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Synthesis of 2(3H)-furanones via electrophilic cyclization

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Synthesis of 2(3*H*)-furanones via electrophilic cyclization

by

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Program of Study Committee:
Richard C. Larock, Major Professor
Walter Trahanovsky
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To my husband, John, my parents and my sisters

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LIST OF ABBREVIATIONS

Ar	aryl or argon
br	broad
Bu^n	*n*-butyl
calcd	calculated
d	doublet
dd	doublet of doublet
DMF	*N,N*-dimethylformamide
DPPF	1,1'-*bis*(diphenylphosphino)ferrocene
eq	equation
equiv	equivalent
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass-spectrometryscopy
Hz	hertz
i-Pr	isopropyl
IR	infrared (spectrum)
J	coupling constant

KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
mg	milligram
mins	minutes
mmol	millimole
mp	melting point
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PPh_3	triphenylphosphine
q	quartet
s	singlet
t	triplet
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
δ	chemical shift in ppm

ABSTRACT

The electrophilic cyclization of functionally-substituted alkynes is a very promising route to an extraordinary range of medicinally-interesting, functionally-substituted heterocycles and carbocycles. A variety of highly substituted 2(3*H*)-furanones are readily prepared from 3-alkynoate esters and the corresponding acids via electrophilic cyclization. This highly efficient approach proceeds under mild conditions, tolerates various functional groups, and generally provides 2(3*H*)-furanones in good to excellent yields. The cyclizations of 3-alkynoate esters and the corresponding acids have been performed using an excess of the electrophile at room temperature using either methylene chloride or acetonitrile as the solvent. Successful electrophiles in this process include I_2, ICl, and PhSeCl. The iodine functionality introduced into the heterocycle facilitates further elaboration by Pd-catalyzed chemistry.

GENERAL INTRODUCTION

The electrophilic cyclization of functionally-substituted alkynes has proven to be a very promising route to an extraordinary range of medicinally-interesting, functionally-substituted heterocycles and carbocycles. Previous work by our group and others has shown that iodine and other electrophiles can be used for the synthesis of benzo[*b*]furans, benzo[*b*]thiophenes, indoles, isoquinolines and a number of other heterocycles and carbocycles. This highly efficient approach to heterocycles and carbocycles proceeds under mild reaction conditions, accommodates various functional groups in the starting alkyne, and the iodo-substituted products can be further elaborated by Pd-catalyzed chemistry.

Our interest in electrophilic cyclization has led us to further explore the generality of this approach for the synthesis of highly substituted 2(3*H*)-furanones. We have extensively studied the reaction of 3-alkynoate esters and the corresponding acids with various electrophiles and obtained highly substituted 2(3*H*)-furanones in fair to excellent yields.

Dissertation Organization

This thesis is composed of one main chapter. The chapter describes the synthesis of various 2(3*H*)-furanones from 3-alkynoate esters and the corresponding acids. The cyclization proceeds under relatively mild reaction conditions. Some 3-alkynoate esters give fair to good yields of 2(3*H*)-furanones, whereas other 3-alkynyl esters with more than one nucleophilic center failed to give the desired 2(3*H*)-furanones. The unsuccessful 3-alkynoate ester substrates can be easily transformed to the corresponding 3-alkynoic acids. These 3-alkynoic acids cyclize in the presence of various electrophiles to give fair to excellent

yields. The iodo-substituted 2(3*H*)-furanone products can be further elaborated by Pd-catalyzed chemistry. The thesis is written following the guidelines for a full paper in the *Journal of Organic Chemistry* and is composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgement, and references.

Finally, all of the ^{1}H and ^{13}C NMR spectra for the 3-alkynoate esters and the corresponding acid starting materials, the electrophilic cyclization products and the palladium-catalyzed products have been compiled in the appendix, following the general conclusions for this thesis.

SYNTHESIS OF 2(3*H*)-FURANONES VIA ELECTROPHILIC CYCLIZATION

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Abstract

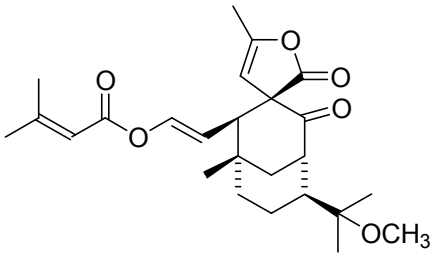
A variety of highly substituted 2(3*H*)-furanones are readily prepared from 3-alkynoate esters and the corresponding acids via electrophilic cyclization. This highly efficient approach proceeds under mild conditions, tolerates various functional groups, and generally provides substituted 2(3*H*)-furanones in good to excellent yields. Successful electrophiles in this process include I_2, ICl, and PhSeCl.

Introduction

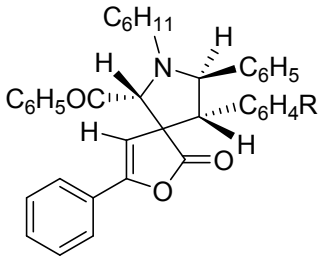
2(3*H*)-Furanone derivatives[1] constitute an important group of natural products and possess a wide range of biological activities. Among the known 2(3*H*)-furanone derivatives, the dihydro-2(3*H*)-furanone moiety is abundant in a large variety of natural and synthetic compounds used as agrochemicals, pharmaceuticals, and in the food industry.[2] However, highly substituted, unsaturated 2(3*H*)-furanones have not been fully studied. Recently, several highly substituted unsaturated 2(3*H*)-furanones have been discovered and attracted great interest due to their biological activities. For example, the naturally-occurring compound Spirovibsanin A (I) has been isolated from the plant *Viburnum awabuki*.[3] Some other highly substituted 2(3*H*)-furanones, such as spiro[butenolide]pyrrolidines (II), have

been studied for their antibacterial and antifungal activity against human pathogenic bacteria and dermatophytic fungi (Scheme 1).[4]

Scheme 1



Spirovibsanin A (**I**)



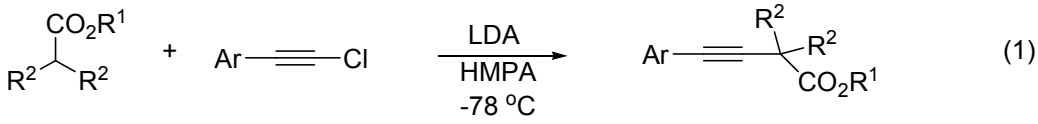
spiro[butenolide]pyrrolidines (**II**)

The electrophilic cyclization of functionally-substituted alkynes has attracted much attention due to its wide utility in the preparation of a range of useful, functionally-substituted heterocycles and carbocycles,[5] such as quinolines,[6] isoxazoles,[7] isoindolin-1-ones,[8] benzo[*b*]thiophenes,[9] bicyclic β-lactams,[10] indoles,[11] chromones,[12] isochromenes,[13] 2-naphthols,[14] benzofurans,[15] cyclic carbonates,[16] pyrroles,[17] furans[18] isocoumarins,[19] α-pyrones,[19] isoquinolines,[20] naphthyridines,[20] polycyclic aromatics,[21] naphthalenes,[22] and furopyridines.[23] Herein, we report an efficient approach to various highly substituted 2(3*H*)-furanones by the electrophilic cyclization of 3-alkynoate esters and acids. The resulting iodine-containing products can be further elaborated to a wide range of functionally-substituted furanones using subsequent palladium-catalyzed processes.

Results and Discussion

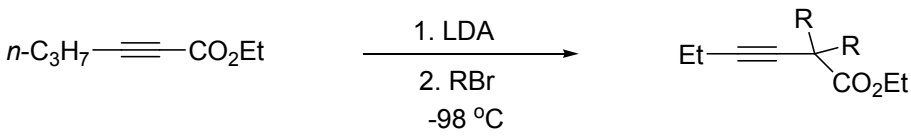
The 3-alkynoate esters required for our reactions have typically been prepared in two or three steps. The 4-aryl-2,2-dialkylbut-3-ynoates have been synthesized by the reaction of

alkyl-substituted ester enolates with the corresponding 1-chloro-2-arylethynes at -78 °C (eq. 1).[24]



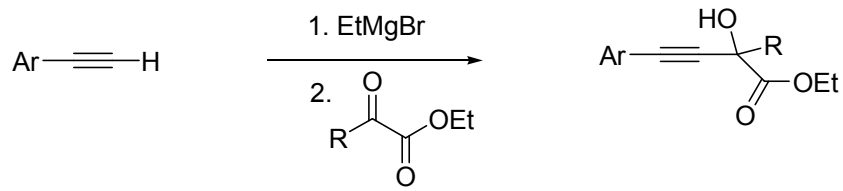
(1)

The 2,2-dialkyl-3-hexynoate esters have been synthesized by a one-pot reaction of ethyl 2-hexynoate with excess LDA at -98 °C, followed by the addition of an excess of the appropriate alkyl bromide (eq. 2).[25]



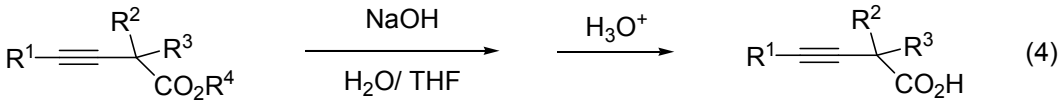
(2)

Various methods have been utilized to prepare the remaining esters. For example, the 2-alkyl-4-aryl-2-hydroxybut-3-ynoate esters were made by reacting a terminal aryl acetylene with the appropiate ethyl 2-oxoalkanoate esters, in the presence of EtMgBr (eq. 3).[26]



(3)

All the 3-alkynoic acids were prepared from the corresponding esters by alkaline hydrolysis (eq. 4).[27] The detailed syntheses of all of the starting materials are provided in the experimental section.



(4)

To examine the reactivity of the 3-alkynoate esters, we first explored the reaction of the 3-alkynoate ester **1** with 1.5 equivalents of I_2 in dichloromethane under our previously established reaction conditions for the synthesis of benzo[*b*]thiophenes[9b] and indoles.[11d] The reaction proceeded smoothly and reached completion in 1.5 h, affording an 87% yield of the iodolactone **2** (Table 1, entry 1). We have also examined the reaction of ester **1** and the readily available electrophiles ICl and PhSeCl. ICl gave the fastest reaction and reached completion in 1 h. However, when using ICl as the electrophile, this alkyne afforded a 1:1 inseparable mixture of the corresponding 4-iodo- and 4-chloro-substituted 2(3*H*)-furanones in a 70% total yield. PhSeCl has also been successfully employed in this electrophilic cyclization, providing a 70% yield of the desired selenium cyclization product **4** in 1 h (Table 1, entry 3).

We next applied this chemistry to various substituted 3-alkynyl esters (Table 1, entries 4-40). 4-Aryl-2,2-dimethylbut-3-ynoate esters bearing an electron-rich aromatic ring, such as **5**, and an electron-deficient aromatic ring, such as **8**, reacted with I_2 smoothly, affording the corresponding lactones **6** and **9** in 78% (Table 1, entry 4) and 67% (Table 1, entry 8) yields respectively. However, when ICl was used in place of I_2, the 3-alkynoate esters **5** and **8** afforded mixtures of the 4-iodo- and 4-chloro-2(3*H*)-furanones. The ratio of these two products depends on the amount of ICl employed. When we utilized 1.1 equivalents of ICl in the cyclization of **5**, the iodo-substituted product **6** was dominant. Lactones **6** and **7** were formed in an 11:1 ratio (Table 1, entry 5). As we increased the amount of ICl to 1.5 equivalents, the ratio of the iodo-substituted product **6** to the chloro-substituted product **7** decreased to 2:1 (Table 1, entry 6). When we employed 3.0 equivalents of ICl in the reaction of **5**, the ratio of **6** to **7** changed to 1:3 (Table 1, entry 7). Furthermore, when ICl was allowed

Table 1. Synthesis of Substituted 2(3*H*)-Furanones by the Electrophilic Cyclization of 3-Alkynoate Esters[a]

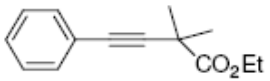
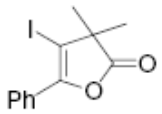
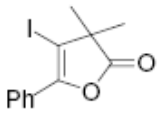
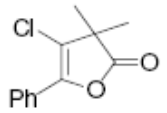
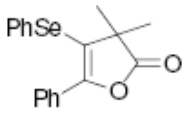
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
1		**1**	I_2	1.5		**2**	87
2		**1**	ICl	1		**2**	70 (1:1)[c]
						**3**	
3		**1**	PhSeCl	1		**4**	70

Table 1. (cont'd)

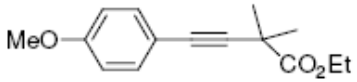
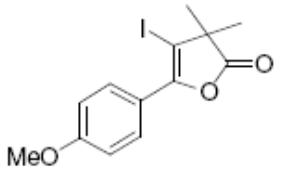
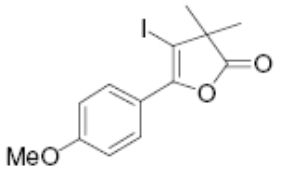
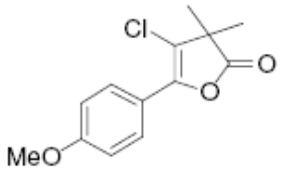
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
4		**5**	I_2	5		**6**	78
5		**5**	ICl[d]	4		**6**	**77** (11:1)[c]
						**7**	
6		**5**	ICl	4			68 (2:1)[c]

Table 1. (cont'd)

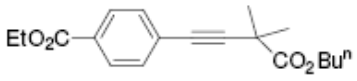
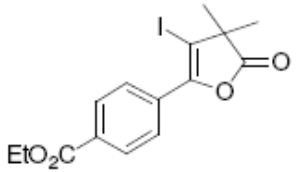
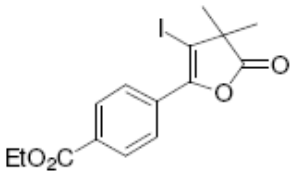
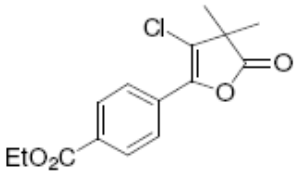
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
7		**5**	ICl[e]	4			40 (1:3)[c]
8		**8**	I_2	2		**9**	67
9[b]		**8**	ICl	2		**9**	70 (1:1)[c]
						**10**	

Table 1. (cont'd)

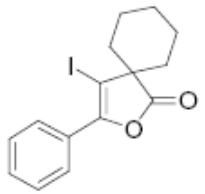
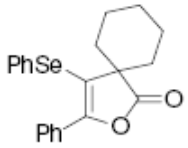
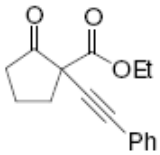
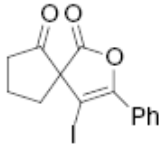
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
10		**11**	I_2	24		**12**	89
11		**11**	ICl	1		**12**	89
12		**11**	PhSeCl	1.5		**13**	73
13		**14**	I_2	9		**15**	80

Table 1. (cont'd)

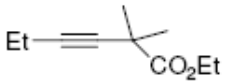
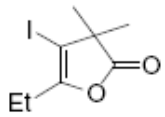
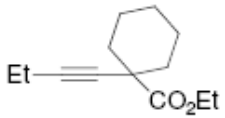
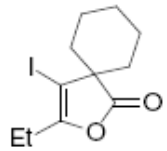
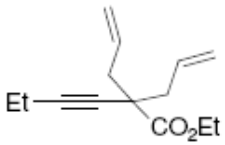
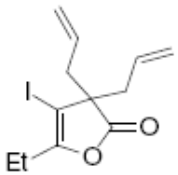
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
14		**16**	I_2	1		**17**	86
15		**16**	ICl	1		**17**	50
16		**18**	I_2	6		**19**	78
17		**18**	ICl	1		**19**	60
18		**20**	I_2	2		**21**	84

Table 1. (cont'd)

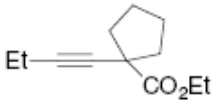
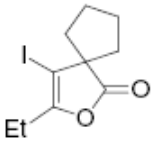
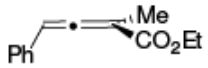
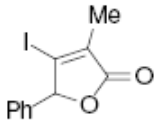
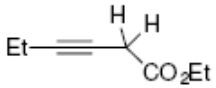
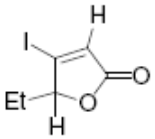
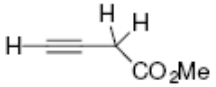
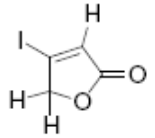
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
19		**22**	I_2	1		**23**	97
20		**22**	ICl	0.5		**23**	86
21		**24**	I_2	1		**25**	96
22		**26**	I_2	24		**27**	62
23		**28**	I_2	48		**29**	0[f]

Table 1. (cont'd)

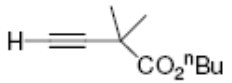
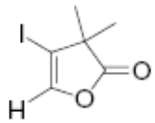
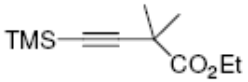
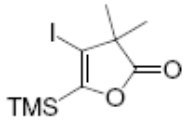
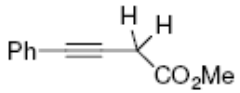
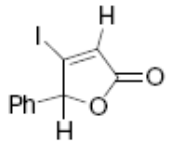
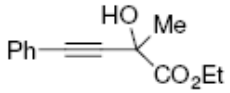
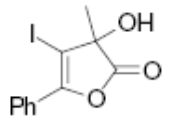
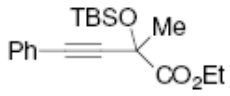
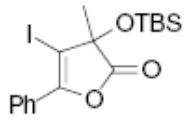
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
24		**30**	I_2	3		**31**	0
25		**32**	I_2	5		**33**	0[f]
26		**34**	I_2	3		**35**	0
27		**36**	I_2	1.5		**37**	0[g]
28		**36**	ICl	1.5		**37**	0[g]
29		**38**	I_2	1.5		**39**	0[g]

Table 1. (cont'd)

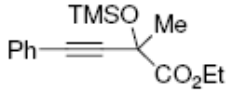
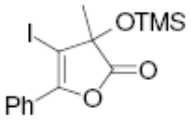
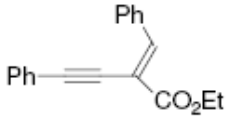
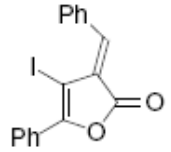
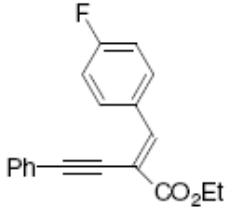
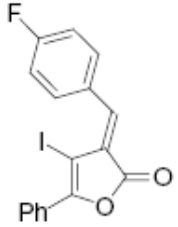
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
30		**40**	I_2	2		**41**	66
31		**40**	ICl	1.5		**41**	0[g]
32		**42**	I_2	24		**43**	0
33		**42**	ICl	24		**43**	-[h]
34		**44**	ICl	24		**45**	-[h]

Table 1. (cont'd)

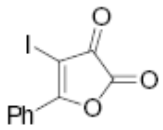
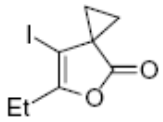
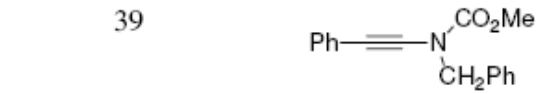
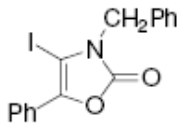
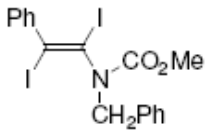
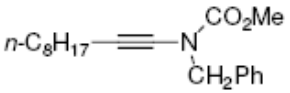
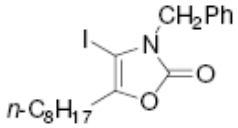
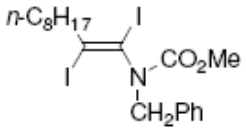
entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
35		**46**	I_2	24		**47**	0[f]
36		**46**	ICl	2		**47**	0[f]
37		**48**	I_2	1		**49**	0[f]
38		**48**	ICl	1		**49**	0
39		**50**	I_2	1		**51**	0[f]
						**52**	70

Table 1. (cont'd)

entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
40		**53**	I_2	2		**54**	0[f]
						**55**	92

[a] All reactions were conducted on a 0.25 mmol scale using 1.5 equiv of electrophile in 4 mL of CH_2Cl_2 at room temperature unless otherwise indicated. [b] All yields are isolated yields. [c] The yield is the combined yields of the iodo-substituted and chloro-substituted products. The ratio of the iodo-substituted and chloro-substituted products, as determined by ^1H NMR spectroscopy, is reported in parentheses. [d] 1.1 Equiv of ICl was employed. [e] 3.0 Equiv of ICl was employed. [f] Only the product of addition of the electrophile across the carbon-carbon triple bond was obtained. Some addition product was not stable and reverted to the starting material upon column chromatography. [g] Only unidentified products, which are not 2-furanones, were obtained. [h] An inseparable mixture was obtained.

Table 2. Synthesis of Substituted 2(3*H*)-Furanones by the Electrophilic Cyclization of Alkynoic Acids[a]

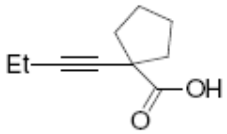
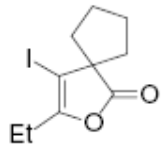
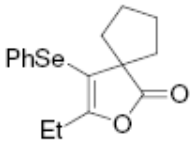
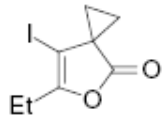
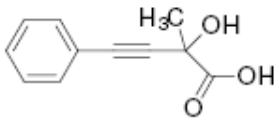
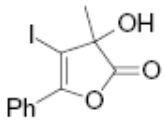
entry	alkynoic acid		electrophile	time (h)	product		yield (%)[b]
1		**56**	I_2	3		**23**	98
2		**56**	ICl	3		**23**	92
3		**56**	PhSeCl	2		**57**	85
4		**58**	I_2	20		**49**	78
5		**58**	ICl	20		**49**	78
6		**59**	I_2	20		**37**	75

Table 2. (cont'd)

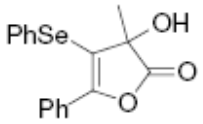
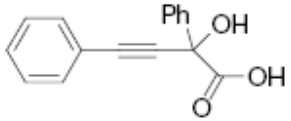
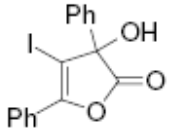
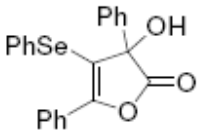
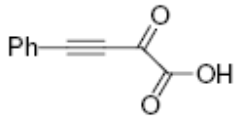
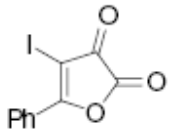
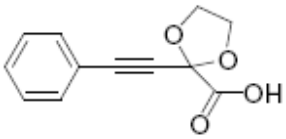
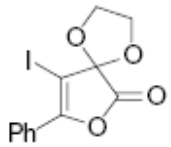
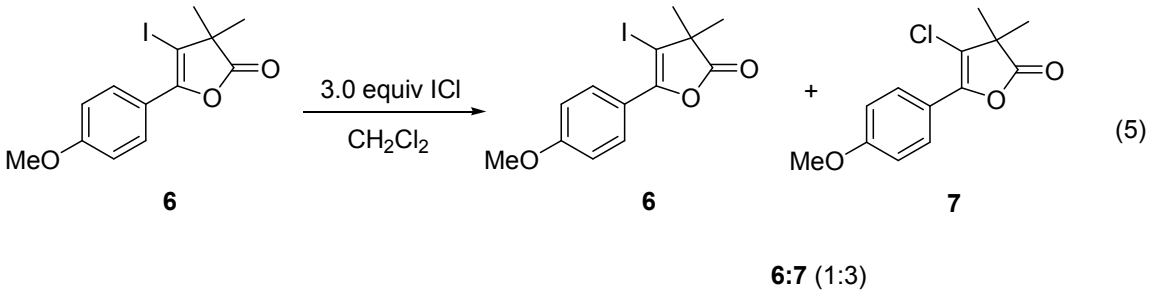
entry	alkynoic acid		electrophile	time (h)	product		yield (%)
7		**59**	ICl	2		**37**	80
8		**59**	PhSeCl	2		**60**	72
9		**61**	I_2	24		**62**	60
10		**61**	ICl	2		**62**	82
11		**61**	PhSeCl	3		**63**	87

Table 2. (cont'd)

entry	alkynoic acid		electrophile	time (h)	product		yield (%)
12		**64**	I_2	24		**47**	0[c]
13		**65**	I_2	24		**66**	67
14		**65**	ICl	4		**66**	96

[a] All reactions employing carboxylic acids were conducted on a 0.25 mmol scale, using 1.5 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in 4 mL of CH_3CN at room temperature. [b] All yields are isolated yields. [c] Only the product of addition of the electrophile across the carbon-carbon triple bond was obtained.

to react directly with the pure iodo-substituted product **6**, a mixture of **6** and **7** was obtained after 24 h (eq. 5). For substrate **8**, cyclization using 1.5 equivalents of ICl also gave a mixture of the iodo-substituted lactone **9** and the chloro-substituted lactone **10** in a 1:1 ratio (Table 1, entry 9). The mechanism for the formation of these two halogen-containing products in the ICl electrophilic cyclizations is not clear, but it is very interesting that two different halogenated products can be obtained in this process.



6 **6** **7**

6:7 (1:3) (5)

When there is a 6-membered ring present next to the ester moiety, the reaction proceeds more slowly than the 2,2-dimethyl counterpart. Cyclization of the 3-alkynoate ester **11** with I_2 reached completion in 24 h and resulted in an 89% yield (Table 1, entry 10). The reaction of **11** with ICl and PhSeCl gave the desired 2-furanone products in 89% and 73% yields respectively (Table 1, entries 11 and 12). The chloro-substituted product was not observed in the ICl cyclization of **11**. In the case of the 3-alkynoate ester **14** bearing β-ketoester functionality, cyclization with I_2 proceeded smoothly and resulted in an 80% yield of the spirocyclic product **15** (Table 1, entry 13). Although the oxygens of both of the carbonyl groups could potentially attack the iodonium intermediate (see the later mechanistic discussion), only the ester oxygen reacted to give the lactone **15** as the exclusive product. Previous work on the electrophilic cyclization of acetylenic ketones and aldehydes has been

reported by others and our group.[12] This chemoselectivity may be explained by the closer proximity of the ester oxygen to the hypothetical iodonium intermediate. However, ICl failed to afford any of the desired product **15**.

When we introduced an alkyl group instead of an aryl group into the 4-position of the 3-alkynoate ester, the reaction was somewhat faster (Table 1, entries 14-20). The cyclization of 3-alkynoate ester **16** proceeded cleanly in 1 h using I_2 and afforded an 86% yield of the iodolactone (Table 1, entry 14). The yield for the analogous ICl cyclization was significantly lower (Table 1, entry 15). However, none of the corresponding chlorolactone was observed. For the 3-alkynoate ester **18** bearing a cyclohexane moiety, the reaction also proceeded more slowly than that of **16,** when employing I_2 (Table 1, entry 16). However, we still obtained a 78% yield of the corresponding iodolactone **19**. Here ICl cyclization of **18** gave exclusively iodolactone **19** in 1 h, but in only a 60% yield (Table 1, entry 17). When we employed I_2 in the cyclization of the 2,2-diallyl-3-alkynoate ester **20**, the reaction proceeded smoothly affording an 84% yield of iodolactone **21** (Table 1, entry 18). However, the terminal double bonds of **20** were vulnerable to ICl and the reaction with this reagent was messy. In the case of the cyclopentane-containing ester **22**, the yield of the corresponding iodolactone **23** was almost quantitative when using I_2 (Table 1, entry 19). ICl cyclization of **22** gave exclusively iodolactone **23** in only 0.5 h in an 86% yield (Table 1, entry 20).

We next examined the possibility of preparing 2(5*H*)-furanones by the cyclization of 3-alkynoate esters bearing one or no α-substituents. Since mono-α-substituted alkynoate esters are not very stable and can be easily isomerized to the corresponding allenic esters in the presence of base,[28] we chose to explore instead the cyclization of the allenic ester **24**, rather than a monosubstituted 3-alkynoate ester. This cyclization resulted in a 96% yield of

the lactone **25**, bearing the more stable conjugated 2-furanone ring (Table 1, entry 21). Similar allenic ester and acid electrophilic cyclizations with different electrophiles have been explored by others under different reaction conditions.[29] So we chose not to examine any additional allenic esters.

When we explored the α-unsubstituted 3-alkynoate ester **26**, extensive isomerization occurred, affording the conjugated 2-furanone **27** in 62% yield (Table 1, entry 22). Substrate **28** with a terminal alkyne failed to give the desired cyclization product **29** even after 2 days. Some starting material reacted with I_2 to form a product resulting from addition of the I_2 across the acetylene moiety (Table 1, entry 23). Introducing two methyl groups in the 2 position did nothing to improve the situation (Table 1, entry 24). Introduction of a trimethylsilyl group on the acetylene failed to afford any of the desired lactone using either I_2 or ICl (Table 1, entry 25). This protected 3-alkynoate ester **32** only gave products of addition of the I_2 across the carbon-carbon triple bond, which decomposed back to the starting material **32** upon column chromatography. The α-unsubstituted substrate **34** also failed to provide any iodolactone; only starting material was recovered after aqueous work up and the desired conjugated cyclization product **35** was not observed (Table 1, entry 26). When we attempted to cyclize the α-hydroxy substrate **36,** where the oxygen from the OH group and the oxygen of the carbonyl group can both serve as nucleophiles, we obtained an unidentified compound, which was not the desired lactone (Table 1, entries 27 and 28). Even after we protected the OH group with a TBS group, the desired I_2 cyclization product was not formed (Table 1, entry 29). Surprisingly, the TMS-protected compound **40** afforded the desired 2-furanone **41** in a fair 66% yield (Table 1, entry 30). However, the ICl cyclization of **40** did not give the desired product (Table 1, entry 31). We also examined substrate **42**, which has

an sp^2 carbon center at the α position. No reaction took place using I_2. With ICl, we obtained a mixture of the desired cyclization product and addition product, which were hard to separate (Table 1, entry 33). Substrate **44** with a fluoro-substituted phenyl group also failed to give pure cyclization product **45** when using ICl (Table 1, entry 34). When we introduced a carbonyl group into the α position (**46**), we only observed addition products when employing either I_2 or ICl (Table 1, entries 35 and 36).

In conclusion, the substitution and the hybridization of the α position of the 3-alkynoate ester are crucial for the electrophilic cyclization to take place successfully. If there is an sp^2 carbon center present on the α carbon, cyclization is difficult apparently due to the wider angle between the alkyne and the ester groups. The nucleophilic oxygen of the ester group is apparently simply too far away for the iodonium intermediate to undergo cyclization. For similar reasons, the 3-alkynoate ester bearing a cyclopropane ring in the α position also failed to cyclize when allowed to react with I_2 and only the product of addition to the alkyne was observed. The addition product was not stable and quickly reverted back to starting material upon aqueous work up (Table 1, entry 37). Due to the strained, rather reactive cyclopropane ring system, a ring opened product was observed in the crude ^{1}H NMR spectrum of the corresponding ICl reaction (Table 1, entry 38).

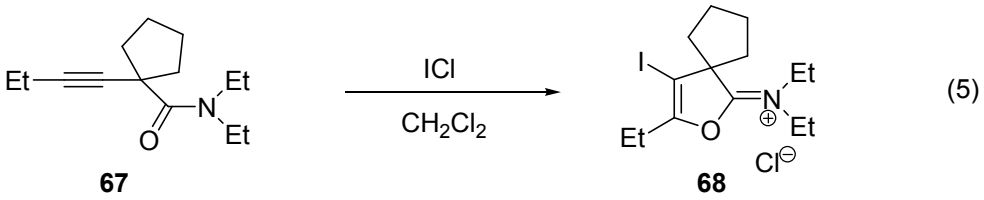
Next, we introduced a nitrogen into the α position (Table 1, entries 39 and 40). Unfortunately, we only obtained alkyne addition products (**52** and **55**). The stereochemistry of **52** was confirmed by X-ray crystallographic analysis.

In an attempt at overcoming some of the limitations encountered in the electrophilic cyclization of the 3-alkynoate esters, we have examined the cyclization of the corresponding alkynoic acids. We hydrolyzed our previous best substrate **22** to the corresponding

3-alkynoic acid **56**. This 3-alkynoic acid reacted with both I_2 and ICl in the presence of 3 equiv of $NaHCO_3$ in CH_3CN in slightly better yields than the corresponding ester (Table 2, entries 1 and 2), suggesting that an acid group or rather the corresponding carboxylate is a better nucleophile than the ester in these cyclization reactions. PhSeCl was also a good electrophile and gave the desired product **57** in an 85% yield (Table 2, entry 3). Next, we transformed an unsuccessful 3-alkynoate ester **48** to the corresponding acid **58** and conducted the same cyclization reaction. As we desired, the acid **58** gave the cyclization product **49** using either I_2 or ICl (Table 2, entries 4 and 5). Under the basic conditions, the acidic hydrogen is removed and the anionic carboxylate becomes a better nucleophile than the ester group (see the later mechanistic discussion). Encouraged by these results, we next prepared acid **59** from the unsuccessful substrate **36**. As expected, the desired lactone **37** was obtained upon I_2 cyclization (Table 2, entry 6). Reactions employing ICl and PhSeCl also afforded high yields of the anticipated products (Table 2, entries 7 and 8). The hydroxy acid **61** also gave good to excellent yields with all of these electrophiles (Table 2, entries 9-11). When we introduced a carbonyl group into the α position, none of the desired furanone product was observed using either I_2 or ICl (Table 2, entry 12). Thus, the presence of an sp^2 carbon in the α position is still a problem even with carboxylic acid substrates. To solve this problem, we protected the α carbonyl group as an acetal and the cyclization of acetal **65** proceeded smoothly using either I_2 or ICl to afford 67% and 96% yields of the anticipated lactone (Table 2, entries 13 and 14).

We also converted the 3-alkynoic acid **22** to the corresponding amide **67** and examined its cyclization. Employing I_2, the cyclization didn't take place and the amide was recovered after aqueous work up. However, cyclization by ICl gave a salt. From the ^1H and ^{13}C NMR spectra,

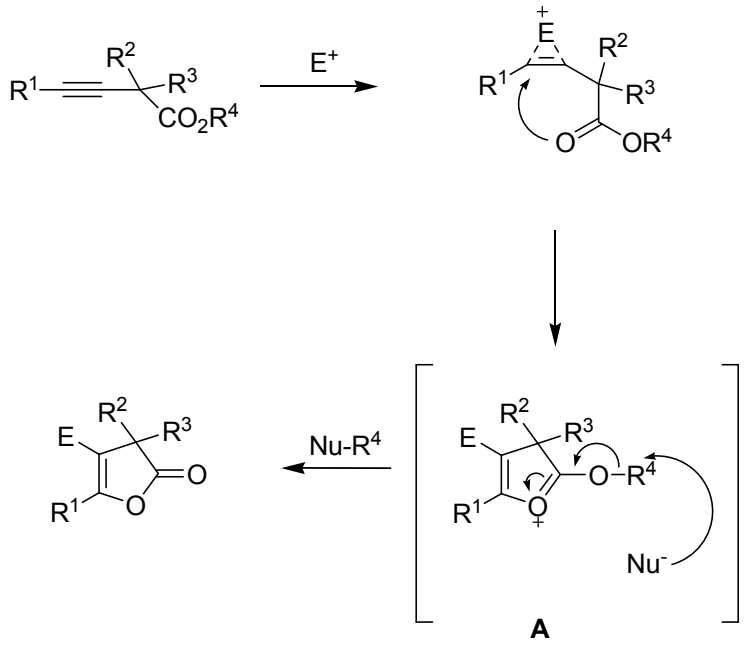
the product we obtained in 78% yield appeared to be the 2-furylidenediethylammonium chloride **68** (eq. 5). A similar cyclization of an allenic amide has been reported by Shengming Ma.[30]



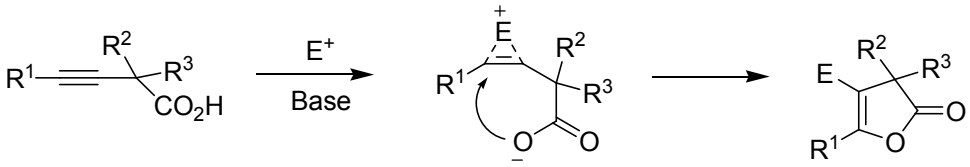
67 **68** (5)

Mechanistically, we believe that the cyclizations of the 3-alkynoate esters proceed by coordination of the carbon-carbon triple bond to the electrophile, followed by nucleophilic attack by the oxygen of the carbonyl group of the ester to produce an intermediate **A**, which undergoes removal of the alkyl group of the ester group via S_N2 displacement by nucleophiles present in the reaction mixture (Scheme 2). For the 3-alkynoic acids, the acidic hydrogen is removed under the basic reaction conditions and the anionic oxygen of the carboxylate serves as a better nucleophile. In this case, after the electrophile coordinates to the carbon-carbon triple bond, the anionic oxygen attacks the intermediate to form the 4-iodo-2(3*H*)-furanone directly (Scheme 3). For both the 3-alkynoate esters and the 3-alkynoic acids, the hybridization of the carbon in the α position is crucial for the cyclization to take place. The presence of an sp^2 carbon center in the α position of either the 3-alkynoate ester or the 3-alkynoic acid produced unsuccessful cyclizations. Overall, 3-alkynoic acids provide better results in these electrophilic cyclizations than the corresponding 3-alkynoate esters.

Scheme 2. Mechanism of the Electrophilic Cyclization of 3-Alkynoate Esters

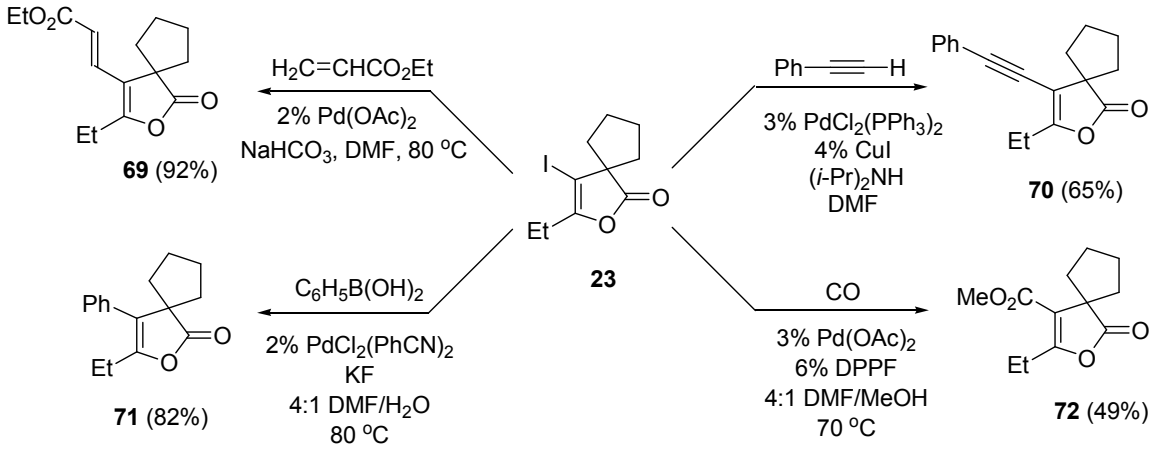


Scheme 3. Mechanism of the Electrophilic Cyclization of 3-Alkynoic Acids



This approach to 4-iodo-2(3*H*)-furanones provides a very useful synthesis of various substituted 2(3*H*)-furanones via elaboration of the resulting iodide functionality into other substituents. For instance, the resulting iodolactones are particularly useful intermediates in many palladium-catalyzed processes, such as Sonogashira, Suzuki, and Heck cross-couplings. For instance, compound **23** can be treated under standard Heck,[31] Sonogashira,[32] Suzuki,[33] and carbonylation[15a] conditions, providing the corresponding coupling products **69-72** respectively (Scheme 4).

Scheme 4. Pd-Catalyzed Diversification of 4-Iodo-2(3*H*)-furanone Derivatives



Conclusions

In conclusion, we have developed a simple, highly efficient approach to various highly functionalized, unsaturated 2(3*H*)-furanones via electrophilic cyclization of acetylenic esters and acids. We have shown that the electrophiles I_2, ICl, and PhSeCl can be used in this chemistry. In most cases, the I_2 cyclization gave one pure product in a high yield. The use of ICl as an electrophile, occasionally gave more than one product. These reactions are run under mild conditions, tolerate a number of functional groups, and generally provide the highly substituted 2(3*H*)-furanones in good to excellent yields. The resulting iodolactones are readily elaborated to more complex compounds by using known organopalladium chemistry.

Experimental Section

General

The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz or 400 MHz and 75 MHz or 100 MHz, respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadruple mass spectrometer. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All palladium salts were donated by Johnson Matthey Inc. or Kawaken Fine Chemicals Co., Ltd. All arylboronic acids were donated by Frontier Scientific or Synthonix. All reagents were used as obtained commercially unless otherwise noted. Ethyl 2,2-dimethyl-4-phenylbut-3-ynoate (**1**),[24] methyl 1-(phenylethynyl)cyclohexanecarboxylate (**11**),[24] ethyl 2-oxo-1-(phenylethynyl)-cyclopentanecarboxylate (**14**),[34] ethyl 2,3-butadienoate (**24**),[35] methyl 3-butynoate (**28**),[36] ethyl 2,2-dimethyl-4-trimethylsilylbut-3-ynoate (**32**),[37] methyl 4-phenylbut-3-ynoate (**34**),[38] ethyl 2-hydroxy-2-methyl-4-phenylbut-3-ynoate (**36**)[26a] and ethyl (*E*)-3-phenyl-2-(phenylethynyl)-propenoate (**42**),[27a] ethyl 2-oxo-4-phenylbut-3-ynoate (**46**),[39] *N*-benzyl-*N*-phenylethynylcarbamic acid methyl ester (**50**),[40] and 2-oxo-4-phenylbut-3-ynoic acid (**64**)[27b] were prepared according to literature procedures. Other starting materials were prepared as indicated.

General procedure for preparation of the 4-iodo-2(3*H*)-furanones from alkynoate esters (Table 1).

To a vial of the corresponding alkynoate ester (0.25 mmol) in 1 mL of CH_2Cl_2 under Ar was added dropwise a solution of I_2 or ICl (0.375 mmol) dissolved in 3 mL of CH_2Cl_2. The reaction was stirred at room temperature for the indicated time. The reaction mixture was then quenched with 20 mL of saturated aqueous $Na_2S_2O_3$ solution and extracted three times with ethyl ether (20 mL each). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product was purified by chromatography on a silica gel column.

General procedure for preparation of the 4-iodo-2(3*H*)-furanones from alkynoic acids (Table 2).

To a vial of the corresponding alkynoic acid (0.25 mmol) in 1 mL of CH_3CN, $NaHCO_3$ (0.75 mmol) was added. The mixture was stirred for 5 mins under Ar. Then I_2 or ICl (0.375 mmol) in 3 mL of CH_3CN was added dropwise to the above solution. The reaction was stirred at the room temperature for the indicated time. The mixture was then quenched with 20 mL of saturated aqueous $Na_2S_2O_3$ solution and extracted three times with ethyl ether (20 mL each). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product was purified by chromatography on a silica gel column.

Characterization data:

4-Iodo-3,3-dimethyl-5-phenyl-2(3*H*)-furanone (2). Light yellow solid: mp 91-92 ^oC; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6H), 7.43-7.46 (m, 3H), 7.96-7.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.8, 49.7, 76.7, 127.7, 128.5, 128.6, 130.4, 148.7, 178.9; IR (CH_2Cl_2) 3068, 2975, 2926, 1796, 1449 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{11}O_2I$ 313.98038, found: 313.98087.

3,3-Dimethyl-5-phenyl-4-phenylseleno-2(3*H*)-furanone (4). White solid: mp 96-97 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 6H), 7.19-7.22 (m, 3H), 7.36-7.40 (m, 5H), 8.07-8.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.0, 49.5, 109.7, 126.9, 127.9, 128.2, 128.4, 129.4, 129.7, 130.4, 130.5, 154.4, 180.5; IR (CH_2Cl_2) 3069, 2969, 1793, 1449, 1264 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{16}O_2Se$ 344.03155, found: 344.03215.

Ethyl 2,2-dimethyl-4-(4-methoxyphenyl)but-3-ynoate (5). This compound was prepared according to a literature procedure.[24] 2.0 M LDA in heptane/THF/ethylbenzene (3.0 mmol) was added to 15 mL of dry THF at -78 °C. Ethyl isobutyrate (3.0 mmol) was then added to the solution, followed immediately by the addition of HMPA (3.0 mmol). The resulting mixture was stirred at -78 °C for 30 min. 4-(2-Chloroethynyl)anisole[41] (3.0 mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. The resulting mixture was poured onto water and extracted with Et_2O three times (25 mL each). The combined extracts were washed four times with water and once with brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford compound **5** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 1.55 (s, 6H), 3.79 (s, 3H), 4.21 (q, J = 7.1 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 8.7Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 27.5, 38.9, 55.5, 61.7, 81.7, 90.6, 114.0, 115.6, 133.3, 159.6, 174.2; IR (CH_2Cl_2) 3039, 2983, 1735, 1511, 1249 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}O_3$ 246.12559, found: 246.12593.

4-Iodo-5-(4-methoxyphenyl)-3,3-dimethyl-2(3*H*)-furanone (6). Yellow solid: mp 94-95 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 6H), 3.85 (s, 3H), 6.95 (d, J = 9.0 Hz, 2H), 7.92 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.8, 49.6, 55.6, 74.4, 114.0, 120.9, 129.3, 148.5, 161.1, 179.1;

IR (CH_2Cl_2) 3054, 2980, 2305, 1796, 1606, 1260 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{13}O_3I$ 343.99095, found: 343.99139.

Ethyl 4-(3-(butoxycarbonyl)-3-methylbut-1-ynyl)benzoate (8). This compound was obtained according to a literature procedure.[42] To a solution of ethyl 4-iodobenzoate (2.0 mmol) and *n*-butyl 2,2-dimethyl-3-butynoate (**30**) (2.0 mmol) in 6 mL of THF were added $Pd(PPh_3)_2Cl_2$ (0.04 mmol), CuI (0.08 mmol), and K_2CO_3 (4.0 mmol). The resulting mixture was stirred at 65 ^oC for 20 h. Subsequently the THF was evaporated under reduce pressure and the residual was extracted with Et_2O three times (25 mL each). The residue was purified by flash chromatography on silica gel (15:1 hexanes/EtOAc) to afford compound **8** in a 60% yield as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.37-1.44 (m, 5H), 1.57 (s, 6H), 1.59-1.69 (m, 2H), 4.17 (t, J = 6.4 Hz, 3H), 4.37 (q, J = 7.2 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.5, 19.3, 27.3, 30.8, 39.1, 61.3, 65.7, 81.4, 95.2, 128.1, 129.5, 129.8, 131.8, 166.3, 173.7; IR (CH_2Cl_2) 3050, 2961, 2874, 1723, 1606, 1466, 1271 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{24}O_4$ 316.16746, found: 316.16796.

5-(4-Ethoxycarbonylphenyl)-4-iodo-3,3-dimethyl-2(3*H*)-furanone (9). Yellow solid: mp 103-105 ^oC; ^1H NMR ($CDCl_3$) δ 1.36 (s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 24.6, 49.8, 61.4, 78.9, 127.4, 129.6, 131.7, 132.2, 147.8, 165.9, 178.3; IR (CH_2Cl_2) 3056, 2980, 2933, 1802, 1714, 1277 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}O_4I$ 386.00151, found: 386.00216.

4-Iodo-2-oxa-3-phenylspiro[4.5]dec-3-en-1-one (12). Light yellow solid: mp 108-109 ^oC; ^1H NMR ($CDCl_3$) δ 1.21-2.08 (m, 10H), 7.42-7.45 (m, 3H), 7.94-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9, 24.7, 32.5, 50.6, 78.6, 127.5, 128.3, 128.46, 128.50, 130.1, 176.0; IR

(CH_2Cl_2) 3054, 2938, 2304, 1787, 1264 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}O_2I$ 354.01168, found: 354.01215.

2-Oxa-3-phenyl-4-(phenylseleno)spiro[4.5]dec-3-en-1-one (13). Yellow solid: mp 90-91 ^oC; ^1H NMR ($CDCl_3$) δ 1.16-2.05 (m, 10H), 7.17-7.24 (m, 3H), 7.29-7.39 (m, 5H), 8.03-8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.0, 24.6, 31.7, 51.4, 109.8, 126.5, 127.8, 128.31, 128.32, 128.8, 129.4, 130.3, 131.2, 155.2, 178.2; IR (CH_2Cl_2) 3059, 2932, 2851, 1789, 1613, 1446 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{20}O_2Se$ 384.06285, found: 384.06331.

4-Iodo-2-oxa-3-phenylspiro[4.4]non-3-en-1,6-dione (15). Light yellow solid: mp 64-65 ^oC; ^1H NMR ($CDCl_3$) δ 2.43-2.47 (m, 6H), 7.44-7.46 (m, 3H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.7, 33.8, 38.4, 65.9, 67.9, 127.82, 127.83, 128.6, 130.9, 152.9, 173.0, 208.9; IR (CH_2Cl_2) 3060, 2967, 2926, 1795, 1745, 1628, 1491, 1445, 1260 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{11}O_3I$ 353.97530, found: 353.97600.

Ethyl 2,2-dimethyl-3-hexynoate (16). This compound was prepared according to a literature procedure.[25] To a round-bottom flask were added ethyl 2-hexynoate (0.6 mmol), THF (9.6 mL), and HMPA (2.4 mL). The solution was allowed to stir at -98 ^oC under argon for 10 min, followed by the dropwise addition of 2.0 M LDA in heptane/THF/ethyl benzene (1.2 mmol) while carefully maintaining the reaction temperature at -98 ^oC. Stirring was continued for an additional 30 min, followed by the addition of neat MeI (4.8 mmol). The reaction mixture was maintained at -98 ^oC for 1 h and then allowed to warm to room temperature over the course of 8 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), followed by extraction with Et_2O twice (10 mL each). The combined ether layers were washed with brine, dried over magnesium sulfate, filtered and evaporated to leave the crude product, which was purified by flash chromatography on silica gel (20:1

hexanes/EtOAc) to afford compound **16** as a yellow oil in a 40% yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.5 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 6H), 2.18 (q, *J* = 7.5 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.1, 18.5, 30.4, 32.4, 61.4, 84.3, 114.8, 172.2; IR (CH_2Cl_2) 2981, 2940, 1737, 1454, 1267 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{16}O_2$ 168.11503, found: 168.11543.

5-Ethyl-4-iodo-2,2-dimethyl-2(3*H*)-furanone (17). Light brown solid: mp 46-47 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, *J* = 7.5 Hz, 3H), 1.22 (s, 6H), 2.41 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.9, 22.3, 24.4, 48.0, 76.5, 155.0, 179.73; IR (CH_2Cl_2) 2975, 2931, 1803, 1460, 1231 cm^{-1}; HRMS (EI) calcd for $C_8H_{11}O_2I$ 265.98038, found: 265.98070.

Ethyl 1-(but-1-ynyl)cyclohexane carboxylate (18). This compound was prepared in a manner analogous to compound **16**. Instead of using MeI, 1,5-dibromopentane (2.4 mmol) was employed to form compound **18** as a light yellow oil in a 42% yield: ^{1}H NMR ($CDCl_3$) δ 1.14 (t, *J* = 7.5 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.58-1.84 (m, 10H), 2.21 (q, *J* = 7.5 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.3, 14.4, 22.7, 25.7, 35.2, 43.7, 61.3, 79.9, 82.3, 174.2; IR (CH_2Cl_2) 2975, 2934, 2858, 2234, 1731, 1450 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_2$ 208.14633, found: 208.14677.

3-Ethyl-4-iodo-2-oxaspiro[4.5]dec-3-en-1-one (19). Yellow solid: mp 65-66 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, *J* = 7.5 Hz, 3H), 1.52-2.00 (m, 10H), 2.40 (q, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.0, 20.1, 22.6, 24.9, 32.5, 49.3, 78.2, 155.5, 177.2; IR (CH_2Cl_2) 2929, 2853, 1784, 1445 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{15}O_2I$ 306.01168, found: 306.01206.

Ethyl 2,2-diallyl-3-hexynoate (20). This compound was prepared in a manner analogous to compound **16**. Instead of using MeI, 3-bromoprop-1-ene (4.8 mmol) was employed to form compound **20** as a light yellow oil in a 15% yield: ^{1}H NMR ($CDCl_3$) δ 1.13 (t, *J* = 7.5

Hz, 3H), 1.25 (t, *J* = 8.0 Hz, 3H), 2.22 (q, *J* = 7.5 Hz, 2H), 2.40 (dd, *J* = 13.8, 6.9 Hz, 2H), 2.51 (dd, *J* = 14.1, 6.9 Hz, 2H), 5.06 (d, *J* = 0.9 Hz, 2H), 5.10-5.12 (m, 2H), 5.78-5.92 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.4, 14.5, 43.0, 47.7, 61.5, 78.7, 86.9, 118.5, 133.8, 172.6; IR (CH_2Cl_2) 3078, 2979, 1736, 1440, 1215 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{20}O_2$ 220.14633, found: 220.14667.

3,3-Diallyl-5-ethyl-4-iodo-2(3*H*)-furanone (21). Yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, *J* = 7.5 Hz, 3H), 2.23-2.29 (dd, *J* = 13.7, 7.0 Hz, 6H), 2.36-2.45 (m, 4H), 5.05-5.19 (m, 4H), 5.44-5.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.3, 22.2, 40.5, 57.1, 71.7, 120.1, 131.1, 156.8, 177.3; IR (CH_2Cl_2) 3079, 2979, 2936, 1803, 1664, 1438 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{15}O_2I$ 318.01168, found: 318.01206.

Ethyl 1-(but-1-ynyl)cyclopentane carboxylate (22). This compound was prepared in a manner analogous to compound **16**. Instead of using MeI, 1,4-dibromobutane (2.4 mmol) was employed to form compound **22** as a light yellow oil in a 43% yield: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, *J* = 7.5 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.68-1.96 (m, 6H), 2.14-2.21 (m, 4H), 4.17 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.28, 14.31, 24.8, 39.3, 48.5, 61.5, 81.5, 83.8, 174.3; IR (CH_2Cl_2) 3054, 2927, 2305, 1726, 1265 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_2$ 194.13068, found: 194.13090.

3-Ethyl-4-iodo-2-oxaspiro[4.4]non-3-en-1-one (23). Light yellow solid: mp 52-53 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, *J* = 7.5 Hz, 3H), 1.88-1.93 (m, 8H), 2.40 (q, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.0, 22.4, 26.7, 37.4, 56.7, 76.1, 155.2, 181.4; IR (CH_2Cl_2) 2959, 2871, 1779, 1663, 1460, 1442, 1278 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{13}O_2I$ 292.99603, found: 292.99645.

4-Iodo-3-methyl-5-phenyl-2(5*H*)-furanone (25). This compound was obtained as a white solid: mp 94-95 °C. The spectra properties were identical to those previously reported.[30] HRMS (EI) calcd for $C_{11}H_8O_2I$ 299.96473, found: 299.96511.

Ethyl 3-hexynoate (26). This compound was prepared in a manner analogous to compound **16**. Instead of using MeI, 2.0 M HCl (4.8 mmol) in Et_2O solution was employed to form compound **22** as a light yellow oil in a 69% yield: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.6 Hz, 3H), 1.27 (t, *J* = 6.8 Hz, 3H), 2.20 (tq, *J* = 7.6, 2.6 Hz, 2H), 2.23 (t, *J* = 2.4 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.5, 13.9, 14.1, 26.1, 61.5, 70.8, 85.2, 169.1; IR (neat) 2979, 1743, 1461, 1260 cm^{-1}; HRMS (EI) calcd for $C_8H_{12}O_2$ 140.08373, found: 140.08395.

5-Ethyl-4-iodo-2(5*H*)-furanone (27). White solid: mp 46-47 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 5.4 Hz, 3H), 1.66-1.73 (m, 1H), 2.08-2.12 (m, 1H), 4.94-4.97 (m, 1H), 6.52 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.5, 25.5, 88.7, 124.9, 130.4, 171.2; IR ($CDCl_3$) 3054, 2984, 2254, 1758, 1589, 1265 cm^{-1}; HRMS (EI) calcd for $C_6H_7O_2I$ 237.94908, found: 237.94944.

***n*-Butyl 2,2-dimethyl-3-butynoate (30)**. This compound was prepared by the esterification of 2,2-dimethylbut-3-ynoic acid[43] (0.05 mol), *n*-butanol (0.075 mol) and sulfuric acid (0.05 mol). The mixed solution was stirred at room temperature for 24 h. The resulting mixture was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford compound **30** as a colorless oil in a 20% yield: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.38-1.43 (m, 2H), 1.48 (s, 6H), 1.62-1.67 (m, 2H), 2.25 (s, 1H), 4.14 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.1, 27.1, 30.6, 38.2, 65.5, 69.8, 86.4, 173.5; IR (neat) 3290, 2961, 1739 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{16}O_2$ 168.11503, found: 168.11543.

2-Hydroxy-4-iodo-2-methyl-5-phenyl-2(3*H*)-furanone (37). Yellow solid: mp 90-91 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H), 2.60 (s, 1H), 7.46-7.48 (m, 3H), 8.00-8.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1, 73.1, 127.6, 127.8, 128.5, 131.0, 150.8, 174.6; IR (CH_2Cl_2) 3410, 3062, 2982, 2926, 1807, 1491, 1258 cm^{-1}; HRMS (EI) calcd for $C_{11}H_9O_3I$ 315.95965, found: 315.96016.

Ethyl 2-(1,1-dimethylethyl)dimethylsilyloxy-2-methyl-4-phenylbut-3-ynoate (38). Brown oil: ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 6H), 0.93 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.76 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 7.30-7.33 (m, 3H), 7.42-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 0.2, 14.3, 18.4, 26.0, 30.2, 62.0, 70.6, 85.2, 89.9, 122.6, 128.5, 128.8, 131.8, 172.0; IR (CH_2Cl_2) 3475, 3061, 2955, 2856, 1729, 1677, 1449, 1256 cm^{-1}; MS (EI) m/z (rel intensity) 275 (M-57, 93).

Ethyl 2-methyl-4-phenyl-2-(trimethylsilyl)oxy-but-3-ynoate (40). Light yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.77 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 7.31-7.34 (m, 3H), 7.43-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 1.5, 14.1, 30.0, 62.0, 70.4, 85.3, 89.4, 122.3, 128.4, 128.7, 131.6, 171.7; IR (neat) 3058, 2981, 2902, 2236, 1752, 1490, 1250 cm^{-1}; MS (EI) m/z (rel intensity) 275 (M-15, 71), 217 (M-73, 100).

4-Iodo-2-methyl-5-phenyl-2-(trimethylsilyl)oxy-2(3*H*)-furanone (41). Light yellow solid: mp 92-93 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9H), 1.53 (s, 3H), 7.46-7.48 (m, 3H), 7.98-8.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 0.0, 25.4, 28.9, 75.2, 126.2, 126.3, 127.1, 129.4, 148.1, 173.0; IR (CH_2Cl_2) 3054, 2986, 2305, 1784, 1638, 1449, 1266 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{14}O_2ISi$ 387.99917, found: 387.99960.

Ethyl (*E*)-3-(4-fluorophenyl)-2-(phenylethynyl)propenoate (44). This compound was prepared according to a literature procedure.[27a] Phenylacetylene (1.5 mmol) was dissolved in

3 mL of THF and then a 2.5 M solution of *n*-BuLi in hexanes (1.5 mmol) was added dropwise under argon at -78 °C. The resulting mixture was stirred for 5 min and then the temperature was raised to 0 °C. A 0.5 M solution of $ZnCl_2$ in THF was added to this mixture and the resulting mixture was warmed to room temperature and stirred for 30 min. $Pd(PPh_3)_4$ (0.05 mmol) and a solution of an ethyl (*Z*)-2-bromo-3-(4-fluorophenyl)acrylate[27a] (1.0 mmol) in 2 mL of THF were sequentially added to the previously prepared mixed solution. The resulting mixture was stirred for 1.5 h at room temperature and then the temperature was raised to 70 °C. The reaction was allowed to run for 15 h. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was then dried over magnesium sulfate, and evaporated to leave the crude product, which was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford as a yellow solid in an 89% yield: mp 44-45 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.11-7.15 (m, 2H), 7.38-7.39 (m, 3H), 7.53-7.55 (m, 2H), 7.90 (s, 1H), 8.08-8.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.9, 85.2, 98.2, 112.9, 115.9, 122.9, 128.6, 128.9, 130.9, 131.6, 132.5, 132.6, 143.8, 165.7; IR (CH_2Cl_2) 3056, 2983, 2204, 1714, 1598, 1508 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{15}O_3F$ 294.10561, found: 294.10602.

Ethyl 1-(but-1-ynyl)cyclopropane carboxylate (48). This compound was prepared in a manner analogous to compound **16**. Instead of using MeI, 1,2-dibromoethane (2.4 mmol) was added to form compound **48** as a light yellow oil in a 52% yield: ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.5 Hz, 3H), 1.16-1.19 (dd, *J* = 7.5, 3.9 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.43 (dd, *J* = 7.7, 3.8 Hz, 2H), 2.15 (q, *J* = 7.5 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.7, 14.1, 14.3, 16.0, 20.6, 61.7, 78.4, 81.1, 172.7; IR (CH_2Cl_2) 2978, 2938, 2360, 1725, 1451, 1285 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.09938, found: 166.09966.

3-Ethyl-4-iodo-2-oxaspiro[4.2]hept-3-en-1-one (49). Light yellow solid: mp 29-30 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.5 Hz, 3H), 1.33-1.48 (m, 2H), 2.50 (q, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.2, 17.4, 22.7, 31.2, 68.2, 156.3, 177.6; IR (CH_2Cl_2) 2977, 2939, 1790, 1650, 160, 1284 cm^{-1}; HRMS (EI) calcd for $C_8H_9O_2I$ 263.96473, found: 263.96516.

***N*-Benzyl-*N*-phenylethynyl-3,4-diiodocarbamic acid methyl ester (52).** White solid: ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 4.44 (d, *J* = 18.8 Hz, 1H), 4.93 (d, *J* = 14.1 Hz, 1H), 7.10-7.12 (m, 2H), 7.31-7.39 (m, 6H), 7.52-7.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.6, 54.3, 100.9, 127.4, 128.2, 128.4, 128.5, 128.6, 128.7, 129.0, 131.1, 134.2, 145.3 cm^{-1}; MS (EI) m/z (rel intensity) 392 (M-127, 35).

***N*-Benzyl-*N*-(1-decynyl)carbamic acid methyl ester (53).** This compound was prepared according to a literature procedure.[44] A solution of methyl benzylcarbamate (1.0 mmol) in 4 mL of pyridine was cooled to 0 °C and a 0.91 M solution of KHMDS in THF (1 mmol) was added via syringe over 4 min. The reaction mixture was stirred at 0 °C for 10 min, and then a solution of CuI (1.0 mmol) in 2 mL of pyridine was added. The ice bath was then removed, and the resulting solution was stirred at room temperature for 2 h. A solution of 1-bromonon-1-yne (2.0 mmol) in 3 mL of benzene was then added slowly, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with 25 mL of Et_2O and washed with three 10 mL portions of a 2:1 mixture of saturated NaCl solution and concentrated NH_4OH. The combined aqueous layers were extracted with three 10 mL portions of Et_2O, and the combined organic layers were washed with 25 mL of saturated NaCl solution. The organic extract was then dried over magnesium sulfate, filtered and evaporated to leave the crude product, which was purified by flash chromatography on silica gel (20:1 hexanes/EtOAc) to afford a brown oil in an 89% yield: ^{1}H NMR ($CDCl_3$) δ

0.89 (t, J = 6.8 Hz, 3H), 1.24-1.26 (m, 10H), 1.28-1.31 (m, 2H), 2.24 (t, J = 6.9 Hz, 2H), 3.80 (s, 3H), 4.60 (s, 2H), 7.31-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.7, 22.9, 29.0, 29.2, 29.3, 29.5, 32.1, 54.2, 128.1, 128.6, 128.7, 136.5, 156.4; IR (neat) 3032, 2952, 2855, 2262, 1726, 1445, 1289 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{11}O_3I$ 301.20418, found: 301.20470.

***N*-Benzyl-*N*-(1-decynyl)-3,4-diiodocarbamic acid methyl ester (55).** colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 8.4 Hz, 3H), 1.28 (m, 10H), 1.45-1.47 (m, 2H), 2.50-2.58 (m, 2H), 3.81 (s, 3H), 4.40 (d, J = 18.8 Hz, 1H), 4.72 (d, J = 14.4 Hz, 1H), 7.26-7.33 (m, 3H), 7.40-7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.9, 28.3, 28.39, 28.43, 29.6, 32.1, 47.5, 54.1, 108.3, 128.3, 128.4, 128.8, 130.9, 134.3; MS (EI) m/z (rel intensity) 428 (M-127, 13).

1-(But-1-ynyl)cyclopentane carboxylic acid (56). This compound was prepared according to a literature procedure.[27a] A solution of 3N aqueous NaOH (20 mmol) was added to a solution of the corresponding ester **22** (2.0 mmol) in 10 mL of THF, which was cooled to 0 ^{o}C. The resulting mixture was stirred at room temperature for 24 h and then concentrated using a rotary evaporator. The residue was diluted with water and extracted repeatly with CH_2Cl_2. The resulting aqueous suspension was cooled to 0 ^{o}C, acidified with 10 % H_2SO_4 and extracted repeatly with a 1:1 mixture of THF and Et_2O. The collected organic extracts were washed with water, dried over magnesium sulfate, filtered and evaporated to leave the crude product, which was purified by flash chromatography on silica gel (1:5 hexanes/EtOAc) to afford a yellow oil in an 84% yield: ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.6 Hz, 3H), 1.74-2.01 (m, 6H), 2.21 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.7, 14.2, 25.0. 39.6, 48.5, 80.7, 84.8, 180.3; IR (CH_2Cl_2) 3574, 2974, 2876, 2240, 1707, 1453, 1277 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.09938, found: 166.09966.

3-Ethyl-2-oxa-4-(phenylseleno)spiro[4.4]non-3-en-1-one (57). Light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.5 Hz, 3H), 1.74-1.88 (m, 8H), 2.62 (q, *J* = 7.5 Hz, 2H), 7.22-7.26 (m, 3H), 7.32-7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.6, 21.2, 26.3, 36.8, 56.7, 108.0, 127.0, 129.6, 129.7, 131.4, 162.0, 182.9; IR (CH_2Cl_2) 3058, 2957, 2872, 1795, 1475, 1217 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{18}O_2Se$ 322.04720, found: 322.04770.

1-(But-1-ynyl)cyclopropane carboxylic acid (58). This compound was prepared similar to compound **56**. The product was obtained from the corresponding ester **48** as a white solid in an 80% yield: mp 74-75 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.6 Hz, 3H), 1.32 (dd, *J* = 8.0, 4.0 Hz, 2H), 1.56 (dd, *J* = 8.0, 4.0 Hz, 2H), 2.19 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.5, 13.9, 15.8. 21.4, 77.3, 81.8, 178.8; IR (CH_2Cl_2) 3053, 2981, 2305, 1695, 1423, 1266 cm^{-1}; HRMS (EI) calcd for $C_8H_{10}O_2$ 138.06808, found: 138.06828.

2-Hydroxy-2-methyl-4-phenylbut-3-ynoic acid (59). This compound was prepared in a manner analogous to compound **56**. The acid was obtained from ethyl 2-hydroxy-2-methyl-4-phenylbut-3-ynoate (**36**)[26a] as a white solid in a 77% yield: mp 98-99 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 3H), 7.30-7.34 (m, 3H), 7.44-7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.2, 68.4, 84.9, 87.3, 121.6, 128.4, 129.0, 131.9, 177.0; IR (CH_2Cl_2) 3436, 3059, 2981, 2926, 1810 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{10}O_3$ 190.06299, found: 190.06320.

3-Hydroxy-3-methyl-5-phenyl-4-phenylseleno-2(3*H*)-furanone (60). Light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3H), 2.48 (s, 1H), 7.23-7.24 (m, 3H), 7.42-7.46 (m, 5H), 8.07-8.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.5, 77.4, 106.9, 127.3, 127.7, 128.3, 128.5, 129.7, 130.1, 130.3, 131.2, 156.3, 176.2; IR (CH_2Cl_2) 3418, 3059, 2980, 1812 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{14}O_3Se$ 346.01081, found: 346.01135.

2-Hydroxy-2,4-diphenylbut-3-ynoic acid (61). This compound was prepared in a manner analogous to compound **56**. The acid was obtained from the corresponding ester ethyl 2-hydroxy-2,4-diphenylbut-3-ynoate[26b] as a light yellow solid in a 92% yield: 105-106 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 1H), 7.32-7.43 (m, 6H), 7.52-7.54 (m, 2H), 7.77-7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 73.3, 86.2, 87.1, 121.6, 126.4, 128.4, 128.6, 129.20, 129.23, 132.1, 138.6, 175.5; IR (CH_2Cl_2) 3479, 3055, 2986, 2231, 1726, 1491, 1265 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}O_3$ 252.07864, found: 252.07909.

3-Hydroxy-4-iodo-3,5-diphenyl-2(3*H*)-furanone (62). Yellow solid: mp 109-110 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.18 (s, 1H), 7.42-7.52 (m, 8H), 8.08-8.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 73.5, 81.6, 125.5, 127.5, 127.9, 128.6, 129.0, 129.4, 131.3, 137.1, 151.9, 173.5; IR (CH_2Cl_2) 3441, 3061, 1802 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{11}O_3I$ 377.97530, found: 377.97601.

3-Hydroxy-3,5-diphenyl-4-phenylseleno-2(3*H*)-furanone (63). Yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.97 (s, 1H), 7.11-7.16 (m, 3H), 7.28-7.35 (m, 5H), 7.43-7.48 (m, 5H) 8.12-8.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 81.9, 107.7, 125.5, 127.4, 127.6, 128.4, 128.6, 128.8, 129.1, 129.4, 129.5, 130.9, 131.3, 137.7, 156.5, 175.0; IR (CH_2Cl_2) 3438, 3059, 1809, 1264 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{16}O_3Se$ 408.02647, found: 408.026996.

2-(Phenylethynyl)-1,3-dioxolane-2-carboxylic acid (65). This compound was obtained from the corresponding ester ethyl 2-(phenylethynyl)-1,3-dioxolane-2-carboxylate (**65a**). This ester was obtained by protection of compound **46** according to a literature procedure.[45] $BF_3 \cdot Et_2O$ (5.0 mmol) was added dropwise to a solution of ethane-1,2-diol (5.0 mmol) and **46** (5.0 mmol) in 15 mL of MeCN. The mixture was stirred for 16 h and then quenched with 5 mL of saturated aqueous $NaHCO_3$. The resulting mixture was allowed to stir for an additional 20 min and then extracted with Et_2O. The organic extract was then dried over

magnesium sulfate, and evaporated to leave the crude product, which was purified by flash chromatography on silica gel (5:1 hexanes/EtOAc) to afford ethyl 2-(phenylethynyl)-1,3-dioxolane-2-carboxylate (**65a**) as a light yellow oil in a 42% yield: ^{1}H NMR ($CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.17-4.23 (m, 4H), 4.32 (q, *J* = 7.2 Hz, 2H), 7.31-7.36 (m, 3H), 7.48-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 62.8, 66.2, 83.2, 86.2, 98.6, 121.2, 128.3, 129.3, 132.2, 166.1; IR (CH_2Cl_2) 3059, 2983, 2900, 2235, 1754, 1490 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{14}O_4$ 246.08921, found 246.08962. Acid **65** was obtained from hydrolysis of ethyl 2-(phenylethynyl)-1,3-dioxolane-2-carboxylate (**65a**) as a light yellow solid in an 86% yield: mp 72-73 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 4.19-4.29 (m, 4H), 7.30-7.39 (m, 3H), 7.50-7.52 (m, 2H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 66.4, 82.2, 87.0, 98.3, 120.8, 128.4, 129.6, 132.2, 170.2; IR (CH_2Cl_2) 3438, 3055, 2986, 2235, 1738, 1490, 1265 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{10}O_4$ 218.05791, found: 218.05829.

9-Iodo-1,4,7-trioxaspiro[4.4]non-8-en-6-one (66). Yellow solid: mp 113-115 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 4.32-4.35 (m, 2H), 4.45-4.49 (m, 2H), 7.45-7.51 (m, 3H), 8.02-8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 66.0, 66.6, 103.7, 127.6, 128.0, 128.6, 131.7, 154.8, 169.2; IR (CH_2Cl_2) 3055, 2964, 2903, 2360, 1820, 1677, 1264 cm^{-1}; HRMS (EI) calcd for $C_{12}H_9O_4I$ 343.95456, found: 343.95494.

***N*,*N*-Diethyl-1-(but-1-ynyl)cyclopentanecarboxamide (67).** Colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.5 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.64-1.75 (m, 4H), 1.88-1.96 (m, 2H), 2.12-2.23 (m, 4H), 3.32 (q, *J* = 6.9 Hz, 2H), 3.65 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.7, 12.8, 13.8, 14.3, 24.91, 24.93, 39.6, 40.5, 47.4, 83.1, 84.1, 171.9; IR (CH_2Cl_2) 2971, 2873, 1639, 1422 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{23}ON$ 221.17796, found: 221.17827.

***N*-(3-Ethyl-4-iodo-2-oxaspiro[4.4]non-3-en-1-ylidene)diethylamonium chloride (68).** Yellow solid: mp 114-115 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 1.47 (s, 3H), 1.58 (s, 3H), 2.10-2.41 (m, 8H), 2.61 (q, J = 7.2 Hz, 2H), 3.95 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 11.0, 13.0, 13.6, 21.6, 28.5, 39.0, 48.0, 48.5, 61.7, 80.8, 154.8; IR (CH_2Cl_2) 2969, 2944, 2878, 1700, 1658, 1453 cm^{-1}.

Ethyl (2*E*)-3-(3-ethyl-2-oxaspiro[4.4]non-3-en-1-one-4-yl)acrylate (69). Light pink solid: mp 60-61 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.4 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.90-2.04 (m, 8H), 2.54 (q, J = 7.4 Hz, 2H), 4.20 (q, J = 7.0 Hz, 2H), 5.74 (d, J = 16.0 Hz, 1H), 7.33 (d, J = 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.5, 14.4, 19.5, 27.1, 35.5, 52.7, 60.6, 115.7, 117.8, 133.1, 159.7, 167.0, 182.9; IR (CH_2Cl_2) 3055, 2980, 2876, 1794, 1705, 1638, 1451, 1265 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_4$ 264.13616, found: 264.13661.

3-Ethyl-2-oxa-4-(phenylethynyl)spiro[4.4]non-3-en-1-one (70). Light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.6 Hz, 3H), 1.92-2.06 (m, 8H), 2.56 (q, J = 7.6 Hz, 2H), 7.32-7.35 (m, 3H), 7.42-7.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.9, 21.2, 26.6, 37.0, 54.9, 80.1, 94.9, 106.0, 123.1, 128.37, 128.44, 131.3, 158.9, 181.9; IR ($CDCl_3$) 3061, 2959, 2875, 2231, 1762, 1449, 1267 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}O_2$ 266.13068, found: 266.13101.

3-Ethyl-2-oxa-4-phenylspiro[4.4]non-3-en-1-one (71). Light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.4 Hz, 3H), 1.51-1.52 (m, 2H), 1.89-1.93 (m, 4H), 2.02-2.04 (m, 2H), 2.25 (q, J = 7.4 Hz, 2H), 7.16-7.18 (m, 2H), 7.34-7.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 11.7, 19.7, 26.2, 36.2, 56.0, 121.3, 127.8, 128.5, 129.8, 132.4, 150.8, 183.7; IR (CH_2Cl_2) 3056, 2965, 2874, 1789 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{18}O_2$ 242.13068, found: 242.13103.

Methyl 3-ethyl-2-oxaspiro[4.4]non-3-en-1-one-4-carboxylate (72). Light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.4 Hz, 3H), 1.93-1.94 (m, 6H), 2.08-2.10 (m, 2H), 2.82 (q, J =

7.6 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 11.0, 21.4, 27.0, 36.7, 51.3, 53.0, 113.1, 163.7, 166.6, 182.0; IR (CH_2Cl_2) 2954, 2874, 1805, 1710 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}O_4$ 224.10486, found: 224.10519.

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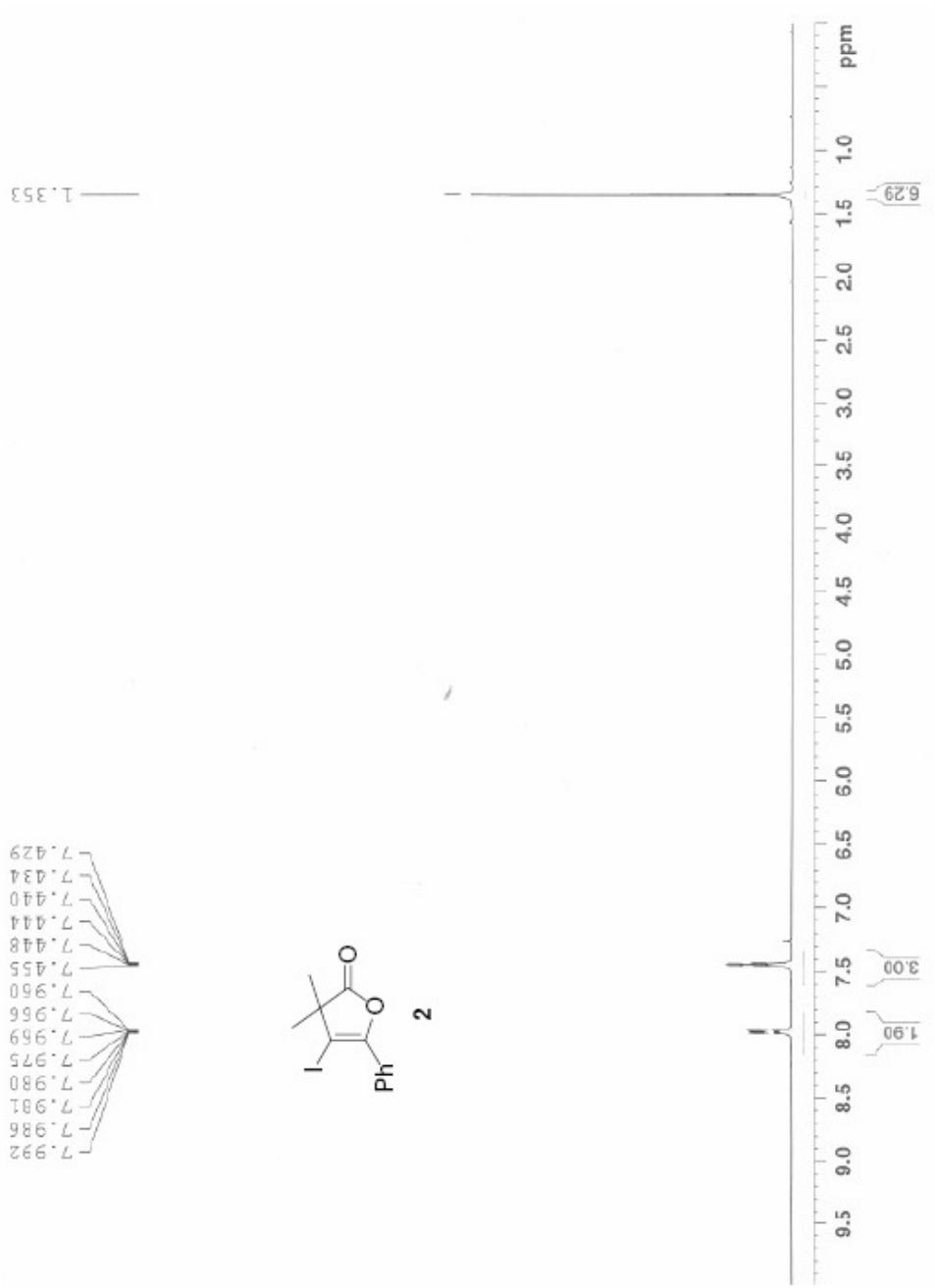
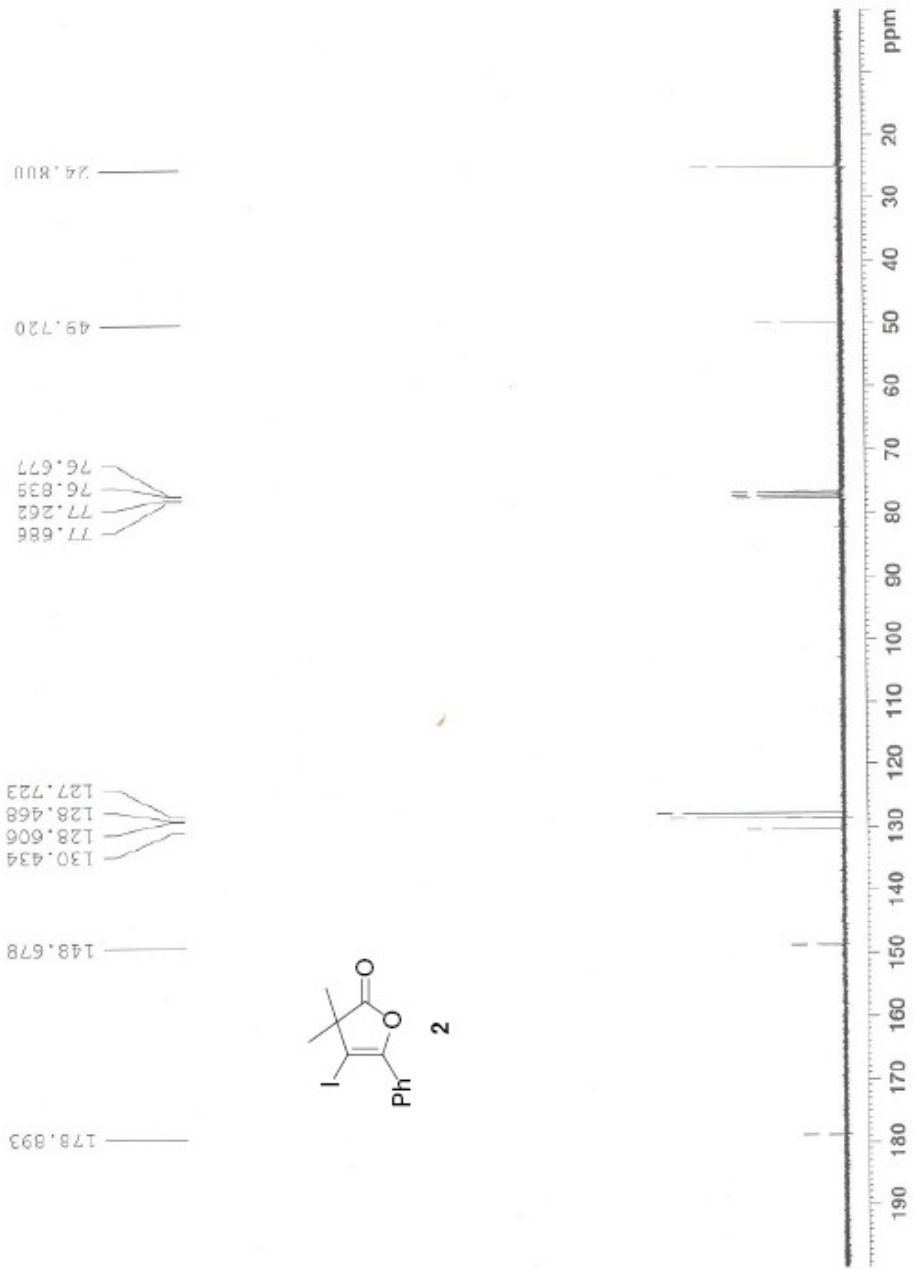
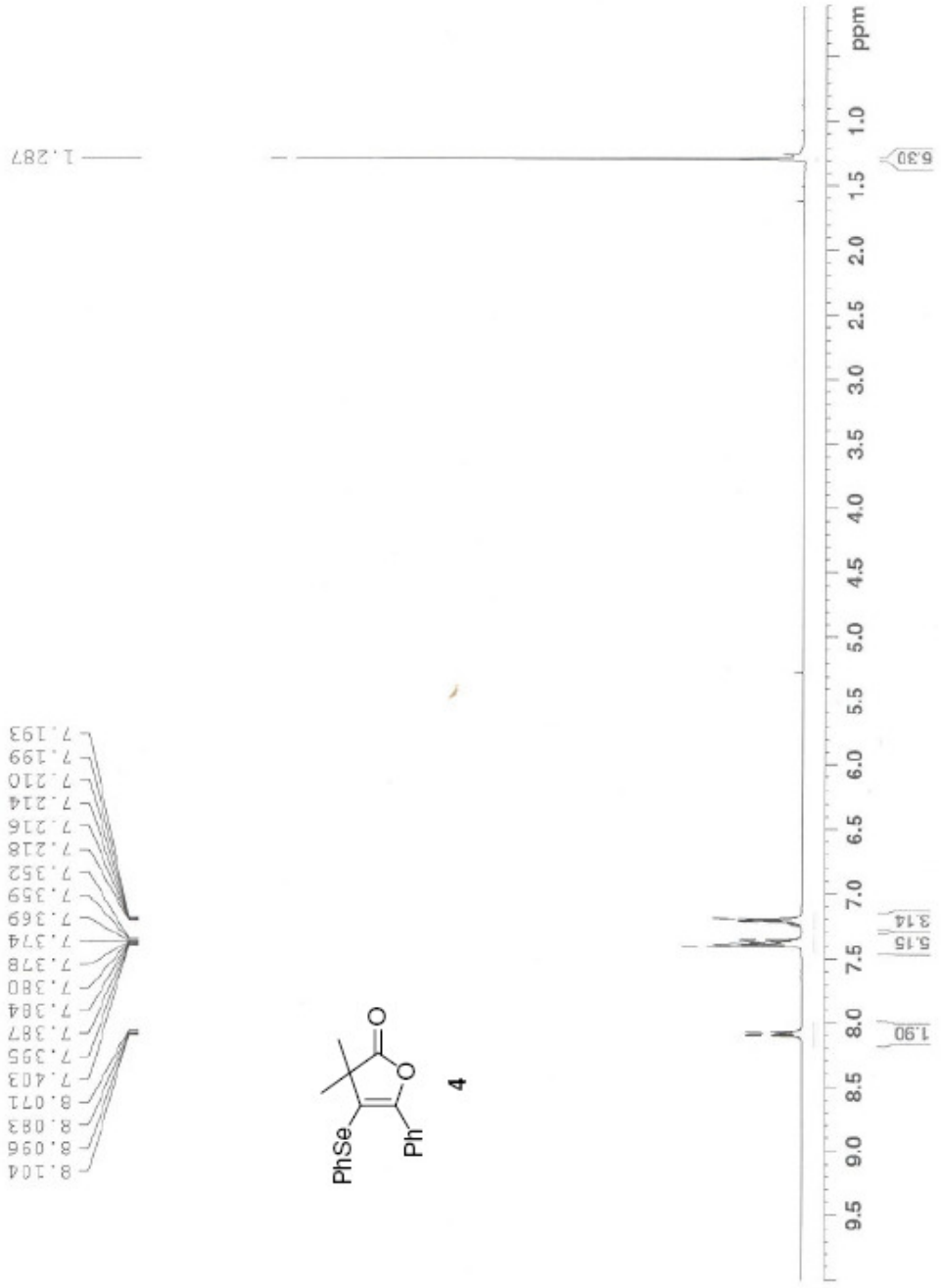
GENERAL CONCLUSIONS

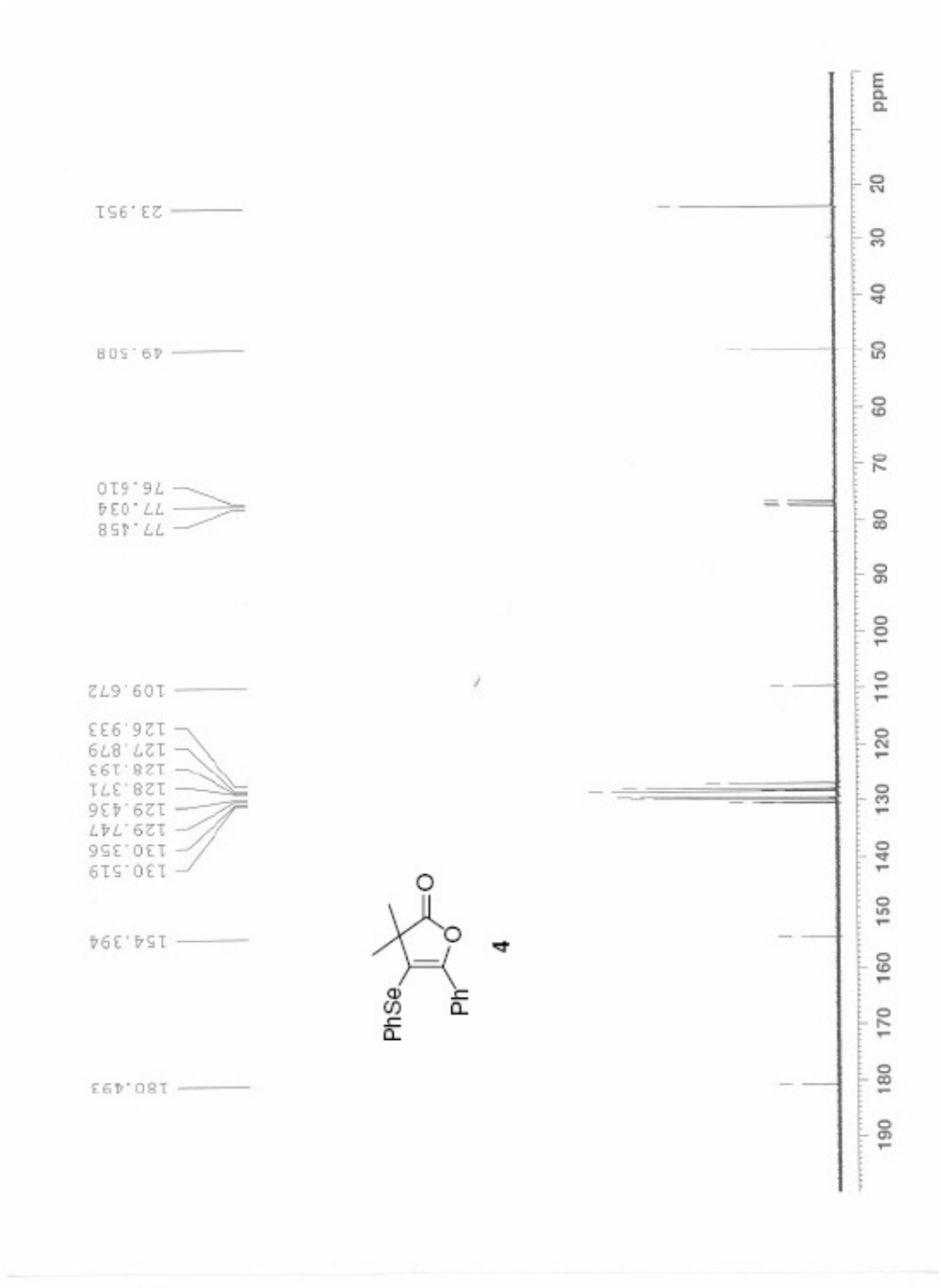
In this thesis, the scope and the limitations of the electrophilic cyclization of 3-alkynoate esters and 3-alkynoic acids have been presented for the synthesis of highly substituted 2(3*H*)-furanones. This methodology is fairly general for 3-alkynoate esters and better results can be provided by 3-alkynoic acids in these electrophilic cyclizations. It is important to point out that the hybridization of the α position of both the 3-alkynoate ester and 3-alkynoic acid is crucial for the electrophilic cyclization to take place successfully. Various functional groups on the 3-alkynoate ester and the corresponding acids have been successfully employed in this process with moderate to excellent yields. The resulting highly substituted 4-iodo-2(3*H*)-furanones can be readily modified by palladium chemistry. The electrophilic cyclization of 3-alkynoate esters and 3-alkynoic acids provides a useful, new synthetic route for the preparation of highly substituted 2(3*H*)-furanones.

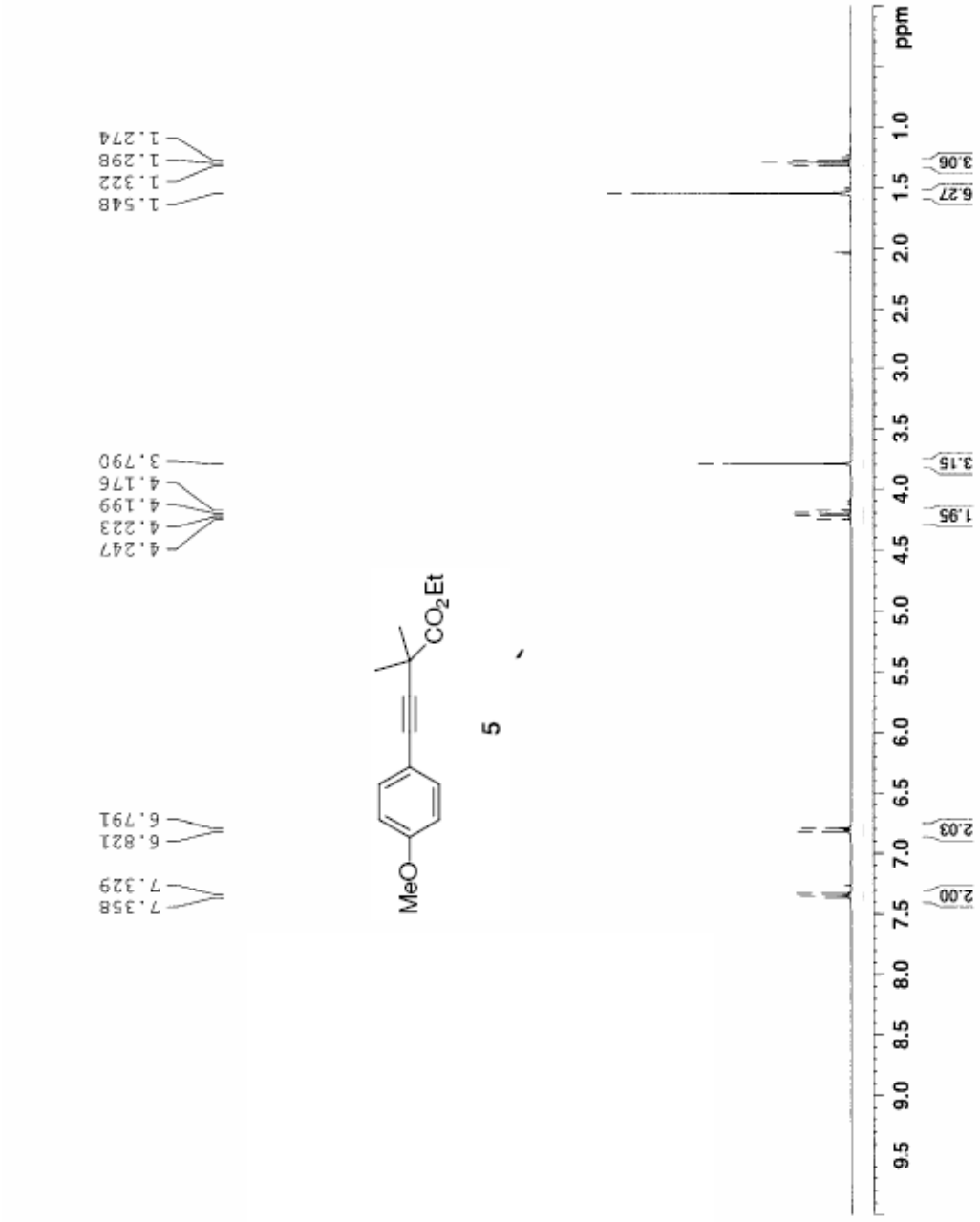
APPENDIX. THESIS ^{1}H AND ^{13}C NMR SPECTRA

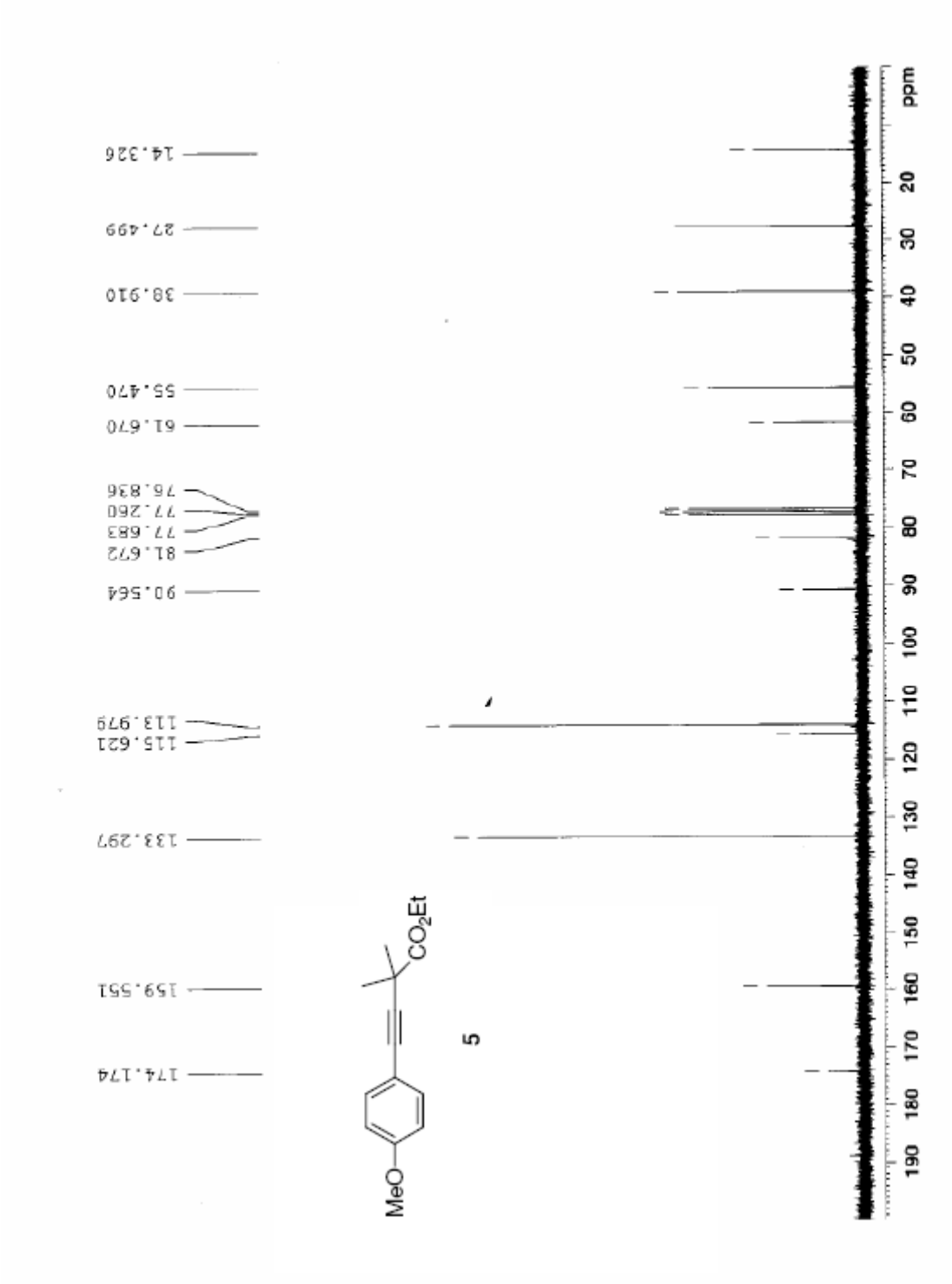


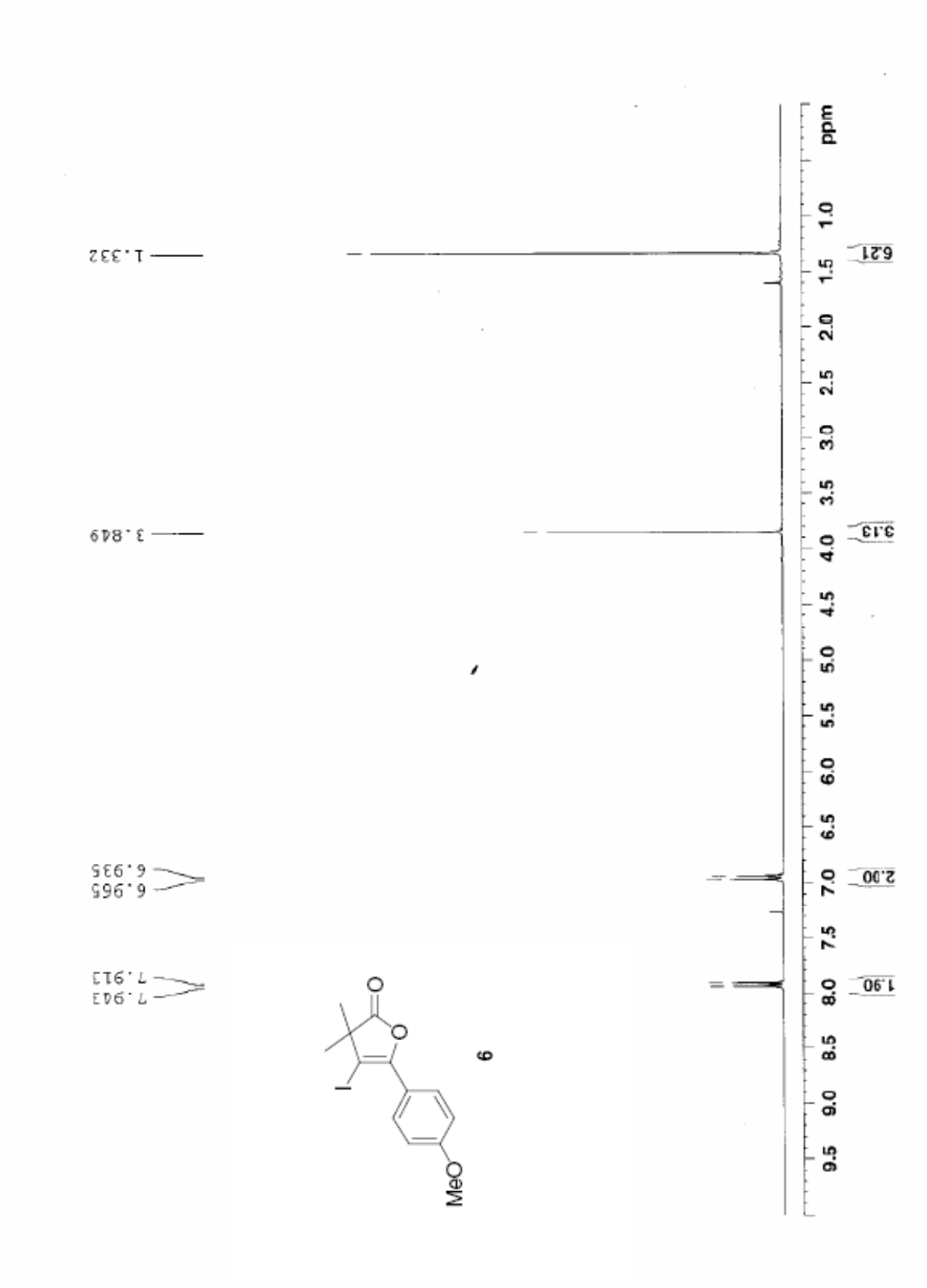


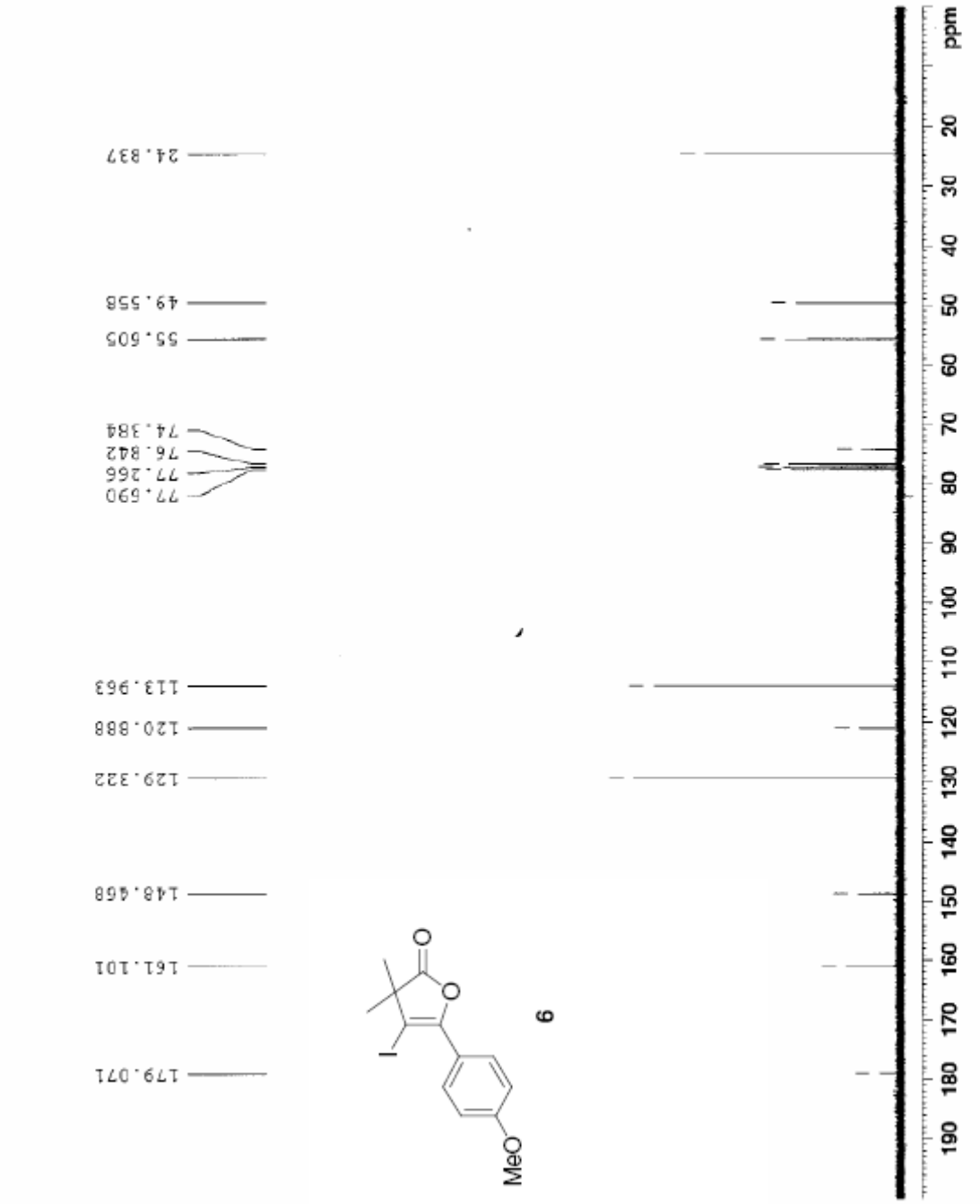


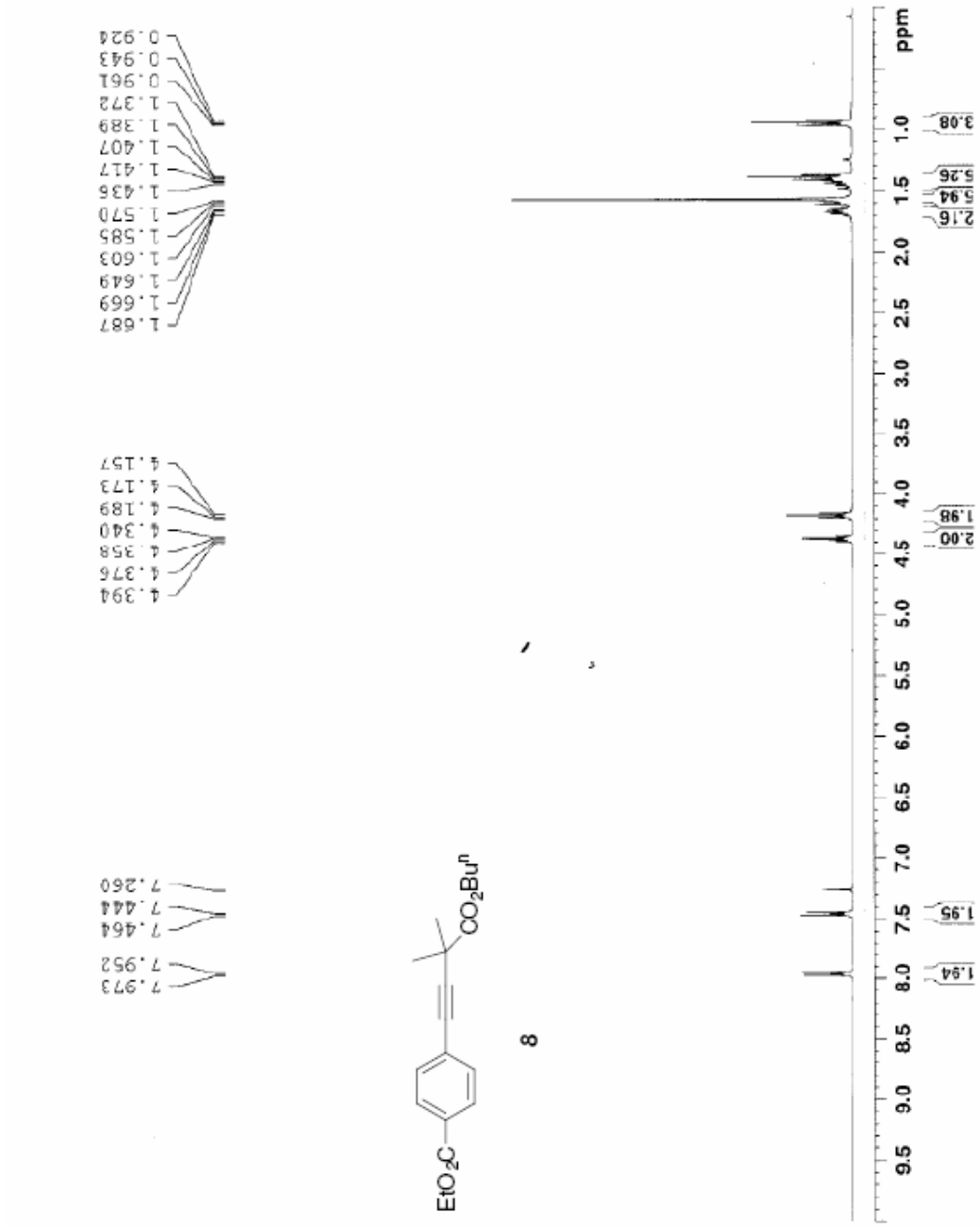


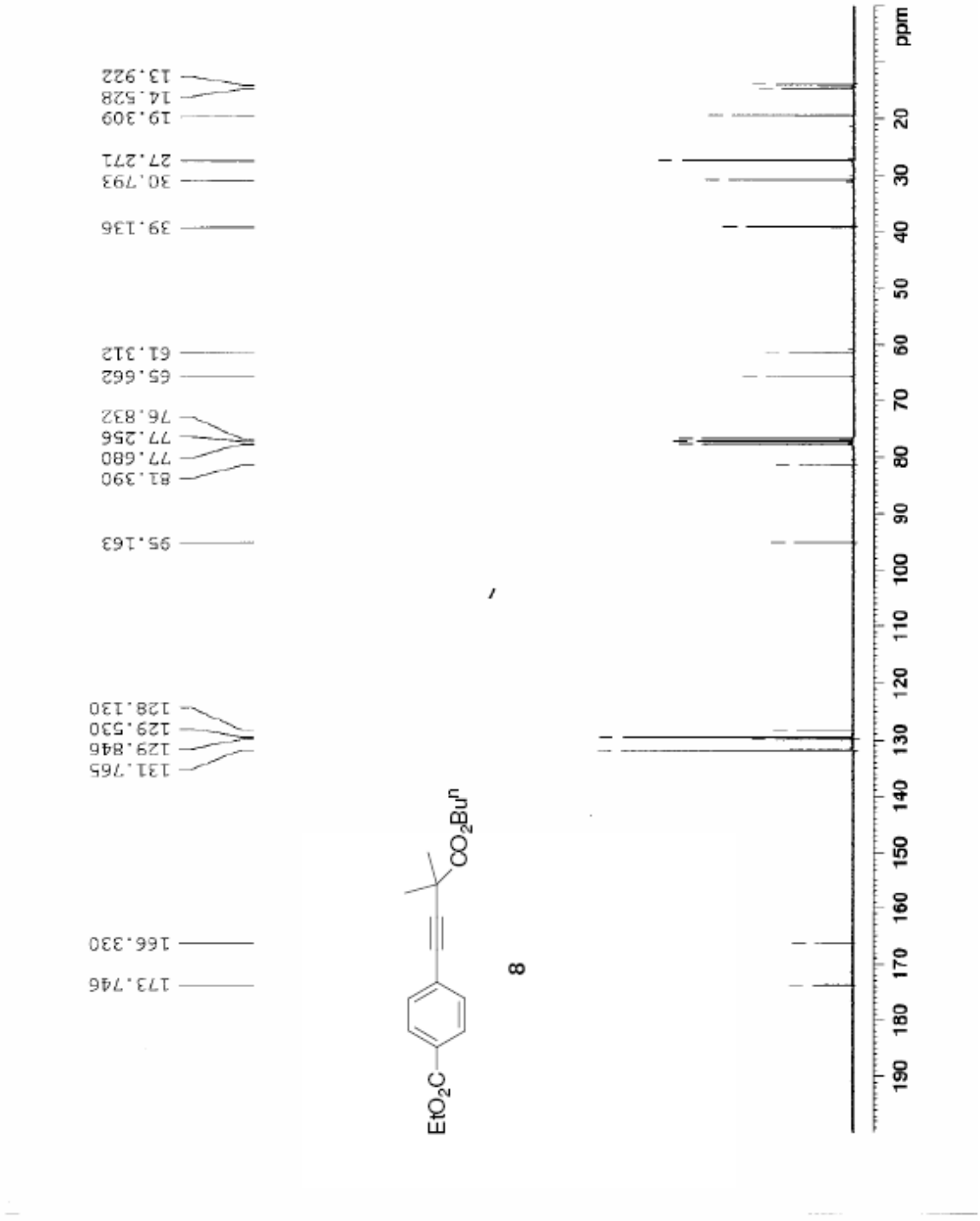


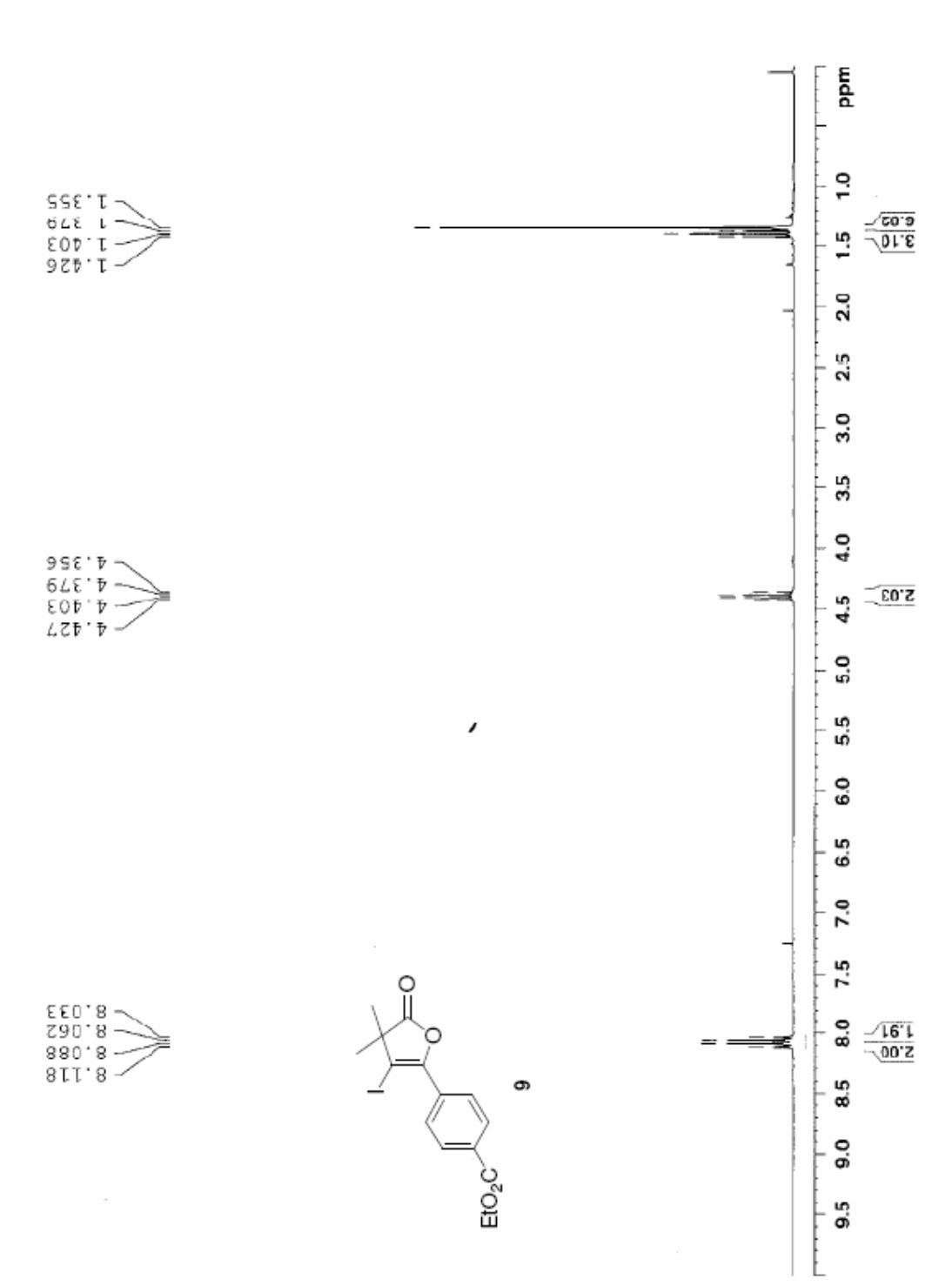


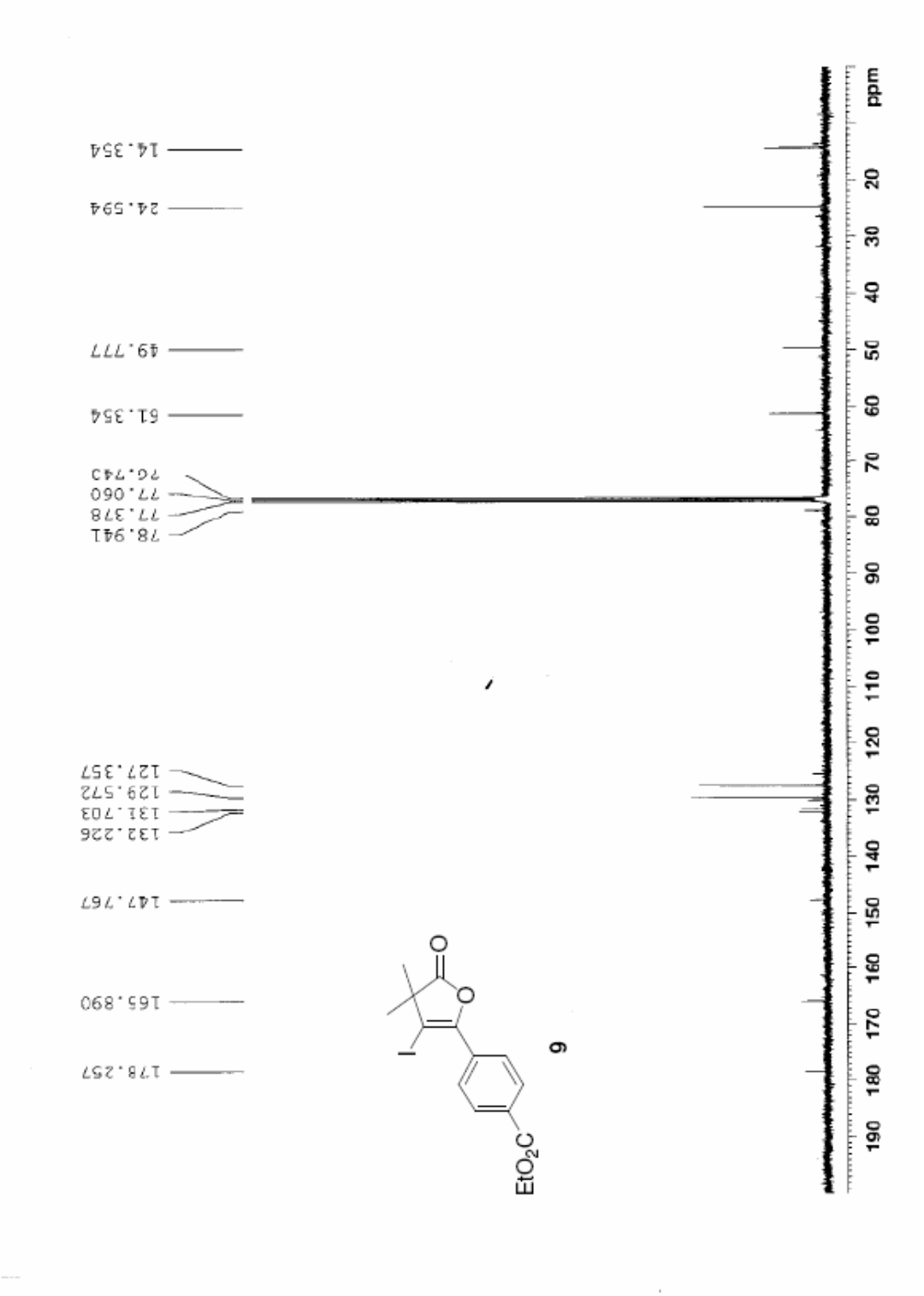


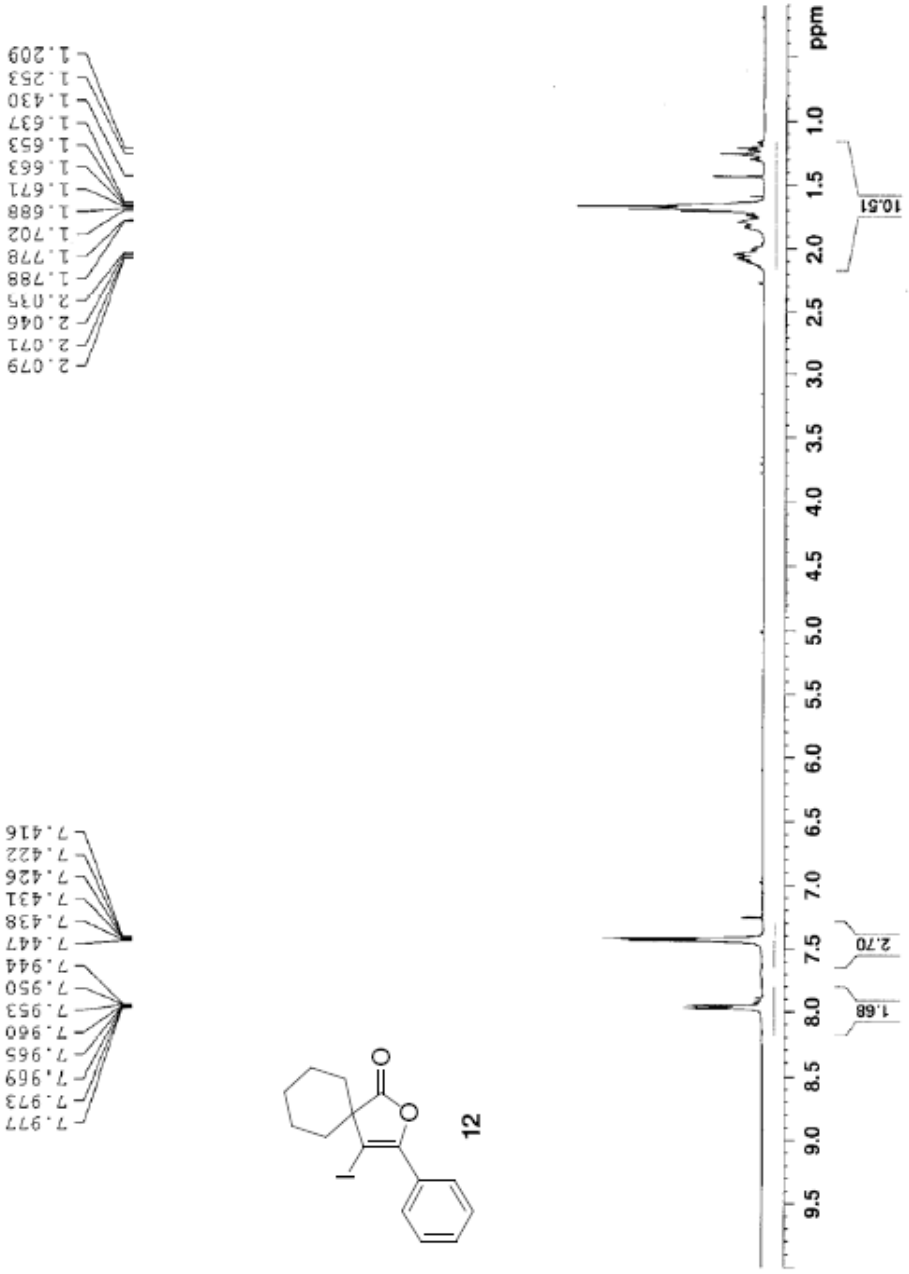


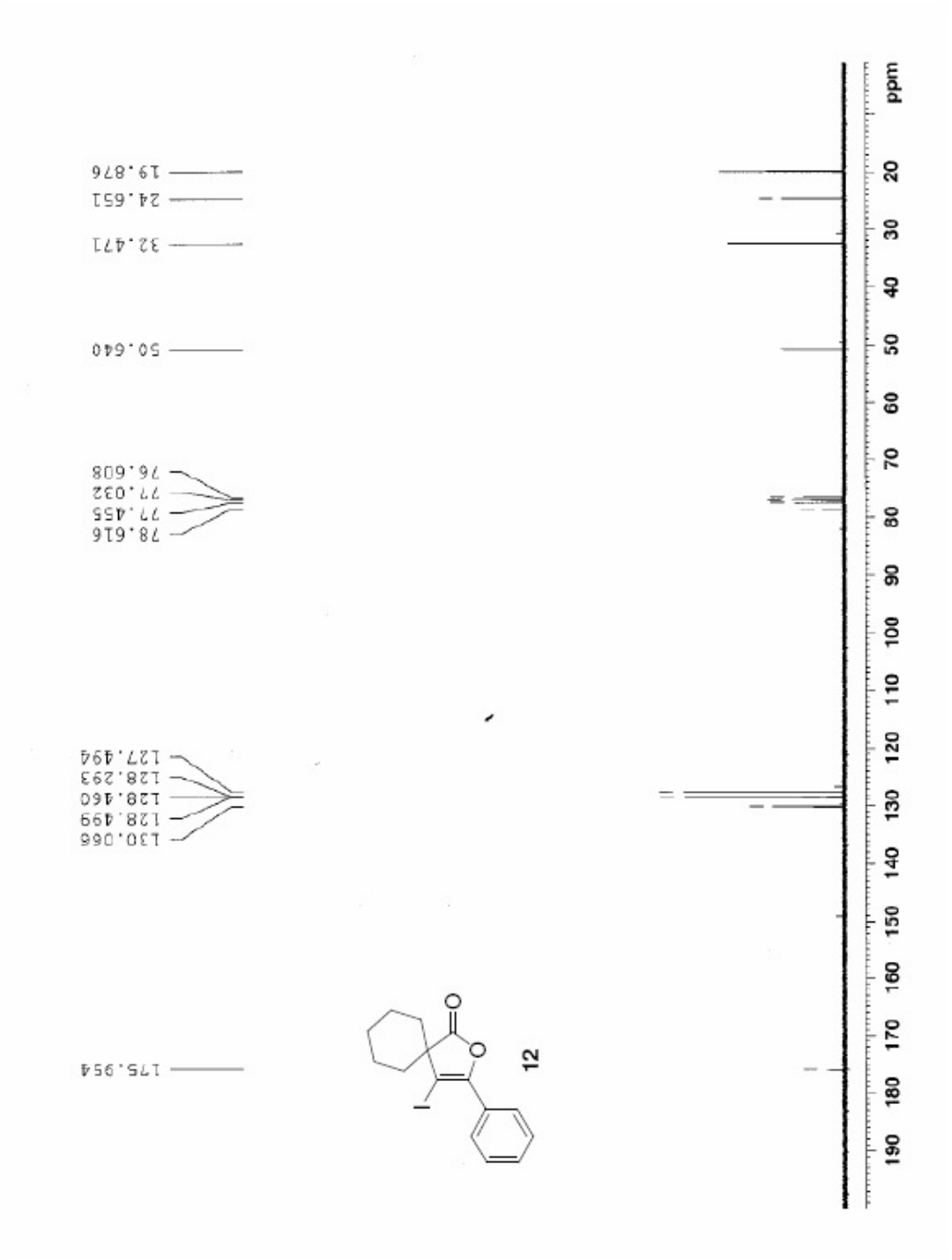


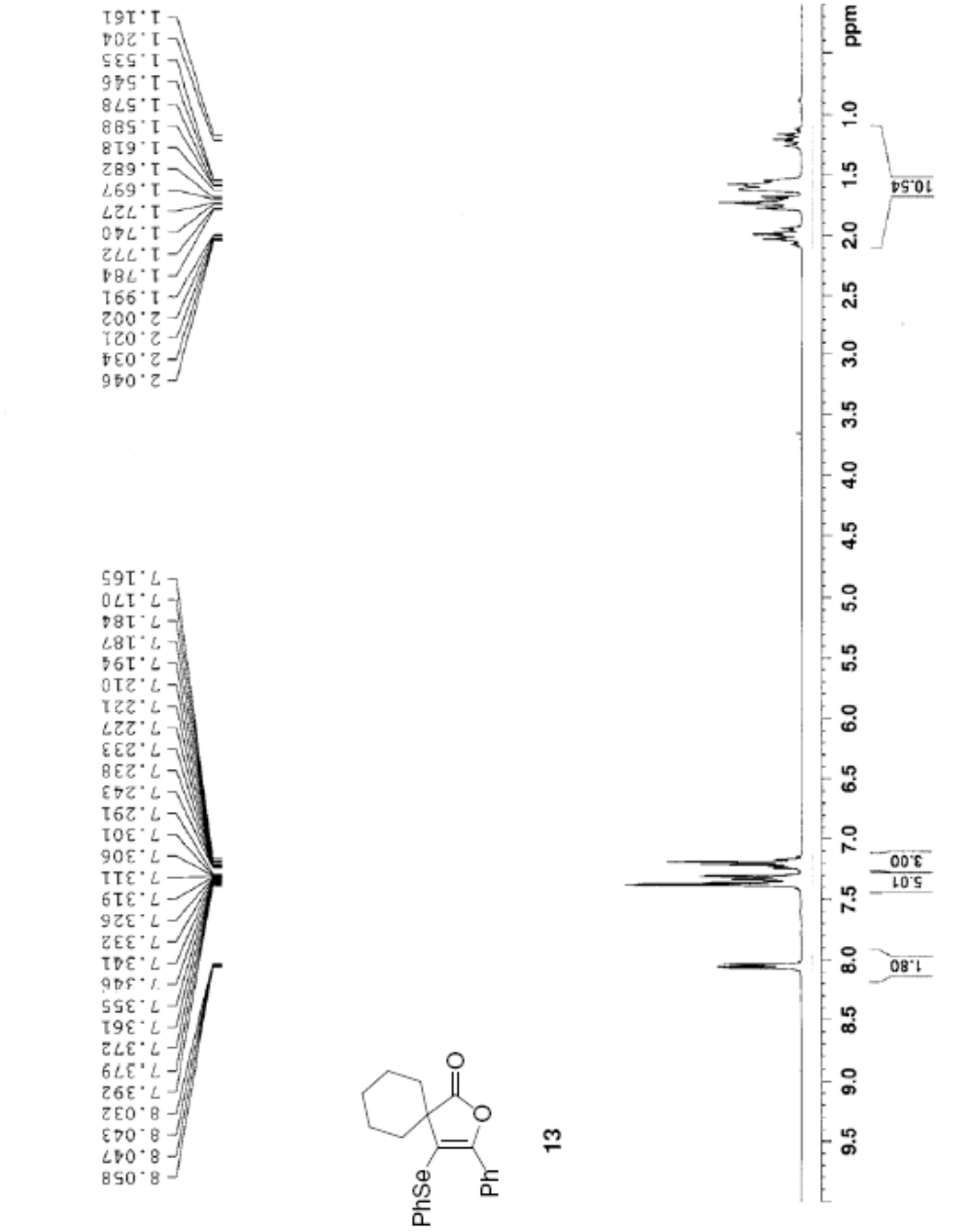


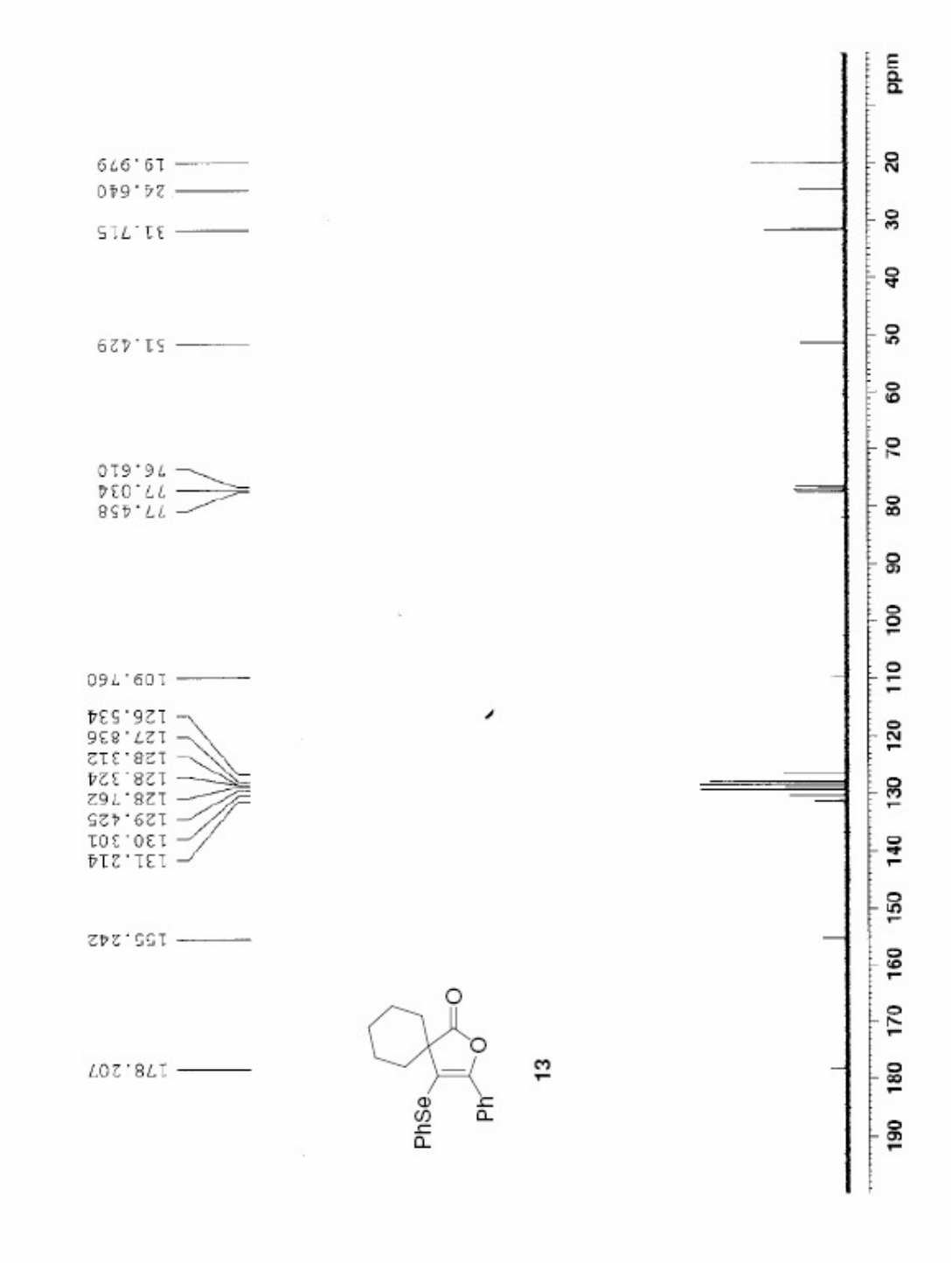


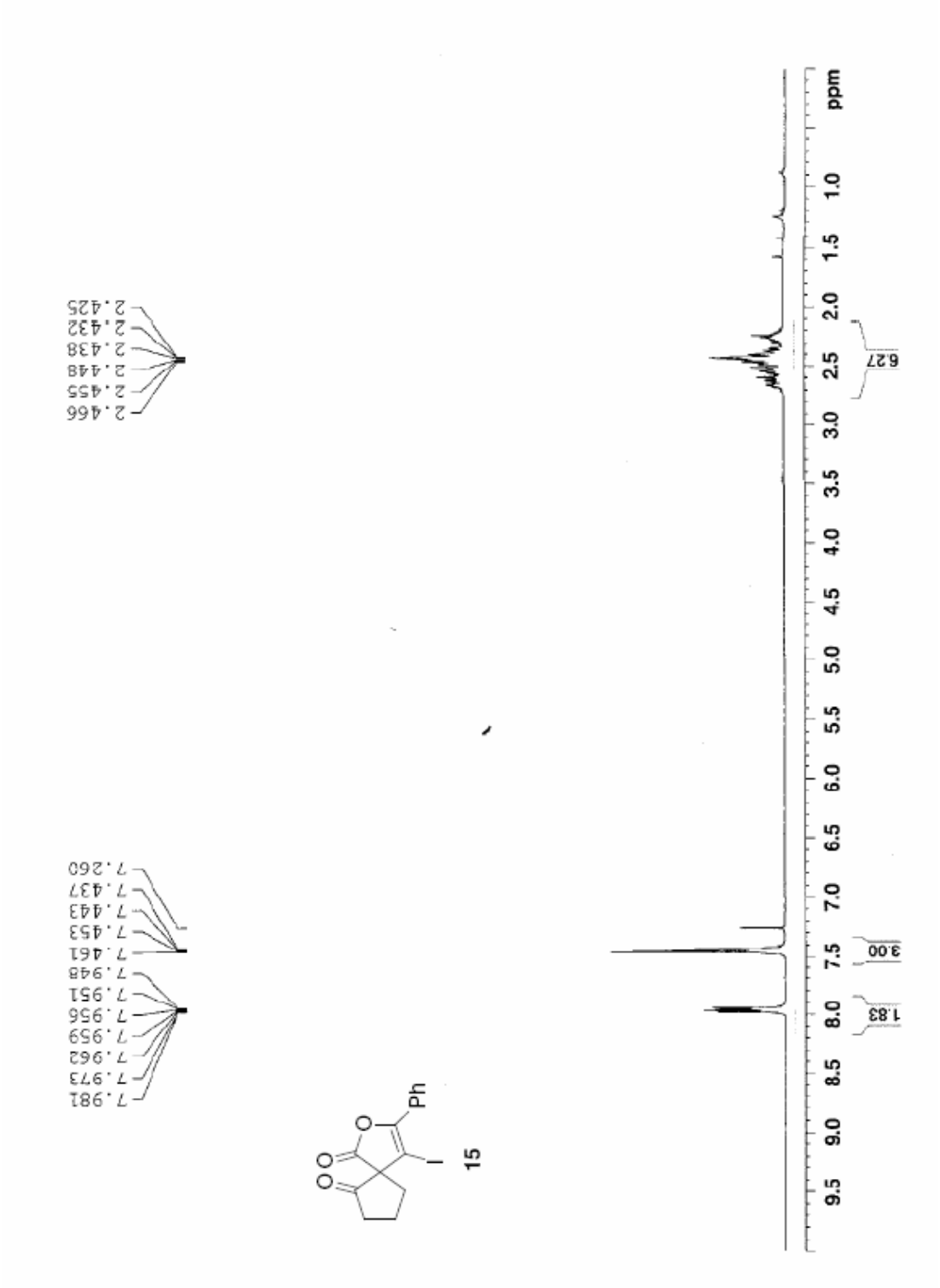


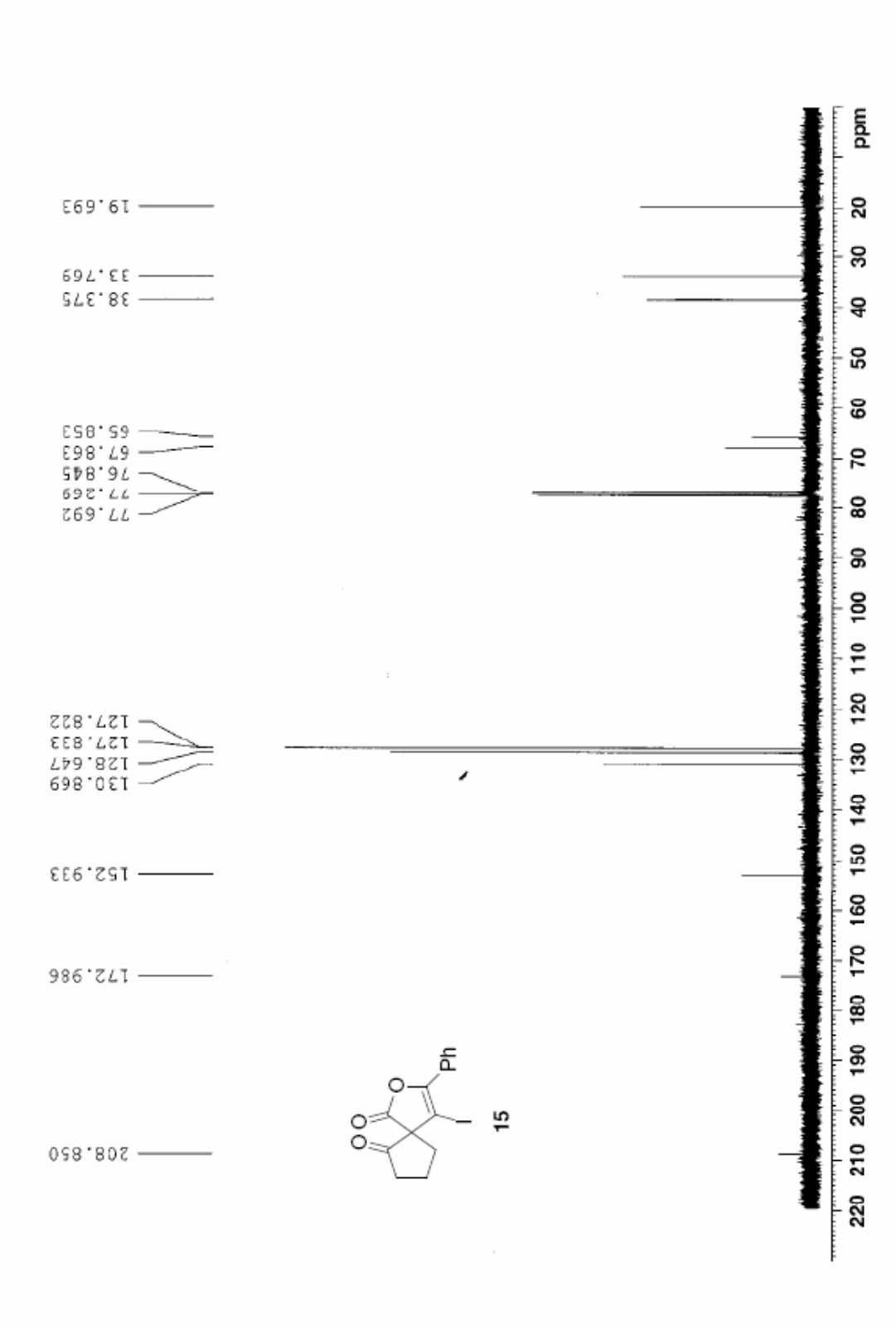


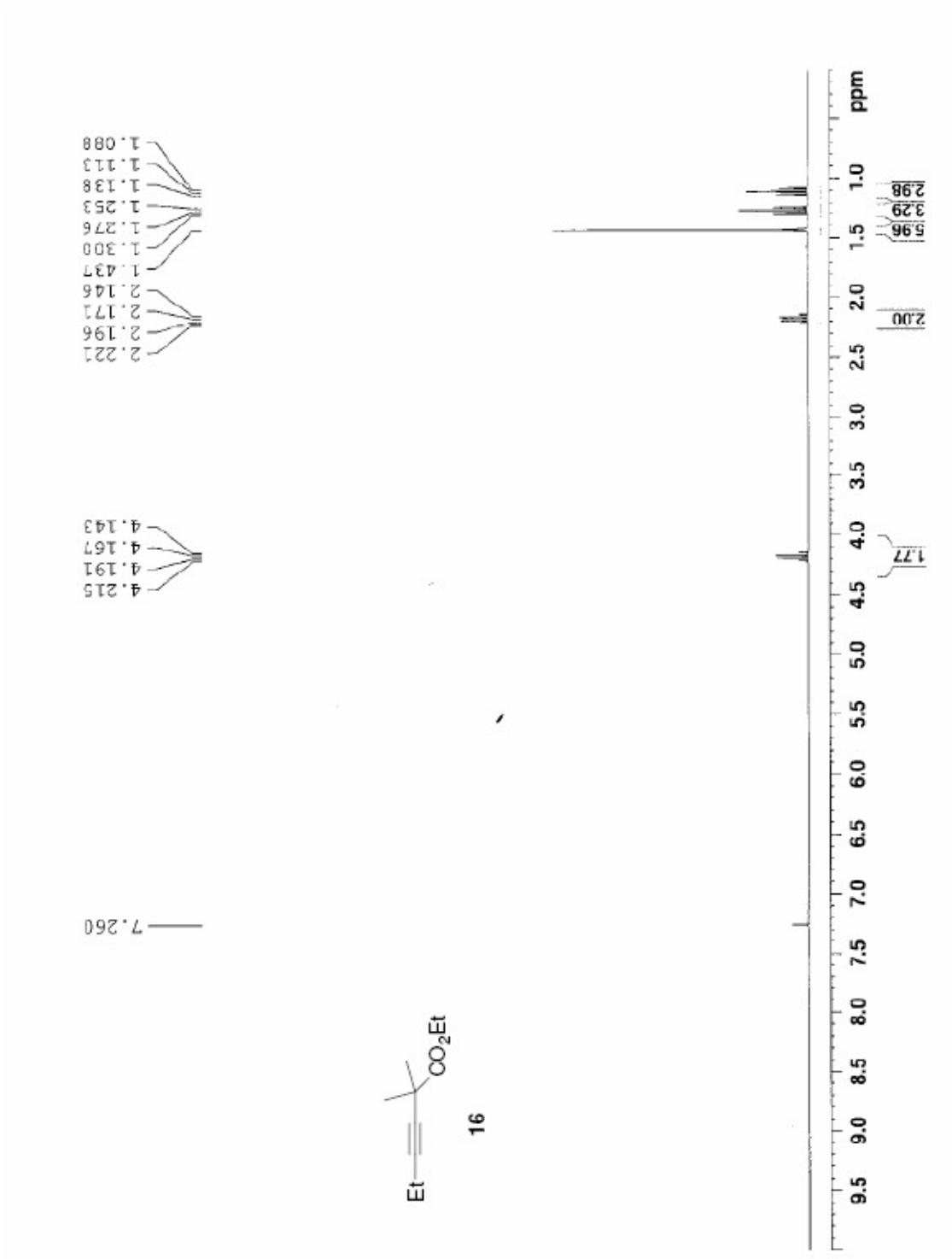


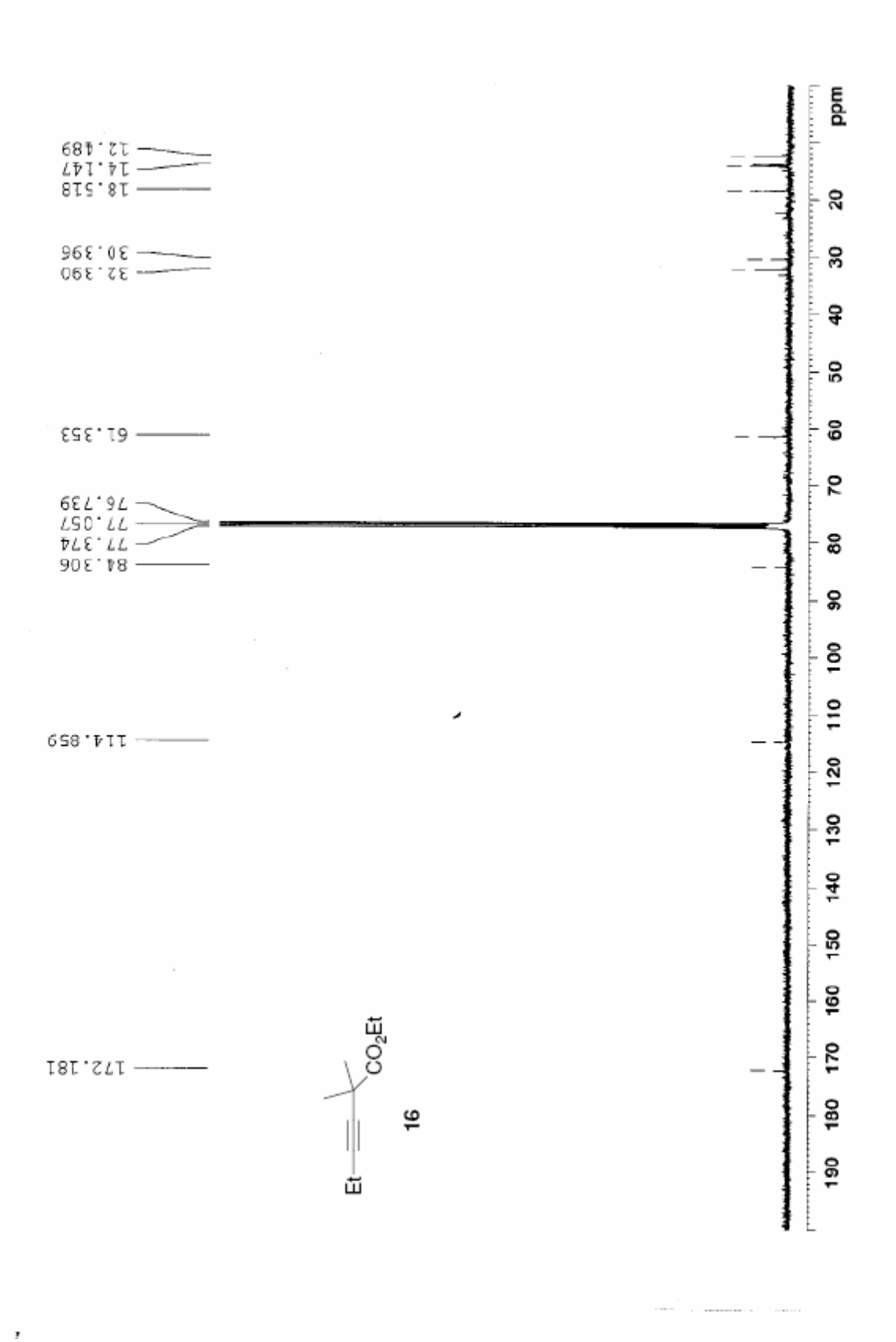


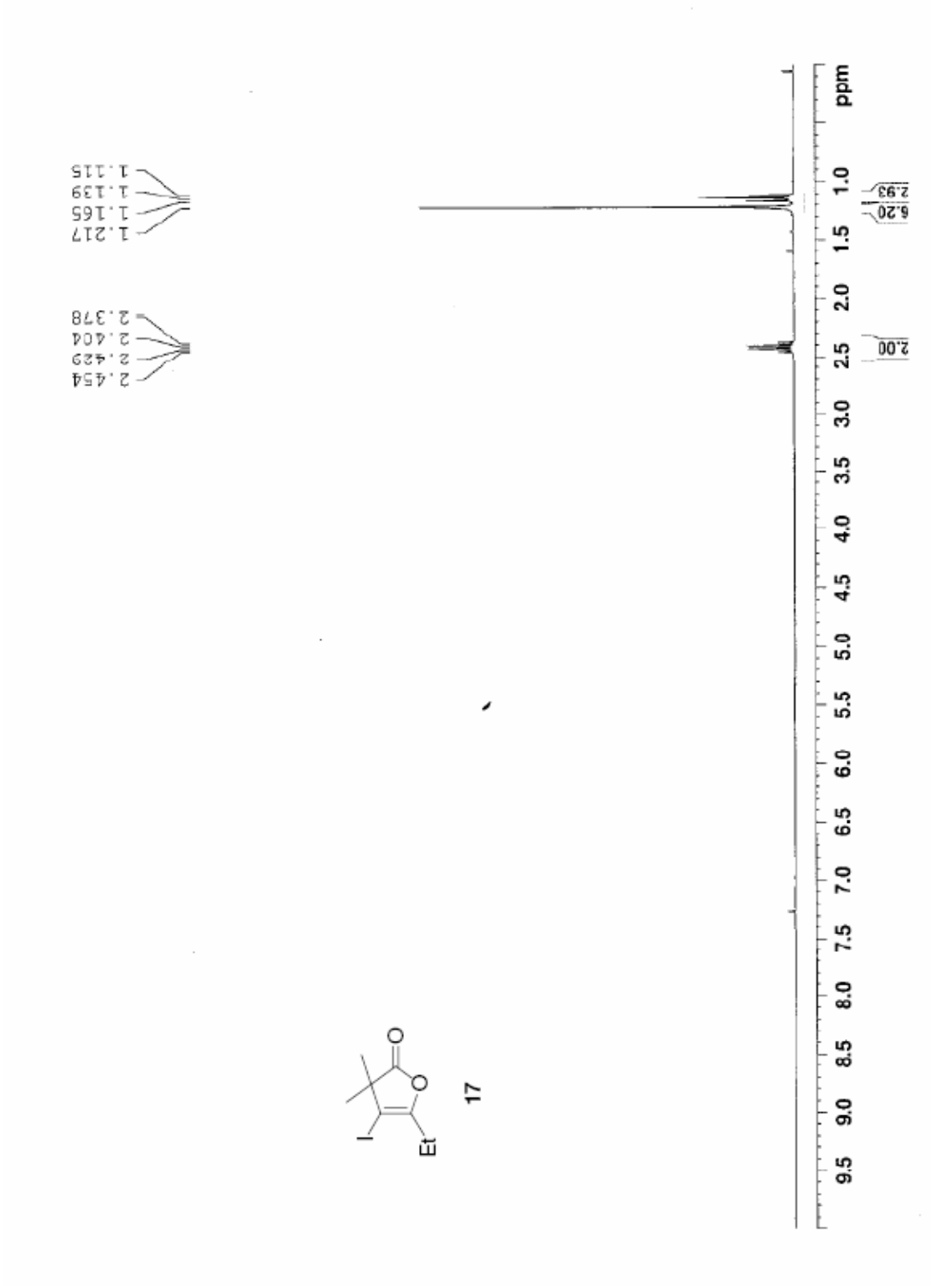


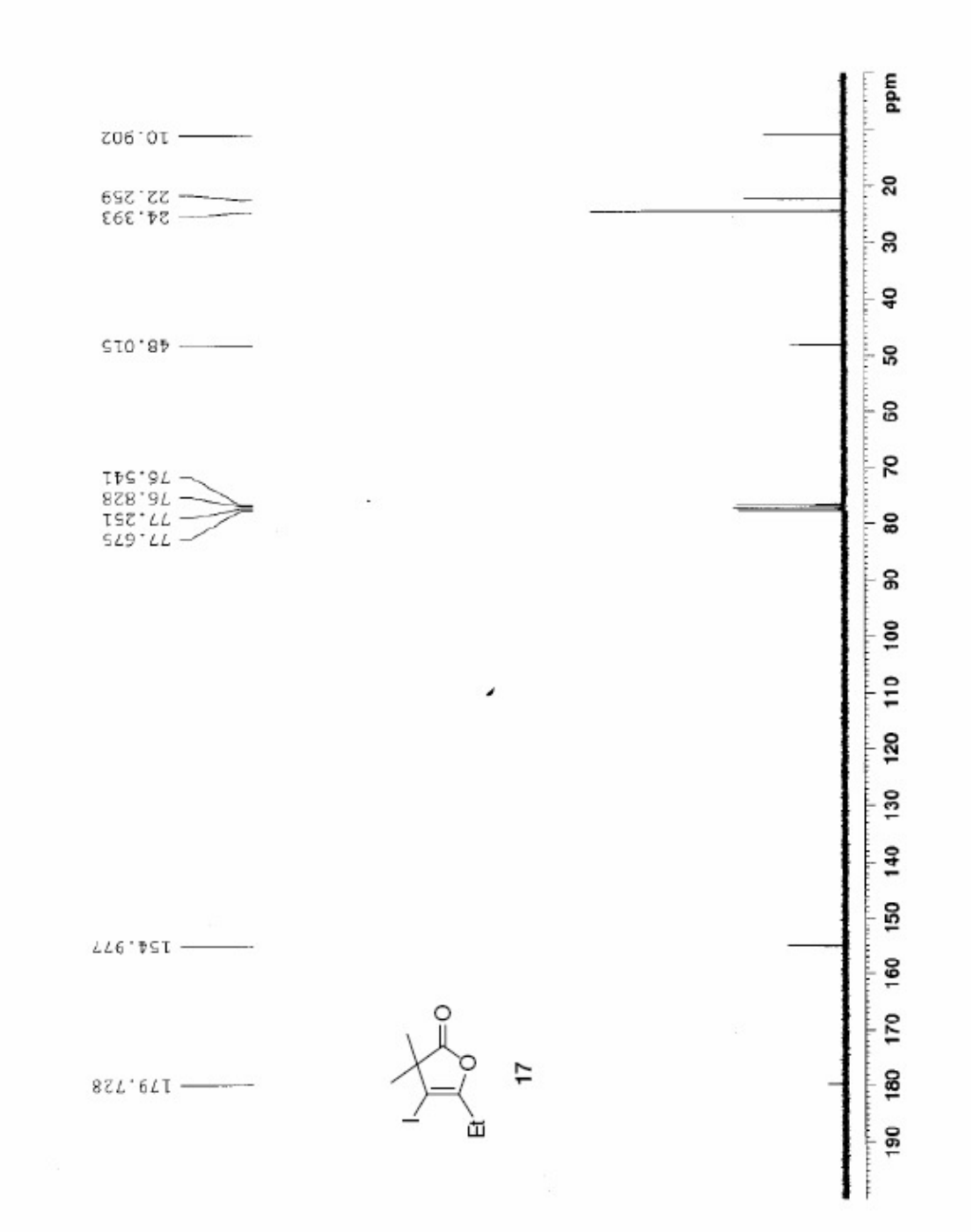


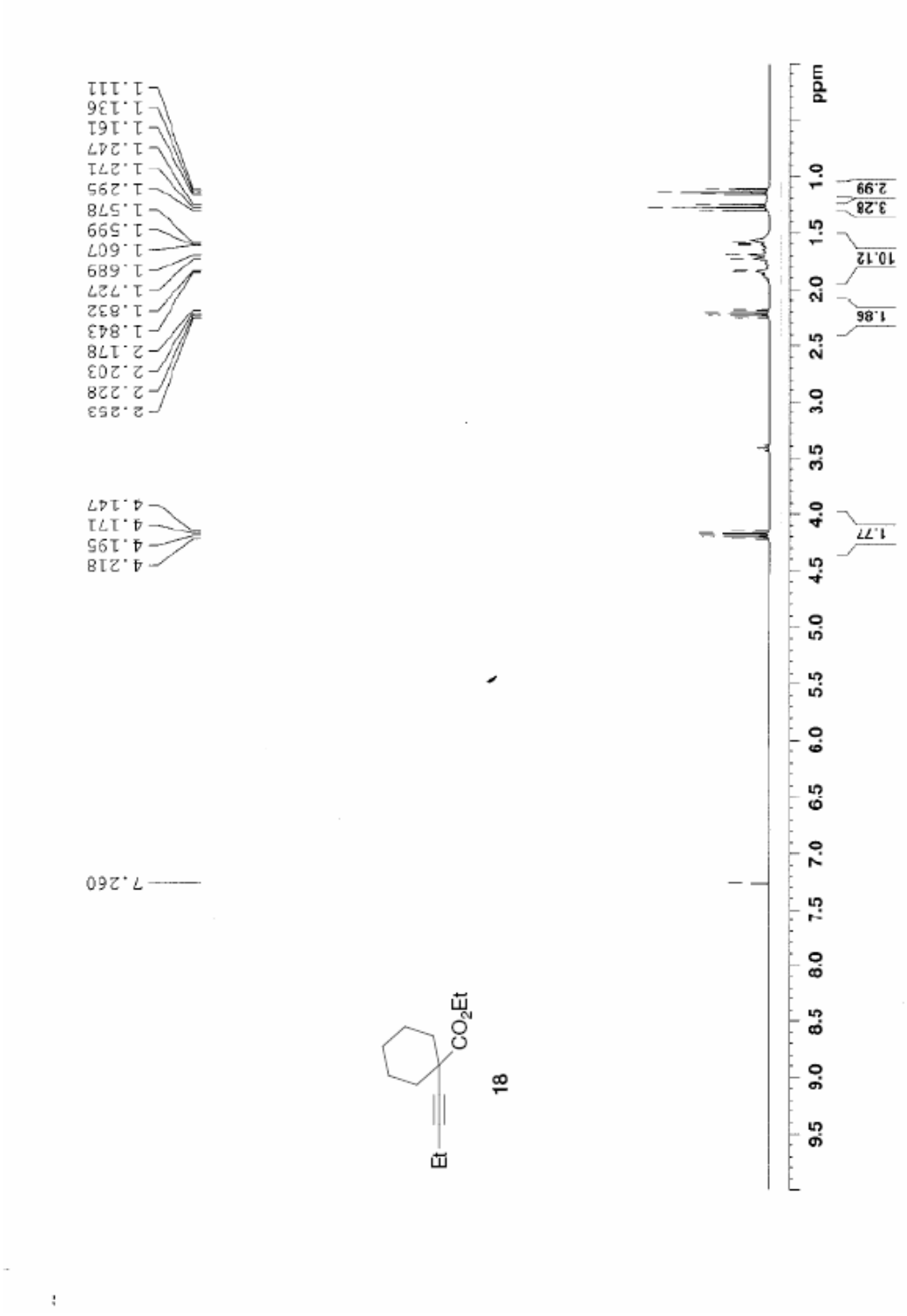


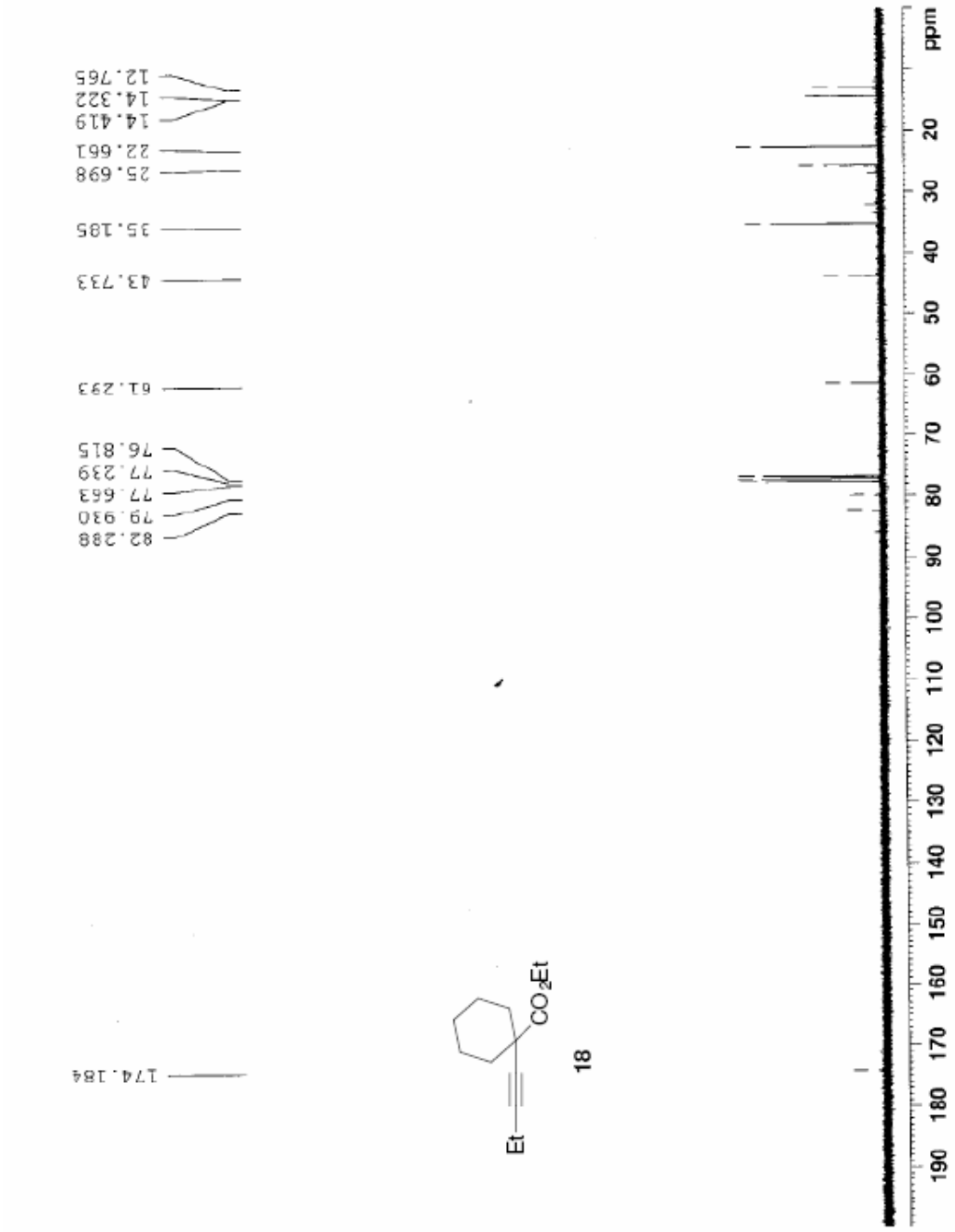


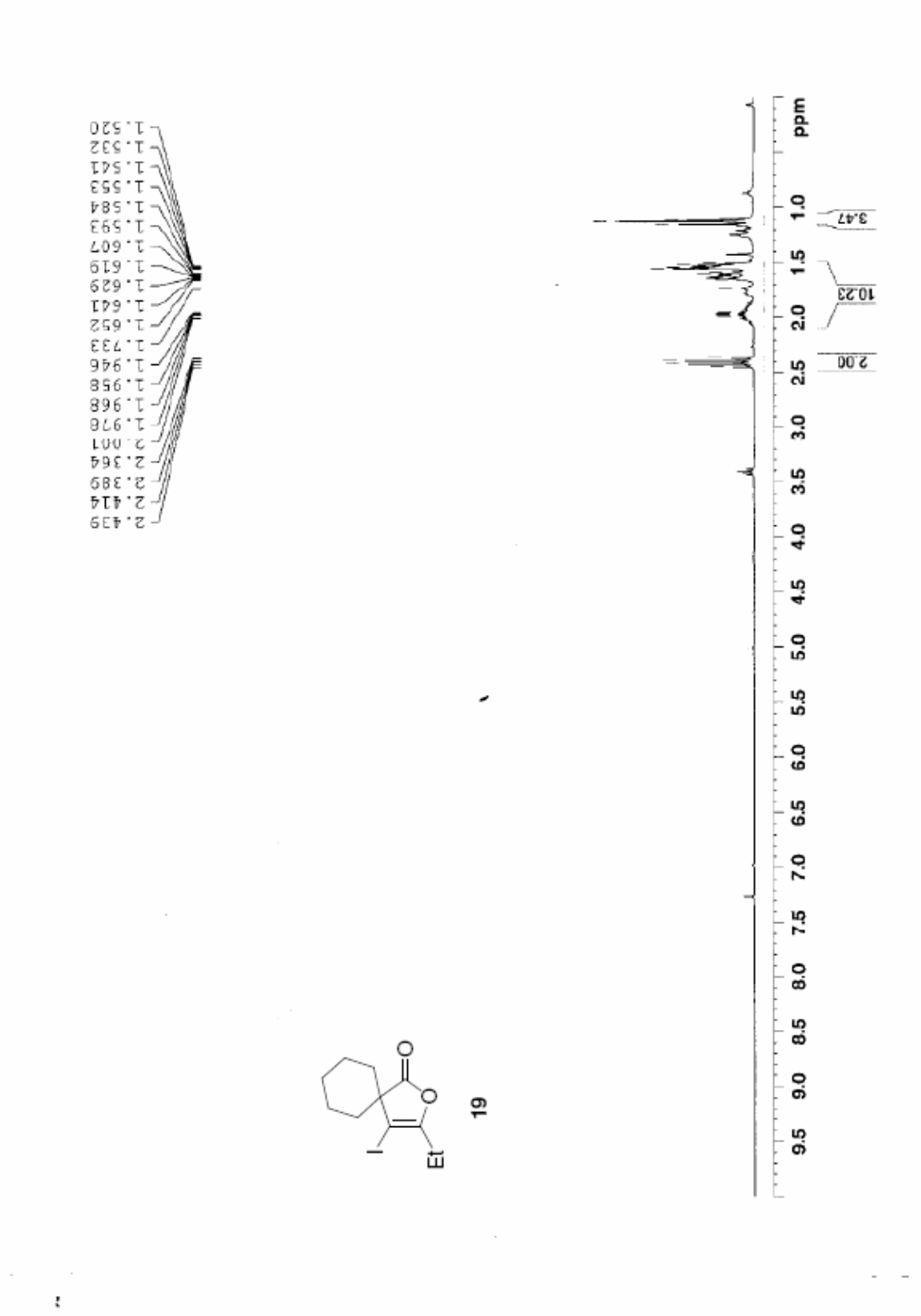


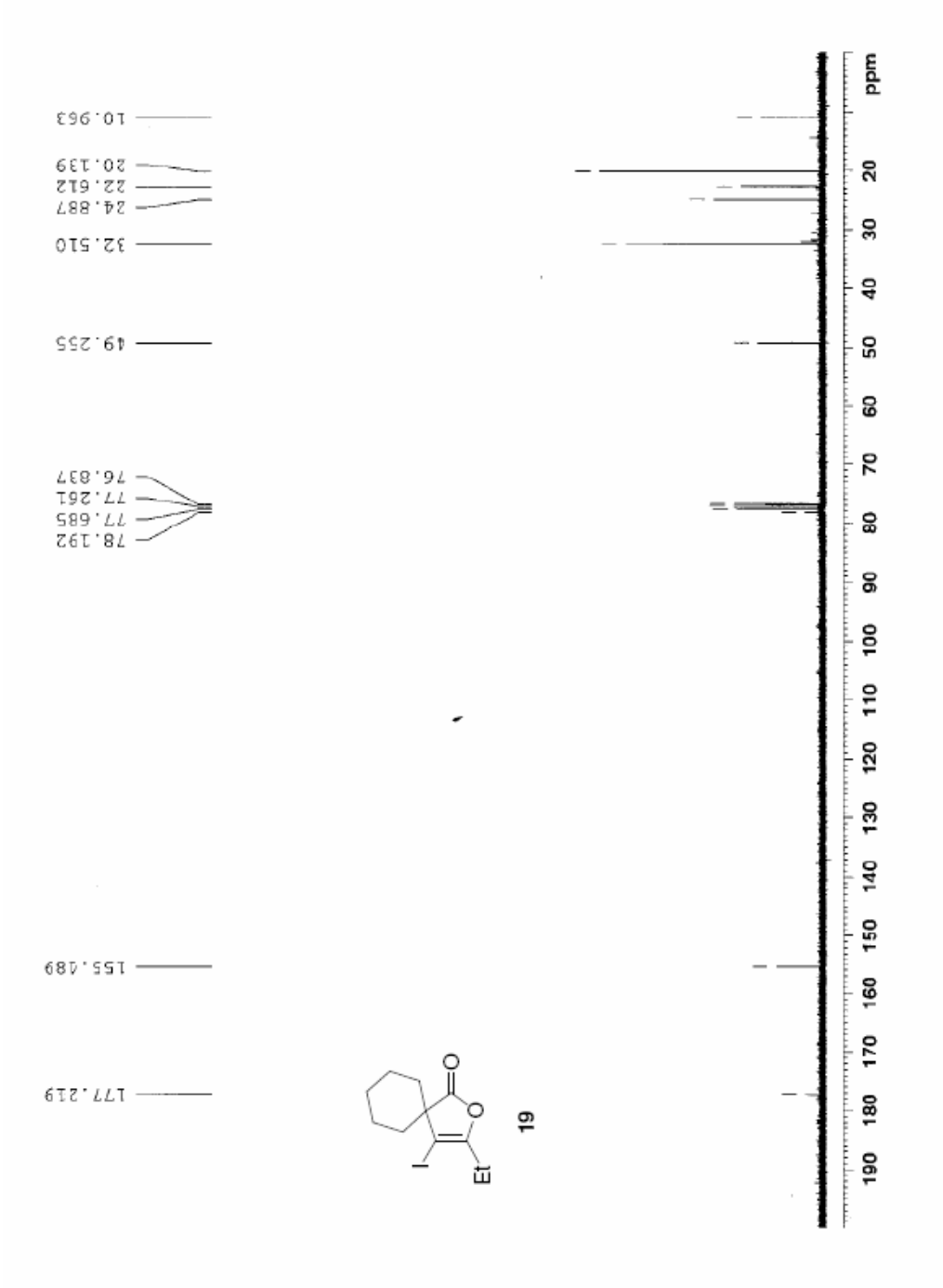


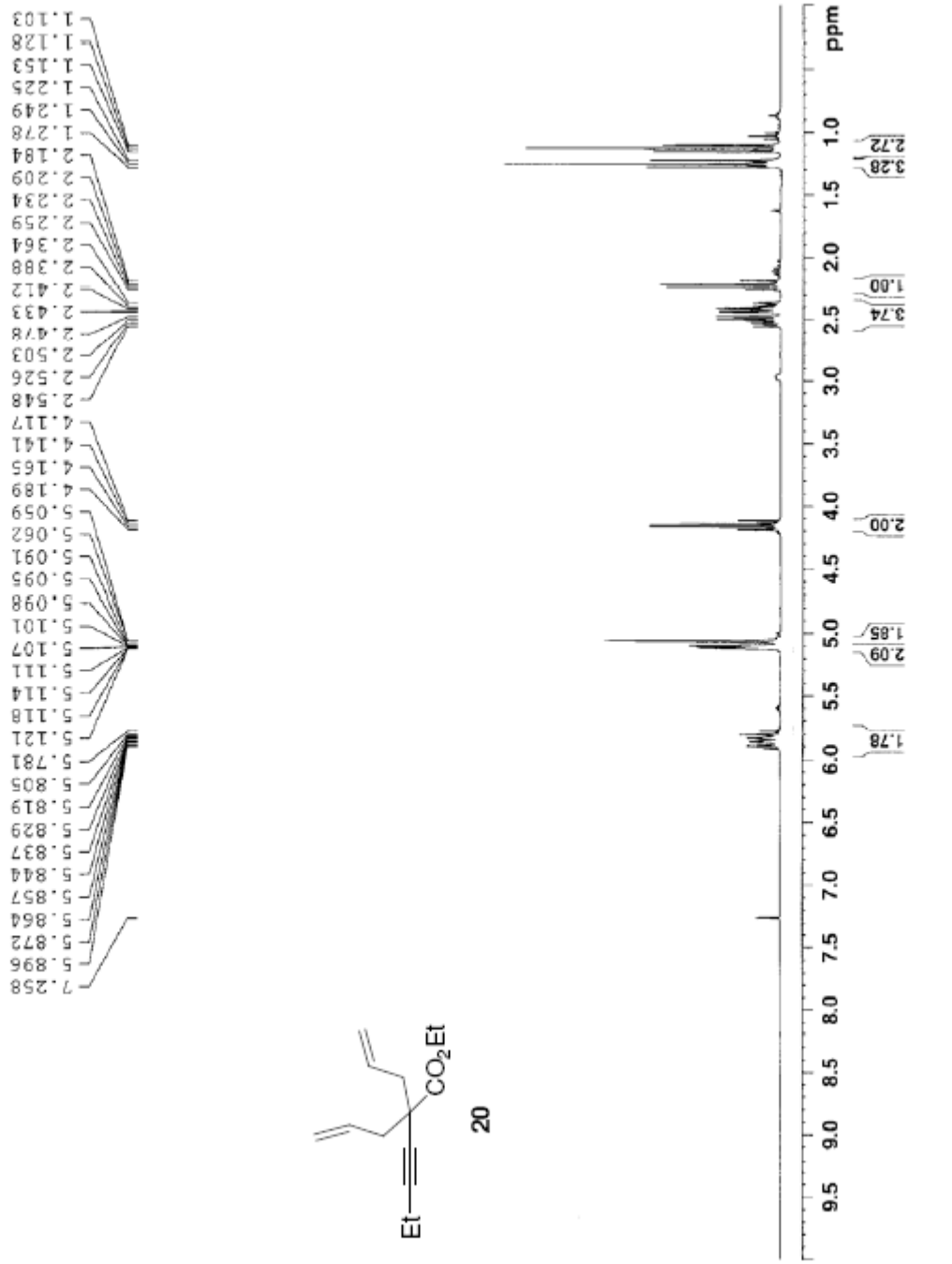


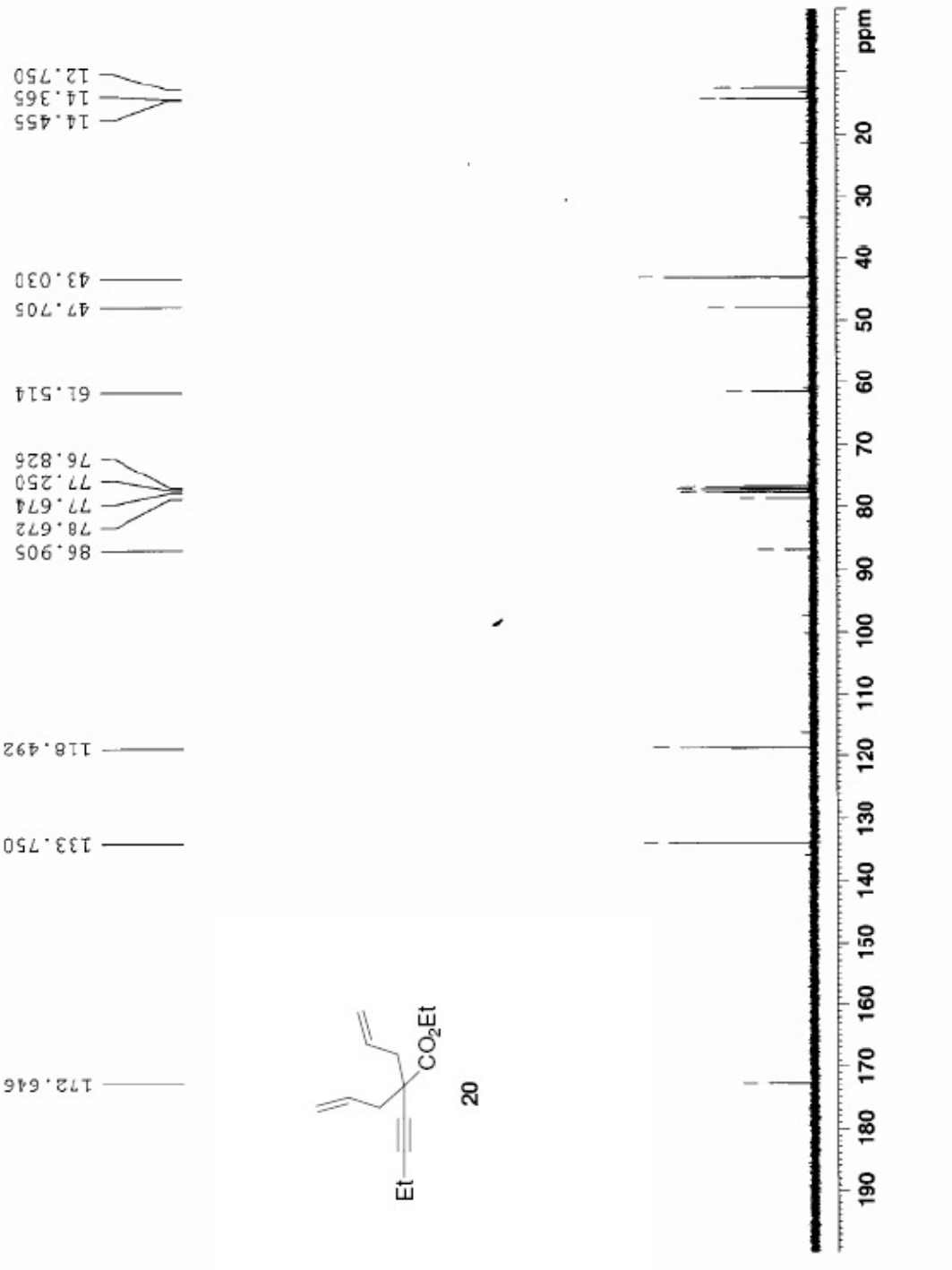


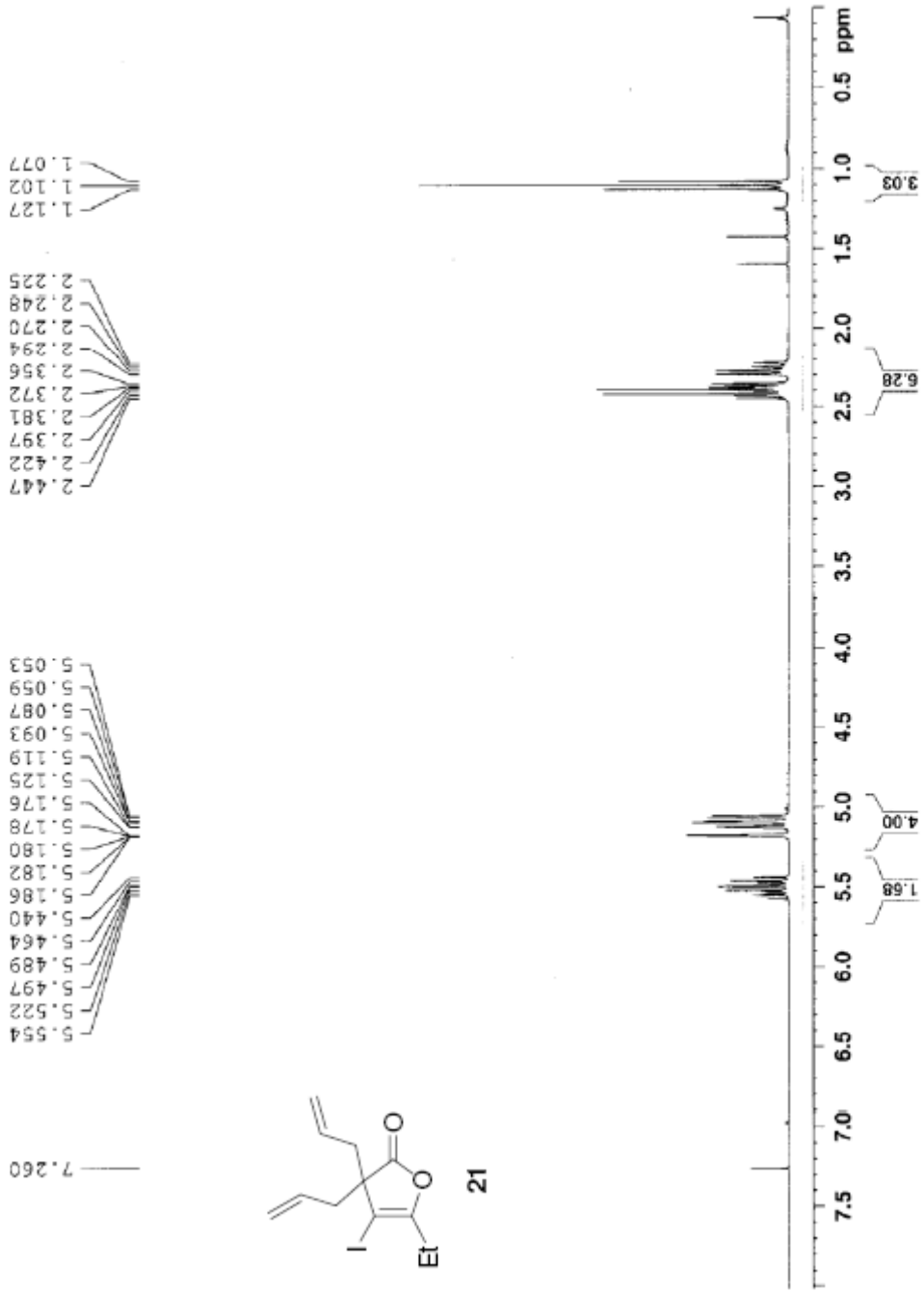


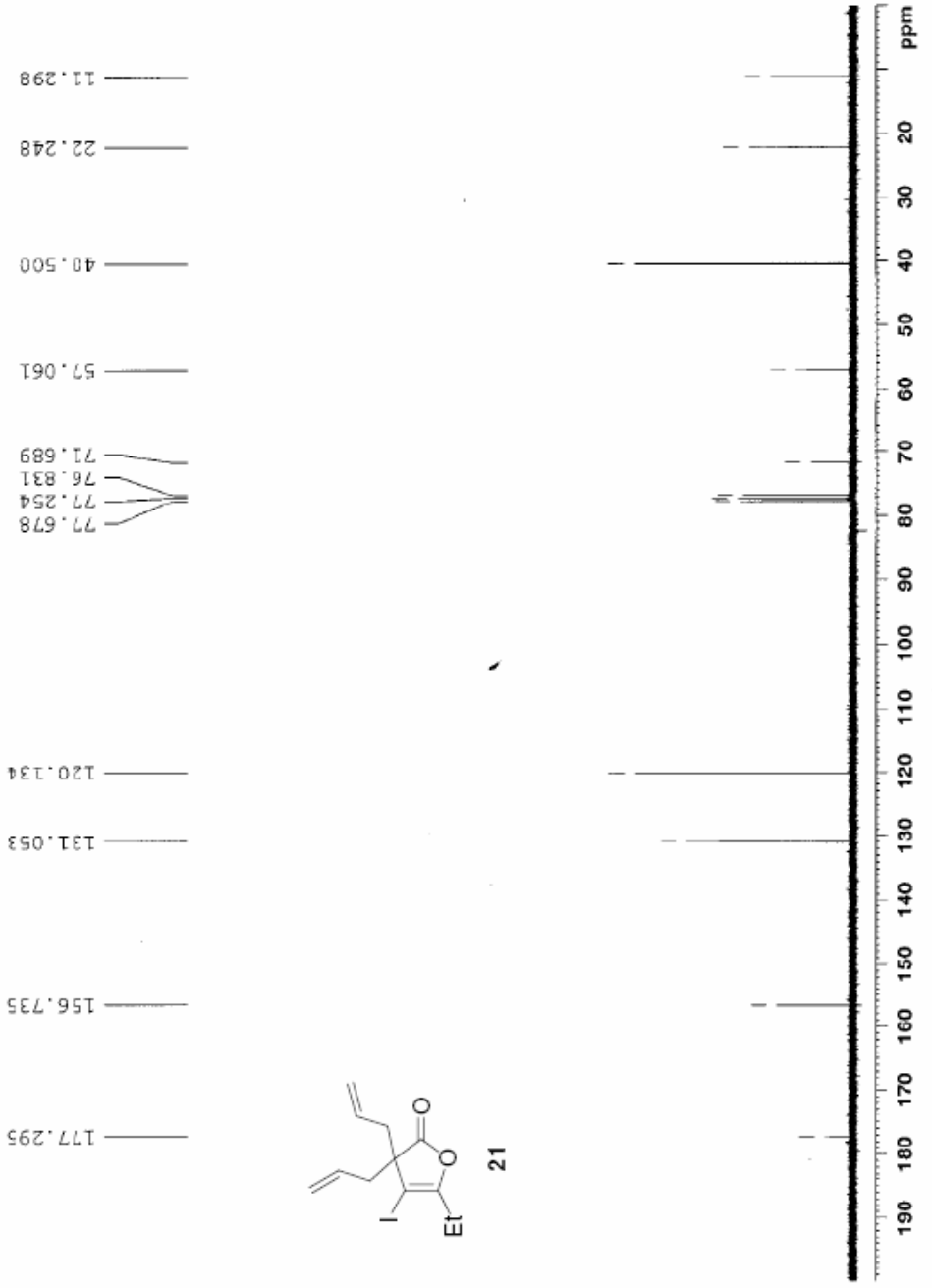


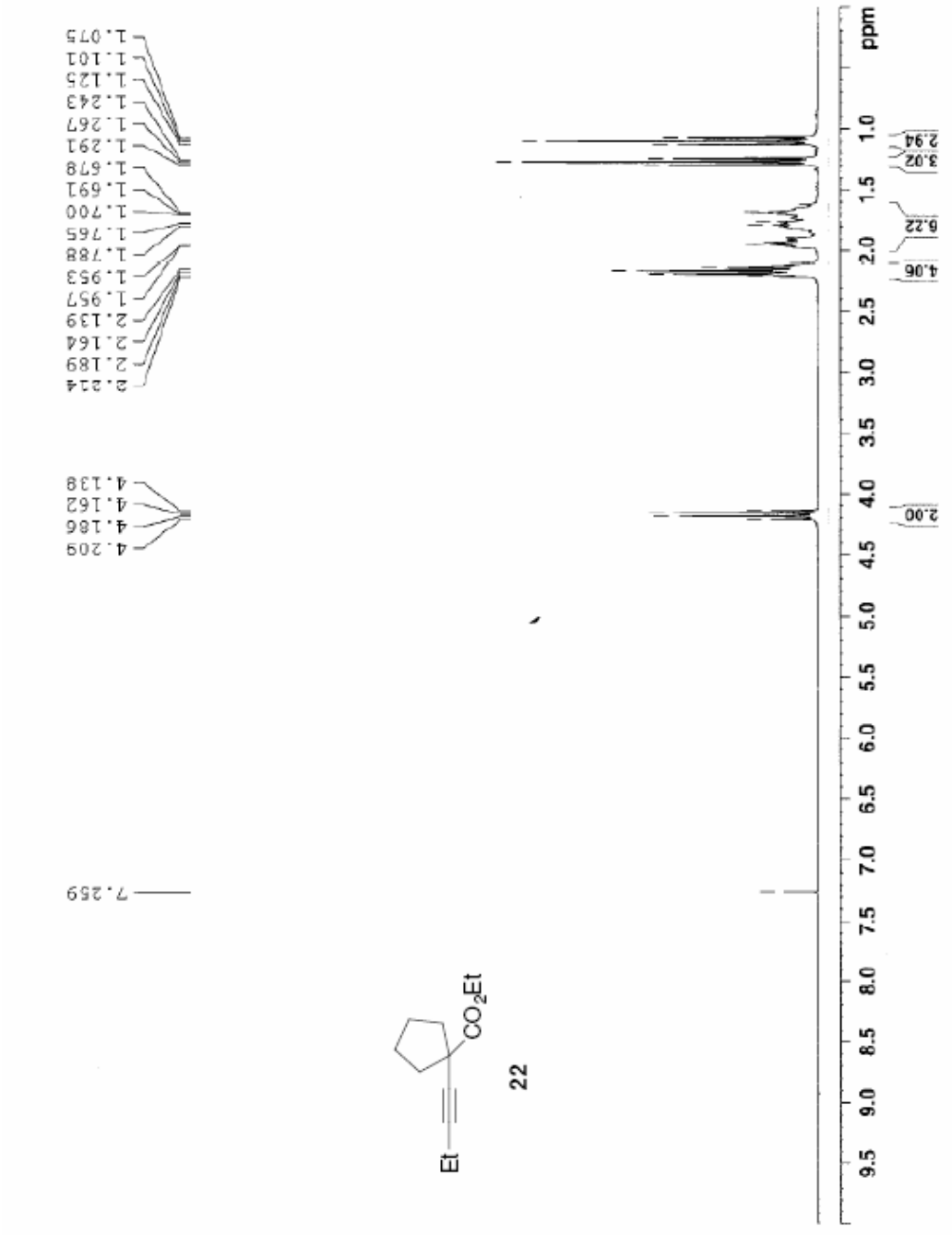


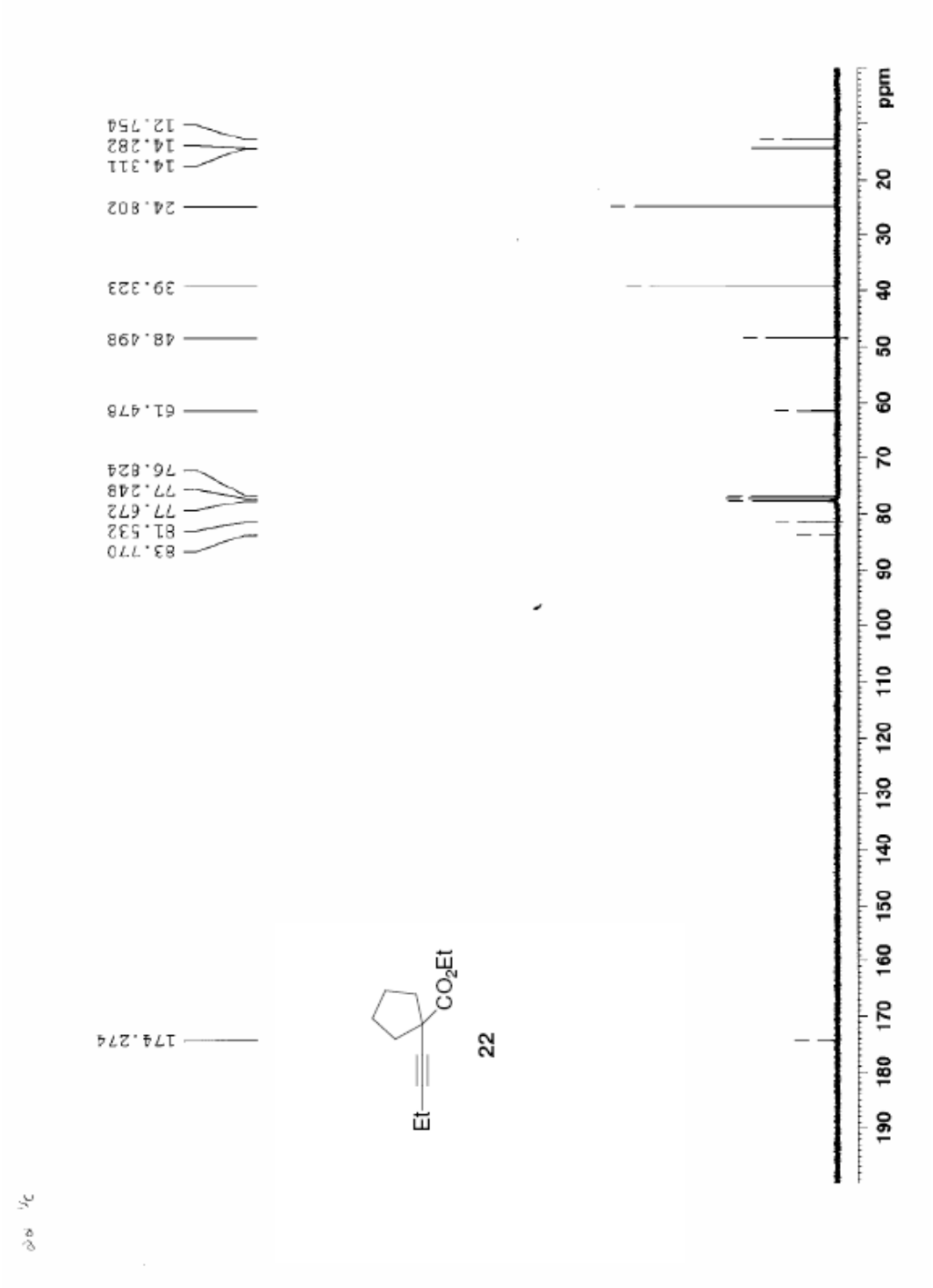


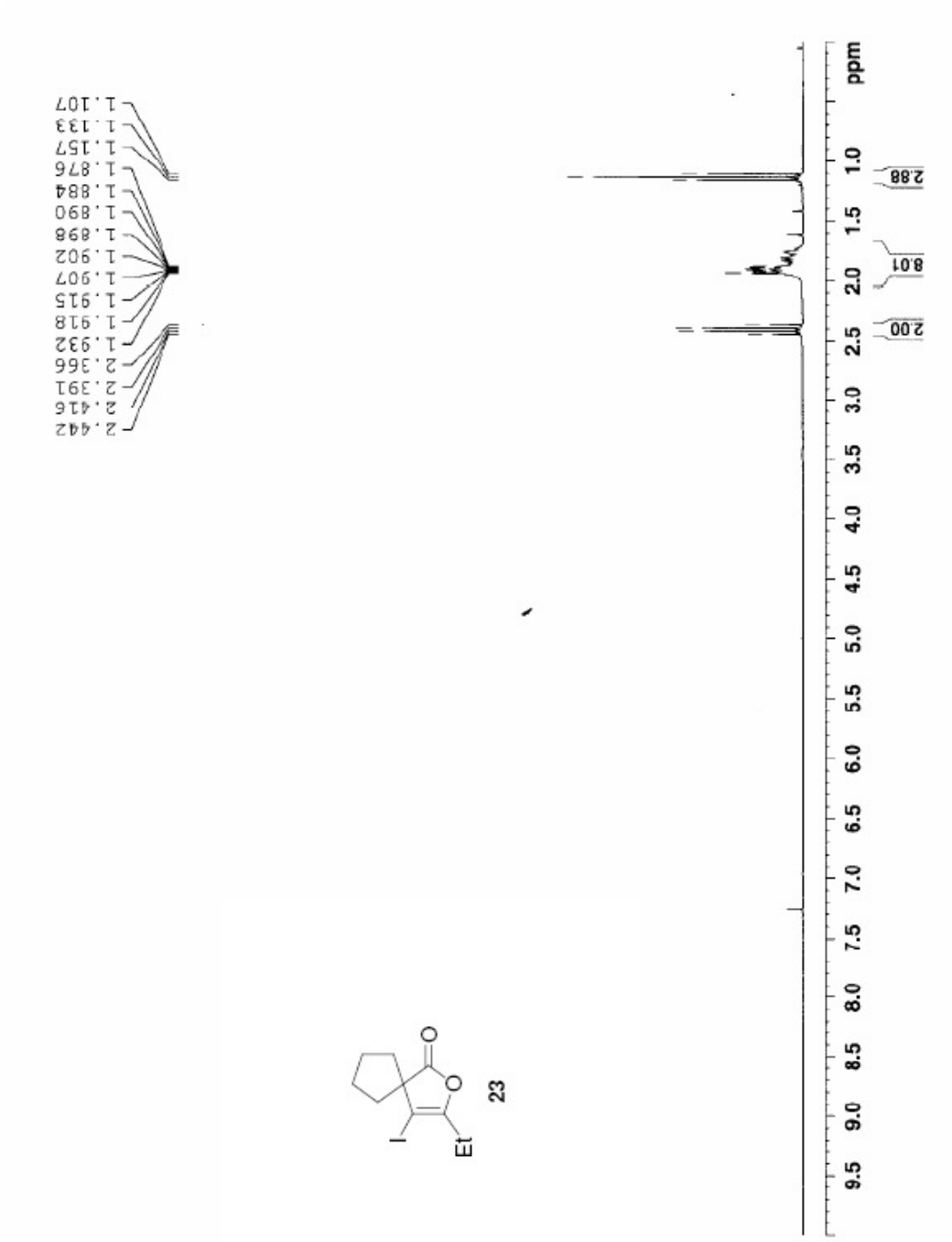


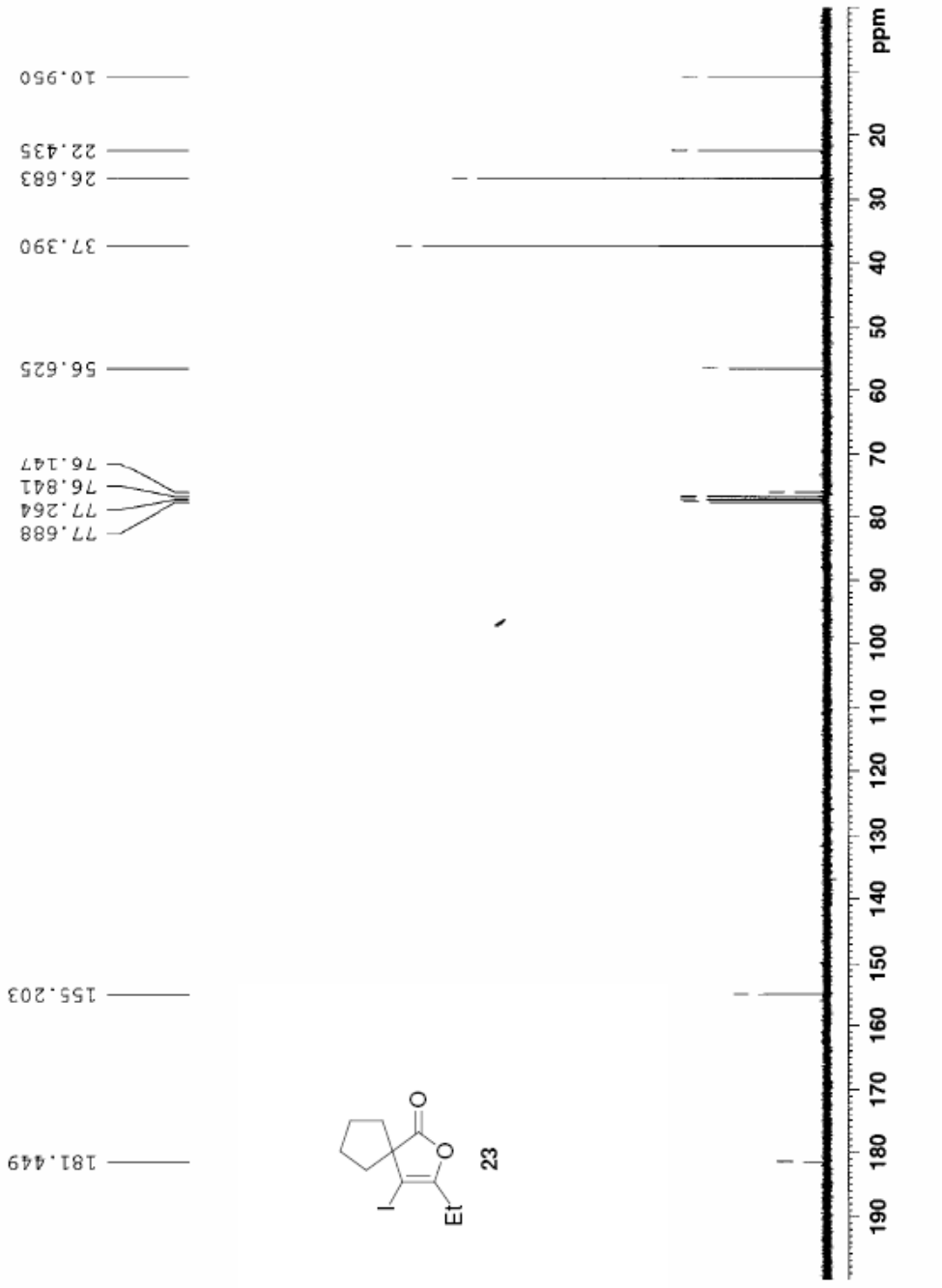


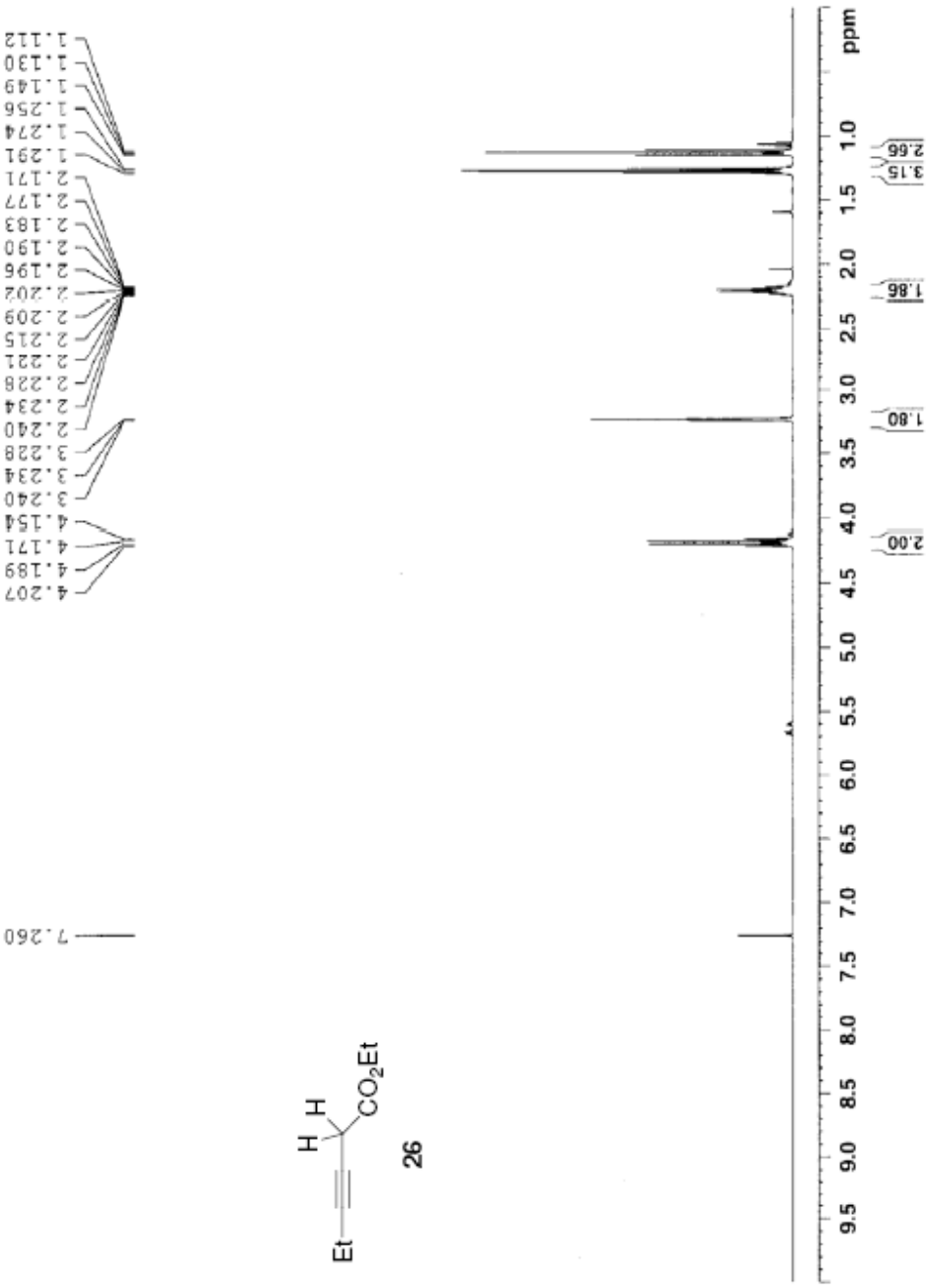


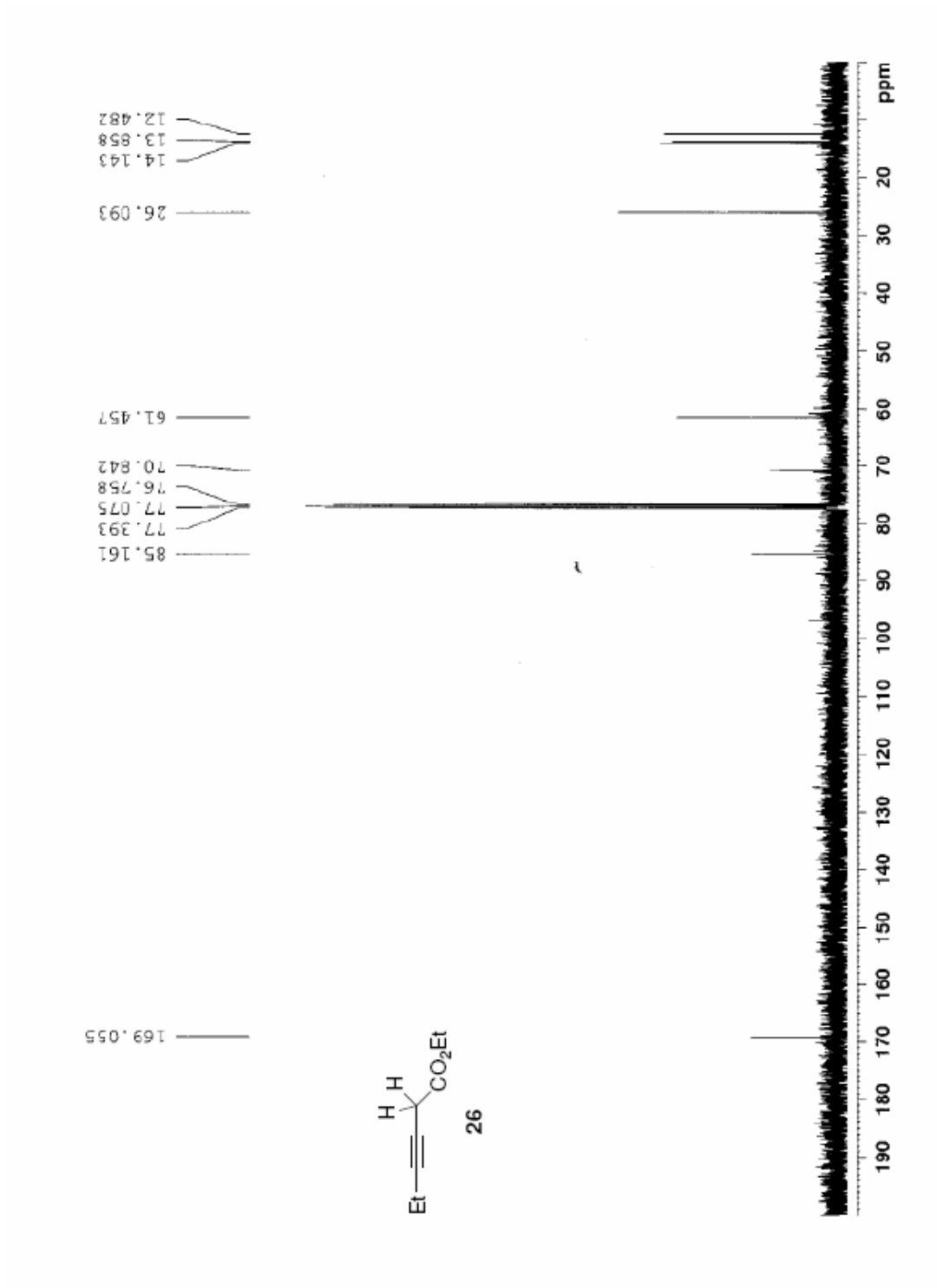


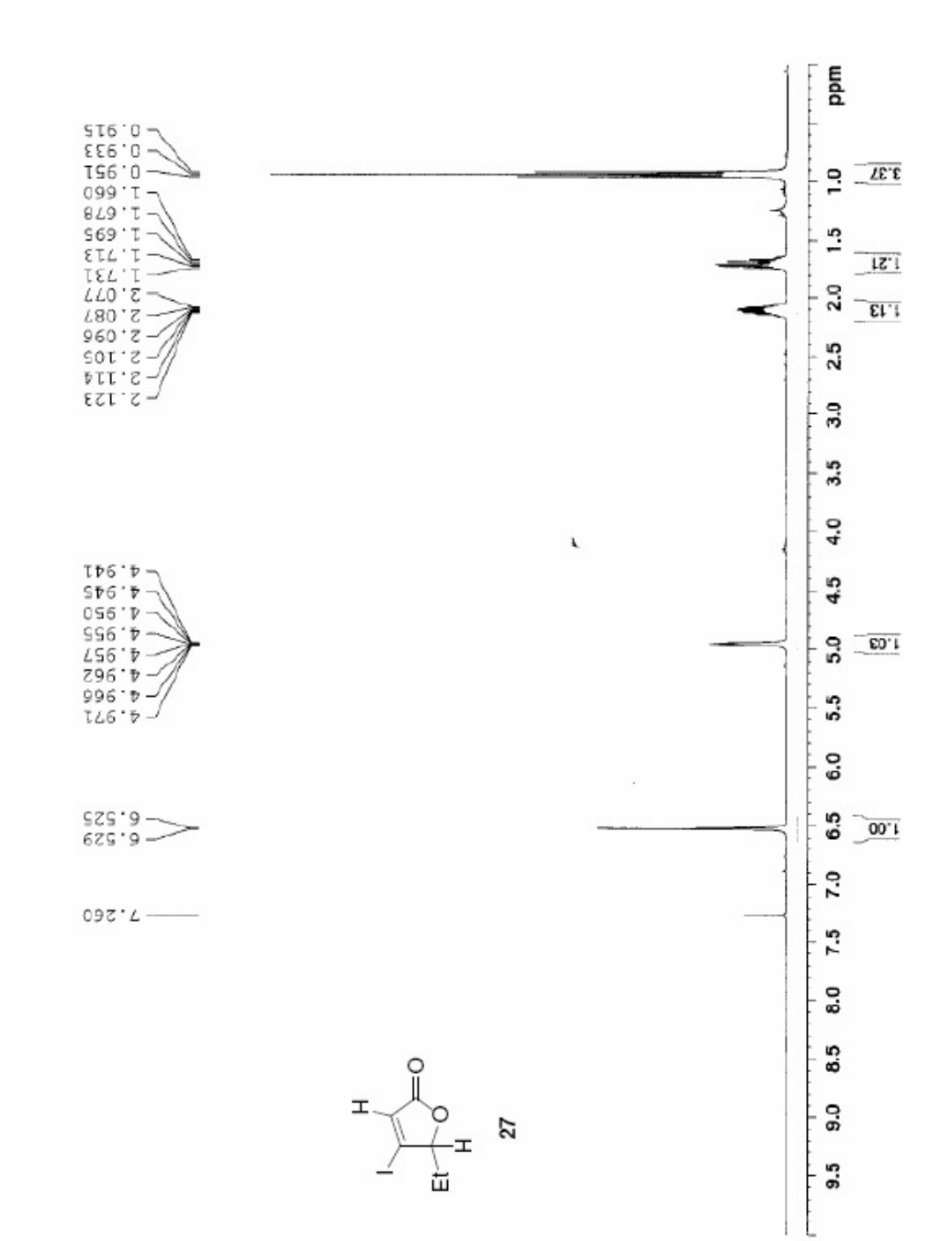


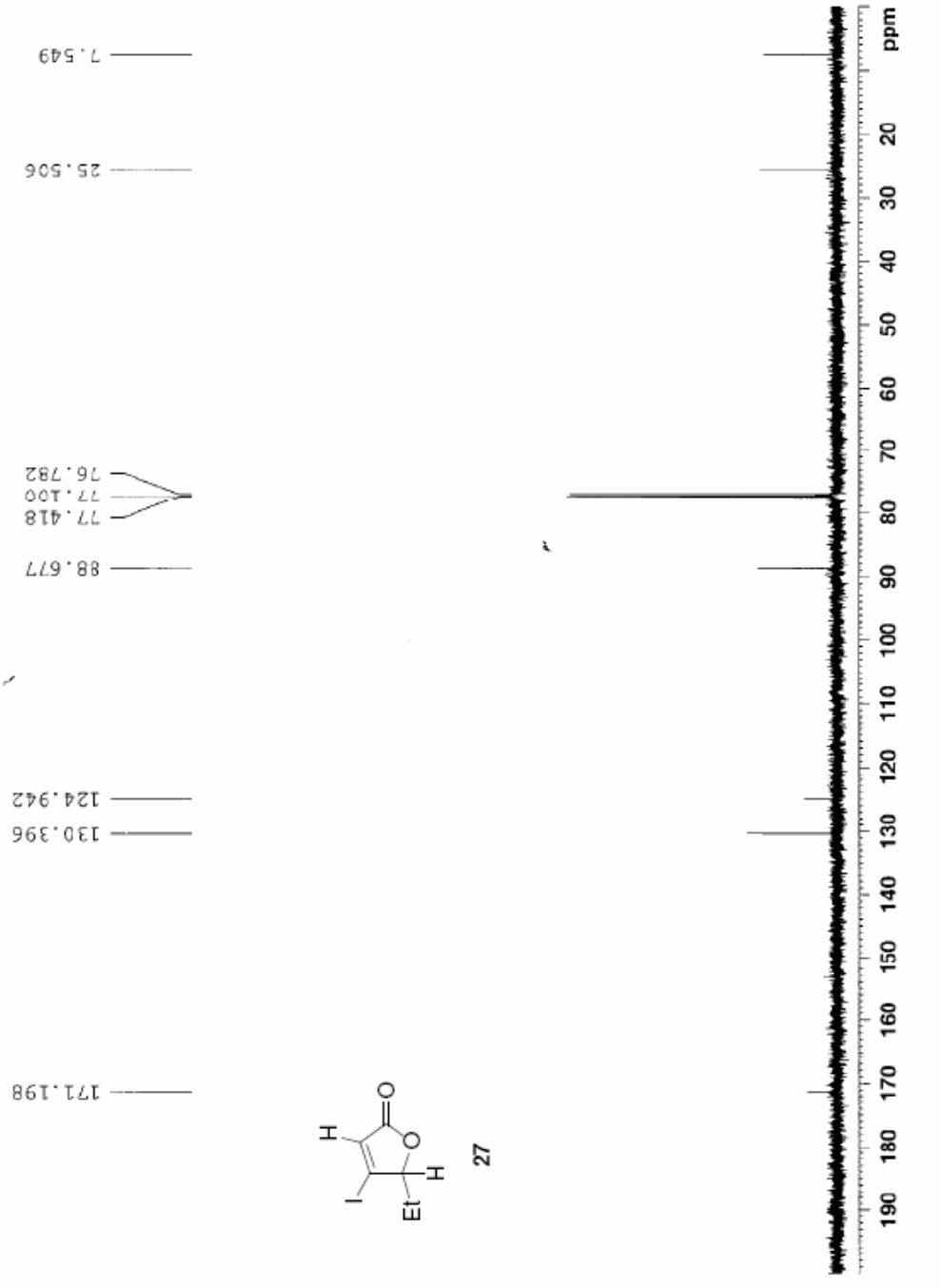


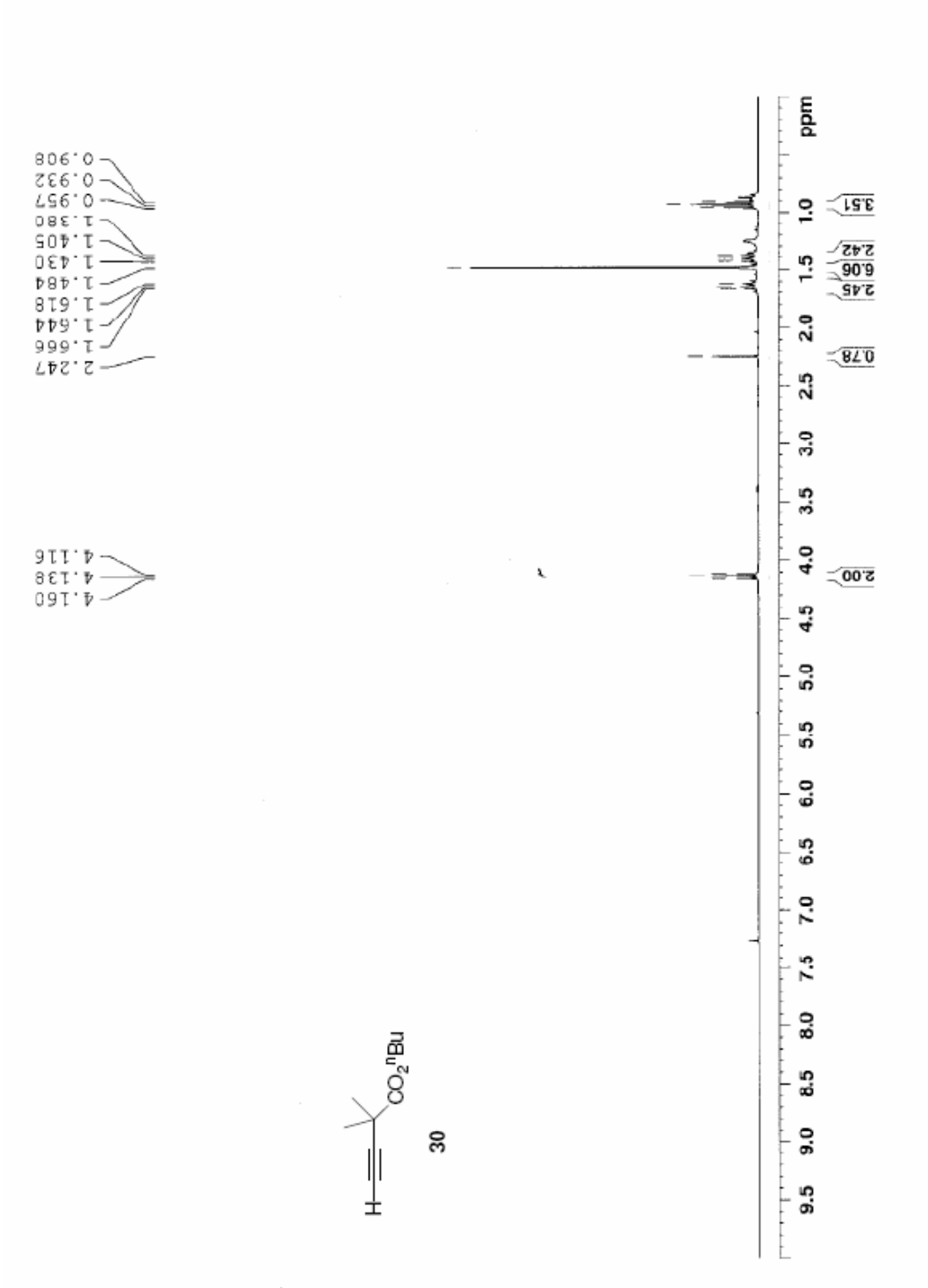


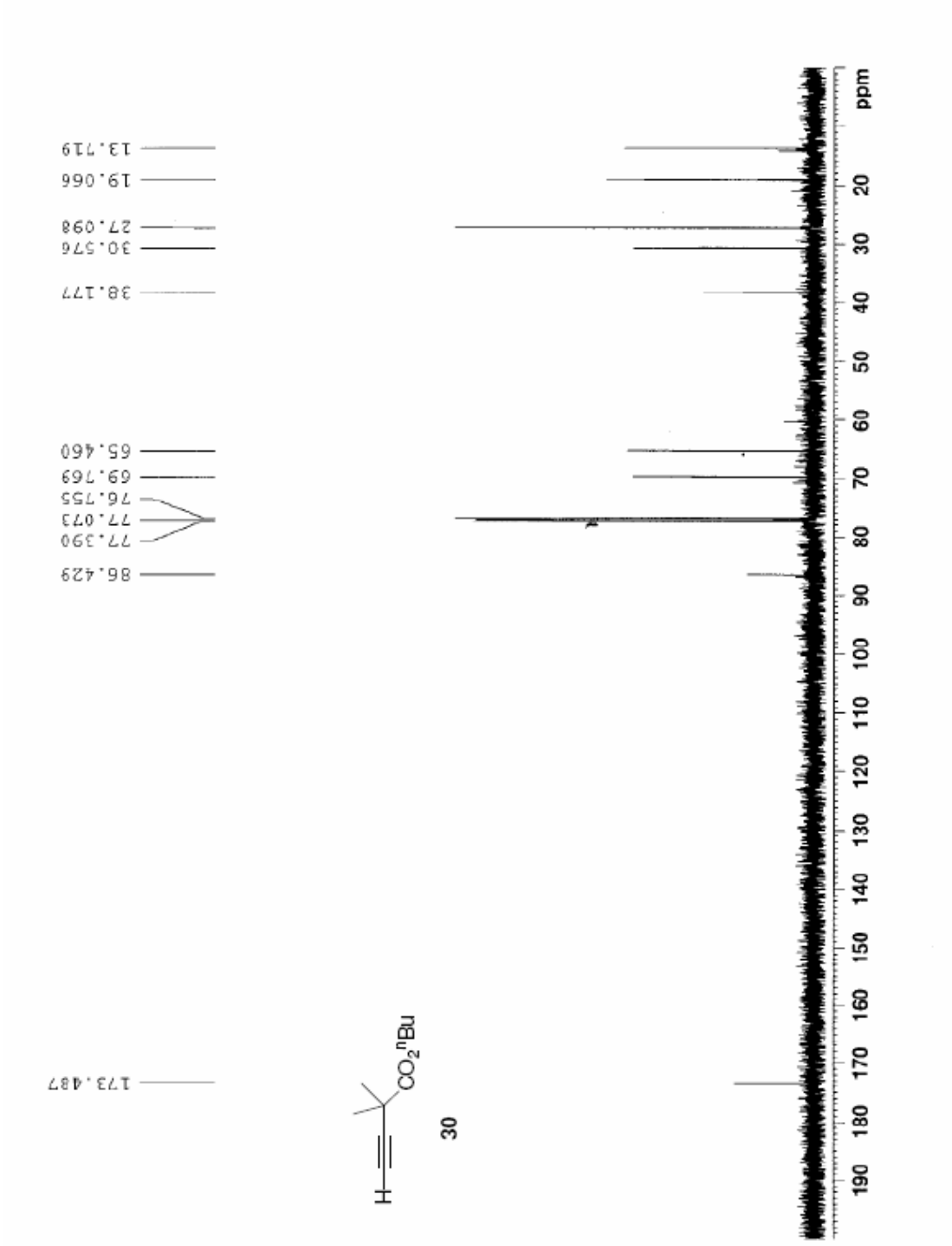


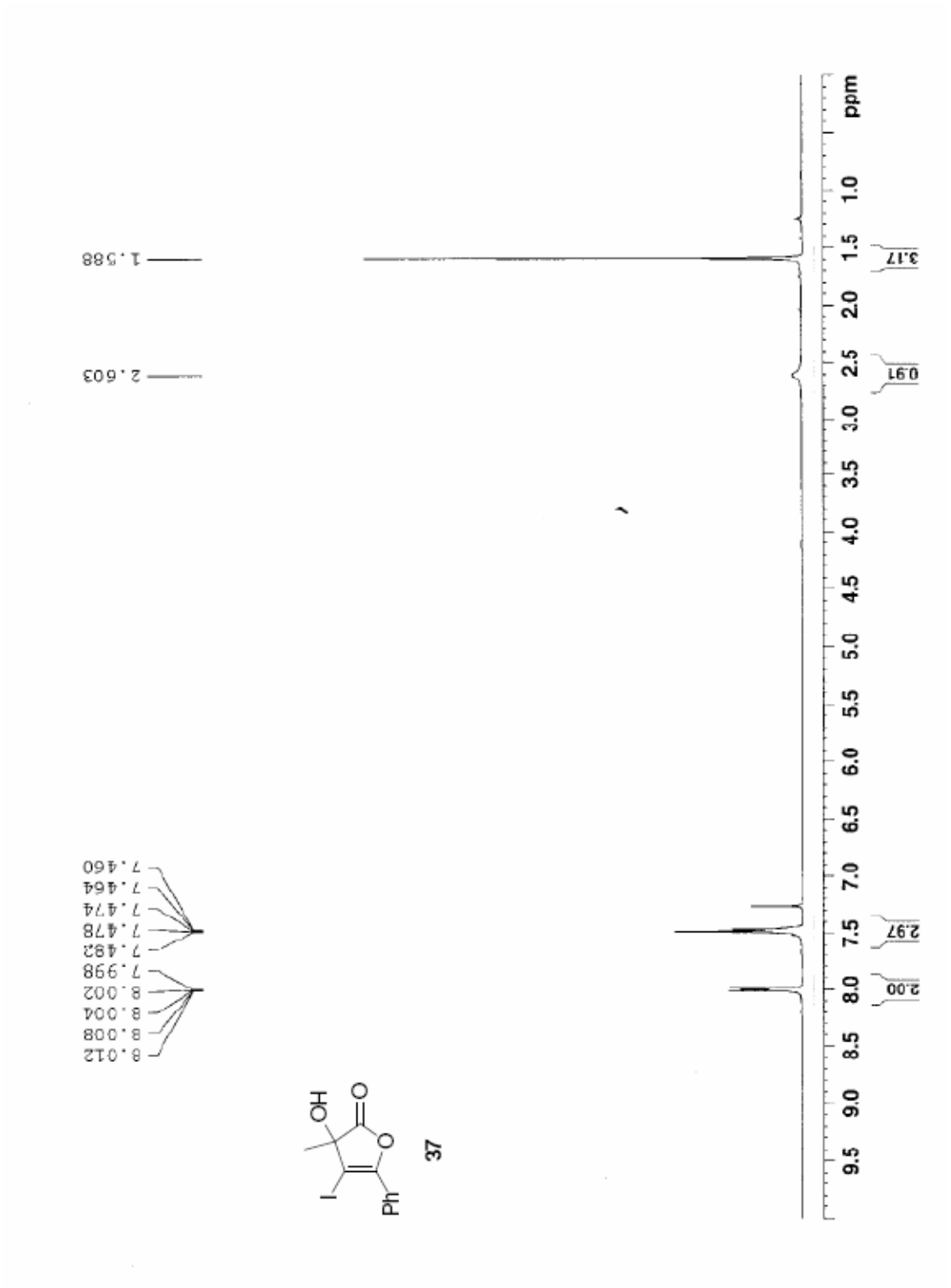


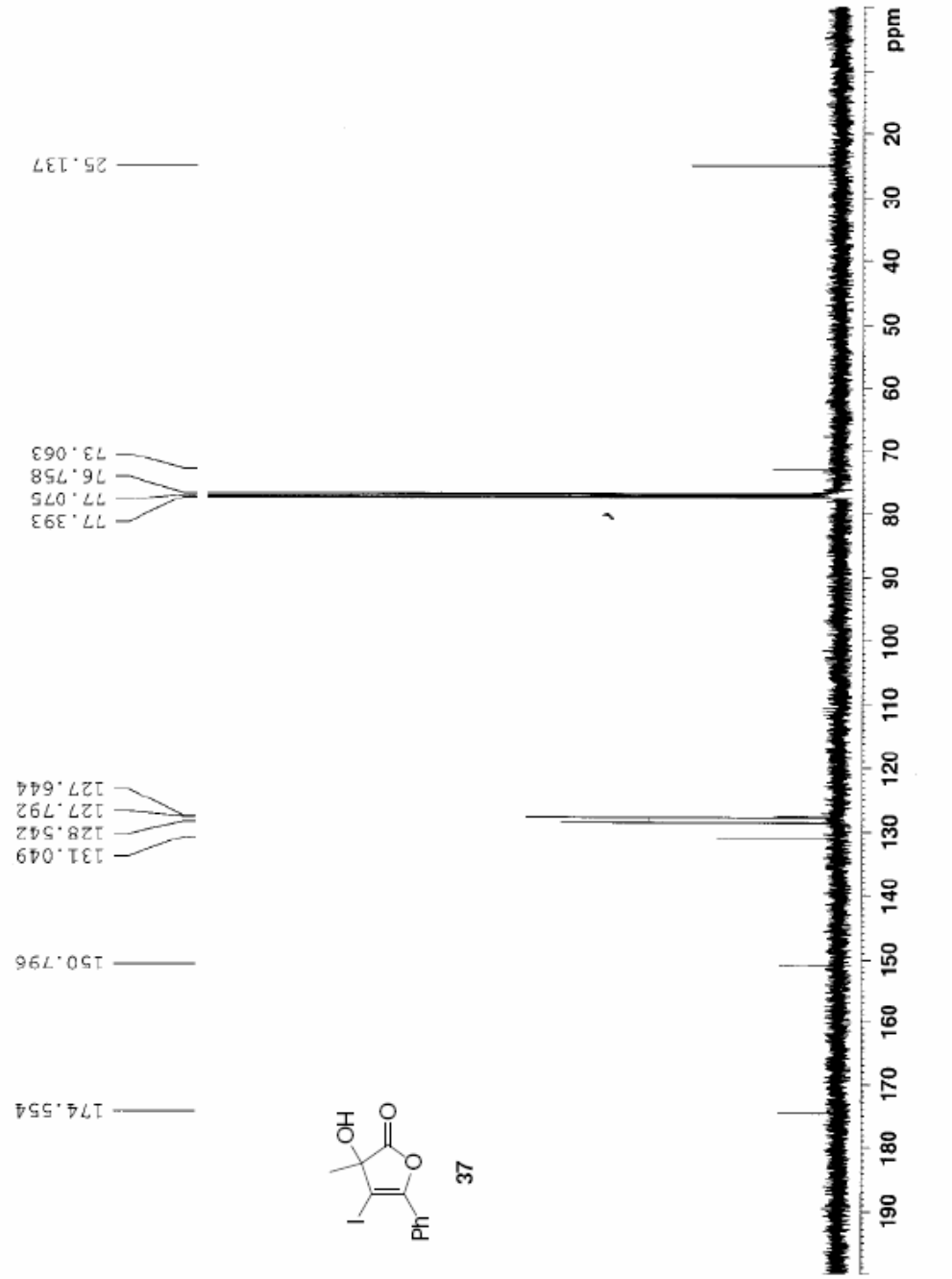


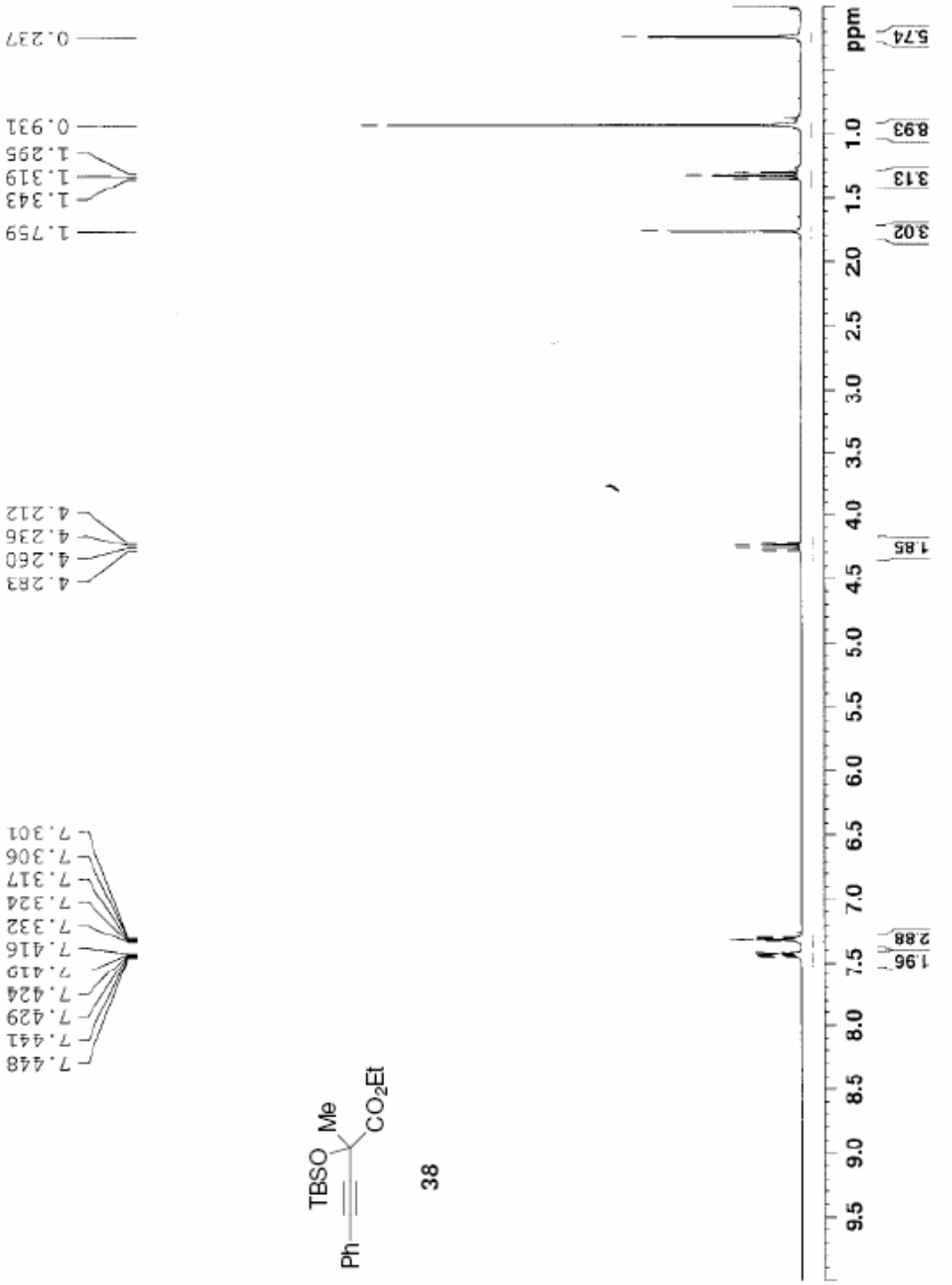


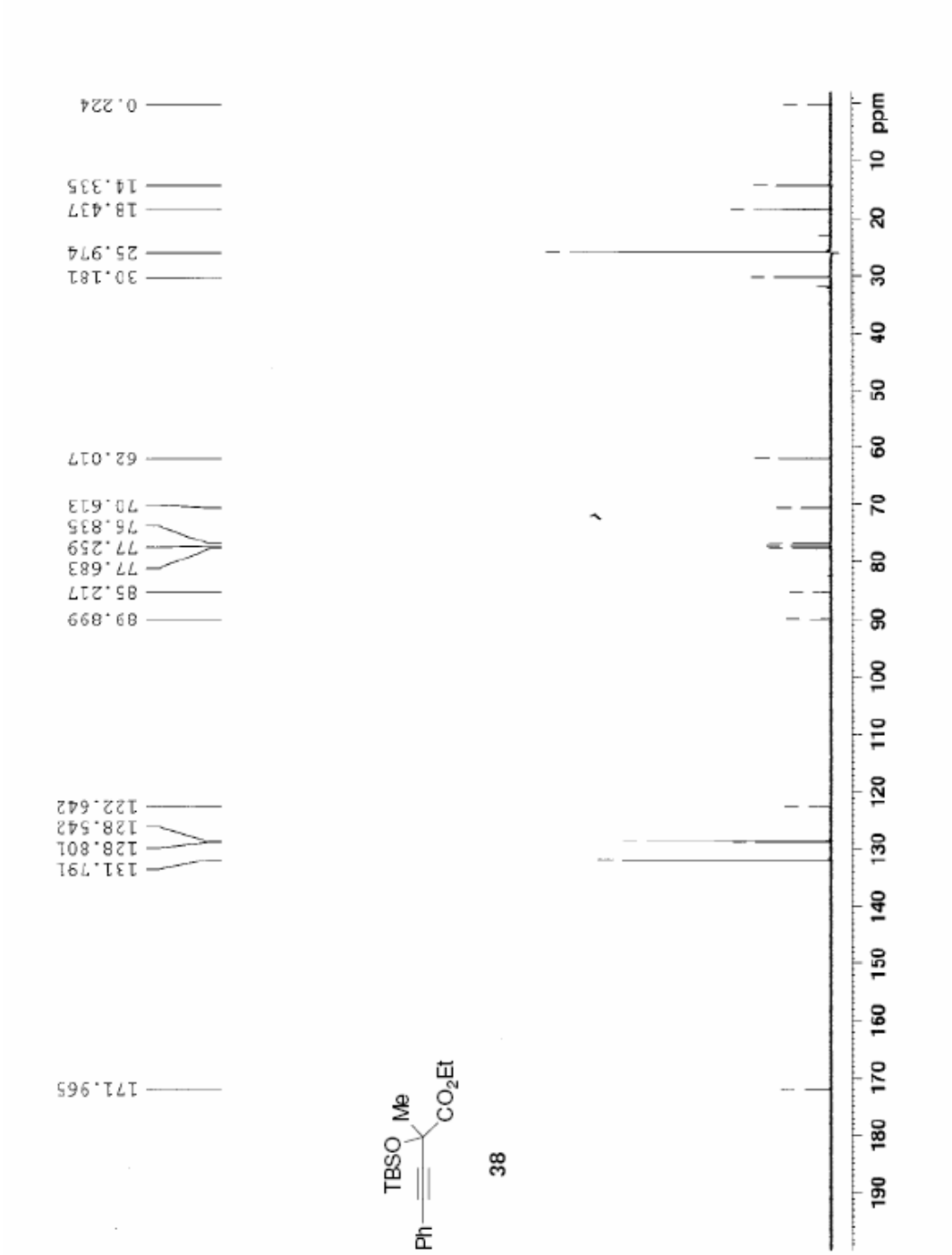


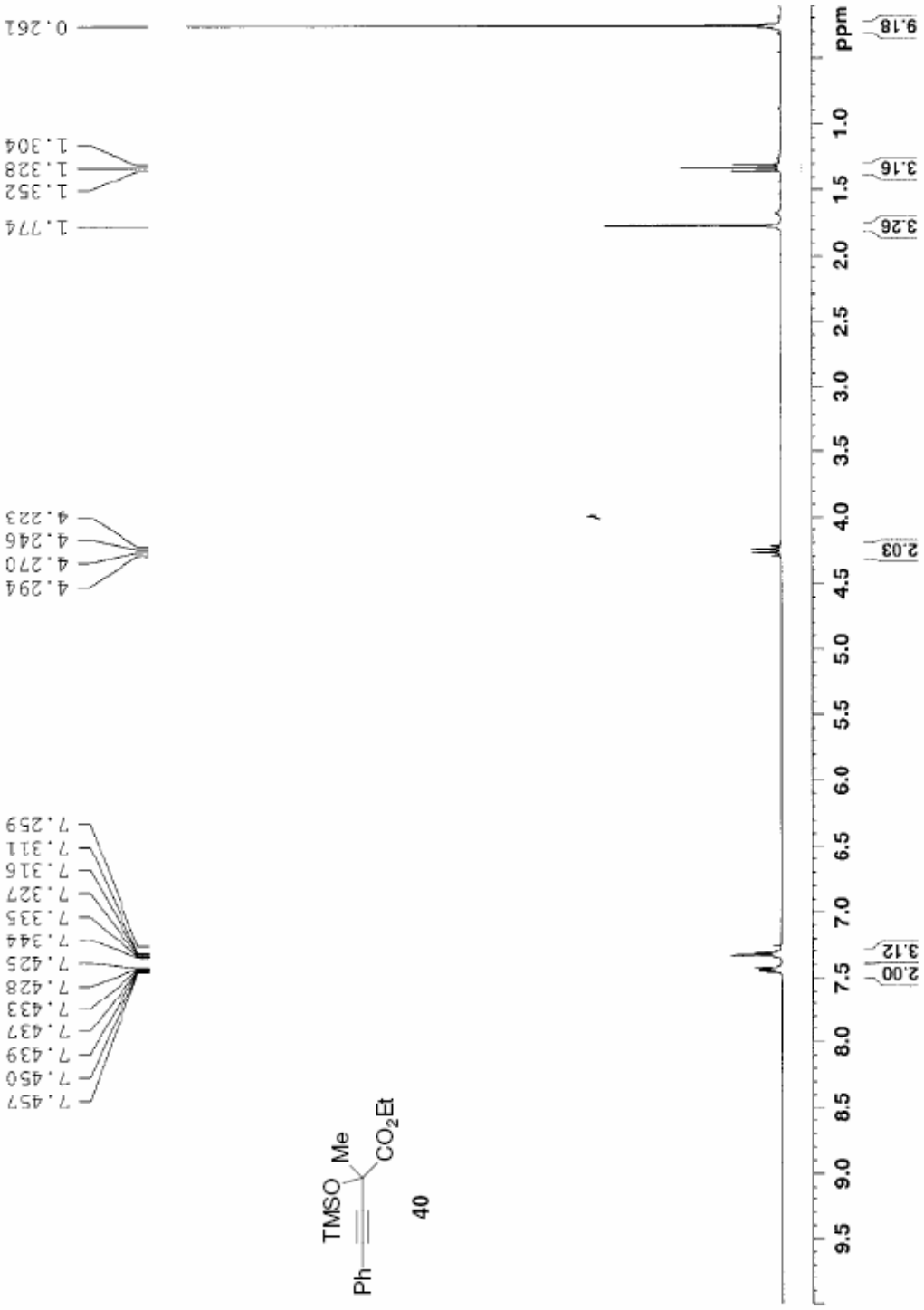


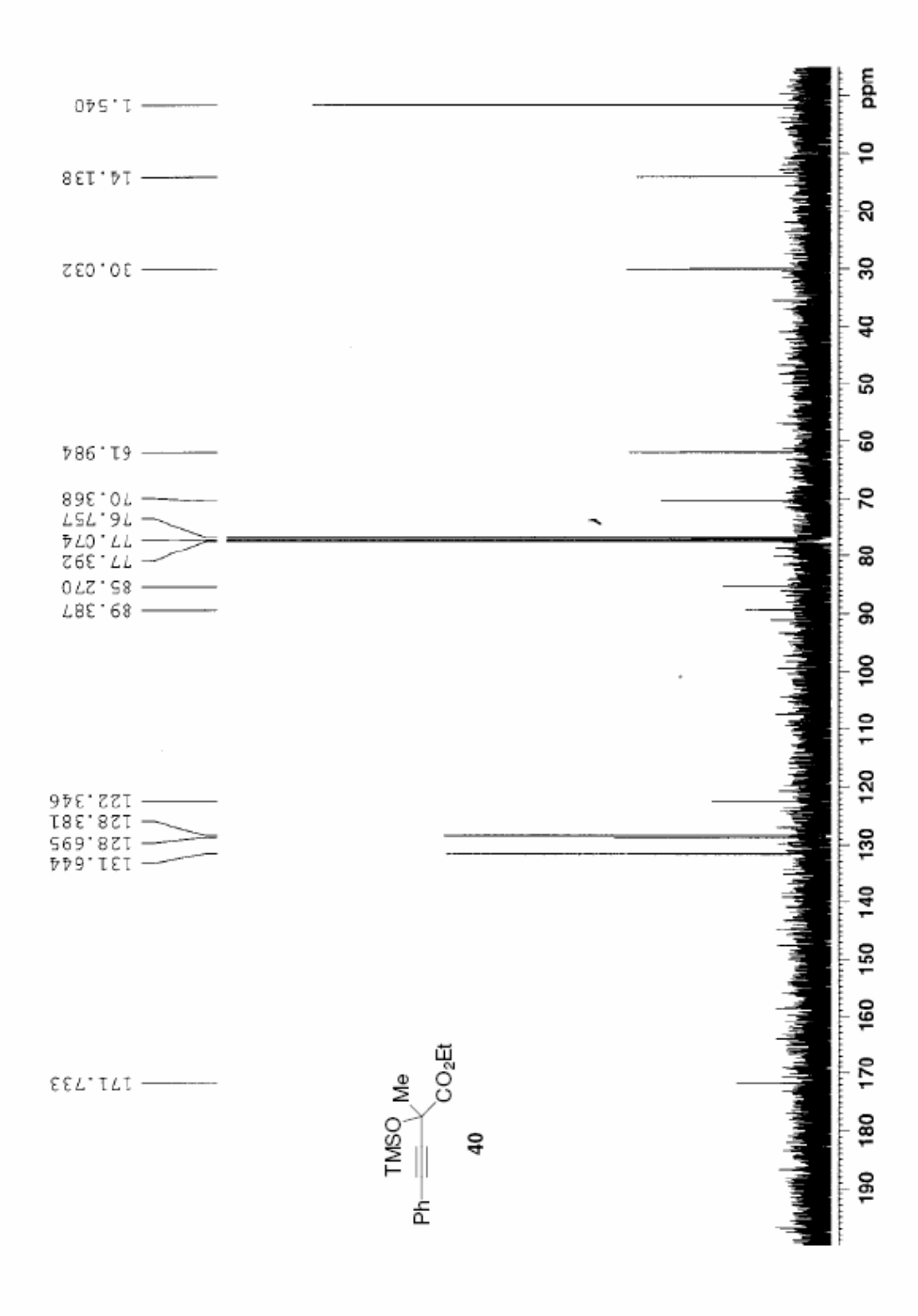


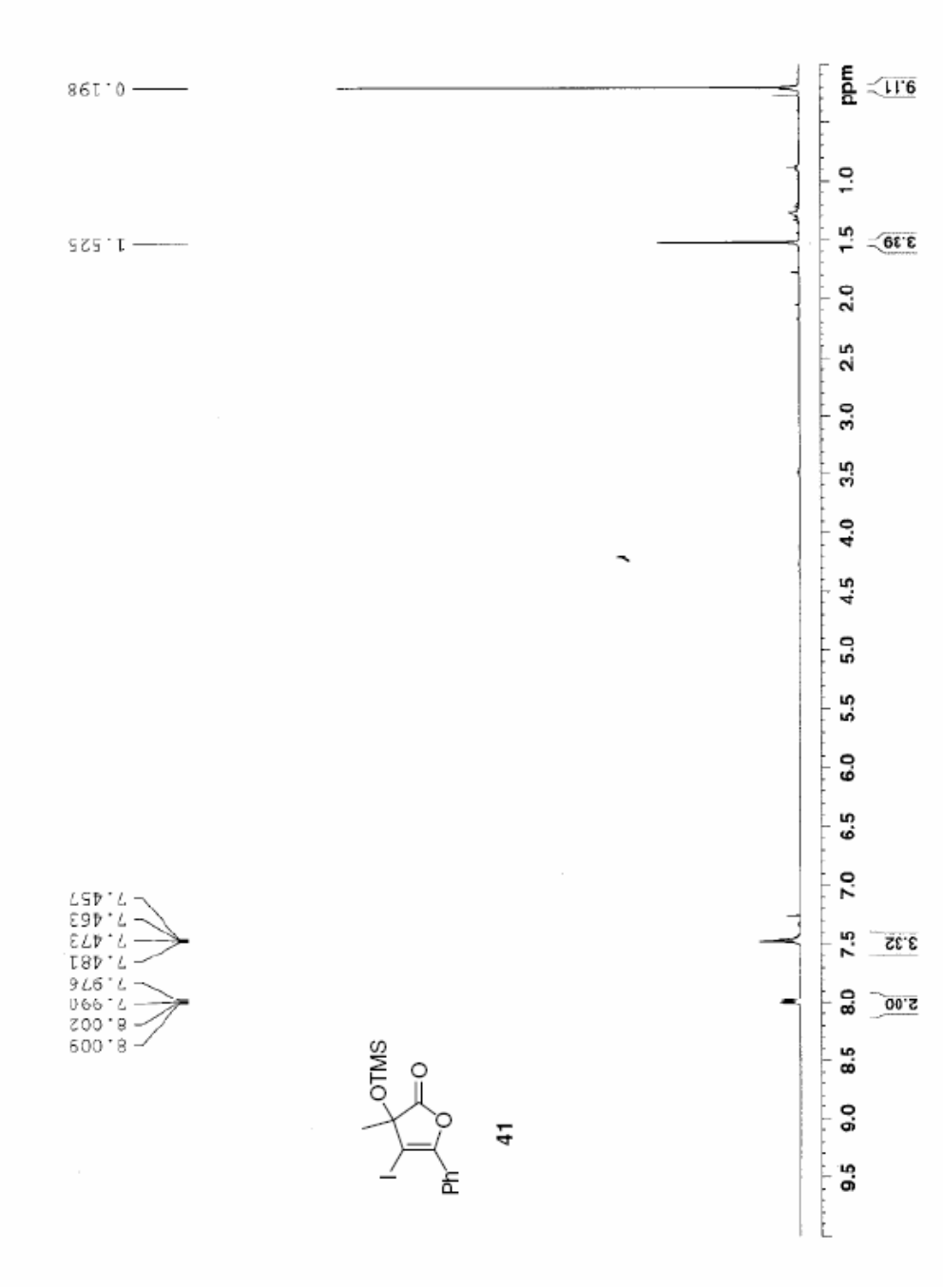


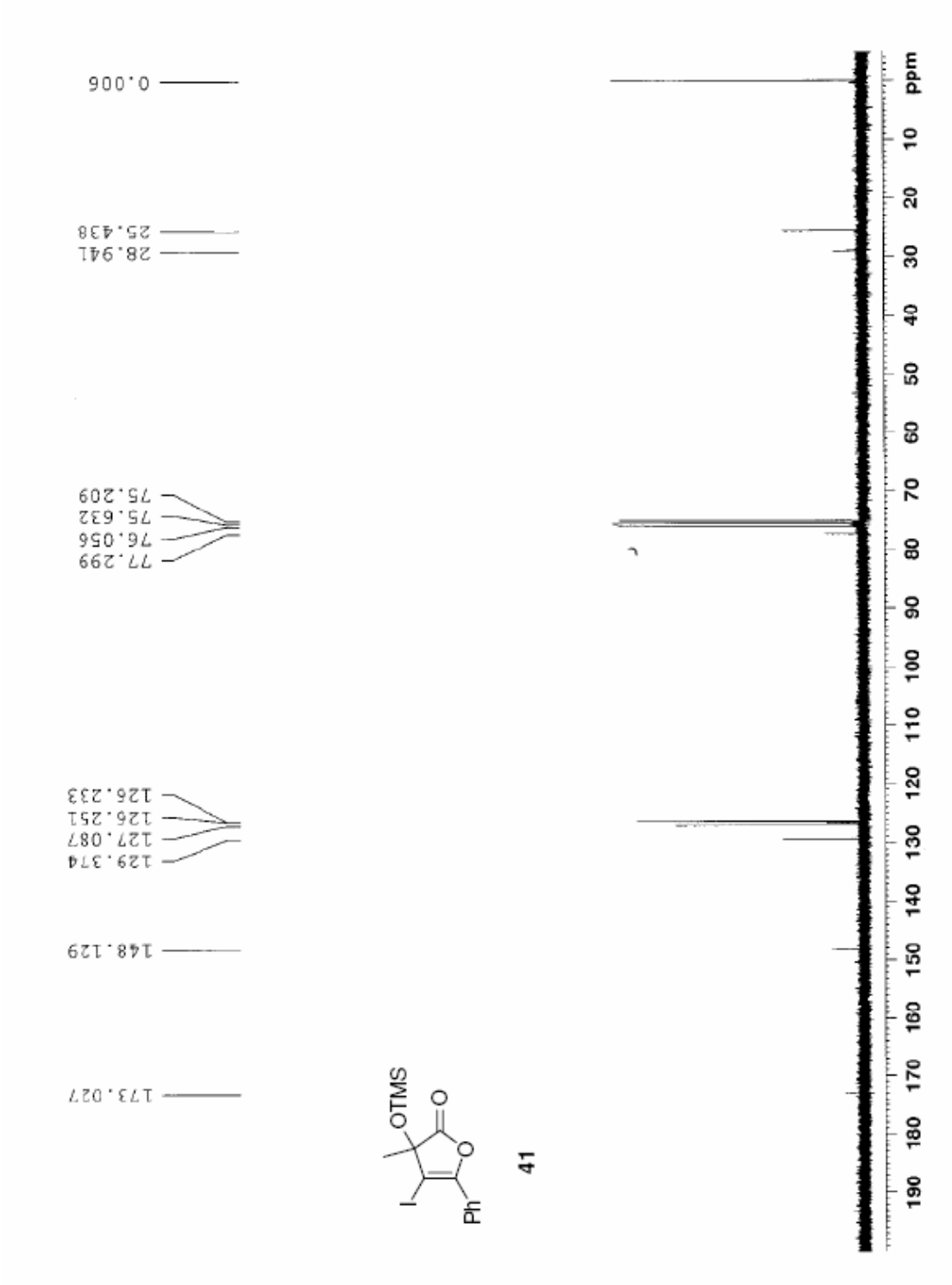


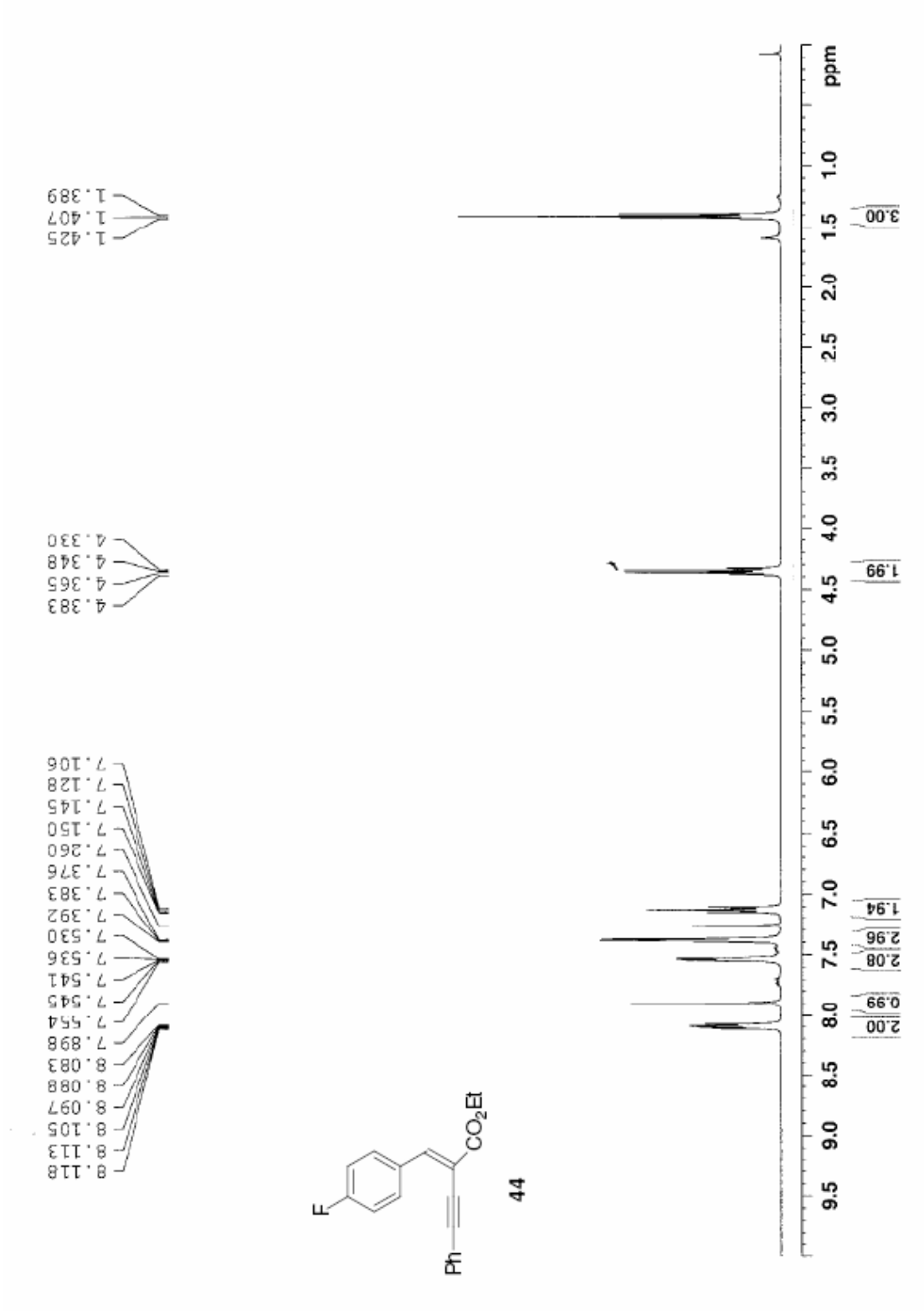


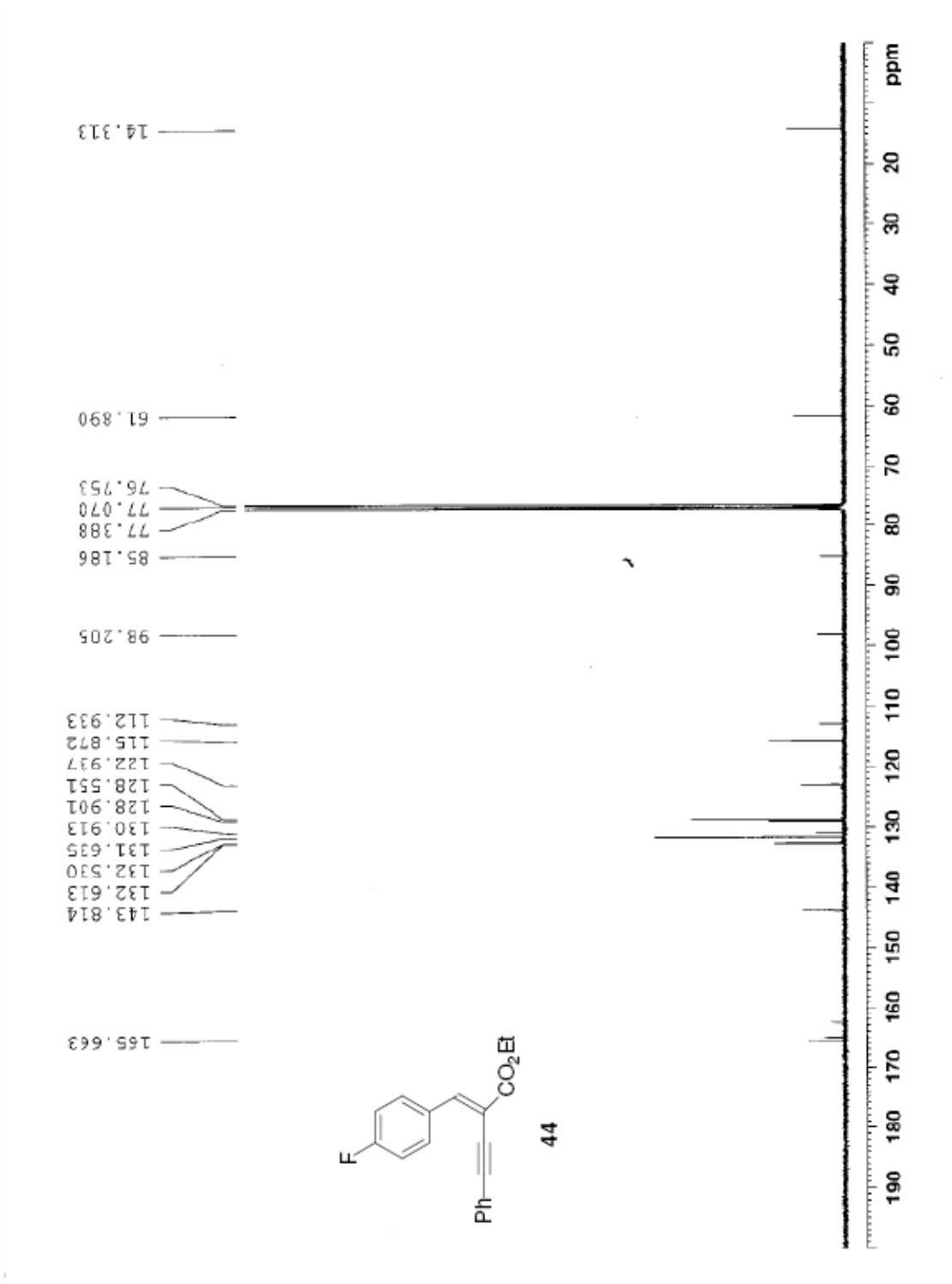


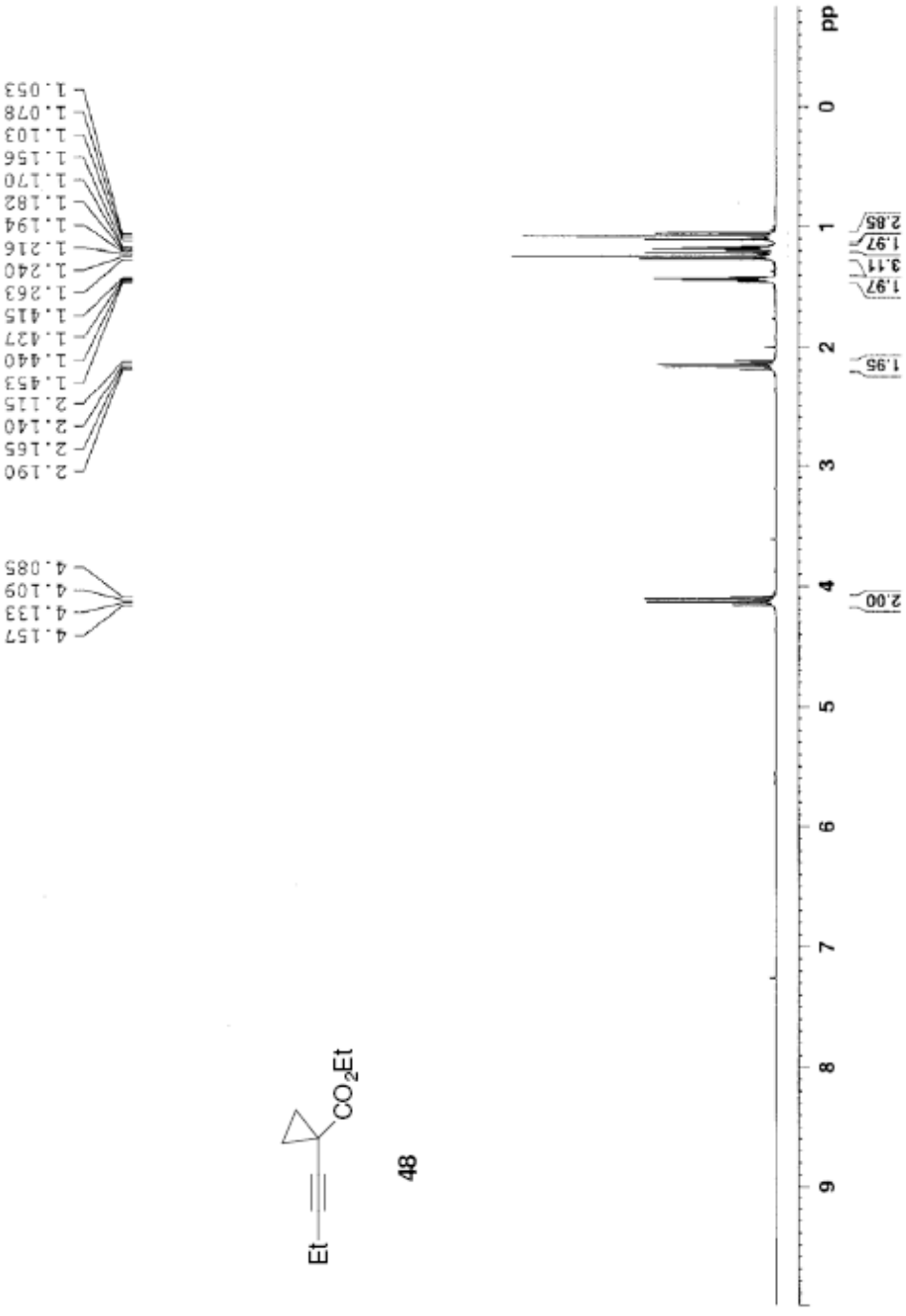












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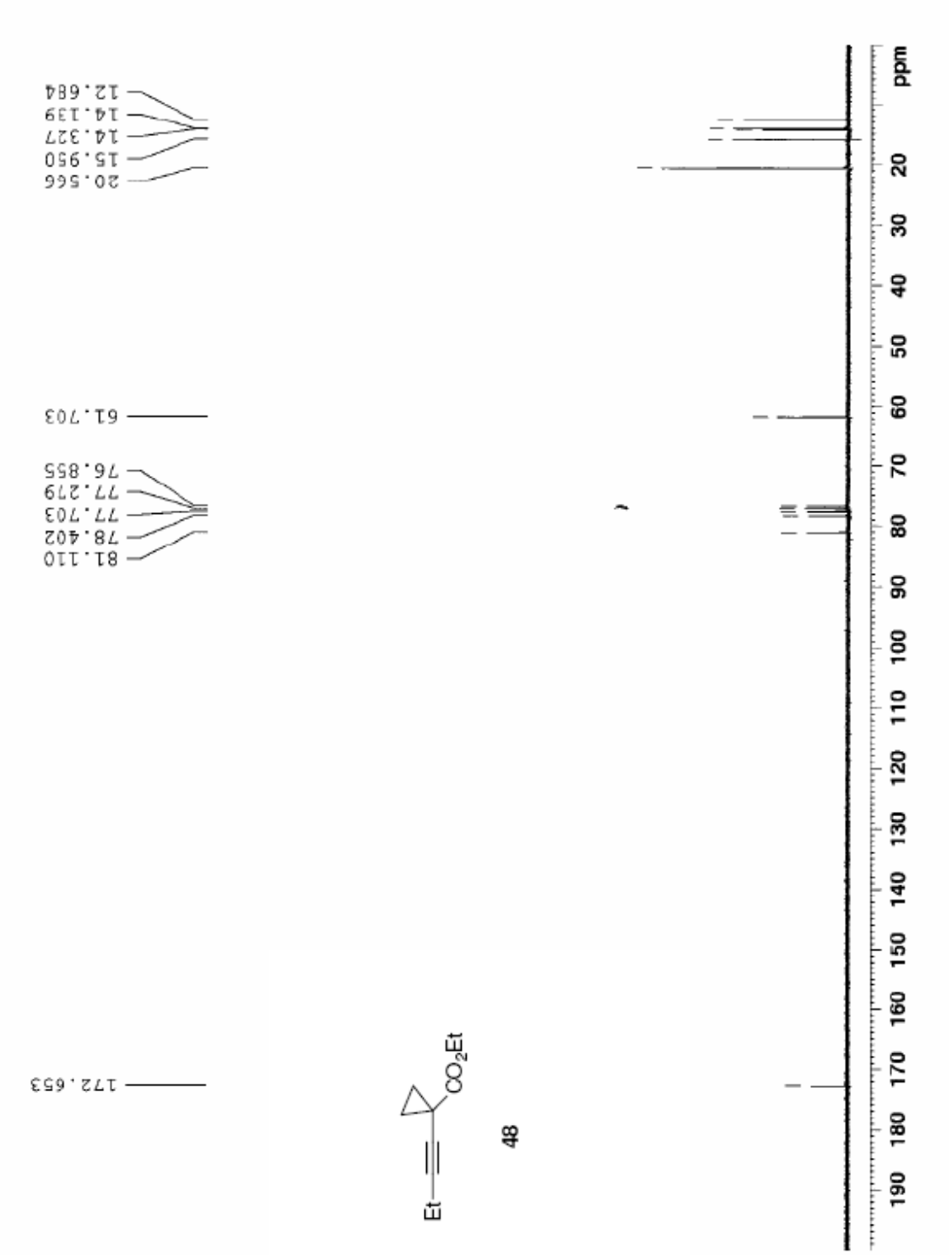

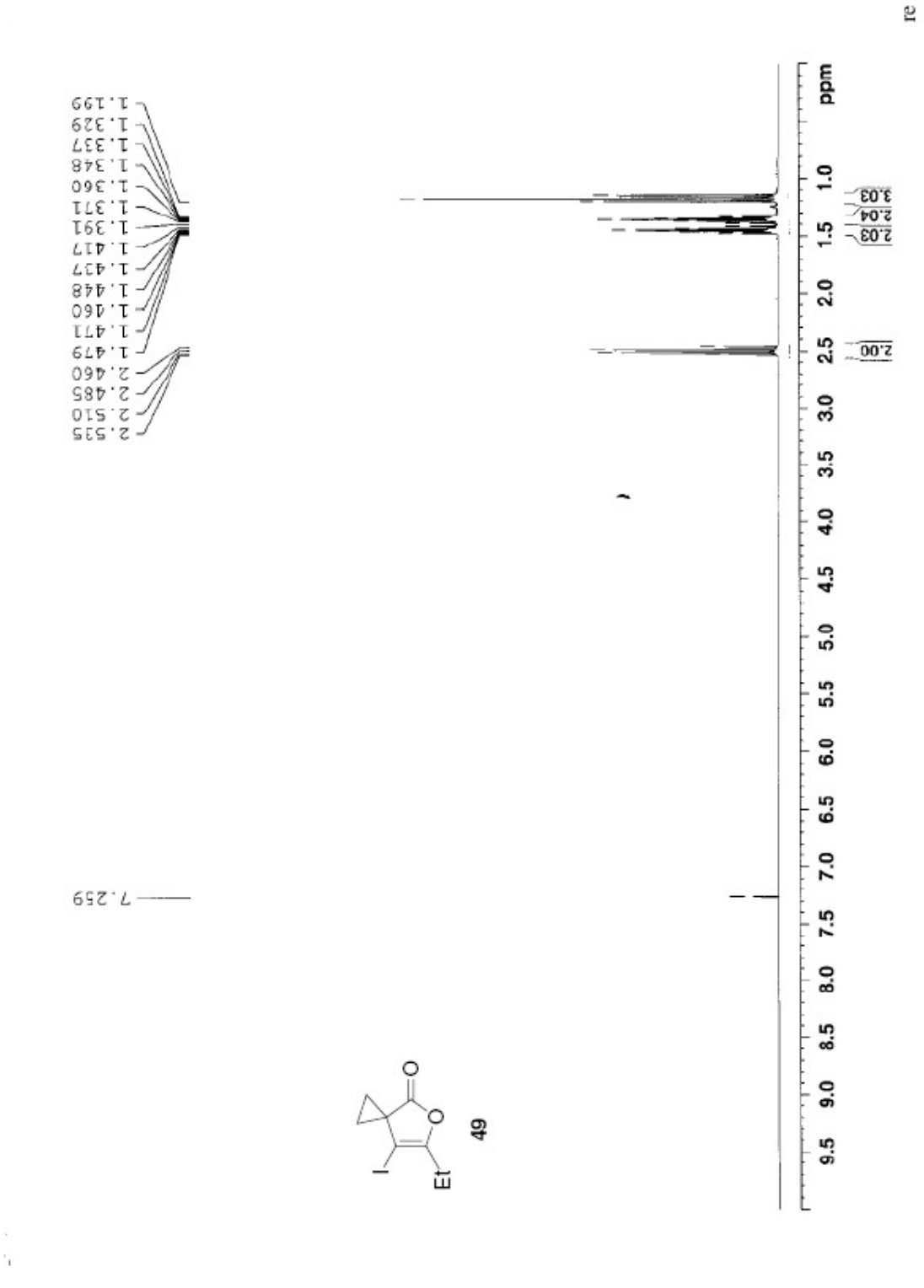

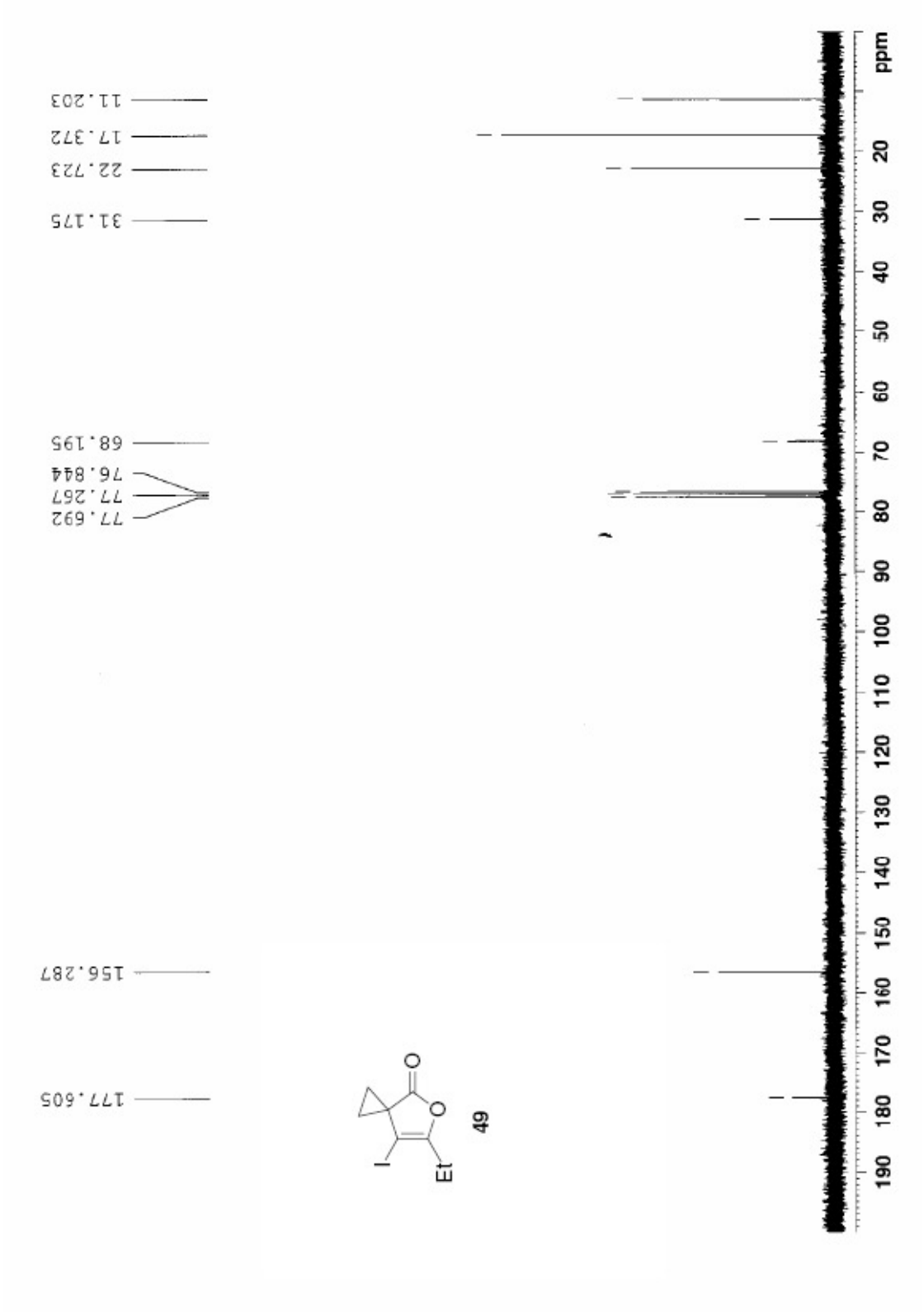

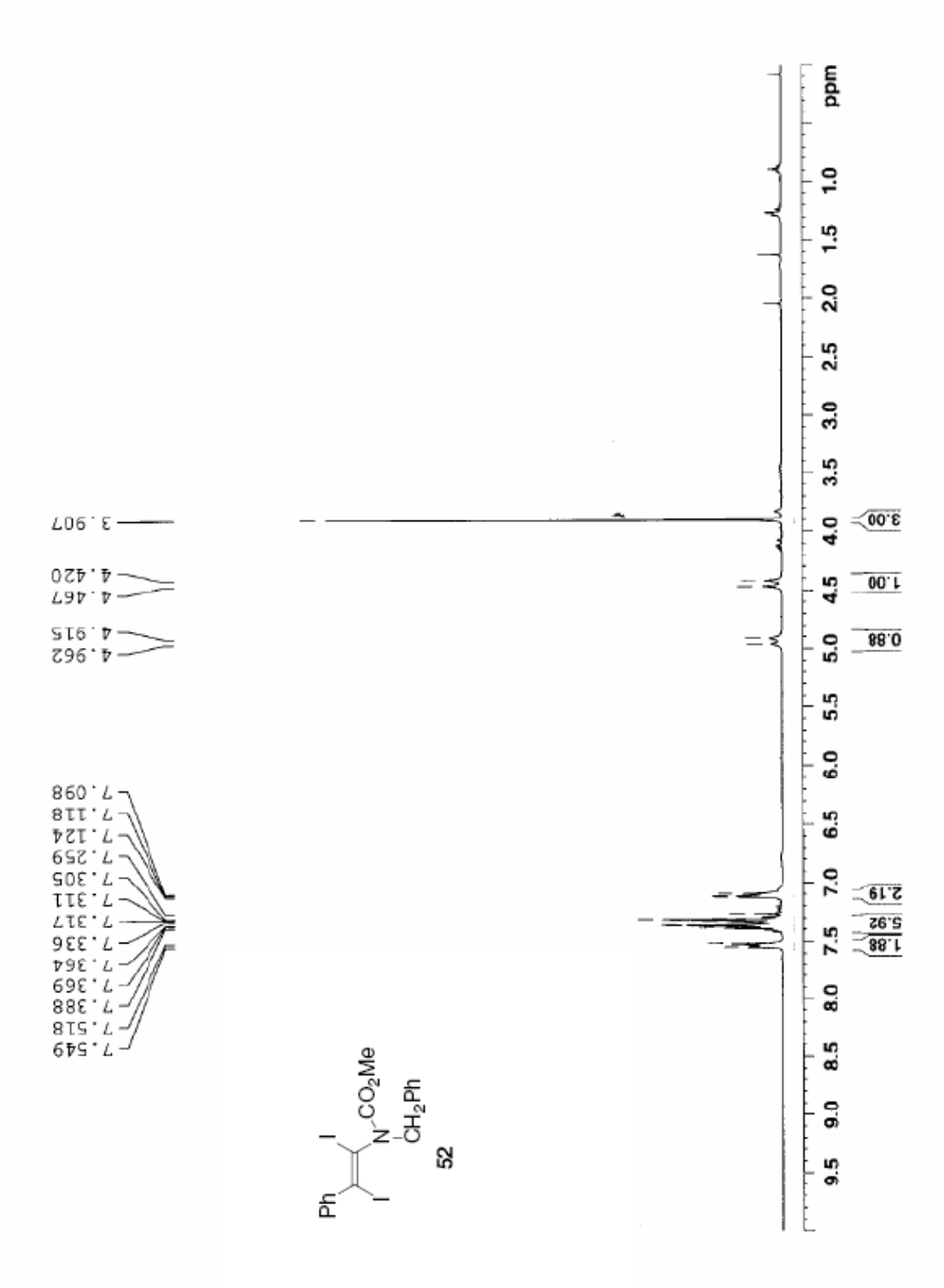

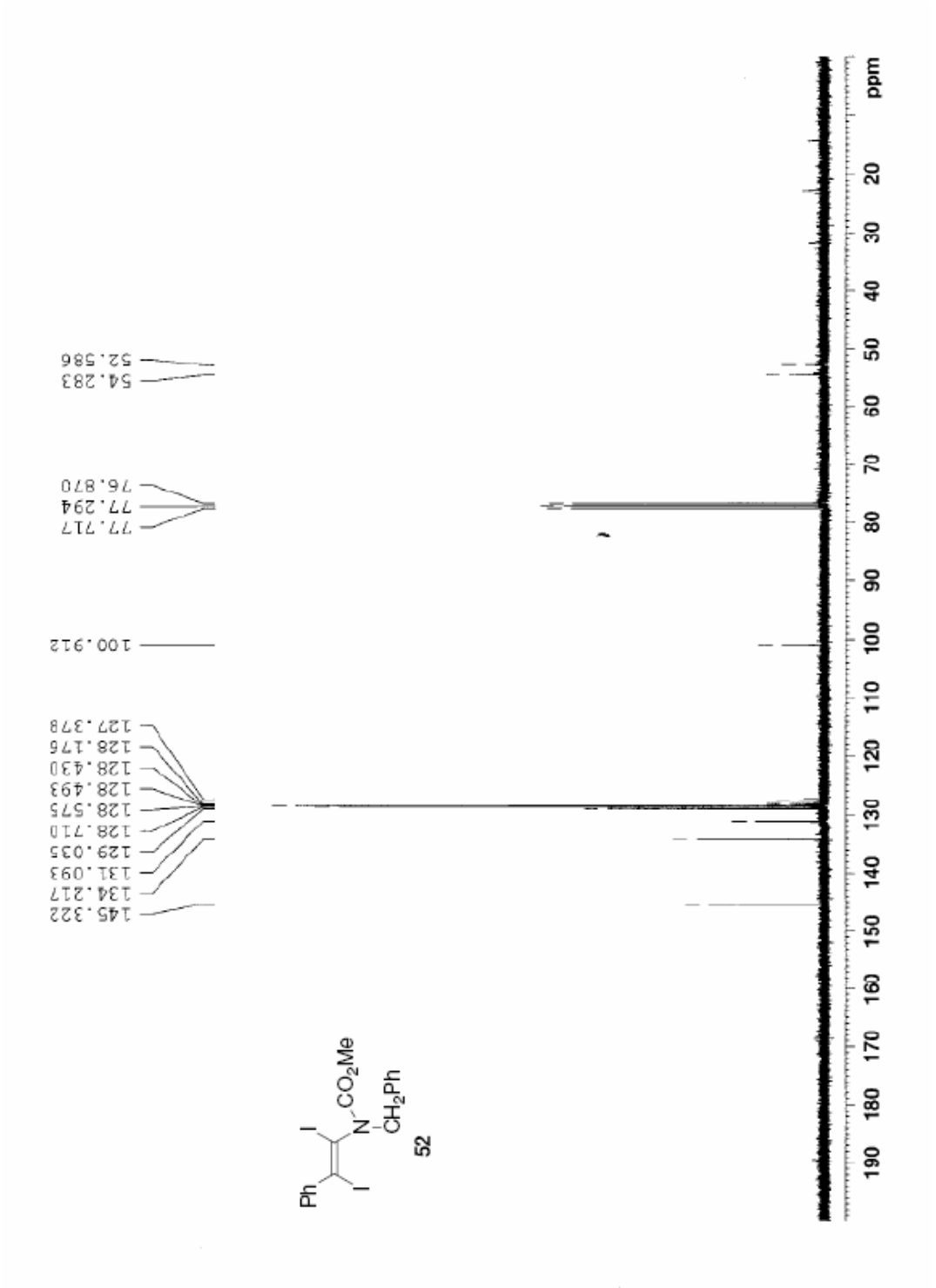

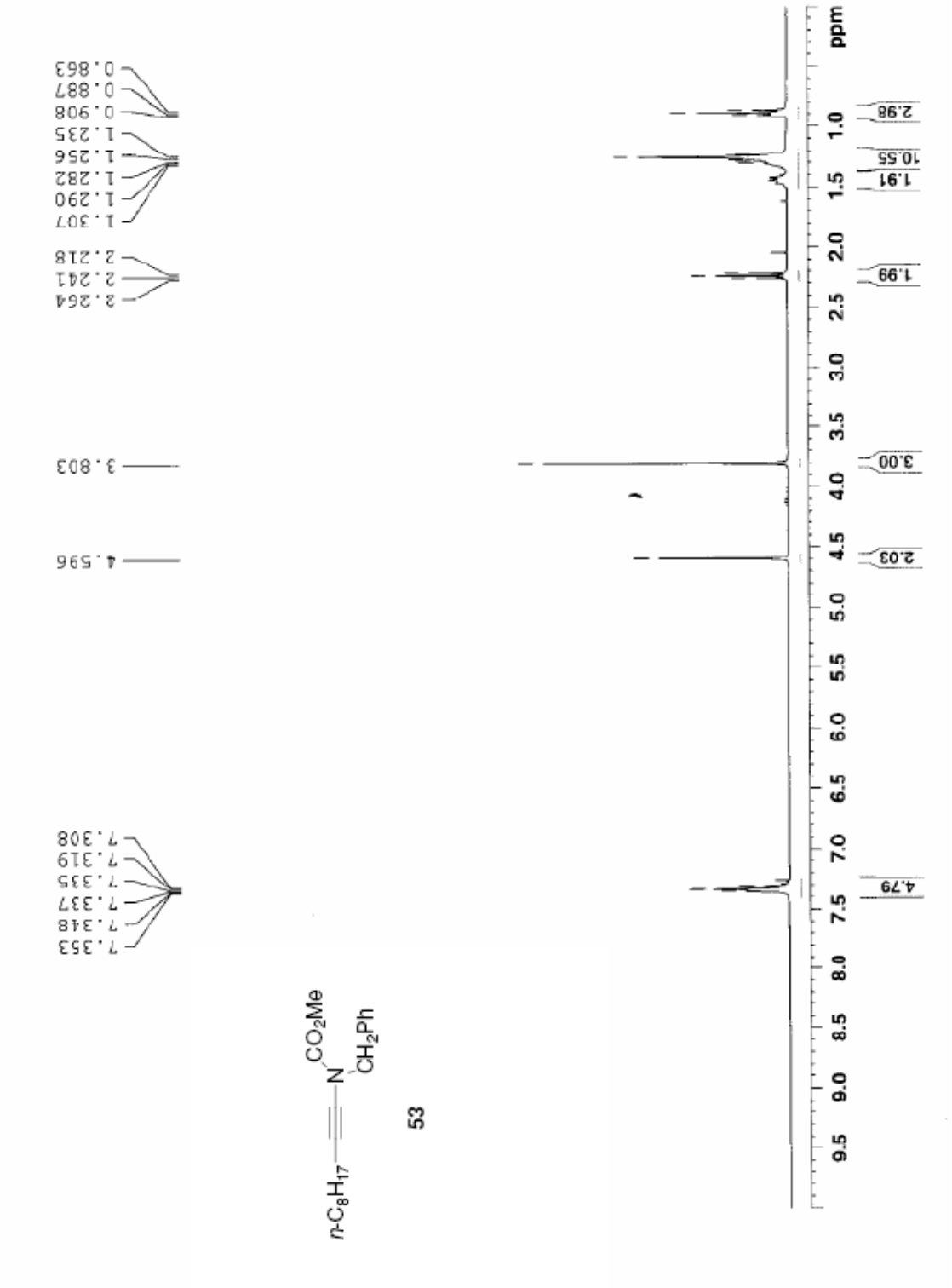

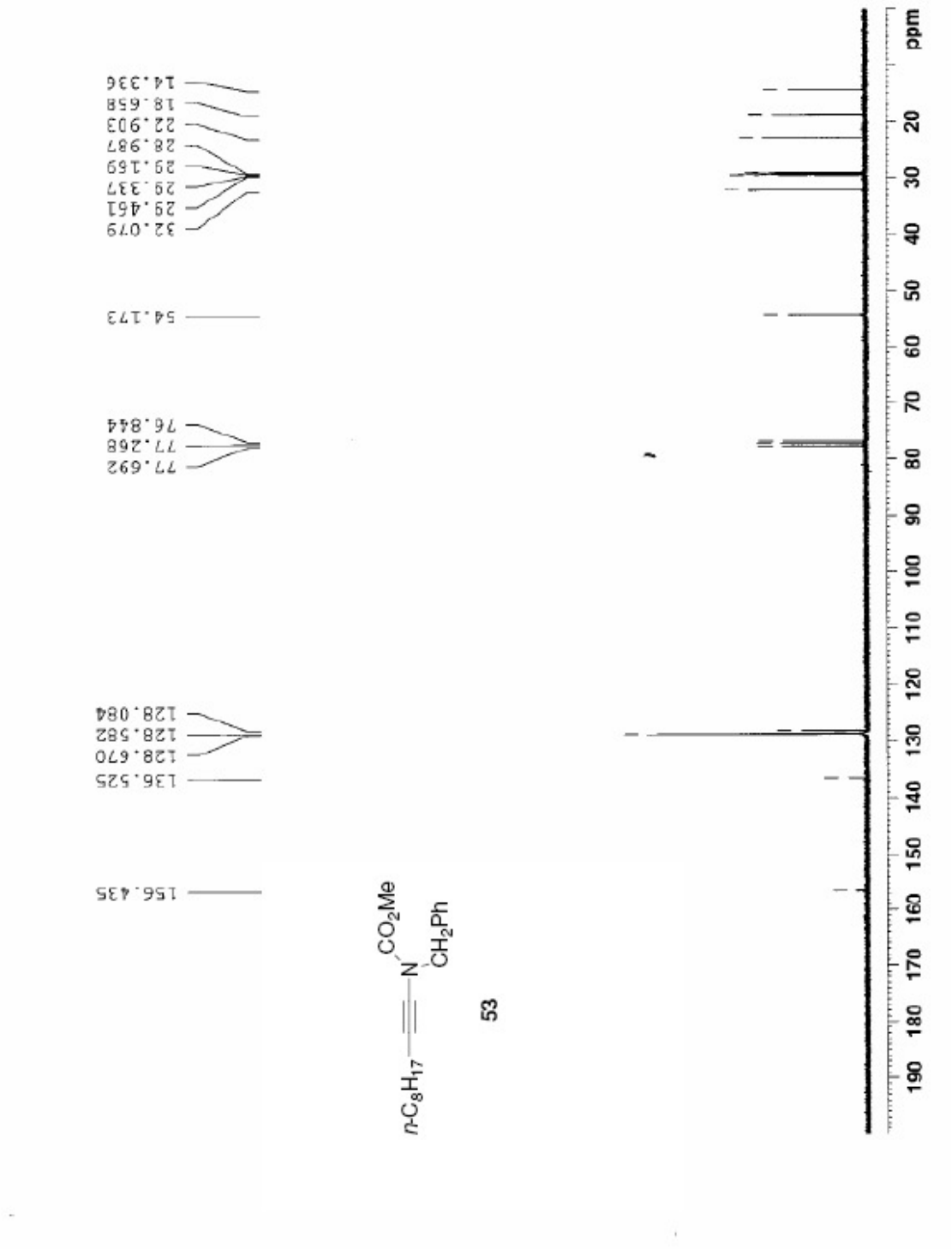

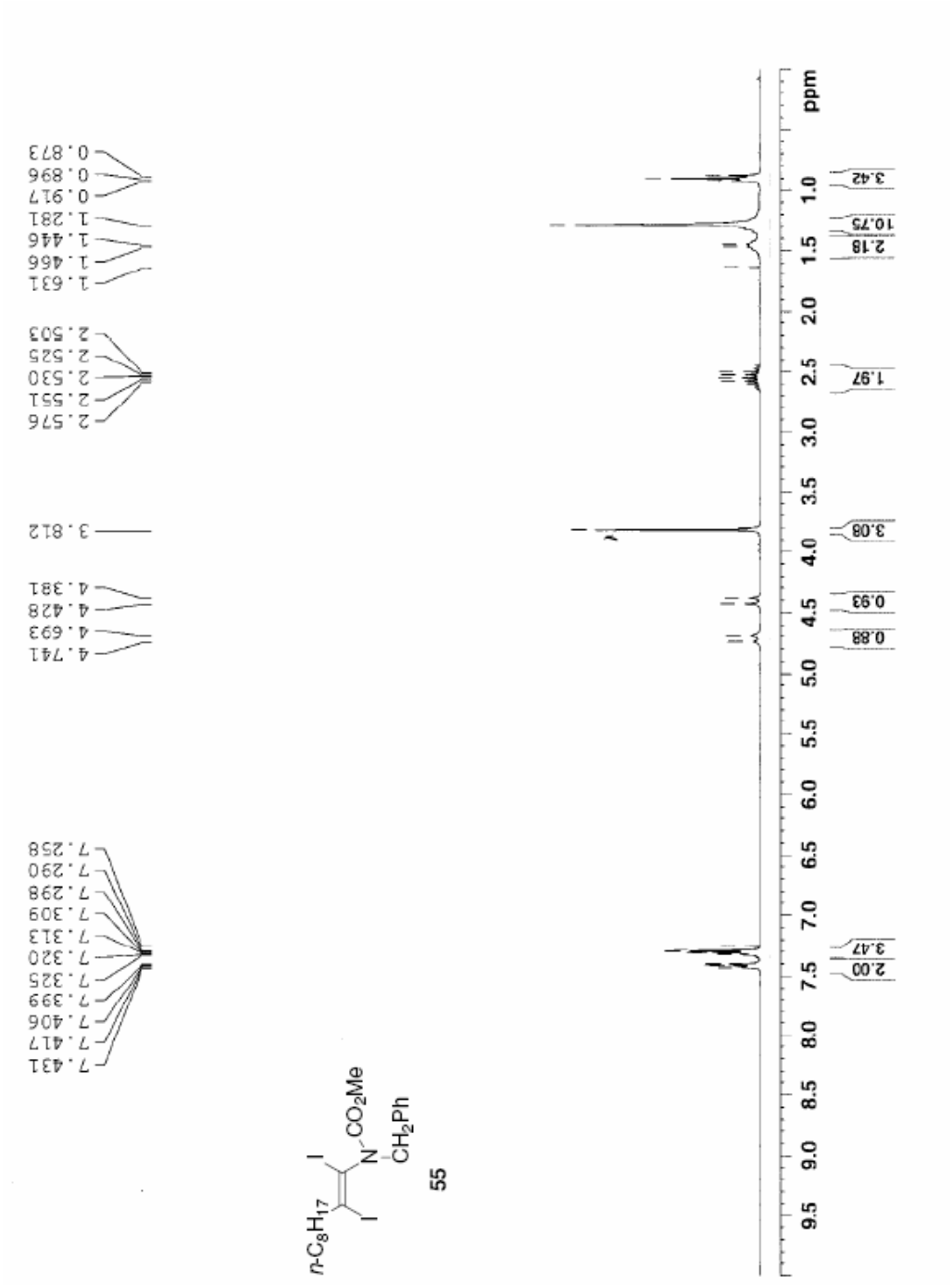

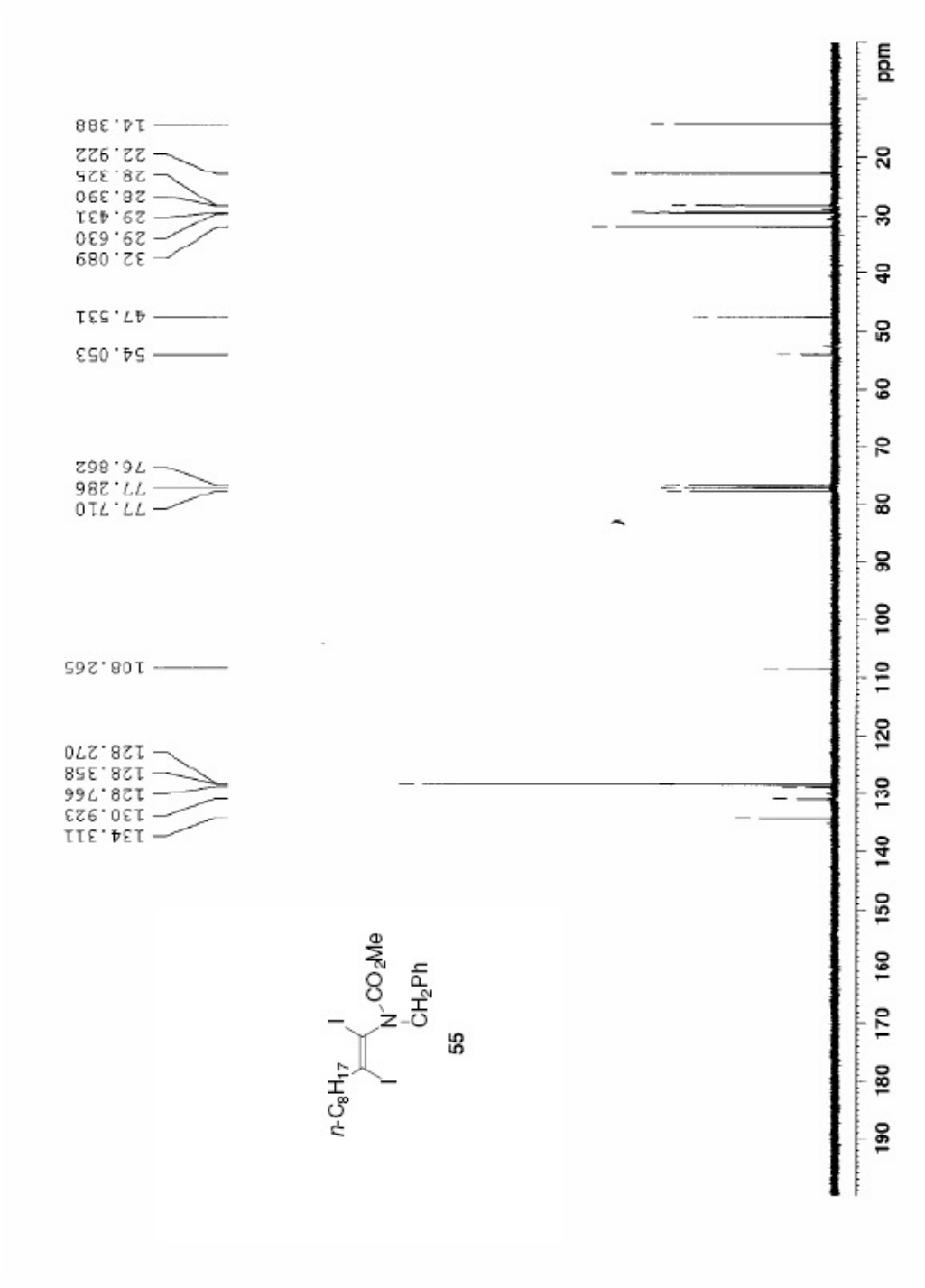

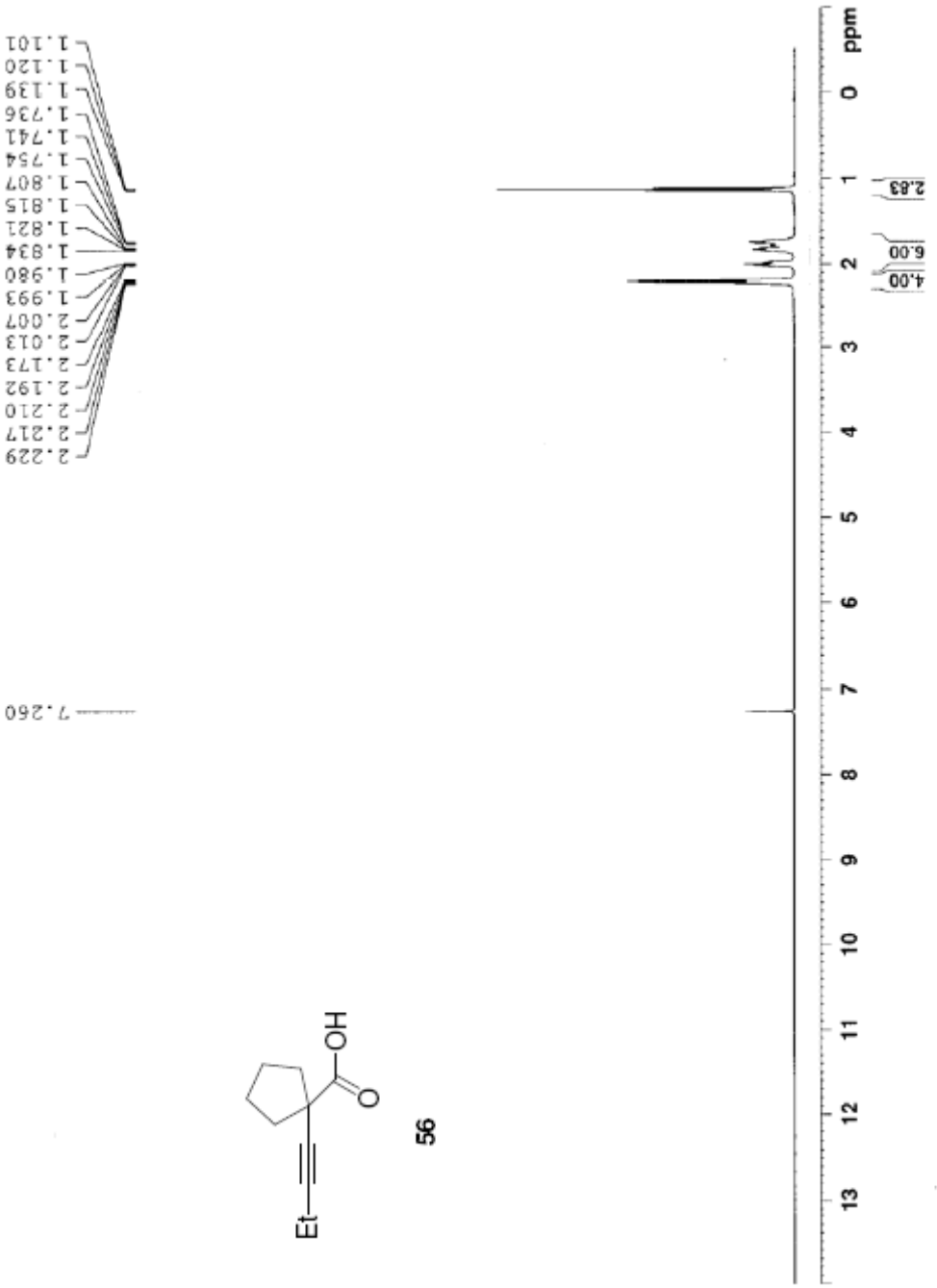

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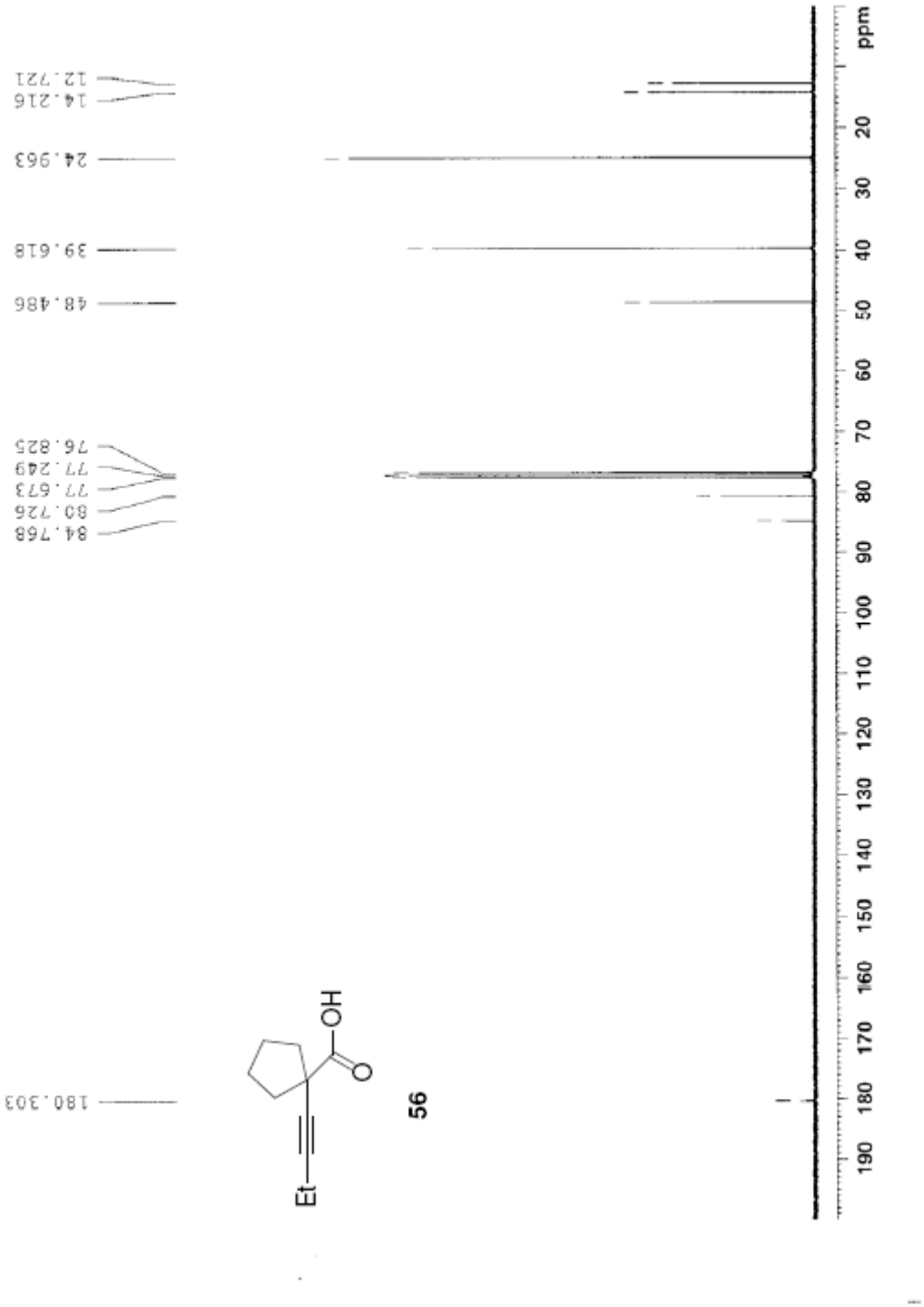

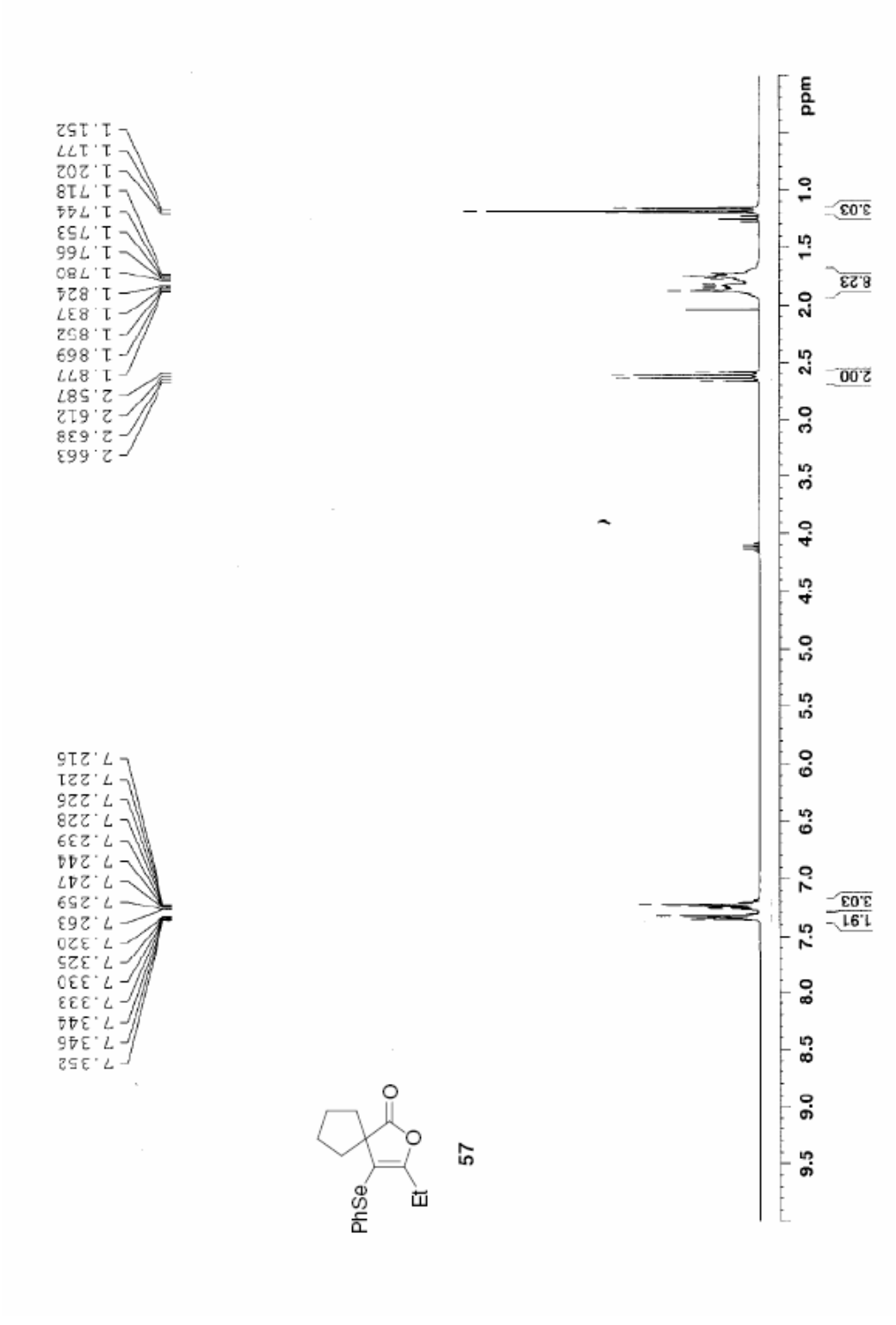

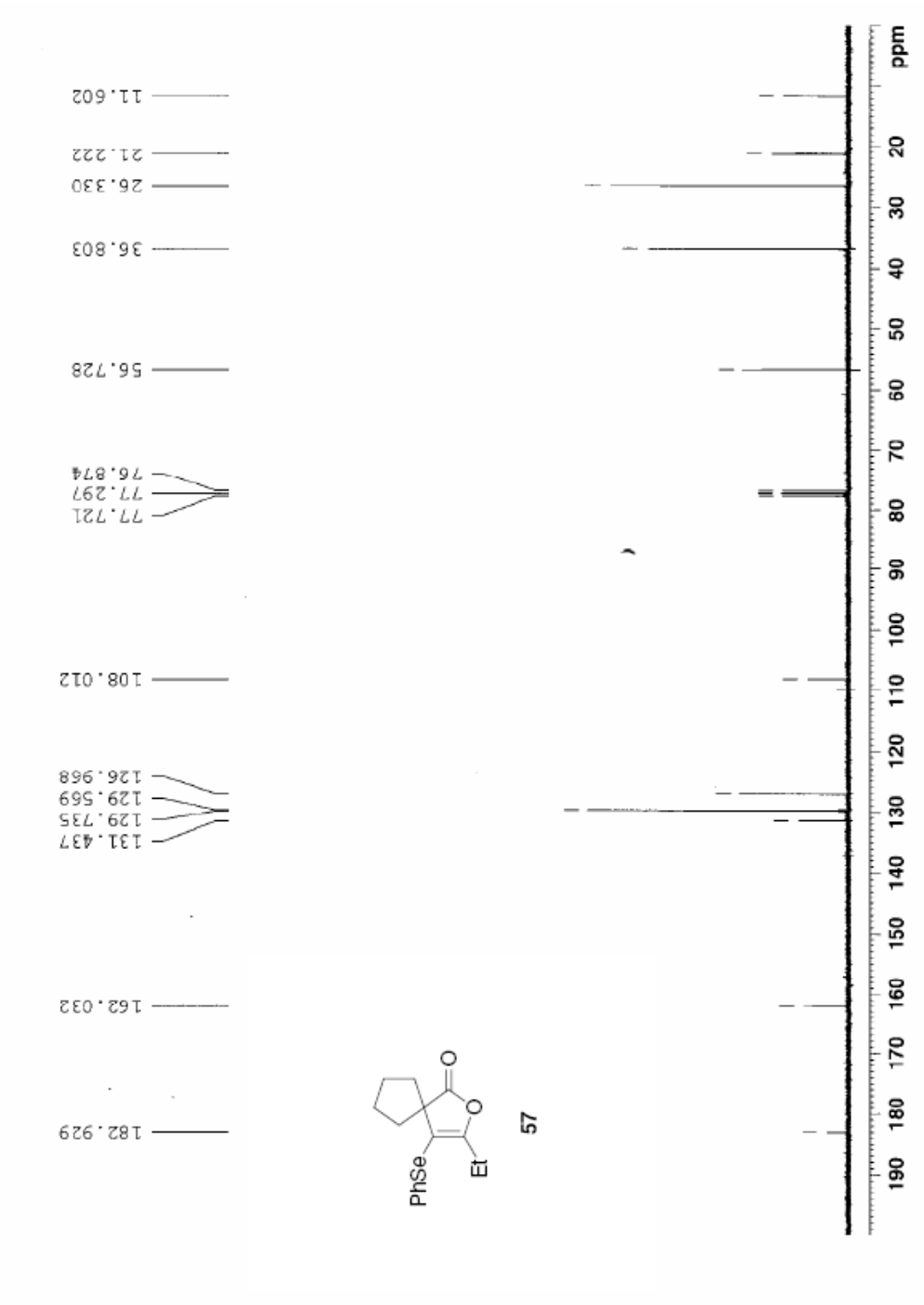

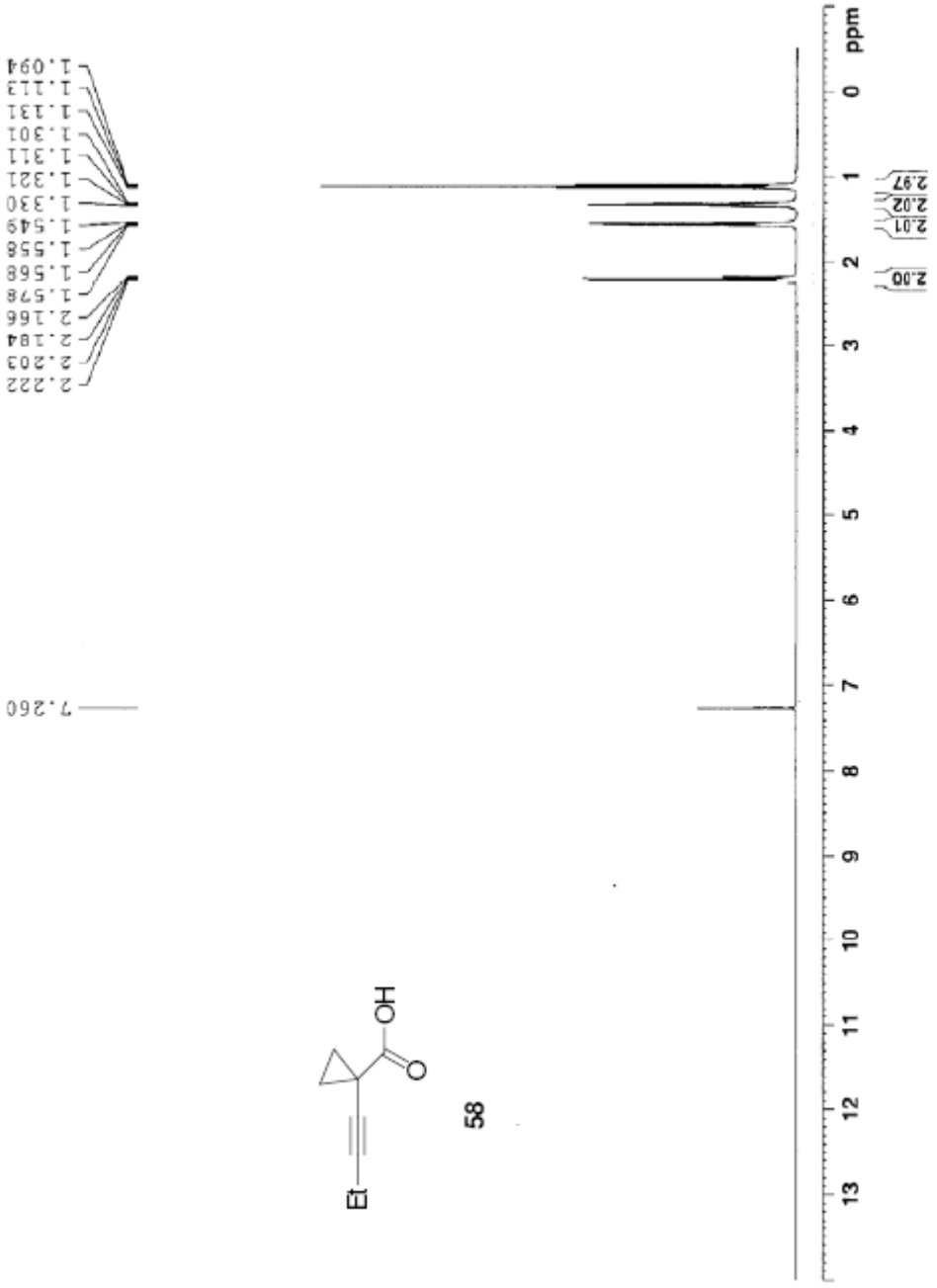

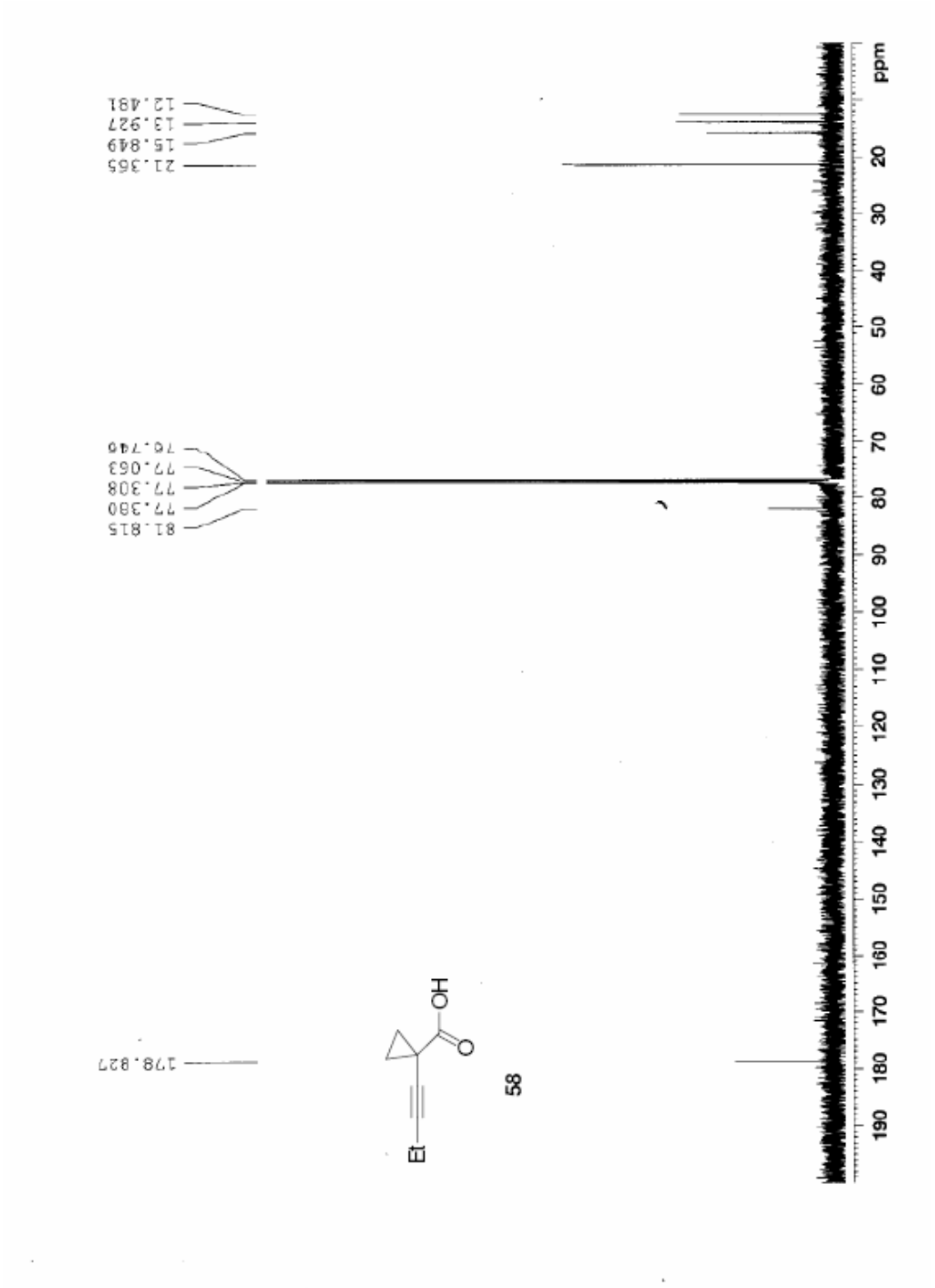

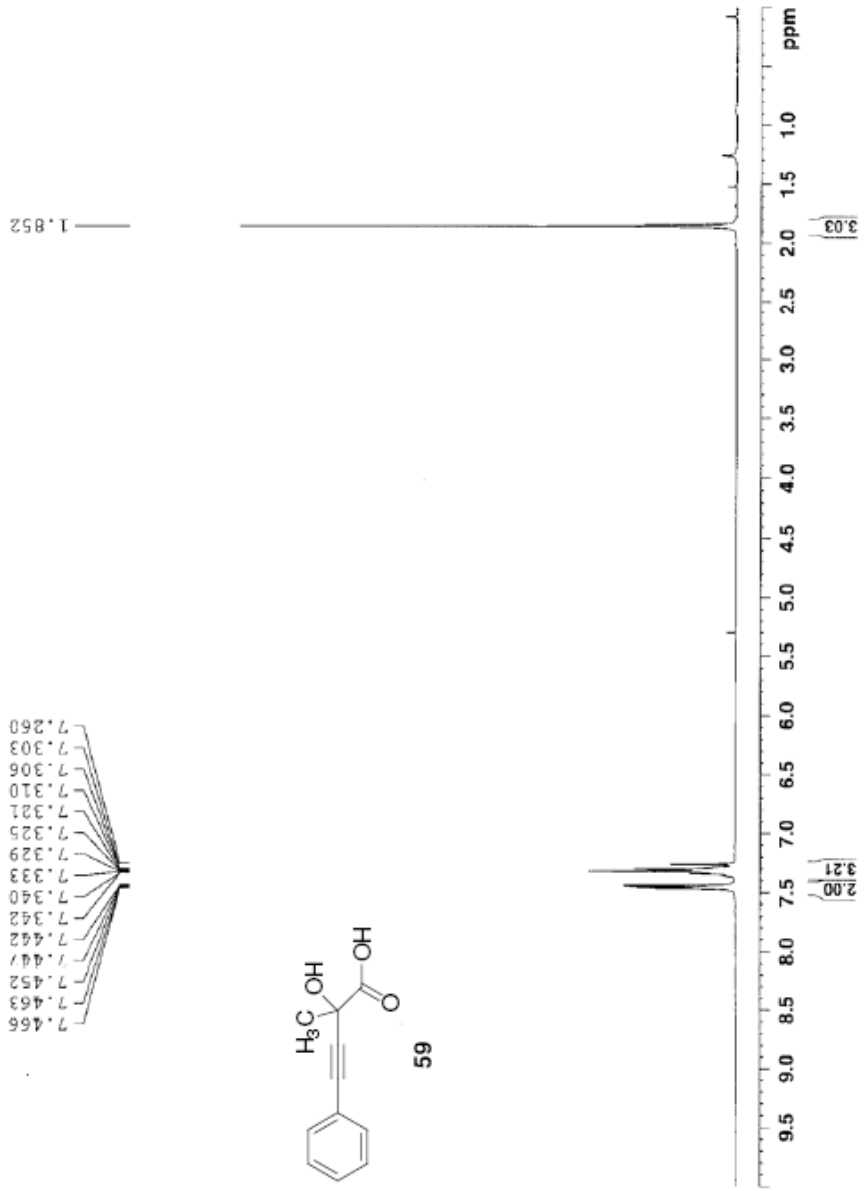

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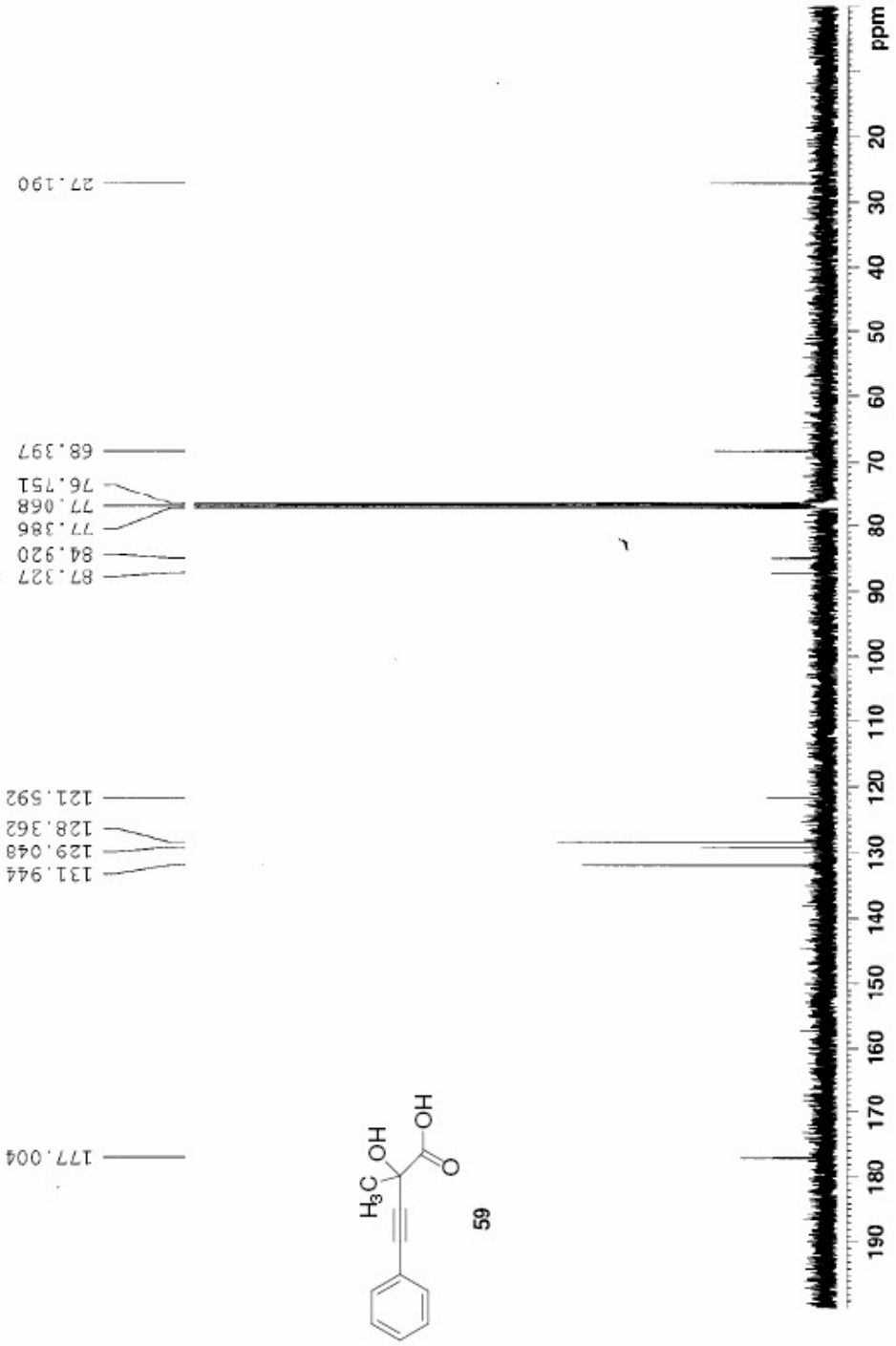

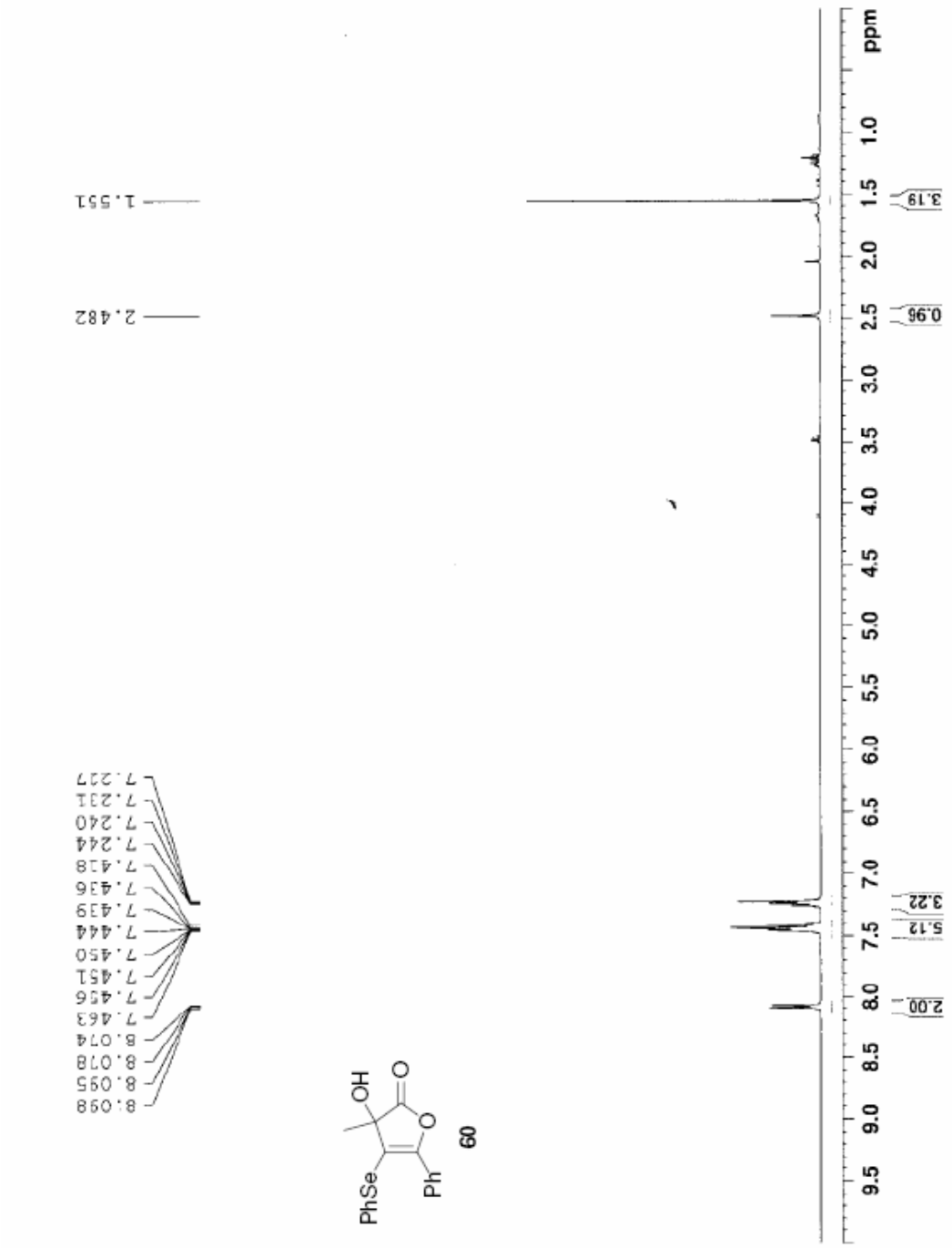

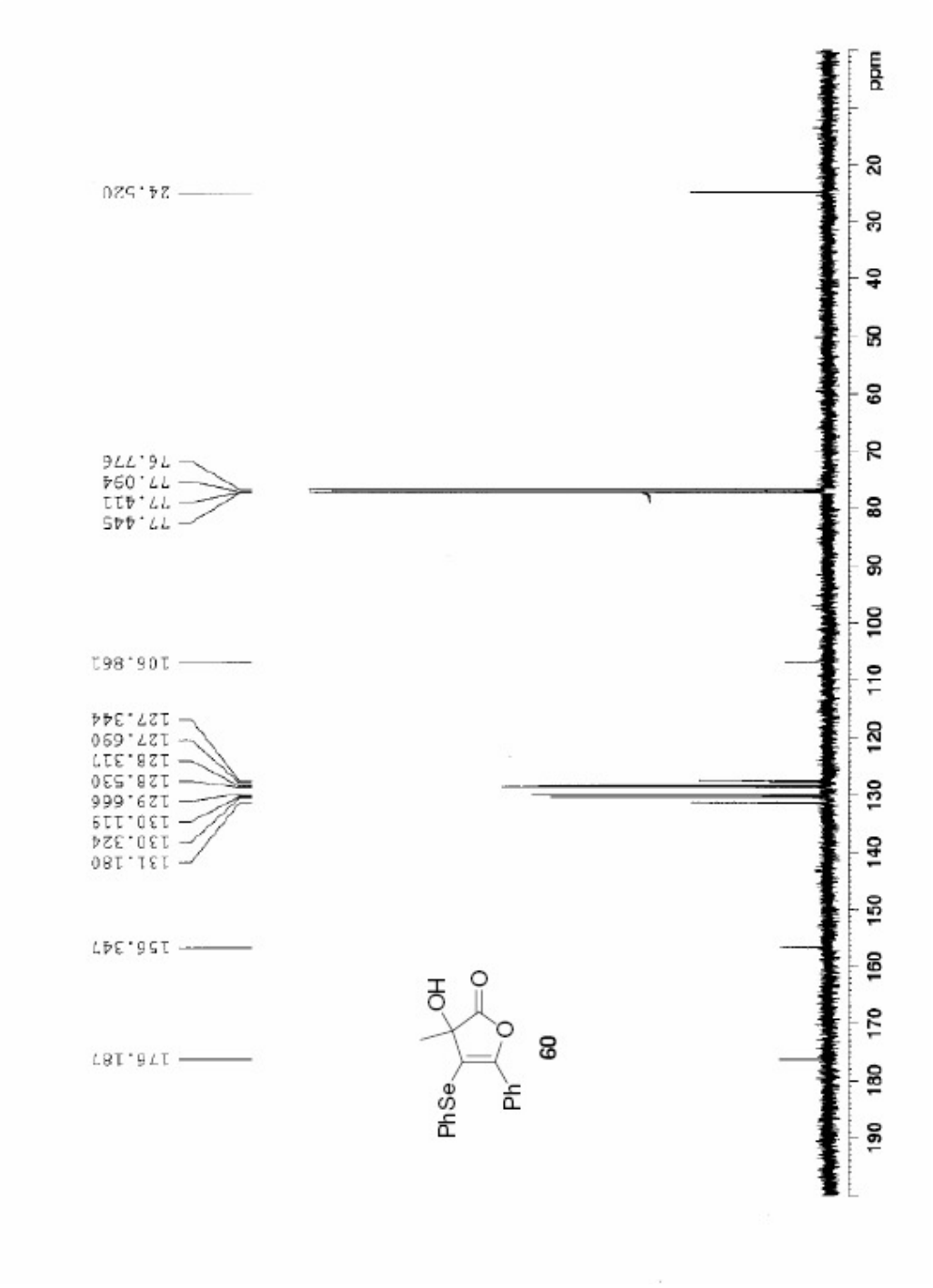

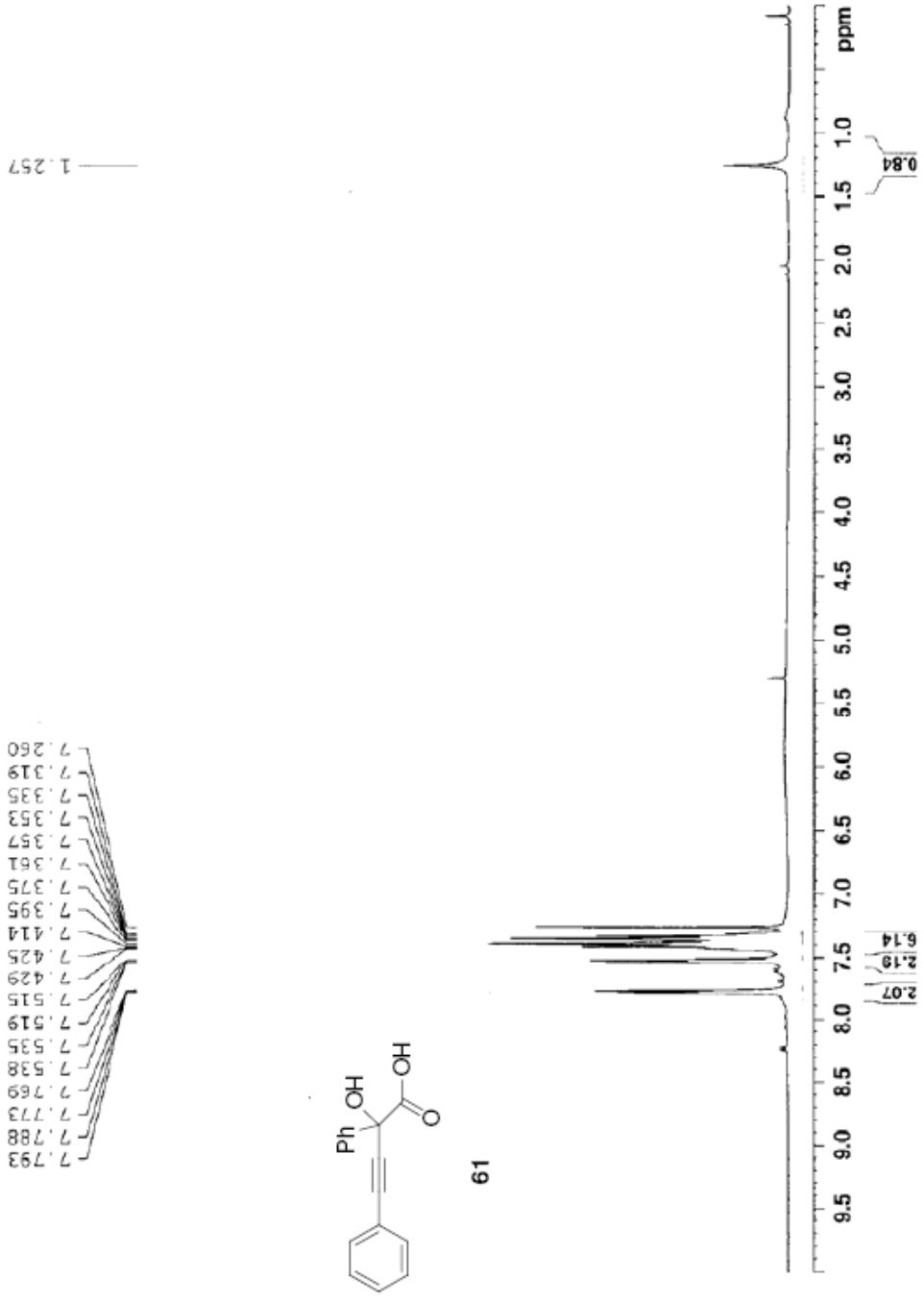

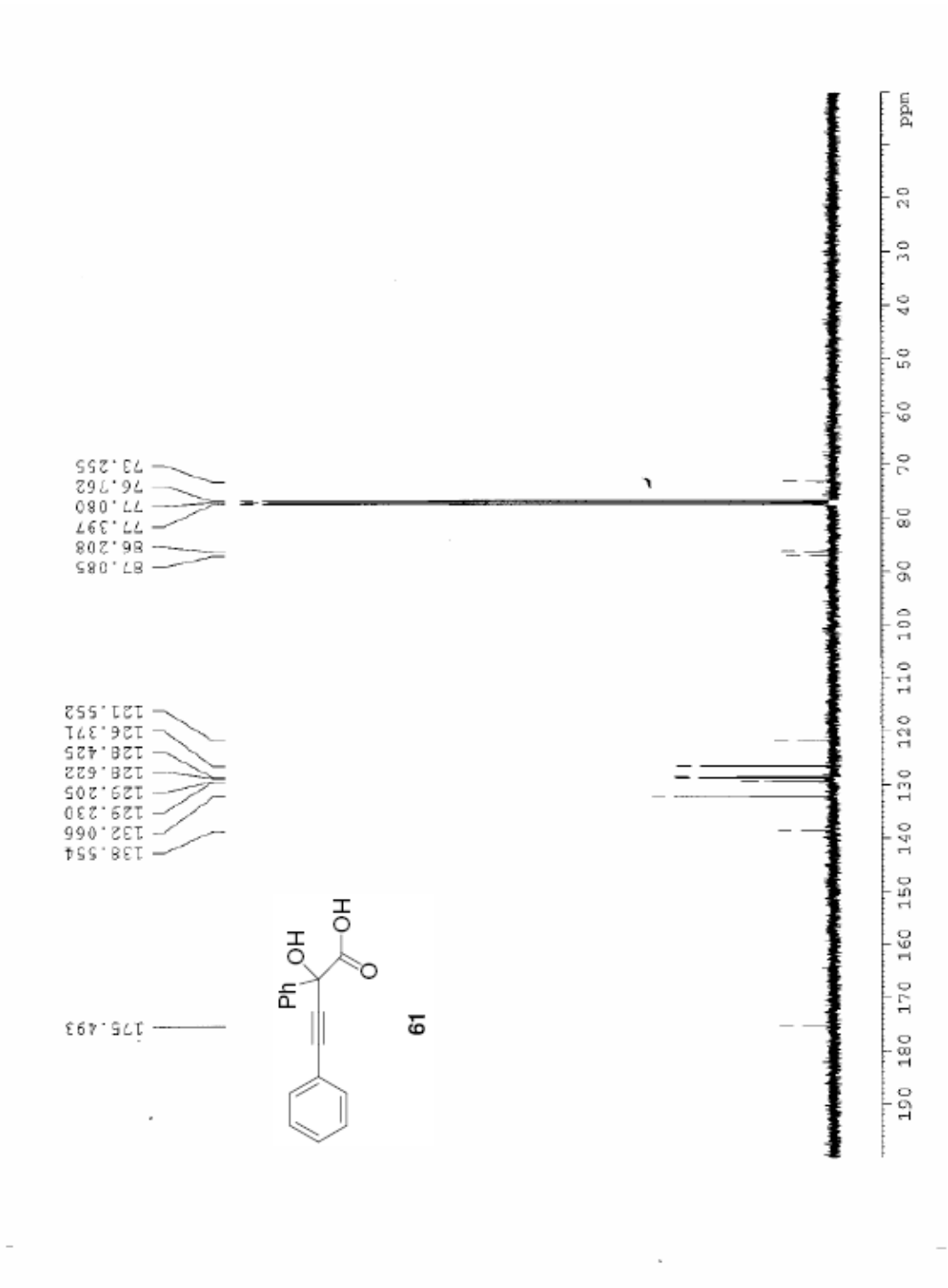

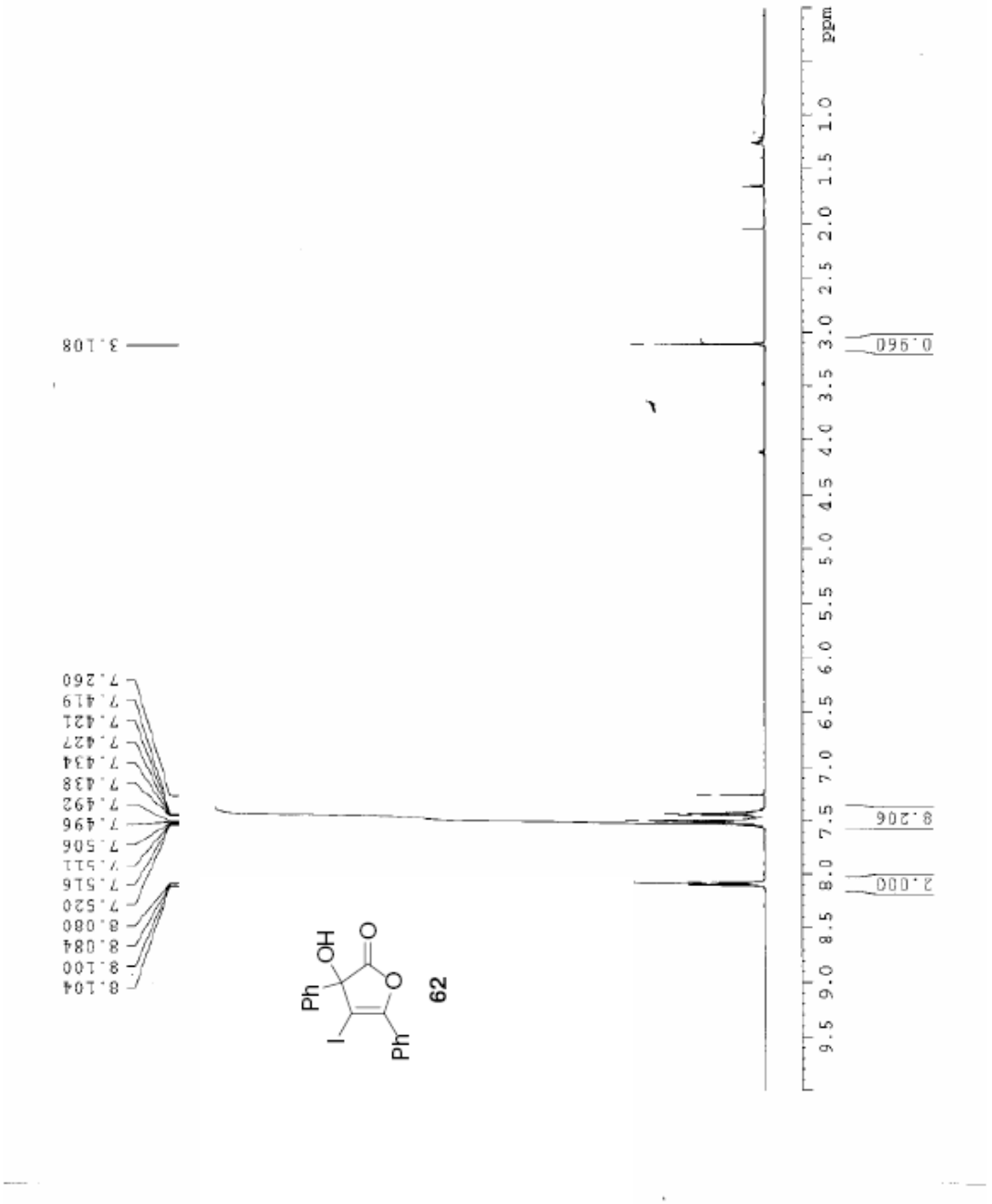

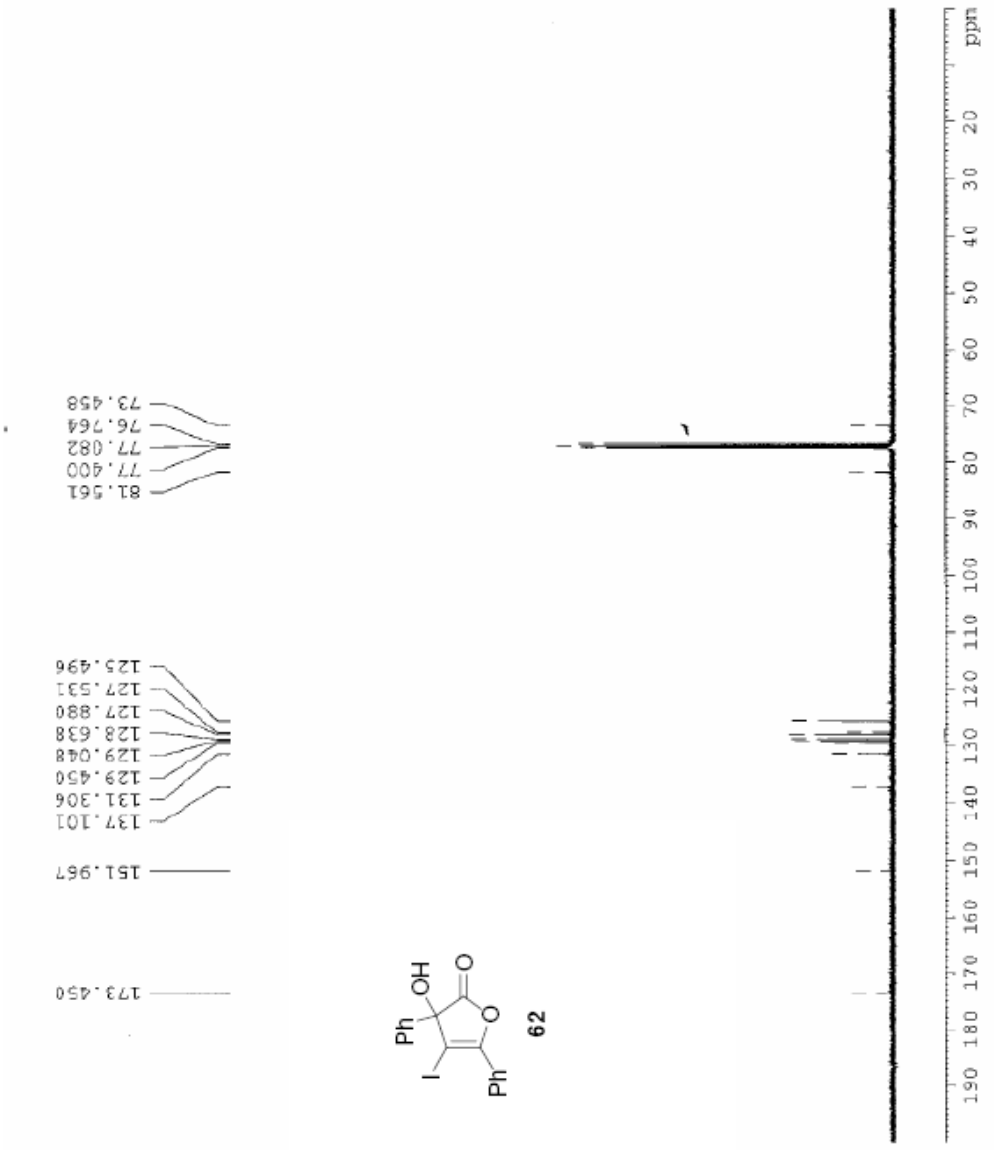

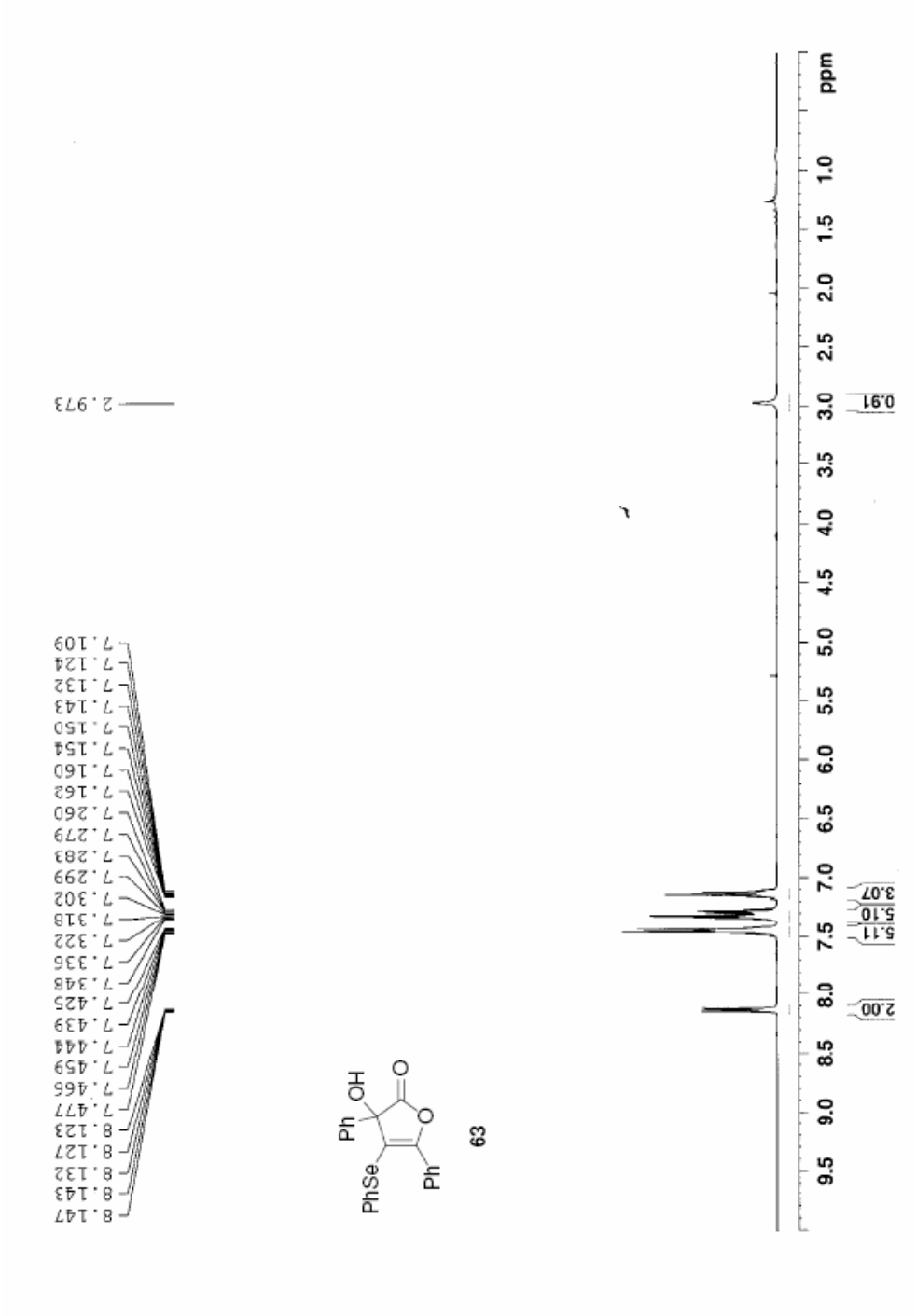

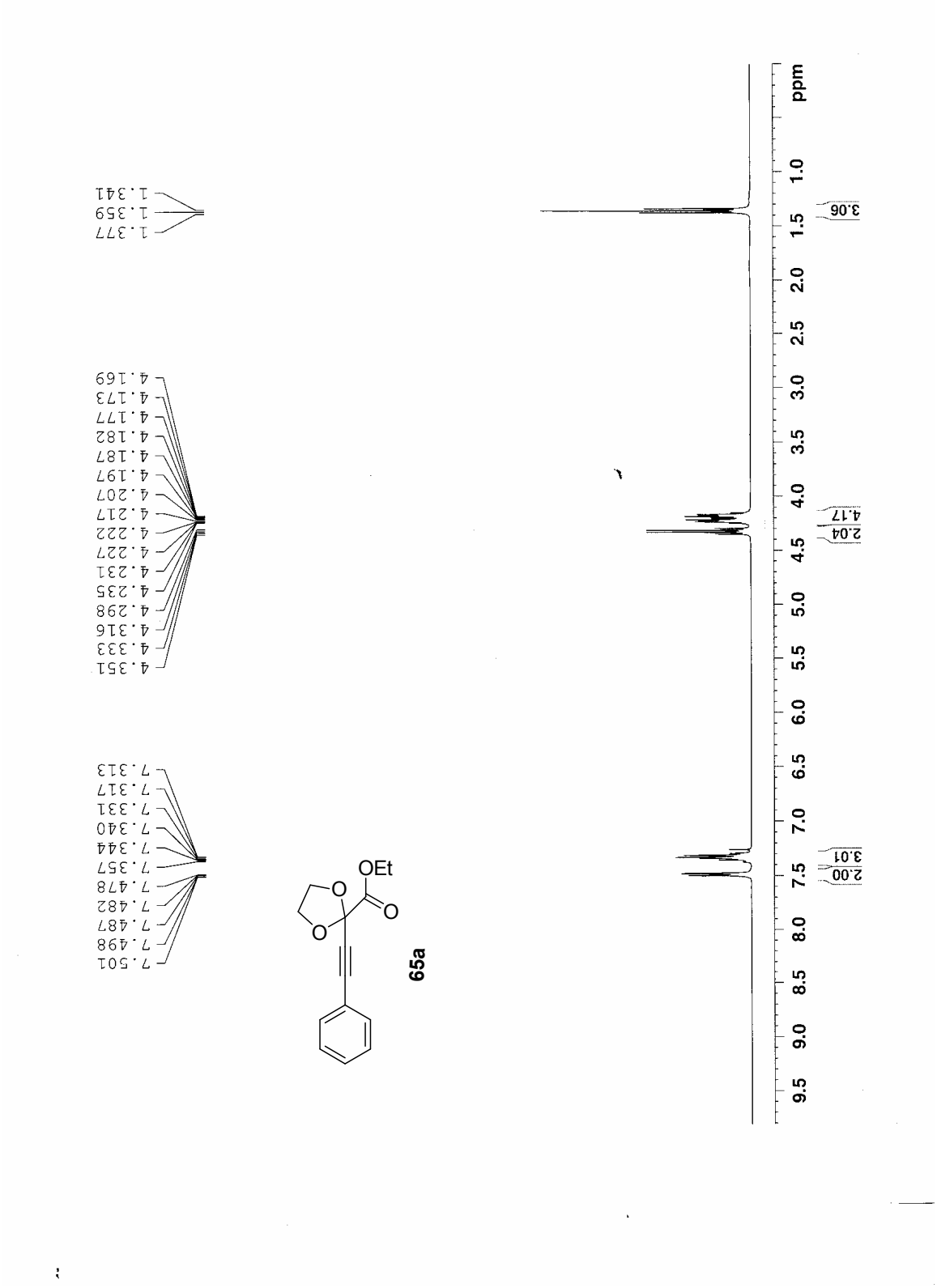

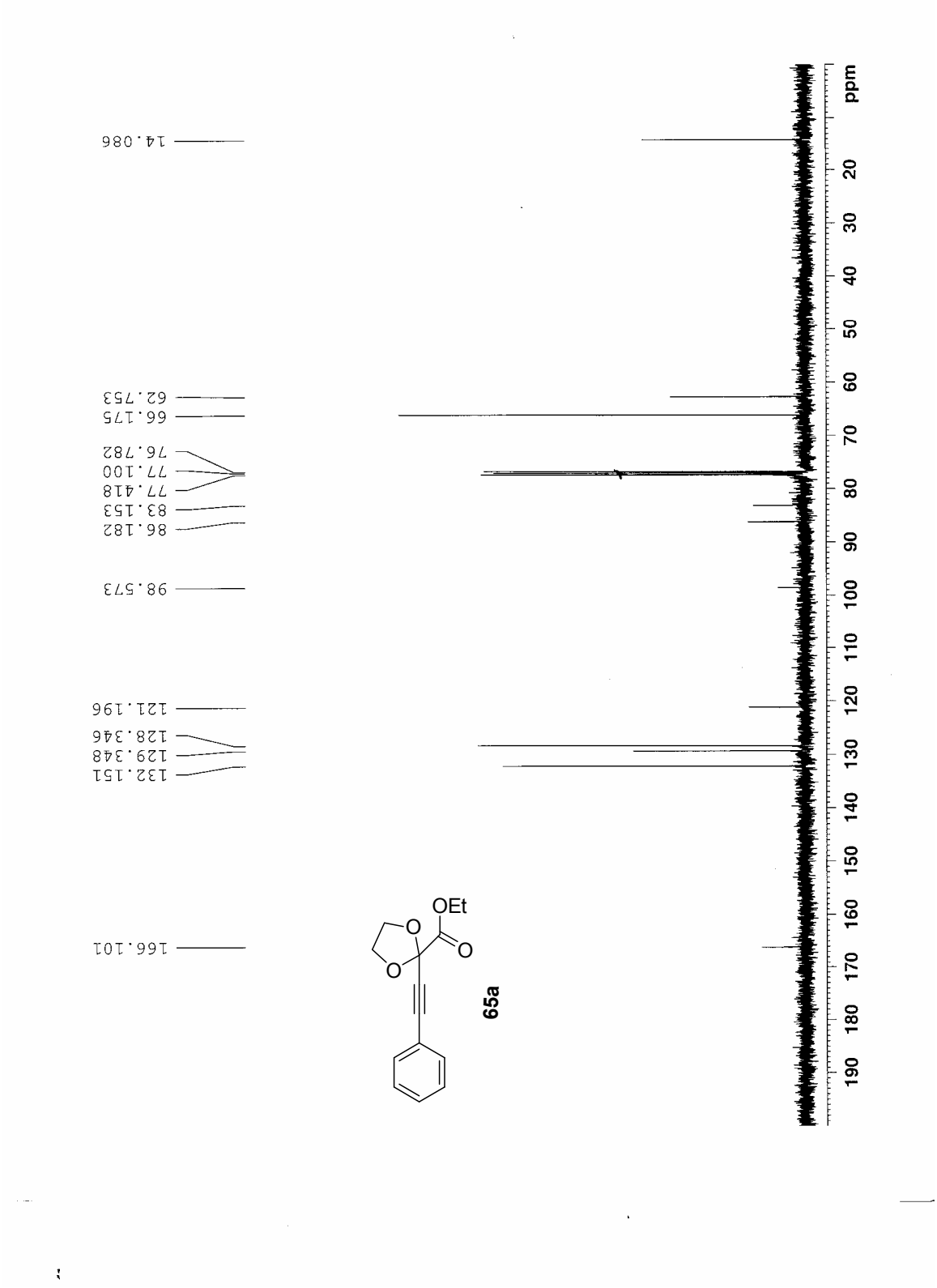

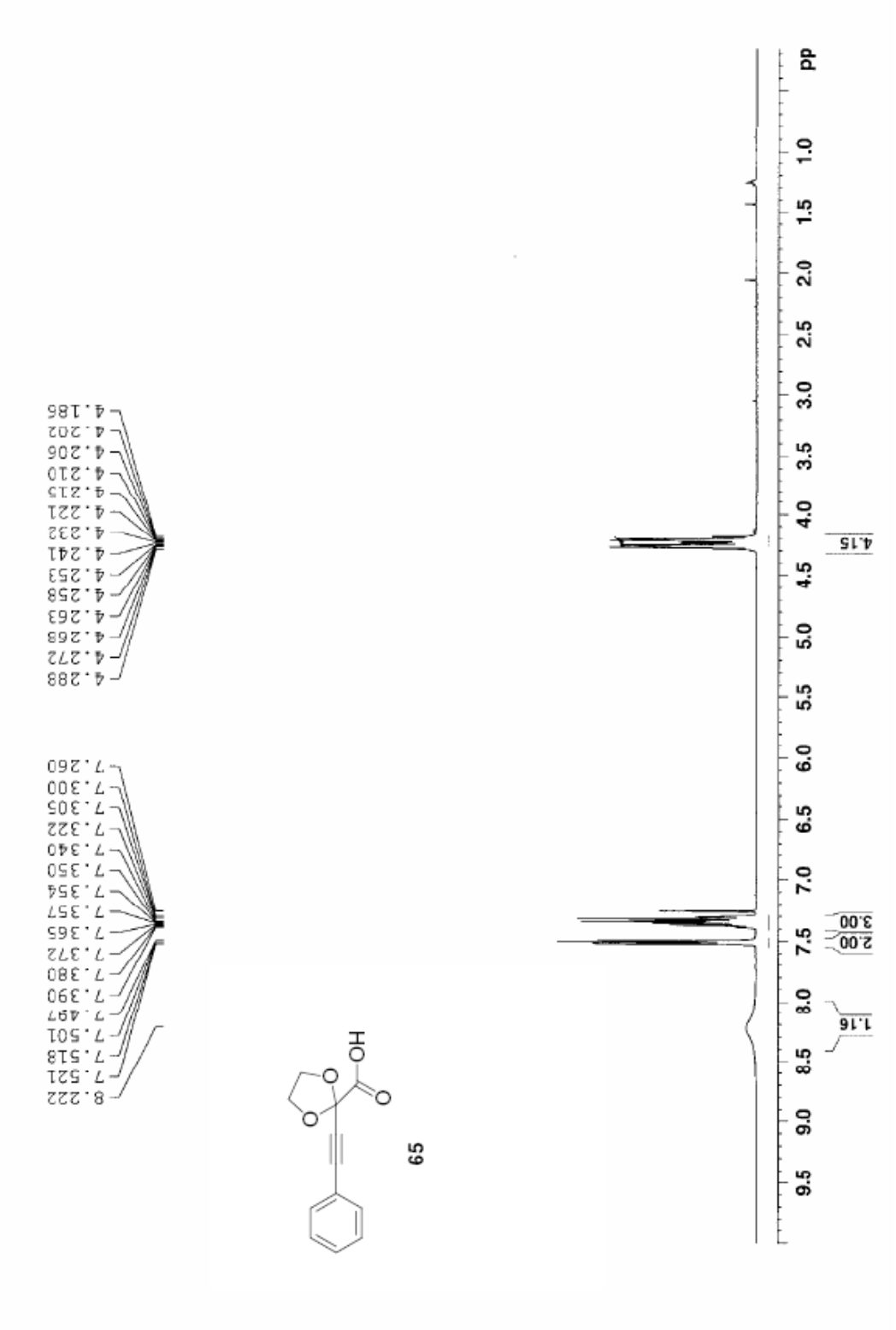

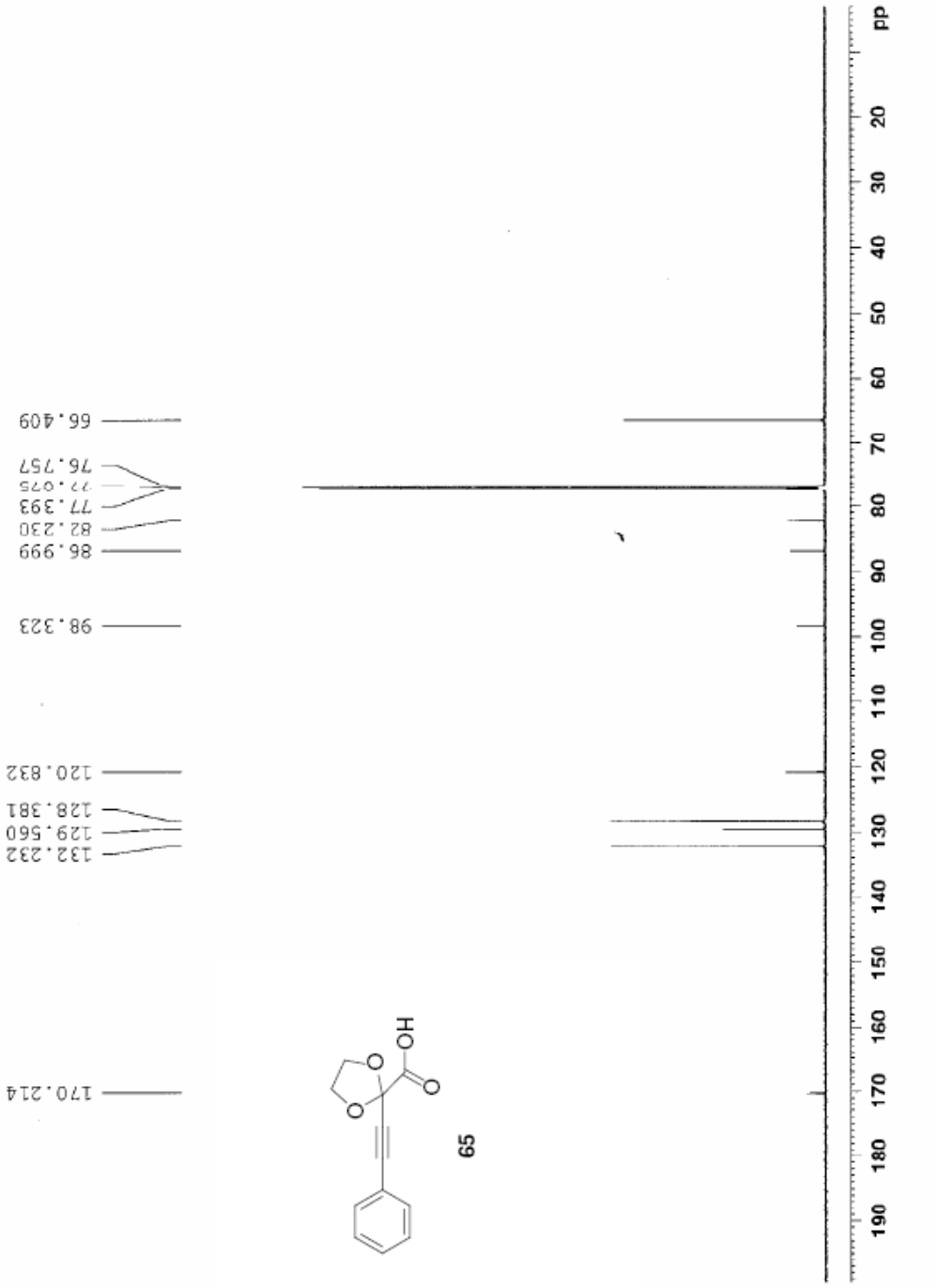

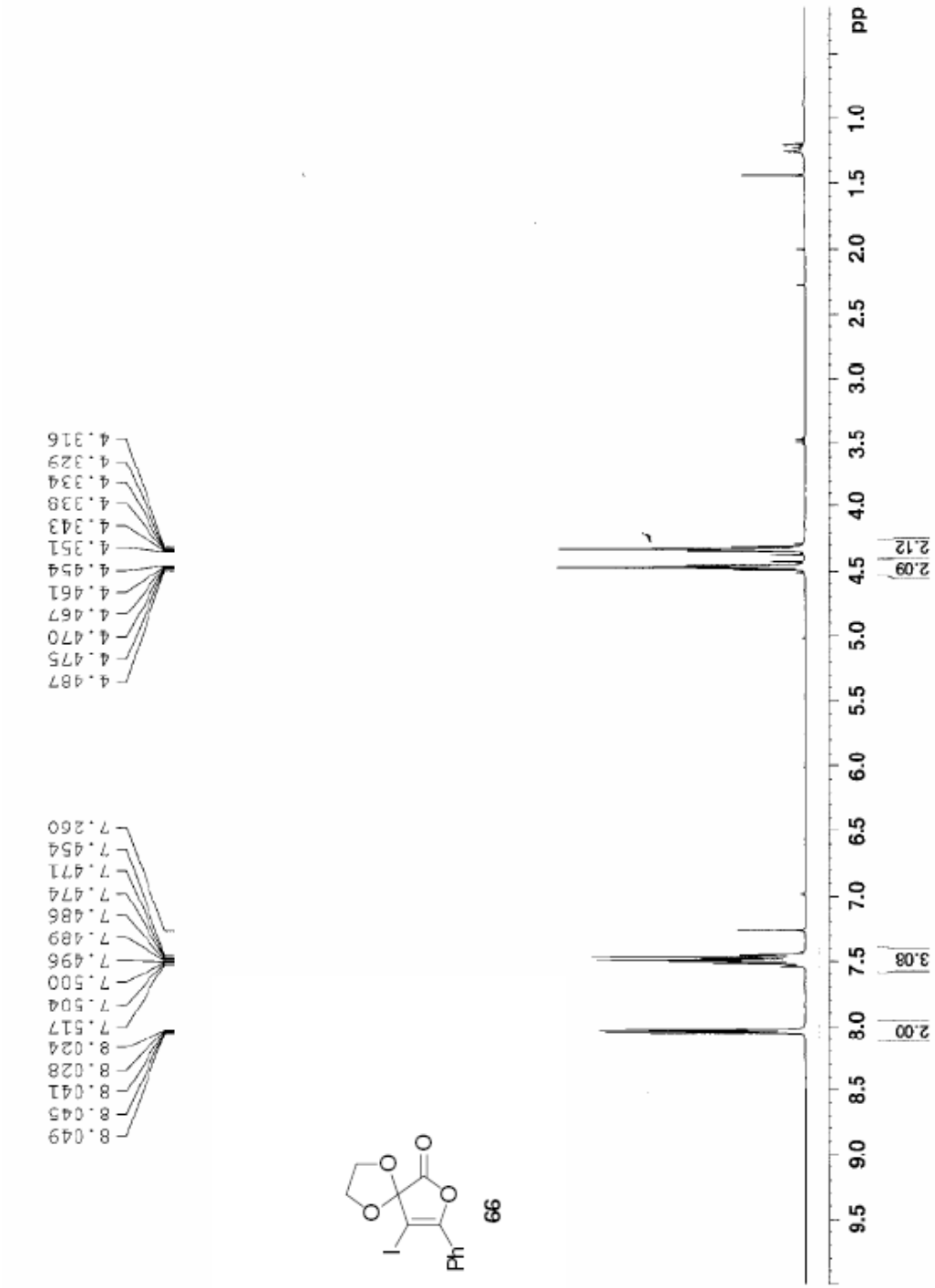

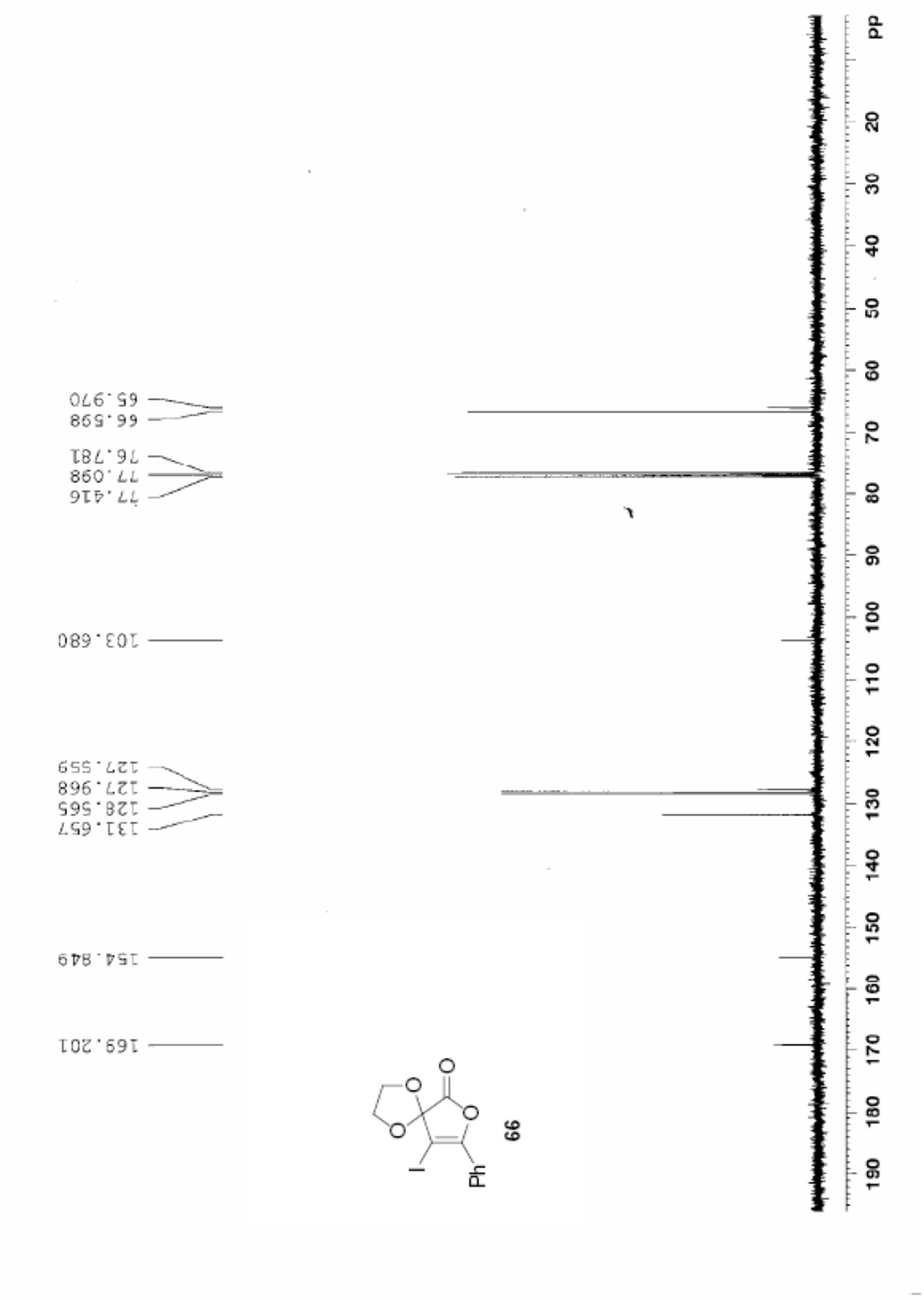

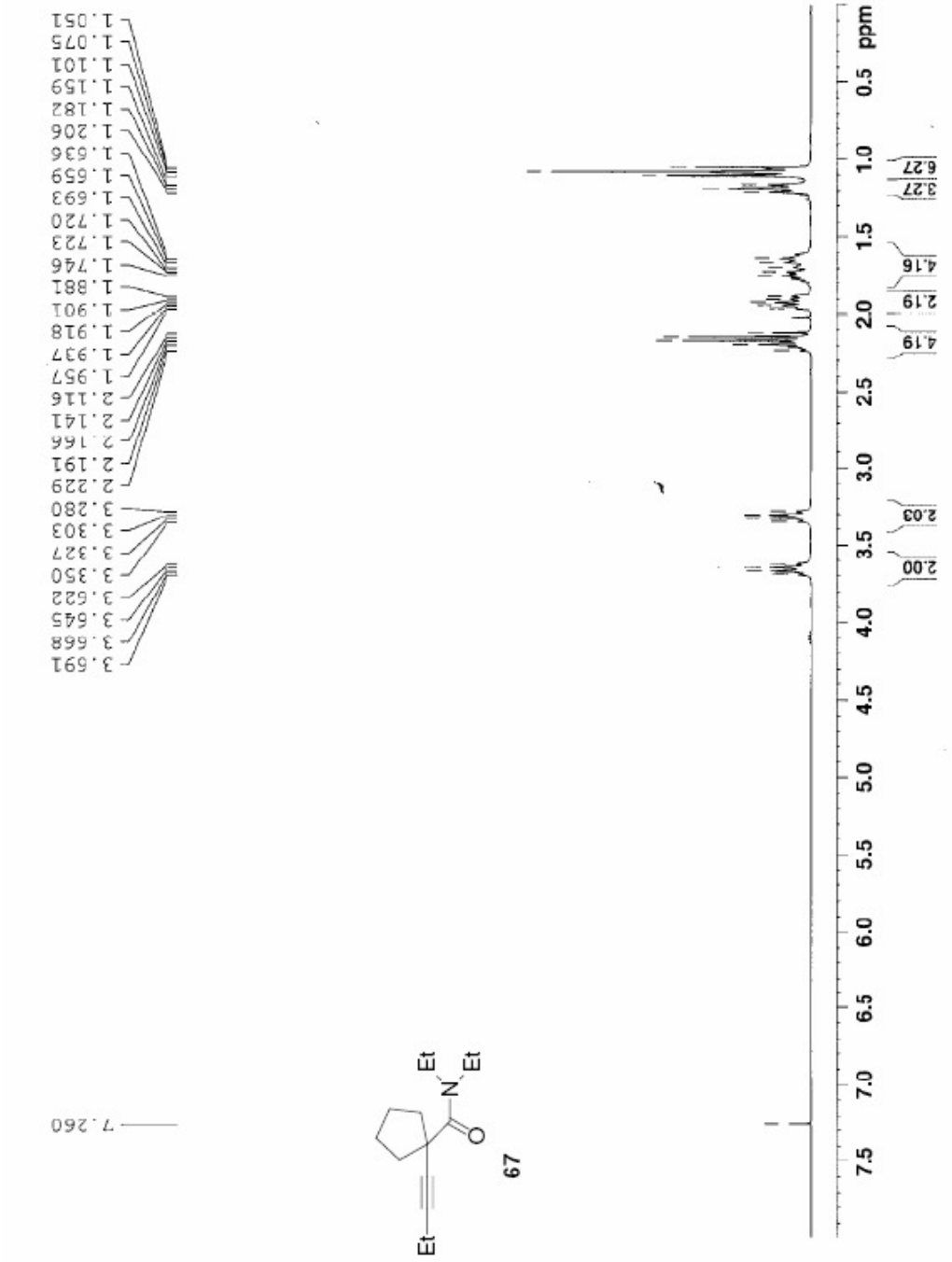

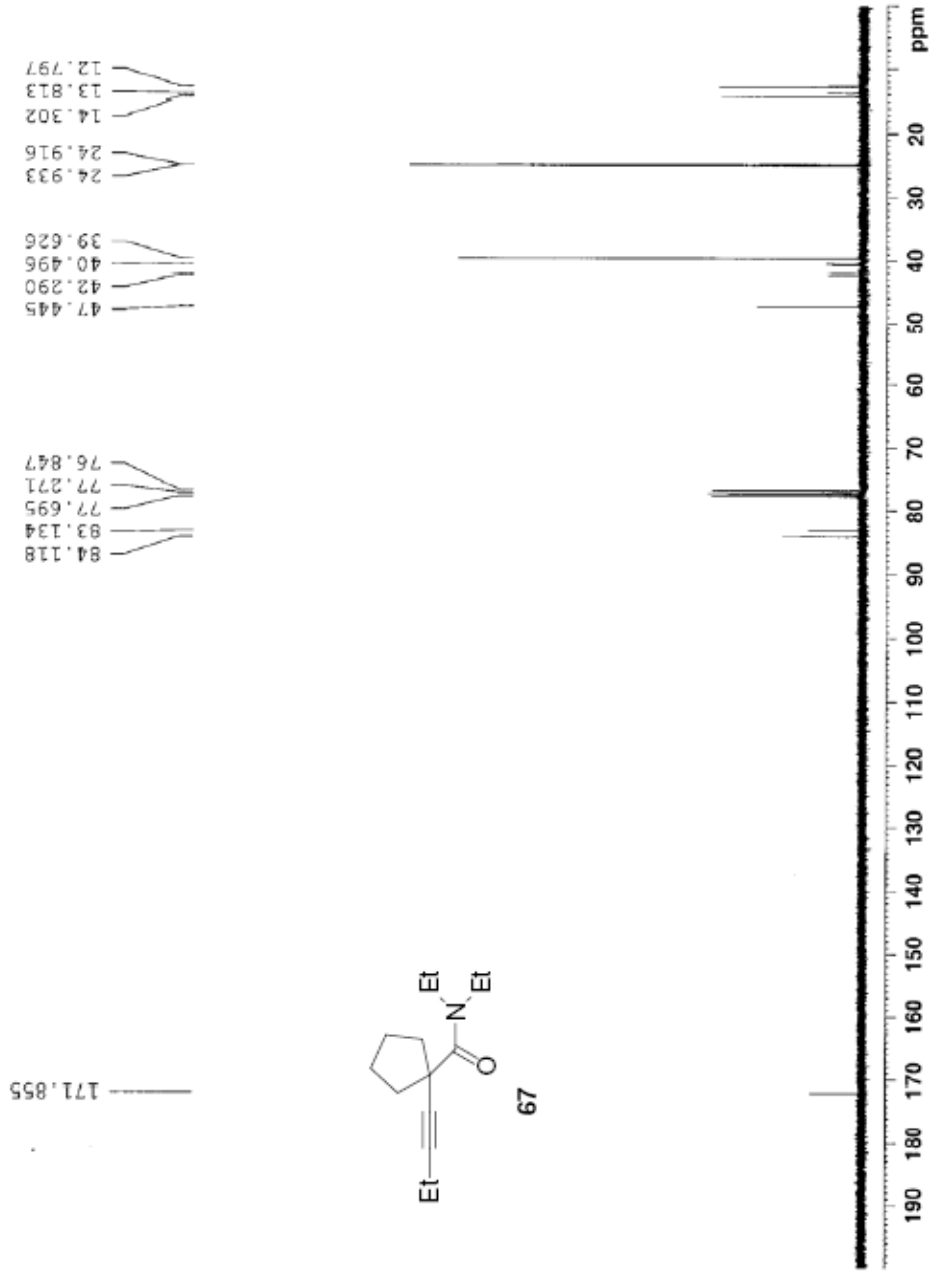

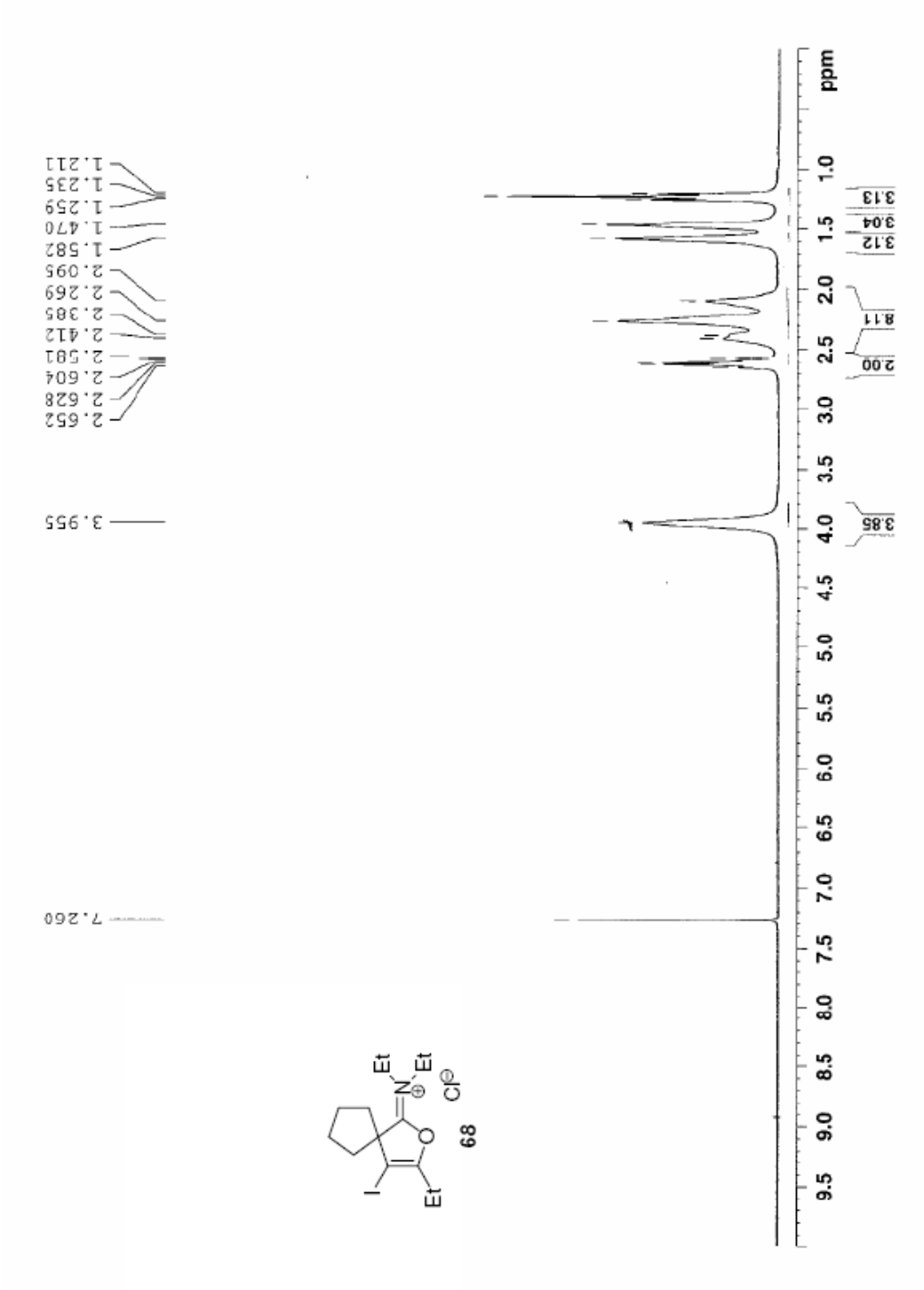

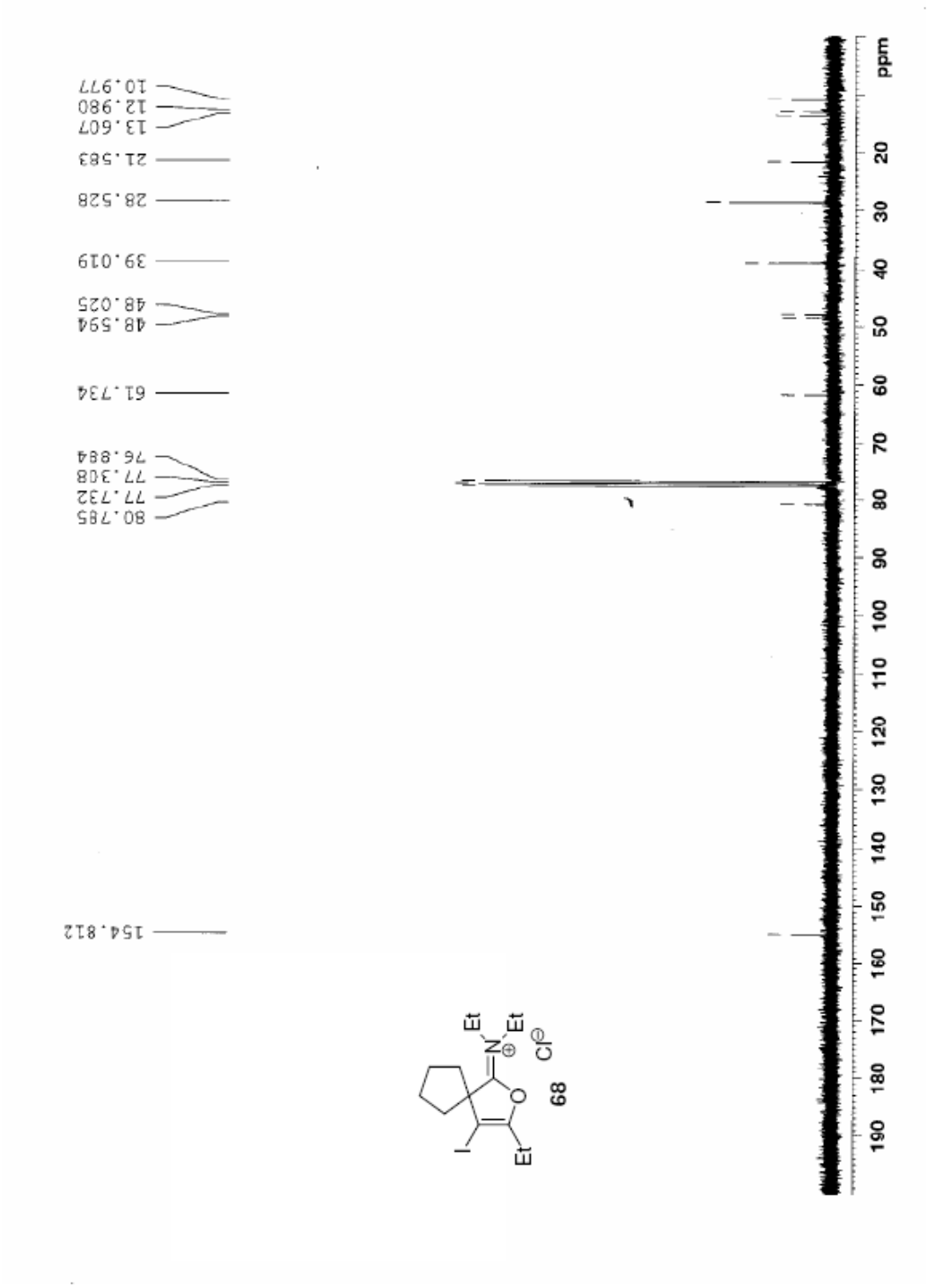

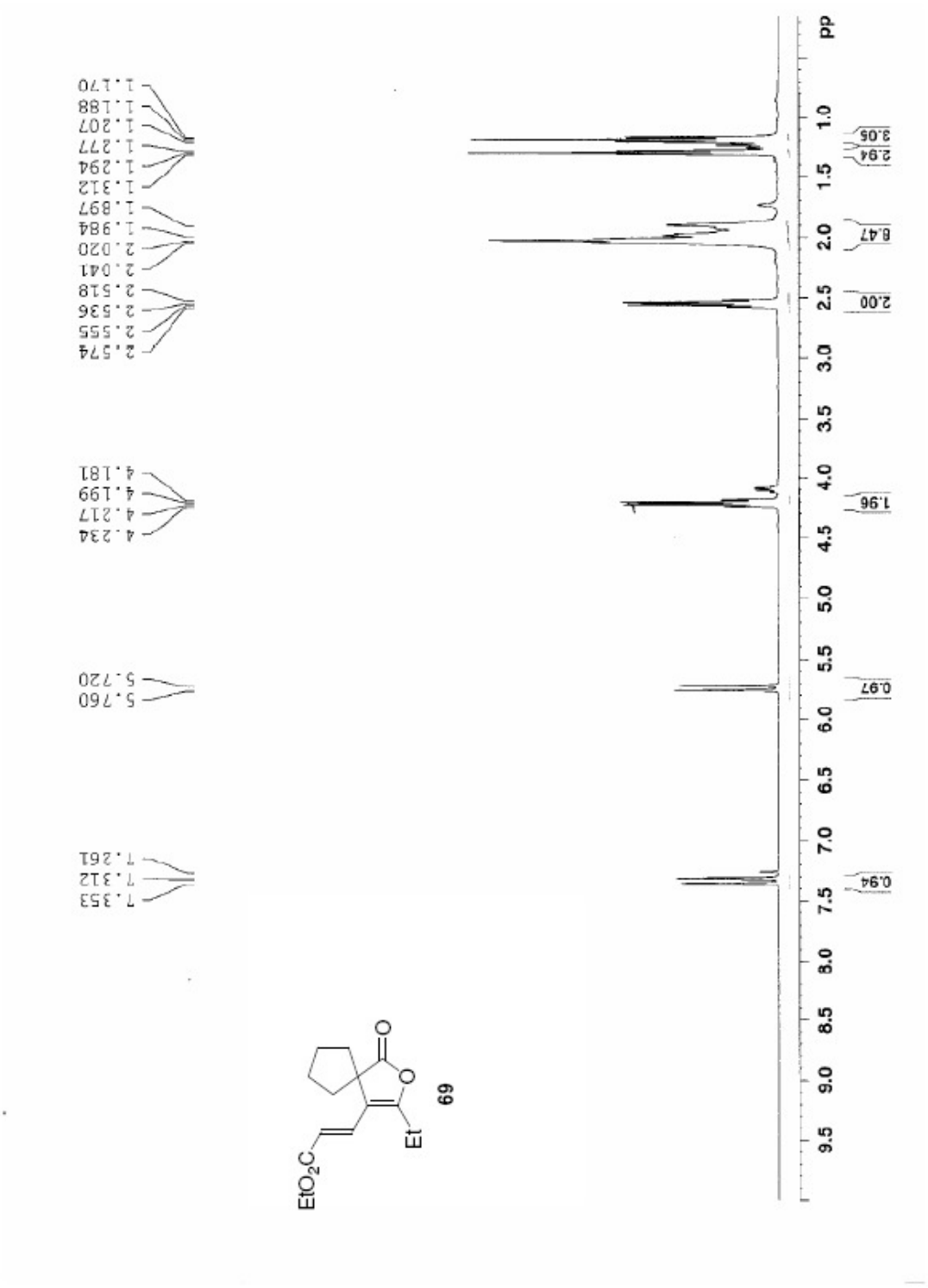

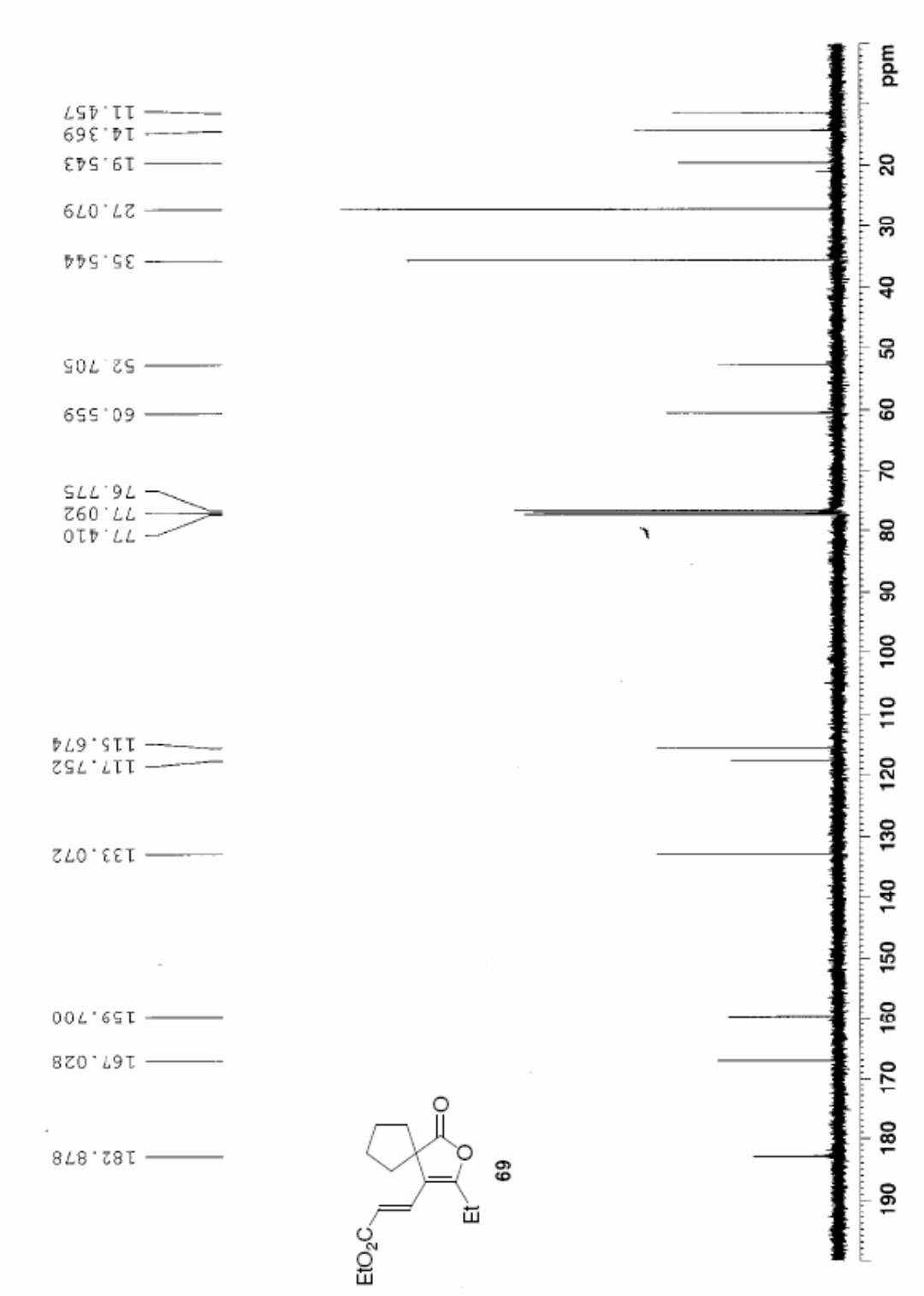

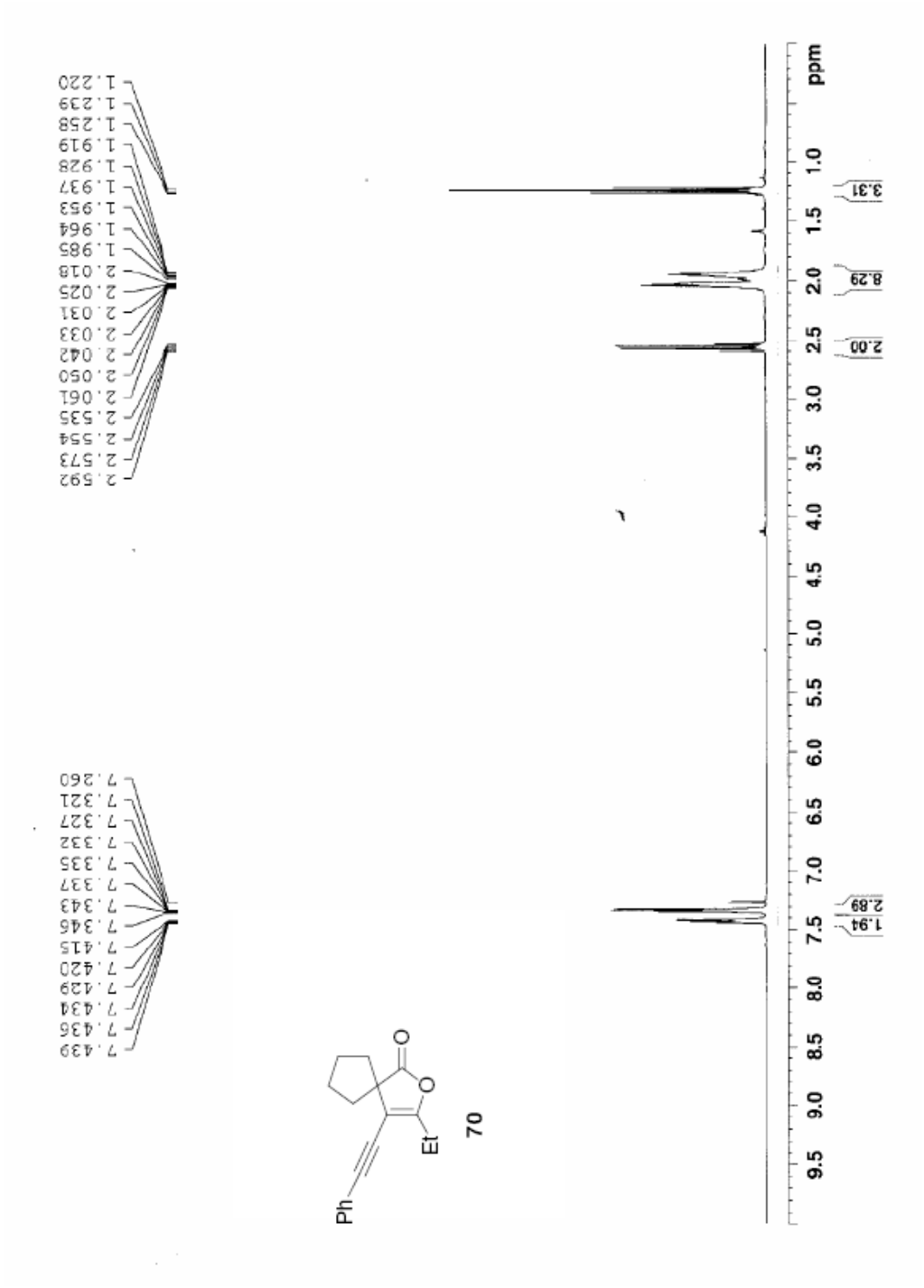

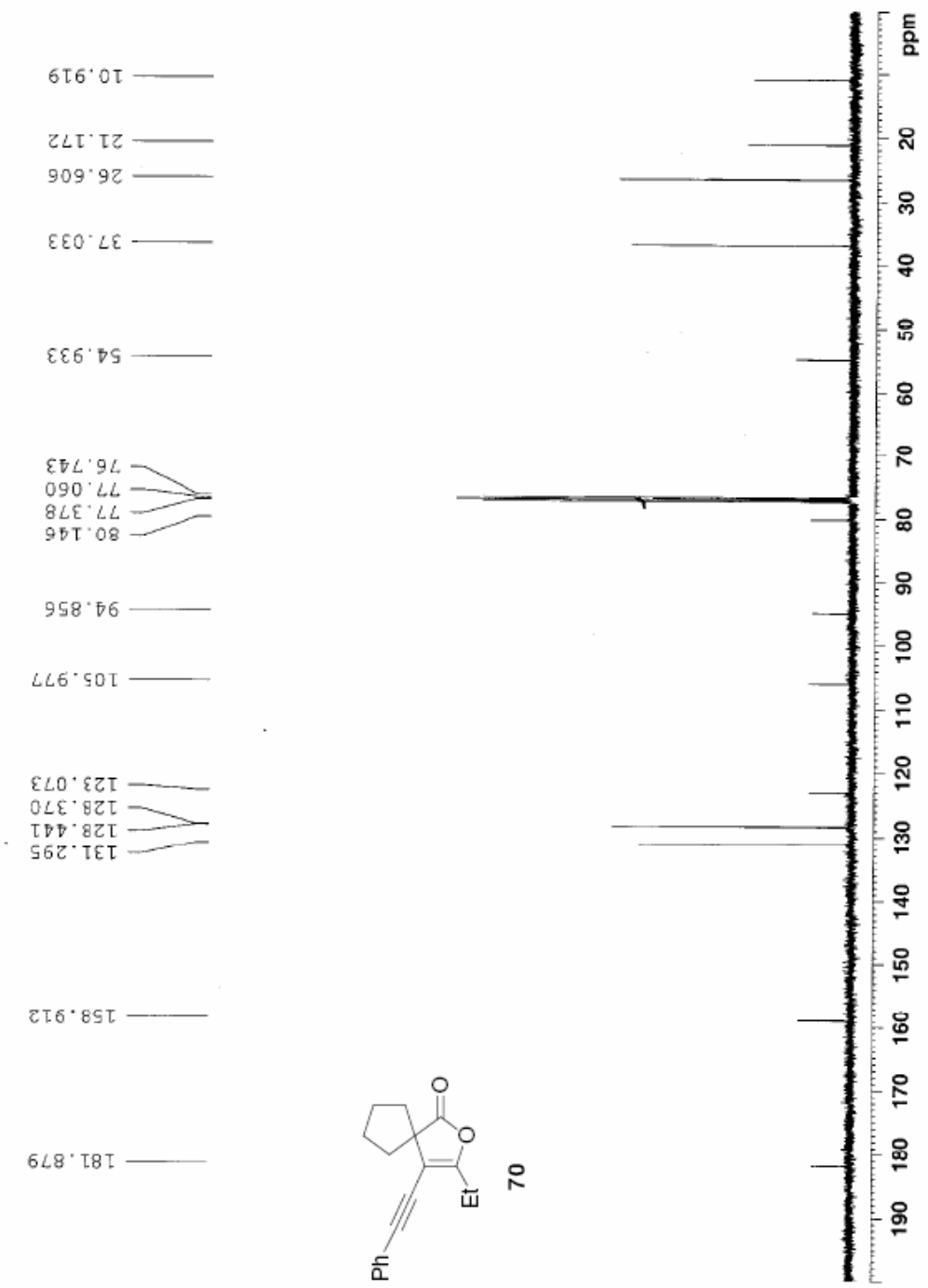

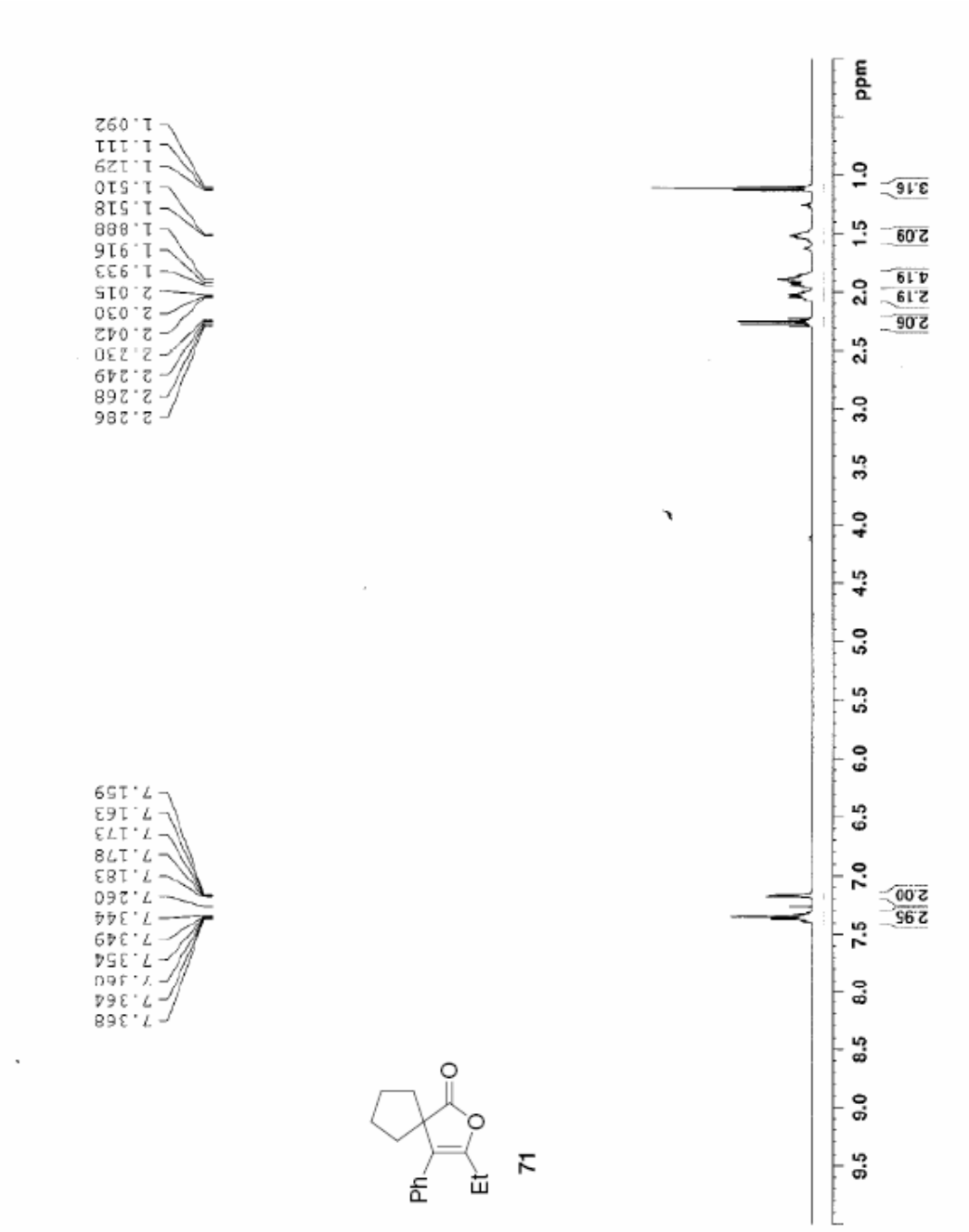

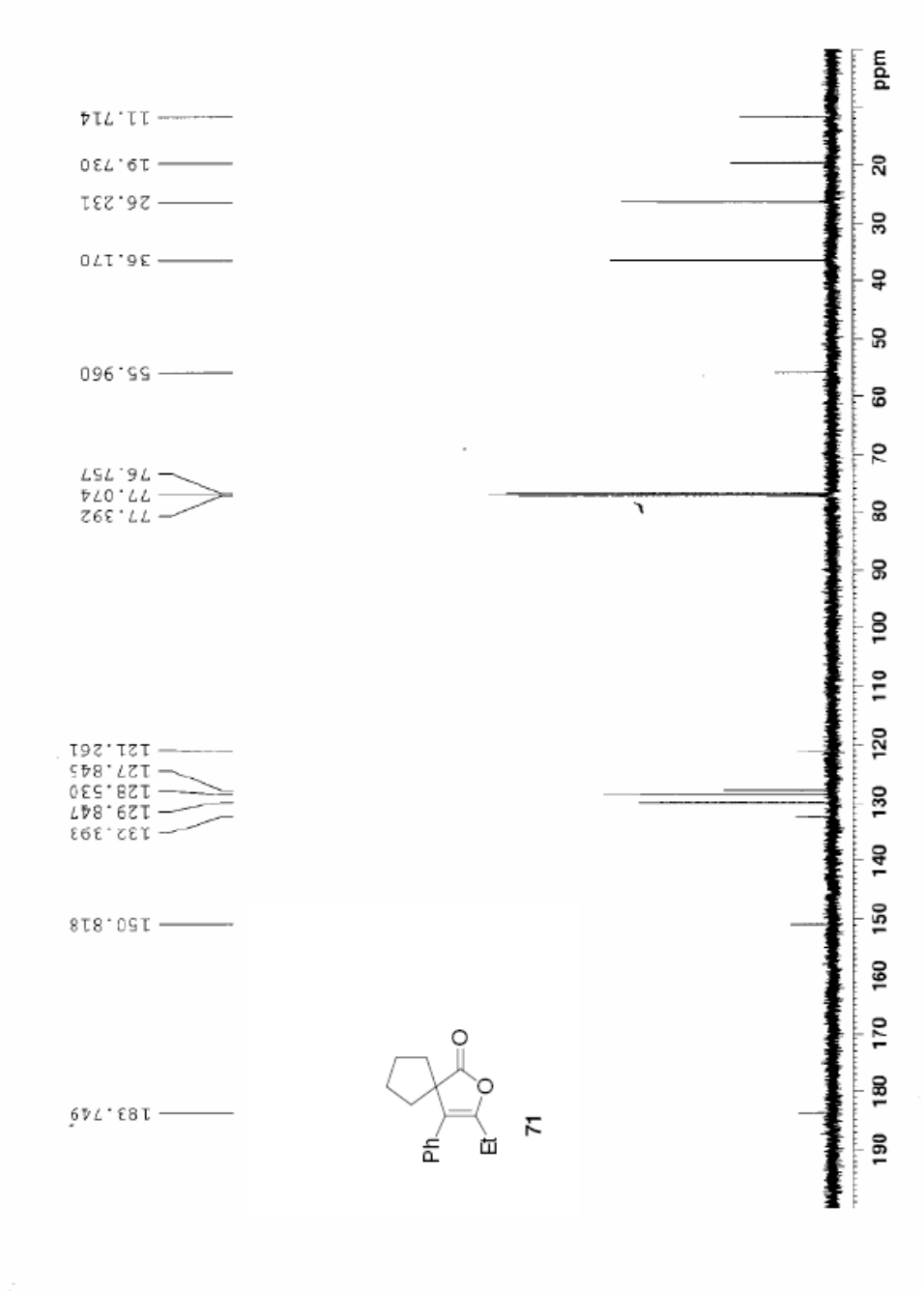

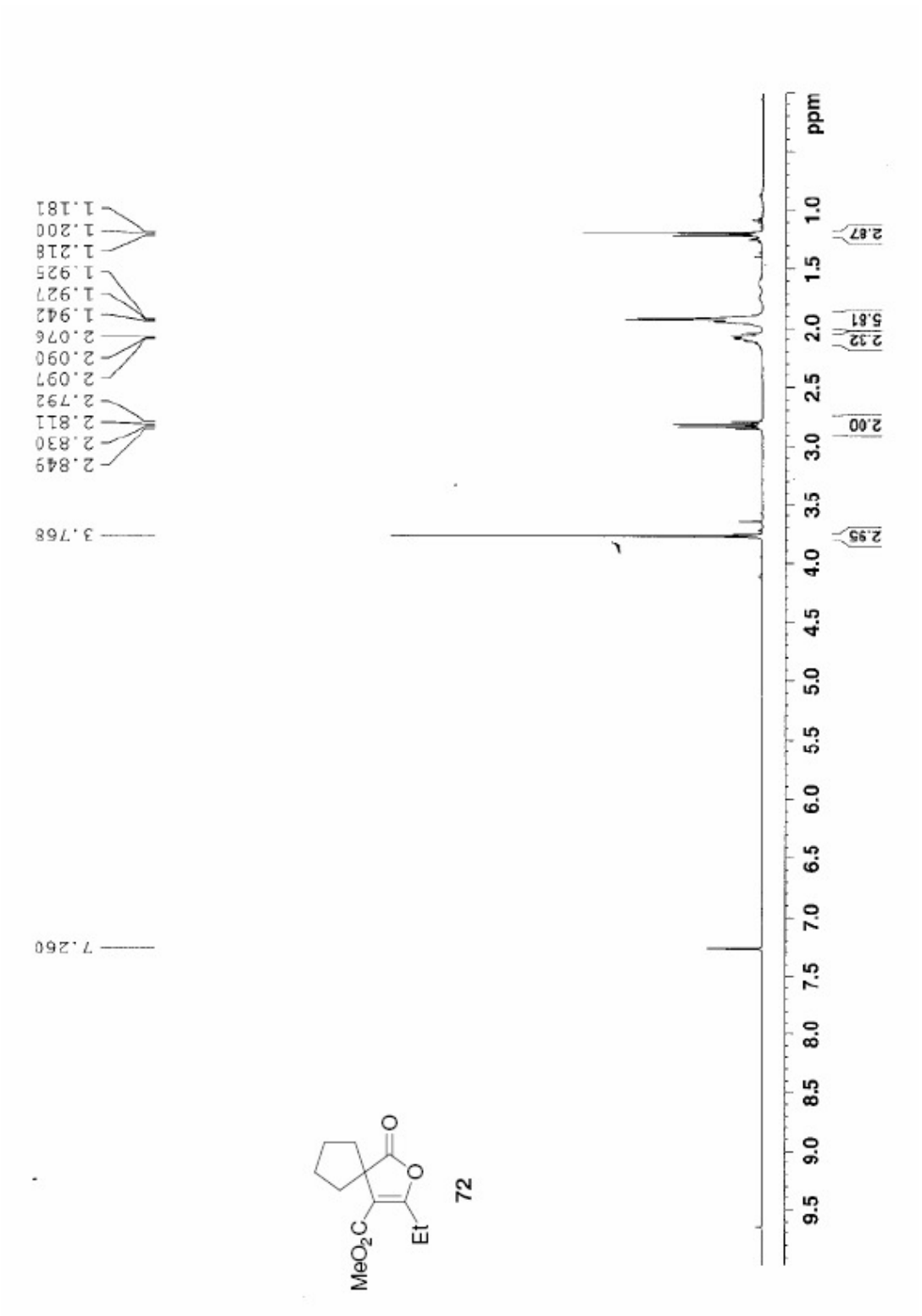

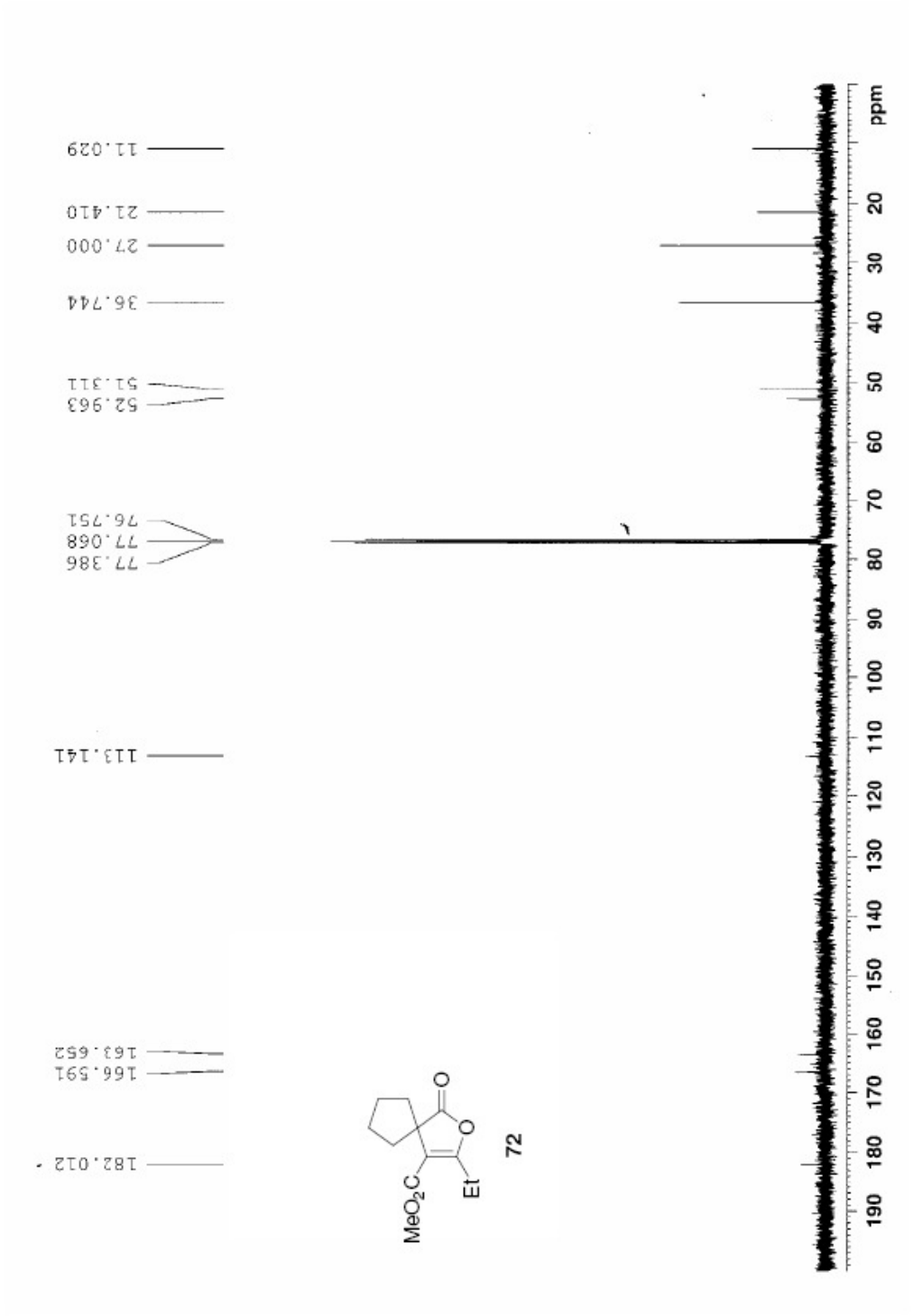

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