THE DEVELOPMENT OF NICKEL CATALYZED [2+2+2] CYCLOADDITIONS AND CYCLOISOMERIZATIONS

by

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The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

An improved method for the [2+2+2] cycloaddition of diynes with CO_2 to synthesize pyrones was developed using a Ni/NHC catalyst system. The new catalyst system boasts improved yields, lower reaction temperatures, and lower reaction pressures compared to the previously known methods. Furthermore, certain unsymmetrical diynes could be employed in the reaction to generate a single pyrone regioisomer. Extensive studies suggest that the regioselectivity arises from steric interactions between the NHC ligand and the substituents on the alkyne termini.

In an effort to synthesize pyrans, attempts at cyclizing aldehydes and ketones with diynes and enynes were made. When aldehydes and diynes were employed, the expected pyran cycloadduct was not obtained. Instead, the [3,3] electrocyclic ring opened tautomer was obtained. The use of enynes with aldehydes prevented this tautomerization, but the synthesis of the desired pyran was highly substrate dependent due to competitive side product formation.

The use of ketones and enynes in the cycloaddition allowed for the chemoselective formation of dihydropyrans in excellent yields. However, it was necessary to carefully tune the reaction conditions to each particular substrate in order to achieve high yields. Nonetheless, this represents the first [2+2+2] cycloaddition of ketones and enynes.

Due to the air sensitivity of the Ni(0) precursor and the carbene ligand, a method was devised for generating the active catalyst in situ from air stable precursors. While this method worked very well for the cyclization of diynes and nitriles, the coupling of diynes with CO_2, aldehydes, and isocyanates was less successful.

The Ni/NHC cycloisomerization of enynes to 1,3-dienes was also discovered. While the yields of this reaction were excellent, the substrate scope was limited. Attempts at improving the system were initiated though an in-depth study reaction mechanism. Deuterium labeling experiments suggest that the active catalyst is formed by an unprecedented C-H activation of the carbene ligand by the Ni(0).

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STANDARD LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
appt	apparent (spectral)
atm	atmospheres (pressure)
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binathalene
bipy	2,2’-bipyridine
Bn	benzyl
br	broad (spectral)
Bu	butyl
t-Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
calcd	calculated
COD	cyclooctadiene
Cp	cyclopentadienyl anion
Cy	cyclohexyl
CI	chemical ionization

d	day(s); doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
DMF	dimethylformamide
DMP	dimethoxypropane
DMSO	dimethyl sulfoxide
dppf	(diphenylphosphino) ferrocene
ee	enantiomeric excess
E’	ethyl ester
equiv	equivalents
Et	ethyl
EtOAc	ethyl acetate
EI	electron impact
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
HMPA	hexamethylphosphoramide
h	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HRMS	high-resolution mass spectrum

HRFAB	high-resolution fast atom bombardment
Hz	hertz
IAd	1,3-diadamantylimidazol-2-ylidene
I^{t}Bu	1,3-di-*tert*-butylimidazol-2-ylidene
IL	ionic liquid
IMes	1,3-bis-(1,3,5-trimethyl)-imidazol-2-Ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	coupling constant (in NMR)
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LUMO	lowest unoccupied molecular orbital
M	moles per liter
MA	maleic anhydride
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry, molecular sieves
Ms	methanesulfonyl
m/z	mass to charge ratio

NBS	N-bromosuccinimide
NHC(s)	*N*-Heterocyclic carbene(s)
NMR	nuclear magnetic resonance
PE	polyethylene
Ph	phenyl
PNB	polynorbornene
ppm	parts per million (in NMR)
i-Pr	isopropyl
n-Pr	propyl
Py	pyridine
q	quartet (spectral)
RCM	ring closing metathesis
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral); second(s)
SIMes	1,3-bis-(1,3,5-trimethyl)-4,5-dihydroimidazolin-2-ylidene
SIPr	1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidene
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TESH	triethylsilane

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl, tetramethylsilane
TON	turn over number
Ts	*p*-toluenesulfonyl

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CHAPTER 1

N-HETEROCYCLIC CARBENES AS LIGANDS IN NICKEL CATALYSIS

Introduction

The development of transition-metal catalysts has grown exponentially over the past several decades. These catalysts, in turn, have been used extensively in several synthetically useful reactions such as cross-couplings, metathesis, oxidations, reductions, and annulations. One obvious benefit of using a transition-metal catalyst as opposed to stoichiometric reagents is that the catalyst is more atom economical (i.e., one molecule of catalyst converts several molecules of reactant to product). Another benefit of transition-metal catalysts is their reactivity can be easily tuned by changing which ligand is employed. For instance, replacing a nonchiral ligand with a chiral ligand can render a reaction enantioselective.

The vast majority of the datively bound ligands employed in transition-metal catalysis have been P, N, S, or O based. With Arduengo's disclosure of the isolation of stable, crystalline *N*-Heteorcyclic carbenes (NHC's) from reliable synthetic routes, a new class of ligands for transition-metal catalysis has been rapidly emerging.[1] Electronically, this class of carbenes has been shown to be very nucleophilic which is attributed to the nitrogen lone-pair donation into the empty *p*-orbital of the carbene carbon.[2,3] When coordinated to transition metals, carbenes are found to be much like traditional phosphines and phosphates as they are excellent σ-donors and poor π-aceptors.[4]

While carbenes are electronically similar to phosphines, research has shown that they are much better donors than phosphines. By replacing phosphines with the better donating carbenes, more reactive metal centers have been created improving the performance of several transition-metal catalysts.[5,6,7] While several examples exist for the improvement of Pd-catalyzed processes by replacing phosphines with carbenes, much less success has been achieved in the more economical Ni-catalysis.

Oligomerization and Polymerization

When Ni(II)-NHC complexes contain an alkyl, aryl, or acyl group, reductive elimination can occur, affording Ni(0) compounds and 2-alkylated organoimidazolium salts (Figure 1.1). This pathway results in catalyst decomposition for reactions by Ni-NHC systems.[8] In Ni-NHC catalyzed olefin dimerization, Cavell and Wasserscheid showed that this decomposition is inhibited when reactions are run in ionic liquids rather than more classical solvents such as toluene.[9]

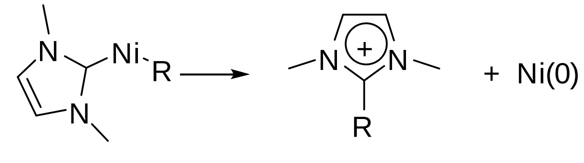


Figure 1.1. Carbene reductive elimination from Ni.

A series of $Ni(NHC)_2I_2$ complexes were prepared and evaluated as catalysts in both toluene and ionic liquids. In toluene, no butene oligomers were formed at 20 °C. Instead, butene was incorporated into the imidazolylidene cation in the 2-position (Figure 1.2). These results suggest that although Ni hydrides and alkyls were being formed, these species reductively eliminated too rapidly for chain growth to occur. In contrast, all reactions run in a buffered melt (composed of a mixture of 1-butyl-3-methylimidazolium chloride, $AlCl_3$, and *N*-methylpyrrole) showed complete conversion to propene dimers. Interestingly, greater turnover numbers were observed in reactions catalyzed by Ni-NHC complexes versus $NiCl_2(PCy_3)_2$ (Table 1.1).

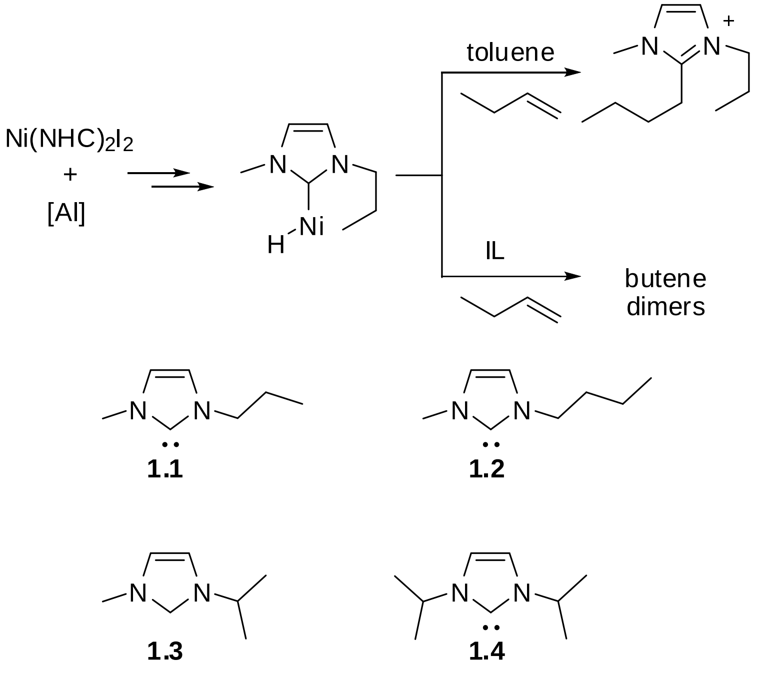


Figure 1.2. Ni/Carbene catalyzed dimerization of 1-butene vs. reductive elimination.

Table 1.1. 1-Butene dimerization in IL.

Entry	catalyst	yield (%)	TON	TOF (h^{-1})
1	NiI_2(**1.1**)$_2$	56.3	2815	5630
2	NiI_2(**1.2**)$_2$	70.2	3510	7020
3	NiI_2(**1.3**)$_2$	38.2	1910	3820
4	NiI_2(**1.4**)$_2$	50.7	2535	5070
5	$NiCl_2(PCy_3)_2$	29.5	1475	2950

In addition, Ni(**1.1**)$_2$$I_2$ displayed different selectivity than $NiCl_2(PCy_3)_2$ toward different isomers in the dimerization of propene. Desirable highly branched propene dimers were obtained in higher ratios with $NiCl_2(PCy_3)_2$. Changes in the organic side chain of the carbene did not lead to an increase in branching which may suggest the formation of a common active species resulting from incorporation of the imidazolium cation onto the Ni complex. Also, in ionic liquids, phosphine dissociation may not play a significant role.

By changing the NHC ligands to NHCs possessing a hemilabile pyridine linkage, Jin and coworkers were able to use Ni(II)-NHC complexes as catalysts for the polymerization of norbornene and ethylene in the presence of methylaluminoxane (MAO) as a cocatalyst.[10] The Ni complexes were prepared as shown in Figure 1.3. Although the free carbenes of **1.5** could not be generated successfully, the desired Ni compounds (**1.6**) could be prepared via the preparation of Ag-NHCs and subsequent reaction with $Ni(PPh_3)_2Cl_2$. X-ray analysis revealed that both compounds possess essentially square planar geometries and the two chelates adopt a cis arrangement around the nickel atom.

The catalytic activity for olefin polymerization was evaluated for complex **1.6**. High molecular weight addition-type polynorbornene with a moderate molecular weight

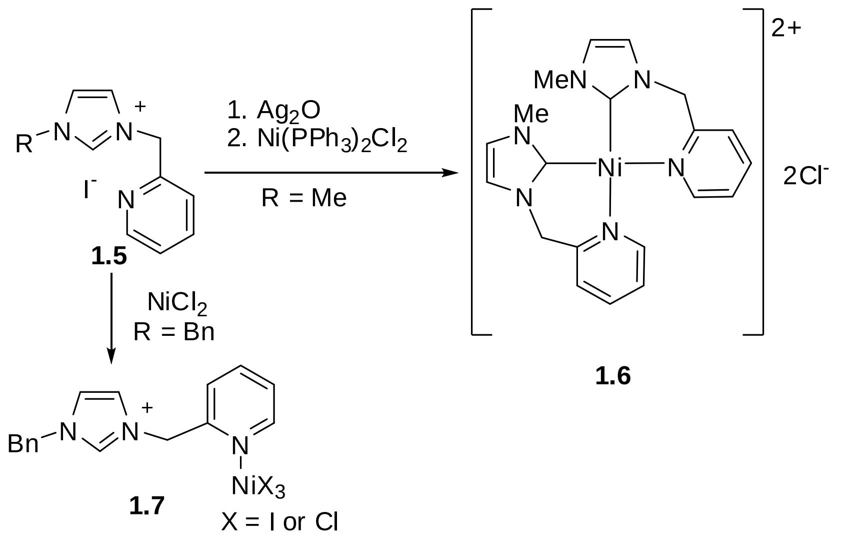


Figure 1.3. Preparation of Ni complexes for polymerization.

distribution (M_w = 10^6, M_w/M_n =2.3-3.5) was obtained when **1.6** was activated with MAO. The activity was highest at 80 °C (10^7 g of PNB/(mol of Ni) h^{-1}) resulting from an increase in the concentration of active catalyst centers at that temperature. However, further increase in temperatures led to catalyst decomposition rather than higher turnover numbers.

Complex **1.6** displayed moderate catalytic activity towards the polymerization of ethylene (3.3 x 10^5 g/mol h). In addition, higher molecular weight distributions were observed (M_w/M_n =12.8). The ^{13}C NMR analysis of the polyethylene showed that methyl branches predominate (with *ca*. 3.4 methyl branches per 1000 carbon atoms) suggesting that chain walking does not affect polymerization to a high degree. When only the pyridine moiety (and not the imidazolium salt) is ligated (**1.7**),[11] ethylene polymerization occurs twice as effectively (6 x 10^5 g PE/(mol of Ni) h^{-1}) under similar conditions (only 30 min rather than 60 min).

Transfer Hydrogenation

Fort and Schneider showed recently that the combination of Ni(0) and IMes catalyzed the transfer hydrogenation of imines to the corresponding amines in the presence of $NaOCHEt_2$ (Figure 1.4).[12] A variety of aldimines and ketimines were reduced in good to excellent yields under mild conditions. A range of NHC ligands were explored, including ones possessing pendant, hemilabile pyridines. However, only IMes was effective (97%). Surprisingly, under identical conditions, IPr showed only 4% yield. Although ICyPic gave respectable results (86%), IMesPic showed marginal activity (15%). Clearly, no correlation between catalyst activity and NHC ligand could be rationalized. Nevertheless, the authors used the combination of Ni(0) and IMes to catalyze the transfer hydrogenation of a variety of aldimines and ketimines. Amines possessing a wide range of functionalities were obtained in yields ranging from 5-99%. No hydrogenation was observed with cyano- and pyridine-substituted imines and is likely due to ligand displacement and subsequent catalyst deactivation.

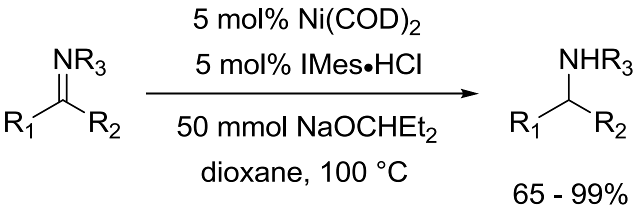


Figure 1.4. Ni-catalyzed transfer hydrogenation of imines.

Kumada-Corriu Cross-Coupling

The use of metals other than Pd for the cross-coupling reactions is an area of intense research due to the economic restraints of using Pd salts in large quantities. Along these lines, Böhm and Herrmann have shown that 5 mol% of the $Ni(IPr)_2$ complex efficiently catalyzes the coupling of aryl Grignards and aryl fluorides to yield the biaryls in high GC yields.[13] Further investigation led to the discovery that a better catalyst could be generated in situ from a 1:1 mixture of $Ni(acac)_2$ and the $IPr{\cdot}HBF_4$ salt, eliminating the need to synthesize the air sensitive $Ni(IPr)_2$ complex (Figure 1.5). It is believed that this mixture generates a highly reactive 12-electron Ni complex bearing a single carbene. Using this system, both electron rich and electron poor aryl fluorides were successfully coupled with a variety of aryl Grignards generating the biaryls in good to excellent yields. While four different pathways can be considered for the C-F bond transformation (i. nucleophilic aromatic substitution, ii. elimination-addition via aryne intermediates, iii. radical pathways, and iv. polar pathways via oxidative addition), experimental data strongly support a polar pathway.

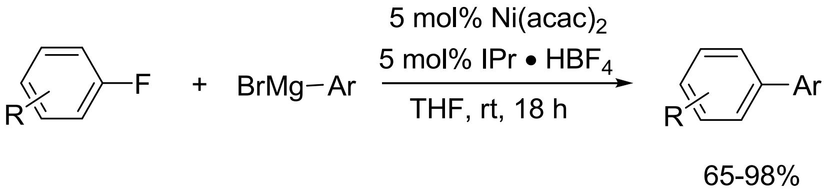


Figure 1.5. Ni/carbene catalyzed Kumada-Corriu Coupling.

Suzuki-Miyaura Cross-Coupling

Nickel/carbene complexes have also been successfully employed in the Suzuki-Miyaura cross coupling reaction. One of the first successful applications of this was demonstrated by Blakey and MacMillan wherein boronic acids were coupled with aryltrimethylammonium salts.[14] It was found that the transformation could be accomplished using 10 mol% $Ni(COD)_2$, 10 mol% IMes·HCl and 3 equivalents of CsF in dioxane. (Figure 1.6). A wide range of aryltrimethylammonium triflates and aryl boronic acids were successfully coupled using this protocol.

A system similar to that of Blakey-MacMillan was later developed by Liu and Robins in which purine derivatives containing imidazol-1-yl, 1,2,4-triazol-4-yl, and fluoro leaving groups at the 6 position could be coupled with both electron rich and poor aryl boronic acids (Figure 1.7).[15] While the Blakey-MacMillan system used the IMes·HCl carbene, it was found that the purine derivatives required the use of the larger SIPr·HCl (or IPr·HCl, in the case of triazole leaving groups). It is also interesting to note that the choice of base is highly substrate dependent. In the purine reaction, K_3PO_4 was found to generally be the best base while in the trimethylammoniumtriflate reaction, CsF was far superior to K_3PO_4.

Examples of well-defined, highly active Ni/carbene complexes catalyzing the Suzuki reaction have also been reported. McGuinness and coworkers have shown that using as little as 0.03 mol% of $Ni(tmiy)_2I_2$ or $Ni(tmiy)_2$(o-tolyl)Br (Figure 1.8) in the coupling of 4-bromoacetophenone with phenylboronic acid led to 19% (TON = 630) and 58% (TON = 1930) conversion of the aryl halide, respectively.[16]

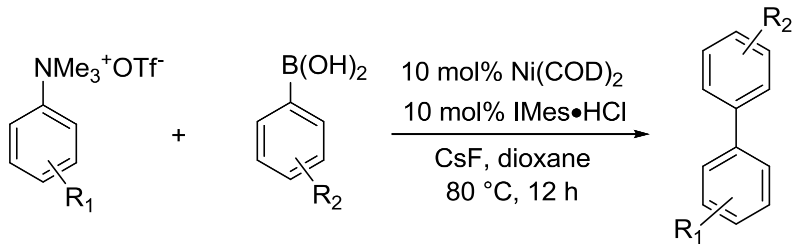

NMe3+OTf-
R1
+
B(OH)2
R2
10 mol% Ni(COD)2
10 mol% IMes•HCl
CsF, dioxane
80 °C, 12 h
R2
R1

Figure 1.6. Ni/NHC catalyzed Suzuki-Miyaura coupling of ammonium triflates.

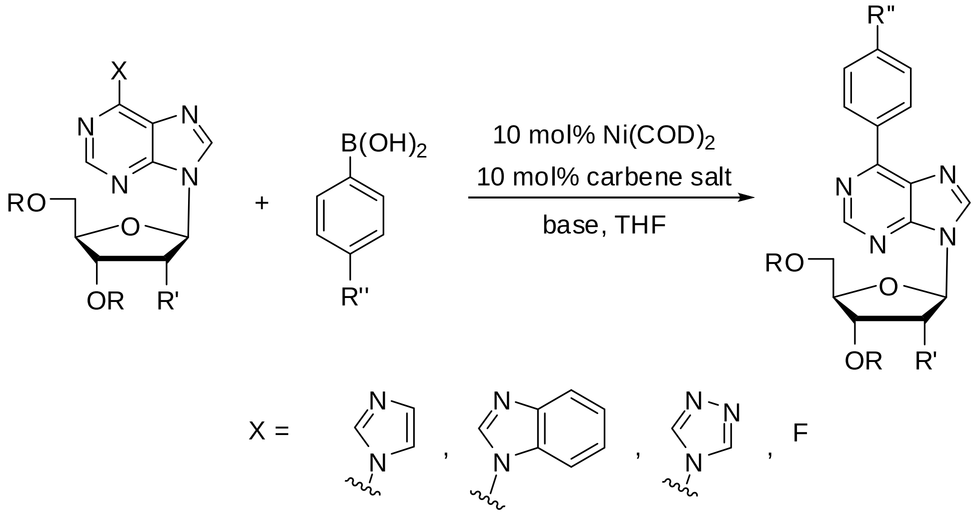

X
N
N
N
N
RO
O
OR
R'
+
B(OH)2
R''
10 mol% Ni(COD)2
10 mol% carbene salt
base, THF
R"
N
N
N
N
RO
O
OR
R'
X =
N
N
N
N
N
N
N
F

Figure 1.7. Ni/Carbene catalyzed Suzuki-Miyaura Coupling of purine derivatives.

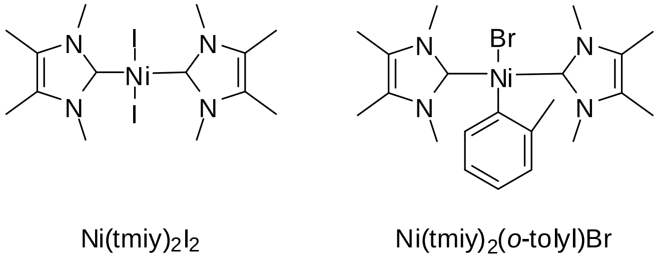
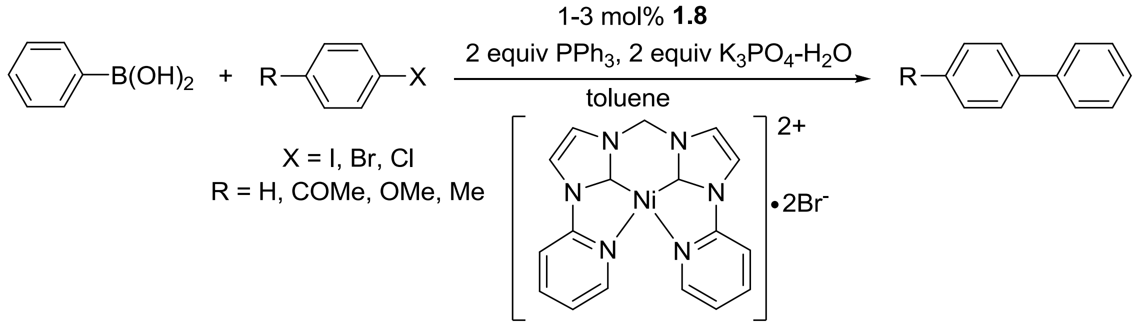

N
N
I
Ni
I
N
N
Ni(tmiy)2I2
N
N
Br
Ni
N
N
Ni(tmiy)2(o-tolyl)Br

Figure 1.8. Well-defined Ni/NHC catalysts for Suzuki-Miyaura Coupling.

Chiu and coworkers have developed a Ni complex containing a tetradentate pyridine/NHC ligand (complex **1.8**, Figure 1.9), which catalyzes the Suzuki reaction at catalyst loadings between 1 and 3 mol%.[17] Aryl halides with both electron rich and poor aryl rings were compatible. However, electronically poor or neutral aryl bromides performed much better than did electron rich aryl bromides. It was also found that the use of 2 equivalents of PPh_3 was crucial to achieving high yields with aryl chlorides.

Heck Cross-Coupling

Nickel/NHC complexes have also been examined as catalysts for the Heck coupling. Inamoto and coworkers have discovered that a variety of aryl bromides and iodides could be coupled with acrylates using 5 mol% $Ni(acac)_2$ and 5 mol% of the appropriate NHC salt in the presence of Na_2CO_3 (Figure 1.10).[18] While the majority of aryl halides could be coupled using the IMes·HCl salt, this was substrate dependent. For instance, aryl iodides possessing OMe groups at the *para* or *meta* position required the use of the IPr·Cl salt as the ligand while 4-bromobenzaldehyde required the use of the $SIPr{\cdot}HBF_4$ salt.



1.8

Figure 1.9. Chiu’s Ni/NHC catalyst for Suzuki-Miyaura couplings.

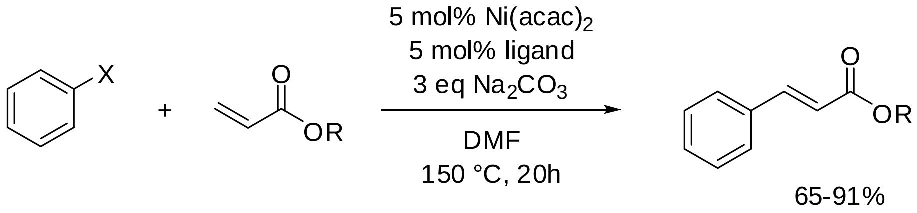

5 mol% Ni(acac)2
5 mol% ligand
3 eq Na2CO3
DMF
150 °C, 20h
X
O
OR
+
65-91%

Figure 1.10. Ni/NHC catalyzed Heck coupling.

Aminations

The use of Ni/NHC catalysts has also been extended to carbon-nitrogen bond forming reactions. Fort and coworkers have found that in situ generation of the Ni(0) and SIPr carbene efficiently catalyze the coupling of aryl chlorides with various amines (Figure 1.11).[19] During the course of the study, it was discovered that Ni(0) could be generated from Ni(acac)$_2$ in the presence of NaH and *t*-BuOH. It is believed that the *in situ* generated NaO*t*-Bu serves three purposes in the reaction: (i) it activates the NaH used to reduce the Ni(II) to Ni(0), (ii) it deprotonates the imidazolium salt to generate the free carbene, and (iii) it serves to deprotonate the amine. While several imidazolium salts were tested for the reaction, SIPr·HCl was found to be the most effective, even surpassing the originally disclosed bipy. Using the protocol developed, both electron rich and poor aryl chlorides were successfully coupled with secondary cyclic and acyclic amines, primary and secondary anilines, and primary alkyl amines all in good yields.

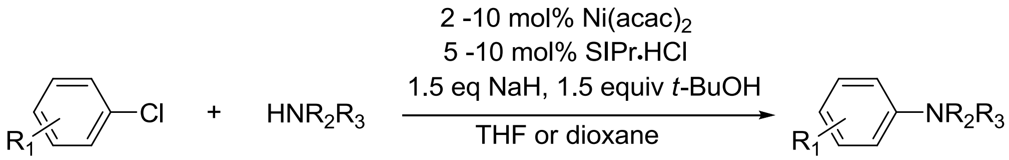

2 -10 mol% Ni(acac)2
5 -10 mol% SIPr.HCl
1.5 eq NaH, 1.5 equiv t-BuOH
THF or dioxane
Cl
+
HNR2R3
R1
NR2R3
R1

Figure 1.11. Ni/carbene catalyzed intermolecular amination.

An intramolecular variant of this reaction was also developed to synthesize five, six, and seven-membered rings (Figure 1.12).[20] Again the use of the SIPr ligand was found to be the most effective catalyst, but in a 1:1 Ni:SIPr ratio. It is interesting to note that the use of the SIPr ligand is complimentary to the use of the bipy ligand. Specifically, the SIPr ligand can catalyze the coupling of primary amines with aryl chlorides where the bipy ligand can not. However, when X = O, only bipy was found to be able to synthesize the seven-membered ring.

Nolan and coworkers have also recently developed an animation of aryl bromides and chlorides with morpholine using 5 mol% of the well-defined CpNi(NHC)Cl catalyst.[21] The catalyst can be easily prepared by refluxing the NHC·HCl in THF solution of nickelocene (Figure 1.13). The well-defined catalyst has the advantage of not having to generate the free carbene, which can sometimes be problematic depending on the stability of the carbene. While the IMes, SIMes, IPr and SIPr complexes were all tested for catalytic activity, the SIPr complex was found to be the most effective. It should be noted that while the reaction conditions are very similar to those developed by Fort, Nolan found that KO^{t}Bu rather than NaO^{t}Bu was necessary to achieve good results.

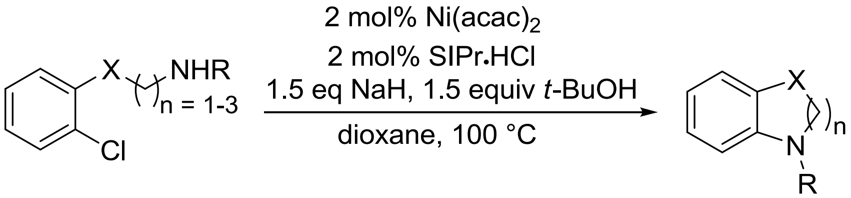


Figure 1.12. Ni/carbene catalyzed intramolecular amination.

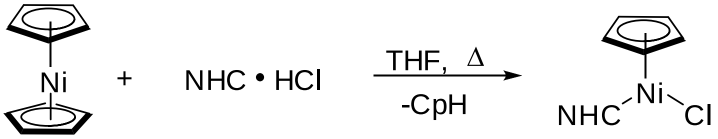


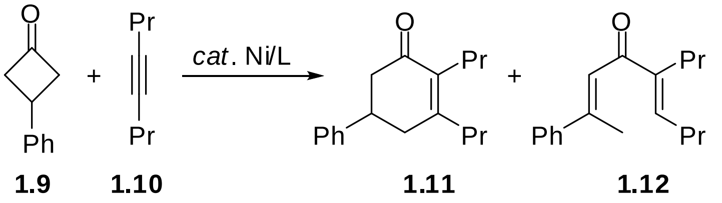
Figure 1.13. Synthesis CpNi(NHC)Cl.

Reductive Coupling Reactions: No Added Reductant

Murakami and co-workers recently reported that cyclobutanones can be coupled with alkynes to afford ring expanded cyclohexenones (such as **1.11**, Table 1.2).[22] While phosphine ligands were generally employed to facilitate the reaction, the authors also demonstrated that IPr was an effective ligand. In reactions involving asymmetrically substituted alkynes, such as 1-phenyl-1-propyne (R_3 = Ph, R_4 = Me), the methyl group was located α to the carbonyl group in the major product. The observed regioselectivity can be explained in terms of a favorable electronic interaction when the aryl substituent (R_3) is located on the α carbon in nickelacycle **1.13** (Figure 1.14). A similar phenomenon has been observed in other nickel promoted coupling reactions involving alkynes.[23]

The first step of these ring expansion reactions is believed to involve the initial oxidative coupling between the carbonyl and the alkyne to afford a nickelapentenacycle (**1.13**, Figure 1.14).[24] Subsequent *β*-carbon elimination relieves ring strain and affords a seven-membered nickelacycle **1.14** that reductively eliminates the cyclohexenone product and regenerates the catalyst. When a *β*-hydrogen is available (i.e., R_2 = H), *β*-H elimination becomes competitive with reductive elimination and acyclic products (**1.12**) are seen in appreciable amounts. However, replacement of the phosphine ligand with an NHC ligand such as IPr appeared to suppress this side reaction and afforded good yields of the desired cyclohexenone product (Table 1.2).

Table 1.2. Ligand effects of reductive coupling.


O
Ph
Pr
Pr
cat. Ni/L
Pr
Pr
Ph
O
Pr
Pr
Ph
O
1.9
1.10
1.11
1.12

(11)

entry	mol % Ni(COD)$_2$	L (mol %)	**1.11** (%)	**1.12** (%)
1	10	P(*c*-Hex)$_3$ (20)	41	54
2	10	PPh$_3$ (20)	37	26
3	10	IPr (10)	61	--
4	20	IPr (20)	79	--

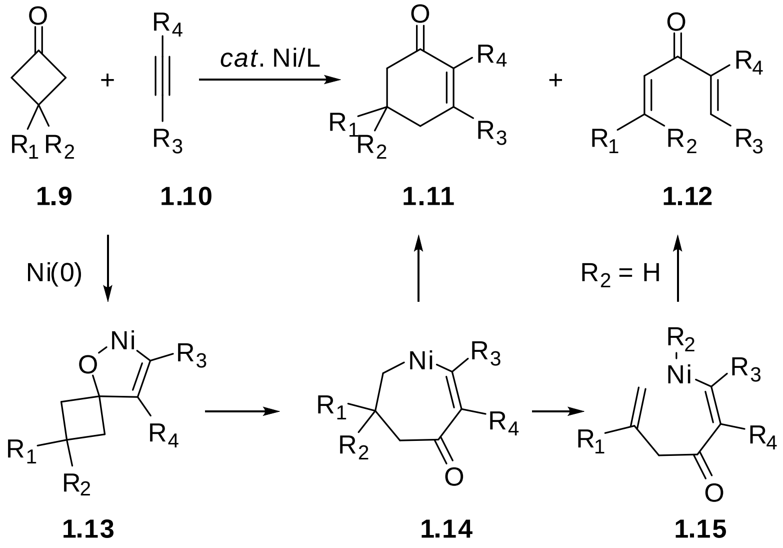

O
R_1 R_2
R_4
R_3
cat. Ni/L
O
R_4
R_3
R_1
R_2
O
R_4
R_1
R_2
R_3
1.9
1.10
1.11
1.12
Ni(0)
R_2 = H
Ni
O
R_3
R_4
R_1
R_2
Ni
R_3
R_1
R_2
R_4
O
R_2
Ni
R_3
R_1
R_4
O
1.13
1.14
1.15

Figure 1.14. Product formation of reductive coupling.

Reductive Coupling Reactions in the Presence of a Reductant

Nickel-catalyzed cyclizations, couplings, and cycloadditions involving three reactive components have been an active area of research for the past decade.[25] Central to these reactions is the involvement of a low valent nickel capable of facilitating oxidative coupling of an unsaturated hydrocarbon (such as an alkyne, allene, or alkene) and a carbonyl substrate (such as an aldehyde or ketone). The use of NHC as ligands has been evaluated for couplings of aldehydes. Such reactions typically afford *O*-protected allylic alcohols in good yields.

In 2001, Mori and coworkers showed that the use of NHC ligands can dramatically influence the olefinic geometry in the Ni-catalyzed coupling reaction of 1,3-dienes and aldehydes.[26] Specifically, when Ni/PPh_3 is used as the catalyst, homoallylic silyl alcohol products were obtained in the E configuration. However, when PPh_3 was replaced with IPr, homoallylic alcohol products were obtained in the Z configuration. The reaction of diene **1.16** with a handful of aryl aldehydes was investigated. Electron-withdrawing substituents on the aldehydes seemed to somewhat retard the reaction. Yields were generally good and ranged from 54 to 95% (Figure 1.15).

This paper was one of the first to demonstrate the generation of a Ni(0)/NHC catalyst in situ from air-stable Ni(II) precursors and an NHC·HCl salt. It was known that the addition of base to NHC·HCl generates the free NHC carbene ligand. In addition, it was also known that Ni(II) can be reduced by organolithium reagents. Mori combined these protocols by using BuLi to reduce the Ni(II) starting material and to deprotonate IPr·HCl. Although Grignard reagents were also evaluated, no Ni(0)/NHC species were observed by ^{13}C NMR.

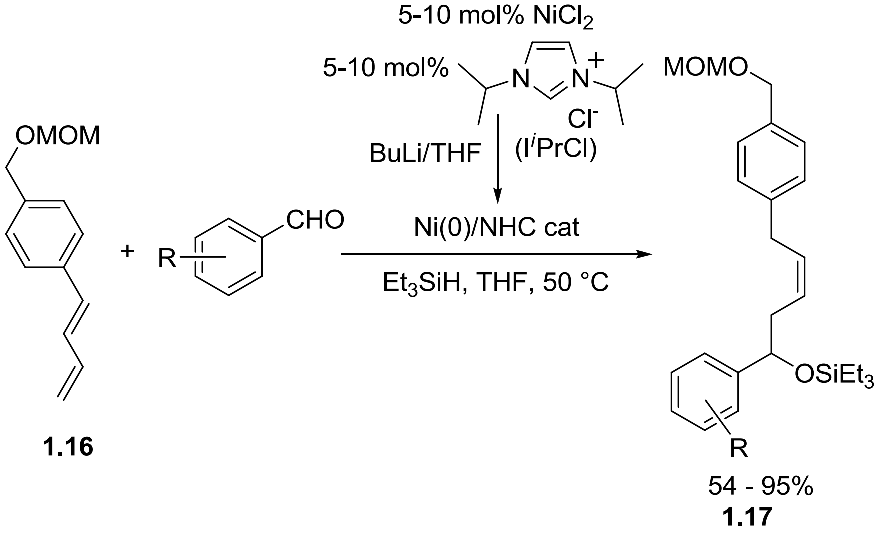


Figure 1.15. Reductive coupling of 1,3-dienes with aldehydes.

Mori later found that a silyl diene could serve as a substrate in Ni-catalyzed coupling reactions with aryl aldehydes (Figure 1.16).[27] No comment on the ability to use more substituted diene partners was mentioned. IMes proved to be a superior ligand to I^{i}Pr, in contrast to reactions of aryl dienes described above. However, in analogy to the reactions of aryl dienes, reactions run with PPh_3 and reactions run with IMes displayed differences in product distribution. That is, reactions run with PPh_3 gave E products, whereas reactions run with IMes gave Z products (Figure 1.16). Interestingly, higher yields were obtained when an equivalent of PPh_3 was added to reactions. It is possible that the added PPh_3 serves to stabilize the coordinatively unsaturated Ni-NHC complex thereby increasing the lifetime of the catalyst. In all cases, reaction times were consistently longer in reactions run with IMes than with PPh_3.

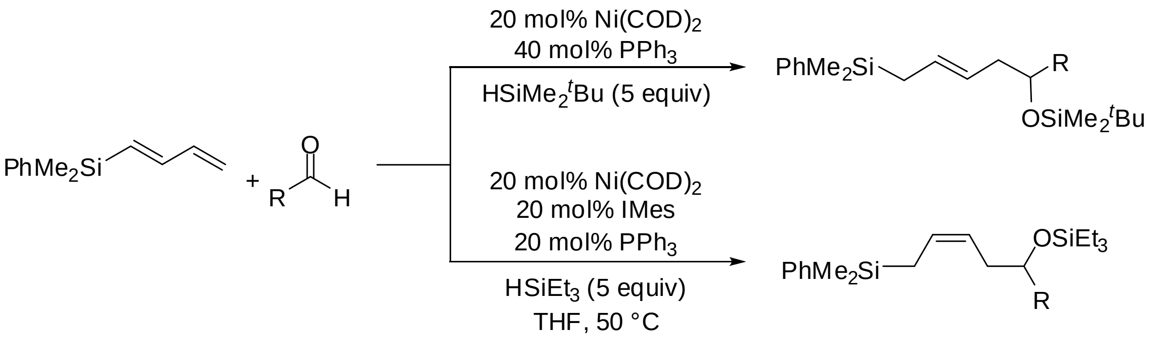

20 mol% Ni(COD)2
40 mol% PPh3
HSiMe2tBu (5 equiv)
PhMe2Si
R
OSiMe2tBu
PhMe2Si
O
R
H
20 mol% Ni(COD)2
20 mol% IMes
20 mol% PPh3
HSiEt3 (5 equiv)
THF, 50 °C
OSiEt3
PhMe2Si
R

Figure 1.16. Ligand effect on olefin geometry of reductive coupling.

Montgomery and coworkers have focused much attention on the development of Ni-catalyzed reductive couplings.[25] More recently, they have employed NHCs as ligands in the reductive coupling of alkynes and aldehydes with silanes as the reductant (Figure 1.17). For example, it was found that the combination of Ni and IMes provides an excellent catalyst system to afford allylic silyl ethers from both aromatic and aliphatic aldehydes in good to excellent yields (56-84%). Both aromatic and aliphatic aldehydes, including electron-rich aromatic aldehydes and sterically demanding aliphatic aldehydes, were used as coupling partners. The alkyne may be internal or terminal, with aromatic or aliphatic substitution patterns being tolerated in both cases. In almost all cases, good regioselectivity was observed (generally 98:2) except with an internal aliphatic alkyne (1.3:1).

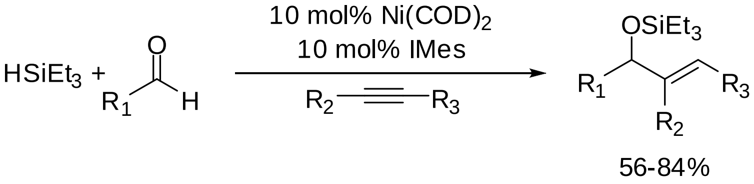

HSiEt3 +
O
R1
H
10 mol% Ni(COD)2
10 mol% IMes
R2
R3
OSiEt3
R1
R3
R2
56-84%

Figure 1.17. Ni/carbene catalyzed coupling of alkynes and aldehydes.

Interestingly, the reactions run with the NHC ligand displayed different reactivity than their original Ni(COD)$_2$/PBu$_3$ system. It appears that the two catalyst systems may proceed through different mechanisms (Figure 1.18). Crossover experiments revealed significant crossover occurred in reactions run with PBu$_3$ whereas negligible crossover was observed in reactions run with IMes. Although the actual mechanism and reason for the difference in crossover between the two reactions is still not clearly understood, it is clear that two distinct mechanisms are involved. In reactions run with PBu$_3$, the authors suggest that either a nickel hydride or nickel silyl species, but not both, is involved. In contrast, the lack of crossover seen with IMes suggests that oxidative coupling of the aldehyde and alkyne and subsequent reaction of the silane may be operative. Alternatively, the Ni/IMes catalyst may oxidatively add the silane, undergo successive alkyne and aldehyde insertions, and ultimately reductively eliminate the product.

Montgomery and coworkers later used this procedure for the macrocyclization of ynals (Figure 1.19).[28] Macrocyclic rings ranging in size (e.g., 14- to 22-membered rings) and all possessing endocyclic *E*-olefins were obtained from terminal ynals in good yields (62-70%) using a catalyst derived from Ni(COD)$_2$, KO*t*-Bu, and IMes·Cl. Internal alkynes were also examined. Phenyl-substituted alkynes afforded macrocycles possessing an exocyclic olefin selectively, regardless of ligand employed (phosphine or NHC). However, the selectivity for exocyclic versus endocyclic olefins diminished with methyl-substituted alkynes.

Jamison and coworkers have used a similar approach for the coupling of allenes, aldehydes, and silanes (Figure 1.20).[29] They first explored the use of phosphines such as P(Cyp)$_3$ and observed an excellent ratio of allylic and homoallylic products (>95:5).

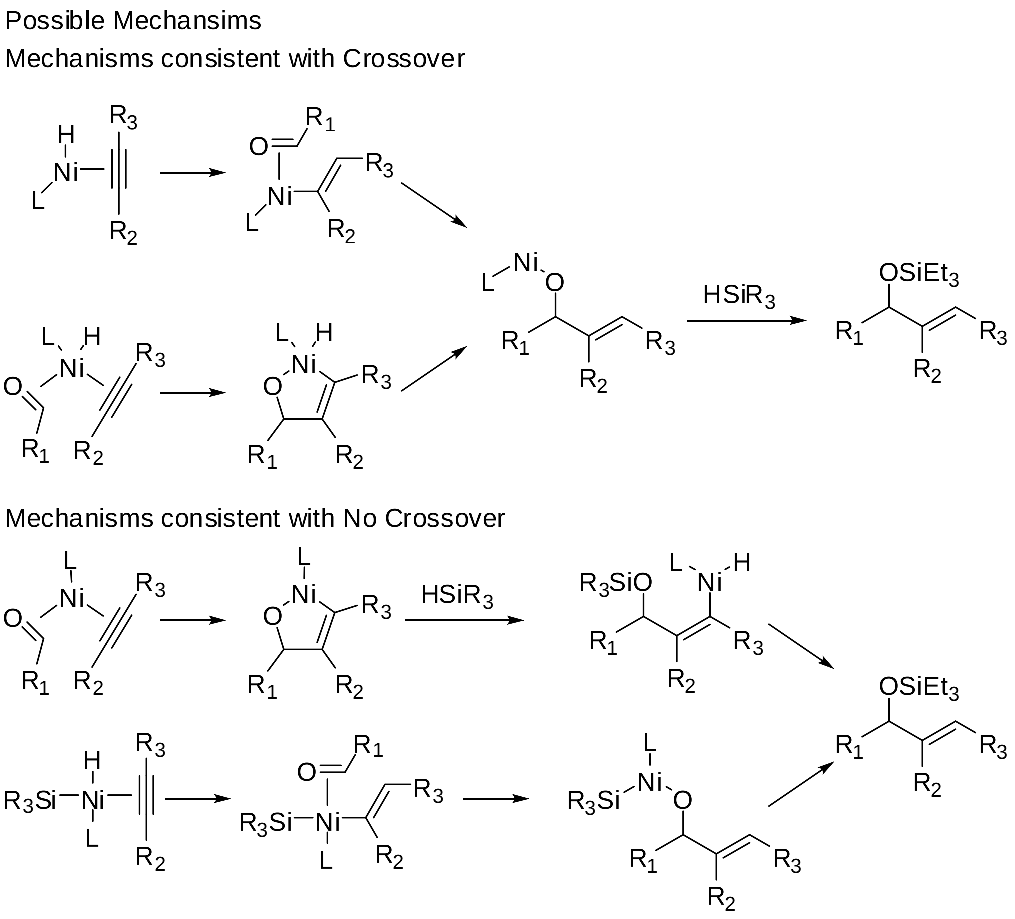

Possible Mechansims
Mechanisms consistent with Crossover
Mechanisms consistent with No Crossover
HSiR3
OSiEt3
R1
R2
R3
Ni
L
H
R3Si
R3SiO

Figure 1.18. Mechanistic investigations into the coupling of alkynes and aldehydes.

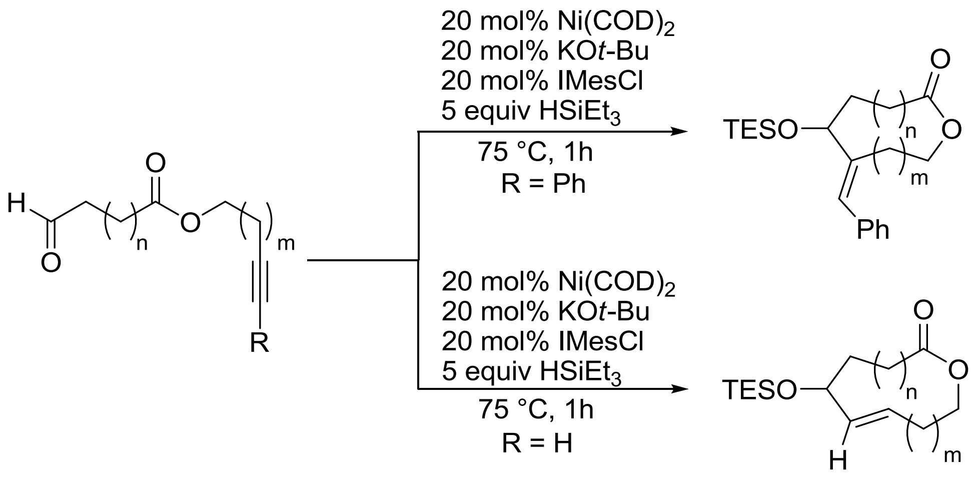

20 mol% Ni(COD)2
20 mol% KOt-Bu
20 mol% IMesCl
5 equiv HSiEt3
75 °C, 1h
R = Ph
R = H
TESO
Ph
n
m
R

Figure 1.19. Macrocyclization of aldehydes and alkynes.

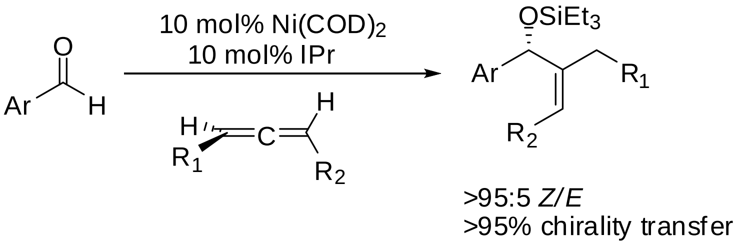


Figure 1.20. Ni/carbene catalyzed coupling of allenes and aldehydes.

The use of phosphine ligands lead to poor enantiomeric purity (95 to 62%), however,. the use of the IPr ligand solved this problem and a range of internal allenes and aryl aldehydes were converted to the corresponding allylic silyl ethers in yields ranging from 40-80%. In all cases, the Z geometry corresponded to attachment of the aldehyde to the more hindered face of the allene.

Conclusion

The number of new synthetic methods catalyzed by transition metal complexes (such as Ni, Cu, Rh, Ir, Ru, and Pd) has arisen since the discovery that NHCs can serve as ligands for transition metals. By coordinating a NHC ligand, the stability of the transition metal typically increases. In addition, the increased donacity of the NHC ligand helps to enhance the catalytic activity. Clearly, the arrival of these NHCs has opened new venues in the ever-growing field of transition metal-mediated catalysis.

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CHAPTER 2

NICKEL CATALYZED [2+2+2] CYCLOADDITIONS OF DIYNES AND CARBON DIOXIDE

Introduction

The incorporation of carbon dioxide (CO_2) into organic compounds (e.g., carbohydrates) is an important chemical process used by plants and algae for sustaining life. Chemists have also intensely studied the fixation of CO_2 as it makes an ideal C_1 source because it is naturally abundant, relatively nontoxic, and nonflammable.[1] An increased interest in the utilization of CO_2 has recently occurred due to concerns that its abundance in the earth's atmosphere is believed contribute to the warming of the earth. Although biosynthetic machinery can easily accomplish this process at ambient temperatures and pressures, chemists often resort to extreme measures to exploit its use in synthetic applications due to the high thermodynamic stability (in some instances this high stability makes it the ideal reaction medium). By far, the most widely used method for activating CO_2 has been through the use of strong nucleophiles such as Grignard reagents. These conditions can be extremely harsh and thus severely limit the scope of the reaction. More recently, transition metals have been used as templates to lower the activation energy of CO_2 and expand its use in synthetic chemistry.[2-7]

The Activation of Carbon Dioxide with Nickel Complexes

The activation of CO_2 with nickel complexes has received a great deal of attention. Hoberg and co-workers have shown that CO_2 can be added across alkynes in the presence of the appropriate Ni(0) complex to generate a five-membered nickelacycle (Figure 2.1).[8] This nickelacycle can then be subjected to acidic conditions to liberate the corresponding α,β-unsaturated carboxylic acid. Unfortunately, symmetrical diynes were required for the reaction as no regioselectivity was observed. Yamamoto and co-workers later found that by using 1 equiv of $Ni(COD)_2$ and 2 equiv of DBU under an atmosphere of CO_2, regioselectivity could be obtained as the CO_2 reacted preferentially with the less hindered side of the alkyne (Figure 2.2).[9]

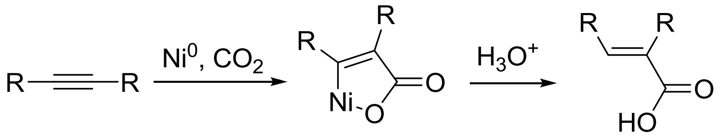


Figure 2.1. Nickel mediated addition of CO_2 to alkynes.

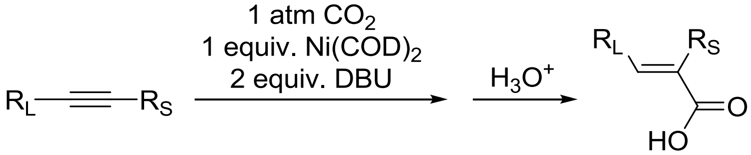


Figure 2.2. Regioselective nickel mediated addition of CO_2 to alkynes.

It is believed that the regioselectivity arises via the formation of the kinetically favored nickelacycle **2.3** (Figure 2.3).[9] The formation of **2.3** is kinetically favored compared to **2.4** for both steric and electronic reasons. Sterically, the CO_2 will preferentially react with the less encumbered carbon atom, R_S. Electronically, the CO_2 prefers to react with the carbon with the highest HOMO coefficient, again R_S. Due to the basicity of DBU generating such an electron rich metal center, once the kinetically favored **2.3** is formed, its formation is essentially irreversible. Upon hydrolysis of **2.3**, the observed α,β-unsaturated carboxylic acid **2.5** is obtained as the sole regioisomer.

More recently, Mori and co-workers have found that the nickel mediated addition of CO_2 to alkynes could be made catalytic using organozinc reagents (Figure 2.4).[10,11] Upon oxidative coupling of CO_2 and the alkyne, the oxanickelacycle is formed as in the Yamamoto system. However instead of hydrolyzing nickelacycle **2.6** with acid, an organozinc reagent was used to generate nickel complex **2.7**. This then reductively eliminates forming the carboxylic acid. Initial attempts at coupling phenylacetylene with CO_2 using $Ni(COD)_2$, DBU, and Me_2Zn were shown to effect the reaction.[10] However, a stoichiometric amount of nickel and DBU (1:2) were needed for complete conversion. Upon further examination, it was surmised that the zinc could be competing with nickel for the binding of DBU. Therefore, the use of an excess of DBU relative to nickel and zinc would counteract this competition and allow the reaction to become catalytic.[11]

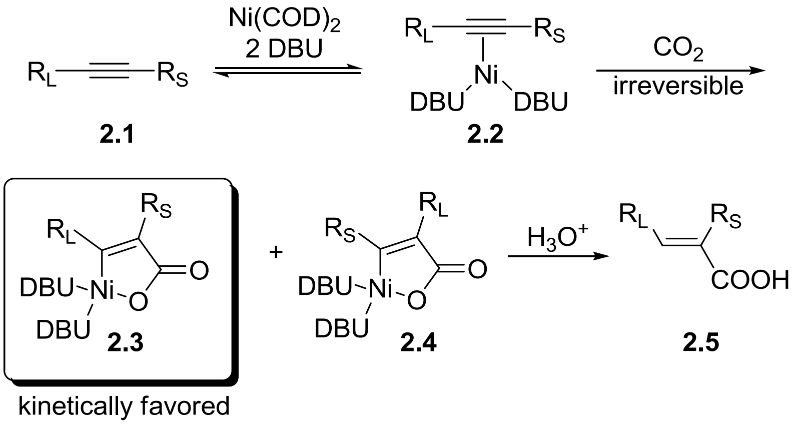

Ni(COD)$_2$
2 DBU
CO$_2$
irreversible
H$_3$O$^+$
2.1
2.2
2.3
2.4
2.5
kinetically favored

Figure 2.3. Rationale for regiochemistry of Ni-mediated addition of CO$_2$ to alkynes.

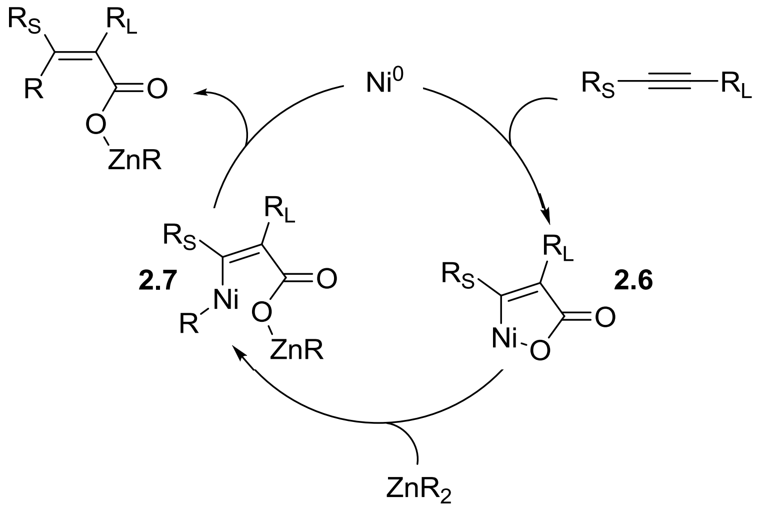

Ni^0
2.6
2.7
ZnR$_2$

Figure 2.4. Proposed catalytic cycle for addition of CO$_2$ to alkynes.

When alkyne **2.8** was treated with CO_2 (1 atm) in the presence of $Ni(COD)_2$ (20 mol%), DBU (10 equiv), and Me_2Zn (3 equiv), the expected methylester **2.9** was obtained in 81% yield following a diazomethane work up (Figure 2.5).[11] While this regioselectivity agrees with the observation made by Yamamoto, when alkyne **2.10** (possessing a TMS group at the terminal position) was reacted under these conditions the opposite regioisomer was obtained (**2.11**, Figure 2.5). In this case, the electronic stabilization of having the carbon with the TMS group bound to the nickel center of nickelacycle **2.6** overrides the steric constraints.

In a related system, Walther and co-workers found the proposed oxanickelacycles could be synthesized and isolated if a bidentate amine was used as a ligand.[12] By reacting 3-hexyne with CO_2 in the presence of 1 equivalent $Ni(COD)_2$ and 1 equivalent of TMEDA, oxanickelacycle **2.12** could be isolated and characterized by single crystal x-ray analysis.

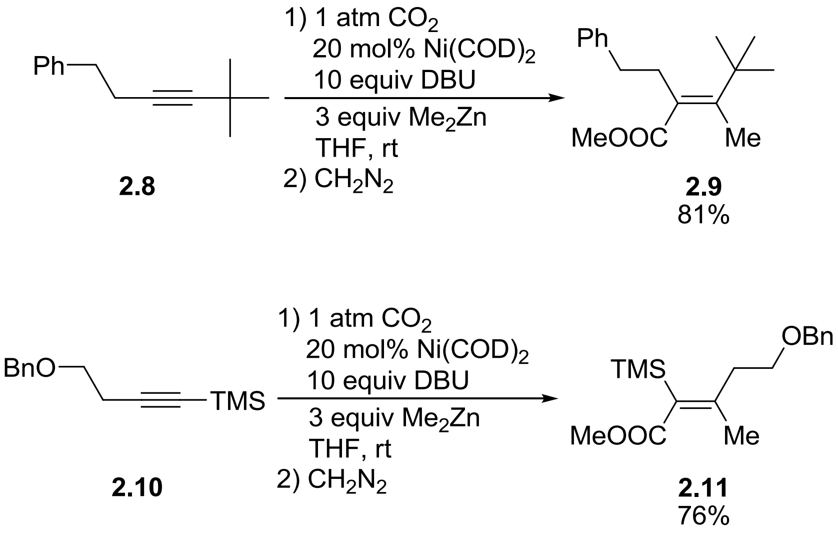

Ph
2.8
1) 1 atm CO2
20 mol% Ni(COD)2
10 equiv DBU
3 equiv Me2Zn
THF, rt
2) CH2N2
Ph
MeOOC
Me
2.9
81%
BnO
TMS
2.10
1) 1 atm CO2
20 mol% Ni(COD)2
10 equiv DBU
3 equiv Me2Zn
THF, rt
2) CH2N2
OBn
TMS
MeOOC
Me
2.11
76%

Figure 2.5. Regioselectivity of Ni-catalyzed addition of CO_2 to alkynes.

It was also found that upon subjecting **2.12** to another equivalent of 3-hexyne, pyrone **2.14** was generated (Figure 2.6). It was proposed that the 3-hexyne inserts into the C-Ni bond of **2.12** generating seven-membered oxanickelacycle **2.13** which reductively eliminates to produce pyrone **2.14**.

Upon the reductive elimination of **2.13** and formation of pyrone **2.14**, a Ni(0) complex is also generated (Figure 2.6). Since a Ni(0) complex is used in the synthesis of **2.12**, the formation of pyrones could be performed catalytically using 2 equivalents of alkyne and 1 equivalent of CO_2. A very electron donating ligand was required, however, to stabilize the Ni(0) and facilitate CO_2 binding for efficient catalysis. This was accomplished by replacing the amine ligand with the proper phosphine ligand.

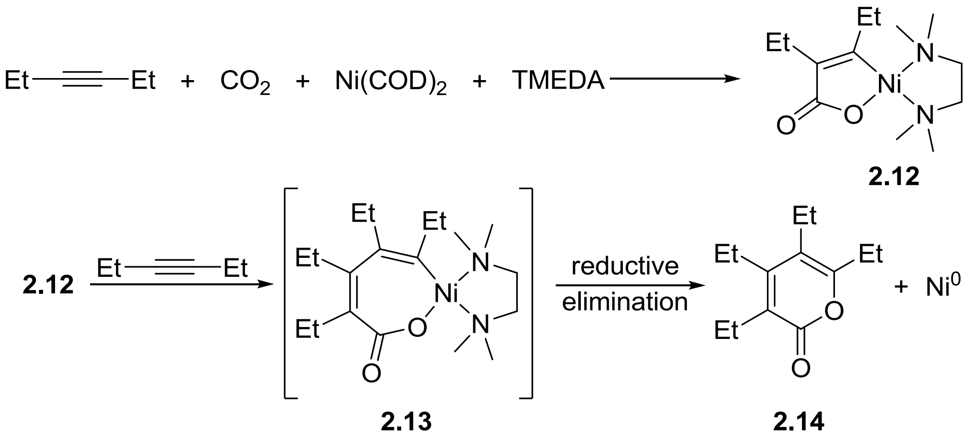

Et—≡—Et + CO_2 + $Ni(COD)_2$ + TMEDA
Et
Et
N
Ni
N
O
O
2.12
2.12
Et—≡—Et
Et
Et
Et
Et
N
Ni
N
O
O
2.13
reductive
elimination
Et
Et
Et
Et
O
O
2.14
+ Ni^0

Figure 2.6. Pyrone formation from well-defined oxanickelacycles.

The choice of phosphine ligand was critical in achieving high yields of the desired 2-pyrone (Figure 2.7). If a bulky phosphine was employed, a low yield of the pyrone was obtained with a majority of hexyne being converted to oligomers such as **2.15** (Table 2.1). When smaller phosphines were employed in the reaction, the higher pyrone to oligomer ratios were observed (Table 2.1). This is most likely due to the bulky ligand favoring insertion of the smaller CO_2 molecule rather than the larger alkyne.

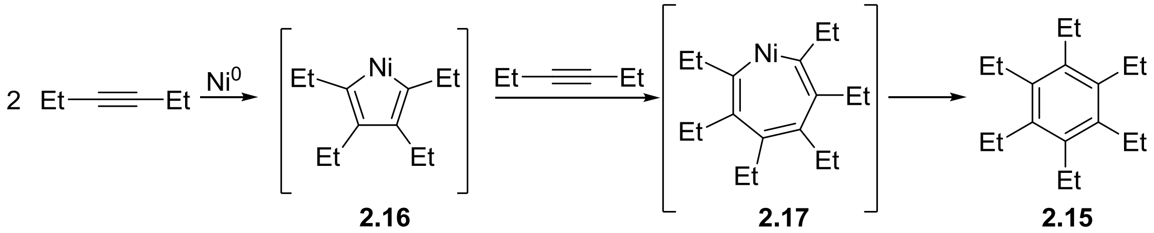
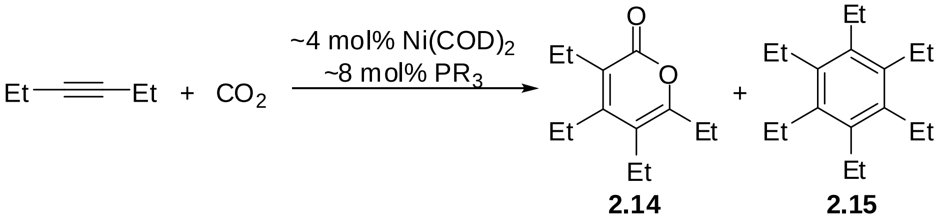

2 Et—≡—Et
Ni^0
Et
Ni
Et
Et
Et
2.16
Et—≡—Et
Et
Ni
Et
Et
Et
Et
Et
2.17
Et
Et
Et
Et
Et
Et
2.15

Figure 2.7. Proposed formation of oligomer.

Table 2.1. Ligand effects on catalytic formation of pyrone.


Et—≡—Et + CO_2
~4 mol% Ni(COD)$_2$
~8 mol% PR$_3$
O
O
Et
Et
Et
Et
2.14
+
Et
Et
Et
Et
Et
Et
2.15

PR_3	conversion (%)	yield **2.14** (%)	yield **2.15** (%)
Cy_3P	96	29	71
Ph_2EtP	95	75	25
$PhMe_2P$	98	92	8
Et_3P	100	96	4

The formation of oligomer **2.15** is proposed to occur via the oxidative coupling of two alkynes to form the metallacyclopentadiene **2.16** (Figure 2.7). Insertion of a third equivalent of alkyne would generate seven-membered metalacycle **2.17** which then reductively eliminates to produce **2.15**. Interestingly, the formation of oligomer **2.15** introduces another possible mechanism for the formation of pyrone **2.14**. Upon generating **2.16**, it can be imagined that a molecule of CO_2 could insert rather than another equivalent of alkyne. This would result in oxanickelacycle **2.13** which would then reductively eliminate to yield the pyrone. Although some studies have been completed to deduce the operable mechanism, it is unclear which mechanism (or if possibly both) leads to pyrone formation.

Although Walther was able to successfully synthesize pyrones from alkynes and CO_2 and a nickel catalyst, the reaction suffered from a lack of regioselectivity. This, in turn, meant that only symmetrical alkynes could be employed in the reaction. One solution to this problem is to tether the two alkynes thereby "forcing" selectivity. Tsuda and Saegusa found that in doing this, bicyclic pyrones can be generated in low to good yields using a Ni/PR_3 catalyst (Figure 2.8).[13,14]

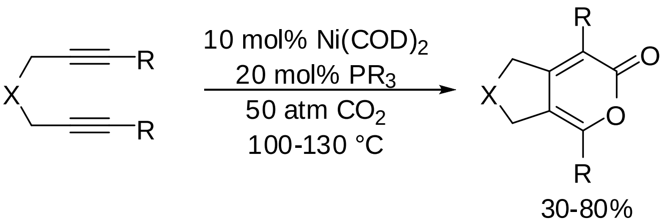


Figure 2.8. Ni/PR_3 catalyzed cycloaddition of diynes and CO_2

The formation of these pyrones is proposed to occur via one of the two mechanisms previously proposed by Walther. In mechanism A, oxidative coupling of the two alkynes generates the bicyclic metalacyclopentadiene **2.18** (Figure 2.9). Insertion of CO_2 into one of the C-Ni bonds produces metallacycle **2.19**. A C-O bond forming reductive elimination yields the observed pyrone **2.20**. Alternatively, in mechanism B, an oxidative coupling between one of the alkynes and CO_2 would create the five-membered oxanickelacycle **2.21** (Figure 2.9). Insertion of the pendent alkyne would result in **2.19** which undergoes reductive elimination to yield pyrone **2.20**. As was observed by Walther, the formation of oligomers such as **2.22** from **2.18** were observed and accounted for the mass balance of the low yielding reactions (Figure 2.9). The formation of oligomer could be suppressed by the fine tuning of the ligand to each particular substrate.

Nickel/NHC Catalyzed [2+2+2] Cycloaddition of Diynes with CO_2

While Tsuda and Saegusa were able to develop a nickel catalyzed protocol to synthesize bicyclic pyrones from diynes and CO_2, there were still aspects of the reaction which were not ideal. For instance, the reaction conditions were considerably harsh, requiring 50 atm of CO_2 and temperatures in excess of 100 °C. Furthermore, the yields were variable due to the formation of oligomers. In an effort to improve upon these drawbacks, our group began exploring ways to improve this reaction. As a logical starting point, the mechanism of pyrone formation was examined. Since the exact nature of the mechanism was not clear both mechanisms were examined for potential pitfalls (Figure 2.9).

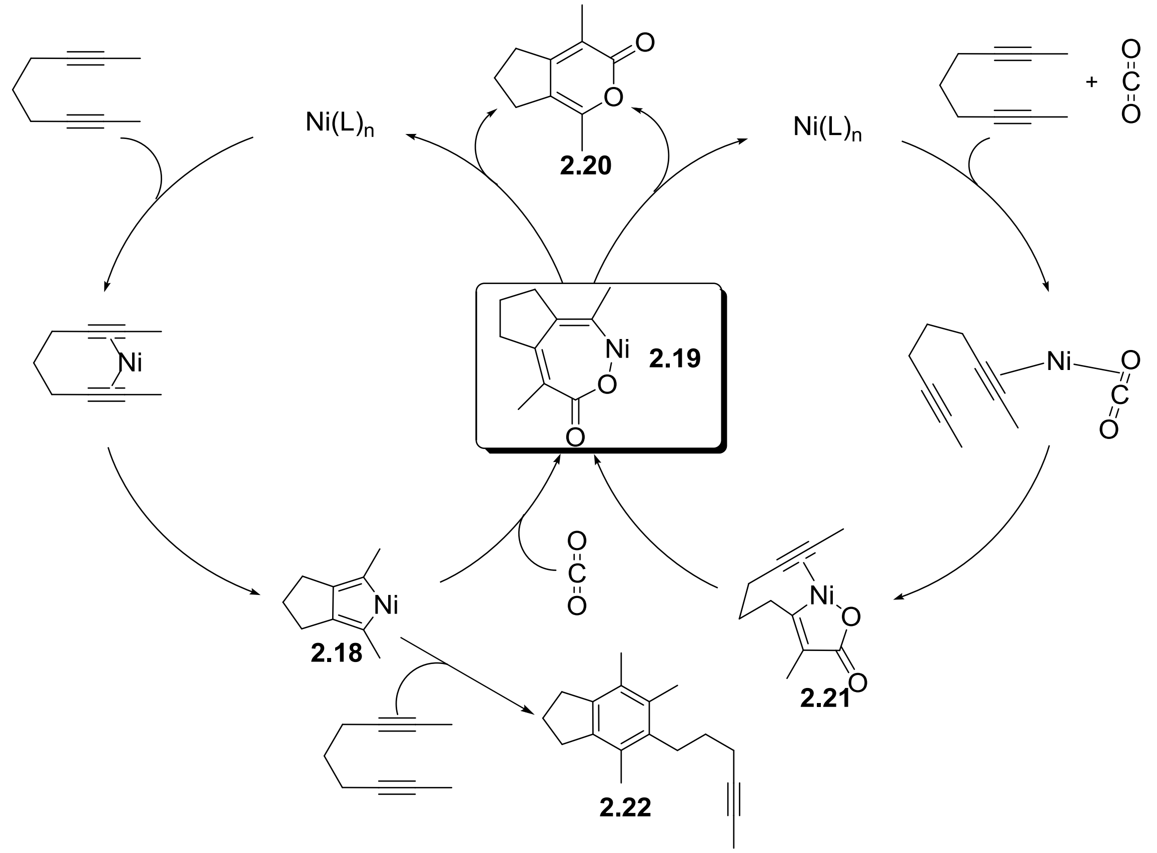

Ni(L)n
Ni(L)n
2.20
+
Ni
2.19
Ni
Ni
2.18
Ni
2.21
2.22

Figure 2.9. Proposed mechanisms for Ni-catalyzed cycloaddition of CO_2 and diynes.

If mechanism A was operating, two steps were identified for possible improvement. The first was that upon formation of **2.18**, insertion of a third alkyne would create the unwanted oligomer lowering the pyrone yield. Thus, it was necessary to promote the insertion of CO_2 and prevent the insertion of an alkyne. The second problem area was the reductive elimination of **2.19**. Typically in catalysis, reductive eliminations have been observed for C-C bond forming. In pyrone formation, a C-O bond forming reductive elimination is required. Energetically, C-O bond forming reductive eliminations have been calculated to be as much as 19 Kcal/mol greater than the analogous C-C bond forming reductive elimination thus making the reductive elimination much more difficult.[15]

In mechanism B the initial oxidative coupling of CO_2 and one of the alkynes to generate **2.21** was identified as a potential problem. In order for this oxidative coupling to proceed, the CO_2 must first bind to the Ni center. Unfortunately, CO_2 is not a good ligand for Ni. Thus, it was necessary to the render the Ni sufficiently electron rich to efficiently bind the CO_2.

It was thought that due to the large size and excellent electron donating abilities of NHC's (Figure 2.10), these could replace phosphines as ligands in the cycloaddition to improve on the previously discussed drawbacks. In particular, the electron donating ability of the NHC's may create an electron rich Ni center to facilitate the binding of CO_2. Furthermore, the donating ability may also enhance the ability of **2.19** to reductively eliminate. It was also proposed that the ligands' large size would further promote reductive elimination of **2.19** as well as impede the insertion of large alkynes into **2.18** and possibly favor the insertion of the smaller CO_2.

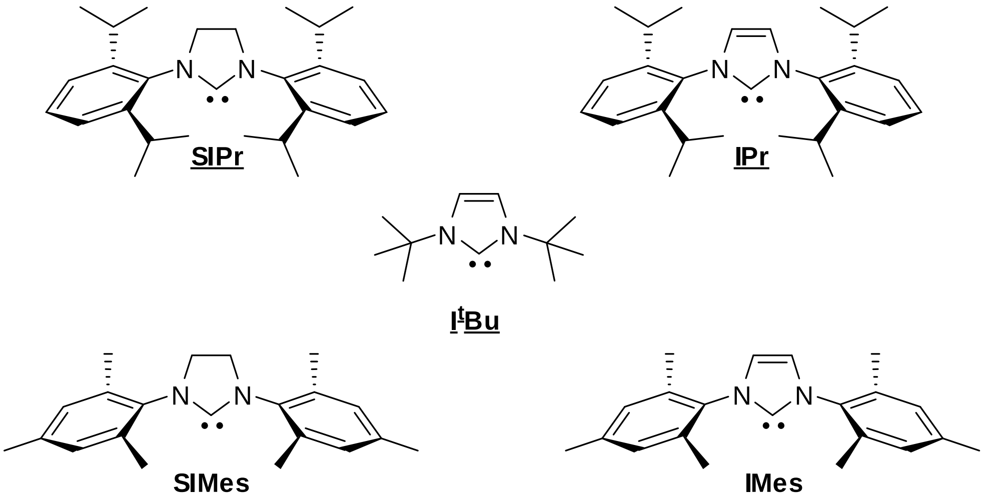


Figure 2.10. *N*-Heterocyclic carbenes.

Based on these hypotheses, IPr and IMes were employed as ligands in the Ni-catalyzed [2+2+2] cycloaddition of diyne **2.23** and CO_2 (Figure 2.11).[16] Both ligands showed excellent catalytic activity at 60 °C under only 1 atm of CO_2, but the IPr ligand produced better yields of the pyrone **2.24**. The lower yield with the IMes ligand was attributed to an increase in the amount of oligomer produced due to the smaller size of the IMes ligand relative to the IPr ligand.

A variety of internal diynes were subjected to the Ni-catalyzed cycloadditions under the optimized conditions of 5 mol% Ni(COD)$_2$, 10 mol% IPr, and a substrate concentration of 0.1 M in toluene, benzene, or THF at 60 °C under 1 atm CO_2 (Table 2.2).[16] The reaction conditions tolerated acid and base sensitive functionalities such as esters, ethers, and silylethers. The formation of six-membered rings, which have been proven to be more difficult in transition metal catalyzed cyclizations, was also possible using this methodology (entry 5). In addition, unsubstituted diyne **2.39** could be cyclized to yield pyrone **2.40** in good yield showing that the Thorpe-Ingold effect was not necessary to aid in the cyclization.

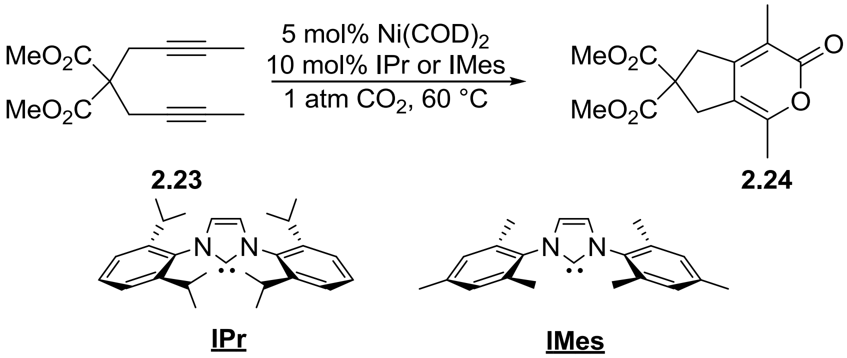
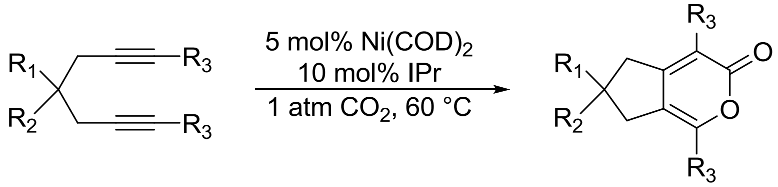
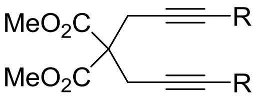
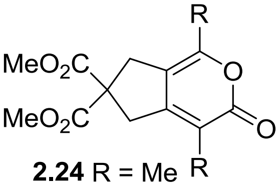
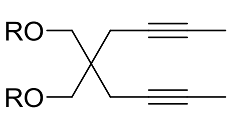
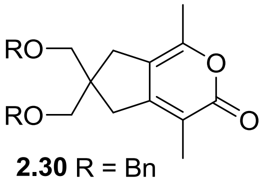
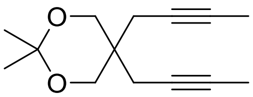
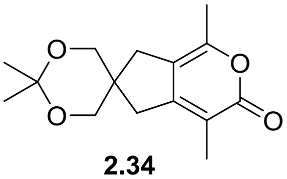
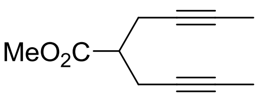
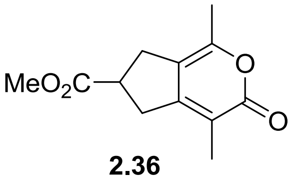
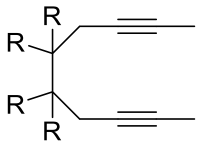
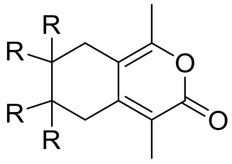

MeO2C
MeO2C
5 mol% Ni(COD)2
10 mol% IPr or IMes
1 atm CO2, 60 °C
MeO2C
MeO2C
O
O
2.23
2.24
N
N
N
N
IPr
IMes

Figure 2.11. Ni-catalyzed cycloaddition with IMes and IPr ligands.

Table 2.2. Ni-catalyzed cycloaddition of diynes and carbon dioxide.


R1
R2
R3
R3
5 mol% Ni(COD)2
10 mol% IPr
1 atm CO2, 60 °C
R1
R2
R3
R3
O
O

entry	substrate	product	yield (%)[a]
1	 **2.23** R = Me **2.25** R = Et **2.27** R = *i*Pr	 **2.24** R = Me **2.26** R = Et **2.28** R = *i*Pr	93 94 86
2	 **2.29** R = Bn **2.31** R = TBS	 **2.30** R = Bn **2.32** R = TBS	93 92
3	 **2.33**	 **2.34**	96
4	 **2.35**	 **2.36**	82
5	 **2.37** R = CO_2Et **2.39** R = H	 **2.38** R = CO_2Et **2.40** R = H	97 75

[a] Isolated yield (average of two runs).

While methyl, ethyl, and isopropyl groups were tolerated at the alkyne termini (entry 1, Table 2.2), attempts at cyclizing diynes with *tert*-butyl (**2.41**) or TMS (**2.42**) groups at this position failed with IPr and the sterically less demanding IMes (Figure 2.12). Unsymmetrical diyne **2.43,** which posseses a TMS group at one terminal position and a methyl group at the other, cyclized smoothly to produce pyrone **2.44** in 83% yield (Figure 2.12).[17]

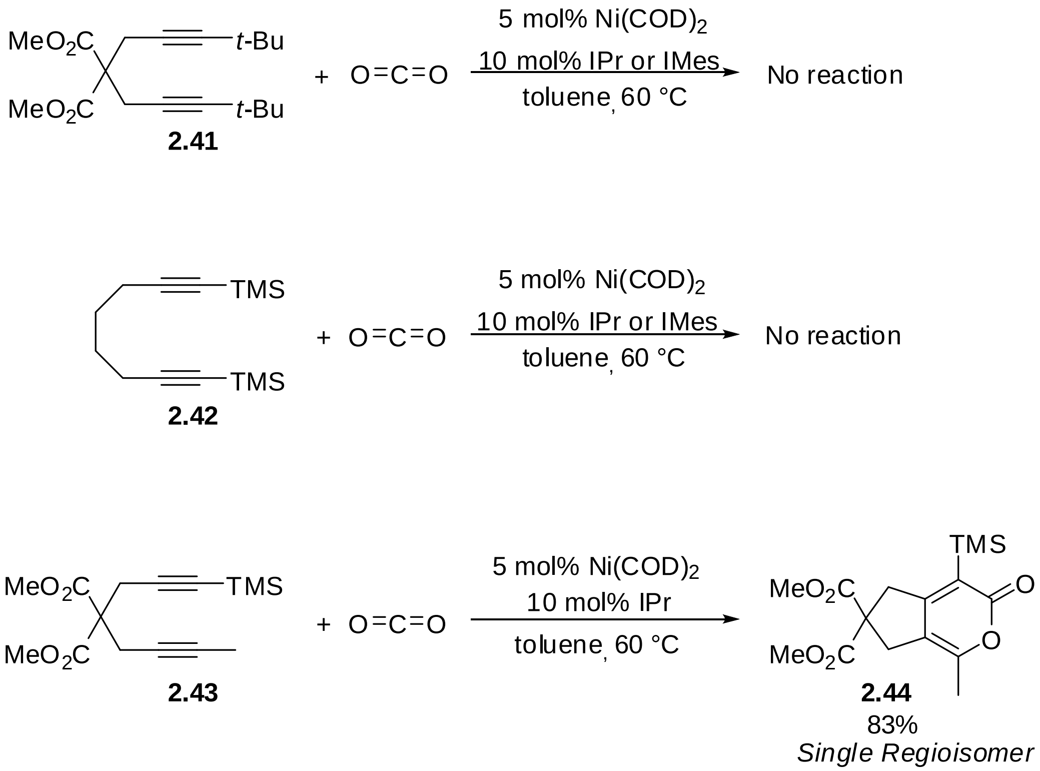

MeO2C
MeO2C
t-Bu
t-Bu
2.41
+ O=C=O
5 mol% Ni(COD)2
10 mol% IPr or IMes
toluene, 60 °C
No reaction
TMS
TMS
2.42
+ O=C=O
5 mol% Ni(COD)2
10 mol% IPr or IMes
toluene, 60 °C
No reaction
MeO2C
MeO2C
TMS
2.43
+ O=C=O
5 mol% Ni(COD)2
10 mol% IPr
toluene, 60 °C
TMS
MeO2C
MeO2C
O
O
2.44
83%
Single Regioisomer

Figure 2.12. Cyloadditions with large groups at terminal position of alkynes.

Even more exciting was that pyrone **2.44** was produced as a single regioisomer where the large TMS group resided α to the carbonyl of the pyrone (as confirmed by x-ray analysis).[17] Tsuda and Saegusa had previously reported that under their conditions, unsymmetrical diyne **2.45** could be cyclized regioselectively to pyrone **2.46** (Figure 2.13).[14] The reported regioselectivity is the opposite of what we found for pyrone **2.44** as the TMS group resides α to the oxygen of the pyrone ring. Unfortunately, the regiochemistry of **2.46** was not rigorously determined, and thus, it is not certain whether or not the reported regiochemistry is the actual regiochemistry.

While we were excited that complete regioselectivity could be obtained using our Ni/IPr catalyst system, it was unclear whether the regioselectivty was being imparted by steric encumbrance or the electronic effects of the TMS group (as witnessed by Mori and co-workers).[11] We therefore embarked upon an in-depth study to ascertain the origins of regioselectivity in the [2+2+2] cycloaddition of unsymmetrical diynes and CO_2.

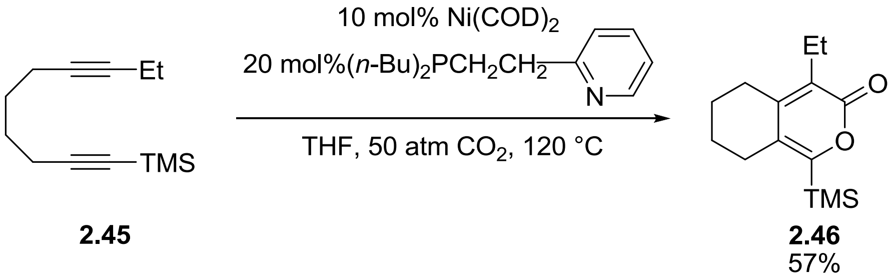
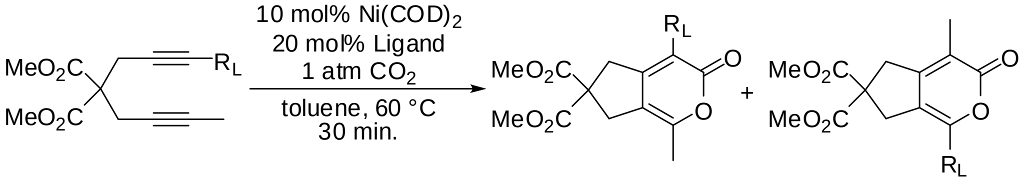


Figure 2.13. Reported regioselectivity by Tsuda and Saegusa.

A series of unsymmetrically substituted diynes, containing a methyl group on one terminus and groups of varying size on the other terminus (R = Et, *i*-Pr, *t*-Bu, and TMS) were prepared.[17] Regioselectivity for the reaction of these substrates was examined under standard conditions with IPr and IMes. As shown in Table 2.3, when the steric difference between the two terminal substituents on the diyne was small (e.g., Me vs. Et), a nearly equal mixture of the two pyrone regioisomers was obtained (entry 1). As the relative difference between the two groups was increased, the regioselectivity of the reaction improved favoring the formation of the pyrone with the larger group α to the carbonyl. The use of diyne **2.43** afforded only one regioisomer (entry 7).



2.43 - 2.46 **2.44 - 2.52a** **2.44 - 2.52b**

entry	substrate	R$_L$	ligand	product	a:b[a]	yield (%)[b]
1	**2.46**	Ethyl	IMes	**2.50**	53:47	ND[c]
2	**2.46**	Ethyl	IPr	**2.50**	62:38	75
3	**2.47**	*i*-Pr	IMes	**2.51**	56:44	57
4	**2.47**	*i*-Pr	IPr	**2.51**	80:20	64
5	**2.48**	*t*-Bu	IMes	**2.52**	64:36	ND[c]
6	**2.48**	*t*-Bu	IPr	**2.52**	100:0	64
7	**2.43**	TMS	IMes	**2.44**	100:0	67
8	**2.43**	TMS	IPr	**2.44**	100:0	83

[a] Determined by GC and ^{1}H NMR analysis. [b] Isolated yields (average of two runs). [c] Not determined

Table 2.3. Cycloaddition with various unsymmetrical diynes.

Exploration of the effect of the size of the ligand on the regioselectivity of the reaction was carried out with the electronically similar, but larger, IPr ligand.[17] As shown in Table 2.3, this ligand afforded significant improvements in the regioselectivity. For example, even in cases when the difference between the terminal diyne substituents was small (Me vs. Et, entry 2 and Me vs, *i*-Pr, entry 4), a considerable excess of one regioisomer was observed. Complete regioselectivity was observed when the bulky substituent was *t*-Bu (entry 6) or larger (TMS, entry 7). From these results, it was clear that the regioselectivity was arising from steric rather than electronic factors.

We next explored whether regioselectivity could be influenced by varying the steric bulk of the internal tether of the diyne. Diyne **2.53**, which contains an α-methyl substituted ether which links the methyl-terminated alkynyl groups, did not have any effect on the regioselectivity of the reaction as an equal mixture of both regioisomers was formed (Figure 2.14). Similar results were obtained from the cycloaddition of diyne **2.55** which contains an α,α-substituted ether linkage.

Several attempts were made to delineate whether or not electronic factors could also be used to influence the regioselectivity of the reaction. Unfortunately, diynes bearing a terminal electron-withdrawing substituent (e.g., Ph or CO_2Me, Figure 2.15) undergo oligomerization at a faster rate than pyrone formation and do not produce reasonable yields of the pyrone products. Alternatively, the use of alkynes bearing an electron donating ethoxy substituent resulted in the formation of complex mixtures. Diynes bearing thioethers did not undergo cycloaddition chemistry, which may be due to the incompatibility of this functional group with the nickel catalyst.

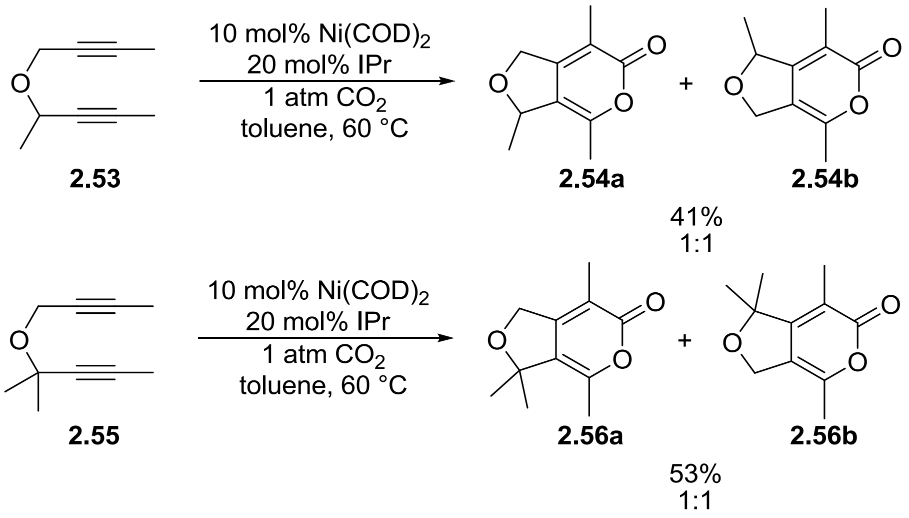

10 mol% Ni(COD)2
20 mol% IPr
1 atm CO2
toluene, 60 °C
2.53
2.54a
2.54b
41%
1:1
10 mol% Ni(COD)2
20 mol% IPr
1 atm CO2
toluene, 60 °C
2.55
2.56a
2.56b
53%
1:1

Figure 2.14. Cycloaddition with diynes containing sterically hindered internal linkages.

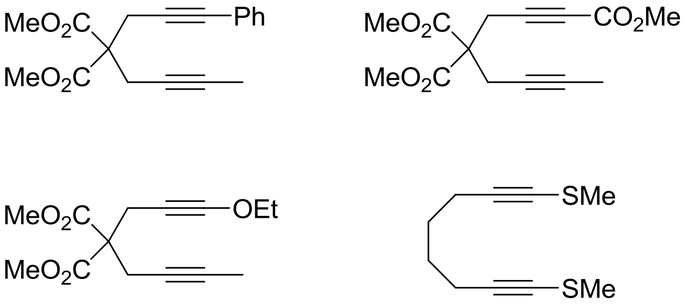

MeO2C
MeO2C
Ph
MeO2C
MeO2C
CO2Me
MeO2C
MeO2C
OEt
SMe
SMe

Figure 2.15. Diynes used for studying electronic effects in regioselective cyclizations.

The regioselectivity of this reaction may be explained using either of the two previously proposed mechanisms (Figure 2.9).[17] If mechanism A were operating, upon forming the metalacyclopentadiene **2.57**, the CO_2 can insert into either one of the two C-Ni bonds (Figure 2.16). When R_L is large and the ligand is large, steric interactions between the two groups cause the ligand to reside closer to the smaller methyl group.

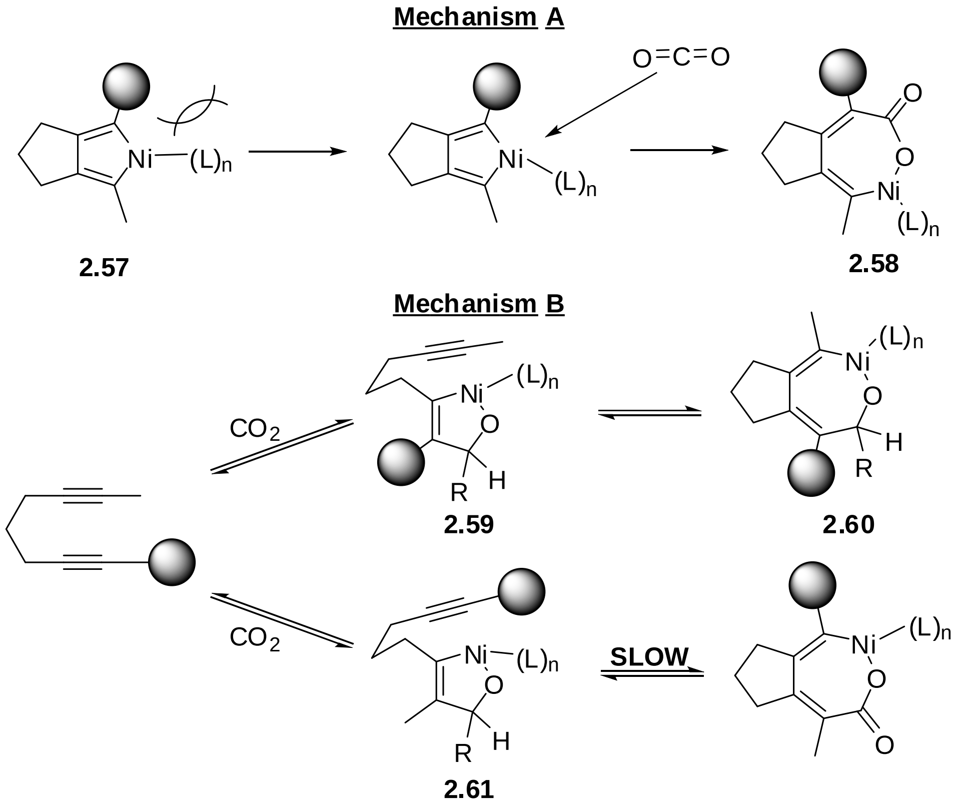

Mechanism A
O=C=O
Ni—(L)n
Ni
(L)n
O
O
Ni
(L)n
2.57
2.58
Mechanism B
CO2
CO2
Ni
(L)n
O
R
H
2.59
(L)n
Ni
O
H
R
2.60
Ni—(L)n
O
R
H
2.61
SLOW
Ni
(L)n
O
O

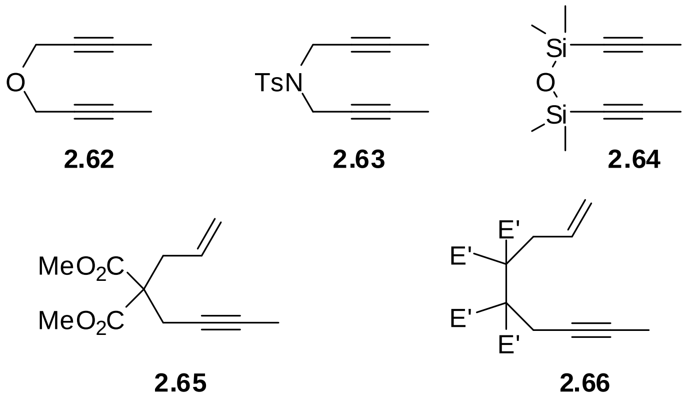
Figure 2.16. Rationale for observed regioselectivity in cycloaddition.

This relieves the crowding around the C(R_L)-Ni bond making it easier for CO_2 to insert nto this bond. Upon insertion, nickelacycle **2.58** is generated which then reductively eliminates to produce the observed regioisomer.

If mechanism B were operating, when unsymmetrical diynes are used, the two regioisomeric products that are possible are ultimately dependent upon the five-membered nickelacycle **2.59** or **2.61**. Initial oxidative coupling between the larger alkynyl unit (R_L) and CO_2 leads to the formation of nickelacycle **2.59**. Subsequent insertion of the pendent alkynyl unit affords pyrones with the bulky R_L group α to the carbonyl. Although binding and oxidative coupling of the least sterically hindered group is favored (**2.61**), subsequent insertion of the bulky R_L group is hindered as it is placed adjacent to the bulky carbene ligand. The larger the R_L group is, the less likely it is to insert. Thus, if **2.61** is formed and the R_L is large, it cannot insert and **2.61** undergoes the reverse reaction. The R_L substituted alkyne can then oxidatively couple with CO_2 to generate **2.59**. Facile insertion of the alkyne with the smaller group generates **2.60** which reductively eliminates to form the observed pyrone. Inhibition of the oxidative coupling would slow the overall rate of pyrone formation and permit the formation of side products to become competitive. This would explain why increased amounts of oligomeric side products are observed when unsymmetrical diynes are used as substrates.

While the cycloaddition could be performed both regioselectivly and under mild conditions, the substrate scope was not as broad as expected. Although ethereal diynes **2.53** and **2.55** cyclized in modest yield, diyne **2.62** (which lacks substitution α to the oxygen) did not yield any of the desired pyrone (Figure 2.17). Similarly, diynes **2.63** and **2.64** also failed to produce any of the pyrone cycloadduct (Figure 2.17). Attempts at expanding the substrate scope to include enynes met with similar resistance as enynes **2.65** and **2.66** failed to react (Figure 2.17).

Concurrent with the attempts at expansion of the substrate scope, it was discovered that the free carbenes react with CO_2 to form zwitterionic carboxylates (Figure 2.18).[18] These carboxylates were found to be sparingly soluble in most solvents.



2.62 **2.63** **2.64**

2.65 **2.66**

Figure 2.17. Attempted substrates for cycloaddition reaction.

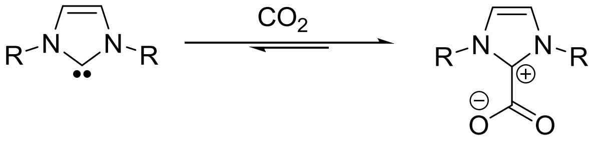


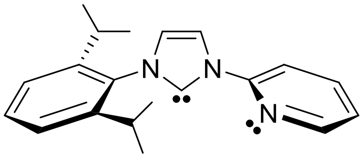
Figure 2.18. Formation of zwetterionic carbene carboxylate.

Because the binding of carbenes to the Ni is reversible, when the carbenes are not bound to the metal they rapidly react with the CO_2 in solution. Upon formation of the zwitterionic carboxylate, the ligand precipitates out of solution and is therefore unable to stabilize the Ni(0).

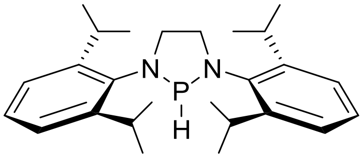
It has been reported that in the absence of proper ligands to stabilize it, Ni(0) precipitates out of solution to inactive Ni metal.[8c] Therefore, it was thought that if rapid cyclization did not occur, the catalyst would decompose to its inactive form. In order to increase the longevity of the catalyst, several attempts were made to prevent the ligand from reacting with the CO_2.

Initially, the bidentate ligand **2.67** was tested for reactivity under the standard conditions as it was thought that a bidentate ligand would be less likely to dissociate and react with CO_2 (Figure 2.19). While complete conversion of **2.23** was observed, only trace amounts of the pyrone were formed. The majority of the remaining mass balance was accounted for by the formation of oligomers.

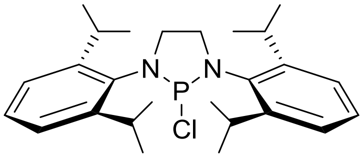
Various cyclic phosphanes were also tested for catalytic activity in the conversion of **2.23** to **2.24**. While these ligands are bulky and electron donating like their analogous carbenes, no conversion of **2.23** was observed by GC.



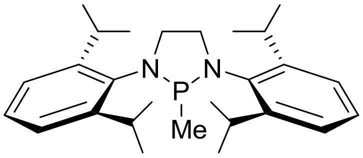
2.67



2.68



2.69



2.70

Figure 2.19. Additionally attempted ligands for cyclization reaction.

Conclusion

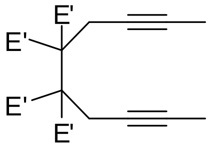
Imidazolylidene-based ligands in conjuction with a Ni(0) precursor efficiently catalyzed the reaction between diynes and CO_2 to afford the corresponding pyrones in good to excellent yields. The conditions were very mild, requiring only slightly elevated temperatures and 1 atm of CO_2. When unsymmetrical diynes were used, the reaction was found to be regioselective. The degree of regioselectivity, however, was highly dependent on the ligand employed and the size of the terminal groups on the alkyne. When one alkynyl group was substituted with a TMS group (and the other with a relatively small methyl group), the IMes ligand afforded only one pyrone regioisomer. Improved performance was obtained with the IPr ligand as high regioselectivities were observed with diynes which contained a terminal *i*-Pr, *t*-Bu, or TMS substituent. X-ray diffraction analysis indicated that the predominant regioisomer placed the relatively large substituent at the 3-postion of the pyrone ring (α to the carbonyl).

Experimental Section

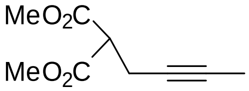
All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove-box. Toluene, pentane, and diethyl ether were dried over neutral alumina under N_2 using a Grubbs type solvent system. THF was freshly distilled from Na/benzophenone. DMF was freshly distilled from CaH_2 under reduced pressure. $Ni(COD)_2$ was purchased from Strem and used without further purification. IPr and IMes ligands were prepared as previously reported.[19,20] *n*-Butyl lithium and methyl lithium were titrated with 1,10-phenantheradine/*sec*-butanol prior to use.[21] 1-bromo-4-methylpent-2-yne and 1-bromo-4,4-dimethylpent-2-yne were prepared from the corresponding alcohols by the method described by Brandsma.[22] (3-Bromoprop-1-ynyl)trimethylsilane was prepared from propargyl bromide according to the method described by Brandsma.[23] Sodium hydride was thoroughly washed with pentane and dried in vacuo prior to use. All other reagents were purchased and used without further purification unless otherwise noted.

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 75 MHz, respectively unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, q, qt, quint, sept, septt, m, brm, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, quartet, quartet of triplets, quintet, septet, septet of triplets, multiplet, broad multiplet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. HRMS were performed at the mass spectrometry facility at The University of California, Riverside. Analytical C & H combustion analyses were performed by Midwest Microlab, LLC, Indianapolis, Indiana.

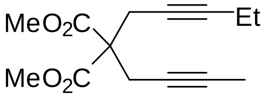
Synthetic Procedures and Analysis



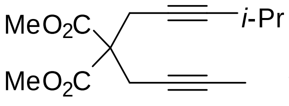
Preparation of 2-but-2–ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester (2.37). To a stirred suspension of NaH (255.0 mg, 10.6 mmol) and dry THF (40 mL) in a 100 mL RBF was added tetraethyl 1,1,2,2-ethanetetracarboxylate (1.3000 g, 4.1 mmol) under N_2 counter-flow in two portions. The resulting solution was stirred at room temperature for 1 h after which time 1-bromo-2-butyne (1.409 g, 10.6 mmol) was added. The reaction mixture was then heated at reflux for 44 hrs at which time GC analysis showed no remaining starting ester or mono-alkylated ester. The solution was cooled to room temperature and quenched with 20 mL sat. NH_4Cl solution. The aqueous layer was extracted 3 x 10 mL Et_2O. The collected organics were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude yellow oil was purified by flash column chromatography on SiO_2 eluting with 15% EtOAc/hexanes then 25% EtOAc/hexanes to yield a pale yellow oil. The yellow oil was further purifed by triturating with hexanes to afford **2.37** (1.4848 g, 86%) as a white solid. ^1H and ^{13}C NMR were identical to those reported in literature.



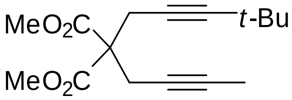
Preparation of 2-but-2-ynyl malonic acid dimethyl ester (2.71). To a stirring suspension of NaH (1.32g, 55mmol) in 100 mL THF, dimethyl malonate (5.71 mL, 50 mmol) was added dropwise. The solution was stirred at room temperature for 1 h followed by the addition of 1-bromo-2-butyne (4.8 mL, 55 mmol). The resulting solution was stirred at reflux until starting material was no longer visible by TLC. The mixture was then cooled to room temperature, quenched with H_2O (20 mL), and extracted 2 x 75 mL diethyl ether. The collect organics were then washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to yield a yellow oil. The crude oil was further purified by distillation to yield **2.71** (5.6 g, 61%) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.70 (s, 6H), 3.49 (t, *J* = 7.7 Hz, 2H), 2.65 (dq, *J* = 7.7, 2.54 Hz, 1H), 1.68 (t, *J* = 2.54 Hz, 3H). $^{13}C\ \{^1H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 168.6, 77.9, 74.6, 52.7, 51.4, 18.9, 3.4.



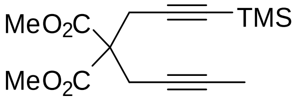
Preparation of 2-acetoxy-2-but-2-ynyl-hept-4-ynoic acid methyl ester (2.46). To a stirring suspension of NaH (264 mg, 11 mmol) in 25 mL THF, monoyne **2.71** (1.842 g, 10 mmol) was added dropwise. The resulting solution was stirred at room temperature for 1 h followed by the addition of 1-bromo-2-pentyne (1.12 mL, 11 mmol). The resulting solution was stirred at reflux until starting material was no longer visible by TLC. The mixture was cooled to room temperature, quenched with H_2O (5 mL), extracted 3 x 10 mL diethyl ether. The collect organics were washed with brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude oil was purified by flash column chromatography on SiO_2 eluting with 5% EtOAc/hexanes to yield **2.46** (1.827 g, 73%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$,): δ (ppm) 3.75 (s, 6H), 2.91 (brs, 4H), 2.12 (qt, *J* = 7.57 Hz, 2.44 Hz, 2H), 1.76 (t, *J* = 2.44 Hz, 3H), 1.08 (t, *J* = 7.57 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 170.7, 164.3, 155.0, 151.8, 115.9, 115.5, 59.4, 53.2, 38.6, 35.4, 17.4, 12.7. IR (neat): 2955, 1742, 1436, 1328, 1293, 1212, 1055 cm^{-1}. Anal. calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25, found: C, 67.29; H, 7.20.



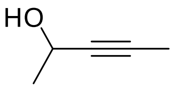
Preparation of 2-acetoxy-2-but-2-ynyl-6-methyl-hept-4-ynoic acid methyl ester (2.47). Prepared analogously to diyne **2.46** using **2.71** (1.75 g, 9.5 mmol), NaH (285 mg, 11.9 mmol) and 1-bromo-4-methylpent-2-yne (2.77 g, 10.4 mmol). The reaction mixture was purified by flash column chromatography on SiO_2 eluting with 5% EtOAc/hexanes to yield **2.47** (1.67 g, 67%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.74 (s, 6H), 2.90 (m, 4H), 2.48 (septt, *J* = 7.08 Hz, 2.2 Hz, 1H), 1.76 (t, *J* = 2.44 Hz, 3H), 1.11 (d, *J* = 7.08, 6H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.9, 89.6, 79.1, 73.5, 73.3, 57.5, 53.0, 23.3, 23.1, 20.6, 3.7. IR (neat): 2970, 1743, 1437, 1327, 1293, 1212, 1056 cm^{-1}. Anal. calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63, found: C, 67.97; H, 7.55.



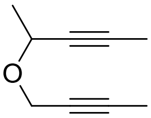
Preparation of 2-acetoxy-2-but-2-ynyl-6,6-dimethyl-hept-4-ynoic acid methyl ester (2.48). Prepared analogously to diyne **2.46** using **2.71** (1.33 g, 7.2 mmol), NaH (30.0 mg, 9 mmol) and 1-bromo-4,4-dimethylpent-2-yne (2.4 g, 9.1 mmol). The reaction mixture was purified by flash column chromatography on SiO_2 eluting with 5% EtOAc/hexanes to yield **2.48** (1.23 g, 62%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.74 (s, 6H), 2.88 (brs, 4H), 1.75 (brt, 2H), 1.16 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 170.0, 92.6, 79.1, 73.5, 73.0, 57.7, 53.1, 31.4, 27.6, 23.2, 3.8. IR (neat): 2969, 2868, 1744, 1437, 1212, 1063, 951 cm^{-1}. Anal. calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97, found: C, 68.96; H, 7.96.



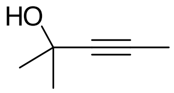
Preparation of 2-but-2-ynyl-2(3-trimethylsilanyl-prop-2-ynyl) -malonoic acid dimethyl ester (2.43). Prepared analogously to diyne **2.46** using **2.71** (2.5 g, 13.6 mmol), NaH (360 mg, 15 mmol) and (3-bromoprop-1-ynyl)trimethylsilane (3.25 g, 17.0 mmol). The reaction mixture was purified by flash column chromatography on SiO_2 eluting with 5% EtOAc/hexanes to yield **2.43** (2.21 g, 55%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.73 (s, 6H), 2.96 (s, 2H), 2.89 (q, *J* = 2.44 Hz, 2H), 1.74 (t, 2.44 Hz, 3H) 0.11 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.6, 101.3, 88.4, 79.3, 73.2, 57.3, 53.1, 24.2, 23.2, 3.7, 0.1.



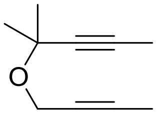
Preparation of pent-3-yn-2-ol (2.72). To a flame dried three-necked flask with a stir bar at -78 °C, propyne (~3 g) was condensed and 25 mL Et_2O was added slowly. Methyl lithium in Et_2O (42.5 mL, 59.4 mmol) was slowly added and the resulting solution was stirred at -78 °C for 1 h. A solution of acetylaldehyde (3.66 mL, 65.4 mmol) in 8 mL Et$_2$O was added to the mixture. The cold bath was removed and the reaction was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH$_4$Cl solution (20 mL), extracted 3 x 15 mL Et$_2$O, and dried over MgSO$_4$. The excess solvent was carefully removed by distillation through a 13 cm Vigreux column at atmospheric pressure. The resulting yellow oil was further purified by distillation through a 16 cm Vigreux column to yield **2.72** (2.214 g, 44%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 4.41 (m, 1H), 2.95 (brt, *J* = 4.4 Hz, 1H), 1.75 (d, *J* = 2.19 Hz, 3H), 1.34 (d, *J* = 6.59 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 81.6, 79.9, 58.3, 24.5, 3.4.



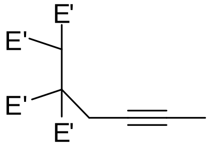
Preparation of 4-but-2-ynyloxy-pent-2-yne (2.53). To a stirring suspen-sion of NaH (396.4 mg, 16.5 mmol) in DMF (75 mL) at 0 °C, alcohol **2.72** (0.9262 mg, 11 mmol) dissolved in 2 mL DMF was added dropwise. The resulting solution was stirred for 1 h followed by the addition of 1-bromo-2-butyne (1.19 mL, 13.2 mmol). The mixture was stirred at 0 °C until starting material was no longer visible by TLC. The reaction was quenched with saturated aqueous NH$_4$Cl solution (15 mL) and extracted 3 x 20 mL 50:50 EtOAc:pentane. The collected organics were washed with 2 x 10 ml H$_2$O, dried over MgSO$_4$, and concentrated in vacuo to yield a yellow oil. The crude oil was further purified by vacuum distillation to yield **2.53** (703 mg, 47%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 4.33-4.05 (m, 3H), 1.81 (m, 6H), 1.37 (d, 6.59 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 82.3, 81.5, 78.5, 75.1, 64.2, 56.2, 22.3, 3.7, 3.6. IR (neat): 2986, 2922, 2857, 1444, 1334, 1084 cm^{-1}. HRMS(EI): calcd for C$_9$H$_{11}$O (M$^+$-H) 135.0804, obsd 135.0804.



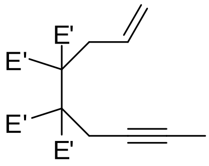
Preparation of 2-methyl-pent-3-yn-2-ol (2.73). To a flame dried three-necked flask with a stir bar at -78 °C, propyne (~3g) was condensed and 40 mL THF was added slowly. *n*-BuLi in hexanes (16.3 mL, 40.8 mmol), was slowly added and the resulting solution was stirred at ⁻78 °C for 1 h. A solution of dry acetone (3.14 mL, 65.4 mmol) in 5 mL THF was added to the mixture. The cold bath was removed and the reaction was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted 3 x 15 mL Et_2O, and dried over $MgSO_4$. The excess solvent was carefully removed by distillation through a 13 cm Vigruex column at 1 atmosphere. The resulting yellow oil was further purified by distillation through a 16 cm Vigreux column to yield **2.73** (1.85 g, 46%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.06 (brs, 1H), 1.81 (s, 3H), 1.48(s, 6H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 84.4, 78.2, 65.5, 31.8, 3.6.



Preparation of 4-but-2-ynyloxy-4-methyl-pent-2-yne (2.55). Prepared analogously to 4-but-2-ynyloxy-pent-2-yne (**2.53)** with alcohol **2.73** (979.9 mg, 9.99 mmol), NaH (359.9 mg, 10.98 mmol) and propargyl bromide (1.45 g, 10.98 mmol). Purification was achieved via vacuum distillation to yield **2.55** (632.1 mg, 42%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.18 (q, *J* = 2.44 Hz, 2H), 1.82 (t, *J* = 2.44 Hz, 3H), 1.81 (s, 3H), 1.42 (s, 6H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 81.7, 80.9, 80.7, 76.2, 71.1, 52.9, 29.1, 3.9, 3.6. IR (neat): 2984, 2922, 2861, 2422, 1439, 1255, 1154, 1050 cm^{-1}.

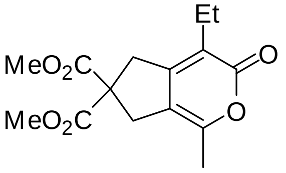


Preparation of 2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester (2.74). To a stirring suspension of NaH (356.0 mg, 14.9 mmol) in 135 mL THF was added tetraethyl 1,1,2,2-ethanetetracarboxylate (4.2970 g, 13.5 mmol) under N_2 counter-flow in two portions. The resulting solution was stirred at room temperature for 3 h after which time 1-bromo-2-butyne (1.9748 g, 14.9 mmol) was added. The reaction mixture was then heated at reflux for 8 h and then cooled to room temperature and quenched with 20 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude yellow oil was purified by flash column chromatography on SiO_2 eluting with 15% EtOAc/hexanes then 25% EtOAc/hexanes to yield **2.74** (4.5511 g, 91%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.34 (s, 1H), 4.30-4.17 (m, 8H), 2.93 (q, *J* = 2.6Hz, 2H), 1.78 (t, *J* = 2.6 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 12H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 168.7, 167.3, 79.4, 73.4, 62.0, 61.7, 57.7, 54.8, 24.6, 13.95, 13.91, 3.6. IR (neat): 2985, 1741, 1447, 1370, 1210, 1033, 863 cm^{-1}. HRMS(EI): calcd for $C_{18}H_{26}O_8$ (M^+) 370.1628, obsd 370.1627.

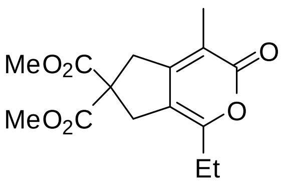


Preparation of 2-allyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester (2.66). To a stirring suspension of NaH (129.6 mg , 5.4 mmol) in 25 mL THF was added tetra-ester **2.74** (1.0000 g, 2.7 mmol) in 2 mL THF. The resulting solution was stirred at room temperature for 1 h at which time allyl bromide (496.0 mg , 5.4 mmol) was added in a single portion via syringe. The flask was the equipped with a reflux condenser and the mixture was stirred at reflux until no starting material was observed by GC analysis (~36 h). The mixture was then cooled to room temperature and quenched with 20 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to yield a yellow oil. The crude oil was purified by flash column chromatography on SiO_2 eluting with 15% EtOAc/hexanes producing a yellow oil which was then triturated with cold hexanes to yield enyne **2.66** (982.3 mg, 89%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.07-5.90 (m, 1H), 5.11 (d, J = 17.0 Hz, 1H), 5.05 (d, J = 10.1 Hz, 1H), 4.35-4.10 (m, 8H), 3.07 (q, J = 2.4 Hz, 2H), 2.86 (d, J = 7.2 Hz, 2H), 1.75 (t, 2.4 Hz, 3H), 1.28 (appt. q, 12H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.2, 161.1, 134.0, 119.1, 78.1, 74.8, 62.6, 62.3, 61.9, 61.7, 36.3, 22.8, 14.01, 13.99, 3.8. IR (neat): 2982, 1731, 1367, 1330, 1211, 1035 cm^{-1}. HRMS(CI): calcd for $C_{21}H_{31}O_8$ (MH^+) 411.2019, obsd 411.1999.

General [2+2+2] cycloaddition procedure. An oven dried two-neck round bottomed flask equipped with a magnetic stir bar, septum, gas adapter and balloon is evacuated and filled with CO_2. A solution of diyne is added and the flask is submerged into a 60 °C oil bath. To the stirring solution, a solution of $Ni(COD)_2$ and IPr or IMes (previously equilibrated for at least 6 h) is added. The dark greenish-black reaction mixture is heated for 30 minutes (or until complete consumption of starting material was observed as judged by GC or TLC). The mixture was cooled to ambient temperature, concentrated, and purified by flash column chromatography on SiO_2.

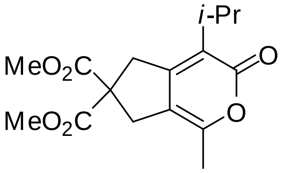


2.50a

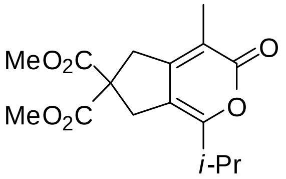


2.50b

Preparation of 4-Ethyl-1-methyl-3-oxo-3,5-dihydro-7*H*-cyclopenta[c]pyran-6,6-dicarboxylic acid dimethyl ester (2.50a) and 1-ethyl-4-methyl-3-oxo-3,5-dihydro-7-cyclopentapyran-6,6-dicarboxylic acid dimethyl ester (2.50b). The general procedure was used with 2-acetoxy-2-but-2-ynyl-hept-4-ynoic acid methyl ester **2.46** (127.6 mg, 0.51 mmol), Ni(COD)$_2$ (6.9 mg, 0.025 mmol), IPr (19.8 mg, 0.051 mmol), and 5.1 mL of toluene. The reaction mixture was purified by flash column chromatography on SiO$_2$ eluting with 2% Et$_2$O/CH$_2$Cl$_2$ then 4% Et$_2$O/CH$_2$Cl$_2$ to yield pyrones **2.50a** and **2.50b** in a 62:38 mixture (111.6 mg, 74%) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 3.78 (s, 12H), 3.33 (brs, 4H), 3.27 (brm, 4H), 2.44 (app. quint, 4H), 2.16 (s, 3H), 2.00 (s, 3H), 1.21 (t, *J* = 7.57 Hz, 3H), 1.11 (t, *J* = 7.57 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 171.1, 171.1, 164.8, 164.1, 156.8, 155.4, 154.9, 152.5, 121.8, 116.3, 116.1, 115.4, 98.8, 59.93, 59.89, 53.6, 39.0, 38.6, 35.7, 35.6, 25.3, 21.3, 17.8, 13.1, 12.7, 11.7. IR (neat): 2958, 1738, 1674, 1606, 1436, 1262, 1071, 968 cm^{-1}. HRMS(CI): calcd for $C_{15}H_{19}O_6$ (MH$^+$) 295.1176, obsd 295.1191.



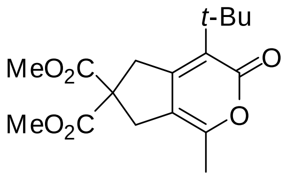
2.51a



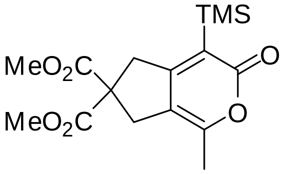
2.51b

Preparation of 4-Isopropyl-1-methyl-3-oxo-3,5-dihydro-7*H*-cyclopenta[c]pyran-6,6-dicarboxylic acid dimethyl ester (2.51a) and1-isopropyl-4-methyl-3-oxo-3,5-dihydro-7*H*-cyclopenta[c]pyran-6,6-dicarboxylic acid dimethyl ester (2.51b). The general procedure was used with 2-acetoxy-2-but-2-ynyl-

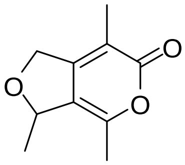
6-methyl-hept-4-ynoic acid methyl ester **2.47** (105.7 mg, 0.40 mmol), Ni(COD)$_2$ (11.0 mg, 0.04 mmol), IPr (31.1 mg, 0.08 mmol), and 4.0 mL of toluene. The reaction mixture was purified by flash column chromatography in SiO$_2$ eluting with 12% EtOAc/hexanes then 20% EtOAc/hexanes to yield pyrones **2.51a** and **2.51b** in an 80:20 mixture (94.2 mg, 76%) as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 3.76 (s, 12H), 3.36 (s, 2H), 3.31 (q, J = 1.1 Hz, 2H), 3.27 (s, 2H), 3.21 (q, J = 1.2 Hz, 2H), 2.95 (sept, J = 7.0 Hz, 1H), 2.72 (sept, J = 7.0 Hz, 1H), 2.13 (t, J = 1.1 Hz, 3H), 1.98 (brt, 3H), 1.24 (d, J = 7.0 Hz, 6H), 1.21 (d, J = 6.87 Hz, 6H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 171.1, 171.0, 164.6, 162.9, 159.7, 155.5, 154.1, 152.4, 125.0, 116.2, 116.0, 114.3, 59.83, 59.80, 53.4, 38.90, 38.85, 35.5, 35.2, 31.3, 28.9, 20.1, 20.0, 19.9, 17.7, 13.1. IR (neat): 2959, 1714, 1598, 1435, 1384, 1263, 1204, 1070, 1003, 940 cm^{-1}. HRMS(CI): calcd for $C_{16}H_{21}O_6$ (MH$^+$) 309.1333, obsd 309.1329.



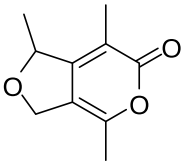
Preparation of 4-*tert*-Butyl-1-methyl-3-oxo-3,5-dihydro-7-cyclopentapyran-6,6-dicarboxylic acid dimethyl ester (2.52). The general procedure was used with 2-acetoxy-2-but-2-ynyl-6,6-dimethyl-hept-4-ynoic acid methyl ester **2.48** (129.5 mg, 0.47 mmol), Ni(COD)$_2$ (12.8 mg, 0.047 mmol), IPr (36.2 mg, 0.093 mmol), and 4.7 mL of toluene. The reaction mixture was purified by flash chromatography (12.5% EtOAc/Hexanes then 25% EtOAc/Hexanes) to yield pyrone **2.52** (96.2 mg, 64%) as a white solid. X-ray quality crystals were obtained by vapor diffusion of cyclohexane into a saturated solution of pyrone in ether/cyclohexane. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 3.78 (s, 6H), 3.62 (s, 2H), 3.15 (s, 2H), 2.14 (s, 3H), 1.41 (s, 9H); ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 171.2, 162.7, 152.7, 151.7, 127.9, 166.6, 59.7, 53.5, 41.6, 36.7, 34.4, 30.1, 17.6. IR (neat): 2956, 1712, 1674, 1562, 1435, 1264, 1209, 1104, 998 cm^{-1}. HRMS: calcd for $C_{17}H_{23}O_6$ (M^+) 323.1489, obsd 323.1486.



Preparation of 1-Methyl-3-oxo-4-trimethylsilanyl-3,5-dihydro-7*H*-cyclopenta [c]pyran-6,6-dicarboxylic acid dimethyl ester (2.44). The general procedure was used with 2-but-2-ynyl-2-(3-trimethylsilanyl-prop-2-ynyl)-malonoic acid dimethyl ester **2.43** (130.5 mg, 0.44 mmol), Ni(COD)$_2$ (6.1 mg, 0.022 mmol), IMes (13.5 mg, 0.044 mmol), and 4.4 mL of toluene. The reaction mixture was purified by flash chromatography (12.5% EtOAc/Hexanes then 25% EtOAc/Hexanes) to yield pyrone **2.44** (101.3 mg, 68%) as a white solid. X-ray quality crystals were obtained by slow evaporation of a saturated solution of **2.44** in ether/cyclohexane. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 3.78 (s, 6H), 3.37 (s, 2H), 3.21 (s, 2H), 2.16 (s, 3H), 0.30 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 171.2, 162.7, 152.7, 151.7, 127.9, 166.6, 59.7, 53.5, 41.6, 36.7, 34.4, 30.1, 17.6.

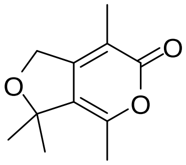


2.54a

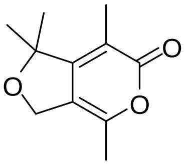


2.54b

Preparation of 3*H*-furo[3,4-c]pyran-6-one (2.54a), 1, 4, 7-Trimethyl-1*H*, 3*H*-furo[3,4-c]pyran-6-one (2.54b) and 3, 4, 7-trimethyl-1*H*,. The general procedure was used with 4-but-2-ynyloxy-pent-2-yne **2.53** (75.6 mg, 0.555 mmol), Ni(COD)$_2$ (15.3 mg, 0.0555 mmol), IPr (43.1 mg, 0.111 mmol), and 5.5 mL of toluene. The reaction mixture was purified by flash column chromatography on SiO$_2$ eluting with 12% EtOAc/hexanes to yield pyrones **2.54a** and **2.54b** in ~50:50 mixture (41.3 mg, 41%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 5.12 (q, J = 6.59 Hz, 2H), 4.90-4.68 (m, 4H), 1.43 (d, *J* = 6.59 Hz, 6H), 2.20 (s, 3H), 2.16 (s, 3H), 2.02 (s 3H), 1.97 (s, 3H). $^{13}C\ \{^1H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 165.0, 164.5, 158.1, 155.2, 151.0, 150.2, 120.6, 116.1, 113.2, 113.0, 78.1, 76.9, 69.4, 67.2, 21.0, 19.4, 18.1, 17.6, 13.0, 12.6. IR (neat): 2977, 2925, 1717, 1680, 1615, 1070, 1022, 863 cm^{-1}.



2.56a



2.56b

Preparation of 3,3,4,7-tetramethyl-1*H*, 3*H*-furo[3,4-c]pyran-6-one (2.56a) and 1,1,4,7-Tetramethyl-1*H*, 3*H*-furo[3,4-c]pyran-6-one (2.56b). The general procedure was used with 4-but-2-ynyloxy-4-methyl-pent-2-yne **2.55** (54.9 mg, 0.206 mmol), $Ni(COD)_2$ (5.7 mg, 0.0206 mmol), IPr (16 mg, 0.0412 mmol), and 2.0 mL of toluene. The reaction mixture was purified by flash column chromatography on SiO_2 eluting with 12% EtOAc/hexanes, then 15% EtOAc/hexanes, then 20% EtOAc/hexanes) to yield pyrones **2.56a** and **2.56b** in ~50:50 crude mixture (79.7 mg, 53%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.76 (q, *J* = 1.1 Hz, 2H), 4.7 (q, *J* = 1.2 Hz, 2H), 2.23 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H), 1.96 (s, 3H), 1.52 (s, 6H), 1.49 (s, 6H). $^{13}C\ \{^1H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 165.4, 164.3, 160.0, 155.6, 150.9, 149.6, 123.7, 116.5, 113.0, 84.7, 83.6, 67.9, 65.3, 27.0, 25.5, 17.8, 16.8, 12.7. IR (neat): 2978, 2931, 1719, 1610, 1441, 1387, 1366, 1317, 1118, 908 cm^{-1}.

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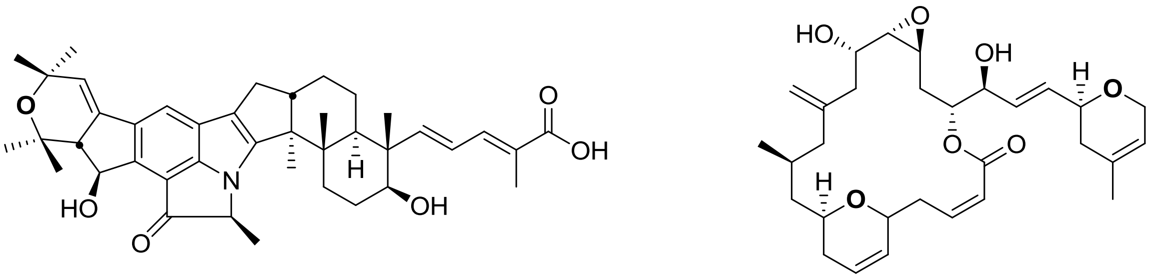
CHAPTER 3

NICKEL CATALYZED CYLOADDITIONS OF ALDEHYDES AND KETONES WITH DIYNES AND ENYNES

Introduction

The pyran moiety is a common motif found in a myriad of biologically active natural products such as nodulisporic acid and laulimalide (Figure 3.1). Due to its prevalence, several unique and clever methods have been derived to access the pyran structure. A brief review of the literature reveals that pyrans can be accessed via a number of methods including nucleophilic displacement,[1] Michael additions,[2] Petasis-Ferrier rearrangements,[3] hetero Diels-Alder reactions,[4] and Prins-related cyclizations.[5]



nodulisporic acid

laulimalide

Figure 3.1. Pyran containing natural products.

While each of these methods has distinct advantages, they have limitations. One limitation some of these transformations face is the need for a stoichiometric amount of a reagent to complete the transformation. This, in turn, generates excess waste which needs to be removed and lowers the over-all atom economy of the process.[6] Another disadvantage is the need for highly specialized and advanced reagents. With the ever pressing need to synthesize not only the target natural product, but also various analogs for biological testing, the efficient synthesis of highly specialized intermediates becomes important. A third limitation often encountered is the use of “harsh” conditions such as excessive heat, acids, and bases. These conditions have been shown on several occasions to decompose sensitive, advanced intermediates.

With these challenges in mind, it would be advantageous to develop a protocol for the synthesis of pyrans which uses a catalytic amount of reagent, can be carried out from simple starting materials, and can be done under mild conditions (i.e., room temperature and neutral pH). One potential method that meets all of these criteria is the transition-metal catalyzed [2+2+2] cycloaddition of aldehydes and/or ketones with unsaturated hydrocarbons (Figure 3.2).

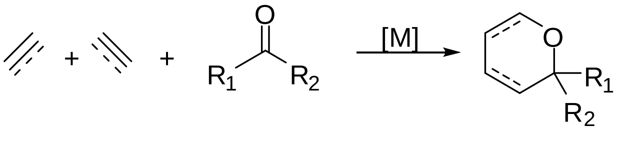


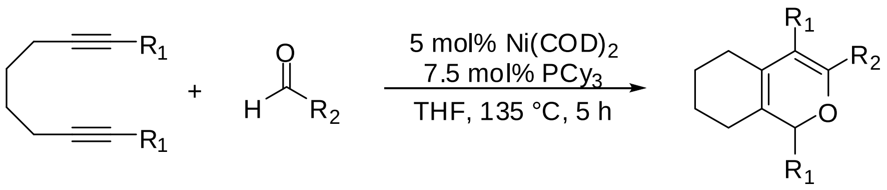
Figure 3.2. Pyran synthesis via transition-metal catalyzed [2+2+2] cycloaddition.

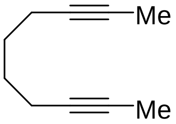
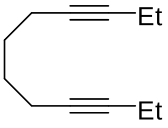
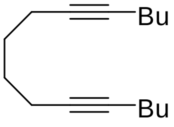
Previous Investigations of Transition-Metal Catalyzed [2+2+2] Cycloadditions of Aldehydes and Ketones with Diynes

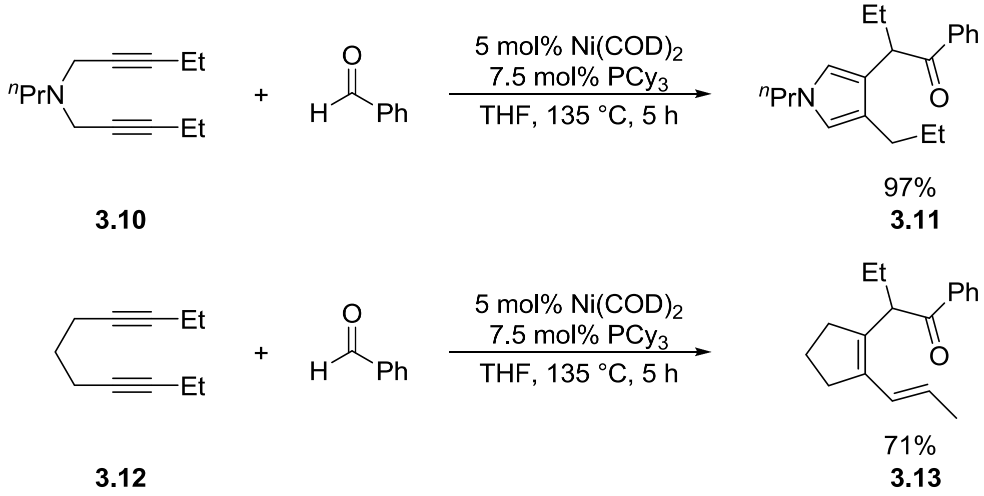
Nickel-Catalyzed Approach

The first transition-metal catalyzed [2+2+2] cycloaddition of aldehydes and diynes was disclosed by Tsuda and Saegusa in 1988.[7] In this protocol, various 1,7-diynes were successfully coupled with aldehydes in the presence of Ni(COD)$_2$ and tricyclohexyl phosphine to yield the bicyclic α-pyran (Table 3.1). When 1,6-diynes were employed under the same conditions, ketones were obtained instead of the bicyclic α-pyran (Figure 3.3).

Table 3.1. Ni/phosphine catalyzed cycloaddition of 1,7-diynes and aldehydes.



entry	diyne	aldehyde	pyran	yield (%)
1	 **3.1**	PhCHO	**3.2**	39
2	 **3.3**	MeCHO ^{n}PrCHO ^{i}PrCHO PhCHO	**3.4** **3.5** **3.6** **3.7**	28 90 69 79
3	 **3.8**	PhCHO	**3.9**	78



nPrN
Et
Et
+
O
H
Ph
5 mol% Ni(COD)2
7.5 mol% PCy3
THF, 135 °C, 5 h
Et
Ph
O
Et
97%
3.10
3.11
Et
Et
+
O
H
Ph
5 mol% Ni(COD)2
7.5 mol% PCy3
THF, 135 °C, 5 h
Et
Ph
O
71%
3.12
3.13

Figure 3.3. Ni/phosphine catalyzed cycloaddition of 1,6-diynes and aldehydes.

This disparity of products can be explained as illustrated in Figure 3.4. Upon diyne coupling with the aldehyde and Ni-catalyst, seven-membered oxanickelcyle **3.14** is generated. This complex then undergoes reductive elimination to form the bicyclic pyran **3.15**. The alkoxy proton of this bicyclic pyran then undergoes a [1,5] migration to generate compound **3.16**. When Z = CH_2CH_2, the fused [6,6] bicyclic pyan is stable and no further reaction occurs. When Z = CH_2 or ^{n}PrN however, a [5,6] fused ring system is formed which is not stable and a [3,3] electrocyclic ring opening occurs generating dieneone **3.17**. Base catalyzed olefin isomerization of **3.17** then leads to **3.11** and **3.13** for Z = CH_2 and ^{n}PrN, respectively.

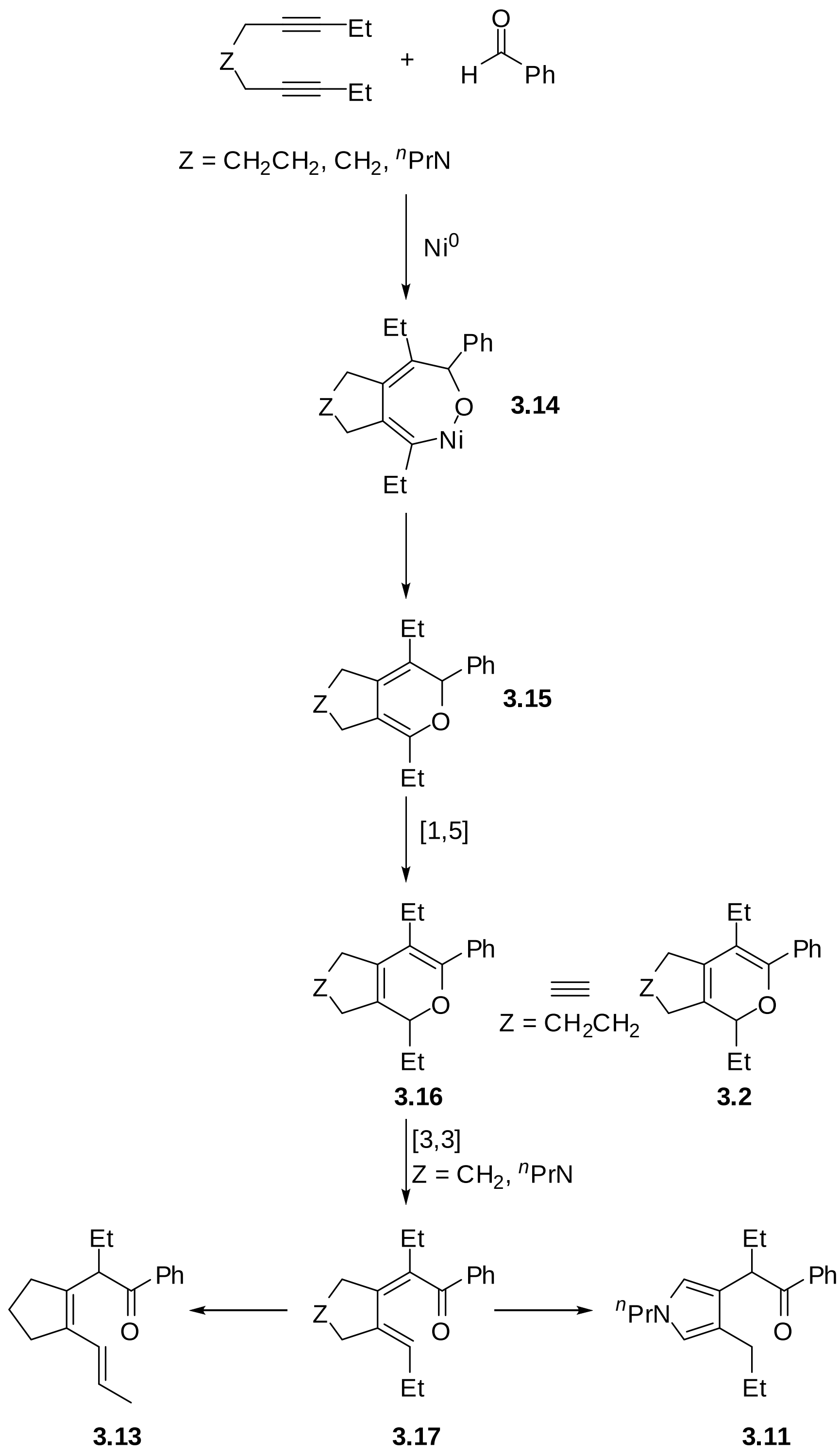
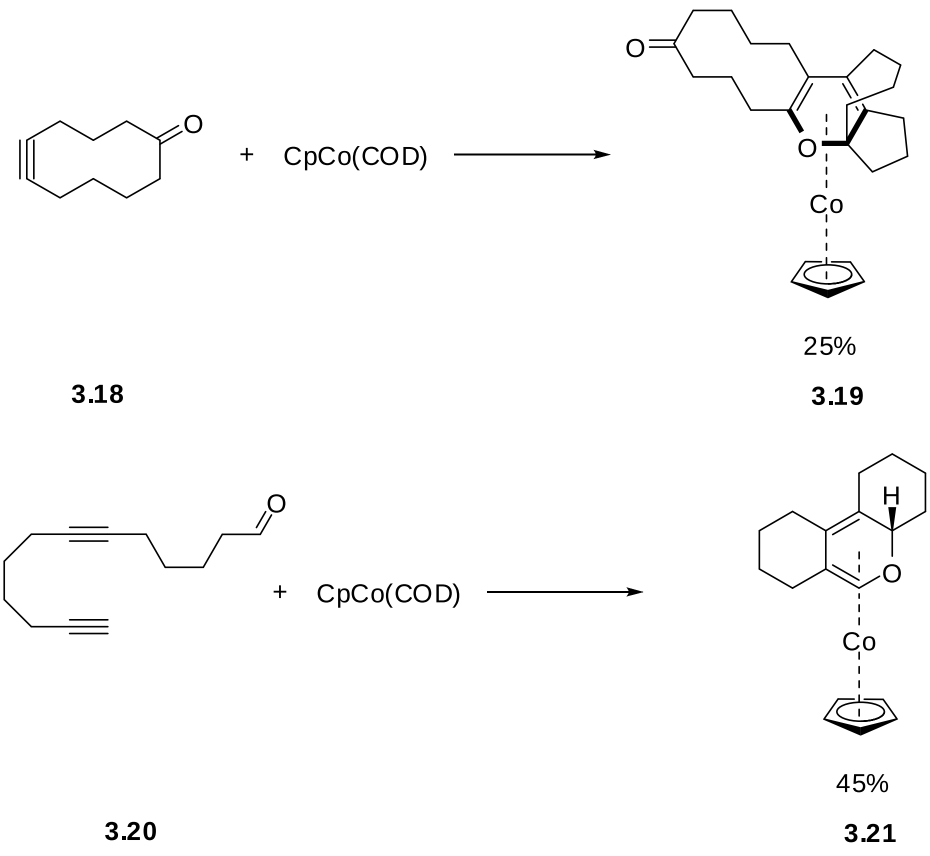

Et
Et
Z
+
O
H
Ph
Z = CH2CH2, CH2, nPrN
Ni0
Et
Ph
Z
O
Ni
Et
3.14
Et
Ph
Z
O
Et
3.15
[1,5]
Et
Ph
Z
O
Et
3.16
Z = CH2CH2
Et
Ph
Z
O
Et
3.2
[3,3]
Z = CH2, nPrN
Et
Ph
O
3.13
Et
Ph
Z
O
Et
3.17
Et
Ph
nPrN
O
Et
3.11

Figure 3. 4. Mechanistic explanation of products.

Cobalt-Mediated Approach

A year after Tsuda and Saegusa's disclosure of the nickel catalyzed [2+2+2] cycloaddition of aldehydes and diynes, two cobalt mediated procedures were reported. The first was by Gleiter and Schelman who found that Cp(Co)(COD) could promote the [2+2+2] cycloaddition of cyclic ynones to yield the pyran as a cobalt complex in a low 25% yield (Figure 3.5).[8] In an effort to increase the yield, an intramolecular variant was attempted with compound **3.20** to yield the cobalt complex **3.21** in a slightly higher 45% yield.



3.18 **3.19**

3.20 **3.21**

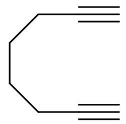
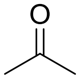
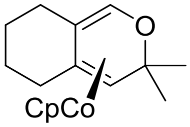
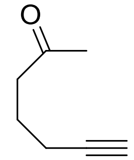
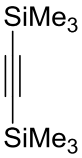
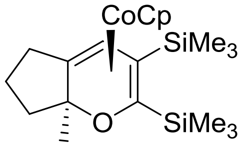
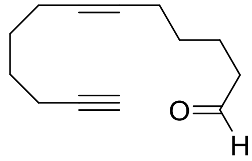
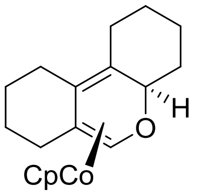
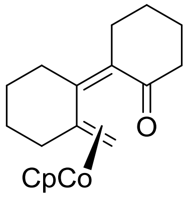
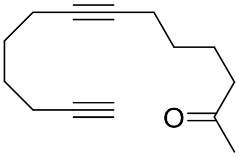
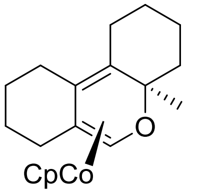
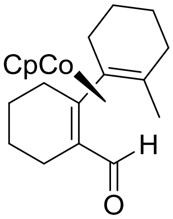
Figure 3.5. Intramolecular Co-mediated cycloadditions.

The other cobalt mediated process was reported by Vohlhardt and coworkers.[9] In this report, both aldehydes and ketones could be cyclized with alkynes to yield the corresponding cobalt complexed pyrans (Table 3.2). As seen in Table 3.2, this protocol was more expansive as various inter- and intramolecular processes were realized in acceptable yields. For instance, diynes could be cyclized successfully with ketones as in entry 1 or ynones could be cyclized with alkynes as in entry 2. Both aldehydes and ketones could be employed in the intramolecular process (entry 3 and 4, respectively). It should also be noted that in both intramolecular processes, enone cobalt complexes **3.28** and **3.29** were also obtained. Enone **3.28** reportedly arises from a [1,5] H-shift of the alkoxy proton of compound **3.27** followed by a six-pi electrocyclic ring opening. This process is exactly analogous to the process reported by Tsuda and Saegusa in the Ni-catalyzed cycloadditions. Enone **3.31** is simply the electrocyclic ring opened product of pyran **3.30**.

Ruthenium Catalyzed Approach

More recently, Itoh and coworkers have reported that unsymmetrical diynes can be cyclized with tricarbonyl compounds in the presence of a Ru catalyst to generate the cycloadduct (Figure 3.6). However the expected pyran **3.33** was not obtained. Instead, the electrocylic ring opened product **3.34** was obtained as the sole product. A variety of 1,6-diynes could be employed in this coupling to obtain the dienone as a single regioisomer in moderate yields (42-75%). Unfortunately, one of the alkynes of the diyne must remain unsubstituted as the cyclization of two internal alkynes failed. Furthermore, the ketone scope was limited to the highly activated tricarbonyl compounds.

Table 3.2. Co-mediated cycloadditions.

entry	reactant(s)[1]	product(s)
1	 **3.22** 	 **3.23** 41%
2	 **3.24** 	 **3.25** 86%
3	 **3.26**	 **3.27** 25%  **3.28** 25%
4	 **3.29**	 **3.30** 57%  **3.31** 17%

[1] Reacted with a stoichiometric amount of CoCp complex.

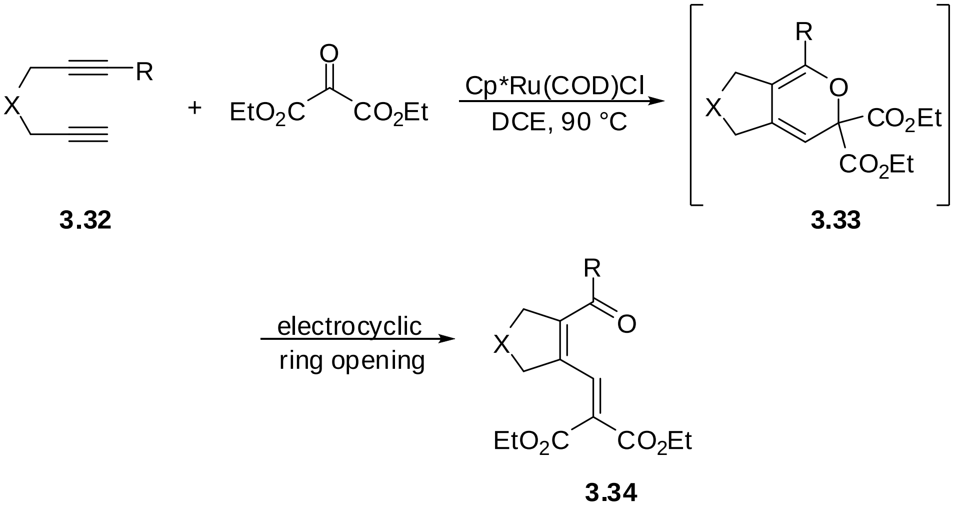


Figure 3.6. Ru-catalyzed cycloaddition.

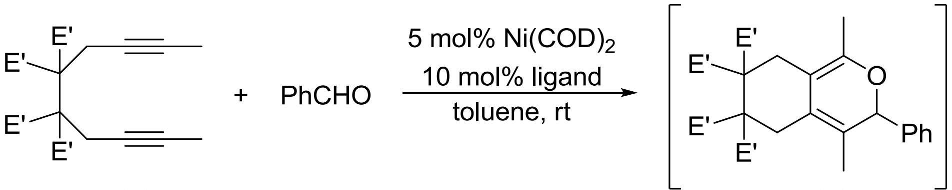
Nickel-Carbene Catalyzed Cycloadditions of Aldehydes with Diynes and Enynes

Due to the limited substrate scopes and the high temperatures required for the previously reported cycloadditions of aldehydes and ketones with alkynes, we felt that our Ni/carbene system may provide some improvement given the previous success with the cycloaddition of diynes and CO_2.

Although the transition from CO_2 to aldehydes is conceptually not very difficult, it is much more difficult from a practical standpoint. The difficultly arises from the increased steric hindrance of aldehydes relative to CO_2. The C-atom of CO_2 is sp-hybridized which translates to CO_2 being a linear molecule. On the other hand, the C-atom of aldehydes is sp^2-hybridized which translates to a trigonal planar molecule. Such a simple change in hybridization severely limits the “faces” from which an electrophile can be attacked. A linear molecule such as CO_2 can easily be attacked from any face in its 360° radius. Trigonal planar molecules, like aldehydes, can only be easily attacked from one of two faces (i.e., the top face or the bottom face).

A variety of conditions were evaluated using diyne **2.37** and benzaldehyde as model substrates for the cycloaddition reaction. Initially, several phosphines and carbenes were screened as potential ligands for this reaction (Table 3.3). Although Tsuda and Saegusa's original protocol used trialkyl phosphines as ligands, several new phosphine ligands have since been disclosed and we thought it prudent to test them for activity. As shown in Table 3.3, none of the traditional alkyl phosphines had any effect on the reaction.

Table 3.3. Screen of ligands for cycloaddition of diyne **2.37** and benzaldehdye.



2.37 **3.35**

entry	ligand	conversion (%)	yield (%)
1	none	0	0
2	PPh_3	6	0
3	PCy_3	0	0
4	dppf	0	0
5	(±) BINAP	0	0
7	I^tBu	95	8
8	IMes	23	23
9	IPr	87	56
10	SIPr	98	80

[a] GC conversions and yields based on napthalene as an internal standard

Ultimately, a protocol similar to the one found effective for the cycloaddition of alkynes and CO_2 cleanly afforded dienone **3.36**, which is derived from electrocyclic ring opening of the initial pyran **3.35** (Figure 3.7). Excellent yields (as determined using gas chromatography) were obtained using 5 mol% of $Ni(COD)_2$, 10 mol% of SIPr, a diyne concentration of 0.1 M in toluene, and a slight excess (1.25 equiv) of aldehyde at room temperature.

As illustrated in Table 3.4, the Ni/SIPr combination catalyzes the cycloaddition reaction of diynes and various aldehydes. For example, benzaldehyde cyclized smoothly at room temperature with diynes **2.37** and **3.42** to afford dienones **3.37** and **3.43** in good yields (entries 1 and 6, respectively). The cycloaddition of an aryl aldehyde bearing an electron-donating group (*p*-OMe) afforded the dienone product in a higher yield than the reaction of an aryl aldehyde possessing an electron-withdrawing group (*p*-CF_3) (entries 2 and 3, respectively). Aliphatic aldehydes also underwent facile cycloaddition (entries 4 and 5) using slightly modified conditions (10 mol% $Ni(COD)_2$ and 10 mol% SIPr). In addition, excess butyraldehyde (entry 5, 5 equiv) was necessary to ensure complete dienone formation.

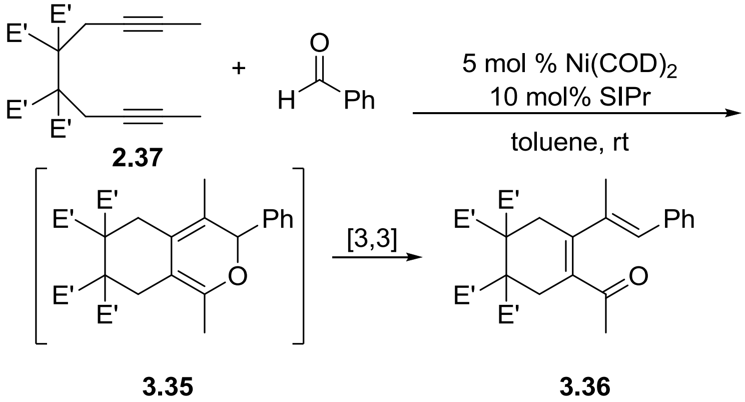
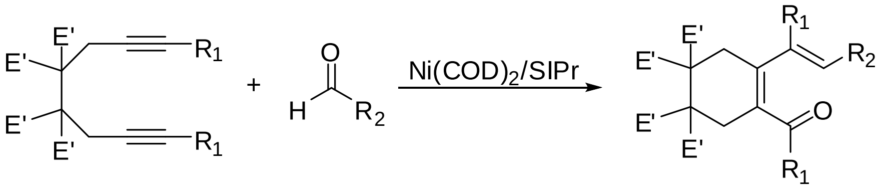


Figure 3.7. Ni/SIPr catalyzed cycloaddition of diyne **2.37** and benzaldehyde.

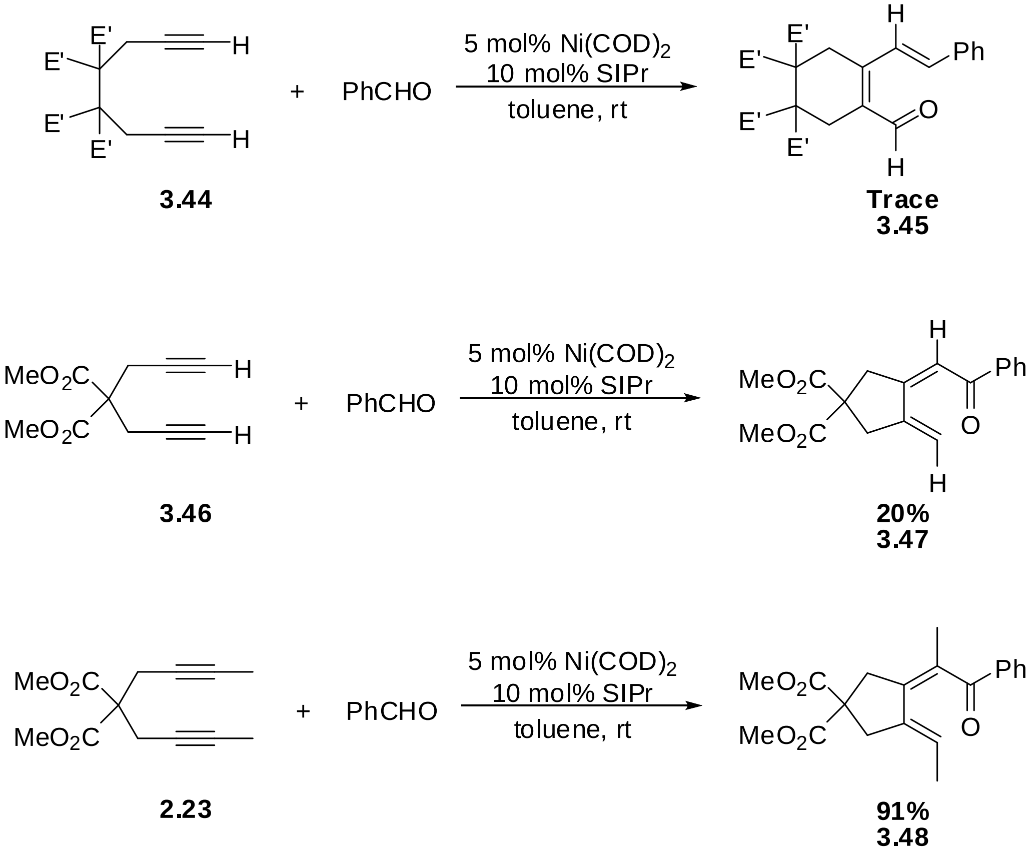
Table 3.4. Aldehyde scope of Ni/SIPr catalyzed cycloaddition.



entry	diyne	aldehyde	dienone product	yield (%)^{b}
1	**2.37** R_1 = Me	$R_2 = C_6H_5$	**3.37**	78
2	**2.37**	R_2 = 4-MeO-C_6H_4	**3.38**	91
3	**2.37**	R_2 = 4-CF_3-C_6H_4	**3.39**	65^{c}
4	**2.37**	R_2 = *i*-Pr	**3.40**	58^{d,e}
5	**2.37**	R_2 = *n*-Pr	**3.41**	72^{d,e}
6	**3.42** R_1 = Et	$R_2 = C_6H_5$	**3.43**	80

[a]Reaction conditions: 0.1M diyne, 0.125M aldehyde, 5 mol% Ni(COD)$_2$, 10 mol% SIPr, room temperature. [b] Isolated yields (average of two runs). [c]10 mol% Ni(COD)$_2$, 20 mol% SIPr. [d]10 mol% Ni(COD)$_2$, 10 mol% SIPr. [e]Product exists as an equilibrium mixture of dienone (major) and ether (minor).

Attention was next focused on the diyne substrate scope. Initially, the cyclization of several 1,6- and 1,7-diynes was attempted under the optimized reaction conditions. Diynes **2.62** and **2.63** (Figure 2.17), which had also proved problematic in the CO_2 chemistry, failed to undergo cyclization. Diyne **3.44** containing two terminal alkynes also failed to undergo the desired cyclization in high yield (Figure 3.8). Diynes **3.46** and **2.23** did undergo cyclization to produce dieneones **3.47** and **3.48** in 20% and 91% yield respectively (Figure 3.8). Surprisingly, the connectivity of these dienones was different than those obtained from diynes possessing a four carbon linkage (Figure 3.7, Table 3.4). Specifically, the Ph group of benzaldehyde remains connected to the carbonyl in dienones **3.47** and **3.48**. In contrast, this bond has been cleaved in the dienones **3.37-3.43**.



3.44

Trace
3.45

3.46

20%
3.47

2.23

91%
3.48

Figure 3.8. Ni/SIPr catalyzed cycloaddition of 1,6-diynes with benzadehyde.

The difference in the reactivity of diynes **2.23** and **3.46** (where n = 1) may be attributed to a slower rate of reductive elimination, relative to β-hydride elimination, from nickelacycle **3.49** to form a strained [5,6] ring system (Figure 3.9). However when n = 2, as in diynes **2.37** and **3.43**, the rate of reductive elimination to form the less strained [6,6] ring system **3.52** is more facile, ultimately producing the observed electrocyclic ring opened cycloadducts (**3.37-3.43**).

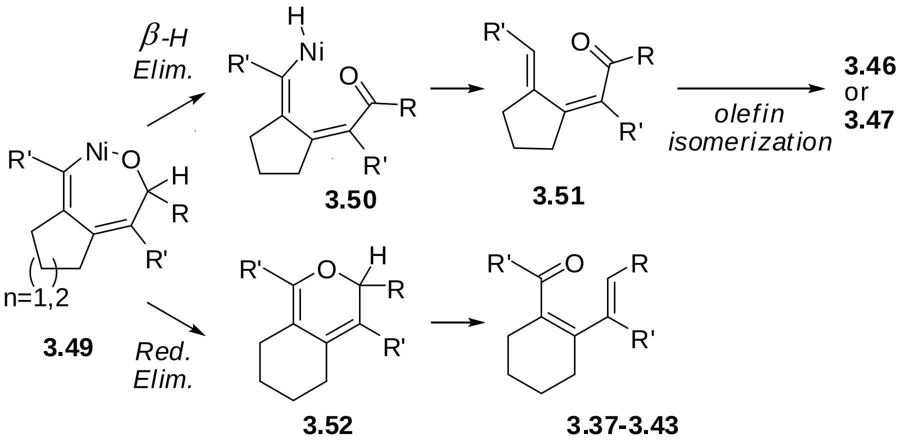


Figure 3.9. Mechanistic explanation for dichotomy of products.

It should be noted that the electrocyclic ring opened tautomers of pyrans **3.2-3.9** have the same connectivity as ketones **3.46** and **3.47**. Because of this similar connectivity, one would expect that both pyrans **3.2-3.9** and dienones arise from the same mechanistic sequence. However, it was proposed by Tsuda and Saegusa that pyrans **3.2-3.9** arise from the reductive elimination of **3.49** followed by a [1,5] sigmatropic shift.[7] Based on our isolation of dienones **3.37-3.43** and Itoh's isolation of similar dienones (which arise from a C-O reductive elimination/electrocyclic ring opening), we believe that mechanistic explanation offered by Tsuda and Saegusa is incorrect. Rather, we feel that all of the products reported by Tsuda and Saegusa arise from a β-hydride elimination of metallacycle **3.49** followed by a C-H reductive elimination. When the tether between the diynes is four atoms, the dienone exists in its tautomeric pyran form. When the tether between the alkynes is three atoms, the dienone form is favored which then undergoes base catalyzed isomerization to generate the observed product.

Support for the mechanistic explanation illustrated in Figure 3.9 comes from the cyclization of enyne **2.66** with benzaldehyde under the standard reaction conditions (Figure 3.10). The two observed products, enone **3.53** and ketone **3.54**, both have the same connectivity as dienones **3.46** and **3.47** and the tautomers of pyrans **3.2-3.9**. (i.e. the aryl group remains attached to the carbonyl carbon). These products can not arise from a [1,5] sigmatropic rearrangement because a [1,5] H shift is not possible from metalacycles **3.55** and **3.56** or their respective pyrans. The most plausible mechanism of formation of these products is via the previously described β-hydride elimination pathway.

While the cyclization of enyne **2.66** provided mechanistic insight, it also represents the first [2+2+2] cycloaddition with an enyne. Even more astounding was the formation of ketone **3.54** as the major product. This product signifies a reversal of the expected chemoselectivity as the olefin reacts preferentially with the aldehyde in the presence of the alkyne. While this reactivity was surprising, it presented an unexpected problem with controlling the chemoselectivity of the reaction. Because the regioselectivity of the [2+2+2] cycloaddition of diynes and CO_2 was highly dependent on steric interactions, the effect of steric interactions on the selectivity of the enyne/aldehyde cycloaddition was investigated.

Enynes **3.57-3.63** were reacted with benzaldehyde under the standard cycloadition conditions (Table 3.5). When the R group at the terminal position of the alkyne was a proton (entry 1), only ketone **3.58** was observed. Conversely, with an ethyl group or larger (entries 3-5), only the respective enones were observed. Thus, the aldehyde clearly reacted preferentially with the more sterically hindered unsaturated hydrocarbon.

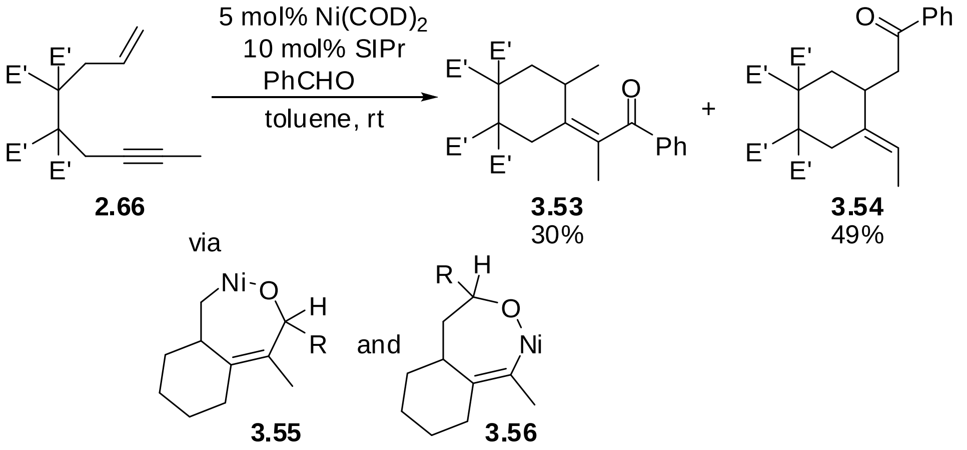
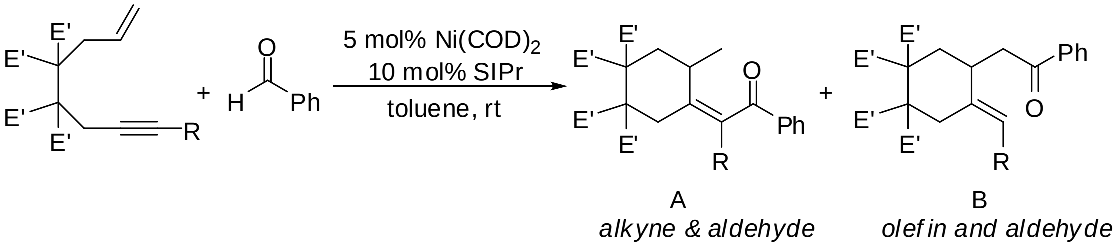

5 mol% Ni(COD)$_2$
10 mol% SIPr
PhCHO
toluene, rt
E'
2.66
3.53
30%
3.54
49%
Ph
O
via
Ni
H
R
and
3.55
3.56

Figure 3.10. Ni/SIPr catalyzed cycloaddition of enyne **2.66** and benzadehyde.

Table 3.5. Effects of alkyne size on chemoselectivity.


5 mol% Ni(COD)$_2$
10 mol% SIPr
toluene, rt
E'
R
H
O
Ph
A
alkyne & aldehyde
B
olefin and aldehyde

entry	enyne	ratio A:B[a]	product	yield (%)[b]
1	**3.57** R = H	<5:95	**3.58**	57
2	**2.66** R = Me	38:62	**3.53; 3.54**	79
3	**3.59** R = Et	>95:5	**3.60**	87
4	**3.61** *R* = *i*-Pr	>95:5	**3.62**	89
5	**3.63** R = *n*-Pr	>95:5	**3.64**	91

[a] Determined by ^{1}H NMR analysis of crude reaction mixture.
[b] Isolated yield, average of two runs.

Further investigation showed that the varying substitution on the backbone did not affect the observed trend. Enynes **3.65**, **3.67**, and **3.66**, having an ethyl group at the alkyne terminus, all provided only the corresponding enones as the only observed product in good yield (Figure 3.11). Likewise, when enyne **3.69** was reacted with various aldehydes, only the enone product was observed further supporting the idea that steric hindrance of the enyne govern the chemoselectivity (Table 3.6).

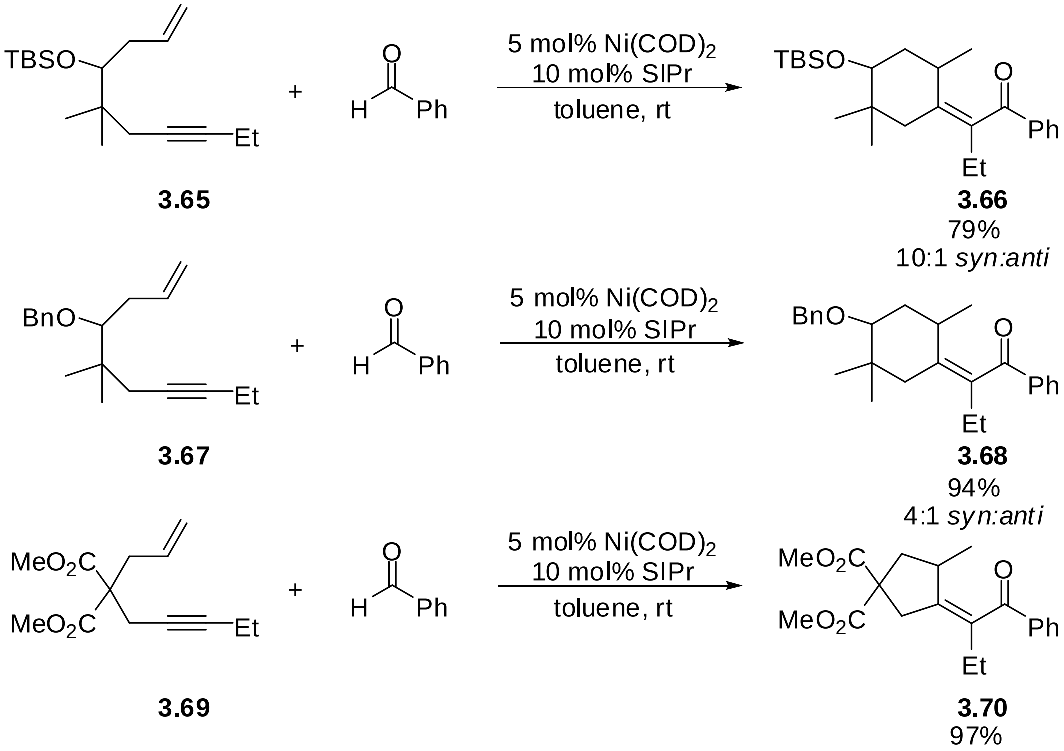
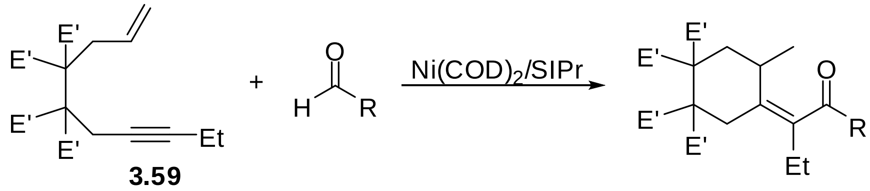

TBSO
Et
+
O
H
Ph
5 mol% Ni(COD)$_2$
10 mol% SIPr
toluene, rt
TBSO
O
Ph
Et
3.65
3.66
79%
10:1 *syn:anti*
BnO
Et
+
O
H
Ph
5 mol% Ni(COD)$_2$
10 mol% SIPr
toluene, rt
BnO
O
Ph
Et
3.67
3.68
94%
4:1 *syn:anti*
MeO$_2$C
MeO$_2$C
Et
+
O
H
Ph
5 mol% Ni(COD)$_2$
10 mol% SIPr
toluene, rt
MeO$_2$C
MeO$_2$C
O
Ph
Et
3.69
3.70
97%

Figure 3.11. Effects of backbone substitution of chemoselectivity.

Table 3.6. Effects of aldehyde on chemoselectivity.



entry	aldehyde	enone product	yield (%)^{b}
1	R = 2-Me-C_6H_4	**3.71**	91
2	R = 4-MeO-C_6H_4	**3.72**	91
3	R = 4-CF_3-C_6H_4	**3.73**	67^{c}
4	R = *i*-Pr	**3.74**	80
5	R = *n*-Pr	**3.75**	74

[a] Reaction conditions: 0.1M diyne, 0.125M aldehyde, 5 mol% Ni(COD)$_2$, 10 mol% SIPr, room temperature. [b] Isolated yields (average of two runs). [c] 7.5 mol% Ni(COD)$_2$, 15 mol% SIPr.

Probing the steric hindrance of the alkene on the chemoselectivity of the reaction showed a similar phenomenon. While enyne **3.76** possessing a trans substituted olefin failed to react, enyne **3.77** with a cis olefin geometry cyclized with benzaldehyde to yield ketone **3.78** and pyran **3.79** (Figure 3.12). Likewise, the cyclization of enyne **3.80** with benzaldehyde produced similar results with the formation of ketone **3.81** and pyran **3.82**.

The chemoselectivity of this reaction can be rationalized similarly to regioselectivity of the [2+2+2] cycloadditions of diynes and CO_2 via one of two mechanisms. In the first mechanism, the aldehyde can oxidatively couple with either the olefin (path A) or alkyne (path B), followed by insertion of the pendent group to afford the seven-membered nickelacycle (**3.83** or **3.84** respectively, Figure 3.13). If pathway A is followed and the R group on the alkyne is large, then insertion of the pendent alkyne group to form seven-membered nickelacycle **3.86** is slow because of steric interations with the large ligand.

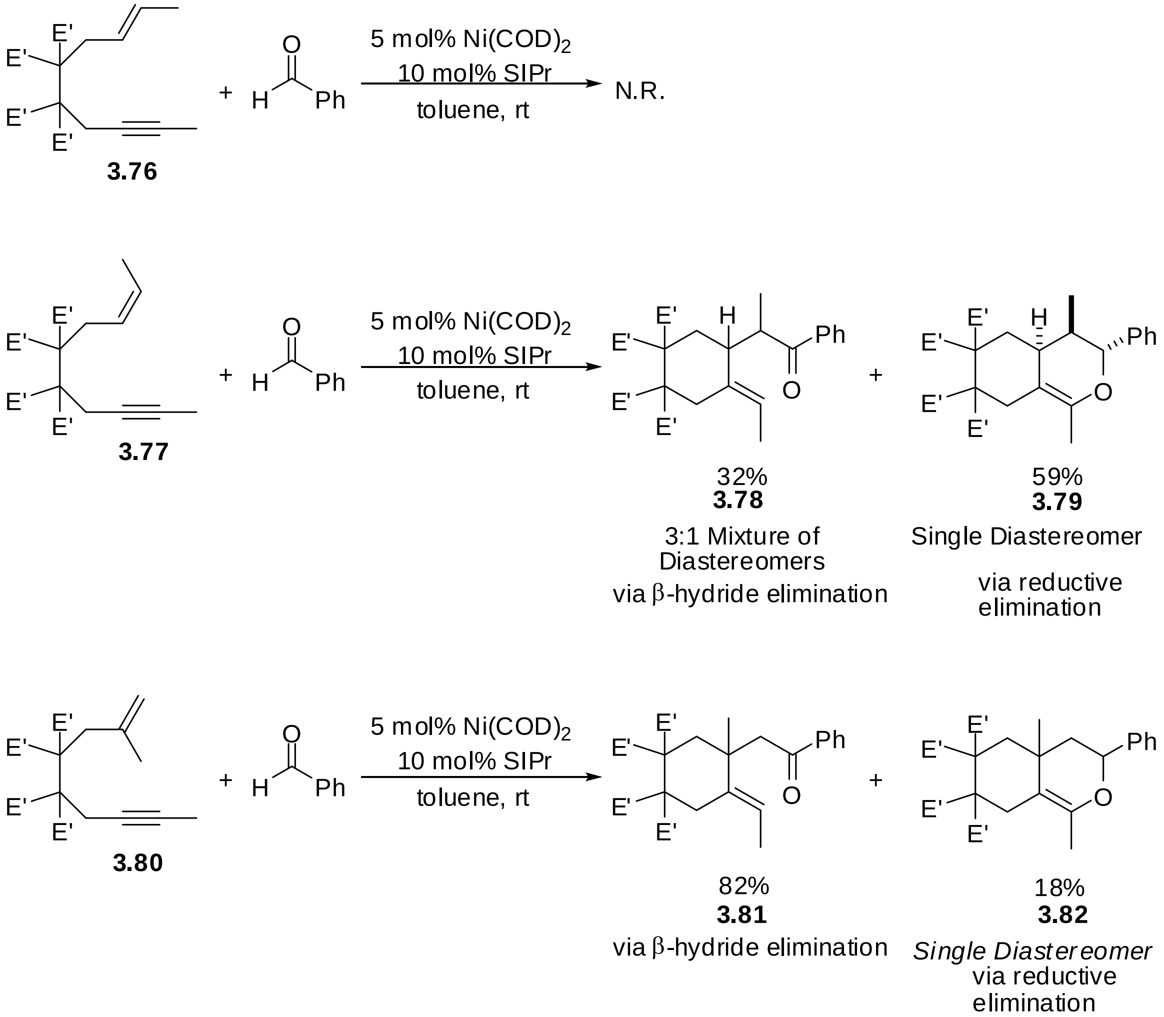

E'
E'
E'
E'
3.76
O
H
Ph
+
5 mol% Ni(COD)$_2$
10 mol% SIPr
toluene, rt
N.R.
3.77
E'
H
Ph
O
32%
3.78
3:1 Mixture of Diastereomers
via β-hydride elimination
59%
3.79
Single Diastereomer
via reductive elimination
3.80
82%
3.81
via β-hydride elimination
18%
3.82
Single Diastereomer
via reductive elimination

Figure 3.12. Effects of olefin steric hindrance on chemoselectivity.

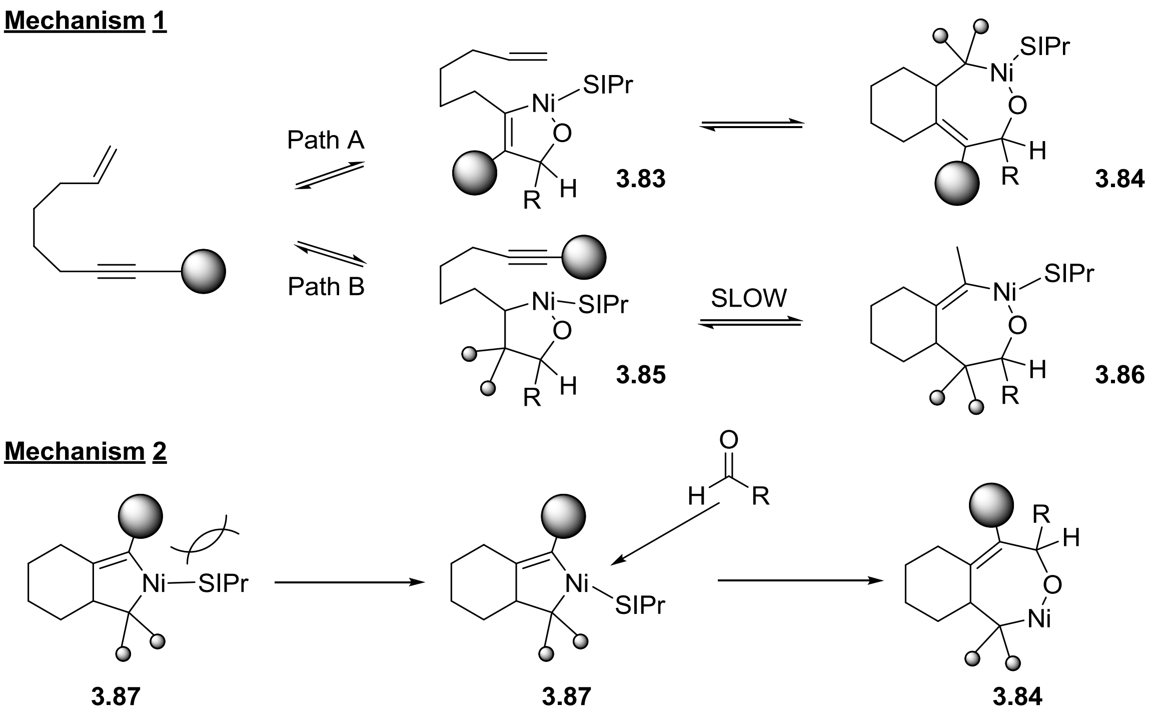


Figure 3.13. Explanation for observed chemoselectivity with bulky alkynes.

Instead of inserting, the five-membered oxanickelacycle reductively uncouples to regenerate the starting materials. The alkyne and aldehyde can then couple, generating five-membered oxanickelacycle **3.83**. The less sterically hindered olefin can then undergo facile insertion to generate seven-membered nickelacycle **3.84**. The observed product is then generated via an alkoxy β-hydride elimination/C-H reductive elimination sequence.

The same rationale can be applied to the observed chemoselectivity in the cyclization of enynes **3.77** and **3.80**. In these cases, the more sterically hindered olefin is preferentially reacts with the aldehyde to generate seven-membered metalacycle **3.91**(Figure 3.14). This metalacycle ultimately yields the observed pyran.

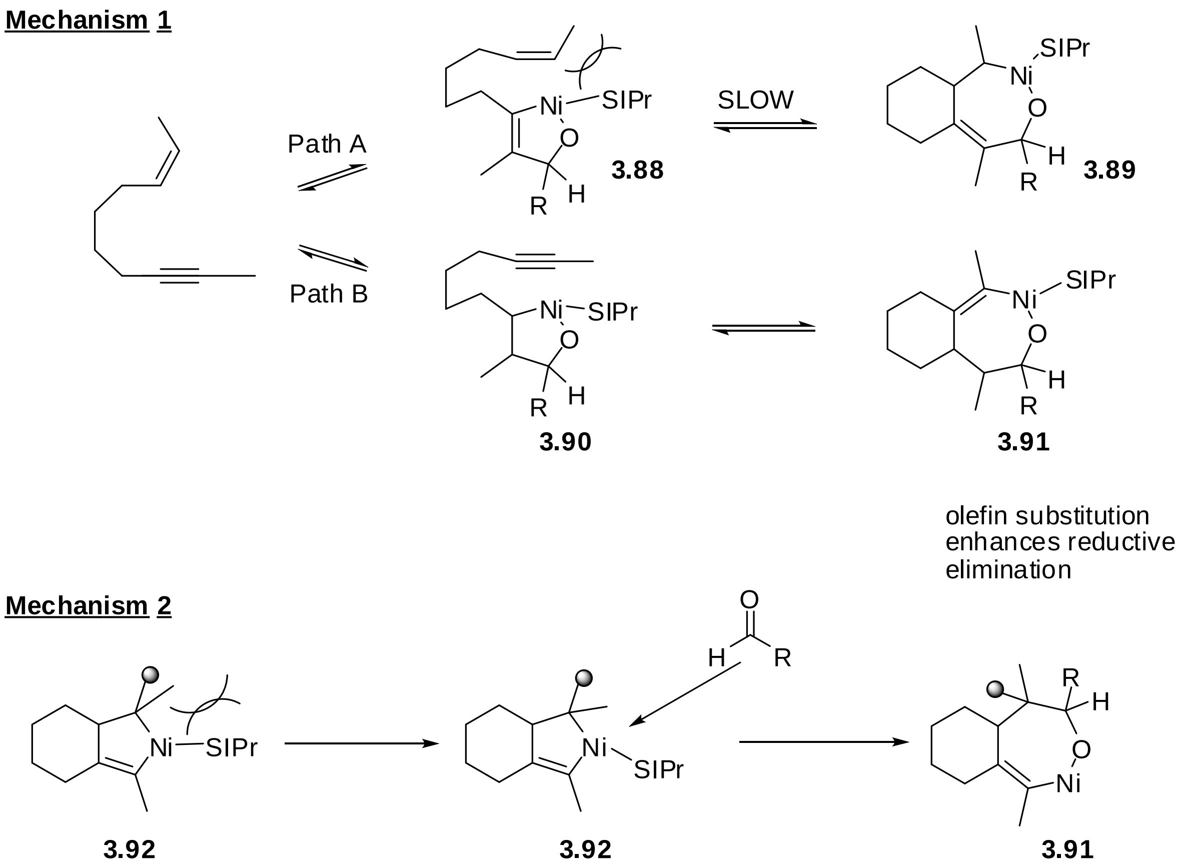

Mechanism 1
Path A
Path B
Ni
SIPr
O
R
H
3.88
SLOW
3.89
3.90
3.91
olefin substitution enhances reductive elimination
Mechanism 2
H
R
3.92
3.92
3.91

Figure 3.14. Explanation for observed chemoselectivity for bulky olefins.

Nickel-Carbene Catalyzed Cycloadditions of

Ketones with Diynes and Enynes

Although our approach towards the cyclization of diynes and aldehydes was successful, the ability to generate pyrans still remained difficult. The main problem was competitive β-hydride elimination of the aldehydic proton. Thus, in an attempt to circumvent this problem and further expand the scope of the reaction, the cyclization was attempted with ketones in lieu of aldehydes. At the onset, it was unclear whether or not ketones would be suitable substrates for the cycloaddition. As seen with the CO_2 and aldehyde systems, the Ni/carbene catalyzed cycloadditions are extremely sensitive to steric hindrance. Thus, ketones may be too sterically hindered to undergo cyclization. It was also a concern that simple alkyl ketones may not have sufficient electrophilicity as evident from Itoh's need to use tricarbonyls in the Ru-catalyzed system.

We found that cyclohexanone smoothly reacted with diyne **2.37** under slightly modified conditions to yield pyran **3.93** (Figure 3.15). Unfortunately, pyran **3.93** existed in thermal equilibrium with its dienone tautomer **3.94** (10:1).

In order to prevent this equilibrium and obtain the pyran as the sole product, it was surmised that the cycloaddition could be carried out using ketones and enynes as coupling partners. The use of ketones would ensure no β-hydride eliminated products were formed, and the use of enynes would prevent any unwanted tautomerization.

Gratifyingly, the slow addition of enyne **2.66** at room temperature to a stirring solution of Ni(COD)$_2$ (10 mol%), IPr (15 mol%) and acetone (1.25 equiv) in toluene afforded dihydropyran **3.95** as a *single regioisomer* in 70-83% yield (Figure 3.16). To our knowledge, this is the only example in which both an unactivated ketone and enyne participate in a cycloaddition reaction. Furthermore, dihydropyran formation likely results from the difficult to achieve C-O bond forming reductive elimination.

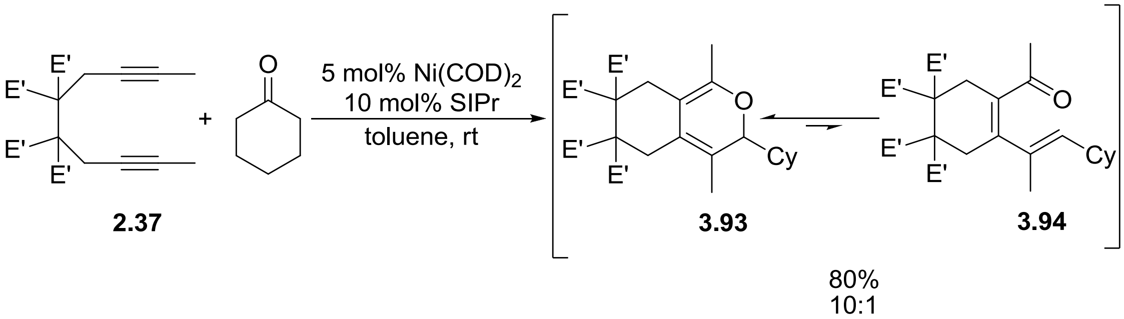
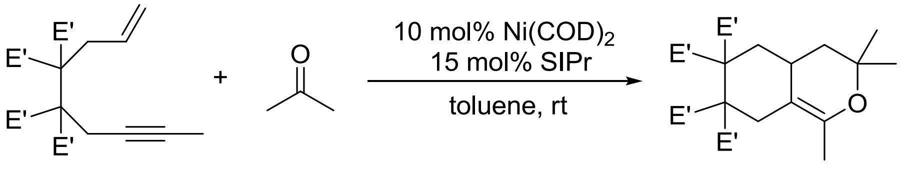


Figure 3.15. Ni/SIPr catalyzed cycloaddition of diyne **2.37** and cyclohexanone.



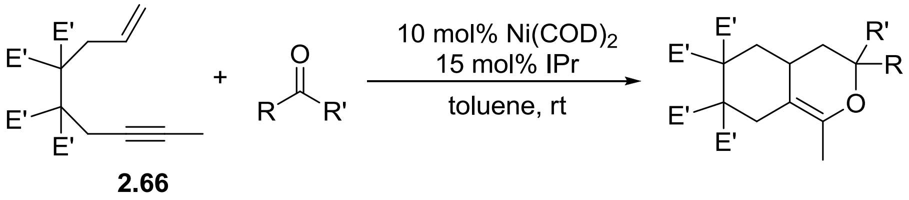
2.66 **3.95**

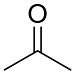
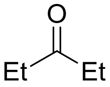
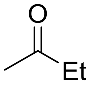
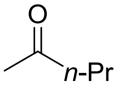
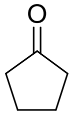
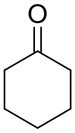
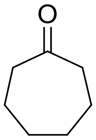
Figure 3.16. Ni/SIPr catalyzed cycloaddition of enyne **2.66** and acetone.

Optimization of the reaction conditions showed that the addition of 3Å molecular sieves (150 mg/mmol) further improved yields. Using these conditions, a variety of unactivated ketones cyclized to afford pyrans in excellent yields (>91%). As illustrated in Table 3.7, steric hindrance about the carbonyl played a large role in determining the reaction conditions. Both the ketone concentration and enyne addition time needed to be adjusted to accordingly to minimize oligomeric side products. For instance, 1.25 equiv of acetone smoothly reacted with enyne **2.66** by adding the enyne over 0.5 h (entry 1). However, when 3-pentanone was used (entry 2), 4.0 equivalents of ketone and an enyne addition time of 4 h was needed to obtain a comparable yield. Unsymmetrical methyl ketones also produced the cycloadducts in excellent yields (entries 3, 4). Cyclic ketones possessing a 5, 6 and 7 carbon tether were also suitable substrates for the reaction requiring 1.25-4 equivalents of ketone and enyne addition times of 0.5- 2 h (entries 5-7).

As shown in Table 3.8, enynes with variable substitution patterns and functionality were also tolerated. Enyne **3.80** (entry 1), possessing a methyl group at the internal position of the olefin, smoothly cyclized using only 2 equivalents of acetone and an enyne addition time of 2 h. However, placing substituents at the terminal position of the olefin proved more problematic.

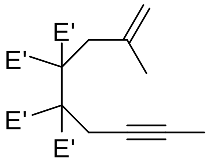
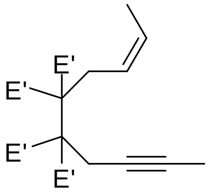
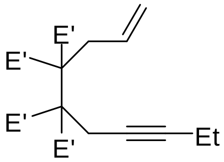
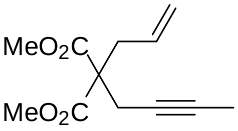
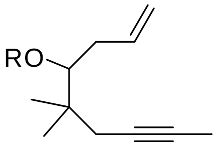
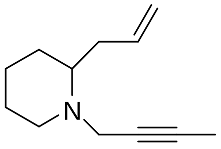
Table 3.7. Ketone substrate scope of cycloaddition.


E'
E'
E'
E'
2.66
+
O
R
R'
10 mol% Ni(COD)2
15 mol% IPr
toluene, rt
E'
E'
E'
E'
R'
R
O

entry	ketone	ketone equiv	enyne addition time (h)	product	% yield^{b}
1		1.25	0.5	**3.95**	92
2		4^{c}	4	**3.96**	91
3		2^{c}	1	**3.97**	97^{d}
4		2^{c}	2	**3.98**	98^{d}
5		2^{c}	2	**3.99**	96
6		1.25	0.5	**3.100**	95
7		4^{c}	2	**3.101**	95

[a] Reaction conditions: 10 mol% Ni(COD)$_2$, 15 mol% IPr, 150 mg/mmol 3Å molecular sieves, 0.1 M toluene, rt. [b] Isolated yield, average of two runs. [c] Fewer equivalents of ketone could be used to obtain more modest yields. [d] Isolated as a 1:1 mixture of diastereomers.

Table 3.8. Enyne substrate scope of cycloaddition.

entry	enyne	acetone equiv	enyne addition time (h)	product	% yield[b]
1	 **3.80**	2[c]	2	**3.102**	87
2	 **3.77**	10[c]	2	**3.103**	80[d]
3	 **3.59**	2[c]	4	**3.104**	90
4	 **2.65**	6[c]	4	**3.105**	75
5	 **3.106** R = Bn **3.108** R = TBS	2[c]	1	**3.107** **3.109**	85[e] 80[e]
6	 **3.110**	10[c]	2	**3.111**	80[d]

[a] Reaction conditions: 10 mol% $Ni(COD)_2$, 15 mol% IPr, 150 mg/mmol 3Å molecular sieves, 0.1M toluene, rt. [b] Isolated yields, average of two runs. [c] Fewer equivalents could be used to obtain more modest yields. [d] Isolated as single diastereomer. [e] 3:1 *syn:anti*.

While an internal olefin with *cis* geometry (entry 3) required 10 equivalents of acetone to obtain a high yield of the dihydropyran (entry 2), internal olefins with a *trans* geometry failed to produce any of the desired product. On the other hand, increasing substituent length on the alkyne had little effect on the reaction (entry 3). A fused [5,6] ring system was obtained from the cyclization of enyne **3.105** (entry 4), although a slightly higher amount of acetone was required. Enynes containing functionalities such as ethers (entry 5) and amines (entry 6) also cyclized proficiently.

Two possible mechanisms explain the chemoselectivity of this reaction. The first mechanism involves initial oxidative coupling of the olefin and alkyne to form a metallocyclopentene **3.114** (Figure 3.17). Nucleophilic attack of the more reactive alkyl group on the ketone then affords the seven-membered nickelacycle **3.115** which subsequently undergoes reductive elimination to produce the observed dihydropyran.

An alternative mechanism begins with the oxidative coupling of ketone with either the olefin (path A) or alkyne (path B), followed by insertion of the pendent group to afford the seven-membered nickelacycle (**3.116** or **3.119,** respectively, Figure 3.17). In path B, reductive elimination to form the dihydropyran would require a demanding sp^3 C-O reductive elimination. Conversely, path A allows for the more facile sp^2 C-O reductive elimination to produce the observed dihydropyran.

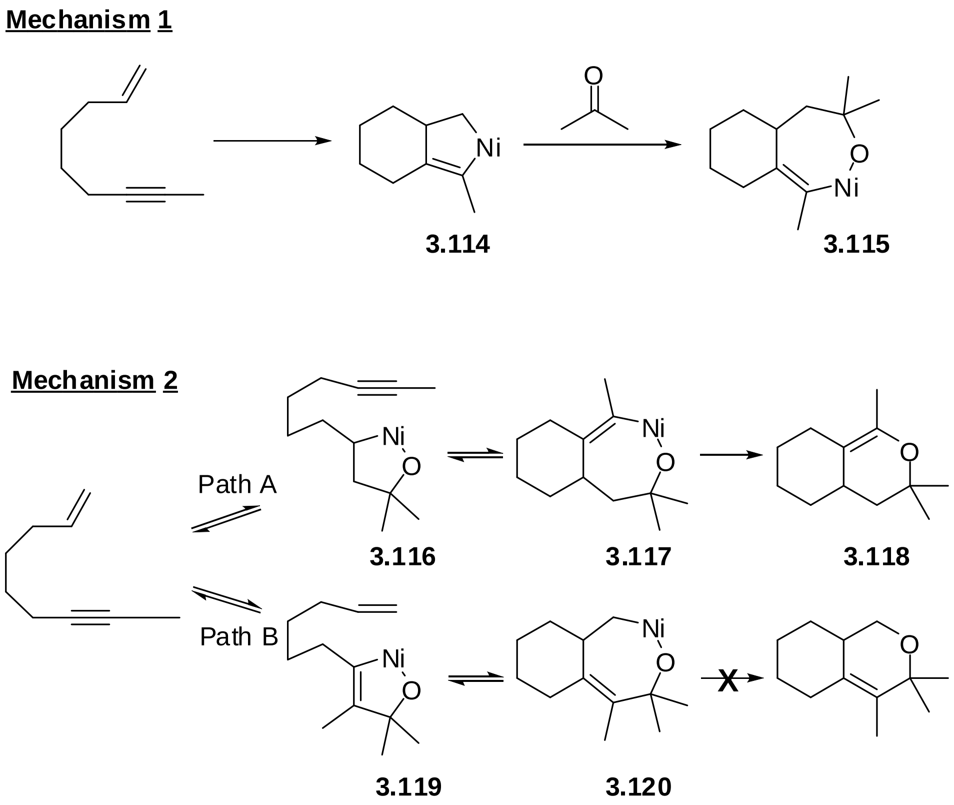

Mechanism 1
Ni
O
O
Ni
3.114
3.115
Mechanism 2
Path A
Path B
Ni
O
Ni
O
O
3.116
3.117
3.118
Ni
O
Ni
O
X
O
3.119
3.120

Figure 3.17. Explanation of chemoselectivity for cycloaddition of ketones and enynes.

Conclusion

It was found that diynes can undergo a [2+2+2] cycloaddition with aldehydes in the presence of a Ni/carbene catalyst. While dienones were obtained for the cyclization of 1,6- and 1,7-diynes, their connectivity was different. It is thought that in the cyclization of 1,6-diynes, the dienone arises from a β-hydride elimination/C-H reductive elimination. In the case of 1,7-diynes, the observed dienone arises from a C-O reductive elimination/electrocyclic ring opening sequence.

This methodology was expanded to include enynes as substrates to generate ketones, enones, or pyrans. Evidence suggests that the chemoselectivity of the reaction is governed by steric hindrance about the enyne; with the aldehyde reacting preferentially with the more sterically hindered unsaturated hydrocarbon.

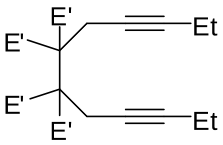
Finally, it was found that pyrans can be obtained chemoselectively in excellent yields from the cyclization of enynes and ketones. This represents the first successful attempt at using enynes and ketones as coupling partners in a [2+2+2] cycloaddition reaction.

Experimental Section

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove-box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem and used without further purification. SIPr, IPr, IMes and I*t*Bu ligands were prepared as previously reported.[12,13] Sodium hydride was thoroughly washed with pentane and dried in vacuo prior to use. All other reagents were purchased and used without further purification unless otherwise noted.

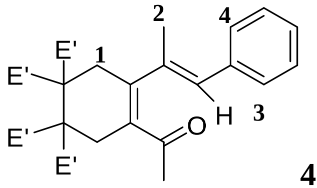
^1H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 75 MHz, respectively unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^1H and to the center line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, tq q, qt, quint, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. HRMS were performed at the mass spectrometry facility at The University of Utah. Gas Chormatographies were performed on an Alient 6890 gas chomatograph with a 30 m HP-5 column using the following conditions: intial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 min; detector temperature: 250 ºC.

Synthetic Procedures and Analyses

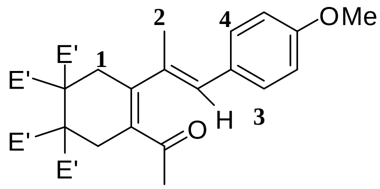


2-(1,1-bis-ethoxycarbonyl-hex-3-ynyl)-2-ethoxycarbonyl-hept-4-ynoic acid ethyl ester (3.42). Prepared analogously to **2.37** with 351.6 mg NaH (14.7 mmol), 2.1197 g tetraethyl 1,1,2,2-ethanetetracarboxylate (6.7 mmol), and 2.1538 g 1-bromo-2-pentyne (6.7 mmol). Purified by column chromatography eluting with 15% EtOAc/hexanes to yield **3.42** (2.4211 g, 81%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.30-4.16 (m, 8H), 3.10 (t, *J* = 2.2 Hz, 4H), 2.12 (qt, *J* = 7.5, 2.2Hz, 4H), 1.29 (t, *J* = 7.1 Hz, 12H), 1.08 (t, *J* = 7.5 Hz, 6H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 168.8, 84.0, 75.1, 62.0, 61.8, 22.8, 14.0, 13.9, 12.5. IR (neat): 2981, 1734, 1448, 1368, 1206, 1097, 1039 cm^{-1}. HRMS(EI): calcd for $C_{24}H_{35}O_8$ (MH$^+$) 451.2332, obsd 451.2328.

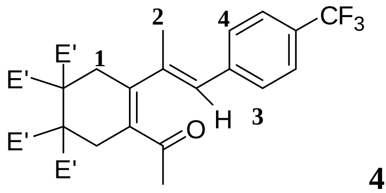
General [2+2+2] cycloaddition procedure 3.1. In a glove box, the diyne and aldehyde were added to an oven dried scintillation vial equipped with a magnetic stir bar and dissolved in toluene. To the stirring solution, a solution of Ni(COD)$_2$ and SIPr (previously equilibrated for at least 6 h) was added. The reaction mixture was stirred at room temperature for 2 h (or until complete consumption of starting material was observed as judged by GC or TLC) over which time the color changed from orange to brown. The mixture was concentrated in vacuo and purified by silica gel column chromatography.



4-Acetyl-5-(1-methyl-2-phenyl-vinyl)-cyclohex-4-ene-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.37). General procedure **3.1** was used with 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester **2.37** (165.6 mg, 0.39 mmol), benzaldehyde (52.0 mg, 0.49 mmol), Ni(COD)$_2$ (5.4 mg, 0.020 mmol), SIPr (15.3 mg, 0.039 mmol), and 3.9 mL of toluene. The reaction mixture was purified by flash chromatography (12% EtOAc/hexanes then 15% EtOAc/hexanes) to yield dienone **3.37** (166.3 mg, 80%) as a sticky pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 7.36-7.29 (m, 2H), 7.25-7.19 (m, 3H), 6.24 (br s, 1H), 4.30-4.14 (br m, 8H), 3.12 (s, 2H), 3.07 (s, 2H), 2.20 (s, 3H), 2.10 (br s, 3H), 1.27 (t, *J* = 7.2 Hz, 12H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 202.7, 169.72, 169.65, 145.9, 137.5, 137.0, 132.5, 130.4, 128.8, 128.4, 127.2, 62.0, 61.9, 57.3, 56.6, 35.2, 32.1, 30.3, 16.9, 14.0. IR (neat): 2983, 1723, 1672, 1264, 1200, 1098, 1056 cm^{-1}. HRMS(CI): calcd for $C_{29}H_{36}O_9$ (M$^+$) 528.2359, obsd 528.2369. COSY summary; the following pertinent cross peaks were observed: H(3) and H(2) and H(4). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1) and H(4).

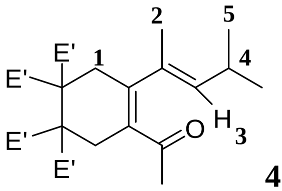


Prepartation of 4-acetyl-5-[2-(4-methoxy-phenyl)-1-methyl-vinyl]-cyclohex-4-ene-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.38). General procedure **3.1** was used with 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester **2.37** (135.1 mg, 0.32 mmol), anisaldehyde (54.5 mg, 0.40 mmol) Ni(COD)$_2$ (4.4 mg, 0.016 mmol), SIPr (12.5 mg, 0.032 mmol), and 3.2 mL of toluene. The reaction mixture was purified by flash chromatography (12% EtOAc/hexanes then 15% EtOAc/hexanes) to yield dienone **3.38** (163.8 mg, 92%) as a sticky pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 7.18 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.18 (brs, 1H), 4.31-4.15 (brm, 8H), 3.79 (s, 3H), 3.11 (s, 2H), 3.06 (s, 2H), 2.17 (s, 3H), 2.06 (brs, 3H), 1.26 (t, *J* = 6.8 Hz, 12H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 203.0, 169.82, 169.75, 158.7, 146.7, 135.7, 132.5, 130.3, 130.2, 129.7, 113.9, 62.1, 62.0, 57.5, 56.7, 55.4, 35.2, 32.1, 30.4, 16.9, 14.0. IR (neat): 2983, 1738, 1670, 1607, 1260, 1036 cm^{-1}. HRMS(EI): calcd for $C_{30}H_{38}O_{10}$ (M$^+$) 558.2465, obsd 558.2471. COSY summary; the following pertinent cross peaks were observed: H(3) and H(2) and H(4). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1) and H(4).

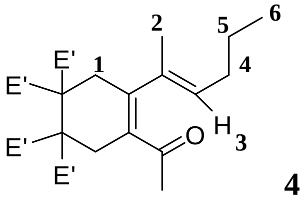


4-Acetyl-5-[1-methyl-2-(4-trifluoromethyl-phenyl)-vinyl]-cyclohex-4-ene-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.39). General procedure **3.1** was used with 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester

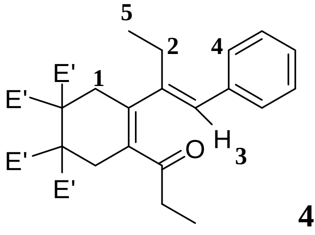
2.37 (134.3 mg, 0.32 mmol), α,α,α-trifluoro-*p*-tolualdehyde (69.2 mg, 0.40 mmol), Ni(COD)$_2$ (8.8 mg, 0.032 mmol), SIPr (24.8 mg, 0.064 mmol), and 3.2 mL of toluene. The reaction mixture was purified by flash chromatography (12% EtOAc/hexanes then 15% EtOAc/hexanes) to yield dienone **3.39** (127.1 mg, 67%) as a sticky yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 7.60 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.27 (brs, 1H), 4.33-4.17 (brm, 8H), 3.12 (brs, 2H), 3.08 (brs, 2H), 2.21 (s, 3H), 2.07 (d, *J* = 1.2 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 12H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 204.4, 169.8, 169.7, 145.2, 140.7, 140.2, 132.7, 129.1 (q, *J* = 32.3 Hz), 128.6, 125.46, 125.42, 62.2, 62.1, 57.4, 56.6, 35.4, 32.2, 30.3, 17.1, 14.1. IR (neat): 2985, 1734, 1617, 1416, 1230, 1124, 867 cm^{-1}. HRMS(EI): calcd for $C_{30}H_{35}F_3O_9$ (M$^+$) 596.2233, obsd 596.2241. COSY summary; the following pertinent cross peaks were observed: H(3) and H(2) and H(4). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1) and H(4).



4-Acetyl-5-(1,3-dimethyl-but-1-enyl)-cyclohex-4-ene-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.40). General procedure **3.1**was used with 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester **2.37** (140.0 mg, 0.33 mmol), isobutyraldehyde (29.9 mg, 0.41 mmol) Ni(COD)$_2$ (9.1 mg, 0.033 mmol), SIPr (12.9 mg, 0.033 mmol), and 3.3 mL of toluene. The reaction mixture was purified by flash chromatography (12% EtOAc/hexanes then 15% EtOAc/hexanes) collecting the fractions containing the spot with Rf 0.28 in 30% EtOAc/hexanes (purple with anisaldehyde stain). The remaining mixed fractions containing the dienolic ether and impurities were combined and allowed to re-equilibrate for 4 h. The re-equilibrated mixture was then re-chromatographed (12% EtOAc/hexanes then 15% EtOAc/hexanes). This process was repeated twice to yield dienone **3.40** and a small amount of the dienolic ether (98.5 mg, 60%) as a sticky yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.04 (dq, *J* = 9.1, 1.1 Hz, 1H), 4.32-4.12 (brm, 8H), 3.00 (s, 4H), 2.52 (septd, *J* = 6.6, 2.4 Hz, 1H), 2.16 (s, 3H), 1.82 (d, *J* = 1.1 Hz, 3H), 1.27 (appt td, *J* = 7.1, 1.7 Hz, 12H), 0.94 (d, *J* = 6.7 Hz, 6H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 203.4, 169.9, 169.8, 145.8, 138.8, 132.9, 131.8, 62.1, 61.9, 57.4, 56.7, 35.3, 32.0, 30.5, 27.5, 22.1, 15.1, 14.0. IR (neat): 2963, 1742, 1676, 1265, 1096, 1052 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{38}O_9$ (M^+) 494.2516, obsd 494.2509. COSY summary; the following pertinent cross peaks were observed: H(3) and H(2) and H(4); H(4) and H(3) and H(5). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1) and H(4); irradiation of H(4) resulted in the enhancement of H(2).

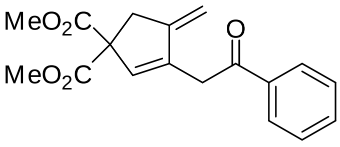


4-Acetyl-5-(1-methyl-pent-1-enyl)-cyclohex-4-ene-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.41). General procedure **3.1**was used with 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester **2.37** (96.7mg, 0.22 mmol), butyraldehyde (82.6 mg, 1.15 mmol), Ni(COD)$_2$ (6.3 mg, 0.023 mmol), SIPr (9.0 mg, 0.023 mmol), and 2.2 mL of toluene. The reaction mixture was purified by flash chromatography (12% EtOAc/hexanes then 15% EtOAc/hexanes) collecting the fractions containing the spot with Rf = 0.28 in 30% EtOAc/hexanes (purple with anisaldehyde stain). The remaining mixed fractions containing the dienolic ether and impurities were combined and allowed to re-equilibrate for 4 h. The re-equilibrated mixture was then re-chromatographed (12% EtOAc/hexanes then 15% EtOAc/hexanes). This process was repeated twice to yield dienone **3.41** and a small amount of the dienolic ether (88.9 mg, 73%) as a sticky pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.22 (tq, *J* = 7.2, 1.4 Hz, 1H), 4.29-4.09 (brm, 8H), 2.98 (s, 4H), 2.12 (s, 3H), 1.97 (q, *J* = 7.3 Hz, 2H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.33 (quint, *J* = 7.4 Hz, 2H) 1.24 (appt td, *J* = 7.1, 1.9 Hz, 12H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 203.5, 169.9, 146.0, 135.2, 132.1, 131.9, 62.0, 61.9, 57.5, 56.7, 35.4, 32.0, 30.6, 30.4, 22.1, 15.2, 14.2, 14.1, 14.0. IR (neat): 2982, 1738, 1674, 1445, 1367, 1265, 1051 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{38}O_9$ (M^+) 494.2516, obsd 494.2495. COSY summary; the following pertinent cross peaks were observed: H(3) and H(2) and H(4); H(4) and H(3) and H(5). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1) and H(4); irradiation of H(4) resulted in the enhancement of H(2).

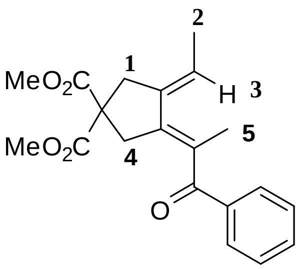


4-(1-Benzylidene-propyl)-5-propionyl-cyclohex-4-ene-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.43). General procedure **3.1** was used with 2-(1,1-bis-ethoxycarbonyl-hex-3-ynyl)-2-ethoxycarbonyl-hept-4-ynoic acid ethyl ester **3.42** (153.3 mg, 0.34 mmol), benzaldehyde (45.1 mg, 43 mmol) Ni(COD)$_2$ (13.3 mg, 0.017 mmol), SIPr (19.8 mg, 0.034 mmol), and 3.4 mL of toluene. The reaction mixture was purified by flash chromatography (12% EtOAc/hexanes then 15% EtOAc/hexanes) to yield dienone **3.43** (158.4 mg, 84%) as a sticky pale yellow oil. ^{1}H NMR (300 MHz,

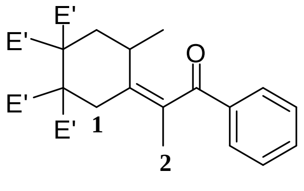
$CDCl_3$): δ (ppm) 7.37-7.15 (m, 5H), 6.26 (brs, 1H), 4.31-4.18 (brm, 8H), 3.09 (brs, 4H), 2.59 (q, *J* = 7.3 Hz, 2H), 2.48 (q, 7.6Hz, 2H), 1.29 (t, *J* = 7.2, 12H), 1.12 (t, *J* = 7.6 Hz, 3H), 1.00 (t, *J* = 7.3 Hz, 3H). $^{13}C\ \{^1H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 207.8, 169.7, 143.4, 140.6, 137.0, 134.2, 130.0, 128.7, 128.3, 127.1, 62.0, 61.9, 57.3, 56.6, 36.2, 34.9, 33.1, 23.0, 14.0, 13.9, 12.7, 8.7. IR (neat): 2981, 2939, 1737, 1681, 1136, 1040 cm^{-1}. HRMS(EI): calcd for $C_{31}H_{40}O_9$ (M^+) 556.2672, obsd 556.2681 COSY summary; the following pertinent cross peaks were observed: H(3) and H(2) and H(4); H(2) with H(5). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1) and H(4).



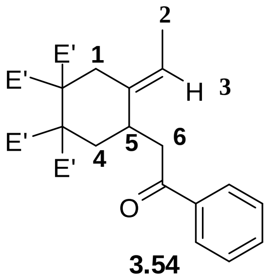
4-Methylene-3-(2-oxo-2-phenyl-ethyl)-cyclopent-2-ene-1,1-dicarboxylic acid dimethyl ester (3.47). General procedure **3.1** was used with 2,2-di-prop-2-ynyl-malonic acid dimethyl ester **3.46** (118.4 mg, 0.57 mmol), benzaldehyde (63.4 mg, 0.60 mmol), $Ni(COD)_2$ (7.8 mg, 0.028 mmol), SIPr (21.8 mg, 0.056 mmol), and 5.7 mL of toluene. The reaction mixture was purified by flash chromatography (5% EtOAc/hexanes) to yield ketone **3.47** (36.1 mg, 20%) as an oily colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.95 (d, *J* = 8.3, 2H), 7.57 (m, 1H), 7.46 (m, 2H) 6.07 (s, 1H), 4.99 (td, $J_1 = J_2$ = 1.9 Hz, 1H), 4.95 (t, J = 2.3 Hz, 1H), 3.85 (d, *J* = 1.5, 2H), 3.70 (s, 6H), 3.23 (t, *J* = 1.9 Hz, 2H). $^{13}C\ \{^1H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 196.6, 170.8, 149.8, 141.8, 136.6, 134.2, 133.5, 128.8, 128.6, 104.6, 63.8, 53.1, 38.0, 37.4. IR (neat): 3065, 2955, 2846, 1733, 1687, 1434, 1256 cm^{-1}. HRMS(CI): calcd for $C_{18}H_{18}O_5$ (M^+) 314.1154, obsd 315.1217.



3-Ethylidene-4-(1-methyl-2-oxo-2-phenyl-ethylidene)-cyclopentane-1,1-dicarboxylic acid dimethyl ester (3.48). General procedure **3.1** was used with 2,2-di-but-2-ynyl-malonic acid dimethyl ester **2.23** (131.5 mg, 0.56 mmol), bezaldehyde (**2a**, 73.8 mg, 0.70 mmol), Ni(COD)$_2$ (7.7 mg, 0.028 mmol), SIPr (21.8 mg, 0.056 mmol), and 5.6 mL of toluene. The reaction mixture was purified by flash chromatography (10% EtOAc/hexanes then 12% EtOAc/hexanes) to yield dienone **3.48** as the major isomer (111.6 mg, 92%). ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.82 (m, 2H), 7.58-7.43 (m, 3H), 6.01 (q, 6.9 Hz, 1H) 3.65 (s, 6H), 3.04 (brs, 2H), 2.88 (brs, 2H), 2.10 (brs, 3H), 1.84 (d, 7.0 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 200.4, 171.8, 138.6, 137.9, 136.7, 133.2, 129.6, 128.9, 126.1, 57.4, 53.0, 41.1, 37.9, 18.6, 16.0. IR (neat): 2955, 2856, 1737, 1662, 1443, 1269, 1067, 972 cm^{-1}. HRMS(EI): calcd for $C_{20}H_{22}O_5$ (M^+) 342.1467, obsd 342.1468. COSY summary; the following pertinent cross peaks were observed: H(3) and H(1) and H(2); H(4) with H(5). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) resulted in the enhancement of H(2); irradiation of H(2) resulted in the enhancement of H(1); irradiation of H(3) results in the enhancement of H(5); irradiation of H(5) results in the enhancement of H(3).



3.53

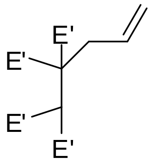


3.54

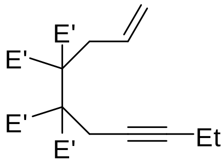
Preparation of 4-Methyl-5-(1-methyl-2-oxo-2-phenyl-ethylidene)-cyclohexane-1,1,2,2-tetracarboxylic acidtetraethyl ester (3.53) and 4-Ethylidene-5-(2-oxo-2-phenyl-ethyl)-cyclohexane-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.54). General procedure **3.1** was used with 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester **2.66** (130.1 mg, 0.32 mmol), benzaldehyde (42.0 mg, 0.40 mmol), Ni(COD)$_2$ (4.4 mg, 0.016 mmol), SIPr (12.5 mg, 0.032 mmol), and 3.2 mL of toluene. The reaction mixture was purified by flash chromatography (12% EtOAc/hexanes then 15% EtOAc/hexanes) to yield enone **3.53** (46.3 mg, 28%) and ketone **3.54** (82.7 mg, 51%) sticky, pale yellow oils.

4-Methyl-5-(1-methyl-2-oxo-2-phenyl-ethylidene)-cyclohexane-1,1,2,2-tetra carboxy-lic acid tetraethyl ester (3.53). ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 8.11 (d, *J* = 7.7 Hz, 2H), 7.61-7.45 (m, 3H), 4.33-4.05 (m, 8H) 3.13 (d, *J* = 15.7, 1H), 2.84 (dd, *J* = 15.7, 0.9 Hz, 1H), 2.75 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.69 (brt, *J* = 6.1 Hz, 1H), 2.27 (dd, *J* = 13.7, 2.6 Hz, 1H), 1.83 (brs, 3H), 1.35-1.23 (m, 12H), 0.96 (d, *J* = 7.3 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 201.3, 170.8, 170.5, 170.4, 168.9, 136.7, 136.3, 133.4, 130.9, 129.8, 128.9, 62.1, 61.8, 61.7, 61.5, 58.7, 58.4, 36.0, 32.8, 29.1, 20.5, 16.1, 14.03, 13.99, 13.97, 13.92. IR (neat): 2982, 1735, 1666, 1596, 1450, 1266, 1058 cm^{-1}. HRMS(EI): calcd for $C_{28}H_{36}O_9$ (M$^+$) 516.2359, obsd 516.2341. COSY summary; the following pertinent cross peaks were observed: H(1) and H(2). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1); irradiation of H(1) resulted in the enhancement of H(2).

4-Ethylidene-5-(2-oxo-2-phenyl-ethyl)-cyclohexane-1,1,2,2-tetracarboxylic acid tetraethyl ester (3.54). ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 7.97 (d, *J* = 7.3 Hz, 2H), 7.62-7.42 (m, 3H), 5.20 (q, *J* = 6.6 Hz, 1H), 4.32-4.03 (m, 8H) 3.35 (dd, *J* = 16.4, 6.2 Hz, 1H), 3.27 (d, *J* = 14.7 Hz, 1H), 3.13 (brm, 1H), 2.84 (dd, *J* = 16.3, 7.1 Hz, 1H), 2.80 (d, *J* = 15.4 Hz, 1H), 2.40 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.20 (dd, $J_1 = J_2$ = 13.0 Hz, 1H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.30-1.18 (m, 12H). ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$): δ (ppm) 198.8, 170.45, 170.37, 169.4, 168.9, 137.2, 134.9, 133.2, 128.7, 128.1, 117.9, 61.9, 61.62, 61.57, 59.5, 41.1, 36.3, 34.6, 31.9, 14.0, 13.92, 13.86, 13.2. IR (neat): 2984, 1735, 1688, 1448, 1261, 1100, 1040 cm^{-1}. HRMS(EI): calcd for $C_{28}H_{36}O_9$ (M$^+$) 516.2359, obsd 516.2364. COSY summary; the following pertinent cross peaks were observed: H(2) and H(1) and H(3); H(5) and H(6) and H(7). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) resulted in the enhancement of H(1); irradiation of H(3) resulted in the enhancement of H(6).

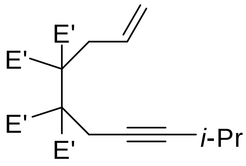


Preparation of 2-(1,1-bis-ethoxycarbonyl-but-3-enyl)-2-ethoxycarbonyl-hept-4-ynoic acid ethyl ester (3.121). To a stirring suspension of NaH (515.6 mg, 21.5 mmol) in 195 THF was added tetraethyl 1,1,2,2-ethanetetracarboxylate (6.2168 g, 19.5 mmol) under N$_2$ counter-flow in two portions. The resulting solution was stirred at room temperature for 1 h after which time allylbromide (2.5987 g, 21.5 mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux for 8 h at which time GC analysis showed no starting ester remained. The solution was cooled to room temperature and quenched with 50 mL of a saturated NH$_4$Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organics were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude yellow oil was purified by flash column chromatography (10% EtOAc/hexanes then 12% EtOAc/hexanes) to yield intermediate **3.121** (6.1658 g, 88%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.98 (m, 1H), 5.11 (m, 1H), 5.08 (m, 1H), 4.27-4.19 (m, 8H), 4.05 (s, 1H), 2.73 (d, *J* = 7.32 Hz, 2H), 1.28 (m, 12H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.2, 167.4, 133.0, 119.6, 61.9, 61.8, 58.7, 55.8, 38.5, 14.0. IR (neat): 2985, 2940, 1740, 1446, 1369, 1250, 1216, 1034 cm^{-1}. HRMS(CI): calcd for $C_{17}H_{27}O_8$ (MH^+) 359.1706, obsd 359.1693.

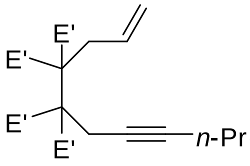


Preparation of enyne 2-Allyl-2,3,3-tris-ethoxycarbonyl-oct-5-ynoic acid ethyl ester (3.59). To a stirring suspension of NaH (237.6 mg, 9.9 mmol) in 47 mL THF was added intermediate **3.121** (1.6880 g, 4.7 mmol) in 2 mL THF. The mixture was stirred at room temperature for 1 h at which time a reflux condenser was attached and 1-bromo-2-pentyne was added (1.5239g, 10.4 mmol). The resulting solution was stirred at reflux until no starting material remained by GC analysis (~36 h). The solution was cooled to room temperature, quenched with 40 mL of a saturated NH_4Cl solution, and extracted with Et_2O (3 x 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to yield a yellow oil. The crude oil was further purified by flash column chromatography eluting with 10% EtOAc/Hexanes then 12% EtOAc/Hexanes to yield a pale yellow oil which was tritrated with cold hexanes to yield **3.59** (1.6354 g, 83%) as a white solid. mp = 44 °C. ^1H NMR (300

MHz, $CDCl_3$): δ (ppm) 5.99 (m, 1H), 5.12 (m, 1H), 5.06 (m, 1H) 4.32-4.10 (m, 8H), 3.10 (t, J = 2.3 Hz, 2H), 2.86 (brd, J = 7.0 Hz, 2H), 2.13 (qt, J_1 = 2.3, J_2 = 7.6 Hz, 2H), 1.28 (appt. q, 12H), 1.08 (t, J = 7.5 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.1, 169.0, 141.7, 116.3, 78.0, 74.8, 62.9, 62.8, 61.8, 61.7, 38.0, 24.6, 22.9, 14.0, 13.9, 3.8. IR (neat): 3080, 2982, 1737, 1445, 1208, 1036, 921 cm^{-1}. HRMS(CI): calcd for $C_{18}H_{26}O_8$ (MH$^+$) 425.2175, obsd 425.2170.



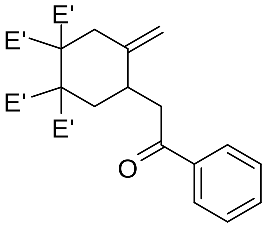
Preparation of enyne 2-Allyl-2,3,3-tris-ethoxycarbonyl-7-methyl-oct-5-ynoic acid ethyl ester (3.61). A procedure analogous to the preparation of enyne **3.59** was used with alkene **3.121** (1.0579 g, 2.95 mmol), NaH (105.6 mg, 4.40 mmol), and 1-bromo-4-methylpent-2-yne (950.1 g, 5.9 mmol) in 30 mL THF. The enyne **3.61** was obtained as a white solid (1.1211 g, 87%). mp = 46 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.99 (m, 1H), 5.11 (brd, J = 17.6 Hz, 1H), 5.05 (brd, J = 10.3 Hz, 1H), 4.30-4.12 (m, 8H), 3.11 (brs, 2H), 2.86 (d, J = 6.8 Hz, 2H), 2.49 (sept. t, J_1 = 2.0, J_2 = 6.8 Hz), 1.33-1.24 (m, 12H), 1.11 (d, J = 6.8 Hz, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 169.3, 169.0, 134.1, 119.0, 88.2, 75.3, 62.6, 62.5, 61.8, 61.7, 36.4, 23.2, 22.6, 20.7, 13.99, 13.96. IR (neat): 2978, 1740, 1448, 1213, 1100, 1038, 922 cm^{-1}. HRMS(CI): calcd for $C_{23}H_{35}O_8$ (MH$^+$) 439.2332, obsd 439.2324.



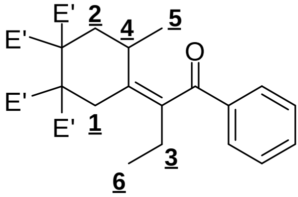
Preparation of enyne 2-Allyl-2,3,3-tris-ethoxycarbonyl-non-5-ynoic acid ethyl ester (3.63). A procedure analogous to the preparation of enyne **3.59** was used with alkene **3.121** (1.9758 g, 5.51 mmol), NaH (198.5 mg, 8.27 mmol), and 1-

bromo-2-hexyne (1.7747 g, 11.02 mmol) in 55 mL THF. Enyne **3.63** was obtained as viscous oil (2.0031 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.98 (m, 1H), 5.11 (brd, J = 17.0 Hz, 1H), 5.05 (brd, J = 10.3 Hz, 1H), 4.30-4.12 (m, 8H), 3.11 (brs, 2H), 2.86 (d, J = 6.8 Hz, 2H), 2.09 (tt, J_1 = 2.4, J_2 = 7.3 Hz, 2H) 1.47 (sext, J = 7.3 Hz, 2H), 1.32-1.22 (m, 12H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 169.2, 168.9, 134.0, 119.0, 82.5, 75.9, 62.5, 62.3, 61.7, 61.6, 36.3, 22.7, 22.3, 20.9, 13.9, 13.5. IR (neat): 2979, 1740, 1448, 1214, 1100, 1037, 865 cm^{-1}. HRMS(CI): calcd for $C_{23}H_{35}O_8$ (MH^+) 439.2332, obsd 439.2325.

General [2+2+2] cycloaddition procedure 3.2. In a glove box, the enyne and aldehyde were added to an oven dried scintillation vial equipped with a magnetic stir bar and dissolved in toluene. To the stirring solution, a solution of $Ni(COD)_2$ and SIPr (previously equilibrated for at least 6 h) was added. The reaction mixture was stirred at room temperature for 2 h (or until complete consumption of starting material was observed as judged by GC or TLC) over which time the color changed from orange to brown. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

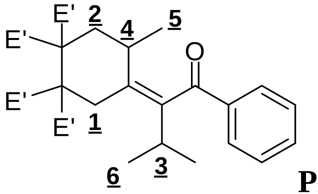


Preparation of tetraethyl 4-methylene-5-(2-oxo-2-phenylethyl) cyclohexane-1,1,2,2-tetracarboxylate (3.58). General procedure **3.2** was used with enyne **3.57** (150 mg, 0.378 mmol), benzaldehyde (50.2 mg, 0.473 mmol), $Ni(COD)_2$ (5.2 mg, 0.0189 mmol), SIPr (14.8 mg, 0.0378 mmol) and 3.78 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield ketone **3.58** (110.3 mg, 58%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.99-7.96 (m, 2H), 7.60-7.55 (m, 1H), 7.50-7.45 (m, 2H), 4.83 (s, 1H), 4.68 (s, 1H), 4.31-4.11 (m, 8H), 3.35 (dd, J_1 = 6.0, J_2 = 16.5 Hz, 1H), 3.14 (d, J = 14.4 Hz, 2H), 2.91 (dd, J_1 = 7.33, J_2 = 16.6 Hz, 1H), 2.88 (d, J = 14.5 Hz, 1H), 2.43 (dd, J_1 = 4.6, J_2 = 13.4 Hz, 1H), 2.24 (dd, J_1 = J_2 = 13.2 Hz, 1H), 1.30-1.22 (m, 12H). 13C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 198.6, 170.5, 170.3, 169.4, 168.8, 145.0, 137.2, 133.3, 128.9, 110.0, 62.2, 61.8, 61.75, 61.71, 60.2, 59.7, 41.2, 39.4, 36.2, 34.1, 14.1, 14.04, 14.02, 13.98. IR (neat): 2983, 2905, 1732, 1687, 1448, 1259, 1184, 1036, 756 cm^{-1}. HRMS(CI): calcd for $C_{27}H_{35}O_9$ (MH$^+$) 503.2281, obsd 502.2272**.**



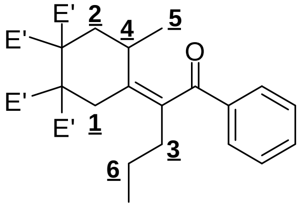
Preparation of (Z)-tetraethyl 4-methyl-5-(1-oxo-1-phenyl butan-2-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (3.60). General procedure **3.2** was used with enyne **3.59** (200 mg, 0.471 mmol), benzaldehyde (62.5 mg, 0.589 mmol), $Ni(COD)_2$ (6.5 mg, 0.0236 mmol), SIPr (18.4 mg, 0.0471 mmol) and 4.71 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield eneone **3.60** (212.5 mg, 85%) as a sticky, pale yellow oil. mp = 61 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.16 (d, J = 7.3 Hz, 2 H), 7.57 (m, 1H), 7.50 (m, 2H), 4.34-4.19 (m, 6H), 4.17-4.07 (m, 2H), 3.13 (d, J = 15.6 Hz, 1H), 2.84 (d, J = 15.6 Hz, 1H), 2.77 (dd, J_1 = 5.9, J_2 = 13.7 Hz, 1H), 2.60 (m, 1H), 2.31 (dddd, J_1 = J_2 = J_3 = 7.4, J_4 = 14.9 Hz, 1H), 2.27-2.17 (m, 2H), 1.35-1.23 (m, 12H), 0.931 (d, J = 7.3Hz, 3H), 0.929 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 201.3, 170.9, 170.5, 168.8, 137.3, 137.1, 135.8, 133.4, 129.9, 128.9,

62.1, 61.81, 61.80, 61.5, 58.7, 58.4, 35.8, 32.8, 28.6, 23.3, 20.7, 14.1, 14.04, 14.02, 14.96, 13.5. IR (neat): 3063, 2980, 2905, 2874, 1731, 1661, 1596, 1454, 1269, 1048, 863 cm^{-1}. HRMS(CI): calcd for $C_{29}H_{39}O_9$ (M^+) 531.2594, obsd 531.2599**.** COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).

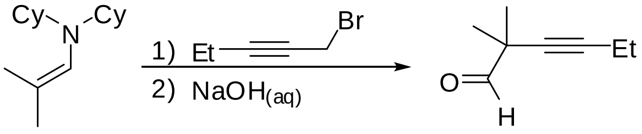


Preparation of (Z)-tetraethyl 4-methyl-5-(3-methyl-1-oxo-1-phenylbutan-2-ylidene) cyclohexane-1,1,2,2-tetracarboxylate (3.62). Cycloaddition procedure **3.2** used with enyne **3.61** (150 mg, 0.342 mmol), benzaldehyde (45.4 mg, 0.428 mmol), $Ni(COD)_2$ (4.7 mg, 0.0171 mmol), SIPr (13.4 mg, 0.0342 mmol) and 3.42 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield enone **3.62** (167.5 mg, 90%) as a sticky, pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.24 (d, *J* = 6.8 Hz, 2H), 7.56 (m, 1H) 7.50 (m, 2H), 4.34-4.19 (m, 6H), 4.17-4.06 (m, 2H), 3.19 (d, *J* = 15.6 Hz, 1H), 2.92 (sept, *J* = 7.1 Hz, 1H), 2.84-2.76 (m, 2H), 2.51 (m, 1H), 2.20 (d, *J* = 13.7 Hz, 1H), 1.35-1.21 (m, 12H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.3Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (ppm) 201.0, 171.0, 170.6, 170.5, 168.6, 140.7, 138.4, 133.7, 133.3, 129.9, 128.8, 62.1, 61.8, 61.5, 58.5, 58.4, 35.3, 32.9, 28.6, 28.0, 22.7, 21.3, 20.5, 14.1, 14.03, 14.01, 13.94. IR (neat): 2978, 2938, 1734, 1661, 1270, 1254, 1081,

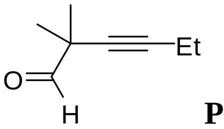
1055, 721 cm^{-1}. HRMS(CI): calcd for $C_{30}H_{41}O_9$ (MH$^+$) 545.2750, obsd 545.2746**.** COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).



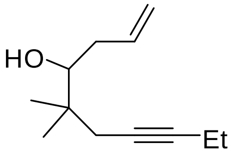
Preparation of (Z)-tetraethyl 4-methyl-5-(1-oxo-1-phenyl pentan-2-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (3.64). General procedure **3.2** was used with enyne **3.63** (150 mg, 0.342 mmol), benzaldehyde (45.4 mg, 0.428 mmol), $Ni(COD)_2$ (4.7 mg, 0.0171 mmol), SIPr (13.4 mg, 0.0342 mmol) and 3.42 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield enone **3.64** (167.8 mg, 90%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.15 (m, 2H), 7.56 (m, 1H), 7.49 (m, 2H), 4.34-4.18 (m, 6H), 4.16-4.06 (m, 2H), 3.14 (d, *J* = 15.8 Hz, 1H), 2.78 (dd, J_1 = 6.1, J_2 = 13.9 Hz, 1H), 2.60 (m, 1H), 2.31-2.21 (m, 2H), 2.13 (dd, J_1 = 6.1, J_2 = 9.0 Hz, 1H), 2.10 (dd, J_1 = 5.4, J_2 = 8.8 Hz, 1H), 1.38-1.23 (m, 15H), 0.95 (d, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 201.3, 170.9, 170.6, 170.5, 168.7, 137.0, 136.4, 136.2, 133.3, 129.9, 128.9, 62.1, 61.8, 61.5, 58.6, 58.4, 35.7, 33.0, 32.1, 28.7, 22.2, 20.8, 14.1, 14.02, 14.01, 13.96. IR (neat): 2980, 2938, 2906, 2873, 1735, 1664, 1594, 1266, 1227, 1052, 722 cm^{-1}. HRMS(CI): calcd for $C_{30}H_{41}O_9$ (MH$^+$) 545.2751, obsd 545.2742**.** COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).



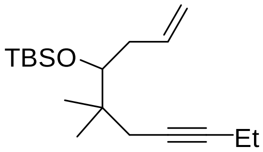
3.122 **3.123**



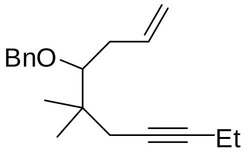
Preparation of 2,2-dimethylhex-3-ynal (3.123). To a stirring suspension of enamine **3.122**[14] (8.00 g, 34.0 mmol) in 10.6 mL CH_3CN was added 1-bromo-2-pentyne (5.23 g, 35.6 mmol). The resulting mixture was stirred at room temperature for 96 h at which time the solvent was removed in vacuo. The resulting oil was poured into 100 mL of a 10% aqueous solution of NaOH and stirred for 2 h. The mixture was then extracted with Et_2O (3 x 30 mL). The combined organics were washed with brine (2 mL) and dried over Na_2SO_4. The solvent was carefully removed at 1 atm on a rotary evaporator to yield a yellow oil which was purified by flash column chromatography eluting with 2% Et_2O/pentane. The product containing fractions were combined and the solvent was carefully removed at 1 atm with a rotary evaporator to yield aldehyde **3.123** (3.5032 g, 75%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.55 (s, 1H), 2.31 (t, J = 2.4 Hz, 2H), 2.16 (qt, J_1 = 2.4, J_2 = 7.3 Hz, 2H), 1.14 (s, 6H), 1.12 (t, J = 7.3 Hz, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (ppm) 205.4, 84.8, 75.0, 45.8, 27.4, 21.4, 14.4, 12.6. IR (neat): 2974, 2935, 2878, 1728, 1467, 1321, 890 cm^{-1}.



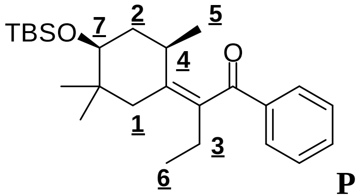
5,5-dimethyldec-1-en-7-yn-4-ol (3.124). To a stirring solution of aldehyde **3.123** (1.000 g, 7.235 mmol) in 50 mL THF was added allylmagnesium chloride dropwise (10.9 mL, 21.7 mmol, 2 M in THF). After the addition was complete, the mixture was stirred for an additional 20 min. at which time the reaction mixture was quenched with 20 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting yellow oil was purified by flash column chromatography eluting with 6% Et_2O/hexanes to yield alcohol **3.124** (1.1124g, 85%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.90 (dddd, J_1 = 5.9, J_2 = 8.3, J_3 = 10.3, J_4 = 17.1 Hz, 1H), 5.19-5.13 (m, 2H), 3.51 (dd, J_1 = 2.0, J_2 = 10.7 Hz, 1H), 2.40-2.33 (m, 1H), 2.24 (dt, J_1 = 2.4, J_2 = 16.1 Hz, 1H), 2.18 (qt, J_1 =2.4, J_2 = 7.3 Hz, 2H), 2.11 (dt, J_1 = 2.4, J_2 = 16.1 Hz, 1H), 2.08-2.00 (m, 1H), 1.85 (s, 1H), 1.14 (t, J = = 7.3 Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H). 13C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 136.6, 117.7, 84.0, 77.1, 76.5, 37.8, 36.5, 29.6, 23.8, 22.3, 14.5, 12.6. IR (neat): 3464, 2937, 2873, 1470, 1320, 1062, 992 cm^{-1}. HRMS(CI): calcd for $C_{12}H_{21}O$ (M^+) 181.1592, obsd 181.1593**.**



Preparation of tert-butyl (5,5-dimethyldec-1-en-7-yn-4-yloxy) dimethylsilane (3.65). To a stirring solution of alcohol **3.124** (1.00 g, 5.55 mmol) and 2,6-lutidine (1.487 g, 13.88 mmol) in 50 mL CH_2Cl_2 at -78 °C was added TBSOTf (1.393 g, 6.100 mmol). The resulting solution was then gradually warmed to room temperature and stirring was continued for an additional 15 h. The reaction mixture was poured into 20 mL H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo***.** The resulting oil was purified by flash column chromatography eluting with hexanes to yield **3.65** (1.4059 g, 86%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.90 (dddd, $J_1 = J_2 = 7.1$, $J_3 = 10.2$, $J_4 = 17.1$ Hz, 1H), 5.03 (d, $J = 17.1$ Hz, 1H), 5.00 (d, $J = 10.3$ Hz, 1H), 3.61(t, $J = 5.1$ Hz, 1H), 2.42-2.35 (m, 1H), 2.22-2.13 (m, 1H) 2.08-2.02 (m, 1H), 1.14 (t, $J = 7.3$ Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (ppm) 137.6, 115.9, 83.8, 77.8, 77.7, 39.4, 38.3, 30.0, 26.3, 24.0, 23.0, 18.5, 14.7, 12.7, -3.2, -4.2. IR (neat): 2958, 2931, 2858, 1472, 1254, 1087, 910, 836, 774 cm^{-1}. HRMS(CI): calcd for $C_{18}H_{35}OSi$ (MH^+) 295.2457, obsd 295.2457**.**

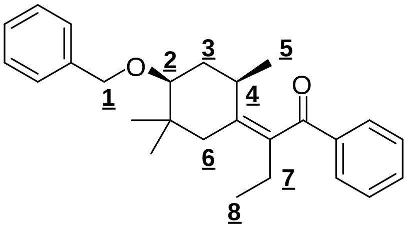


Preparation of ((5,5-dimethyldec-1-en-7-yn-4-yloxy)methyl) benzene (3.67). To a stirring suspension of KH (267 mg, 6.65 mmol) in 25 mL THF was added alcohol **3.124** (800 mg, 4.43 mmol) in 8 mL THF. The resulting mixture was stirred at room temperature for 30 min, at which time benzyl bromide (1.14 g, 6.65 mmol) was added. Stirring was continued at room temperature until starting alcohol could no longer be detected by TLC analysis (~15 h). The mixture was then quenched with a saturated NH_4OH solution (10 mL) and stirred for an additional 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash column chromatography eluting with 1% EtOAc/hexanes then 2% EtOAc/hexanes to yield **3.67** (1.150 mg, 96%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.39-7.31 (m, 4H), 7.29-7.25 (m, 1H), 5.98 (dddd, $J_1 = J_2 = 7.1$, $J_3 = 10.0$, $J_4 = 17.3$ Hz, 1H), 5.14 (dddd, $J_1 = J_2 = J_3 = 1.6$, $J_4 = 17.1$ Hz, 1H), 5.04 (brd, $J = 10.6$ Hz, 1H), 4.68 (d, $J = 11.2$ Hz, 1H), 4.56 (d, $J = 11.2$ Hz, 1H), 3.39 (dd, $J_1 = 3.2$, $J_2 = 8.5$ Hz, 1H), 2.42-2.35 (m, 1H), 2.34-2.24 (m, 2H), 2.20 (qt, $J_1 = 2.3$, $J_2 = 7.5$ Hz, 2H), 2.11 (dt, $J_1 = 2.3$, $J_2 = 16.3$ Hz, 1H), 1.15 (t, 7.6 Hz, 3H), 1.00 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 139.9, 137.4, 128.4, 127.8, 127.5, 116.4, 85.2, 83.9, 77.4, 74.4, 39.2, 35.8, 30.0, 24.1, 23.0, 14.7, 12.7. IR (neat): 2974, 2934, 2877, 1454, 1432, 1074, 911, 697 cm^{-1}. HRMS(CI): calcd for $C_{19}H_{27}O$ (MH$^+$) 271.2062, obsd 271.2060.



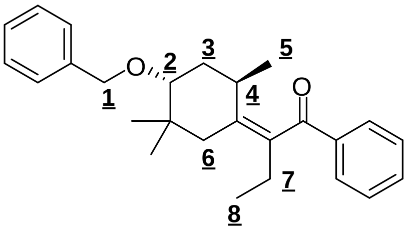
Preparation of (Z)-2-((2R,4S)-4-(tert-butyldimethylsilyloxy)-2,5,5-trimethylcyclohexylidene)-1-phenylbutan-1-one (3.66). General procedure **3.2** was used with enyne **3.65** (100 mg, 0.340 mmol), benzaldehyde (45.0 mg, 0.424 mmol), $Ni(COD)_2$ (4.7 mg, 0.0170 mmol), SIPr (13.3 mg, 0.0340 mmol) and 3.40 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 3% EtOAc/hexanes to yield enone **3.66** as an inseparable mixture of diastereomers (106.9 mg, 79%, 10:1 syn:anti) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.94 (m, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 3.45 (dd, $J_1 = J_2 = 2.7$ Hz, 1H), 2.48 (d, $J = 13.7$ Hz, 1H), 2.40-2.23 (m, 3H), 2.01 (d, $J = 13.7$ Hz, 1H), 1.78 (ddd, $J_1 = 2.9$, $J_2 = 6.4$, $J_3 = 14.7$ Hz, 1H), 1.38 (ddd, $J_1 = J_2 = 2.4$, $J_3 = 14.7$ Hz, 1H), 1.12 (d, $J = 7.3$ Hz, 3H), 1.02-0.96 (m, 9H), 0.91 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C {^{1}H} NMR (125

MHz, $CDCl_3$): δ (ppm) 201.8, 141.1, 137.7, 134.9, 133.1, 129.5, 128.7, 75.9, 38.5, 36.1, 32.9, 28.0, 26.3, 25.8, 23.3, 22.5, 18.3, 13.7, -3.7, -4.9. IR (neat): 2978, 2938, 2874, 1738, 1686, 1466, 1266, 1097, 864 cm^{-1}. HRMS(CI): calcd for $C_{25}H_{41}O_2Si$ (MH^+) 401.2876, obsd 401.2881. COSY summary, the following pertinent cross-peaks were observed: H(2) with H(7) and H(4), H(4) with H(2) and H(5), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(7) showed enhancement of H(4); irradiation of H(4) showed enhancement of H(7).

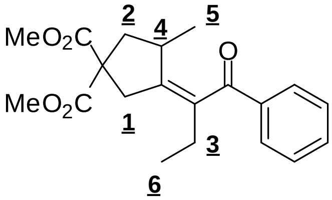


Preparation of (Z)-2-((2R,4S)-4-(benzyloxy)-2,5,5-trimethylcyclohexylidene)-1-phenylbutan-1-one (3.68). General procedure **3.2** was used with enyne **3.67** (150 mg, 0.555 mmol) benzaldehyde (73.6 mg, 0.693 mmol), $Ni(COD)_2$ (7.6 mg, 0.0277 mmol), SIPr (21.7 mg, 0.0555 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 2% EtOAc/hexanes to yield enone **3.68** as mixture of diastereomers (187.2 mg, 90%, 4:1 syn:anti) as a sticky, pale yellow oil. Analytically pure samples of each diastereomer could be obtained by flash column chromatography of the mixture eluting with 60% CH_2Cl_2/hexanes. Major diastereomer. ^1H NMR (500 MHz, C_6D_6): δ (ppm) 8.06 (m, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.17-7.03 (m, 6H), 4.37 (d, J = 11.7 Hz, 1H), 4.02 (d, J = 11.7 Hz, 1H), 2.87 (dd, $J_1 = J_2$ = 2.7 Hz, 1H), 2.52 (m, 2H), 2.27 (dddd, $J_1 = J_2 = J_3$ =7.4, J_4 = 14.9 Hz, 1H), 2.20 (dddd, $J_1 = J_2 = J_3$ = 7.4, J_4 = 14.9 Hz, 1H), 1.96 (d, J = 13.7 Hz, 1H), 1.51 (ddd, J_1 = 2.9, J_2 = 5.9, J_3 = 14.7, 1H), 1.45 (ddd, $J_1 = J_2$ = 2.9, J_3 = 14.7 Hz, 1H), 1.23 (t J = 7.3 Hz, 3H), 1.08 (s, 3H), 0.96 (t, J = 7.6 Hz, 3H), 0.88 (s, 3H). ^{13}C {^1H}

NMR (125 MHz, $CDCl_3$): δ (ppm) 201.7, 141.0, 139.5, 137.6, 135.1, 133.2, 129.5, 128.7, 128.4, 127.6, 82.6, 71.2, 38.0, 33.4, 33.3, 30.5, 27.5, 26.1, 23.3, 21.5, 13.7. IR (neat): 2973, 2934, 1732, 1685, 1596, 1455, 1367, 1168, 1095 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{33}O_2$ (MH^+) 377.2481, obsd 377.2477**.** COSY summary, the following pertinent cross-peaks were observed: H(3) with H(2) and H(4), H(4) with H(3) and H(5), H(3) with H(8). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(5); irradiation of H(5) showed enhancement of H(1) and no enhancement of H(2); irradiation of H(7) showed enhancement of H(6) and no enhancement of H(5); irradiation of H(6) showed enhancement of H(7).

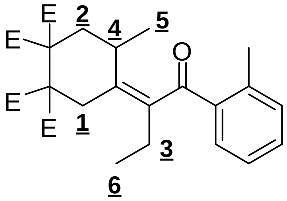


Minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.96 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 7.34 (m, 4H), 7.31-7.24 (m, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 3.43 (dd, J_1 = 4.9, J_2 = 11.7 Hz, 1H), 2.49 (m, 2H), 2.38 (dddd, J_1 = J_2 = J_3 =7.4, J_4 = 15.1 Hz, 1H), 2.32-2.22 (m, 2H), 2.06 (d, J = 14.2 Hz, 1H), 1.62 (ddd, J_1 = 2.2, J_2 = 4.6, J_3 = 12.9, 1H), 1.52 (ddd, J_1 = 5.4, J_2 = J_3 = 12.7 Hz, 1H), 1.14 (s, 3H), 1.04 (s, 3H), 1.01 (d, J = 7.3 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 201.6, 139.3, 139.1, 137.4, 135.8, 133.4, 129.4, 128.9, 128.4, 127.7, 80.4, 71.7, 38.3, 37.8, 34.7, 33.3, 29.3, 23.5, 19.7, 19.3, 13.7. IR (neat): 2973, 2934, 1732, 1685, 1596, 1455, 1367, 1168, 1095. HRMS(CI): calcd for $C_{26}H_{33}O_2$ (MH^+) 377.2481, obsd 377.2477**.** COSY summary, the following pertinent cross-peaks were observed: H(3) with H(2) and H(4), H(4) with H(3) and H(5), H(3) with H(8). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(5); irradiation of H(2) showed enhancement of H(5); irradiation of H(7) showed enhancement of H(6) and no enhancement of H(5); irradiation of H(6) showed enhancement of H(7).



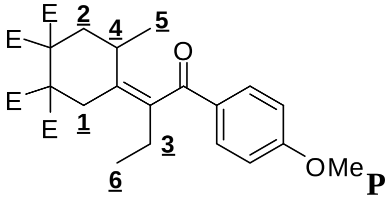
Preparation of (Z)-dimethyl 3-methyl-4-(1-oxo-1-phenyl butan-2-ylidene)cyclopentane-1,1-dicarboxylate (3.70). General procedure **3.2** was used with enyne **3.69** (150 mg, 0.630 mmol), benzaldehyde (83.5 mg, 0.787 mmol), Ni(COD)$_2$ (8.6 mg, 0.0314 mmol), SIPr (24.6 mg, 0.0630 mmol) and 6.30 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield enone **3.70** (210.8 mg, 97%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.88 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.21 (d, J = 16.7 Hz, 1H), 3.03 (d, J = 16.6 Hz, 1H), 2.60 (m, 1H), 2.52 (dd, J_1 = 7.8 , J_2 = 12.7 Hz, 1H), 2.43 (dddd, $J_1 = J_2 = J_3$ = 7.3, J_4 = 14.7 Hz, 1H), 2.33 (dddd, $J_1 = J_2 = J_3$ = 7.5, J_4 = 15.1 Hz, 1H), 1.89 (dd, J_1 = 7.3, J_2 = 13.2 Hz, 1 H), 1.01 (t, J = 7.6 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 200.4, 172.3, 172.2, 145.3, 137.4, 135.1, 133.3, 129.5, 128.8, 58.8, 53.06, 53.04, 42.2, 38.7, 35.8, 26.2, 21.0, 12.7. IR (neat): 2964, 2868, 1734, 1661, 1596, 1449, 1203, 1068 cm^{-1}. HRMS(CI): calcd for $C_{20}H_{25}O_5$ (MH$^+$) 345.1702, obsd 345.1704**.** COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3);

irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).

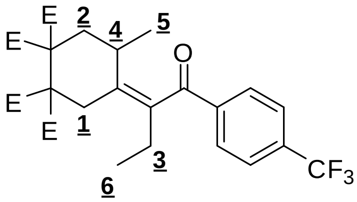


Preparation of (Z)-tetraethyl 4-methyl-5-(1-oxo-1-o-tolylbutan-2-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (3.71). General procedure **3.2** was used with enyne **3.59** (150 mg, 0.353 mmol), *o*-tolylaldehyde (53.1 mg, 0.442 mmol), Ni(COD)$_2$ (4.9 mg, 0.0177 mmol), SIPr (13.8 mg, 0.0353 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield eneone **3.71** (181.6 mg, 94%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.01 (dd, J_1 = 1.0, J_2 = 7.8 Hz, 1H), 7.37 (td, J_1 = 1.5, J_2 = 7.3 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 4.33-4.16 (m, 6H), 4.15-4.08 (m, 2H), 3.11 (d, J = 15.6 Hz, 1H), 2.83 (d, J = 15.6 Hz, 1H), 2.80 (dd, J_1 = 5.9, J_2 = 13.7 Hz, 1H), 2.57 (s, 3H), 2.36-2.25 (m, 2H), 2.13 (dddd, $J_1 = J_2 = J_3$ = 7.3, J_4 = 14.7 Hz, 1H), 1.31-1.23 (m, 12H), 0.98 (d, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 203.1, 170.9, 170.6, 170.5, 168.7, 139.6, 139.0, 137.7, 136.9, 132.04, 131.98, 131.8, 126.0, 62.1, 61.8, 61.5, 58.8, 58.4, 35.9, 32.7, 28.7, 23.2, 21.5, 20.8, 14.1, 13.99, 13.94, 13.5. IR (neat): 2978, 1731, 1662, 1571, 1457, 1235, 1051 cm^{-1}. HRMS(CI): calcd for $C_{30}H_{41}O_9$ (MH$^+$) 545.2751, obsd 545.2752. COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3);

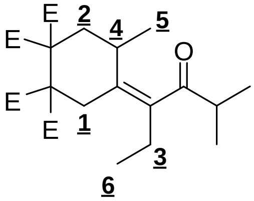
irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).



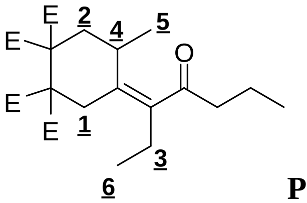
Preparation of (Z)-tetraethyl 4-(1-(4-methoxy-2-methylphenyl)-1-oxobutan-2-ylidene)-5-methylcyclohexane-1,1,2,2-tetracarboxylate (3.72). General procedure **3.2** was used with enyne **3.59** (130 mg, 0.306 mmol), anisaldehyde (52.1 mg, 0.383 mmol), Ni(COD)$_2$ (4.2 mg, 0.0153 mmol), SIPr (12.0 mg, 0.0306 mmol) and 3.06 mL toluene. The reaction mixture was purified by flash column chromatography eluting 12% EtOAc/hexanes to yield enone **3.72** (155.6 mg, 91%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.16 (d, *J* = 9.3 Hz, 2H), 6.98 (d, *J* = 9.3 Hz, 2H), 4.34-4.20 (m, 6H), 4.17-4.07 (m, 2H), 3.89 (s, 3H), 3.11 (d, *J* = 16.1 Hz, 1H), 2.82 (d, *J* = 16.1 Hz, 1H), 2.78 (dd, J_1 = 6.1, J_2 = 13.9 Hz, 1H), 2.60 (m, 1H), 2.34-2.18 (m, 3H), 1.34-1.24 (m, 12H), 0.93 (t, *J* = 7.8 Hz 3H), 0.92 (d, *J* = 7.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 200.0, 171.0, 170.6, 170.5, 168.8, 163.9, 137.5, 134.8, 132.3, 130.3, 114.1, 62.1, 61.8, 61.5, 58.7, 58.5, 55.7, 35.7, 32.8, 28.5, 23.5, 20.6, 14.1, 14.05, 14.03, 13.97, 13.5. IR (neat): 2979, 2906, 2974, 1733, 1654, 1598, 1574, 1263, 861 cm^{-1}. HRMS(CI): calcd for $C_{30}H_{41}O_{10}$ (MH$^+$) 561.2700, obsd 561.2709**.** COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).



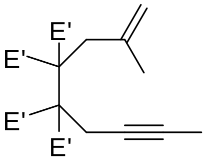
Preparation of (Z)-tetraethyl 4-methyl-5-(1-(2-methyl-4-(trifluoromethyl)phenyl)-1-oxobutan-2-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (3.73). General procedure **3.2** was used with enyne **3.59** (150 mg, 0.353 mmol), 4-(trifluoromethyl)benzaldehyde (76.9 mg, 0.442 mmol), Ni(COD)$_2$ (7.3 mg, 0.0265 mmol), SIPr (20.7 mg, 0.0530 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield enone **3.73** (142.7 mg, 67%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.32 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 4.34-4.20 (m, 6H), 4.17-4.08 (m, 2H), 3.13 (d, J = 15.6 Hz, 1H), 2.83 (d, *J* = 15.6 Hz, 1H), 2.76 (dd, J_1 = 5.9, J_2 = 13.7 Hz, 1H), 2.53 (m, 1H), 2.33 (dddd, J_1 = J_2 = J_3 = 7.5, *J* = 15.1 Hz, 1H), 2.26 (dd, J_1 = 2.4, J_2 = 13.7 Hz, 1H), 2.19 (dddd, J_1 = J_2 = J_3 = 7.4, J_4 = 14.9 Hz, 1H), 1.35-1.24 (m, 12H), 0.94 (d, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 200.2, 170.8, 170.45, 170.43, 168.8, 139.9, 137.1, 136.7, 130.2, 126.0 (q, *J* = 32.6 Hz), 62.2, 61.87, 61.86, 61.6, 58.5, 58.4, 35.7, 33.1, 28.7, 23.2, 20.8, 14.1, 14.02, 13.96, 13.4. IR (neat): 2981, 2937, 1745, 1722, 1672, 1446, 1410, 1266 cm^{-1}. HRMS(CI): calcd for $C_{30}H_{38}F_3O_9$ (MH$^+$) 599.2468, obsd 599.2470**.** COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).



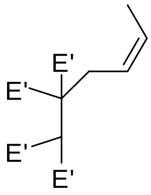
Preparation of (Z)-tetraethyl 4-methyl-5-(5-methyl-4-oxohexan-3-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (3.74). General procedure **3.2** was used with enyne **3.59** (150 mg, 0.353 mmol), isobutyraldehyde (31.9 mg, 0.442 mmol), Ni(COD)$_2$ (4.9 mg, 0.0177 mmol), SIPr (13.8 mg, 0.03534 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting 12% EtOAc/hexanes to yield enone **3.74** (141.6 mg, 81%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 4.34-4.04 (m, 8H), 3.00 (d, *J* = 15.6 Hz, 1H), 2.89-2.77 (m, 2H), 2.74 (d, *J* = 15.8 Hz, 1H), 2.66 (m, 1H), 2.33 (dd, J_1 = 2.0, J_2 = 13.7 Hz, 1H), 2.28 (dddd, J_1 = J_2 = J_3 = 7.4, J_4 = 15.1 Hz, 1 H), 2.12 (dddd, J_1 = J_2 = J_3 = 7.4, J_4 = 14.9 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.24 (m, 9H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 213.0, 170.7, 170.5, 170.4, 168.4, 138.9, 137.5, 62.0, 61.7, 61.6, 61.4, 59.0, 58.2, 39.0, 35.9, 32.9, 28.4, 22.2, 21.2, 18.6, 18.1, 14.0, 13.9, 13.8. IR (neat): 2978, 2938, 2874, 1738, 1686, 1466, 1266, 1097, 864 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{41}O_9$ (MH$^+$) 497.2752, obsd 497.2746**.** COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).



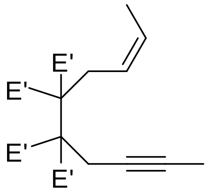
Preparation of (Z)-tetraethyl 4-methyl-5-(4-oxoheptan-3-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (3.75). General procedure **3.2** was used with enyne **3.59** (150 mg, 0.353 mmol), butyraldehyde (31.9 mg, 0.442 mmol), $Ni(COD)_2$ (4.9 mg, 0.0177 mmol), SIPr (13.8 mg, 0.0353 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield enone **3.59** (148.8 mg, 85%) as a sticky, pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.34-4.08 (m, 8H), 3.01 (d, J = 15.6 Hz, 1H), 2.84-2.70 (m, 3H), 2.56-2.50 (m, 2H), 2.35 (dd, J_1 = 1.7, J_2 = 13.4 Hz, 1H), 2.26 (dddd, J_1 = J_2 = J_3 = 7.4, J_4 = 14.9 Hz, 1 H), 2.17 (dddd, J_1 = J_2 = J_3 = 7.5, J_4 = 15.1 Hz, 1 H), 1.65 (sext, J = 7.3 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.29-1.24 (m, 9H), 1.01 (d, J = 7.3 Hz, 3H), 0.95 (m, 6H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (ppm) 209.5, 170.7, 170.49, 170.47, 168.7, 139.5, 136.4, 62.0, 61.8, 61.6, 61.5, 59.1, 58.4, 44.5, 35.9, 32.3, 28.3, 22.1, 21.1, 17.2, 14.0, 13.9, 13.66, 13.65. IR (neat): 2978, 2938, 2875, 1738, 1691, 1464, 1267, 1051, 864 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{41}O_9$ (MH^+) 497.2751, obsd 497.2746 COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(2) and H(5), H(5) with H(4), H(3) with H(6). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(5); irradiation of H(5) showed no enhancement of H(3).



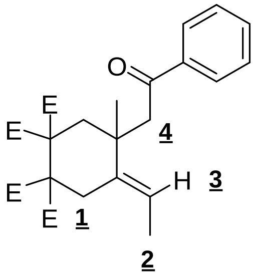
Preparation of 2,3,3-tris-ethoxycarbonyl-2-(2-methyl-allyl)-hept-5-ynoic acid ethyl ester (3.80). To a stirring suspension of NaH (116.6 mg ,4.9 mmol) in 16 mL THF was added tetra-ester **2.74** (1.2000 g, 2.7 mmol) in 2 mL THF. The resulting solution was stirred at room temperature for 1 h at which time 3-bromo-2-methylpropene (874.6 mg , 6.5 mmol) was added in a single portion via syringe. The flask was then equipped with a reflux condenser and the mixture was stirred at reflux for 36 h at which time GC analysis showed some of the starting ester remained. Under N_2 counter flow, additional NaH (60.0 mg, 2.5 mmol) and 3-bromo-2-methylpropene (874.6 mg , 6.5 mmol) were added and the mixture was stirred at reflux until no more starting material was observed by GC analysis (~36 h). The mixture was then cooled to room temperature and quenched with 40 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organics were washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo to yield a yellow oil. The crude oil was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes producing **3.80** (1.1121 g, 81%) as colorless oil which solidified upon standing. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.86 (brs, 1H), 4.83 (brs, 1H), 4.35-4.08 (m, 8H), 3.01 (q, *J* = 2.6 Hz, 2H), 2.99 (brs, 2H), 1.76 (brs, 3H), 1.74 (t, 2.6 Hz, 3H), 1.28 (appt. q, 12H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.9, 169.0, 141.7, 116.3, 78.0, 74.8, 62.9, 62.8, 61.8, 61.7, 38.0, 24.6, 22.9, 14.0, 13.9, 3.8. IR (neat): 2984, 1738, 1643, 1447, 1368, 1205, 1096, 1042 cm^{-1}. HRMS(CI): calcd for $C_{22}H_{33}O_8$ (MH^+) 425.2175 , obsd 425.2177.



Preparation of (Z)-tetraethyl hex-4-ene-1,1,2,2-tetracarboxylate (3.125). To a N_2 purged 100 mL two-necked flask equipped with 3-way adapter and a balloon was added Pd/$BaSO_4$ (453.7 mg). The flask was evacuated with a water aspirator and the catalyst was then suspended in 54 mL benzene. Quinoline (113.0 mg, 0.87 mmol) was then added to the suspension. The balloon and flask were then filled with H_2. Tetra-ester **2.74** (2.0082 g, 5.4 mmol) in 2 mL benzene was added via syringe. The resulting suspension was stirred at room temperature until no starting material remained by GC analysis (~11 h). The mixture was then filtered through a pad of celite and concentrated *in vacuo* to yield a yellow oil which was further purified by flash column chromatography eluting with 12% EtOAc/hexanes to yield intermediate **3.125** (1.8787 g, 93%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.59 (m, 2H), 4.27-4.17 (m, 8H), 4.09 (s, 1H), 2.74 (d, *J* = 6.4 Hz, 2H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.28 (m, 12H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (ppm) 169.4, 167.4, 128.0, 124.3, 61.8, 61.7, 58.5, 55.9, 14.0, 12.9, 3.8. IR (neat): 2985, 2939, 1739, 1447, 1870, 1250, 1206, 1034 cm^{-1}. HRMS(CI): calcd for $C_{18}H_{29}O_8$ (MH^+) 373.1862, obsd 373.1858.



Preparation of 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-enoic acid ethyl ester (3.77). To a stirring suspension of NaH (228.4 mg, 9.5 mmol) in 48 mL dry THF was added intermediate **3.125** (1.7717 g, 4.8 mmol) in 2 mL THF. The resulting solution was stirred at room temperature for 1 h at which time a reflux condenser was attached and 1-bromo-2-butyne was added (1.3918 g, 10.5 mmol). The resulting solution was stirred at reflux until no starting ester remained by GC analysis (~36 h). The solution was cooled to room temperature and quenched with 40 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to yield a yellow oil. The crude oil was further purified by flash column chromatography eluting with 10% EtOAc/hexanes. Then 12% EtOAc/hexanes to yield a pale yellow oil which was tritrated with cold hexanes to yield **3.77** (1.4253 g, 71%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.56 (m, 2H), 4.34-4.08 (m, 8H), 3.06 (q, *J* = 2.5 Hz, 2H), 2.93 (d, *J* = 4.8Hz, 2H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.64 (d, *J* = 4.8Hz, 3H) 1.28 (appt. q, 12H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.5, 169.2, 127.5, 125.6, 78.1, 74.9, 62.4, 61.9, 61.8, 29.0, 22.9, 14.0, 13.1. IR (neat): 2984, 2937, 2361, 1738, 1446, 1205, 1037 cm^{-1}. HRMS(CI): calcd for $C_{22}H_{33}O_8$ (MH^+) 425.2175, obsd 425.2179.



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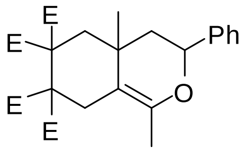
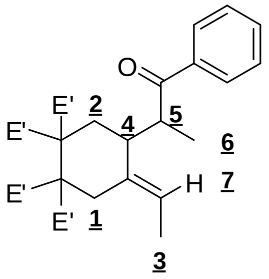


3.82

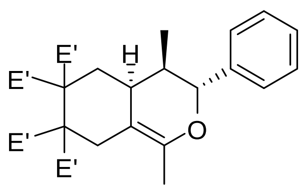
Preparation of tetraethyl 1,4a-dimethyl-3-phenyl-4a,5-dihydro-3H-isochromene-6,6,7,7(4H,8H)-tetracarboxylate 3.81. and (E)-tetraethyl 5-ethylidene-4-methyl-4-(2-oxo-2-phenylethyl)cyclohexane-1,1,2,2-tetracarboxylate (3.82). General procedure **3.2** was used with enyne **3.80** (150 mg, 0.353 mmol), benzaldehyde (46.9 mg, 0.442 mmol), $Ni(COD)_2$ (4.9 mg, 0.0177 mmol), SIPr (13.7 mg, 0.0353 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.82** (34.4 mg, 18%) as a sticky, pale yellow oil and ketone **3.81** (152.9 mg, 82%) as a sticky, pale yellow oil.

(E)-tetraethyl 5-ethylidene-4-methyl-4-(2-oxo-2-phenylethyl)cyclohexane-1,1,2,2-tetracarboxylate (3.81). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.85 (m, 2H), 7.52 (m, 1H), 7.43 (m, 2H), 5.39 (q, *J* = 6.7 Hz, 1H), 4.30-4.09 (m, 7H), 3.92-3.80 (m, 3H), 3.09-3.02 (m, 3H), 2.87 (d, *J* = 14.7 Hz, 1H), 2.86 (d, *J* = 16.1 Hz, 1H), 2.65 (d, *J* = 14.7Hz, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.32 (s, 3H), 1.30-1.22 (m, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 199.3, 170.8, 170.6, 170.2, 169.4, 139.5, 138.6, 132.9, 128.7, 120.0, 119.7, 62.1, 62.0, 61.6, 61.5, 59.2, 59.0, 46.8, 40.0, 38.7, 28.6, 26.6, 14.1, 14.0, 13.9, 13.2. IR (neat): 2983, 2940, 1740, 1693, 1597, 1448, 1272, 1095 cm^{-1}. HRMS(CI): calcd for $C_{29}H_{39}O_9$ (MH^+) 531.2594, obsd 531.2599. COSY summary, the following pertinent cross-peaks were observed: H(2) with H(3). NOE summary; the following pertinent enhancements were observed: irradiation of H(2) showed enhancement of H(1); irradiation of H(3) showed enhancement of H(4).

Tetraethyl 1,4a-dimethyl-3-phenyl-4a,5-dihydro-3H-isochromene-6,6,7,7(4H,8H)-tetracarboxylate (3.82). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.39-7.17 (m, 5H), 4.89 (dd, J_1 = 2.9, J_2 = 10.7 Hz, 1H), 4.32-4.06 (m, 8H), 2.98-2.84 (m, 3H), 2.24 (d, *J* = 10.2 Hz, 1H), 1.93-1.81 (m, 2H), 1.75 (s, 3H), 1.32-1.21 (m, 12H), 1.00 (s, 3H). 13C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 170.8, 170.5, 170.4, 168.0, 147.5, 142.0, 128.6, 127.7, 126.2, 109.1, 74.4, 62.1, 61.8, 61.6, 61.4, 59.9, 59.7, 49.0, 43.0, 33.3, 29.8, 27.5, 16.8, 14.2, 14.1, 14.0. IR (neat): 2983, 2938, 1738, 1679, 1254, 1230, 1186, 1057, 701 cm^{-1}. HRMS(CI): calcd for $C_{29}H_{39}O_9$ (MH^+) 531.2594, obsd 531.2593.



3.78

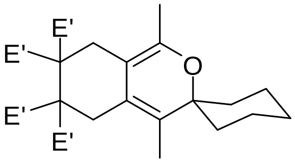


3.79

Preparation of (3R,4R,4aS)-tetraethyl 1,4-dimethyl-3-phenyl-4a,5-dihydro-3H-isochromene-6,6,7,7(4H,8H)-tetracarboxylate (3.78) and (E)-tetraethyl 4-ethylidene-5-(1-oxo-1-phenylpropan-2-yl)cyclohexane-1,1,2,2-tetracarboxylate (3.79). General procedure **3.2** was used with enyne **3.77** (150 mg, 0.353 mmol), benzaldehyde (46.9 mg, 0.442 mmol), $Ni(COD)_2$ (4.9 mg, 0.0177 mmol), SIPr (13.8 mg, 0.0353 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.79** (119.4 mg, 64%) as a sticky, pale yellow oil and ketone **3.78** (61.5 mg, 33%) as a viscous oil. X-ray quality crystals of dihydropyran **3.79** were obtained by slow solvent evaporation of a Et_2O/hexanes solution.

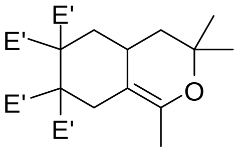
(E)-tetraethyl 4-ethylidene-5-(1-oxo-1-phenylpropan-2-yl)cyclohexane-1,1,2,2-tetracarboxylate (3.78). ^1H NMR (asterisk denotes minor diastereomer peak, 500 MHz, $CDCl_3$): δ (ppm) 7.96 (m, 4H), 7.59-7.54 (m, 2H), 7.50-7.45 (m, 4H), 5.40 (q, J = 6.7 Hz, 1H), 5.23* (q, J = 6.7 Hz, 1H), 4.32-4.00 (m, 14H), 3.97-3.73 (m, 4H), 3.20* (d, J = 14.7 Hz, 1H), 3.02 (d, J = 14.7 Hz, 1H), 2.92 (d, J = 14.7 Hz, 1H), 2.76 (m, 2H), 2.59* (d, J = 15.1 Hz, 1H), 2.51 (dd, J_1 = 4.6, J_2 = 14.2 Hz, 1H), 2.46-2.37 (m, 2H), 2.35* (dd, J_1 = 4.6, J_2 = 13.4 Hz, 1H), 1.62 (d, J = 6.8 Hz, 3H), 1.56* (d, J = 6.7 Hz, 3H), 1.32-1.23 (m, 18H), 1.22* (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.11-1.05 (m, 6H). $^{13}C\ \{^1H\}$ NMR (asterisk denotes minor diastereomer peak, 125 MHz, $CDCl_3$): δ (ppm) 202.7, 170.6, 170.5, 169.5, 169.1, 136.2, 134.0, 133.1, 129.8*, 128.9, 128.8*, 128.5*, 128.4, 118.6, 61.9, 61.8, 61.7, 61.5, 60.2, 59.2, 40.8, 40.6, 32.0, 31.81*, 31.77, 14.1, 14.0, 13.9, 13.3, 13.1. IR (neat): 2973, 2934, 1732, 1685, 1455, 1367, 1259, 1169, 1094 cm^{-1}. HRMS(CI): calcd for $C_{29}H_{39}O_9$ (MH^+) 531.2594, obsd 531.2593. COSY summary, the following pertinent cross-peaks were observed: H(2) with H(4), H(4) with H(5) and H(2), H(5) with H(4) and H(6), H(3) with H(7). NOE summary; the following pertinent enhancements were observed: irradiation of H(5) showed enhancement of H(7) and H(6); irradiation of H(7) showed enhancement of H(5) and H(6); irradiation of H(1) showed enhancement of H(3); irradiation of H(3) showed enhancement of H(1); irradiation of H(6) showed enhancement of H(7).

(3R,4R,4aS)-tetraethyl 1,4-dimethyl-3-phenyl-4a,5-dihydro-3H-isochromene-6,6,7,7(4H,8H)-tetracarboxylate (3.79). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.34 (m, 2H), 7.30-7.26 (m, 3H), 4.40 (d, *J* = 9.3 Hz, 1H), 4.32-4.07 (m, 8H), 3.05-2.95 (m, 2H), 2.50 (m, 1H), 2.29-2.15 (m, 3H), 1.81 (s, 3H), 1.33-1.21 (m, 12H), 0.69 (d, *J* = 7.3 Hz, 3H). $^{13}C\ \{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 171.0, 170.7, 169.7, 169.1, 146.4, 140.6, 128.5, 127.9, 127.0, 103.8, 79.5, 61.8, 61.73, 61.66, 61.56, 60.4, 59.2, 36.6, 33.3, 33.0, 31.9, 16.5, 14.1, 14.00, 13.99, 13.96, 13.4. IR (neat): 2981, 2938, 2905, 1734, 1680, 1262, 1193, 1096, 1036, 733 cm^{-1}. HRMS(CI): calcd for $C_{29}H_{39}O_9$ (MH^+) 531.2594, obsd 531.2598.

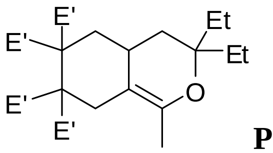


Preparation of spiropyran (3.93). In a glove box, cyclohexanone (43.6 mg, 0.44 mmol) was added to a scintillation vial equipped with a magnetic stir bar and dissolved in 2.2 mL toluene. The vial was sealed with a septum and placed under N_2. To the stirring solution of cyclohexanone, a solution of $Ni(COD)_2$ (9.8 mg, 0.036 mmol) and SIPr (27.7 mg, 0.071 mmol) in 0.4 mL toluene (previously equilibrated for at least 6 h) was added. A solution of 2-but-2-ynyl-2,3,3-tris-ethoxycarbonyl-hept-5-ynoic acid ethyl ester **2.73** (150.0 mg, 0.36 mmol) in 0.9 mL toluene was then added via syringe pump over 30 min. The resulting brownish orange solution was stirred at room temperature for an additional 1.5 h. The crude reaction mixture was concentrated in vacuo and purified by flash column chromatography on SiO_2 (12% EtOAc/hexanes then 15% EtOAc/hexanes). The fractions containing both the dienolic ether (upper red spot, anisaldehyde stain) and dienone (lower purple spot, anisaldehyde stain) were combined to yield dienolic ether **3.93** and a small amount dienone **3.94** (144.8 mg, 83%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.27-4.13 (m, 8H), 3.01 (s, 2H), 2.88 (s, 2H), 1.92 (brd, *J* = 13.0 Hz, 2H), 1.86 (s, 3H), 1.60 (s, 3H), 1.70-1.56 (brm, 3H), 1.51-1.40 (brm, 3H), 1.36-1.20 (m, 14H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 170.2, 170.1, 143.9, 124.0, 121.8, 104.9, 77.7, 61.8, 61.7, 58.7, 57.9, 31.7, 31.1, 30.3, 25.8, 21.4, 16.1, 14.0, 12.5. IR (neat): 2934, 2960, 1740, 1662, 1446, 1266, 1408 cm^{-1}. HRMS(EI): calcd for $C_{28}H_{40}O_9$ (M^+) 520.2672, obsd 520.2673.

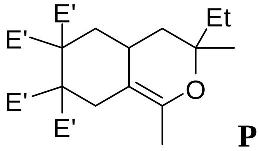
General [2+2+2] cycloaddition procedure 3.3. To a stirring solution of Ni(COD)$_2$, IPr, and 3Å molecular sieves in toluene (previously equilibrated for at least 8 h) was added ketone. A solution of enyne in toluene (~ 0.4 M) was then added to the ketone/catalyst solution via syringe pump over the indicated time. The resulting solution was stirred at room temperature for an additional 2 h or until no starting enyne could be detected by GC analysis. The reaction mixture was then filtered through a pad of celite and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to yield the dihydropyran.



Preparation of 1,3,3-trimethyl-3,4,4a,5-tetrahydro-8H-isochromene-6,6,7,7-tetracarboxylic acid tetraethyl ester (3.95). General procedure **3.3** was used with enyne **2.66** (150 mg, 0.365 mmol), acetone (26.5 mg, 0.456 mmol), 3Å molecular sieves (54.5 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (10.0 mg, 0.0365 mmol), IPr (21.3 mg, 0.0548 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.95** (159.2 mg, 93%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 4.30-4.08 (m, 8H), 3.01 (brs, 2H), 2.54 (m, 1H), 2.29 (dd, J_1 = 4.9, J_2 = 14.2 Hz, 1H), 1.82 (dd, J_1 = 12.2, J_2 = 14.2 Hz, 1H), 1.75 (brs, 3H), 1.70 (dd, J_1 = 6.4, 13.2 Hz, 1H), 1.31-1.22 (m, 16H), 1.14 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 170.8, 169.6, 169.1, 144.0, 100.8, 72.9, 61.6, 61.5, 61.2, 60.3, 58.3, 41.6, 35.9, 31.8, 29.8, 26.7, 23.8, 16.7, 14.0, 13.9, 13.8. IR (neat): 2980, 2936, 1735, 1679, 1448, 1264, 1187, 1038 cm^{-1}. HRMS(CI): calcd for $C_{24}H_{37}O_9$ (MH$^+$) 469.2438, obsd 469.2430.

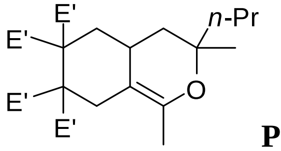


Preparation of 3,3-diethyl-1-methyl-3,4,4a,5-tetrahydro-8H-isochromene-6,6,7,7-tetracarboxylic acid tetraethyl ester (3.96). General procedure **3.3** was used with enyne **2.66** (150 mg, 0.365 mmol), 3-pentanone (125.9 mg, 1.462 mmol), 3Å molecular sieves (54.5 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (10.0 mg, 0.0365 mmol), IPr (21.3 mg, 0.0548 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.96** (176.0 mg, 97%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 4.30-4.09 (m, 8H), 2.98 (m, 2H), 2.48 (m, 1H), 2.29 (dd, J_1 = 5.4, J_2 = 14.2 Hz, 1H), 1.83 (dd, J_1 = 12.2, J_2 = 14.2 Hz, 1H), 1.77-1.72 (m, 4H), 1.63-1.35 (m, 6H), 1.31-1.18 (m, 13H), 0.86 (t, J = 7.3 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 170.9, 170.8, 176.6, 169.2, 143.9, 100.9, 76.9, 61.6, 61.5, 61.3, 60.3, 58.4, 37.1, 36.1, 31.8, 30.5, 26.0, 25.4, 16.5, 14.0, 13.9, 7.8. IR (neat): 2977, 2940, 1736, 1680, 1448, 1262, 1099, 1042, 935 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{41}O_9$ (MH$^+$) 497.2751, obsd 497.2746.



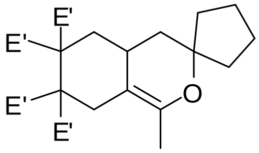
Preparation of 3-ethyl-1,3-dimethyl-3,4,4a,5-tetrahydro-8H-isochromene-6,6,7,7-tetracarboxylic acid tetraethyl ester (3.97). General procedure **3.3** was used with enyne **2.66** (150 mg, 0.365 mmol), 2-butanone (52.7 mg, 0.731 mmol), 3Å molecular sieves (54.5 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (10.0 mg, 0.0365 mmol), IPr (21.3 mg, 0.0548 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12%

EtOAc/hexanes to yield dihydropyran **3.97** (167.3 mg, 95%) as a sticky, pale yellow oil. The product was isolated a 1:1 mixture of inseparable diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.29-4.07 (m, 16H), 3.05-2.93 (m, 4H), 2.51 (m, 2H), 2.33-2.25 (m, 2H), 1.86-1.76 (m, 3H), 1.74 (brs, 6H), 1.69-1.50 (m, 6H), 1.40 (m, 1H), 1.32-1.22 (m, 24H), 1.19 (s, 3H), 1.09 (s, 3H), 0.09 (t, J = 7.6 Hz, 3H), 0.84 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 170.8, 169.5, 169.1, 169.0, 144.0, 143.7, 101.1, 100.7, 75.3, 75.0, 61.5, 61.2, 60.2, 58.3, 39.9, 39.1, 36.0, 35.9, 35.2, 31.8, 28.3, 26.3, 26.2, 25.9, 21.3, 16.6, 16.5, 14.0, 13.9, 13.8, 8.1, 7.8. IR (neat): 2979, 2938, 1736, 1679, 1449, 1370, 1262, 1099, 1040 cm^{-1}. HRMS(CI): calcd for $C_{25}H_{39}O_9$ (MH^+) 483.2594, obsd 483.2583.

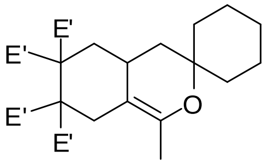


Preparation of 1,3-Dimethyl-3-propyl-3,4,4a,5-tetrahydro-8H-isochromene-6,6,7,7-tetracarboxylic acid tetraethyl ester (3.98). General procedure **3.3** was used with enyne **2.66** (150 mg, 0.365 mmol), 2-pentanone (63.0 mg, 0.731 mmol), 3Å molecular sieves (54.5 mg, 150 mg/mmol enyne), $Ni(COD)_2$ (10.0 mg, 0.0365 mmol), IPr (21.3 mg, 0.0548 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.98** (178.6 mg, 98%) as a sticky, colorless oil. The product was isolated as a 1:1 mixture of inseparable diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.29-4.07 (m, 16H), 3.04-2.95 (m, 4H), 2.51 (m, 2H), 2.29 (dd, J_1 = 4.9, J_2 = 9.8 Hz, 1H), 2.27 (dd, J_1 = 4.9, J_2 = 9.8 Hz, 1H), 1.85-1.76 (m, 3H), 1.74 (s, 3H), 1.73 (s, 3H), 1.66 (dd, J_1 = 6.4, J_2 = 13.2 Hz, 1H), 1.55-1.44 (m, 3H), 1.41-

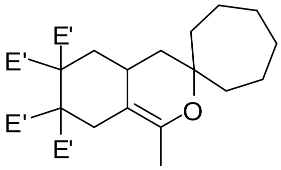
1.21 (m, 31H), 1.20 (s, 3H), 1.10 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). $^{13}C\ \{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 170.9, 170.8, 169.7, 169.6, 169.2, 169.1, 144.1, 143.8, 101.1, 100.8, 75.1, 75.0, 61.6, 61.3, 60.3, 58.4, 45.2, 40.5, 39.7, 38.3, 36.0, 31.9, 26.6, 26.4, 26.3, 21.9, 17.2, 16.7, 16.6, 14.8, 14.7, 14.0, 13.9. IR (neat): 2979, 2874, 1735, 1680, 1449, 1370, 1262, 1099, 1041 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{41}O_9$ (MH^+) 497.2751, obsd 497.2745.



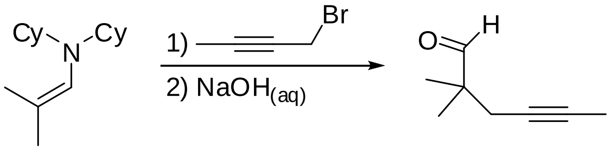
Preparation of spiro dihydropyran 3.99. General procedure **3.3** was used with enyne **2.66** (150 mg, 0.365 mmol), cyclopentanone (61.5 mg, 0.731 mmol), 3Å molecular sieves (54.5 mg, 150 mg/mmol enyne), $Ni(COD)_2$ (10.0 mg, 0.0365 mmol), IPr (21.3 mg, 0.0548 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.99** (174.6 mg, 97%) as a sticky, colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.31-4.05 (m, 8H), 3.00 (brs, 2H), 2.58 (m, 1H), 2.29 (dd, J_1 = 5.4, J_2 = 14.2 Hz, 1H), 1.88-1.76 (m, 4H), 1.75-1.60 (m, 5H), 1.65-1.44 (m, 4H), 1.37-1.21 (m, 13H). $^{13}C\ \{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 170.9, 169.6, 169.1, 144.4, 101.9, 84.5, 61.6, 61.3, 60.4, 58.4, 40.0, 39.6, 36.1, 36.0, 32.0, 27.7, 24.3, 24.0, 16.8, 14.1, 14.0, 13.9. IR (neat): 2961, 2873, 1735, 1679, 1447, 1261, 1100, 1039 cm^{-1}. HRMS(CI): calcd for $C_{26}H_{39}O_9$ (MH^+) 495.2594, obsd 495.2586.



Preparation of spiro dihydropyran 3.100. General procedure **3.3** used with enyne **2.66** (150 mg, 0.365 mmol), cyclohexanone (44.8 mg, 0.457 mmol), 3Å molecular sieves (54.5 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (10.0 mg, 0.0365 mmol), IPr (21.3 mg, 0.0548 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.100** (183.2 mg, 99%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 4.30-4.07 (m, 8H), 3.00 (brs, 1H), 2.99 (brs, 1H), 2.53 (m, 1H), 2.27 (dd, J_1 = 5.4, J_2 = 14.2 Hz, 1H), 1.85-1.14 (m, 28H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 170.9, 169.6, 169.2, 143.8, 101.2, 73.7, 61.6, 61.3, 60.5, 58.3, 40.6, 38.4, 36.1, 31.9, 26.1, 26.0, 22.0, 21.9, 16.7, 14.1, 14.0, 13.9. IR (neat): 2983, 2935, 2861, 1735, 1680, 1447, 1368, 1261 cm^{-1}. HRMS(CI): calcd for $C_{27}H_{41}O_9$ (MH$^+$) 509.2751, obsd 509.2773**.**

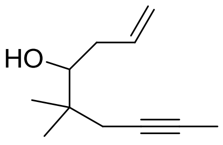


Preparation of spiro dihydropyran 3.101. General procedure **3.3** was used with enyne **2.66** (150 mg, 0.365 mmol), cycloheptanone (164 mg, 1.46 mmol), 3Å molecular sieves (54.5 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (10.0 mg, 0.0365 mmol), IPr (21.3 mg, 0.0548 mmol) and 3.65 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.101** (183.3 mg, 96%) as a sticky, pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 4.28-4.08 (m, 8H), 3.00 (m, 2H), 2.50 (m, 1H), 2.28 (dd, J_1 = 5.4, J_2 = 14.2 Hz, 1H), 1.92-1.45 (m, 14H), 1.44-1.22 (m, 15H), 1.15 (dd, J_1 = 11.2, J_2 = 13.2 Hz, 1H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 170.9, 169.6, 169.2, 143.9, 101.4, 78.1, 61.7, 61.6, 61.3, 60.4, 58.4, 42.0, 41.9, 36.0, 34.9, 31.9, 30.2, 30.0, 26.2, 22.4, 22.1, 16.8, 14.1, 14.0, 13.9. IR (neat): 2982, 2931, 2859, 1735, 1679, 1448, 1385, 1261, 1101 cm^{-1}. HRMS(CI): calcd for $C_{28}H_{43}O_9$ (MH$^+$) 523.2907, obsd 523.2891.

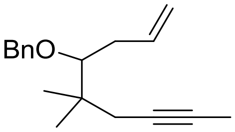


3.122 **3.126**

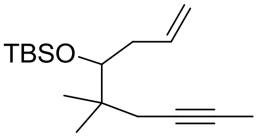
Preparation of 2,2-dimethylhex-4-ynal (3.126). To a stirring suspension of enamine **3.122**[14] (4.0000 g, 17.0 mmol) in 5.3 mL CH_3CN was added 1-bromo-2-butyne (2.3737g, 17.8 mmol). The resulting mixture was stirred at room temperature for 96 h at which time the solvent was removed in vacuo. The resulting oil was poured into 50 mL of a 10% aqueous solution of NaOH and stirred for 2 h. The mixture was then extracted with Et_2O (3 x 15 mL). The combined organics were washed with brine (2 mL) and dried over Na_2SO_4. The solvent was carefully removed at 1 atm on a rotary evaporator to yield a yellow oil which was purified by flash column chromatography eluting with 2% Et_2O/pentane. The product containing fractions were combined and the solvent was carefully removed at 1 atm with a rotary evaporator to yield aldehyde **3.126** (1.6687 g, 79%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.54 (s, 1H), 2.29 (q, *J* = 2.6 Hz, 2H), 1.78 (t, *J* = 2.6 Hz, 3H), 1.14 (s, 6H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 205.2, 78.4, 74.7, 45.7, 27.2, 21.2, 3.4. IR (neat): 2970, 2925, 2874, 2709, 1729, 1466 cm^{-1}. HRMS(CI): calcd for $C_8H_{13}O$ (MH$^+$) 125.0966, obsd 125.0957.



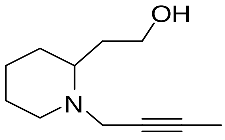
Preparation of 5,5-dimethylnon-1-en-7-yn-4-ol (3.127). To a stirring solution of aldehyde **3.126** (1.0000 g, 8.1 mmol) in 50 mL THF was added dropwise a 2 molar THF solution of allylmagnesium chloride (12.15 mL, 24.3 mmol). After the addition was complete, the mixture was stirred for an additional 20 min. at which time the reaction mixture was quenched with 20 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting yellow oil was purified by flash column chromatography eluting with 6% Et_2O/hexanes to yield alcohol **3.127** (1.1230g, 84%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.97-5.80 (m, 1H), 5.17 (m, 1H), 5.13 (m, 1H), 3.50 (ddd, J_1 = 2.3, J_2 = 4.0, J_3 = 10.7, 1H), 2.41-1.96 (m, 4H), 1.86 (dd, J_1 = 1.2, J_2 = 3.9 Hz, 1H), 1.80 (t, J = 2.6 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 136.6, 117.9, 77.0, 76.9, 37.8, 36.5, 29.7, 23.9, 22.7, 3.7. IR (neat): 3466, 2966, 2921, 1468, 1434, 1387, 1062, 994 cm^{-1}. HRMS(CI): calcd for $C_{11}H_{19}O$ (MH^+) 167.1436, obsd 167.1433.



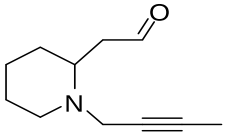
Preparation of (1-allyl-2,2-dimethyl-hex-4-ynyloxymethyl)-benzene (3.108). To a stirring suspension of KH (603.0 mg, 4.51 mmol) in 25 mL THF was added alcohol **3.127** (500.0 mg, 3.00 mmol) in 5 mL THF. The resulting mixture was stirred at room temperature for 30 min. at which time benzyl bromide (771.1 mg, 4.51 mmol) was added. Stirring was continued at room temperature until starting alcohol could no longer be detected by TLC analysis (~15 h). The mixture was then quenched with a saturated NH_4OH solution (10 mL) and stirred for an additional 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash column chromatography eluting with 1% EtOAc/hexanes then 2% EtOAc/hexanes to yield **3.108** (742.9 mg, 96%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.39-7.28 (m, 5H), 5.99 (dddd, $J_1 = J_2 = 7.0$, $J_3 = 10.2$, $J_4 = 17.0$ Hz, 1H), 5.14 (m, 1H), 5.04 (dddd, $J_1 = J_2 = 1.1$, $J_3 = 2.2$, $J_4 = 10.0$ Hz, 1H), 4.68 (d, $J = 11.1$ Hz, 1H) 4.55 (d, $J = 11.1$ Hz, 1H), 3.37 (dd, $J_1 = 3.4$, $J_2 = 8.4$ Hz, 1H), 2.44-2.20 (m, 3H), 2.09 (dq, $J_1 = 2.6$, $J_2 = 16.2$ Hz, 1H), 1.82 (t, $J = 2.6$ Hz, 3H), 0.99 (s, 6H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 139.2, 137.3, 128.4, 128.7, 127.5, 116.4, 85.1, 77.5, 77.1, 74.4, 39.2, 35.8, 30.0, 24.1, 22.9, 3.7. IR (neat): 3070, 3032, 2967, 2920, 1497, 1077, 912 cm^{-1}. HRMS(CI): calcd for $C_{18}H_{25}O$ (MH$^+$) 257.1905, obsd 257.1906.



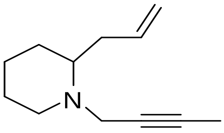
Preparation of (1-Allyl-2,2-dimethyl-hex-4-ynyloxy)-tert-butyl-dimethyl-silane (3.107). To a stirring solution of alcohol **3.127** (400.0 mg, 2.41 mmol) and 2,6-lutidine (774.8 mg, 7.23 mmol) in 24 mL CH_2Cl_2 at -78 °C was added TBSOTf (700.5 mg, 2.65 mmol). The resulting solution was then gradually warmed to room temperature and stirring was continued for an additional 15 h. The reaction mixture was poured into 20 mL H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash column chromatography eluting with hexanes to yield **3.107** (561.4 mg, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.90 (m, 1H), 5.07-4.96 (m, 2H), 3.58 (dd, $J_1 = 4.5$, $J_2 = 5.9$ Hz, 1H), 2.38 (m, 1H), 2.22-1.98 (m, 3H), 1.81 (t, $J = 2.61$ Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 137.6, 116.0, 77.8, 77.5, 77.4, 39.4, 38.3, 30.0, 26.3, 24.1, 22.9, 18.5, 3.7, -3.2, -4.2. IR (neat): 2958, 2859, 1469, 1433, 1387, 1254, 1086, 1004, 910, 835 cm^{-1}. HRMS(CI): calcd for $C_{17}H_{33}OSi$ (MH^+) 281.2301, obsd 281.2291.



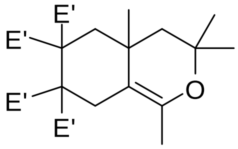
Preparation of 2-(1-(but-2-ynyl)piperidin-2-yl)ethanol (3.128). To a stirring solution of 2-piperadineethanol (2.153 g, 15 mmol) in 75 mL THF was added Hünig's base (3.92 mL, 22.5 mmol) and 1-bromo-2-butyne (1.5 mL 16.5 mmol). The resulting solution was stirred at room temperature for 24 h and then quenched by the addition of 20 mL of a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude oil was purified by flash column chromatography eluting with 10% MeOH/CH_2Cl_2 to yield alcohol **3.128** (1.4411 g, 53%) as a yellow/brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.97 (ddd, J_1 = 4.5, J_2 = 9.6, J_3 = 11.0 Hz, 1H), 3.84 (dq, J_1 = 2.3, J_2 = 17.2 Hz, 1H), 3.70 (ddd, J_1 = 4.5, J_2 = 5.6, J_3 = 11.0 Hz, 1H), 3.35 (dq, J_1 = 2.3, J_2 = 17.2 Hz, 1H), 2.87 (m, 1H), 2.73 (m, 1H), 2.50 (td, J_1 = 3.6, J_2 = 11.3 Hz, 1H), 2.05 (dddd, J_1 = J_2 = 5.3, J_3 = 9.6, J_4 = 14.8 Hz, 1H), 1.85 (t, J = 2.3 Hz, 3H), 1.81-1.49 (m, 6H), 1.41-1.24 (m, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 81.9, 72.8, 60.1, 57.8, 53.1, 43.8, 32.7, 29.5, 25.3, 24.0, 3.6. IR (neat): 3375, 2933, 2858, 1445, 1332, 1051 cm^{-1}. HRMS(CI): calcd for $C_{11}H_{20}NO$ (MH^+) 182.1545, obsd 182.1550.



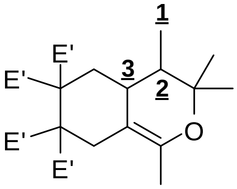
Preparation of 2-(1-(but-2-ynyl)piperidin-2-yl)acetaldehyde (3.129). To a stirring solution of $(COCl)_2$ (1.460 g, 11.5 mmol) in 65 mL CH_2Cl_2 at -78 °C was added DMSO (1.797 g, 23.0 mmol) dropwise. The resulting solution was stirred for 10 min after which time alcohol **3.128** (1.3911 g, 7.67 mmol) in 10 mL CH_2Cl_2 was added. Stirring was continued for an addition 30 min at which time triethylamine (4.2687 g, 42.2 mmol) was added. The solution was allowed to warm to room temperature and quenched by the addition of 25 mL H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL), washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by flash column chromatography eluting with 66% Et_2O/hexanes to yield aldehyde **3.129** (1.1178 g, 81%) as a yellow orange oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.84 (dd, J_1 = 2.0, J_2 = 3.4 Hz, 1H), 3.51 (dq, J_1 = 2.4, J_2 = 17.6 Hz, 1H), 3.26 (dq, J_1 = 2.4, J_2 = 17.6 Hz, 1H), 2.90-2.84 (m, 1H), 2.75 (m, 1H), 2.56 (ddd, J_1 = 2.2, J_2 = 4.1, J_3 = 16.1 Hz, 1H), 2.53-2.45 (m, 2H), 1.84 (t, J_1 = 2.4 Hz, 1H), 1.78-1.63 (m, 3H), 1.61-1.43 (m, 2H), 1.38-1.25 (m, 1H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (ppm) 202.6, 81.6, 73.2, 54.9, 53.3, 47.2, 44.1, 32.4, 26.0, 24.1, 3.7. IR (neat): 2932, 2855, 1722, 1447, 1329, 1129, 1076 cm^{-1}. HRMS(CI): calcd for $C_{11}H_{18}NO$ (MH^+) 180.1388, obsd 180.1389.



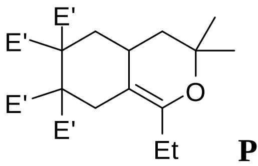
Preparation of 2-allyl-1-(but-2-ynyl)piperidine (3.110). To a stirring solution of KO^tBu (1.2532 g, 11.16 mmol) in 80 mL THF was added $[CH_2PPh_3]^+Br^-$ (4.983 g, 13.95 mmol) in a single portion. The resulting yellow mixture was stirred at room temperature for 1 h to generate the phosphorus ylid. To a stirring solution of aldehyde **3.129** (1.00 g, 5.58 mmol) in 55 mL THF was added the phosphorus ylid dropwise until a canary yellow color persisted. The mixture was quenched by the addition of 20 mL H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL), washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash column chromatography eluting with 66% Et_2O/hexanes to yield enyne **3.110** (870.5 mg, 88%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.85 (dddd, J_1 = 6.4, J_2 = 8.3, J_3 = 10.3, J_4 = 16.6 Hz, 1H), 5.08 (ddd, J_1 = 1.5, J_2 = 3.4, J_3 = 11.7 Hz, 1H), 5.05 (dd, J_1 = 1.5, J_2 = 2.9 Hz, 1H), 3.58 (dq, J_1 = 2.4, J_2 = 17.1 Hz, 1H), 3.28 (dq, J_1 = 2.4, J_2 = 17.1 Hz, 1H), 2.77 (m, 1H), 2.44 (td, J_1 = 2.9, J_2 = 11.7 Hz, 1H), 2.39-2.28 (m, 2H), 2.25-2.17 (m, 1H), 1.85 (t, J_1 = 2.4 Hz, 3H), 1.75-1.49 (m, 4H), 1.39-1.21 (m, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 135.5, 116.8, 80.8, 73.7, 58.6, 53.6, 43.6, 37.4, 31.1, 26.2, 24.5, 3.6. IR (neat): 2931, 2855, 2800, 1444, 1326, 1109, 911 cm^{-1}. HRMS(CI): calcd for $C_{12}H_{20}NO$ (MH^+) 178.1596, obsd 178.1588.



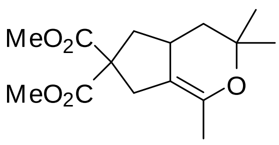
Preparation of 1,3,3,4a-tetramethyl-3,4,4a,5-tetrahydro-8H-isochromene-6,6,7,7-tetracarboxylic acid tetraethyl ester (3.102). General procedure **3.3** was used with enyne **3.80** (150 mg, 0.353 mmol), acetone (82.1 mg, 0.707 mmol), 3Å molecular sieves (53.0 mg, 150 mg/mmol enyne), $Ni(COD)_2$ (9.7 mg, 0.035 mmol), IPr (20.6 mg, 0.0530 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes then 12% EtOAc/hexanes to yield dihydropyran **3.102** (153.6 mg, 90%) as a colorless solid. Crystals suitable for X-ray analysis were obtained by dissolving the dihydropyran in hexanes and allowing the hexanes to evaporate slowly in air at room temperature. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.32-4.03 (m, 8H), 2.93 (d, J = 15.6 Hz, 1H), 2.83 (d, *J* = 15.2 Hz, 1H), 2.54 (d, *J* = 13.7 Hz, 1H), 2.33 (d, *J* = 13.7 Hz, 1H), 1.72-1.66 (m, 4H), 1.61-1.56 (m, 1H), 1.32-1.21 (m, 18H), 1.05 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 170.6, 170.4, 168.8, 143.9, 104.2, 72.7, 61.9, 61.7, 61.5, 61.3, 59.5, 59.2, 49.8, 44.6, 31.6, 30.8, 29.5, 27.4, 25.3, 17.1, 14.0, 13.9. IR (neat): 2981, 2936, 1741, 1678, 1448, 1369, 1265, 1164, 1066, 1036 cm^{-1}. HRMS(CI): calcd for $C_{25}H_{39}O_9$ (MH^+) 483.2594, obsd 483.2593**.**



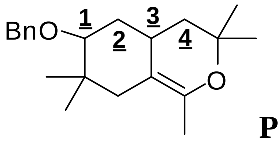
Preparation of 1,3,3,4-tetramethyl-3,4,4a,5-tetrahydro-8H-isochromene-6,6,7,7-tetracarboxylic acid tetraethyl ester (3.103). General procedure **3.3** was used with enyne **3.77** (150 mg, 0.353 mmol), acetone (205 mg, 3.54 mmol), 3Å molecular sieves (53.0 mg, 150 mg/mmol enyne), $Ni(COD)_2$ (9.7 mg, 0.035 mmol), IPr (20.6 mg, 0.0530 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 8% EtOAc/hexanes, then 10% EtOAc/hexanes, then 12% EtOAc/hexanes to yield dihydropyran **3.103** (136.3 mg, 80%) as a sticky, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.28-4.11 (m, 8H), 3.03-2.91 (m, 2H), 2.62 (m, 1H), 2.23 (dd, J_1 = J_2 = 13.4 Hz, 1H), 2.08 (dd, J_1 = 5.1, J_2 = 13.5 Hz , 1H), 1.71 (s, 3H), 1.62 (quint, *J* = 6.8 Hz 1H), 1.31-1.23 (m, 12H), 1.22 (s, 3H), 1.19 (s, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 171.1, 171.0, 169.7, 169.3, 143.4, 100.3, 76.1, 61.7, 61.6, 61.5, 59.9, 58.9, 38.4, 32.1, 31.3, 31.0, 26.1, 25.2, 16.7, 14.2, 14.1, 14.0, 10.6. IR (neat): 2982, 2938, 1735, 1679, 1447, 1369, 1261, 1089 cm^{-1}. HRMS(CI): calcd for $C_{25}H_{39}O_9$ (MH^+) 483.2594, obsd 483.2584. COSY summary, the following pertinent cross-peaks were observed: H(1) with H(2), H(2) with H(3) and H(1), H(3) with H(2). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(1).



Preparation of 1-ethyl-3,3-dimethyl-3,4,4a,5-tetrahydro-8H-isochromene-6,6,7,7-tetracarboxylic acid tetraethyl ester (3.104). General procedure **3.3** was used with enyne **3.59** (150 mg, 0.353 mmol), acetone (41.1 mg, 0.707 mmol), 3Å molecular sieves (53.0 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (9.7 mg, 0.035 mmol), IPr (20.6 mg, 0.0530 mmol) and 3.53 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10% EtOAc/hexanes, then 12% EtOAc/hexanes to yield dihydropyran **3.104** (154.1 mg, 90%) as a sticky, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 4.28-4.08 (m, 8H), 3.05-2.95 (m, 2H), 2.52 (m, 1H), 2.34 (dd, J_1 = 7.3, J_2 = 14.2 Hz, 1H), 2.29 (dd, J_1 = 5.4, J_2 = 14.2 Hz , 1H), 1.85 (m, 2H), 1.69 (dd, J_1 = 6.3, J_2 = 13.2 1H), 1.31-1.22 (m, 16H), 1.11 (s, 3H), 0.96 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 171.0, 169.7, 169.1, 149.3, 100.2, 72.7, 61.7, 61.4, 60.3, 58.5, 41.6, 35.9, 31.4, 29.9, 26.8, 23.7, 23.6, 14.1, 14.0, 12.4. IR (neat): 2979, 2937, 1736, 1675, 1449, 1368, 1263, 1099, 1041 cm^{-1}. HRMS(CI): calcd for $C_{25}H_{39}O_9$ (MH$^+$) 483.2594, obsd 483.2582.

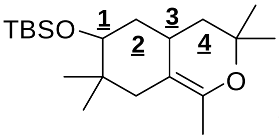


Preparation of 1,3,3-trimethyl - 3, 4, 4a, 5 – tetrahydro - 7H – cyclopenta[c]pyran-6,6-dicarboxylic acid dimethyl ester (3.105). General procedure **3.3** was used with enyne **2.65** (150 mg, 0.669 mmol), acetone (234 mg, 4.01 mmol), 3Å molecular sieves (100 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (18.4 mg, 0.0669 mmol), IPr (40.0 mg, 0.100 mmol) and 6.69 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 5% EtOAc/hexanes to yield dihydropyran **3.105** (143.1 mg, 76%) as a colorless solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 3.76 (s, 3H), 3.73 (s, 3H), 2.99 (d, J = 16.5 Hz, 1H), 2.89 (d, J = 16.2 Hz, 1H), 2.56 (dd, J_1 = 6.4, J_2 = 12.2 Hz, 1H), 2.44 (m, 1H), 1.84 (dd, J_1 = 5.6, J_2 = 12.9 Hz, 1H), 1.71 (brs, 3H), 1.64 (dd, J_1 = J_2 = 12.0 Hz, 1H), 1.29 (s, 3H), 1.15-1.11 (m, 4H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 173.0, 172.7, 142.0, 106.3, 73.9, 59.5, 52.9, 52.8, 41.3, 39.4, 35.9, 33.9, 30.1, 24.8, 17.2. IR (neat): 2973, 2928, 1733, 1702, 1434, 1263, 1154, 1062 cm^{-1}. HRMS(CI): calcd for $C_{15}H_{23}O_5$ (MH$^+$) 283.1546, obsd 283.1534.

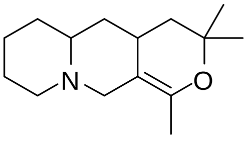


Preparation of 6-Benzyloxy-1,3,3,7,7-pentamethyl-4,4a,5,6,7,8-hexahydro-3H-isochromene (3.109). General procedure **3.3** was used with enyne **3.108** (100 mg, 0.390 mmol), acetone (45.3 mg, 0.780 mmol), 3Å molecular sieves (58.5 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (10.7 mg, 0.039 mmol), IPr (22.7 mg, 0.0585 mmol) and 3.9 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 2% EtOAc/hexanes to yield dihydropyran **3.109** as a 3:1 (syn:anti) mixture of diastereomers (106.5 mg, 87%) as an off-white solid. Analytically pure samples of each diastereomer were obtained by flash column chromatography eluting with 10% CH$_2$Cl$_2$ /hexanes. Major diastereomer. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.43-7.27 (m, 5H), 4.69 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 3.15 (dd, J_1 = 3.9, J_2 = 11.7 Hz, 1H), 2.14 (d, J = 13.7 Hz, 1H), 2.02 (m, *2*H), 1.74 (m, 5H), 1.43 (dd, J_1 = 11.0, J_2 = 13.0 Hz, 1H), 1.30 (s, 3H), 1.15 (s, 3H), 1.14 (m, 1H), 1.08 (s, 3H), 0.87 (s, 3H). ^{13}C

$\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 142.4, 139.6, 128.4, 127.6, 127.5, 104.7, 84.4, 72.8, 71.5, 42.3, 42.0, 36.8, 34.4, 30.7, 30.0, 28.8, 23.7, 18.8, 16.7. IR (neat): 2920, 2863, 1677, 1094, 1451, 1378, 1094 cm^{-1}. HRMS(CI): calcd for $C_{21}H_{31}O_2$ (MH^+) 315.2324, obsd 315.2331. COSY summary; the following pertinent cross-peaks were observed: H(1) with H(2); H(2) with H(1) and H(3); H(3) with H(2) and H(4); and H(4) with H(3). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed enhancement of H(3); irradiation of H(3) showed enhancement of H(1). Minor diastereomer. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.39-7.24 (m, 5H), 4.65 (d, J = 12.2 Hz, 1H), 4.43 (d, J = 12.2 Hz, 1H), 3.13 (brs, 1H), 2.32-2.22 (m, 1H), 2.18 (d, J = 13.7 Hz, 1H), 1.94 (ddd, J_1 = 3.4, J_2 = 4.8, J_3 = 14.1 Hz, 1H), 1.85 (d, J = 13.7, 1H), 1.70 (brs, 3H), 1.66 (dd, J_1 = 6.8, J_2 = 13.2 Hz, 1H), 1.34-1.20 (m, 5H), 1.11 (s, 3H), 1.03 (s, 3H), 0.81 (s, 3H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 141.8, 139.8, 128.4, 127.6, 127.4, 105.7, 82.5, 72.7, 71.3, 42.6, 36.3, 32.7, 30.1, 27.7, 25.7, 25.5, 23.7, 16.6.COSY summary; the following pertinent cross-peaks were observed: H(1) with H(2); H(2) with H(1) and H(3); H(3) with H(2) and H(4); and H(4) with H(3). NOE summary; the following pertinent enhancements were observed: irradiation of H(1) showed no enhancement of H(3); irradiation of H(3) showed no enhancement of H(1).



Preparation of *tert*-butyl-dimethyl-(1,3,3,7,7-pentamethyl-4,4a,5,6,7,8-hexahydro-3H-isochromen-6-yloxy)-silane (3.107). General procedure **3.3** was used with enyne **3.106** (120 mg, 0.4278 mmol), acetone (49.7 mg, 0.8556 mmol), 3Å molecular sieves (64.2 mg, 150 mg/mmol enyne), $Ni(COD)_2$ (11.8 mg, 0.04278 mmol), IPr (24.9 mg, 0.06417 mmol) and 4.3 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 2% EtOAc/hexanes to yield dihydropyran **3.107** as a 3:1 (syn:anti) mixture of diastereomers (117.1 mg, 81%) as a colorless oil. ^{1}H NMR (asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$): δ (ppm) 3.42* (m, 1H), 3.36 (dd, J_1 = 4.4, J_2 = 11.4 Hz, 1H), 2.32* (m, 1H), 2.15* (d, J = 14.1 Hz, 1H), 2.10 (d, J = 14.1 Hz, 1H), 2.01 (m, 1H), 1.78* (d, J = 13.7 Hz, 1H), 1.71 (brs, 3H), 1.69-1.64 (m, 3H), 1.55* (brs, 3H), 1.37 (dd, J_1 = 11.2, J_2 = 13.2 Hz, 1H), 1.27 (s, 3H), 1.14 (m, 1H), 1.12 (s, 3H), 0.94 (s, 3H), 0.92* (s, 3H), 0.92* (s, 9H), 0.90 (s, 9H), 0.79* (s, 3H), 0.75 (s, 3H), 0.08* (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C {^{1}H} NMR (asterisk denotes minor diastereomer peaks, 125 MHz, $CDCl_3$): δ (ppm) 142.2, 141.5*, 106.0*, 104.8*, 77.4, 75.6*, 72.8, 72.6*, 42.5*, 42.4, 41.5, 39.0, 37.7*, 37.1, 36.6*, 35.6*, 30.7, 30.1*, 30.0, 29.2, 28.2*, 26.1*, 26.1, 25.3*, 24.9*, 23.7, 23.7*, 18.4*, 18.3, 18.0, 16.7, 16.6*, 1.3*, -3.7, -4.1*, -4.7*. IR (neat): 2934, 2858, 1681, 1467, 1380, 1256, 1098, 838 cm^{-1}. HRMS(CI): calcd for $C_{20}H_{39}O_2Si$ (MH^+) 339.2680, obsd 339.2719. COSY summary (major diastereomer); the following pertinent cross-peaks were observed: H(1) with H(2); H(2) with H(1) and H(3); H(3) with H(2) and H(4); and H(4) with H(3). NOE summary (major diastereomer); the following pertinent enhancements were observed: irradiation of H(1) showed enhancement of H(3); irradiation of H(3) showed enhancement of H(1).



Preparation 1,3,3-trimethyl-4,4a,5,6,7,8,10,10a-octahydro-3H,9H-2-oxa-8a-aza-anthracene (3.111). General procedure **3.3** was used with enyne **3.110** (75 mg, 0.423 mmol), acetone (245.7 mg, 4.23 mmol), 3Å molecular sieves (63.5 mg, 150 mg/mmol enyne), Ni(COD)$_2$ (11.6 mg, 0.0423 mmol), IPr (24.7 mg, 0.06345 mmol) and 4.2 mL toluene. The reaction mixture was purified by flash column chromatography eluting with 10 % MeOH/ 90% CH_2Cl_2/ 0.1 % NH_3 then MeOH to yield dihydropyran **3.111** as a single diastereomer (79.2 mg, 80%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.38 (d, *J* = 12.2 Hz, 1H), 2.83 (brd, *J* = 11.1 Hz, 1H), 2.45 (brd, *J* = 12.7, 1H), 2.08 (m, 2H), 1.79-1.51 (m, 10H), 1.362-1.20 (m, 6H), 1.10 (s, 3H), 0.95 (q, *J* = 12.7 Hz, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 142.5, 104.2, 72.8, 62.1, 56.9, 56.4, 41.8, 40.7, 33.2, 30.1, 25.9, 24.7, 23.8, 16.8. IR (neat): 2928, 2853, 2728, 1685, 1445, 1268, 1167, 1110 cm^{-1}. HRMS(CI): calcd for $C_{15}H_{26}NO$ (MH$^+$) 236.2014, obsd 236.2027.

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CHAPTER 4

AN IN SITU APPROACH FOR NICKEL CATALYZED CYCLOADDITIONS

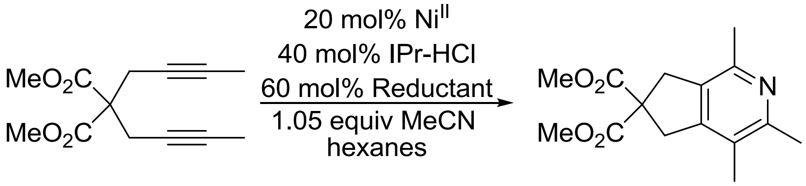
Introduction

Aside from the CO_2,[1] aldehydes,[2] and ketones,[2] our group has also effectively utilized isocyanates[3] and nitriles[4] in the [2+2+2] cycloaddition with diynes to generate pyridones and pyridines respectively. Although the conditions are extremely mild and the yields of the reactions are typically high, one drawback is the use of air-sensitive compounds such as $Ni(COD)_2$ and the free NHC ligands. Several other groups using Ni/carbene catalysts have found that the active Ni(0)/NHC species can be generated in situ from air-stable Ni(II) salts and imidalzolium salts. Thus, in an effort to expand the applicability and convenience of this chemistry, we have explored the use of air-stable, readily available precursors that produce the active Ni(0)/NHC catalyst in situ.

Results and Discussion

The standard reaction of a dimethyl 2,2-*di*-but-2-ynylmalonate (**2.23**) and acetonitrile was chosen as a model cycloaddition to evaluate reaction parameters (Table 4.1).

Table 4.1. Evaluation of Ni(II) salts and reductants in the Ni-catalyzed cycloaddition of diyne **2.23** and acetonitrile.



entry	Ni^{II}	reductant	conversion(%)[a]	yield(%)[a]
1[b]	$NiCl_2$	Zn, Na_2CO_3	22	0
2	$NiCl_2$	*n*-BuLi	40	0
3	$NiCl_2$	DIBAL	29	0
4[b]	$Ni(Cp)_2$	Zn, Na_2CO_3	9	0
5	$Ni(Cp)_2$	*n*-BuLi	0	0
6	$Ni(Cp)_2$	DIBAL	0	0
7[b]	$Ni(acac)_2$	Zn, Na_2CO_3	27	0
8	$Ni(acac)_2$	*n*-BuLi	100	97
9	$Ni(acac)_2$	DIBAL	0	0

[a]Determined by GC analysis using napthalene as an internal standard. [b]20 mol% Zn, 40 mol% Na_2CO_3 were used.

Our initial screen centered around finding a suitable combination of Ni(II) salt and reductant that would not only generate the Ni(0), but would also simultaneously deprotonate the imidazolium salt under reaction conditions.[5] Accordingly, we evaluated several Ni(II) salts in conjunction with reasonable reductants (Table 4.1). Both $NiCl_2$ and $NiCp_2$ have been used to provide Ni/HC compounds in situ to catalyze coupling reactions. However, under our reaction conditions, pyridines were observed only when $Ni(acac)_2$ was used as a nickel source. Only *n*-BuLi served as both an effective base and reductant to provide a quantitative yield of the pyridine (entry 8). Moreover, catalyst formation and the reaction were performed at room temperature eliminating the need for a cryogen.

During our earlier investigations involving the cycloaddition of carbon dioxide, we found the active Ni(IPr)$_n$ catalyst could be generated by reacting Ni(COD)$_2$ with a solution of IPr·BF$_4$ and KO-*t*-Bu. Interestingly, IPr·Cl was ineffective, and no pyrone product was observed. In contrast, when Ni(acac)$_2$ and *n*-BuLi are employed, both IPr salt precursors could be used without compromising heterocycle yields (entries 1 and 2, Table 4.2). No noticeable difference in yield was observed with the saturated NHC ligand, SIPr·HCl (entry 3). In the absence of a NHC salt, no product was observed as expected (entry 4). A greater dependence on solvent was seen and may be due to the reactivity of the *n*-BuLi in various solvents. Cycloaddition proceeded smoothly in hexanes but was inhibited in other functionalized hydrocarbon solvents such as THF.

The next challenge was to lower Ni(acac)$_2$ loadings as typical cycloaddition reactions required only 5 mol% Ni(COD)$_2$. Thus, Ni(acac)$_2$ concentrations were systematically decreased while keeping the Ni:ligand ratios (1:2) and the Ni(II):*n*-BuLi ratios constant (1:3). Cycloadditions run with catalyst loadings of 10 mol % and higher gave quantitative diyne conversions (entries 1 and 2, Table 4.3). When 5 mol % was employed, a marked decrease in pyridine yield was observed (entry 3). We surmised that the reduction of the Ni(acac)$_2$ and deprotonation of the NHC salt by the stoichiometric amounts of *n*-BuLi may not be complete. Indeed, 5 mol % Ni(acac)$_2$ adequately converted the diyne to pyridine when a small excess of *n*-BuLi (relative to Ni(acac)$_2$) was employed (entries 7 and 8). Importantly, pyridine yields did not depend on equilibration time of these catalyst precursors. Catalyst solutions of Ni(acac)$_2$, IPr·HCl, and *n*-BuLi prepared an hour in advance afforded the same yields as freshly prepared catalyst solutions.

Table 4.2. Evaluation of NHC salts.

entry	NHC salt	conversion(%)[a]	yield(%)[a]
1[b]	IPr·HBF$_4$	100	0
2	IPr·HCl	100	0
3	SIPr·HCl	100	0
4[b]	none	0	0

[a] Reaction conditions: 0.1 M diyne, 0.015 M MeCN, 20 mol% Ni(acac)$_2$, 40 mol% NHC salt, 60 mol% *n*-BuLi, hexanes, rt.
[b] Deternimed by GC analysis using napthalene as an internal standard.

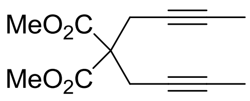
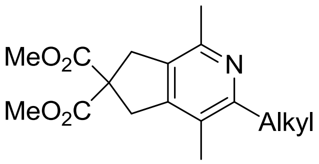
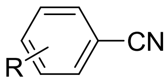
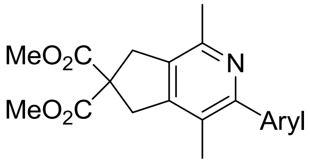
Table 4.3. Evaluation of catalyst loading and reductant concentration.

entry[a]	Ni(acac)$_2$, mol%	IPr·HCl, mol%	*n*-BuLi, mol%	conversion[b] (%)	yield[b] (%)
1	20	40	60	100	81
2	10	20	30	100	90
3	5	10	15	65	57
4	2.5	5	7.5	27	21
5	1	2	3	0	0
6	5	10	20	94	89
7	5	10	25	100	91
8	5	10	30	100	90

[a] Reaction conditions: 0.1 M diyne, 0.105 M MeCN, hexanes, rt.
[b] Determined by GC analysis using napthalene as an internal standard.

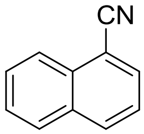
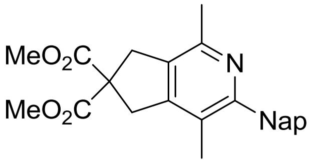
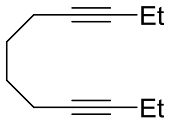
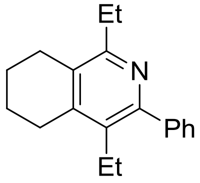
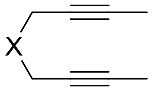
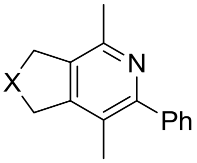
A variety of pyridines were prepared by using either of the readily available IPr·HCl or SIPr·HCl salts (Table 4.4). The in situ method converts both alkyl and aryl nitriles to their respective pyridines. Sterically hindered nitriles such as *o*-tolunitrile and *tert*-butylnitrile also reacted cleanly (entries 2 and 4 respectively). Diynes devoid of internal substitution, such as 3,9-dodecadiyne and diynes containing either an internal sulfonamide group or the analogous ether, also coupled with aryl nitriles to give the corresponding pyridines (entries 6-8). In all cases, air-stable, readily available catalyst precursors were employed and afforded pyridines in yields that were comparable to yields obtained with our previously reported Ni(COD)$_2$ and IPr system.

Table 4.4. In situ Ni-catalyzed cycloaddition of diynes and nitriles.

entry	diyne	nitrile	product, yield^{c,d}
			
1^a	**2.23**	MeCN	**4.1**, 64% (69%)
2^b	**2.23**	*t*-BuCN	**4.2**, 49% (56%)
			
3^a	**2.23**	R = H	**4.3**, 83% (86%)
4^b	**2.23**	R = *o*-Me	**4.4**, 80% (81%)

^{a}Reaction conditions: 0.1 M diyne, 0.11 M nitrile, 5 mol% Ni(acac)$_2$, 10 mol% SIPr-HCl, 25 mol% *n*-BuLi, benezene, rt. ^{b}Reaction conditions: 0.1 M diyne, 0.105 M nitrile, 5 mol% Ni(acac)$_2$, 10 mol% IPr-HCl, 25 mol% *n*-BuLi, hexanes, rt. ^{c}Isolated yield, average of two runs. ^{d}Reported yield using Ni(COD)$_2$/SIPr in parenthesis.[4]

Table 4.4 continued. In Situ Ni-Catalyzed Cycloaddition of Diynes and Nitiles.

entry	diyne	nitrile	product, yield^{c,d}
5^{b}	**2.23**		 **4.5**, 92% (91%)
6^{a}	 **2.39**	PhCN	 **4.6**, 84% (92%)
7^{b}	 X = NTs **2.63**	PhCN	 **4.7**, 75% (78%)
8^{a}	X = O **2.62**	PhCN	**4.8**, 85% (93%)

[a] Reaction conditions: 0.1 M diyne, 0.11 M nitrile, 5 mol% Ni(acac)$_2$, 10 mol% SIPr-HCl, 25 mol% *n*-BuLi, benezene, rt. [b] Reaction conditions: 0.1 M diyne, 0.105 M nitrile, 5 mol% Ni(acac)$_2$, 10 mol% IPr-HCl, 25 mol% *n*-BuLi, hexanes, rt. [c] Isolated yield, average of two runs. [d] Reported yield using Ni(COD)$_2$/SIPr in parenthesis.[4]

In an effort to expand this method, other heteroatom-containing substrates were explored as cycloaddition partners. As shown in Figure 4.1, carbon dioxide and diyne **2.23** could be converted to the expected pyrone **2.24** in 57% yield although a higher catalyst loading was required.

Reactions involving carbonyls (both aldehydes and ketones) and isocyanates were less successful. The reaction between diyne **2.37** and benzaldehyde did result in the formation of dienone **3.36** (Figure 4.2); however, low yields and multiple side products were obtained. The addition of a Lewis acid (e.g., Ti(O*i*Pr)$_4$)[6] that could possibly enhance oxidative coupling had no effect on the transformation. Furthermore, reactions involving isocyanates afforded no desired pyridine heterocycles.

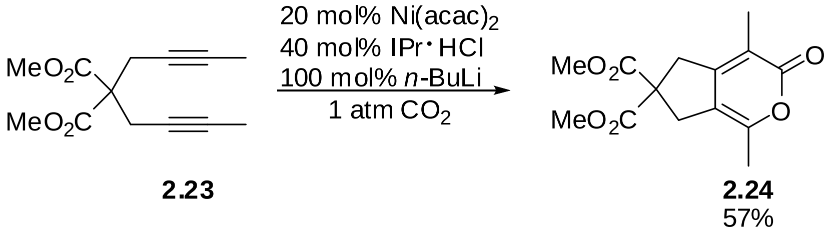

MeO2C
MeO2C
20 mol% Ni(acac)2
40 mol% IPr•HCl
100 mol% n-BuLi
1 atm CO2
MeO2C
MeO2C
O
O
2.23
2.24
57%

Figure 4.1. In situ Ni-catalyzed cylcoaddition of diyne **2.23** and CO$_2$.

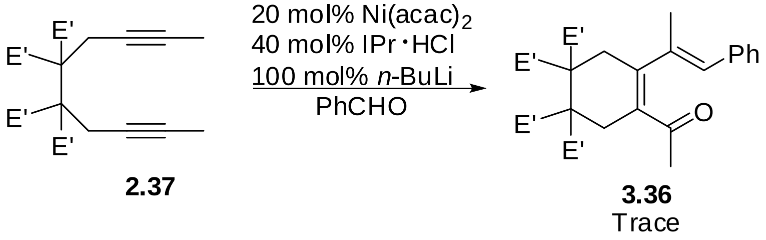

E'
E'
E'
E'
20 mol% Ni(acac)2
40 mol% IPr•HCl
100 mol% n-BuLi
PhCHO
E'
E'
E'
E'
Ph
O
2.37
3.36
Trace

Figure 4.2. In Situ Ni-catalyzed cycloaddition of diyne **2.37** and benzaldehyde.

Conclusion

The combination of Ni(acac)$_2$, NHC salt, and *n*-BuLi generates an NHC-ligated Ni(0) catalyst in situ for the cycloaddition of diynes and nitriles. *N*-BuLi serves as both a base, which deprotonates the NHC salt, and a reductant, which converts the Ni(II) to the active Ni(0) catalyst. Pyridine yields were comparable to those obtained when using the standard Ni(COD)$_2$/NHC catalyst system. Thus, pyridines can be conveniently prepared at room temperature from inexpensive, air-stable, commercially available starting materials without requiring a drybox or special Schlenk equipment.

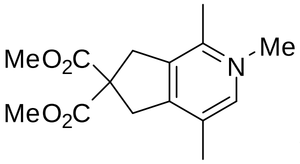
Experimental Section

All reactions were conducted under an atmosphere of N$_2$. Toluene and hexanes were dried over neutral alumina under N$_2$ using a Grubbs type solvent purification system. Ni(acac)$_2$ and *n*-BuLi (2.5 M in hexanes) were purchased from Aldrich Chemical Company and were used without further purification. IPr·HCl and SIPr·HCl were synthesized according to the procedure reported by Herrmann[7]. Anhydrous acetonitrile was purchased from the Acros chemical company. *o*-Tolunitrile and benzonitrile were purchased from the Aldrich Chemical Company and were distilled from CaH$_2$ prior to use. Diynes 2,2-di-but-2-ynyl-malonic acid dimethyl ester (**2.23**)[8], *N*,*N*-di-2-butynyl-*p*-toluenesulfonamide (**2.63**)[9], and 1-but-2-ynyloxy-but-2-yne (**2.62**)[10], were prepared according to literature procedures. 3,9-Dodecadiyne was purchased from GFS.

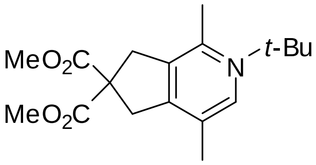
^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 75 MHz, respectively unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, t, q and m stand for singlet, doublet, triplet, quartet, and multiplet in that order. All ^{13}C NMR spectra were proton decoupled. Gas Chromatography was performed on an Alient 6890 gas chromatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min; final temperature: 300°C held for 7 minutes; detector temperature: 250°C.

Synthetic Procedures and Analyses

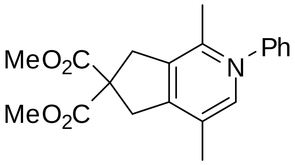
General procedure for the [2+2+2] cycloaddition of diynes and nitriles. Method (a): To a stirring suspension of $Ni(acac)_2$ and IPr·HCl in hexanes was added *n*-BuLi (2.5 M in hexanes) dropwise at room temperature. The resulting suspension was stirred for an additional 5 min at which time a solution of diyne (~ 0.2 M in toluene) was added followed by the nitrile. The reaction mixture was stirred at room temperature until no starting diyne was detected by TLC analysis (~ 30 min.). The reaction mixture was then quenched by the addition of 5 drops of MeOH and concentrated in vacuo. The residue was purified by flash column chromatography to yield the desired pyridine. Method (b): To a stirring suspension of $Ni(acac)_2$ and SIPr·HCl in benzene was added *n*-BuLi (2.5 M in hexanes) dropwise at room temperature. The resulting suspension was stirred for an additional 5 min at which time a solution of diyne (0.3 M in benzene) was added followed by the nitrile (0.3 M in benzene). The reaction mixture was stirred at room temperature until no starting diyne was detected by TLC analysis (~ 30 min). The reaction mixture was concentrated in vacuo and residue was purified by flash column chromatography on SiO_2 to yield the desired pyridine.



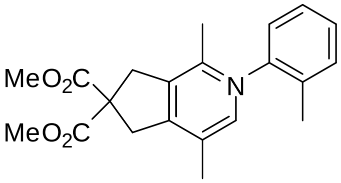
Preparation of 2,3,6-Trimethyl pyridine (4.1).[4] Method **b** of the general procedure was used with diyne **2.23** (42.5 mg, 0.18 mmol), acetonitrile (8.2 mg, 0.20 mmol), Ni(acac)$_2$ (2.3 mg, 0.009 mmol), SIPr·HCl (7.7 mg, 0.018 mmol), *n*-BuLi (18 μL, 0.045 mmol), and 0.6 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 25 % EtOAc/hexanes to yield title compound **4.1** (33.5 mg, 67%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 15.2, 21.8, 22.2, 39.1, 40.0, 53.3, 59.6, 124.7, 131.4, 148.4, 149.7, 154.9 and 172.0.



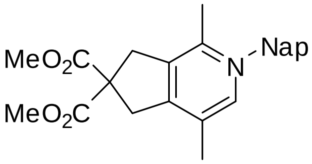
Preparation of 2-*tert*-Butyl-3,6-dimethl pyridine (4.2).[4] Method **a** of the general procedure was used with diyne **2.23** (135.0mg, 0.5741 mmol, 0.2588 M in toluene), *t*-Butyl nitrile (61.9 mg, 0.600 mmol), Ni(acac)$_2$ (7.3 mg, 0.028 mmol), IPr·HCl (24.3 mg, .0573 mmol), *n*-BuLi (57 μL, 0.14 mmol), and 3.47 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **4.2** (96.5 mg, 53%) as a pale yellow oil. ^{1}H NMR ($CDCL_3$) δ 1.40 (s, 9H), 2.35 (s, 3H), 2.37 (s, 3H), 3.52 (s, 2H), 3.53 (s, 2H), 3.53 (s, 2H) and 3.77 (s, 6H); 13C NMR (CDCl3) δ 17.5, 22.1, 30.4, 38.6, 39.1, 40.5, 53.3, 59.5, 124.3, 130.8, 148.3, 150.0, 1603.5 and 172.3.



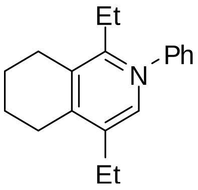
Preparation of 3,6-Dimethyl-2-phenyl pyridine (4.3).[4] Method **b** of the general procedure was used with diyne **2.23** (34.8 mg, 0.15 mmol), benzonitrile (16.5 mg, 0.165 mmol), Ni(acac)$_2$ (2.1 mg, 0.008mmol), SIPr·HCl (6.8 mg, 0.016 mmol), *n*-BuLi (16 µL, 0.04 mmol), and 0.5 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 50% EtOAc/hexanes to yield title compound **4.3** (42.7 mg, 85%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 2.19 (s, 3H), 2.48 (s, 3H), 3.60 (s, 2H), 3.63 (s, 2H), 3.80 (s, 6H), and 7.34-7.43 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 16.3, 22.0, 39.3, 40.3, 53.3, 59.5, 124.3, 127.7, 128.2, 129.2, 132.5, 140.8, 149.4, 150.5, 157.1 and 172.0.



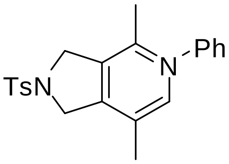
Preparation of 3,6-Dimethyl-2-o-tolyl pyridine (4.4).[4] Method **a** of the general procedure was used with diyne **2.23** (135.0 mg, 0.5741 mmol, 0.2551 M in toluene), *o*-tolunitrile (70.3 mg, 0.600 mmol), Ni(acac)$_2$ (7.3 mg, 0.028 mmol), IPr·HCl (24.3 mg, 0.0573 mmol), *n*-BuLi (57 µL, 0.14 mmol), and 3.47 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **4.4** (161.5 mg, 80%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 1.98 (s,3H), 2.08 (s,3H), 2.48 (s, 3H), 3.62 (s, 2H), 3.66 (s, 2H), 3.82 (s, 6H) and 7.24-7-7.28 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 15.4, 19.7, 22.0, 39.4, 40.2, 53.4, 59.5, 124.9, 125.8, 127.8, 129.0, 130.3, 132.5, 135.9, 140.4, 148.9, 150.4, 157.7 and 172.1.



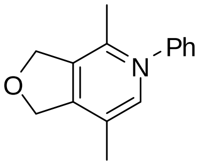
Preparation of 3,6-Dimethyl-2-napthalene-1-yl pyridine (4.5).[4] Method **a** of the general procedure was used with diyne **2.23** (135.0 mg, 0.5741 mmol, 0.2563 M in toluene), 1-cyanonapthalene (91.9 mg, 0.600 mmol, 1.3 M in toluene), Ni(acac)$_2$ (7.3 mg, 0.028 mmol), IPr·HCl (24.3 mg, 0.0573 mmol), *n*-BuLi (57 μL, 0.14 mmol), and 3.05 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **4.5** (206.8 mg, 92%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 1.94 (s, 3H), 2.51 (s, 3H), 3.66 (s, 2H), 3.72 (s, 2H), 3.84 (s, 6H), 7.39-7.56 (m, 5H), 7.86-7.90 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 15.8, 22.1, 39.5, 40.3, 53.5, 59.5, 125.2, 125.8, 125.9, 126.3, 126.8, 128.2, 128.4, 131.9, 132.9, 133.9, 138.6, 149.0, 150.7, 156.6, and 172.2.



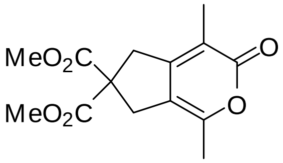
Preparation of 1,4-Diethyl-3-phenyl-5,6,7,8-tetrahydro isoquinoline (4.6).[4] Method **b** of the general procedure was used with 3,9-dodecadiyne **2.39** (30.6 mg, 0.19 mmol), benzonitrile (21.6 mg, 0.21 mmol), Ni(acac)$_2$ (6.3 mg, 0.025 mmol), SIPr·HCl (8.2 mg, 0.019 mmol), *n*-BuLi (20 μL, 0.05 mmol), and 0.6 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **4.6** (43.4 mg, 87%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 1.02 (t, 3H, J=7 Hz), 1.27 (t, 3H, J=7 Hz), 1.85 (m, 4H), 2.72 (q, 4H, J=7 Hz), 2.80 (m, 4H) and 7.37-7.43 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 13.5, 14.4, 21.9, 22.7, 26.1, 26.6, 28.4, 127.3, 128.2, 128.9, 129.7, 132.6, 142.3, 144.7, 155.6, and 158.4.



Preparation of 3,6-Dimethyl-2-o-tolyl pyridine (4.7).[4] Method **a** of the general procedure was used with *N*,*N*-di-2-butynyl-*p*-toluenesulfonamide **2.63** (135.0 mg, 0.4908 mmol, 0.2226 M in toluene), benzonitrile (53.1 mg, 0.515 mmol), Ni(acac)$_2$ (6.3 mg, 0.025 mmol), IPr·HCl (20.9 mg, 0.0491 mmol), *n*-BuLi (49 μL, 0.12 mmol), and 2.65 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **4.7** (140.9 mg, 76%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 2.15 (s, 3H), 2.44 (s, 6H), 4.63 (s, 2H), 4.66 (s, 2H), 7.34-7.43 (m, 7H) and 7.83 (d, 2H, J=8 Hz); ^{13}C NMR (CDCl$_3$) δ 16.2, 21.8, 22.0, 53.0, 53.7, 123.1, 127.8, 128.2, 128.5, 129.2, 130.2, 133.9, 140.1, 144.2, 145.9, 149.6 and 158.1.



Preparation for 3,6-Dimethyl-2-phenyl pyridine (4.8).[4] Method **b** of the general procedure was used with 1-but-2-ynyloxy-but-2-yne **2.62** (27.1 mg, 0.22 mmol), benzonitrile (24.7 mg, 0.24 mmol), Ni(acac)$_2$ (2.8 mg, 0.011 mmol), SIPr·HCl (9.4 mg, 0.22 mmol), *n*-BuLi(22 μL, 0.055 mmol), and 0.7 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **4.8** (44.5 mg, 89%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 2.19 (s, 3H), 2.48 (s, 3H), 5.14 (s, 2H), 5.19 (s, 2H) and 7.40-7.50 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 16.4, 22.3, 73.2, 73.7, 121.9, 128.0, 128.4, 129.3, 131.8, 140.4, 149.0, and 157.7.



Preparation of 1,4-Dimethl-3-oxo-3,5-dihydro-7H-cyclopenta-pyran-6,6-dicarboxylic acid dimethyl ester (2.24).[1] To a stirring suspension of Ni(acac)$_2$ (29.0 mg, 0.0113 mmol) and IPr·HCl (96.0 mg, 0.226 mmol) in 2.38 mL hexanes was added *n*-BuLi (226 μL, 2.5 M in hexanes) dropwise at room temperature. The resulting mixture was transferred via syringe to a two-necked flask containing a stirring solution of diyne **2.23** (133.3 mg, 0.5645 mmol) in 3.04 mL toluene under a balloon of CO$_2$ at 60 °C. The reaction mixture was stirred at 60 °C until no starting diyne was observed by TLC analysis (~30 min.). The reaction mixture was then quenched by the addition of 2 drops of MeOH and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on SiO$_2$ eluting with 35% EtOAc/hexanes to yield title compound **2.24** (92 mg, 58%) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): δ 3.72 (s, 6H), 3.28 (s, 2H), 3.22 (s, 2H), 2.11 (s, 3H), 1.94 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, CDCl$_3$, ppm): δ 170.7, 164.3, 155.0, 15.18, 115.9, 115.5, 59.4, 53.2, 38.6, 35.4, 17.4, 12.7.

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CHAPTER 5

NICKEL CATALYZED ENYNE CYCLOISOMERIZATIONS

Introduction

The Alder-ene reaction, in which an olefin containing an allylic hydrogen (the “ene”) reacts with another molecule containing a л-bond (“the enophile”), has been known for several years (Figure 5.1).[1] Like the mechanistically similar Diels-Alder reaction, the Alder-ene reaction is a concerted, six electron, pericyclic reaction which results in the formation of two new σ-bonds.[2] In the overall process of the Diels-Alder reaction, two C-C π-bonds are broken in favor of the formation of the two new C-C σ-bonds. While two σ-bonds are also created in the ene reaction, one C-C π-bond and one strong C-H σ-bond must be broken. This makes the activation energy, and hence reaction temperatures, significantly higher for Alder-ene reactions relative to Diels-Alder reactions.

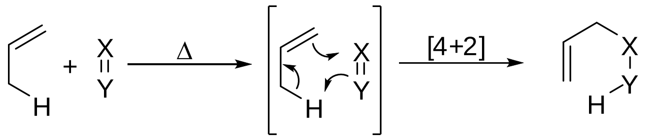


Figure 5.1. Thermal Alder-ene reaction.

Due to the higher temperatures required for the Alder-ene reaction, the scope is severely limited. One exception has been the use of carbonyls as the enophile in the presence of a Lewis acid catalyst.[3] Because of the LUMO lowering effect of the Lewis acid coordination, oxaene reactions proceed at lower temperatures and have thus received much attention in organic chemistry. Unlike carbonyls, alkynes are unable to participate in the Lewis acid promoted process and have been relativity unexplored as enophiles in the Alder-ene reaction. With the discovery that transition metals can serve as templates to catalyze this reaction, a renewed interest in alkynes as enophiles has emerged.

Previous Transition Metal Catalyzed Alder-ene Reactions

Palladium Catalyzed Cycloisomerizations

Trost and co-workers found that palladium catalysts are highly effective for the intramolecular version of the Alder-ene reaction, or enyne cycloisomerization, under mild conditions.[4] These reactions are believed to proceed via one of two mechanisms depending upon the choice of precatalyst and the reaction conditions (Figure 5.2). If a Pd(II) precatalyst is used without a reducing agent, mechanism A is favored. Alternatively, if a Pd(0) source is used as a precatalyst in the presence of a carboxylic acid, mechanism B is favored (Figure 5.2).[5]

In both mechanisms, the possibility for the formation of a 1,3-diene or a 1,4-diene is possible depending on whether H_a (1,3-diene formation) or H_b (1,4-diene formation) undergoes β-hydride elimination (Figure 5.2).

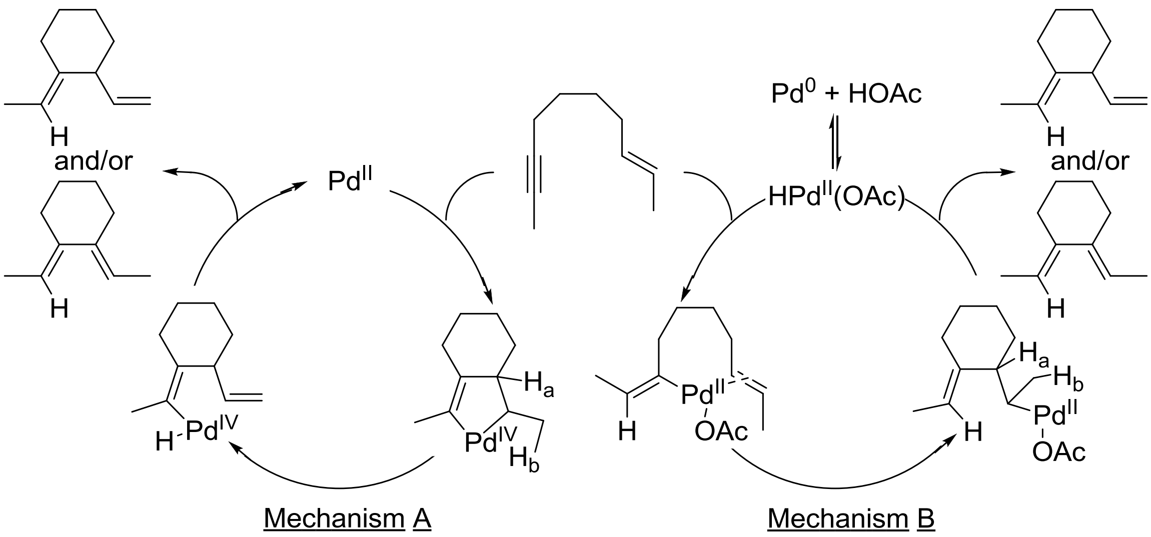
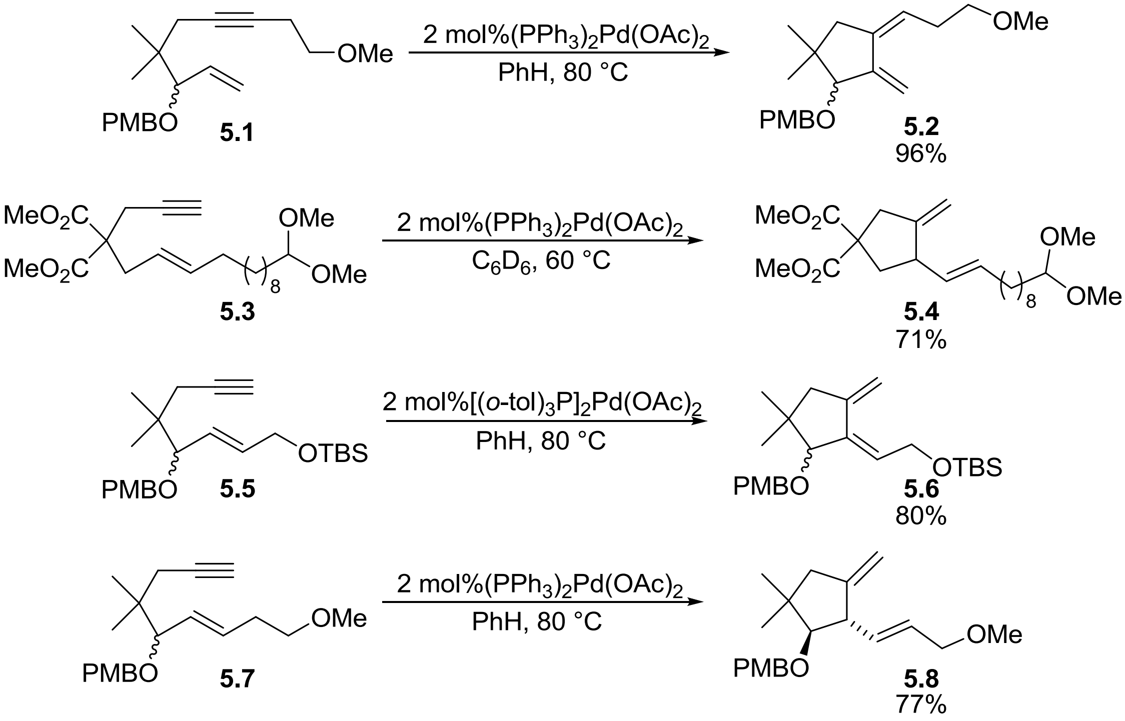


Figure 5.2. Proposed mechanisms for Pd-catalyzed enyne cycloisomerization.

Trost and co-workers found that the regiochemistry of the reaction is governed by the olefin substitution pattern, with both sets of conditions following the same general trends. For instance, when enyne **5.1** (a primary olefin) is cyclized, only the 1,3-diene **5.2** is obtained (Figure 5.3).[6]

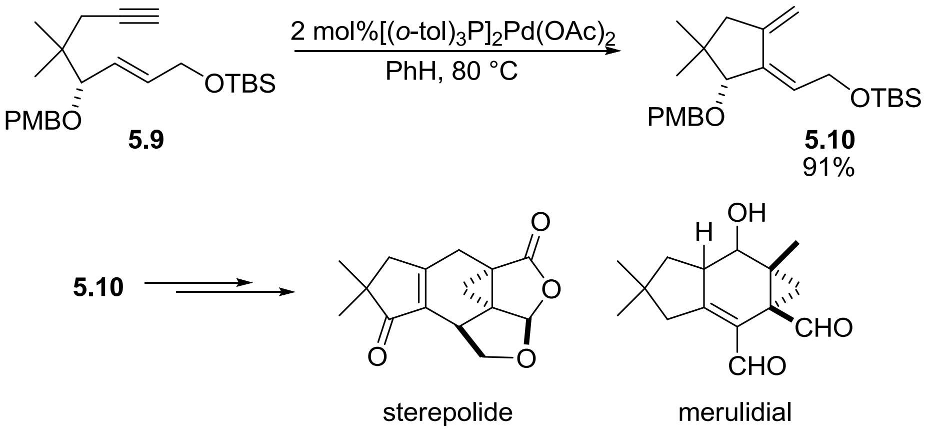
When enynes such as **5.3** (possessing an internal olefin) are cyclized, the 1,4-diene **5.4** is obtained as the major product. An exception to this selectivity has been noted with enynes possessing an oxygen at the allylic position (such as with enyne **5.5)**.[7] When the oxygen was placed in the homoallylic position **(5.7)**, the expected 1,4-diene (**5.8**) was observed.[8]

The Pd-catalyzed enyne cycloisomerization has proven useful in the synthesis of various natural products. The isolactranes sterepolide and merulidial were obtained via the elaboration of diene **5.10** (Figure 5.4). Diene **5.10** was obtained in an excellent yield from enyne **5.9** using the Pd-catalyzed protocol.[7]



OMe
PMBO
5.1
2 mol%(PPh$_3$)$_2$Pd(OAc)$_2$
PhH, 80 °C
OMe
PMBO
5.2
96%
MeO$_2$C
MeO$_2$C
OMe
OMe
8
5.3
2 mol%(PPh$_3$)$_2$Pd(OAc)$_2$
C$_6$D$_6$, 60 °C
MeO$_2$C
MeO$_2$C
OMe
OMe
8
5.4
71%
OTBS
PMBO
5.5
2 mol%[(o-tol)$_3$P]$_2$Pd(OAc)$_2$
PhH, 80 °C
PMBO
OTBS
5.6
80%
OMe
PMBO
5.7
2 mol%(PPh$_3$)$_2$Pd(OAc)$_2$
PhH, 80 °C
OMe
PMBO
5.8
77%

Figure 5.3. Regioselectivity in Pd-catalyzed enyne isomerizations.

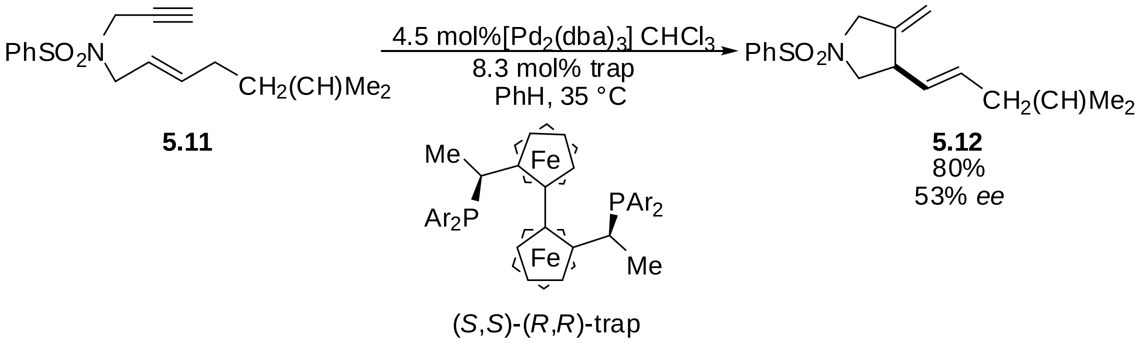


OTBS
PMBO
5.9
2 mol%[(o-tol)$_3$P]$_2$Pd(OAc)$_2$
PhH, 80 °C
PMBO
OTBS
5.10
91%
5.10
O
O
O
O
O
sterepolide
H
OH
CHO
CHO
merulidial

Figure 5.4. Synthesis of isolactranes.

Another benefit of these reactions is the generation of a new stereogenic center when1,4-dienes are formed. This provides the possibility to further develop the reaction asymmetrically. Preliminary studies by Trost focused on the Pd(0)-Pd(II) catalytic cycle. It was surmised that enantioselectivty could be induced using chiral carboxylic acids to generate the active "H-Pd-OCOR" catalyst. Initial results using Mosher's acid and binaptholic acid showed that enantioselectivity could be achieved; however the *ee's* were only modest (33% *ee*).[9]

More efficient phosphane ligands were introduced by Ito and co-workers.[10] It was reported that the trap ligand could be used in the presence of Pd(0) and HOAc to induce enantioselective cyclization of enyne **5.11** to diene **5.12** (Figure 5.5). Unfortunately, the *ee*'s were generally modest, the substrate scope was limited, and a mixture of 1,3 and 1,4-dienes were observed.



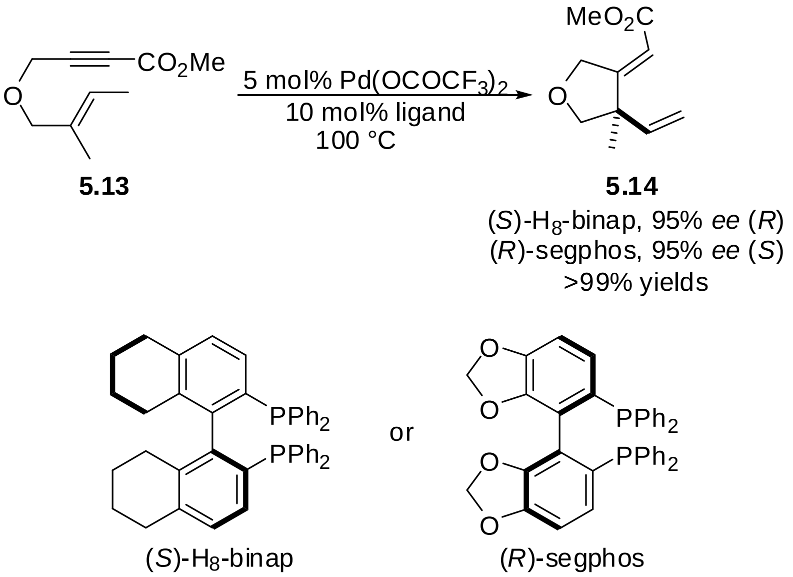
PhSO2N
CH2(CH)Me2
5.11
4.5 mol%[Pd2(dba)3] CHCl3
8.3 mol% trap
PhH, 35 °C
Me
Ar2P
Fe
Fe
PAr2
Me
(S,S)-(R,R)-trap
PhSO2N
CH2(CH)Me2
5.12
80%
53% ee

Figure 5.5. Enantioselective cyclization using chiral phosphanes.

More recently, Mikami found that both high *ee*'s and yields could be obtained using $Pd(OCOCF_3)_2$ and chiral phosphines such as segphos or H_8-binap (Figure 5.6).[11] Although the yields and *ee*'s were excellent, the scope was limited to enynes such as **5.13** with an alkyl group at the internal position of the olefin. This was most likely necessary to prevent unwanted 1,3-diene formation (via isomerization of the final product) as well as to aid in the enantioselectivity.

Titanium Catalyzed Cycloisomerization

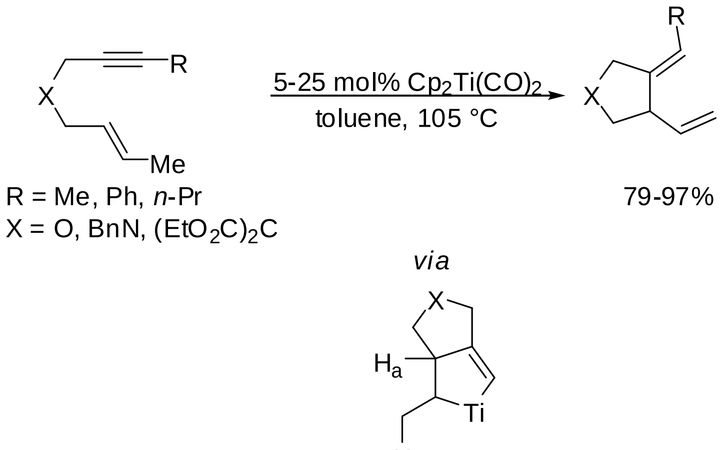
Titanium has also been reported to catalyze the cycloisomerization of 1,6-enynes to 1,4-dienes exclusively. Buchwald and co-workers found that a variety of enynes could be cyclized to generate 1,4-dienes using $Cp_2Ti(CO)_2$ (Figure 5.7).[12] The selectivity for 1,4-diene formation can be explained by the inability for the bridge head hydrogen (H_a) to adopt the necessary conformation to undergo β-hydride elimination (**5.15**, Figure 5.7).



(*S*)-H_8-binap, 95% *ee* (*R*)
(*R*)-segphos, 95% *ee* (*S*)
>99% yields

(*S*)-H_8-binap
(*R*)-segphos

Figure 5.6. Enantioselective enyne cycloisomerization with segphos and H_8-binap.



5.15

Figure 5.7. Titanium catalyzed enyne cycloisomerization.

For β-hydride elimination to occur, the dihedral angle between hydrogen-carbon bond the titanium-carbon bond must be 0°. Due to conformational constraints of the fused [5,5] titanacycle, H_a is unable achieve the necessary 0° dihedral angle. Thus, only H_b is able to undergo facile β-hydrogen elimination and only the 1,4-diene is observed.

Rhodium Catalyzed Cycloisomerization

Zhang and co-workers have reported on the efficiency of a Rh based catalyst for the cycloisomerization of enynes to 1,4-dienes.[13] The reaction tolerated a variety of functional groups, but was limited the cis substituted olefins (Figure 5.8). Additionally, only 1,4-dienes were produced because the internal hydrogen to unable to undergo β–hydride elimination. The reaction could be performed enantioselectively using chiral phosphine and phosphinite ligands (Figure 5.8).[14]

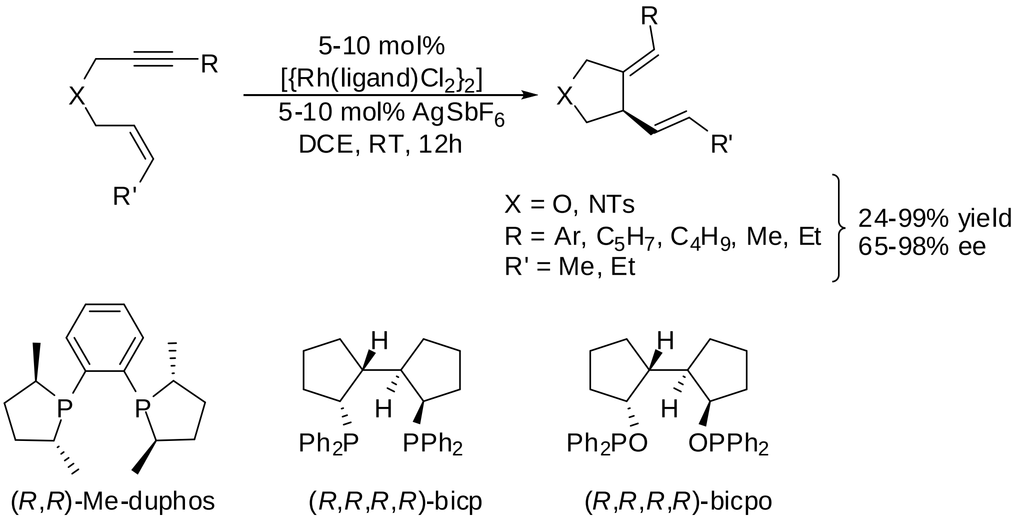
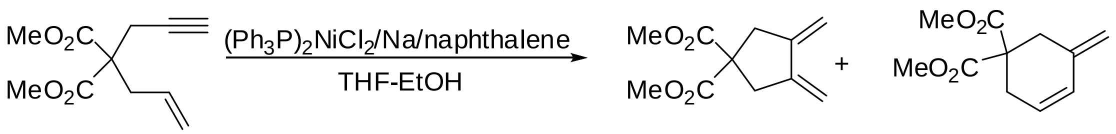

5-10 mol%
[{Rh(ligand)Cl2}2]
5-10 mol% AgSbF6
DCE, RT, 12h
X = O, NTs
R = Ar, C5H7, C4H9, Me, Et
R' = Me, Et
24-99% yield
65-98% ee
(R,R)-Me-duphos
(R,R,R,R)-bicp
(R,R,R,R)-bicpo

Figure 5.8. Rhodium catalyzed enyne cycloisomerizations.

Nickel/Chromium Catalyzed Cycloisomerization

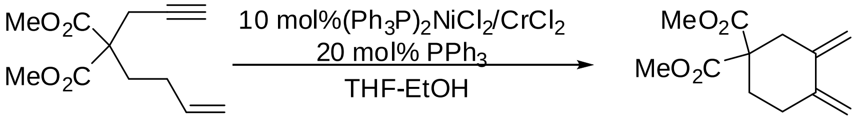
In an effort to achieve the cycloisomerization with a less expensive metal, Trost and co-workers explored the use of nickel as a catalyst.[15] Initial attempts at mimicking the Pd^{II}-Pd^{IV} system (mechanism B, Figure 5.2) with various Ni^{II} sources proved unfruitful. When $(PPh_3)_2NiCl_2$ was treated with sodium naphthalenide to generate a Ni^{I}-Ni^{III} system, however, enyne **2.65** cyclized to give a mixture of dienes **5.16** and **5.17** in a 38% yield (Figure 5.9).

Upon replacing the Na/naphthalenide with chromous chloride, another 1-electron reductant, similar results were observed. The use of excess triphenylphosphine rendered the reaction catalytic and enyne **5.18** could be cyclized in a 55% yield using 10 mol% $(PPh_3)_2NiCl_2/CrCl_2$ and 20 mol% PPh_3 (Figure 5.10).


MeO$_2$C
MeO$_2$C
(Ph$_3$P)$_2$NiCl$_2$/Na/naphthalene
THF-EtOH
MeO$_2$C
MeO$_2$C
+
MeO$_2$C
MeO$_2$C

2.65 **5.16** **5.17**

Figure 5.9. Ni-catalyzed cycloisomerization.

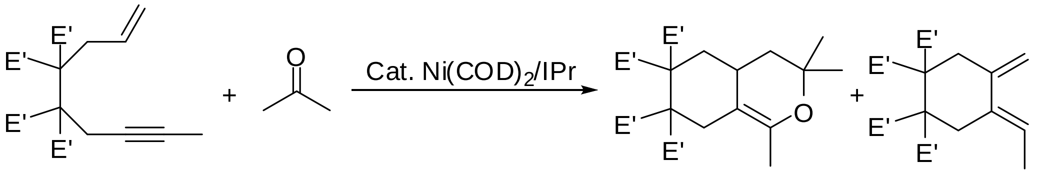

MeO$_2$C
MeO$_2$C
10 mol%(Ph$_3$P)$_2$NiCl$_2$/CrCl$_2$
20 mol% PPh$_3$
THF-EtOH
MeO$_2$C
MeO$_2$C

5.18 **5.19**
55%

Figure 5.10. Ni/Cr catalyzed cycloisomerization.

Nickel-Carbene Catalyzed Enyne Cycloisomerizations

During the study of the Ni/IPr catalyzed [2+2+2] cycloadditions of enynes and ketones, it was discovered that a major side product was 1,3-diene **5.20** (Figure 5.11). Although the diene formation could be stopped by adding molecular sieves to the reaction, we were surprised with the ability of the Ni species to catalyze the enyne isomerization. Noting the synthetic utility of 1,3-dienes, we pursued the reaction as a more economical alternative to the more commonly used Pd, Rh, and Ru catalysts for generating cyclic dienes. Although it was previously noted that Trost has explored the use of Ni as an economical alternative to the Pd catalyzed cyclization, the need to use polymer supported catalyst was a drawback. Furthermore, the use of 30 mol% CrCl$_2$ was detrimental to the overall atom economy of the reaction.

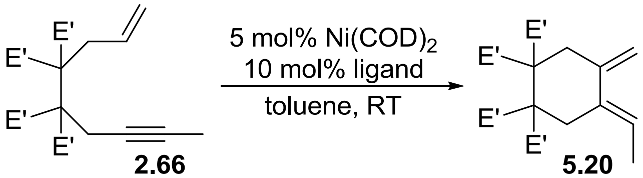

E'
E'
E'
E'
+
O
Cat. Ni(COD)2/IPr
E'
E'
E'
E'
O
+
E'
E'
E'
E'

2.66 **3.95** **5.20**

Figure 5.11. Formation of 1,3-diene **5.20**.

The reaction was investigated further by screening several different ligands to determine which ligand provided the best conversion. This ligand screen revealed that the best ligands for the reaction were N-aryl carbenes possessing an unsaturated backbone (Table 5.1, entries 1-3). The N-alkyl ligands (entries 4 and 5) and N-aryl ligands with saturated backbones (entries 6-8) that were screened failed to produce any of the 1,4-diene.

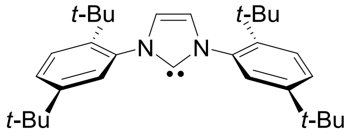
Table 5.1. Ligand screen of enyne isomerization.


E'
E'
E'
E'
5 mol% Ni(COD)2
10 mol% ligand
toluene, RT
E'
E'
E'
E'

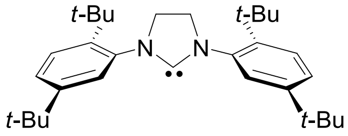
2.66 **5.20**

entry	ligand	conversion (%)	yield (%)[a]
1	IDTB	26	30
2	IPr	38	20
3	IMes	52	20
4	IAd	100	0
5	I^{t}Bu	100	0
6	SIDTB	13	0
7	SIpr	40	0
8	SIMes	52	0

[a]Uncorrected GC yield based on napthalene internal standard.


t-Bu
t-Bu
N
N
t-Bu
t-Bu

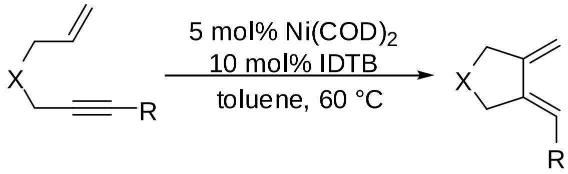
IDTB

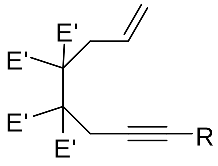
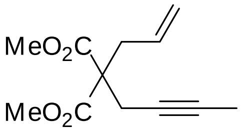

t-Bu
t-Bu
N
N
t-Bu
t-Bu

SIDTB

A cursory examination of the substrate scope under optimized conditions (5 mol% Ni(COD)$_2$, 10 mol% IDTB, toluene, 60 °C) showed that several enynes were substrates for the reaction (Table 5.2). Substituent groups of varying lengths at the terminal position of the alkyne were tolerated and produced the corresponding dienes in excellent yield (Table 5.2, entry 1). Increasing the steric encumberance of this group did not adversely affect the reaction as the ^{i}Pr substituted enyne also lead to excellent diene formation. The synthesis of five-member rings, which we have found to be problematic at times, was successful as **5.24** was obtained in good yield (entry 2).

Table 5.2. Initial substrate scope of enyne isomerization.



entry	enyne	product	yield (%)[a,b]
1	 **2.66** R = Me **3.59** R = Et **3.61** R = ^{i}Pr **3.63** R = ^{n}Pr	**5.20** **5.21** **5.22** **5.23**	90 92 99 97
2	 **2.65**	**5.24**	82

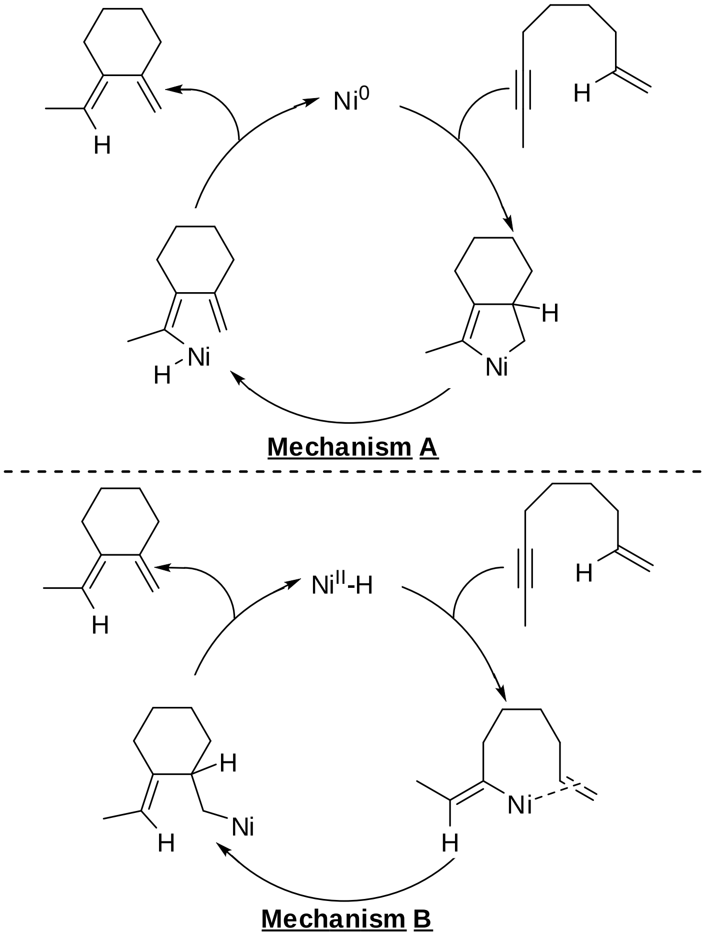
[a] Isolated yield, average of two runs. [b] >95:5 E:Z based on ^{1}H NMR analysis of crude reaction mixture.

Unfortunately, attempts at cyclizing other enynes were less fruitful. Enynes similar to **2.62** and **2.63** (Figure 2.17) possessing a heteroatom in the tether failed to react under the reaction conditions. Even more interesting was that enynes **3.57** and **3.77** (Table 3.5 and Figure 3.12, respectively) which smoothly cyclized with aldehydes, also failed to react under the standard conditions.

Thus, in an attempt to further understand and develop the reaction in a rational manner, an in-depth mechanistic study was embarked upon. Based on the previously reported Pd catalyzed process, two general mechanisms may be proposed (Figure 5.12). In mechanism A, the enyne oxidatively couples with the Ni^0 catalyst to generate a metalacyclopentene. This metalacyclopentene undergoes a β-hydride elimination, generating a vinyl nickel hydride which reductively eliminates to yield the observed 1,3-diene.

Alternatively, in mechanism B, the alkyne component of the enyne undergoes hydro-metallation with a Ni^{II}-H to generate a vinyl nickel species. The pendant olefin then inserts into the vinyl nickel bond, forming an alkyl nickel species which reductively eliminates to yield the observed 1,3-diene.

Differentiating between the two mechanisms was possible through deuterium labeling studies. When enyne **5.25** (95% deuterium incorporation) was reacted under optimized conditions, diene **5.20** was isolated in 65% yield with only 80% deuterium incorporation (Figure 5.13). The decrease in the amount of deuterium in the product relative to the substrate suggests that mechanism B maybe operating.


Ni^0
H
H
H
Ni
H
Ni
H
Ni^{II}-H
H
H
H
Ni
Ni
H

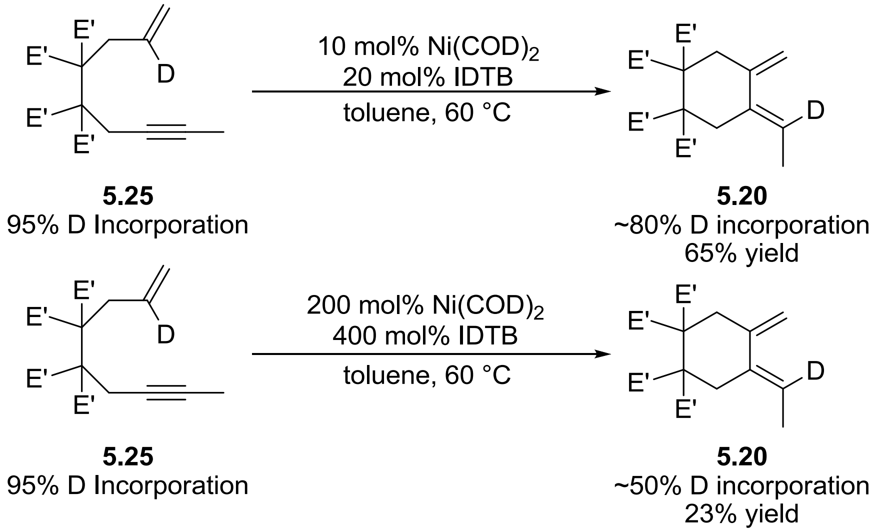
Mechanism A

Mechanism B

Figure 5.12. Potential mechanisms for Ni/IDTB cylcloisomerization of enynes.

If only mechanism A was operating, there would be no deuterium washing as mechanism A is an intramolecular process (i.e., the deuterium is shifted from the olefin to the alkyne of the same molecule). Conversely, if mechanism B is operational, the protium in the product must come from a source other than the substrate. The initial formation of the Ni-H catalyst can account for the deuterium washing observed in the product. To further confirm this, the initial Ni-H concentration was increased by increasing the catalyst loading to 200 mol% Ni(COD)$_2$ and 400 mol% IDTB (Figure 5.13). Under these conditions, further washing was observed as the diene was isolated in a 23% yield containing only 50% deuterium incorporation.

This experiment suggested that a Ni^{II}-H species was contributing to the formation of the product; however, it was unclear how the Ni-H was forming. Initially, it was thought that a H-Ni-OH species could be formed via the insertion of Ni^0 to the H-O bond of trace amounts of water in the solvent. This theory seemed most likely as the addition of molecular sieves to enyne/ketone cycloadditions inhibited 1,3-diene formation.



5.25
95% D Incorporation

5.20
~80% D incorporation
65% yield

5.25
95% D Incorporation

5.20
~50% D incorporation
23% yield

Figure 5.13. Deuterium incorporation studies.

Upon attempting to stop the enyne isomerization, molecular sieves were added to enyne cycloisomerization reaction. Surprisingly, this had no effect on the reaction and the 1,3-diene was produced in a high yield.

Although the formation of the Ni-H by H_2O seemed unlikely, another mechanism for the Ni-H formation could be proposed. Previously, it has been found that Ru, Ir, and Rh can oxidatively add to aryl and allylic C-H bonds of ligated carbenes.[17] It was therefore proposed, although unprecedented, the Ni-H species could arise from a C-H activation of the IDTB ligand (Figure 5.14). It was found that by replacing the IDTB ligand with its sterically and electronically identical deuterium labeled analog, IDTB-d_4 (>95% D incorporation) (Figure 5.15), the cycloisomerization was severely retarded (90% yield with IDTB vs. 37% with IDTB-d_4).

Because the C_{aryl}-D bond is more difficult to break than the C_{aryl}-H bond, the breaking the C_{aryl}-H bond of the ligand is crucial for the reaction to proceed. While this isotope effect does not rule out Mechanism A as a competing mechanism, it suggests it is most likely not the major product generating pathway as deuteration at the *ortho* and *para* positions of the ligand *would not* affect the product formation in mechanism A. Furthermore, the isotope effect supports formation of the active Ni-H catalyst via an unprecedented C-H activation of a carbene ligand by nickel (0).

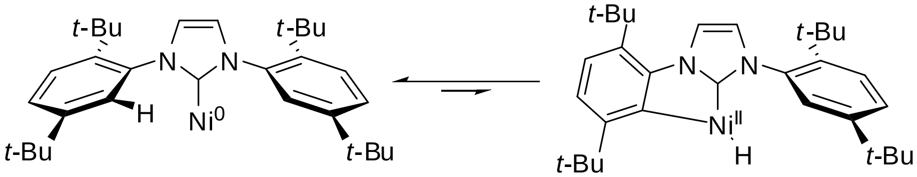


Figure 5.14. Formation of Ni-H via C-H activation.

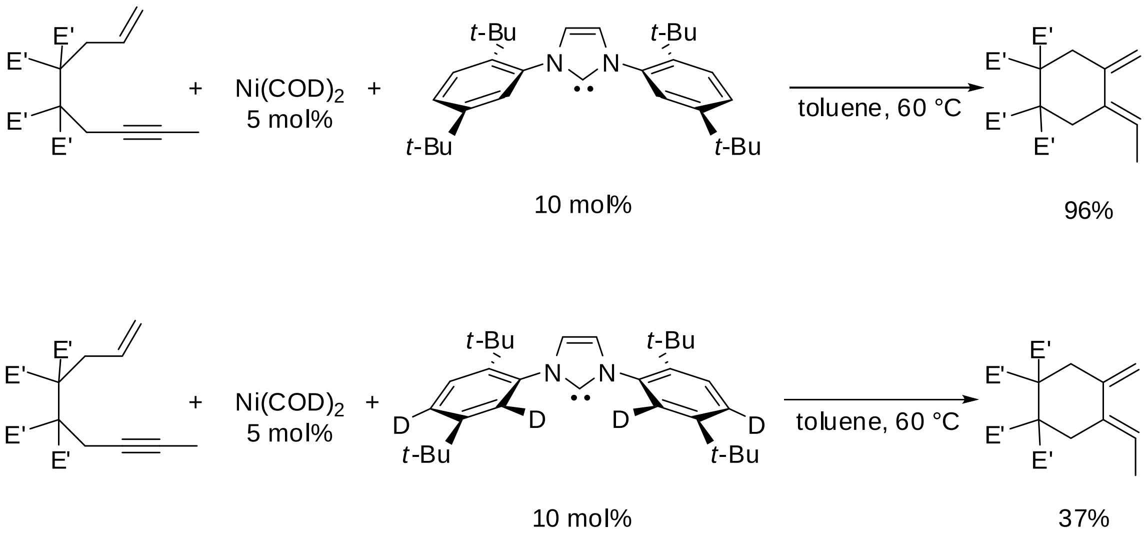


Figure 5.15. Retardation of cycloaddition with deuterated ligand.

Further evidence to refute the possibility of the Ni-H species formed via trace amounts of water was obtained by reacting enyne **2.66** with Ni(COD)$_2$ (10 mol%), IDTB-d4 (20 mol%), and H_2O (10 mol%). If the Ni-H species were being formed by water, the yield should be comparable to the yield in Figure 5.13. This is not the case however as the yield of the reaction with additional water and deuterated ligand is only 20%, whereas the reaction without water and the nondeuterated ligand gave a 65% yield (Figure 5.16).

The activation of C-H bonds has long been a significant challenge for chemists. By activating these typically inert bonds, one can readily functionalize feedstock hydrocarbons into more precious, synthetically useful materials. Recently, great success has been realized in this area using Rh, Ru, Ir, Pd and Pt transition metal complexes. Unfortunately, these metals are expensive and their use in industrial scale reactions is therefore limited. With the ever pressing need to develop more economical reactions for C-H activation reactions in industrial applications, the discovery that nickel/carbene complexes can undergo C-H activation is a promising advancement.

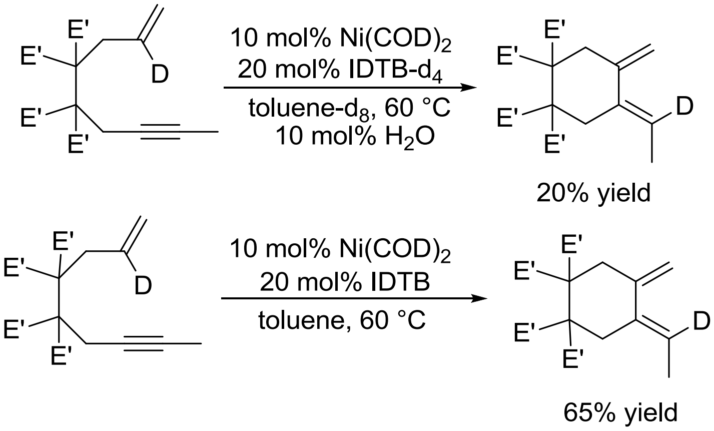


Figure 5.16. Cyclization in the presence of excess water.

Conclusion

We have shown that the $Ni(COD)_2$/IDTB system is a successful catalyst for the cycloisomerization of linear enynes to synthetically valuable cyclic 1,3-dienes. Mechanistic studies suggest that the active catalyst species is a Ni^{II}-H species which is generated via an extremely rare Ni^0 C-H activation. More extensive studies are currently underway to determine the full substrate scope of the reaction.

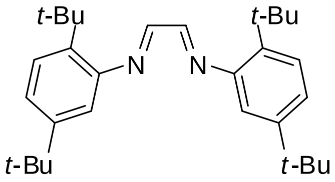
Experimental Section

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove-box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem and used without further purification. The IPr, SIPr, IMes, SIMes, IAd, and I^tBu ligands were prepared as previously reported.[1,2] Sodium hydride was thoroughly washed with pentane and dried in vacuo prior to use. All other reagents were purchased and used without further purification unless otherwise noted.

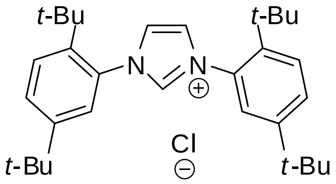
^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 500 and 125 MHz, respectively unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, tq, q, qt, quint, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. HRMS were performed at the mass spectrometry facility at The University of Utah.

Gas chromatographies were performed on an Alient 6890 gas chromatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 min; detector temperature: 250 ºC.

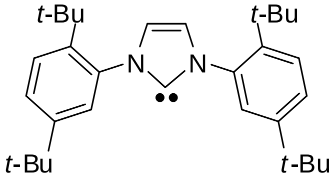
Synthetic Procedures and Analyses



Preparation of (N,N'E,N,N'E)-N,N'-(ethane-1,2-diylidene) bis(2,5-di-tert-butylaniline) 5.26. To a stirring solution of 2,5-di-*tert*-butyl aniline (13.95 g, 68 mmol) in 130 mL EtOH was added glyoxal (3.9 mL 34 mmol) and 4 drops of formic acid. The resulting yellow solution was stirred at room temperature for 2 h at which time a yellow precipitate formed. The mixture was stirred for an additional 12 h and then cooled to -78 °C. The cold mixture was then quickly filtered and the collected yellow solids were washed with cold MeOH (-78 °C) until the filtrate ran clear. The yellow solid was dried in vacuo to yield **5.26** (12.21 g, 83%). mp: 186 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.28 (s, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.26 (dd, J_1 = 2.0, J_2 = 8.3 Hz), 6.87 (d, *J* = 2 Hz), 1.44 (s, 18H), 1.36 (s, 18H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 158.8, 150.3, 150.2, 140.7, 126.2, 124.0, 116.2, 35.5, 34.7, 31.6, 30.7. IR (neat): 2959, 2872, 1608, 1554, 1262, 926, 880, 827 cm^{-1}. HRMS(FAB): calcd for $C_{30}H_{44}N_2$ (M^+) 432.3504, obsd 432.3468.

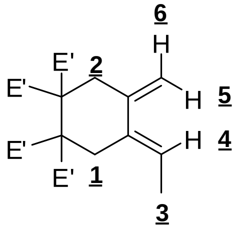


Preparation of 1,3-bis(2,5-di-tert-butylphenyl)-1H-imidazol-3-ium chloride (5.27): A stirring suspension of bisimine **5.26** (6.43 g, 14.88 mmol) and paraformaldehyde (447.0 mg, 14.88 mmol) in toluene (35 mL) was heated at 80 °C for 1 h. The solution was then cooled to room temperature and HCl (3.7 mL, 22.3 mmol, 6M in dioxane) was added dropwise at a rate such that the previous drop had fully dispersed before addition of the next drop. The resulting dark red/brown solution was stirred at room temperature for 8 h and then filtered. The collected solids were washed with cold THF (-78 °C) until the filtrate ran clear. The tan solid was further purified by dissolving the solid in hot acetone and re-precipitating it by the addition of hexanes. The beige solids were collected by vacuum filtration, washed with Et$_2$O (30 mL), and dried in vacuo to yield crude imidazolium salt **5.27** (2.51 g, 35%). HRMS(FAB): calcd for $C_{31}H_{45}N_2$ (M^+) 445.3583, obsd 445.3587.

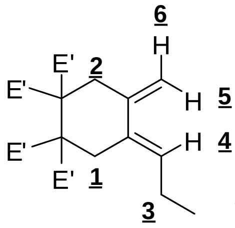


Preparation of IDTB: In a glove box, imidazolium salt **5.27** (534.1 mg, 1.11mmol) and KO^tBu (186.9 mg, 1.67 mmol) were weighed into a vial and suspended in toluene (4 mL). The resulting suspension was stirred at room temperature for 4 h and the solvent was removed in vacuo. The solids were then suspended in 2 mL toluene and the excess salts were precipitated by the addition of 7 mL pentane. The mixture was then vacuum filtered and the collected solids were subjected to the suspension, precipitation, filtration sequence two more times. The collected filtrate was concentrated *in vacuo* to yield IDTB as a beige solid (412.4 mg 84%). Analytically pure sample could be obtained by cooling a saturated solution of IDTB in Et_2O to -40 °C. mp: Decomp. 206 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 2.0 Hz), 7.27 (dd, J_1 = 2.0, J_2 = 8.3 Hz, 2H), 6.77 (s, 2H), 1.47 (s, 18H), 1.16 (s, 18H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 221.4, 149.9, 144.0, 142.5, 129.0, 125.8, 123.0, 36.3, 34.5, 32.6, 31.5. IR (neat): 2959, 2872, 1608, 1554, 1262, 926, 880, 827 cm^{-1}. HRMS(CI): calcd for $C_{31}H_{44}N_2$ (MH^+) 445.3583, obsd 445.3580.

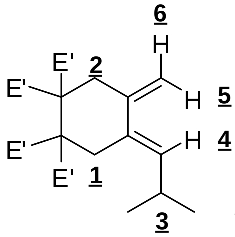
General procedure for the cycloisomerization of enynes. To a stirring solution of enyne in toluene (~0.4 M) at 60 °C was added the catalyst solution ($Ni(COD)_2$ and IDTB which was previously equilibrated for at least 8 h at room temperature at a concentration of ~0.04 M). The resulting solution was stirred for 1 h at 60 °C, cooled to room temperature, and quenched with the addition of MeOH (0.5 mL). The crude mixture was then concentrated in vacuo and the residue was purified by flash column chromatography on SiO_2 to yield the 1,3-diene.



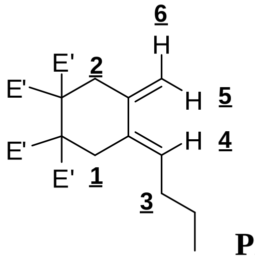
Preparation of (E)-tetraethyl 4-ethylidene-5-methylene cyclohexane-1,1,2,2-tetracarboxylate (5.20). The general procedure was used with enyne **2.66** (200.0 mg, 0.4873 mmol), $Ni(COD)_2$ (6.7 mg, 0.0244 mmol), IDTB (21.7 mg, 0.0588 mmol) and 4.87 mL toluene. The reaction mixture was purified by flash column chromatography on SiO_2 eluting with 10% EtOAc/hexanes to yield diene **5.20** (191.2 mg, 96%) as a sticky, pale yellow oil. (^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.75 (q, *J* = 6.83 Hz, 1H), 5.00 (brs, 1H), 4.66 (brs, 1H), 4.27-4.16 (m, 8H), 3.07 (s, 2H), 2.94 (s, 2H), 1.68 (d, *J* = 6.83, 3H), 1.27 (app. td, 12H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 169.9, 169.7, 144.7, 134.7, 121.4, 110.3, 61.9, 61.7, 59.6, 59.2, 38.1, 31.6, 14.0, 13.4. IR (neat): 2983, 2938, 2907, 1738, 1300, 1266, 1202, 1042, 865 cm^{-1}. HRMS(CI): calcd for $C_{21}H_{31}O_8$ (MH^+) 411.2019, obsd 411.2023. COSY summary, the following pertinent cross-peaks were observed: H(4) with H(1) and H(3), H(5) with H(6) and H(2), H(6) with H(5) and H(2). NOE summary; the following pertinent enhancements were observed: irradiation of H(4) showed enhancement of H(3) and H(5); irradiation of H(5) showed enhancement of H(4); irradiation of H(1) showed enhancement of H(3); irradiation of H(3) showed enhancement of H(1).



Preparation of (E)-tetraethyl 4-methylene-5-propylidenecyclohexane-1,1,2,2-tetracarboxylate (5.21). The general procedure was used with enyne **3.59** (200.0 mg, 0.471 mmol), Ni(COD)$_2$ (6.5 mg, 0.0236 mmol), IDTB (20.9 mg, 0.0471 mmol) and 4.71 mL toluene. The reaction mixture was purified by flash column chromatography on SiO$_2$ eluting with 10% EtOAc/hexanes to yield diene **5.21** (189.5 mg, 95%) as a sticky, pale yellow oil. (^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 5.66 (t, *J* = 7.32 Hz, 1H), 5.02 (brs, 1H), 4.67 (brs, 1H), 4.27-4.16 (m, 8H), 3.05 (s, 2H), 2.97 (s, 2H), 2.10 (quint, *J* = 7.32 Hz, 2H), 1.27 (app. td, 12H), 0.99 (t, *J* = 7.32 Hz). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 169.9, 169.7, 144.7, 133.2, 129.1, 110.5, 61.9, 61.8, 59.5, 59.4, 38.2, 31.9, 21.1, 14.2, 14.07, 14.05. IR (neat): 2983, 2938, 2907, 1738, 1300, 1266, 1202, 1042, 865 cm^{-1}. HRMS(CI): calcd for $C_{22}H_{33}O_8$ (MH$^+$) 425.2175, obsd 425.2164. COSY summary, the following pertinent cross-peaks were observed: H(4) with H(1) and H(3), H(5) with H(6) and H(2), H(6) with H(5) and H(2). NOE summary; the following pertinent enhancements were observed: irradiation of H(4) showed enhancement of H(3) and H(5); irradiation of H(5) showed enhancement of H(4); irradiation of H(1) showed enhancement of H(3); irradiation of H(3) showed enhancement of H(1).

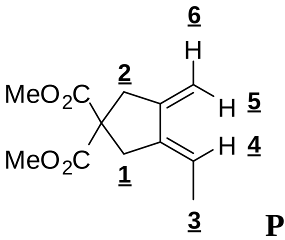


Preparation of (E)-tetraethyl 4-methylene-5-(2-methylpropylidene) cyclohexane-1,1,2,2-tetracarboxylate (5.22). The general procedure was used with enyne **3.61** (150.0 mg, 0.342 mmol), Ni(COD)$_2$ (4.7 mg, 0.0171 mmol), IDTB (15.2 mg, 0.0342 mmol) and 3.42 mL toluene. The reaction mixture was purified by flash column chromatography on SiO$_2$ eluting with 10% EtOAc/hexanes to yield diene **5.22** (149.0 mg, 99%) as a sticky, pale yellow oil. (^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 5.50 (d, *J* = 9.27 Hz, 1H), 5.02 (brs, 1H), 4.66 (brs, 1H), 4.27-4.16 (m, 8H), 3.05 (s, 2H), 2.99 (s, 2H), 2.59 (m, 1H), 1.31-1.23 (m, 12H), 0.97 (d, *J* = 6.83 Hz, 6H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 169.9, 169.7, 144.7, 134.7, 131.6, 110.6, 61.9, 61.8, 59.45, 59.36, 38.1, 32.1, 26.8, 23.1, 14.04, 14.02. IR (neat): 2982, 2961, 2907, 2869, 1738, 1267, 1234, 1202, 1040, 865 cm^{-1}. HRMS(CI): HRMS(CI): calcd for $C_{23}H_{35}O_8$ (MH$^+$) 439.2332, obsd 439.2335. COSY summary, the following pertinent cross-peaks were observed: H(4) with H(1) and H(3), H(5) with H(6) and H(2), H(6) with H(5) and H(2). NOE summary; the following pertinent enhancements were observed: irradiation of H(4) showed enhancement of H(3) and H(5); irradiation of H(5) showed enhancement of H(4); irradiation of H(1) showed enhancement of H(3); irradiation of H(3) showed enhancement of H(1).

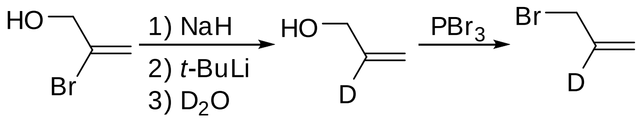


Preparation of (E)-tetraethyl 4-butylidene-5-methylenecyclohexane-1,1,2,2-tetracarboxylate (5.23). The general procedure was used with enyne **3.62** (150.0 mg, 0.342 mmol), Ni(COD)$_2$ (4.7 mg, 0.017 mmol), IDTB (15.2 mg, 0.0342 mmol) and 3.42 mL toluene. The reaction mixture was purified by flash column chromatography on SiO$_2$ eluting with 10% EtOAc/hexanes to yield diene **5.23** (147.6 mg,

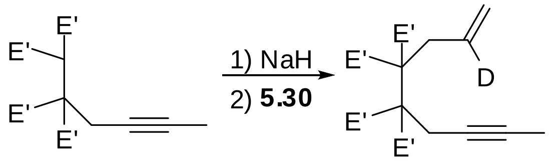
98%) as a sticky, pale yellow oil. (^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 5.68 (t, *J* = 7.32 Hz, 1H), 5.02 (brs, 1H), 4.66 (brs, 1H), 4.27-4.16 (m, 8H), 3.05 (s, 2H), 2.97 (s, 2H), 2.06 (q, *J* = 7.32, 2H), 1.40 (sext, *J* = 7.32, 2H) 1.31-1.23 (m, 12H), 0.92 (t, *J* = 7.32 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 169.8, 169.7, 144.7, 133.8, 127.3, 110.4, 61.9, 61.7, 59.4, 59.3, 38.1, 32.0, 29.8, 22.9, 14.1, 14.008, 13.997. IR (neat): 2982, 2934, 2873, 1738, 1367, 1266, 1159, 1040, 865 cm^{-1}. HRMS(CI): HRMS(CI): calcd for $C_{23}H_{35}O_8$ (MH$^+$) 439.2332, obsd 439.2350. COSY summary, the following pertinent cross-peaks were observed: H(4) with H(1) and H(3), H(5) with H(6) and H(2), H(6) with H(5) and H(2). NOE summary; the following pertinent enhancements were observed: irradiation of H(4) showed enhancement of H(3) and H(5); irradiation of H(5) showed enhancement of H(4); irradiation of H(1) showed enhancement of H(3); irradiation of H(3) showed enhancement of H(1).



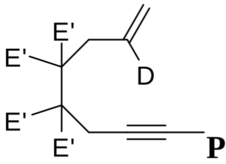
Preparation of (E)-dimethyl 3-ethylidene-4-methylenecyclopentane-1,1-dicarboxylate (5.24). The general procedure was used with enyne **2.65** (150.0 mg, 0.669 mmol), Ni(COD)$_2$ (9.2 mg, 0.0334 mmol), IDTB (29.7 mg, 0.0668 mmol) and 6.69 mL toluene. The reaction mixture was purified by flash column chromatography on SiO$_2$ eluting with 6% EtOAc/hexanes to yield diene **5.24** (125.2 mg, 83%) as a pale yellow oil. (^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 5.94 (qt, J_1 = 2.4, J_2 = 7.3 Hz, 1H), 5.23 (s, 1H), 4.81 (s, 1H), 3.73 (s, 6H), 3.01 (t, *J* = 2.0 Hz, 2H), 2.98 (s, 2H), 1.71 (d, *J* = 7.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ (ppm) 172.1, 145.3, 137.0, 117.0, 102.8, 57.7, 53.0, 41.7, 37.7, 15.0. IR (neat): 2956, 2917, 2855, 1737, 1436, 1248, 1202, 1073, 880 cm^{-1}. HRMS(CI): calcd for $C_{12}H_{17}O_4$ (MH^+) 225.1127, obsd 225.1098.



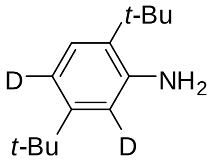
5.28 **5.29** **5.30**



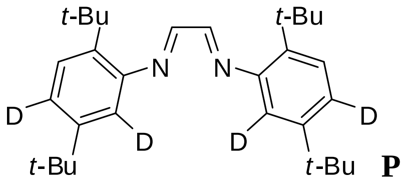
2.74 **5.25**



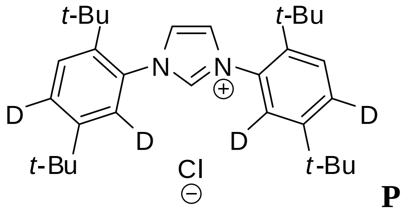
Preparation of deuterated enyne (5.25). To a stirring suspension of NaH (2.412 g, 100.5 mmol) in Et_2O (250 mL) was added vinyl bromide **5.28** dropwise (10.59 g, 77.27 mmol). The resulting brown solution was stirred at room temperature for 1 h. The solution was then cooled to -78 °C and *t*-BuLi was added dropwise. The resulting pale yellow solution was warmed to -10 °C for 2 h and then cooled to -78 °C at which time D_2O (20.00, 1000 mmol) was added. The reaction mixture was warmed to room temperature and stirred for an additional 2 h. The reaction mixture was then quenched by the addition of saturated NH_4Cl solution (50 mL) and the two phases were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the collected organics were washed with brine (15 mL) and dried with $MgSO_4$. The mixture was concentrated via careful distillation through a Vigeruex column. The concentrate was further purified via fractional distillation through a Vigreux column. The fraction boiling from 46 °C -94 °C was collected to yield the crude alcohol **5.29** as a colorless oil (2.2147 g, 49%). To a stirring solution of PBr_3 (1.35 mL, 14.2 mmol) in Et_2O (15 mL) was added crude alcohol **5.29** (2.10 g, 35.5 mmol) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 1 h and then carefully quenched by the addition brine (7 mL). The layers were separated and the organics were washed with a saturated solution of $NaHCO_3$ (3 x 5 mL), brine (5 mL) and dried over $MgSO_4$. The volatiles were carefully removed via distillation through a Vigeruex column. Crude allyl bromide **5.30** was obtained as yellow oil (1.9712 g, 46%). To a stirring suspension of NaH (194.4 mg , 8.100 mmol) in 18 mL THF was added tetra-ester **2.74** (1.000 g, 2.702 mmol) in 2 mL THF. The resulting solution was stirred at room temperature for 1 h at which time crude allyl bromide **5.30** (1.000 g , 8.197 mmol) was added in a single portion via syringe. The flask was the equipped with a reflux condenser and the mixture was stirred at reflux until no starting material was observed by GC analysis (~36 h). The mixture was then cooled to room temperature and quenched with 20 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to yield a yellow oil. The crude oil was purified by flash column chromatography eluting with 15% EtOAc/hexanes producing a yellow oil which was then triturated with cold hexanes to yield enyne **5.25** (892.3 mg, 80%) as a white solid. mp: 67 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.10 (brs, 1H), 5.05 (brs, 1H), 4.31-4.12 (m, 8H), 3.07 (brs, 2H), 2.85 (brs, 2H), 1.75 (t, J = 2.4 Hz, 3H), 1.31-1.25 (m, 12H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 169.2, 161.1, 133.7 (t, J = 24.0 Hz), 119.0, 78.1, 74.8, 62.5, 62.3, 61.9, 61.7, 36.1, 22.8, 14.01, 13.99, 3.8. IR (neat): 3458, 2984, 1739, 1446, 1214, 1042, 923 cm^{-1}. HRMS(CI): calcd for $C_{21}H_{30}DO_8$ (MH^+) 412.2082, obsd 412.2078.



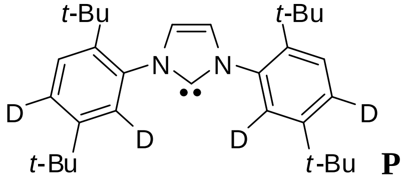
Preparation of deuterated aniline (5.31): To a N_2 flushed thick walled bomb with a Teflon screw top was added 2,5-di-*tert*-butylaniline (10.0 g, 48.7 mmol), DCl (10 mL, 20 mmol, 2N in D_2O), D_2O (20 mL) and EtOD (20 mL). The flask was sealed and heated at 105 °C for 3 days at which time the flask was cooled to room temperature and the solvents were removed in vacuo. The flask was flushed with N_2 and DCl (10 mL, 20 mmol), D_2O (20 mL), and EtOD (20 mL) were added. The flask was resealed and heated to 105 °C for 5 days. The flask was cooled to room temperature and the solvents were removed in vacuo. The flask was flushed with N_2 and DCl (10 mL, 20mmol), D_2O (20 mL), and EtOD (40 mL) were added. The flask was resealed and heated to 105 °C for another 5 days. The flask was cooled to room temperature and the reaction mixture was quenched by the addition of 2 N NH_4OH to pH 10. The mixture was then extracted with Et_2O (3 x 75 mL) and the collected organics were washed with brine (20 mL) then dried of $MgSO_4$. The volatiles were removed in vacuo to yield **5.31** as an off-white solid (8.93 g, 89%). mp: 104 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.18 (s, 1H), 3.98 (brs, 2H), 1.42 (s, 9H), 1.29 (s, 9H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (ppm) 149.9, 144.2, 131.1, 126.4, 115.7 (t, J = 23.8 Hz), 115.0 (t, J = 22.9 Hz), 34.2, 34.1, 31.5, 29.9. IR (neat): 3470, 2957, 2872, 1620, 1548, 1470, 792 cm^{-1}. HRMS(CI): calcd for $C_{14}H_{21}D_2N$ (M^+) 207.1956, obsd 207.1966.



Preparation of deuterated bisimine (5.32). The procedure was identical to the procedure used in the synthesis of bisimine **5.26** using deuterated aniline **5.31** (7.038 g, 33.94 mmol), glyoxal (1.95 mL, 17.0 mmol), formic acid (4 drops) in 65 mL EtOH. The title compound was isolated as a yellow solid in 93% yield. mp: 182 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.28 (s, 2H), 1.44 (s, 18H), 1.35 (s, 18H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 158.8, 150.2, 150.1, 140.7, 126.1, 123.7 (t, *J* = 22.4 Hz), 115.9 (t, *J* = 20.6 Hz), 35.5, 34.6, 31.5, 30.7. IR (neat): 2959, 2872, 1612, 1539, 1362, 1265, 909, 873 cm^{-1}. HRMS(CI): calcd for $C_{30}H_{41}D_4N_2$ (MH^+) 437.3834, obsd 437.3845.



Preparation of deuterated imidazolium salt (5.33). The procedure was identical to the procedure used in the synthesis of imidazolium salt **5.27** using bisimine **5.32** (6.500 g, 14.88 mmol), paraformaldehyde (447.0 mg, 14.88 mmol), and DCl (1M in Et_2O, 22.3 mL, 22.3 mmol) in 35 mL toluene. The crude imidazolium salt **5.33** was isolated as a light tan solid in 42% yield. HRMS(FAB): calcd for $C_{31}H_{41}D_4N_2$ (M^+) 450.3897, obsd 450.3923.



Preparation of (IDTB-d$_4$): The procedure used was identical to the procedure used in the synthesis of the IDTB carbene using deuterated imidazolium salt **5.33** (508 mg, 1.04 mmol) and KO^{t}Bu (176 mg, 1.57 mmol) in 4 mL toluene. The title compound was isolated as a beige solid in 24% yield. Analytically pure sample could be obtained by cooling a saturated solution of the carbene in Et_2O to -40 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 2H), 6.77 (s, 2H), 1.48 (s, 18H), 1.16 (s, 18H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 221.4, 149.9, 144.0, 142.5, 129.0, 125.8 (t, J = 22.4 Hz), 123.0, 36.3, 34.5, 32.6, 31.5. IR (neat): 2959, 2872, 1608, 1554, 1262, 926, 880, 827 cm^{-1}. HRMS(CI): calcd for $C_{31}H_{40}D_4N_2$ (MH^+) 449.3834, obsd 449.3837.

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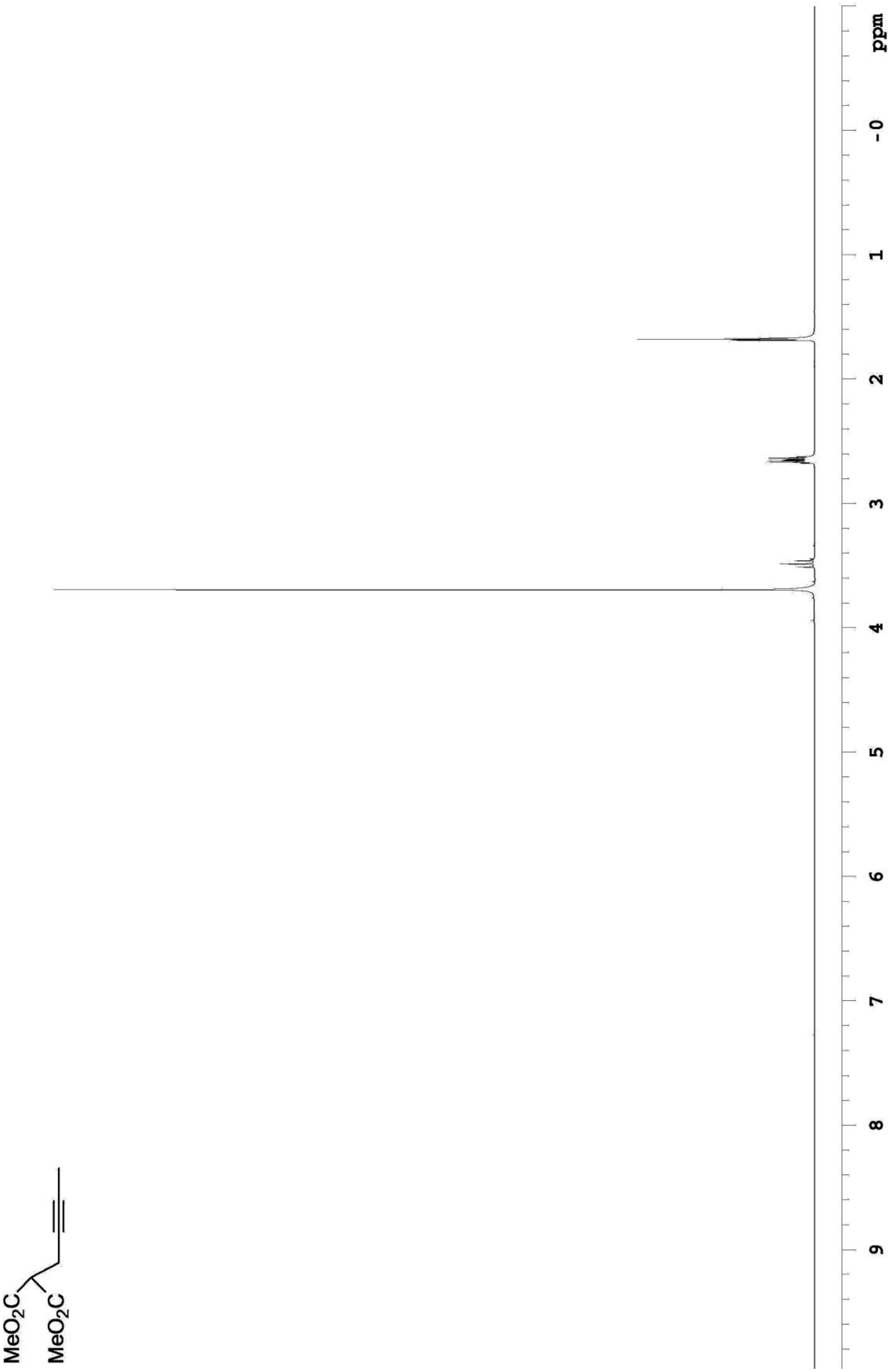
APPENDIX A

^{1}H NMR AND ^{13}C NMR SPECTRA AND X-RAY DATA FOR CHAPTER 2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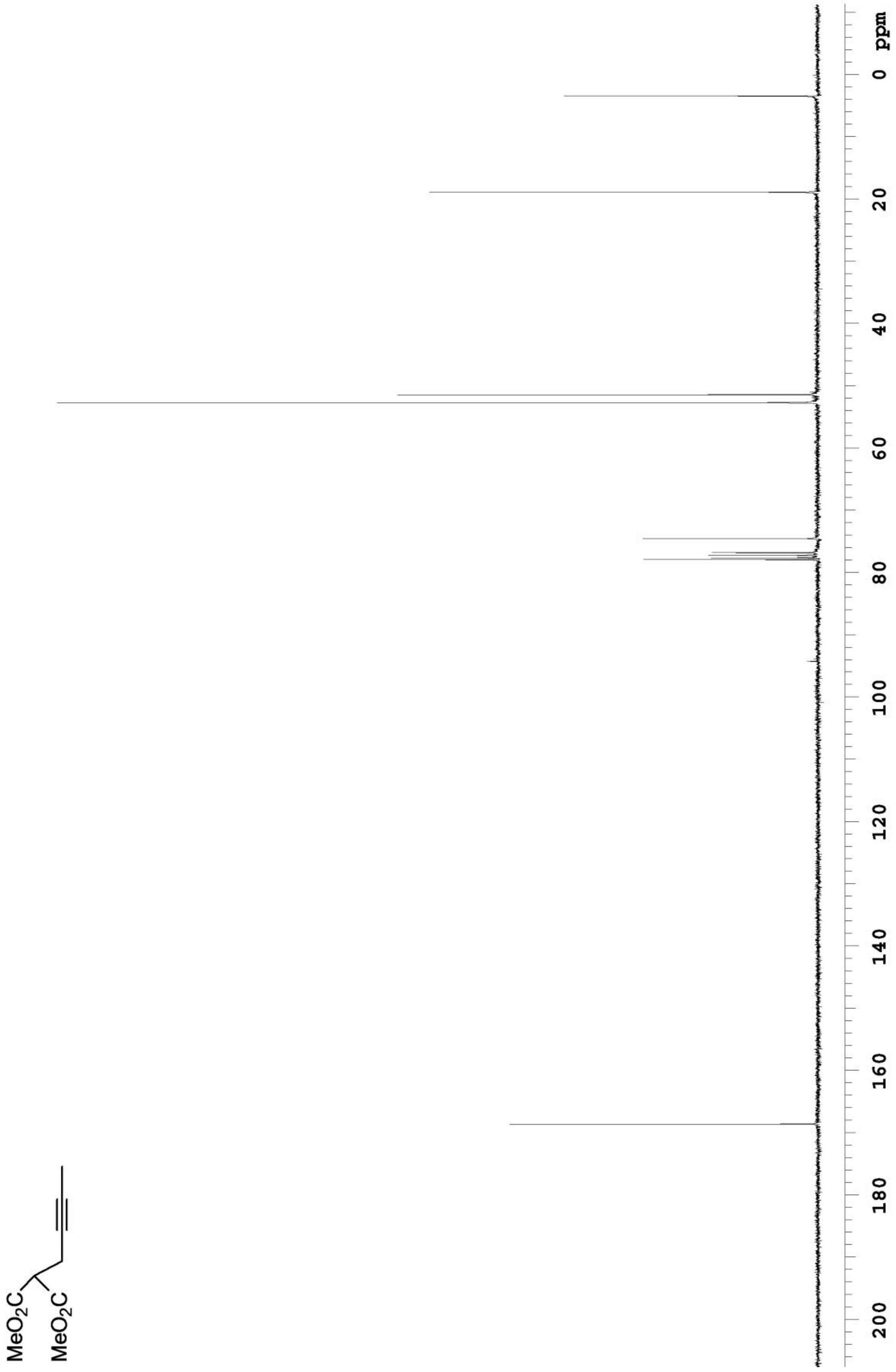
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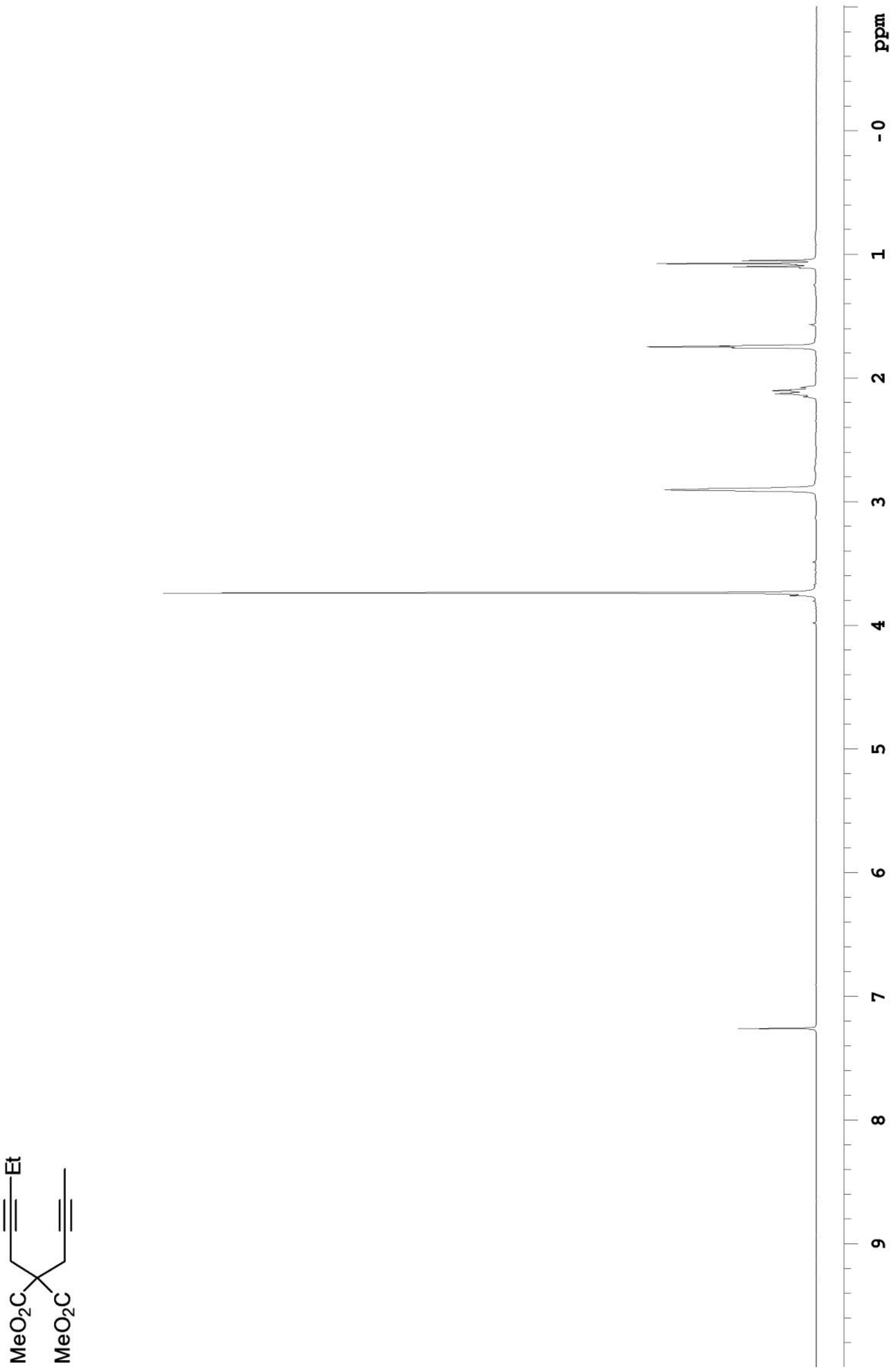
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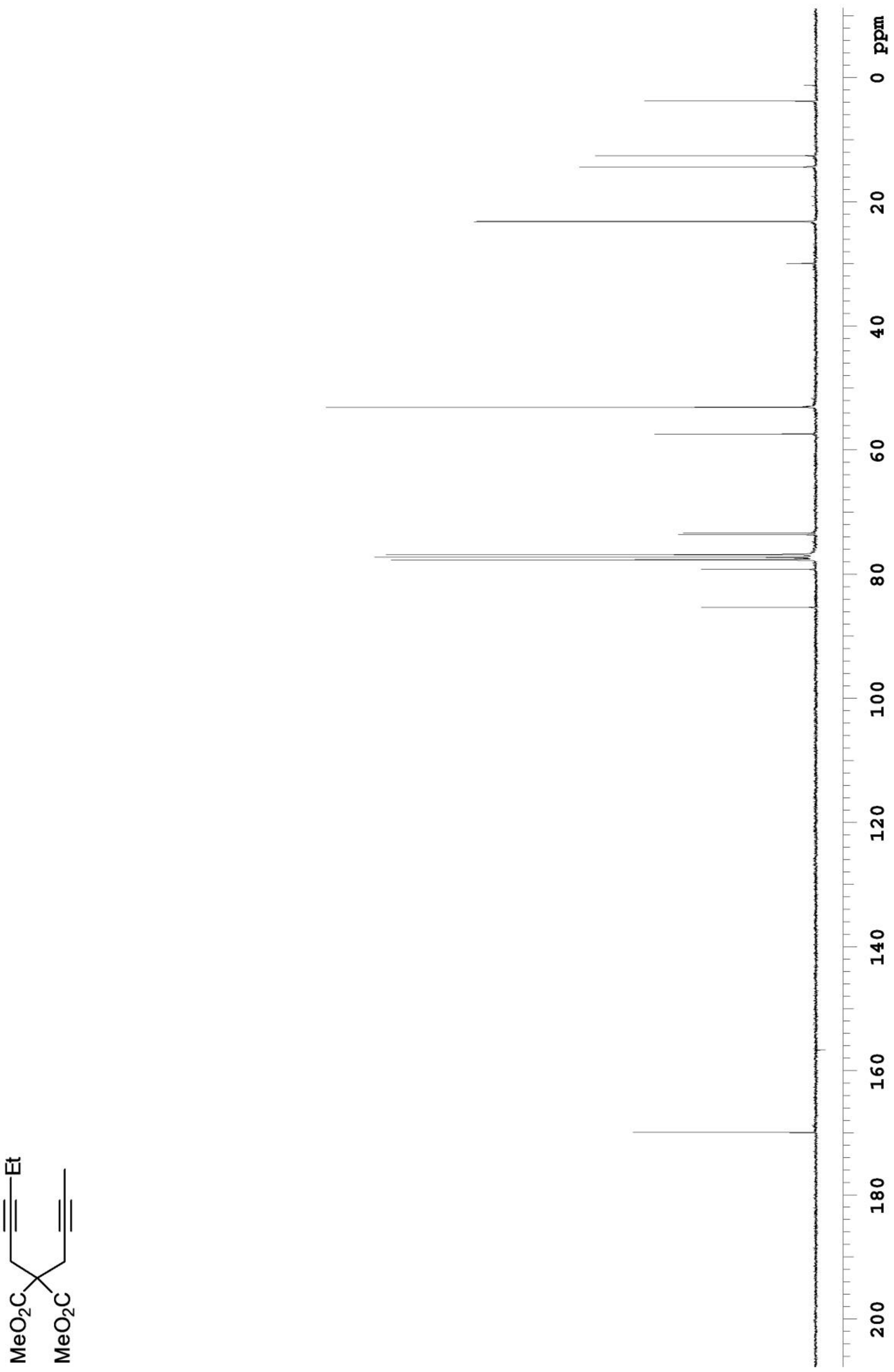
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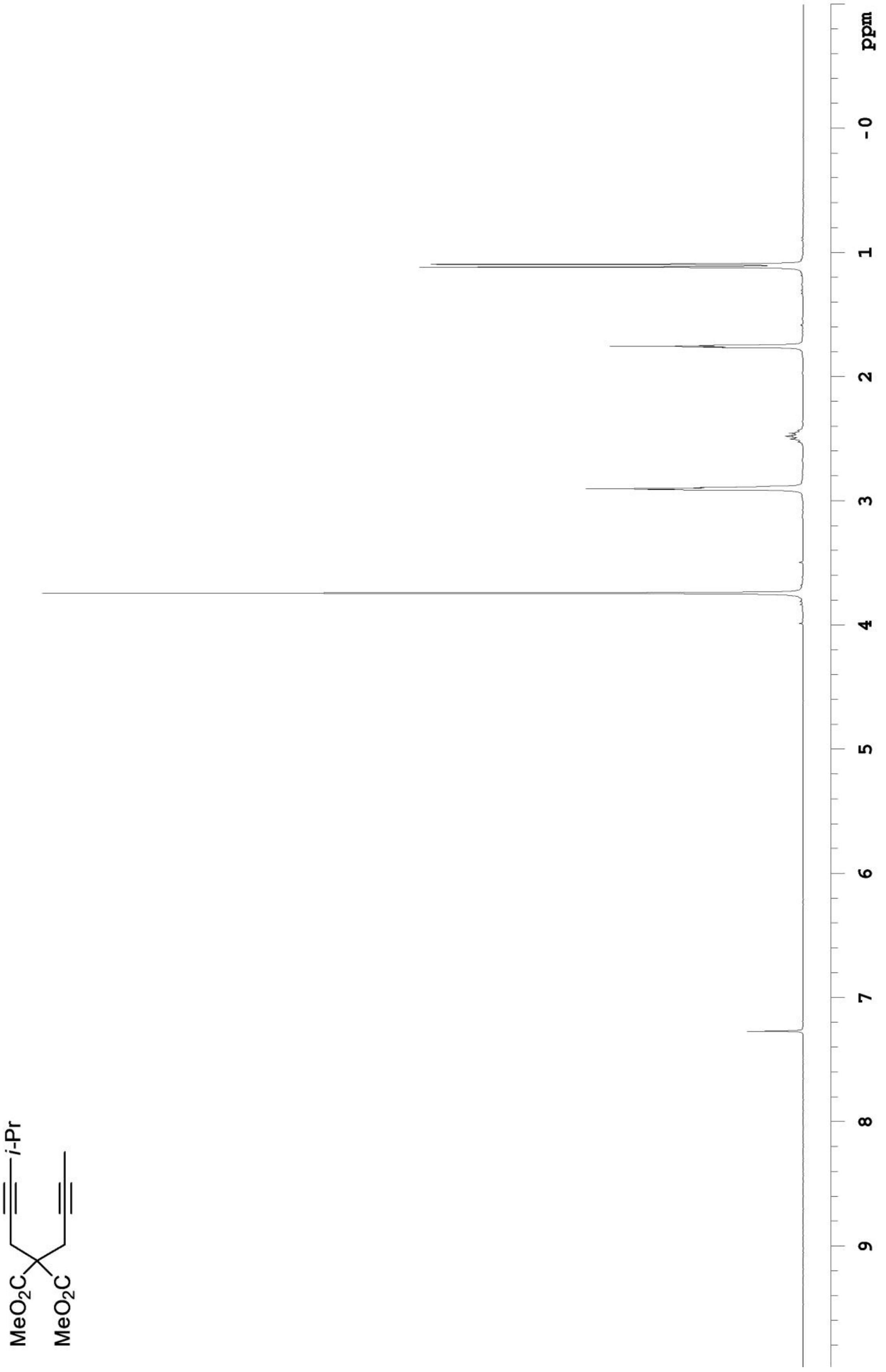
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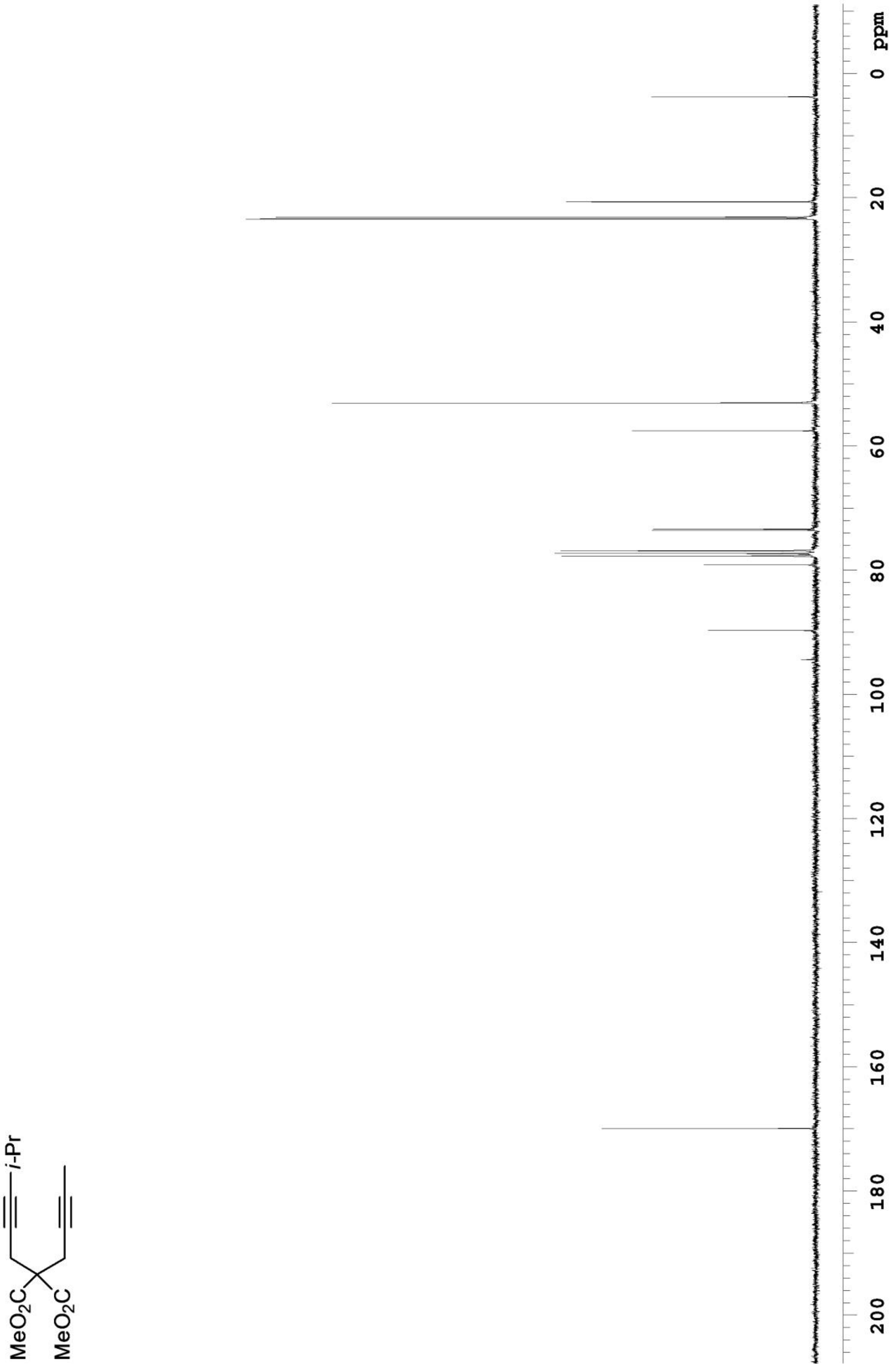
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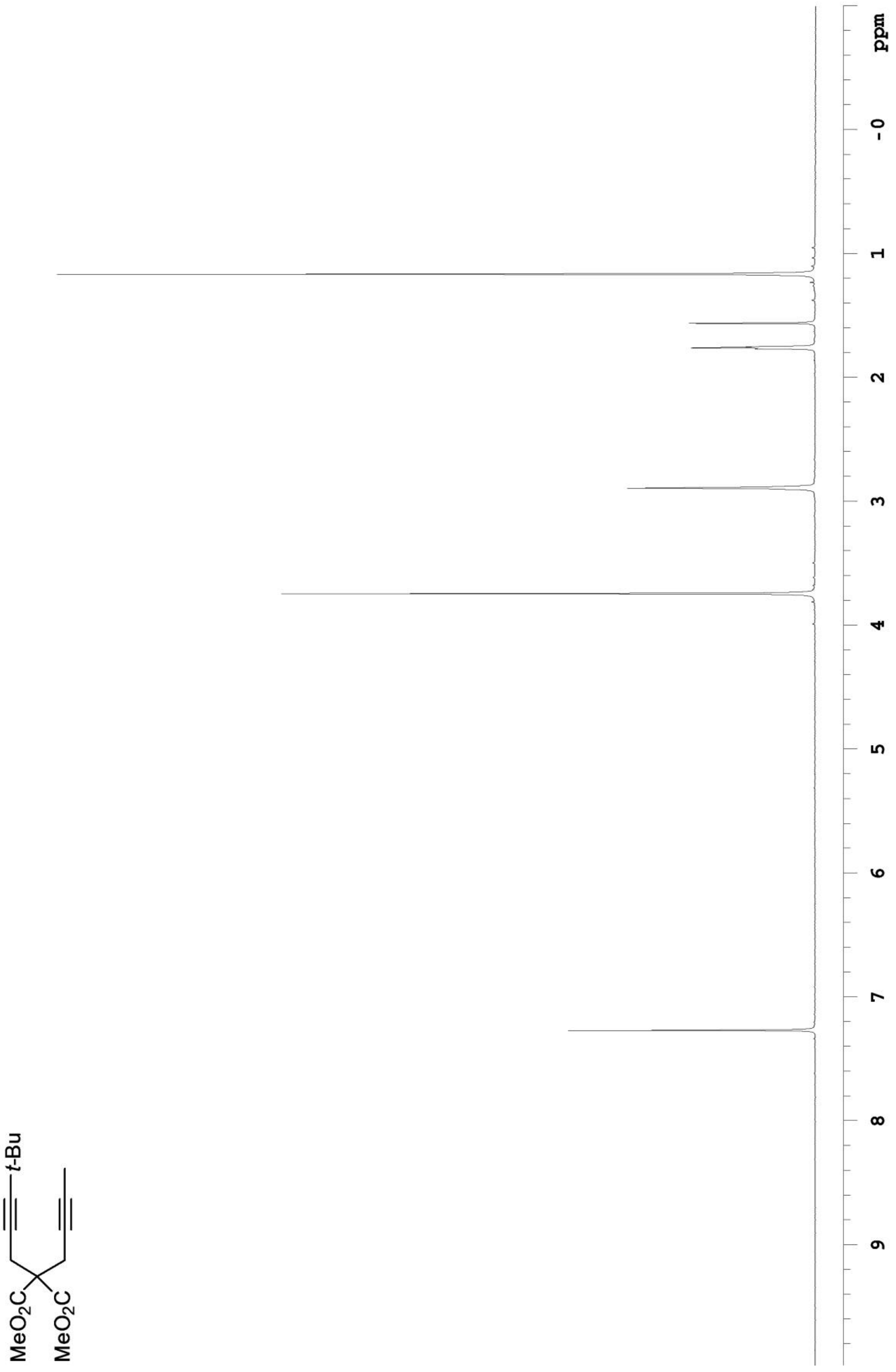
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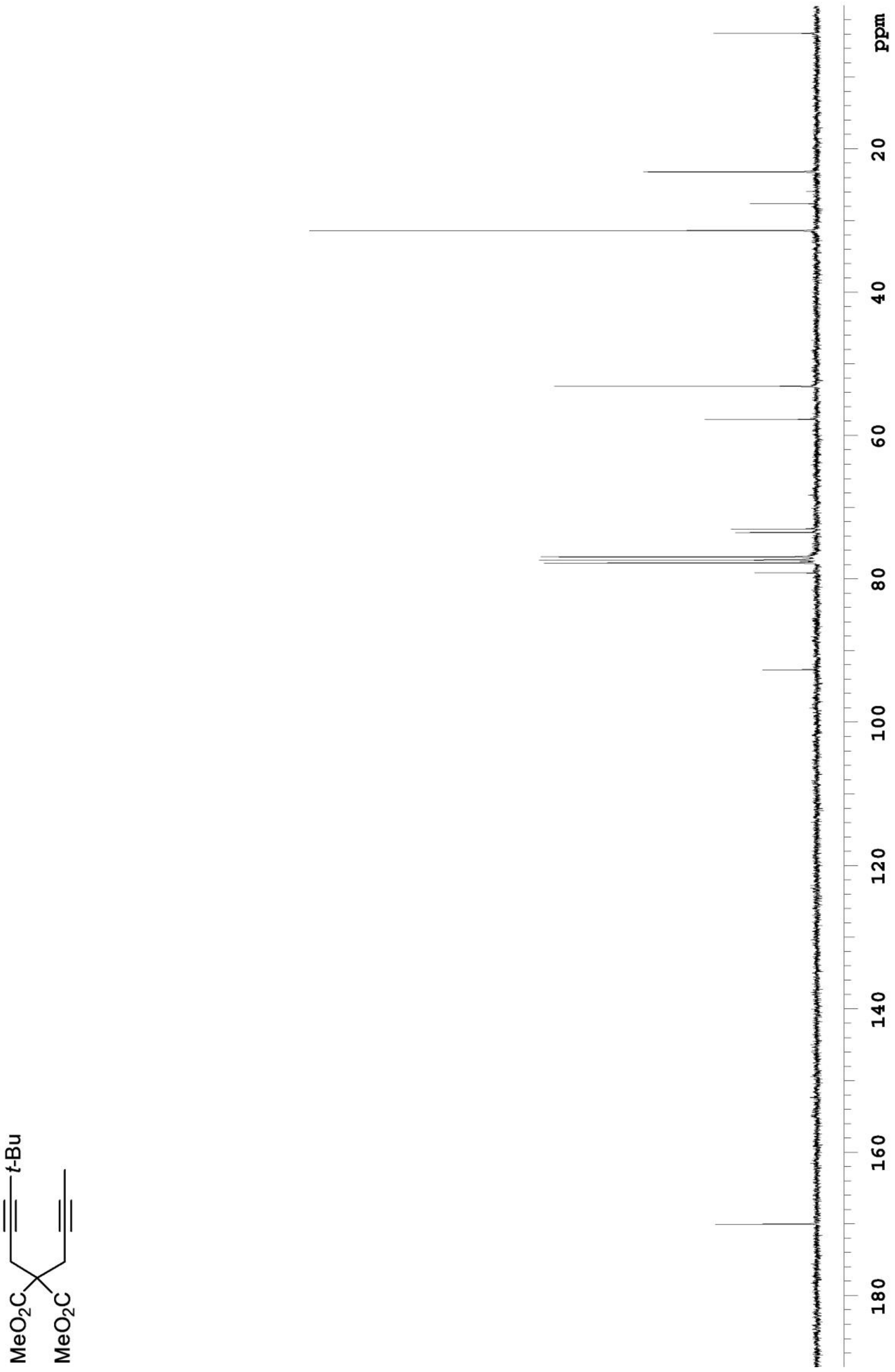
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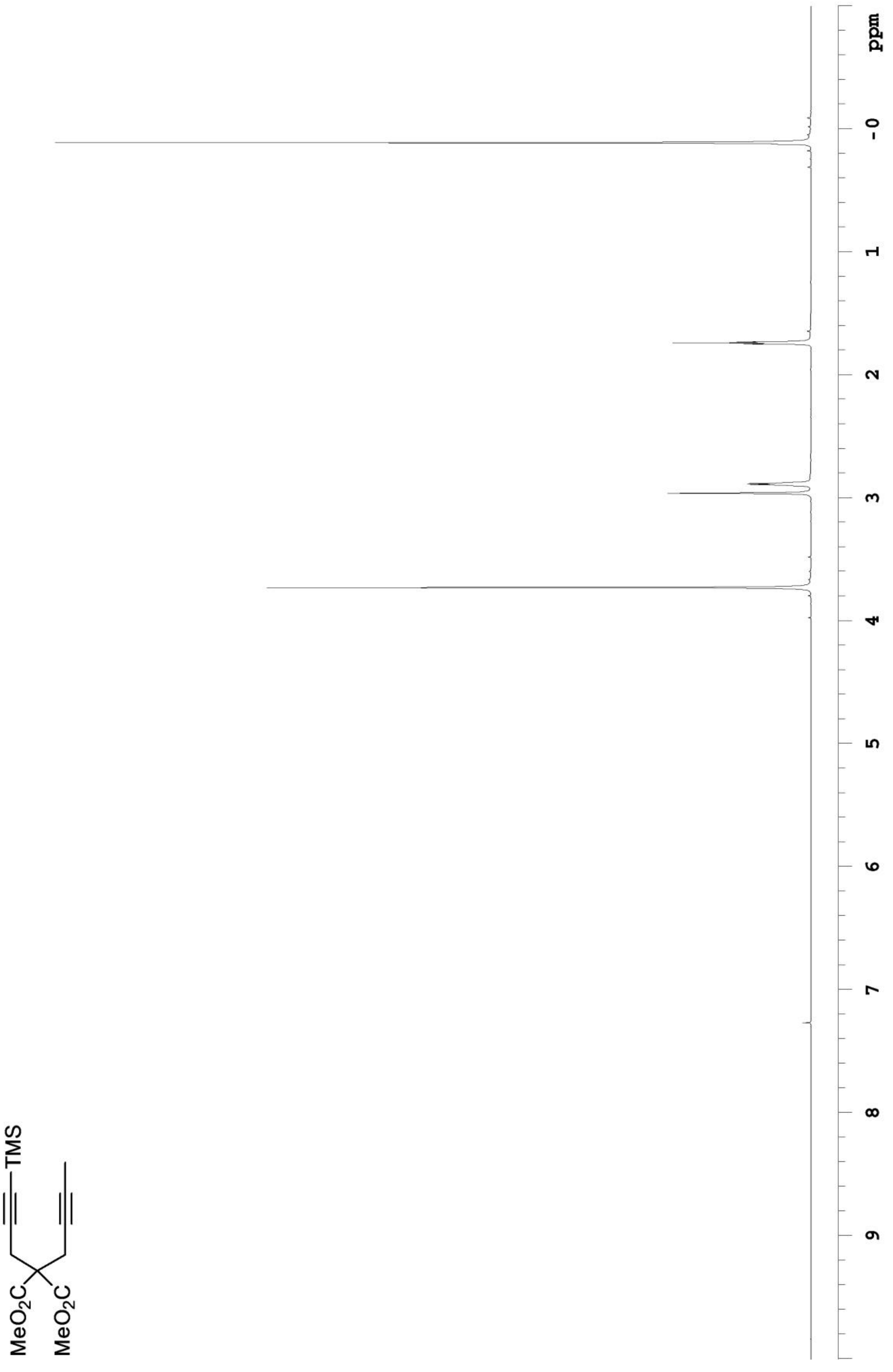
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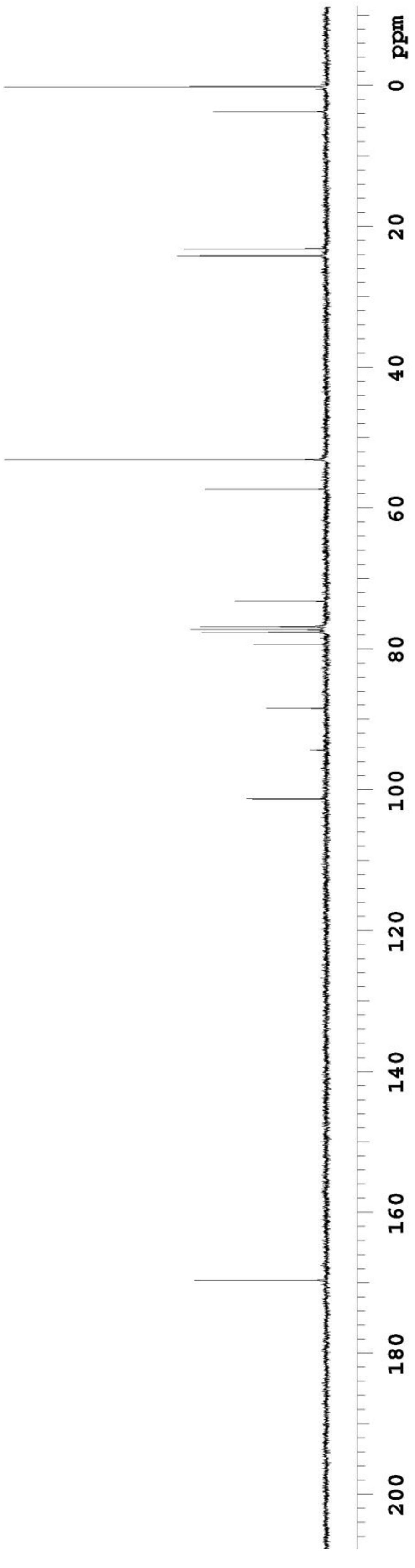
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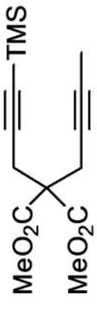
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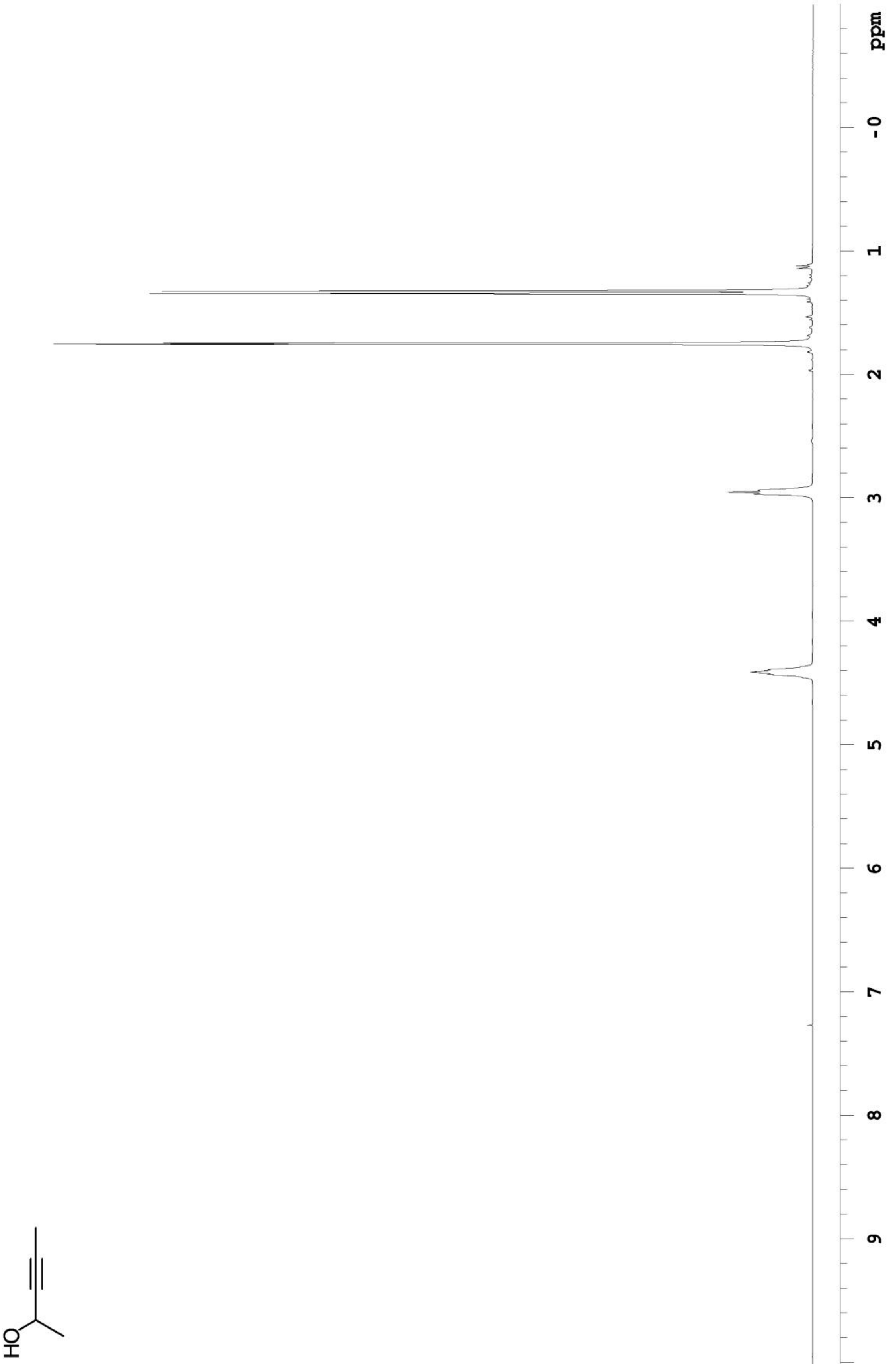
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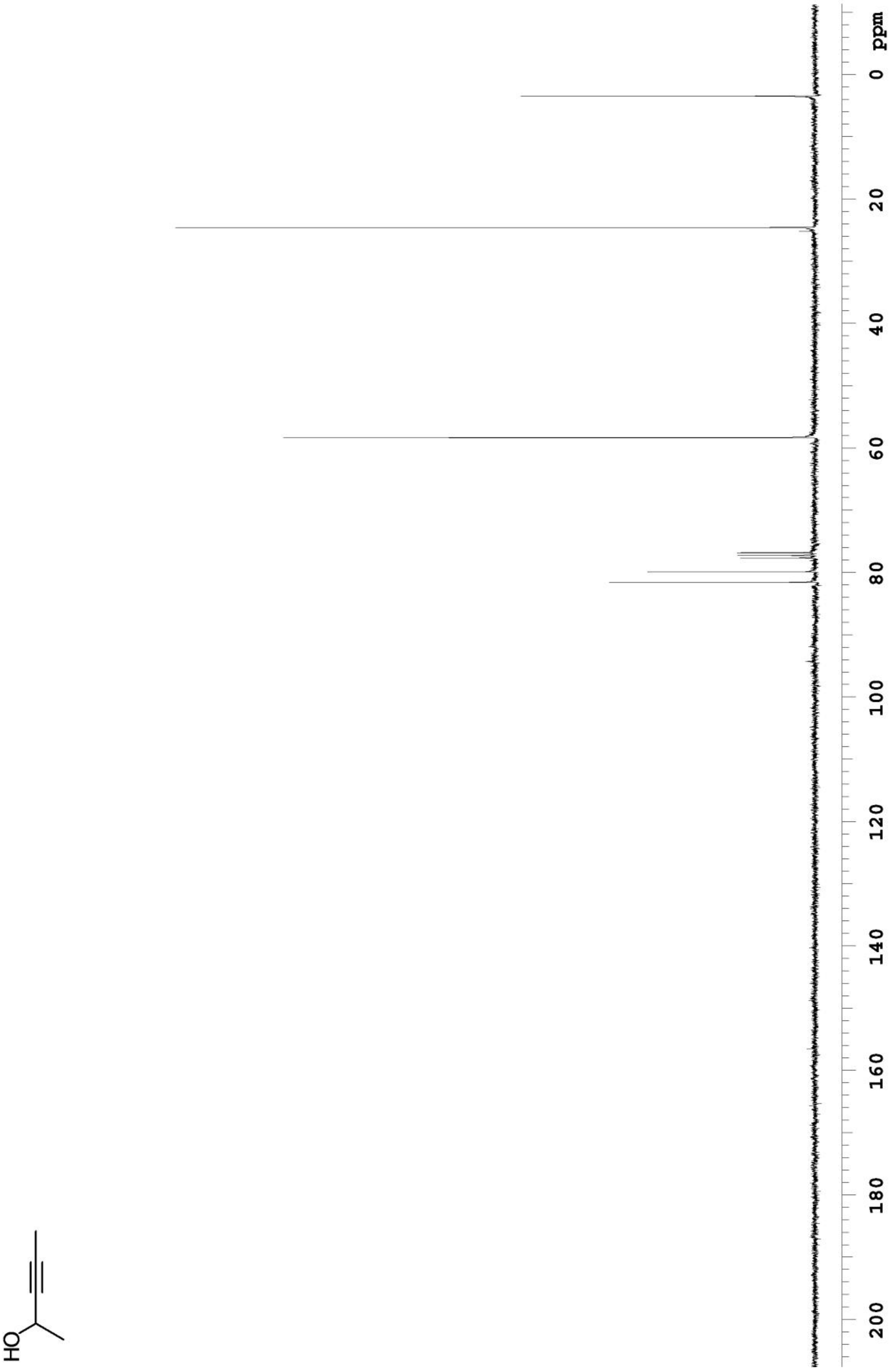
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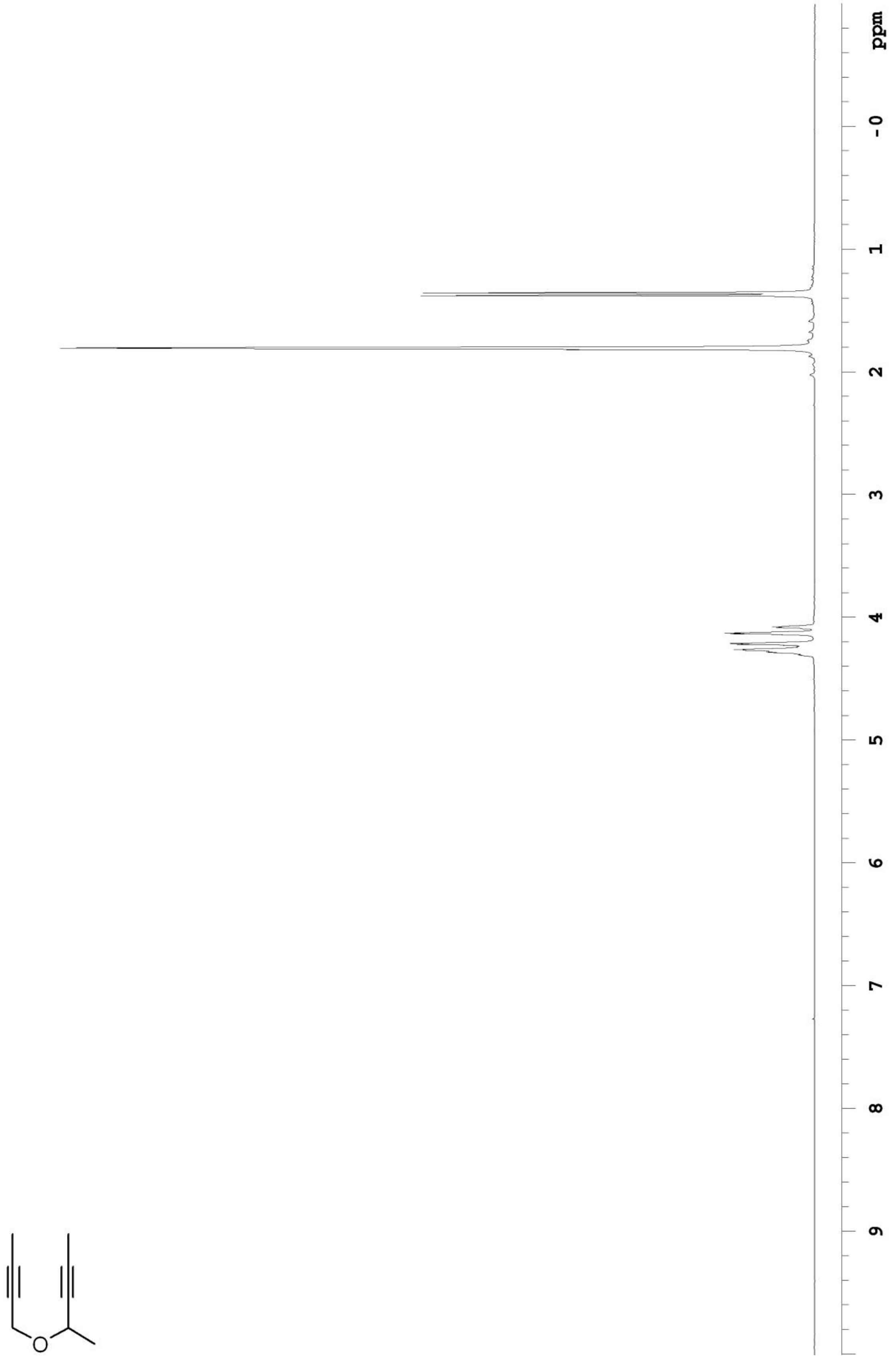
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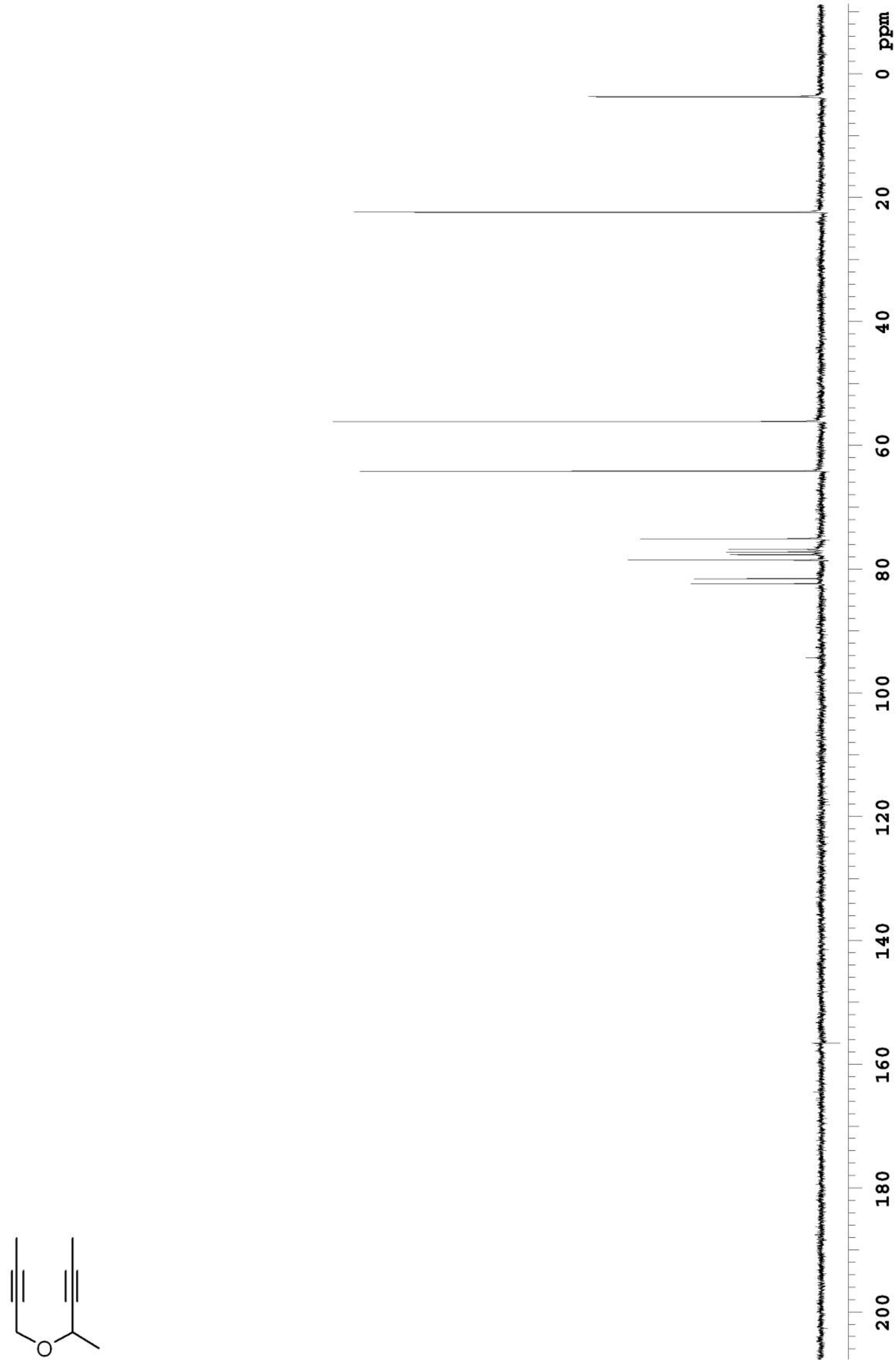
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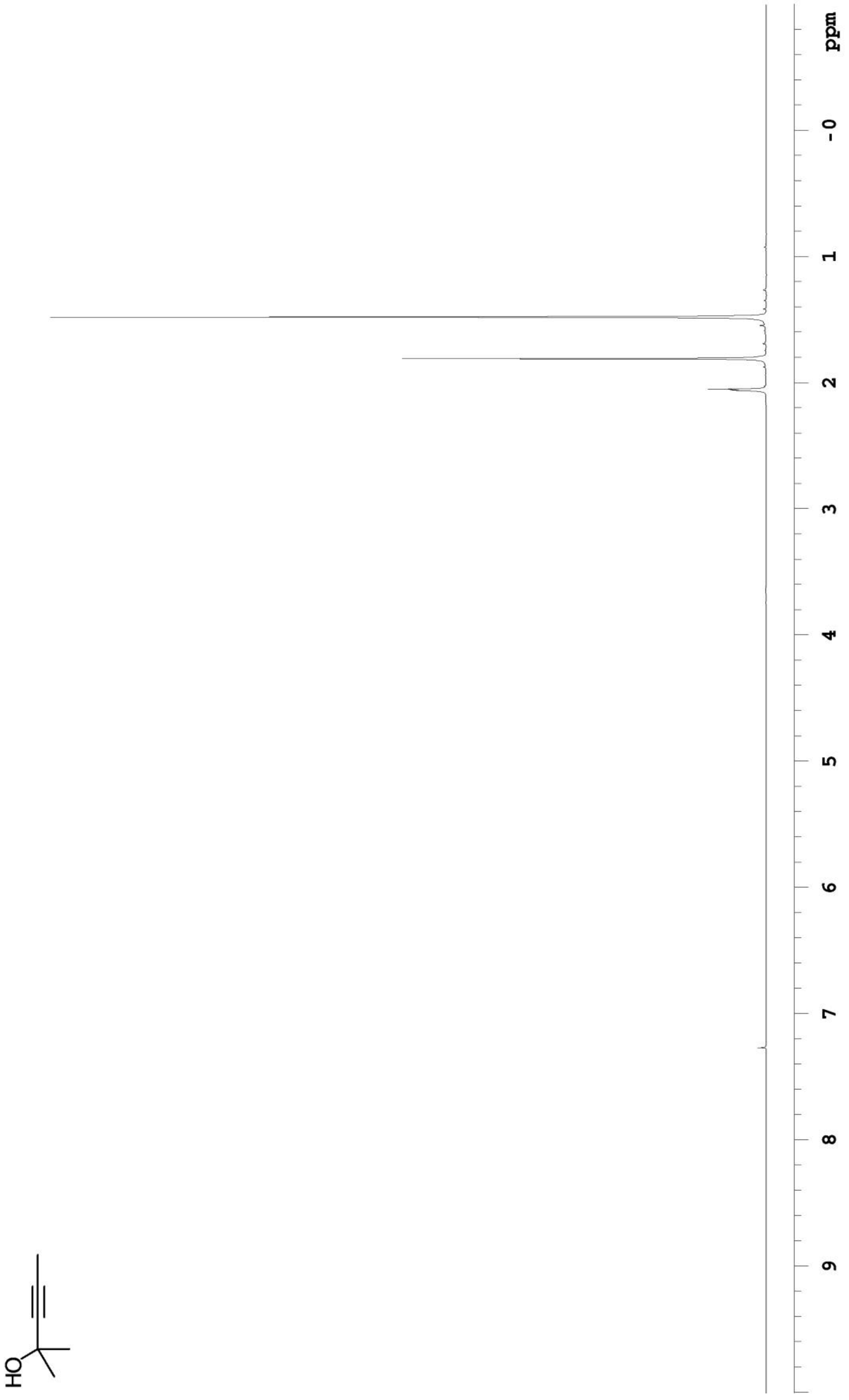
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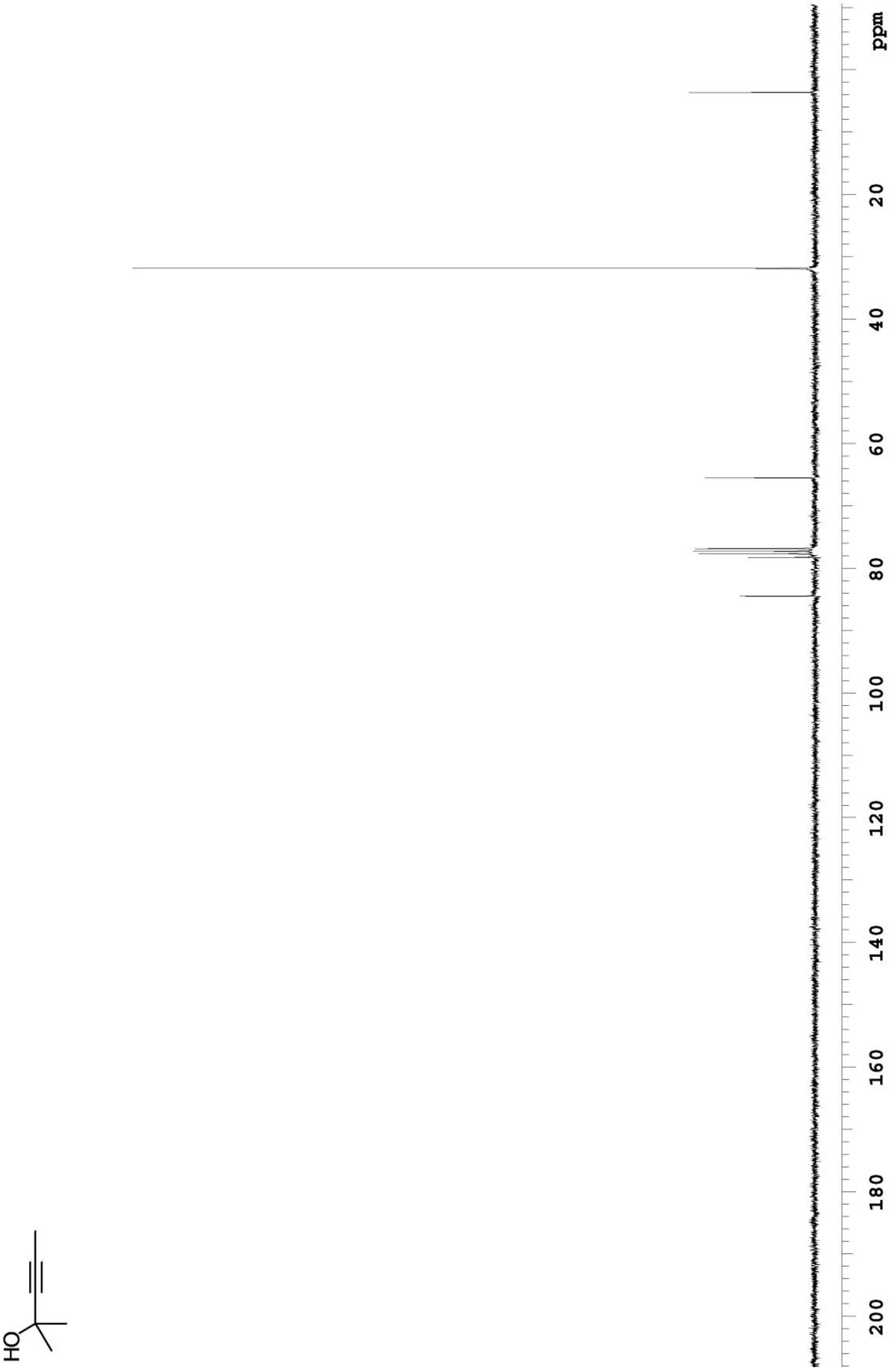
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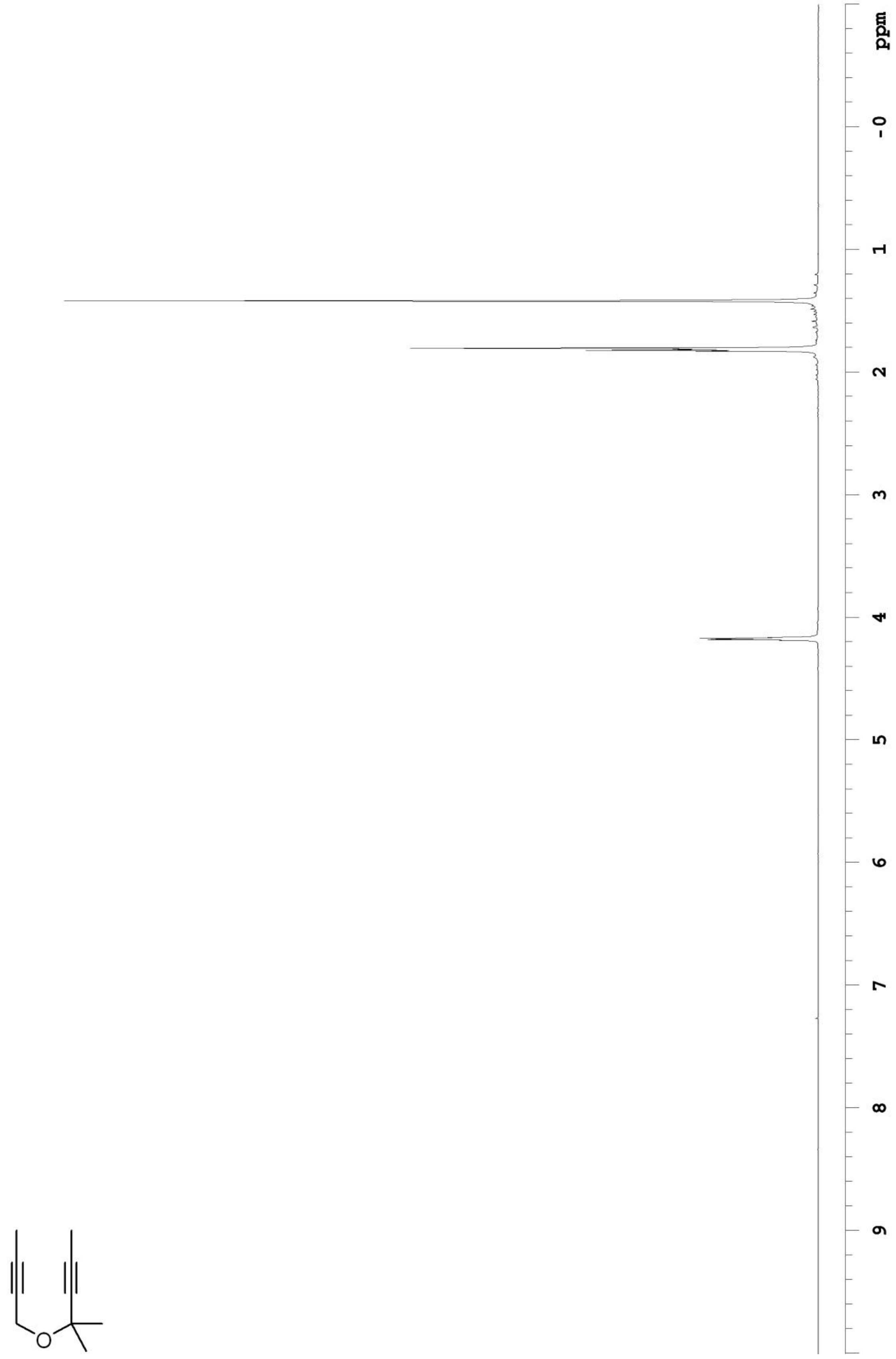
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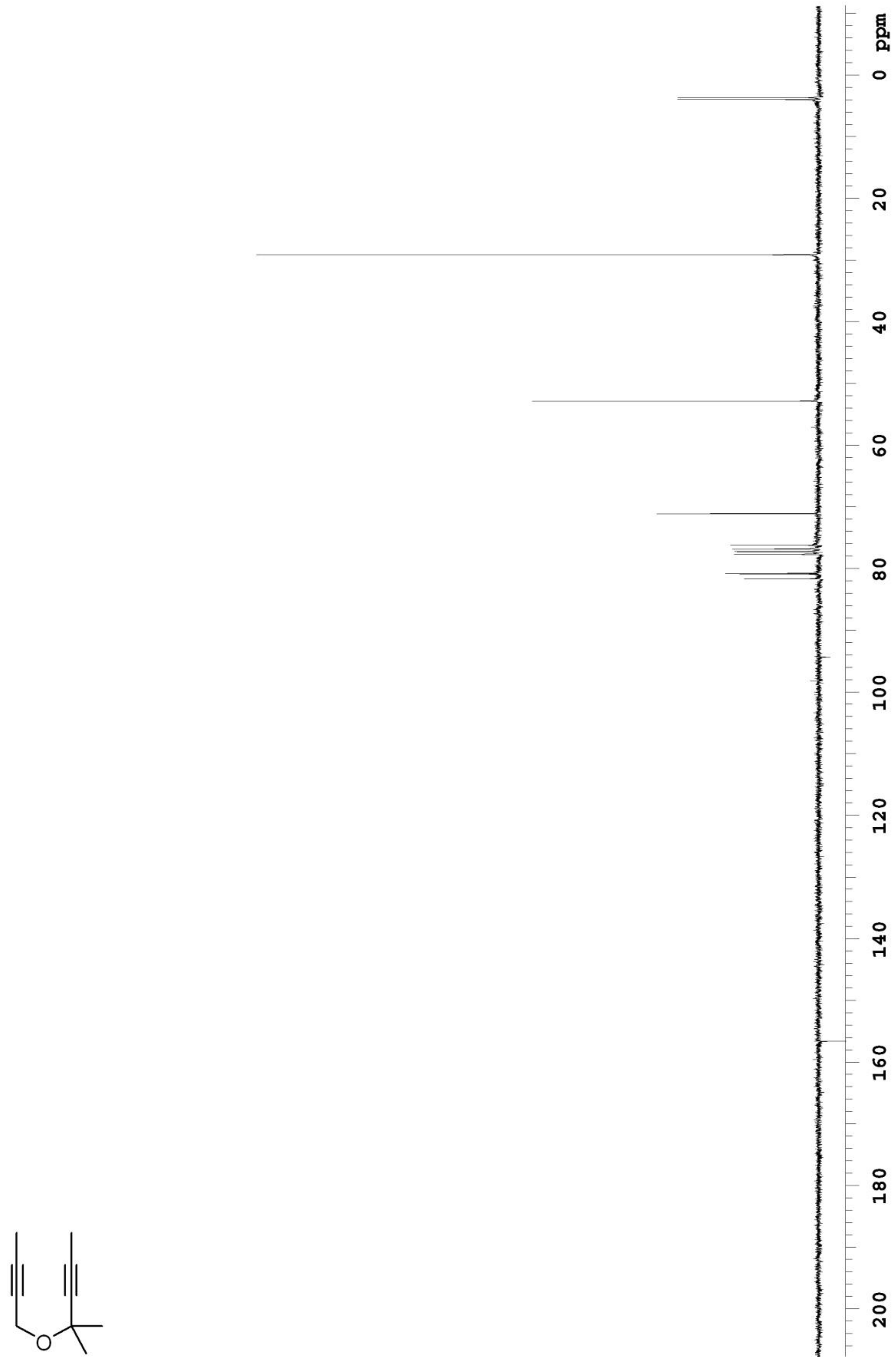
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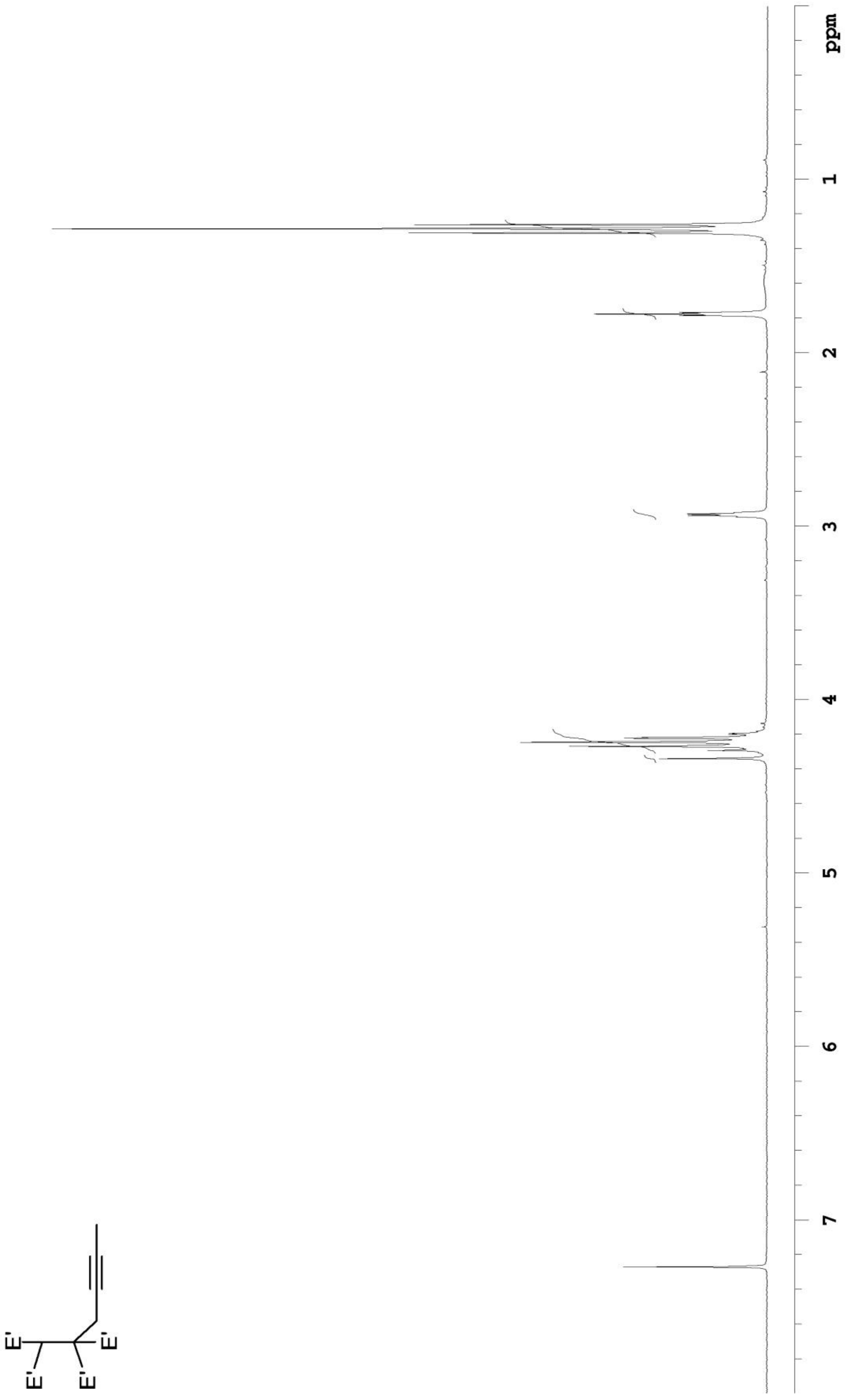
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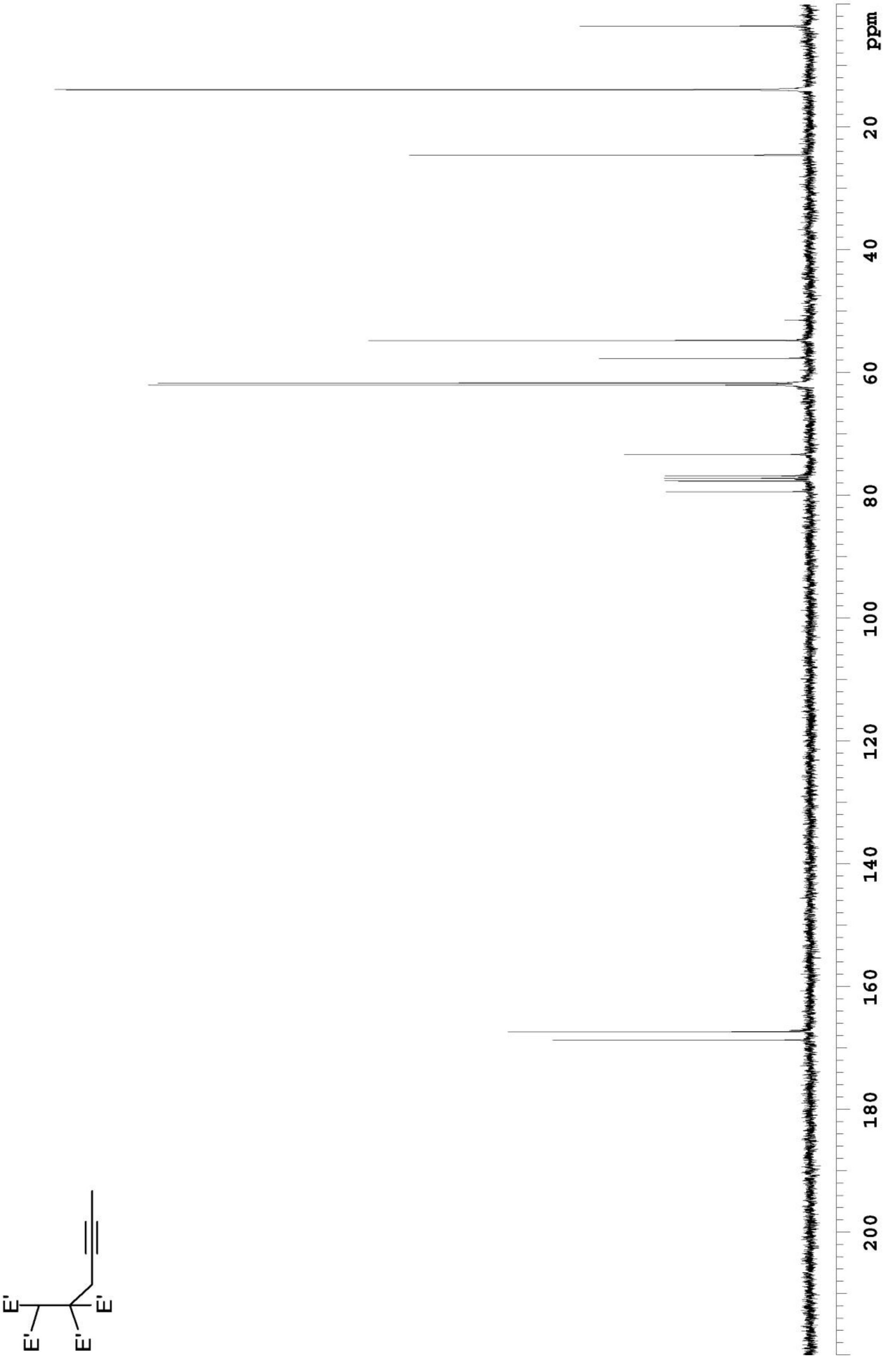
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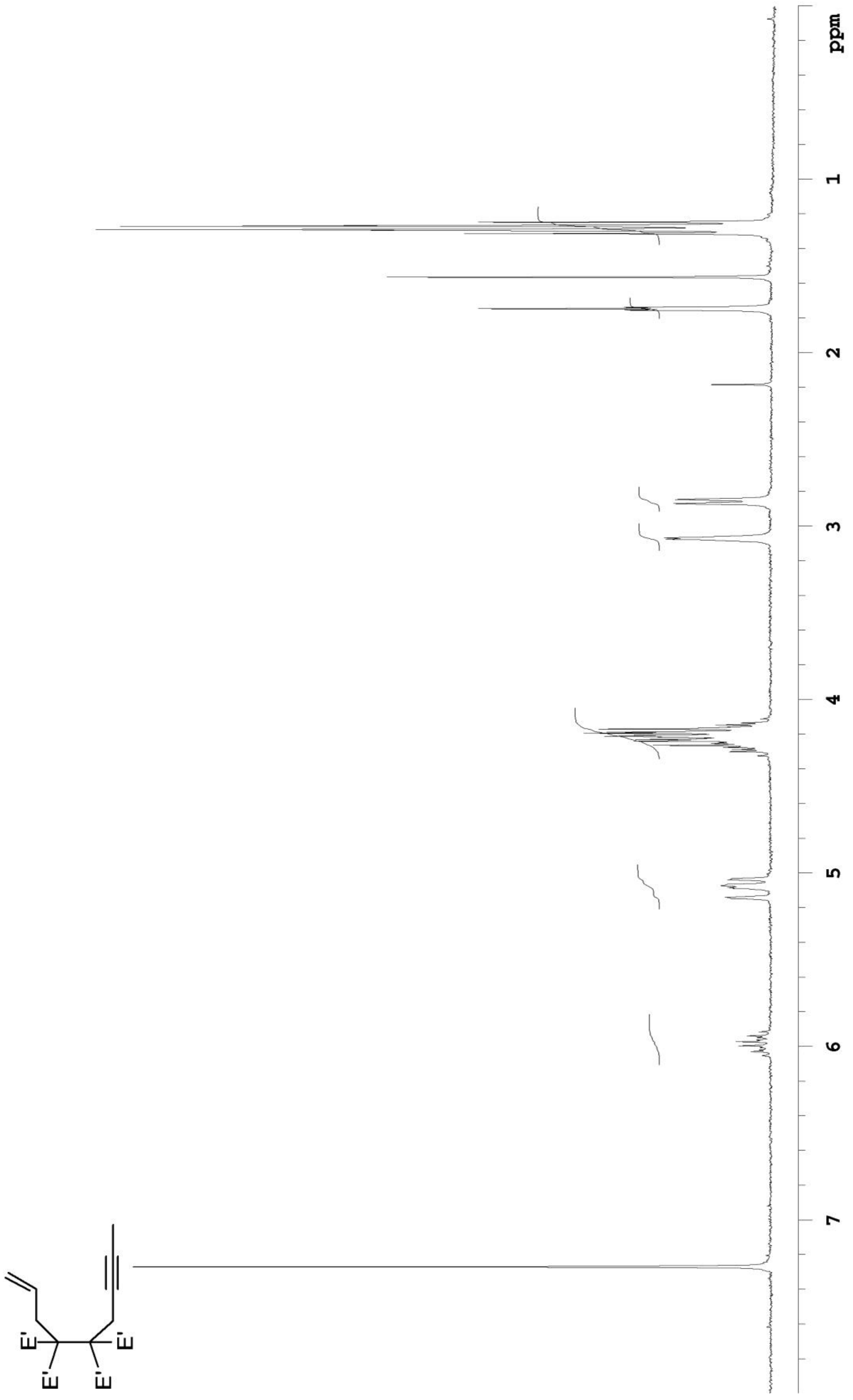
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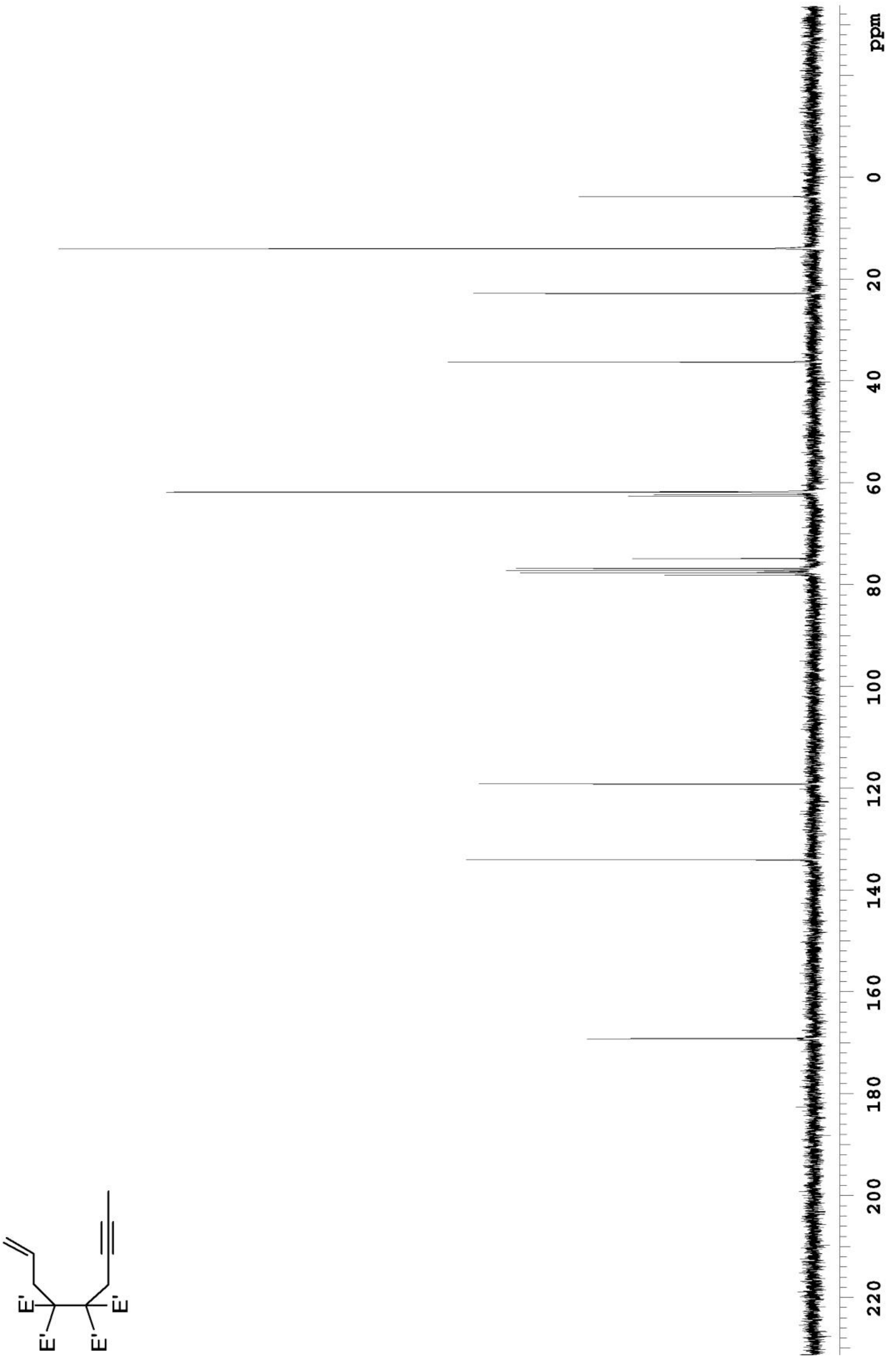

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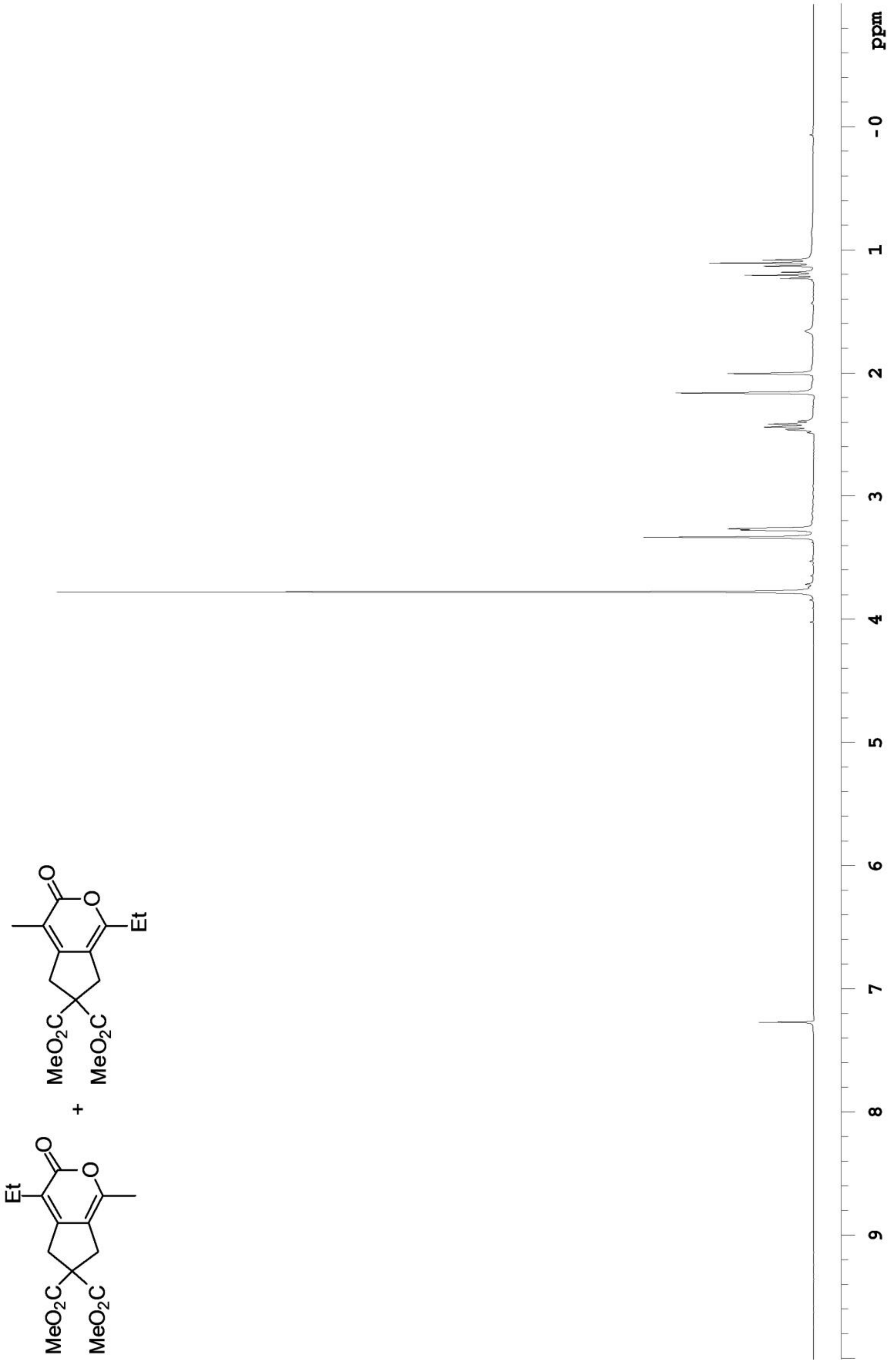
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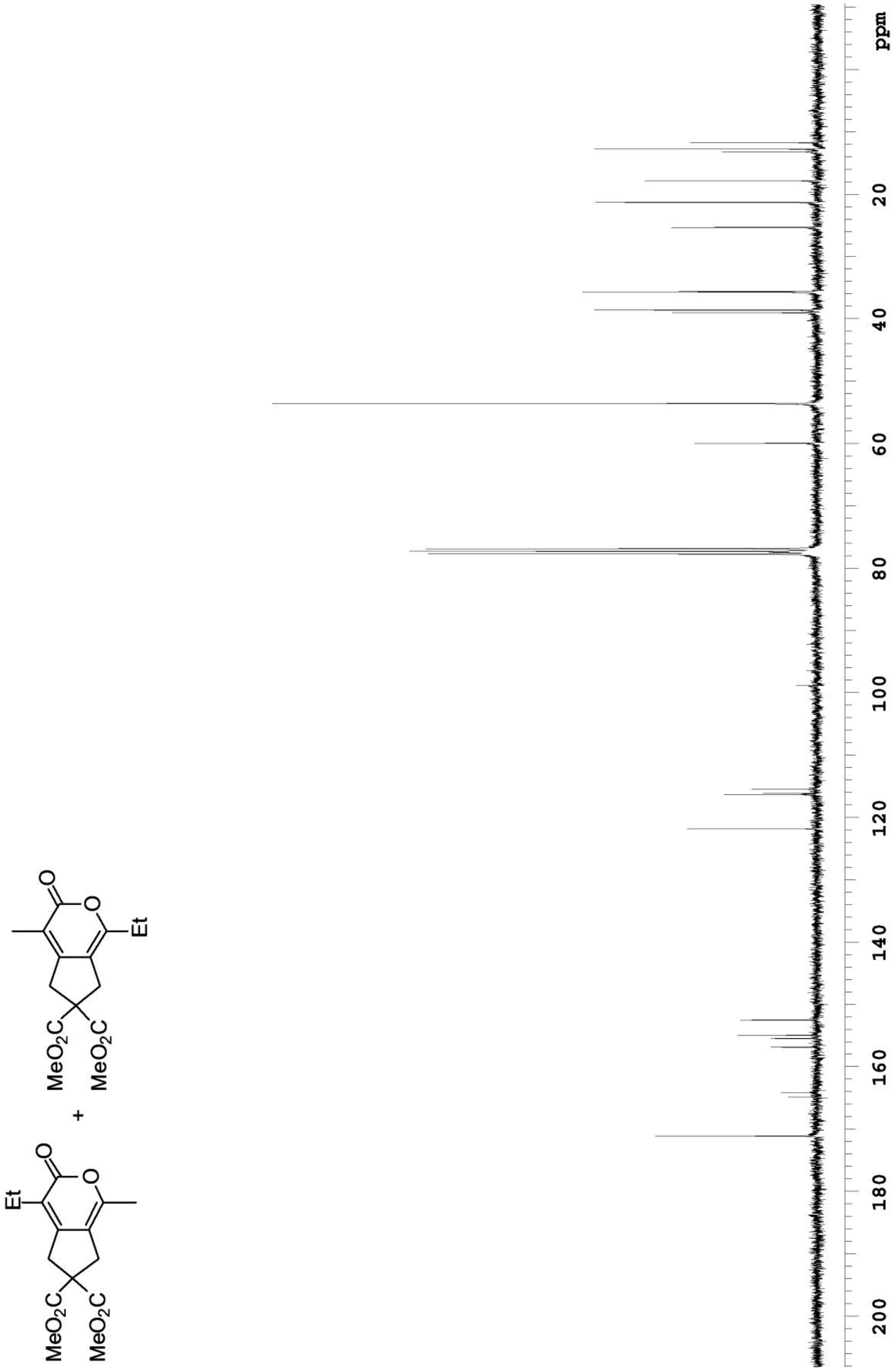

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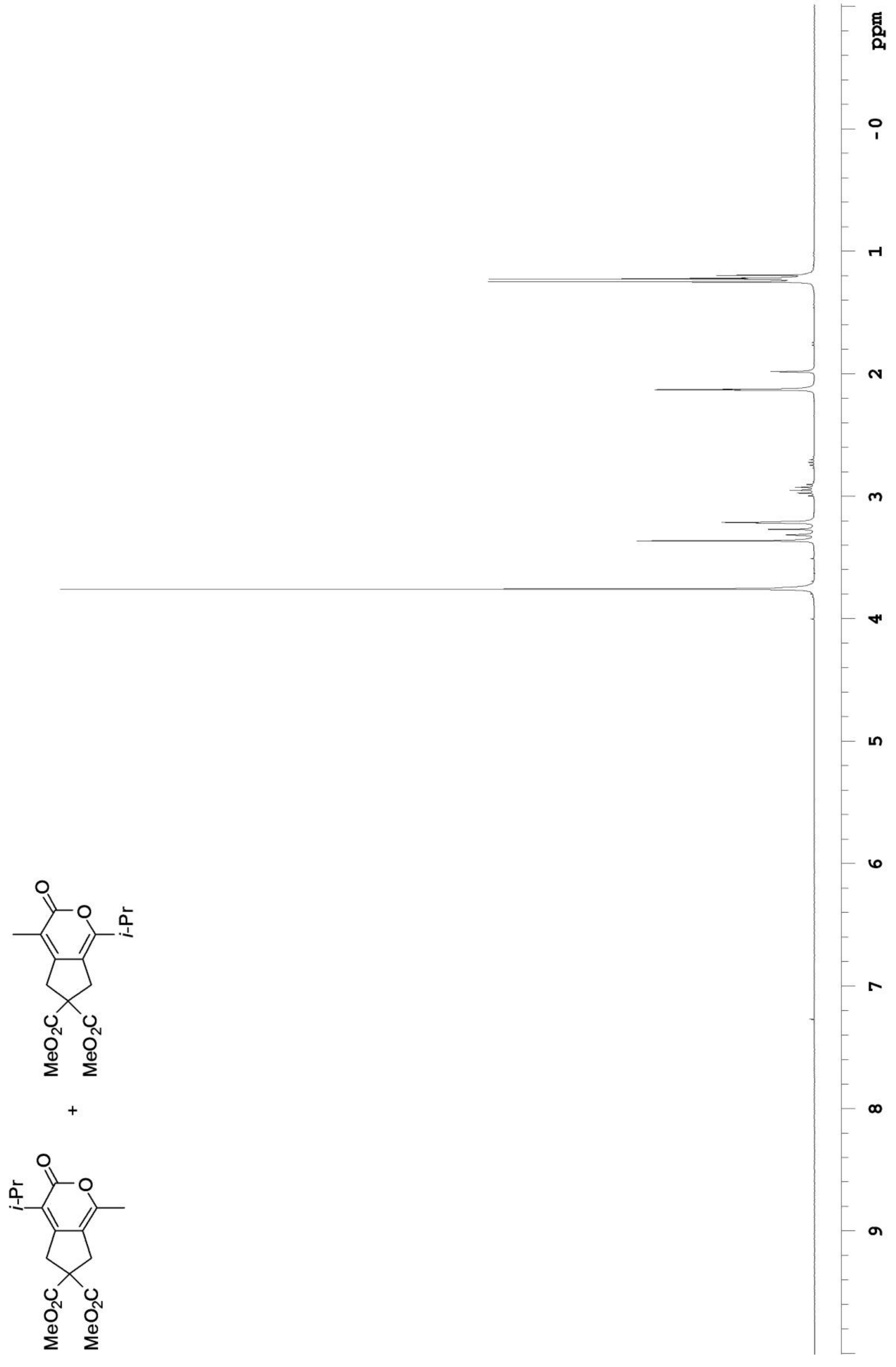
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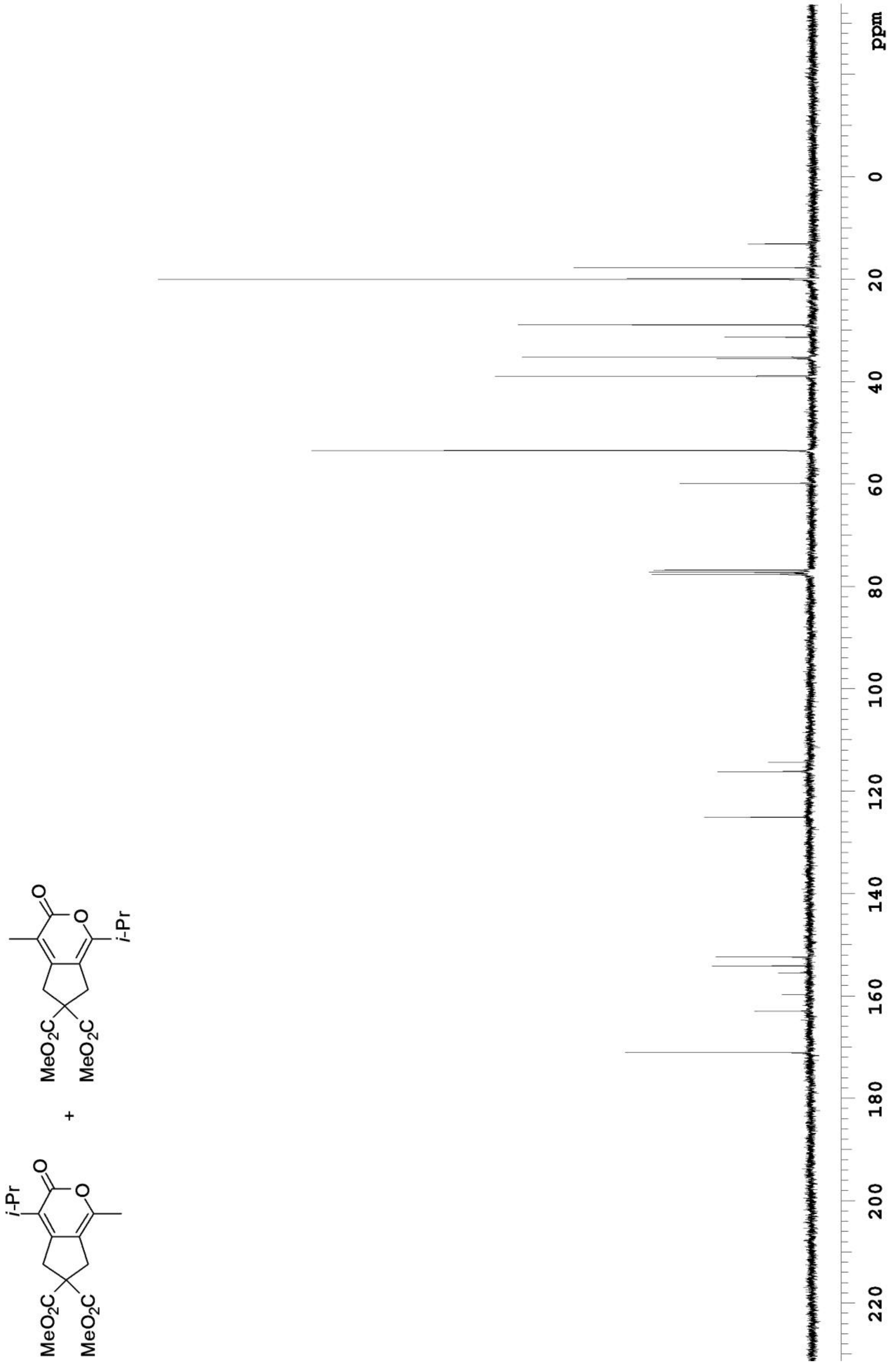
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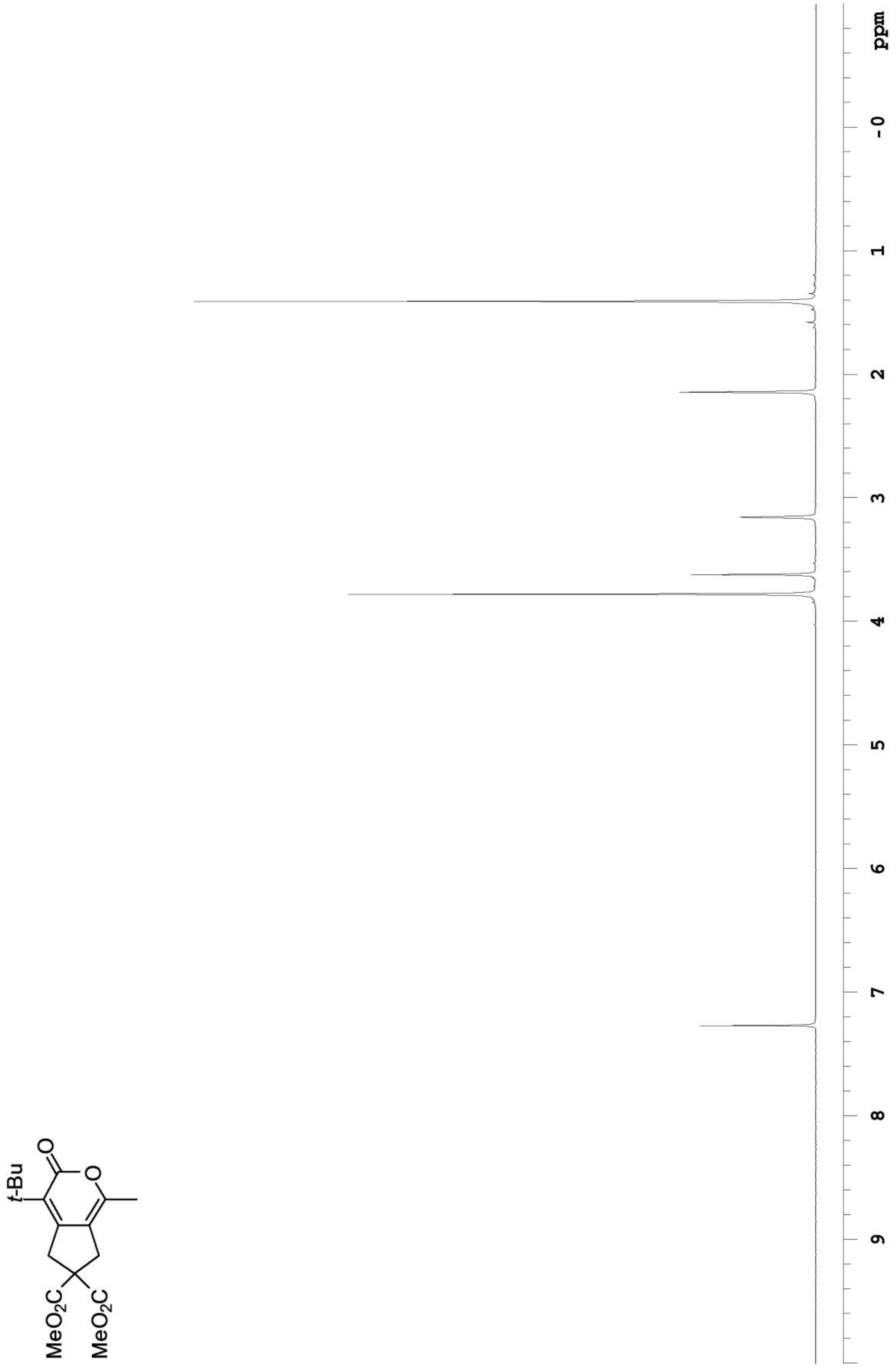
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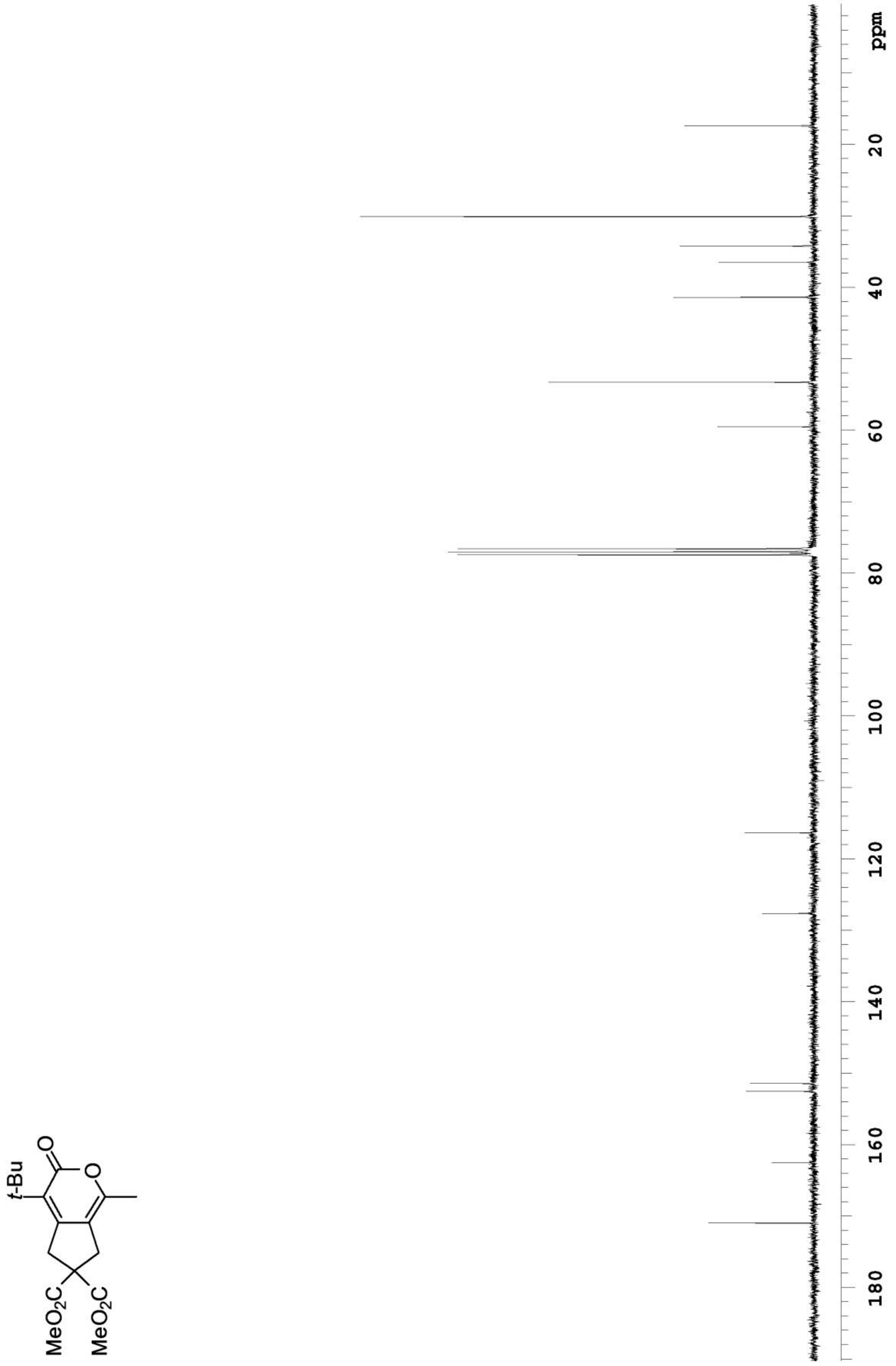
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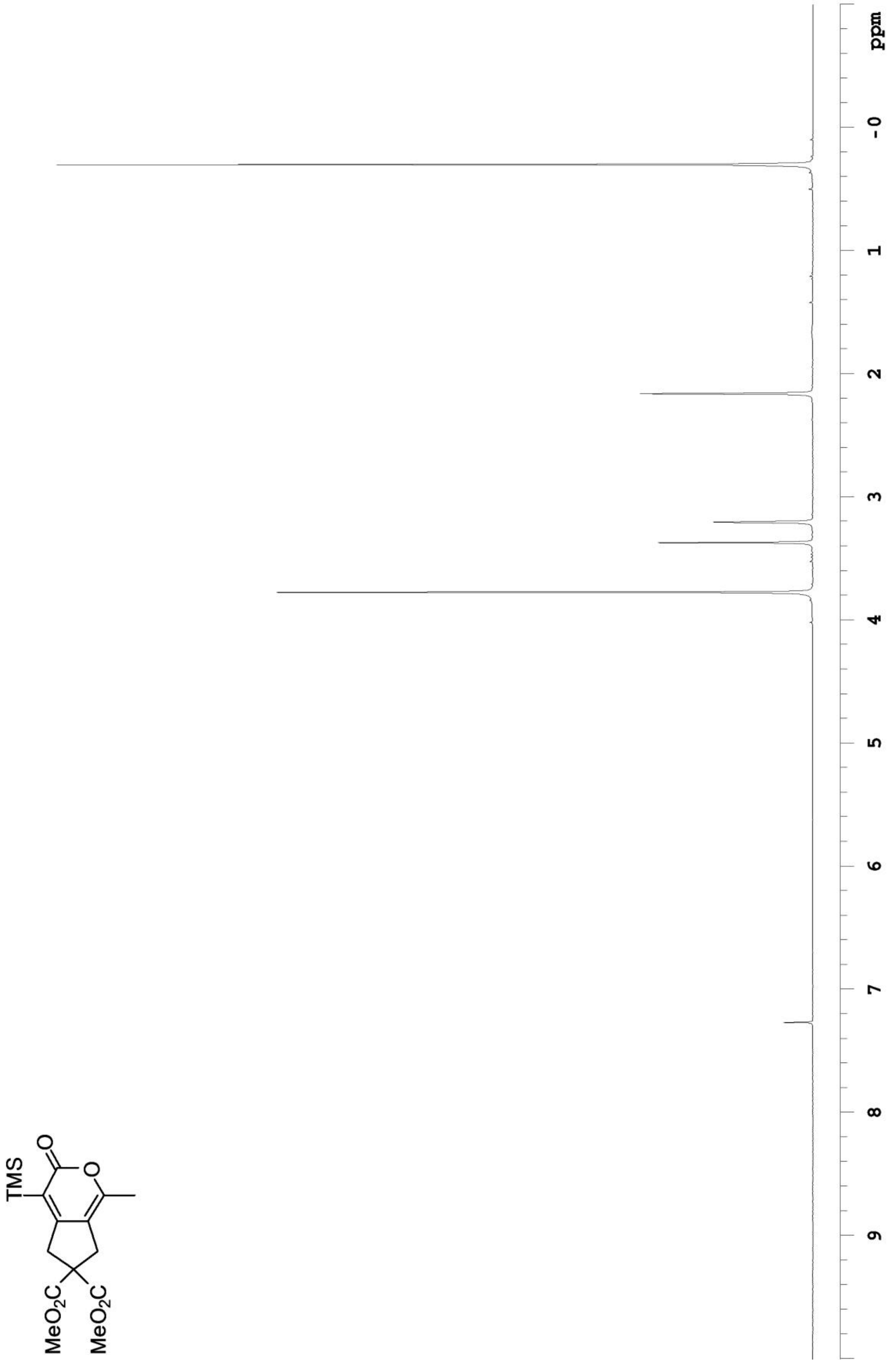
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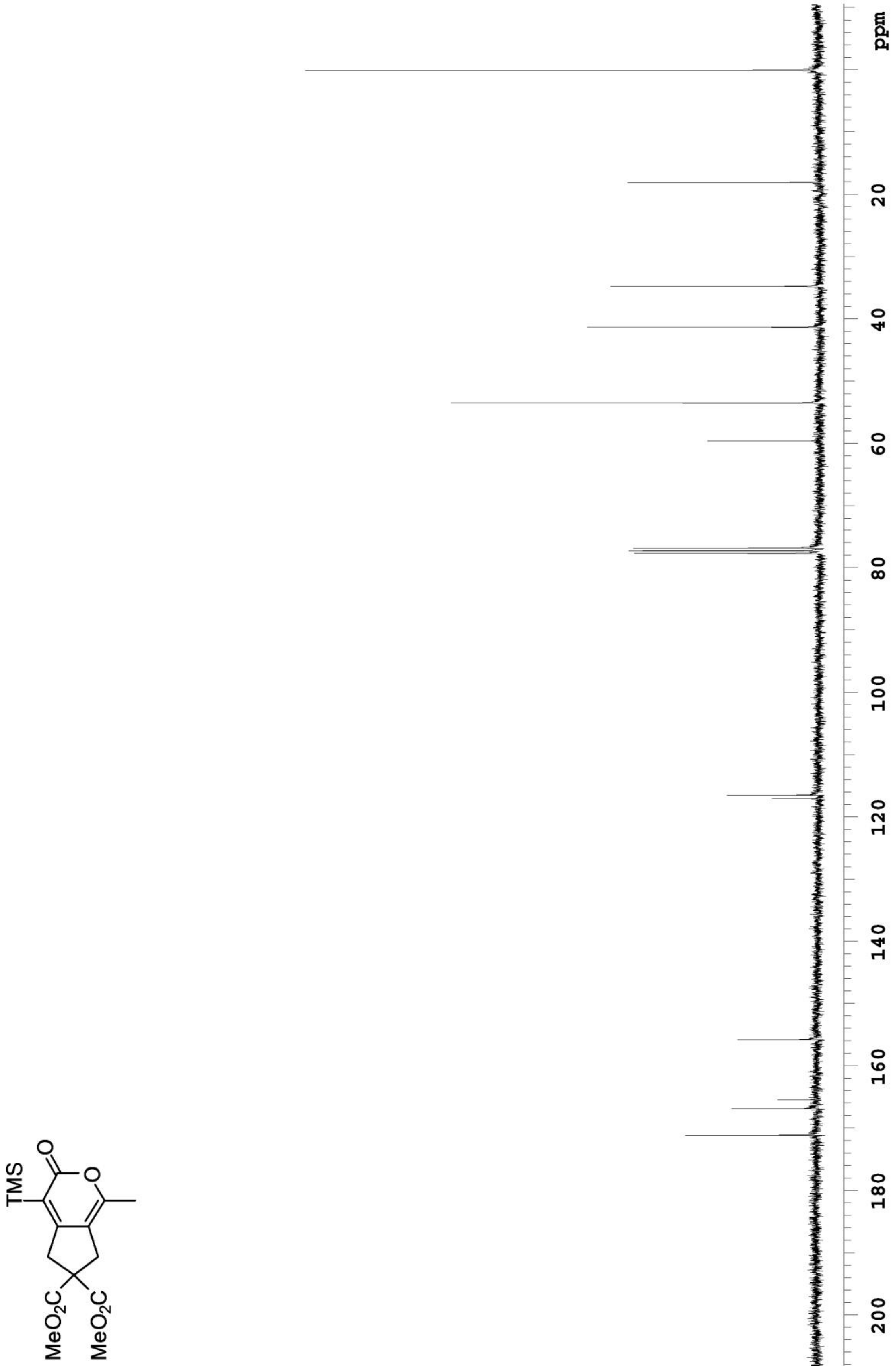
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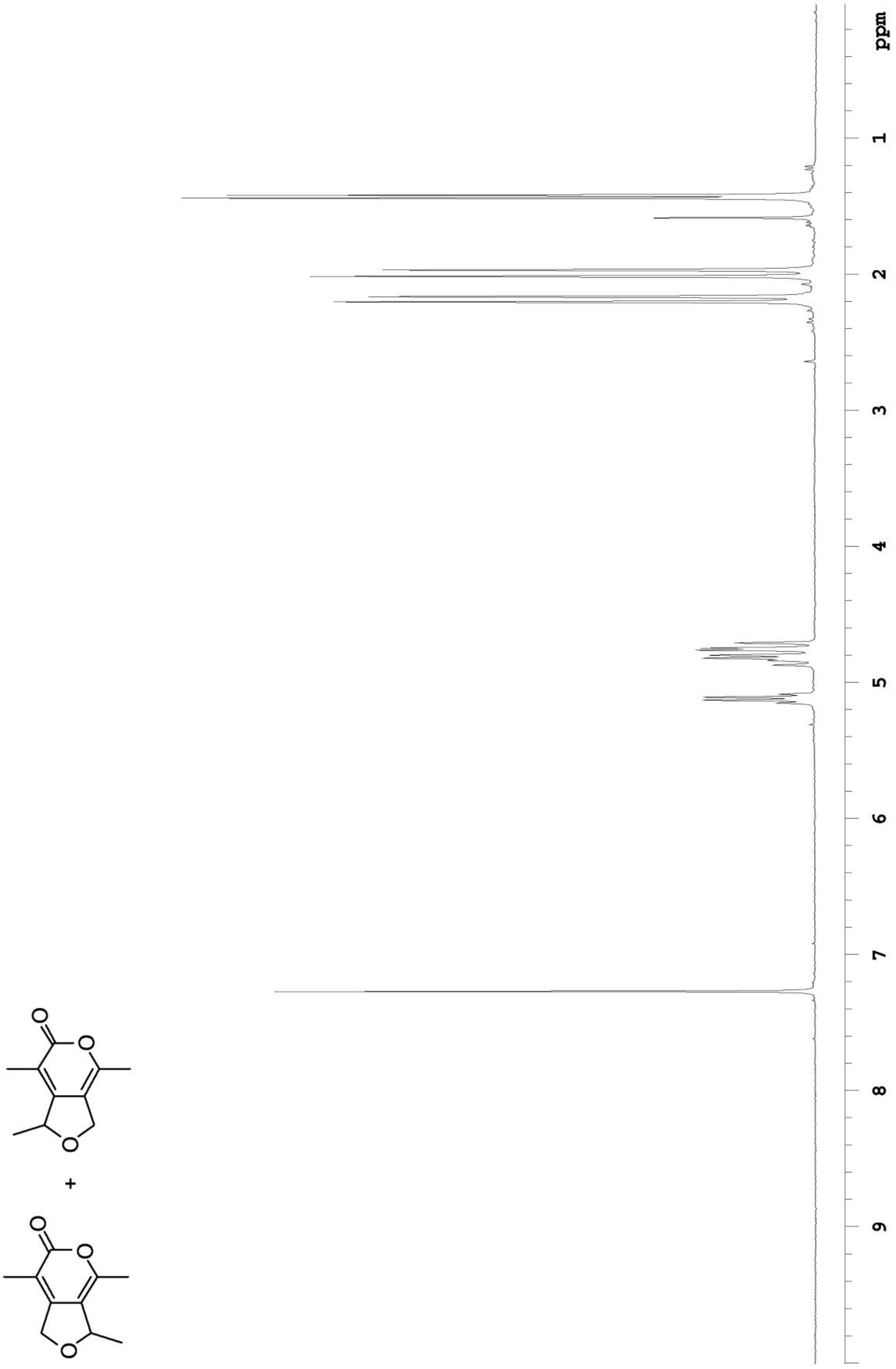
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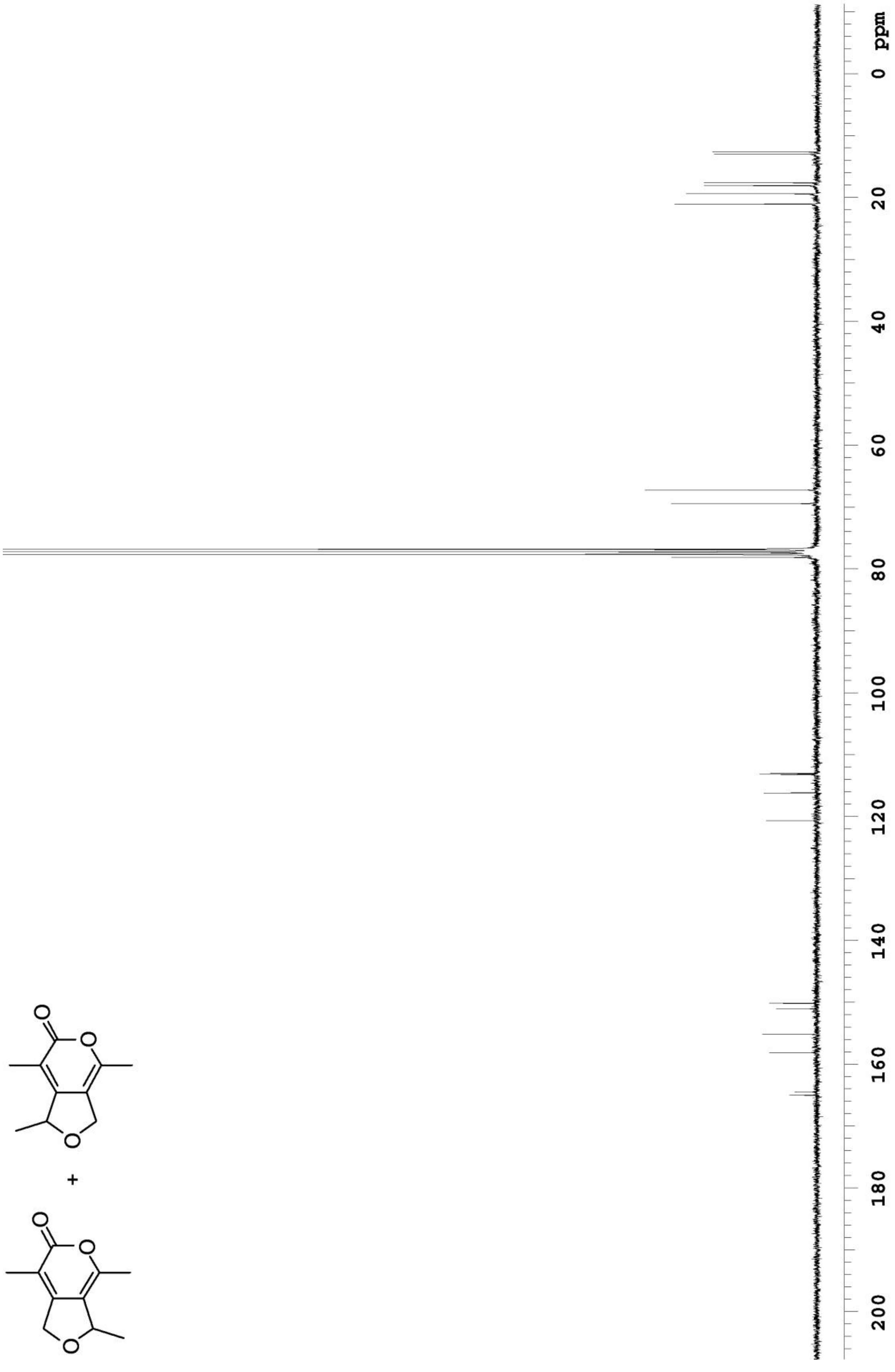
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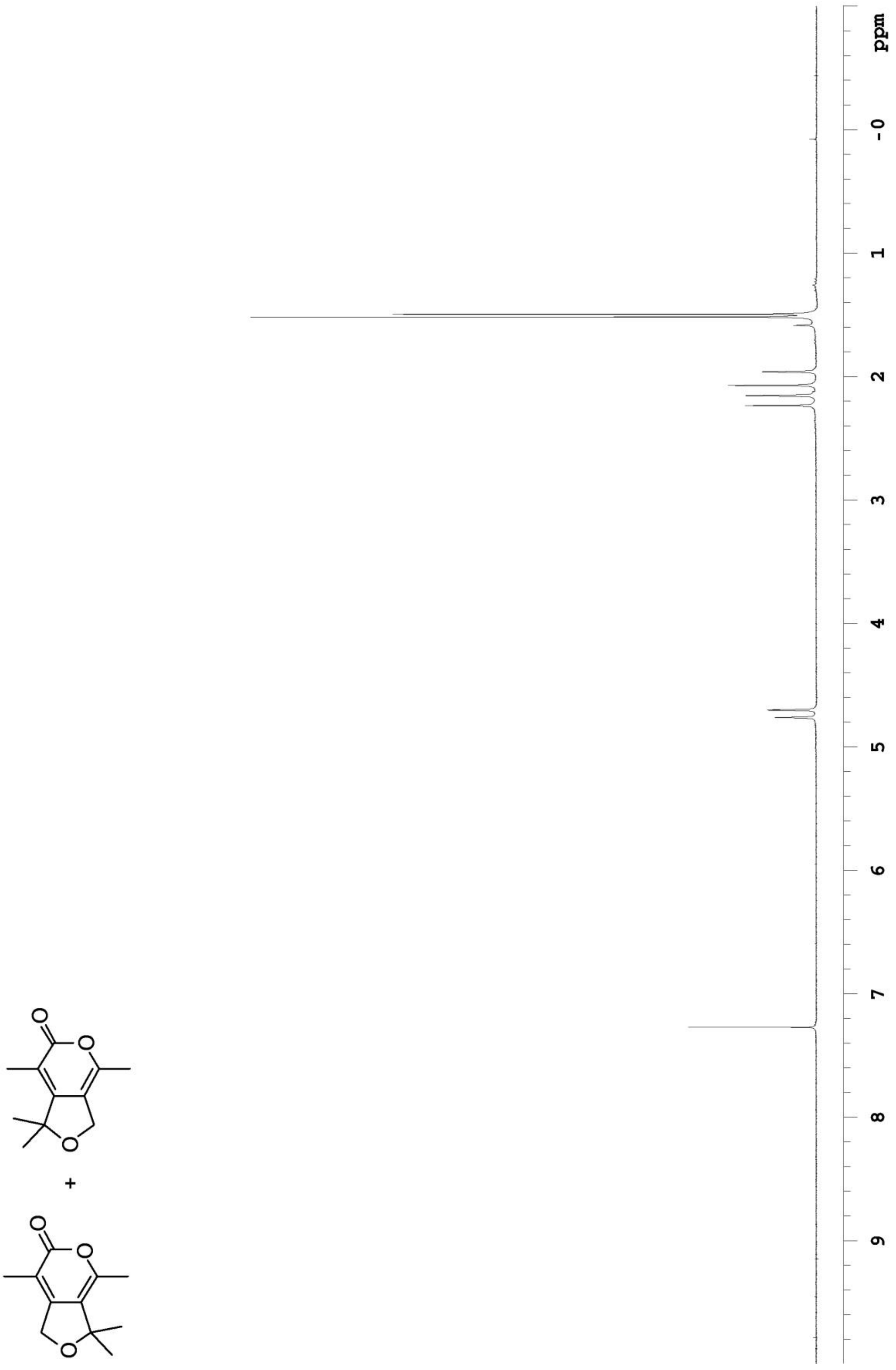
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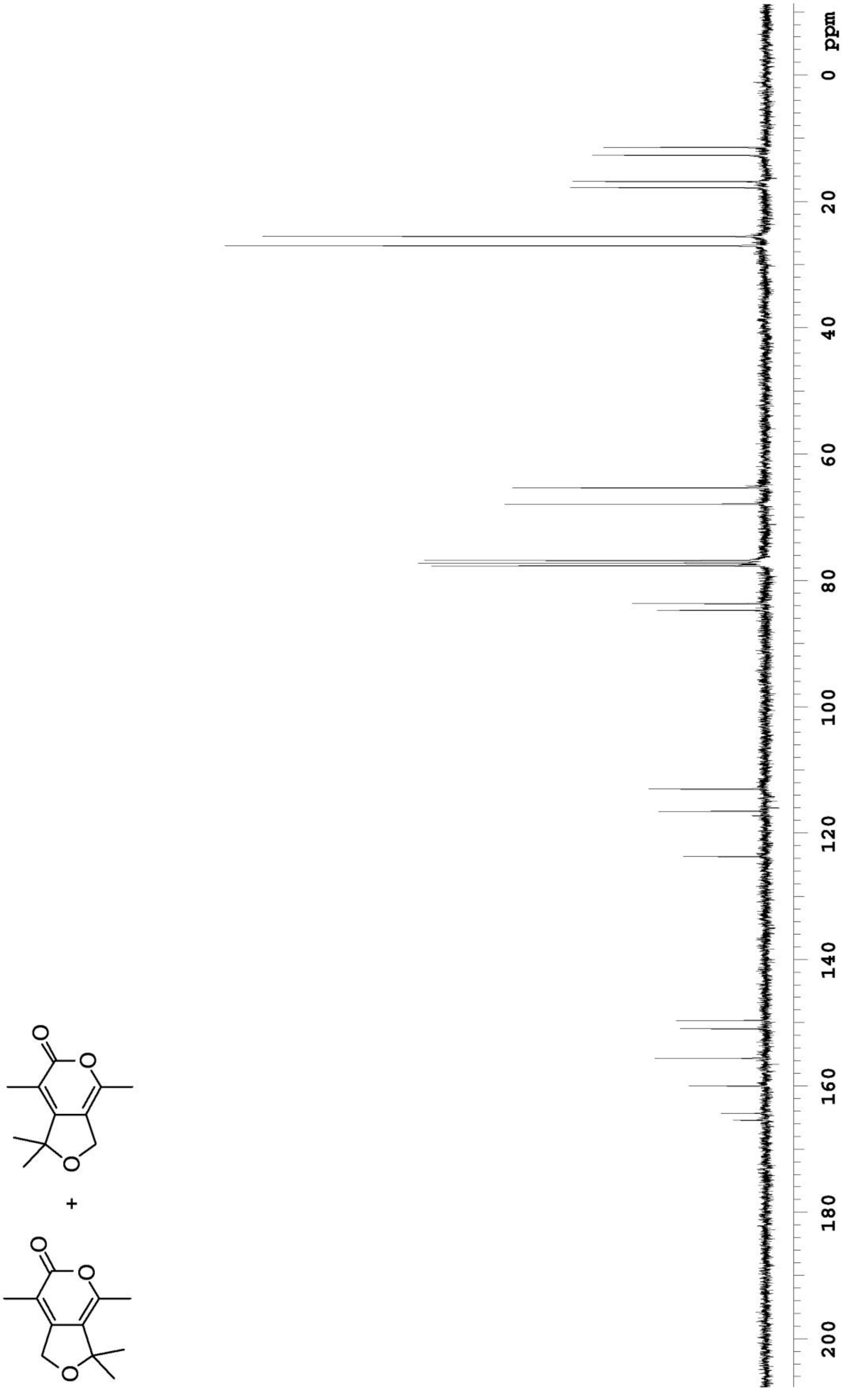
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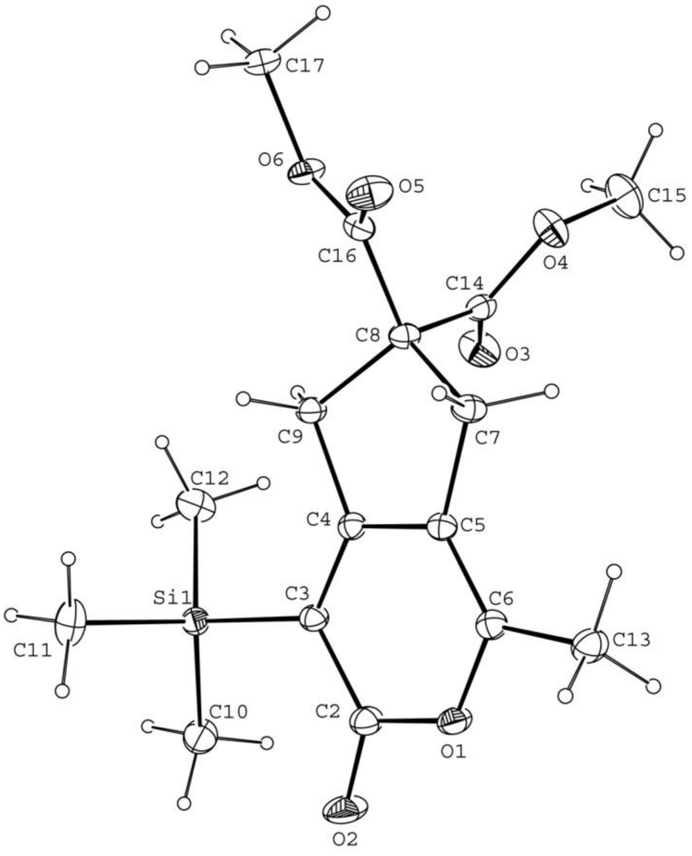
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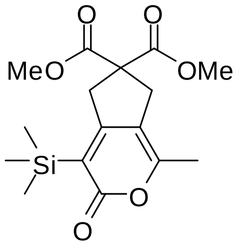
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2.43

Table A.1. Crystal data and structure refinement for jl003.

Identification code	jl003	
Empirical formula	C16 H22 O6 Si	
Formula weight	338.43	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.0883(3) Å	α= 90°.
	b = 7.5199(2) Å	β= 94.6394(16)°.
	c = 18.8890(5) Å	γ = 90°.
Volume	1711.44(8) $Å^3$	
Z	4	
Density (calculated)	1.313 Mg/m^3	
Absorption coefficient	0.164 mm^{-1}	
F(000)	720	
Crystal size	0.40 x 0.25 x 0.14 mm^3	
Theta range for data collection	4.23 to 27.50°.	
Index ranges	-15<=h<=15, -9<=k<=8, -24<=l<=24	
Reflections collected	6521	
Independent reflections	3911 [R(int) = 0.0208]	
Completeness to theta = 27.50°	99.2 %	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9774 and 0.9372	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3911 / 0 / 297	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 = 0.0901	
R indices (all data)	R1 = 0.0549, wR2 = 0.0994	
Extinction coefficient	0.007(2)	
Largest diff. peak and hole	0.301 and -0.278 e.$Å^{-3}$	

Table A.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jl003. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	1045(1)	6166(1)	8310(1)	22(1)
O(1)	697(1)	2236(2)	9850(1)	26(1)
O(2)	-525(1)	3962(2)	9259(1)	42(1)
O(3)	3613(1)	1072(2)	8003(1)	37(1)
O(4)	5093(1)	-11(2)	8655(1)	32(1)
O(5)	5989(1)	3140(2)	9816(1)	34(1)
O(6)	5832(1)	3923(2)	8665(1)	27(1)
C(2)	447(1)	3549(2)	9335(1)	26(1)
C(3)	1347(1)	4253(2)	8949(1)	21(1)
C(4)	2377(1)	3575(2)	9130(1)	19(1)
C(5)	2586(1)	2242(2)	9667(1)	20(1)
C(6)	1748(1)	1620(2)	10017(1)	22(1)
C(7)	3797(1)	1752(2)	9764(1)	23(1)
C(8)	4274(1)	2560(2)	9095(1)	21(1)
C(9)	3470(1)	4092(2)	8854(1)	22(1)
C(10)	-436(2)	6198(3)	7953(1)	37(1)
C(11)	1408(2)	8232(3)	8817(1)	41(1)
C(12)	1901(2)	5997(3)	7529(1)	36(1)
C(13)	1803(2)	285(2)	10600(1)	30(1)
C(14)	4264(1)	1155(2)	8513(1)	22(1)
C(15)	5185(2)	-1427(3)	8144(1)	42(1)
C(16)	5458(1)	3221(2)	9251(1)	22(1)
C(17)	6978(1)	4543(3)	8732(1)	30(1)

Table A.3. Bond lengths [Å] and angles [°] for jl003.

Si(1)-C(11)	1.8588(19)
Si(1)-C(10)	1.8621(18)
Si(1)-C(12)	1.8736(18)
Si(1)-C(3)	1.8941(15)
O(1)-C(6)	1.3652(18)
O(1)-C(2)	1.4024(19)
O(2)-C(2)	1.2126(19)
O(3)-C(14)	1.1952(18)
O(4)-C(14)	1.3413(18)
O(4)-C(15)	1.447(2)
O(5)-C(16)	1.2027(17)
O(6)-C(16)	1.3366(18)
O(6)-C(17)	1.4571(18)
C(2)-C(3)	1.457(2)
C(3)-C(4)	1.363(2)
C(4)-C(5)	1.434(2)
C(4)-C(9)	1.5109(19)
C(5)-C(6)	1.338(2)
C(5)-C(7)	1.507(2)
C(6)-C(13)	1.488(2)
C(7)-C(8)	1.555(2)
C(7)-H(7A)	0.989(18)
C(7)-H(7B)	0.991(19)
C(8)-C(16)	1.522(2)
C(8)-C(14)	1.524(2)
C(8)-C(9)	1.551(2)
C(9)-H(9A)	0.979(19)
C(9)-H(9B)	0.968(18)
C(10)-H(10A)	0.97(2)
C(10)-H(10B)	0.99(2)
C(10)-H(10C)	0.97(2)
C(11)-H(11A)	0.99(3)
C(11)-H(11B)	0.89(3)

Table A.3 continued.

C(11)-H(11C)	1.00(3)
C(12)-H(12A)	0.97(2)
C(12)-H(12B)	0.95(2)
C(12)-H(12C)	1.02(2)
C(13)-H(13A)	0.98(2)
C(13)-H(13B)	0.97(2)
C(13)-H(13C)	0.90(3)
C(15)-H(15A)	0.99(3)
C(15)-H(15B)	0.94(3)
C(15)-H(15C)	0.97(3)
C(17)-H(17A)	0.97(2)
C(17)-H(17B)	0.98(2)
C(17)-H(17C)	0.97(2)
C(11)-Si(1)-C(10)	110.85(10)
C(11)-Si(1)-C(12)	109.91(10)
C(10)-Si(1)-C(12)	106.95(9)
C(11)-Si(1)-C(3)	106.33(8)
C(10)-Si(1)-C(3)	111.74(8)
C(12)-Si(1)-C(3)	111.10(8)
C(6)-O(1)-C(2)	122.92(11)
C(14)-O(4)-C(15)	116.42(13)
C(16)-O(6)-C(17)	115.94(12)
O(2)-C(2)-O(1)	114.45(13)
O(2)-C(2)-C(3)	127.14(15)
O(1)-C(2)-C(3)	118.40(12)
C(4)-C(3)-C(2)	116.23(13)
C(4)-C(3)-Si(1)	124.69(11)
C(2)-C(3)-Si(1)	118.79(11)
C(3)-C(4)-C(5)	122.99(13)
C(3)-C(4)-C(9)	128.57(13)
C(5)-C(4)-C(9)	108.39(12)
C(6)-C(5)-C(4)	119.79(13)
C(6)-C(5)-C(7)	128.43(13)

Table A.3 continued.

C(4)-C(5)-C(7)	111.77(12)
C(5)-C(6)-O(1)	119.64(13)
C(5)-C(6)-C(13)	127.70(14)
O(1)-C(6)-C(13)	112.65(13)
C(5)-C(7)-C(8)	103.06(11)
C(5)-C(7)-H(7A)	111.5(10)
C(8)-C(7)-H(7A)	109.3(10)
C(5)-C(7)-H(7B)	113.3(10)
C(8)-C(7)-H(7B)	110.7(10)
H(7A)-C(7)-H(7B)	108.8(15)
C(16)-C(8)-C(14)	108.54(12)
C(16)-C(8)-C(9)	111.80(12)
C(14)-C(8)-C(9)	109.59(12)
C(16)-C(8)-C(7)	112.01(11)
C(14)-C(8)-C(7)	109.49(12)
C(9)-C(8)-C(7)	105.36(12)
C(4)-C(9)-C(8)	104.58(12)
C(4)-C(9)-H(9A)	109.7(10)
C(8)-C(9)-H(9A)	109.1(10)
C(4)-C(9)-H(9B)	113.6(10)
C(8)-C(9)-H(9B)	110.5(10)
H(9A)-C(9)-H(9B)	109.2(15)
Si(1)-C(10)-H(10A)	112.1(13)
Si(1)-C(10)-H(10B)	112.2(13)
H(10A)-C(10)-H(10B)	107.9(19)
Si(1)-C(10)-H(10C)	107.5(13)
H(10A)-C(10)-H(10C)	110.2(19)
H(10B)-C(10)-H(10C)	106.8(19)
Si(1)-C(11)-H(11A)	112.0(15)
Si(1)-C(11)-H(11B)	113.5(16)
H(11A)-C(11)-H(11B)	108(2)
Si(1)-C(11)-H(11C)	110.3(15)
H(11A)-C(11)-H(11C)	109(2)

Table A.3 continued.

H(11B)-C(11)-H(11C)	104(2)
Si(1)-C(12)-H(12A)	114.7(13)
Si(1)-C(12)-H(12B)	109.2(13)
H(12A)-C(12)-H(12B)	107.8(18)
Si(1)-C(12)-H(12C)	111.8(12)
H(12A)-C(12)-H(12C)	105.7(17)
H(12B)-C(12)-H(12C)	107.2(17)
C(6)-C(13)-H(13A)	109.4(13)
C(6)-C(13)-H(13B)	113.0(13)
H(13A)-C(13)-H(13B)	112.9(19)
C(6)-C(13)-H(13C)	107.6(16)
H(13A)-C(13)-H(13C)	109(2)
H(13B)-C(13)-H(13C)	104.5(19)
O(3)-C(14)-O(4)	123.98(14)
O(3)-C(14)-C(8)	125.66(14)
O(4)-C(14)-C(8)	110.36(12)
O(4)-C(15)-H(15A)	109.5(18)
O(4)-C(15)-H(15B)	106.3(19)
H(15A)-C(15)-H(15B)	113(3)
O(4)-C(15)-H(15C)	112.5(16)
H(15A)-C(15)-H(15C)	107(2)
H(15B)-C(15)-H(15C)	109(2)
O(5)-C(16)-O(6)	124.29(13)
O(5)-C(16)-C(8)	125.55(13)
O(6)-C(16)-C(8)	110.16(12)
O(6)-C(17)-H(17A)	105.9(13)
O(6)-C(17)-H(17B)	110.0(13)
H(17A)-C(17)-H(17B)	107.8(18)
O(6)-C(17)-H(17C)	109.2(13)
H(17A)-C(17)-H(17C)	112.0(18)
H(17B)-C(17)-H(17C)	111.7(17)

Symmetry transformations used to generate equivalent atoms:

Table A.4. Anisotropic displacement parameters ($Å^2$x 10^3)for jl003. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	20(1)	21(1)	24(1)	0(1)	0(1)	0(1)
O(1)	18(1)	31(1)	30(1)	5(1)	4(1)	-2(1)
O(2)	16(1)	56(1)	53(1)	19(1)	4(1)	3(1)
O(3)	33(1)	45(1)	32(1)	-11(1)	-9(1)	5(1)
O(4)	37(1)	29(1)	28(1)	-5(1)	-4(1)	11(1)
O(5)	24(1)	51(1)	27(1)	1(1)	-5(1)	-4(1)
O(6)	16(1)	36(1)	28(1)	4(1)	1(1)	-4(1)
C(2)	20(1)	30(1)	29(1)	2(1)	1(1)	-1(1)
C(3)	17(1)	23(1)	22(1)	-2(1)	1(1)	-1(1)
C(4)	19(1)	20(1)	19(1)	-2(1)	2(1)	-2(1)
C(5)	18(1)	22(1)	19(1)	-1(1)	1(1)	0(1)
C(6)	21(1)	24(1)	21(1)	-2(1)	1(1)	-2(1)
C(7)	19(1)	31(1)	20(1)	4(1)	2(1)	3(1)
C(8)	16(1)	26(1)	20(1)	1(1)	1(1)	1(1)
C(9)	17(1)	25(1)	24(1)	4(1)	2(1)	1(1)
C(10)	26(1)	35(1)	51(1)	10(1)	-6(1)	1(1)
C(11)	60(1)	26(1)	35(1)	-2(1)	1(1)	-9(1)
C(12)	35(1)	45(1)	27(1)	6(1)	5(1)	9(1)
C(13)	29(1)	34(1)	28(1)	6(1)	6(1)	-1(1)
C(14)	19(1)	26(1)	22(1)	4(1)	3(1)	-2(1)
C(15)	55(1)	34(1)	38(1)	-11(1)	2(1)	12(1)
C(16)	19(1)	24(1)	23(1)	-2(1)	1(1)	3(1)
C(17)	16(1)	36(1)	39(1)	0(1)	3(1)	-4(1)

Table A.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for jl003.

	x	y	z	U(eq)
H(7A)	4167(14)	2310(20)	10195(10)	32(5)
H(7B)	3926(14)	450(30)	9787(9)	28(4)
H(9A)	3738(14)	5200(30)	9079(9)	29(4)
H(9B)	3432(14)	4230(20)	8342(10)	30(4)
H(10A)	-682(18)	5050(30)	7770(12)	57(6)
H(10B)	-941(19)	6570(30)	8317(12)	59(7)
H(10C)	-509(18)	7080(30)	7579(12)	59(6)
H(11A)	920(20)	8430(30)	9204(14)	68(7)
H(11B)	1390(20)	9210(30)	8547(13)	66(7)
H(11C)	2190(20)	8180(40)	9027(14)	78(8)
H(12A)	2011(18)	4790(30)	7362(12)	53(6)
H(12B)	1556(18)	6660(30)	7145(12)	53(6)
H(12C)	2674(19)	6510(30)	7638(11)	49(6)
H(13A)	2573(19)	-90(30)	10706(11)	53(6)
H(13B)	1297(19)	-710(30)	10504(12)	54(6)
H(13C)	1560(20)	820(30)	10986(13)	66(7)
H(15A)	4560(30)	-2270(40)	8176(16)	104(11)
H(15B)	5890(30)	-1950(40)	8252(16)	96(10)
H(15C)	5150(20)	-1000(40)	7661(15)	80(9)
H(17A)	7120(18)	5010(30)	8271(12)	51(6)
H(17B)	7060(18)	5520(30)	9074(11)	53(6)
H(17C)	7465(18)	3550(30)	8873(11)	47(6)

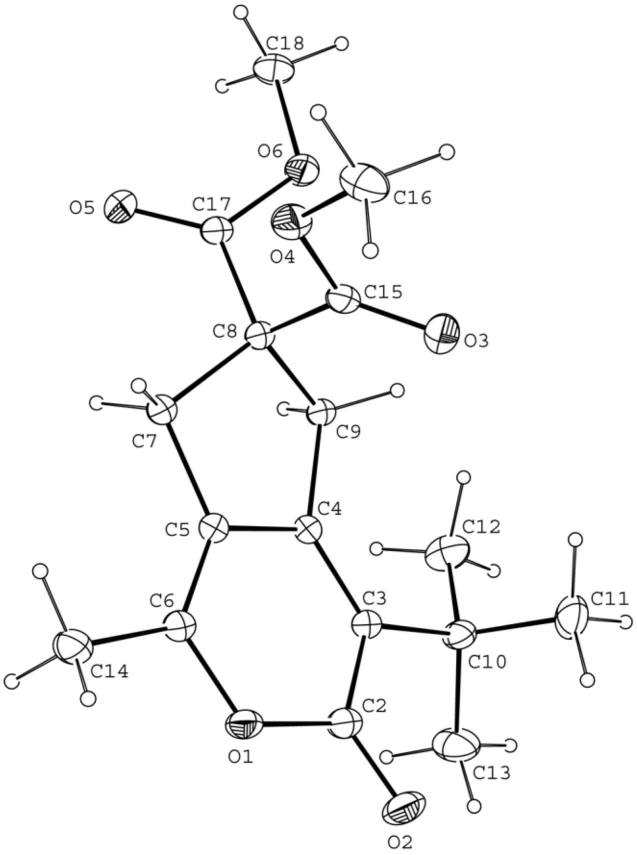
Table A.6. Torsion angles [°] for jl003.

C(6)-O(1)-C(2)-O(2)	-178.91(14)
C(6)-O(1)-C(2)-C(3)	1.5(2)
O(2)-C(2)-C(3)-C(4)	179.91(16)
O(1)-C(2)-C(3)-C(4)	-0.6(2)
O(2)-C(2)-C(3)-Si(1)	5.8(2)
O(1)-C(2)-C(3)-Si(1)	-174.69(10)
C(11)-Si(1)-C(3)-C(4)	-79.08(15)
C(10)-Si(1)-C(3)-C(4)	159.85(13)
C(12)-Si(1)-C(3)-C(4)	40.49(15)
C(11)-Si(1)-C(3)-C(2)	94.47(14)
C(10)-Si(1)-C(3)-C(2)	-26.60(15)
C(12)-Si(1)-C(3)-C(2)	-145.96(13)
C(2)-C(3)-C(4)-C(5)	0.1(2)
Si(1)-C(3)-C(4)-C(5)	173.76(11)
C(2)-C(3)-C(4)-C(9)	-176.95(14)
Si(1)-C(3)-C(4)-C(9)	-3.2(2)
C(3)-C(4)-C(5)-C(6)	-0.4(2)
C(9)-C(4)-C(5)-C(6)	177.14(13)
C(3)-C(4)-C(5)-C(7)	-179.38(14)
C(9)-C(4)-C(5)-C(7)	-1.84(17)
C(4)-C(5)-C(6)-O(1)	1.3(2)
C(7)-C(5)-C(6)-O(1)	-179.94(14)
C(4)-C(5)-C(6)-C(13)	-178.21(15)
C(7)-C(5)-C(6)-C(13)	0.6(3)
C(2)-O(1)-C(6)-C(5)	-1.9(2)
C(2)-O(1)-C(6)-C(13)	177.67(14)
C(6)-C(5)-C(7)-C(8)	166.82(15)
C(4)-C(5)-C(7)-C(8)	-14.30(16)
C(5)-C(7)-C(8)-C(16)	146.01(12)
C(5)-C(7)-C(8)-C(14)	-93.54(14)
C(5)-C(7)-C(8)-C(9)	24.25(15)
C(3)-C(4)-C(9)-C(8)	-165.33(14)
C(5)-C(4)-C(9)-C(8)	17.32(15)

Table A.6 continued.

C(16)-C(8)-C(9)-C(4)	-147.65(12)
C(14)-C(8)-C(9)-C(4)	91.96(13)
C(7)-C(8)-C(9)-C(4)	-25.75(15)
C(15)-O(4)-C(14)-O(3)	0.6(2)
C(15)-O(4)-C(14)-C(8)	-179.97(15)
C(16)-C(8)-C(14)-O(3)	-134.06(16)
C(9)-C(8)-C(14)-O(3)	-11.7(2)
C(7)-C(8)-C(14)-O(3)	103.39(17)
C(16)-C(8)-C(14)-O(4)	46.55(15)
C(9)-C(8)-C(14)-O(4)	168.90(12)
C(7)-C(8)-C(14)-O(4)	-76.00(15)
C(17)-O(6)-C(16)-O(5)	2.8(2)
C(17)-O(6)-C(16)-C(8)	-177.48(12)
C(14)-C(8)-C(16)-O(5)	-120.60(16)
C(9)-C(8)-C(16)-O(5)	118.40(17)
C(7)-C(8)-C(16)-O(5)	0.4(2)
C(14)-C(8)-C(16)-O(6)	59.73(15)
C(9)-C(8)-C(16)-O(6)	-61.28(15)
C(7)-C(8)-C(16)-O(6)	-179.27(12)

Symmetry transformations used to generate equivalent atoms: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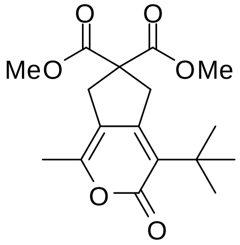
O6
C16
O5
C17
O4
C15
C8
O3
C7
C9
C4
C12
C5
C6
C3
C11
C10
C14
C2
O1
C13
O2


O
O
MeO
OMe
O
O

2.52

Table A.7. Crystal data and structure refinement for jl002.

Identification code	jl002	
Empirical formula	C17 H22 O6	
Formula weight	322.35	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/a$	
Unit cell dimensions	a = 12.1818(2) Å	α= 90°.
	b = 15.5664(5) Å	β= 105.9915(15)°.
	c = 18.4323(5) Å	γ = 90°.
Volume	3360.00(15) $Å^3$	
Z	8	
Density (calculated)	1.274 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	1376	
Crystal size	0.43 x 0.35 x 0.28 mm^3	
Theta range for data collection	2.86 to 27.47°.	
Index ranges	-15<=h<=15, -18<=k<=20, -23<=l<=23	
Reflections collected	13326	
Independent reflections	7635 [R(int) = 0.0218]	
Completeness to theta = 27.47°	99.4 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9736 and 0.9598	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7635 / 0 / 592	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0454, wR2 = 0.1127	
R indices (all data)	R1 = 0.0770, wR2 = 0.1319	
Extinction coefficient	0.0079(13)	
Largest diff. peak and hole	0.242 and -0.223 e.$Å^{-3}$	

Table A.8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jl002. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1622(1)	-166(1)	1356(1)	34(1)
O(1A)	3388(1)	172(1)	3593(1)	33(1)
O(2)	2063(1)	940(1)	756(1)	48(1)
O(2A)	2861(1)	-929(1)	4159(1)	40(1)
O(3)	1217(1)	1650(1)	3525(1)	39(1)
O(3A)	3943(1)	-1587(1)	1472(1)	41(1)
O(4)	905(1)	611(1)	4285(1)	37(1)
O(4A)	4365(1)	-535(1)	763(1)	41(1)
O(5)	-1883(1)	-20(1)	3456(1)	37(1)
O(5A)	7116(1)	8(1)	1634(1)	38(1)
O(6)	-1560(1)	1395(1)	3631(1)	37(1)
O(6A)	6776(1)	-1406(1)	1467(1)	38(1)
C(2)	1427(1)	679(1)	1110(1)	32(1)
C(2A)	3539(1)	-676(1)	3832(1)	29(1)
C(3)	518(1)	1158(1)	1311(1)	25(1)
C(3A)	4456(1)	-1174(1)	3657(1)	24(1)
C(4)	148(1)	818(1)	1885(1)	23(1)
C(4A)	4919(1)	-825(1)	3127(1)	23(1)
C(5)	496(1)	-24(1)	2188(1)	25(1)
C(5A)	4631(1)	32(1)	2837(1)	26(1)
C(6)	1182(1)	-510(1)	1900(1)	28(1)
C(6A)	3907(1)	520(1)	3089(1)	29(1)
C(7)	-14(1)	-246(1)	2822(1)	28(1)
C(7A)	5234(1)	258(1)	2251(1)	29(1)
C(8)	-347(1)	650(1)	3056(1)	26(1)
C(8A)	5543(1)	-637(1)	2004(1)	26(1)
C(9)	-625(1)	1191(1)	2328(1)	26(1)
C(9A)	5742(1)	-1198(1)	2720(1)	26(1)
C(10)	183(1)	2034(1)	926(1)	30(1)

Table A.8 continued.

	x	y	z	U(eq)
C(10A)	4704(1)	-2064(1)	4029(1)	27(1)
C(11)	1067(2)	2701(1)	1330(1)	43(1)
C(11A)	3752(2)	-2683(1)	3624(1)	38(1)
C(12)	-999(2)	2326(1)	961(1)	41(1)
C(12A)	5843(1)	-2436(1)	3983(1)	36(1)
C(13)	121(2)	1993(1)	82(1)	51(1)
C(13A)	4782(2)	-2010(1)	4878(1)	41(1)
C(14)	1555(2)	-1409(1)	2089(1)	38(1)
C(14A)	3563(2)	1425(1)	2896(1)	43(1)
C(15)	678(1)	1043(1)	3638(1)	29(1)
C(15A)	4522(1)	-990(1)	1391(1)	29(1)
C(16)	1920(2)	888(1)	4859(1)	42(1)
C(16A)	3369(2)	-771(2)	153(1)	53(1)
C(17)	-1347(1)	613(1)	3401(1)	28(1)
C(17A)	6569(1)	-619(1)	1687(1)	29(1)
C(18)	-2466(2)	1454(1)	4002(1)	41(1)
C(18A)	7693(2)	-1481(1)	1107(1)	43(1)

Table A.9. Bond lengths [Å] and angles [°] for jl002.

O(1)-C(6)	1.3690(17)
O(1)-C(2)	1.3892(18)
O(1A)-C(6A)	1.3713(17)
O(1A)-C(2A)	1.3879(18)
O(2)-C(2)	1.2129(18)
O(2A)-C(2A)	1.2136(17)
O(3)-C(15)	1.2010(18)
O(3A)-C(15A)	1.1997(18)
O(4)-C(15)	1.3317(18)
O(4)-C(16)	1.454(2)
O(4A)-C(15A)	1.3263(18)
O(4A)-C(16A)	1.456(2)
O(5)-C(17)	1.2010(17)
O(5A)-C(17A)	1.2004(18)
O(6)-C(17)	1.3375(18)
O(6)-C(18)	1.4521(18)
O(6A)-C(17A)	1.3370(18)
O(6A)-C(18A)	1.4530(18)
C(2)-C(3)	1.4652(19)
C(2A)-C(3A)	1.4673(19)
C(3)-C(4)	1.3661(19)
C(3)-C(10)	1.539(2)
C(3A)-C(4A)	1.3671(18)
C(3A)-C(10A)	1.5392(19)
C(4)-C(5)	1.4418(19)
C(4)-C(9)	1.5202(18)
C(4A)-C(5A)	1.4433(19)
C(4A)-C(9A)	1.5229(18)
C(5)-C(6)	1.3420(19)
C(5)-C(7)	1.5062(19)
C(5A)-C(6A)	1.3406(19)
C(5A)-C(7A)	1.5061(19)
C(6)-C(14)	1.482(2)

Table A.9 continued.

C(6A)-C(14A)	1.485(2)
C(7)-C(8)	1.5462(19)
C(7)-H(7A)	0.965(17)
C(7)-H(7B)	0.985(16)
C(7A)-C(8A)	1.543(2)
C(7A)-H(7C)	0.990(17)
C(7A)-H(7D)	0.964(17)
C(8)-C(17)	1.5229(18)
C(8)-C(15)	1.531(2)
C(8)-C(9)	1.542(2)
C(8A)-C(17A)	1.5193(19)
C(8A)-C(15A)	1.533(2)
C(8A)-C(9A)	1.545(2)
C(9)-H(9A)	0.968(16)
C(9)-H(9B)	1.013(17)
C(9A)-H(9C)	0.980(16)
C(9A)-H(9D)	0.981(17)
C(10)-C(12)	1.529(2)
C(10)-C(11)	1.532(2)
C(10)-C(13)	1.539(2)
C(10A)-C(12A)	1.527(2)
C(10A)-C(11A)	1.534(2)
C(10A)-C(13A)	1.544(2)
C(11)-H(11A)	1.02(2)
C(11)-H(11B)	1.04(2)
C(11)-H(11C)	0.96(2)
C(11A)-H(11D)	1.01(2)
C(11A)-H(11E)	1.029(19)
C(11A)-H(11F)	0.97(2)
C(12)-H(12A)	1.02(2)
C(12)-H(12B)	0.97(2)
C(12)-H(12C)	0.96(2)
C(12A)-H(12D)	0.997(19)

Table A.9 continued.

C(12A)-H(12E)	0.96(2)
C(12A)-H(12F)	0.989(19)
C(13)-H(13A)	0.98(2)
C(13)-H(13B)	0.97(2)
C(13)-H(17C)	0.98(2)
C(13A)-H(13D)	0.99(2)
C(13A)-H(13E)	0.98(2)
C(13A)-H(13F)	0.96(2)
C(14)-H(14A)	0.97(2)
C(14)-H(14B)	0.93(3)
C(14)-H(14C)	0.95(2)
C(14A)-H(14D)	0.98(2)
C(14A)-H(14E)	0.94(3)
C(14A)-H(14F)	0.93(3)
C(16)-H(16A)	1.02(2)
C(16)-H(16B)	0.98(2)
C(16)-H(16C)	0.98(2)
C(16A)-H(16D)	1.02(2)
C(16A)-H(16E)	0.95(2)
C(16A)-H(16F)	0.98(3)
C(18)-H(18A)	0.95(2)
C(18)-H(18B)	1.01(2)
C(18)-H(18C)	0.97(2)
C(18A)-H(18D)	0.95(2)
C(18A)-H(18E)	0.99(2)
C(18A)-H(18F)	0.98(2)
C(6)-O(1)-C(2)	122.92(11)
C(6A)-O(1A)-C(2A)	123.02(11)
C(15)-O(4)-C(16)	115.30(13)
C(15A)-O(4A)-C(16A)	115.45(15)
C(17)-O(6)-C(18)	116.45(12)
C(17A)-O(6A)-C(18A)	116.39(13)
O(2)-C(2)-O(1)	114.58(13)

Table A.9 continued.

O(2)-C(2)-C(3)	127.20(14)
O(1)-C(2)-C(3)	118.21(12)
O(2A)-C(2A)-O(1A)	114.58(12)
O(2A)-C(2A)-C(3A)	127.05(14)
O(1A)-C(2A)-C(3A)	118.35(12)
C(4)-C(3)-C(2)	115.62(13)
C(4)-C(3)-C(10)	126.74(12)
C(2)-C(3)-C(10)	117.21(12)
C(4A)-C(3A)-C(2A)	115.88(12)
C(4A)-C(3A)-C(10A)	127.42(12)
C(2A)-C(3A)-C(10A)	116.40(11)
C(3)-C(4)-C(5)	121.82(12)
C(3)-C(4)-C(9)	130.75(13)
C(5)-C(4)-C(9)	107.42(11)
C(3A)-C(4A)-C(5A)	121.72(12)
C(3A)-C(4A)-C(9A)	131.04(13)
C(5A)-C(4A)-C(9A)	107.22(11)
C(6)-C(5)-C(4)	120.58(13)
C(6)-C(5)-C(7)	127.80(13)
C(4)-C(5)-C(7)	111.61(12)
C(6A)-C(5A)-C(4A)	120.73(13)
C(6A)-C(5A)-C(7A)	127.88(13)
C(4A)-C(5A)-C(7A)	111.39(12)
C(5)-C(6)-O(1)	118.73(13)
C(5)-C(6)-C(14)	128.54(14)
O(1)-C(6)-C(14)	112.73(12)
C(5A)-C(6A)-O(1A)	118.78(13)
C(5A)-C(6A)-C(14A)	128.55(14)
O(1A)-C(6A)-C(14A)	112.66(13)
C(5)-C(7)-C(8)	101.90(11)
C(5)-C(7)-H(7A)	113.4(10)
C(8)-C(7)-H(7A)	111.4(10)
C(5)-C(7)-H(7B)	111.5(9)

Table A.9 continued.

C(8)-C(7)-H(7B)	108.4(9)
H(7A)-C(7)-H(7B)	110.0(14)
C(5A)-C(7A)-C(8A)	101.96(11)
C(5A)-C(7A)-H(7C)	111.7(10)
C(8A)-C(7A)-H(7C)	109.1(10)
C(5A)-C(7A)-H(7D)	112.6(10)
C(8A)-C(7A)-H(7D)	112.3(10)
H(7C)-C(7A)-H(7D)	109.0(14)
C(17)-C(8)-C(15)	108.36(11)
C(17)-C(8)-C(9)	112.03(11)
C(15)-C(8)-C(9)	109.36(12)
C(17)-C(8)-C(7)	112.63(12)
C(15)-C(8)-C(7)	109.29(12)
C(9)-C(8)-C(7)	105.10(11)
C(17A)-C(8A)-C(15A)	107.99(11)
C(17A)-C(8A)-C(7A)	112.97(12)
C(15A)-C(8A)-C(7A)	109.08(12)
C(17A)-C(8A)-C(9A)	112.77(12)
C(15A)-C(8A)-C(9A)	109.32(12)
C(7A)-C(8A)-C(9A)	104.63(11)
C(4)-C(9)-C(8)	103.79(11)
C(4)-C(9)-H(9A)	113.7(9)
C(8)-C(9)-H(9A)	111.2(9)
C(4)-C(9)-H(9B)	109.8(10)
C(8)-C(9)-H(9B)	110.2(9)
H(9A)-C(9)-H(9B)	108.1(13)
C(4A)-C(9A)-C(8A)	103.60(11)
C(4A)-C(9A)-H(9C)	109.5(9)
C(8A)-C(9A)-H(9C)	111.1(9)
C(4A)-C(9A)-H(9D)	114.0(9)
C(8A)-C(9A)-H(9D)	110.4(9)
H(9C)-C(9A)-H(9D)	108.3(12)
C(12)-C(10)-C(11)	108.77(14)

Table A.9 continued.

C(12)-C(10)-C(13)	105.68(14)
C(11)-C(10)-C(13)	110.61(15)
C(12)-C(10)-C(3)	112.16(13)
C(11)-C(10)-C(3)	108.35(13)
C(13)-C(10)-C(3)	111.25(13)
C(12A)-C(10A)-C(11A)	108.19(13)
C(12A)-C(10A)-C(3A)	112.73(12)
C(11A)-C(10A)-C(3A)	108.63(12)
C(12A)-C(10A)-C(13A)	105.86(13)
C(11A)-C(10A)-C(13A)	110.74(13)
C(3A)-C(10A)-C(13A)	110.66(13)
C(10)-C(11)-H(11A)	109.6(12)
C(10)-C(11)-H(11B)	111.2(11)
H(11A)-C(11)-H(11B)	109.5(16)
C(10)-C(11)-H(11C)	107.7(12)
H(11A)-C(11)-H(11C)	107.8(17)
H(11B)-C(11)-H(11C)	111.0(16)
C(10A)-C(11A)-H(11D)	110.6(11)
C(10A)-C(11A)-H(11E)	111.4(10)
H(11D)-C(11A)-H(11E)	108.6(15)
C(10A)-C(11A)-H(11F)	109.5(11)
H(11D)-C(11A)-H(11F)	108.0(15)
H(11E)-C(11A)-H(11F)	108.6(15)
C(10)-C(12)-H(12A)	112.2(11)
C(10)-C(12)-H(12B)	113.3(12)
H(12A)-C(12)-H(12B)	103.9(15)
C(10)-C(12)-H(12C)	109.9(12)
H(12A)-C(12)-H(12C)	108.5(17)
H(12B)-C(12)-H(12C)	108.8(16)
C(10A)-C(12A)-H(12D)	113.6(10)
C(10A)-C(12A)-H(12E)	108.7(11)
H(12D)-C(12A)-H(12E)	106.6(15)
C(10A)-C(12A)-H(12F)	112.2(11)

Table A.9 continued.

H(12D)-C(12A)-H(12F)	105.2(14)
H(12E)-C(12A)-H(12F)	110.4(15)
C(10)-C(13)-H(13A)	112.3(13)
C(10)-C(13)-H(13B)	110.9(14)
H(13A)-C(13)-H(13B)	108.5(18)
C(10)-C(13)-H(17C)	109.4(13)
H(13A)-C(13)-H(17C)	105.7(17)
H(13B)-C(13)-H(17C)	110.0(18)
C(10A)-C(13A)-H(13D)	112.5(11)
C(10A)-C(13A)-H(13E)	110.4(12)
H(13D)-C(13A)-H(13E)	106.7(17)
C(10A)-C(13A)-H(13F)	108.8(11)
H(13D)-C(13A)-H(13F)	106.6(15)
H(13E)-C(13A)-H(13F)	111.8(16)
C(6)-C(14)-H(14A)	110.3(12)
C(6)-C(14)-H(14B)	112.1(15)
H(14A)-C(14)-H(14B)	110.3(19)
C(6)-C(14)-H(14C)	110.7(14)
H(14A)-C(14)-H(14C)	105.1(18)
H(14B)-C(14)-H(14C)	108(2)
C(6A)-C(14A)-H(14D)	110.9(13)
C(6A)-C(14A)-H(14E)	112.3(17)
H(14D)-C(14A)-H(14E)	107(2)
C(6A)-C(14A)-H(14F)	110.5(16)
H(14D)-C(14A)-H(14F)	107(2)
H(14E)-C(14A)-H(14F)	109(2)
O(3)-C(15)-O(4)	124.41(14)
O(3)-C(15)-C(8)	124.93(14)
O(4)-C(15)-C(8)	110.65(12)
O(3A)-C(15A)-O(4A)	124.92(14)
O(3A)-C(15A)-C(8A)	124.89(14)
O(4A)-C(15A)-C(8A)	110.18(12)
O(4)-C(16)-H(16A)	110.0(10)

Table A.9 continued.

O(4)-C(16)-H(16B)	109.6(13)
H(16A)-C(16)-H(16B)	114.2(16)
O(4)-C(16)-H(16C)	103.7(13)
H(16A)-C(16)-H(16C)	108.7(16)
H(16B)-C(16)-H(16C)	110.2(17)
O(4A)-C(16A)-H(16D)	108.7(12)
O(4A)-C(16A)-H(16E)	110.4(14)
H(16D)-C(16A)-H(16E)	109.8(19)
O(4A)-C(16A)-H(16F)	104.6(14)
H(16D)-C(16A)-H(16F)	113.5(18)
H(16E)-C(16A)-H(16F)	109.8(19)
O(5)-C(17)-O(6)	124.23(13)
O(5)-C(17)-C(8)	125.56(13)
O(6)-C(17)-C(8)	110.21(12)
O(5A)-C(17A)-O(6A)	124.46(13)
O(5A)-C(17A)-C(8A)	125.43(14)
O(6A)-C(17A)-C(8A)	110.11(12)
O(6)-C(18)-H(18A)	109.2(13)
O(6)-C(18)-H(18B)	110.1(12)
H(18A)-C(18)-H(18B)	108.9(17)
O(6)-C(18)-H(18C)	105.5(12)
H(18A)-C(18)-H(18C)	112.0(18)
H(18B)-C(18)-H(18C)	111.1(17)
O(6A)-C(18A)-H(18D)	109.2(14)
O(6A)-C(18A)-H(18E)	109.8(12)
H(18D)-C(18A)-H(18E)	108.3(18)
O(6A)-C(18A)-H(18F)	105.2(12)
H(18D)-C(18A)-H(18F)	116.5(18)
H(18E)-C(18A)-H(18F)	107.8(17)

Symmetry transformations used to generate equivalent atoms:

Table A.10. Anisotropic displacement parameters ($Å^2$x 10^3)for jl002. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[$h^2a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	46(1)	27(1)	37(1)	3(1)	28(1)	7(1)
O(1A)	44(1)	26(1)	38(1)	4(1)	26(1)	6(1)
O(2)	61(1)	37(1)	64(1)	10(1)	48(1)	7(1)
O(2A)	47(1)	35(1)	53(1)	7(1)	35(1)	5(1)
O(3)	47(1)	34(1)	37(1)	-2(1)	14(1)	-11(1)
O(3A)	46(1)	40(1)	41(1)	-6(1)	16(1)	-12(1)
O(4)	49(1)	35(1)	27(1)	0(1)	14(1)	-1(1)
O(4A)	55(1)	41(1)	27(1)	3(1)	12(1)	4(1)
O(5)	48(1)	31(1)	42(1)	-3(1)	28(1)	-9(1)
O(5A)	48(1)	35(1)	41(1)	-2(1)	26(1)	-10(1)
O(6)	48(1)	27(1)	47(1)	-4(1)	32(1)	1(1)
O(6A)	49(1)	30(1)	47(1)	-1(1)	33(1)	2(1)
C(2)	42(1)	27(1)	34(1)	1(1)	22(1)	2(1)
C(2A)	37(1)	24(1)	30(1)	0(1)	17(1)	1(1)
C(3)	31(1)	23(1)	25(1)	-1(1)	13(1)	-2(1)
C(3A)	29(1)	22(1)	23(1)	-1(1)	11(1)	-2(1)
C(4)	27(1)	21(1)	25(1)	-4(1)	11(1)	-3(1)
C(4A)	27(1)	22(1)	23(1)	-3(1)	9(1)	-3(1)
C(5)	33(1)	21(1)	25(1)	-2(1)	13(1)	-2(1)
C(5A)	35(1)	21(1)	25(1)	-2(1)	14(1)	-3(1)
C(6)	37(1)	24(1)	28(1)	0(1)	15(1)	0(1)
C(6A)	40(1)	24(1)	28(1)	0(1)	18(1)	0(1)
C(7)	41(1)	20(1)	30(1)	-1(1)	19(1)	0(1)
C(7A)	43(1)	22(1)	29(1)	0(1)	20(1)	-2(1)
C(8)	36(1)	21(1)	28(1)	0(1)	18(1)	-1(1)
C(8A)	35(1)	22(1)	27(1)	0(1)	17(1)	-1(1)
C(9)	34(1)	21(1)	28(1)	0(1)	18(1)	0(1)
C(9A)	33(1)	24(1)	26(1)	2(1)	16(1)	0(1)
C(10)	39(1)	26(1)	28(1)	5(1)	17(1)	4(1)
C(10A)	33(1)	26(1)	27(1)	5(1)	14(1)	2(1)

Table A.10 continued.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(11)	50(1)	26(1)	58(1)	6(1)	21(1)	-3(1)
C(11A)	41(1)	26(1)	49(1)	6(1)	16(1)	-3(1)
C(12)	40(1)	47(1)	38(1)	14(1)	15(1)	13(1)
C(12A)	37(1)	39(1)	35(1)	12(1)	17(1)	10(1)
C(13)	80(2)	47(1)	33(1)	10(1)	28(1)	15(1)
C(13A)	58(1)	42(1)	30(1)	9(1)	22(1)	9(1)
C(14)	52(1)	28(1)	39(1)	2(1)	24(1)	8(1)
C(14A)	62(1)	27(1)	48(1)	6(1)	31(1)	10(1)
C(15)	39(1)	24(1)	27(1)	-2(1)	18(1)	2(1)
C(15A)	39(1)	26(1)	27(1)	-3(1)	17(1)	4(1)
C(16)	50(1)	47(1)	29(1)	-6(1)	9(1)	4(1)
C(16A)	59(1)	63(2)	31(1)	-10(1)	3(1)	20(1)
C(17)	38(1)	25(1)	25(1)	0(1)	16(1)	0(1)
C(17A)	40(1)	27(1)	23(1)	1(1)	16(1)	1(1)
C(18)	46(1)	41(1)	46(1)	-8(1)	31(1)	2(1)
C(18A)	50(1)	44(1)	46(1)	-5(1)	32(1)	5(1)

Table A.11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for jl002.

	x	y	z	U(eq)
H(7A)	513(14)	-534(11)	3238(10)	34(4)
H(7B)	-715(14)	-590(11)	2640(9)	31(4)
H(7C)	5945(14)	585(11)	2472(9)	37(4)
H(7D)	4757(14)	581(11)	1836(10)	36(4)
H(9A)	-498(12)	1797(11)	2440(8)	26(4)
H(9B)	-1453(15)	1111(11)	2034(9)	36(4)
H(9C)	6526(14)	-1139(10)	3040(9)	30(4)
H(9D)	5605(12)	-1805(11)	2582(9)	29(4)
H(11A)	1848(18)	2551(13)	1257(11)	60(6)
H(11B)	1127(16)	2725(13)	1906(12)	54(6)
H(11C)	840(17)	3245(14)	1095(11)	58(6)
H(11D)	2987(17)	-2484(13)	3680(11)	53(5)
H(11E)	3697(15)	-2727(12)	3058(11)	45(5)
H(11F)	3905(15)	-3250(13)	3847(11)	49(5)
H(12A)	-1009(16)	2495(13)	1491(12)	54(6)
H(12B)	-1574(17)	1880(14)	822(11)	57(6)
H(12C)	-1242(17)	2809(14)	636(12)	59(6)
H(12D)	5842(14)	-2622(12)	3466(11)	43(5)
H(12E)	6010(15)	-2936(13)	4297(11)	49(5)
H(12F)	6472(16)	-2014(12)	4136(10)	45(5)
H(13A)	869(19)	1892(14)	-3(12)	64(6)
H(13B)	-395(19)	1541(15)	-169(13)	68(7)
H(13D)	4051(17)	-1845(12)	4971(10)	49(5)
H(13E)	5344(18)	-1574(14)	5126(12)	59(6)
H(13F)	4973(15)	-2570(13)	5100(11)	46(5)
H(14A)	1417(16)	-1575(13)	2562(12)	56(6)
H(14B)	2320(20)	-1490(16)	2110(14)	82(8)
H(14C)	1111(19)	-1796(16)	1724(14)	73(7)
H(14D)	3750(19)	1601(15)	2433(13)	74(7)

Table A.11 continued.

	x	y	z	U(eq)
H(14E)	2770(30)	1509(18)	2812(16)	102(9)
H(14F)	3960(20)	1794(18)	3279(15)	91(9)
H(16A)	1879(15)	1529(13)	4950(10)	49(5)
H(16B)	2603(19)	707(14)	4718(12)	66(6)
H(16C)	1869(17)	583(14)	5312(13)	66(7)
H(16D)	3356(18)	-1421(15)	91(12)	65(6)
H(16E)	2690(20)	-586(15)	263(13)	73(7)
H(16F)	3465(19)	-461(16)	-288(15)	81(8)
H(17C)	-137(18)	2548(15)	-154(12)	67(6)
H(18A)	-3138(19)	1192(14)	3691(12)	62(6)
H(18B)	-2234(17)	1145(14)	4505(12)	60(6)
H(18C)	-2572(17)	2066(15)	4069(12)	60(6)
H(18D)	8360(20)	-1205(15)	1413(13)	73(7)
H(18E)	7473(18)	-1192(14)	611(13)	65(6)
H(18F)	7759(16)	-2095(14)	1019(11)	56(6)

Table A.12. Torsion angles [°] for jl002.

C(6)-O(1)-C(2)-O(2)	164.63(14)
C(6)-O(1)-C(2)-C(3)	-14.1(2)
C(6A)-O(1A)-C(2A)-O(2A)	-166.44(14)
C(6A)-O(1A)-C(2A)-C(3A)	12.2(2)
O(2)-C(2)-C(3)-C(4)	-161.69(16)
O(1)-C(2)-C(3)-C(4)	16.9(2)
O(2)-C(2)-C(3)-C(10)	11.3(2)
O(1)-C(2)-C(3)-C(10)	-170.09(13)
O(2A)-C(2A)-C(3A)-C(4A)	164.11(15)
O(1A)-C(2A)-C(3A)-C(4A)	-14.36(19)
O(2A)-C(2A)-C(3A)-C(10A)	-10.1(2)
O(1A)-C(2A)-C(3A)-C(10A)	171.45(12)
C(2)-C(3)-C(4)-C(5)	-9.5(2)
C(10)-C(3)-C(4)-C(5)	178.20(13)
C(2)-C(3)-C(4)-C(9)	169.13(14)
C(10)-C(3)-C(4)-C(9)	-3.1(2)
C(2A)-C(3A)-C(4A)-C(5A)	8.2(2)
C(10A)-C(3A)-C(4A)-C(5A)	-178.36(13)
C(2A)-C(3A)-C(4A)-C(9A)	-169.96(13)
C(10A)-C(3A)-C(4A)-C(9A)	3.5(2)
C(3)-C(4)-C(5)-C(6)	-1.6(2)
C(9)-C(4)-C(5)-C(6)	179.52(13)
C(3)-C(4)-C(5)-C(7)	179.24(13)
C(9)-C(4)-C(5)-C(7)	0.31(16)
C(3A)-C(4A)-C(5A)-C(6A)	0.9(2)
C(9A)-C(4A)-C(5A)-C(6A)	179.46(13)
C(3A)-C(4A)-C(5A)-C(7A)	-178.86(13)
C(9A)-C(4A)-C(5A)-C(7A)	-0.31(16)
C(4)-C(5)-C(6)-O(1)	5.4(2)
C(7)-C(5)-C(6)-O(1)	-175.53(14)
C(4)-C(5)-C(6)-C(14)	-174.56(15)
C(7)-C(5)-C(6)-C(14)	4.5(3)

Table A.12 continued.

C(2)-O(1)-C(6)-C(5)	2.7(2)
C(2)-O(1)-C(6)-C(14)	-177.32(14)
C(4A)-C(5A)-C(6A)-O(1A)	-4.0(2)
C(7A)-C(5A)-C(6A)-O(1A)	175.73(14)
C(4A)-C(5A)-C(6A)-C(14A)	176.00(17)
C(7A)-C(5A)-C(6A)-C(14A)	-4.3(3)
C(2A)-O(1A)-C(6A)-C(5A)	-2.8(2)
C(2A)-O(1A)-C(6A)-C(14A)	177.16(15)
C(6)-C(5)-C(7)-C(8)	161.57(15)
C(4)-C(5)-C(7)-C(8)	-19.29(16)
C(6A)-C(5A)-C(7A)-C(8A)	-159.48(15)
C(4A)-C(5A)-C(7A)-C(8A)	20.27(16)
C(5)-C(7)-C(8)-C(17)	152.55(12)
C(5)-C(7)-C(8)-C(15)	-86.96(14)
C(5)-C(7)-C(8)-C(9)	30.32(14)
C(5A)-C(7A)-C(8A)-C(17A)	-154.81(12)
C(5A)-C(7A)-C(8A)-C(15A)	85.09(14)
C(5A)-C(7A)-C(8A)-C(9A)	-31.78(14)
C(3)-C(4)-C(9)-C(8)	-159.80(14)
C(5)-C(4)-C(9)-C(8)	19.00(15)
C(17)-C(8)-C(9)-C(4)	-153.40(12)
C(15)-C(8)-C(9)-C(4)	86.44(13)
C(7)-C(8)-C(9)-C(4)	-30.78(14)
C(3A)-C(4A)-C(9A)-C(8A)	158.46(14)
C(5A)-C(4A)-C(9A)-C(8A)	-19.89(14)
C(17A)-C(8A)-C(9A)-C(4A)	155.37(12)
C(15A)-C(8A)-C(9A)-C(4A)	-84.49(13)
C(7A)-C(8A)-C(9A)-C(4A)	32.21(14)
C(4)-C(3)-C(10)-C(12)	-27.4(2)
C(2)-C(3)-C(10)-C(12)	160.44(14)
C(4)-C(3)-C(10)-C(11)	92.68(17)
C(2)-C(3)-C(10)-C(11)	-79.48(16)
C(4)-C(3)-C(10)-C(13)	-145.52(16)

Table A.12 continued.

C(2)-C(3)-C(10)-C(13)	42.31(19)
C(4A)-C(3A)-C(10A)-C(12A)	21.2(2)
C(2A)-C(3A)-C(10A)-C(12A)	-165.35(13)
C(4A)-C(3A)-C(10A)-C(11A)	-98.66(17)
C(2A)-C(3A)-C(10A)-C(11A)	74.76(16)
C(4A)-C(3A)-C(10A)-C(13A)	139.57(15)
C(2A)-C(3A)-C(10A)-C(13A)	-47.01(17)
C(16)-O(4)-C(15)-O(3)	-3.6(2)
C(16)-O(4)-C(15)-C(8)	175.37(12)
C(17)-C(8)-C(15)-O(3)	-126.22(15)
C(9)-C(8)-C(15)-O(3)	-3.8(2)
C(7)-C(8)-C(15)-O(3)	110.71(16)
C(17)-C(8)-C(15)-O(4)	54.81(15)
C(9)-C(8)-C(15)-O(4)	177.19(11)
C(7)-C(8)-C(15)-O(4)	-68.26(14)
C(16A)-O(4A)-C(15A)-O(3A)	3.4(2)
C(16A)-O(4A)-C(15A)-C(8A)	-175.87(13)
C(17A)-C(8A)-C(15A)-O(3A)	126.06(15)
C(7A)-C(8A)-C(15A)-O(3A)	-110.82(16)
C(9A)-C(8A)-C(15A)-O(3A)	3.0(2)
C(17A)-C(8A)-C(15A)-O(4A)	-54.67(15)
C(7A)-C(8A)-C(15A)-O(4A)	68.45(14)
C(9A)-C(8A)-C(15A)-O(4A)	-177.70(11)
C(18)-O(6)-C(17)-O(5)	3.2(2)
C(18)-O(6)-C(17)-C(8)	-177.56(13)
C(15)-C(8)-C(17)-O(5)	-125.07(16)
C(9)-C(8)-C(17)-O(5)	114.19(17)
C(7)-C(8)-C(17)-O(5)	-4.1(2)
C(15)-C(8)-C(17)-O(6)	55.68(15)
C(9)-C(8)-C(17)-O(6)	-65.06(15)
C(7)-C(8)-C(17)-O(6)	176.70(12)
C(18A)-O(6A)-C(17A)-O(5A)	-3.2(2)
C(18A)-O(6A)-C(17A)-C(8A)	176.34(14)

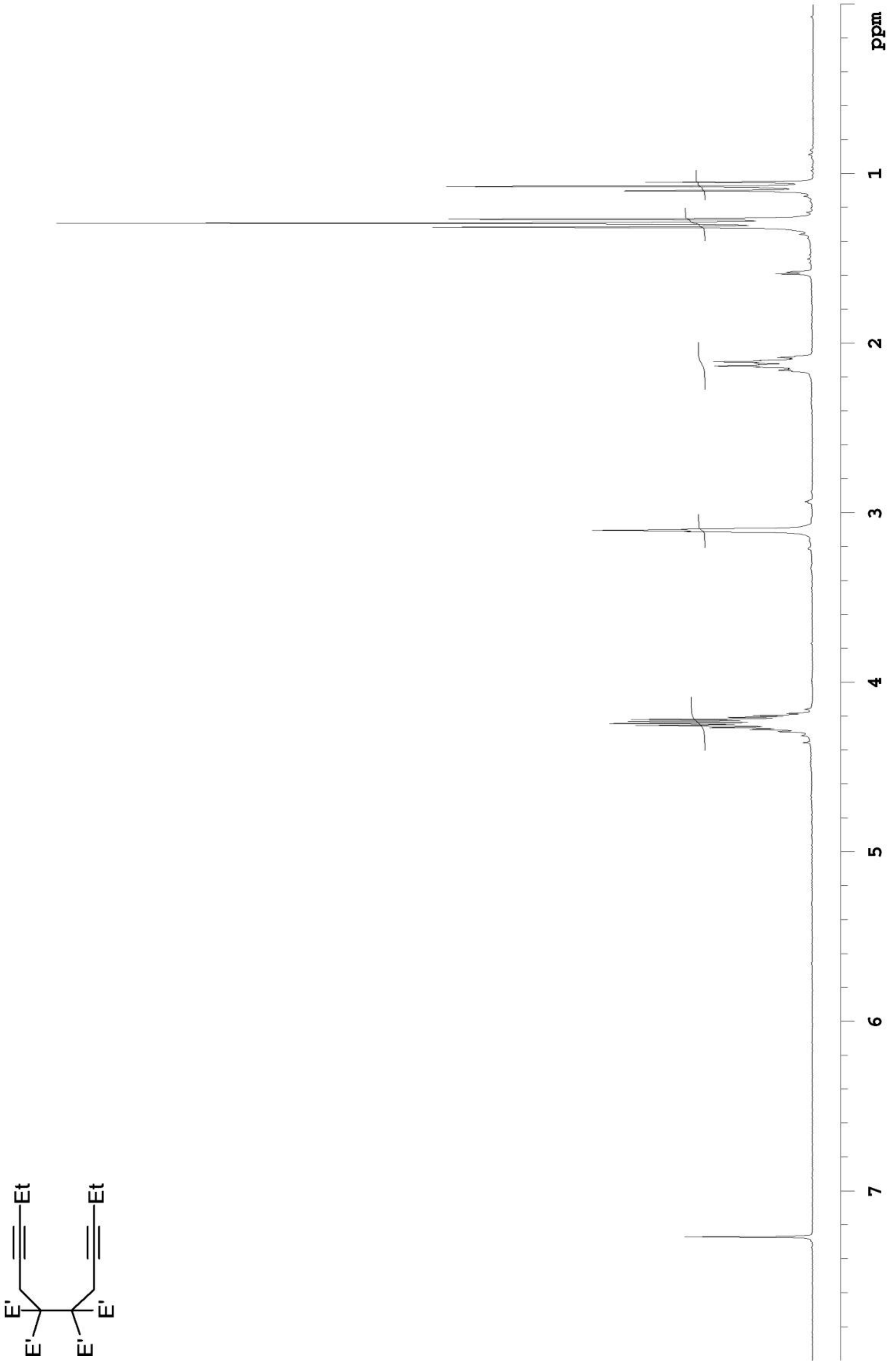
Table A.12 continued.

C(15A)-C(8A)-C(17A)-O(5A)	121.83(16)
C(7A)-C(8A)-C(17A)-O(5A)	1.1(2)
C(9A)-C(8A)-C(17A)-O(5A)	-117.28(16)
C(15A)-C(8A)-C(17A)-O(6A)	-57.75(15)
C(7A)-C(8A)-C(17A)-O(6A)	-178.47(12)
C(9A)-C(8A)-C(17A)-O(6A)	63.14(16)

Symmetry transformations used to generate equivalent atoms:

APPENDIX B

^{1}H NMR AND ^{13}C NMR SPECTRA AND X-RAY DATA FOR CHAPTER 3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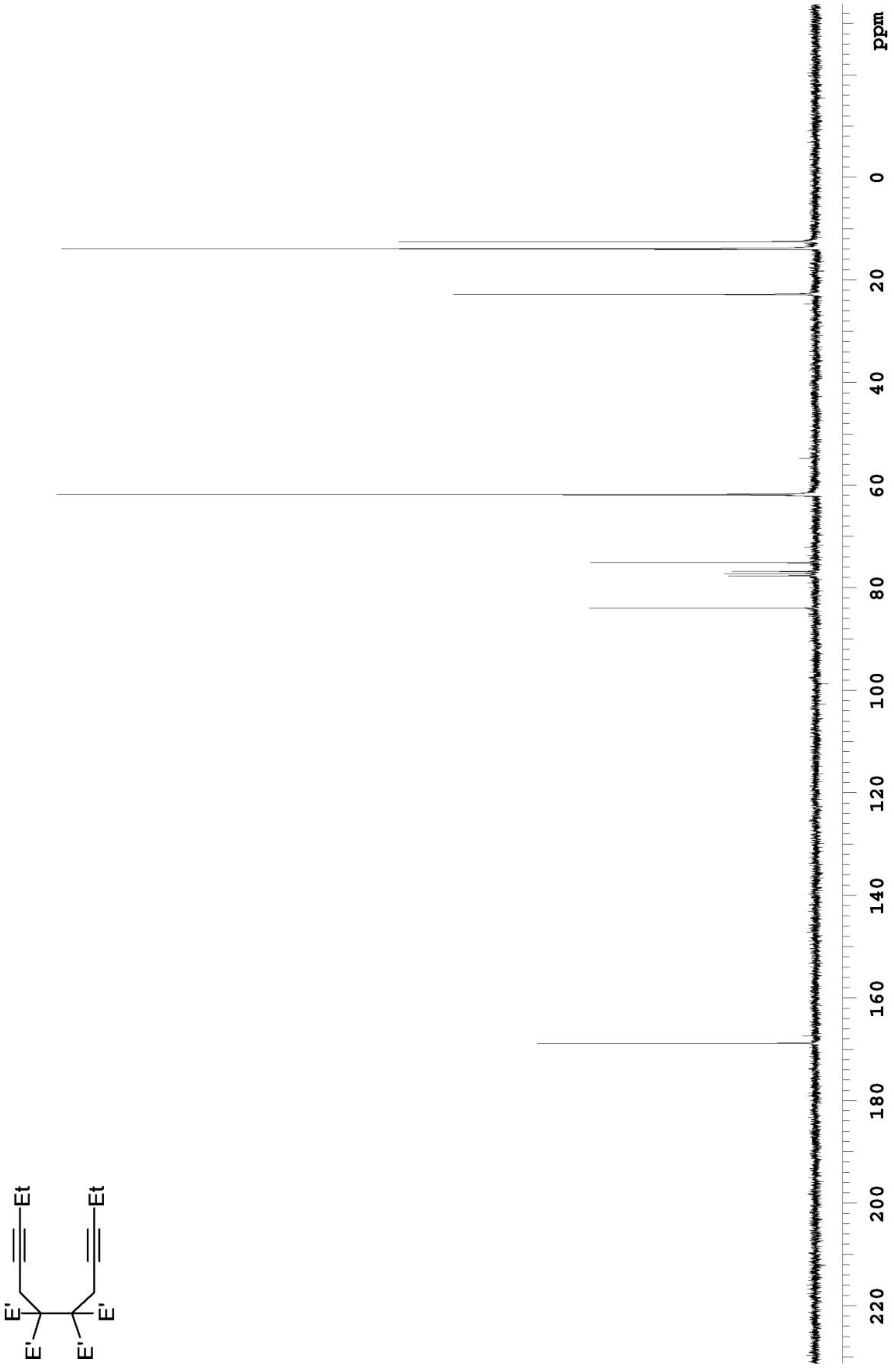
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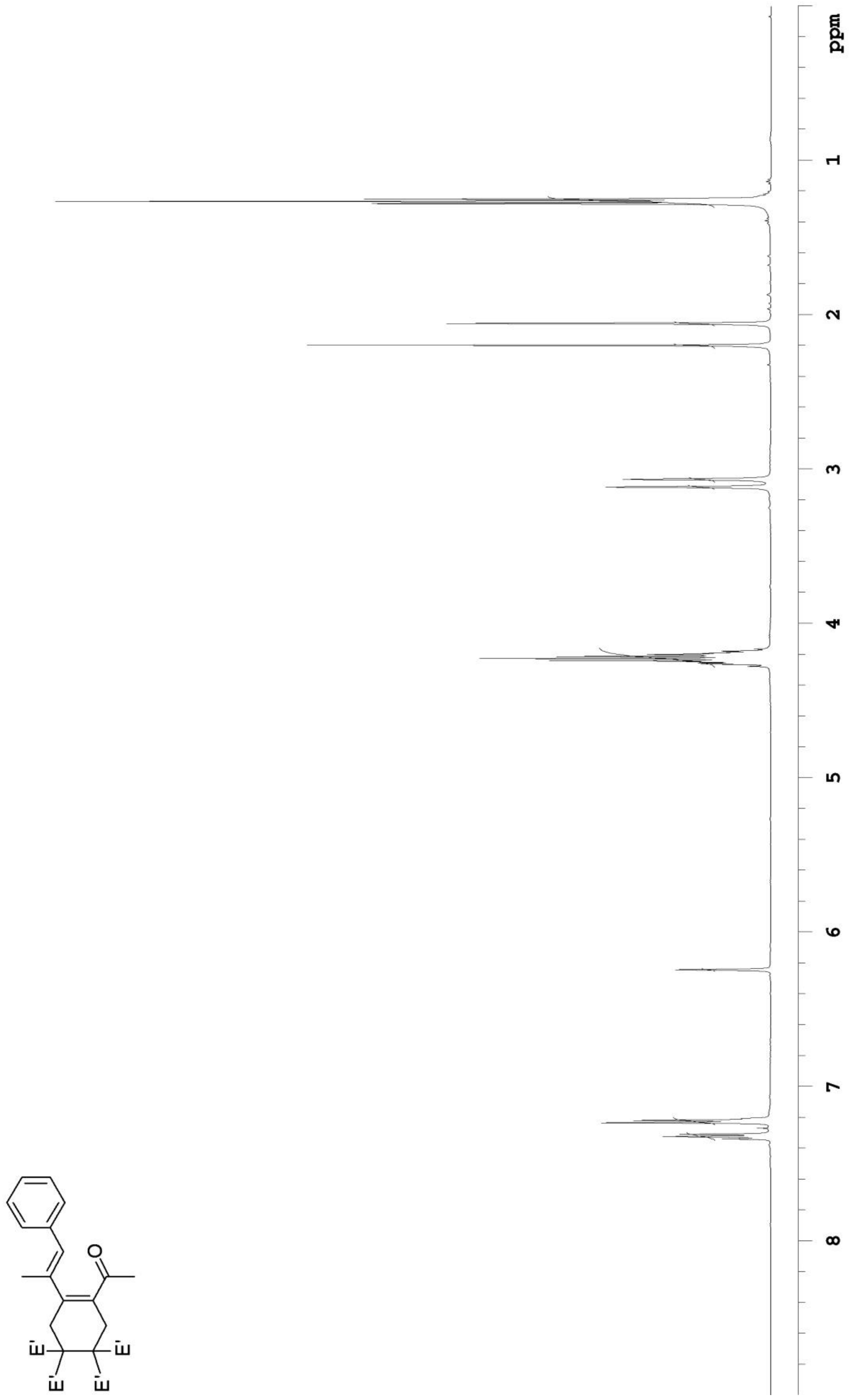
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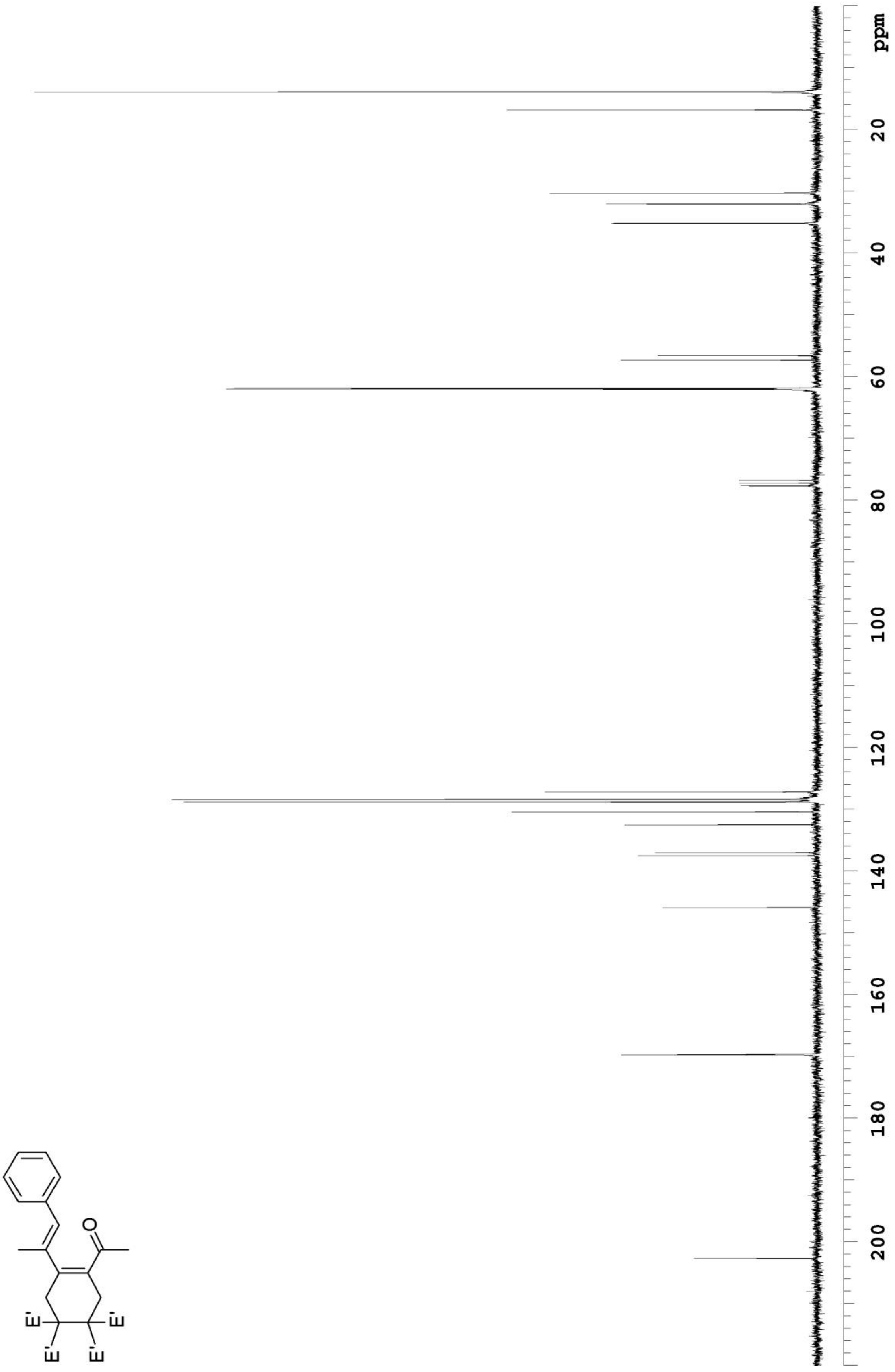
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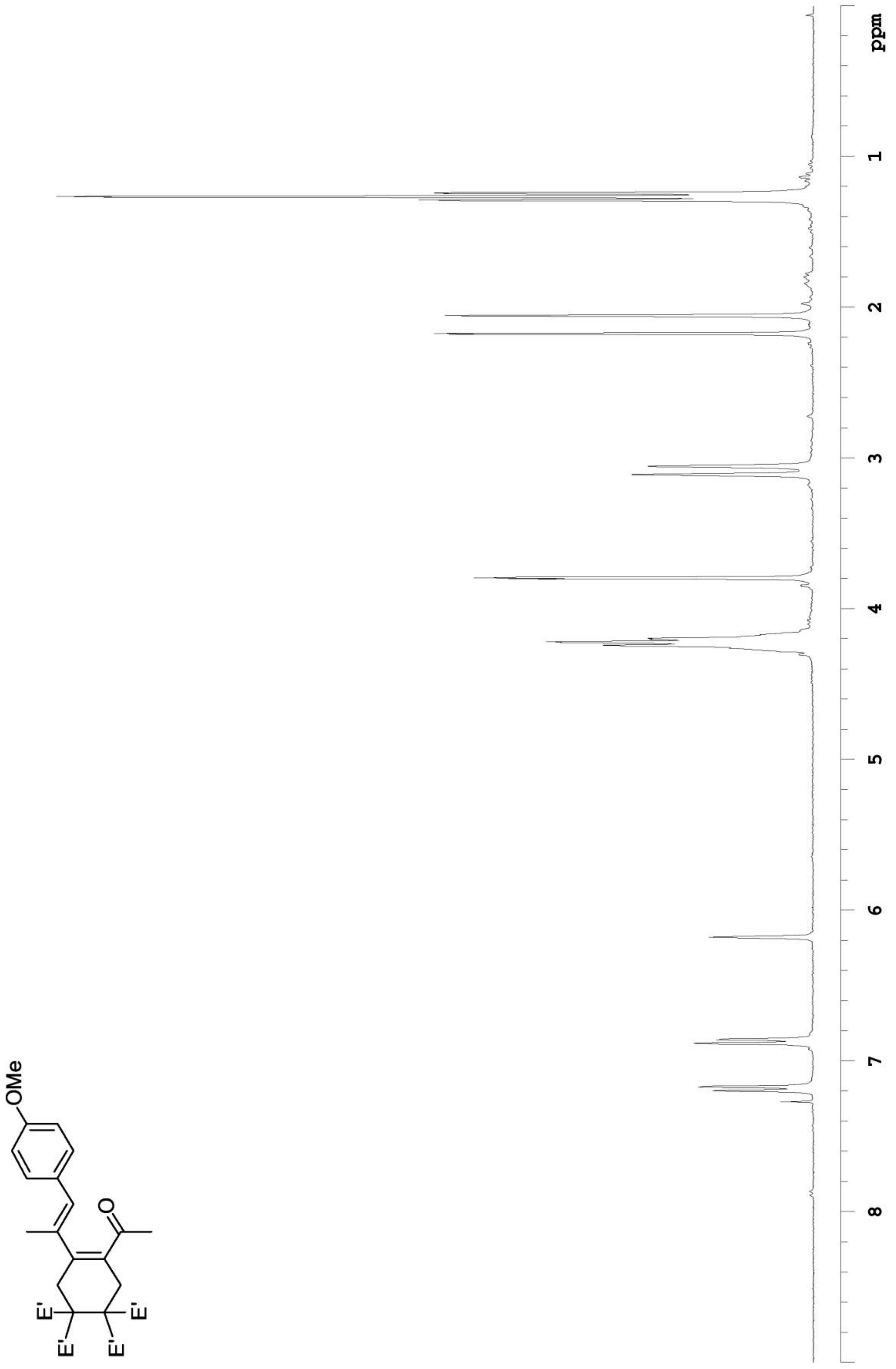
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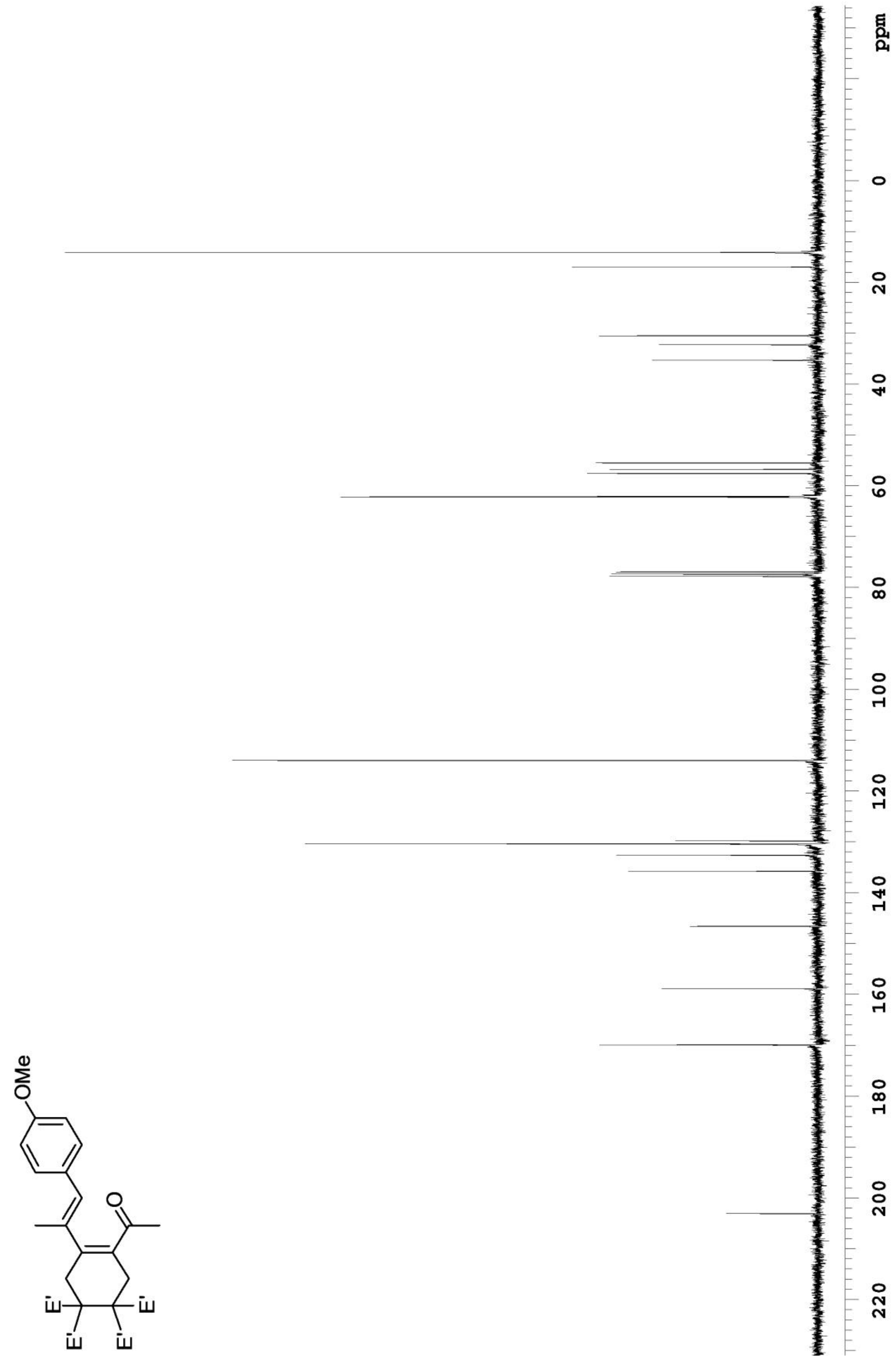
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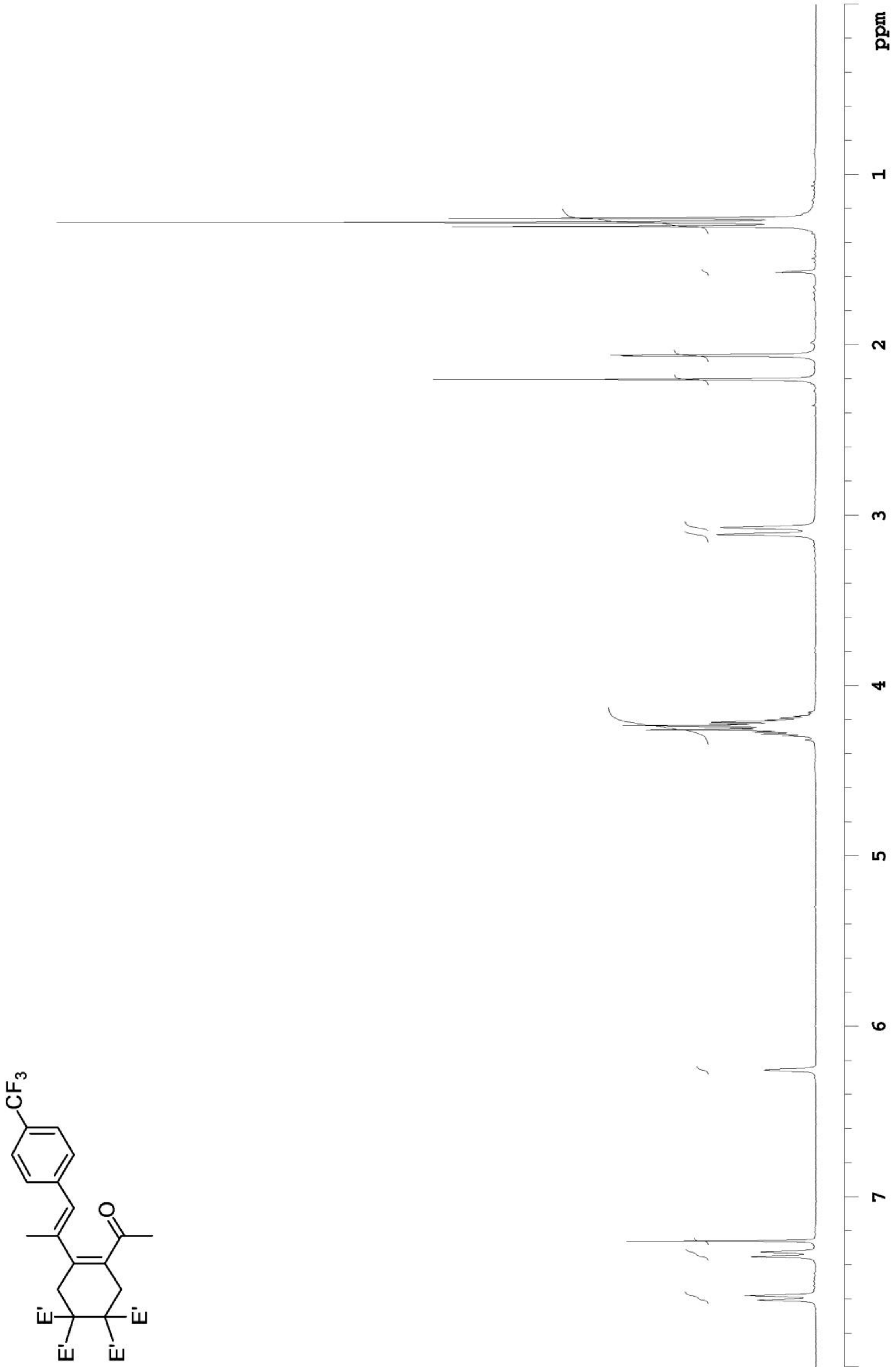
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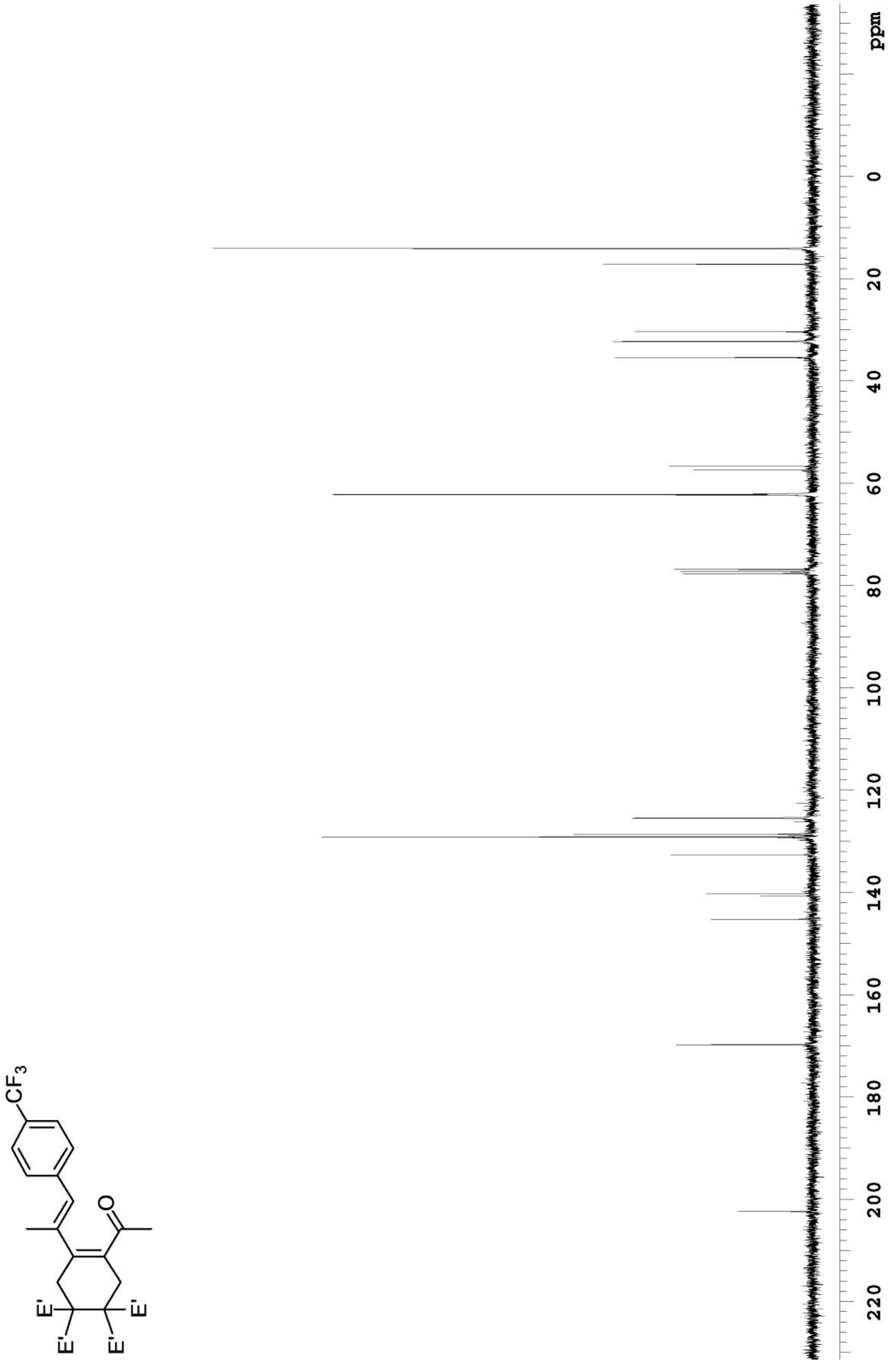
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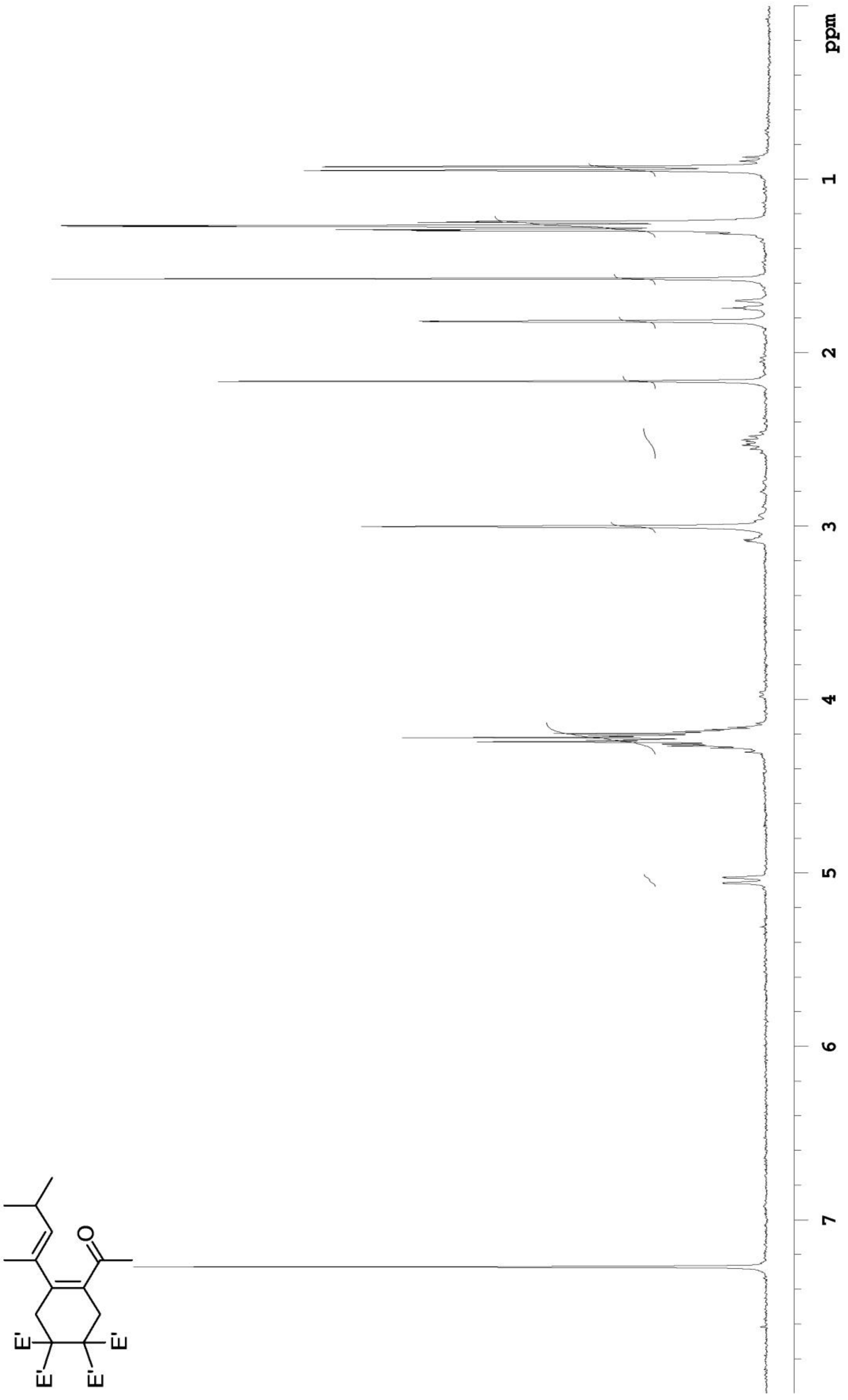
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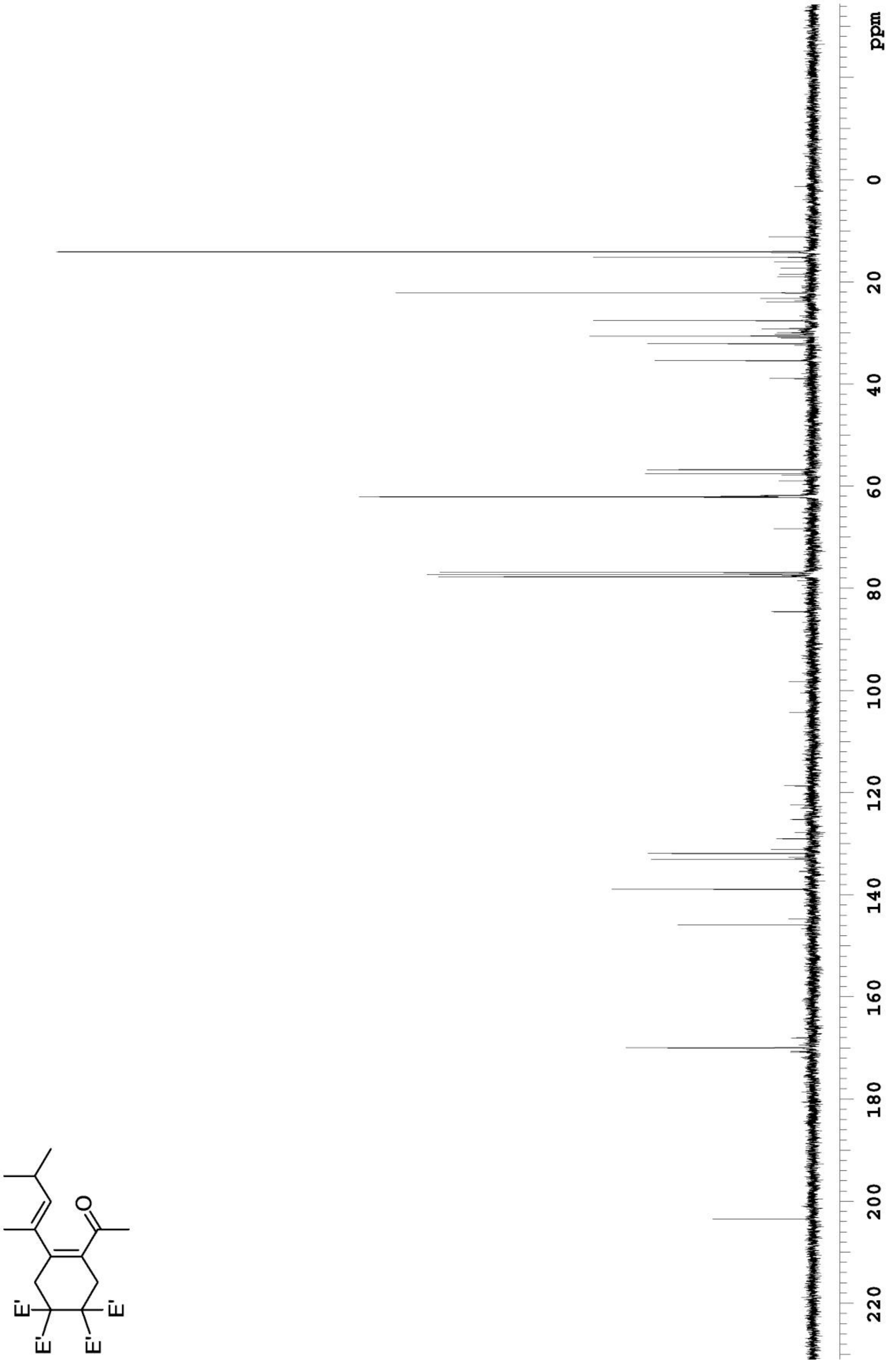
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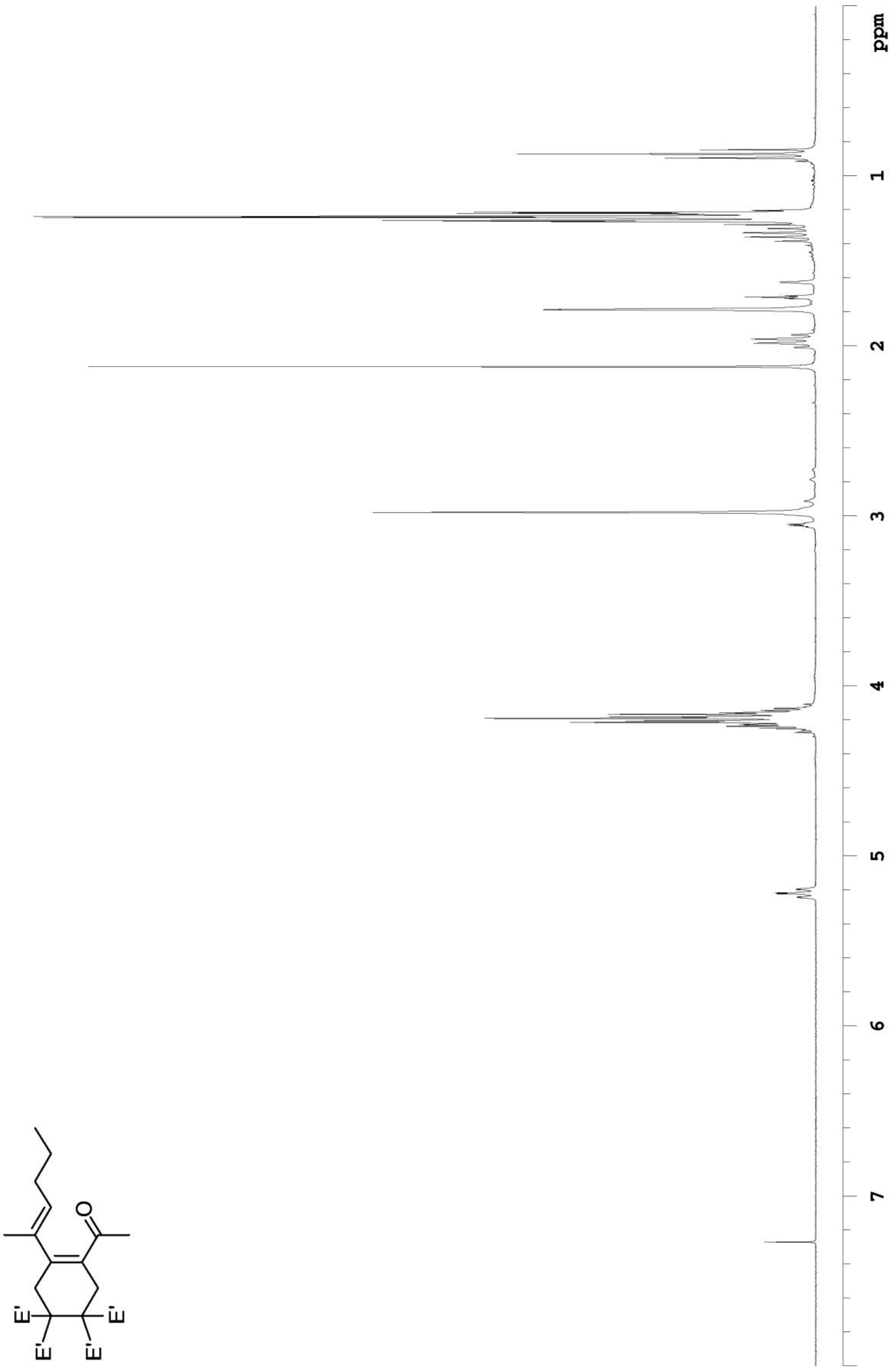
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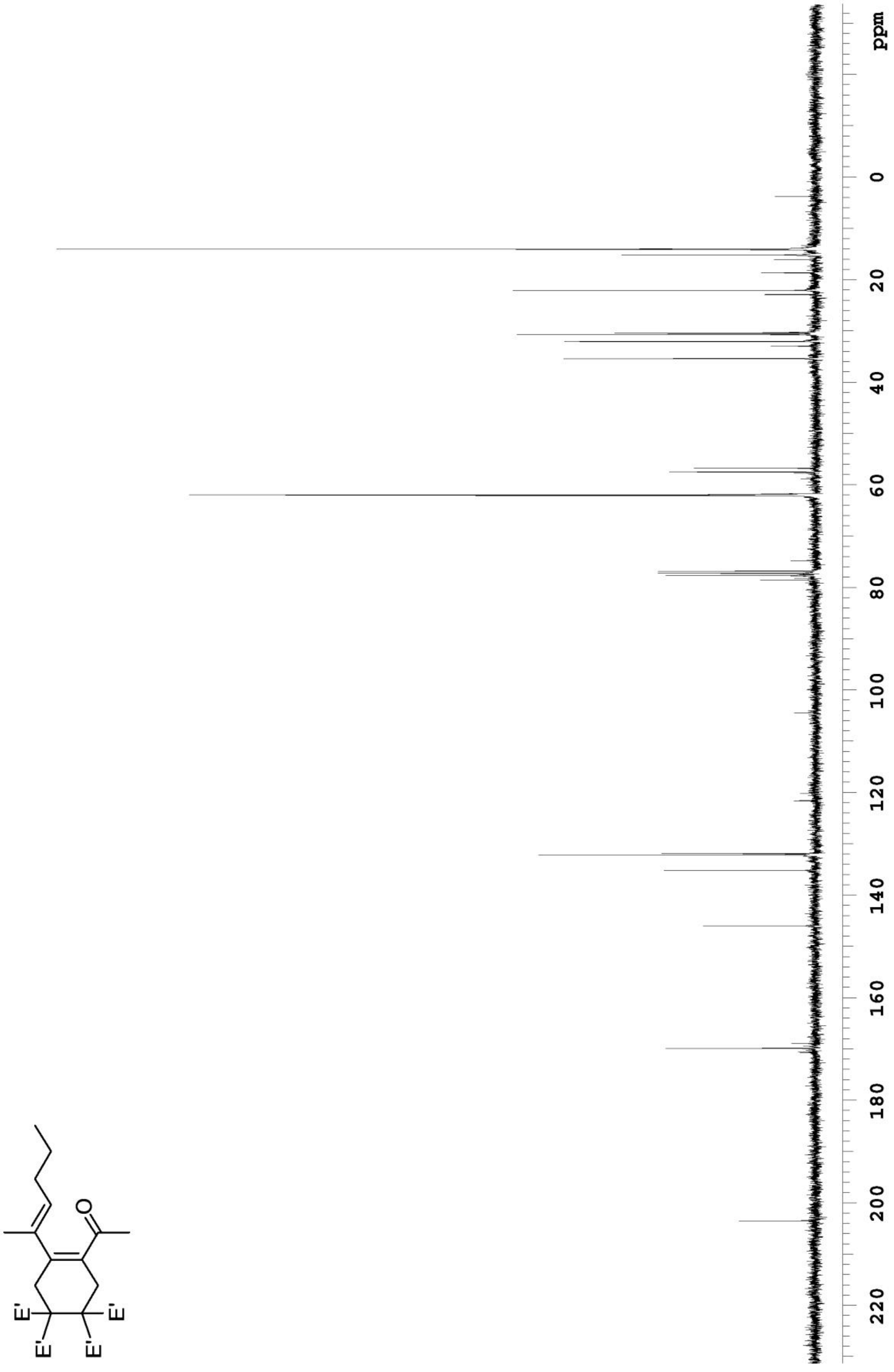
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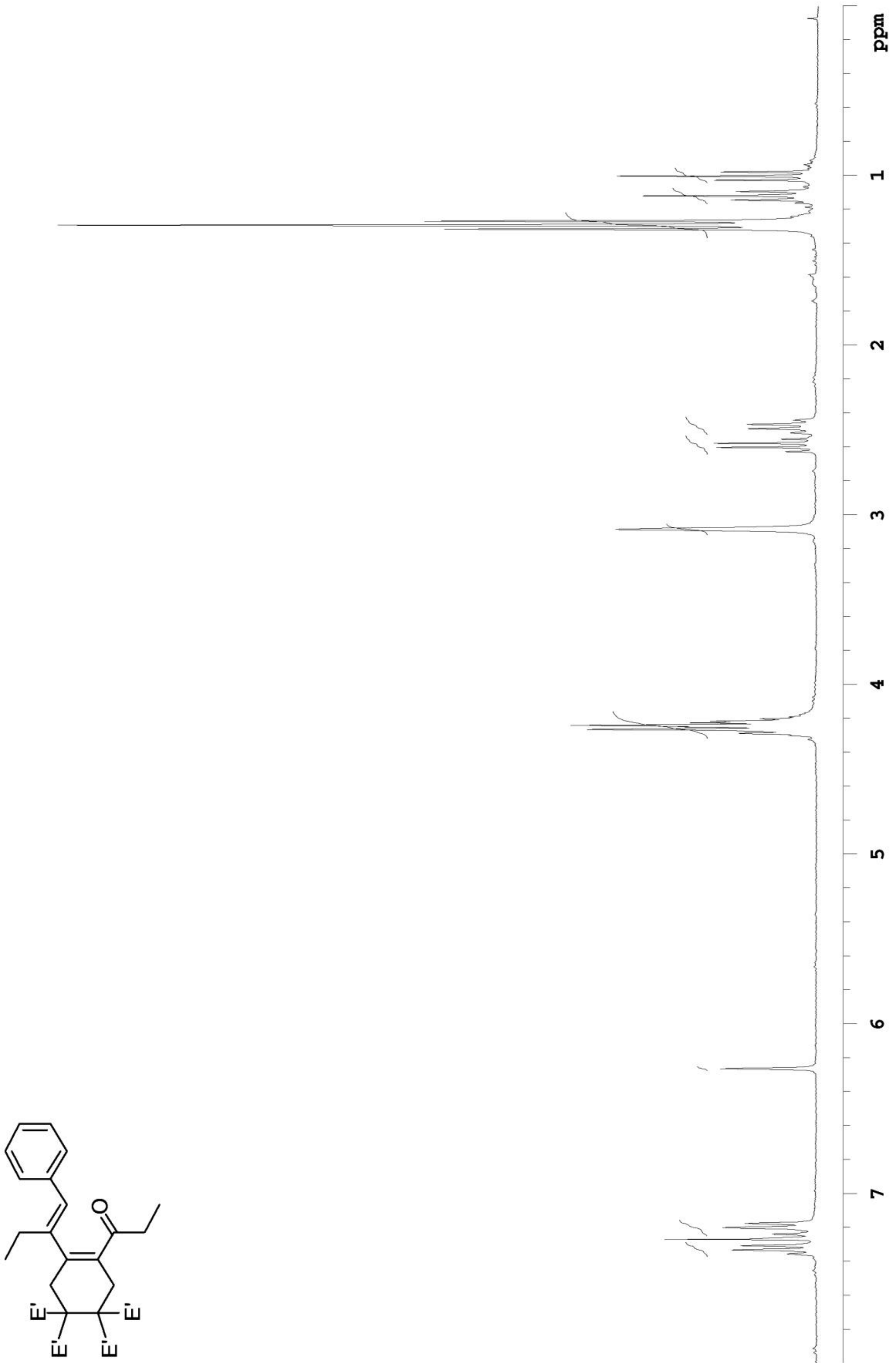
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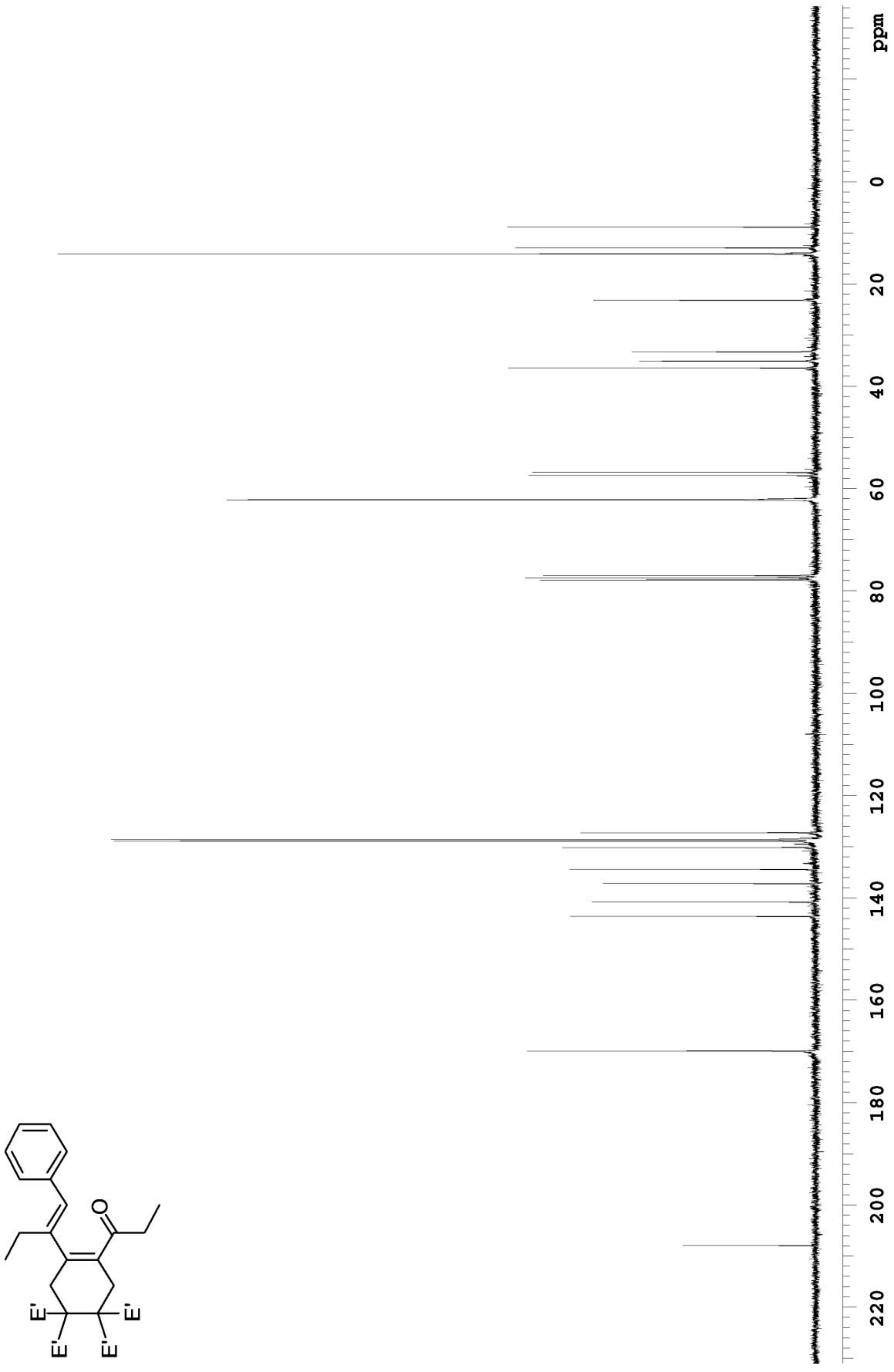
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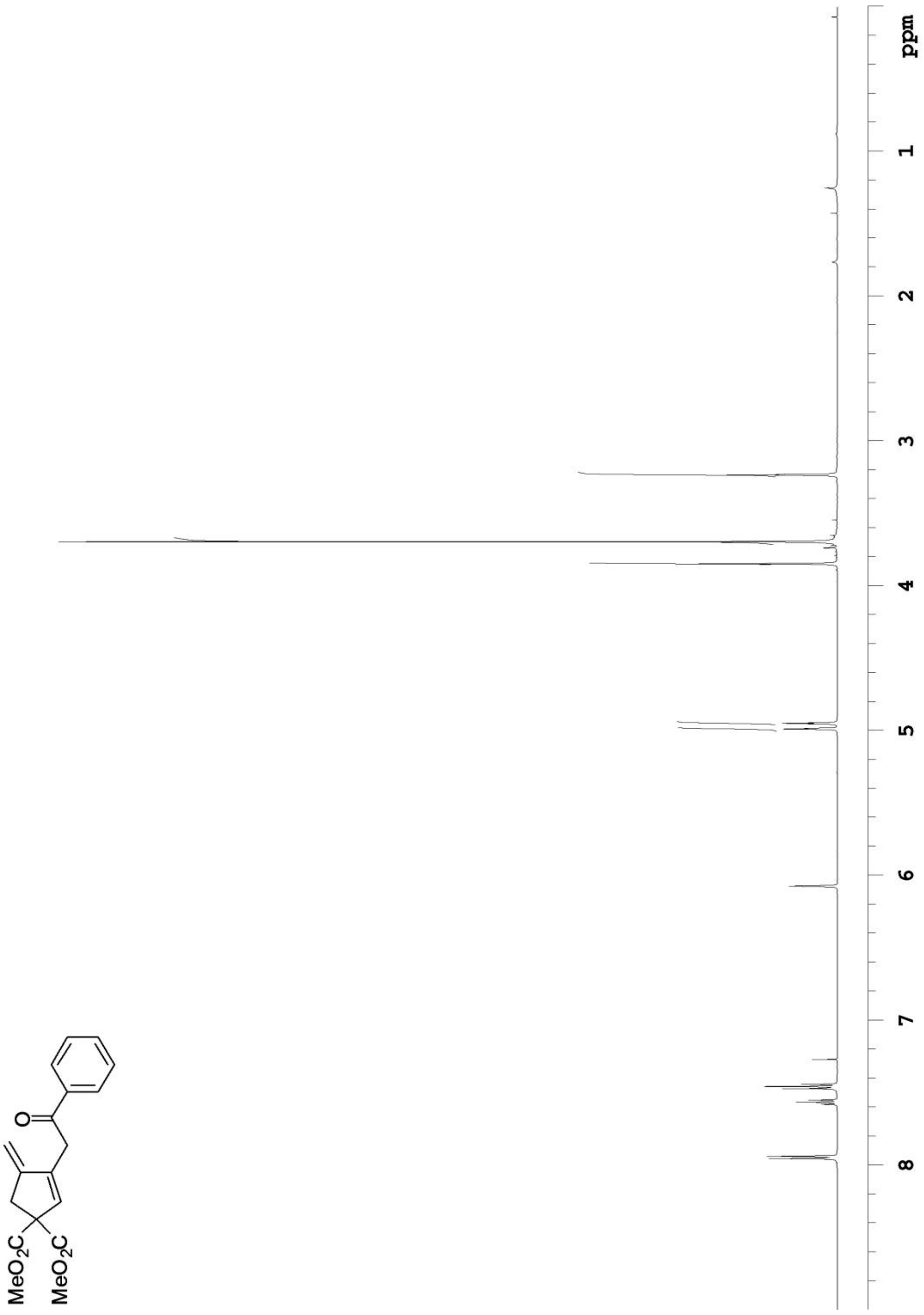
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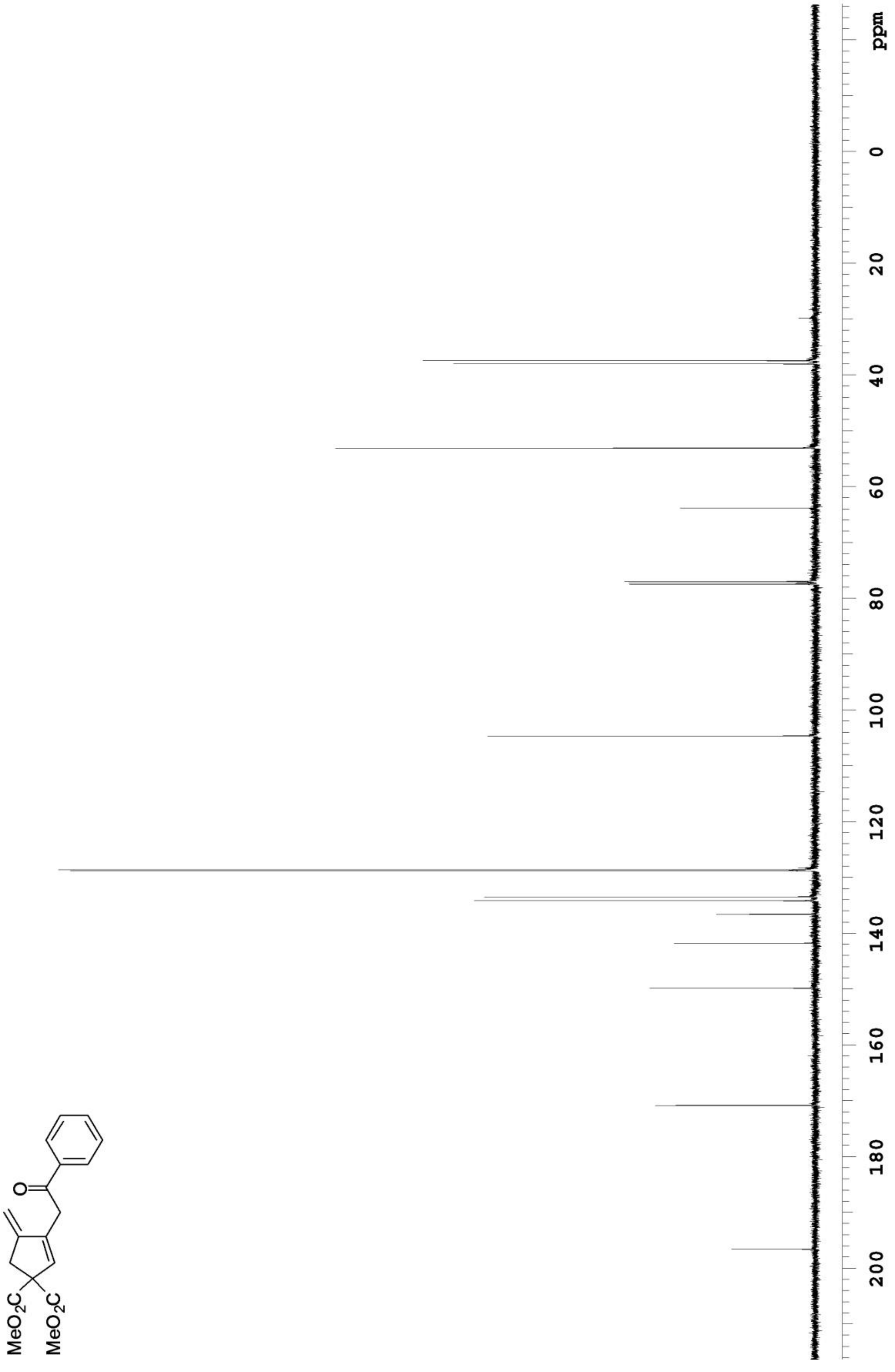
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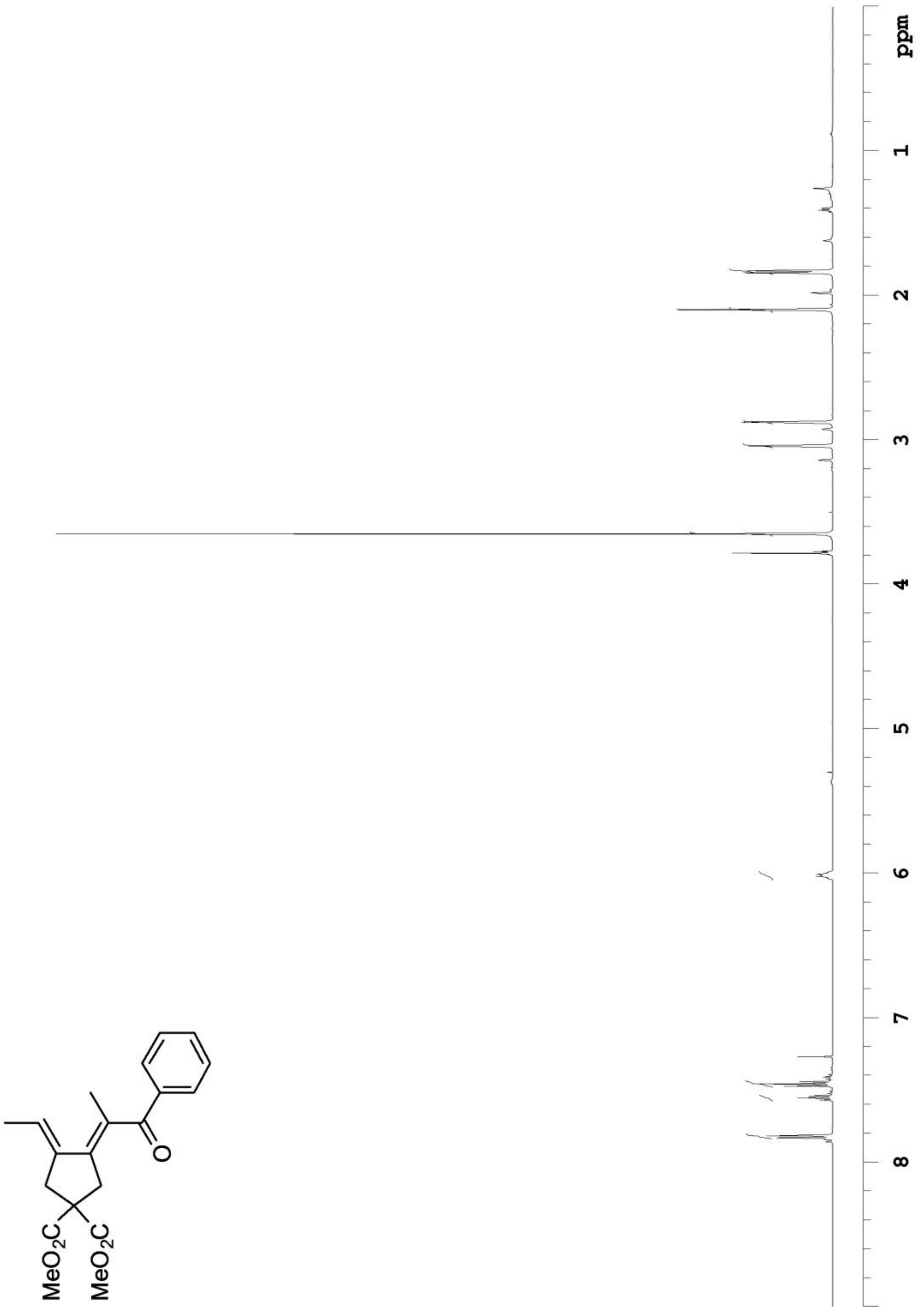
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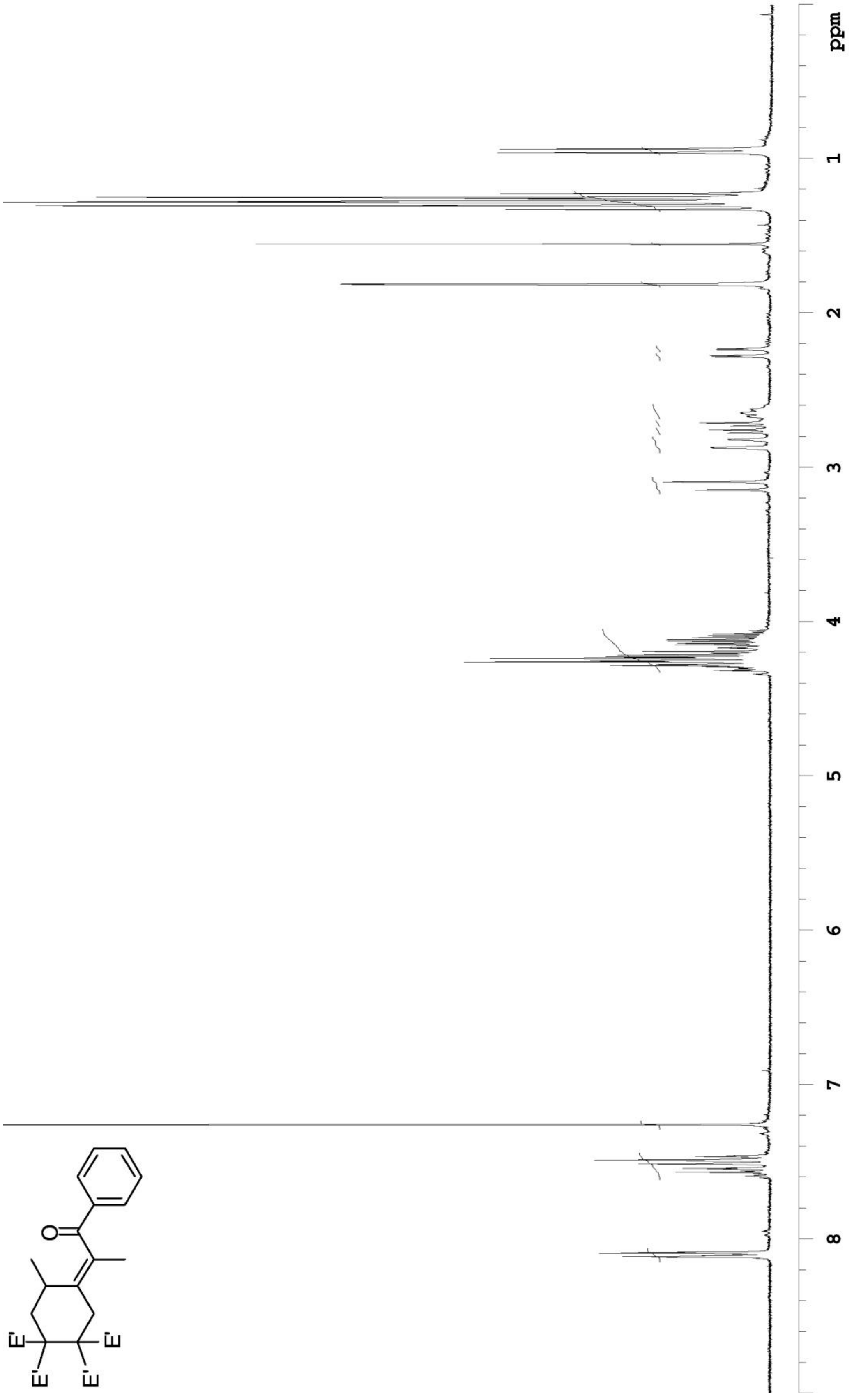
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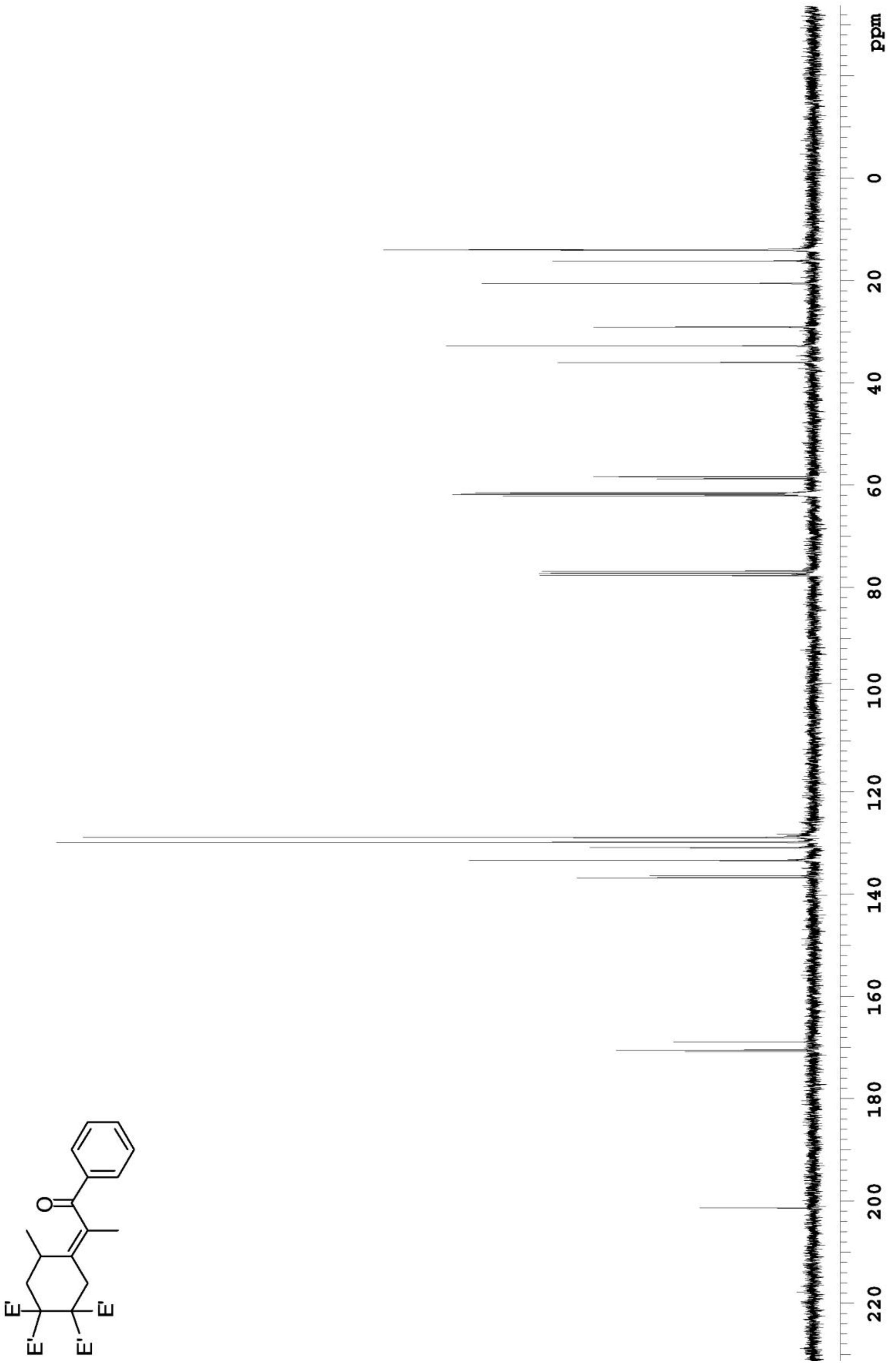
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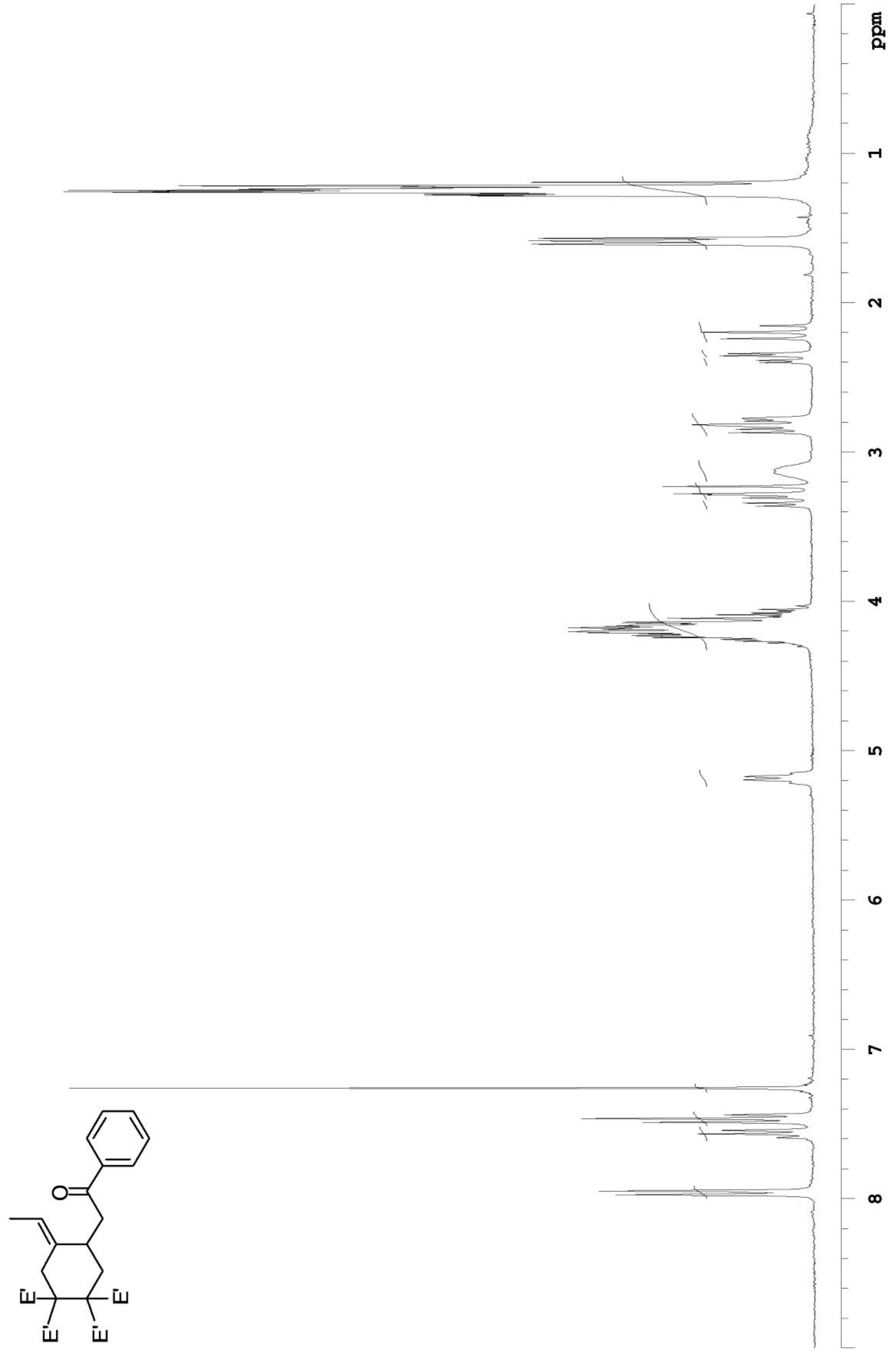
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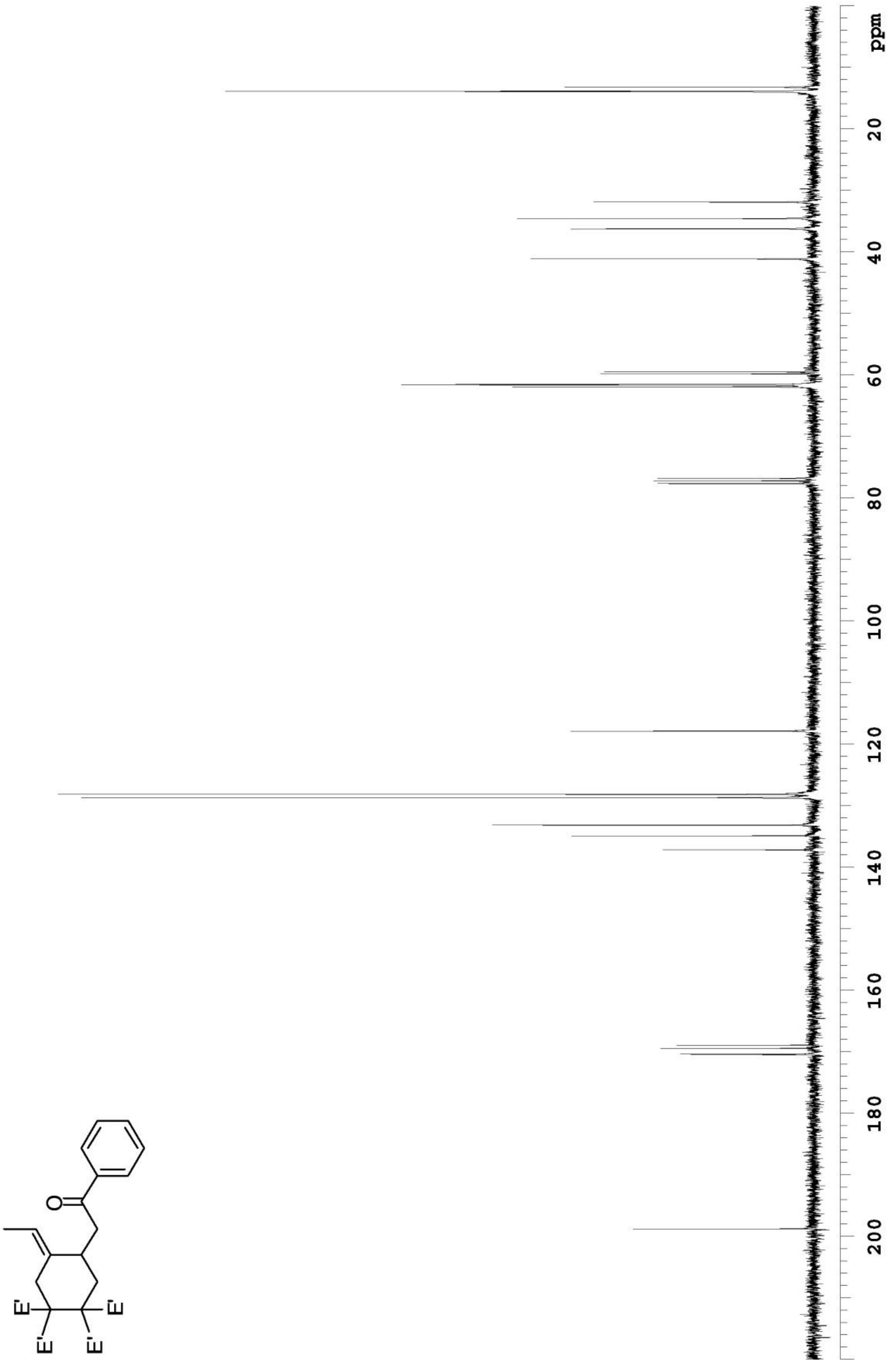
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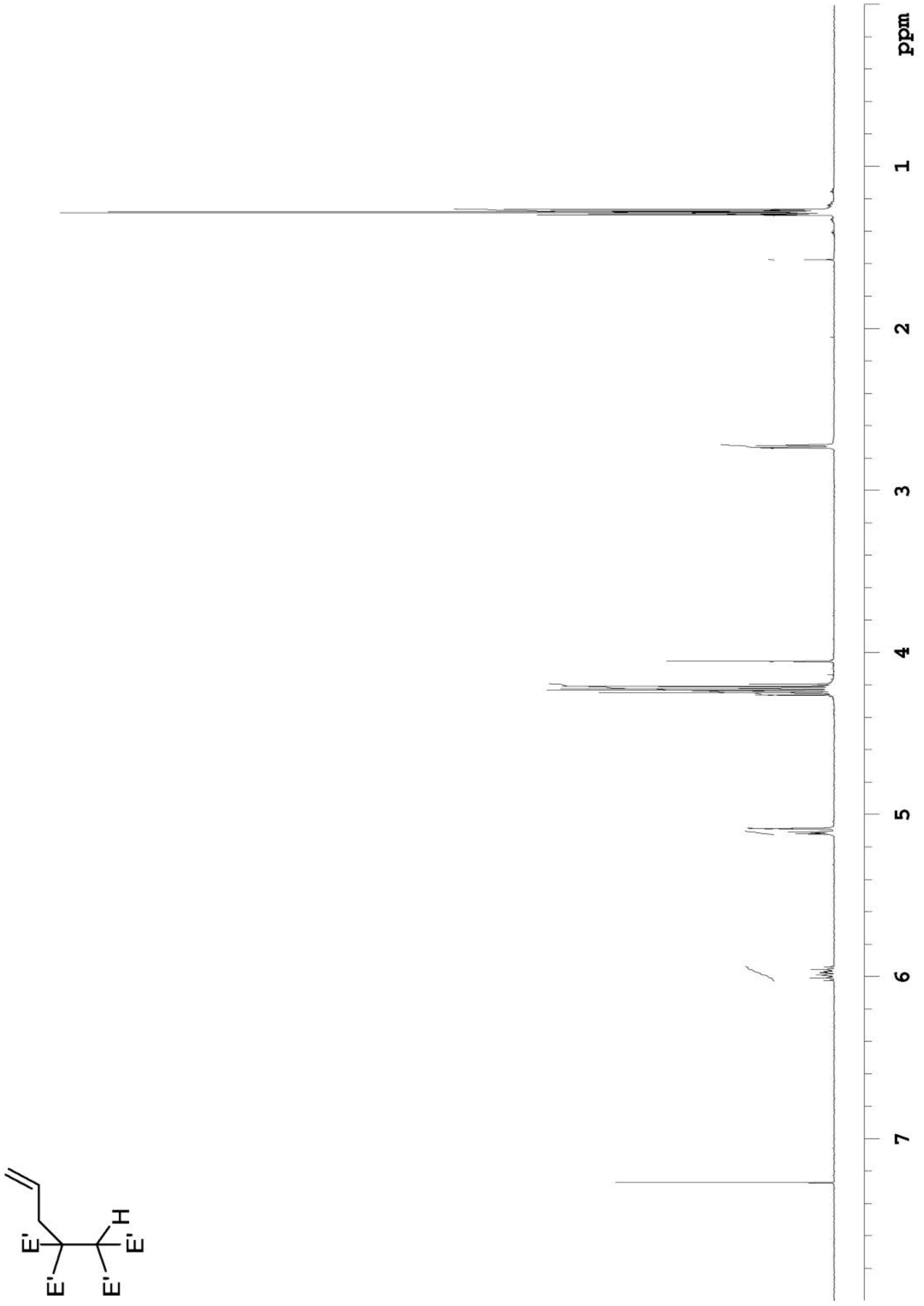
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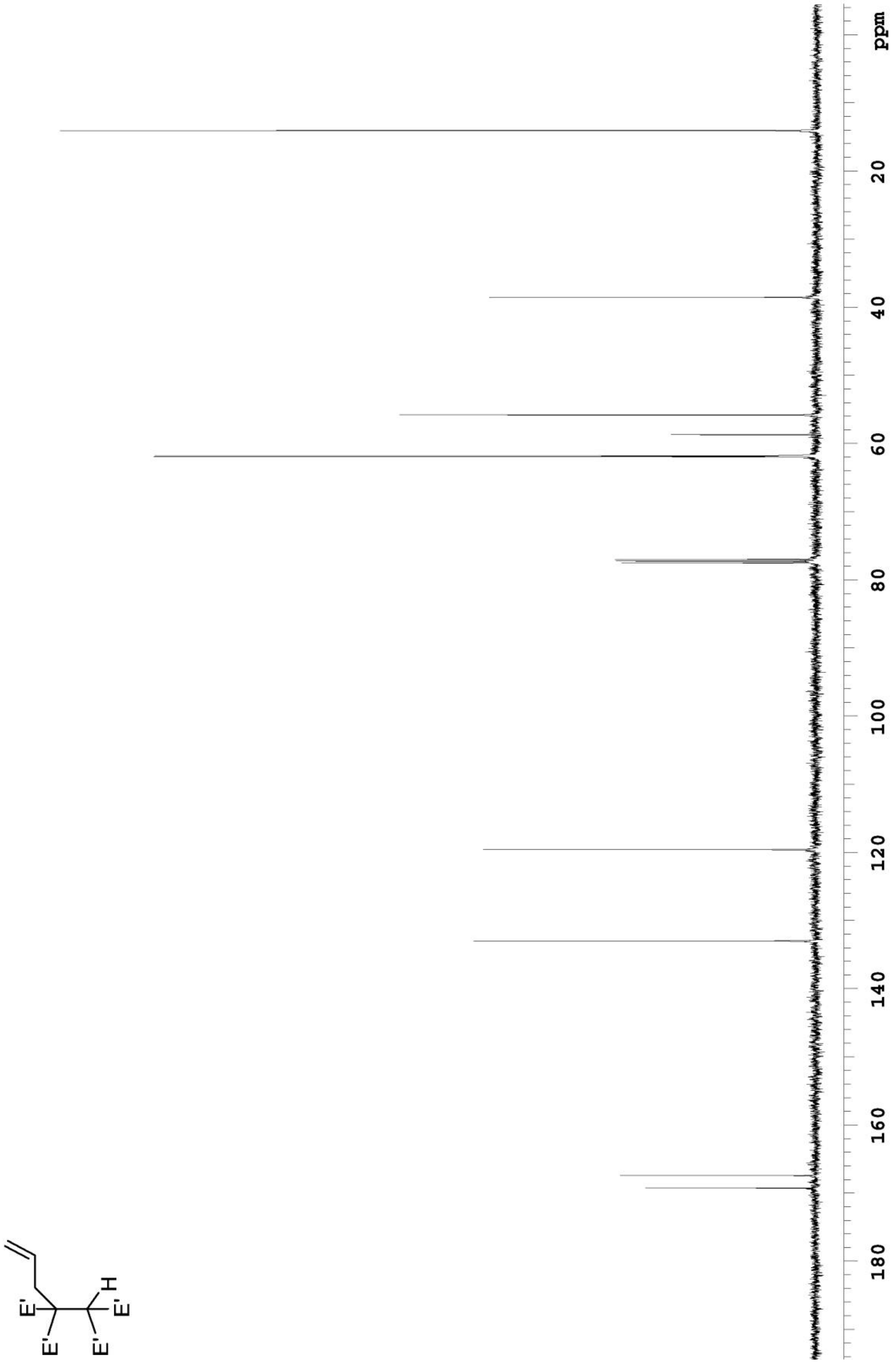
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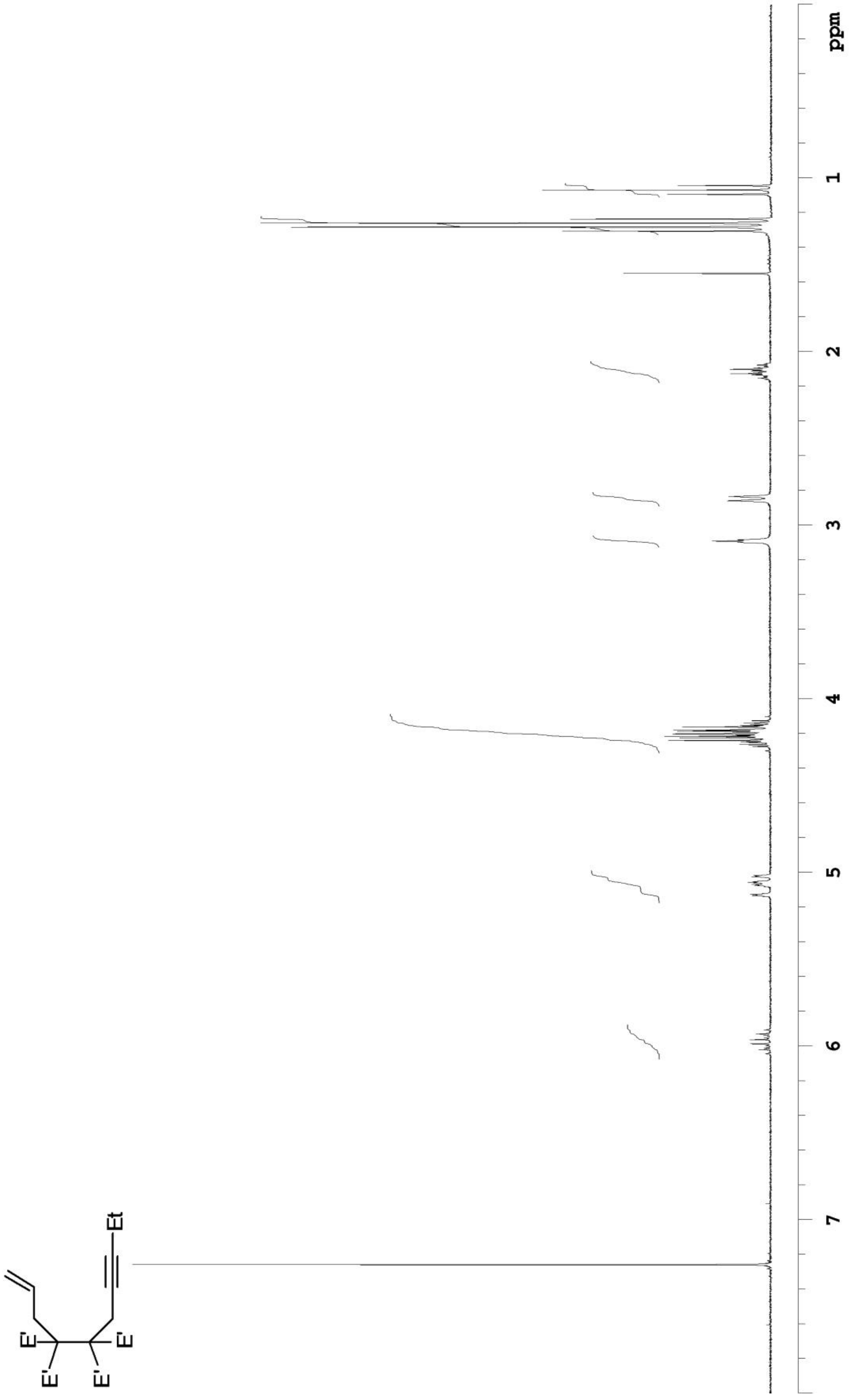
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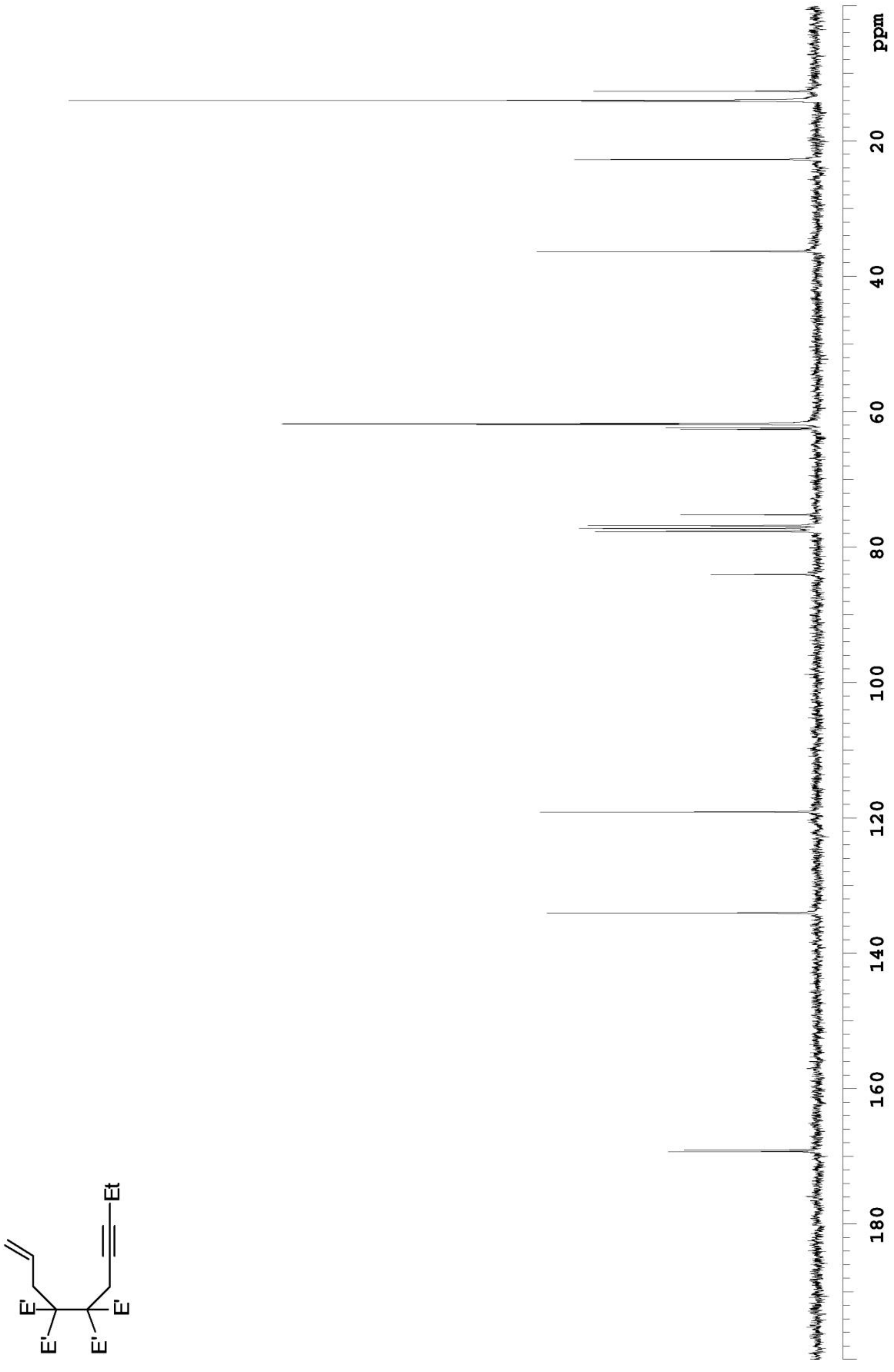
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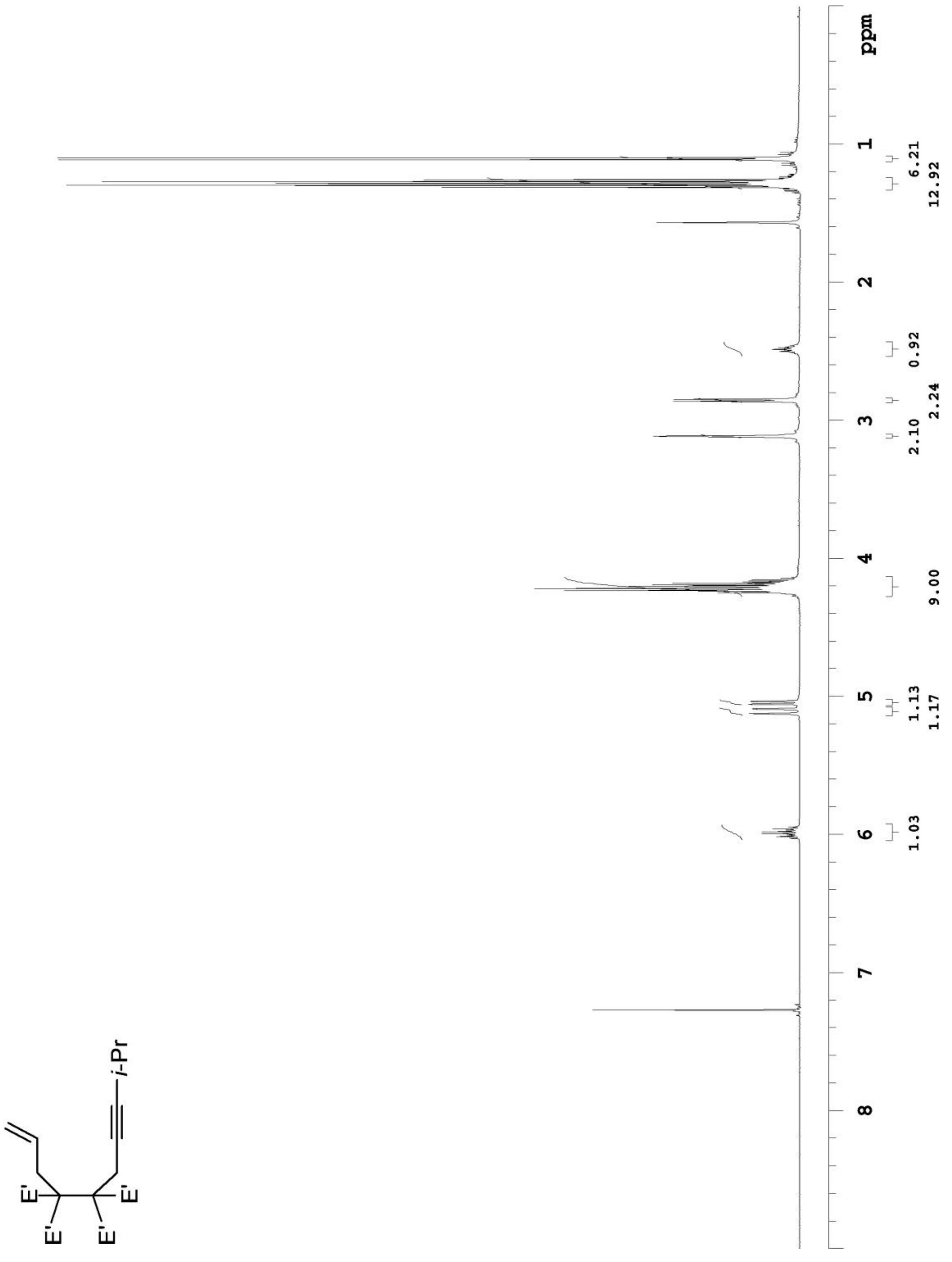
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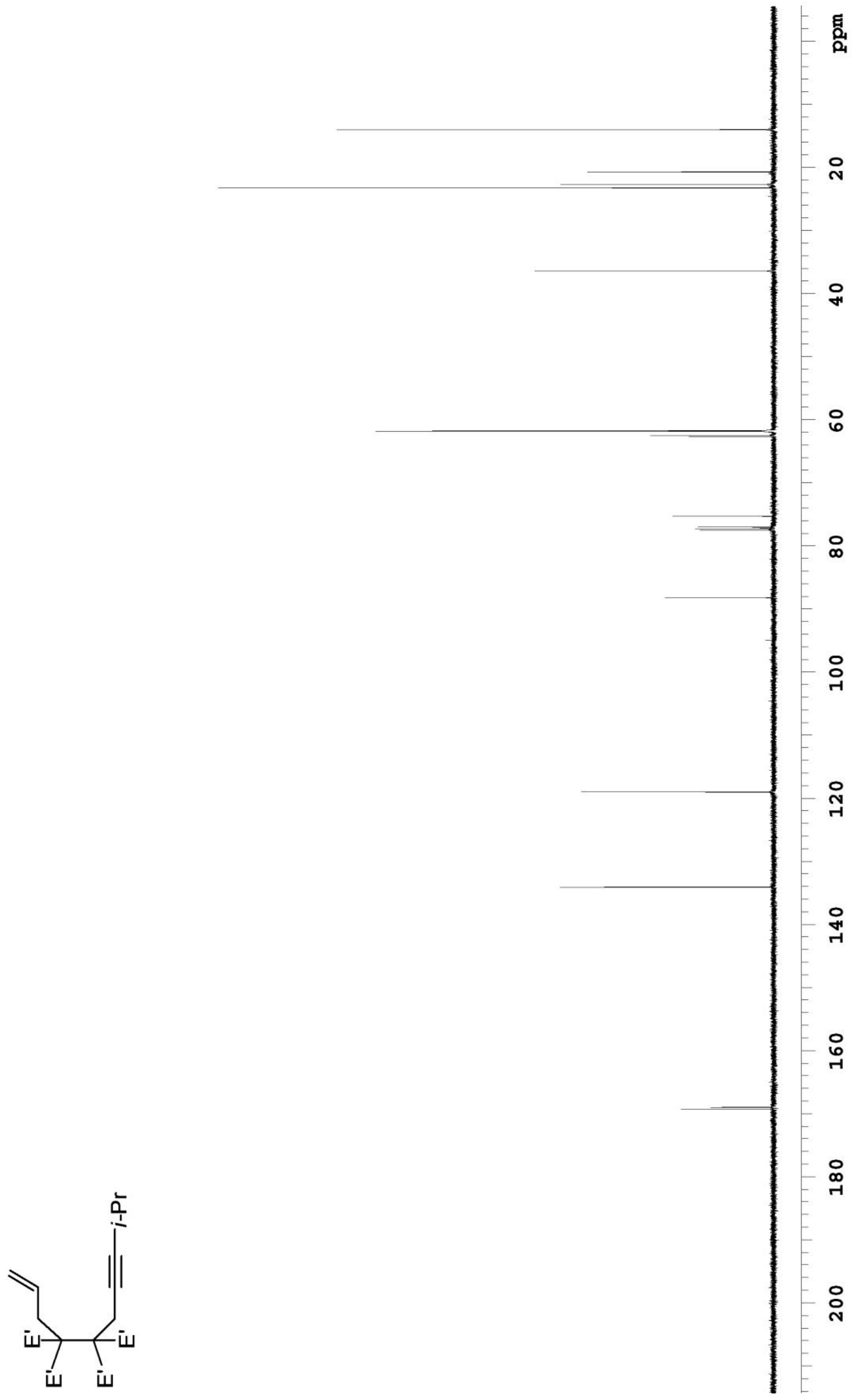
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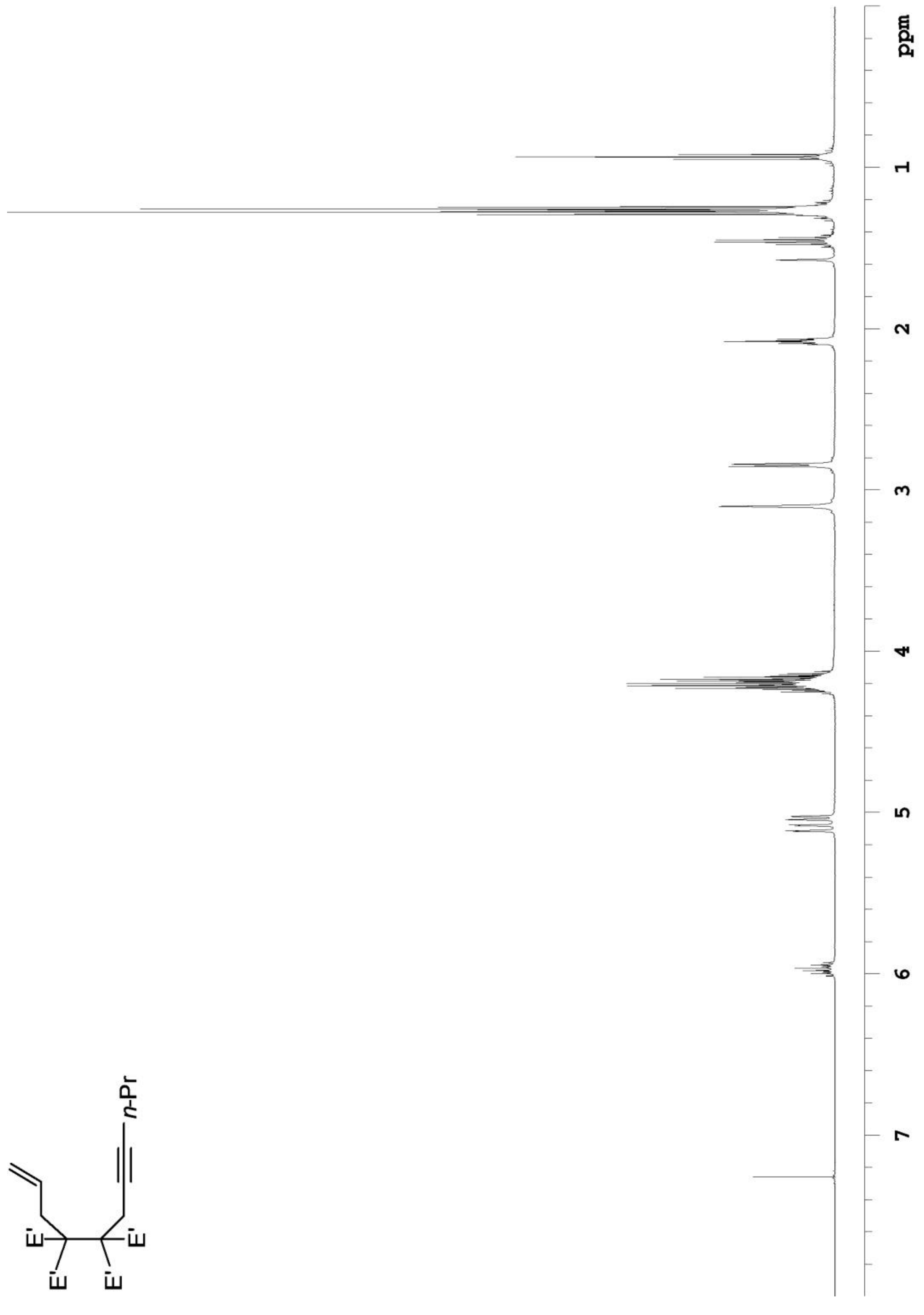
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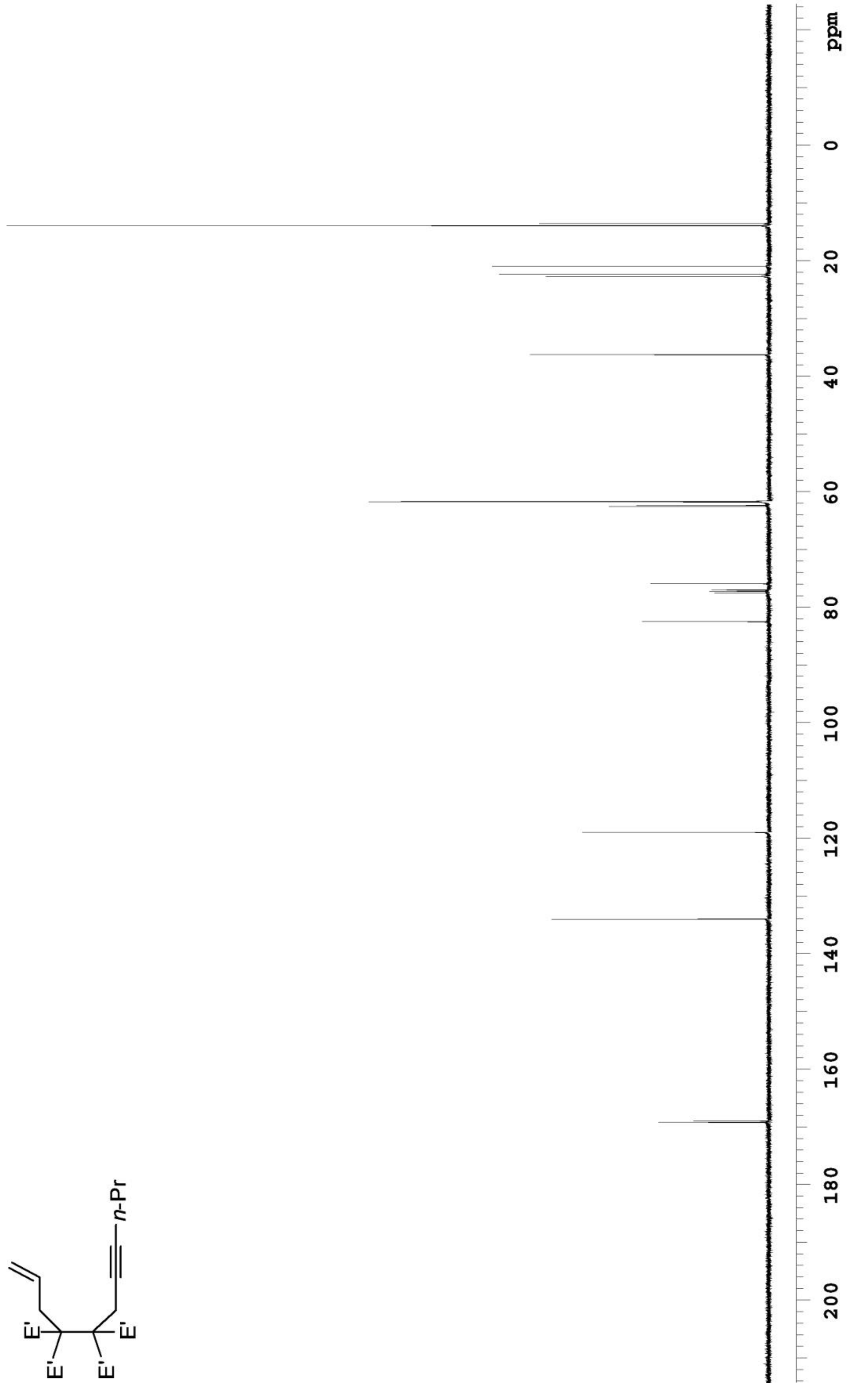
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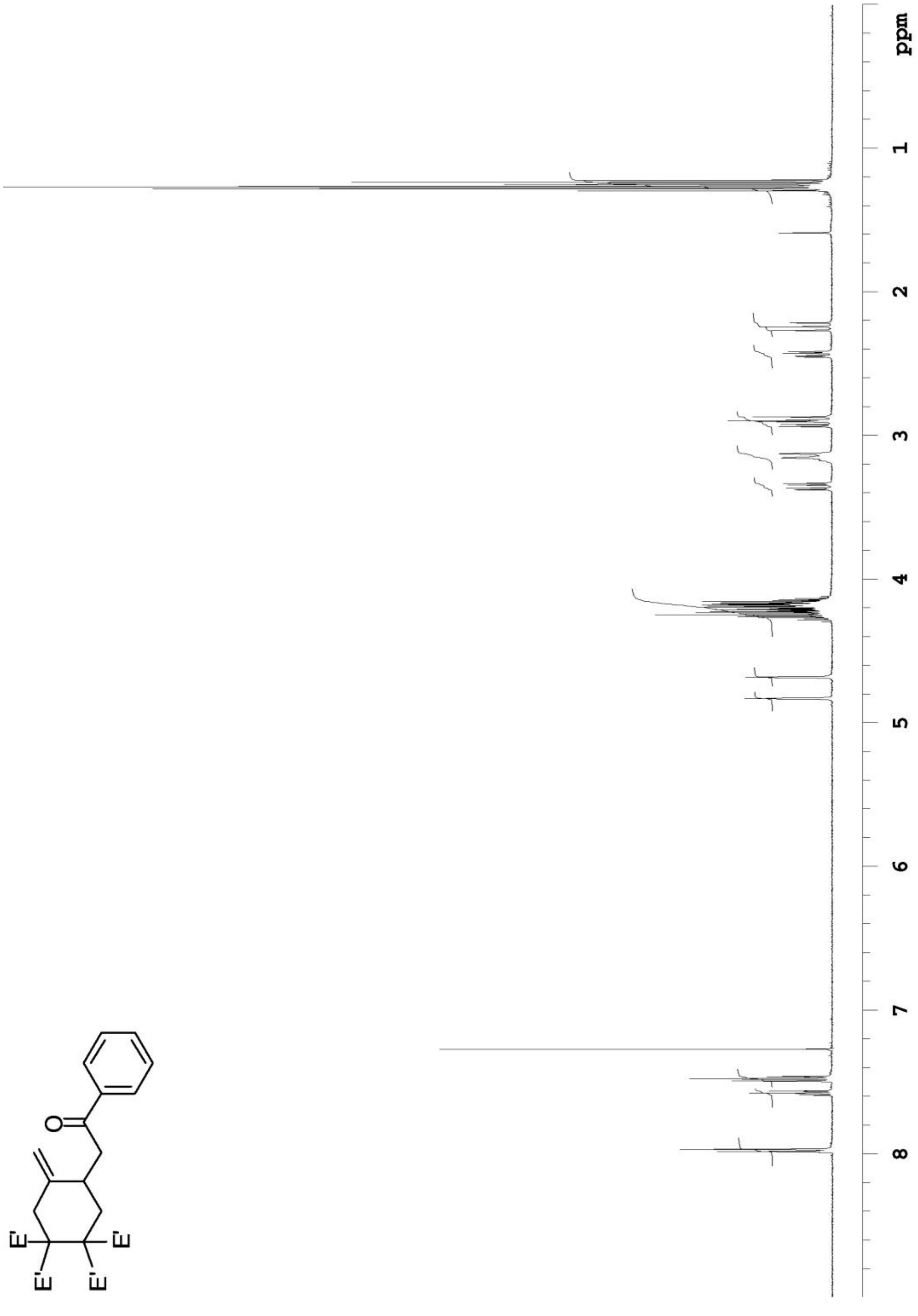
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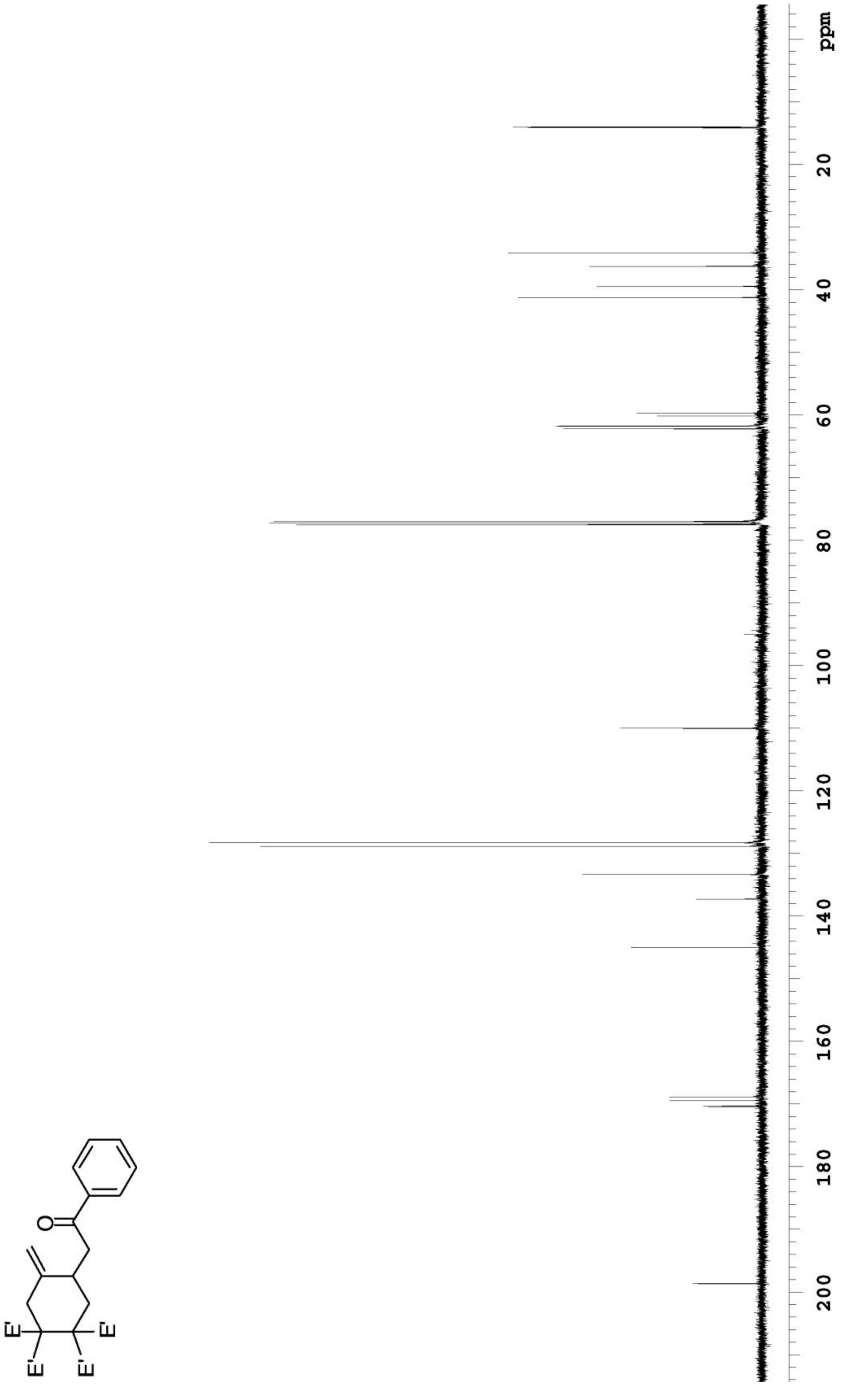
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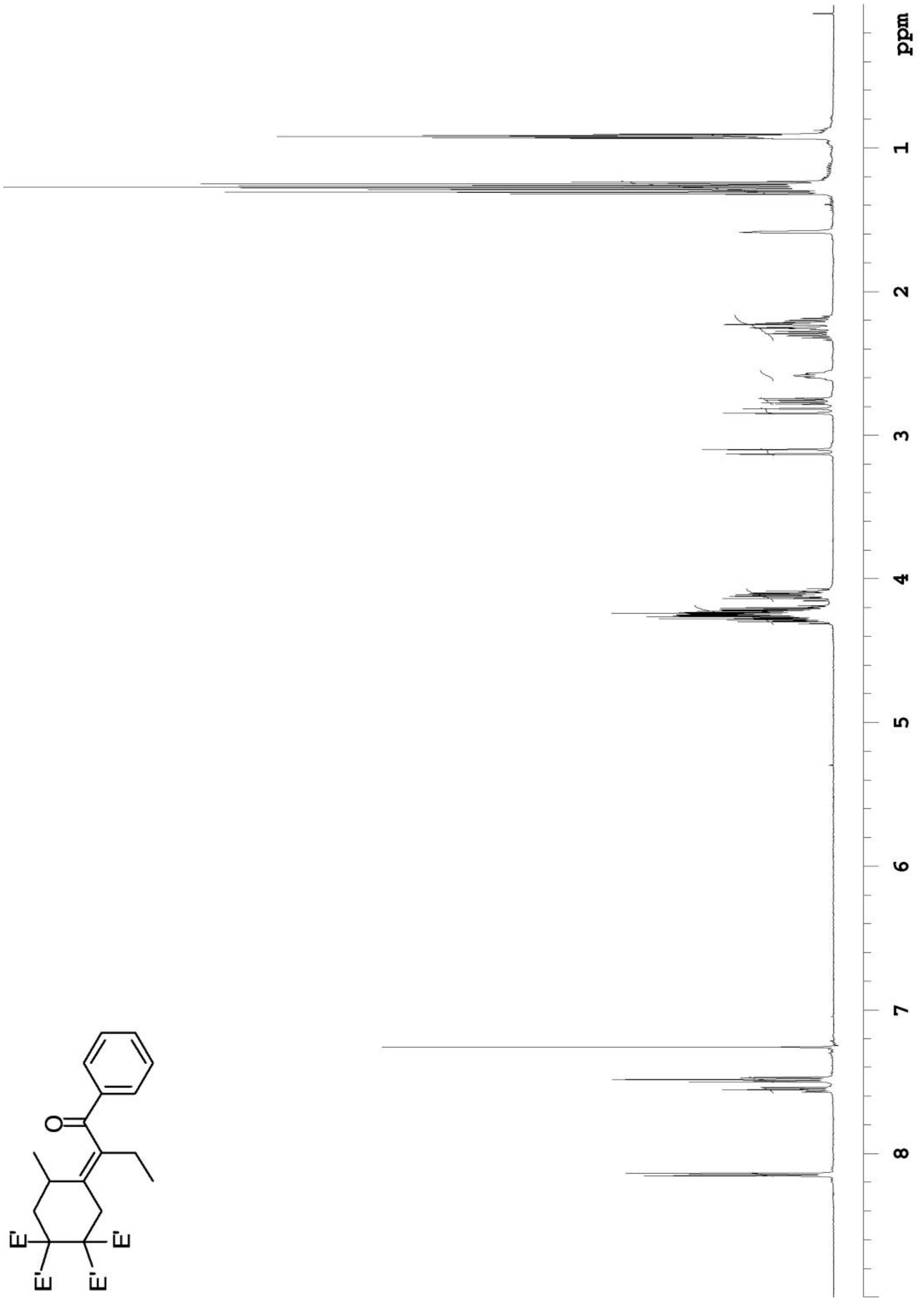
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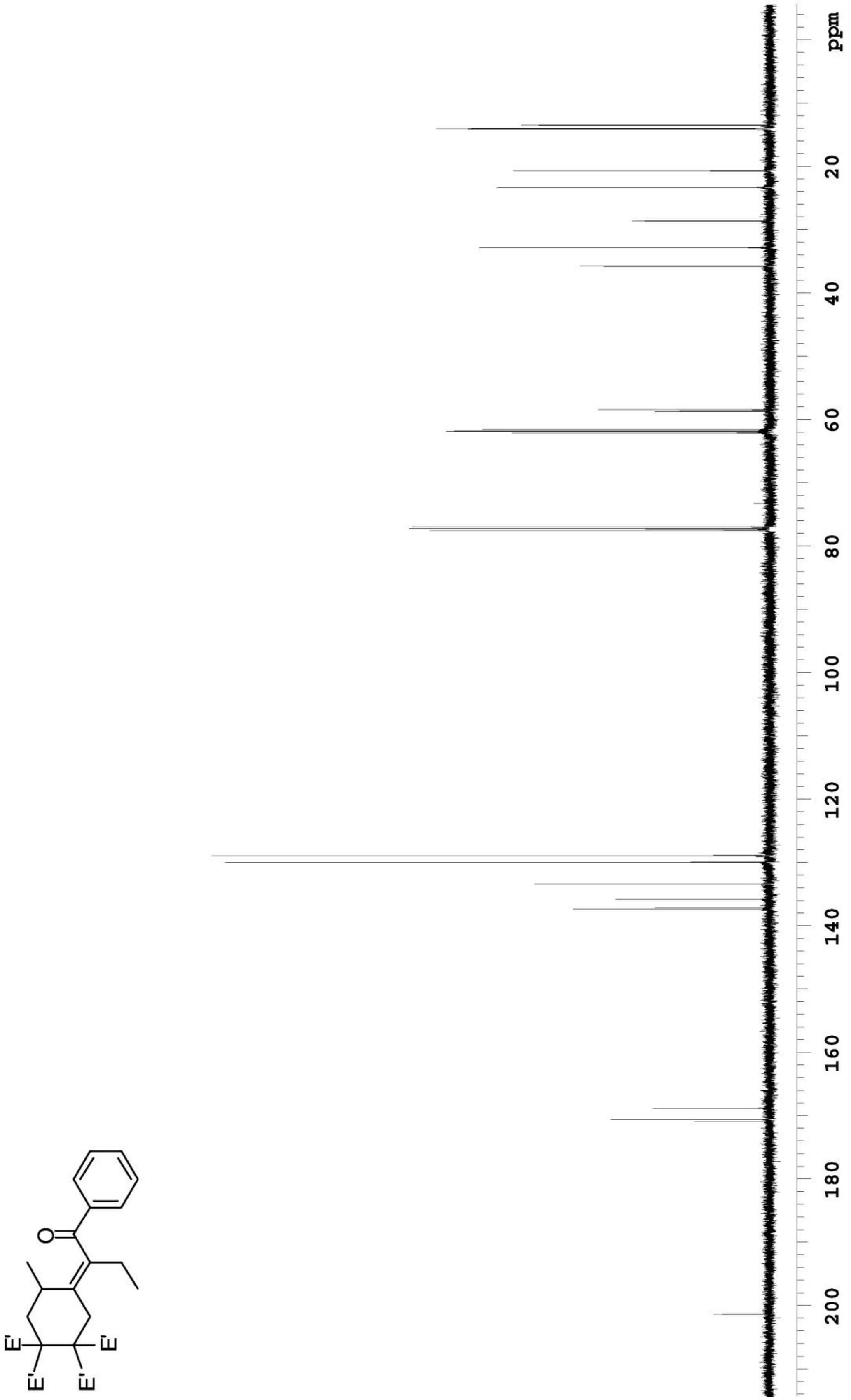
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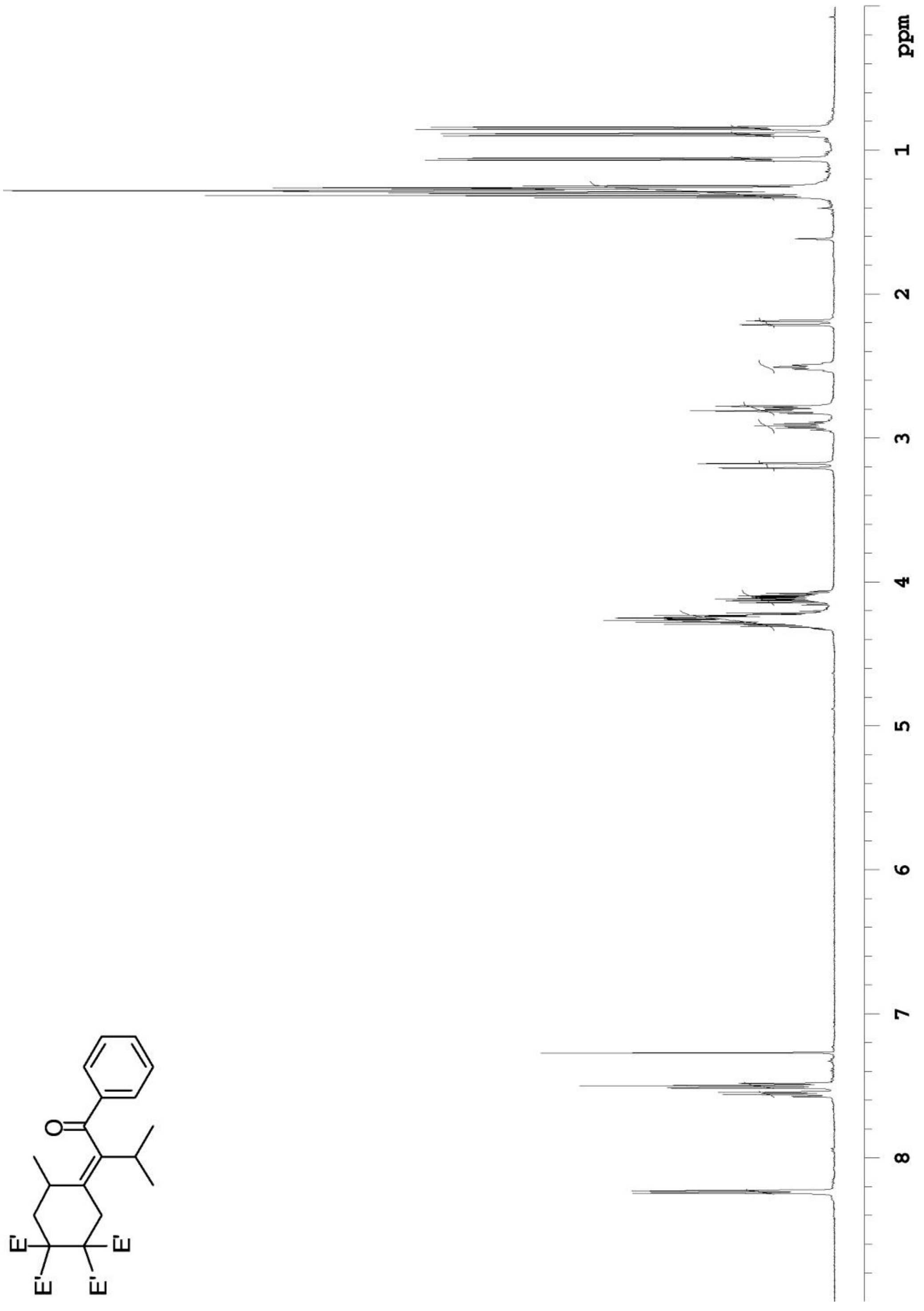
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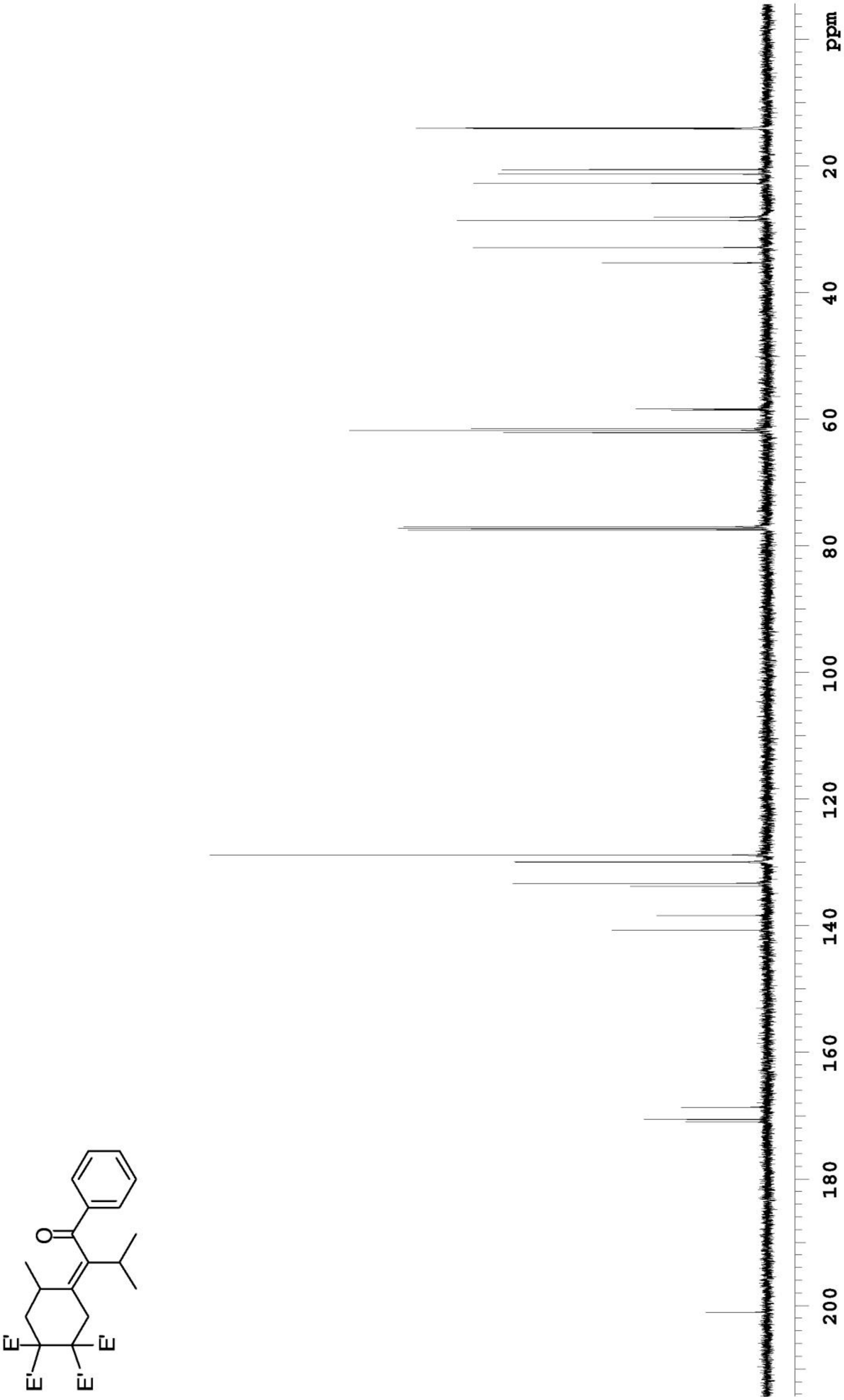
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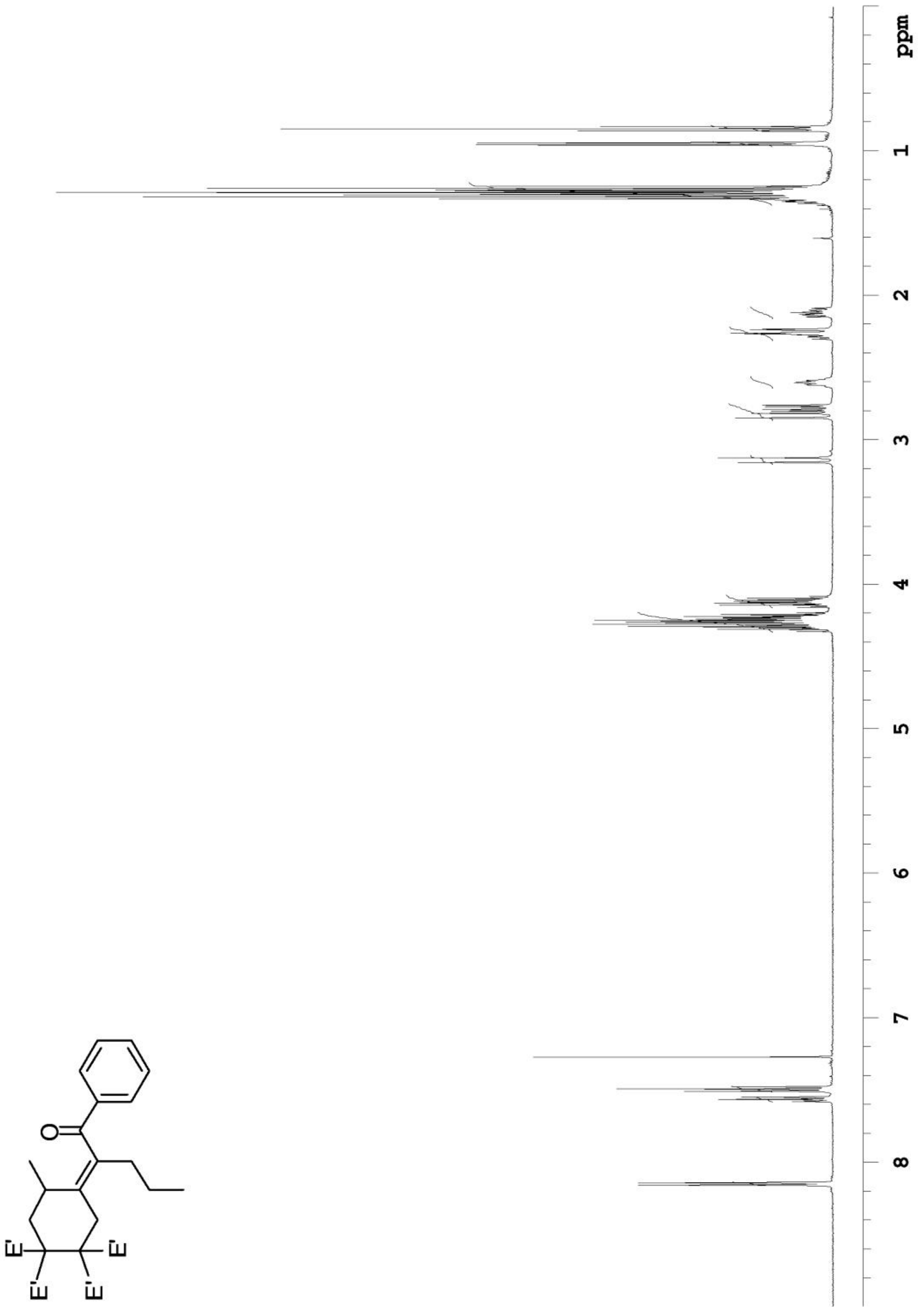
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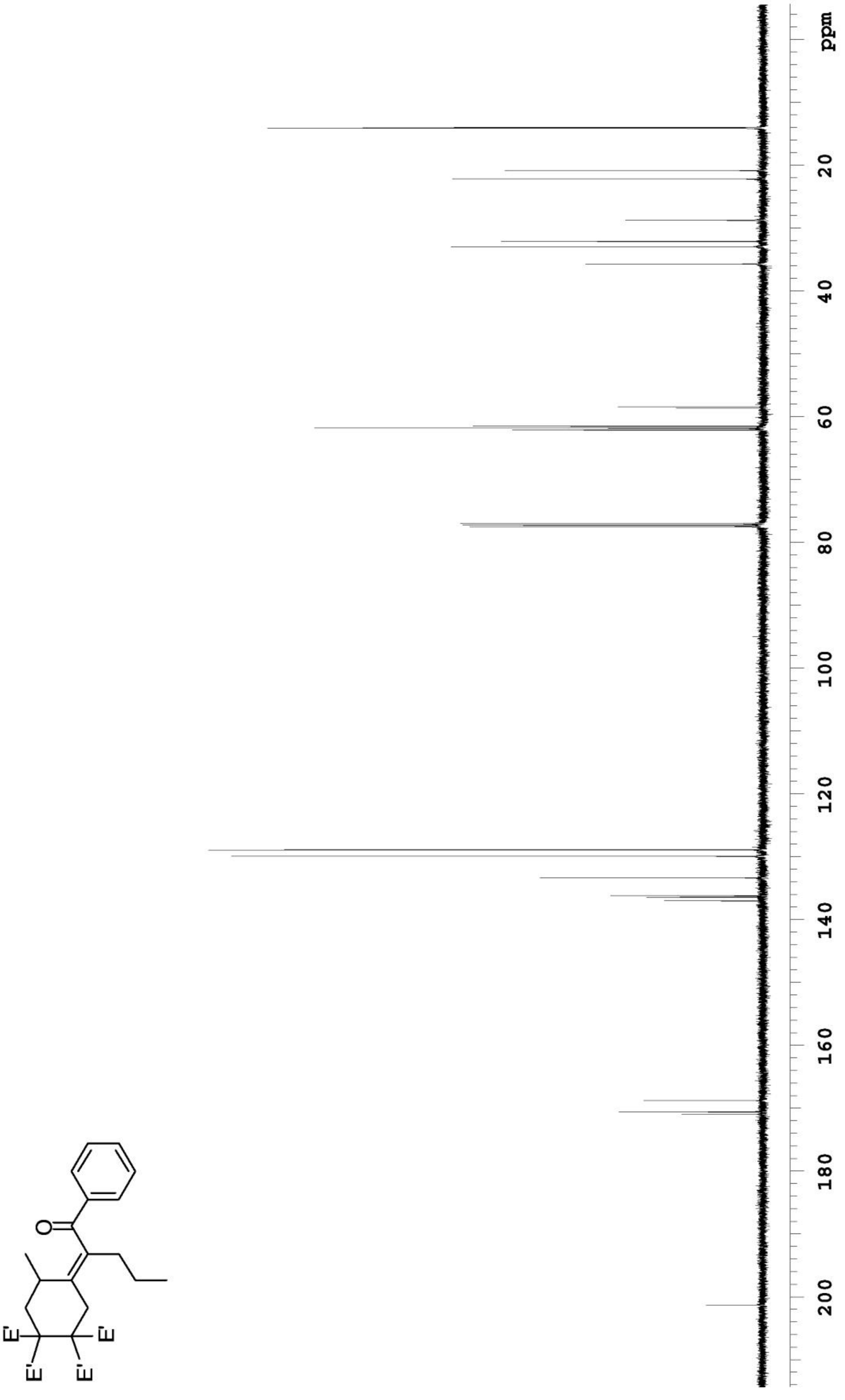
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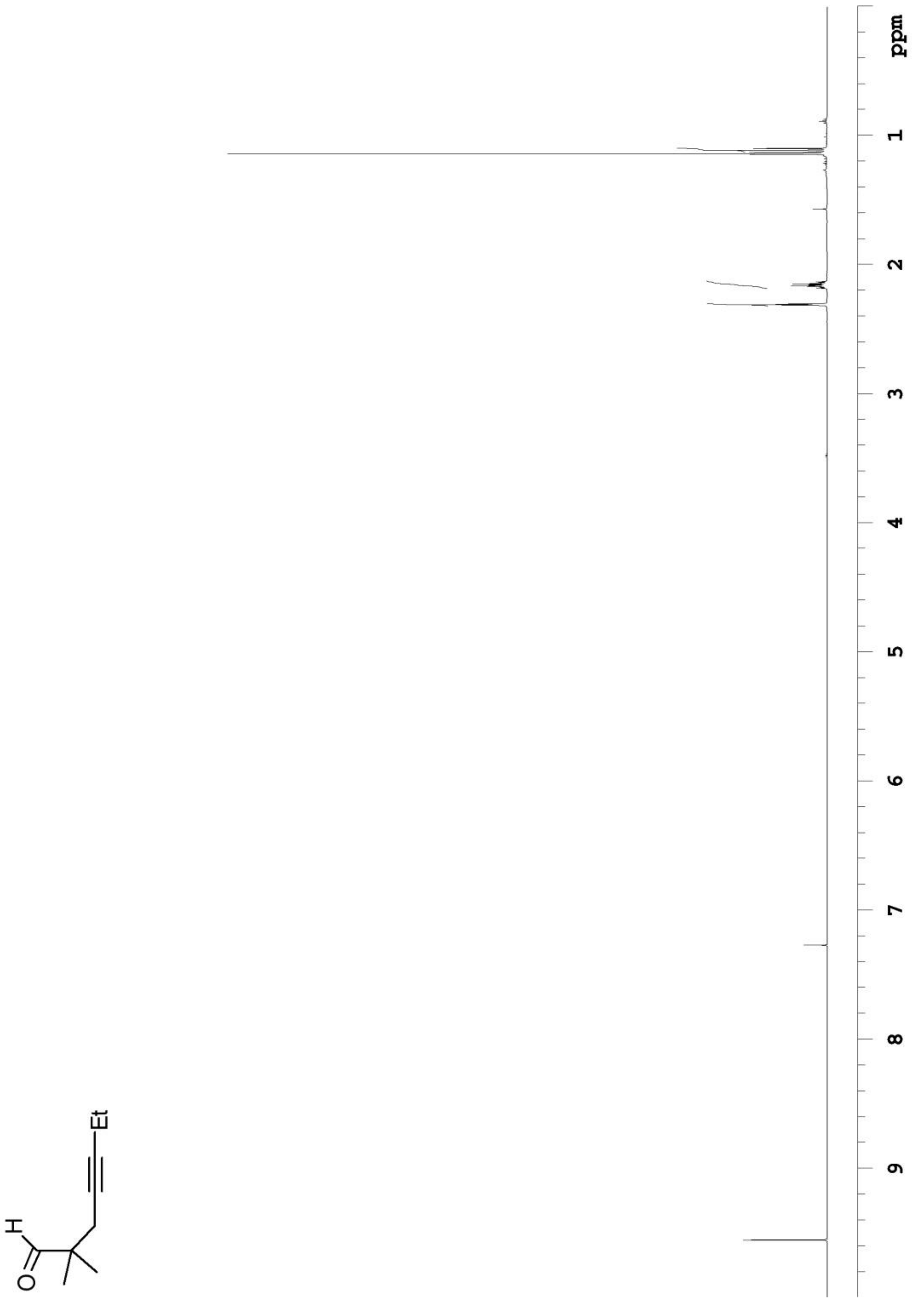
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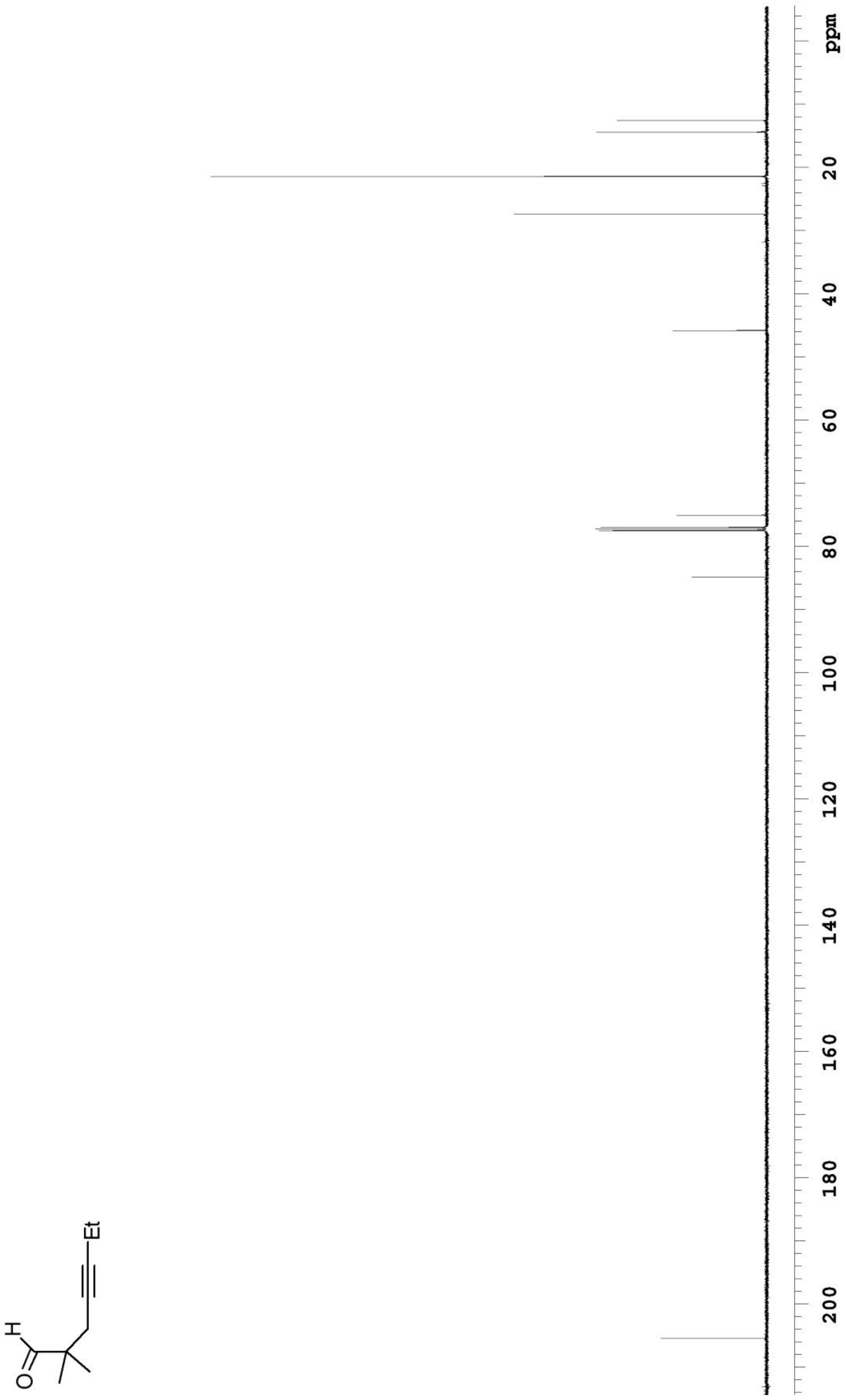
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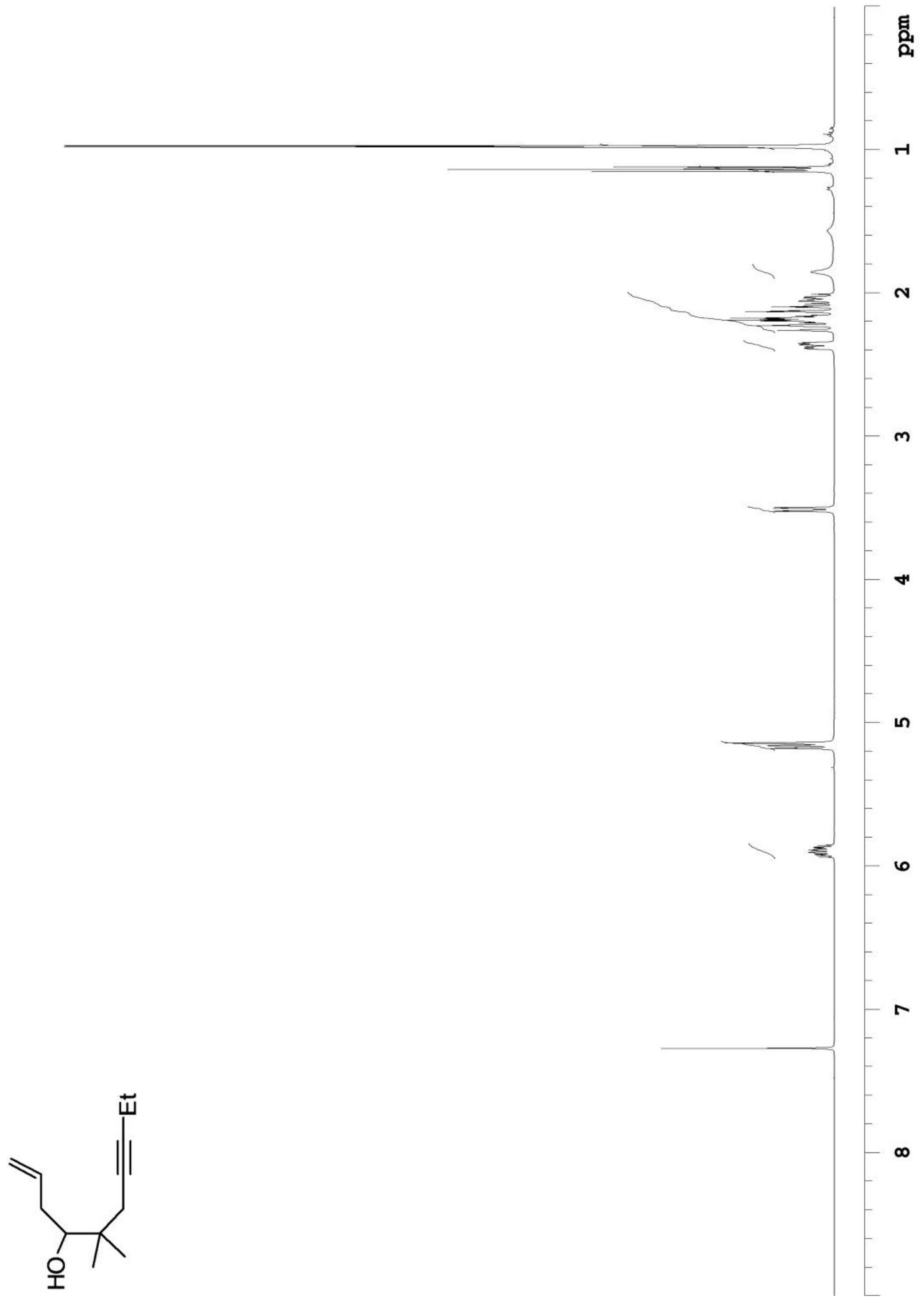
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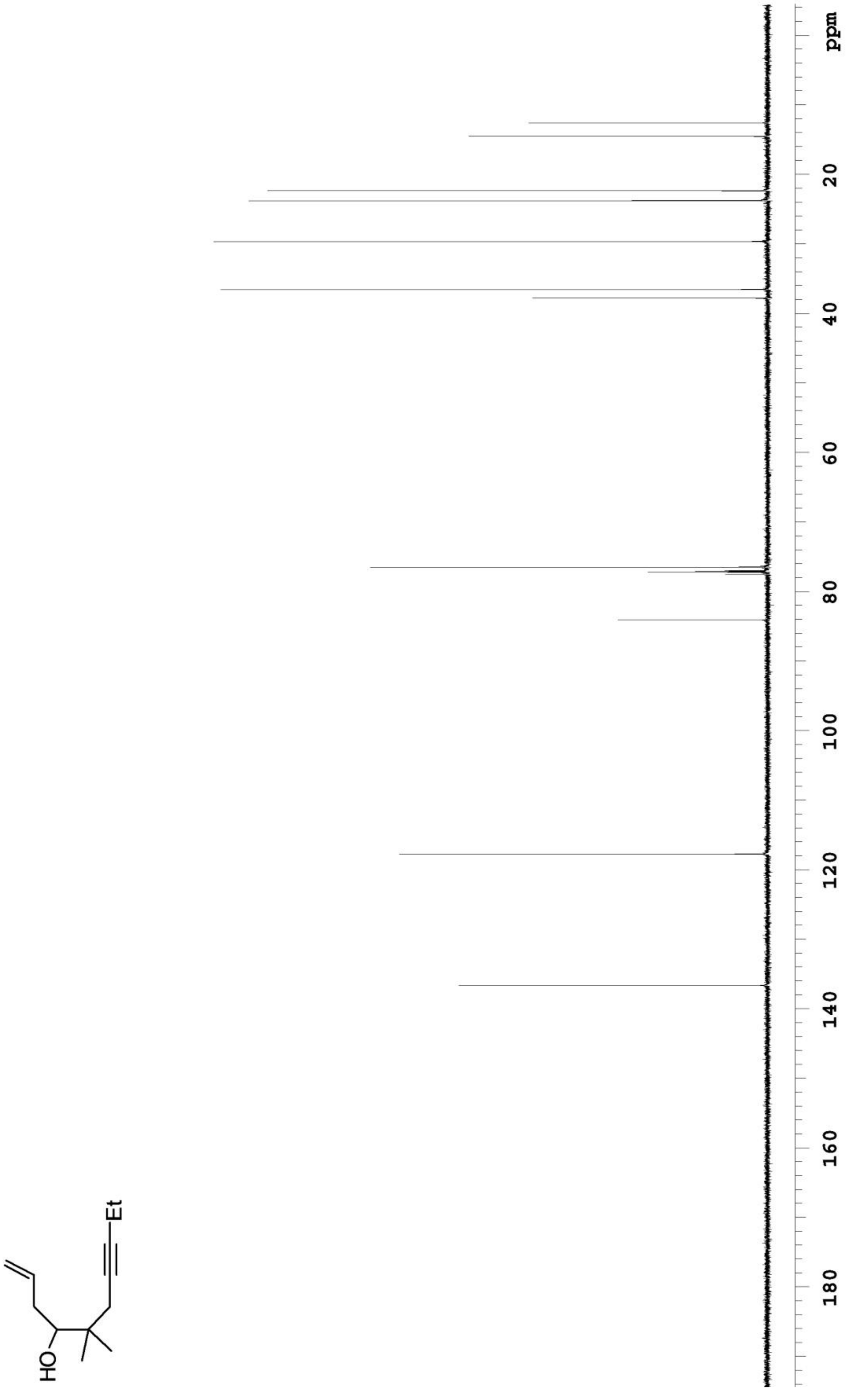
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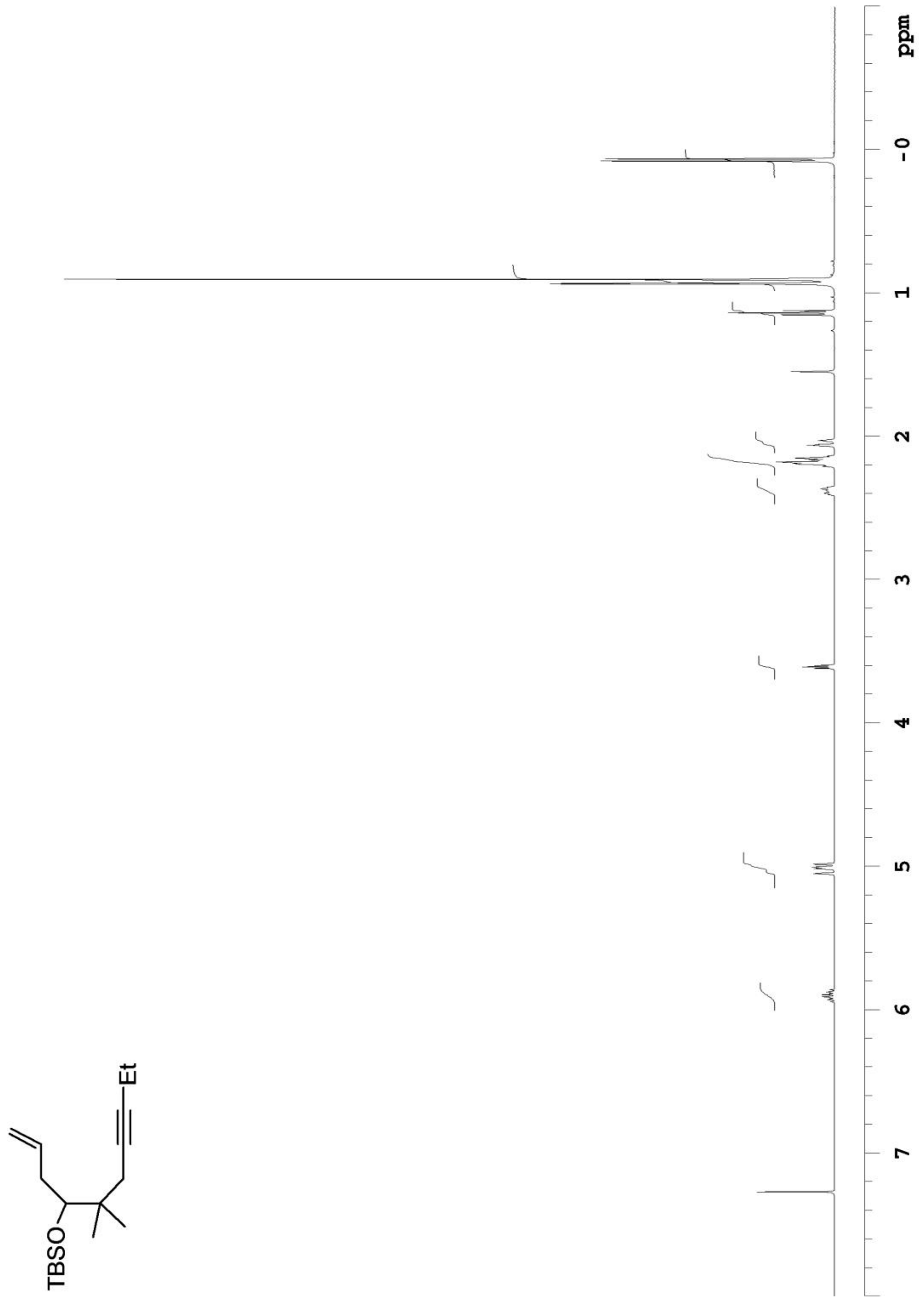
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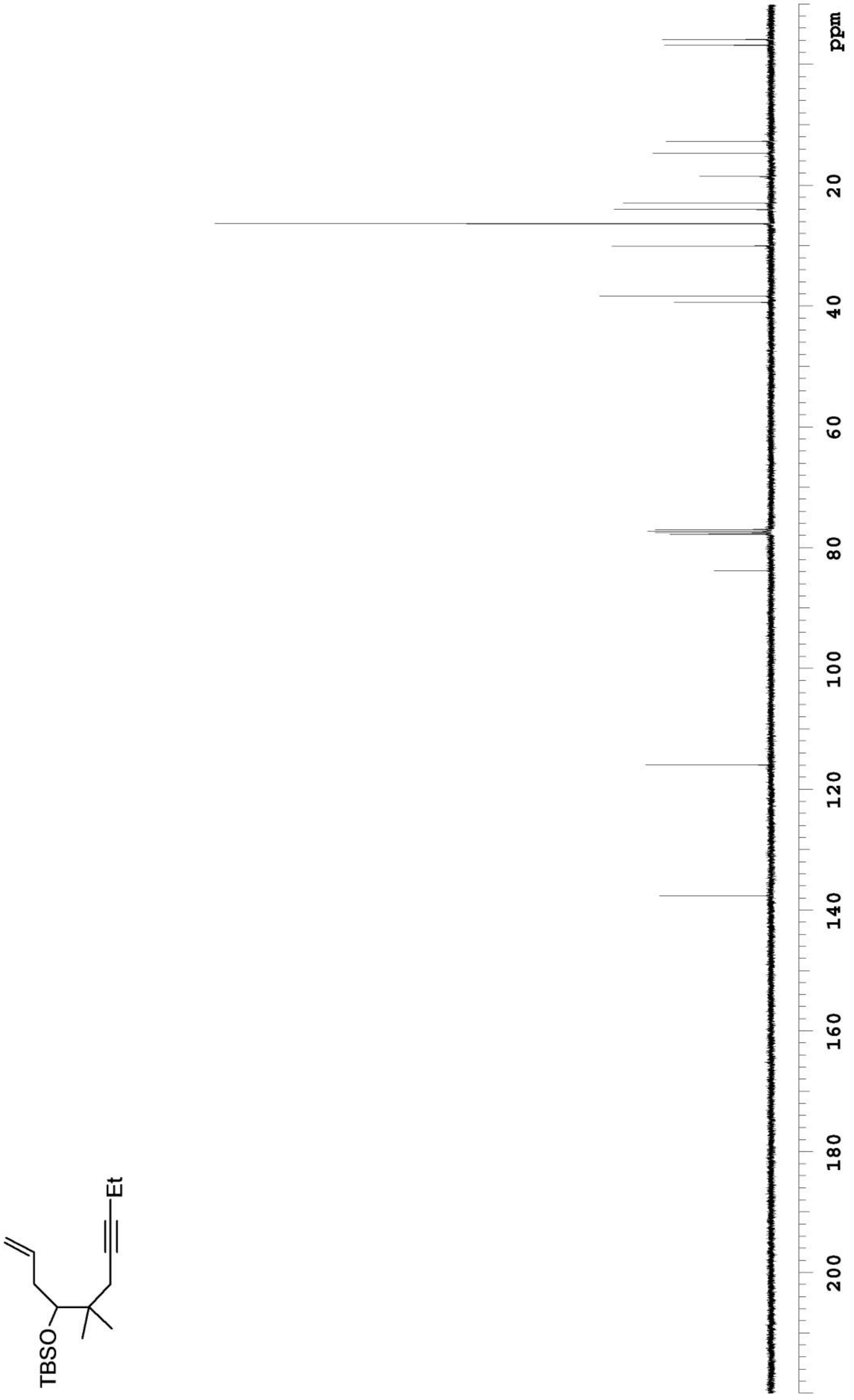
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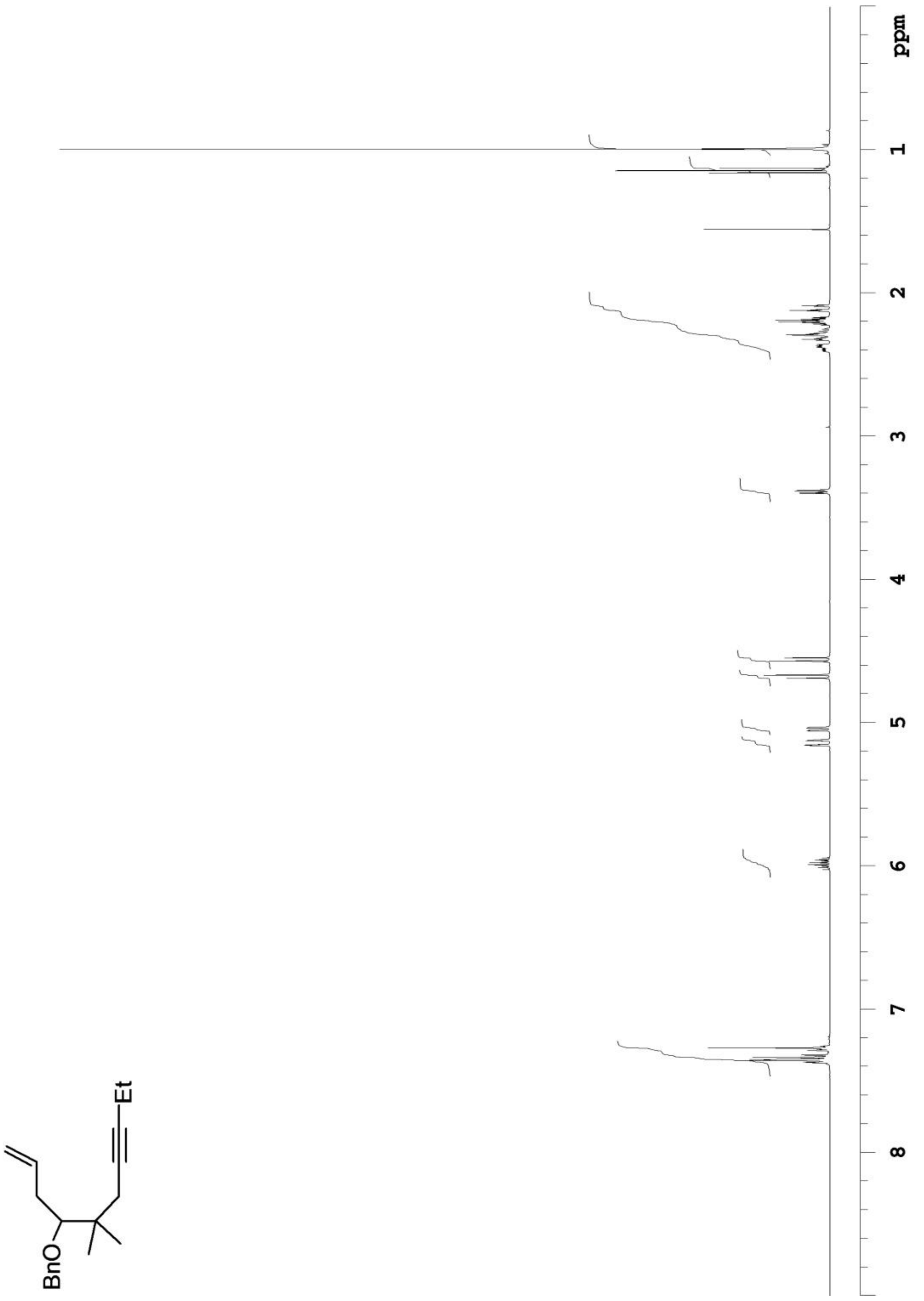
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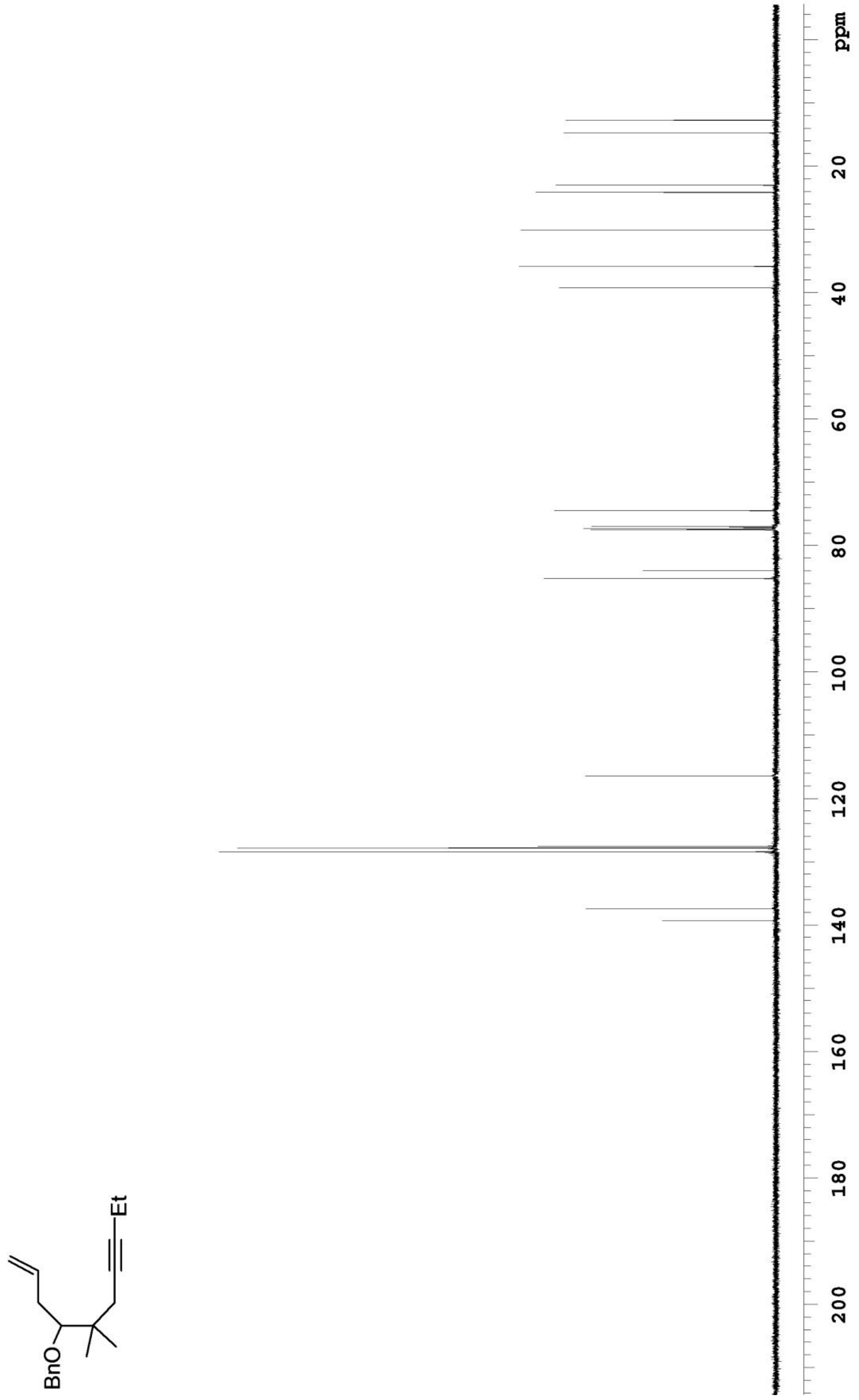
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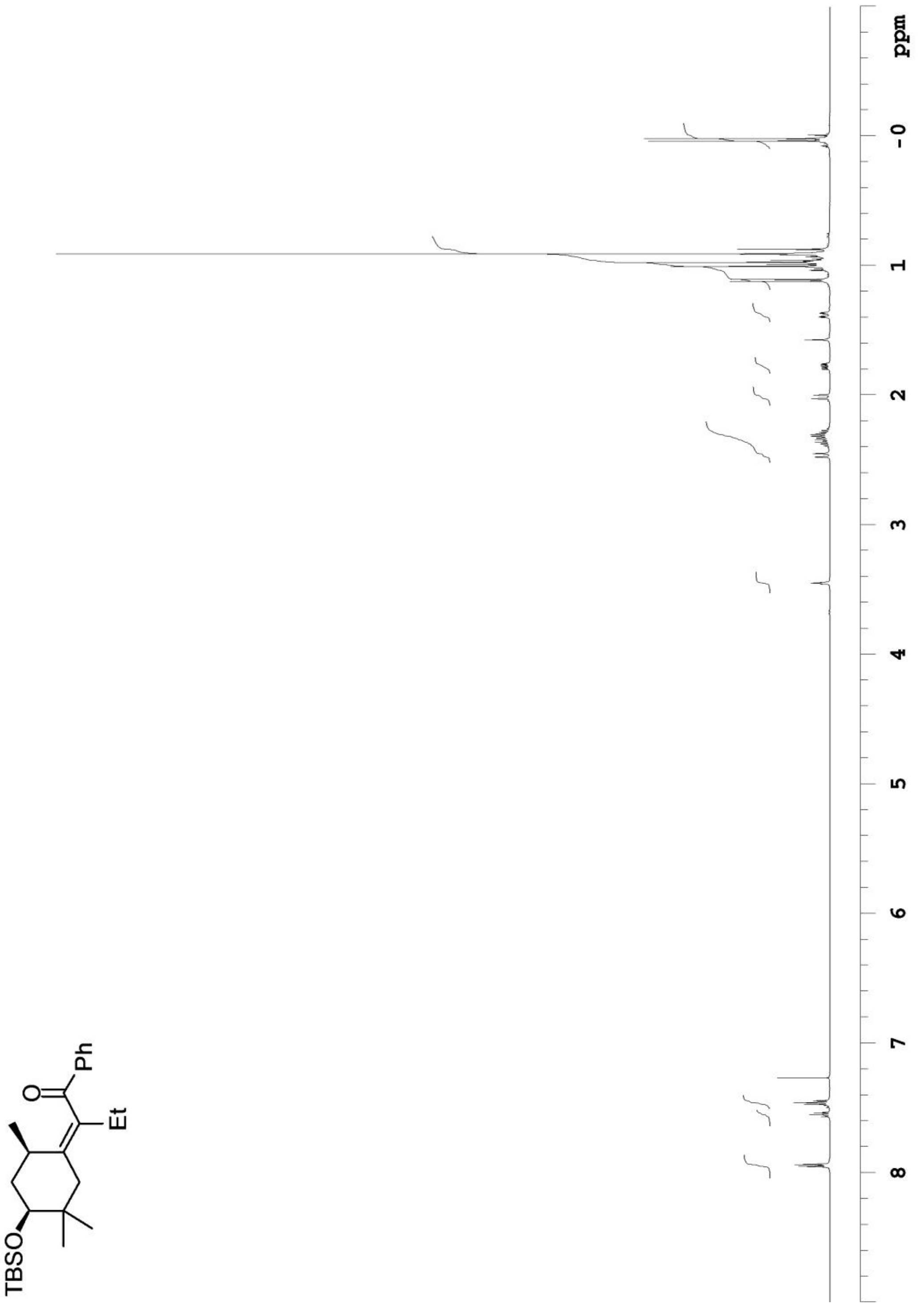
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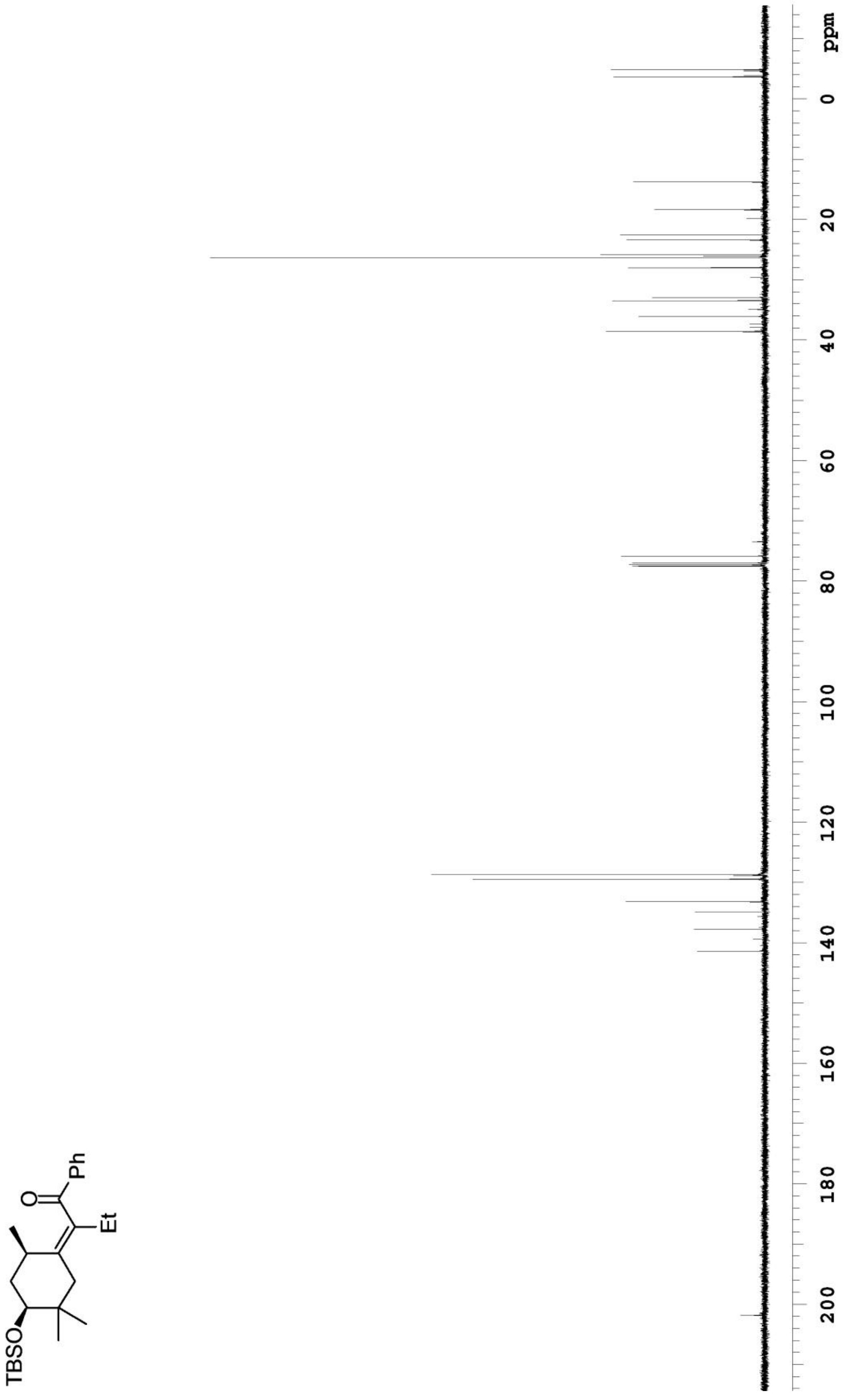
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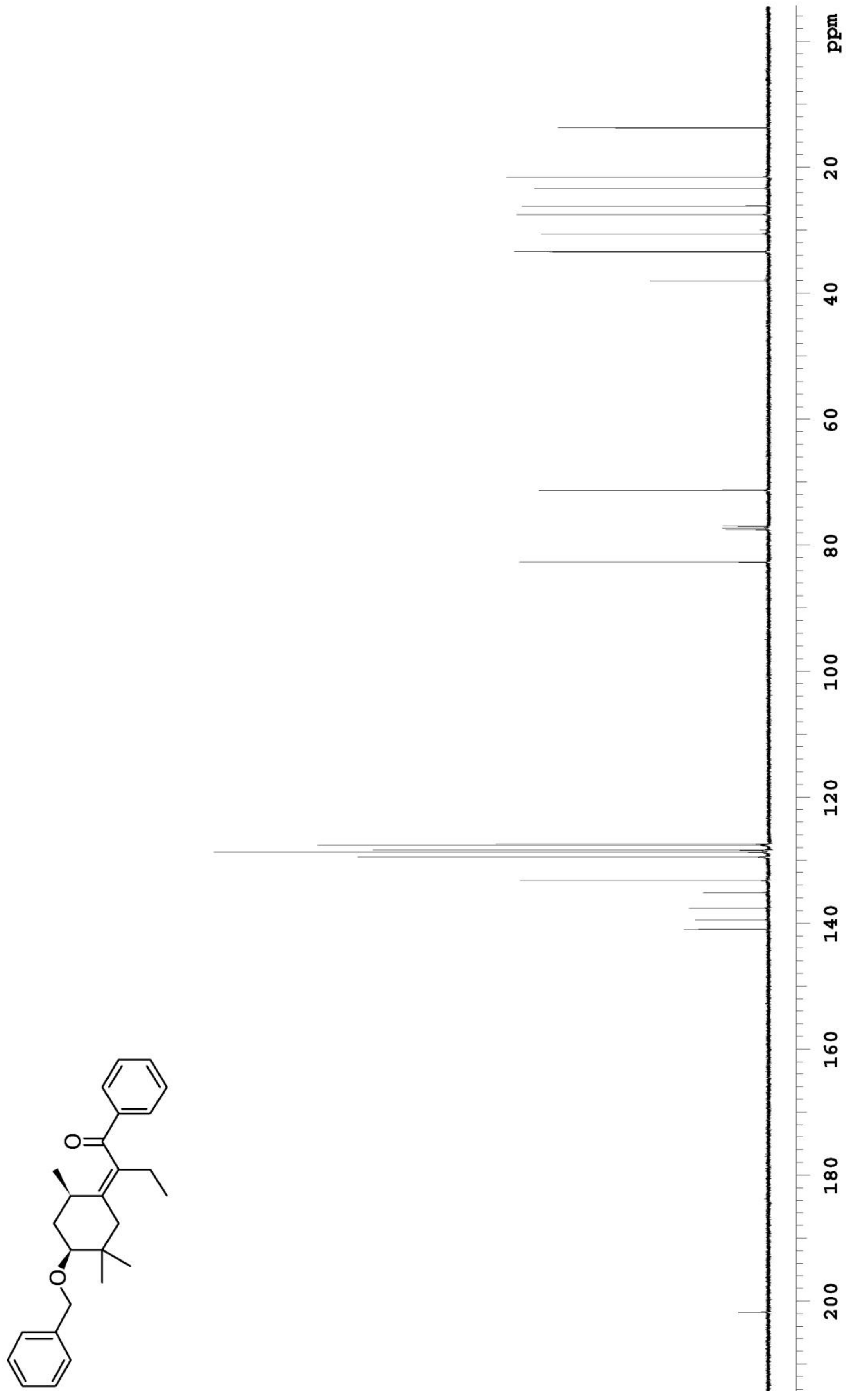
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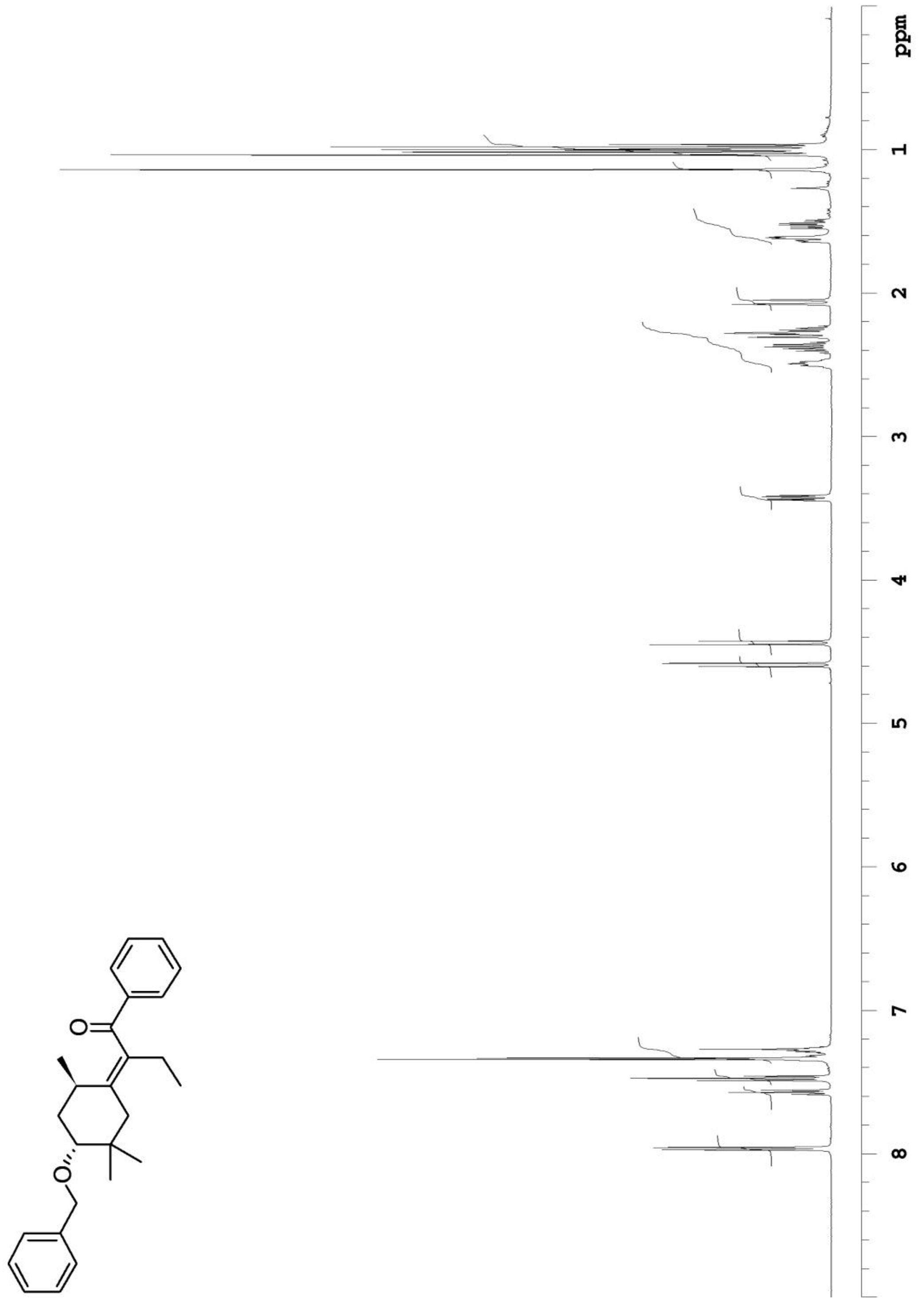
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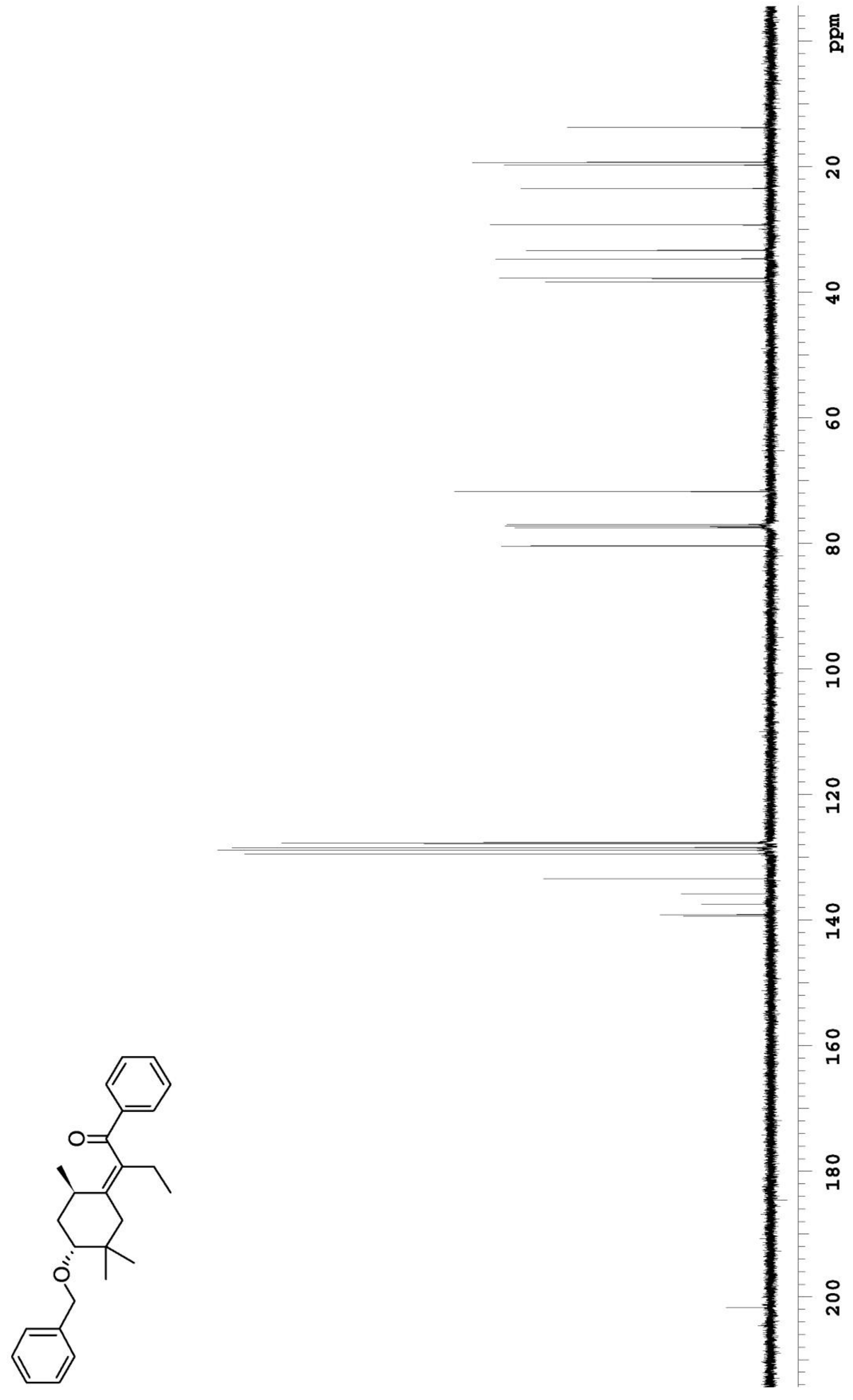
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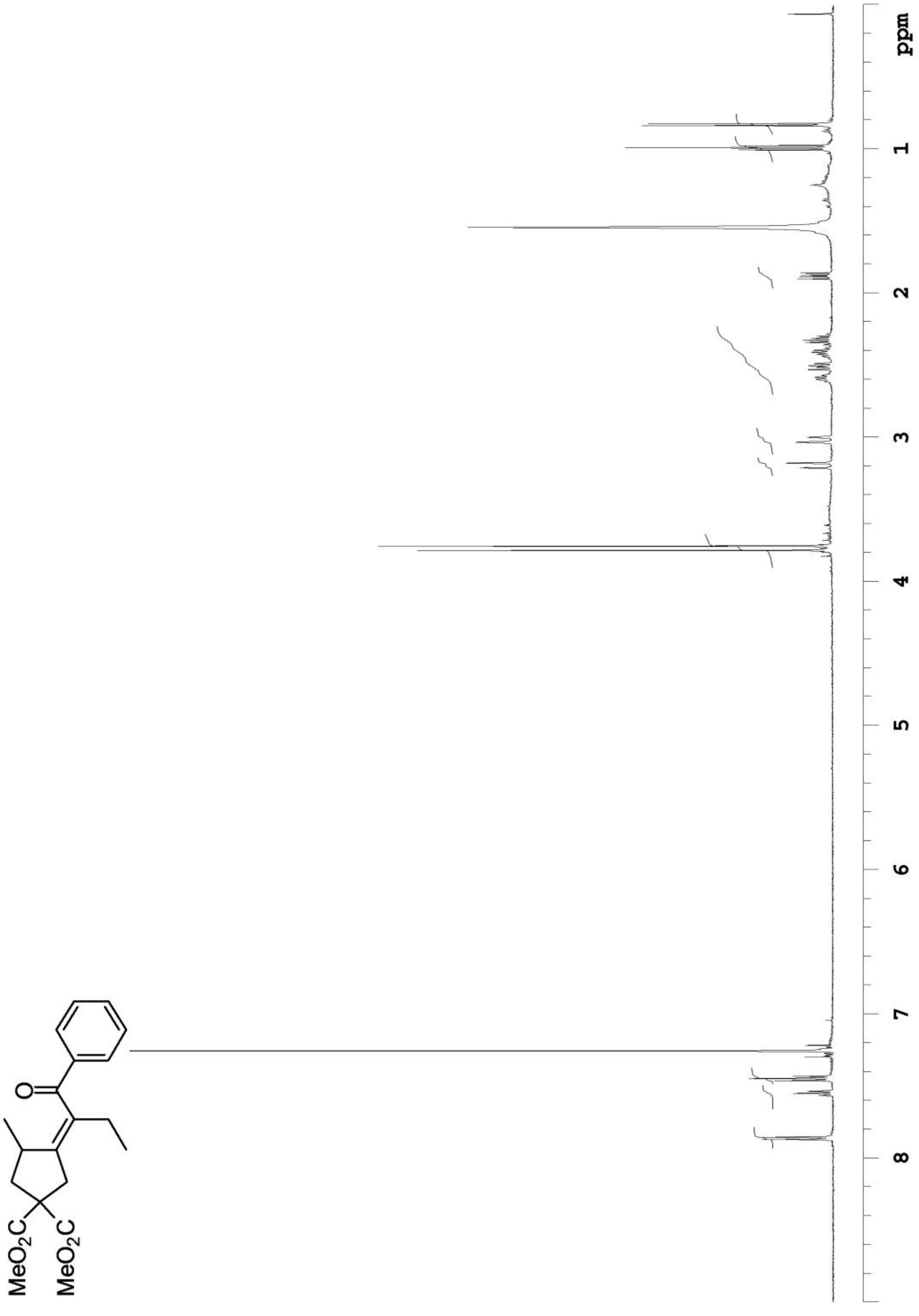
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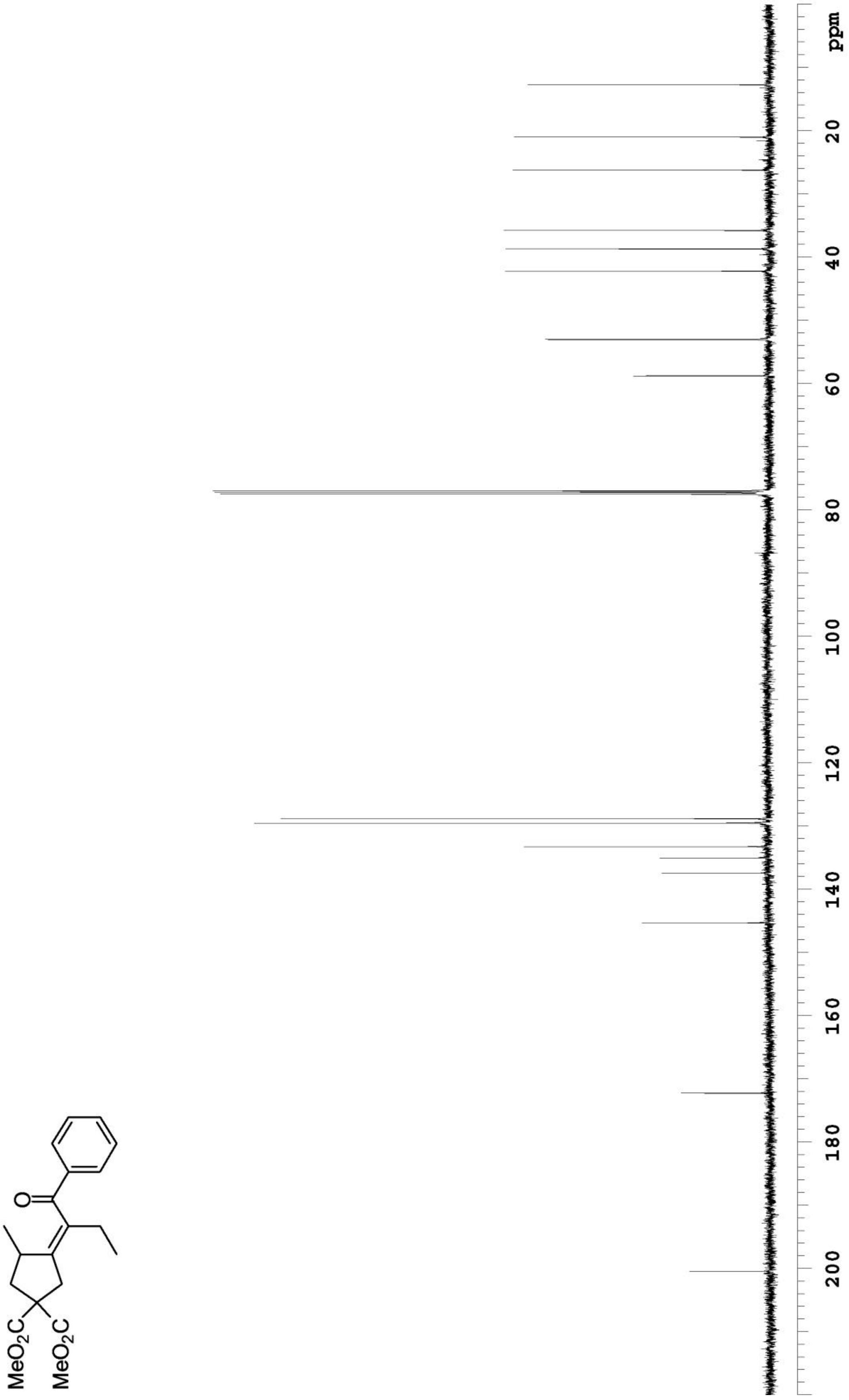
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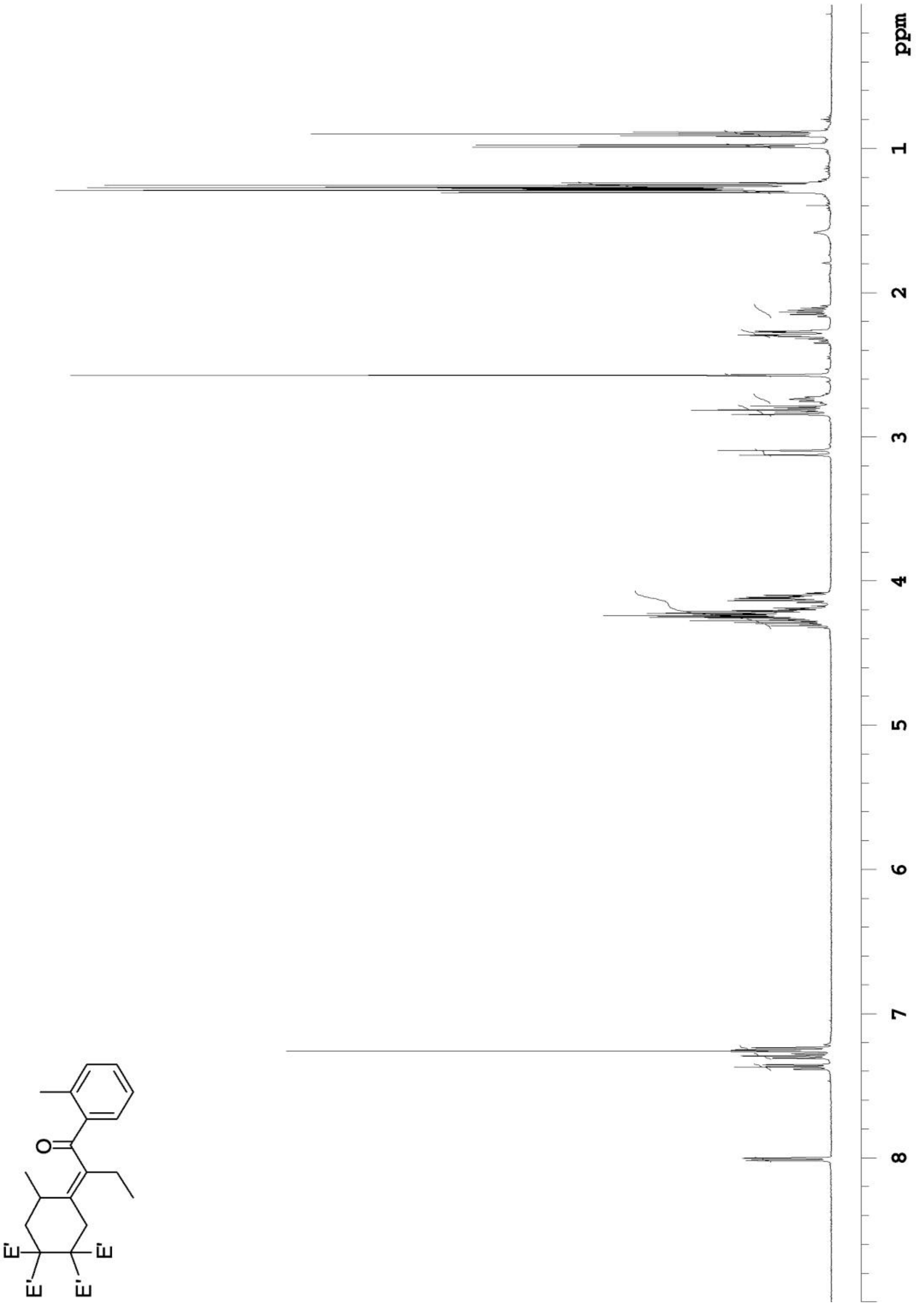
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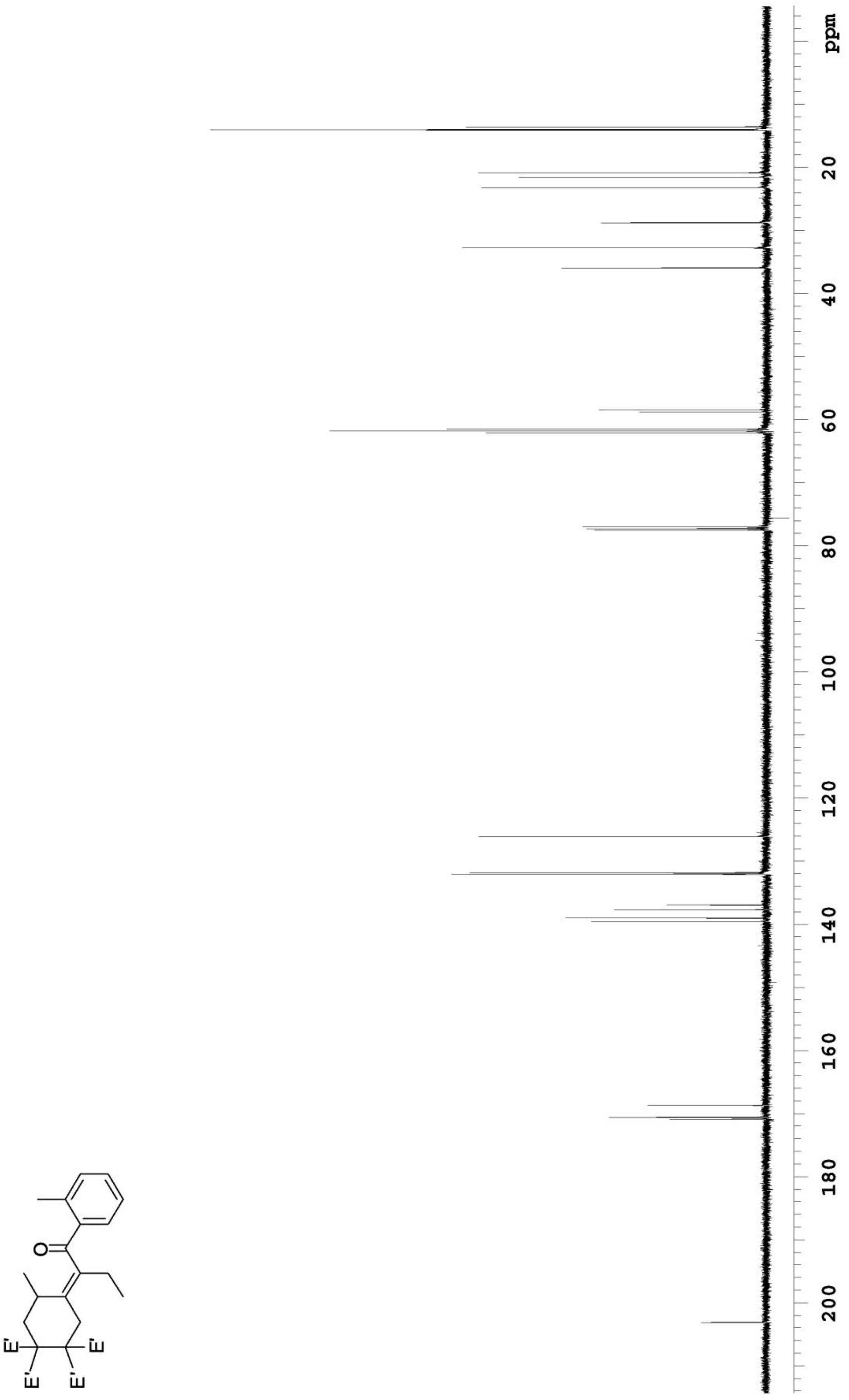
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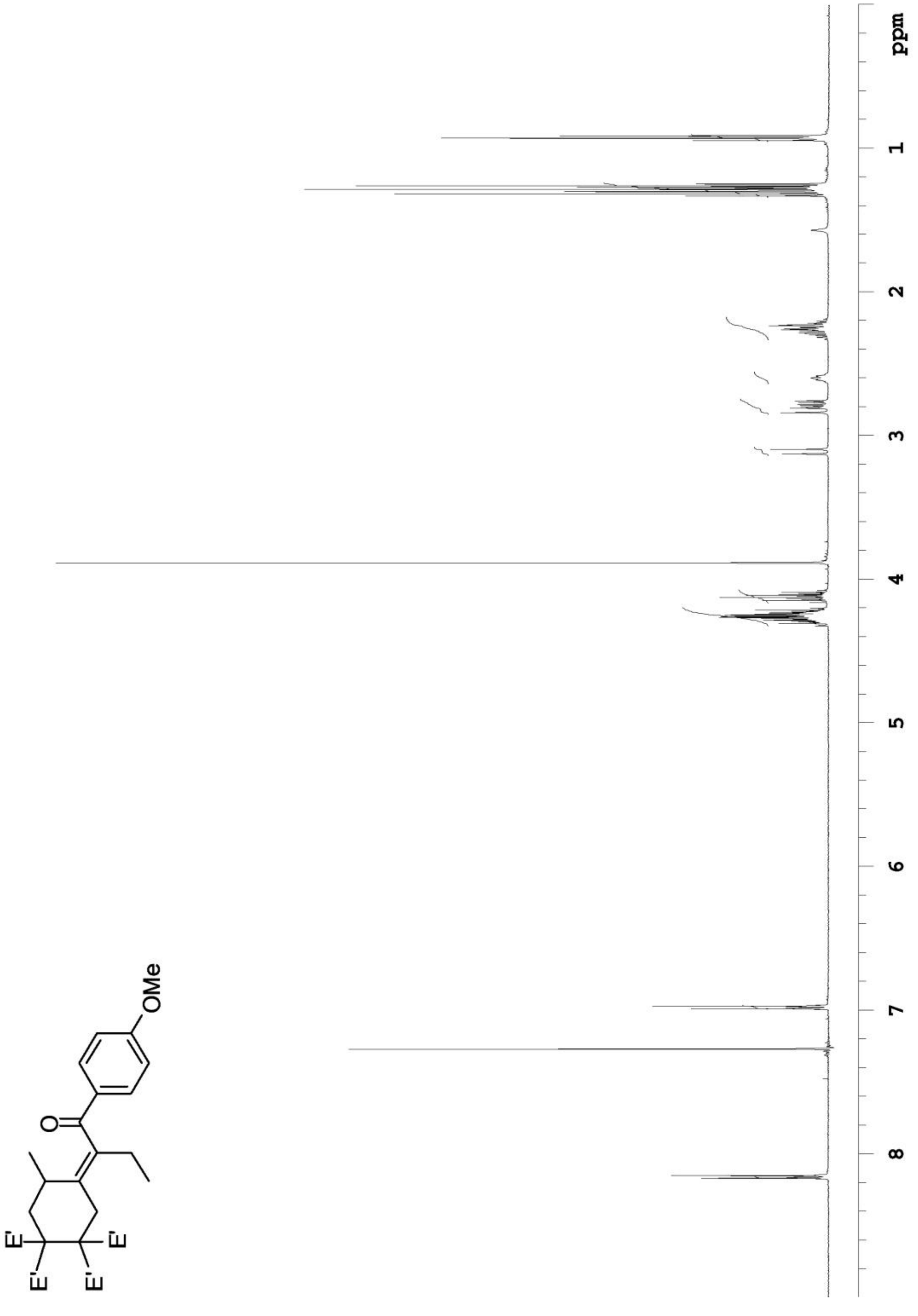
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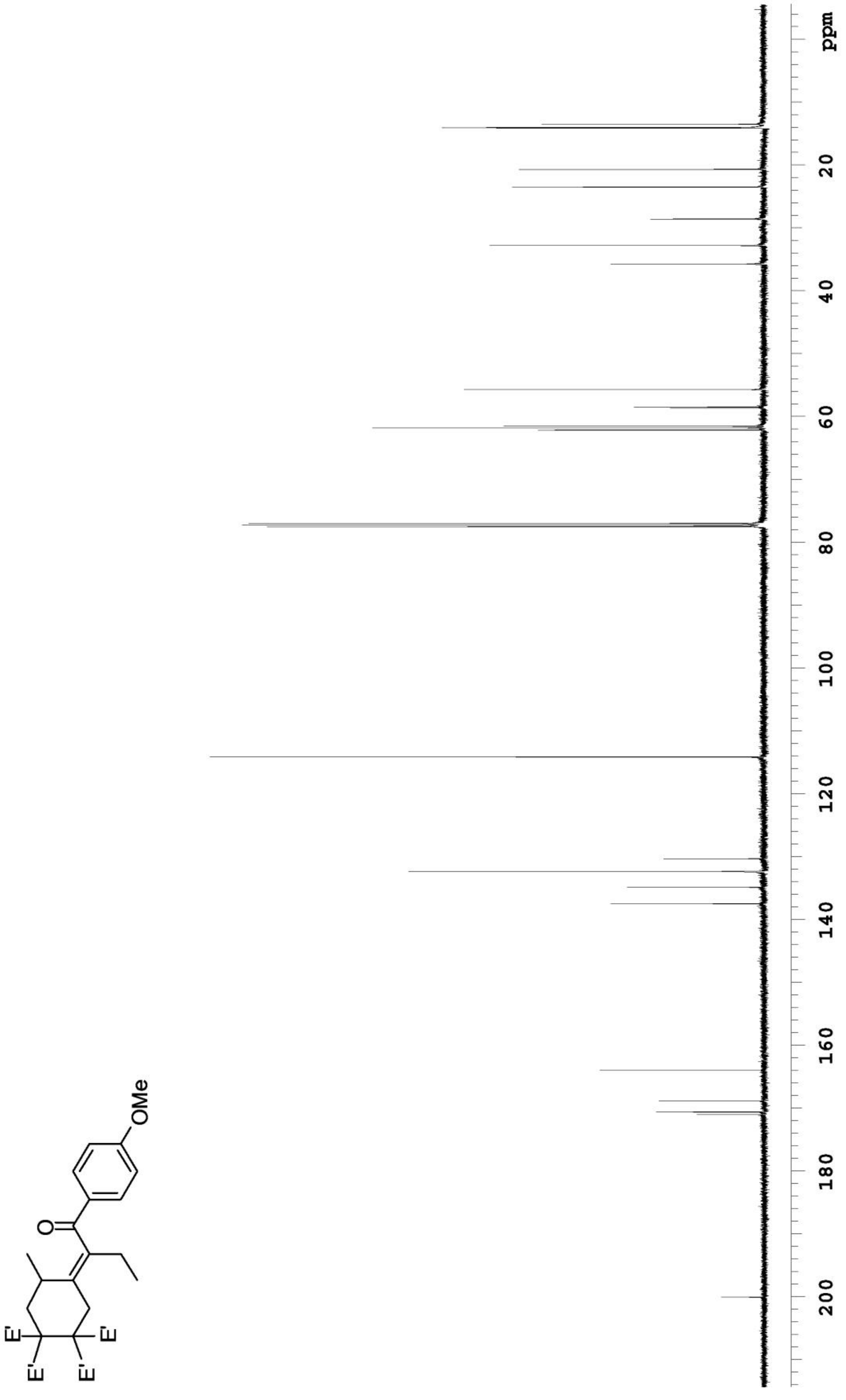
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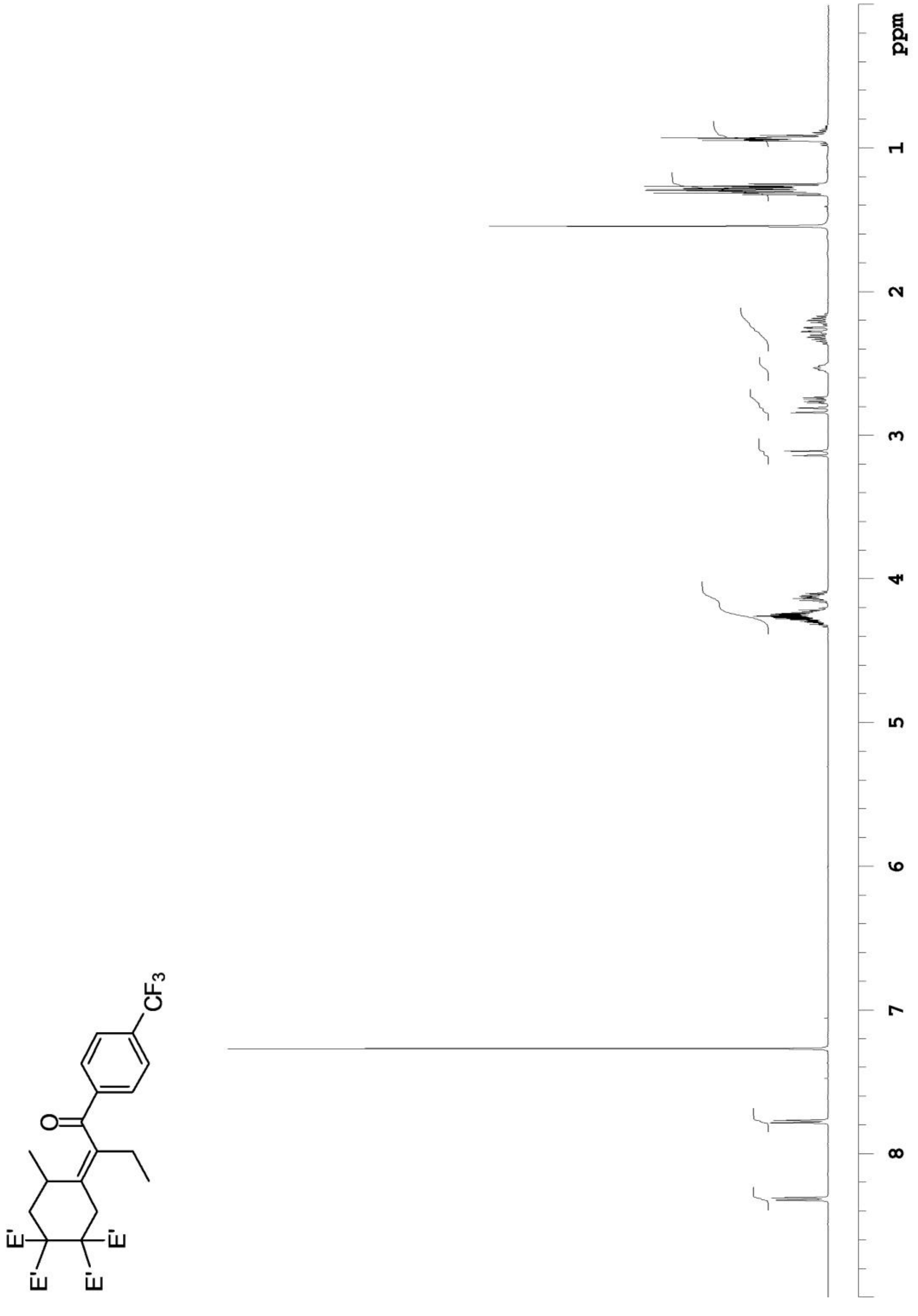

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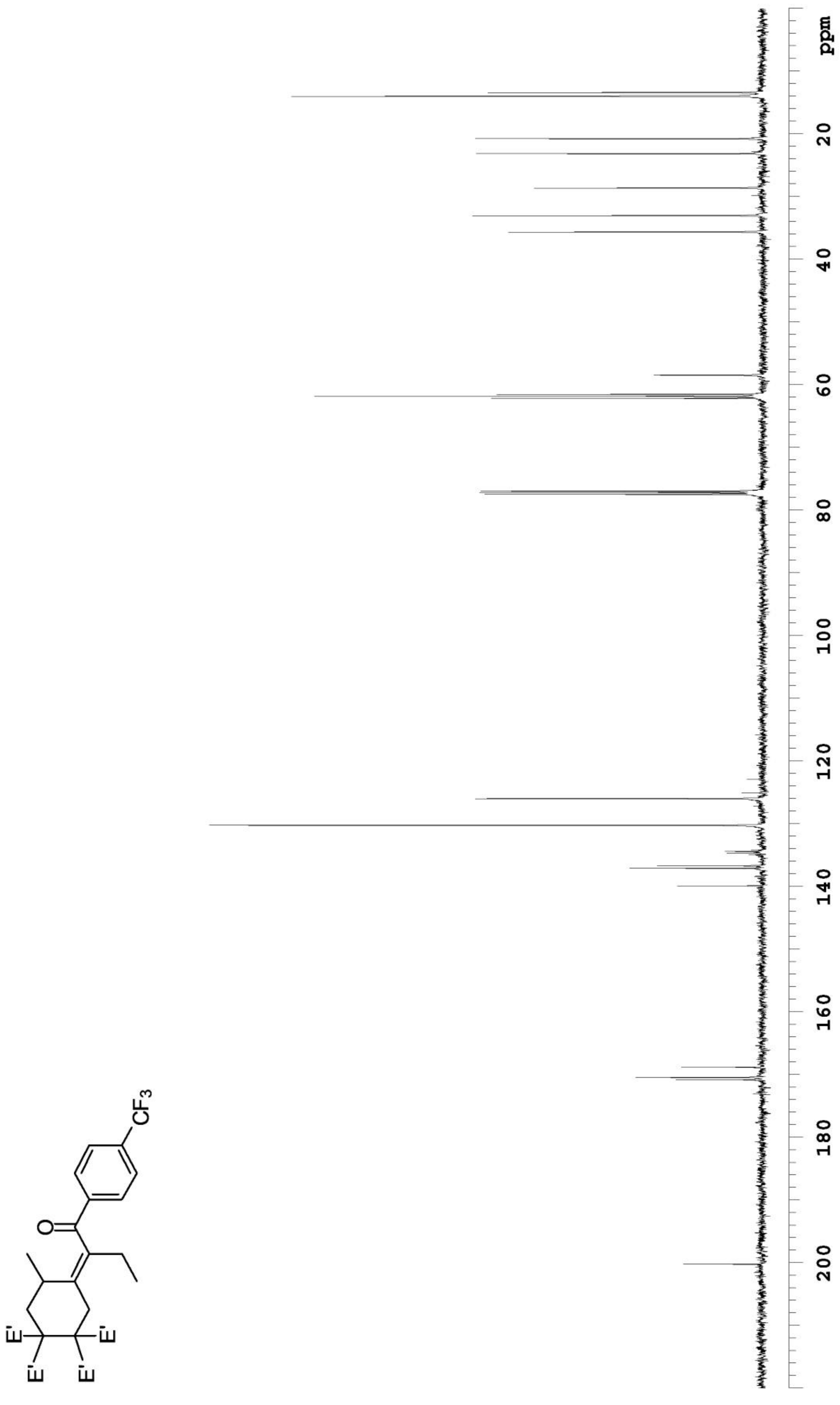
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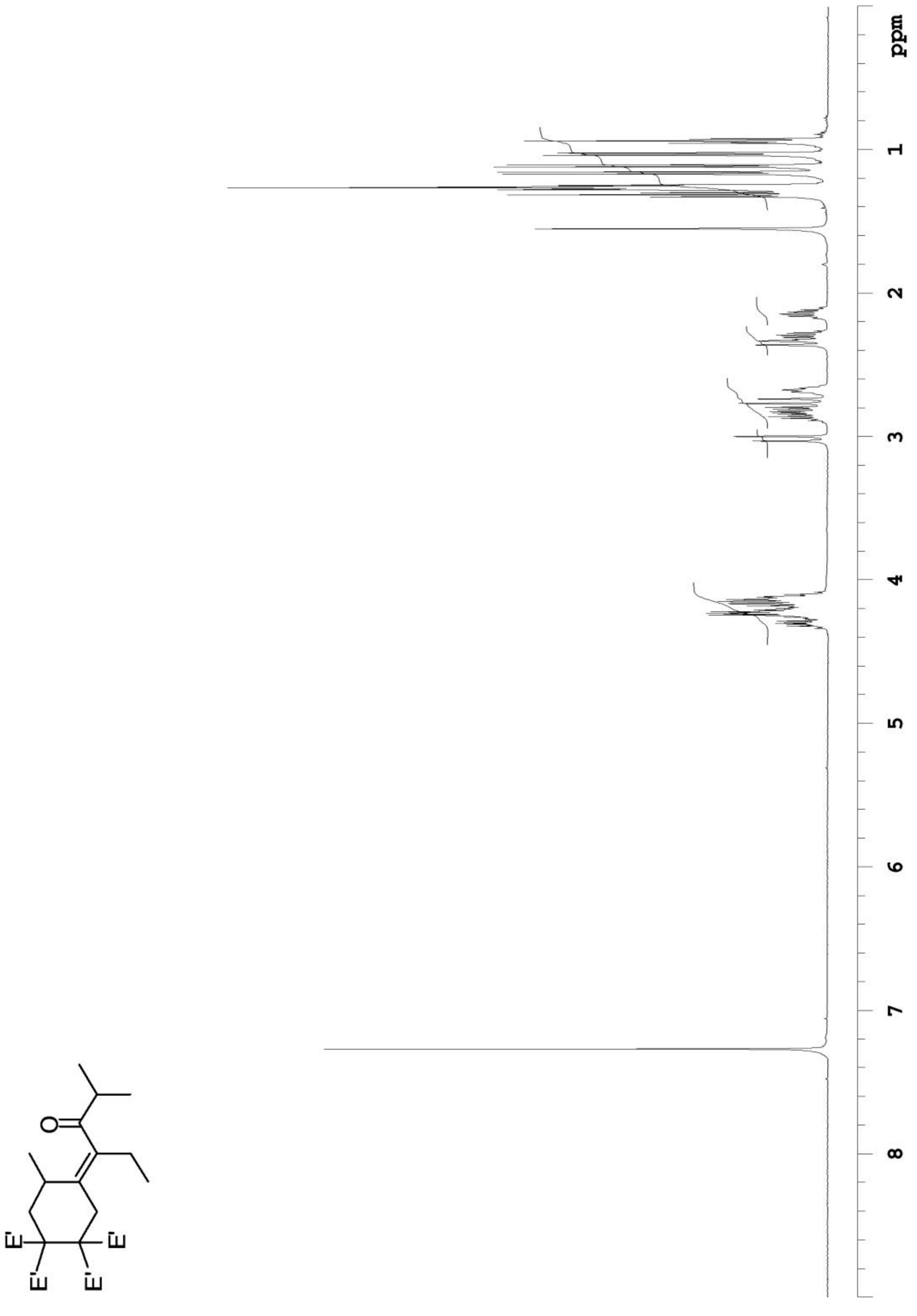
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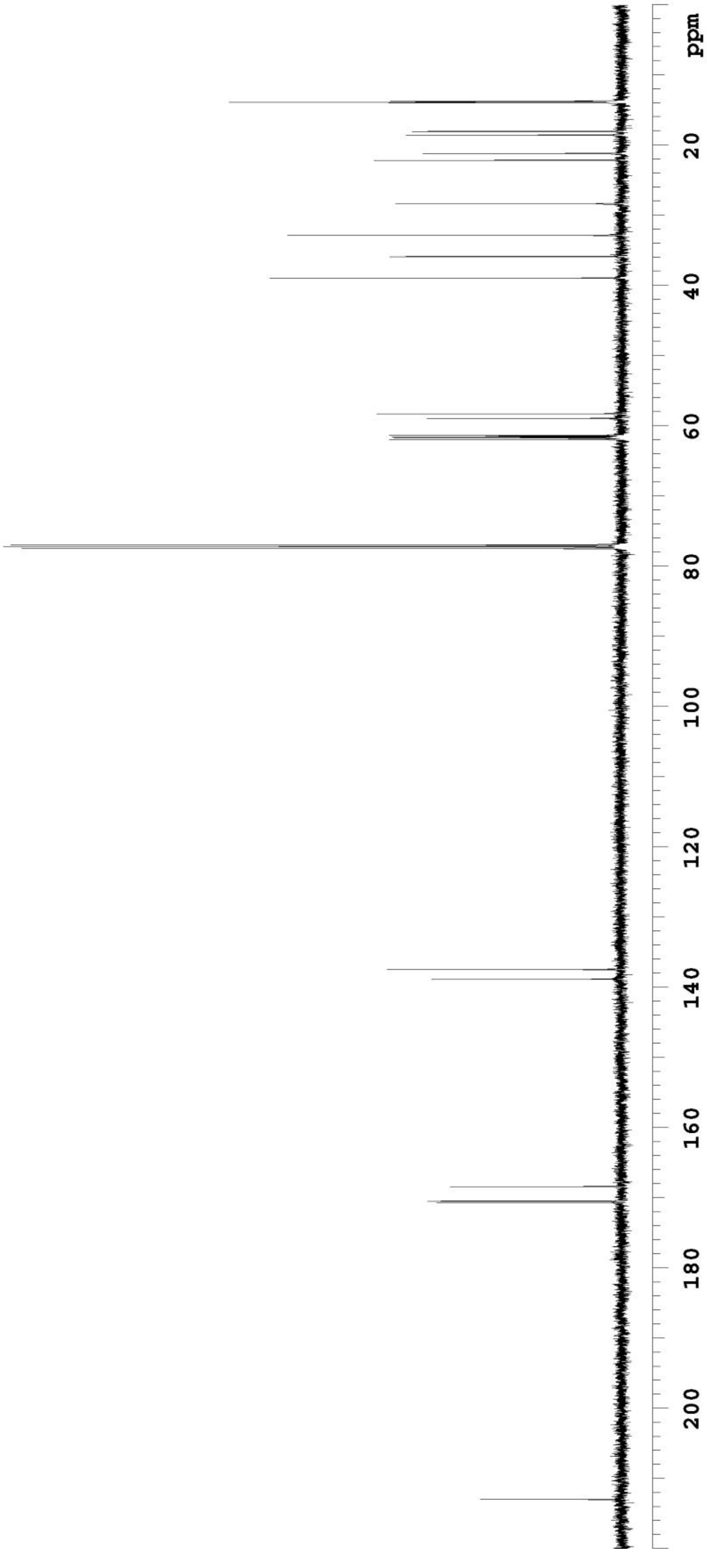
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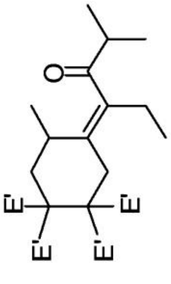
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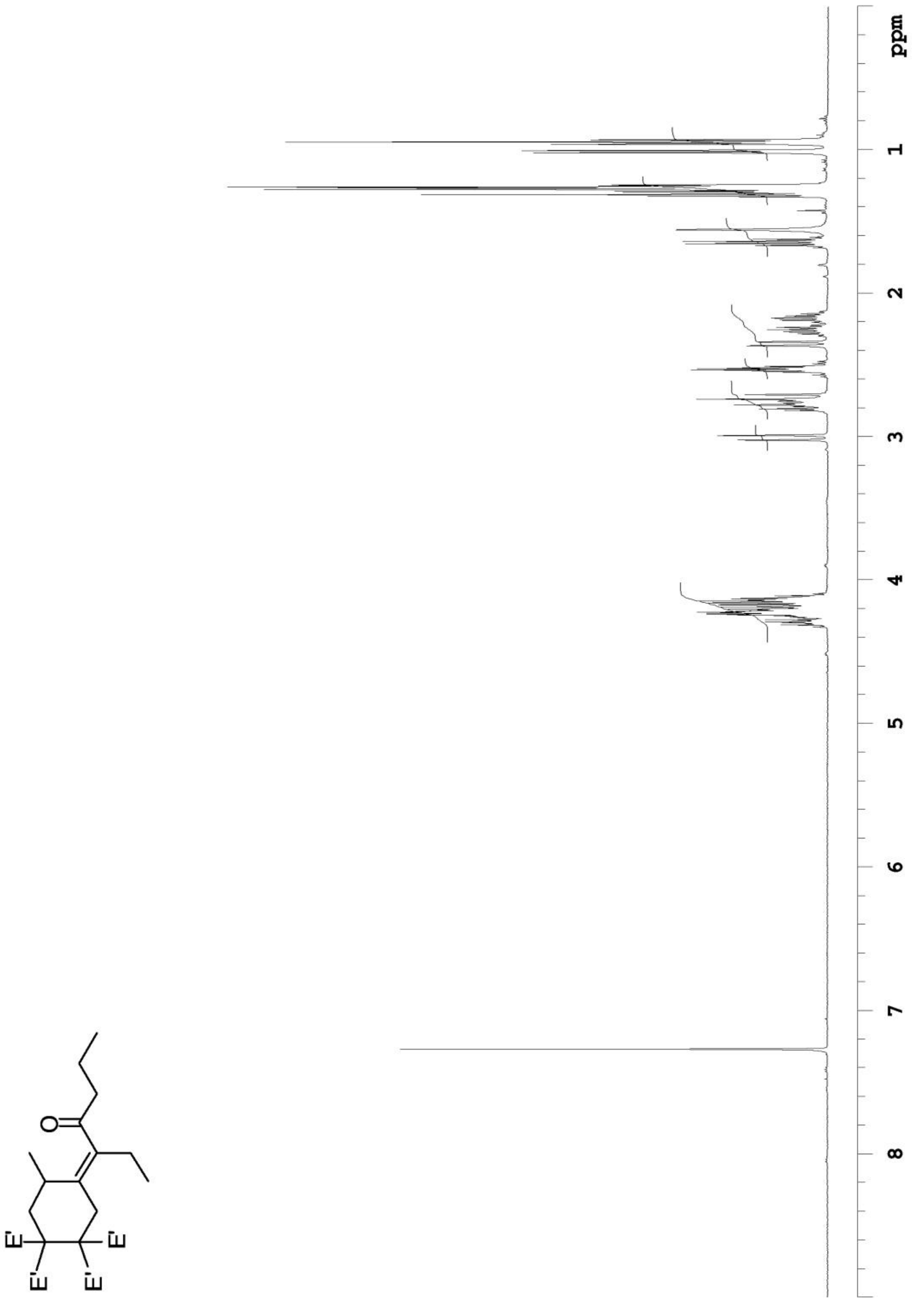
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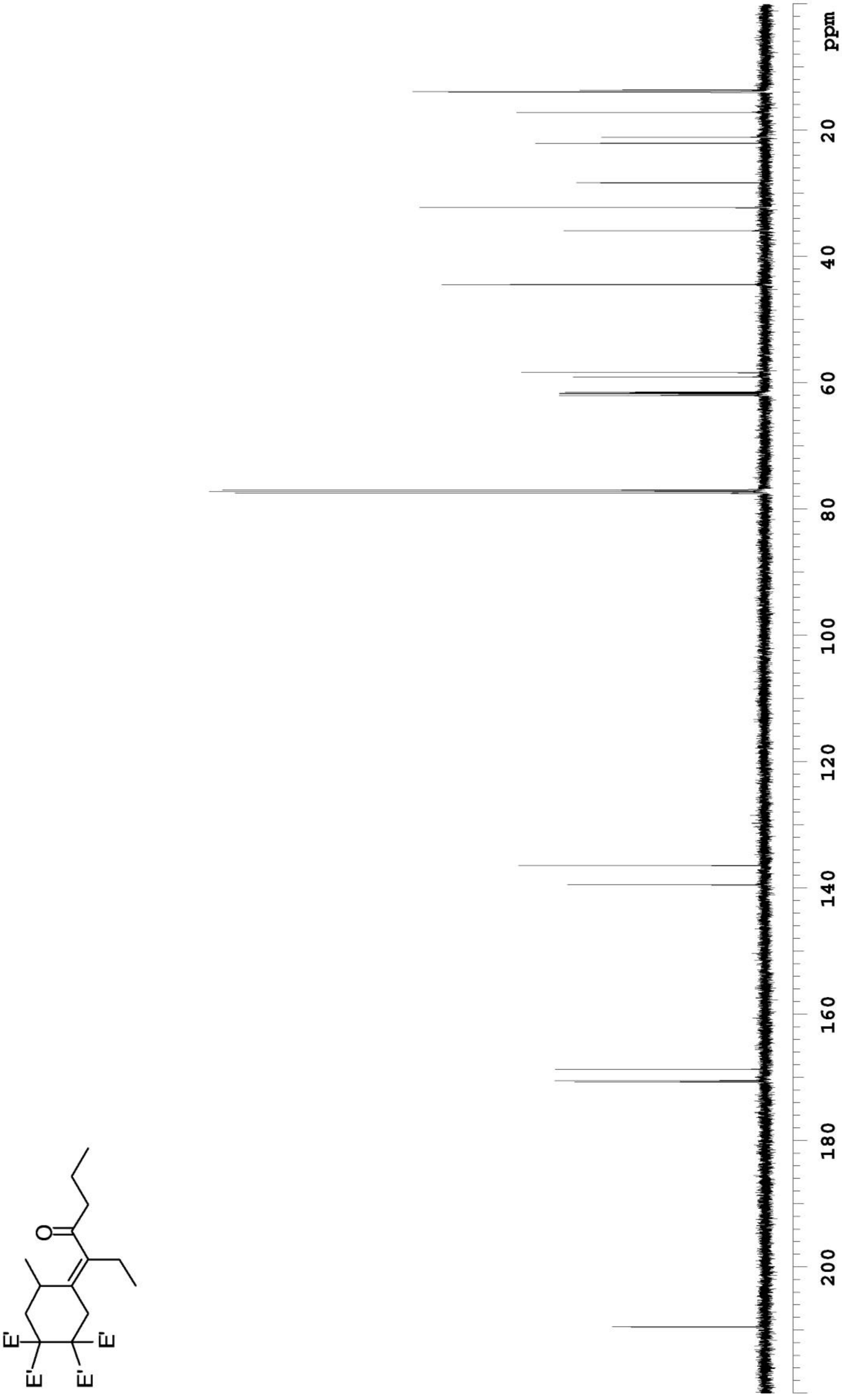
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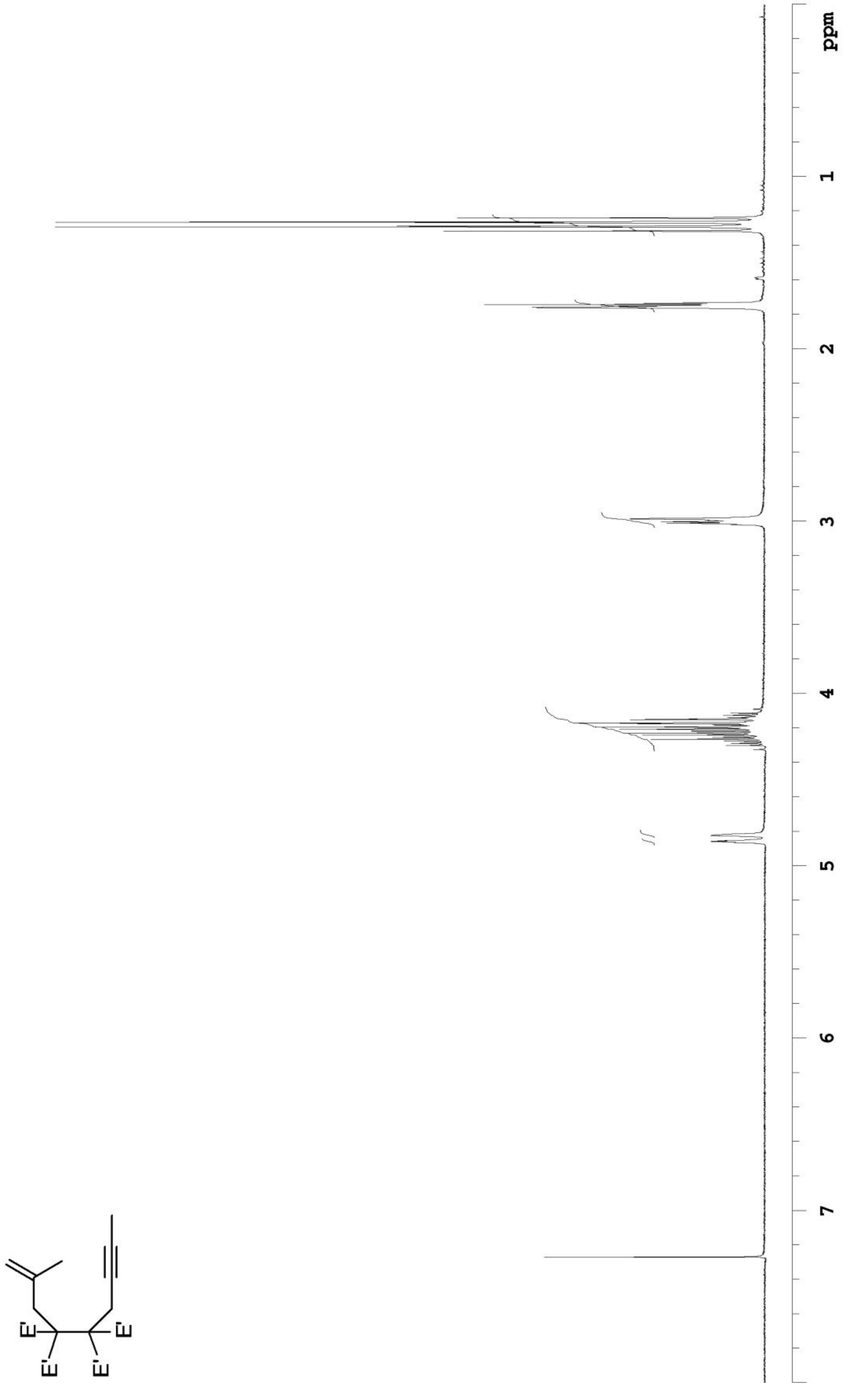
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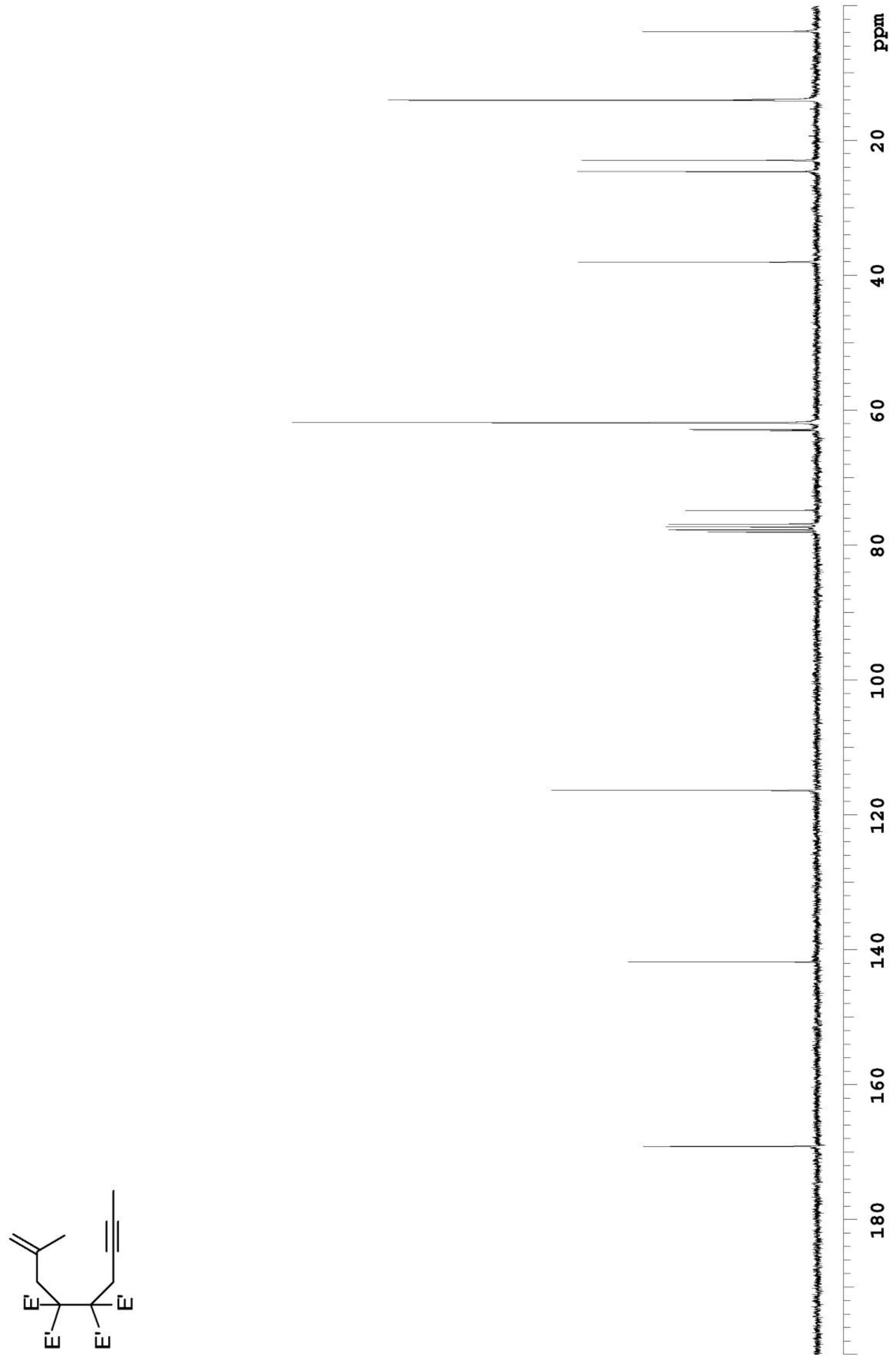
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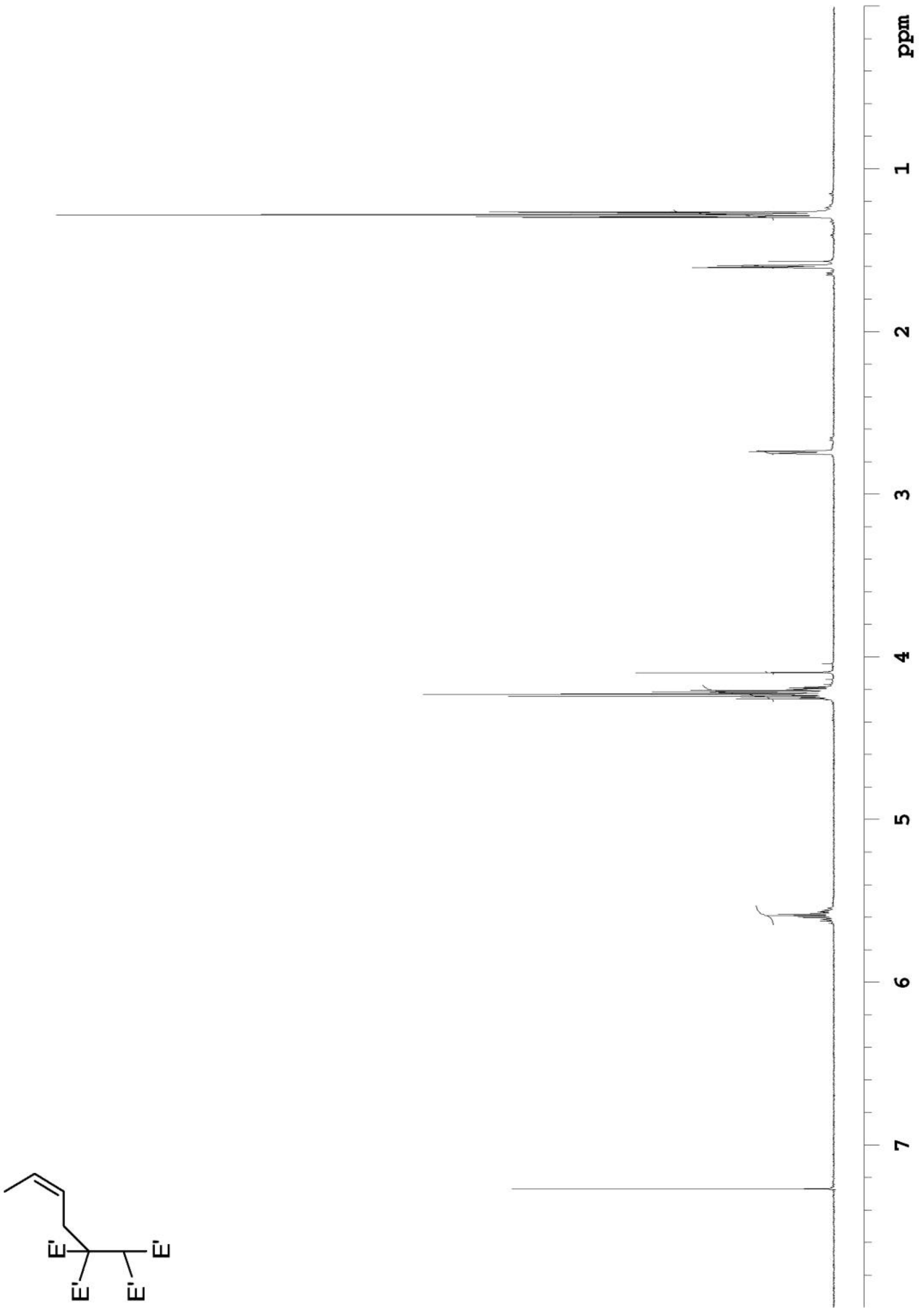
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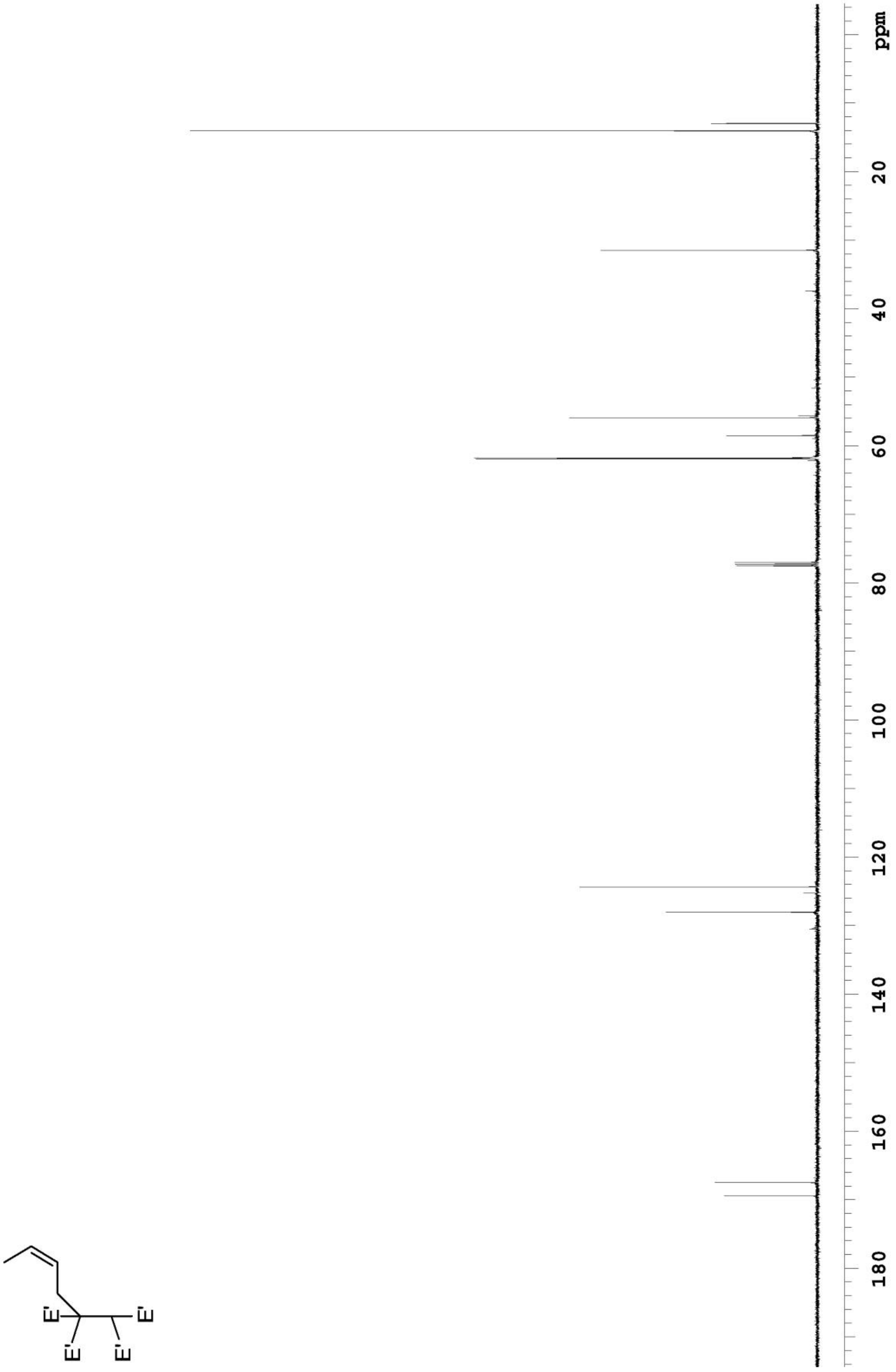
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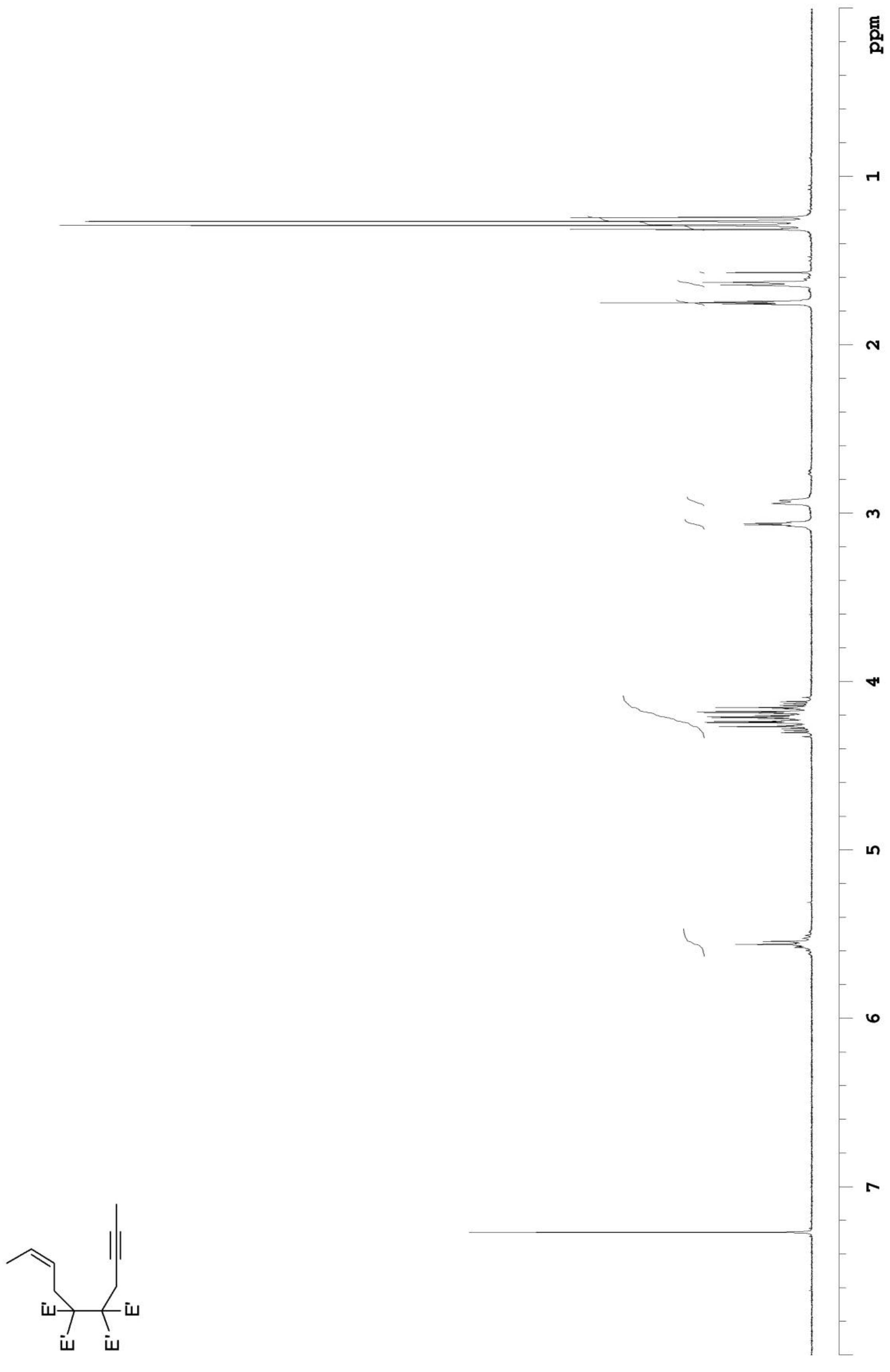
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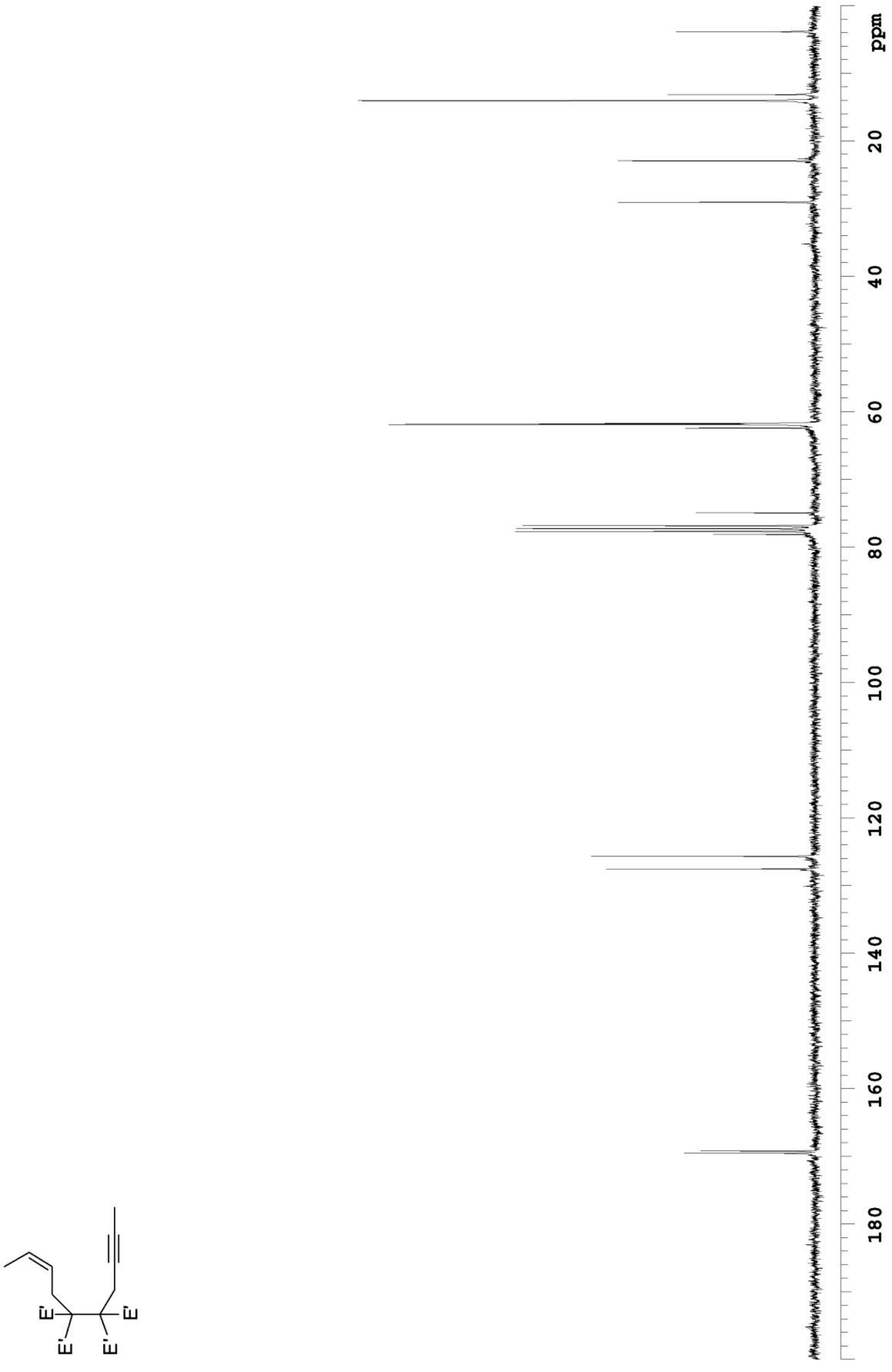
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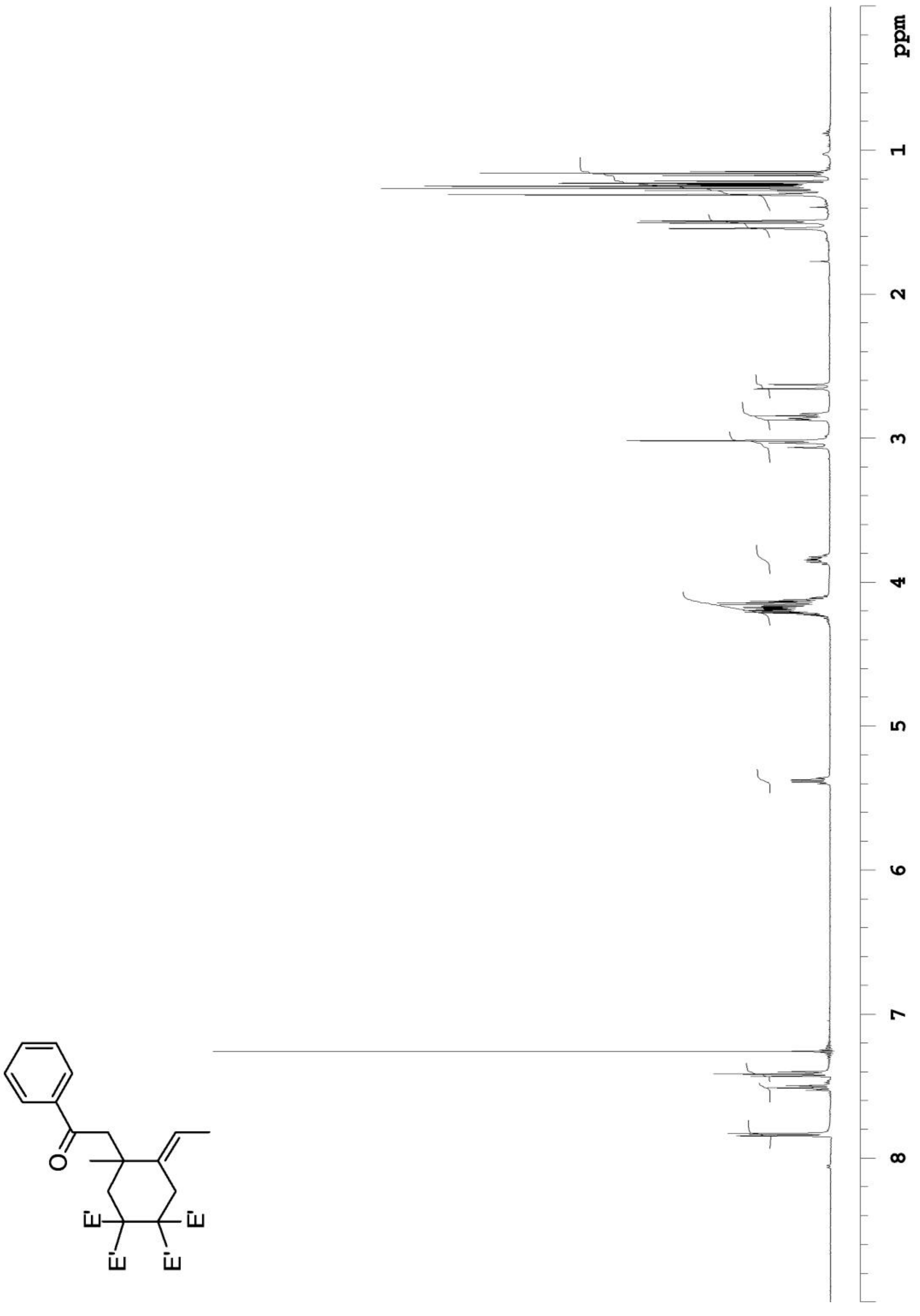
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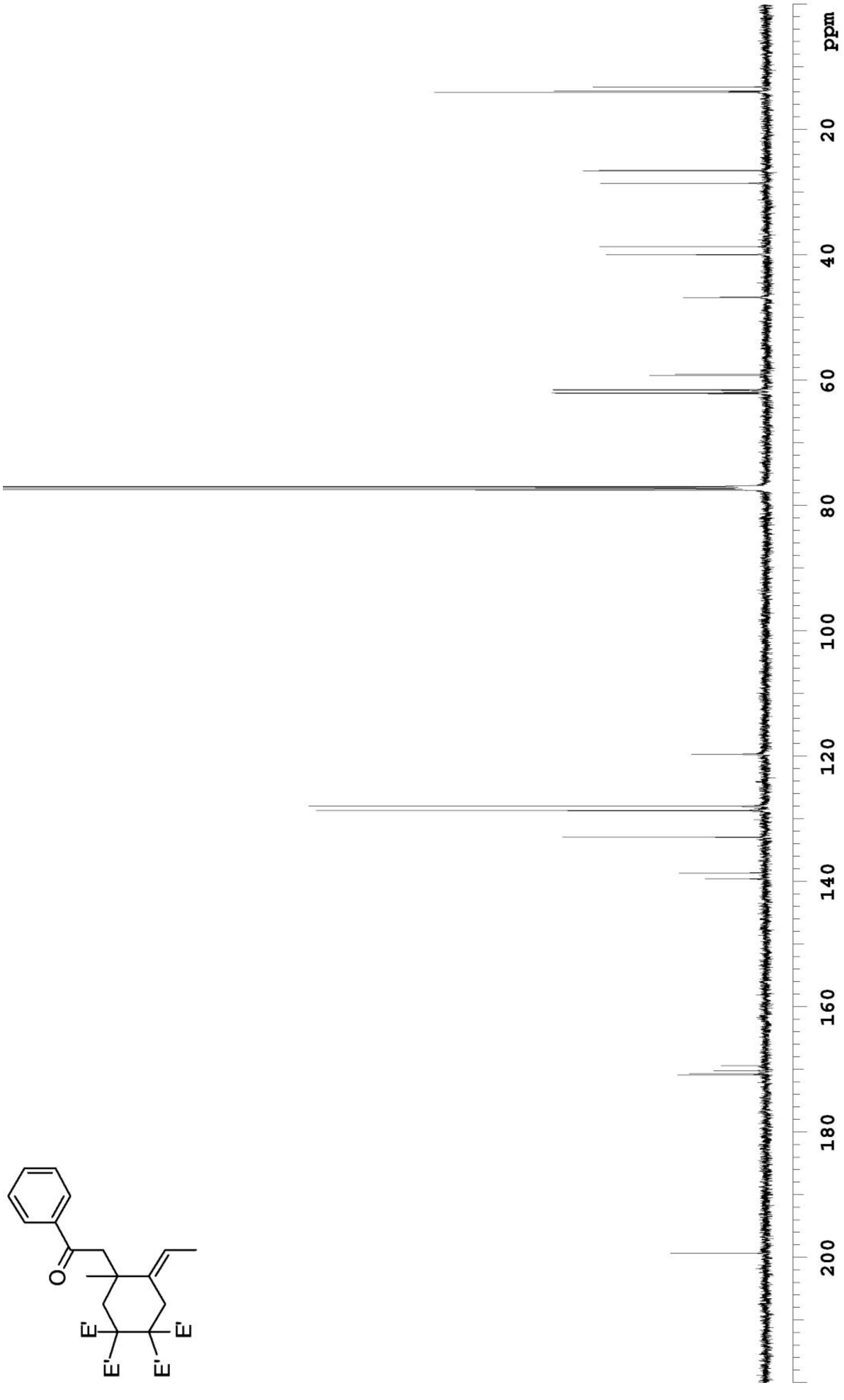
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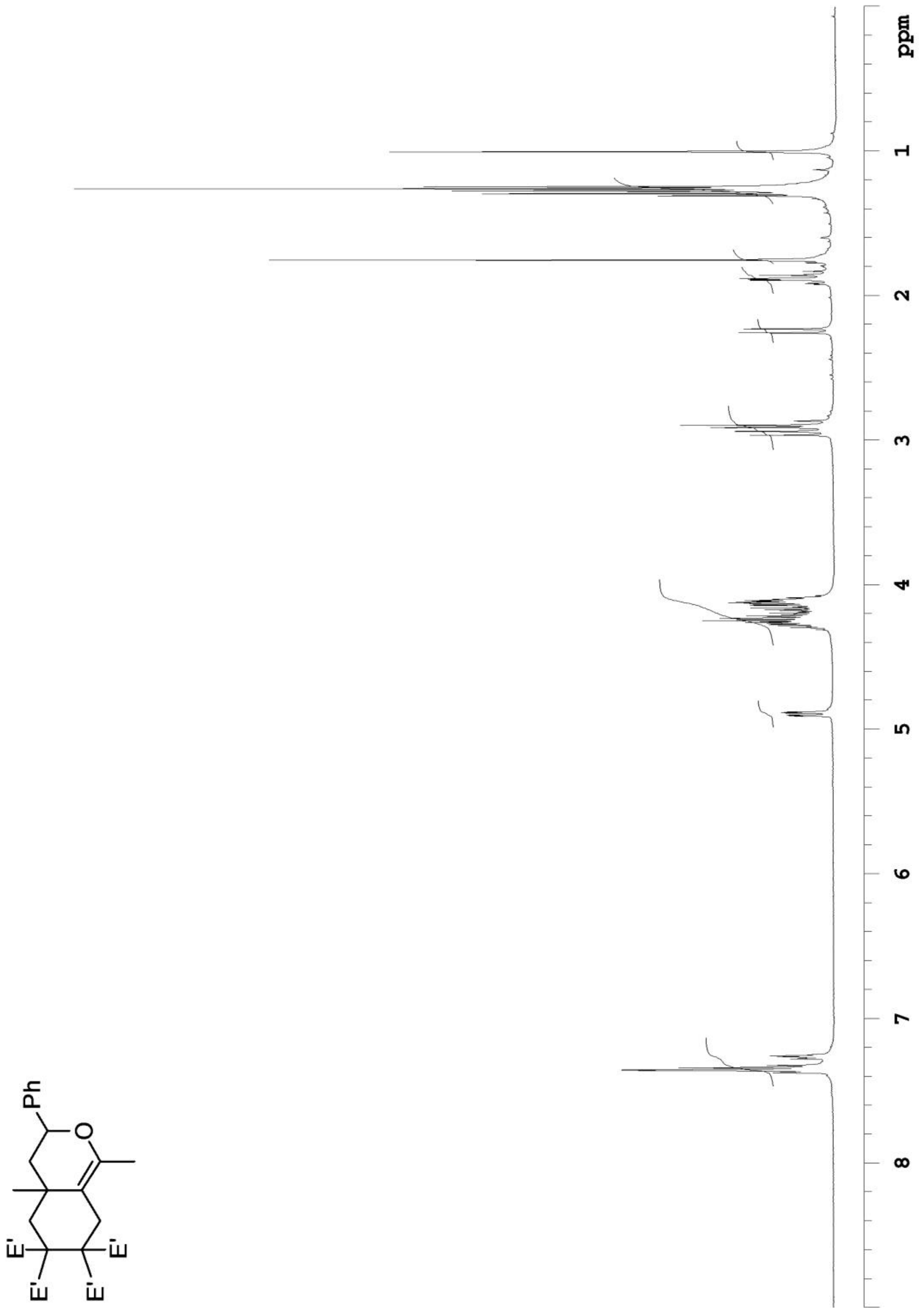
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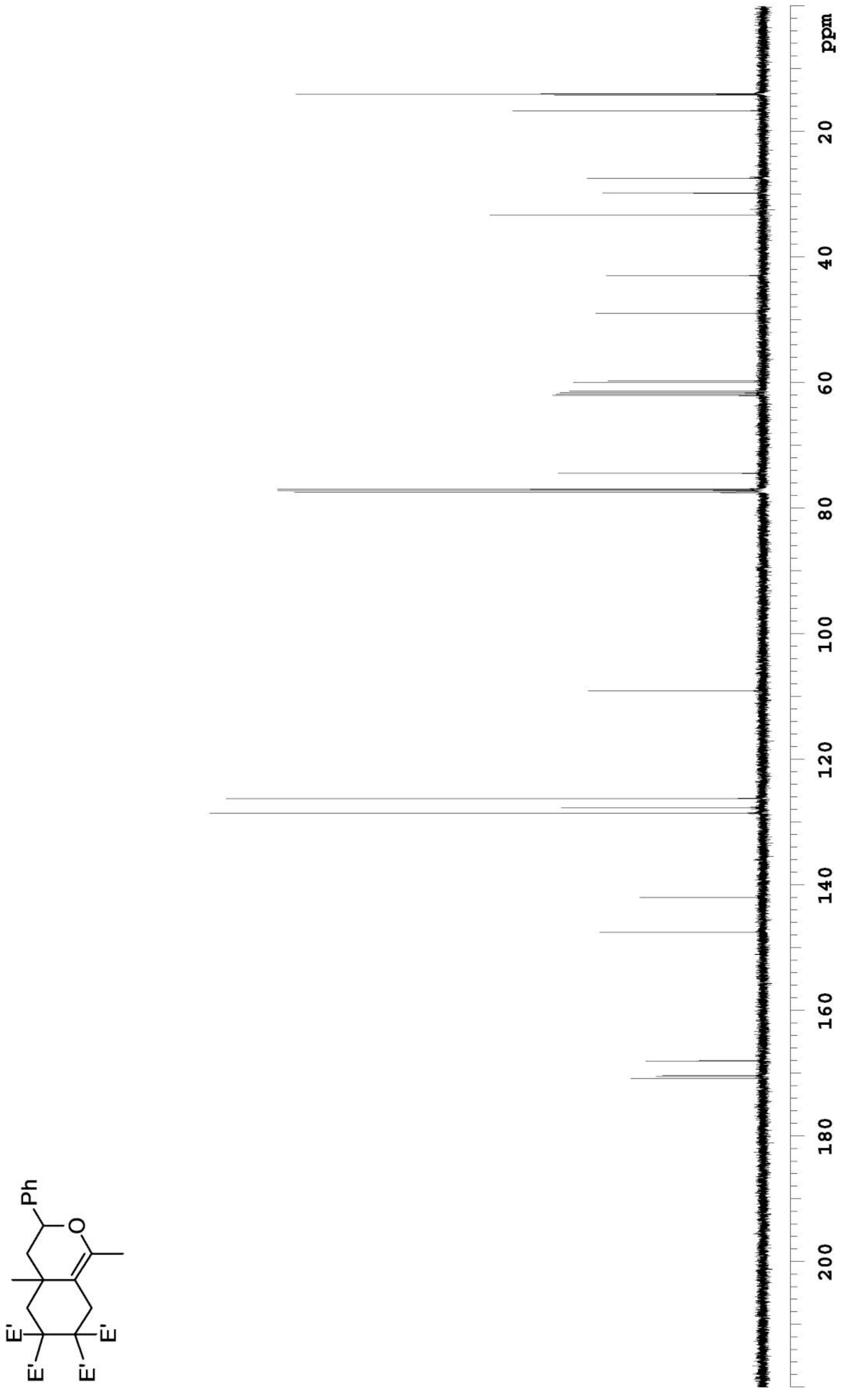
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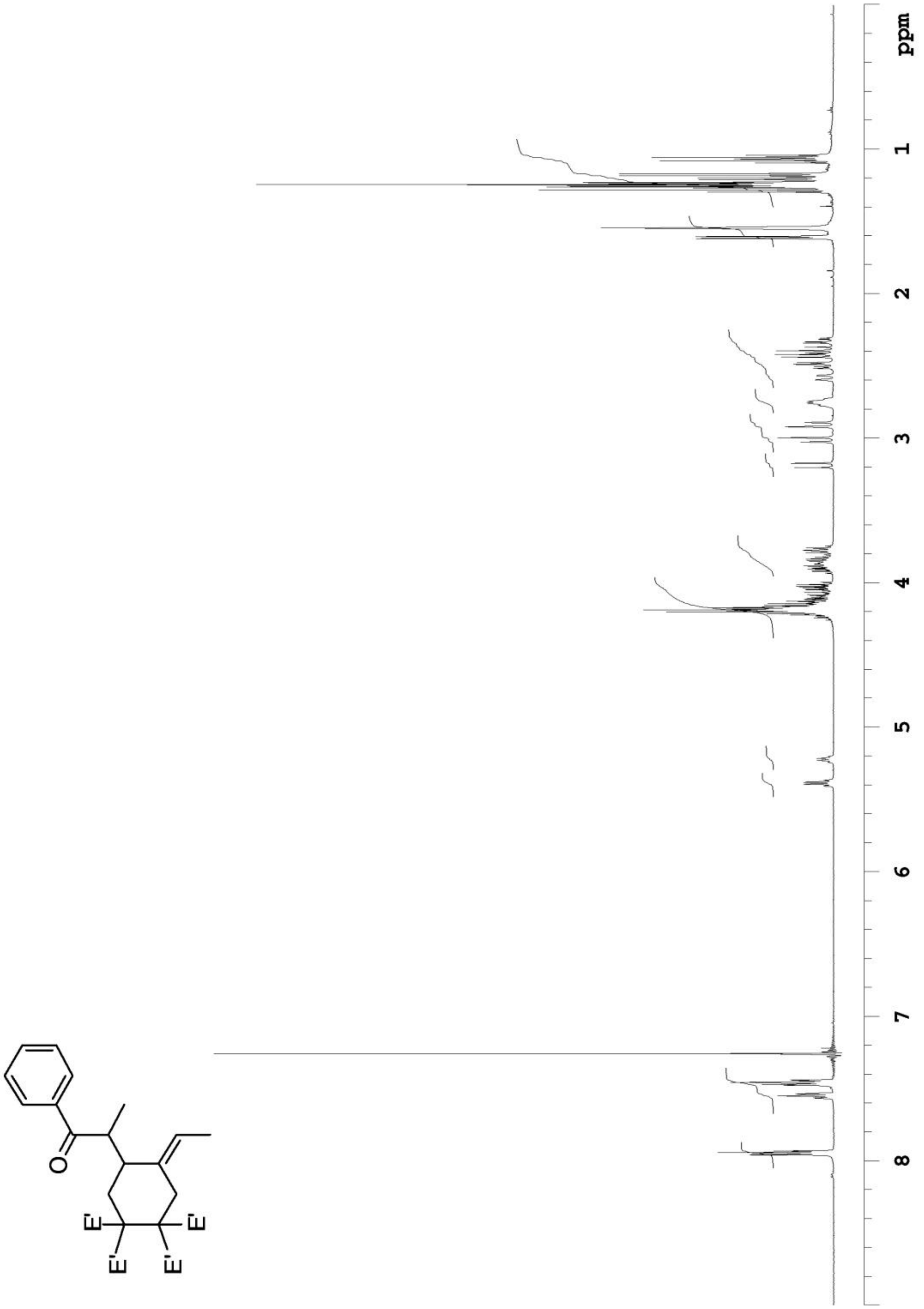
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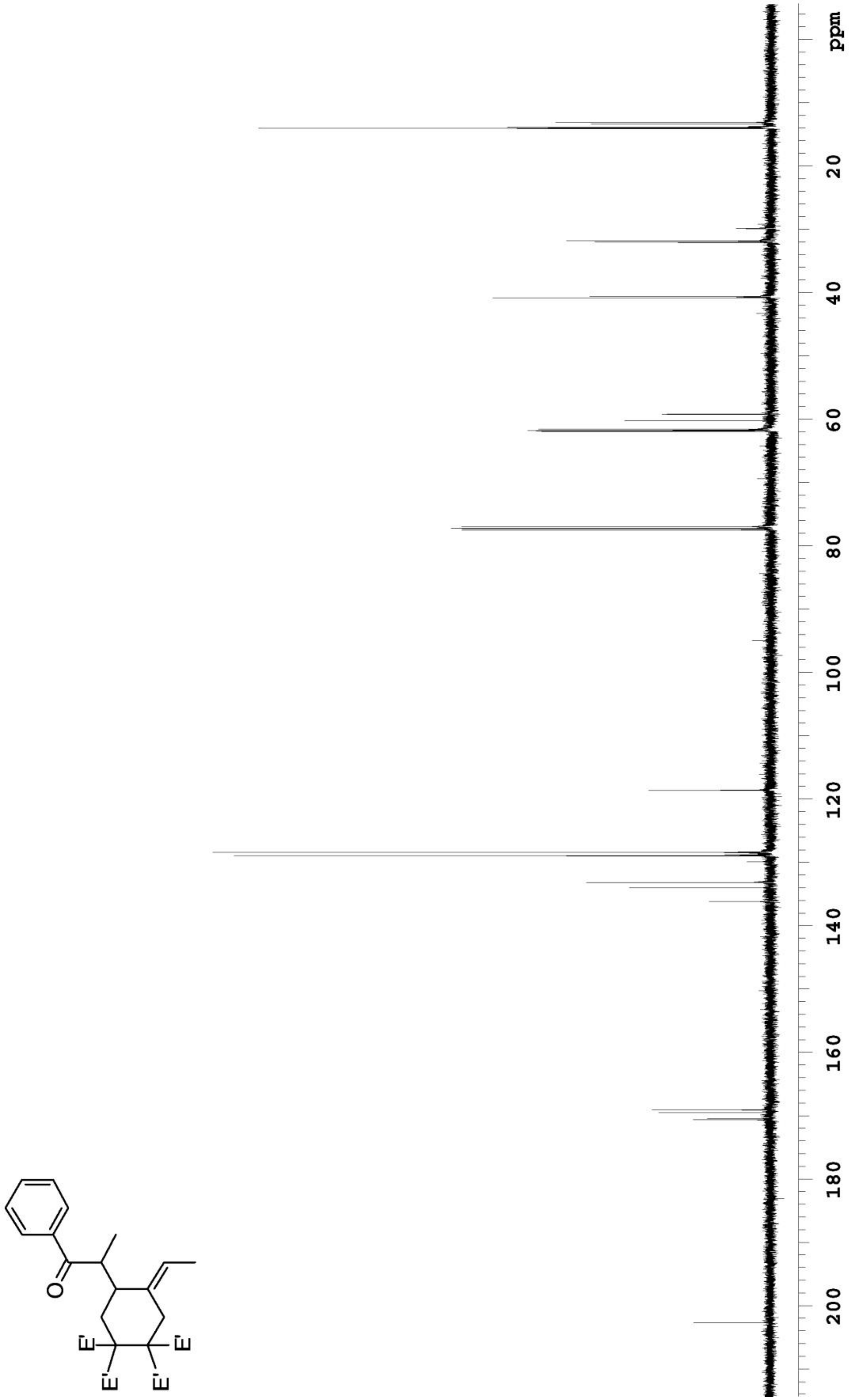
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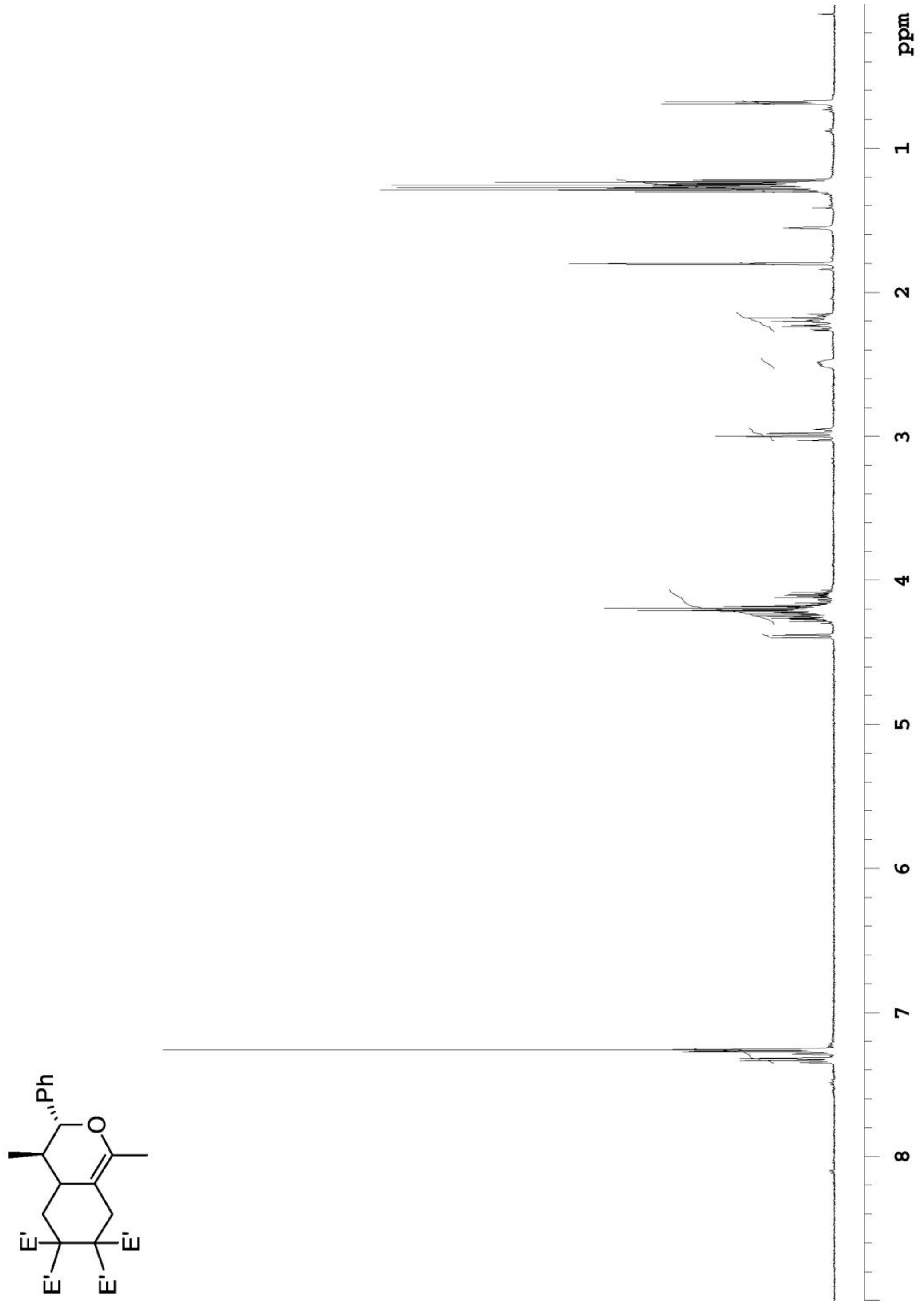
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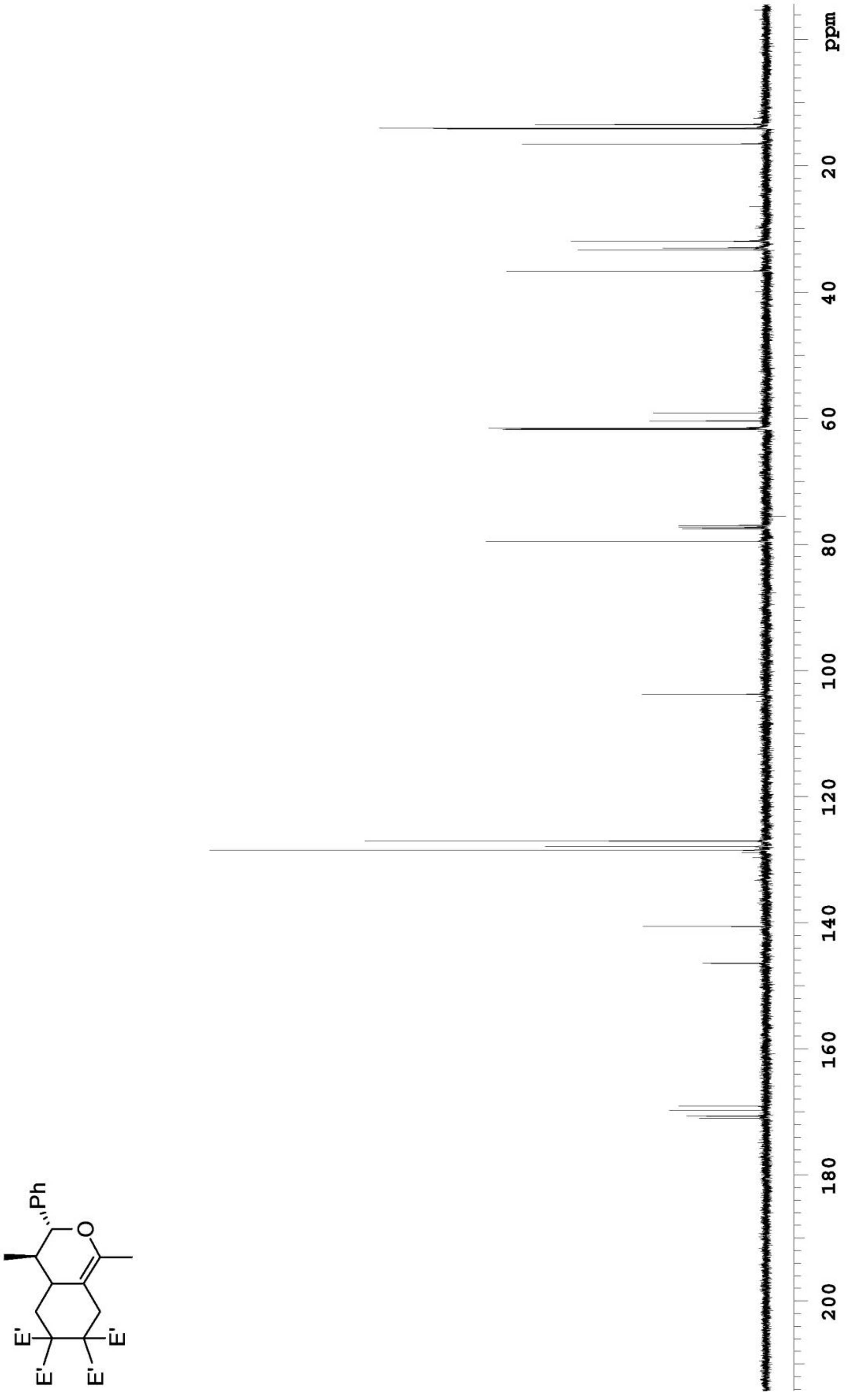
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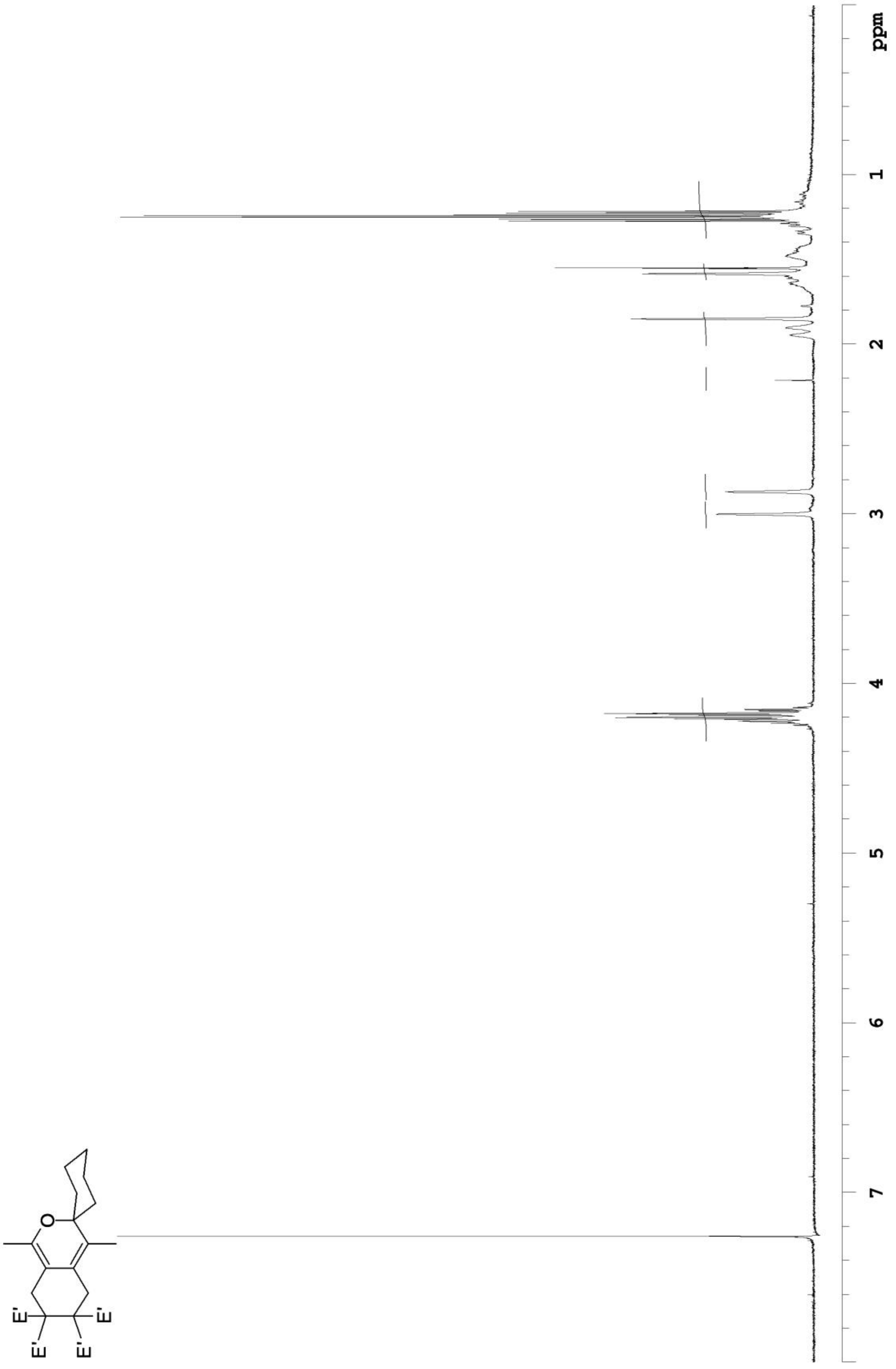
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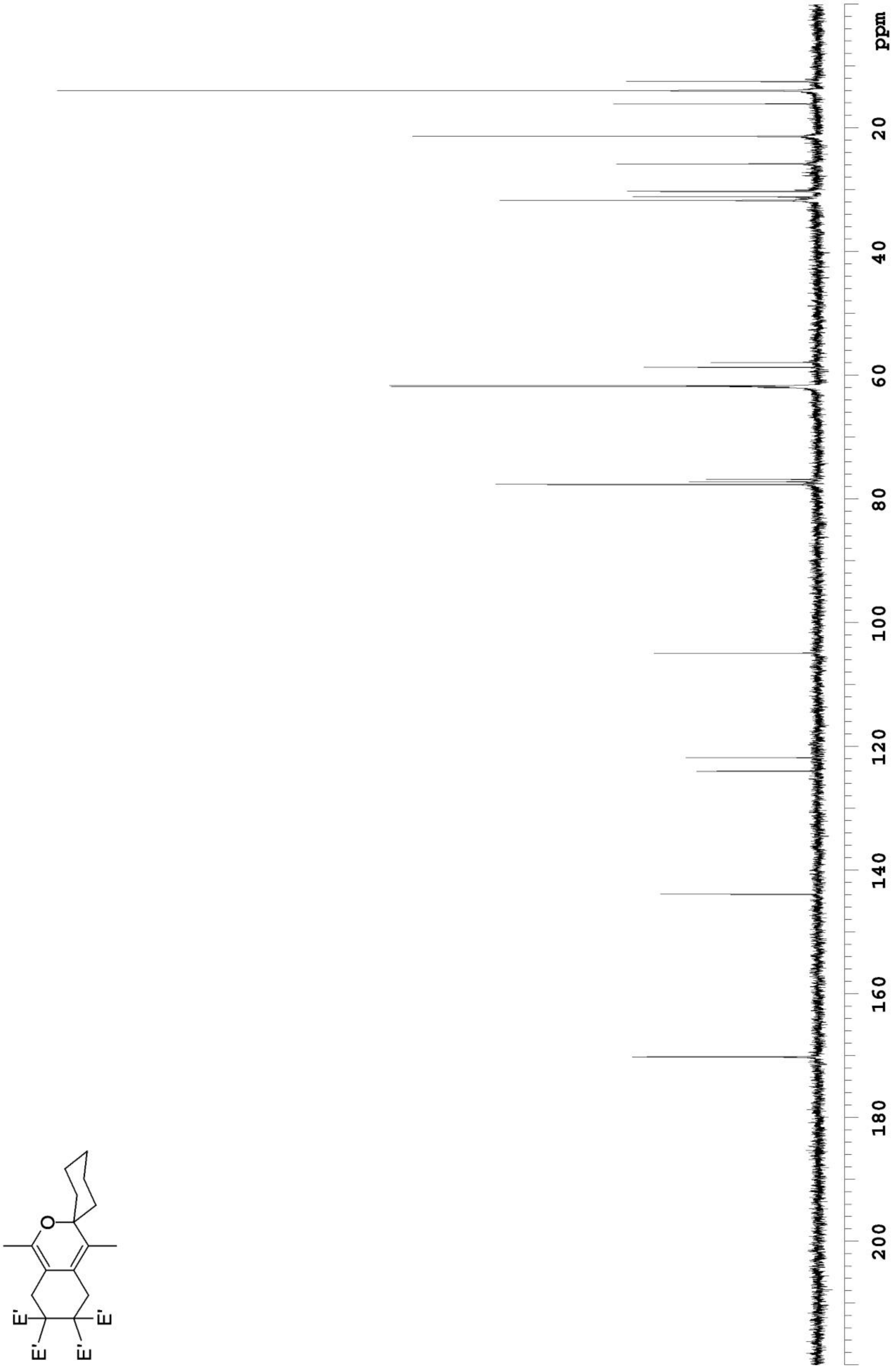
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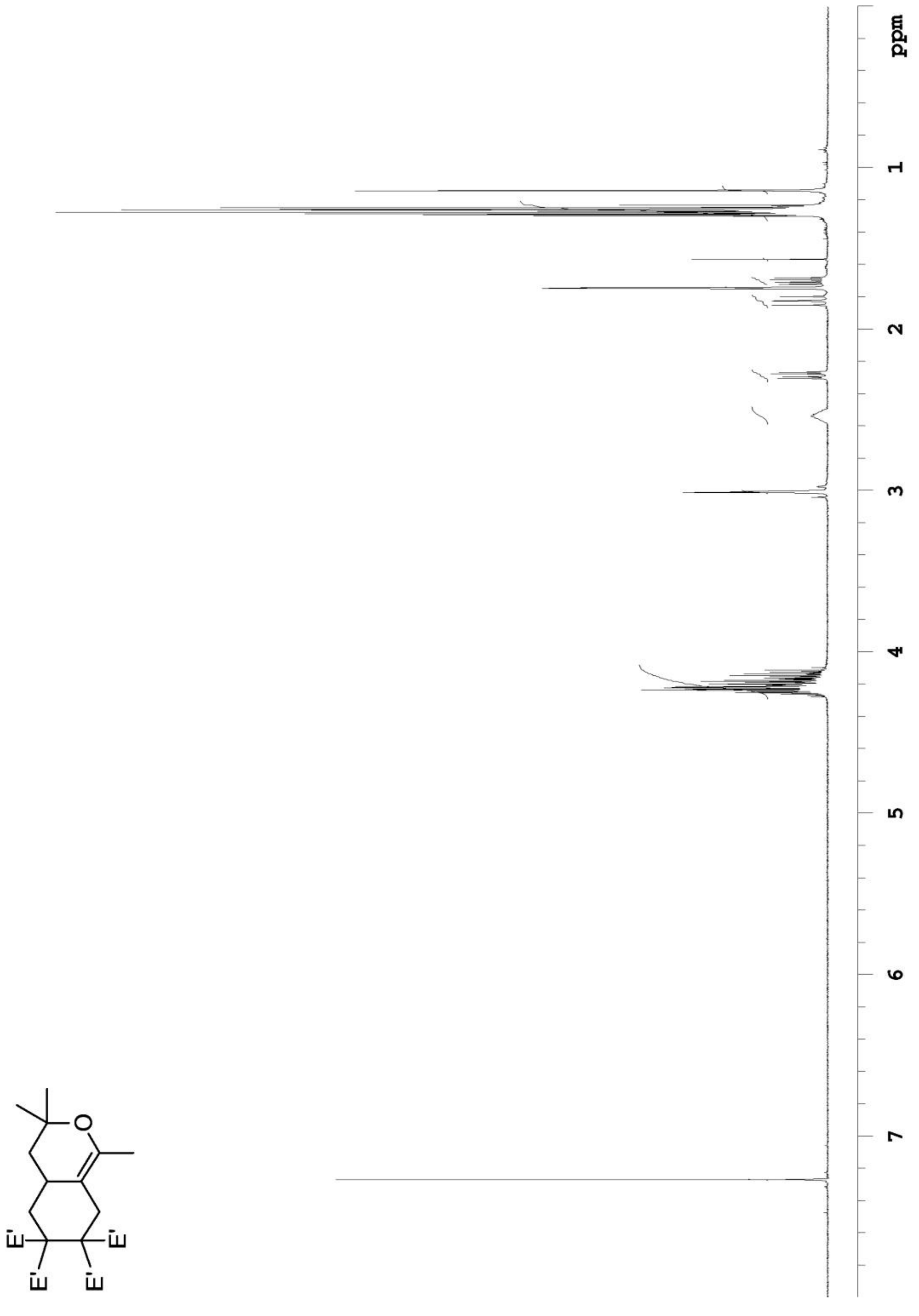
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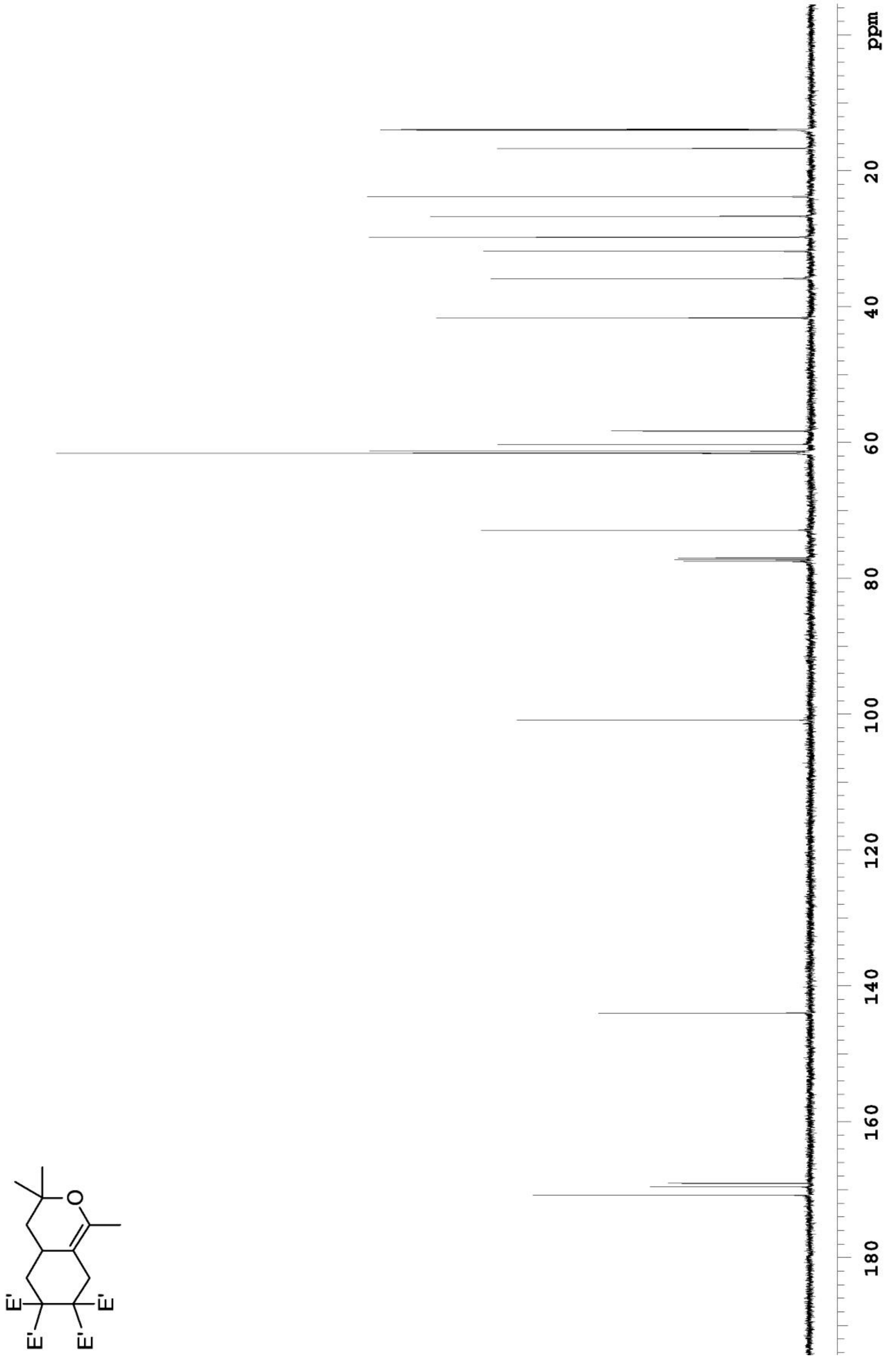
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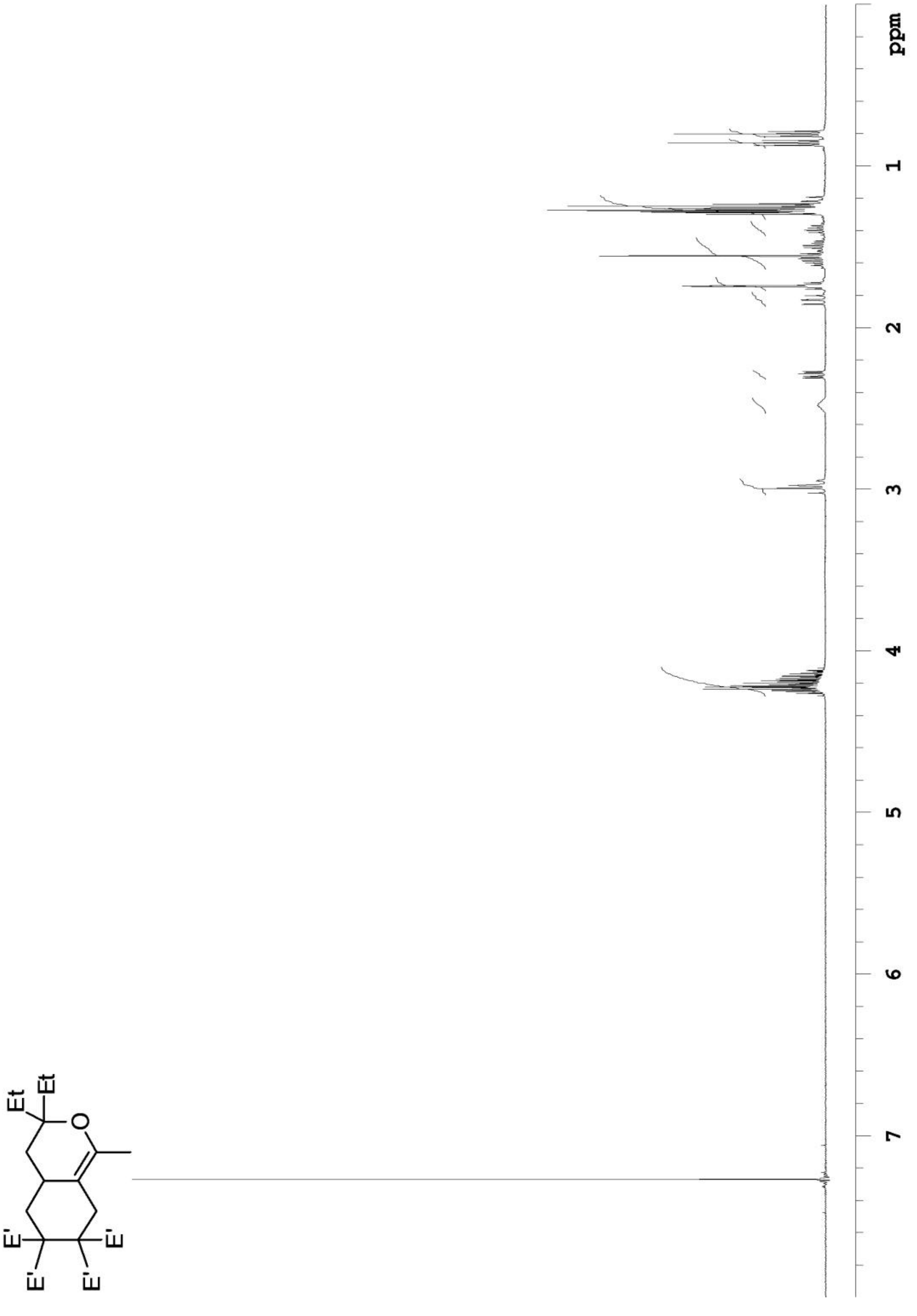
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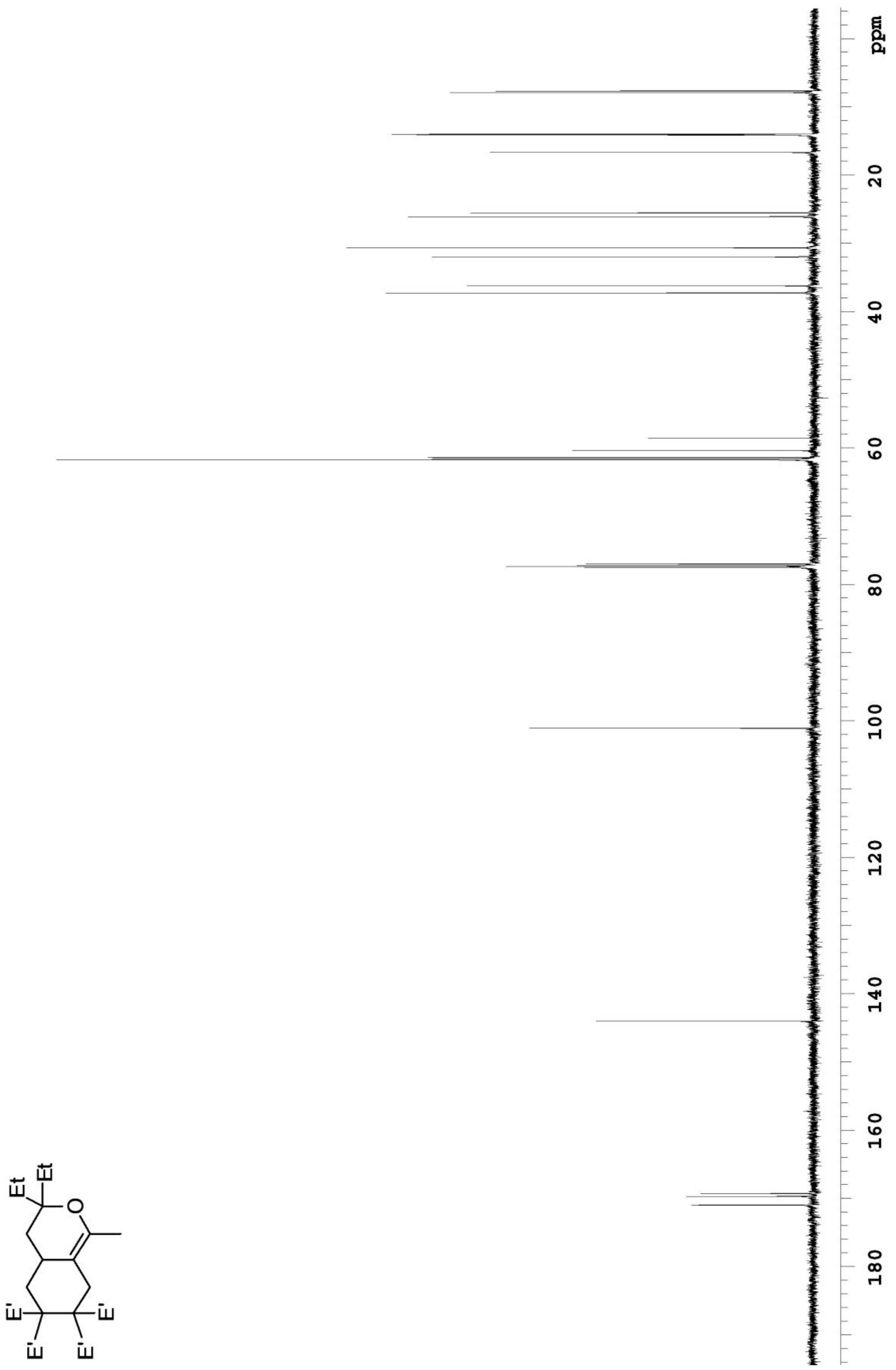
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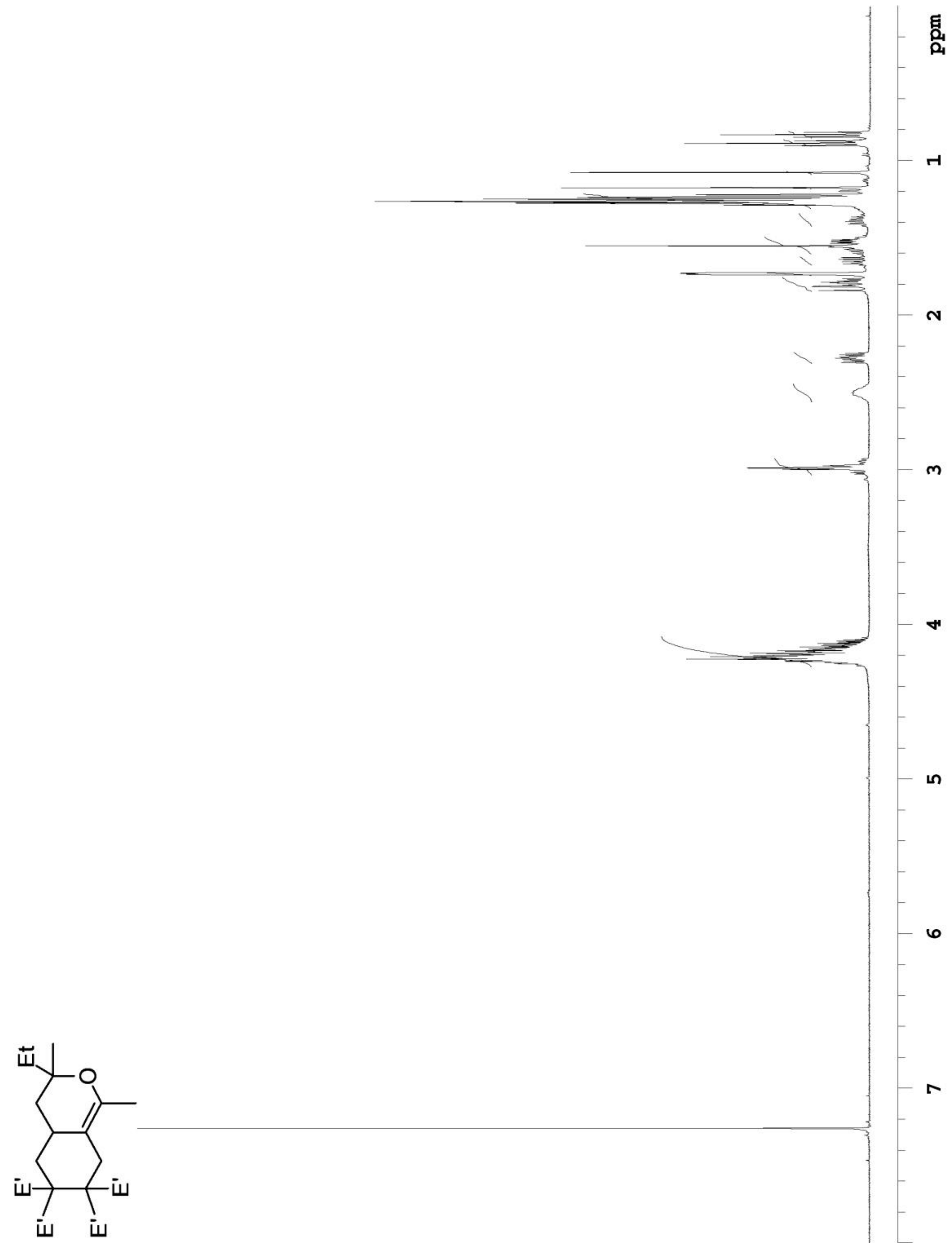
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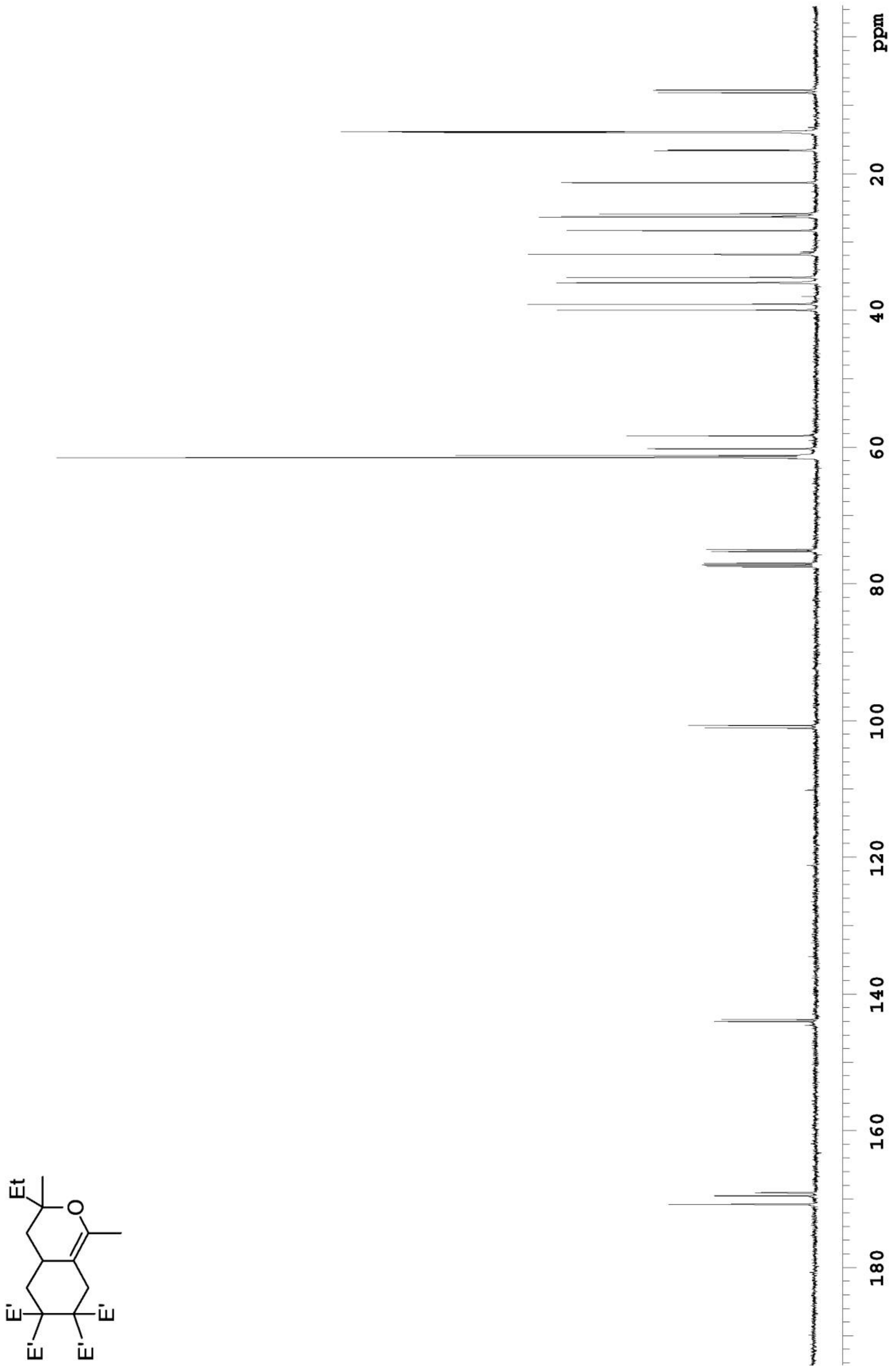
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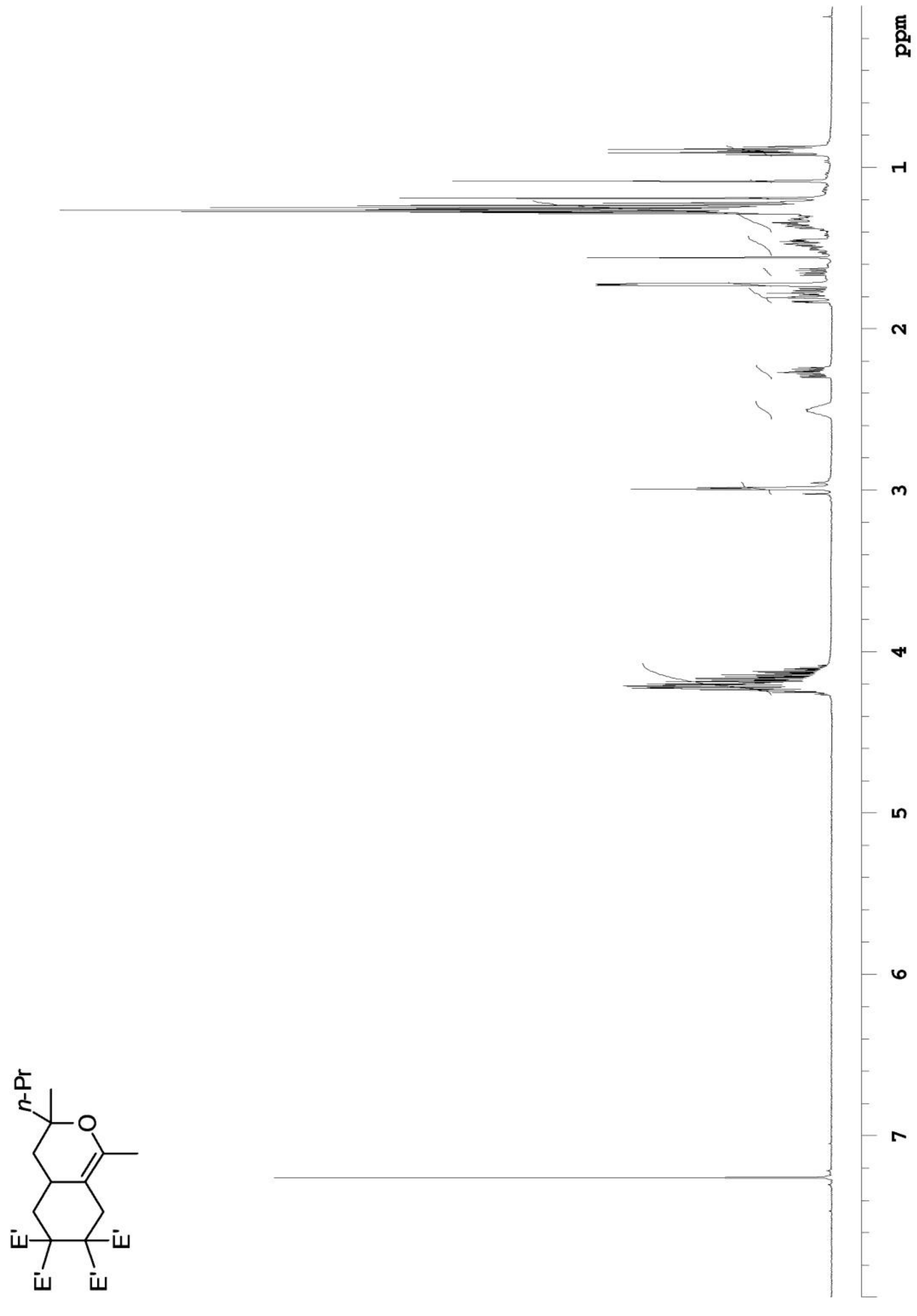
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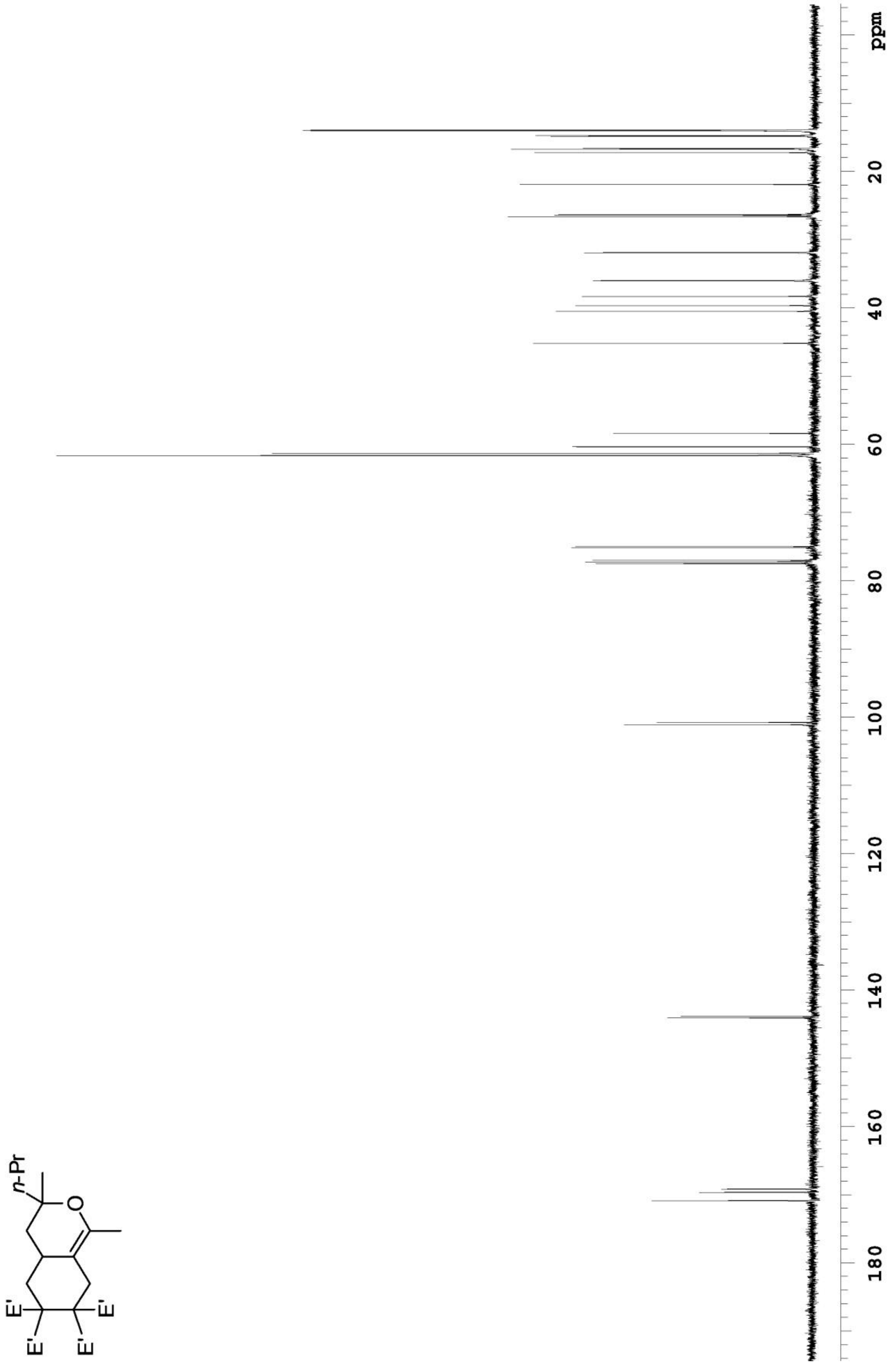
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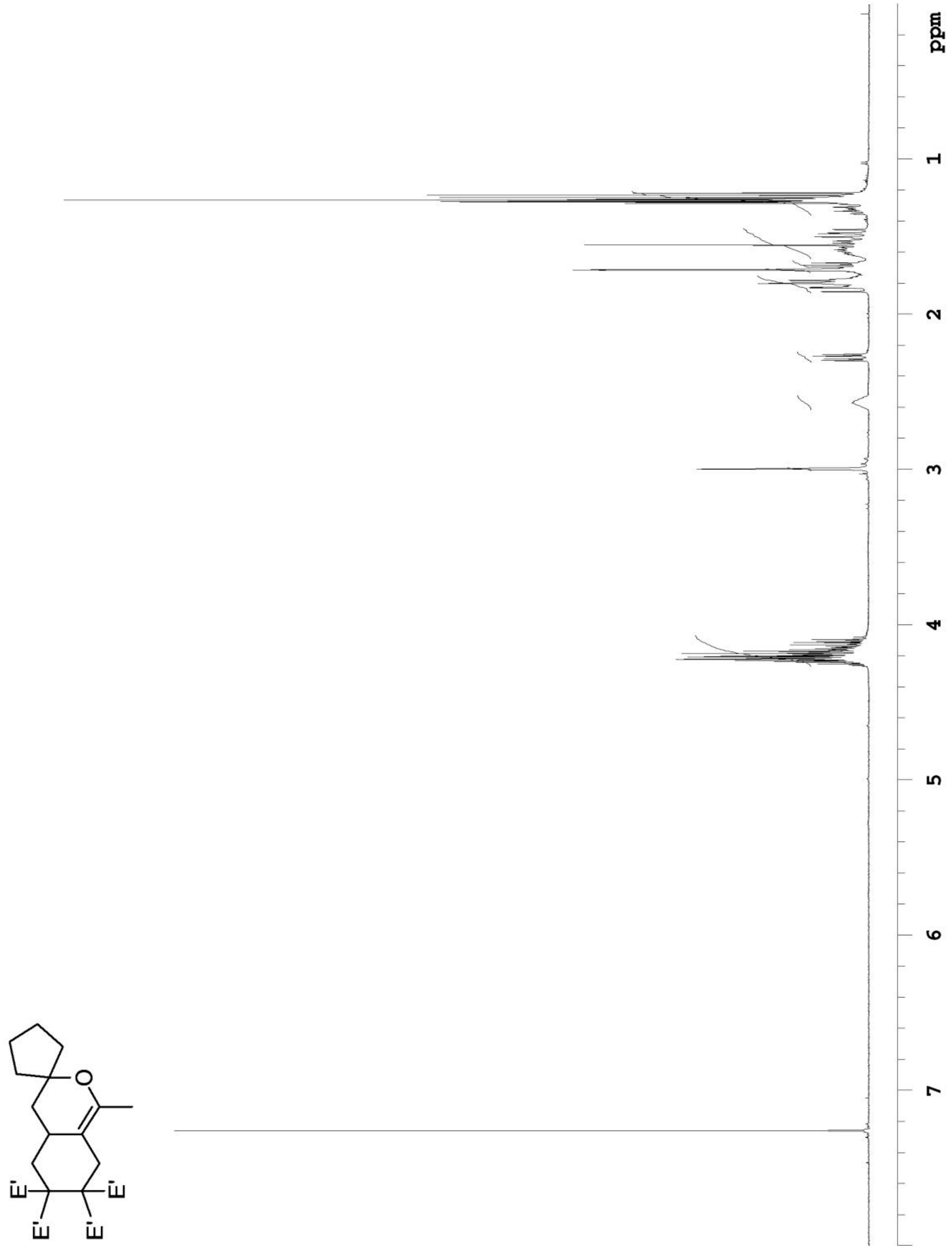
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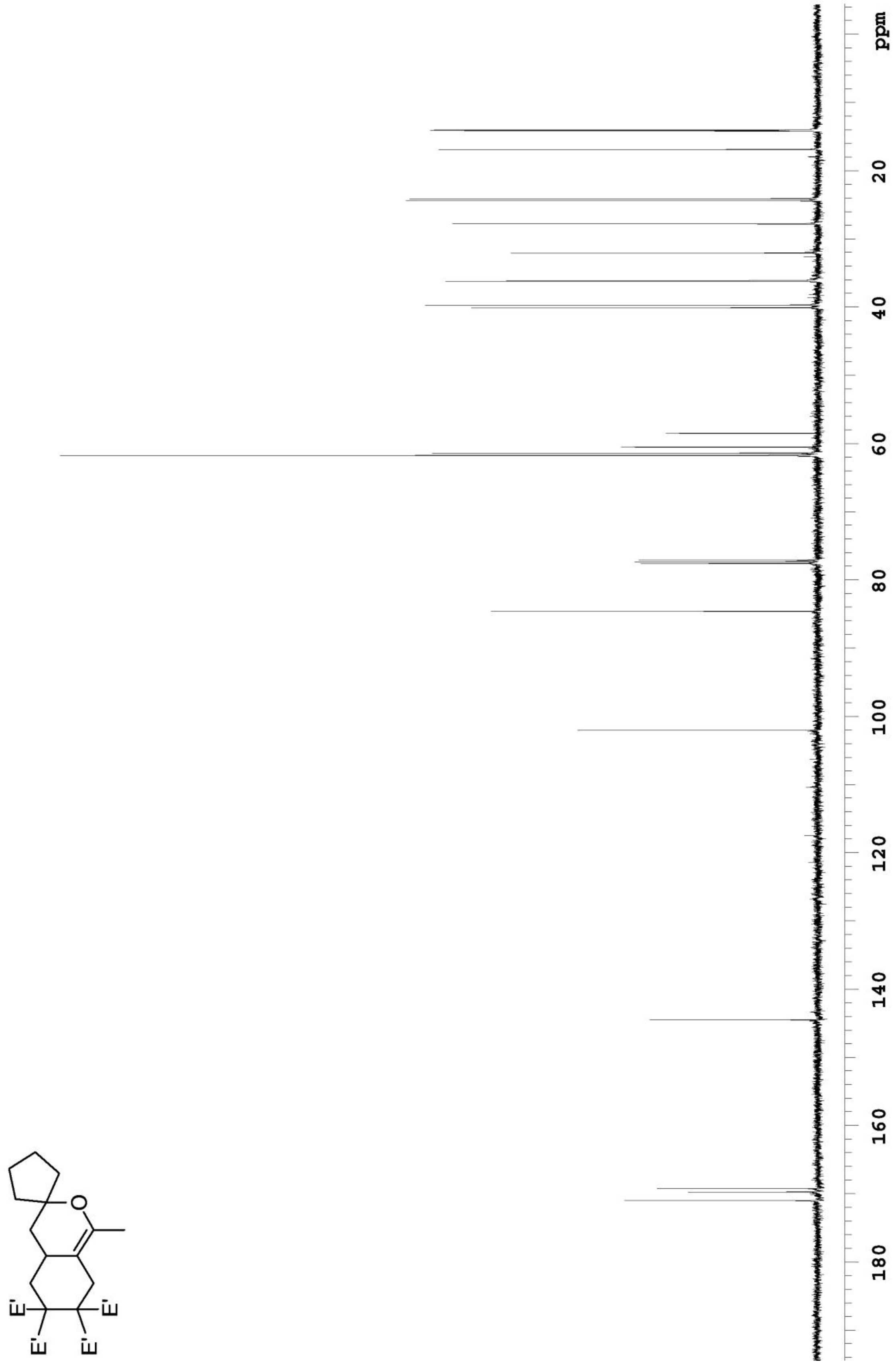
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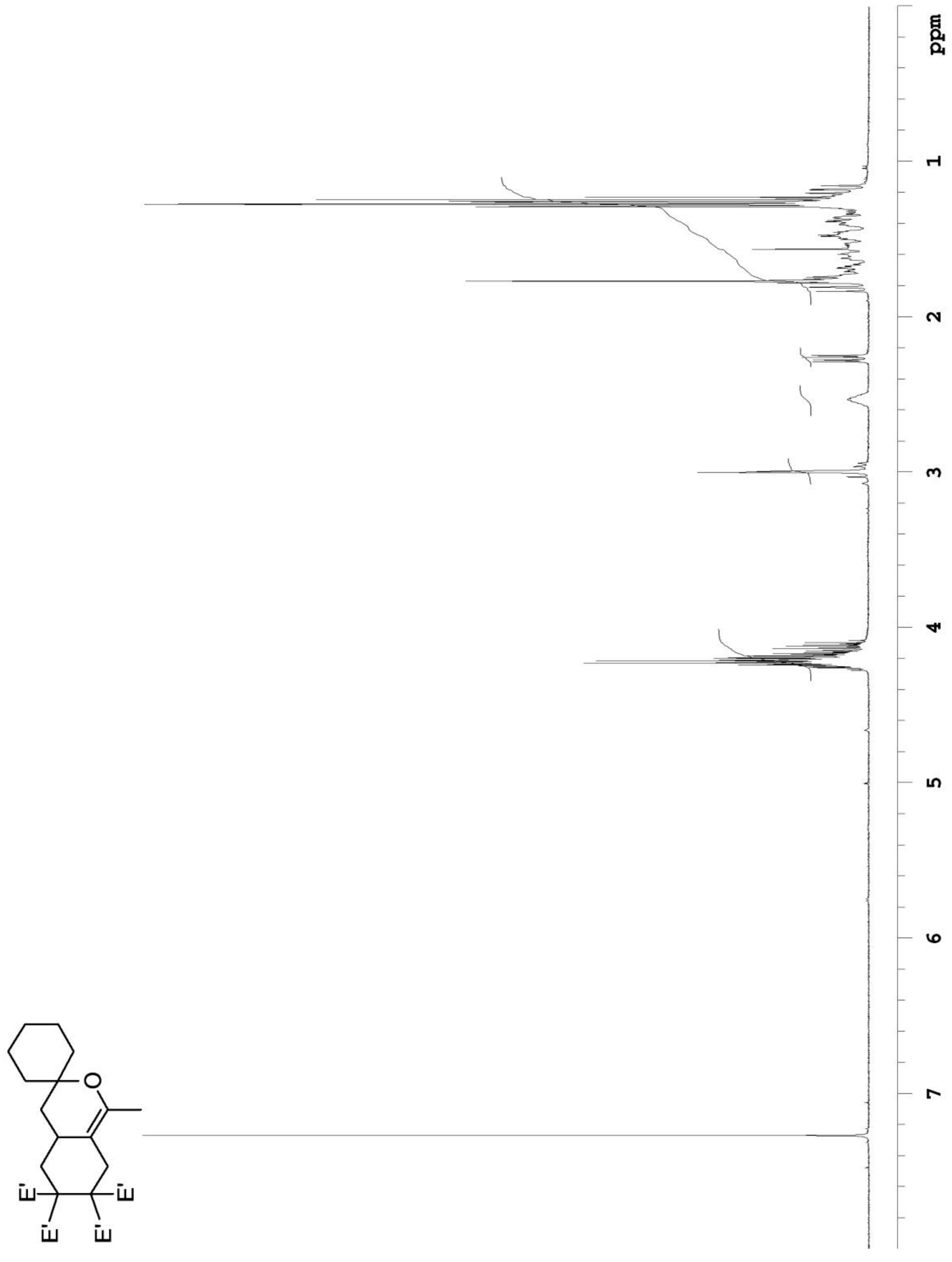
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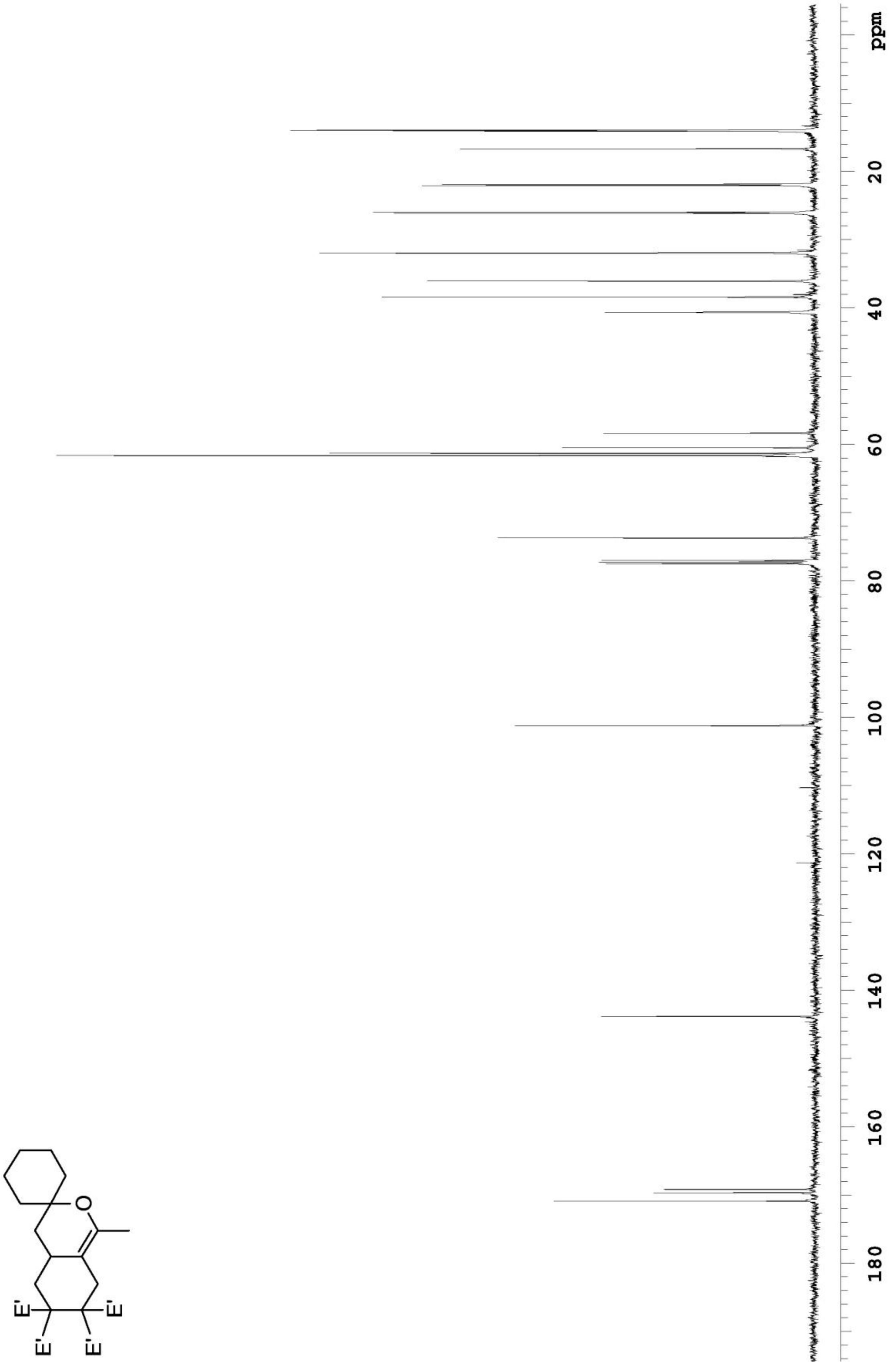
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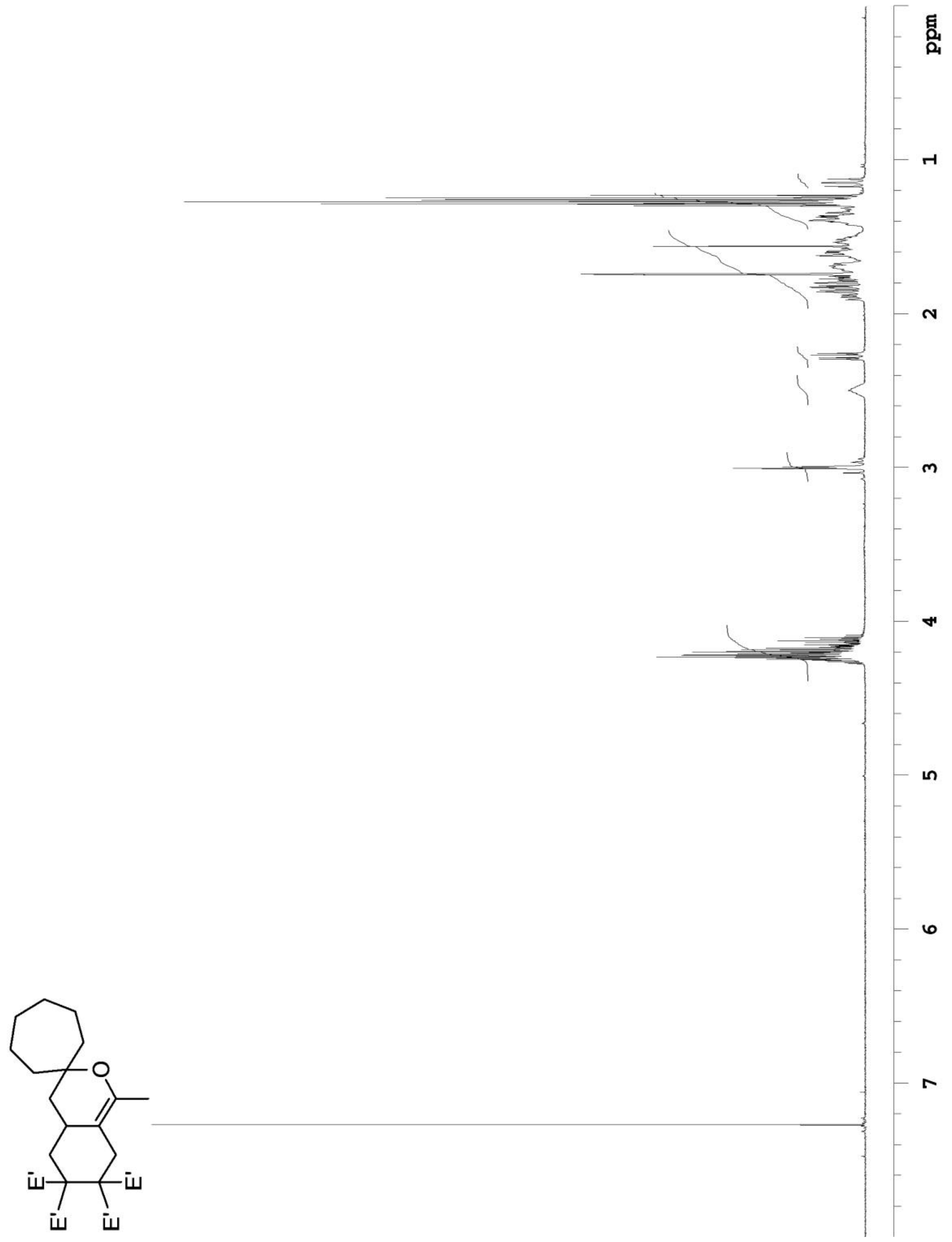
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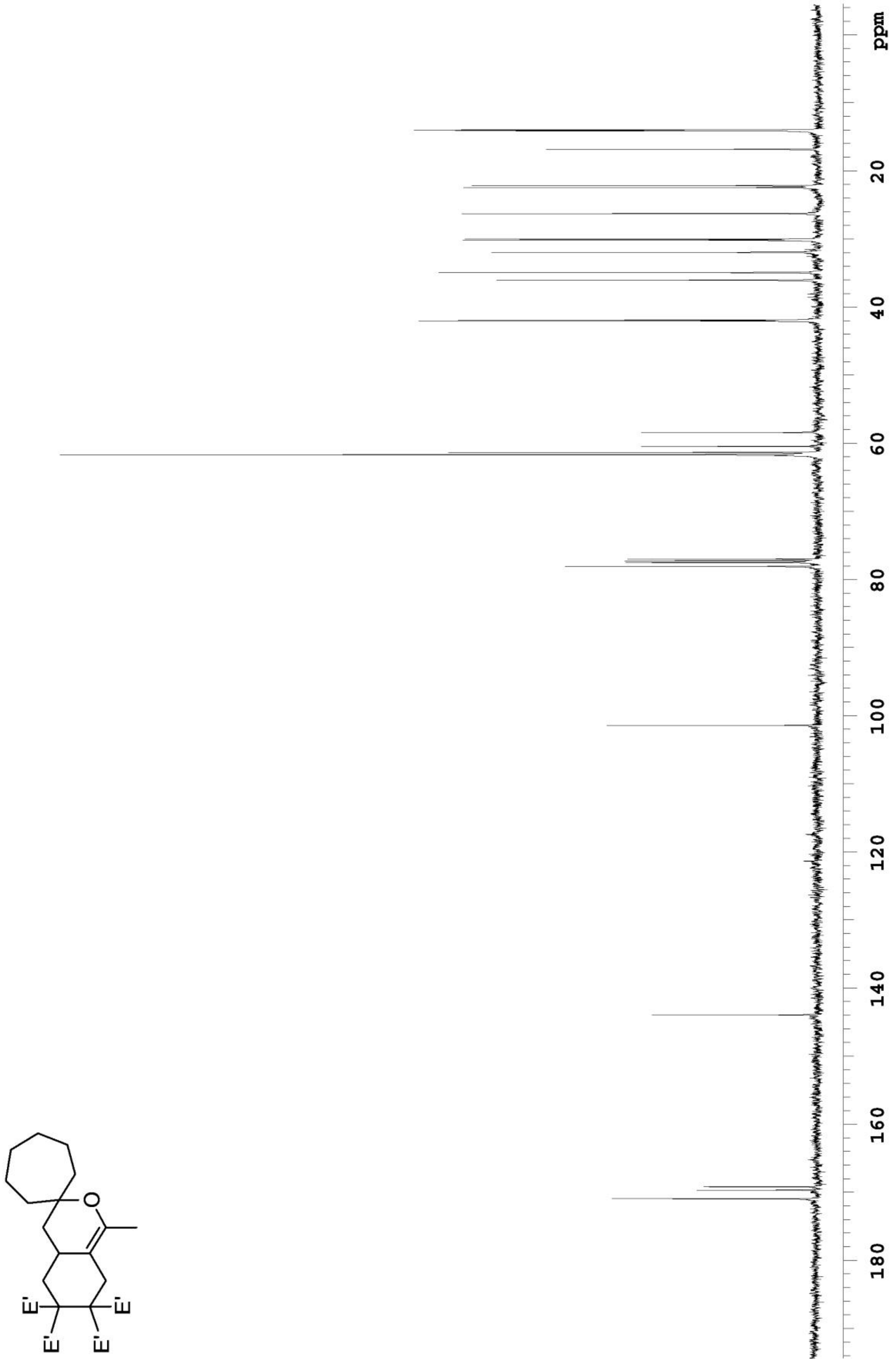
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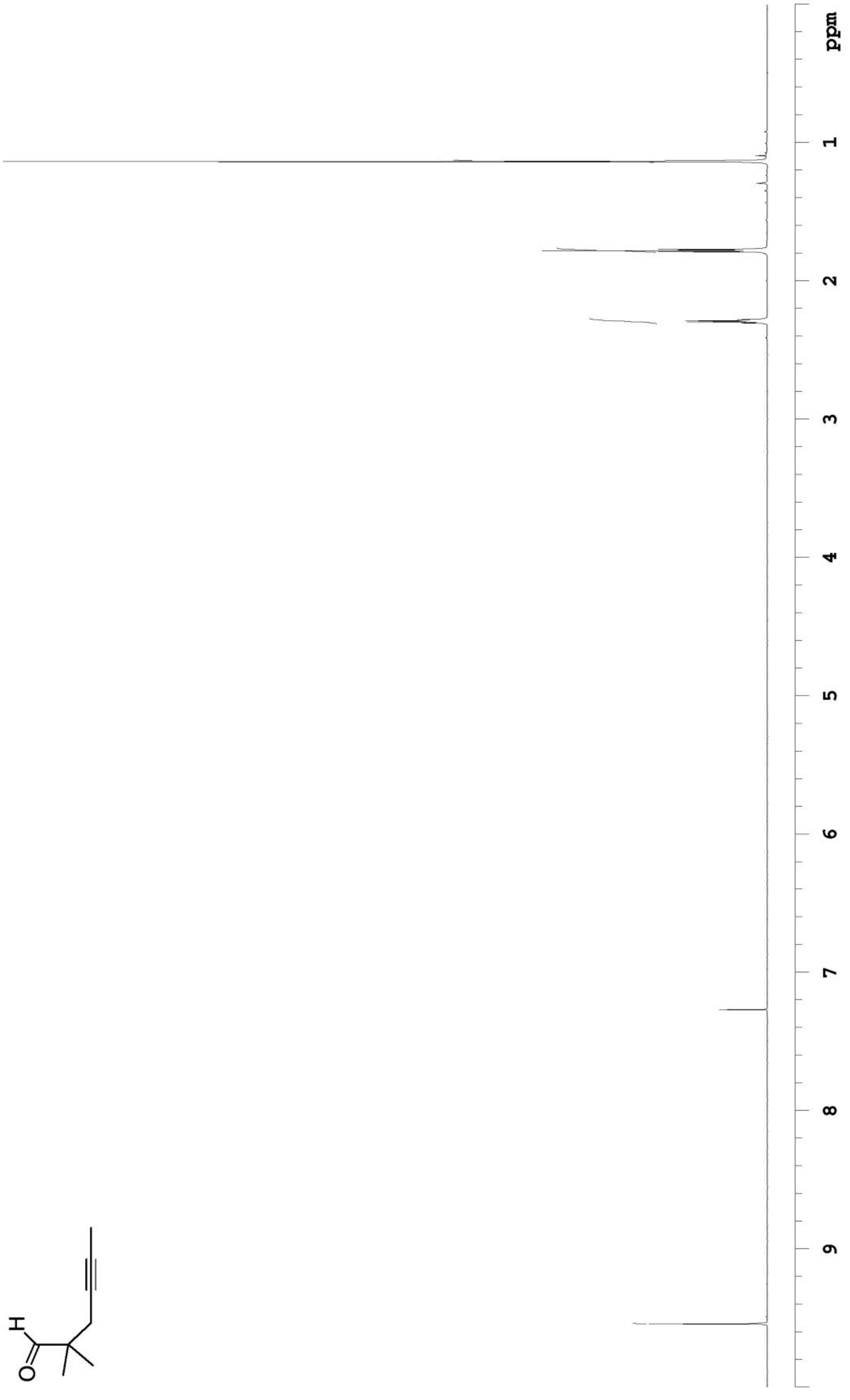
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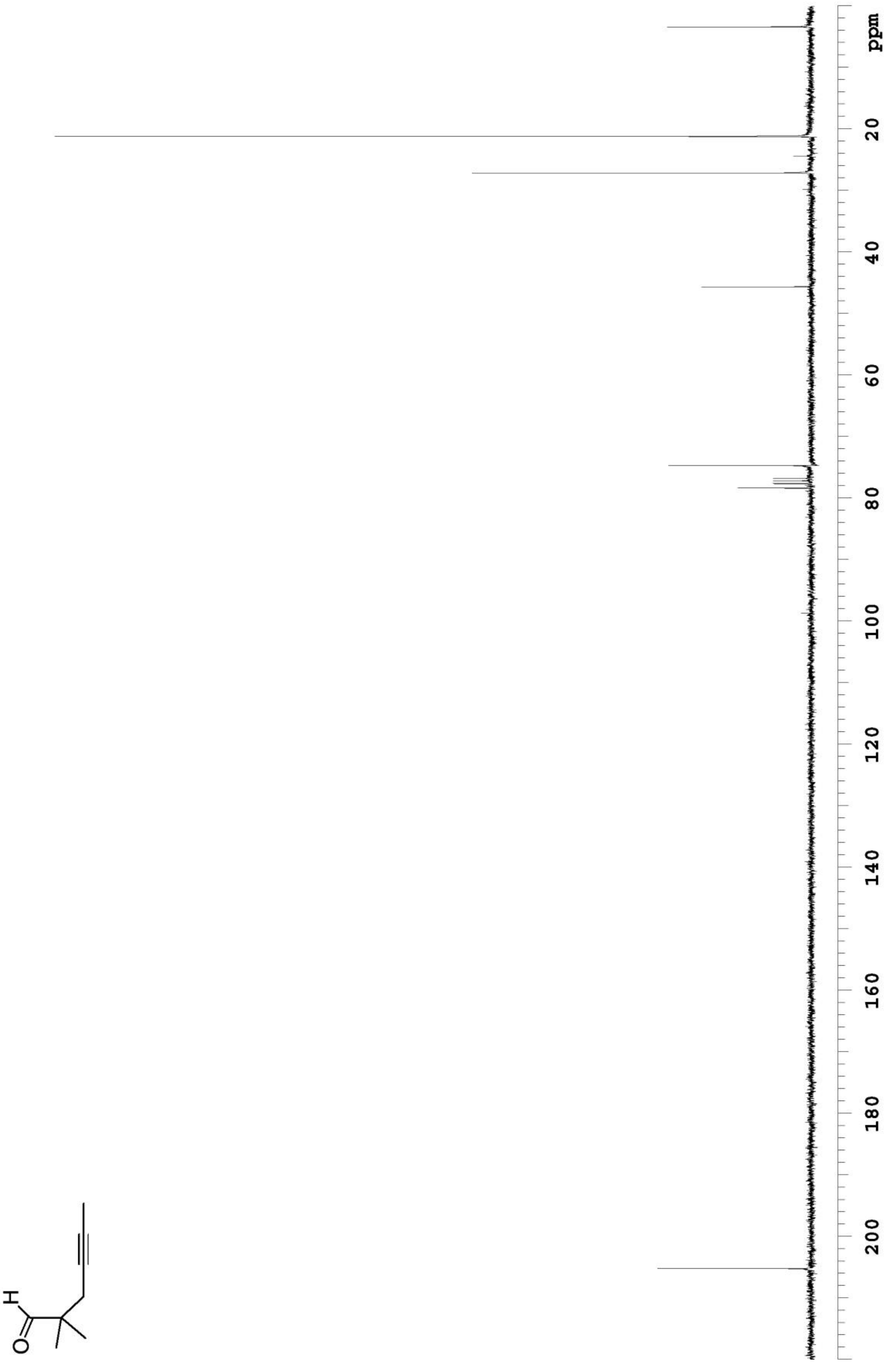
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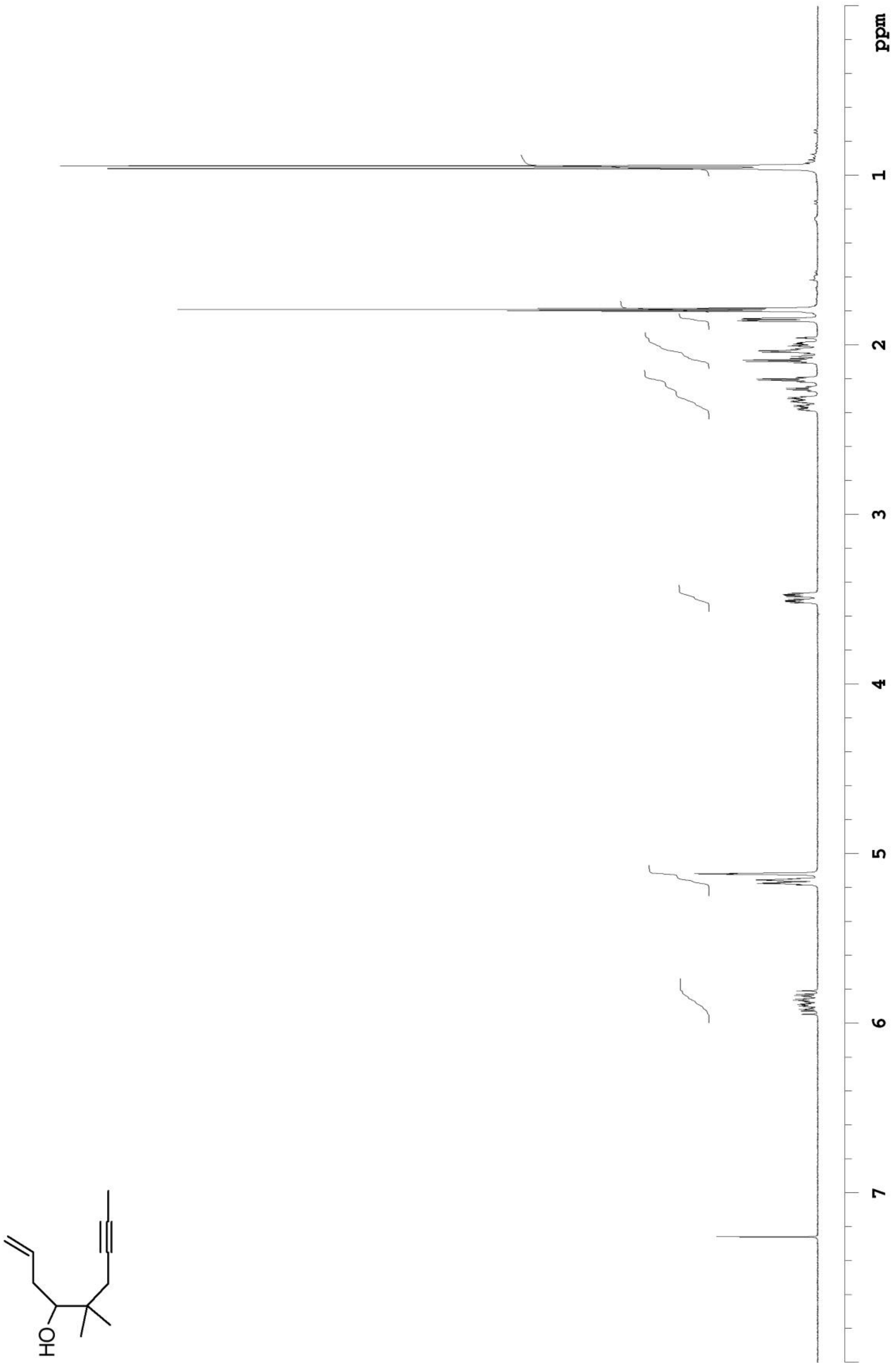
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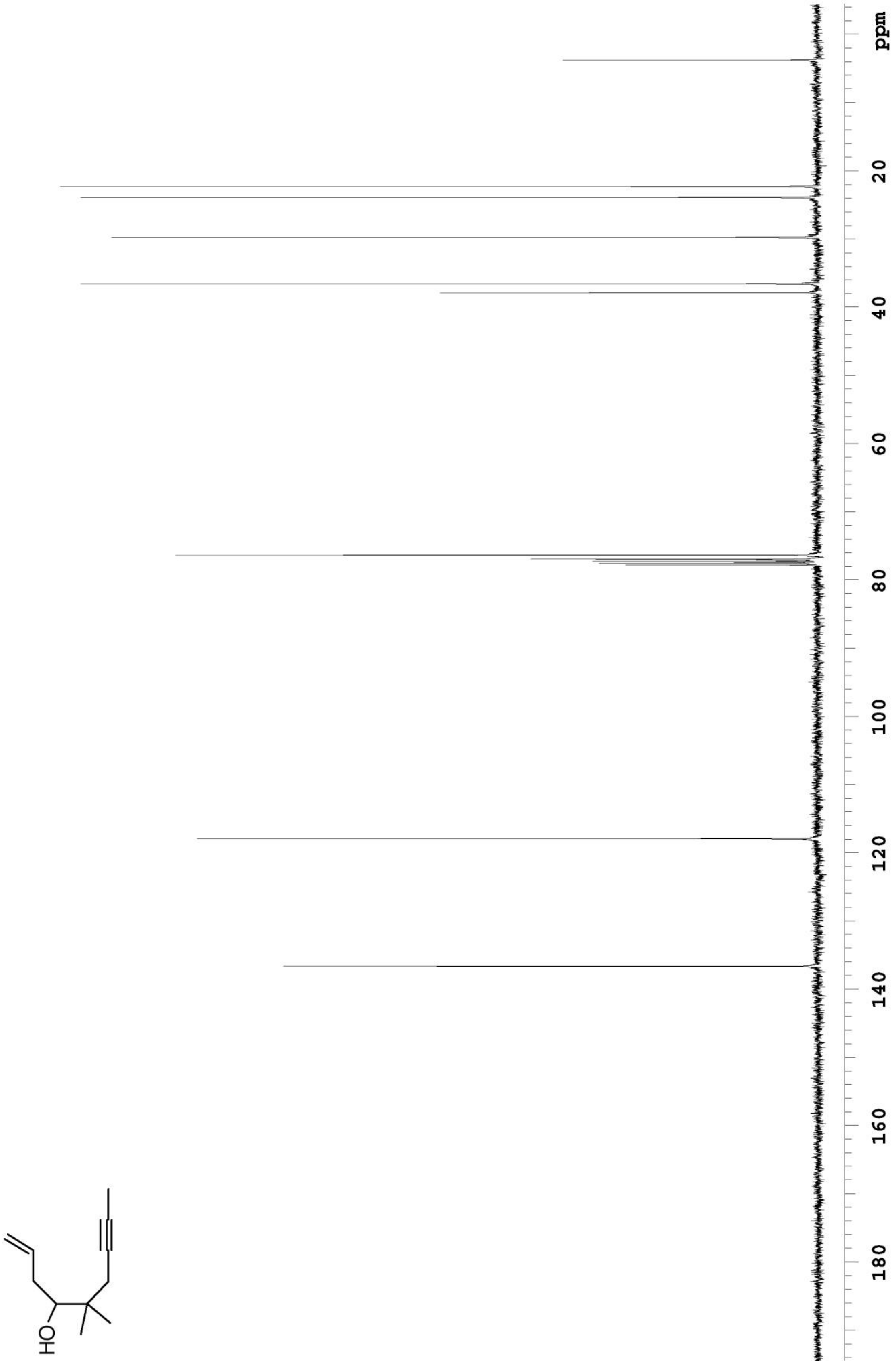
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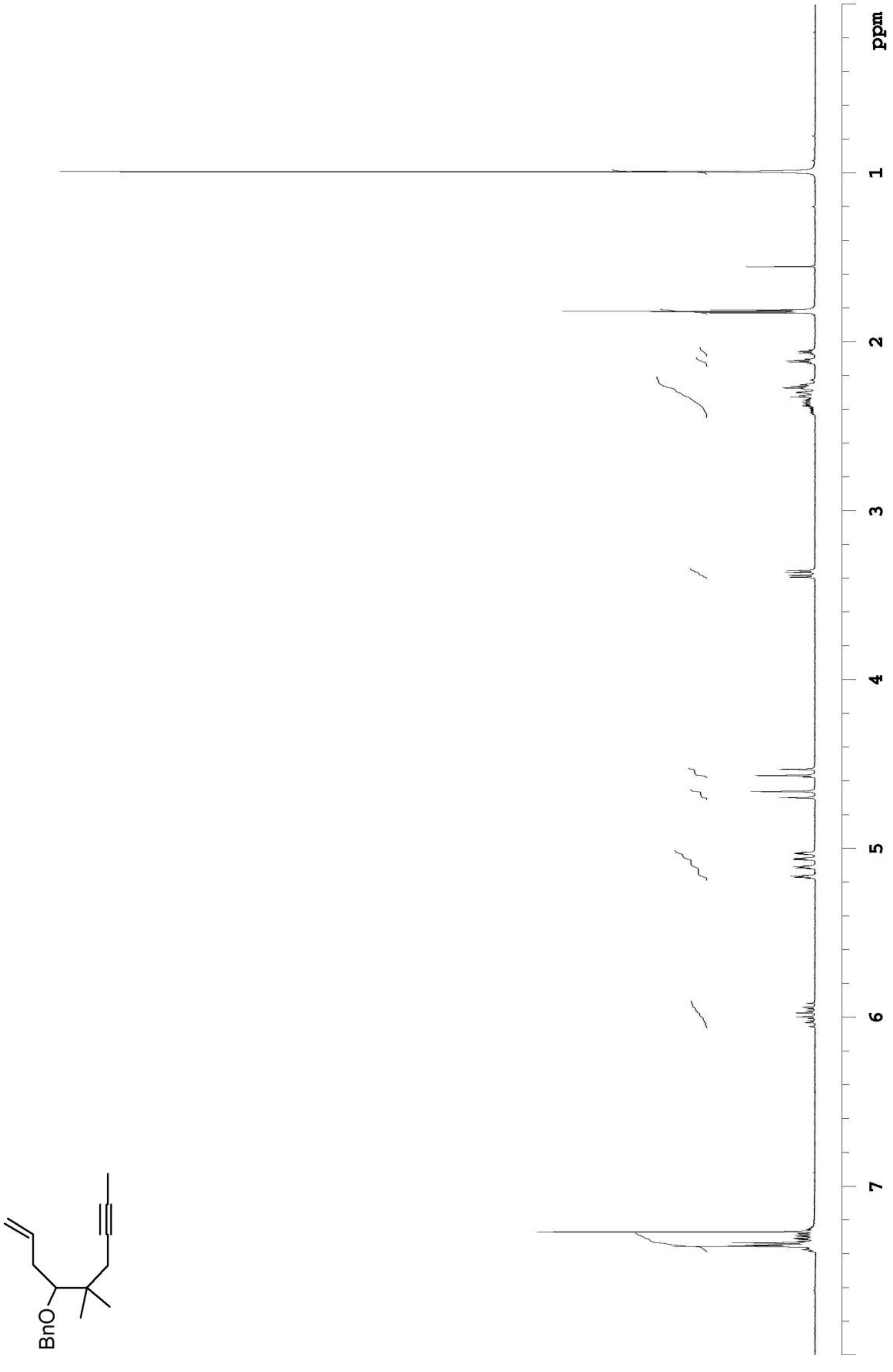
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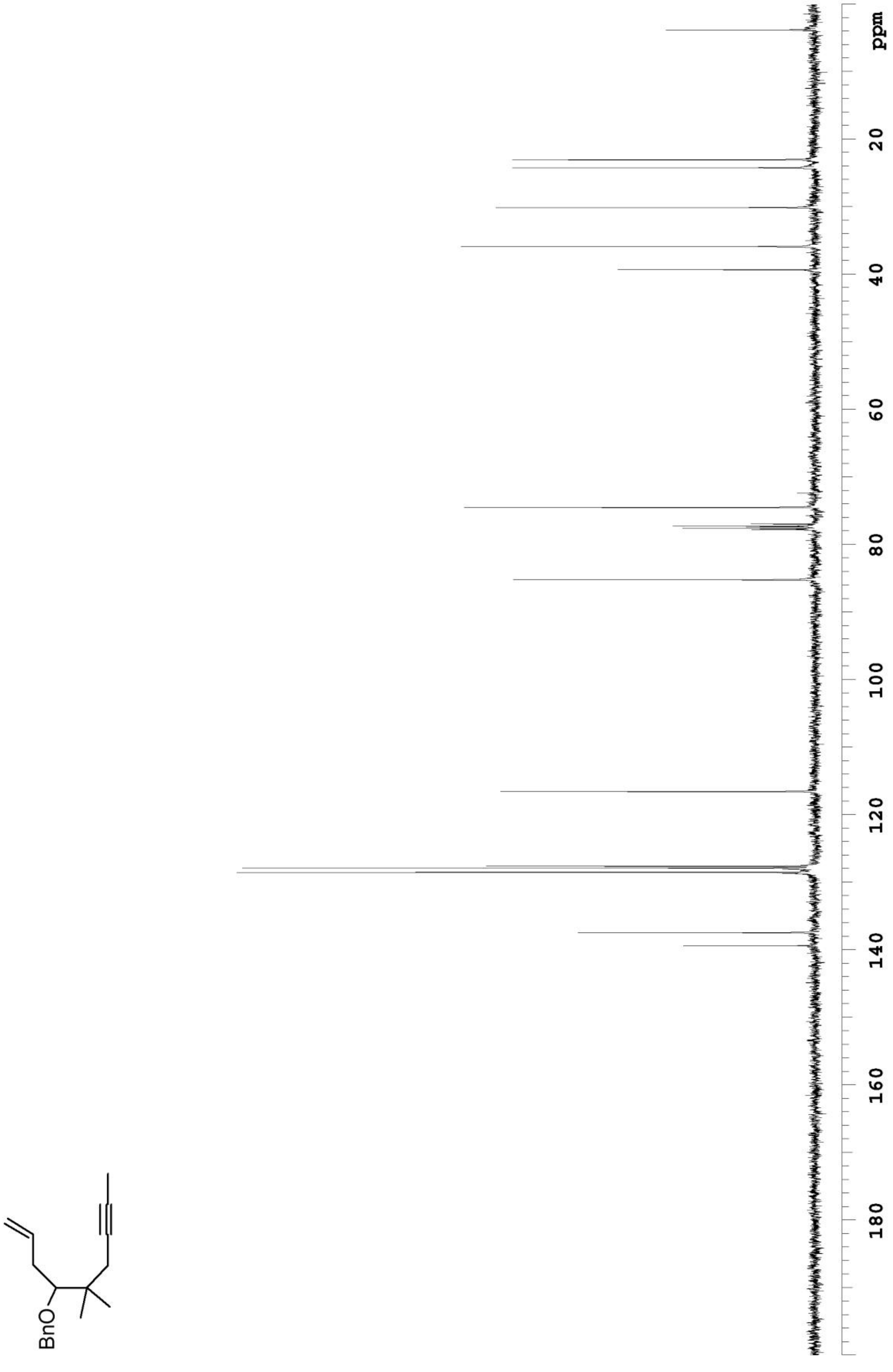
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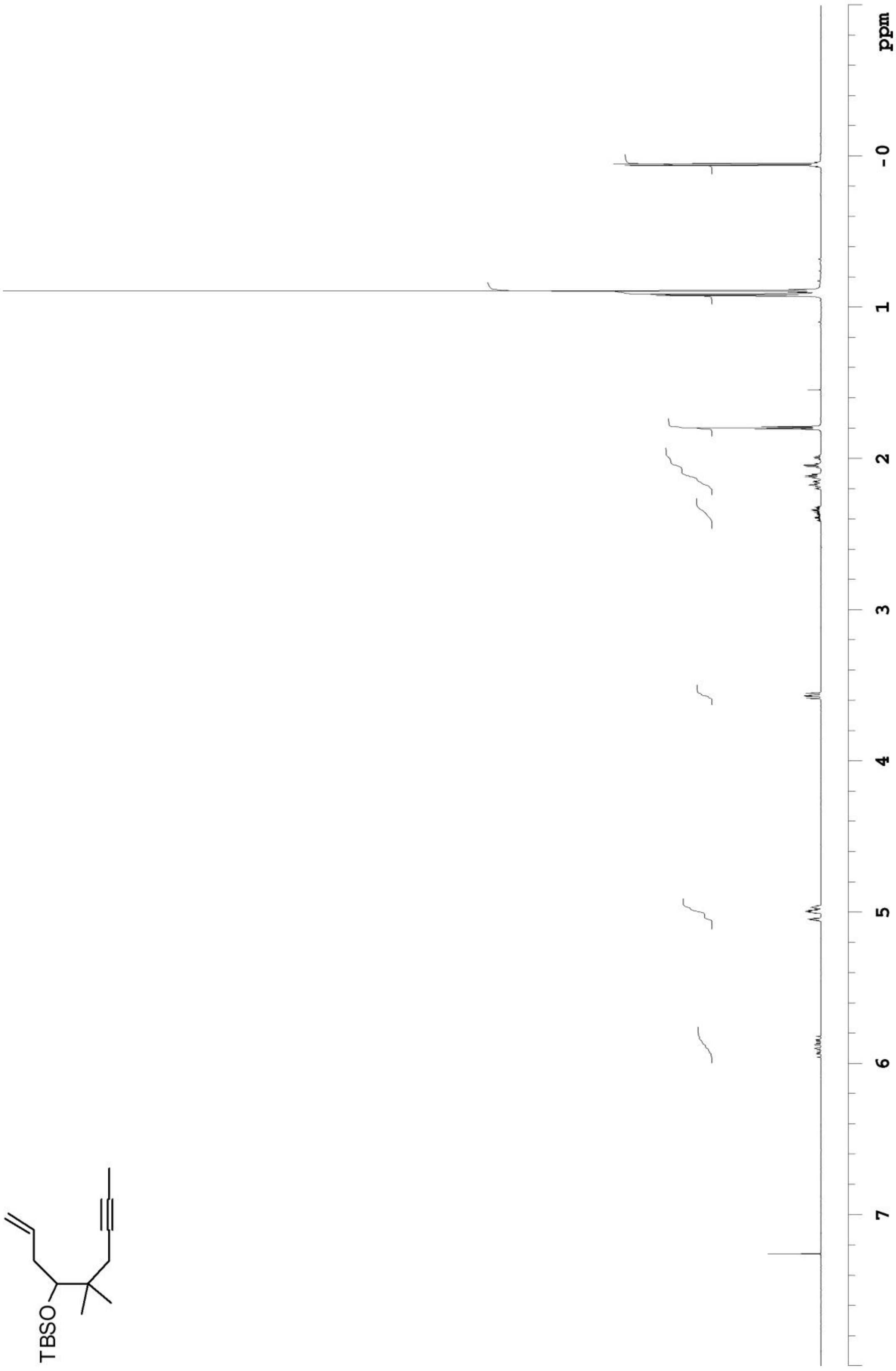
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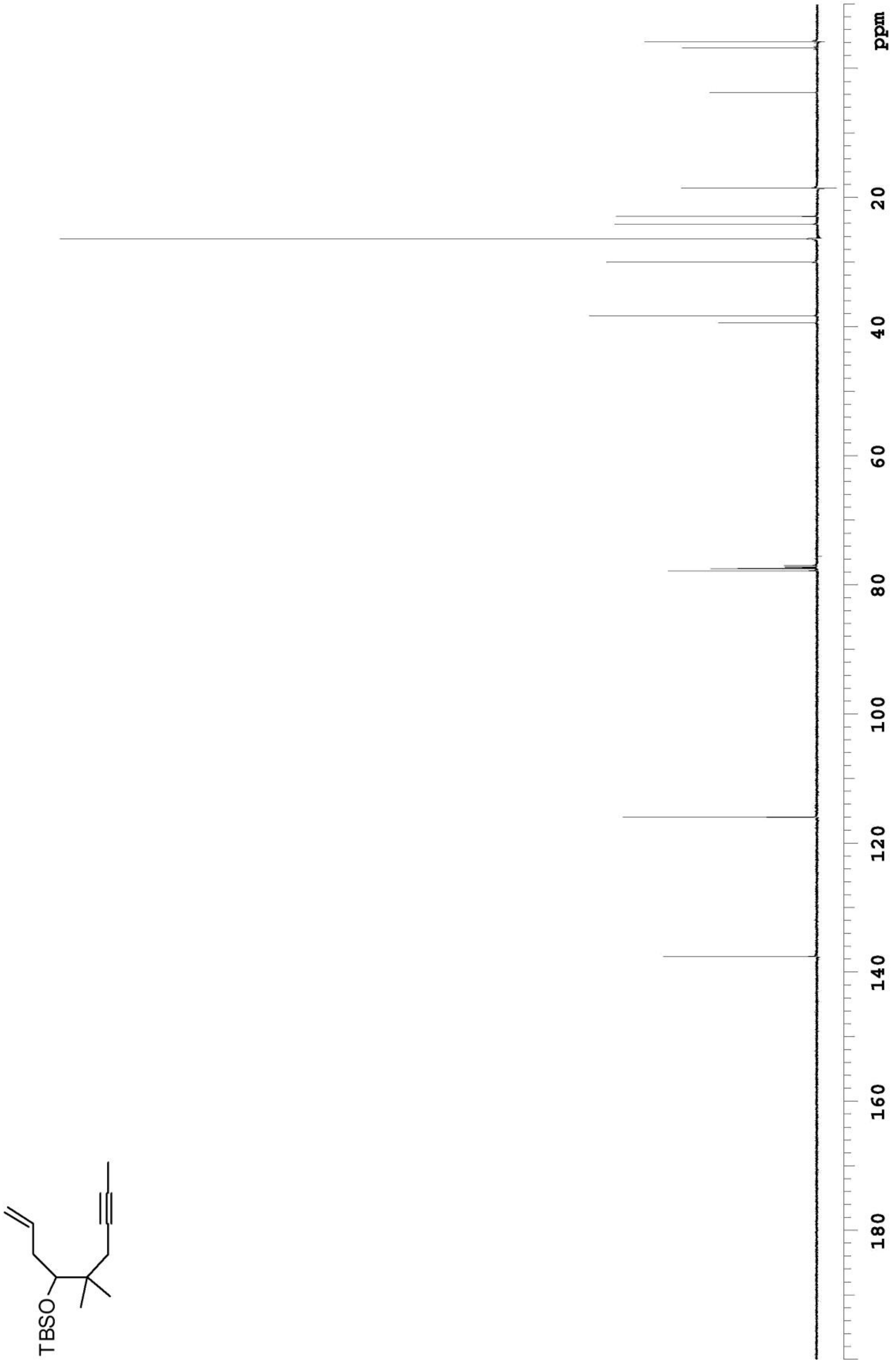
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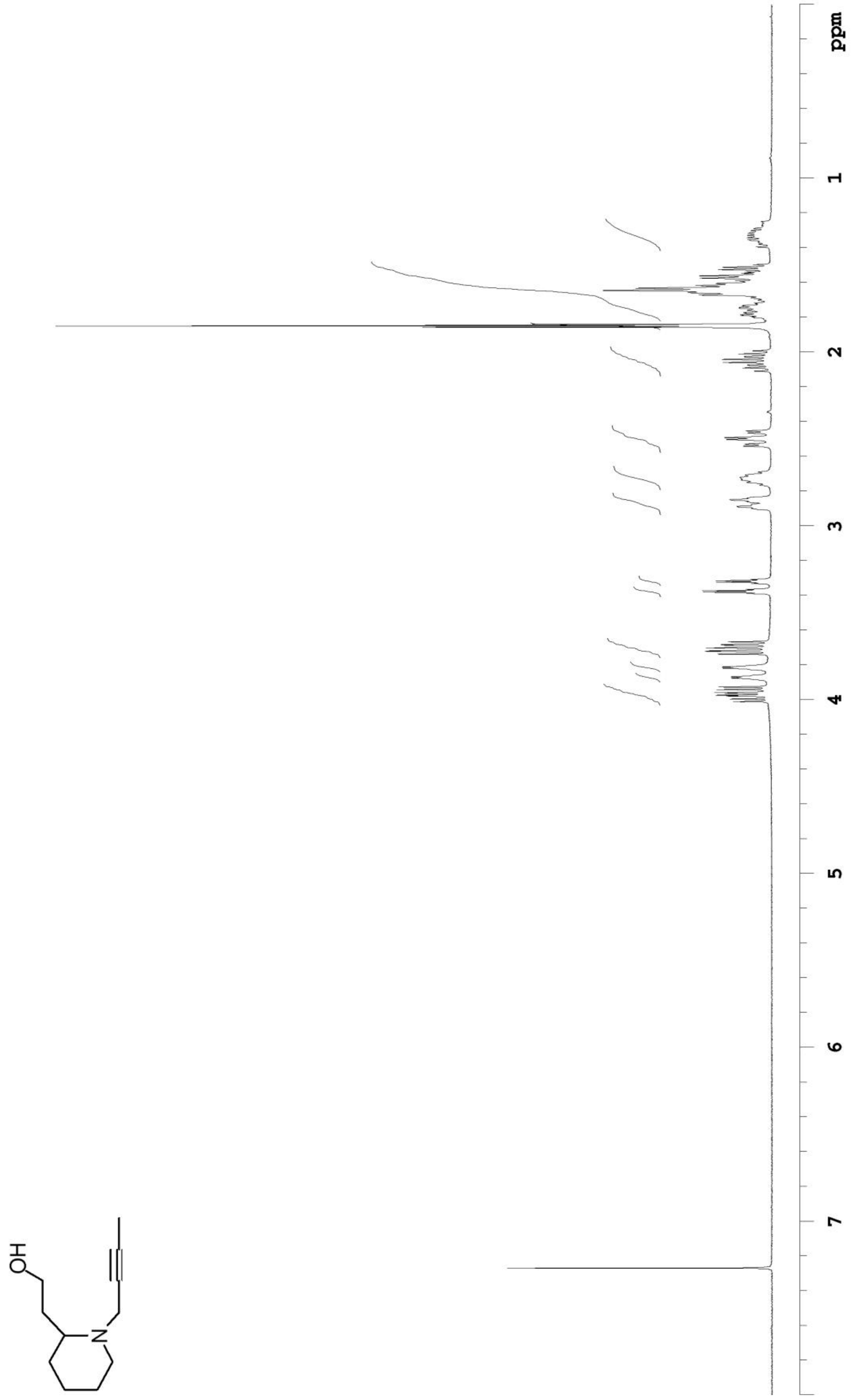
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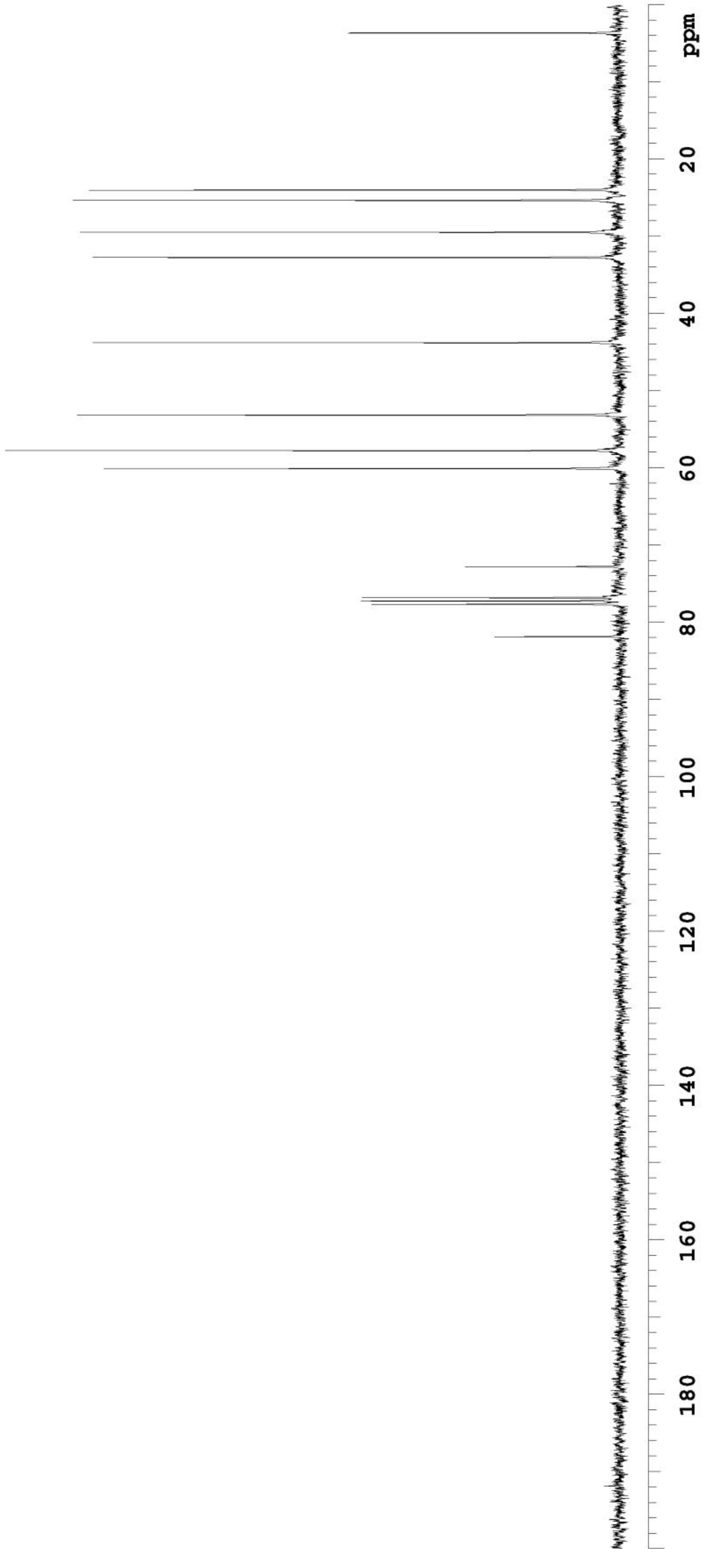
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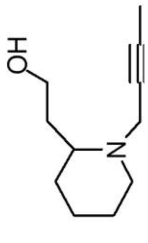
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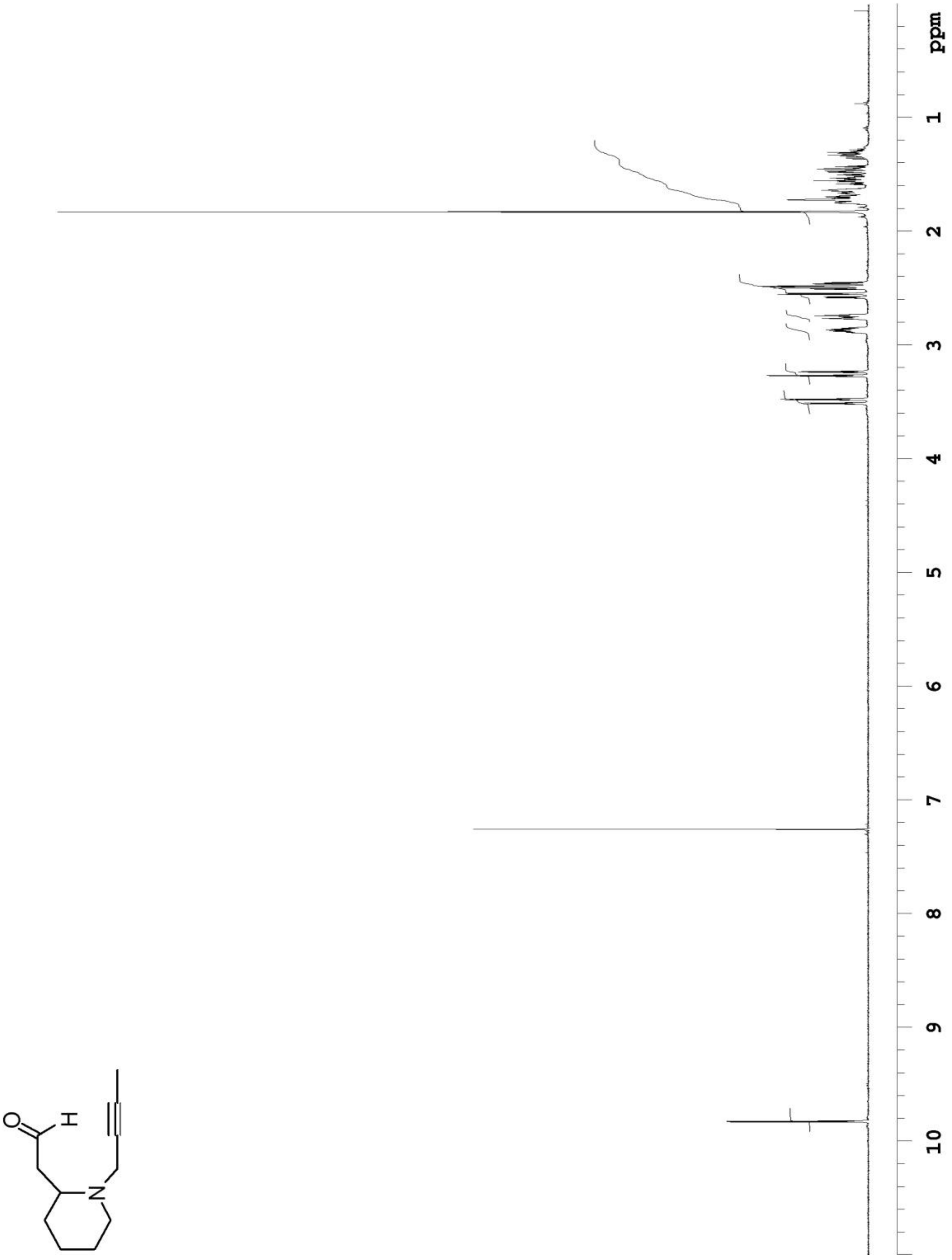
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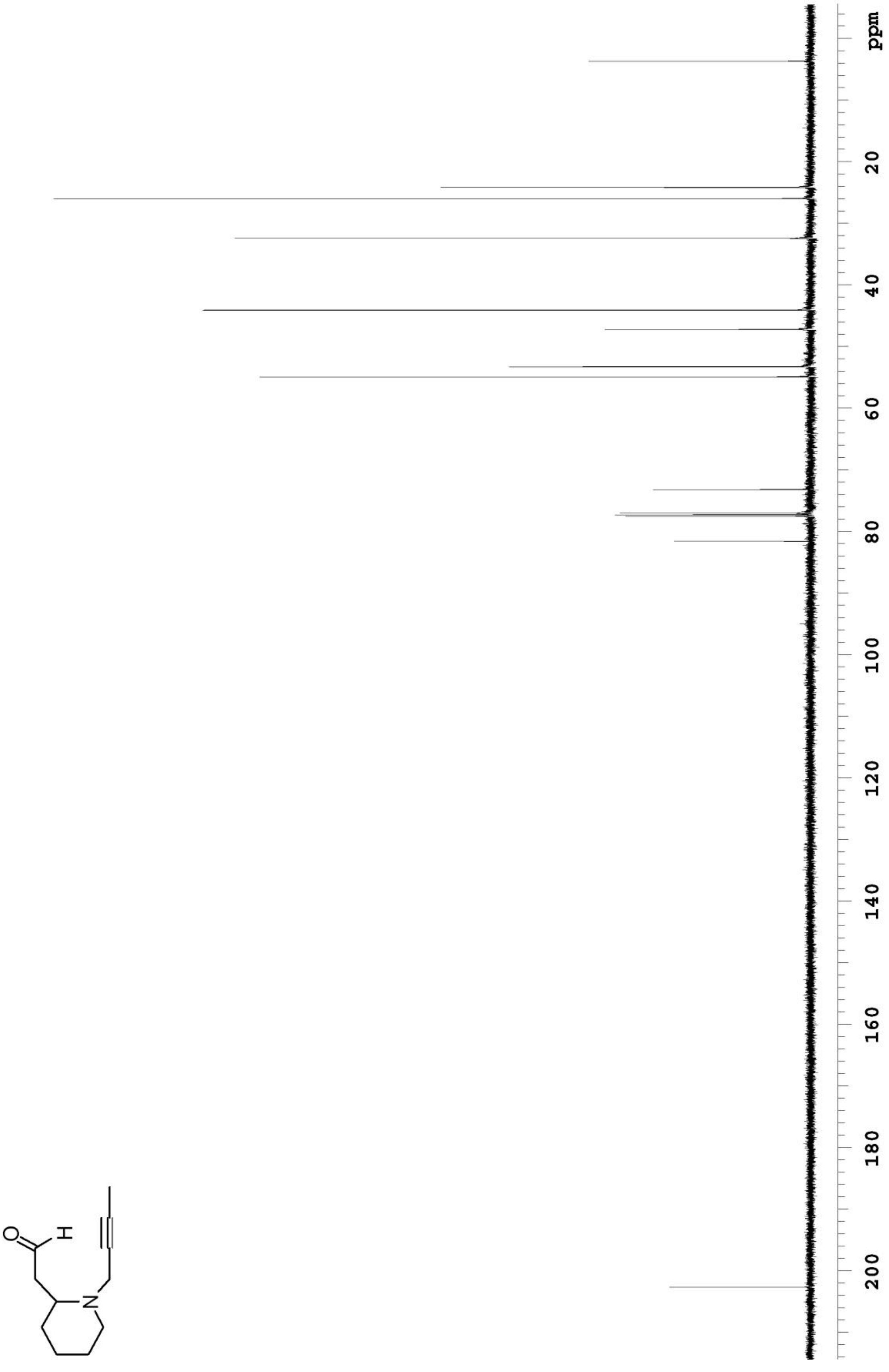
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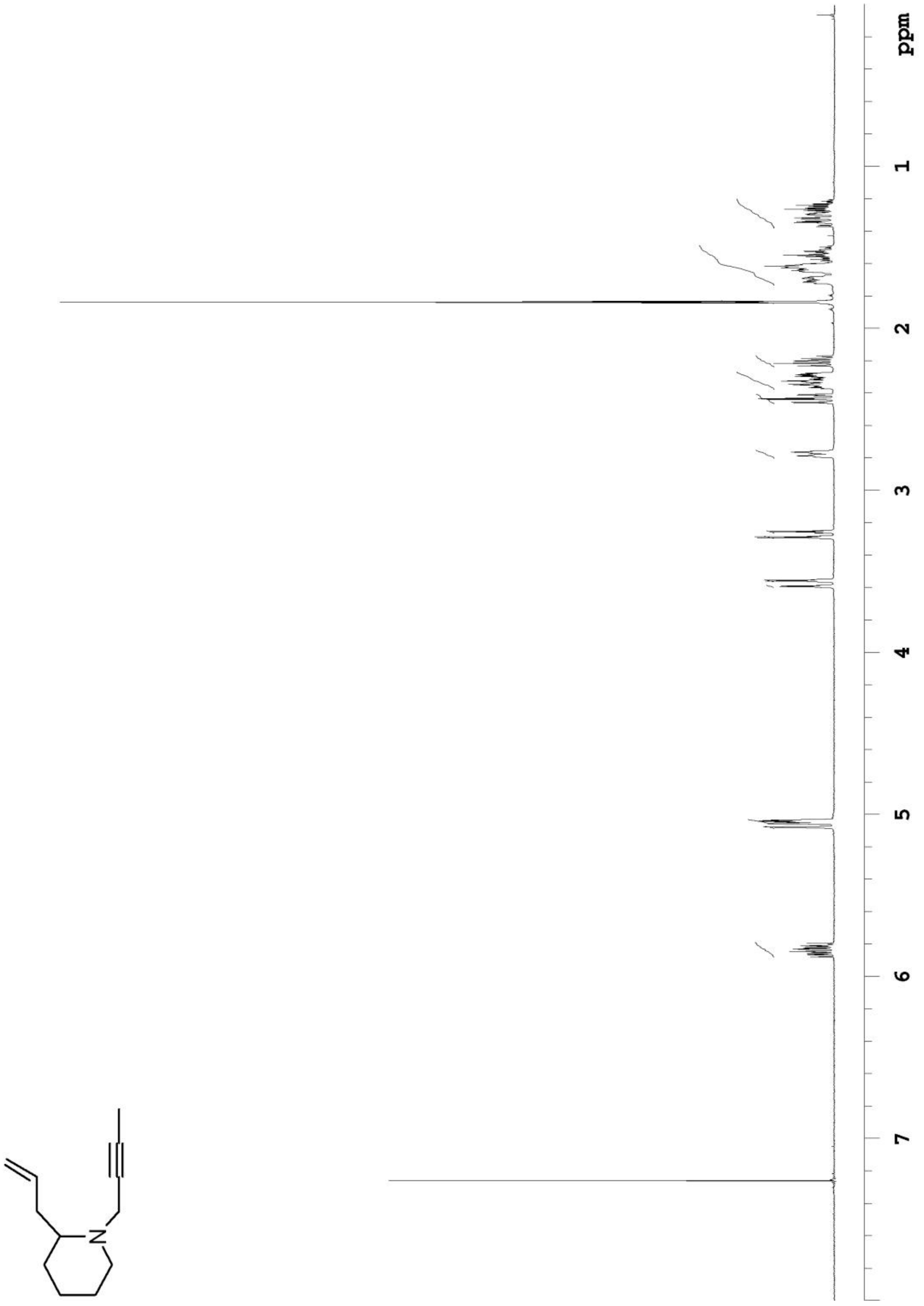
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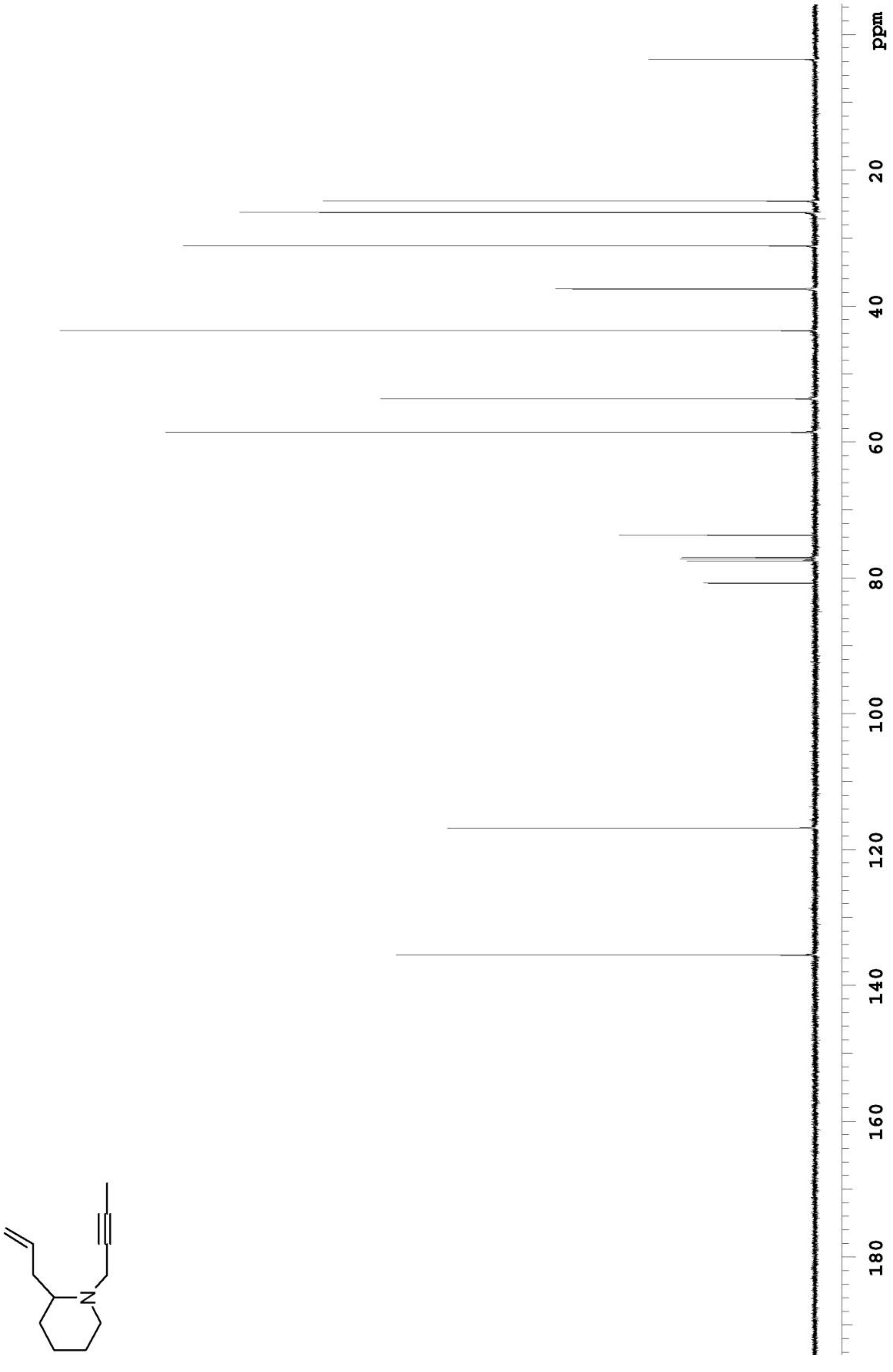
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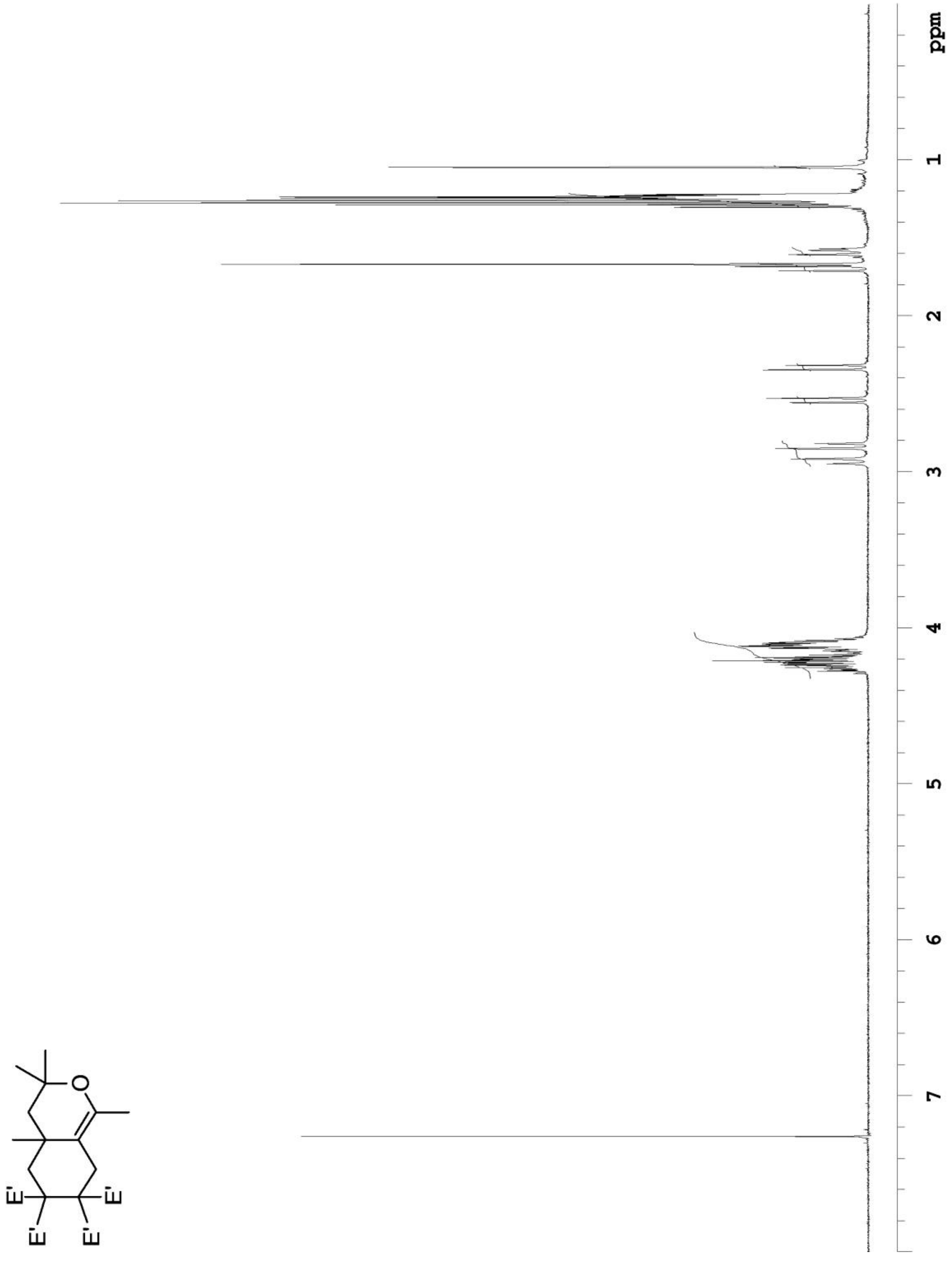
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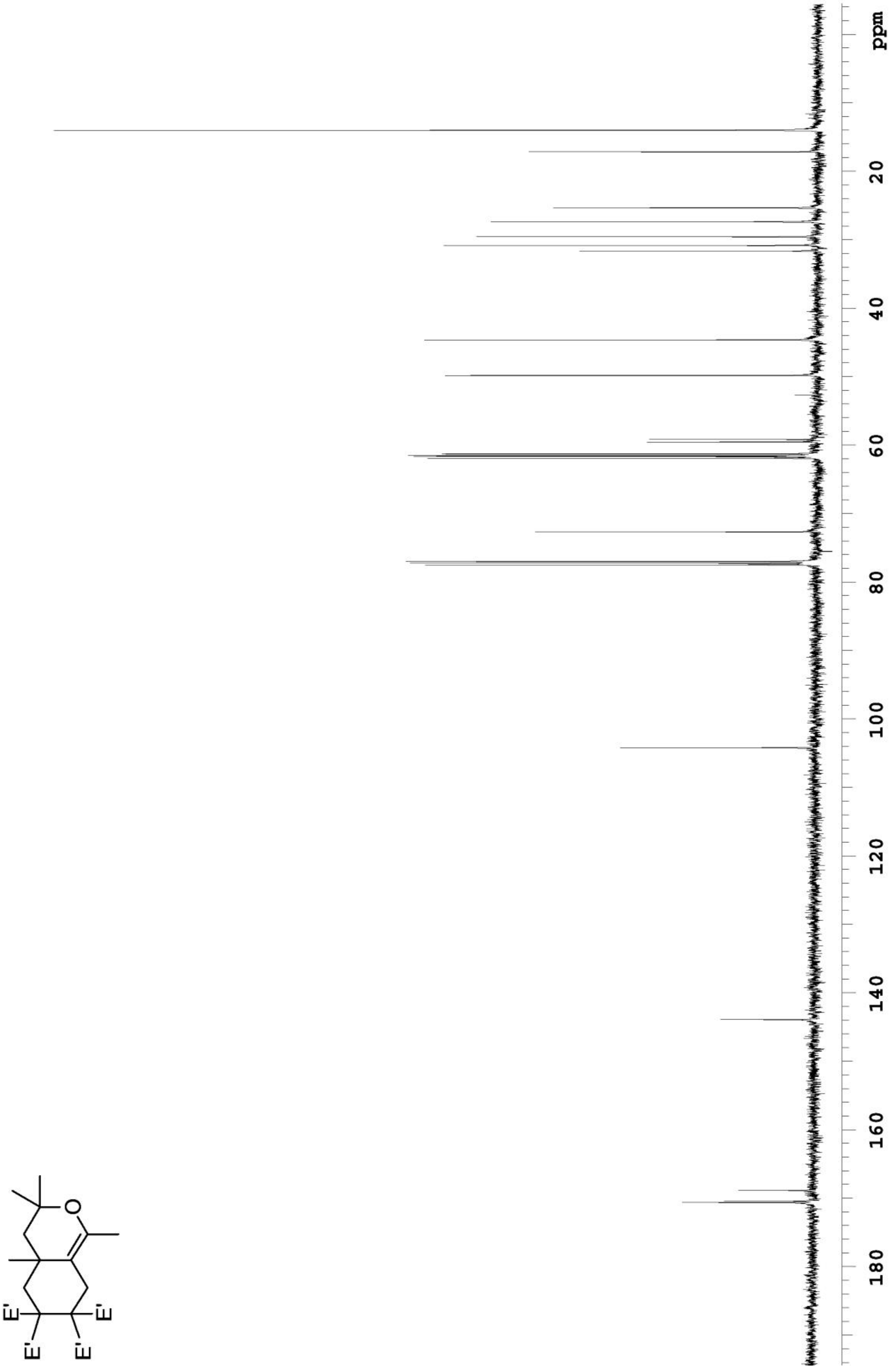
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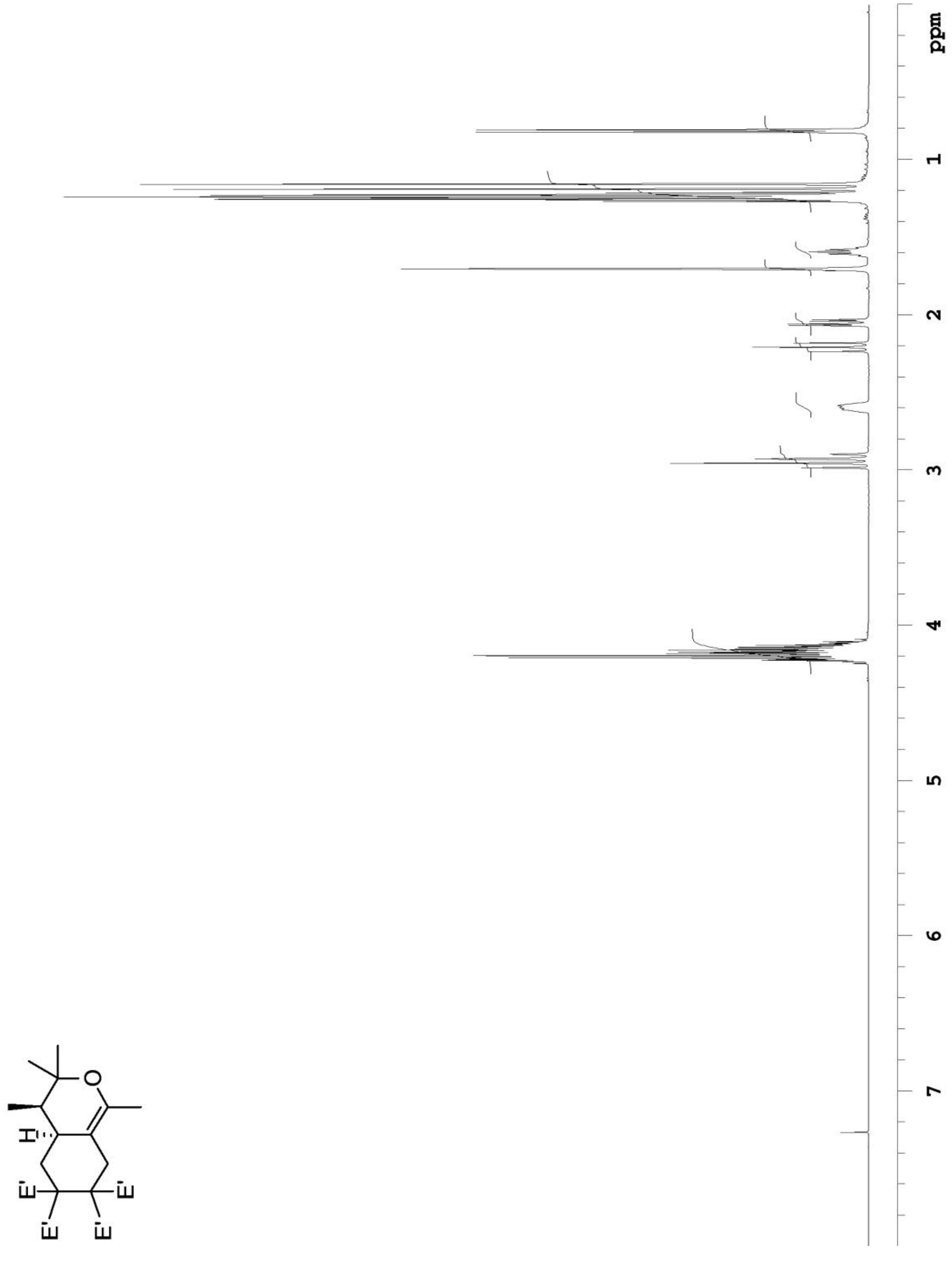
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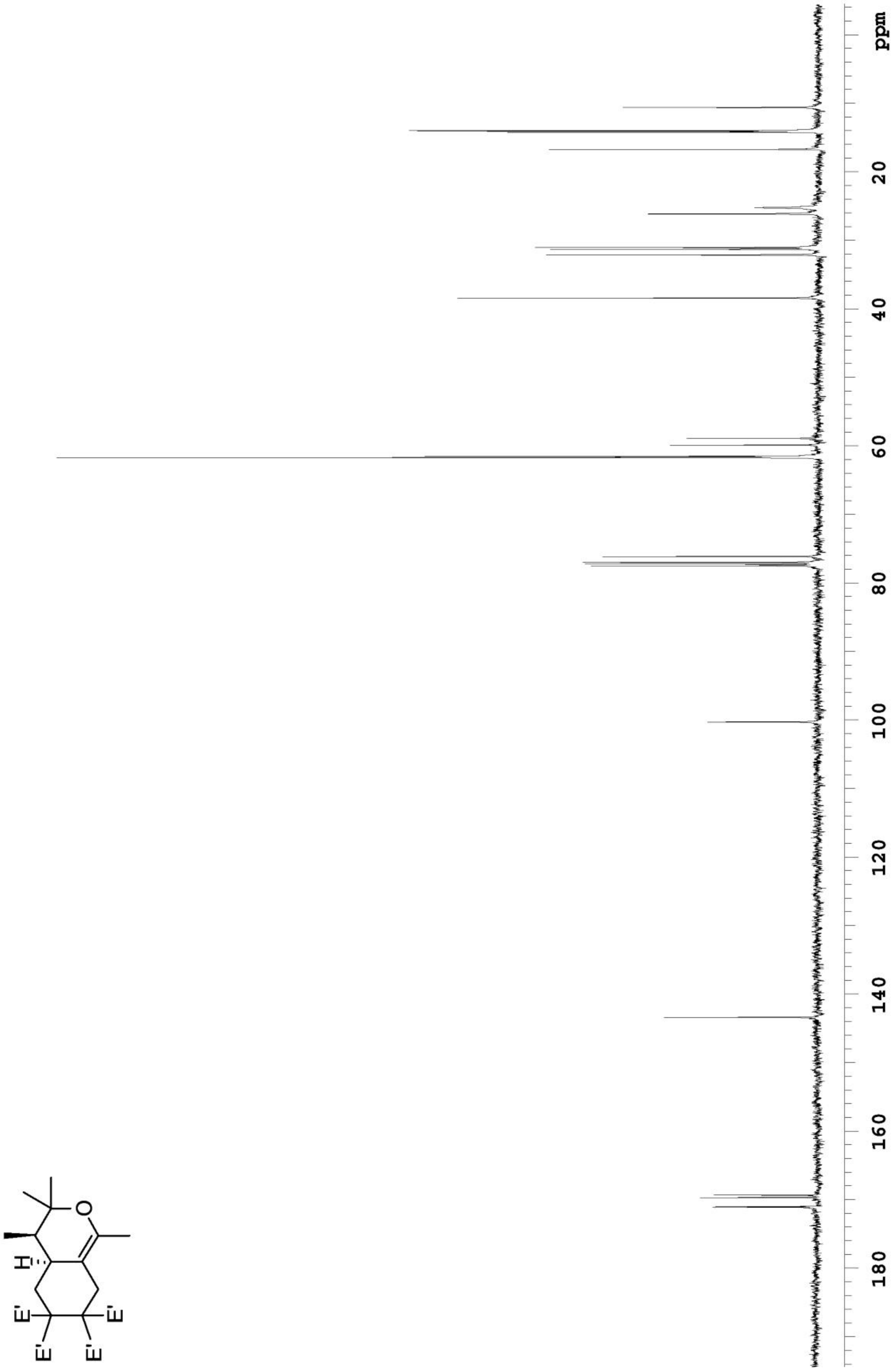
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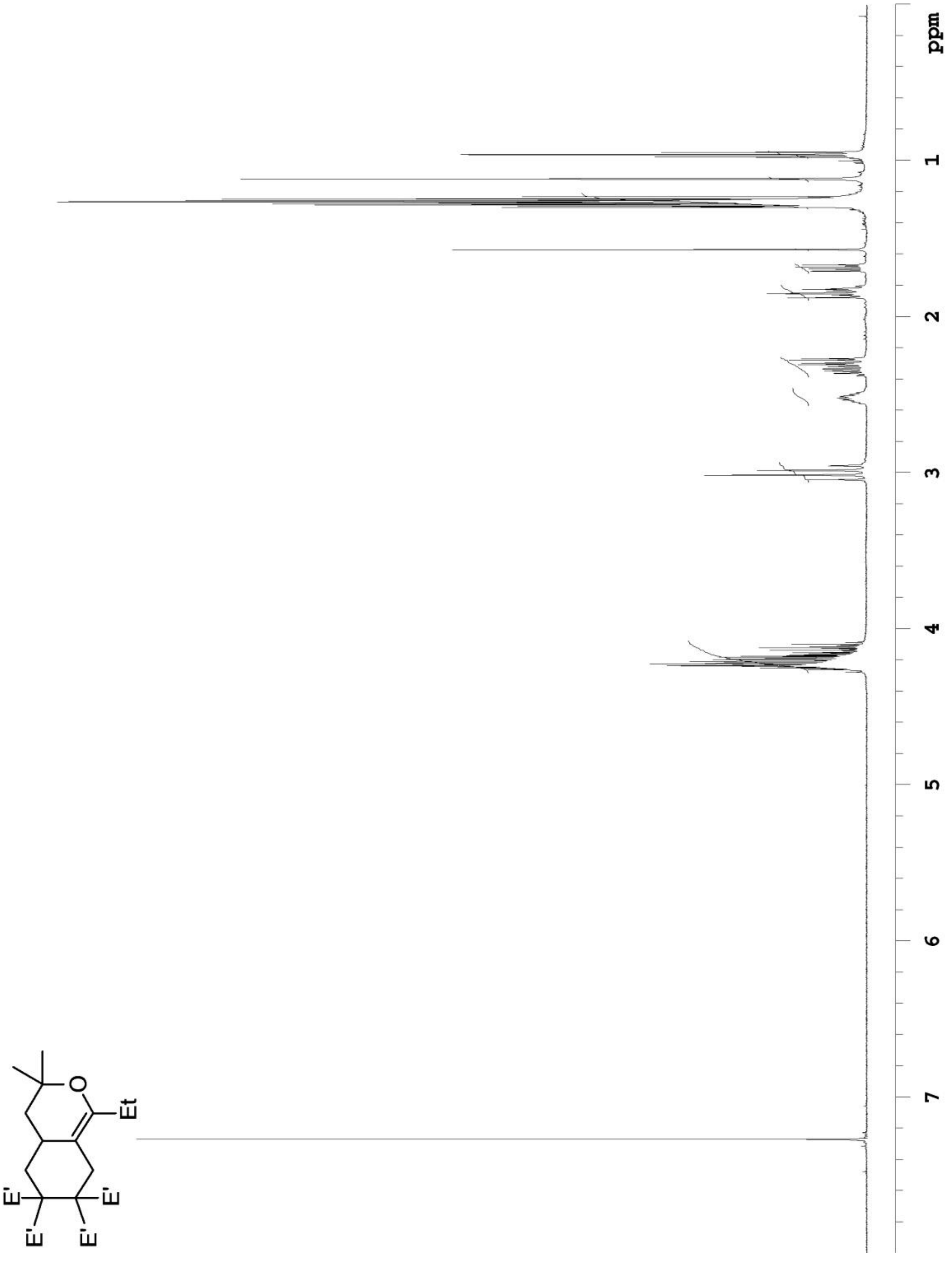
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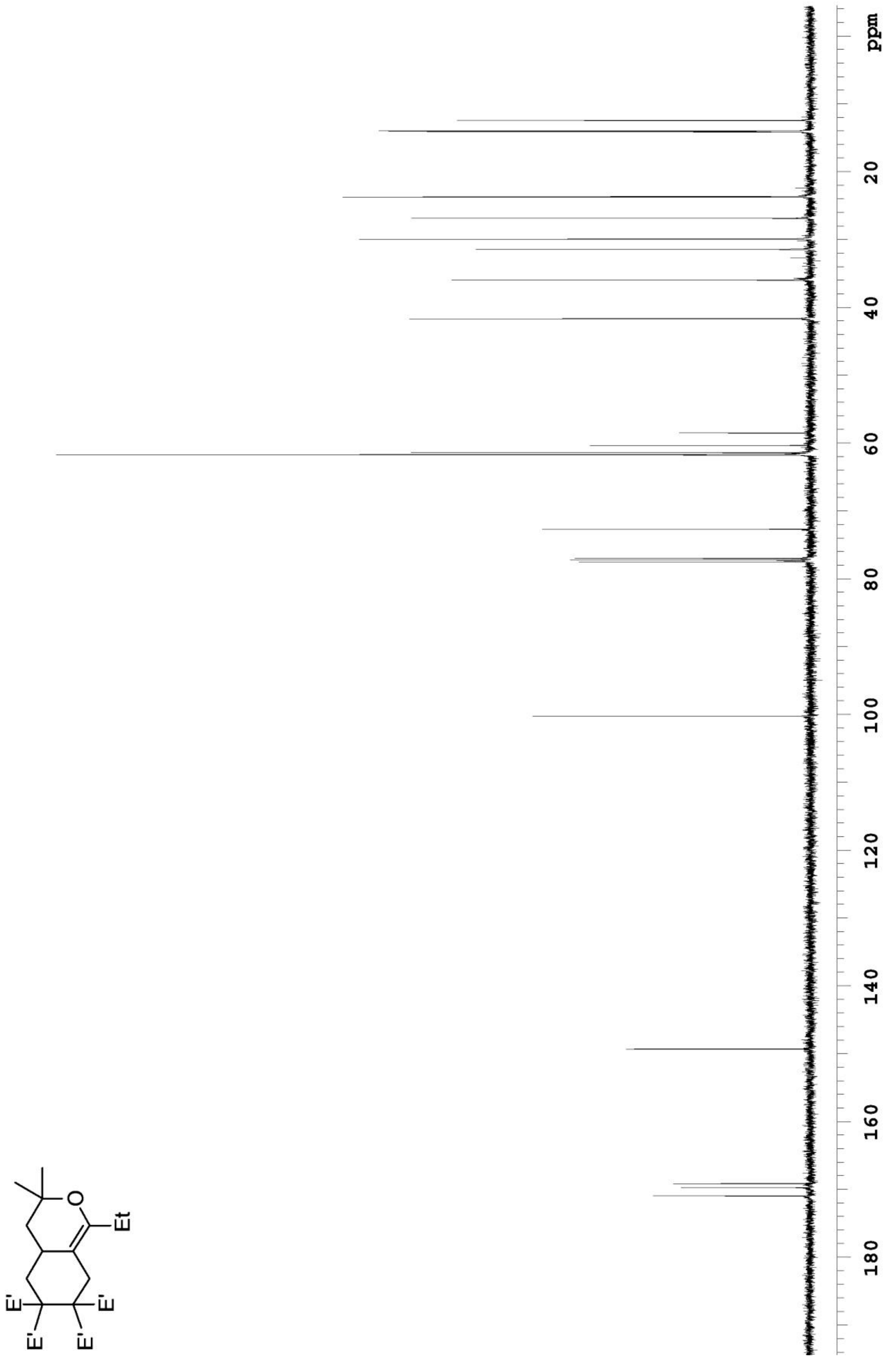
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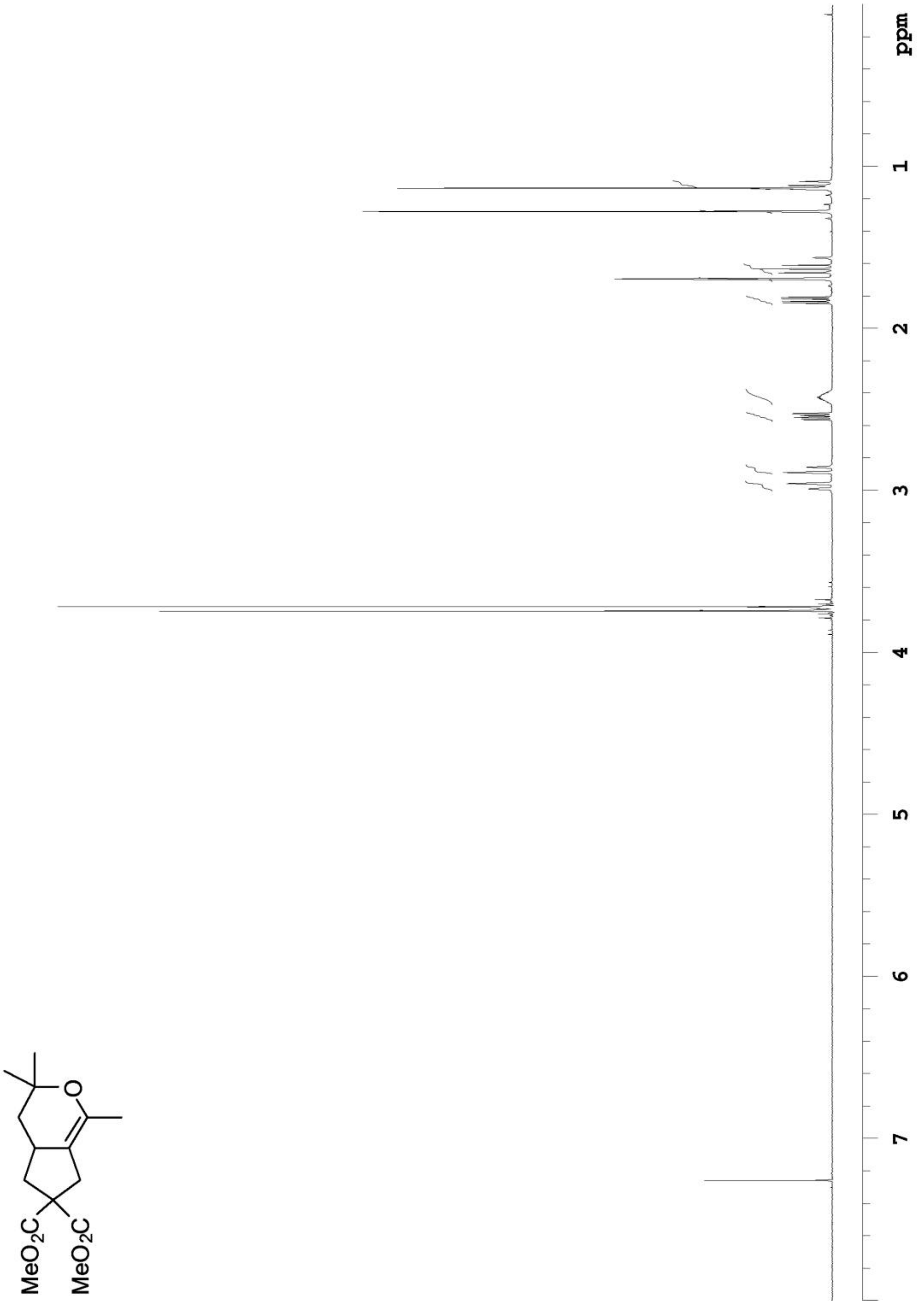

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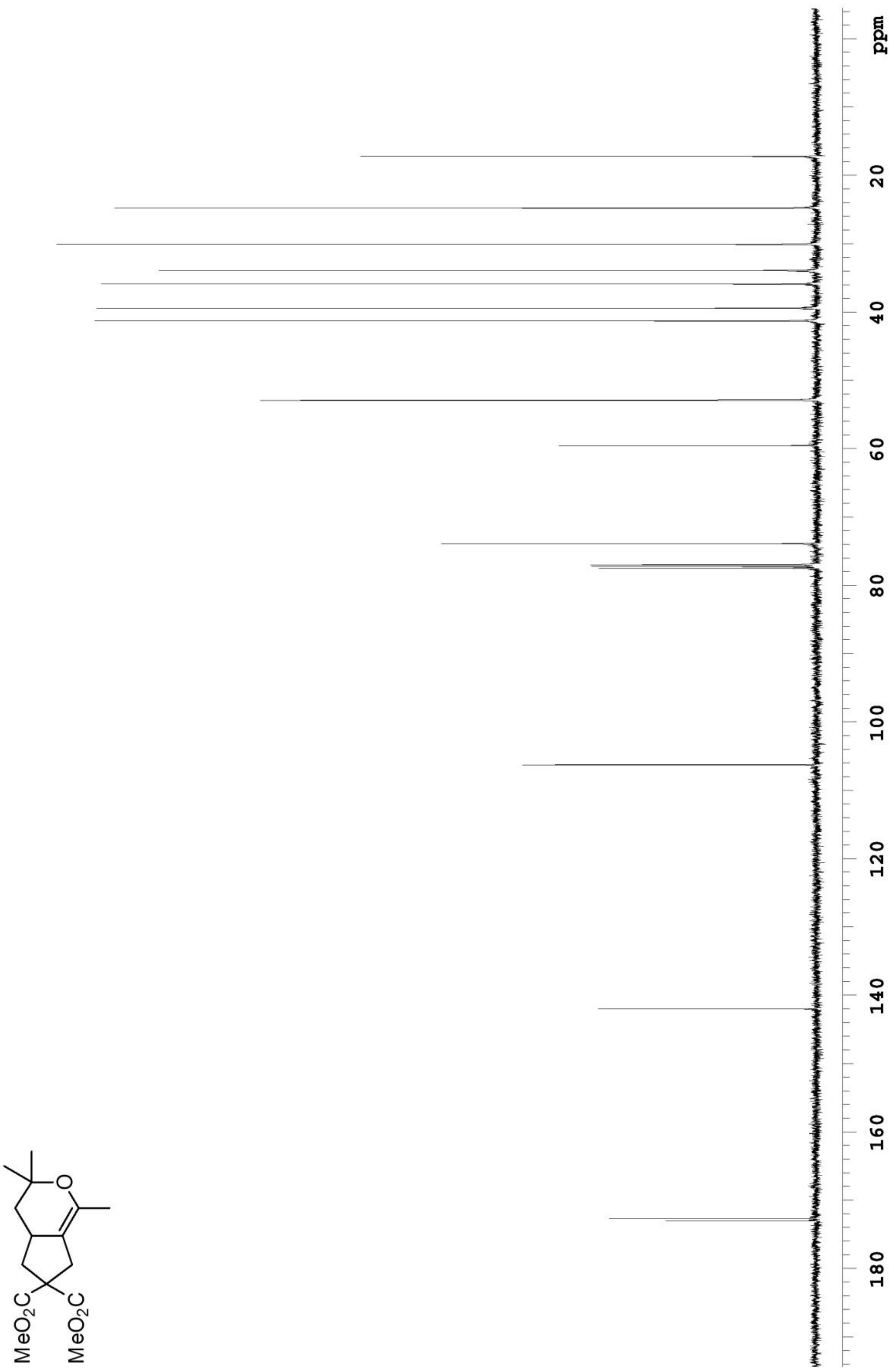
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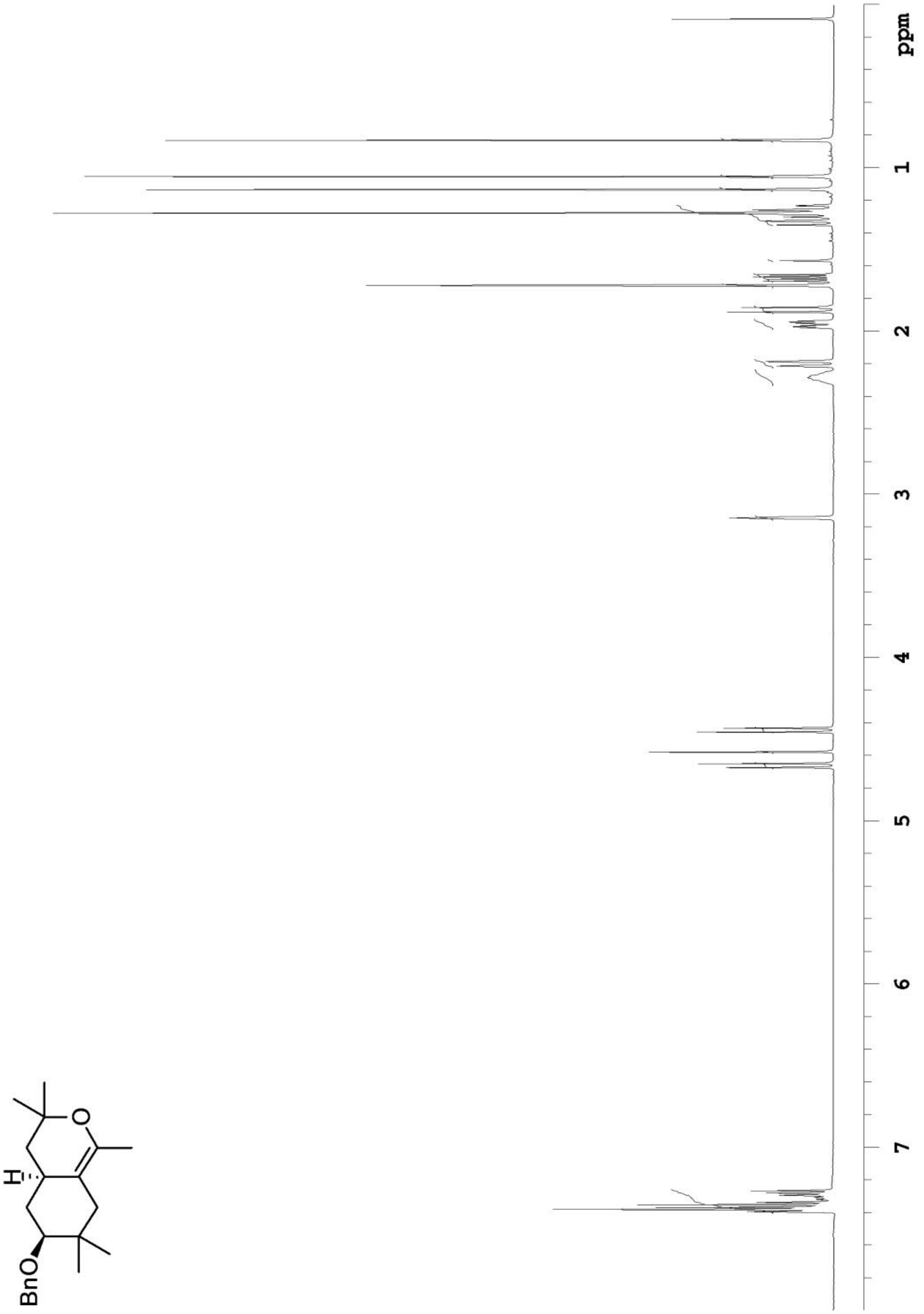
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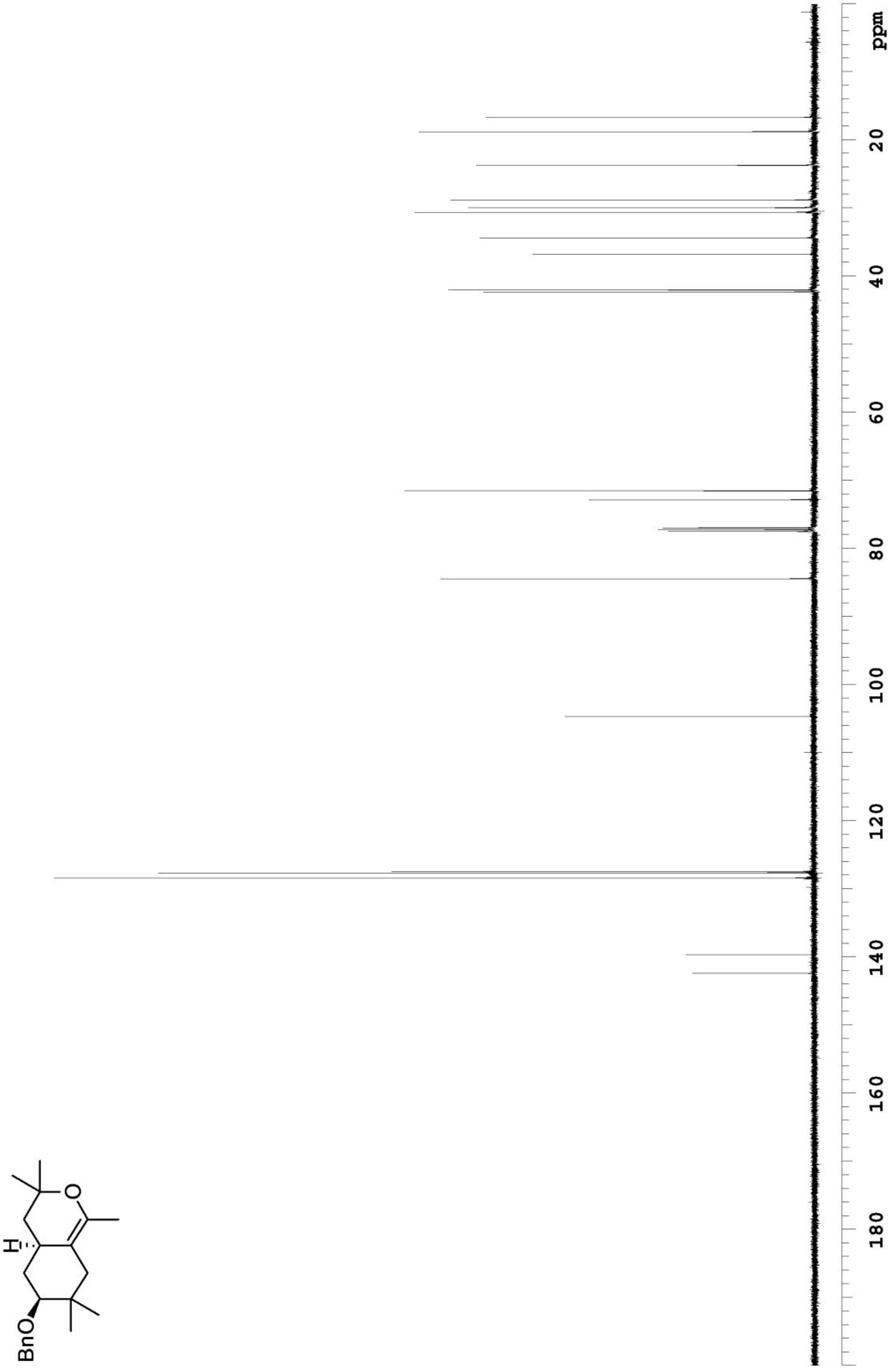
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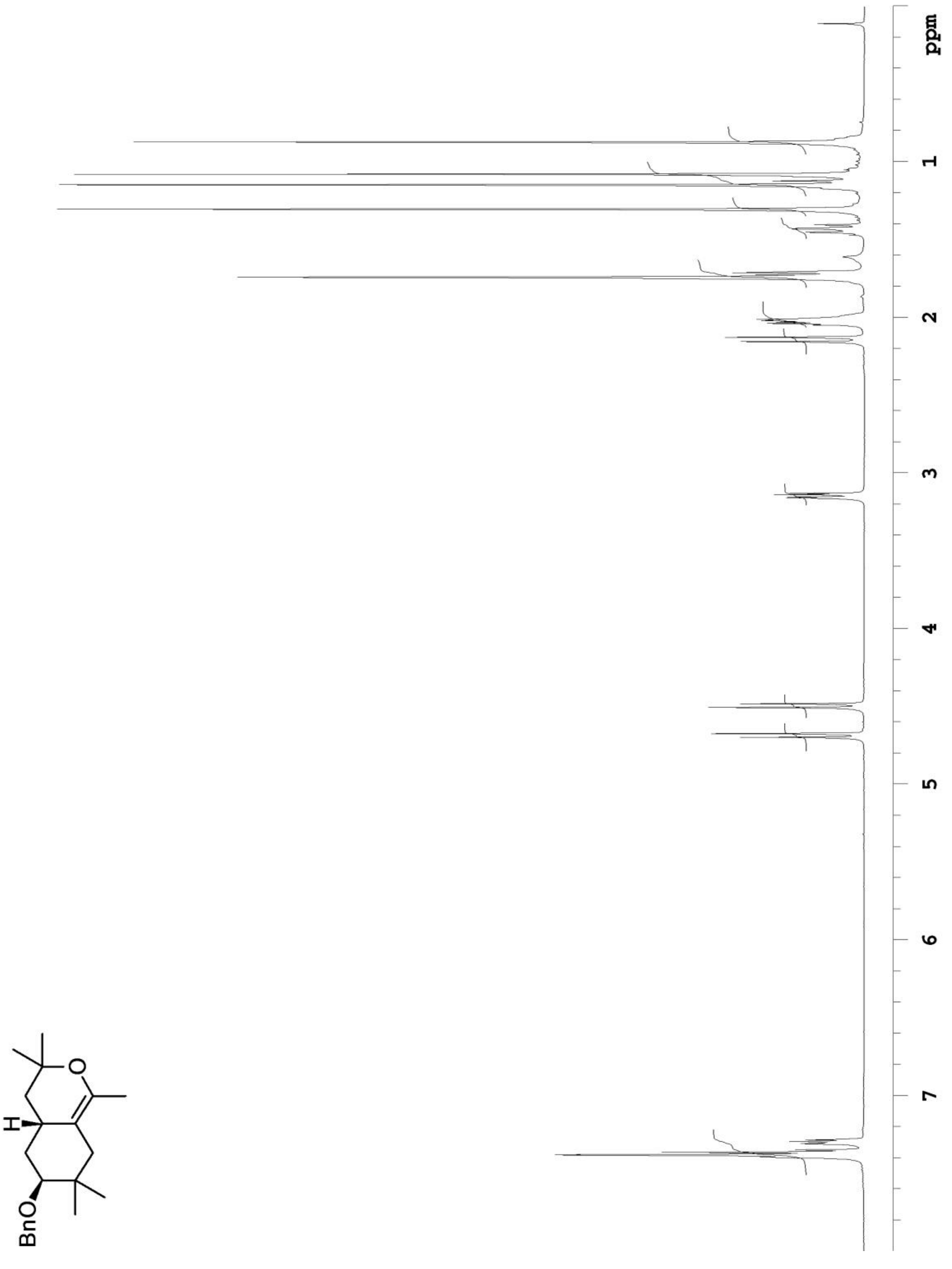
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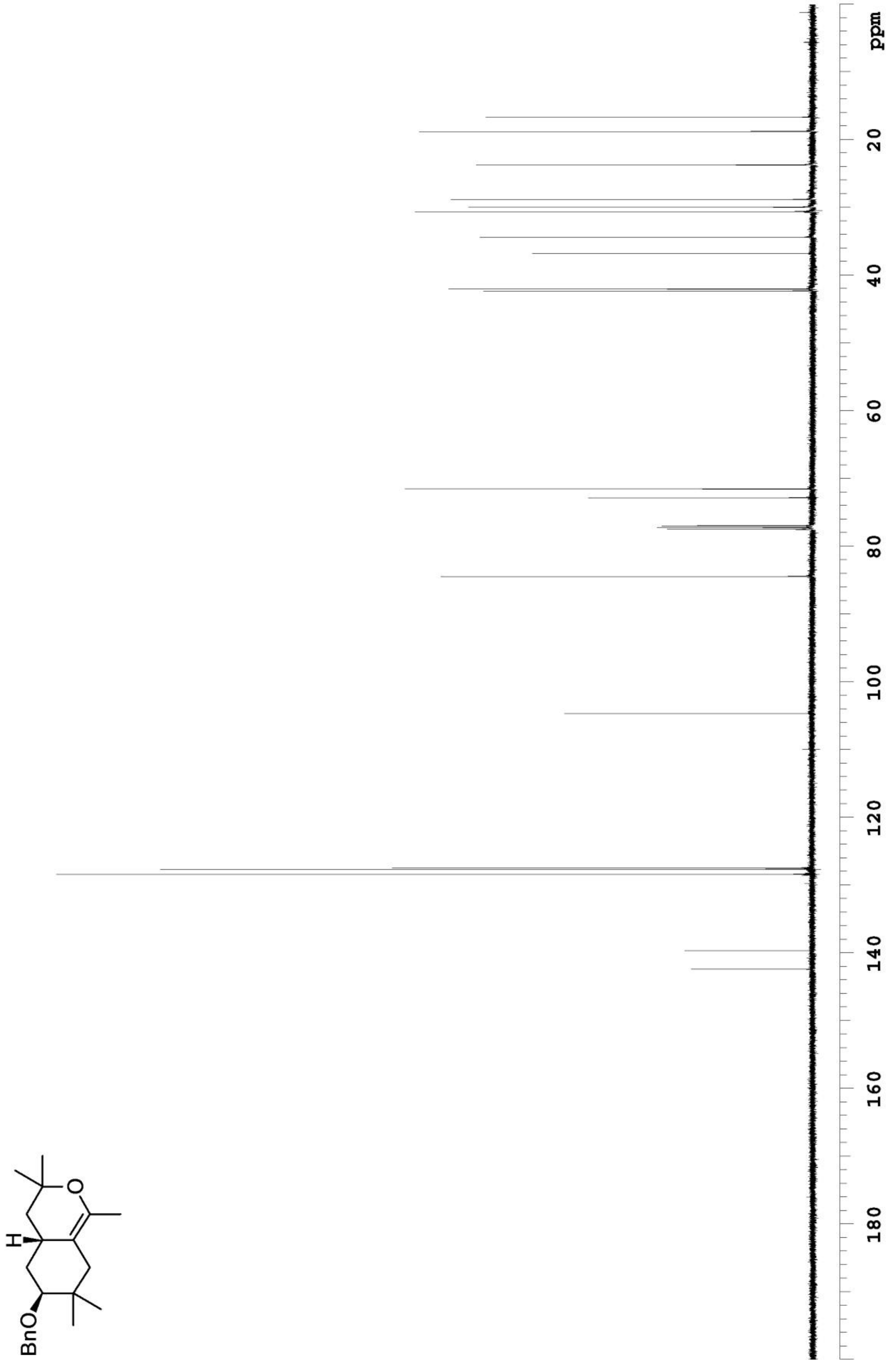
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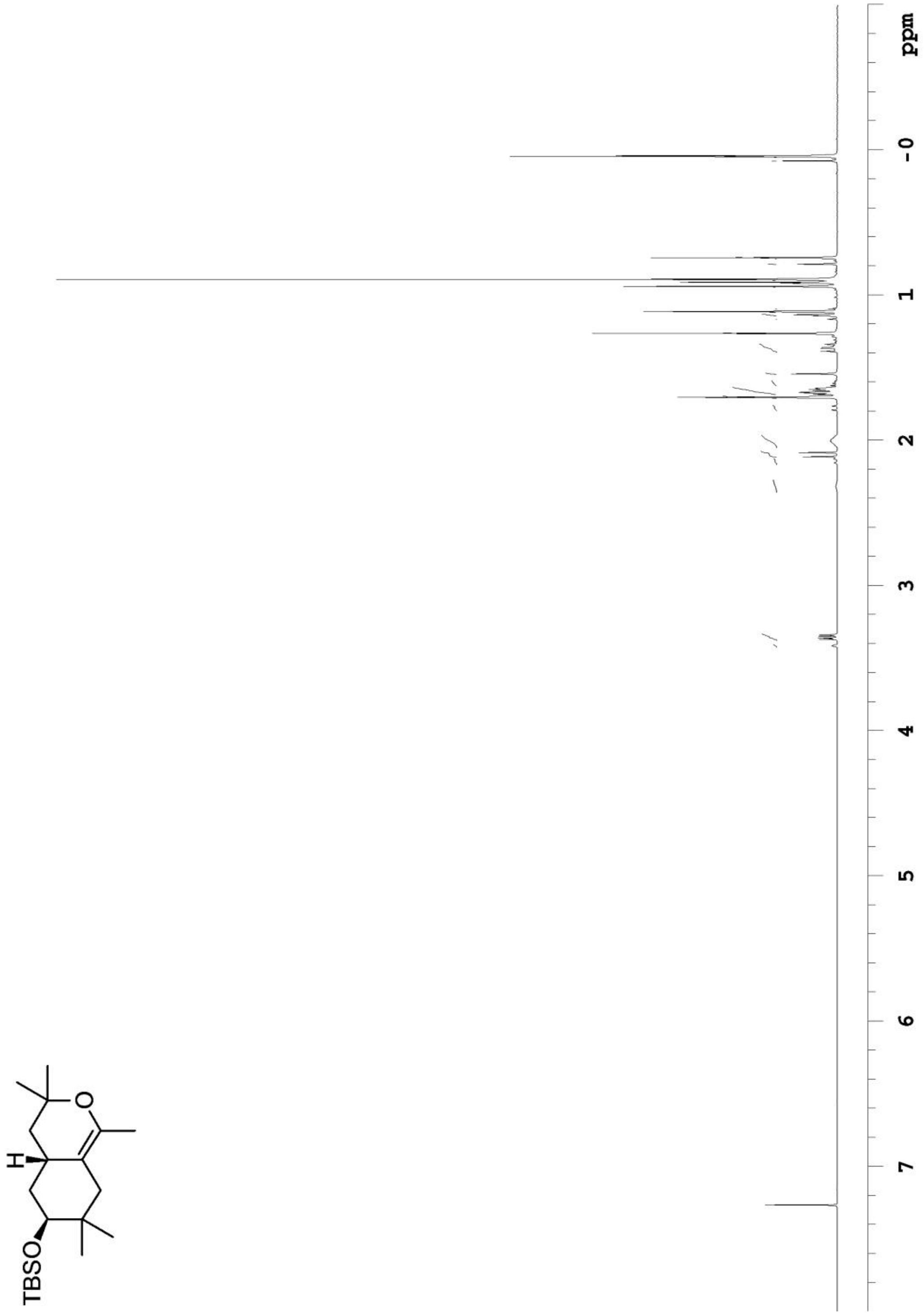
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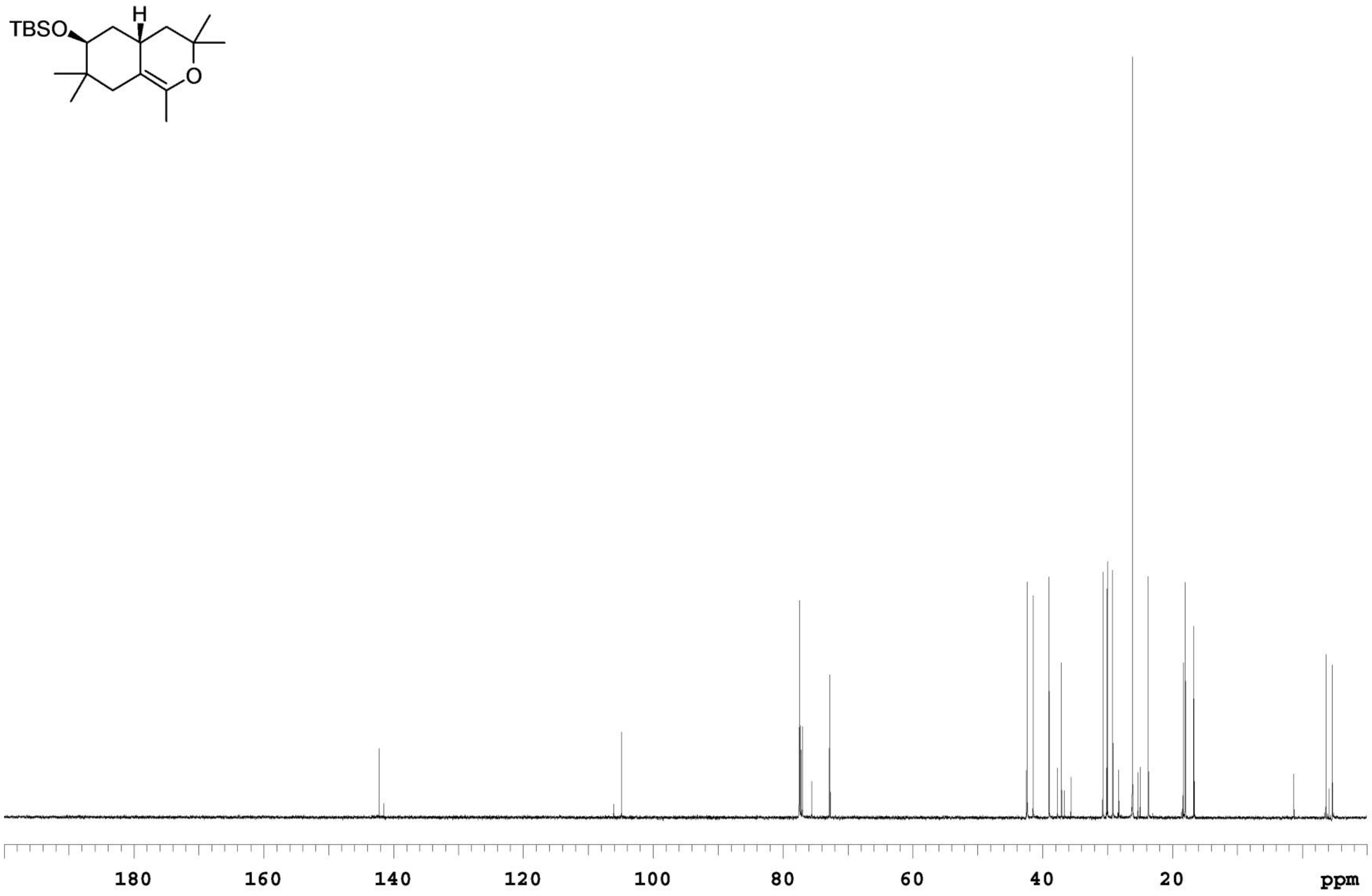
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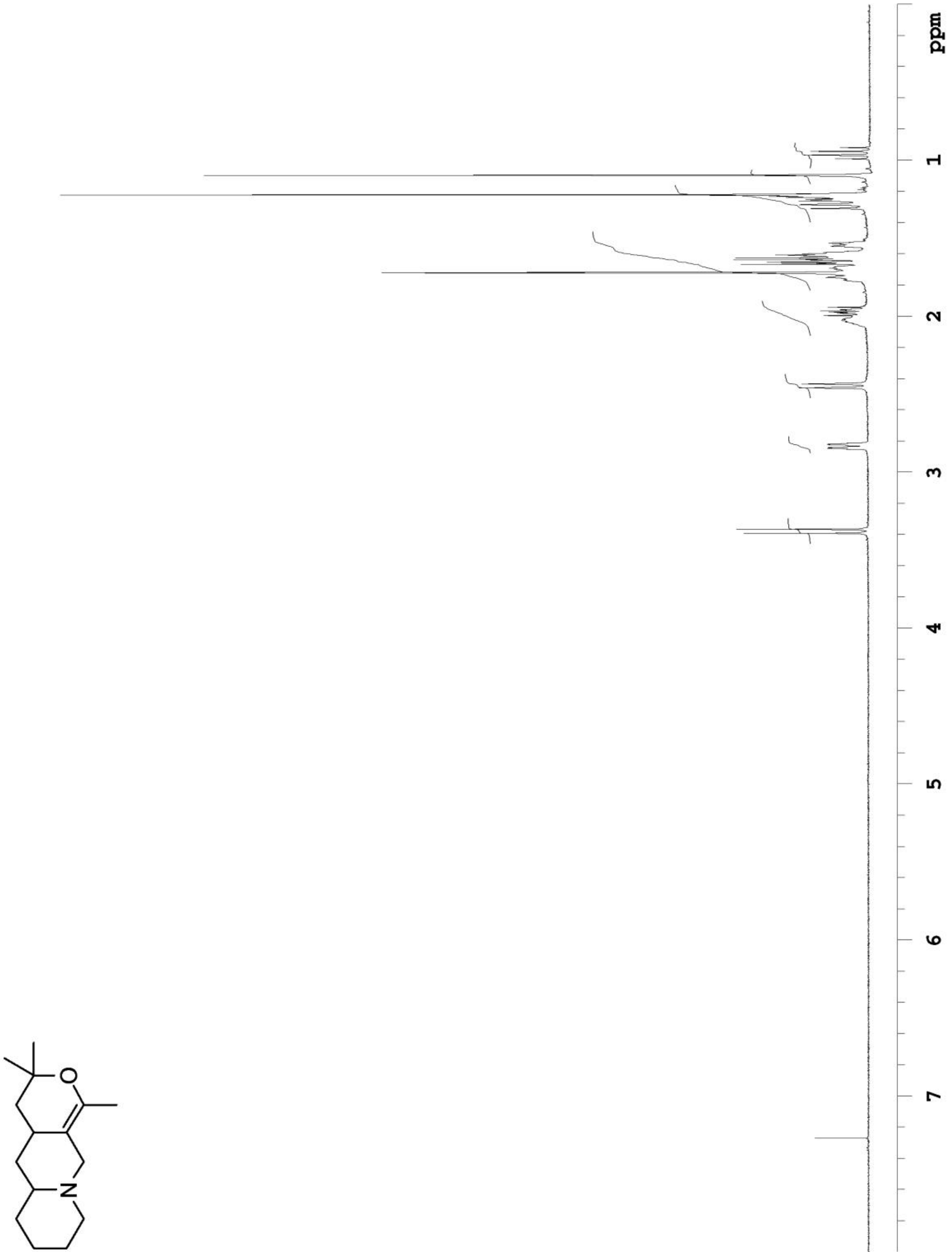
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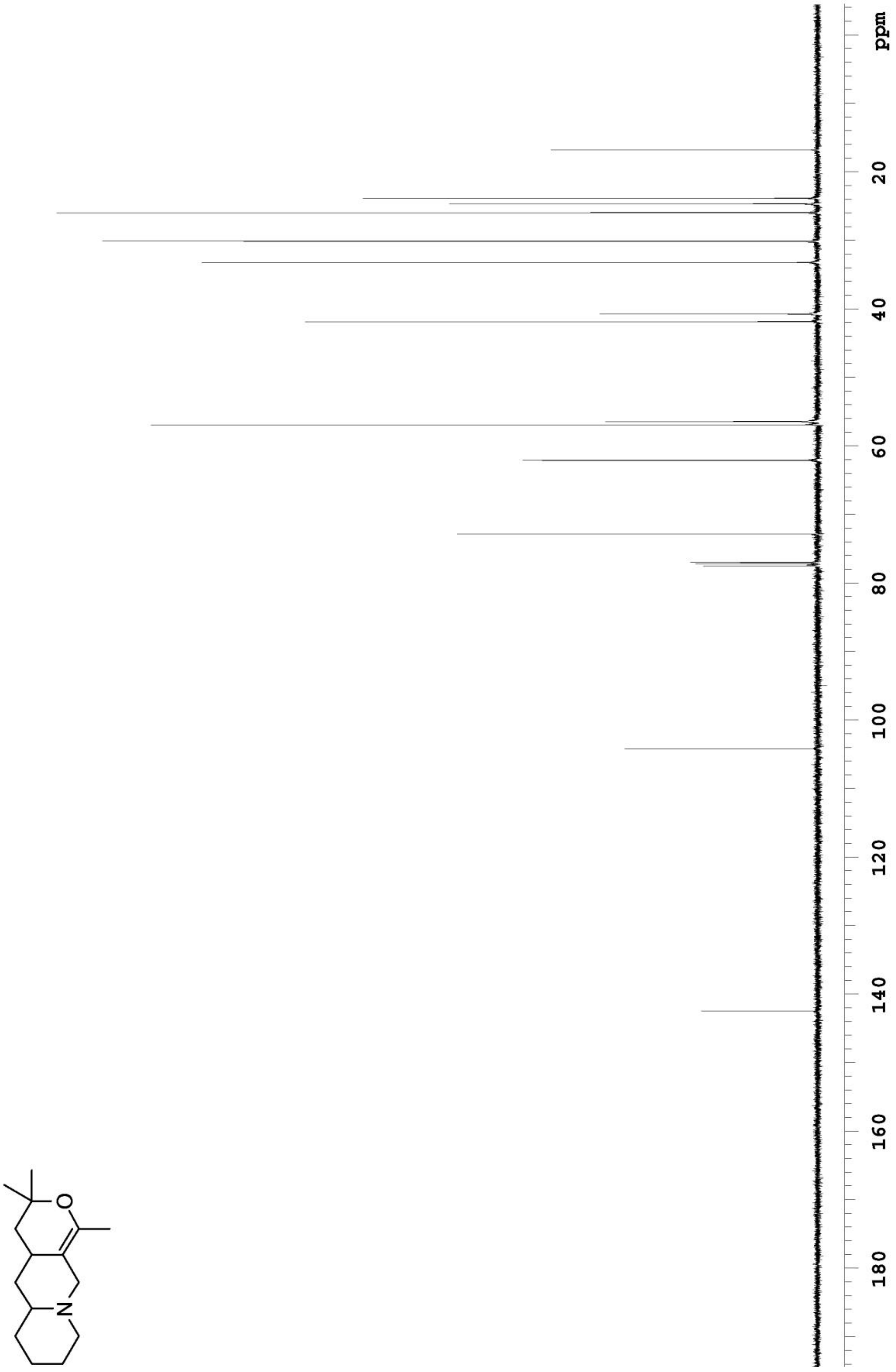
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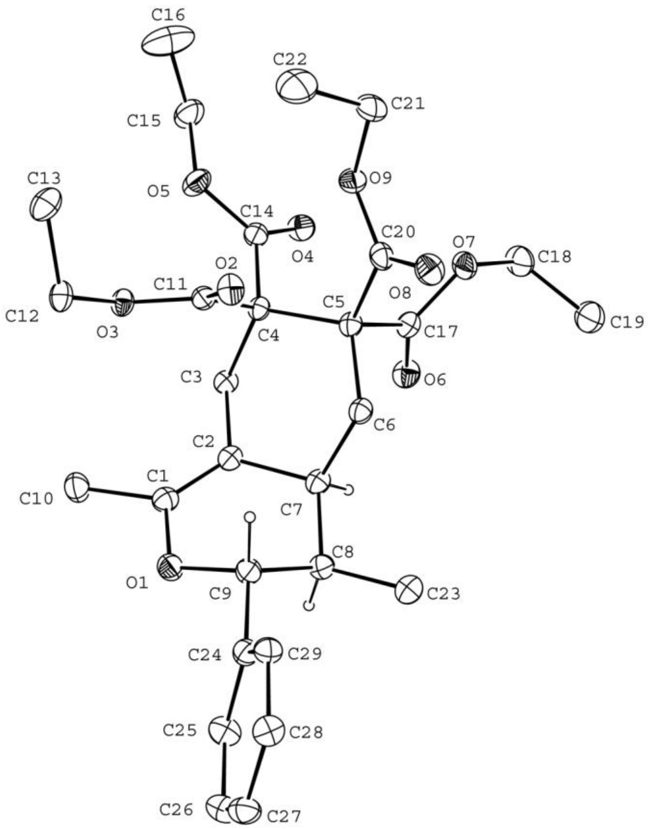
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C15
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O4
O2
C11
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C5
C12
O3
C4
C17
C19
C3
O6
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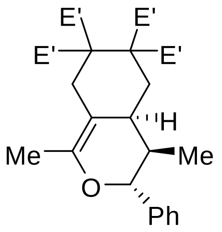
C29
C25
C28
C26
C27


E'
E'
E'
E'
H
Me
Me
O
Ph

3.79

Table B.1. Crystal data and structure refinement for jl010.

Identification code	jl010	
Empirical formula	C29 H38 O9	
Formula weight	530.59	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$\boldsymbol{P}\bar{1}$	
Unit cell dimensions	a = 9.4654(3) Å	α= 115.7718(17)°.
	b = 12.0269(5) Å	β= 93.782(3)°.
	c = 13.8261(5) Å	γ = 101.877(3)°.
Volume	1365.30(9) Å^3	
Z	2	
Density (calculated)	1.291 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	568	
Crystal size	0.30 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.54 to 27.48°.	
Index ranges	-12<=h<=12, -15<=k<=15, -17<=l<=17	
Reflections collected	11774	
Independent reflections	6205 [R(int) = 0.0269]	
Completeness to theta = 27.48°	99.3 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9812 and 0.9720	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6205 / 0 / 465	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.1533	
R indices (all data)	R1 = 0.0944, wR2 = 0.1708	
Largest diff. peak and hole	0.728 and -0.311 e.Å^{-3}	

Table B.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jl010. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7986(2)	8470(2)	8428(1)	32(1)
O(2)	5006(2)	4534(2)	5980(1)	31(1)
O(3)	3736(2)	5784(2)	7087(1)	27(1)
O(4)	3704(2)	3293(2)	8500(1)	34(1)
O(5)	2332(2)	3701(2)	7368(2)	39(1)
O(6)	6988(2)	4096(2)	9292(1)	35(1)
O(7)	6251(2)	2146(2)	7836(1)	35(1)
O(8)	6671(2)	2485(2)	5757(1)	38(1)
O(9)	4372(2)	2159(2)	6115(1)	32(1)
C(1)	6793(3)	7814(2)	8680(2)	29(1)
C(2)	6754(2)	6740(2)	8735(2)	26(1)
C(3)	5425(3)	5913(2)	8848(2)	24(1)
C(4)	4920(2)	4631(2)	7768(2)	23(1)
C(5)	6186(2)	3932(2)	7510(2)	25(1)
C(6)	7647(3)	4848(2)	7576(2)	27(1)
C(7)	8054(2)	6164(2)	8592(2)	26(1)
C(8)	9426(3)	7087(2)	8577(2)	30(1)
C(9)	8953(3)	7705(2)	7888(2)	29(1)
C(10)	5647(3)	8547(3)	8900(2)	37(1)
C(11)	4554(2)	4953(2)	6829(2)	25(1)
C(12)	3383(3)	6181(3)	6260(2)	31(1)
C(13)	2129(3)	5208(3)	5383(2)	41(1)
C(14)	3591(3)	3789(2)	7918(2)	27(1)
C(15)	1000(3)	2942(3)	7485(3)	47(1)
C(16)	30(4)	2220(5)	6416(3)	84(1)
C(17)	6498(3)	3428(2)	8337(2)	29(1)
C(18)	6514(3)	1559(3)	8537(3)	43(1)
C(19)	8106(4)	1580(3)	8724(3)	53(1)
C(20)	5789(3)	2788(2)	6352(2)	30(1)

Table B.2 continued.

	x	y	z	U(eq)
C(21)	3817(3)	1120(3)	5018(2)	42(1)
C(22)	3070(4)	1551(4)	4315(3)	62(1)
C(23)	10704(3)	6489(3)	8228(3)	38(1)
C(24)	10191(3)	8562(2)	7703(2)	29(1)
C(25)	10974(3)	9739(3)	8550(2)	35(1)
C(26)	12123(3)	10511(3)	8371(2)	38(1)
C(27)	12522(3)	10111(3)	7358(2)	36(1)
C(28)	11782(3)	8935(3)	6511(2)	33(1)
C(29)	10607(3)	8162(2)	6674(2)	31(1)

Table B.3. Bond lengths [Å] and angles [°] for jl010.

O(1)-C(1)	1.394(3)
O(1)-C(9)	1.443(3)
O(2)-C(11)	1.207(3)
O(3)-C(11)	1.331(3)
O(3)-C(12)	1.463(3)
O(4)-C(14)	1.203(3)
O(5)-C(14)	1.330(3)
O(5)-C(15)	1.460(3)
O(6)-C(17)	1.204(3)
O(7)-C(17)	1.347(3)
O(7)-C(18)	1.461(3)
O(8)-C(20)	1.209(3)
O(9)-C(20)	1.337(3)
O(9)-C(21)	1.454(3)
C(1)-C(2)	1.319(3)
C(1)-C(10)	1.500(3)
C(2)-C(3)	1.498(3)
C(2)-C(7)	1.516(3)
C(3)-C(4)	1.561(3)
C(3)-H(3A)	0.99(3)
C(3)-H(3B)	0.91(3)
C(4)-C(14)	1.530(3)
C(4)-C(11)	1.546(3)
C(4)-C(5)	1.575(3)
C(5)-C(20)	1.546(3)
C(5)-C(17)	1.546(3)
C(5)-C(6)	1.550(3)
C(6)-C(7)	1.540(3)
C(6)-H(6A)	0.99(3)
C(6)-H(6B)	1.01(3)
C(7)-C(8)	1.534(3)
C(7)-H(7)	0.97(3)
C(8)-C(23)	1.532(4)

Table B.3 continued.

C(8)-C(9)	1.534(3)
C(8)-H(8)	1.04(3)
C(9)-C(24)	1.508(3)
C(9)-H(9)	1.05(3)
C(10)-H(10A)	1.04(3)
C(10)-H(10B)	1.08(4)
C(10)-H(10C)	1.00(4)
C(12)-C(13)	1.501(4)
C(12)-H(12A)	0.93(3)
C(12)-H(12B)	0.93(3)
C(13)-H(13A)	0.91(3)
C(13)-H(13B)	1.03(3)
C(13)-H(13C)	0.96(4)
C(15)-C(16)	1.470(5)
C(15)-H(15A)	0.96(4)
C(15)-H(15B)	0.98(4)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(18)-C(19)	1.506(4)
C(18)-H(18A)	1.11(3)
C(18)-H(18B)	0.98(3)
C(19)-H(19A)	1.08(4)
C(19)-H(19B)	1.03(4)
C(19)-H(19C)	1.06(4)
C(21)-C(22)	1.487(4)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	1.04(3)
C(23)-H(23B)	1.03(3)

Table B.3 continued.

C(23)-H(23C)	1.04(3)
C(24)-C(25)	1.392(4)
C(24)-C(29)	1.403(3)
C(25)-C(26)	1.388(4)
C(25)-H(25)	1.00(3)
C(26)-C(27)	1.375(4)
C(26)-H(26)	1.01(3)
C(27)-C(28)	1.381(4)
C(27)-H(27)	0.87(3)
C(28)-C(29)	1.394(4)
C(28)-H(28)	0.93(3)
C(29)-H(29)	0.98(3)
C(1)-O(1)-C(9)	114.23(18)
C(11)-O(3)-C(12)	115.72(18)
C(14)-O(5)-C(15)	117.0(2)
C(17)-O(7)-C(18)	116.2(2)
C(20)-O(9)-C(21)	117.5(2)
C(2)-C(1)-O(1)	123.3(2)
C(2)-C(1)-C(10)	127.6(2)
O(1)-C(1)-C(10)	109.0(2)
C(1)-C(2)-C(3)	124.8(2)
C(1)-C(2)-C(7)	122.1(2)
C(3)-C(2)-C(7)	112.9(2)
C(2)-C(3)-C(4)	108.57(18)
C(2)-C(3)-H(3A)	115.3(16)
C(4)-C(3)-H(3A)	107.1(16)
C(2)-C(3)-H(3B)	108.6(19)
C(4)-C(3)-H(3B)	108.6(19)
H(3A)-C(3)-H(3B)	108(2)
C(14)-C(4)-C(11)	112.54(18)
C(14)-C(4)-C(3)	107.51(17)
C(11)-C(4)-C(3)	107.88(18)
C(14)-C(4)-C(5)	110.03(18)

Table B.3 continued.

C(11)-C(4)-C(5)	108.02(17)
C(3)-C(4)-C(5)	110.87(18)
C(20)-C(5)-C(17)	108.24(19)
C(20)-C(5)-C(6)	107.86(18)
C(17)-C(5)-C(6)	106.46(18)
C(20)-C(5)-C(4)	110.96(18)
C(17)-C(5)-C(4)	111.58(18)
C(6)-C(5)-C(4)	111.54(18)
C(7)-C(6)-C(5)	114.76(19)
C(7)-C(6)-H(6A)	109.0(15)
C(5)-C(6)-H(6A)	108.1(15)
C(7)-C(6)-H(6B)	109.0(16)
C(5)-C(6)-H(6B)	110.1(16)
H(6A)-C(6)-H(6B)	106(2)
C(2)-C(7)-C(8)	111.3(2)
C(2)-C(7)-C(6)	109.94(19)
C(8)-C(7)-C(6)	113.27(19)
C(2)-C(7)-H(7)	109.2(16)
C(8)-C(7)-H(7)	104.8(16)
C(6)-C(7)-H(7)	108.2(16)
C(23)-C(8)-C(7)	114.3(2)
C(23)-C(8)-C(9)	113.8(2)
C(7)-C(8)-C(9)	107.69(19)
C(23)-C(8)-H(8)	109.6(16)
C(7)-C(8)-H(8)	100.7(16)
C(9)-C(8)-H(8)	109.9(16)
O(1)-C(9)-C(24)	107.33(19)
O(1)-C(9)-C(8)	108.76(19)
C(24)-C(9)-C(8)	115.0(2)
O(1)-C(9)-H(9)	106.8(14)
C(24)-C(9)-H(9)	108.5(14)
C(8)-C(9)-H(9)	110.1(14)
C(1)-C(10)-H(10A)	113.4(17)

Table B.3 continued.

C(1)-C(10)-H(10B)	111.1(19)
H(10A)-C(10)-H(10B)	107(2)
C(1)-C(10)-H(10C)	109(2)
H(10A)-C(10)-H(10C)	106(3)
H(10B)-C(10)-H(10C)	111(3)
O(2)-C(11)-O(3)	124.3(2)
O(2)-C(11)-C(4)	123.7(2)
O(3)-C(11)-C(4)	112.01(18)
O(3)-C(12)-C(13)	111.7(2)
O(3)-C(12)-H(12A)	109.3(17)
C(13)-C(12)-H(12A)	111.5(17)
O(3)-C(12)-H(12B)	104.8(16)
C(13)-C(12)-H(12B)	110.5(17)
H(12A)-C(12)-H(12B)	109(2)
C(12)-C(13)-H(13A)	111(2)
C(12)-C(13)-H(13B)	113.8(18)
H(13A)-C(13)-H(13B)	105(3)
C(12)-C(13)-H(13C)	106(2)
H(13A)-C(13)-H(13C)	112(3)
H(13B)-C(13)-H(13C)	109(3)
O(4)-C(14)-O(5)	124.7(2)
O(4)-C(14)-C(4)	122.1(2)
O(5)-C(14)-C(4)	113.20(19)
O(5)-C(15)-C(16)	108.3(3)
O(5)-C(15)-H(15A)	111(2)
C(16)-C(15)-H(15A)	107(2)
O(5)-C(15)-H(15B)	102(2)
C(16)-C(15)-H(15B)	120(2)
H(15A)-C(15)-H(15B)	108(3)
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5

Table B.3 continued.

H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
O(6)-C(17)-O(7)	124.0(2)
O(6)-C(17)-C(5)	124.6(2)
O(7)-C(17)-C(5)	111.22(19)
O(7)-C(18)-C(19)	111.1(3)
O(7)-C(18)-H(18A)	106.8(15)
C(19)-C(18)-H(18A)	101.4(15)
O(7)-C(18)-H(18B)	108.6(18)
C(19)-C(18)-H(18B)	110.6(18)
H(18A)-C(18)-H(18B)	118(2)
C(18)-C(19)-H(19A)	113(2)
C(18)-C(19)-H(19B)	112(2)
H(19A)-C(19)-H(19B)	102(3)
C(18)-C(19)-H(19C)	107(2)
H(19A)-C(19)-H(19C)	108(3)
H(19B)-C(19)-H(19C)	115(3)
O(8)-C(20)-O(9)	124.8(2)
O(8)-C(20)-C(5)	123.6(2)
O(9)-C(20)-C(5)	111.56(19)
O(9)-C(21)-C(22)	111.2(2)
O(9)-C(21)-H(21A)	109.4
C(22)-C(21)-H(21A)	109.4
O(9)-C(21)-H(21B)	109.4
C(22)-C(21)-H(21B)	109.4
H(21A)-C(21)-H(21B)	108.0
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(8)-C(23)-H(23A)	109.1(18)

Table B.3 continued.

C(8)-C(23)-H(23B)	104.3(17)
H(23A)-C(23)-H(23B)	116(2)
C(8)-C(23)-H(23C)	108.5(16)
H(23A)-C(23)-H(23C)	112(2)
H(23B)-C(23)-H(23C)	107(2)
C(25)-C(24)-C(29)	118.7(2)
C(25)-C(24)-C(9)	121.1(2)
C(29)-C(24)-C(9)	120.2(2)
C(26)-C(25)-C(24)	120.5(2)
C(26)-C(25)-H(25)	121.3(17)
C(24)-C(25)-H(25)	118.0(17)
C(27)-C(26)-C(25)	120.4(3)
C(27)-C(26)-H(26)	121.4(18)
C(25)-C(26)-H(26)	117.9(18)
C(26)-C(27)-C(28)	120.2(3)
C(26)-C(27)-H(27)	119(2)
C(28)-C(27)-H(27)	121(2)
C(27)-C(28)-C(29)	119.9(2)
C(27)-C(28)-H(28)	122(2)
C(29)-C(28)-H(28)	118(2)
C(28)-C(29)-C(24)	120.2(2)
C(28)-C(29)-H(29)	118.8(18)
C(24)-C(29)-H(29)	120.9(18)

Symmetry transformations used to generate equivalent atoms:

Table B.4. Anisotropic displacement parameters (Å^{2}x 10^3)for jl010. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[$h^2a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	32(1)	29(1)	37(1)	16(1)	9(1)	9(1)
O(2)	40(1)	36(1)	24(1)	15(1)	9(1)	16(1)
O(3)	30(1)	32(1)	23(1)	14(1)	3(1)	13(1)
O(4)	35(1)	36(1)	33(1)	20(1)	3(1)	6(1)
O(5)	23(1)	48(1)	54(1)	34(1)	1(1)	4(1)
O(6)	39(1)	41(1)	27(1)	16(1)	2(1)	12(1)
O(7)	41(1)	31(1)	36(1)	18(1)	-1(1)	11(1)
O(8)	43(1)	37(1)	31(1)	8(1)	11(1)	15(1)
O(9)	33(1)	29(1)	27(1)	9(1)	-2(1)	6(1)
C(1)	28(1)	30(1)	27(1)	11(1)	5(1)	7(1)
C(2)	25(1)	30(1)	20(1)	9(1)	5(1)	8(1)
C(3)	26(1)	28(1)	19(1)	9(1)	4(1)	7(1)
C(4)	23(1)	26(1)	20(1)	11(1)	3(1)	8(1)
C(5)	27(1)	27(1)	21(1)	11(1)	3(1)	9(1)
C(6)	26(1)	30(1)	25(1)	11(1)	5(1)	10(1)
C(7)	26(1)	31(1)	21(1)	11(1)	3(1)	8(1)
C(8)	27(1)	29(1)	31(1)	11(1)	3(1)	7(1)
C(9)	29(1)	27(1)	27(1)	10(1)	5(1)	8(1)
C(10)	37(1)	34(1)	45(2)	19(1)	12(1)	15(1)
C(11)	26(1)	25(1)	23(1)	11(1)	2(1)	6(1)
C(12)	35(1)	37(1)	30(1)	20(1)	6(1)	17(1)
C(13)	37(2)	56(2)	30(1)	20(1)	1(1)	15(1)
C(14)	28(1)	26(1)	24(1)	9(1)	4(1)	8(1)
C(15)	29(1)	52(2)	68(2)	39(2)	4(1)	4(1)
C(16)	43(2)	99(3)	76(3)	28(2)	1(2)	-18(2)
C(17)	27(1)	34(1)	29(1)	16(1)	4(1)	10(1)
C(18)	52(2)	39(2)	44(2)	27(1)	0(1)	12(1)
C(19)	54(2)	45(2)	56(2)	24(2)	-9(2)	14(2)
C(20)	37(1)	27(1)	26(1)	12(1)	3(1)	13(1)
C(21)	49(2)	29(1)	33(1)	3(1)	-6(1)	7(1)

Table B.4 continued.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(22)	71(2)	57(2)	41(2)	14(2)	-13(2)	8(2)
C(23)	30(1)	39(2)	46(2)	19(1)	7(1)	10(1)
C(24)	28(1)	30(1)	34(1)	18(1)	6(1)	8(1)
C(25)	44(2)	33(1)	26(1)	11(1)	8(1)	7(1)
C(26)	45(2)	30(1)	33(1)	14(1)	1(1)	1(1)
C(27)	34(1)	34(1)	38(1)	20(1)	2(1)	0(1)
C(28)	35(1)	38(1)	27(1)	14(1)	8(1)	9(1)
C(29)	30(1)	27(1)	30(1)	10(1)	0(1)	5(1)

Table B.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for jl010.

	x	y	z	U(eq)
H(16A)	-948	1857	6507	126
H(16B)	430	1529	5934	126
H(16C)	-39	2795	6095	126
H(21A)	3118	408	5052	51
H(21B)	4641	798	4692	51
H(22A)	2663	823	3594	93
H(22B)	3779	2215	4239	93
H(22C)	2277	1899	4649	93
H(3A)	4570(30)	6280(30)	8990(20)	36(7)
H(3B)	5680(30)	5740(30)	9410(20)	39(8)
H(6A)	7570(30)	4970(20)	6910(20)	29(7)
H(6B)	8480(30)	4430(30)	7540(20)	32(7)
H(7)	8310(30)	6040(30)	9230(20)	32(7)
H(8)	9700(30)	7760(30)	9400(20)	38(7)
H(9)	8350(30)	6990(20)	7130(20)	27(6)
H(10A)	4740(30)	8140(30)	9140(20)	46(8)
H(10B)	5240(40)	8620(30)	8180(30)	64(10)
H(10C)	6080(40)	9420(40)	9530(30)	76(12)
H(12A)	4220(30)	6340(30)	5970(20)	34(7)
H(12B)	3130(30)	6950(30)	6640(20)	31(7)
H(13A)	1340(40)	5000(30)	5680(30)	50(9)
H(13B)	2360(30)	4350(30)	4920(30)	47(8)
H(13C)	1900(40)	5580(30)	4920(30)	53(9)
H(15A)	1220(40)	2320(40)	7700(30)	68(11)
H(15B)	690(40)	3580(40)	8100(30)	60(10)
H(18A)	5990(30)	510(30)	8050(20)	39(7)
H(18B)	6200(30)	2020(30)	9230(30)	43(8)
H(19A)	8520(40)	1140(40)	7980(30)	75(12)
H(19B)	8270(40)	1030(40)	9100(30)	77(12)

Table B.5 continued.

	x	y	z	U(eq)
H(19C)	8710(40)	2550(40)	9150(30)	65(10)
H(23A)	10420(30)	5820(30)	7410(30)	47(8)
H(23B)	10910(30)	6140(30)	8770(30)	46(8)
H(23C)	11630(30)	7220(30)	8370(20)	36(7)
H(25)	10630(30)	10040(30)	9270(20)	40(8)
H(26)	12590(30)	11400(30)	8980(30)	48(8)
H(27)	13250(30)	10610(30)	7260(20)	40(8)
H(28)	12060(30)	8620(30)	5830(30)	46(8)
H(29)	10050(30)	7360(30)	6050(30)	44(8)

Table B.6. Torsion angles [°] for jl010.

C(9)-O(1)-C(1)-C(2)	19.5(3)
C(9)-O(1)-C(1)-C(10)	-162.3(2)
O(1)-C(1)-C(2)-C(3)	-171.1(2)
C(10)-C(1)-C(2)-C(3)	11.0(4)
O(1)-C(1)-C(2)-C(7)	3.7(4)
C(10)-C(1)-C(2)-C(7)	-174.2(2)
C(1)-C(2)-C(3)-C(4)	111.7(3)
C(7)-C(2)-C(3)-C(4)	-63.4(2)
C(2)-C(3)-C(4)-C(14)	178.32(19)
C(2)-C(3)-C(4)-C(11)	-60.1(2)
C(2)-C(3)-C(4)-C(5)	58.0(2)
C(14)-C(4)-C(5)-C(20)	70.8(2)
C(11)-C(4)-C(5)-C(20)	-52.4(2)
C(3)-C(4)-C(5)-C(20)	-170.36(18)
C(14)-C(4)-C(5)-C(17)	-49.9(2)
C(11)-C(4)-C(5)-C(17)	-173.15(18)
C(3)-C(4)-C(5)-C(17)	68.8(2)
C(14)-C(4)-C(5)-C(6)	-168.87(18)
C(11)-C(4)-C(5)-C(6)	67.9(2)
C(3)-C(4)-C(5)-C(6)	-50.1(2)
C(20)-C(5)-C(6)-C(7)	168.61(19)
C(17)-C(5)-C(6)-C(7)	-75.4(2)
C(4)-C(5)-C(6)-C(7)	46.5(3)
C(1)-C(2)-C(7)-C(8)	9.5(3)
C(3)-C(2)-C(7)-C(8)	-175.17(18)
C(1)-C(2)-C(7)-C(6)	-116.8(2)
C(3)-C(2)-C(7)-C(6)	58.5(2)
C(5)-C(6)-C(7)-C(2)	-49.4(3)
C(5)-C(6)-C(7)-C(8)	-174.56(19)
C(2)-C(7)-C(8)-C(23)	-169.3(2)
C(6)-C(7)-C(8)-C(23)	-44.8(3)
C(2)-C(7)-C(8)-C(9)	-41.8(2)
C(6)-C(7)-C(8)-C(9)	82.6(2)

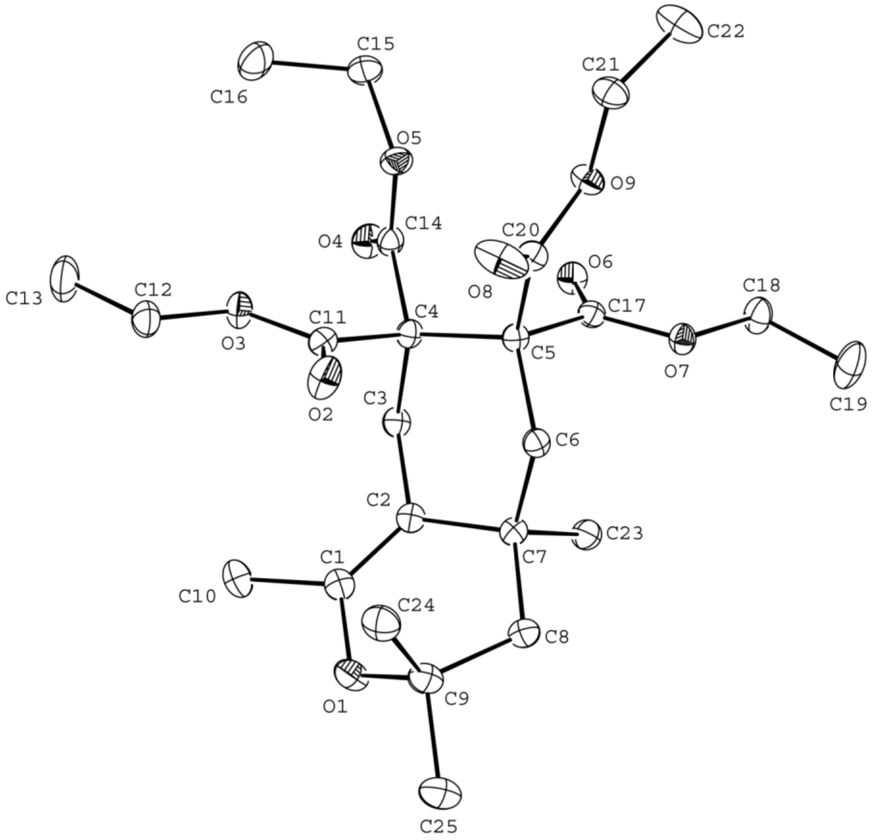
Table B.6 continued.

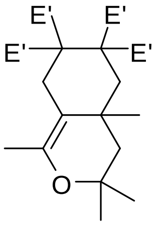
C(1)-O(1)-C(9)-C(24)	-178.61(19)
C(1)-O(1)-C(9)-C(8)	-53.7(2)
C(23)-C(8)-C(9)-O(1)	-167.5(2)
C(7)-C(8)-C(9)-O(1)	64.7(2)
C(23)-C(8)-C(9)-C(24)	-47.2(3)
C(7)-C(8)-C(9)-C(24)	-175.0(2)
C(12)-O(3)-C(11)-O(2)	0.3(3)
C(12)-O(3)-C(11)-C(4)	177.76(18)
C(14)-C(4)-C(11)-O(2)	-110.4(3)
C(3)-C(4)-C(11)-O(2)	131.2(2)
C(5)-C(4)-C(11)-O(2)	11.3(3)
C(14)-C(4)-C(11)-O(3)	72.2(2)
C(3)-C(4)-C(11)-O(3)	-46.3(2)
C(5)-C(4)-C(11)-O(3)	-166.15(18)
C(11)-O(3)-C(12)-C(13)	80.6(3)
C(15)-O(5)-C(14)-O(4)	-0.2(4)
C(15)-O(5)-C(14)-C(4)	-178.5(2)
C(11)-C(4)-C(14)-O(4)	169.3(2)
C(3)-C(4)-C(14)-O(4)	-72.0(3)
C(5)-C(4)-C(14)-O(4)	48.8(3)
C(11)-C(4)-C(14)-O(5)	-12.3(3)
C(3)-C(4)-C(14)-O(5)	106.4(2)
C(5)-C(4)-C(14)-O(5)	-132.8(2)
C(14)-O(5)-C(15)-C(16)	-140.8(3)
C(18)-O(7)-C(17)-O(6)	4.3(4)
C(18)-O(7)-C(17)-C(5)	179.8(2)
C(20)-C(5)-C(17)-O(6)	171.7(2)
C(6)-C(5)-C(17)-O(6)	55.9(3)
C(4)-C(5)-C(17)-O(6)	-66.0(3)
C(20)-C(5)-C(17)-O(7)	-3.9(3)
C(6)-C(5)-C(17)-O(7)	-119.6(2)
C(4)-C(5)-C(17)-O(7)	118.5(2)
C(17)-O(7)-C(18)-C(19)	-84.6(3)

Table B.6 continued.

C(21)-O(9)-C(20)-O(8)	-7.0(4)
C(21)-O(9)-C(20)-C(5)	175.2(2)
C(17)-C(5)-C(20)-O(8)	-94.1(3)
C(6)-C(5)-C(20)-O(8)	20.7(3)
C(4)-C(5)-C(20)-O(8)	143.1(2)
C(17)-C(5)-C(20)-O(9)	83.7(2)
C(6)-C(5)-C(20)-O(9)	-161.50(19)
C(4)-C(5)-C(20)-O(9)	-39.1(3)
C(20)-O(9)-C(21)-C(22)	-98.0(3)
O(1)-C(9)-C(24)-C(25)	50.7(3)
C(8)-C(9)-C(24)-C(25)	-70.5(3)
O(1)-C(9)-C(24)-C(29)	-131.5(2)
C(8)-C(9)-C(24)-C(29)	107.4(3)
C(29)-C(24)-C(25)-C(26)	1.4(4)
C(9)-C(24)-C(25)-C(26)	179.2(2)
C(24)-C(25)-C(26)-C(27)	-1.3(4)
C(25)-C(26)-C(27)-C(28)	0.0(4)
C(26)-C(27)-C(28)-C(29)	1.4(4)
C(27)-C(28)-C(29)-C(24)	-1.3(4)
C(25)-C(24)-C(29)-C(28)	0.0(4)
C(9)-C(24)-C(29)-C(28)	-177.9(2)

Symmetry transformations used to generate equivalent atoms:


C22
C15
C21
C16
O5
O9
O4
C14
C20
O6
O8
C13
C12
C18
C11
C4
C17
O3
C5
O7
O2
C3
C19
C6
C2
C23
C7
C1
C10
C24
C8
O1
C9
C25


E'
E'
E'
E'
O

3.102

Table B.7. Crystal data and structure refinement for jl005.

Identification code	jl005	
Empirical formula	C25 H38 O9	
Formula weight	482.55	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 8.4030(2) Å	α= 78.4712(13)°.
	b = 9.8777(2) Å	β= 75.5040(12)°.
	c = 16.3375(4) Å	γ = 79.3216(12)°.
Volume	1273.25(5) $Å^3$	
Z	2	
Density (calculated)	1.259 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	520	
Crystal size	0.50 x 0.38 x 0.15 mm^3	
Theta range for data collection	3.09 to 27.48°.	
Index ranges	-10<=h<=10, -12<=k<=12, -19<=l<=21	
Reflections collected	9048	
Independent reflections	5756 [R(int) = 0.0271]	
Completeness to theta = 27.48°	98.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9859 and 0.9541	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5756 / 0 / 460	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0463, wR2 = 0.1106	
R indices (all data)	R1 = 0.0638, wR2 = 0.1227	
Extinction coefficient	0.032(5)	
Largest diff. peak and hole	0.267 and -0.231 e.$Å^{-3}$	

Table B.8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for jl005. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5387(2)	554(2)	1836(1)	29(1)
C(2)	4117(2)	1575(2)	2001(1)	25(1)
C(3)	3158(2)	1770(2)	2891(1)	26(1)
C(4)	3413(2)	3163(1)	3116(1)	23(1)
C(5)	2890(2)	4418(1)	2429(1)	22(1)
C(6)	3751(2)	4139(2)	1505(1)	23(1)
C(7)	3591(2)	2704(2)	1303(1)	25(1)
C(8)	4694(2)	2497(2)	412(1)	30(1)
C(9)	6441(2)	1702(2)	406(1)	33(1)
C(10)	6048(2)	-598(2)	2464(1)	36(1)
C(11)	5269(2)	2980(2)	3128(1)	25(1)
C(12)	7261(2)	1856(2)	3931(1)	36(1)
C(13)	7299(3)	996(3)	4790(1)	53(1)
C(14)	2456(2)	3277(2)	4042(1)	27(1)
C(15)	2124(2)	4587(2)	5166(1)	39(1)
C(16)	3350(3)	3767(3)	5679(1)	51(1)
C(17)	987(2)	4664(1)	2553(1)	24(1)
C(18)	-1244(2)	5864(2)	1927(1)	34(1)
C(19)	-1492(2)	6531(3)	1060(1)	54(1)
C(20)	3346(2)	5819(2)	2530(1)	26(1)
C(21)	2267(2)	7976(2)	3026(1)	33(1)
C(22)	591(2)	8739(2)	3366(2)	49(1)
C(23)	1794(2)	2622(2)	1262(1)	31(1)
C(24)	7618(2)	2506(2)	623(1)	37(1)
C(25)	7194(2)	1227(2)	-457(1)	43(1)
O(1)	6309(1)	418(1)	1020(1)	35(1)
O(2)	6365(1)	3384(1)	2559(1)	39(1)
O(3)	5532(1)	2184(1)	3860(1)	32(1)
O(4)	1675(1)	2415(1)	4513(1)	36(1)

Table B.8 continued.

	x	y	z	U(eq)
O(5)	2724(1)	4437(1)	4263(1)	31(1)
O(6)	30(1)	4206(1)	3185(1)	30(1)
O(7)	540(1)	5487(1)	1869(1)	26(1)
O(8)	4702(2)	6160(1)	2297(1)	50(1)
O(9)	2009(1)	6631(1)	2893(1)	30(1)

Table B.9. Bond lengths [Å] and angles [°] for jl005.

C(1)-C(2)	1.339(2)
C(1)-O(1)	1.3827(18)
C(1)-C(10)	1.497(2)
C(2)-C(3)	1.506(2)
C(2)-C(7)	1.517(2)
C(3)-C(4)	1.557(2)
C(3)-H(3A)	0.967(18)
C(3)-H(3B)	0.996(17)
C(4)-C(11)	1.5405(19)
C(4)-C(14)	1.5422(19)
C(4)-C(5)	1.5737(19)
C(5)-C(17)	1.5399(19)
C(5)-C(20)	1.5521(19)
C(5)-C(6)	1.5570(18)
C(6)-C(7)	1.5532(19)
C(6)-H(6A)	0.973(17)
C(6)-H(6B)	0.981(16)
C(7)-C(23)	1.547(2)
C(7)-C(8)	1.5471(19)
C(8)-C(9)	1.529(2)
C(8)-H(8A)	0.986(19)
C(8)-H(8B)	1.024(18)
C(9)-O(1)	1.4542(19)
C(9)-C(25)	1.521(2)
C(9)-C(24)	1.521(2)
C(10)-H(10A)	0.97(2)
C(10)-H(10B)	0.98(2)
C(10)-H(10C)	1.00(2)
C(11)-O(2)	1.1958(17)
C(11)-O(3)	1.3374(17)
C(12)-O(3)	1.4577(19)
C(12)-C(13)	1.493(3)
C(12)-H(12A)	0.97(2)

Table B.9 continued.

C(12)-H(12B)	0.98(2)
C(13)-H(13A)	1.01(3)
C(13)-H(13B)	0.99(3)
C(13)-H(13C)	0.99(2)
C(14)-O(4)	1.2003(18)
C(14)-O(5)	1.3387(18)
C(15)-O(5)	1.4636(18)
C(15)-C(16)	1.507(3)
C(15)-H(15A)	0.99(2)
C(15)-H(15B)	0.98(2)
C(16)-H(16A)	0.97(3)
C(16)-H(16B)	1.04(2)
C(16)-H(16C)	0.99(3)
C(17)-O(6)	1.2044(17)
C(17)-O(7)	1.3361(17)
C(18)-O(7)	1.4597(17)
C(18)-C(19)	1.486(2)
C(18)-H(18A)	0.98(2)
C(18)-H(18B)	0.98(2)
C(19)-H(19A)	0.96(3)
C(19)-H(19B)	0.99(3)
C(19)-H(19C)	0.98(2)
C(20)-O(8)	1.1962(18)
C(20)-O(9)	1.3334(17)
C(21)-O(9)	1.4509(18)
C(21)-C(22)	1.497(2)
C(21)-H(21A)	1.000(19)
C(21)-H(21B)	0.984(19)
C(22)-H(22A)	0.98(2)
C(22)-H(22B)	1.02(3)
C(22)-H(22C)	1.01(2)
C(23)-H(23A)	0.983(19)
C(23)-H(23B)	1.006(18)

Table B.9 continued.

C(23)-H(23C)	0.99(2)
C(24)-H(24A)	0.97(2)
C(24)-H(24B)	0.992(18)
C(24)-H(24C)	1.03(2)
C(25)-H(25A)	0.98(2)
C(25)-H(25B)	0.99(2)
C(25)-H(25C)	0.97(2)
C(2)-C(1)-O(1)	123.34(14)
C(2)-C(1)-C(10)	127.67(15)
O(1)-C(1)-C(10)	108.99(13)
C(1)-C(2)-C(3)	123.68(14)
C(1)-C(2)-C(7)	122.50(13)
C(3)-C(2)-C(7)	113.69(12)
C(2)-C(3)-C(4)	111.18(11)
C(2)-C(3)-H(3A)	113.4(10)
C(4)-C(3)-H(3A)	106.3(10)
C(2)-C(3)-H(3B)	110.8(9)
C(4)-C(3)-H(3B)	107.5(9)
H(3A)-C(3)-H(3B)	107.4(14)
C(11)-C(4)-C(14)	105.95(11)
C(11)-C(4)-C(3)	105.01(11)
C(14)-C(4)-C(3)	108.73(11)
C(11)-C(4)-C(5)	113.13(11)
C(14)-C(4)-C(5)	114.03(11)
C(3)-C(4)-C(5)	109.51(11)
C(17)-C(5)-C(20)	104.97(11)
C(17)-C(5)-C(6)	110.94(11)
C(20)-C(5)-C(6)	107.56(11)
C(17)-C(5)-C(4)	109.61(11)
C(20)-C(5)-C(4)	112.74(11)
C(6)-C(5)-C(4)	110.86(11)
C(7)-C(6)-C(5)	115.61(11)
C(7)-C(6)-H(6A)	108.3(9)

Table B.9 continued.

C(5)-C(6)-H(6A)	107.1(9)
C(7)-C(6)-H(6B)	109.1(9)
C(5)-C(6)-H(6B)	107.4(9)
H(6A)-C(6)-H(6B)	109.3(13)
C(2)-C(7)-C(23)	109.70(12)
C(2)-C(7)-C(8)	111.17(12)
C(23)-C(7)-C(8)	106.48(12)
C(2)-C(7)-C(6)	108.16(11)
C(23)-C(7)-C(6)	111.73(12)
C(8)-C(7)-C(6)	109.61(12)
C(9)-C(8)-C(7)	116.01(13)
C(9)-C(8)-H(8A)	108.3(10)
C(7)-C(8)-H(8A)	109.7(10)
C(9)-C(8)-H(8B)	105.5(10)
C(7)-C(8)-H(8B)	108.6(10)
H(8A)-C(8)-H(8B)	108.4(14)
O(1)-C(9)-C(25)	104.83(13)
O(1)-C(9)-C(24)	108.53(14)
C(25)-C(9)-C(24)	109.91(14)
O(1)-C(9)-C(8)	108.55(12)
C(25)-C(9)-C(8)	110.00(14)
C(24)-C(9)-C(8)	114.55(13)
C(1)-C(10)-H(10A)	110.6(12)
C(1)-C(10)-H(10B)	107.7(12)
H(10A)-C(10)-H(10B)	106.8(16)
C(1)-C(10)-H(10C)	114.5(12)
H(10A)-C(10)-H(10C)	106.8(16)
H(10B)-C(10)-H(10C)	110.2(17)
O(2)-C(11)-O(3)	123.06(13)
O(2)-C(11)-C(4)	126.97(13)
O(3)-C(11)-C(4)	109.77(11)
O(3)-C(12)-C(13)	107.53(15)
O(3)-C(12)-H(12A)	109.1(12)

Table B.9 continued.

C(13)-C(12)-H(12A)	113.1(12)
O(3)-C(12)-H(12B)	107.5(12)
C(13)-C(12)-H(12B)	112.0(12)
H(12A)-C(12)-H(12B)	107.4(16)
C(12)-C(13)-H(13A)	110.1(14)
C(12)-C(13)-H(13B)	110.1(16)
H(13A)-C(13)-H(13B)	104(2)
C(12)-C(13)-H(13C)	109.5(13)
H(13A)-C(13)-H(13C)	110.5(19)
H(13B)-C(13)-H(13C)	112(2)
O(4)-C(14)-O(5)	125.04(13)
O(4)-C(14)-C(4)	125.15(13)
O(5)-C(14)-C(4)	109.66(12)
O(5)-C(15)-C(16)	110.25(14)
O(5)-C(15)-H(15A)	104.7(11)
C(16)-C(15)-H(15A)	112.5(11)
O(5)-C(15)-H(15B)	108.4(11)
C(16)-C(15)-H(15B)	111.1(11)
H(15A)-C(15)-H(15B)	109.6(15)
C(15)-C(16)-H(16A)	111.6(15)
C(15)-C(16)-H(16B)	108.0(13)
H(16A)-C(16)-H(16B)	111.2(19)
C(15)-C(16)-H(16C)	108.7(14)
H(16A)-C(16)-H(16C)	110(2)
H(16B)-C(16)-H(16C)	107.3(19)
O(6)-C(17)-O(7)	124.53(13)
O(6)-C(17)-C(5)	124.87(13)
O(7)-C(17)-C(5)	110.57(11)
O(7)-C(18)-C(19)	107.67(13)
O(7)-C(18)-H(18A)	110.9(13)
C(19)-C(18)-H(18A)	112.1(13)
O(7)-C(18)-H(18B)	108.4(12)
C(19)-C(18)-H(18B)	111.3(13)

Table B.9 continued.

H(18A)-C(18)-H(18B)	106.5(17)
C(18)-C(19)-H(19A)	110.6(16)
C(18)-C(19)-H(19B)	110.4(15)
H(19A)-C(19)-H(19B)	107(2)
C(18)-C(19)-H(19C)	109.0(14)
H(19A)-C(19)-H(19C)	110(2)
H(19B)-C(19)-H(19C)	110(2)
O(8)-C(20)-O(9)	123.57(14)
O(8)-C(20)-C(5)	125.24(13)
O(9)-C(20)-C(5)	111.16(12)
O(9)-C(21)-C(22)	106.99(14)
O(9)-C(21)-H(21A)	107.0(10)
C(22)-C(21)-H(21A)	113.4(10)
O(9)-C(21)-H(21B)	106.2(11)
C(22)-C(21)-H(21B)	111.5(10)
H(21A)-C(21)-H(21B)	111.3(15)
C(21)-C(22)-H(22A)	104.7(13)
C(21)-C(22)-H(22B)	110.7(15)
H(22A)-C(22)-H(22B)	113(2)
C(21)-C(22)-H(22C)	108.7(13)
H(22A)-C(22)-H(22C)	110.0(19)
H(22B)-C(22)-H(22C)	110(2)
C(7)-C(23)-H(23A)	110.1(11)
C(7)-C(23)-H(23B)	114.3(10)
H(23A)-C(23)-H(23B)	105.8(14)
C(7)-C(23)-H(23C)	110.5(11)
H(23A)-C(23)-H(23C)	110.1(15)
H(23B)-C(23)-H(23C)	105.9(15)
C(9)-C(24)-H(24A)	110.7(11)
C(9)-C(24)-H(24B)	113.4(10)
H(24A)-C(24)-H(24B)	106.0(15)
C(9)-C(24)-H(24C)	113.3(12)
H(24A)-C(24)-H(24C)	105.8(17)

Table B.9 continued.

H(24B)-C(24)-H(24C)	106.9(16)
C(9)-C(25)-H(25A)	110.1(12)
C(9)-C(25)-H(25B)	110.7(13)
H(25A)-C(25)-H(25B)	108.0(17)
C(9)-C(25)-H(25C)	110.6(12)
H(25A)-C(25)-H(25C)	106.8(17)
H(25B)-C(25)-H(25C)	110.5(18)
C(1)-O(1)-C(9)	116.24(11)
C(11)-O(3)-C(12)	115.40(12)
C(14)-O(5)-C(15)	116.45(12)
C(17)-O(7)-C(18)	115.87(11)
C(20)-O(9)-C(21)	116.70(11)

Symmetry transformations used to generate equivalent atoms:

Table B.10. Anisotropic displacement parameters ($Å^2 x 10^3$)for jl005. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	28(1)	26(1)	34(1)	-4(1)	-7(1)	-7(1)
C(2)	25(1)	23(1)	28(1)	-2(1)	-6(1)	-8(1)
C(3)	28(1)	22(1)	27(1)	0(1)	-6(1)	-6(1)
C(4)	24(1)	24(1)	21(1)	0(1)	-4(1)	-5(1)
C(5)	22(1)	22(1)	22(1)	-1(1)	-4(1)	-5(1)
C(6)	23(1)	24(1)	21(1)	0(1)	-3(1)	-4(1)
C(7)	26(1)	26(1)	24(1)	-4(1)	-6(1)	-4(1)
C(8)	32(1)	32(1)	25(1)	-6(1)	-5(1)	-3(1)
C(9)	32(1)	32(1)	31(1)	-8(1)	-1(1)	-4(1)
C(10)	32(1)	28(1)	47(1)	0(1)	-10(1)	-1(1)
C(11)	27(1)	26(1)	24(1)	-4(1)	-6(1)	-6(1)
C(12)	29(1)	42(1)	38(1)	-5(1)	-13(1)	2(1)
C(13)	48(1)	62(1)	45(1)	4(1)	-23(1)	7(1)
C(14)	26(1)	30(1)	22(1)	-1(1)	-5(1)	-2(1)
C(15)	43(1)	45(1)	24(1)	-11(1)	-2(1)	2(1)
C(16)	50(1)	72(2)	28(1)	-8(1)	-10(1)	2(1)
C(17)	24(1)	22(1)	24(1)	-4(1)	-4(1)	-4(1)
C(18)	19(1)	49(1)	31(1)	0(1)	-5(1)	-1(1)
C(19)	28(1)	94(2)	32(1)	5(1)	-9(1)	2(1)
C(20)	25(1)	26(1)	26(1)	-4(1)	-3(1)	-5(1)
C(21)	34(1)	26(1)	41(1)	-9(1)	-6(1)	-7(1)
C(22)	39(1)	34(1)	73(2)	-20(1)	-1(1)	-5(1)
C(23)	29(1)	33(1)	33(1)	-8(1)	-9(1)	-5(1)
C(24)	28(1)	43(1)	39(1)	-9(1)	0(1)	-6(1)
C(25)	42(1)	44(1)	38(1)	-15(1)	2(1)	-2(1)
O(1)	35(1)	28(1)	36(1)	-7(1)	-1(1)	0(1)
O(2)	28(1)	57(1)	31(1)	5(1)	-7(1)	-14(1)
O(3)	27(1)	36(1)	30(1)	4(1)	-9(1)	-2(1)
O(4)	36(1)	40(1)	26(1)	3(1)	0(1)	-10(1)
O(5)	38(1)	33(1)	22(1)	-6(1)	-4(1)	-3(1)

Table B.10 continued.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(6)	24(1)	34(1)	27(1)	0(1)	-1(1)	-7(1)
O(7)	20(1)	31(1)	26(1)	-1(1)	-5(1)	-3(1)
O(8)	31(1)	40(1)	78(1)	-27(1)	11(1)	-15(1)
O(9)	26(1)	24(1)	38(1)	-9(1)	-4(1)	-3(1)

Table B.11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for jl005.

	x	y	z	U(eq)
H(3A)	3480(20)	1038(18)	3332(11)	30(4)
H(3B)	1950(20)	1803(17)	2942(10)	28(4)
H(6A)	4920(20)	4197(17)	1425(10)	26(4)
H(6B)	3270(19)	4886(16)	1106(10)	22(4)
H(8A)	4790(20)	3410(20)	43(12)	34(4)
H(8B)	4130(20)	1923(18)	138(11)	33(4)
H(10A)	6010(20)	-1500(20)	2325(12)	44(5)
H(10B)	7220(30)	-530(20)	2407(13)	52(6)
H(10C)	5430(30)	-600(20)	3074(14)	54(6)
H(12A)	7720(20)	2720(20)	3844(13)	47(5)
H(12B)	7870(20)	1350(20)	3464(13)	49(5)
H(13A)	6550(30)	1510(30)	5255(17)	73(7)
H(13B)	6810(30)	140(30)	4851(18)	86(9)
H(13C)	8450(30)	790(20)	4870(14)	60(6)
H(15A)	1990(20)	5600(20)	5168(12)	42(5)
H(15B)	1040(20)	4262(19)	5373(12)	39(5)
H(16A)	4470(30)	3990(20)	5427(16)	69(7)
H(16B)	3300(30)	2710(30)	5716(14)	61(7)
H(16C)	2990(30)	3980(30)	6269(17)	73(7)
H(18A)	-1820(30)	5050(20)	2149(14)	56(6)
H(18B)	-1680(30)	6510(20)	2342(14)	54(6)
H(19A)	-960(30)	5920(30)	646(18)	81(8)
H(19B)	-970(30)	7390(30)	869(17)	76(8)
H(19C)	-2690(30)	6740(20)	1078(15)	64(6)
H(21A)	2850(20)	8454(19)	2461(12)	38(5)
H(21B)	2970(20)	7777(19)	3448(12)	36(5)
H(22A)	10(30)	8900(20)	2897(15)	58(6)
H(22B)	-10(30)	8170(30)	3913(18)	83(8)
H(22C)	740(30)	9660(30)	3494(15)	66(7)

Table B.11 continued.

	x	y	z	U(eq)
H(23A)	1730(20)	1710(20)	1128(12)	39(5)
H(23B)	950(20)	2722(18)	1813(12)	33(4)
H(23C)	1420(20)	3380(20)	824(12)	41(5)
H(24A)	8720(30)	1970(20)	579(12)	44(5)
H(24B)	7270(20)	2725(18)	1214(12)	32(4)
H(24C)	7780(30)	3440(20)	215(14)	59(6)
H(25A)	8250(30)	610(20)	-437(12)	46(5)
H(25B)	7420(30)	2040(20)	-915(15)	60(6)
H(25C)	6460(30)	690(20)	-594(13)	50(6)

Table B.12. Torsion angles [°] for jl005.

O(1)-C(1)-C(2)-C(3)	-177.06(13)
C(10)-C(1)-C(2)-C(3)	3.0(2)
O(1)-C(1)-C(2)-C(7)	-1.4(2)
C(10)-C(1)-C(2)-C(7)	178.67(14)
C(1)-C(2)-C(3)-C(4)	114.52(16)
C(7)-C(2)-C(3)-C(4)	-61.47(16)
C(2)-C(3)-C(4)-C(11)	-64.94(14)
C(2)-C(3)-C(4)-C(14)	-177.97(11)
C(2)-C(3)-C(4)-C(5)	56.83(15)
C(11)-C(4)-C(5)-C(17)	-171.43(11)
C(14)-C(4)-C(5)-C(17)	-50.26(15)
C(3)-C(4)-C(5)-C(17)	71.82(13)
C(11)-C(4)-C(5)-C(20)	-54.89(15)
C(14)-C(4)-C(5)-C(20)	66.28(15)
C(3)-C(4)-C(5)-C(20)	-171.64(11)
C(11)-C(4)-C(5)-C(6)	65.76(14)
C(14)-C(4)-C(5)-C(6)	-173.06(11)
C(3)-C(4)-C(5)-C(6)	-50.99(14)
C(17)-C(5)-C(6)-C(7)	-71.53(15)
C(20)-C(5)-C(6)-C(7)	174.19(11)
C(4)-C(5)-C(6)-C(7)	50.51(15)
C(1)-C(2)-C(7)-C(23)	117.87(15)
C(3)-C(2)-C(7)-C(23)	-66.09(15)
C(1)-C(2)-C(7)-C(8)	0.36(19)
C(3)-C(2)-C(7)-C(8)	176.41(12)
C(1)-C(2)-C(7)-C(6)	-120.03(14)
C(3)-C(2)-C(7)-C(6)	56.01(15)
C(5)-C(6)-C(7)-C(2)	-51.12(15)
C(5)-C(6)-C(7)-C(23)	69.73(15)
C(5)-C(6)-C(7)-C(8)	-172.48(12)
C(2)-C(7)-C(8)-C(9)	-25.61(18)
C(23)-C(7)-C(8)-C(9)	-145.05(14)
C(6)-C(7)-C(8)-C(9)	93.93(15)

Table B.12 continued.

C(7)-C(8)-C(9)-O(1)	50.14(17)
C(7)-C(8)-C(9)-C(25)	164.31(14)
C(7)-C(8)-C(9)-C(24)	-71.32(18)
C(14)-C(4)-C(11)-O(2)	-148.04(15)
C(3)-C(4)-C(11)-O(2)	96.98(17)
C(5)-C(4)-C(11)-O(2)	-22.4(2)
C(14)-C(4)-C(11)-O(3)	37.07(15)
C(3)-C(4)-C(11)-O(3)	-77.91(13)
C(5)-C(4)-C(11)-O(3)	162.71(11)
C(11)-C(4)-C(14)-O(4)	-110.98(16)
C(3)-C(4)-C(14)-O(4)	1.4(2)
C(5)-C(4)-C(14)-O(4)	123.95(15)
C(11)-C(4)-C(14)-O(5)	64.65(14)
C(3)-C(4)-C(14)-O(5)	177.07(11)
C(5)-C(4)-C(14)-O(5)	-60.43(15)
C(20)-C(5)-C(17)-O(6)	-105.24(15)
C(6)-C(5)-C(17)-O(6)	138.86(14)
C(4)-C(5)-C(17)-O(6)	16.10(19)
C(20)-C(5)-C(17)-O(7)	73.19(13)
C(6)-C(5)-C(17)-O(7)	-42.71(15)
C(4)-C(5)-C(17)-O(7)	-165.47(11)
C(17)-C(5)-C(20)-O(8)	-162.58(16)
C(6)-C(5)-C(20)-O(8)	-44.4(2)
C(4)-C(5)-C(20)-O(8)	78.16(19)
C(17)-C(5)-C(20)-O(9)	15.67(15)
C(6)-C(5)-C(20)-O(9)	133.89(12)
C(4)-C(5)-C(20)-O(9)	-103.59(13)
C(2)-C(1)-O(1)-C(9)	29.1(2)
C(10)-C(1)-O(1)-C(9)	-150.92(13)
C(25)-C(9)-O(1)-C(1)	-168.91(13)
C(24)-C(9)-O(1)-C(1)	73.68(16)
C(8)-C(9)-O(1)-C(1)	-51.40(17)
O(2)-C(11)-O(3)-C(12)	1.2(2)

Table B.12 continued.

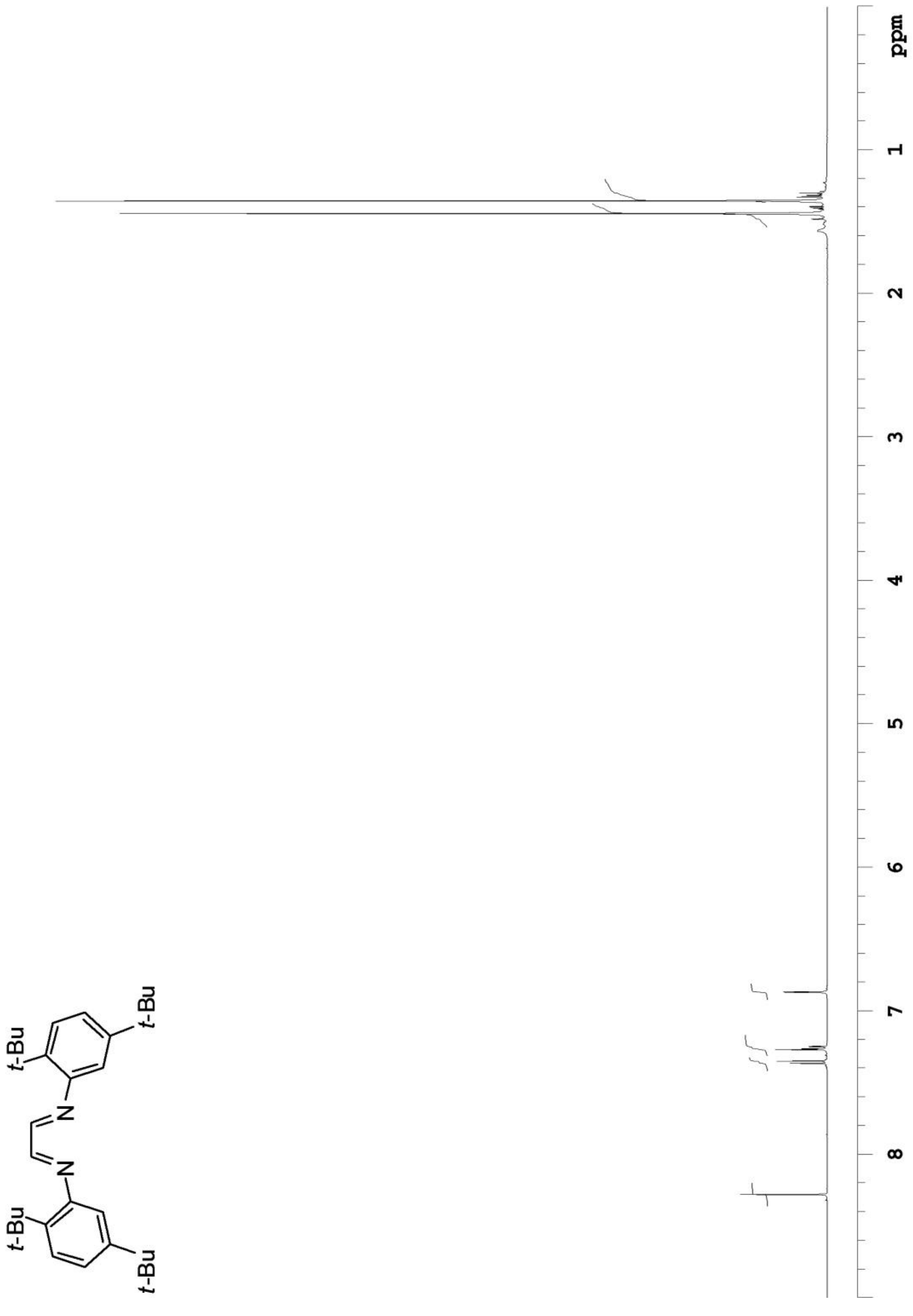
C(4)-C(11)-O(3)-C(12)	176.31(12)
C(13)-C(12)-O(3)-C(11)	178.74(15)
O(4)-C(14)-O(5)-C(15)	5.2(2)
C(4)-C(14)-O(5)-C(15)	-170.42(12)
C(16)-C(15)-O(5)-C(14)	81.6(2)
O(6)-C(17)-O(7)-C(18)	1.7(2)
C(5)-C(17)-O(7)-C(18)	-176.72(12)
C(19)-C(18)-O(7)-C(17)	-169.04(16)
O(8)-C(20)-O(9)-C(21)	-1.9(2)
C(5)-C(20)-O(9)-C(21)	179.85(12)
C(22)-C(21)-O(9)-C(20)	175.23(15)

Symmetry transformations used to generate equivalent atoms:

APPENDIX C

^{1}H NMR AND ^{13}C NMR SPECTRA

FOR CHAPTER 5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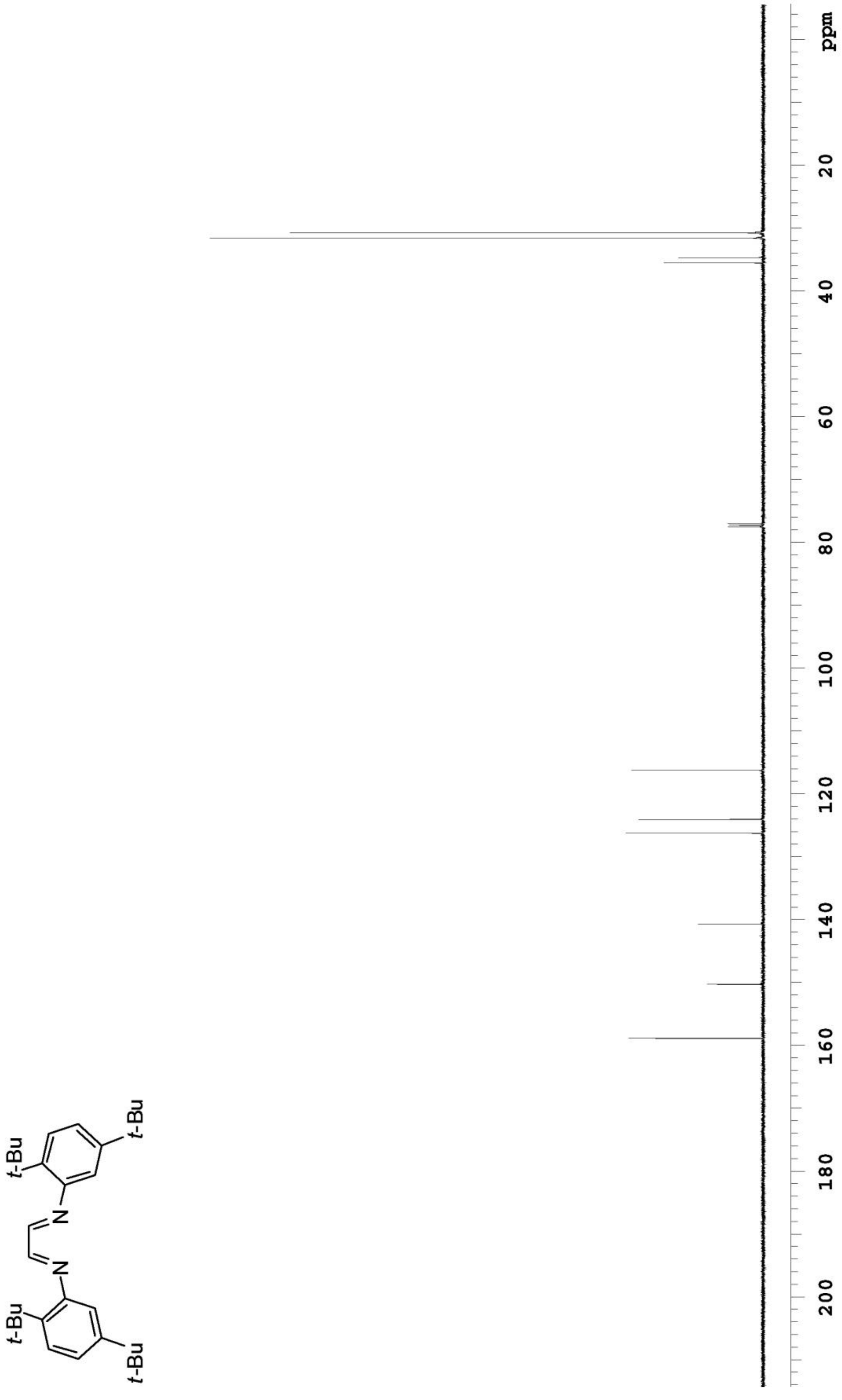
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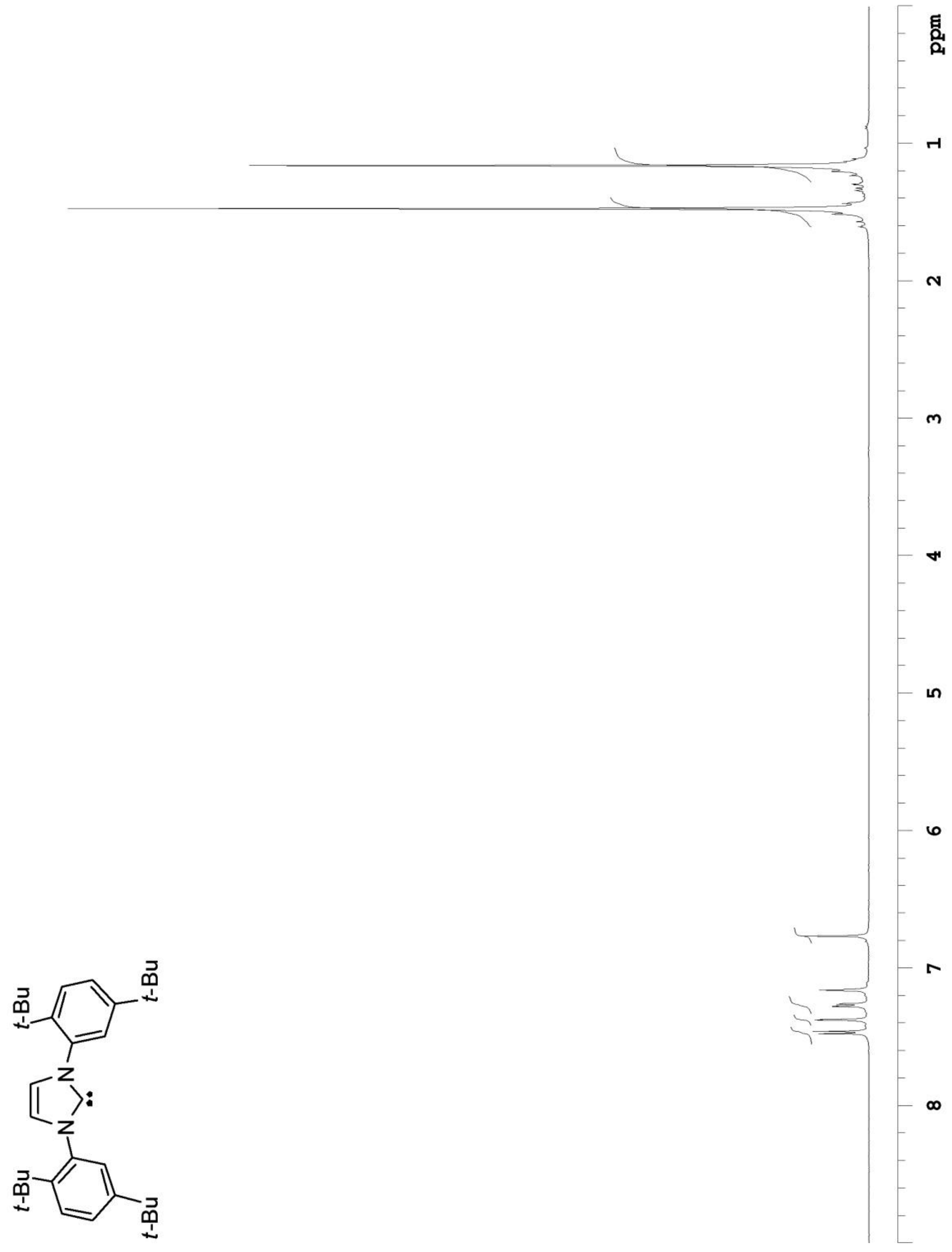
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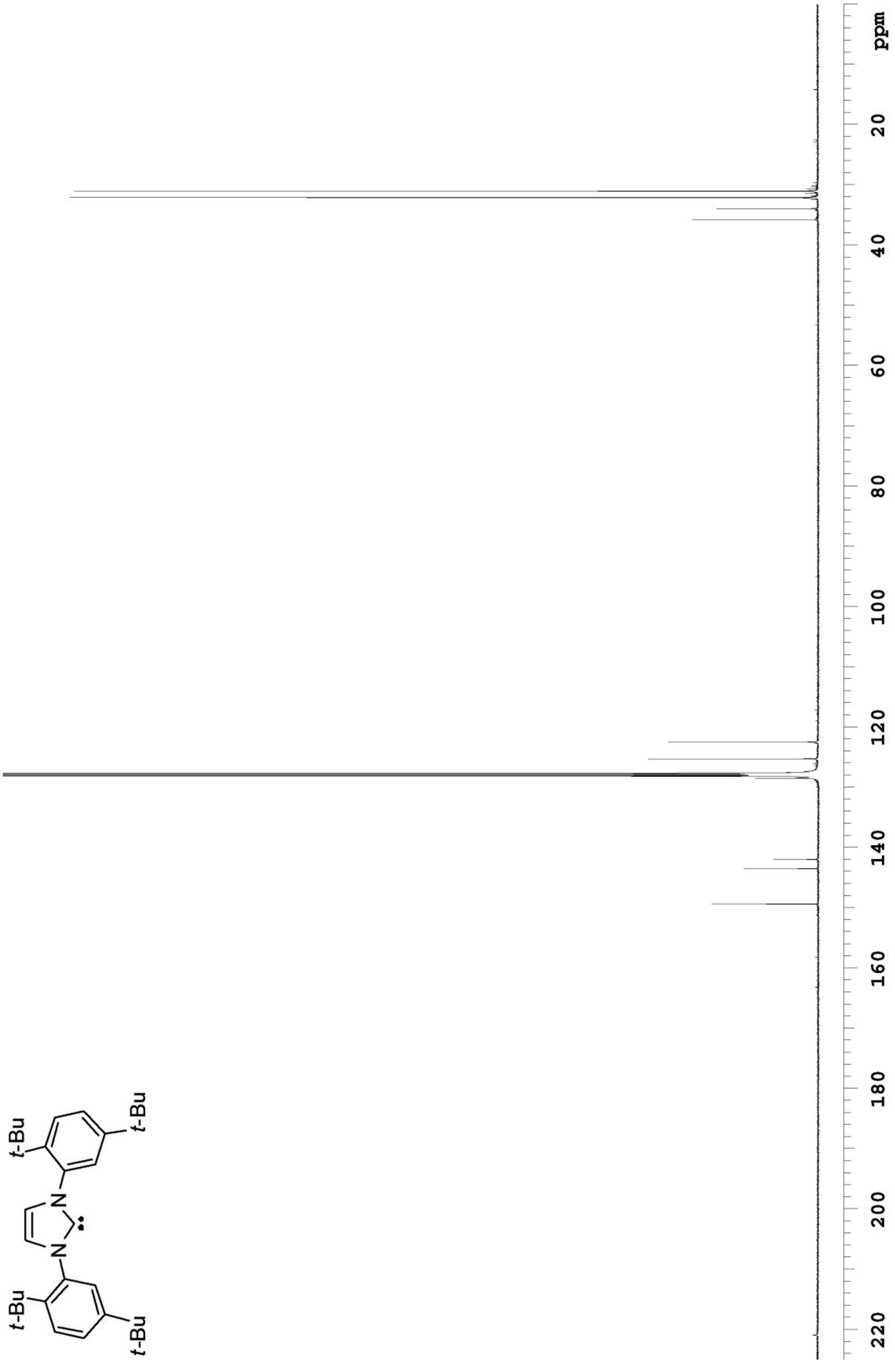
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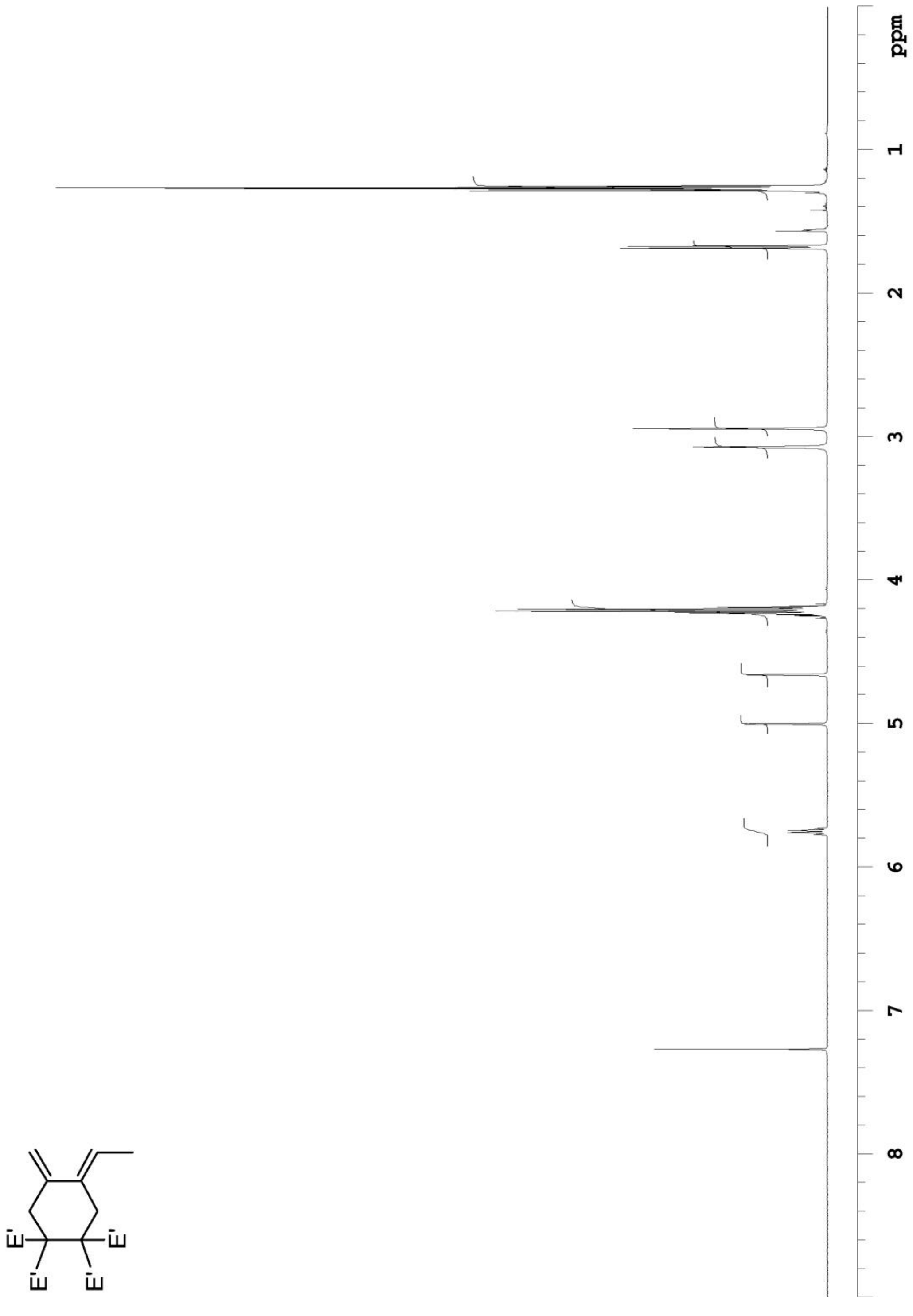
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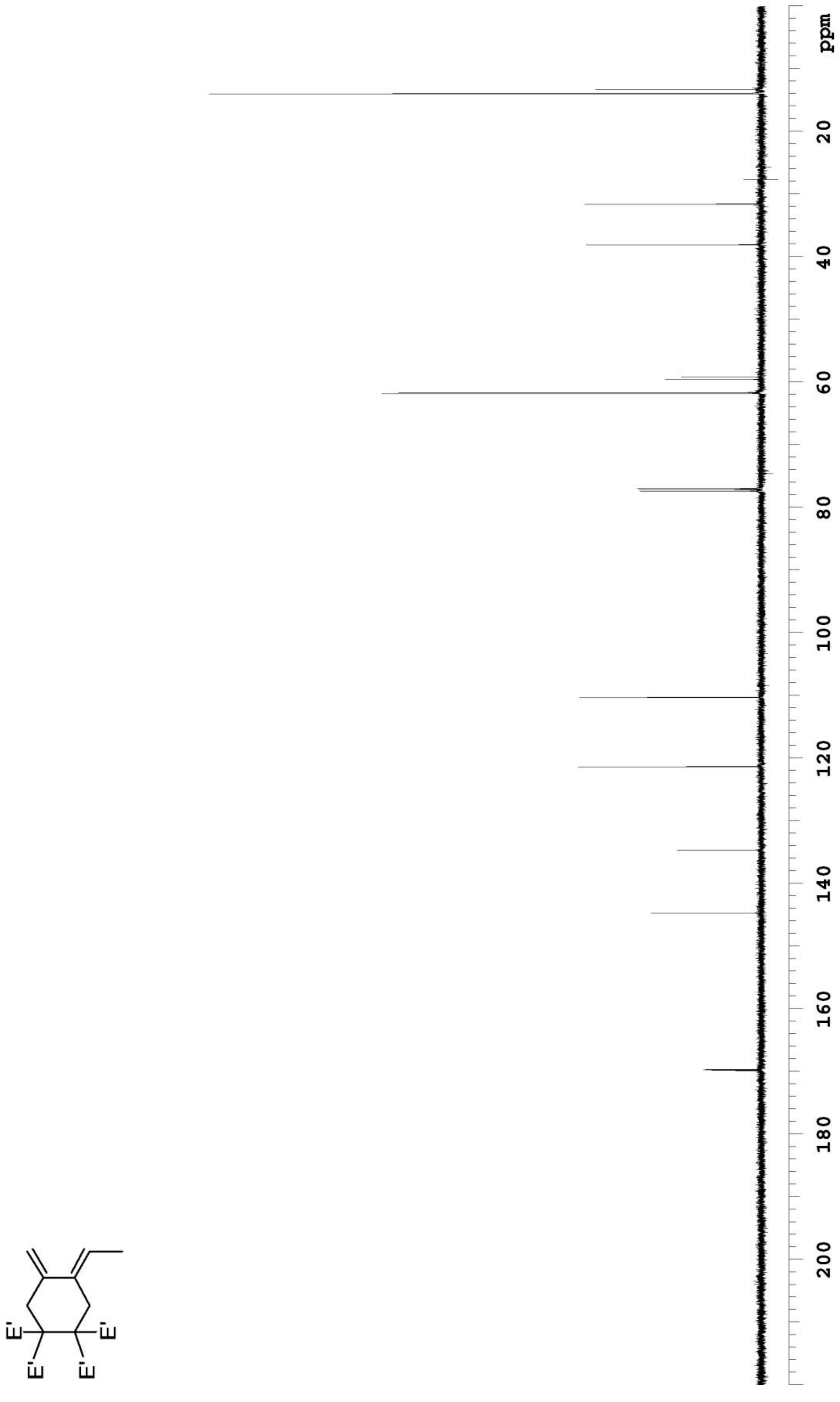
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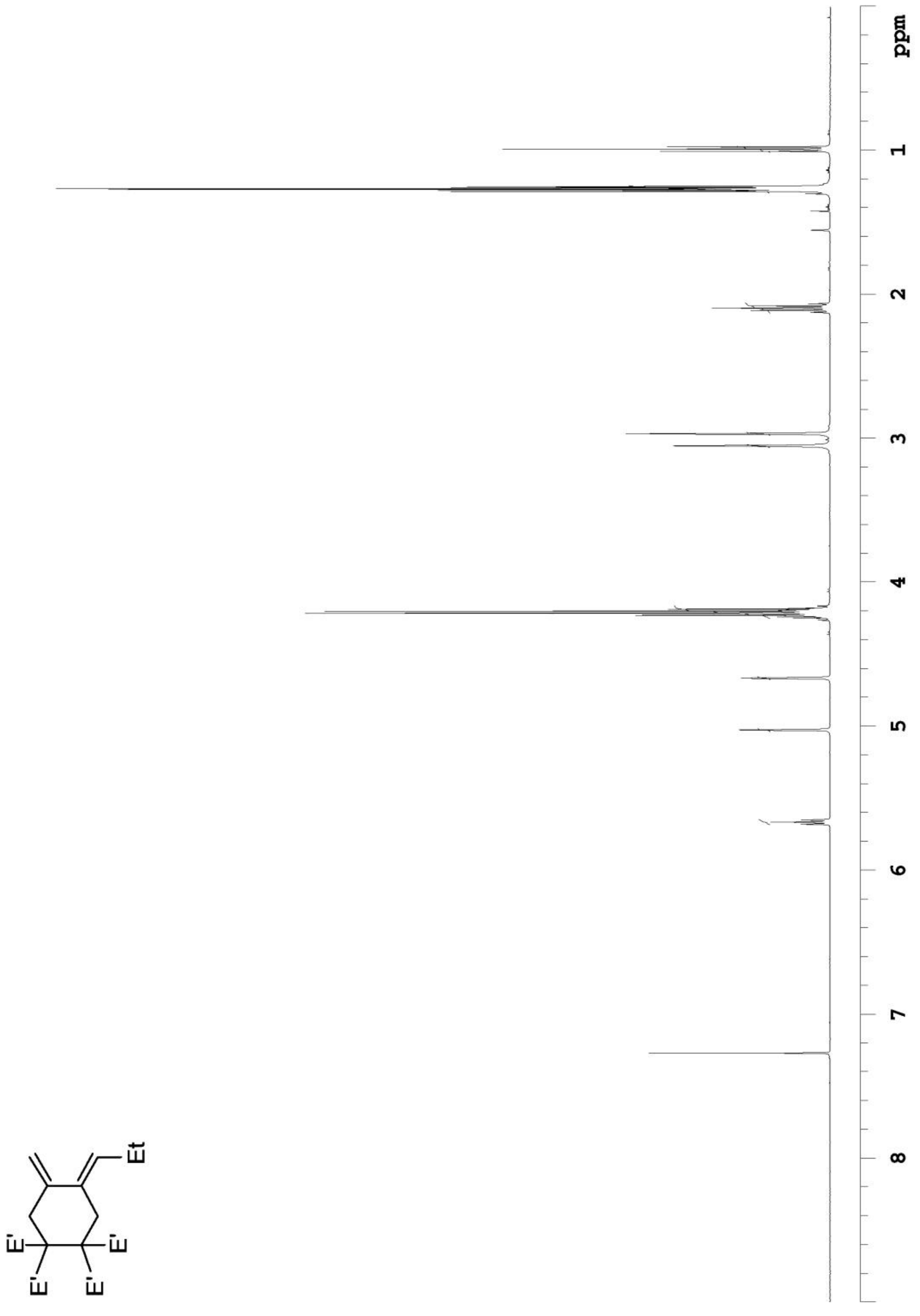
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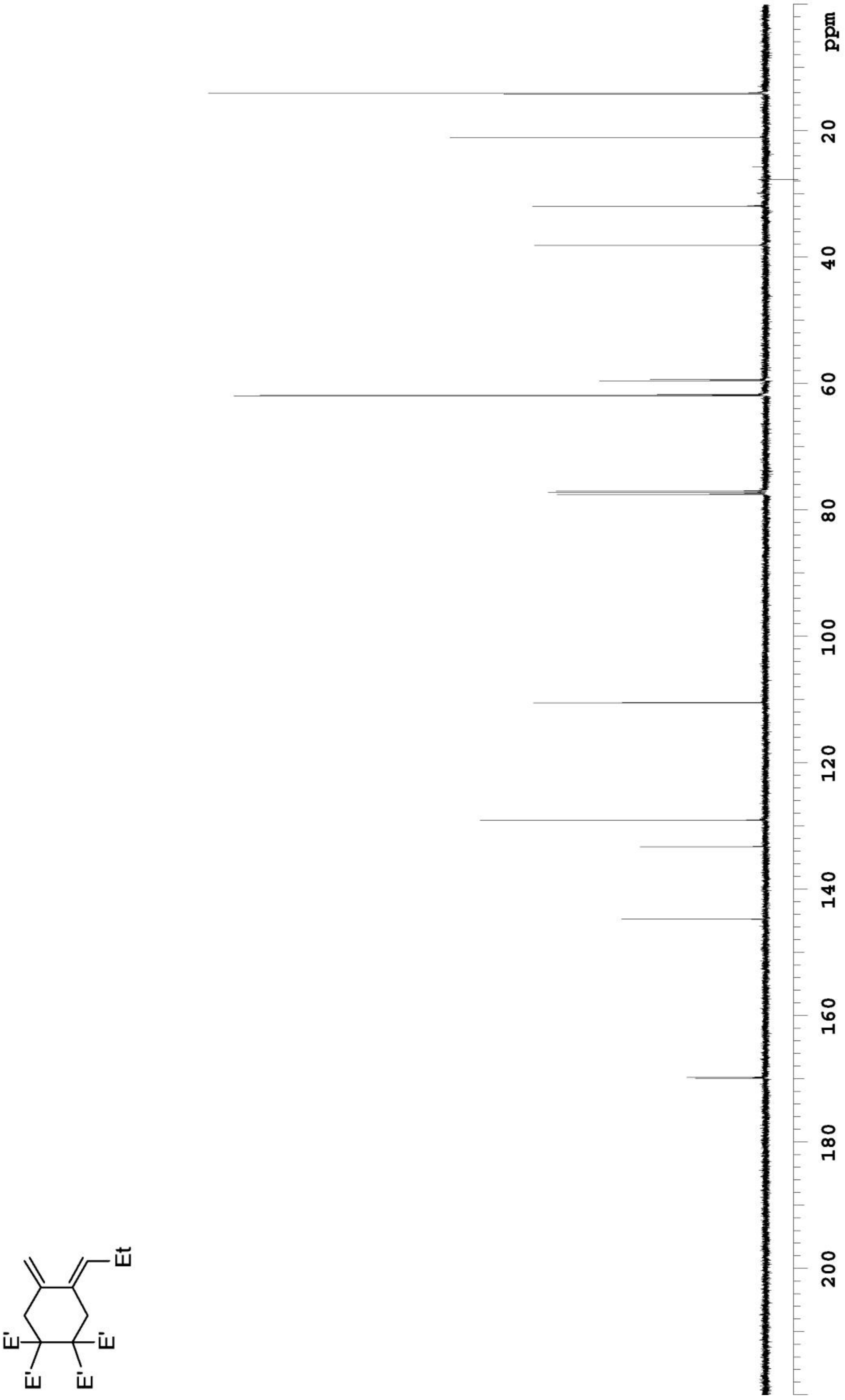
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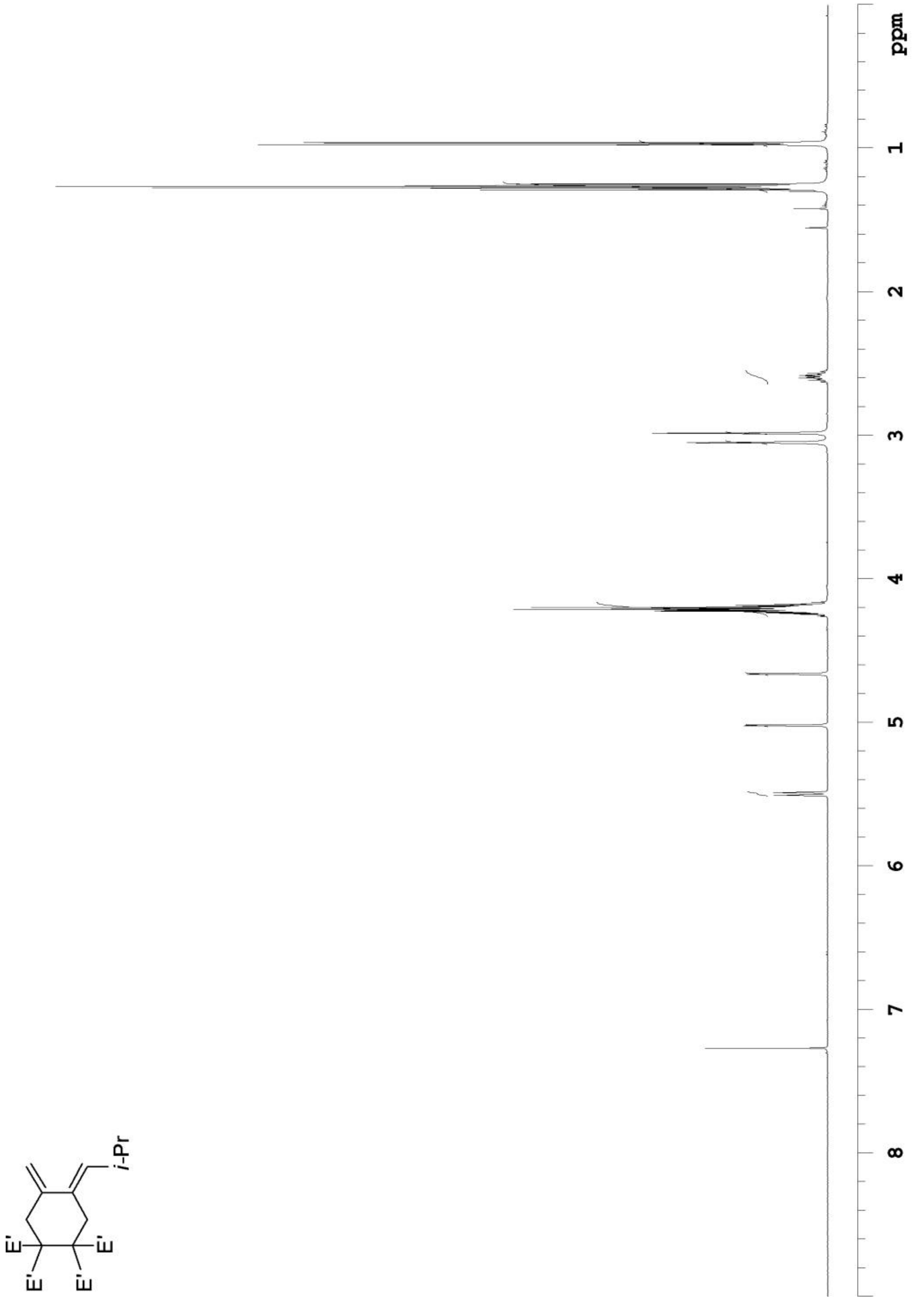
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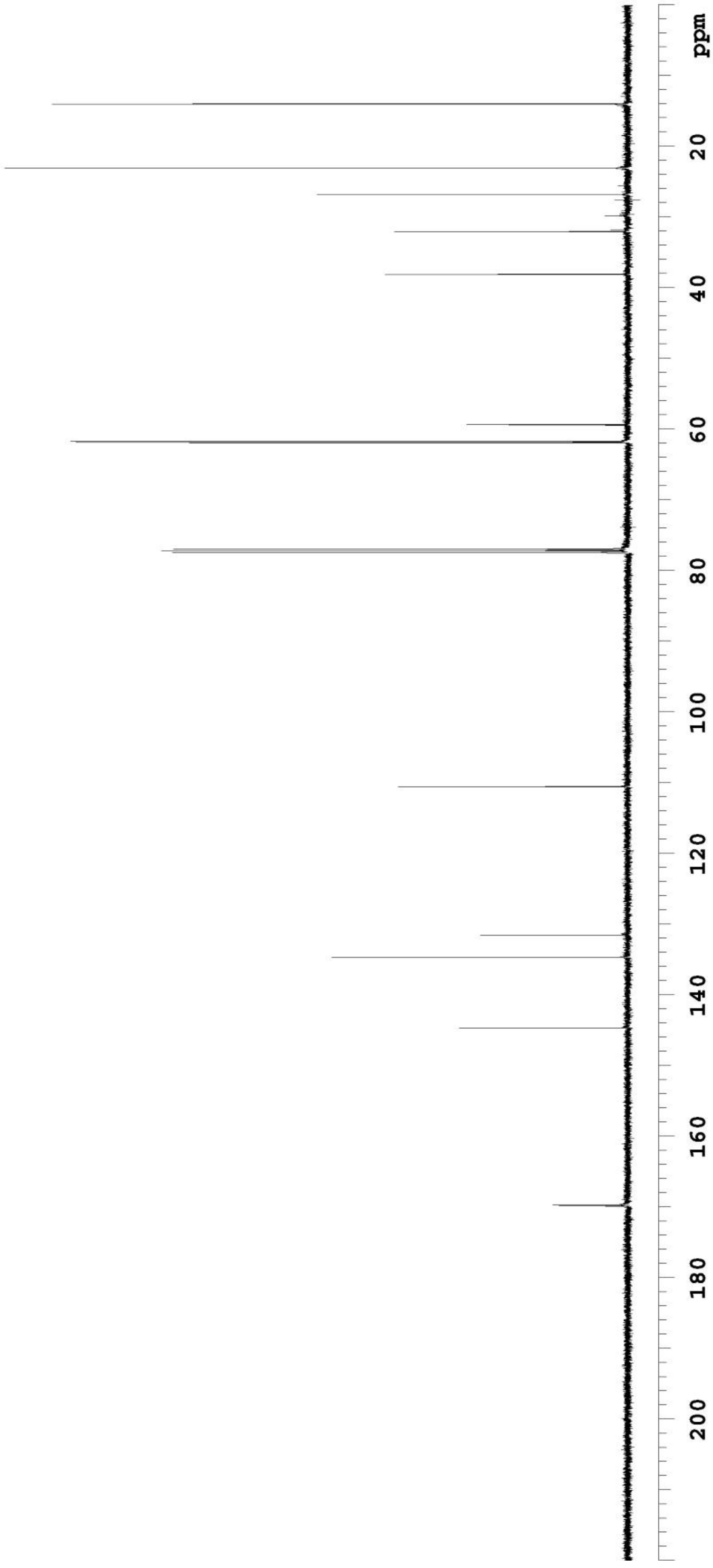
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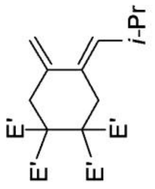
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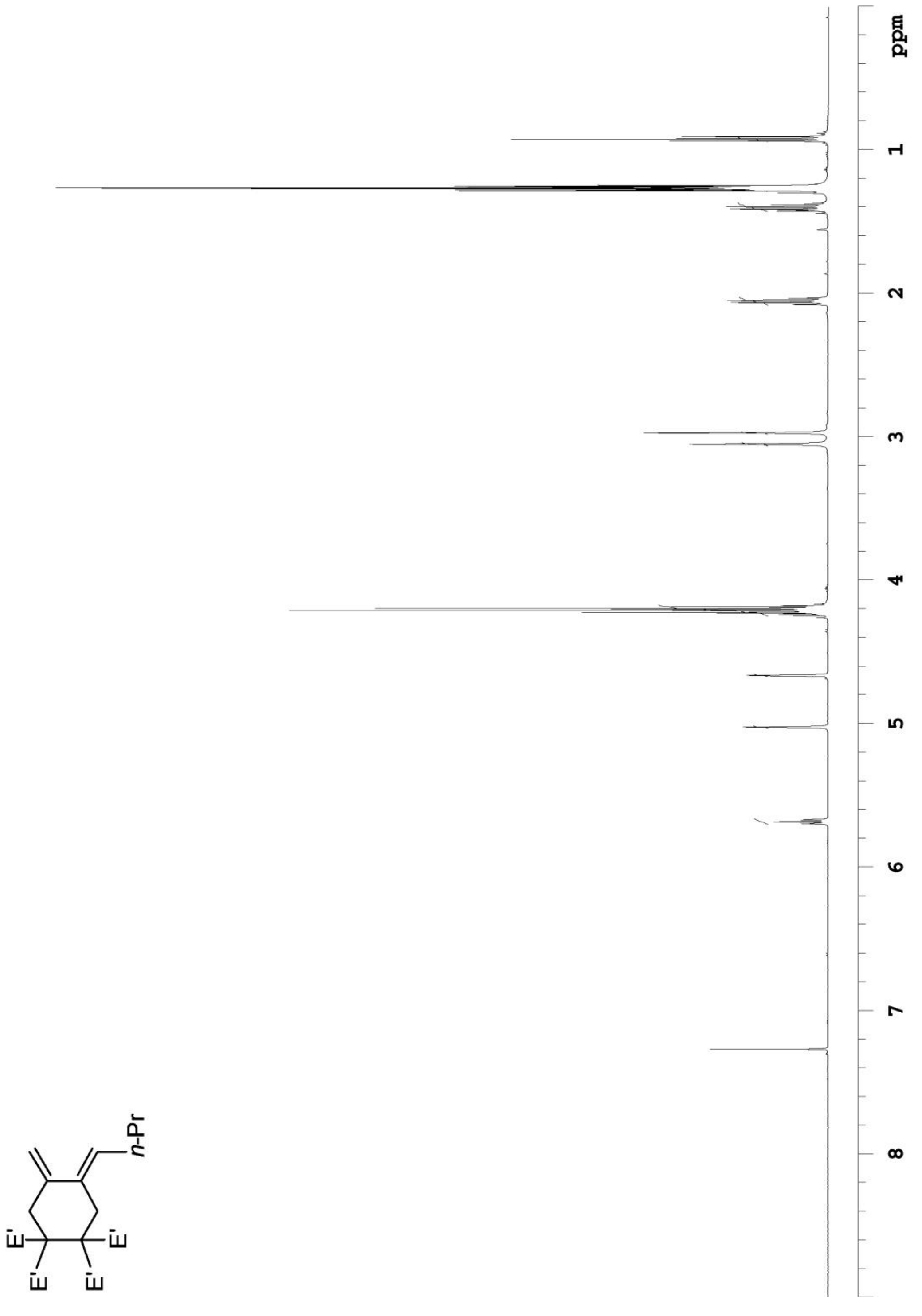
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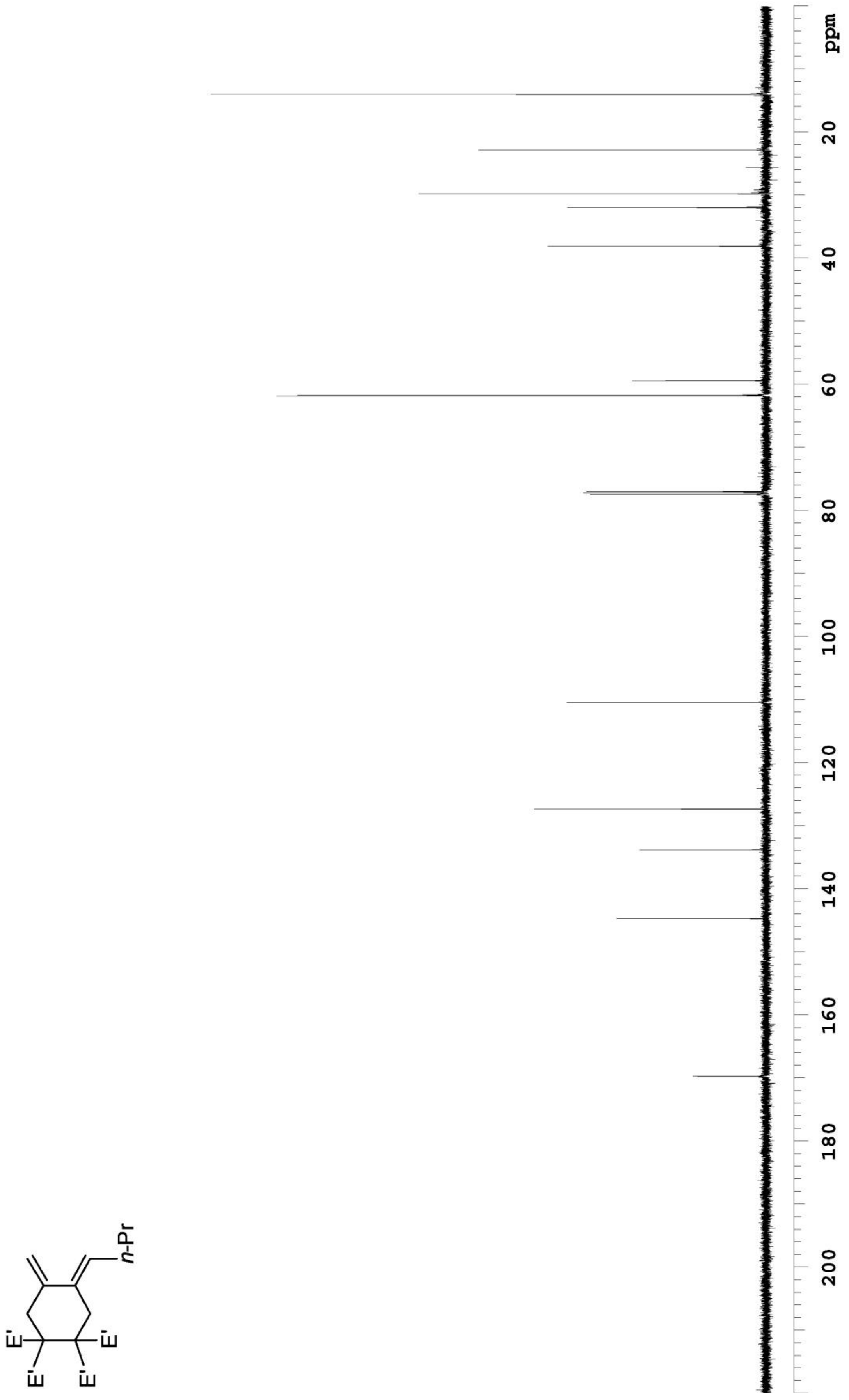
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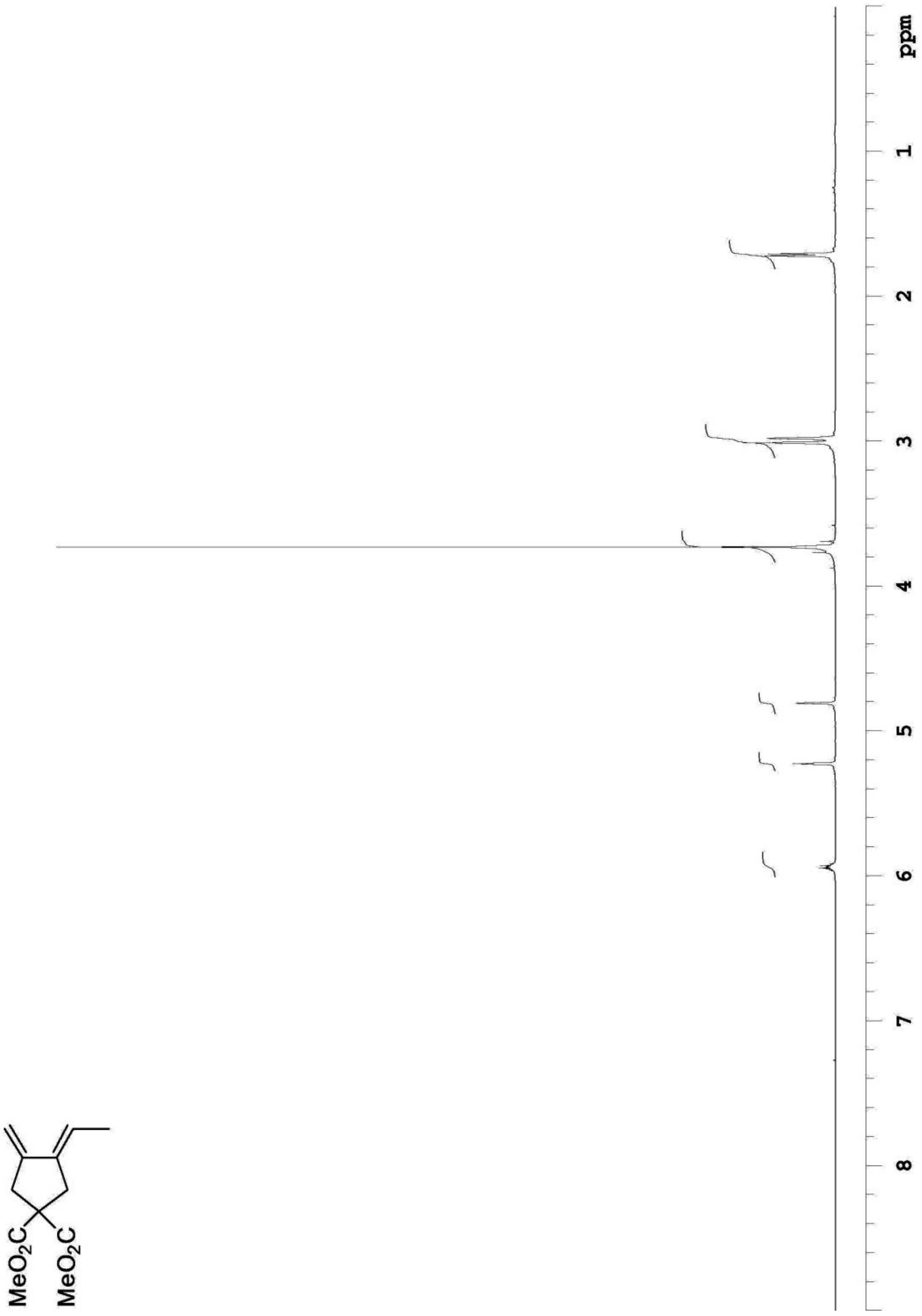
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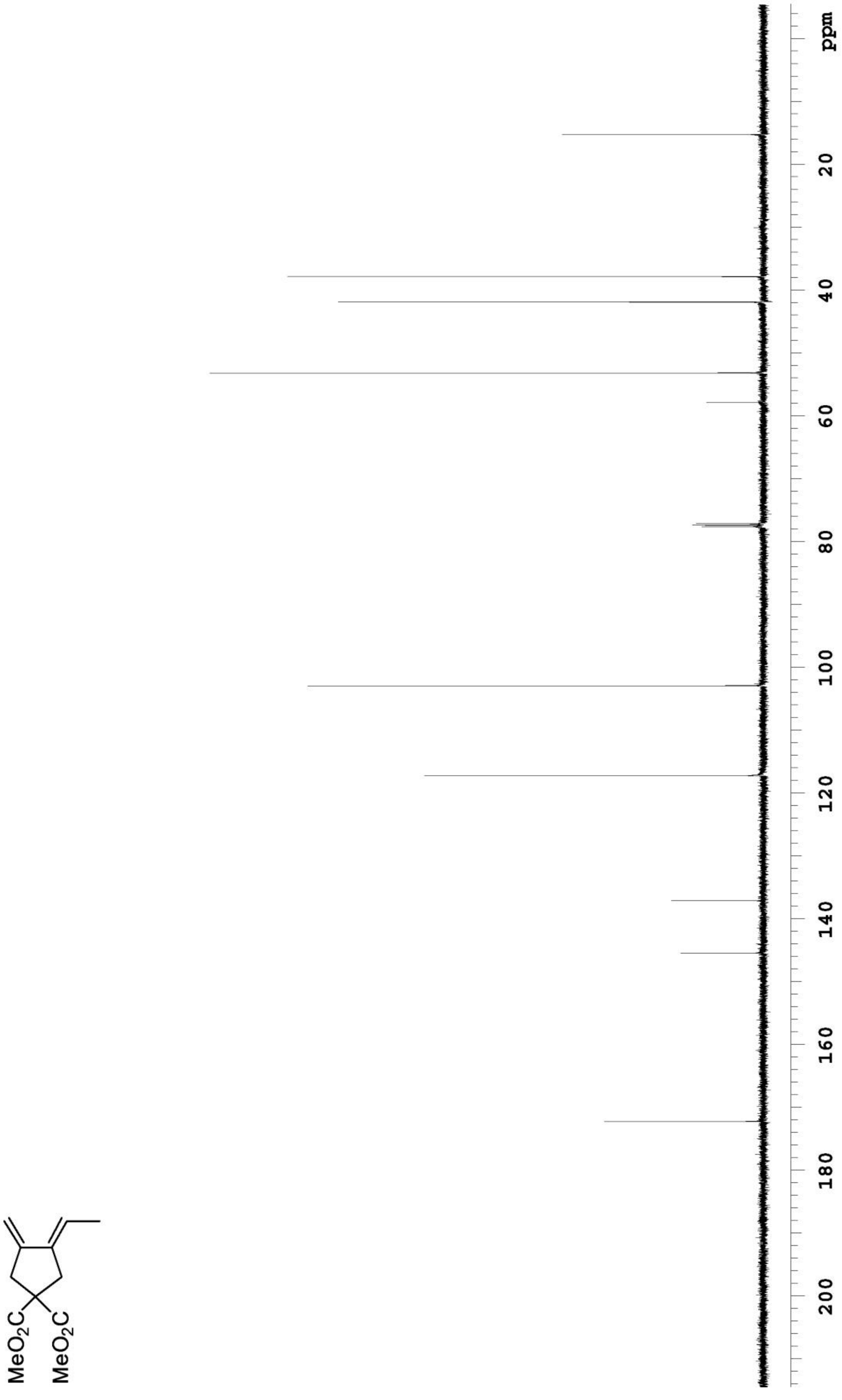
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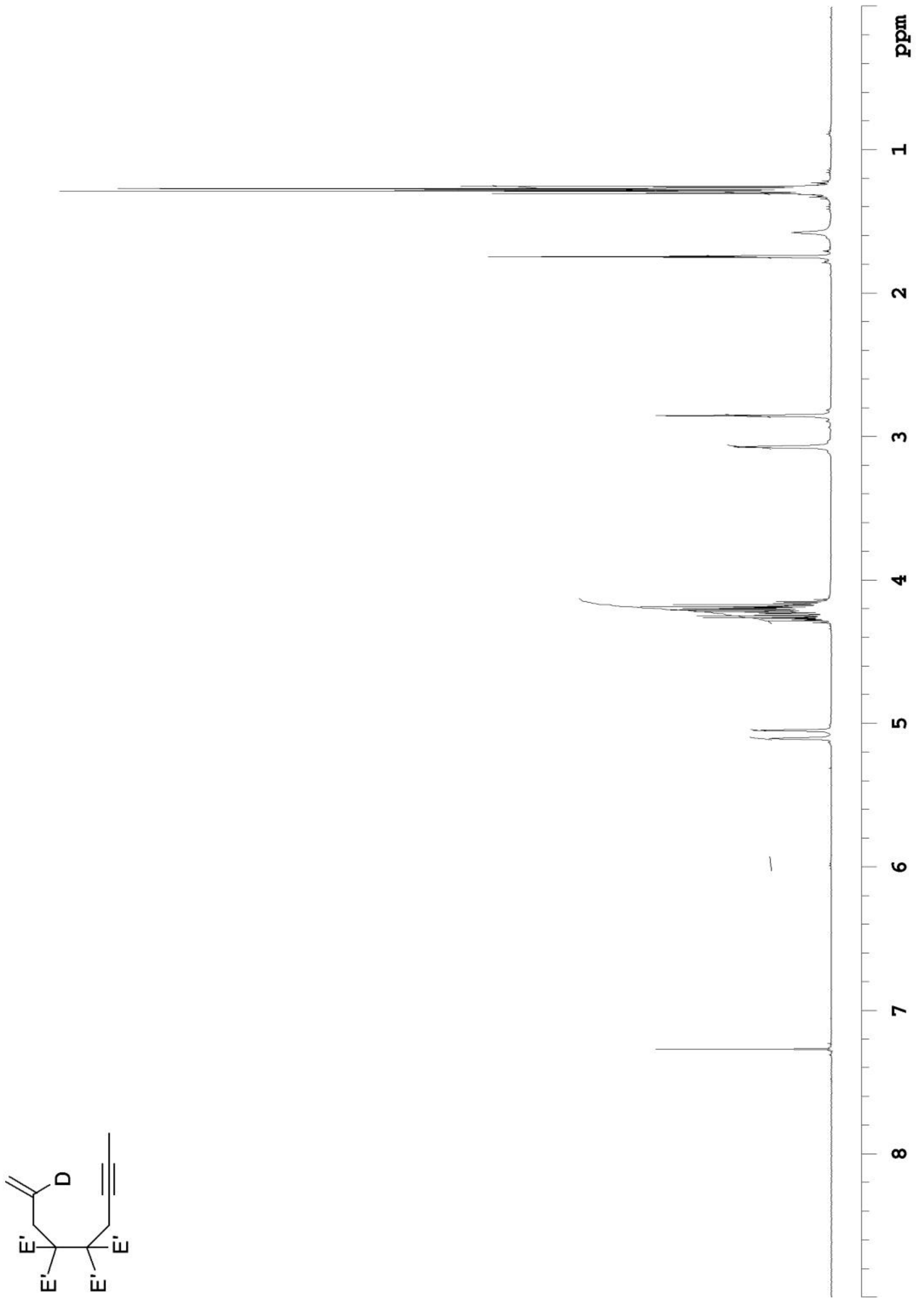
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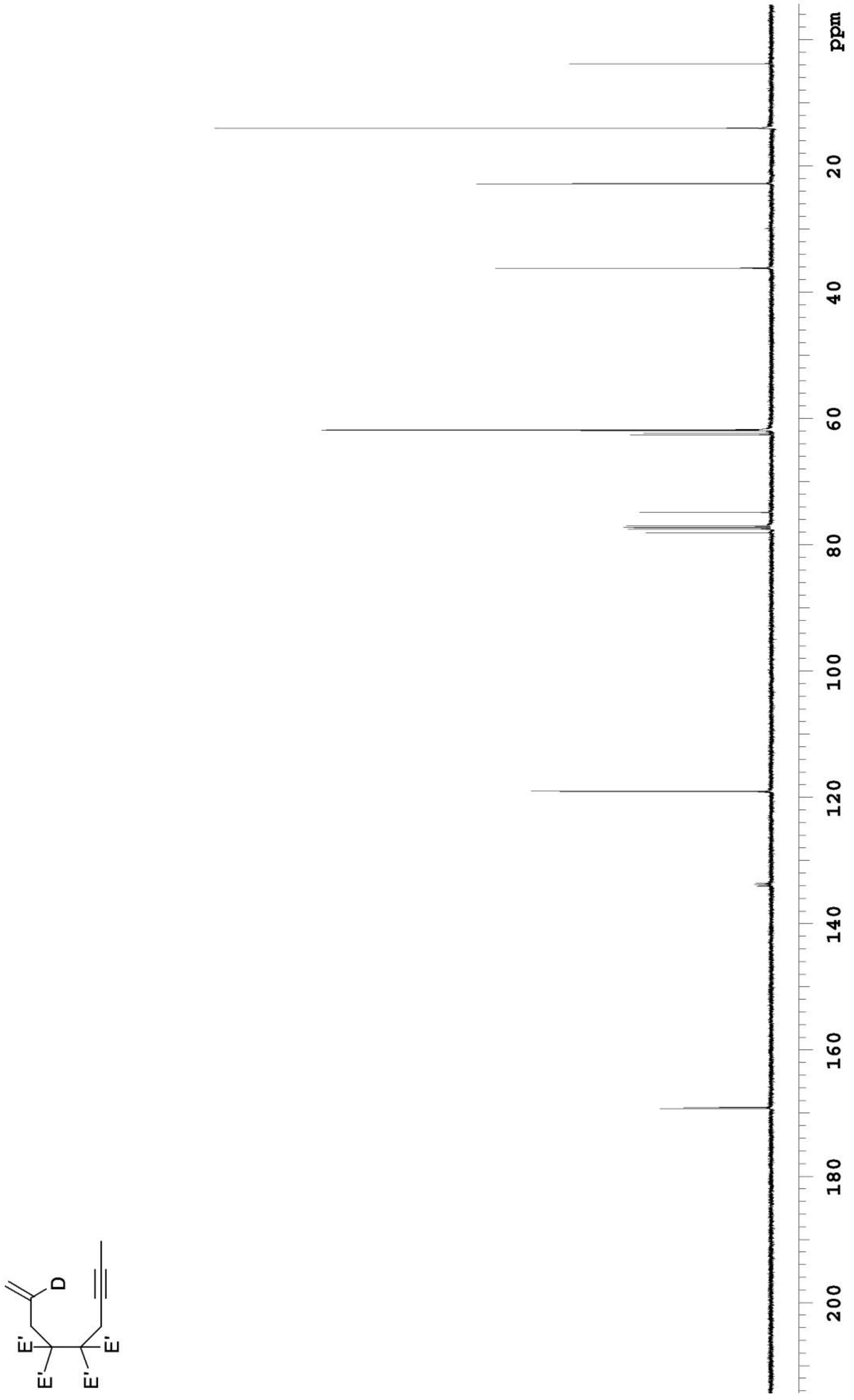
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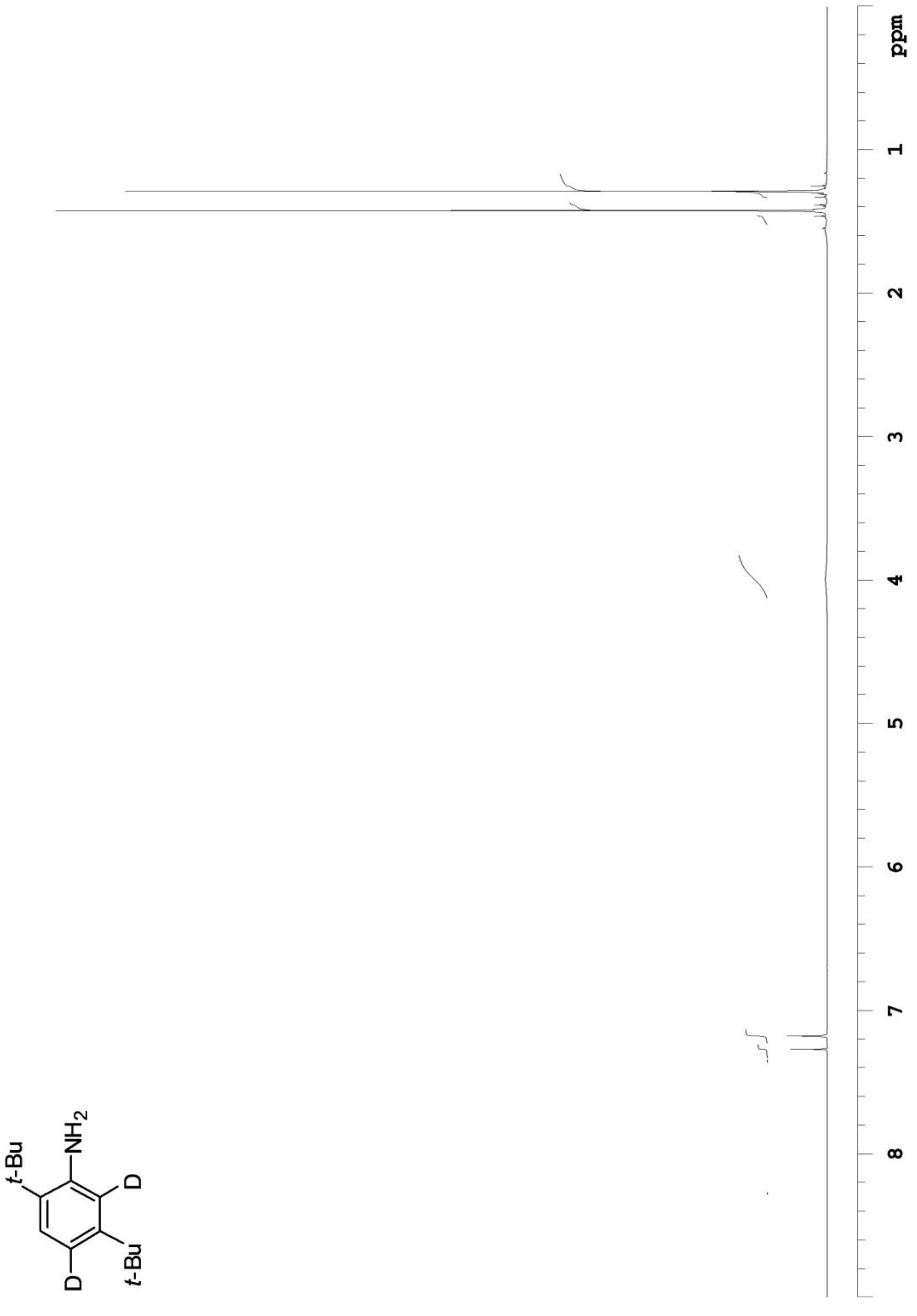
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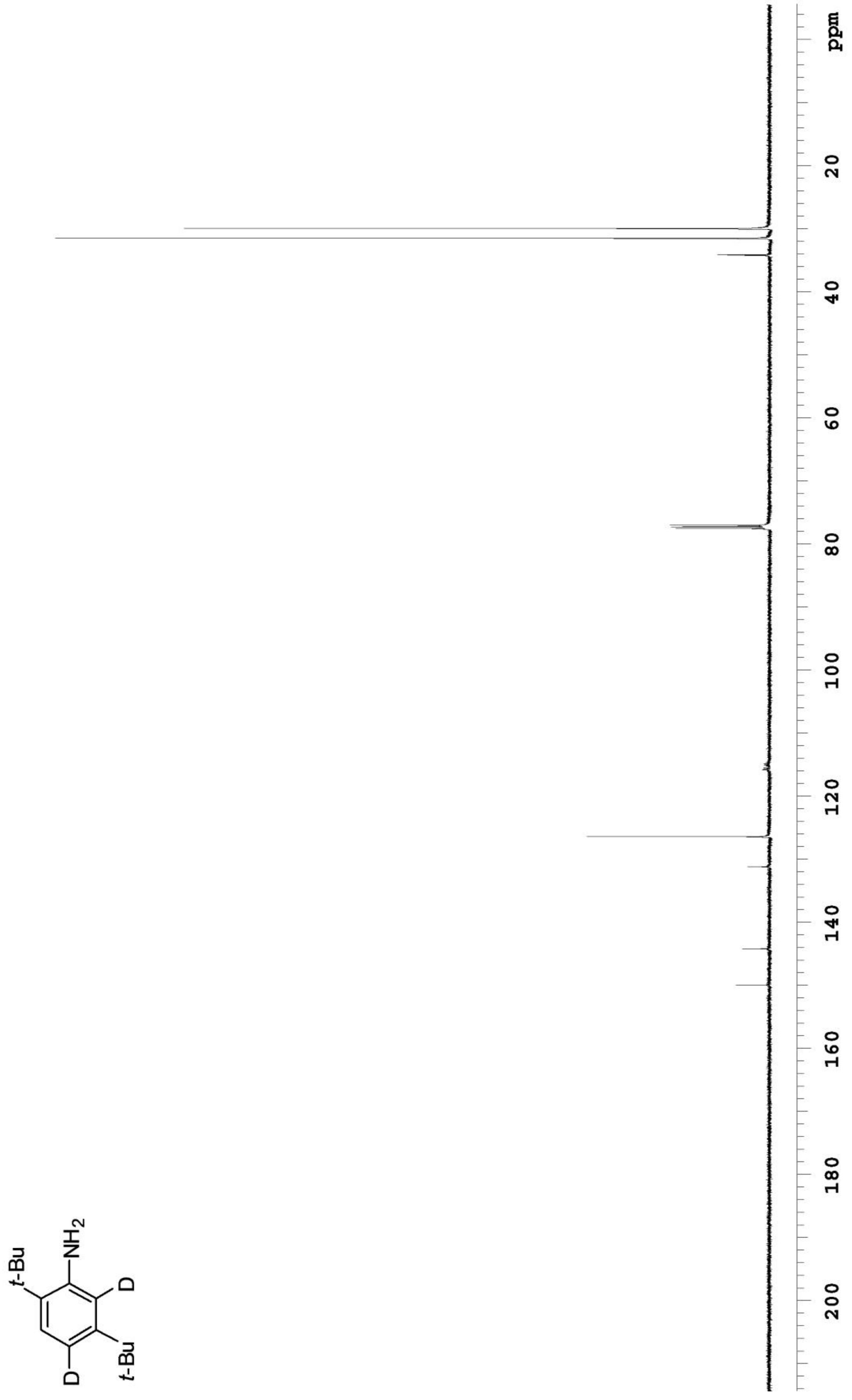
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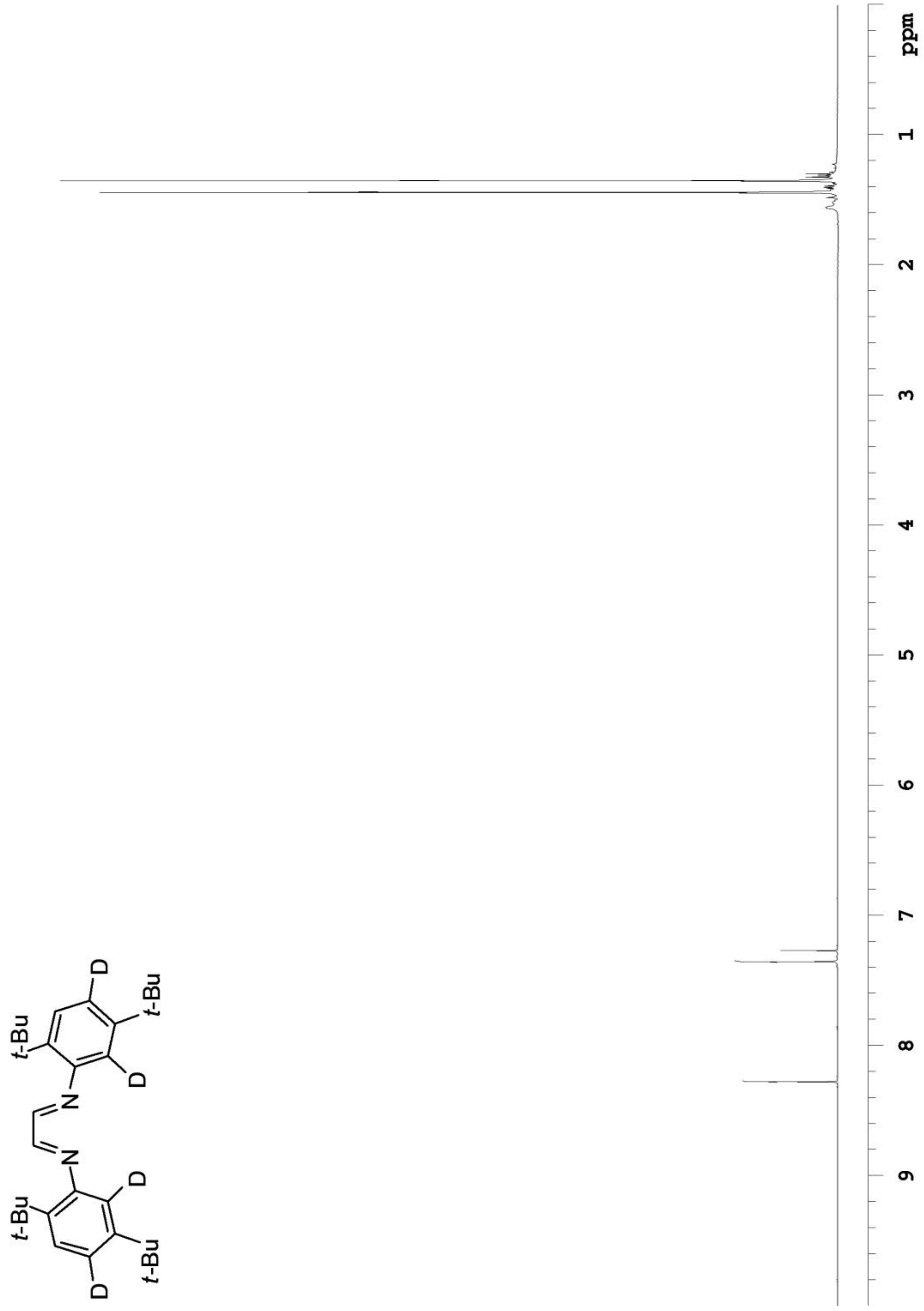
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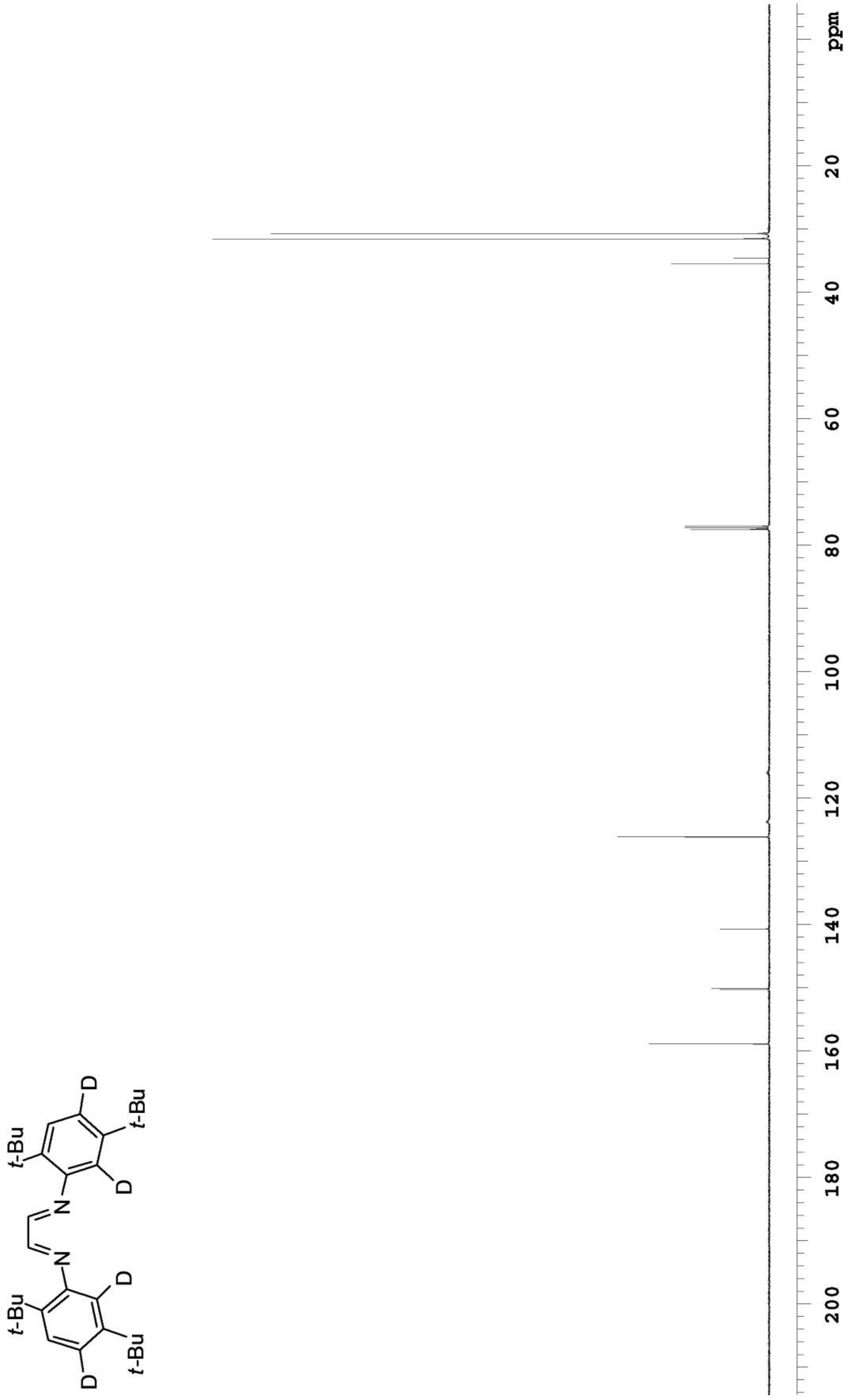
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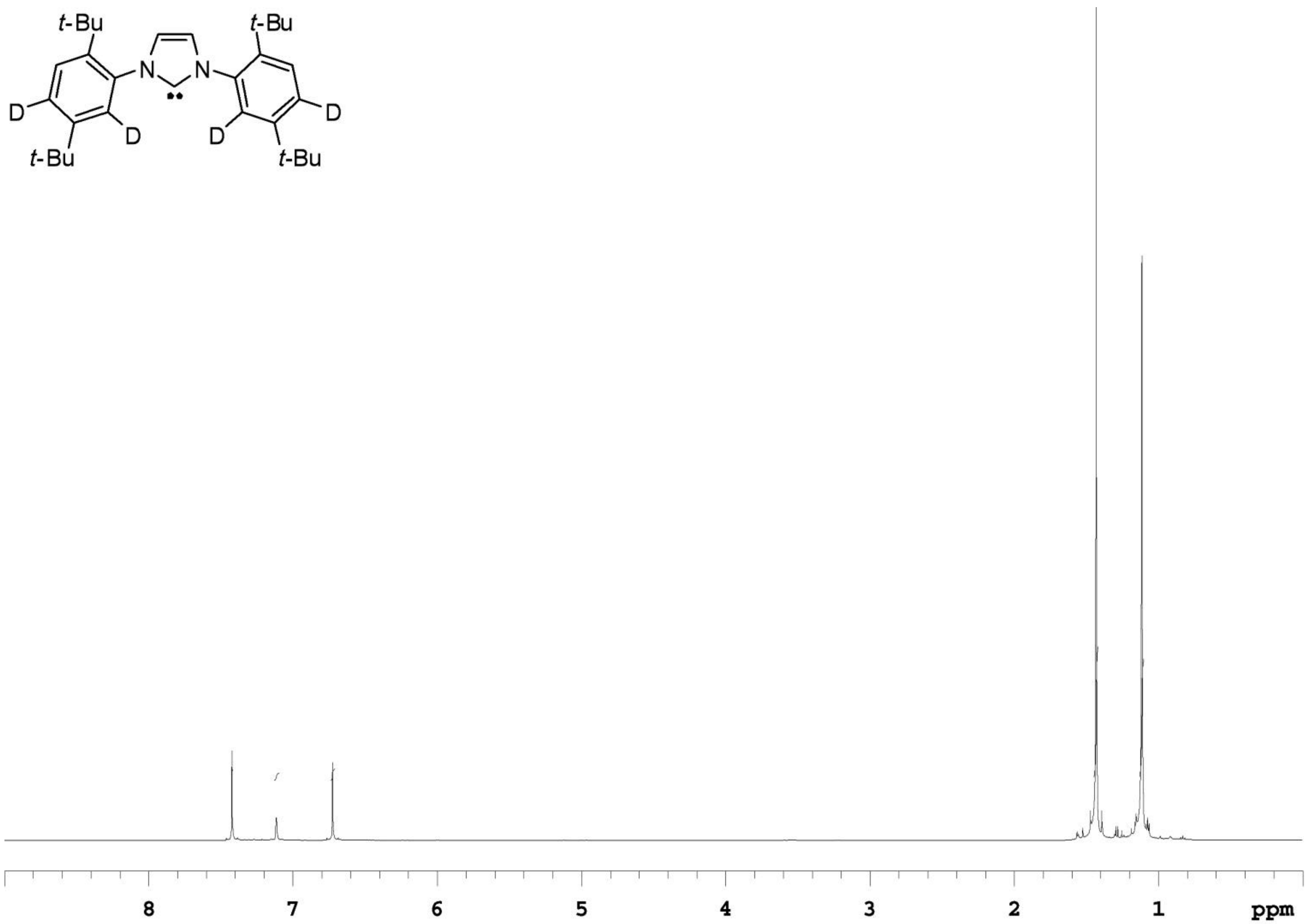
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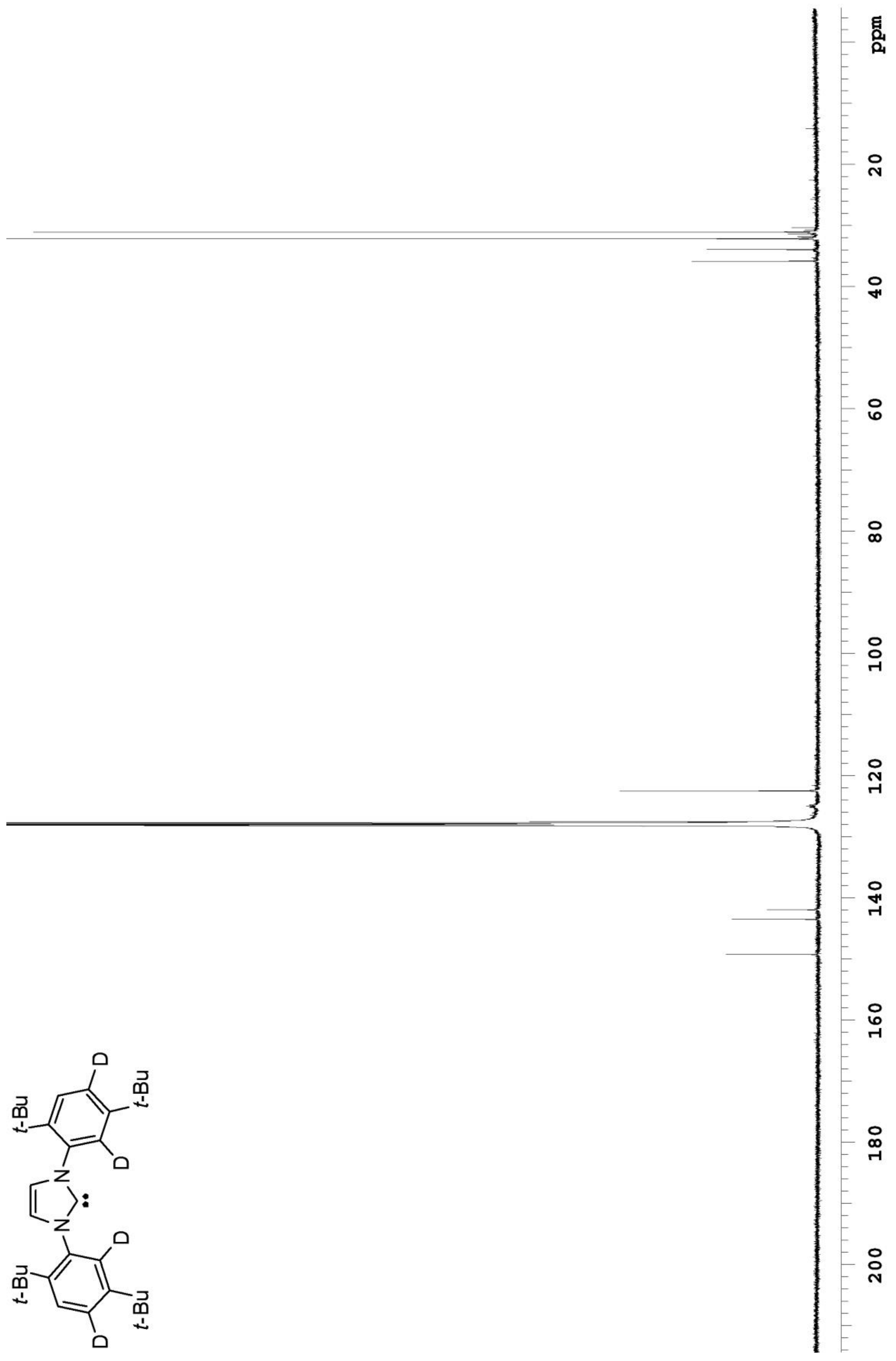
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