

Synthesis of dihydrobenzofurans via palladium-catalyzed heteroannulations

by

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This is to certify that the doctoral dissertation of

Roman Vladimirovich Rozhkov

has met the dissertation requirements of Iowa State University

Major Professor

For the Major Program

To my wife Elena and my son Nikita.

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LIST OF ABBREVIATIONS

aq	aqueous
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
cat.	catalytic
calcd	calculated
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
dppe	1,2- <i>bis</i> (diphenylphosphino)ethane
dppf	1,1'- <i>bis</i> (diphenylphosphino)ferrocene
dq	doublet of quartets
dt	doublet of triplets
eq	equation
equiv	equivalent
Et	ethyl
h	hours
HRMS	high resolution mass-spectroscopy
Hz	Hertz
IR	infrared

m	multiplet
Me	methyl
mL	milliliters
mol	mole(s)
mp	melting point
NMR	nuclear magnetic resonance
<i>o</i>	ortho
Ph	phenyl
q	quartet
s	singlet
soln	solution
t	triplet
TBAC	tetra- <i>n</i> -butylammonium chloride
TMS	trimethylsilyl

GENERAL INTRODUCTION

The palladium-catalyzed heteroannulations are of a great utility for organic synthesis. These transformations are very general, regio- and stereoselective and allow a rapid assembly of fairly complex heterocyclic systems. Importantly, palladium-catalyzed transformations tolerate moisture, oxygen and a wide variety of functional groups.

During last 20 years the Larock research group has developed a number of new palladium-catalyzed annulations of alkenes, alkynes and dienes. This dissertation is focused on the development of heteroannulations of 1,3-dienes by various vinyl- and aryl iodides and application of this methodology for the synthesis of natural products and their close analogues. This dissertation is organized into four different chapters that are published or will be published shortly. The author of the dissertation is a primary investigator and author of each of the papers reported in the thesis.

Dissertation organization

This dissertation is divided into four chapters. Each of the chapters is written according to the guidelines for a full paper in the *Journal of Organic Chemistry* and is composed of an abstract, introduction, results and discussion, conclusions, experimental, acknowledgments, and references.

Chapter 1 describes the palladium-catalyzed annulation of 1,3-dienes by vinylic halides. The presence of a β -hydrogen in the vinylic halide results in β -hydride elimination giving the corresponding alkyne. The presence of a bulky group in the α -position of the vinylic halide results in failure or deceleration of the annulation. Despite the limited scope, our studies provides a deeper insight into this process.

Chapter 2 is a publication that presents a synthesis of biologically active dihydrofurocoumarins via palladium-catalyzed heteroannulation of 1,3-dienes by *o*-iodoacetoxycoumarins. Preliminary studies using *o*-iodophenols revealed a major problem with rapid dehalogenation. To solve this problem, we have developed “optimal” reaction conditions using acetoxy derivatives. This reaction is very general, regio- and stereoselective, and a wide variety of terminal, cyclic and internal 1,3-dienes can be utilized. Derivatization of the annulation products provides an efficient approach to numerous analogues of natural products.

Chapter 3 is focused on synthesis of dihydrofuroflavonoids via palladium-catalyzed annulation of 1,3-dienes. Dihydrofuroflavonoids occur commonly in plants and fruits and are very important because of their pronounced biological properties. Despite significant interest, no efficient, general method for the synthesis of dihydrofuroflavonoids has really been developed. Our annulation methodology provides a convenient and efficient approach to a wide variety of functionalized flavonoids.

Chapter 4 concerns synthesis of dihydrobenzofurans via palladium-catalyzed annulation of 1,3-dienes. The annulation of electron-rich *o*-iodophenols in earlier studies has been quite problematic due to the undesired dehalogenation. The application of our methodology led to the development of an efficient and general approach to dihydrobenzofurans. This reaction is very general, regioselective, stereoselective and a wide variety of terminal, cyclic and internal 1,3-dienes as well as electron-rich and electron deficient *o*-acetoxyiodobenzenes can be utilized.

Finally, all of the ^1H and ^{13}C NMR spectra for the starting materials and annulation products are compiled in appendices A-D.

CHAPTER 1. PALLADIUM-CATALYZED HETEROANNULATION OF 1,3-DIENES BY VINYLIC HALIDES

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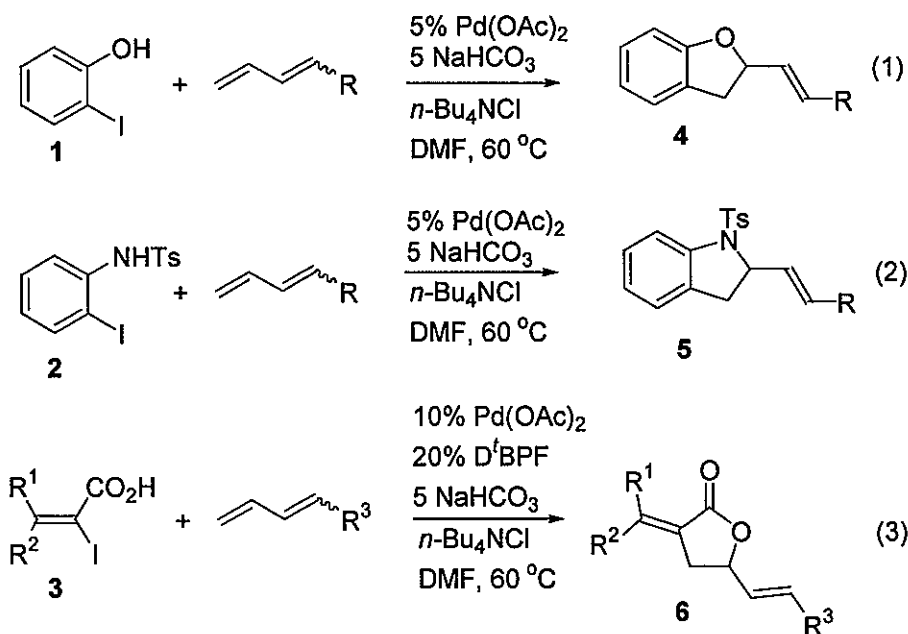
Abstract

Palladium-catalyzed heteroannulation of 1,3-dienes with 3-iodo-2-alkenols, and 2-iodo-2-alkenols, as well as their amino analogs, affords the corresponding cyclic ethers and amines respectively. The presence of a β -hydrogen in the vinylic halide results in β -hydride elimination giving the corresponding alkyne. The presence of a bulky group in the α -position of the vinylic halide results in failure or reduced amounts of annulation products. A chloride source, pyridine base and electron-rich phosphine are essential for this reaction.

Introduction

Annulation processes are among the most efficient transformations in organic synthesis.¹ We have recently developed in our laboratories annulations of 1,3-dienes using *o*-iodophenols (**1**),² *o*-iodoanilines (**2**)³ and α -iodoalkenoic acids (**3**),⁴ which allow an efficient approach to heterocycles **4**, **5** and **6** respectively (eqs 1-3). This reaction proceeds through oxidative addition of the aryl or vinylic halide to Pd(0), followed by 1,2-addition to the 1,3-

diene and formation of a stable π -allylpalladium complex. The next step involves coordination of the palladium to the hydroxyl or amino group present in the π -allylpalladium moiety, followed by the reductive elimination. Herein, we report the palladium-catalyzed annulation of 1,3-dienes by certain other functionally-substituted vinylic halides.



Results and Discussion

Initially we selected vinylic halide **7** and 1,3-cyclohexadiene as model substrates for our optimization work. According to our previous results, the best reaction conditions for the annulation of 1,3-dienes by *o*-iodophenols are *o*-iodophenol (0.5 mmol), diene (2.5 mmol), Pd(OAc)₂ (0.025 mmol), Na₂CO₃ (1.0 mmol), LiCl (0.5 mmol), DMF (5 mL) as a solvent at 100 °C for 3 d (eq 1).² Unfortunately, under these conditions the reaction failed to give any of the desired annulation product and 90 % of the starting material was recovered. When the temperature was raised to 120 °C, only traces of the desired *cis*-product **8** were isolated (Table 1, entry 1). The addition of triphenylphosphine (15 mol %) gave ether **8** in a 5 % yield and Heck-products **9** and **10** in a combined 10 % yield (entry 2).

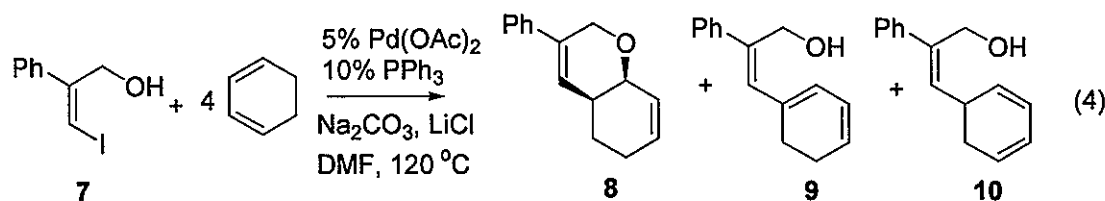


Table 1. Optimization.^a

entry	catalyst	phosphine, (mol%)	% yield of 8	% yield of 9+10	% recovery of 7
1	$\text{Pd}(\text{OAc})_2$	-	trace	-	30
2	$\text{Pd}(\text{OAc})_2$	15	6	10	26
3	$\text{Pd}(\text{dba})_2$	10	10	13	15
4	$\text{Pd}(\text{PPh}_3)_4$	-	14	16	15
5	$\text{PdCl}_2(\text{PPh}_3)_2$	-	4	trace	15

^aReaction conditions: vinylic iodide **7** (0.5 mmol), 1,3-cyclohexadiene (2.0 mmol), palladium catalyst (5 mol %, 0.025 mmol), LiCl (0.5 mmol), DMF (5 mL), 120°C , 24 h.

Next we examined the effect of various palladium(II) catalysts on the annulation reaction (Table 1). Although $\text{Pd}(\text{PPh}_3)_4$ gave the best yield (entry 4), separation of the annulation product was complicated by the presence of numerous side products. Moreover, the presence of four strongly coordinated ligands on the palladium atom retards formation of the presumed reactive $\text{Pd}(\text{PPh}_3)_2$ intermediate and limits the possibility of utilizing other phosphine ligands. As one can see from Table 1, the presence of the phosphine increases the yield of the annulation product.

Then we investigated the effect of the phosphine on the annulation reaction (Table 2). As one can see from Table 2 (entries 1-4), an increase in the phosphine concentration does not significantly effect the yield of the desired product **8**. According to recent reports,

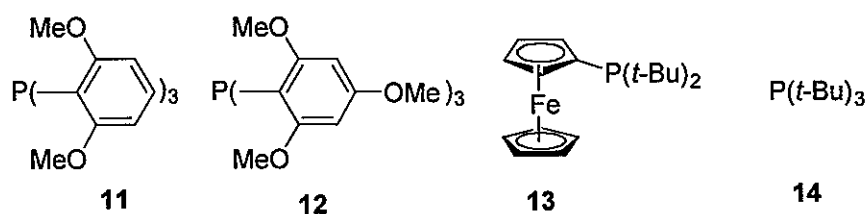


Figure 1. Phosphine ligands.

Table 2. Effect of Phosphine.^a

entry	catalyst	phosphine	% yield of 8	% yield of 9+10	% recovery of 7
1	Pd(dba) ₂	10% PPh ₃	8	13	16
2	Pd(dba) ₂	15% PPh ₃	10	15	20
3	Pd(dba) ₂	20% PPh ₃	10	30	32
4	Pd(dba) ₂	25% PPh ₃	14	20	17
5	Pd(OAc) ₂	15% 11	10	14	30
6	Pd(OAc) ₂	15% 12	12	18	25
7	Pd(OAc) ₂	15% 13	7	15	20
8	Pd(OAc) ₂	15% 14	trace	trace	45
9	Pd(dba) ₂	10% 11	9	9	25
10	Pd(dba) ₂	10% 12	16	10	46
11	Pd(dba) ₂	10% 13	15	10	18
12	Pd(dba) ₂	10% 14	trace	trace	41

^aReaction conditions: vinylic iodide **7** (0.5 mmol), 1,3-cyclohexadiene (2.0 mmol), palladium catalyst (5 mol %, 0.025 mmol), LiCl (0.5 mmol), DMF (5 mL), 120 °C, 24 h.

the electron rich and sterically hindered phosphines **11-14** greatly increase the rate of oxidative addition of vinylic and aryl halides to palladium(0) and prevent undesired

chelation.⁵ According to our results, phosphine **12** gives the best results with both Pd(OAc)₂ and Pd(dba)₂ (entries 6 and 10). We have also found that Pd(dba)₂ works better than Pd(OAc)₂ for most of the studied phosphines (entries 5-8 versus entries 9-12).

The choice of base can often play an important role at various stages of organopalladium reactions. First, it promotes the elimination of HI and generation of the palladium(0) complex. Second, the base should deprotonate the hydroxyl group in our reaction and activate it towards nucleophilic attack on the π -allylpalladium complex. Therefore, in our next set of optimizations, the effect on a yield of a wide range of organic and inorganic bases was investigated (Fig. 2). As one can see from Table 3, the base has a dramatic effect on this reaction and the organic bases give a better yield of the product **8** than the inorganic bases. This is presumably due to the ability of the pyridine bases to act as both a base and a ligand. In fact, removal of the phosphine from the reaction mixture results in only a slight decrease in the annulation yield (entries 8 and 9). The presence of sterically demanding groups in positions C-2 and C-6 of the pyridine ring inhibits coordination of the pyridine to the palladium and decreases the annulation yield (entries 10 and 11). Removal of the chloride source results in a sharp decrease in the reaction yield (entry 12). On the other hand, the substitution of LiCl for *n*-Bu₄NCl (entry 13) does not effect the annulation yield significantly. This indicates that the nature of the cation is not important for this reaction. Presumably, the chloride anion prevents undesired chelation and, therefore, increases the

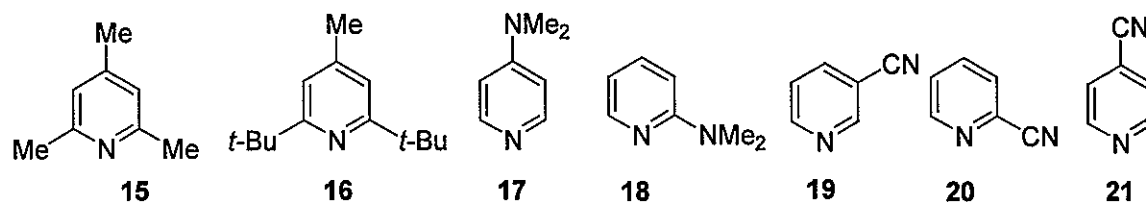


Figure 2. Pyridine bases.

Table 3. Effect of the base.^a

entry	base	% yield of 8	% yield of 9+10	% recovery of 7
1	Na ₂ CO ₃	16	10	46
2	K ₂ CO ₃	8	7	10
3	NaHCO ₃	13	7	34
4	KHCO ₃	5	6	28
5	NEt ₃	23	6	23
6	EtN(<i>i</i> -Pr) ₂	35	7	54
7	Py	52	6	40
8 ^b	Py	60	7	10
9 ^{b,c}	Py	50	6	4
10 ^{b,c}	15	40	15	7
11 ^{b,c}	16	36	25	10
12 ^{b,d}	Py	15	trace	50
13 ^{b,e}	Py	63	trace	trace
14 ^{b,c}	PhNMe ₂	53	trace	5
15	17	34	trace	30
16	18	48	trace	8
17 ^b	imidazole	10	trace	70
18	19	70	trace	trace
19	20	65	trace	trace
20	21	63	trace	trace
21 ^{b,f}	19	45	trace	25
22 ^{b,g}	19	43	trace	trace

^aReaction conditions: vinylic iodide **7** (0.5 mmol), 1,3-cyclohexadiene (2.0 mmol), Pd(dba)₂ (5 mol %, 0.025 mmol), phosphine (5 mol %, 0.05 mmol), base (0.75 mmol), LiCl (0.5 mmol), DMF (5 mL), 120 °C, 24 h. ^bThe reaction time was increased to 48 h. ^cNo phosphine was added. ^dNo chloride source was added. ^e*n*-Bu₄NCl was used as a chloride source. ^fThe temperature was decreased to 80 °C. ^gThe temperature was decreased to 100 °C.

reactivity of the vinylic palladium intermediate. The use of *N,N*-dimethylaniline (entry 14), which has a basicity similar to pyridine, gives a yield similar to the unsubstituted pyridine (entry 9).

The use of electron-rich 2- and 4-(dimethylamino)pyridines (entries 15 and 16) decreases the yields of the annulation reactions to 34 and 48% respectively. Highly basic imidazole (entry 17) inhibits the reaction. Pyridines with an electron-withdrawing substituent are superior among all investigated bases (entries 18-20) and 3-cyanopyridine is the most effective base among all the bases investigated.

The high temperature employed in this reaction can cause evaporation of the 1,3-diene and thermal decomposition of the vinylic halide and the product of the annulation. But when we decreased the temperature to 80 and 100 °C (entries 21 and 22), the reaction slowed down and the yield dropped from 70% to 45% and 43% respectively. After optimization of the base, we again optimized the phosphine ligand employed with 3-cyanopyridine (Table 4).

It can be seen from Table 4 that variation of the ligand does not improve the yield of the annulation product. The yields in entries 1-4 are similar to the yield of the reaction without any phosphine (Table 3, entry 9). Bidentate ligands, such as dppe and phenanthraline (entries 5 and 6), inhibit the annulation process. Based on these results, our “optimal” conditions for the annulation reaction (Table 3, entry 18) are vinylic halide (0.5 mmol), 1,3-diene (2.0 mmol), Pd(dba)₂ (5 mol %, 0.025 mmol), phosphine **12** (10 mol %), 3-cyanopyridine (0.75 mmol), LiCl (0.5 mmol), 5 mL of DMF at 120 °C for 24 h (eq. 5).

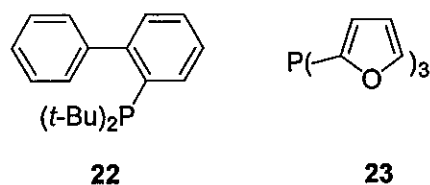
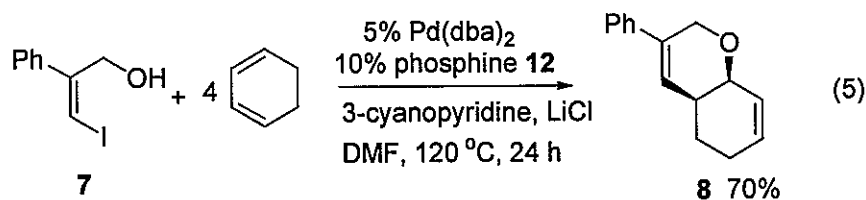


Figure 3. Phosphine ligands.

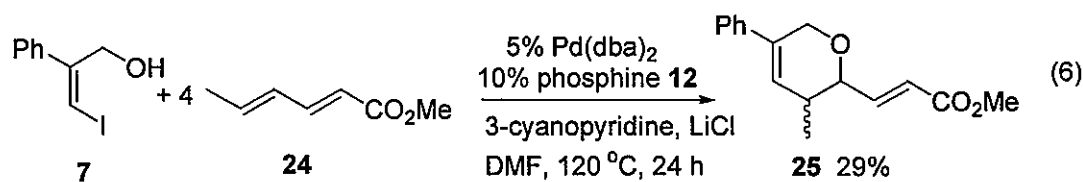
Table 4. Optimization of the phosphine ligand with 3-cyanopyridine.^a

entry	ligand	% yield of 8	% yield of 9+10	% recovery of 7
1	13	53	15	10
2	22	54	13	16
3	23	60	trace	traces
4	PPh ₃	53	trace	10
5	dppe	5	trace	75
6	1, 10-phenanthroline	-	-	90

^aReaction conditions: vinylic iodide **7** (0.5 mmol), 1,3-cyclohexadiene (2.0 mmol), Pd(dba)₂ (5 mol %, 0.025 mmol), ligand (10 mol %, 0.05 mmol), LiCl (0.5 mmol), 3-cyanopyridine (0.75 mmol), DMF (5 mL), 120 °C, 24 h.



Next, the annulation of various 1,3-dienes using the model vinylic halide **7** was investigated. The annulation of methyl 2,4-hexadienoate (**24**) gives the desired product **25** in only a 29% yield (eq. 6).



Unfortunately, dienes **26-37** (Figure 4) do not undergo the desired annulation by vinylic iodide **7** and only trace amounts of vinylic halide **7** was recovered.

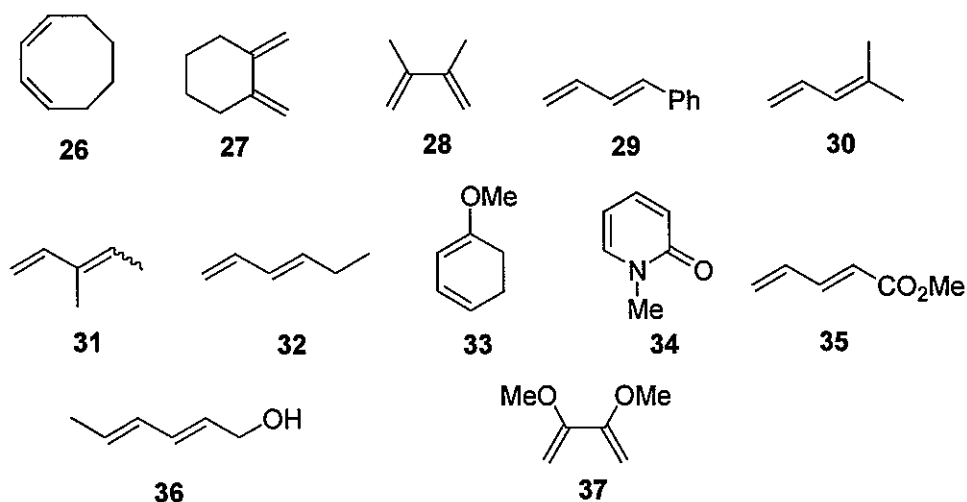


Figure 4. 1,3-Dienes investigated.

Since very few 1,3-dienes have been successful in this process, we investigated the annulation of 1,3-cyclohexadiene with various other vinylic halides. The introduction of a sterically hindered trimethylsilyl or phenyl group in the C-3 position of the 3-iodo-2-propenols **38-42** results in a complete failure of the annulation reaction. Vinylic halide **43** does not give the desired annulation product, although the starting material completely disappeared within 24 h. This is, presumably, due to rapid palladium β -hydride elimination of corresponding vinylpalladium complexes rather than addition to the 1,3-diene. This suggestion has been confirmed when the annulation of vinylic halide **44** gave β -hydride elimination product 3-phenyl-2-propynol in a 45% yield. The annulation of 1,3-cyclohexadiene by vinylic bromide **45** or triflate **46** does not give the desired product and

over 60% of the corresponding starting material was recovered. This could be due to the low reactivity of the vinylic triflates and bromides in the oxidative addition process under our reaction conditions.

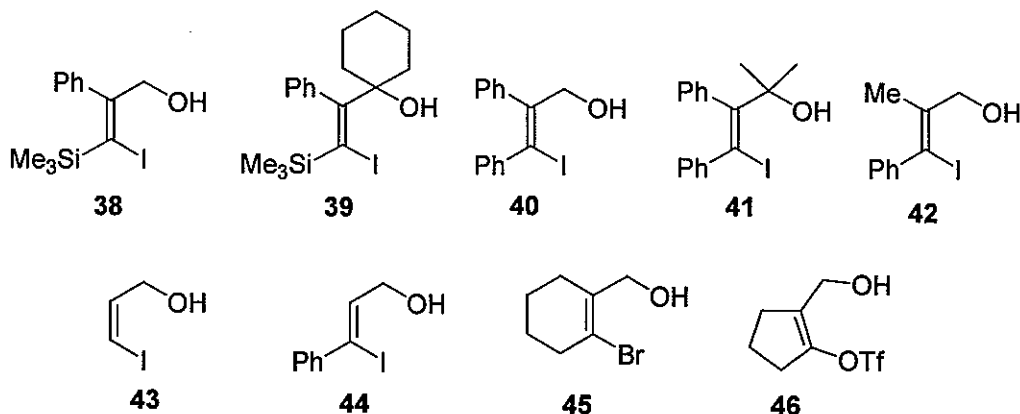
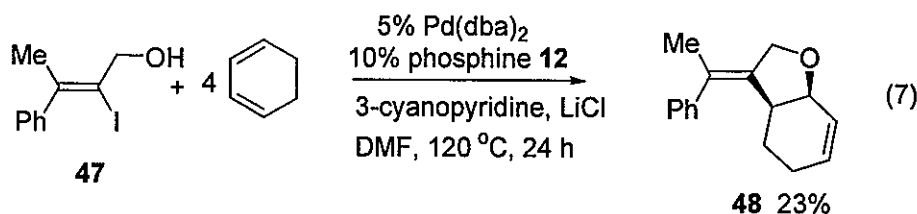


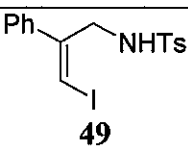
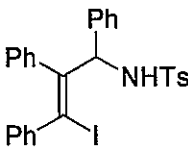
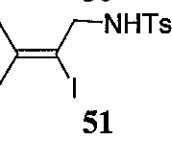
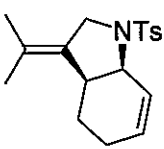
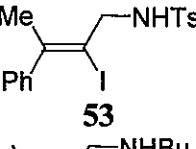
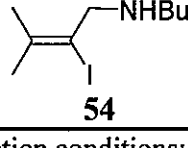
Figure 5. Vinylic halides investigated.

One can assume that 2-iodo-2-alkenols will react more readily than 3-iodo-2-alkenols due to the more favorable formation of a 5-membered ring over a 6-membered ring. In fact, vinylic halide **47** gives the corresponding annulation product **48** in a 23% yield (eq 7).



Since intramolecular nucleophilic attack of the internal nucleophile on the π -allylpalladium intermediate is an important step in our annulation, the reaction rate can be presumably enhanced by increasing the nucleophilicity of the group displacing the palladium moiety. Therefore, we substituted an amino group for the hydroxyl group and investigated the annulation of 1,3-cyclohexadiene with 2- and 3-iodo-2-alkenamine derivatives (Table 5).

Table 5. Annulation 1,3-Cyclohexadiene by Vinylic Halides.^a

entry	vinylic halide	base	phosphine	% yield of the product	% starting material recovered
1	 49	12	19	0	0
2		12	-	0	0
3		Na ₂ CO ₃	19	0	0
4		NaHCO ₃	19	0	0
5		NaOAc	19	0	0
6		NEt ₃	19	0	0
7	 50	12	19	0	55
8	 51	12	19	 52, 31%	23
9	 53	12	19	0	25
10	 54	12	19	0	20

^aReaction conditions: vinylic iodide (0.5 mmol), 1,3-cyclohexadiene (2.0 mmol), Pd(dba)₂ (5 mol %, 0.025 mmol), phosphine **12** (10 mol %), LiCl (0.5 mmol), 3-cyanopyridine (0.75 mmol), DMF (5 mL), 120 °C, 48 h.

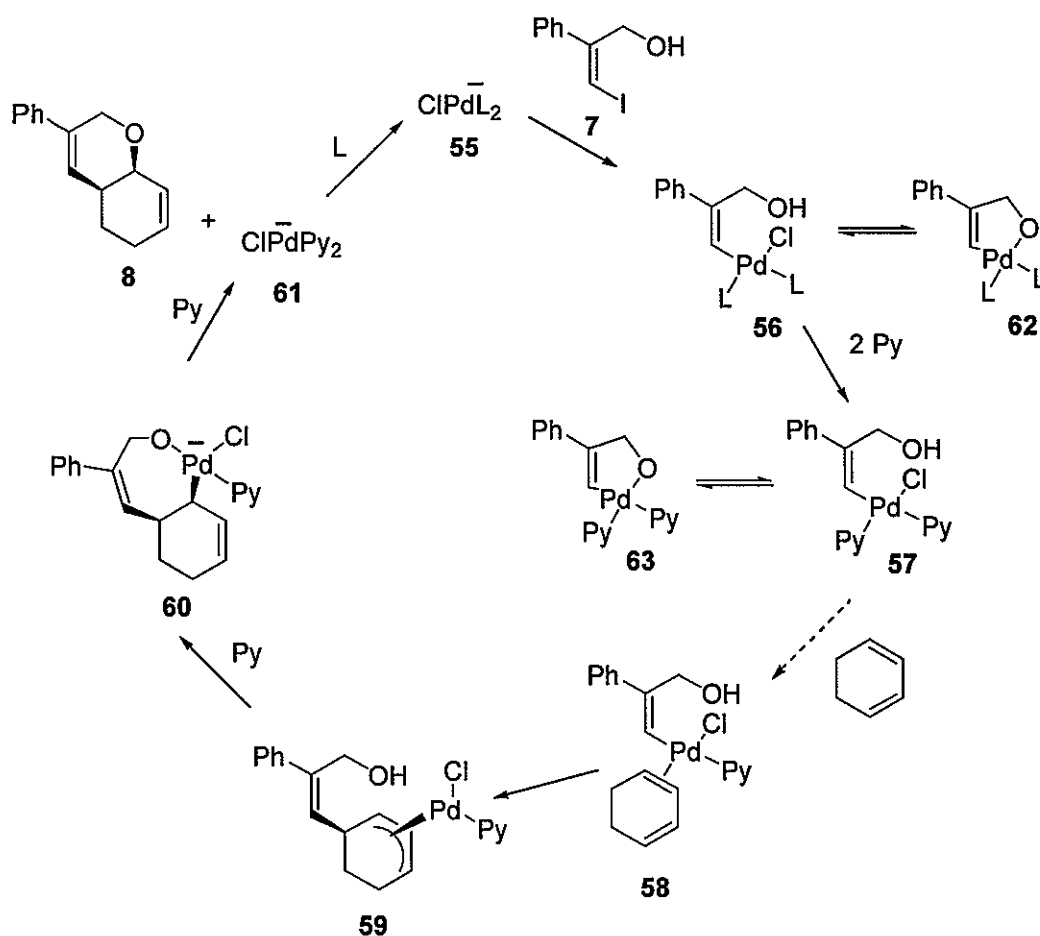
Unfortunately, tosylamide **49** does not affect the annulation of 1,3-cyclohexadiene (entry 1).

Several attempts to optimize reaction conditions by employing various bases or removing the

phosphine ligand failed (entries 1-6). Annulation using more sterically hindered tosylamide **50** failed as well. Only tosylamide **51** gives the desired product **52** in a 31% yield. This can be rationalized by kinetically favorable formation of the 5-membered ring compared to a 6-membered ring. The annulation using vinylic halides **53** and **54** does not result in the formation of any of the expected annulation products.

A proposed mechanism for this annulation process, based on our experimental results and previously reported mechanistic investigations of palladium-catalyzed reactions by Amatore⁶ and Crisp⁷, is shown in Scheme 1. The process starts with oxidative addition of the vinylic halide **7** to anionic palladium intermediate **55** formed *in situ*, which affords complex **56**. The positive effect of pyridine can be explained by reversible displacement of phosphine ligands by pyridine and formation of a less sterically hindered and more reactive intermediate **57** towards insertion of 1,3-diene. Coordination of 1,3-cyclohexadiene to the intermediate **57** gives complex **58**, which then undergoes alkene insertion to produce first a σ -allylpalladium complex and then π -allylpalladium complex **59**. Next, coordination of the oxygen atom to the palladium center gives complex **60**. After reductive elimination, the final product **8** and anionic intermediate **61** are formed. Front-side attack on the palladium center is confirmed by the presence of *cis*-stereochemistry in the final product **8**. Finally, the anionic intermediate **61** undergoes exchange of a pyridine ligand by phosphine and eventually regenerates the anionic complex **55**, which is presumed to be more reactive towards oxidative addition. This is consistent with a 15-20% decline in the yield when phosphine is removed from the reaction. The presence of a chloride source is essential for the formation of reactive intermediate **55** and prevention of intramolecular chelation that generates less reactive complexes like **62** and **63**.

Scheme 1



Conclusions

The palladium-catalyzed heteroannulation of 1,3-dienes by 2- and 3-iodo-2-propenols and their amino-analogs gives corresponding cyclic ethers and amines. The reaction proceeds with good stereoselectivity and affords in most cases *cis*-product. Unfortunately, this heteroannulation process lacks generality and, therefore, its usefulness for practical purposes is limited to 1,3-cyclohexadiene and several less hindered vinylic halides. There are also some limitations on the vinylic halide. For example, the presence of a hydrogen atom in the β -position of the vinylic halide results in β -hydride elimination that gives the

corresponding alkynes. Sterically demanding groups on the vinylic halide lead to complete inhibition of this reaction.

EXPERIMENTAL SECTION

General. All ^1H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz respectively. Thin layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was performed with UV light (254 nm) and an acidic KMnO_4 solution.

Reagents. All reagents were used directly as obtained commercially, unless otherwise noted. Pyridine, DMF, DMA, THF, hexanes, ethyl acetate, chloroform and ethyl ether were purchased from Fisher Scientific. The palladium reagents $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_4$, and $\text{PdCl}_2(\text{PPh}_3)_2$ were donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. Phosphines **11**, **12**, and **23**, pyridines **15-21** and the 1,3-dienes 1,3-cyclohexadiene, **24**, **26-28**, **30-37** were purchased from Aldrich Chemical Co. Inc. Phosphines **13**, **14**, and **22** were purchased from Strem Chemical Co. Inc. The palladium catalyst $\text{Pd}(\text{dba})_2$,⁸ 1,3-diene **29** and vinylic halides **7**,⁹ **38**,¹¹ **39**,¹⁰ **40**,⁹ **41**,¹² **42**,⁹ **43**,¹³ **44**,⁹ **45**,¹⁴ **46**,¹⁵ **47**,¹⁶ **49**,¹⁶ **50**,¹⁶ **51**,¹⁶ **52**,¹⁶ **53**,¹⁶ **54**¹⁶ were prepared according to literature procedures. A better overall yield of the vinylic halide **7** was achieved by adding phenylmagnesium bromide to 3-(trimethylsilyl)propargylic alcohol,¹⁷ followed by quenching with I_2 and subsequent desilylation.¹⁸

General procedure for the Pd-catalyzed annulation of 1,3-dienes by vinylic halides.

The vinylic halide (0.5 mmol), $\text{Pd}(\text{dba})_2$ (5 mol %, 0.025 mmol), phosphine ligand **12** (10 mol %), LiCl (0.5 mmol), 3-cyanopyridine (0.75 mmol) and DMF (5 mL) were stirred in a

capped vial for 5 min, and then the 1,3-diene (2.0 mmol) is added. The resulting reaction mixture is stirred at 100 °C for 24 h, cooled to room temperature, diluted with ethyl ether and then washed with satd aq NH₄Cl. The ethyl ether is evaporated and the resulting residue is purified by column chromatography using silica gel as a solid phase and 8:1 hexanes/ethyl acetate as the eluent to afford after solvent removal the final product. The following new compounds have been prepared using this procedure.

***cis*-3-Phenyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran (8).** Obtained in a 70% overall yield, recrystallized from 1:1 ethanol/water: white solid, mp 75-76 °C; ¹H NMR (CDCl₃) δ 1.50-2.35 (m, 5H), 3.90-4.10 (m, 1H), 4.53 (d, *J* = 15.8 Hz, 1H), 4.57 (d, *J* = 15.8 Hz, 1H), 5.80-5.95 (m, 1H), 6.00-6.10 (m, 1H), 6.15 (d, *J* = 2.8 Hz, 1H), 7.30-7.40 (m, 5H); ¹³C NMR (CDCl₃) δ 24.8, 25.6, 34.9, 67.1, 69.1, 125.1, 126.1, 126.2, 127.7, 128.7, 133.3, 136.1, 138.4; IR (neat) 3022, 1595 cm⁻¹; elemental analysis: found C, 85.44; H, 7.86 (calcd for C₁₅H₁₆IO, C, 84.87; H, 7.60).

6-(*E*-2-*trans*-Carbomethoxyethenyl)-5-methyl-3-phenyl-5,6-dihydro-2H-1-pyran (25). Obtained in a 29% overall yield, yellow oil: ¹H NMR (CDCl₃) δ 0.99 (d, *J* = 5.4 Hz, 3H), 2.40-2.50 (m, 1H), 3.77 (s, 3H), 4.36 (s, 1H), 4.57 (d, *J* = 15.8 Hz, 1H), 4.67 (d, *J* = 15.8 Hz, 1H), 6.17 (d, *J* = 16.0 Hz, 1H), 6.21 (d, *J* = 5.4 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 7.30-7.50 (m, 5H). The amount of this material obtained was insufficient for further analysis.

***cis*-3-(*E*-1-Phenylethylidene)-2,3,3a,4,5,7a-hexahydrobenzofuran (48).** Obtained in a 23% overall yield, yellow oil; ¹H NMR (CDCl₃) δ 1.20-1.40 (m, 4H), 1.90 (s, 3H), 2.65-2.75 (m, 1H), 4.19 (s, 1H), 4.42 (d, *J* = 9.6 Hz, 1H), 4.58 (d, *J* = 9.6 Hz, 1H), 5.80-5.90 (m, 1H),

5.95-6.00 (m, 1H), 7.20-7.50 (m, 5H); HRMS m/z 226.1360 (calcd for $C_{16}H_{18}O$, 226.1358).

The amount of this material obtained was insufficient for further analysis.

***cis*-3-Isopropylidene-1-*p*-toluenesulfonyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole (52).**

Obtained in a 31% overall yield, yellow oil: 1H NMR ($CDCl_3$) δ 1.52 (s, 3H), 1.58 (s, 3H), 1.90-2.15 (m, 2H), 2.42 (s, 3H), 2.52-2.64 (m, 1H), 4.42 (s, 1H), 3.65 (d, $J = 14.0$ Hz, 1H), 4.04 (d, $J = 14.0$ Hz, 1H), 5.95-6.05 (m, 1H), 6.10-6.20 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 21.0, 21.8, 24.1, 24.6, 40.8, 51.6, 57.6, 124.2, 125.3, 128.1, 128.6, 129.8, 130.7, 131.6, 143.6; HRMS m/z 318.1533 (calcd for $C_{18}H_{23}NO_2S$, 318.1528).

Scanned 1H and ^{13}C spectra for compounds **8**, **25**, **48**, and **52** are included in Appendix A (pp. 87-93).

Acknowledgments

We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of $Pd(OAc)_2$.

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**CHAPTER 2. AN EFFICIENT APPROACH TO DIHYDROFURO-
COUMARINS VIA PALLADIUM-CATALYZED ANNULATION OF 1,3-
DIENES BY *o*-IODOACETOXYCOUMARINS**

A paper submitted to the *Journal of Organic Chemistry*

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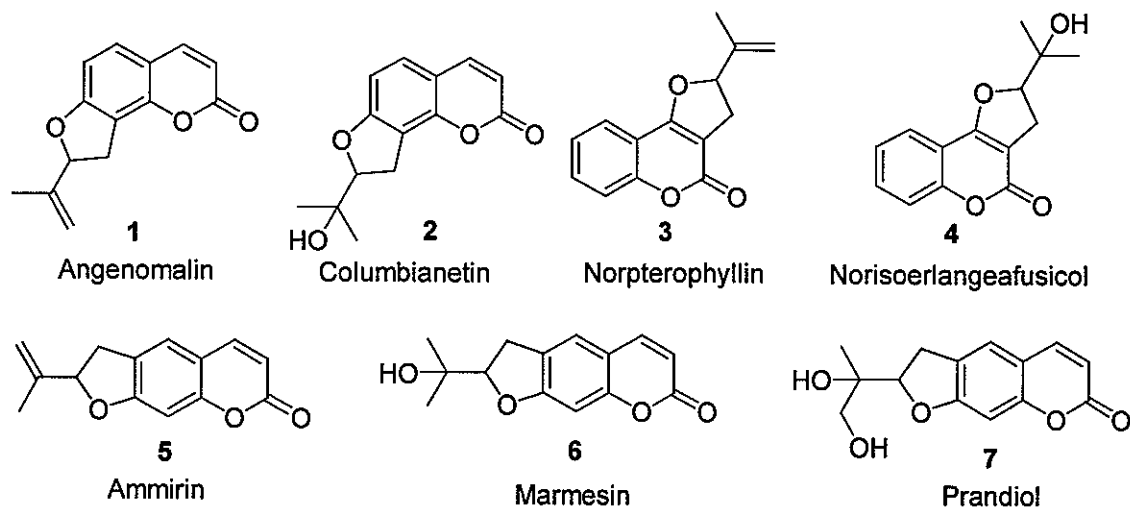
Abstract

The palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxycoumarins provides an efficient method for the synthesis of biologically interesting dihydrofurocoumarins. The presence of the acetyl group on the phenolic oxygen and the use of silver carbonate as a base are crucial for this process. This reaction is very general, regio- and stereoselective, and a wide variety of terminal, cyclic and internal 1,3-dienes can be utilized. Derivatization of the annulation products provides an efficient approach to numerous analogues of natural products.

Introduction

Dihydrofurocoumarins, such as compounds 1-7, are commonly occurring plant metabolites that exhibit pronounced biological properties.¹ Derivatives of columbianetin (2)

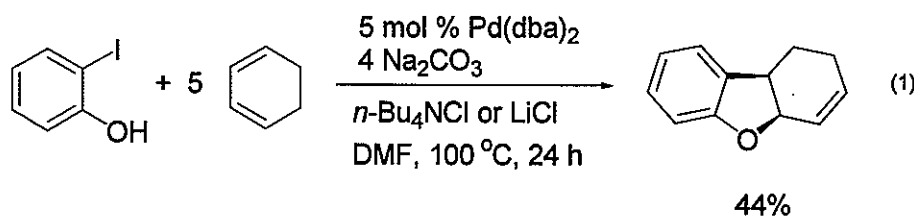
exhibit significant cytotoxicity against KB cells.² Derivatives of norpterophyllin (3) have high anticoagulant and antifungal activities.³ Marmesin (6) is an effective inhibitor of c-AMP synthetase⁴ and acetylcholinesterase,⁵ and prandiol (7) is an effective antidote against rattlesnake poison.⁶



Numerous attempts to synthesize dihydrofurocoumarins have been reported during the last 30 years. Early methods have involved multiple steps and generally suffer from low (2-20%) overall yields.⁷ Modern synthetic approaches involving the Claisen rearrangement of 7-(allyloxy)coumarins,⁸ the Sonogashira coupling of *o*-iodohydroxycoumarins with terminal alkynes,⁹ Ag(I)- and Ce(IV)-promoted oxidative cycloadditions of 4-hydroxycoumarin to alkenes and dienes,¹⁰ and the Rh(II)-catalyzed annulation of alkenes by 3-diazo-2,4-chromenediones¹¹ give 30-60 % overall yields, but these methods lack broad generality and, therefore, cannot be used for the synthesis of large libraries of biologically active dihydrofurocoumarins.

Palladium-catalyzed annulations developed in our laboratories have provided a versatile route for the construction of complex cyclic systems.¹² Previously we reported an efficient

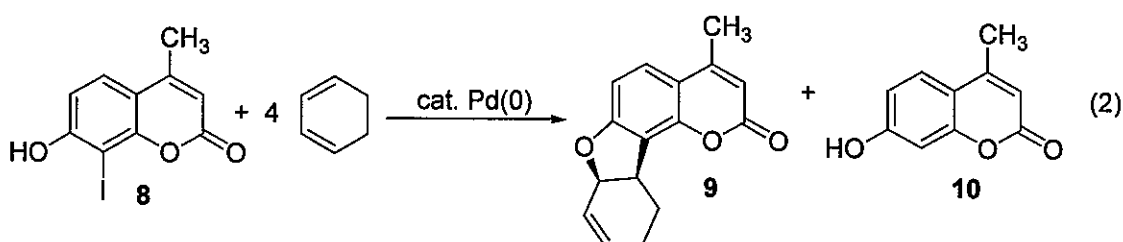
method for the synthesis of *cis*-dihydrobenzofurans by the palladium-catalyzed annulation of 1,3-dienes by *o*-iodophenols (eq 1).¹³ Recently we communicated a significantly modified procedure for the synthesis of dihydrofurocoumarins.¹⁴ Herein, we report our complete results on the palladium-catalyzed annulation of 1,3-dienes by *o*-iodohydroxycoumarin derivatives that provides a very general and effective route to a wide variety of angular and linear dihydrofurocoumarins.



Results and Discussion

For our initial optimization work, the annulation of 1,3-cyclohexadiene by iodocoumarin **8** was selected as a model reaction (eq 2). Surprisingly, under the optimal reaction conditions used in the dihydrobenzofuran project (see eq 1),¹³ the annulation gave only a 6% yield of the desired *cis*-dihydrofurocoumarin **9**. Instead, the reduced coumarin **10** was isolated in an 88% yield. Possible pathways for formation of the product **10** include reduction of the arylpalladium intermediate by formate formed from the DMF solvent and thermal decomposition of the starting aryl iodide or arylpalladium intermediate. Carrying out this reaction without any palladium catalyst resulted in 95% recovery of the starting coumarin **8**. On the other hand, the use of non-reducing solvents, such as *N,N*-dimethylacetamide (DMA), acetonitrile and THF did not inhibit the undesired reduction. Therefore, formation of the undesired product **10** might reasonably be attributed to thermal decomposition of the arylpalladium intermediate. Variation of the bases, phosphine ligands and solvents used in this reaction had little effect on the outcome of the reaction. The best

result was achieved using Ag_2CO_3 as a base, dppe as a ligand, and THF as the solvent at 60 °C. This provided a 17% yield of the desired product **9**, a 15% yield of the reduced coumarin **10** and 63% of the starting material **8**. The positive effect of the Ag_2CO_3 is presumably due to abstraction of a halide from an intermediate arylpalladium halide complex and formation of a cationic arylpalladium intermediate, which is assumed to be more reactive towards addition to the C=C bond.¹⁵



From our preliminary results, it appeared that electron-rich aryl iodides have a great propensity to undergo the undesired reduction.¹³ The introduction of an electron-withdrawing acetyl group on the phenolic oxygen would be expected to decrease the electron density of the aromatic ring and might, therefore, be expected to improve the yield of the desired coumarin **9** if there were some way to remove the acetyl group during the annulation process. Acylated phenols are fairly stable in the pH range from 5 to 8 and, therefore, would be expected to tolerate our reaction conditions.¹⁶

Using the annulation of 1,3-cyclohexadiene by acetoxyiodocoumarin **11** as a model system, we have examined the effect on the yield of the desired coumarin **9** of various reaction parameters, including the solvent, palladium catalyst, silver salt, phosphine ligand, and reaction temperature (eq 3). Several representative examples are shown in Table 1. Although the annulation using coumarin **11** under our best previous reaction conditions obtained for coumarin **8** did not show very promising results (entry 1), the addition of water raised the yield of coumarin **9** to 21% (entry 2). In sharp contrast to the annulation of

coumarin **8**, the acetoxy derivative **11** did not give any of the reduced coumarin **10** or its acetoxy analogue. Besides that, the recovery of 78% of the starting material **11** indicated that the undesired reduction is completely inhibited under these reaction conditions.

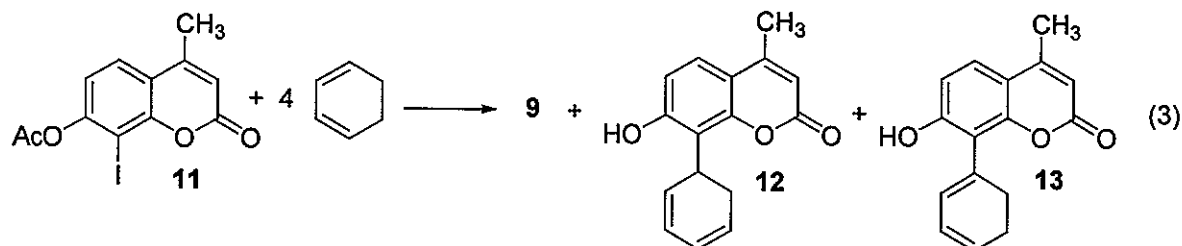


Table 1. Optimization of the annulation (eq 3).^a

entry	solvent(s) (ratio)	temp (°C)	9 %	11 %
1	THF	60	5	90
2	THF-H ₂ O (4:1)	60	21	78
3	1,4-dioxane-H ₂ O (4:1)	80	44	50
4	1,4-dioxane-H ₂ O (4:1)	100	64	13
5	1,4-dioxane-H ₂ O (1:1)	100	40	10

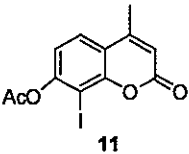
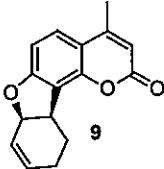
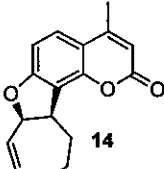
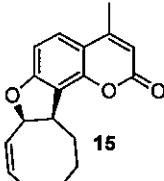
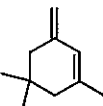
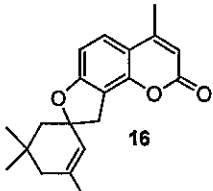
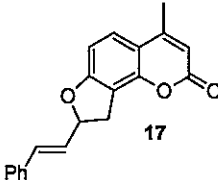
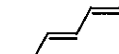
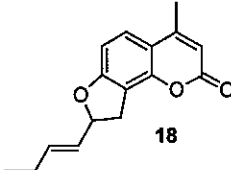
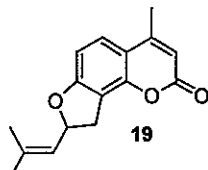
^aCoumarin **11** (0.25 mmol), Pd(dba)₂ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag₂CO₃ (0.5 mmol), 1,3-cyclohexadiene (1.0 mmol), and 5 mL of the solvent were stirred at 100 °C for 24 h.

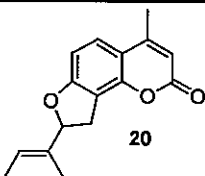
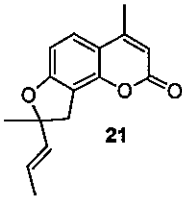
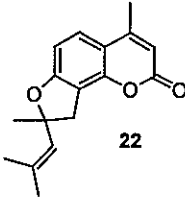
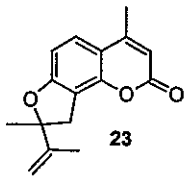
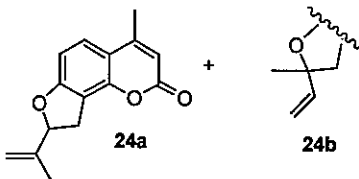
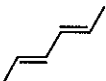
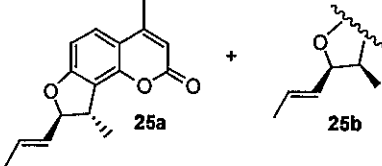
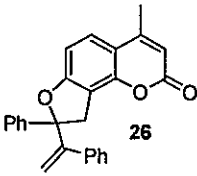
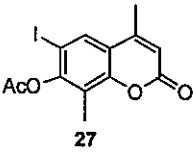
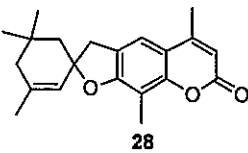
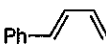
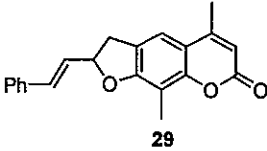
Great improvements were subsequently achieved using a 4:1 1,4-dioxane/water mixture as the solvent at higher temperatures. Increasing the reaction temperature to 80 and 100 °C improved the yield of the desired product **2** to 44% (entry 3) and 64% (entry 4) respectively. Besides the desired product, significant amounts of Heck-type products **12** and **13** were detected among the inseparable mixture of side products. A further increase in the water concentration resulted in a decrease in the yield of **9**, perhaps due to partial hydrolysis of the starting material **11** (entry 5). The use of polar solvents, such as DMF, DMA and acetonitrile, apparently resulted in rapid hydrolysis of the starting material **11**. Further

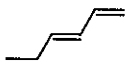
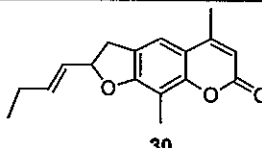
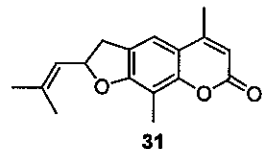
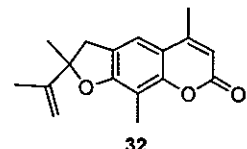
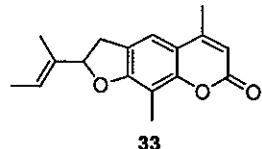
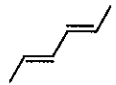
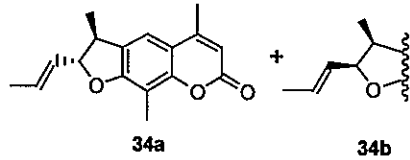
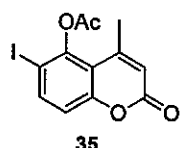
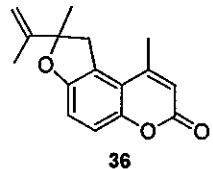
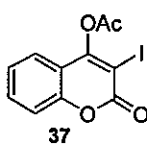
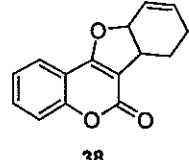
optimizations, which utilized $\text{Pd}(\text{OAc})_2$ as the catalyst; dppp, dppb, BINAP and PPh_3 as the phosphine ligand; and AgOAc , Ag_3PO_4 and Ag_2O as the silver salt, only resulted in a lower yield of the annulated product **9**. We have thus used the following “optimal” procedure for all subsequent annulations: the iodoacetoxycoumarin (0.25 mmol), $\text{Pd}(\text{dba})_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag_2CO_3 (0.5 mmol), the 1,3-diene (1.0 mmol), and 5 mL of a 4:1 1,4-dioxane/water mixture were stirred at 100 °C for 24 h.

Next, the scope and limitations of this annulation have been studied using various 1,3-dienes and representative examples are shown in Table 2. An increase in the ring size of the cyclic 1,3-diene leads to a significantly lower yield of annulation product (entries 1-3). Cyclopentadiene failed to give any annulation products, presumably due to rapid dimerization or some other side reaction. Most terminal 1,3-dienes have given the expected annulation products **16-23** in 61 to 83% yields with excellent regioselectivity (entries 4-11). Running the reaction of 2,3-dimethyl-1,3-butadiene on a 2.0 mmol scale using only 10 mL of the 4:1 1,4-dioxane/water mixture resulted in an even higher 91% yield (entry 11), indicating the utility of this procedure for practical applications. The higher yield in the larger scale reaction is presumably due to an increase in the concentration of the reagents by a factor of four that facilitates coordination of the 1,3-diene to the arylpalladium intermediate. The regioselectivity in these experiments can be explained by the greater affinity of the arylpalladium intermediate for the less hindered terminal double bond over an internal double bond. The annulation of isoprene gave a 3:2 mixture of regioisomers **24a** and **24b** in a 73% yield (entry 12). The annulation of isoprene by *o*-iodophenol is mostly governed by steric factors, favoring addition to the less hindered double bond and affording a 7:1 ratio of the corresponding annulation products.¹³ The poor regioselectivity in entry 12 presumably

Table 2. Synthesis of dihydrofurocoumarins by the annulation of 1,3-dienes.^a

entry	coumarin	1,3-diene	product(s)	% yield ^b (ratio of isomers)
1				64
2				25
3				28
4				61
5				79
6				80
7				78

8		 20	83
9		 21	78
10		 22	75
11		 23	75, 91 ^c
12		 24a + 24b	73 (3:2)
13		 25a + 25b	60 (3:2) ^d 70 (20:1) ^e
14		 26	10
15	 27	 28	72
16		 29	73

17			75	
18			79	
19			70	
20			75	
21			60 (3:2) ^d 67 (20:1) ^e	
22				58
23 ^f				48

^aSee the text for the experimental procedure. ^bAll yields are isolated and based on a single run. ^cThis experiment was performed on a 2.0 mmol scale. ^dA 3:2 mixture of *trans,trans* and *cis,trans* isomers was used. ^eThe diene used was 95% *trans,trans*. ^fNo water has been employed in the solvent.

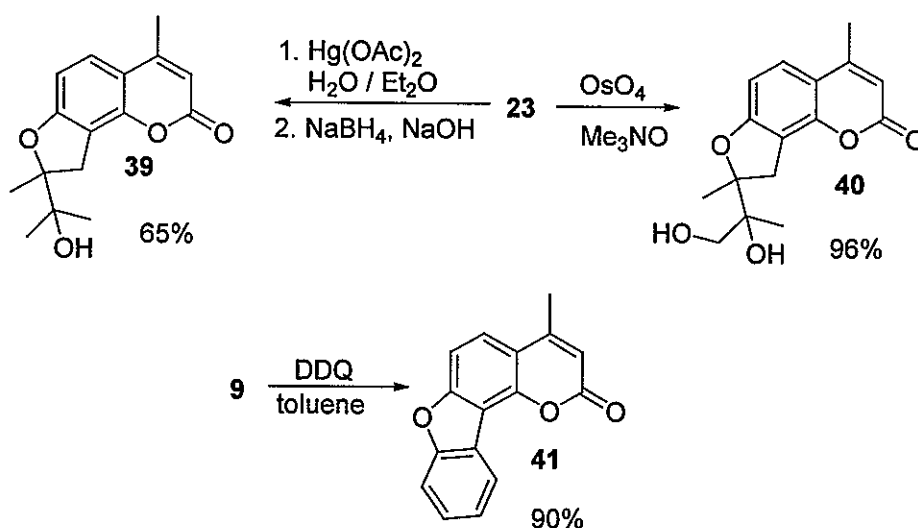
results from the higher reactivity of the presumed cationic arylpalladium intermediate towards the more electron-rich disubstituted double bond leading to a competition between steric and electronic factors, which produces the two different products.

2,4-Hexadiene (a 3:2 mixture of *trans,trans* and *cis,trans* stereoisomers),¹⁷ which has generally been unreactive and afforded dismal yields in most of our previous palladium annulation chemistry, gave a 3:2 ratio of *trans*- and *cis*-stereoisomers **25a** and **25b** in a 60 % overall yield (entry 13). Surprisingly, the use of 95% pure *trans,trans*-2,4-hexadiene gave a 20:1 ratio of isomers **25a** and **25b** in a 70% yield (entry 13). This result will be discussed further in our later discussion of the reaction mechanism. Remarkably, in all of our previous palladium annulation chemistry, relatively hindered 1,3-dienes, like those employed in entries 2, 3, 9-11 and 13, were completely unreactive and only 1,3-dienes bearing monosubstituted terminal double bonds have given satisfactory results. The exclusive generation of *E*-stereochemistry in the newly formed double bond in products **17**, **18**, **20** and **21** is consistent with the intermediacy of a *syn*- π -allylpalladium intermediate in these reactions.¹⁸ The annulation of methyl *trans,trans*-2,4-hexadienoate failed, presumably because of the low affinity of the cationic arylpalladium intermediate for the electron-deficient double bond. Relatively sterically hindered 2,3-diphenyl-1,3-butadiene gave only a 10% yield of the desired product **26** (entry 14), while the even more hindered dienes 1,4-diphenyl-1,3-butadiene and 2,5-dimethyl-2,4-hexadiene were completely unreactive. The attempted annulations of 2,3-dimethoxy-1,3-butadiene, 1-methoxy-1,3-cyclohexadiene, 1,4-pentadiene, cycloheptatriene and cyclohexene did not afford any recognizable products.

In an effort to broaden the scope of this reaction, similar reactions have been performed on coumarins **27**, **35** and **37**. All 1,3-dienes investigated have reacted with coumarin **27** to give the expected annulation products **28-34** in high yields (entries 15-21). Coumarin **35** gave the expected product **36** in a good yield, even when using relatively hindered 2,3-dimethyl-1,3-butadiene (entry 22). Annulation of the coumarin **37** under our "optimal"

reaction conditions resulted in hydrolysis of the acetyl group. The facile hydrolysis is consistent with the higher acidity of 4-hydroxycoumarin than 7-hydroxycoumarin.¹⁹ The same reaction without the addition of water gave a 48 % yield of dihydrofurocoumarin **38** (entry 23). In this experiment, the acetyl group is quite possibly still being hydrolyzed by trace amounts of water present in commercial 1,4-dioxane.

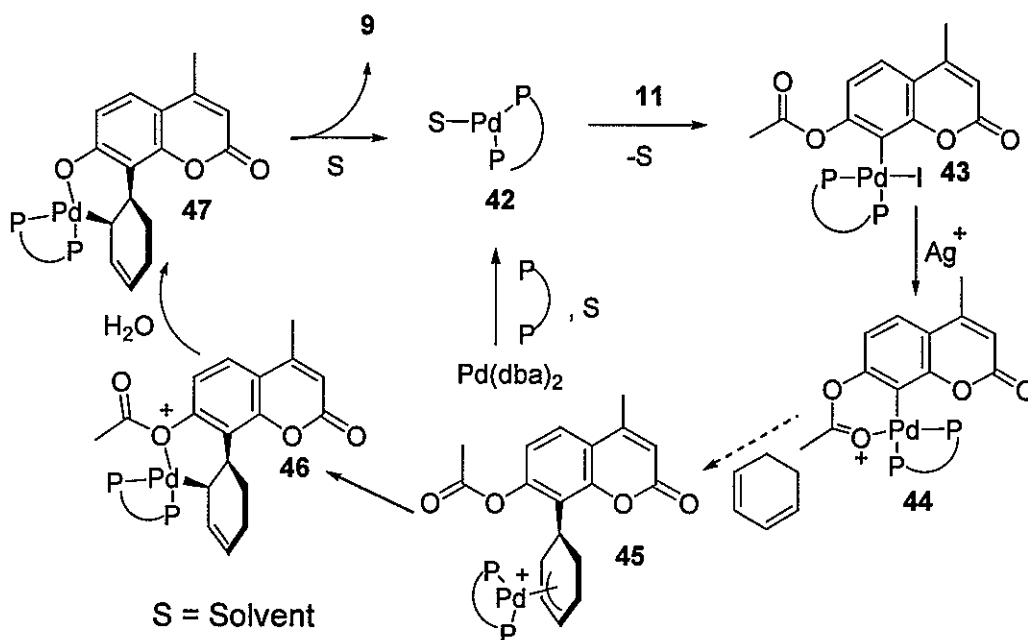
Scheme 1



Chemical modification of the prepared dihydrofurocoumarins enhances the utility of our approach for the synthesis of various potentially biologically interesting products. For example, the hydroxymercuration/demercuration²⁰ and dihydroxylation²¹ of coumarin **23** gave the corresponding alcohol **39** and diol **40**, close analogues of columbianetin (**2**) and prandiol (**7**) respectively, in high yields (Scheme 1). The dehydrogenation²² of coumarin **9** afforded benzofurocoumarin **41** in a 90% yield. According to previous reports benzofurocoumarins, have a high potential for the treatment of psoriasis and related diseases.^{22,23}

A proposed mechanism for this annulation process is shown in Scheme 2. Initial oxidative addition of the iodocoumarin **11** to palladium(0) intermediate **42** generated *in situ* forms arylpalladium intermediate **43**. Abstraction of the iodide by Ag_2CO_3 leads to a cationic intermediate **44**, presumably stabilized by coordination to the neighboring acetyl group. According to our results, the presence of the acetyl group completely inhibits formation of the undesired reduction product **10** and dramatically improves the yield of the desired product **9**. This may be due to the lower propensity of the complex **44**, compared to its phenol analog, to undergo thermal decomposition. Next, complex **44** adds to the 1,3-diene in a *cis*-fashion to give a σ -allylpalladium complex and then π -allylpalladium intermediate **45**. Coordination of the acetoxy oxygen to the palladium atom leading to the formation of intermediate **46** restricts rotation of the C-C bonds in the allyl moiety, and is, presumably, responsible for the high stereoselectivity when *trans,trans*-2,4-hexadiene is utilized (Table 2, entries 13 and 21).

Scheme 2



Since no hydrolysis of the starting material **11** has been observed under our reaction conditions, the deacylation of intermediate **46** is presumably accelerated by coordination of the acetyl oxygen atom to the cationic palladium center. Finally, complex **47** undergoes reductive elimination to give the final product **9** and regenerates the palladium catalyst **42**.

Conclusions

In summary, we have developed an efficient palladium-catalyzed annulation of 1,3-dienes by *o*-acetoxyiodocoumarins, which affords good yields of dihydrofurocoumarins. The process is quite general, regio- and stereoselective, and a variety of *o*-iodoacetoxy coumarins, as well as symmetrical and unsymmetrical 1,3-dienes can be utilized. Derivatization of the annulation products provides an efficient approach to numerous analogues of a very important class of biologically active natural products.

Experimental Section

General. All ^1H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz respectively. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. Iodine, acetic anhydride, pyridine, mercury(II) acetate, trimethylamine *N*-oxide, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, osmium tetroxide, 4-hydroxycoumarin, 7-hydroxy-4-methylcoumarin, 1,3-cyclohexadiene, 1,3-cycloheptadiene, 1,3-cyclooctadiene, *E*-

1,3-hexadiene, 2,3-dimethoxy-1,3-butadiene, 1-methoxy-1,3-cyclohexadiene, 3-methyl-1,3-pentadiene (mixture is isomers), 2,4-dimethyl-1,3-pentadiene, 2,3-dimethyl-1,3-butadiene, isoprene, 2,4-hexadiene (mixture is isomers) and 2,3-diphenyl-1,3-butadiene were purchased from Aldrich Chemical Co., Inc. *E*-2-Methyl-1,3-pentadiene was purchased from Lancaster Co., Inc. *trans,trans*-2,4-Hexadiene was purchased from ChemSamp Co., Inc. 1-Phenyl-1,3-butadiene and 1,5,5-trimethyl-3-methylenecyclohexene were prepared by Wittig condensation according to the literature procedure.²⁴ 5-Hydroxy-4-methylcoumarin and 6-hydroxycoumarin were prepared as described by Harayama *et al.*²⁵ 4,8-Dimethyl-7-hydroxycoumarin was synthesized by a Pechman condensation.²⁶

Synthesis of *o*-Iodoacetoxycoumarins

General procedure. Compounds **11**, **27**, **35** and **37** were prepared by acylation of the corresponding *o*-iodohydroxycoumarins, which in turn were prepared by iodination of the corresponding hydroxycoumarins,²⁷ as indicated below. Iodine (5.0 mmol) dissolved in 50 mL of satd aq KI solution was slowly added to a solution of the corresponding hydroxycoumarin (5.0 mmol) in the minimal amount of aq NH₃ solution at 0-5 °C. The resulting reaction mixture was stirred for 2 h, left overnight in the refrigerator, and then acidified by 20% aq HCl to pH = 4-5. The precipitated *o*-iodohydroxycoumarin was filtered, washed with water and dried in air. The resulting white solid was dissolved in 20 mL of acetyl chloride (a minimal amount of DMF can be used as a co-solvent) in the presence of 1 mL of pyridine and stirred for 48 h at room temperature. Then the reaction mixture was quenched with chilled water (caution, heat evolution!) and extracted by CH₂Cl₂. The organic extract was washed with water and aq NH₄Cl solution, dried over anhydrous MgSO₄ for 4 h

and concentrated. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes-ethyl acetate as the eluent to afford after solvent removal the final product. The following compounds were prepared using this procedure.

7-Acetoxy-8-iodo-4-methylcoumarin (11). Obtained in a 90% overall yield from 7-hydroxy-4-methylcoumarin, recrystallized from 1:1 ethanol/water: white solid, mp 173-175 °C; ^1H NMR (CDCl_3) δ 2.43 (s, 3H), 2.45 (d, $J = 0.8$ Hz, 3H), 6.28 (d, $J = 0.8$ Hz, 1H), 7.09 (d, $J = 8.8$ Hz, 1H), 7.61 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.0, 21.5, 82.8, 115.2, 118.6, 119.7, 125.5, 151.9, 154.4, 154.6, 159.9, 168.4; IR (neat) 1760, 1729 cm^{-1} ; HRMS m/z 343.9550 (calcd for $\text{C}_{13}\text{H}_{11}\text{O}_4\text{I}$, 343.9546).

7-Acetoxy-6-iodo-4,8-dimethylcoumarin (27). Obtained in a 92% overall yield from 7-hydroxy-4,8-dimethylcoumarin, recrystallized from 1:1 ethanol/water: white solid, mp 176-178 °C; ^1H NMR (CDCl_3) δ 2.32 (s, 3H), 2.42 (d, $J = 1.2$ Hz, 3H), 2.44 (s, 3H), 6.28 (d, $J = 1.2$ Hz, 1H), 7.90 (s, 1H); ^{13}C NMR (CDCl_3) δ 10.6, 19.0, 21.2, 85.5, 115.2, 120.0, 121.5, 131.9, 151.3, 152.0, 152.7, 160.1, 167.9; IR (neat) 1767, 1703 cm^{-1} ; HRMS m/z 357.9707 (calcd for $\text{C}_{13}\text{H}_{11}\text{O}_4\text{I}$, 357.9702).

5-Acetoxy-6-iodo-4-methylcoumarin (35). Obtained in an 85% overall yield from 5-hydroxy-4-methylcoumarin, purified by column chromatography using 4:1 hexanes-ethyl acetate: white solid, mp 144-150 °C; ^1H NMR (CDCl_3) δ 2.46 (s, 3H), 2.47 (d, $J = 1.2$ Hz, 3H), 6.27 (d, $J = 1.2$ Hz, 1H), 7.07 (d, $J = 8.8$ Hz, 1H), 7.93 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 22.2, 22.8, 87.6, 115.8, 117.4, 117.9, 118.4, 141.0, 150.4, 155.1, 159.3, 168.6; IR (neat) 1754, 1733 cm^{-1} ; HRMS m/z 343.9551 (calcd for $\text{C}_{11}\text{H}_7\text{IO}_4$, 343.9546).

4-Acetoxy-3-iodocoumarin (37). Obtained in a 40% overall yield from 4-hydroxycoumarin, purified by column chromatography using 4:1 hexanes-ethyl acetate:

white solid, mp 166-168 °C; ^1H NMR (CDCl_3) δ 2.53 (s, 3H), 7.33 (ddd, $J = 8.0, 7.2, 1.0$ Hz, 1H), 7.42 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.49 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.64 (ddd, $J = 8.5, 7.2, 1.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.4, 82.8, 116.2, 117.2, 122.9, 125.1, 133.6, 153.1, 159.0, 162.6, 165.8; IR (neat) 1779, 1717 cm^{-1} ; HRMS m/z 329.9396 (calcd for $\text{C}_{11}\text{H}_7\text{IO}_4$, 329.9389).

General procedure for the Pd-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxycoumarins. The *o*-iodoacetoxycoumarin (0.25 mmol), $\text{Pd}(\text{dba})_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag_2CO_3 (0.5 mmol) and 1,4-dioxane (4 mL) were stirred in a capped vial for 5 min, and then water (1 mL) and the 1,3-diene (1.0 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature, filtered and the filtrate was concentrated to give a yellow residue. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes/ethyl acetate as the eluent to afford after solvent removal the final product. Solid products were then recrystallized from 1:1 ethanol/water. The following new compounds were prepared using this procedure.

7a,10,11,11a-Tetrahydro-4-methylbenzo[*b*]-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (9). Obtained in a 64% yield: white solid, mp 164-165 °C; ^1H NMR (CDCl_3) δ 1.43-2.32 (m, 4H), 2.40 (d, $J = 1.2$ Hz, 3H), 3.67 (m, 1H), 5.07 (m, 1H), 6.04 (m, 1H), 6.11 (d, $J = 1.2$ Hz, 1H), 6.21 (m, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.2, 23.3, 24.2, 38.4, 80.6, 107.2, 111.4, 114.3, 118.6, 123.3, 125.6, 134.8, 151.3, 153.4, 161.4, 163.1; IR (neat) 1733, 1615 cm^{-1} ; HRMS m/z 254.0946 (calcd for $\text{C}_{16}\text{H}_{14}\text{O}_3$, 254.0943).

8,9-Dehydro-4-methylcyclohepta[*b*]-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (14). Obtained in a 25% yield: white solid, mp 154-168 °C; ^1H NMR (CDCl_3) δ 1.53-2.34 (m, 6H),

2.39 (d, $J = 1.2$ Hz, 3H), 3.77 (ddd, $J = 10.3, 9.1, 2.8$ Hz, 1H), 5.60 (dd, $J = 9.1, 1.8$ Hz, 1H), 5.80-5.84 (m, 2H), 6.10 (d, $J = 1.2$ Hz, 1H), 6.75 (d, $J = 8.6$ Hz, 1H), 7.41 (d, $J = 8.6$ Hz, 1H); ^{13}C (CDCl_3) δ 19.3, 22.4, 26.7, 26.8, 42.3, 87.2, 106.8, 111.4, 114.3, 118.7, 125.7, 127.1, 129.9, 151.1, 153.4, 161.4, 162.4; IR (neat) 1725, 1605 cm^{-1} ; HRMS m/z 268.1102 (calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3$, 268.1099).

8,9-Dehydro-4-methylcycloocta[*b*]-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (15).

Obtained in a 28% yield: white solid mp 126-130 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.18-2.30 (m, 8H), 2.38 (d, $J = 1.2$ Hz, 3H), 2.78 (m, 1H), 3.85 (dt, $J = 10.1, 2.3$ Hz, 1H), 5.40 (ddt, $J = 11.8, 5.1, 1.4$ Hz, 1H), 5.75-5.95 (m, 2H), 6.09 (d, $J = 1.2$ Hz, 1H), 6.78 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H); ^{13}C (CDCl_3) δ 19.4, 25.6, 26.4, 29.7, 30.4, 47.9, 86.0, 107.1, 111.4, 114.5, 117.1, 125.7, 127.9, 134.1, 152.0, 153.4, 161.2, 162.9; IR (heat) 1733, 1607 cm^{-1} ; HRMS m/z 282.1259 (calcd for $\text{C}_{18}\text{H}_{18}\text{O}_3$, 282.1256).

Dihydrofurocoumarin 16. Obtained in a 61% yield: white solid mp 70-74 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.02 (s, 3H), 1.09 (s, 3H), 1.70-2.20 (m, 4H), 1.78 (d, $J = 1.2$ Hz, 3H), 2.39 (d, $J = 1.2$ Hz, 3H), 3.24 (s, 2H), 5.92 (q, $J = 1.2$ Hz, 1H), 6.03 (d, $J = 1.2$ Hz, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.2, 24.1, 29.1, 29.5, 31.0, 40.5, 44.3, 48.2, 90.2, 106.9, 111.0, 113.7, 113.8, 122.6, 125.5, 138.4, 151.1, 153.4, 161.6, 162.8; IR (neat) 1732, 1615 cm^{-1} ; HRMS m/z 310.1572 (calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3$ 310.1569).

8,9-Dihydro-4-methyl-8-(*E*-2-phenylethenyl)-2*H*-furo[2,3-*h*]-1-benzopyran-2-one

(17). Obtained in a 79% yield: white solid mp 145-148 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 2.32 (d, $J = 0.8$ Hz, 3H), 3.16 (dd, $J = 16.1, 7.5$ Hz, 1H), 3.55 (dd, $J = 16.1, 9.4$ Hz, 1H), 5.49 (dddd, $J = 9.4, 7.5, 7.4, 1.0$ Hz, 1H), 6.03 (d, $J = 0.8$ Hz, 1H), 6.28 (dd, $J = 15.8, 7.4$ Hz, 1H), 6.67 (dd, $J = 15.8, 1.0$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 7.17-7.36 (m, 5H), 7.35 (d, $J = 8.4$ Hz,

1H); ^{13}C NMR (CDCl_3) δ 19.24, 33.28, 85.90, 106.77, 111.50, 113.69, 114.34, 125.76, 126.97, 127.33, 128.51, 128.85, 133.32, 136.02, 151.10, 153.26, 161.28, 163.44; IR (neat) 1727, 1615 cm^{-1} ; HRMS m/z 304.1104 (calcd for $\text{C}_{20}\text{H}_{16}\text{O}_3$ 304.1099).

8-(*E*-1-butenyl)-8,9-Dihydro-4-methyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (18).

Obtained in an 80% yield: white solid, mp 142-146 °C; ^1H NMR (CDCl_3) δ 1.04 (t, $J = 7.6$ Hz, 3H), 2.08-2.18 (m, 2H), 2.39 (s, 3H), 3.11 (dd, $J = 16.0, 7.8$ Hz, 1H), 3.52 (dd, $J = 16.0, 9.4$ Hz, 1H), 5.33 (q, $J = 7.8$ Hz, 1H), 5.66 (ddq, $J = 15.2, 7.8, 1.4$ Hz, 1H), 5.93 (dt, $J = 15.2, 6.3$ Hz, 1H), 6.09 (s, 1H), 6.74 (d, $J = 8.4$ Hz, 1H); 7.41 (d, $J = 8.4$ Hz, 1H); ^{13}C (CDCl_3) 13.3, 19.2, 21.4, 33.1, 86.4, 106.7, 111.3, 113.9, 114.2, 125.6, 127.3, 137.6, 151.0, 153.3, 161.4, 163.5; IR (heat) 1732, 1613 cm^{-1} ; HRMS m/z 256.1103 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$, 256.1099).

8,9-Dihydro-4-methyl-8-(2-methylpropenyl)-2*H*-furo[2,3-*h*]-1-benzopyran-2-one

(19). Obtained in a 78% yield: white solid, mp 140-146 °C; ^1H NMR (CDCl_3) δ 1.81 (d, $J = 1.2$ Hz, 3H), 1.82 (d, $J = 1.4$ Hz, 3H), 2.39 (d, $J = 1.2$ Hz, 3H), 3.04 (dd, $J = 16.0, 8.8$ Hz, 1H), 3.53 (dd, $J = 16.0, 8.8$ Hz, 1H), 5.45 (dt, $J = 8.8, 1.2$ Hz, 1H), 5.65 (q, $J = 8.8$ Hz, 1H), 6.09 (d, $J = 1.2$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H); 7.40 (d, $J = 8.4$ Hz, 1H); ^{13}C (CDCl_3) δ 18.6, 19.2, 26.0, 33.5, 82.3, 106.7, 111.3, 114.0, 114.1, 123.9, 125.6, 139.6, 151.0, 153.3, 161.4, 163.6; IR (heat) 1727, 1610 cm^{-1} ; HRMS m/z 256.1103 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$, 256.1099).

8-(2-*E*-buten-2-yl)-8,9-Dihydro-4-methyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (20).

Obtained in an 83% yield: white solid, mp 140-4 °C; ^1H NMR (CDCl_3) δ 1.64 (s, 3H), 1.68 (d, $J = 6.8$ Hz, 3H), 2.40 (s, 3H), 3.18 (dd, $J = 16.4, 8.0$ Hz, 1H), 3.45 (dd, $J = 16.4, 9.6$ Hz, 1H), 5.33 (t, $J = 9.0$ Hz, 1H), 5.68 (q, $J = 6.8$ Hz, 1H), 6.10 (s, 1H), 6.76 (d, $J = 8.4$ Hz,

1H); 7.41 (d, $J = 8.4$ Hz, 1H); ^{13}C (CDCl_3) δ 10.8, 13.4, 19.2, 31.2, 90.5, 106.5, 111.3, 114.1, 124.0, 125.6, 133.8, 151.0, 153.3, 161.4, 164.0; IR (heat) 1728, 1613 cm^{-1} ; HRMS m/z 256.11025 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$, 256.10994).

8,9-Dihydro-4,8-dimethyl-8-*E*-propenyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (21).

Obtained in a 78% yield: white solid, mp 91-93 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.59 (s, 3H), 1.72 (d, $J = 5.6$ Hz, 3H), 2.39 (d, $J = 0.8$ Hz, 3H), 3.17 (d, $J = 15.9$ Hz, 1H), 3.32 (d, $J = 15.9$ Hz, 1H), 5.71 (d, $J = 15.7$ Hz, 1H), 5.80 (dq, $J = 15.7, 5.6$ Hz, 1H), 6.09 (d, $J = 0.8$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H); 7.41 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) 18.0, 19.3, 26.7, 39.2, 90.8, 106.2, 111.3, 113.7, 114.1, 125.3, 125.6, 134.1, 151.3, 153.4, 161.5, 162.9; IR (neat) 1735, 1615 cm^{-1} ; HRMS m/z 256.1102 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$, 256.1099).

8,9-Dihydro-4,8-dimethyl-8-(2-methylpropenyl)-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (22).

Obtained in a 75% yield: white solid, mp 78-80 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.56 (s, 3H), 1.72 (s, 3H), 1.76 (s, 3H), 2.39 (s, 3H), 3.30 (d, $J = 15.8$ Hz, 1H), 3.40 (d, $J = 15.8$ Hz, 1H), 5.57 (s, 1H), 6.09 (s, 1H), 6.74 (d, $J = 8.5$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (CDCl_3) 19.3, 19.5, 26.9, 28.7, 40.8, 91.1, 106.9, 111.2, 113.9, 114.0, 125.7, 129.6, 136.2, 151.2, 153.4, 161.5, 162.6; IR (heat) 1728, 1614 cm^{-1} ; HRMS m/z 270.1262 (calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$, 270.1256).

8,9-Dihydro-4,8-dimethyl-8-(2-propenyl)-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (23).

Obtained in 75% and 91% (2 mmol scale) yields: white solid, mp 101-103 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.61 (s, 3H), 1.83 (d, $J = 0.8$ Hz, 3H), 2.39 (d, $J = 1.2$ Hz, 3H), 3.18 (d, $J = 16.0$ Hz, 1H), 3.39 (d, $J = 16.0$, 1H), 4.88 (q, $J = 0.8$ Hz, 1H), 5.10 (q, $J = 0.8$ Hz, 1H), 6.09 (d, $J = 1.2$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9,

19.2, 26.4, 38.4, 93.1, 106.8, 110.7, 111.3, 113.6, 114.1, 125.7, 146.9, 151.3, 153.4, 161.4, 163.0; IR (neat) 1728, 1615 cm^{-1} ; HRMS m/z 256.1102 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$, 256.1099).

8,9-Dihydro-4-methyl-8-(2-propenyl)-2H-furo[2,3-*h*]-1-benzopyran-2-one (24a) and **8-ethenyl-8,9-dihydro-4,8-dimethyl-2H-furo[2,3-*h*]-1-benzopyran-2-one (24b)** were isolated as a 3:2 inseparable mixture of regioisomers in a 73% overall yield. The ratio of regioisomers was confirmed by ^1H NMR spectroscopy and HPLC. Isomer **24a**: ^1H NMR (CDCl_3) δ 1.77 (s, 3H), 2.40 (s, 3H), 3.19 (dd, $J = 16.0, 9.6$ Hz, 1H), 3.53 (dd, $J = 16.0, 9.6$ Hz, 1H), 4.96 (s, 1H), 5.11 (s, 1H), 5.35 (dd, $J = 16.0, 9.6$ Hz, 1H), 5.35 (t, $J = 9.6$ Hz, 1H), 6.10 (s, 1H), 6.79 (d, $J = 8.5$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 1H). isomer **24b**: ^1H NMR (CDCl_3) δ 1.61 (s, 3H), 2.40 (s, 3H), 3.20 (d, $J = 15.6$ Hz, 1H), 3.35 (d, $J = 15.6$ Hz, 1H), 5.15 (d, $J = 10.8$ Hz, 1H), 5.34 (d, $J = 17.3$ Hz, 1H), 6.06 (dd, $J = 17.3, 10.8$ Hz, 1H), 6.10 (s, 1H), 6.77 (d, $J = 8.5$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 1H). The following ^{13}C NMR, IR and HRMS data were obtained on the mixture of isomers: ^{13}C NMR (CDCl_3) δ 17.3, 19.3, 19.3, 26.5, 31.7, 38.9, 88.0, 90.8, 106.6, 106.9, 111.4, 111.5, 113.0, 113.5, 113.7, 114.2, 114.3, 115.6, 125.7, 125.8, 140.9, 143.2, 151.1, 153.3, 153.4, 161.3, 161.4, 162.9, 163.9; IR (neat) 1731, 1614 cm^{-1} ; HRMS, 242.0946 (calcd for $\text{C}_{15}\text{H}_{14}\text{O}_3$ 242.0943).

8,9-Dihydro-4,9-dimethyl-8-(*E*-1-propenyl)-2H-furo[2,3-*h*]-1-benzopyran-2-one (3:2 mixture of *trans*- and *cis*-isomers) (25a and 25b). Obtained as a white solid in a 60% overall yield when a mixture of isomeric 2,4-hexadienes was used. *trans,trans*-2,4-Hexadiene gave a 20:1 ratio of **25a** and **25b** in a 70% yield. *trans*-Isomer (**25a**): ^1H NMR (CDCl_3) δ 1.27 (d, $J = 7.2$ Hz, 3H), 1.82 (dd, $J = 7.0, 1.5$ Hz, 3H), 2.39 (s, 3H), 3.74 (p, $J = 7.7$ Hz, 1H), 5.52 (t, $J = 8.4$ Hz, 1H), 5.73 (ddq, $J = 15.2, 8.4, 1.5$ Hz, 1H), 5.88-6.01 (m, 1H), 6.10 (s, 1H), 6.75 (d, $J = 8.6$ Hz, 1H); 7.40 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR δ 15.1, 18.3, 19.3, 38.3, 89.7, 107.0,

111.5, 114.4, 119.9, 125.6, 125.6, 132.7, 151.1, 153.4, 161.4, 162.7; IR (neat) 1720, 1605 cm^{-1} . *cis*-Isomer (**25b**): ^1H NMR (CDCl_3) δ 1.50 (d, $J = 7.0$ Hz, 3H), 1.77 (dd, $J = 6.6$, 1.5 Hz, 3H), 2.39 (s, 3H), 3.49 (p, $J = 7.2$ Hz, 1H), 4.76 (t, $J = 7.3$ Hz, 1H), 5.64 (ddq, $J = 15.4$, 7.7, 1.5 Hz, 1H), 5.82-5.91 (m, 1H), 6.10 (s, 1H), 6.74 (d, $J = 8.6$ Hz, 1H); 7.40 (d, $J = 8.6$ Hz, 1H). The following ^{13}C NMR, IR and HRMS data were obtained on the mixture of stereoisomers: ^{13}C NMR (CDCl_3) δ 15.1, 18.0, 18.1, 18.2, 19.3, 38.0, 38.3, 41.5, 89.7, 93.7, 106.9, 107.0, 111.4, 111.5, 114.3, 114.4, 118.3, 119.9, 125.6, 125.7, 125.8, 129.0, 131.0, 132.7, 151.1, 151.4, 153.3, 153.4, 161.2, 161.3, 162.7, 163.0; IR (neat) 1729, 1613 cm^{-1} ; HRMS m/z 256.1105 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$, 256.1099).

8,9-Dihydro-4-methyl-8-phenyl-8-(1-phenylethenyl)-2H-furo[2,3-*h*]-1-benzopyran-2-one (26). Obtained in a 10% yield: white solid, mp 60-64 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 2.38 (d, $J = 1.2$ Hz, 3H), 3.81 (d, $J = 15.8$ Hz, 1H), 3.83 (d, $J = 15.8$ Hz, 1H), 5.43 (d, $J = 0.8$ Hz, 1H), 5.60 (d, $J = 0.8$ Hz, 1H), 6.08 (d, $J = 1.2$ Hz, 1H), 6.86 (d, $J = 7.6$ Hz, 1H), 7.05-7.34 (m, 10H), 7.31 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.2, 38.7, 95.9, 106.9, 111.6, 113.6, 114.5, 116.8, 125.8, 126.4, 127.8, 128.1, 128.3, 128.6, 128.7, 139.4, 142.6, 150.9, 151.0, 153.3, 161.2, 162.3; IR (neat) 1727, 1612 cm^{-1} ; HRMS m/z 380.1419 (calcd for $\text{C}_{26}\text{H}_{20}\text{O}_3$, 380.1412).

Dihydrofurocoumarin 28. Obtained in a 72% yield: white solid, mp 180-184 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.00 (s, 3H), 1.11 (s, 3H), 1.66 (d, $J = 13.8$ Hz, 1H), 1.74 (s, 3H), 1.81 (d, $J = 17.6$ Hz, 1H), 1.90 (d, $J = 17.6$ Hz, 1H), 1.99 (d, $J = 13.8$ Hz, 1H), 2.25 (s, 3H), 2.37 (d, $J = 1.2$ Hz, 3H), 3.12 (d, $J = 16.0$ Hz, 1H), 3.14 (d, $J = 16.0$ Hz, 1H), 5.51 (s, 1H), 6.07 (d, $J = 1.2$ Hz, 1H), 7.20 (s, 1H); ^{13}C NMR (CDCl_3) δ 8.8, 19.3, 24.2, 28.6, 30.2, 31.0, 43.4, 44.4,

48.1, 89.5, 107.9, 110.7, 113.4, 117.4, 122.9, 123.7, 138.6, 153.3, 153.4, 160.9, 162.2; IR (neat) 1720, 1616 cm^{-1} ; HRMS m/z 324.1731 (calcd for $\text{C}_{21}\text{H}_{24}\text{O}_3$, 324.1725).

2,3-Dihydro-5,9-dimethyl-2-(*E*-2-phenylethenyl)-7*H*-furo[3,2-*g*][1]-benzopyran-7-one (29). Obtained in a 73% yield: white solid, mp 140-144 °C; ^1H NMR (CDCl_3) δ 2.32 (s, 3H), 2.39 (d, $J = 1.0$ Hz, 3H), 3.16 (dd, $J = 15.6, 7.7$ Hz, 1H), 3.52 (dd, $J = 15.6, 9.2$ Hz, 1H), 5.49 (dt, $J = 9.2, 7.7$ Hz, 1H), 6.11 (q, $J = 1.0$ Hz, 1H), 6.36 (dd, $J = 15.8, 7.7$ Hz, 1H), 6.73 (d, $J = 15.8$ Hz, 1H), 7.27-7.48 (m, 6H); ^{13}C NMR (CDCl_3) δ 8.8, 19.3, 36.2, 85.2, 108.2, 111.2, 113.9, 117.5, 119.2, 123.1, 126.8, 127.8, 128.5, 129.0, 132.3, 133.2, 136.1, 153.2, 153.4, 161.4, 170.0; IR (neat) 1714, 1616, 1585 cm^{-1} ; HRMS m/z 318.1263 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256).

2-(*E*-Butenyl)-2,3-dihydro-5,9-dimethyl-7*H*-furo[3,2-*g*][1]-benzopyran-7-one (30). Obtained in an 75% yield: white solid, mp 127-129 °C; ^1H NMR (CDCl_3) δ 1.04 (t, $J = 7.6$ Hz, 3H), 2.19 (pd, $J = 7.6, 1.7$ Hz, 2H), 2.29 (s, 3H), 2.38 (d, $J = 1.2$ Hz, 3H), 3.04 (ddd, $J = 15.6, 8.1, 1.2$ Hz, 1H), 3.40 (ddd, $J = 15.6, 9.0, 1.0$ Hz, 1H), 5.27 (q, $J = 8.2$ Hz, 1H), 5.65 (ddt, $J = 15.3, 7.8, 1.7$ Hz, 1H), 5.92 (dtd, $J = 15.3, 6.2, 0.8$ Hz, 1H), 6.09 (d, $J = 1.2$ Hz, 1H), 7.22 (s, 1H); ^{13}C (CDCl_3) δ 8.8, 13.3, 19.3, 25.4, 36.0, 85.6, 108.0, 111.0, 113.7, 117.4, 123.5, 127.7, 137.2, 153.2, 153.3, 161.5, 162.1; IR (neat) 1713, 1614 cm^{-1} ; HRMS m/z 270.1262 (calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$, 270.1256).

2,3-Dihydro-5,9-dimethyl-2-(2-methylpropenyl)-7*H*-furo[3,2-*g*][1]benzopyran-7-one (31). Obtained in a 79% yield: white solid, mp 176-180 °C; ^1H NMR (CDCl_3) δ 1.81 (d, $J = 1.2$ Hz, 3H), 2.28 (s, 3H), 2.38 (d, $J = 1.0$ Hz, 3H), 2.98 (ddd, $J = 15.5, 8.6, 1.3$ Hz, 1H), 3.39 (ddd, $J = 15.5, 8.7, 1.0$ Hz, 1H), 5.44 (dt, $J = 9.1, 1.1$ Hz, 1H), 5.57 (q, $J = 8.6$ Hz, 1H), 6.09 (d, $J = 1.2$ Hz, 1H), 7.22 (s, 1H); ^{13}C δ (PPM) 8.6, 18.4, 19.1, 25.9, 36.2, 81.4, 107.7, 110.7,

113.4, 117.0, 123.5, 124.0, 138.7, 152.9, 153.1, 161.4, 161.8; IR (neat) 1704, 1622 cm^{-1} ; HRMS m/z 270.1262 (calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$, 270.1256).

2,3-Dihydro-2,5,9-trimethyl-2-(2-propenyl)-7H-furo[3,2-g][1]-benzopyran-7-one

(32). Obtained in a 70% yield: white solid, mp 142-144 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.60 (s, 3H), 1.83 (s, 3H), 2.31 (s, 3H), 2.37 (d, $J = 1.2$ Hz, 3H), 3.08 (dd, $J = 15.6, 1.0$ Hz, 1H), 3.31 (dd, $J = 15.6, 0.9$ Hz, 1H), 4.87 (t, $J = 1.4$ Hz, 1H), 5.08 (s, 1H), 6.09 (d, $J = 1.2$ Hz, 1H), 7.21 (s, 1H); ^{13}C NMR (CDCl_3) δ 8.7, 18.9, 19.3, 26.4, 41.2, 91.9, 108.0, 110.6, 110.9, 113.7, 117.6, 123.2, 147.2, 153.2, 153.4, 161.0, 162.1; IR (neat) 1705, 1618 cm^{-1} ; HRMS m/z 270.1262 (calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$, 270.1256).

2-(2-E-Buten-2-yl)-2,3-dihydro-5,9-dimethyl-7H-furo[3,2-g][1]-benzopyran-7-one

(33). Obtained in a 75% yield: white solid, mp 180-186 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.82 (d, $J = 1.2$ Hz, 3H), 2.28 (s, 3H), 2.38 (d, $J = 1.2$ Hz, 3H), 2.97 (ddd, $J = 15.6, 7.5, 0.9$ Hz, 1H), 3.39 (ddd, $J = 15.6, 8.8, 0.8$ Hz, 1H), 5.44 (dt, $J = 9.2, 1.2$ Hz, 1H), 5.57 (q, $J = 8.8$ Hz, 1H), 6.09 (d, $J = 1.2$ Hz, 1H), 7.22 (s, 1H); ^{13}C (CDCl_3) δ 8.8, 18.7, 19.3, 26.1, 36.4, 81.7, 108.0, 111.0, 113.6, 117.3, 123.8, 124.3, 139.0, 153.2, 153.4, 161.6, 162.1; IR (neat) 1698, 1613 cm^{-1} ; HRMS m/z 270.1262 (calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$, 270.1256).

2,3-Dihydro-3,5,9-trimethyl-8-(E-1-propenyl)-7H-furo[3,2-g][1]-benzopyran-7-one

(3:2 mixture of *trans*- and *cis*-isomers) (34a and 34b). Obtained as a white solid in a 60% overall yield when a mixture of isomeric 2,4-hexadienes was used. *trans,trans*-2,4-Hexadiene gave a 20:1 ratio of 34a and 34b in 70% yield. *trans*-Isomer (34a): ^1H NMR (CDCl_3) δ 1.20 (d, $J = 7.2$ Hz, 3H), 1.80 (dd, $J = 6.5, 1.5$ Hz, 3H), 2.29 (s, 3H), 2.40 (s, 3H), 3.54 (p, $J = 7.4$ Hz, 1H), 5.21 (t, $J = 8.5$ Hz, 1H), 5.57-5.75 (m, 1H), 5.80-6.00 (s, 1H), 6.10 (s, 1H), 7.17 (s, 1H). *cis*-Isomer (34b): ^1H NMR (CDCl_3) δ 1.36 (d, $J = 6.9$ Hz, 3H), 1.80

(dd, $J = 6.5, 1.5$ Hz, 3H), 2.28 (s, 3H), 2.40 (s, 3H), 3.25 (p, $J = 7.2$ Hz, 1H), 4.65 (t, $J = 8.3$ Hz, 1H), 5.57-5.75 (m, 1H), 5.80-6.00 (m, 1H), 6.10 (s, 1H), 7.14 (s, 1H). The following ^{13}C NMR, IR and HRMS data were obtained on the mixture of stereoisomers: ^{13}C NMR (CDCl_3) δ 8.8, 16.5, 17.7, 18.3, 19.4, 39.9, 42.6, 89.0, 93.5, 108.1, 111.0, 111.1, 113.9, 116.2, 116.7, 126.2, 129.29, 129.7, 131.6, 131.9, 153.3, 153.4, 160.8, 162.0; IR (neat) 1714, 1620 cm^{-1} ; HRMS m/z 270.1262 (calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$, 270.1256).

2,3-Dihydro-2,9-dimethyl-8-(2-propenyl)-7H-furo[2,3-*f*]-1-benzopyran-7-one (36).

Obtained in a 58% yield: white solid, mp 73-76 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.59 (s, 3H), 1.85 (q, $J = 0.6$ Hz, 3H), 2.57 (d, $J = 1.2$ Hz, 3H), 3.03 (dd, $J = 15.4, 0.8$ Hz, 1H), 3.26 (dd, $J = 15.4, 0.8$ Hz, 1H), 4.88 (t, $J = 1.6$ Hz, 1H), 5.08 (s, 1H), 6.10 (d, $J = 1.2$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.1, 22.7, 26.6, 40.6, 93.0, 106.6, 108.8, 110.5, 113.7, 122.3, 127.5, 147.4, 153.3, 154.1, 156.5, 161.4; IR (neat) 1725, 1615 cm^{-1} ; HRMS m/z 256.1102 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$, 256.1099).

1a,5,6,6a-Tetrahydrobenzo[*b*]-4H-furo[3,2-*c*][1]-benzopyran-4-one (38). Obtained in a 48% yield: white solid, mp 140-144 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.55-1.67 (m, 1H), 1.92-2.06 (m, 1H), 2.13-2.27 (m, 2H), 3.54 (ddd, $J = 10.0, 8.7, 4.7$ Hz, 1H), 5.28 (d, $J = 10.2$ Hz, 1H), 6.06 (d, $J = 10.2$ Hz, 1H), 6.26-6.33 (m, 1H), 7.28 (ddd, $J = 7.6, 7.5, 1.0$ Hz, 1H), 7.38 (dd, $J = 8.4, 1.0$ Hz, 1H), 7.56 (ddd, $J = 8.4, 7.5, 1.5$ Hz, 1H), 7.67 (dd, $J = 7.6, 1.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 22.5, 23.6, 38.0, 82.5, 106.3, 112.9, 116.9, 122.6, 122.8, 123.8, 132.2, 135.7, 154.9, 160.7, 166.4; IR (neat) 1718, 1640 cm^{-1} ; HRMS m/z 240.0791 (calcd for $\text{C}_{15}\text{H}_{12}\text{O}_3$, 240.0786).

Derivatization of dihydrofurocoumarins

Preparation of dihydrofurocoumarin 39. A modified general solvomercuration procedure was used.²⁸ Coumarin **23** (0.25 mmol, 64 mg) and Hg(OAc)₂ (0.5 mmol, 163 mg) were dissolved in 2 mL of a 1:1 ether-water solution and 2 drops of 48% HClO₄ was added to dissolve the precipitated mercury(II) oxide. The reaction mixture was stirred at room temperature for 24 h, then quenched with a solution of NaBH₄ (0.3 mmol, 11.4 mg) in 5 % NaOH (0.5 mL). The resulting reaction mixture was stirred for 10 min, gently acidified with 10 mL of satd NH₄Cl (use of HCl results in only a 10% yield of the product **39**), and extracted with diethyl ether. Then the ether extract was dried over anhydrous MgSO₄ and concentrated. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes-ethyl acetate as the eluent to afford after solvent removal the final product.

8,9-Dihydro-4,8-dimethyl-8-(2-hydroxy-2-propyl)-2H-furo[2,3-*h*]-1-benzopyran-2-one (39). Obtained in a 65% yield: white solid, mp 118-120 °C; ¹H NMR (CDCl₃) δ 1.26 (s, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 2.39 (d, *J* = 1.2 Hz, 3H), 2.98 (d, *J* = 16.0 Hz, 1H), 3.59 (d, *J* = 16.0, 1H), 6.11 (d, *J* = 1.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 19.3, 23.0, 24.5, 24.9, 34.9, 74.5, 97.1, 106.8, 111.4, 114.2, 114.3, 125.6, 151.3, 153.3, 161.4, 162.8; IR (neat) 3469, 1727, 1614 cm⁻¹; HRMS *m/z* 274.1212 (calcd for C₁₆H₁₈O₄, 274.1205).

Preparation of the diol 40. A modified general dihydroxylation procedure was used.²⁹ A solution of coumarin **23** (0.25 mmol, 64 mg) and NMO dihydrate (0.55 mmol, 61 mg) in acetone-water (8:1, 2 mL) was treated with 1 mL of 5 % OsO₄ solution in ethanol (0.02 mmol, 5 mg). The reaction was stirred at 70 °C for 2 h, then diluted with 10 % aq NaHCO₃ (2 mL) and extracted with ethyl acetate. The organic extract was washed with water and aq

NH₄Cl solution, dried over anhydrous MgSO₄ for 4 h and concentrated. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes-ethyl acetate as the eluent to afford after solvent removal the final product.

8,9-Dihydro-4,8-dimethyl-8-(1,2-dihydroxy-2-propyl)-2H-furo[2,3-*h*]-1-benzopyran-2-one (40). Obtained as a pair of diastereomers in a 96% yield: white solid, mp 163-173 °C; ¹H NMR (CDCl₃) δ 1.26 (s, 3H), 1.37 (s, 3H), 1.47 (s, 6H), 2.39 (d, *J* = 0.8 Hz, 6H), 2.70-4.40 (m, 8H), 6.11 (q, *J* = 0.8 Hz, 1H), 6.70-6.77 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 2H); ¹³C (CDCl₃) δ 19.3, 20.2, 20.5, 23.1, 23.3, 35.0, 35.2, 66.4, 66.9, 75.3, 76.2, 95.9, 97.4, 106.8, 106.9, 111.5, 111.7, 113.8, 114.0, 114.4, 14.5, 125.6, 125.7, 151.2, 151.3, 153.2, 153.3, 161.2, 161.3, 162.2, 162.3; IR (neat) 3406, 1709, 1608 cm⁻¹; HRMS *m/z* 290.1160 (calcd for C₁₆H₁₈O₅, 290.1154).

Preparation of the coumarin 41. A standard general dehydrogenation procedure was used.³⁰ A solution of coumarin 9 (0.25 mmol, 64 mg) and DDQ (0.50 mmol, 60 mg) in 1 mL of toluene was stirred at 100 °C for 24 h. Then the resulting reaction mixture was cooled to room temperature, filtered and the filtrate was concentrated. The resulting residue was purified by column chromatography using silica gel as a solid phase and 8:1 hexanes-ethyl acetate as the eluent to afford after solvent removal the final product.

4-Methylbenzo[*b*]-2H-furo[2,3-*h*]-1-benzopyran-2-one (41). Obtained in a 90% yield: white solid, mp 216-219 °C; ¹H NMR (CDCl₃) δ 2.53 (d, *J* = 1.2 Hz, 3H), 6.07 (d, *J* = 1.2 Hz, 1H), 7.45 (td, *J* = 7.3, 1.0 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.53 (td, *J* = 7.6, 1.2 Hz, 1H), 7.60 (dt, *J* = 7.3, 1.0 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 8.42 (ddd, *J* = 7.6, 1.2, 0.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 19.6, 108.5, 111.7, 111.7, 113.2, 115.2, 122.1, 123.4, 123.8, 124.0,

128.0, 149.7, 153.5, 156.3, 158.5, 160.8; IR (neat) cm^{-1} ; HRMS m/z 250.0635 (calcd for $\text{C}_{16}\text{H}_{14}\text{O}_3$, 250.0630).

Scanned ^1H and ^{13}C spectra for compounds **9**, **11**, and **14-41** are included in Appendix B (pp. 94-156).

Acknowledgments

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CHAPTER 3. SYNTHESIS OF DIHYDROFUROFLAVONIDS VIA PALLADIUM-CATALYZED ANNULATION OF 1,3-DIENES

A paper to be submitted to the *Journal of Organic Chemistry*

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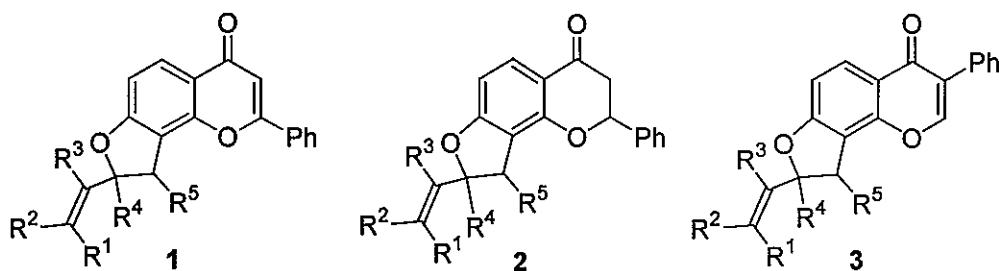
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Abstract

The palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids provides an efficient approach to biologically interesting dihydrofuroflavonoids. This reaction is very general, regioselective, and a wide variety of terminal, cyclic and internal 1,3-dienes can be utilized.

Introduction

Dihydrofuroflavonoids occur commonly in plants and fruits and are very important because of their pronounced biological properties.¹ According to recent reports, derivatives of dihydrofuroflavones (1) have high cytotoxicity against P-388 cells.² Derivatives of dihydrofuroflavanones (2) are effective inhibitors of protein kinase,³ aromatase,⁴ and larvae growth.⁵ Derivatives of dihydrofuroisoflavones (3) exhibit high antifungal activity.⁶



Despite significant interest, no efficient, general method for the synthesis of dihydrofuroflavonoids has really been developed. Recently, we reported an efficient method for the synthesis of dihydrofurocoumarins,⁷ which looked very promising for the synthesis of dihydrofuroflavonoids. We now wish to report the success of this latter project.

Results and Discussion

Herein, we report our results on the palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids that provides a very general and effective route to a wide variety of dihydrofuroflavonoids. Using our previously developed reaction conditions,⁷ the scope and limitations of this annulation (Scheme 1) have been studied using various *o*-iodoacetoxyflavonoids and 1,3-dienes and representative examples are shown in Table 1.

Scheme 1

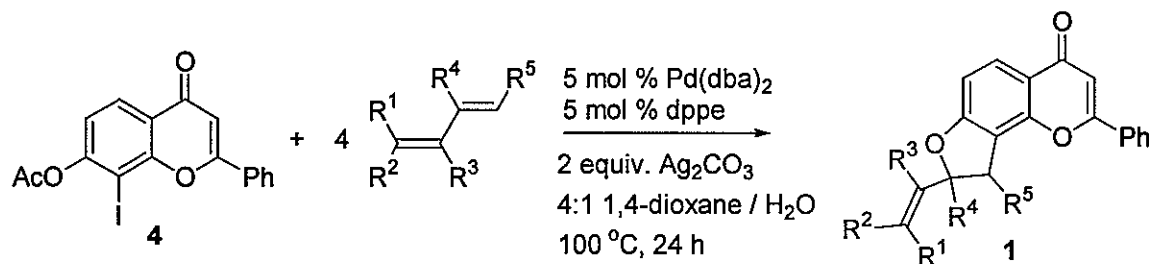
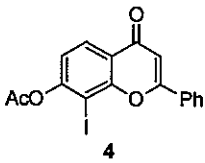
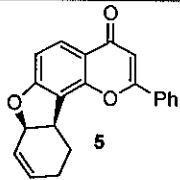
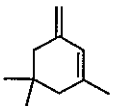
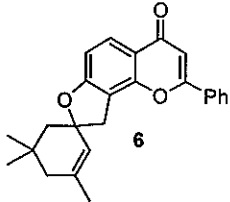
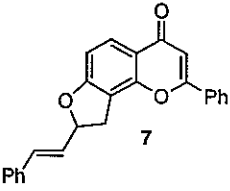
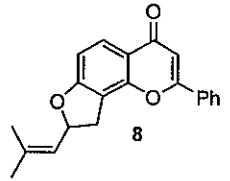
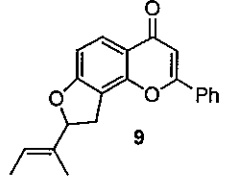
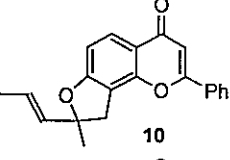
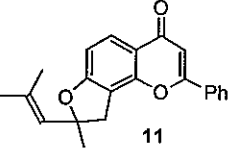
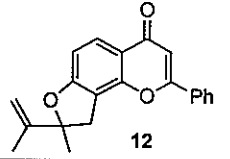
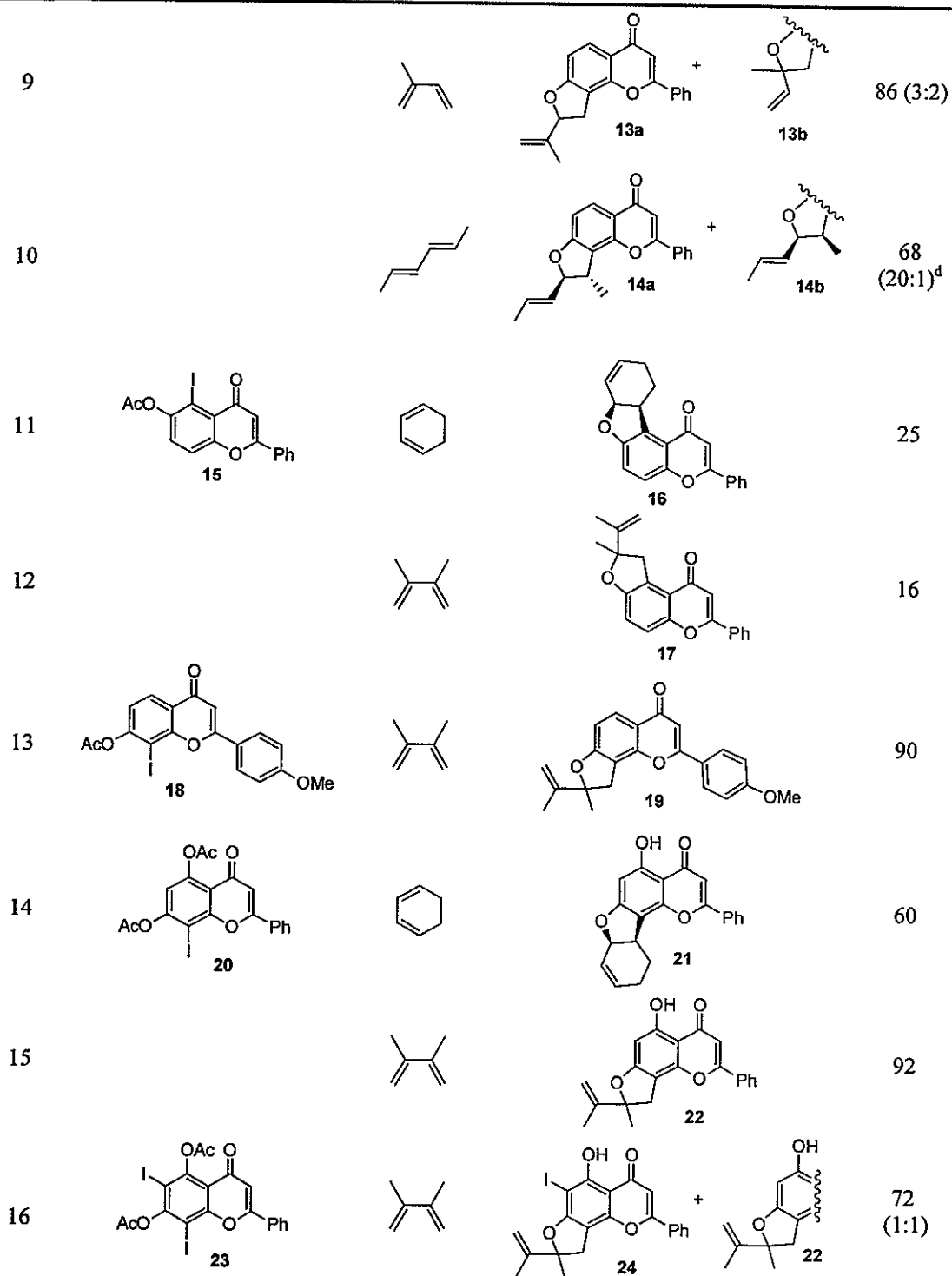
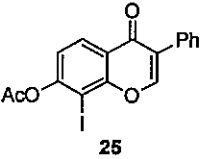
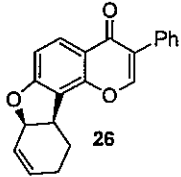
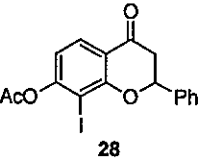
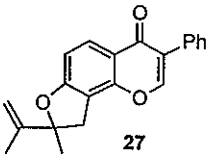
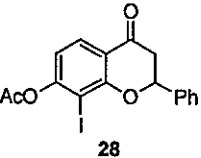
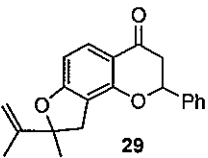


Table 1. Synthesis of dihydrofuroflavonoids by palladium-catalyzed annulation.^a

entry	flavonoid	1,3-diene	product(s)	% yield ^b (ratio of isomers)
1				62
2				75
3				80
4				82
5				76
6				96
7				85
8				77, 90 ^c



17				70
18				95
19				88, 96 ^c

^aThe iodoacetoxycoumarin (0.25 mmol), Pd(dba)₂ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag₂CO₃ (0.5 mmol), the 1,3-diene (1.0 mmol), and 5 mL of a 4:1 1,4-dioxane/water mixture were stirred at 100 °C for 24 h. ^bAll yields are isolated and based on a single run. ^cThis experiment was performed on a 2.0 mmol scale. ^dThe diene used was 95% *trans,trans*.

Analogous to the annulation of *o*-iodoacetoxycoumarins,⁷ the annulation of various 1,3-dienes by the flavone **4** has given the expected products **5-12** in 62 to 96% yields with excellent regioselectivity (entries 1-8). Running the preparation of **12** on a 2.0 mmol scale resulted in an even higher 90% yield (entry 8), indicating the utility of this procedure for practical applications. The annulation of isoprene gave a 3:2 mixture of regioisomers **13a** and **13b** in an 86% yield (entry 9). The analogous annulation of isoprene by *o*-iodophenol has been shown to be mostly governed by steric factors, favoring addition to the less hindered double bond and thus affording a 7:1 ratio of the corresponding annulation products.⁸ The poor regioselectivity in entry 9 presumably results from the higher reactivity of the cationic arylpalladium intermediate (see the later mechanistic discussion) towards the more electron-rich disubstituted double bond, leading to a competition between steric and electronic factors, which produces a mixture of the two isomeric products. The use of

trans,trans-2,4-hexadiene (95% purity) gave a 20:1 ratio of isomers **14a** and **14b** in a 68% yield (entry 10). The exclusive generation of *E*-stereochemistry in the newly formed carbon-carbon double bond in products **7**, **9**, **10** and **14** is consistent with the intermediacy of a *syn*- π -allylpalladium intermediate in these reactions.⁹

In order to broaden the scope of this reaction, similar reactions have been performed on flavonoids **15**, **18**, **20**, **23**, **25**, and **28**. Steric hindrance in the vicinity of the iodo group in the flavone **15** gave lower yields of the desired annulation products **16** and **17**, presumably due to slower oxidative addition to the Pd(0) catalyst or insertion of the diene (entries 11 and 12).

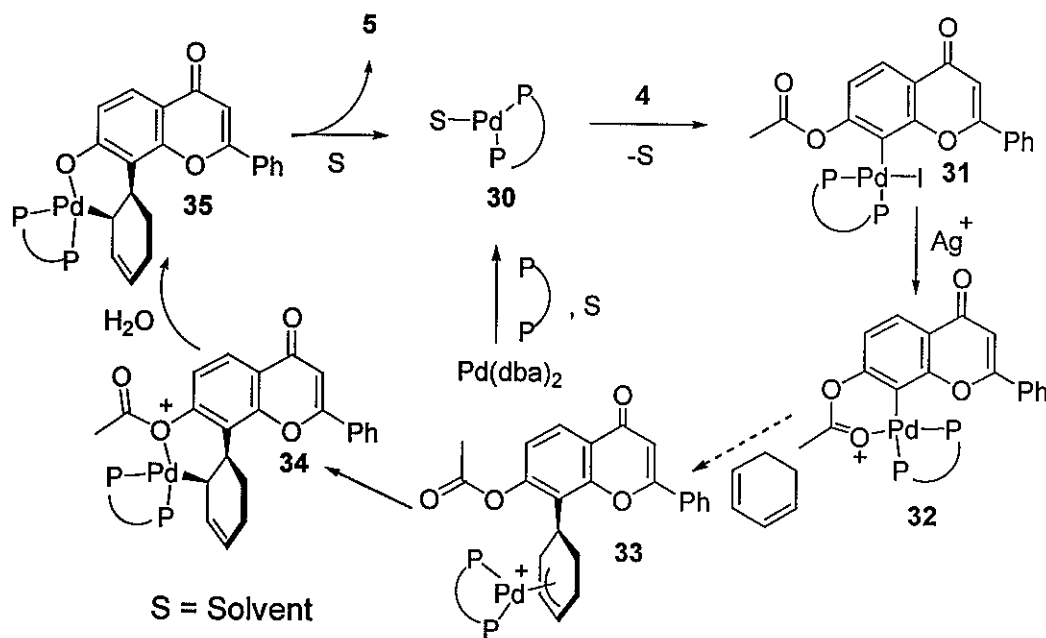
Since annulations of 1,3-dienes with electron-rich *o*-iodophenols have given lower yields of the desired annulation products in previous studies in our group,⁸ the electron-rich flavones **18**, **20** and **23** presented a significant challenge to our methodology. Contrary to our earlier results, using our current reaction conditions, the annulation of 2,3-dimethyl-1,3-butadiene by flavone **18** gave a 90 % yield of the expected annulation product **19** (entry 13). Despite a longer reaction time (96 h), the annulation of 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene by flavone **20**, followed by a basic work-up, afforded annulated products **21** and **22** in 60 % and 92 % yields respectively (entries 14 and 15). Our attempts to accomplish a *bis*-annulation using electron-rich flavone **23** failed, presumably due to significant steric hindrance at the C-6 position of the flavone moiety. Instead, this process gave a 1:1 mixture of monoannulated product **24** and deiodinated monoannulated product **22** in a 72 % overall yield (entry 16).

The annulation of 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene by isoflavone **25** produced the desired annulation products **26** and **27** in 70 and 95 % yields respectively (entries 17 and 18). Finally, the annulation of 2,3-dimethyl-1,3-butadiene by flavanone **28**

afforded the desired annulation product **29** in an 88 % yield. Running the latter reaction on a 2.0 mmol scale increased the isolated yield to 96 % (entry 19).

A proposed mechanism for this annulation process is shown in Scheme 2. Initial oxidative addition of the iodo-flavone **4** to palladium intermediate **30** generated *in situ* forms arylpalladium intermediate **31**. Abstraction of the iodide by silver carbonate leads to a cationic intermediate **32**, presumably stabilized by coordination to the neighboring acetyl group. Next, complex **32** adds to the 1,3-diene in a *cis*-fashion to give σ -allylpalladium complex and then π -allylpalladium intermediate **33**. Coordination of the acetoxy oxygen to the palladium atom, leading to the formation of intermediate **34**, restricts rotation of the C-C bonds in the allyl moiety, and is,

Scheme 2



presumably, responsible for the high stereoselectivity when *trans,trans*-2,4-hexadiene is utilized (Table 1, entry 10). Since no hydrolysis of the starting material **4** has been observed under our reaction conditions, the deacylation of intermediate **34** is presumably accelerated

by coordination of the acetyl oxygen atom to the cationic palladium center. Finally, complex **35** undergoes reductive elimination to give the final product **5** and regenerates the palladium catalyst **30**.

Conclusions

In summary, we have developed an efficient palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids, which affords good yields of dihydrofuroflavonoids. The process is quite general, regio- and stereoselective, and a variety of *o*-iodoacetoxyflavonoids, as well as symmetrical and unsymmetrical 1,3-dienes can be utilized.

EXPERIMENTAL SECTION

General. All ^1H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz respectively. All melting points are uncorrected. Thin layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was performed with UV light (254 nm) and an acidic KMnO_4 solution. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. Iodine, acetic anhydride, pyridine, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene, 4-methyl-1,3-pentadiene, and isoprene were purchased from Aldrich Chemical Co., Inc. *E*-2-Methyl-1,3-pentadiene, 3-methyl-1,3-pentadiene (a mixture of *E* and *Z* isomers) and 2,4-dimethyl-1,3-pentadiene were purchased from Lancaster Co., Inc. *trans,trans*-2,4-Hexadiene (95% pure) was purchased from ChemSamp Co., Inc. 5-Hydroxyflavone, 6-hydroxyflavone, 7-hydroxyflavone, 7-hydroxyflavanone and 5,7-

dihydroxyflavone were purchased from Indofine Co., Inc. 7-Hydroxyisoflavone was prepared according to a literature procedure.¹⁰ *E*-1-Phenyl-1,3-butadiene and 1,5,5-trimethyl-3-methylenecyclohexene were prepared by Wittig condensation according to a literature procedure.¹¹

Synthesis of *o*-iodoacetoxyflavonoids

General iodination procedure A. Compounds **4**, **15**, **18**, **20**, **25** and **28** were prepared by acylation of the corresponding *o*-iodohydroxyflavonoids, which in turn were prepared by iodination of the corresponding hydroxyflavonoids according to the procedure for the iodination of hydroxycoumarins¹² indicated below. Iodine (5.0 mmol) dissolved in 50 mL of aq KI solution was slowly added to a solution of the corresponding hydroxyflavonoid (5.0 mmol) in the minimal amount of aq ammonia solution at 0-5 °C. The resulting reaction mixture was stirred for 2 h, left overnight in the refrigerator, and then acidified by 20% aq HCl to pH = 4-5. The precipitated *o*-iodohydroxyflavonoid was filtered, washed with water and dried in air. The resulting white solid was dissolved in 20 mL of acetic anhydride (a minimal amount of DMF can be used as a co-solvent) in the presence of 1 mL of pyridine and stirred for 24 h at 100 °C. Then the reaction mixture was quenched with chilled water (caution, heat evolution!) and after 2 h extracted by CH₂Cl₂. The organic extract was washed with water and aq NH₄Cl solution, and dried over anhydrous MgSO₄ for 4 h. After evaporation of the CH₂Cl₂, the resulting white solid was purified by column chromatography using silica gel as a stationary phase and 5:1 hexanes-ethyl acetate as the eluent. The following compounds were prepared using this procedure.

7-Acetoxy-8-iodoflavone (4). Obtained in a 90 % overall yield from 7-hydroxyflavone, recrystallized from 1:1 ethanol-water: white solid, mp 180-182 °C; ^1H NMR (CDCl_3) δ 2.45 (s, 3H), 6.87 (s, 1H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.50-7.60 (m, 3H), 8.00-8.10 (m, 2H), 8.24 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.5, 83.1, 107.4, 115.6, 120.7, 122.7, 126.9, 127.3, 129.5, 131.3, 132.3, 156.5, 164.3, 168.2, 177.5; IR (neat) 1765, 1647 cm^{-1} ; HRMS m/z 405.9707 (calcd for $\text{C}_{17}\text{H}_{11}\text{IO}_4$, 405.9702).

6-Acetoxy-5-iodoflavone (15). Obtained in an 89 % overall yield from 6-hydroxyflavone, recrystallized from 1:1 ethanol-water: white solid, mp 227-228 °C; ^1H NMR (CDCl_3) δ 2.45 (s, 3H), 6.84 (s, 1H), 7.39 (d, $J = 9.0$ Hz, 1H), 7.50-7.58 (m, 3H), 7.62 (d, $J = 9.0$ Hz, 1H), 8.00-8.10 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.6, 88.2, 107.6, 120.1, 126.4, 127.3, 127.4, 129.3, 131.2, 132.1, 150.0, 154.7, 162.0, 169.1, 176.7; IR (neat) 1762, 1642 cm^{-1} ; HRMS m/z 405.9800 (calcd for $\text{C}_{17}\text{H}_{11}\text{IO}_4$, 405.9702).

7-Acetoxy-8-iodo-4'-methoxyflavone (18). Obtained in a 95 % overall yield from 7-hydroxy-4'-methoxyflavone, recrystallized from 1:1 ethanol-water: white solid, mp 212-217 °C; ^1H NMR (CDCl_3) δ 2.44 (s, 3H), 3.88 (s, 3H), 6.76 (s, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.99 (d, $J = 8.8$ Hz, 2H), 8.21 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.5, 55.8, 83.0, 105.8, 114.8, 120.4, 122.6, 123.5, 127.3, 128.6, 156.2, 156.4, 162.9, 164.2, 168.2, 177.3; IR (neat) 1771, 1645 cm^{-1} ; HRMS m/z 442.0284 (calcd for $\text{C}_{18}\text{H}_{13}\text{IO}_5$, 442.0277).

5,7-Diacetoxy-8-iodoflavanone (20). Obtained in an 80 % overall yield from 5,7-dihydroxyflavanone, purified by column chromatography using 4:1 hexanes-ethyl acetate: white solid, mp 192-194 °C; ^1H NMR (CDCl_3) δ 2.44 (s, 3H), 2.52 (s, 3H), 6.70 (s, 1H), 7.40

(s, 1H), 7.45-7.60 (m, 3H), 7.80-7.90 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.5, 21.6, 87.2, 108.7, 110.8, 116.1, 126.5, 129.4, 131.0, 132.2, 151.5, 154.6, 157.8, 162.8, 167.8, 168.5, 175.6; IR (neat) 1777, 1645, 1602 cm^{-1} ; HRMS m/z 463.9765 (calcd for $\text{C}_{19}\text{H}_{13}\text{IO}_6$, 463.9757).

7-Acetoxy-8-iodoisoflavone (25). Obtained in a 90 % overall yield from 7-hydroxyisoflavone, recrystallized from 1:1 ethanol-water: white solid, mp 224-226 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 2.45 (s, 3H), 7.21 (d, $J = 8.4$ Hz, 1H), 7.40-7.48 (m, 3H), 7.52-7.60 (m, 2H), 8.13 (s, 1H), 8.34 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.5, 82.8, 120.7, 123.3, 125.8, 128.2, 128.8, 128.9, 129.1, 131.3, 153.5, 156.4, 156.5, 168.1, 175.5; IR (neat) 1766, 1591 cm^{-1} ; HRMS m/z 405.9707 (calcd for $\text{C}_{17}\text{H}_{11}\text{IO}_4$, 405.9702).

7-Acetoxy-8-iodoflavanone (28). Obtained in an 85 % overall yield from 7-hydroxyflavanone, purified by column chromatography using 4:1 hexanes-ethyl acetate: white solid, mp 86-89 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 2.40 (s, 3H), 2.90-3.20 (m, 2H), 5.63 (dd, $J = 12.0, 3.6$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 7.30-7.60 (m, 5H), 7.96 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.6, 43.9, 80.3, 80.4, 83.8, 108.5, 117.0, 119.4, 126.1, 128.5, 129.0, 129.1, 138.3, 158.0, 161.9, 168.2, 190.5; IR (neat) 1766, 1690 cm^{-1} ; HRMS m/z 407.9867 (calcd for $\text{C}_{17}\text{H}_{13}\text{IO}_4$, 407.9859).

General iodination procedure B. Compound **23** was prepared by acylation of the corresponding *o*-iodohydroxyflavonoids, which in turn were prepared by iodination of the corresponding hydroxyflavonoids using iodine monochloride. Iodine monochloride (5.0 mmol) dissolved in 5 mL of CH_2Cl_2 was slowly added to a solution of the corresponding hydroxyflavonoid (5.0 mmol) in the minimal amount DMF at room temperature. The resulting reaction mixture was stirred for 24 h and diluted with water (50 mL). The

precipitated *o*-iodohydroxyflavonoid was filtered, washed with water and dried in air. The resulting white solid was dissolved in 20 mL of acetic anhydride (a minimal amount of DMF can be used as a co-solvent) in the presence of 1 mL of pyridine and stirred for 24 h at 100 °C. Then the reaction mixture was quenched with chilled water (caution, heat evolution!) and after 2 h extracted by CH₂Cl₂. The organic extract was washed with water and aq NH₄Cl solution, and dried over anhydrous MgSO₄ for 4 h. After evaporation of the CH₂Cl₂, the resulting white solid was purified by column chromatography using silica gel as a stationary phase and 5:1 hexanes-ethyl acetate as the eluent. The following compounds were prepared using this procedure.

5,7-Diacetoxy-6,8-diiodoflavone (23). Obtained in a 93% overall yield from 5,7-dihydroxyflavone, purified by column chromatography using 4:1 hexanes-ethyl acetate: white solid, mp 218-220 °C; ¹H NMR (CDCl₃) δ 2.44 (s, 3H), 2.52 (s, 3H), 6.74 (s, 1H), 7.48-7.58 (m, 3H), 7.95-8.05 (m, 2H); ¹³C NMR (CDCl₃) δ 21.5, 21.7, 80.8, 87.6, 108.2, 116.2, 126.9, 129.5, 129.6, 130.7, 132.5, 151.8, 156.4, 157.1, 163.2, 175.4; IR (neat) 1780, 1645 cm⁻¹; HRMS *m/z* 589.8728 (calcd for C₁₉H₁₂I₂O₆, 589.8723).

Palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids.

General procedure. The *o*-iodoacetoxyflavonoid (0.25 mmol), Pd(dba)₂ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag₂CO₃ (0.5 mmol) and 1,4-dioxane (4 mL) were stirred in a capped vial for 5 min, and then water (1 mL) and the 1,3-diene (1.0 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature, filtered and the filtrate was concentrated to give a yellow residue. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1

hexanes/ethyl acetate as the eluent to afford after solvent removal the final product. Solid products were then recrystallized from 1:1 ethanol/water. The following new compounds were prepared using this procedure.

2-Phenyl-7a,10,11,11a-tetrahydrobenzo[*b*]-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (5).

Obtained in a 62 % yield: white solid, mp 122-124 °C; ¹H NMR (CDCl₃) δ 1.63-1.76 (m, 1H), 2.05-2.33 (m, 3H), 3.81 (ddd, *J* = 11.9, 8.0, 4.9 Hz, 1H), 5.18 (dt, *J* = 8.0, 1.7 Hz, 1H), 6.08 (dp, *J* = 10.2, 2.0 Hz, 1H), 6.27 (dd, *J* = 10.2, 4.9 Hz, 1H), 6.75 (s, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 7.52-7.57 (m, 3H), 7.84-7.90 (m, 2H), 8.07 (d, *J* = 8.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 23.3, 24.8, 38.7, 80.7, 107.7, 109.5, 115.6 (solvent impurity), 118.2, 118.5, 123.7, 126.2, 127.5, 129.4, 131.6, 132.3, 134.4, 154.2, 162.6, 164.6, 178.1; IR (neat) 1645, 1604 cm⁻¹; HRMS *m/z* 316.1104 (calcd for C₂₁H₁₆O₃, 316.1099).

Dihydrofuroflavone 6. Obtained in a 75 % yield: white solid, mp 110-114 °C; ¹H NMR (CDCl₃) δ 1.06 (s, 3H), 1.12 (s, 3H), 1.75 (s, 3H), 1.79 (d, *J* = 14.0 Hz, 1H), 1.84 (d, *J* = 15.0 Hz, 1H), 1.92 (d, *J* = 15.0 Hz, 1H), 2.08 (s, *J* = 14.0 Hz, 1H), 3.35 (s, 2H), 5.86 (s, 1H), 6.75 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 7.45-7.60 (m, 3H), 7.80-7.95 (m, 2H), 8.04 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 24.1, 28.8, 29.9, 31.1, 40.5, 44.3, 48.4, 91.0, 107.5, 109.2, 113.4, 117.9, 122.6, 126.3, 127.3, 129.3, 131.6, 132.1, 138.5, 153.9, 162.5, 164.3, 178.3; IR (neat) 1635, 1604 cm⁻¹; HRMS *m/z* 372.1730 (calcd for C₂₅H₂₄O₃, 372.1725).

2-Phenyl-8-(*E*-2-phenylethenyl)-8,9-dihydro-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (7).

Obtained in an 80 % yield: white solid mp 117-120 °C; ¹H NMR (CDCl₃) δ 3.38 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.75 (dd, *J* = 15.6, 9.6 Hz, 1H), 5.62-5.67 (m, 1H), 6.41 (dd, *J* = 15.6, 7.2 Hz, 1H), 6.75 (s, 1H), 6.77 (d, *J* = 15.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 7.20-7.70 (m, 8H),

7.85-7.88 (m, 2H), 8.07 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 33.3, 86.1, 107.5, 109.0, 113.5, 115.6 (solvent impurity), 118.5, 126.3, 127.0, 127.3, 127.6, 128.6, 128.9, 129.3, 131.7, 132.0, 133.4, 136.0, 153.8, 162.6, 165.0, 178.2; IR (neat) 1640, 1604 cm^{-1} ; HRMS m/z 366.1261 (calcd for $\text{C}_{25}\text{H}_{18}\text{O}_3$, 366.1256).

8-(2-Methyl-1-propenyl)-2-phenyl-8,9-dihydro-4H-furo[2,3-*h*]-1-benzopyran-4-one

(8). Obtained in an 82% yield: white solid, mp 122-124 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.82 (s, 3H), 1.83 (s, 3H), 3.16 (dd, $J = 15.6, 8.0$ Hz, 1H), 3.63 (dd, $J = 15.6, 9.2$ Hz, 1H), 5.50 (d, $J = 7.8$ Hz, 1H), 5.72 (q, $J = 8.4$ Hz, 1H), 6.87 (s, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 7.40-7.60 (m, 3H), 7.80-7.90 (m, 2H), 8.03 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.7, 26.1, 33.6, 82.6, 107.5, 108.9, 113.8, 115.6 (solvent impurity), 118.2, 124.0, 126.2, 127.4, 129.2, 131.6, 132.1, 139.5, 153.7, 162.5, 165.1, 178.1; IR (neat) 1640, 1604 cm^{-1} ; HRMS m/z 318.1262 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256).

8-(2-*E*-Buten-2-yl)-2-phenyl-8,9-dihydro-4H-furo[2,3-*h*]-1-benzopyran-4-one (9).

Obtained in a 76 % yield: white solid, mp 125-128 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.65-1.72 (m, 6H), 3.16 (dd, $J = 15.9, 8.2$ Hz, 1H), 3.58 (dd, $J = 15.9, 9.9$ Hz, 1H), 5.42 (t, $J = 9.0$ Hz, 1H), 5.72 (q, $J = 7.0$ Hz, 1H), 6.75 (s, 1H), 6.88 (d, $J = 8.6$ Hz, 1H), 7.45-7.55 (m, 3H), 7.85-7.90 (m, 2H), 8.06 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 10.9, 13.5, 31.3, 90.7, 107.6, 108.7, 113.8, 118.3, 124.0, 126.3, 127.5, 129.3, 131.6, 132.1, 133.9, 153.7, 162.5, 165.5, 178.1; IR (neat) 1636, 1602 cm^{-1} ; HRMS m/z 318.1262 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256).

8-Methyl-2-phenyl-8-(*E*-1-propenyl)-8,9-dihydro-4H-furo[2,3-*h*]-1-benzopyran-4-

one (10). Obtained in a 96 % yield: white solid, mp 136-138 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.65 (s, 3H), 1.74 (d, $J = 5.9$ Hz, 3H), 3.31 (d, $J = 15.5$ Hz, 1H), 3.45 (d, $J = 15.5$ Hz, 1H), 5.70-5.90

(m, 2H), 6.76 (s, 1H), 6.87 (d, $J = 8.6$ Hz, 1H), 7.45-7.60 (m, 3H), 7.81-7.93 (m, 2H), 8.06 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.0, 26.8, 39.3, 91.0, 107.5, 109.1, 113.3, 118.2, 125.4, 126.2, 127.4, 129.2, 131.6, 132.1, 134.1, 154.0, 162.5, 164.3, 178.2; IR (neat) 1640, 1600 cm^{-1} ; HRMS m/z 318.1262 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256).

8-Methyl-8-(2-methyl-1-propenyl)-2-phenyl-8,9-dihydro-4H-furo[2,3-*h*]-1-benzopyran-4-one (11). Obtained in an 85 % yield: white solid, mp 120-122 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.62 (s, 3H), 1.77-1.79 (m, 6H), 3.41 (d, $J = 15.6$ Hz, 1H), 3.52 (d, $J = 15.6$ Hz, 1H), 5.60 (m, 1H), 6.75 (s, 1H), 6.87 (d, $J = 8.6$ Hz, 1H), 7.48-7.56 (m, 3H), 7.85-7.92 (m, 2H), 8.07 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.6, 27.0, 28.9, 40.9, 91.2, 107.6, 109.1, 113.4, 118.2, 126.3, 127.4, 129.3, 129.4, 131.6, 132.2, 136.7, 153.9, 162.4, 164.1, 178.1; IR (neat) 1639, 1605 cm^{-1} ; HRMS m/z 332.1417 (calcd for $\text{C}_{22}\text{H}_{20}\text{O}_3$, 332.1412).

8-Methyl-2-phenyl-8-(2-propenyl)-8,9-dihydro-4H-furo[2,3-*h*]-1-benzopyran-4-one (12). Obtained in a 77 % yield: white solid, mp 148-151 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.66 (s, 3H), 1.87 (s, 3H), 3.30 (d, $J = 15.6$ Hz, 1H), 3.50 (d, $J = 15.6$, 1H), 4.92 (s, 1H), 5.15 (s, 1H), 6.75 (s, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 7.45-7.55 (m, 3H), 7.85-7.90 (m, 2H), 8.08 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.5, 38.4, 93.3, 107.6, 109.0, 110.9, 113.2, 115.6 (from solvent), 118.2, 126.3, 127.5, 129.2, 131.6, 132.1, 146.9, 153.9, 162.5, 164.4, 178.2; IR (neat) 1640, 1599 cm^{-1} ; HRMS m/z 318.1262 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256).

2-Phenyl-8-(2-propenyl)-8,9-dihydro-4H-furo[2,3-*h*]-1-benzopyran-4-one (13a) and 8-ethenyl-8-methyl-2-phenyl-8,9-dihydro-4H-furo[2,3-*h*]-1-benzopyran-4-one (13b). Compounds **13a** and **13b** were isolated as a 3:2 inseparable mixture of regioisomers

respectively in an 86 % overall yield. The ratio of regioisomers was confirmed by ^1H NMR spectroscopy and HPLC. **13a**: ^1H NMR (CDCl_3) δ 1.83 (s, 3H), 3.30 (dd, $J = 16.0, 8.0$ Hz, 1H), 3.65 (dd, $J = 16.0, 10.0$ Hz, 1H), 4.99 (s, 1H), 5.15 (s, 1H), 5.44 (t, $J = 8.8$ Hz, 1H), 6.12 (s, 1H), 6.90 (d, $J = 8.7$ Hz, 1H), 7.45-7.55 (m, 3H), 7.80-7.90 (m, 2H), 8.07 (d, $J = 8.7$ Hz, 1H). **13b**: ^1H NMR (CDCl_3) δ 1.67 (s, 3H), 3.33 (d, $J = 15.7$ Hz, 1H), 3.47 (d, $J = 15.7$ Hz, 1H), 5.18 (dd, $J = 10.8, 0.7$ Hz, 1H), 5.38 (dd, $J = 17.2, 0.7$ Hz, 1H), 6.11 (dd, $J = 17.2, 10.8$ Hz, 1H), 6.07 (s, 1H), 6.89 (d, $J = 8.7$ Hz, 1H), 7.45-7.55 (m, 3H), 7.80-7.90 (m, 2H), 8.07 (d, $J = 8.7$ Hz, 1H). The following ^{13}C NMR, IR and HRMS data were obtained on the mixture of isomers: ^{13}C NMR (CDCl_3) δ 17.3, 26.7, 31.8, 39.1, 88.1, 91.0, 107.6, 108.7, 109.0, 113.1, 113.2, 113.4, 113.8, 118.4, 118.5, 126.3, 127.5, 127.6, 129.3, 131.7, 132.0, 132.1, 140.9, 143.2, 153.7, 153.9, 162.4, 162.5, 164.2, 165.3, 178.1, 178.1; IR (neat) 1645, 1609 cm^{-1} ; HRMS m/z 304.1105 (calcd for $\text{C}_{20}\text{H}_{16}\text{O}_3$, 304.1099)

9-Methyl-2-phenyl-8-(*E*-1-propenyl)-8,9-dihydro-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (20:1 mixture of *trans*- and *cis*-isomers **14a** and **14b** respectively). Obtained as a white solid in a 68 % overall yield. *trans*-Isomer **14a**: ^1H NMR (CDCl_3) δ 1.37 (d, $J = 7.1$ Hz, 3H), 1.84 (dd, $J = 6.5, 1.6$ Hz, 3H), 3.74 (p, $J = 7.8$ Hz, 1H), 5.31 (t, $J = 8.4$ Hz, 1H), 5.76 (ddq, $J = 15.3, 8.4, 1.6$ Hz, 1H), 5.98 (dq, $J = 15.3, 6.5$ Hz, 1H), 6.75 (s, 1H), 6.87 (d, $J = 8.5$ Hz, 1H), 7.45-7.60 (m, 3H), 7.85-7.95 (m, 2H), 8.06 (d, $J = 8.5$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 15.5, 18.3, 38.4, 89.8, 107.6, 109.2, 118.6, 119.5, 125.5, 126.2, 127.4, 129.3, 131.6, 132.2, 132.8, 153.9, 162.5, 164.2, 178.1; IR (neat) 1640, 1604 cm^{-1} ; HRMS m/z 318.1262 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256). *Cis*-isomer **14b** was detected as a minor isomer by ^1H NMR spectroscopy and HPLC chromatography.

2-Phenyl-4c,7,8,8a-tetrahydrobenzo[*b*]-4*H*-furo[3,2-*f*]-1-benzopyran-4-one (16).

Obtained in a 25 % yield: yellow oil; ^1H NMR (CDCl_3) δ 1.10-1.30 (m, 2H), 2.30-2.40 (m, 1H), 3.95-4.08 (m, 1H), 4.95-5.02 (m, 1H), 6.10-6.17 (m, 1H), 6.27-6.32 (m, 1H), 6.77 (s, 1H), 7.16 (d, $J = 7.2$ Hz, 1H), 7.40 (d, $J = 7.2$ Hz, 1H), 7.45-7.60 (m, 3H), 7.85-7.97 (m, 2H); ^{13}C NMR (CDCl_3) δ 24.3, 25.0, 41.0, 80.4, 107.7, 116.3, 118.2, 121.4, 123.1, 126.5, 129.2, 130.4, 131.7, 132.2, 135.1, 151.8, 156.5, 163.2, 179.3; IR (neat) 1636, 1466 cm^{-1} ; HRMS m/z 316.1104 (calcd for $\text{C}_{21}\text{H}_{16}\text{O}_3$, 316.1099).

6-Methyl-2-phenyl-6-(2-propenyl)- 5,6-dihydro-4*H*-furo[3,2-*f*]-1-benzopyran-4-one

(17). Obtained in a 16 % yield: yellow oil; ^1H NMR (CDCl_3) δ 1.60 (s, 3H), 1.86 (s, 3H), 3.65 (dd, $J = 16.0, 0.8$ Hz, 1H), 3.76 (dd, $J = 16.0, 0.8$ Hz, 1H), 4.86 (s, 1H), 5.11 (s, 1H), 6.74 (s, 1H), 7.14 (d, $J = 8.8$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.47-7.54 (m, 3H), 7.85-7.93 (m, 2H); ^{13}C NMR (CDCl_3) δ 19.0, 26.5, 29.9, 42.7, 92.3, 107.5, 110.2, 115.6 (from solvent), 118.0, 121.8, 124.3, 126.5, 129.2, 131.6, 132.2, 147.7, 151.5, 156.5, 163.4, 179.9; IR (neat) 1638, 1591 cm^{-1} ; HRMS m/z 318.1262 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256).

2-(4-Methoxyphenyl)-8-methyl-8-(2-propenyl)-8,9-dihydro-4*H*-furo[2,3-*h*]-1-

benzopyran-4-one (19). Obtained in a 90 % yield: white solid, mp 82-84 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.66 (s, 3H), 1.88 (s, 3H), 3.30 (d, $J = 15.6$ Hz, 1H), 3.46 (d, $J = 15.6$ Hz, 1H), 3.89 (s, 3H), 4.92 (s, 1H), 5.14 (s, 1H), 6.65 (s, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 7.01 (d, $J = 9.6$ Hz, 2H), 7.82 (d, $J = 9.6$ Hz, 2H), 8.06 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.5, 38.4, 55.7, 93.1, 106.2, 108.8, 110.9, 113.0, 114.6, 115.6, 118.2, 124.4, 127.4, 127.9, 147.0, 153.8, 162.4, 164.2, 178.1; IR (neat) 1638, 1605 cm^{-1} ; HRMS m/z 348.1370 (calcd for $\text{C}_{22}\text{H}_{20}\text{O}_4$, 348.1362).

5-Hydroxy-2-phenyl-7a,10,11,11a-tetrahydrobenzo[*b*]-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (21). The reaction mixture was stirred for 96 h and then NaOH (500 mg) was added. The resulting mixture was stirred for 24 h, acidified with 5 % aq HCl and extracted with CH₂Cl₂. The organic extract was washed with water and aq NH₄Cl solution, and dried over anhydrous MgSO₄ for 4 h. After evaporation of the CH₂Cl₂, the resulting white solid was purified by column chromatography using silica gel as a stationary phase and 5:1 hexanes-ethyl acetate as the eluent. Obtained in a 60 % yield: white solid, mp 186-188 °C; ¹H NMR (CDCl₃) δ 1.57-1.62 (m, 1H), 1.95-2.09 (m, 1H), 2.10-2.22 (m, 2H), 3.55-3.65 (m, 1H), 5.05-5.12 (m, 1H), 5.95-6.05 (m, 1H), 6.20-6.28 (m, 1H), 6.44 (s, 1H), 6.66 (s, 1H), 7.45-7.60 (m, 3H), 7.85-7.95 (m, 2H); ¹³C NMR (CDCl₃) δ 23.2, 23.9, 37.6, 81.2, 90.0, 106.0, 106.4, 113.8, 123.5, 126.5, 129.3, 131.6, 131.9, 135.0, 157.5, 158.3, 163.9, 165.9, 183.0; IR (neat) 3033, 1667, 1626 cm⁻¹; HRMS *m/z* 332.1054 (calcd for C₂₁H₁₆O₄, 332.1049).

5-Hydroxy-8-methyl-2-phenyl-8-(2-propenyl)-8,9-dihydro-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (22). The preparation of this compound is similar to the preparation of flavone 21. Obtained in a 92% yield: white solid, mp 90-92 °C; ¹H NMR (CDCl₃) δ 1.62 (s, 3H), 1.84 (s, 3H), 3.04 (d, *J* = 15.6 Hz, 1H), 3.24 (d, *J* = 15.6 Hz, 1H), 4.89 (s, 1H), 5.10 (s, 1H), 6.47 (s, 1H), 6.66 (s, 1H), 7.50-7.55 (m, 3H), 7.85-7.90 (m, 2H); ¹³C NMR (CDCl₃) δ 18.9, 26.4, 37.5, 89.6, 93.6, 105.9, 106.1, 109.0, 110.7, 126.5, 129.3, 131.6, 131.9, 147.0, 157.1, 158.4, 163.8, 165.7, 182.8; IR (neat) 3200, 1669, 1625 cm⁻¹; HRMS *m/z* 334.1212 (calcd for C₂₁H₁₈O₄, 334.1205).

5-Hydroxy-6-iodo-8-methyl-2-phenyl-8-(2-propenyl)-8,9-dihydro-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (24). The preparation of this compound is similar to the preparation of

flavone **21**. Obtained as an inseparable 2:1 mixture of **24** and **22** in a 72 % overall yield: white solid, mp 92-95 °C; ^1H NMR (CDCl_3) δ 1.61 (s, 3H), 1.83 (s, 3H), 3.03 (d, $J = 15.6$ Hz, 1H), 3.24 (d, $J = 15.6$ Hz, 1H), 4.89 (s, 1H), 5.09 (s, 0.5 H), 6.47 (s, 1H), 7.50-7.55 (m, 3H), 7.85-7.90 (m, 2H); ^{13}C NMR (CDCl_3) δ 18.9, 26.4, 36.1, 37.5, 89.5, 93.6, 105.9, 106.1, 109.0, 110.7, 126.5, 129.3, 131.9, 147.0, 157.1, 163.9, 165.9, 182.8; IR (neat) 3200, 1667, 1627 cm^{-1} ; MS m/z 333 ($\text{M}^+ - \text{I}$).

3-Phenyl-7a,10,11,11a-tetrahydrobenzo[*b*]-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (26).

Obtained in a 70 % yield: white solid, mp 100-103 °C; ^1H NMR (CDCl_3) δ 2.00-2.30 (m, 4H), 3.65-3.80 (m, 1H), 5.10-5.20 (m, 1H), 6.05-6.13 (m, 1H), 6.22-6.32 (m, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 7.30-7.65 (m, 5H), 7.94 (s, 1H), 8.16 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 23.3, 24.5, 38.6, 80.8, 109.6, 118.1, 119.2, 123.6, 125.4, 128.3, 128.7, 129.3, 132.3, 134.6, 152.3, 154.1, 164.5, 176.0; IR (neat) 1643, 1446 cm^{-1} ; HRMS m/z 316.1104 (calcd for $\text{C}_{21}\text{H}_{16}\text{O}_3$, 316.1099).

8-Methyl-3-phenyl-8-(2-propenyl)-8,9-dihydro-4*H*-furo[2,3-*h*]-1-benzopyran-4-one

(27). Obtained in a 95 % yield: white solid, mp 86-88 °C; ^1H NMR (CDCl_3) δ 1.64 (s, 3H), 1.86 (s, 3H), 3.20 (d, $J = 15.6$ Hz, 1H), 3.42 (d, $J = 15.6$ Hz, 1H), 4.91 (s, 1H), 5.13 (s, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 7.35-7.48 (m, 3H), 7.50-7.60 (m, 2H), 7.91 (s, 1H), 8.18 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.5, 38.4, 93.0, 109.2, 110.9, 113.0, 118.9, 125.4, 128.3, 128.6, 128.7, 129.3, 132.3, 146.7, 152.3, 154.0, 164.2, 175.9; IR (neat) 1644, 1628 cm^{-1} ; HRMS m/z 318.1262 (calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1256).

8-Methyl-2-phenyl-8-(2-propenyl)-2,3,8,9-tetrahydro-4*H*-furo[2,3-*h*]-1-benzopyran-

4-one (29). Obtained as a mixture of 2 diastereomers in an 88 % yield: yellow oil; ^1H NMR

(CDCl₃) δ 1.58 (s, 3H), 1.82 (s, 3H), 2.83 (m, 1H), 2.95-3.10 (m, 2H), 3.15-3.25 (m, 1H), 4.84-4.89 (m, 1H), 5.08 (s, 1H), 5.44-5.52 (m, 1H), 6.54 (d, J = 8.5 Hz, 1H), 7.30-7.60 (m, 5H), 7.84 (d, J = 8.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 18.9, 26.5, 38.3, 44.7, 80.0, 93.1, 105.1, 110.6, 113.2, 115.4, 126.3, 128.9, 129.0, 139.2, 147.1, 159.0, 159.1, 166.3, 190.5; IR (neat) 1681, 1599 cm⁻¹; HRMS m/z 320.1421 (calcd for C₂₁H₂₀O₃, 320.1412).

Scanned ¹H and ¹³C spectra for compounds 4-29 are included in Appendix C (pp. 157-209).

Acknowledgments

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CHAPTER 4. SYNTHESIS OF DIHYDROBENZOFURANS VIA PALLADIUM-CATALYZED ANNULATION OF 1,3-DIENES

To be submitted to the *Journal of Organic Chemistry*

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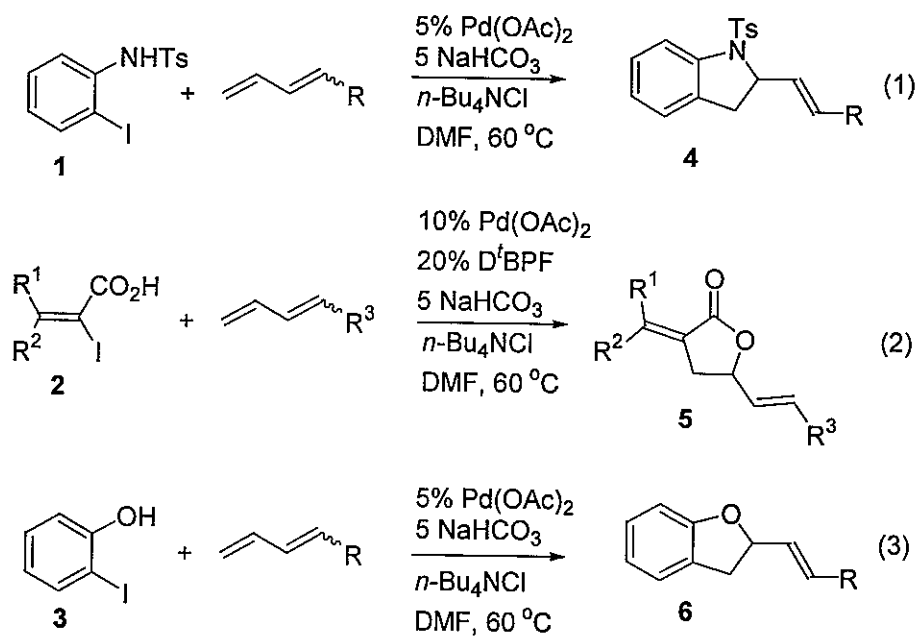
Abstract

The palladium-catalyzed annulation of 1,3-dienes by *o*-iodophenyl acetates provides an efficient approach to biologically interesting dihydrobenzofurans. The annulation is believed to proceed via (1) oxidative addition of the aryl iodide to Pd(0), (2) *cis*-addition of the resulting arylpalladium complex to the 1,3-diene, (3) intramolecular coordination of the phenolic oxygen to the Pd center, (4) hydrolysis of the acetyl group, and (5) reductive elimination of Pd(0), which regenerates the catalyst. This reaction is very general, regioselective, and stereoselective and a wide variety of terminal, cyclic and internal 1,3-dienes, as well as electron-rich and electron-deficient *o*-iodophenyl acetates, can be utilized.

Introduction

Heteroannulation reactions involving π -allylpalladium intermediates are of great utility for the synthesis of heterocyclic systems.¹ We have recently developed in our laboratories

annulations of 1,3-dienes using *o*-iodoanilines (**1**),² 2-iodo-2-alkenoic acids (**2**)³ and *o*-iodophenols (**3**),⁴ which allow an elegant approach to heterocycles **4-6** respectively (eqs 1-3).



Unfortunately, the latter annulation was limited to relatively unhindered 1,3-dienes and electron-deficient *o*-iodophenols.⁴ Our recent success in the synthesis of dihydrofurocoumarins⁵ and dihydrofuroflavonoids⁶ via palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxycoumarins and *o*-iodoacetoxylavonoids respectively prompted us to explore the utility of this methodology for the synthesis of dihydrobenzofurans. We now wish to report the success of this project.

Results and Discussion

We have studied the scope and limitations of the palladium-catalyzed annulation of 1,3-dienes by various *o*-iodophenyl acetates (eq 1) under our previously developed reaction conditions (Table 1).^{5,6}

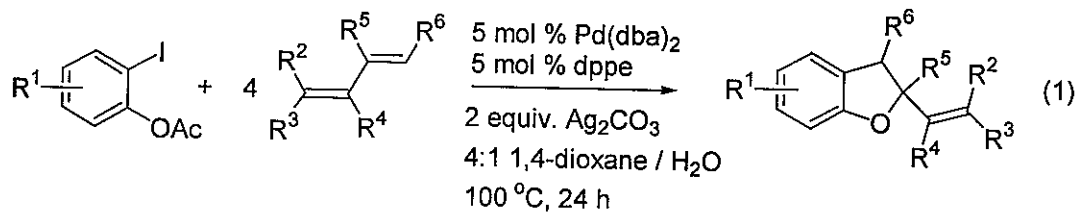
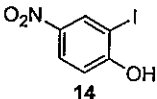
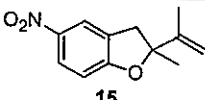
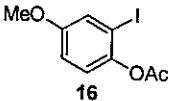
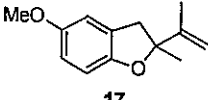
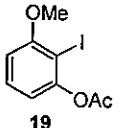
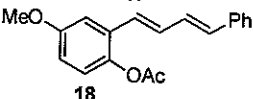
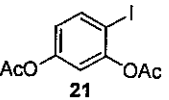
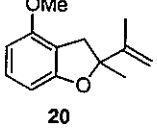
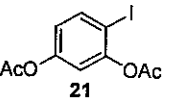
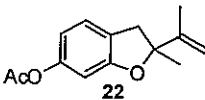
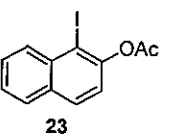
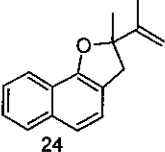


Table 1. Synthesis of dihydrobenzofurans by palladium-catalyzed annulation.^a

entry	aryl iodide	1,3-diene	product(s)	% yield ^b (ratio of isomers)
1				72
2				92, 48, ^c 18 ^d
3				75
4				100, 70, ^c 52 ^d
5				96
6				77
7				60
8				88
9				98

10			72
11			58
12			64
13			67
14			40
15			48

^aThe *o*-iodophenyl acetate (0.25 mmol), Pd(dba)₂ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag₂CO₃ (0.5 mmol), the 1,3-diene (1.0 mmol), and 5 mL of a 4:1 1,4-dioxane/water mixture were stirred at 100 °C for 24 h. ^bAll yields are isolated and based on a single run. ^c*o*-Iodophenol was used as the starting material. ^dThe *o*-iodophenol (0.25 mmol), Pd(OAc)₂ (5 mol %, 0.0125 mmol), diene (1.75 mmol), Na₂CO₃ (0.5 mmol), LiCl (0.5 mmol), and DMF (5 mL) were heated at 100 °C for 3d.

The annulation of 1,3-cyclohexadiene by aryl iodide **1** gave the desired annulation product **2** in a 72 % yield (entry 1). The use of 2,3-dimethyl-1,3-butadiene gave an even higher 92 % yield of dihydrobenzofuran **3** (entry 2). At this point, we examined the necessity of employing the acetyl group and compared our optimal reaction conditions to our previously reported results using *o*-iodophenol.⁴ The use of *o*-chloro- and *o*-bromophenyl acetates, instead of aryl iodide **1**, led to only a trace amount of the desired annulation product **3** and virtually all starting materials were recovered. This could be due to slow oxidative addition of the aryl chlorides and bromides to the Pd(0) complex generated *in situ*. Employing the methyl, benzyl, pivaloyl and benzoyl groups on the phenolic oxygen did not lead to any significant amount of the dihydrobenzofuran **3**, presumably due to a slower rate of hydrolysis

compared to the acetyl group. The annulation carried out under our standard reaction conditions using *o*-iodophenol gave a much lower 48 % yield. The yield of dihydrobenzofuran **3** obtained using reaction conditions employed in our earlier *o*-iodophenol annulation project was disappointingly low and the dehalogenated phenol was isolated in a 70 % yield as a major side-product. These results clearly demonstrate the superiority of our "optimal" reaction conditions. The use of *trans,trans*-2,4-hexadiene gives exclusively *trans*-dihydrobenzofuran **4** in a 75 % yield (entry 3). The stereospecificity of the latter annulation is presumably due to coordination of the phenolic oxygen to the palladium center in the π -allylpalladium intermediate (see the later mechanistic discussion).

Next, a wide variety of electron-rich and electron-deficient aryl iodides were studied. Annulation using various dienes and electron-deficient substrate **5** gave the desired annulation products **6-9** in excellent yields (entries 4-7). We have also compared our "optimal" reaction conditions with the procedure used in our earlier research (entry 4).⁴ Despite a less dramatic difference, compared to the electron-rich substrate **1** (entry 2), our "optimal" reaction conditions have again provided the highest yield of annulation product **6**. The annulation of 2,3-dimethyl-1,3-butadiene by electron-deficient substrates **10** and **12** also gave the desired dihydrobenzofurans **11** and **13** in 88 and 98 % yields respectively (entries 8 and 9). Although the acylated derivative of aryl halide **14** could not be prepared due to its high propensity to hydrolyze, the phenol **14** itself gave the desired dihydrobenzofuran **15** in a 72 % yield (entry 10).

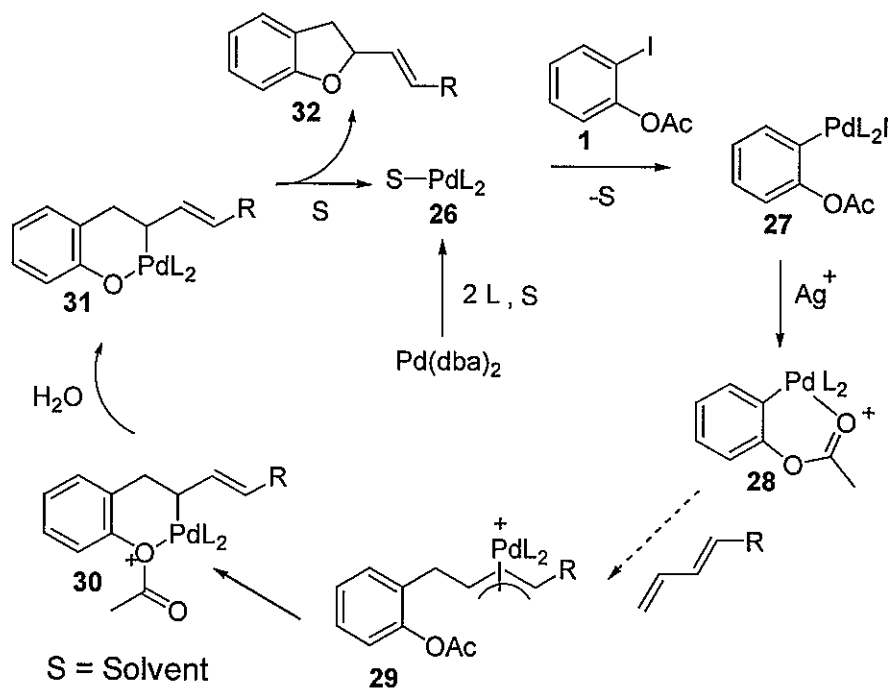
Since electron-rich aryl iodides failed to undergo annulation in our previous studies,⁴ we examined the effectiveness of our new methodology on substrates **16**, **19**, **21** and **23**. The annulation of 2,3-dimethyl-1,3-butadiene by aryl iodide **16** gave the desired annulation

products **17** in a 58 % yield (entry 8). Surprisingly, employing 1-phenyl-1,3-butadiene lead to formation of Heck product **18** in a 64 % yield (entry 11). The 1,3-dienes 1,3-cyclohexadiene and 2,4-hexadiene gave inseparable, complex mixtures of what appear to be Heck-type products.

The increased steric hindrance in substrate **19** seems to have little effect on the yield of dihydrobenzofuran **20** (entry 13). Surprisingly, the remote acetyl group in *bis*-acylated 4-iodoresorcinol **21** was not cleaved during the course of the reaction giving annulated product **22** in a 40 % yield (entry 14). The annulation of sterically hindered substrate **23** gave the desired product **24** in a 48 % yield (entry 15).

A possible mechanism for this annulation process is shown in Scheme 2. Initial oxidative addition of the iodoarene **1** to palladium intermediate **26** generated *in situ* forms arylpalladium intermediate **27**. Abstraction of the iodide by Ag_2CO_3 leads to a cationic intermediate **28**, presumably stabilized by coordination to the neighboring acetyl group. Next, complex **28** adds to the 1,3-diene in a *cis*-fashion to give σ -allylpalladium complex and then π -allylpalladium intermediate **29**. Coordination of the acetoxy oxygen to the palladium atom, leading to the formation of intermediate **30**, restricts rotation of the C-C bonds in the allyl moiety, and is presumably responsible for the high stereoselectivity observed when *trans,trans*-2,4-hexadiene is utilized (Table 1, entries 3 and 6). Since no hydrolysis of the starting material **1** has been observed under our reaction conditions, the deacylation of intermediate **31** is presumably accelerated by coordination of the acylated oxygen atom to the cationic palladium center. Finally, complex **31** undergoes reductive elimination to give the final product **32** with simultaneous regeneration of the palladium catalyst **26**.

Scheme 1



Conclusions

In summary, we have developed an efficient palladium-catalyzed annulation of 1,3-dienes by *o*-acetoxyiodobenzenes, which affords good yields of dihydrobenzofurans. The process is quite general, regio- and stereoselective, and a large variety of electron-deficient and electron-rich *o*-acetoxyiodobenzenes, as well as cyclic, terminal and internal 1,3-dienes can be utilized.

EXPERIMENTAL SECTION

General. All ^1H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz respectively. All melting points are uncorrected. Thin layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was performed with UV light (254 nm) and an acidic KMnO_4 solution. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass

spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. Iodine, acetic anhydride, pyridine, 1,3-cyclohexadiene, and 2,3-dimethyl-1,3-butadiene, *o*-iodophenol, methyl *p*-hydroxybenzoate, *p*-hydroxyacetophenone, *p*-hydroxybenzaldehyde, *p*-nitrophenol, *o*-methoxyphenol, *m*-methoxyphenol, *p*-methoxyphenol, resorcinol and β -naphthol were purchased from Aldrich Chemical Co., Inc. *trans,trans*-2,4-Hexadiene (95% pure) was purchased from ChemSamp Co., Inc. 2-Iodophenol acetate (1),⁷ 4-acetyl-2-iodophenol acetate (10),⁷ 4-formyl-2-iodophenol acetate (12),⁸ 4-iodoresorcinol diacetate (21),⁹ 1-iodo-2-naphthol acetate,¹⁰ 4-methoxy-2-iodophenol,¹¹ 3-methoxy-2-iodophenol,¹¹ *E*-1-phenyl-1,3-butadiene¹² and 1,5,5-trimethyl-3-methylenecyclohexene¹² were prepared according to literature procedures.

General iodination/acylation procedure. Compounds 16, 21 and 23 were prepared by direct acylation of the corresponding phenols. Compounds 5 and 7 were prepared by acylation of the corresponding *o*-iodophenols, which in turn were prepared by iodination of the corresponding phenols according to the procedure for the iodination of hydroxycoumarins¹³ indicated below.

Iodine (5.0 mmol) dissolved in 50 mL of satd aq KI solution was slowly added to a solution of the corresponding phenol (5.0 mmol) in the minimal amount of aq ammonia solution at 0-5 °C. The resulting reaction mixture was stirred for 2 h, left overnight in the refrigerator, and then acidified by 20 % aq HCl to pH = 4-5. The precipitated *o*-iodophenol was extracted with ether, and the organic layer was washed with water. After evaporation of the ether, the resulting solid was dissolved in 20 mL of acetic anhydride (a minimal amount of DMF can be used as a co-solvent) in the presence of 1 mL of pyridine and stirred for 24 h

at 100 °C. Then the reaction mixture was quenched with chilled water (caution, heat evolution!) and after 2 h extracted by CH₂Cl₂. The organic extract was washed with water and aq NH₄Cl solution, and dried over anhydrous MgSO₄ for 4 h. After evaporation of the CH₂Cl₂, the resulting white solid was purified by column chromatography using silica gel as a stationary phase and 5:1 hexanes-ethyl acetate as the eluent. The following compounds were prepared using this procedure.

Methyl 4-acetoxy-3-iodobenzoate (5). Obtained in a 96 % yield: white solid, mp 69-72 °C; ¹H NMR (CDCl₃) δ 2.38 (s, 3H), 3.92 (s, 3H), 7.17 (d, *J* = 8.0 Hz, 1H), 8.04 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.5, 52.8, 90.6, 123.1, 129.6, 131.1, 141.1, 155.0, 165.2, 168.3; IR (neat) 1788, 1766 cm⁻¹; HRMS *m/z* 319.9551 (calcd for C₉H₉IO₃, 319.9546).

2-Iodo-4-nitrophenol (14). Obtained in a 98 % yield as a yellow solid; the ¹H and ¹³C NMR spectra matched data reported in the literature.¹⁴

2-Iodo-4-methoxyphenyl acetate (16). Obtained in a 65 % yield as a colorless solid, mp 89-91 °C; ¹H NMR (CDCl₃) δ 2.36 (s, 3H), 3.77 (s, 3H), 6.60 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.5, 55.9, 79.1, 109.5, 114.4, 139.4, 152.1, 161.1, 168.8; IR (neat) 1766, 1588 cm⁻¹; HRMS *m/z* 291.9601 (calcd for C₁₀H₉IO₄, 291.9596).

2-Iodo-3-methoxyphenyl acetate (19). Obtained in a 63 % yield: yellow solid, mp 92-94 °C; ¹H NMR (CDCl₃) δ 2.37 (s, 3H), 3.90 (s, 3H), 6.65-6.77 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.6, 56.0, 83.7, 108.6, 115.7, 130.0, 152.8, 159.9, 168.8; IR (neat) 1771, 1583 cm⁻¹; HRMS *m/z* 291.9601 (calcd for C₉H₉IO₃, 291.9596).

General procedure for the synthesis of dihydrobenzofurans. The *o*-iodophenyl acetate (0.25 mmol), Pd(dba)₂ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag₂CO₃ (0.5 mmol) and 1,4-dioxane (4 mL) were stirred in a capped vial for 5 min, and then water (1 mL) and the 1,3-diene (1.0 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature, filtered and the filtrate was concentrated to give a yellow residue. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes/ethyl acetate as the eluent to afford after solvent removal the final product. The following new compounds were prepared using this procedure.

1',4,5,5'-Tetrahydrodibenzofuran (2). Obtained in a 72 % yield as a colorless oil; the ¹H and ¹³C NMR spectra matched the data reported in the literature.⁴

2-Methyl-2-(2-propenyl)-2,3-dihydrobenzofuran (3). Obtained in a 92 % yield as a colorless oil; the ¹H and ¹³C NMR spectra matched the data reported in the literature.¹⁵

3-Methyl-2-(*E*-1-propenyl)-2,3-dihydrobenzofuran (4). Obtained in a 75 % yield as a colorless oil: ¹H NMR (CDCl₃) δ 1.16 (d, *J* = 7.2 Hz, 3H), 1.77 (d, *J* = 8.0 Hz, 3H), 3.40-3.50 (m, 1H), 5.09 (t, *J* = 8.4 Hz, 1H), 5.60-5.70 (m, 1H), 5.83-5.90 (m, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.08-7.15 (m, 2H); IR (neat) 3029, 1593 ⁻¹; HRMS *m/z* 174.1048 (calcd for C₁₂H₁₄O, 174.1045). This compound was sufficiently stable to get a clean ¹³C spectra.

Methyl 2-methyl-2-(2-propenyl)-2,3-dihydrobenzofuran-5-carboxylate (6). Obtained in a 100 % yield as a colorless oil: ¹H NMR (CDCl₃) δ 1.55 (s, 3H), 1.80 (dd, *J* = 1.2, 0.8 Hz, 3H), 3.02 (d, *J* = 16.0 Hz, 1H), 3.24 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H), 4.84 (q, *J* = 1.2 Hz, 1H), 5.06 (q, *J* = 0.8 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 0.8 Hz, 1H), 7.86 (dd, *J* =

8.4, 0.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 40.9, 52.1, 91.8, 109.4, 110.6, 122.6, 127.1, 127.2, 131.4, 147.3, 163.2, 167.3; IR (neat) 1714, 1612 cm^{-1} ; m/z 232.1102 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, 232.1099).

Methyl 2-(*E*-2-phenylethenyl)-2,3-dihydrobenzofuran-5-carboxylate (7). Obtained in a 98 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 3.11 (dd, $J = 15.6, 7.6$ Hz, 1H), 3.48 (dd, $J = 15.6, 9.2$ Hz, 1H), 3.88 (s, 3H), 5.42-5.70 (m, 1H), 6.35 (dd, $J = 16.0, 7.6$ Hz, 1H), 6.71 (d, $J = 16.0$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 7.24-7.45 (m, 3H), 7.85-7.95 (m, 2H); ^{13}C NMR (CDCl_3) δ 35.9, 52.1, 85.0, 109.4, 123.0, 127.0, 127.3, 127.8, 128.5, 128.9, 129.2, 131.5, 133.1, 136.2, 163.7, 167.2; IR (neat) 1713, 1615 cm^{-1} ; HRMS m/z 280.1103 (calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3$, 280.1099).

Methyl *trans*-3-methyl-2-(*E*-1-propenyl)-2,3-dihydrobenzofuran-5-carboxylate (8). Obtained in a 77 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.18 (d, $J = 7.2$ Hz, 3H), 1.78 (d, $J = 6.6$ Hz, 3H), 3.45-3.55 (m, 1H), 3.87 (s, 3H), 5.19 (t, $J = 8.8$ Hz, 1H), 5.62 (dd, $J = 16.0, 8.0$ Hz, 1H), 5.88 (dq, $J = 16.0, 6.6$ Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 7.80 (d, $J = 0.8$ Hz, 1H), 7.82 (dd, $J = 7.6, 0.8$ Hz); ^{13}C NMR (CDCl_3) δ 16.14, 18.16, 39.49, 52.07, 89.02, 109.4, 115.6, 122.9, 126.1, 126.2, 131.3, 131.9, 133.6, 163.0, 167.2; IR (neat) 1714, 1612 cm^{-1} ; HRMS m/z 232.1102 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, 232.1099).

Dihydrobenzofuran 9. Obtained in a 60 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 0.99 (s, 3H), 1.07 (s, 3H), 1.71 (s, 3H), 1.45-2.05 (m, 4H), 3.09 (s, 2H), 3.85 (s, 3H), 5.49 (s, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 1.2$ Hz, 1H), 7.84 (dd, $J = 8.0, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 24.1, 29.0, 29.7, 31.0, 43.1, 44.4, 48.2, 52.0, 77.0, 77.3, 77.6, 89.4, 109.3, 122.2, 122.9, 126.9, 127.6, 131.3, 138.0, 163.0, 167.3; IR (neat) 1712, 1611 cm^{-1} ; HRMS m/z 286.1572 (calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3$, 286.1569).

5-Acetyl-2-methyl-2-(2-propenyl)-2,3-dihydrobenzofuran (11). Obtained in an 88 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.57 (s, 3H), 1.82 (dd, $J = 1.6, 0.8$ Hz, 3H), 2.54 (s, 3H), 3.04 (d, $J = 15.6$ Hz, 1H), 3.27 (d, $J = 15.6$ Hz, 1H), 4.87 (q, $J = 1.2$ Hz, 1H), 5.08 (q, $J = 0.8$ Hz, 1H), 6.81 (d, $J = 9.2$ Hz, 1H), 7.78-7.85 (m, 2H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 26.7, 40.9, 92.0, 109.3, 110.6, 125.9, 127.6, 130.7, 130.8, 147.2, 163.4, 196.9; IR (neat) 1674, 1606 cm^{-1} ; HRMS m/z 216.1153 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2$, 216.1150).

2-methyl-2-(2-propenyl)-2,3-dihydrobenzofuran-5-carboxaldehyde (13). Obtained in an 98 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.59 (s, 3H), 1.82 (dd, $J = 1.2, 0.8$ Hz, 3H), 3.07 (d, $J = 15.6$ Hz, 1H), 3.29 (d, $J = 15.6$ Hz, 1H), 4.88 (q, $J = 1.2$ Hz, 1H), 5.08 (q, $J = 0.8$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 7.67-7.73 (m, 2H), 9.82 (s, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 40.7, 92.4, 110.0, 110.8, 126.3, 128.4, 130.5, 133.4, 147.0, 164.6, 190.9; IR (neat) 2747, 1688, 1606 cm^{-1} ; HRMS m/z 202.0997 (calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2$, 202.0994).

2-Methyl-5-nitro-2-(2-propenyl)-2,3-dihydrobenzofuran (15). Obtained in a 72 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.82 (dd, $J = 1.2, 0.8$ Hz, 3H), 1.83 (s, 3H), 3.09 (d, $J = 15.6$ Hz, 1H), 3.32 (d, $J = 15.6$ Hz, 1H), 4.90 (q, $J = 1.2$ Hz, 1H), 5.08 (q, $J = 0.8$ Hz, 1H), 6.82 (dd, $J = 8.8, 2.0$ Hz, 1H), 8.05 (d, $J = 2.0$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 40.7, 93.3, 109.5, 111.1, 121.7, 126.1, 128.3, 141.9, 146.6, 164.5; IR (neat) 1598, 1516 cm^{-1} ; HRMS m/z 219.0898 (calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3$, 219.0895).

5-Methoxy-2-methyl-2-(2-propenyl)-2,3-dihydrobenzofuran (17). Obtained in a 58 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.56 (s, 3H), 1.81 (dd, $J = 1.2, 0.8$ Hz, 3H), 2.94 (d, $J = 14.8$ Hz, 1H), 3.18 (d, $J = 14.8$ Hz, 1H), 3.77 (s, 3H), 4.83 (q, $J = 1.2$ Hz, 1H), 5.07 (d, $J = 0.8$ Hz, 1H), 6.36-6.43 (m, 2H), 7.00 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.2,

26.3, 41.0, 55.7, 91.1, 96.4, 105.9, 110.1, 118.7, 125.2, 148.0, 160.3, 160.6; IR (neat) 1616, 1497 cm^{-1} ; HRMS m/z 204.1153 (calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$, 204.1150).

4-Methoxy-2-(*E,E*-4-phenyl-1,3-butadienyl)phenyl acetate (18). Obtained in a 64 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 2.37 (s, 3H), 3.84 (s, 3H), 6.64 (d, $J = 14$ Hz, 1H), 6.67 (d, $J = 14.4$ Hz, 1H), 6.81 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.90-7.10 (m, 3H), 7.12 (d, $J = 2.8$ Hz, 1H), 7.26 (dd, $J = 8.8, 7.2$ Hz, 1H), 7.35 (t, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 21.2, 55.9, 110.7, 114.4, 123.7, 125.8, 126.8, 128.1, 128.9, 129.3, 130.8, 131.7, 134.2, 137.3, 142.0, 157.6, 170.0; IR (neat) 1755, 1589 cm^{-1} ; HRMS m/z 294.1261 (calcd for $\text{C}_{19}\text{H}_{18}\text{O}_3$, 294.1256).

4-Methoxy-2-methyl-2-(2-propenyl)-2,3-dihydrobenzofuran (20). Obtained in a 67 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.55 (s, 3H), 1.81 (dd, $J = 1.6, 0.8$ Hz, 3H), 2.96 (d, $J = 15.6$ Hz, 1H), 3.18 (d, $J = 15.6$ Hz, 1H), 3.82 (s, 3H), 4.83 (q, $J = 0.8$ Hz, 1H), 5.09 (d, $J = 1.2$ Hz, 1H), 6.40 (d, $J = 8.0$ Hz, 1H), 6.47 (d, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.0, 26.4, 39.1, 55.6, 90.7, 102.8, 103.1, 110.0, 113.6, 129.3, 147.9, 156.8, 160.4; IR (neat) 1609, 1493 cm^{-1} ; HRMS m/z 204.1153 (calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$, 204.1150).

6-Acetoxy-2-methyl-2-(2-propenyl)-2,3-dihydrobenzofuran (22). Obtained in a 40 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.55 (s, 3H), 1.81 (t, $J = 0.8$ Hz, 3H), 2.28 (s, 3H), 2.98 (d, $J = 15.6$ Hz, 1H), 3.22 (d, $J = 15.6$ Hz, 1H), 4.84 (q, $J = 0.8$ Hz, 1H), 5.07 (d, $J = 0.8$ Hz, 1H), 6.50-6.58 (m, 2H), 7.09 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.0, 21.4, 26.3, 41.1, 91.5, 103.9, 110.3, 113.3, 124.4, 125.1, 147.6, 151.0, 159.9, 169.8; IR (neat) 1762, 1607 cm^{-1} ; HRMS m/z 232.1102 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, 232.1099).

2-Methyl-2-(2-propenyl)-2,3-dihydrofuro[3,2-*b*]naphthalene (24). Obtained in a 48 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.63 (s, 3H), 1.86 (s, 3H), 3.29 (d, $J = 16.0$ Hz, 1H), 3.51 (d, $J = 16.0$ Hz, 1H), 4.88 (s, 1H), 5.15 (s, 1H), 7.13 (d, $J = 11.6$ Hz, 1H), 7.23-7.34 (m, 1H), 7.40-7.50 (m, 1H), 7.55 (d, $J = 11.6$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 7.80 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.0, 26.6, 40.6, 91.0, 110.2, 112.5, 118.0, 122.8, 122.9, 126.8, 129.0, 129.2, 129.3, 131.2, 148.1, 156.6; IR (neat) 1631, 1465 cm^{-1} ; HRMS m/z 224.1205 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}$, 224.1201).

Scanned ^1H and ^{13}C spectra for compounds **4-9**, **11**, **13**, **15-20**, **22**, and **24** are included in Appendix D (pp. 210-243).

Acknowledgments

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GENERAL CONCLUSIONS

In this dissertation a new efficient heteroannulation approach to various natural products via palladium-catalyzed annulation of 1,3-dienes by iodoalkenols and acylated *o*-iodophenols is presented. Developed methodology is very general and can be utilized for the synthesis of various substituted dihydrofuroumarins, dihydrofuroflavones, and dihydrobenzofurans.

Chapter 1 describes the palladium-catalyzed annulation of 1,3-dienes by vinylic halides. The presence of a β -hydrogen in the vinylic halide results in β -hydride elimination giving the corresponding alkyne. The presence of a bulky group in the α -position of the vinylic halide results in failure or deceleration of the annulation. A chloride source, pyridine base and electron-rich phosphine are essential for this reaction. Despite the limited scope, our studies provides a deeper insight into this process.

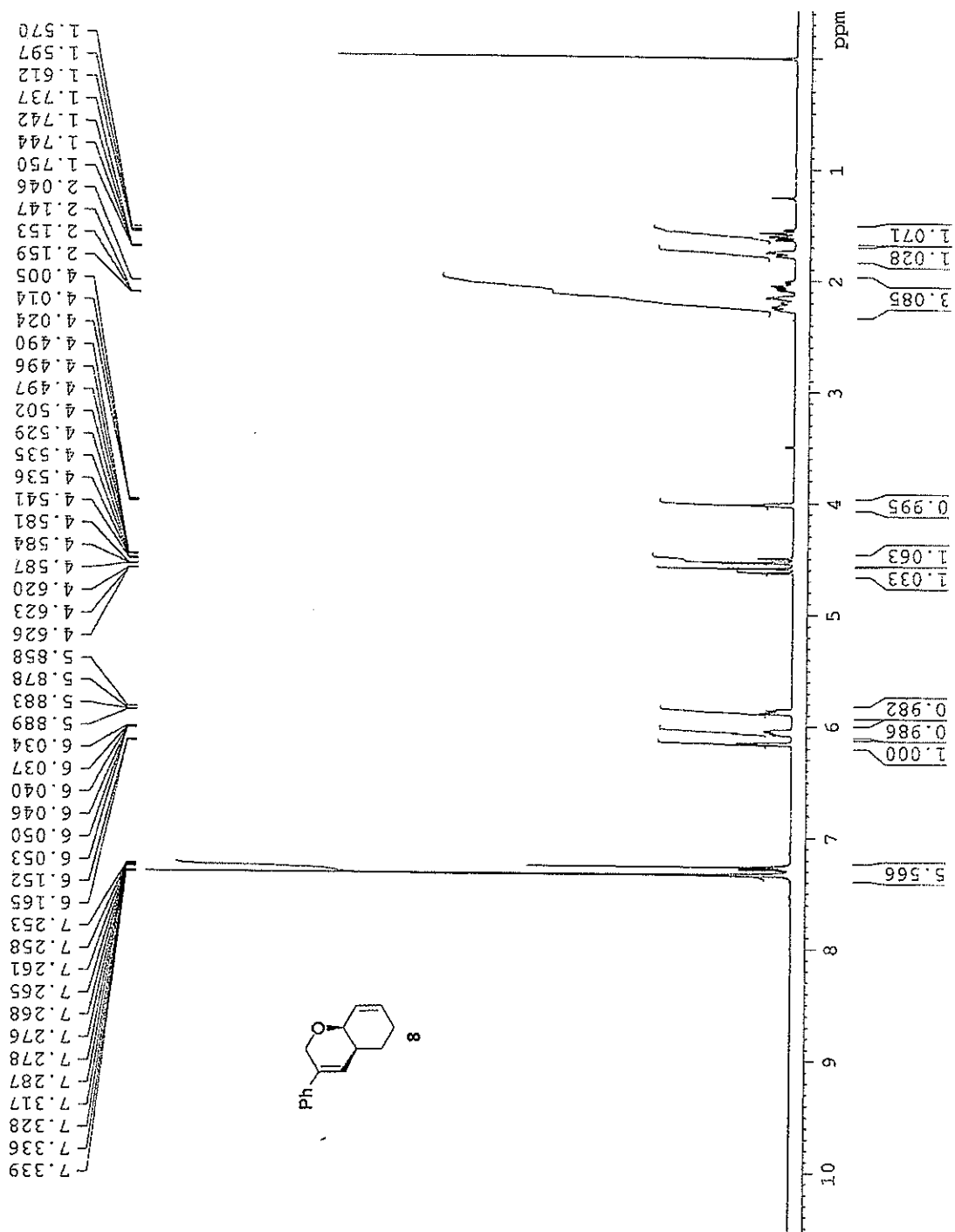
Chapter 2 is a publication that presents a synthesis of biologically active dihydrofurocoumarins via palladium-catalyzed heteroannulation of 1,3-dienes by *o*-iodoacetoxycoumarins. Preliminary studies using *o*-iodophenols revealed a major problem with rapid dehalogenation. The presence of the acetyl group on the phenolic oxygen and the use of silver carbonate as a base are crucial for the successful annulation. This reaction is very general, regio- and stereoselective, and a wide variety of terminal, cyclic and internal 1,3-dienes can be utilized. Derivatization of the annulation products provides an efficient approach to numerous analogues of natural products.

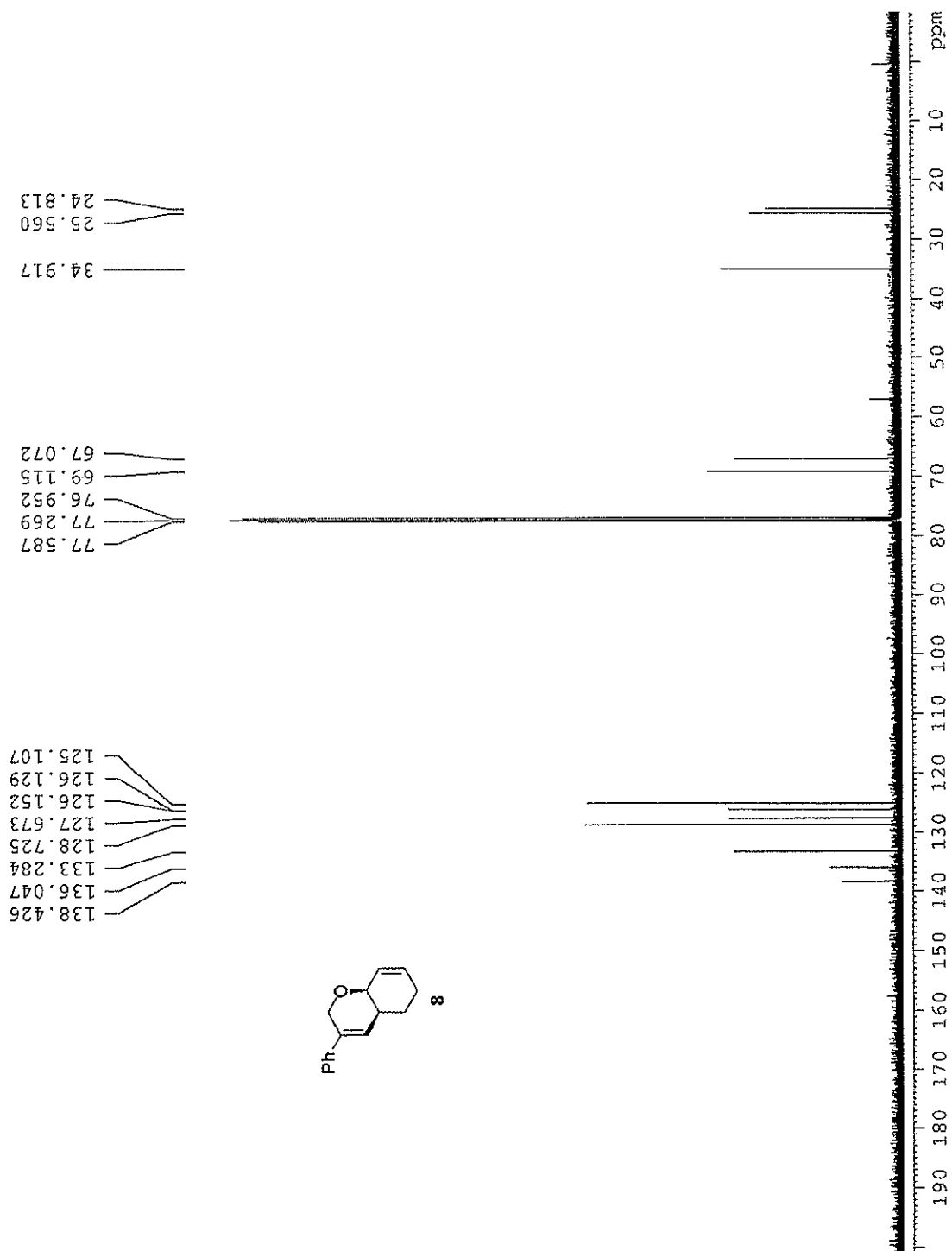
Chapter 3 is focused on synthesis of dihydrofuroflavonoids via palladium-catalyzed annulation of 1,3-dienes. Dihydrofuroflavonoids occur commonly in plants and fruits and are very important because of their pronounced biological properties. Despite significant interest, no efficient, general method for the synthesis of dihydrofuroflavonoids has really

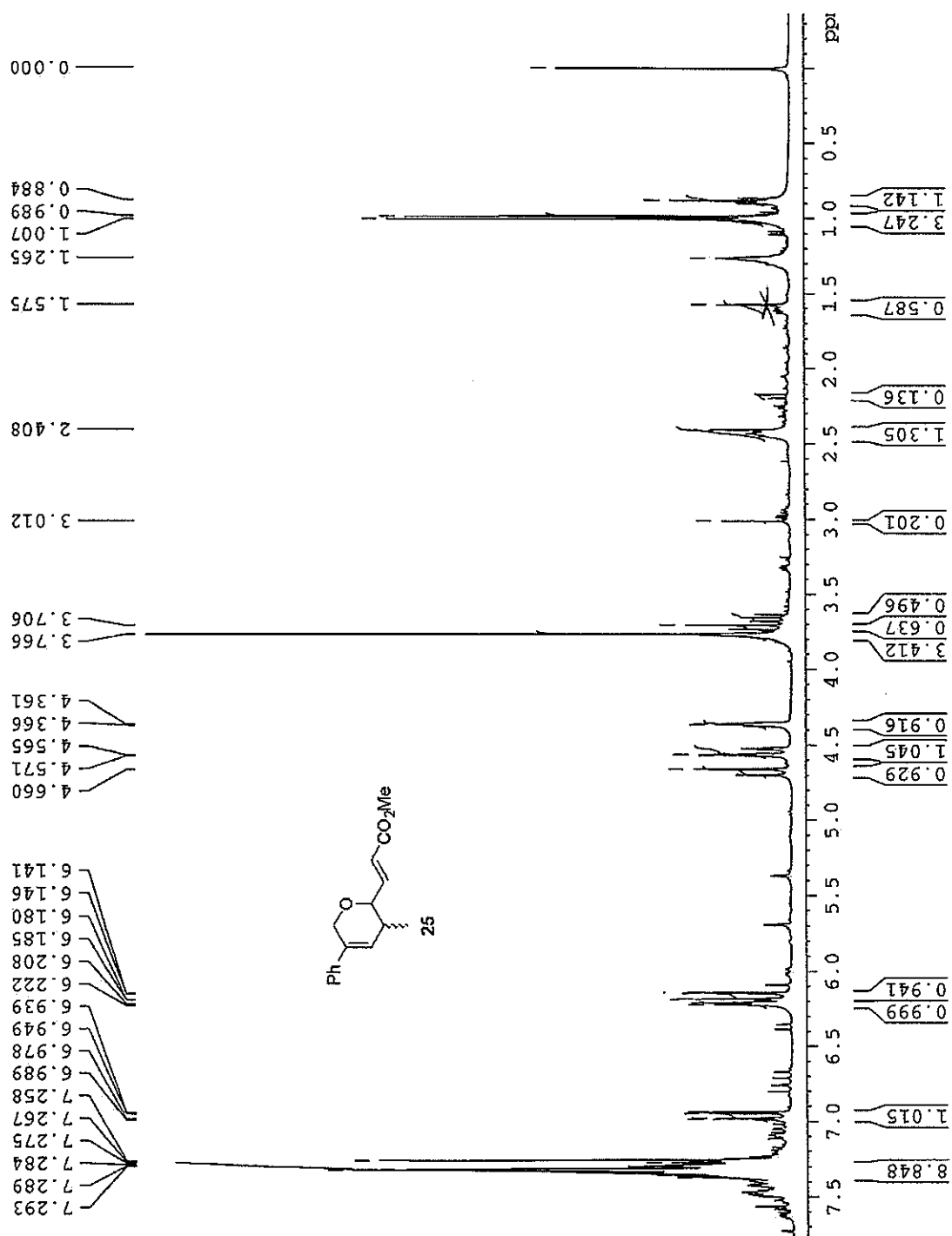
been developed. Our annulation methodology provides a convenient and efficient approach to a wide variety of functionalized flavonoids. This reaction is very general, regioselective, and a wide variety of terminal, cyclic and internal 1,3-dienes can be utilized.

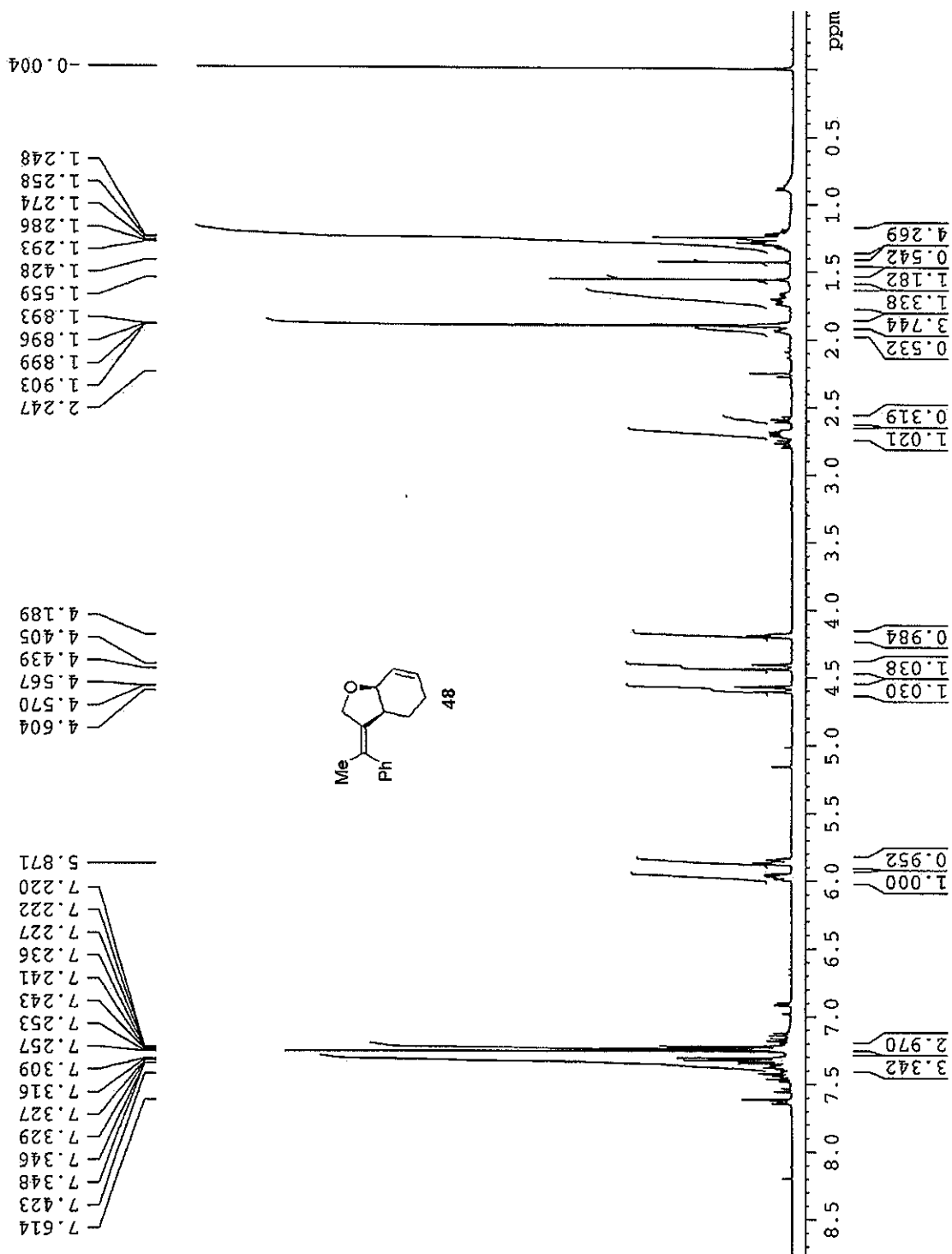
Chapter 4 concerns synthesis of dihydrobenzofurans via palladium-catalyzed annulation of 1,3-dienes. The annulation of electron-rich *o*-iodophenols in earlier studies has been quite problematic due to the undesired dehalogenation. The application of our methodology led to the development of more efficient and general approach to dihydrobenzofurans. Although electron-deficient *o*-iodophenyl acetates give higher yields of corresponding annulation products than electron-rich ones *o*-iodophenyl acetates, this reaction is very general, regioselective, stereoselective and a wide variety of terminal, cyclic and internal 1,3-dienes can be utilized.

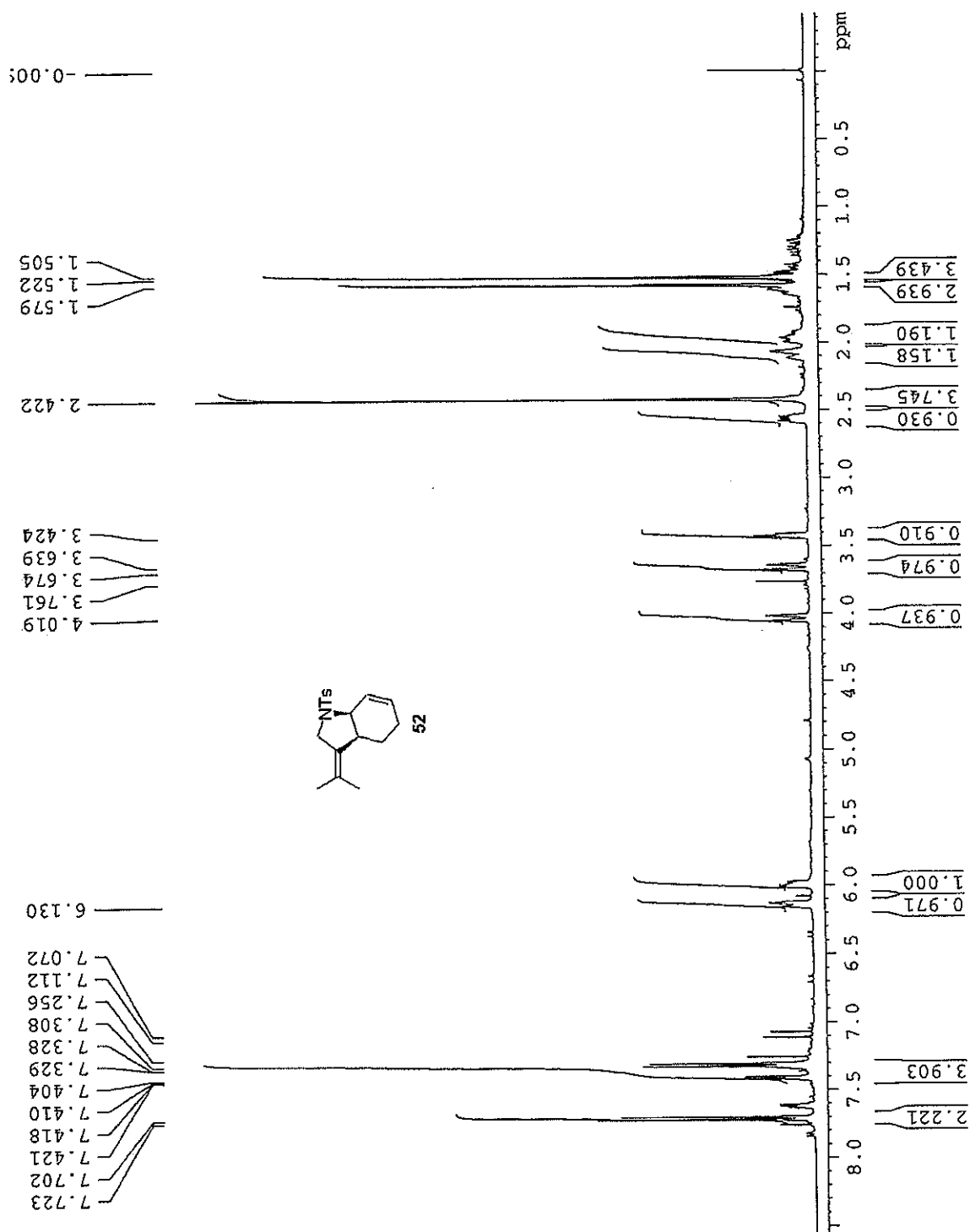
APPENDIX A. CHAPTER 1 ^1H and ^{13}C SPECTRA

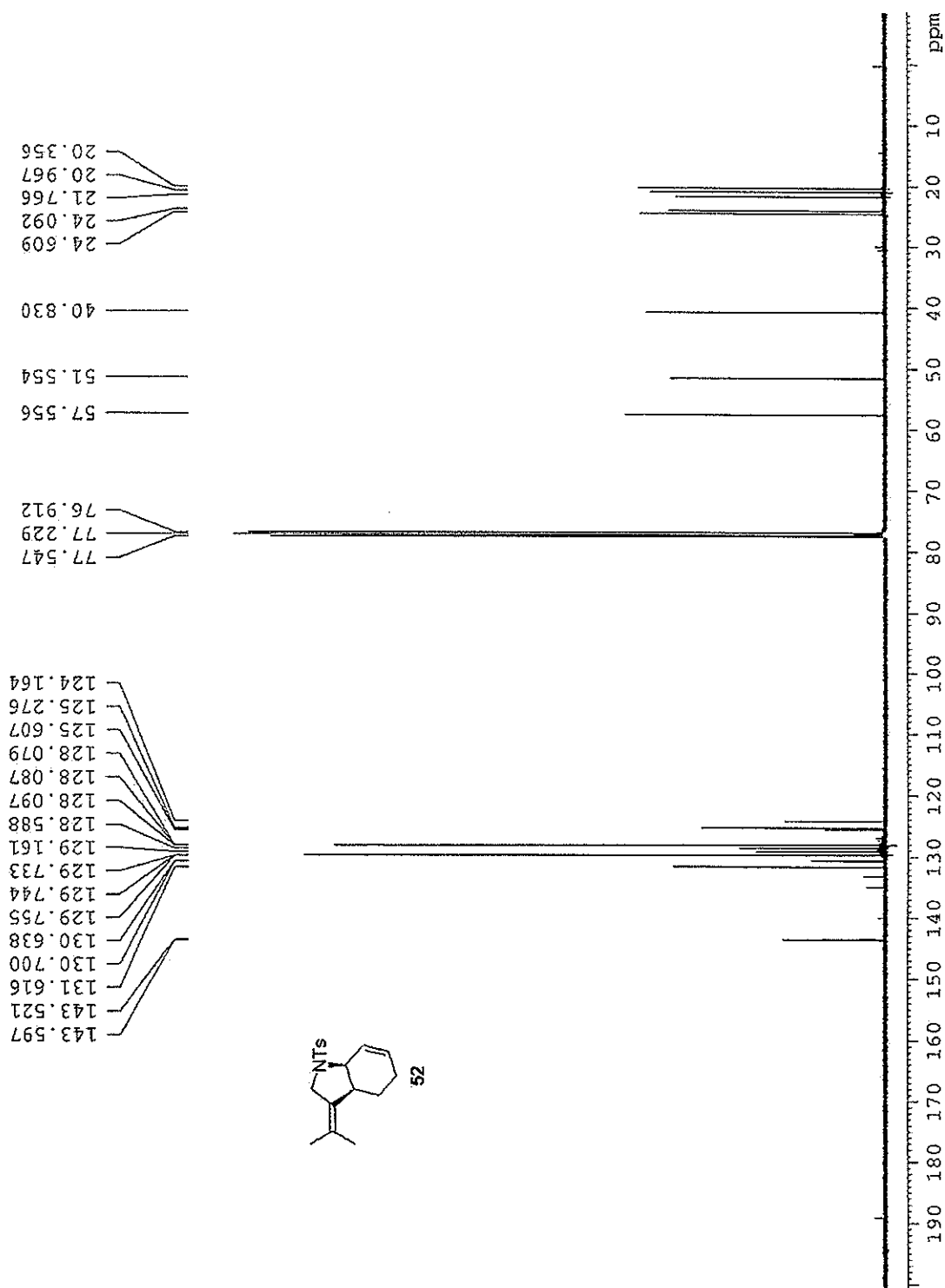




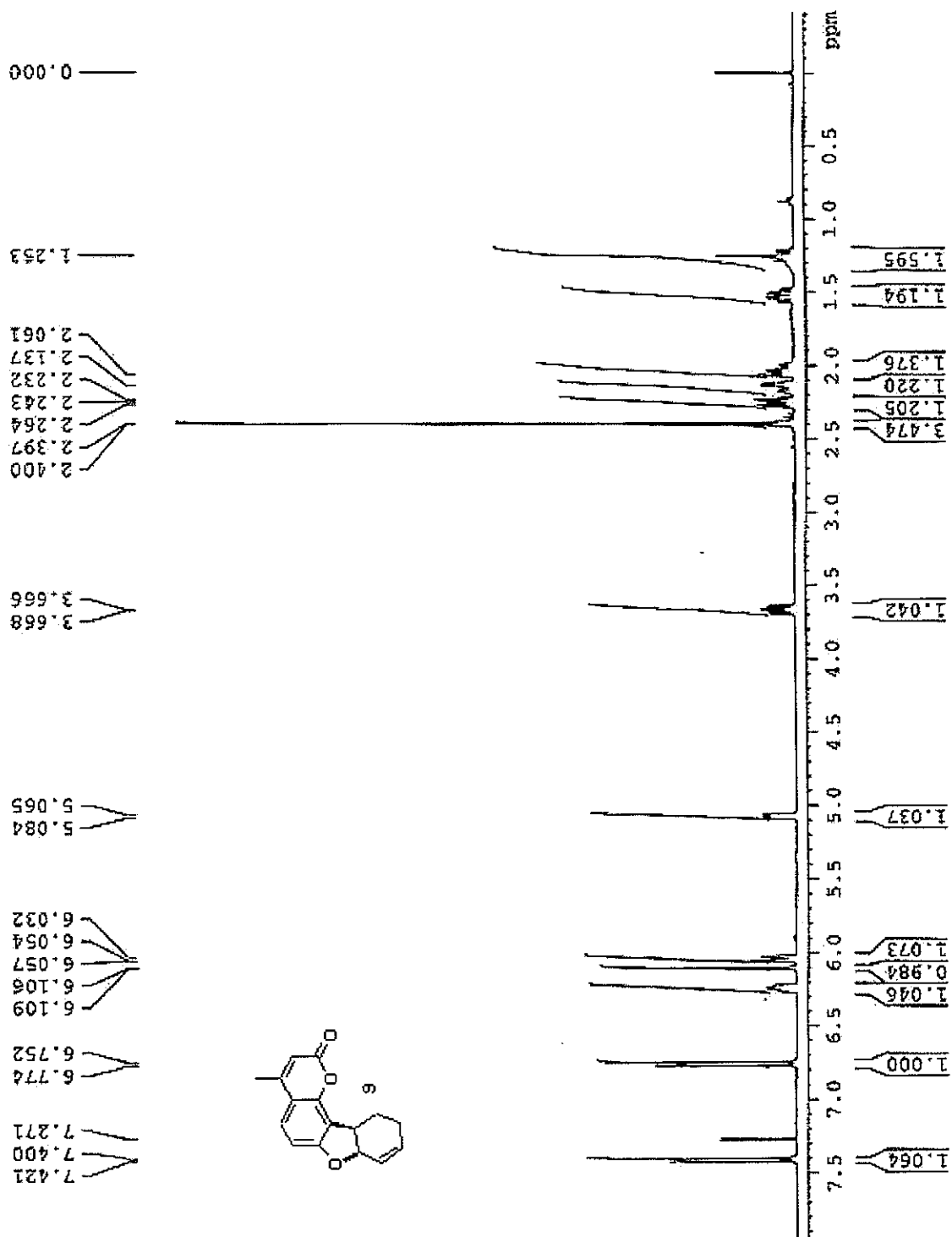


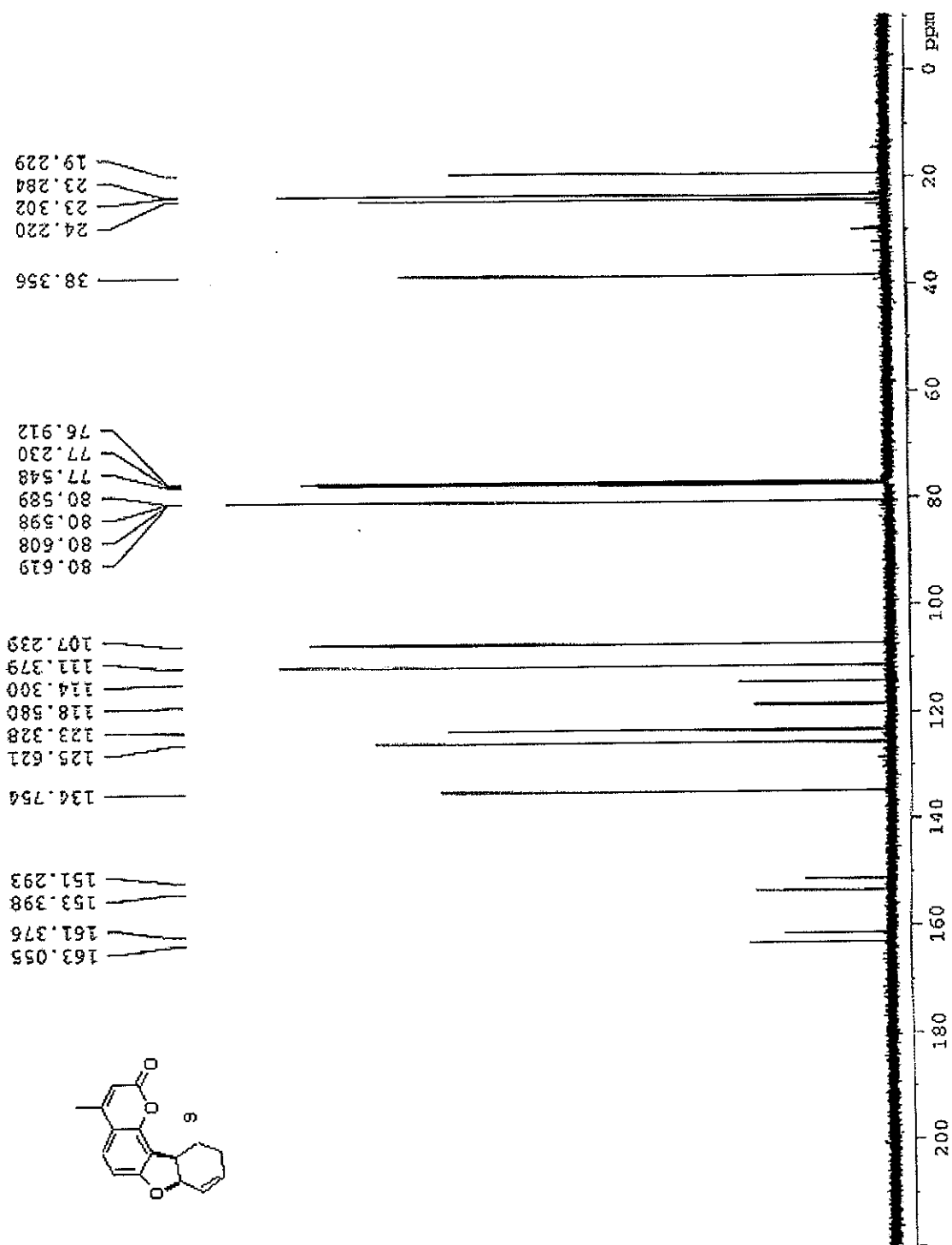


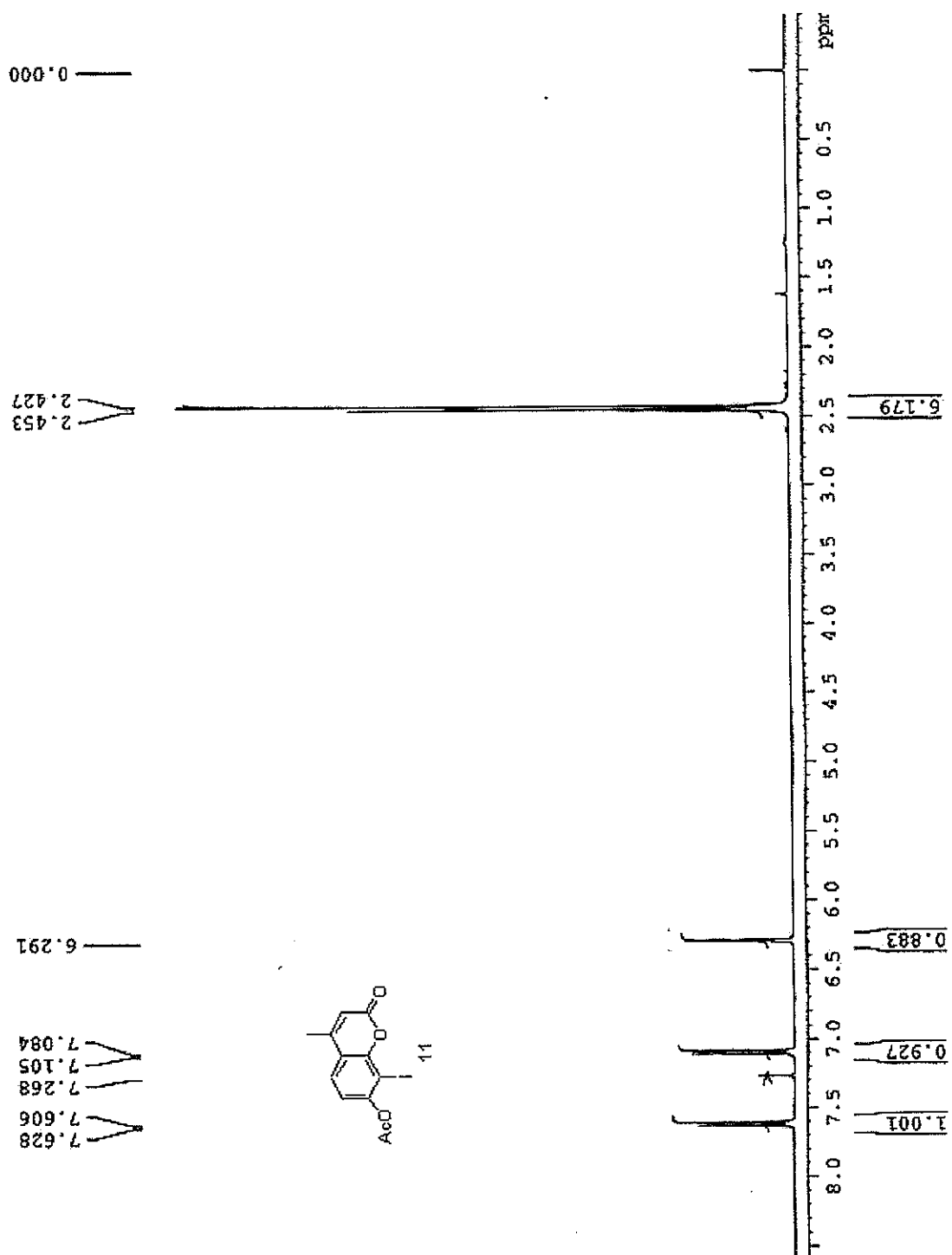


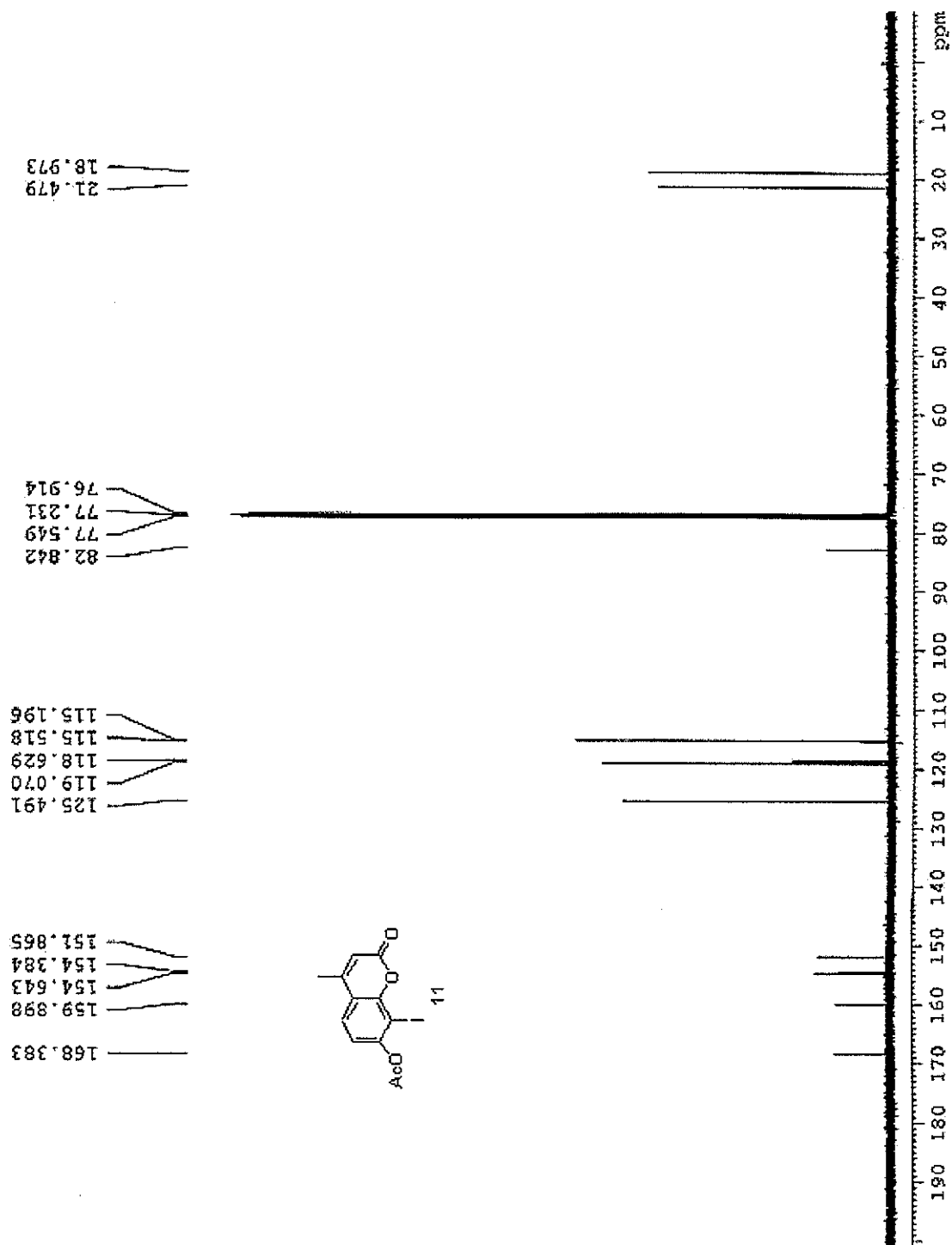


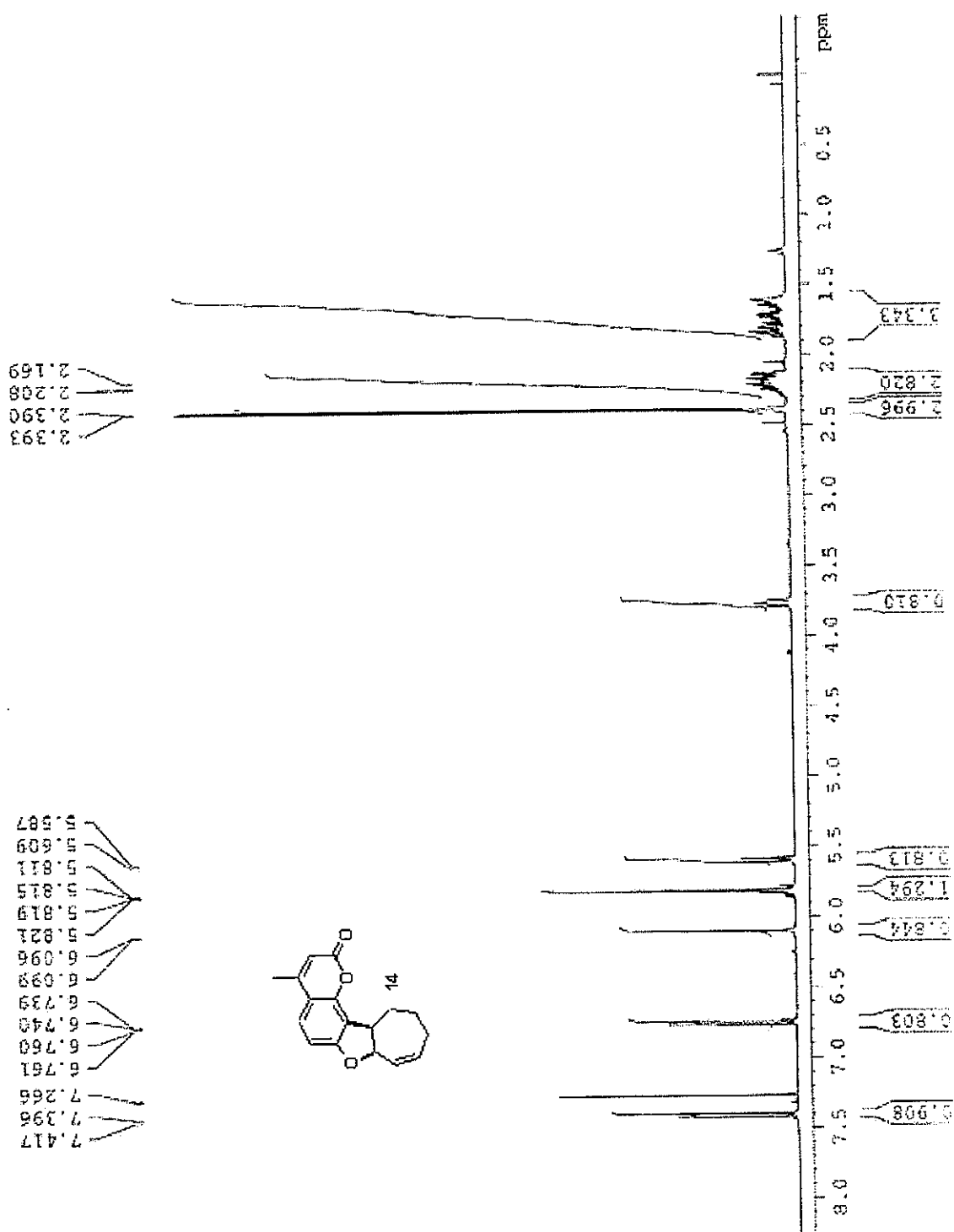
APPENDIX B: CHAPTER 2 ^1H and ^{13}C SPECTRA

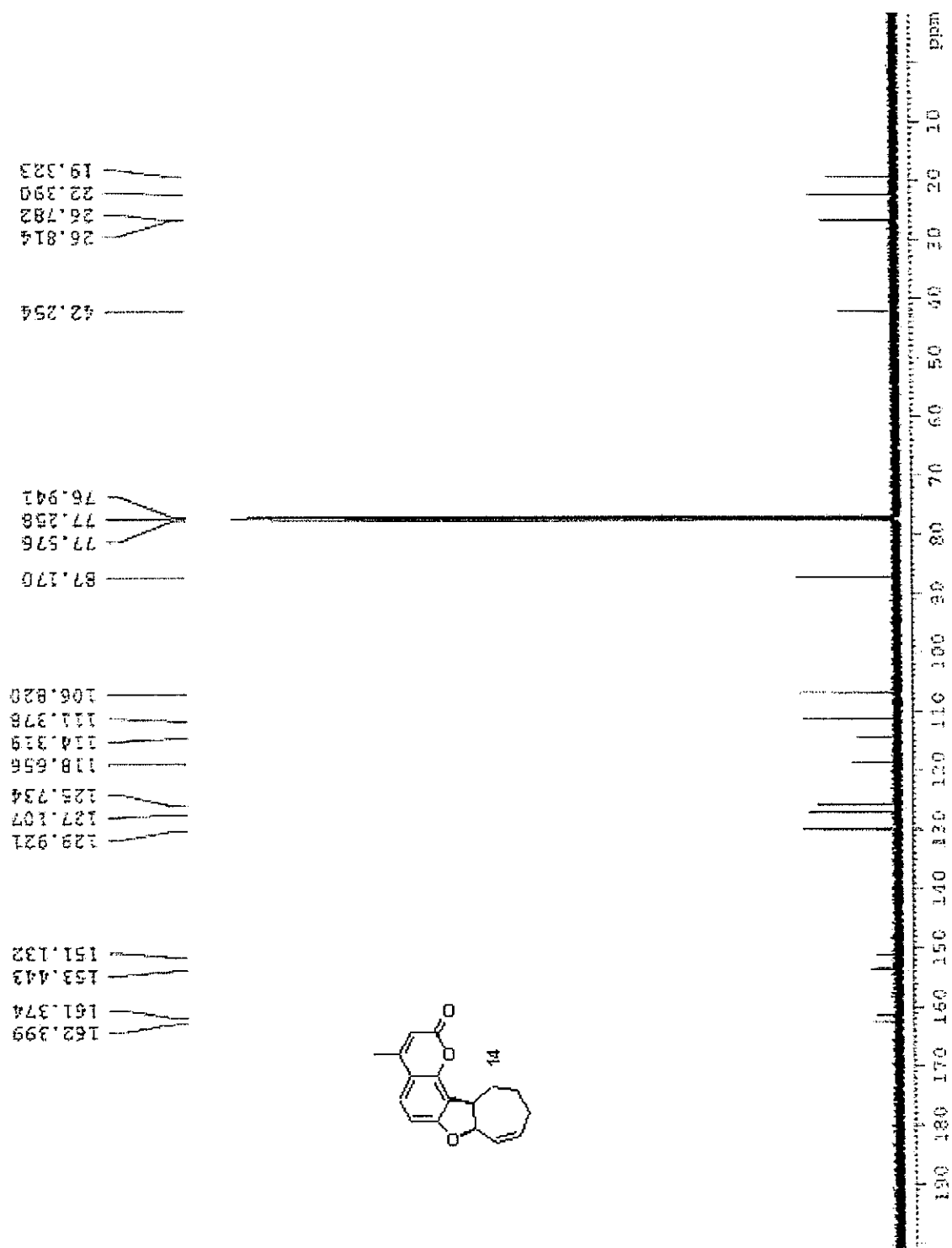


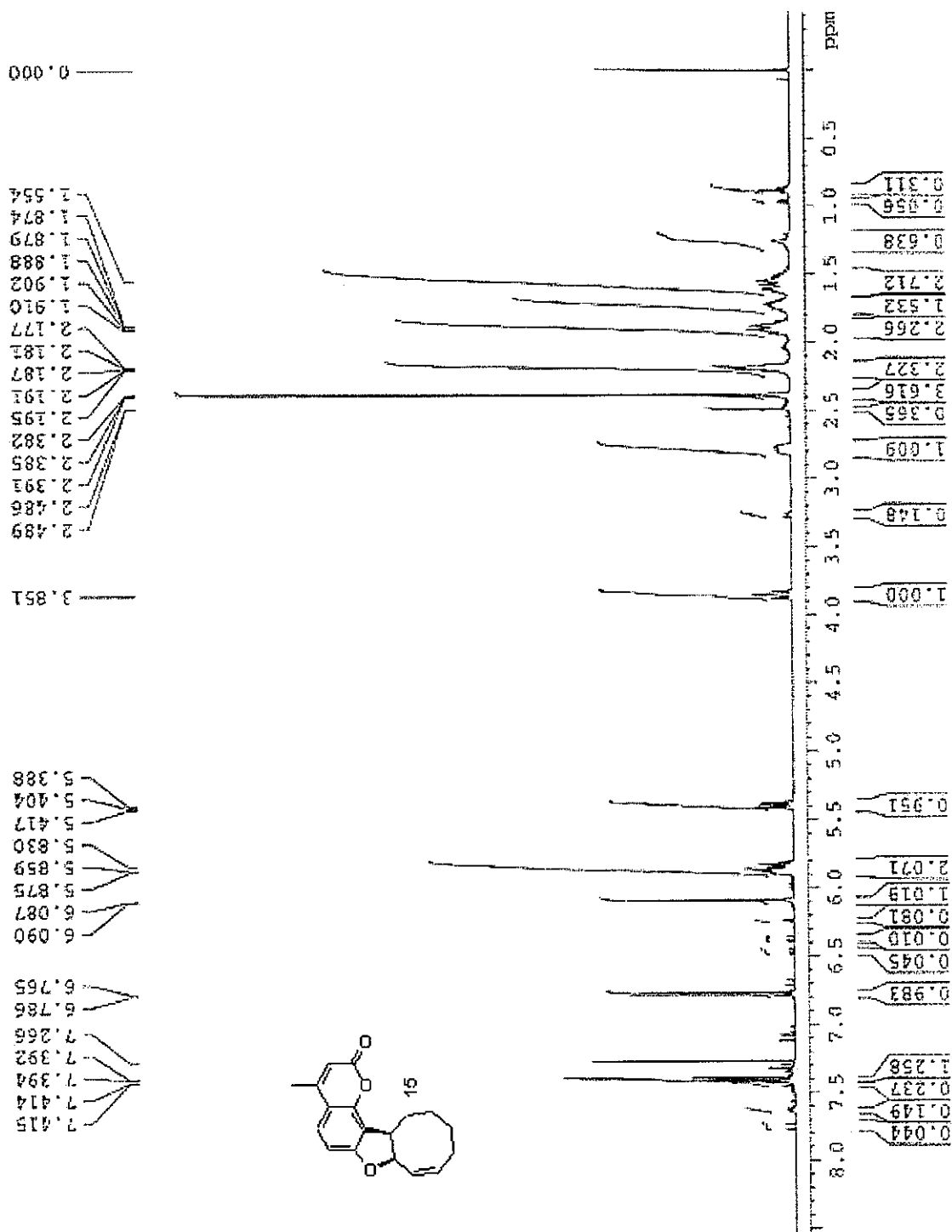


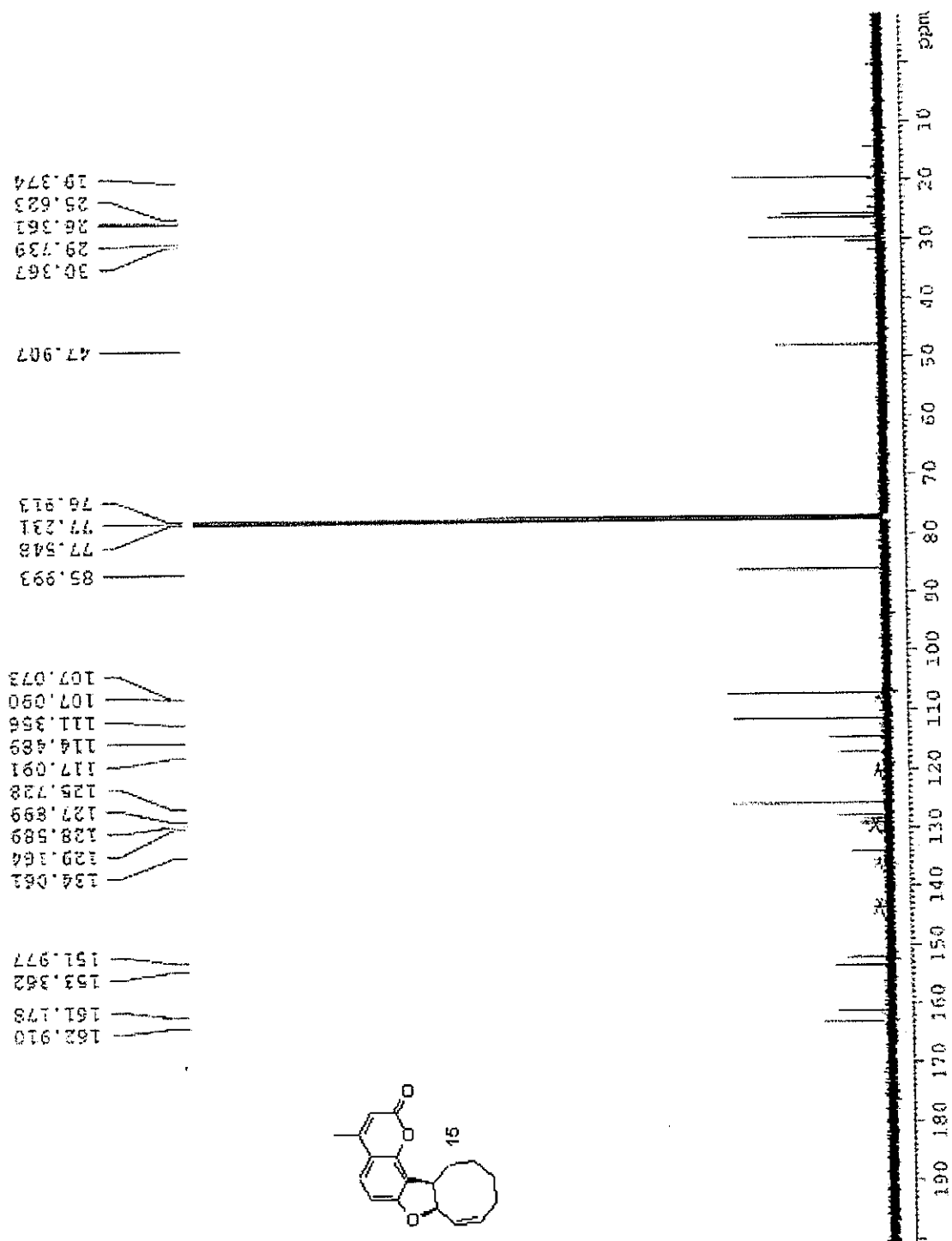


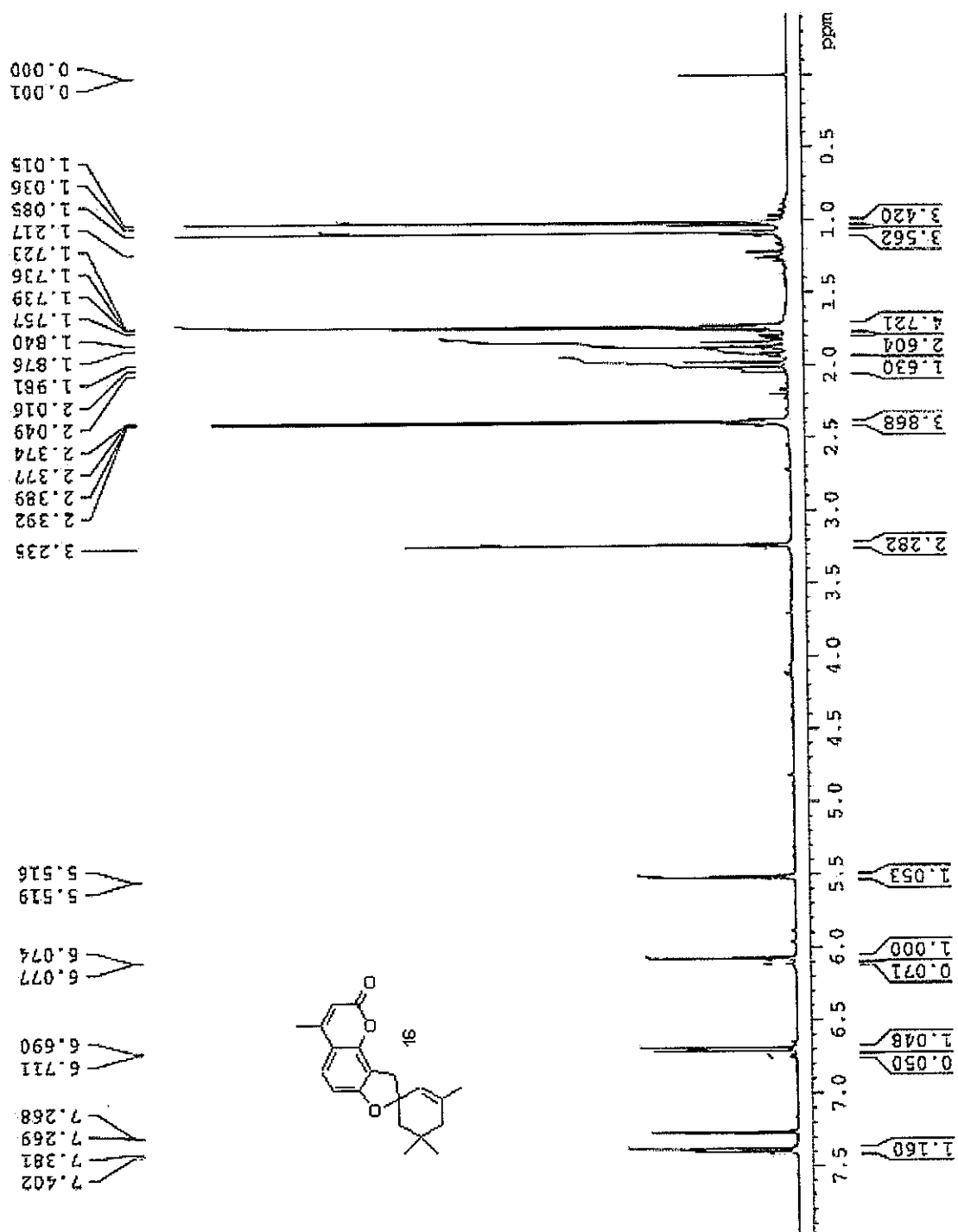


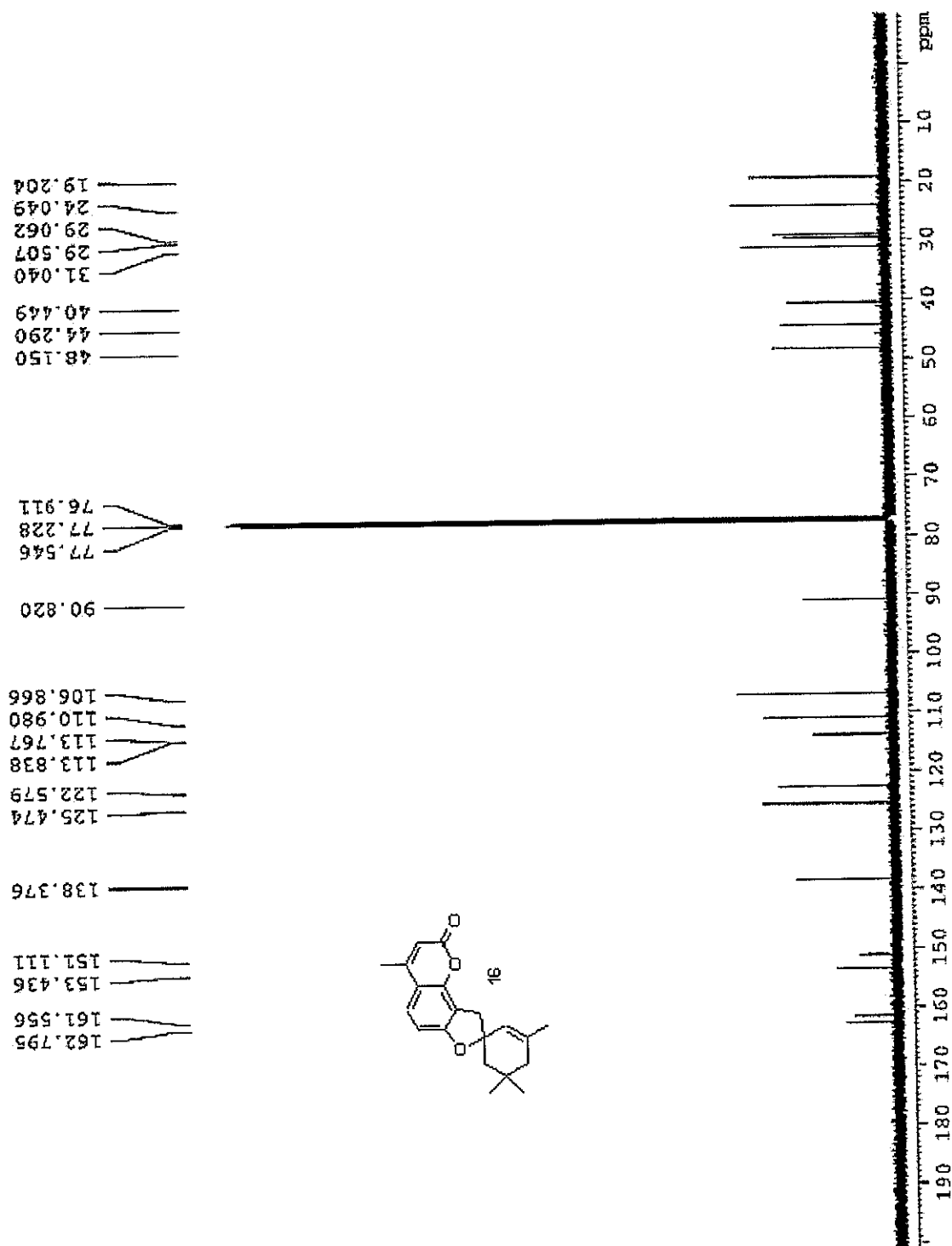


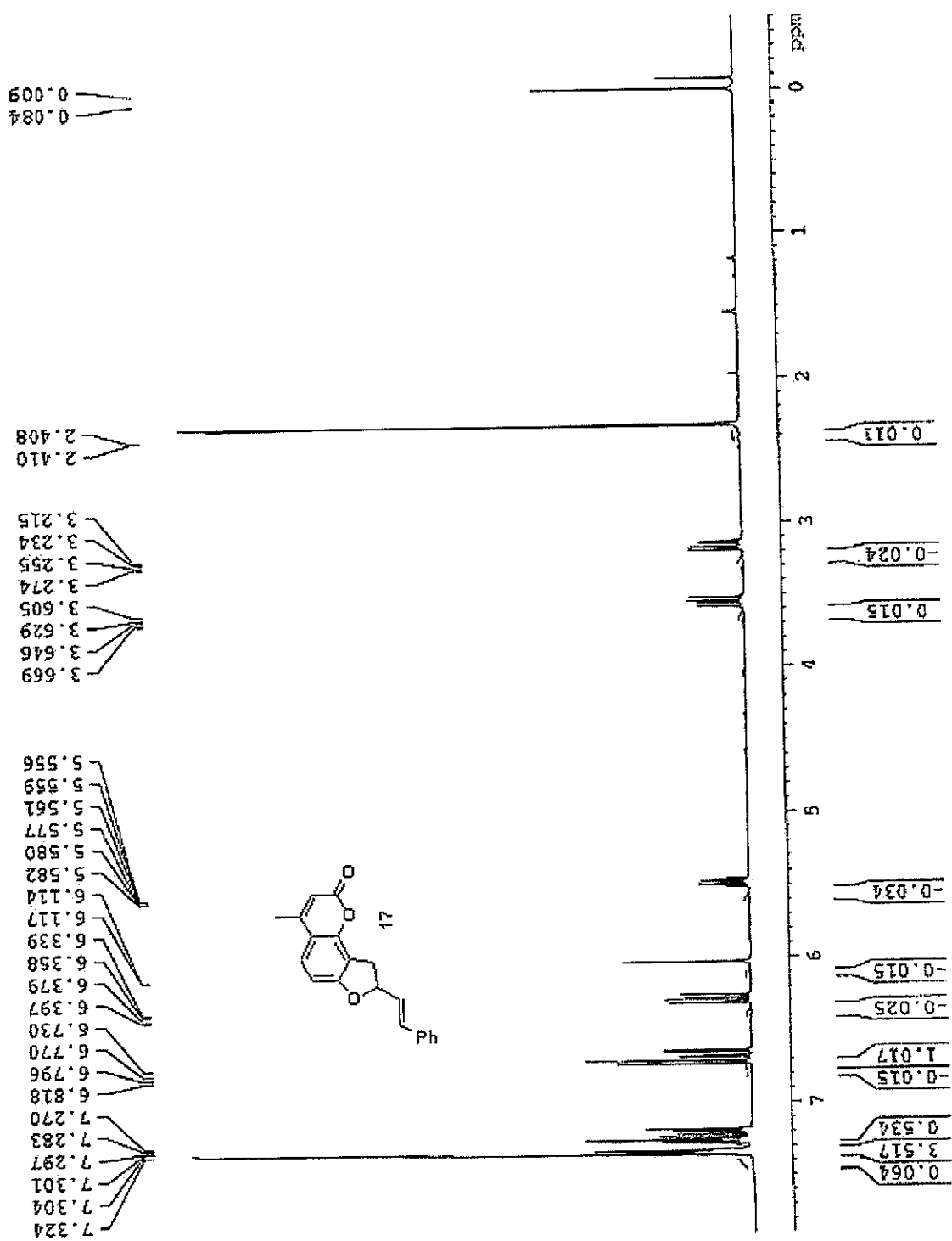


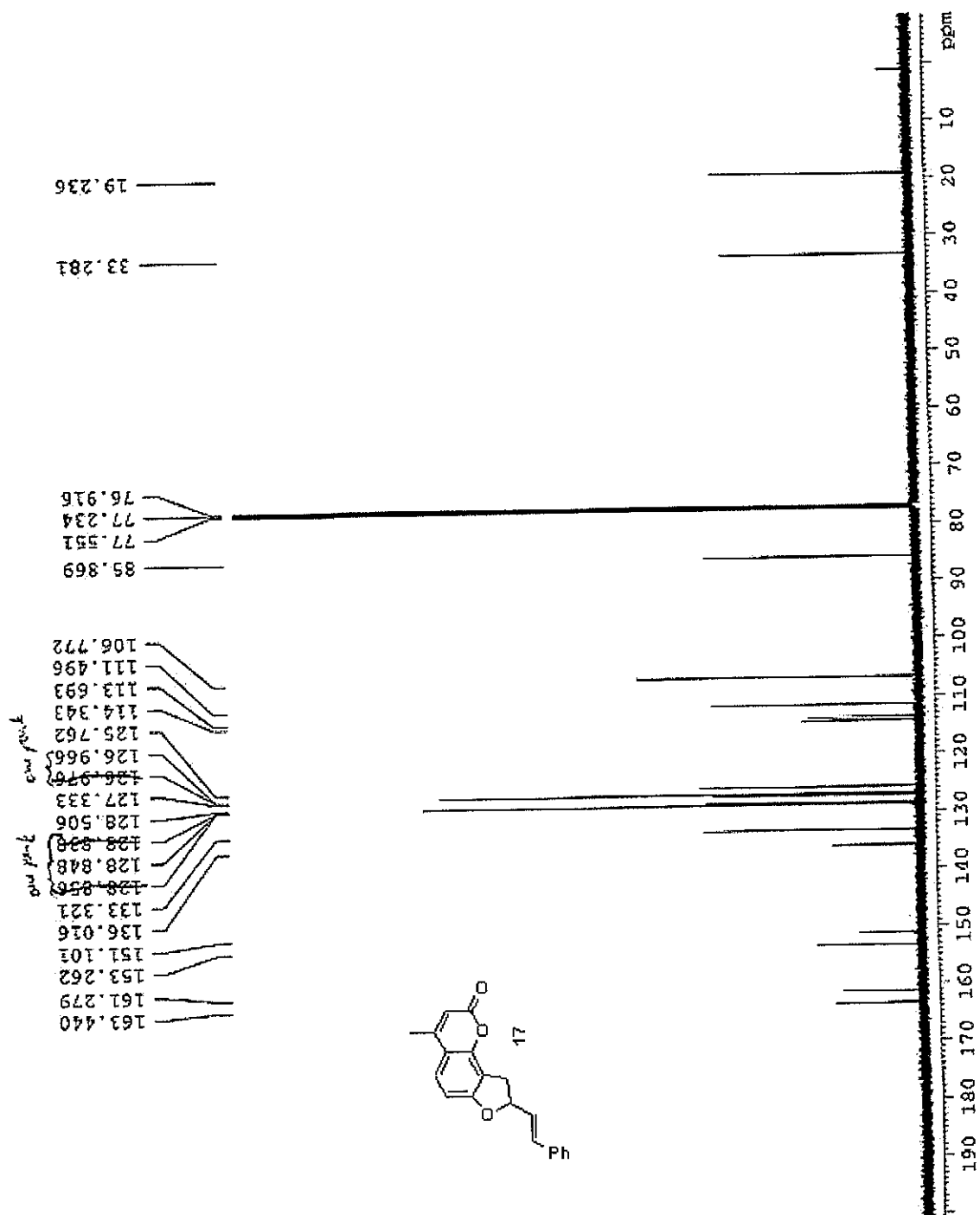


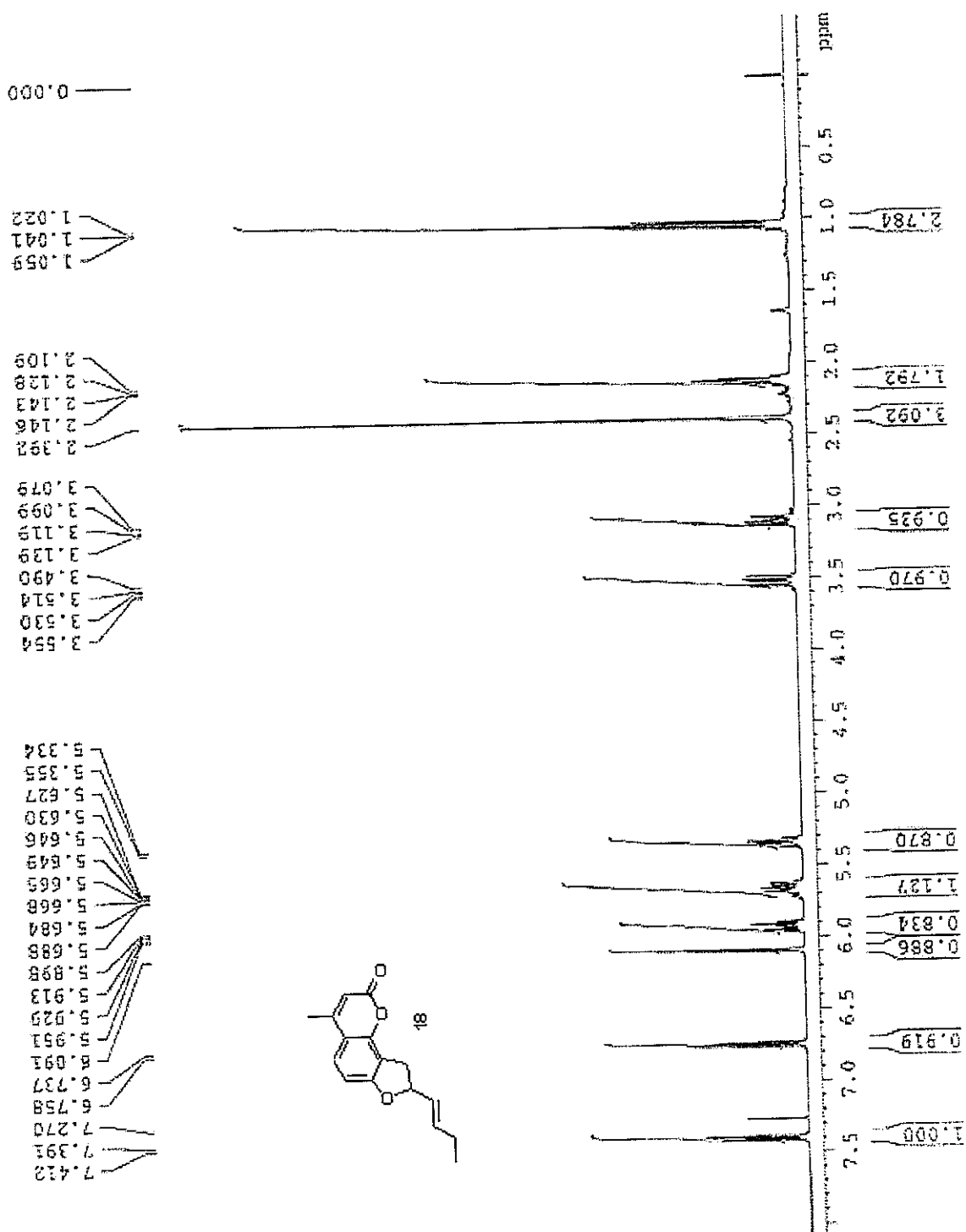


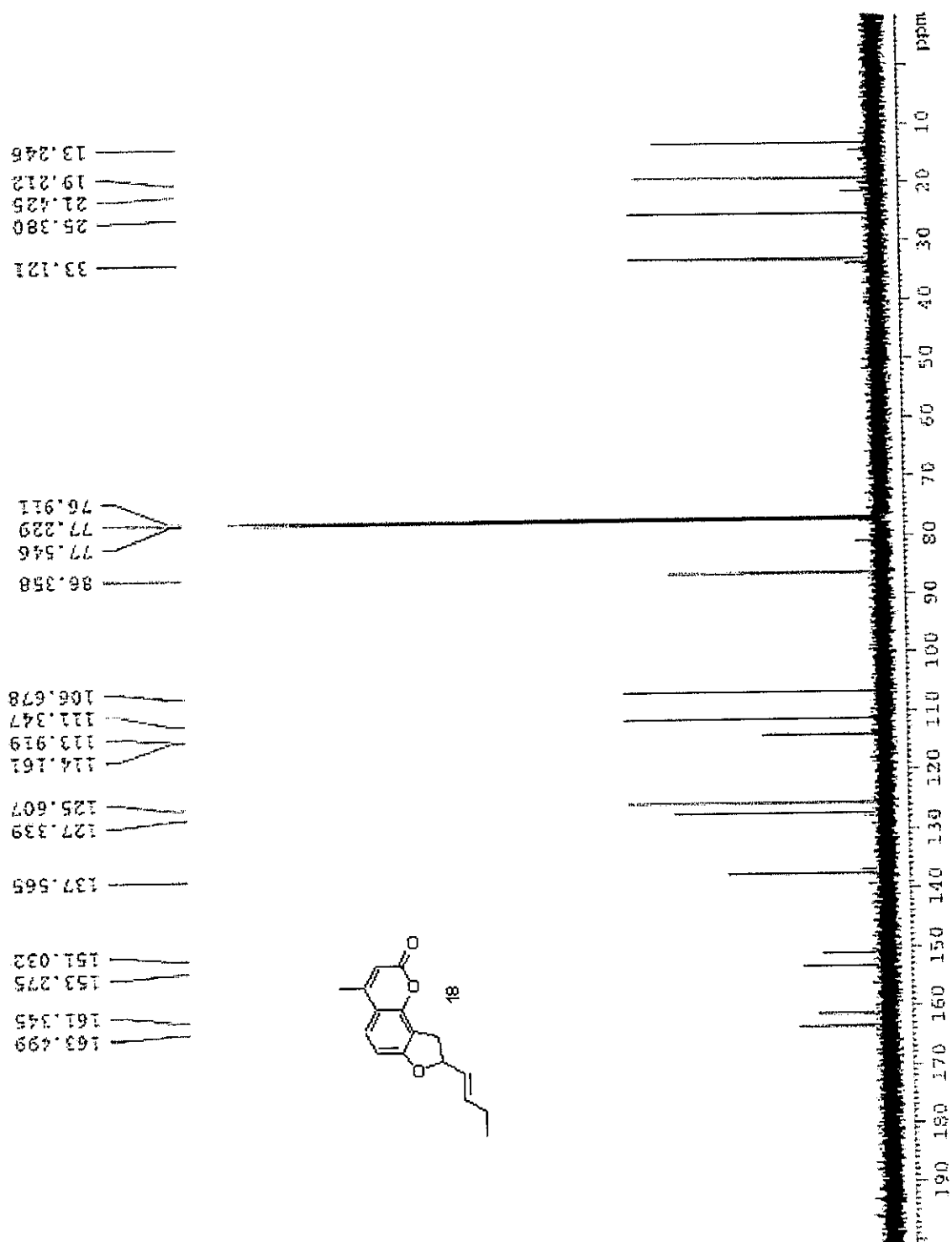


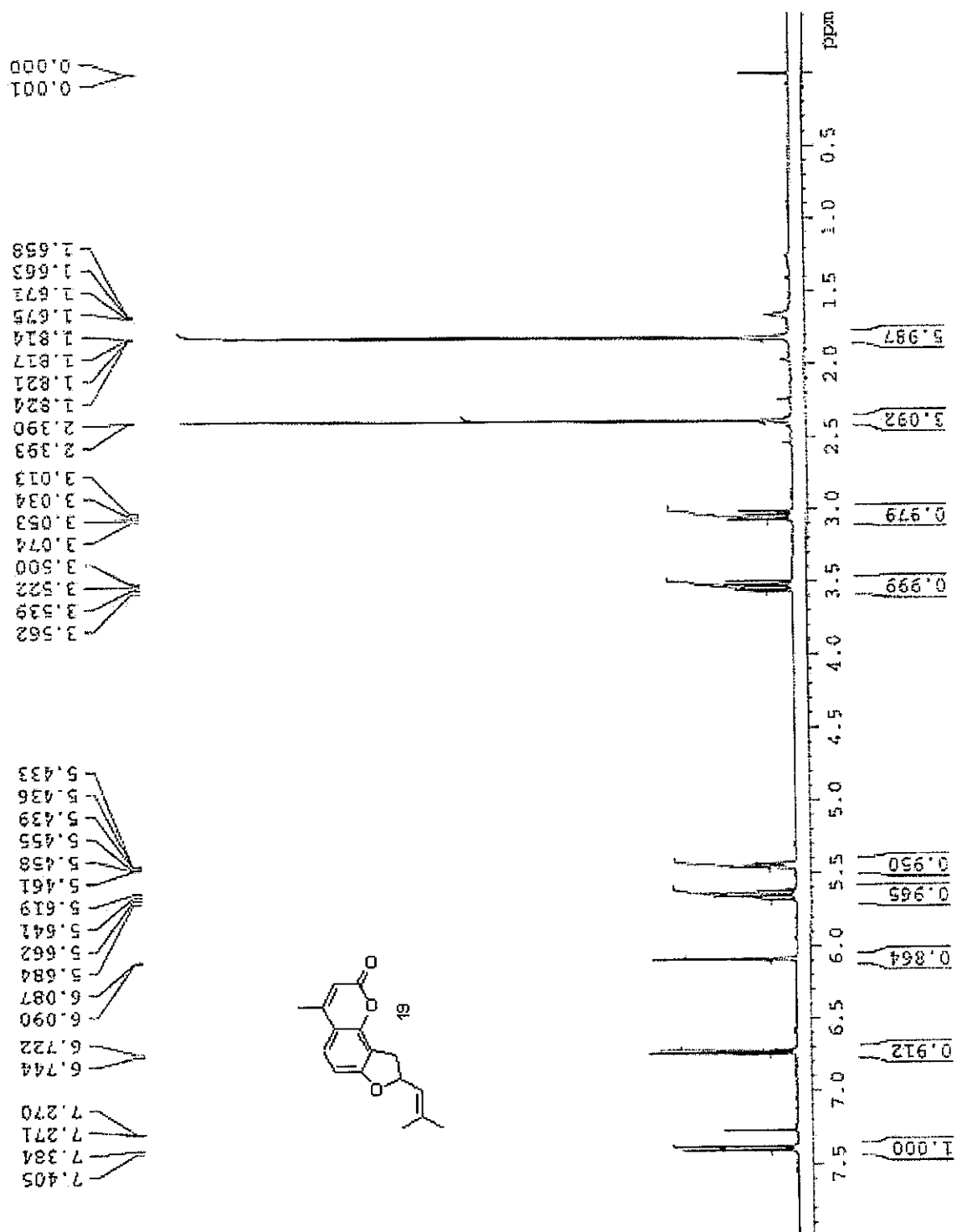


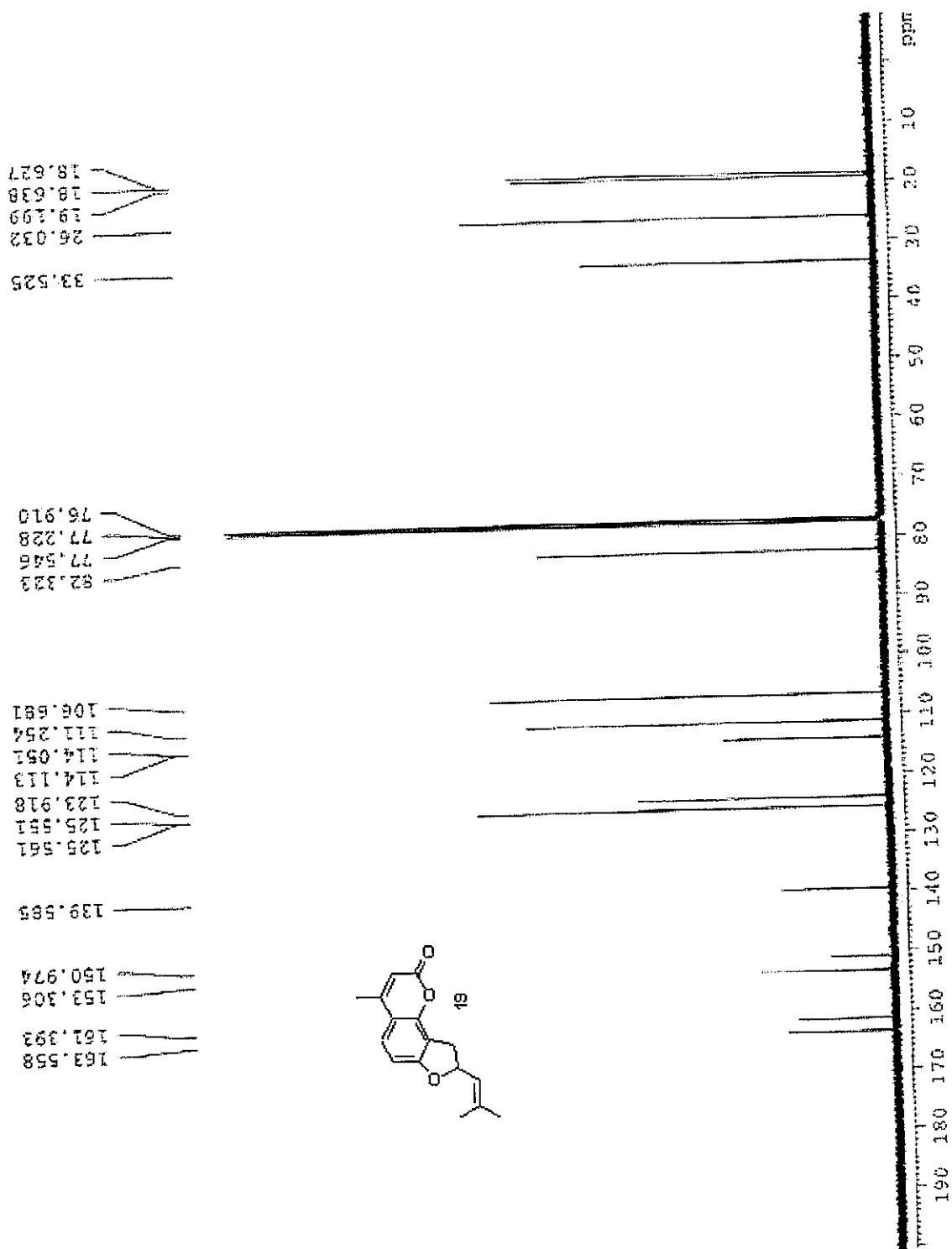


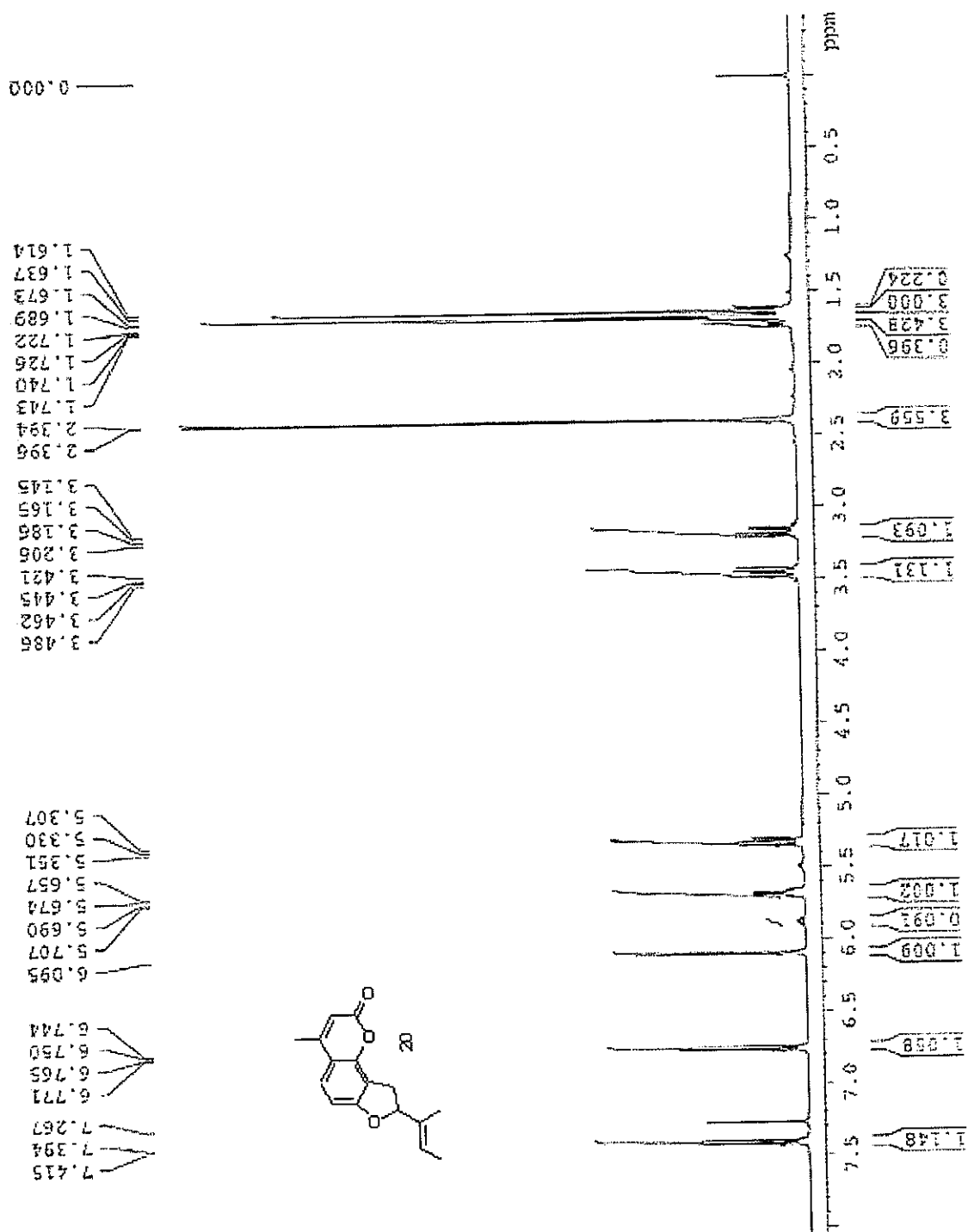


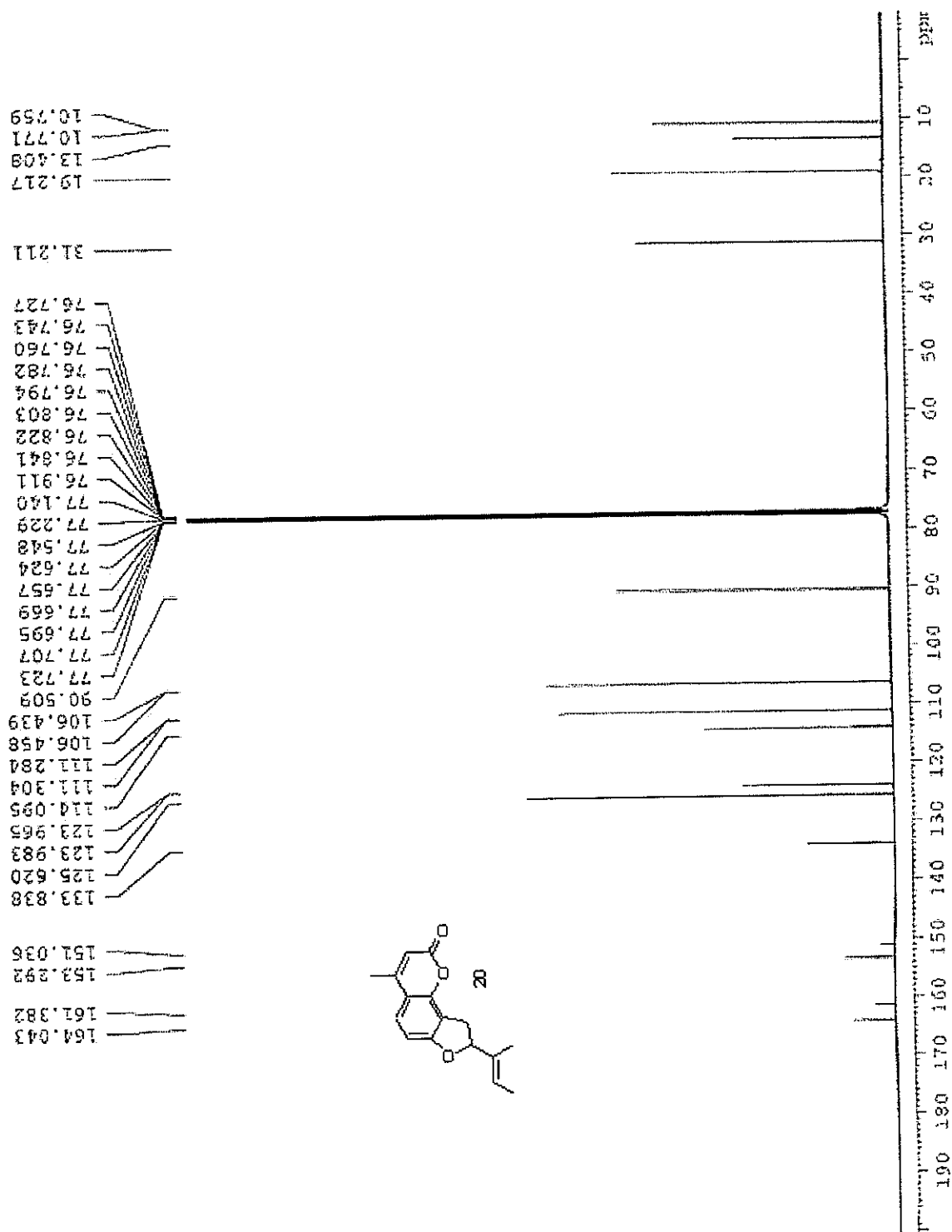


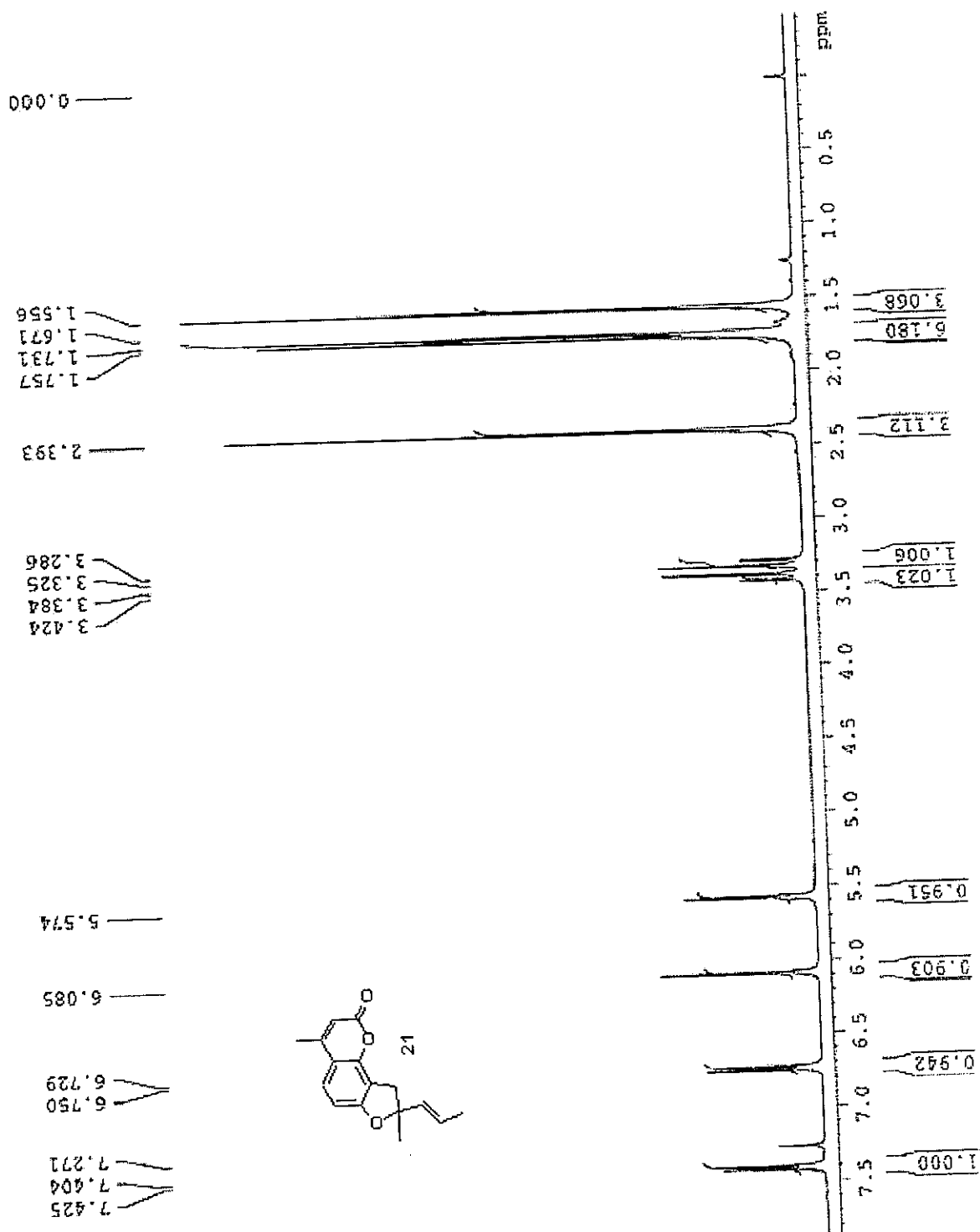


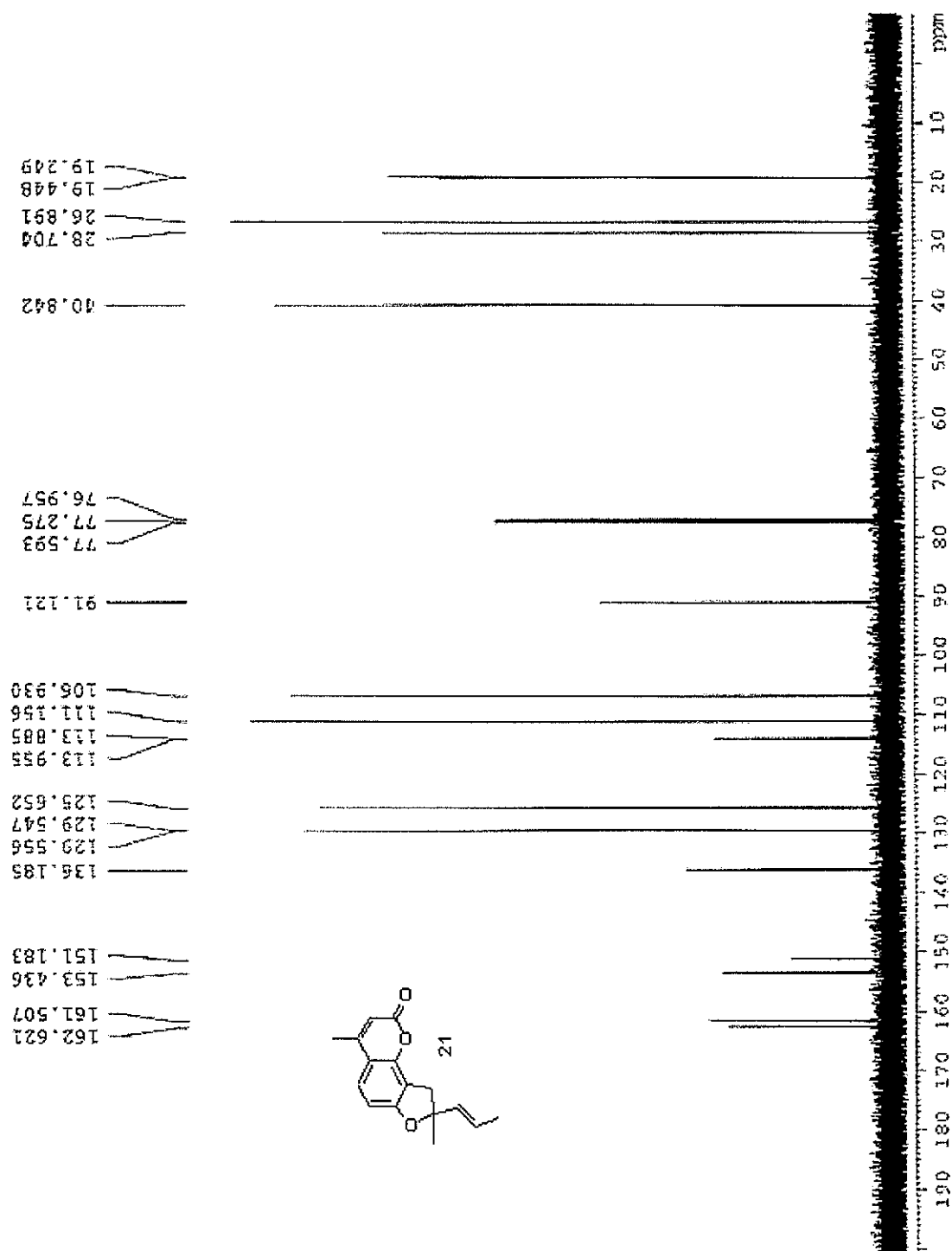


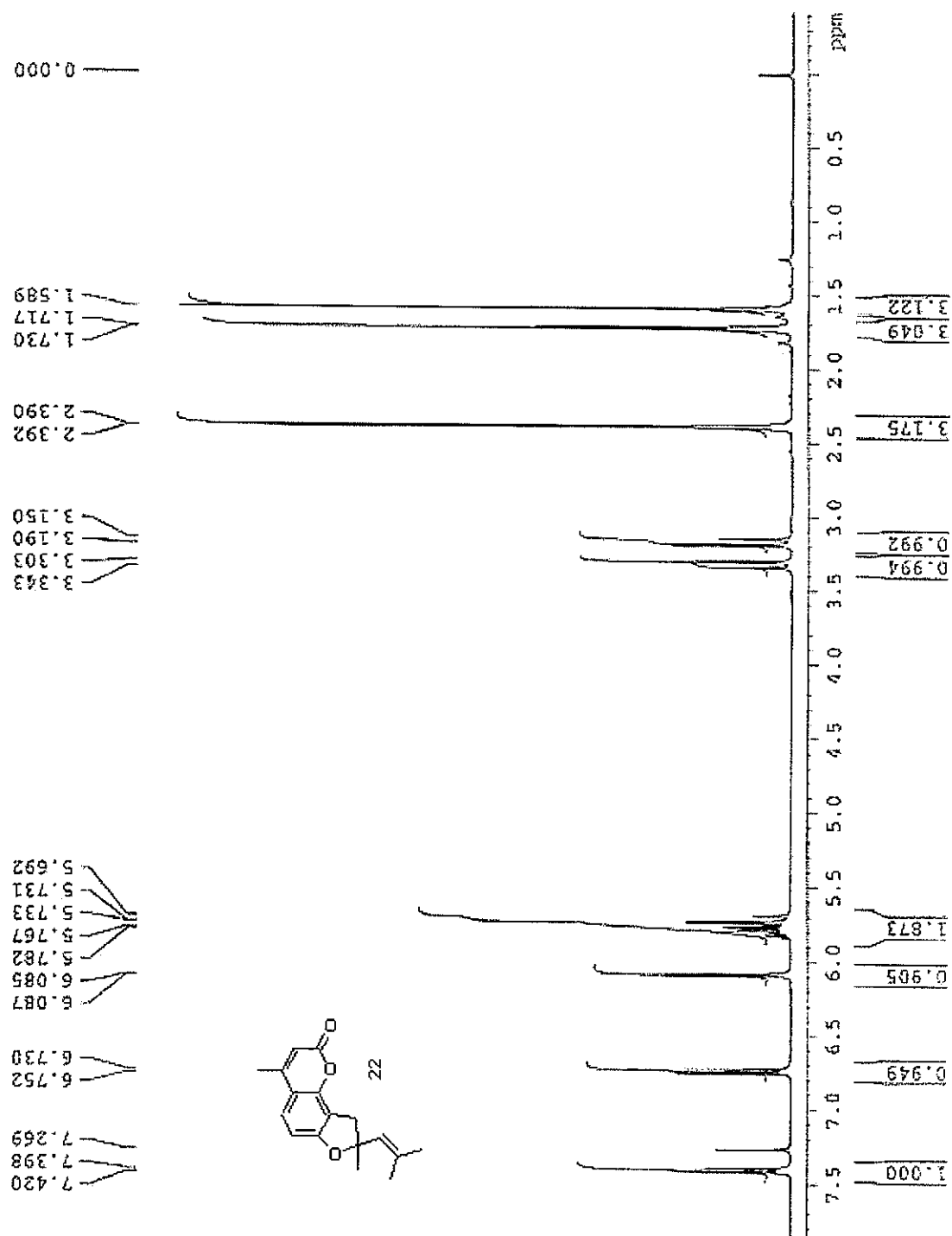


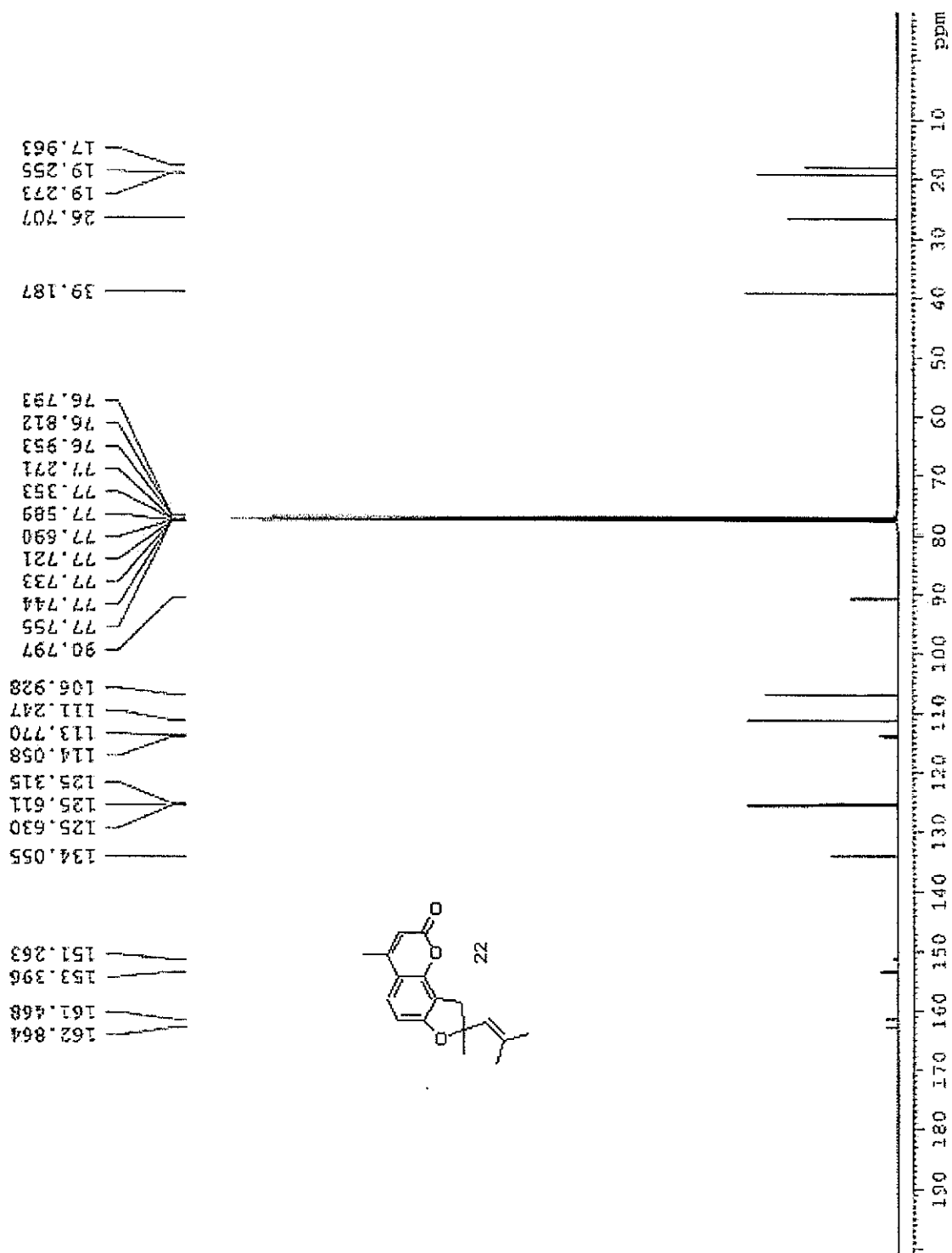


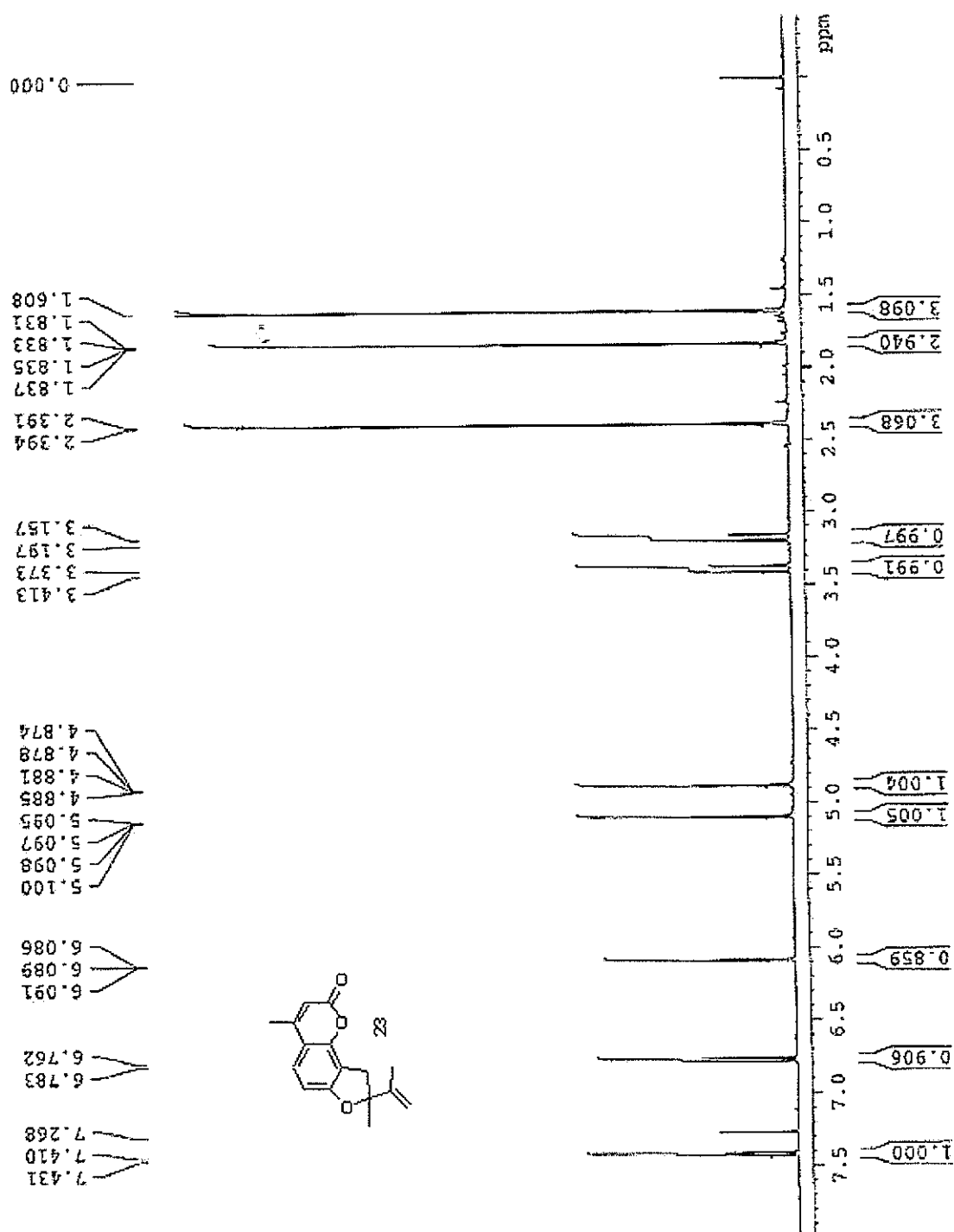


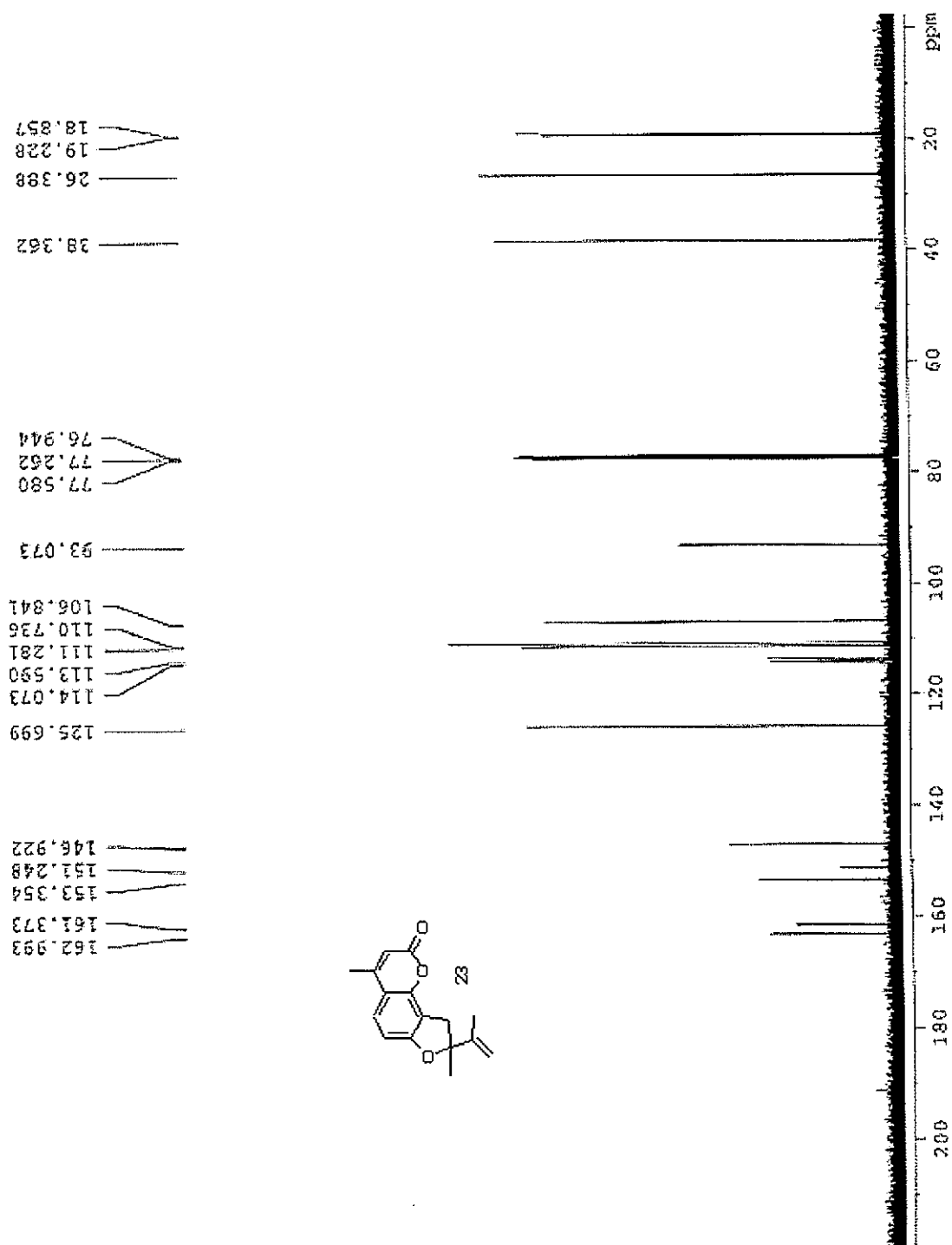


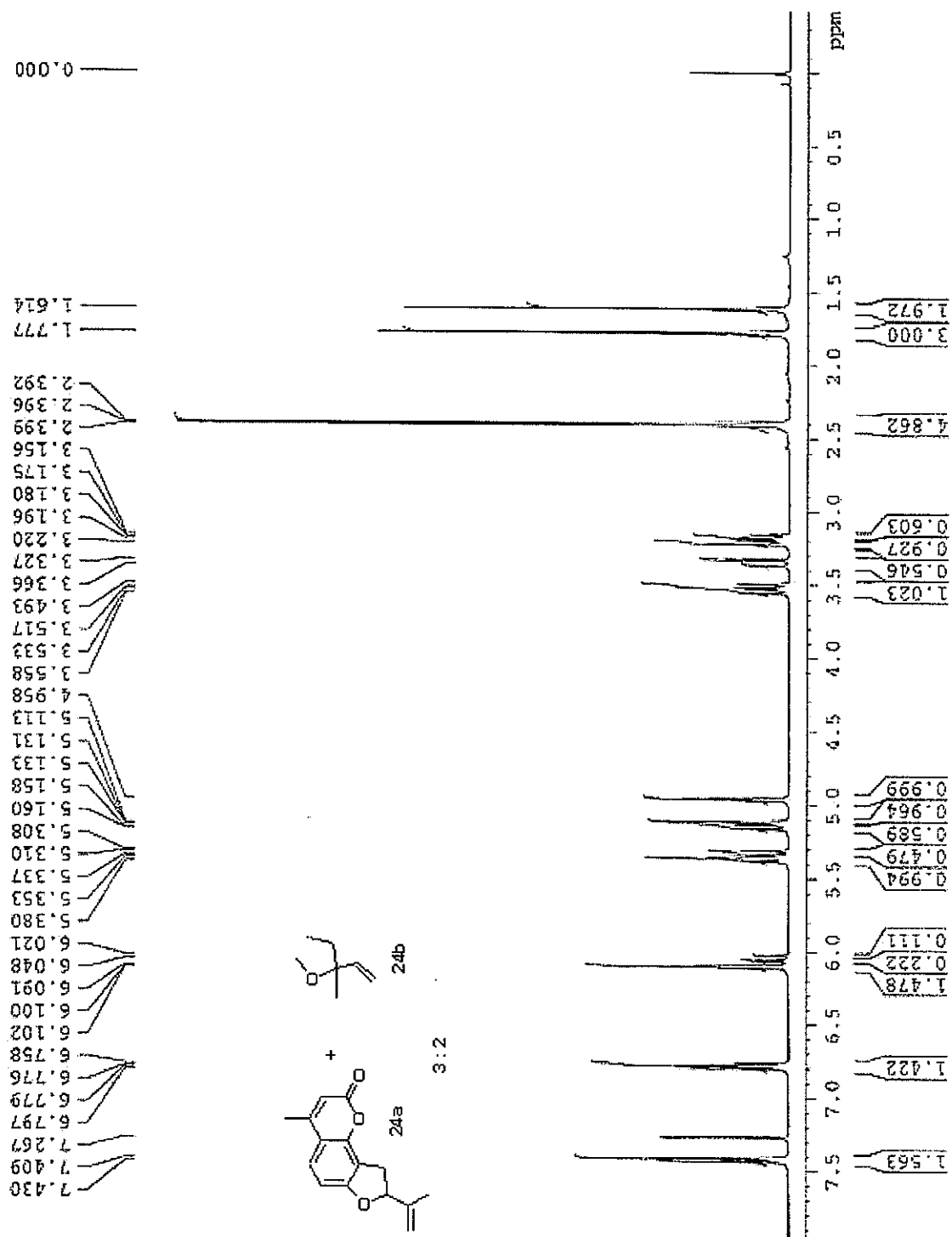


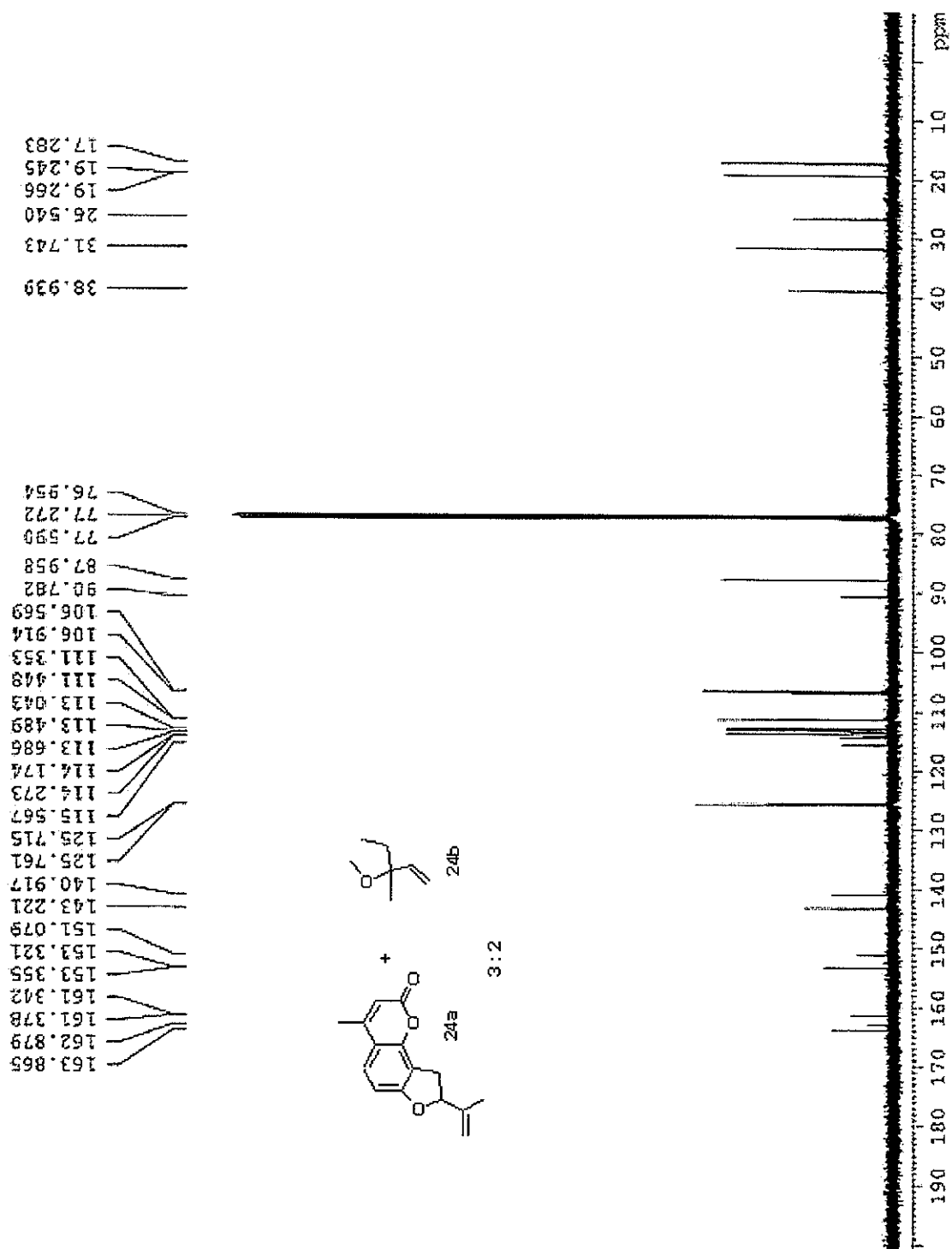


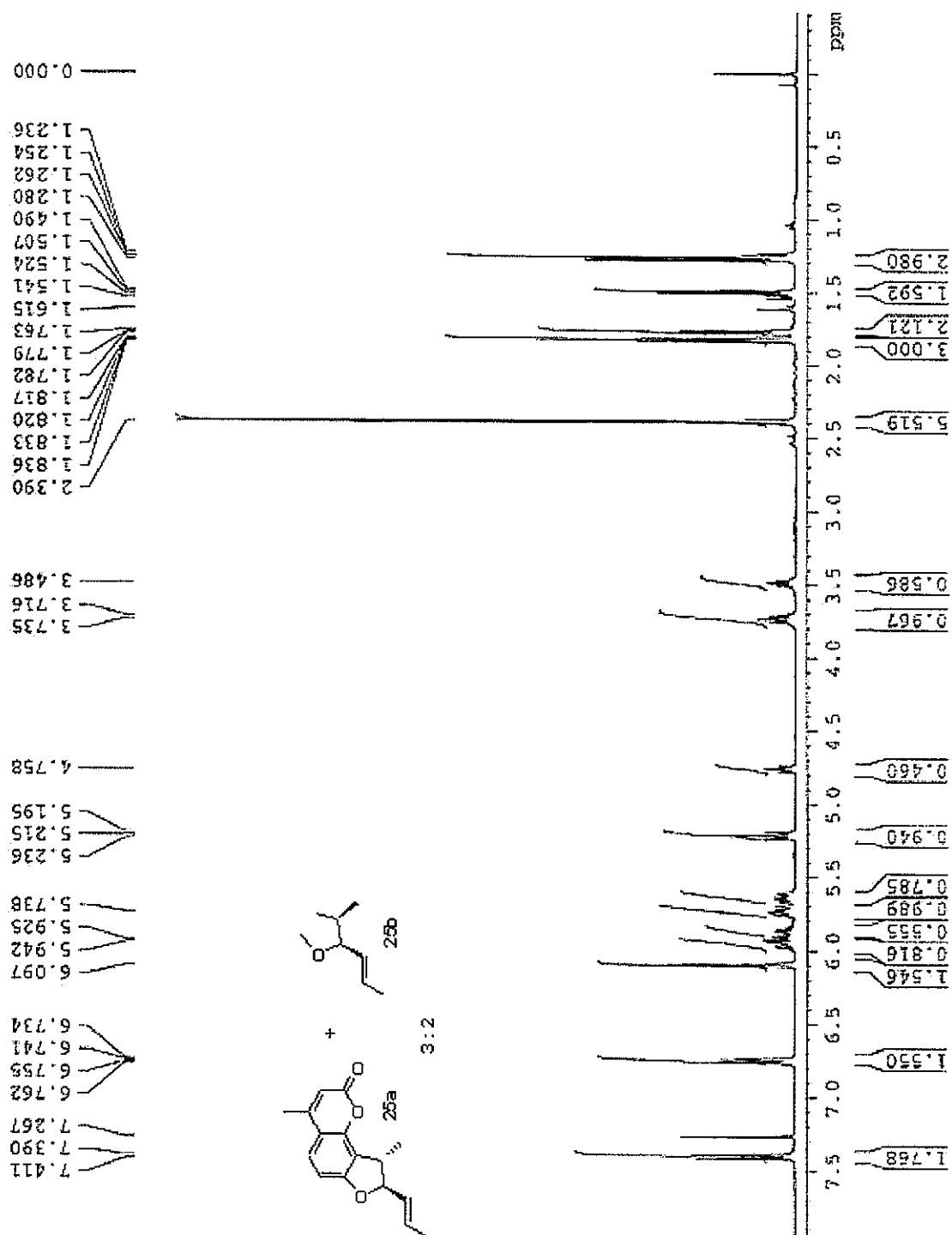




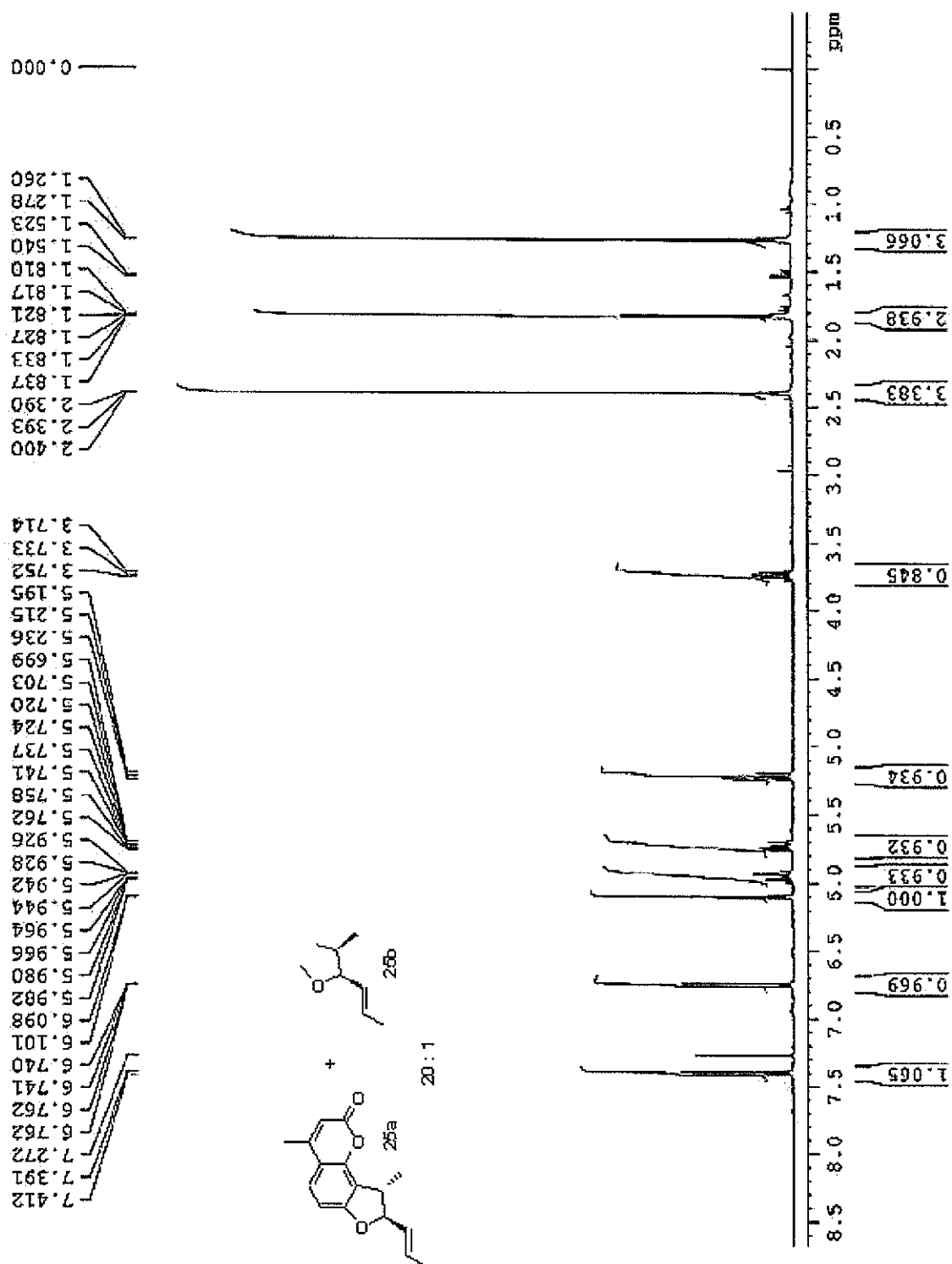


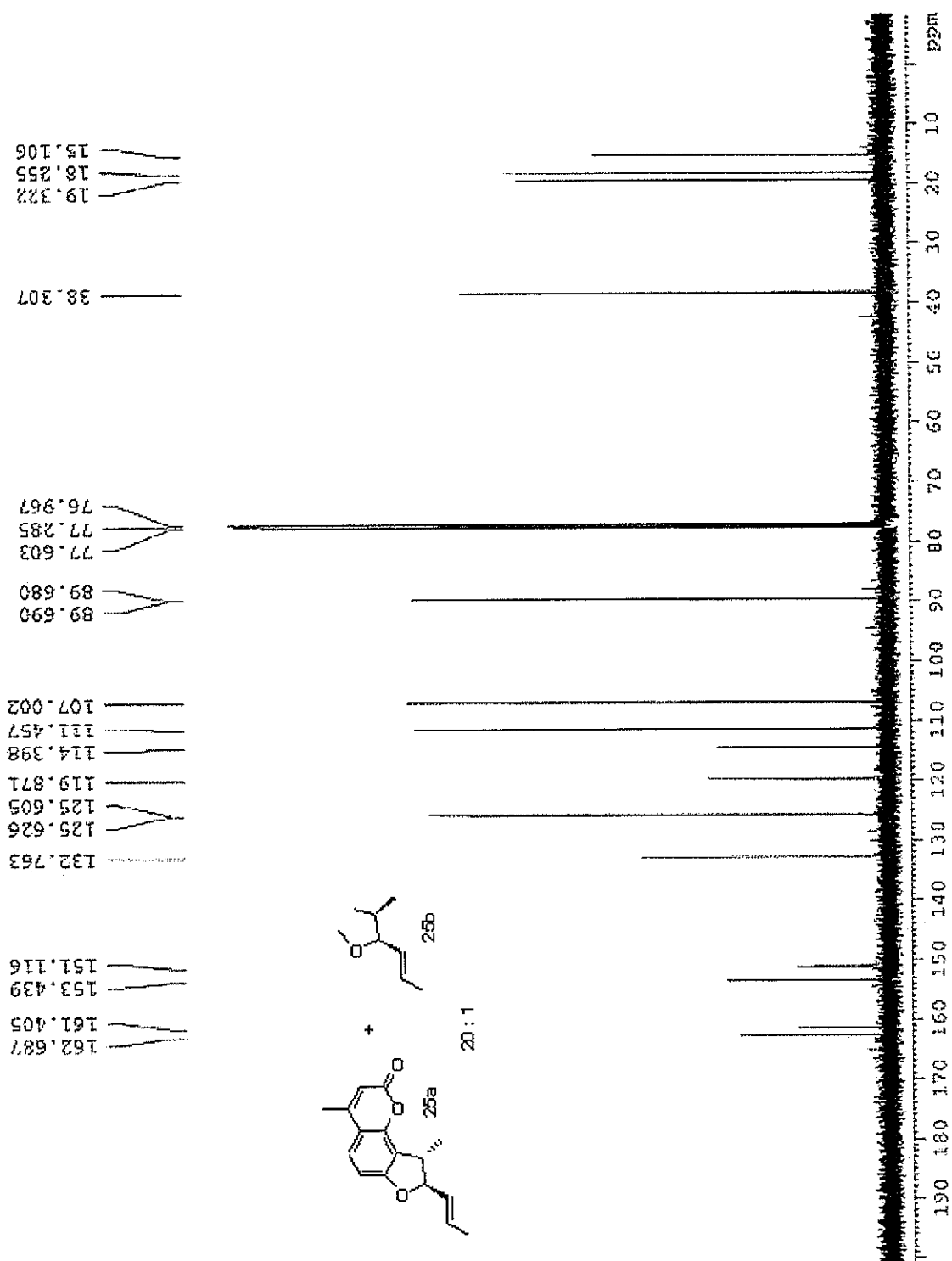


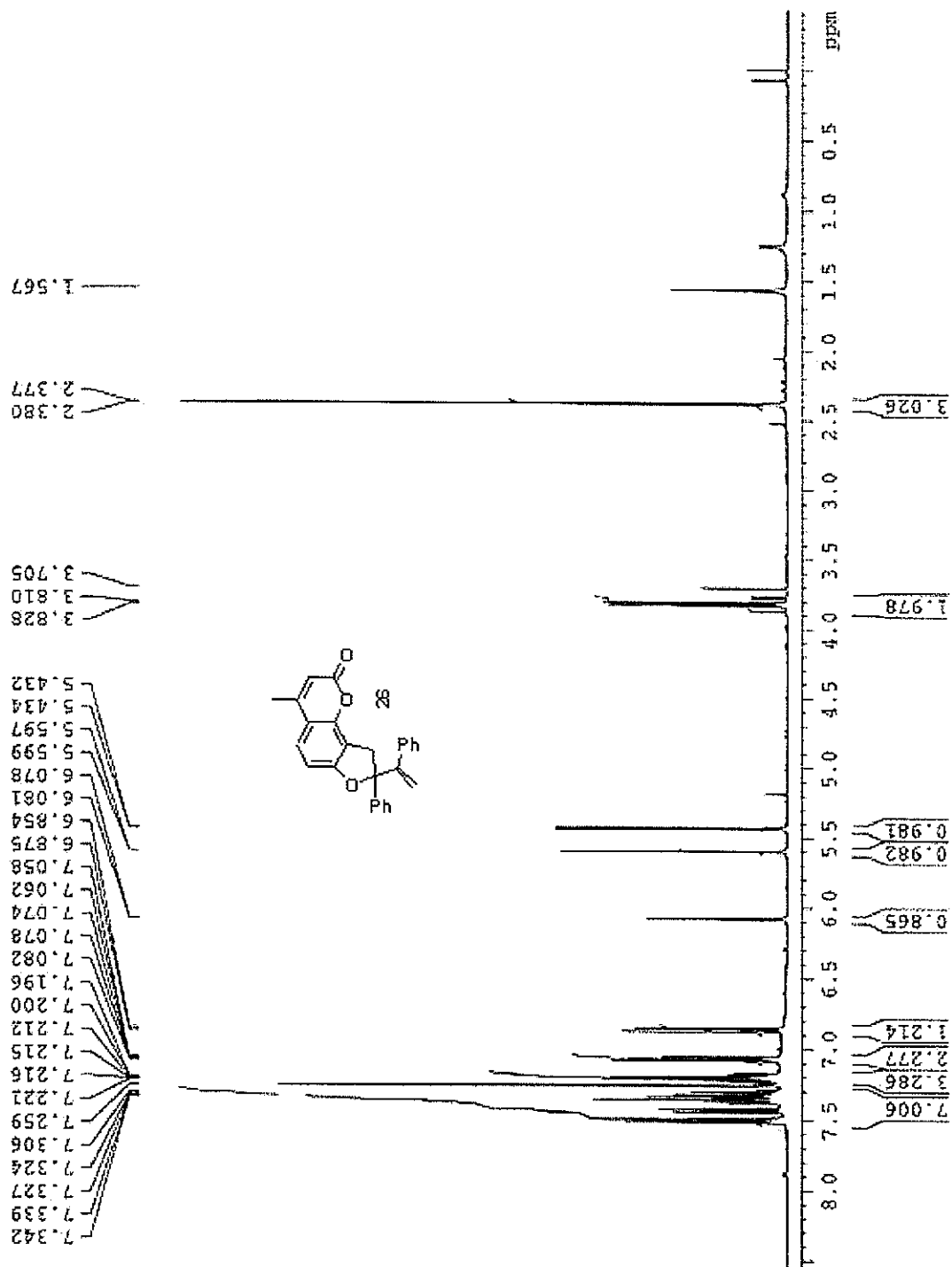


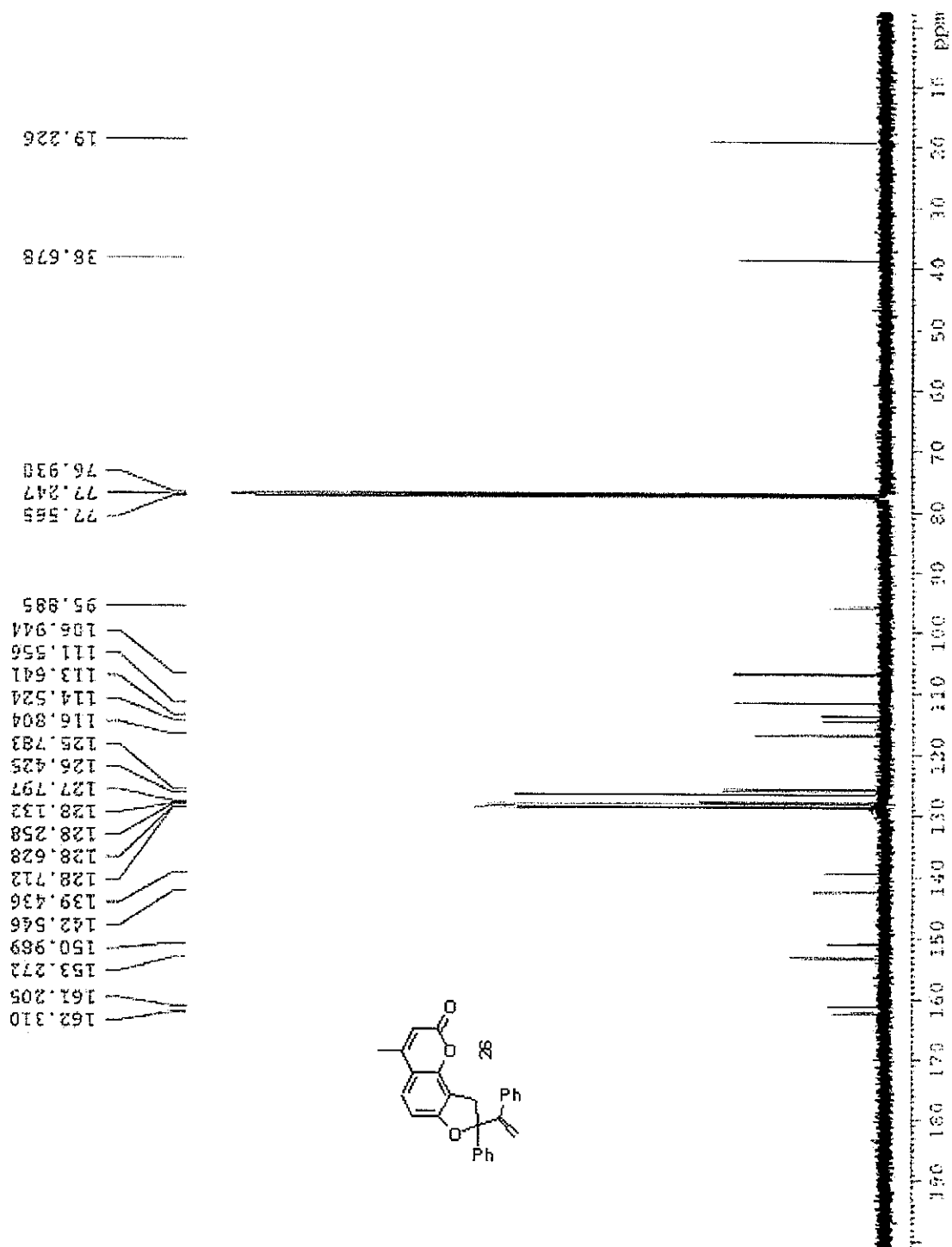


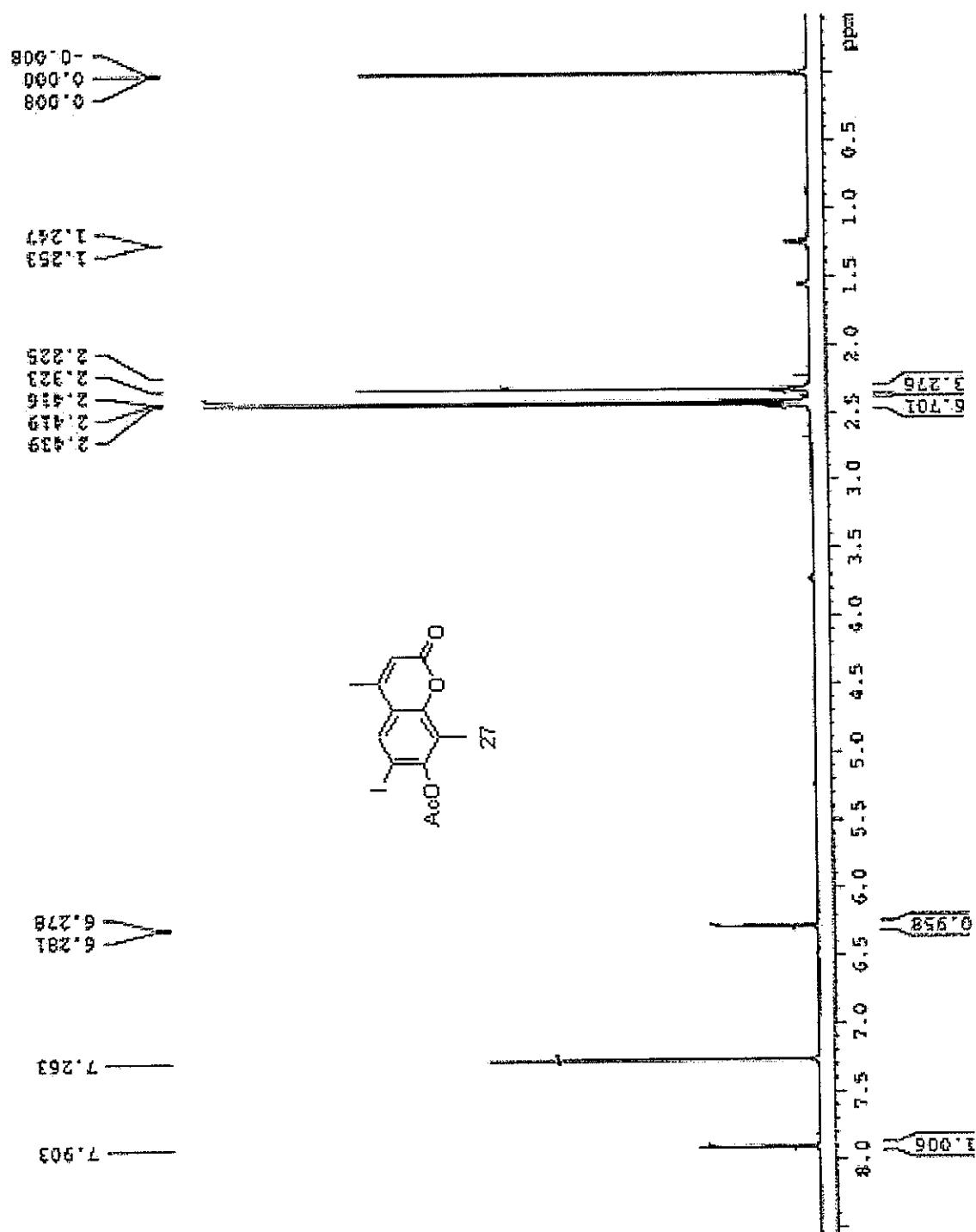


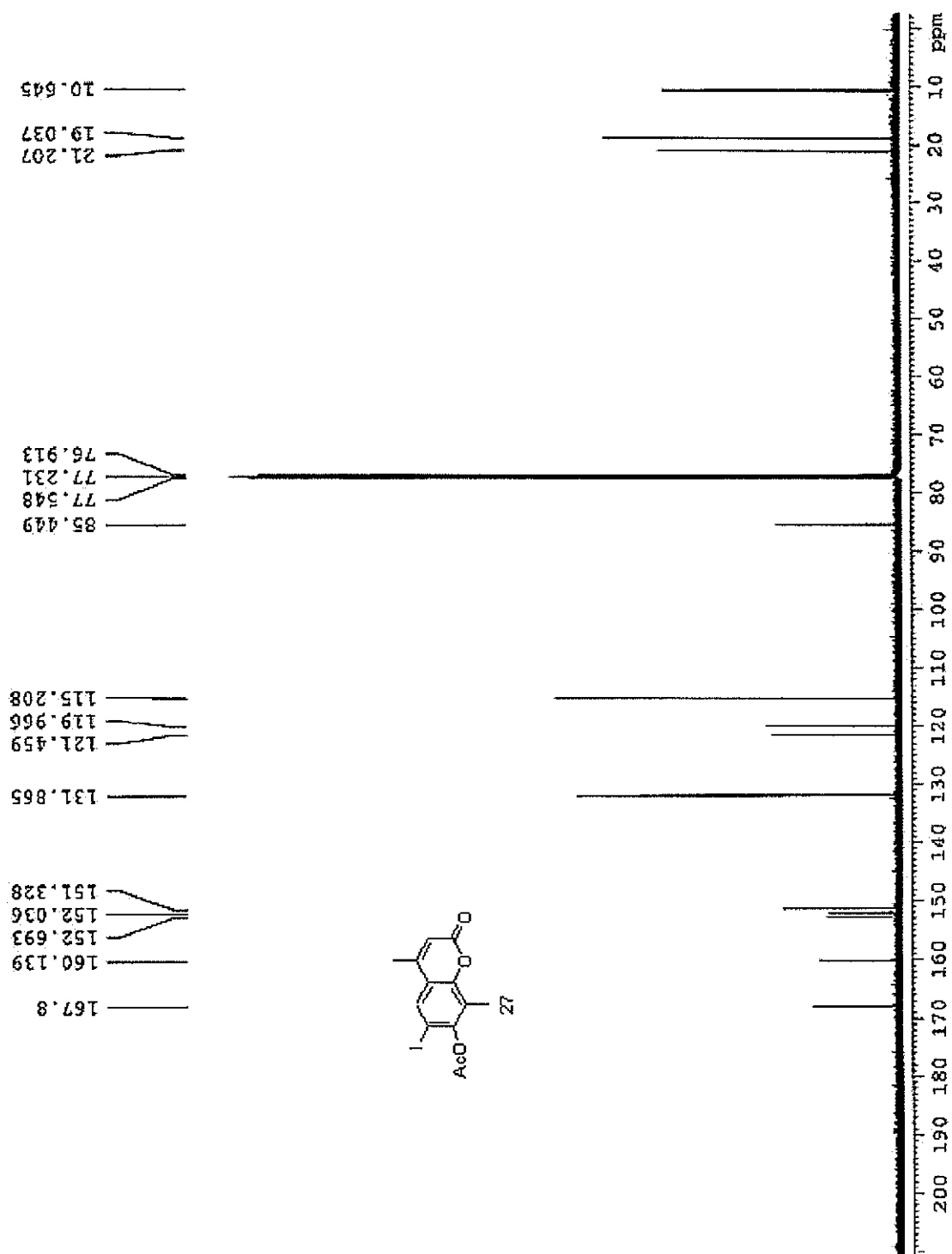


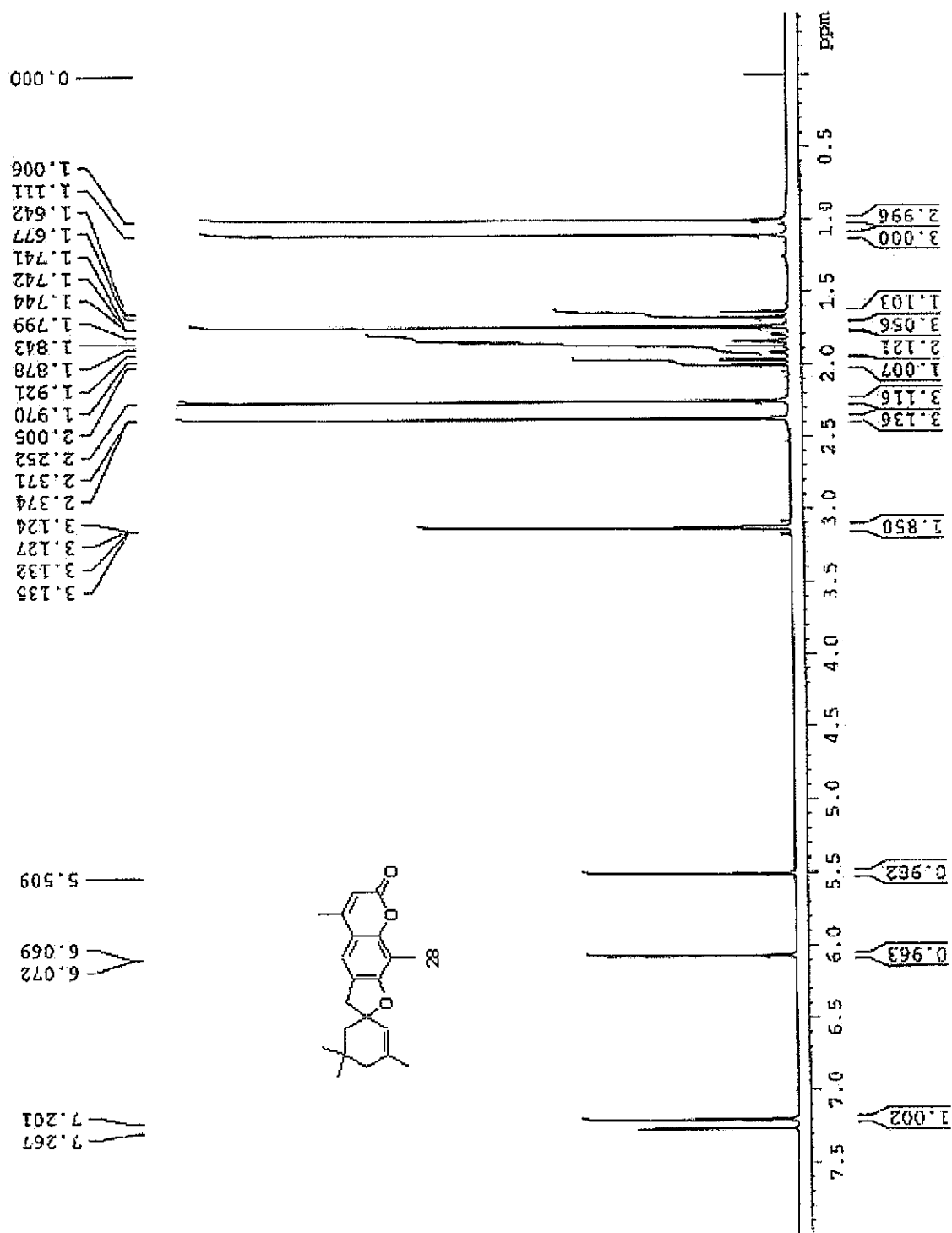


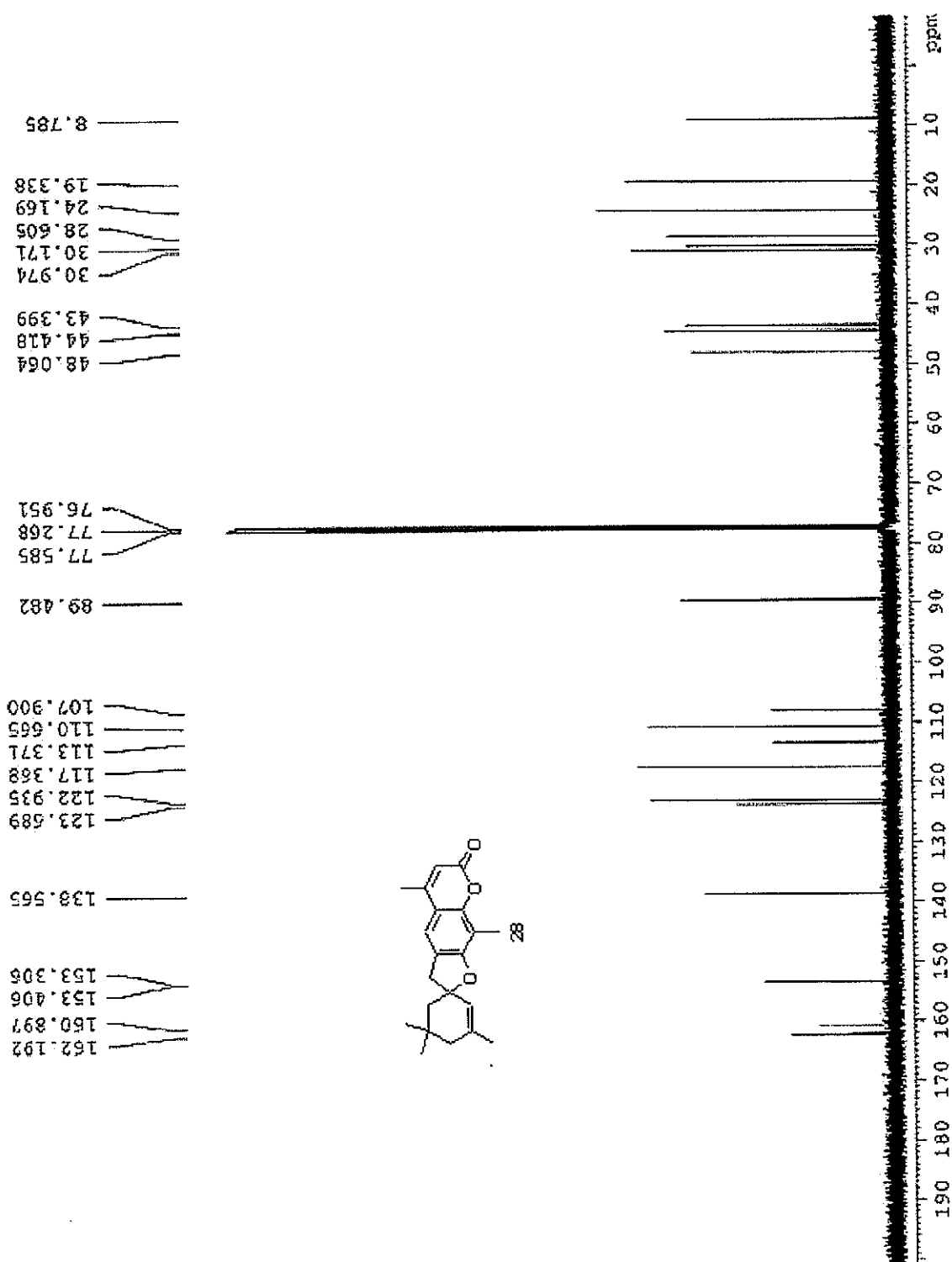


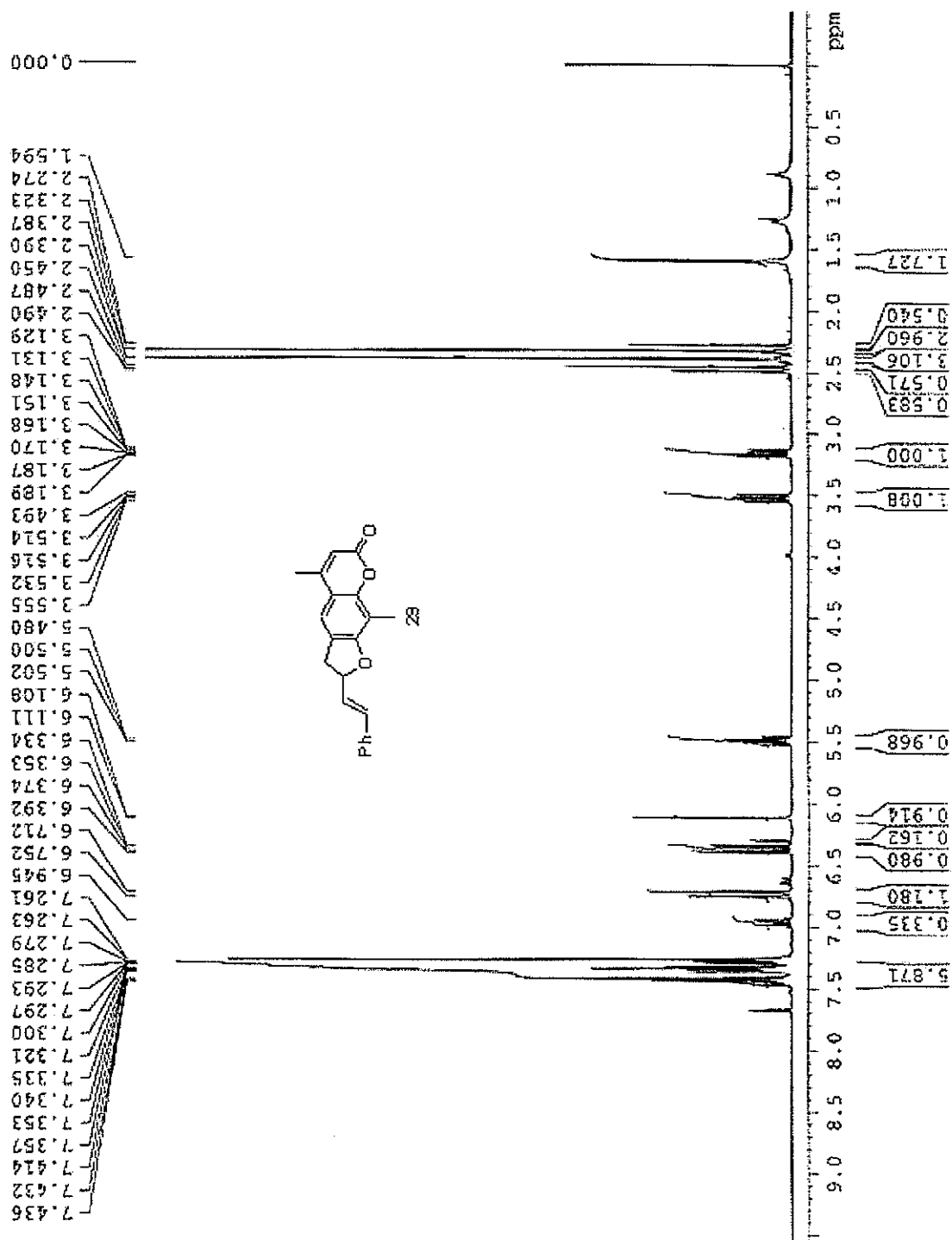


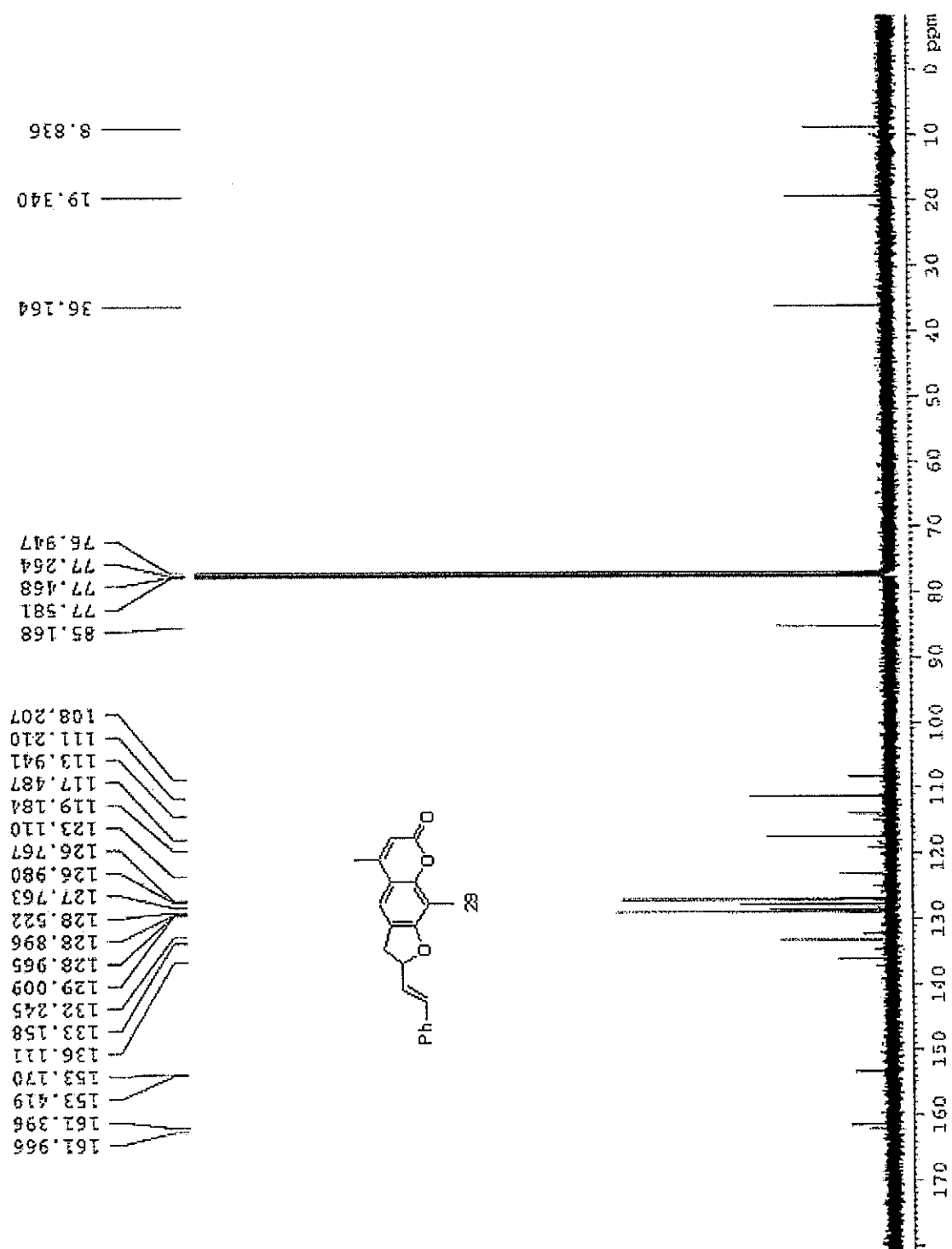


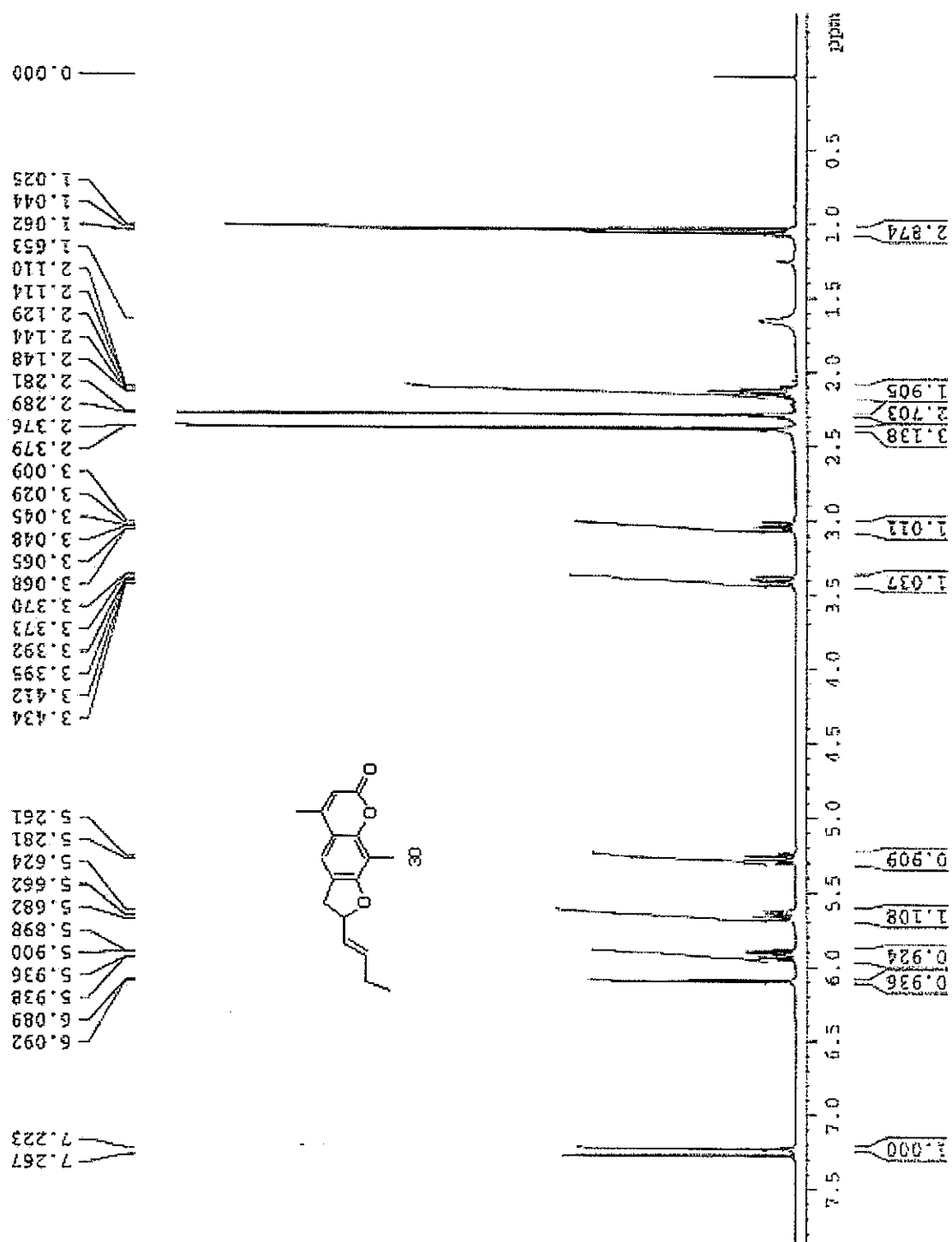


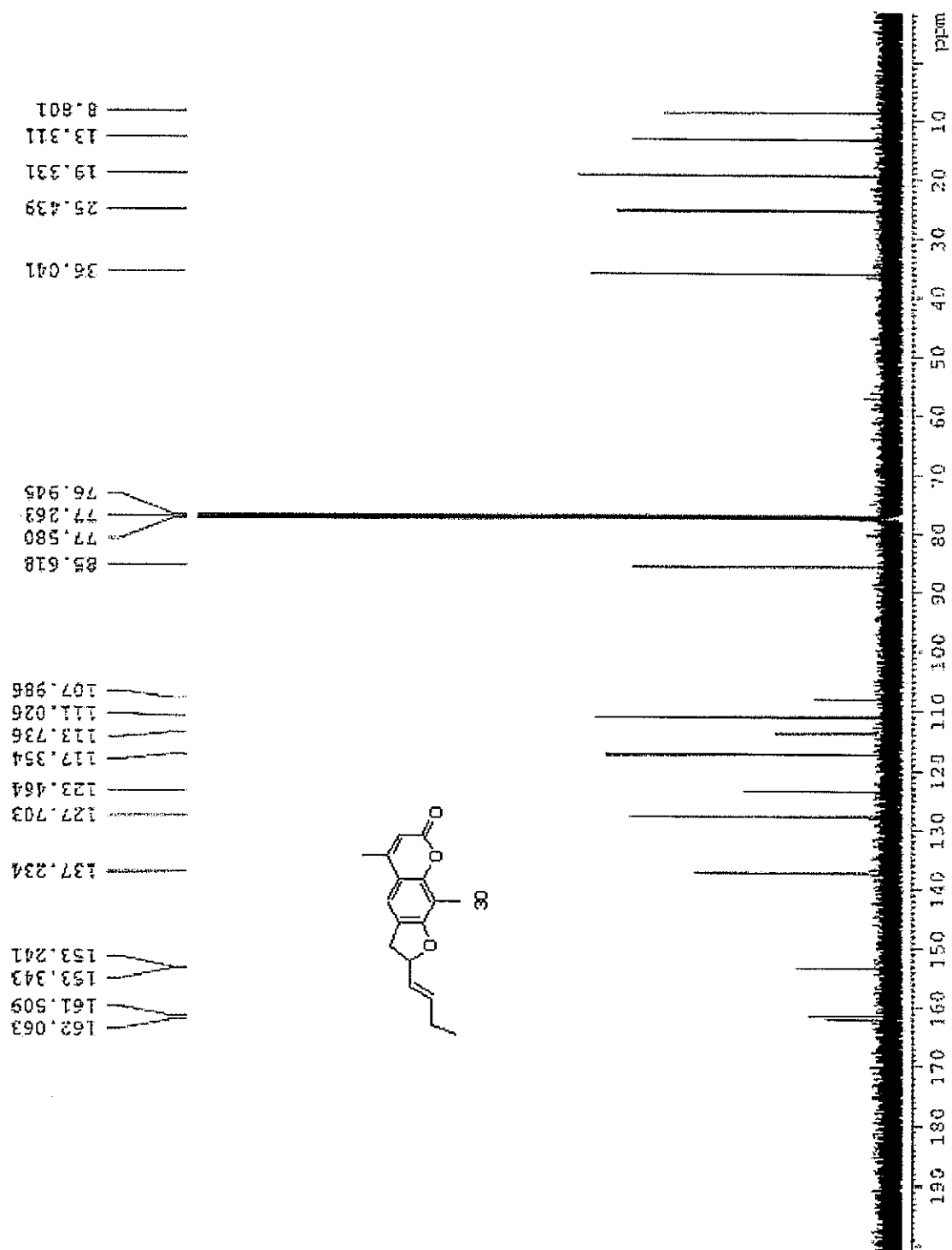


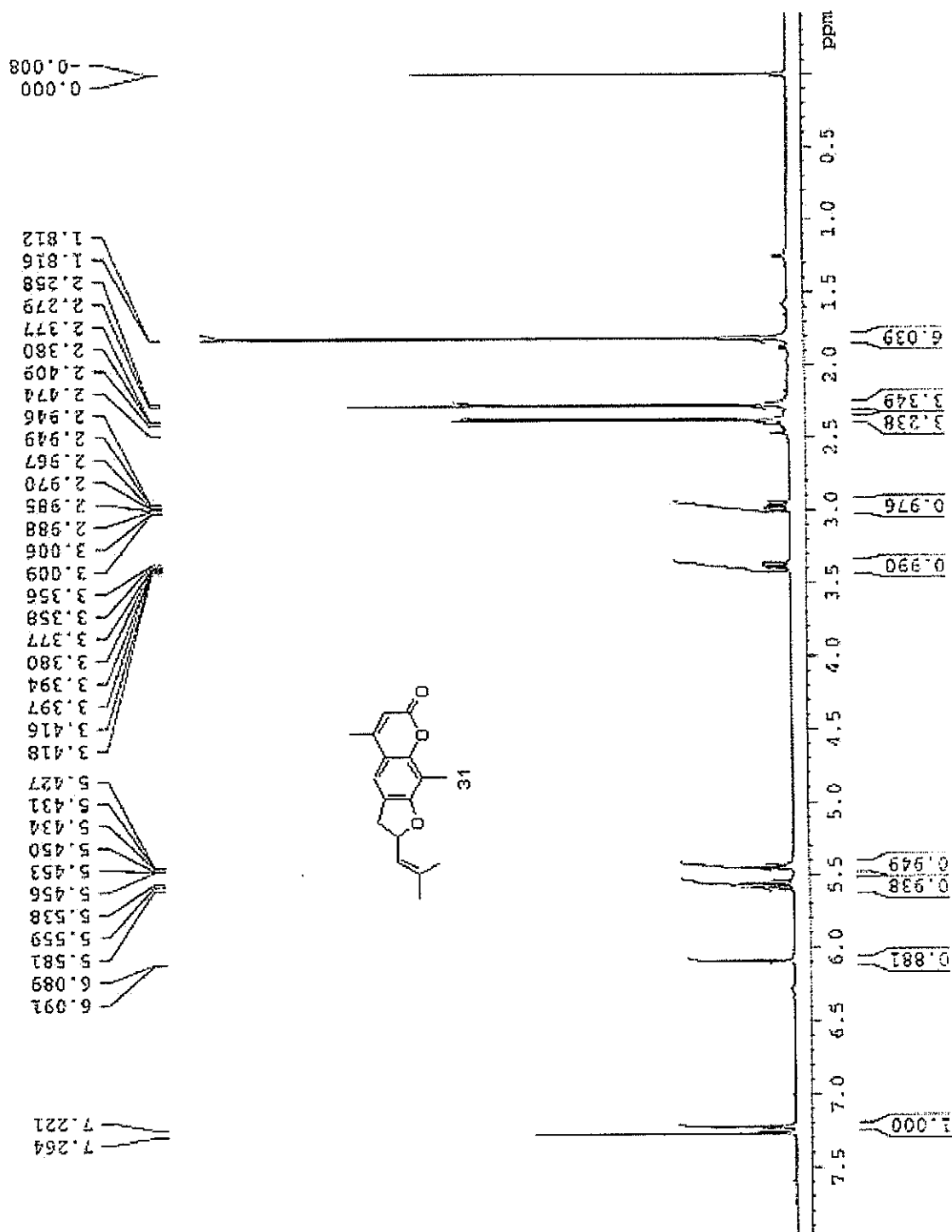


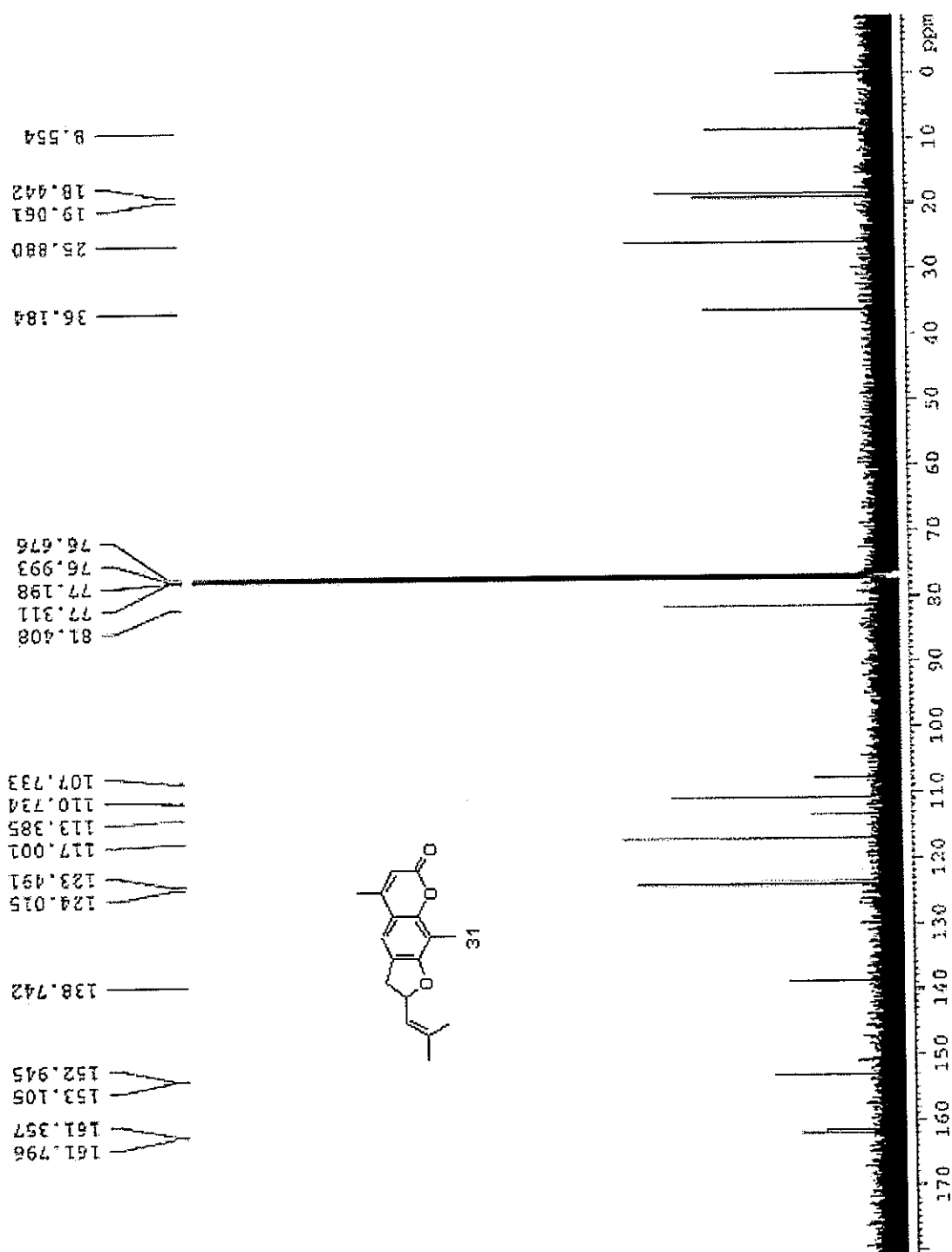


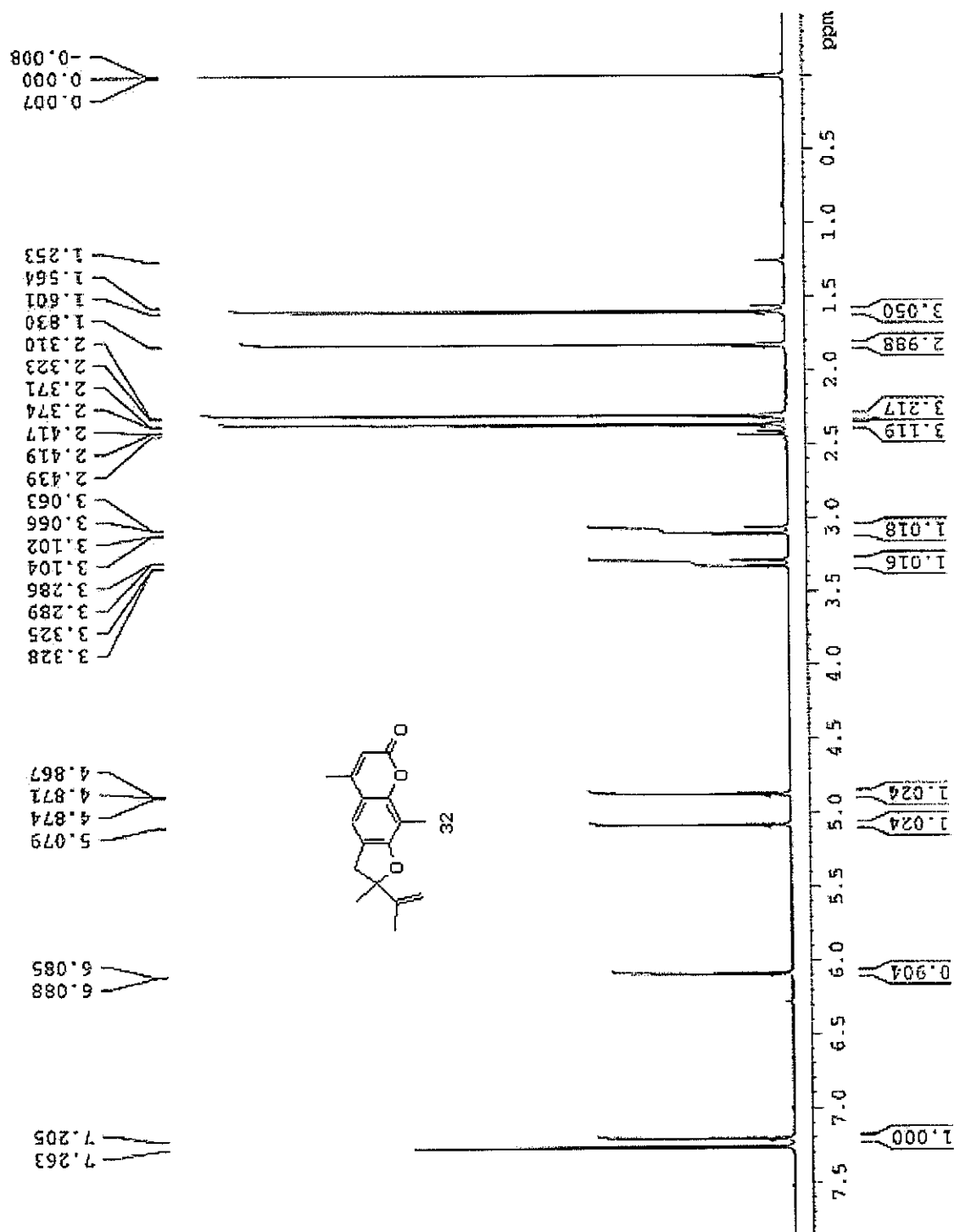


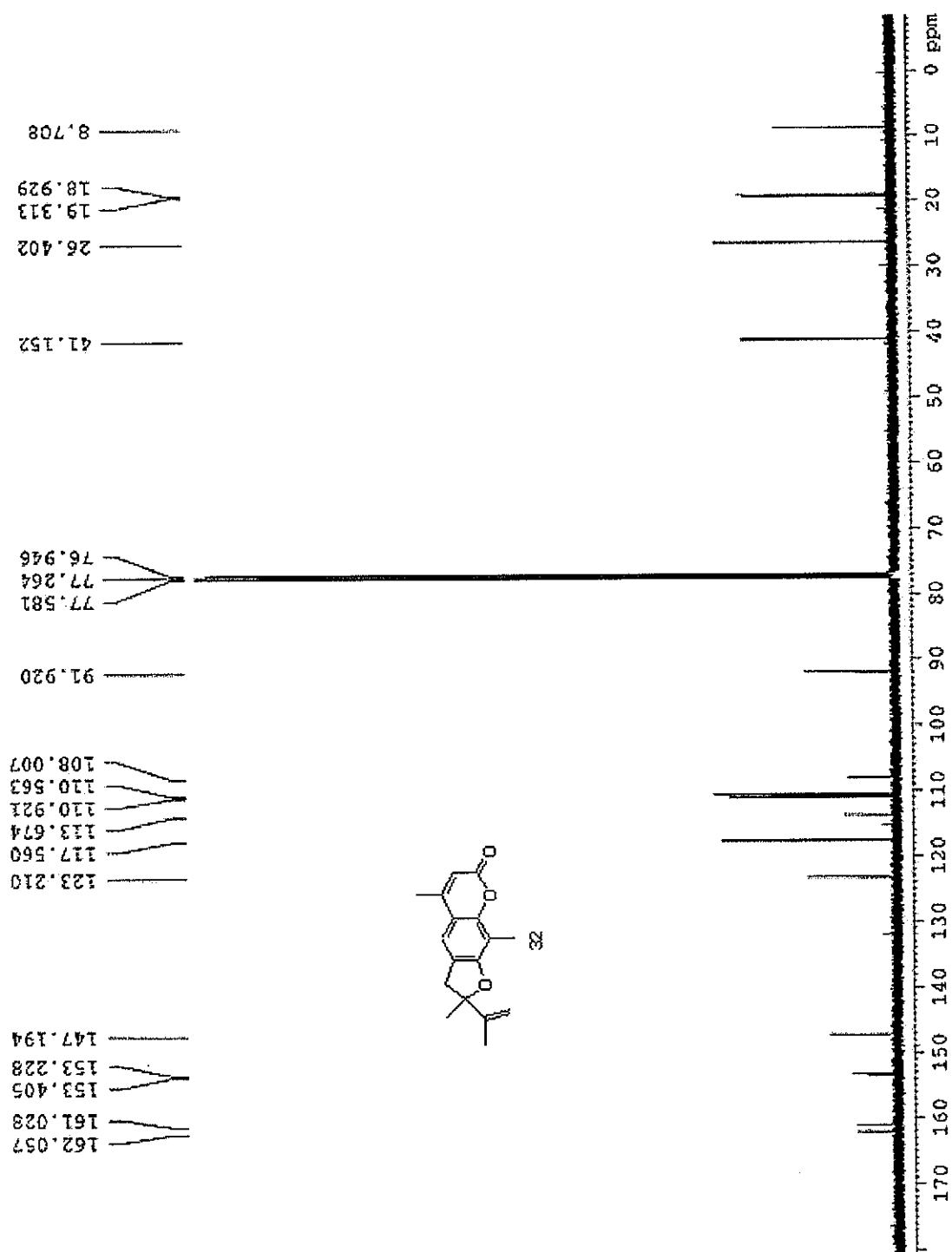


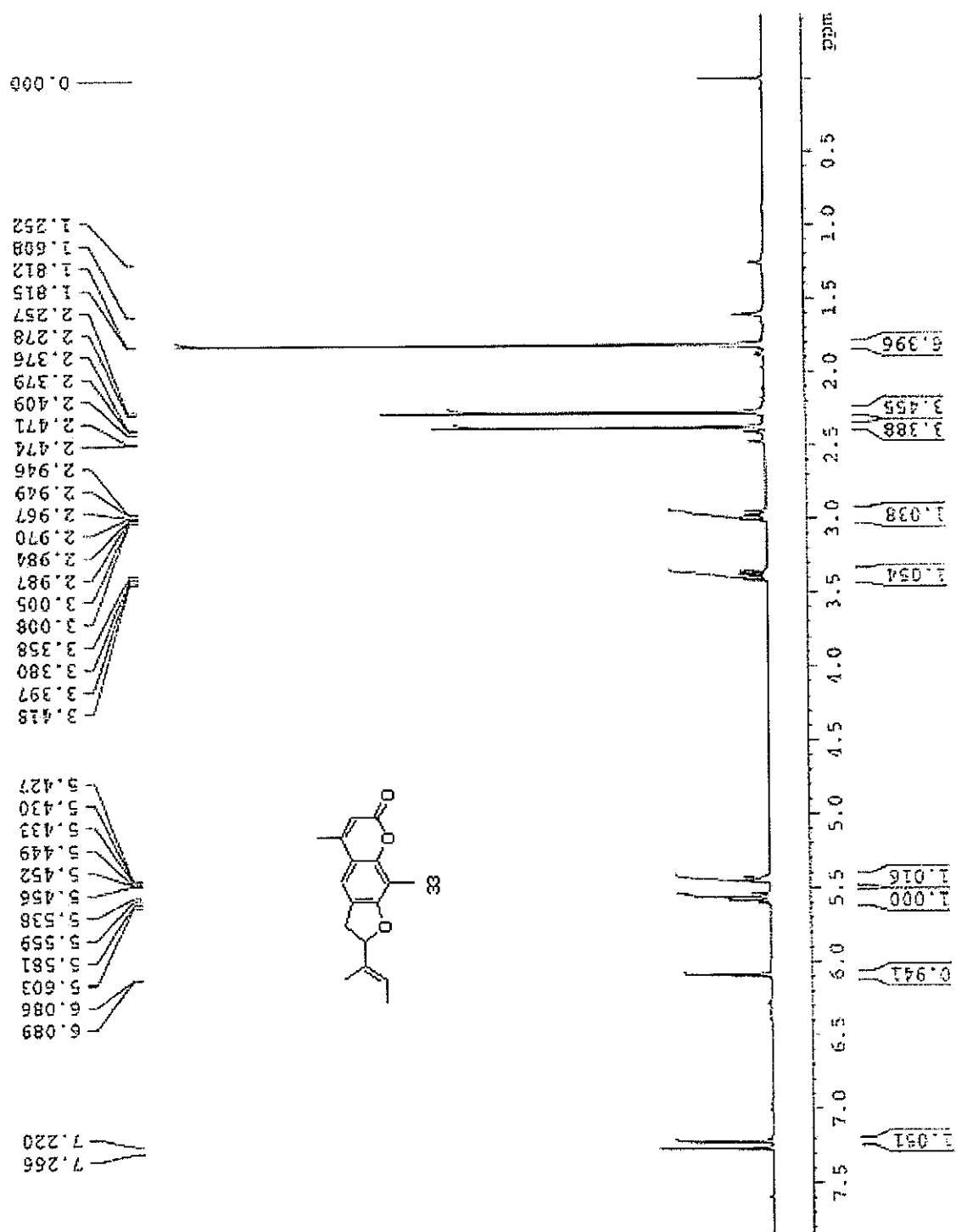


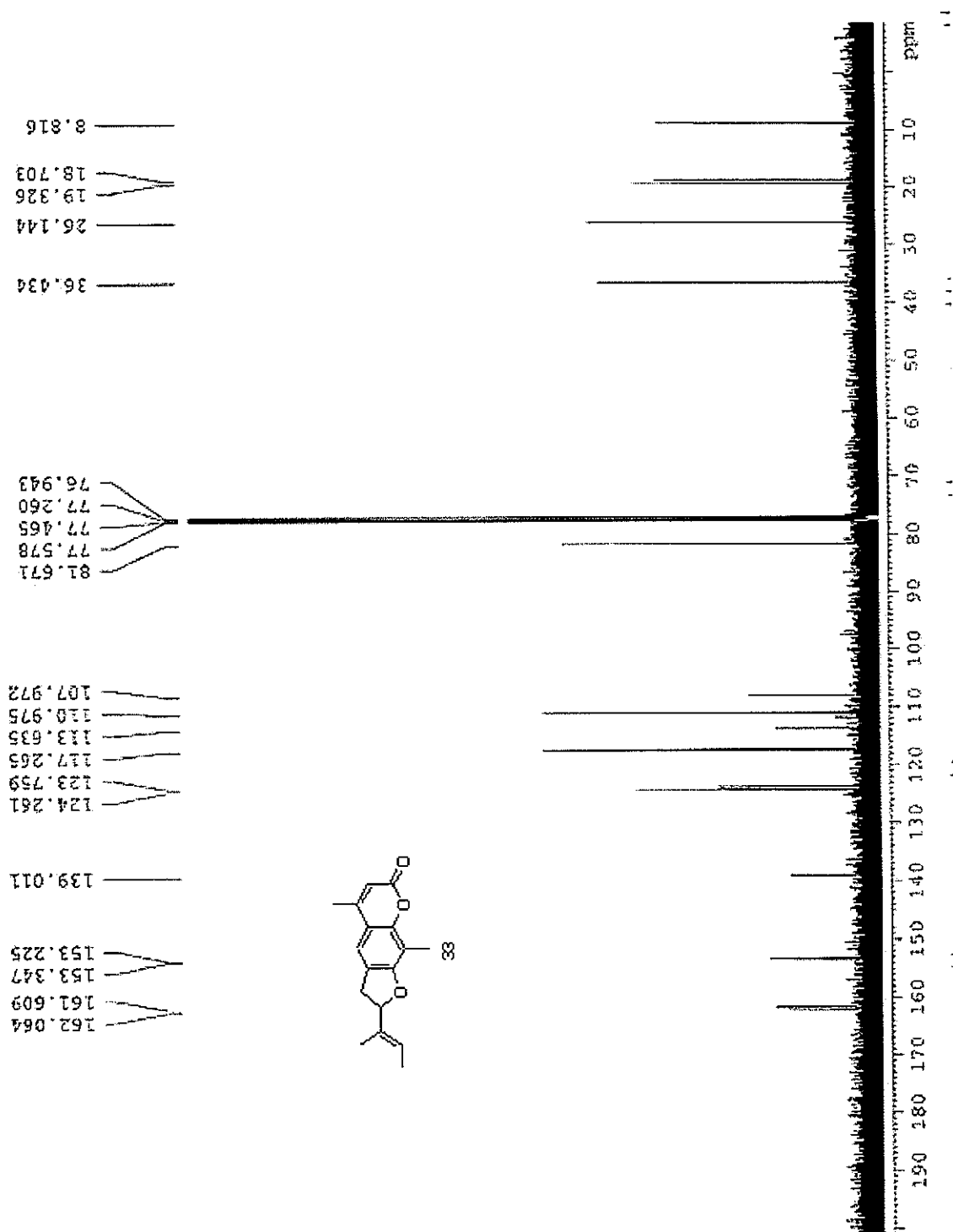


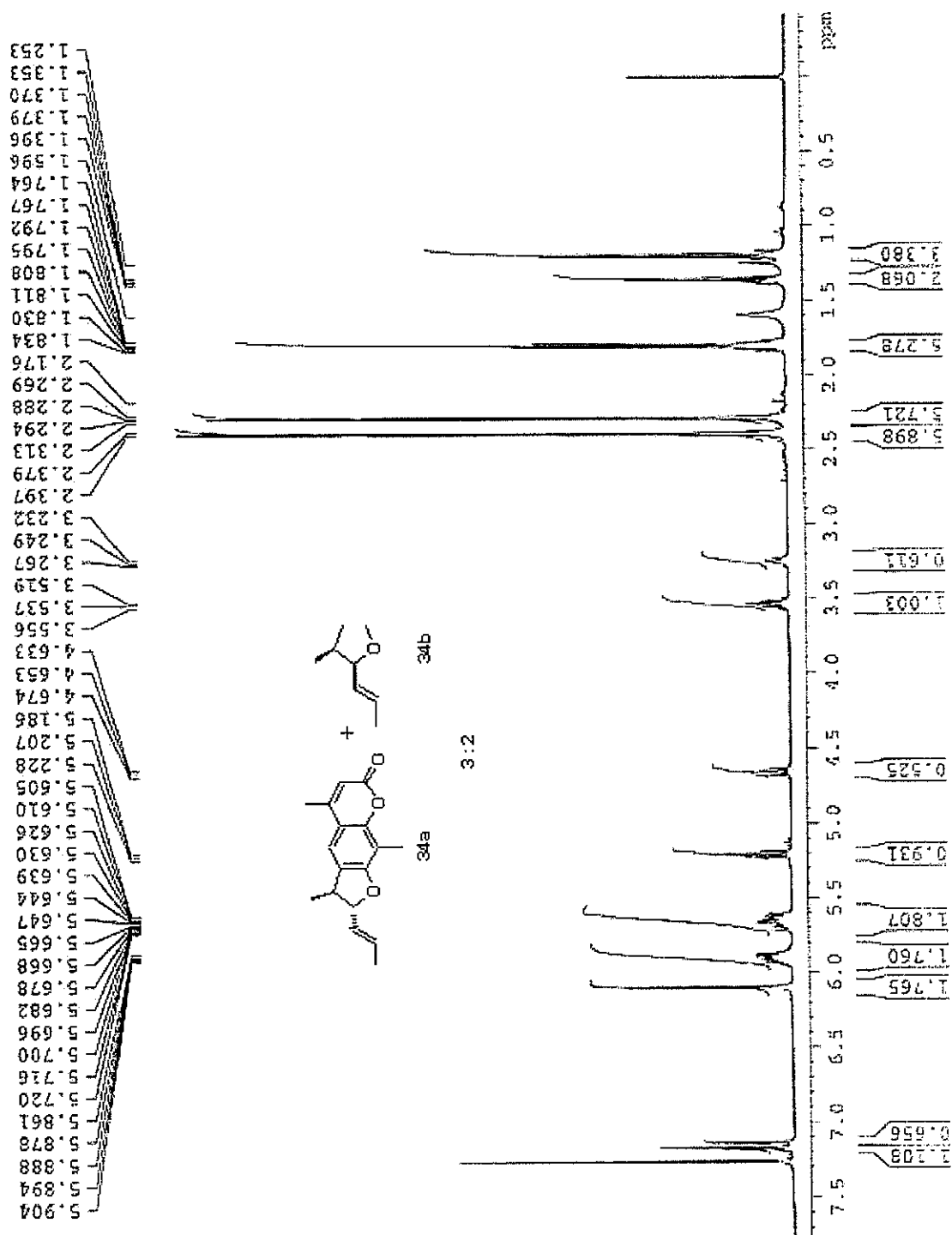


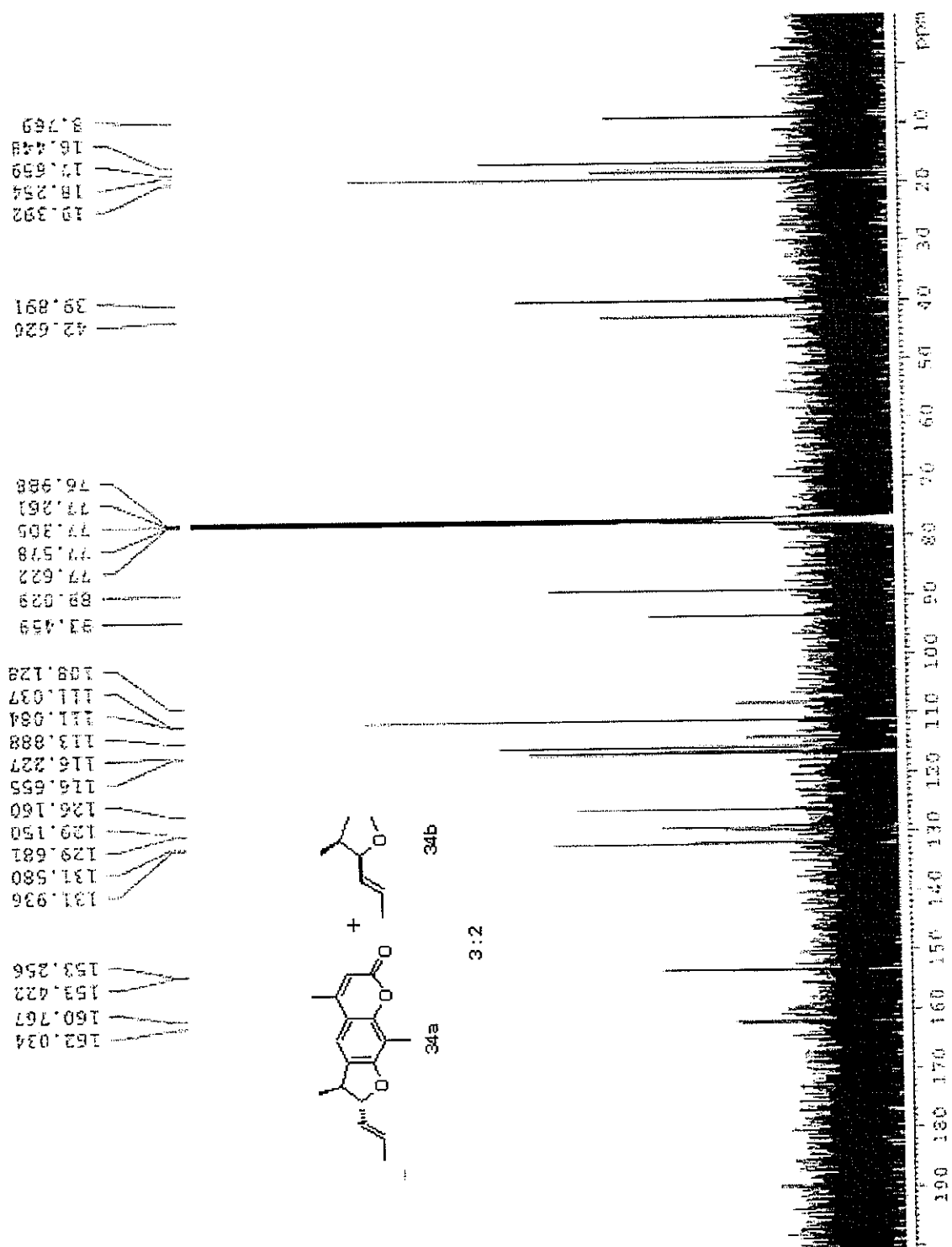


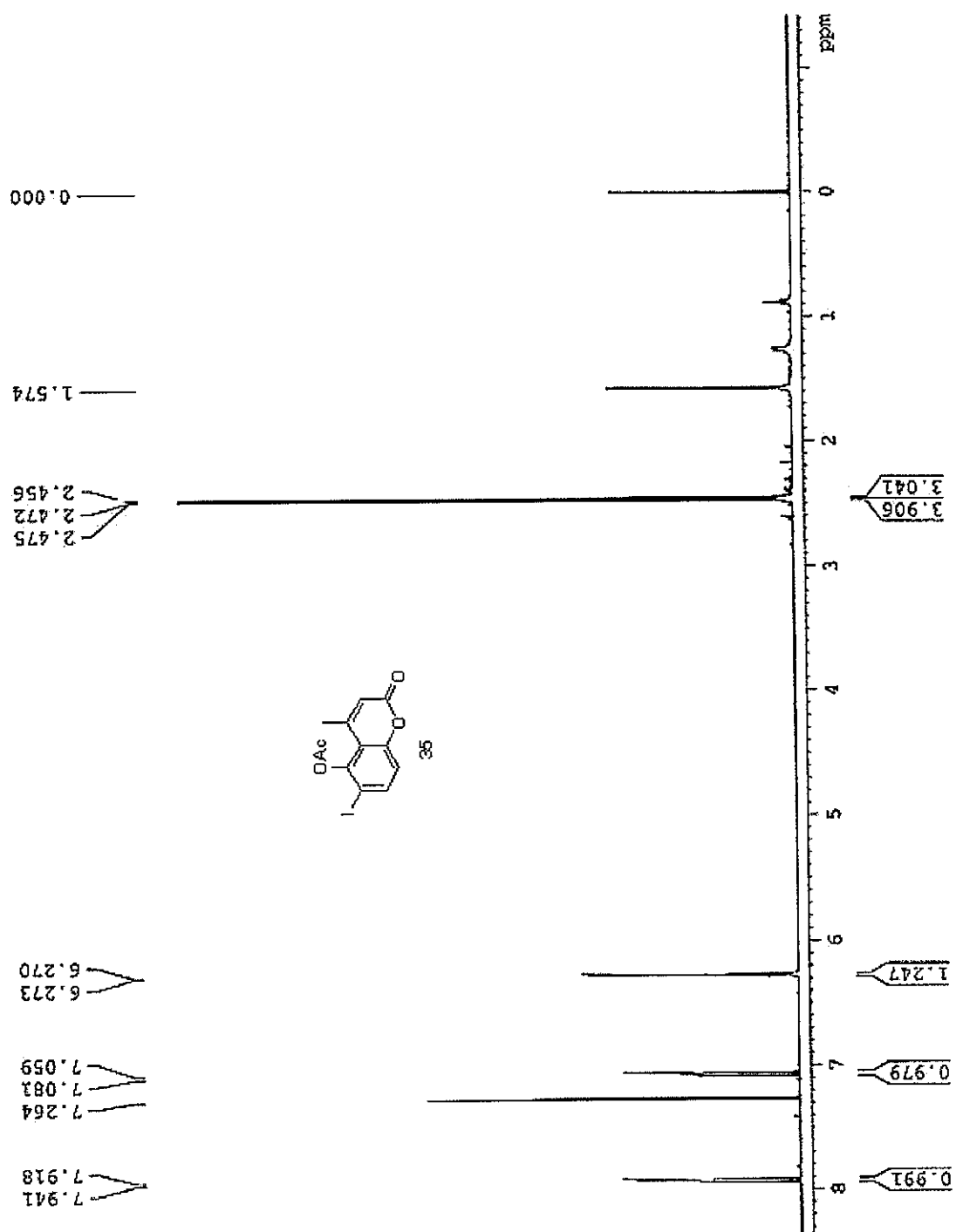


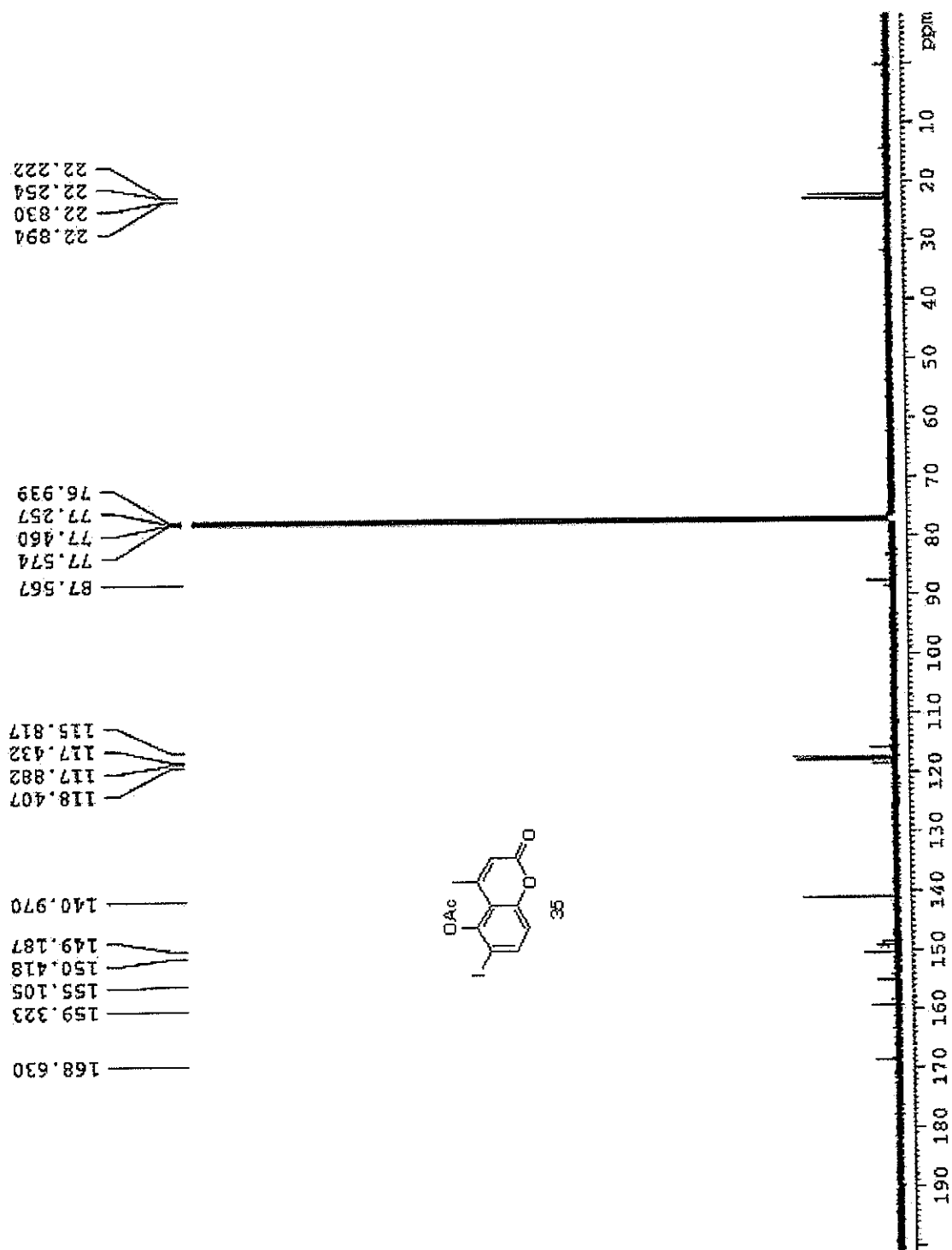


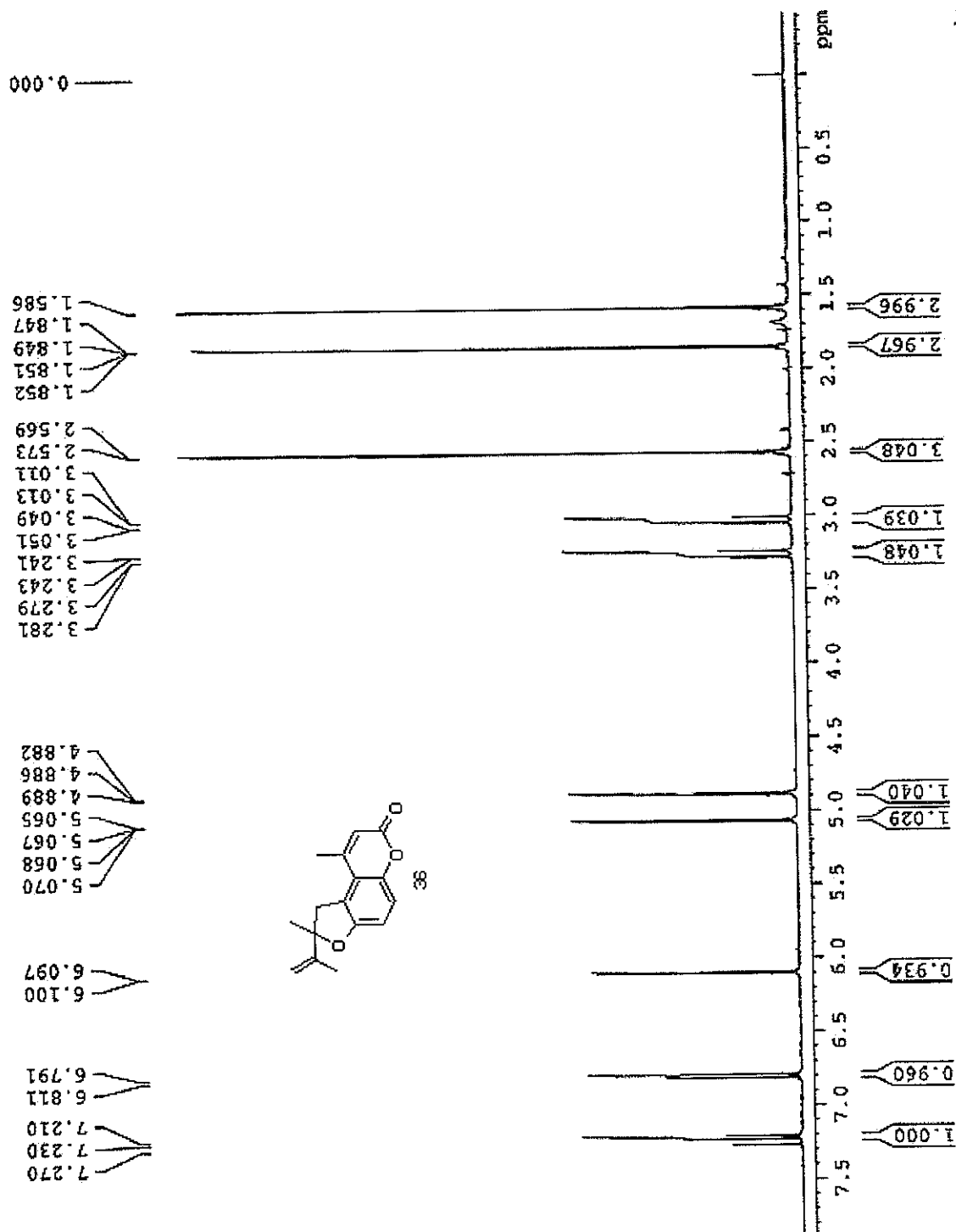


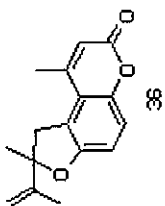


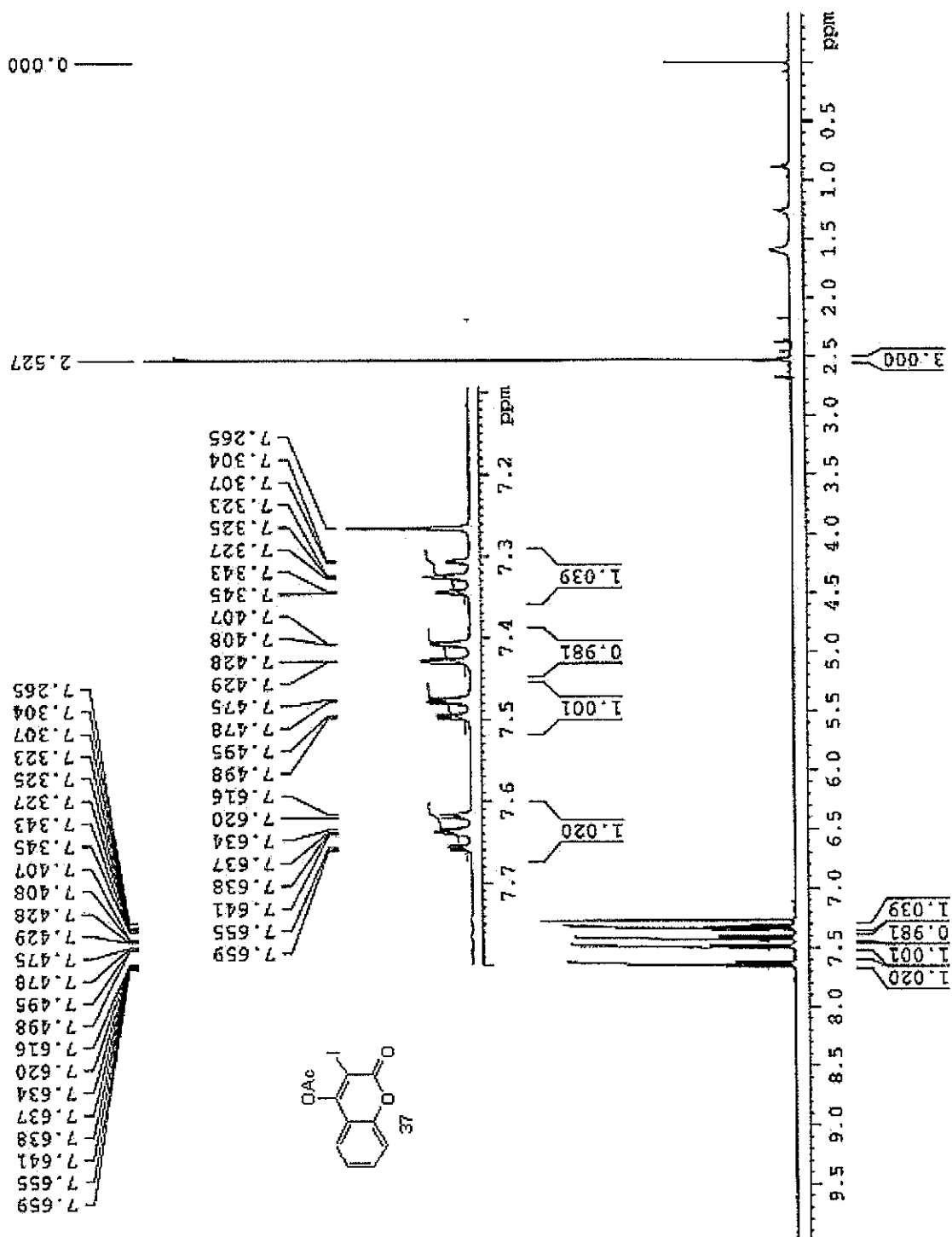


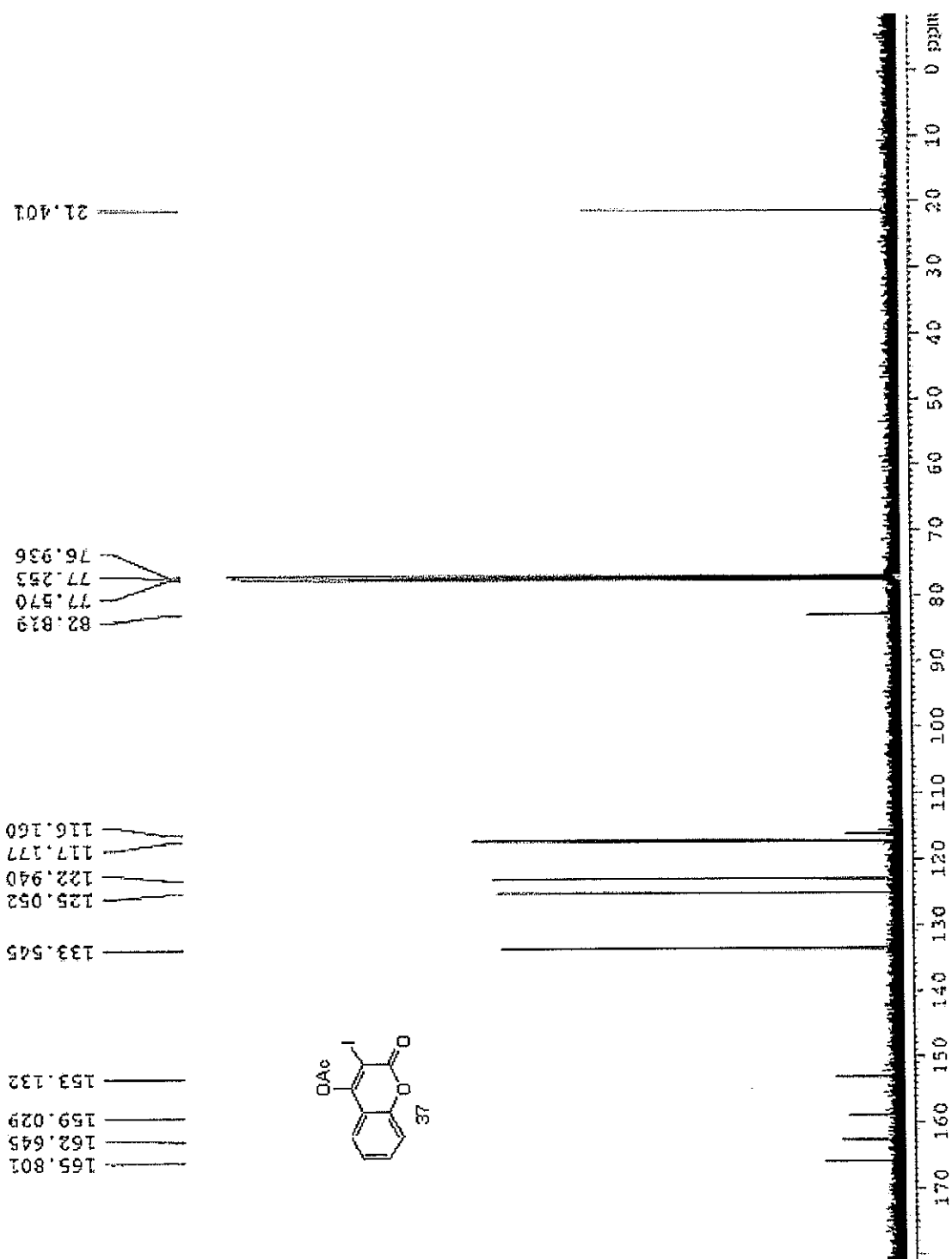


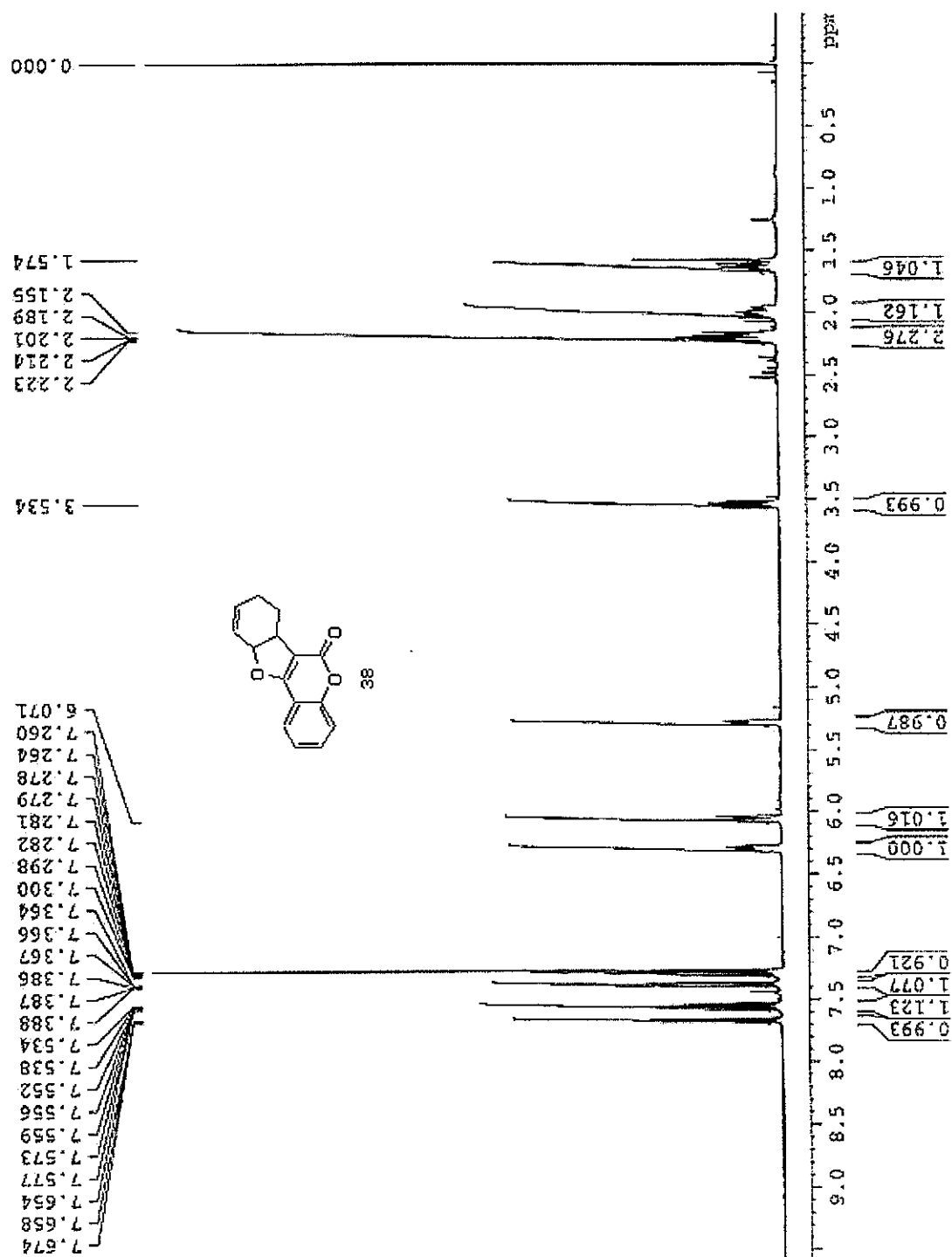


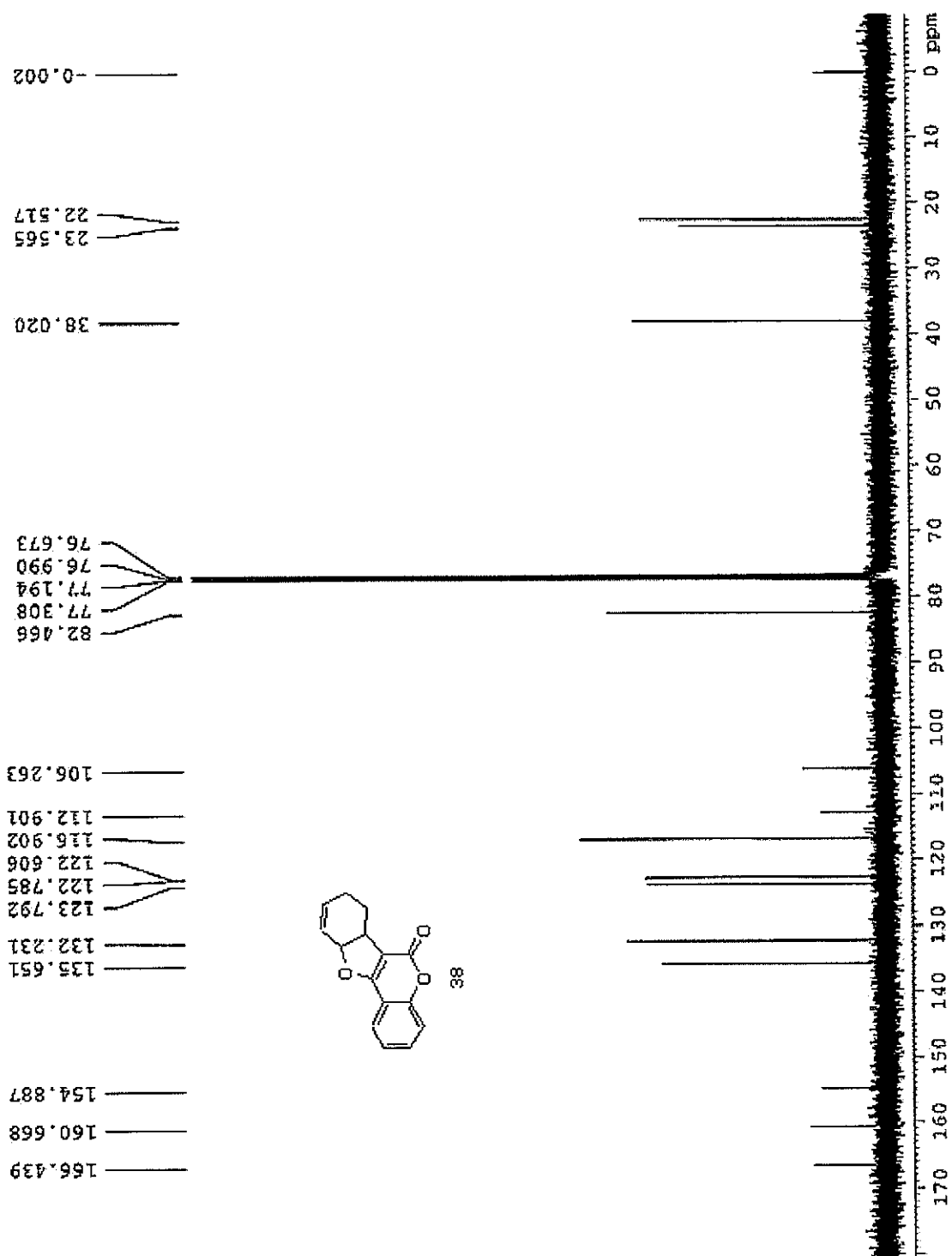


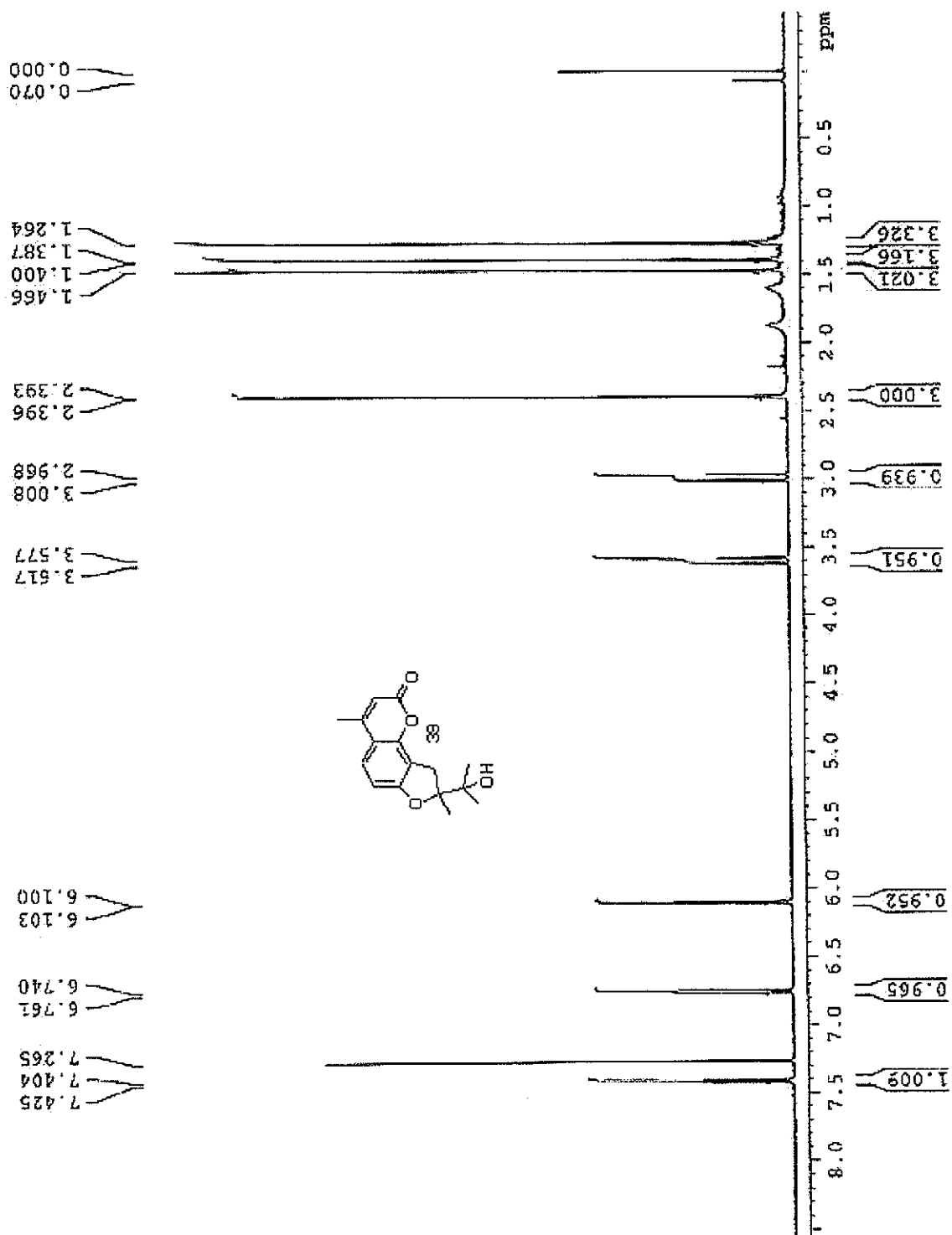


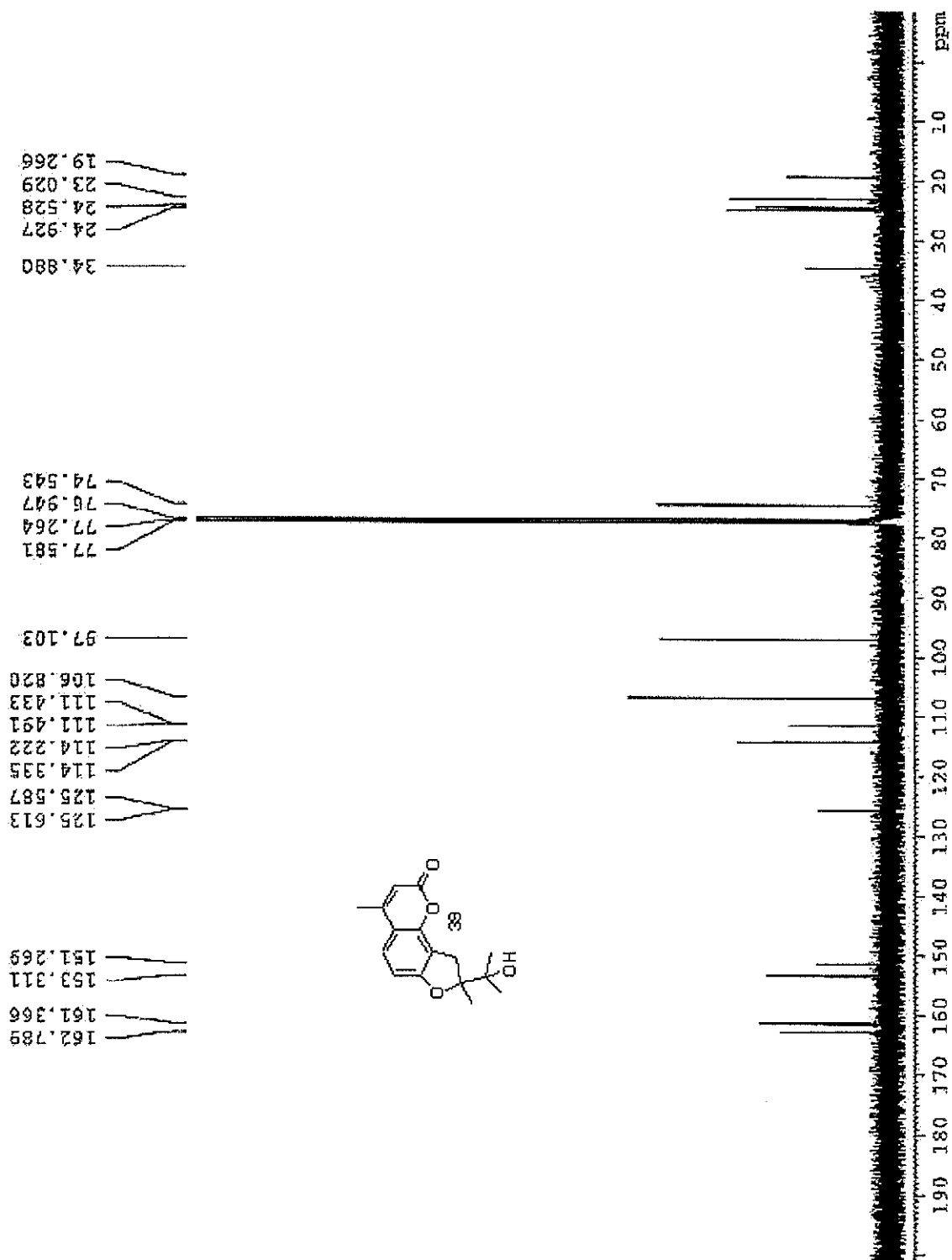


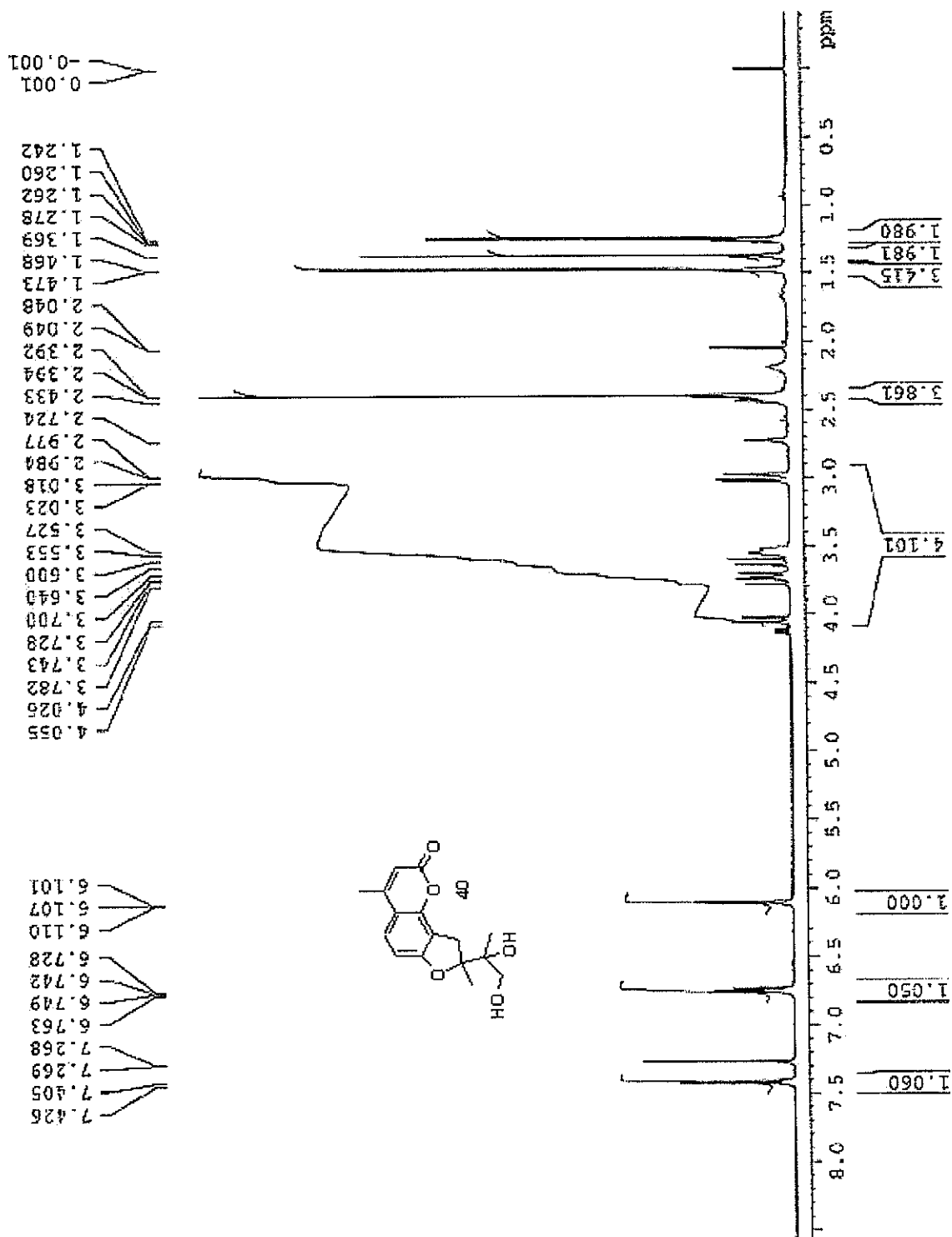


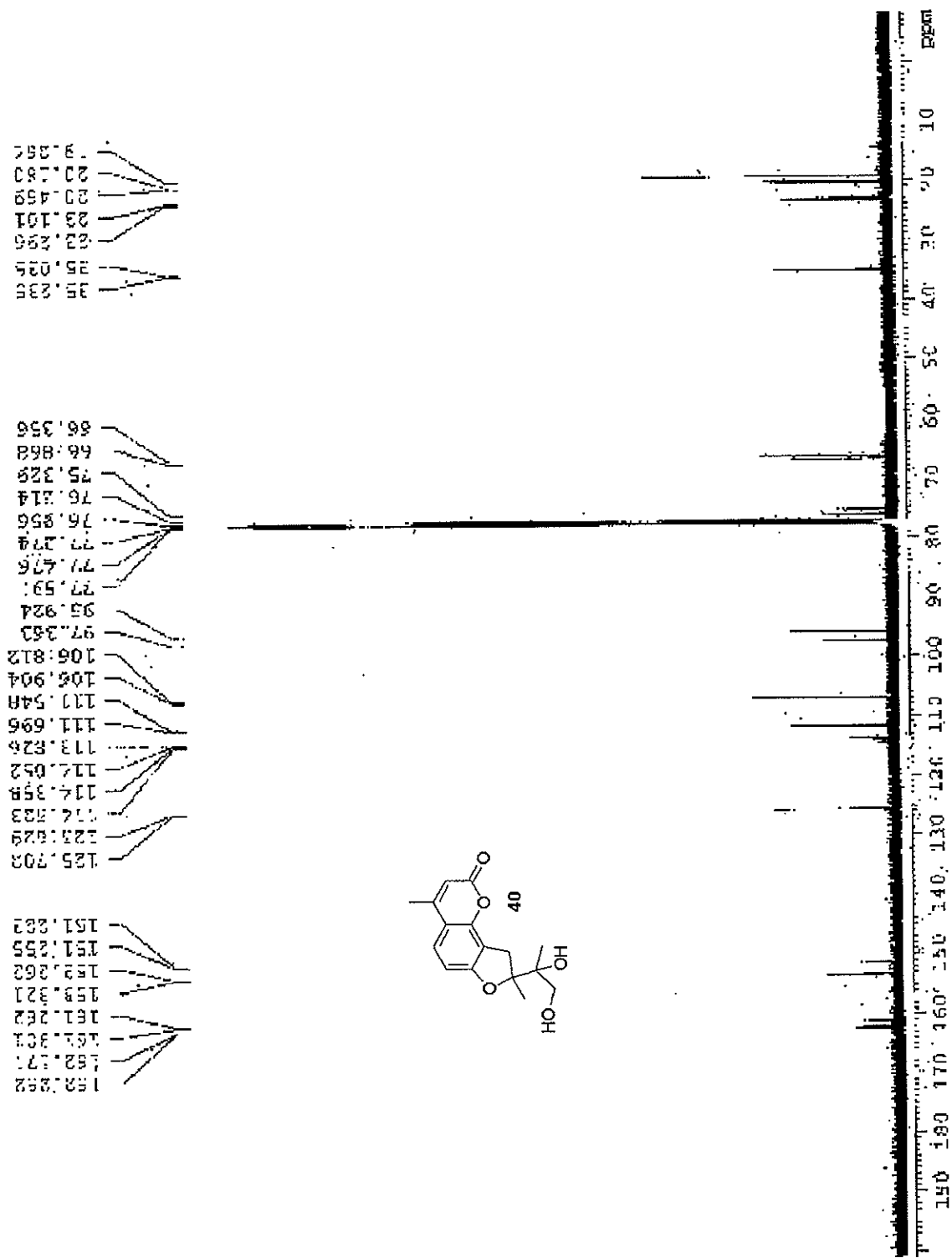


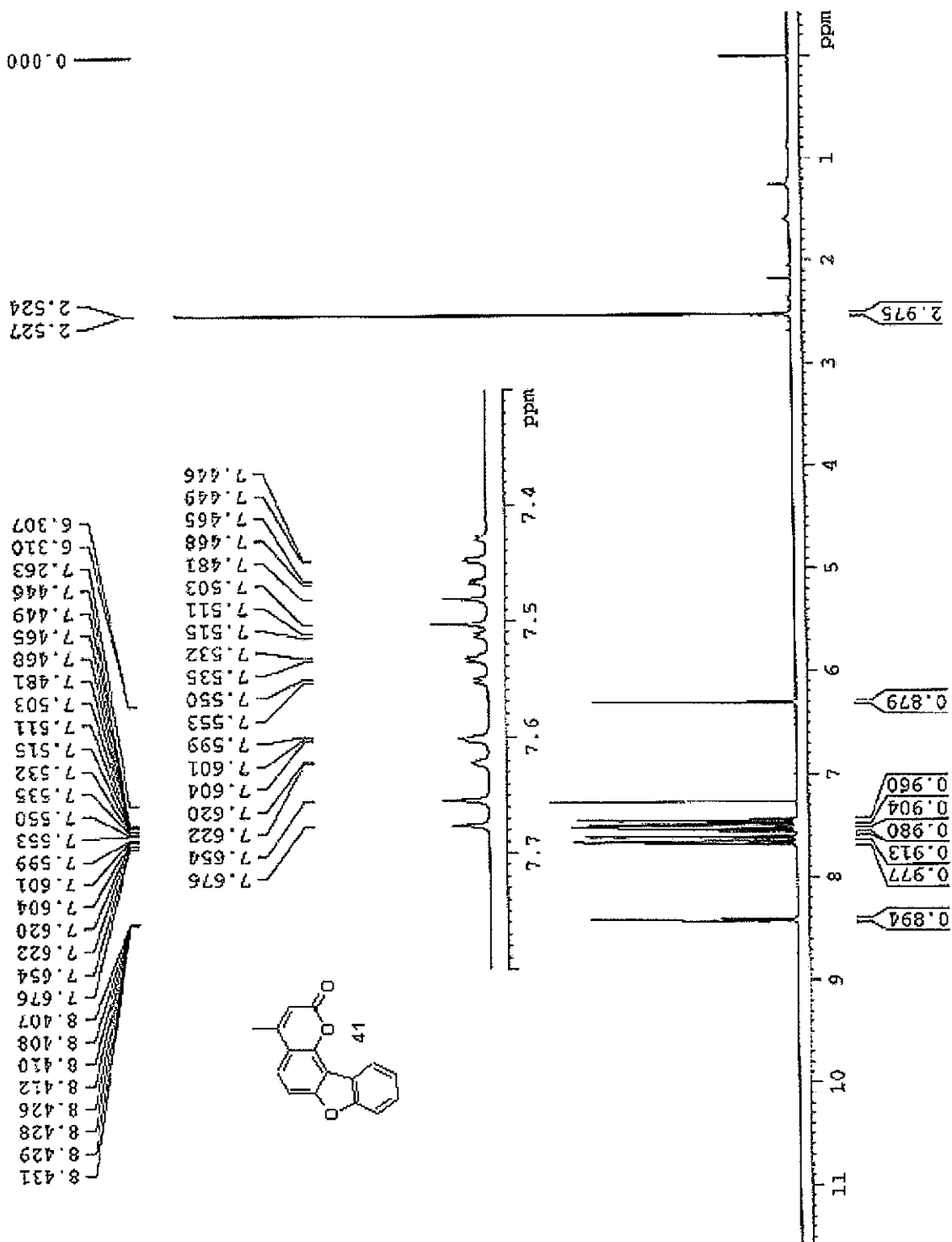


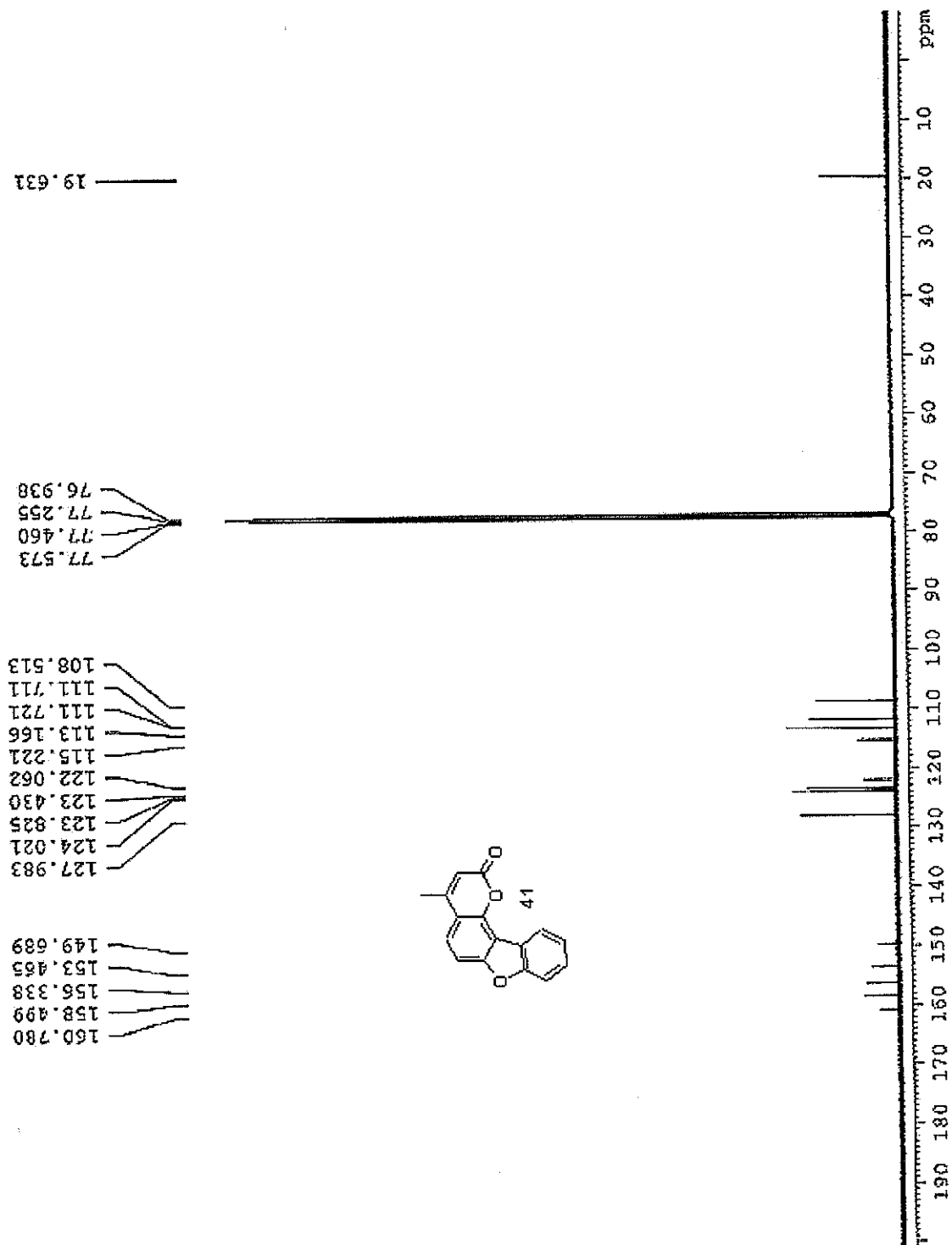




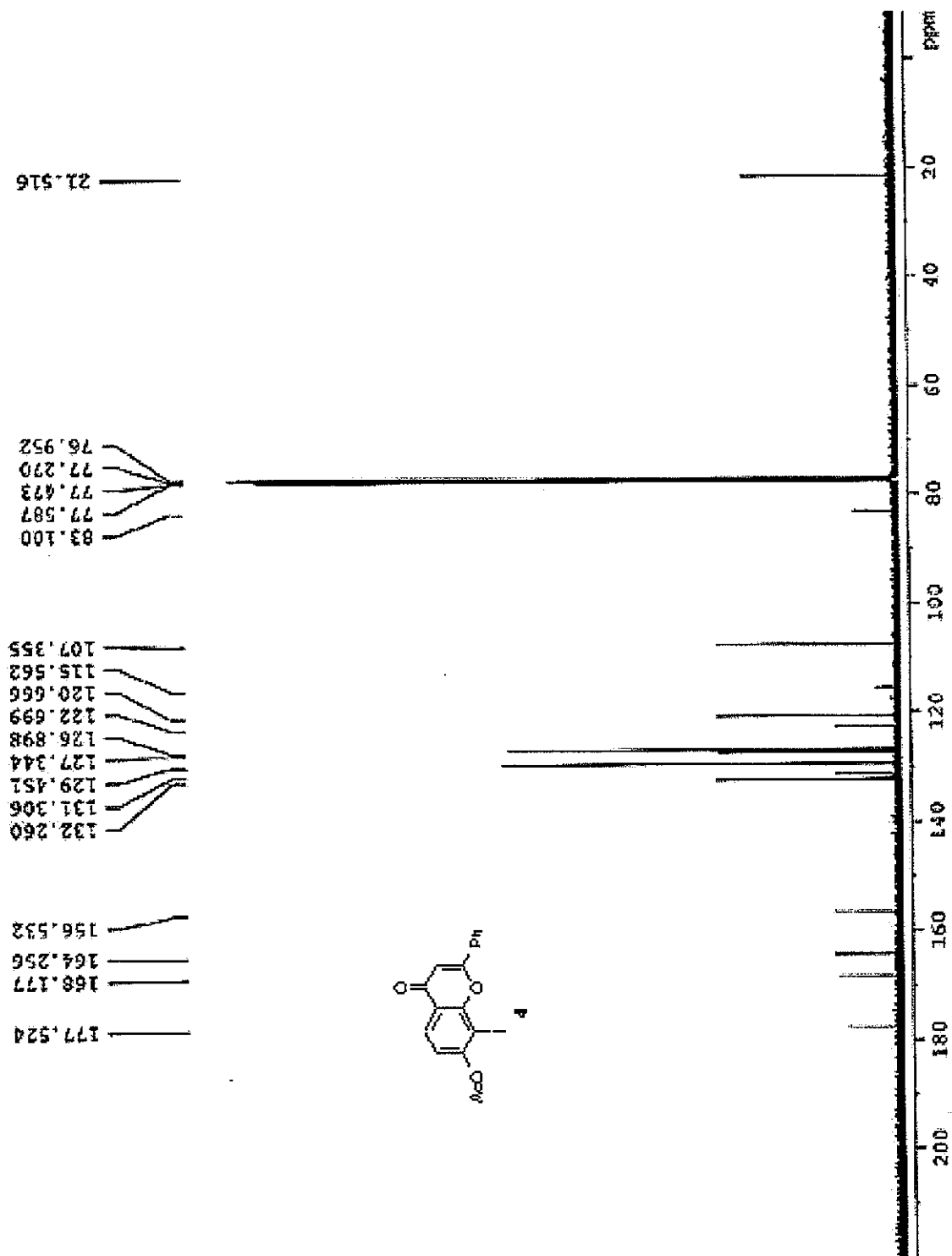


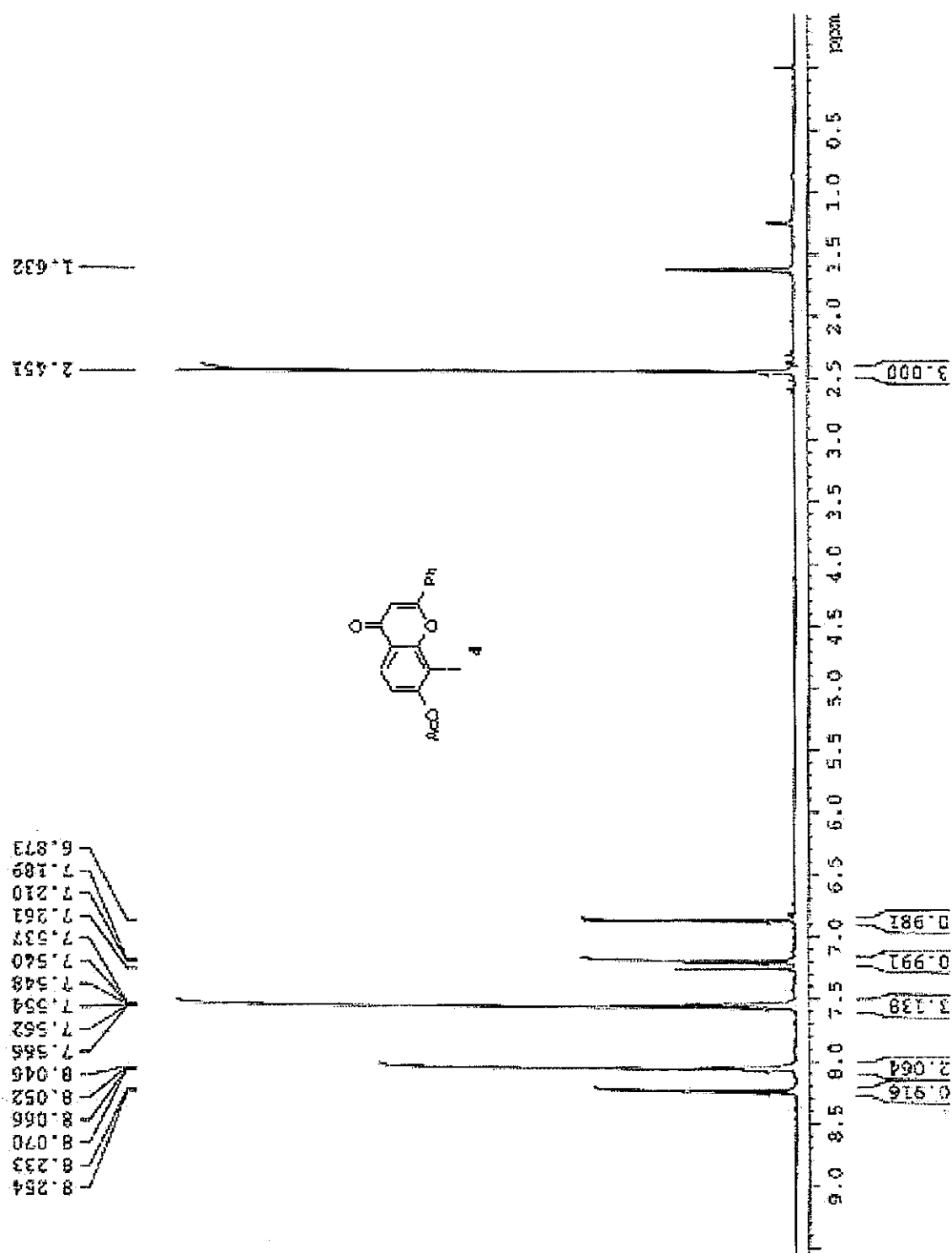


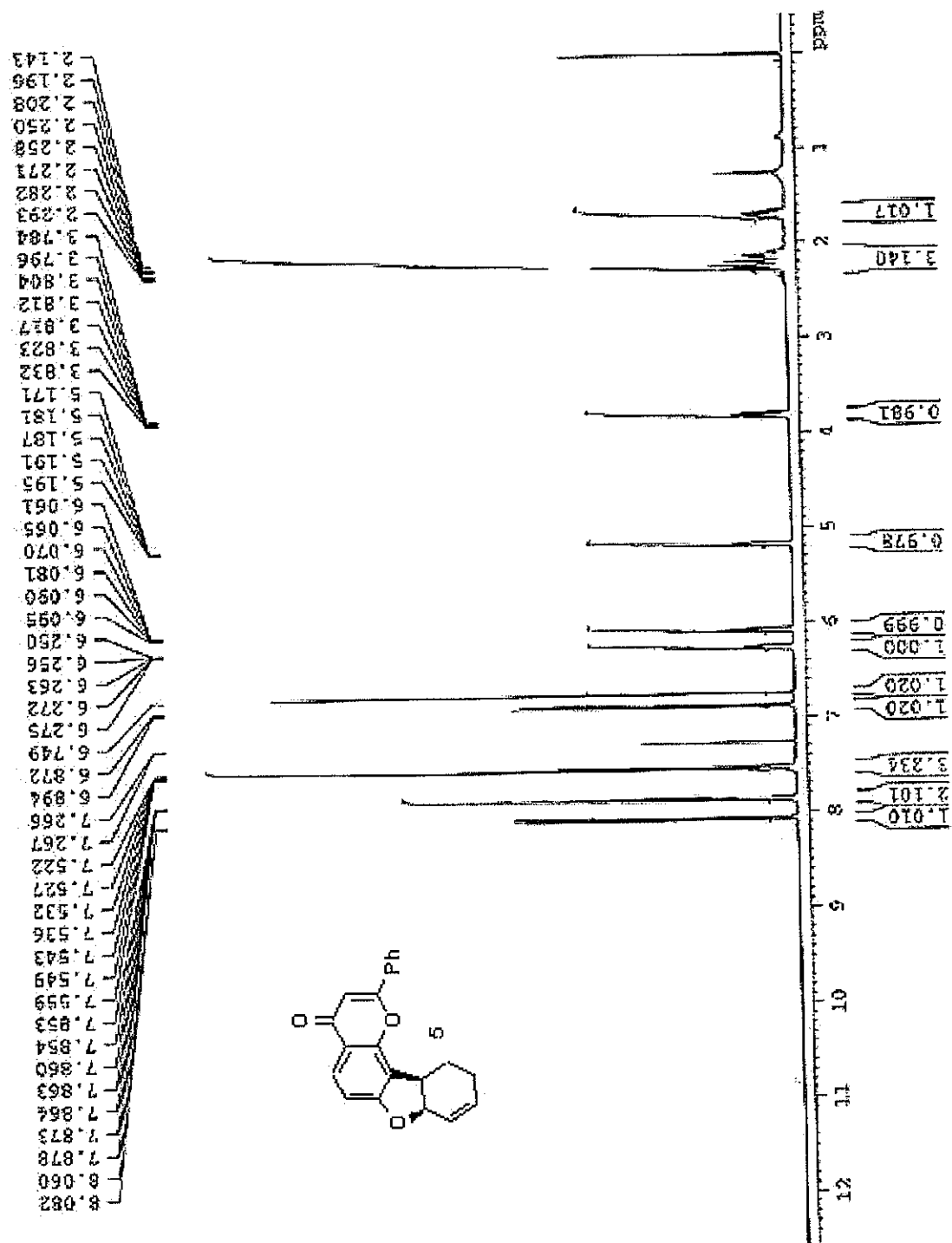


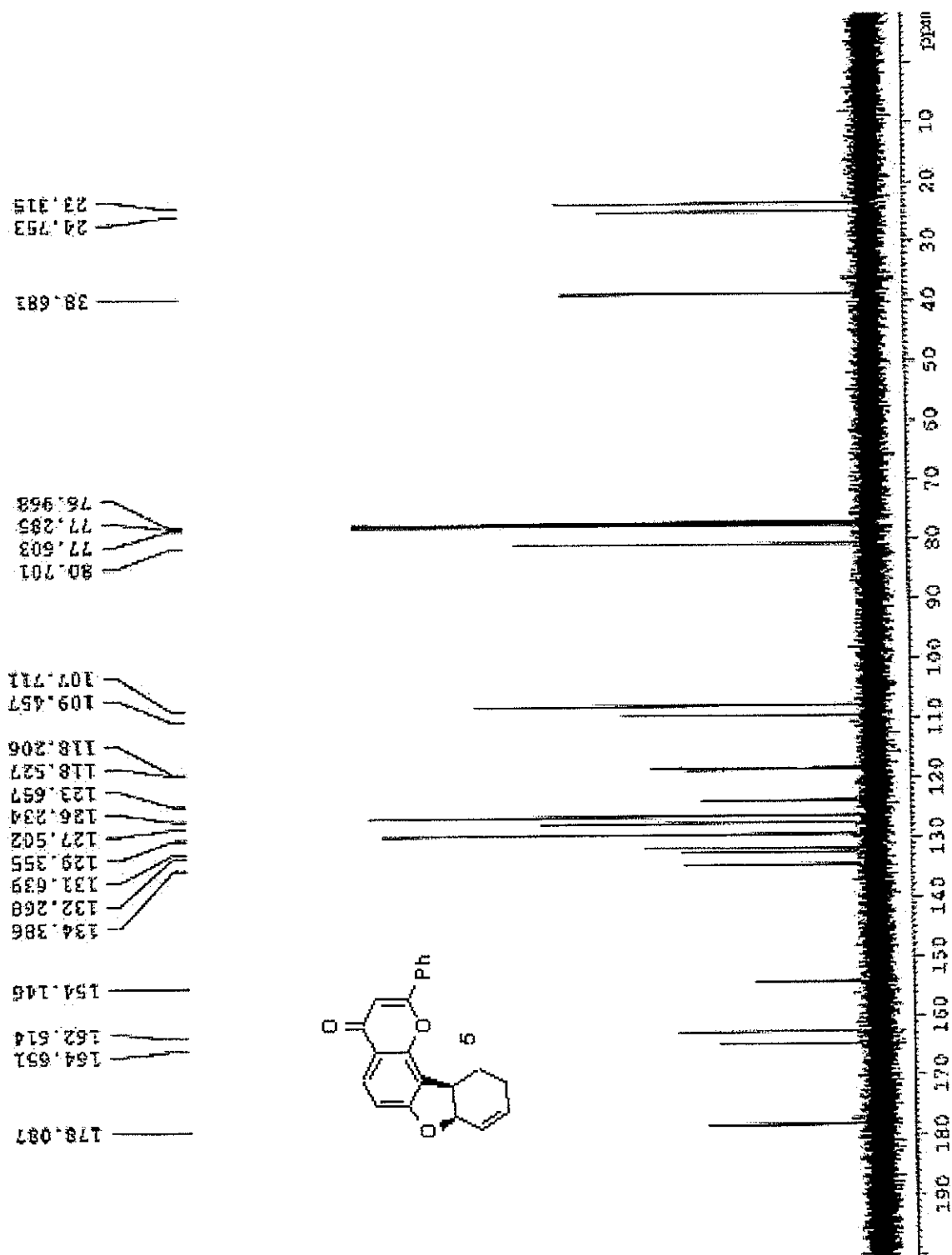


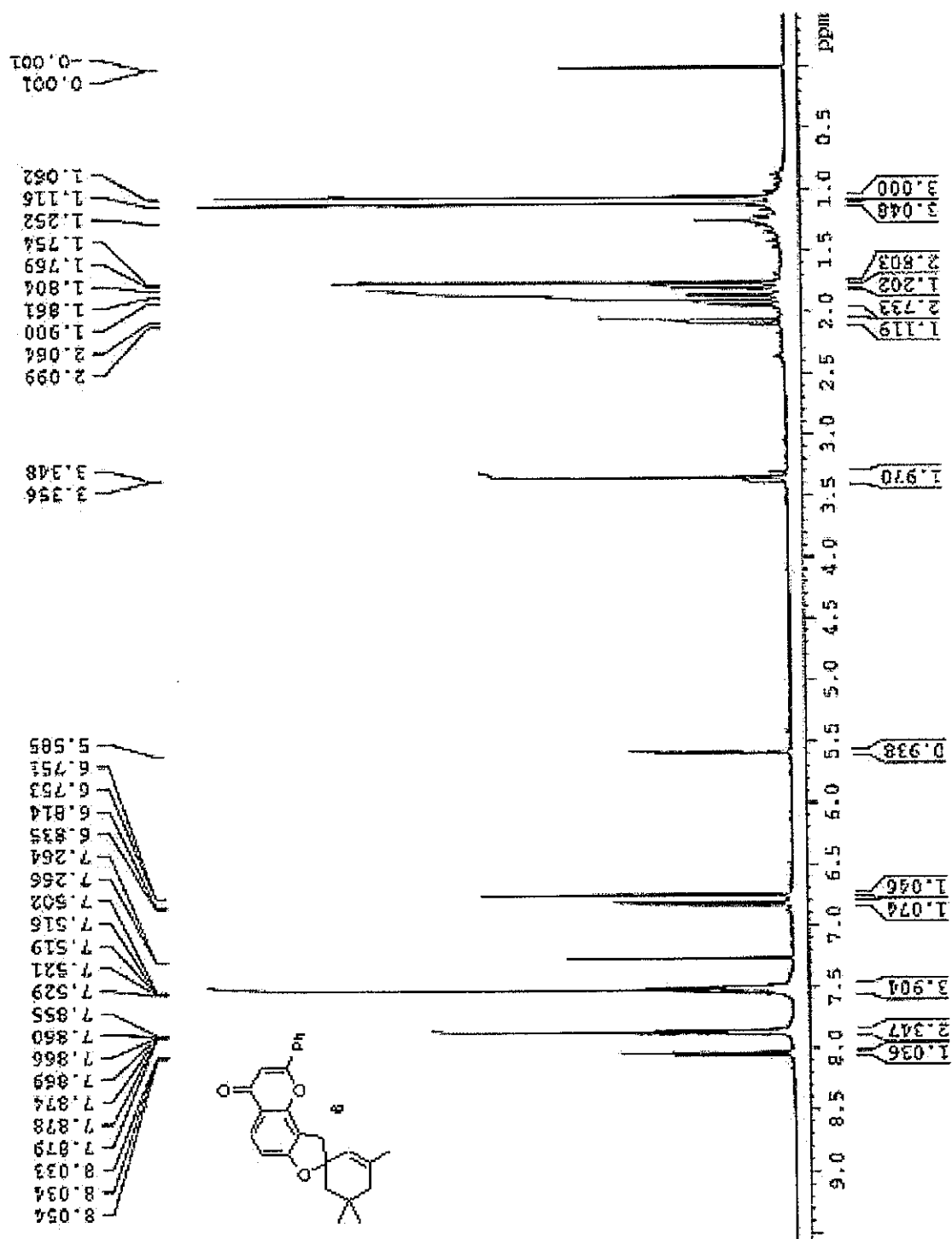
APPENDIX C. CHAPTER 3 ^1H and ^{13}C SPECTRA

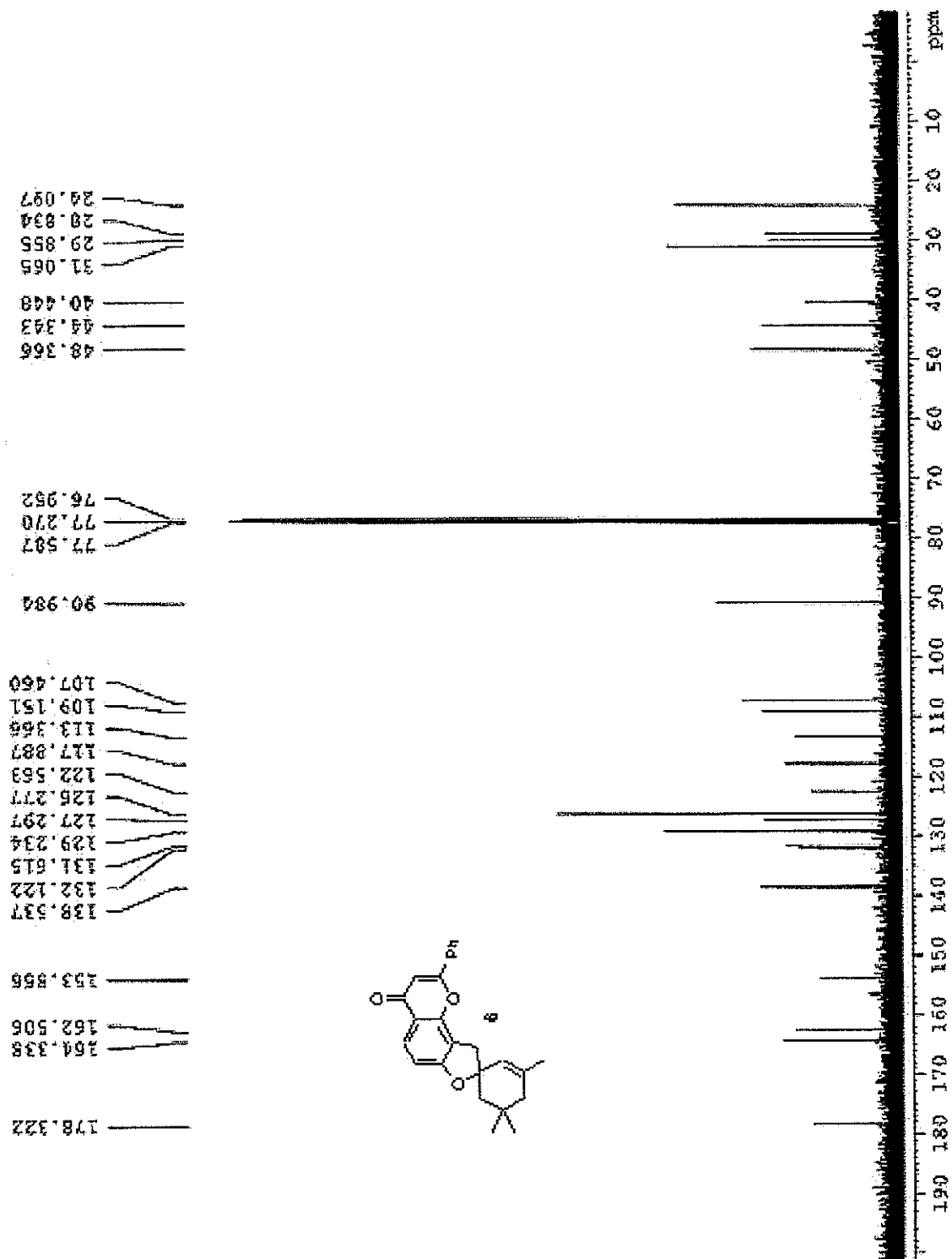


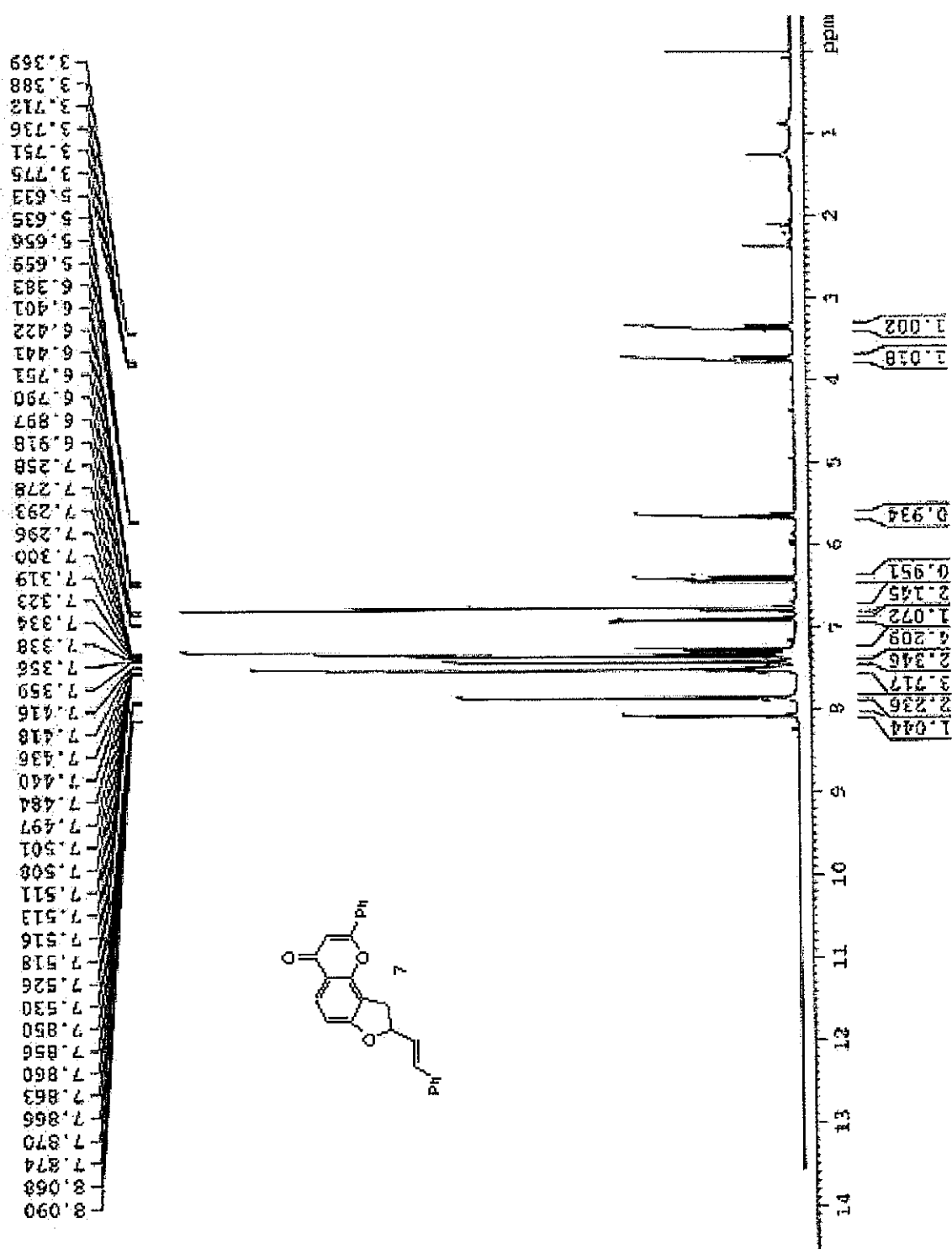


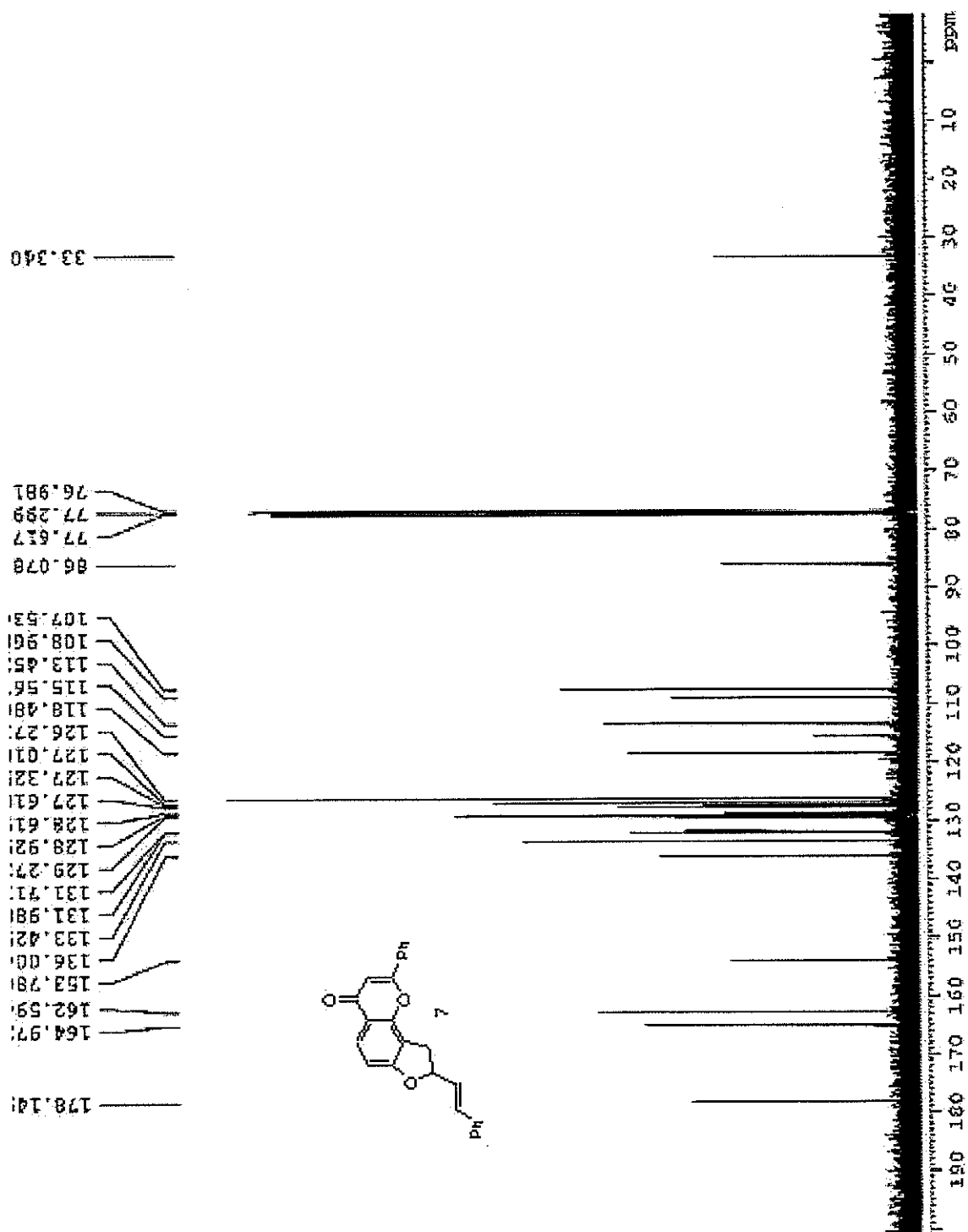


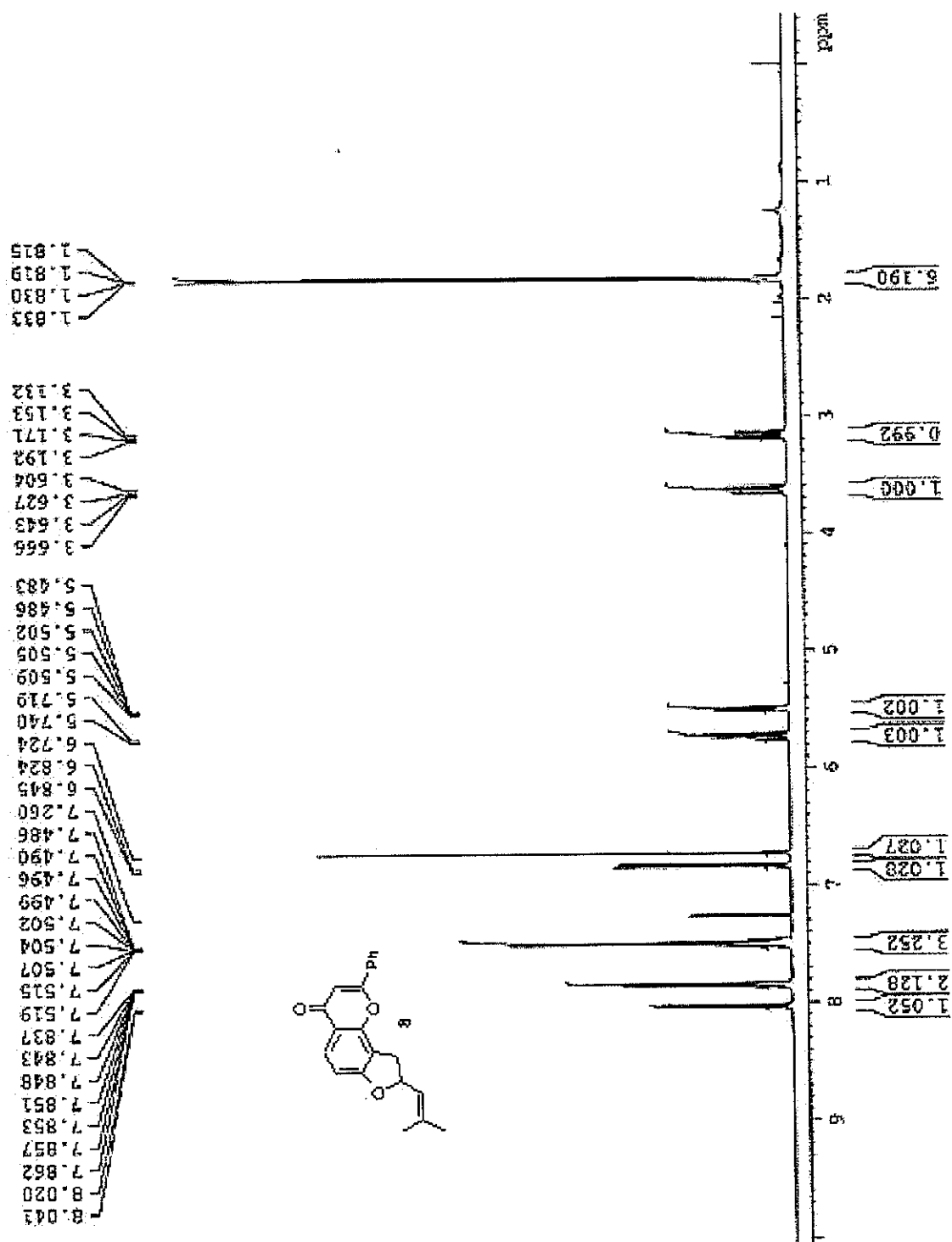


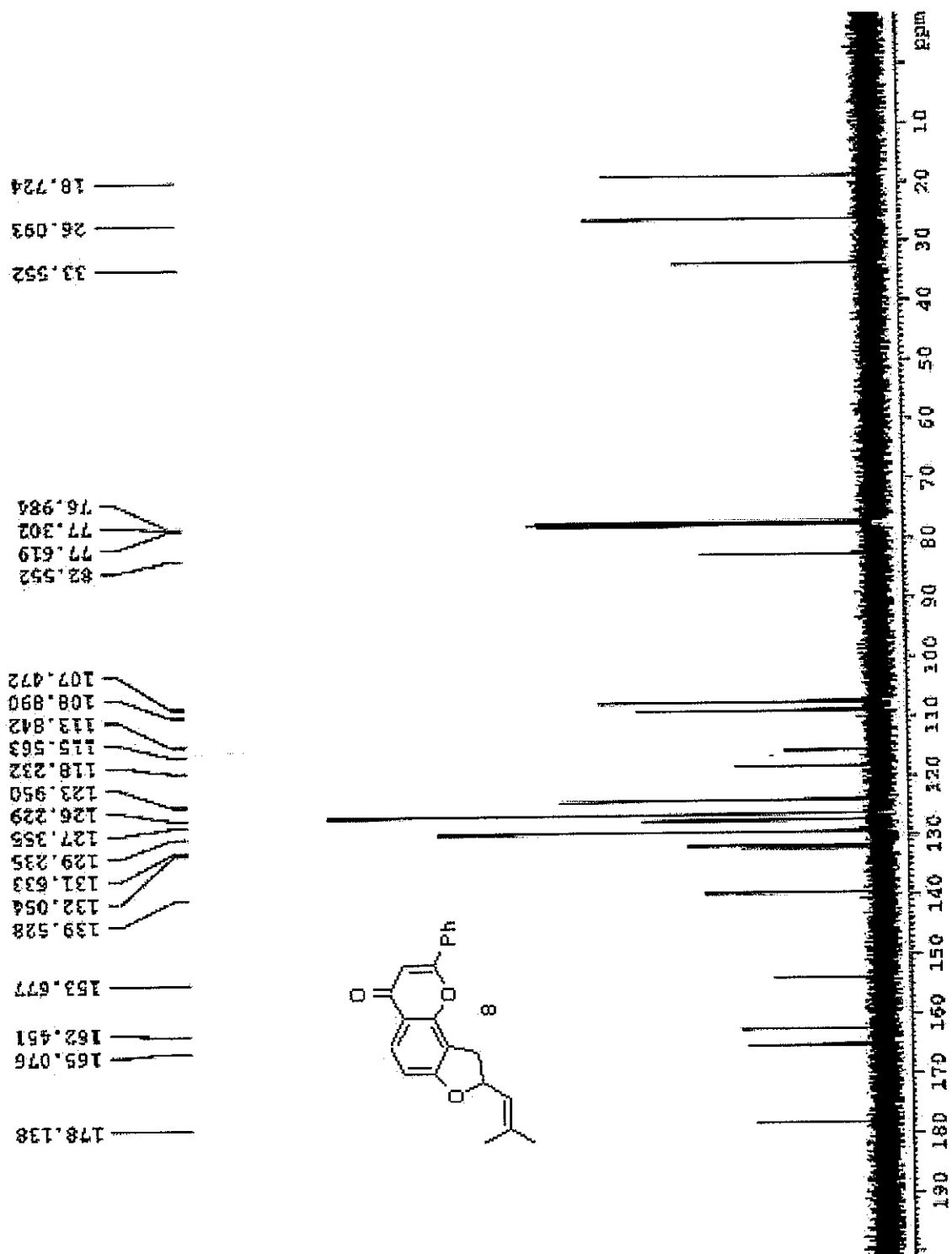


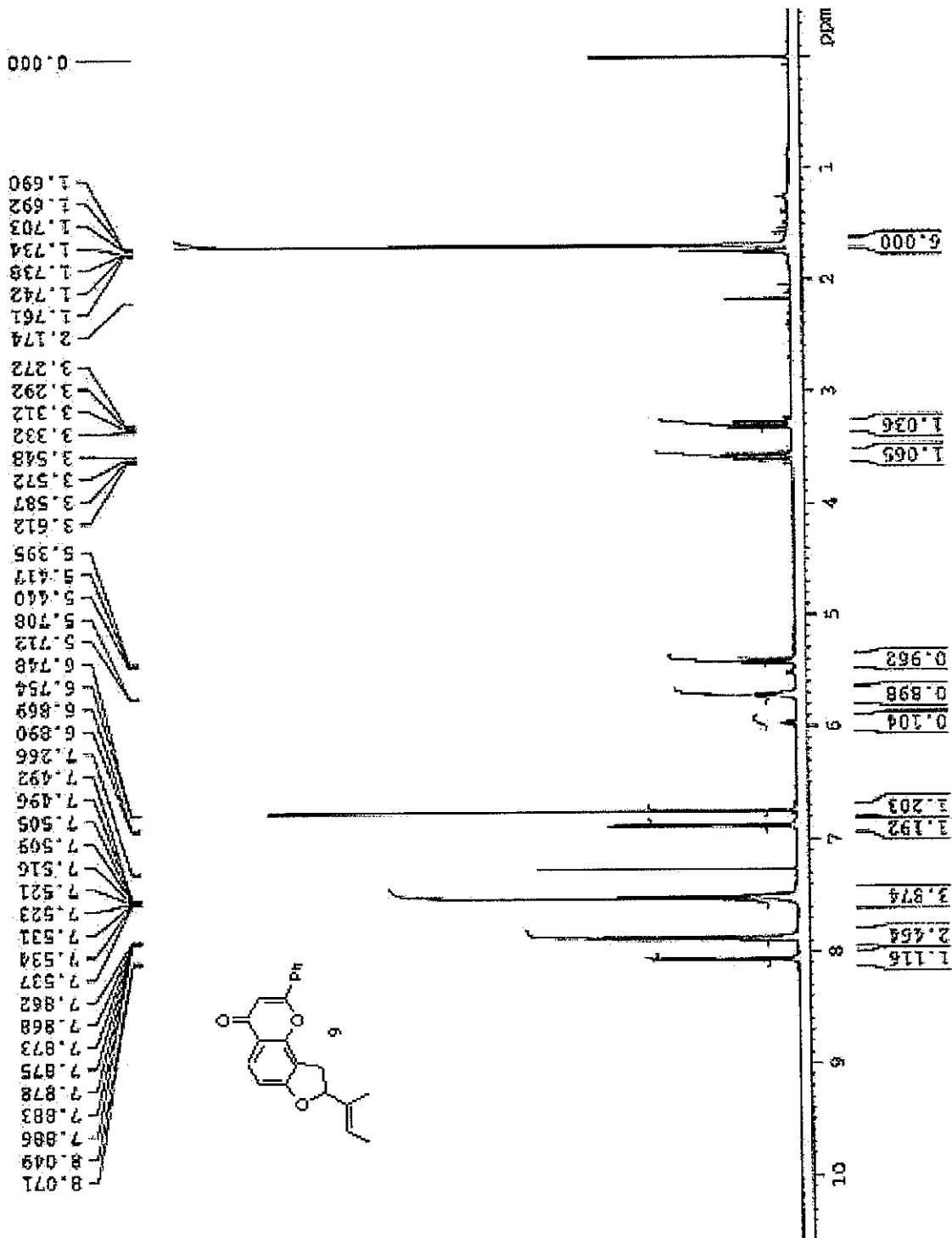


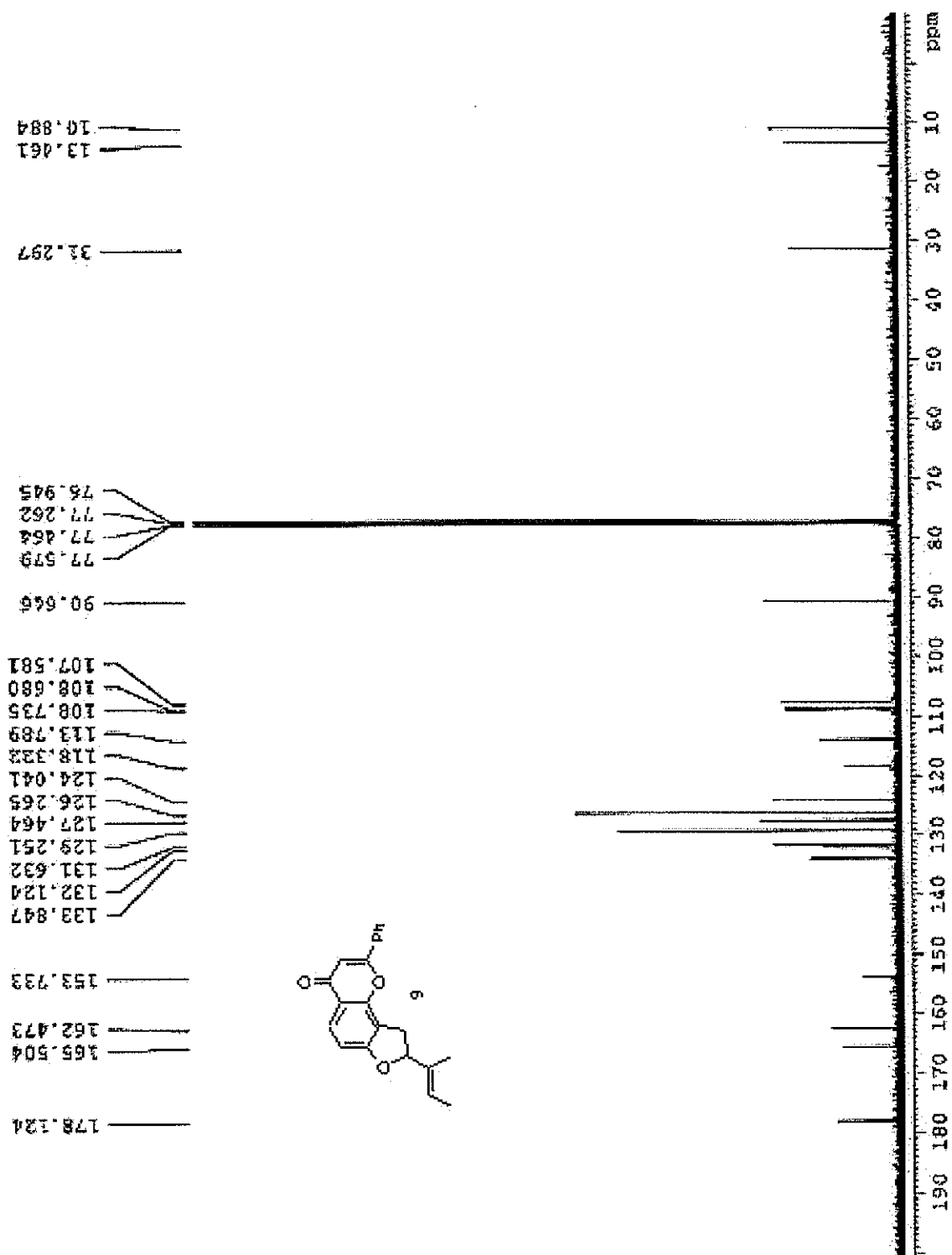


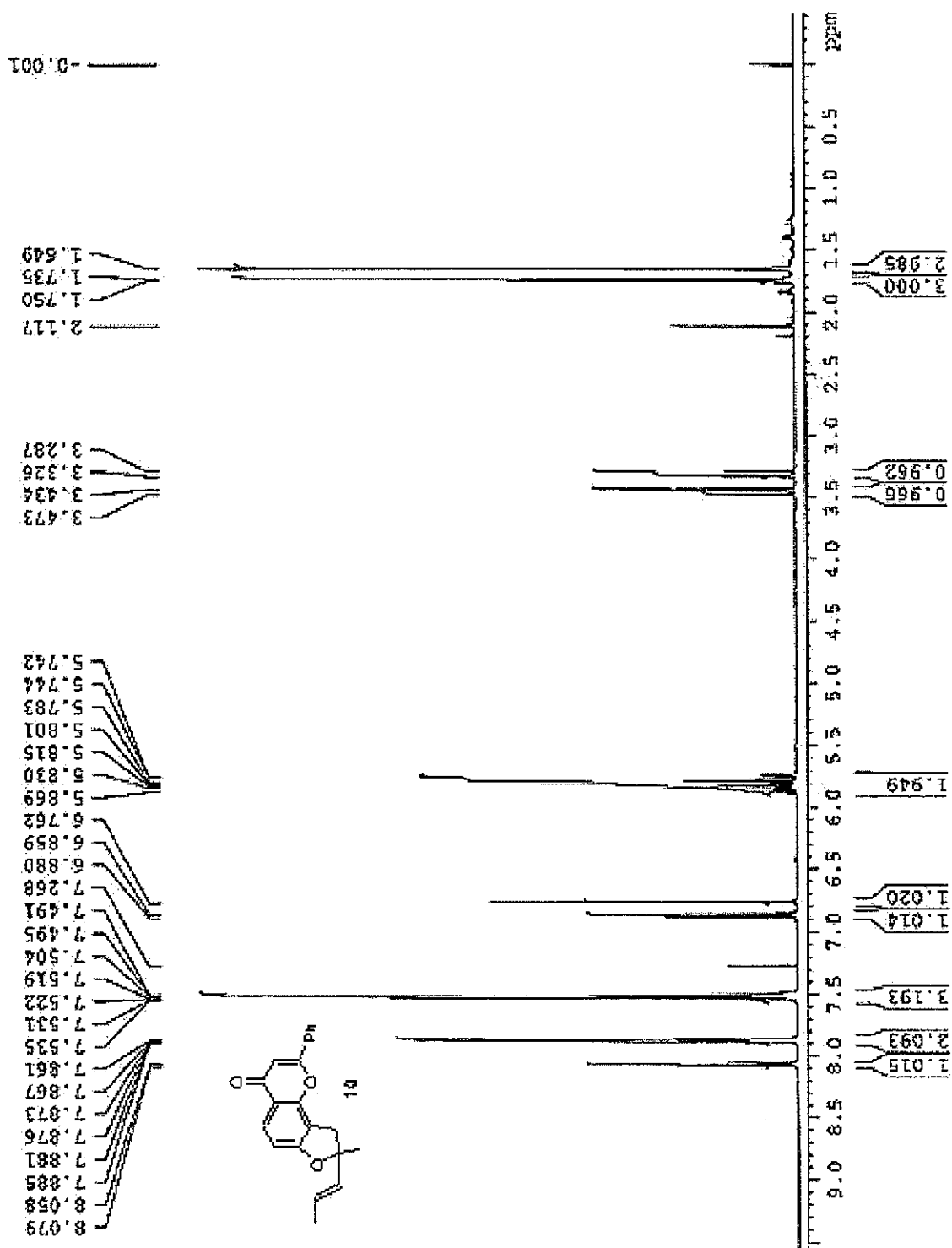


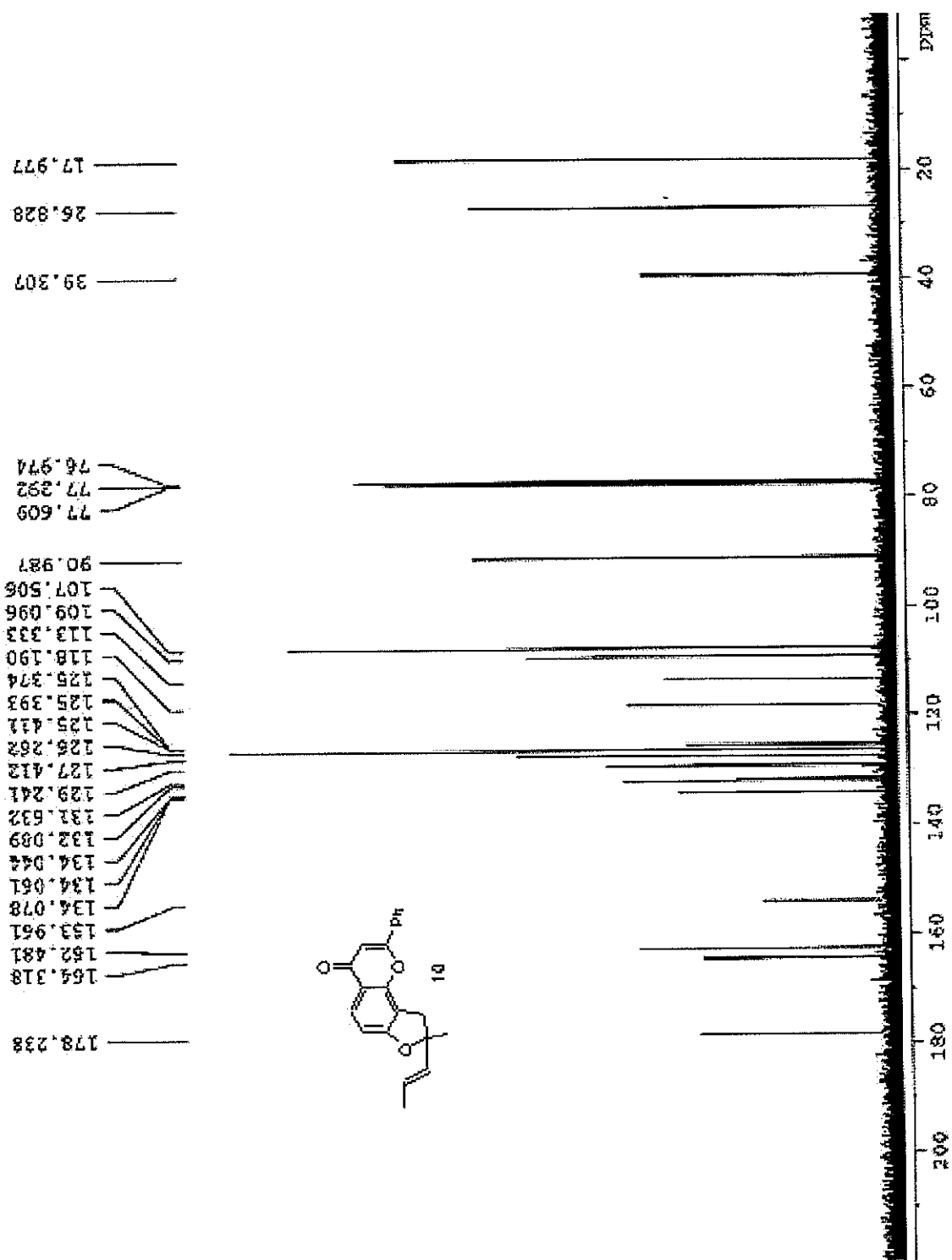


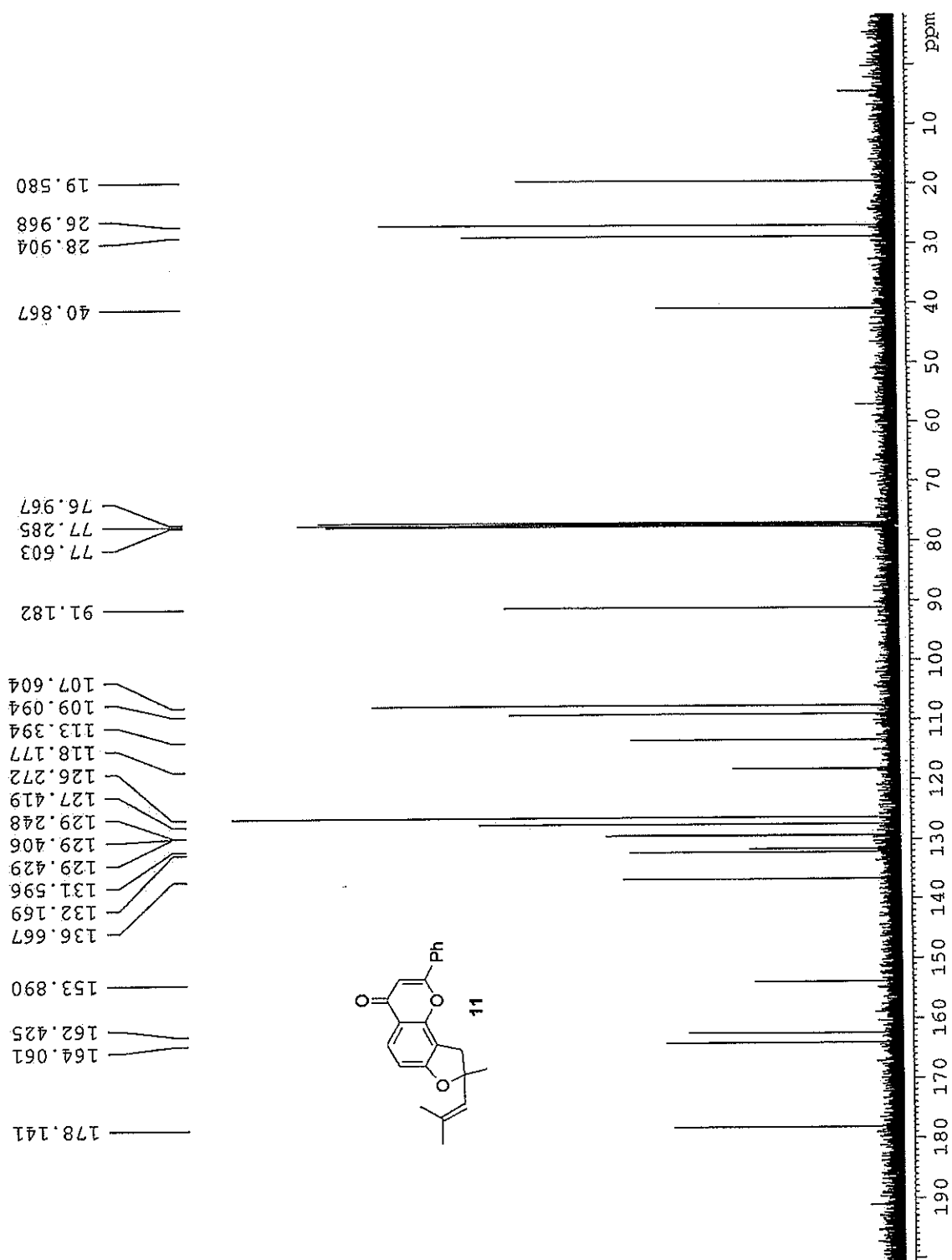


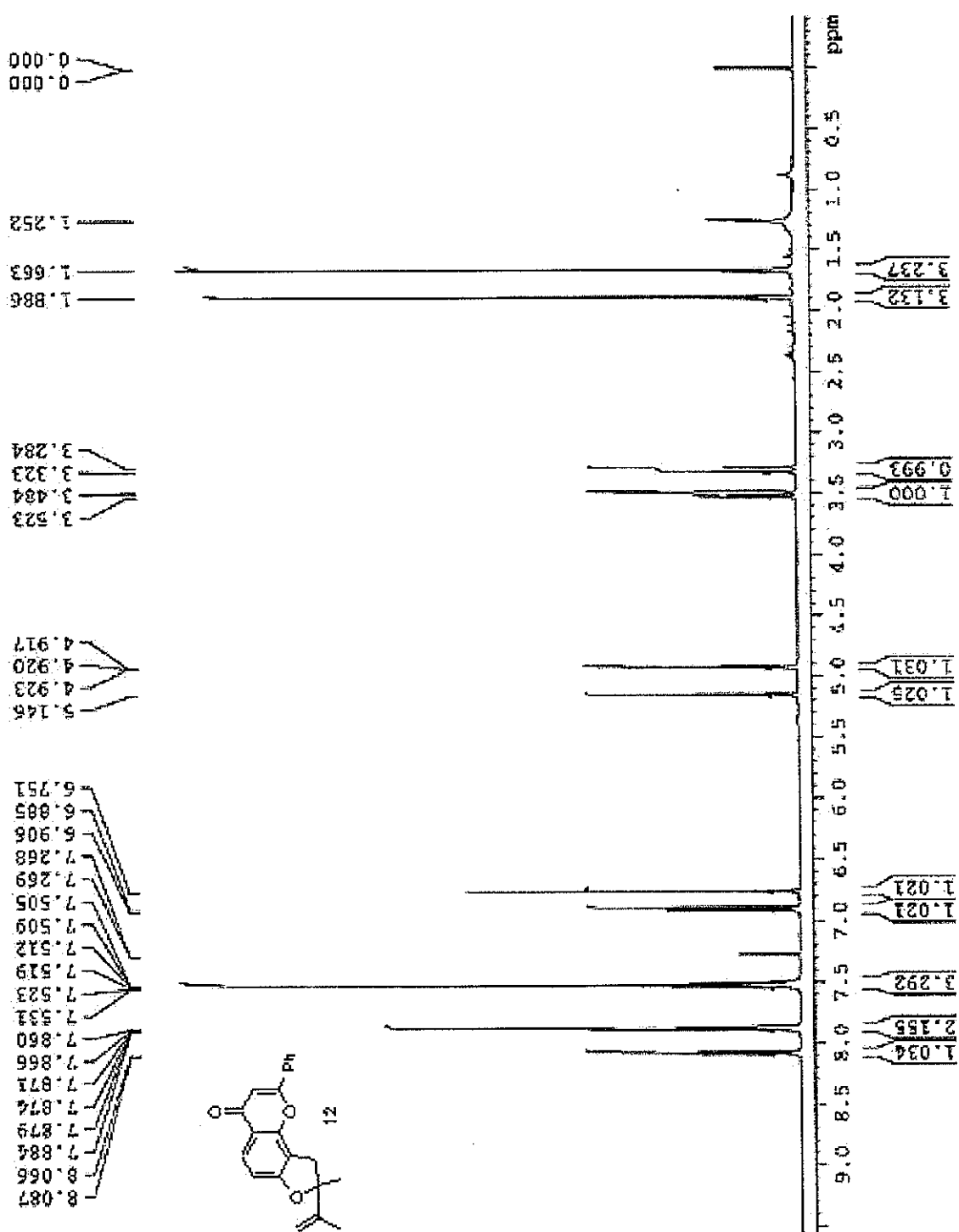


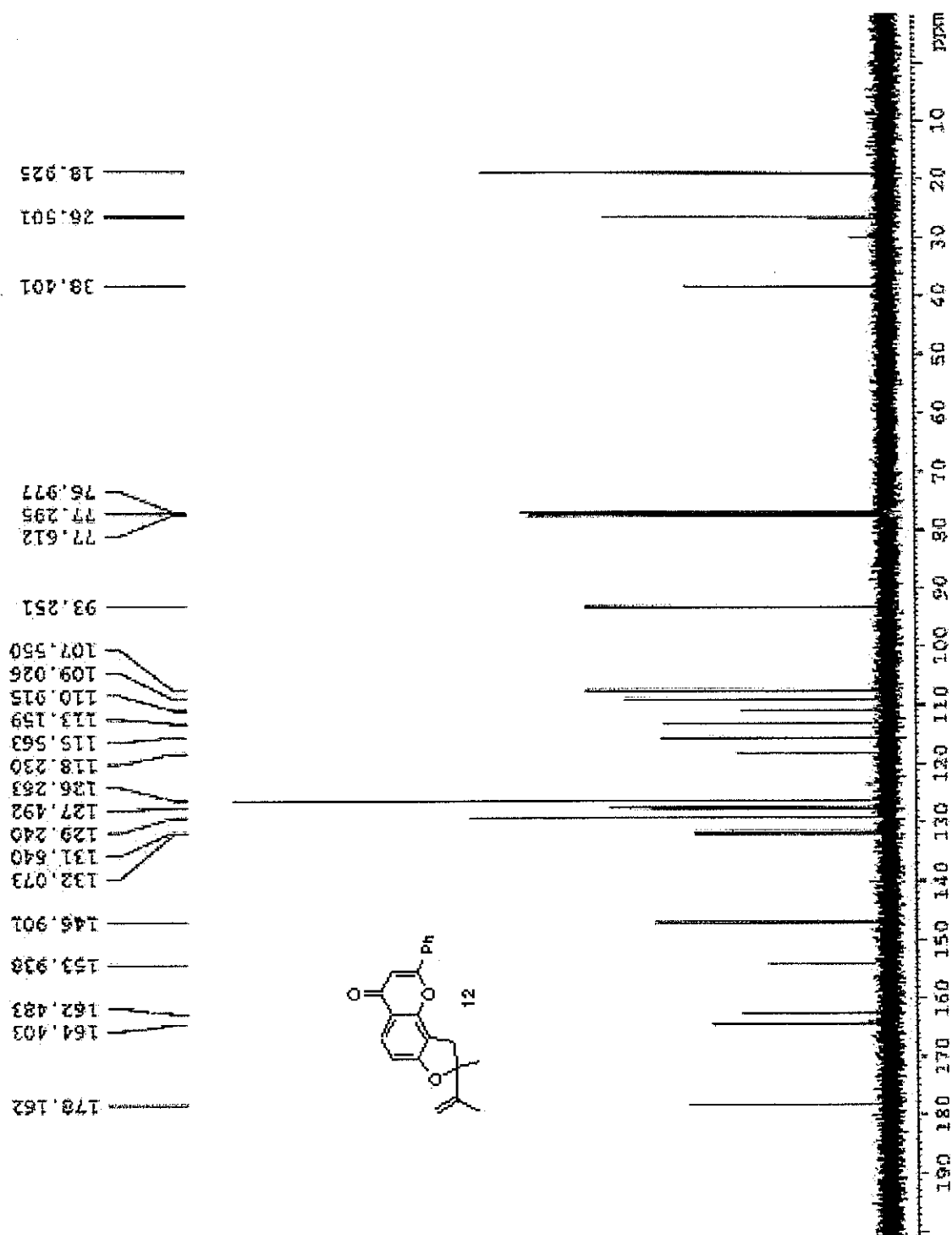


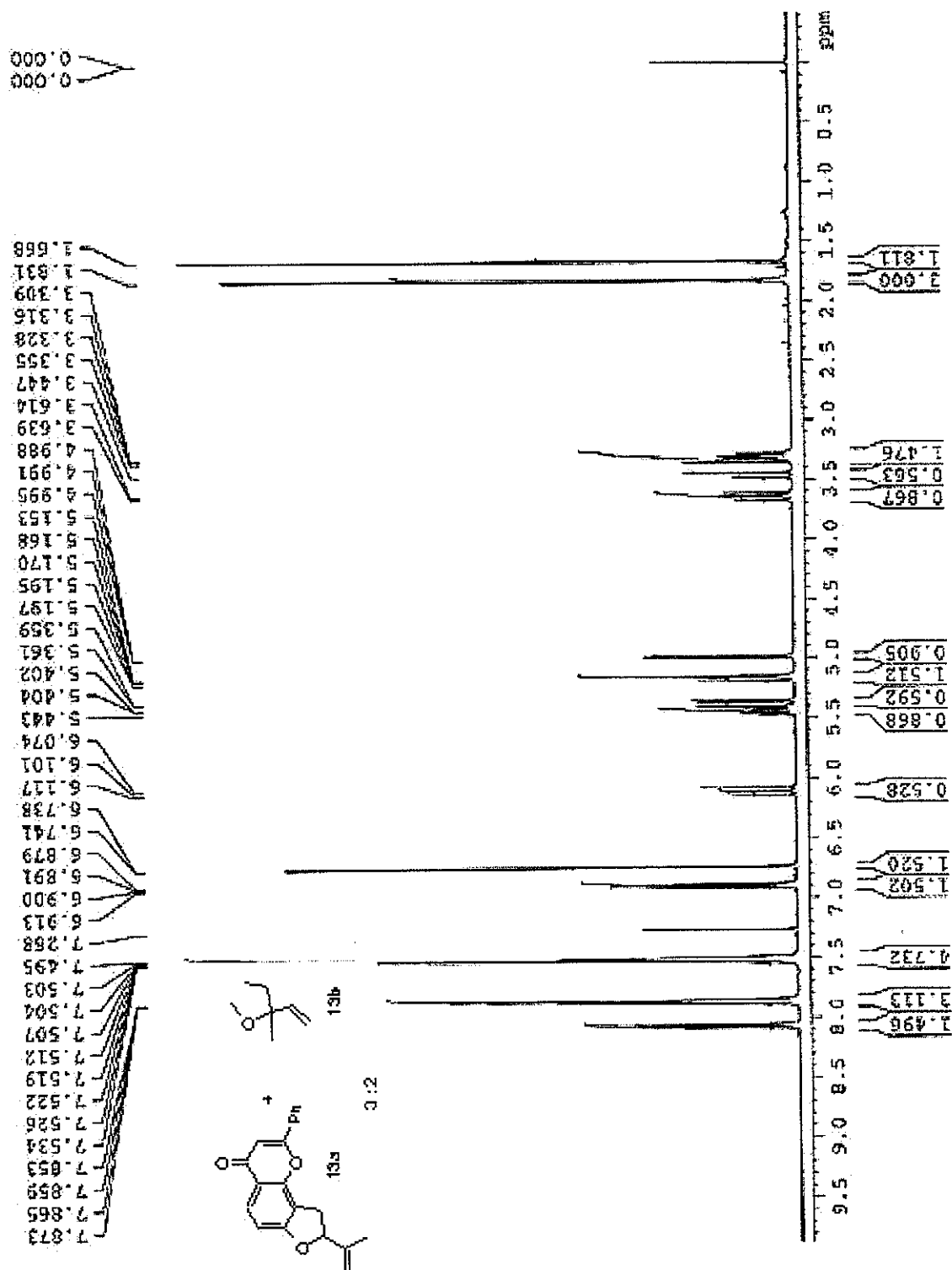


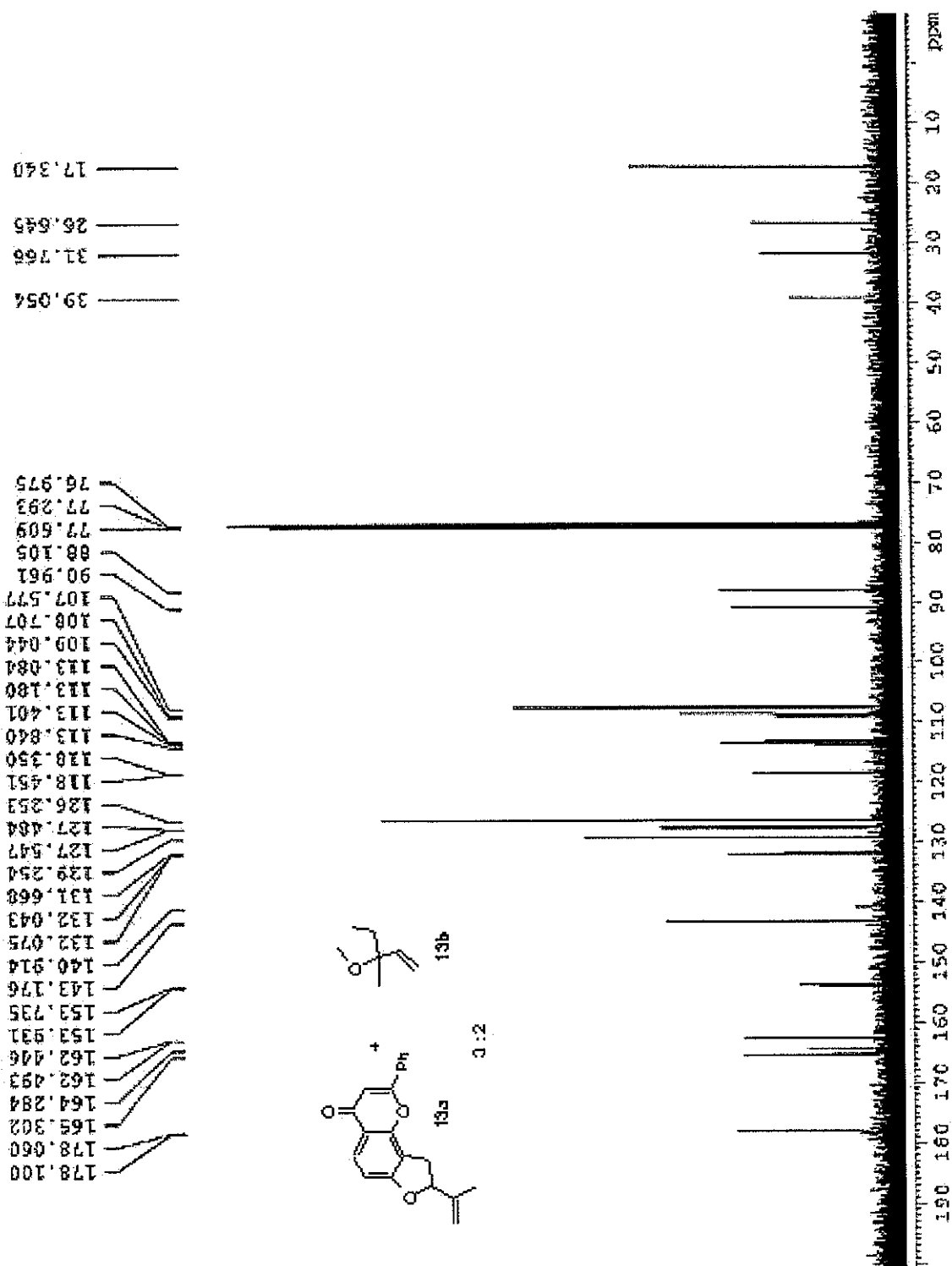


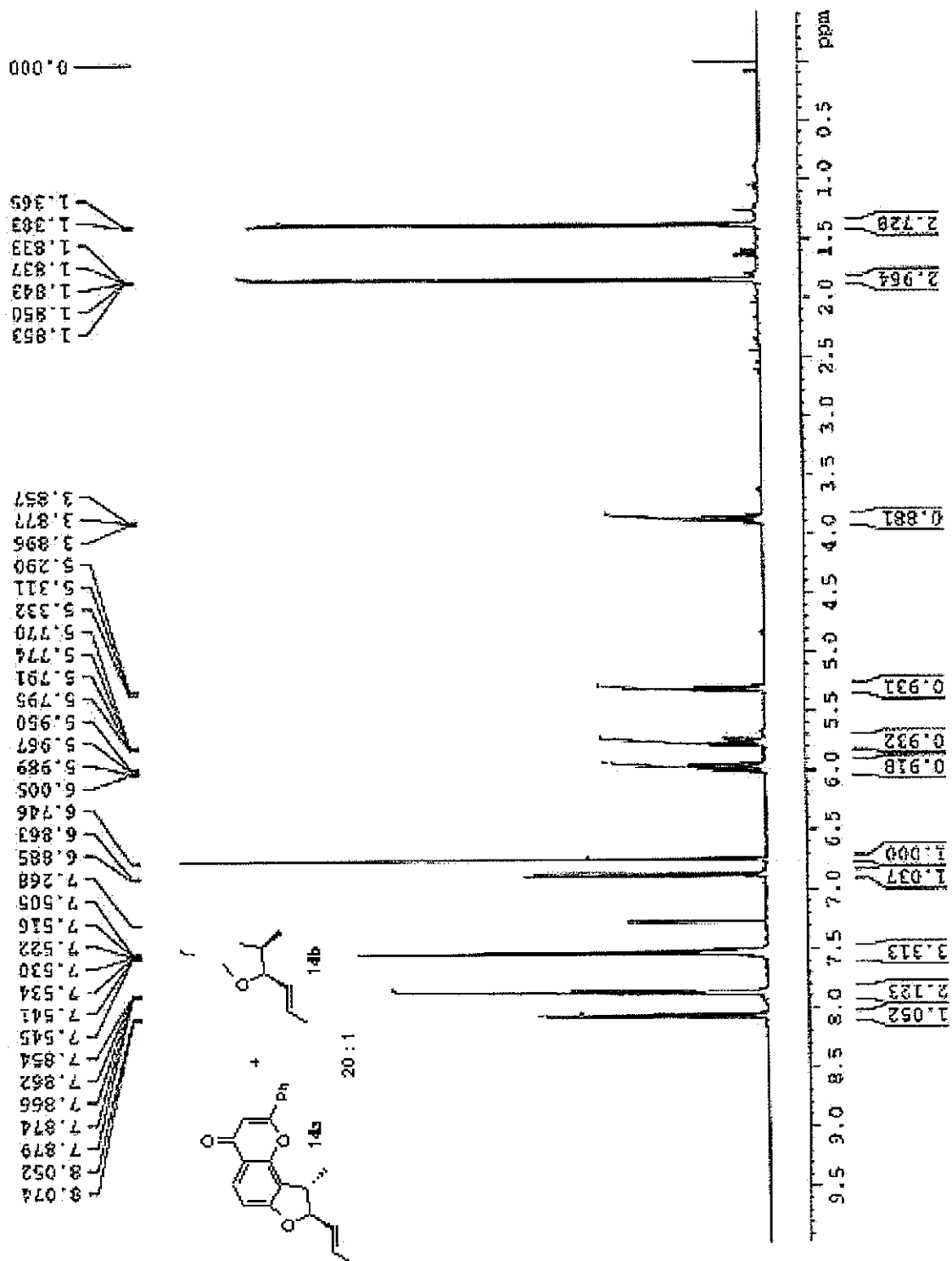


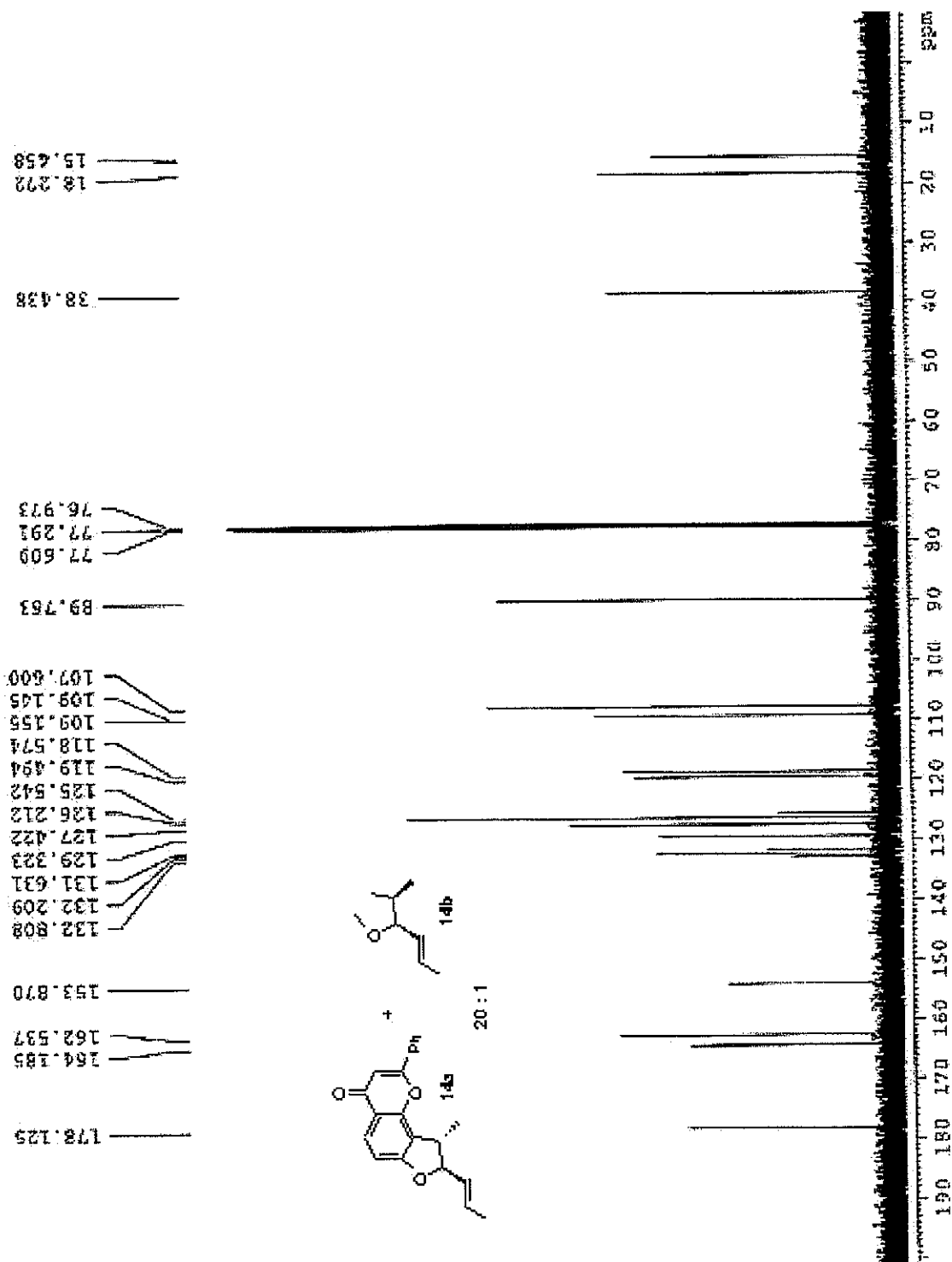




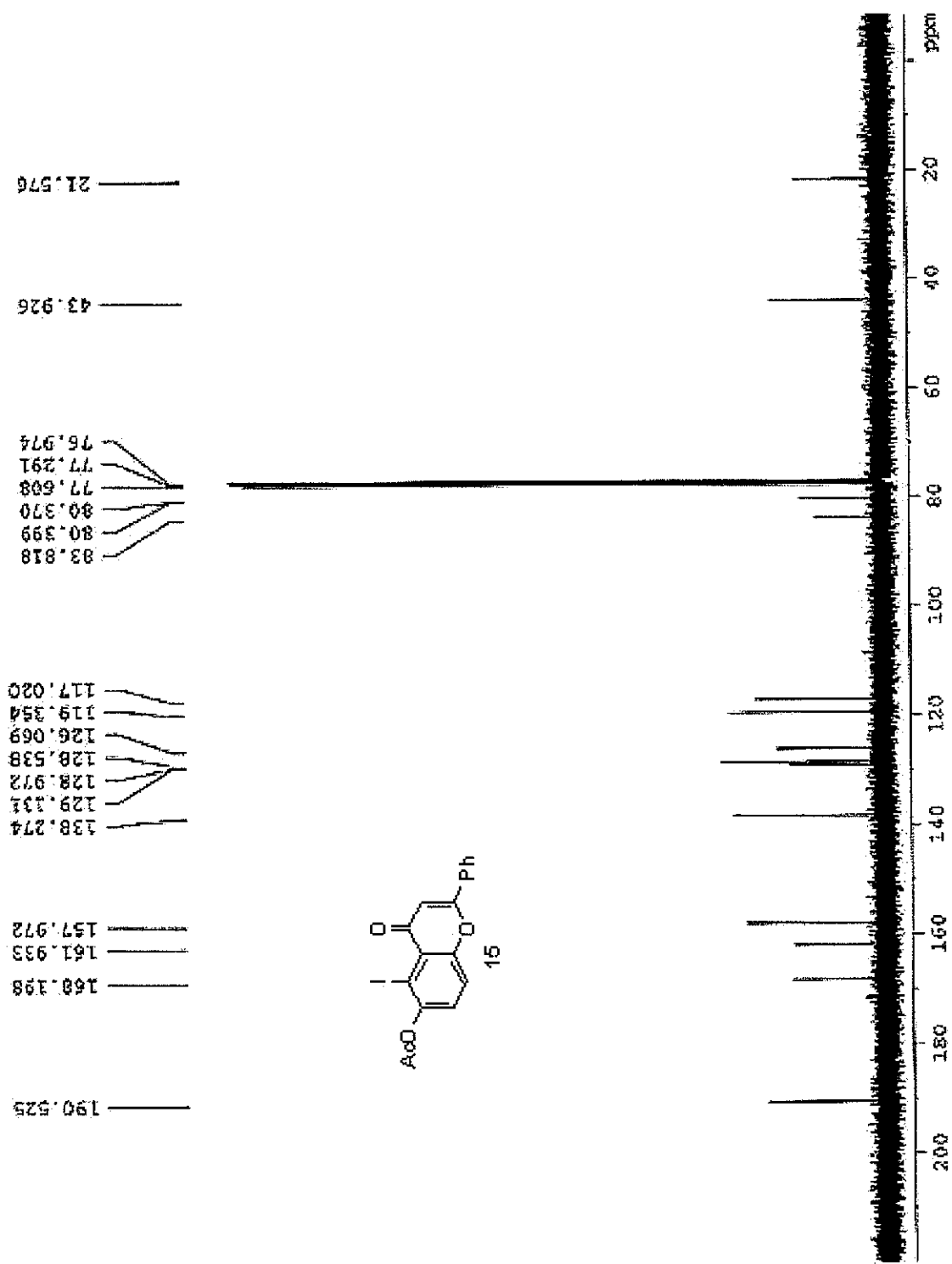


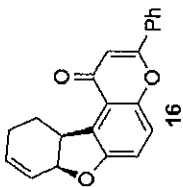


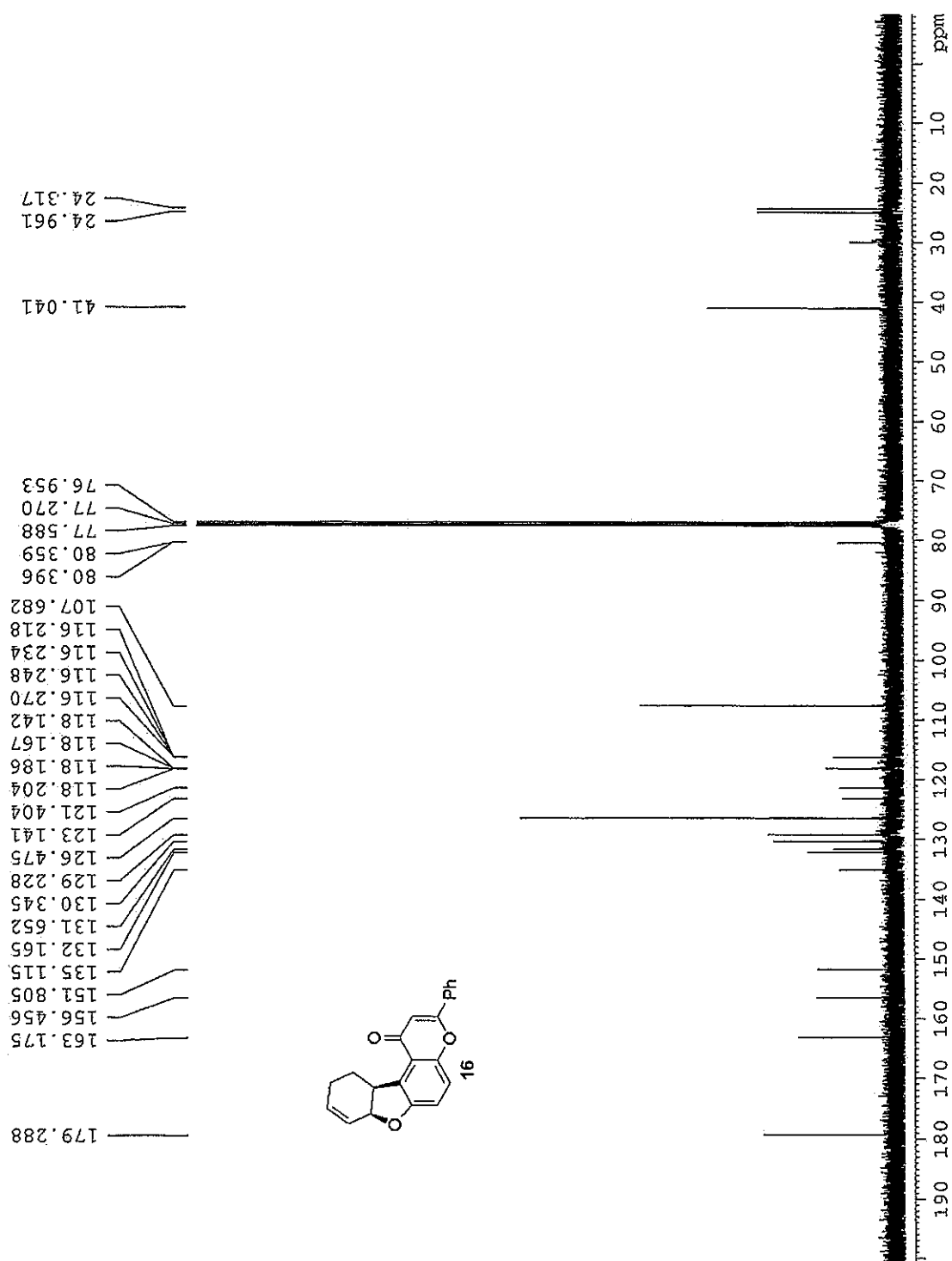


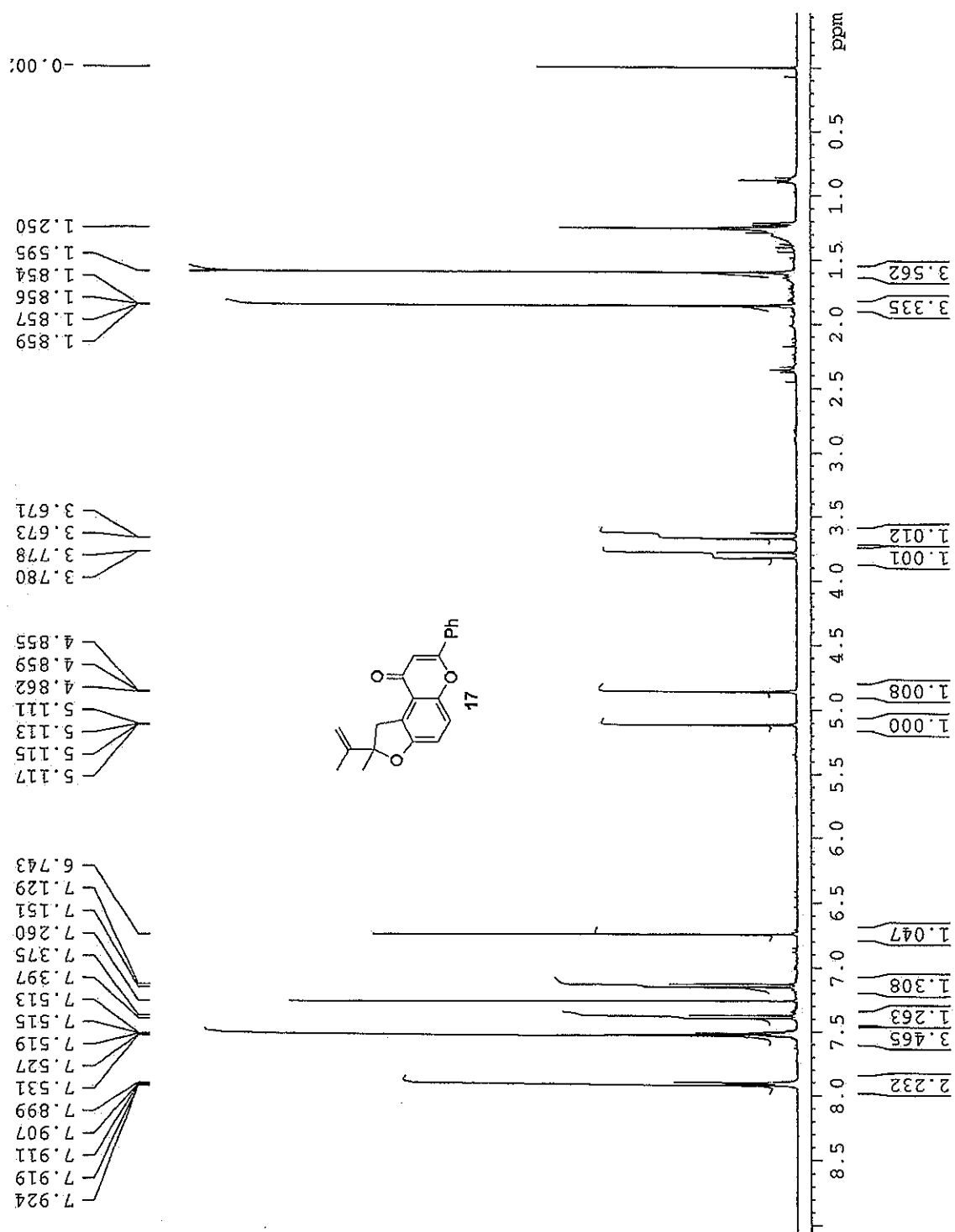


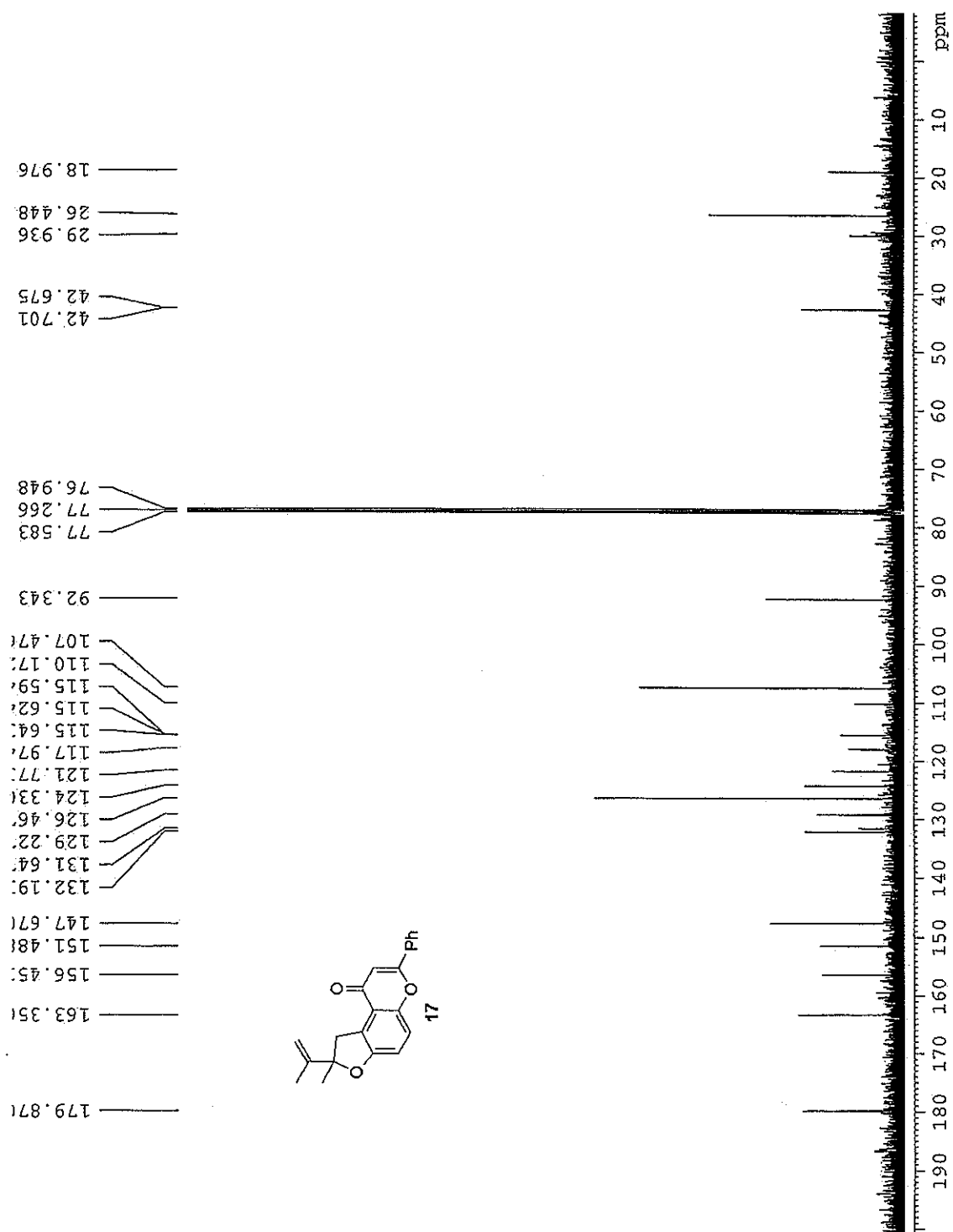


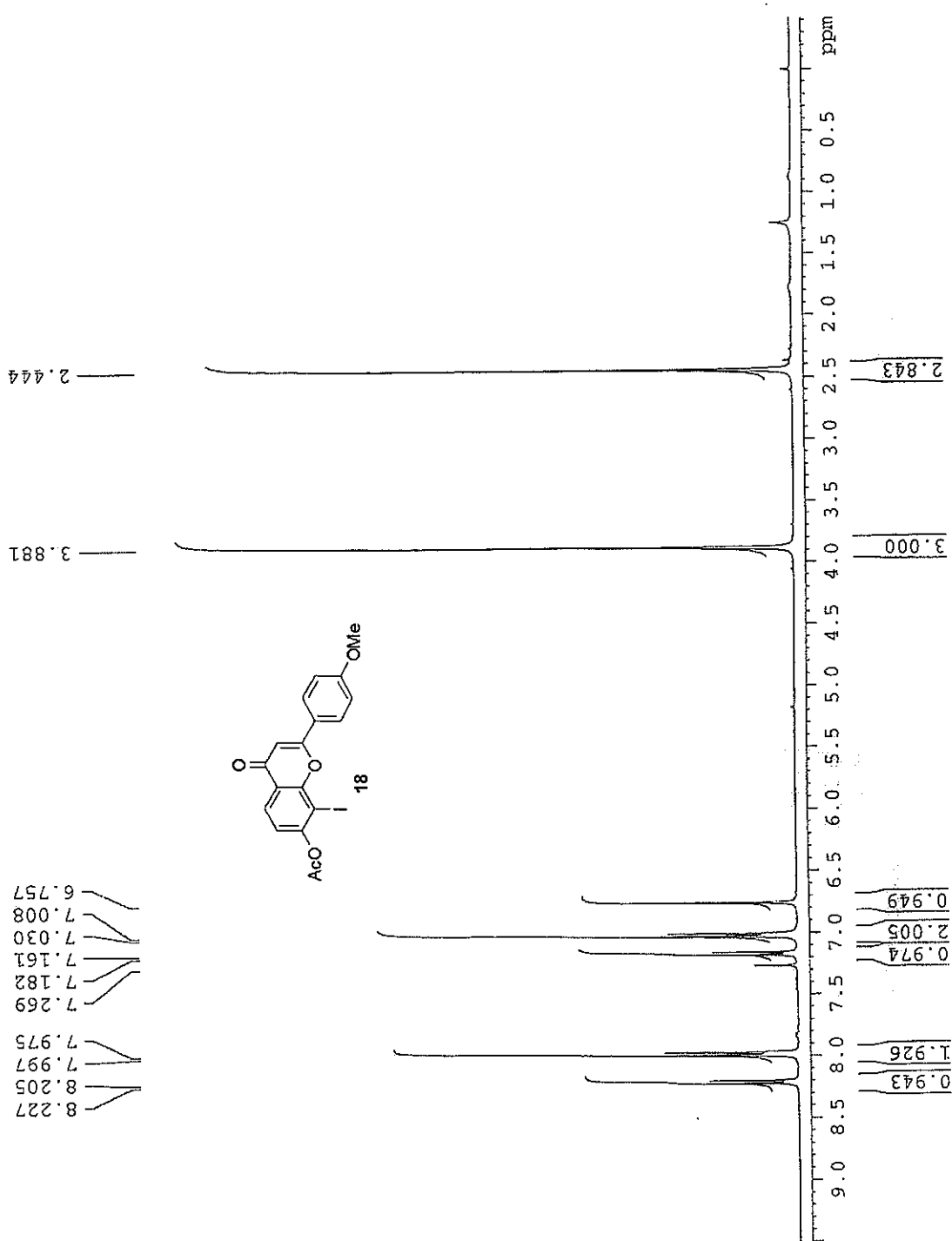


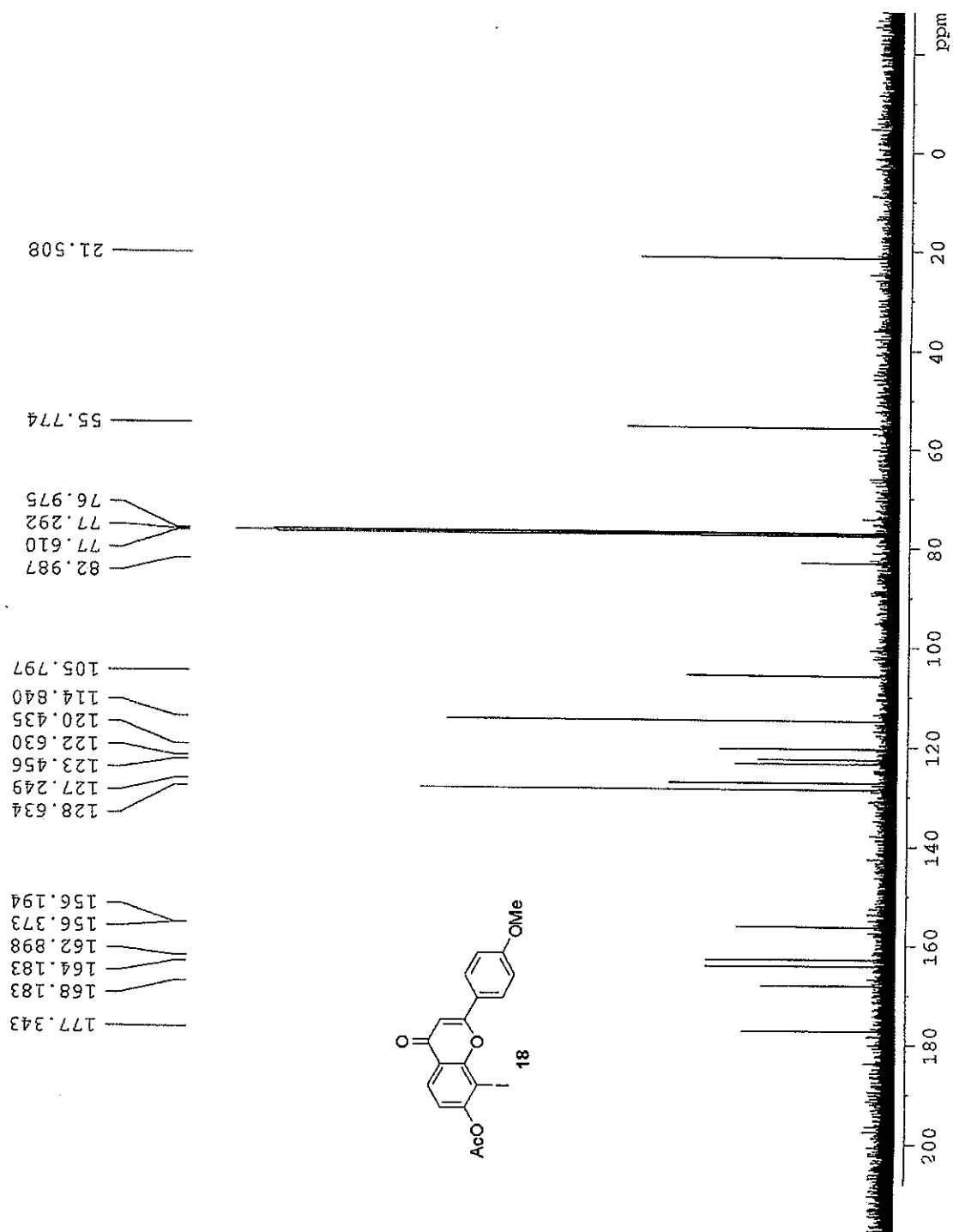


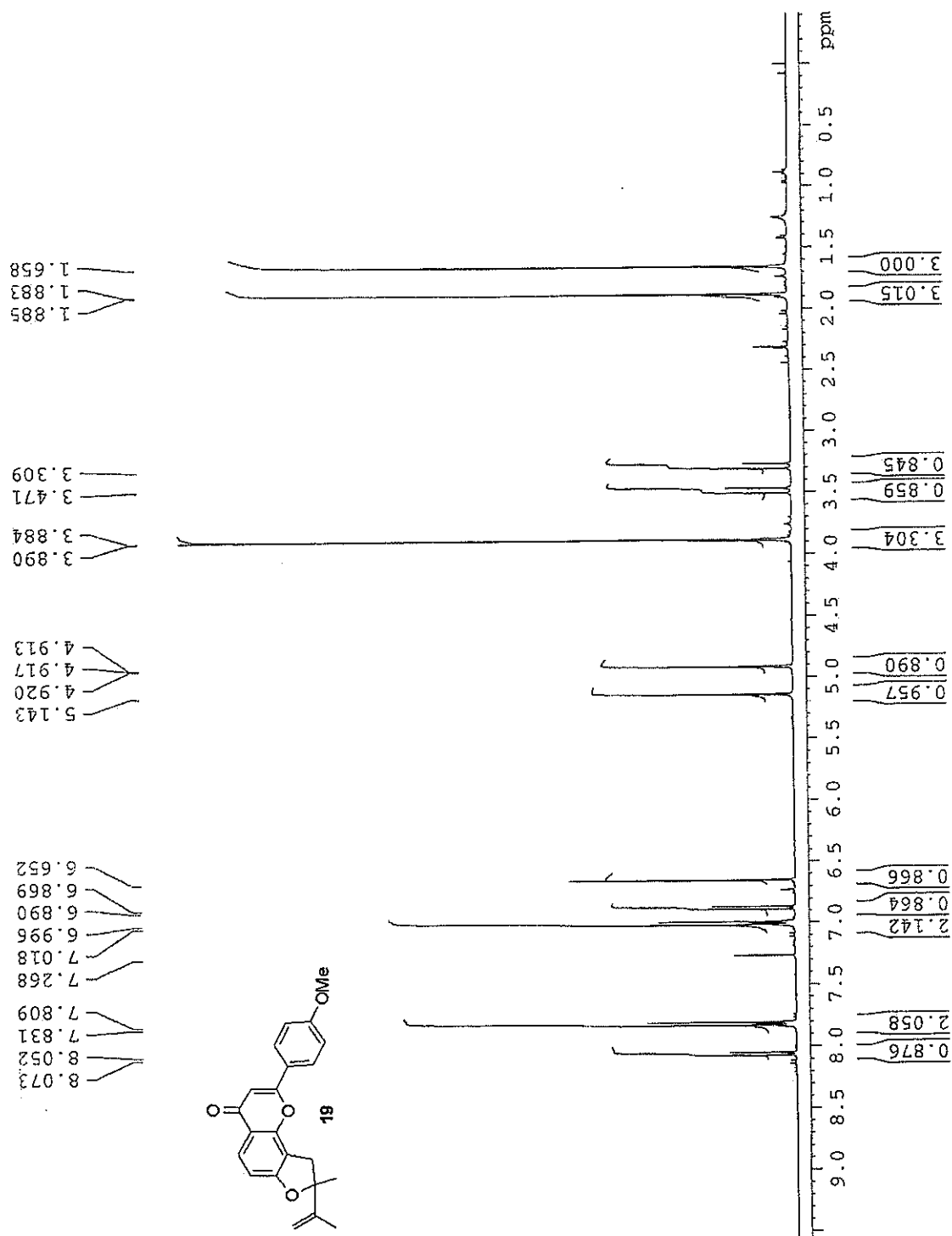


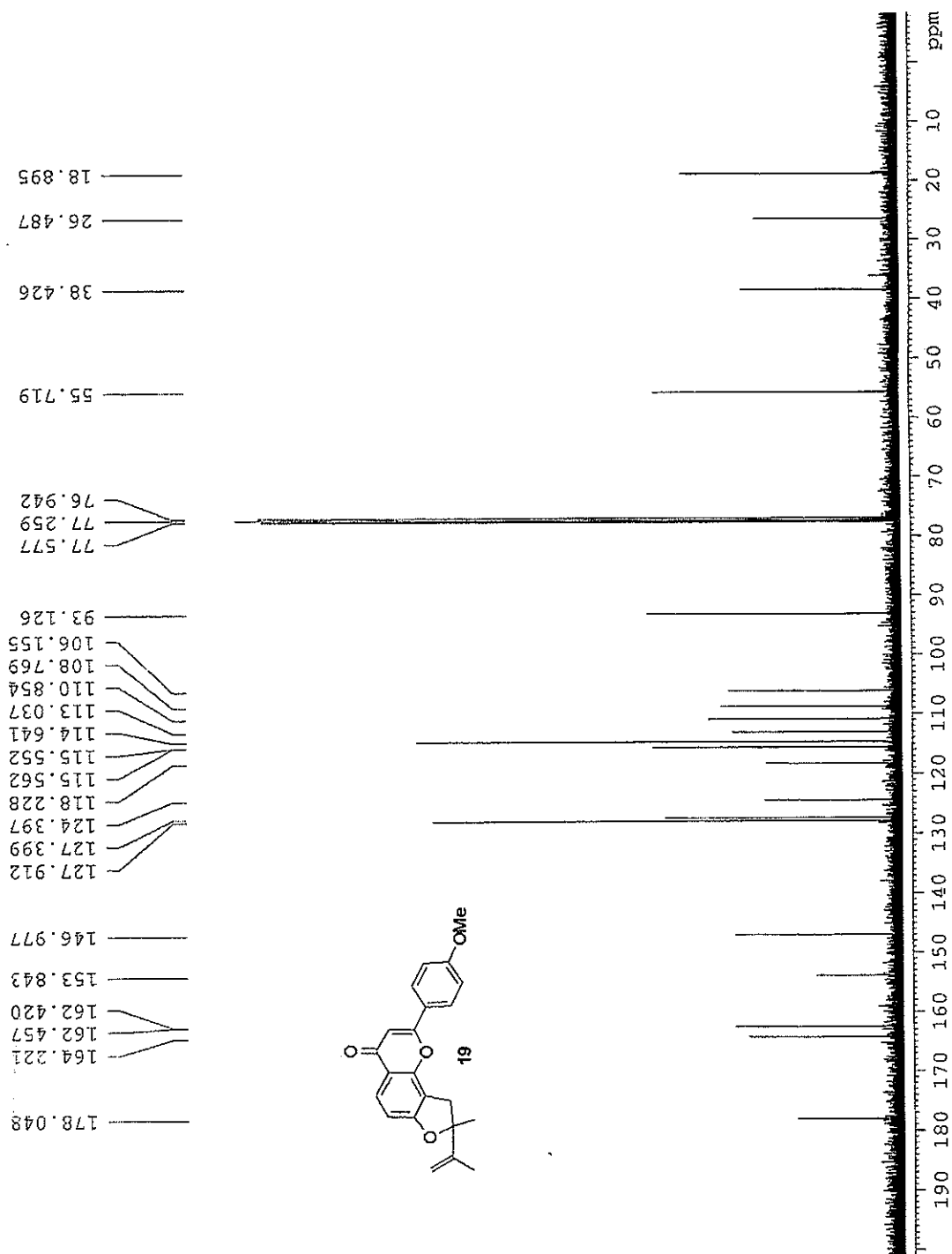


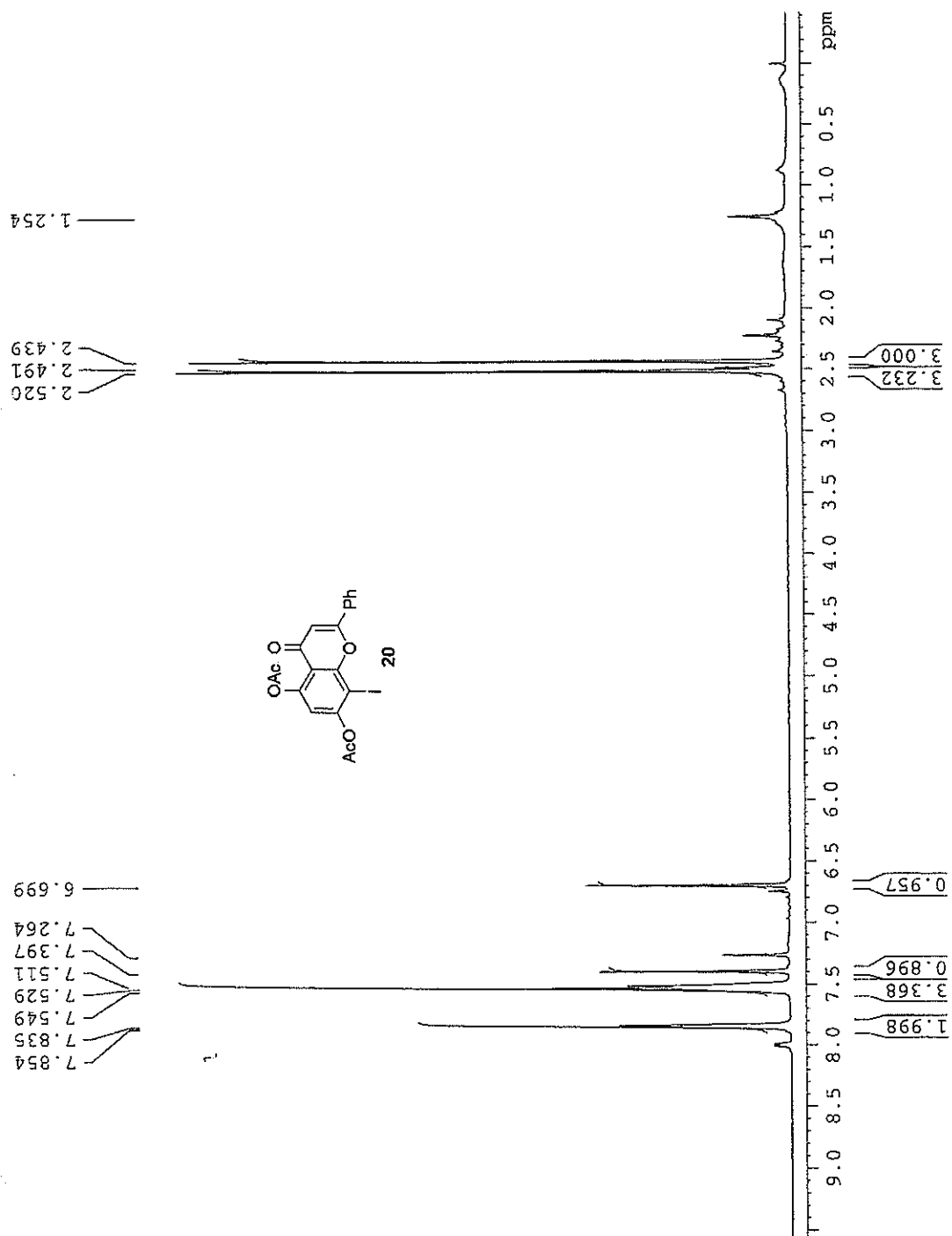


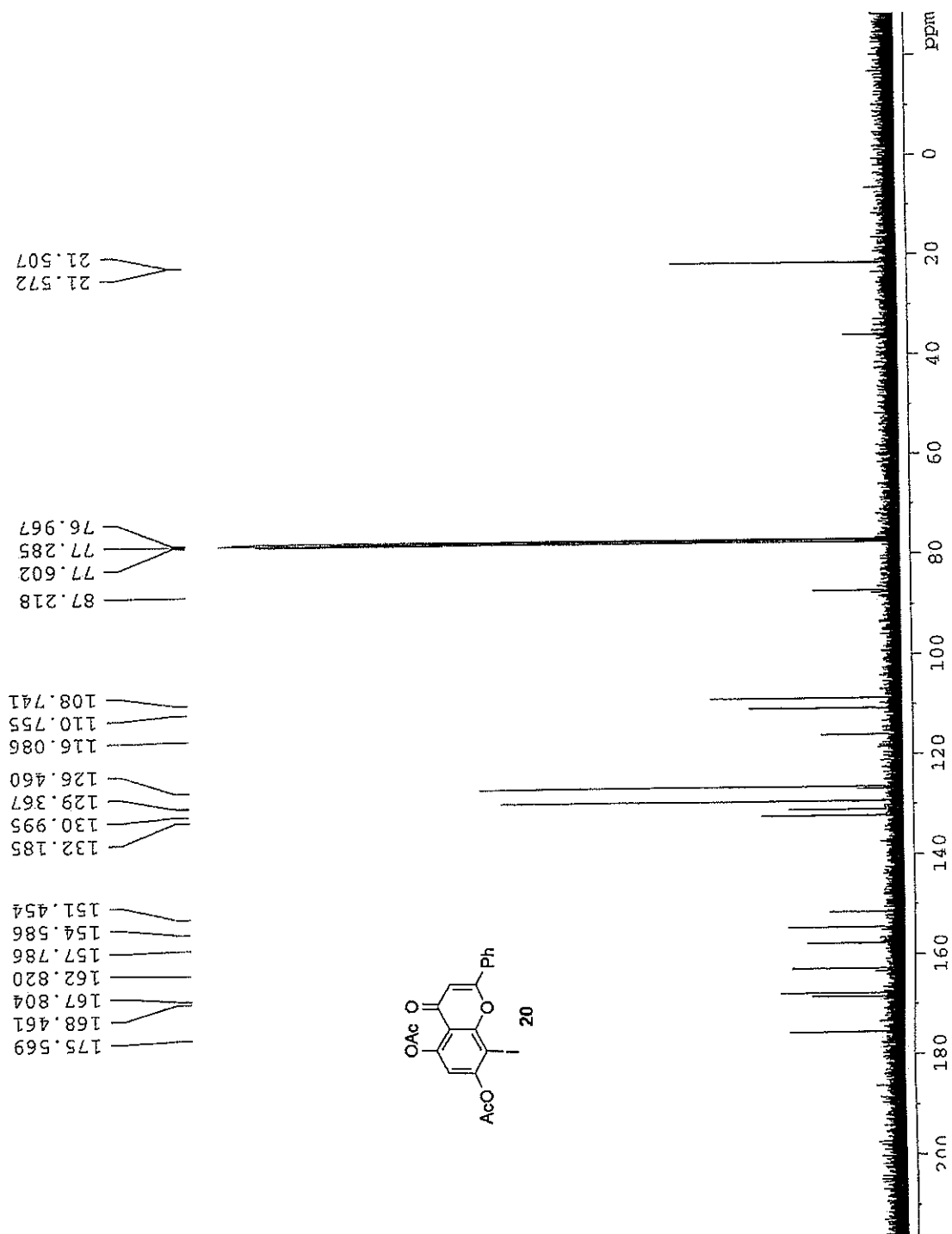


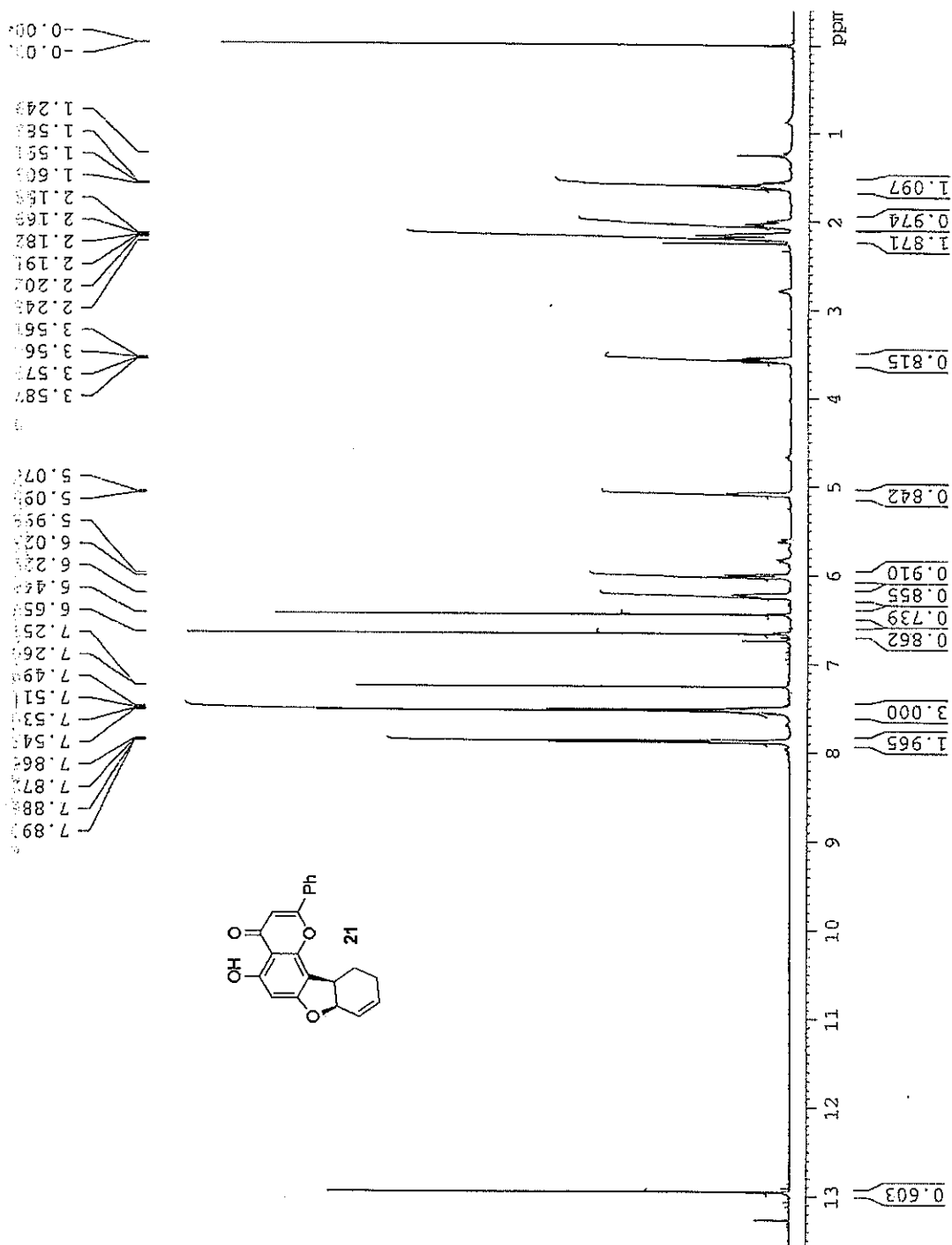


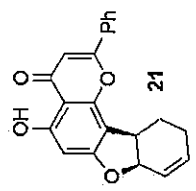
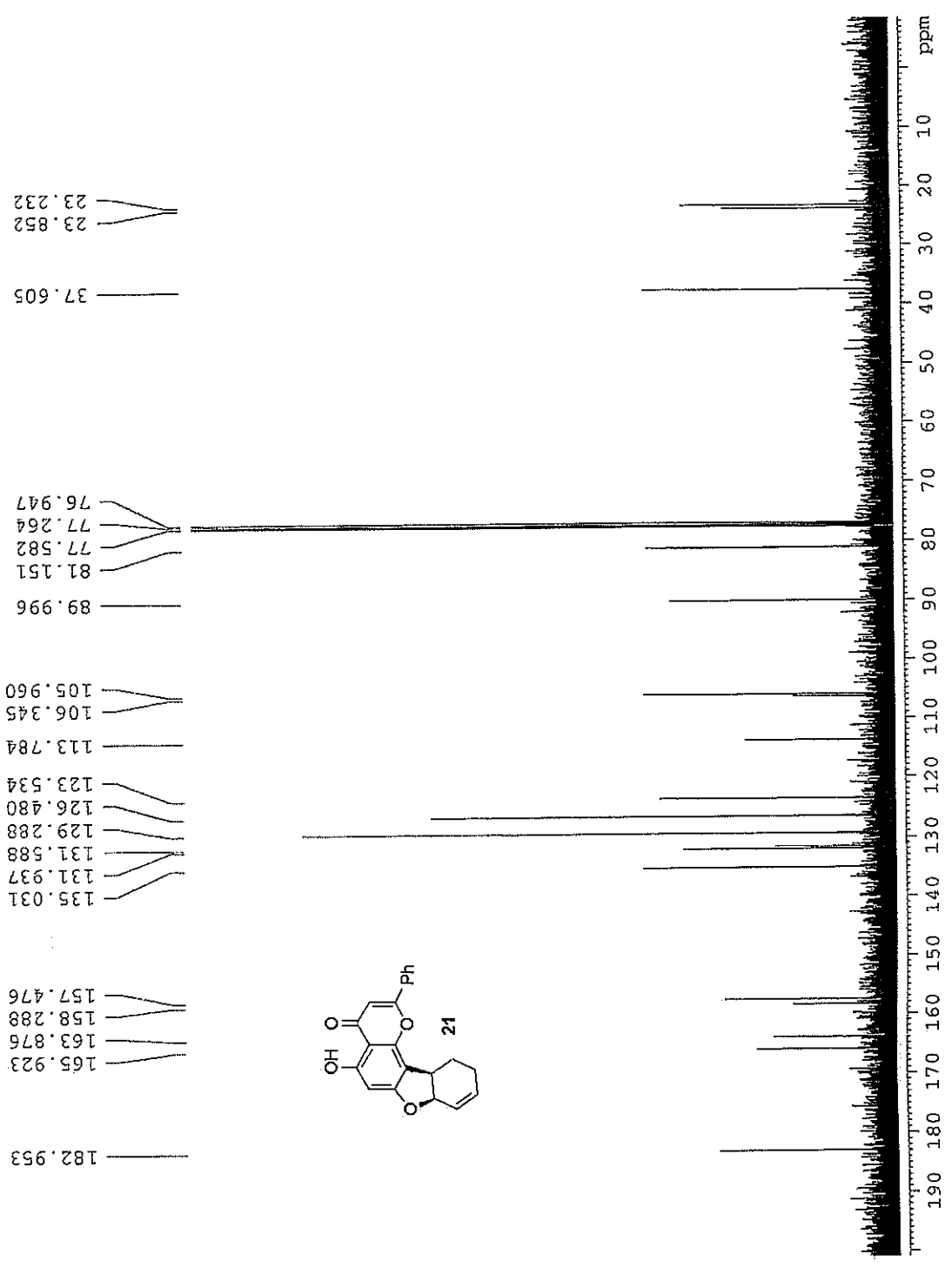


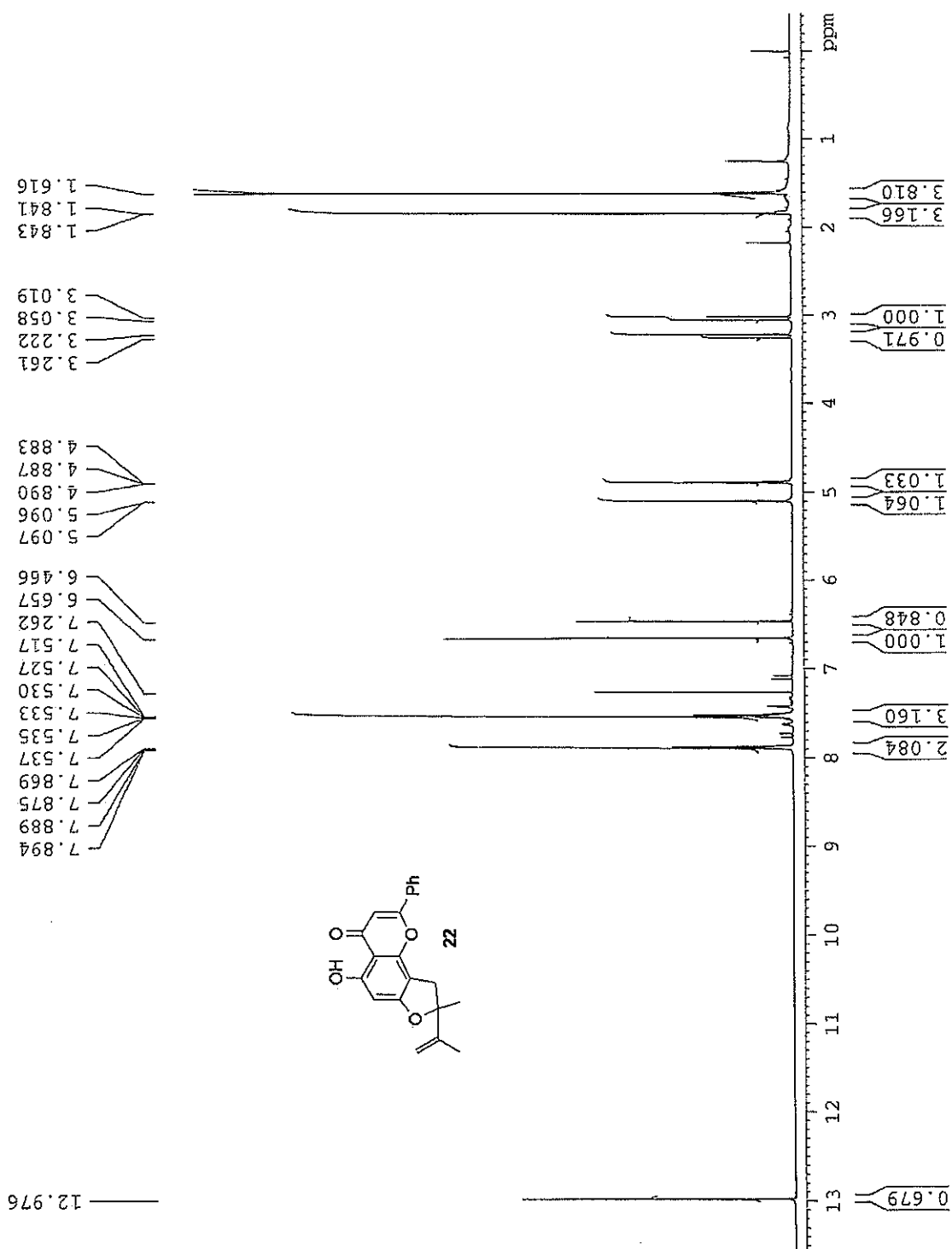


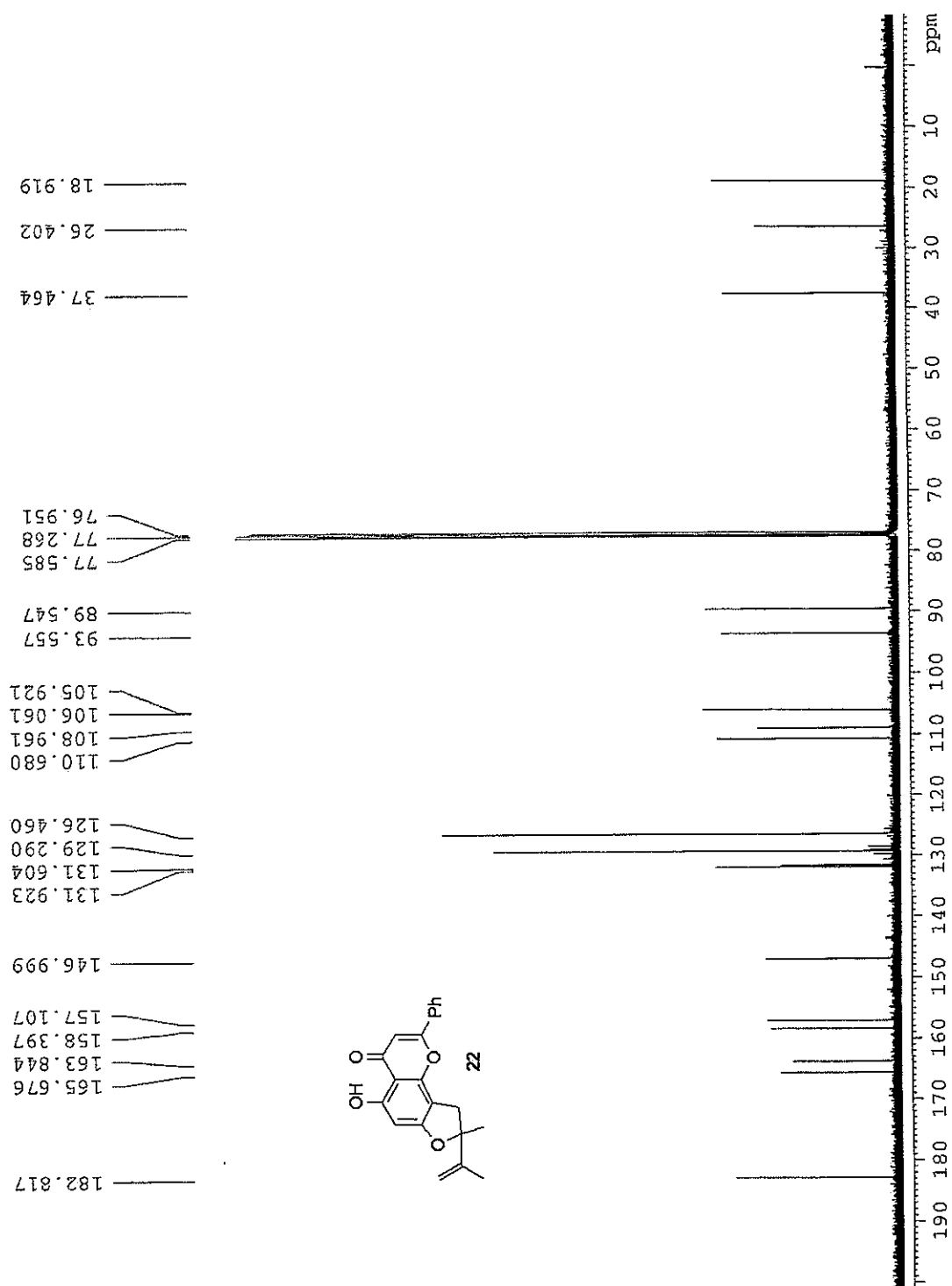


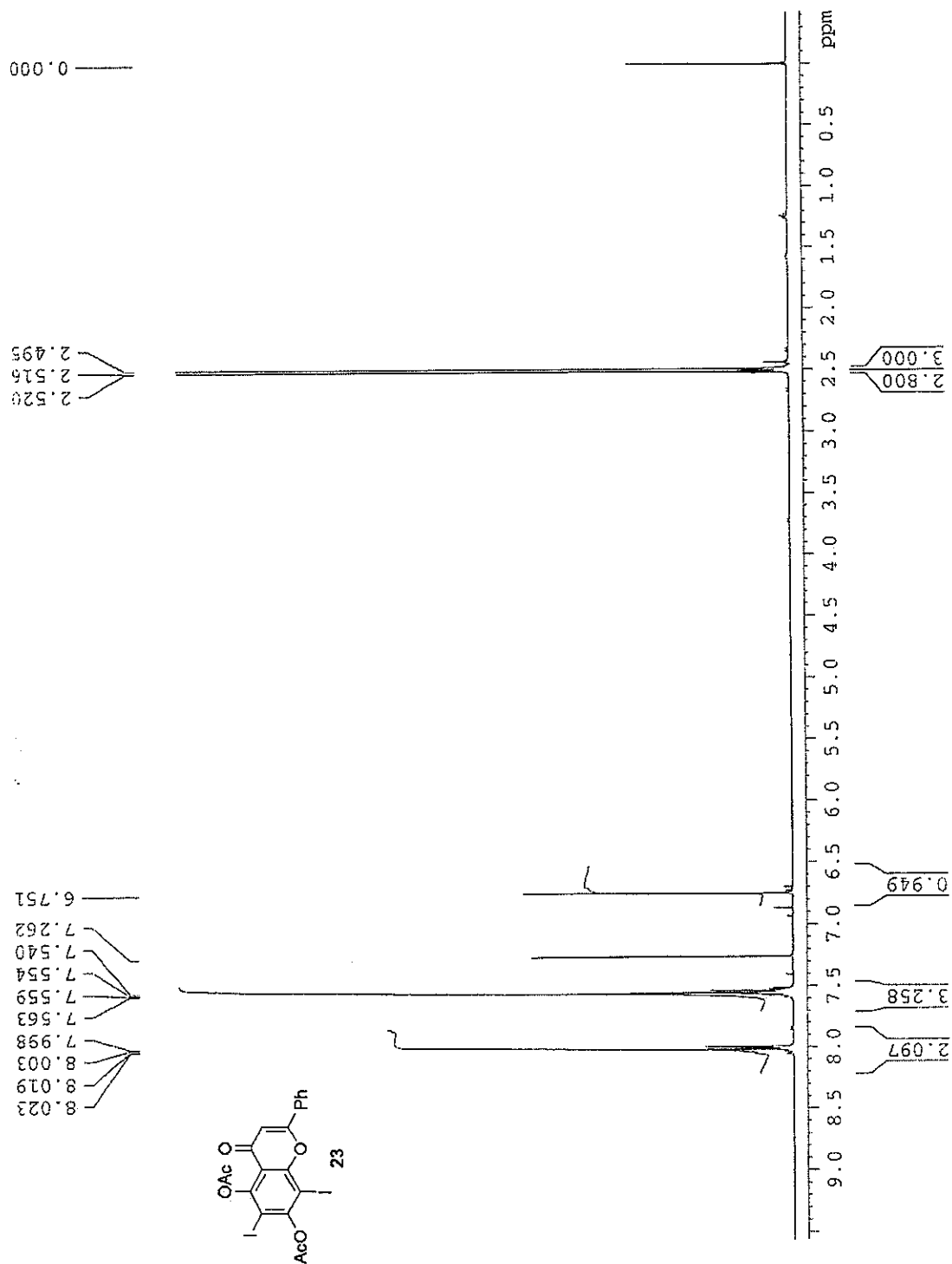


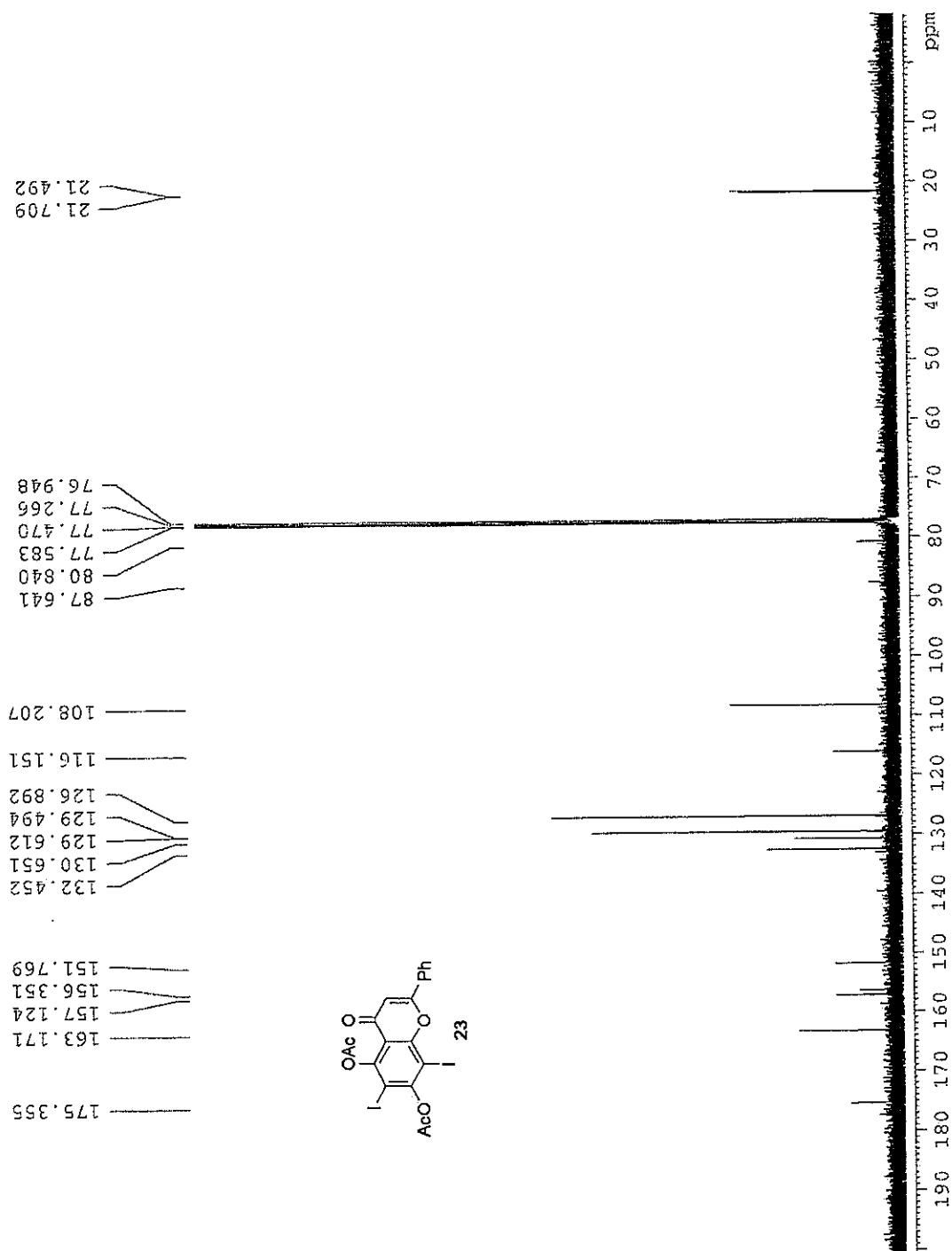


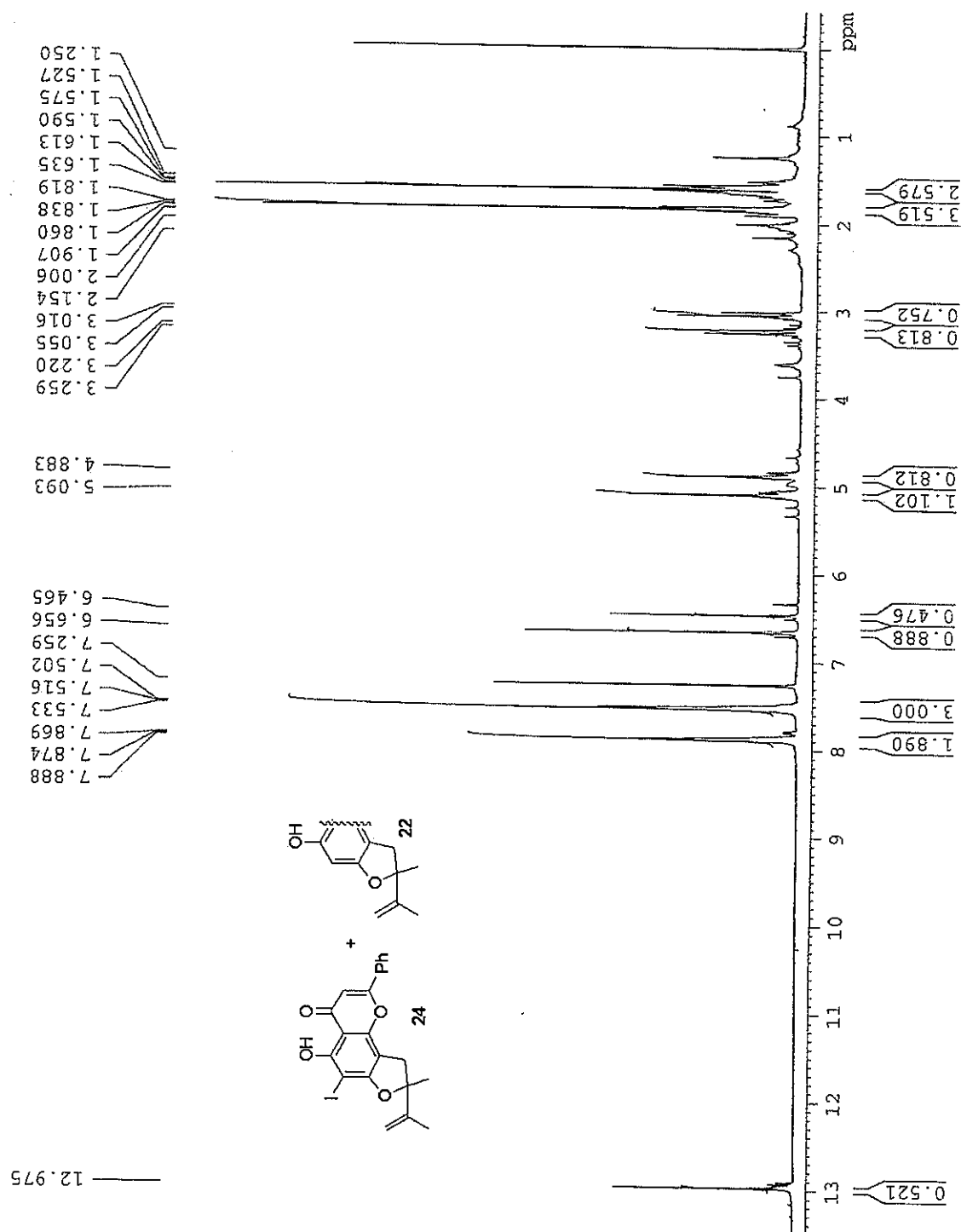


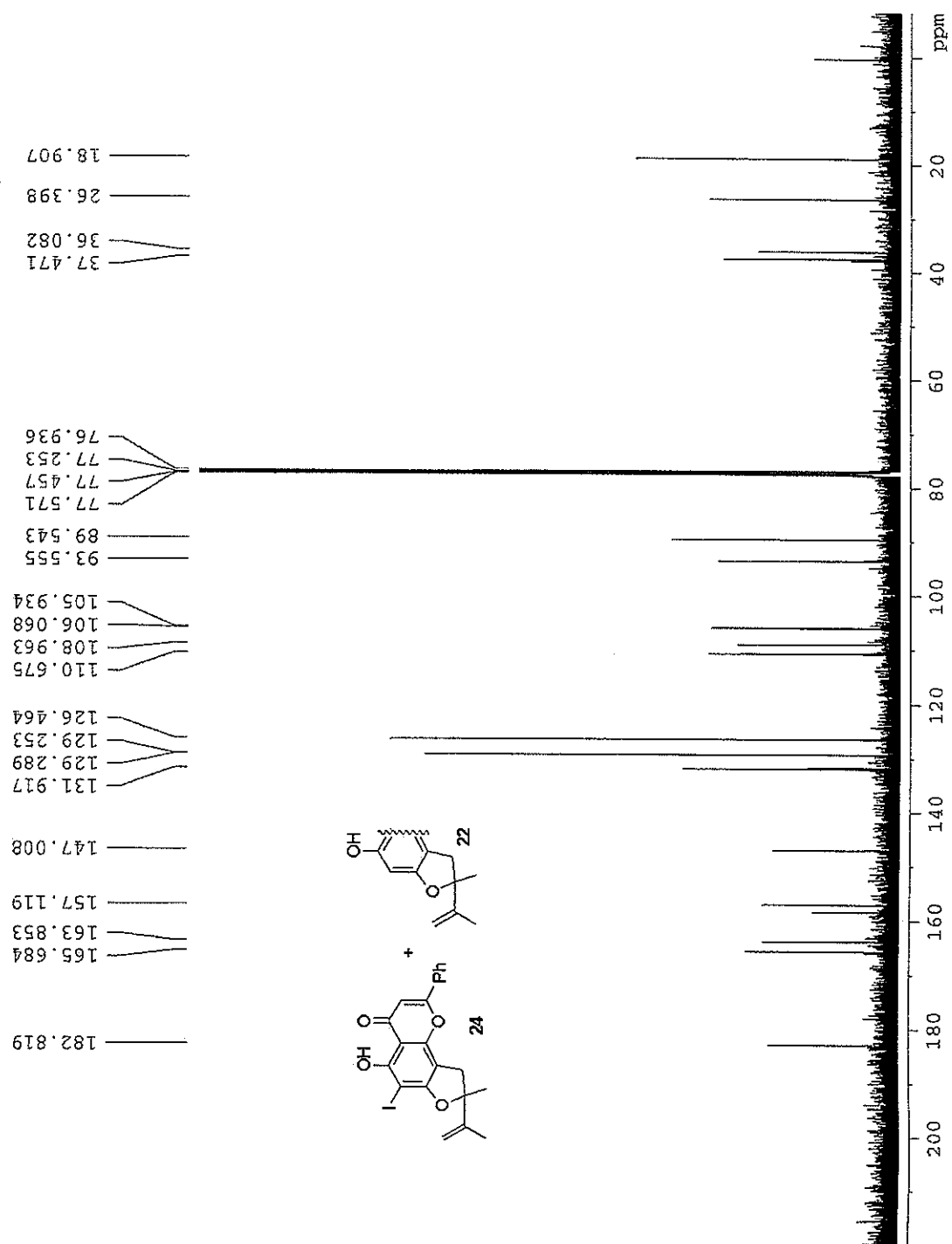


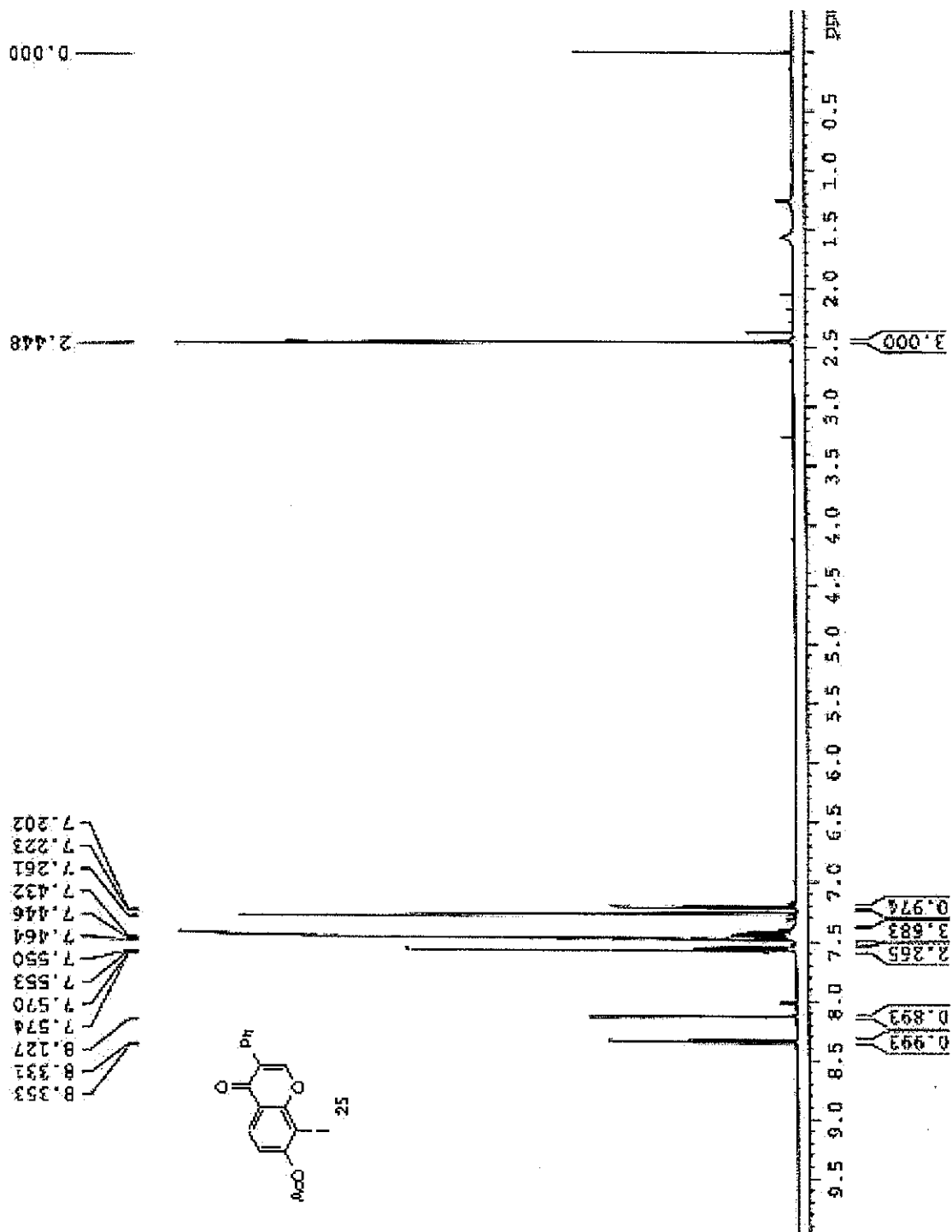


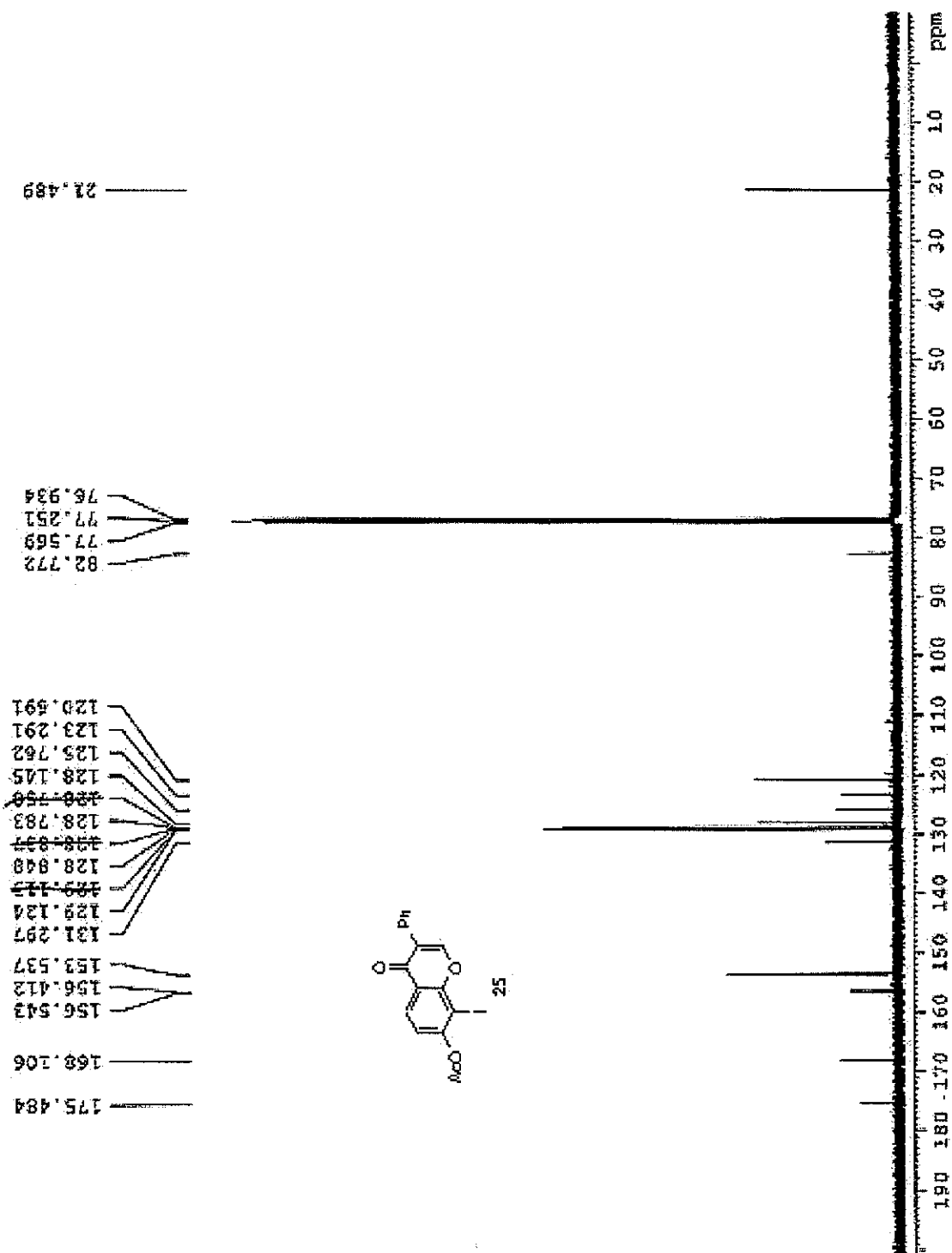


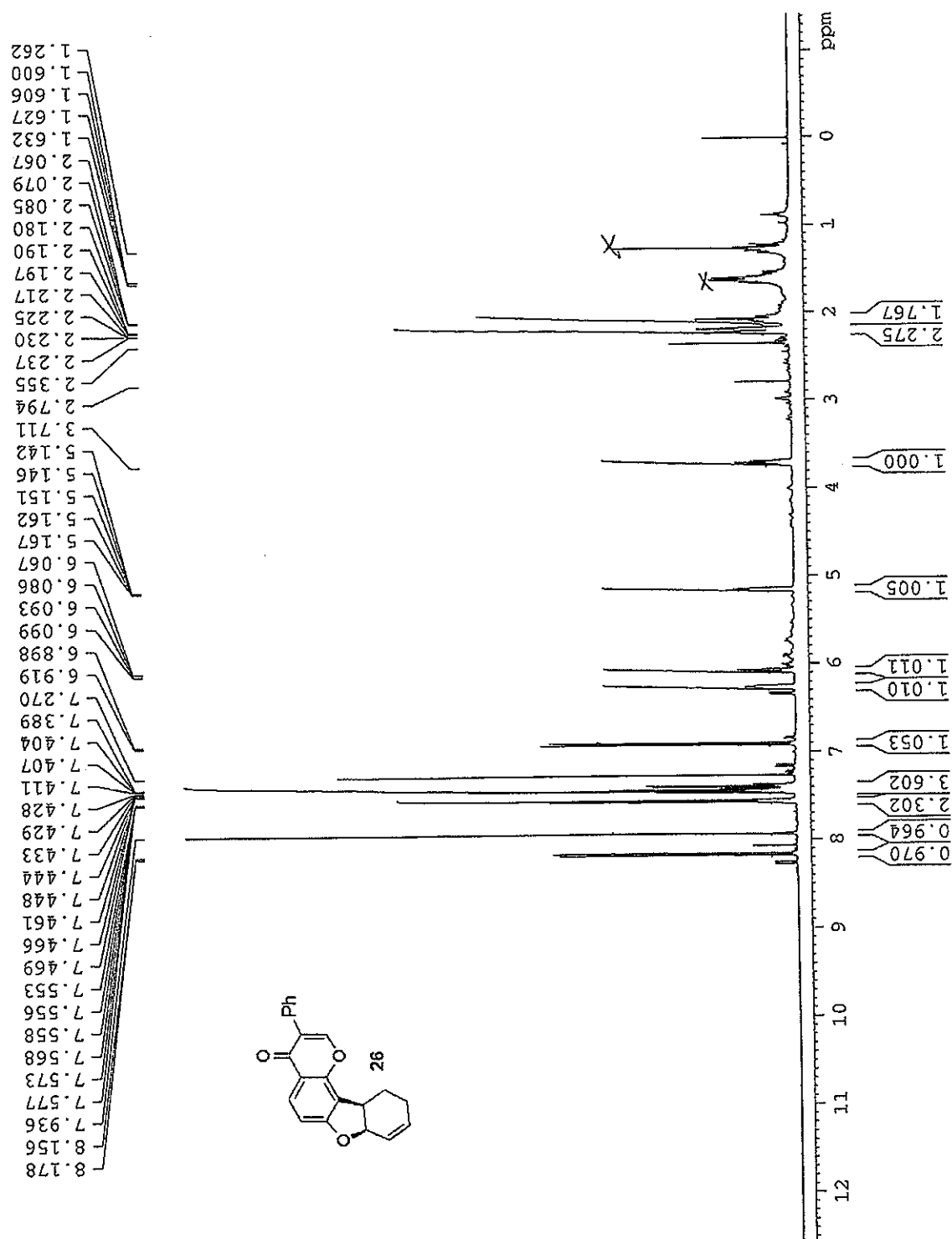


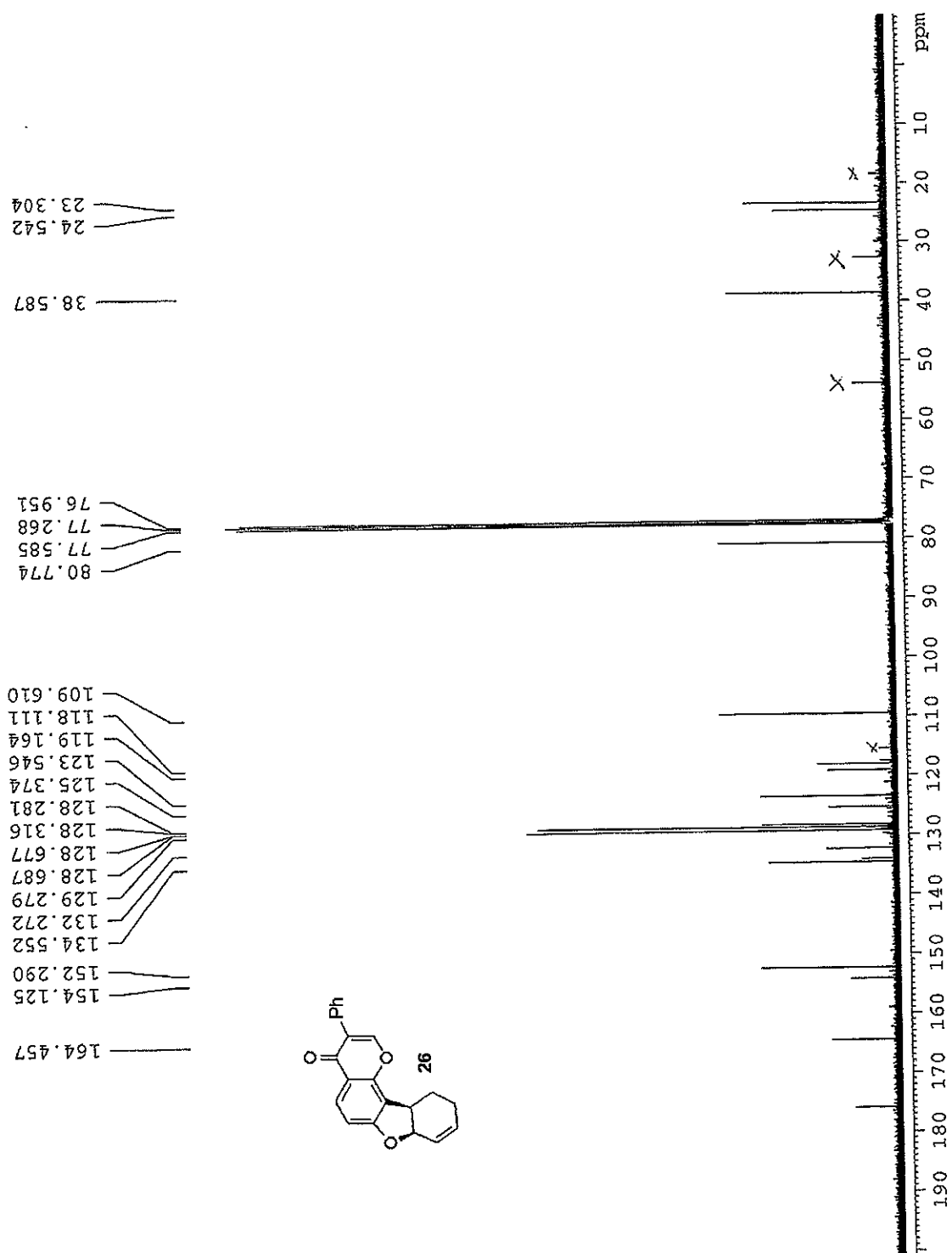


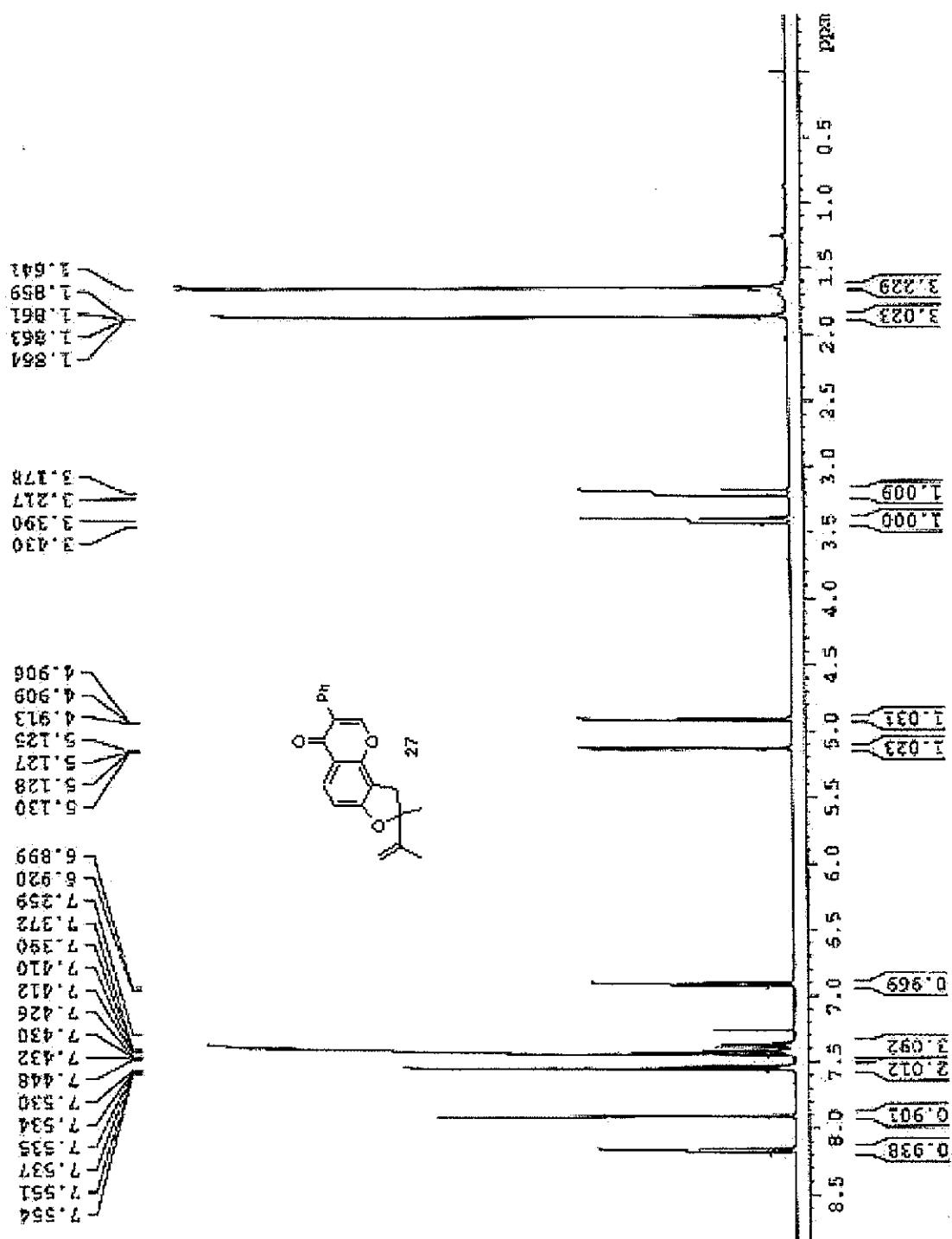


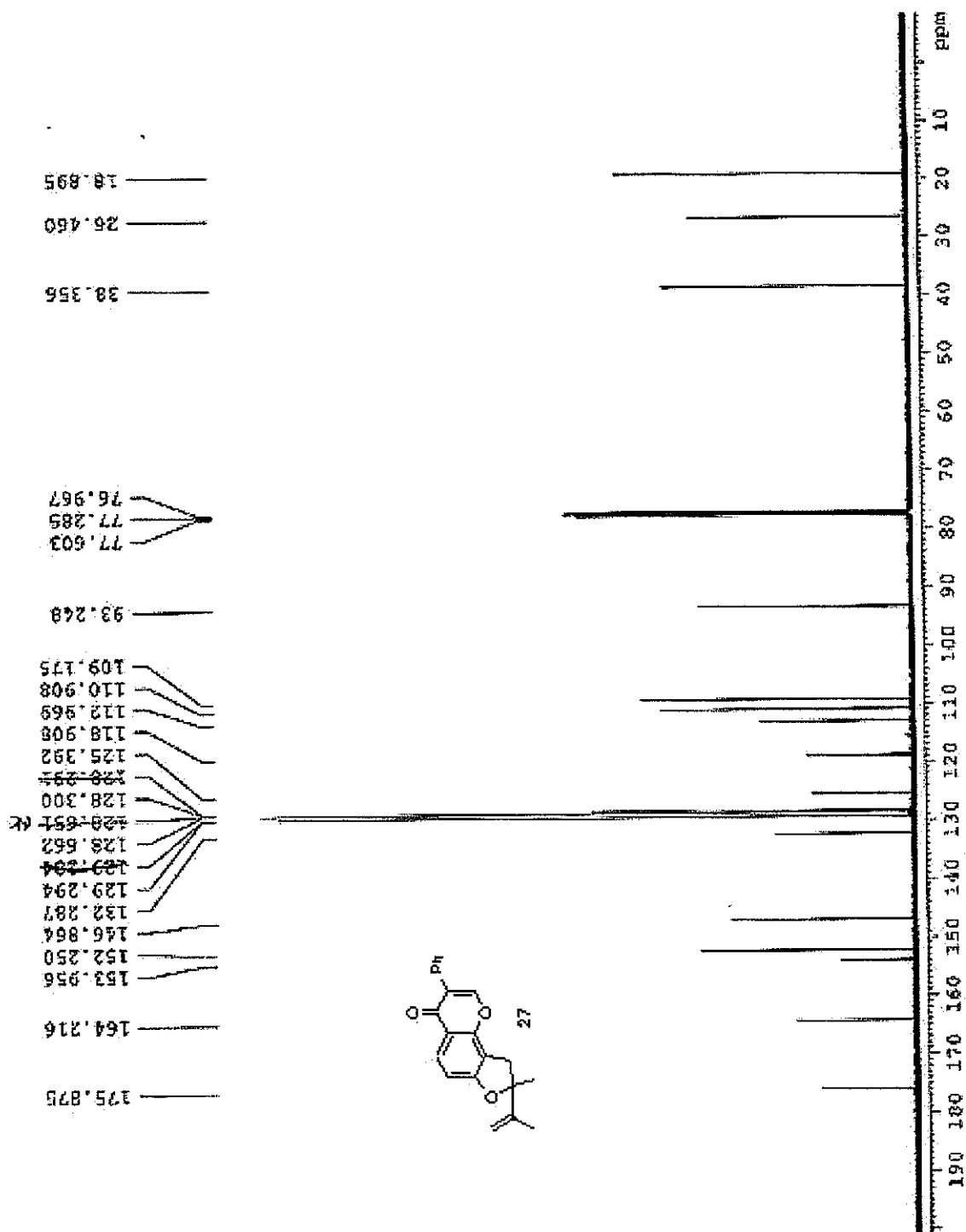


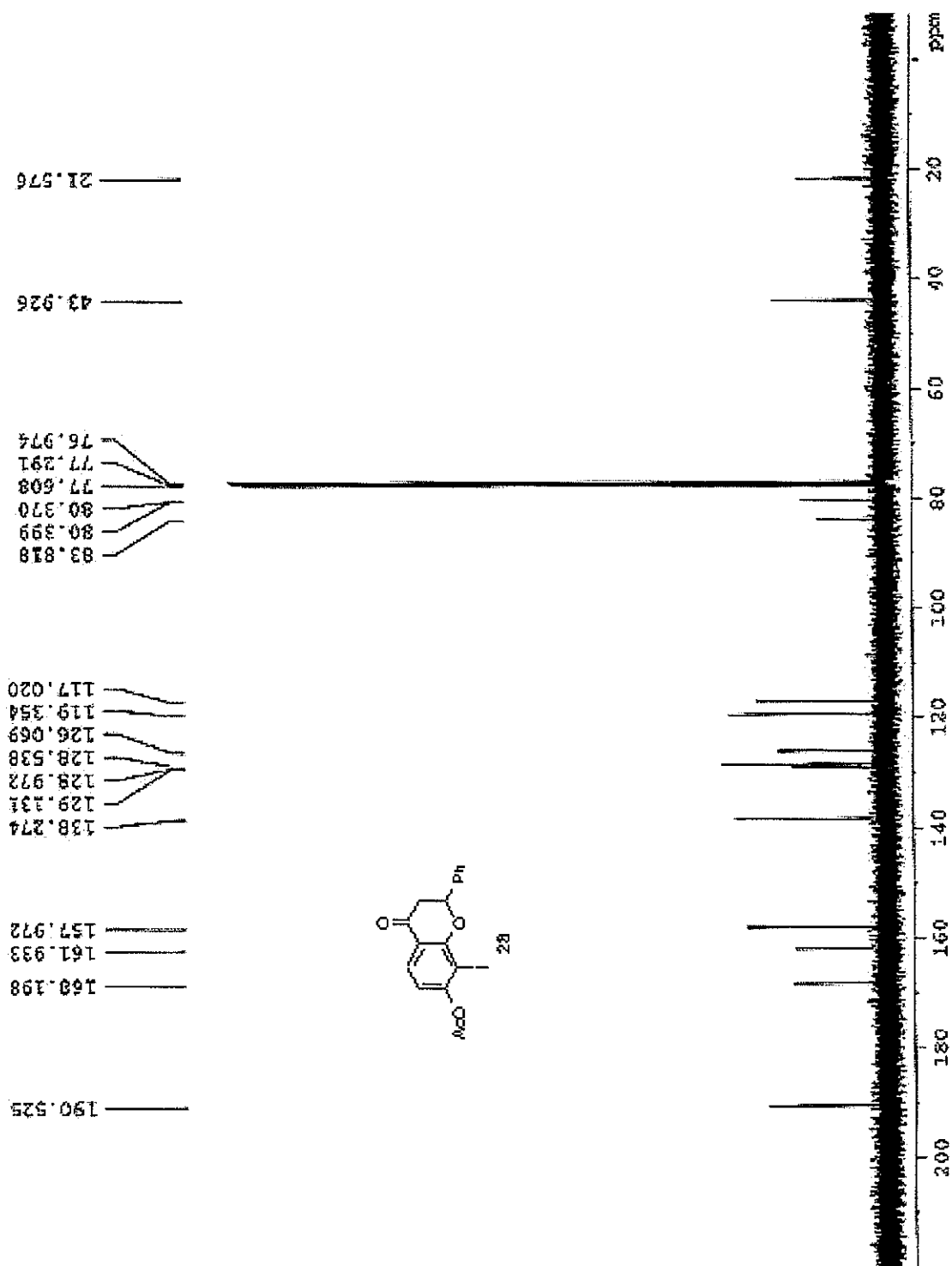


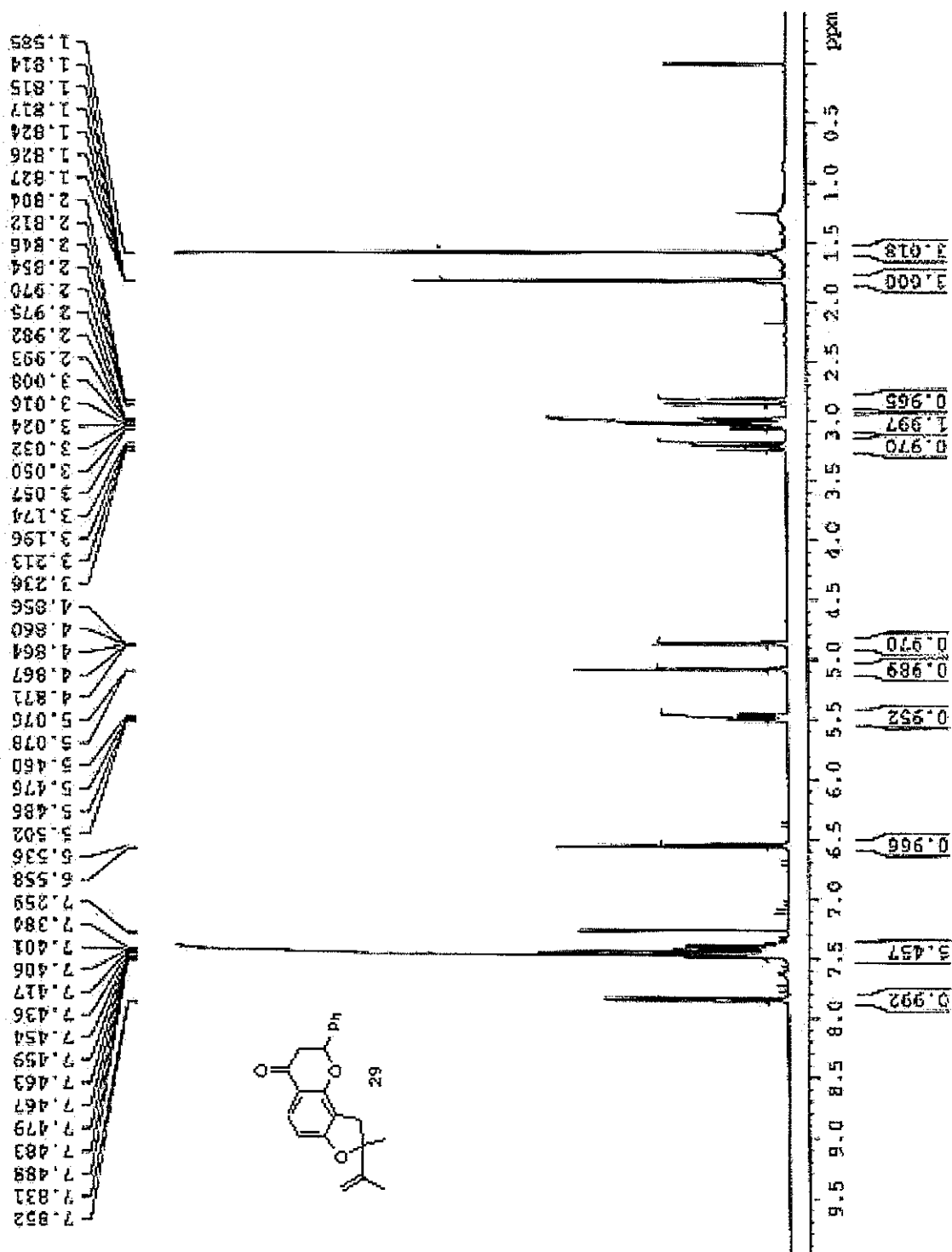


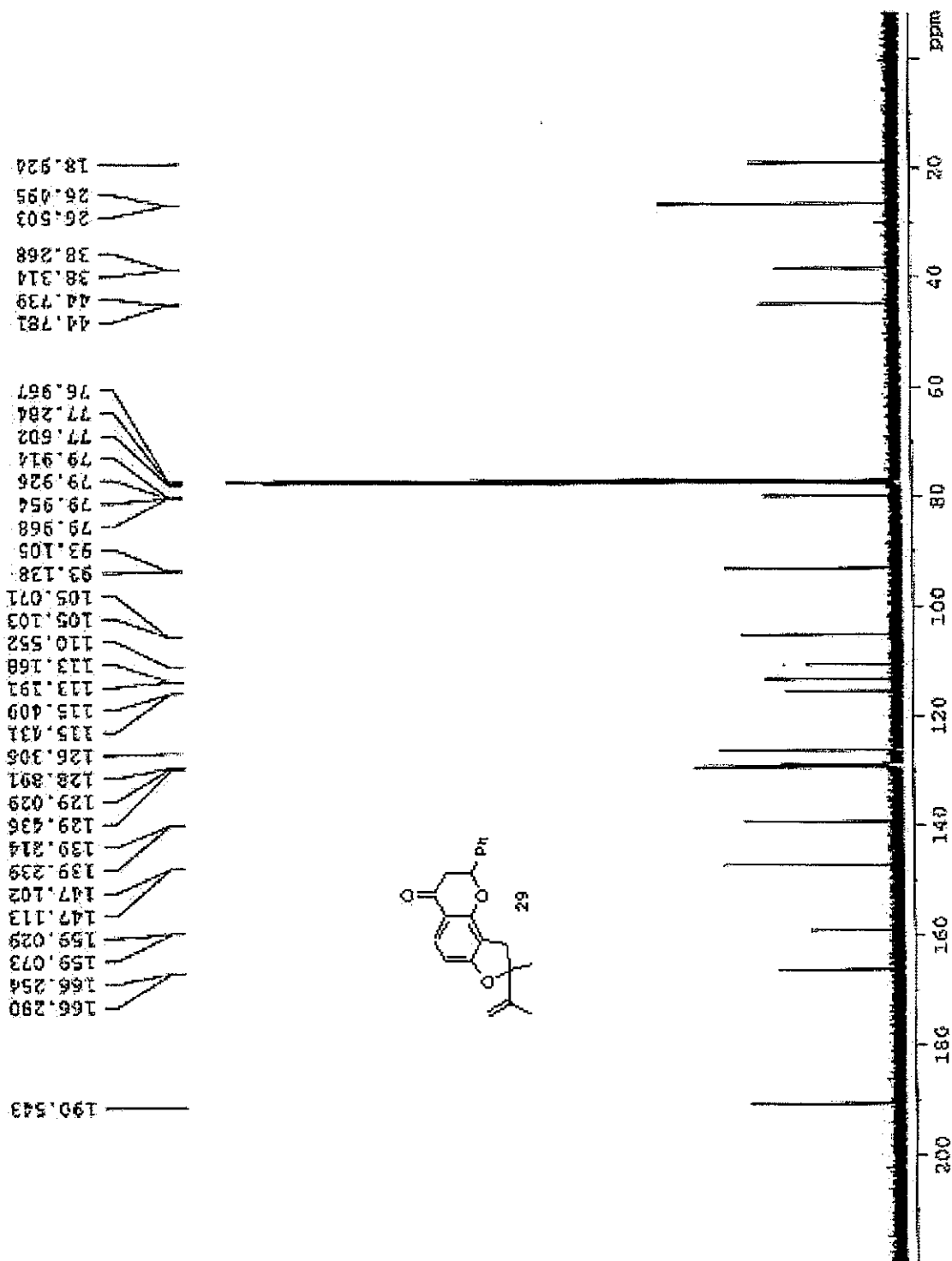




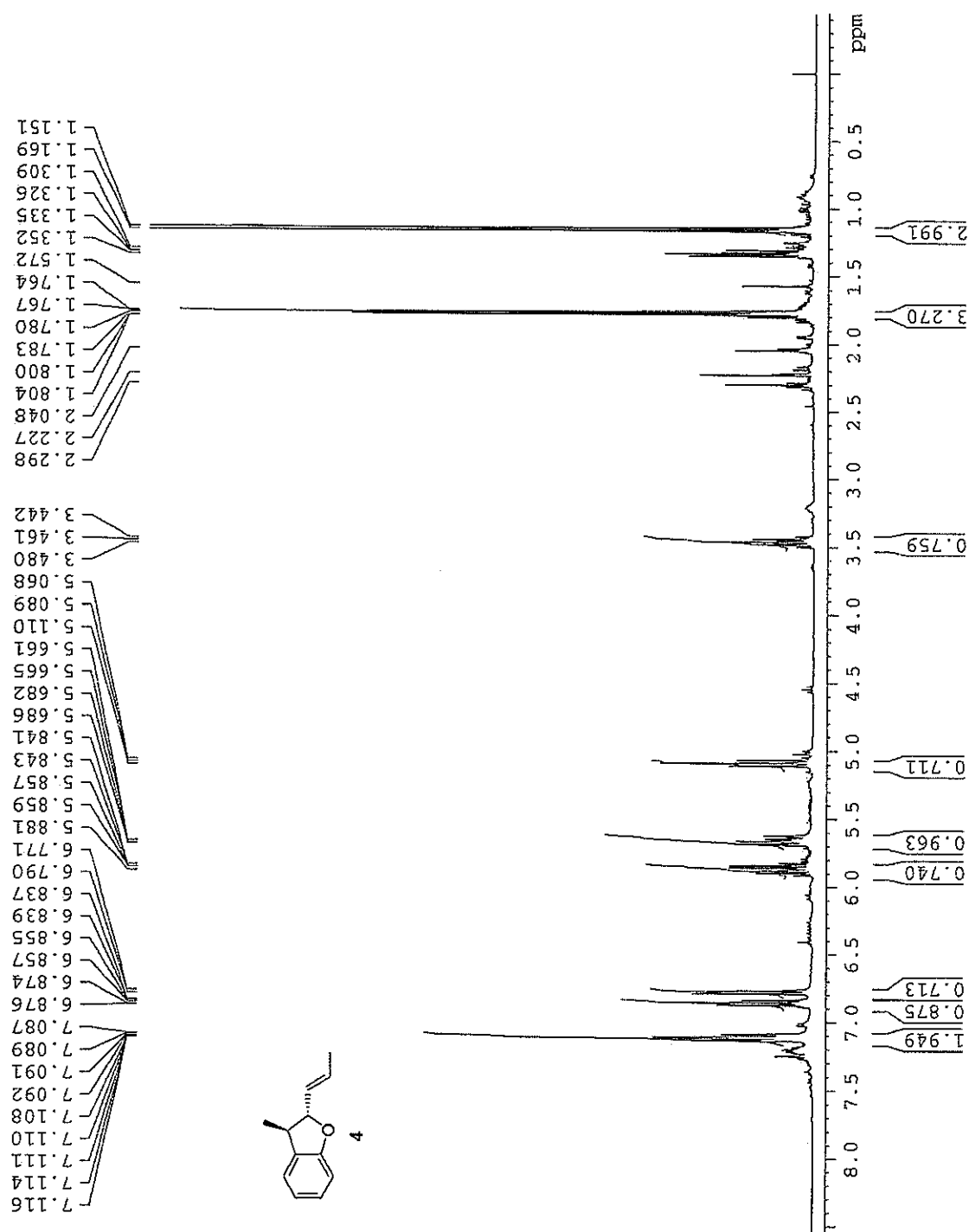


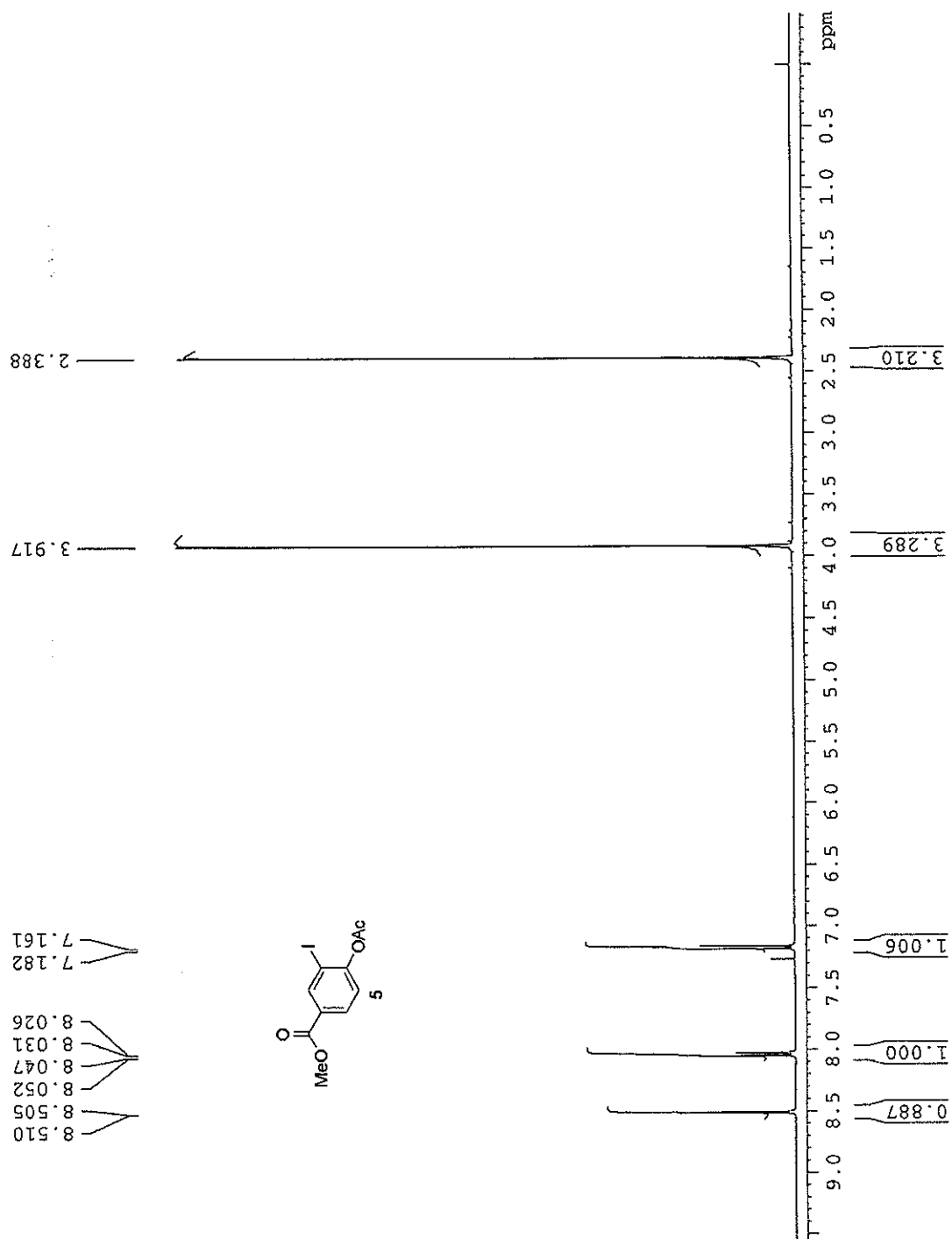


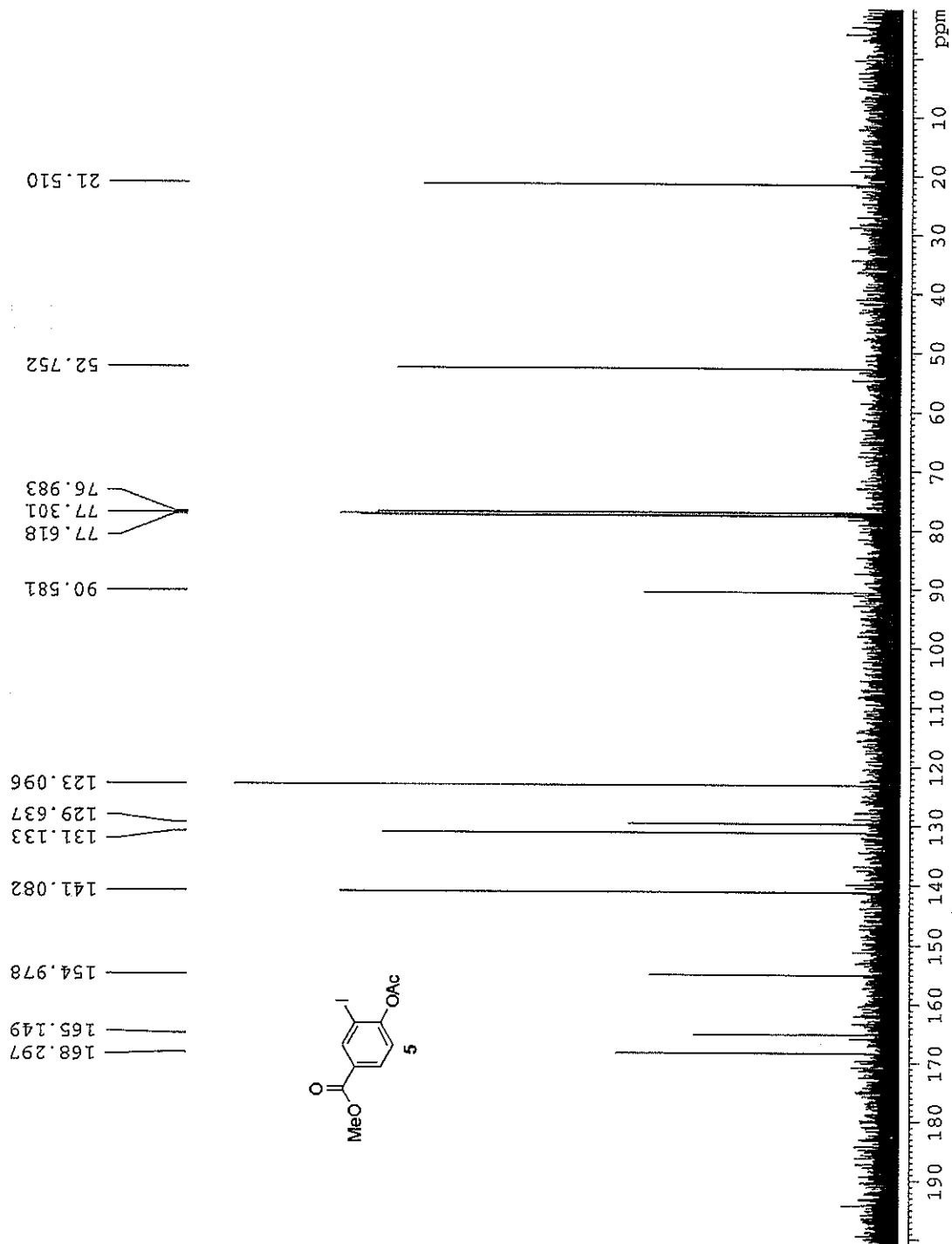


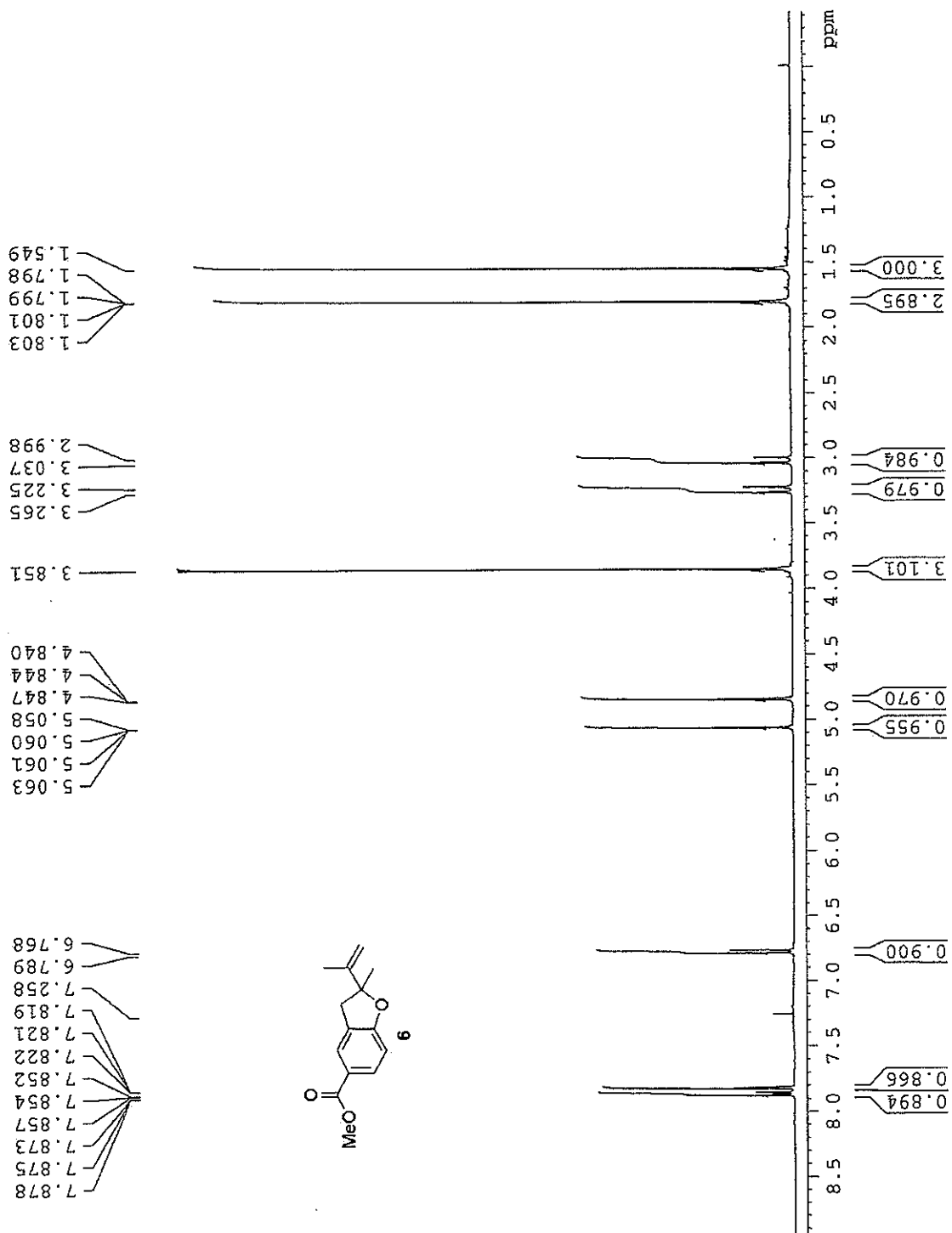


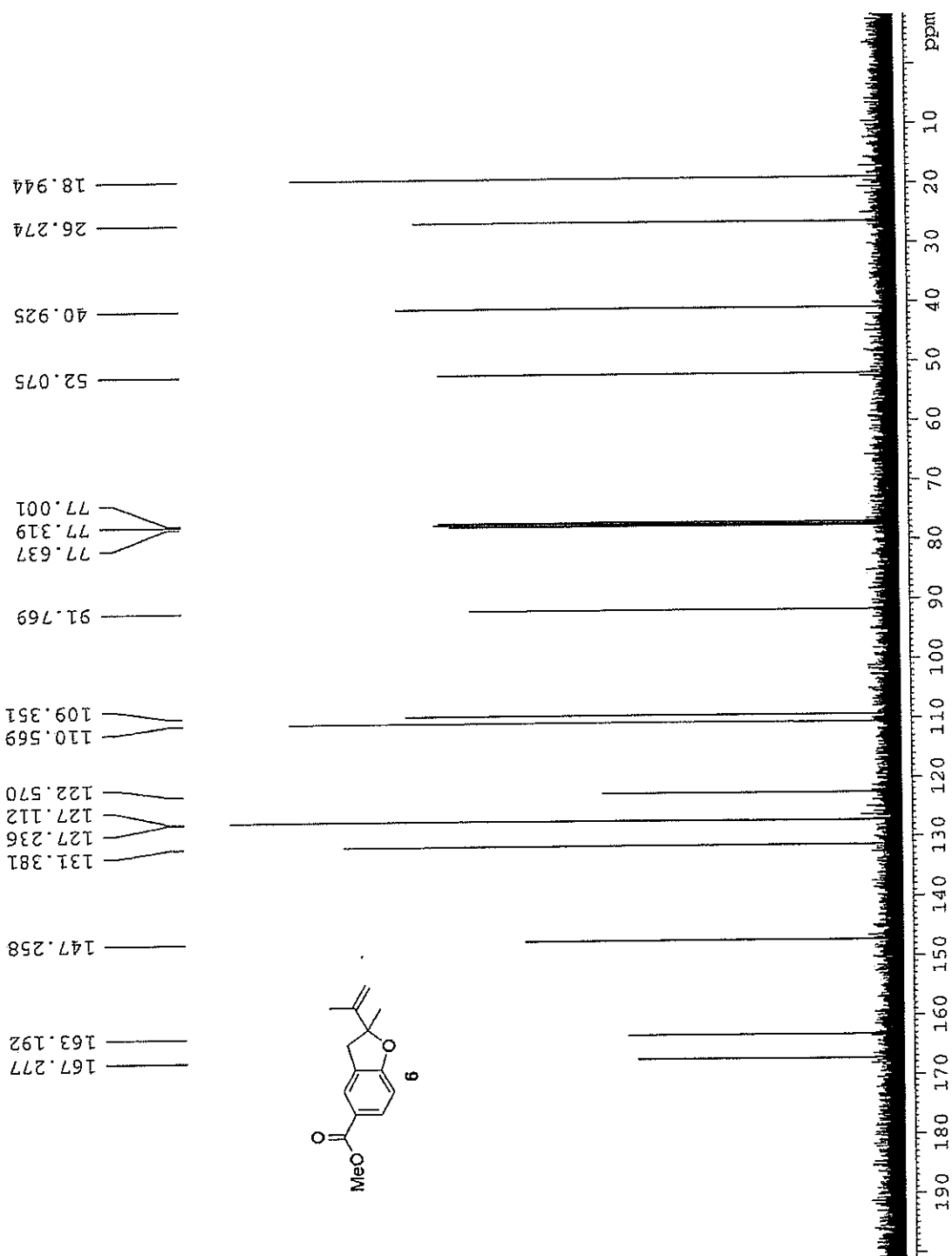
APPENDIX D. CHAPTER 4 ^1H and ^{13}C SPECTRA

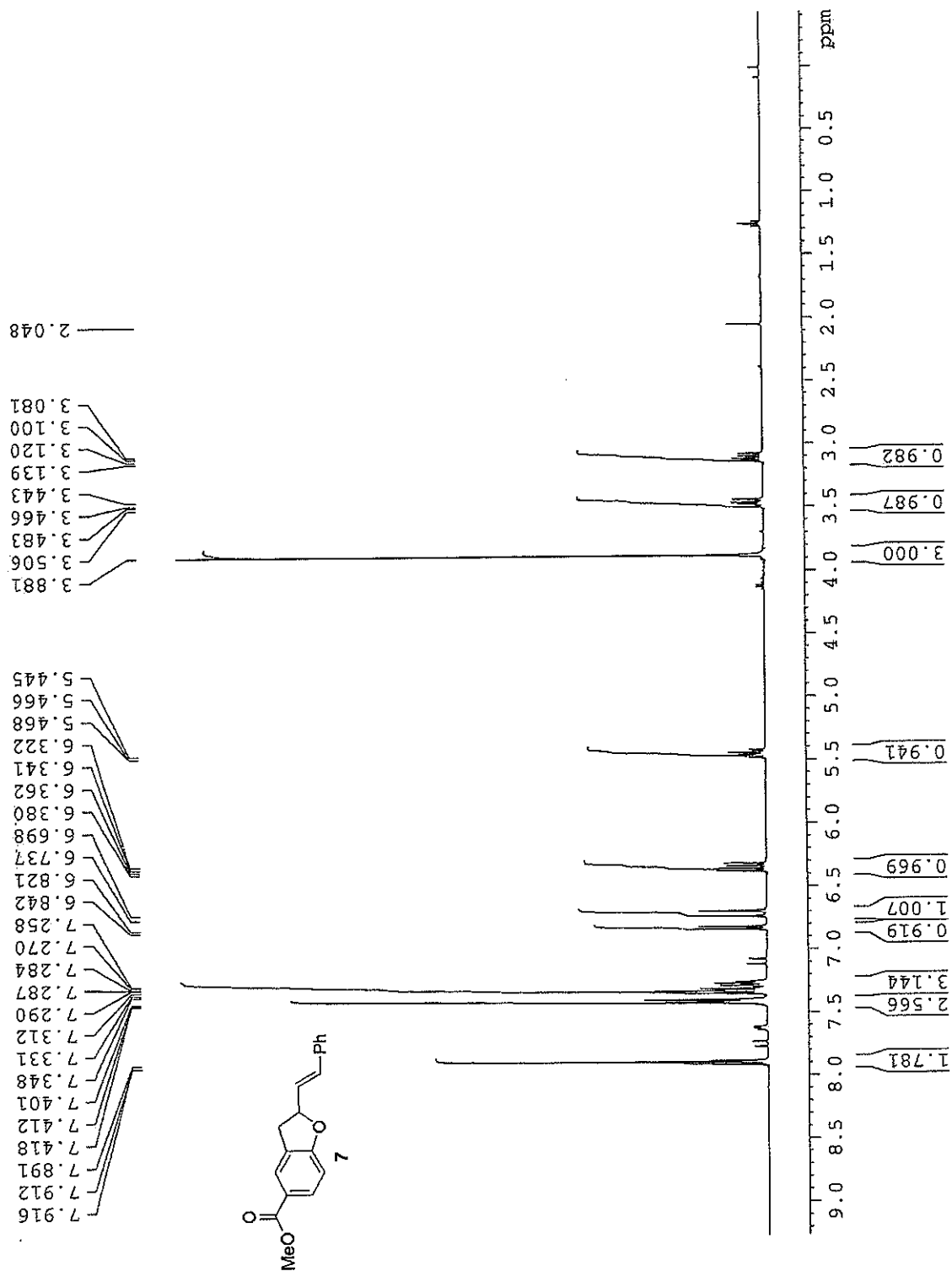


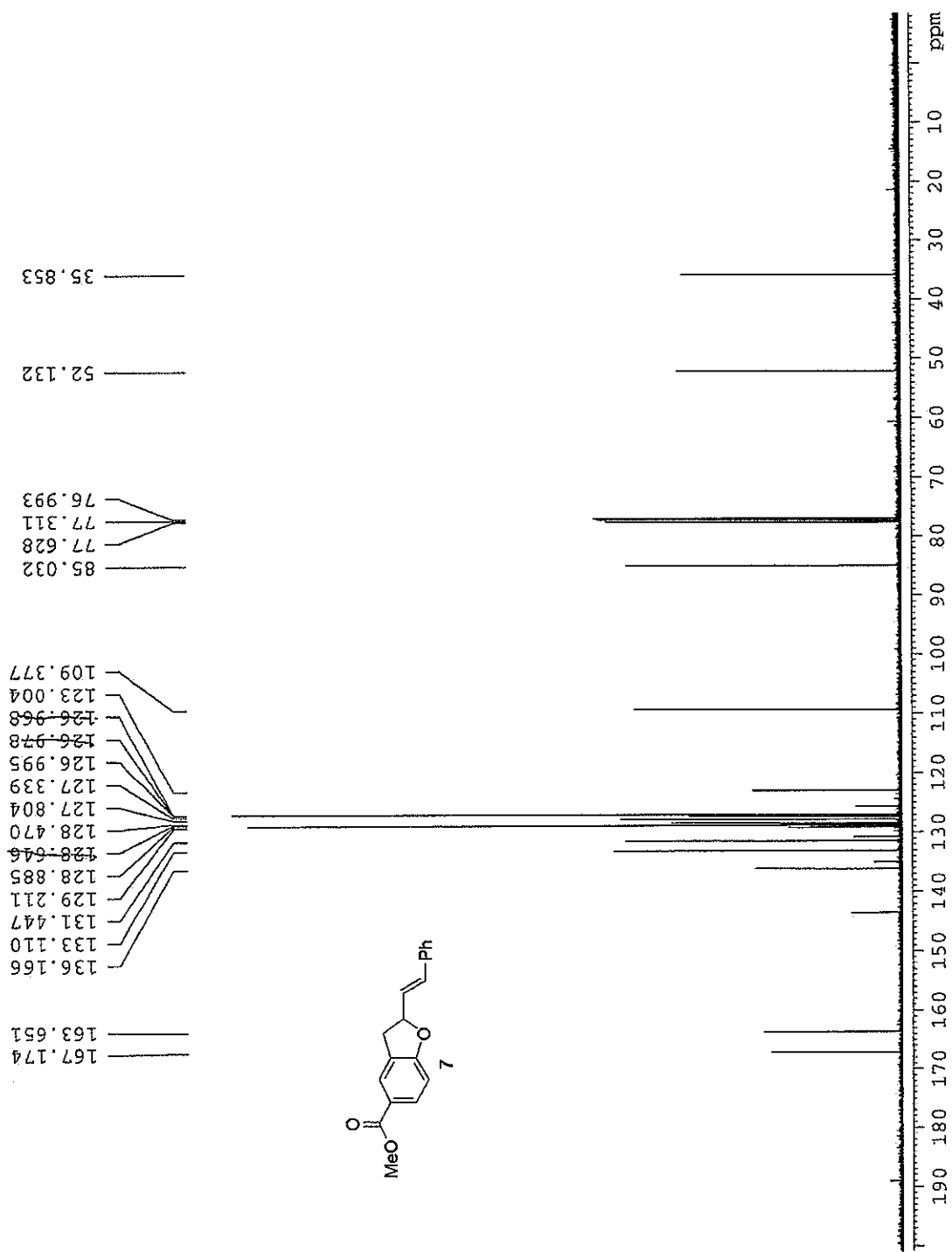


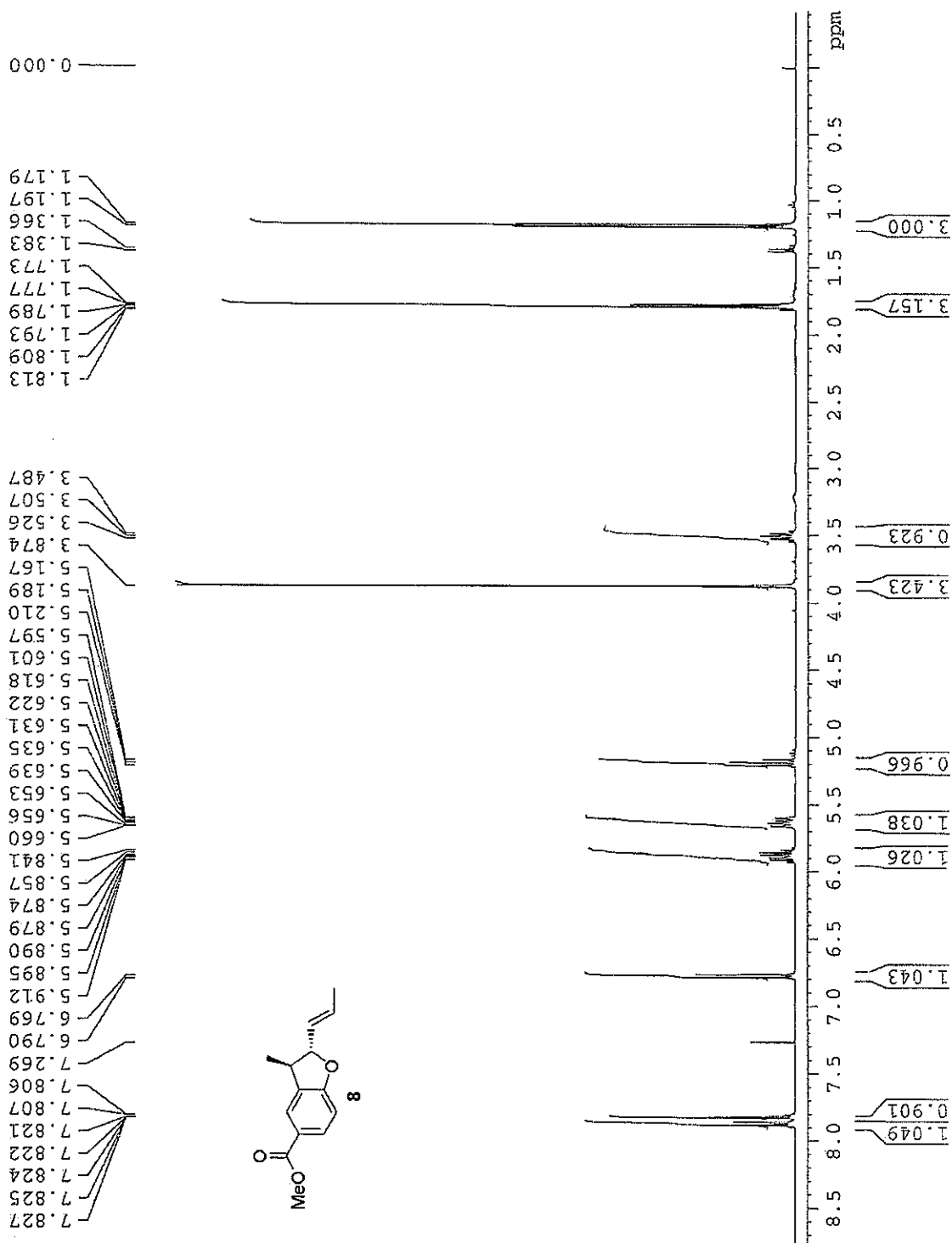


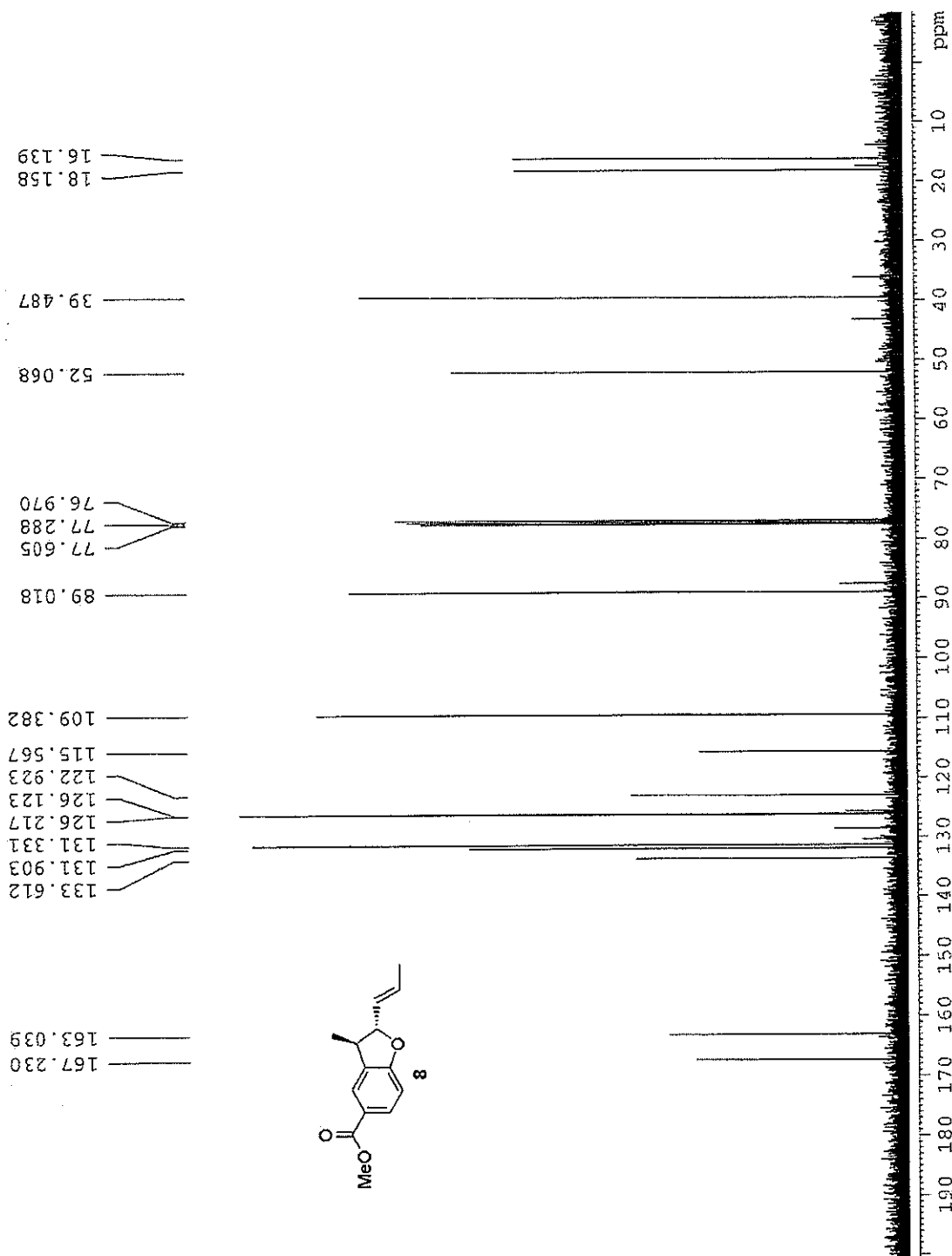


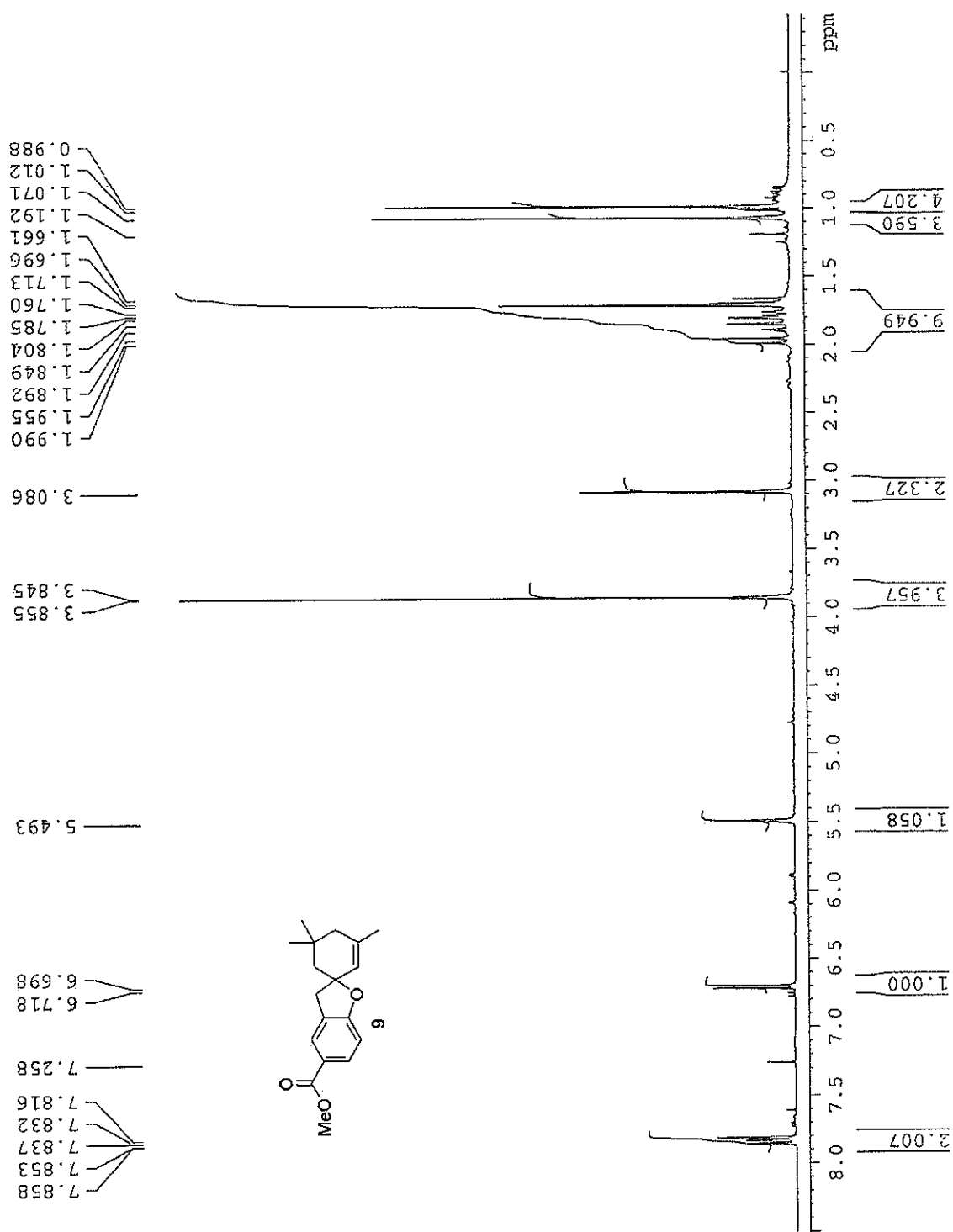


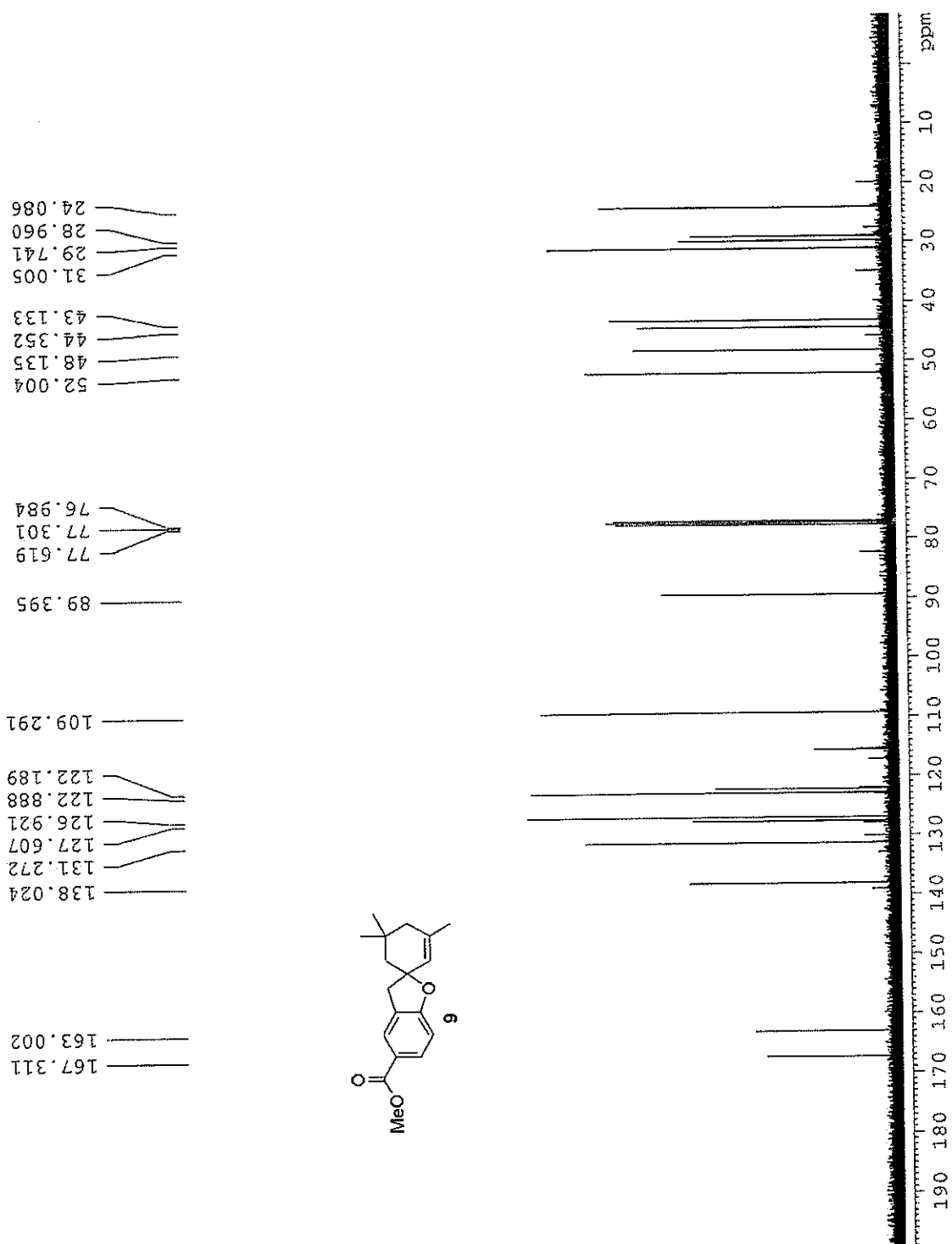


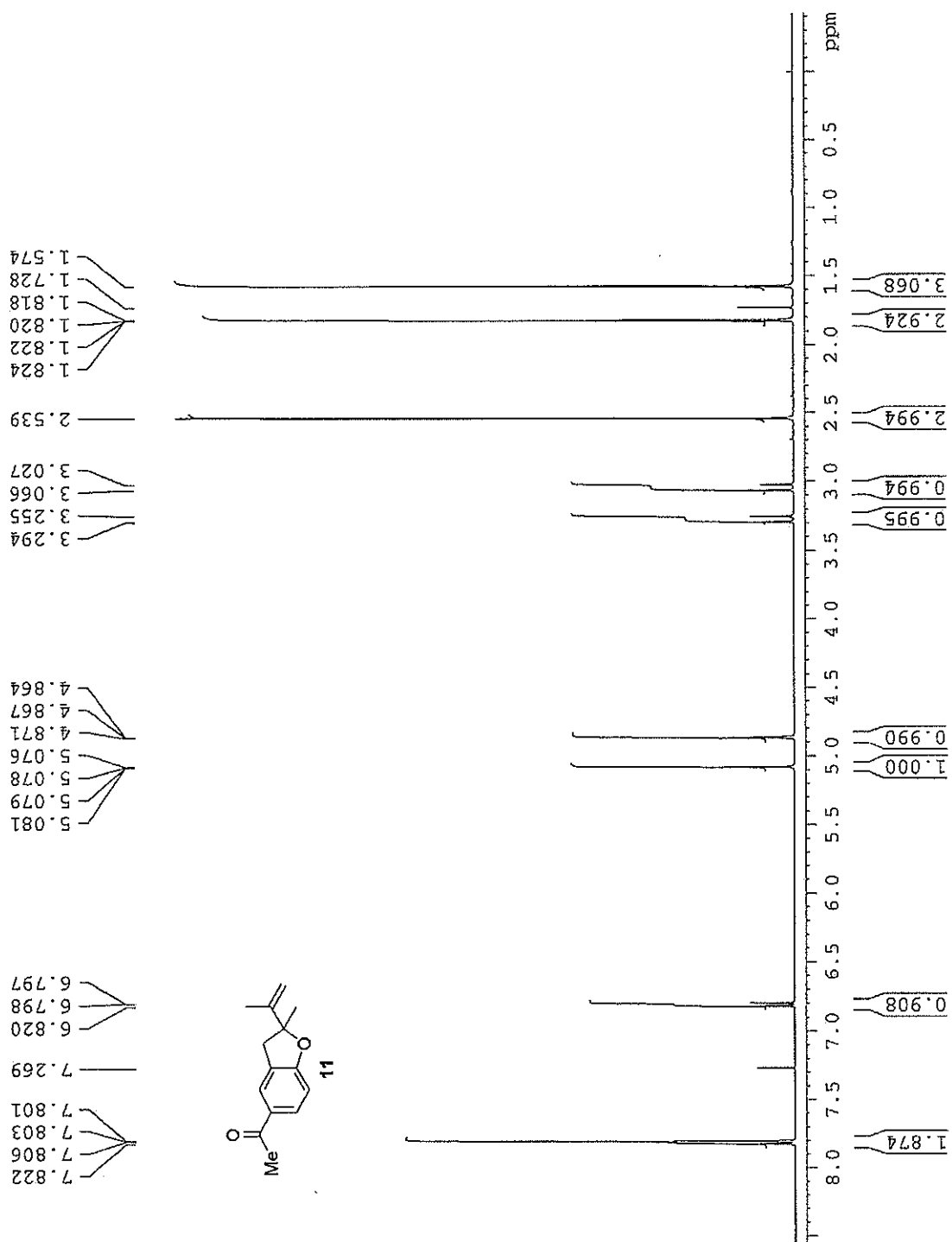


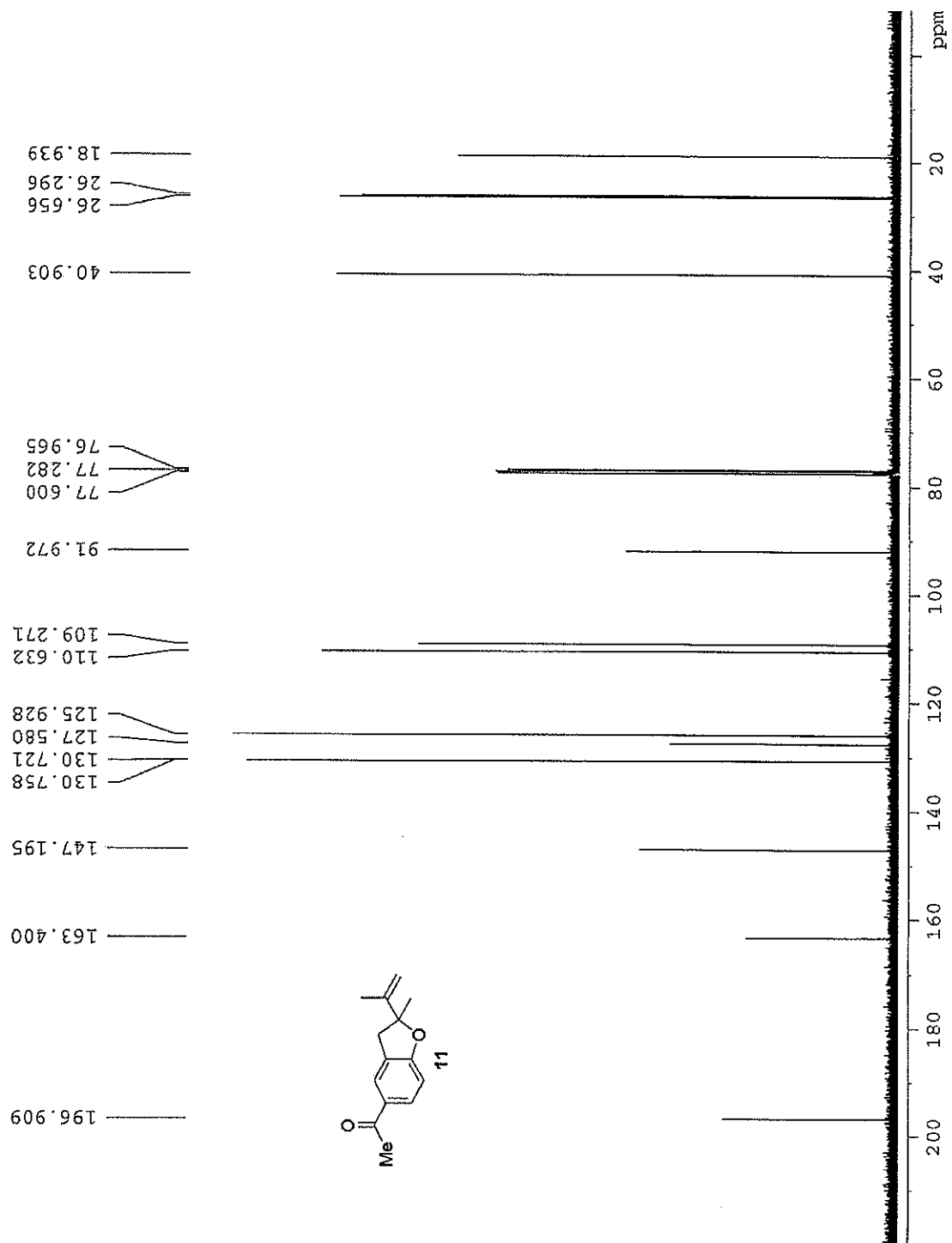


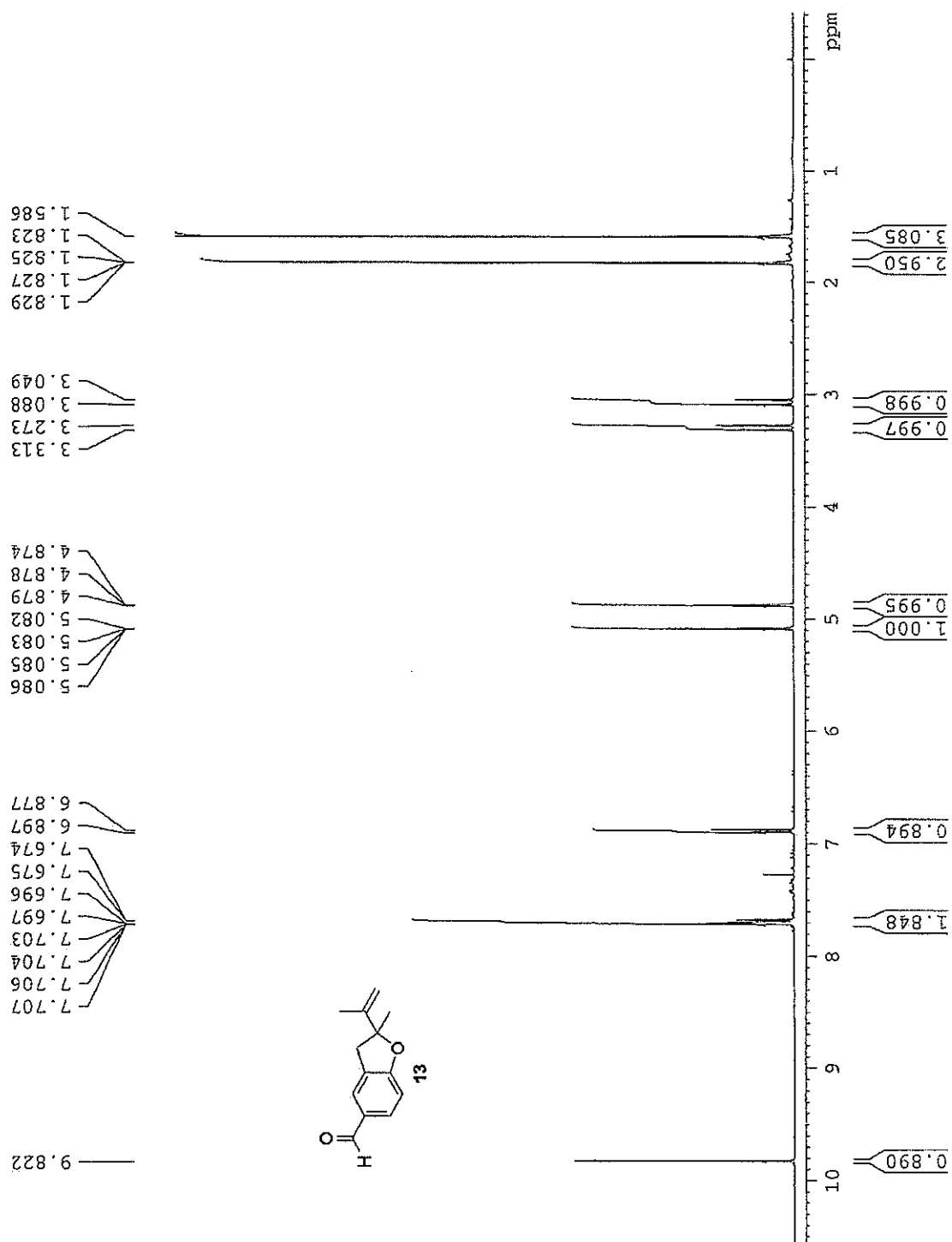


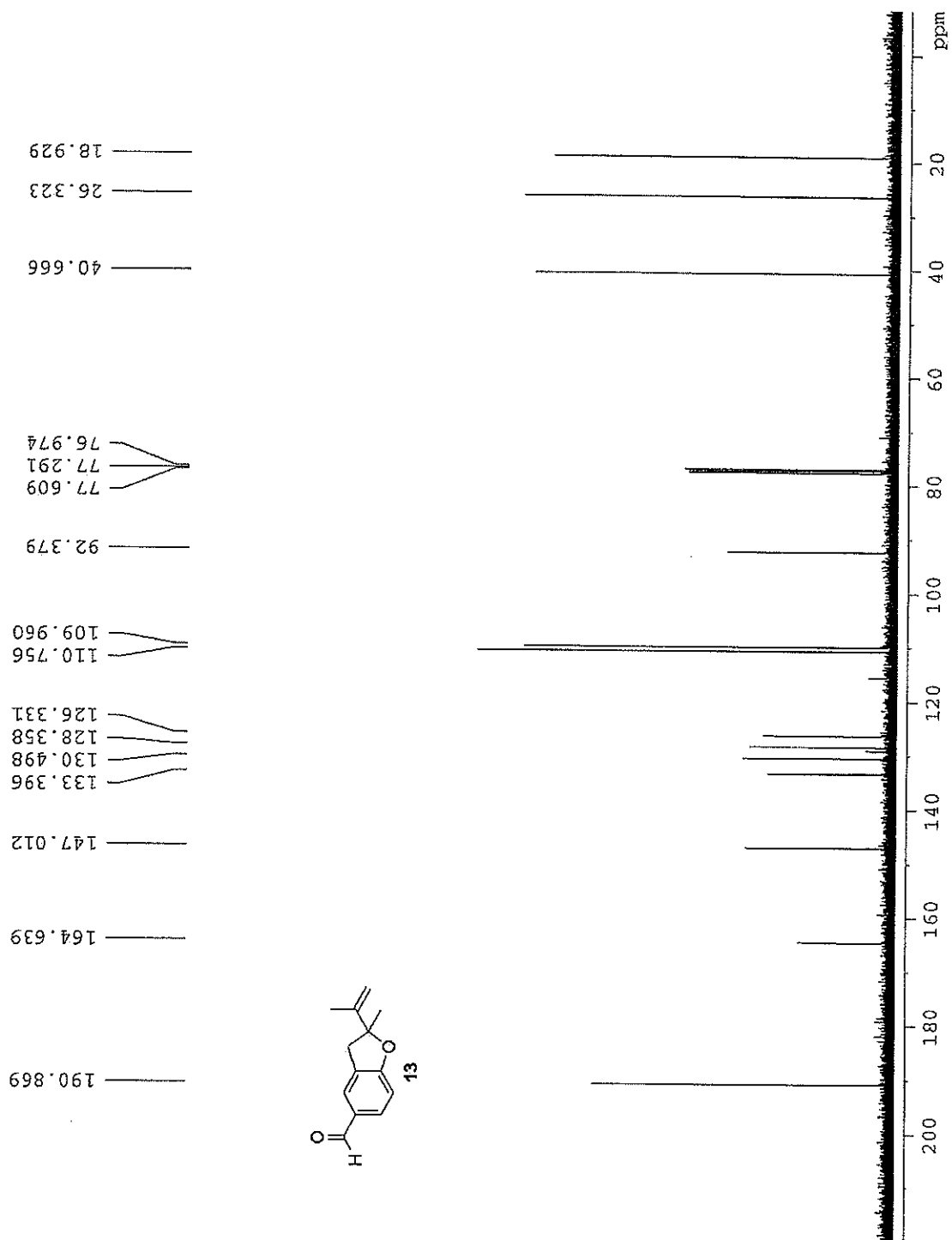


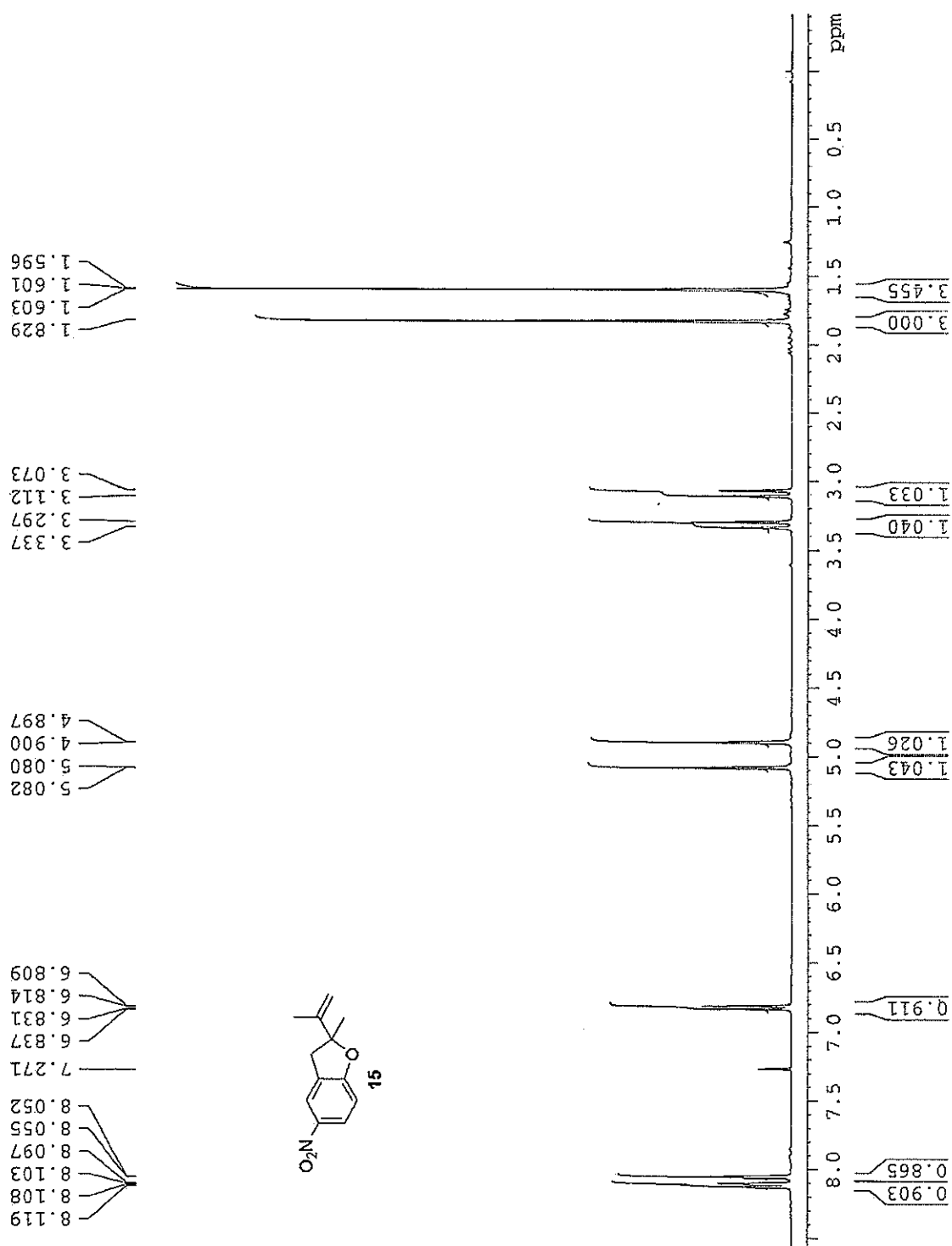


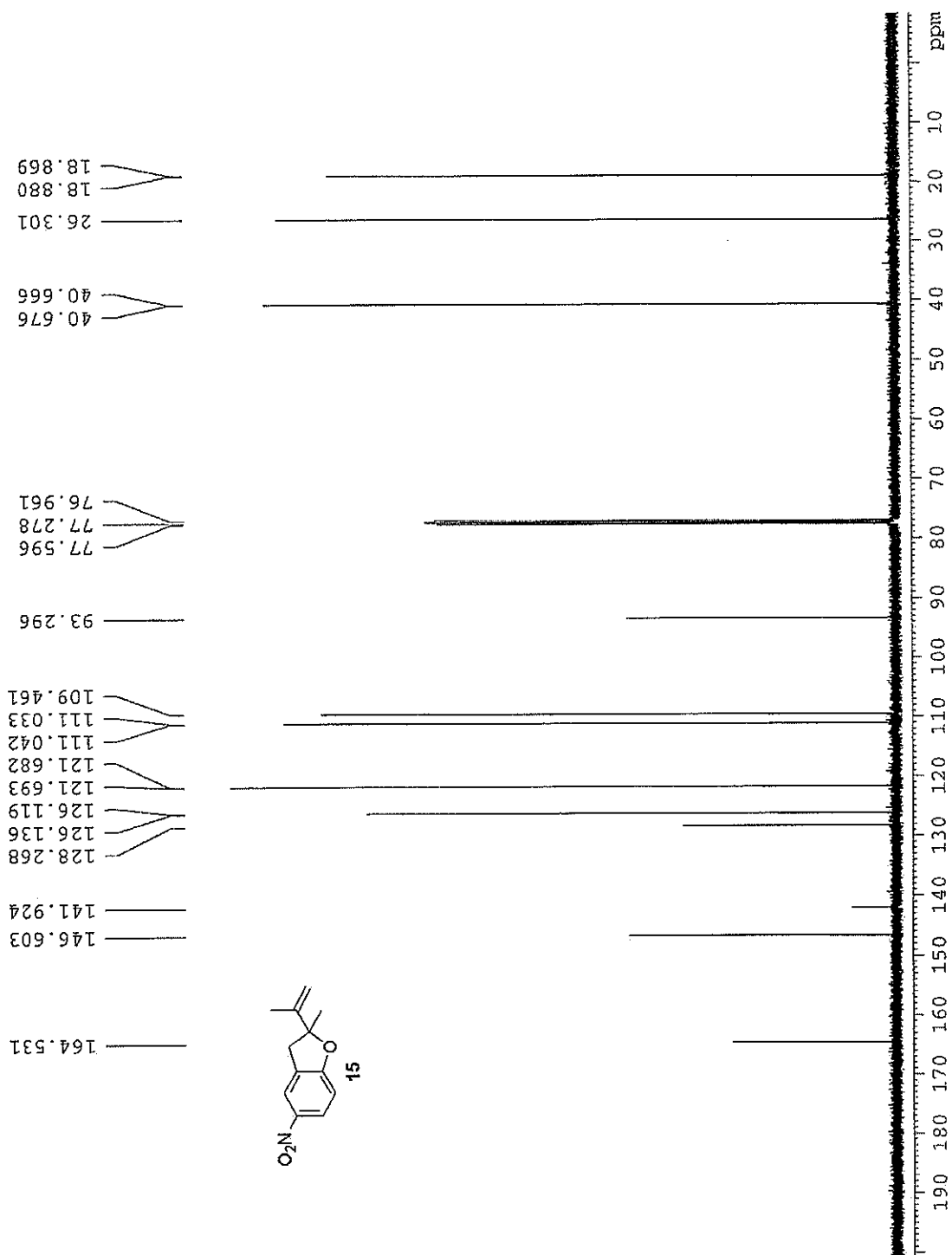


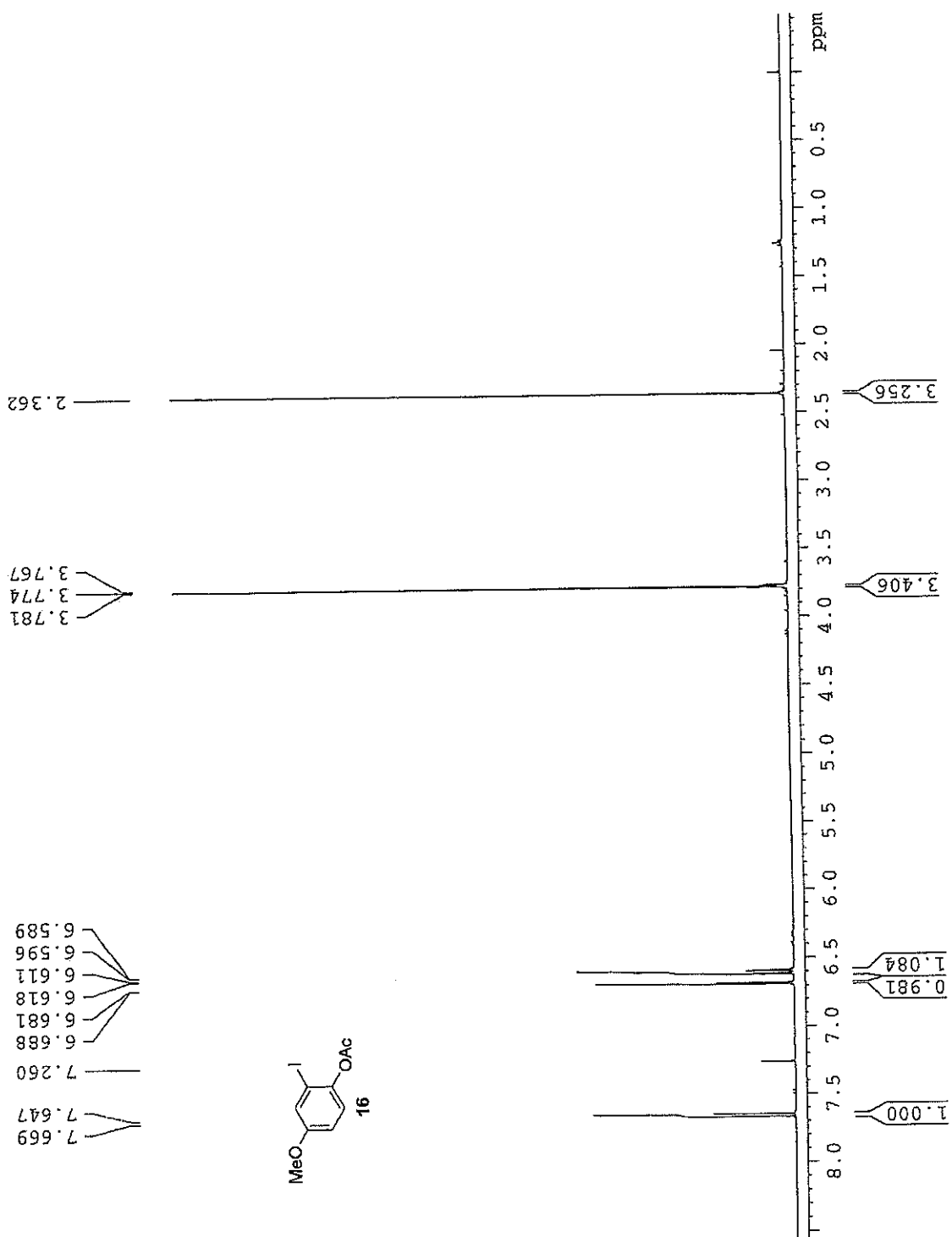


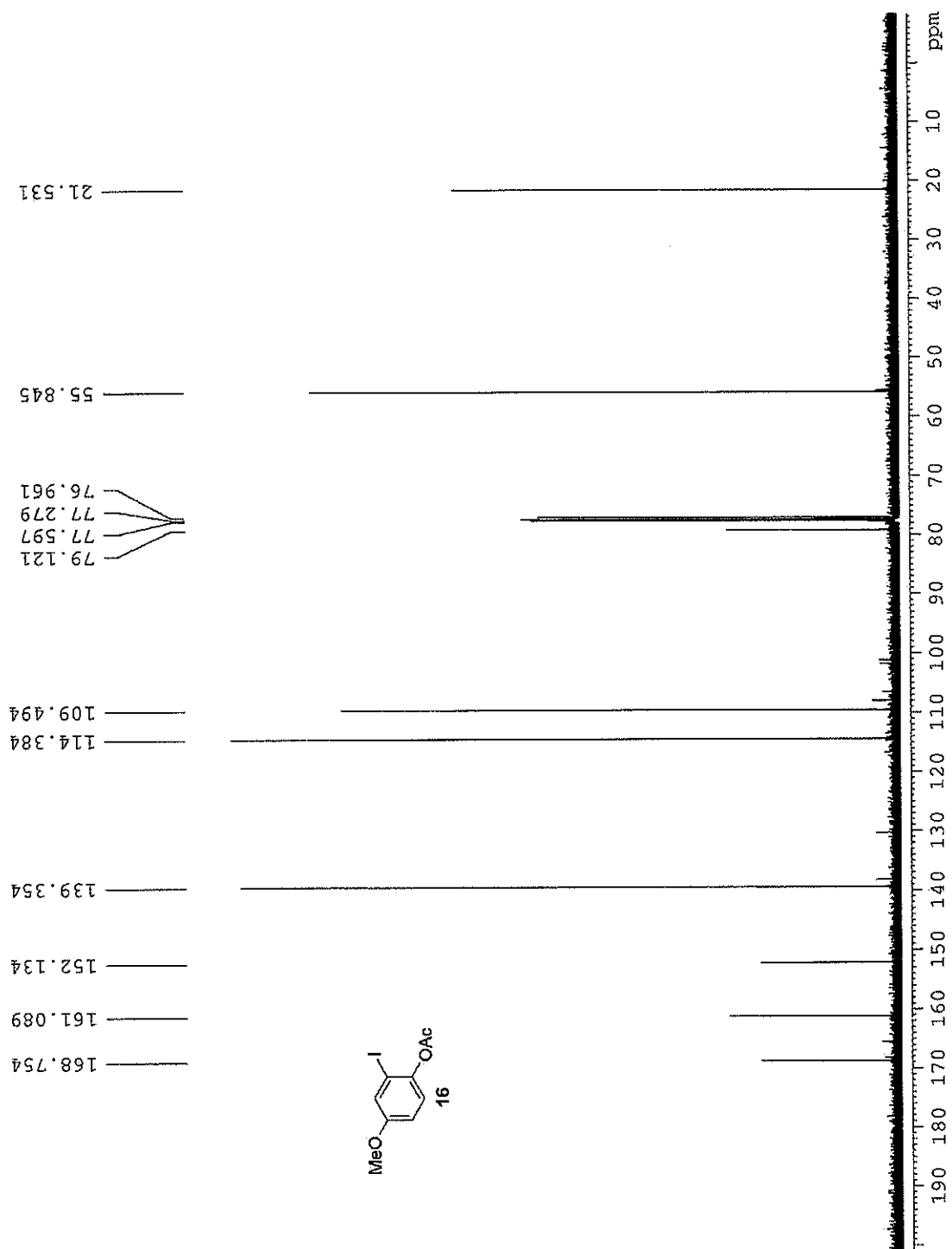


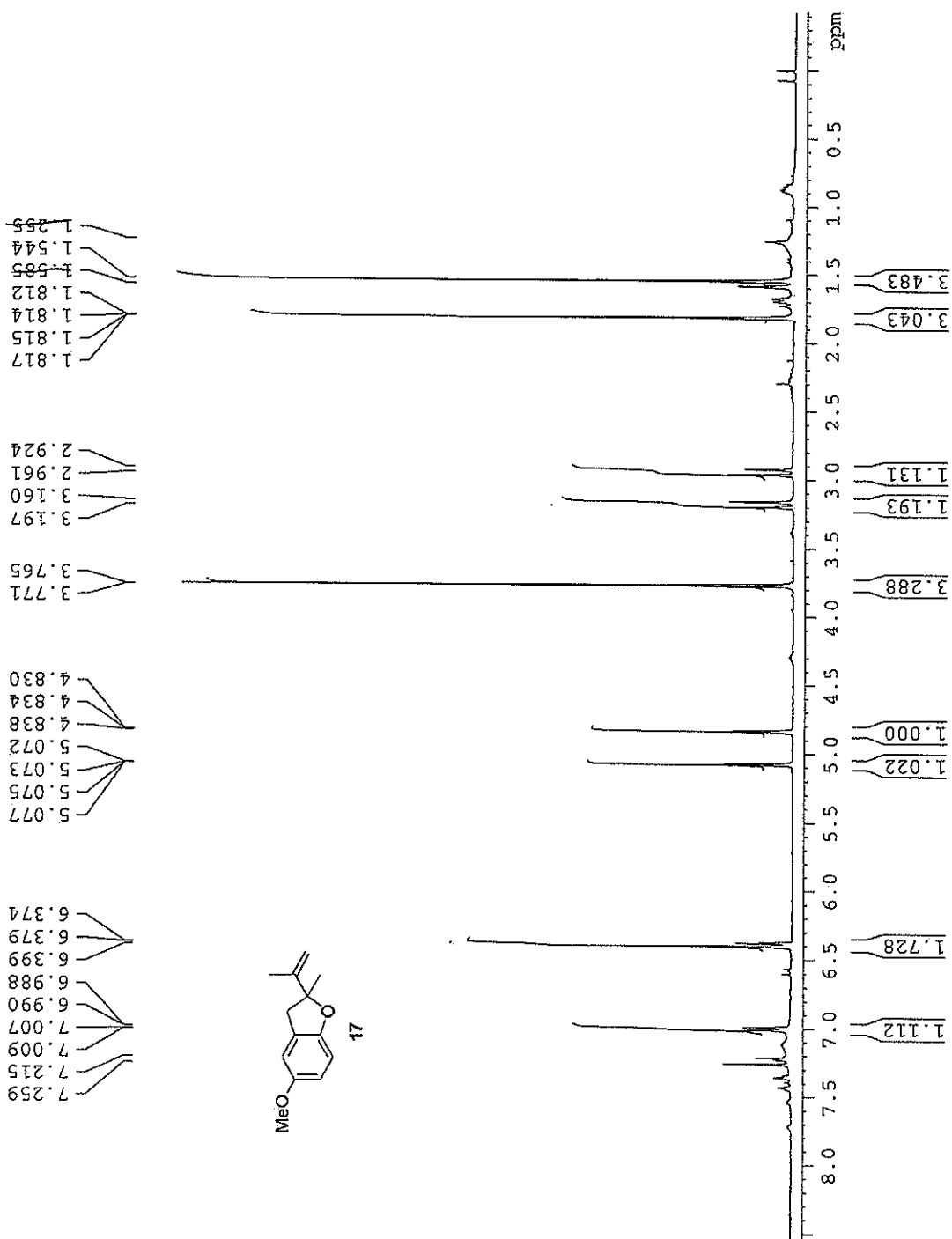


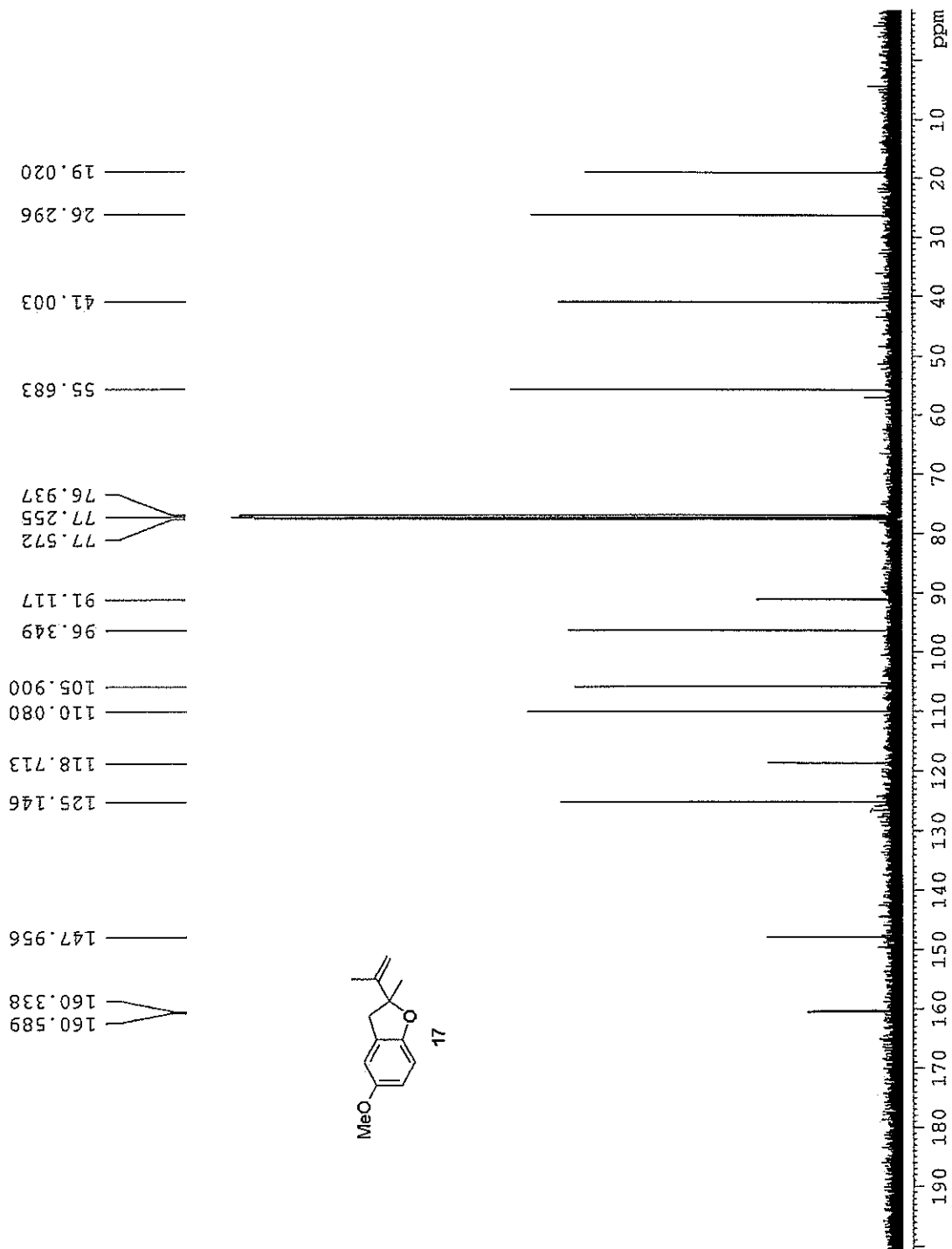


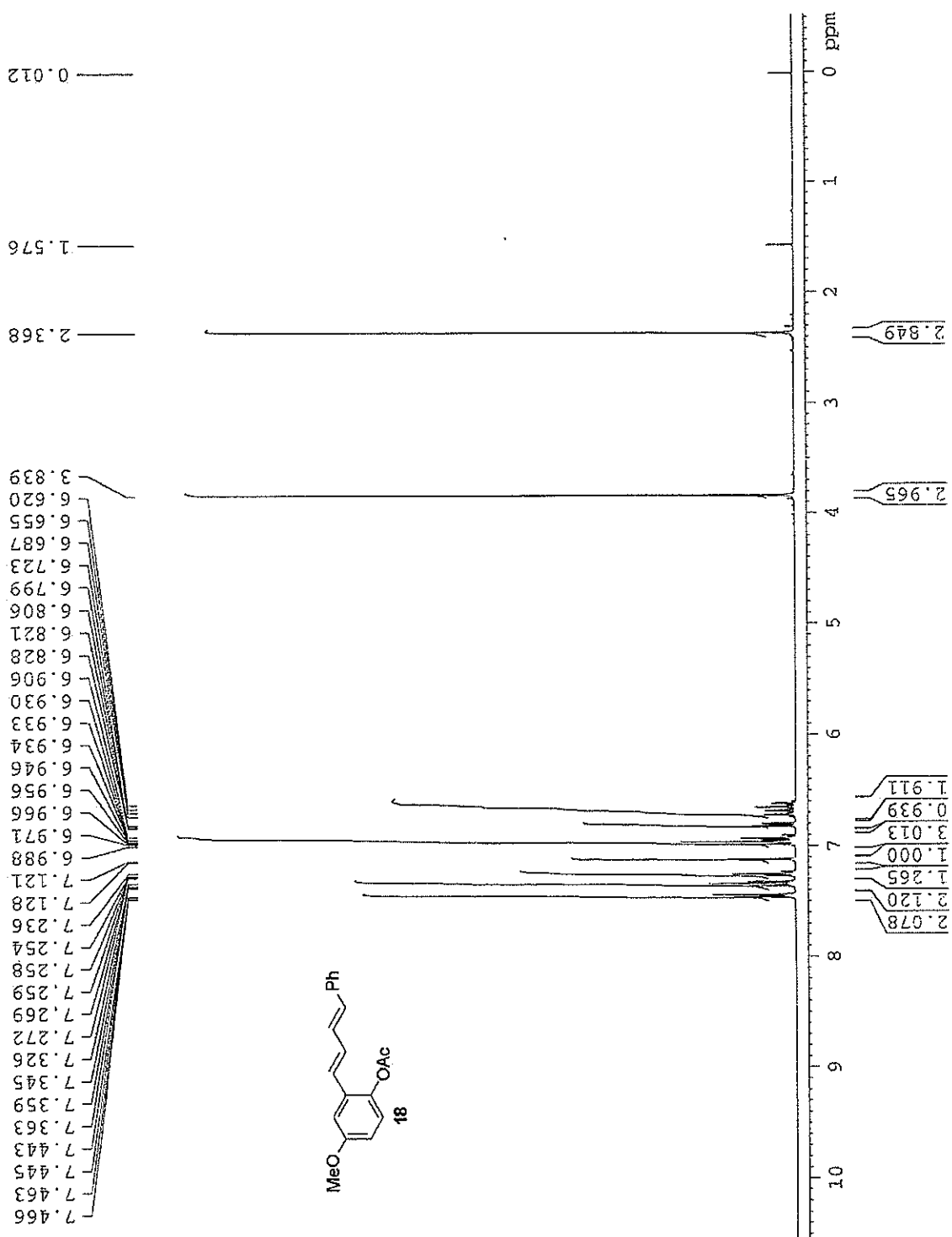


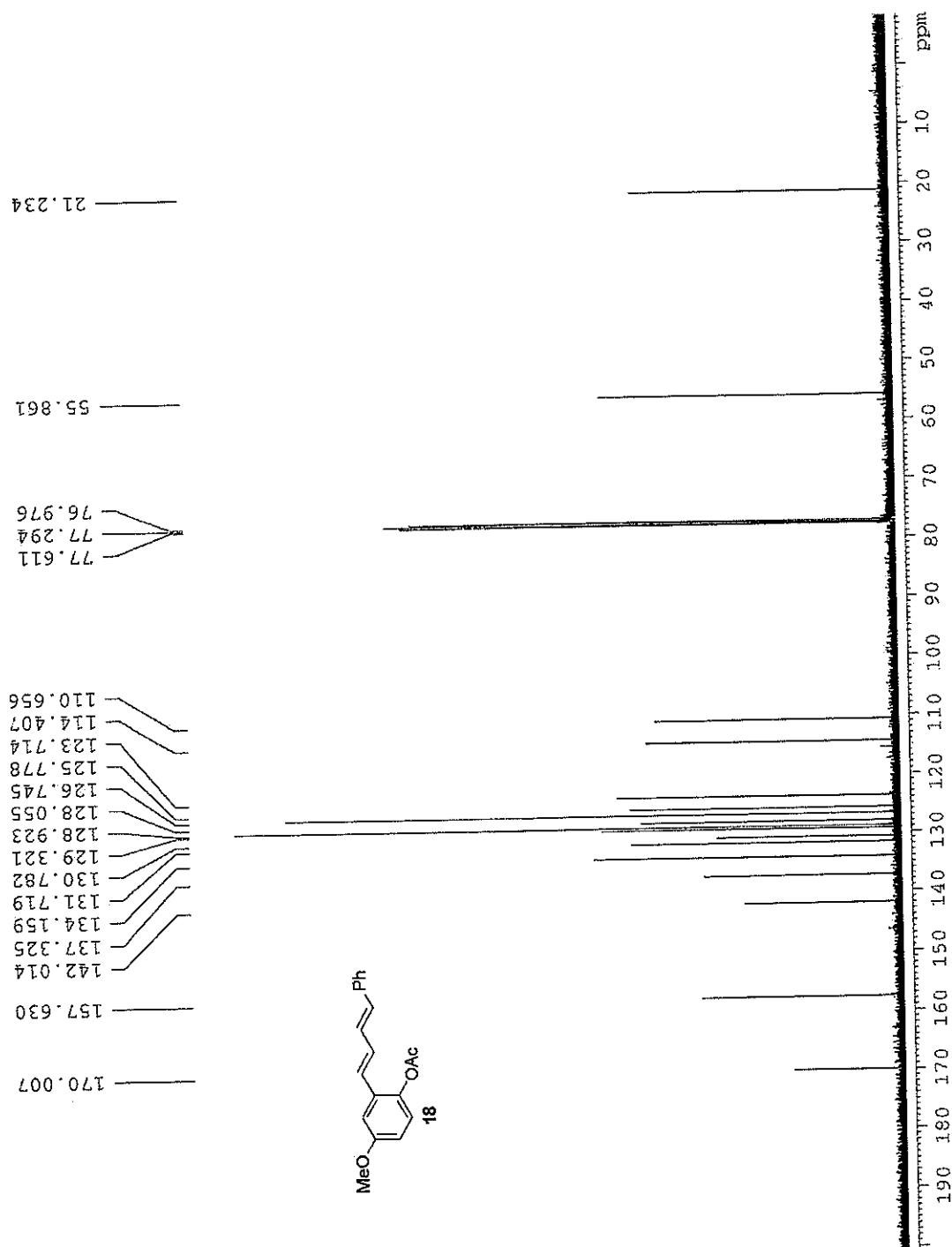


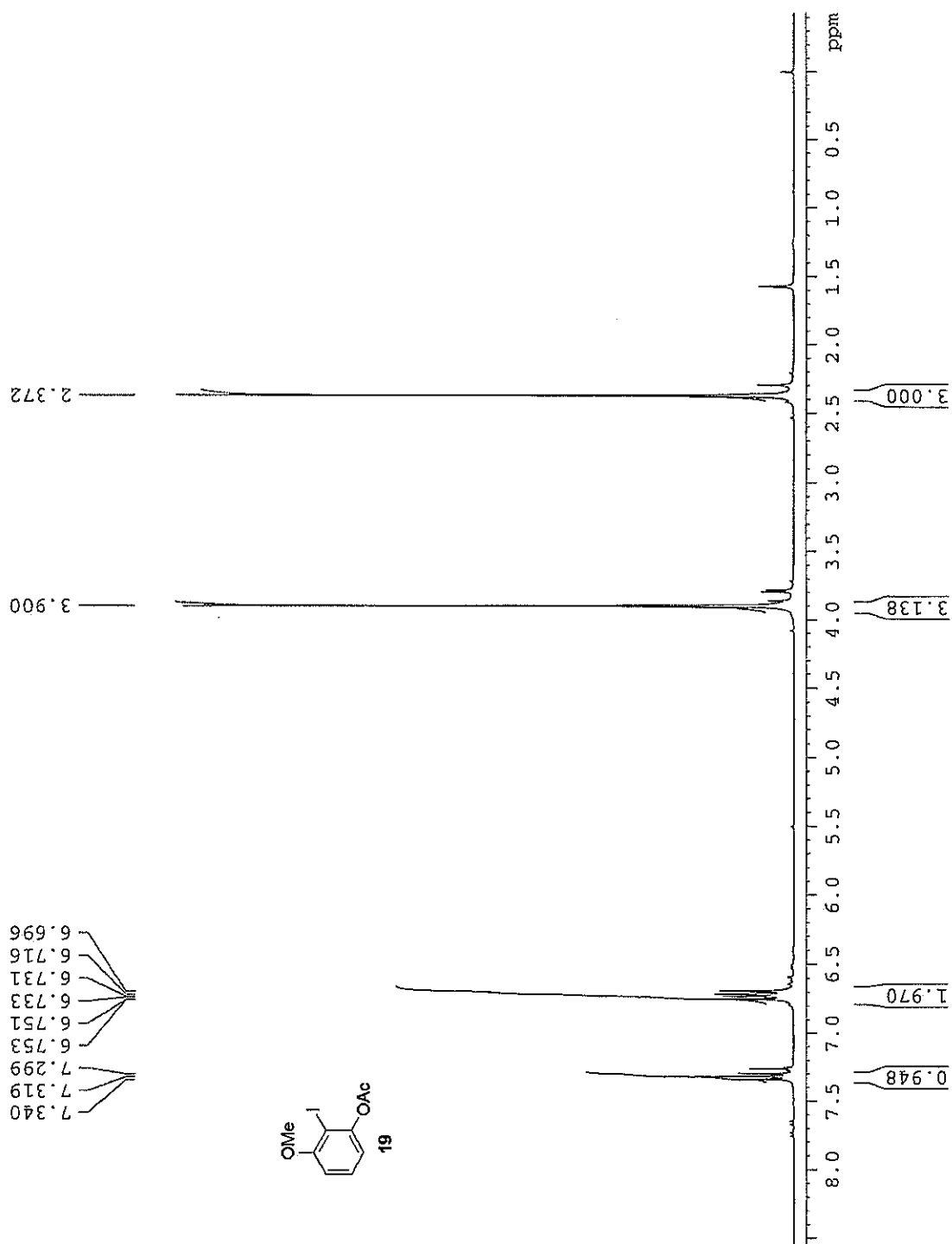


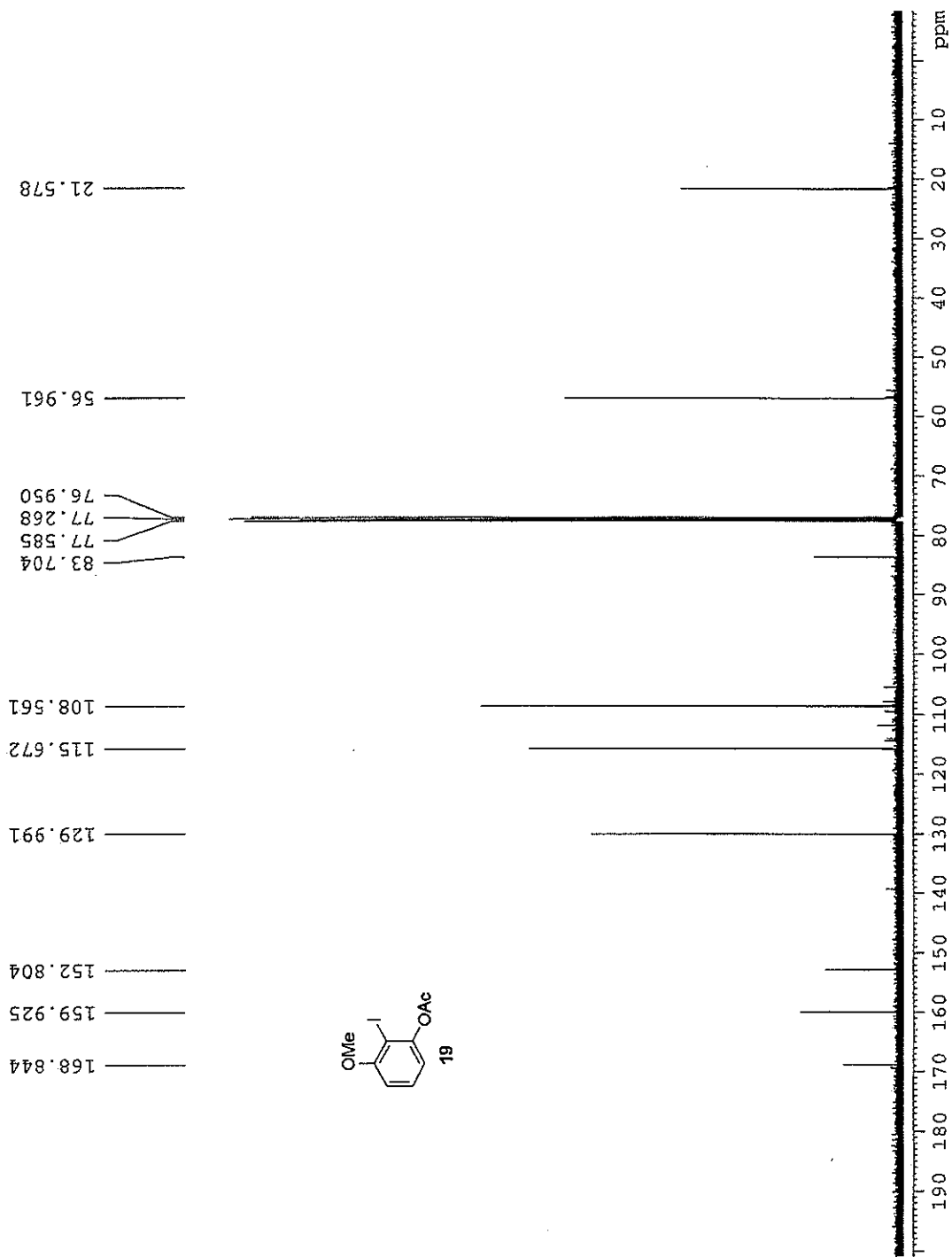


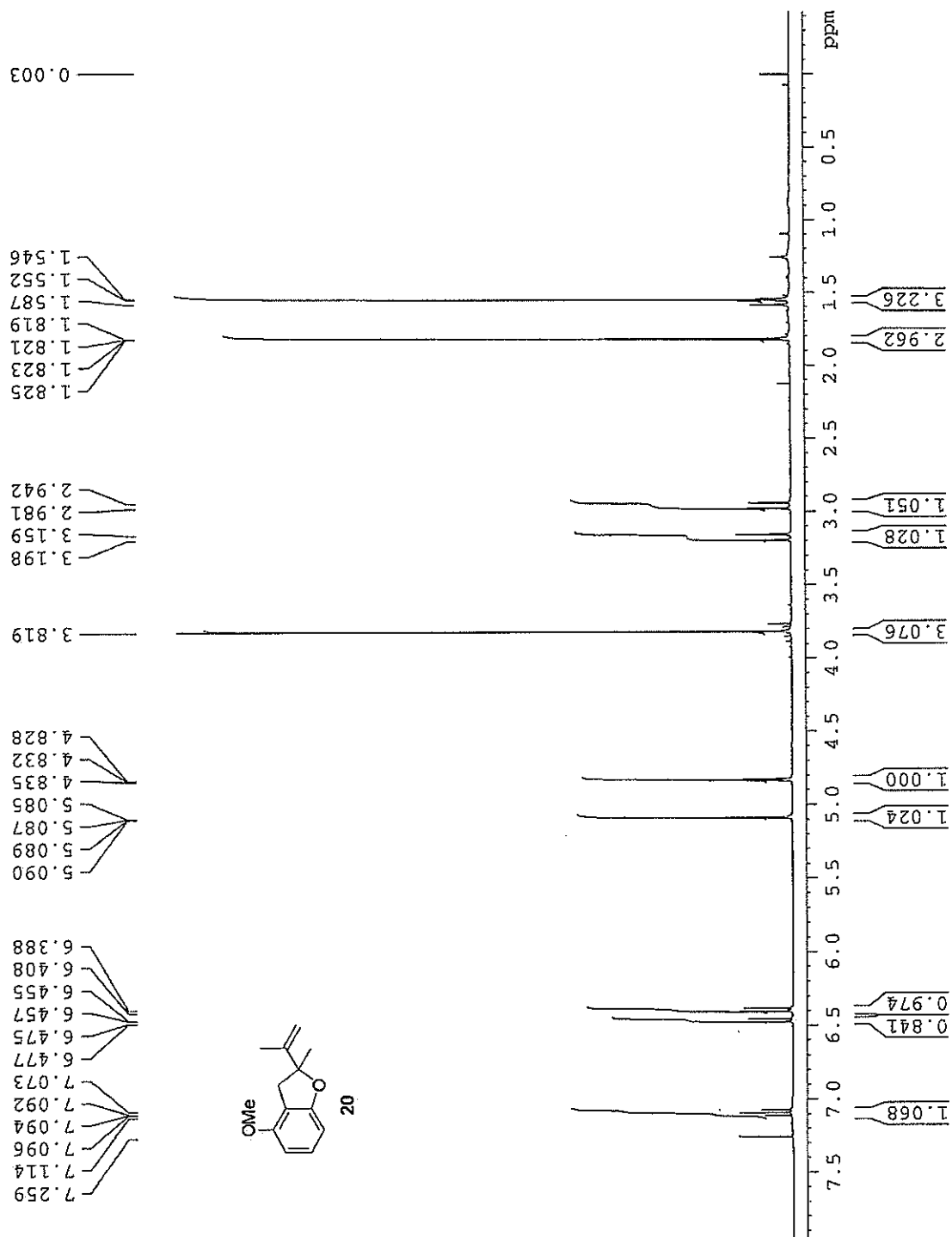


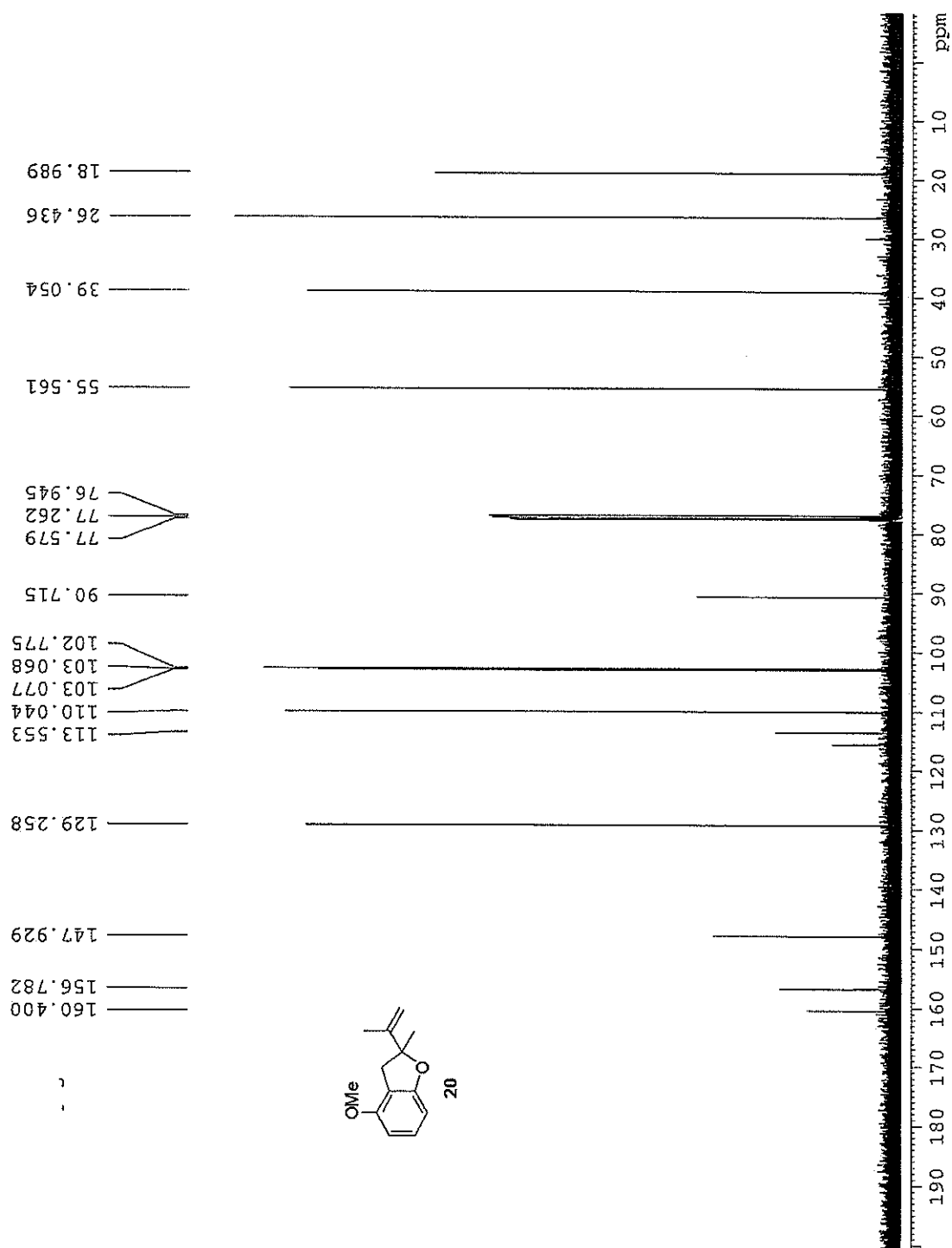


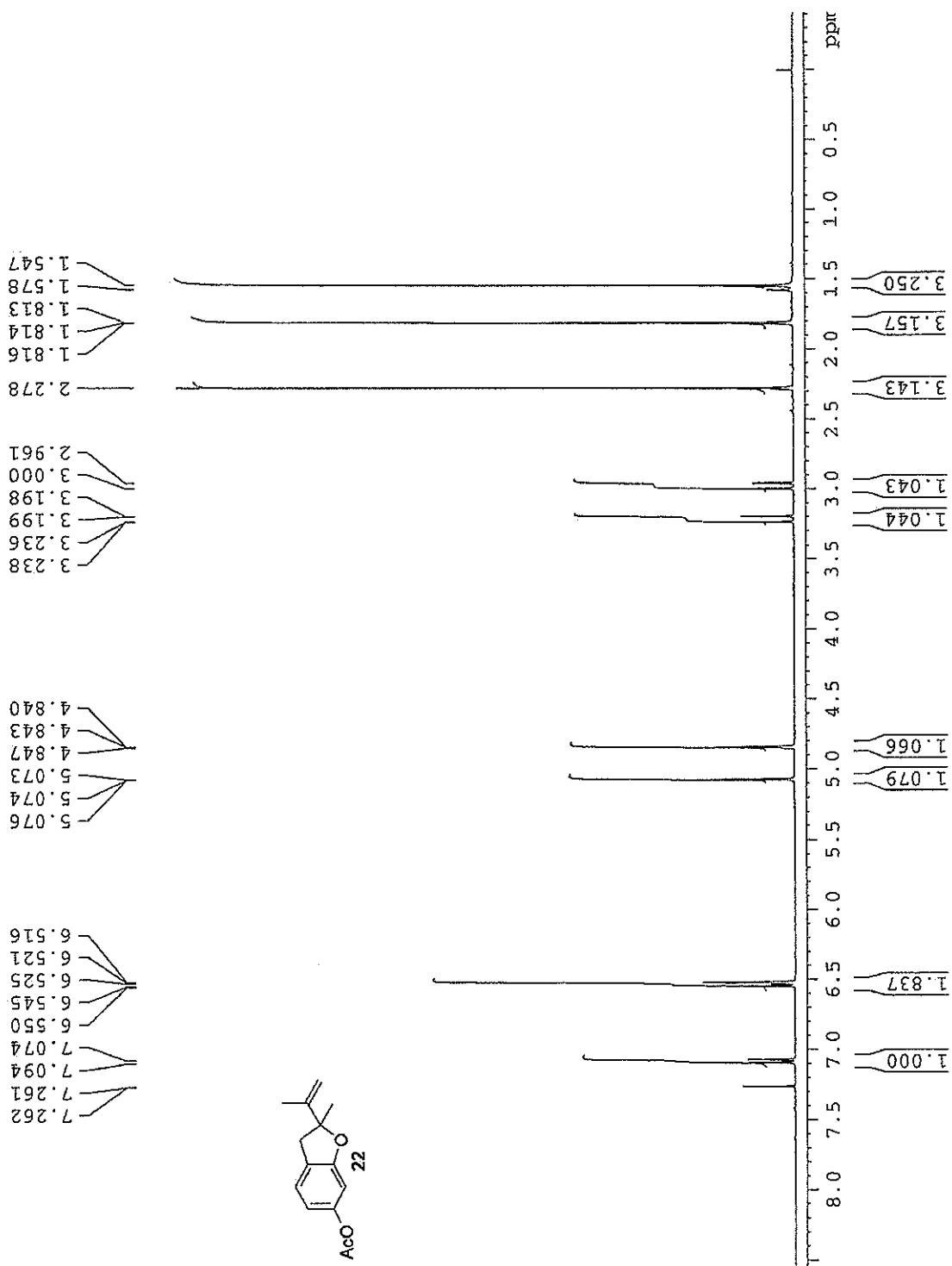


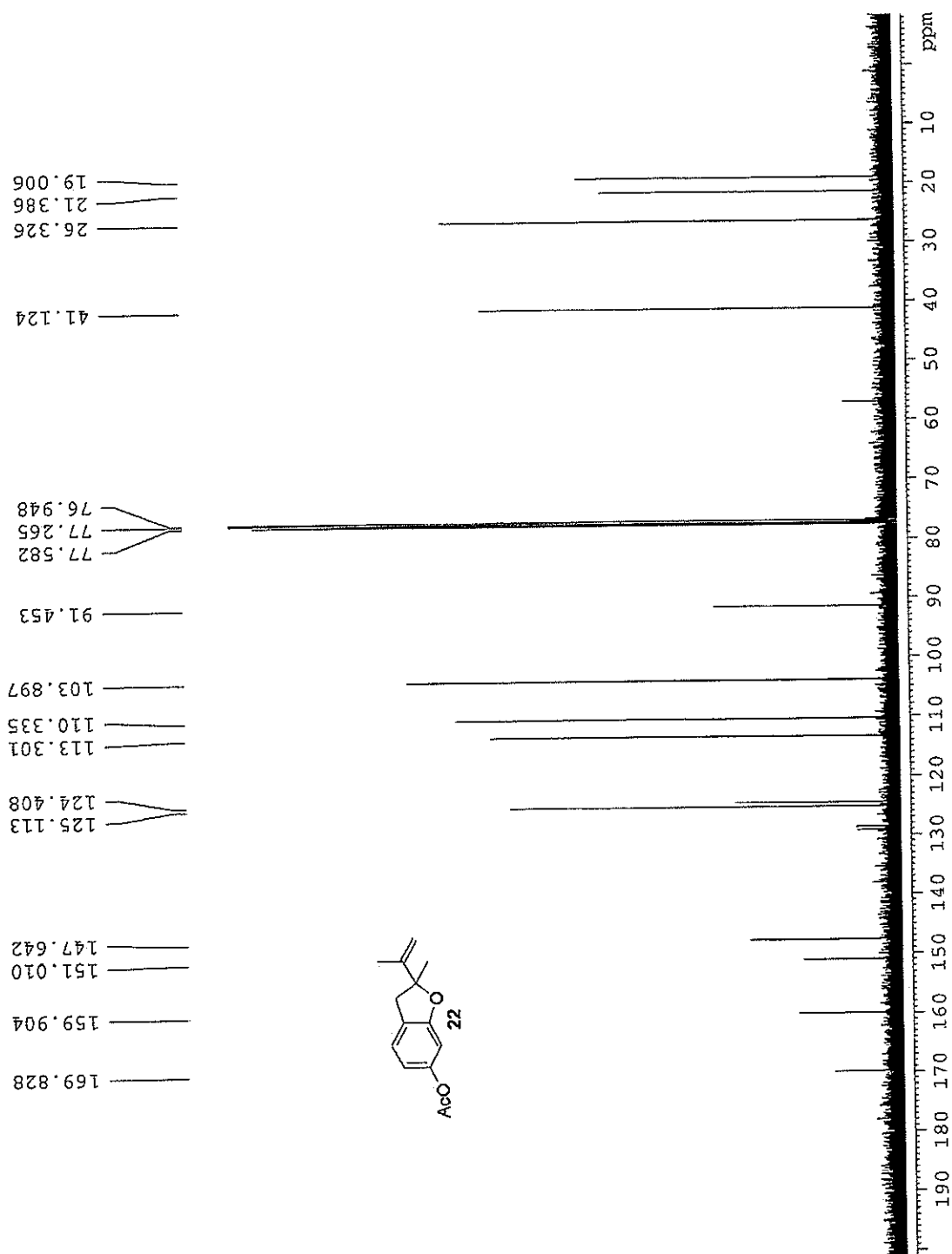


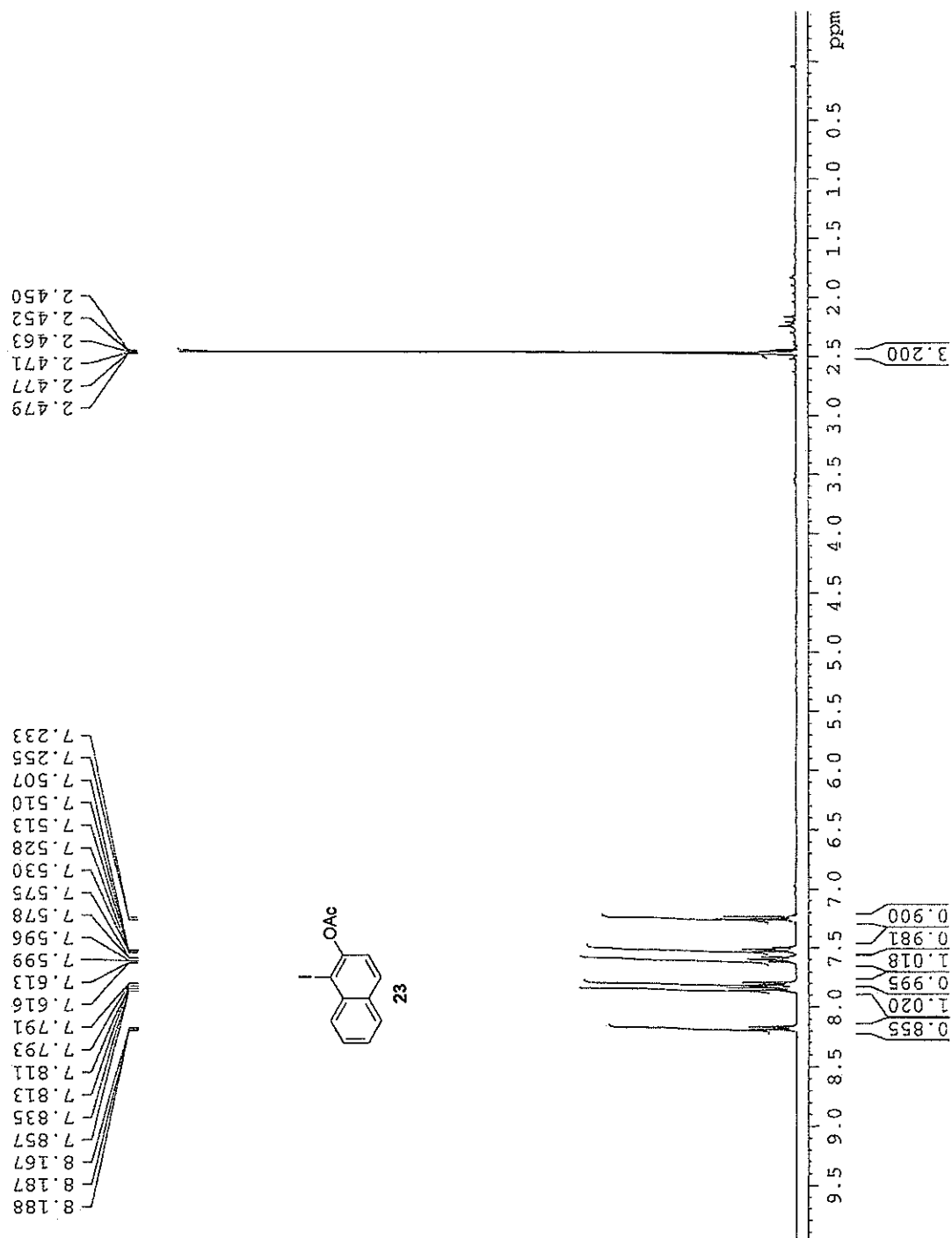


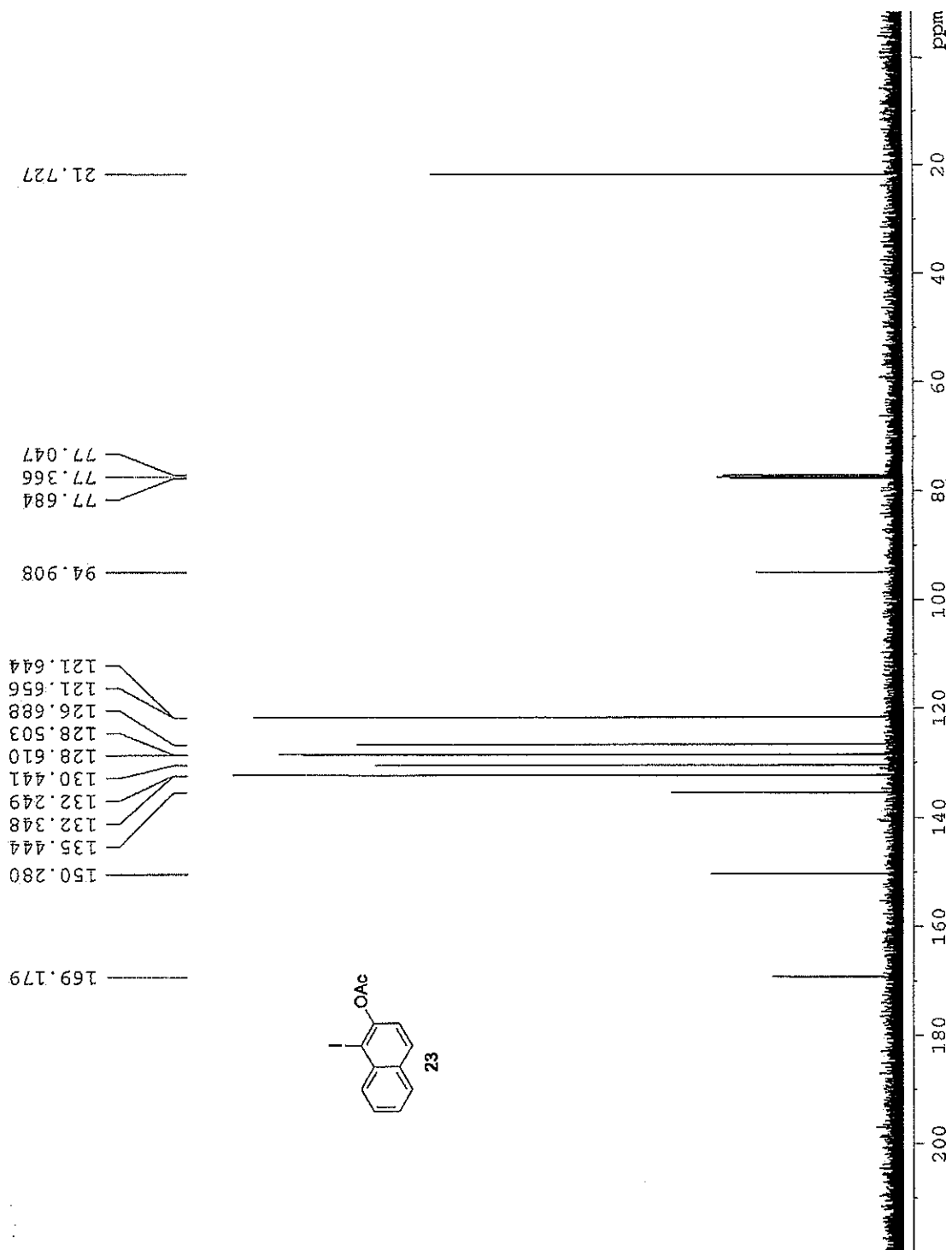


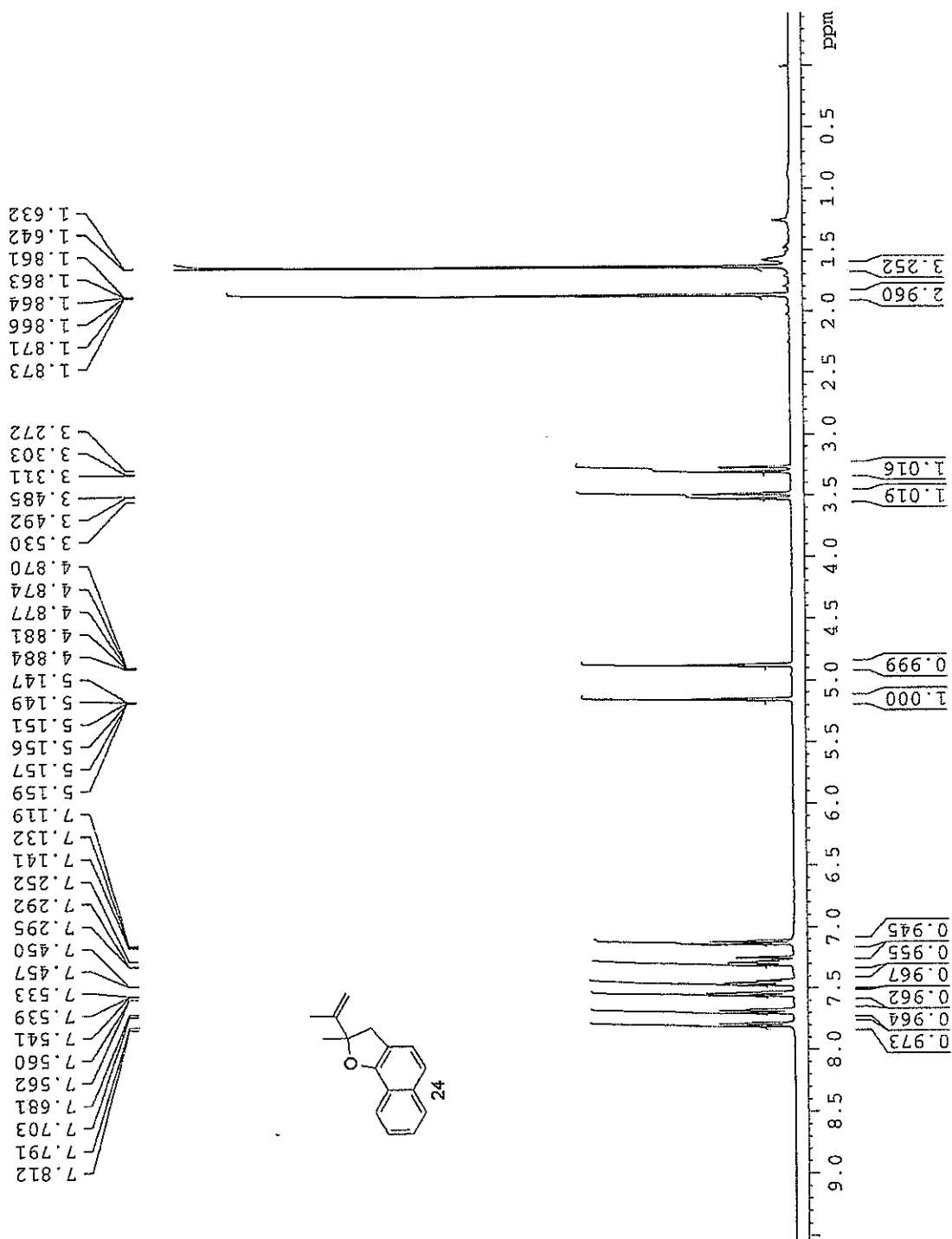


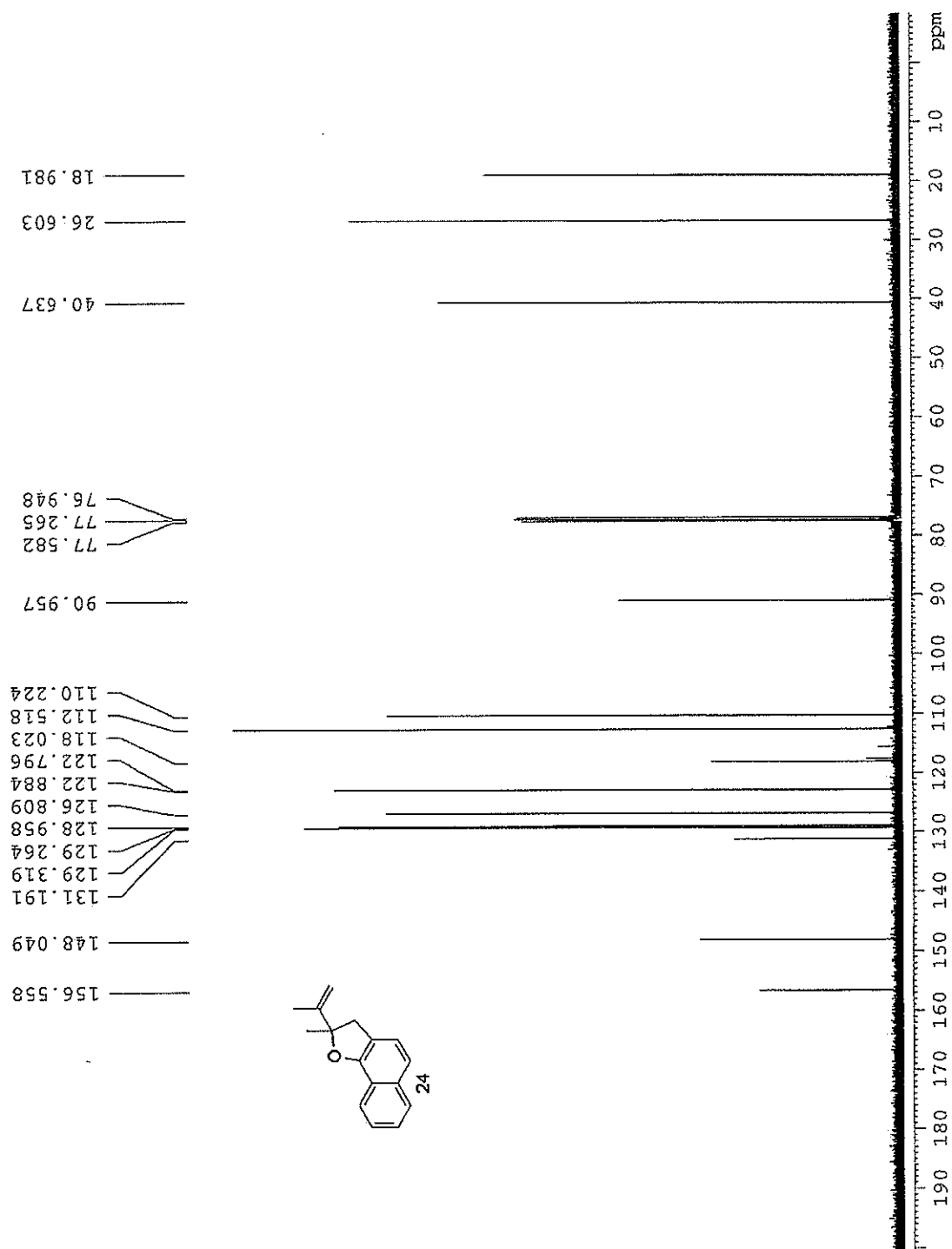












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