142 mg (74% yield) of a red solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 5.88-5.65 (m, 2H), 4.66 (s, 2H), 4.00 (d, $J = 1.6$ Hz, 2H), 3.74 (s, 6H), 3.65 (s, 2H), 2.14 (bs, 2H), 2.02-1.96 (m, 2H), 1.41 (bs, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 199.4 (C \equiv O), 170.8 (C=O), 136.2, 128.4, 95.0 (Co-C \equiv C-Co), 87.0 (Co-C \equiv C-Co), 70.5, 66.6, 58.0, 52.6, 38.2, 28.7, 28.2, 23.2;

IR (neat ATR): 2947, 2855, 2089, 2050, 1998, 1730, 1301, 1242, 1205, 1182, 1059, 1013;

HRMS (DART): calcd $[M+H]^+$ 566.97424, found 566.97174.

4.5. References and Notes

1. For selected reviews, see: a) Heck, R. F. *Synlett* **2006**, 2855. b) Omae, I. *Appl. Organometal. Chem.* **2007**, *21*, 318. c) Taylor, C. J. S.; Ward, B. D. *New J. Chem.* **2008**, *32*, 1850. d) Gandeepan, P.; Cheng, C. H. *Acc. Chem. Res.* **2015**, *48*, 1194. e) Ott, I.; Schmidt, K.; Kircher, B.; Schumacher, P.; Wiglenda, T.; Gust, R.; *J. Med. Chem.* **2005**, *48*, 622.
2. Schwab E. *Chem. Eng. News.* **2003**, 80.
3. Mond, L.; Hirtz, H.; Cowap, M. D. *J. Chem. Soc.* **1910**, 798.
4. a) Octacarbonyldicobalt. *e-EROS Encyclopedia of Reagents in Organic Synthesis* [Online]; John Wiley & Sons, 2014. DOI: 10.1002/047084289X.ro001.pub3 b) Fischer, S. *Synlett* **2002**, 1558.
5. a) Nicholas, K. M.; Pettit, R. *Tetrahedron* **1971**, *37*, 3475. b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. c) Kuhn, O.; Rau, D.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 900. d) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. e) Montana, A. M.; Cano, M. *Tetrahedron* **2002**, *58*, 933. For a recent review on the topic, see: f) Amin, J.; Motevalli, M.; Richards, C. J. *J. Organomet. Chem.* **2015**, *776*, 43. (also see chapter 3 ref 19)
6. For selected examples, see: a) Seyferth, D.; Nestle, M. O.; Wehman, A. T. *J. Am. Chem. Soc.* **1975**, *97*, 7417. b) Marshall, J. A.; Robinson, E. D.; Lebreton, J. *J. Org. Chem.* **1990**, *55*, 227. c) Jones, G. B.; Hynd, G.; Wright, J. M.; Purohit, A.; Plourde, I. I. G. W.; Huber, R. S.; Mathews, J. E.; Li, A.; Kilgore, M. W.; Bublely, G. J.; Yancisin, M.; Brown, M. A. *J. Org. Chem.* **2001**, *66*, 3688. d) Gobbo, P.; Romagnoli, T.; Barbon, S. M.; Price, J. T.; Keir, J.; Gilroy, J. B.; Workentin, M. S. *Chem. Commun.* **2015**, *51*, 6647. (also see chapter 2 ref 11c, 26a-c, 29b, 31)

7. a) Cragg, R. H.; Jeffery, J. C.; Went, M. J. *Dalton Trans.* **1991**, 137. b) Magnus, P.; Annoura, H.; Harling, J. *J. Org. Chem.* **1990**, 55, 1709. c) Magnus, P.; Davies, M. *Chem. Commun.* **1991**, 1522. d) Magnus, P.; Pitterna, T. *Chem. Commun.* **1991**, 541. e) Najdi, S. D.; Olmstead, M. M.; Schore, N. E. *J. Organomet. Chem.* **1992**, 431, 335. f) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, 112, 4966. g) Iwasawa, N.; Ooi, I.; Inaba, K.; Takaya, J. *Angew. Chem. Int. Ed.* **2010**, 49, 7534. h) Zhang, J.; Xing, S.; Ren, J.; Jiang, S.; Wang, Z. *Org. Lett.* **2015**, 17, 218.
8. a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *Chem. Commun.* **1971**, 36. b) Khand, I. U.; Konox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans. 1* **1973**, 977.
9. a) Gibe, R.; Green, J. R. *Chem. Commun.* **2002**, 1550. b) Shea, K. M.; Closser, K. D.; Quintal, M. M. *J. Org. Chem.* **2005**, 70, 9088. c) Alvaro, E.; De la Torre, M. C.; Sierra, M. A. *Chem. Commun.* **2006**, 985. d) Zhao, L.; Northrop, B. H.; Stang, P. J. *J. Am. Chem. Soc.* **2008**, 130, 11886. e) Carrillo, R.; Martin, T.; Loopez-Rodriguez, M.; Crisostomo, F. *P. Org. Lett.* **2014**, 16, 552. (also see chapter 3 ref 19a)
10. a) King, R. B.; Haiduc, I.; Efraty, A. *J. Organomet. Chem.* **1973**, 47, 145. b) Hamilton, D. G.; Sanders, J. K. M. *Chem. Commun.* **1998**, 1749. c) Davies, J. E.; Hope-Weeks, L. J.; Mays, M. J.; Raithby, P. R. *Chem. Commun.* **2000**, 1411. d) Song, L. –C.; Jin, J. –X.; Wang, H. –T.; Zhang, W. –X.; Hu, Q. –M. *Organometallics* **2005**, 24, 6464. e) Song, L. –C.; Jin, J. –X.; Zhang, W. –X.; Hu, Q. –M. *Organometallics* **2005**, 24, 700. f) Cetin, A.; Durfee, W. S.; Ziegler, C. J. *Inorg. Chem.* **2007**, 46, 6236. g) Baillargeon, P.; Fortin, D.; Dory, Y. L. *Cryst. Growth Des.* **2010**, 10, 4357.
11. Berthelot, M. *C. R. Hebd. Seances Acad. Sci.* **1866**, 62, 905.

12. For selected reviews, see: Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. b) Chopadea, P. R.; Louiea, J. *Adv. Synth. Catal.* **2006**, 348, 2307. c) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, 40, 4525. d) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741.
13. Amatore, M.; Aubert, C. *Eur. J. Org. Chem.* **2015**, 265.
14. Pla-Quintana, A.; Roglans, A. *Molecules* **2010**, 15, 9230.
15. Okamoto, S.; Sugiyama, Y. *Synlett* **2013**, 24, 1044.
16. Bennett, M. A.; Donaldson, P. B. *Inorg. Chem.* **1978**, 17, 1995.
17. a) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. b) Das, S. K.; Roy, R. *Tetrahedron Lett.* **1999**, 40, 4015. c) Roy, R.; Das, S. K.; Dominique, R.; Trono, M. C.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Pure Appl. Chem.* **1999**, 71, 565.
18. a) Mamane, V.; Gref, A.; Lefloch, F.; Riant, O. *J. Organomet. Chem.* **2001**, 637, 84. b) Xie, R. -J.; Han, L. -M.; Zhu, N.; Hong, H. -L.; Suo, Q. -L.; Fu, P. *Polyhedron* **2012**, 38, 7. c) Fletcher, J. T.; Therien, M. J. *J. Am. Chem. Soc.* **2000**, 122, 12393. d) Fletcher, J. T.; Therien, M. J. *J. Am. Chem. Soc.* **2002**, 124, 4298. e) Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *Org. Lett.* **2004**, 6, 3405.
19. a) Geng, Y.; Fechtenkotter, A.; Müllen, K. *J. Mater. Chem.* **2001**, 11, 1634. b) Kobayashi, K.; Shirasaka, T.; Sato, A.; Horn, E.; Furukawa, N. *Angew. Chem. Int. Ed.* **1999**, 38, 3483. c) Al-Smadi, M.; Ratrout, S. *J. Heterocyclic Chem.* **2004**, 41, 887.
20. a) Dötz, F.; Brand, J. D.; Ito, S.; Gherghel, L.; Müllen, K. *J. Am. Chem. Soc.* **2000**, 122, 7707. b) Pisula, W.; Kastler, M.; Wasserfallen, D.; Pakula, T.; Mullen, K. *J. Am. Chem. Soc.* **2004**, 126, 8074.
21. Mohamed, A. B.; Green, J. R. *Chem. Commun.* **2003**, 2936.

22. Son, S. U.; Choi, D. S.; Chung, Y. K. *Org. Lett.* **2000**, 2, 2097.
23. Gervasio, G.; Sappa, E. *J. Organomet. Chem.* **1993**, 444, 203.
24. Baxter, R. J.; Knox, G. R.; Moir, J. H.; Pauson, P. L.; Spicer, M. D. *Organometallics* **1999**, 18, 206.
25. a) Sigman, M. S.; Fatland, A. W.; Eaton, B. E. *J. Am. Chem. Soc.* **1998**, 120, 5130. b) Hecht, S.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1999**, 121, 4084.
26. a) Elwahy, A. H. M. *Tetrahedron Lett.* **2001**, 42, 5123. b) Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron Lett.* **2006**, 47, 1303.
27. a) Manen, H. -J.; Fokkens, R. H.; Veggel, F. C. J. M.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **2002**, 3189. b) Yin, X. -Y.; Tan, M. -Y. *Synth. Commun.* **2003**, 33, 1113. c) Sanz, D.; Jimenez, J. A.; Claramunt, R. M.; Elguero, J. *Arkivoc* **2004**, 100. d) Liu, Q. -P.; Chen, Y. -J.; Wu, Y.; Zhu, J.; Geng, J. -G. *Synlett* **2006**, 1503. e) Reger, D. L.; Foley, E. A.; Smith, M. D. *Inorg. Chem.* **2010**, 49, 234.
28. Jyothish, K.; Vemula, P. K.; Jadhav, S. R.; Francesconi, L. C.; John, G. *Chem. Commun.* **2009**, 5368.
29. Perry, M. R.; Shaver, M. P. *Can. J. Chem.* **2011**, 89, 499.
30. a) Eubank, J. F.; Mouttaki, H.; Cairns, A. J.; Belmabkhout, Y.; Wojtas, L.; Luebke, R.; Alkordi, M.; Eddaoudi, M. *J. Am. Chem. Soc.* **2011**, 133, 14204. b) Wang, Y.; Yang, J.; Liu, Y. -Y.; Ma, J. F. *Chem. Eur. J.* **2013**, 19, 14591.
31. a) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem. Int. Ed.* **1997**, 36, 2801. b) Rajeah, T.; Periasamy, M. *Tetrahedron Lett.* **1998**, 39, 117. c) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, 7, 1589.

- 32.** For selected recent reviews on the importance and utility of hydroquinone derivatives, see: a) Gueven, N.; Woolley, K.; Smith, J. *Redox Biol.* **2015**, *4*, 289. b) Bertanha, C. S.; Januario, A. H.; Alvarenga, T. A.; Pimenta, L. P.; Silva, M. L. A.; Cunha, W. R.; Pauletti, P. M. *Mar. Drugs* **2014**, *12*, 3608. c) Pochorovski, I.; Diederich, F. *Acc. Chem. Res.* **2014**, *47*, 2096. d) Kim, S. B.; Pike, R. D.; Sweigart, D. A. *Acc. Chem. Res.* **2013**, *46*, 2485. e) Xue, M.; Yang, Y.; Chi, X.; Zhang, Z.; Huang, F. *Acc. Chem. Res.* **2012**, *45*, 1294.
- 33.** a) Liebeskind, L. S.; Jewell, C. F. Jr. *J. Organomet. Chem.* **1985**, 285, 305. b) Jewell, C. F. Jr.; Liebeskind, L. S.; Williamson, M. *J. Am. Chem. Soc.* **1985**, *107*, 6715. c) Gleiter, V. R.; Schehlmann, V. *Angew. Chem.* **1990**, *102*, 1450. d) Liebeskind, L. S.; Yin, J. *J. Org. Chem.* **1998**, *63*, 5726. e) Schuster-Haberhauer, A.; Gleiter, R.; Korner, O.; Leskovar, A.; Werz, D. B.; Fischer, F. R.; Rominger, F. *Organometallics* **2008**, *27*, 1361.
- 34.** a) Iwasawa, N.; Owada, Y.; Matsuo, T. *Chem. Lett.* **1995**, 115. b) Owada, Y.; Matsuo, T.; Iwasawa, N. *Tetrahedron* **1997**, *53*, 11069.
- 35.** a) Cho, S. H.; Wirtz, K. R.; Liebeskind, L. S. *Organometallics* **1990**, *9*, 3067. b) Jewell, C. F. Jr.; Liebeskind, L. S. *Inorg. Chim. Acta.* **1994**, 222, 235.
- 36.** a) Reppe, W.; Schweckendiek, W. J. *Liebigs Ann. Chem.* **1948**, 560, 104. b) Reppe, W.; Wetter, H. *Carbonylierung* **1953**, *6*, 133. c) Reppe, W.; Kutepov, N.; Magin, A. *Angew. Chem. Int. Ed.* **1969**, *8*, 727.
- 37.** a) Reppe, W. German Pat. BASF. 874910, 1951. b) Reppe, W.; Magnin, A. German Pat. BASF. 1232974, 1965.
- 38.** a) Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759. b) Liebeskind, L. S.; Chidambarama, R.; Nimkar, S.; Lioatta, S. *Tetrahedron Lett.* **1990**, *31*, 3723.

39. a) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. b) Cambeiro, X. C.; Pericas, M. A. The Mechanism of the Pauson-Khand Reaction: Hypothesis, Experimental Facts, and Theoretical Investigations. In *The Pauson-Khand Reaction Scope, Variations and Applications*; Torres, R. R., Eds.; Wiley & Sons: Chichester, 2012; pp 23-46.
40. a) Blanco-Urgoiti, J; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. b) Lee, H. –W.; Kwong, F. –Y. *Eur. J. Org. Chem.* **2010**, 789. c) Kerr, W. J. The Pauson-Khand Reaction – an Introduction. In *The Pauson-Khand Reaction Scope, Variations and Applications*; Torres, R. R., Eds.; Wiley & Sons: Chichester, 2012; pp 1-17.
41. Kitagaki, S.; Inagaki, F.; Mukai, C. *Chem. Soc. Rev.* **2014**, *43*, 2956.
42. Gibson, S. E.; Stevenazzi, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1800.
43. Torres, R. R.; Vesely, J. Other Transition Metal-Mediated Cyclizations Leading to Cyclopentenones. In *The Pauson-Khand Reaction Scope, Variations and Applications*; Torres, R. R., Eds.; Wiley & Sons: Chichester, 2012; pp 276-299.
44. a) Kamlar, M.; Vesely, J.; Torres, R. R. Diastereoselective Pauson-Khand Reaction using Chiral Pool Techniques (Chiral Substrates). In *The Pauson-Khand Reaction Scope, Variations and Applications*; Torres, R. R., Eds.; Wiley & Sons: Chichester, 2012; pp 69-91. b) Lledo, A.; Verdaguer, X.; Riera, A. The Enantioselective Pauson-Khand Reaction. In *The Pauson-Khand Reaction Scope, Variations and Applications*; Torres, R. R., Eds.; Wiley & Sons: Chichester, 2012; pp 148-176.
45. For selected examples, see: a) Su, S.; Rodriguez, R. A.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 13922. b) Bihelovic, F.; Saicic, R. N. *Angew. Chem. Int. Ed.* **2012**, *51*, 5687. c) Liu, Q.; Yue, G.; Wu, N.; Lin, G.; Li, Y.; Quan, J.; Li, C.; Wang, G.; Yang, Z. *Angew.*

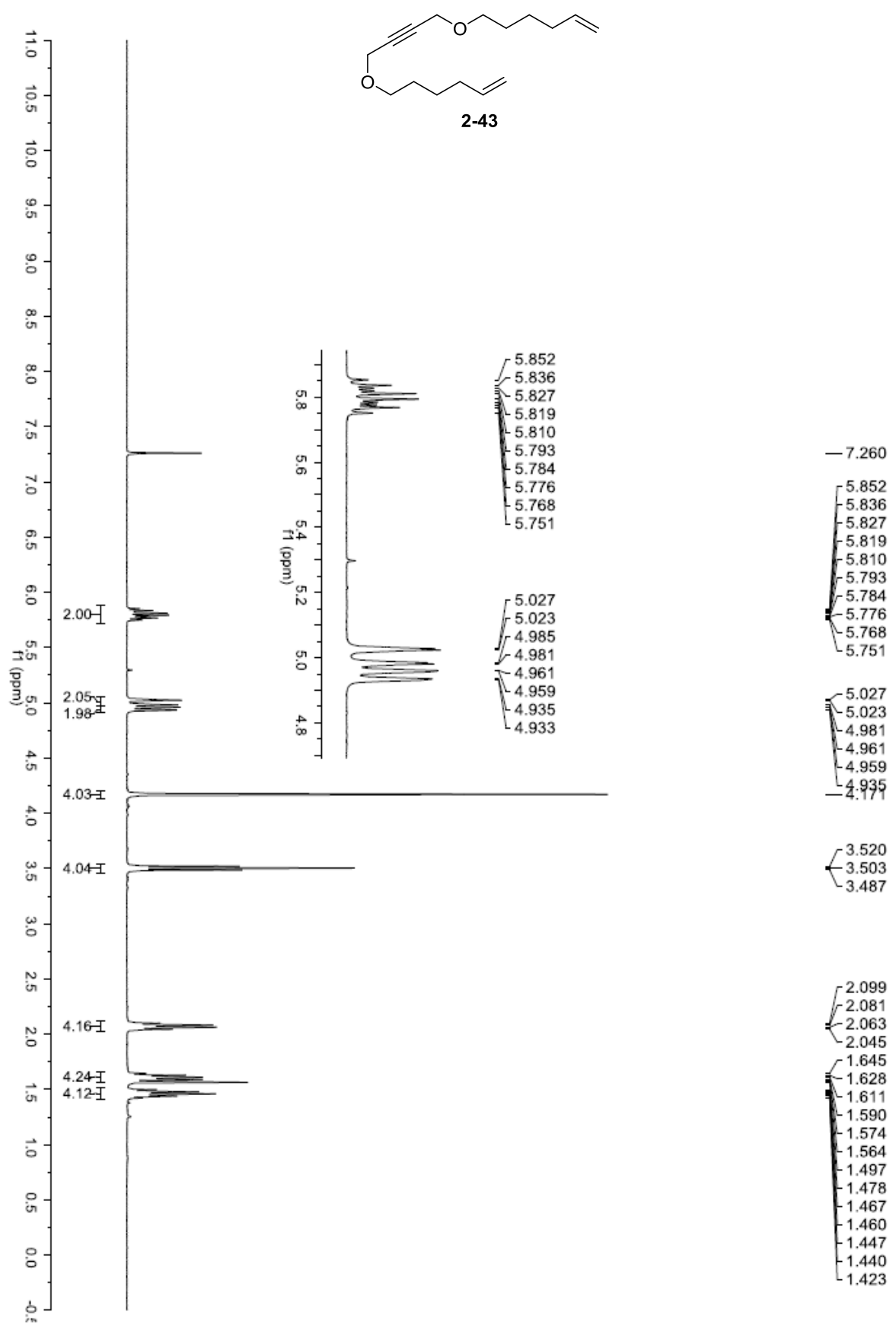
- Chem. Int. Ed.* **2012**, *51*, 12072. d) McKerrall, S. J.; Jorgensen, L.; Kuttruff, C. A.; Ungeheuer, F.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5799. e) Min, S. –J.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2199. e) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.
- 46.** For a review, see: Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795.
- 47.** a) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771. b) Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Chem. Commun.* **2001**, 2602.
- 48.** a) Khand, I. U.; Pauson, P. L.; Habib, J. A. M. *J. Chem. Research (S)* **1978**, 346. b) Becheanu, A.; Bell, T.; Laschat, S.; Baro, A.; Frey, W.; Steinke, N.; Fischer, P. Z. *Naturforsch.* **2006**, 589. c) Park, K. H.; Choi, S. Y.; Kim, S. Y.; Chung, Y. K. *Synlett* **2006**, 527.
- 49.** For a review, see: Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, 19.
- 50.** a) Franck-Neumann, M.; Vernier, J. –M. *Tetrahedron Lett.* **1992**, *33*, 7365. b) Seigal, B. A.; An, M. H.; Snapper, M. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4929.
- 51.** Iafe, R. G.; Chan, D. G.; Kuo, J. L.; Boon, B. A.; Faizi, D. J.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2012**, *14*, 4282.
- 52.** Williams, D. R.; Shah, A. A.; Mazumder, S.; Baik, M. –H. *Chem. Sci.* **2013**, *4*, 238.
- 53.** a) Ahmar, M.; Locatelli, C.; Colombier, D.; Cazes, B. *Tetrahedron Lett.* **1997**, *38*, 5281. b) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1998**, *63*, 6786. c) Lovely, C. J.; Seshadri, H.; Wayland, B. R.; Cordes, A. W. *Org. Lett.* **2001**, *3*, 2607. (Characterization of products by Lovely group revealed that the intramolecular PK products are in fact 2,4-substituted bicyclopentenones.)

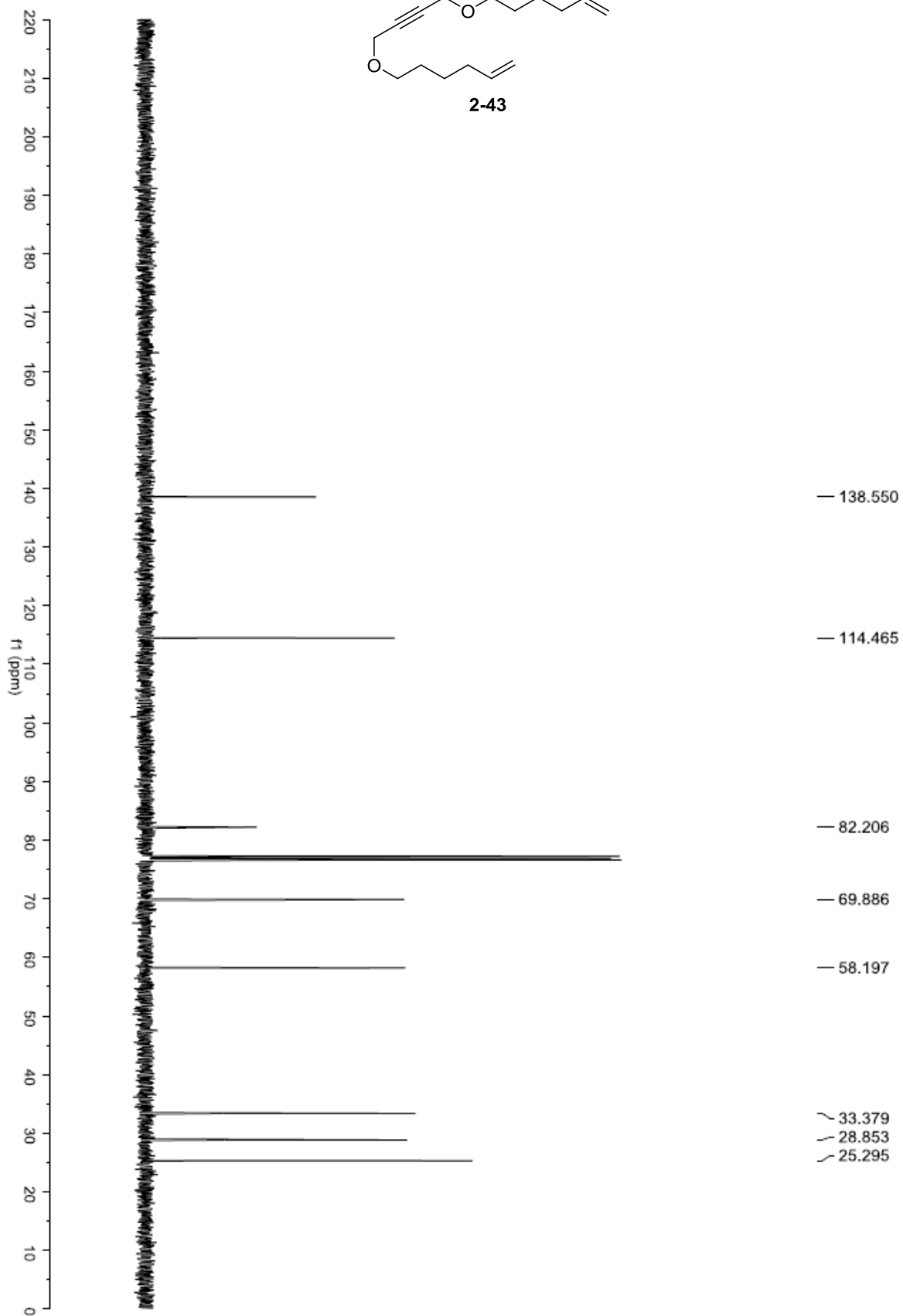
54. Krafft, M. E.; Fu, Z.; Bonaga, L. V. R. *Tetrahedron Lett.* **2001**, 42, 1427.

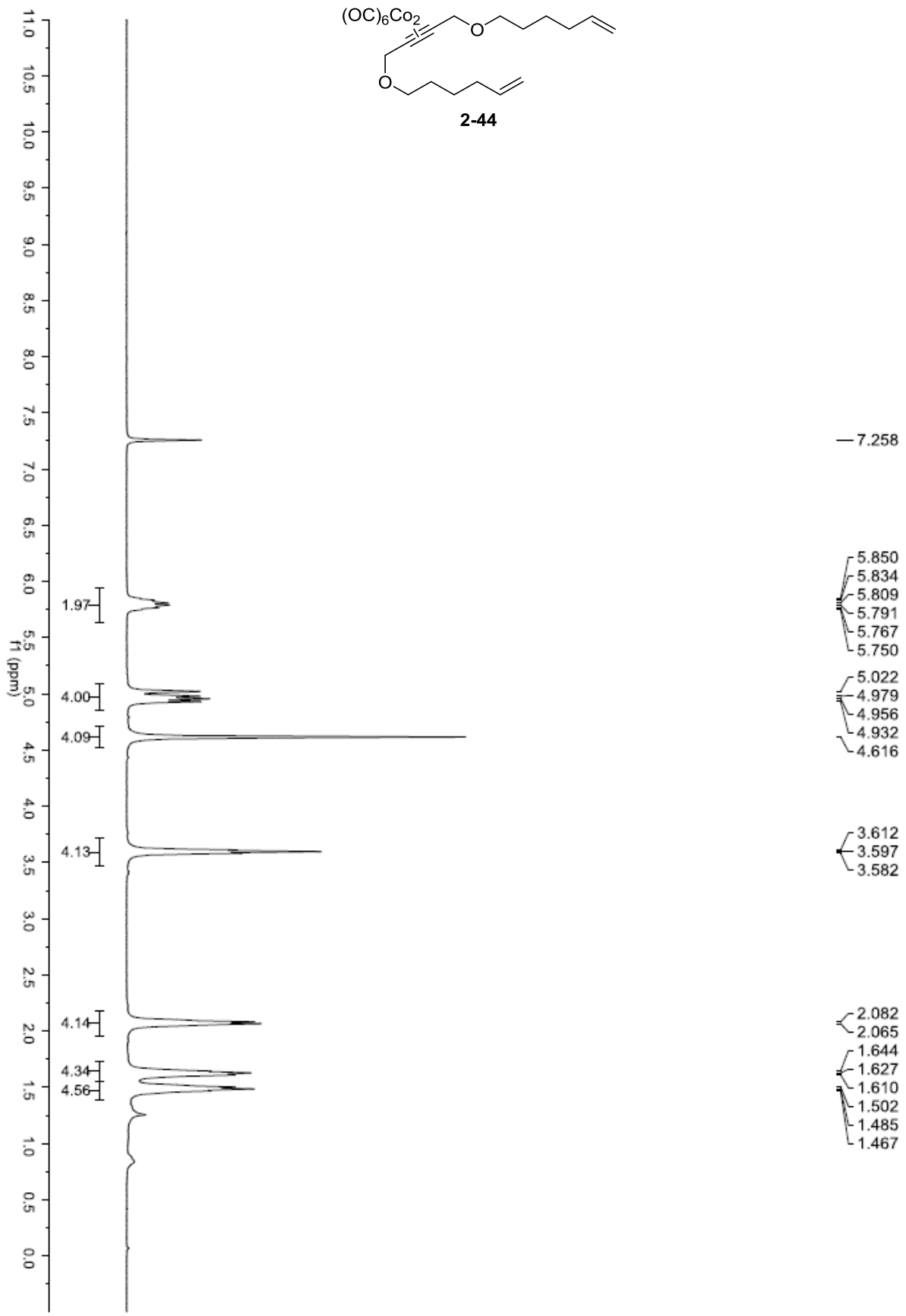
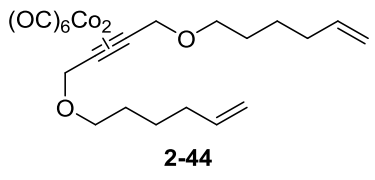
55. Bennacer, B.; Fujiwara, M.; Lee, S.; Ojima, I. *J. Am. Chem. Soc.* **2005**, 127, 17756.

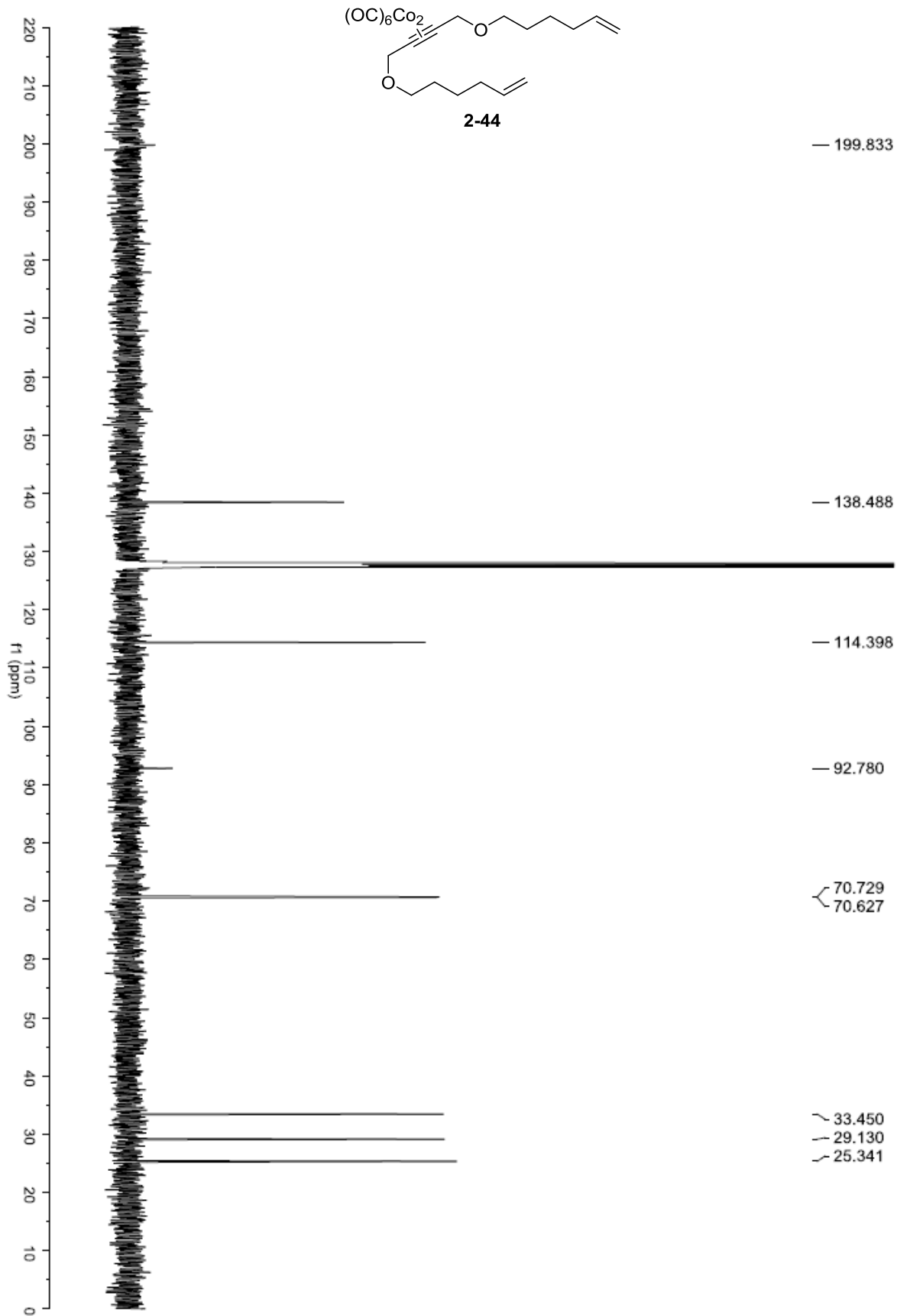
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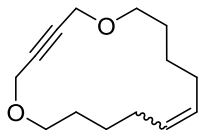
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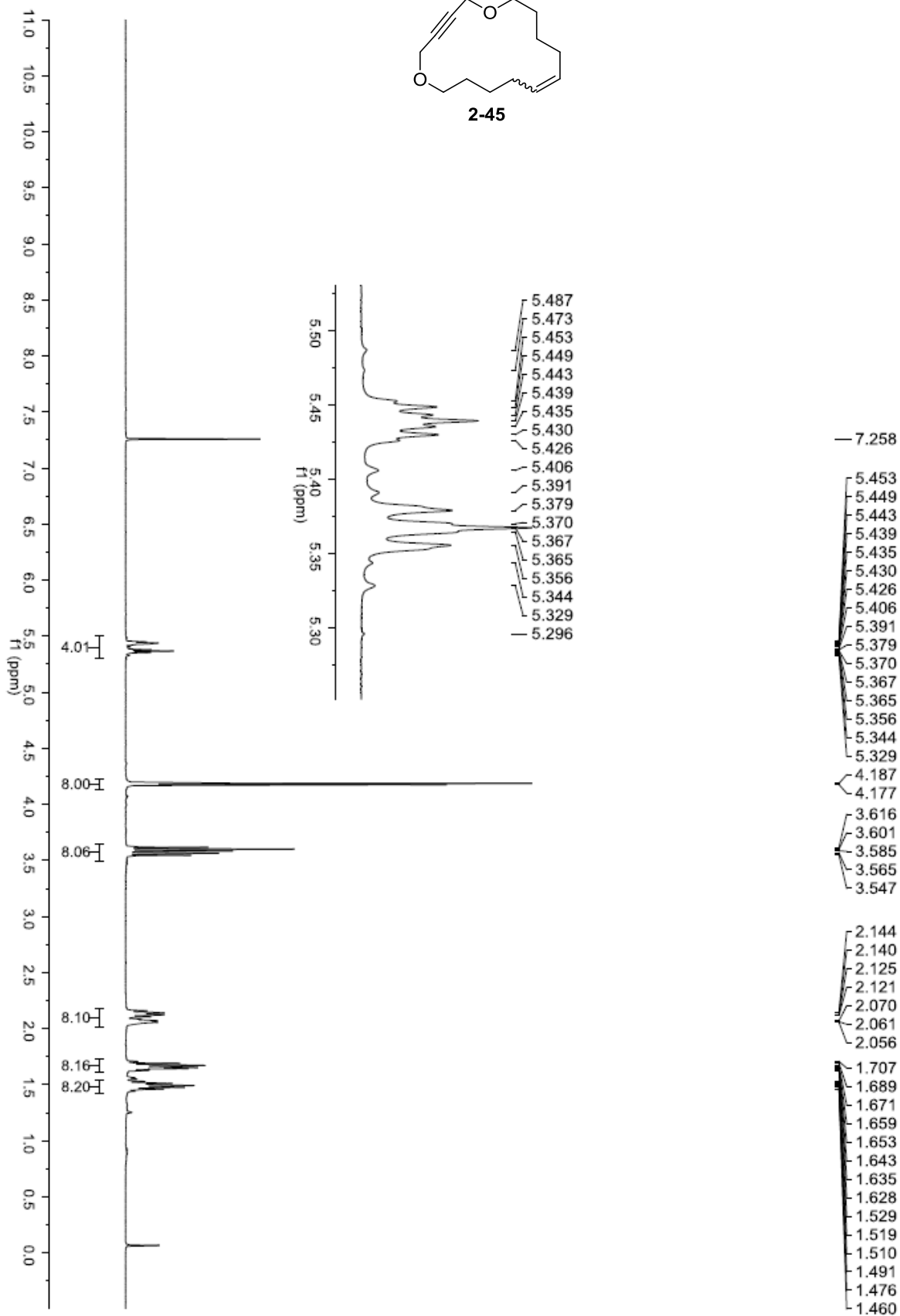


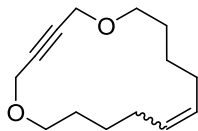




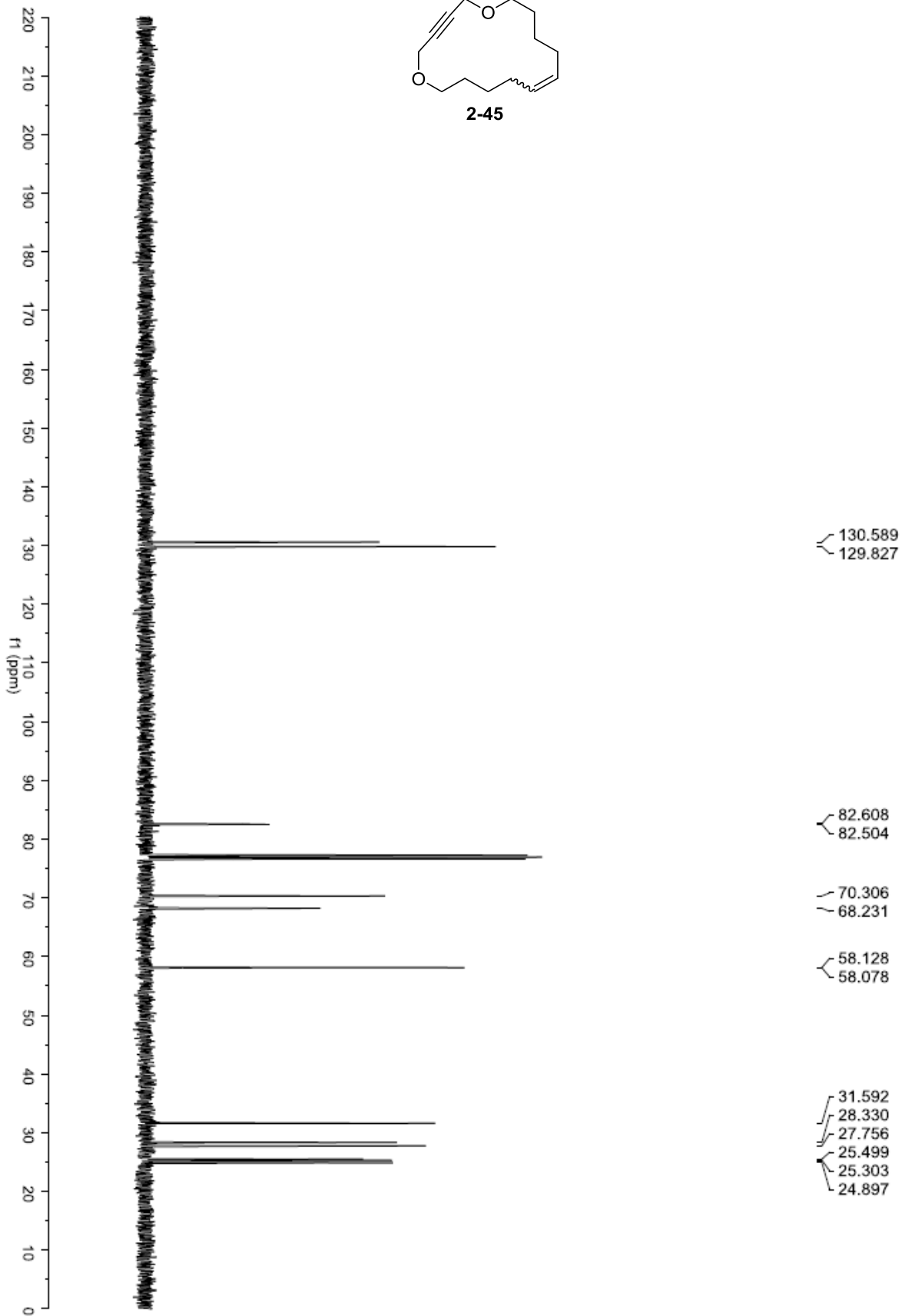


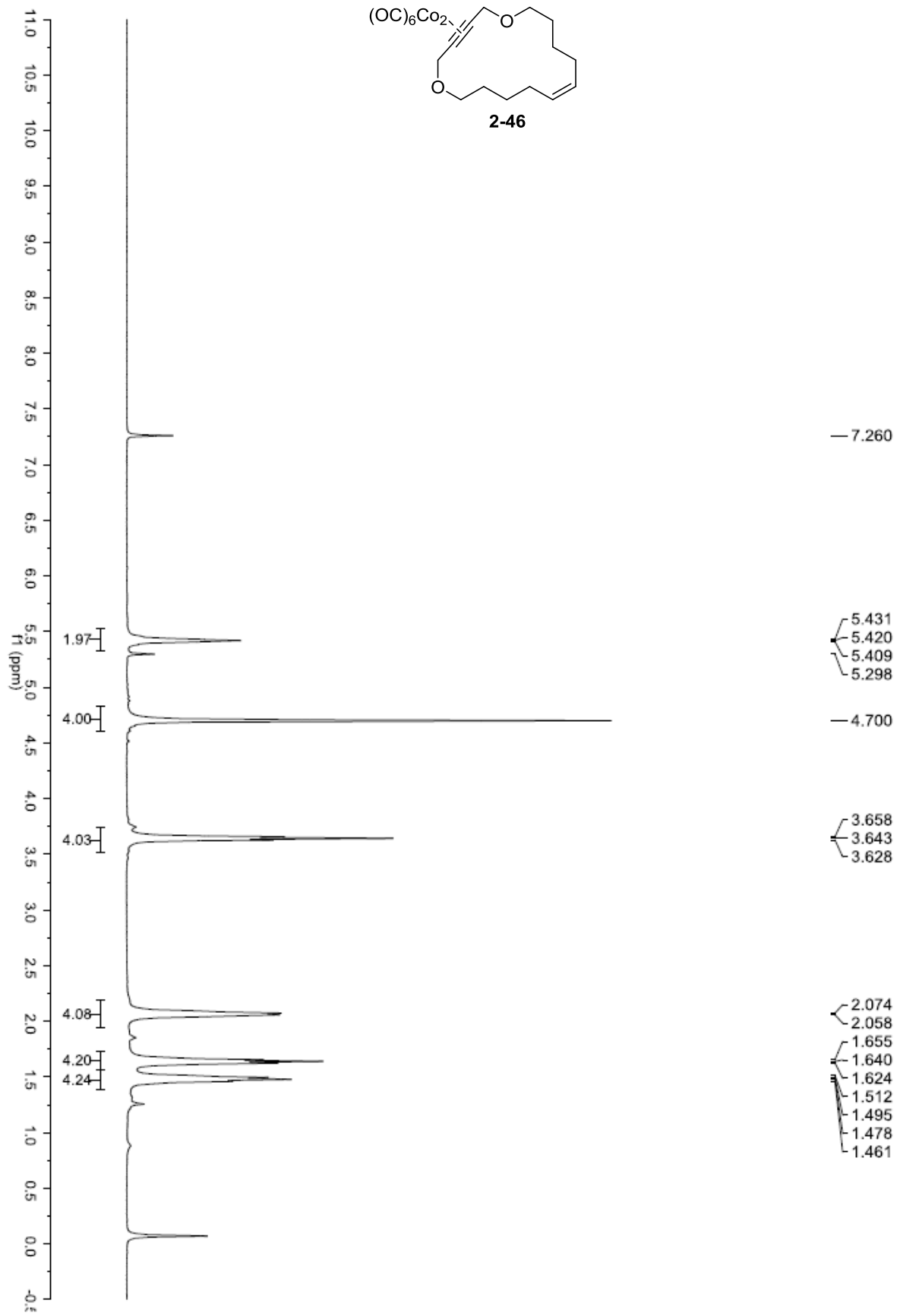
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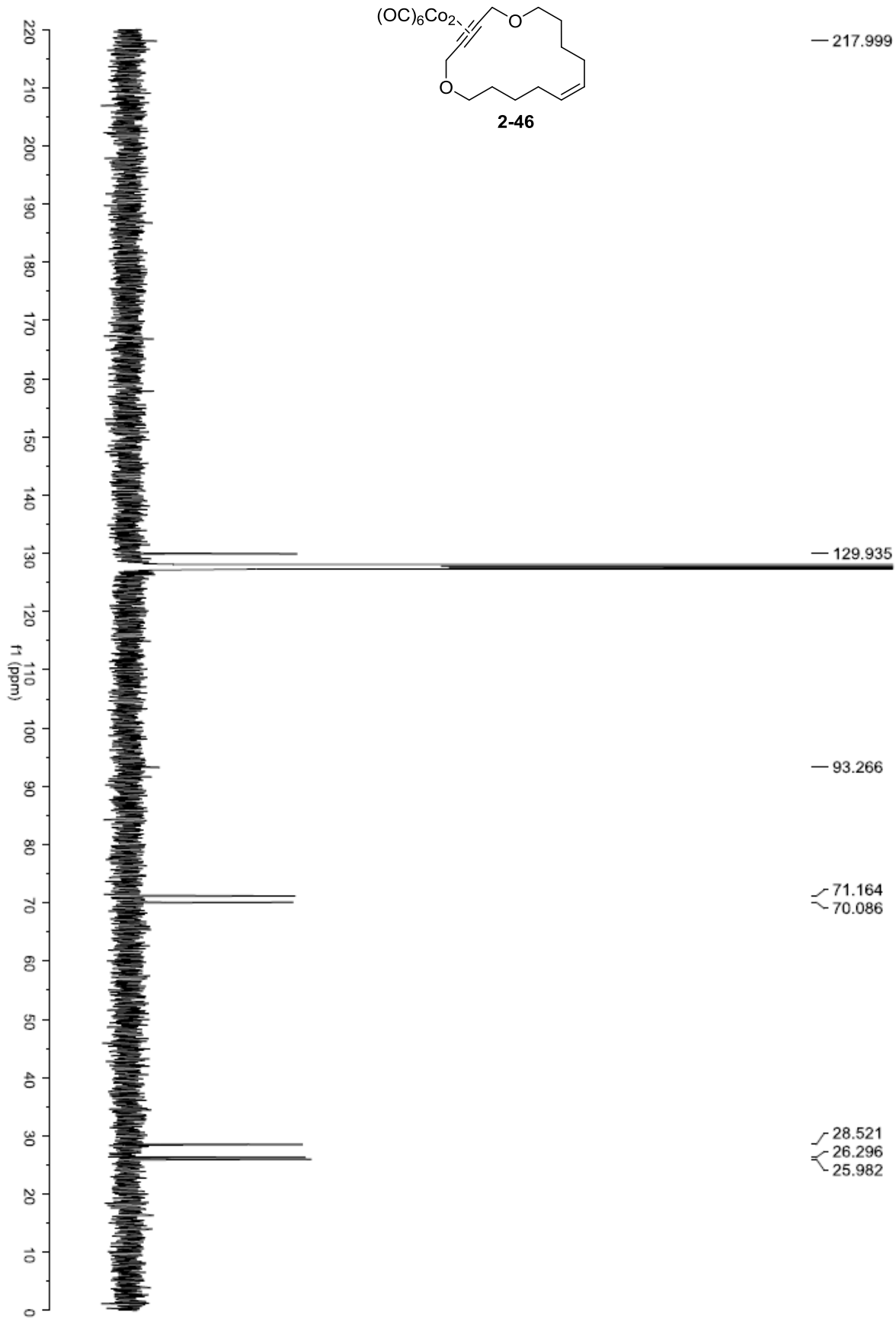


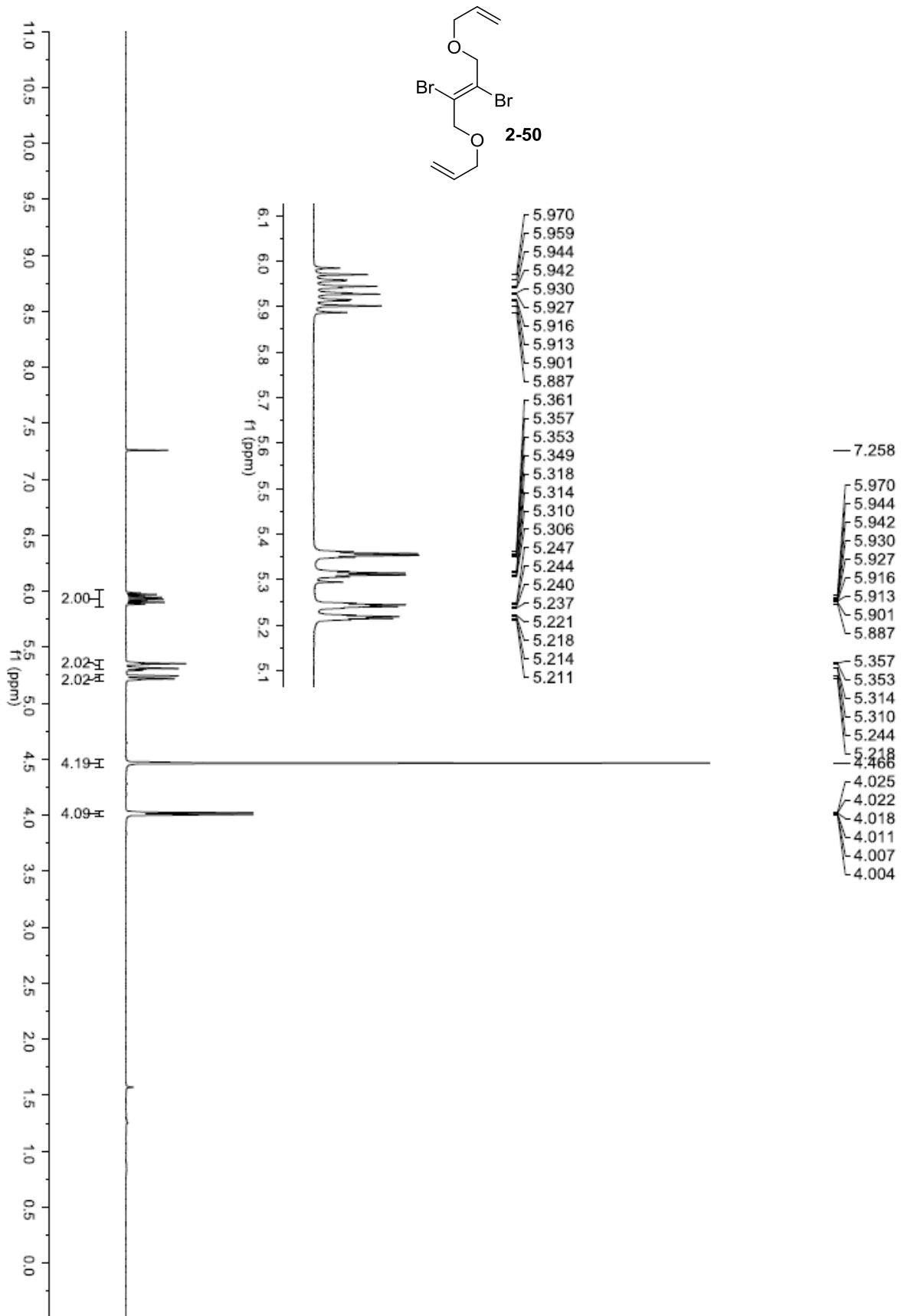


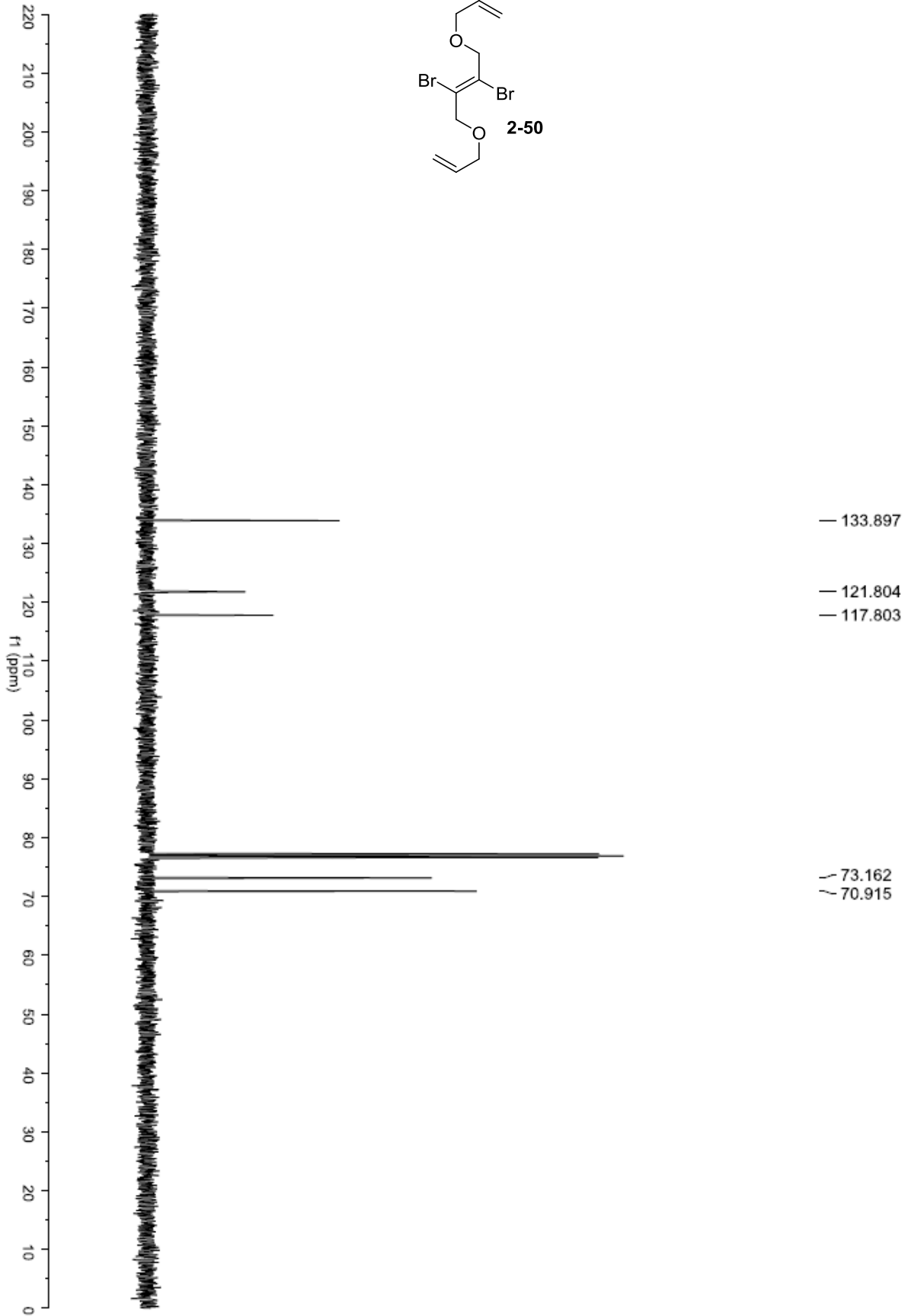
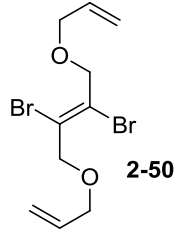
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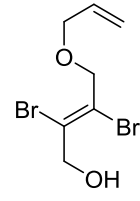




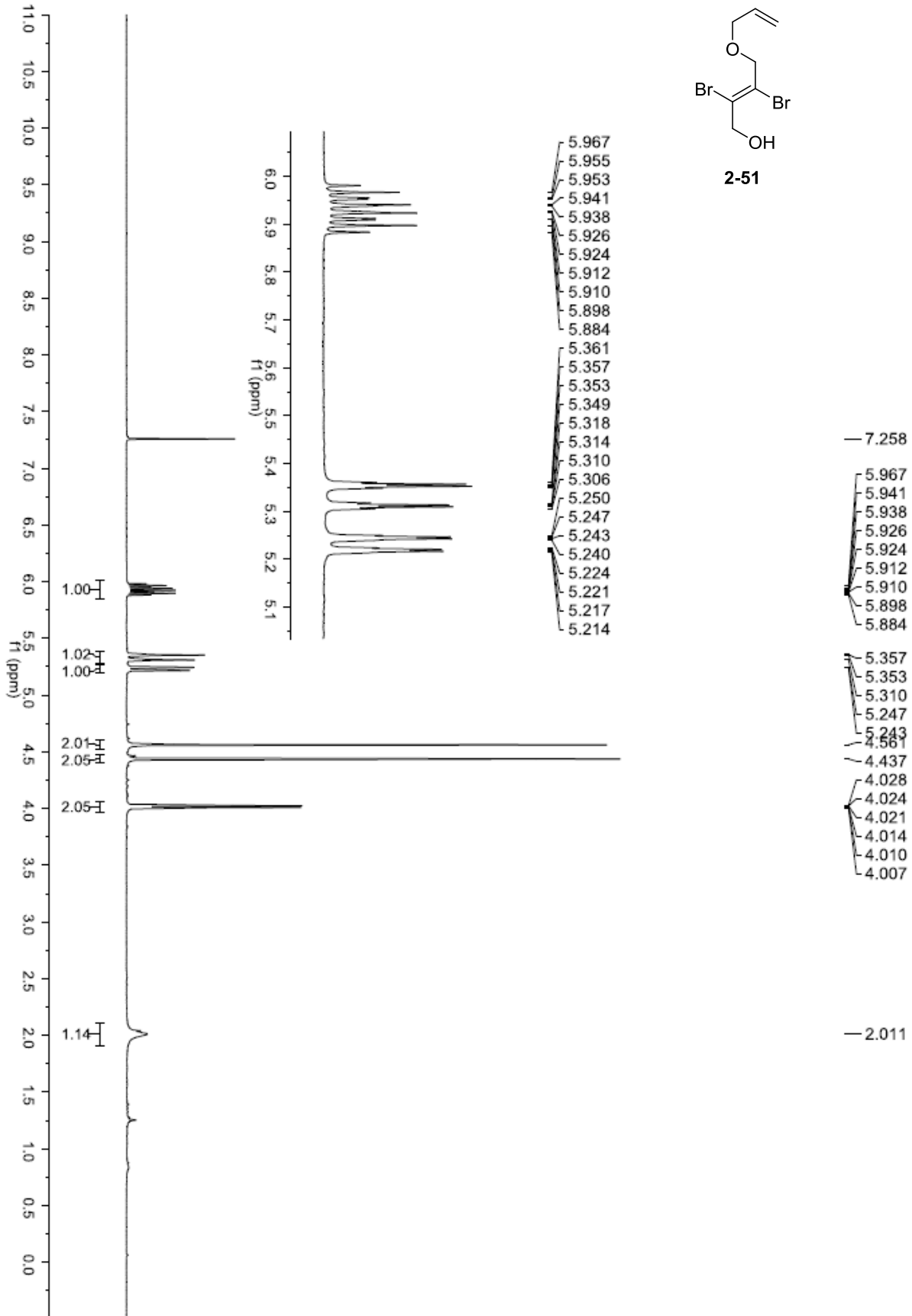


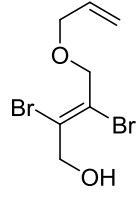




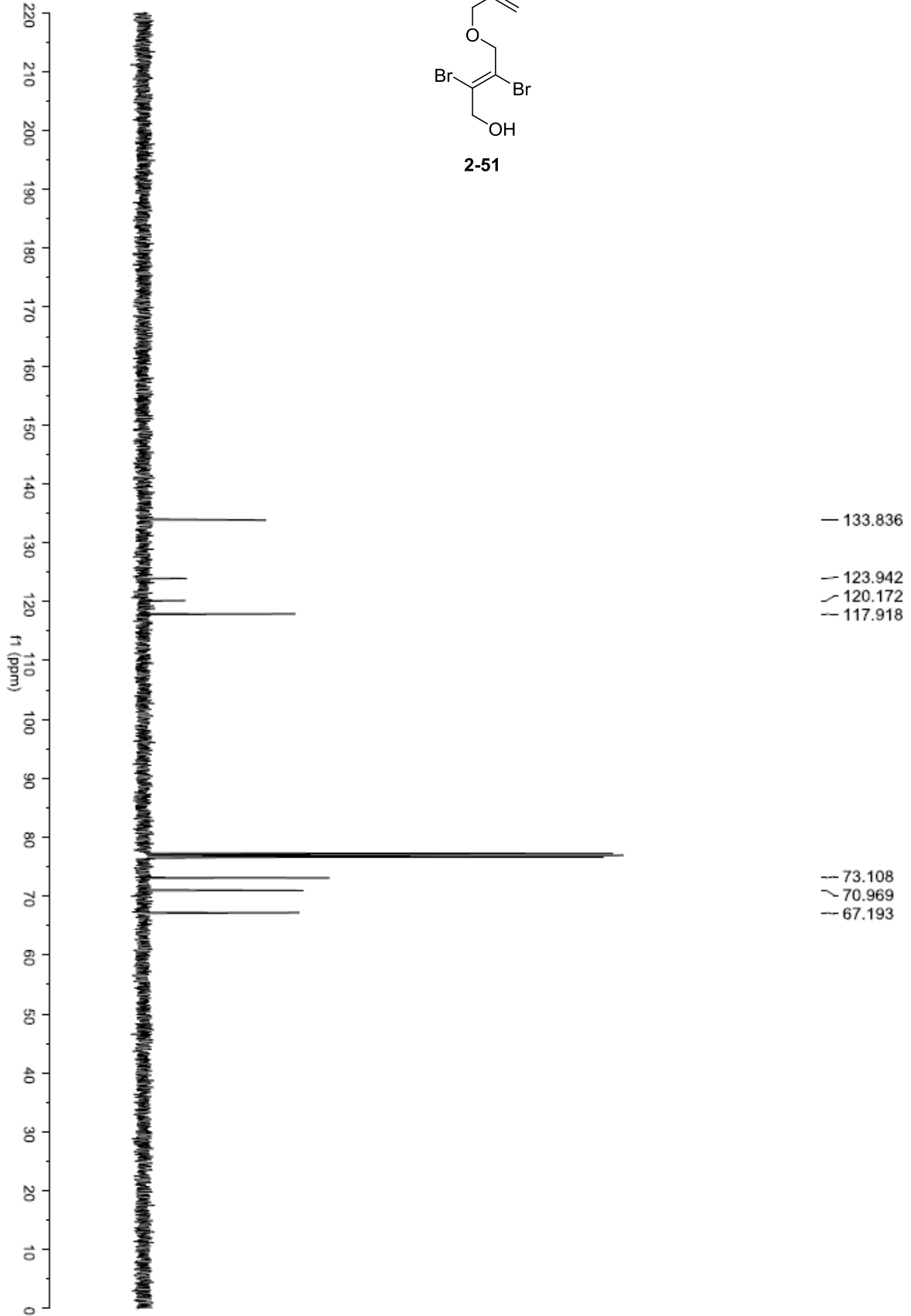


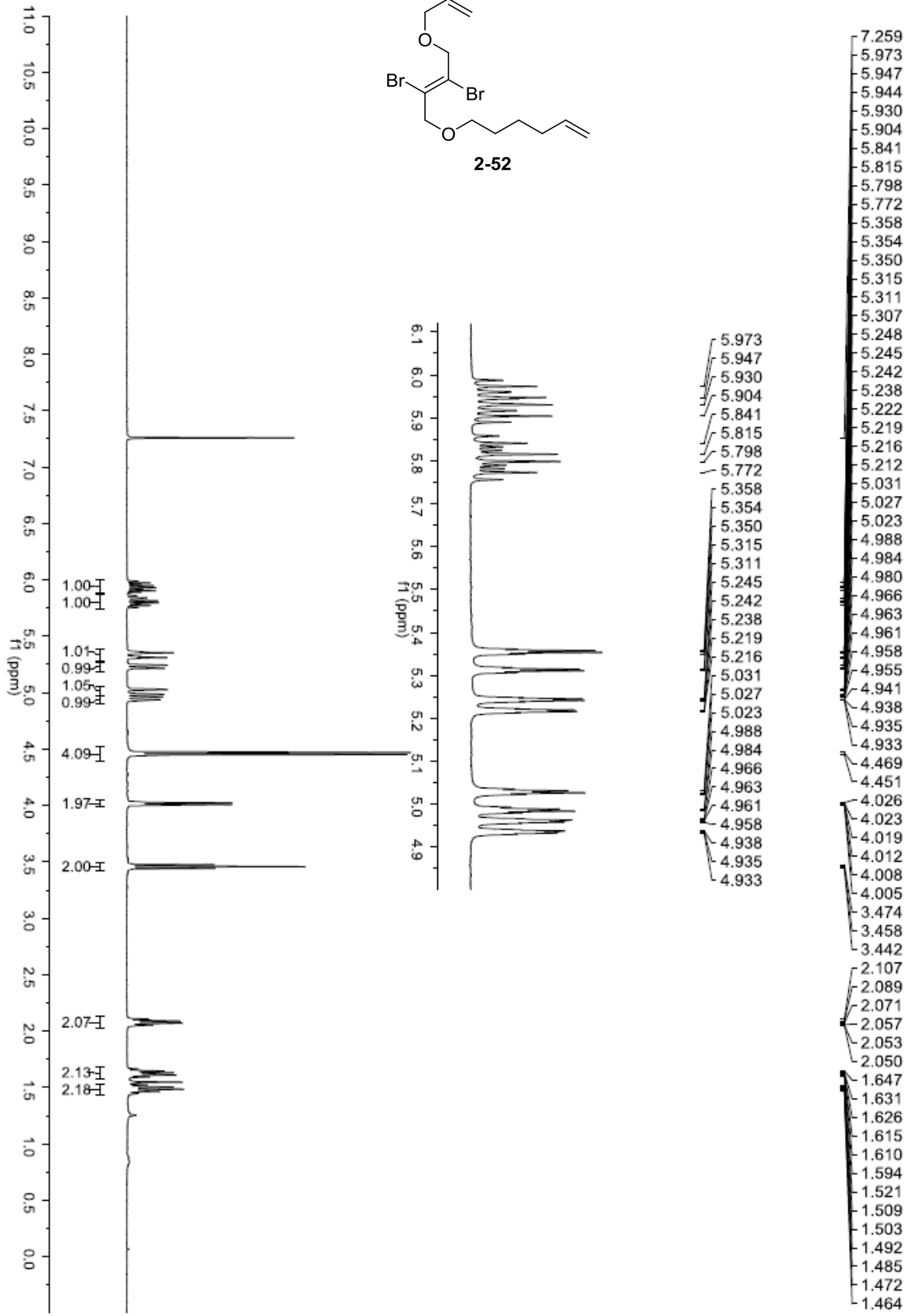
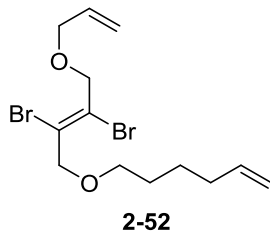
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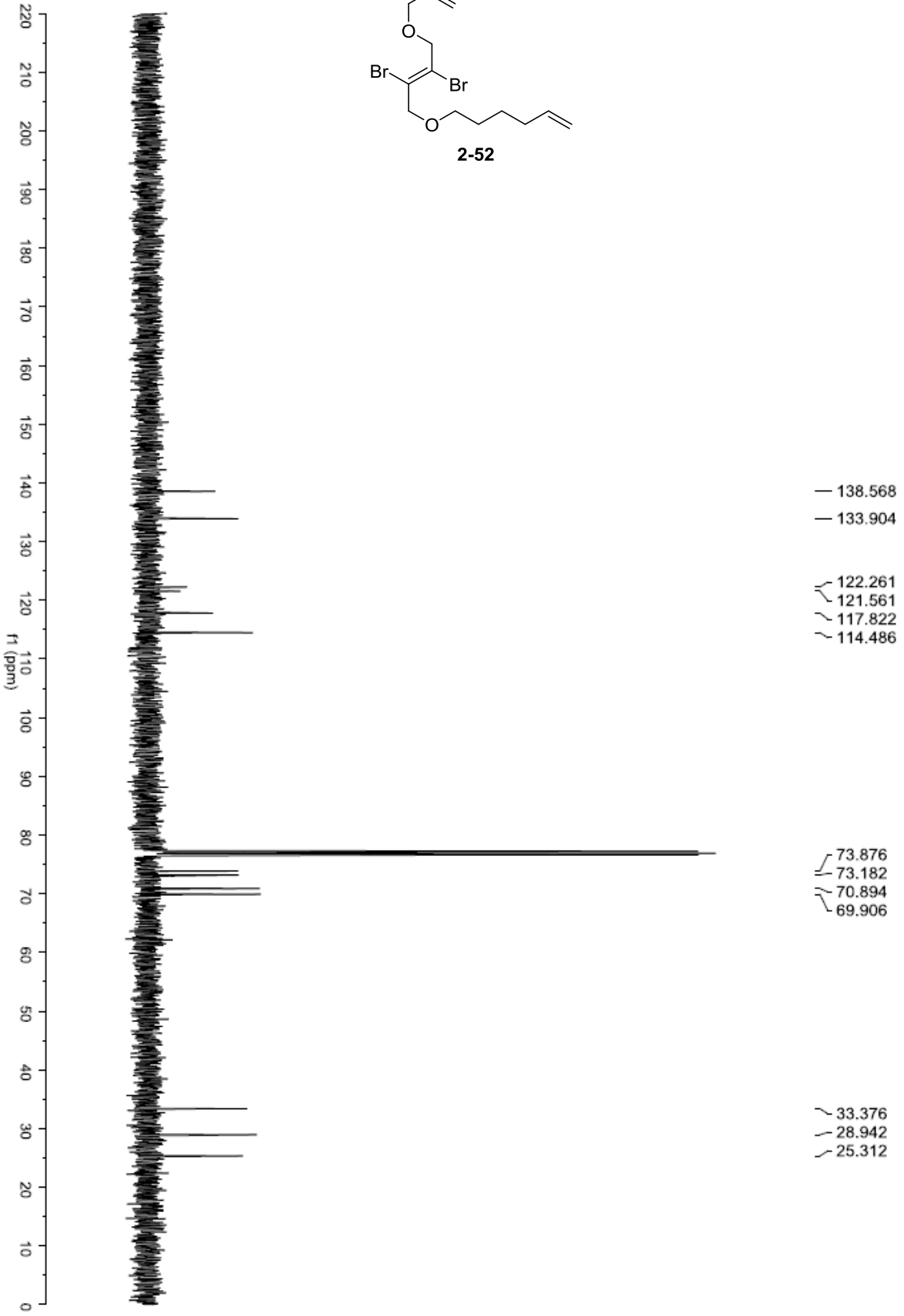
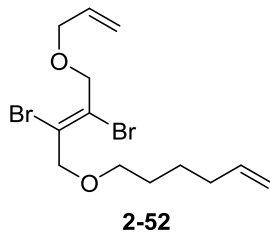


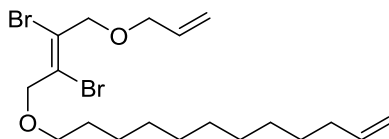


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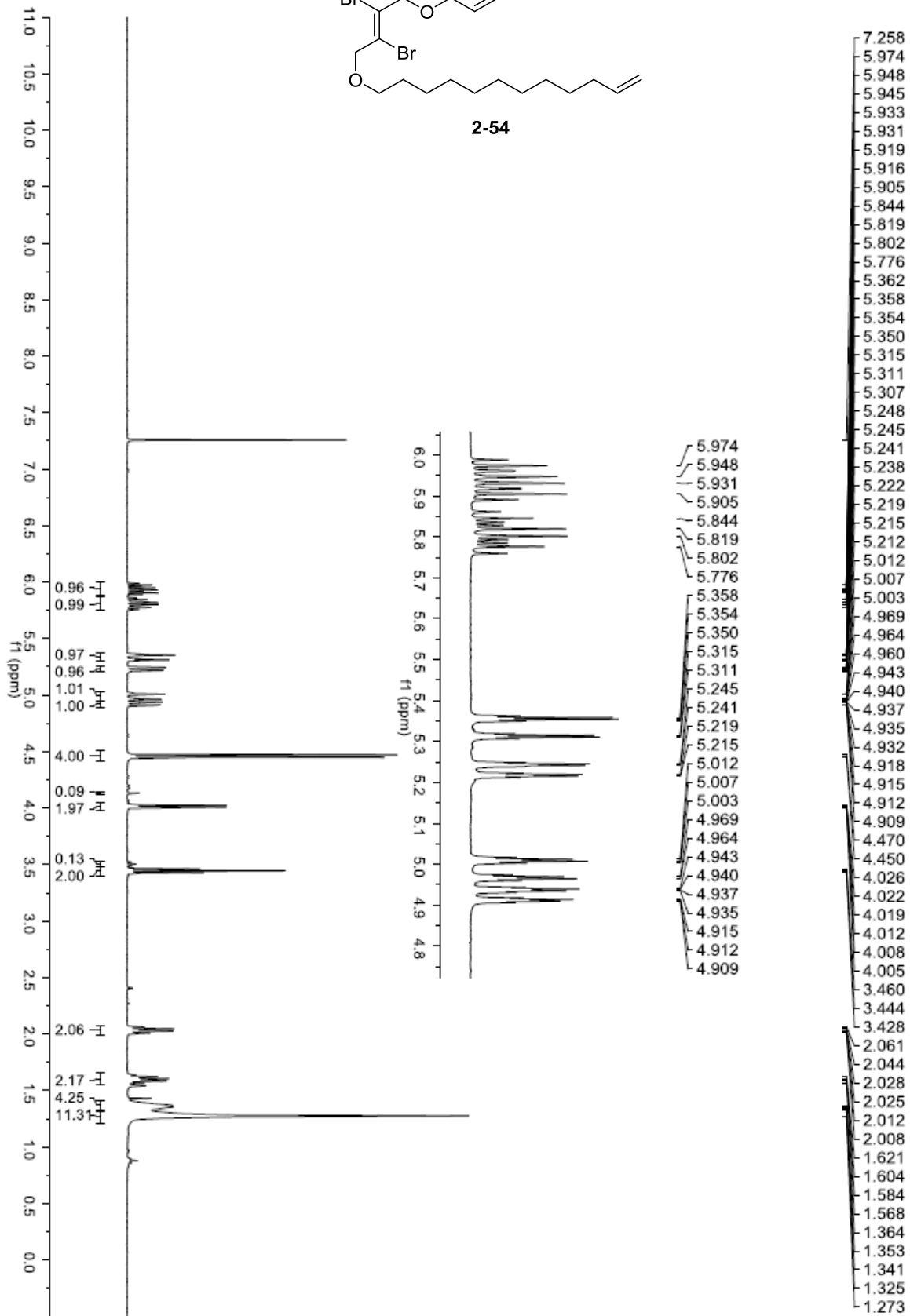


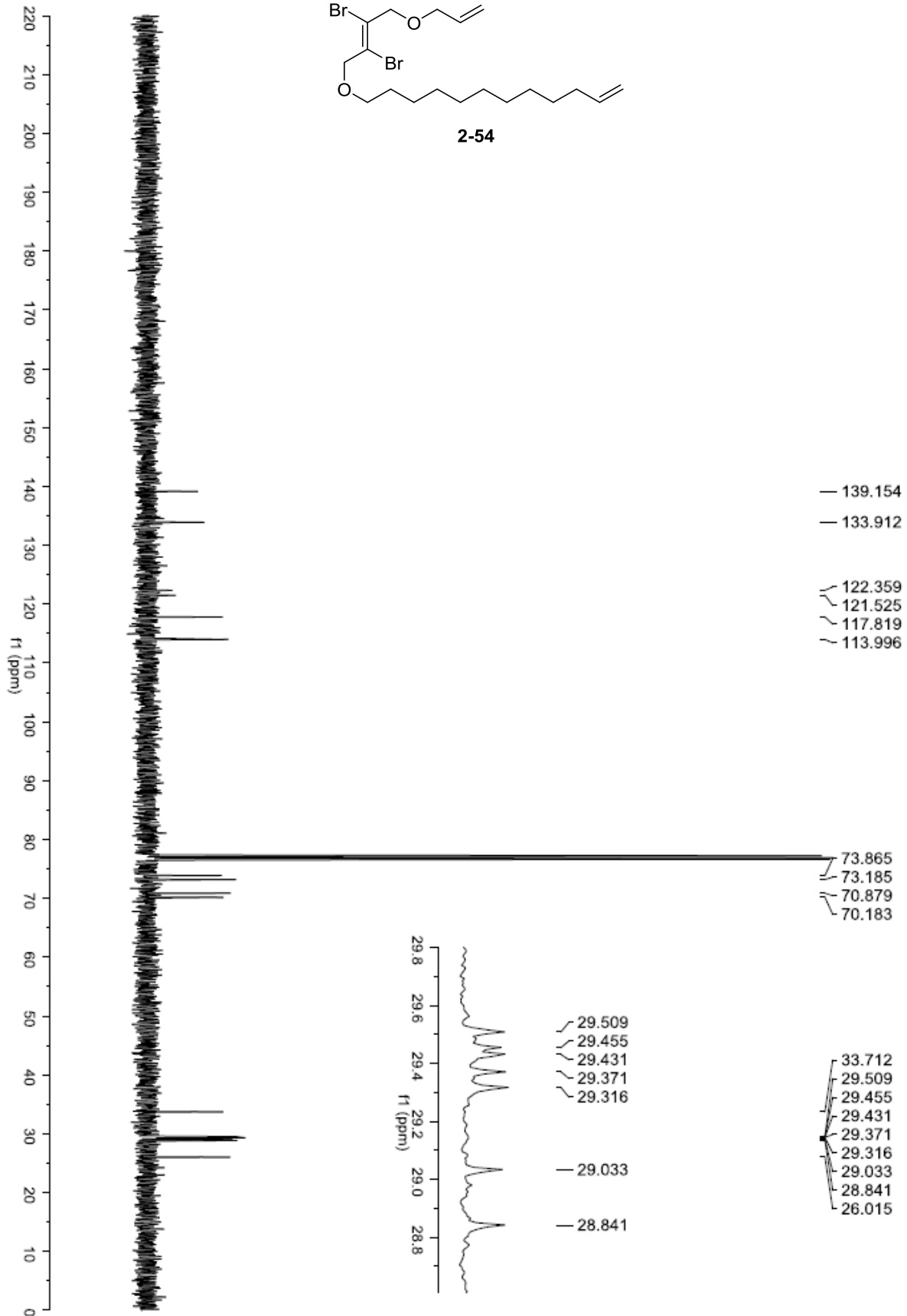
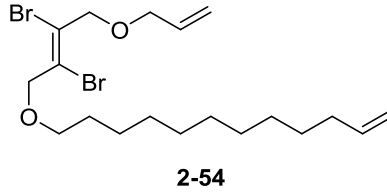


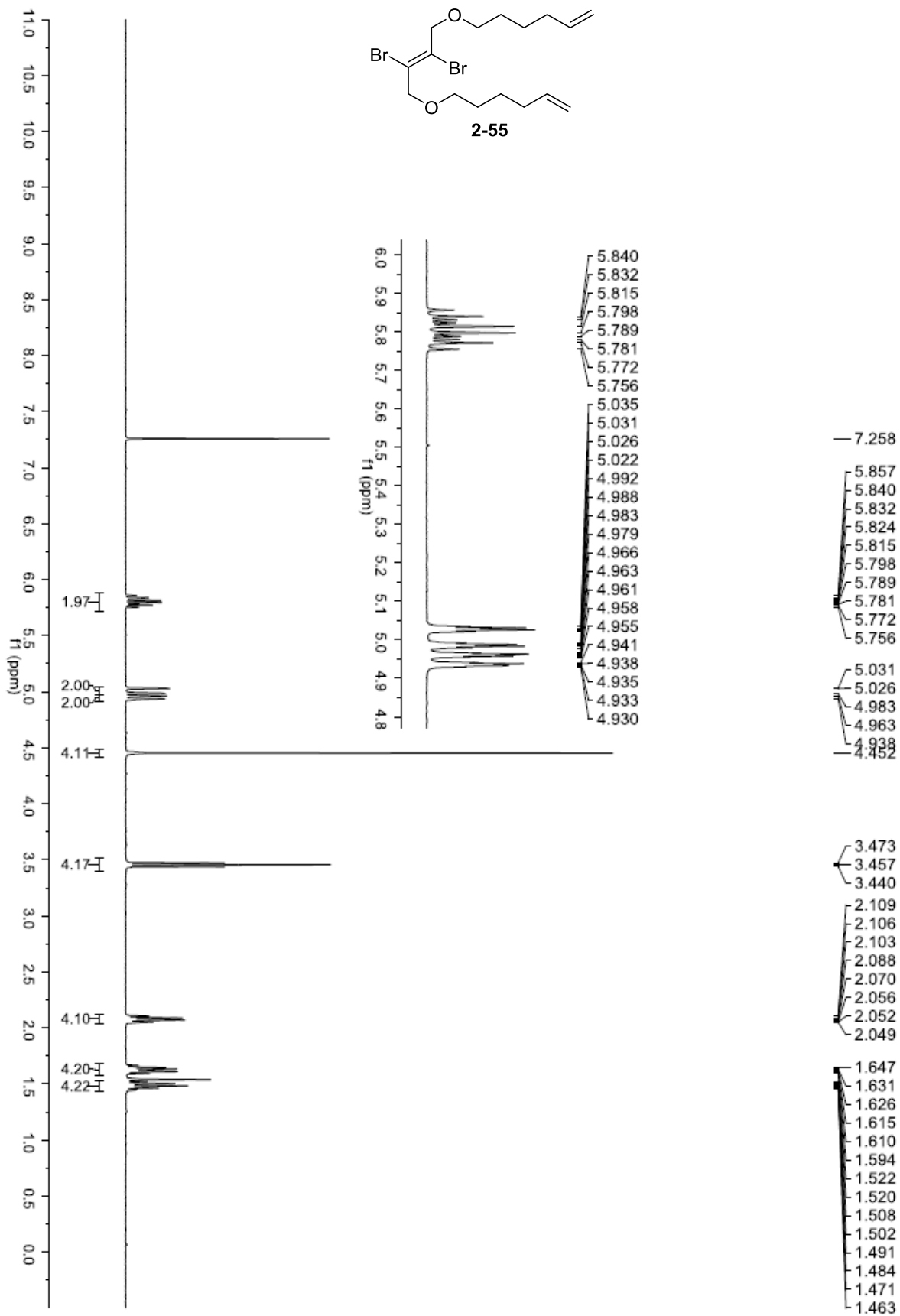


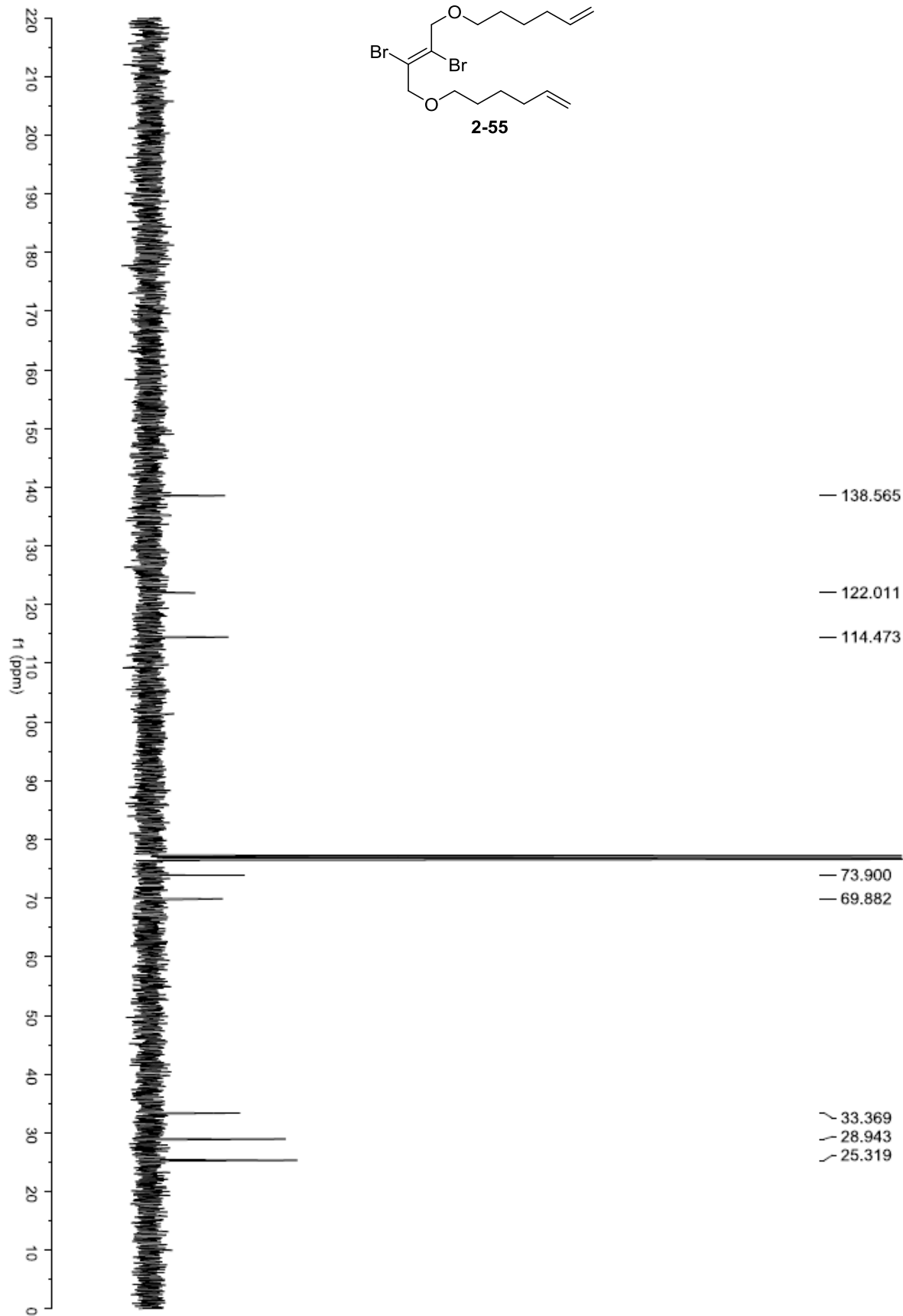
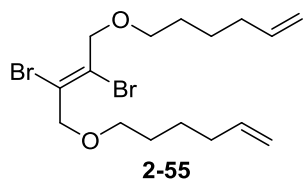


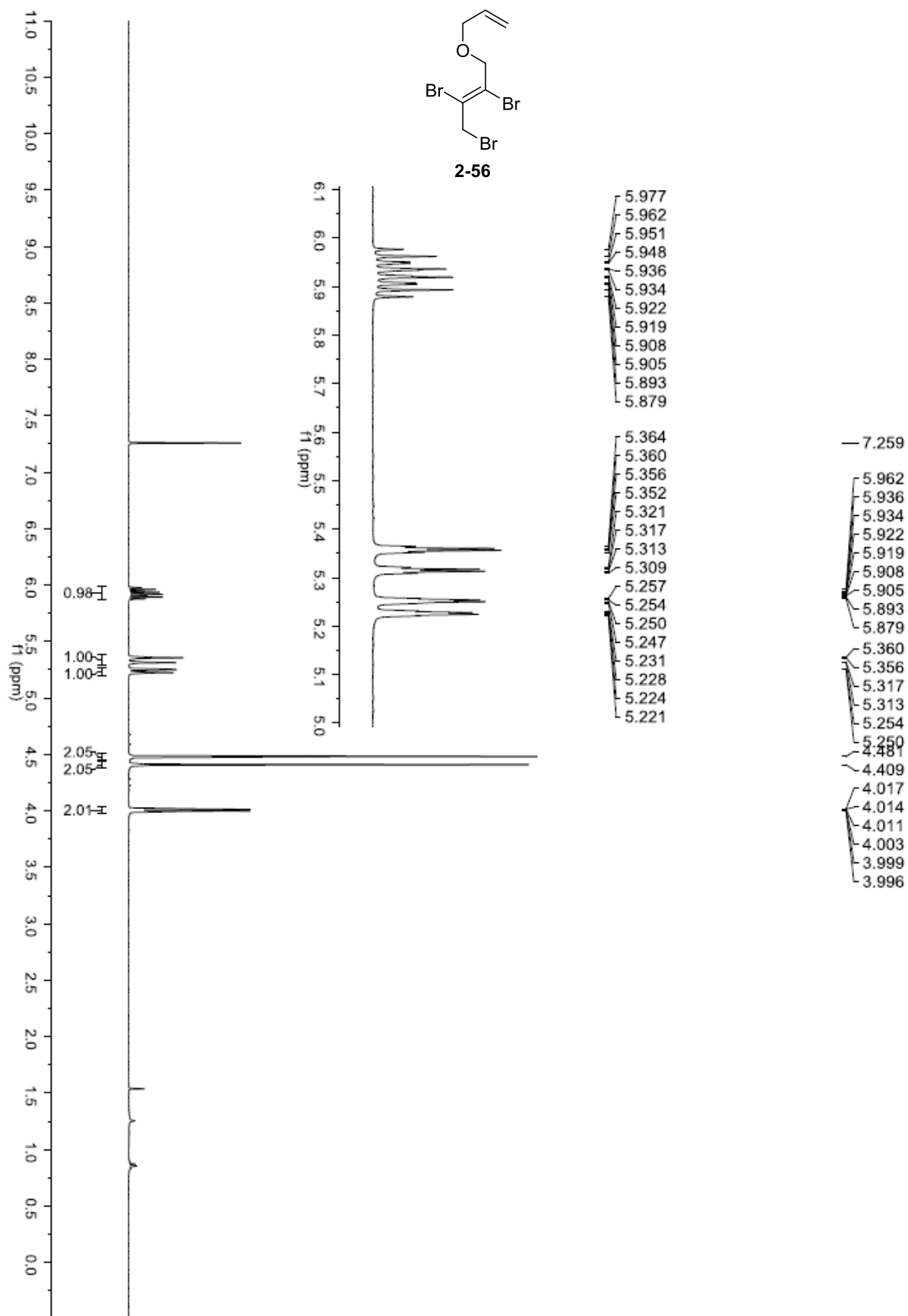
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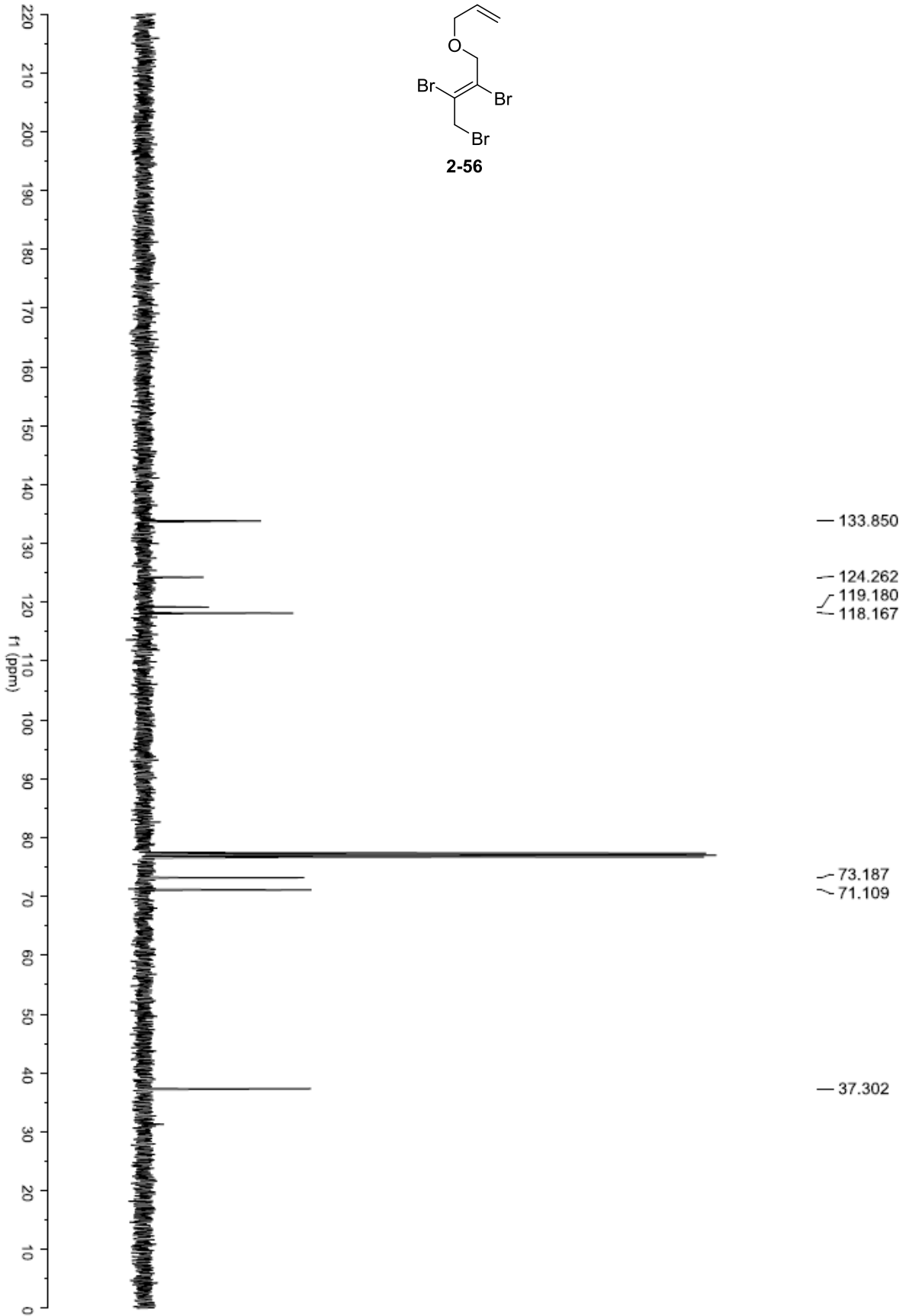
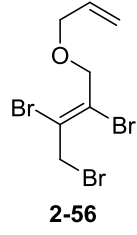


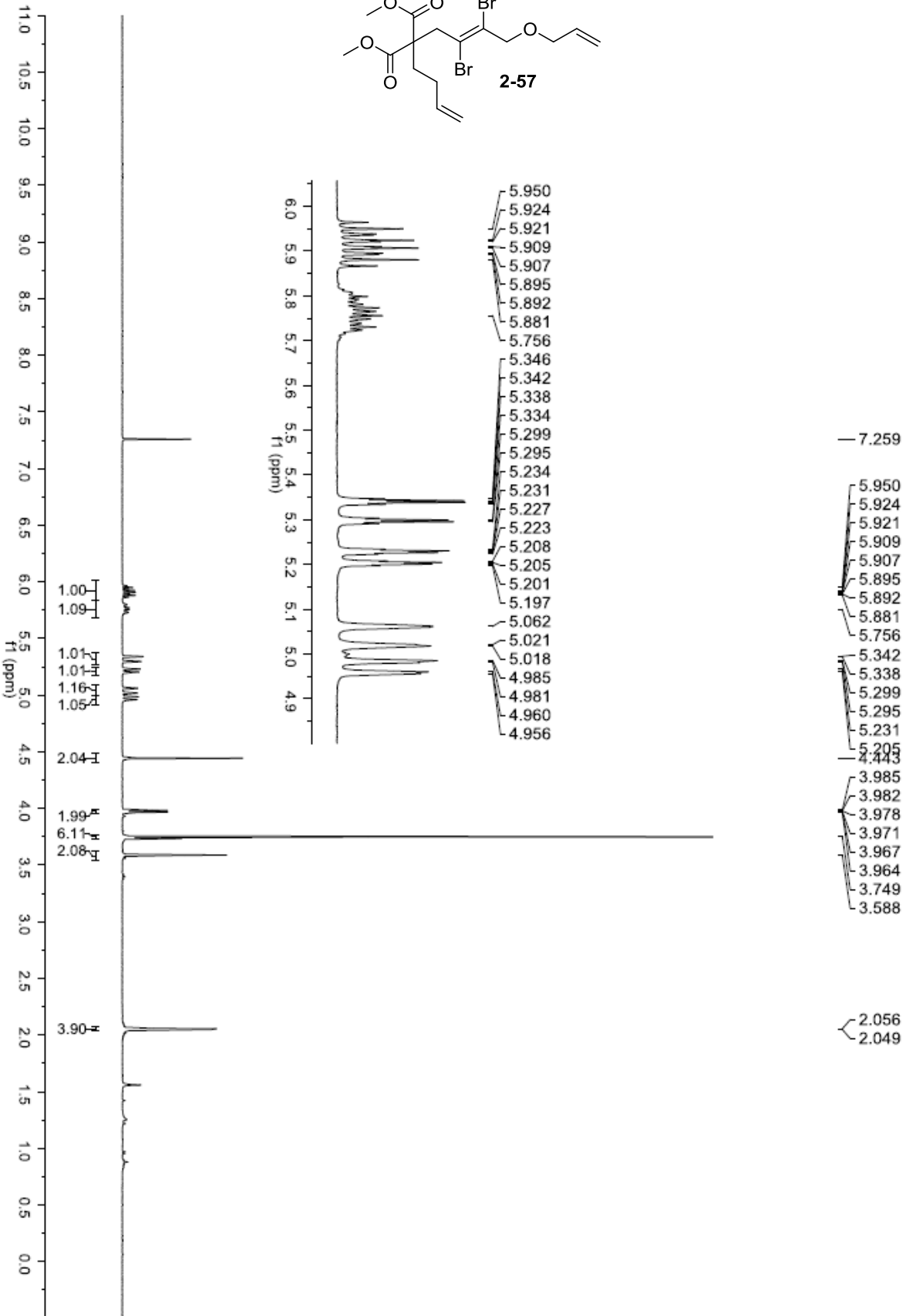
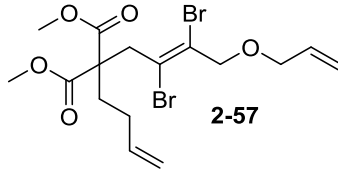


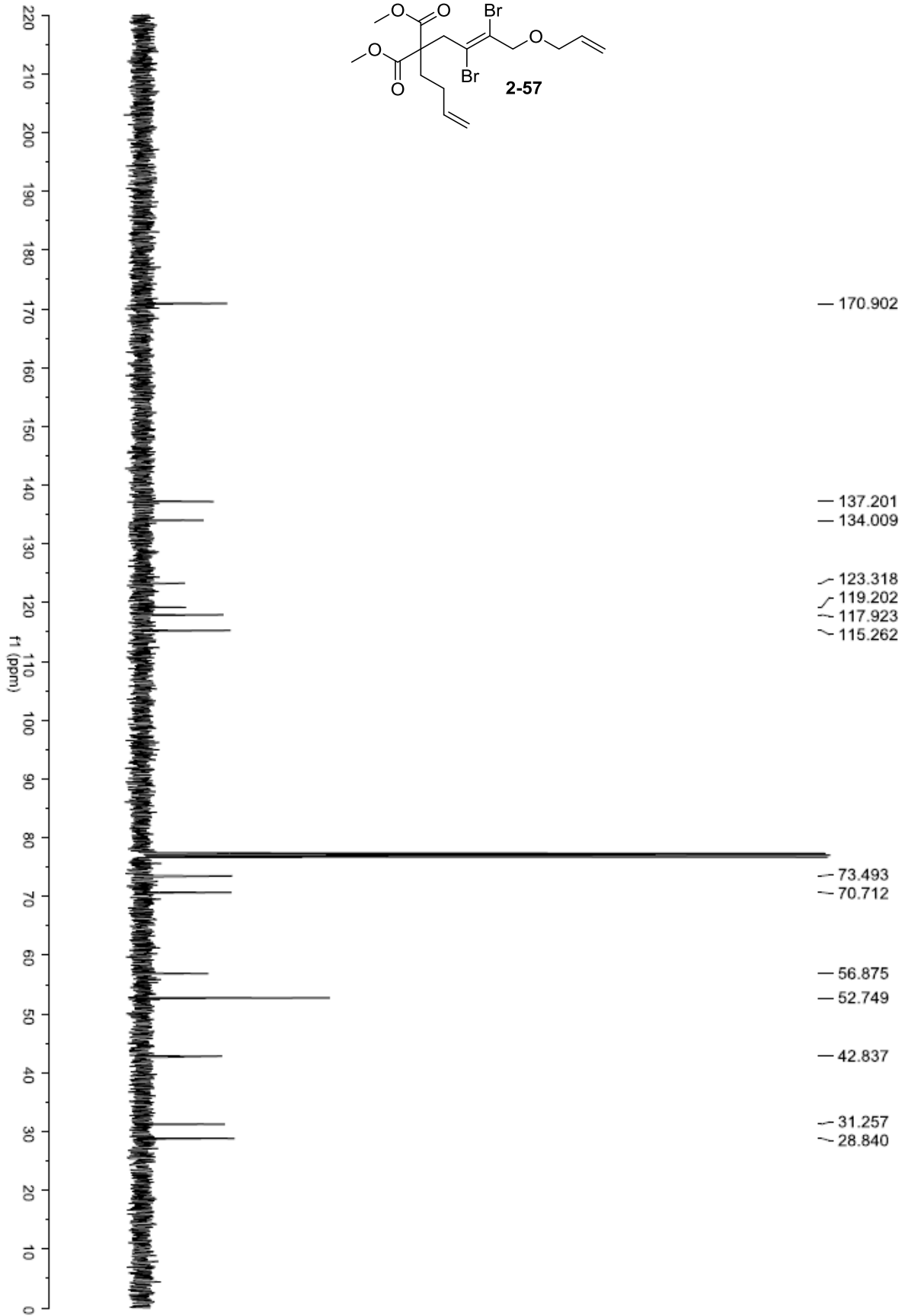
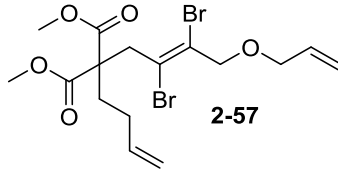


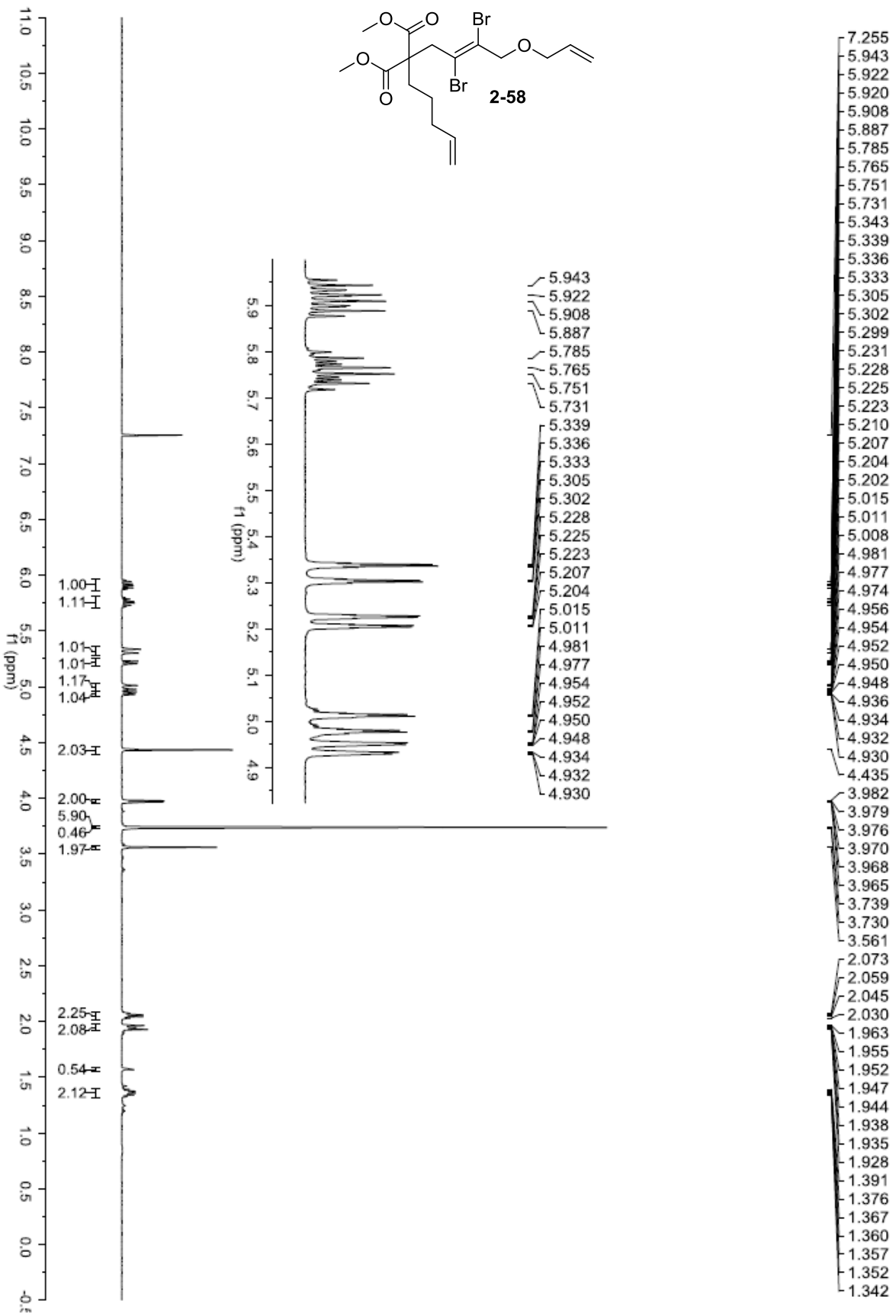


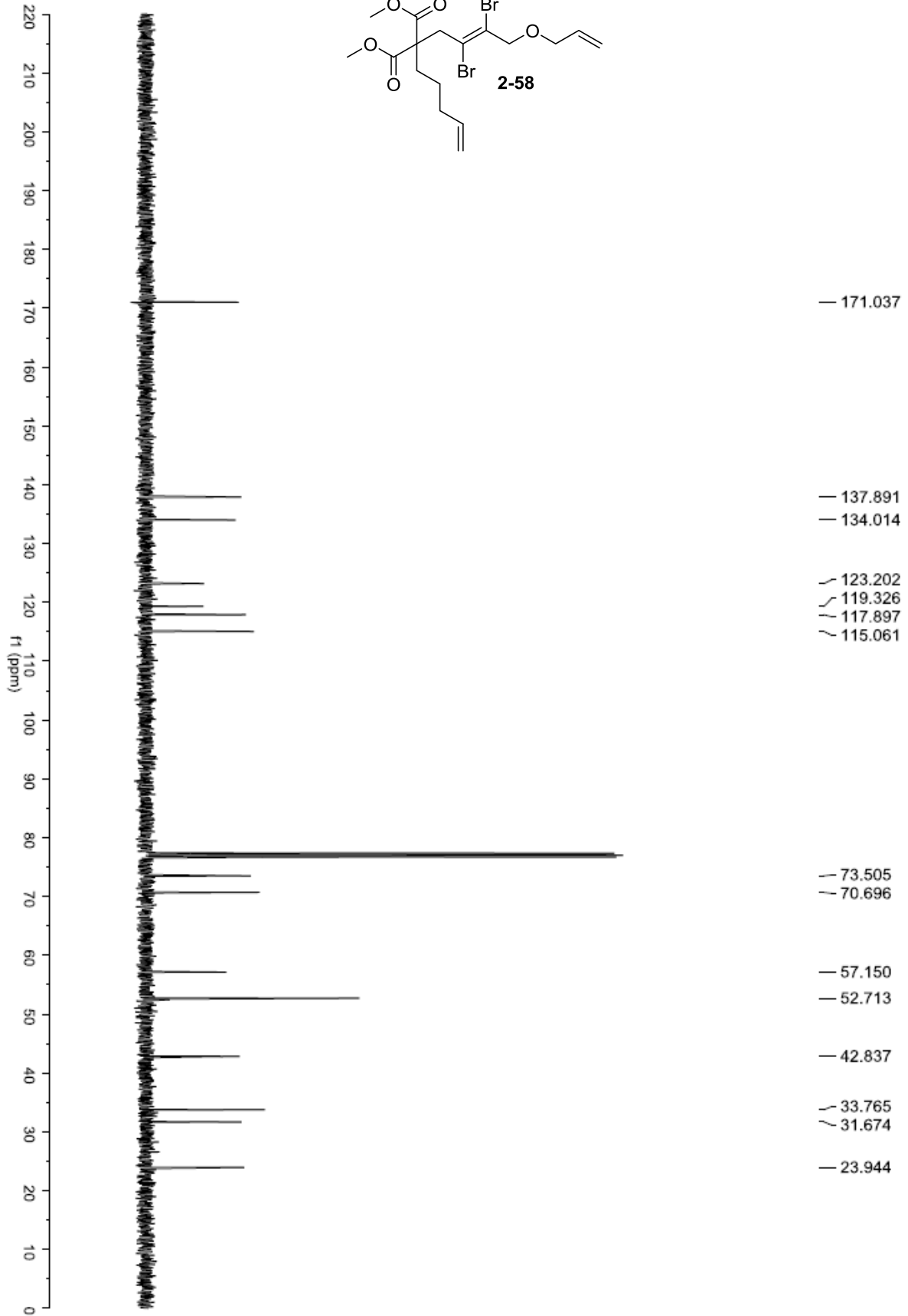
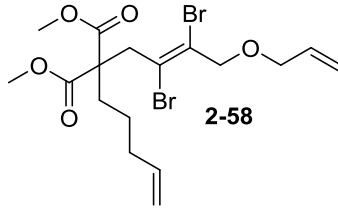


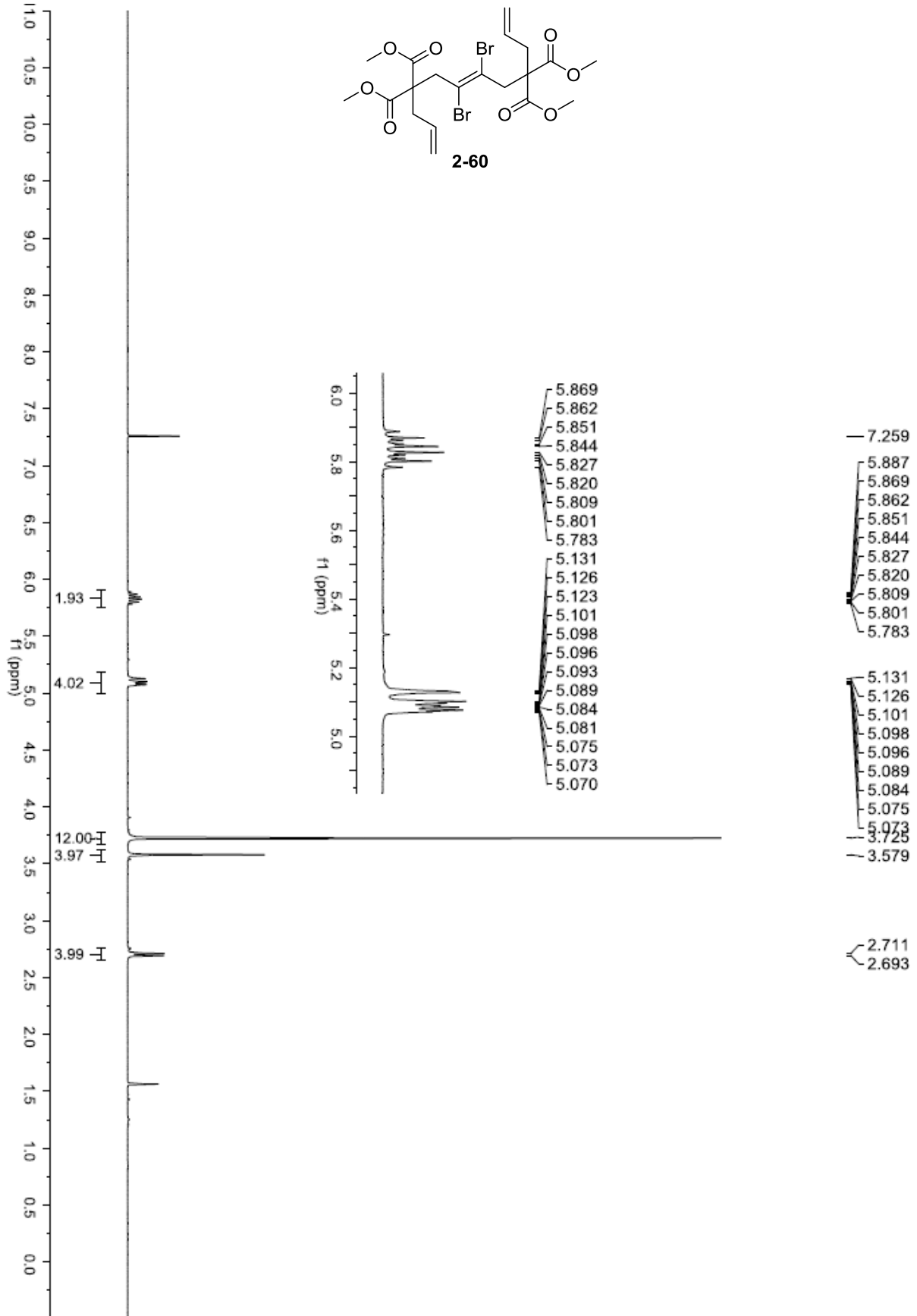
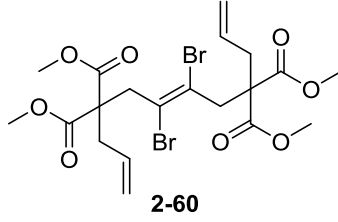


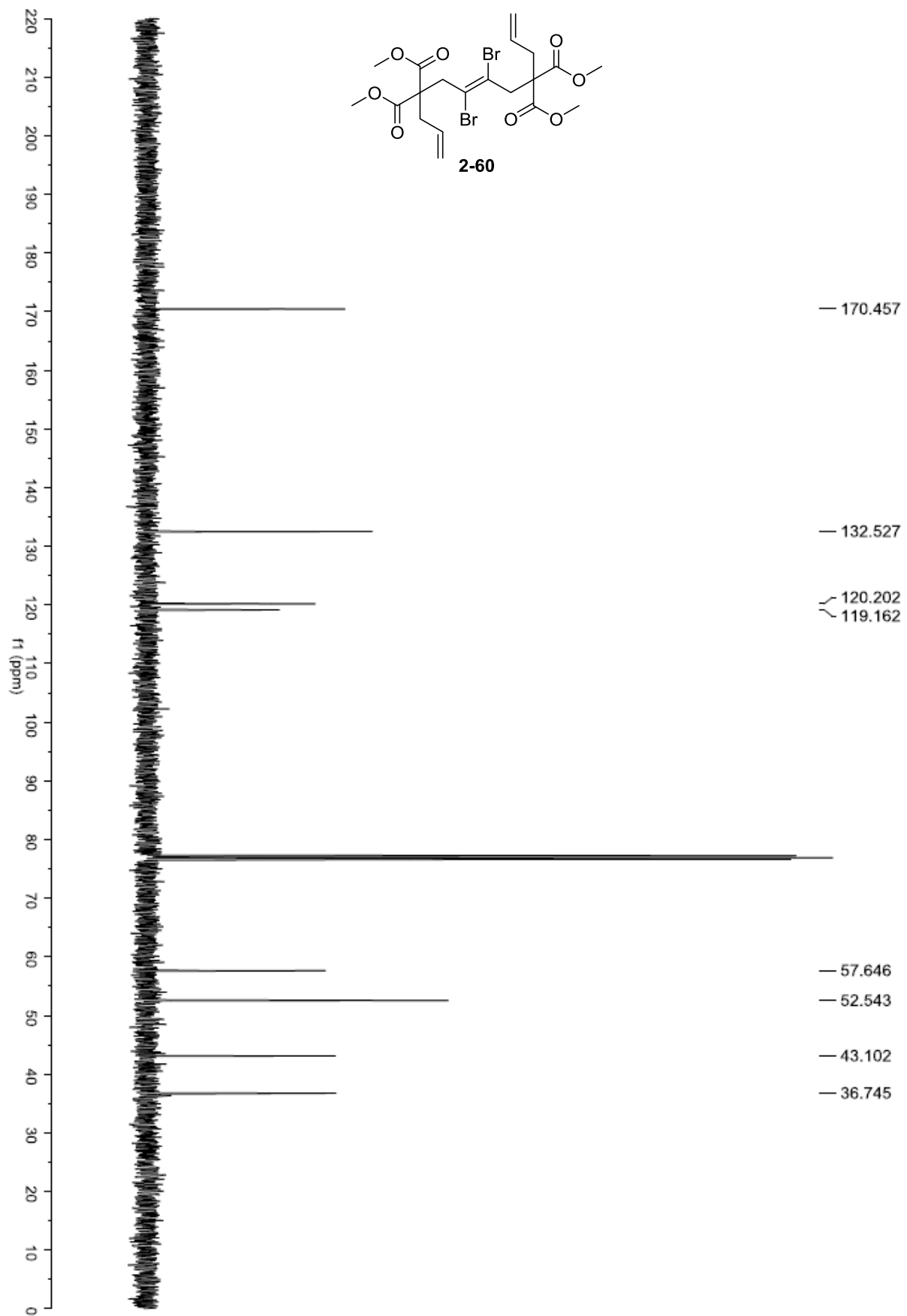


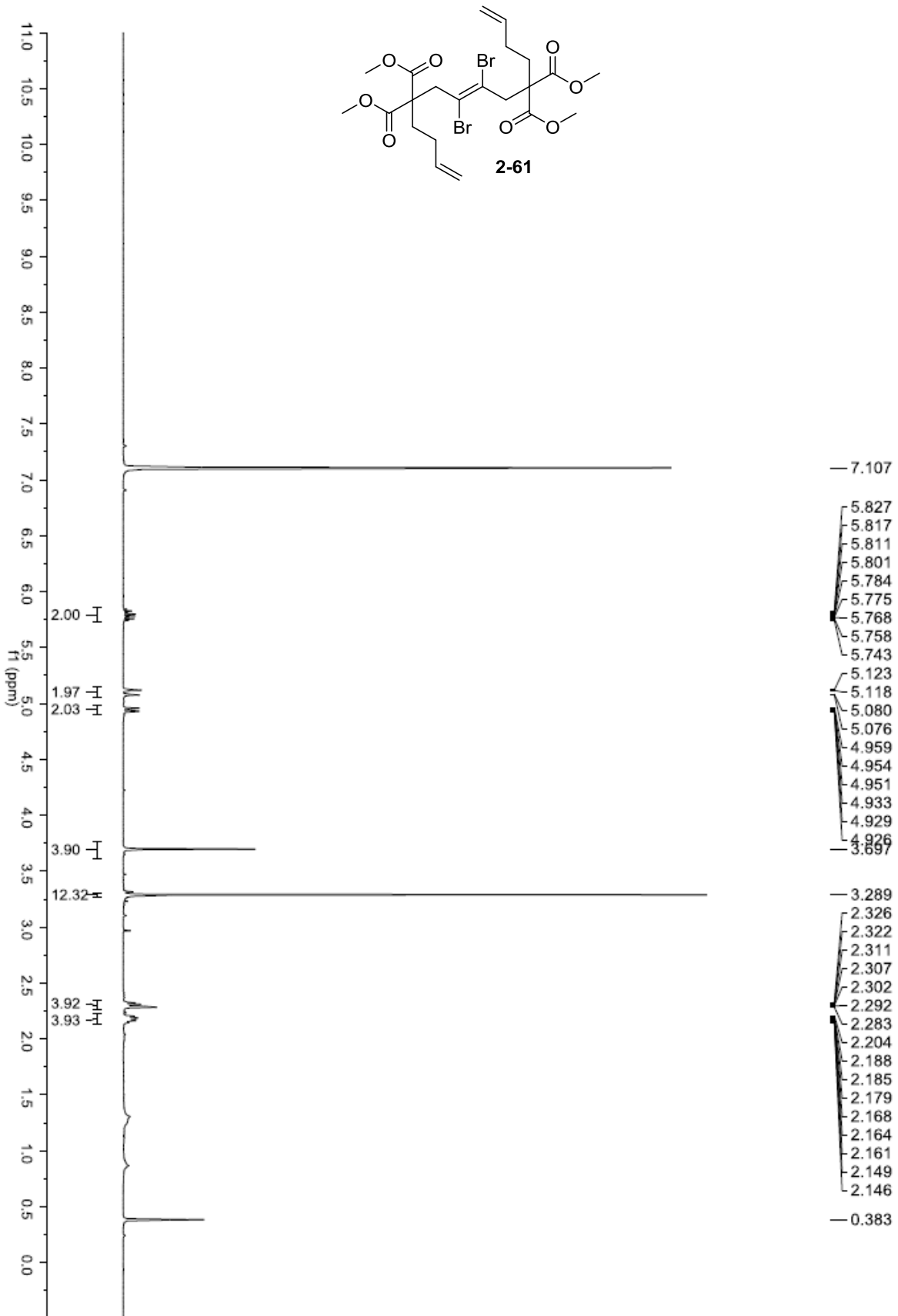


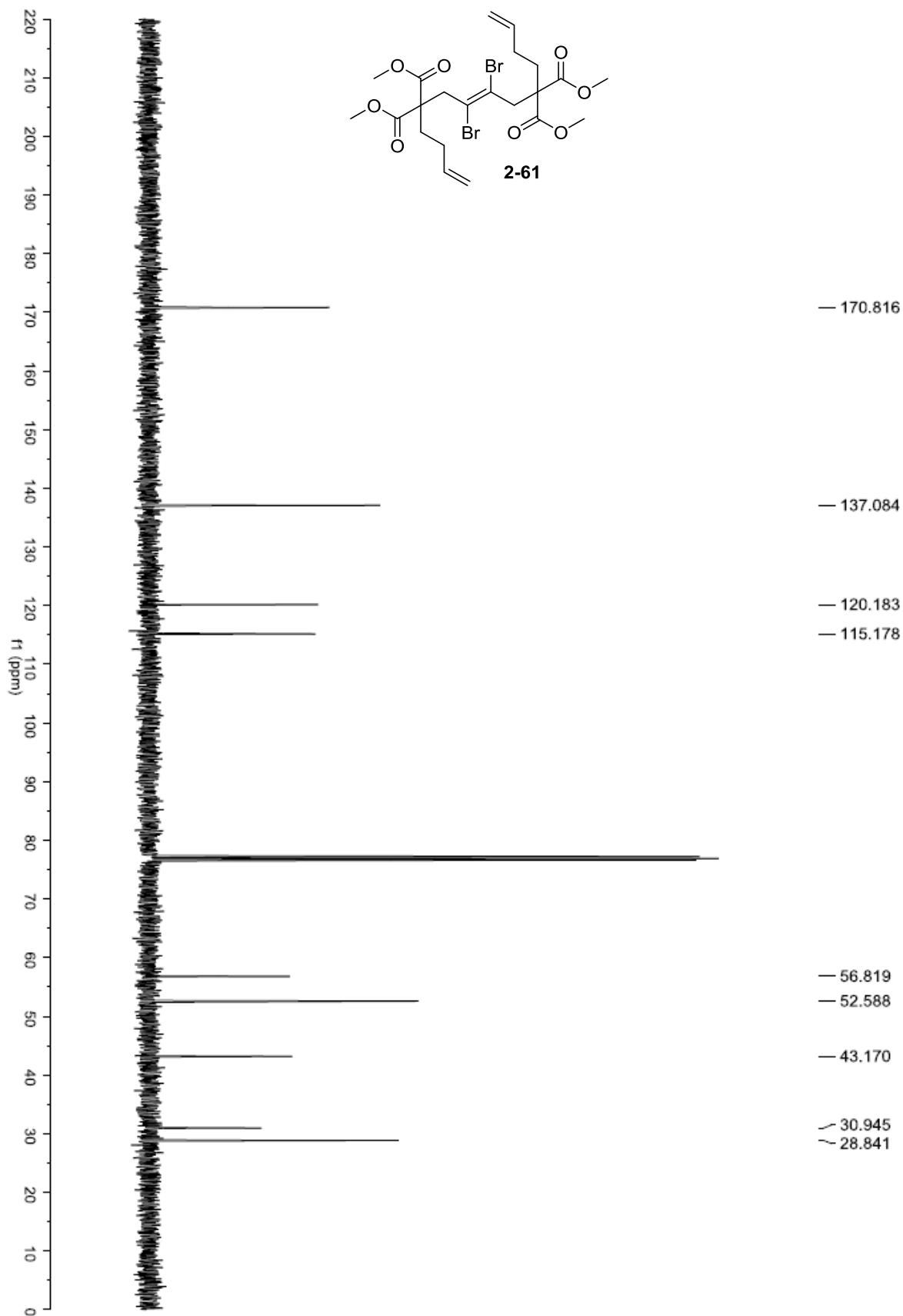


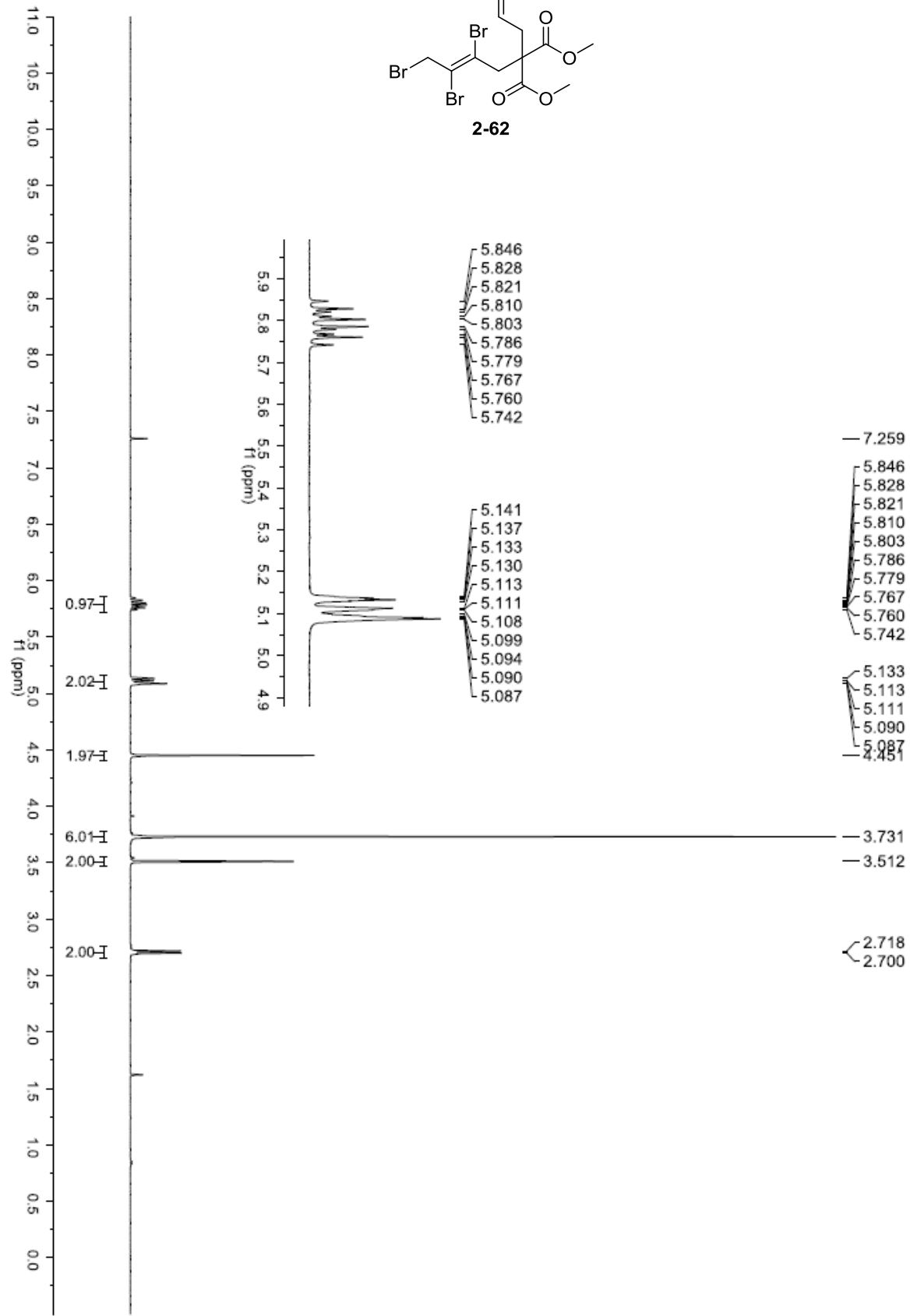
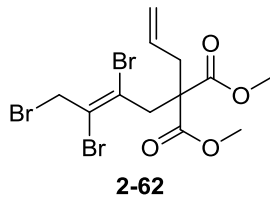


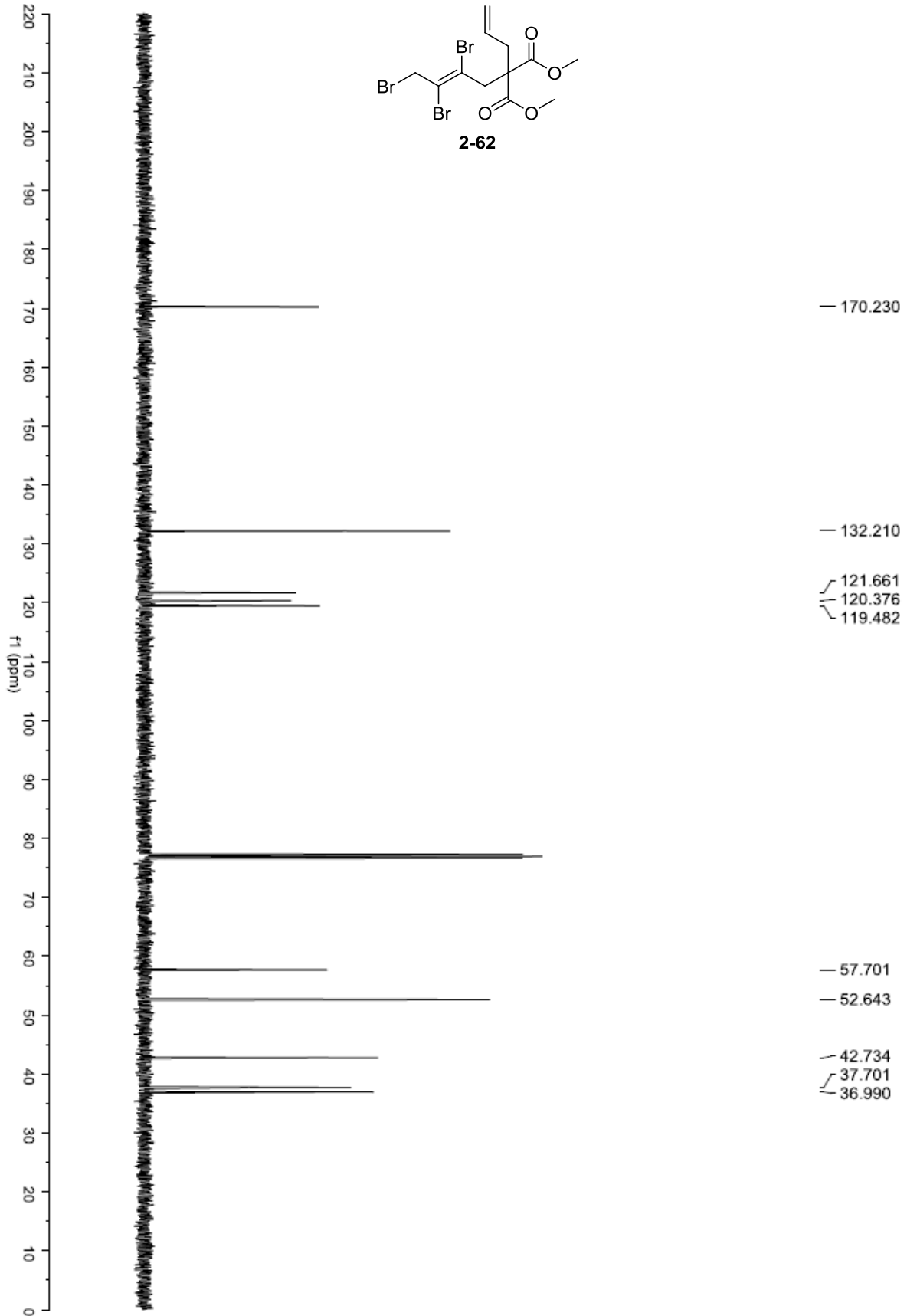
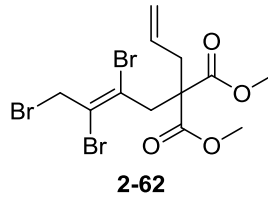


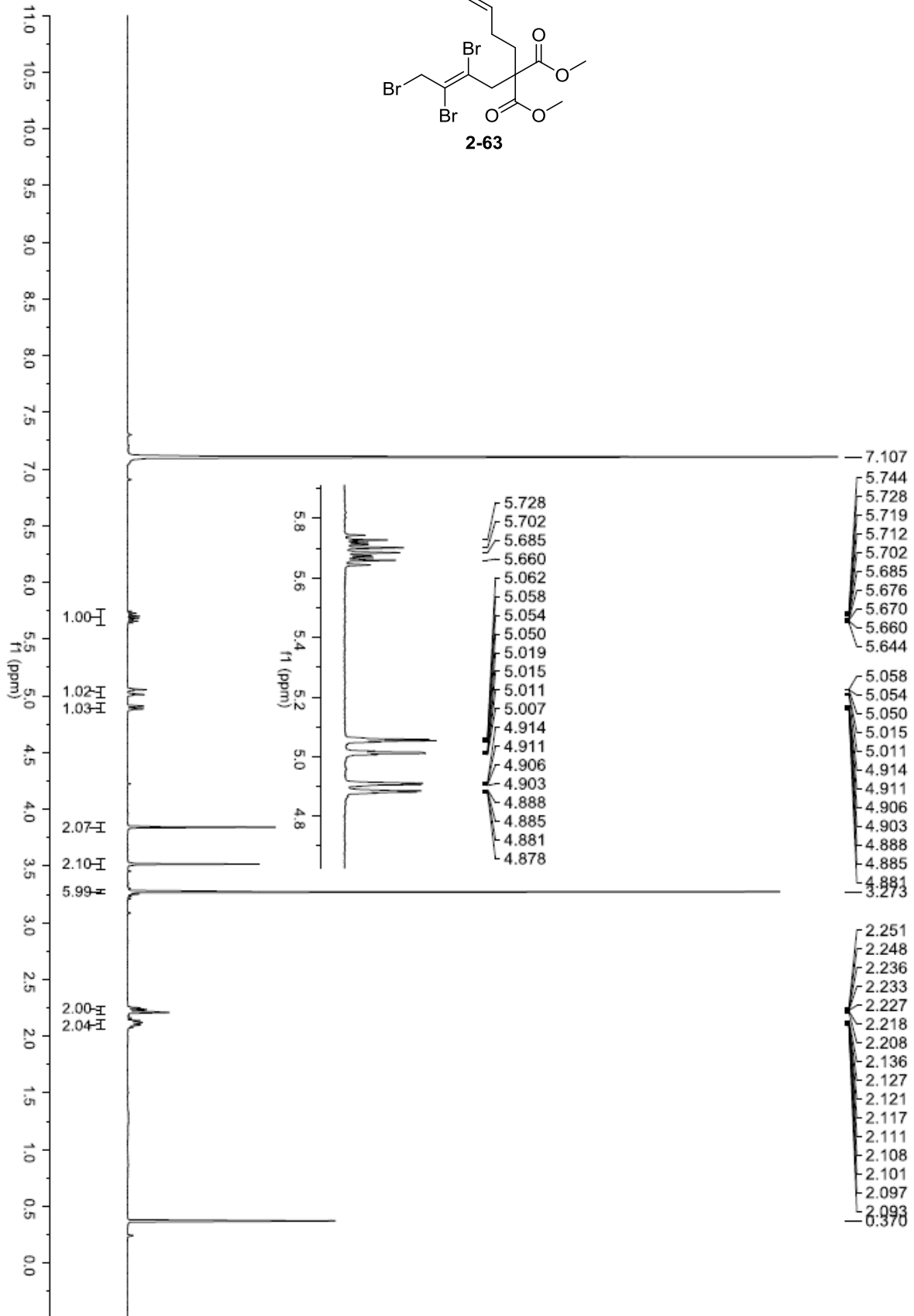
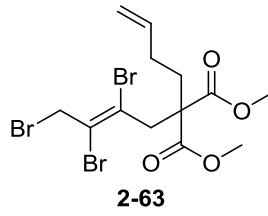


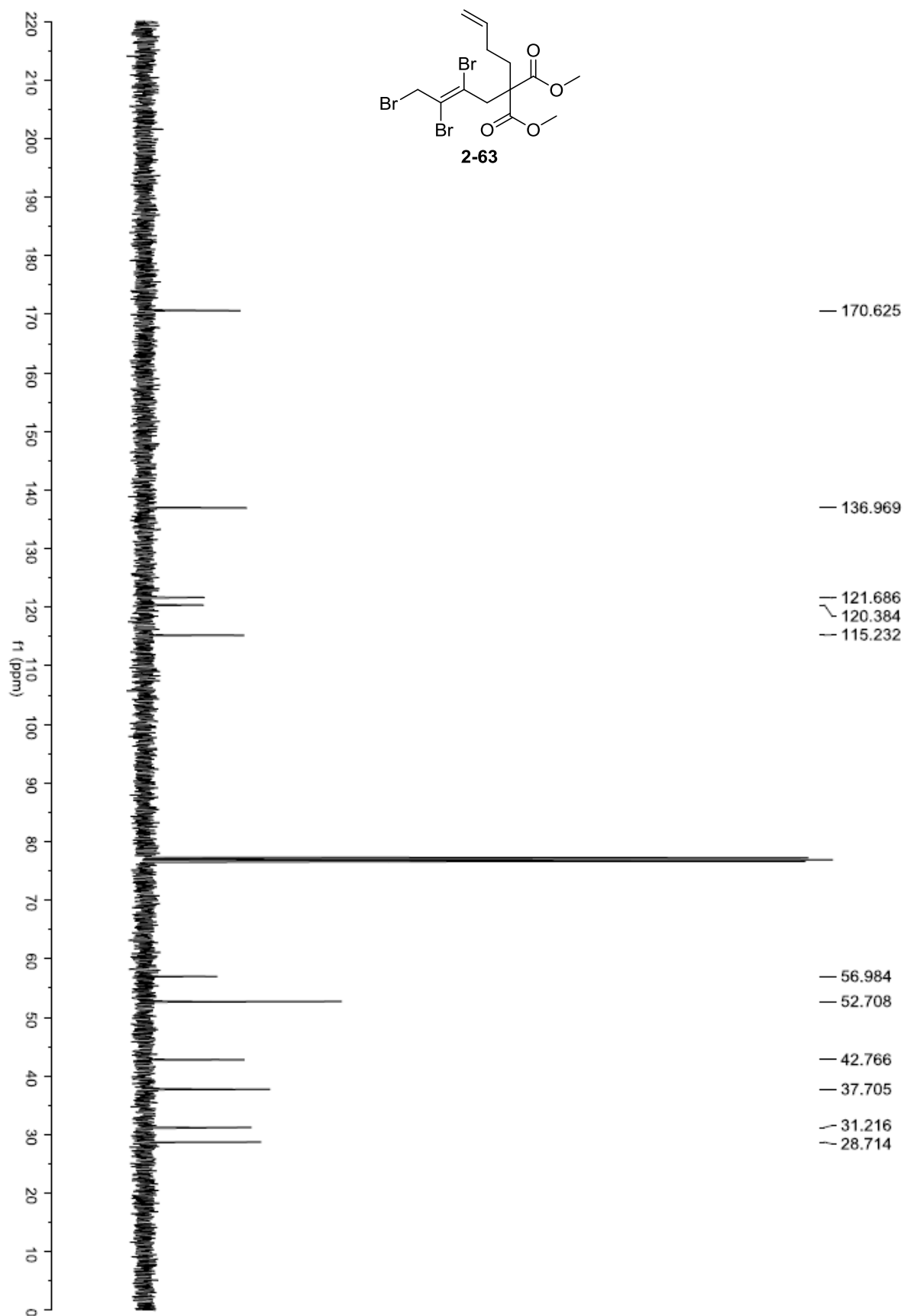


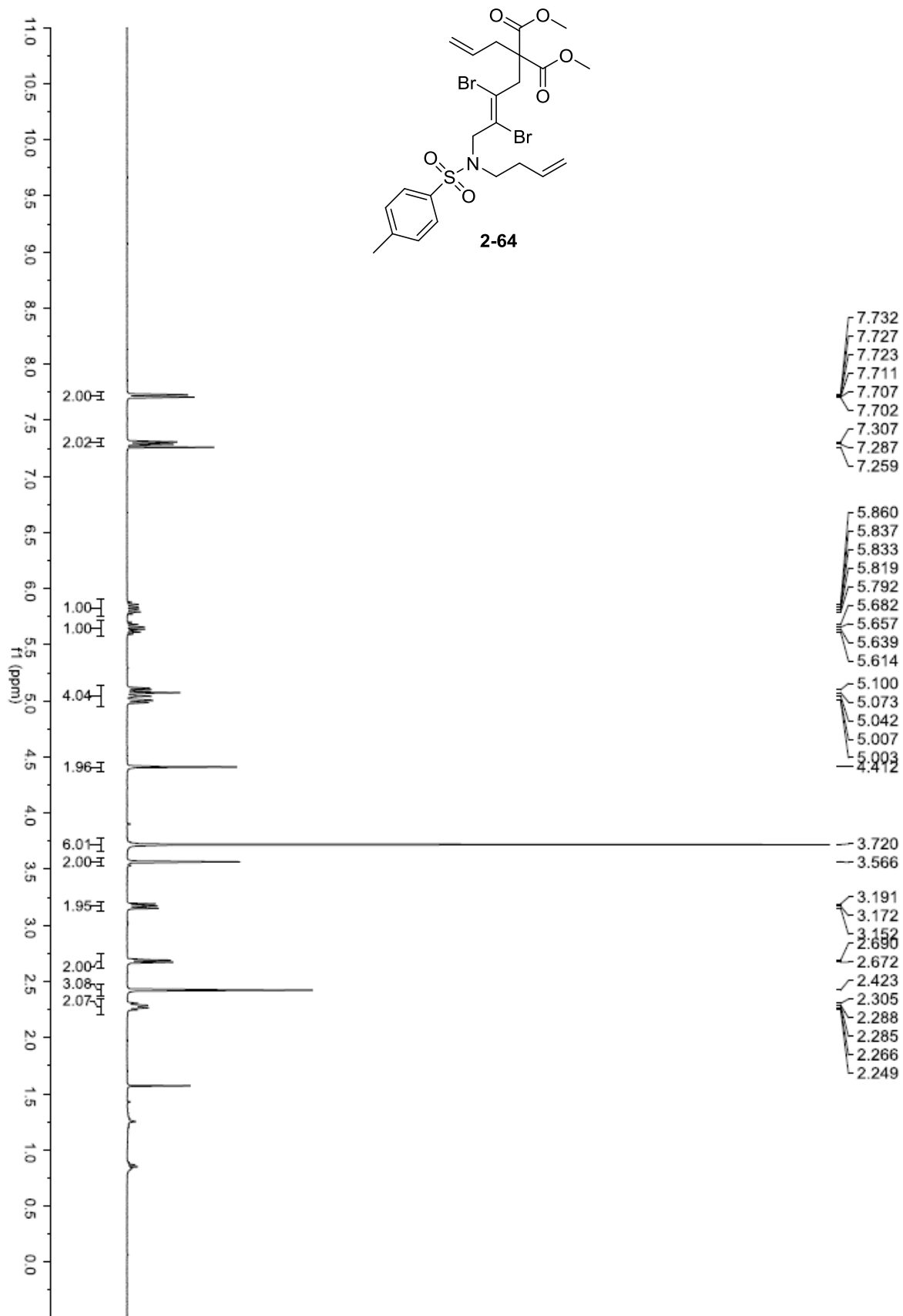


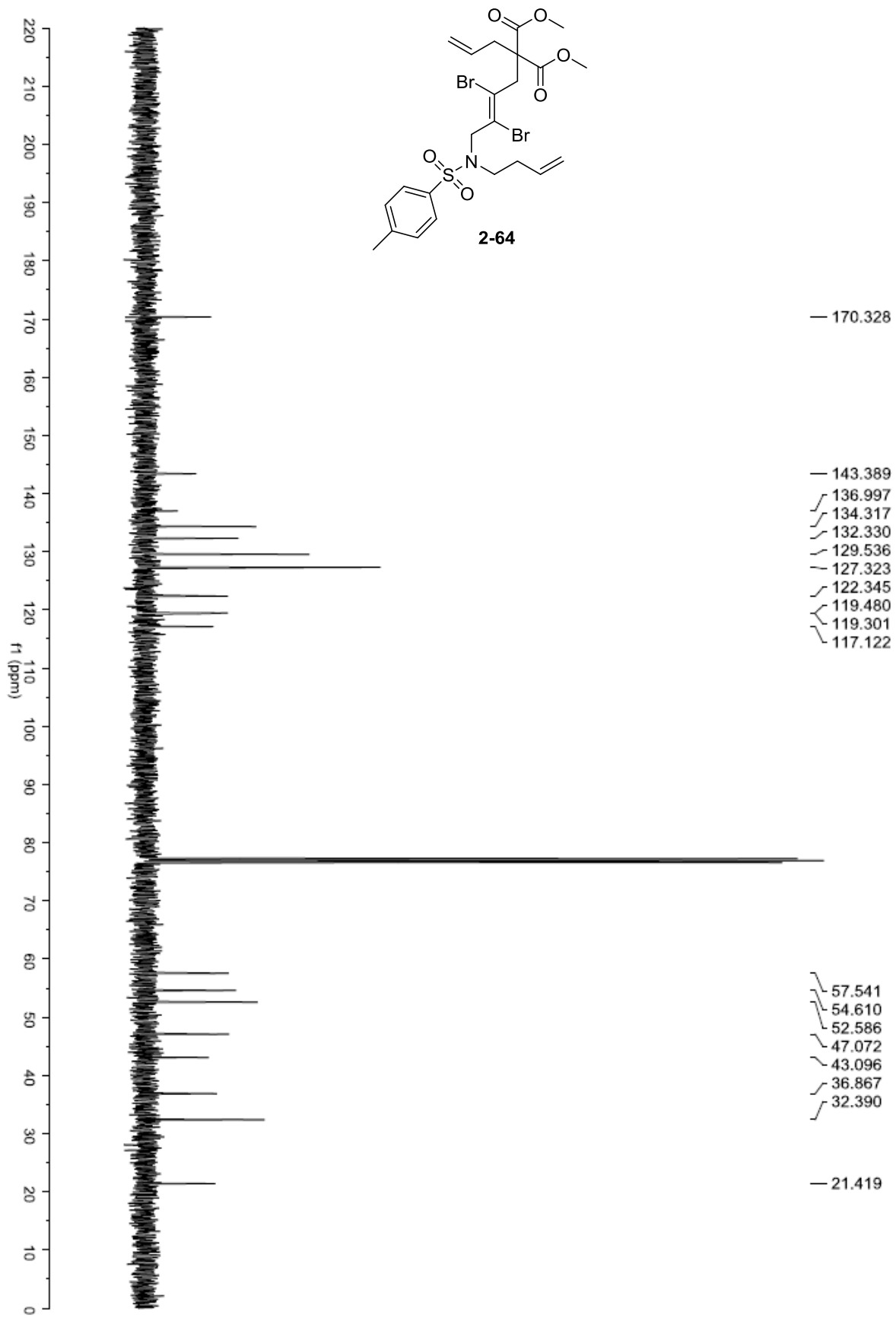


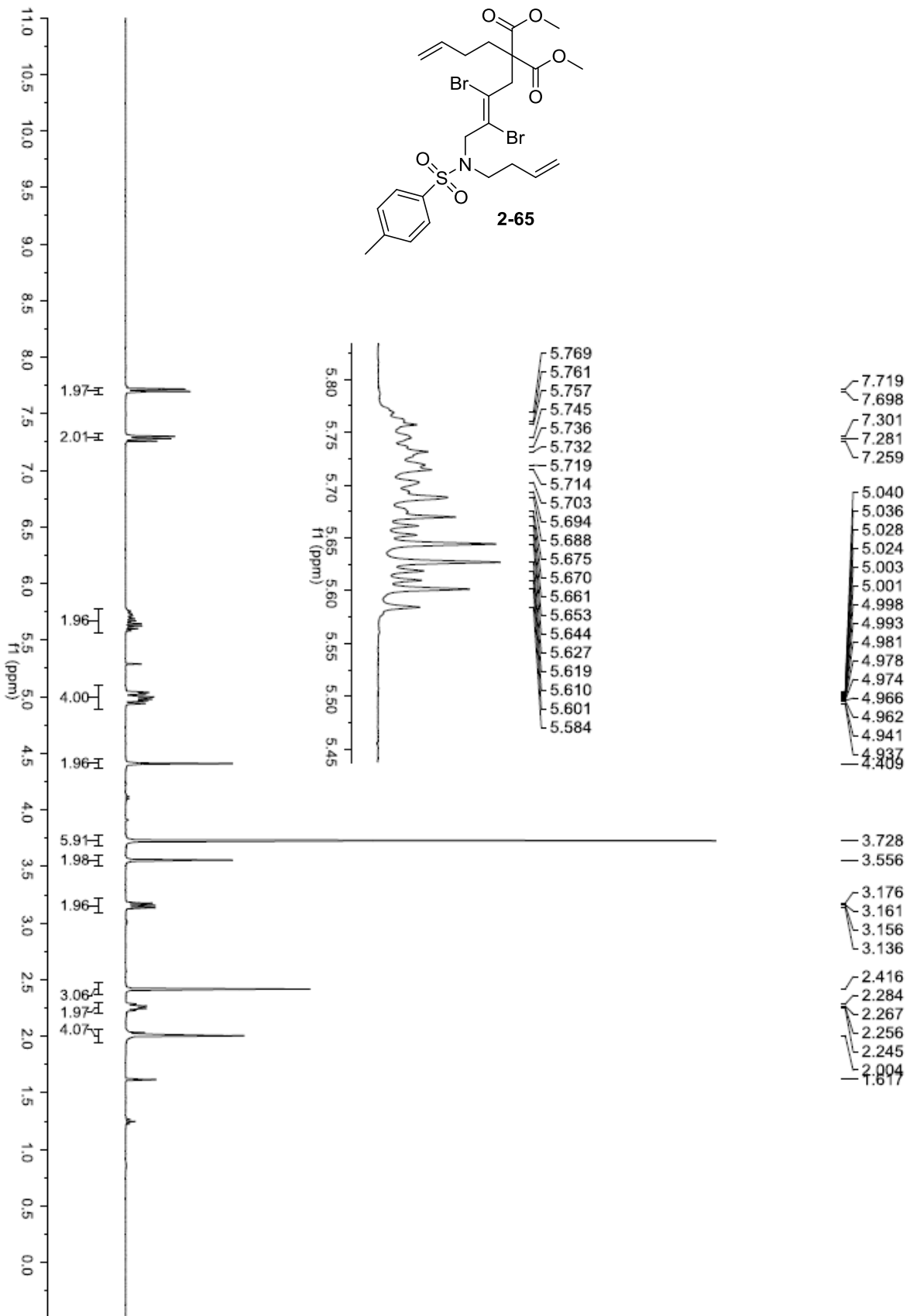


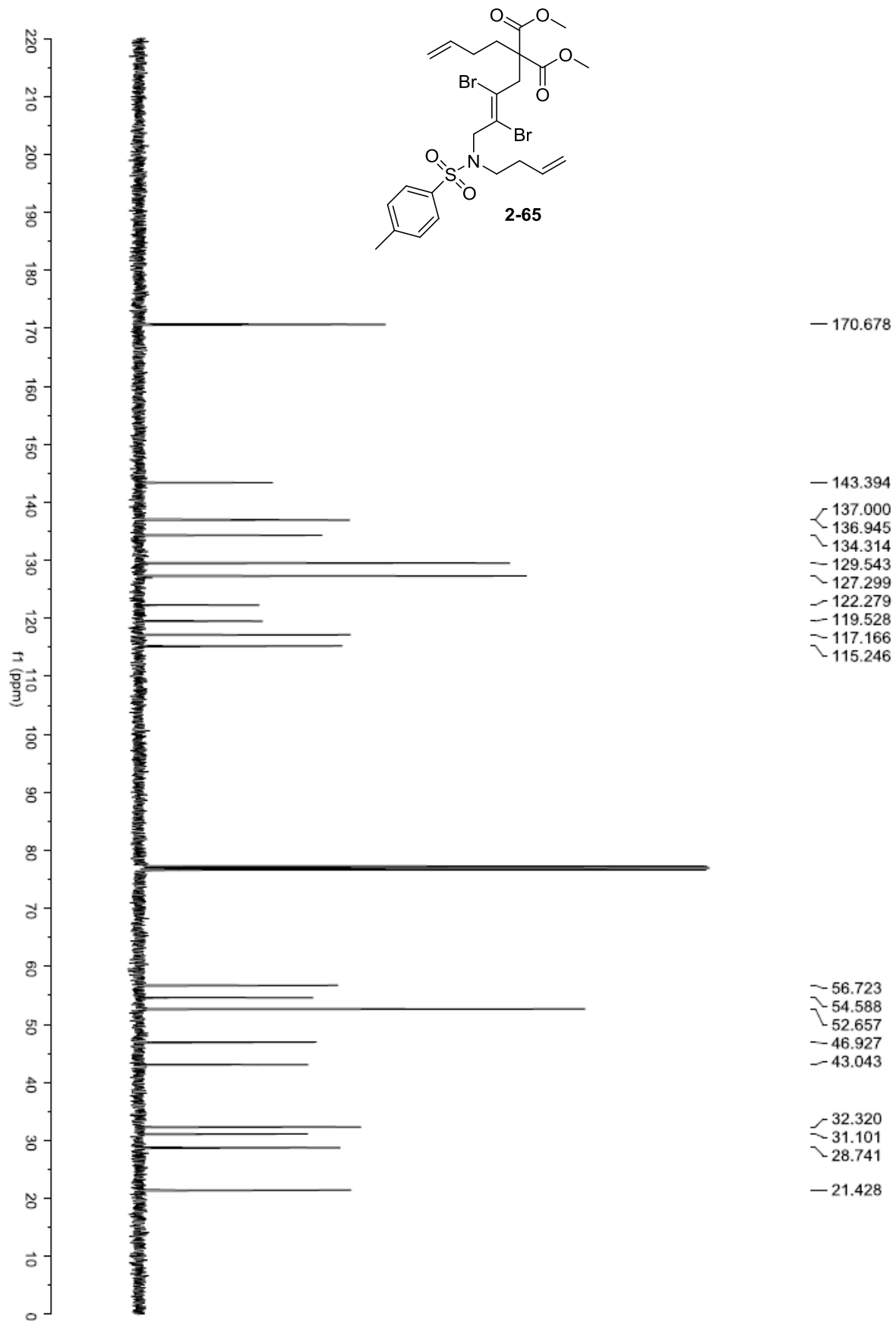


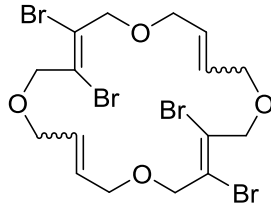




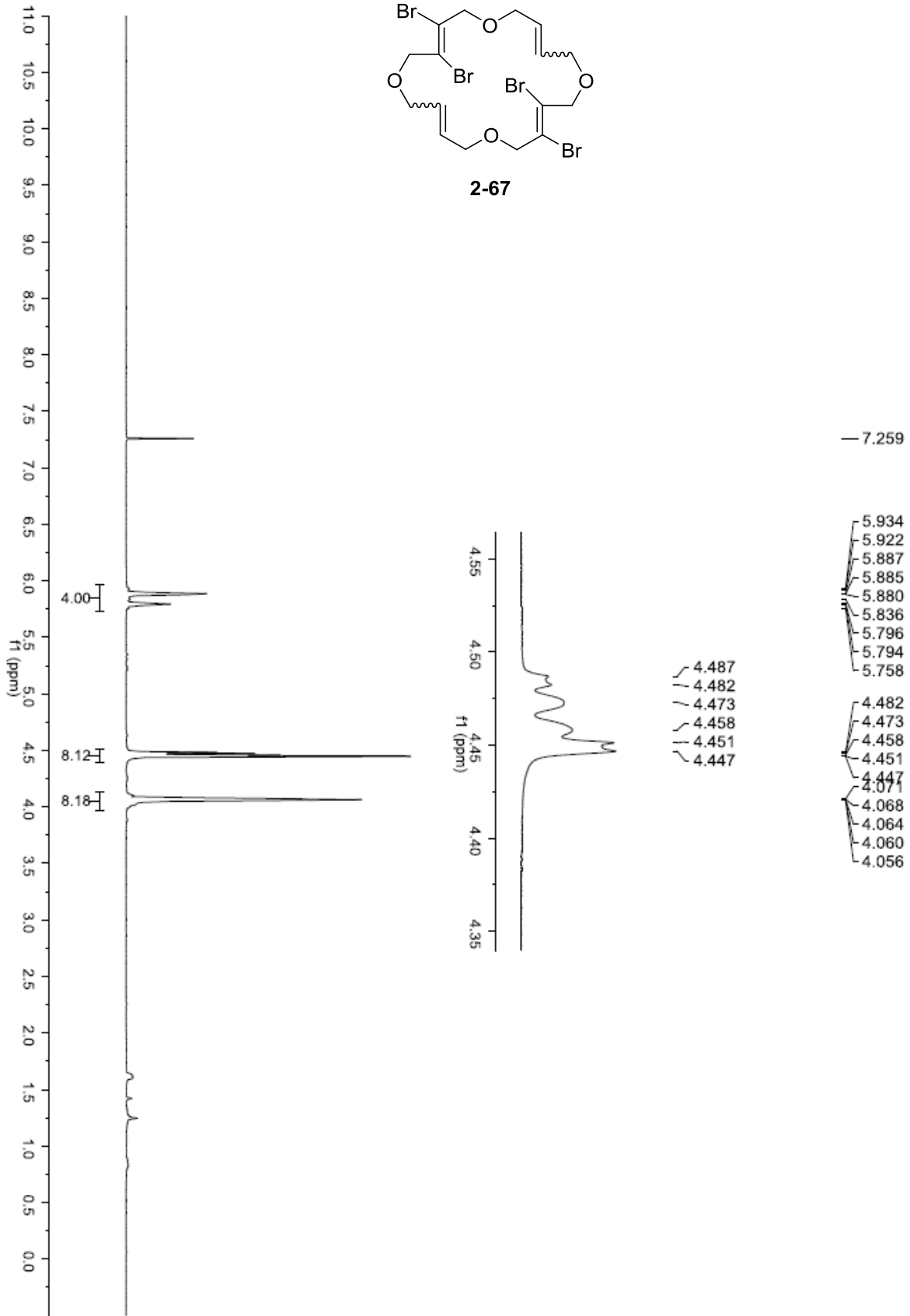


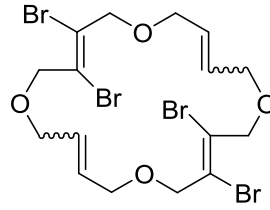




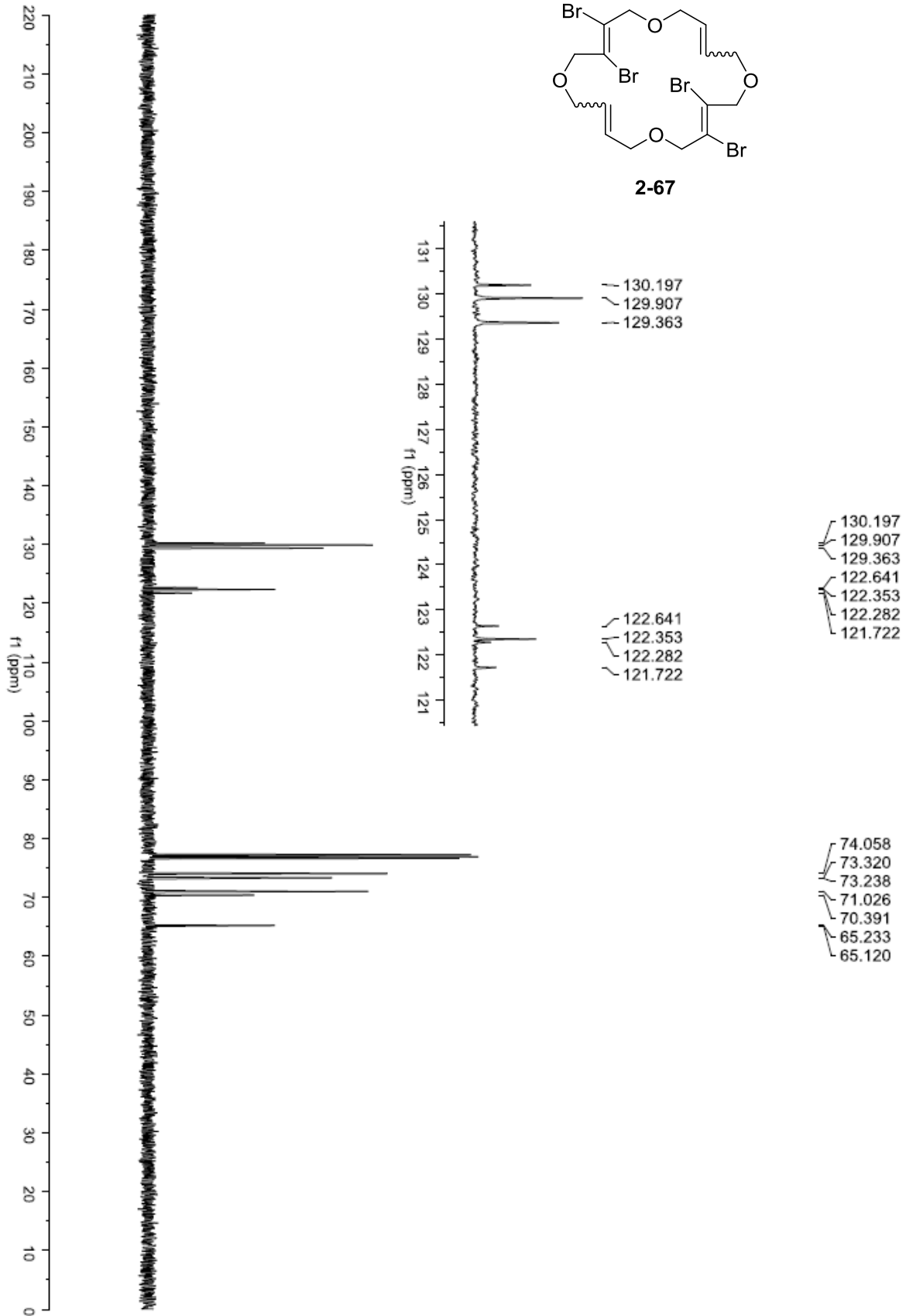


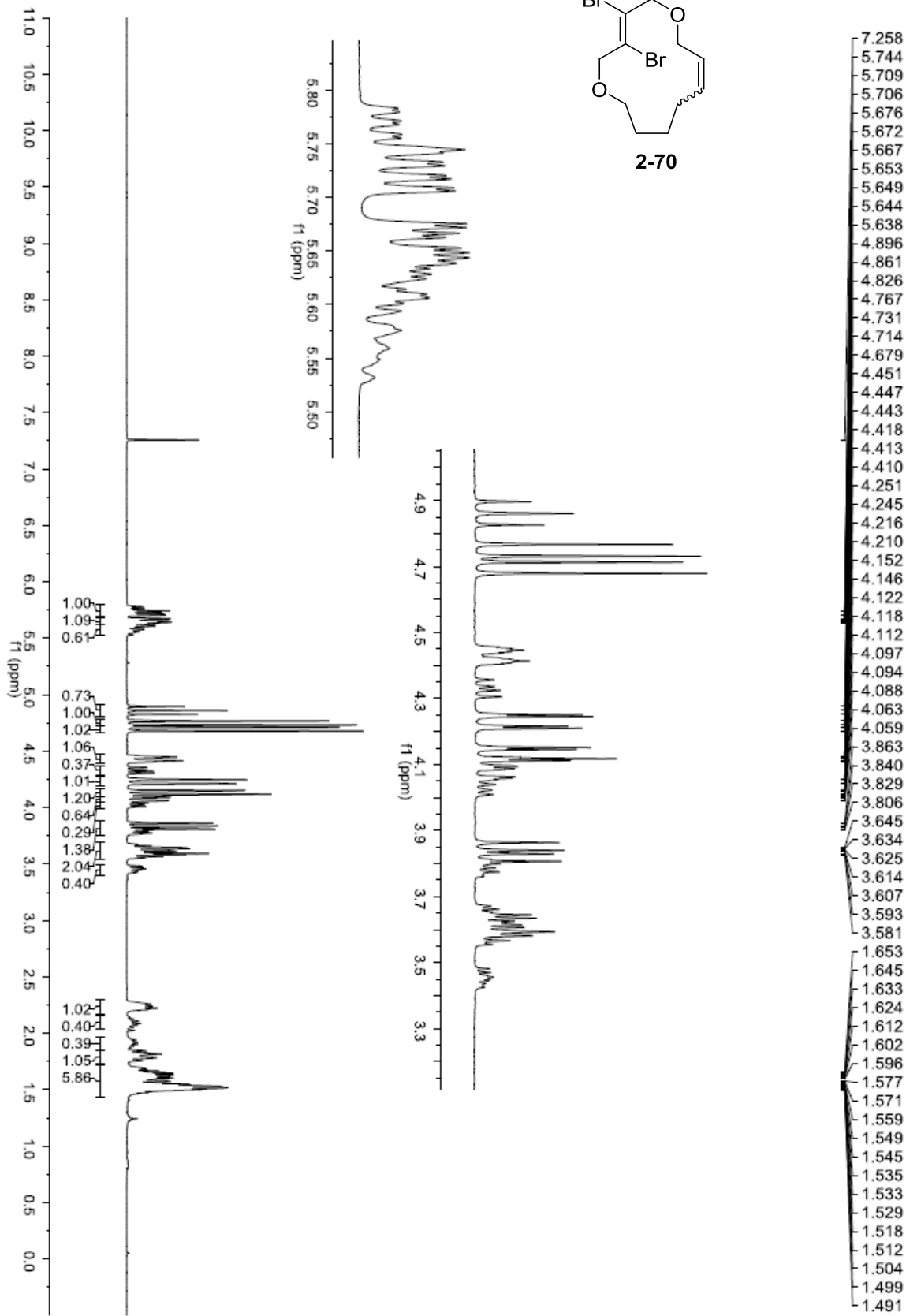
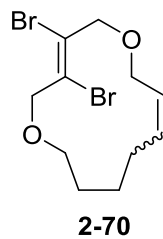
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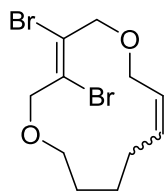




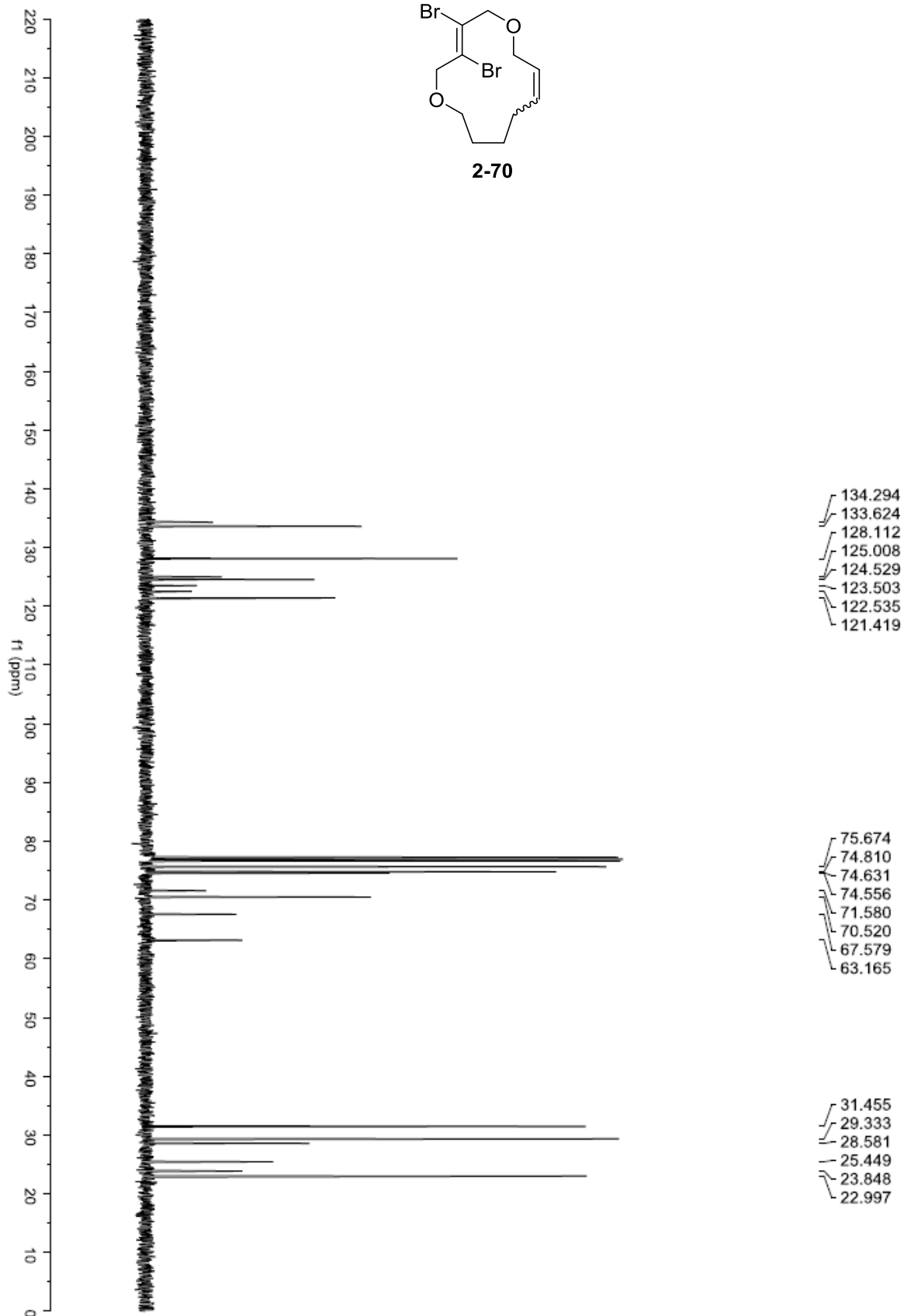
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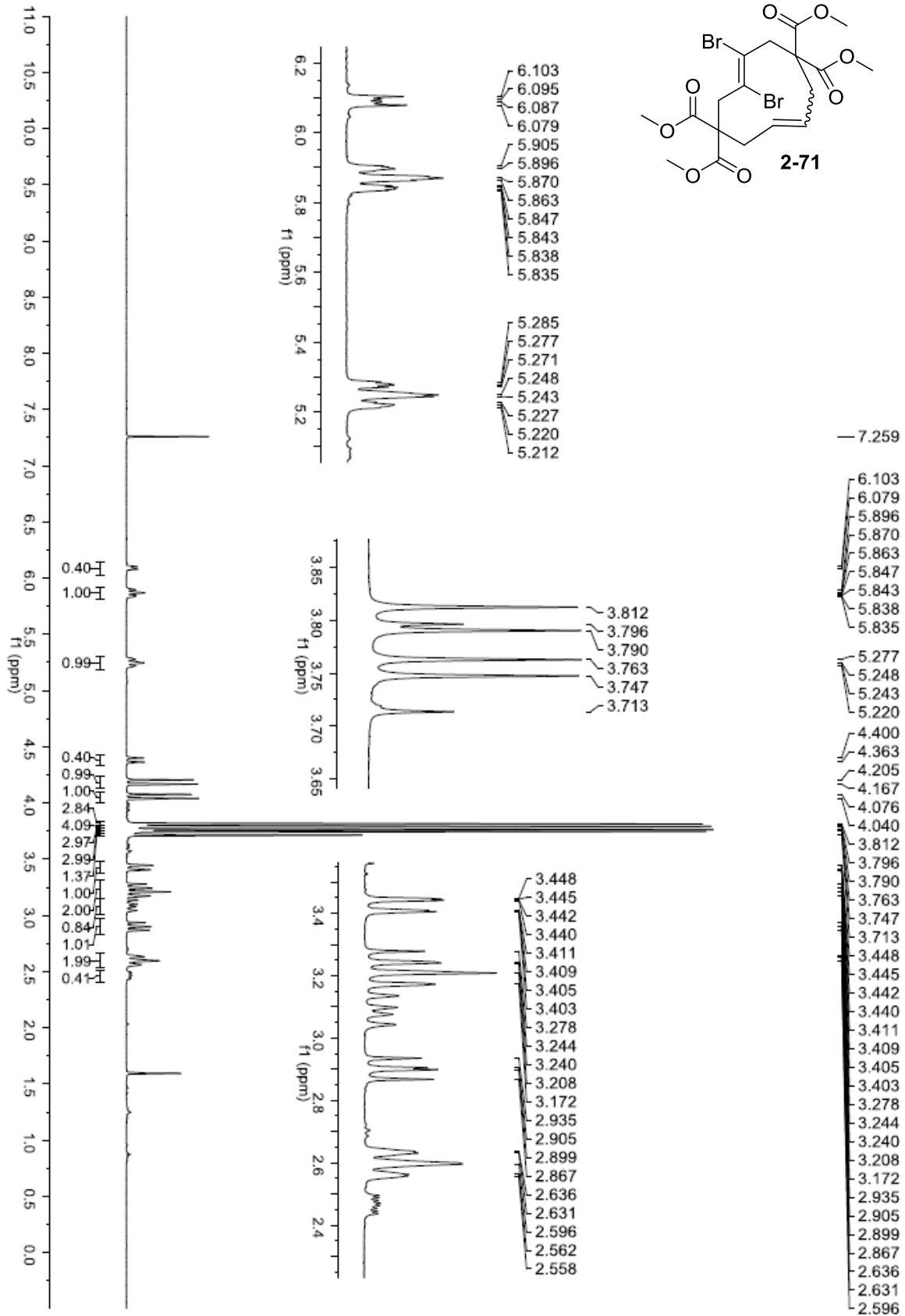
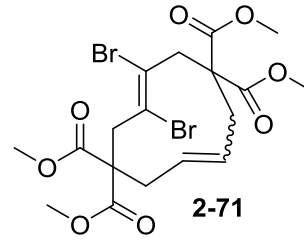


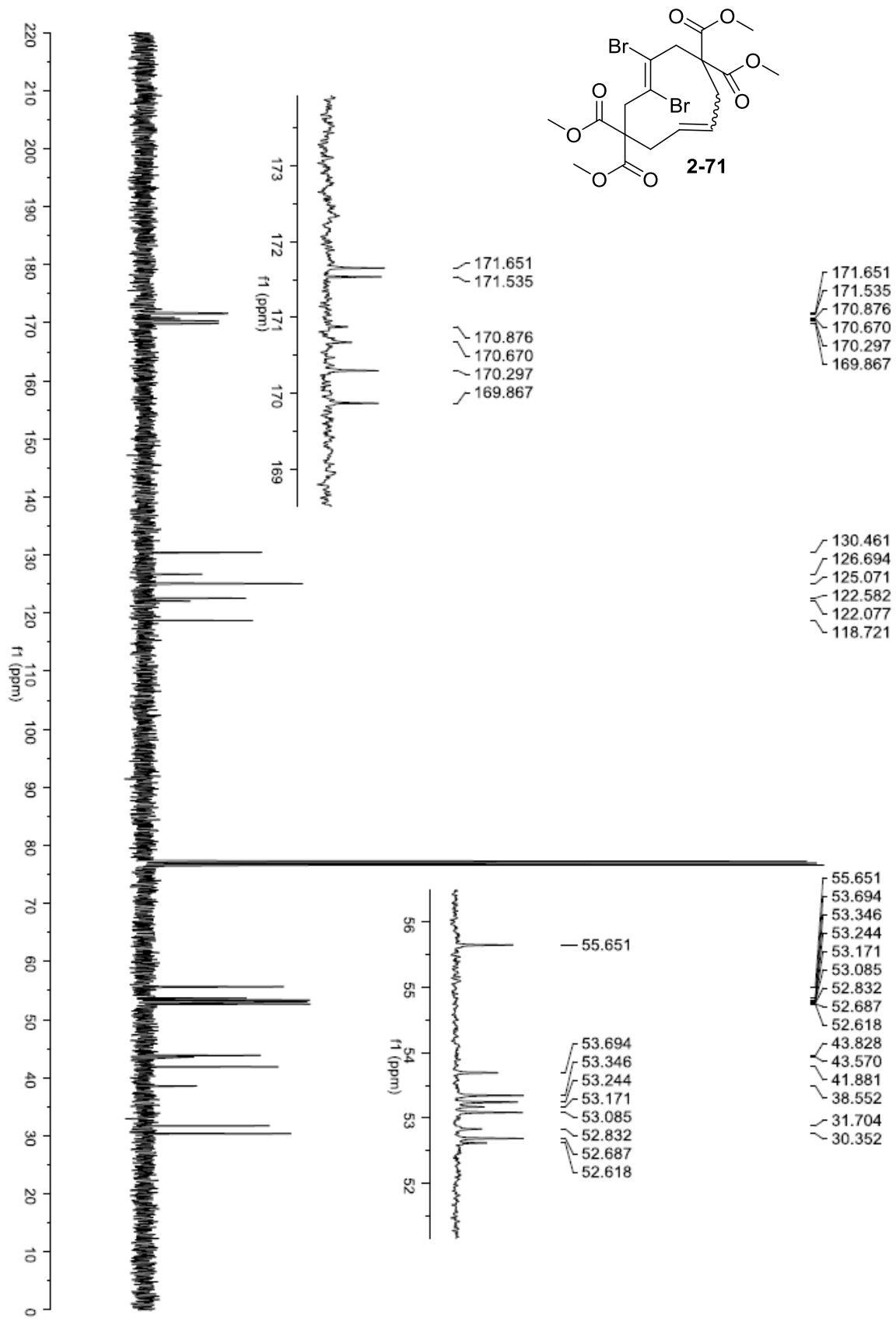


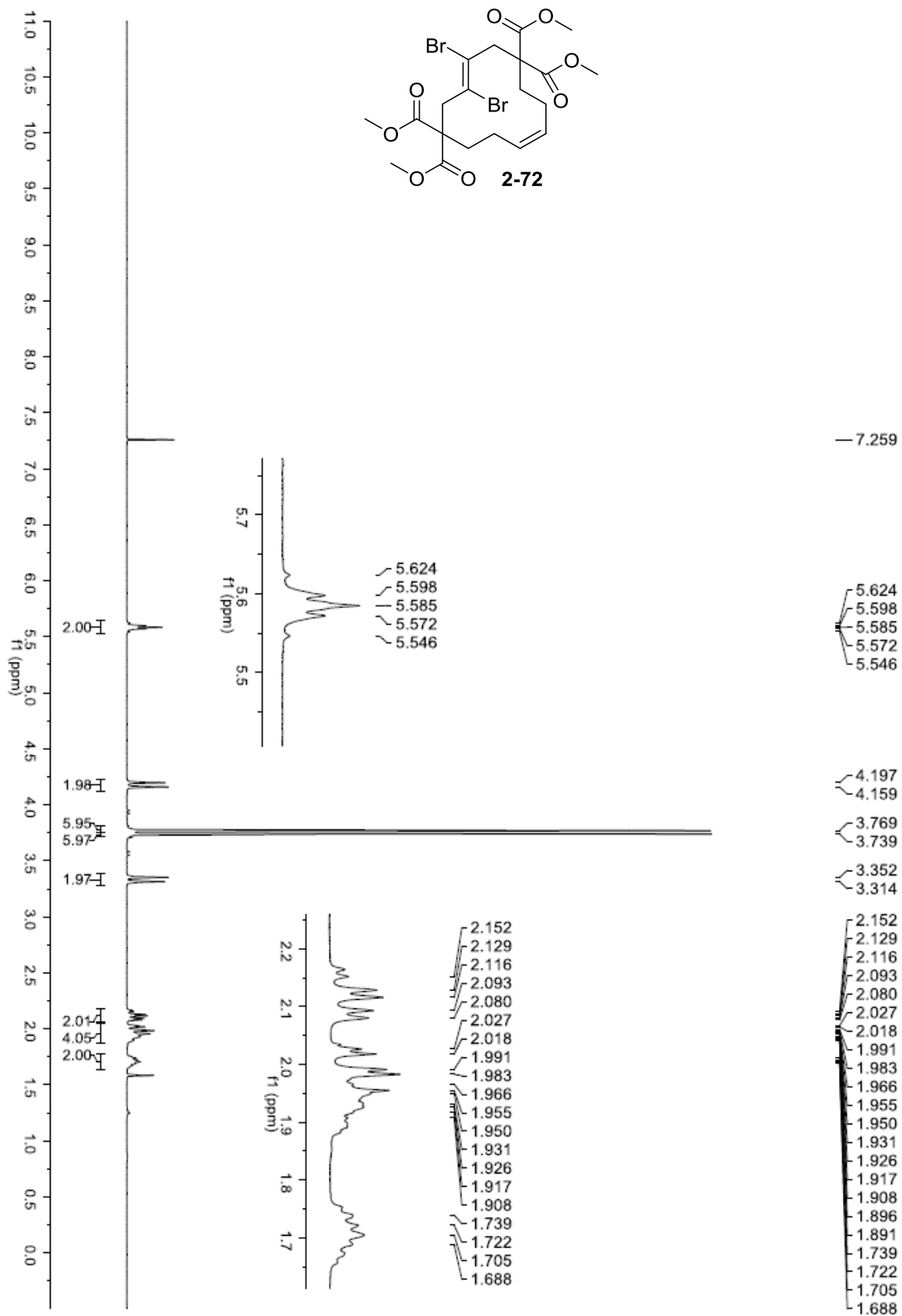


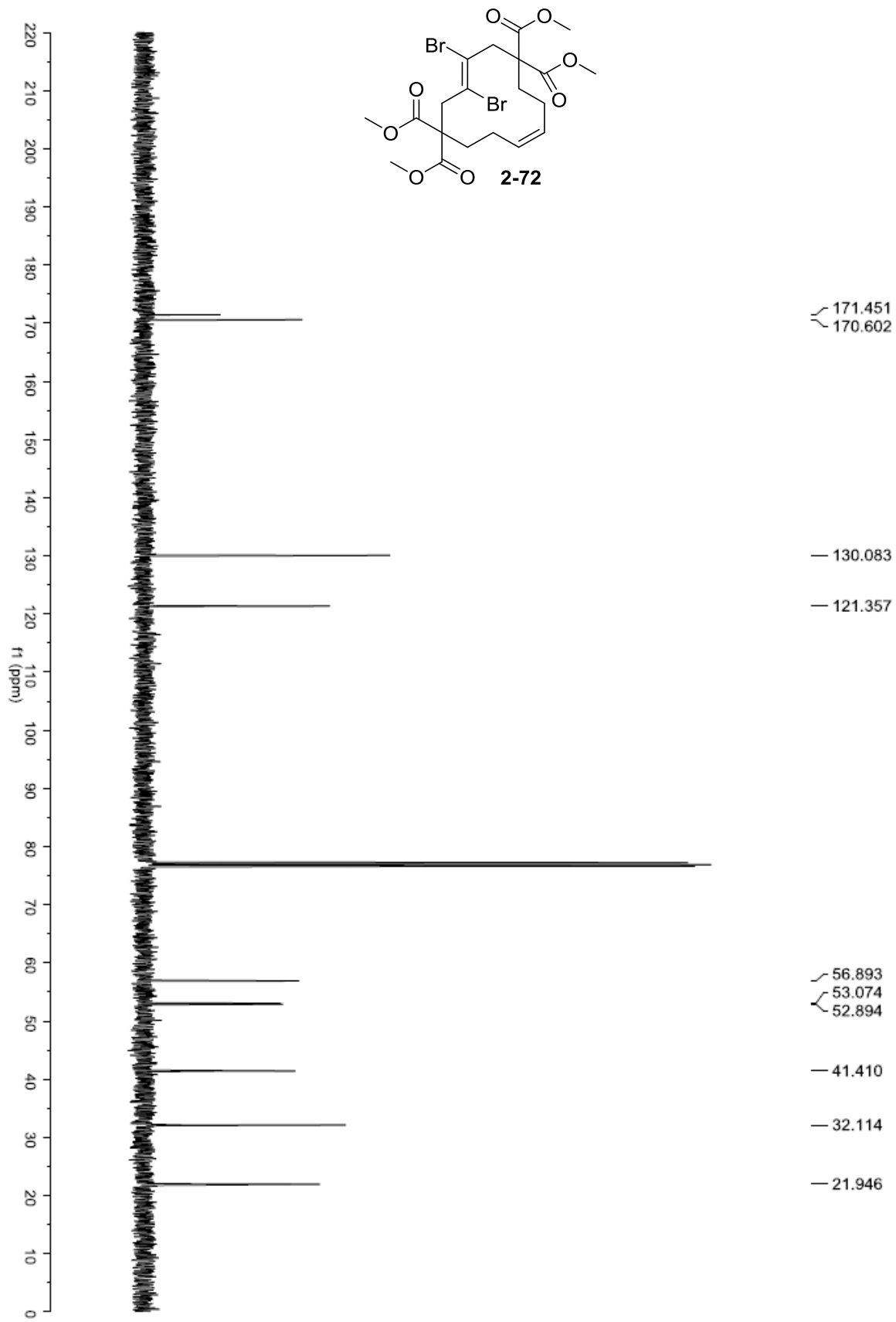
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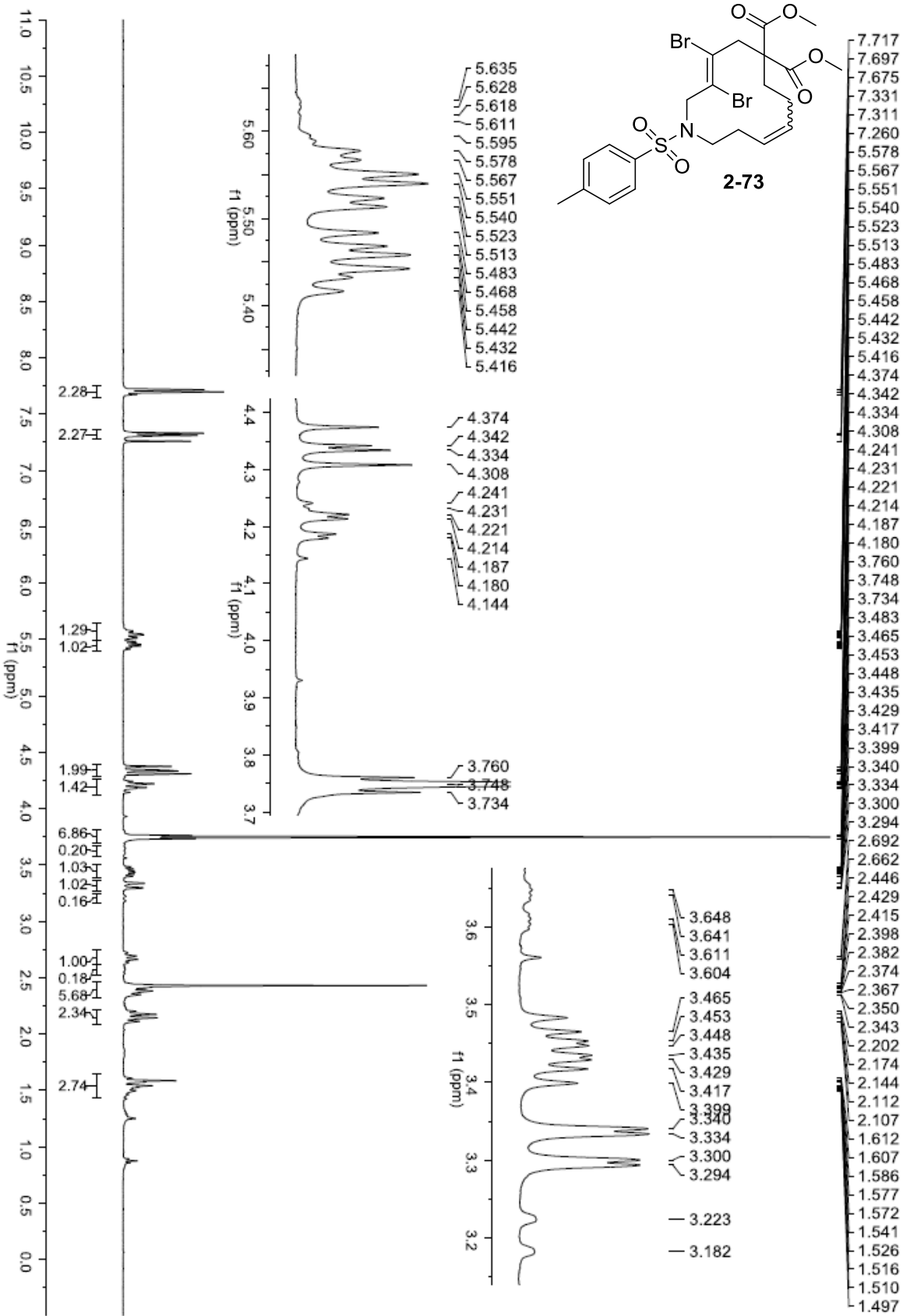


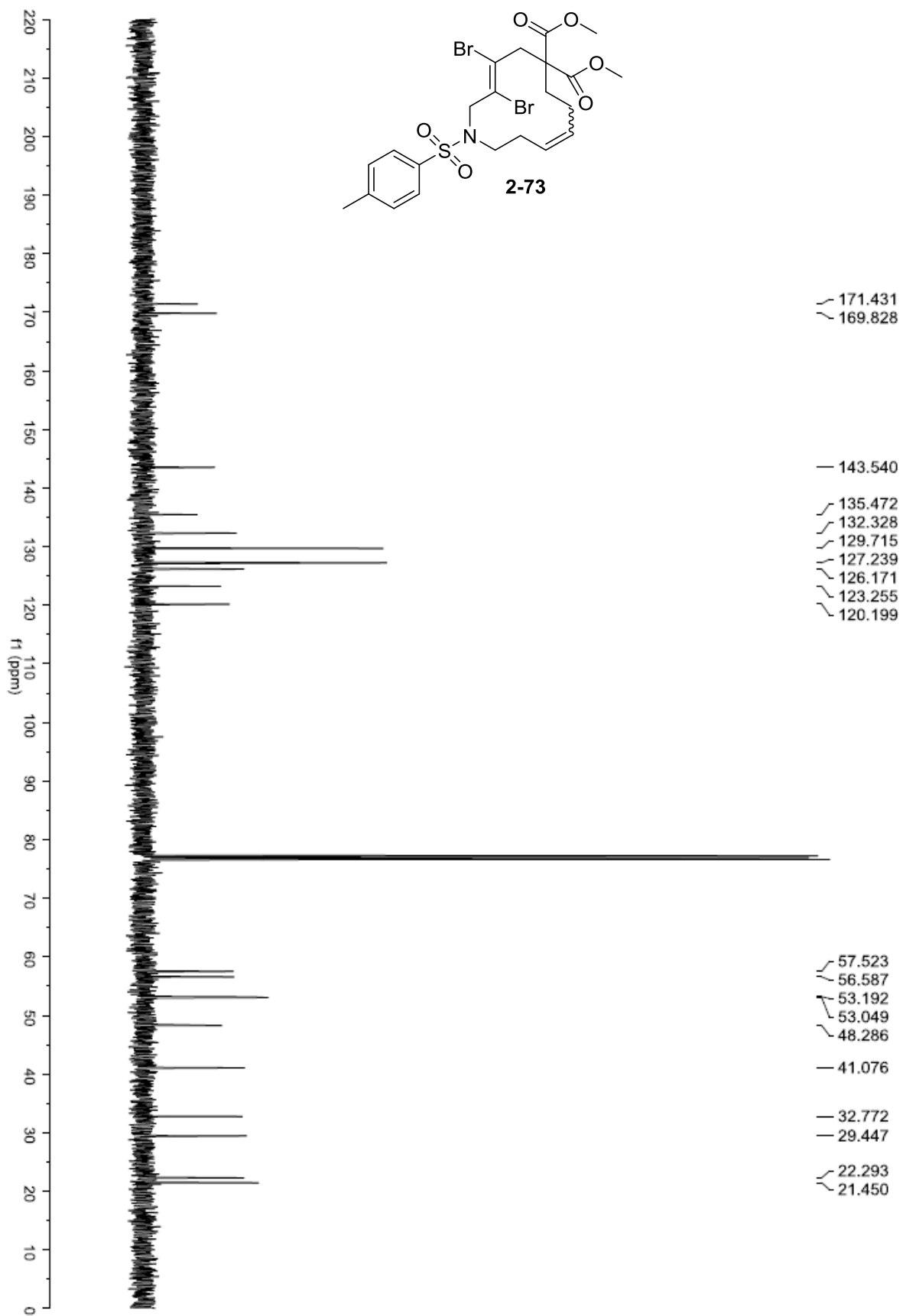


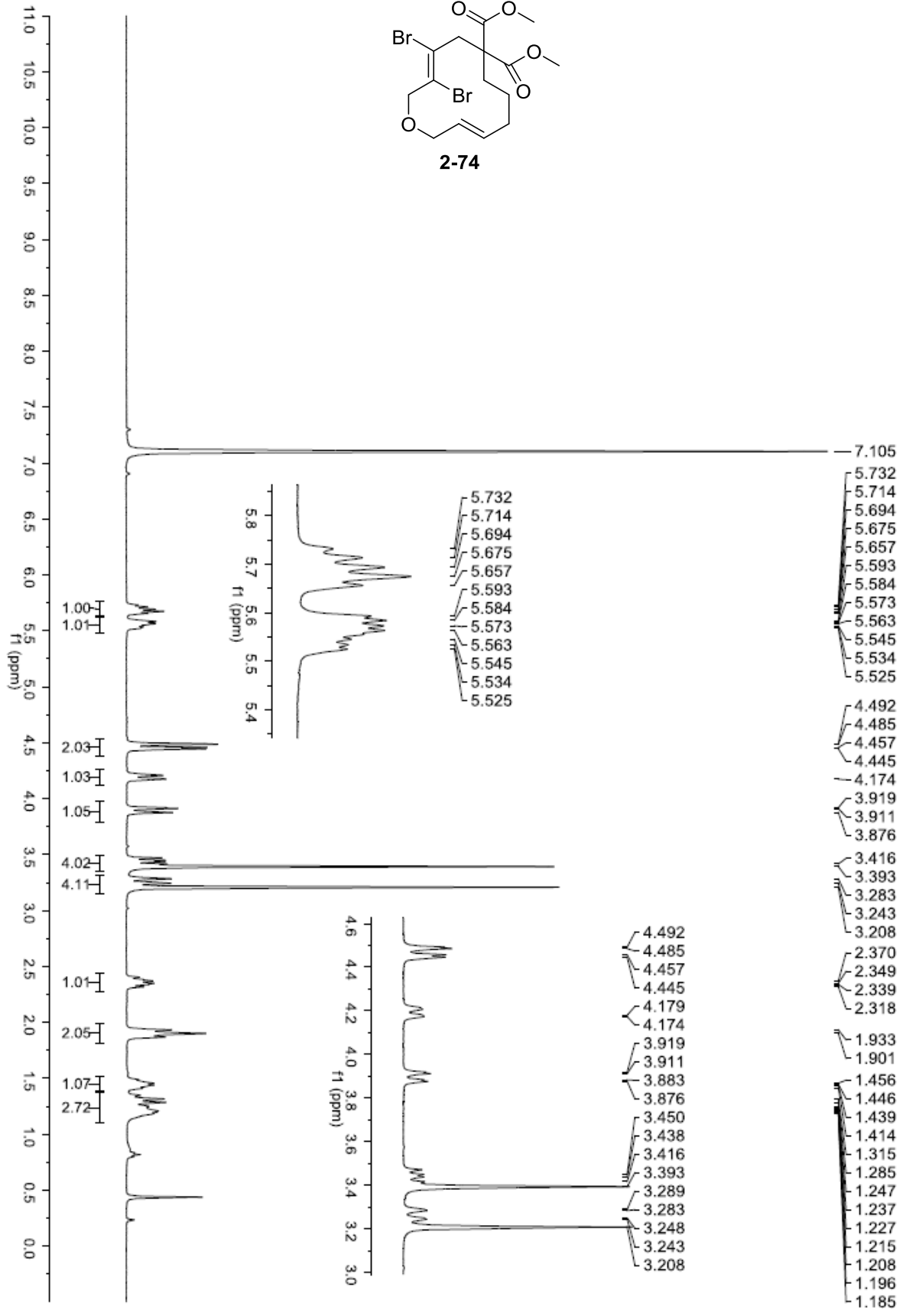
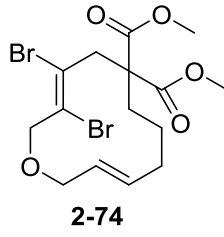


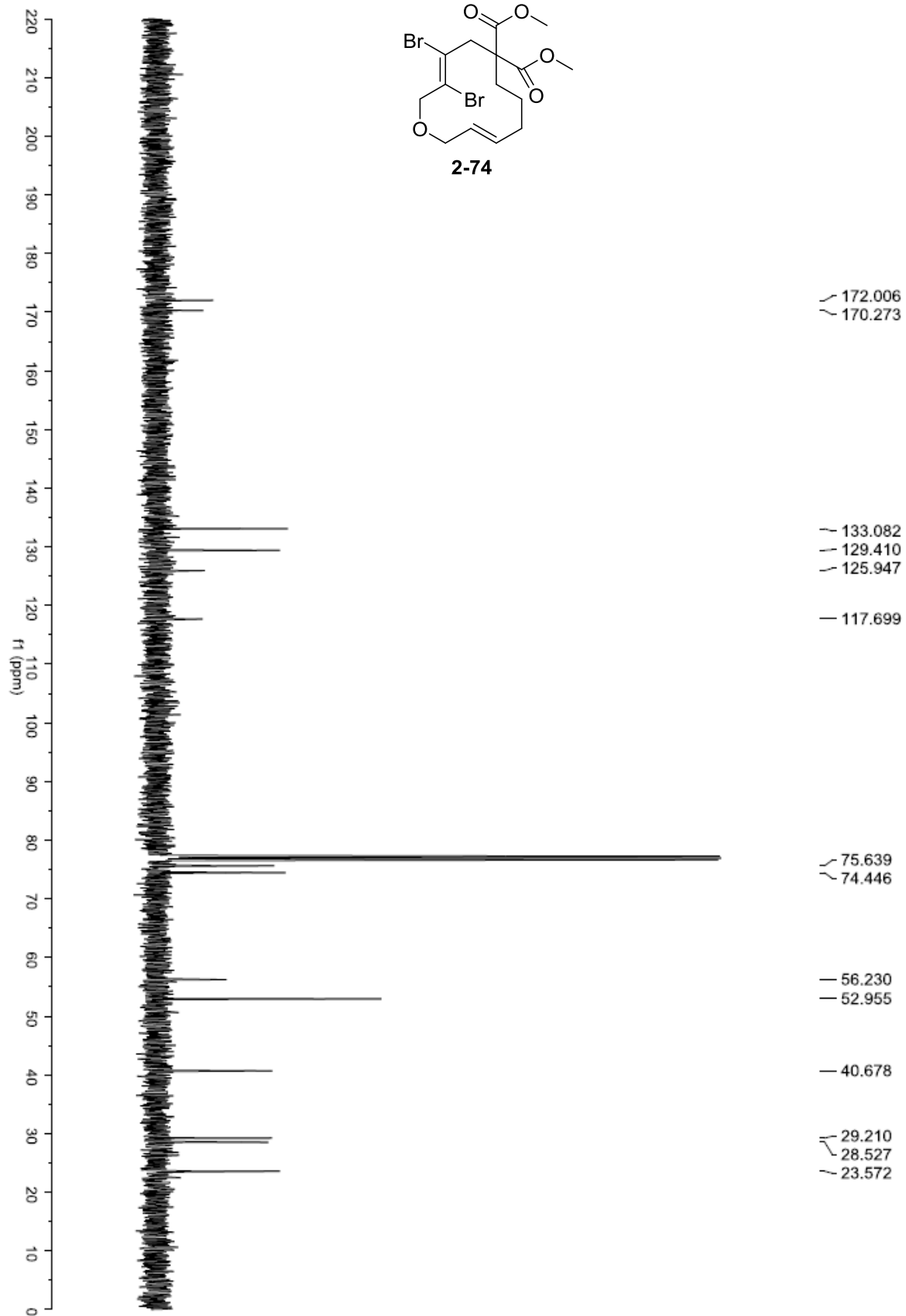
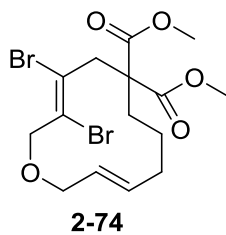


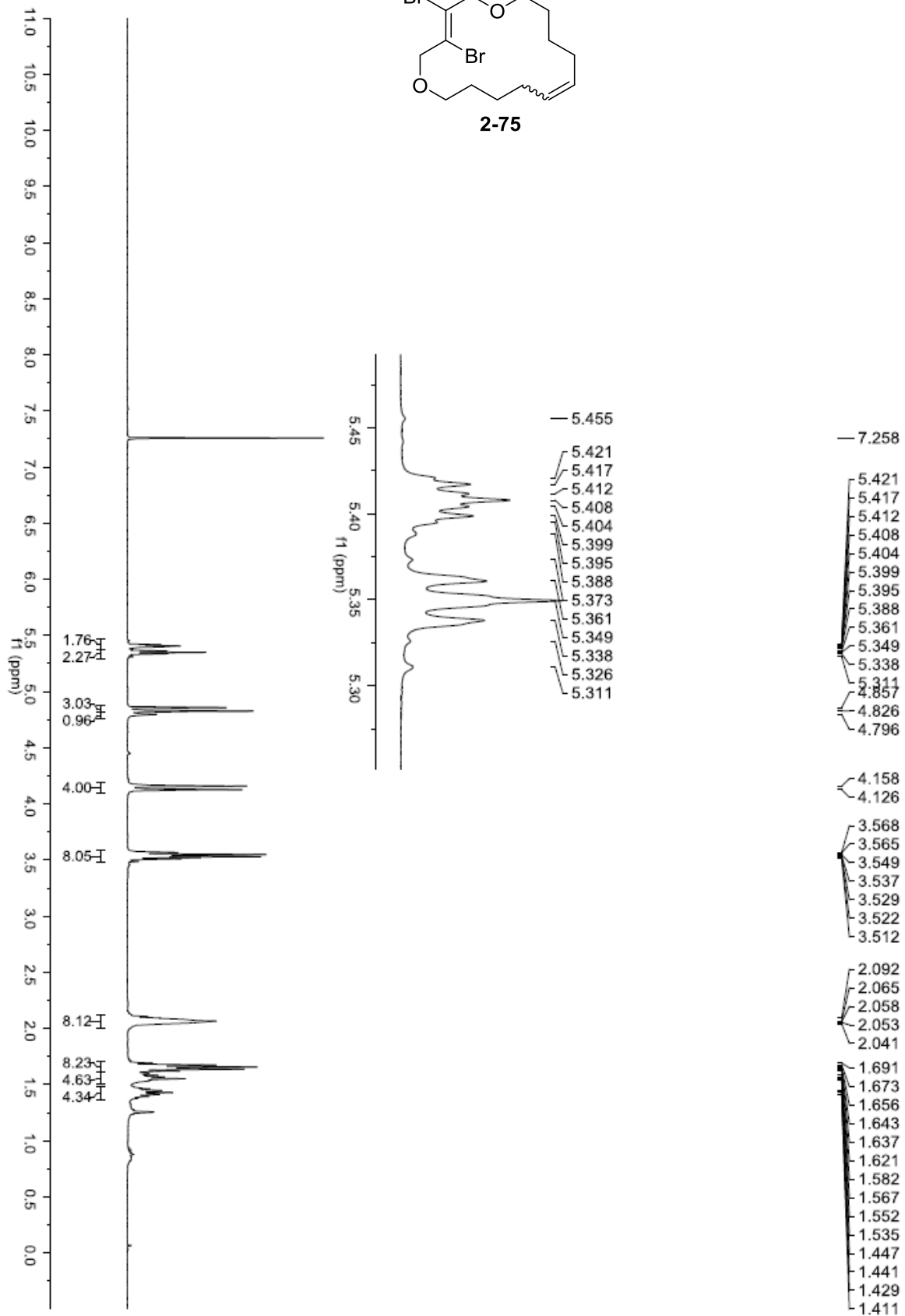
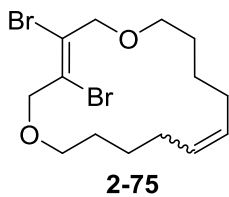


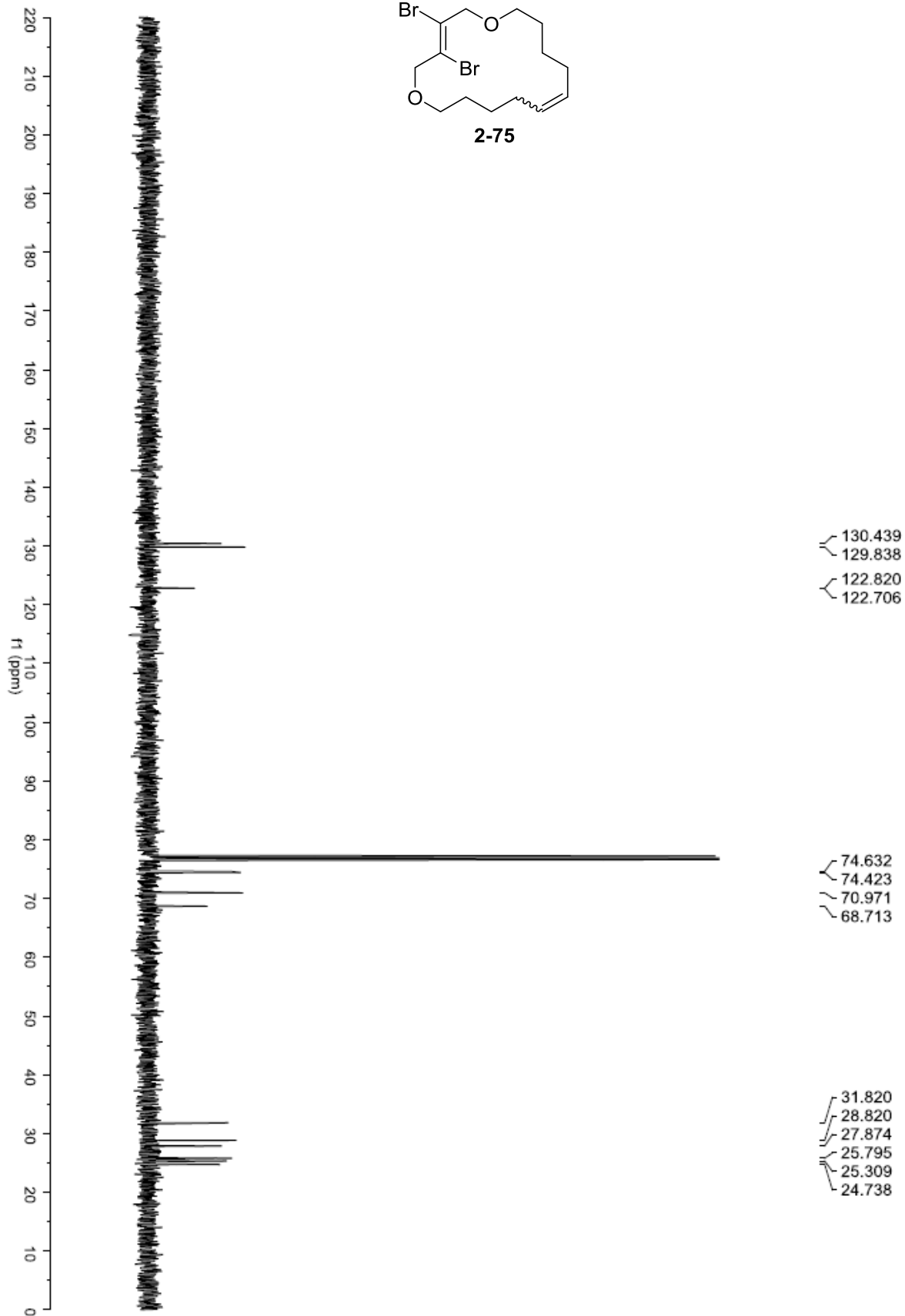
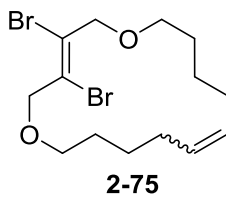


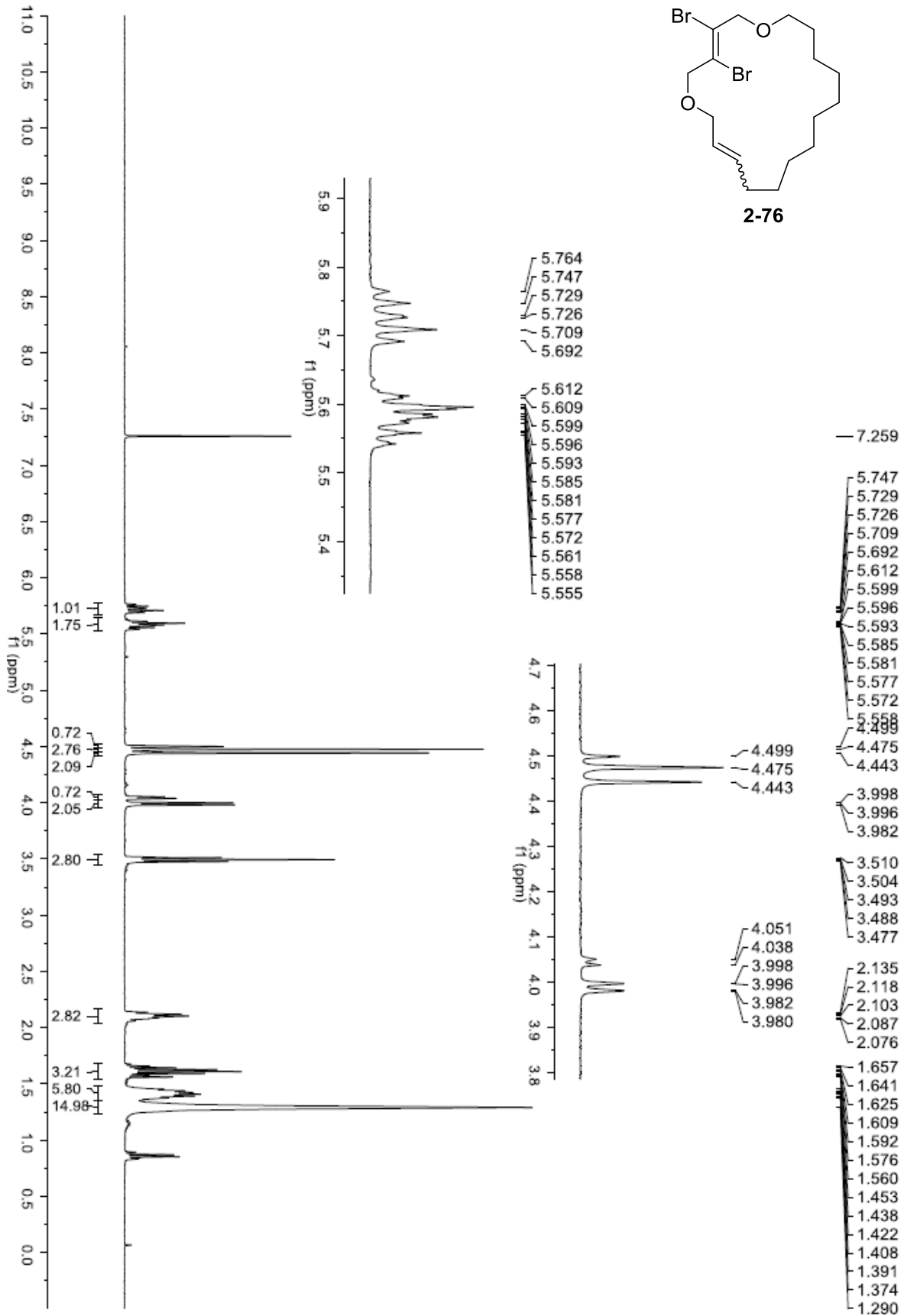
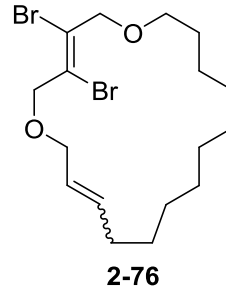


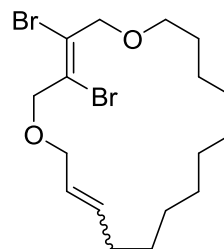




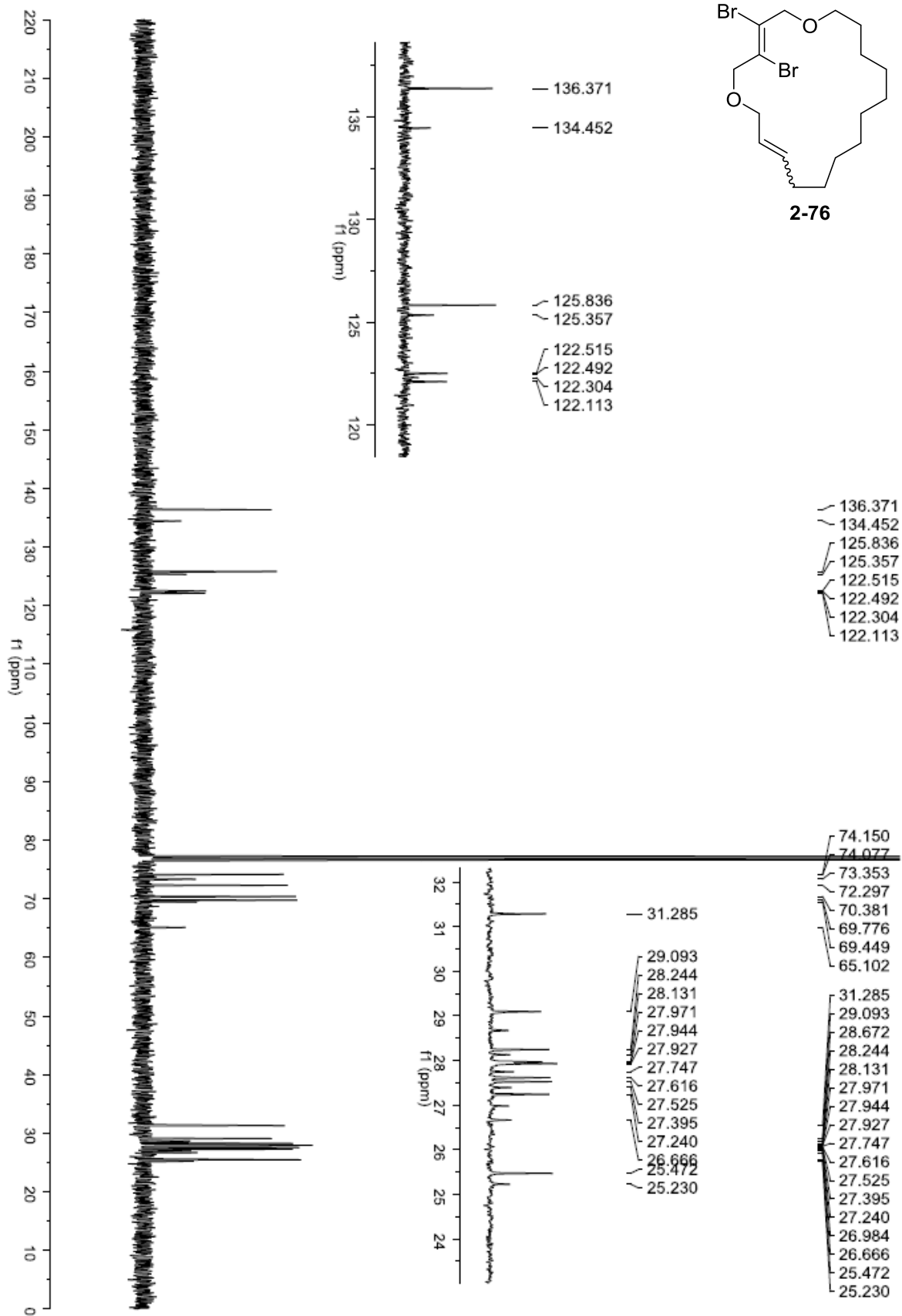


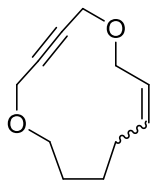




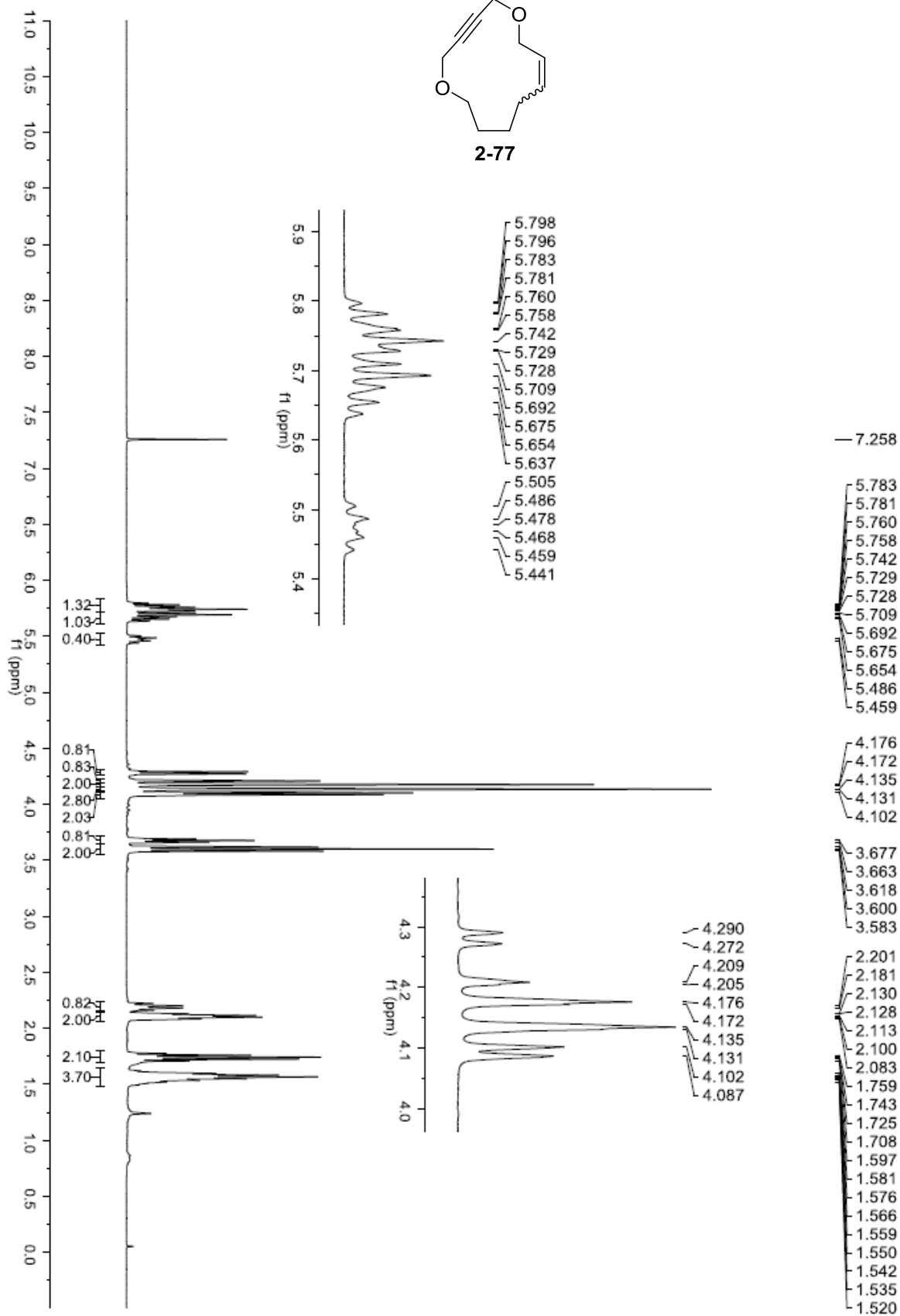


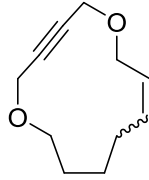
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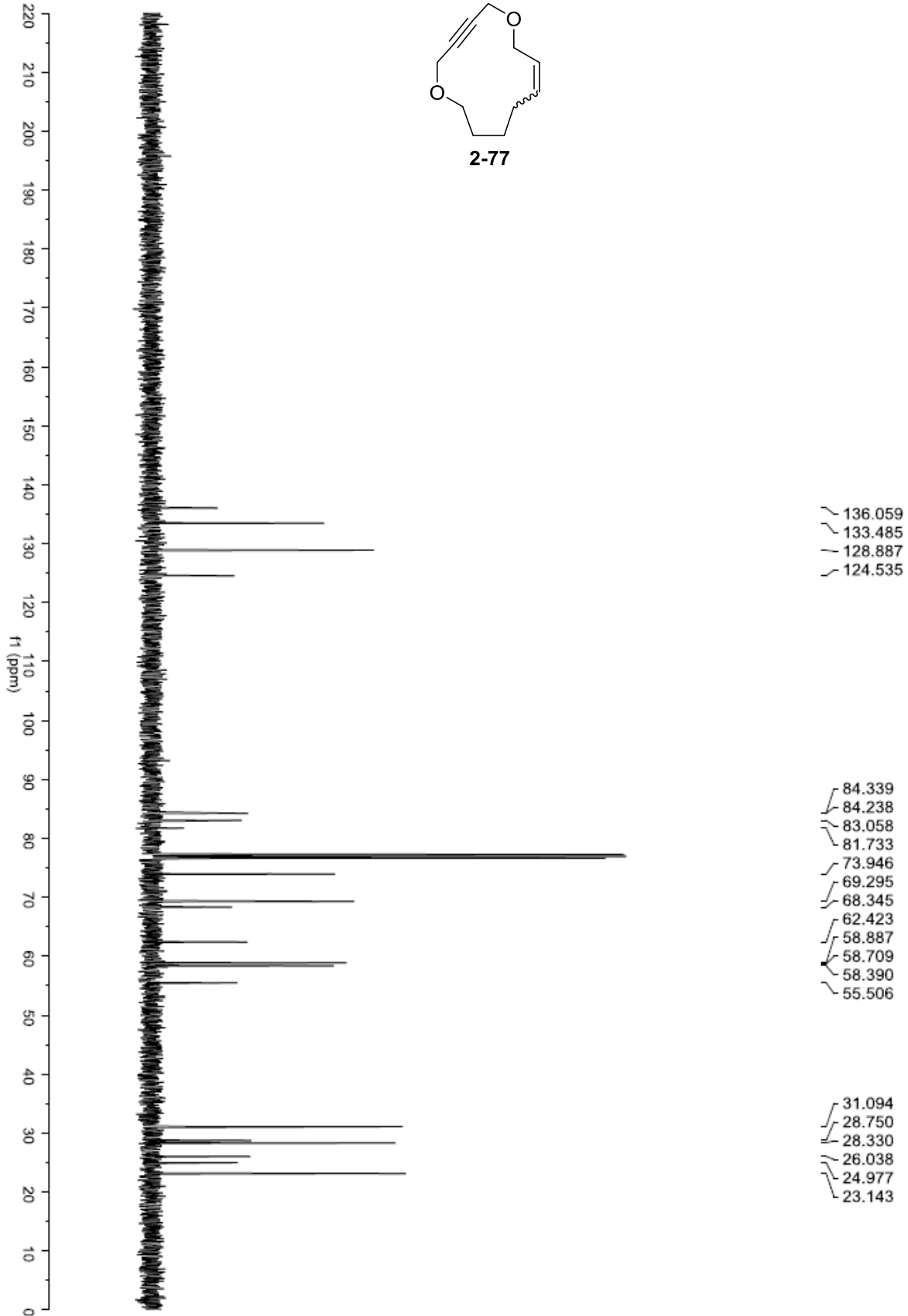


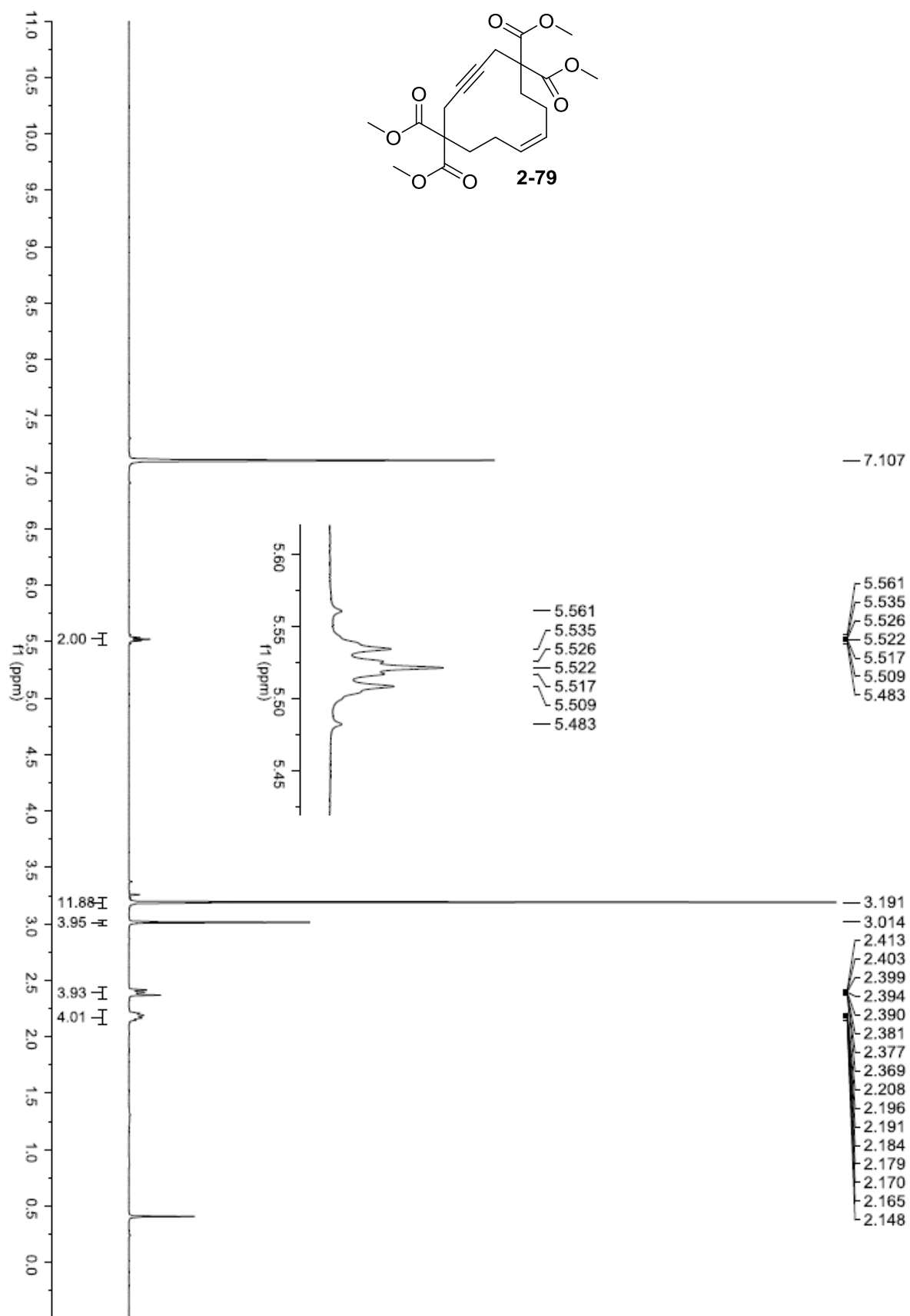
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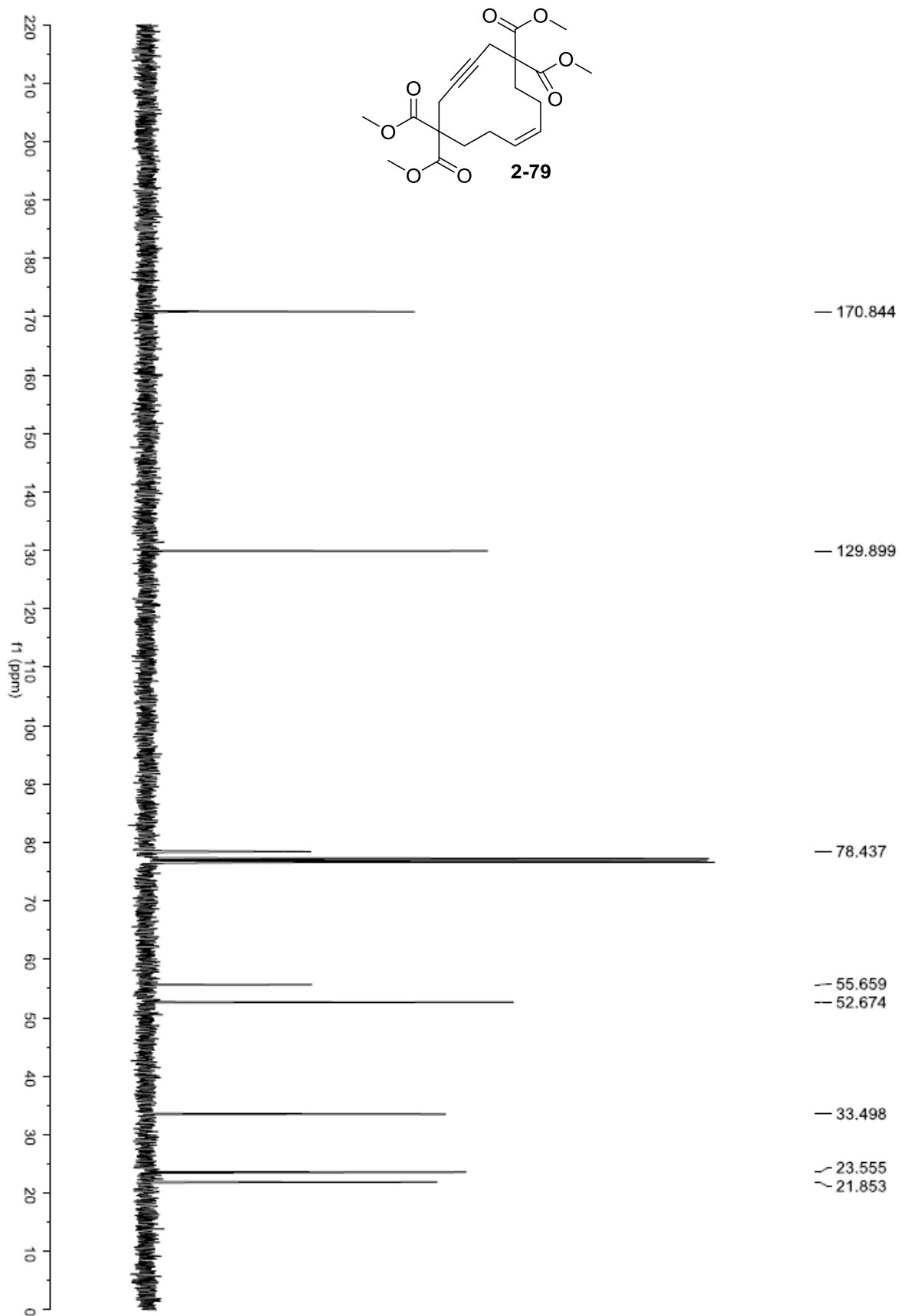


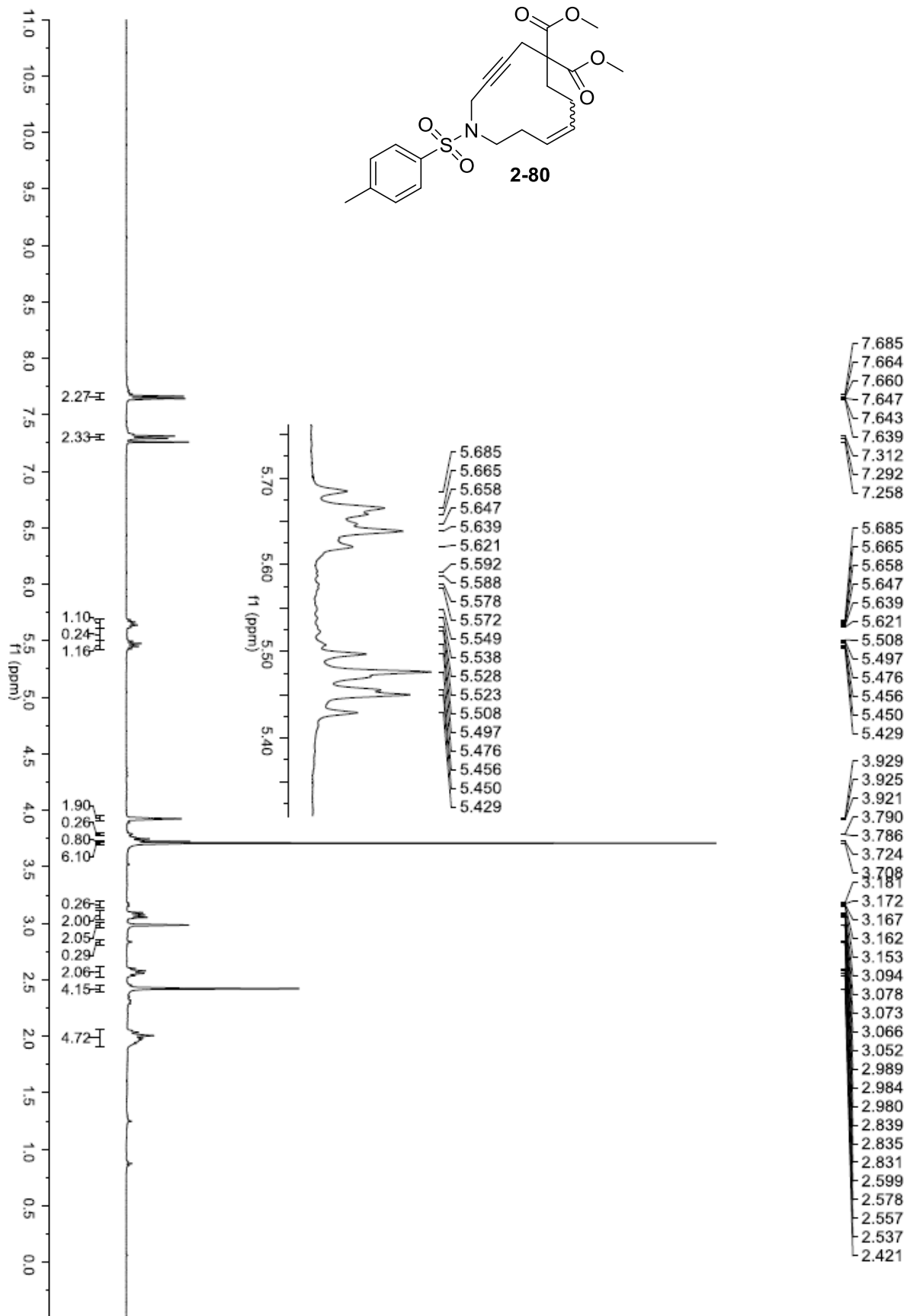


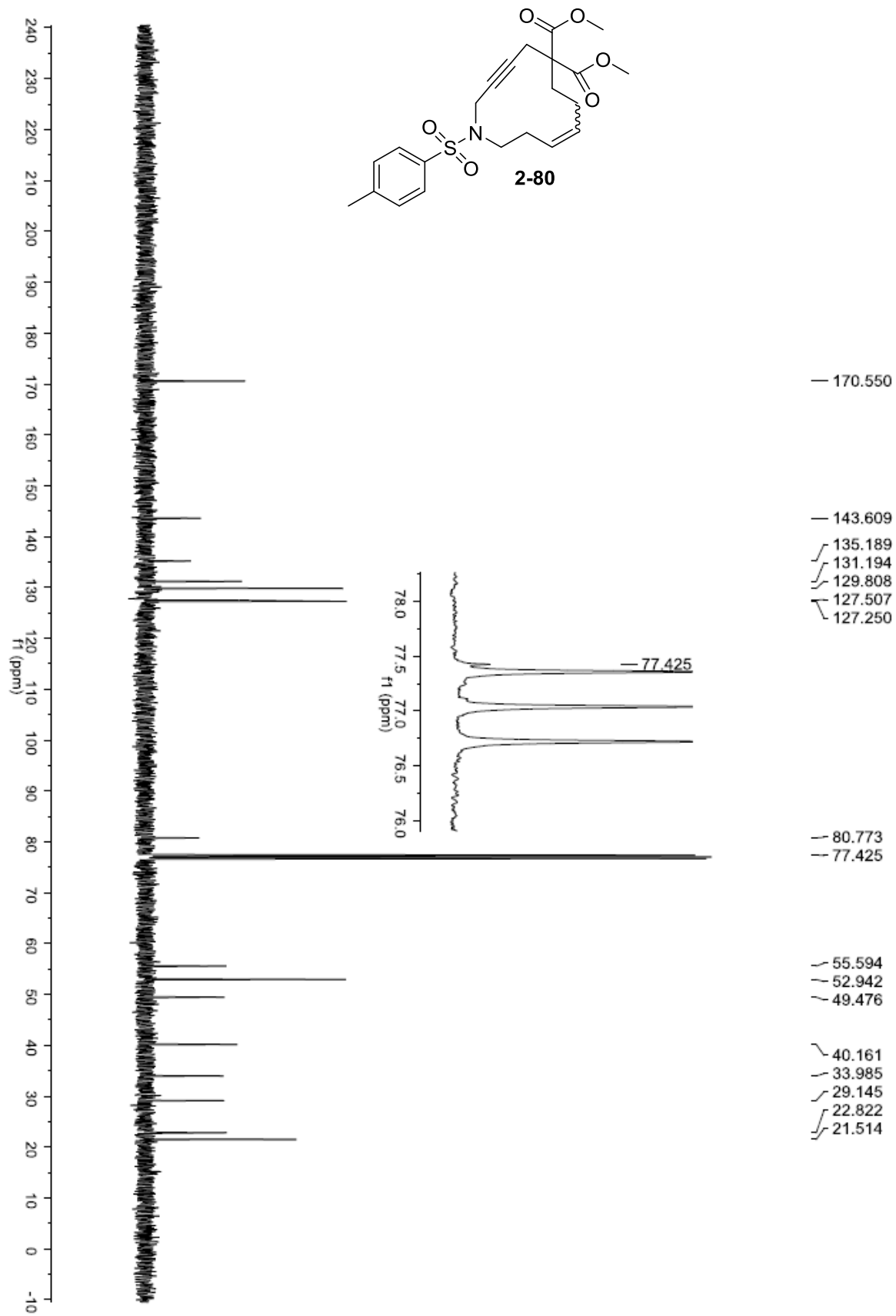
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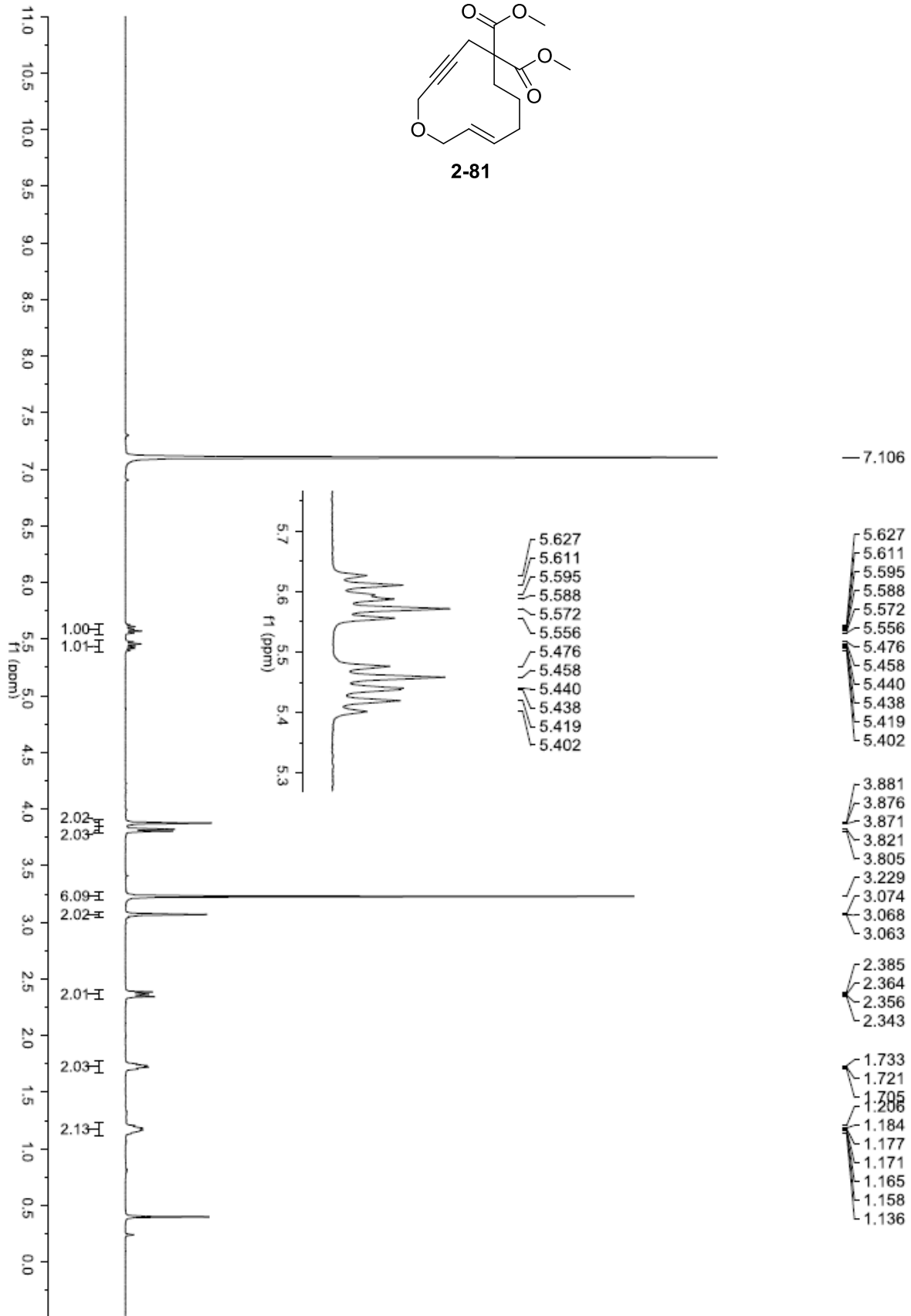
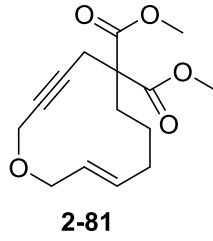


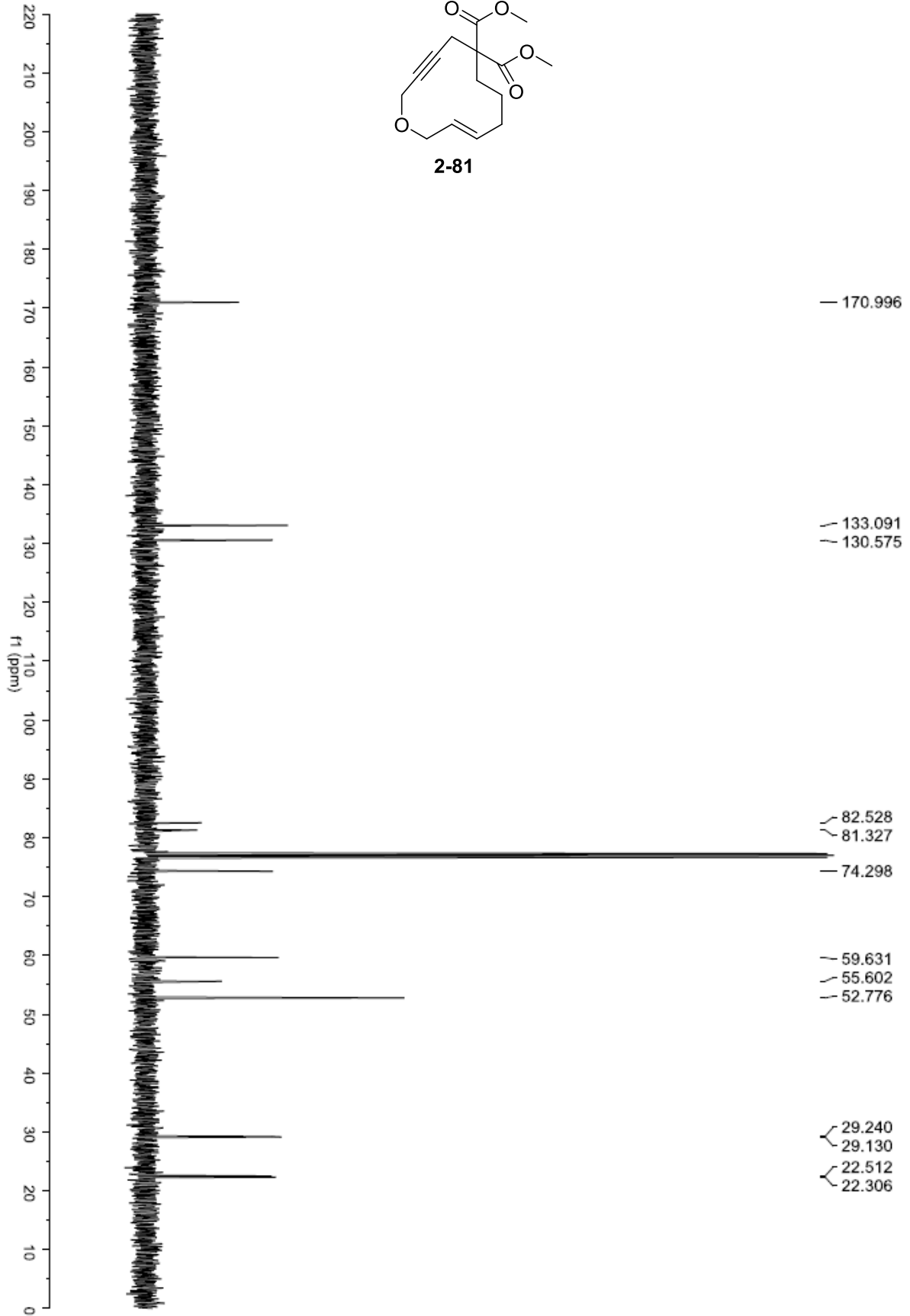
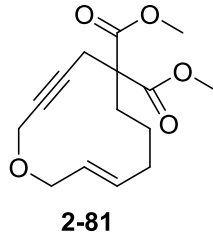


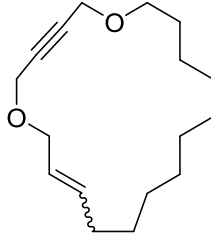




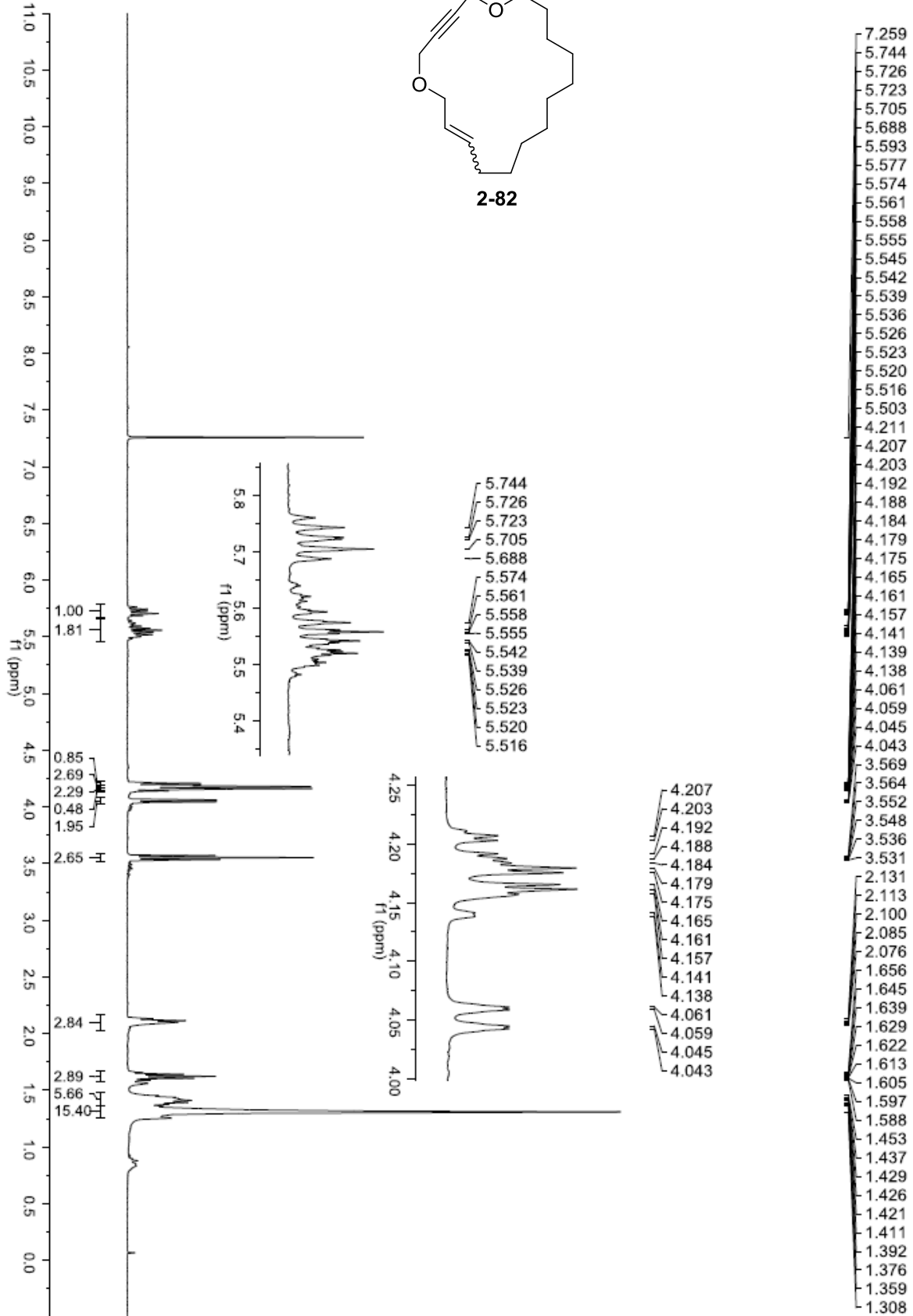


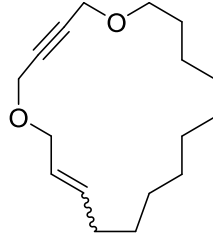




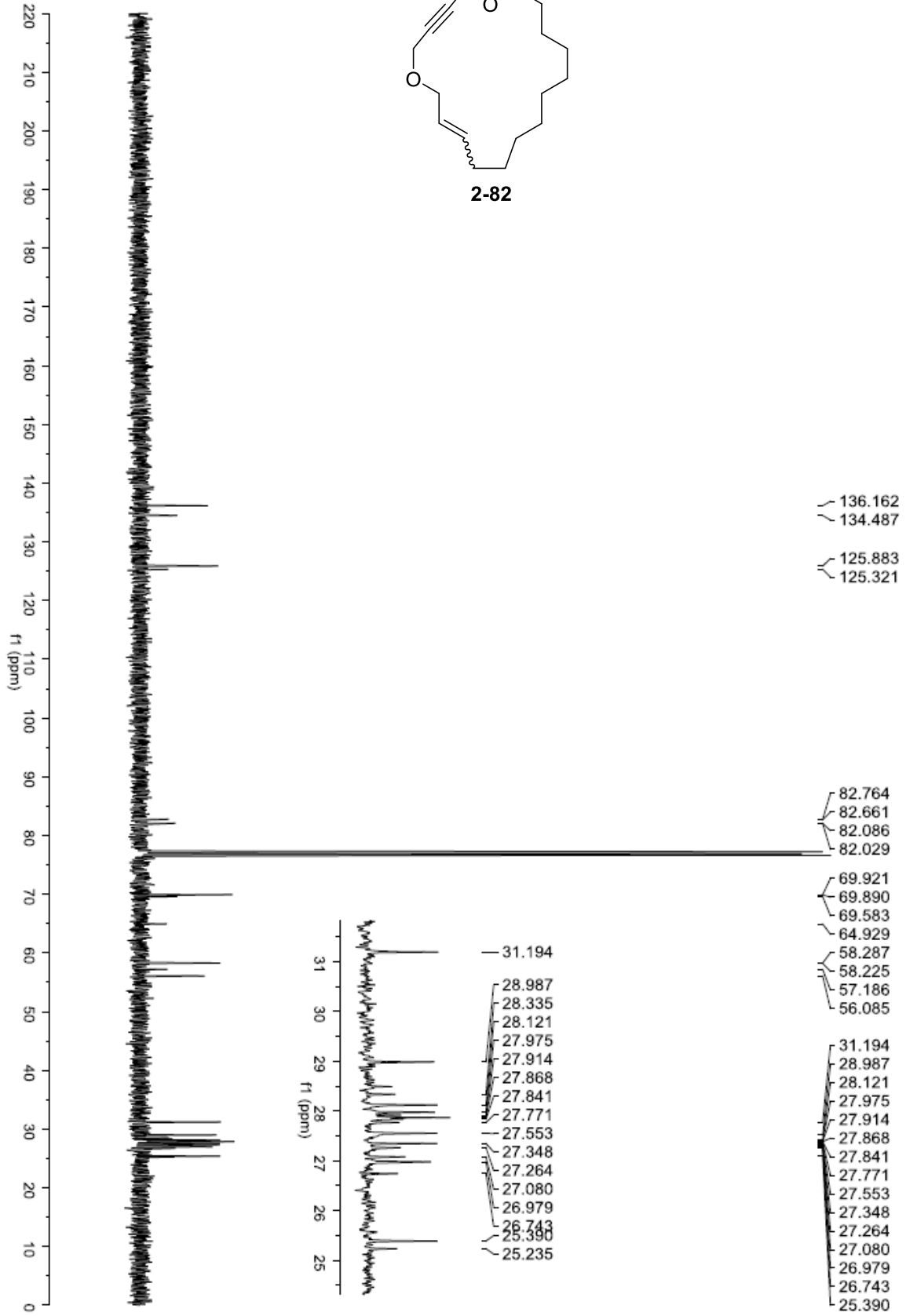


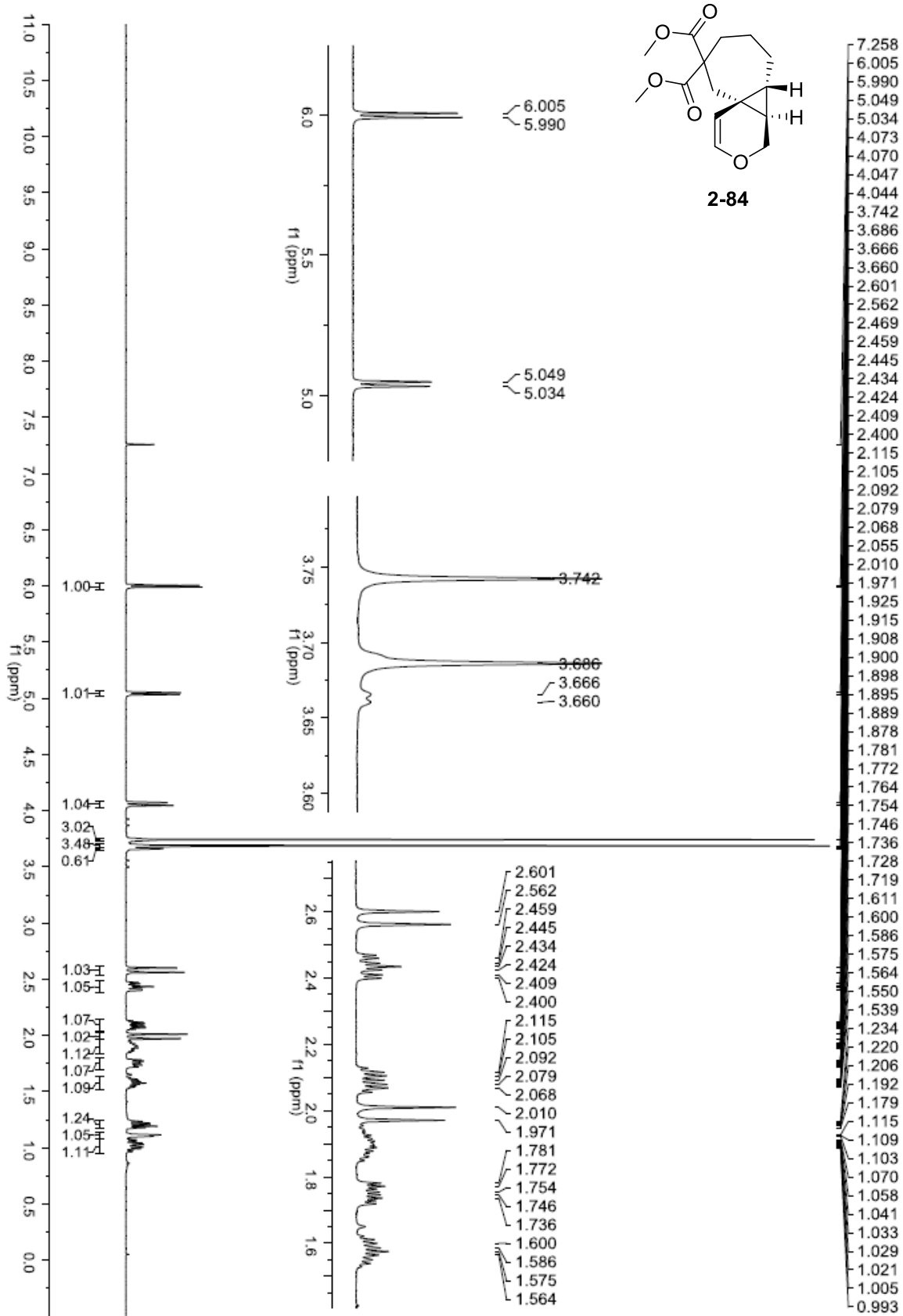
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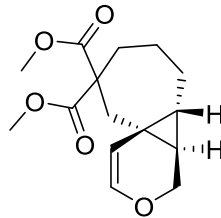




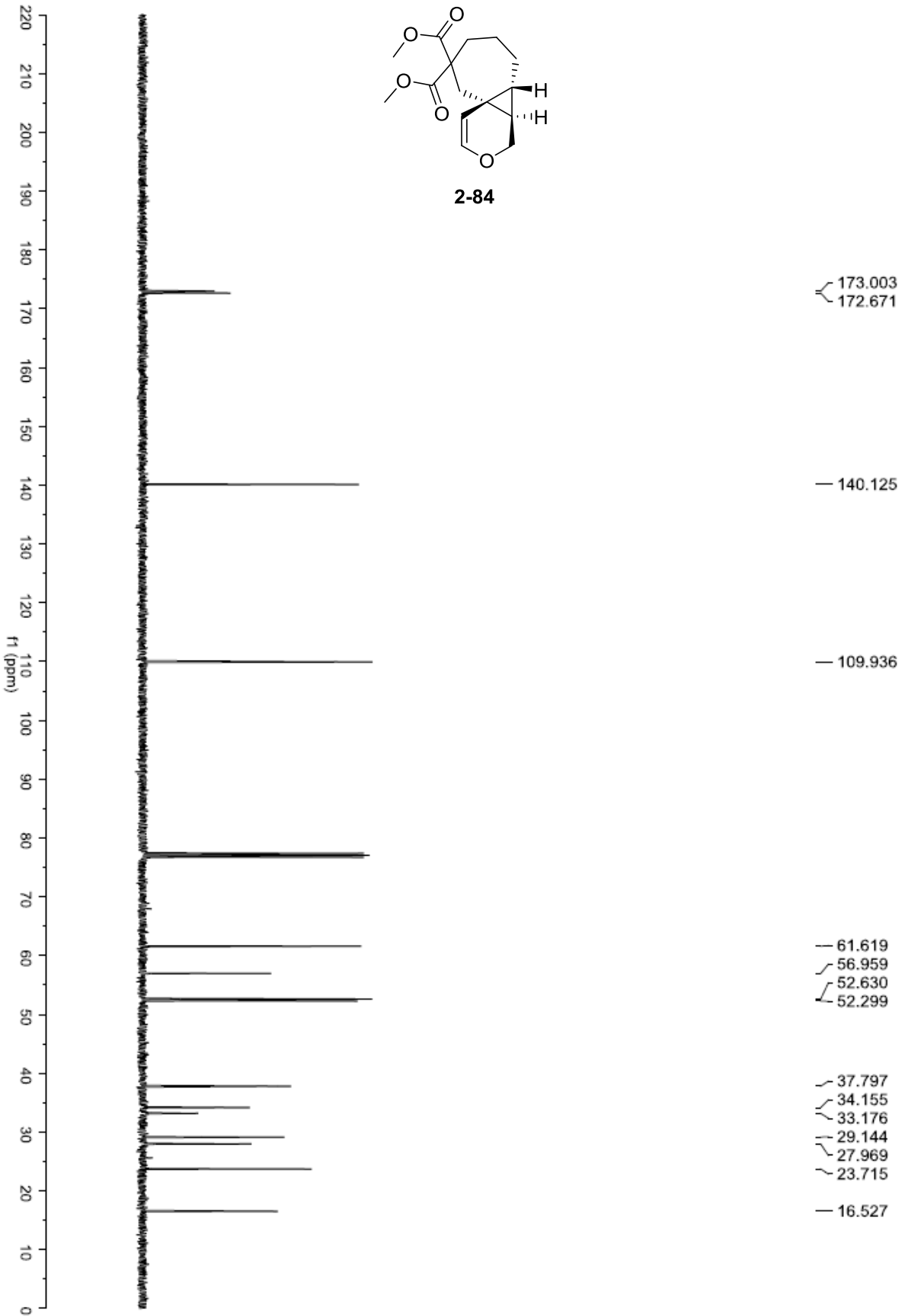
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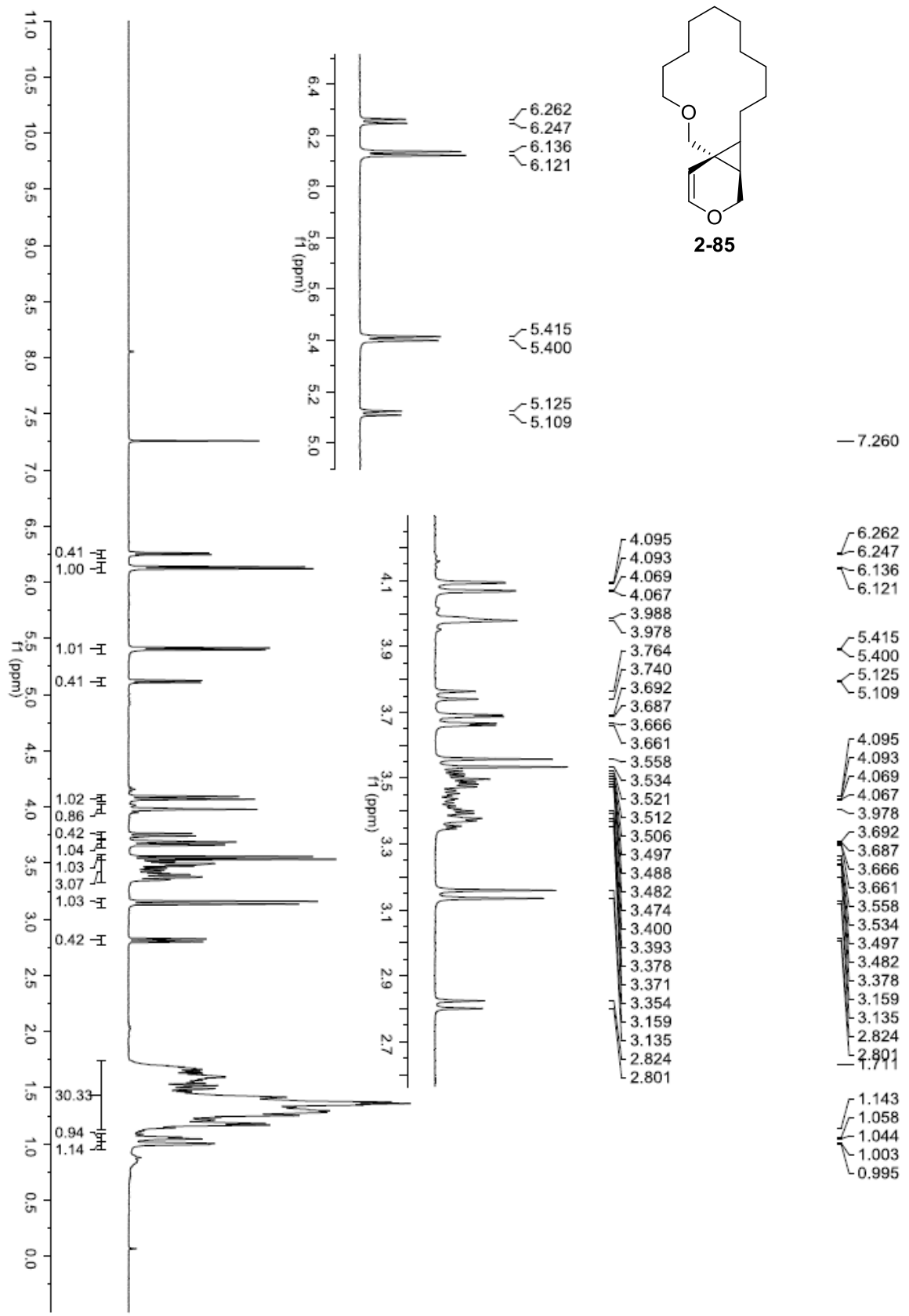
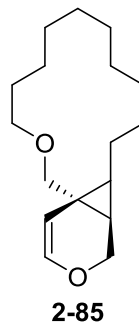


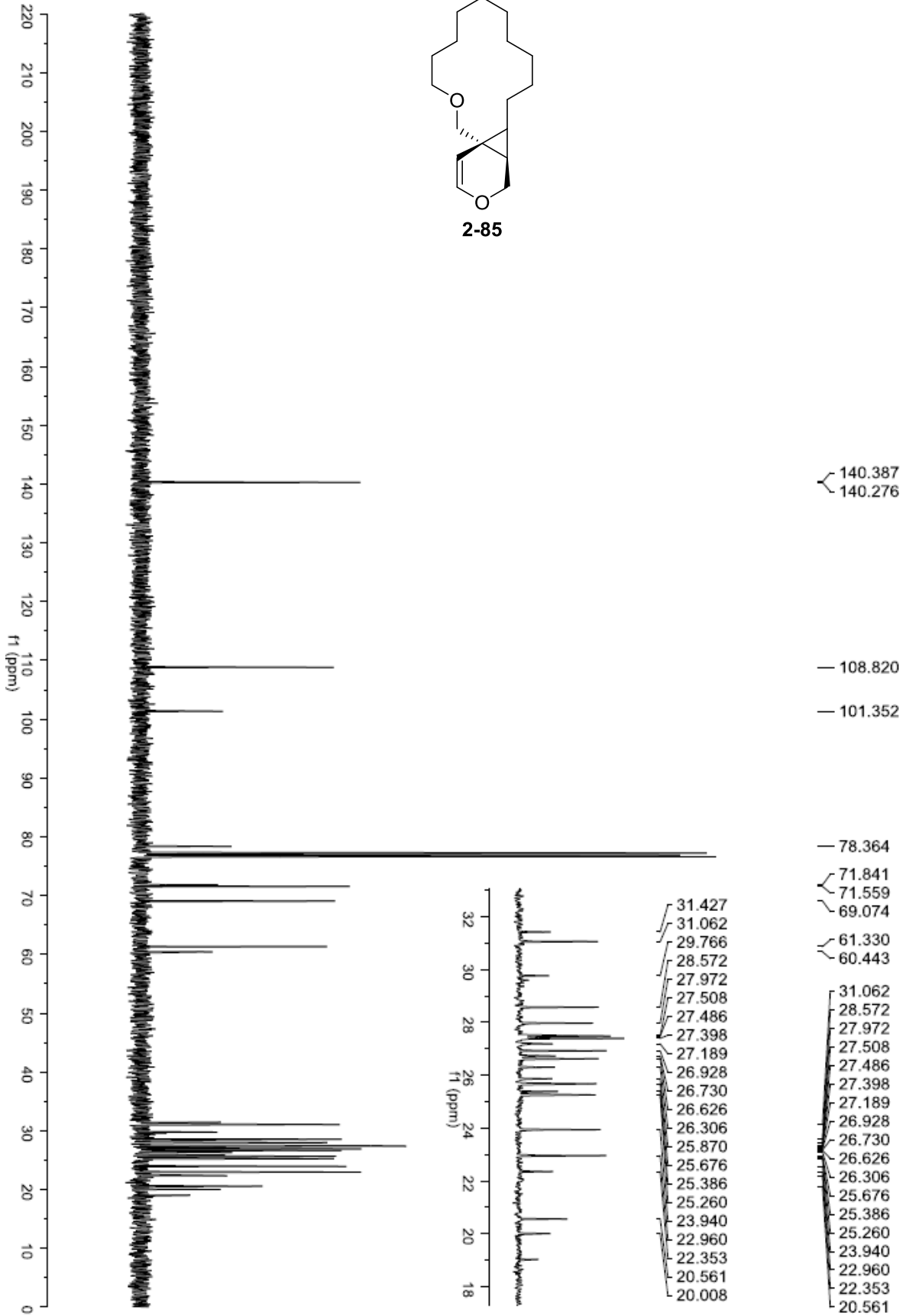
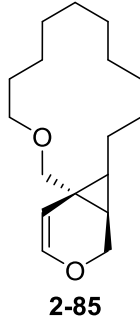


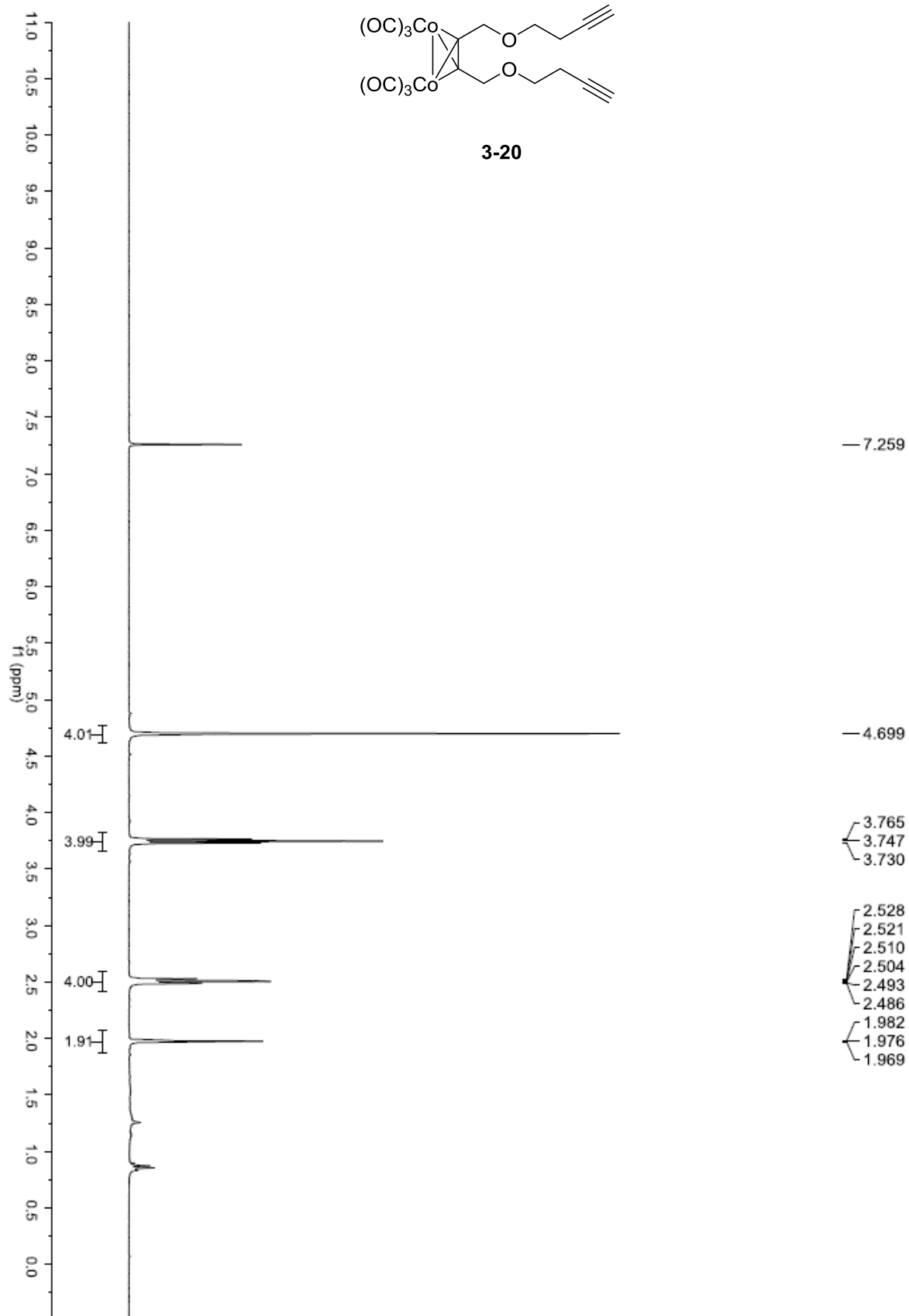


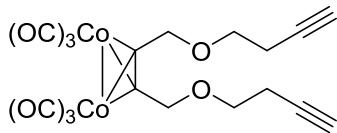
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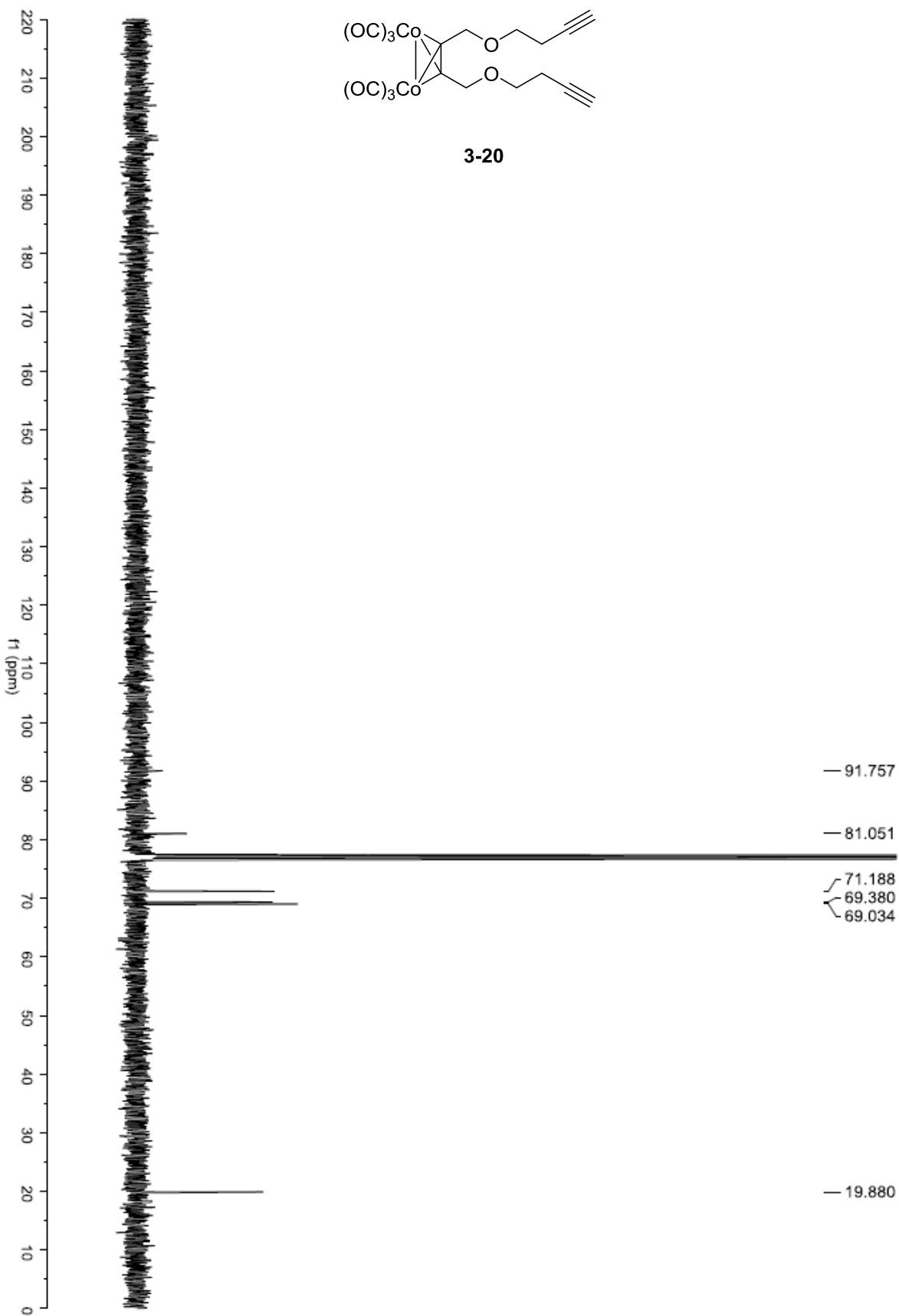


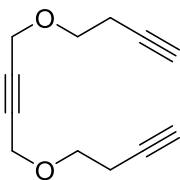




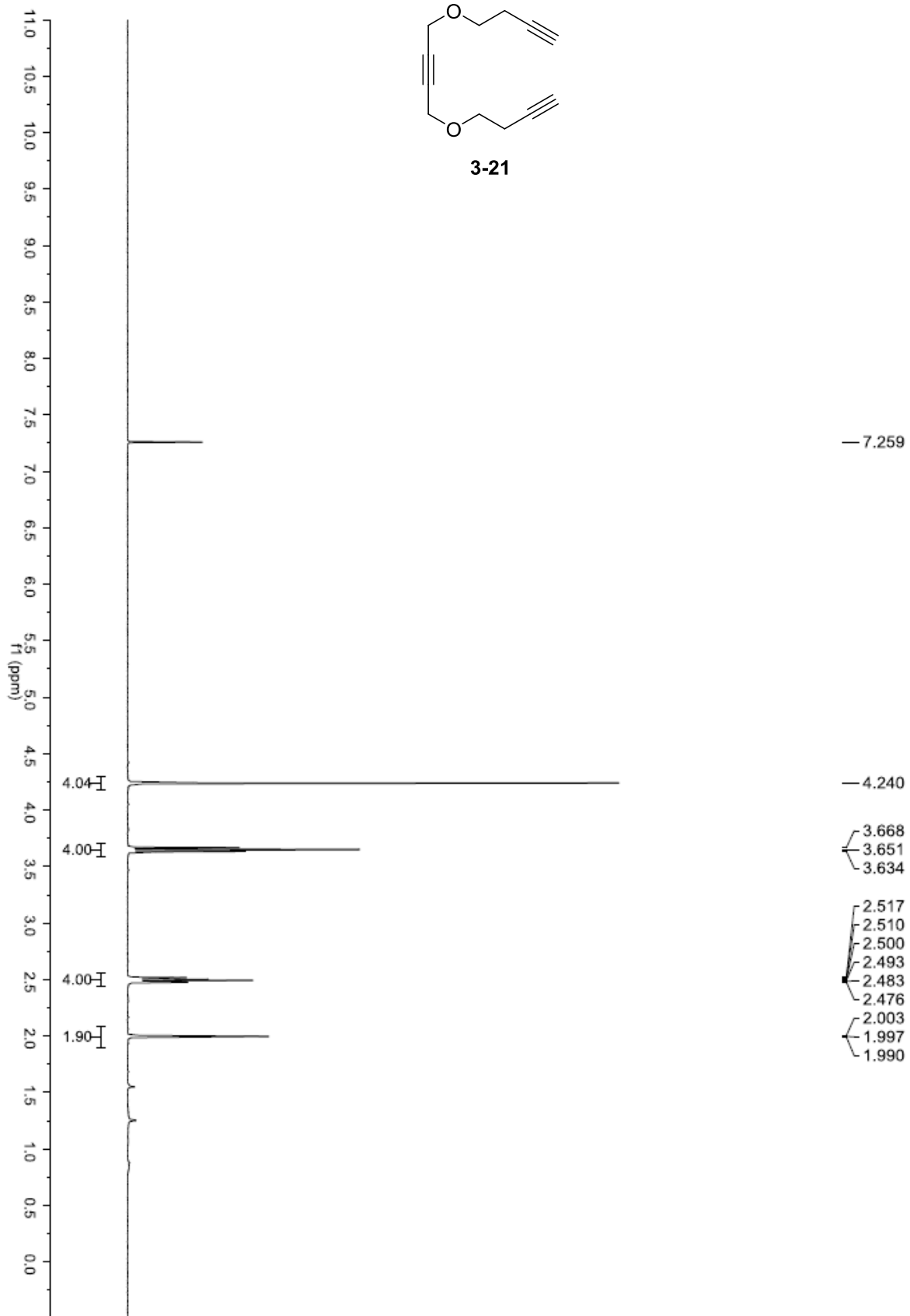


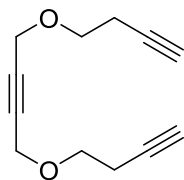
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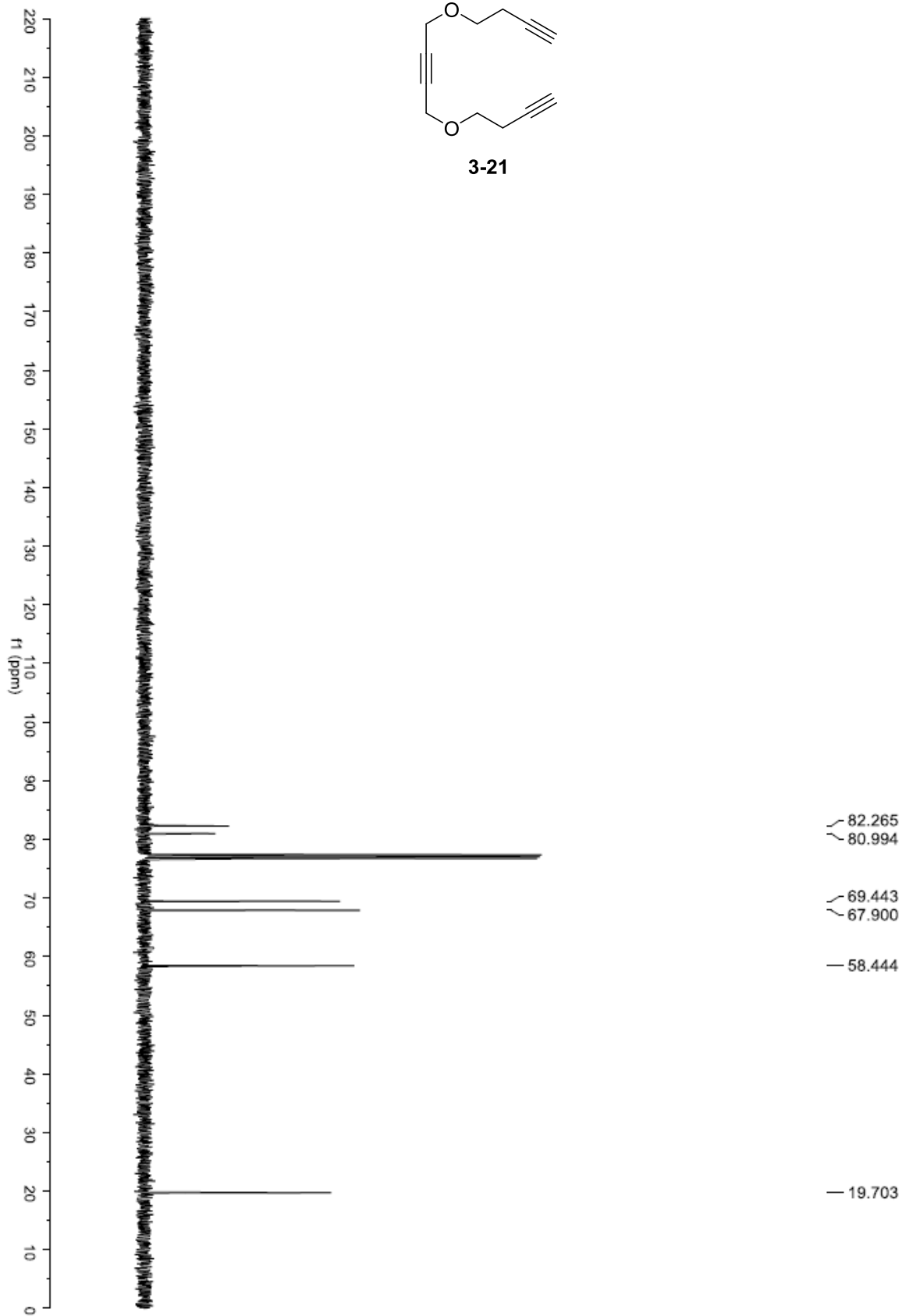


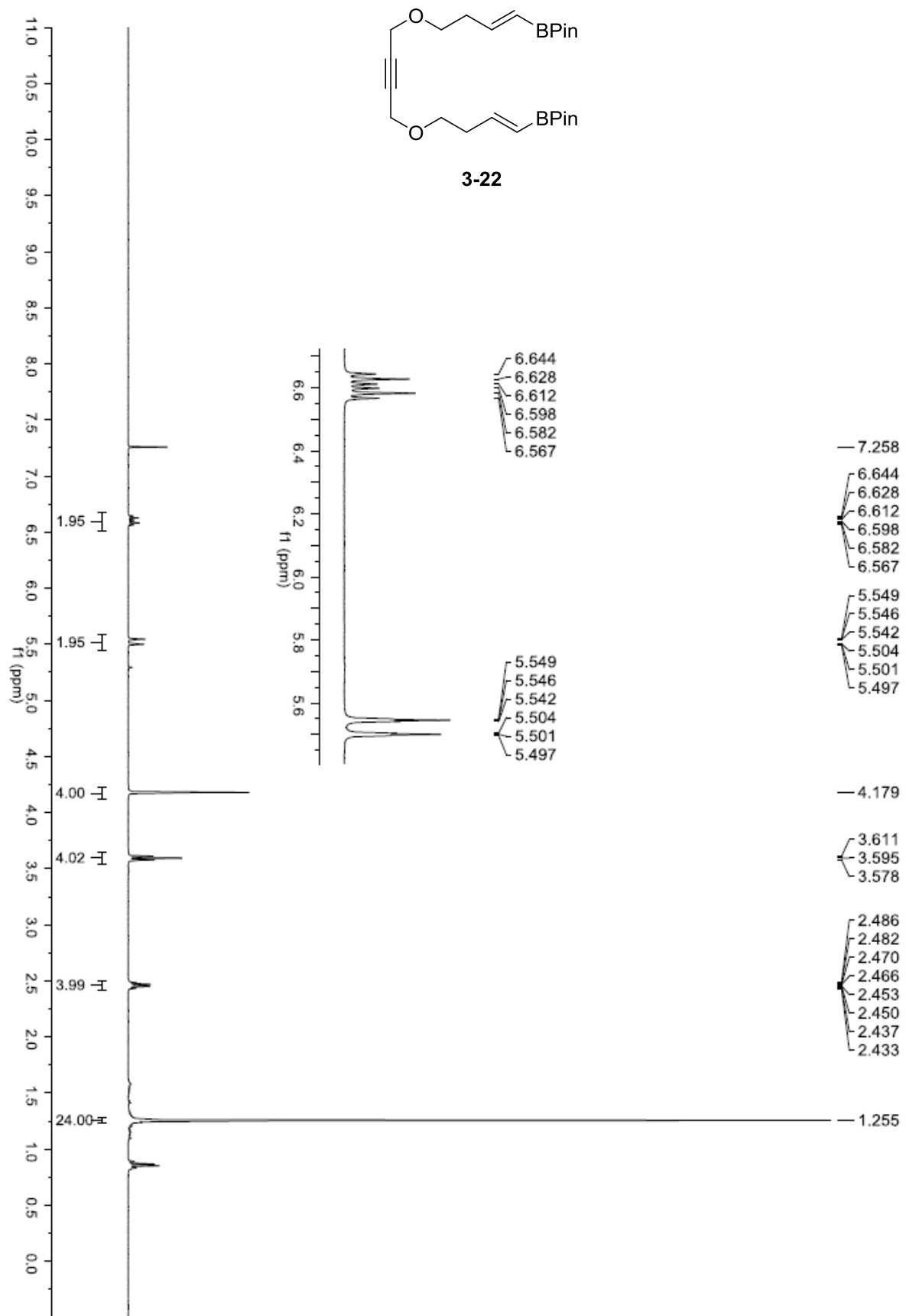
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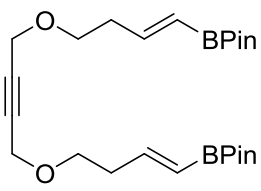




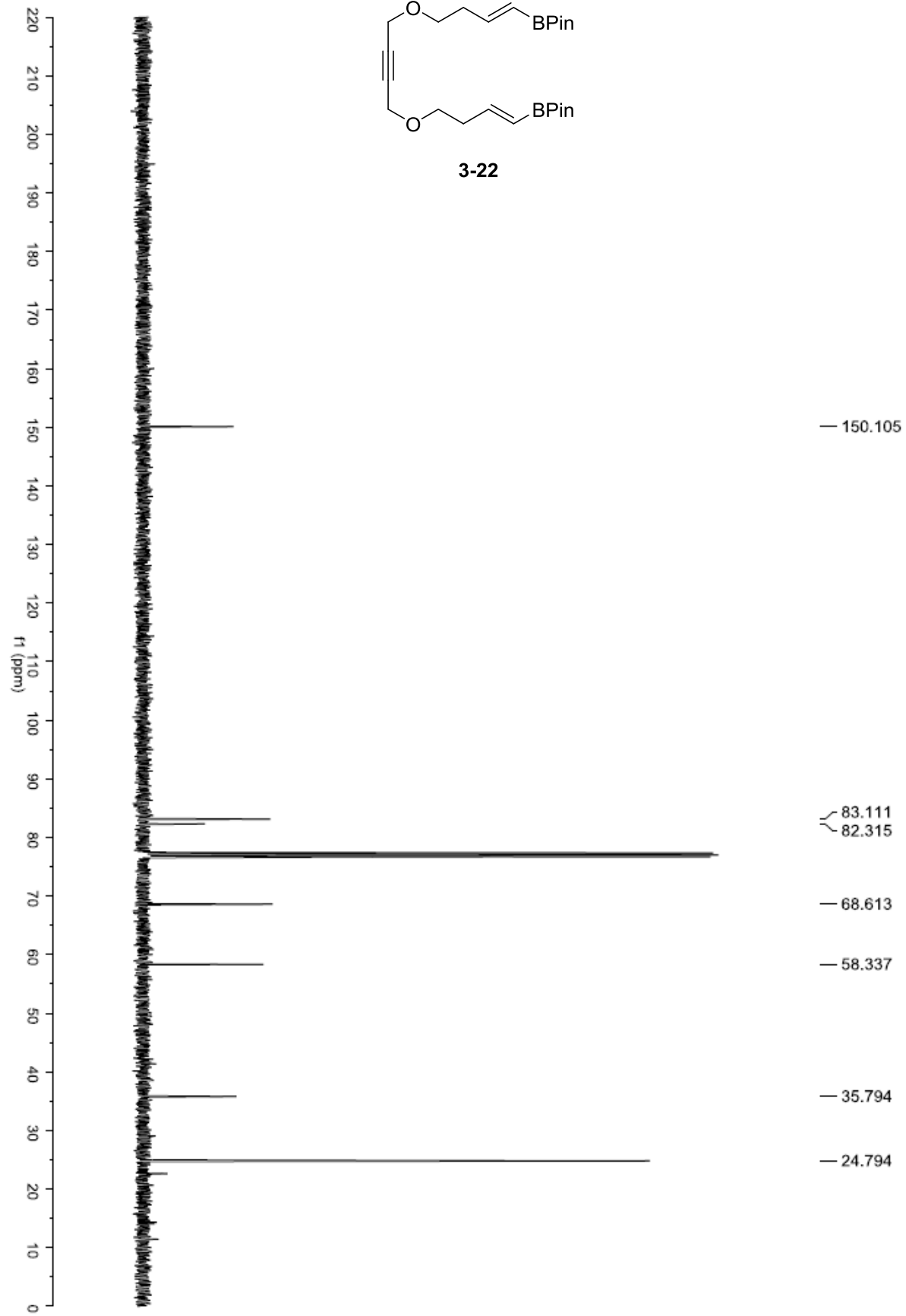
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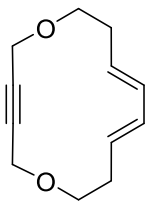




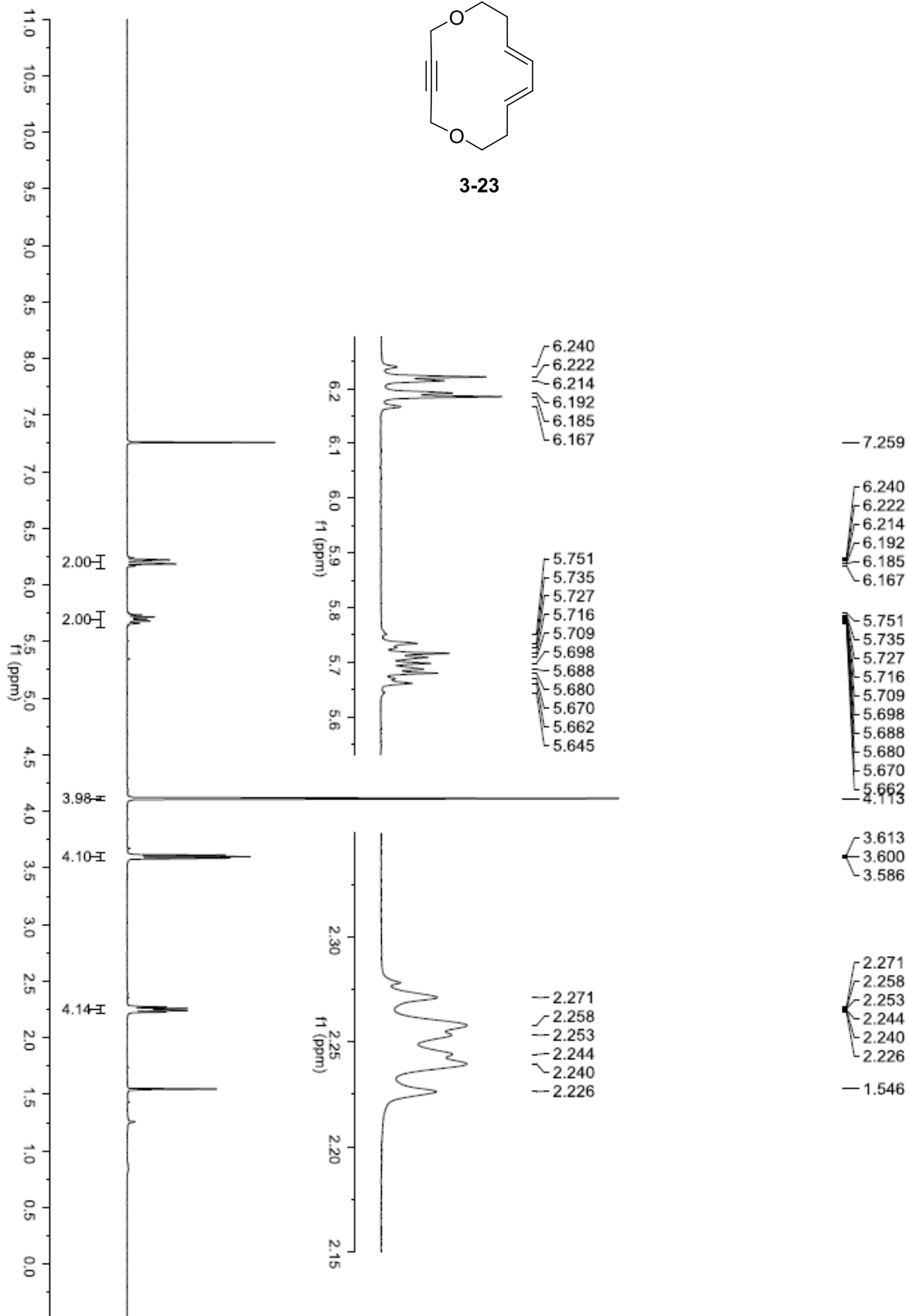


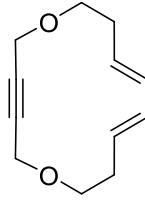
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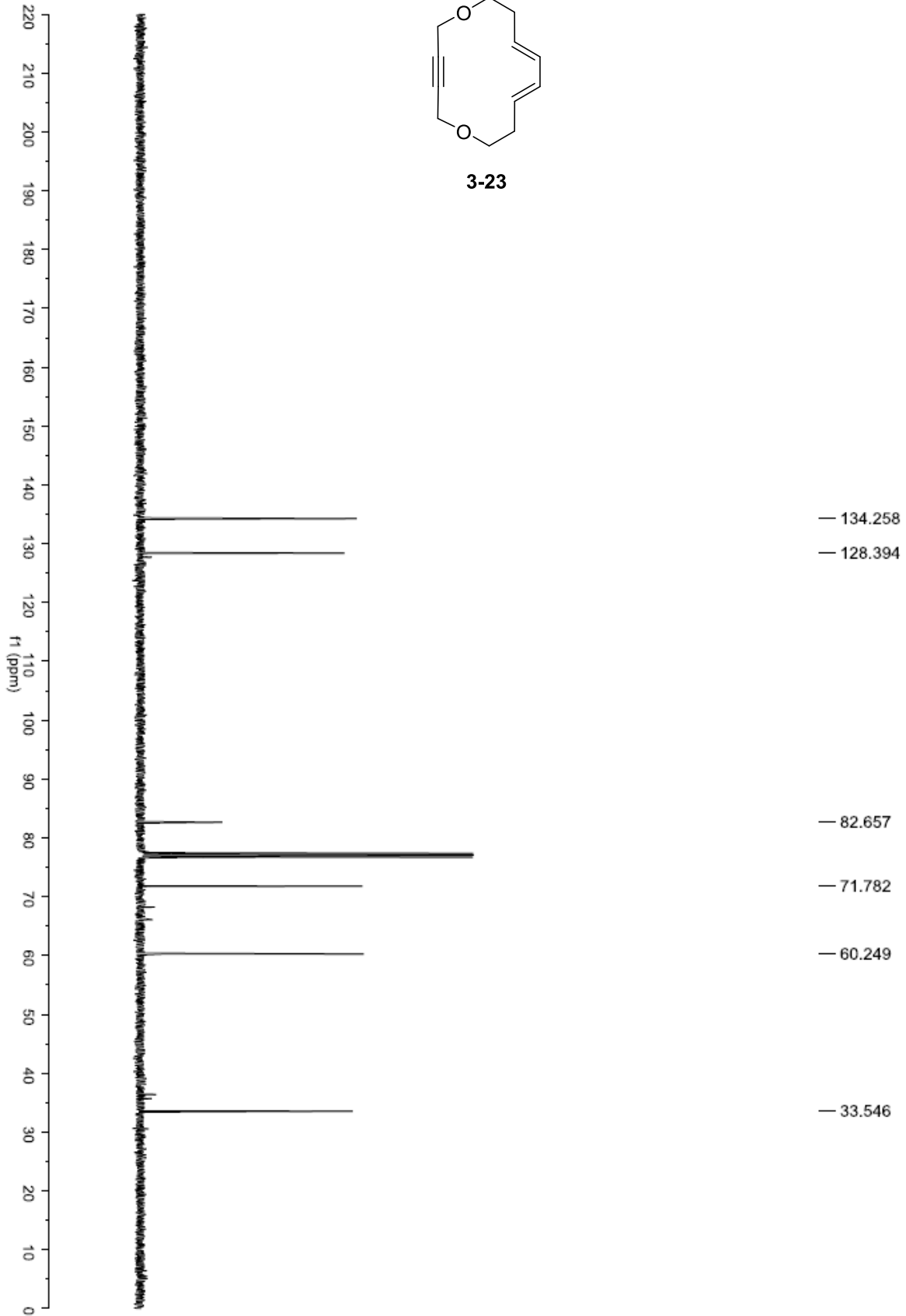


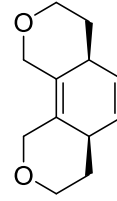
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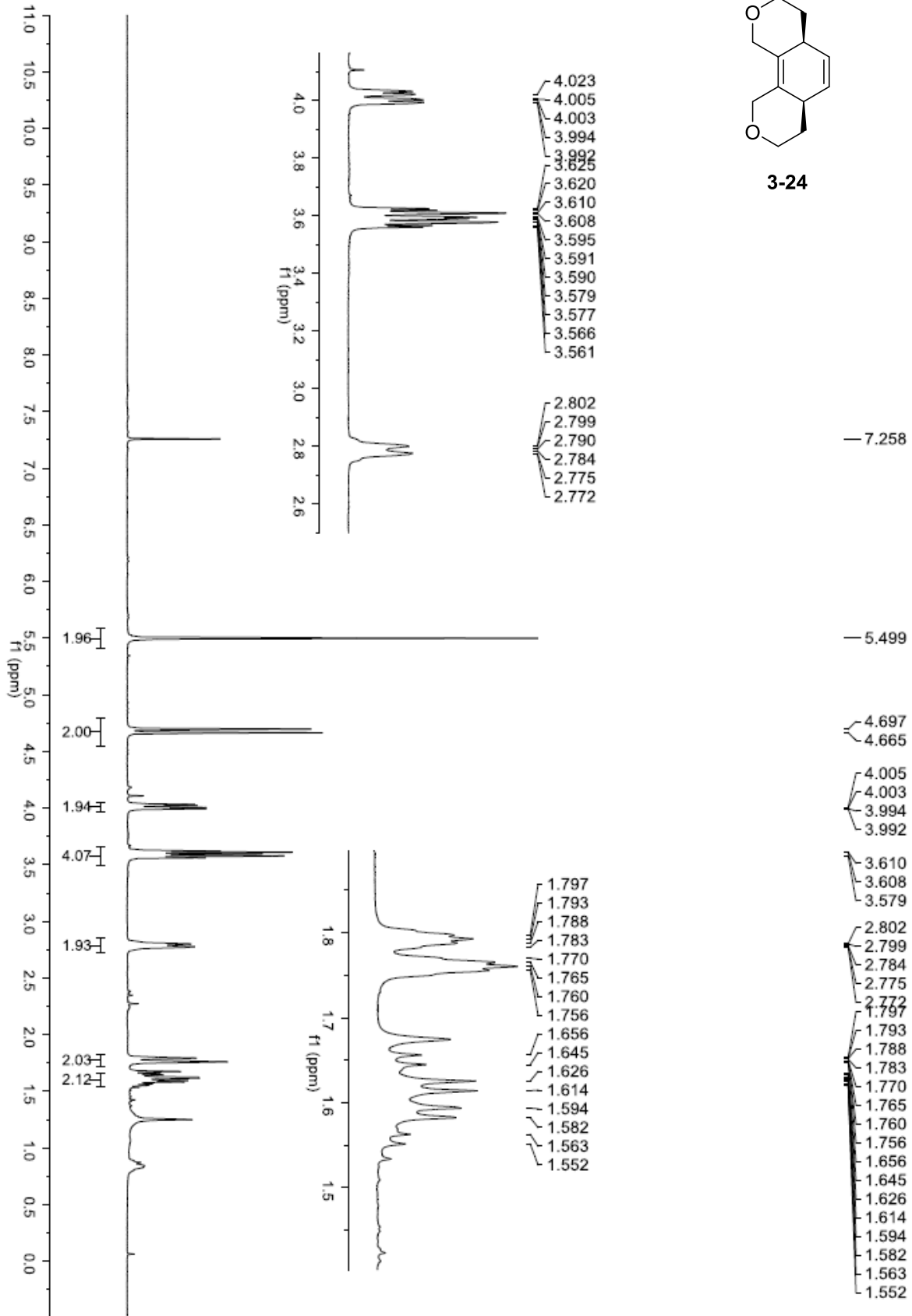


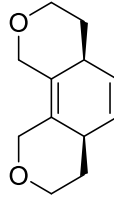
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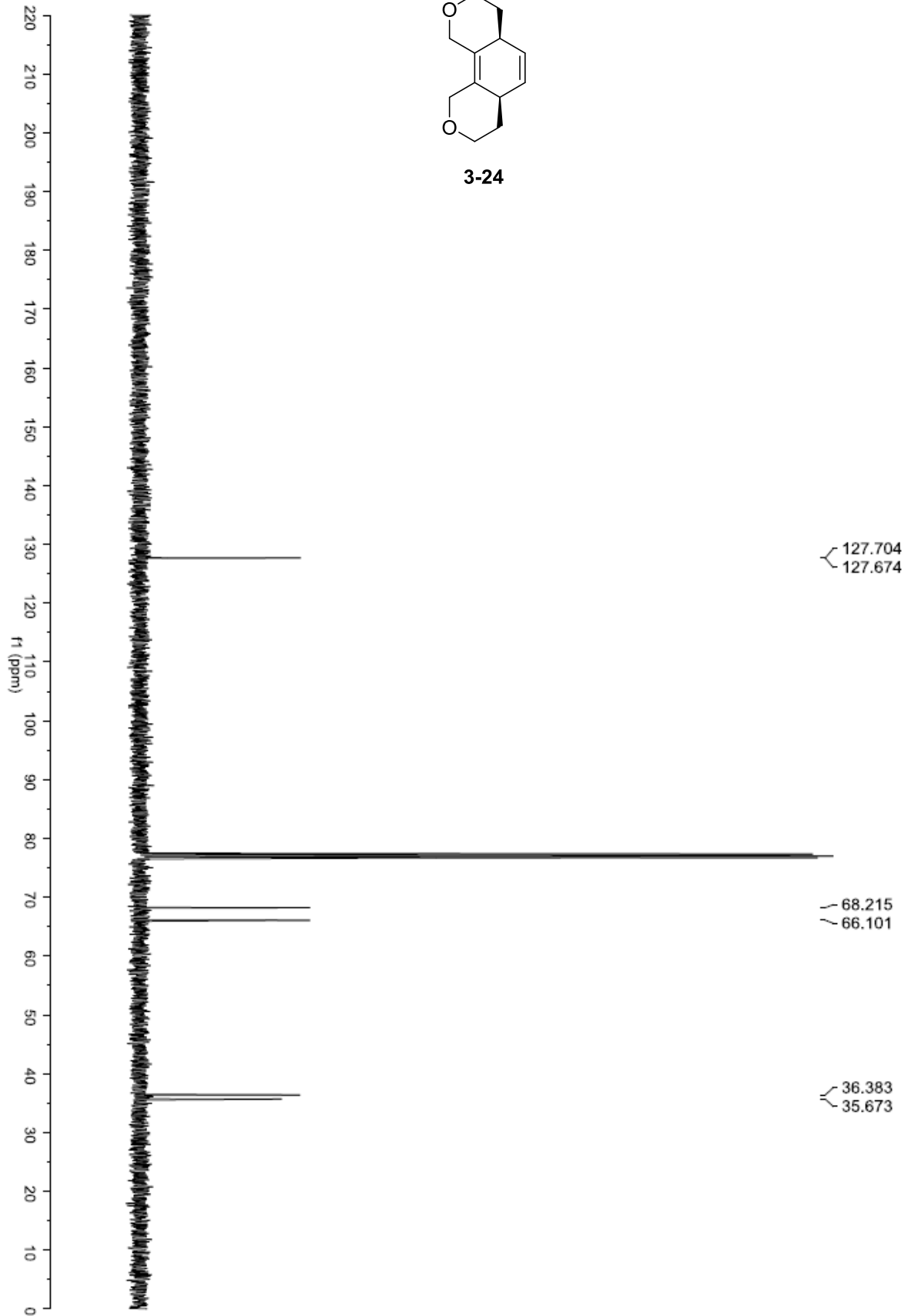


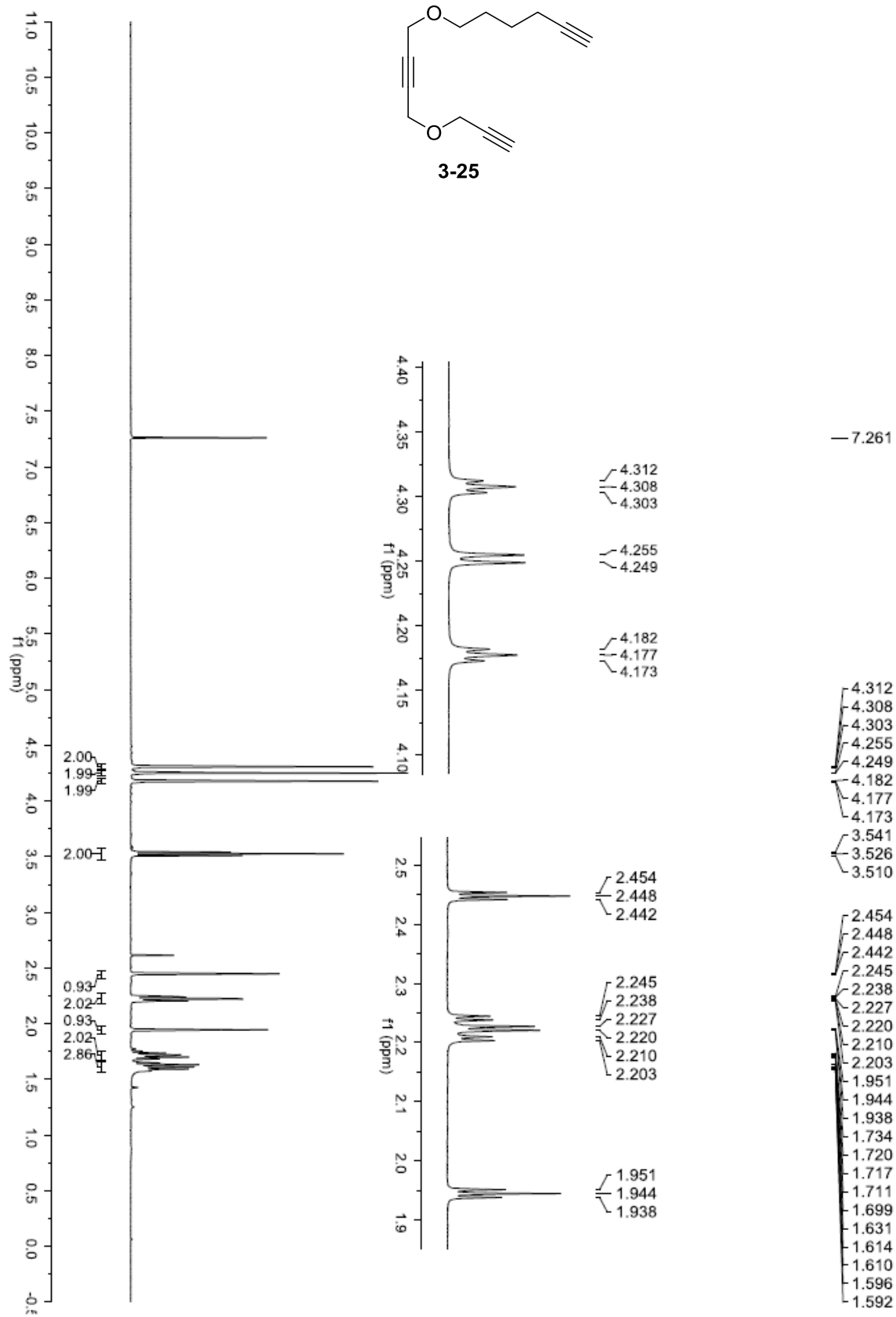
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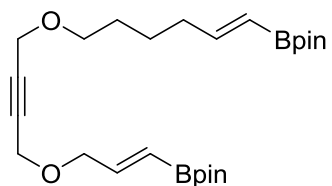




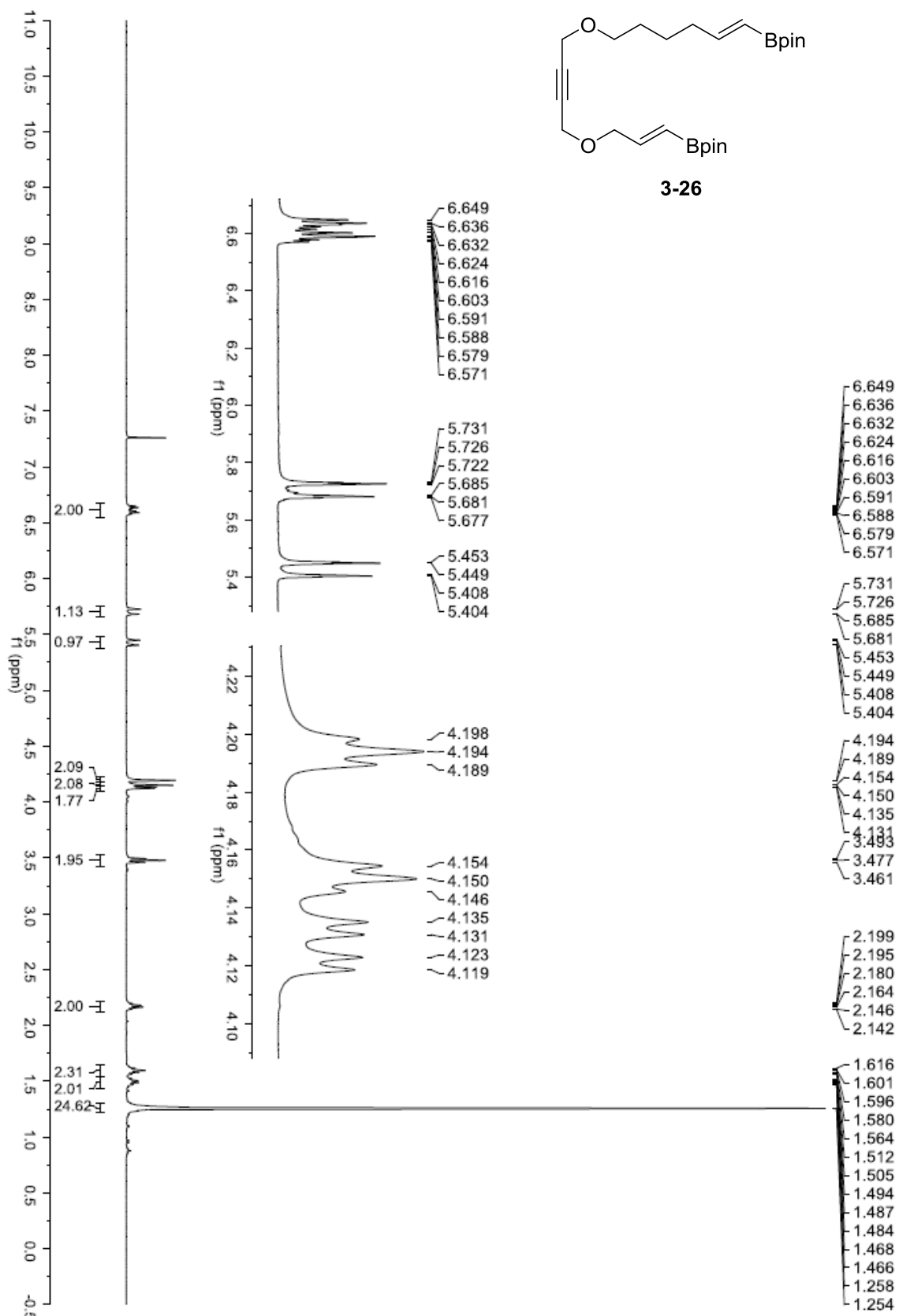
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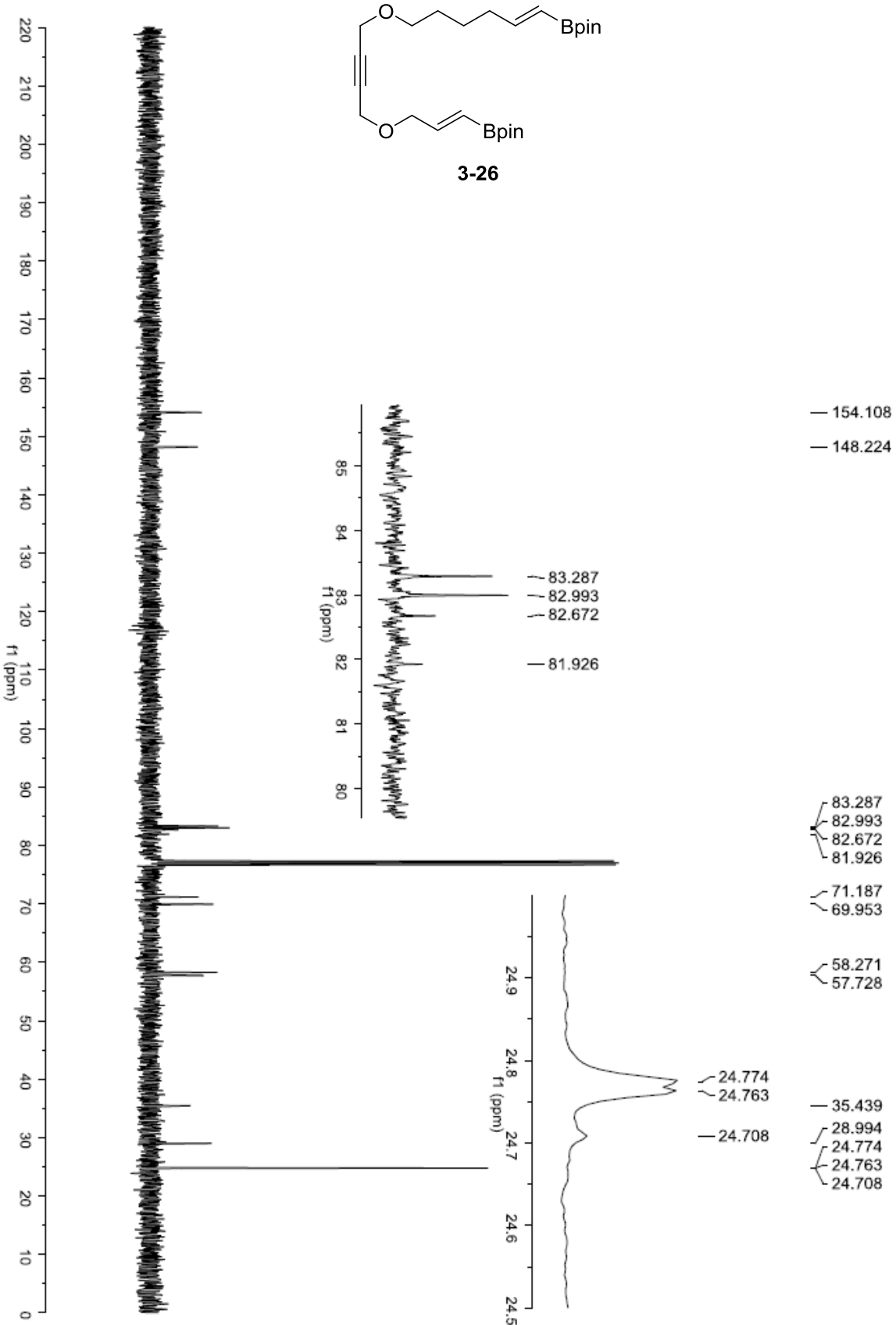


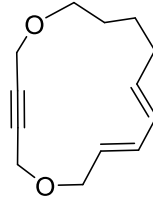




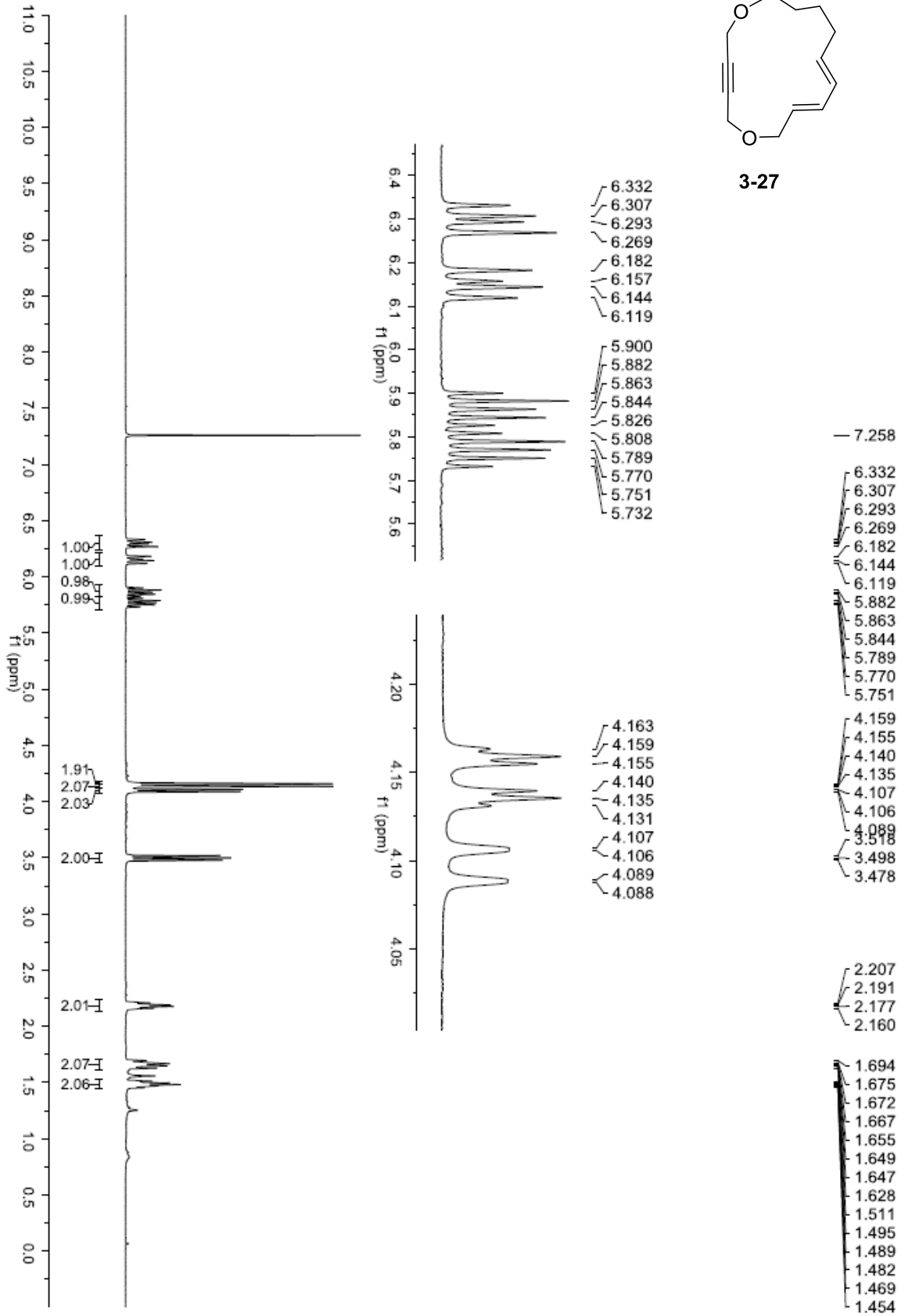
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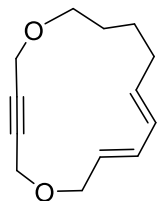




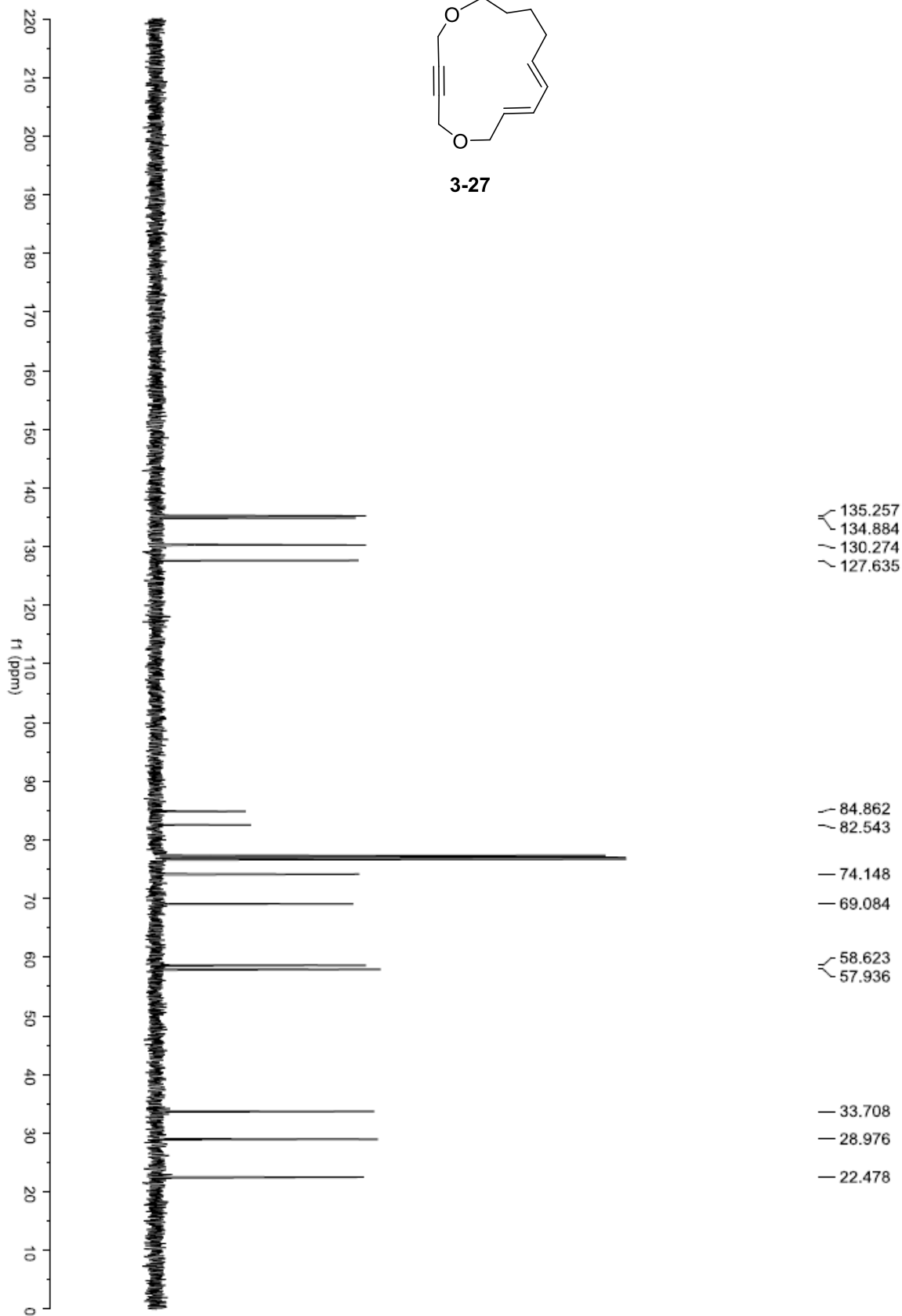


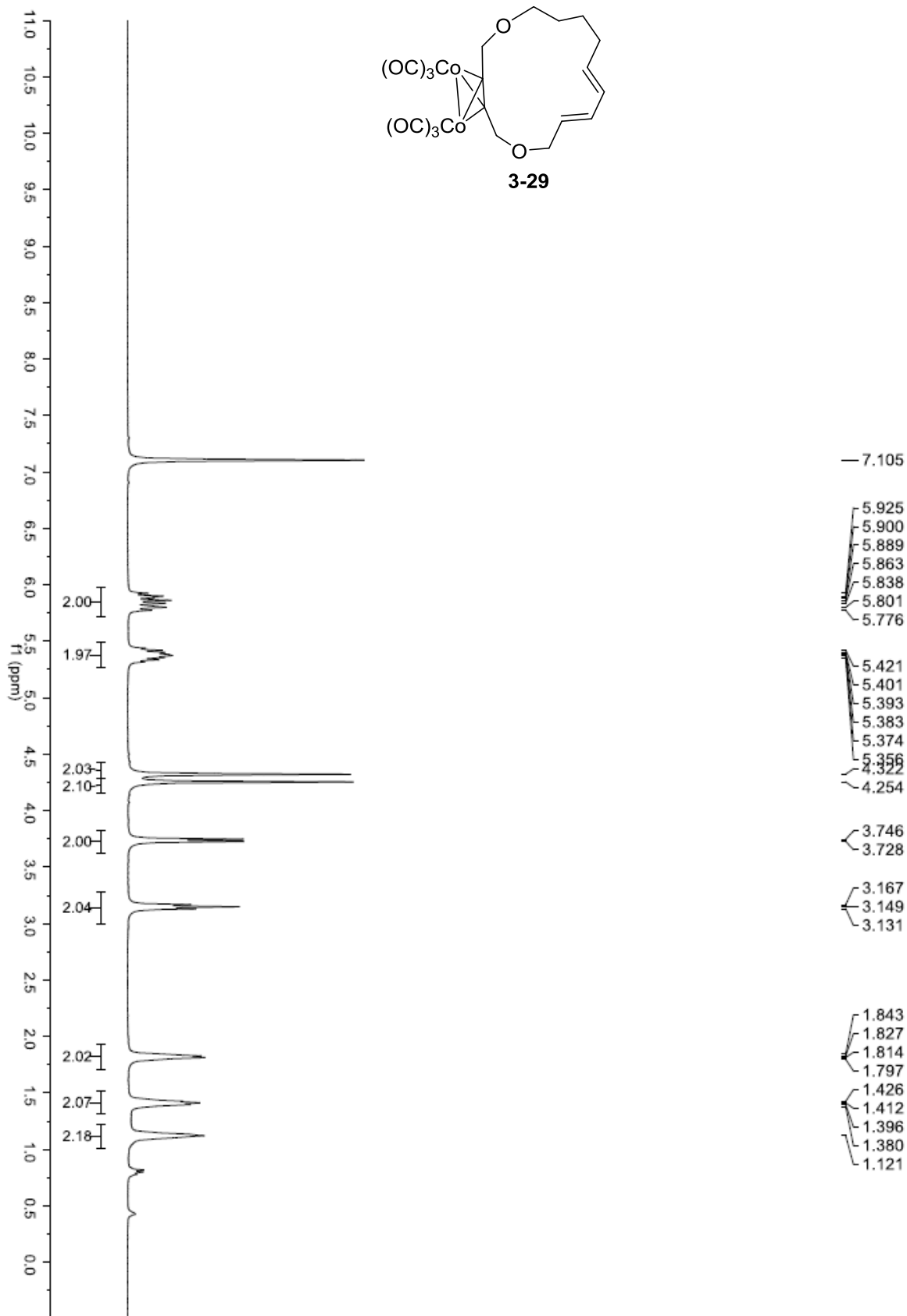
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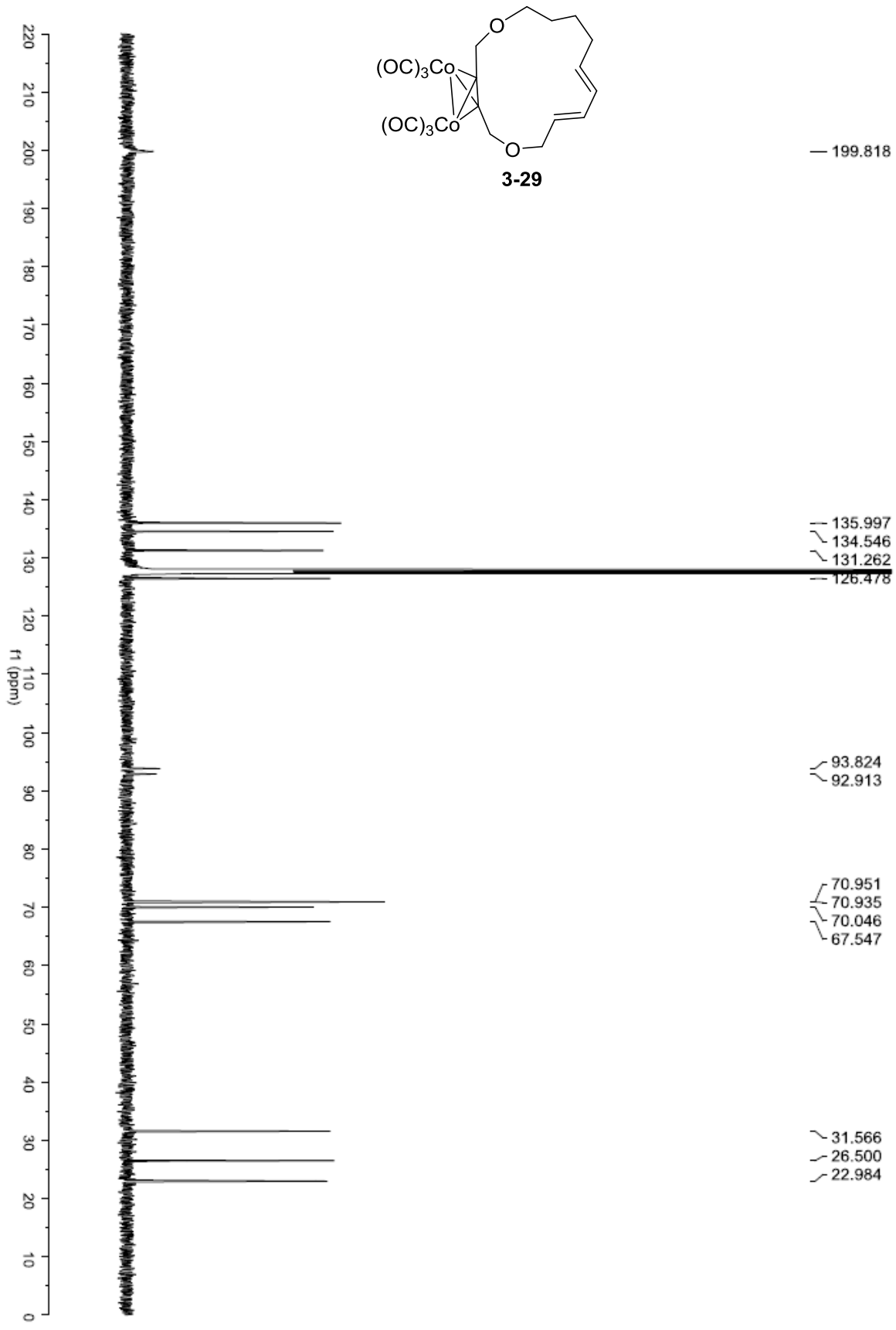


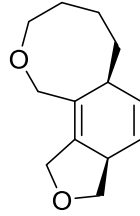


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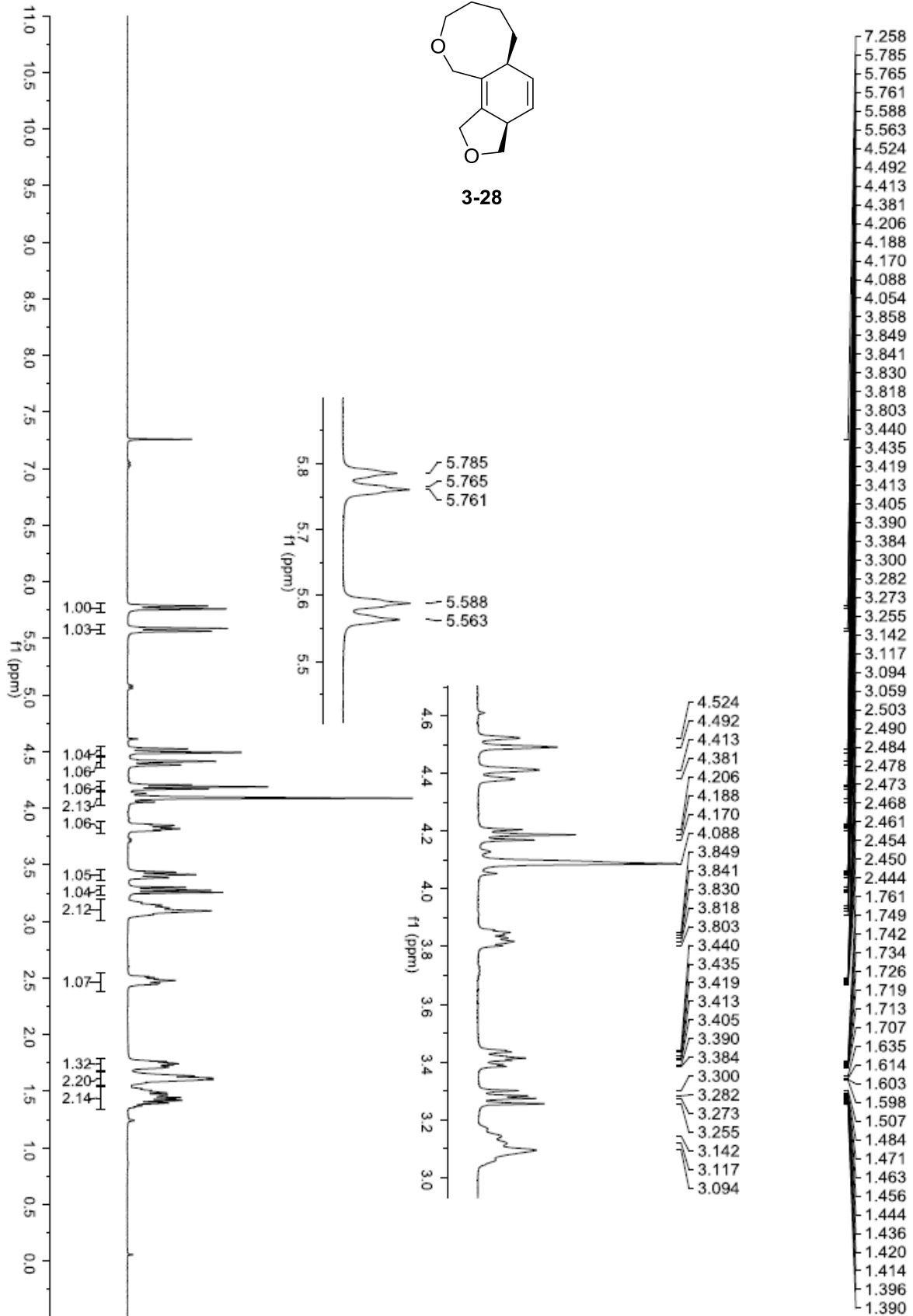


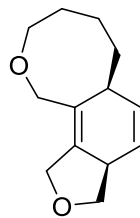




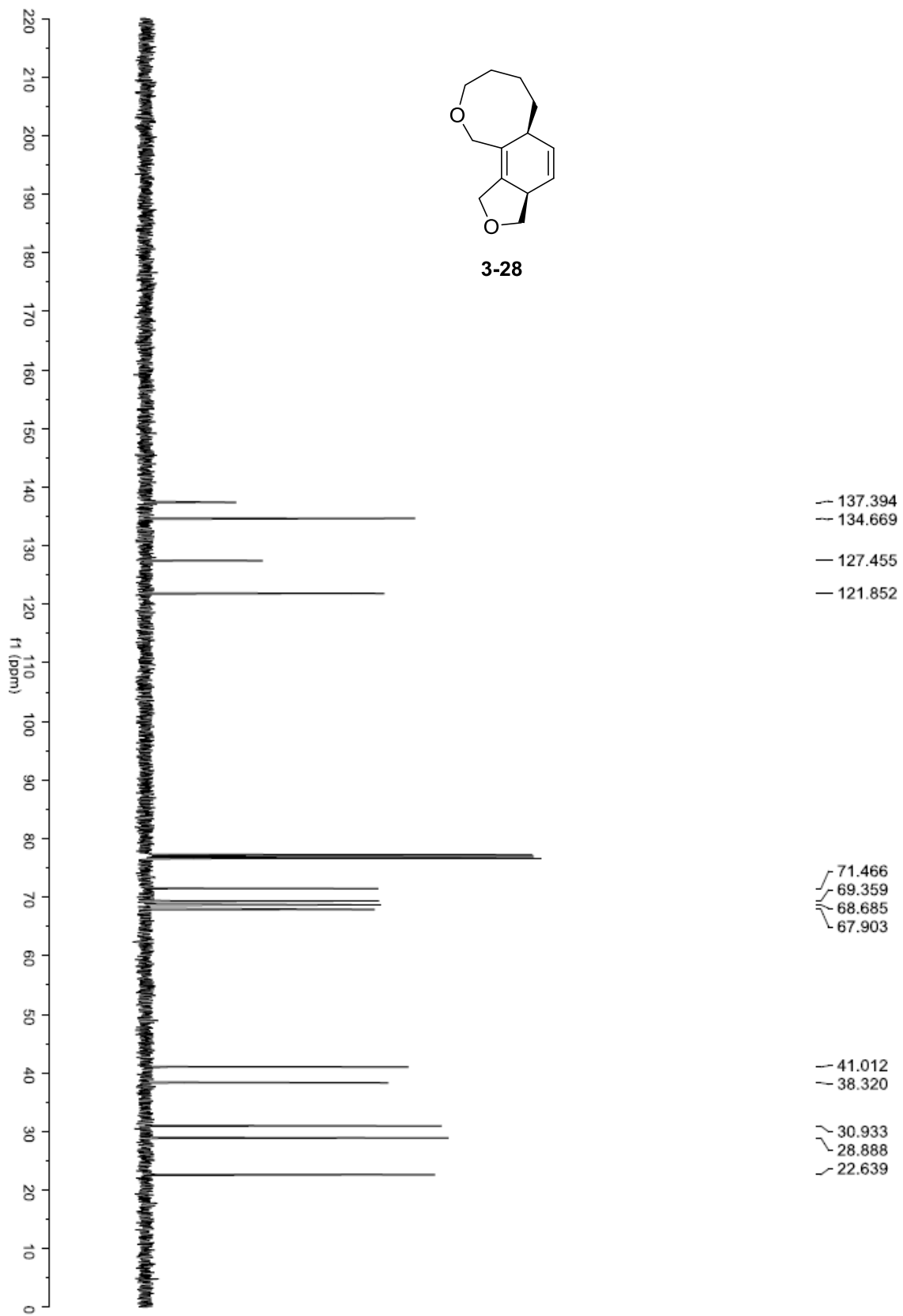


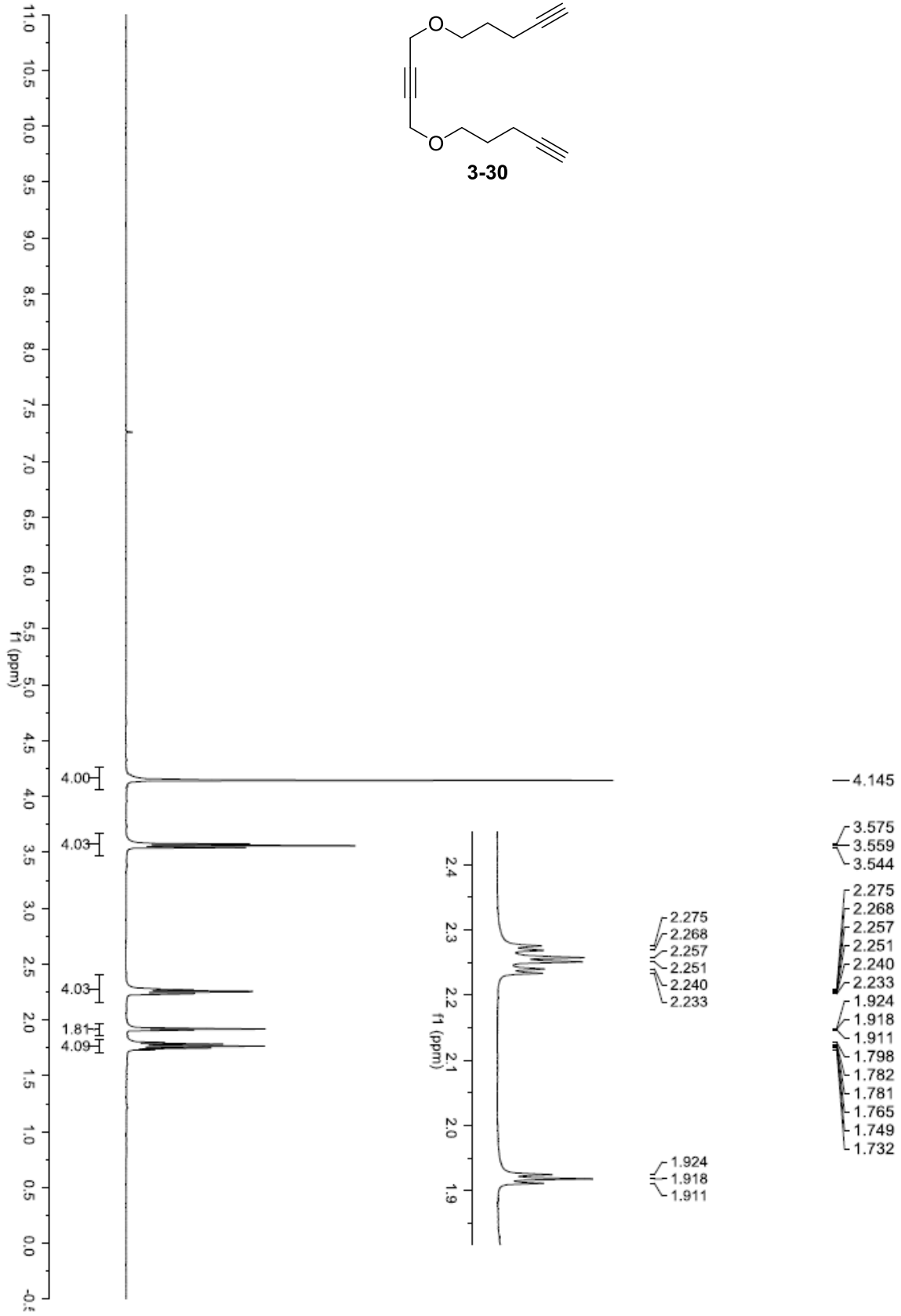
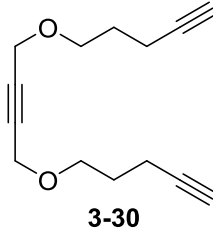
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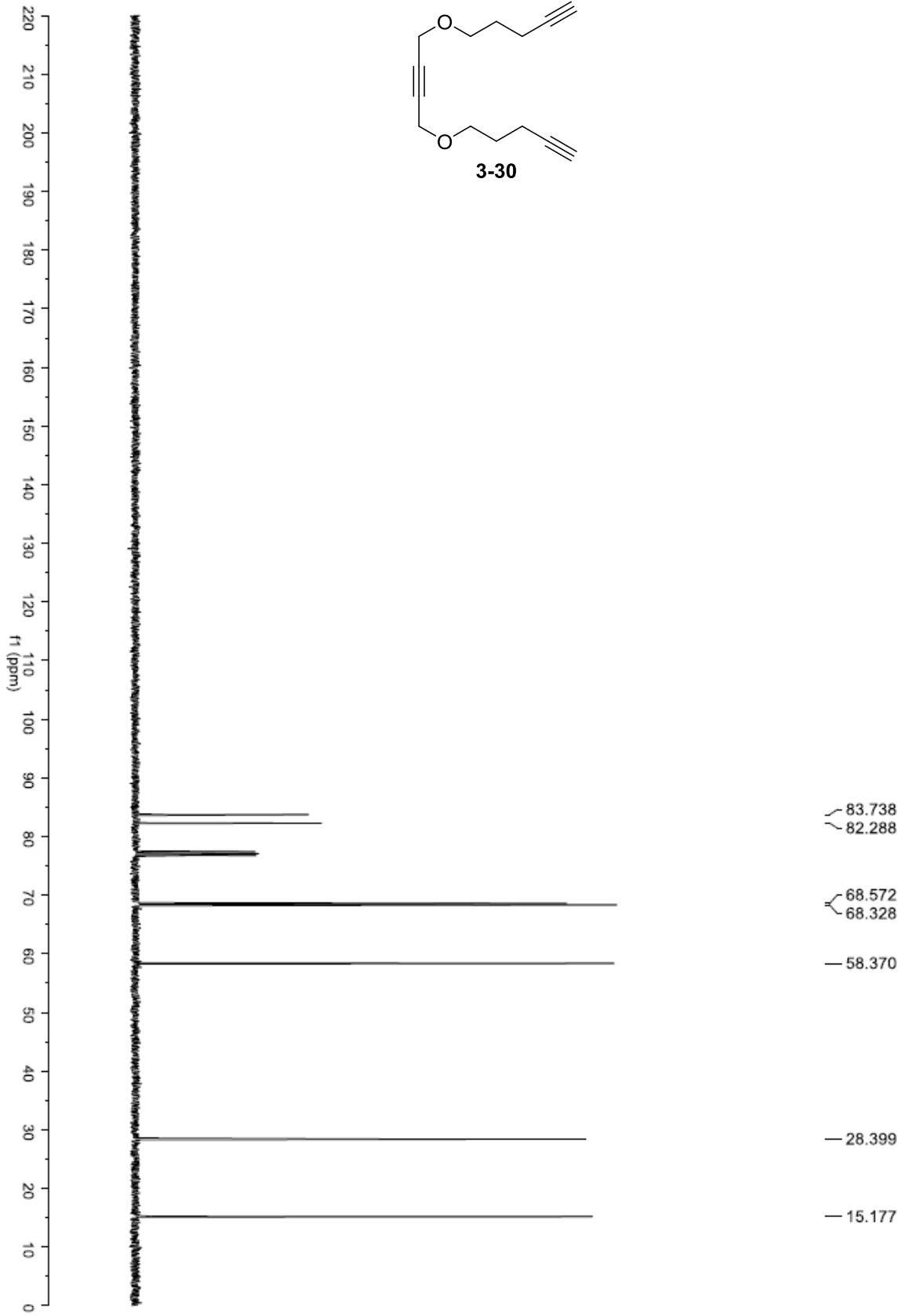
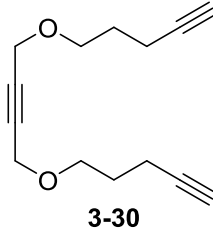


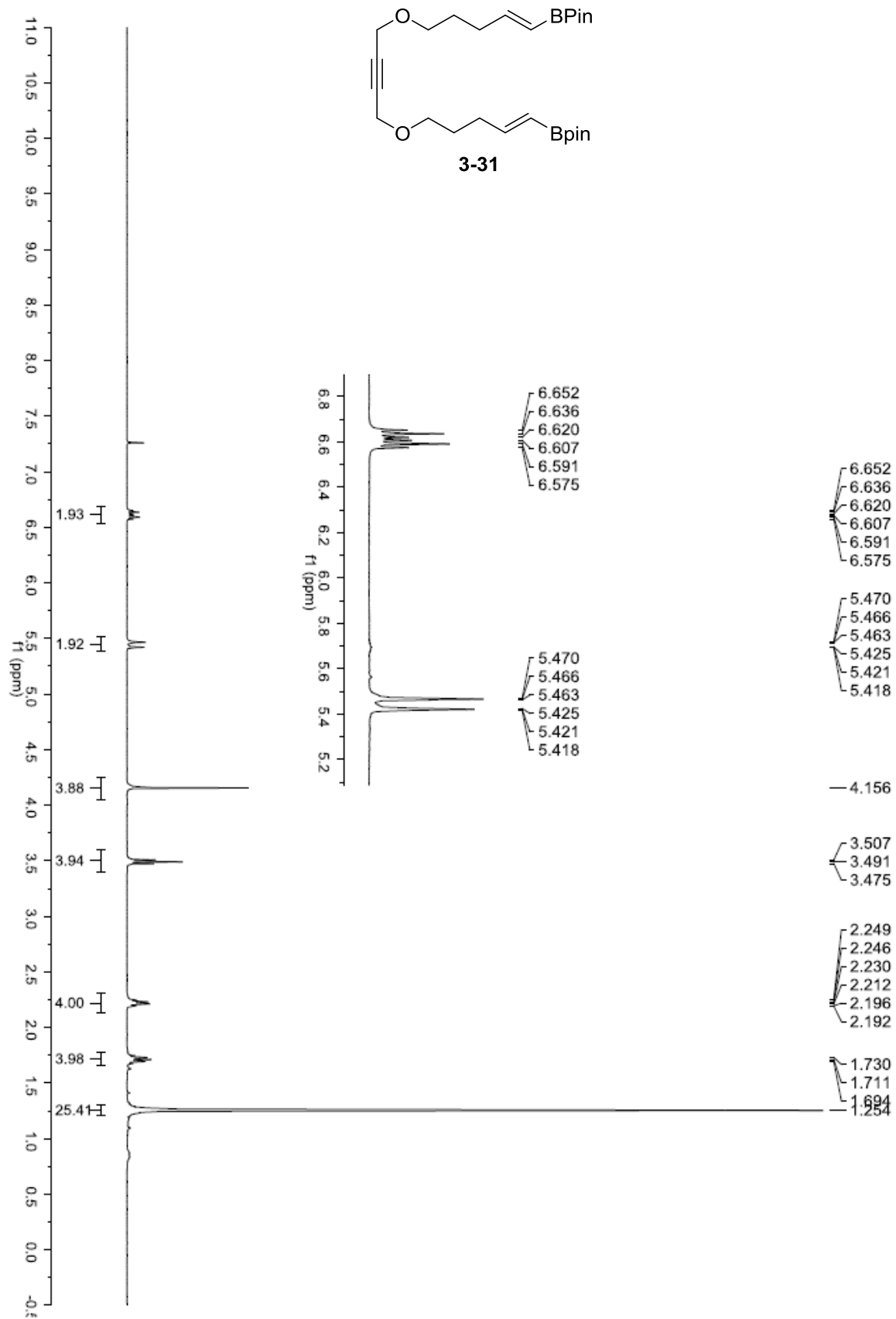


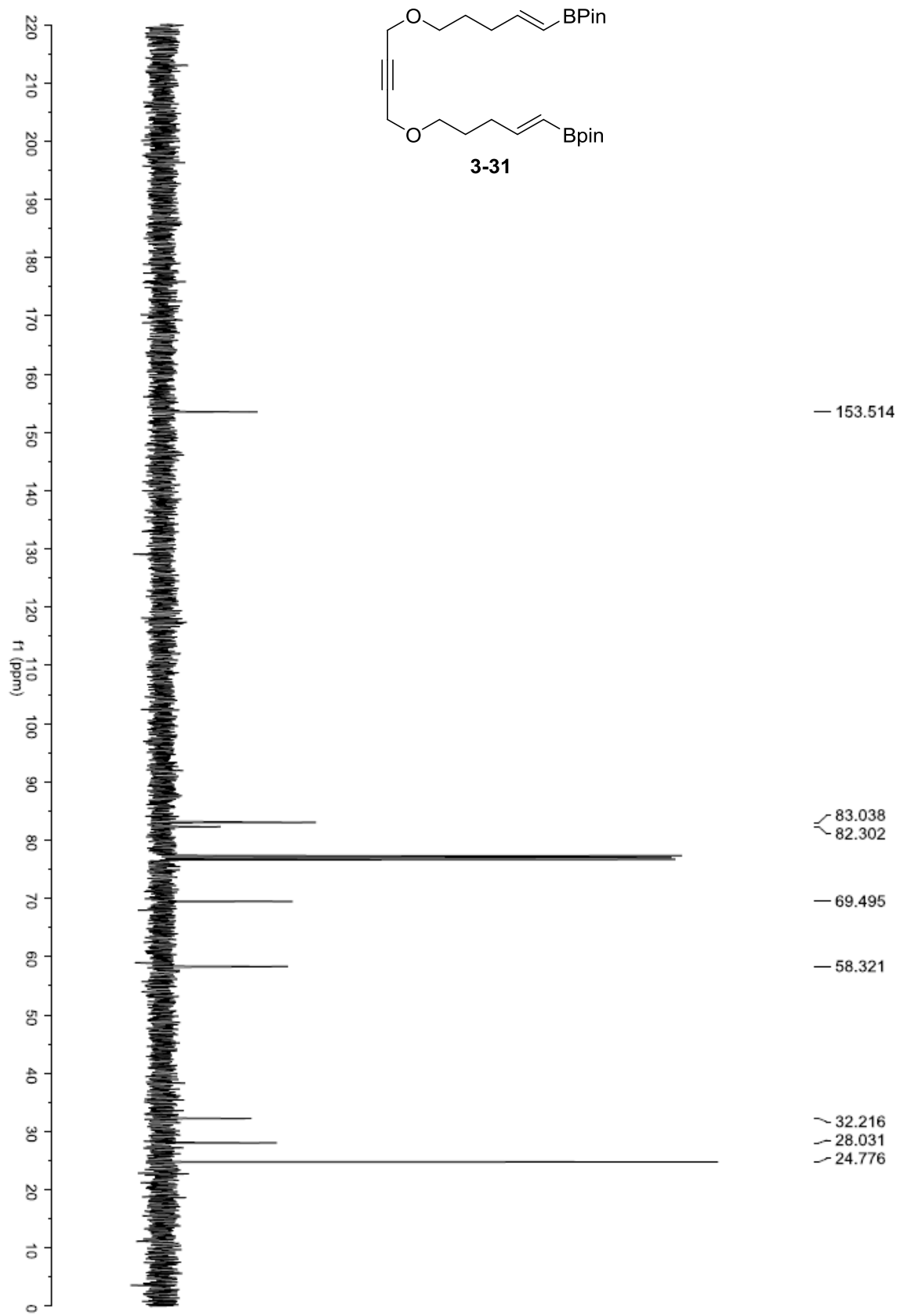
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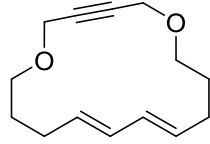




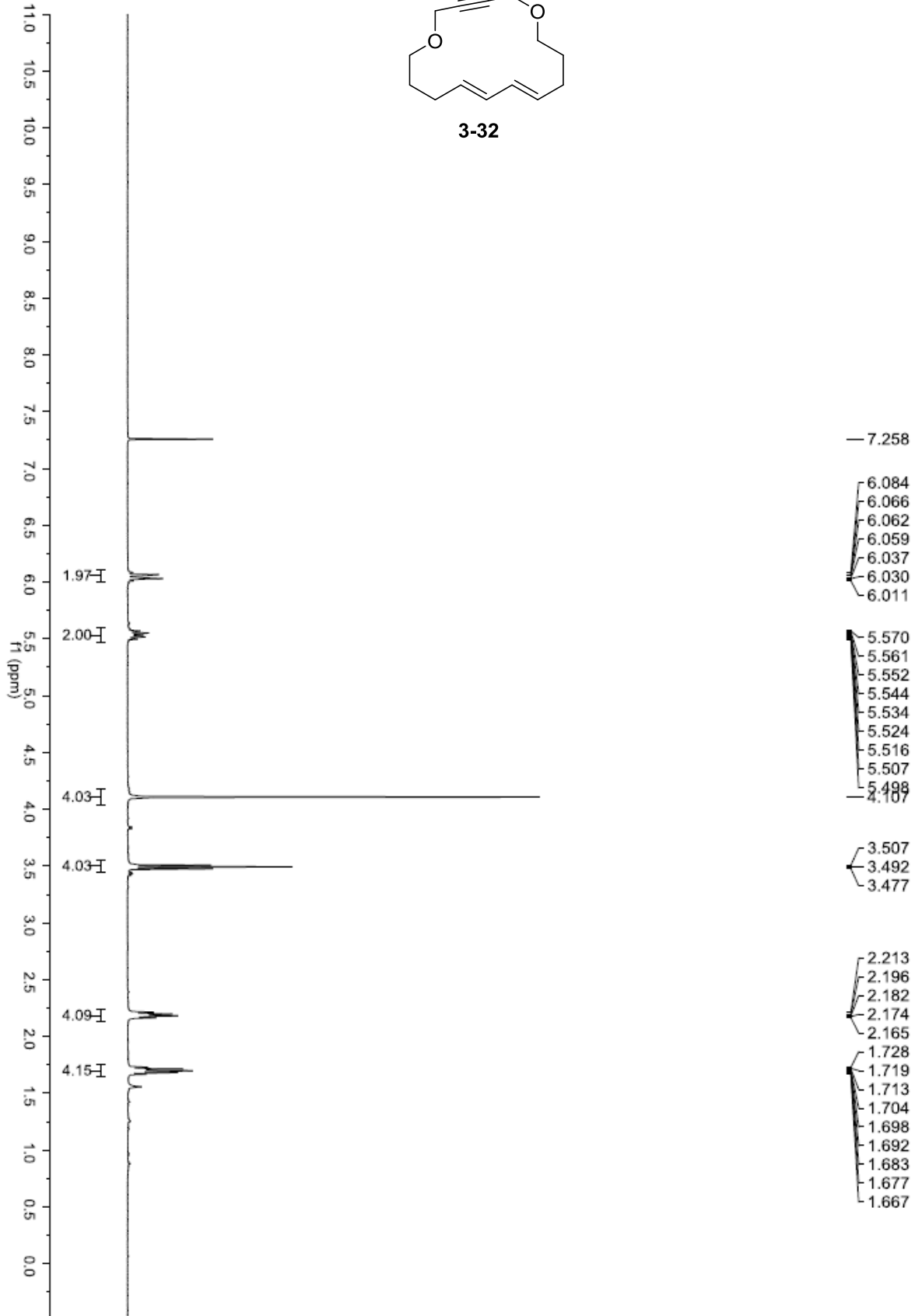


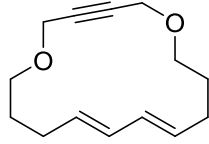




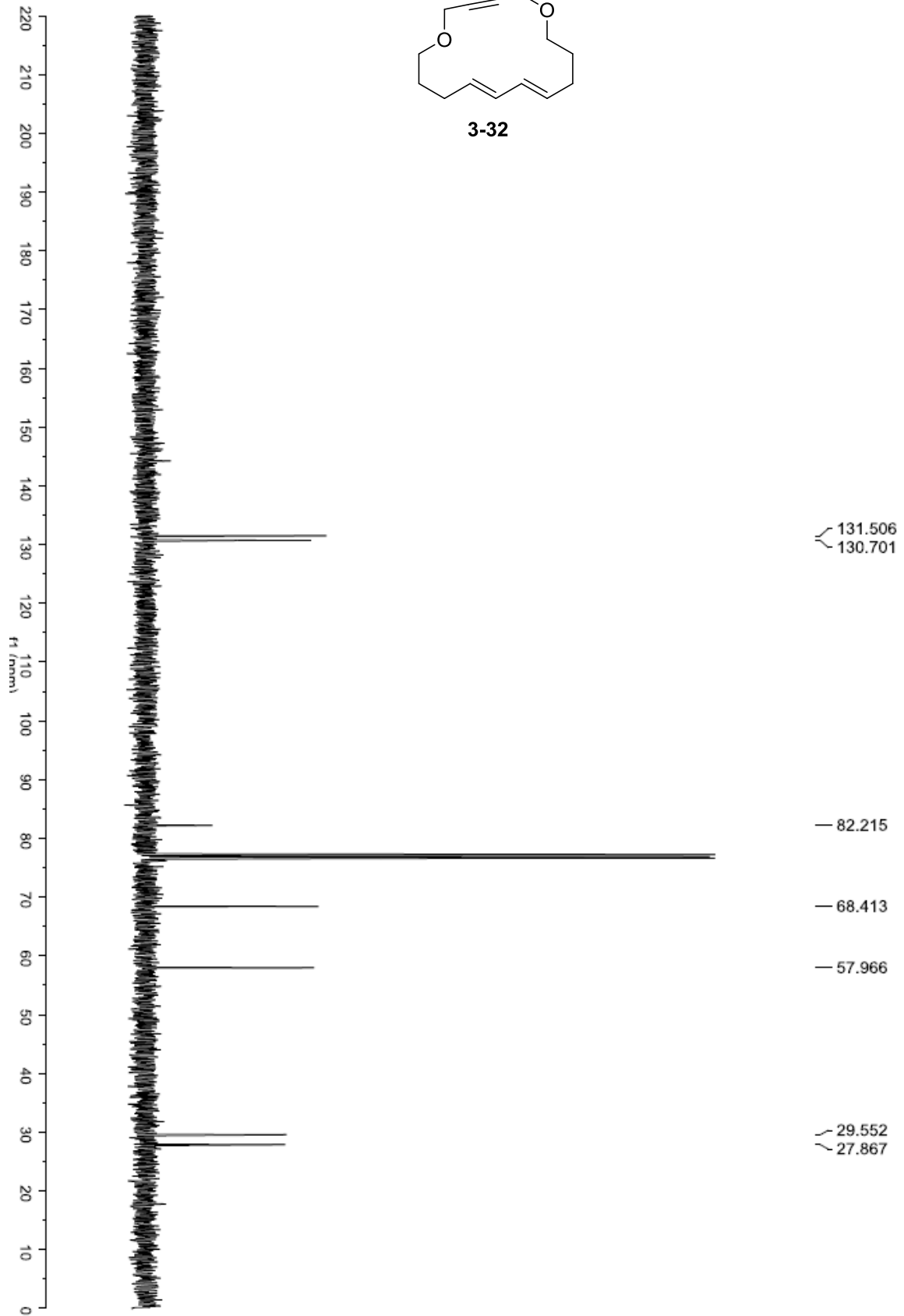


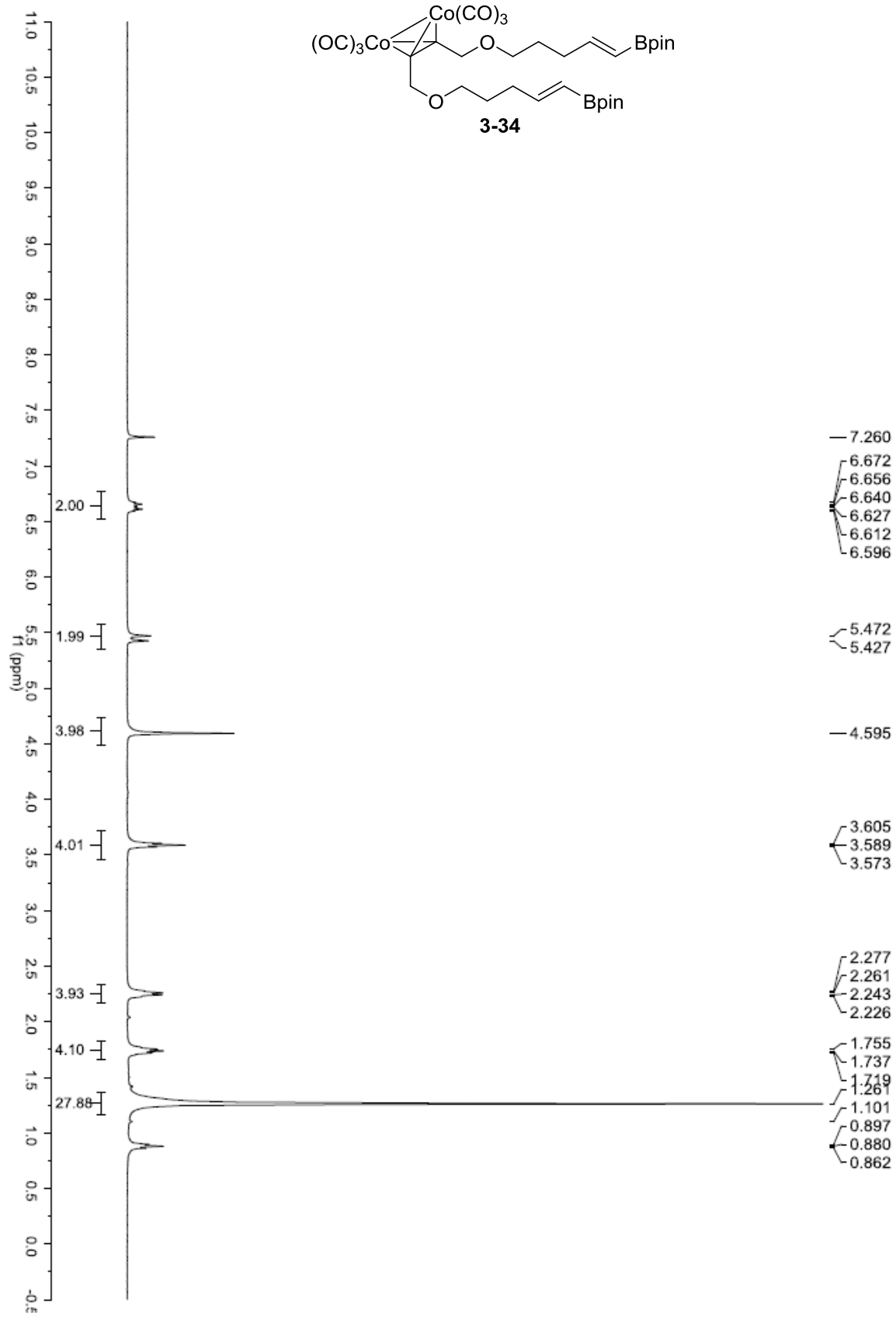
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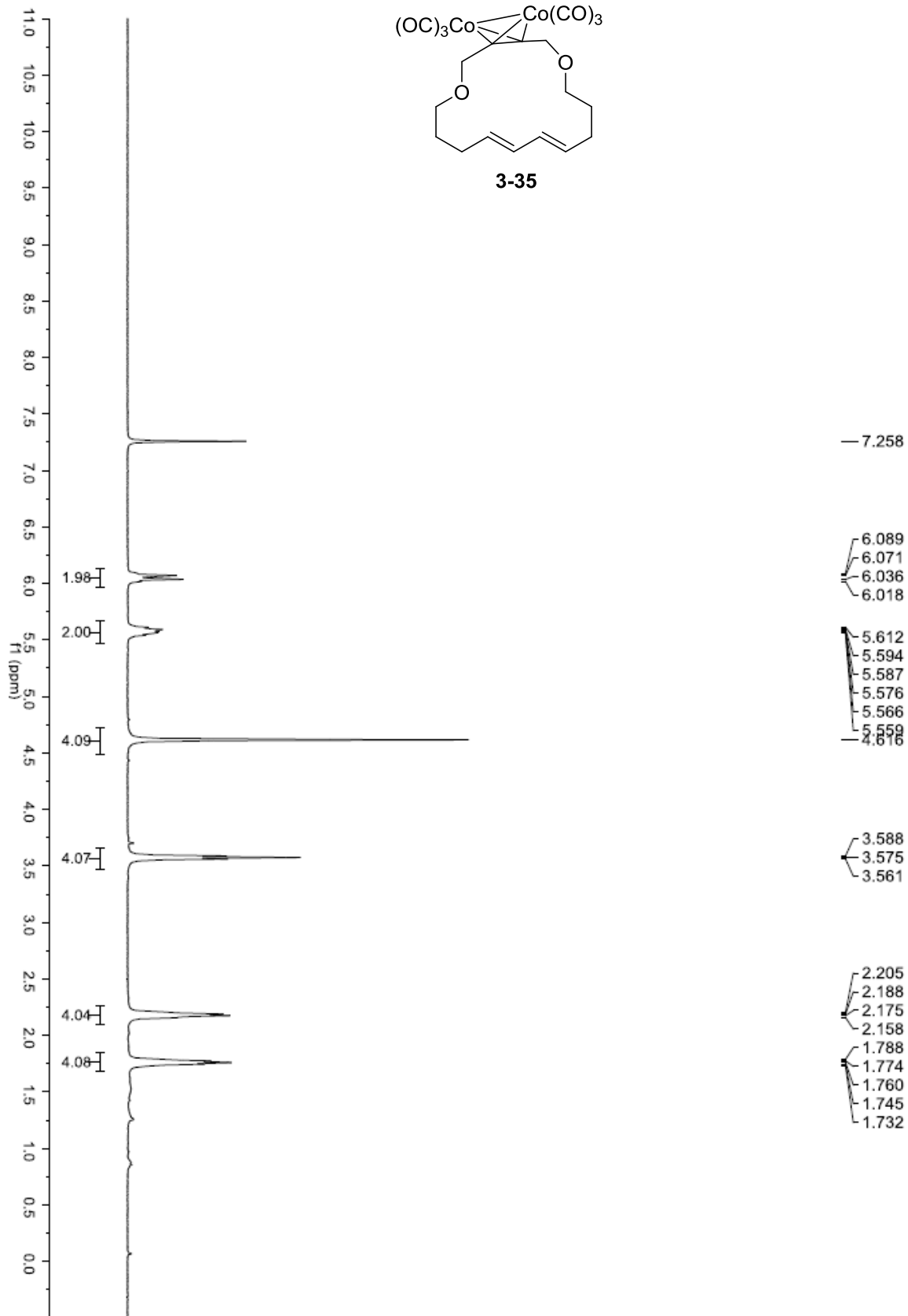


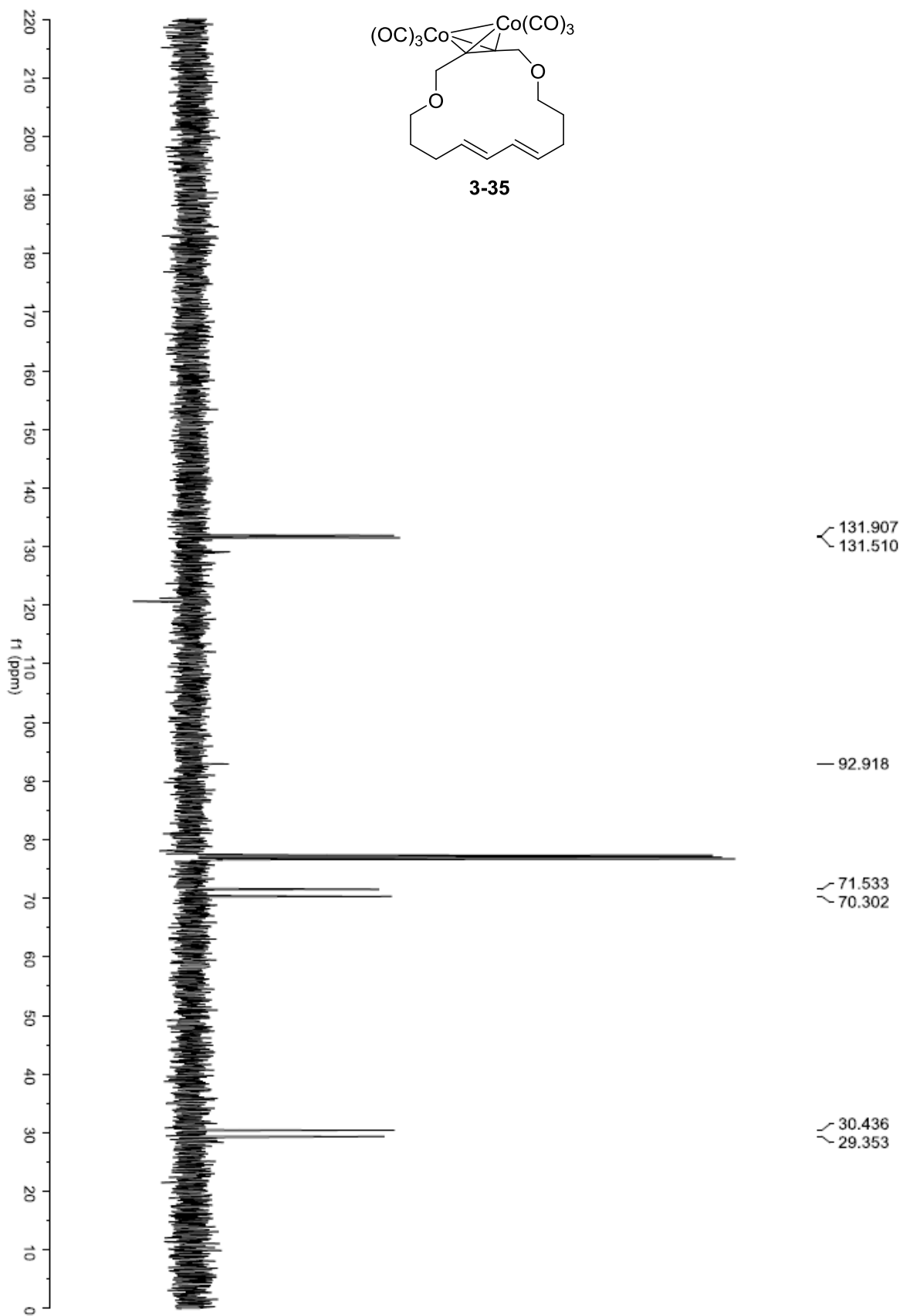


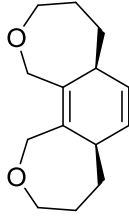
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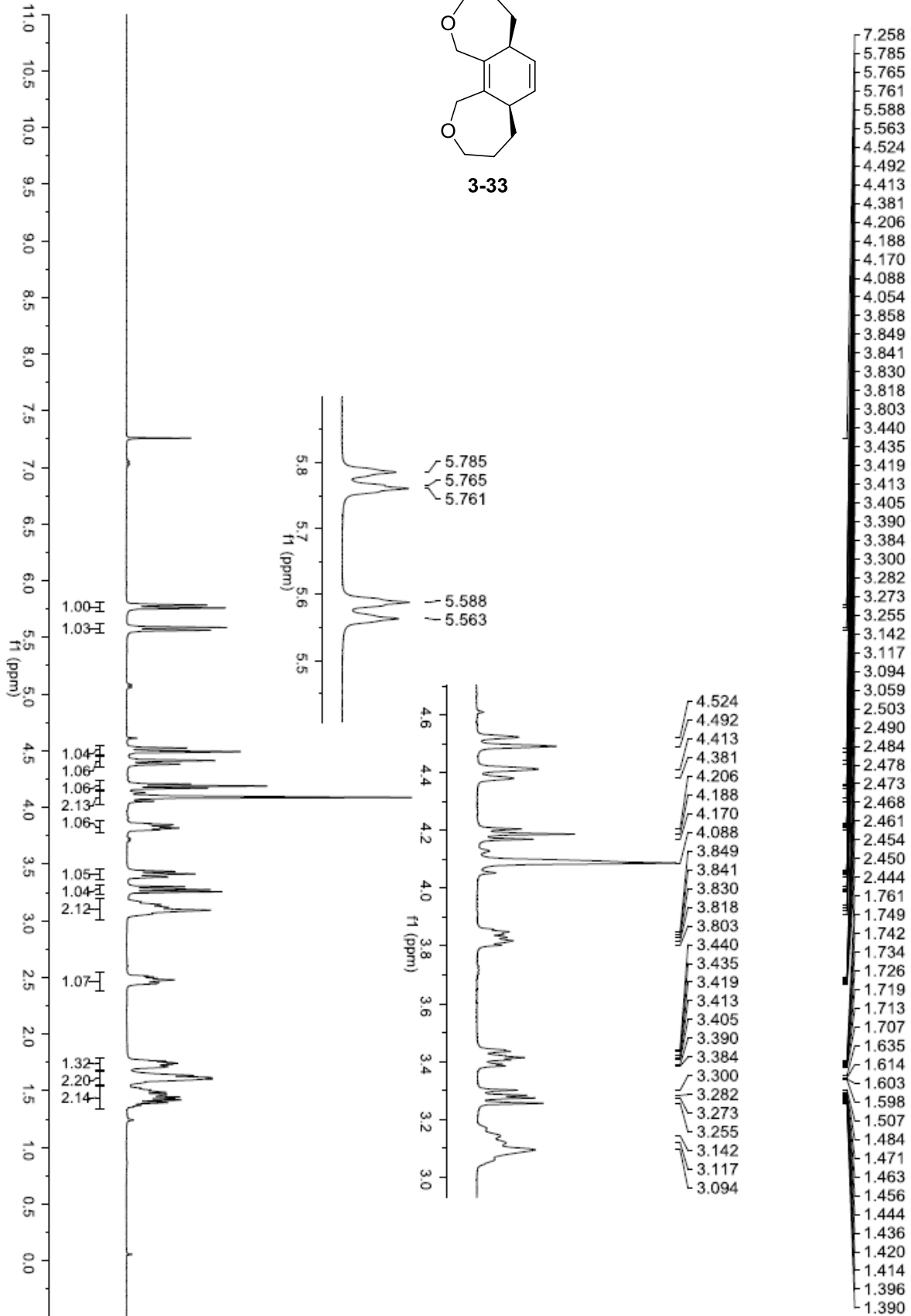


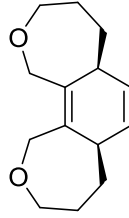




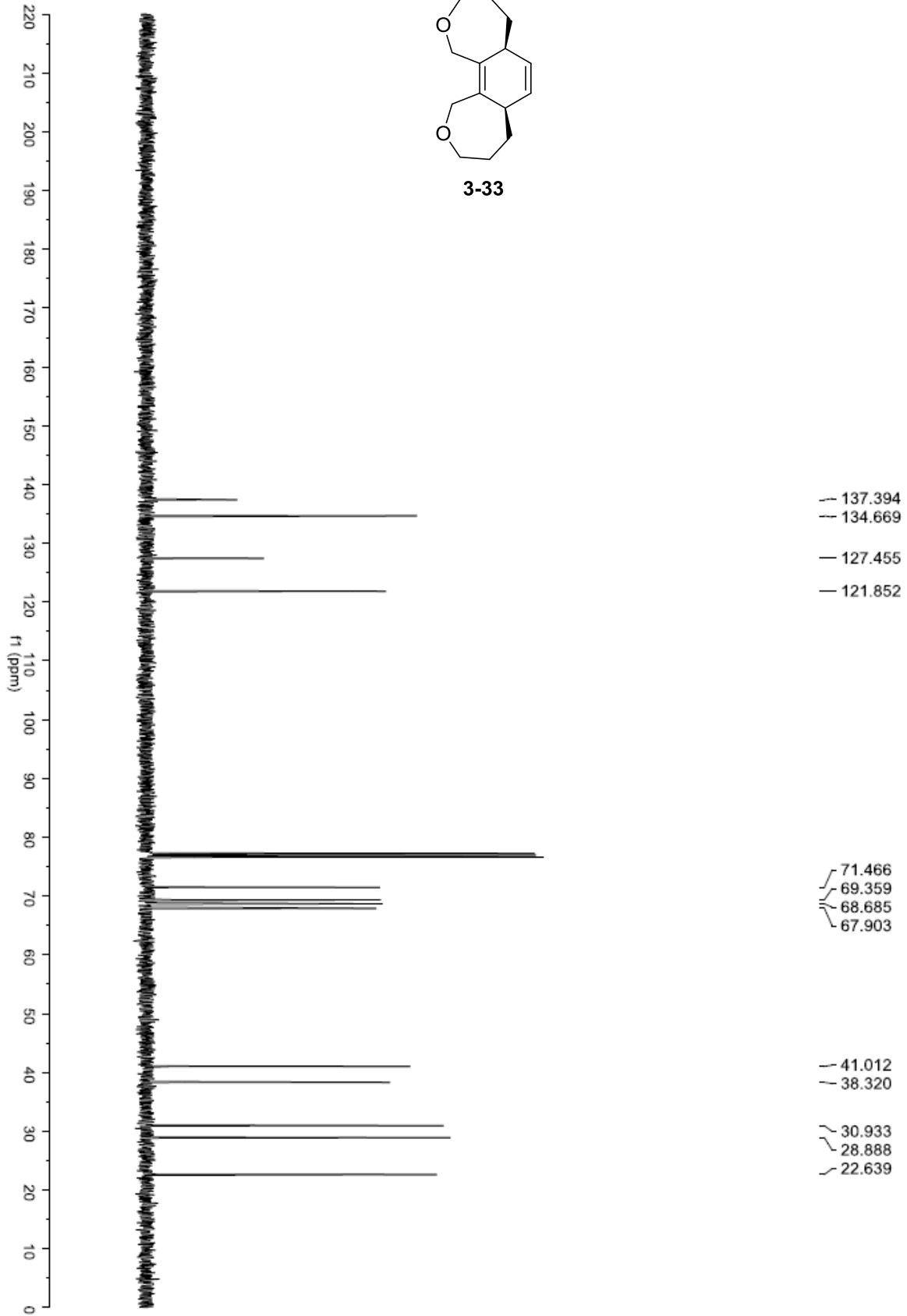


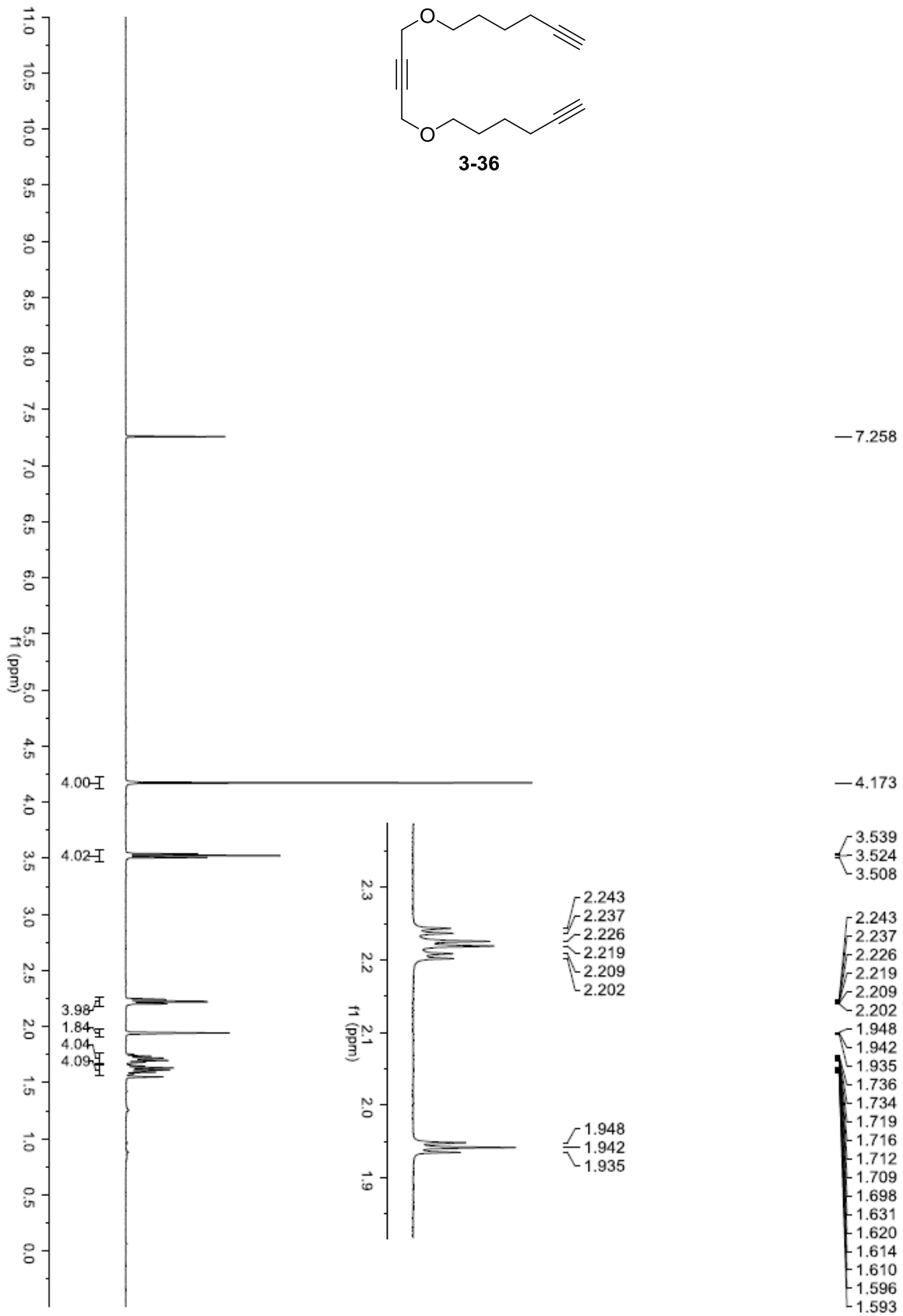
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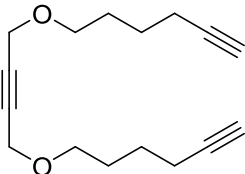




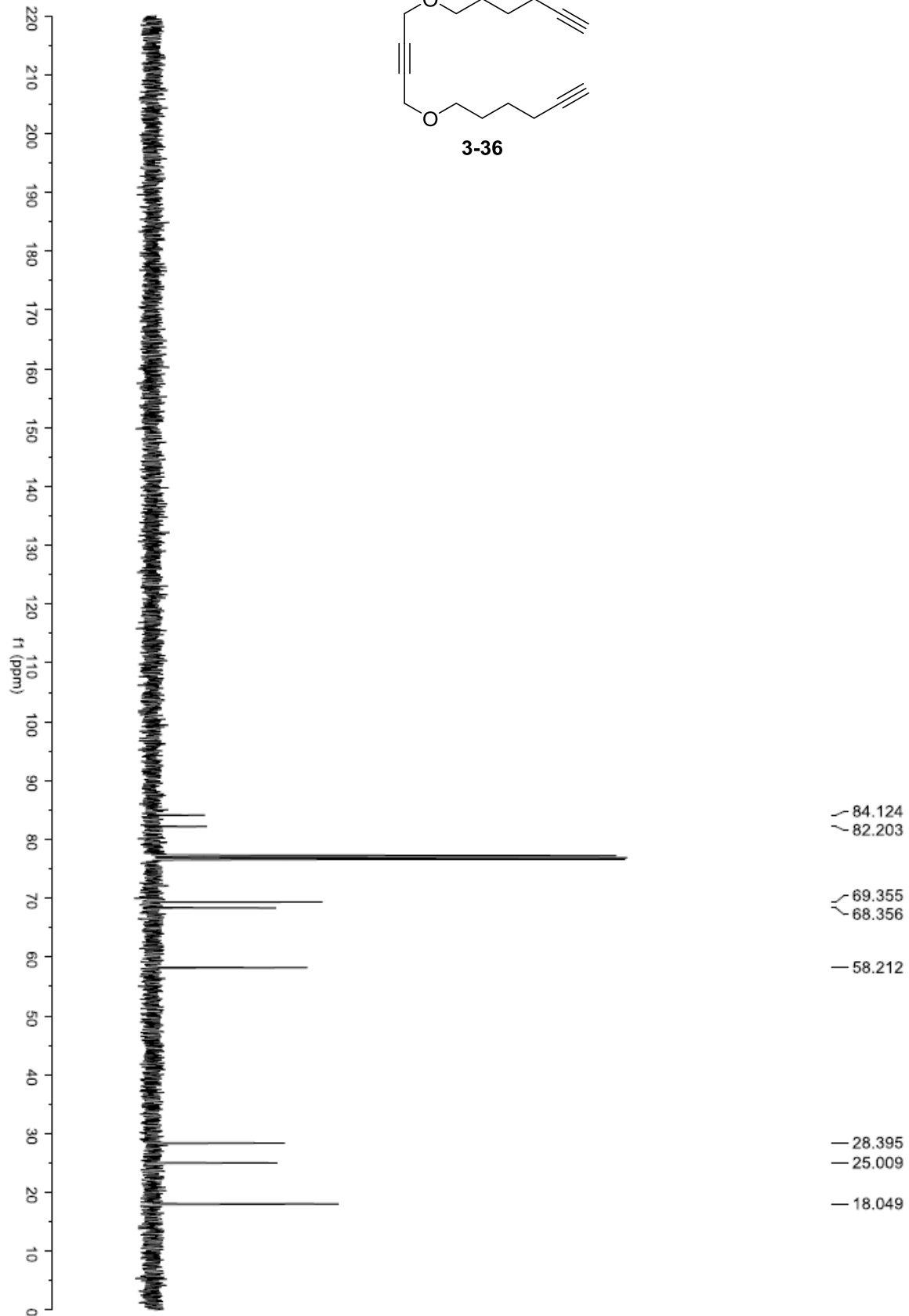
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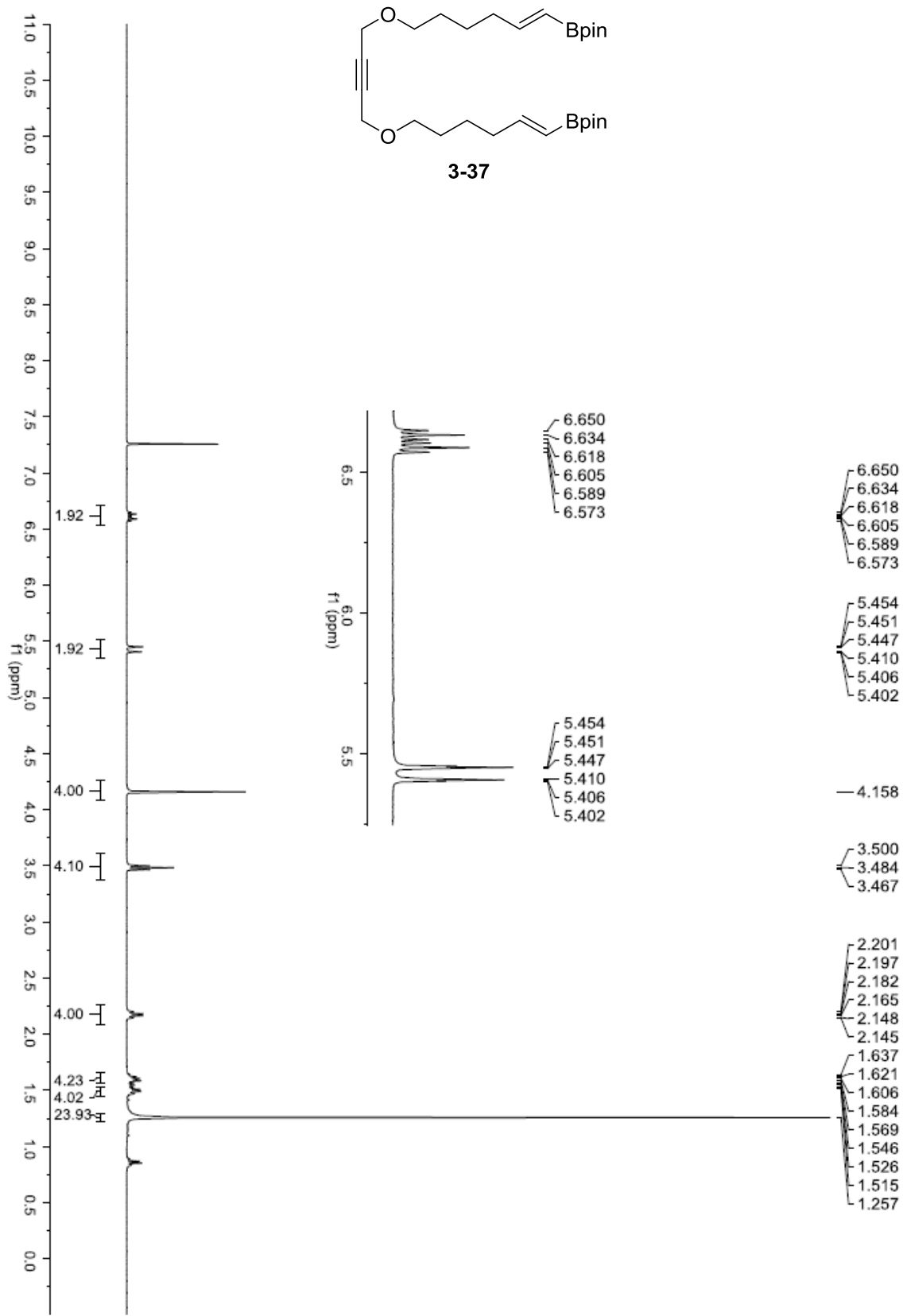


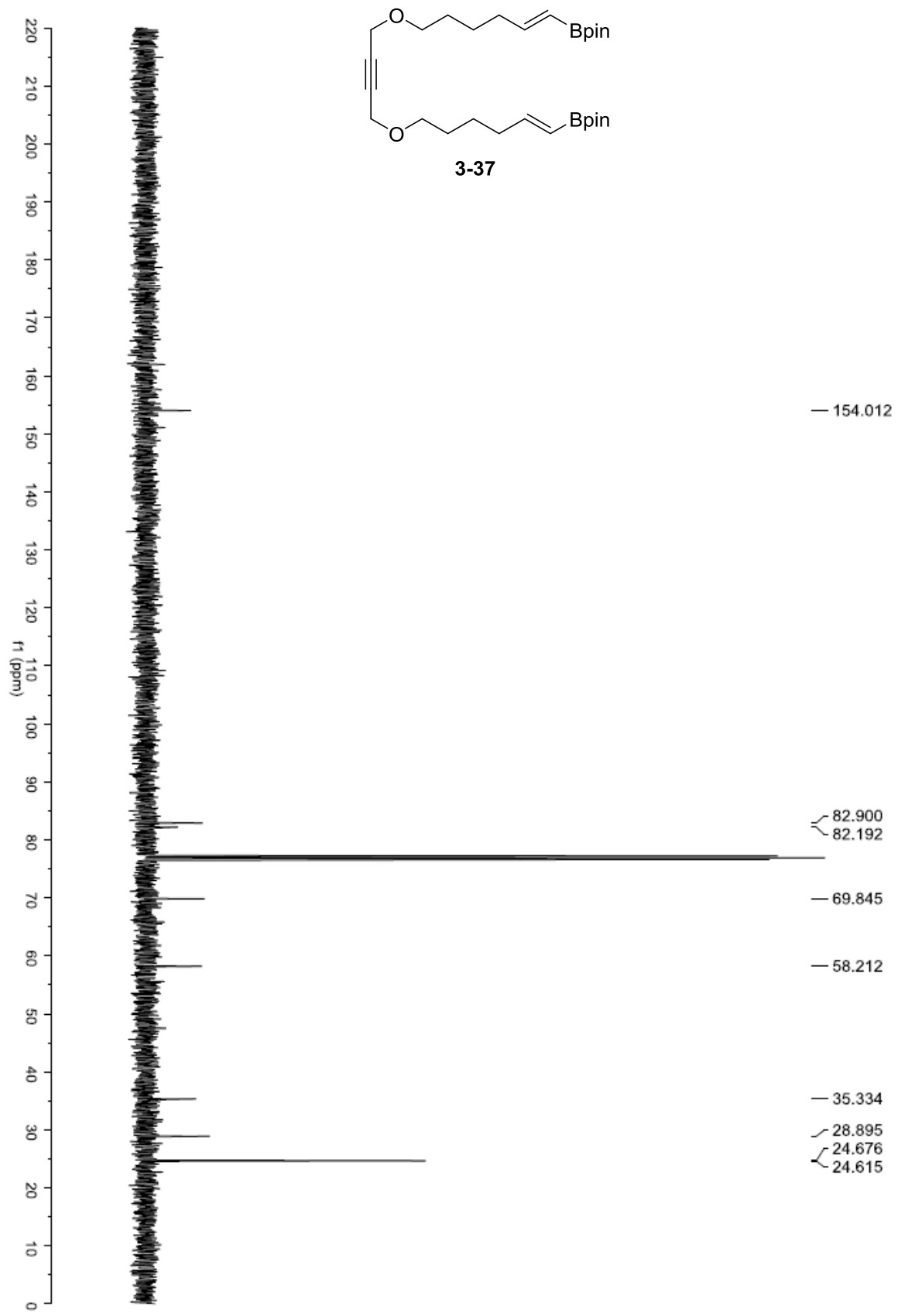


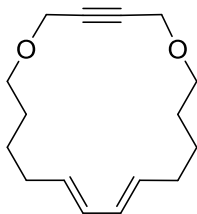


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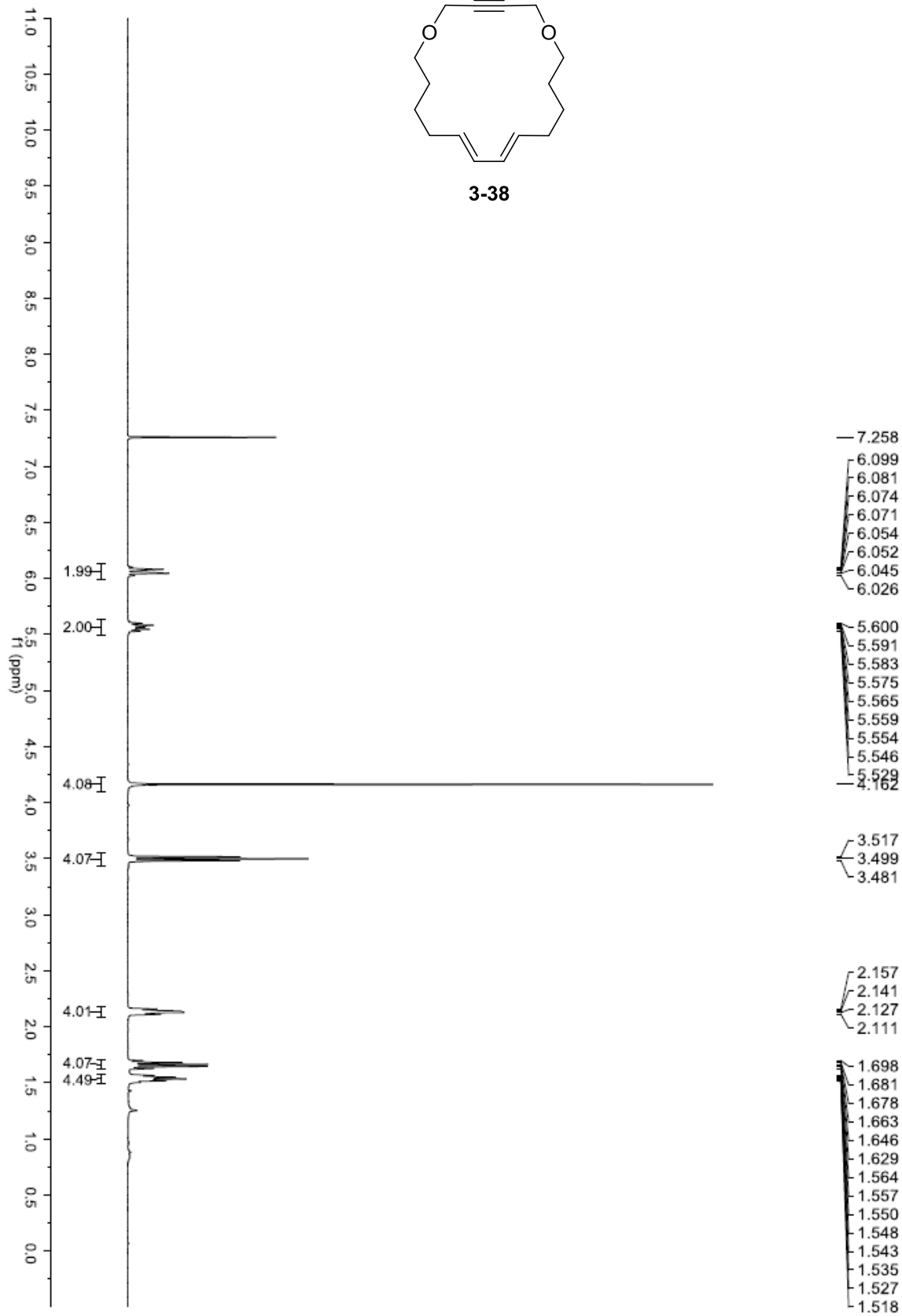


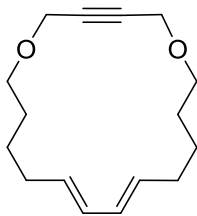




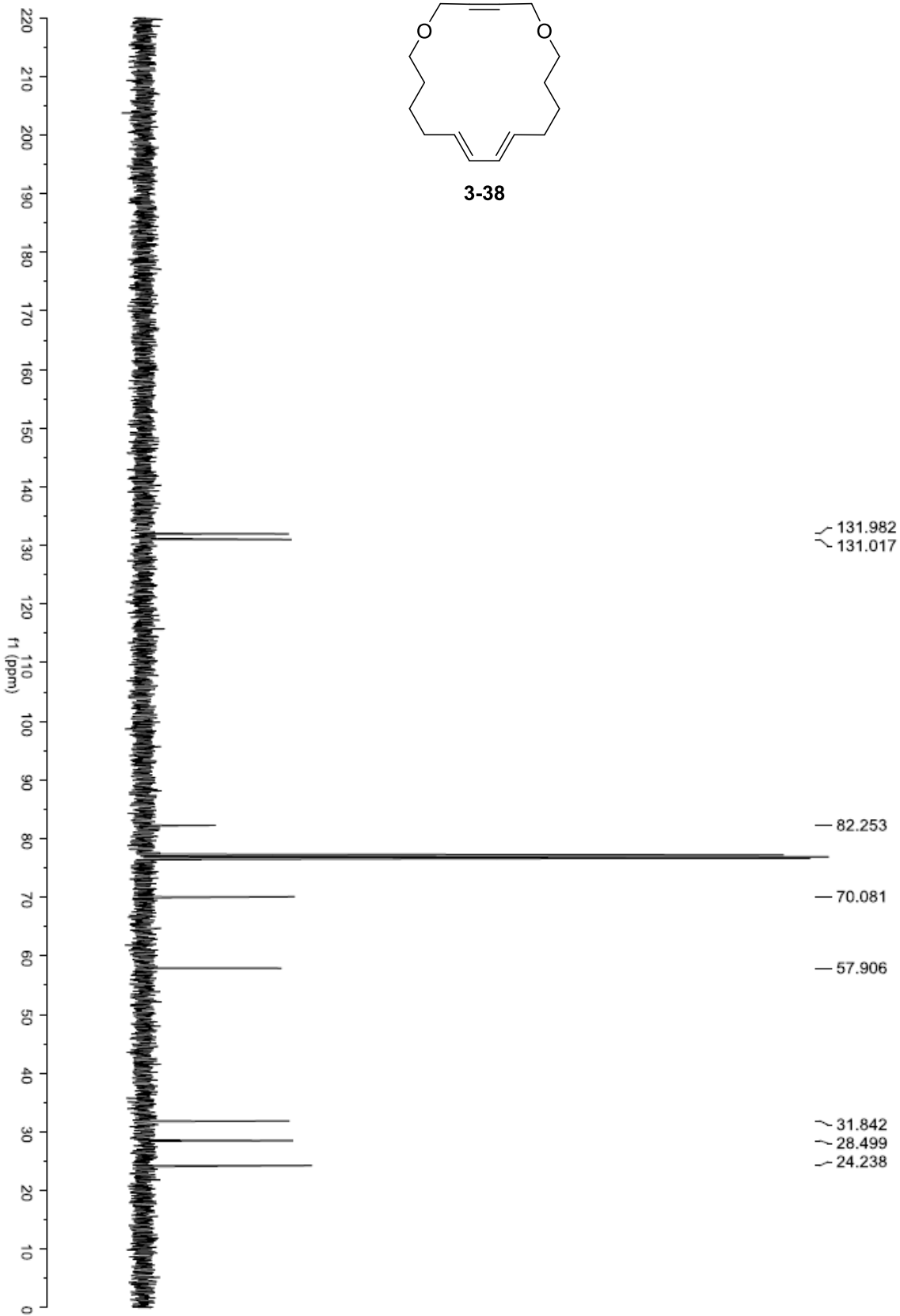


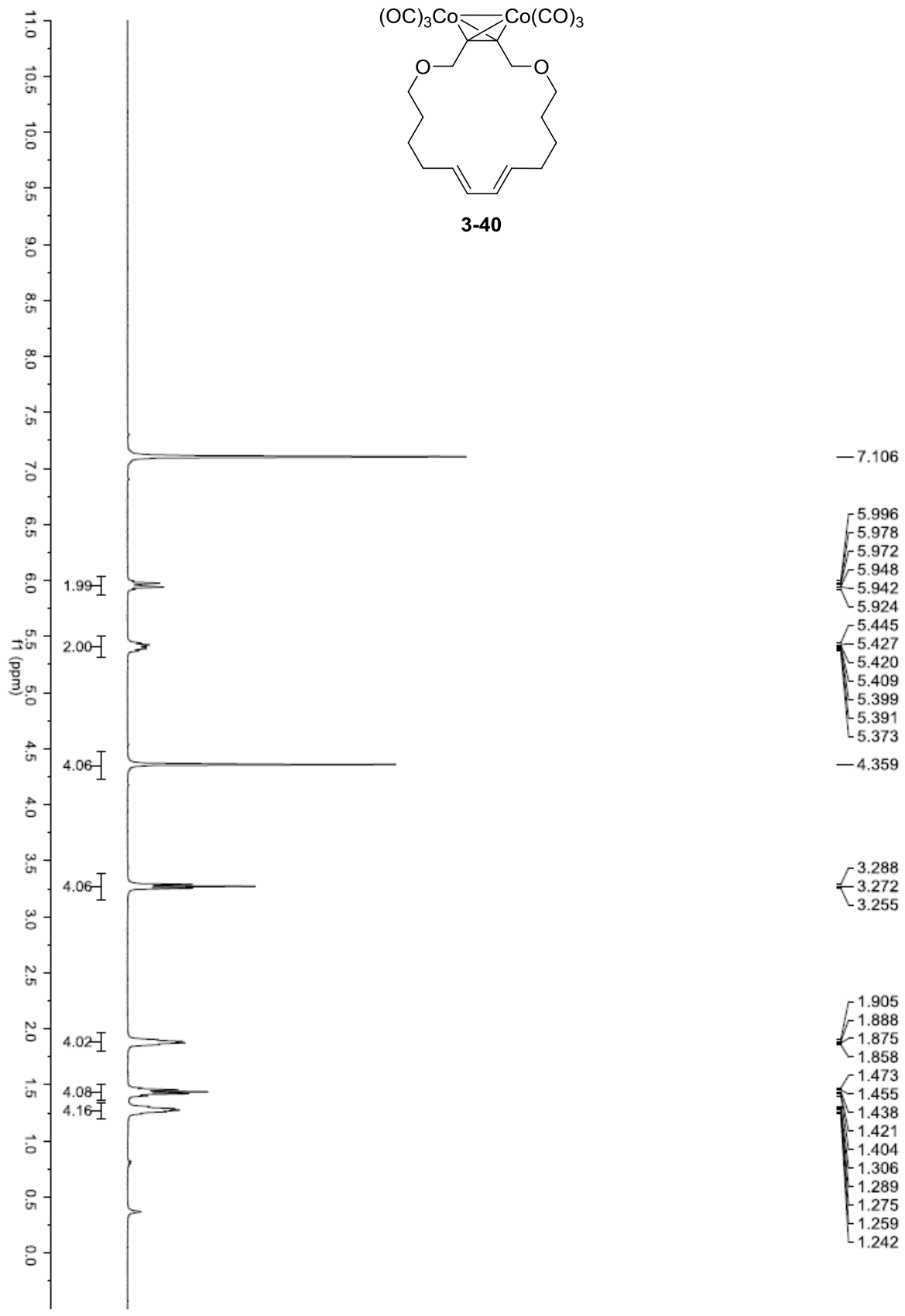
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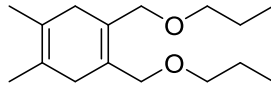




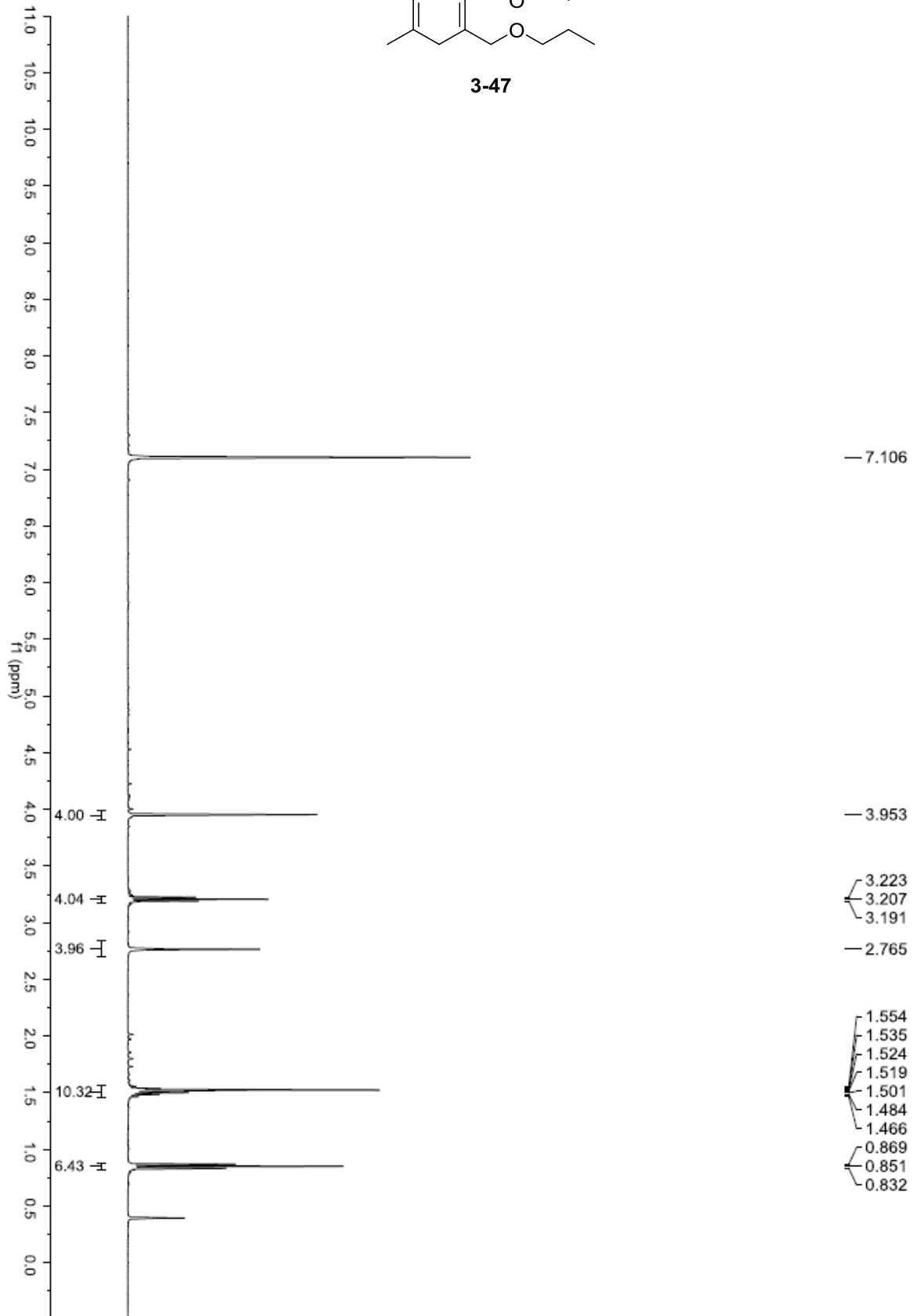
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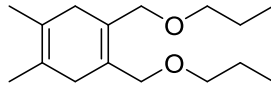




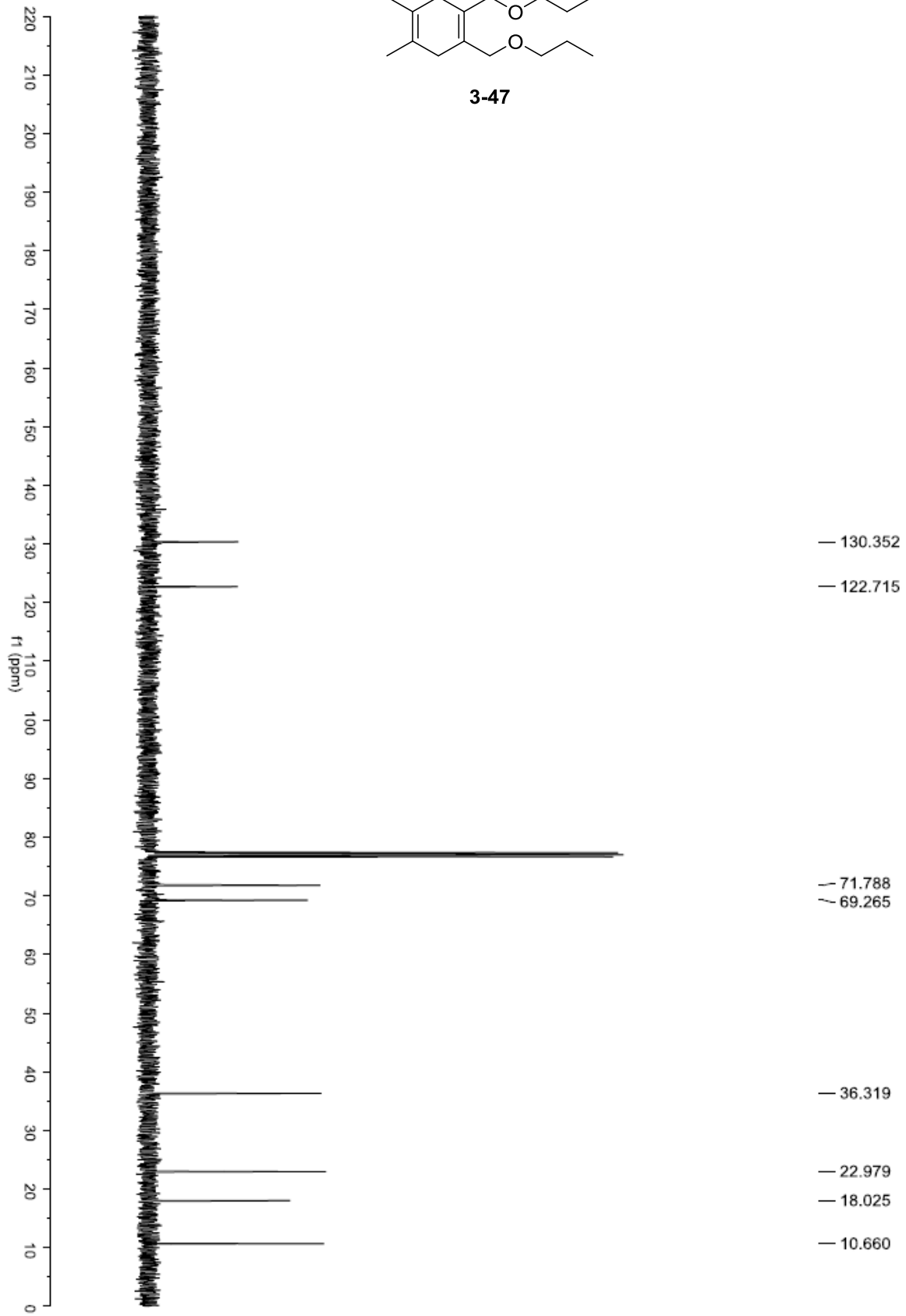


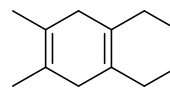
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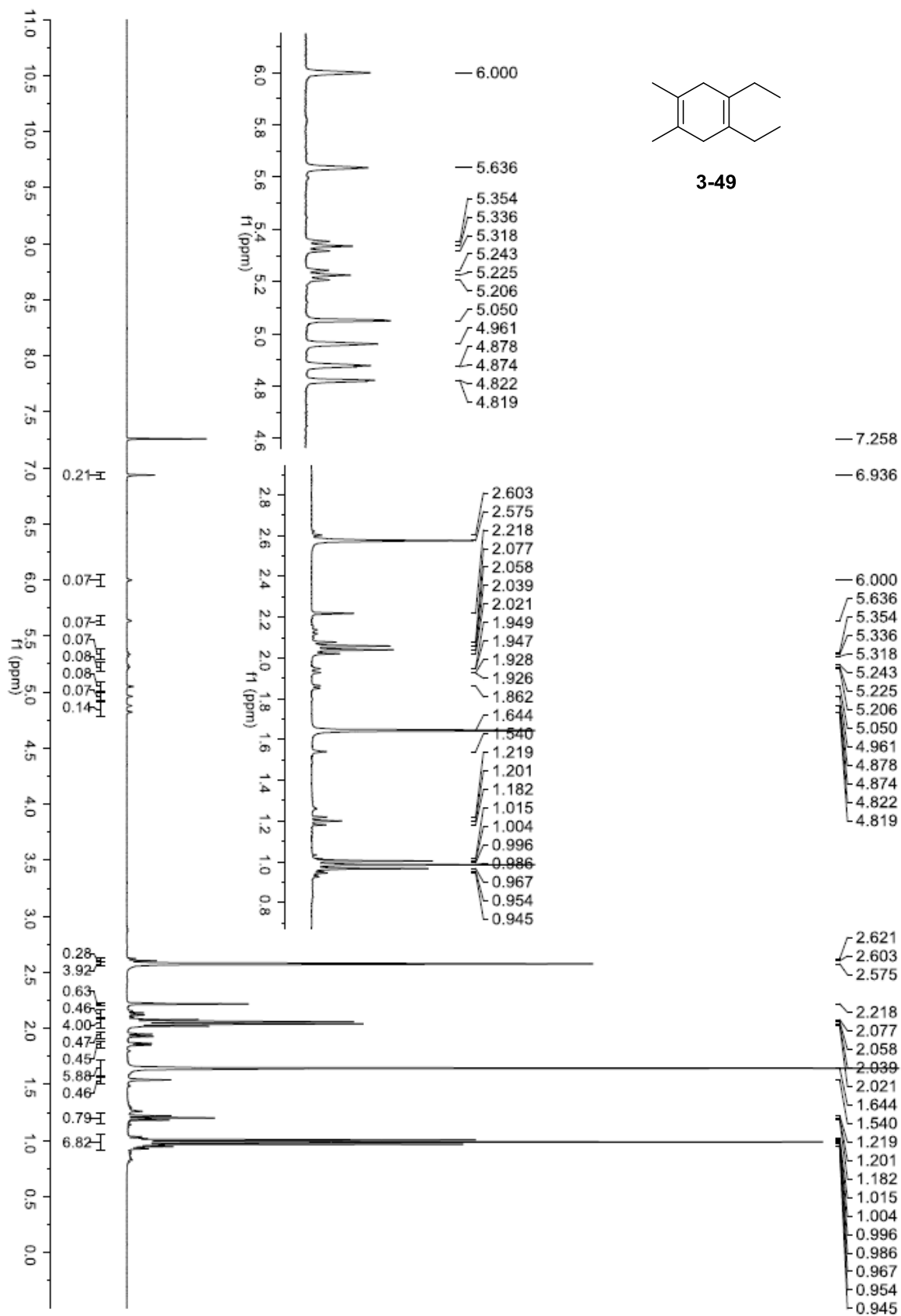


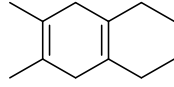
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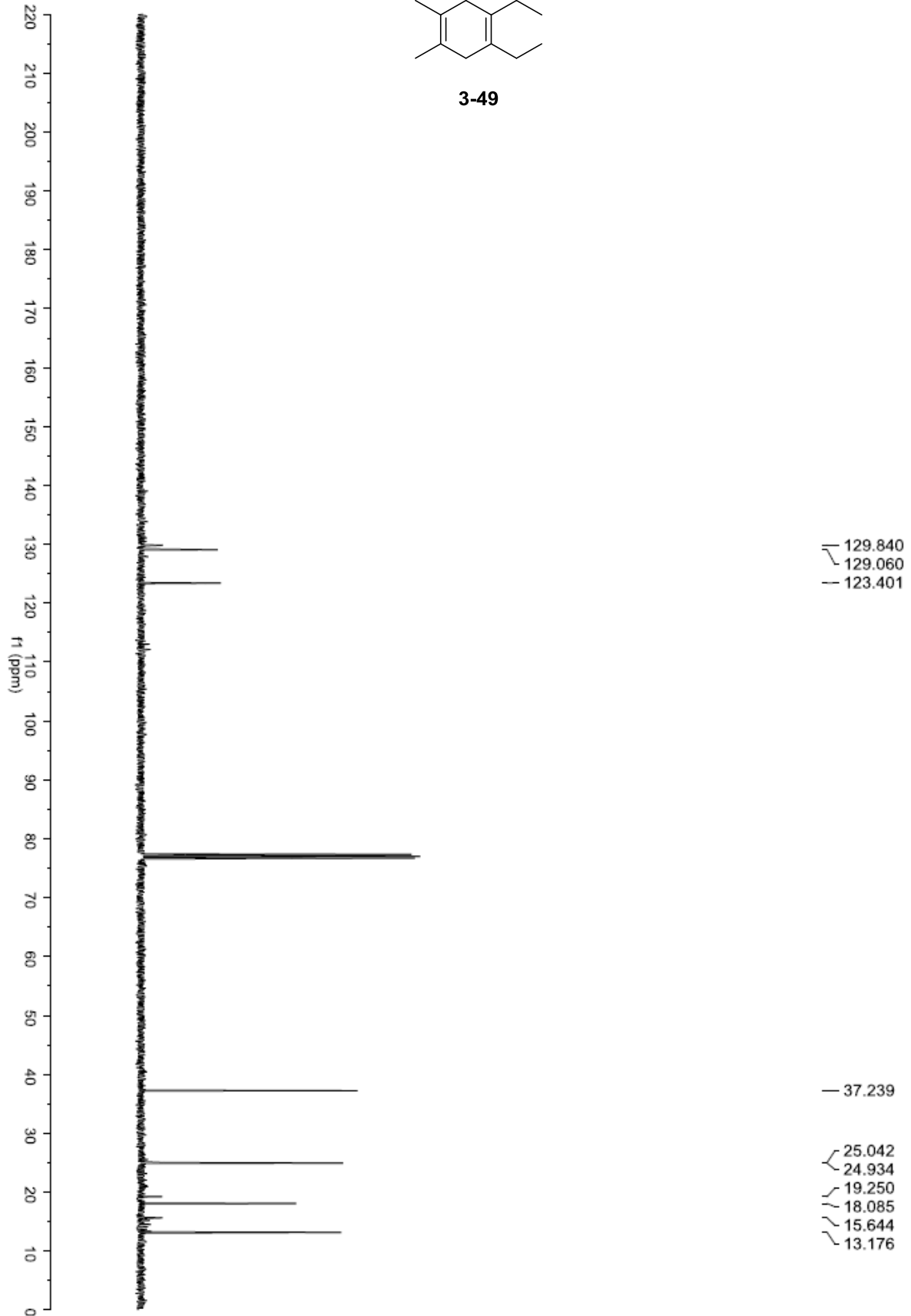


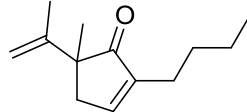
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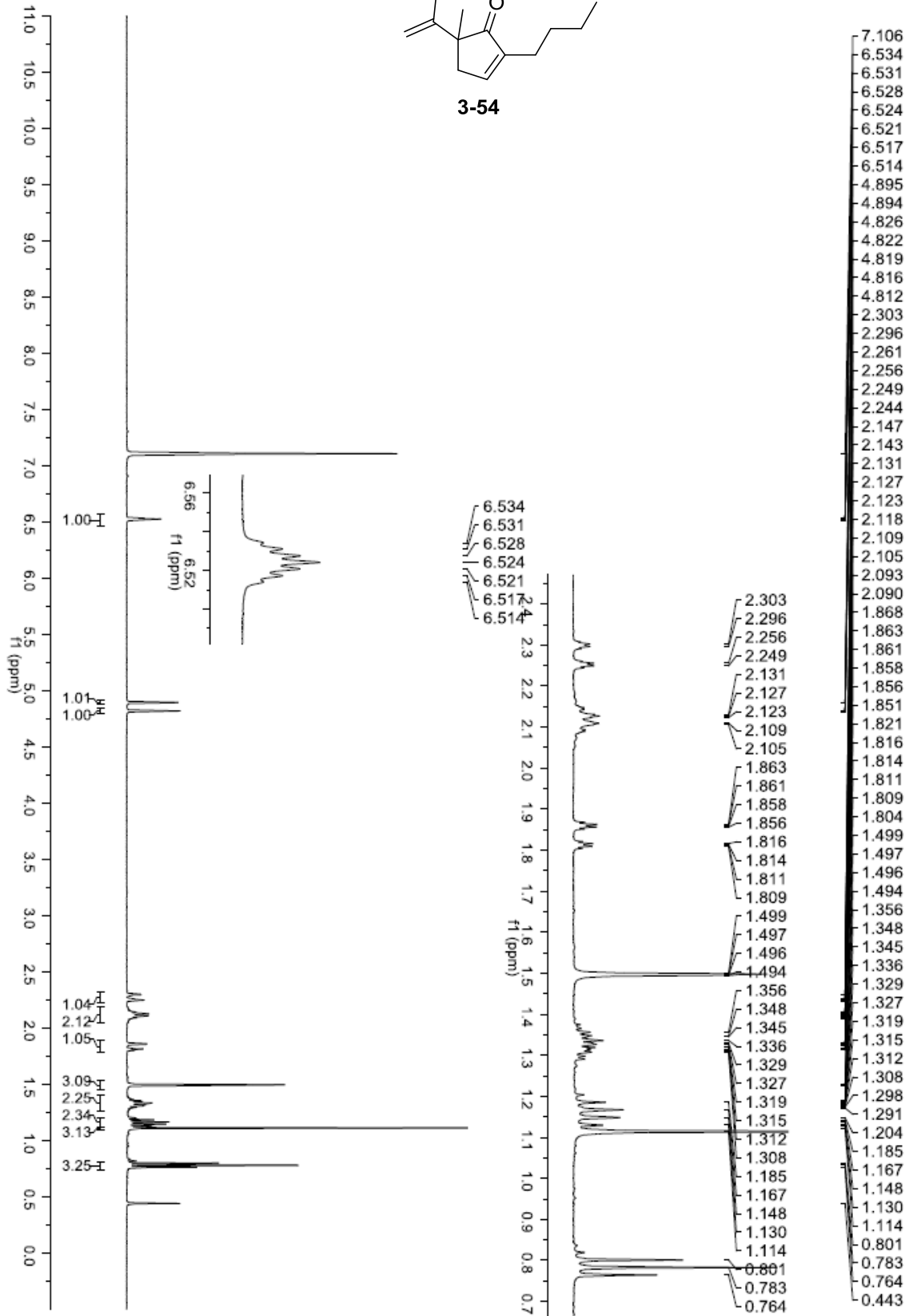


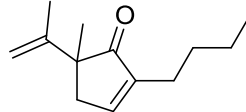
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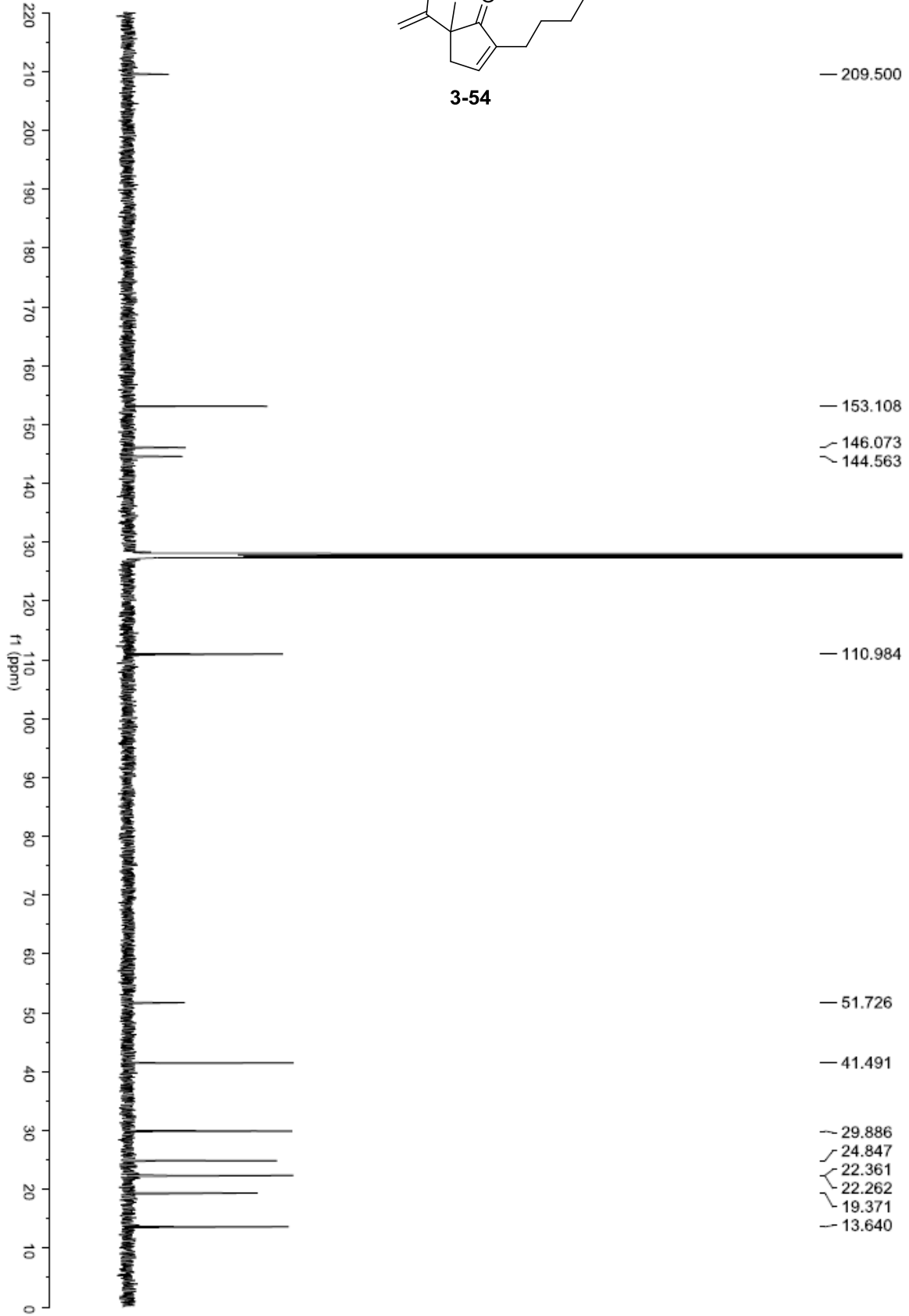


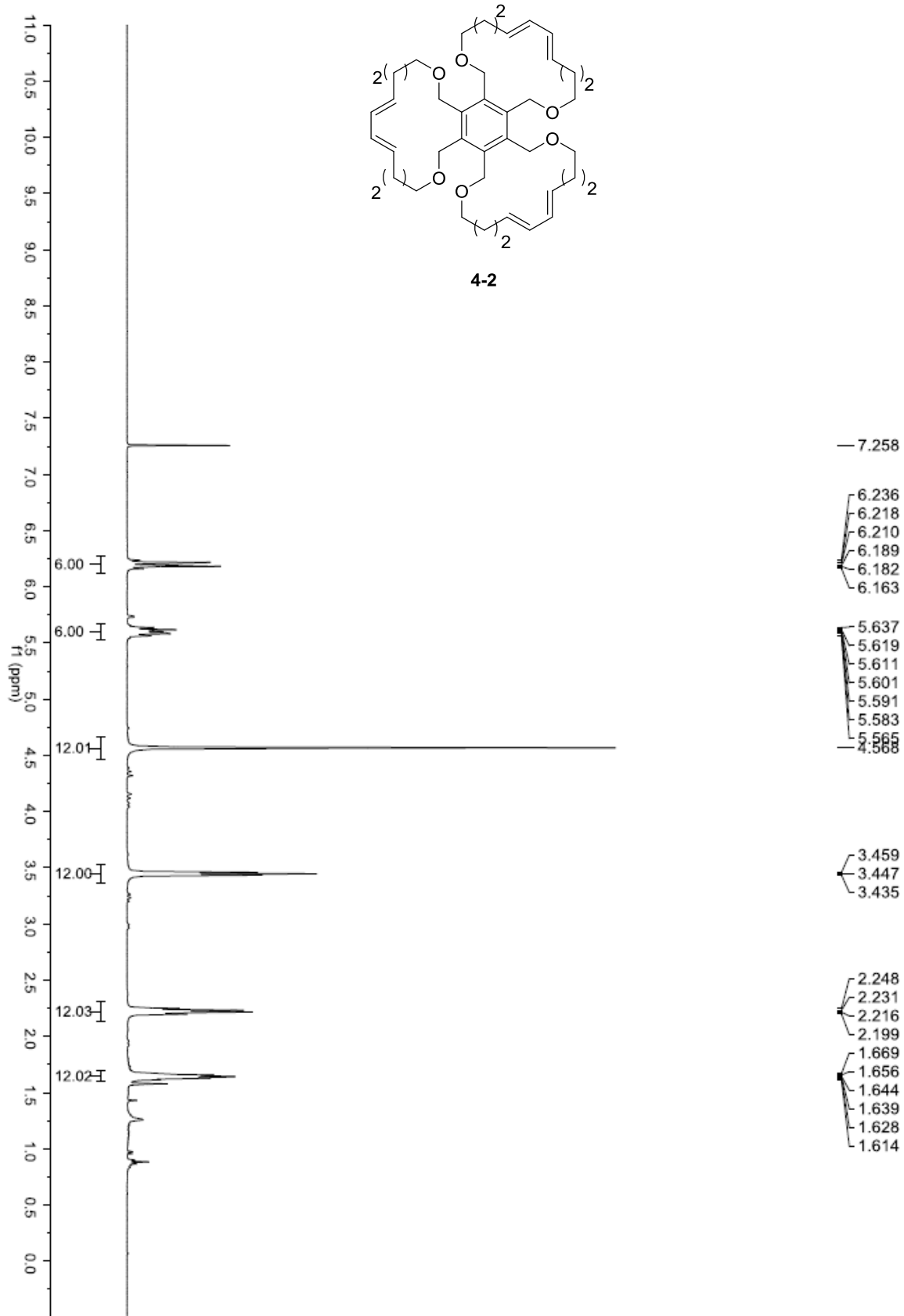
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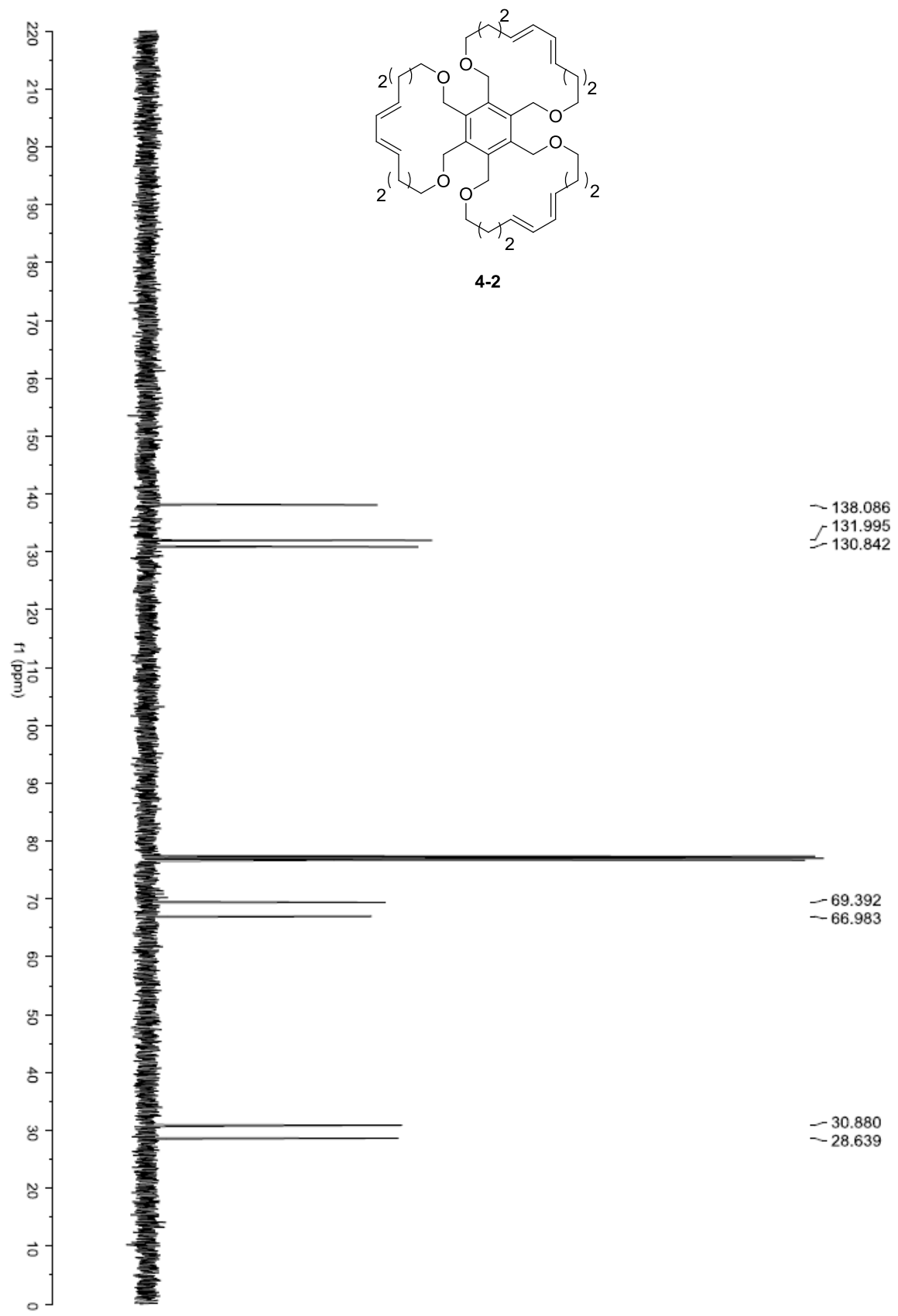


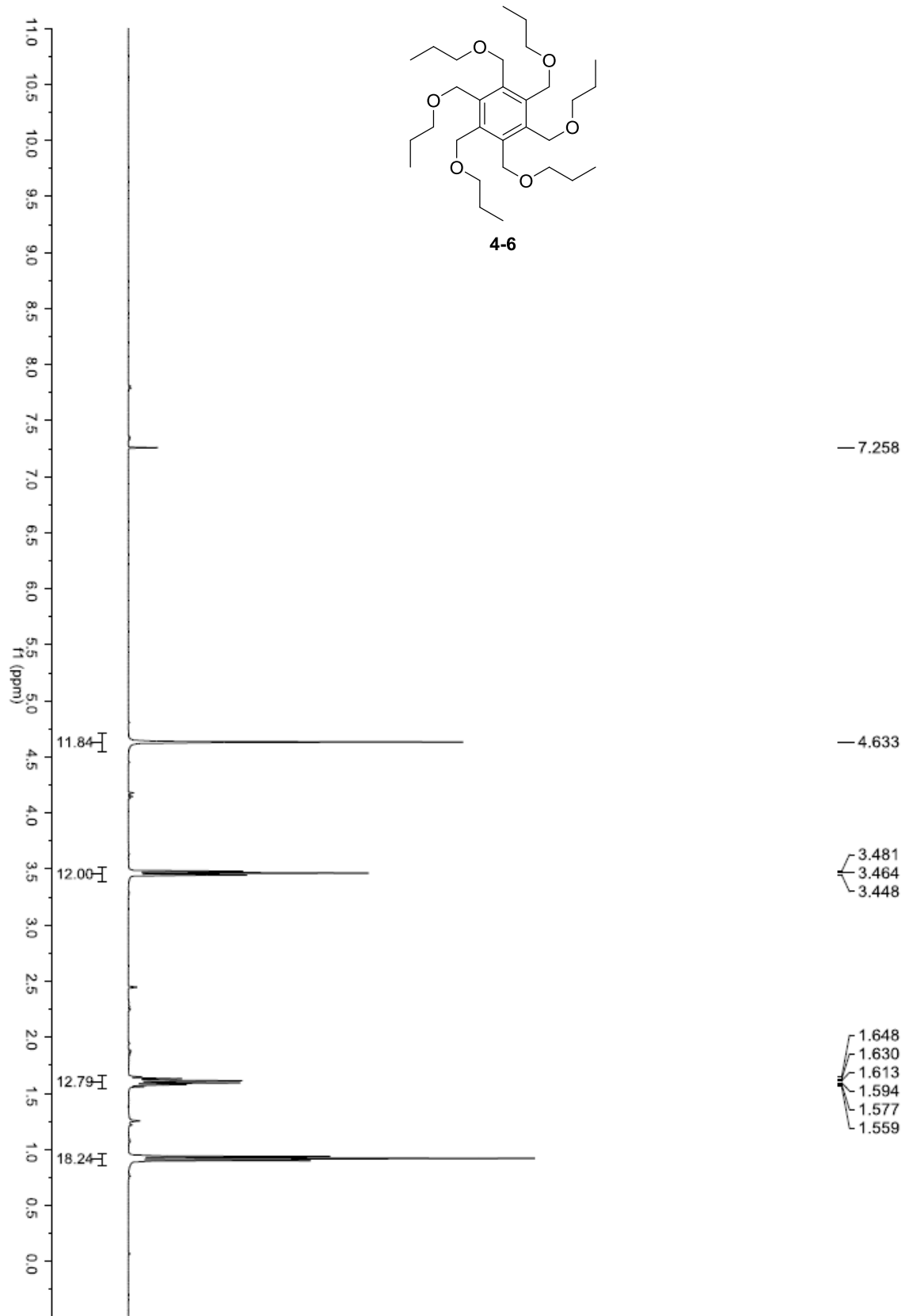


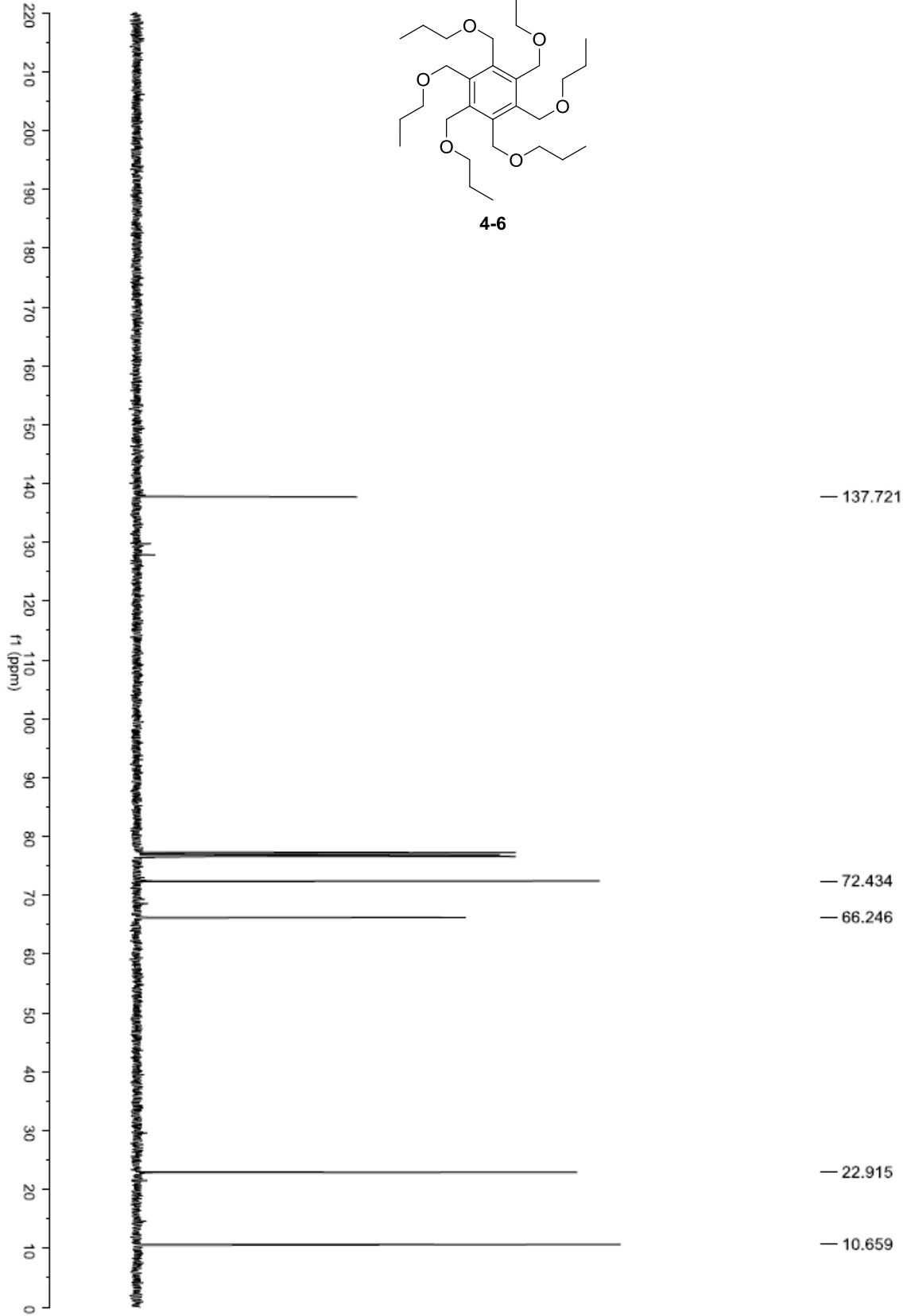
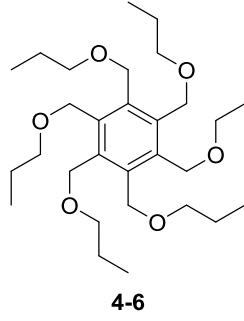
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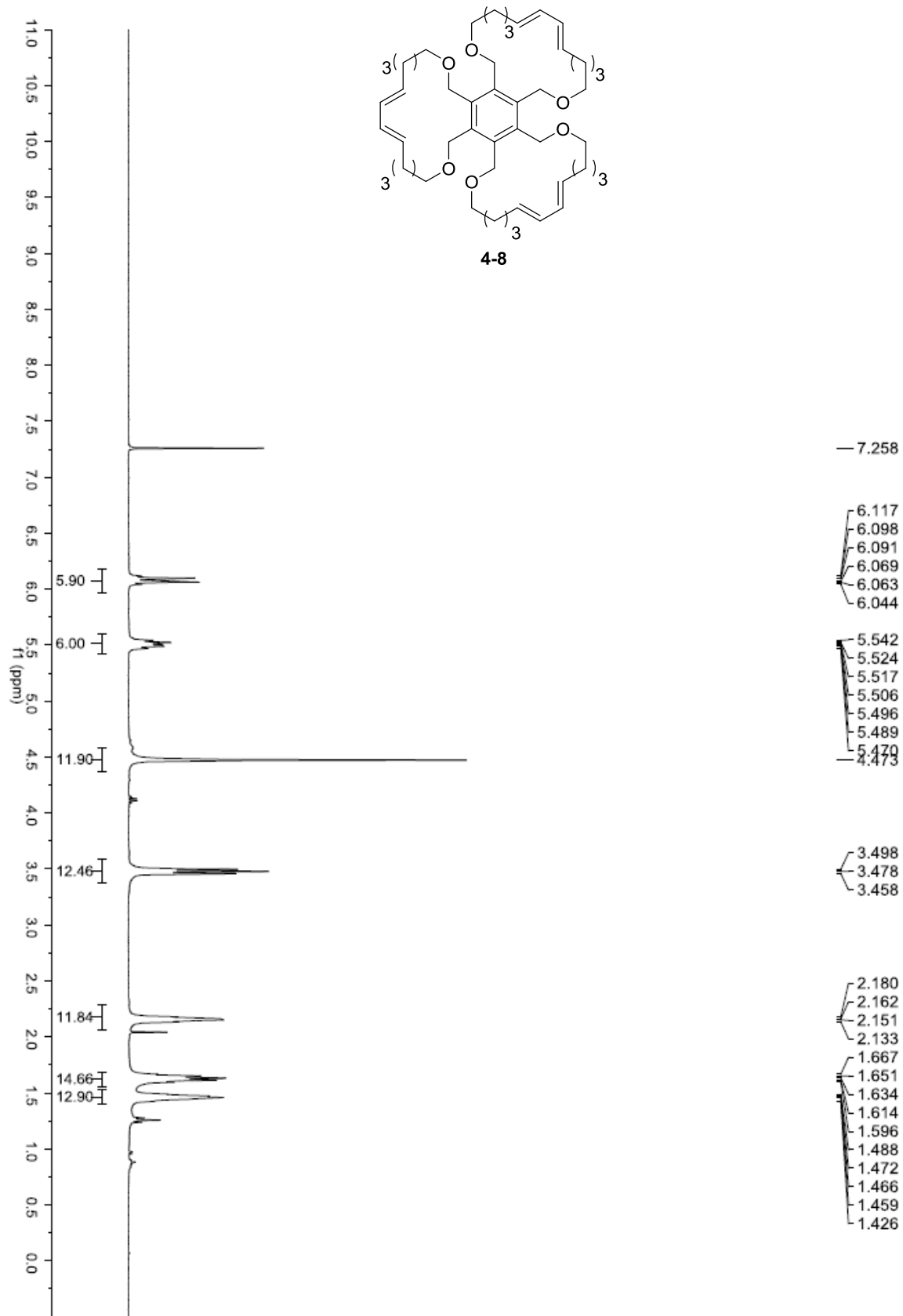


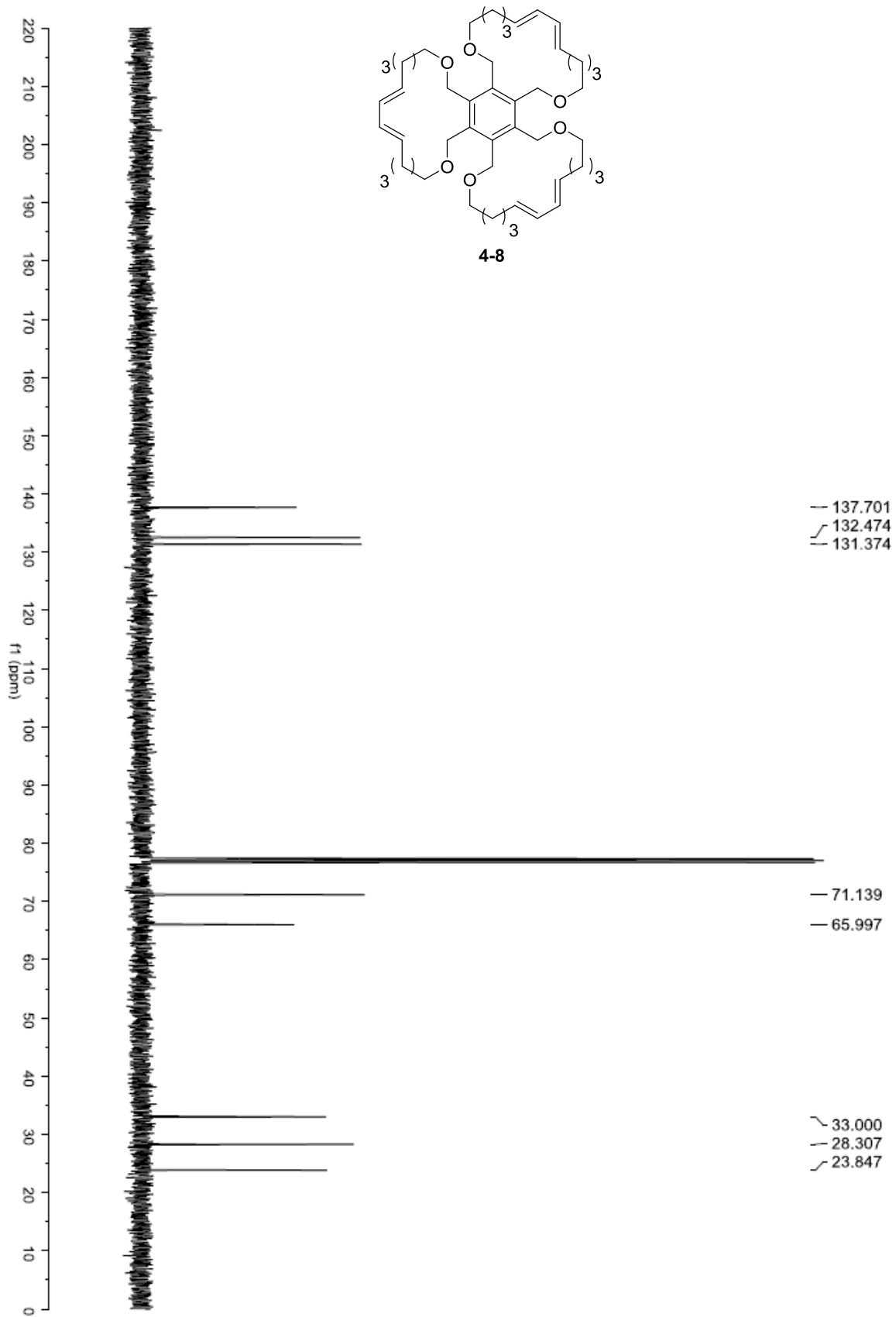


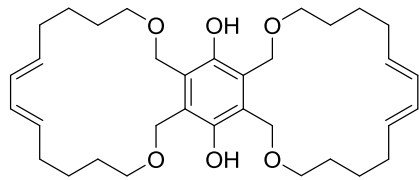




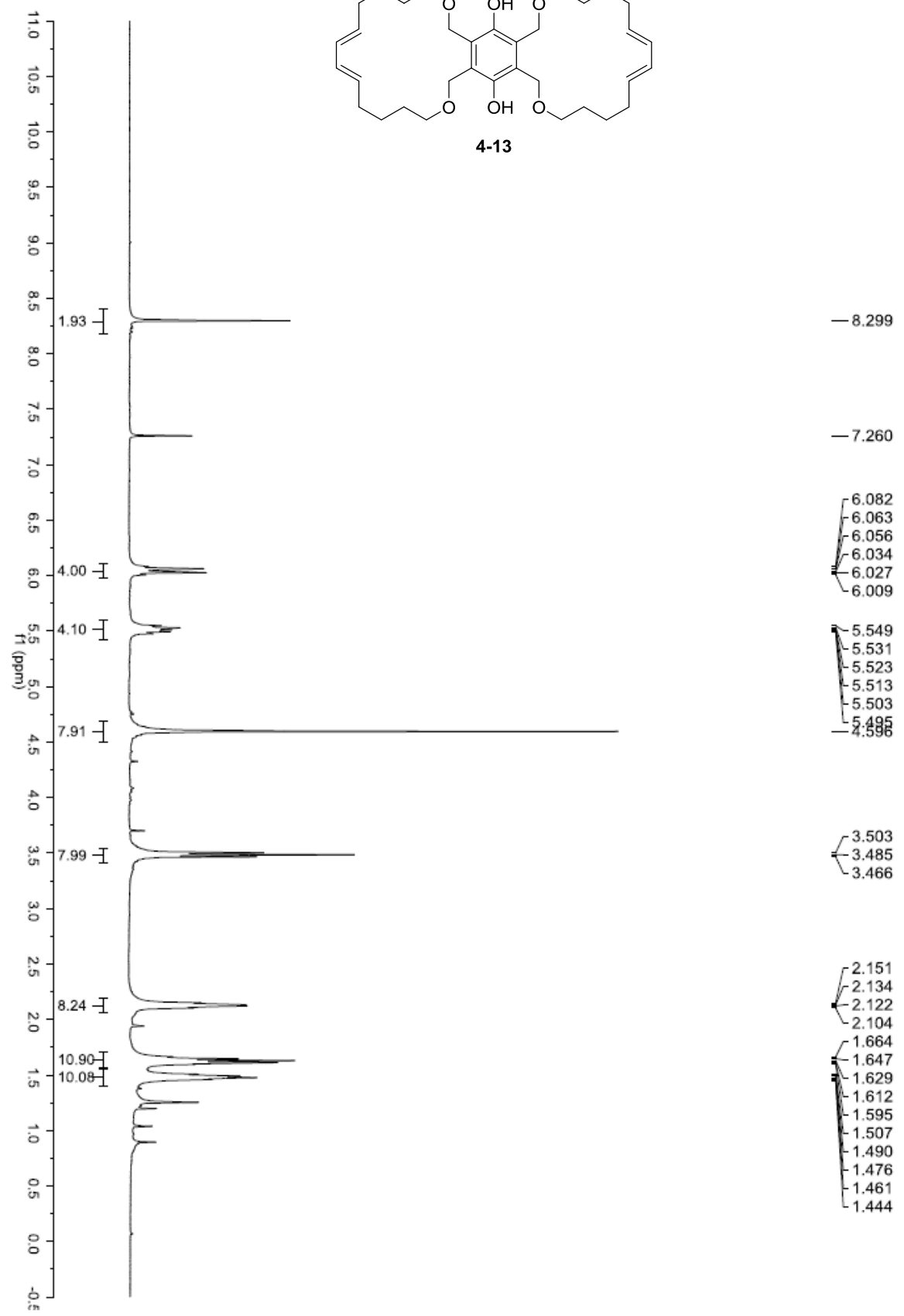






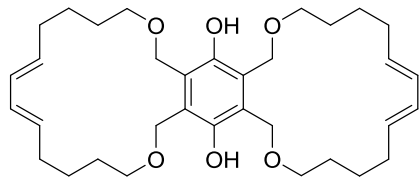


4-13



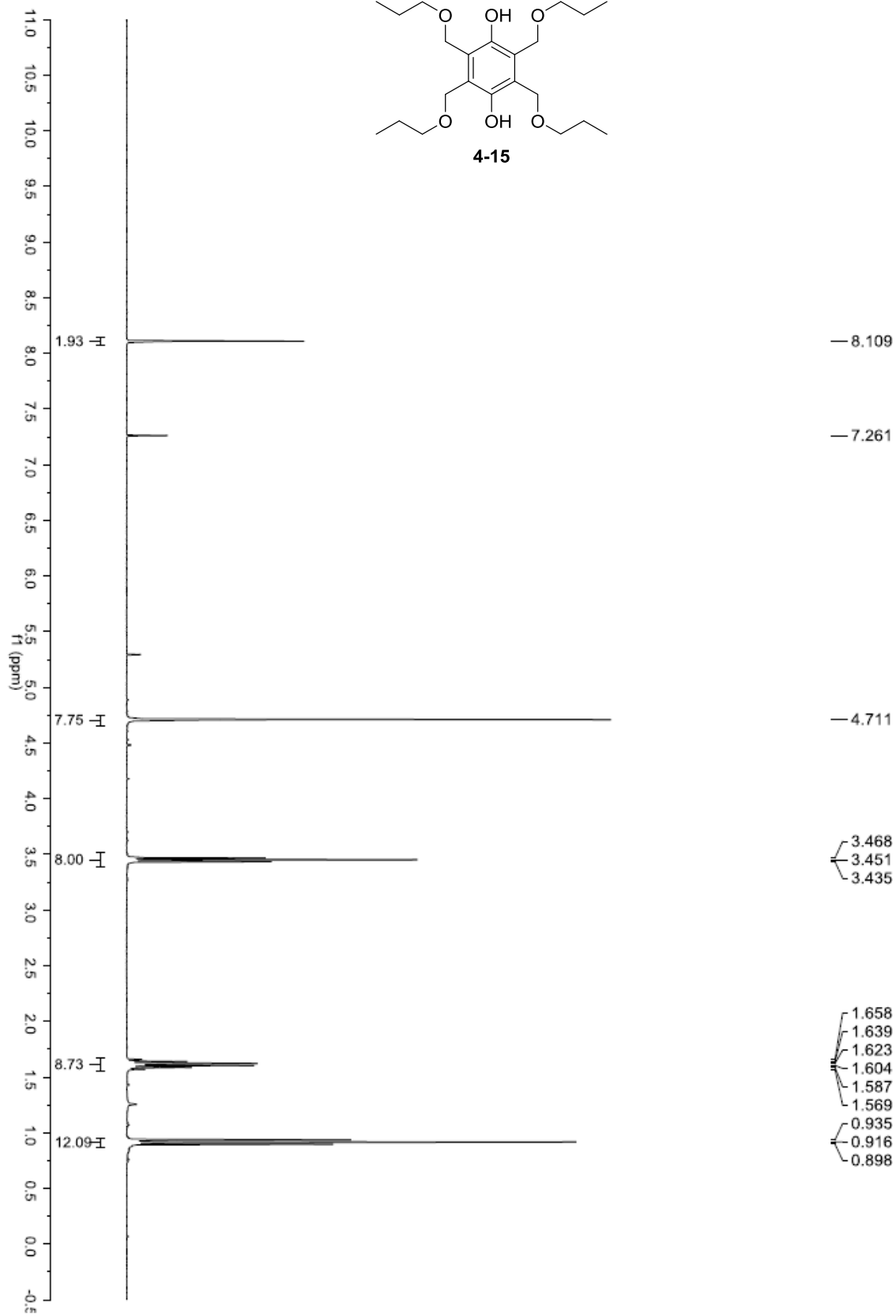
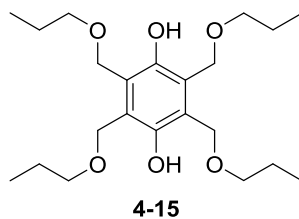
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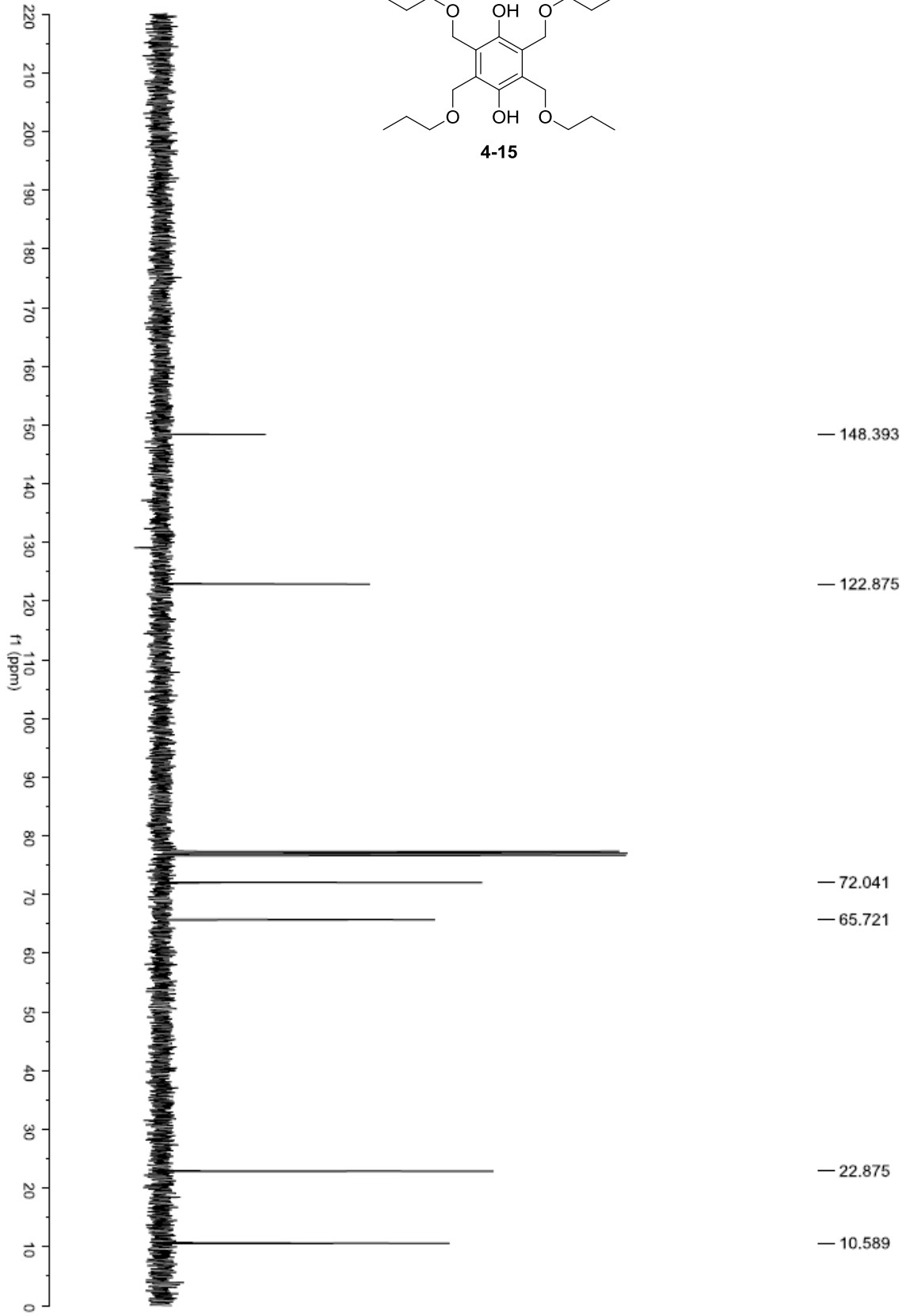
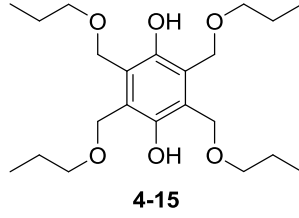
f1 (ppm)

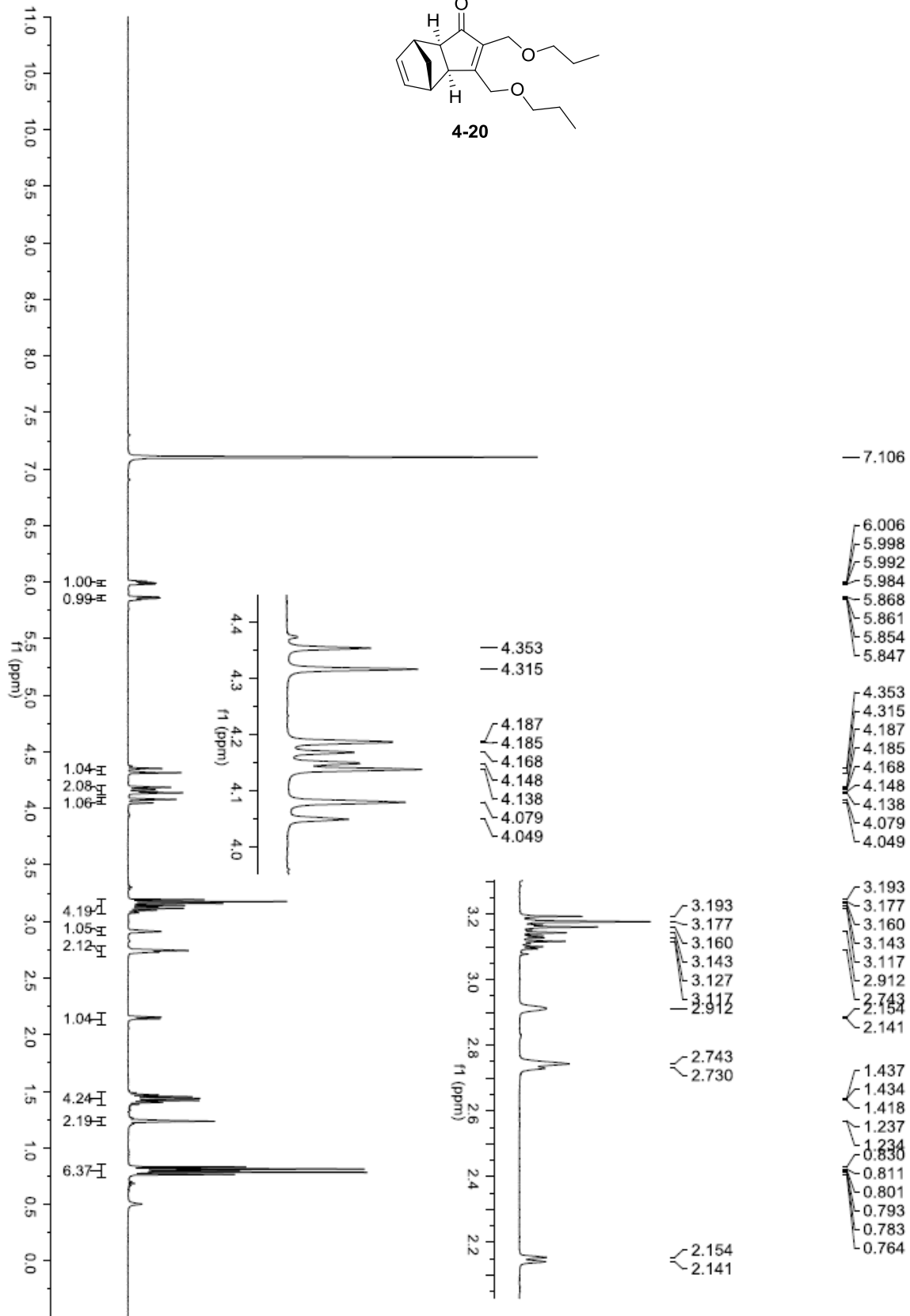
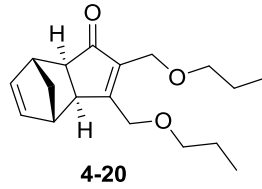


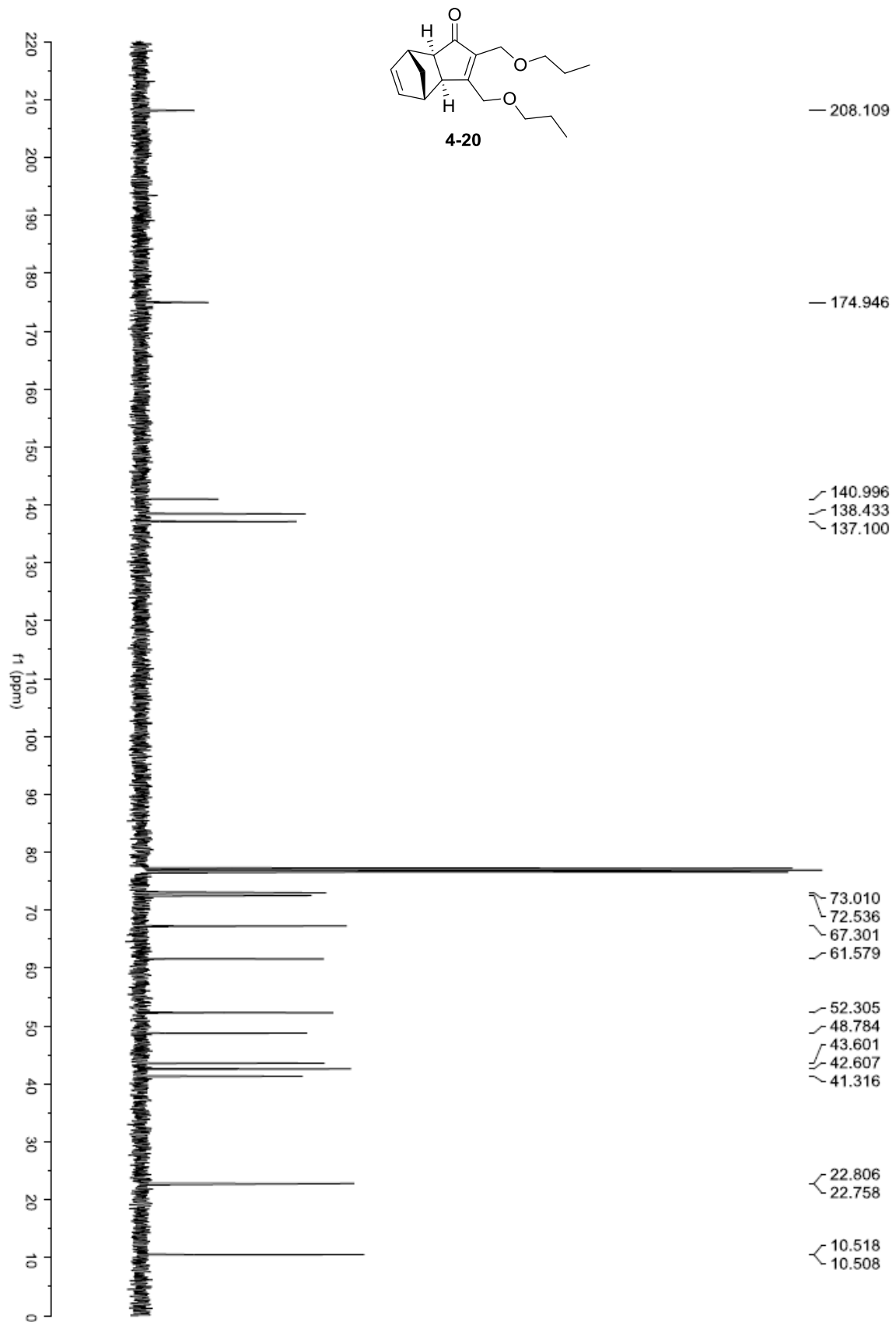
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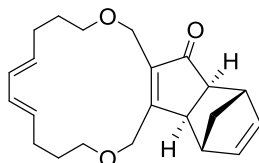
- 148.337
- 132.174
- 131.544
- 122.492
- 69.861
- 65.499
- 32.011
- 27.600
- 23.653



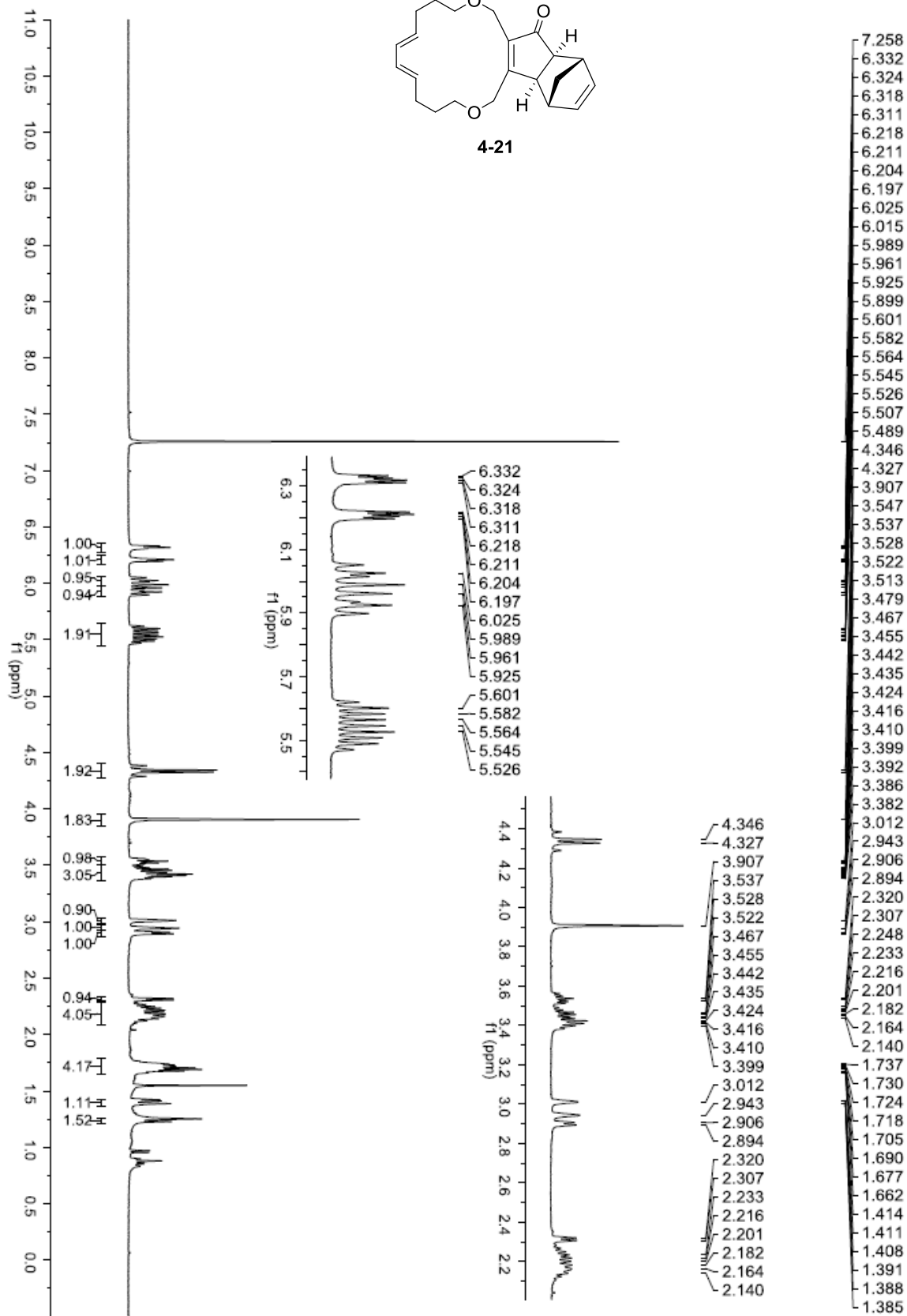


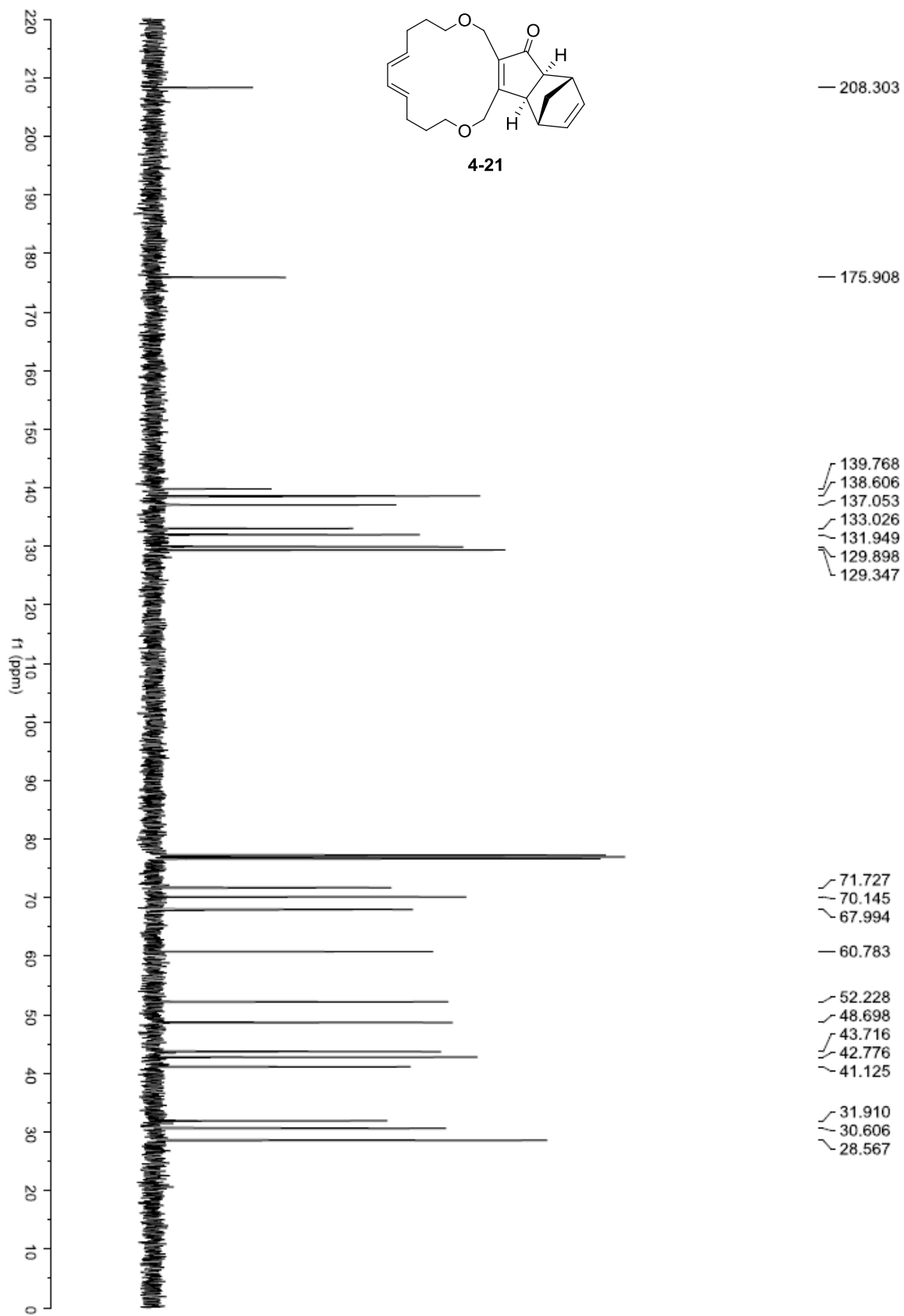


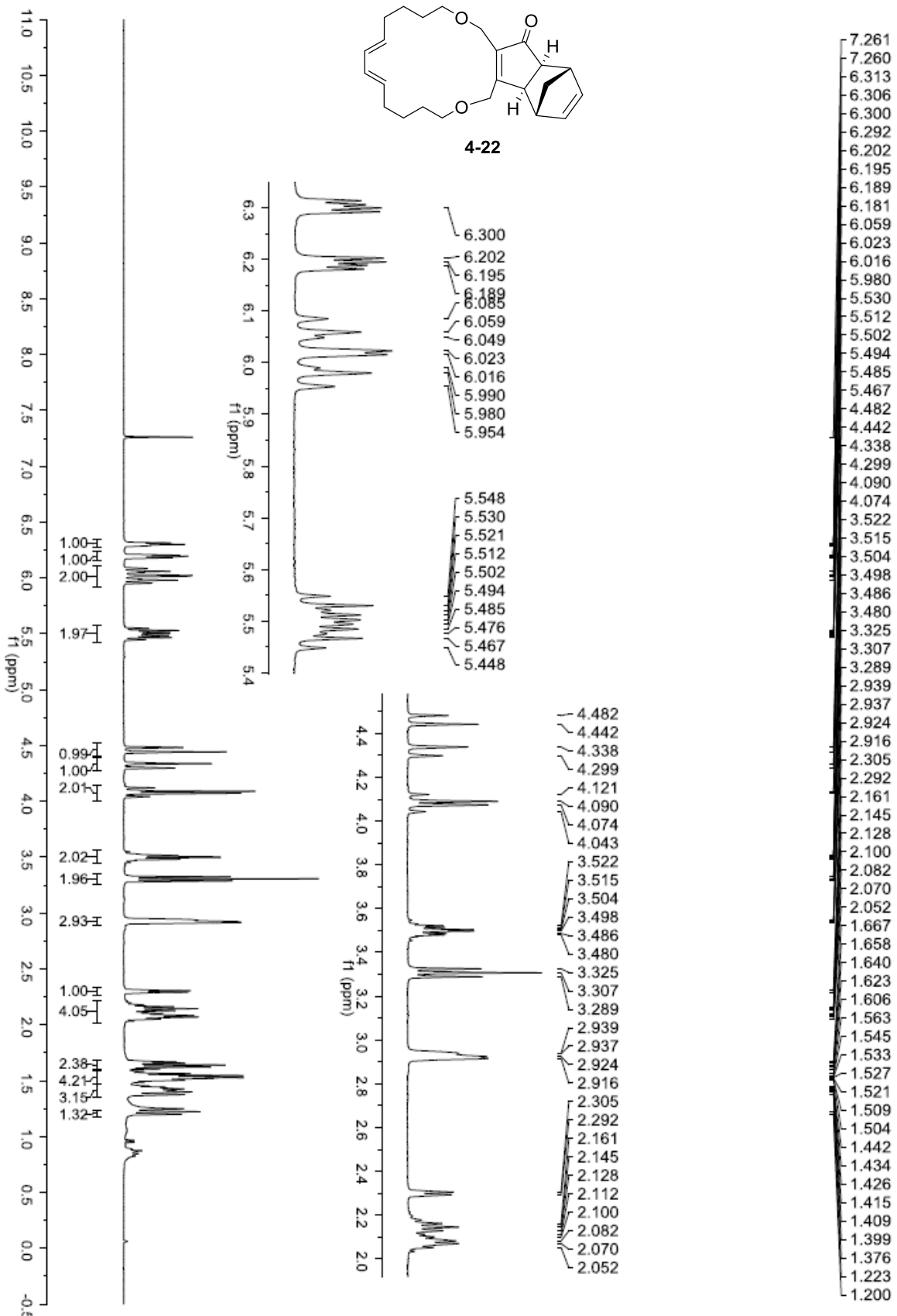


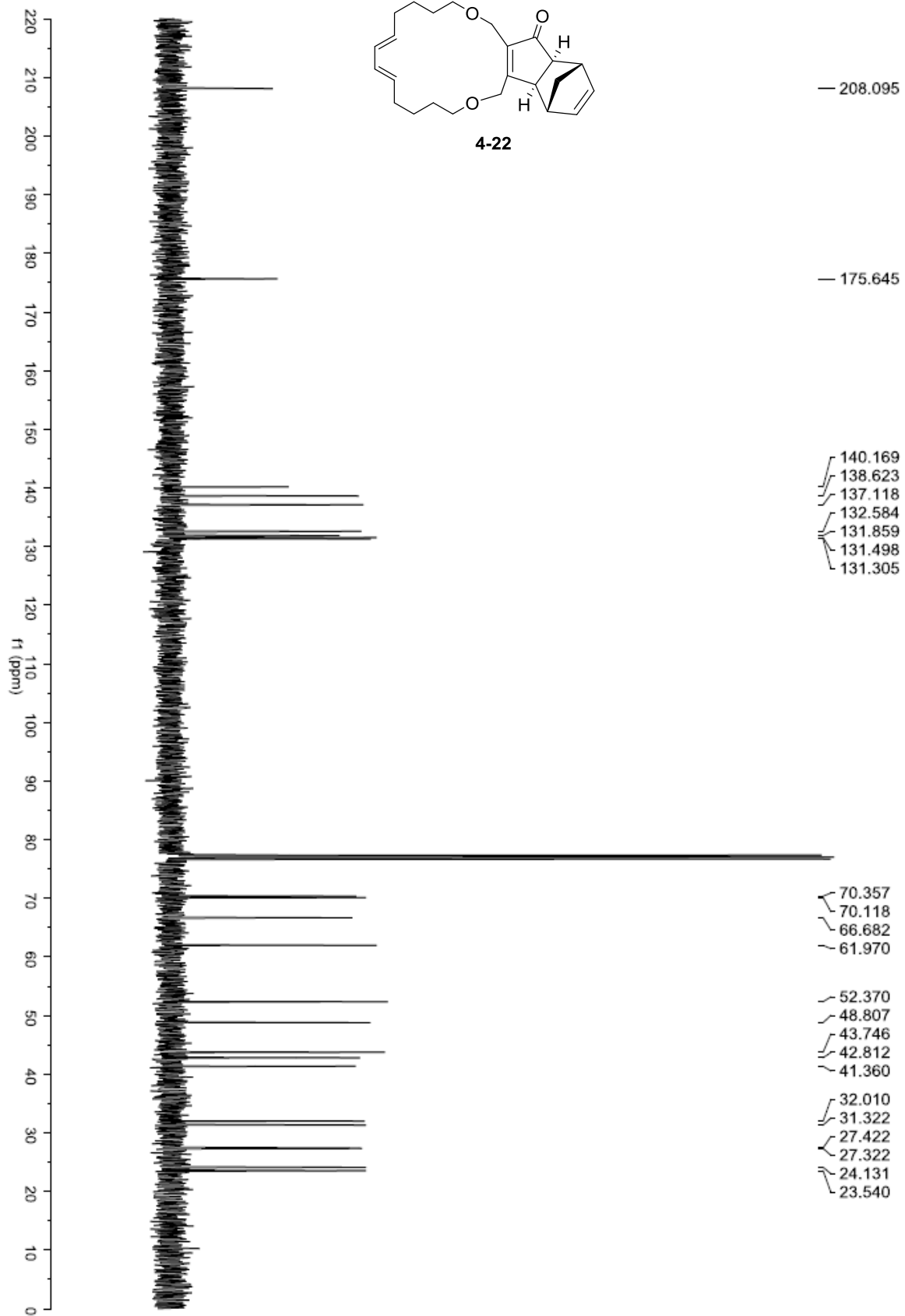


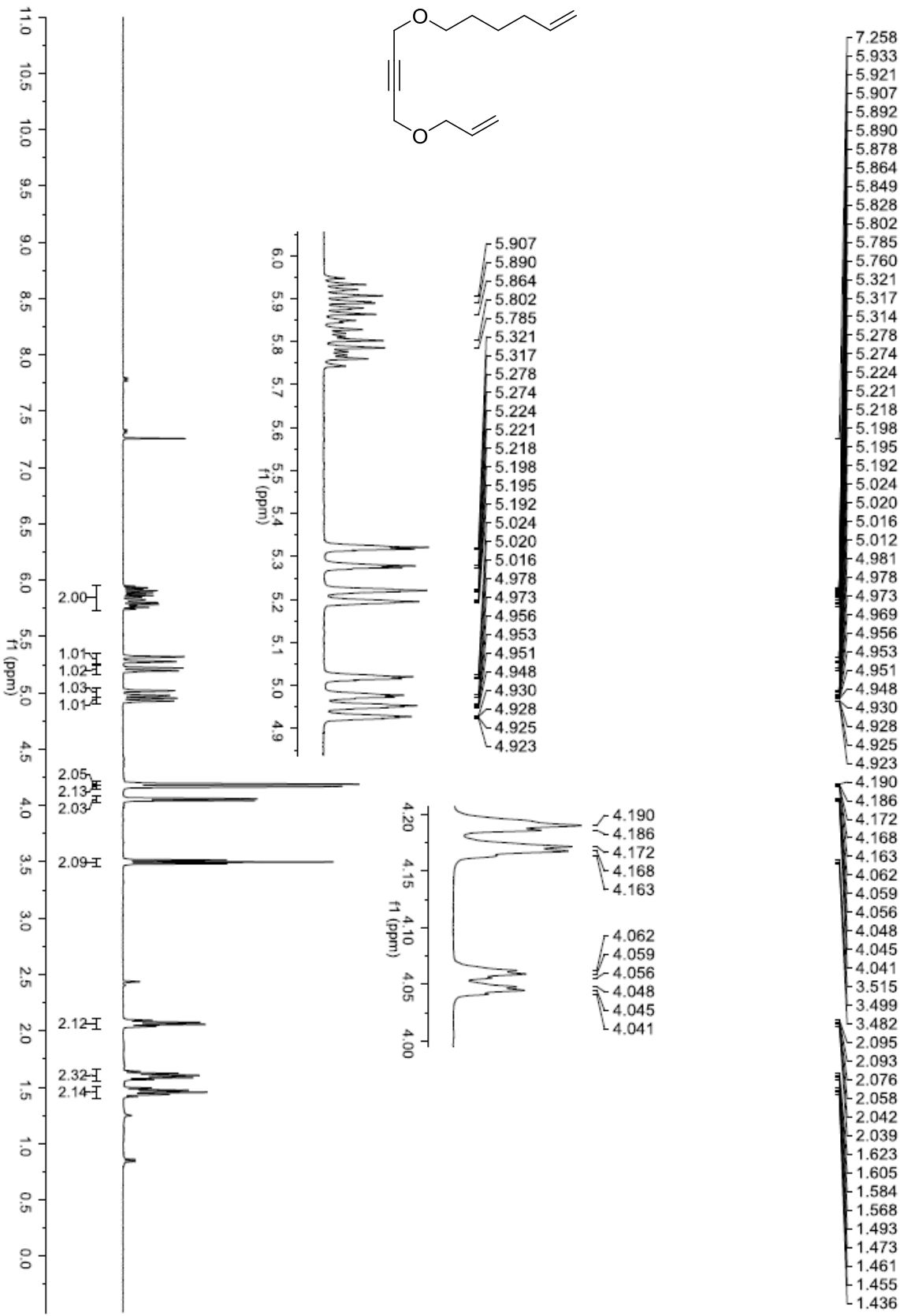
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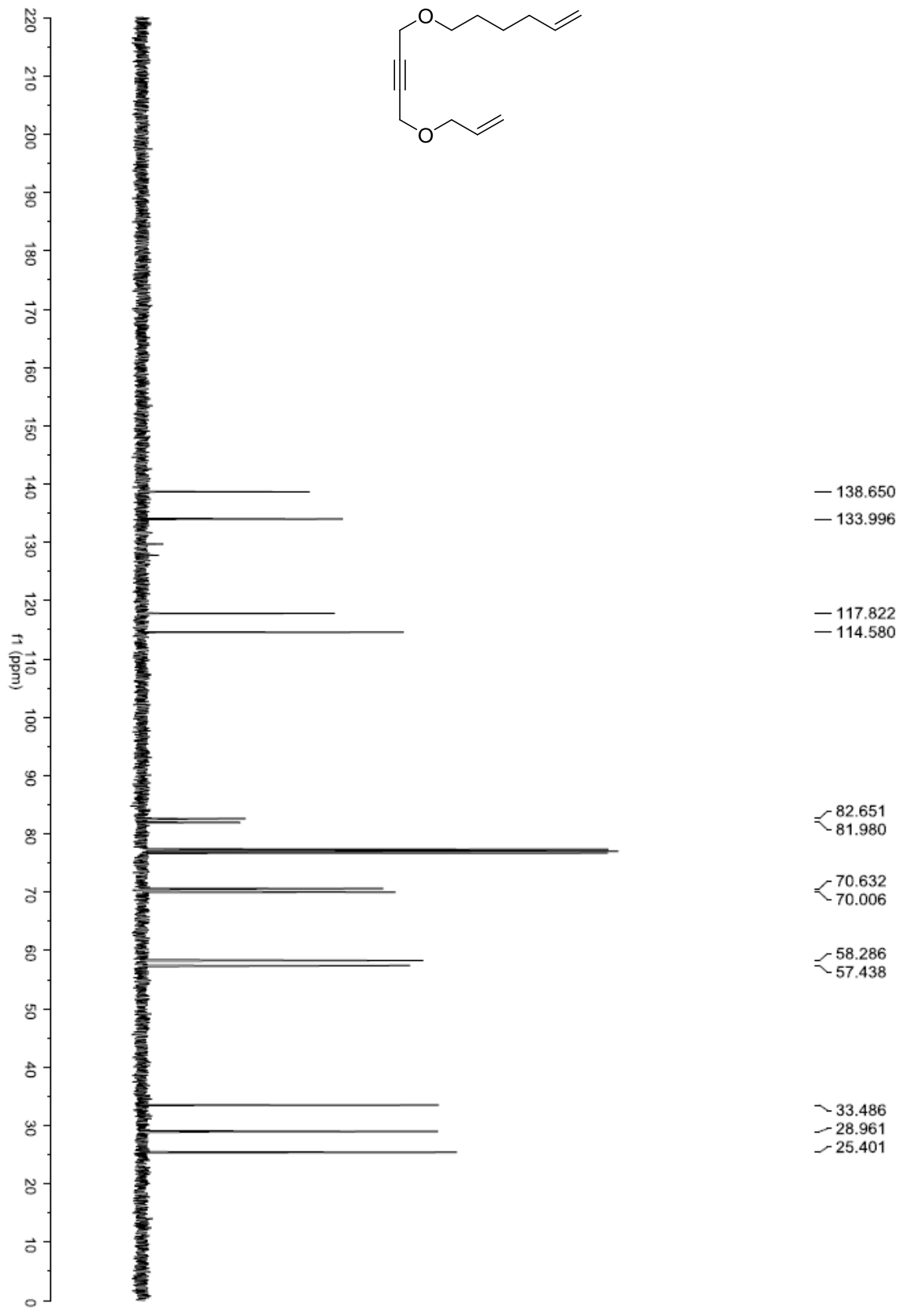


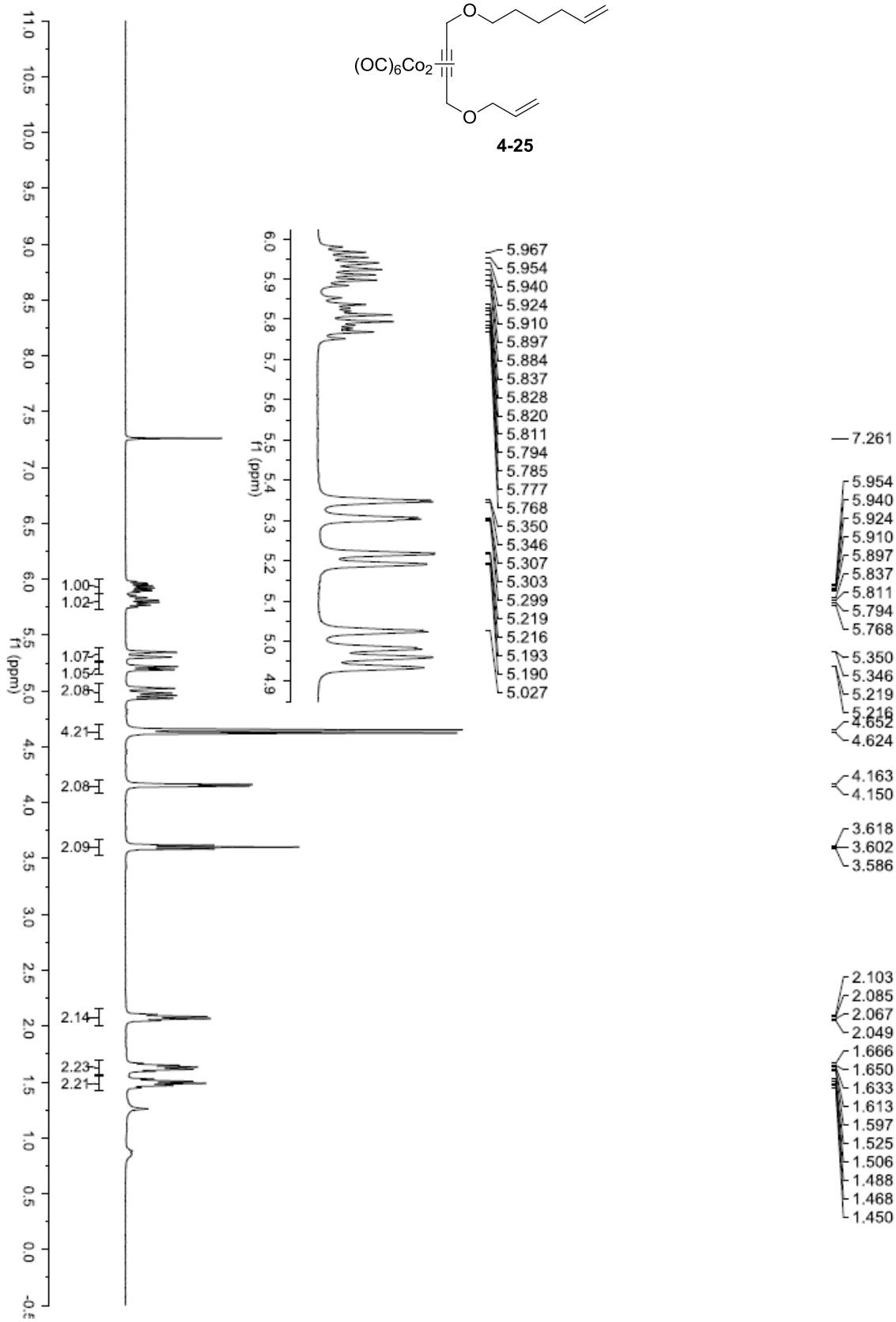






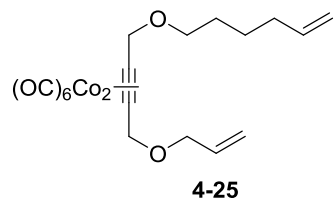






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f1 (ppm)

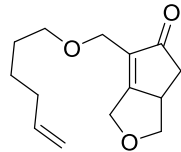


- 138.737
- 134.387

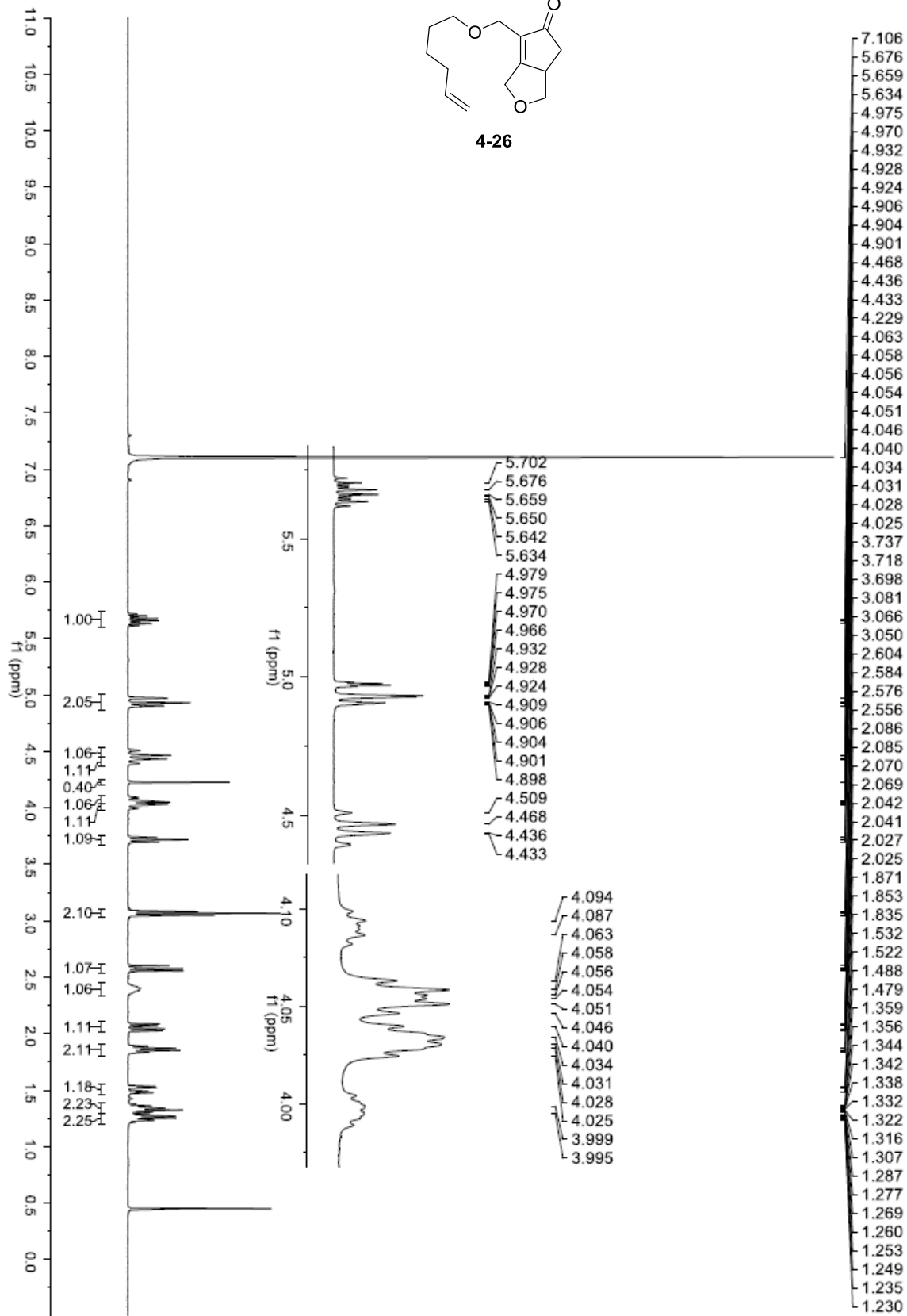
- 116.834
- 114.467

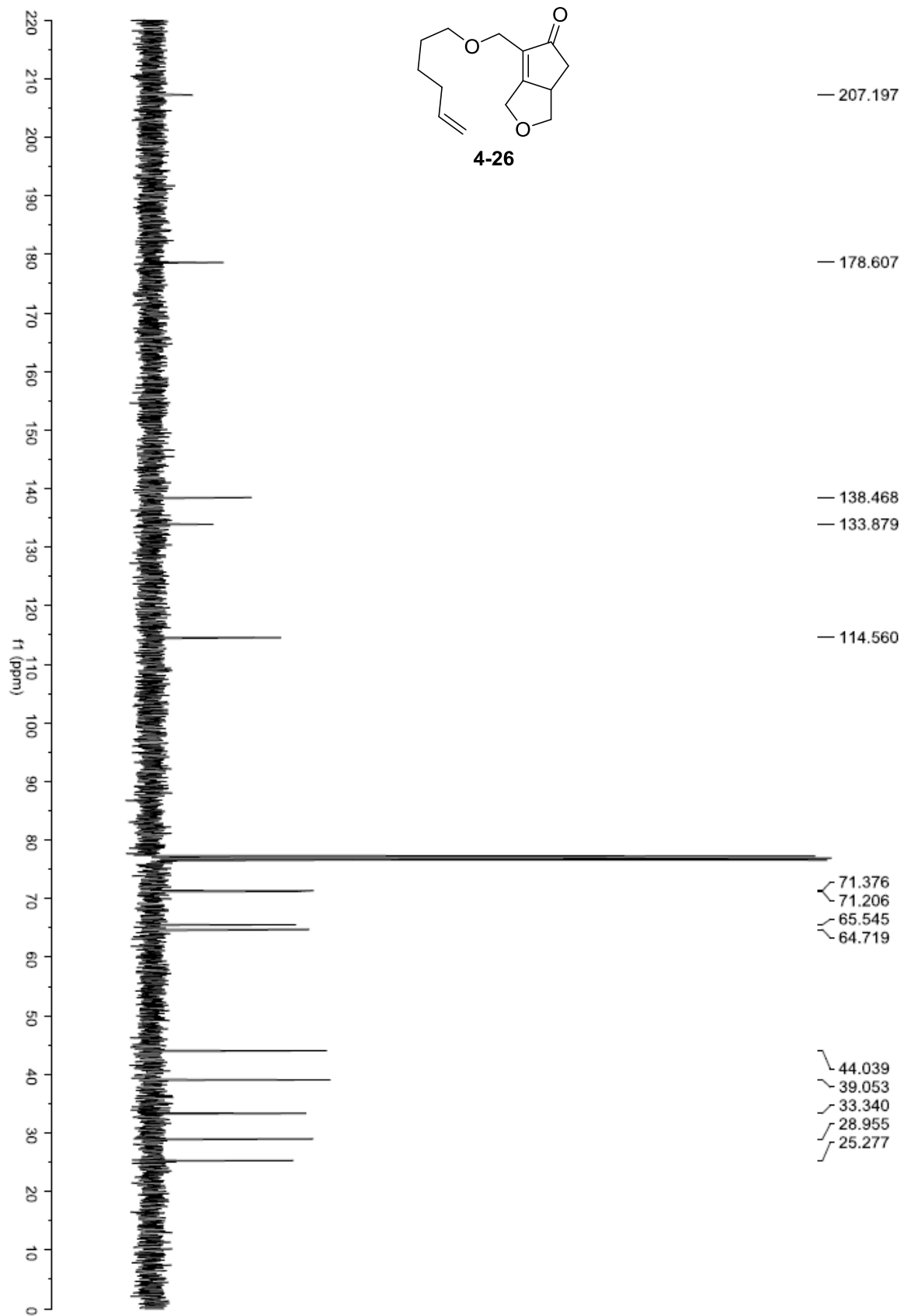
- { 71.652
- { 70.994
- { 70.957
- { 70.220

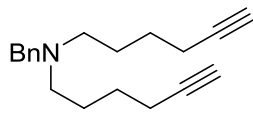
- ~ 33.493
- 29.195
- ~ 25.350



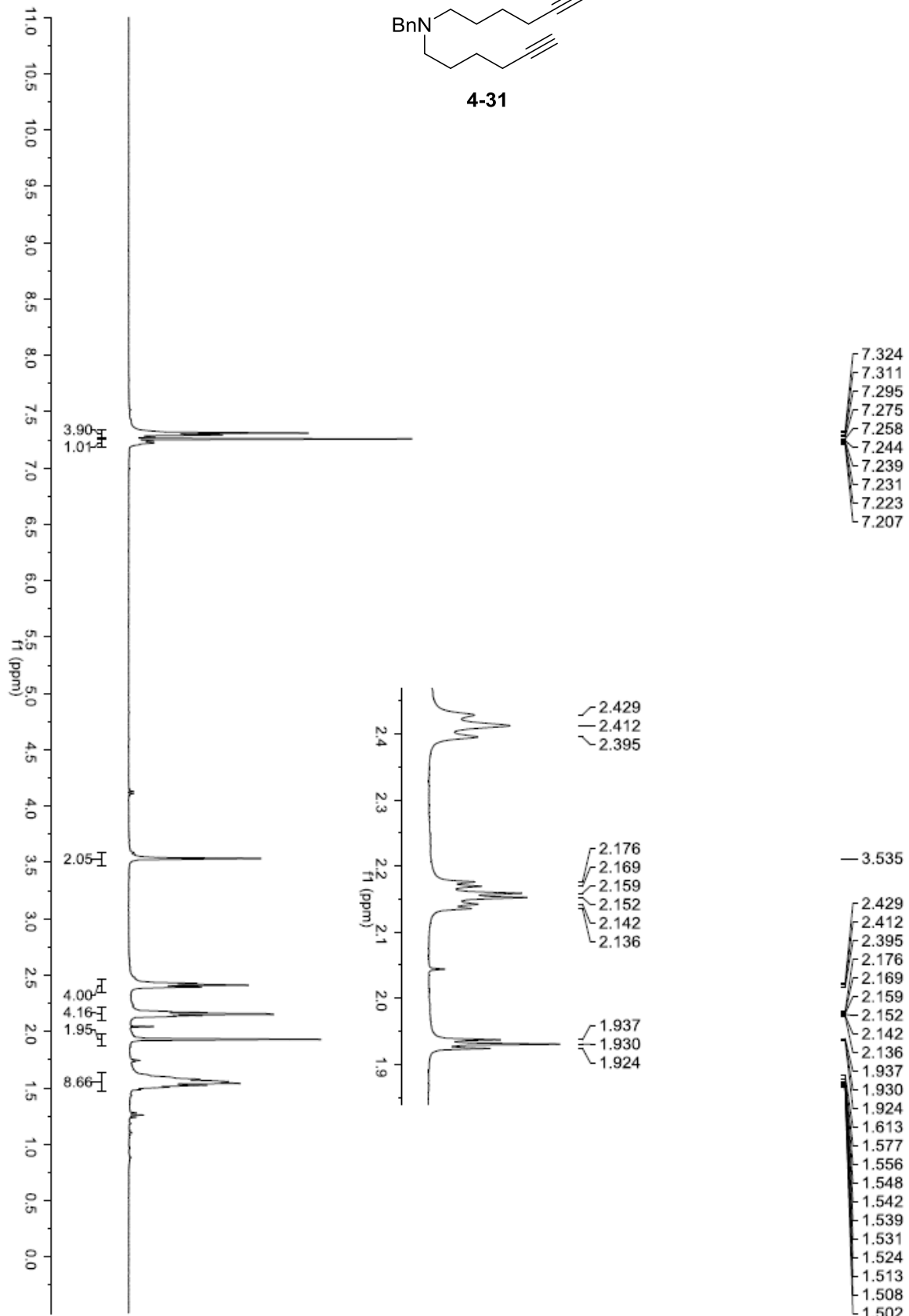
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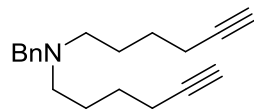




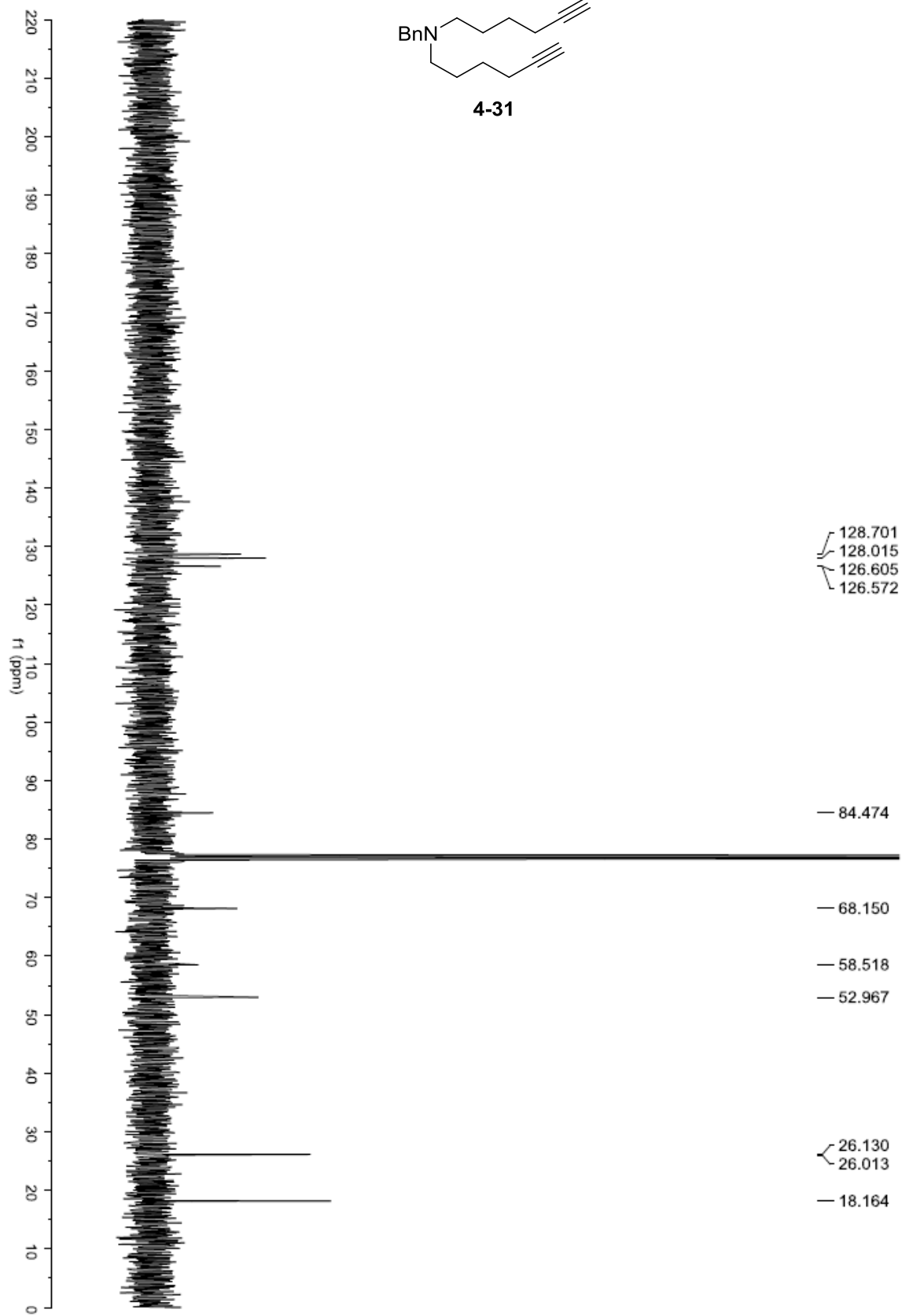


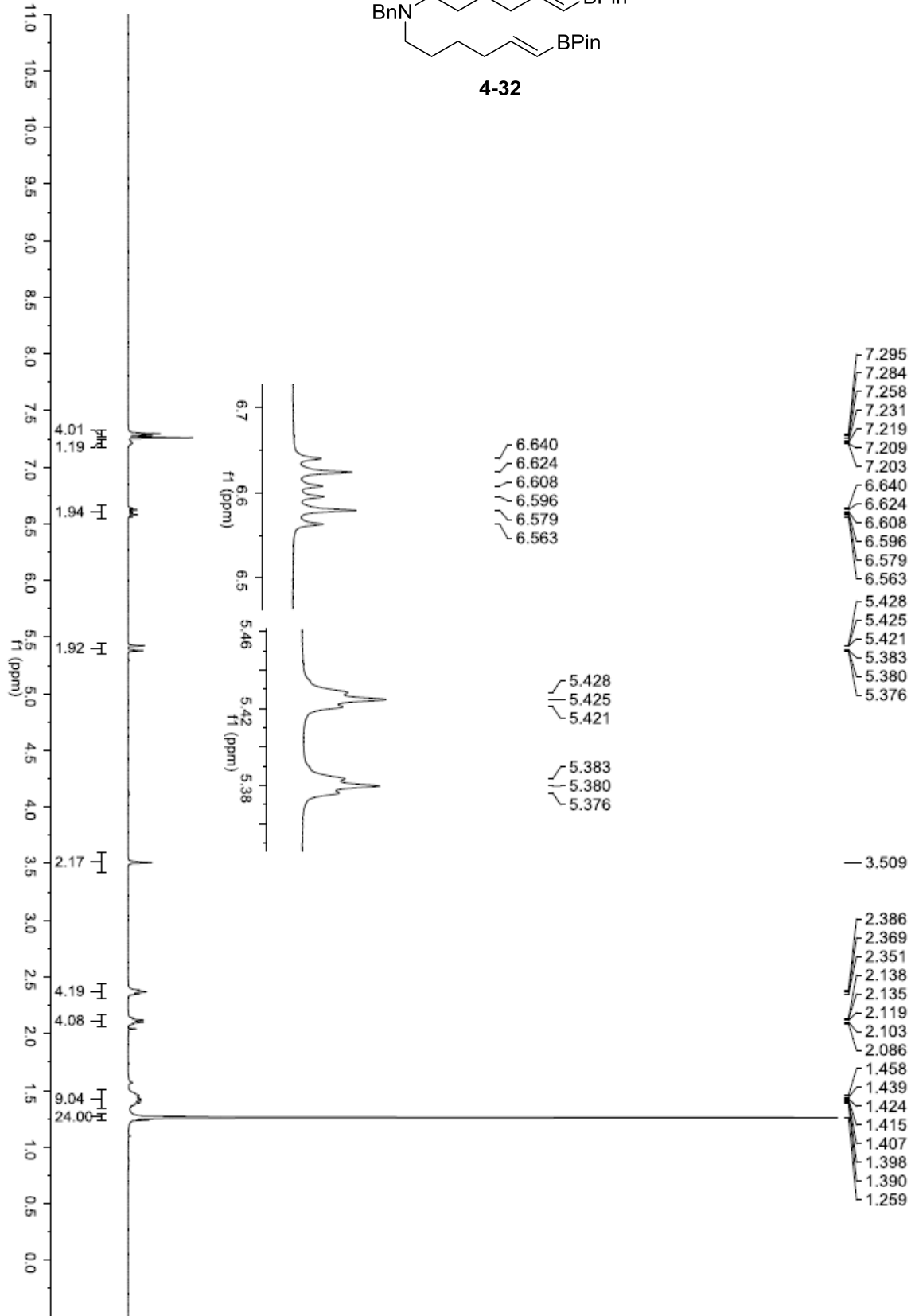
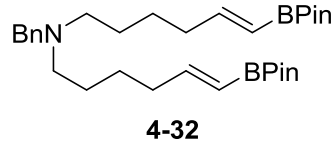
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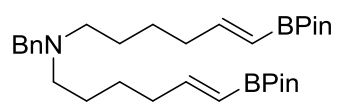




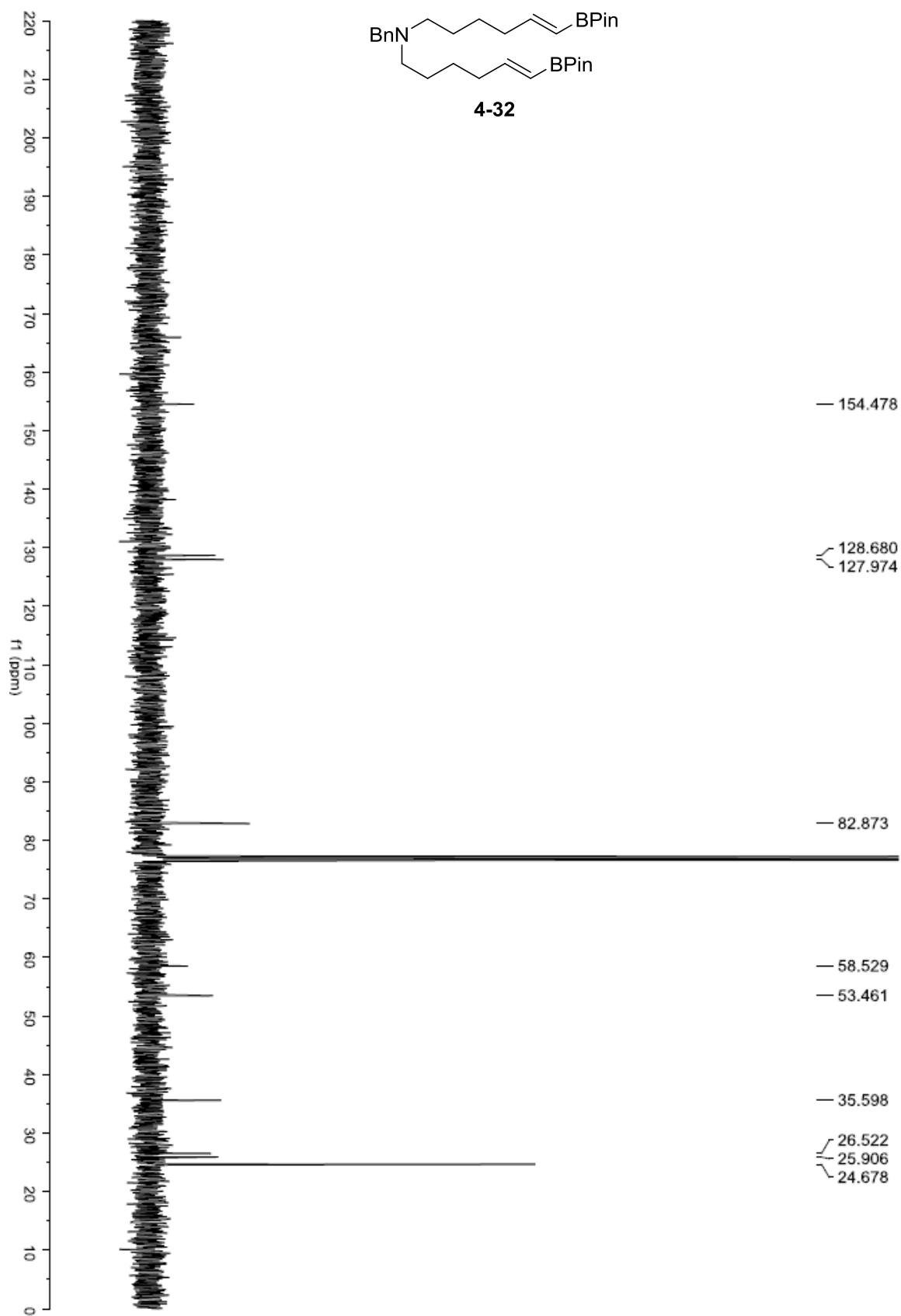
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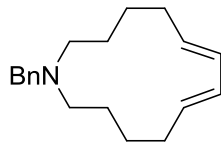




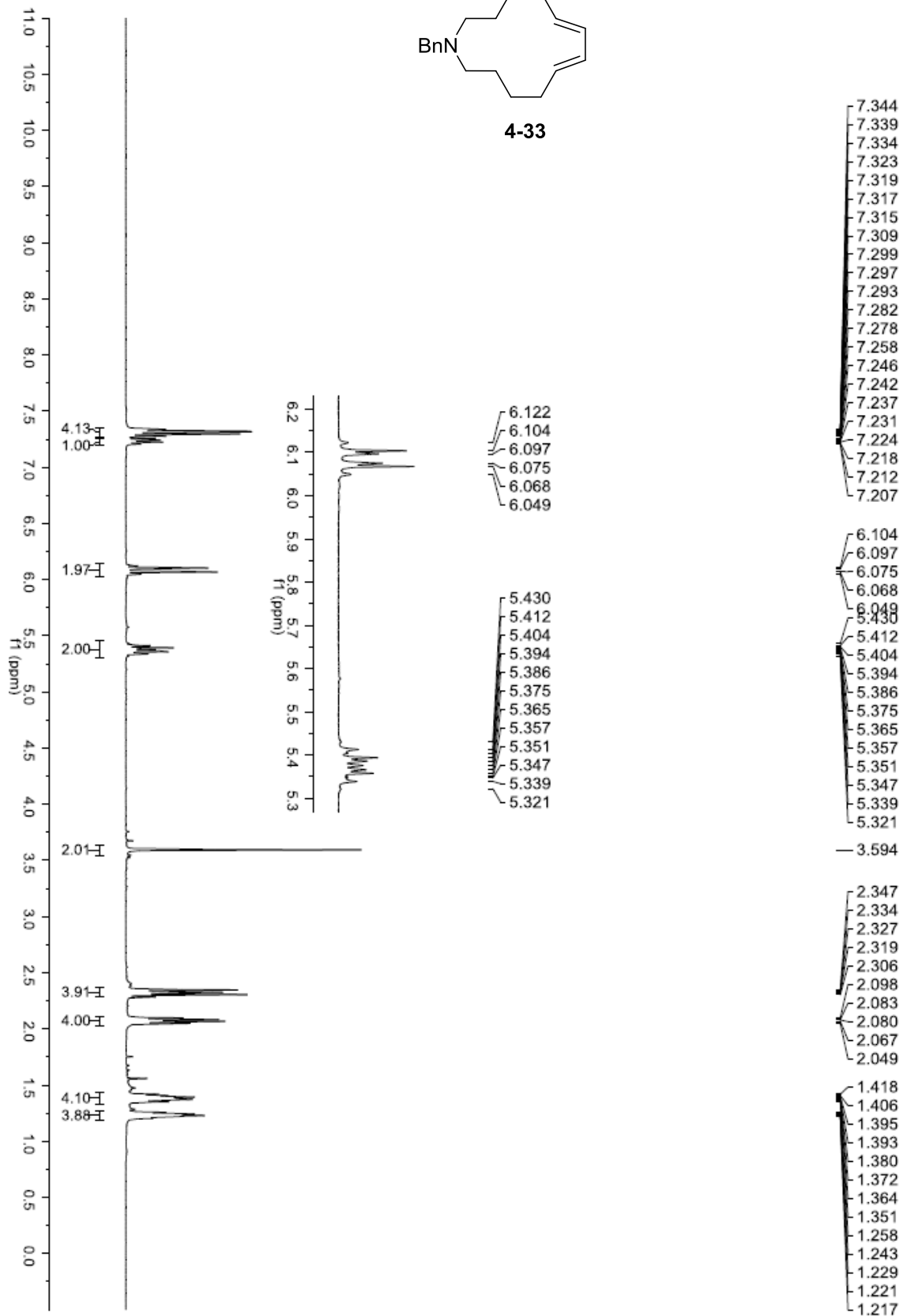


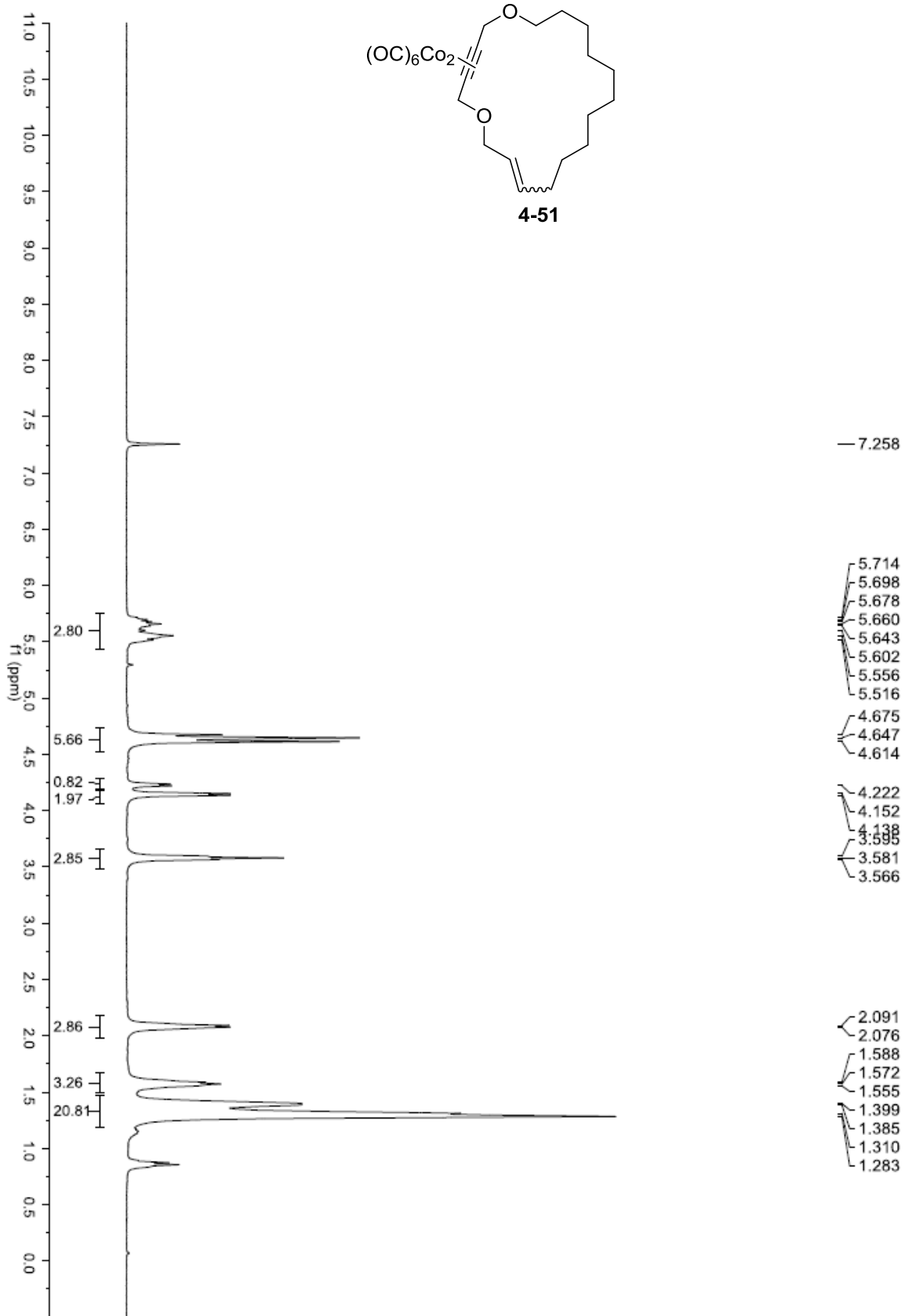
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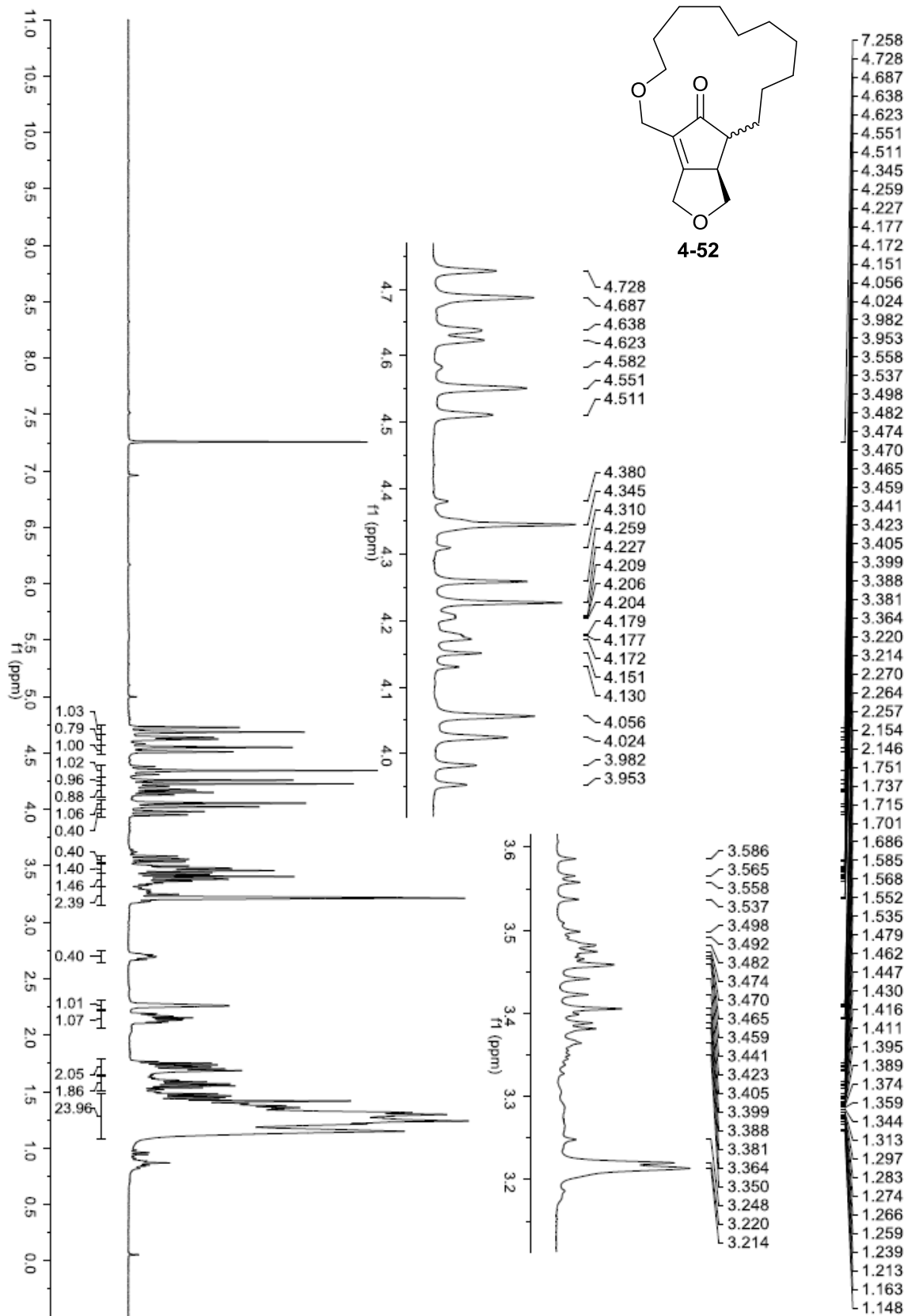


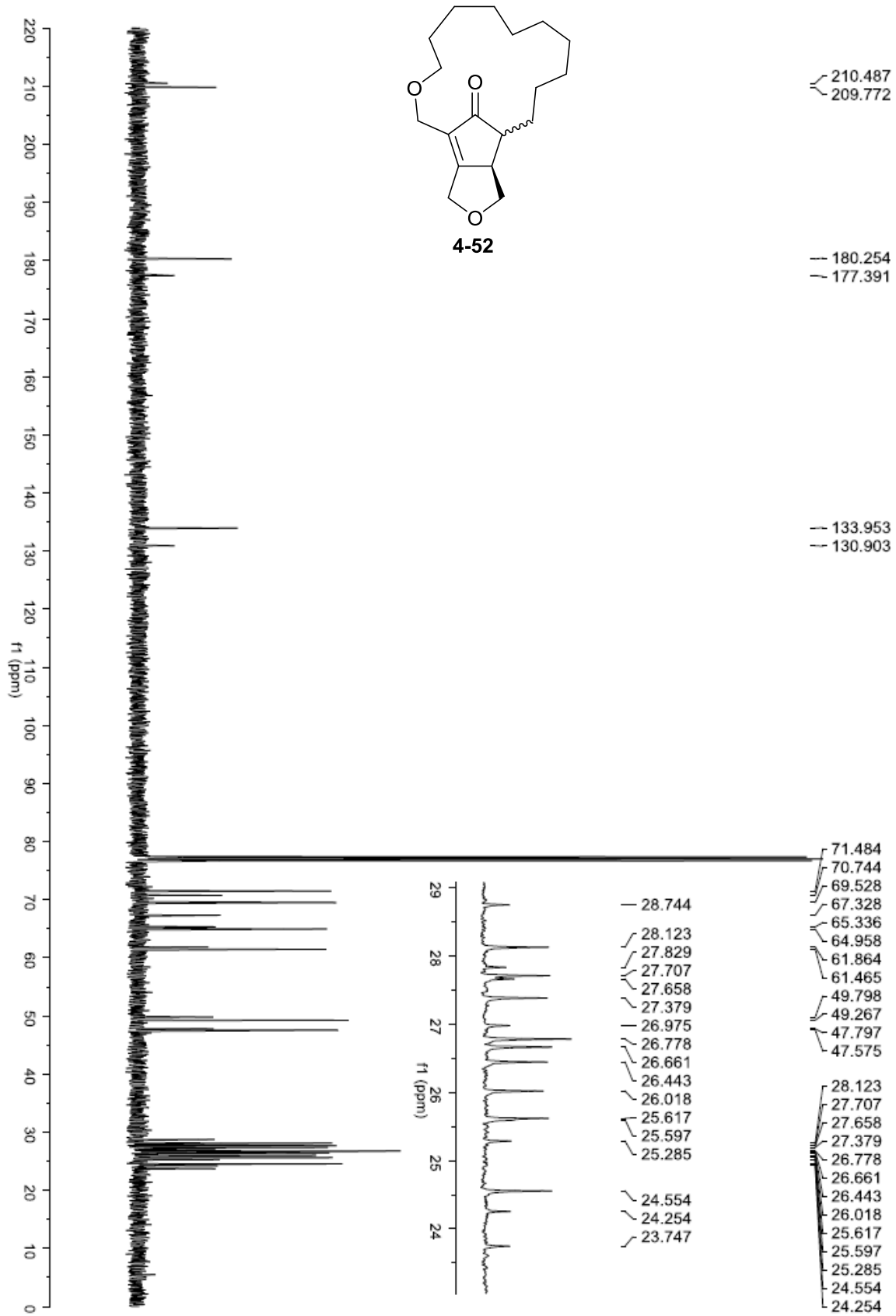


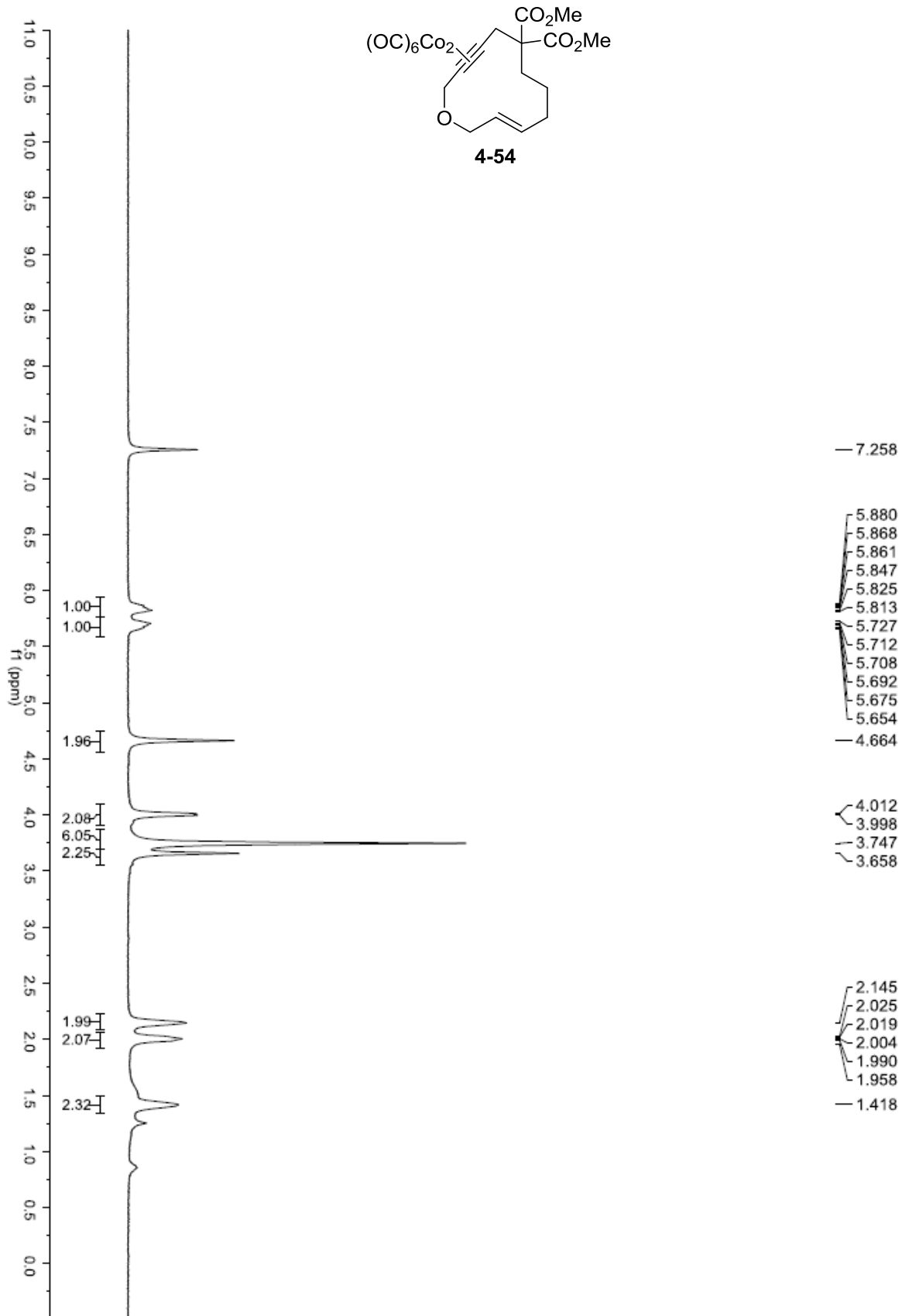
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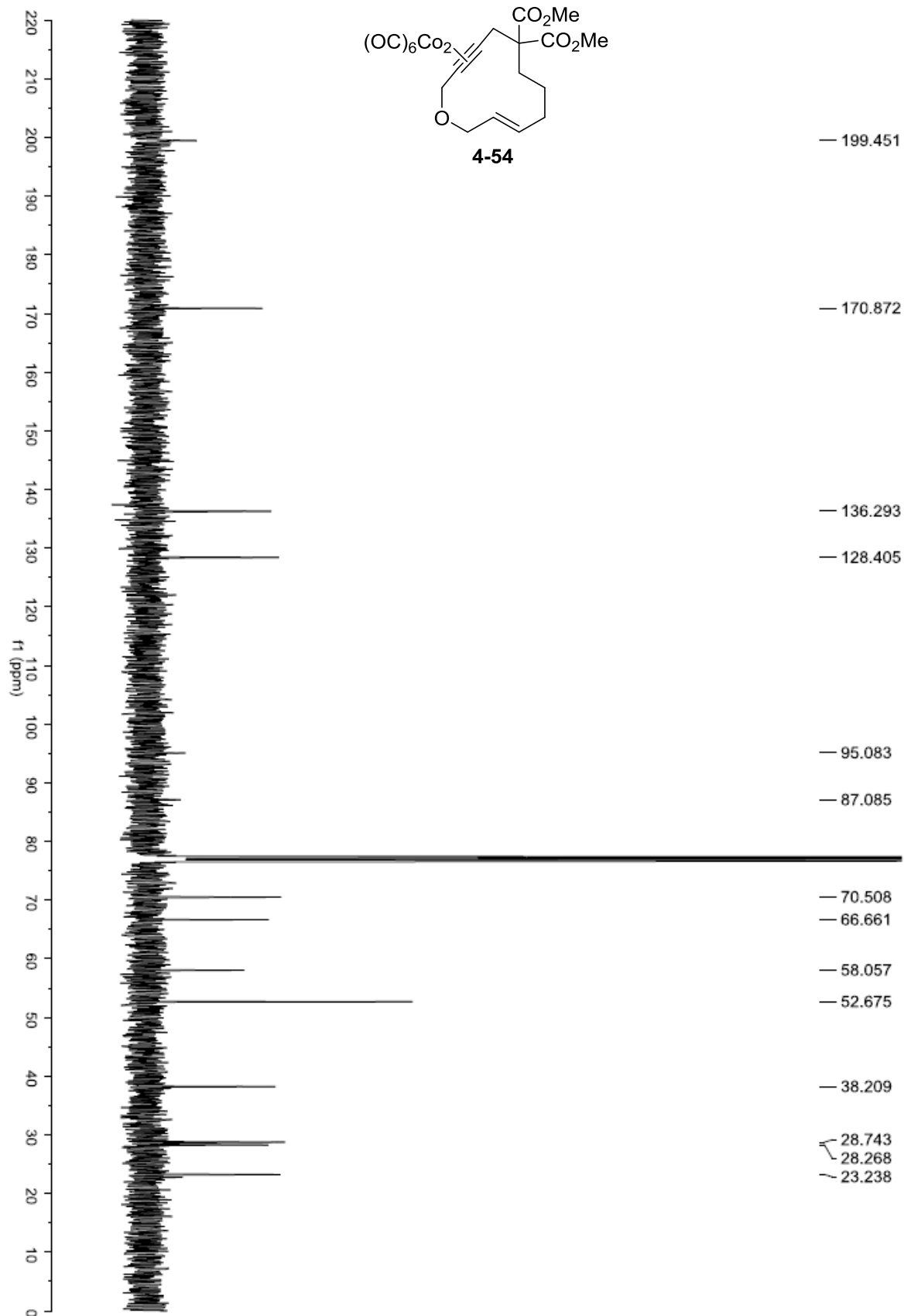












NMR conversion study

