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Synthesis of heterocycles via palladium-catalyzed carbonylative annulation of internal and terminal alkynes

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Synthesis of heterocycles via palladium-catalyzed carbonylative annulation of internal and terminal alkynes

by

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This is to certify that the doctoral dissertation of

Dmitry Valerievich Kadnikov

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Program

To my family
To Katya

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

aq	aqueous
br s	broad singlet
n-Bu	butyl
t-Bu	*tert*-butyl
cat	catalytic
calcd	calculated
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
eq	equation
equiv	equivalent
Et	ethyl
h	hours
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared
m	multiplet

m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
ml	milliliter
mol	mole(s)
mp	melting point
NMR	nuclear magnetic resonance
o	ortho
Ph	phenyl
q	quartet
s	singlet
satd	saturated
t	triplet
TBDMS	*tert*-butyldimethylsilyl
Ts	*p*-toluenesulfonyl

GENERAL INTRODUCTION

The use of transition metal complexes in general, and palladium complexes in particular, has revolutionized synthetic organic chemistry. Among the many advantages of palladium complexes are tolerance of a wide variety of organic functional groups, relative stability to moisture and air, and the possibility to fine tune their reactivity by proper choice of the ligands, bases and other additives. However, probably the most important feature of transition metal catalysis that has attracted the attention of synthetic organic chemists and led to the development of such an astonishing number of versatile new synthetic methods is the novel and unprecedented modes of reactivity. Functional groups, which previously have been of limited synthetic utility, are now widely used to construct carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon-sulfur bonds.

One of the classes of organic compounds enjoying this renaissance are unsaturated compounds, such as alkenes, allenes, various other dienes, alkynes, and carbon monoxide. The best known transition metal-catalyzed reactions, such as the Heck or Pauson-Khand reactions, utilize this class of organic compounds. This new chemistry exploits the propensity of unsaturated molecules to insert into transition metal-carbon bonds. In the last fifteen years, the Larock group has extensively studied the palladium-catalyzed reactions of allenes; 1,3-, 1,4- and other dienes; alkynes and other unsaturated molecules with a variety of aryl and vinylic halides bearing a neighboring nucleophilic substituent. This methodology has been successfully developed as an efficient and versatile way to synthesize a wide variety of carbo- and heterocyclic compounds.

This dissertation serves to expand this methodology to encompass the three-component processes involving an aryl iodide, an alkyne and carbon monoxide. It is

organized into three different papers that are suitable for publication. The author of this dissertation was the primary investigator and author of each of the papers.

Dissertation Organization

This dissertation is divided into three chapters. Each of the chapters is written following the *Journal of Organic Chemistry* guidelines for a full paper, and consists of an abstract, introduction, results and discussion, conclusions, experimental section, acknowledgements, and references.

Chapter I describes the synthesis of 3,4-disubstituted coumarins by the palladium-catalyzed carbonylative annulation of internal alkynes by *o*-iodophenols. The transformation requires only 1 atm of CO, and the use of an unhindered pyridine base is crucial for the success of the reaction. A wide variety of iodophenols and internal alkynes are utilized in this process, although unsymmetrical alkynes afford mixtures of regioisomers. The process exhibits unusual chemoselectivity in that the alkyne inserts into the arylpalladium bond prior to carbon monoxide. Studies to determine the origin of such chemoselectivity are also described in this chapter.

Chapter II presents an extension of the above methodology to the synthesis of 3,4-disubstituted 2(1*H*)-quinolones by utilizing *N*-substituted *o*-iodoanilines as annulating agents, instead of *o*-iodophenols. The nature of the nitrogen substituent is the main factor determining the success of the process. The process also tolerates a variety of functional groups, but suffers from poor regioselectivity.

Chapter III examines the possibility of using terminal alkynes in the synthesis of coumarins and 2(1*H*)-quinolones and shows that the reaction conditions developed in the

previous chapters of this dissertation are effective for this class of alkynes as well. Even though the yields of the desired products are modest, this process represents one of the few known examples of insertion of terminal alkynes into the carbon-palladium bond.

The general conclusion summarizes the scope and limitations of the carbonylative annulation methodology, and discusses the important features that tie all of the chapters together. Finally, ^{1}H and ^{13}C spectra for all new compounds are compiled in Appendices A-C of this dissertation.

CHAPTER I. SYNTHESIS OF COUMARINS VIA PALLADIUM-CATALYZED CARBONYLATIVE ANNULATION OF INTERNAL ALKYNES BY *o*-IODOPHENOLS

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

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Abstract

The palladium-catalyzed annulation of internal alkynes by *o*-iodophenols in the presence of carbon monoxide results in the exclusive formation of coumarins **12**. No isomeric chromones **13** have been observed. One atmosphere of carbon monoxide is sufficient for this process. The use of a sterically unhindered pyridine base is essential to achieve high yields. The best reaction conditions utilize 0.5 mmol of *o*-iodophenol, 5 equiv of alkyne, 5 mol % of $Pd(OAc)_2$, 2 equiv of pyridine, 1 equiv of *n*-Bu_4NCl in 5 ml of DMF at 120 °C.

A wide variety of 3,4-disubstituted coumarins containing alkyl, aryl, silyl, alkoxy, acyl, and ester groups have been prepared in moderate to good yields. However, mixtures of regioisomers have been obtained when unsymmetrical alkynes are employed. Iodophenols with electron-withdrawing and electron-donating substituents and 3-iodo-2-pyridone are effective in this annulation process.

The reaction is believed to proceed via (1) oxidative addition of *o*-iodophenol to Pd(0), (2) insertion of the alkyne triple bond into the arylpalladium bond, (3) insertion of carbon monoxide into the carbon-palladium bond, and (4) nucleophilic attack of the phenolic oxygen on the carbonyl carbon of the acylpalladium complex with simultaneous regeneration of the Pd(0) catalyst. This annulation process is the first example of the insertion of an alkyne occurring in preference to the insertion of carbon monoxide.

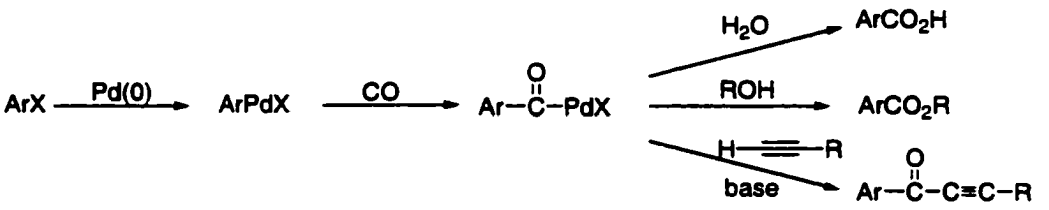
Introduction

The development of methods for the formation of several carbon-carbon and/or carbon-heteroatom bonds in one reaction is one of the most important goals of the synthetic chemist, because such processes allow assembly of complex molecular structures from relatively simple molecules in a single step. One of the fastest growing areas of research directed toward this goal is the development of transition metal-catalyzed reactions involving the insertion of unsaturated molecules, such as alkenes, alkynes, and carbon monoxide, into a carbon-metal bond. For example, the palladium-catalyzed annulation of dienes and internal alkynes by aromatic and vinylic halides bearing a neighboring nucleophilic substituent has been developed in our laboratories in the last ten years[1] as an efficient way to synthesize a wide variety of carbo- and heterocyclic compounds, such as indoles,[2] isoquinolines,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4,5a] α-pyrones,[5] indenones,[6] naphthalenes,[7] and phenanthrenes.[8]

The insertion of carbon monoxide into the arylpalladium bond leading to the formation of an acylpalladium complex is now a ubiquitous process in organic synthesis.[9]

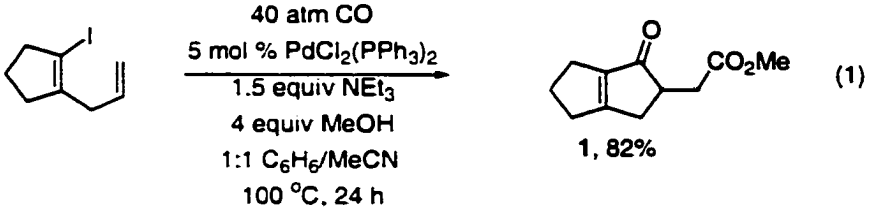
Reactions of the resulting acylpalladium complexes with various nucleophiles are among the most useful methods of synthesis of aryl carbonyl compounds known (Scheme 1). However,

Scheme 1

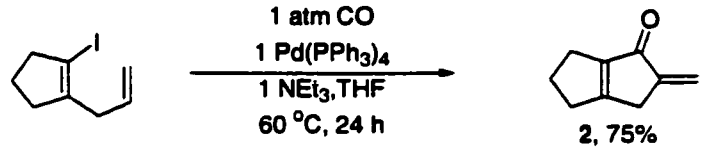


the consecutive insertion of carbon monoxide and unsaturated hydrocarbons (alkenes and alkynes) into the carbon-palladium bond has received relatively little attention, and factors controlling the sequence of insertion are not well understood.

Negishi and co-workers have extensively studied the intramolecular carbonylation of aryl and vinylic halides with substituents containing carbon-carbon double bonds.[10] When these reactions are run in the presence of an external nucleophile, usually methanol, successive insertion of carbon monoxide, a double bond, and another molecule of carbon monoxide into a carbon-palladium bond, followed by trapping of the final acylpalladium complex with methanol leads to the formation of keto esters, such as **1** (eq 1). In the absence of an external nucleophile, insertion of the second carbon monoxide molecule is not observed and dienones, such as **2**, are isolated (eq 2). In many cases, especially when aryl iodides have been employed, complex mixtures of products have been obtained.

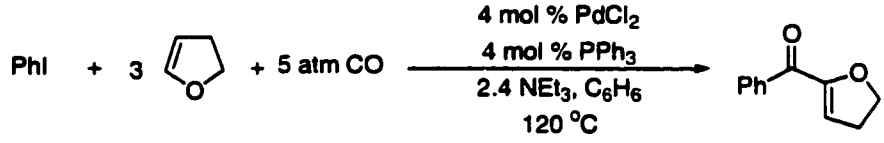


(1)



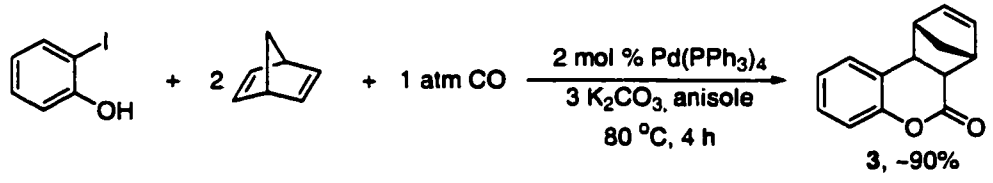
(2)

Only a few intermolecular reactions involving carbon monoxide and alkenes are known. Miura reported the palladium-catalyzed synthesis of ketones, in which the insertion of CO occurs prior to the insertion of the cycloalkenes (eq 3).[11]



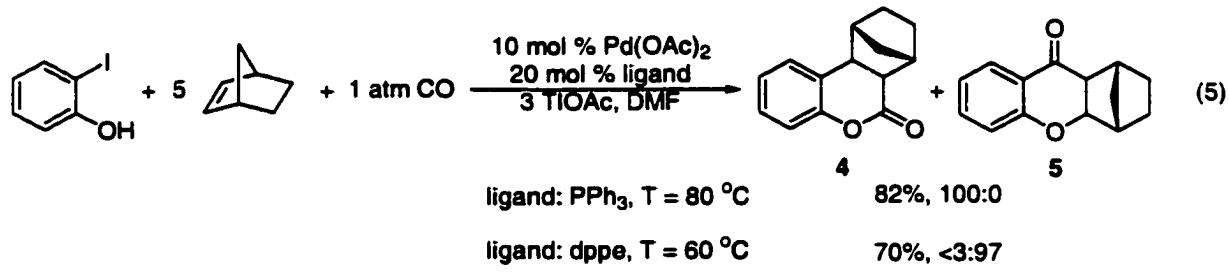
(3)

Several examples of annulation processes involving carbon monoxide and alkenes have been reported. Chiusoli found that the palladium-catalyzed reaction of *o*-iodophenols with norbornadiene under 1 atm of carbon monoxide results in the formation of **3** by a process obviously involving alkene insertion prior to CO insertion (eq 4).[12] Grigg observed



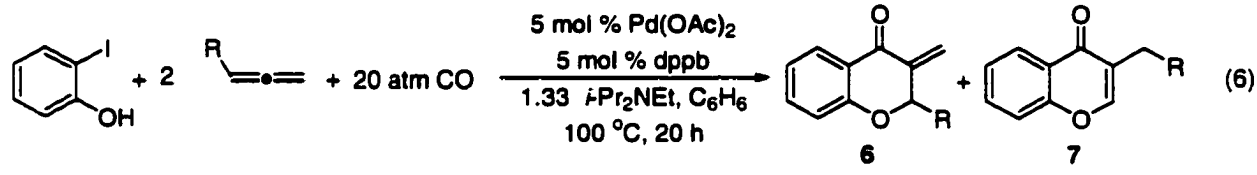
(4)

the same order of insertion in the reactions of norbornene with 5-iodovanillin and *N*-benzyl-*o*-iodoaniline in the presence of 1 atm of CO and 5 mol % of $Pd(OAc)_2$.[13] Fiaud and co-workers established that the sequence of insertion of norbornene and carbon monoxide into the carbon-palladium bond can be controlled by the choice of the phosphine added and the reaction temperature (eq 5).[14] The use of triphenylphosphine and higher temperatures favors the insertion of norbornene, while the use of chelating phosphines and lower temperatures favors the insertion of carbon monoxide.



(5)

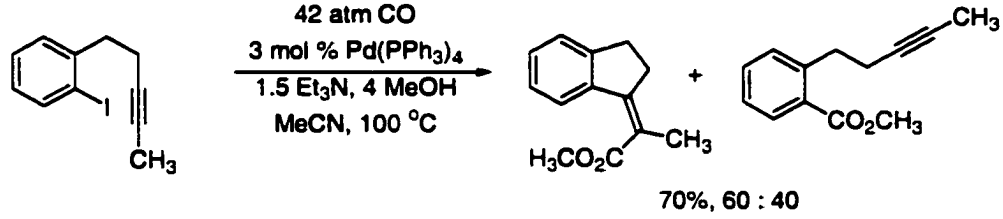
Alper reported that the reaction of *o*-iodophenol with allenes under 20 atm of carbon monoxide catalyzed by 5 mol % of $Pd(OAc)_2$ results in the exclusive formation of benzopyran-4-one derivatives **6** or **7**, depending on the substituent on the double bond (eq 6).[15] Alkyl-substituted allenes, such as 1,2-nonadiene, form exclusively compound **6**, while



(6)

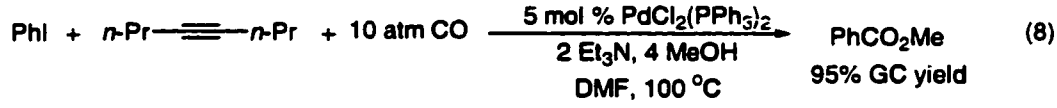
electron-poor allenes, e.g. ethyl 2,3-butadienoate (R = CO_2Et), react to give compound **7**. Electron-rich allenes (R = OCH_3) failed to react under these reaction conditions.

Even fewer examples of reactions involving carbon monoxide and carbon-carbon triple bonds are known. Negishi reported that, even in an intramolecular process run under 42 atm of carbon monoxide, insertion of carbon monoxide is competitive with insertion of the alkyne (eq 7).[16] Moreover, once formed, the acylpalladium complex reacts exclusively



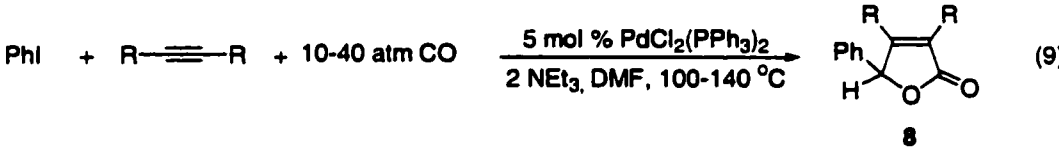
(7)

with methanol, rather than adding to the carbon-carbon triple bond. In an intermolecular version of this process (eq 8), only the product of CO insertion, followed by capture of the acylpalladium complex by methanol, has been observed.[17]



(8)

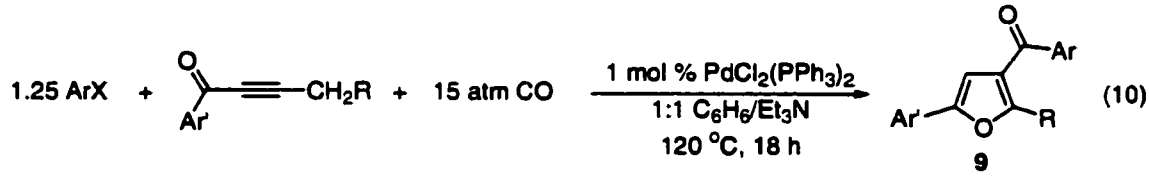
Nevertheless, intermolecular addition of an acylpalladium complex to a triple bond can be achieved in the absence of alcohols. Thus, iodobenzene reacts with an internal alkyne and carbon monoxide to form a trisubstituted 2(1*H*)-furanone **8** (eq 9).[17] In this process,



8

(9)

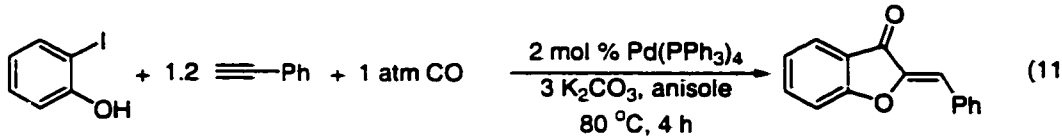
three molecules, CO, an alkyne, and another CO, insert consecutively into the arylpalladium bond. In another example reported by Miura, iodobenzene reacts with 1-aryl-2-alkyn-1-ones and carbon monoxide to give rise to 2-alkyl-3-aroyl-5-arylfurans **9** (eq 10).[18] Again, insertion of carbon monoxide occurs prior to insertion of the carbon-carbon triple bond.



9

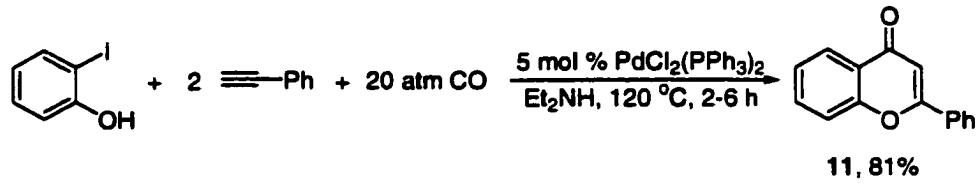
(10)

Terminal alkynes also undergo palladium-catalyzed annulation with *o*-iodophenol in the presence of carbon monoxide forming either aurones (**10**)[12a,19] or chromones (**11**)[19-21] depending on the reaction conditions (eqs 11 and 12). These reactions, however, follow a



10, 82%

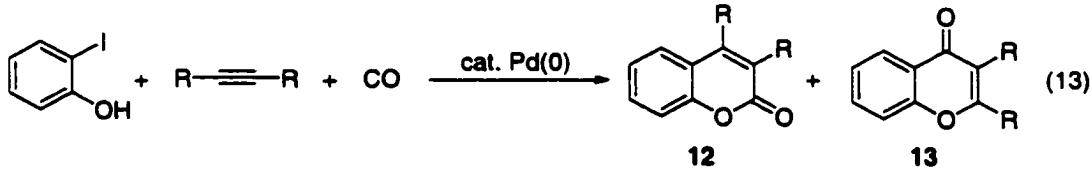
(11)



11, 81% (12)

path different from that of the reactions of internal alkynes. The terminal alkyne does not insert into the carbon-palladium bond, but instead acts as a nucleophile attacking the carbonyl carbon of the acylpalladium complex. This leads to the formation of an aryl alkynyl ketone, which then undergoes either 5-*exo*- or 6-*endo*-cyclization. It has been proposed that 5-*exo*-cyclization is catalyzed by palladium, while 6-*endo*-cyclization proceeds by an addition-elimination mechanism involving a β-aminovinyl ketone as an intermediate.

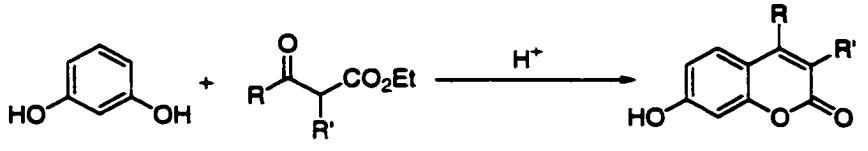
Our interest in palladium-catalyzed annulations of internal alkynes prompted us to explore the reaction of *o*-iodophenols with internal alkynes in the presence of carbon monoxide (eq 13). Depending on the sequence of insertion of the alkyne and carbon



12 13 (13)

monoxide into the carbon-palladium bond, formation of one of the two isomeric heterocycles, coumarins (**12**) or chromones (**13**), is expected.

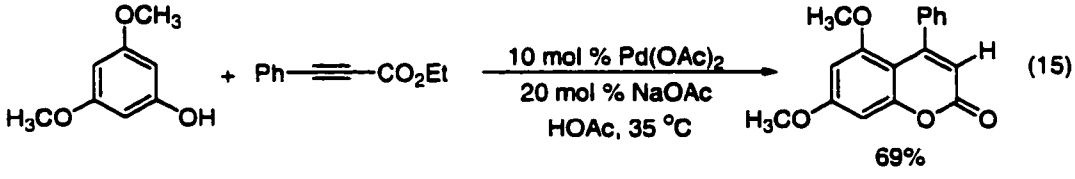
Naturally-occurring coumarins[22] and chromones possess biological activity, including anticancer and HIV-1-specific reverse transcriptase inhibitor properties. However, the existing methods for the synthesis of coumarins suffer major disadvantages. Two classical methods for the synthesis of coumarins, the Perkin[23] and Pechman reactions[24] (eq 14),



(14)

require the use of stoichiometric amounts of strong acids and often high temperatures. Only simple alkyl substituents can be installed at C-3, since they are introduced into the starting β-ketoester by alkylation, and few functional groups in general can tolerate the harsh reaction conditions. Moreover, phenols with electron-withdrawing substituents fail to react in these reactions. Many other syntheses of coumarins also utilize strong acidic or basic conditions, consist of several steps, and are often limited to the synthesis of monosubstituted coumarins.

Only a few palladium-catalyzed approaches to the synthesis of coumarins have been reported. Chiusoli developed a two-step synthesis, in which compound **3**, prepared by carbonylative annulation of norbornadiene by *o*-iodophenol (eq 4), was heated at 150 °C leading to the extrusion of cyclopentadiene and formation of coumarin.[12b] Another approach is based on the intramolecular Heck reaction of *o*-iodophenyl 3-alkenoates.[25] However, the scope of these processes is very limited with only a few examples being reported. A more general approach involves the palladium(II)-catalyzed reaction of phenols with 2-alkynoates (eq 15).[26] Still, only polyoxygenated phenols have been used, and the reaction is limited to the synthesis of 4-monosubstituted coumarins.

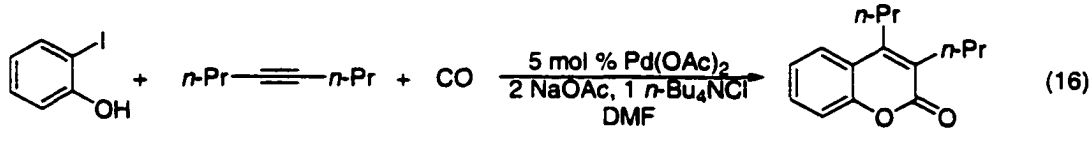


(15)

Herein, we report that the palladium-catalyzed carbonylative annulation of internal alkynes by *o*-iodophenols affords a very efficient synthesis of 3,4-disubstituted coumarins bearing a variety of functional groups.

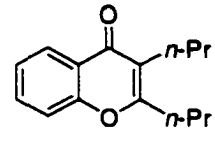
Results and Discussion

Optimization of the Reaction Conditions. In our initial studies the reaction of *o*-iodophenol with diphenylacetylene under one atmosphere of carbon monoxide was chosen as a model system. The reactions were run using reaction conditions similar to those used previously in other annulation reactions [5 mol % $Pd(OAc)_2$; NaOAc, Na_2CO_3, or *i*-Pr_2NEt as bases; with and without PPh_3; *n*-Bu_4NCl or LiCl; in DMF at 100 °C]. In no instances have any of the desired products been observed, and the starting materials were recovered. Next, conditions for the carbonylative annulation of norbornene [5 mol % $Pd(OAc)_2$, 5 mol % dppp, 3 equiv of TlOAc in DMF at 60 and 100 °C][14] were examined using diphenylacetylene and 4-octyne. Only in the reaction of 4-octyne run at 100 °C for 72 h was the desired 3,4-di-*n*-propylcoumarin (**14**) observed, albeit in a very low yield (< 10%) (eq 16). The isomeric



(16)

14



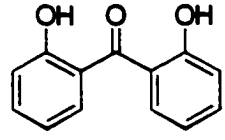
15

2,3-di-*n*-propylchromone (**15**) was not detected. When the same reaction was run using NaOAc and 10 mol % PPh_3, coumarin **14** was isolated in only a 4% yield. However, the yield improved significantly (23%) when the reaction temperature was raised to 120 °C.

At this point, we decided to systematically study the effects of various reaction parameters on the outcome of the reaction using the reaction with 4-octyne as a model system. First, the effect of the base has been studied. The reaction conditions employed are

0.5 mmol of *o*-iodophenol, 2 equiv of 4-octyne, 1 atm of CO, 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, 2 equiv of base, 1 equiv of *n*-Bu_4NCl in 10 ml of DMF at 120 °C for 24 h. The results are summarized in Table 1.

Inorganic bases have been examined first (entries 1-11). Low yields of the desired coumarin **14** have been obtained in all cases, and the isomeric chromone **15** has not been detected. Two by-products were isolated from virtually every reaction. 2,2'-Dihydroxybenzophenone (**16**) was obtained in 5% yield when NaOAc was used as the base (entry 10). With any other base, 9-xanthone (**17**) was the only by-product, obtained usually in 3 to 9% yields, depending on the base used. With $NaHCO_3$ as the base, 9-xanthone was obtained in a 19% yield, a yield higher than that of coumarin **14** (12%, entry 4).



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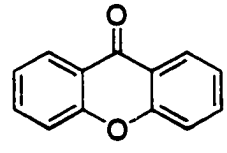
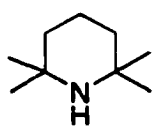
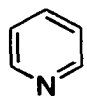


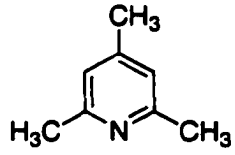
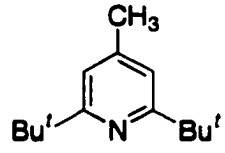
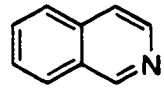
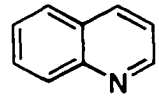
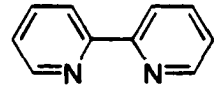
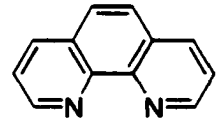
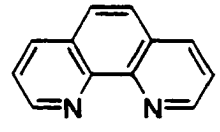
17

Among the bases examined, carbonates generally gave better yields of **14** than bicarbonates and acetates, although the nature of the cation seems to have a larger effect on the yield. The best yields have been obtained with cesium salts (30 and 22%, entries 9 and 11), although NaOAc (23%, entry 10) and K_2CO_3 (21%, entry 8) gave similar results. Since poor solubility of many of these salts in DMF might be one of the reasons for the low yields, sodium benzoate was used as a base (entry 6). However, no improvement was observed. The yield obtained with NaO_2CPh (16%) is lower than that obtained with K_2CO_3 (21%, entry 8), a salt very poorly soluble in DMF.

It is likely that inorganic bases react with the intermediate acylpalladium complex during the course of the reaction, thus lowering the yield of the desired product. Therefore,

Table 1. Effect of base on the carbonylative annulation of 4-octyne with *o*-iodophenol (eq 16).

entry	base	% yield of **14**
1	KOAc	3
2	LiOAc	7
3	TlOAc	9
4	$NaHCO_3$	12
5	$KHCO_3$	13
6	NaO_2CPh	16
7	Na_2CO_3	17
8	K_2CO_3	21
9	CsOAc	22
10	NaOAc	23
11	Cs_2CO_3	30
12	Et_3N	12
13	*i*-Pr_2NEt	13
14		15
15	DBU	4
16		37

entry	base	% yield of **14**
17		5
18		37
19		20
20		38
21		27
22		7
23		0
24[a]		33

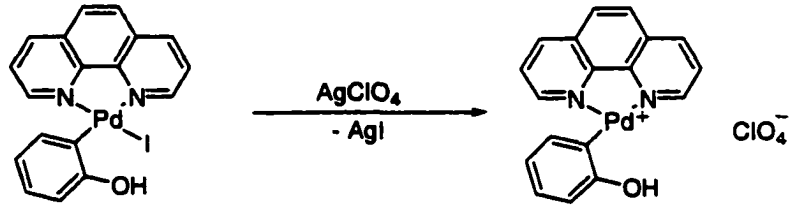
[a] 1.1 Equiv of $AgClO_4$ and no *n*-Bu_4NCl have been used in this reaction.

organic amines were examined as bases. First, Et_3N and *i*-Pr_2NEt were examined (entries 12 and 13), since these bases are used very often in carbonylation reactions.[10,15,18]

However, only low yields of coumarin **14** were obtained using these bases. It may be that coordination of the amine to the palladium atom, followed by β-hydride elimination,

leads to formation of a palladium hydride complex and decomposition of the catalyst, thus resulting in the low yields of **14**. Therefore, amines unable to undergo β-hydride elimination were examined (entries 14-17). Only pyridine improved the yield of the coumarin (37%, entry 16). The appearance of the reaction mixture also changed dramatically. The reaction mixture retained a yellow color throughout the reaction, and no precipitation of palladium black was observed, while in all previous reactions the reaction mixture turned brown and palladium black precipitated after only a few hours of reaction.

Since only pyridine improved the yield, it is unlikely that β-hydride elimination is the reason for the low yields with other amines. Therefore, to understand the effect of pyridine on the reaction, sterically hindered pyridines, along with quinoline and isoquinoline, have been examined as bases (entries 18-21). The yield of **14** decreases with an increase in the steric hindrance around the nitrogen atom (compare 2,4,6-collidine with 2,6-di-*tert*-butyl-4-methylpyridine, entries 18 and 19, and isoquinoline with quinoline, entries 20 and 21). These results suggest that pyridine serves as a ligand on the palladium metal. This idea was further supported by experiments with bidentate pyridine ligands, 2,2'-bipyridyl and 1,10-phenanthroline (entries 22-24). The use of these bases, instead of pyridine, results in a precipitous decrease in the yield of **14** (entries 22 and 23). However, the addition of $AgClO_4$ to the reaction employing 1,10-phenanthroline as the base afforded coumarin **14** in a 33% yield. These results can be rationalized by invoking the formation of complex **18** after oxidative addition of *o*-iodophenol to a palladium(0) complex. Complex **18** lacks labile ligands that can easily dissociate to open a coordination site necessary for the reaction to proceed. The silver cation presumably removes the iodide atom from this complex, thus opening a coordination site and allowing the reaction to proceed (eq 17).

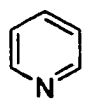


18 (17)

The effect of an added phosphine ligand and the stoichiometry of the reagents on the outcome of the reaction have also been examined. The results are summarized in Table 2. The reaction conditions employed here were 0.5 mmol of *o*-iodophenol, 1 atm of CO, 5 mol % of $Pd(OAc)_2$, 2 equiv of base, 1 equiv of *n*-Bu_4NCl in 10 ml of DMF at 120 °C for 24 h. The initial studies were conducted before the cesium salts or pyridine bases were examined and, therefore, NaOAc and K_2CO_3 were used as the bases during this optimization work. Later on, these experiments were repeated using pyridine as the base.

First, the phosphine ligand was varied (entries 1-12). With NaOAc as the base, removal of triphenylphosphine from the reaction (entry 1) did not improve the yield of coumarin **14**, but increased the amount of by-product **16**, which was obtained in a 16% yield. It has been reported that chelating diphosphines, such as 1,3-bis(diphenylphosphino)propane (dppp), improve the yield of some carbonylation reactions.[27] Therefore, various chelating phosphines have been examined with NaOAc as the base (entries 5-7), but no significant changes in the yield of the desired product were observed. Likewise, no changes were observed when dppf was used in reactions with K_2CO_3 (entry 10, compare with entry 8) or pyridine (entry 12, compare with entry 11). To gain a better understanding of the effect of the phosphine, a phosphine that is a stronger electron donor than PPh_3, but has a similar size, namely tri(*o*-furyl)phosphine, was examined with pyridine as the base (entry 13). A slight decrease in the yield of **14** was observed. In contrast, a reaction run without any phosphine

Table 2. The effect of phosphine and the reagent stoichiometry (eq 16).

entry	base	phosphine (mol %)	alkyne equiv	% yield of **14**
1	NaOAc	none	2	23
2		PPh_3 (10)		23
3			1	26
4			5	25
5		dppe (5)	2	22
6		dppp (5)		21
7		dppf (5)		25
8	K_2CO_3	PPh_3 (10)		21
9		none		19
10		dppf (5)		27
11		PPh_3 (10)		37
12		dppf (5)		35
13		P(2-furyl)$_3$ (10)		31
14		none		43
15			3	50
16			5	63
17			10	67

resulted in a slightly higher yield of **14** (entry 14). These observations also suggest that pyridine serves as a ligand on the palladium metal, and this coordination promotes the

annulation reaction. Therefore, further experiments with pyridine as a base were run without any phosphine present.

Optimization of the stoichiometry of the reactants was conducted next. The results are shown in Table 2, entries 3, 4 and 15-17. When NaOAc and PPh_3 were employed, neither a decrease, nor an increase, in the amount of 4-octyne resulted in a change in the yield of coumarin **14** (entries 3 and 4). On the contrary, in the reactions using pyridine as the base, the yield of **14** increased significantly as the amount of 4-octyne increased (entries 15-17).

In these reactions, unreacted alkyne was never recovered from the reaction mixture, most likely due to the volatility of 4-octyne. Indeed, less volatile alkynes, such as 1-phenyl-1-butyne, have been recovered. For example, when 5 equiv of 1-phenyl-1-butyne was used, the corresponding coumarin was obtained in a 78% yield, and 40% of the alkyne has been recovered. In the reaction with 2 equiv of 1-phenyl-1-butyne, the yield of coumarin dropped to 46%, but still about 30% of the alkyne was recovered. These observations further support the need for an excess of the alkyne.

Having established the optimal base, phosphine, and stoichiometry for this process, we explored various palladium catalysts. The results are presented in Table 3. Although a palladium(II) salt has been used as the catalyst, the reaction is actually catalyzed by palladium(0) (see the discussion of the mechanism below). Therefore, two palladium(0) complexes, $Pd(dba)_2$ and $Pd(PPh_3)_4$, have been examined in the reaction. The former complex produced coumarin **14** in almost the same yield as $Pd(OAc)_2$ (entry 2), while the latter gave a substantially lower yield (entry 3). This result is likely due to the lower reactivity of $Pd(PPh_3)_4$. The active catalyst is probably a 14-electron complex PdL_2, and

Table 3. The effect of the palladium catalyst on the yield of 14 (eq 16).

entry	palladium catalyst	% yield of **14**
1	$Pd(OAc)_2$	63
2	$Pd(dba)_2$	60
3	$Pd(PPh_3)_4$	40

dissociation of two phosphine ligands occurs much slower than dissociation of one dibenzylideneacetone ligand.

The amount of pyridine and a chloride source were optimized next. The results are summarized in Table 4. Analysis of the data presented in the table allows one to conclude that an increase in the amount of pyridine affects the yield of the reaction differently in the presence and absence of *n*-Bu_4NCl. In the absence of *n*-Bu_4NCl (entries 1-4), there is virtually no dependence of the reaction yield on the amount of pyridine used. An increase in the amount of pyridine from 1 to 2 to 3 equivalents results in only a slight increase in the yield (55 to 59 to 63%; entries 1, 3 and 4). When 1 equiv of *n*-Bu_4NCl is present in the reaction mixture (entries 5-9), an increase in the amount of pyridine from 1 to 1.5 equivalents leads to a significant improvement in the yield, while any further increase in the amount of pyridine has no effect on the yield of the coumarin. An increase in the amount of *n*-Bu_4NCl from 1 to 2 equiv results in a decrease in the reaction yield (entries 7 and 10). Although there is little improvement in the yield of coumarin **14** when the chloride source is added (compare entries 2 and 6, 3 and 7, etc.), the use of *n*-Bu_4NCl generally results in a cleaner reaction mixture and no precipitation of palladium black is observed. In the reactions without *n*-Bu_4NCl, a significant amount of palladium black appears already during the purging of the

Table 4. The effect of the pyridine and *n*-Bu_4NCl stoichiometry (eq 16).

entry	pyridine (equiv)	*n*-Bu_4NCl (equiv)	% yield of **14**
1	1	0	55
2	1.5	0	58
3	2	0	59
4	3	0	63
5	1	1	46
6	1.5	1	62
7	2	1	63
8	3	1	60
9	4	1	60
10	2	2	51

reaction mixture with carbon monoxide.

At this point, the main parameters of the model system have been established, and the optimized reaction conditions are 0.5 mmol of *o*-iodophenol, 5 equiv of 4-octyne, 5 mol % of $Pd(OAc)_2$, 2 equiv of pyridine and 1 equiv of *n*-Bu_4NCl. To conclude the optimization, a few other variables, such as solvent and concentration of the reagents were studied. Table 5 summarizes the results of these studies.

Three solvents that have been previously employed in palladium-catalyzed annulation reactions were examined (entries 2-4), and all of them proved to be inferior to DMF. An especially devastating effect on the outcome of the reaction was evident with DMSO, the only non-amide solvent examined. Having established DMF as the solvent of choice, we

Table 5. Effect of the solvent and the concentration of the reagents (eq 16).

entry	solvent (ml)	% yield of **14**
1	DMF (10)	63
2	DMA (10)	50
3	NMP (10)	42
4	DMSO (10)	8
5	DMF (5)	59
6	DMF (2)	47

examined the possibility of reducing the volume of the reaction mixture (entries 5 and 6). It was found that the amount of solvent could be reduced two-fold without much of a decrease in the yield of **14**, while further reduction leads to a significant decline in the yield.

Finally, we attempted to reduce the reaction temperature and/or the reaction time. The results of these studies are presented in Table 6. It can be concluded from this data that 120 °C is a temperature crucial for the success of the annulation. Even after 48 h at 100 °C (entry 2), the yield of the desired product reaches only 75% of the yield achieved after just 12 h at 120 °C (entry 3). Extending the reaction time from 12 to 24 h results in a slight improvement in the yield, while further extension results in a slight decrease in the yield (entries 3-5).

In another attempt to reduce the reaction time, the use of a larger amount of $Pd(OAc)_2$ was investigated (entries 6-8). Unexpectedly, we have been unable to improve the yield of coumarin **14**, although the reaction time has indeed been reduced. Approximately the same yields of **14** can be achieved in half the time when 10 mol % of the catalyst is employed

Table 6. The effect of the reaction temperature and reaction time (eq 16).

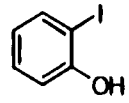
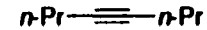
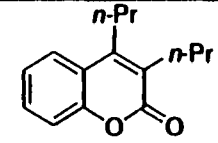
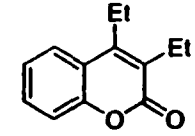
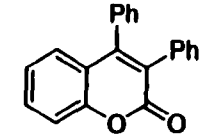
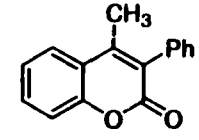
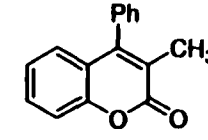
entry	mol % $Pd(OAc)_2$	temperature (°C)	time (h)	% yield of **14**
1	5	100	24	29
2			48	39
3		120	12	53
4			24	63
5			48	57
6	10		6	52
7			12	58
8			24	51

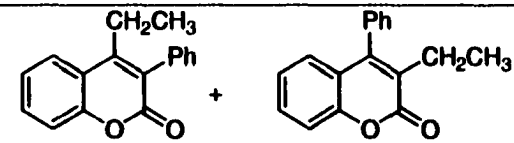
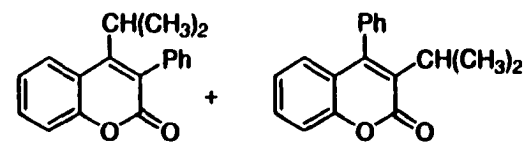
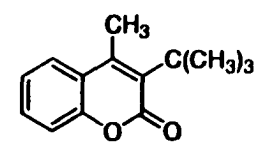
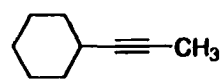
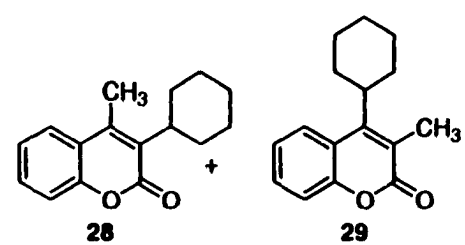
instead of 5 mol % (compare entries 3 and 6, and 4 and 7). It is noteworthy that again, after reaching a maximum at some optimal time, the yield of **14** decreases when the reaction is carried out beyond that optimal time (entry 8). Apparently, the coumarin is not completely stable under the reaction conditions. The final optimized reaction conditions for the reaction of *o*-iodophenol with 4-octyne and carbon monoxide have been determined to be 0.5 mmol of *o*-iodophenol, 5 equiv of 4-octyne, 5 mol % of $Pd(OAc)_2$, 2 equiv of pyridine, 1 equiv of *n*-Bu_4NCl in 5 ml of DMF at 120 °C for 24 h.

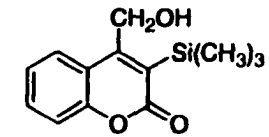
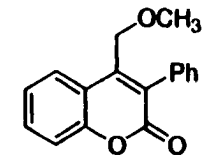
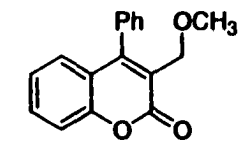
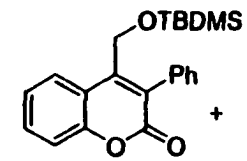
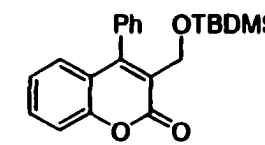
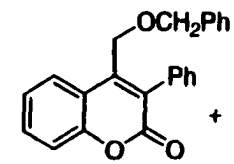
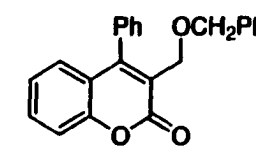
Scope and Limitations. The scope and limitations of this annulation reaction have been studied by reacting a wide variety of internal alkynes with various *o*-iodophenols under our optimized reaction conditions. The results of this study are summarized in Table 7.

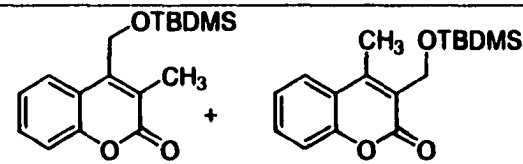
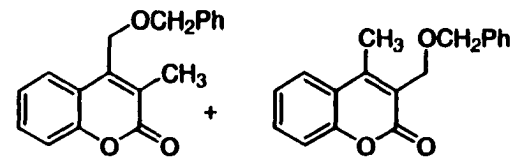
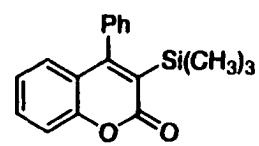
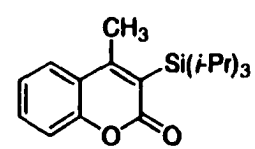
First, the carbonylative annulation of alkyl- and aryl-substituted acetylenes was investigated. Both dialkyl- (entries 1 and 2) and diaryl-substituted alkynes (entries 3 and 4)

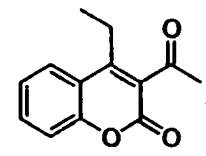
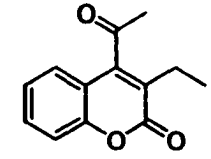
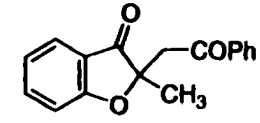
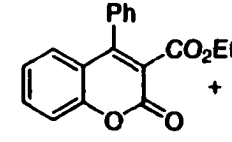
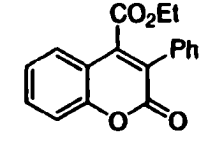
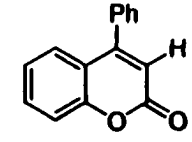
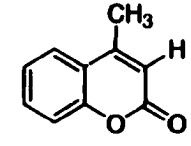
Table 7. Synthesis of coumarins by the carbonylative annulation of internal alkynes by *o*-iodophenols .[a]

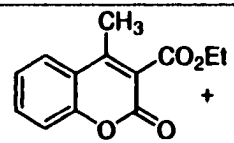
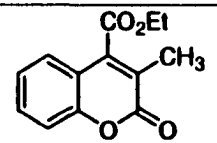
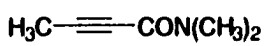
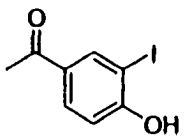
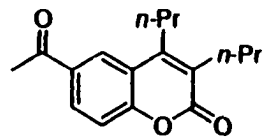
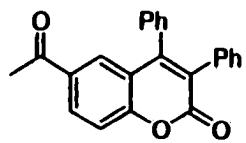
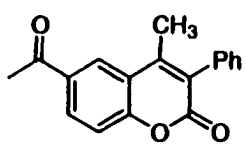
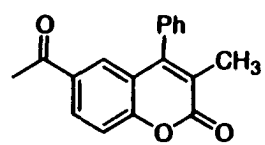
entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
1			24	 **14**	63
2				 **19**	55
3				 **20**	54
4[c]				**20**	62
5				 +  **21** **22**	72 (3.8:1)

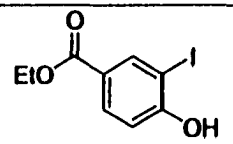
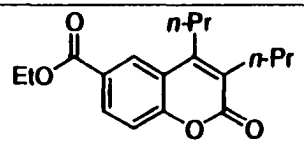
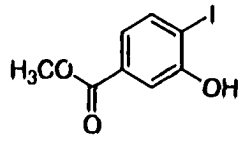
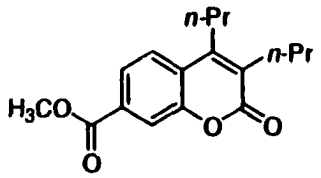
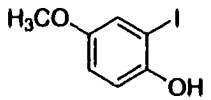
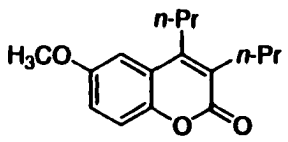
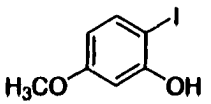
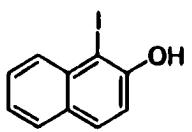
entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
6		Ph—≡—CH_2CH_3		 **23** + **24**	78 (2.6:1)
7[d]		Ph—≡—CH_2CH_3	72	**23 + 24**	47 (2.4:1)
8		Ph—≡—$CH(CH_3)_2$	24	 **25** + **26**	62 (1.7:1)
9		Ph—≡—$C(CH_3)_3$			0
10		H_3C—≡—$C(CH_3)_3$		 **27**	9
11				 **28** + **29**	57 (2.8:1)
12		Ph—≡—$C(CH_3)_2OH$			0

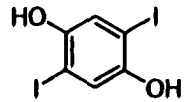
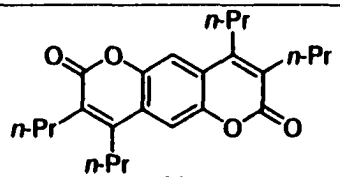
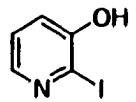
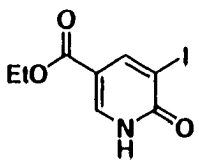
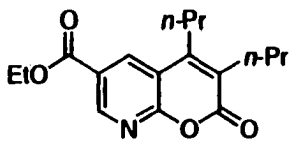
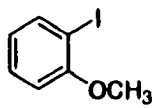
entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
13		Ph—≡—CH_2OH			0
14		H_3C—≡—CH_2OH			0
15		$(H_3C)_3Si$—≡—CH_2OH		 **30**	27
16		Ph—≡—$(CH_2)_4OH$			0
17		Ph—≡—CH_2OCH_3		 **31** +  **32**	65 (3:1)
18		Ph—≡—$CH_2OTBDMS$		 **33** +  **34**	20 (2:1)
19		Ph—≡—CH_2OCH_2Ph		 **35** +  **36**	65 (3:1)

entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
20		$H_3C-\equiv-CH_2OTBDMS$		 **37** + **38**	16 (1:1.7)
21		$H_3C-\equiv-CH_2OCH_2Ph$		 **39** + **40**	45 (1:1.4)
22		$H_3C-\equiv-CH(OCH_2CH_3)_2$			0
23		$H_3C-\equiv-Si(CH_3)_3$		 **41**	43
24		$Ph-\equiv-Si(CH_3)_3$		 **42**	20
25		$H_3C-\equiv-Si(i\text{-}Pr)_3$		 **43**	20

entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
26		$CH_3CH_2-\equiv-COCH_3$		 +  **44** **45**	61 (9:1)
27		$H_3C-\equiv-COPh$	10	 **46**	75
28		$Ph-\equiv-CO_2Et$	24	 +  + **47** **48**	45 (1:3)
				 **49**	5
29		$H_3C-\equiv-CO_2Et$	24	 + **50**	24

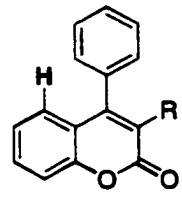
entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
				 +  **51** **52**	22 (3.4 : 1)
30				**50**	16
31	 **52**		24	 **53**	56
32			24	 **54**	48
33			24	 +  **55** **56**	57 (2.6:1)

entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
34	 **57**	*n*-Pr—≡—*n*-Pr	24	 **58**	59
35	 **59**	*n*-Pr—≡—*n*-Pr	6	 **60**	66
36	 **61**	*n*-Pr—≡—*n*-Pr	12	 **62**	62
37	 **63**	*n*-Pr—≡—*n*-Pr	24		0[c]
38	 **64**	*n*-Pr—≡—*n*-Pr	24		0[f]

entry	phenol	alkyne	time (h)	product(s)	% yield (ratio)[b]
39	 **65**	*n*-Pr—≡—*n*-Pr	24	 **66**	54
40	 **67**	*n*-Pr—≡—*n*-Pr	24		0
41	 **68**	*n*-Pr—≡—*n*-Pr	24	 **69**	70
42		*n*-Pr—≡—*n*-Pr	24	 **14**	27

[a] A representative procedure for the carbonylative annulation of internal alkynes: *o*-iodophenol (0.5 mmol), alkyne (2.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol), and DMF (5 ml) were placed in a 4 dram vial. The vial was purged with CO for 2 minutes, then connected to a balloon of CO, and the reaction mixture was stirred at 120 °C for the specified time. [b] Isolated yields are reported; the isomer ratio is reported in parentheses. [c] The reaction was run at 135 °C. [d] The reaction was run at 100 °C. [e] 3-Methoxyphenol was obtained in an 80% yield. [f] 2-Naphthol was obtained in an 82% yield and 12% of 1-iodo-2-naphthol was recovered.

afford coumarins in 54-63% yields, although a higher temperature was required in the latter case to drive the reaction to completion. A series of phenyl alkyl acetylenes, where the alkyl group is methyl, ethyl, *iso*-propyl or *tert*-butyl, has also been successfully employed in reactions with *o*-iodophenol (entries 5-9). Mixtures of regioisomers were obtained in all cases with only modest regioselectivity. The regioisomers were identified by comparison of the ^{1}H NMR chemical shift of the hydrogen at C-5 in both isomers.



The signal of this hydrogen is shifted upfield in 3-alkyl-4-phenylcoumarins relative to 4-alkyl-3-phenylcoumarins, because of the deshielding effect of the benzene ring. As a result, it has been determined that in all cases the major isomer is the 3-phenyl-4-alkylcoumarin. This pattern of alkyne insertion, in which the palladium atom adds to the more sterically hindered end of the triple bond, is consistent with results obtained in all of our previous annulation reactions.[1,2,3a,5a]

Both the regioselectivity and the yields of the annulations of phenyl alkyl acetylenes are affected by the steric bulk of the alkyl substituent. An increase in the size of the alkyl group generally results in a decrease in the regioselectivity and the yield of the reaction (entries 5, 6 and 8). However, the dependence of the yield on the size of the alkyl substituent is not linear. The yield of the coumarin decreases in the following order: Me ~ Et > *i*-Pr >>> *t*-Bu. The effect of the *tert*-butyl group is enormous. No product has been obtained when 3,3-dimethyl-1-phenyl-1-butyne was employed as the alkyne (entry 9). The reaction with another alkyne bearing a *tert*-butyl group, 4,4-dimethyl-2-pentyne (entry 10), resulted in only

a 9% yield of the desired product. This unusual sensitivity of the annulation to steric hindrance is even more surprising considering that these alkynes have been among the best in our previous annulation reactions.[1,2,4,6a,7] The reaction temperature does not have any significant effect on the regioselectivity. The carbonylative annulation of 1-phenyl-1-butyne at 120 °C (entry 6) affords coumarins **24** and **25** as a 2.6:1 mixture in 78% yield, while the analogous reaction run at 100 °C affords a 2.4:1 mixture of regioisomers in 47% yield (entry 7). The annulation of 1-cyclohexyl-1-propyne also produced a mixture of regioisomers (entry 11).

We next turned to the annulation of alkynes bearing various functional groups. Propargylic alcohols were examined first (entries 12-15), and in all cases, except the reaction with 3-trimethylsilyl-2-propyn-1-ol (entry 15), no coumarins have been detected. Significant amounts of the starting acetylenes were recovered from all of these reactions, and in the reaction with 3-phenyl-2-propyn-1-ol, a small amount (~ 0.2 mmol) of the corresponding formate was also isolated. The annulation of 6-phenyl-5-hexyn-1-ol (entry 16) did not produce any of the desired coumarin either. However, when 1-phenyl-3-methoxy-1-propyne was employed, the desired product was obtained in a 65% yield as a 3:1 mixture of the regioisomers **31** and **32** (entry 17). It is clear that hydroxyl substituents generally interfere with the reaction, regardless of the distance from the hydroxyl group to the carbon-carbon triple bond. Presumably, the acylpalladium intermediate generated in this process reacts directly with the free hydroxyl group to form esters, although no such esters have been observed.

The success of the reaction with 1-phenyl-3-methoxy-1-propyne motivated us to explore the annulation of propargylic alcohols with other, more easily removable, protecting

groups. 3-Phenyl-2-propyn-1-ol and 2-butyn-1-ol protected with *tert*-butyldimethylsilyl and benzyl groups were subjected to reactions with *o*-iodophenol (entries 18-21). For both alcohols, the benzyl ethers gave significantly better yields of the coumarins, on a par with the yield of the reaction of the corresponding methyl ether (compare entries 17 and 19). It is noteworthy that the regioselectivity of the annulation is reversed for the 3-phenyl-2-propynyl- and the 2-butynyl ethers (entries 18-21). In the latter case, the assignment of the regioisomers is based on the ^{1}H NMR chemical shifts of the methyl protons of the coumarins. The signals for the α-hydrogens of the 4-alkyl-3-phenylcoumarins are shifted downfield relative to the signals of the α-hydrogens of the 3-alkyl-4-phenylcoumarins. Assuming that the same relationship holds true for methyl(alkoxymethyl)coumarins, coumarins **38** and **40** have been assigned as the major products. This assignment is consistent with the steric bulk of the substituents on the triple bond.

The carbonylative annulation of the diethyl acetal of 2-butynal (entry 22) failed. None of the desired coumarin could be isolated. The reason for this dramatic effect of the second alkoxy group is not known.

The annulation of silyl-substituted acetylenes was examined next (entries 23-25). Single regioisomers were obtained in all cases, and the structures of the products were assigned based on the steric size of the substituents, in analogy with previous annulation chemistry.[2a,4,5,6a] The improved regioselectivity is undoubtedly due to the steric bulk of the silyl groups. Unfortunately, the steric bulk also leads to a decrease in the overall yield of the coumarins. Only the reaction of 1-trimethylsilyl-1-propyne (entry 23) afforded a coumarin in a moderate yield. It is noteworthy that the yield from the reaction of the silyl acetylene with a longer C-Si bond (entry 23) is significantly higher than the yield from the reaction of 4,4-

dimethyl-2-pentyne (entry 10). Significantly lower yields for the two other acetylenes may be due to either the increased steric bulk of the silyl group (for 1-triisopropylsilyl-1-propyne) or the higher propensity for desilylation for 1-trimethylsilyl-2-phenylacetylene.

Electron-deficient alkynes (alkynones and alkynoates) behave in these carbonylative annulation reactions quite differently from other alkynes. 3-Hexyn-2-one (entry 26) affords the desired coumarins in a good yield with good regioselectivity (9:1). The major product is coumarin **44**, identified by comparison of its ^{1}H NMR spectrum with literature data.[28] The high regioselectivity of the annulation is clearly governed not only by steric (an ethyl and an acetyl groups are not very different in size), but also by electronic factors. Electronic factors apparently favor insertion of the alkyne into the arylpalladium bond so that the palladium moiety ends up on the carbon next to the carbonyl group.

While the annulation of 3-hexyn-2-one was successful, none of the desired coumarin was observed in the annulation of 1-phenyl-2-butyn-1-one (entry 27). The major product isolated from the reaction mixture has been identified as 2-benzoylmethyl-2-methyl-1-benzofuran-3(2*H*)-one (**46**), which was obtained in 75% yield. The structure of the product has been confirmed by comparison of its ^{1}H and ^{13}C NMR spectra with the spectra of the known 2-benzoylmethyl-2-*n*-butyl-1-benzofuran-3(2*H*)-one.[29] The mechanism for the formation of this interesting product will be discussed later.

Unexpected products have also been observed in the reactions of 2-alkynoates. The carbonylative annulation of ethyl phenylpropiolate resulted in the formation of the desired coumarins **47** and **48** in a 1:3 ratio and 45% yield (entry 28). Here, the regioselectivity of the reaction is clearly determined by the size of the substituents on the carbon-carbon triple bond. Besides these two coumarins, a small amount of 4-phenylcoumarin (**49**) has been

detected by GCMS and ^{1}H NMR spectroscopy, although we have been unable to isolate it in pure form and fully characterize it. This coumarin is likely the result of *in situ* decarboalkoxylation of coumarin **47**.

The annulation of ethyl 2-butynoate (entry 29) also affords three coumarins **50-52**, and the total yield of the annulation products is similar to that of the reaction of ethyl phenylpropiolate. In this case, however, the decarboalkoxylated coumarin **50** is the major product (24% yield). Coumarin **51** has been identified by comparison of its ^{1}H NMR spectral data with literature data.[30] Thus, the selectivity of this reaction is only (**50** + **51**): **52** = (24 + 5): 17 = 1.7:1. This result is similar to the result obtained with 1-benzyloxy-2-butyne (entry 21) and is, therefore, most probably due only to the difference in size between the methyl and ethoxycarbonyl groups. Hence, unlike the reaction with 3-hexyn-2-one, no major electronic effects have been detected in the carbonylative annulation of alkynoates.

In another effort to obtain derivatives of 4-methylcoumarin-3-carboxylic acid, *N,N*-dimethyl-2-butynamide was prepared and allowed to react with *o*-iodophenol (entry 30). However, the desired coumarin was not observed, and the only isolated product is coumarin **50**, obtained in only a 16% yield.

Various functionalized iodophenols have also been successfully employed in the carbonylative annulation of internal alkynes. Thus, the annulation of *o*-iodophenols bearing electron-withdrawing groups *para* to the hydroxyl group have proven to be nearly as successful as the annulation of *o*-iodophenol itself (entries 31-34). It is noteworthy that the regioselectivity of the reaction of 1-phenyl-1-propyne is significantly reduced by introducing an electron-withdrawing acetyl group into the *o*-iodophenol (compare entries 5 and 33). An electron-withdrawing group can also be introduced at C-7 of the coumarin (entry 35). Again,

the yield is comparable to the yield obtained with the parent iodophenol. In addition, the reaction of **59** is much faster, reaching completion within 6 h. This result is consistent with the higher reactivity of an electron-poor aryl iodide in oxidative addition to Pd(0). These results are all the more important, because coumarins possessing electron-withdrawing groups cannot be prepared using classical methods, such as the Pechman reaction.[24]

On the other hand, an electron-donating group, such as a methoxy group, cannot be as easily introduced into the coumarin. While 2-iodo-4-methoxyphenol reacted with 4-octyne to afford the desired coumarin in a 62% yield (entry 36), the annulation of 4-octyne with 2-iodo-5-methoxyphenol (entry 37) afforded none of the desired coumarin, and the only product isolated from the reaction was 3-methoxyphenol, which was obtained in 80% yield. The same strange behavior has been observed in the reaction with 1-iodo-2-naphthol (entry 38), in which the only product was 2-naphthol, isolated in 82% yield along with 12% of the recovered starting material.

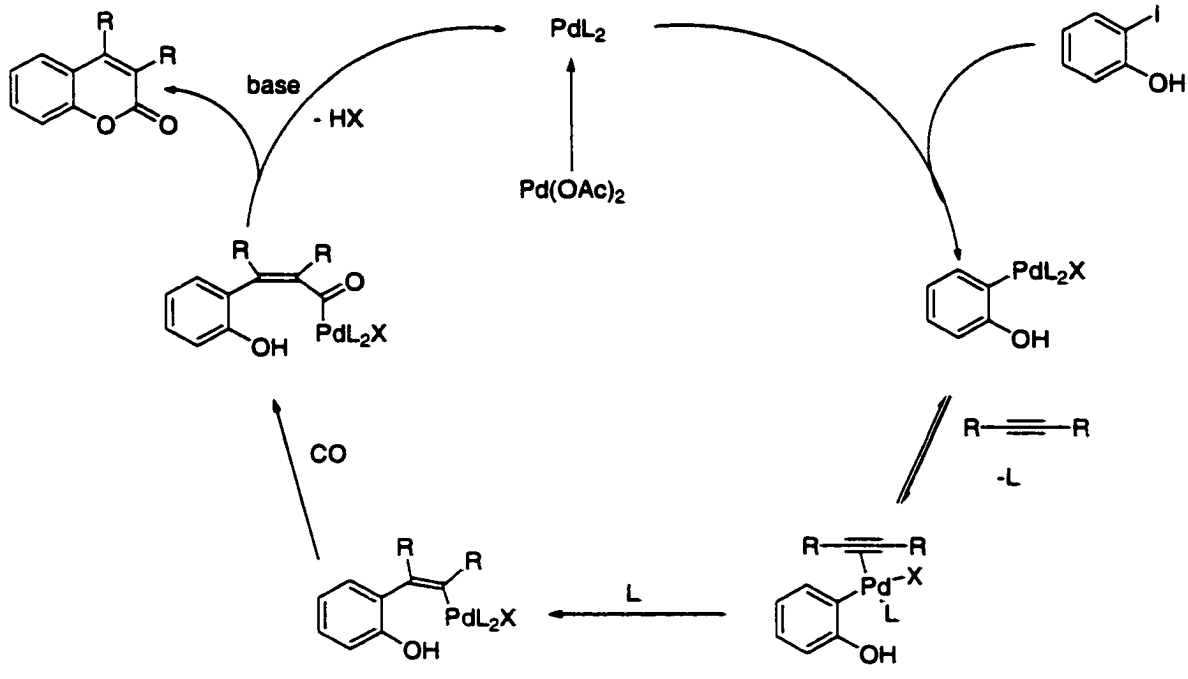
The reaction of 4-octyne with 2,5-diiodo-1,4-hydroquinone (**65**) (entry 39) shows that double annulation can be successfully accomplished using the standard reaction conditions, even without increasing the alkyne to iodophenol ratio beyond the usual 5:1 ratio. The yield of the doubly annulated product **66** (54%) is only slightly lower than the yield of coumarin **14** in the reaction of the parent *o*-iodophenol (entry 1, 63%). Thus, in the reaction with 2,5-diiodo-1,4-hydroquinone, 1.08 equiv of 4-octyne end up in the coumarin product, while the largest amount of 4-octyne incorporated into the coumarin product in the reaction with the monophenol is 0.70 equiv (entry 41, see below). This result and the absence of the product of monoannulation seem to indicate that the first pyrone ring activates the intermediate toward formation of the second pyrone ring.

Heterocyclic analogues of *o*-iodophenol have also been examined in the carbonylative annulation. 3-Hydroxy-2-iodopyridine (**67**) failed to give any of the desired product (entry 40). A small amount of an unknown coupling product has been observed in the reaction, and the starting material almost completely disappeared. On the other hand, the substituted 3-iodo-2-pyridone **68** affords the azacoumarin **69** in a 70% yield, the highest yield obtained thus far in the annulation of 4-octyne (entry 41).

Surprisingly, 2-iodoanisole is also reactive in the carbonylative annulation, producing coumarin **14** in a 27% yield (entry 42). Although, this is only half of the yield obtained with *o*-iodophenol, it is interesting to see that the free hydroxyl group is not necessary for the reaction to proceed.

Mechanism. A possible mechanism for the carbonylative annulation is shown in Scheme 2. First, $Pd(OAc)_2$ is reduced to generate a Pd(0) complex, which is the actual

Scheme 2

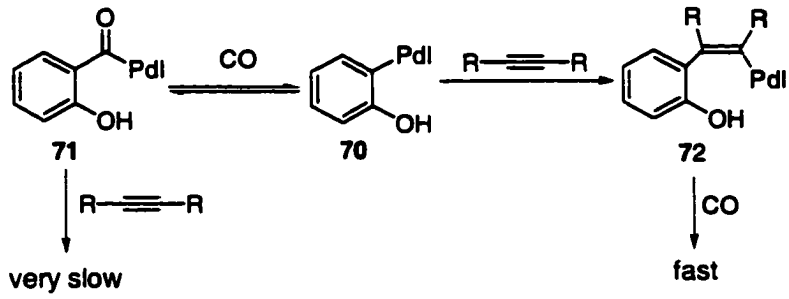


reaction. It is known to reduce Pd(II) to Pd(0) in the presence of alcohols and phenols.[31] Oxidative addition of *o*-iodophenol to Pd(0) to form an arylpalladium complex starts the catalytic cycle. Dissociation of one of the neutral ligands from the palladium opens up a coordination site, which is then occupied by an internal alkyne. Alkyne insertion provides a vinylic palladium species. Insertion of carbon monoxide into the vinylpalladium bond gives rise to an acylpalladium complex. Intramolecular nucleophilic attack on the carbonyl group of the latter complex by the phenolic oxygen produces the desired coumarin and regenerates Pd(0).

This process represents the first example of insertion of an internal alkyne into an arylpalladium bond in preference to CO insertion. The reverse is true in all examples previously reported in the literature.[16b,17,18] In fact, Negishi determined the relative rates of various processes to be as follows: CO insertion ≅ 5-*exo*- or 6-*exo*-alkyne carbopalladation > 5-*exo*-alkyne acylpalladation > trapping of an acylpalladium with MeOH > intermolecular carbopalladation or acylpalladation.[16b] Thus, the preferential insertion of an alkyne and, moreover, the complete absence of products arising from the initial insertion of CO are quite surprising. Therefore, we attempted to establish the origins of such unusual behavior.

The observed order of insertion can be rationalized in two ways. The first explanation, shown in Scheme 3, assumes that insertions of both CO and the alkyne readily occur under our reaction conditions. The alkyne inserts irreversibly to afford the vinylpalladium complex **72**, which then reacts with CO, eventually forming the coumarin. In contrast, CO inserts in a reversible fashion. Therefore, if the acylpalladium complex **71** reacts with the alkyne very slowly, or not at all, then, in the absence of any other reaction pathways, it could undergo decarbonylation, giving back the original arylpalladium complex

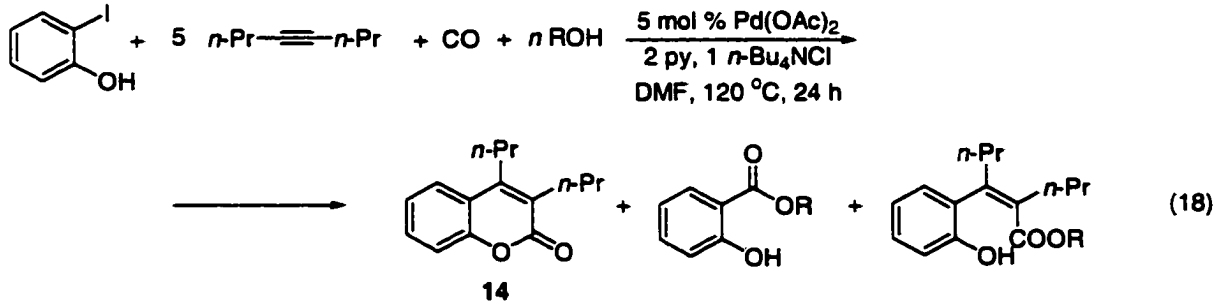
Scheme 3



70. Eventually, most of the arylpalladium complex **70** will react with the internal alkyne affording the desired coumarin.

In the case shown in Scheme 3, insertion of the alkyne may be either faster or slower than the insertion of CO. On the other hand, it is possible that no insertion of CO into the arylpalladium bond takes place under our reaction conditions. Indeed, our reaction conditions [$Pd(OAc)_2$, pyridine, *n*-Bu_4NCl] are quite different from the conditions usually employed for the palladium-catalyzed carbonylation [$PdCl_2(PPh_3)_2$, Et_3N, no chloride source].[10,15,32]

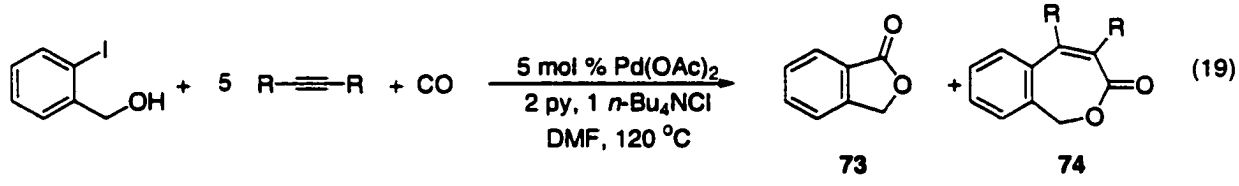
To establish whether the insertion of CO occurs under our standard conditions, we attempted to trap the acylpalladium complex formed from *o*-iodophenol by reaction with a nucleophile. Initially, alcohols were used as external nucleophiles. The formation of at least three products is possible (eq 18). However, in all cases only coumarin **14** has been isolated



(18)

in yields comparable to the yield of the reaction without any alcohol present. For example, when *n*-pentanol (20 equiv) was used as the alcohol, **14** has been obtained in a 66% yield. This is even more surprising considering that internal alkynes bearing an unprotected hydroxyl group are almost completely ineffective in the carbonylative annulation (see Table 7, entries 12-16).

Since an attempt to use an external nucleophile failed, we employed an aryl iodide with an internal nucleophile. *o*-Iodobenzyl alcohol was the obvious choice. If the insertion of CO into the arylpalladium bond occurs, the resulting acylpalladium complex should be easily trapped by the adjacent hydroxyl group leading to formation of the 5-membered ring lactone **73** (eq 19).[33] Alternatively, formation of the 7-membered ring lactone **74** might occur upon insertion of an alkyne and CO.



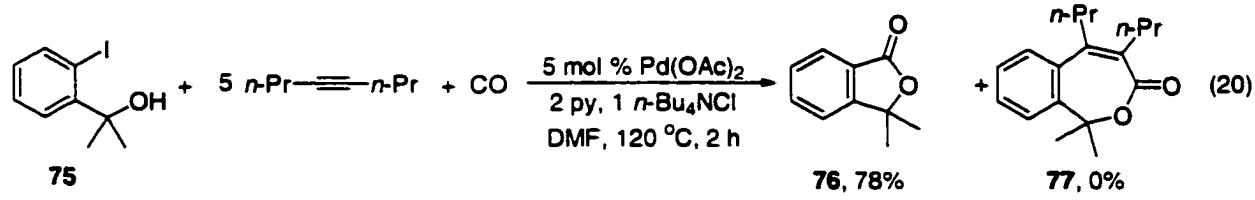
73 **74** (19)

Under our standard carbonylative annulation conditions, the reaction with 4-octyne was complete within 4 h and both possible products **73** and **74a** (R = *n*-Pr) have been isolated in 24% and 43% yields, respectively. The temperature has a remarkable effect on the chemoselectivity of the reaction (Table 8, entries 1-3). The yield of **74a** drops dramatically with a decrease in the reaction temperature, while the yield of **73** increases. The nature of the alkyne is also a very important factor in determining the selectivity of the reaction. Thus, when diphenylacetylene was used (entry 4), the 5-membered ring lactone **73** was obtained in 46% yield, while the yield of the 7-membered ring lactone **74b** (R = Ph) was only 16%.

Table 8. Carbonylative annulation of internal alkynes with *o*-iodobenzyl alcohol (eq 19).

entry	R	temp. (°C)	time (h)	% yield	
				73	**74**
1	*n*-Pr	120	4	24	43
2		100	8	45	28
3		80	24	67	<5
4	Ph	120	4	46	16

When the tertiary benzylic alcohol **75** was employed in the reaction, only the five-membered lactone **76** was isolated in a 78% yield and none of the product from alkyne insertion was detected (eq 20). Apparently, the presence of two methyl groups forces the alcohol into a conformation in which the hydroxyl group is in close proximity to the iodine atom, and, consequently, trapping of the acylpalladium intermediate is much more effective than in the case of *o*-iodobenzyl alcohol.



75 **76**, 78% **77**, 0% (20)

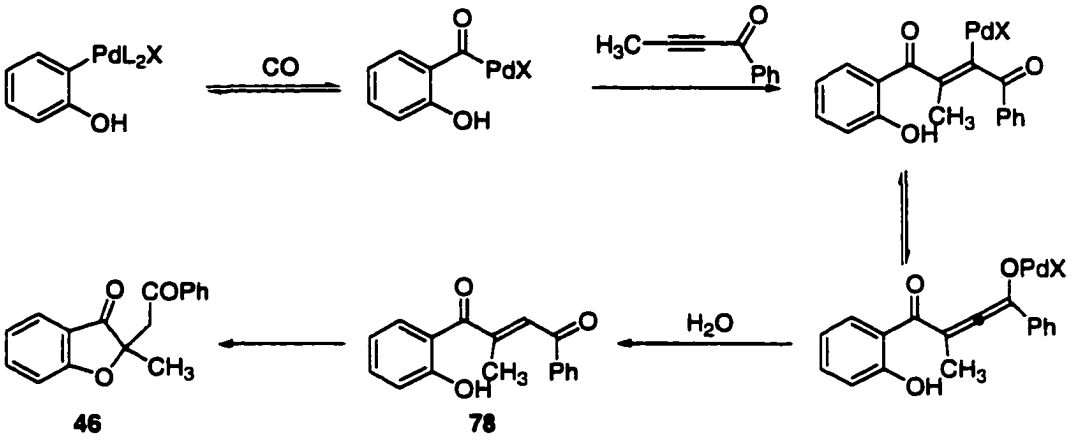
These results suggest that carbon monoxide does insert into the arylpalladium bond under our reaction conditions. Moreover, the outcome of the reaction with alcohol **75** shows that even at 120 °C the insertion of CO is faster than the insertion of an internal alkyne. Consequently, the ratio of products arising from the initial CO insertion to those of the initial

alkyne insertion is determined by the relative rates of the two processes: the reaction of the acylpalladium complex **71** with either a nucleophile or some other species (alkene or alkyne) and the insertion of an alkyne into the arylpalladium bond of the complex **70**. The factors affecting the relative reactivity of one of these (or both) complexes change the ratio of the products of the initial CO insertion and the initial alkyne insertion.

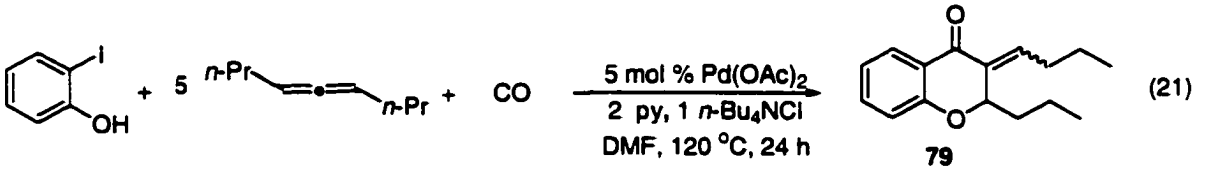
The more favorable conformation of the hydroxyl group in 2-(2-iodophenyl)-2-propanol (**75**) than in *o*-iodobenzyl alcohol increases the rate of trapping of the acylpalladium complex corresponding to **71**, while a decrease in the temperature slows insertion of the alkyne in the complex corresponding to **70**. Diphenylacetylene is less reactive than 4-octyne; thus, the yield of **74** increases.

Thus, the apparent reason for the exclusive formation of coumarins is the slow insertion of the internal alkyne into the acylpalladium bond. Only in one case, the reaction of *o*-iodophenol with 1-phenyl-2-butyn-1-one (Table 7, entry 27), have we observed the product apparently arising from the insertion of an internal alkyne into the acylpalladium bond. Surprisingly, the product of this reaction is not a chromone, but a 1-benzofuran-3(2*H*)-one derivative **46**. A probable mechanism for its formation is shown in Scheme 4. Addition of the acylpalladium complex to the carbon-carbon triple bond generates a vinylpalladium intermediate that probably exists in equilibrium with the palladium enolate complex. The hydrolysis of this enolate by water present in DMF leads to enone **78**. Intramolecular Michael addition of the phenol then affords the final product **46**. No coumarins have been detected in this reaction, while no products arising from the insertion of the alkyne into the acylpalladium bond have been observed in the reaction with 3-hexyn-2-one (Table 7, entry26). The origins of this complete reversal of the reactivity are not clear at this point.

Scheme 4



We were interested to see whether the unusual selectivity would be observed with other unsaturated compounds, such as allenes. However, only the product of initial CO insertion, 3-*n*-butylene-2-*n*-propyl-2,3-dihydro-4*H*-1-benzopyran-4-one (**79**), has been obtained in the carbonylative annulation of 4,5-nonadiene under our standard annulation conditions (eq 21). The same order of insertion has been observed by Alper under different reaction conditions (eq 5).[15] This result shows that the carbon-carbon double bond easily inserts into the acylpalladium bond, and, therefore, the unusual order of insertion observed by us is probably limited to internal alkynes.



(21)

Conclusions

An efficient palladium-catalyzed synthesis of 3,4-disubstituted coumarins has been developed. A wide variety of alkynes containing alkyl, aryl, silyl, alkoxy, acyl and ester groups afford coumarins in moderate to good yields. The process is sensitive to the steric

bulk of the alkynes, and alkynes bearing tertiary alkyl substituents generally fail to undergo annulation. Unsymmetrical alkynes produce mixtures of regioisomers with generally only modest selectivity. The regioselectivity of the process is governed by both steric and electronic factors. Substituted *o*-iodophenols with both electron-donating and electron-withdrawing substituents, as well as substituted pyridinones, are effective in this process, thus creating a fast and efficient route to coumarins that are not easily accessible by classical methods.

This carbonylative annulation process represents the first example of a domino process in which the insertion of an internal alkyne into an arylpalladium bond occurs prior to the insertion of carbon monoxide. Trapping experiments suggest that the reason for this unusual selectivity is not the intrinsic inability of the carbon monoxide to undergo insertion under our reaction conditions, but the absence of any species able to react with the resulting acylpalladium complex faster than it undergoes decarbonylation.

Experimental Section

General. All ^{1}H 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 (Aldrich Chemical Co.), and visualization was effected with short wavelength UV light (254 nm) or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5 %) + 300 ml of H_2O]. 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.

Elemental analyses were performed at Iowa State University on the Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Na_2CO_3, K_2CO_3, NaOAc, KOAc, NaO_2CPh, $NaHCO_3$, $KHCO_3$, DMF, DMSO, hexanes and ethyl acetate were purchased from Fisher Scientific Co. Pyridine was purchased from Fisher Scientific Co and purified by distillation from CaH_2. CsOAc, TlOAc, $AgClO_4$, Et_3N, *i*-Pr_2NEt, 2,2,6,6-tetramethylpiperidine, 2,6-di-*tert*-butyl-4-methylpyridine, imidazole, isoquinoline, 2,2'-dipyridyl, 1,10-phenanthroline, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, tri(2-furyl)phosphine and DMA were purchased from Aldrich Chemical Co. $LiOAc{\cdot}2H_2O$ was purchased from Aldrich Chemical Co. and dehydrated by heating *in vacuo* at 100 °C for 3 h. *n*-Bu_4NCl was purchased from Lancaster Synthesis, Inc. 2,4,6-Trimethylpyridine was purchased form J. T. Baker Chemical Co. 1,1'-Bis(diphenylphosphino)ferrocene was purchased from Strem Chemicals, Inc. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. Triphenylphosphine was donated by Kawaken Fine Chemicals Co. Ltd.

Alkynes. Diphenylacetylene, 1-phenyl-1-propyne, 1-trimethylsilyl-1-propyne, 1-phenyl-2-(trimethylsilyl)acetylene, 1-triisopropylsilyl-1-propyne, ethyl phenylpropiolate and 2-butynoic acid were purchased from Aldrich Chemical Co. 4-Octyne, 3-hexyne, 1-phenyl-1-butyne, 1-cyclohexyl-1-propyne, 2-methyl-4-phenyl-3-butyn-2-ol, 2-butyn-1-ol, 2-butynal diethyl acetal, 3-hexyn-2-one and ethyl 2-butynoate were purchased from Farchan Chemical Co. 4,4-Dimethyl-2-pentyne, 3-phenyl-2-propyn-1-ol and 3-trimethylsilyl-2-propyn-1-ol were purchased from Lancaster Synthesis, Inc. 1-Phenyl-3-methyl-1-butyne,[34] 1-phenyl-3,3-

dimethyl-1-butyne,[35] 1-phenyl-1-hexyn-6-ol,[36] 1-phenyl-3-methoxy-1-propyne[36] and 1-phenyl-2-butyn-1-one[37] were prepared according to previous literature procedures.

Phenols. *o*-Iodophenol was purchased from Aldrich Chemical Co. and purified by recrystallization from hexanes. 2-Iodo-3-pyridinol was purchased from Lancaster Synthesis, Inc. 2-Iodoanisole and 2-iodobenzyl alcohol were purchased from Aldrich Chemical Co. 4'-Hydroxy-3'-iodoacetophenone (**52**),[38] ethyl 4-hydroxy-3-iodobenzoate (**57**),[39] 1-iodo-2-naphthol (**60**),[39] 2,5-diiodo-1,4-hydroxyquinone (**65**),[40] ethyl 1,6-dihydro-5-iodo-6-oxo-3-pyridinecarboxylate (**68**)[41] and 2-(2-iodophenyl)-2-propanol (**72**)[42] were prepared according to previous literature procedures. 2-Iodo-4-methoxyphenol (**61**) and 2-iodo-5-methoxyphenol (**63**) were obtained from Dr. George A. Kraus.[43]

The following starting materials were prepared as indicated.

1-(*tert*-Butyldimethylsilyloxy)-3-phenyl-2-propyne. 3-Phenyl-2-propyn-1-ol (0.66 g, 5.0 mmol), *tert*-butyldimethylsilyl chloride (1.01 g, 6.0 mmol), and imidazole (0.85 g, 12.5 mmol) were dissolved in 2 ml of DMF and the reaction mixture was stirred at 35 °C for 1 d. Then the reaction mixture was diluted with satd aq NH_4Cl and extracted with ether. The ethereal extracts were combined, washed with water, dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and dried *in vacuo*. Column chromatography on silica gel using 10:1 hexanes /EtOAc as eluent afforded 1.14 g (93 %) of the desired product as a colorless, transparent liquid: ^{1}H NMR ($CDCl_3$) δ 7.42-7.44 (m, 2H), 7.29-7.32 (m, 3H), 4.54 (s, 2H), 0.94 (s, 9H), 0.17 (s, 6H): ^{13}C NMR ($CDCl_3$) δ 131.8, 128.5, 128.4, 123.2, 95.0, 85.0, 52.5, 26.1, 15.6, – 4.8.

1-(*tert*-Butyldimethylsilyloxy)-2-butyne. This compound was prepared using the above method, but employing 2-butyn-1-ol (0.70 g, 10 mmol), *tert*-butyldimethylsilyl

chloride (2.02 g, 12 mmol), and imidazole (1.70 g, 25 mmol) in 5 ml of DMF for 20 h. Column chromatography on silica gel using 10:1 hexanes /EtOAc as eluent afforded 1.82 g (99 %) of the desired product as a colorless, transparent liquid: ^{1}H NMR ($CDCl_3$) δ 4.27 (q, J = 2.4 Hz, 2H), 1.83 (t, J = 2.4 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 81.1, 78.0, 52.2, 26.1, 18.6, 38, – 5.0. The spectral data were identical with those previously reported.[44]

1-Benzyloxy-3-phenyl-2-propyne. A solution of 3-phenyl-2-propyn-1-ol (1.32 g, 10 mmol) in dry THF (5 ml) was added dropwise over 30 min to a suspension of 95 % dry NaH (0.265 g, 10.5 mmol) in dry THF (5 ml) cooled to 0 °C. The mixture was stirred at 0 °C for 5 min, and then allowed to warm up to room temperature. A solution of benzyl chloride (1.65 g, 13 mmol) and 25 mg of potassium iodide in dry THF (5 ml) was added to the resulting mixture over 10 min. The reaction mixture was stirred at room temperature for 4.5 h, then 20 ml of water was added, and the mixture was extracted with hexanes. The organic extracts were combined, washed with water, dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and dried *in vacuo*. Column chromatography on silica gel using 8:1 hexanes/EtOAc as eluent afforded 0.61 g (27 %) of the desired compound as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 7.45-7.47 (m, 2H), 7.31-7.40 (m, 8H), 4.68 (s, 2H), 4.40 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 137.7, 132.0, 128.7, 128.6, 128.5, 128.4, 128.1, 122.9, 86.7, 85.2, 71.9, 58.1.

1-Benzyloxy-2-butyne. This ether was prepared using the above method, but employing 2-butyn-1-ol (0.70 g, 10 mmol). Column chromatography on silica gel using 8:1 hexanes/EtOAc as eluent afforded 0.43 g (27 %) of the desired compound as a yellow liquid:

^{1}H NMR ($CDCl_3$) δ 7.28-7.36 (m, 6H), 4.57 (d, J = 0.4 Hz, 2H), 4.10-4.14 (m, 2H), 1.86 (t, J = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.8, 128.6, 128.2, 128.1, 82.9, 75.2, 71.6, 57.9, 3.8.

***N,N*-Dimethyl 2-butynamide**. 2-Butynoic acid (0.84 g, 10 mmol) and thionyl chloride (1.2 ml, 1.96 g, 16 mmol) were refluxed for 1.5 h in a flask fitted with a $CaCl_2$ trap. The reaction mixture was cooled to 0 °C and treated with a 1.0 M solution of dimethylamine in THF (2.5 ml, 25 mmol). The reaction mixture was stirred at room temperature for 1 h, treated with a 2N aqueous solution of KOH and extracted with ether. The ethereal extracts were concentrated under reduced pressure. Column chromatography on silica gel using 2:1 hexanes/EtOAc as eluent afforded 0.46 g (41 %) of the desired amide as a colorless, transparent liquid with spectral properties matching those reported in the literature.[45]

Methyl 3-hydroxy-4-iodobenzoate (59). A solution of $NaNO_2$ (0.45 g, 6.6 mmol) in 2.5 ml of water was added over 15 min to an ice-cold solution of methyl 4-amino-3-hydroxybenzoate (1.0 g, 6.0 mmol) in 3 ml of conc. HCl and 4 g of ice. The resulting solution was stirred at 0 °C for 20 min, and then added over 25 min to a stirred and cooled (0 °C) solution of KI (9.96 g, 16 mmol) in 15 ml of water. The resulting mixture was stirred at room temperature for 18 h, and extracted with CH_2Cl_2. The organic extracts were combined, washed with 10% aq $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel using 2:1 hexanes/EtOAc as eluent afforded 0.61 g (37%) of the desired compound as a red solid: mp 164-166 °C (lit.[46] 145-148 °C); ^{1}H NMR (d_6-acetone) δ 9.46 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 2.0, 8.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (d_6-acetone) δ 166.8, 157.7,

140.5, 132.7, 122.8, 116.0, 91.0, 52.6; MS m/z (rel intensity) 278 (100, M^+), 247 (77); HRMS calcd for $C_8H_7IO_3$: 277.9440, found: 277.9445.

General procedure for the palladium-catalyzed synthesis of coumarins. The *o*-iodophenol (0.5 mmol), the alkyne (2.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol) and DMF (5 ml) were placed in a 4 dram vial. The vial was purged with CO for 2 min and then connected to a balloon of CO. The reaction mixture was stirred at 120 °C for the reaction times specified in Table 7, then allowed to cool to room temperature, diluted with EtOAc, washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by column chromatography on silica gel. The following coumarins were prepared using this procedure.

3,4-Dipropyl-2*H*-1-benzopyran-2-one (14). White solid, mp 58-60 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.45 (ddd, *J* = 1.2, 8.0, 8.4 Hz, 1H), 7.25-7.32 (m, 2H), 2.77-2.81 (m, 2H), 2.59-2.63 (m, 2H), 1.55-1.70 (m, 4H), 1.11 (t, *J* = 7.6 Hz, 3H), 1.03 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.1, 152.8, 150.1, 130.5, 126.6, 124.7, 124.2, 120.0, 117.2, 30.7, 29.9, 23.1, 22.5, 14.7, 14.5; IR ($CHCl_3$, cm^{-1}) 3073, 2962, 2872, 1716; MS m/z (rel intensity) 230 (67, M^+), 215 (77), 201 (66), 187 (100). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.05; H, 8.05.

3,4-Diethyl-2*H*-1-benzopyran-2-one (19). Yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ 7.61 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.44 (ddd, *J* = 1.2, 7.6, 8.4 Hz, 1H), 7.26-7.32 (m, 2H), 2.85 (q, *J* = 7.6 Hz, 2H), 2. 67 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.19 (t, *J* = 7.6 Hz,

3H); ^{13}C NMR ($CDCl_3$) δ 161.9, 152.8, 151.1, 130.5, 127.5, 124.5, 124.2, 119.6, 117.1, 21.7, 21.0, 14.0, 13.6; IR (neat, cm^{-1}) 3063, 2973, 2938, 2878, 1711, 1606; MS m/z (rel intensity) 202 (100, M^+), 201 (79), 187 (37), 159 (35). HRMS Calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0997.

3,4-Diphenyl-2*H*-1-benzopyran-2-one (20). White solid, mp 229-230 °C (lit.[47] mp 228-230 °C); ^{1}H NMR ($CDCl_3$) δ 7.54 (ddd, J = 2.0, 7.2, 8.4 Hz, 1H), 7.44 (dd, J = 0.8, 8.4 Hz, 1H), 7.29-7.32 (m, 3H), 7.11-7.25 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 161.5, 153.4, 151.8, 134.6, 134.0, 131.6, 130.7, 129.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.2, 124.3, 120.7, 116.9; IR ($CHCl_3$, cm^{-1}) 1717, 1707, 1604, 1596; MS m/z (rel intensity) 298 (85, M^+), 297 (100). Anal. Calcd for $C_{21}H_{14}O_2$: C, 84.53; H, 4.74. Found: C, 84.41; H, 4.9.

4-Methyl-3-phenyl-2*H*-1-benzopyran-2-one (21). White solid, mp 151-153°C (lit.[30] mp 156-157 °C); all spectral properties are identical to those reported in the literature.[30]

3-Methyl-4-phenyl-2*H*-1-benzopyran-2-one (22). Colorless viscous liquid; the spectral properties are identical with those reported in the literature.[48]

4-Ethyl-3-phenyl-2*H*-1-benzopyran-2-one (23). White solid, mp 181-182 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (dd, J = 1.2, 8.0 Hz, 1H), 7.54 (ddd, J = 1.2, 8.0, 8.4 Hz, 1H), 7.38-7.49 (m, 4H), 7.28-7.35 (m, 3H), 2.68 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.4, 153.5, 134.7, 131.4, 129.7, 128.8, 128.4, 127.1, 125.3, 124.4, 119.4, 117.4, 23.0, 14.4; IR ($CHCl_3$, cm^{-1}) 3155, 2981, 1720, 1700, 1606; MS m/z (rel intensity) 250 (100, M^+), 207 (70), 187 (50). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.57; H, 5.64. Found: C, 81.61; H, 5.95.

3-Ethyl-4-phenyl-2*H*-1-benzopyran-2-one (24). White solid, mp 67-68 °C; ^{1}H NMR ($CDCl_3$) δ 7.43-7.56 (m, 4H), 7.36 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.23-7.25 (m, 2H), 7.12 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H), 6.94 (dd, *J* = 0.8, 7.6 Hz, 1H), 2.40 (q, *J* = 7.6 Hz, 2H), 1.07 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.9, 152.7, 150.6, 135.0, 130.7, 129.0, 128.9, 128.8, 128.4, 127.4, 124.1, 121.2, 116.7, 22.4, 13.7. Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.57; H, 5.64. Found: C, 81.51; H, 6.03.

4-Isopropyl-3-phenyl-2*H*-1-benzopyran-2-one (25). White solid, mp 205-206 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.39-7.54 (m, 5H), 7.25-7.31 (m, 3H), 3.24 (septet, *J* = 7.2 Hz, 1H), 1.38 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 161.6, 156.6, 153.6, 135.5, 131.0, 129.6, 128.8, 128.3, 127.2, 126.8, 123.8, 118.7, 117.8, 31.7, 21.5; IR ($CHCl_3$, cm^{-1}) 2983, 1714, 1699; MS m/z (rel intensity) 264 (100, M^+), 221 (50). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.68; H, 6.16.

3-Isopropyl-4-phenyl-2*H*-1-benzopyran-2-one (26). White solid, mp 113-115 °C; ^{1}H NMR ($CDCl_3$) δ 7.49-7.55 (m, 3H), 7.43 (ddd, *J* = 1.2, 8.0, 8.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.21-7.23 (m, 2H), 7.09 (ddd, *J* = 0.8, 7.6, 8.4 Hz, 1H), 6.87 (dd, *J* = 1.2, 8.0 Hz, 1H), 2.74 (septet, *J* = 7.1 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 160.1, 152.8, 150.2, 135.6, 131.7, 130.6, 129.1, 128.6, 128.2, 127.7, 123.9, 121.2, 116.4, 30.6, 20.1; IR (neat, cm^{-1}) 2956, 1716; MS m/z (rel intensity) 264 (53, M^+), 263 (100), 249 (21); HRMS calcd for $C_{18}H_{16}O_2$: 264.1150, found: 264.1156.

3-*tert*-Butyl-4-methyl-2*H*-1-benzopyran-2-one (27). Yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.43 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H), 7.22-7.26 (m, 2H), 2.59 (s, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 160.4, 151.8, 145.4, 134.0, 130.4, 124.5,

123.8, 122.2, 116.3, 37.1, 31.5, 18.3; MS m/z (rel intensity) 216 (M^+, 36), 201(99), 173 (100); HRMS calcd for $C_{14}H_{16}O_2$: 216.11503, found: 216.11530.

3-Cyclohexyl-4-methyl-2*H*-1-benzopyran-2-one (28). White solid, mp 126-128 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.44 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H), 7.24-7.29 (m, 2H), 2.89-2.95 (m, 1H), 2.46 (s, 3H), 2.15-2.23 (m, 2H), 1.84-1.86 (m, 2H), 1.70-1.72 (m, 1H), 1.54-1.58 (m, 2H), 1.32-1.36 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 160.4, 152.5, 145.5, 130.7, 130.4, 124.8, 124.0, 121.1, 116.7, 40.2, 29.4, 27.2, 25.9, 15.0; IR ($CHCl_3$, cm^{-1}) 2919, 2864, 1709, 1602; MS m/z (rel intensity) 242 (100, M^+), 227 (97), 227 (99), 225 (66), 186(47), 173 (49); HRMS calcd for $C_{16}H_{18}O_2$: 242.1307, found: 242.1312. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.52; H, 7.78.

4-Cyclohexyl-3-methyl-2*H*-1-benzopyran-2-one (29). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.42 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.30 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.20-7.29 (m, 2H), 3.13-3.19 (m, 1H), 2.28 (s, 3H), 1.99-2.10 (m, 2H), 1.81-1.94 (m, 5H), 1.40-1.47 (m, 3H); only a small amount has been isolated, so no other spectral data were obtained; MS m/z (rel intensity) 242 (28, M^+), 84 (100); HRMS calcd for $C_{16}H_{18}O_2$: 242.1307, found: 242.1312.

4-Hydroxymethyl-3-trimethylsilyl-2*H*-1-benzopyran-2-one (30). White solid, mp 55-60 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.50 (ddd, *J* = 1.6, 7.2, 8.4 Hz, 1H), 7.26-7.29 (m, 2H), 4.89 (s, 2H), 0.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.6, 158.2, 154.4, 131.9, 128.8, 125.5, 124.2, 119.3, 117.0, 60.4, 1.4. Anal. Calcd for $C_{13}H_{16}O_3Si$: C, 62.87; H, 6.49. Found: C, 62.95; H, 6.57.

4-Methoxymethyl-3-phenyl-2*H*-1-benzopyran-2-one (31) and **3-methoxymethyl-4-phenyl-2*H*-1-benzopyran-2-one (32)**. These compounds were obtained after column chromatography as a 3:1 inseparable mixture. Recrystallization from hexanes/ethyl acetate

afforded pure **4-methoxymethyl-3-phenyl-2*H*-1-benzopyran-2-one (31)** (major isomer): off-white solid, mp 151-154 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, J = 1.2, 8.0 Hz, 1H), 7.53 (ddd, J = 0.4, 7.6, 8.0 Hz, 1H), 7.43-7.49 (m, 3H), 7.31-7.38 (m, 4H), 4.42 (s, 2H), 3.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.3, 153.3, 145.4, 133.5, 131.6, 130.3, 129.5, 128.9, 128.6, 126.4, 124.6, 119.4, 117.0, 68.7, 58.8; IR ($CHCl_3$, cm^{-1}) 3063, 2908, 1721, 1606; MS m/z (rel intensity) 266 (100, M^+), 251 (40); HRMS calcd for $C_{17}H_{14}O_3$: 266.0943, found: 266.0948. Spectral data for **3-methoxymethyl-4-phenyl-2*H*-1-benzopyran-2-one (32)** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 7.31-7.55 (m, 7H), 7.15 (d, J = 1.2, 6.8, 8.0 Hz, 1H), 7.10 (dd, J = 1.2, 8.0 Hz, 1H), 4.13 (s, 2H), 3.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.7, 154.9, 153.5, 133.7, 132.0, 129.2, 128.8, 128.5, 128.2, 124.3, 122.6, 120.4, 67.3, 59.0 (one sp^2 carbon missing due to overlap).

4-(*tert*-Butyldimethylsilyloxy)methyl-3-phenyl-2*H*-1-benzopyran-2-one (33). White solid, mp 130-131 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.30-7.55 (m, 8H), 4.64 (s, 2H), 0.85 (s, 9H), – 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 161.6, 153.5, 147.8, 133.5, 131.4, 130.4, 128.9, 128.5, 127.9, 126.8, 124.4, 119.6, 117.0, 60.1, 25.9, 18.4, – 5.3; MS m/z (rel intensity) 309 (89, M^+-57), 215 (77), 178(100). Anal. Calcd for $C_{22}H_{26}O_3Si$: C, 72.08; H, 7.16. Found: C, 72.14, H, 7.48.

3-(*tert*-Butyldimethylsilyloxy)methyl-4-phenyl-2*H*-1-benzopyran-2-one (34). White solid; ^{1}H NMR ($CDCl_3$) δ 7.32-7.52 (m, 7H), 7.11-7.14 (m, 2H), 4.35 (s, 2H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 161.5, 160.3, 153.6, 133.9, 132.1, 131.6, 129.1, 128.6, 128.1, 125.0, 124.2, 120.8, 117.0, 58.4, 26.1, 18.6, – 5.3. Only a small amount was isolated, therefore no other data were obtained.

4-Benzyloxymethyl-3-phenyl-2*H*-1-benzopyran-2-one (35). White solid, mp 93-96 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.53 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.41-7.44 (m, 2H), 7.24-7.38 (m, 9H), 4.49-4.50 (2 overlapping s, 4H); ^{13}C NMR ($CDCl_3$) δ 161.3, 153.4, 145.5, 137.3, 133.4, 131.6, 130.3, 129.5, 128.9, 128.7, 128.5, 128.3, 126.5, 124.6, 119.4, 117.0, 73.4, 66.3 (one sp^2 carbon is missing due to overlap); IR ($CHCl_3$, cm^{-1}) 1718; MS m/z (rel intensity) 342 (14, M^+), 251 (25), 236 (100), 91 (73). Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.57; H, 5.40.

3-Benzyloxymethyl-4-phenyl-2*H*-1-benzopyran-2-one (36). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.49-7.53 (m, 4H), 7.34-7.39 (m, 3H), 7.23-7.31 (m, 5H), 7.15 (ddd, *J* = 1.2, 6.8, 8.0 Hz, 1H), 7.09 (dd, *J* = 1.6, 8.0 Hz, 1H), 4.50 (s, 2H), 4.25 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 161.8, 154.9, 153.6, 138.3, 133.8, 132.0, 129.2, 128.9, 128.7, 128.5, 128.2, 128.0, 127.8, 124.3, 122.8, 120.5, 117.0, 73.6, 65.3; IR ($CHCl_3$, cm^{-1}) 1716, 1605; MS m/z (rel intensity) 342 (M^+, 11), 236 (68), 235 (100). HRMS calcd for $C_{23}H_{18}O_3$: 342.1256, found: 342.1260.

4-(*tert*-Butyldimethylsilyloxy)methyl-3-methyl-2*H*-1-benzopyran-2-one (37) and **3-(*tert*-butyldimethylsilyloxy)methyl-4-methyl-2*H*-1-benzopyran-2-one (38)** have been obtained as an inseparable 1:1.7 mixture. **3-(*tert*-Butyldimethylsilyloxy)methyl-4-methyl-2*H*-1-benzopyran-2-one (38)** (major isomer): ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, *J* = 0.4, 8.4 Hz, 1H), 7.51 (ddd, *J* = 0.4, 7.2, 8.4 Hz, 1H), 7.26-7.32 (m, 2H), 4.77 (s, 2H), 2.55 (s, 3H), 0.90 (s, 9H), 0.12 (s, 6H). **4-(*tert*-Butyldimethylsilyloxy)methyl-3-methyl-2*H*-1-benzopyran-2-one (37)** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 7.84 (dd, *J* = 0.4, 8.0 Hz, 1H), 7.46 (ddd, *J* = 0.4, 7.2, 8.0 Hz, 1H), 7.26-7.32 (m, 2H), 4.87 (s, 2H), 2.27 (s, 3H), 0.90 (s, 9H), 0.13 (s, 6H). Additional spectral data for the product mixture: ^{13}C NMR ($CDCl_3$) δ 162.7, 161.4, 153.0,

152.7, 150.7, 146.7, 131.6, 130.6, 125.7, 125.0, 124.9, 124.3, 124.2, 123.3, 120.9, 119.5, 117.1, 116.9, 58.8, 57.6, 26.1, 26.0, 18.5, 18.4, 15.1, 13.3, –5.0, –5.1.

4-Benzyloxymethyl-3-methyl-2*H*-1-benzopyran-2-one (39). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.46 (ddd, *J* = 1.2, 8.0, 8.4 Hz, 1H), 7.24-7.39 (m, 7H), 4.71 (s, 2H), 4.63 (s, 2H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.3, 152.5, 144.1, 137.4, 130.8, 128.8, 128.4, 128.2, 125.4, 125.3, 124.4, 119.4, 116.9, 73.2, 64.7, 13.4; IR (neat, cm^{-1}) 2929, 2848, 1726, 904; MS m/z (rel intensity) 280 (16, M^+), 174 (100), 146 (51), 115 (24), 91 (45); HRMS calcd for $C_{18}H_{16}O_3$: 280.1099, found: 280.1104.

3-Benzyloxymethyl-4-methyl-2*H*-1-benzopyran-2-one (40). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.52 (ddd, *J* = 1.6, 7.6, 8.4 Hz, 1H), 7.24-7.39 (m, 7H), 4.65 (s, 2H), 4.62 (s, 2H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.7, 153.0, 151.8, 138.2, 131.9, 128.6, 128.2, 128.0, 125.1, 124.4, 122.5, 120.6, 117.1, 73.2, 64.2, 15.3; IR (neat, cm^{-1}) 3063, 2926, 2858, 1717, 1700, 1606, 1085; MS m/z (rel intensity) 281 (100), 280 (42, M^+), 174 (31), 91 (23); HRMS calcd for $C_{18}H_{16}O_3$: 280.1099, found: 280.1104.

4-Methyl-3-trimethylsilyl-2*H*-1-benzopyran-2-one (41). White solid, mp 92-93 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.48 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.23-7.28 (m, 2H), 2.53 (s, 3H), 0.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.2, 158.5, 153.8, 131.7, 126.0, 124.7, 123.9, 120.9, 116.9, 18.9, 1.6; IR ($CHCl_3$, cm^{-1}) 2953, 1701, 1691, 1604, 1598; MS m/z (rel intensity) 232 (10, M^+), 217 (100), 115 (26). Anal. Calcd for $C_{13}H_{16}O_2Si$: C, 67.20; H, 6.94. Found: C, 67.32; H, 7.10.

4-Phenyl-3-trimethylsilyl-2*H*-1-benzopyran-2-one (42). White solid, mp 149-151 °C; ^{1}H NMR ($CDCl_3$) δ 7.44-7.49 (m, 4H), 7.32 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.23-7.25 (m, 2H),

7.08 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 6.95 (dd, J = 1.6, 8.0 Hz, 1H), – 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.4, 162.2, 154.0, 137.2, 131.8, 128.9, 128.9, 128.6, 127.6, 127.1, 123.8, 121.2, 116.7, 0.0; IR ($CHCl_3$, cm^{-1}) 1716, 1699; MS m/z (rel intensity) 294 (10, M^+), 279 (100). Anal. Calcd for $C_{18}H_{18}O_2Si$: C, 73.43; H, 6.16. Found: C, 73.40; H, 6.07.

4-Methyl-3-tri(isopropyl)silyl-2*H*-1-benzopyran-2-one (43). White solid, mp 82-85 °C; ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, J = 1.2, 8.0 Hz, 1H), 7.49 (ddd, J = 1.2, 7.6, 8.0 Hz, 1H), 7.22-7.29 (m, 2H), 2.58 (s, 3H), 1.65 (septet, J = 7.4 Hz, 3H), 1.43 (d, J = 7.6 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 163.6, 159.8, 153.7, 131.7, 124.7, 123.9, 123.8, 121.0, 116.8, 20.1, 19.4, 13.3; MS m/z (rel intensity) 273 (100, $[M-C_3H_7]^+$); HRMS $(M-C_3H_7)^+$ calcd for $C_{16}H_{21}O_2Si$: 273.1311, found: 273.1317.

3-Acetyl-4-ethyl-2*H*-1-benzopyran-2-one (44) and **4-acetyl-3-ethyl-2*H*-1-benzopyran-2-one (45)**. Separation of the reaction mixture by column chromatography on silica gel using 4:1 hexanes/ethyl acetate as the eluent afforded two fractions: one containing 36 mg (33 %) of pure 3-acetyl-4-ethyl-2*H*-1-benzopyran-2-one (**44**) (major isomer), and the other containing 30 mg (28 %) of a ~ 4.5:1 mixture of **44** and 4-acetyl-3-ethyl-2*H*-1-benzopyran-2-one (**45**) (minor isomer). **3-Acetyl-4-ethyl-2*H*-1-benzopyran-2-one (44)**: yellow oil, recrystallization from pentane-ether affords a white paste, mp 68-70 °C (lit.[28] mp 75-76 °C); ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, J = 1.2, 8.0 Hz, 1H), 7.59 (ddd, J = 1.6, 7.6, 8.4 Hz, 1H), 7.33-7.39 (m, 2H), 2.82 (q, J = 7.6 Hz, 2H), 2.59 (s, 3H), 1.34 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.8, 159.3, 155.9, 153.7, 132.8, 126.9, 125.8, 124.9, 118.7, 117.7, 31.4, 22.8, 14.9; all spectral properties are identical with those reported in the literature.[28] **4-Acetyl-3-ethyl-2*H*-1-benzopyran-2-one (45)**. ^{1}H NMR ($CDCl_3$) δ 7.52 (ddd, J = 1.2, 8.0,

8.4 Hz, 1H), 7.26-7.29 (m, 2H), 7.14 (dd, J = 1.2, 8.0 Hz, 1H), 2.60 (s, 3H), 2.50 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H). Since only a small amount of **45** could be obtained, a complete ^{13}C NMR spectrum has not been obtained. Only signals in the alkyl portion of the ^{13}C NMR spectrum have been detected: ($CDCl_3$) δ 32.1, 22.6, 14.4.

2-Benzoylmethyl-2-methyl-1-benzofuran-3(2*H*)-one (46). Yellow oil; ^1H NMR ($CDCl_3$) δ 7.86-7.88 (m, 2H), 7.76 (dd, J = 0.8, 8.4 Hz, 1H), 7.57-7.62 (m, 2H), 7.39-7.43 (m, 2H), 7.09-7.13 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 18 Hz, 1H), 3.62 (d, J = 17.6 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.5, 194.9, 170.9, 137.6, 136.3, 133.7, 128.8, 128.4, 124.6, 122.0, 121.2, 86.5, 45.8, 23.0; IR ($CHCl_3$, cm^{-1}) 3019, 1718, 1695, 1616, 1216; MS m/z (rel intensity) 266 (69, M^+), 161 (23), 105 (100); HRMS calcd for $C_{17}H_{14}O_3$: 266.0943, found: 266.0947.

Ethyl 4-phenyl-2-oxo-2*H*-1-benzopyran-3-carboxylate (47). Yellow oil; compound **47** was detected by GCMS (however, it was not isolated in a pure form). Every fraction obtained by column chromatography on silica gel using 4:1 ethyl acetate/hexanes as the eluent contained an unidentified by-product: ^1H NMR ($CDCl_3$) δ 7.59 (ddd, J = 2.0, 6.6, 8.6 Hz, 1H), 7.16-7.51 (m, 8H), 4.08 (q, J = 7.2 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H); GCMS m/z (rel intensity) 294 (35, M^+), 265 (15), 250 (100), 221 (30), 163 (35).

Ethyl 3-phenyl-2-oxo-2*H*-1-benzopyran-4-carboxylate (48). Yellow solid, mp 131-134 °C; ^1H NMR ($CDCl_3$) δ 7.58 (ddd, J = 1.2, 7.2, 8.0 Hz, 1H), 7.52 (dd, J = 1.2, 7.8 Hz, 1H), 7.39-7.45 (m, 6H), 7.33 (ddd, J = 0.8, 7.2, 8.0 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 0.98 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.2, 160.7, 153.6, 143.4, 133.2, 132.3, 129.5, 129.3, 128.5, 126.7, 126.2, 125.0, 117.3, 116.7, 62.4, 13.8; IR ($CHCl_3$, cm^{-1}) 2934,

1724, 1710; MS m/z (rel intensity) 294 (100, M^+), 221 (100). HRMS calcd for $C_{18}H_{14}O_4$: 294.0892, found: 294.0897.

4-Methyl-2*H*-1-benzopyran-2-one (50). White solid; ^{1}H NMR ($CDCl_3$) δ 7.62 (dd, J = 1.2, 8.0 Hz, 1H), 7.54 (ddd, J = 1.2, 7.6, 8.8 Hz, 1H), 7.29-7.36 (m, 2H), 6.31 (d, J = 1.2 Hz, 1H), 2.45 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.0, 153.7, 152.6, 132.0, 132.0, 124.8, 124.4, 120.2, 117.3, 115.3, 18.9. The spectral data are identical to those reported in the literature.[49]

Ethyl 4-methyl-2-oxo-2*H*-1-benzopyran-3-carboxylate (51) was identified by comparison of its ^{1}H NMR spectral data with those previously reported.[30] Only a small amount of **51** was isolated; therefore, no other spectral data have been obtained.

Ethyl 3-methyl-2-oxo-2*H*-1-benzopyran-4-carboxylate (52). White solid, mp 89-90 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, J = 1.2, 8.0 Hz, 1H), 7.59 (ddd, J = 1.6, 7.6, 8.4 Hz, 1H), 7.32-7.37 (m, 2H), 4.44 (q, J = 7.2 Hz, 1H), 2.49 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.1, 158.0, 153.2, 150.2, 133.0, 125.5, 124.9, 121.7, 119.4, 117.4, 62.4, 16.3, 14.4; IR (neat, cm^{-1}) 2914, 1724; MS m/z (rel intensity) 232 (61, M^+), 186 (100), 160 (34); HRMS calcd for $C_{13}H_{12}O_4$: 232.0736, found: 232.0738.

6-Acetyl-3,4-dipropyl-2*H*-1-benzopyran-2-one (53). White solid, mp 114-116 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 2.0, 8.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 2.83-2.87 (m, 2H), 2.61-2.66 (m, 5H), 1.57-1.71 (m, 4H), 1.13 (t, J = 7.4 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 196.6, 161.2, 155.8, 150.0, 133.3, 130.6, 127.7, 125.5, 120.0, 117.4, 30.6, 30.0, 26.8, 23.1, 22.5, 14.7, 14.5; IR (neat, cm^{-1}) 2963, 2933, 2873, 1716, 1676, 1606. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.95; H, 7.40.

6-Acetyl-3,4-diphenyl-2*H*-1-benzopyran-2-one (54). White solid, mp 155-158 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.32-7.36 (m, 3H), 7.19-7.21 (m, 3H), 7.12-7.15 (m, 4H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.3, 160.7, 156.2, 151.5, 133.9, 133.6, 133.4, 131.4, 130.6, 129.5, 129.0, 128.8, 128.7, 128.1, 128.0, 127.9, 120.6, 117.4, 26.6; IR (neat, cm^{-1}) 3063, 1726, 1681, 1601; MS m/z (rel intensity) 340 (100, M^+), 325 (64), 297 (93), 239 (59); HRMS calcd for $C_{23}H_{16}O_3$: 340.1099, found: 340.1107.

6-Acetyl-4-methyl-3-phenyl-2*H*-1-benzopyran-2-one (55). White solid, mp 169-171 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, *J* = 2.0 Hz, 1H), 8.13 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.42-7.49 (m, 4H), 7.23-7.32 (m, 2H), 2.68 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.6, 160.4, 155.7, 147.8, 134.0, 133.4, 131.5, 130.1, 128.7, 128.3, 126.1, 120.7, 117.2, 115.5, 26.8, 16.8; IR (neat, cm^{-1}) 1716, 1677, 1607; MS m/z (rel intensity) 278 (100, M^+), 277 (74), 263 (69), 235 (43), 178 (25); HRMS calcd for $C_{18}H_{14}O_3$: 278.0943, found: 278.0951.

6-Acetyl-3-methyl-4-phenyl-2*H*-1-benzopyran-2-one (56). White solid, mp 173-176 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.53-7.59 (m, 3H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.25-7.27 (m, 2H), 2.47 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.5, 161.8, 155.6, 150.5, 134.3, 133.4, 130.6, 129.3, 128.5, 128.0, 124.2, 120.8, 117.2, 26.6, 15.1; MS m/z (rel intensity) 278 (79, M^+), 277 (48), 263 (100), 178 (18); HRMS calcd for $C_{18}H_{14}O_3$: 278.0943, found: 278.0951.

Ethyl 2-oxo-3,4-dipropyl-2*H*-1-benzopyran-6-carboxylate (58). White solid, mp 82-86 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.82-2.86 (m, 2H), 2.60-2.64 (m, 2H), 1.57-1.70

(m, 4H), 1.43 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 7.4 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.9, 161.4, 155.7, 150.0, 131.4, 127.4, 127.0, 126.6, 119.8, 117.3, 61.6, 30.6, 30.0, 23.1, 22.5, 14.7, 14.5 (one sp^3 carbon is missing due to overlap); IR ($CHCl_3$, cm^{-1}) 2965, 1717, 1612; MS m/z (rel intensity) 302 (100, M^+), 288 (58), 287(81), 259 (96), 201(55). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.43; H, 7.40.

Methyl 2-oxo-3,4-dipropyl-2*H*-1-benzopyran-7-carboxylate (60). White solid, mp 93-95 °C; ^{1}H NMR ($CDCl_3$) δ 7.91-7.94 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H), 2.78-2.83 (m, 2H), 2.61-2.65 (m, 2H), 1.58-1.68 (m, 4H), 1.12 (t, J = 7.4 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.1, 161.6, 152.4, 149.2, 131.7, 129.0, 124.9, 124.8, 123.6, 118.3, 52.8, 30.8, 30.1, 23.0, 22.5, 14.7, 14.5; IR ($CHCl_3$, cm^{-1}) 2965, 2874, 1717, 1701, 1608; MS m/z (rel intensity) 288 (68, M^+), 273 (96), 245 (100). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.75; H, 6.75.

6-Methoxy-3,4-dipropyl-2*H*-1-benzopyran-2-one (62). Slightly yellow solid, mp 83-85 °C; ^{1}H NMR ($CDCl_3$) δ 7.23-7.26 (m, 1H), 7.03-7.05 (m, 2H), 3.86 (s, 3H), 2.73-2.78 (m, 2H), 2.58-2.63 (m, 2H), 1.56-1.69 (m, 4H), 1.10 (t, J = 7.4 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.2, 156.0, 149.7, 147.1, 127.0, 120.5, 117.9, 116.9, 108.5, 56.0, 30.8, 30.0, 22.9, 22.5, 14.7, 14.5; IR ($CHCl_3$, cm^{-1}) 2964, 2873, 1699, 1570, 1497; MS m/z (rel intensity) 260 (100, M^+), 245 (30), 217 (43). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.05, H, 7.83.

3,4,8,9-Tetrapropylbenzo[1,2-*b*:4,5-*b*']dipyran-2,7-dione (66). Yellow solid, mp 188-190 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1H), 2.75-2.80 (m, 2H), 2.62-2.66 (m, 2H), 1.58-1.68 (m, 4H), 1.12 (t, J = 7.4 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.4,

148.9, 148.6, 128.7, 121.6, 111.9, 30.9, 30.1, 22.9, 22.5, 14.7, 14.5; IR ($CHCl_3$, cm^{-1}) 2965, 2874, 1699, 1601; MS m/z (rel intensity) 382 (100, M^+), 353 (41), 339 (52). Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.48; H, 7.93.

Ethyl 3,4-dipropyl-2-oxo-2*H*-pyran[2,3-*b*]pyridine-6-carboxylate (69). White solid, mp 65-69 °C; ^1H NMR ($CDCl_3$) δ 9.05 (d, J = 2.0 Hz, 1H), 8.54 (d, J = 2.4 Hz, 1H), 4.46 (q, J = 7.2 Hz, 1H), 2.81-2.86 (m, 2H), 2.61-2.65 (m, 2H), 1.58-1.70 (m, 4H), 1.45 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.4 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.5, 160.7, 160.0, 150.7, 148.5, 135.6, 129.0, 123.9, 114.9, 62.0, 30.3, 30.0, 22.9, 22.4, 14.6, 14.5 (one sp^3 carbon is missing due to overlap); IR ($CHCl_3$, cm^{-1}) 2966, 2875, 1733, 1717, 1599; MS m/z (rel intensity) 303 (100, M^+), 288 (58), 260 (51). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.02; H, 6.67; N, 4.39.

Trapping of the acylpalladium complexes with an external alcohol. 2-Iodophenol (110 mg, 0.5 mmol), 4-octyne (275 mg, 2.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol), and DMF (5 ml) were placed in a 4 dram vial. The vial was purged with CO for 2 min, then connected to a balloon of CO. An alcohol (10 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred at 120 °C for 24 h, then allowed to cool to room temperature, diluted with EtOAc, washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel.

Carbonylative annulation of internal alkynes with *o*-iodobenzylic alcohols. The *o*-iodobenzylic alcohol (0.5 mmol), the alkyne (2.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-

Bu_4NCl (139 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol) and DMF (5 ml) were placed in a 4 dram vial. The vial was purged with CO for 2 min, then connected to a balloon of CO. Upon completion of the reaction (for the reaction temperatures and times see Table 8), the reaction mixture was cooled to room temperature, diluted with EtOAc, washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel.

1(3*H*)-Isobenzofuranone (73). White solid, the spectral properties were identical to those reported in the literature.[50]

4,5-Dipropyl-1,3-dihydrobenzo[*c*]oxepin-3-one (74a). Colorless oil; ^1H NMR ($CDCl_3$) δ 7.37-7.48 (m, 3H), 7.31 (ddd, J = 1.2, 7.2, 7.6 Hz, 1H), 5.04 (d, J = 11.6 Hz, 1H), 4.81 (d, J = 11.6 Hz, 1H), 2.66-2.73 (m, 3H), 2.53-2.58 (m, 1H), 1.60-1.66 (m, 2H), 1.34-1.45 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.0, 143.5, 139.4, 135.7, 133.1, 129.5, 128.5, 128.2, 127.2, 68.2, 35.1, 34.2, 23.3, 22.5, 14.4, 14.3; IR ($CHCl_3$, cm^{-1}) 2959, 2872, 1707; MS m/z (rel intensity) 244 (45, M^+), 201 (71), 173 (100), 161 (91), 129 (52), 128 (49). HRMS calcd for $C_{16}H_{20}O_2$: 244.1463, found: 244.1468.

4,5-Diphenyl-1,3-dihydrobenzo[*c*]oxepin-3-one (74b). White crystals, mp 200-203 °C; ^1H NMR ($CDCl_3$) δ 7.44-7.50 (m, 3H), 7.39 (ddd, J = 1.2, 7.2, 8.0 Hz, 1H), 7.31 (ddd, J = 1.2, 7.6, 8.4 Hz, 1H), 7.12-7.19 (m, 6H), 6.96-6.98 (m, 3H), 5.51 (br, 1H), 5.05 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 169.3, 145.3, 140.4, 140.2, 136.7, 136.1, 133.0, 131.3, 131.2, 130.7, 129.5, 129.4, 128.4, 128.1, 128.0, 127.9, 127.7, 68.6; IR ($CHCl_3$, cm^{-1}) 3057, 1718; MS m/z (rel intensity) 312 (29, M^+), 235 (42), 233 (100), 260 (51); HRMS calcd for $C_{22}H_{16}O_2$: 312.1150, found: 312.1155.

3,3-Dimethyl-1(3*H*)-isobenzofuranone (76). White solid, the spectral properties were identical to those reported in the literature.[51]

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CHAPTER II. SYNTHESIS OF 2-QUINOLONES VIA PALLADIUM-CATALYZED CARBONYLATIVE ANNULATION OF INTERNAL ALKYNES BY *N*-SUBSTITUTED *o*-IODOANILINES

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

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Abstract

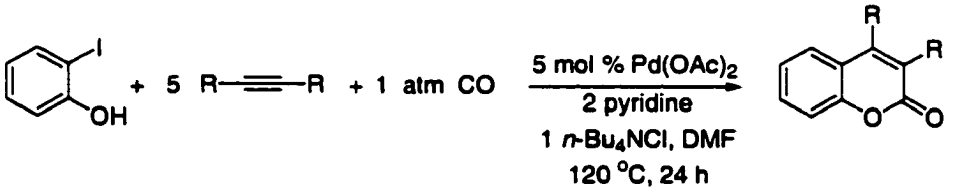
The palladium-catalyzed annulation of internal alkynes by *N*-substituted *o*-iodoanilines under one atmosphere of carbon monoxide results in the formation of 3,4-disubstituted 2-quinolones. The nature of the substituent on the nitrogen is crucial to obtaining high yields of 2-quinolones. The best results are obtained using alkoxycarbonyl, *p*-tolylsulfonyl, and trifluoroacetyl substituents. The nitrogen substituent is lost during the course of the reaction resulting in the formation of *N*-unsubstituted 2-quinolones. A variety of internal alkynes, bearing alkyl, aryl, heteroaryl, hydroxyl and alkoxyl substituents are effective in this process. Electron-rich and electron-poor *N*-substituted *o*-iodoanilines, as well as heterocyclic analogues, can be employed as annulating agents.

Introduction

The development in the last two decades of transition metal-catalyzed multi-component processes, which involve the formation of several carbon-carbon and/or carbon-

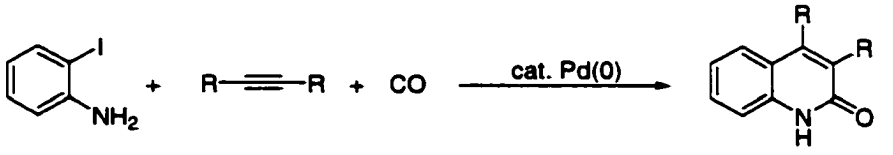
heteroatom bonds in a single step, has significantly expanded the arsenal of synthetic organic chemistry, allowing easy access to complex molecular structures from fairly simple precursors. In particular, palladium-catalyzed annulations of unsaturated molecules, such as 1,3-dienes, allenes, and internal alkynes, with various substituted aryl and vinylic halides provide a concise and efficient route to a wide variety of hetero- and carbocycles.[1] The introduction of a second component, such as carbon monoxide, into these processes would further increase their efficiency and synthetic utility. Several examples of palladium-catalyzed reactions of *o*-iodophenols and *o*-iodoanilines with norbornene,[2] norbornadiene,[3] allenes,[4] and terminal alkynes[3a,5] in the presence of CO have been reported.

We have recently reported that the palladium-catalyzed carbonylative annulation of internal alkynes with *o*-iodophenols results in the exclusive formation of coumarins (eq 1).[6] This method represents a unique reactivity, namely an intermolecular insertion of an internal



(1)

alkyne into an arylpalladium bond in preference to the insertion of CO. We envisioned that this process might be extended to *o*-iodoanilines, which would lead to the formation of 3,4-disubstituted 2-quinolones (eq 2).

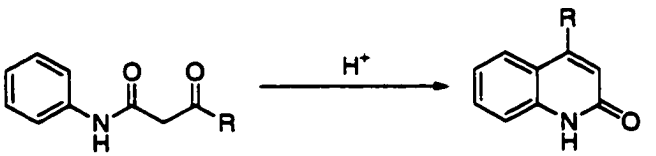


(2)

The 2-quinolone core is widely found in various alkaloids, many of which possess interesting biological activity. There has been considerable interest in developing 2-

quinolones as anticancer,[7] antiviral,[8] and antihypertensive agents.[8] 4-Substituted-3-phenyl-2-quinolones exhibit high affinity in binding to the glycine site of the *N*-methyl-D-aspartate receptor,[9] and such antagonists have promise for the treatment of several central nervous system disorders. Amides of 3-hydroxy- and 3-alkyl-4-carboxylic acids of 2-quinolones also exhibit high affinity for the 5-HT_3 serotonin receptor.[10] 2-Quinolones are also valuable intermediates in organic synthesis, since they are easily converted into 2-chloro- and then 2-aminoquinoline derivatives.[11]

The classic methods of synthesizing 2-quinolones involve the formation of either the C4-C9 or the C3-C4 bond. In both cases the amide bond must be formed first. The former method is known as the Knorr synthesis and involves the acid-catalyzed cyclization of a β-ketoanilide (eq 3).[12] The desired β-ketoanilide is formed by the reaction of the

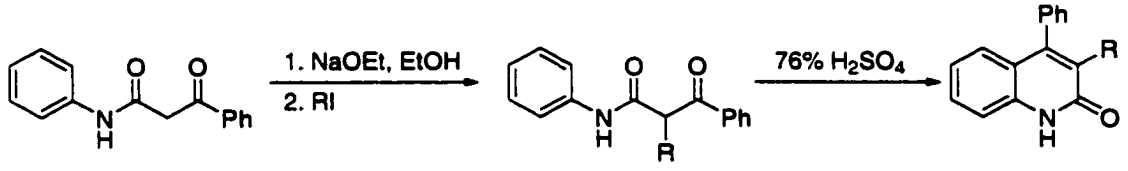


(3)

corresponding aniline and a β-ketoester at high temperatures without an acid catalyst. The use of lower reaction temperatures and the presence of an acid leads to the formation of crotonates and, eventually, 4-quinolones. Alternatively, β-ketoanilides are synthesized using ketenes or ethoxyacryloyl chlorides. Although a wide variety of either 3- or 4-substituted-2-quinolones have been prepared by this method, several factors significantly limit the scope of the reaction. First, the usual reaction medium is concentrated or 76% sulfuric acid, and, therefore, acid-sensitive substituents cannot be introduced into the final 2-quinolones. Besides, side reactions, such as sulfonation, are possible with electron-rich amines. Second, since the first step is nucleophilic attack on the ester by an amino group, electron-poor

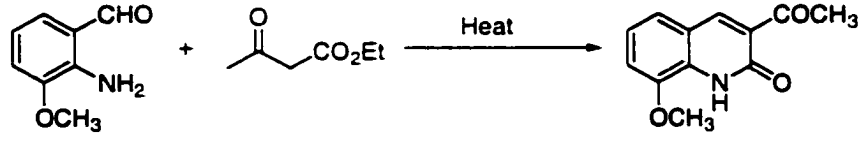
anilines give low yields of the desired 2-quinolones. In addition, some β-ketoanilides are unstable, particularly towards hydrolysis, further limiting the variety of substituents, which can be present on the aniline. Third, the use of *meta*-substituted anilines can result in the formation of two isomeric quinolones, although in many reported cases the 7-substituted isomer is the major product.

3,4-Disubstituted quinolones can be prepared by the Knorr synthesis utilizing α-substituted β-ketoanilides. However, due to difficulties in preparing the corresponding β-ketoanilides, it is more advantageous to introduce the 3-substituent by alkylation of the enolate of a simple β-ketoanilide (eq 4).[13] The increase in the bulk of either the 3- or 4-substituent inhibits the cyclization step, resulting in low yields of 2-quinolones.



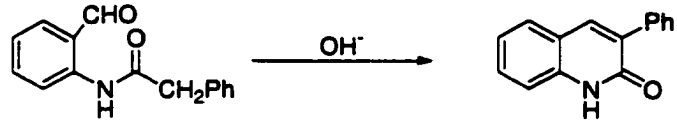
(4)

The reaction of an *o*-aminobenzaldehyde or an *o*-aminoketone with a β-ketoester (the Friedländer synthesis) leads to the formation of either esters of quinoline-3-carboxylic acids or 3-acyl-2-quinolones depending on the reaction conditions employed.[14] Heating the reagents at 130-160 °C without a catalyst leads to condensation between the aromatic amine and the ester group, and thus, produces exclusively 2-quinolones (eq 5). Malonate esters and even malonic acid itself also undergo this reaction, sometimes under milder conditions.



(5)

The base-catalyzed cyclization of an acylated *o*-aminobenzaldehyde or *o*-aminoaryl ketone leads to either a 2- or 4-quinolone, depending on the substrate structure (the Camps modification of the Friedländer synthesis).[15] *o*-(Acylamino)benzaldehydes (eq 6), diaryl ketones, or alkyl ketones containing an activated methylene group in the amide (eq 7) form 2-quinolones, while *o*-aroyl- or *o*-formylanilides form 4-quinolones. Thus, the scope of this



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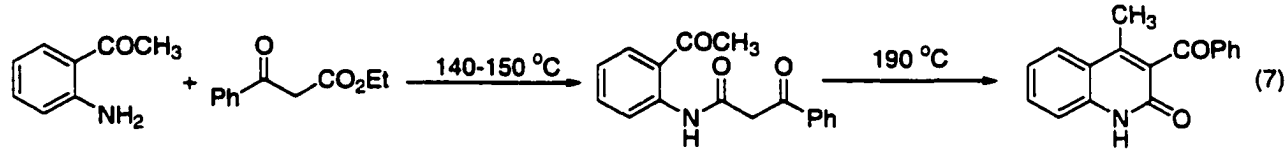
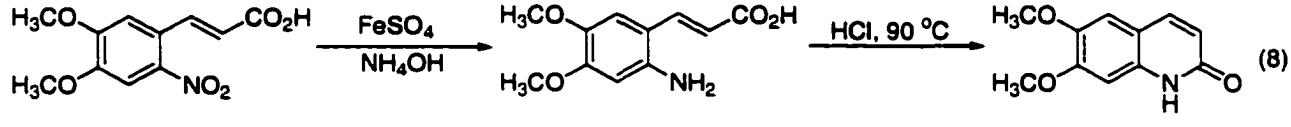


(7)

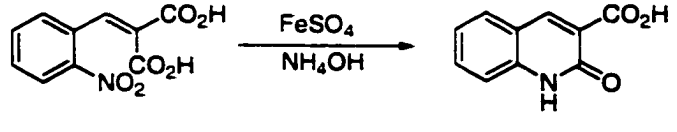
process is somewhat limited. Besides, very high temperatures, up to 200 °C, are required to effect the cyclization. Hydrolysis of the starting amide is also a significant side reaction.

The reductive cyclization of *o*-nitrocinnamic acids also leads to the formation of 2-quinolones (eq 8).[16] Treatment of the intermediate *o*-aminocinnamic acid with an acid to



(8)

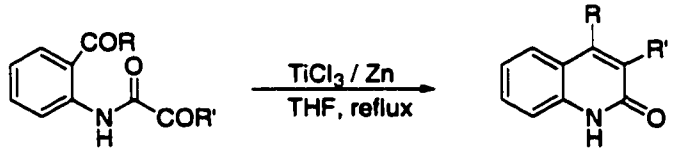
effect *trans-cis* isomerization is absolutely crucial, since simple heating results in decomposition of the *o*-aminocinnamic acid. 2-Quinolone-3-carboxylic acids are produced upon reduction of *o*-nitrobenzylidenemalonic acids (eq 9).[17] The scope of these methods is



(9)

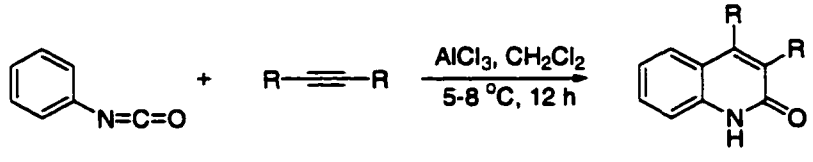
very limited, since a variety of products can be obtained depending on the reducing agent employed.

Several additional methods for the synthesis of 2-quinolones have appeared in the last twenty years. Some of them are variations of the classical Knorr[18] and Friedländer[19] syntheses, and the synthetic utility of these methods is severely limited. An interesting method of forming the C3-C4 double bond of 2-quinolones by the titanium-promoted intramolecular reductive cyclization of *N*-(2-acylphenyl) α-ketoamides (eq 10) has been reported by Furstner and co-workers.[20]



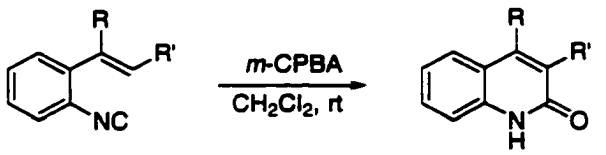
(10)

Two interesting methods employ an isocyanate group as a precursor of the amide fragment of the 2-quinolones. Merault and co-workers reported that $AlCl_3$-promoted annulation of terminal and internal alkynes with phenyl isocyanate produces 2-quinolones in satisfactory yields and excellent regioselectivity (eq 11).[21] This method is an interesting way



(11)

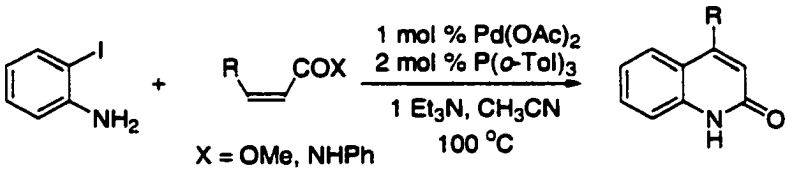
to synthesize 3,4-disubstituted 2-quinolones. However, very few examples are reported in the original paper. Besides, the use of $AlCl_3$ imposes severe limitations on the functional groups that can be introduced. Kobayashi and co-workers recently reported a synthesis of 2-quinolones by the electrocyclic closure of 2-isocyanatostyrenes generated in situ by oxidation of the corresponding 2-cyanostyrenes with *m*-CPBA (eq 12).[22] However, only substrates with monosubstituted double bonds give good yields of the desired quinolones. For example,



(12)

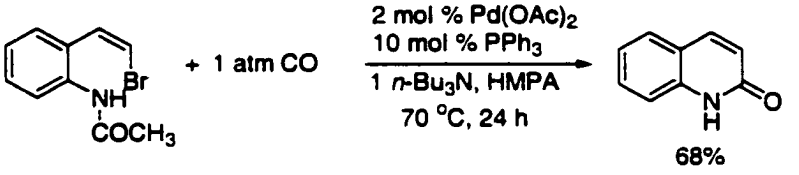
3,4-dimethyl- and 3-methyl-4-phenyl-2-quinolones have been obtained in 43 and 22% yields, respectively. The muti-step preparation of the starting materials further limits the synthetic value of this method.

Very few transition metal-catalyzed syntheses of 2-quinolones have been reported. Heck showed that the palladium-catalyzed reaction of 2-iodoaniline with β-substituted acrylic acid derivatives results in the formation of 4-substituted 2-quinolones (eq 13).[23] The Heck reaction of *o*-bromo- and *o*-triflatonitrobenzenes with acrylic acid, followed by



(13)

reduction of the nitro group and acid-catalyzed cyclization has been reported by Holzapfel and Dwyer as a useful route to 2-quinolones.[24] Mori and co-workers have reported a synthesis of 2-quinolone itself by the palladium-catalyzed carbonylation of (*Z*)-2-acetamino-α-bromostyrene (eq 14).[25]

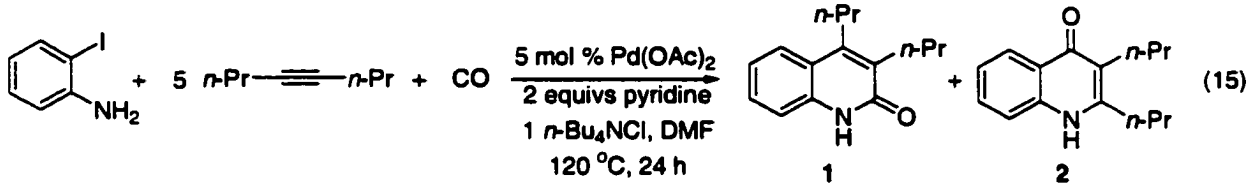


(14)

Herein, we report a new method for the synthesis of 2-quinolones via palladium-catalyzed carbonylative annulation of internal alkynes by *N*-substituted *o*-iodoanilines.

Results and Discussion

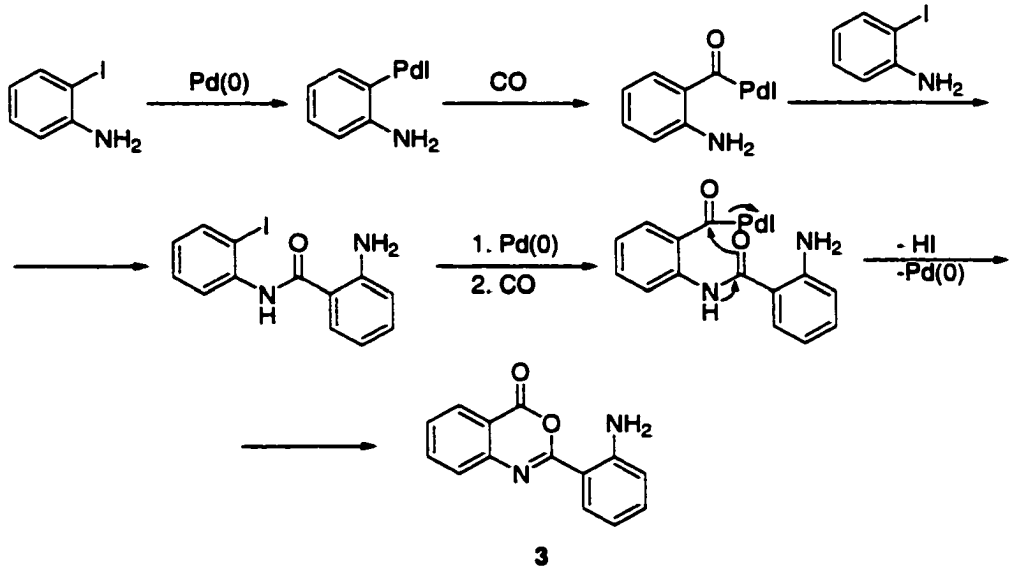
Optimization of the Reaction Conditions. The reaction of *o*-iodoaniline and various internal alkynes, such as 4-octyne and diphenylacetylene, in the presence of 1 atm of CO under the standard reaction conditions for our coumarin synthesis did not afford any of the desired quinolone products **1** or **2** (eq 15). Variations of the palladium catalyst, the base,



(15)

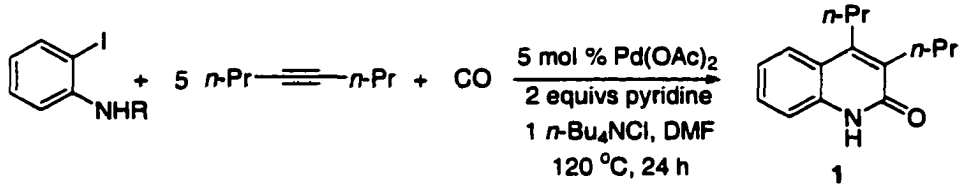
and the temperature, or the addition of phosphine ligands did not result in any improvement. In some of these reactions, small amounts of benzoxazine **3** were isolated. A mechanism for the formation of this product has been proposed by Cacchi (Scheme 1).[26] It involves attack of the amino group on an acylpalladium complex formed from another molecule of *o*-iodoaniline. Another oxidative addition, a CO insertion, and intramolecular attack on the acylpalladium complex lead to the final product.

Scheme 1



Since attack of the amino group is a crucial step in this process, we speculated that the failure of the annulation process can be attributed to the high nucleophilicity of the amino group. Therefore, protection of the amino group has been explored as a possible strategy to alleviate the problem. Indeed, the reaction of 4-octyne with *N*-tosyl-*o*-iodoaniline under our standard coumarin conditions afforded 3,4-dipropyl-2-quinolone (**1**) in 56% yield. Unexpectedly, the tosyl group was removed during the course of the reaction, and no traces of the quinolone containing the tosyl group have been detected. Since *o*-iodoaniline derivatives are generally more reactive than the *o*-iodophenols used in our earlier annulation chemistry,[27] lower reaction temperatures were examined next. At 100 °C, the reaction was incomplete after 24 h, affording only a 42% yield of **1**, along with 38% of the recovered starting material. No starting material was recovered after 48 h, and quinolone **1** was obtained in a 56% yield.

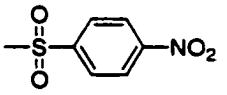
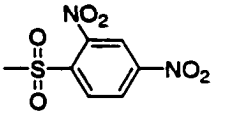
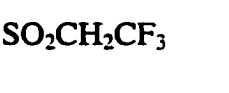
Next, the effect of various protecting groups was examined (eq 16). The results are



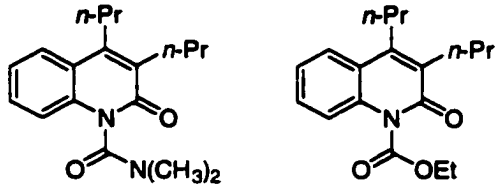
(16)

summarized in Table 1. A variety of substituents, including a methyl (entry 2), sulfonyl (entries 3, 7-9), acyl (entries 4, 6 and 10), aminocarbonyl (entry 5), and alkoxycarbonyl groups (entries 11 and 12) have been examined. None of the desired product was obtained when a simple alkyl substituent was employed (entry 2). Only the reduction product, *N*-methylaniline, has been isolated in 33% yield, along with 26% of the unreacted starting material. Analysis of the results with other substituents (entries 3-11) shows that the yield of quinolone **1** correlates well with the electron-withdrawing ability of the substituent on the

Table 1. Effect of the substituent on the nitrogen (eq 16).[a]

entry	R	% yield of **1**	recovery of starting material, %
1	H	0	0
2	CH_3	0[b]	26
3	SO_2CF_3	traces	55
4	$COCH_3$	12	12
5	$CON(CH_3)_2$	23[c]	0
6	CHO	33	0
7	SO_2CH_3	40	20
8	SO_2-*p*-Tol	42	38
9		56[d]	0
10	$COCF_3$	56	0
11	$CO_2CH_2CH_3$	71[e]	0
12	$CO_2C(CH_3)_3$	75	0
13	$SO_2C_6F_5$	8	*ca.* 30
14		15	*ca.* 40
15		7	*ca.* 50
16	$SO_2CH_2CF_3$	47	*ca.* 30
17		54[d]	0
18	$COCCl_3$	0[f]	38
19	$CO_2CH_2CCl_3$	26	0

[a] The standard reaction conditions: *N*-substituted-*o*-iodoaniline (0.5 mmol), 4-octyne (2.5 mmol), pyridine (1 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 ml) at 100 °C for 24 h. [b] *N*-Methylaniline was isolated in a 33% yield. [c] Isolated as a 70:30 mixture of **1** and **4**. [d] The reaction was run for 48 h. [e] Isolated as an 85:15 mixture of **1** and **5**. [f] *N*-(2-Iodophenyl)dichloroacetamide was isolated in an 11% yield.



4 5

nitrogen, as measured by the pK_a (NH) of the corresponding *N*-substituted anilines (Figure 1). The best yields of quinolone are obtained when strongly electron-withdrawing groups, such as a tosyl or trifluoroacetyl group, are employed (entries 9 and 10), while the use of weaker electron-withdrawing groups, such as an acetyl group (entry 4), results in a significant decrease in the yield. It is worth noting, that the pK_a's of *N*-tosylaniline (8.40) and

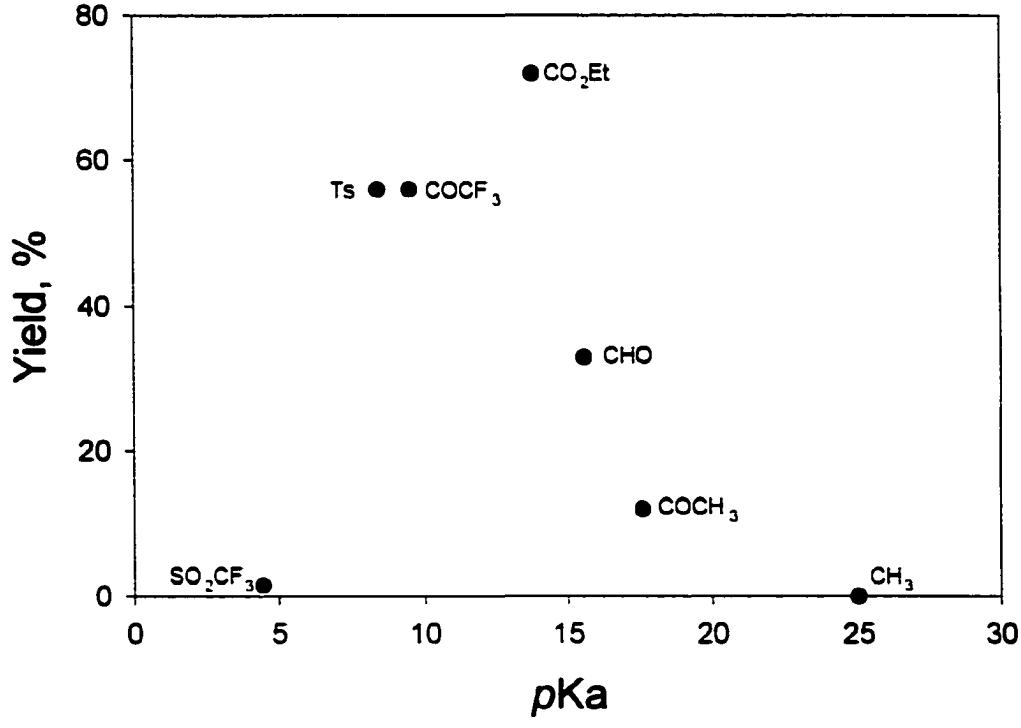
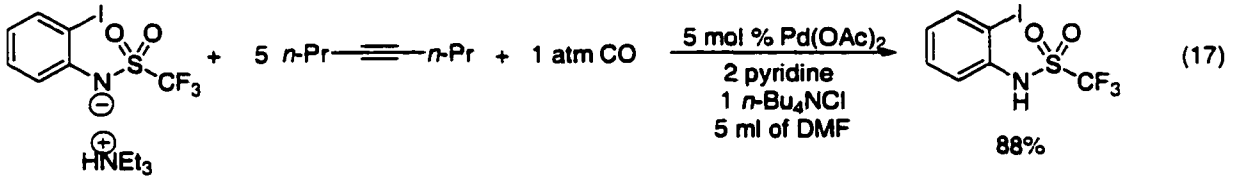


Figure 1. Dependence of the yield of **1** on the pK_a (NH) of PhNHR (the R group is shown in the boxes next to the data points).

trifluoroacetanilide (9.51) are very close to the pK_a of phenol (9.98). Therefore, the effect of the electron-withdrawing strength of the nitrogen substituent likely indicates that deprotonation of the NH group occurs during the reaction. Interestingly, the reaction of the *o*-iodoaniline bearing an extremely strong electron-withdrawing group, such as a triflate (entry 3), did not afford any of the desired product. Moreover, 55% of the starting material was recovered from the reaction mixture. In this case, the amide nitrogen is so acidic (pK_a = 4.55), that it can be fully deprotonated by pyridine (pK_a = 5.20). This deprotonation apparently makes the starting material completely unreactive in the carbonylative annulation. Indeed, the completely ionized version of this compound has been prepared, and subjected to the reaction with 4-octyne under the standard carbonylative annulation conditions (eq 17). None of the desired quinolone has been detected, and *N*-trifluoromethanesulfonyl-*o*-iodoaniline was recovered after the work-up in an 88% yield.



(17)

The best results have been obtained by employing alkoxycarbonyl substituents (entries 11 and 12), even though they are not as strong electron-withdrawing groups as tosyl or trifluoroacetyl (pK_a for $PhNHCO_2Et$ = 13.8, Figure 1), thus indicating that the electron-withdrawing strength of the substituents is not the sole factor determining the yield of the quinolone. Nonetheless, we have attempted to further improve the yield of the reaction by changing the acidity of the amino group and have examined several other sulfonamides, amides, and carbamates. Out of four sulfonamides examined, only the 2,2,2-

trifluoroethanesulfonamide group (entries 16 and 17), which is intermediate in strength between a mesyl and a triflyl group, afforded the desired quinolone in a good yield. Its reactivity appears to be quite similar to that of the tosylamide, and the reaction was complete only after 48 h (entry 17). Three sulfonamides that are more acidic than the tosylamide gave very low yields of **1**. The pentafluorobenzenesulfonyl group (entry 13) appears to be a very strong electron-withdrawing group, and its behavior closely resembles the behavior of the triflyl group. The poor reactivity of both of the nitro-substituted benzenesulfonamides examined (entries 14 and 15) can be attributed both to the higher acidity of these derivatives, as well as the ability of the nitro groups to possibly oxidize Pd(0) to Pd(II).

Substituents bearing chlorine atoms appear to be very unstable in the presence of palladium. In fact, the carbonylative annulation of *N*-trichloroacetyl-*o*-iodoaniline did not afford any of the desired quinolone (entry 18). Instead, a small amount (11%) of *N*-dichloroacetyl-*o*-iodoaniline was isolated along with 38% of the unreacted starting material. Zinc metal is widely used for the deprotection of trichloroacetates,[28] so it is reasonable to believe that a trichloromethyl groups might be very reactive towards metals. This reactivity may also be the reason for the low yield of **1** obtained in the reaction of 2,2,2-trichloroethyl *N*-(2-iodophenyl)carbamate (entry 19).

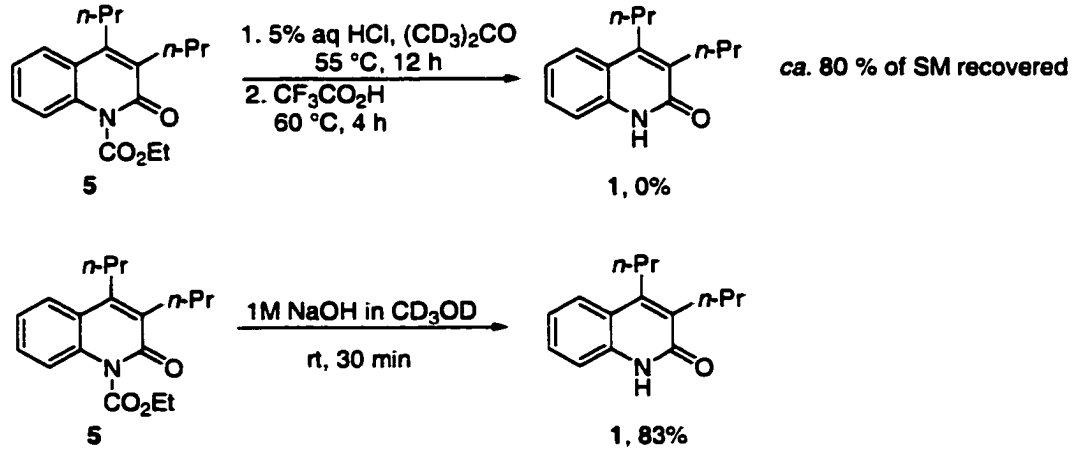
Alkyl carbamate, tosylamide, and trifluoroacetamide groups afforded the best yields of quinolone **1**. Therefore, they have been selected as model systems for further optimization. It should be mentioned here that carbonylative annulation of all but two *N*-substituted *o*-iodoanilines shown in Table 1 afforded only the unprotected quinolone **1**. The *in situ* deprotection of the 2-quinolone nitrogen is not unprecedented. Bolotin and co-workers reported that condensation of *N*-tosyl-2-aminobenzaldehyde with phenylacetic acid

afforded only unprotected 3-phenyl-2-(1*H*)-quinolone in a 90% yield.[29] The palladium-catalyzed carbonylation of (*Z*)-2-acetamino-α-bromostyrene (see eq 14) also produced only the unprotected 2-quinolone.[25]

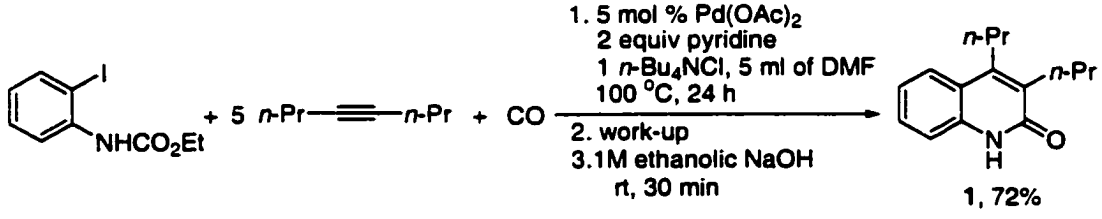
In our studies, only in the reactions of *N,N*-dimethyl-*N'*-(2-iodophenyl)urea (entry 5) and ethyl *N*-(2-iodophenyl)carbamate (entry 11) was the protected quinolone isolated in 7% and 11% yields, along with 16% and 60% yields of the unprotected quinolone **1**, respectively. Since the reaction with ethyl *N*-(2-iodophenyl)carbamate afforded one of the best yields of the desired product, ways to achieve complete deprotection during the reaction have been explored. Increasing the amount of pyridine to 5 equiv did not produce the desired result; the yields of **1** and **5** were 47% and 18%, respectively. Increasing the temperature to 120 °C led to the disappearance of **5**, but the yield of **1** was only 57%. As indicated in Table 1, only the unprotected product **1** can be obtained by employing *tert*-butyl *N*-(2-iodophenyl)carbamate (entry 12).

The protected quinolone **5** has been isolated, and its hydrolysis under acidic and basic conditions has been investigated (Scheme 2). The progress of these reactions was monitored

Scheme 2



by ^{1}H NMR spectroscopic analysis. It was determined that the carbamate is stable under the acidic conditions employed, but is easily hydrolyzed in the presence of a strong base like NaOH. The latter reaction was run for 30 min, but the ^{1}H NMR spectrum taken after only 5 min showed the complete absence of **5**. Pure unprotected quinolone **1** has been isolated from the second reaction after a simple acidic work-up without any further purification. The loss of the starting material (only 83% yield) is most likely due to the small scale of the reaction (0.1 mmol). When the entire reaction mixture from the annulation of 4-octyne was treatedwith 1M ethanolic NaOH (eq 18), quinolone **1** was obtained in a 72% yield. Thus, no loss of the product occurs during this step. In the optimization studies, the reactions with ethyl *N*-(2-iodophenyl)carbamate were run both without the basic work-up (procedure A, eq 16) and with the basic work-up (procedure B, eq 18).



(18)

As indicated in Table 1, the use of *tert*-butyl *N*-(2-iodophenyl)carbamate (entry 12) affords only the unprotected product in a 75% yield. Although this higher yield using a simpler procedure makes the *tert*-butyl carbamate appear to be the protecting group of choice, in most of our studies the ethyl carbamate has been employed, because it is easier to prepare and handle (the ethyl carbamate is a solid, while the *tert*-butyl carbamate is a viscous liquid).

The effects of the palladium catalyst, the base, the chloride source, the stoichiometry of the reactants, the reaction time and the temperature were next examined. The results of

the annulation reactions using various palladium catalysts are summarized in Table 2. All reactions were run under the following reaction conditions: 0.5 mmol of *N*-substituted *o*-iodoaniline, 2.5 mmol of 4-octyne, 1 atm of CO, 1 mmol of pyridine, 0.5 mmol of *n*-Bu_4NCl and 5 mol % of $Pd(OAc)_2$ in 5 ml of DMF.

Reactions with *N*-ethoxycarbonyl- and *N*-trifluoroacetyl-*o*-iodoanilines were run at 100 °C for 24 h, while the reactions with *N*-tosyl-*o*-iodoaniline were run for 24 h at 120 °C. It can be seen from these results that $Pd(OAc)_2$ and $Pd(dba)_2$ are generally equally effective in this process (compare entries 1 and 2, 6 and 7, and 9 and 10). Surprisingly, palladium complexes containing phosphine ligands are completely ineffective in the reactions with

Table 2. The effect of the palladium catalyst on the yield of quinolone 1 (eq 16).

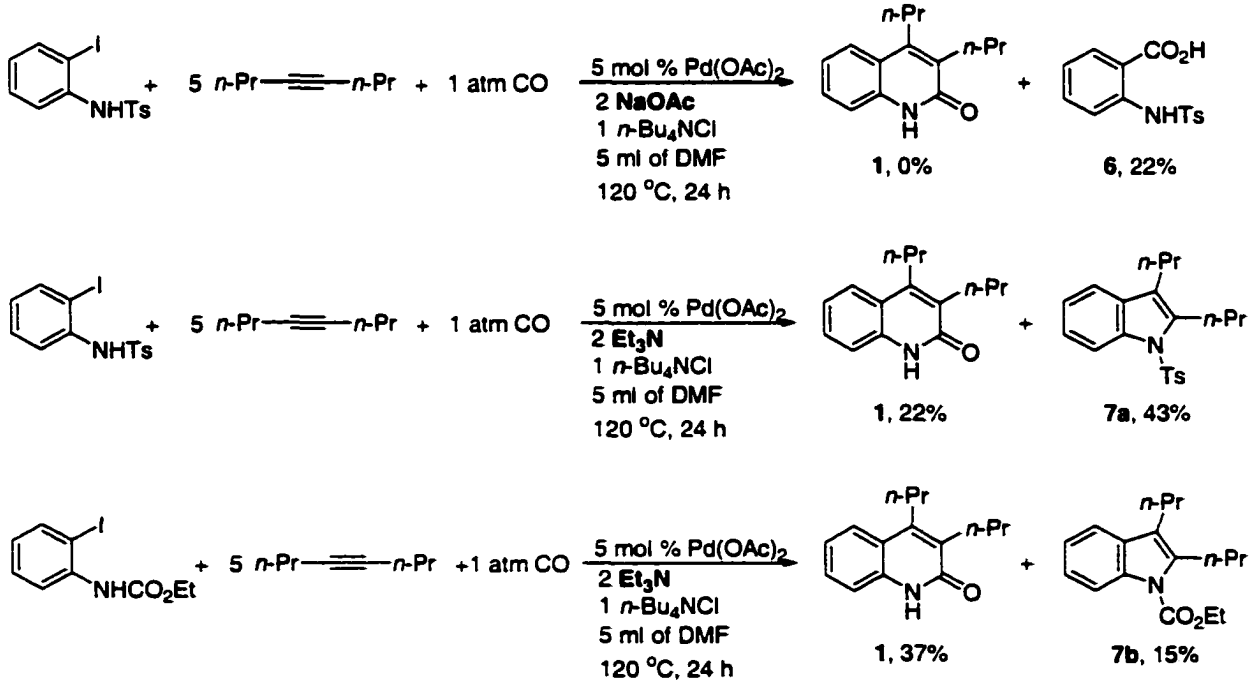
entry	R	catalyst	% yield[a]	recovered starting material, %
1	CO_2Et	$Pd(OAc)_2$	71 (85:15)	
2		$Pd(dba)_2$	66 (86:14)	
3		$Pd(PCy_3)_2$	13 (62:38)	*ca.* 40
4		$Pd(PPh_3)_4$	2	*ca.* 55
5		$Pd(OAc)_2 + 2\ PPh_3$	6	
6	Ts	$Pd(OAc)_2$	56	
7		$Pd(dba)_2$	56	
8		$Pd(OAc)_2 + 2\ PPh_3$	50	
9	$COCF_3$	$Pd(OAc)_2$	56	
10		$Pd(dba)_2$	56	

[a] Ratio of **1/5** is given in parentheses.

ethyl *N*-(2-iodophenyl)carbamate (entries 3-5). Even the simple addition of 10 mol % of triphenylphosphine to the reaction mixture results in almost complete suppression of the reaction (entry 4). However, there is no dramatic effect in the reactions with the tosylamide; a 50% yield of **1** has been obtained when 10 mol % PPh_3 has been employed (entry 8).

The use of pyridine as a base was crucial for the success of the coumarin synthesis.[6] Therefore, several bases have also been examined to determine if this is true for this process as well. The results are shown in Scheme 3. None of the desired quinolone **1** was detected in the reaction of the tosylamide derivative when the inorganic base NaOAc was used. The only product isolated from the reaction mixture was *N*-tosylanthranilic acid (**6**), obtained in only a 22% yield. Triethylamine was used with both the *N*-tosyl and *N*-ethoxycarbonyl derivatives. In both cases, the yields of **1** are considerably lower than in the reactions

Scheme 3



employing pyridine. Moreover, the use of triethylamine leads to the formation of significant amounts of 2,3-dipropylindole derivatives **7a** and **7b**. This is likely because Et_3N is a much stronger base than pyridine, and, therefore, deprotonates the amino group much more easily, especially in the case of such a strong electron-withdrawing substituent as a tosyl group. Thus, in the vinylpalladium complex formed after insertion of the alkyne, the palladium atom is strongly coordinated by the nitrogen atom, and reductive elimination leading to formation of the indole occurs faster than the insertion of CO. Note, that no deprotection of the indole nitrogen occurs during the reaction. A small amount of the protected quinolone **5** (about 5%) has also been detected in the reaction of ethyl *N*-(2-iodophenyl)carbamate with Et_3N as the base.

The formation of benzoic acid **6** shows that some water is present in the reaction mixture. Two likely sources of water are DMF and *n*-Bu_4NCl. Therefore, we have examined the effect of the chloride source on the yield of **1**. All reactions were run with the ethyl carbamate derivative using procedure A (eq 16). The results are summarized in Table 3. Identical results are obtained with *n*-Bu_4NCl and LiCl as the chloride source, while in the

Table 3. The effect of the chloride source (eq 16).

entry	chloride source	combined yield **1** + **5** (%)	ratio of **1**/**5**
1	1 *n*-Bu_4NCl	71	85:15
2	1 LiCl	72	86:14
3	none	66	76:24

absence of any chloride in the reaction mixture the yield is slightly lower. The same results have been observed in the synthesis of coumarins by carbonylative annulation. Therefore, all further reactions have been run in the presence of 1 equiv of *n*-Bu_4NCl.

While all reactions have been run for 24 h, the formation of palladium black has been observed after 6-12 h in all reactions with the carbamate derivative. Thus, the reaction temperature and time have been varied to find the optimal conditions. The results are summarized in Table 4. *N*-(2-Iodophenyl)tosylamide reacts considerably slower than *N*-(2-iodophenyl)trifluoroacetamide or ethyl *N*-(2-iodophenyl)carbamate, and the reactions of the sulfonamide derivatives need to be run at 120 °C to reach completion in 24 h (entries 1-5). With the trifluoroacetamide (entries 6-9), an increase in the reaction time or temperature does not lead to an increase in the yield of **1**. As can be seen from entries 10-15, *N*-ethoxycarbonyl-*o*-iodoaniline is significantly more reactive than the tosylamide or trifluoroacetamide derivatives, and the reaction is complete after 6 h at 100 °C. However, the major product after 6 h is the protected quinolone **5**. It is hydrolyzed to **1** fairly slowly under the reaction conditions and the hydrolysis is incomplete even after 24 h at 100 °C. At higher temperatures (120 °C), only **1** is observed after 24 h, but the yield is considerably lower. At lower temperatures (80 °C), the carbonylative annulation is notably slower. The reaction requires 24 h to reach completion, and even in this case the overall yield is only 52% (entries 10 and 11). Interestingly, almost no deprotection occurred at 80 °C.

Finally, the possibility of using a smaller excess of alkyne has been examined. The results are summarized in Table 5. In the reactions with both *N*-ethoxycarbonyl- and *N*-tosyl-*o*-iodoanilines, no decrease in the yields of quinolone **1** have been observed when 3 equiv of the alkyne have been used, and only a slight decrease in yield has been observed

Table 4. The effect of the reaction time and temperature.[a]

entry	R	temp. (°C)	time (h)	% yield of **1**[b]	% recovery of SM
1	SO_2-*p*-Tol	80	48	30	41
2		100	24	42	38
3			48	56	
4		120	12	47	
5			24	56	
6	$COCF_3$	100	24	56	
7			48	50	
8		120	12	38	
9			24	39	
10	CO_2Et[a]	80	12	37 (8:92)	30
11			24	52 (19:81)	
12		100	6	71 (41:59)	
13			12	75 (69:31)	
14			24	71 (85:15)	
15		120	24	57 (100:0)	

[a] All reactions were run using procedure A (eq 16). [b] Ratio of **1**/**5** in parentheses.

when 2 equiv of the alkyne have been employed. These data show that internal alkynes are more reactive toward insertion into the carbon-palladium bond of the palladium complexes derived from *o*-iodoanilines than the complexes derived from *o*-iodophenol.

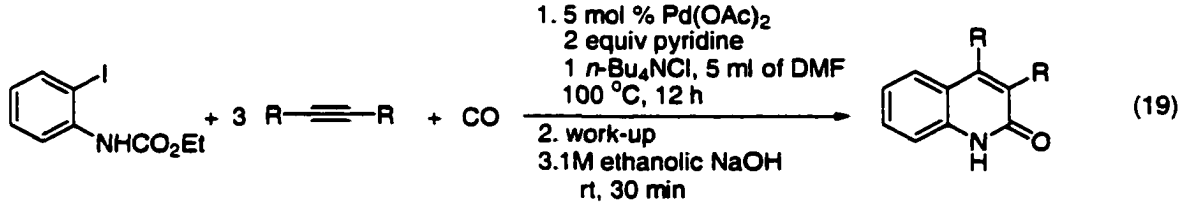
Since the highest yield of **1** has been obtained using *N*-ethoxycarbonyl-*o*-iodoaniline,

Table 5. The effect of the alkyne stoichiometry on the yield of the reaction.[a]

entry	R	alkyne	equiv	% yield of **1**
1	CO_2Et[a]	*n*-Pr—≡—*n*-Pr	5	71
2			3	69
3			2	58
4		Ph—≡—Et	5	81 (69:31)[b]
5			3	82 (68:32)[b]
6	Ts[c]	*n*-Pr—≡—*n*-Pr	5	56
7			3	54

[a] The reactions were run for 12 h at 100 °C using procedure B (eq 18). [b] The ratio of regioisomers (see Table 6). [c] The reactions were run at 120 °C for 24 h.

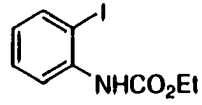
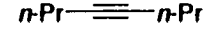
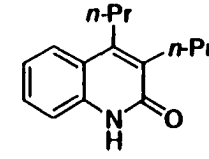
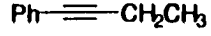
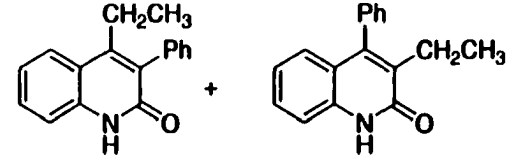
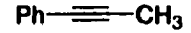
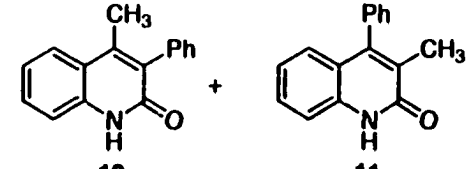
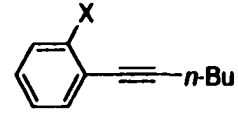
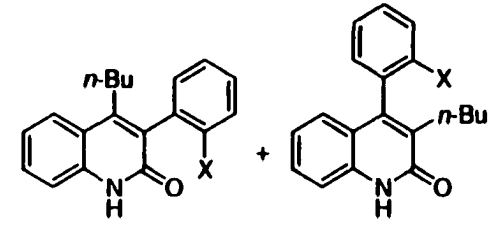
this derivative was used first to study the scope and limitations of this process. The optimal reaction conditions used in all further reactions are shown in eq 19.

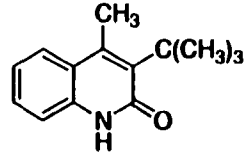
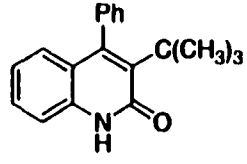
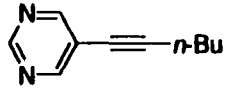
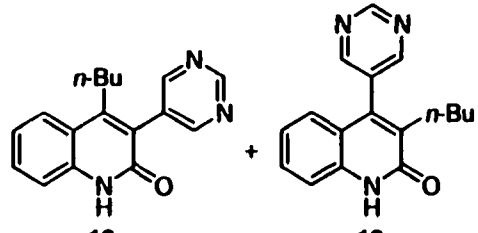


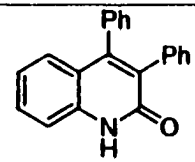
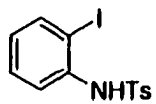
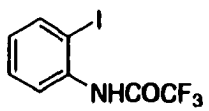
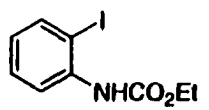
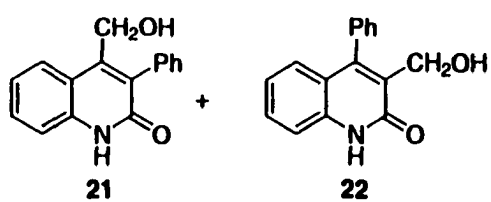
(19)

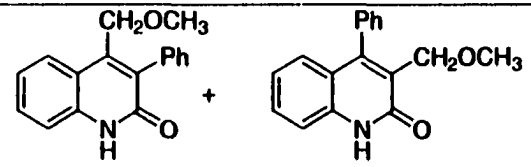
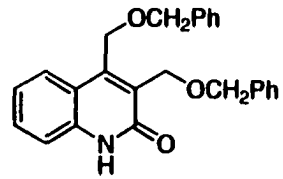
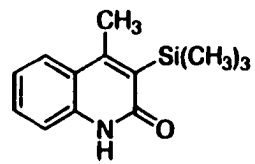
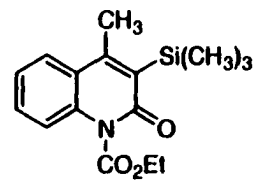
Scope and Limitations. Various internal alkynes and substituted *o*-iodoanilines have been examined to determine the scope and limitations of this reaction and the results are summarized in Table 6. The carbonylative annulation of dialkyl (entry 1), as well as alkylaryl acetylenes (entries 2-5) affords the desired quinolones in 41 to 82% yields. These yields are comparable or slightly better than the yields of the corresponding coumarins (for

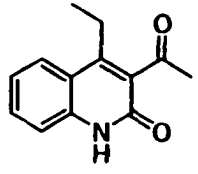
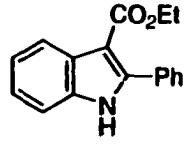
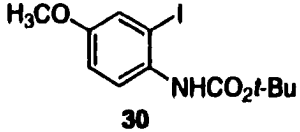
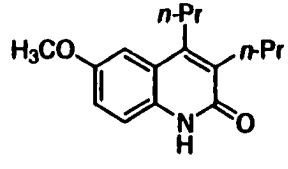
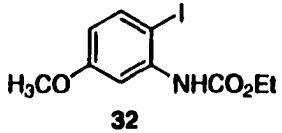
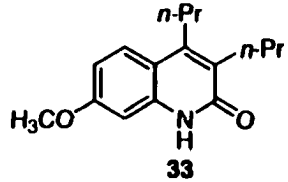
Table 6. Synthesis of 3,4-disubstituted 2(1*H*)-quinolones via palladium-catalyzed annulation of internal alkynes (eq 19).[a]

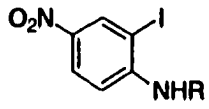
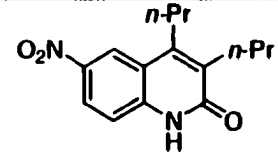
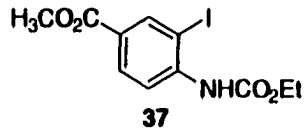
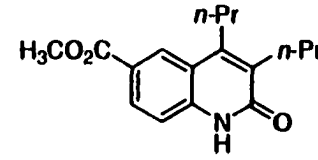
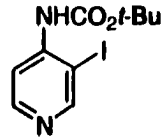
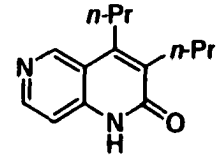
entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield (ratio of isomers)
1			 **1**	69
2			 **8** + **9**	82 (68:32)
3			 **10** + **11**	58 (66:34)
				

entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield (ratio of isomers)
4		X = OCH_3	**12** **13**	56 (74:26)
5		X = NO_2	**14** **15**	41 (81:19)
6		H_3C—≡—$C(CH_3)_3$	 **16**	18
7		Ph—≡—$C(CH_3)_3$	 **17**	14
8			 **18** + **19**	66 (75:25)

entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield (ratio of isomers)
9		Ph—≡—Ph	 **20**	22
10[b]			**20**	15
11[b]			**20**	16
12				0
13		Ph—≡—CH_2OH	 **21** + **22**	42 (66:34)

entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield (ratio of isomers)
14		Ph—≡—CH_2OCH_3	 **23** + **24**	60 (66:34)
15		HOH_2C—≡—CH_2OH		0
16		$PhCH_2OCH_2$—≡—CH_2OCH_2Ph	 **25**	51
17		H_3C—≡—$Si(CH_3)_3$	 **26**	26
18[c]			**26** +  **27**	28 (39:61)

entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield (ratio of isomers)
19[d]			**26**	22
20		$CH_3CH_2-\equiv-COCH_3$	 **28**	19
21		$Ph-\equiv-CO_2Et$	 **29**	32
22	 **30**	*n*-Pr—≡—*n*-Pr	 **31**	67
23	 **32**		 **33**	36

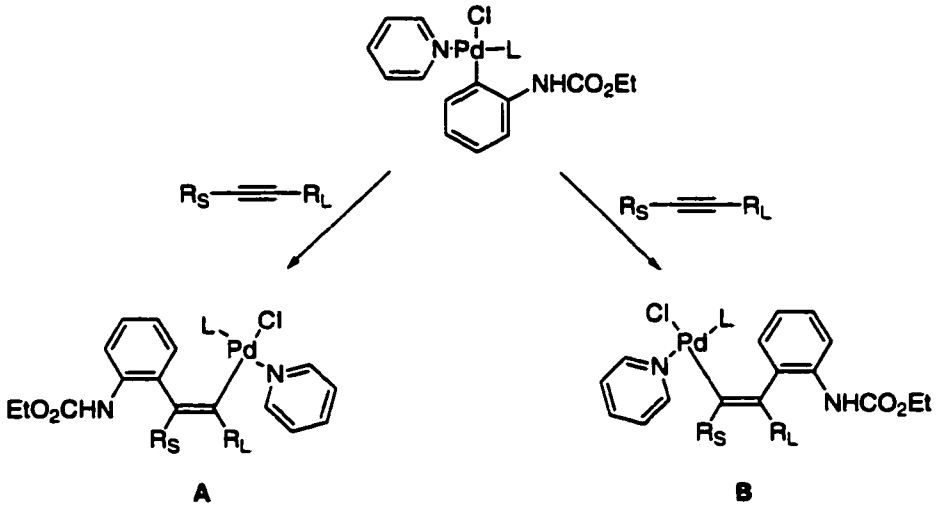
entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield (ratio of isomers)
			 **36**	
24	R = H (**34**)			17[c]
25	R = CO_2Et (**35**)			49
26	 **37**		 **38**	44
27[f]	 **39**		 **40**	31

[a] The standard reaction conditions: *N*-substituted *o*-iodoaniline (0.5 mmol), alkyne (1.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 ml) at 100 °C for 12 h, then the crude product is treated with 1M ethanolic NaOH (5 ml) at rt for 30 min. [b] 5 Equiv of diphenylacetylene were used. [c] The treatment with 1M ethanolic NaOH was omitted. [d] 5 Equiv of alkyne and 120 °C were employed. [e] 4-Nitroaniline was also isolated in a 64% yield. [f] The reaction is complete in 36 h.

example, with 4-octyne 69% and 63%, with 1-phenyl-1-butyne 82% and 78%, respectively), even though a lower temperature and a smaller excess of the alkyne are employed in the 2-quinolone synthesis. The limitations of the process also resemble those of the coumarin synthesis. The annulation of unsymmetrical alkynes, such as 1-phenyl-1-butyne, produces mixtures of regioisomers arising from two possible modes of alkyne insertion into the arylpalladium bond. It is worth noting that annulation of the same alkynes with *o*-iodoaniline and its derivatives leading to 2,3-disubstituted indoles proceeds in most cases with excellent regioselectivity, giving only one regioisomer.[27] Since poor regioselectivity has also been observed in the synthesis of coumarins, it is reasonable to assume that the reaction conditions employed in the carbonylative annulation lead to poor discrimination between the two modes of alkyne insertion. All of our previous results on the annulation of internal alkynes suggest that the regioselectivity of the insertion is controlled almost exclusively by steric factors. The insertion of an alkyne into the arylpalladium bond results in the formation of two vinylpalladium complexes **A** and **B** (Scheme 4). Since the palladium-carbon bond is much longer than the carbon-carbon bond, the steric repulsion between the palladium atom and the larger substituent on the triple bond in the complex **A** should be smaller than the repulsion between the same substitutent and the aryl group in the complex **B**. The major regioisomer in all annulation reactions arises from the complex **A**.

Our previous annulation reactions have been run either in the presence of triphenylphosphine or in the absence of any ligands. However, carbonylative annulation requires the use of pyridine, which most likely functions not only as a base, but also as a ligand. Since a Pd-N bond is much shorter than a Pd-P bond, the steric bulk of the palladium

Scheme 4



increased is significantly. Therefore, the difference in energy between the complexes **A** and **B** is smaller when pyridine is used, and, consequently, the regioselectivity is worse.

The carbonylative annulation of ortho-substituted derivatives of 1-phenyl-1-hexyne (entries 4 and 5) proceeds with improved regioselectivity. The lower overall yield is likely due to an increase in the steric hindrance around the carbon-carbon triple bond. Indeed, like the synthesis of coumarins, this process is very sensitive to steric hindrance, and internal alkynes with very bulky substituents react very sluggishly and afford the desired 2-quinolones in very low yields (entries 6 and 7). It is worth noting, however, that only one regioisomer is obtained in each of these reactions, further supporting the assumption that the regioselectivity is sterically controlled.

Internal alkynes bearing heterocyclic substituents, such as 1-(5-pyrimidinyl)-1-hexyne (entry 8), are also effective in the carbonylative annulation reaction giving the desired products in a 66% yield, comparable to the yields from phenylalkyl acetylenes, and with slightly better regioselectivity.

We were surprised to discover that diphenylacetylene reacts very poorly under the standard reaction conditions and affords the desired 2-quinolone in only a 22% yield (entry 9). Even though diphenylacetylene is less reactive than 4-octyne, a 51% yield of the corresponding coumarin was obtained in the carbonylative annulation of diphenylacetylene by *o*-iodophenol. The reactions of diphenylacetylene with other *o*-iodoaniline derivatives, such as the tosylamide (entry 10) and the trifluoroacetamide (entry 11), afforded **20** in even lower yields, even though 5 equiv of the alkyne were employed. The reasons for such remarkable differences in reactivity between the aniline derivatives and the phenols are not clear. The heterocyclic analogue, bis(2-pyridyl)acetylene, was even less effective, affording none of the desired quinolone (entry 12).

The reactivity of internal alkynes bearing various functional groups was examined next. To our delight, the carbonylative annulation of 3-phenyl-2-propyn-1-ol (entry 13) afforded the desired 2-quinolones in a 42% yield. Even though the yield is only modest, the carbonylative annulation by *o*-iodophenol of this and other alkynes with an hydroxyl group was completely ineffective, and no coumarins were observed. Still, protection of the hydroxyl group, for example as a methyl ether (entry 14), improves the yield of the reaction. Mixtures of regioisomers were obtained in both cases with poor regioselectivity. No products were obtained in the reaction of 2-butyne-1,4-diol (entry 15), while the corresponding dibenzylated alkyne afforded the desired 2-quinolone **25** in a 51% yield (entry 16).

Only a 26% yield of 2-quinolone **26** was obtained when a silyl-substituted alkyne, 1-trimethylsilyl-1-propyne, was employed (entry 17). Initially we suspected that treatment of the crude product with the base ethanolic NaOH might be causing decomposition of the

desired product. When this step was omitted, two products, **26** and the still protected 2-quinolone **27** were obtained in 28% yield as a 39:61 mixture (entry 18). Thus, the overall yield of the annulation did not change. The use of a larger 5-fold excess of the alkyne and a higher reaction temperature (120 °C) (entry 19) did not improve the yield of the desired product either.

Electron-deficient alkynes appear to be very poor substrates for the carbonylative annulation by ethyl *N*-(2-iodophenyl)carbamate. Only a 19% yield of 2-quinolone **28** was obtained in the reaction of 3-hexyn-2-one (entry 20), while the corresponding coumarin was obtained in a 61% yield. Interestingly, only one regioisomer was isolated, and its structure is assumed to be analogous to the structure of the major coumarin isomer. This result is consistent with the excellent regioselectivity (90:10) observed in the carbonylative annulation of this alkyne by *o*-iodophenol. Since only a 19% yield of **28** was obtained, it is likely that if the minor isomer was formed in the reaction, it was lost during the work-up.

The carbonylative annulation of another electron-poor alkyne, ethyl phenylpropiolate (entry 21), did not afford any of the anticipated 2-quinolone. Instead, an indole **29** was obtained in a 32% yield. The structure has been confirmed by comparison with literature data.[30]

We have also examined the reactivity of various electron-rich and electron-poor alkyl *N*-(2-iodophenyl)carbamates as annulating agents in the reaction with 4-octyne. Introduction of an electron-donating substituent, for example a methoxy group, *para* to the amino group (entry 22) does not affect the carbonylative annulation. The corresponding 2-quinolone **31** was obtained in a 67% yield, comparable to the yield of the parent system (entry 1). However, only a 36% yield of the desired product was obtained from the *o*-iodoaniline

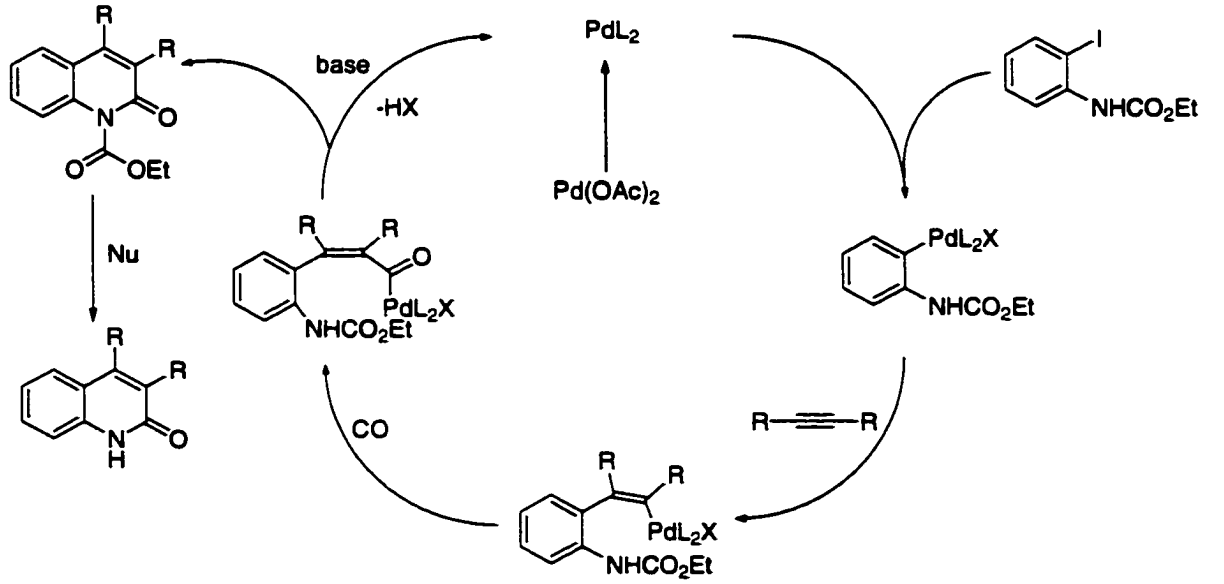
derivative with a methoxy group *para* to the iodine (entry 23). Electron-rich iodoanilines are apparently not very stable. For example, the unprotected 2-iodo-5-methoxyaniline can be stored only at 0 °C in the absence of light.[31] 2-Iodo-5-methoxyphenol is completely unreactive in the carbonylative annulation of 4-octyne, undergoing instead rapid deiodination to give 3-methoxyphenol in an 82% yield.[6] Ethyl *N*-(2-iodo-5-methoxyphenyl)carbamate is not as electron-rich and thus is more reactive in the carbonylative annulation. No deiodination product was isolated from this reaction.

A different picture emerged from the reactions of electron-poor iodoanilines. Initially, 2-iodo-4-nitroaniline was studied. The parent 2-iodoaniline is not an effective reagent in the carbonylative annulation, most likely due to the high nucleophilicity of the amino group. Introduction of an electron-withdrawing group *para* to the amino group should make the amino group less nucleophilic. Thus, the carbonylative annulation of 4-octyne using unprotected 2-iodo-4-nitroaniline was attempted. Indeed, the desired 2-quinolone was obtained, albeit in only a very low 17% yield (entry 24). Unlike the reactions of the parent 2-iodoaniline, this reaction was very clean, and the only other product of the reaction was the deiodinated 4-nitroaniline, isolated in a 64% yield. Protection of the amino group as an ethyl carbamate led to a significant improvement in yield, and 2-quinolone **36** was isolated in a 49% yield (entry 25). The corresponding 4-methoxycarbonyl derivative also afforded the 2-quinolone **38** in a similar 44% yield (entry 26). Thus, electron-withdrawing groups lower the yield of the carbonylative annulation. A possible reason for this is the decreased stability of the carbamates toward hydrolysis, since the presence of an electron-withdrawing group should increase the positive charge on the carbonyl carbon.

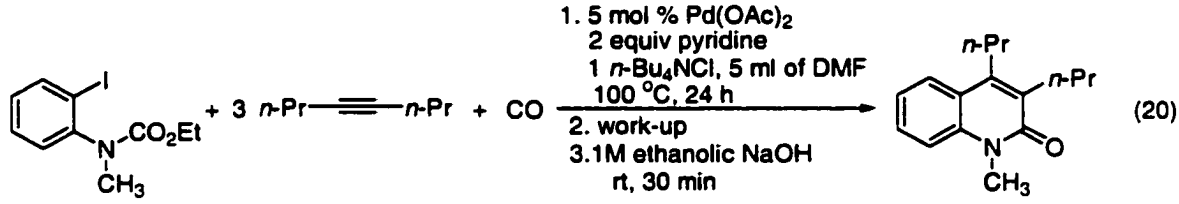
Another electron-poor aniline, a carbamate derivative of 4-amino-3-iodopyridine, also afforded a low yield of the corresponding 6-aza-2-quinolone **40** (entry 27). Moreover, this reaction was very slow and only reached completion in 36 h.

Mechanism. The mechanism of this process is undoubtedly analogous to the mechanism proposed for the synthesis of coumarins.[6] It is shown in Scheme 5, and involves (1) reduction of $Pd(OAc)_2$ to the actual Pd(0) catalyst; (2) oxidative addition of the *N*-substituted *o*-iodoaniline to Pd(0), generating an arylpalladium complex; (3) insertion of the alkyne triple bond into the arylpalladium bond to give a vinylpalladium complex; (4) insertion of CO to generate an acylpalladium complex; and (5) nucleophilic attack of the nitrogen on the carbonyl group of the acylpalladium complex leading to formation of the 2-quinolone and regeneration of Pd(0). Removal of the protecting group from the nitrogen occurs after formation of the amide bond, at least in the case of the carbamate derivatives.

Scheme 5



It is not clear whether deprotonation of the amino group is necessary for the nucleophilic attack to occur. It is likely that the deprotonation occurs in the case of tosyl- and trifluoroacetamide derivatives, but the situation with the carbamate derivatives is not obvious. The carbonylative annulation of 4-octyne with ethyl *N*-methyl-*N*-(2-iodophenyl)carbamate (**41**) (eq 20) did not produce any of the annulation product, and the starting iodoaniline was recovered in a 55% yield.



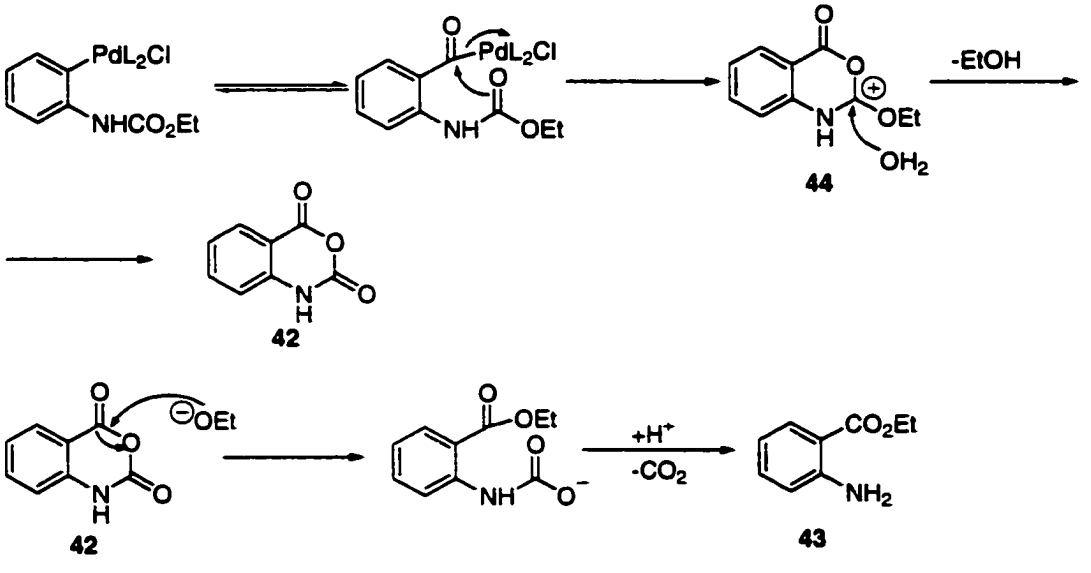
41 0 % (20)

Just as in the carbonylative annulation of internal alkynes with *o*-iodophenols,[6] in this process we have never observed any 4-quinolones, which might arise from initial insertion of CO into the arylpalladium bond, followed by insertion of the internal alkyne. Previously, we have established that even though the insertion of CO into the arylpalladium bond to form an acylpalladium complex occurs under our reaction conditions, the reaction of this acylpalladium complex with an internal alkyne is apparently very slow. Therefore, in the absence of any internal nucleophile capable of trapping the acylpalladium complex, the acylpalladium complex undergoes decarbonylation to the original arylpalladium complex, which eventually reacts with the internal alkyne, and is thus converted into the coumarin or the 2-quinolone. Further evidence supporting this scheme has been obtained during the investigation of the carbonylative annulation of *N*-substituted *o*-iodoanilines.

In most of the reactions employing ethyl *N*-(2-iodophenyl)carbamate a minor by-product can be isolated, along with the desired 2-quinolone. The by-product is either isatoic

anhydride (**42**) (in the reactions without treatment with ethanolic NaOH) or ethyl 2-aminobenzoate (**43**) (in the reactions with a basic work-up). In the reaction with 4-octyne, the yield of the by-product is around 10-12%. However, in the reactions employing a very unreactive alkyne, such as 2,2-dimethyl-4-pentyne or 1-phenyl-3,3-dimethyl-1-butyne (Table 6, entries 6 and 7), ethyl 2-aminobenzoate was isolated in 30 and 39% yields respectively. In almost all reactions, this by-product was detected by ^{1}H NMR spectroscopy, but it was not isolated in a pure form and the exact yield was not determined. The mechanism of formation of these by-products is shown in Scheme 6. Insertion of CO into the arylpalladium bond, followed by intramolecular attack of the carbonyl group coordinated to the palladium atom by the oxygen atom of the carbamate group leads to the intermediate **44**. Attack on the oxonium ion **44** by a water molecule and elimination of ethanol lead to the formation of isatoic anhydride. Upon treatment with ethanolic NaOH, the more electrophilic ester carbonyl group is attacked by an ethoxide anion generating a carbamic acid anion, which spontaneously loses CO_2 giving rise to ethyl 2-aminobenzoate. A similar intramolecular

Scheme 6



attack of an amide oxygen on an acylpalladium complex has been observed by Cacchi (see Scheme 1).[26]

These data support the mechanistic scheme outlined above. It appears that an acylpalladium complex is generated under our reaction conditions, but it is not very reactive. The ratio of the products from initial CO insertion and initial alkyne insertion depends on the rates of intramolecular trapping of the acylpalladium complex and the irreversible insertion of the alkyne into the arylpalladium bond.

Conclusions

We have successfully extended the palladium-catalyzed carbonylative annulation of internal alkynes to reactions with *o*-iodoaniline derivatives, thus providing a new route for the synthesis of 3,4-disubstituted 2-quinolones. A crucial aspect of the synthesis is the choice of the protecting group on the nitrogen atom of the iodoaniline. The most effective groups are alkoxycarbonyl, *p*-toluenesulfonyl and trifluoroacetyl. A wide variety of internal alkynes bearing alkyl, aryl, heteroaryl, hydroxyl and alkoxyl substituents has been employed in this process affording the desired 2-quinolones in 50 to 80 % yields. Electron-rich iodoanilines with substituents para to the amino group are also effective in the carbonylative annulation. The carbonylative annulation by electron-poor iodoanilines affords 2-quinolones in lower yields than the parent system. The two main drawbacks of this method are the poor regioselectivity in the reactions with unsymmetrical alkynes, and sensitivity to the steric bulk of the substituents on the triple bond of the alkyne.

Experimental Section

General. All ^{1}H 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 (Scientific Adsorbents Co.), and visualization was effected with short wavelength UV light (254 nm) or a basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5 %) + 300 ml of H_2O]. 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. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. NaOAc, LiCl, DMF, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. Pyridine was purchased from Fisher Scientific Co. and purified by distillation from CaH_2. Et_3N was purchased from Aldrich Chemical Co. *n*-Bu_4NCl was purchased from Lancaster Synthesis, Inc. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. Triphenylphosphine was donated by Kawaken Fine Chemicals Co. Ltd.

Alkynes. 4-Octyne, diphenylacetylene, 1-phenyl-1-propyne, 1-trimethylsilyl-1-propyne, and ethyl phenylpropiolate were purchased from Aldrich Chemical Co. 1-Phenyl-1-butyne and 3-hexyn-2-one were purchased form Farchan Chemical Co. 4,4-Dimethyl-2-pentyne and 3-phenyl-2-propyn-1-ol were purchased from Lancaster Synthesis, Inc. 1-

Phenyl-3,3-dimethyl-1-butyne[32] and 1-phenyl-3-methoxy-1-propyne[33] were prepared according to previous literature procedures.

Iodoanilines. 2-Iodoaniline, 4-methoxyaniline, 4-nitroaniline, methyl 4-aminobenzoate and 4-aminopyridine were purchased from Aldrich Chemical Co. *N*-Methyl-2-iodoaniline,[27b] 2-iodoacetanilide,[27b] *N*-(2-iodophenyl)formamide,[34] *N*-tosyl-2-iodoaniline,[35] *N*-(2-iodophenyl)methanesulfonamide,[36] *tert*-butyl *N*-(2-iodo-4-methoxyphenyl)carbamate[37] and methyl 3-iodo-4-aminobenzoate[38] were prepared following literature procedures.

Other starting materials were prepared as follows.

***N,N*-Dimethyl-*N'*-(2-iodophenyl)urea** (Table 1, entry 5) was prepared following a literature procedure.[39] A solution of 2-iodoaniline (3.07 g, 14.0 mmol) in 15 ml of dry ethyl acetate was added dropwise to a solution of triphosgene (1.48 g, 5.0 mmol) in 20 ml of dry ethyl acetate. The resulting mixture was refluxed for 30 min, then cooled to room temperature and concentrated under reduced pressure. Dry ether (30 ml) was added to the residue, and the insoluble precipitate was filtered off. A 2M solution of dimethylamine in THF (25 ml, 50.0 mmol) was added to a filtrate cooled to 0 °C over 15 min. The resulting mixture was stirred at room temperature for 3 h. The resulting crystals were filtered off and washed with cold water and ether. Column chromatography on silica gel using 4:1 hexanes/ethyl acetate as an eluent afforded 3.33 g (82%) of the desired product as white crystals: mp 86-88 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (dd, J = 1.6, 8.4 Hz, 1H), 7.73 (dd, J = 1.4, 8.2 Hz, 1H), 7.31 (ddd, J = 1.2, 7.8, 8.4 Hz, 1H), 6.83 (br s, 1H), 6.75 (ddd, J = 1.6, 8.0, 8.8 Hz, 1H), 3.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.3, 139.8, 138.6, 129.4, 124.5, 121.1, 89.9,

36.7. Anal. Calcd for $C_9H_{11}IN_2O$: C, 37.26; H, 3.83; N, 9.66. Found: C, 37.33; H, 3.90; N, 9.59.

***N*-(2-Iodophenyl)trifluoroacetamide** (Table 1, entry 10). Trifluoroacetic anhydride (2.82 g, 10 mmol) was added over 20 min to a solution of 2-iodoaniline (1.10 g, 5 mmol) and triethylamine (1.50 g, 15 mmol) in 15 ml of dry CH_2Cl_2 cooled to 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred for 3 h. Then it was diluted with water and extracted with ether. The ethereal extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The desired product was isolated by column chromatography using 8:1 hexanes/ethyl acetate as an eluent. The spectral properties are identical to those reported in the literature.[36]

Ethyl *N*-(2-iodophenyl)carbamate (Table 1, entry 11). 2-Iodoaniline (2.19 g, 10 mmol), ethyl chloroformate (4.34 g, 40 mmol) and K_2CO_3 (8.29 g, 60 mmol) were stirred in 40 ml of acetone at room temperature for 3 h. The reaction was monitored by TLC to establish completion. Then the reaction mixture was diluted with water. The organic phase was separated, and the aqueous phase was extracted with ether. Organic fractions were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel using 8:1 hexanes/ethyl acetate as an eluent afforded 2.77 g (95%) of the desired product as an off-white solid: mp 44-47 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 1.4, 7.8 Hz, 1H), 7.33 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 6.94 (br s, 1H), 6.79 (ddd, J = 1.6, 7.6, 8.4 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 153.6, 139.1, 138.6, 129.5, 125.2, 120.4, 89.0, 61.8, 14.7.

***N*-(2-Iodophenyl)pentafluorobenzenesulfonamide** (Table 1, entry 13). Pentafluorobenzenesulfonyl chloride (2.93 g, 11 mmol) was added to a cooled solution of 2-iodoaniline (2.19 g, 10 mmol) in pyridine (10 ml). The reaction mixture was stirred at 0 °C for 1 h. The mixture became viscous and purple in color. It was allowed to warm to rt, stirred for 2 h, then diluted with ether, washed with 5% aq HCl and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure affording 1.23 g of a dark solid. Column chromatography on silica gel using 2:1 hexanes/ethyl acetate as an eluent afforded two fractions: a pure product as a colorless solid, 0.168 g (4%), and a mixture of the desired product and an unidentified compound, 0.55 g. Recrystallization of the second fraction afforded another portion of the pure product, 0.2 g (5%) as a colorless solid: mp 79-81 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (dd, J = 1.2, 8.0 Hz, 1H), 7.64 (dd, J = 1.2, 8.0 Hz, 1H), 7.37 (ddd, J = 0.8, 7.2, 8.0 Hz + br s, 2H), 6.94 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 139.8, 136.0, 130.1, 128.3, 122.3, 91.8 (signals from C_6F_5 are not observed).

***N*-(2-Iodophenyl)-4-nitrobenzenesulfonamide** (Table 1, entry 14). 4-Nitrobenzenesulfonyl chloride (1.22 g, 5.5 mmol) was added over 10 min to a solution of 2-iodoaniline (1.10g, 5.0 mmol) in pyridine (10 ml) cooled to 0 °C. The reaction mixture was stirred at 80 °C for 1.5 h, then allowed to cool to rt, diluted with ether, washed with 5% aq HCl and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure affording 1.5 g (75%) of almost pure product as a yellowish solid. Further purification by recrystallization from ethanol afforded 1.05 g (52%) of an orange solid: mp 139-142 °C; ^{1}H NMR ($CDCl_3$) δ 8.25-8.29 (m, 2H), 7.88-7.92 (m, 2H), 7.66-7.72 (m, 2H), 7.38 (ddd, J = 1.2,

6.8, 8.0 Hz, 1H), 6.93 (ddd, J = 1.6, 8.0, 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 150.6, 144.6, 139.6, 136.5, 130.1, 129.0, 128.3, 124.4, 124.3, 93.6.

***N*-(2-Iodophenyl)-2,4-dinitrobenzenesulfonamide** (Table 1, entry 15). This compound was prepared using the same procedure as above, but employing 1.10 g (5.0 mmol) of 2-iodoaniline and 1.47 g (5.5 mmol) of 2,4-dinitrobenzenesulfonyl chloride. The product was obtained by column chromatography on silica gel using 2:1 hexanes/ethyl acetate as the eluent. Yield: 0.55 g (24%). Bright orange solid: mp 158-160 °C; ^{1}H NMR ($CDCl_3$) δ 8.72 (d, J = 2.0 Hz, 1H), 8.46 (dd, J = 2.2, 8.6 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.74 (dd, J = 1.0, 7.8 Hz, 1H), 7.65 (dd, J = 1.2, 8.0 Hz, 2H), 7.42 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 6.99 (ddd, J = 1.2, 7.6, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 150.3, 148.5, 139.9, 139.1, 136.7, 132.7, 129.9, 129.0, 127.4, 126.7, 121.2, 93.6.

***N*-(2-Iodophenyl)-2,2,2-trifluoroethanesulfonamide** (Table 1, entry 16). This compound was prepared using the same procedure as above, but employing 1.10 g (5.0 mmol) of 2-iodoaniline and 1.0 g (5.47 mmol) of 2,2,2-trifluoroethanesulfonyl chloride and stirring the reaction mixture at rt for 1 h. The product was obtained by column chromatography on silica gel using 4:1 hexanes/ethyl acetate as the eluent. Yield: 1.68 g (92%). White solid, mp 69-70 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (dd, J = 1.2, 8.0 Hz, 1H), 7.65 (dd, J = 1.2, 8.0 Hz, 1H), 7.40 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 6.98 (ddd, J = 1.2, 8.0, 8.8 Hz, 1H), 6.93 (br s, 1H), 3.88 (q, J_{HF} = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 140.0, 136.5, 130.3, 128.0, 121.8, 121.4 (J_{CF} = 276 Hz), 91.7, 54.3 (J_{CF} = 32 Hz).

***N*-(2-Iodophenyl)trichloroacetamide** (Table 1, entry 18). Trichloroacetyl chloride (1.81 g, 10 mmol) was added over 20 min to a solution of 2-iodoaniline (1.10 g, 5.0 mmol) in

NEt_3 (20 ml) cooled to 0 °C. The reaction mixture was stirred at rt for 2 h. The reaction was not complete at this time, so it was heated at 40 °C for 2 h. The reaction was stopped, allowed to cool to rt, and quenched with phosphate buffer (pH ~ 7). The organic layer was separated; washed with satd aq $NaHCO_3$, 5% aq HCl, and brine; and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure afforded almost pure product as a viscous yellow oil (1.75 g, 96% yield). Further purification by column chromatography afforded 1.29 g (71 % yield) of the desired product as a very viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.86 (br s, 1H), 8.21 (dd, J = 1.4, 8.2 Hz, 1H), 7.84 (dd, J = 1.2, 8.0 Hz, 1H), 7.43 (ddd, J = 1.6, 8.4, 8.8 Hz, 1H), 6.96 (ddd, J = 1.4, 7.8, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 159.7, 139.4, 136.9, 129.8, 127.7, 121.8, 92.9, 90.5.

2,2,2-Trichloroethyl *N*-(2-iodophenyl)carbamate (Table 1, entry 19). 2,2,2-Trichloroethyl chloroformate (2.33 g, 11 mmol) was added to a solution of 2-iodoaniline (2.20 g, 10 mmol) in 10 ml of pyridine cooled to 0 °C. The reaction mixture was heated at 65 °C for 2.5 h, then allowed to cool to room temperature, diluted with CH_2Cl_2, washed with satd aq NH_4Cl and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 3.86 g (98 %) of the desired product. Recrystallization from pentane/ether afforded an off-white solid: mp 85-88 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 7.6 Hz, 1H), 7.79 (dd, J = 1.2, 8.0 Hz, 1H), 7.37 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.15 (br s, 1H), 6.86 (ddd, J = 1.2, 7.6, 8.8 Hz, 1H), 4.85 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 159.7, 139.4, 136.9, 129.8, 127.7, 121.8, 92.9, 90.5. Anal. Calcd for $C_9H_7Cl_3INO_2$: C, 27.41; H, 1.79; N, 3.55. Found: C, 27.36; H, 1.78; N, 3.41.

Ethyl *N*-(2-iodo-5-methoxyphenyl)carbamate (32). 2-Iodo-5-methoxyaniline was prepared from 2-iodo-5-methoxynitrobenzene following a literature procedure.[31] Then 2-

iodo-5-methoxyaniline (498 mg, 2.0 mmol, used without purification), ethyl chloroformate (0.868 g, 8.0 mmol) and anhydrous K_2CO_3 (1.66 g, 12 mmol) were stirred in acetone (15 ml) at rt for 4 h. The reaction mixture was diluted with water and extracted with ether. The organic fractions were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel using 4:1 hexanes/ethyl acetate as an eluent afforded 0.432 g (67%) of the desired product as a light yellow solid: mp 49-52 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 6.59 (br s, 1H), 6.43 (dd, J = 3.2, 8.8 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2 H), 3.80 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 160.9, 153.6, 139.4, 138.9, 112.2, 105.5, 61.8, 55.6, 14.7 (one sp^2 carbon missing due to overlap).

Ethyl *N*-(2-iodo-4-nitrophenyl)carbamate (35). 2-Iodo-4-nitroaniline was prepared from *p*-nitroaniline following a literature procedure.[31] Compound **35** was then prepared following the procedure above, but employing 2-iodo-4-nitroaniline (1.06 g, 4.0 mmol), ethyl chloroformate (1.75 g, 16 mmol), anhydrous K_2CO_3 (3.32 g, 24 mmol) and stirring the reaction mixture at rt for 48 h. Column chromatography on silica gel using 2:1 hexanes/ethyl acetate as the eluent afforded **35** as an orange-red solid (0.28 g, 21%); mp 105-108 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 2.4 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 8.13 (dd, J = 2.4, 9.2 Hz, 1H), 7.22 (br s, 1H), 4.21 (q, J = 7.2 Hz, 2 H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 152.8, 144.4, 142.9, 134.5, 125.1, 117.9, 86.1, 62.5, 14.5.

Ethyl *N*-(2-iodo-4-methoxycarbonylphenyl)carbamate (37). Methyl 4-amino-3-iodobenzoate was prepared from methyl 4-aminobenzoate following a literature procedure.[40] Compound **37** was then prepared following the procedure above, but employing methyl 4-amino-3-iodobenzoate (1.11 g, 4.0 mmol), ethyl chloroformate (1.74 g, 16 mmol), anhydrous

K_2CO_3 (3.32 g, 24 mmol) and stirring the reaction mixture at rt for 48 h. Column chromatography on silica gel using a gradient of 8:1 to 4:1 hexanes/ethyl acetate as the eluent afforded **37** as an off-white solid (0.26 g, 19%); mp 163-165 °C; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.00 (dd, J = 2.0, 8.8 Hz, 1H), 7.19 (br s, 1H), 4.27 (q, J = 7.2 Hz, 2 H), 3.90 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.5, 153.1, 142.6, 140.6, 131.0, 126.2, 118.5, 87.2, 62.2, 52.4, 14.7.

***tert*-Butyl *N*-(2-iodo-4-pyridinyl)carbamate (39).** 4-Aminopyridine (0.94 g, 10 mmol) and di-*tert*-butyldicarbonate (3.27 g, 15 mmol) were dissolved in dry THF (15 ml), and the resulting solution was stirred at rt for 2 h. The solvent was removed under reduced pressure, water (20 ml) was added, and the resulting suspension was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give an off-white solid. Recrystallization from 1:1 chloroform/hexanes furnished *tert*-butyl *N*-(4-pyridinyl)carbamate as a white solid (1.39 g, 72%): mp 140-142 °C, ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J = 6.0 Hz, 2H), 7.32 (d, J = 6.4 Hz, 2H), 7.07 (br s, 1H), 1.53 (s, 9H); ^{13} C NMR ($CDCl_3$) δ 152.2, 150.7, 145.9, 112.5, 81.8, 28.4. Concentration of the mother liquor and subsequent recrystallization afforded a second portion of the product as a white solid (0.224 g, 12 %), mp 142-143 °C.

A solution of *tert*-butyl *N*-(4-pyridinyl)carbamate (0.78 g, 4.0 mmol) in dry THF (15 ml) was cooled to –20 °C under an Ar atmosphere, and to this solution a 1.7 M solution of *tert*-butyllithium in hexanes (5.5 ml, 9.35 mmol) was added over 10 min. The resulting mixture was stirred at –20 °C for 3 h, then cooled to –78 °C, and to this mixture a solution of I_2 (1.22 g, 4.8 mmol) in dry THF (10 ml) was added dropwise over 25 min. The resulting mixture was stirred at –78 °C for 30 min, then allowed to warm up to rt and stirred overnight.

Then satd aq $Na_2S_2O_3$ (20 ml) was added, the organic layer was separated, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with satd aq $Na_2S_2O_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel using 2:1 hexanes/ethyl acetate as the eluent afforded the desired product **39** (0.510 g, 40%) as a white solid: mp 77-78 °C; ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.31 (d, J = 5.6 Hz, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.01 (br s, 1H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 157.4, 151.7, 150.2, 145.8, 113.5, 86.5, 82.6, 28.3.

General procedure for the carbonylative annulation. Ethyl *N*-(2-iodophenyl)carbamate (0.5 mmol), the alkyne (1.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), and $Pd(OAc)_2$ (5 mol %, 0.025 mmol) were placed in a 4 dram vial and then dissolved in 5 ml of DMF. The vial was purged with CO for 2 min, and then connected to a balloon of CO. The reaction mixture was stirred at 100 °C for 12 h, then allowed to cool to room temperature, diluted with ethyl acetate, washed with water, and concentrated under reduced pressure. The residue was treated with 5 ml of 1 M ethanolic NaOH at room temperature for 30 min. Then 15 ml of satd aq NH_4Cl were added, and the resulting mixture was extracted with ethyl acetate. The organic extracts were combined, washed with satd aq NH_4Cl and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was separated by column chromatography on silica gel. The following 2-quinolones were prepared using this procedure.

3,4-Dipropyl-2(1*H*)-quinolinone (1). White solid, mp 159-160 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1H), 7.43 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.38 (dd, J = 1.2, 8.0 Hz, 1H), 7.20 (ddd, J = 1.4, 6.8, 8.2 Hz, 1H), 2.86-2.90 (m, 2H), 2.74-2.78 (m, 2H), 1.59-

1.71 (m, 4H), 1.05-1.12 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 164.3, 147.6, 137.5, 131.4, 129.2, 124.5, 122.3, 120.4, 116.5, 31.1, 29.3, 23.6, 22.9, 14.8, 14.7; IR (neat, cm^{-1}) 2963, 2868, 1661; MS m/z (rel intensity) 229 (67, M^+), 228 (52), 214 (100), 200 (47), 186 (41); HRMS calcd for $C_{15}H_{19}NO$: 229.1467, found: 229.1470.

4-Ethyl-3-phenyl-2(1*H*)-quinolinone (8). White solid, mp 224-226 °C (lit. 229-230 °C); ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 1H), 7.46-7.51 (m, 2H), 7.37-7.44 (m, 2H), 7.24-7.27 (m, 1H), 7.20 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 2.72 (q, J = 7.6 Hz, 2H), 1.17 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.7, 150.8, 138.6, 136.5, 132.0, 130.0, 128.5, 127.6, 125.0, 122.4, 119.6, 117.0, 23.3, 14.8 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3153, 3015, 2923, 2852, 1646, 1591; MS m/z (rel intensity) 249 (63, M^+), 248 (100), 233 (15), 204 (10); HRMS calcd for $C_{17}H_{15}NO$: 249.1154, found: 249.1159. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.63; H, 6.49; N, 5.51.

3-Ethyl-4-phenyl-2(1*H*)-quinolinone (9). White solid, mp 229-231 °C; ^{1}H NMR ($CDCl_3$) δ 7.42-7.55 (m, 5H), 7.26-7.28 (m, 2H), 7.05 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.00 (dd, J = 1.4, 8.2 Hz, 1H), 2.53 (q, J = 7.6 Hz, 2H), 1.13 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 148.7, 137.3, 137.0, 133,5, 129.5, 128.9, 128.7, 128.1, 127.1, 122.3, 121.5, 116.0, 21.9, 14.1; IR (neat, cm^{-1}) 3164, 2968, 2878, 1651, 1556; MS m/z (rel intensity) 249 (35, M^+), 248 (100); HRMS calcd for $C_{17}H_{15}NO$: 249.1154, found: 249.1160.

4-Methyl-3-phenyl-2(1*H*)-quinolinone (10). White solid; the spectral properties are identical to the literature data.[20]

3-Methyl-4-phenyl-2(1*H*)-quinolinone (11). White solid; the spectral properties are identical to the literature data.[7]

4-*n*-Butyl-3-(2-methoxyphenyl)-2(1*H*)-quinolinone (12). White solid, mp 215-218 °C; ^{1}H NMR δ ($CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 1H), 7.36-7.43 (m, 2H), 7.25-7.29 (m, 1H), 7.16-7.20 (m, 2H), 7.01-7.09 (m, 2H), 3.75 (s, 3H), 2.66-2.71 (m, 1H), 2.55-2.60 (m, 1H), 1.46-1.53 (m, 2H), 1.20-1.30 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.3, 157.6, 150.2, 138.5, 131.5, 129.8, 129.4, 129.3, 125.5, 125.0, 122.2, 120.9, 120.1, 117.0, 111.4, 55.8, 32.0, 30.0, 23.2, 13.9; IR (neat, cm^{-1}) 3173, 2958, 2868, 1646, 1596, 1245; MS m/z (rel intensity) 307 (19, M^+), 276 (51), 250 (100); HRMS calcd for $C_{20}H_{21}NO_2$: 307.1572, found: 307.1580.

3-*n*-Butyl-4-(2-methoxyphenyl)-2(1*H*)-quinolinone (13). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.45 (ddd, J = 2.4, 7.0, 8.8 Hz, 1H), 7.40-7.41 (m, 2H), 7.08-7.13 (m, 2H), 7.01-7.07 (m, 2H), 6.98 (d, J = 8.0 Hz, 1H), 3.70 (s, 3H), 2.49-2.52 (m, 1H), 2.38-2.41 (m, 1H), 1.45-1.49 (m, 2H), 1.22-1.28 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4, 156.7, 146.1, 137.2, 133.0, 130.6, 129.8, 129.2, 126.7, 125.6, 122.3, 121.4, 120.8, 115.8, 111.2, 55.6, 31.0, 28.4, 23.0, 14.1; IR (neat, cm^{-1}) 3163, 2958, 2873, 1651, 1556; MS m/z (rel intensity) 307 (100, M^+), 290 (57), 276 (65), 265 (78), 264 (76), 250 (76), 233 (52); HRMS calcd for $C_{20}H_{21}NO_2$: 307.1572, found: 307.1577.

4-*n*-Butyl-3-(2-nitrophenyl)-2(1*H*)-quinolinone (14). Dark solid, mp 230-233 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, J = 1.0, 8.2 Hz, 1H), 7.70-7.75 (m, 2H), 7.60 (ddd, J = 1.4, 7.2, 8.6 Hz, 1H), 7.48 (ddd, J = 1.0, 7.2, 8.2 Hz, 1H), 7.40 (dd, J = 1.2, 7.6 Hz, 1H), 7.21-7.27 (m, 2H), 2.74-2.79 (m, 1H), 2.60-2.68 (m, 1H), 1.49-1.57 (m, 2H), 1.24-1.31 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.5, 149.7, 148.8, 138.3, 133.4, 132.9, 131.7, 130.5, 129.1, 125.0, 124.9, 122.7, 119.9, 117.2, 31.9, 30.2, 23.2, 13.8 (one sp^2 carbon is

missing due to overlap); IR (neat, cm^{-1}) 3168, 2963, 2873, 1646, 1521, 1345; MS m/z (rel intensity) 322 (18, M^+), 277 (21), 276 (100); HRMS calcd for $C_{19}H_{18}N_2O_3$: 322.1317, found: 322.1323.

3-*n*-Butyl-4-(2-nitrophenyl)-2(1*H*)-quinolinone (15). Red oil; ^1H NMR ($CDCl_3$) δ 8.30 (dd, *J* = 1.0, 8.2 Hz, 1H), 7.80 (ddd, *J* = 1.2, 7.6, 8.2 Hz, 1H), 7.70 (ddd, *J* = 1.6, 7.2, 8.6 Hz, 1H), 7.43 (ddd, *J* = 1.2, 7.4, 8.2 Hz, 1H), 7.32-7.37 (m, 2H), 7.04 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H), 6.80 (dd, *J* = 1.0, 8.2 Hz, 1H), 2.35-2.42 (m, 1H), 2.25-2.32 (m, 1H), 1.36-1.43 (m, 2H), 1.19-1.27 (m, 2H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.3, 145.3, 137.1, 134.0, 132.3, 132.0, 129.89, 129.86, 125.9, 125.3, 122.8, 120.6, 115.9, 30.9, 28.9, 23.2, 14.0 (two sp^2 carbons are missing due to overlap). A very small amount of **15** was isolated, therefore, no other data were obtained.

3-*tert*-Butyl-4-methyl-2(1*H*)-quinolinone (16). Colorless solid, mp 218-221 °C; ^1H NMR ($CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 1H), 7.41 (ddd, *J* = 1.2, 7.4, 8.0 Hz, 1H), 7.25 (dd, *J* = 0.4, 8.0 Hz, 1H), 7.17 (ddd, *J* = 1.2, 7.4, 8.2 Hz, 1H), 2.67 (s, 3H), 1.63 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.1, 143.3, 138.3, 136.7, 129.2, 124.6, 122.6, 122.0, 115.1, 37.7, 31.9, 19.0; MS m/z (rel intensity) 215 (52, M^+), 200 (100), 173 (99); HRMS calcd for $C_{14}H_{17}NO$: 215.1310, found: 215.1315.

3-*tert*-Butyl-4-phenyl-2(1*H*)-quinolinone (17). Colorless solid, mp 288-292 °C; ^1H NMR ($CDCl_3$) δ 7.33-7.44 (m, 5H), 7.22-7.25 (m, 2H), 6.95 (ddd, *J* = 1.6, 6.8, 8.4 Hz, 1H), 6.75 (dd, *J* = 0.8, 8.4 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.4, 147.7, 139.5, 137.9, 136.8, 130.0, 129.5, 127.83, 127.79, 122.7, 121.9, 114.7, 38.2, 31.7 (one sp^2 carbon is

missing due to overlap); MS m/z (rel intensity) 277 (64, M^+), 276 (100), 262 (28), 234 (39); HRMS calcd for $C_{19}H_{19}NO$: 277.1467, found: 277.1469.

4-*n*-Butyl-3-(5-pyrimidinyl)-2(1*H*)-quinolinone (18). Orange solid, mp 218-219 °C; ^{1}H NMR ($CDCl_3$) δ 9.30 (s, 1H), 8.80 (s, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.53 (ddd, J = 1.0, 7.2, 8.2 Hz, 1H), 7.32 (dd, J = 0.8, 8.4 Hz, 1H), 7.28 (ddd, J = 1.0, 7.2, 8.2 Hz, 1H), 2.77 (t, J = 8.0 Hz, 2H), 1.56-1.61 (m, 2H), 1.30-1.36 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.2, 158.2, 157.8, 152.0, 138.5, 131.4, 130.5, 125.3, 124.8, 123.2, 119.5, 117.1, 32.8, 30.1, 23.1, 13.8; IR (neat, cm^{-1}) 3173, 3038, 2956, 2873, 1651, 1551; MS m/z (rel intensity) 279 (39, M^+), 278 (47), 250 (100), 236 (36), 209 (46); HRMS calcd for $C_{17}H_{17}N_3O$: 279.1372, found: 279.1379. Anal Calcd. for $C_{17}H_{17}N_3O$: C, 72,43; H, 6.13; N, 15.04. Found: C, 72.53; H, 6.16; N, 14.85.

3-*n*-Butyl-4-(5-pyrimidinyl)-2(1*H*)-quinolinone (19). White solid, mp 165-167 °C; ^{1}H NMR ($CDCl_3$) δ 9.39 (s, 1H), 8.73 (s, 2H), 7.51 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 7.41 (dd, J = 0.4, 8.0 Hz, 1H), 7.14 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 6.92 (dd, J = 1.0, 8.2 Hz, 1H), 2.48 (t, J = 8.2 Hz, 2H), 1.47-1.52 (m, 2H), 1.25-1.32 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.1, 158.7, 156.9, 141.2, 137.3, 134.7, 131.0, 130.3, 126.2, 123.0, 120.7, 116.0, 31.7, 28.3, 23.1, 14.0; IR (neat, cm^{-1}) 3023, 2958, 2862, 1651, 1556; MS m/z (rel intensity) 279 (38, M^+), 236 (100), HRMS calcd for $C_{17}H_{17}N_3O$ 279.1372, found 279.1379.

3,4-Diphenyl-2(1*H*)-quinolinone (20). White solid, mp 299-303 °C (lit.[40] mp 303-305 °C). The spectral data are identical to those reported in the literature.[40]

4-Hydroxymethyl-3-phenyl-2(1*H*)-quinolinone (21). Light yellow solid, mp 231-233 °C; ^{1}H NMR (d_6-DMSO) δ 8.00 (d, J = 8.0 Hz, 1H), 7.50 (ddd, J = 1.2, 7.4, 8.2 Hz, 1H), 7.37-7.44 (m, 3H), 7.31-7.34 (m, 3H), 7.22 (ddd, J = 0.8, 7.2, 8.0 Hz, 1H), 5.27 (t, J = 4.8

Hz, 1H), 4.47 (d, J = 4.8 Hz, 2H); ^{13}C NMR (d_6-DMSO) δ 161.3, 144.7, 138.2, 135.3, 132.3, 130.3, 129.8, 127.6, 127.3, 126.5, 121.6, 118.9, 115.0, 58.2; MS m/z (rel intensity) 251 (100, M^+), 250 (82), 204 (18), 174 (19), 117 (18); HRMS calcd for $C_{16}H_{13}NO_2$: 251.0946, found: 251.0950.

3-Hydroxymethyl-4-phenyl-2(1*H*)-quinolinone (22). White solid, mp 237-240 °C (lit.[11a] mp 238-239°C). The spectral data are identical to those reported in the literature.[11a]

4-Methoxymethyl-3-phenyl-2(1*H*)-quinolinone (23). White solid, mp 205-206 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 1H), 7.41-7.52 (m, 6H), 7.21-7.26 (m, 2H), 4.48 (s, 2H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4, 143.0, 138.1, 135.0, 134.2, 130.6, 130.4, 128.3, 128.2, 126.0, 122.9, 119.9, 116.4, 69.3, 58.6; IR (neat, cm^{-1}) 3178, 2888, 1651; MS m/z (rel intensity) 265 (100, M^+), 250 (60), 249 (99); HRMS calcd for $C_{17}H_{15}NO_2$: 265.1103, found: 265.1109. Anal Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.88; H, 6.18; N, 5.22.

3-Methoxymethyl-4-phenyl-2(1*H*)-quinolinone (24). White solid, mp 169-171 °C; ^{1}H NMR ($CDCl_3$) δ 7.46-7.54 (m, 4H), 7.35-7.40 (m, 3H), 7.15 (dd, J = 1.2, 8.0 Hz, 1H), 7.08 (ddd, J = 1.2, 7.4, 8.0 Hz, 1H), 4.26 (s, 2H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.7, 153.0, 138.3, 135.7, 130.8, 129.3, 128.6, 128.5, 128.1, 127.2, 122.6, 120.9, 116.0, 66.9, 58.9; IR (neat, cm^{-1}) 2888, 1651, 1090; MS m/z (rel intensity) 265 (14, M^+), 250 (99), 234 (100); HRMS calcd for $C_{17}H_{15}NO_2$: 265.1103, found: 265.1109.

3,4-Di(benzyloxymethyl)-2(1*H*)-quinolinone (25). Off-white solid, mp 166-168 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (dd, J = 0.8, 8.4 Hz, 1H), 7.49 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.28-7.41 (m, 11H), 7.22 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 4.89 (s, 2H), 4.75 (s, 2H), 4.60 (s, 2H),

4.56 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 164.1, 146.9, 138.5, 138.4, 137.9, 130.7, 128.8, 128.7, 128.6, 128.3, 128.2, 128.1, 127.9, 126.1, 122.8, 119.9, 116.5, 73.1, 73.0, 65.4, 62.8; IR ($CHCl_3$, cm^{-1}) 2858, 1666, 1551, 1431; MS m/z (rel intensity) 279 (86, $[M-PhCH_2O]^+$), 188 (98), 173 (100), 91 (50).

4-Methyl-3-trimethylsilyl-2(1*H*)-quinolinone (26). Colorless solid, mp 195-198 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, J = 0.8, 8.0 Hz, 1H), 7.47 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.33 (dd, J = 0.8, 8.4 Hz, 1H), 7.18 (dd, J = 1.2, 7.0, 8.2 Hz, 1H), 2.61 (s, 3H), 0.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.3, 155.5, 139.0, 130.7, 130.5, 124.7, 122.1, 121.4, 116.1, 19.2, 2.4; MS m/z (rel intensity) 231 (13, M^+), 216 (67), 41 (100); HRMS calcd for $C_{13}H_{17}NOSi$: 231.1079, found: 231.1084.

3-Acetyl-4-ethyl-2(1*H*)-quinolone (28). White solid, mp 199-201 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J = 0.8, 8.0 Hz, 1H), 7.55 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.37 (dd, J = 0.8, 8.4 Hz, 1H), 7.28 (ddd, J = 0.8, 7.6, 8.4 Hz, 1H), 2.85 (q, J = 7.6 Hz, 2H), 2.65 (s, 3H), 1.33 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 202.7, 162.2, 151.7, 138.5, 132.0, 131.4, 125.5, 123.3, 119.1, 117.1, 32.0, 23.1, 15.3; IR (neat, cm^{-1}) 1691, 1651; MS m/z (rel intensity) 215 (68, M^+), 200 (100), 196 (87); HRMS calcd for $C_{13}H_{13}NO_2$: 215.0946, found: 215.0949.

6-Methoxy-3,4-dipropyl-2(1*H*)-quinolinone (31). Brown solid, mp 158-161 °C; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 1H), 7.08-7.11 (m, 2H), 3.87 (s, 3H), 2.83-2.87 (m, 2H), 2.74-2.78 (m, 2H), 1.59-1.72 (m, 4H), 1.10 (t, J = 7.2 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.9, 155.0, 147.0, 132.2, 131.8, 121.0, 117.7, 117.6, 107.3, 55.9, 31.2, 29.4, 23.3, 22.9, 14.9, 14.8; IR (neat, cm^{-1}) 2958, 2868, 1646, 1501; MS m/z (rel intensity)

260 (100, M+1), 258 (85), 244 (30); HRMS calcd for $C_{16}H_{21}NO_2$: 259.1572, found: 259.1578.

7-Methoxy-3,4-dipropyl-2(1*H*)-quinolinone (33). Off-white solid, mp 160-163 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, *J* = 9.2 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 2.4, 9.2 Hz, 1H), 3.89 (s, 3H), 2.81-2.85 (m, 2H), 2.69-2.73 (m, 2H), 1.60-1.67 (m, 4H), 1.03-1.10 (m, 6H); ^{13} C NMR ($CDCl_3$) δ 164.9, 160.6, 147.9, 139.2, 128.1, 125.9, 114.5, 112.0, 98.5, 55.6, 31.2, 29.1, 23.7, 23.0, 14.8, 14.7; IR (neat, cm^{-1}) 2963, 2868, 1661, 1606, 1556; MS m/z (rel intensity) 259 (99, M^+), 244 (68), 230 (100), 216 (41). Anal Calcd. for $C_{16}H_{12}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.91; H, 8.07; N, 5.30.

6-Nitro-3,4-dipropyl-2(1*H*)-quinolinone (36). Slightly yellow solid, mp 240-242 °C (decomp); ^{1}H NMR (*d*$_6$-DMSO) δ 8.50 (d, *J* = 2.4 Hz, 1H), 8.27 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 2.86-2.91 (m, 2H), 2.55-2.60 (m, 2H), 1.42-1.60 (m, 4H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (*d*$_6$-DMSO) δ 161.8, 145.7, 142.1, 141.5, 133.2, 124.0, 120.8, 118.5, 116.3, 29.9, 28.6, 23.0, 22.0, 14.23, 14.20; MS m/z (rel intensity) 274 (100, M^+), 273 (43), 258 (81), 231 (61); HRMS calcd for $C_{15}H_{18}N_2O_3$: 274.1317, found: 274.1320. IR was not obtained due to insolubility of **36**.

Methyl 2(1*H*)-oxo-3,4-dipropylquinoline-6-carboxylate (38). White solid, mp 189-191 °C; ^{1}H NMR ($CDCl_3$) δ 8.43 (dd, *J* = 1.6 Hz, 1H), 8.10 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 2.91-2.96 (m, 2H), 2.74-2.78 (m, 2H), 1.62-1.71 (m, 4H), 1.13 (t, *J* = 7.4 Hz, 3H), 1.08 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.0, 164.7, 148.1, 140.7, 132.2, 130.0, 127.2, 124.1, 119.9, 116.5, 52.4, 31.0, 29.3, 23.7, 22.8, 14.8, 14.7; IR (neat,

cm^{-1}) 3158, 2964, 2871, 1718, 1650, 1616, 1567; MS m/z (rel intensity) 287 (83, M^+), 272 (100), 244 (32); HRMS calcd for $C_{17}H_{21}NO_3$: 287.1521, found: 287.1527.

3,4-Dipropyl-6-aza-2(1*H*)-quinolinone (40). Orange solid, mp 182-185 °C; ^1H NMR ($CDCl_3$) δ 8.97 (s, 1H); 8.51 (d, J = 5.6 Hz, 1H), 7.24 (d, J = 5.6 Hz, 1H), 2.91-2.95 (m, 2H), 2.71-2.75 (m, 2H), 1.59-1.74 (m, 4H), 1.13 (t, J = 7.4 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.6, 148.2, 147.5, 147.0, 142.4, 133.1, 116.5, 110.3, 30.5, 29.0, 23.8, 22.8, 14.8, 14.7; IR (neat, cm^{-1}) 3148, 2958, 2873, 1651, 1601, 1556; MS m/z (rel intensity) 230 (100, M^+), 229 (72), 215 (96), 201 (77), 187 (66), 174 (39); HRMS calcd for $C_{14}H_{18}N_2O$: 230.1419, found: 230.1423.

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CHAPTER III. SYNTHESIS OF COUMARINS AND 2-QUINOLONES VIA PALLADIUM-CATALYZED CARBONYLATIVE ANNULATION OF TERMINAL ALKYNES

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

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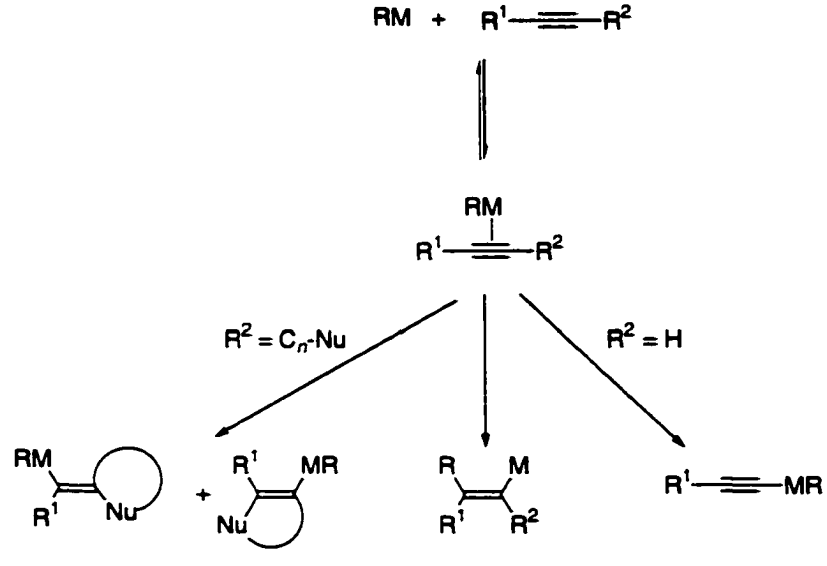
Abstract

o-Iodophenols or *o*-iodoaniline derivatives react with terminal alkynes under 1 atm of CO in the presence of catalytic amounts of $Pd(OAc)_2$ and pyridine to generate coumarins or 2-quinolones, respectively, as the only products. Terminal alkynes bearing alkyl, aryl, silyl, hydroxyl, alkoxyl, ester and cyano substituents are effective in these processes affording the desired products in moderate yields. The formation of coumarins and 2-quinolones in this process is in stark contrast with all previously described palladium-catalyzed reactions of *o*-iodophenols or *o*-iodoanilines with terminal alkynes and CO, which have afforded chromones and 4-quinolones. Moreover, under our conditions terminal alkynes insert into the carbon-palladium bond instead of undergoing a Sonogashira-type coupling. This reaction pathway is confirmed by an isotope labeling experiment.

Introduction

Both internal and terminal alkynes have been utilized in a variety of transition metal-catalyzed reactions for the construction of new carbon-carbon and carbon-heteroatom bonds.[1] However, the reactivity of terminal and internal alkynes is generally quite different. The reactions of internal alkynes catalyzed by transition-metal complexes can be roughly divided into three categories: (1) reactions involving attack of various nucleophiles on the triple bond coordinated to the transition metal, (2) reactions involving insertion of a triple bond into the transition metal-carbon bond, and (3) reactions proceeding through the formation of transition metal-alkynyl complexes (Scheme 1). Both terminal and internal alkynes have been utilized in processes in which a nucleophile attacks the triple bond activated by coordination to a transition-metal complex. The main reaction pathway for internal alkynes, however, is insertion into the transition metal-carbon bond, while most of the reactions involving terminal alkynes proceed through the formation of alkynyl-transition metal complexes.

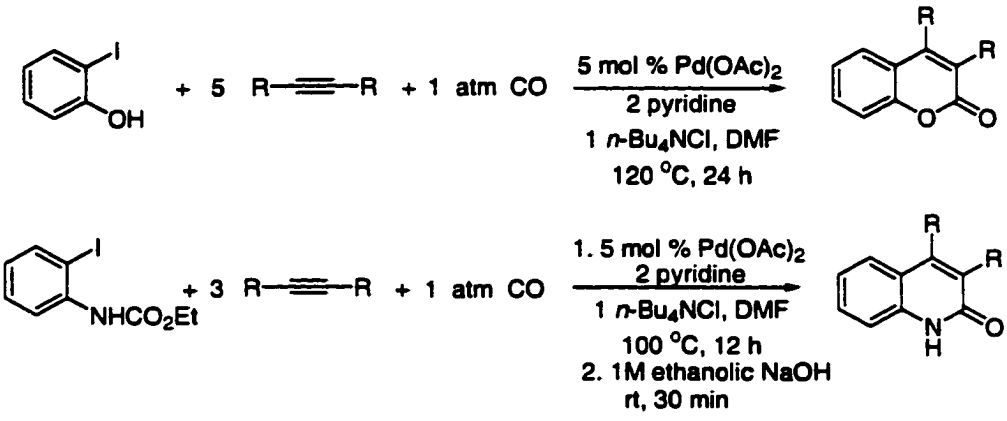
Scheme 1



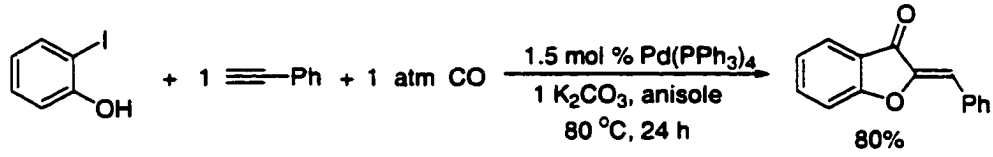
Numerous palladium-catalyzed synthetic transformations involving alkynes based on these three reactivity patterns have been developed.[2] One of the palladium-catalyzed synthetic methodologies based on insertion of an alkyne into a carbon-palladium bond is the annulation of internal alkynes with various *ortho*-substituted aryl iodides that has been developed in our laboratories during the last decade.[3] This methodology represents a powerful and efficient route to a wide variety of hetero- and carbocyclic molecules. Since all of those reactions involve insertion of a carbon-carbon triple bond into the carbon-palladium bond, it is not surprising that terminal alkynes are generally ineffective in those processes. Analogous methods for the synthesis of benzofurans,[4] indoles,[5] isocoumarins,[6] quinolines,[7] pyridines[7] and carbolines[8] from terminal alkynes and related *ortho*-substituted aryl iodides always require the use of a copper co-catalyst and undoubtedly involve the initial formation of an *ortho*-substituted alkynylbenzene by a Sonogashira coupling,[9] followed by cyclization to form the desired heterocycle. Quite often it is necessary to use reagents other than palladium complexes, such as NaOEt,[5a] *n*-Bu_4NF,[5b] $ZnCl_2$[6] or CuI,[7] to affect the cyclization step.

We have recently extended our annulation methodology to three-component processes involving an *ortho*-functionalized aryl iodide, an internal alkyne, and carbon monoxide and developed general and efficient syntheses of 3,4-disubstituted coumarins[10] and 2-quinolones (Scheme 2). One of the interesting features of these two processes is the fact that insertion of the carbon-carbon triple bond into the carbon-palladium bond occurs in preference to insertion of carbon monoxide, while all previous alkyne/CO reactions have afforded products in which CO inserts first.

Scheme 2

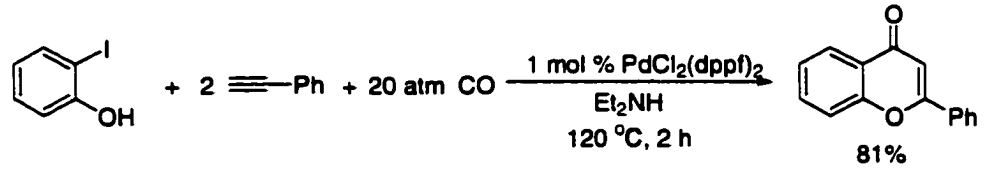


Analogous palladium-catalyzed reactions of terminal alkynes with *o*-iodophenols or *o*-iodoanilines and carbon monoxide are well known. In 1989 Chiusoli and co-workers reported that the reaction of *o*-iodophenol and phenylacetylene under 1 atm of CO afforded an aurone in 82% yield (eq 1).[11] Kalinin and co-workers then reported that the same reaction



(1)

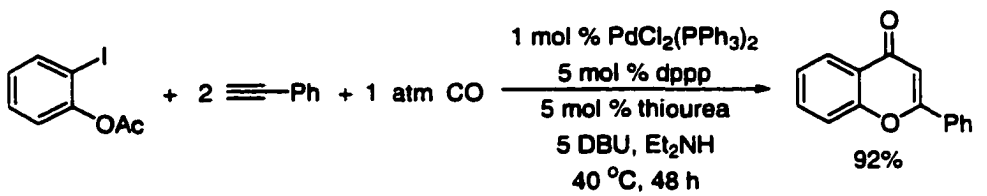
run under a higher pressure of CO (20 atm) in diethylamine as the solvent results in the exclusive formation of 6-membered ring chromones (eq 2).[12] Ortar *et al.* showed that, under



(2)

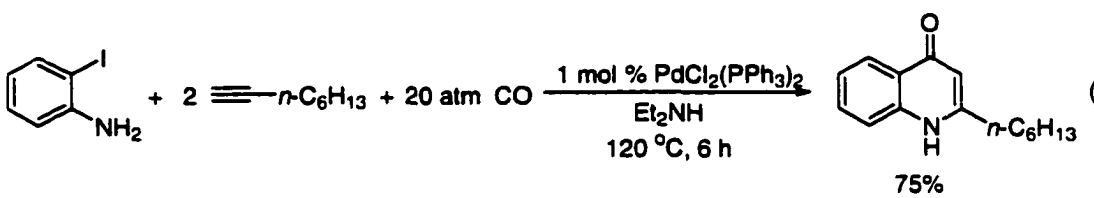
1 atm of CO, the ratio of chromone to aurone product in this reaction strongly depends on the reaction conditions employed.[13] The use of an inorganic base, such as KOAc, and anisole as the solvent favors the formation of aurone, while the use of an organic amine as a base and DMF as the solvent leads to almost exclusive formation of chromones. Recently, Miao and

Yang showed that chromones could be obtained as the sole products under mild conditions (1 atm of CO and 60 °C, instead of 20 atm of CO and 120 °C used by Kalinin *et al.*) by using *o*-iodophenyl acetates as annulating agents, instead of *o*-iodophenols (eq 3).[14]



(3)

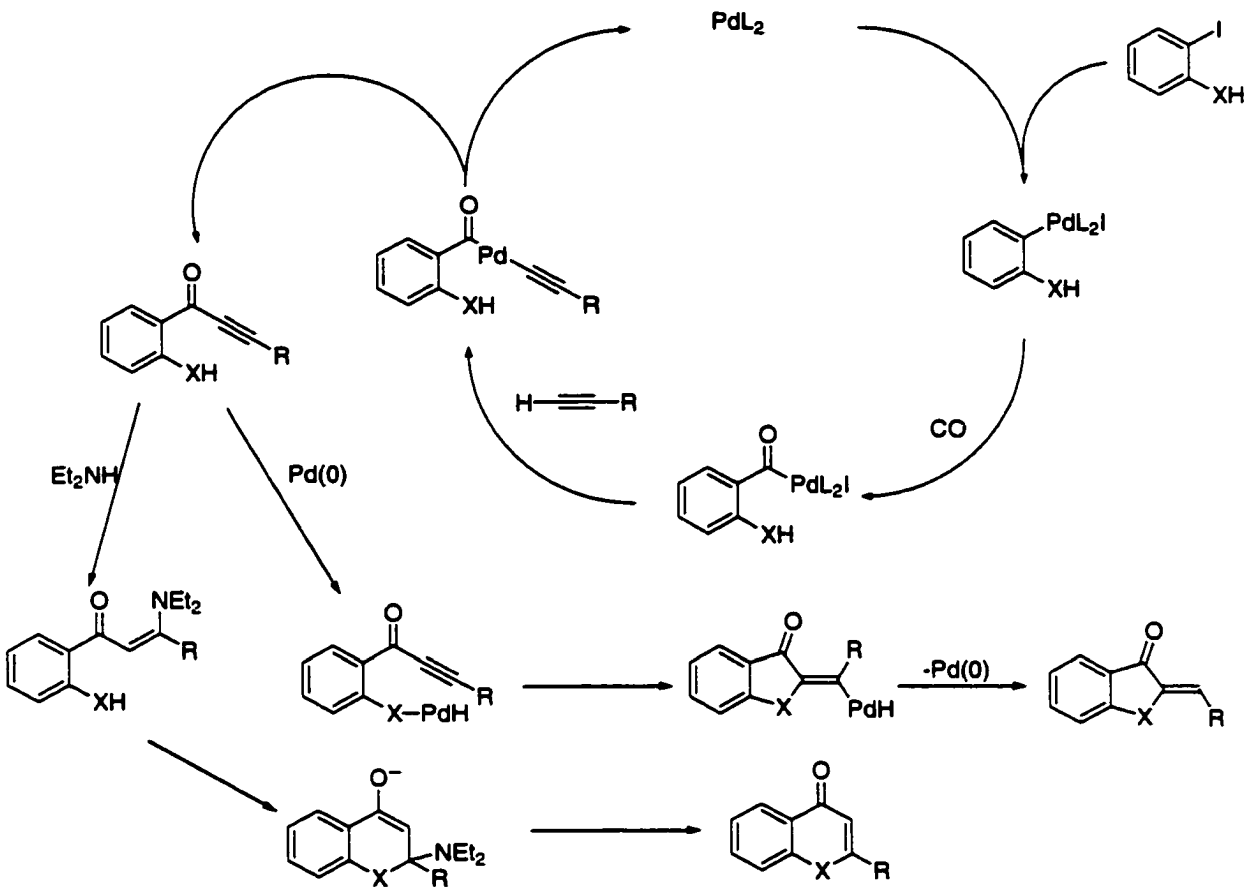
The analogous reaction employing *o*-iodoanilines has also been developed by Torii and co-workers (eq 4).[12b,15] Under reaction conditions similar to the reactions of *o*-iodophenols developed by Kalinin *et al.* (20 atm of CO, Et_2NH as the solvent, 120 °C), this process affords exclusively 6-membered ring 4-quinolones.



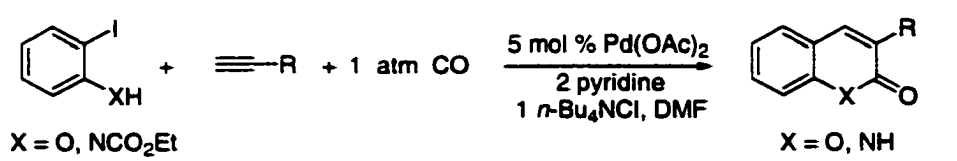
(4)

Thus, the outcome of these reactions is quite different from the carbonylative annulation of internal alkynes developed by us. Mechanistically, the carbonylative annulation of terminal alkynes described thus far is completely different from the analogous reactions of internal alkynes. As shown on Scheme 3, the reactions of terminal alkynes involve (1) oxidative addition of the aryl halide to Pd(0), (2) formation of an acylpalladium complex by CO insertion, (3) coupling of this complex with a terminal alkyne to form an aryl alkynyl ketone, and (4) intramolecular cyclization to afford the desired products. The last step can lead to either 5- or 6-membered rings depending on the base used.

Scheme 3



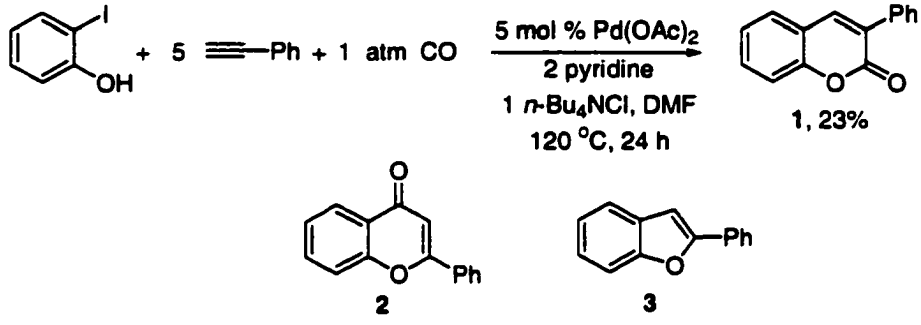
Our success with and the unusual alkyne/CO insertion selectivity of the carbonylative annulation of internal alkynes prompted us to examine the reactions of terminal alkynes in this process. Herein, we wish to disclose full details of this study and to report that, under our conditions for the palladium-catalyzed carbonylative annulation of internal alkynes, terminal alkynes undergo *insertion* into the carbon-palladium bond in preference to the insertion of CO, thus affording coumarins or 2-quinolones (eq 5).



X = O, NCO_2Et X = O, NH (5)

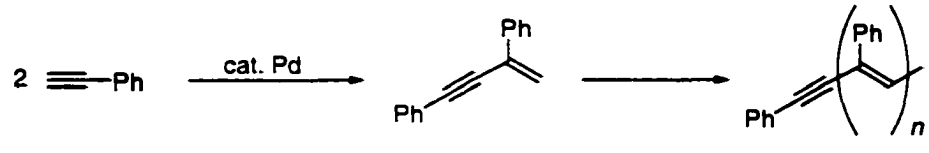
Results and Discussion

Synthesis of Coumarins. The reaction of *o*-iodophenol with phenylacetylene in the presence of 1 atm of CO under the standard reaction conditions for the synthesis of coumarins from internal alkynes used previously by us was examined first (eq 6). Only one



(6)

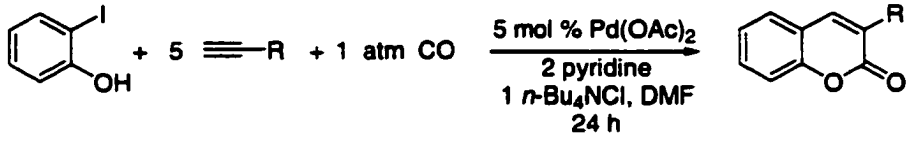
annulation product, 3-phenylcoumarin (**1**), was isolated from the reaction mixture, albeit in a low yield (23%). This is the product that would be expected if the terminal alkyne reacted in the same way as an internal alkyne. None of the other annulation products we might reasonably expected, such as 2-phenylchromone (**2**) or 2-phenylbenzofuran (**3**), have been detected. The reaction, however, was very messy, and a significant amount of a low polarity viscous purple oil was isolated. This oil is most likely the product of polymerization of phenylacetylene (eq 7). The palladium-catalyzed dimerization of terminal acetylenes producing enynes is well-known.[16] In the case of phenylacetylene, the dimer easily undergoes further polymerization, even at room temperature in the absence of any catalyst.[17]



(7)

Thus, it appears that the main competing reaction in this system is not the formation of other annulation products, but dimerization or polymerization of the terminal alkyne. Studies on the palladium-catalyzed dimerization of terminal alkynes have shown that

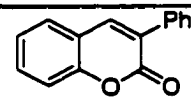
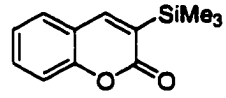
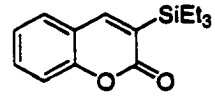
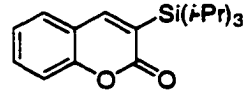
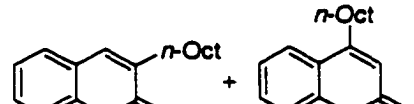
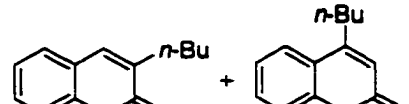
phenylacetylene is by far the most reactive acetylene.[16a] Therefore, a number of different alkynes were examined to identify a more suitable candidate for the optimization studies (eq 8). The results are summarized in Table 1. The reaction with trimethylsilylacetylene (entry



(8)

2) was significantly cleaner, and only the product and the starting *o*-iodophenol were observed by TLC analysis. The yield of the desired product, however, was very low, and the reaction was not complete even after 24 h. The low yield can be attributed to the high volatility of this acetylene (bp 53 °C). Therefore, two other silyl acetylenes with higher boiling points were examined (entries 3 and 4). In both cases a higher yield of the desired coumarin was obtained, and the starting material was almost completely consumed. The slight decrease in the yield in the reaction with triisopropylsilylacetylene relative to the yield in the reaction with triethylsilylacetylene is most likely due to the increased steric hindrance at the triple bond. The alkyl acetylene, 1-decyne, was examined next (entry 5). Surprisingly, both 3- and 4-*n*-octylcoumarins were isolated from the reaction mixture in an approximately 2:1 ratio. The combined yield of the coumarins was the highest observed so far (36%). However, it should be noted that a small amount of apparent polymeric product is present in the isolated coumarin, as evidenced by the alkyl portion of the ^{1}H NMR spectrum. Indeed, a significant amount of polymeric product was also isolated from the reaction mixture. To minimize the amount of polymerization, the reaction was run at lower temperatures (entries 6 and 7). Unfortunately, the decrease in the reaction temperature led to incomplete reactions and significantly lower yields of the coumarins. None of the desired product was formed in

Table 1. Palladium-catalyzed carbonylative annulation of terminal alkynes with *o*-iodophenol (eq 8).[a]

entry	R	temp. (°C)	product(s)	% yield (ratio of isomers)	% recovery of *o*-iodophenol
1	Ph	120	 **1**	23	26
2	$SiMe_3$		 **4**	12	15
3	$SiEt_3$		 **5**	24	5
4	$Si(i\text{-}Pr)_3$		 **6**	18	5
5	$n\text{-}C_8H_{17}$	120	 **7** + **8**	36 (62:38)	
6		100		19 (68:32)	35-40
7		80		0	*ca* 80
8[b]		120		28 (69:31)	
9	$n\text{-}C_4H_9$		 **9** + **10**	33 (70:30)	

[a] Typical reaction conditions: *o*-iodophenol (0.5 mmol), alkyne (2.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), and $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 ml) was stirred at 120 °C for 24 h.
[b] 3 Equiv of alkyne were used.

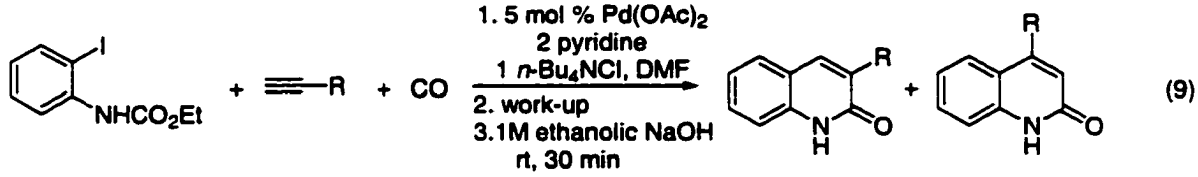
the reaction run at 80 °C.

The experiments conducted with *N*-substituted *o*-anilines (see below) showed that the use of a lower amount of the alkyne improves the yield of the desired product. Higher yields were also obtained using 1-hexyne instead of 1-decyne. Therefore, two experiments were conducted to determine if the same changes would be observed in the reactions of *o*-iodophenol (Table 1, entries 8 and 9). However, no improvement in the yield was observed in either case. The use of 3 equiv of 1-decyne (entry 8) led to a small decrease in the yield of the coumarins. The reaction of 1-hexyne (entry 9) was significantly cleaner than the reaction of 1-decyne, and a much lower amount of the polymeric products was formed. However, the yield of the coumarins did not increase.

Our initial experiments have established that the carbonylative annulation of terminal alkynes under our reaction conditions follows a different mechanism than under previously developed conditions and leads to the formation of different products. The formation of 4-*n*-octylcoumarin (**8**) in the reaction with 1-decyne strongly suggests that the triple bond of the terminal alkyne does insert into the carbon-palladium bond, since no mechanism involving a Sonogashira-like coupling between *o*-iodophenol and a terminal alkyne can account for the formation of such a product.

However, the results of the experiments shown in Table 1, as well as the reactivity patterns established for the carbonylative annulation of internal alkynes, indicate that the number of reaction parameters that can be varied to improve the yield of the process is very limited. Therefore, we decided to switch to *N*-substituted *o*-iodoanilines, which in many cases have proven to be more reactive than *o*-iodophenols.

Synthesis of 2-Quinolones - Optimization of the Reaction Conditions. Ethyl *N*-(2-iodophenyl)carbamate and 1-decyne were chosen as model substrates (eq 9). Under the



(9)

standard coumarin reaction conditions (Table 2, entry 1), the reaction resulted in the formation of 3- and 4-*n*-octyl-2-quinolones (**11** and **12**) in a 73:27 ratio and an overall 29% yield. Although the yield is slightly lower than the yield of the corresponding reaction with *o*-iodophenol (Table 1, entry 5), the quinolones were much purer than the coumarins (as judged by their ^{1}H NMR spectra). The significantly higher polarity of 2-quinolones allows their more efficient separation from the polymeric by-products by column chromatography.

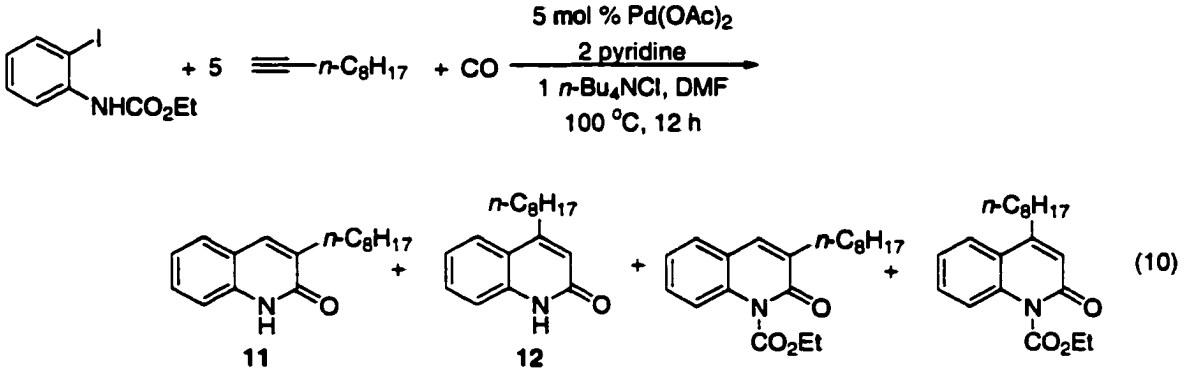
The carbonylative annulation of internal alkynes with *N*-substituted *o*-iodoanilines occurs under milder reaction conditions than the carbonylative annulation with *o*-iodophenols. Therefore, the effect of the reaction temperature on the carbonylative annulation of terminal alkynes was examined. The results are summarized in Table 2. Lowering the temperature to 100 °C and shortening the reaction time to 12 h did not affect the yield of the desired quinolones (entries 2 and 3). When the crude reaction mixture was not treated with ethanolic NaOH (entry 2), four products were isolated (eq 10), just as in the

Since a decrease in the temperature did not lead to a decrease in the reaction yield, 1-hexyne was examined as a model substrate (entry 4). Despite the fact that the boiling point of 1-hexyne is only 71-72 °C, the yield of the 2-quinolone not only did not decrease, but actually increased to 44%. Moreover, both quinolone isomers were essentially pure, as judged by ^{1}H NMR spectroscopy. Therefore, 1-hexyne was used as a model substrate for

Table 2. The effect of the reaction temperature on the palladium-catalyzed carbonylative annulation of terminal alkynes with ethyl *N*-(2-iodophenyl)carbamate (eq 9).[a]

entry	R	temp. (°C)	time (h)	% yield	ratio of isomers[b]
1[c]	*n*-C_8H_{17}	120	24	29	73:27
2[c]		100	12	[d]	
3		100	12	32	76:24
4	*n*-C_4H_9	100	12	44	73:27
5		100	6	43	70:30
6		80	24	31	74:26

[a] Typical reaction conditions: ethyl *N*-(2-iodophenyl)carbamate (0.5 mmol), alkyne (2.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 ml) at 100 °C for 12 h, then the crude product is treated with 1M ethanolic NaOH (5 ml) at rt for 30 min. [b] Ratio of 3-alkyl- to 4-alkyl-2-quinolone. [c] No treatment with ethanolic NaOH. [d] Four possible products have been isolated (eq 10); the yield was not determined due to significant impurities.



(10)

optimization from this point on.

Further variation of the reaction temperature and time (entries 5 and 6) showed that this terminal alkyne behaves similar to internal alkynes. The annulation reaction is complete

after 6 h at 100 °C (entry 5). A further decrease in the reaction temperature to 80 °C results in a very slow reaction, and a lower yield even after 24 h (entry 6).

Since oligomerization of the alkyne is presumed to be the major competing process, the amount of the alkyne in the reaction mixture was varied to establish the optimal aryl iodide to alkyne ratio. The results are shown in Table 3. Increasing the amount of 1-hexyne to 10 equiv (entry 1) led to a significant decline in the yield of the desired product, while the use of lesser amounts of 1-hexyne (entries 3 and 4) resulted in higher yields. The highest yield was obtained using 3 equiv of 1-hexyne (entry 3). It is noteworthy, that even the use of only 2 equiv of the alkyne afforded a higher yield of the quinolones than the use of 5 equiv. These results are in contrast with the carbonylative annulation of internal alkynes, in which the yield of the product increases with an increase in the amount of alkyne up to a certain point and then remains constant.

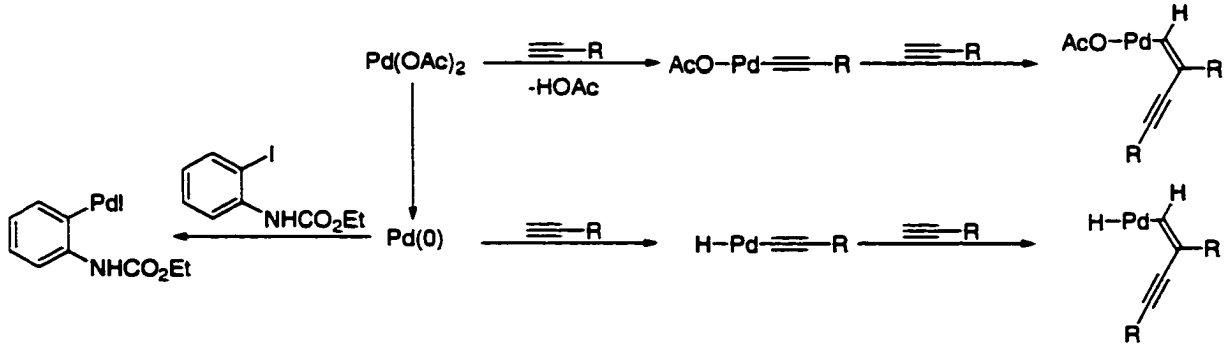
Table 3. The effect of reagent stoichiometry on the palladium-catalyzed carbonylative annulation of 1-hexyne by ethyl *N*-(2-iodophenyl)carbamate (eq 9).[a]

entry	1-hexyne (equiv)	% yield	ratio of isomers[b]
1	10	33	73:27
2	5	44	73:27
3	3	55	70:30
4	2	47	70:30

[a] Typical reaction conditions: ethyl *N*-(2-iodophenyl)carbamate (0.5 mmol), 1-hexyne, pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 ml) at 100 °C for 12 h, then the crude product is treated with 1M ethanolic NaOH (5 ml) at rt for 30 min. [b] Ratio of 3-alkyl- to 4-alkyl-2-quinolone.

The mechanistic hypothesis accounting for these results is depicted in Scheme 4. It appears that two independent palladium-catalyzed reactions occur simultaneously in our system. One of these processes, the homocoupling of the terminal alkynes (the right part of Scheme 4), is presumably catalyzed by both Pd(II) and Pd(0), although Pd(II) is believed to be a more efficient catalyst.[16a] Moreover, regardless of the oxidation state of the initial palladium complex, the catalytic cycle for the alkyne homocoupling can proceed without the regeneration of Pd(0).[16a] A second process, the carbonylative annulation leading to formation of the desired 2-quinolone, starts with oxidative addition of the aryl iodide to Pd(0) (the left side of Scheme 4), and Pd(0) is regenerated at the end of the process. Although the exact details of each cycle are not known, it is apparent that the palladium complexes participating in each of these processes are quite different electronically. Therefore, it is quite likely that the palladium complexes active in one of the reactions are completely or relatively unreactive in the other. Thus, the palladium catalyst is partitioned between two processes, and the effectiveness of each of the processes is decreased by the presence of the other. With an increase in the amount of the alkyne in the reaction mixture, the amount of the palladium species tied up in the homocoupling catalytic cycle increases, thus reducing the

Scheme 4



amount of 2-quinolone formed. The decrease in the yield of the 2-quinolones upon a decrease in the amount of 1-hexyne as we go from 3 to 2 equiv (entries 3 and 4) is most likely due to the competition between CO and 1-hexyne for the arylpalladium complex. Apparently, in the case of the terminal alkynes, this competition becomes important only when a small amount of 1-hexyne is present.

Based on this mechanistic hypothesis, we have chosen to examine other reaction conditions to see if somehow the homocoupling process can be disfavored and the carbonylative annulation can be facilitated. The results are summarized in Table 4. All reactions were run using 3 equiv of 1-hexyne and 5 mol % of the palladium catalyst at 100 °C for 12 h, and the crude products obtained upon an aqueous work-up were treated with 1M ethanolic NaOH at rt for 30 min to completely remove any remaining carbamate protecting group.

The palladium catalyst is likely to have the most impact on the relative efficiency of the two processes, so several Pd(0) and Pd(II) catalysts were examined first (entries 1-5). Interestingly, no change in the yield of the 2-quinolones was observed when a Pd(0) catalyst, $Pd(dba)_2$ (entry 2), was employed. The use of a different Pd(II) catalyst (entry 3) also did not alter the yield significantly. However, the addition of 10 mol % of PPh_3 to the catalytic system lowered the yield by more than one half (entry 4). Interestingly, when a new air-stable Pd(II) complex bearing two phosphinous acid ligands[18] (entry 5) was employed, the yield did not decrease dramatically. It is noteworthy, that the regioselectivity of the reaction is not at all affected by the choice of the palladium catalyst, suggesting that in all cases the reaction proceeds through the same arylpalladium intermediate.

The formation of an alkynylpalladium complex, which occurs during the

Table 4. Optimization of the reaction conditions for the palladium-catalyzed carbonylative annulation of 1-hexyne by ethyl *N*-(2-iodophenyl)carbamate.[a]

entry	catalyst	base	Cl source	% yield	ratio of isomers[b]
1	$Pd(OAc)_2$	pyridine	*n*-Bu_4NCl	55	70:30
2	$Pd(dba)_2$			55	73:27
3	$PdCl_2(PhCN)_2$			52	70:30
4	$Pd(OAc)_2$/ 2 PPh_3			26	73:27
5	$PdCl_2[P(OH)(t\text{-}Bu)_2]_2$			47	72:28
6	$Pd(OAc)_2$	2,4,6-collidine		51	71:29
7		3-cyanopyridine		52	71:29
8		DMAP		42	62:38
9		NEt_3		35	80:20
10		pyridine	no Cl source	56	61:39
11[c]			*n*-Bu_4NCl	56	70:30
12	10 mol % $Pd(OAc)_2$			55	70:30

[a] Typical reaction conditions: ethyl *N*-(2-iodophenyl)carbamate (0.5 mmol),), alkyne (1.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 ml) at 100 °C for 12 h, then the crude product is treated with 1M ethanolic NaOH (5 ml) at rt for 30 min. [b] Ratio of 3-alkyl- to 4-alkyl-2-quinolone. [c] The reaction was run in 10 ml of DMF.

homocoupling reaction, involves the removal of a proton from the alkyne, thus the nature of the base might play an important role in that process. However, the use of a more sterically hindered pyridine base, 2,4,6-collidine (entry 6), did not significantly affect either the yield or the regioselectivity of the reaction. No change has been observed either when a weaker

base, 3-cyanopyridine (entry 7), was employed. The yield of the 2-quinolone suffered, however, when the stronger bases 4-(dimethylamino)pyridine (entry 8) and triethylamine (entry 9) were employed. The use of these stronger bases also affects the regioselectivity of the reaction. The regioselectivity decreased when DMAP was used as a base, but improved when NEt_3 was employed. The first result is particularly surprising, since no changes in the regioselectivity were observed with three other pyridine bases (entries 1, 6 and 7), although each of these pyridines is much less basic. The reason for the decline in regioselectivity is not obvious at this time.

As we have observed previously in the carbonylative annulation of internal alkynes, elimination of the chloride source does not affect the reaction yield (entry 10). The regioselectivity, however, declined significantly in the absence of *n*-Bu_4NCl.

Dilution of the reaction mixture does not lead to any improvement in the yield or the regioselectivity of the annulation (entry 11). Since we demonstrated earlier that a decrease in the amount of the terminal alkyne leads to an improvement in the reaction yield due presumably to a decrease in the alkyne to Pd catalyst ratio, we attempted to improve the yield by increasing the amount of the catalyst. However, the use of 10 mol % of Pd(OAc) leads only to an increase in the reaction rate and not in the yield of the product (entry 12).

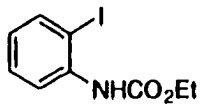
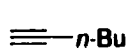
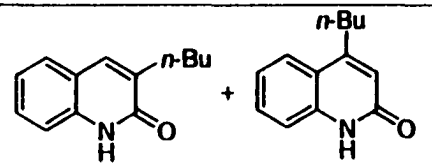
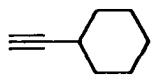
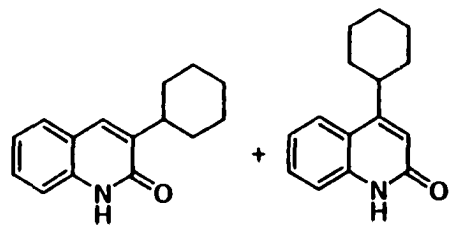
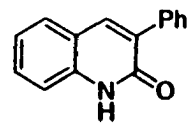
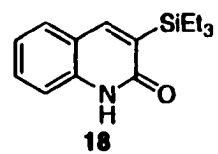
Thus, at this point, the optimized reaction conditions are the same as the reaction conditions used for the carbonylative annulation of internal alkynes: 0.5 mmol of ethyl *N*-(2-iodophenyl)carbamate, 3 equiv of alkyne, 2 equiv of pyridine, 1 equiv of *n*-Bu_4NCl, 5 mol % of $Pd(OAc)_2$ in 5 ml of DMF. The reactions are run at 100 °C for 12 h, and the crude reaction products are treated with 5 ml of ethanolic NaOH at rt for 30 min to remove the

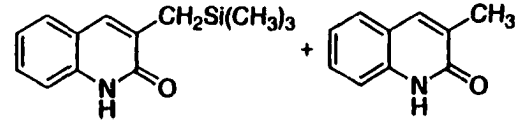
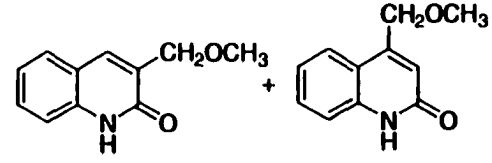
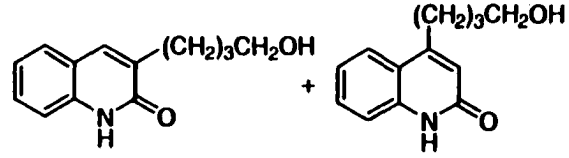
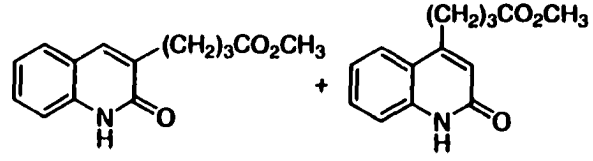
carbamate protecting group. The carbonylative annulation of other terminal alkynes was investigated next using these reaction conditions.

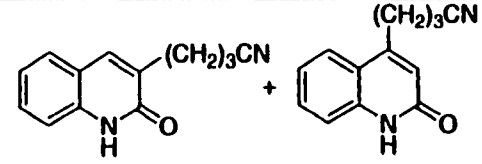
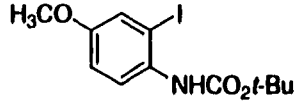
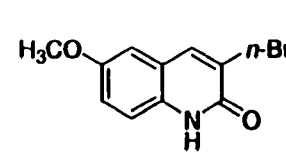
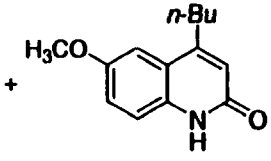
Synthesis of 2-Quinolones - Scope and Limitations. Alkyl-substituted terminal alkynes afford the desired 2-quinolones as mixtures of regioisomers in 50-55% yields (Table 5, entries 1 and 2). The regioselectivity of the reaction improves with an increase in the size of the substituent on the triple bond. These results support our hypothesis that the terminal alkynes behave in this process just like the internal alkynes in our earlier annulation chemistry.[3] Namely, they undergo insertion into the carbon-palladium bond and the regioselectivity of the insertion is governed by steric factors.

The carbonylative annulation of phenylacetylene gives rise to 3-phenyl-2-quinolone (**17**) as the sole product in a 42% yield (entry 3). Despite the fact that phenylacetylene is significantly more reactive in the palladium-catalyzed homocoupling reaction, the yield of **17** is only slightly lower than the yield of the 2-quinolones in the reactions of alkyl acetylenes. Still, a significantly greater amount of polymeric by-products is formed in the reaction with phenylacetylene. In fact, the reaction mixture turns purple at room temperature immediately upon mixing the reagents in the reaction vial. We surmised that the amount of the polymerization might be reduced and the yield of quinolone **17** might be improved if the phenylacetylene were added last to the reaction mixture. Thus, all the reagents, except phenylacetylene, were stirred at 100 °C under one atm of CO for 15 min, and phenylacetylene was then added to the reaction mixture and the rest of the reaction was performed following the standard reaction procedure (entry 4). This operation, however, neither improved the yield of the desired product, nor did it reduce the amount of the polymeric products. The reaction mixture that remained light yellow before addition of the

Table 5. Synthesis of 2(1*H*)-quinolones via palladium-catalyzed annulation of terminal alkynes (eq 11).[a]

entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield	ratio of isomers
1			 **13** **14**	55	70:30
2			 **15** **16**	50	82:18
3			 **17**	42	
4[b]			**17**	41	
5			 **18**	38	

entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield	ratio of isomers
6		≡—$CH_2Si(CH_3)_3$	 **19** + **20**	10 + 9	
7		≡—CH_2OH		0[c]	
8		≡—CH_2OCH_3	 **21** + **22**	26[d]	76:24
9		≡—CO_2Et		0[c]	
10		≡—$(CH_2)_3CH_2OH$	 **23** + **24**	~25	~80:20
11		≡—$(CH_2)_3CO_2CH_3$	 **25** + **26**	47	81:19

entry	*N*-substituted *o*-iodoaniline	alkyne	product(s)	% yield	ratio of isomers
12		$\equiv$—$(CH_2)_3CN$	 **27** + **28**	41	81:19
13		$\equiv$—*n*-Bu	 **29** +  **30**	53	69:31

[a] Typical reaction conditions: ethyl *N*-(2-iodophenyl)carbamate (0.5 mmol), alkyne (1.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 ml) at 100 °C for 12 h, then the crude product is treated with 1M ethanolic NaOH (5 ml) at rt for 30 min. [b] The reaction was run as in footnote a, except that all reagents, but phenylacetylene, were stirred at 100 °C for 15 min, then phenylacetylene (1.5 mmol) in 0.5 ml of DMF was added in one portion. [c] A very messy reaction. None of the desired product was detected in the crude reaction mixture by ^1H NMR spectroscopy. No separation by column chromatography was attempted. [d] Ethyl *N*-(2-iodophenyl)carbamate was recovered in a 25% yield.

alkyne darkened within minutes of the addition and attained the dark purple color in 10-15 minutes.

Excellent regioselectivity is the other interesting feature of this phenylacetylene reaction. The carbonylative annulation of cyclohexylacetylene afforded an approximately 4:1 mixture of isomers (entry 2), although the sizes of the cyclohexyl and phenyl groups are almost the same. Therefore, it is likely that the steric bulk of the substituents on the triple bond is a major, but not the only, factor determining the regioselectivity of the process. The electronic effects of the substituents on the carbon-carbon triple bond should favor alkyne insertion when it affords a vinylpalladium complex with the palladium atom next to a substituent better able to stabilize a negative charge. Since a phenyl group is much more effective in stabilizing a negative charge than a cyclohexyl group is, this would account for the better regioselectivity observed in the reaction of phenylacetylene.

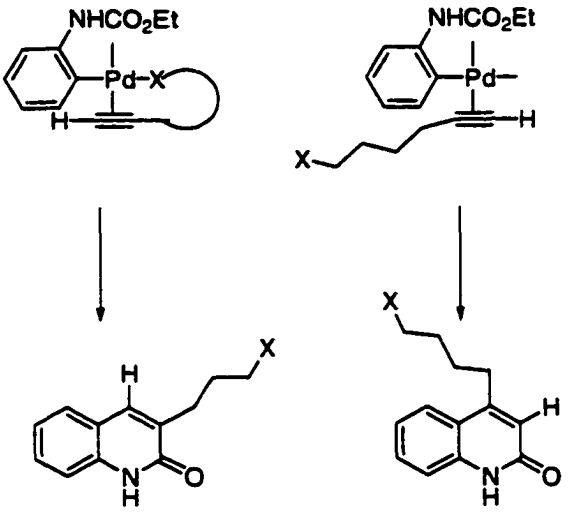
The carbonylative annulation of terminal alkynes bearing various functional groups was examined next. Triethylsilylacetylene afforded the desired product **18** in a 38% yield with excellent regioselectivity (entry 5). However, the reaction of another alkyne bearing a silyl group, propargyltrimethylsilane (entry 6), afforded only low yields of two 2-quinolones, the expected product **19** and the desilylated analogue **20**. The desilylation apparently occurs during treatment of the crude reaction mixture with ethanolic NaOH. The poor yield may be due to two factors, the high reactivity of the starting alkyne toward electrophiles, and the low stability of the desired product.

Carbonylative annulation of terminal alkynes bearing hydroxyl, ester and cyano groups shows that the outcome of the process strongly depends on the proximity of the group to the carbon-carbon triple bond. The carbonylative annulation of propargyl alcohol

appeared to be a very messy reaction, producing a significant amount of polymeric products. None of the desired 2-quinolones have been detected by ^{1}H NMR spectroscopy (entry 7). Protection of the hydroxyl group improved the yield of the reaction (entry 8). However, this reaction was incomplete after 12 h, and 25% of the starting iodoaniline derivative was recovered unchanged. It is possible that the high volatility of propargyl methyl ether (bp 62 °C) is responsible for the low yield of the product. The result of the carbonylative annulation of ethyl propiolate (entry 9) was very similar to that of the reaction with propargyl alcohol. A messy reaction, a significant amount of polymer, and none of the desired product were observed by ^{1}H NMR spectroscopy. Thus, introduction of the functional group near the triple bond is detrimental to the reaction, since it apparently facilitates homocoupling and other side reactions of the terminal acetylenes.

The carbonylative annulation of terminal alkynes in which the same functional groups are 3-4 carbon atoms removed from the triple bond does afford 2-quinolone products. Although the yield in the reaction with 5-hexyn-1-ol remains low (entry 10) perhaps due to carbonylation of the alcohol group, the yield obtained employing methyl 5-hexynoate (entry 11) is only slightly lower than the yield of the reaction with 1-hexyne. The carbonylative annulation of 5-hexynenitrile also afforded the desired products in a 41% yield (entry 12). The surprising feature of these reactions is an evident improvement in the regioselectivity. The ratio of isomers is around 4 to 1 when functionalized acetylenes are used, compared to the 2.2 to 1 ratio obtained in most of the reactions with 1-hexyne (entry 1, see also entry 13). It is conceivable that additional coordination of the palladium atom by the functional group of the alkyne stabilizes the palladium complex from which the major isomer arises upon insertion (Scheme 5). It is surprising, however, that the nature of the functional group does

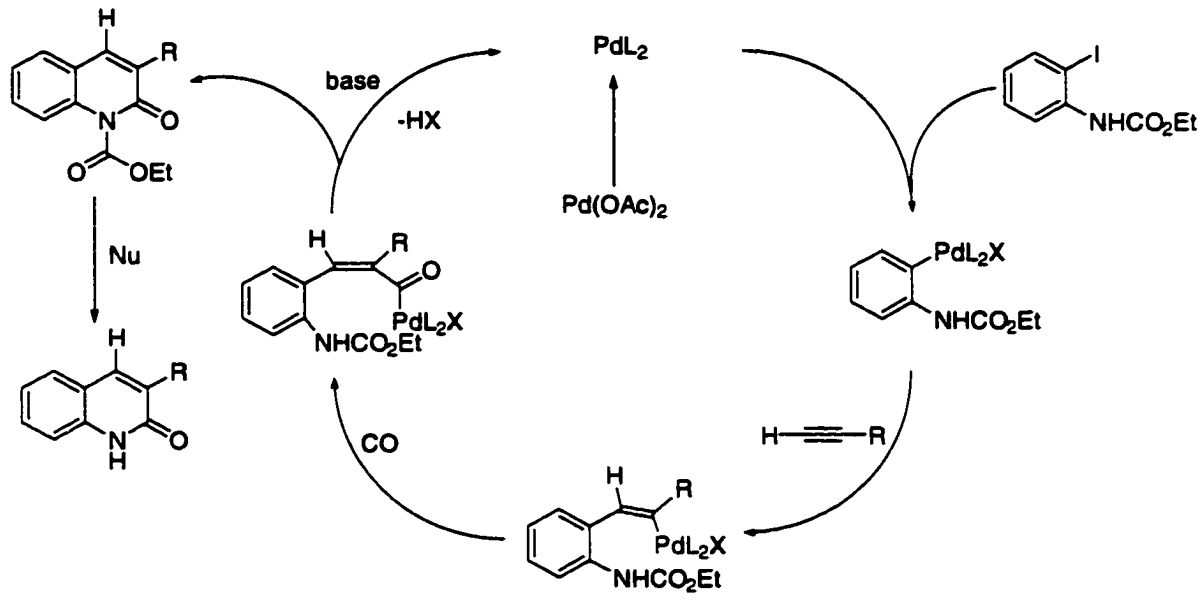
Scheme 5



not affect the regioselectivity, although a cyano and a hydroxyl group are expected to have significantly different affinities towards palladium. The carbonylative annulation of 1-hexyne with an iodoaniline bearing a methoxy group in the para position to the carbamate group afforded the desired product in a 53% yield as a 69:31 mixture of regioisomers (entry 13). Thus, an electron-donating group on the aromatic ring affects neither the yield nor the regioselectivity of the process.

Mechanism. Since the carbonylative annulation of terminal alkynes closely resembles the carbonylative annulation of internal alkynes in all major features (the nature of the products, the regioselectivity, etc.), we believe that the mechanisms of these two processes must be similar. Thus, for the carbonylative annulation of terminal alkynes we propose the mechanism shown in Scheme 6. The *in situ* reduction of $Pd(OAc)_2$ to Pd(0) generates the active catalyst. Oxidative addition of the aryl iodide to Pd(0) leads to formation of an arylpalladium complex, which in turn reacts with the terminal alkyne to

Scheme 6



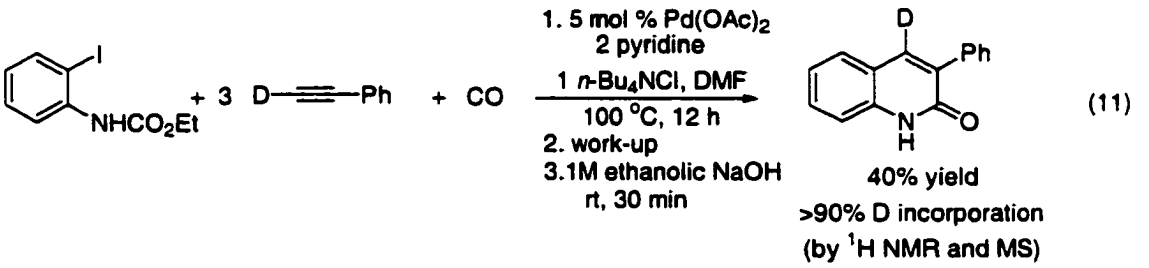
generate a vinylpalladium intermediate. Insertion of CO into the vinylpalladium bond produces an acylpalladium complex. Nucleophilic attack of the carbamate nitrogen on the carbonyl group of the acylpalladium complex leads to formation of the *N*-protected 2-quinolone with regeneration of the Pd(0) catalyst. Subsequent hydrolysis of the carbamate group affords the desired product.

Thus, our process differs from the previously reported palladium-catalyzed reaction of *o*-iodoanilines with terminal alkynes and CO in two aspects.[12b] First, the terminal alkyne inserts into the carbon-palladium bond, instead of undergoing a Sonogashira-type coupling.[9] Second, this insertion of the alkyne occurs prior to the insertion of CO, thus leading to 2- and not 4-quinolone derivatives.

The insertion of a carbon-carbon triple bond of a terminal alkyne into the carbon-palladium bond is not unprecedented.[19] although it is certainly very rare. The Sonogashira-

type coupling prevails in almost all cases, and even in those cases where insertion apparently occurs, it sometimes competes with coupling.[19b] However, in our case, invoking such a coupling as the first step of the process could hardly account for the formation of 3-substituted 2-quinolones, and no reasonable mechanism for formation of the 4-substituted isomer from the coupling product can be envisioned. Indeed, the formation of both regioisomers and the fact that the regioselectivity is apparently governed by steric factors, just as in the annulation of internal alkynes, provides the strongest support for the idea that alkyne insertion does occur.

Still, we sought more direct evidence for the insertion step. Therefore, the carbonylative annulation of deuterated phenylacetylene has been examined (eq 11). To our



(11)

delight, the reaction afforded 3-phenyl-4-deutero-2-quinolone with better than 90% deuterium incorporation, as determined by ^{1}H NMR and MS analysis. This result proves unambiguously that insertion of the terminal alkyne does indeed occur under our reaction conditions. It also shows that relatively little exchange of the acetylenic proton occurs under our reaction conditions, even with phenylacetylene, and, therefore, the formation of alkynylpalladium complexes is irreversible. It is also remarkable that phenylacetylene survives long enough to participate in the annulation, even though it has been reported that the dimerization of phenylacetylene proceeds in a 63% yield after just 40 min at room temperature in the presence of just 2 mol % of an appropriate palladium catalyst.[16]

Conclusions

The reaction of *o*-iodophenol or ethyl *N*-(2-iodophenyl)carbamate with terminal alkynes and CO under standard carbonylative annulation conditions ($Pd(OAc)_2$ / pyridine) affords exclusively coumarins or 2-quinolones. This is the first example of such chemoselectivity. All previous work has reported the formation of chromones or 4-quinolones, respectively. Terminal alkynes with alkyl, phenyl, silyl, hydroxyl, alkoxyl, ester, and cyano substituents react with ethyl *N*-(2-iodophenyl)carbamate to afford 2-quinolones in modest yields. Both 3- and 4-substituted 2-quinolones are obtained in the reactions with terminal alkynes bearing long alkyl chains. Such unusual behavior for terminal alkynes indicates that the key step in this process is insertion of the terminal alkyne into the carbon-palladium bond and not a Sonogashira-type coupling. This reactivity pattern is unambiguously proved by an isotope labeling experiment. The annulation of *d*-phenylacetylene affords 4-deutero-3-phenyl-2-quinolone in 40% yield with better than 90% deuterium incorporation.

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 (Scientific Adsorbents Co.), and visualization was effected with short wavelength UV light (254 nm) or a basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5 %) + 300 ml of H_2O]. 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. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. DMF, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. Pyridine was purchased from Fisher Scientific Co and purified by distillation from CaH_2. Et_3N, 2,4,6-collidine, 3-cyanopyridine and DMAP were purchased from Aldrich Chemical Co. *n*-Bu_4NCl was purchased from Lancaster Synthesis, Inc. 1-Hexyne, 1-octyne, phenylacetylene, *d*-phenylacetylene, trimethylsilylacetylene, triethylsilylacetylene, triisopropylsilylacetylene, propargyl alcohol, propargyl methyl ether, 5-hexyn-1-ol and ethyl propiolate were purchased from Aldrich Chemical Co. Methyl 5-hexynoate and 5-hexynenitrile were purchased from GFS Chemicals Co. Cyclohexylacetylene was purchased from Farchan Chemical Co. Ethyl *N*-(2-iodophenyl)carbamate[20] and *tert*-butyl *N*-(2-iodo-4-methoxyphenyl)carbamate[21] were prepared following literature procedures. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. Triphenylphosphine was donated by Kawaken Fine Chemicals Co. Ltd.

General procedure for the synthesis of coumarins. *o*-Iodophenol (0.5 mmol), the alkyne (2.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol) and DMF (5 ml) were placed in a 4 dram vial. The vial was purged with CO for 2 min and then connected to a balloon of CO. The reaction mixture was stirred at 120 °C for 24 h, then allowed to cool to room temperature, diluted with EtOAc, washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure.

The product was isolated by column chromatography on silica gel. The following coumarins were prepared using this procedure.

3-Phenyl-2*H*-1-benzopyran-2-one (1). The compound was identified by comparing its ^{1}H NMR spectral properties with the literature data.[22]

3-Trimethylsilyl-2*H*-1-benzopyran-2-one (4). Light yellow solid, mp 85-88 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H), 7.45-7.52 (m, 2H), 7.22-7.31 (m, 2H), 0.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.0, 154.9, 150.1, 131.6, 130.1, 127.8, 124.2, 119.5, 116.8, -1.8; MS m/z (rel intensity) 218 (27, M^+), 203 (100), 175 (52), 145 (16), 135 (17), 94 (16); HRMS calcd for $C_{12}H_{14}O_2Si$: 218.0763, found: 218.0770.

3-Triethylsilyl-2*H*-1-benzopyran-2-one (5). White solid, mp 80-83 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.45-7.52 (m, 2H), 7.22-7.31 (m, 2H), 0.96-1.01 (m, 9H), 0.84-0.90 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 163.0, 154.9, 151.4, 131.8, 127.8, 127.6, 124.2, 119.5, 116.8, 7.6, 2.7; IR (neat, cm^{-1}) 2954, 2918, 2873; HRMS calcd for $C_{15}H_{21}O_2Si$: 258.1357, found: 258.1362.

3-Triisopropylsilyl-2*H*-1-benzopyran-2-one (6). Off-white solid, mp 113-118 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 7.46-7.51 (m, 2H), 7.25-7.31 (m, 2H), 1.53 (septet, J = 7.6 Hz, 3H), 1.13 (d, J = 7.6 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 163.2, 154.9, 152.3, 131.9, 127.8, 126.1, 124.1, 119.4, 116.7, 18.9, 11.3; IR (neat, cm^{-1}) 2943, 2868, 1701; MS m/z (rel intensity) 259 (100, $[M-C_3H_7]^+$), 69 (29); HRMS $(M-C_3H_7)^+$ calcd for $C_{15}H_{19}O_2Si$: 259.1154, found: 259.1159.

3-*n*-Octyl-2*H*-1-benzopyran-2-one (7). White solid, mp 59-62 °C (lit.[23] mp 64 °C); ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1H), 7.42-7.46 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.25 (ddd, J =

1.0, 7.2, 8.0 Hz, 1H), 2.56 (t, J = 7.4 Hz, 2H), 1.60-1.66 (m, 2H), 1.20-1.40 (m, 10H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.1, 153.3, 138.5, 130.6, 130.3, 127.3, 124.4, 119.8, 116.6, 32.0, 31.0, 29.6, 29.5, 29.4, 28.2, 22.8, 14.3. All spectral properties are identical to those reported in the literature.[22]

4-*n*-Octyl-2*H*-1-benzopyran-2-one (8). Off-white solid, mp 60-63 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, J = 1.2, 8.0 Hz, 1H), 7.53 (ddd, J = 1.6, 7.0, 8.6 Hz, 1H), 7.27-7.36 (m, 2H), 6.29 (s, 1H), 2.77 (t, J = 7.8 Hz, 2H), 1.66-1.74 (m, 2H), 1.20-1.40 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.3, 156.6, 154.0, 131.8, 124.5, 124.3, 119.6, 117.5, 114.1, 32.01, 31.97, 29.7, 29.5, 29.4, 28.3, 22.8, 14.3; MS (m/z) rel intensity 258 (27, M^+), 173 (19), 160 (100), 132 (37); HRMS calcd for $C_{17}H_{22}O_2$: 258.1620, found: 258.1623.

3-*n*-Butyl-2*H*-1-benzopyran-2-one (9). White solid, mp 60-63 °C (lit.[22] mp 64 °C). The spectral properties are identical to those reported in the literature.[22]

4-*n*-Butyl-2*H*-1-benzopyran-2-one (10). Yellow oil, the spectral properties are identical to those reported in the literature.[24]

General procedure for the synthesis of 2-quinolones. Ethyl *N*-(2-iodophenyl)carbamate (0.5 mmol), an alkyne (1.5 mmol), pyridine (1 mmol), *n*-Bu_4NCl (0.5 mmol), and $Pd(OAc)_2$ (5 mol %, 0.025 mmol) were placed in a 4 dram vial, then dissolved in 5 ml of DMF. The vial was purged with carbon monoxide for 2 min, and then connected to a balloon of CO. The reaction mixture was stirred at 100 °C for 12 h, then allowed to cool to room temperature, diluted with ethyl acetate, washed with water, and concentrated under reduced pressure. The residue was treated with 5 ml of 1M ethanolic NaOH at room temperature for 30 min. Then 15 ml of satd aq NH_4Cl were added, and the resulting mixture

was extracted with ethyl acetate. The organic extracts were combined, washed with satd aq NH_4Cl and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was separated by column chromatography on silica gel. The following 2-quinolones were prepared using this procedure.

3-*n*-Butyl-2(1*H*)quinolinone (13). White solid, mp 145-147 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.40-7.47 (m, 2H), 7.18 (ddd, J = 8.0, 6.4, 2.0 Hz, 1H), 2.70 (t, J = 7.8 Hz, 2H), 1.66-1.74 (m, 2H), 1.41-1.51 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.7, 137.7, 136.6, 134.5, 129.4, 127.1, 122.5, 120.5, 115.9, 30.8, 30.1, 22.8, 14.2; IR ($CDCl_3$, cm^{-1}) 2958, 2859, 1656, 1566; MS m/z (rel intensity) 201 (26, M^+), 172 (25), 159 (100), 158(51), 130 (40); HRMS calcd for $C_{13}H_{15}NO$: 201.1154, found: 201.1158.

4-*n*-Butyl-2(1*H*)quinolinone (14). White solid, mp 140-142 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.48-7.50 (m, 2H), 7.21-7.27 (m, 1H), 6.61 (s, 1H), 2.87 (t, J = 7.6 Hz, 2H), 1.68-1.76 (m, 2H), 1.43-1.52 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.8, 153.6, 138.8, 130.5, 124.3, 122.6, 120.1, 119.6, 117.1, 32.2, 31.1, 22.8, 14.1; IR (neat, cm^{-1}) 2963, 1646, 1556; MS m/z (rel intensity) 201 (28, M^+), 159 (78), 130 (100); HRMS calcd for $C_{13}H_{15}NO$: 201.1154, found: 201.1158.

3-Cyclohexyl-2(1*H*)-quinolinone (15). White solid, mp 229-231 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.45 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.18 (ddd, J = 1.2, 7.2, 8.0 Hz, 1H), 3.00-3.06 (m, 1H), 2.01-2.04 (m, 2H), 1.79-1.89 (m, 3H), 1.48-1.58 (m, 2H), 1.27-1.40 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 164.2, 139.4, 137.3, 134.5, 129.4, 127.4, 122.5, 120.6, 115.7, 37.3, 32.8, 27.0, 26.6; IR (neat, cm^{-1}) 2933,

2853, 1651, 1566; MS m/z (rel intensity) 227 (32, M^+), 198 (44), 183 (54), 170 (100), 154 (64), 128 (44); HRMS calcd for $C_{15}H_{17}NO$: 227.1310, found: 227.1316.

4-Cyclohexyl-2(1*H*)-quinolinone (16). Off-white solid, mp 233-235 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H), 7.50 (ddd, J = 1.2, 7.2, 8.2 Hz, 1H), 7.40 (dd, J = 0.8, 8.0 Hz, 1H), 7.24 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 6.62 (s, 1H), 3.00-3.05 (m, 1H), 1.82-2.02 (m, 5H), 1.25-1.54 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 164.5, 158.2, 138.7, 130.4, 124.0, 122.6, 120.0, 117.3, 117.0, 39.4, 33.3, 27.0, 26.5; IR (neat, cm^{-1}) 2928, 2853, 1656, 1556; HRMS calcd for $C_{15}H_{17}NO$: 227.1310, found: 227.1316.

3-Phenyl-2(1*H*)-quinolinone (17). White solid, mp 230-231 °C (lit.[25] 231-232 °C); ^{1}H NMR (d_6-DMSO) δ 8.10 (s, 1H), 7.72-7.77 (m, 3H), 7.50 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.32-7.45 (m, 4H), 7.19 (dd, J = 7.2, 7.6 Hz, 1H); ^{13}C NMR (d_6-DMSO) δ 161.0, 138.4, 137.6, 136.3, 131.5, 130.2, 128.7, 128.1, 127.9, 127.8, 121.9, 119.5, 114.7; MS m/z (rel intensity) 221 (49, M^+), 220 (100), 165 (39); HRMS calcd for $C_{15}H_{11}NO$: 221.0841, found: 221.0846. IR was not obtained, because **17** is insoluble in any organic solvent.

3-Triethylsilyl-2(1*H*)-quinolinone (18). White solid, mp 138-140 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.53 (dd, J = 1.2, 8.4 Hz, 1H), 7.48 (ddd, J = 1.2 7.2, 8.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.17 (ddd, J = 1.0, 7.0, 8.0 Hz, 1H), 1.00-1.05 (m, 9H), 0.92-0.98 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 167.4, 148.8, 139.7, 131.7, 130.7, 127.8, 122.2, 130.4, 115.9, 7.8, 3.1; IR (neat, cm^{-1}) 2953, 2868, 1636, 1596, 1546; MS m/z (rel intensity) 259 (10, M^+), 230 (100), 174 (30), 172 (48), 144 (43); HRMS calcd for $C_{15}H_{21}NOSi$: 259.1392, found: 259.1397.

3-Trimethylsilylmethyl-2(1*H*)-quinolinone (19). Off-white solid. The compound was identified by comparing its ^{1}H and ^{13}C NMR spectral data with those published in the literature.[26]

3-Methyl-2(1*H*)-quinolinone (20). A small amount was isolated, and the compound was identified by comparing its ^{1}H NMR spectral data with those reported in the literature.[26]

3-Methoxymethyl-2(1*H*)-quinolinone (21). White solid, mp 173-175 °C; ^{1}H NMR δ 7.90 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.50 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.23 (ddd, J = 1.0, 7.4, 8.4 Hz, 1H), 4.58 (d, J = 1.2 Hz, 2H), 3.57 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4, 137.8, 136.5, 130.2, 130.1, 127.9, 122.9, 120.2, 116.0, 69.5, 59.2; IR (neat, cm^{-1}) 2995, 2872, 1666, 1573; MS m/z (rel intensity) 189 (12, M^+), 174 (40), 159 (100); HRMS calcd for $C_{11}H_{11}NO_2$: 189.0790, found: 189.0792.

4-Methoxymethyl-2(1*H*)-quinolinone (22). Colorless solid; ^{1}H NMR ($CDCl_3$) δ 7.68 (dd, J = 0.8, 8.0 Hz, 1H), 7.52 (ddd, J = 1.4, 7.4, 8.4 Hz, 1H), 7.43 (dd, J = 0.8, 8.4 Hz, 1H), 7.24 (ddd, J = 1.0, 7.2, 8.2 Hz, 1H), 6.82 (s, 1H), 4.73 (d, J = 1.2 Hz, 2H), 3.51 (s, 3H); a very small amount of **22** was obtained, therefore, no other data were collected.

3-(4-Hydroxybutyl)-2(1*H*)-quinolinone (23). White solid, mp 148-150 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.47 (ddd, J = 1.4, 7.0, 8.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.20 (ddd, J = 1.0, 7.0, 8.0 Hz, 1H), 3.78 (t, J = 6.2 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 1.99 (br s, 1H), 1.77-1.84 (m, 2H), 1.67-1.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.3, 137.5, 137.1, 134.1, 129.7, 127.3, 122.8, 120.5, 115.7, 62.7, 32.2, 30.0, 25.0; IR (neat, cm^{-1}) 2923, 2848, 1656; MS m/z (rel intensity) 217 (33, M^+), 199 (50), 172 (100), 159 (65), 158 (71), 130 (60); HRMS calcd for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1108.

4-(4-Hydroxybutyl)-2(1*H*)-quinolinone (24). White solid, mp 147-150 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.51 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.24 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 6.59 (s, 1H), 3.73 (t, *J* = 6.4 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.80-1.88 (m, 2H), 1.68-1.79 (m, 2H); only a small amount of **24** was obtained, therefore no other spectral data were obtained.

Methyl 4-(2(1*H*)-oxoquinolin-3-yl)butanoate (25). Colorless solid, mp 145-148 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.47 (ddd, *J* = 1.4 Hz, 7.0, 8.4 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.20 (ddd, *J* = 1.0, 7.0, 8.0 Hz, 1H), 3.69 (s, 3H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.04-2.11 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.2, 164.4, 137.8, 137.4, 133.2, 129.8, 127.4, 122.7, 120.4, 115.8, 51.8, 33.8, 29.9, 23.9; IR (neat, cm^{-1}) 3003, 2953, 2848, 1736, 1661, 1576; MS (m/z) rel intensity 245 (32, M^+), 244 (19), 172 (100), 171 (55), 159 (38), 158 (25); HRMS calcd for $C_{14}H_{15}NO_3$: 245.1052, found: 245.1056.

Methyl 4-(2(1*H*)-oxoquinolin-4-yl)butanoate (26). Brown solid, mp 164-167 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.52 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.26 (dd, *J* = 7.2, 8.0 Hz, 1H), 3.71 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.05-2.11 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.7, 164.3, 152.3, 138.7, 130.7, 124.4, 122.8, 120.0, 119.8, 116.9, 51.9, 33.5, 31.8, 24.2; IR (neat, cm^{-1}) 3013, 2953, 2853, 1736, 1651, 1435, 1171; HRMS calcd for $C_{14}H_{15}NO_3$: 245.1052, found: 245.1056.

4-(2(1*H*)-Oxoquinolin-3-yl)butanenitrile (27). Solid, mp 164-167 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.50 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.23 (ddd, *J* = 1.0, 7.0, 8.0 Hz, 1H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.45 (t, *J* = 7.2

Hz, 2H), 2.08-2.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.2, 138.3, 137.9, 131.6, 130.2, 127.5, 122.9, 120.2, 119.8, 115.9, 30.0, 24.4, 17.0; IR (neat, cm^{-1}) 2953, 2856, 2238, 1655; MS m/z (rel intensity) 212 (M^+, 28), 172 (50), 159 (100); HRMS calcd for $C_{13}H_{12}N_2O$: 212.0950, found: 212.0953.

4-(2(1*H*)-Oxoquinolin-4-yl)butanenitrile (28). Brown oil; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 7.2, 8.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 7.2, 8.0 Hz, 1H), 6.60 (s, 1H), 3.06 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 6.8 Hz, 2H), 2.08-2.16 (m, 2H). HRMS calcd for $C_{13}H_{12}N_2O$: 212.0950, found: 212.0953. Only a small amount was isolated, therefore, no other data were obtained.

6-Methoxy-3-*n*-butyl-2(1*H*)-quinolinone(29). White solid, mp 165-168 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 2.8, 8.8 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 3.85 (s, 3H), 2.69 (t, J = 7.6 Hz, 2H), 1.65-1.73 (m, 2H), 1.41-1.51 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.1, 155.2, 136.2, 135.0, 132.2, 121.1, 118.8, 117.1, 108.5, 55.9, 30.8, 30.2, 22.8, 14.3; IR (neat, cm^{-1}) 2933, 2834, 1651, 1621, 1501; MS (m/z) rel intensity 231 (38, M^+), 202 (61), 189 (86), 188 (56), 174 (100); HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259, found: 231.1263.

6-Methoxy-4-*n*-butyl-2(1*H*)-quinolinone(30). White solid, mp 195-198 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 7.13-7.16 (m, 2H), 3.87 (s, 3H), 2.83 (t, J = 7.6 Hz, 2H), 1.69-1.76 (m, 2H), 1.44-1.51 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.2, 155.2, 152.8, 133.4, 120.8, 120.0, 119.2, 118.2, 106.6, 56.0, 32.2, 30.9, 22.8, 14.1; IR (neat, cm^{-1}) 2963, 1651; MS (m/z) rel intensity 231 (27, M^+), 189 (21), 41 (100); HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259, found: 231.1262.

Isotope labeling experiment. Ethyl *N*-(2-iodophenyl)carbamate (146 mg, 0.5 mmol), *d*-phenylacetylene (98% D, 155 mg, 1.5 mmol), pyridine (79 mg, 1.0 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), and $Pd(OAc)_2$ (5.6 mg, 5 mol %, 0.025 mmol) were placed in a 4 dram vial, then dissolved in 5 ml of DMF. The vial was purged with CO for 2 min, and then connected to a balloon of CO. The reaction mixture was stirred at 100 °C for 12 h, then allowed to cool to room temperature, diluted with ethyl acetate, washed with water, and concentrated under reduced pressure. The residue was treated with 5 ml of 1M ethanolic NaOH at room temperature for 30 min. Then 15 ml of satd aq NH_4Cl were added, and the resulting mixture was extracted with ethyl acetate. The organic extracts were combined, washed with satd aq NH_4Cl and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel using 1:1 hexane/ethyl acetate as an eluent afforded 46 mg (40 %) of **4-deutero-3-phenyl-2(1*H*)-quinolinone**: colorless solid, mp 230-231 °C; ^{1}H NMR (d_6-DMSO) δ 8.10 (s, 0.11H), 7.72-7.77 (m, 3H), 7.50 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.32-7.45 (m, 4H), 7.19 (dd, J = 7.2, 7.6 Hz, 1H); ^{13}C NMR (d_6-DMSO) δ 161.0, 138.4, 136.3, 131.5, 130.2, 128.7, 128.1, 127.9, 127.8, 121.9, 119.5, 114.7, the signal of the carbon bound to the deuterium is not observed; MS m/z (rel intensity): 222 (43, M^+), 221(100), 192(17), 191(14), 166(22), 165(23); HRMS calcd for $C_{15}H_{10}DNO$: 222.0903, found: 222.0906. IR was not obtained due to insolubility of the quinolone

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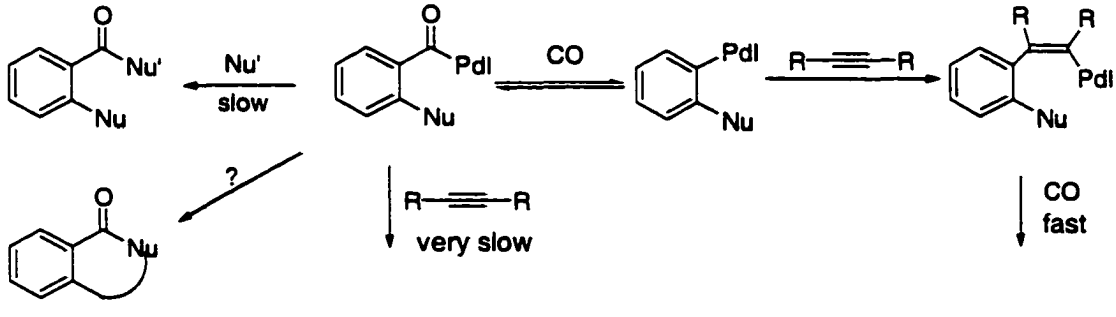
GENERAL CONCLUSIONS

In this dissertation, it has been demonstrated that the palladium-catalyzed carbonylative annulation of internal and terminal alkynes provides an efficient and general route to coumarins and 2-quinolones. The transformations proceed under relatively mild reaction conditions and tolerate a variety of functional groups. The only modest regioselectivity observed with unsymmetrical alkynes is the major drawback of this process, but the regioisomers are easily separable by column chromatography.

The most striking feature of these processes is insertion of an alkyne into the carbon-palladium bond in preference to insertion of CO, even though the insertion of CO is generally considered to be much faster than the insertion of an alkyne. What are the origins of this selectivity, and how can it be utilized synthetically? We have shown that this selectivity appears to arise from the poor reactivity of alkynes towards insertion into the acylpalladium bond (Scheme 1). Thus, in the absence of any other species able to react with an

Scheme 1



acylpalladium complex, the products of the initial alkyne insertion are obtained almost exclusively. Moreover, the experiments with *o*-iodobenzylic alcohols have also demonstrated that the acylpalladium complexes are much less reactive even toward intramolecular nucleophiles, than is usually believed.

Therefore, it appears that the formation of six-membered rings, analogous to those described in this dissertation, could be easily achieve via carbonylative annulation of alkynes utilizing systems where a halide and a nucleophile are separated by two carbon atoms. The formation of larger rings would depend on the rate of intramolecular capture of the acylpalladium complex, and, therefore, on the nucleophilic substituent in the starting aryl (or vinylic) halide. Based on our results, primary alcohols appear promising targets, while tertiary alcohols or tosylamides are too reactive to afford any seven-membered ring products. Exploring various strategies to fine tune the rate of the process, such as the use of protecting groups, might provide solutions.

In summary, we have developed a general and efficient method to synthesize coumarins and 2-quinolones by the palladium-catalyzed carbonylative annulation of internal and terminal alkynes under relatively mild reaction conditions utilizing readily available starting materials.

ACKNOWLEDGMENTS

First and foremost, I would like to express my sincere gratitude to my major professor Richard C. Larock for his guidance and advice, encouragement and understanding, patience and support, for allowing me to explore my own ideas, make my own mistakes and find my own solutions.

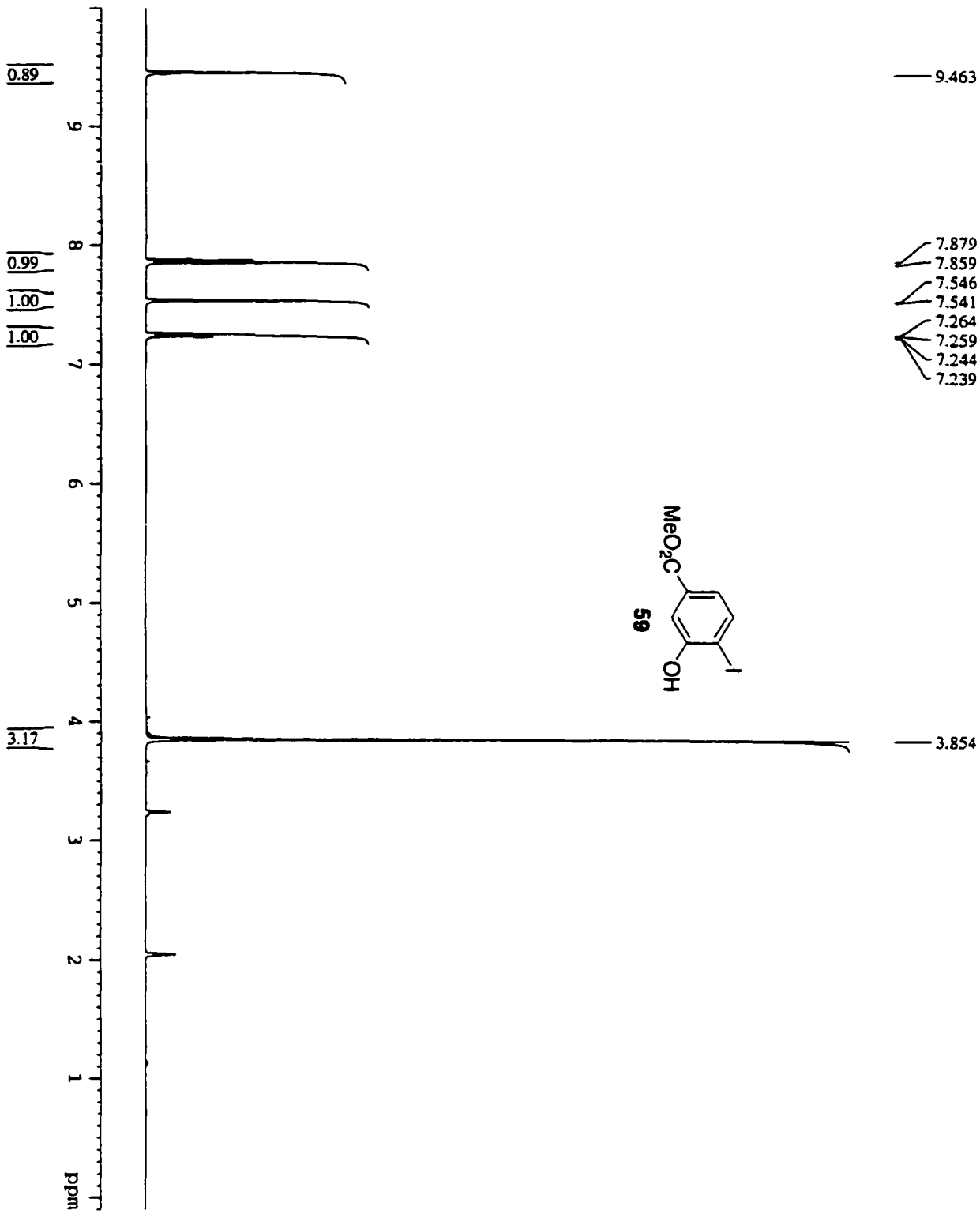
I would like to thank all members of the Larock group, past and present, for creating such a friendly environment in the group, for sharing ideas, advice and starting materials. I especially would like to thank Karl Peterson, for helping me to make my first steps in palladium chemistry, and Roman Rozhkov and Marino Campo for all the talks and arguments about research, chemistry in general, and many, many other things. Roman has also provided invaluable help and assistance, without which this dissertation would not have been completed. I also would like to thank all the people I spent time with having fun outside of Gilman Hall. Oh, those were the parties!

As I come to the end of my formal education, I want to thank all my teachers who taught me through twenty one years of elementary, middle and high school, college, and graduate school. I want especially to mention two people, Sergey Yevgenievich Semenov, the director of Moscow Chemical Lyceum, who introduced me to the magic and wonders of organic chemistry, and Dr. Alexey Feodosievich Bochkov, under whose direction I did my first research on organic synthesis. From him I have learned many valuable lessons about doing research in chemistry, either working by his side in the lab, or discussing syntheses at our weekly seminars in his place. His love and passion for organic chemistry and experimental work will always be an inspiration to me.

I want to thank my parents for their love, support and encouragement, for always believing in me, for making sure I have always done all I can to be the best I can be. Keeping in touch with my brother, my sister, my grandparents, and many other relatives, even only via rare and brief phone conversations or even more rare visits, was very important to me and I always cherished these moments.

Finally, I would like to acknowledge one special person, who made it all worthwhile. Katya, thank you for you love, support, and understanding, for cheering me up when I was down and sharing my joy when I was up. Thank you for just being near me, because that alone made my days brighter and my life happier, and helped me overcome all the obstacles on my way to this last page of my thesis. AND HERE I AM!

APPENDIX A. CHAPTER I ^{1}H AND ^{13}C NMR SPECTRA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7.244
7.239
3.854
MeO2C
OH
I
59
ppm

200
180
160
140
120
100
80
60
40
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ppm
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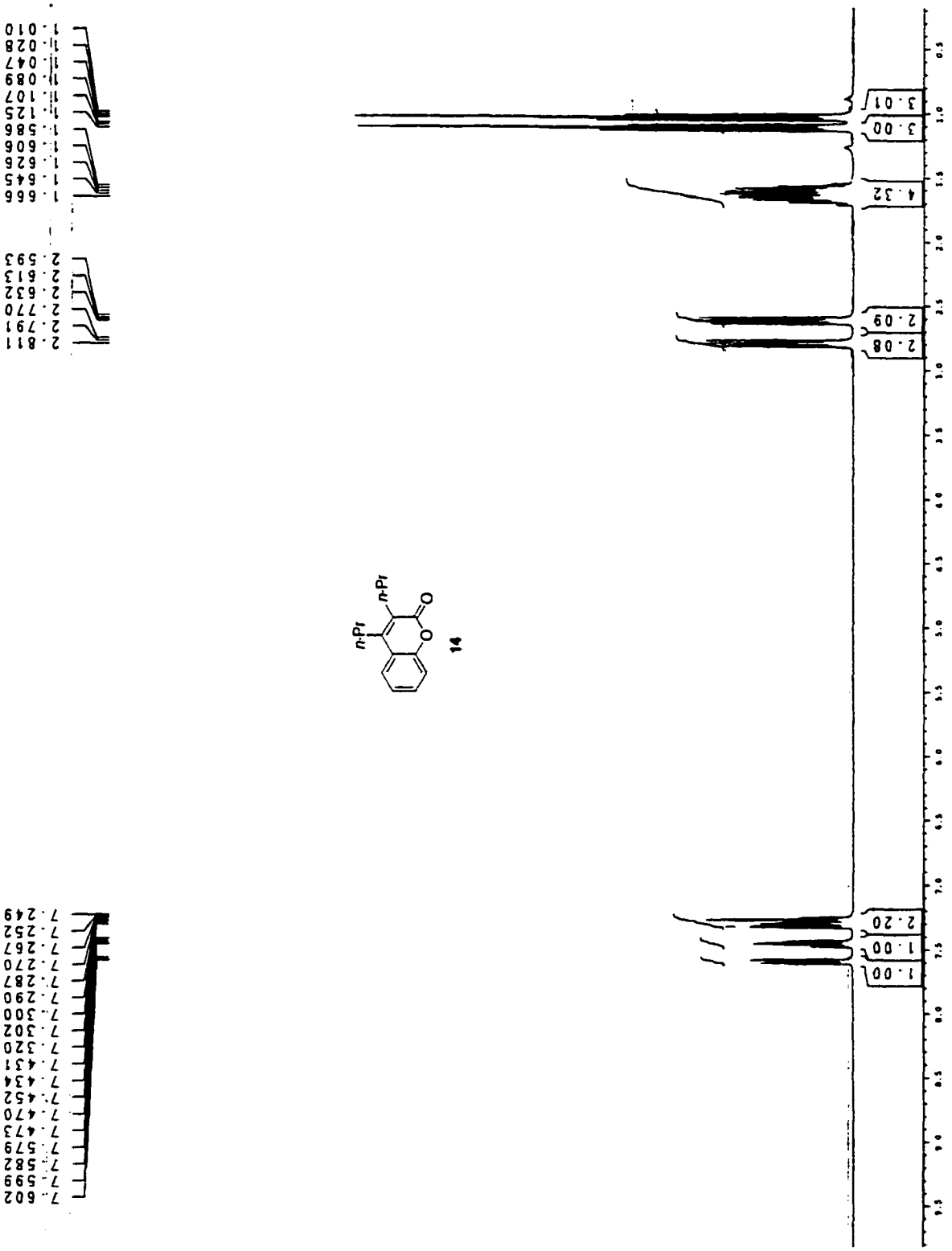
OH
I
59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7.287
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7.267
7.252
7.249
2.811
2.791
2.770
2.632
2.613
2.593
1.666
1.645
1.626
1.606
1.586
1.125
1.107
1.089
1.047
1.028
1.010
2.20
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1.00
2.09
2.08
4.32
3.01
3.00
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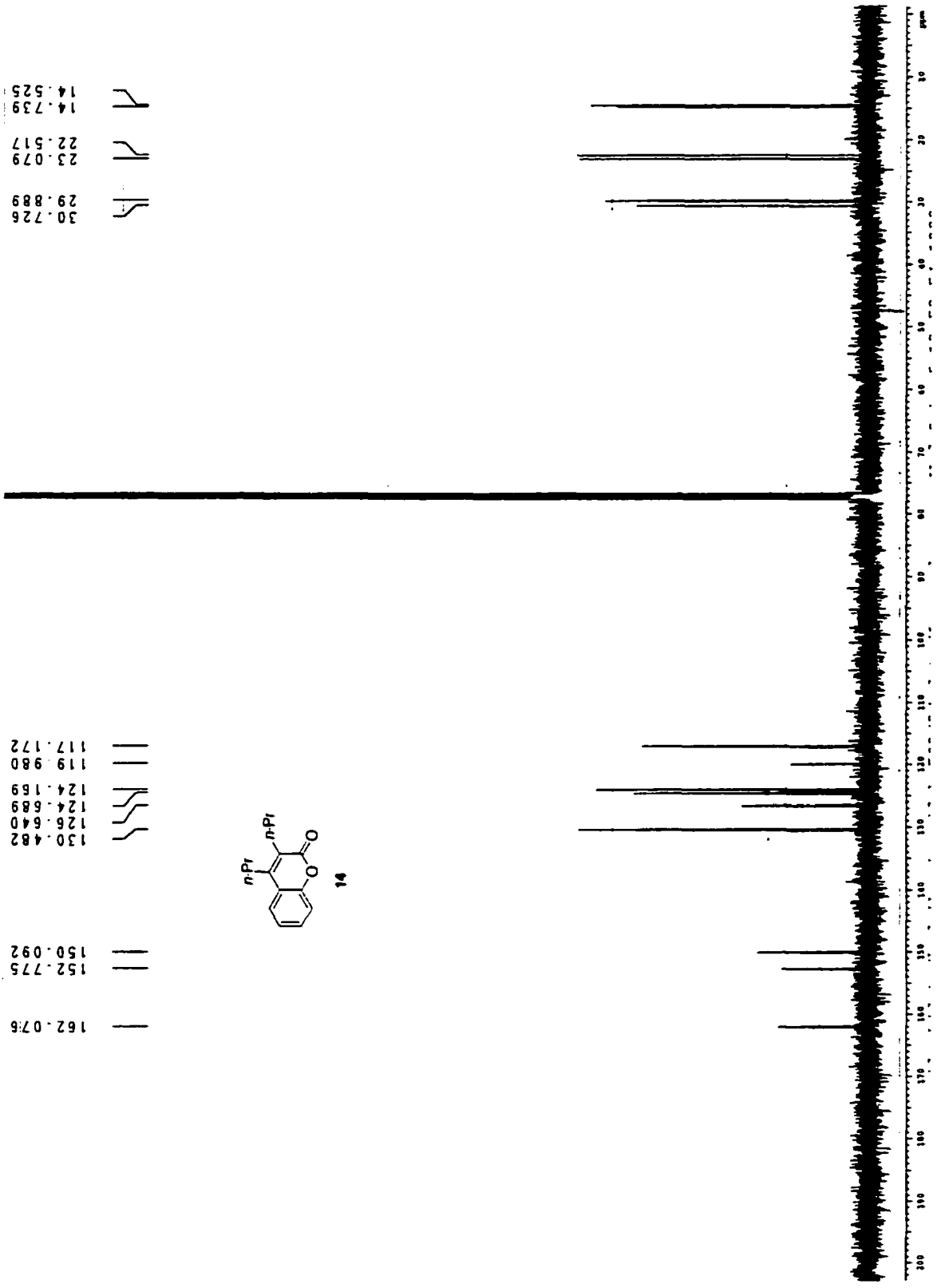
n-Pr
O
O
14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162.076
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n-Pr
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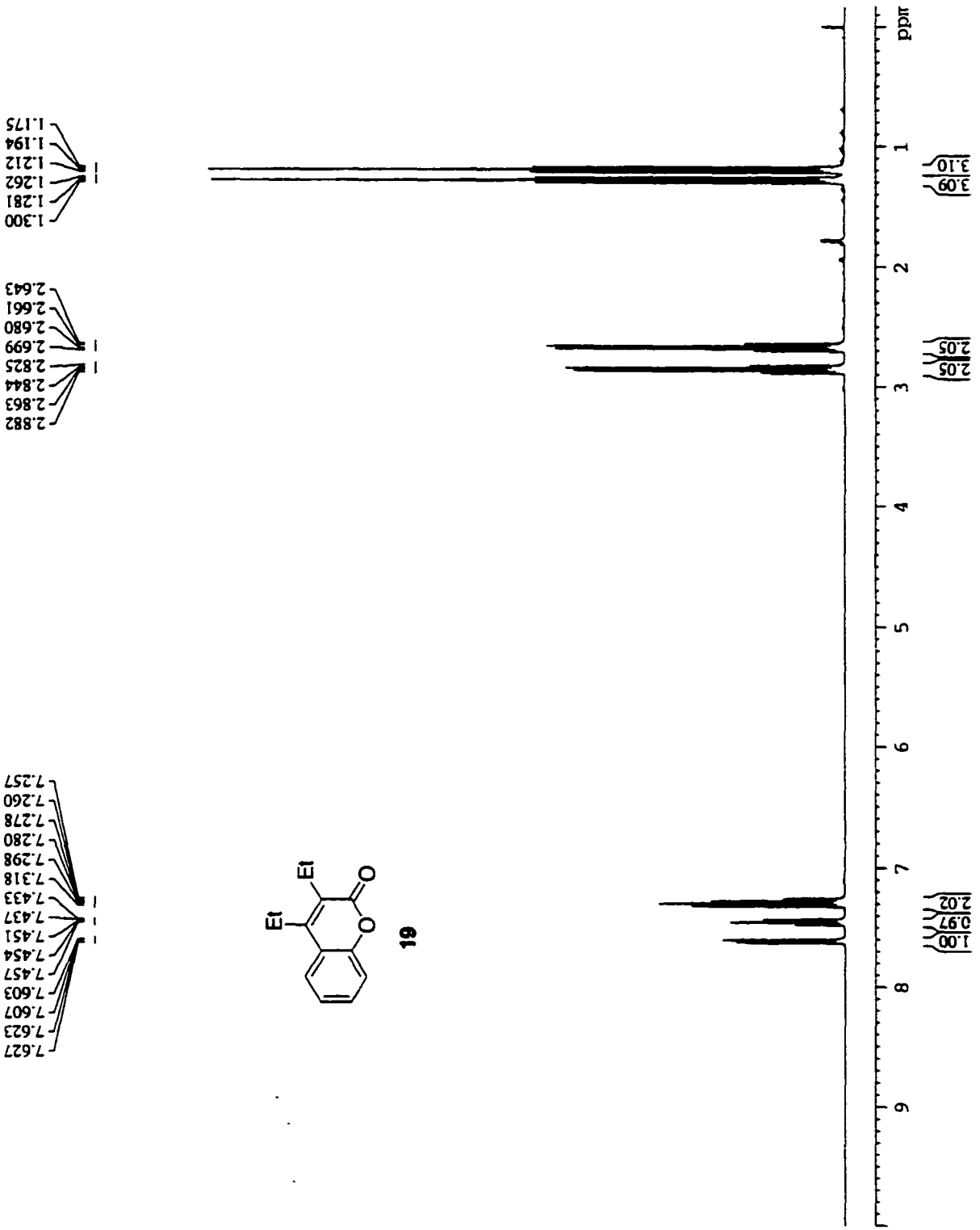
O
14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1.281
1.300
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2.661
2.680
2.699
2.825
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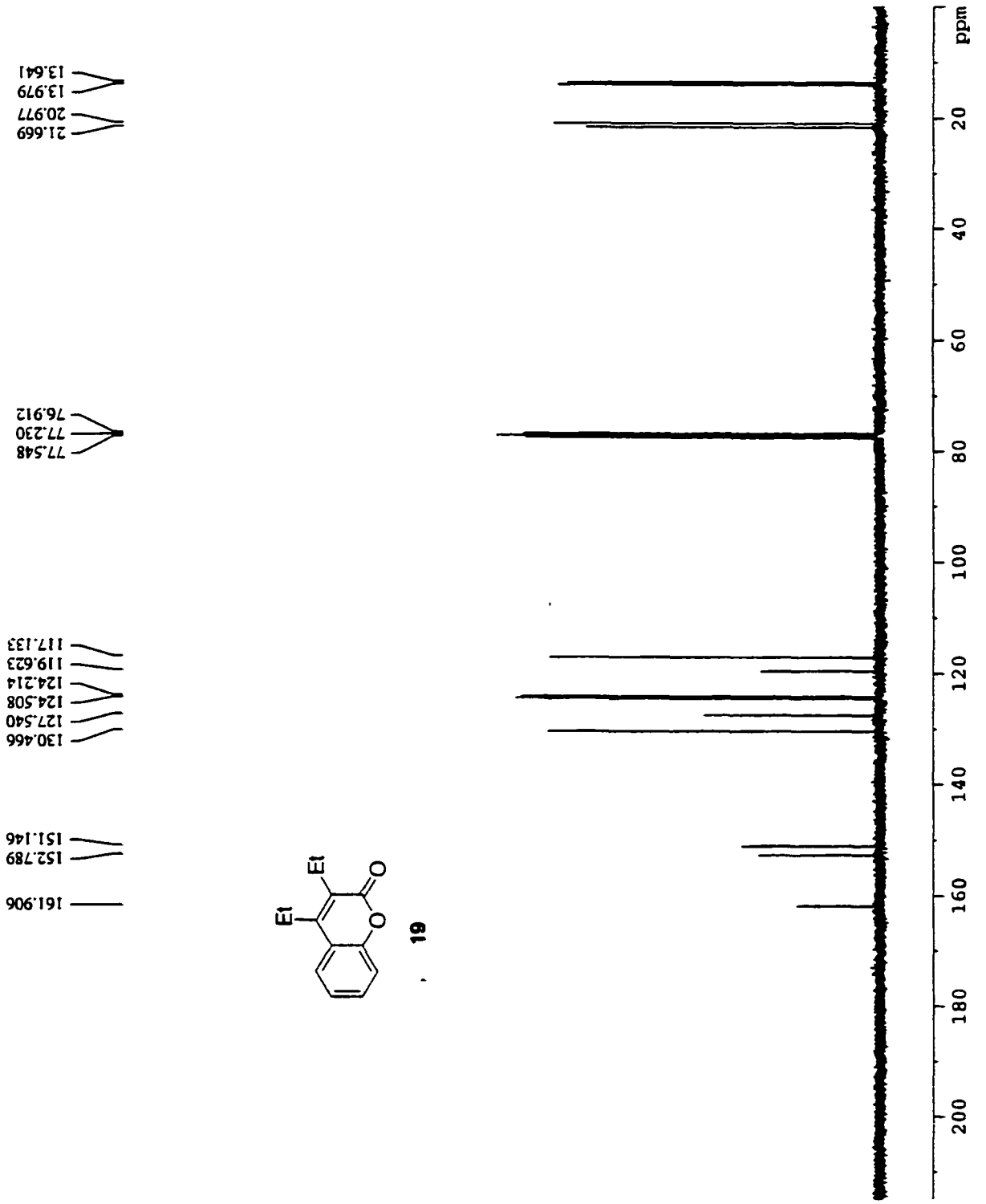
Et
Et
O
O
19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20.977
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Et
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140
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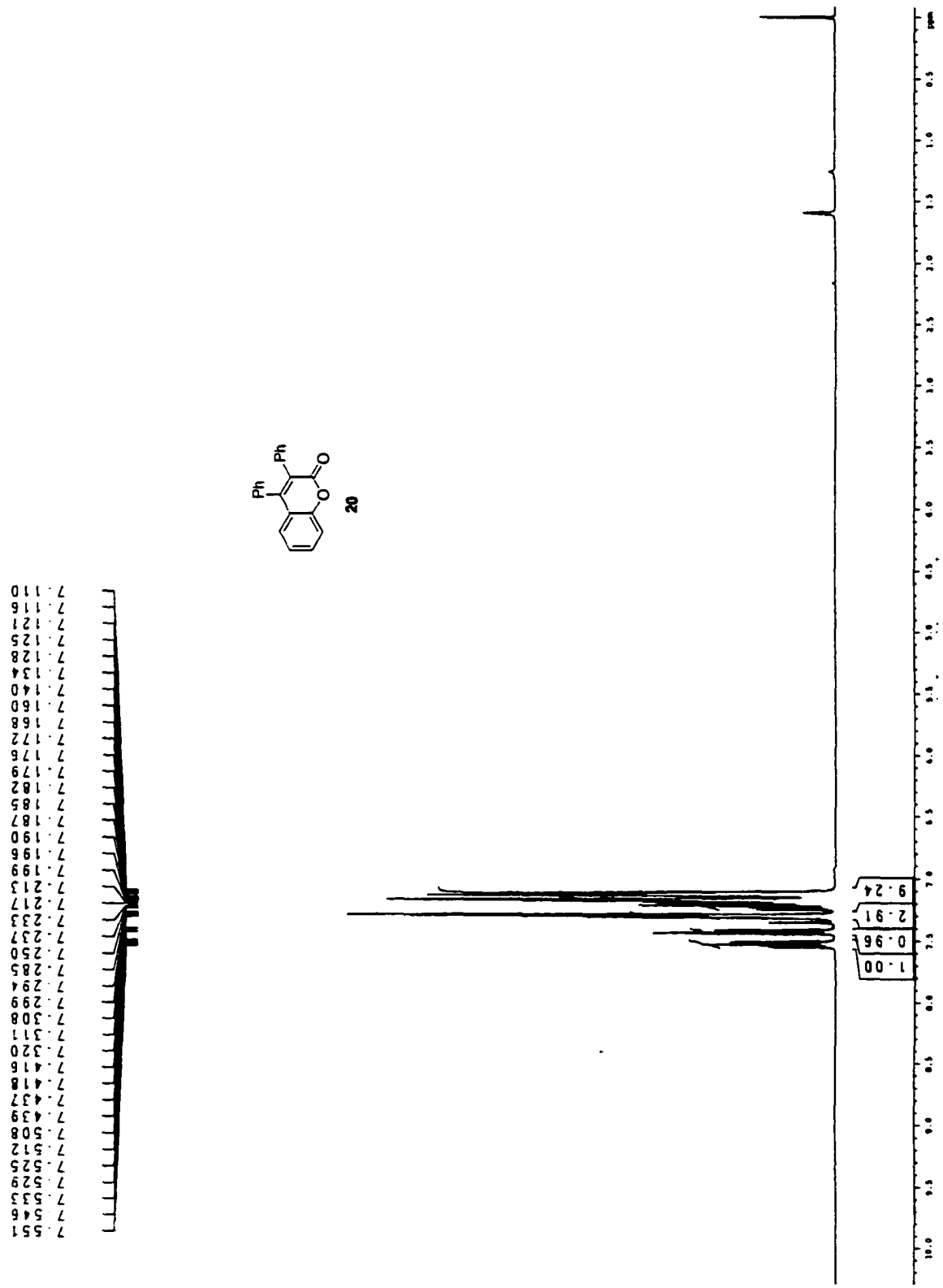
80
60
40
20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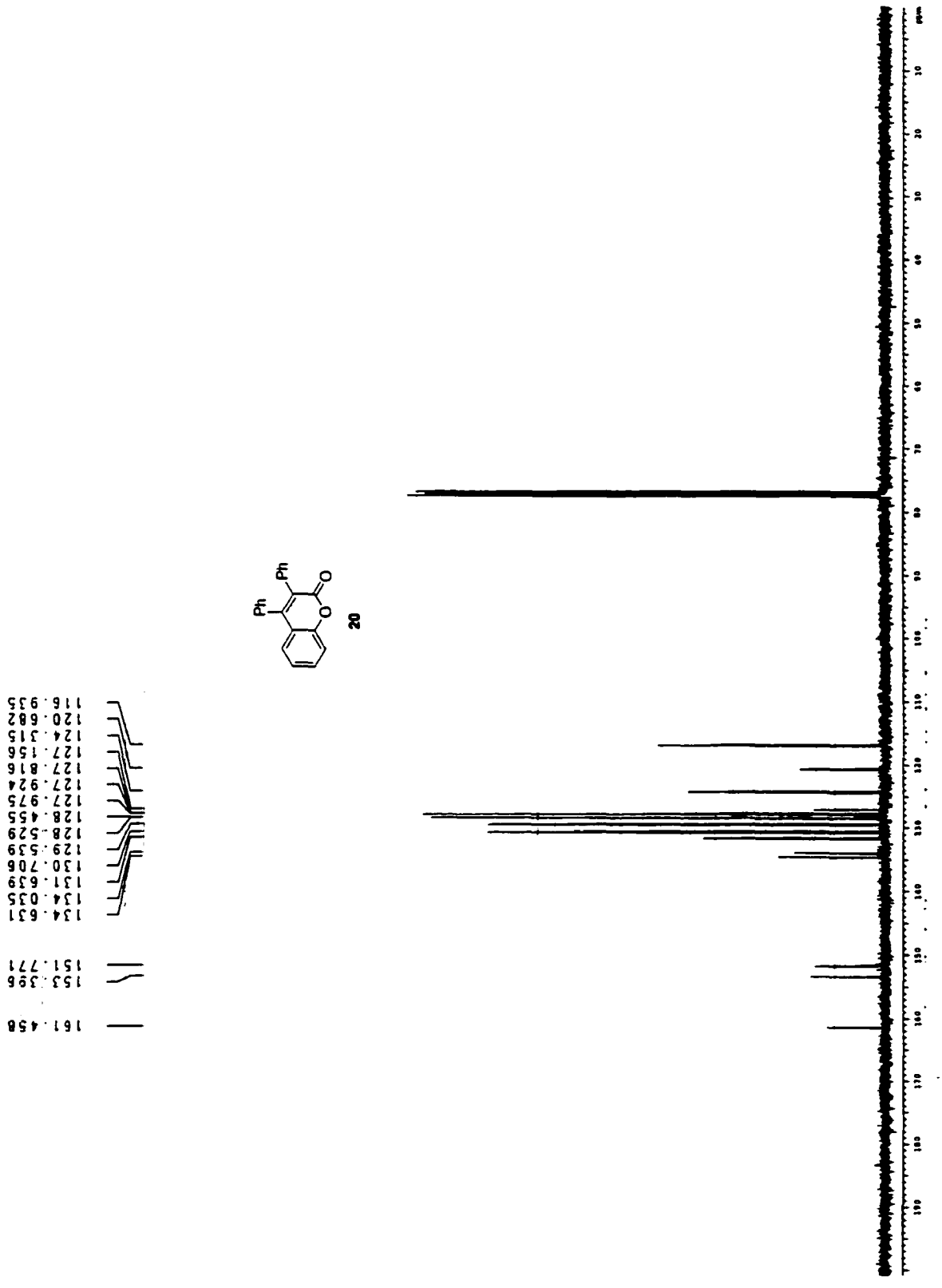
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129.539
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131.639
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134.631
151.771
153.396
161.458

23

1.216
1.197
1.178

2.714
2.695
2.676
2.657

7.713
7.710
7.693
7.690
7.561
7.558
7.540
7.522
7.519
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7.486
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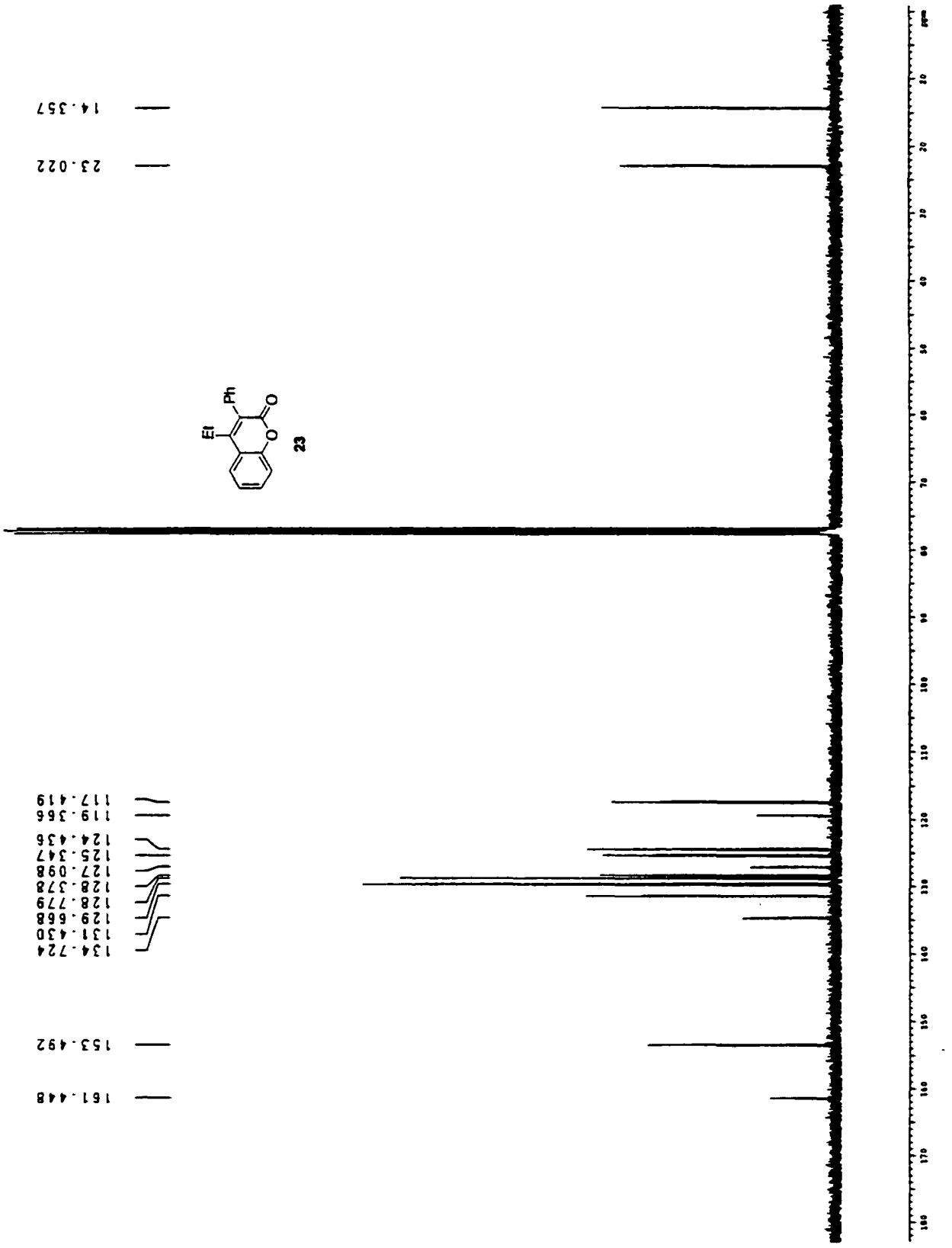
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Ph
O
O
23

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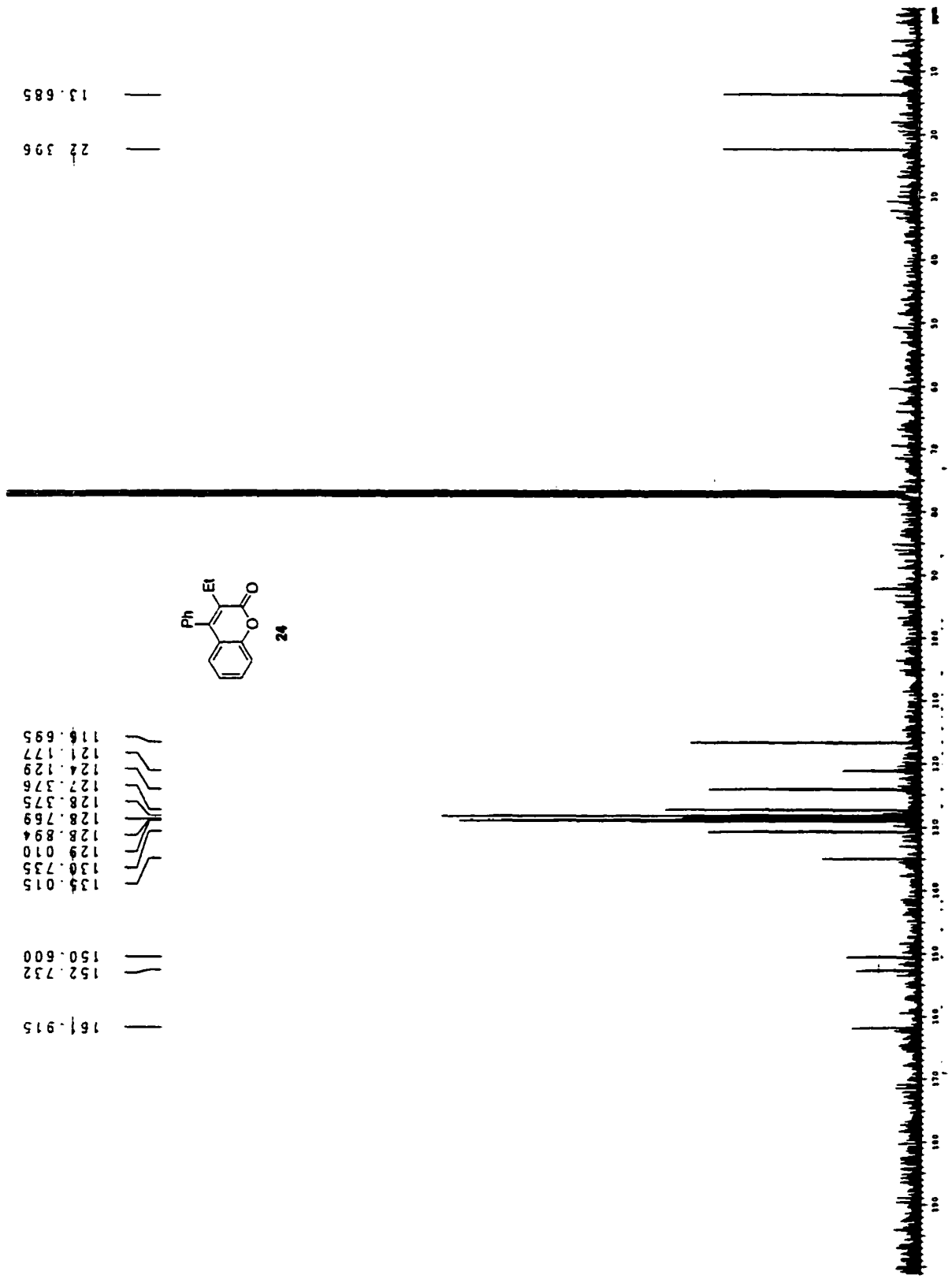
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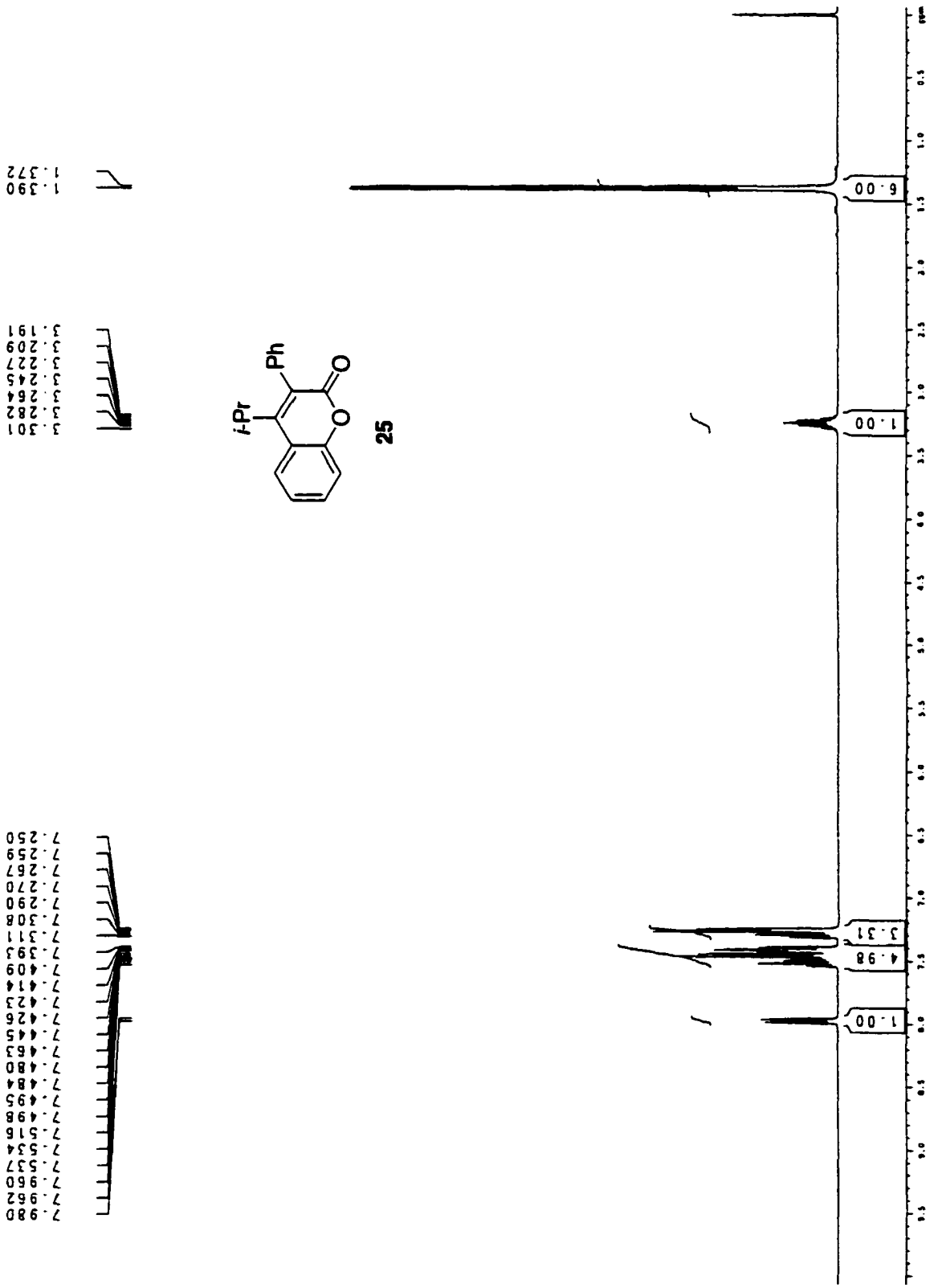
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3.282
3.301
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7.259
7.267
7.270
7.290
7.308
7.311
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7.414
7.423
7.426
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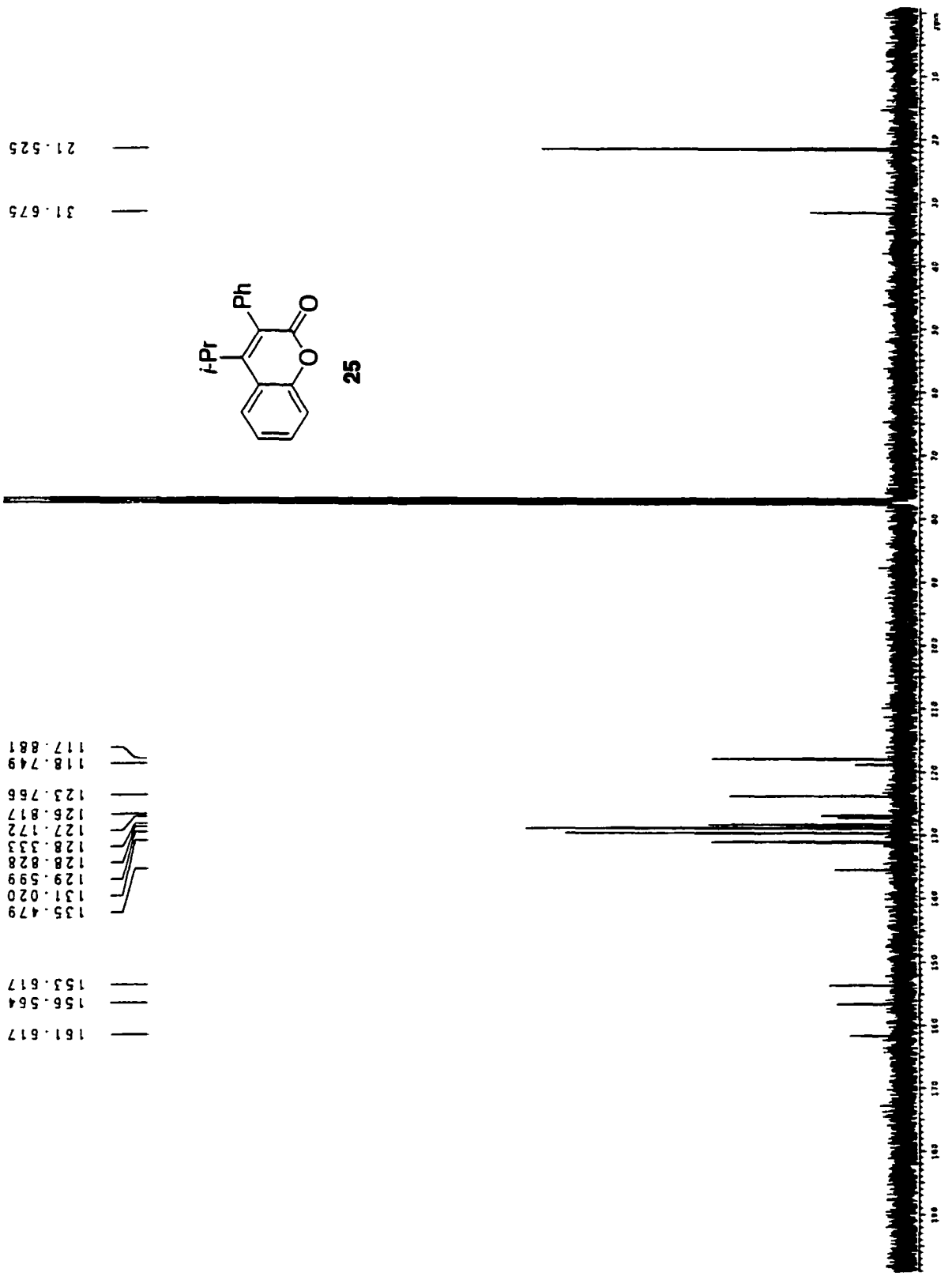
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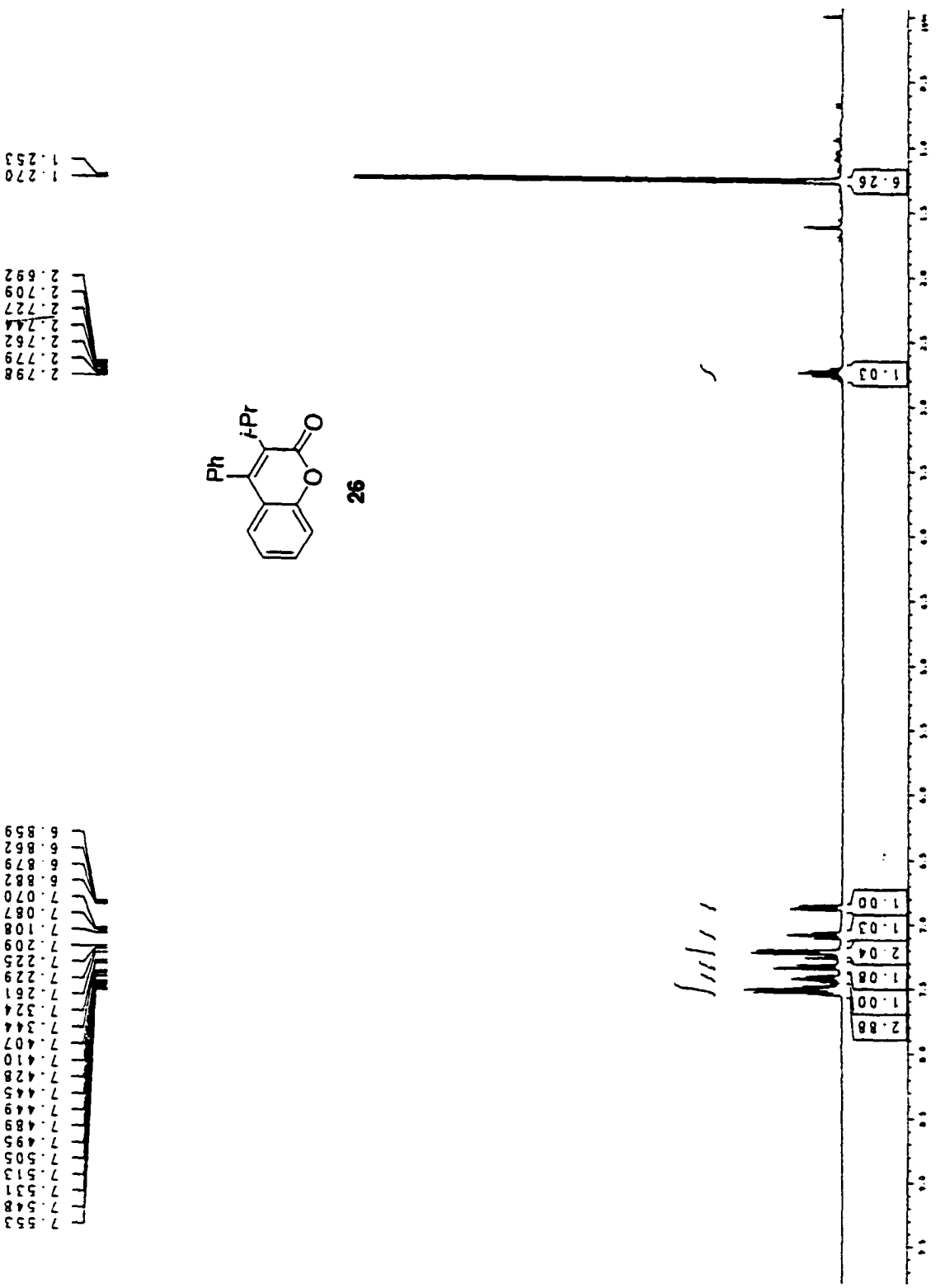
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O

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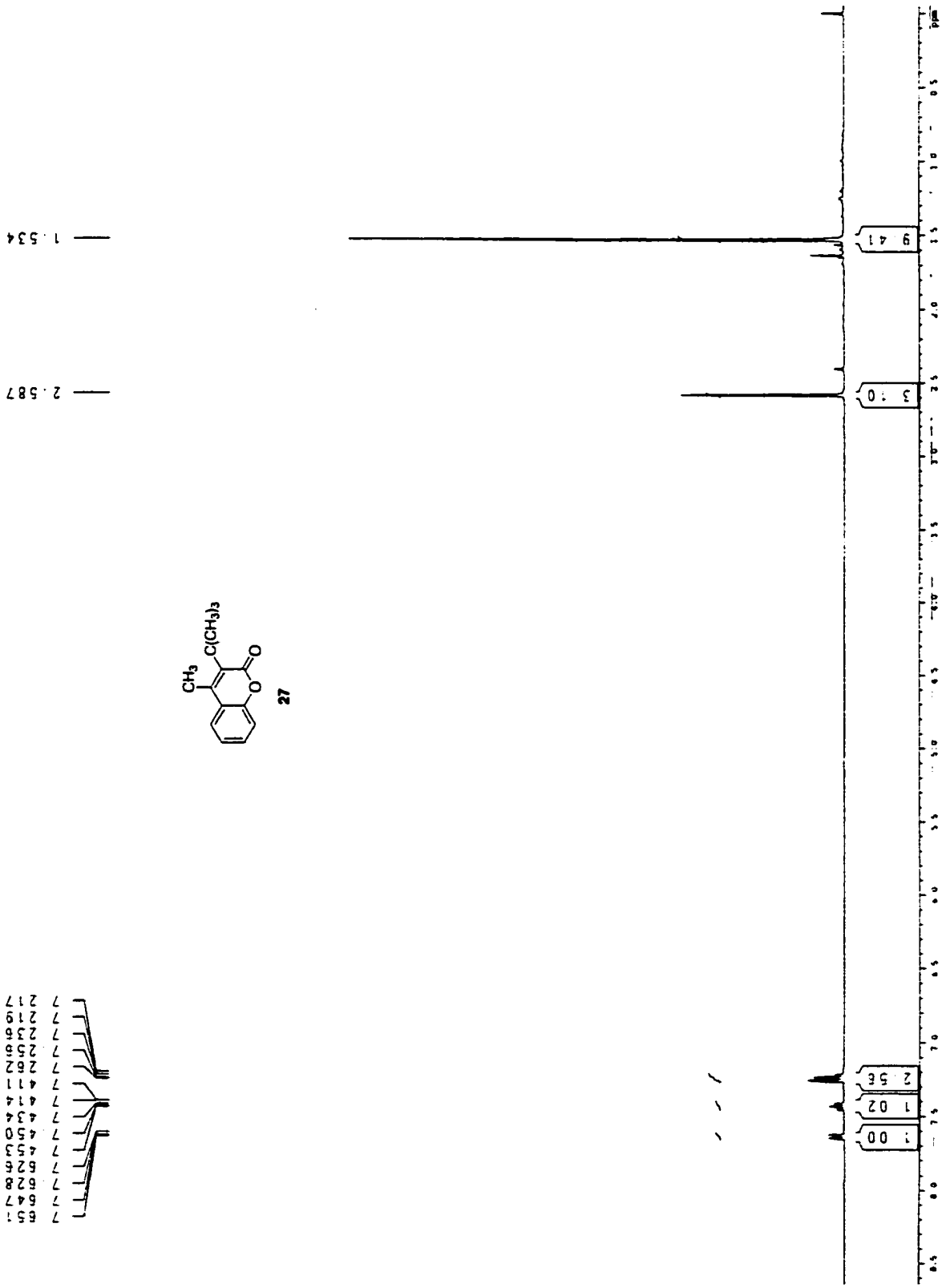
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7.4144
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O
O
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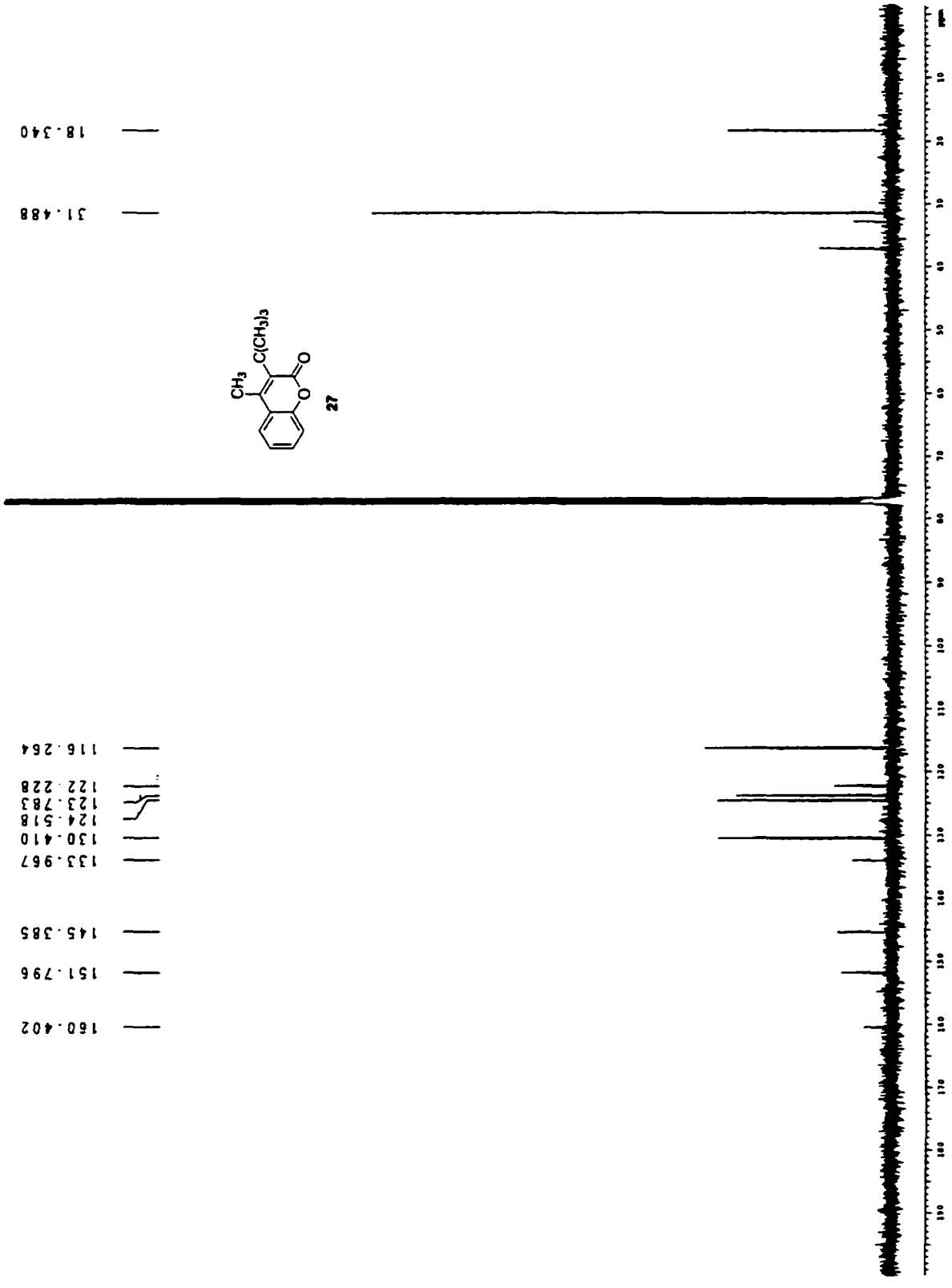
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145.385
151.796
160.402

7.639
7.620
7.465
7.444
7.427
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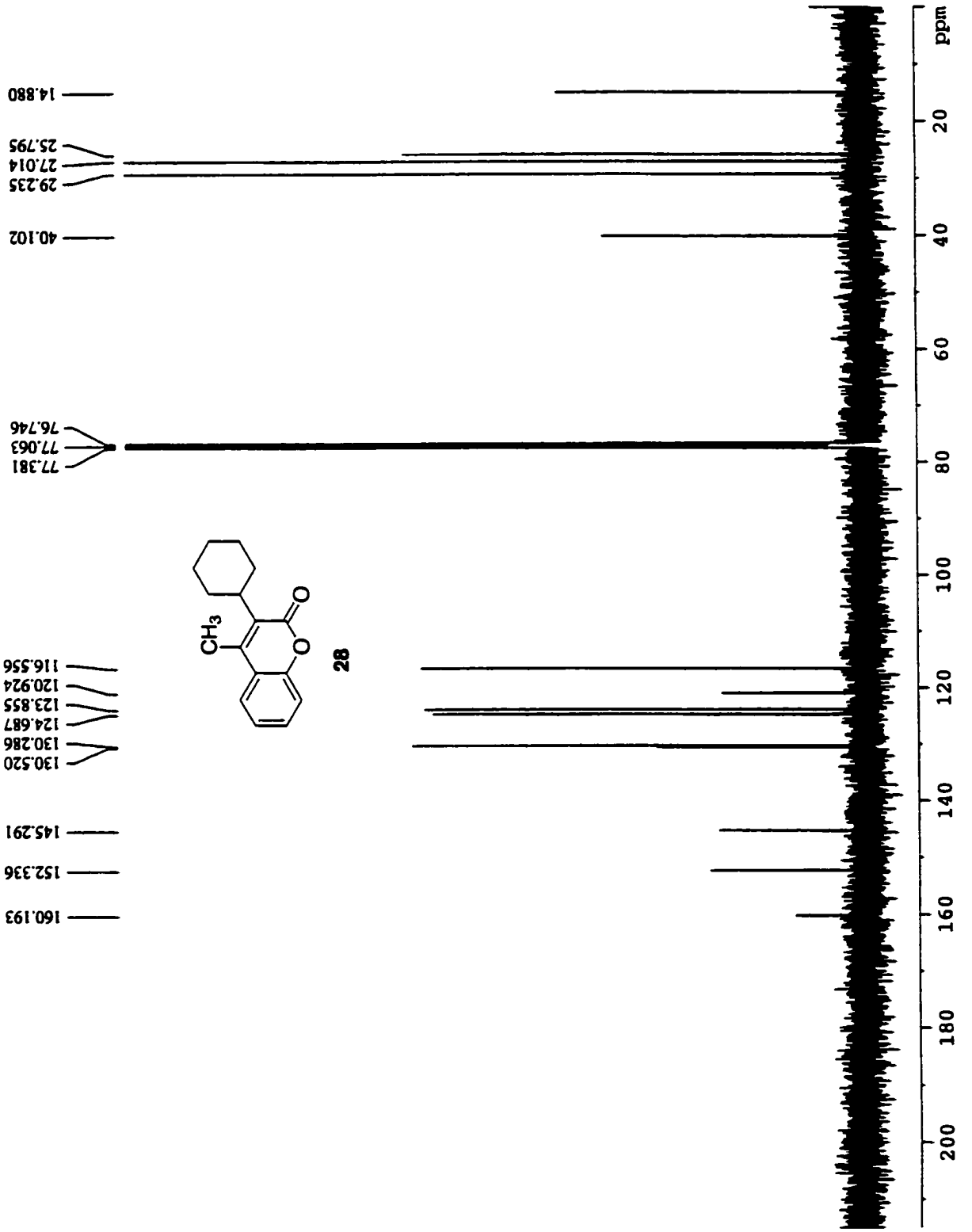
O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180
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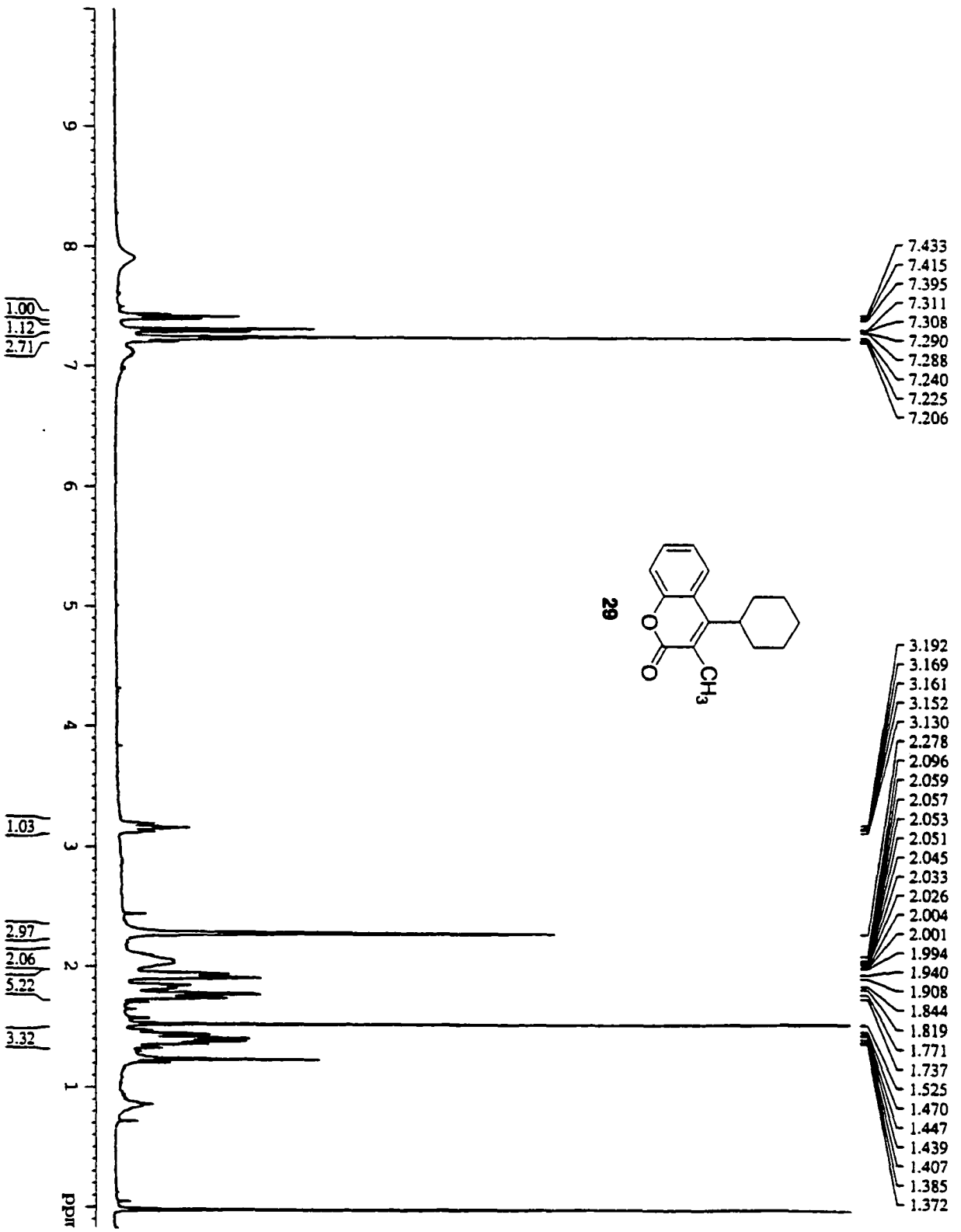
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7.265
7.258
7.255
4.889
2.432

O
O
CH2OH
Si(CH3)3

30


Si(CH3)3
CH2OH
O
O
30

7.872
7.868
7.851
7.848
7.559
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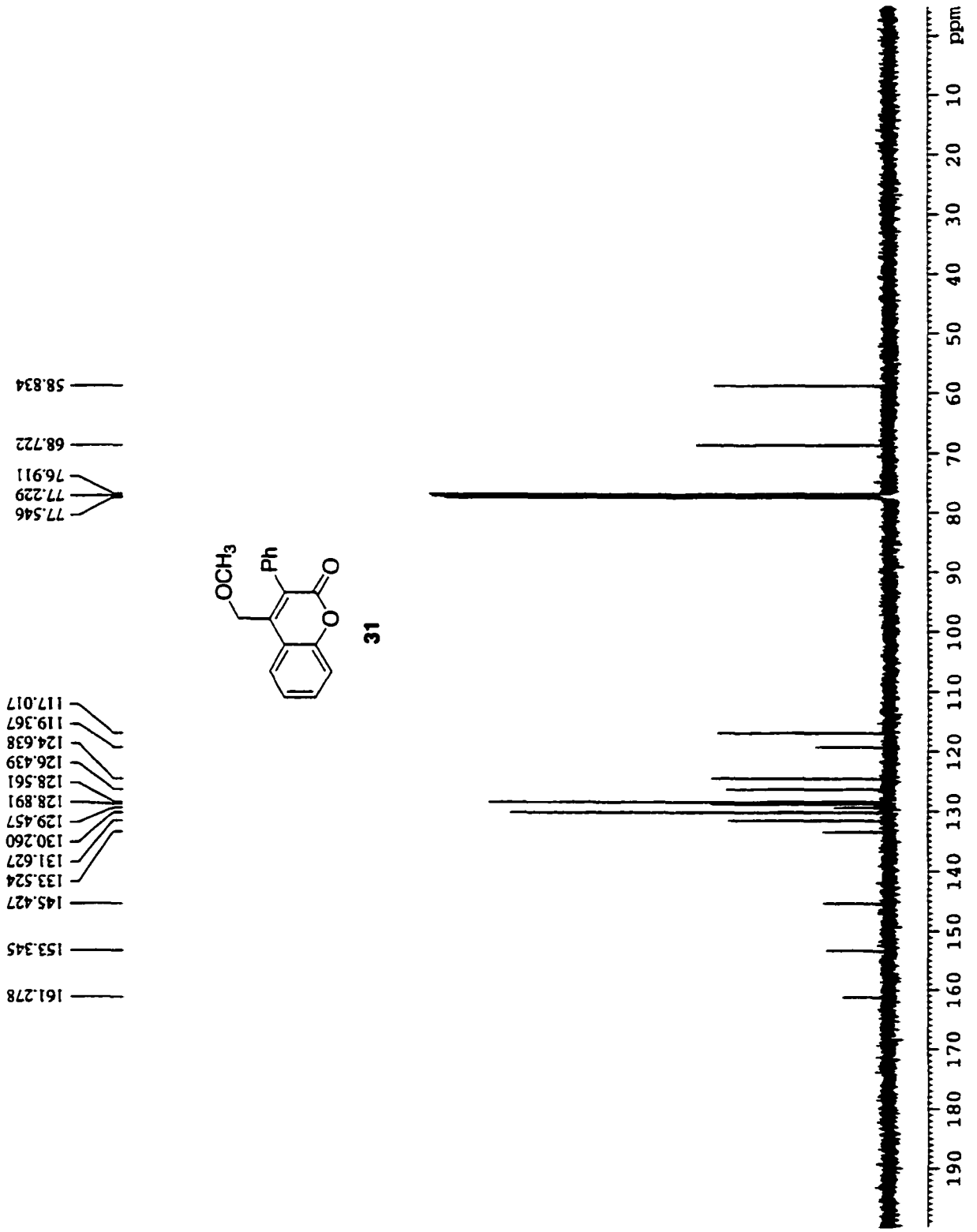
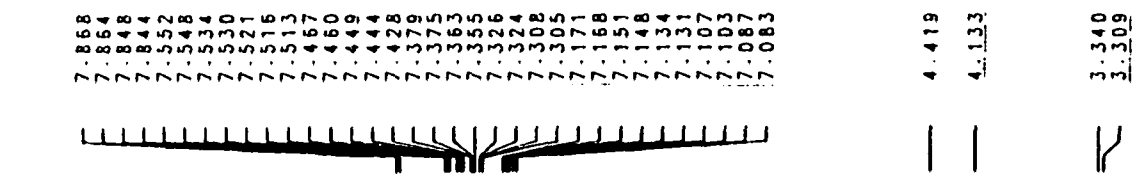
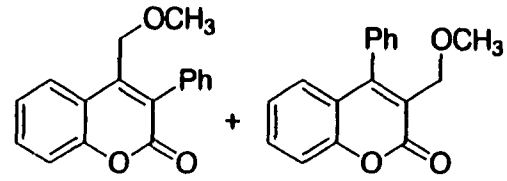
7.356
7.352
7.331
7.313
7.311
7.258
4.424
3.343
0.000
1.00
1.04
3.03
4.00
2.04
3.04
ppm
31
O
O
Ph
OCH3

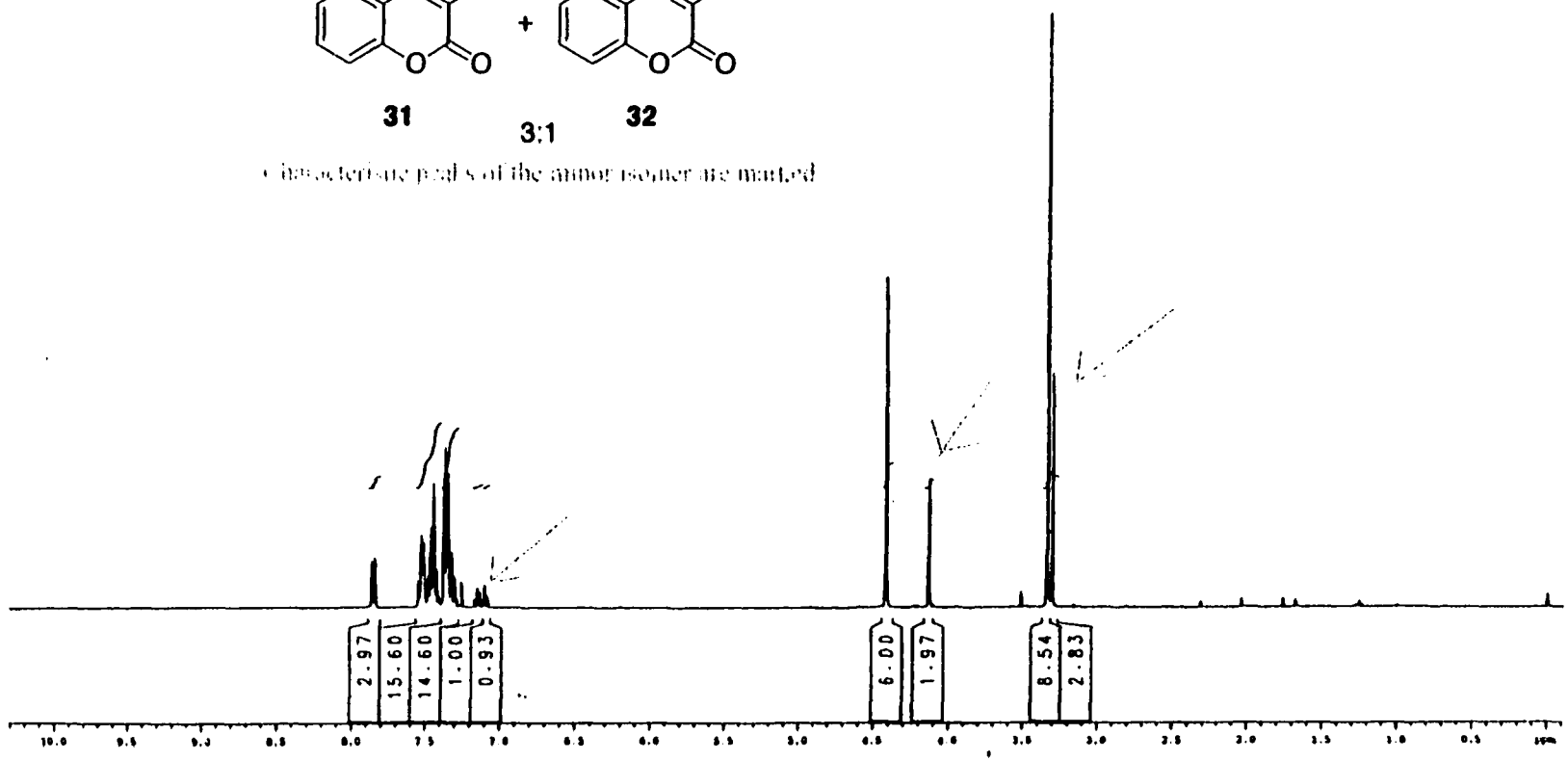

OCH3
Ph
O
O
31
58.834
68.722
76.911
77.229
77.546
117.017
119.367
124.638
126.439
128.561
128.891
129.457
130.260
131.627
133.524
145.427
153.345
161.278
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

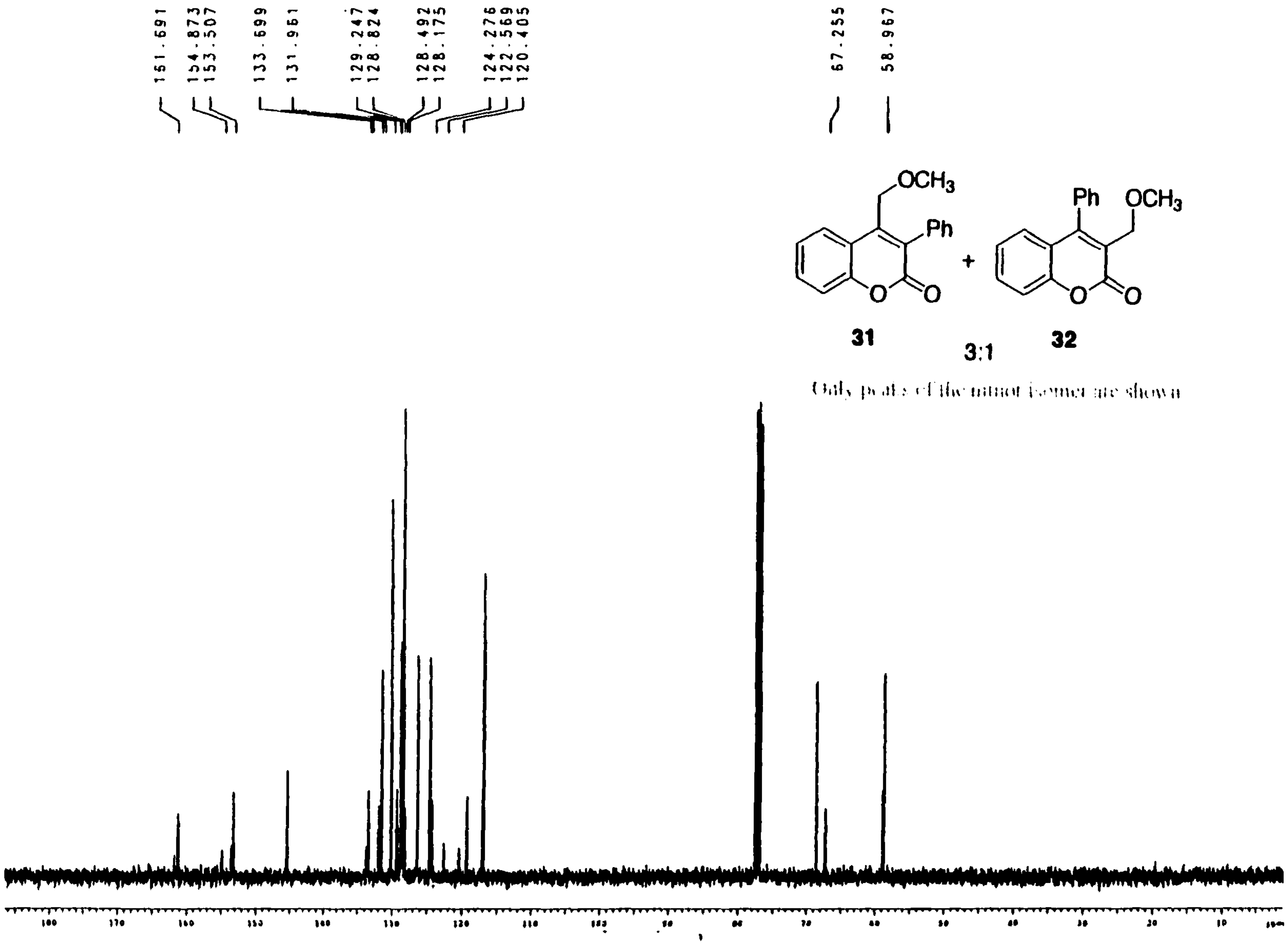


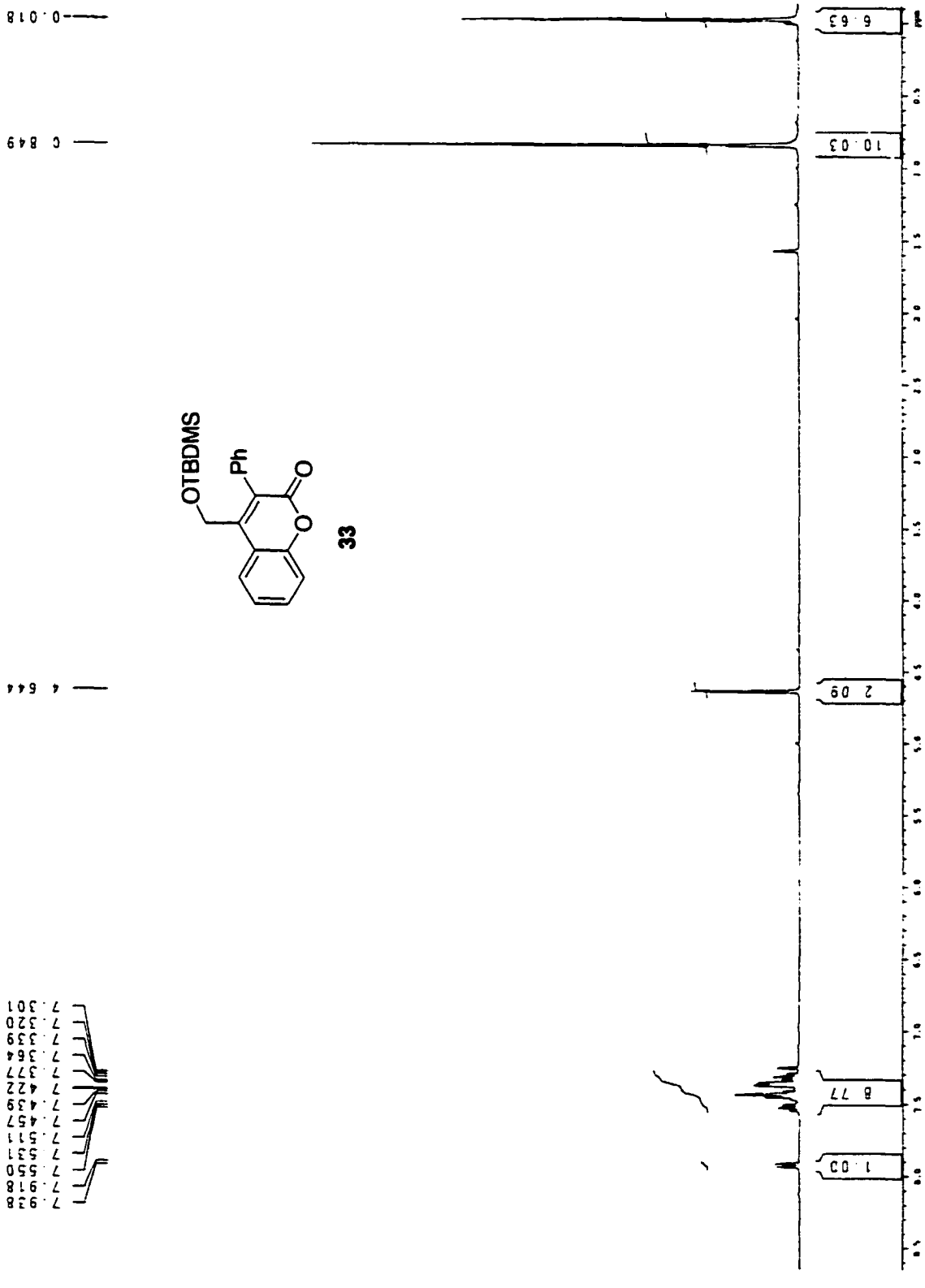


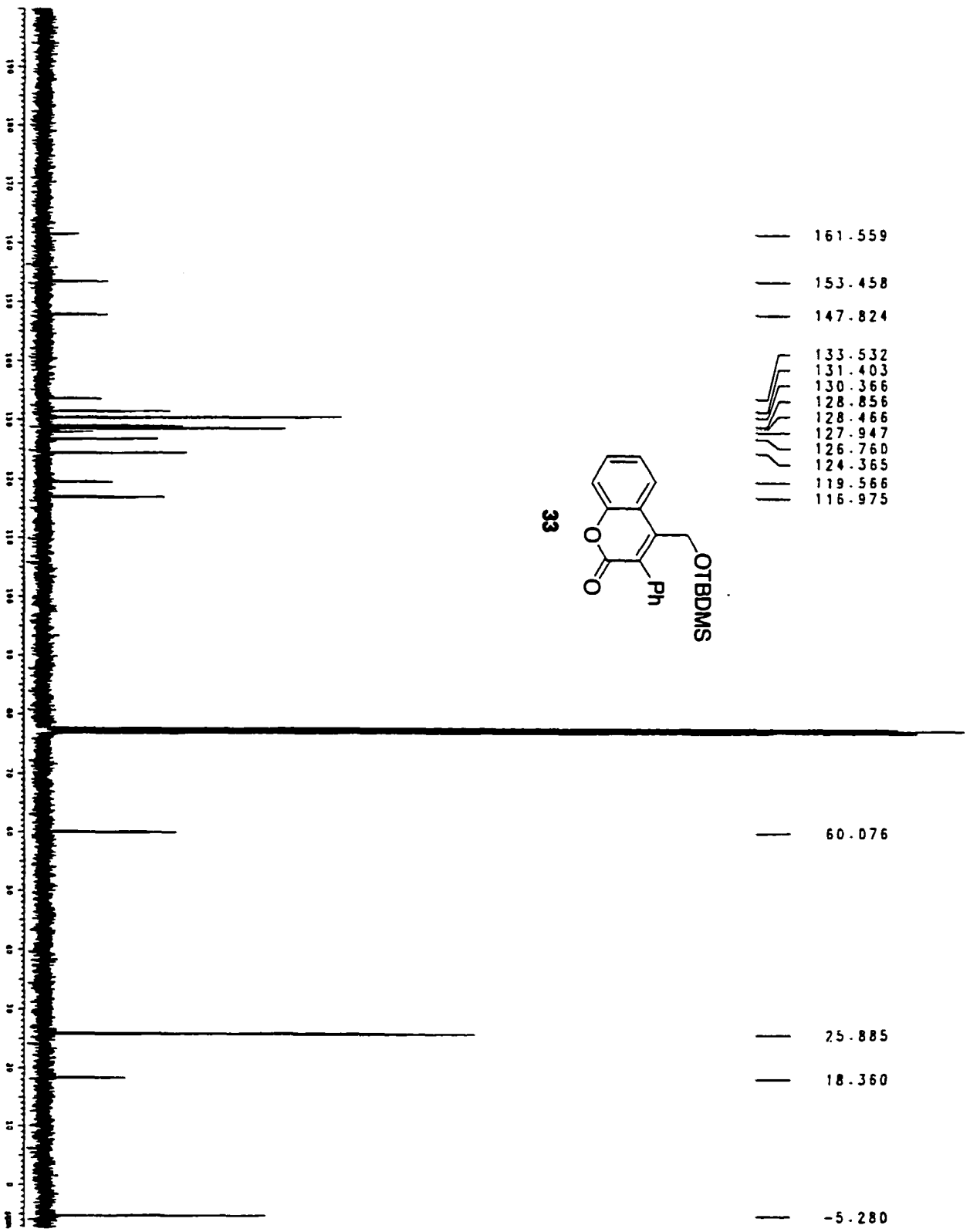
31 3:1 **32**

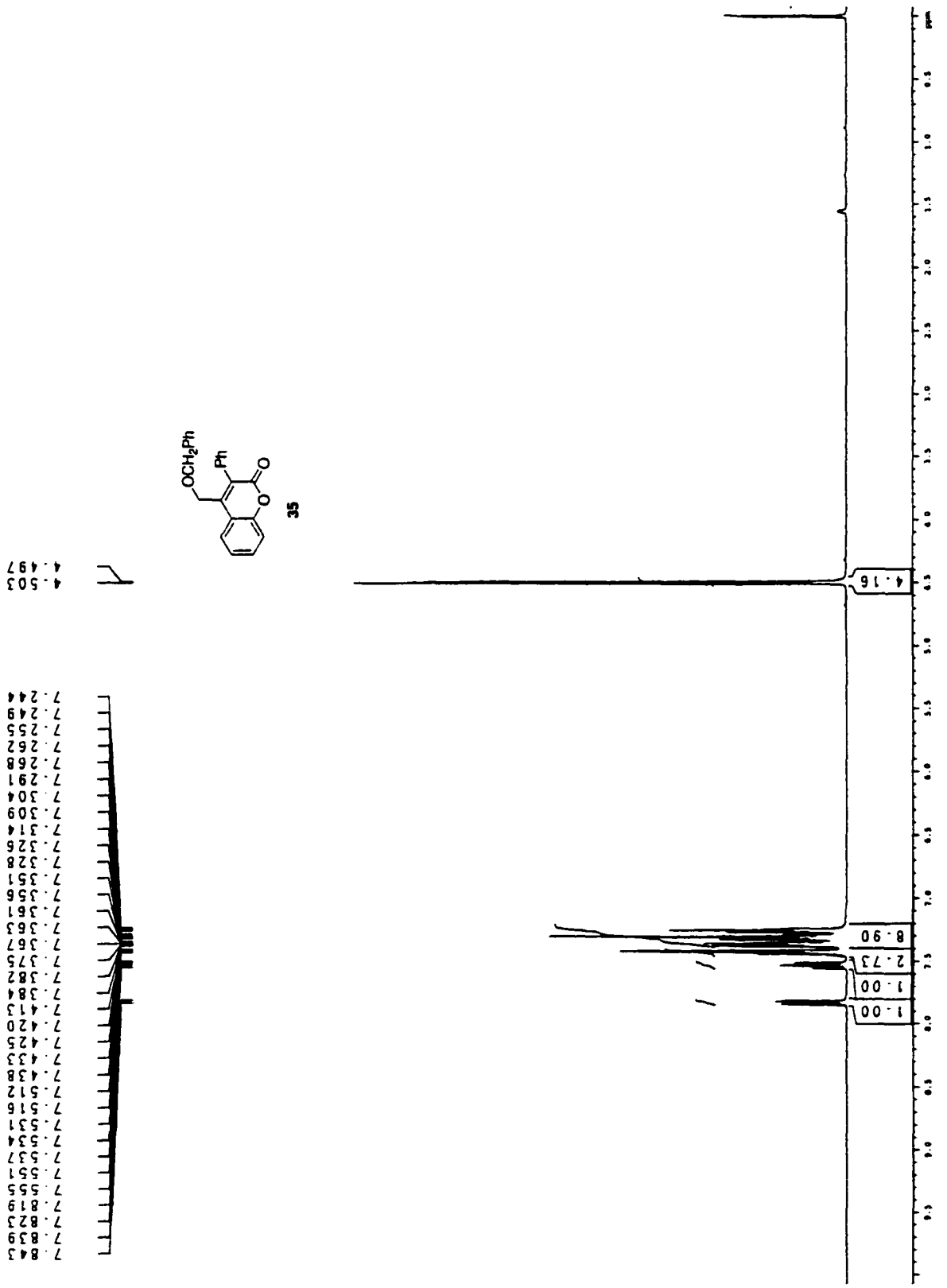
• characteristic peaks of the minor isomer are marked

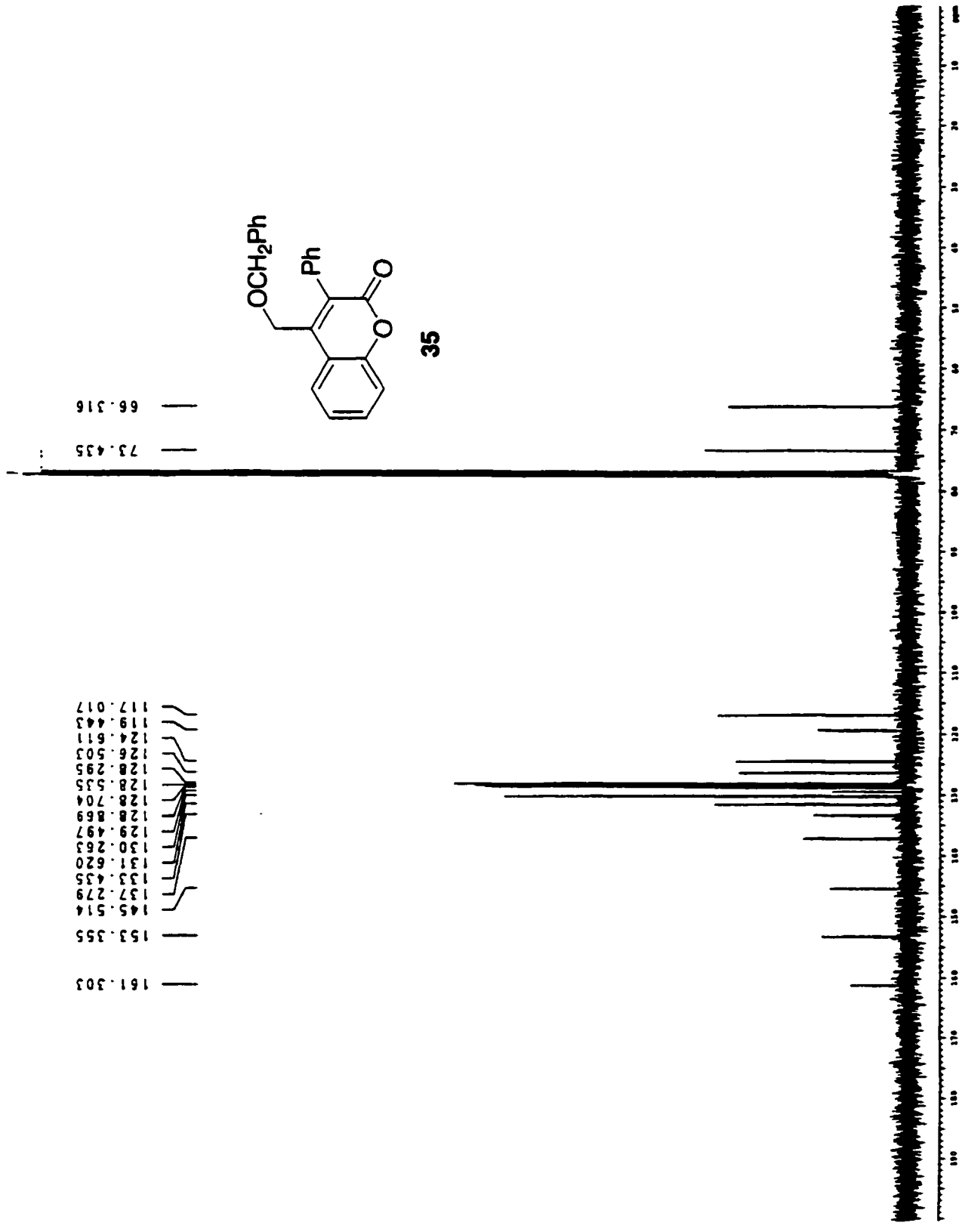


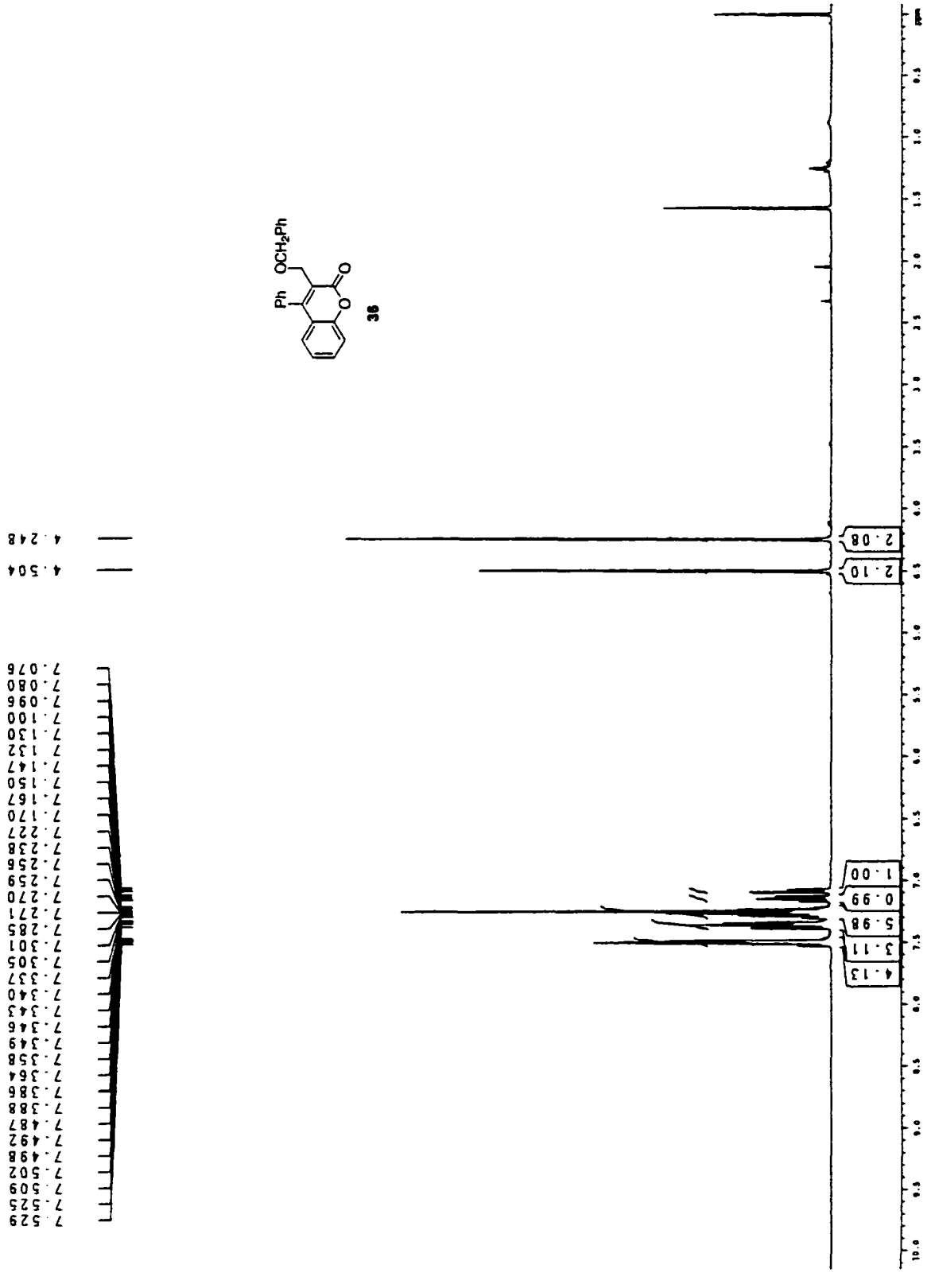

151.691
154.873
153.507
133.699
131.961
129.247
128.824
128.492
128.175
124.276
122.569
120.405
67.255
58.967
OCH3
Ph
OCH3
31
3:1
32
Only peaks of the minor isomer are shown

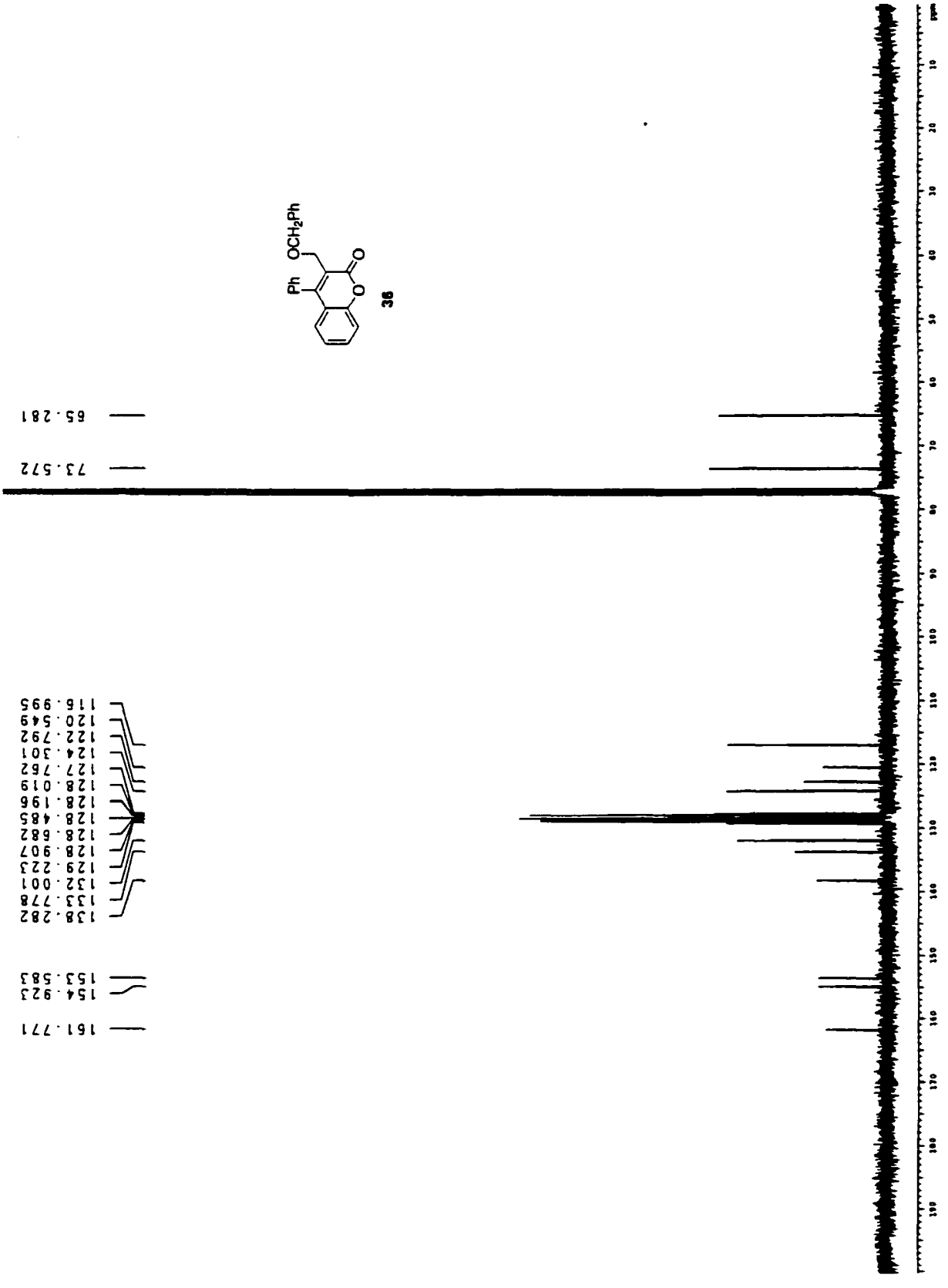

OTBDMS
Ph
O
O
33

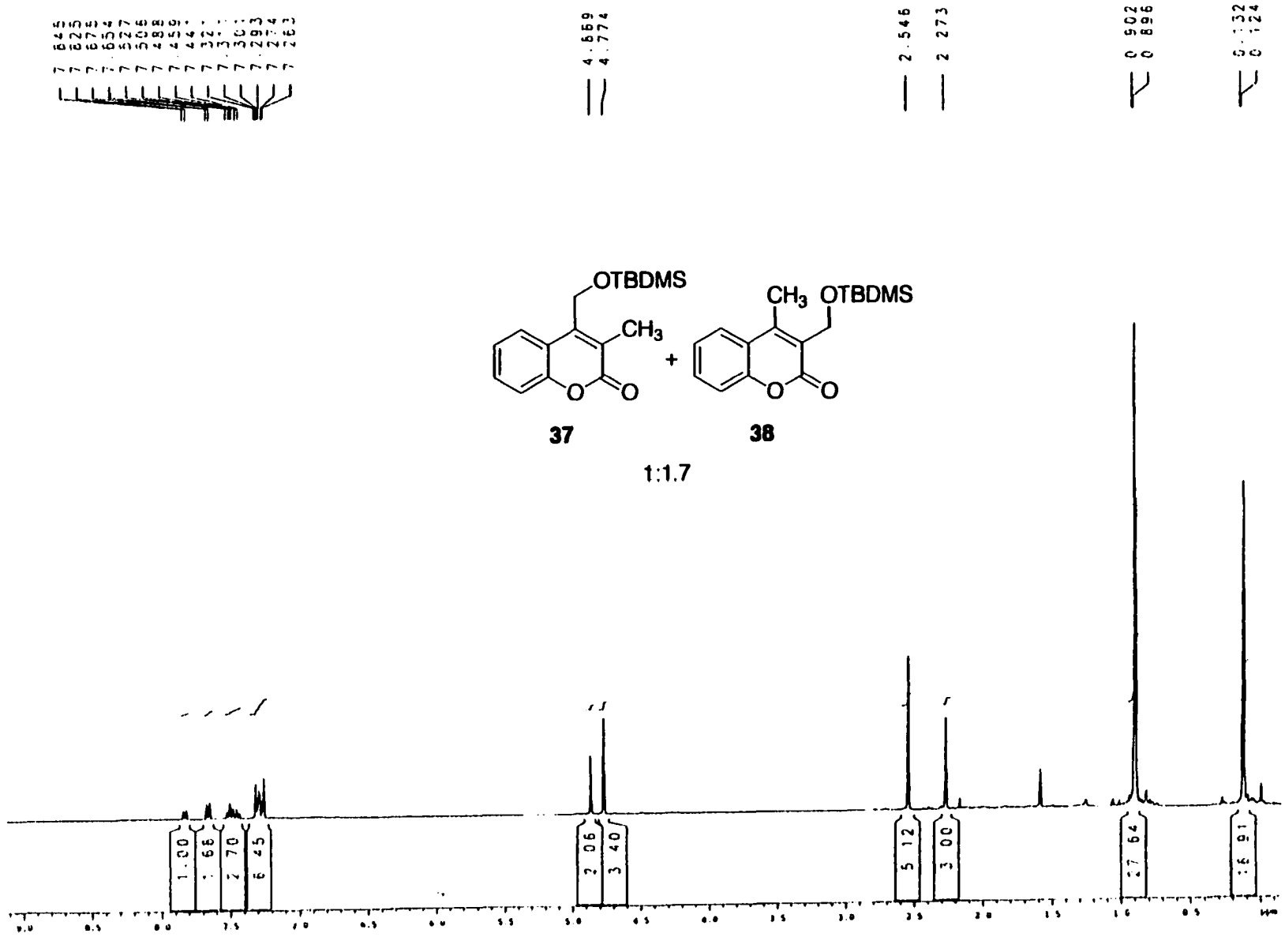

161.559
153.458
147.824
133.532
131.403
130.366
128.856
128.466
127.947
126.760
124.365
119.566
116.975
33
O
O
Ph
OTBDMS
60.076
25.885
18.360
-5.280

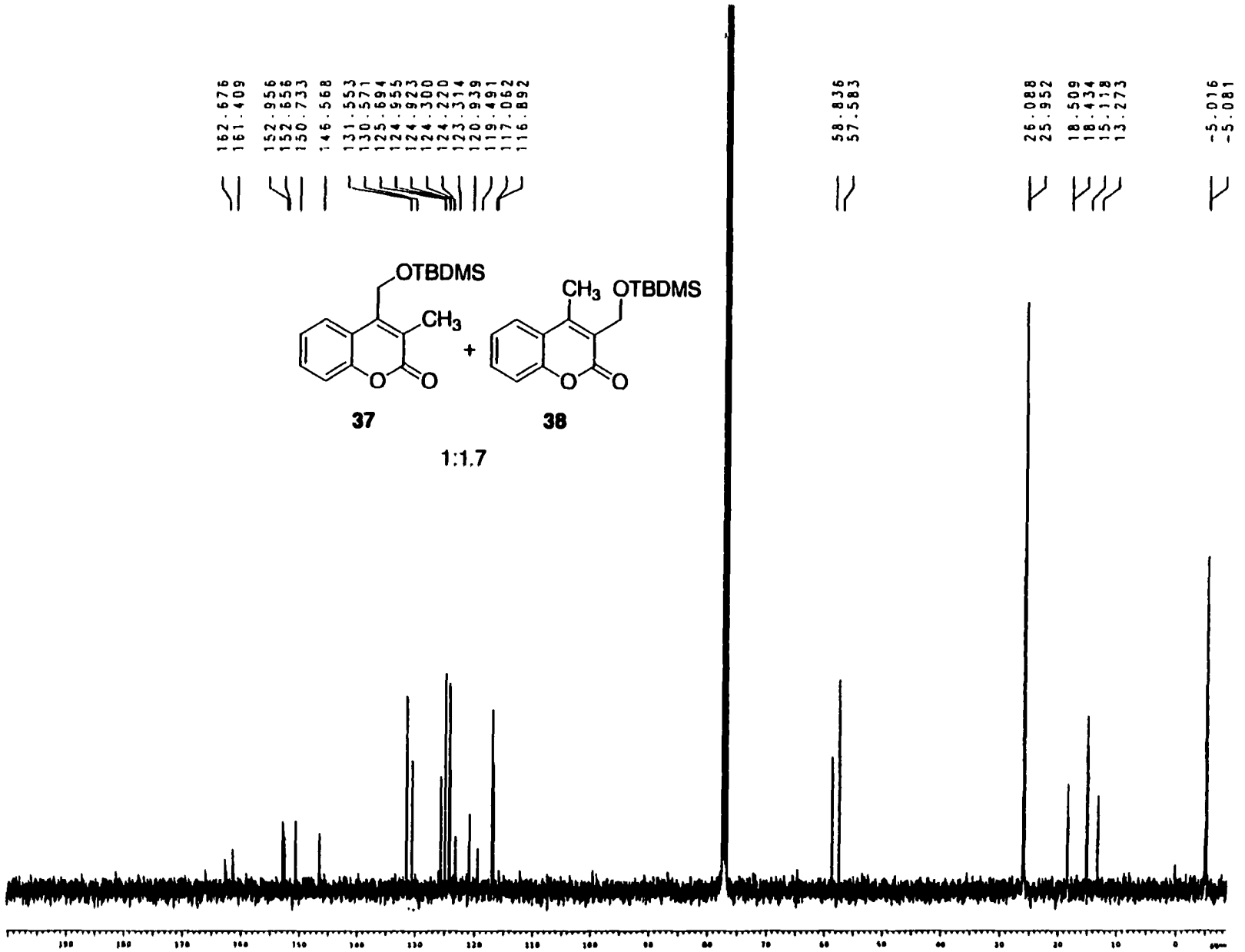

OCH2Ph
Ph
O
O
35
4.16
8.90
2.73
1.00
1.00
4.503
4.497
7.843
7.839
7.823
7.819
7.555
7.551
7.537
7.534
7.531
7.516
7.512
7.438
7.433
7.425
7.420
7.413
7.384
7.382
7.375
7.367
7.363
7.361
7.356
7.351
7.328
7.326
7.314
7.309
7.304
7.291
7.268
7.262
7.255
7.249
7.244

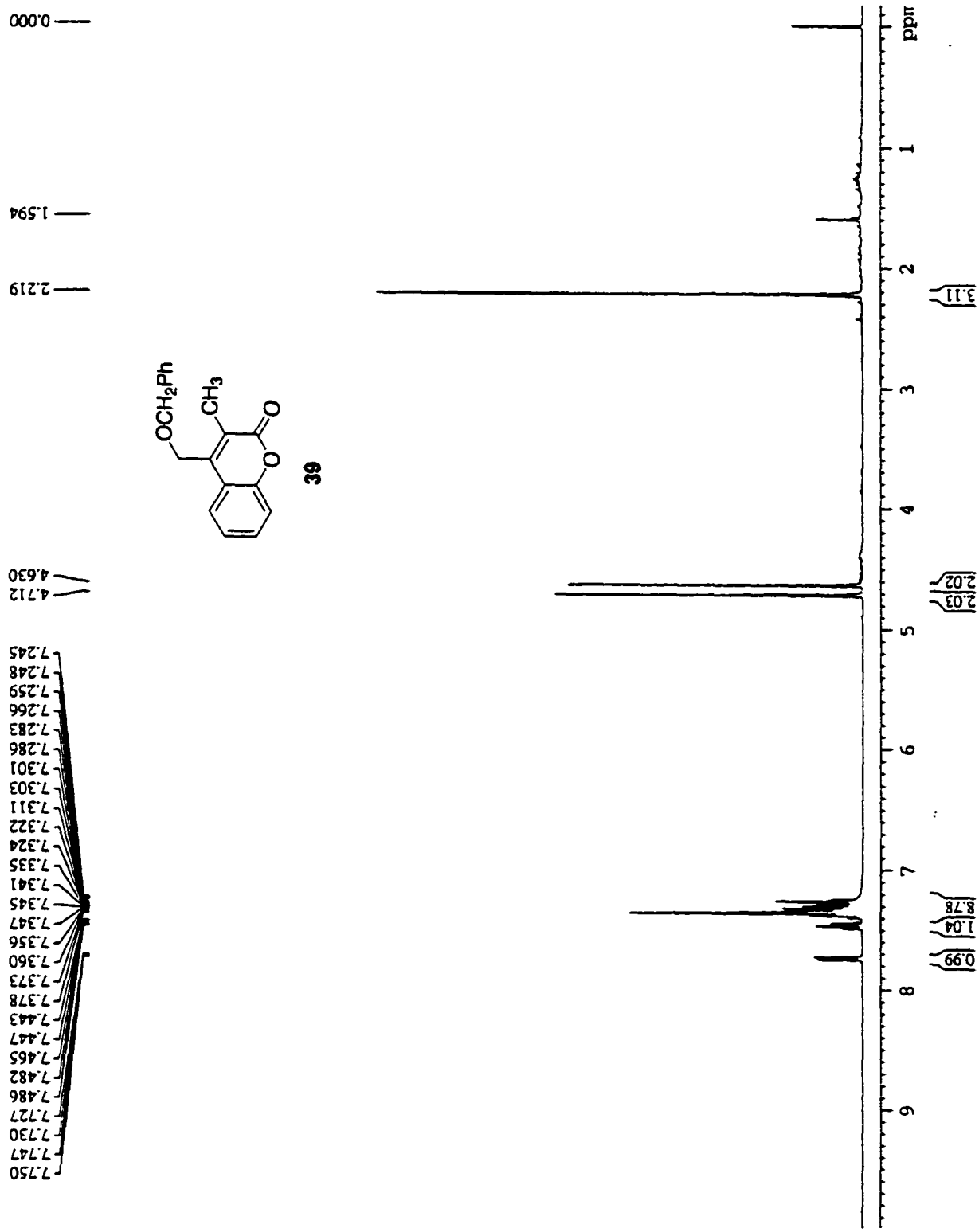

OCH2Ph
Ph
O
O
35
66.316
73.435
117.017
119.443
124.611
126.503
128.295
128.535
128.704
128.869
129.497
130.263
131.620
133.435
137.279
145.514
153.355
161.303


Ph
OCH2Ph
O
O
36
4.248
4.504
7.076
7.080
7.096
7.100
7.130
7.132
7.147
7.150
7.167
7.170
7.227
7.238
7.256
7.259
7.270
7.271
7.285
7.301
7.305
7.337
7.340
7.343
7.346
7.349
7.358
7.364
7.386
7.388
7.487
7.492
7.498
7.502
7.509
7.525
7.529
2.08
2.10
1.00
0.99
5.98
3.11
4.13

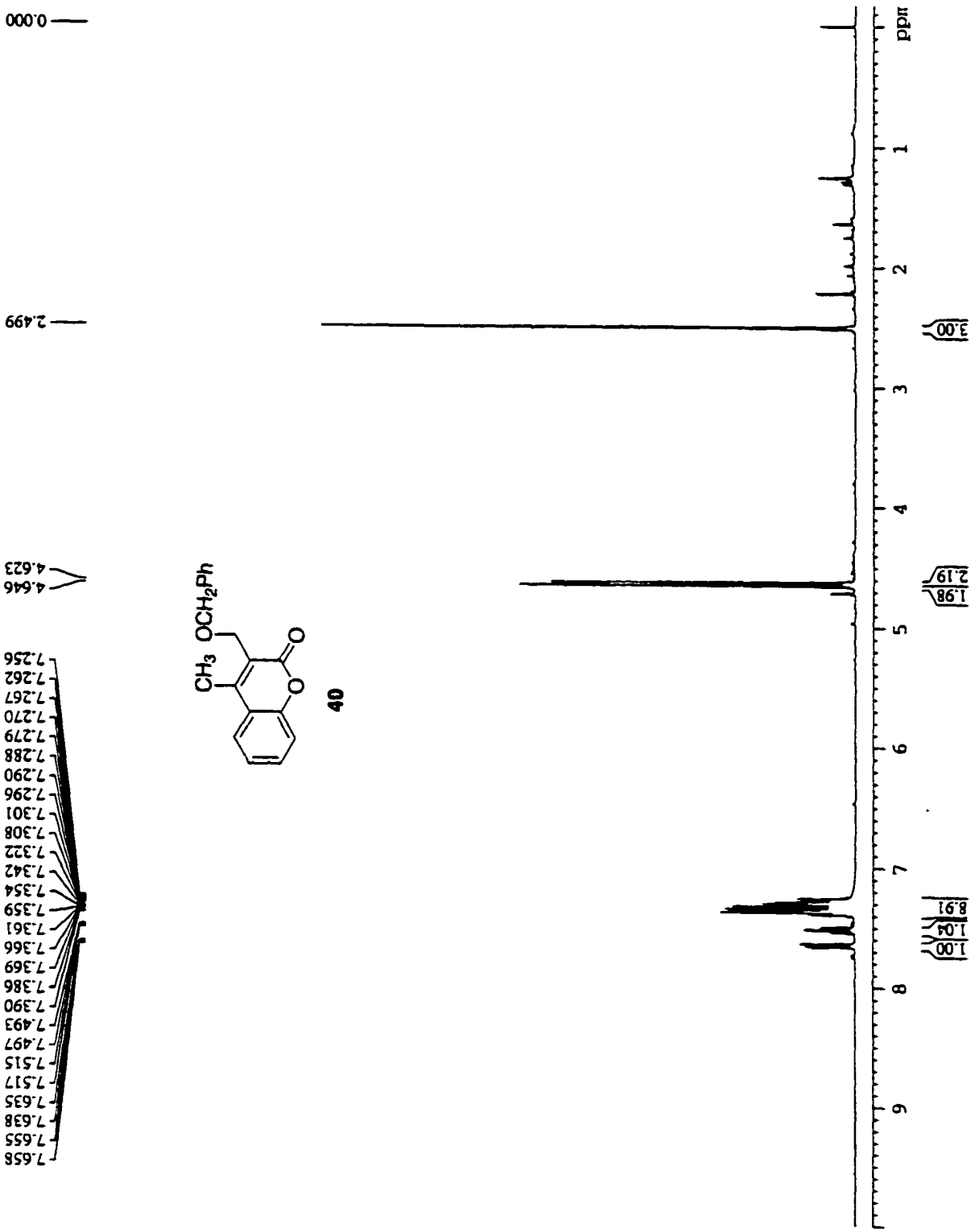

Ph
OCH2Ph
O
O
36
65.281
73.572
116.995
120.549
122.792
124.301
127.762
128.019
128.196
128.485
128.682
128.907
129.223
132.001
133.778
138.282
153.583
154.923
161.771


OTBDMS
CH3
O
O
37
+
CH3
OTBDMS
O
O
38
1:1.7

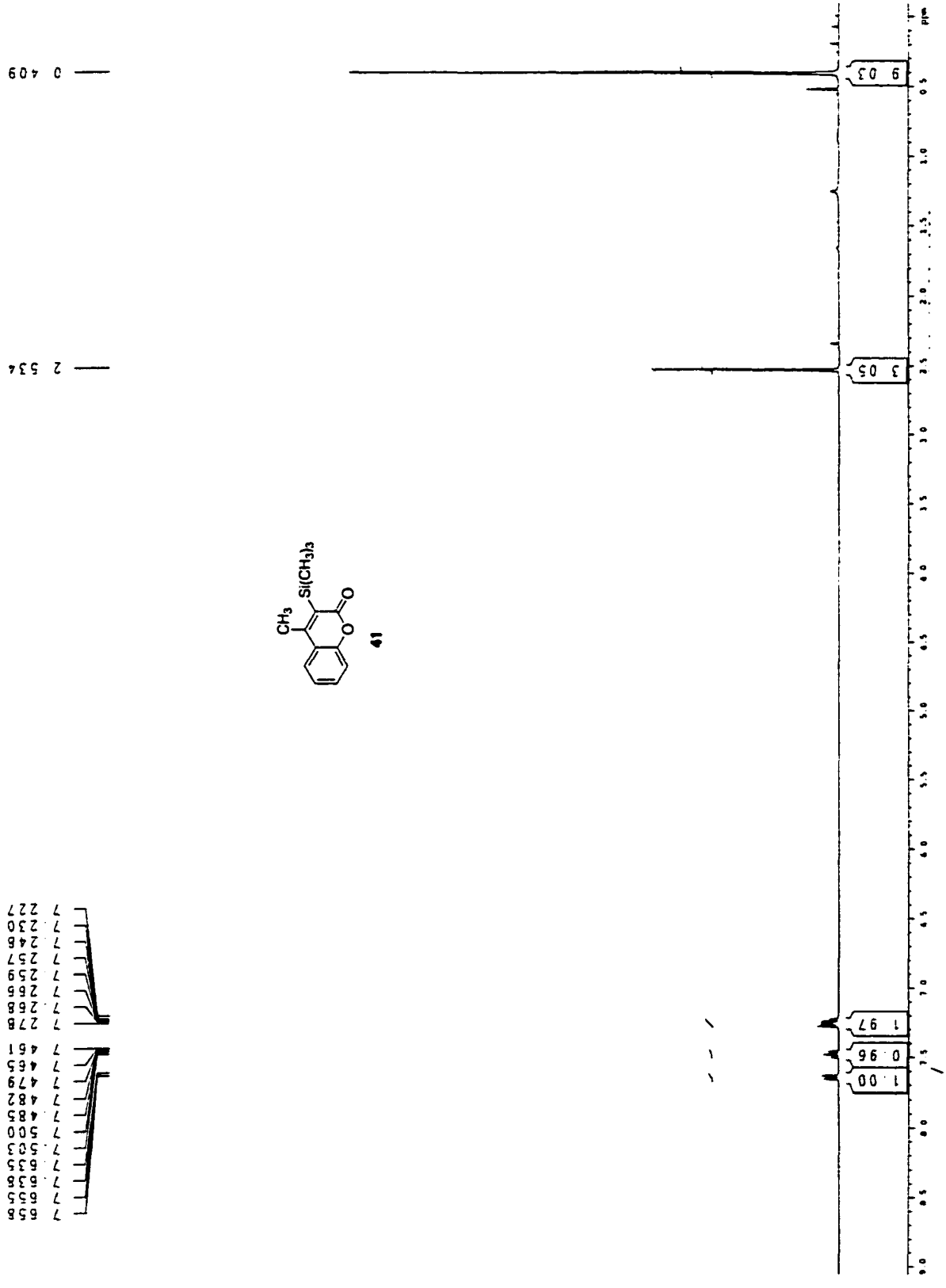

162.676
161.409
152.956
152.656
150.733
146.568
131.553
130.571
125.694
124.955
124.923
124.300
124.220
123.314
120.939
119.491
117.062
116.892
58.836
57.583
26.088
25.952
18.509
18.434
15.118
13.273
-5.016
-5.081
OTBDMS
CH3
CH3
OTBDMS
+
O
O
O
O
37
38
1:1.7

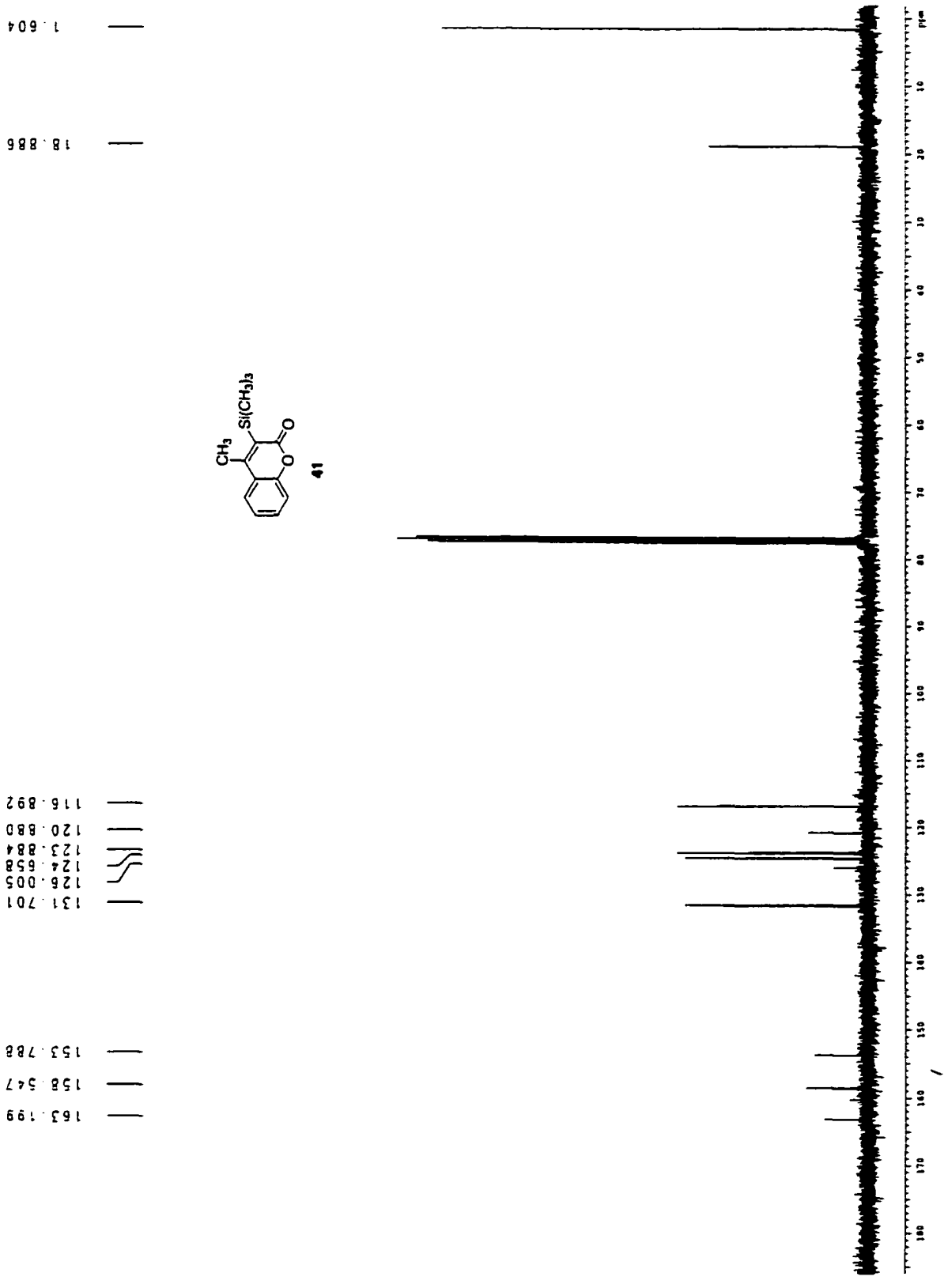

0.000
1.594
2.219
4.630
4.712
7.245
7.248
7.259
7.266
7.283
7.286
7.301
7.303
7.311
7.322
7.324
7.335
7.341
7.345
7.347
7.356
7.360
7.373
7.378
7.443
7.447
7.465
7.482
7.486
7.727
7.730
7.747
7.750
OCH2Ph
CH3
O
O
39
ppm
1
2
3
4
5
6
7
8
9
3.11
2.03
2.02
8.78
1.04
0.99

162.311
152.548
144.069
137.426
130.760
128.797
128.407
128.218
125.374
125.322
124.434
119.452
116.938
77.545
77.228
76.910
73.199
64.684
13.436
39
OCH2Ph
CH3
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.000
2.499
4.623
4.646
7.256
7.262
7.267
7.270
7.279
7.288
7.290
7.296
7.301
7.308
7.322
7.342
7.354
7.359
7.361
7.366
7.369
7.386
7.390
7.493
7.497
7.515
7.517
7.635
7.638
7.655
7.658
CH3 OCH2Ph
O
O
40
ppm
1
2
3
4
5
6
7
8
9
3.00
2.19
1.98
8.91
1.04
1.00

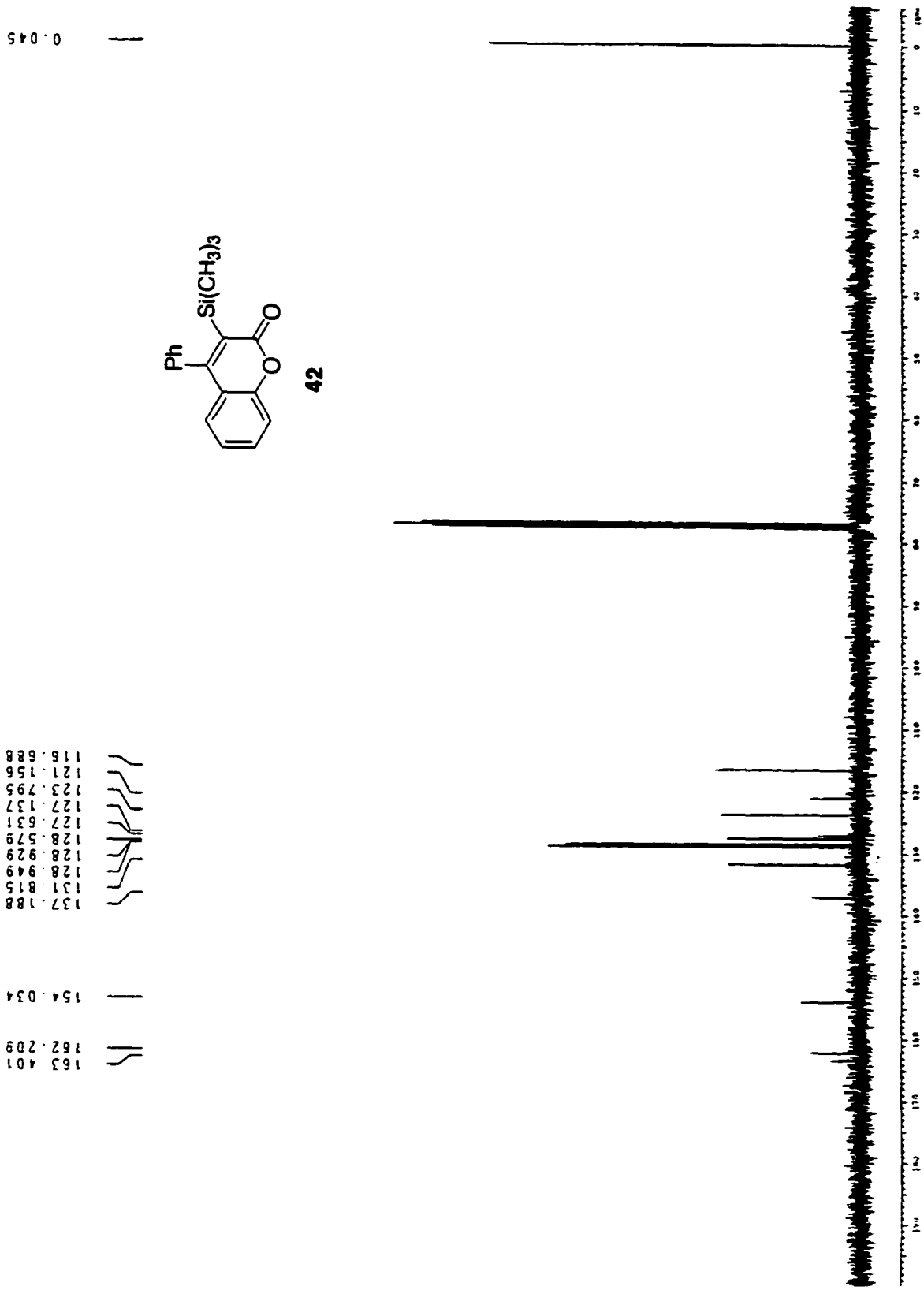
161.700
152.993
151.760
138.222
131.887
128.605
128.147
127.972
125.087
124.411
122.464
120.582
117.072
77.544
77.226
76.909
73.203
64.160
15.260
CH3
OCH2Ph
O
O
40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

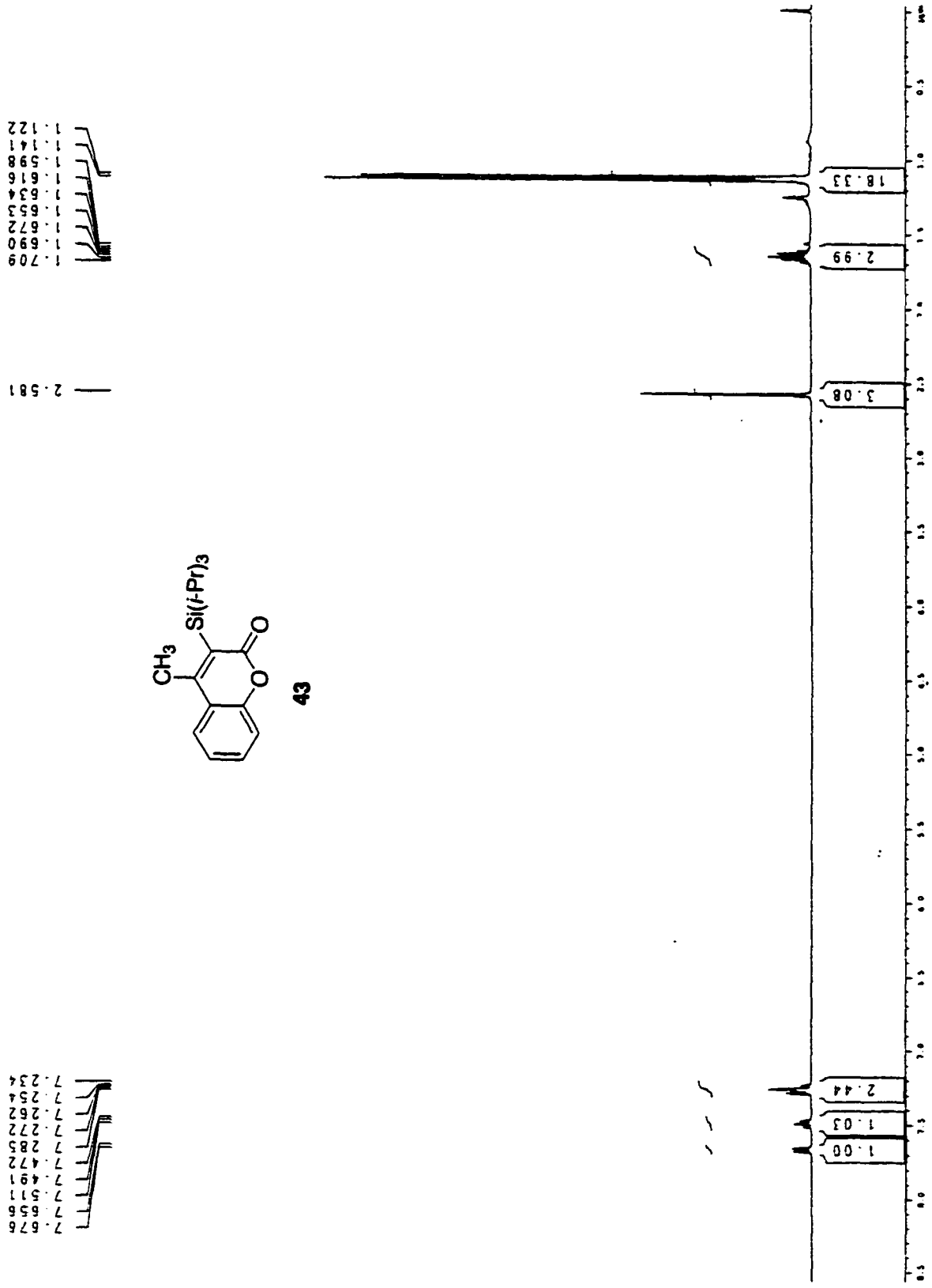

0.409
2.534
9.03
3.05
1.97
0.96
1.00
7.656
7.655
7.638
7.635
7.503
7.500
7.485
7.482
7.479
7.465
7.461
7.278
7.268
7.266
7.259
7.257
7.246
7.230
7.227
Si(CH3)3
CH3
O
O
41

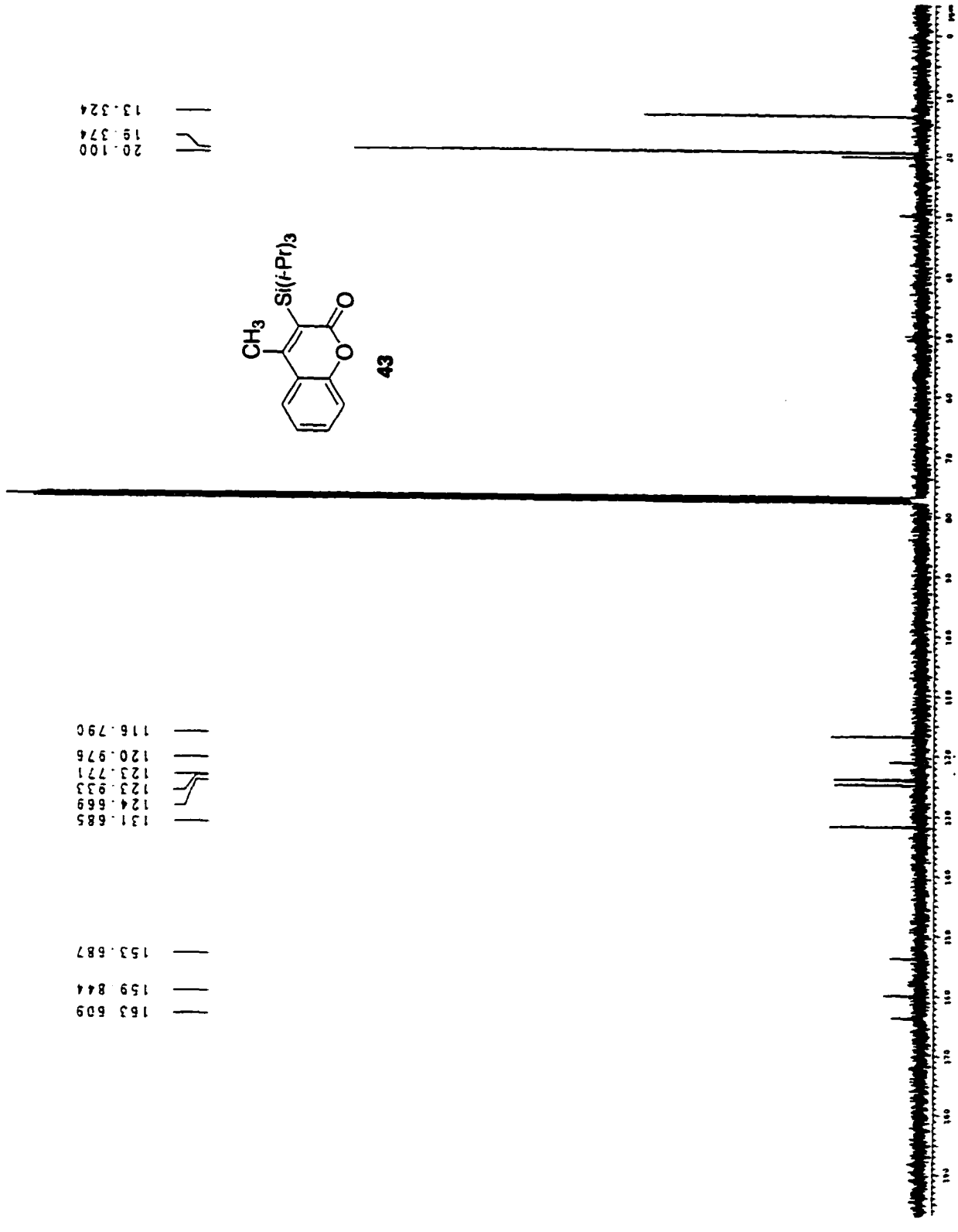

1.604
18.886
116.892
120.880
123.884
124.658
126.005
131.701
153.788
158.547
163.199
41

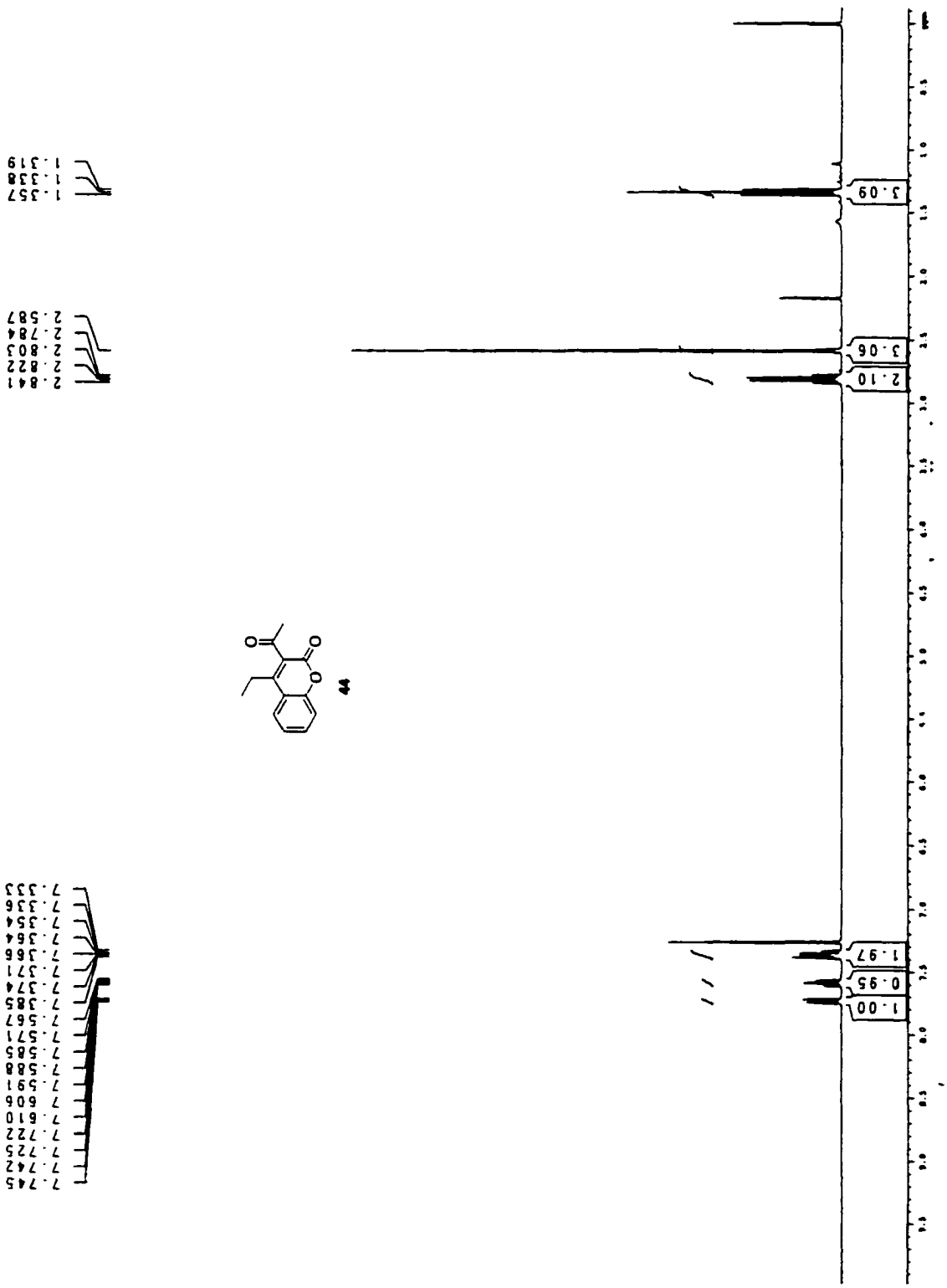
7.491
7.483
7.475
7.468
7.465
7.461
7.447
7.443
7.337
7.335
7.316
7.314
7.249
7.242
7.239
7.235
7.233
7.225
7.108
7.103
7.085
7.068
7.065
6.959
6.955
6.939
6.935
4.13
0.97
2.22
1.01
1.00
96.3
0.044

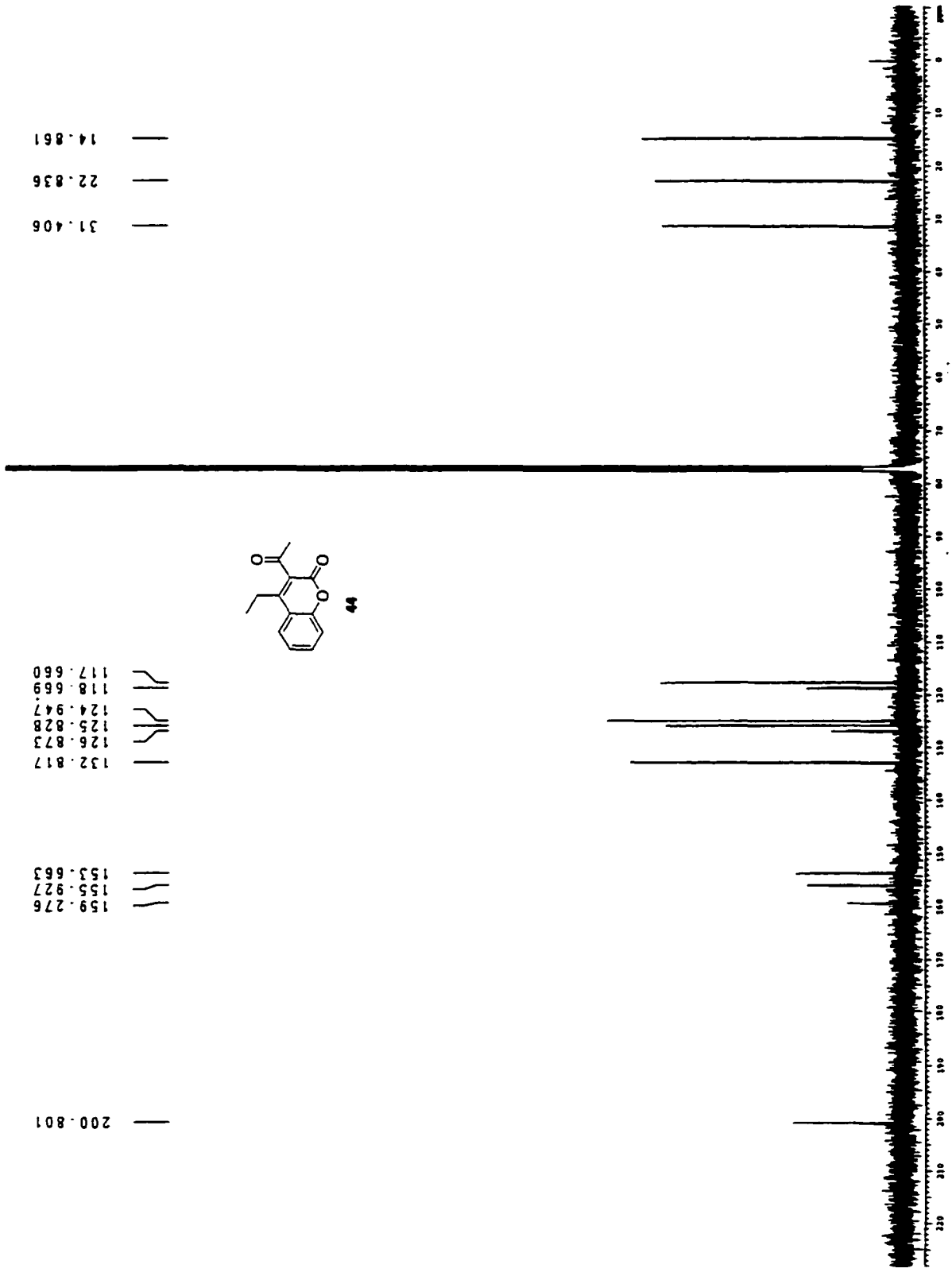
42

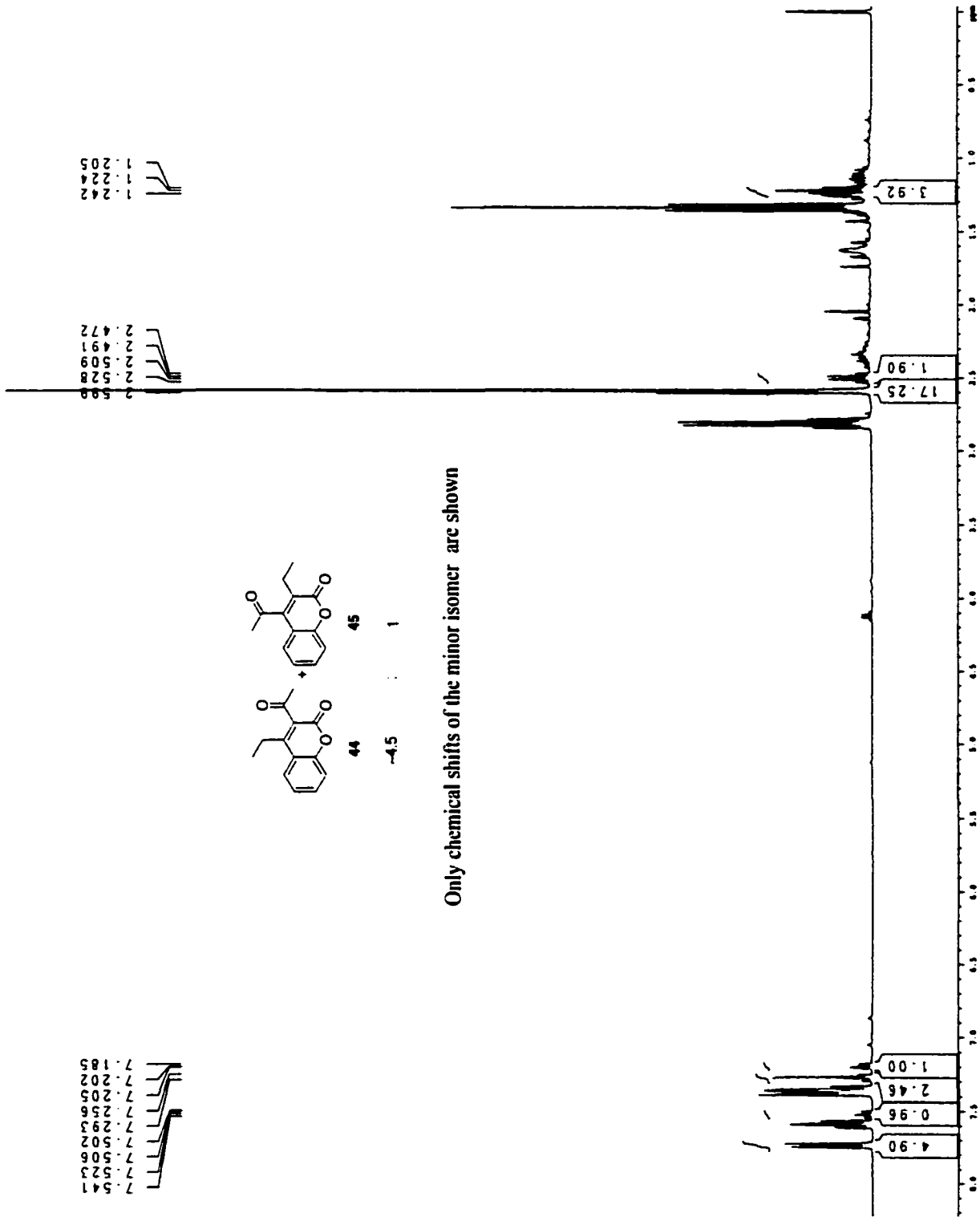

0.045
154.034
162.209
163.401
137.188
131.815
128.949
128.929
128.579
127.631
127.137
123.795
121.156
116.688
Ph
Si(CH3)3
O
O
42


7.676
7.656
7.511
7.491
7.472
7.285
7.272
7.262
7.254
7.234
2.581
1.709
1.690
1.672
1.653
1.634
1.616
1.598
1.141
1.122
2.44
1.03
1.00
2.99
18.33
3.08
CH3
Si(i-Pr)3
O
O
43

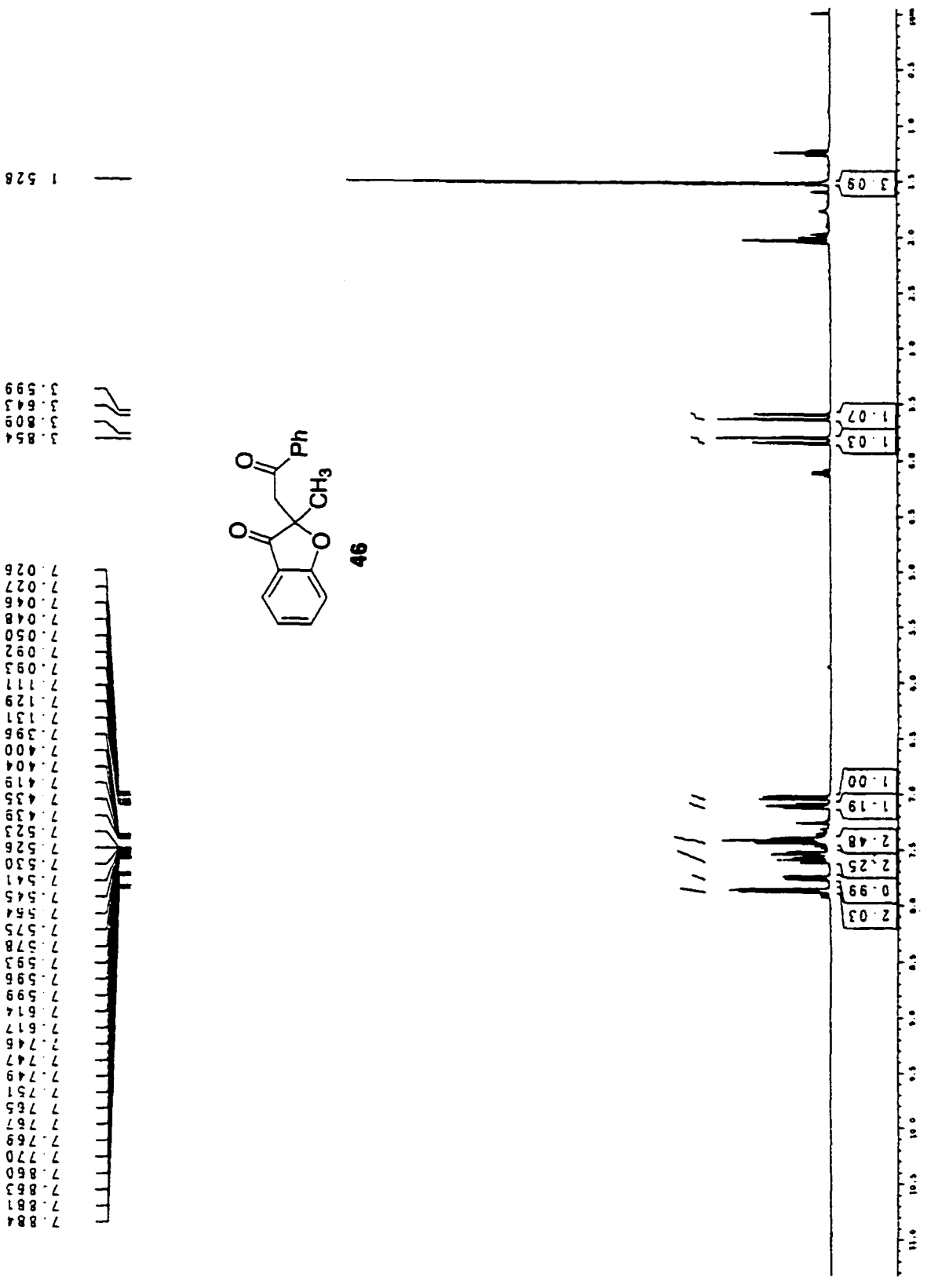

Si(i-Pr)3
CH3
O
O
43
13.324
19.374
20.100
116.790
120.976
123.771
123.933
124.669
131.685
153.687
159.844
163.609

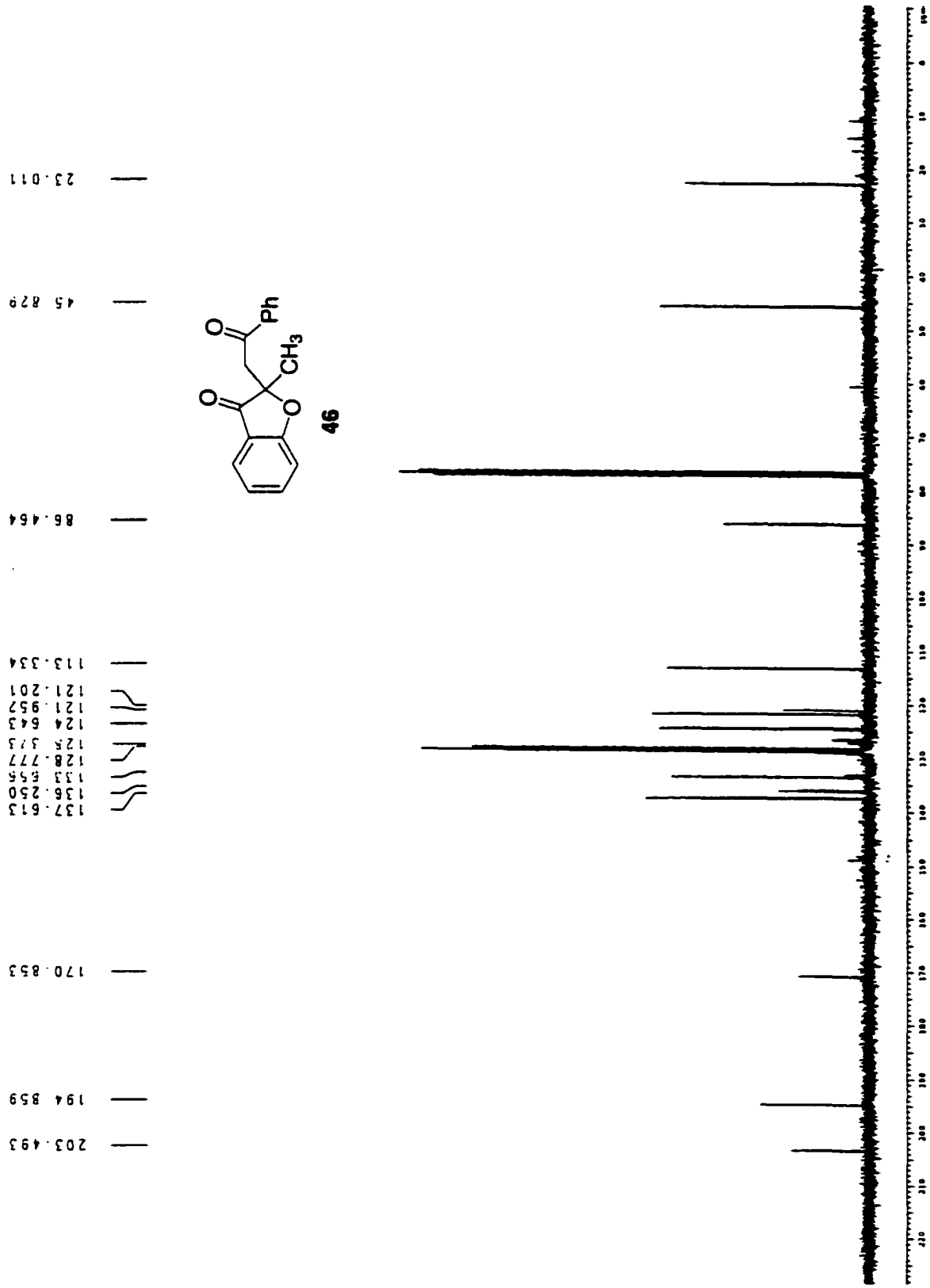

7.333
7.336
7.354
7.364
7.366
7.371
7.374
7.385
7.567
7.571
7.585
7.588
7.591
7.606
7.610
7.722
7.725
7.742
2.841
2.822
2.803
2.784
2.587
1.357
1.338
1.319
1.00
0.95
1.97
2.10
3.06
3.09
44

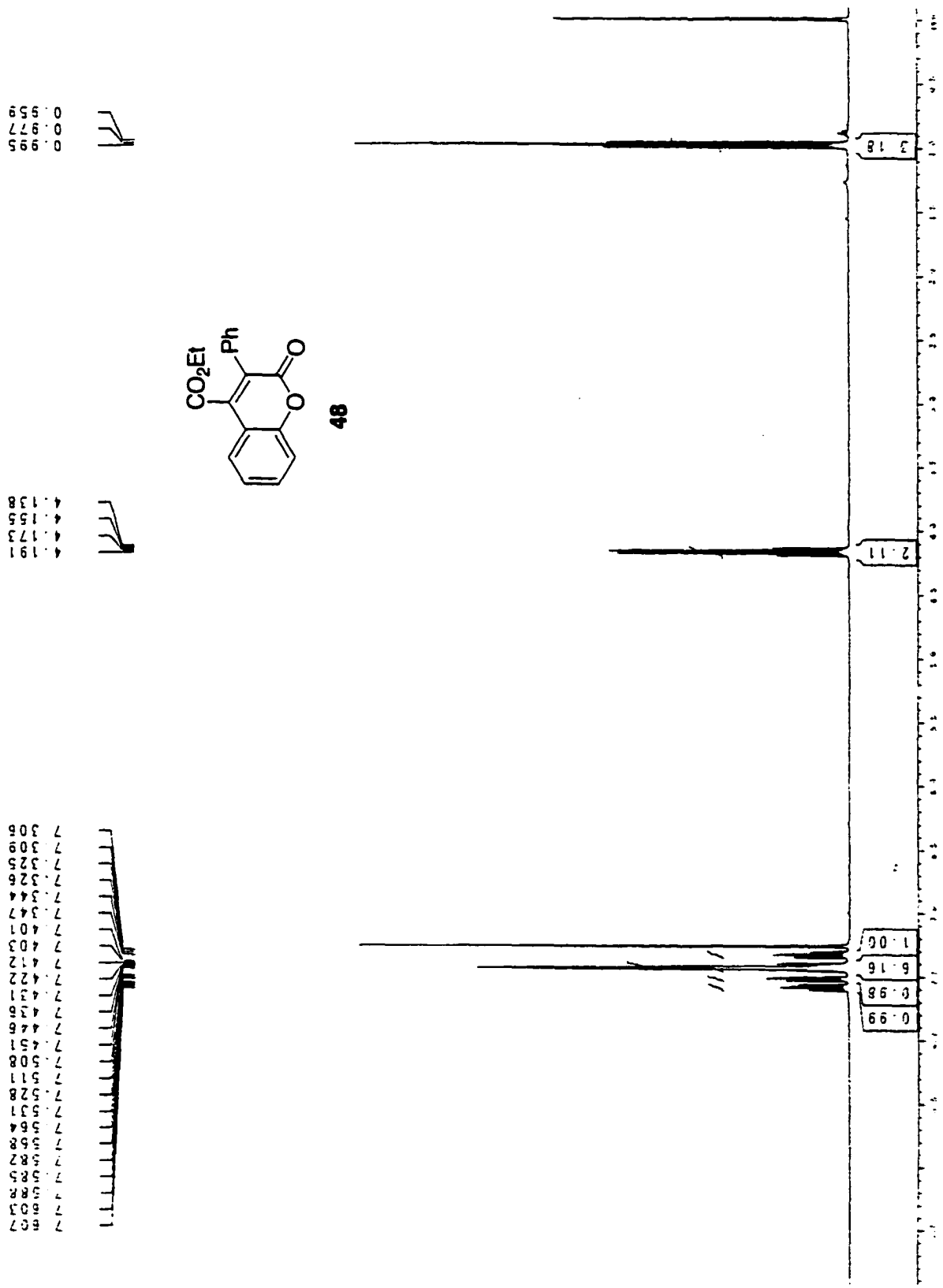

14.861
22.836
31.406
117.660
118.669
124.947
125.828
126.873
132.817
153.663
155.927
159.276
200.801
44

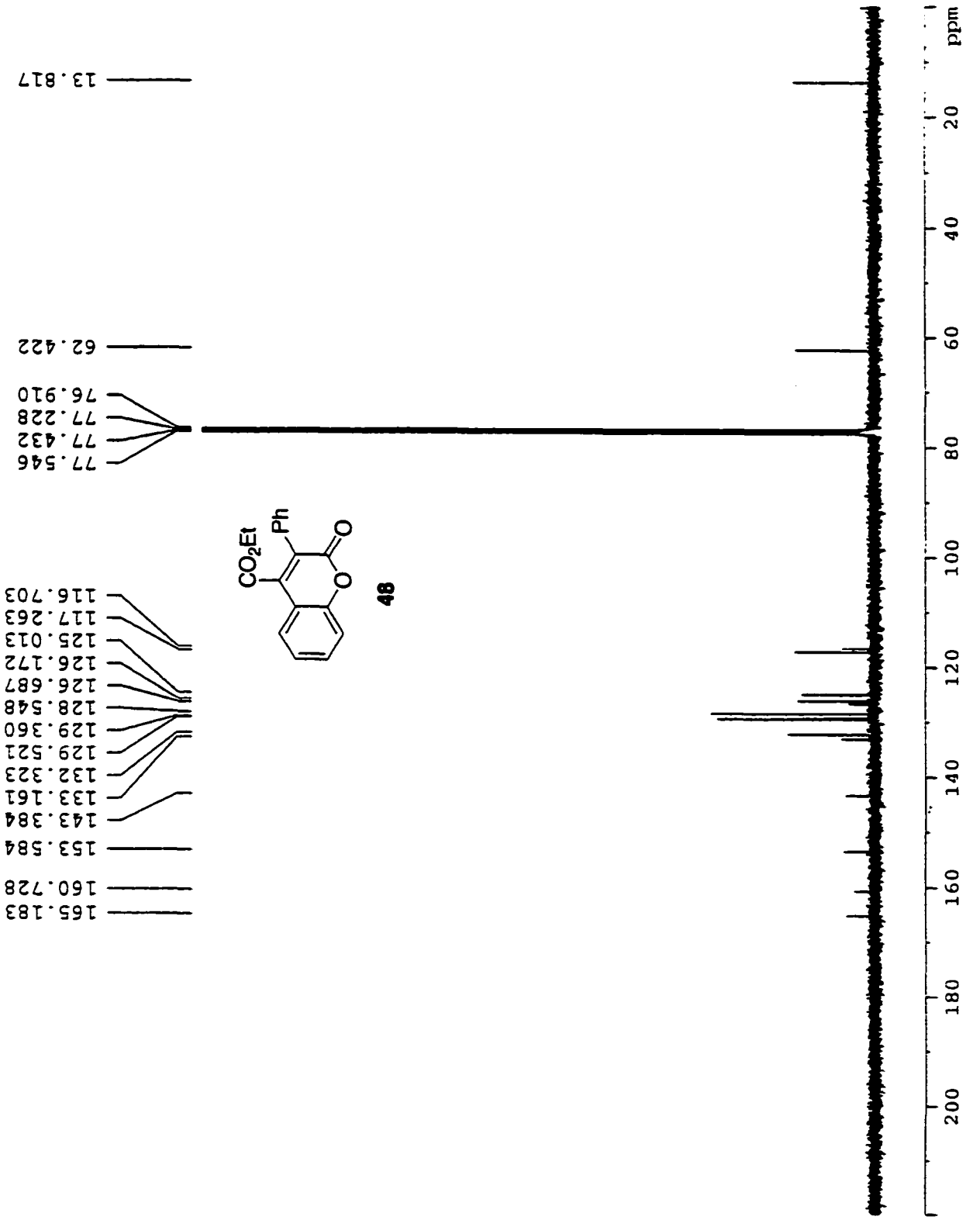


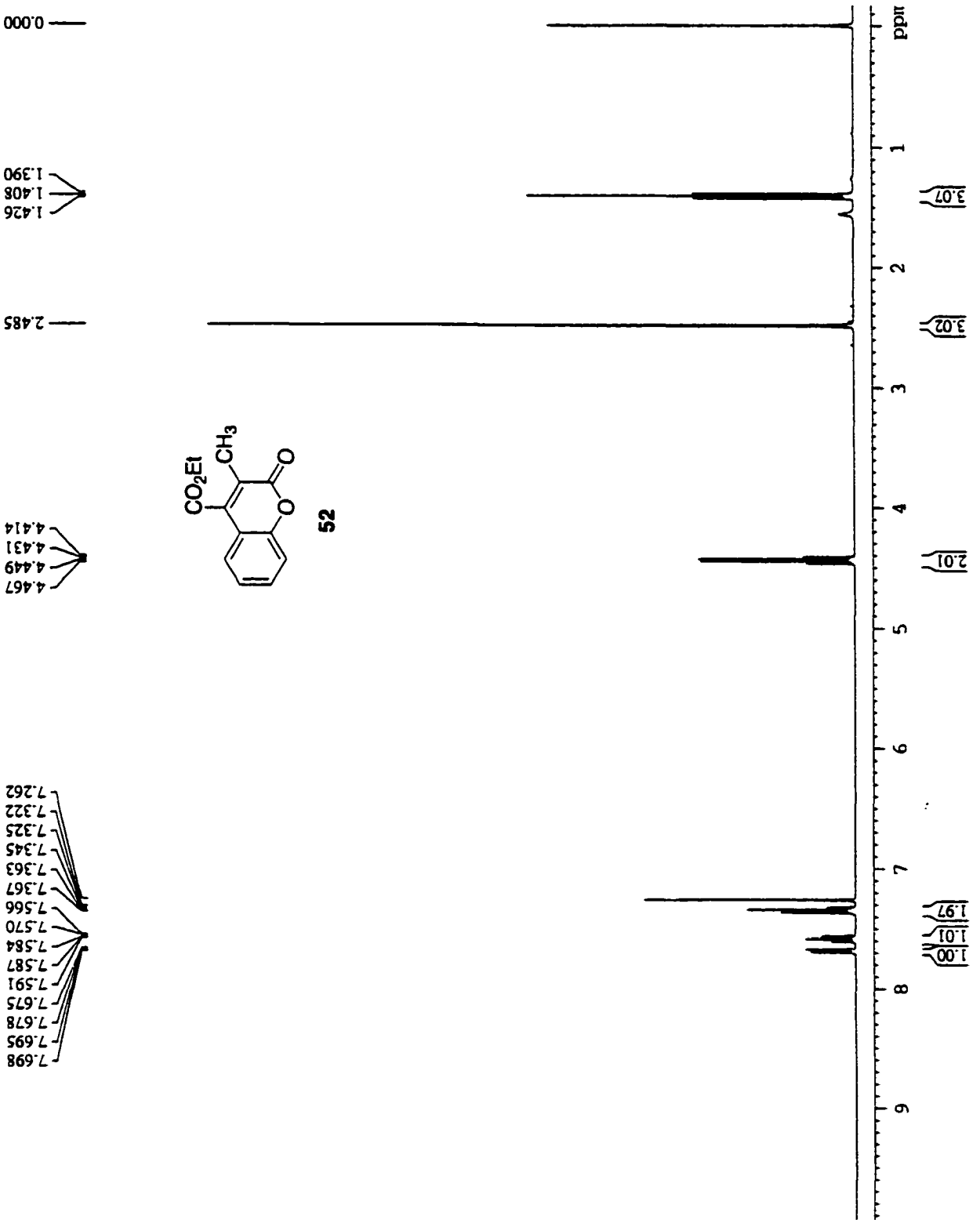
Only chemical shifts of the minor isomer are shown

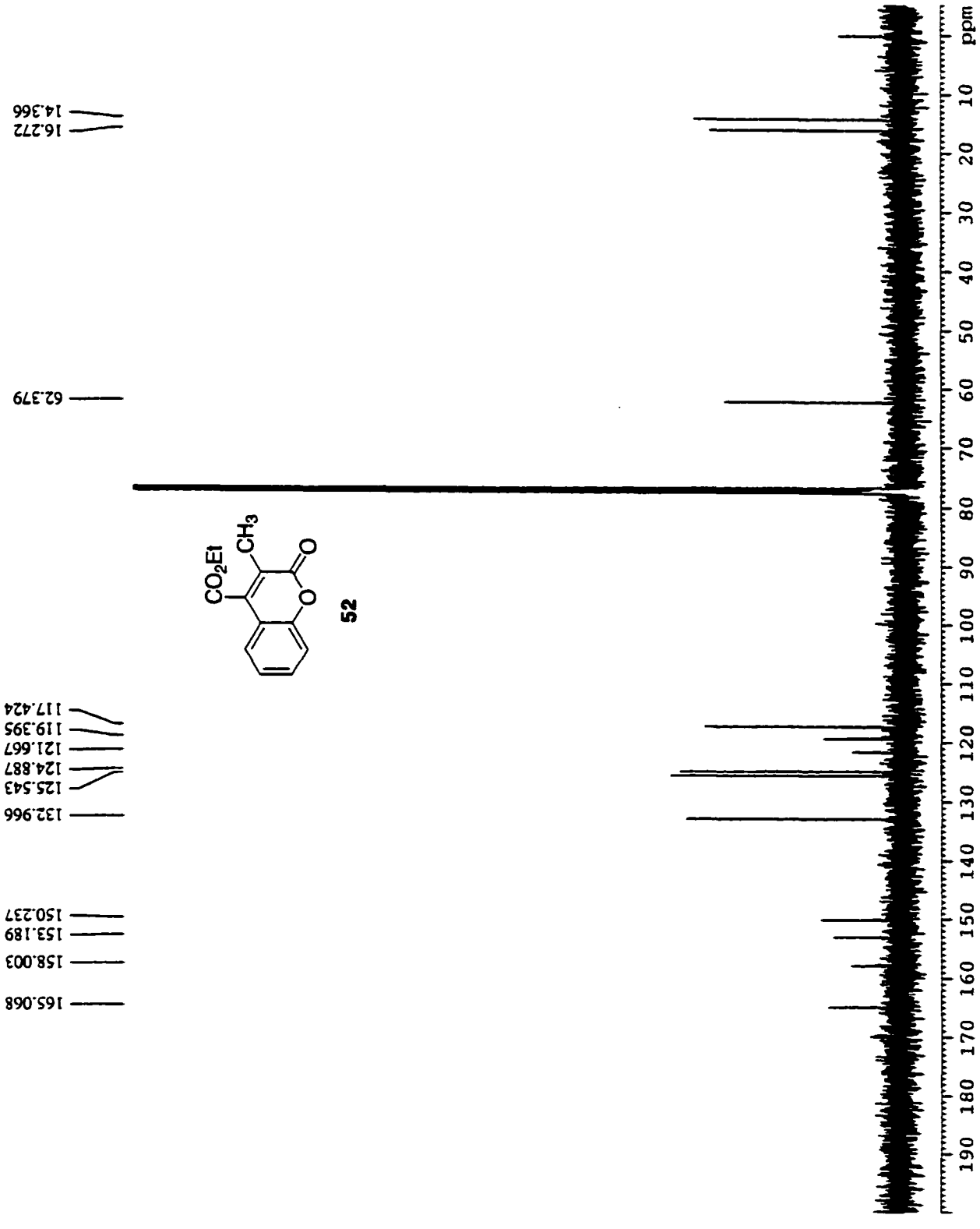

Ph
O
CH3
O
O
46

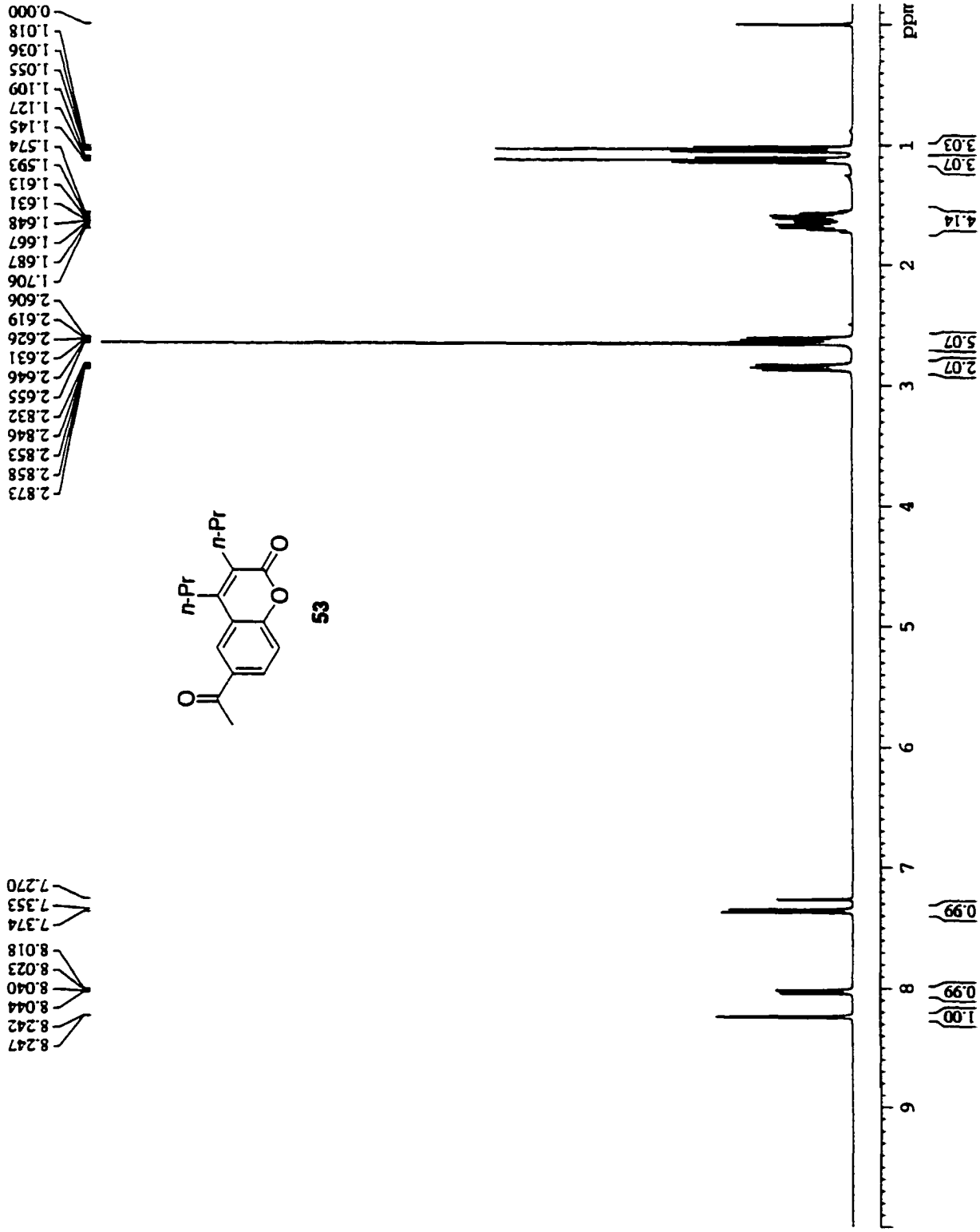

23.011
45.829
86.464
113.334
121.201
121.957
124.643
128.373
128.777
133.655
136.250
137.613
170.853
194.859
203.493
O
Ph
CH3
O
O
46


CO2Et
Ph
O
O
48


13.817
62.422
76.910
77.228
77.432
77.546
116.703
117.263
125.013
126.172
126.687
128.548
129.360
129.521
132.323
133.161
143.384
153.584
160.728
165.183
CO2Et
Ph
O
O
48
ppm
20
40
60
80
100
120
140
160
180
200


0.000
1.390
1.408
1.426
2.485
4.414
4.431
4.449
4.467
7.262
7.322
7.325
7.345
7.363
7.367
7.566
7.570
7.584
7.587
7.591
7.675
7.678
7.695
7.698
3.07
3.02
2.01
1.97
1.01
1.00
ppm
1
2
3
4
5
6
7
8
9
CO2Et
CH3
O
O
52


14.366
16.272
62.379
117.424
119.395
121.667
124.887
125.543
132.966
150.237
153.189
158.003
165.068
CO2Et
CH3
O
O
52
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190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1.127
1.145
1.574
1.593
1.613
1.631
1.648
1.667
1.687
1.706
2.606
2.619
2.626
2.631
2.646
2.655
2.832
2.846
2.853
2.858
2.873
7.270
7.353
7.374
8.018
8.023
8.040
8.044
8.242
8.247
n-Pr
n-Pr
O
O
O
53
ppm
1
2
3
4
5
6
7
8
9
3.03
3.07
4.14
5.07
2.07
0.99
0.99
1.00

196.595
161.234
155.757
149.968
133.270
130.571
127.685
125.481
119.966
117.380
77.544
77.227
76.909
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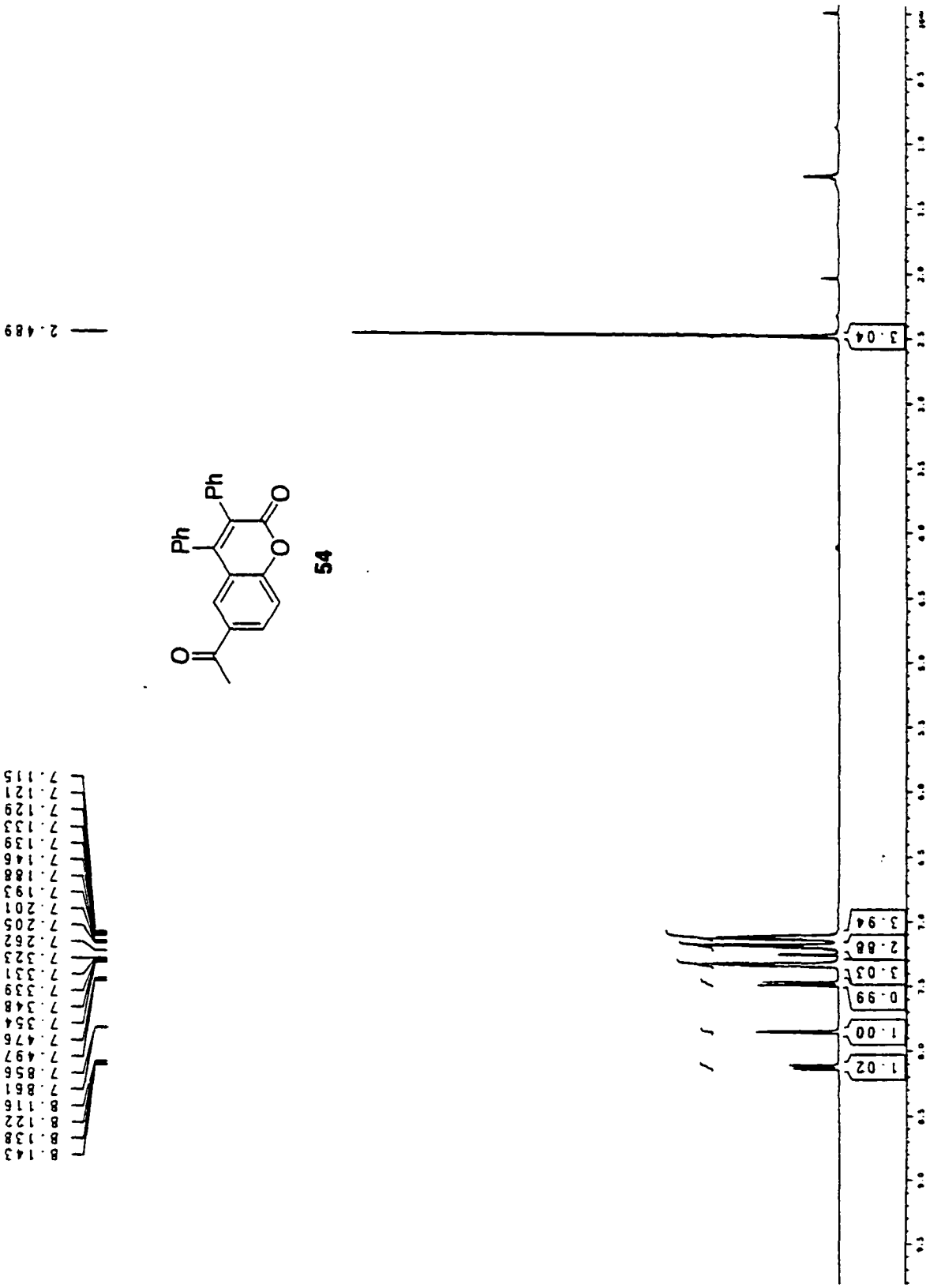
30.005
26.787
23.134
22.459
14.694
14.502
n-Pr
n-Pr
53
ppm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3.94
2.88
3.03
0.99
1.00
1.02
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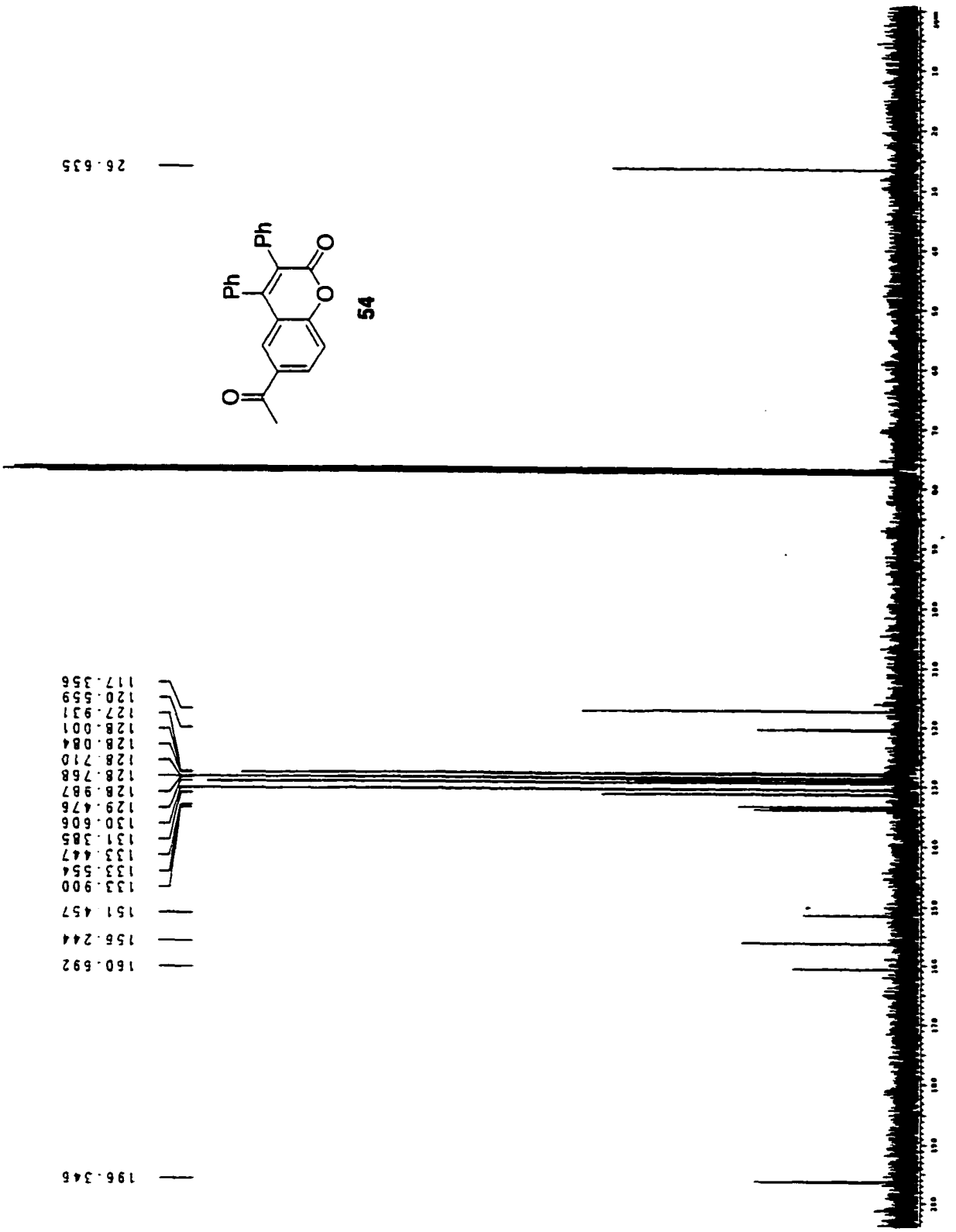
7.121
7.129
7.133
7.139
7.146
7.188
7.193
7.201
7.205
7.262
7.323
7.331
7.339
7.348
7.354
7.476
7.497
7.856
7.861
8.116
8.122
8.138
8.143
Ph
Ph
O
O
O

54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128.710
128.768
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129.476
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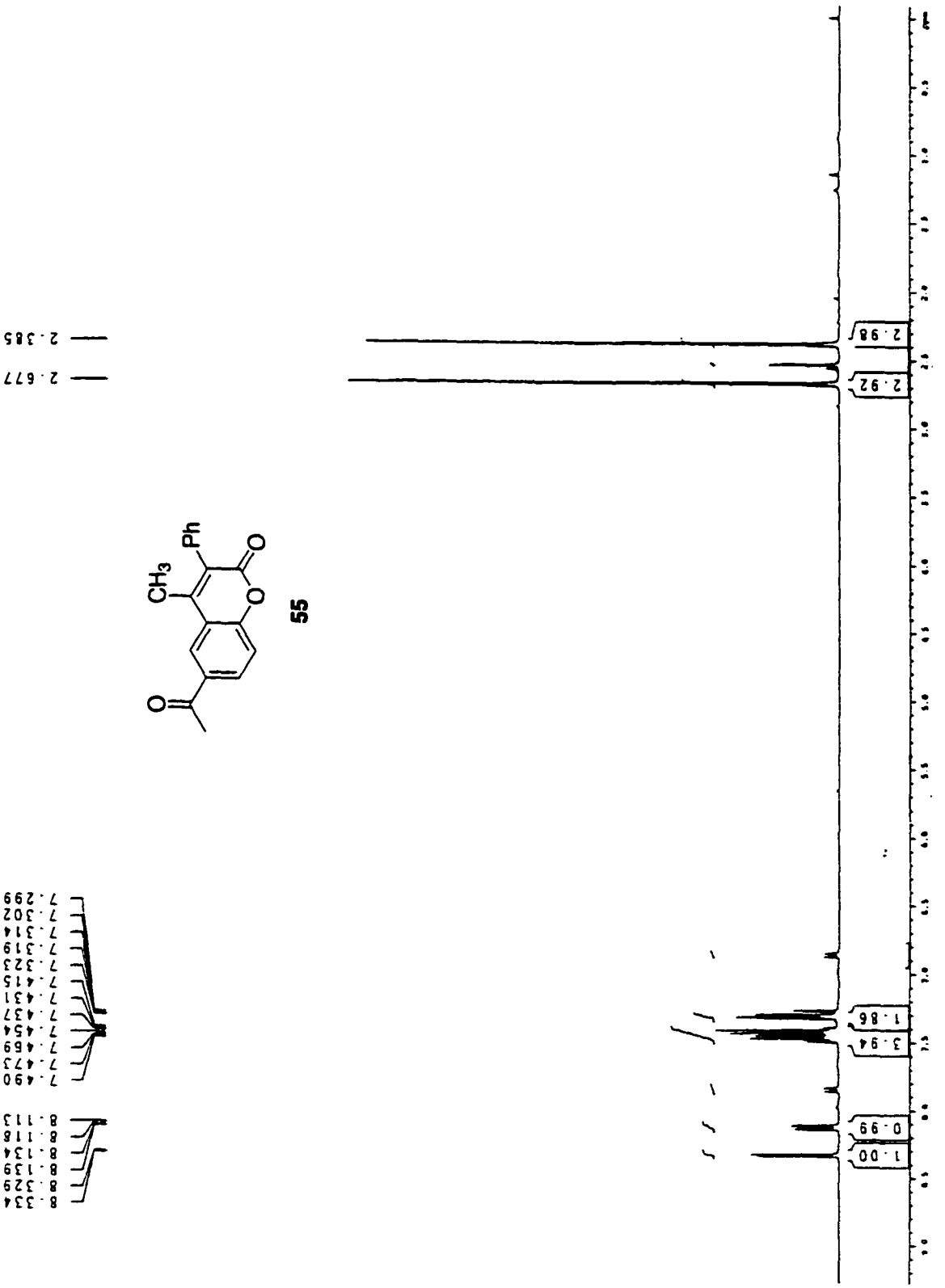
133.447
133.554
133.900
151.457
156.244
160.692
196.346
Ph
Ph
O
O
O
54


Ph
CH3
O
O
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3.94
0.99
1.00
2.385
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7.490
7.473
7.469
7.454
7.437
7.431
7.415
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7.319
7.314
7.302
7.299
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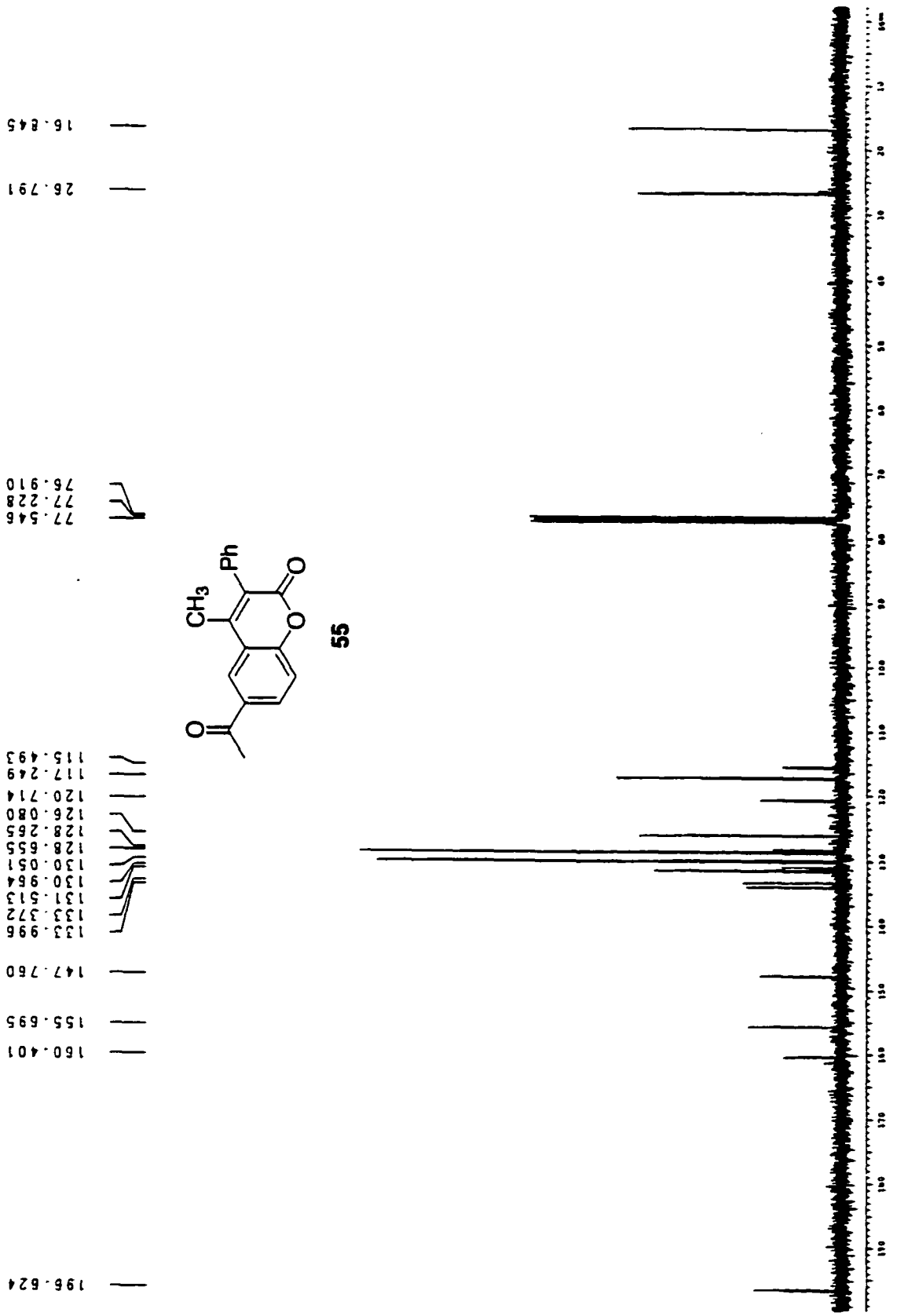
8.329
8.139
8.134
8.118
8.113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120.714
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128.265
128.655
130.051
130.964
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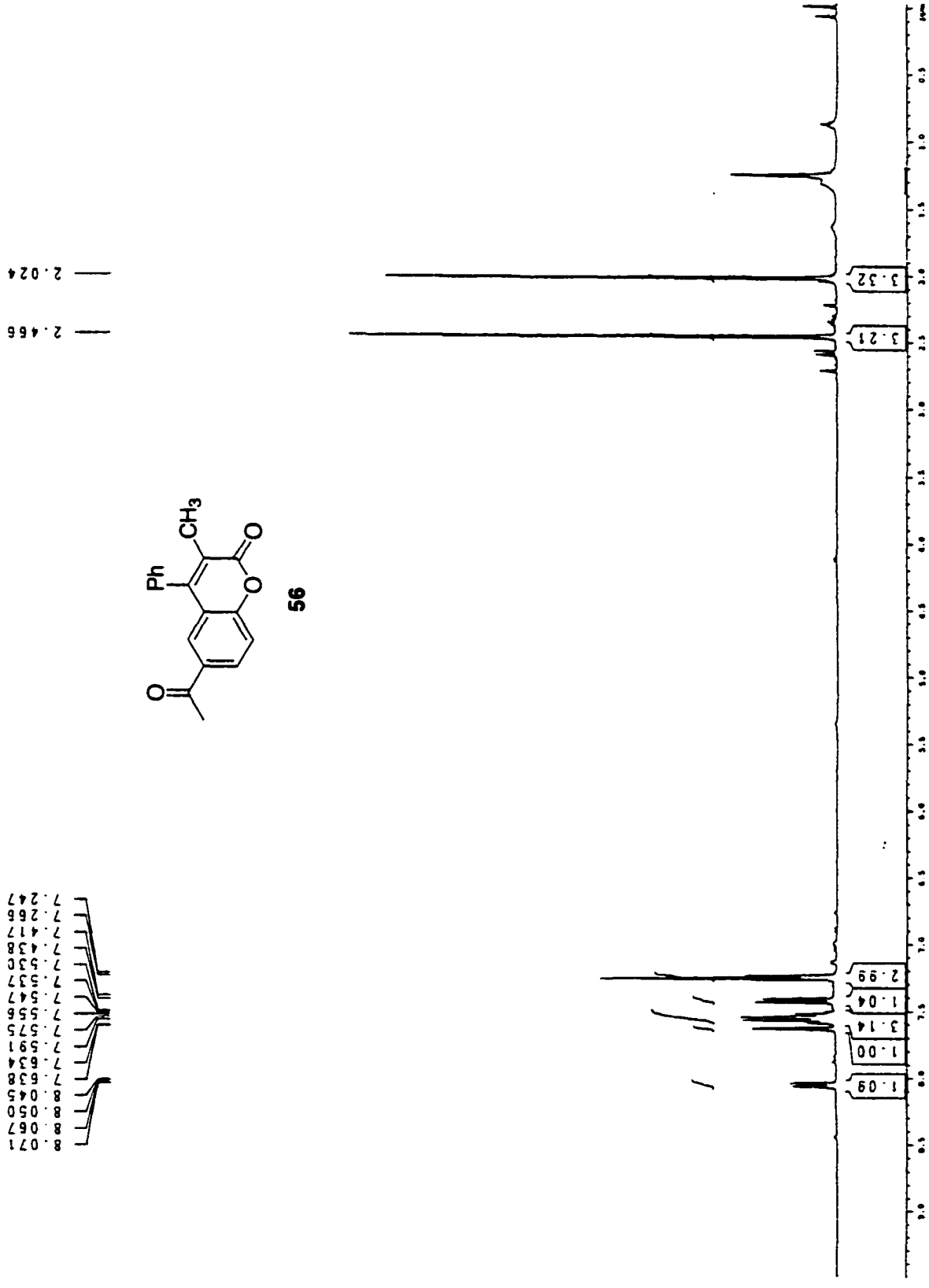
133.372
133.996
147.760
155.695
160.401
196.624
Ph
CH3
O
O
O
55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7.537
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7.266
7.247
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1.00
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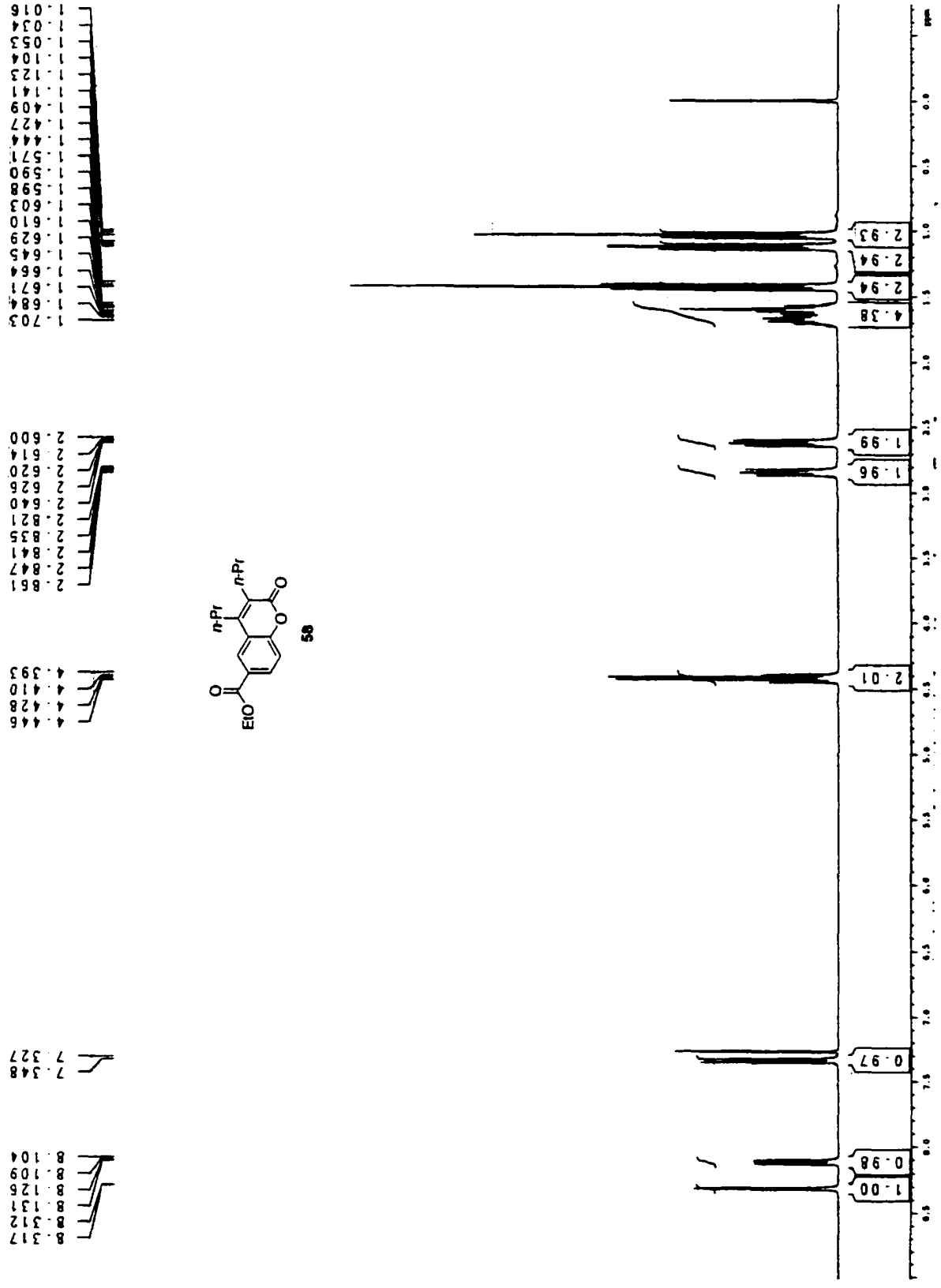
1.04
2.99
3.21
3.32

56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1.427
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1.598
1.603
1.610
1.629
1.645
1.664
1.671
1.684
1.703
2.600
2.614
2.620
2.626
2.640
2.821
2.835
2.841
2.847
2.861
4.393
4.410
4.428
4.446
7.327
7.348
8.104
8.109
8.126
8.131
8.312
8.317
n-Pr
n-Pr
O
O
O
EtO
5a
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0.98
1.00
1.96
1.99
2.01
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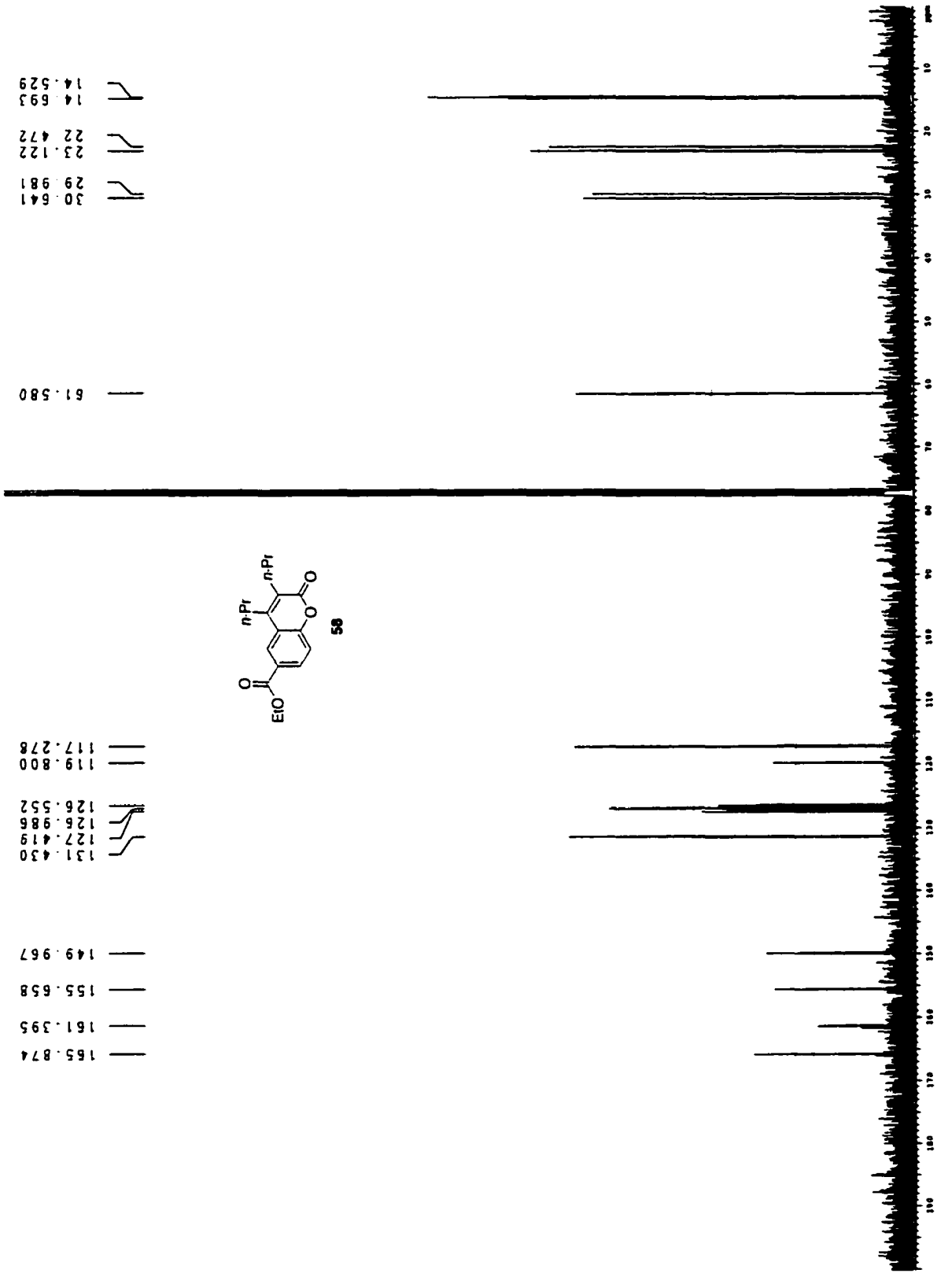
2.94
2.94
4.38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22.472
23.122
29.981
30.641
61.580
117.278
119.800
126.552
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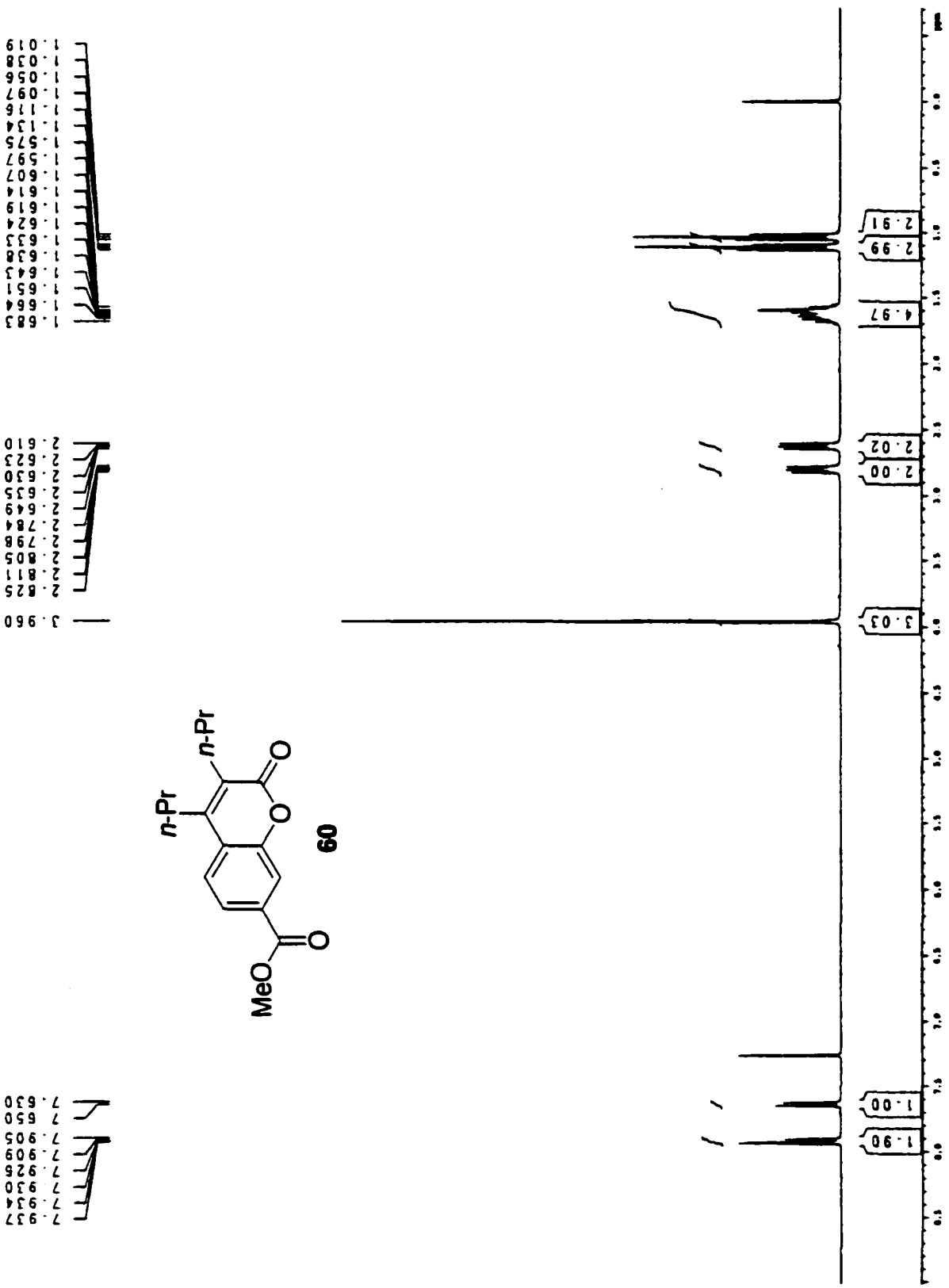
127.419
131.430
149.967
155.658
161.395
165.874
n-Pr
n-Pr
O
O
O
EtO
58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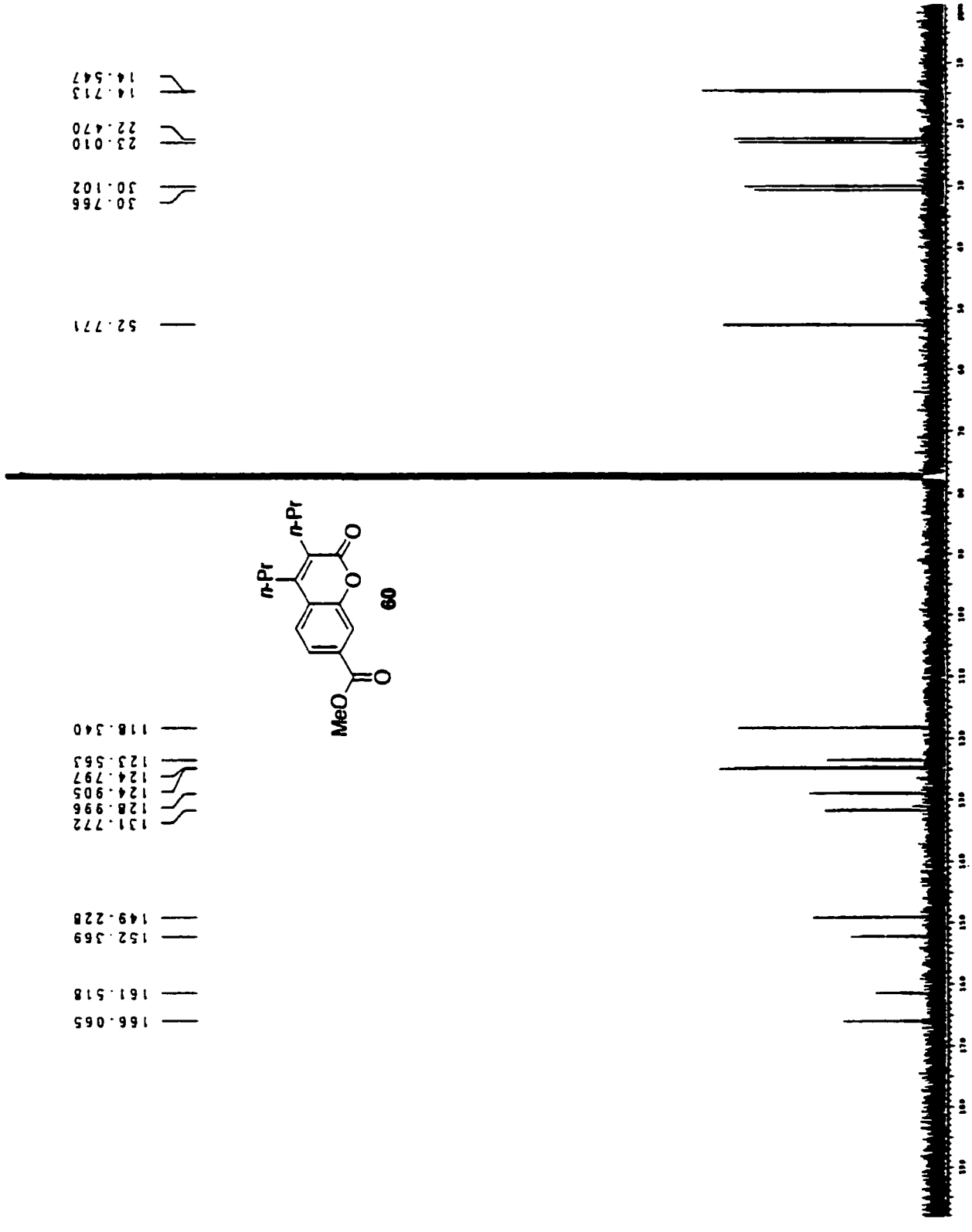
n-Pr
O
O
O
O
MeO
60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149.228
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124.905
124.797
123.563
118.340
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23.010
22.470
14.713
14.547
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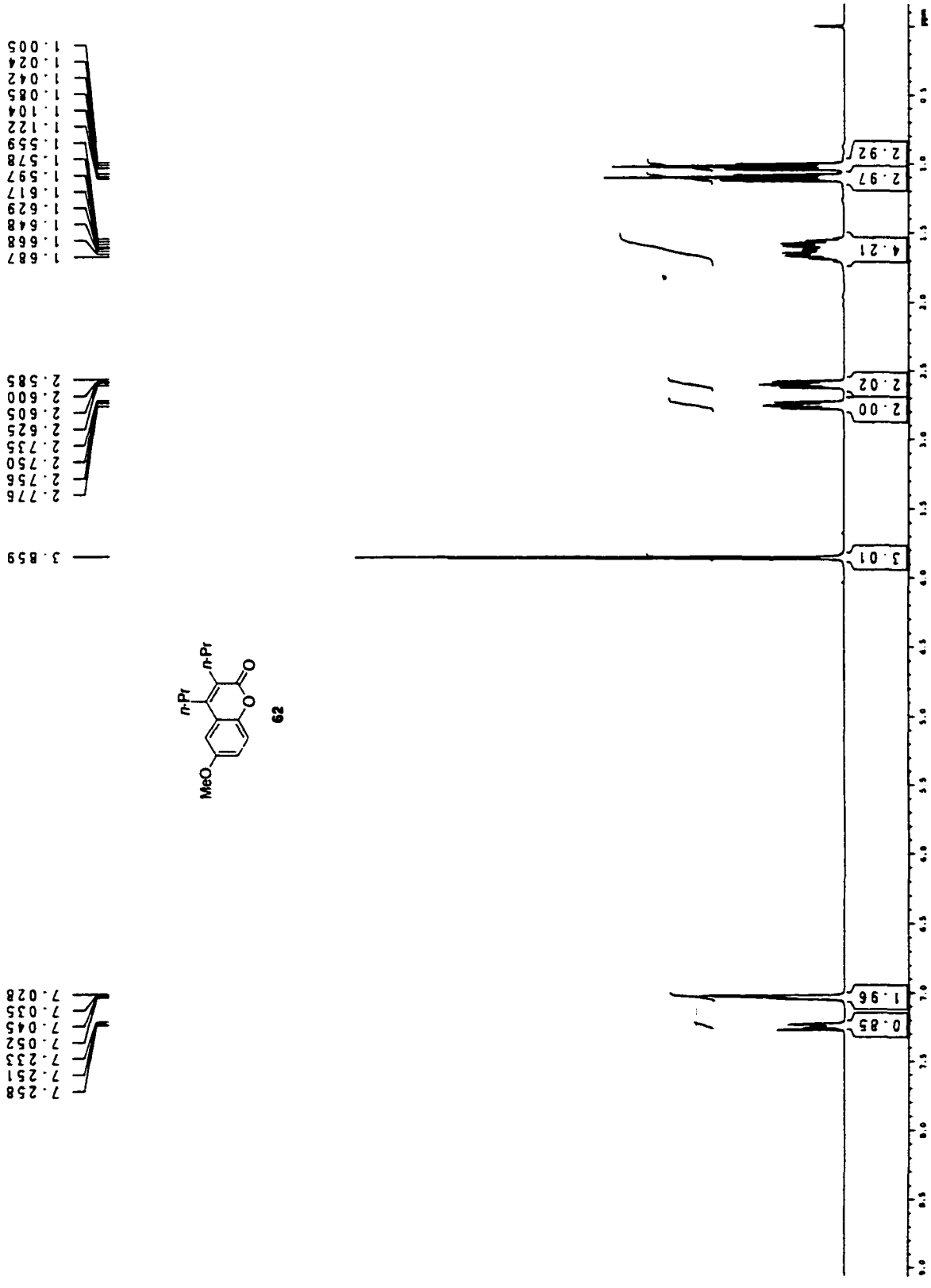
n-Pr
MeO
O
O
O
O
60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7.052
7.045
7.035
7.028
3.859
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2.756
2.750
2.735
2.625
2.605
2.600
2.585
1.687
1.668
1.648
1.629
1.617
1.597
1.578
1.559
1.122
1.104
1.085
1.042
1.024
1.005
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n-Pr
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O
62
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2.00
4.21
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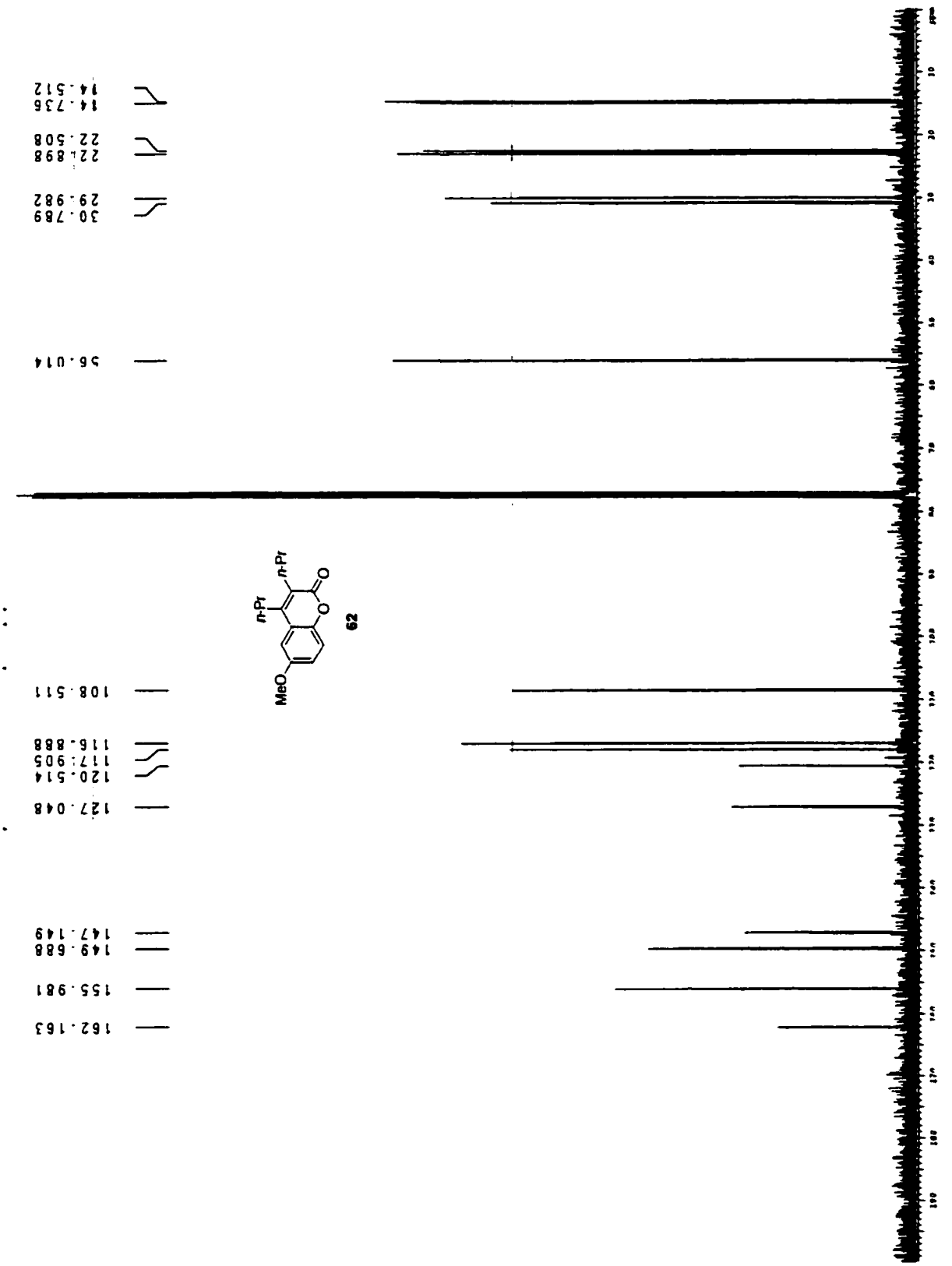
2.97
1.96
0.85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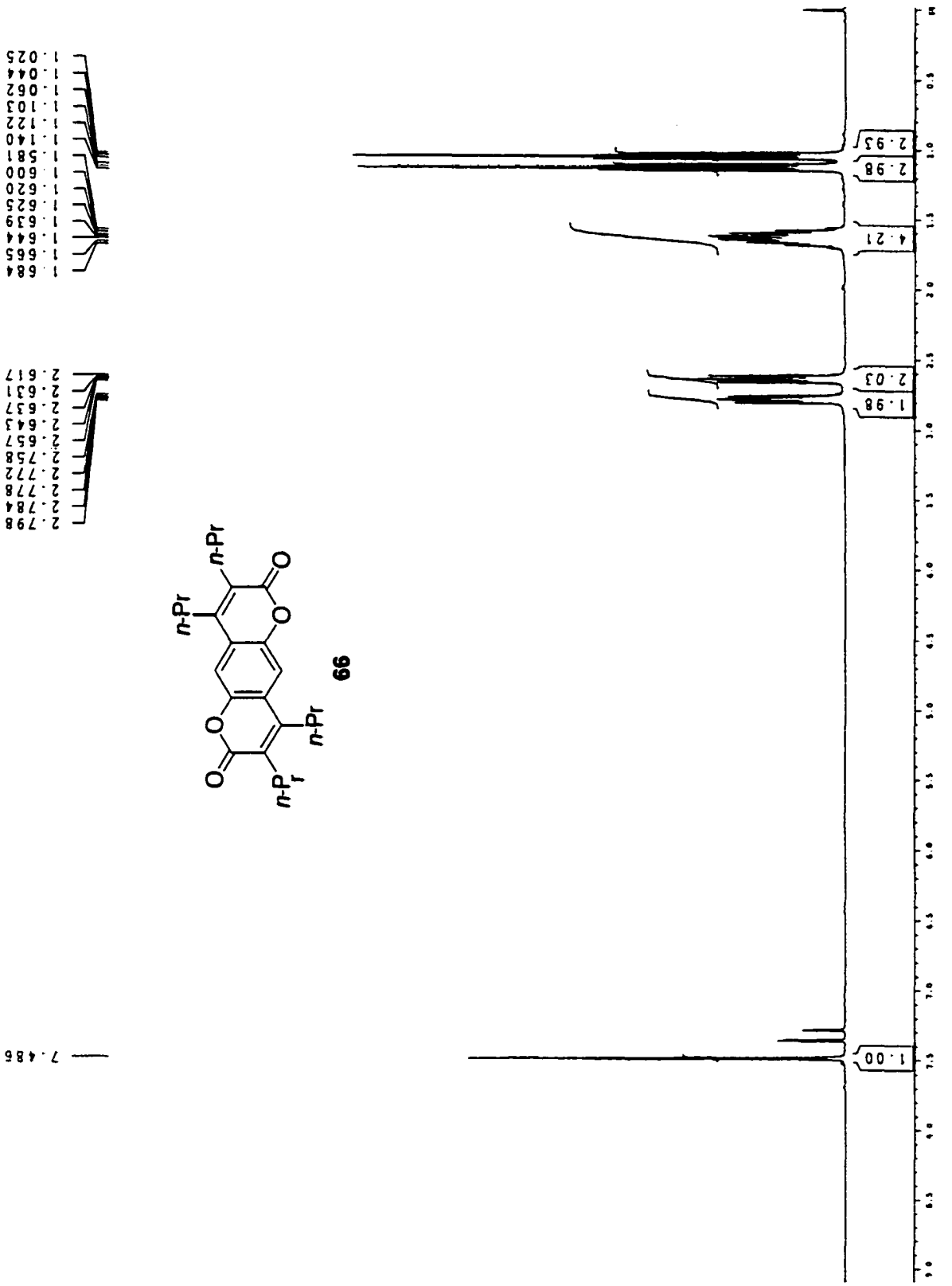
22.898
29.982
30.789
56.014
108.511
116.888
117.905
120.514
127.048
147.149
149.688
155.981
162.163
n-Pr
n-Pr
MeO
O
O
62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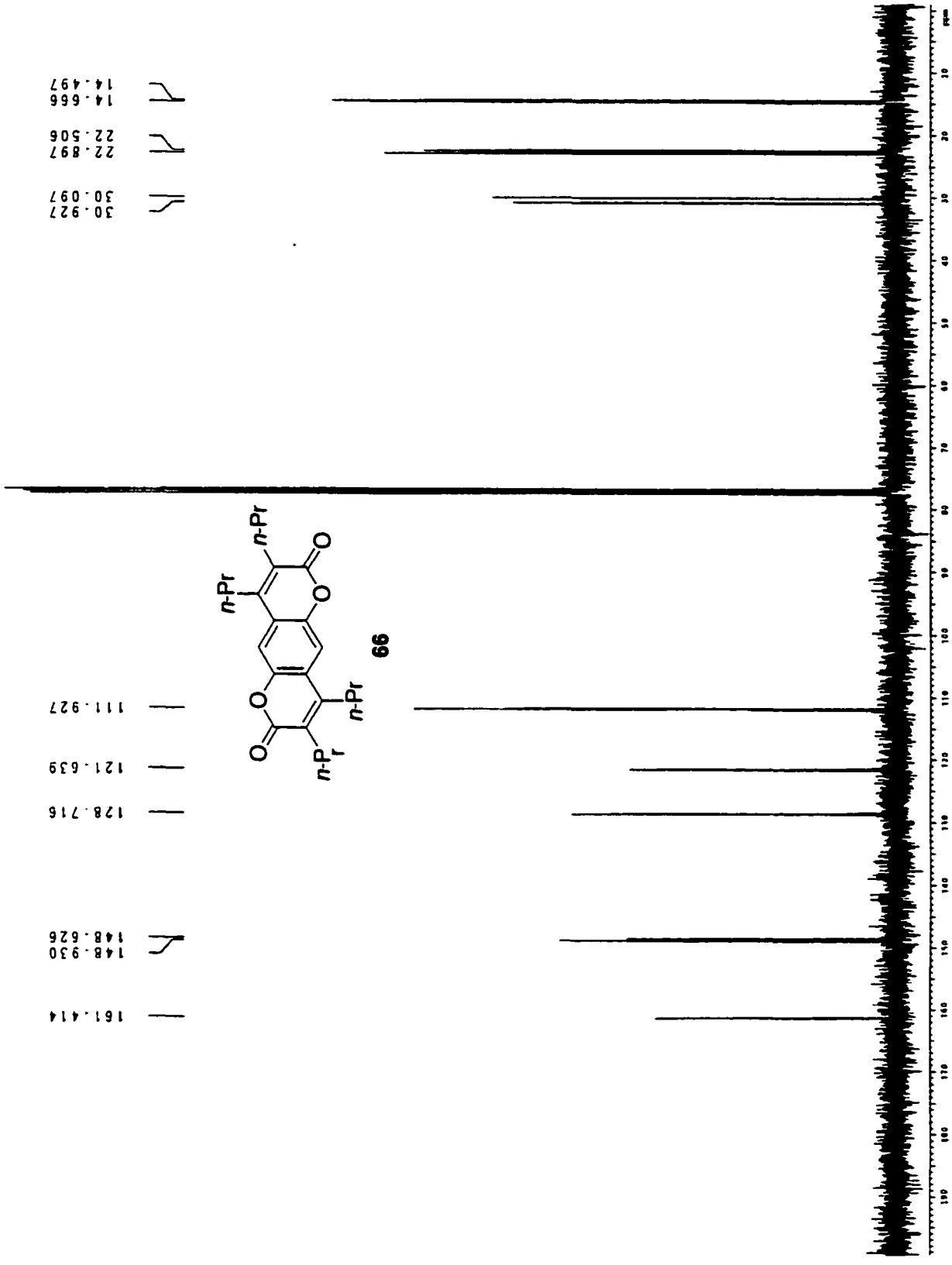
1.644
1.639
1.625
1.620
1.600
1.581
1.140
1.122
1.103
1.062
1.044
1.025
2.798
2.784
2.778
2.772
2.758
2.657
2.643
2.637
2.631
2.617
n-Pr
n-Pr
n-Pr
n-Pr
O
O
O
O
66
1.00
2.93
2.98
4.21
2.03
1.98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22.897
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30.927
111.927
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148.930
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n-Pr
n-Pr
n-Pr
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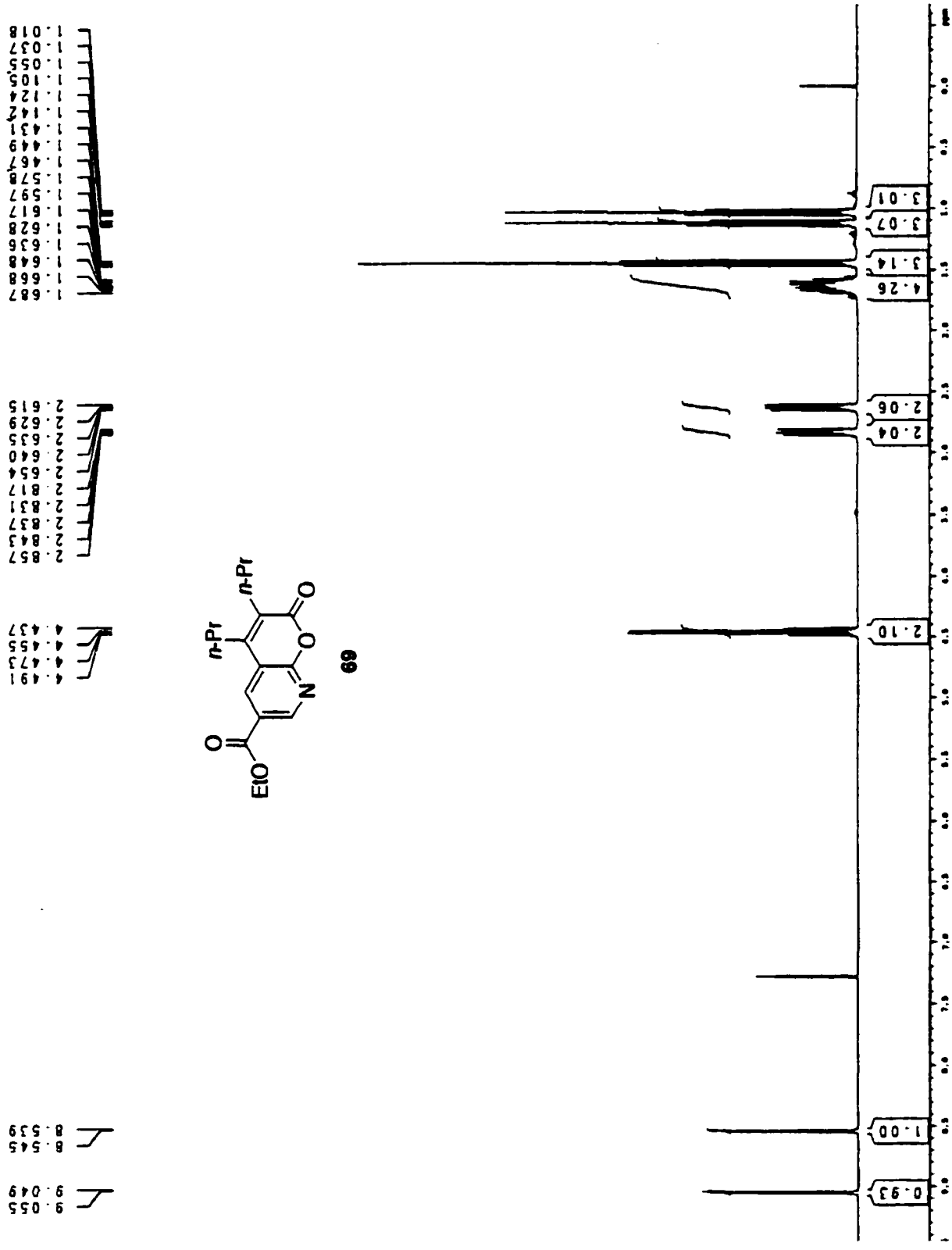
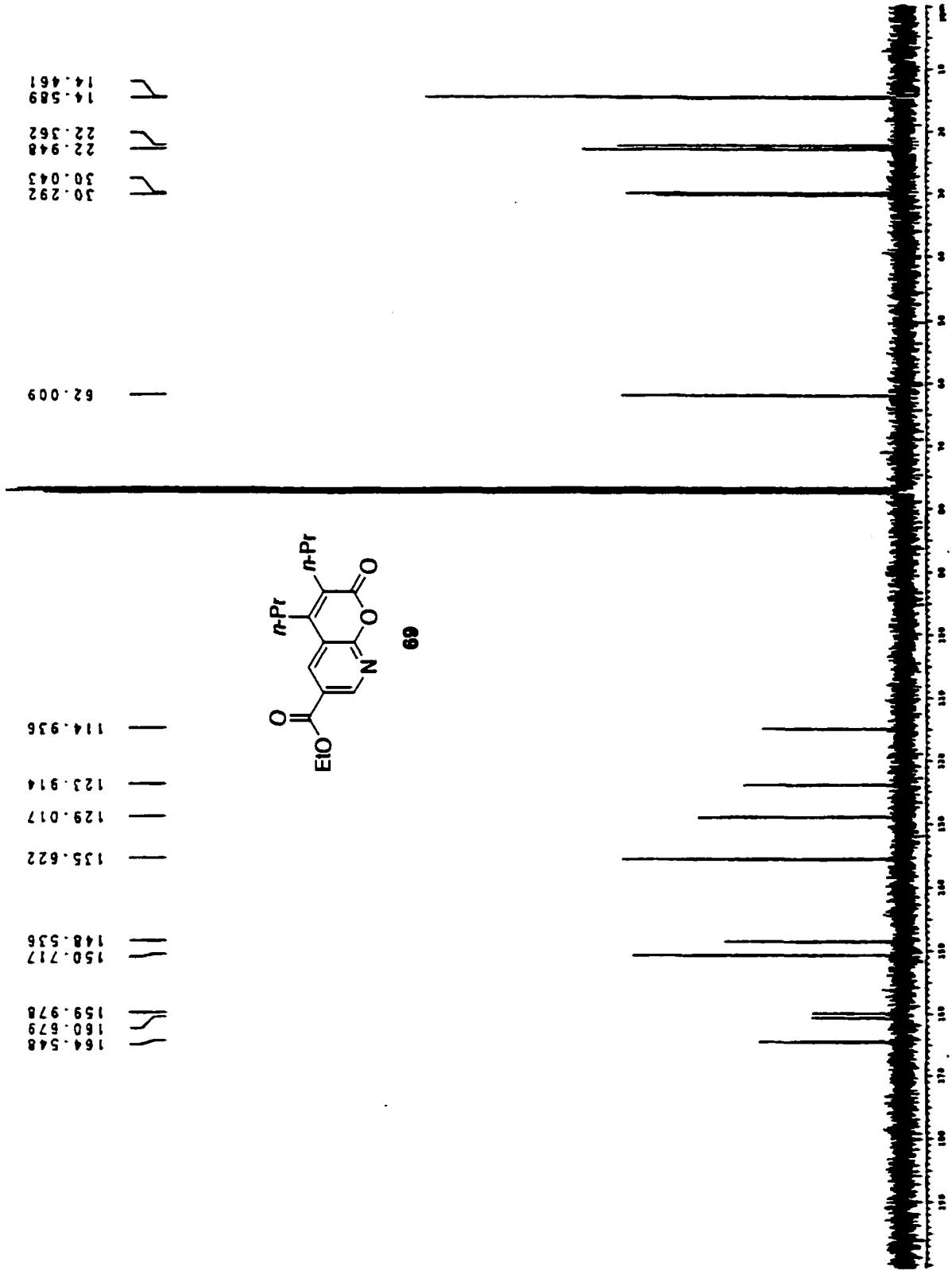
O
O
O

66


n-Pr
n-Pr
O
O
N
O
EtO
O
69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135.622
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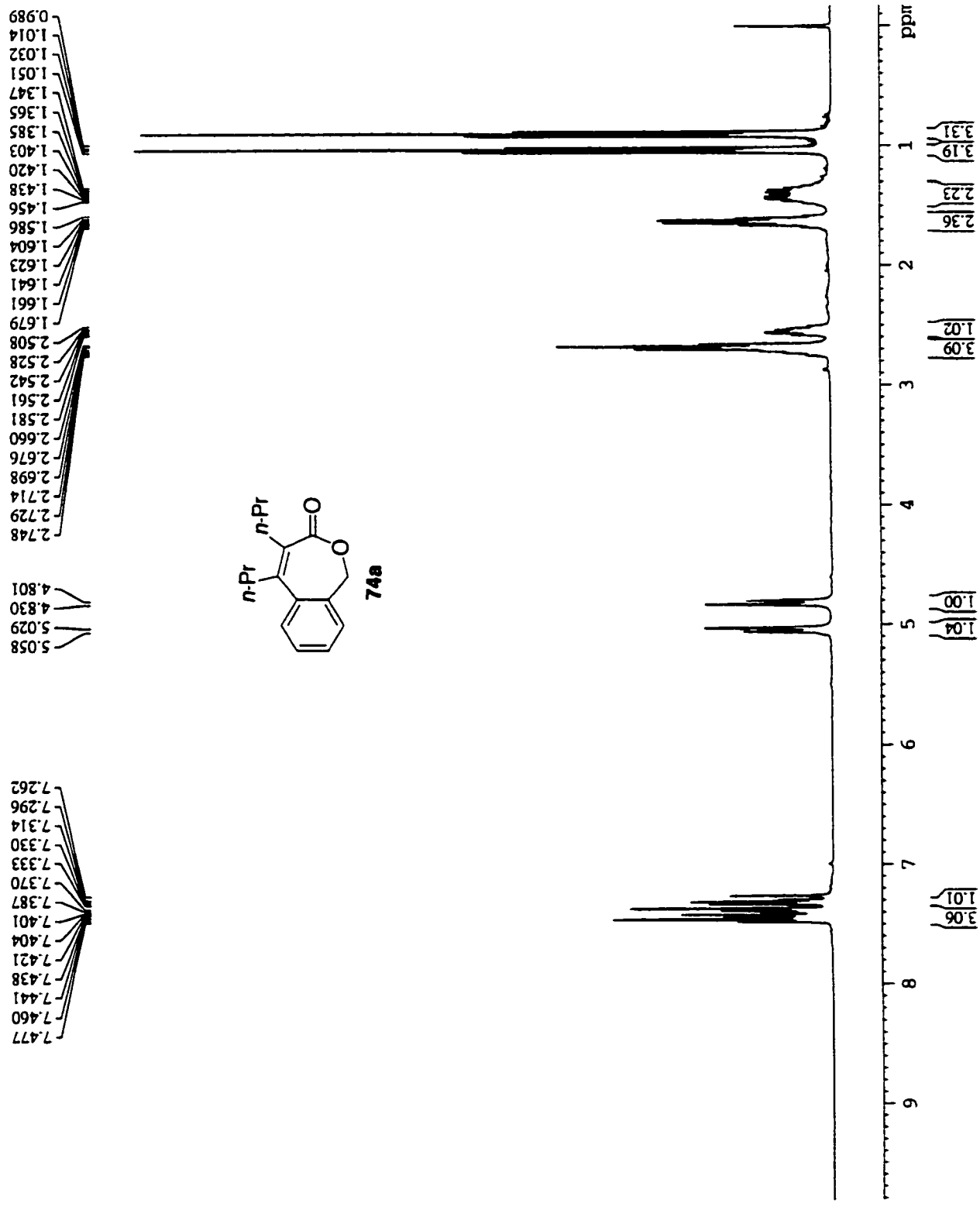
160.679
164.548
n-Pr
n-Pr
EtO
69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1.604
1.623
1.641
1.661
1.679
2.508
2.528
2.542
2.561
2.581
2.660
2.676
2.698
2.714
2.729
2.748
4.801
4.830
5.029
5.058
7.262
7.296
7.314
7.330
7.333
7.370
7.387
7.401
7.404
7.421
7.438
7.441
7.460
7.477
n-Pr
n-Pr
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O
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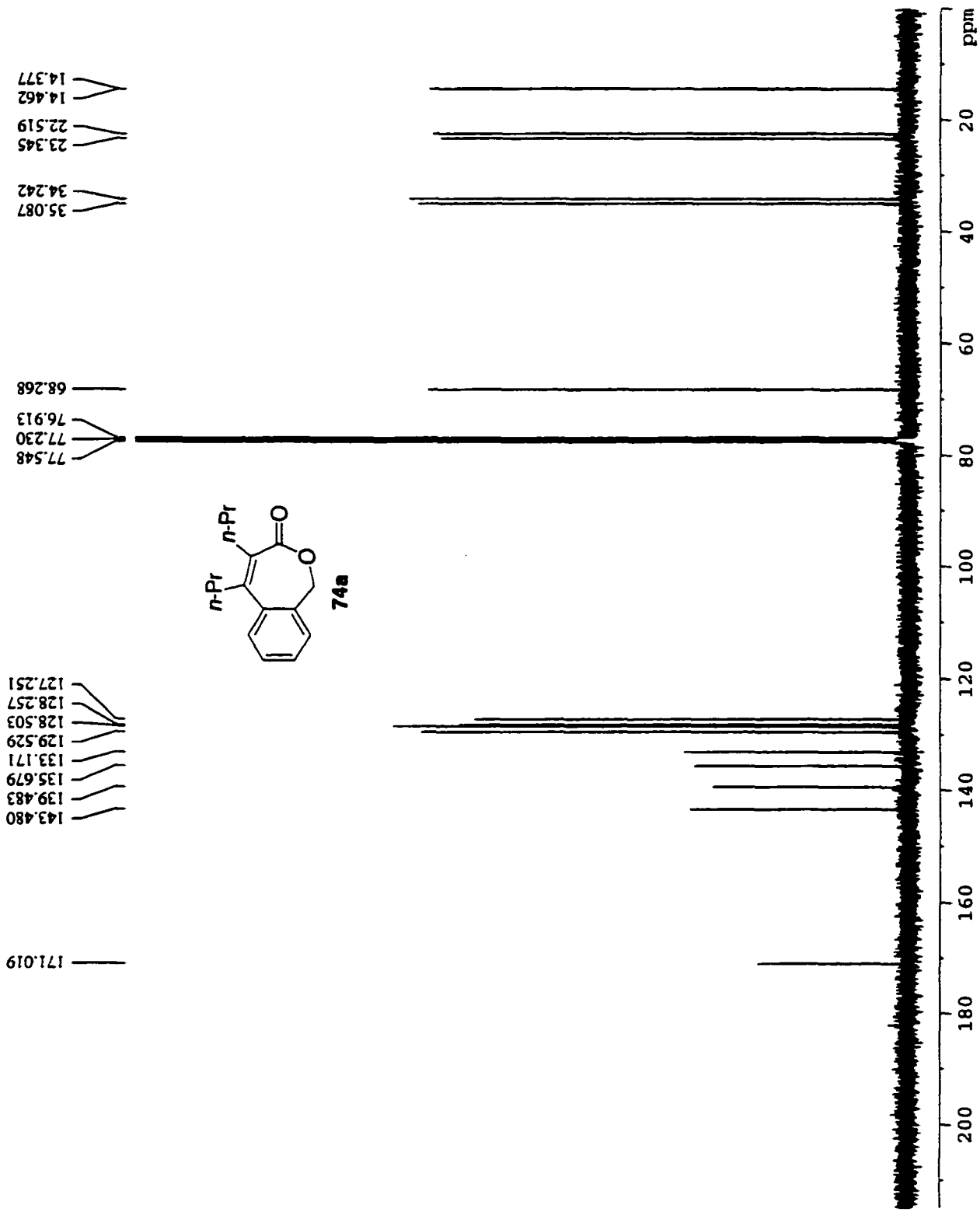
3.09
1.00
1.04
1.01
3.06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76.913
77.230
77.548
127.251
128.257
128.503
129.529
133.171
135.679
139.483
143.480
171.019
n-Pr
n-Pr
74a
ppm
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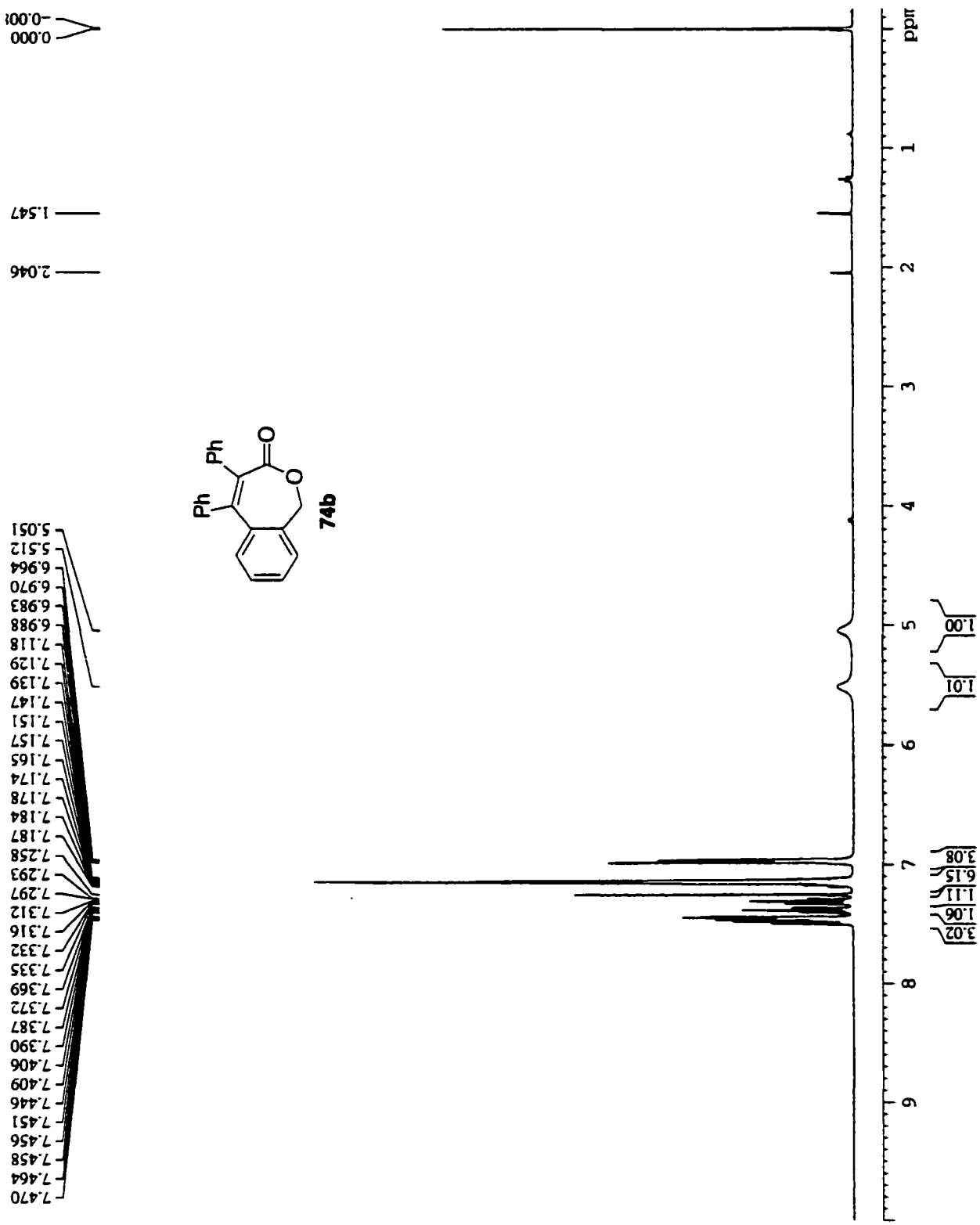
40
60
80
100
120
140
160
180
200


Ph
Ph
O
O
74b
ppm
1 2 3 4 5 6 7 8 9
1.00
1.01
3.02
1.06
1.11
6.15
3.08
0.000
-0.003
1.547
2.046
5.051
5.512
6.964
6.970
6.983
6.988
7.118
7.129
7.139
7.147
7.151
7.157
7.165
7.174
7.178
7.184
7.187
7.258
7.293
7.297
7.312
7.316
7.332
7.335
7.369
7.372
7.387
7.390
7.406
7.409
7.446
7.451
7.456
7.458
7.464
7.470

169.324
145.333
140.445
140.240
136.695
136.062
133.022
131.324
131.225
130.733
129.486
129.399
128.363
128.136
127.965
127.914
127.706
77.550
77.233
76.915
68.599
74b
Ph
Ph
O
O
200
180
160
140
120
100
80
60
40
20
ppm

APPENDIX B. CHAPTER II ^{1}H AND ^{13}C NMR SPECTRA

8.168
8.164
8.147
8.143
7.739
7.735
7.719
7.716
7.330
7.327
7.309
7.291
7.288
7.265
6.826
6.769
6.765
6.751
6.749
6.747
6.731
6.727
3.095
1.699
0.000
1.00
1.00
1.05
0.97
1.08
6.39
ppm
Table 1, entry 5
N(CH3)2

155.329
139.774
138.614
129.406
124.476
121.050
89.909
77.549
77.231
76.914
36.748
Table 1, entry 5
N(CH3)2
O
N
H
I
ppm

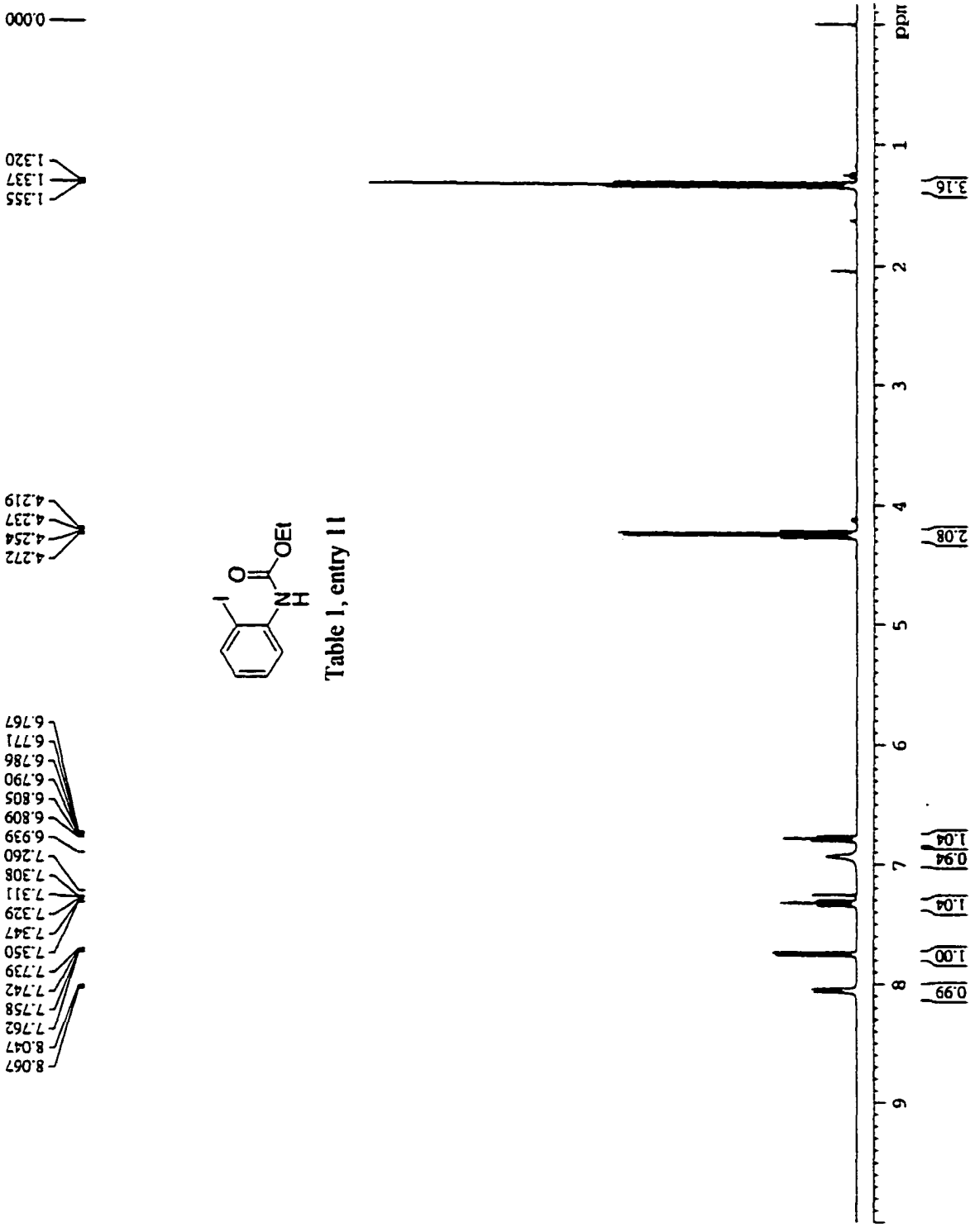
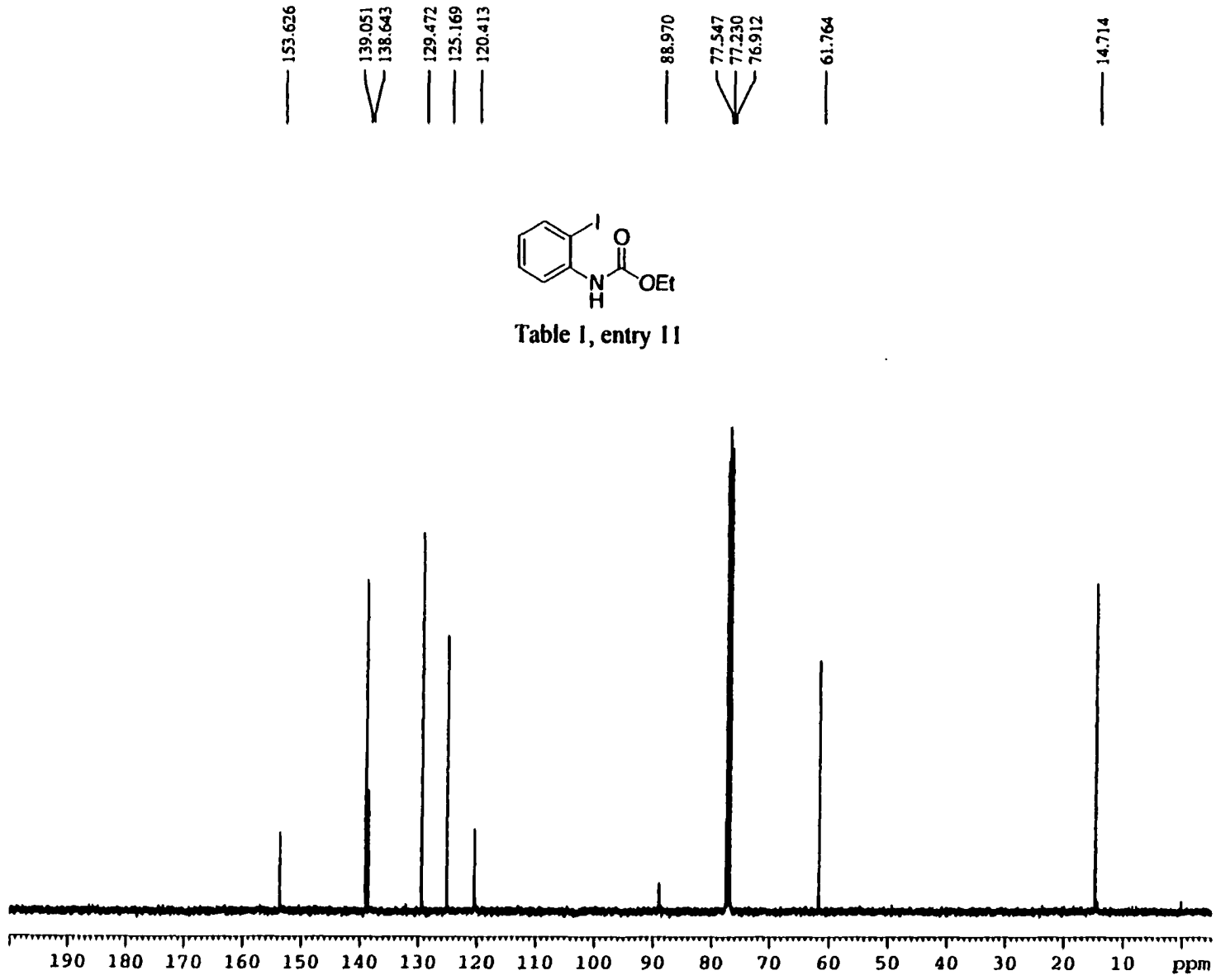


Table 1, entry 11



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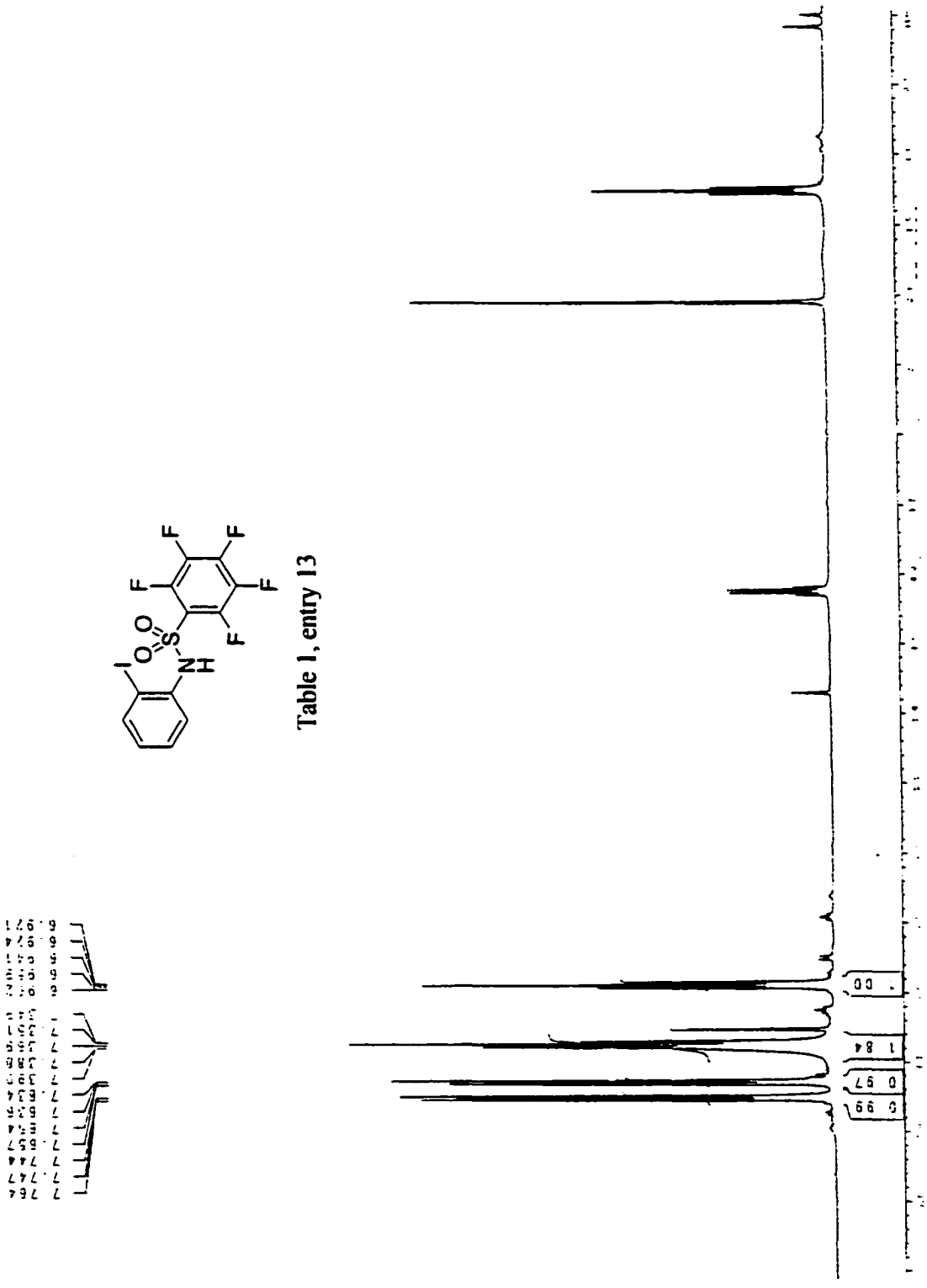

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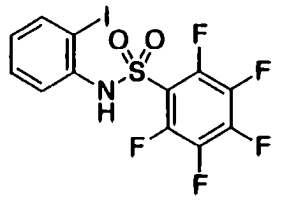


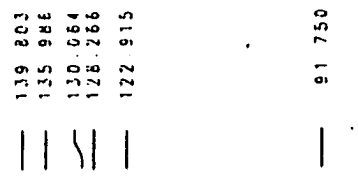
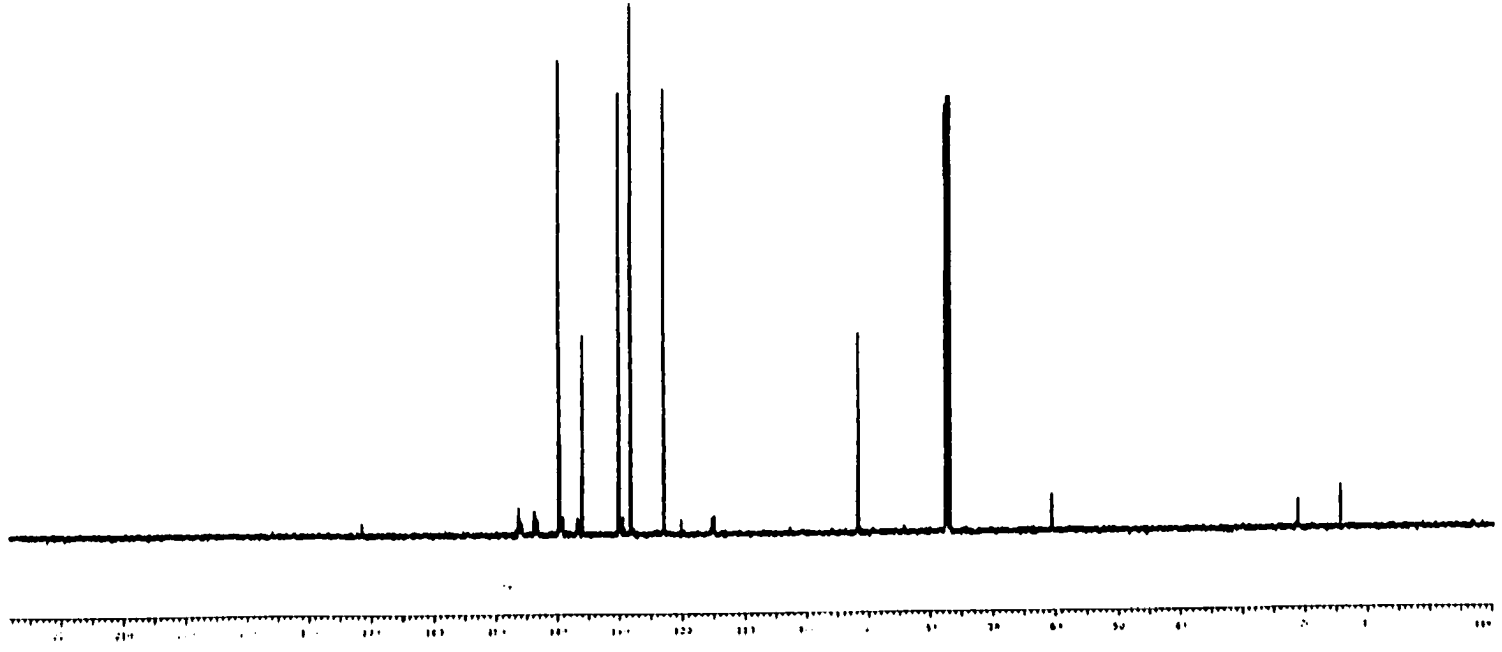
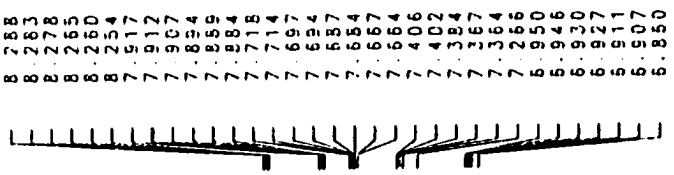
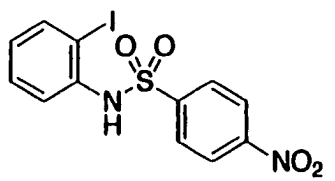


Table 1, entry 13
(signals from C6F5 are not shown)







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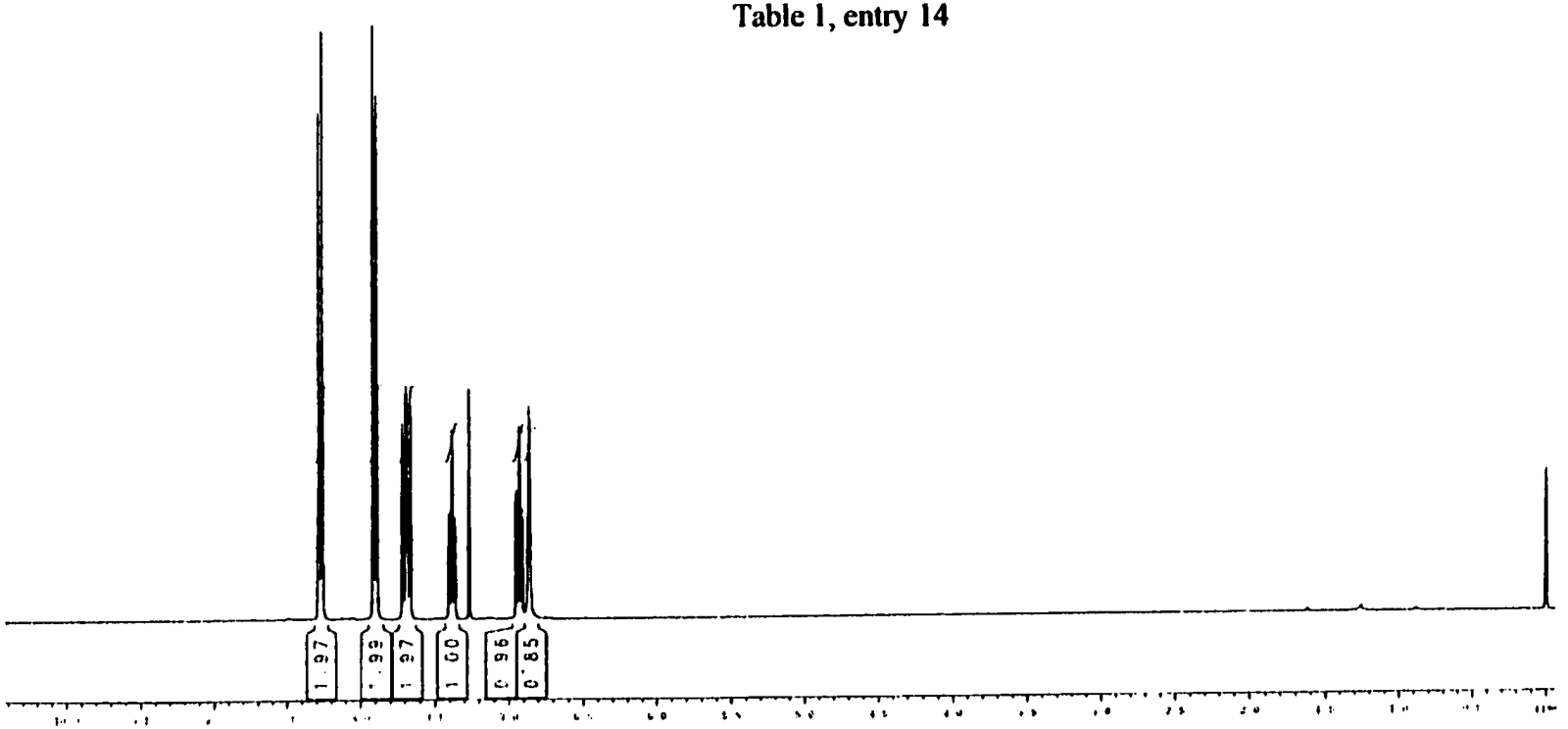

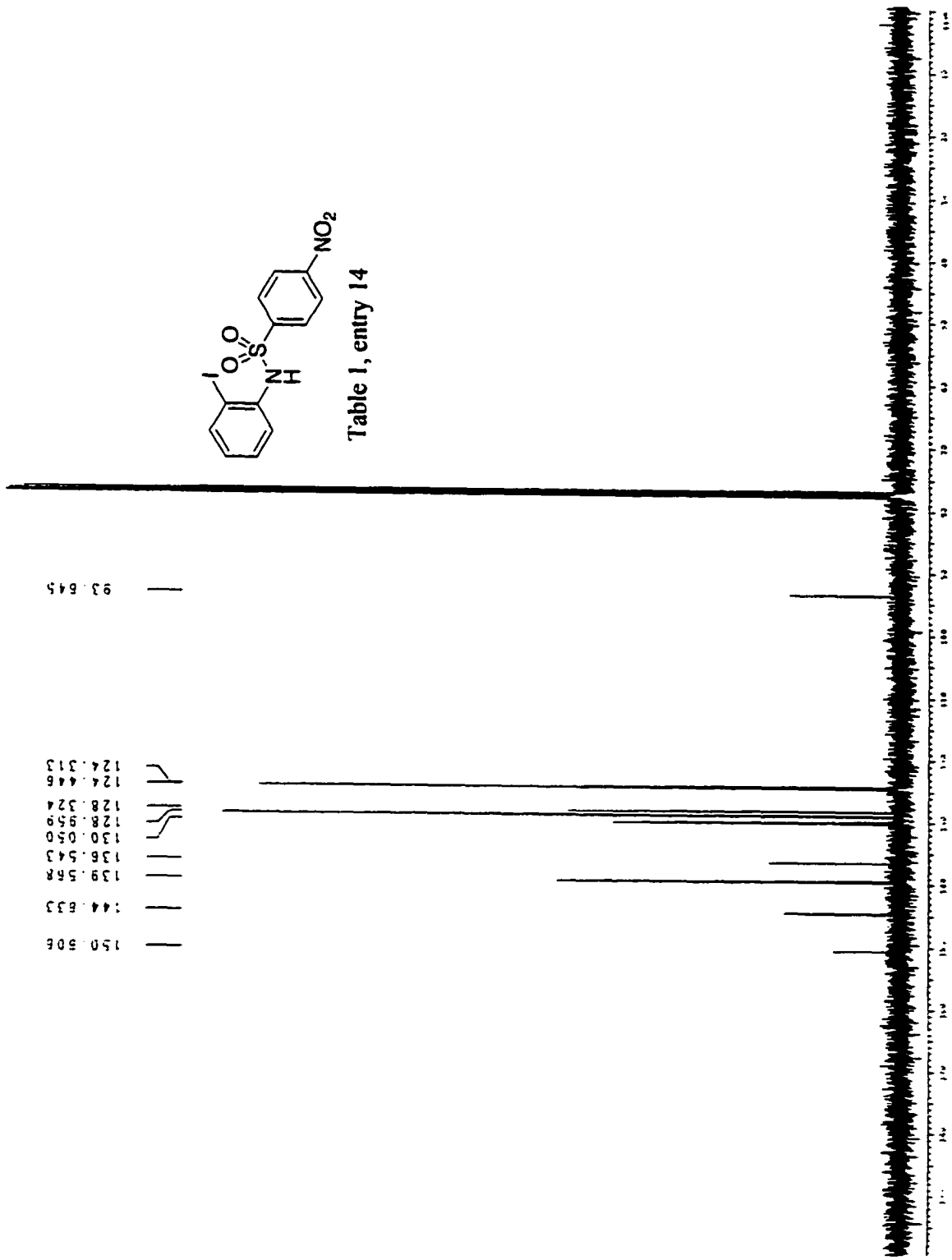
Table 1, entry 14
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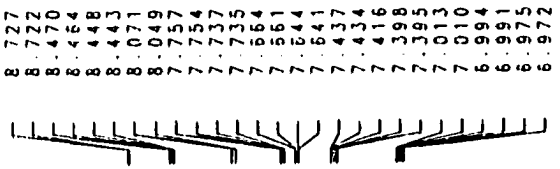
130.050
128.959
128.324
124.446
124.313
93.645



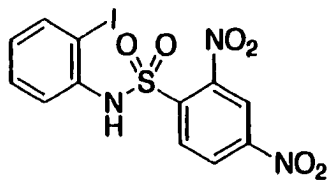
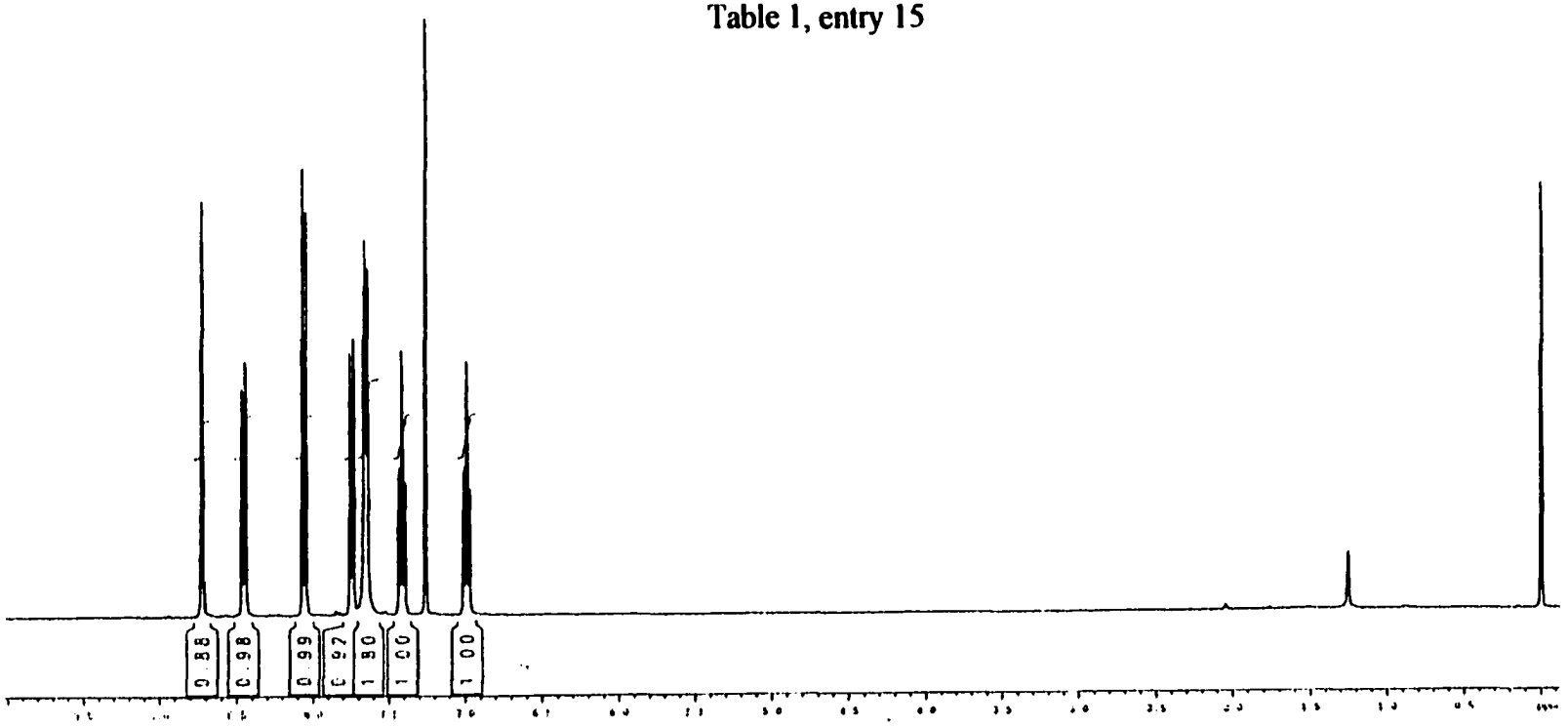


Table 1, entry 15



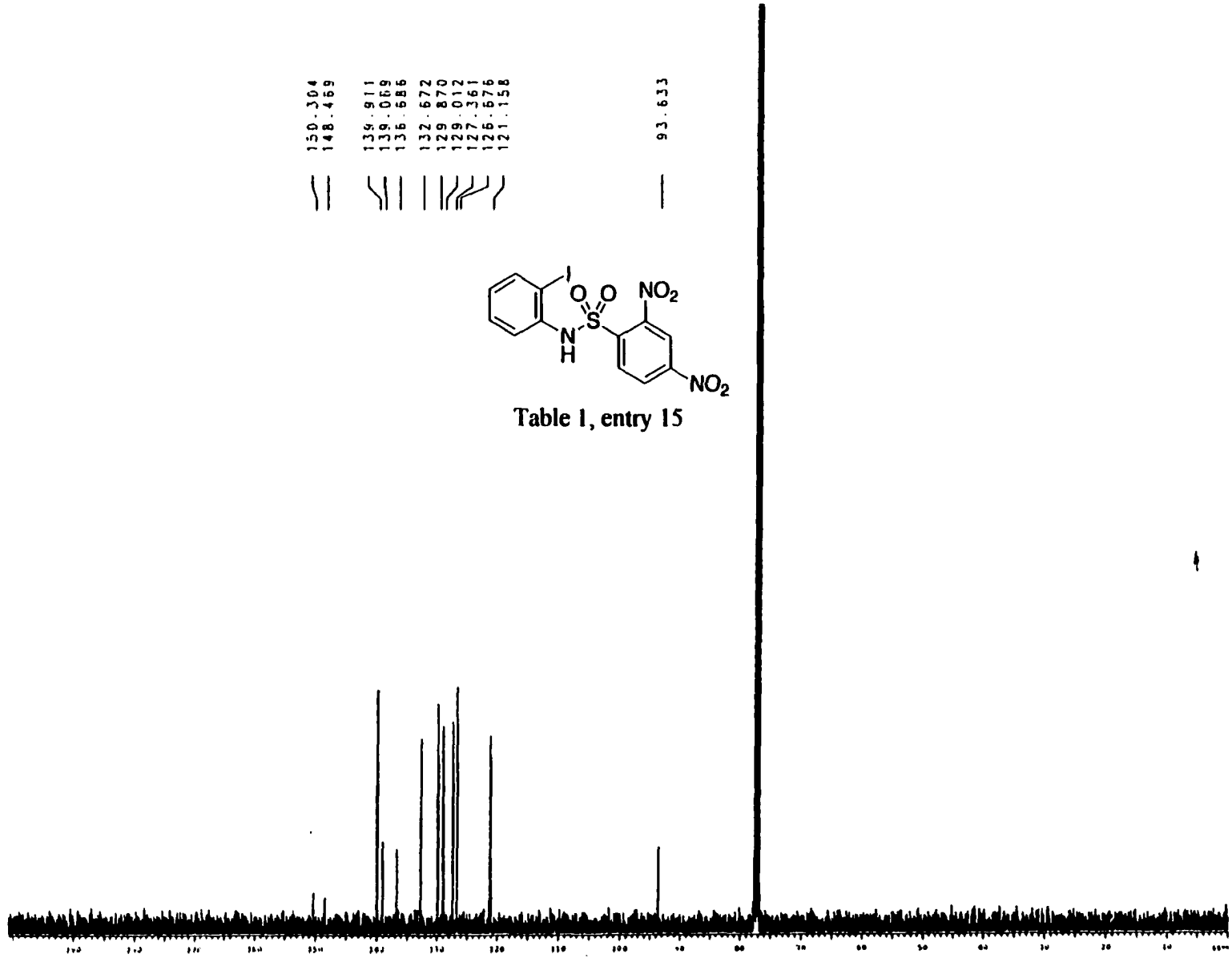
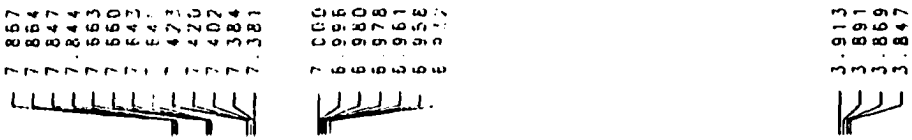


Table 1, entry 15



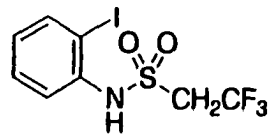
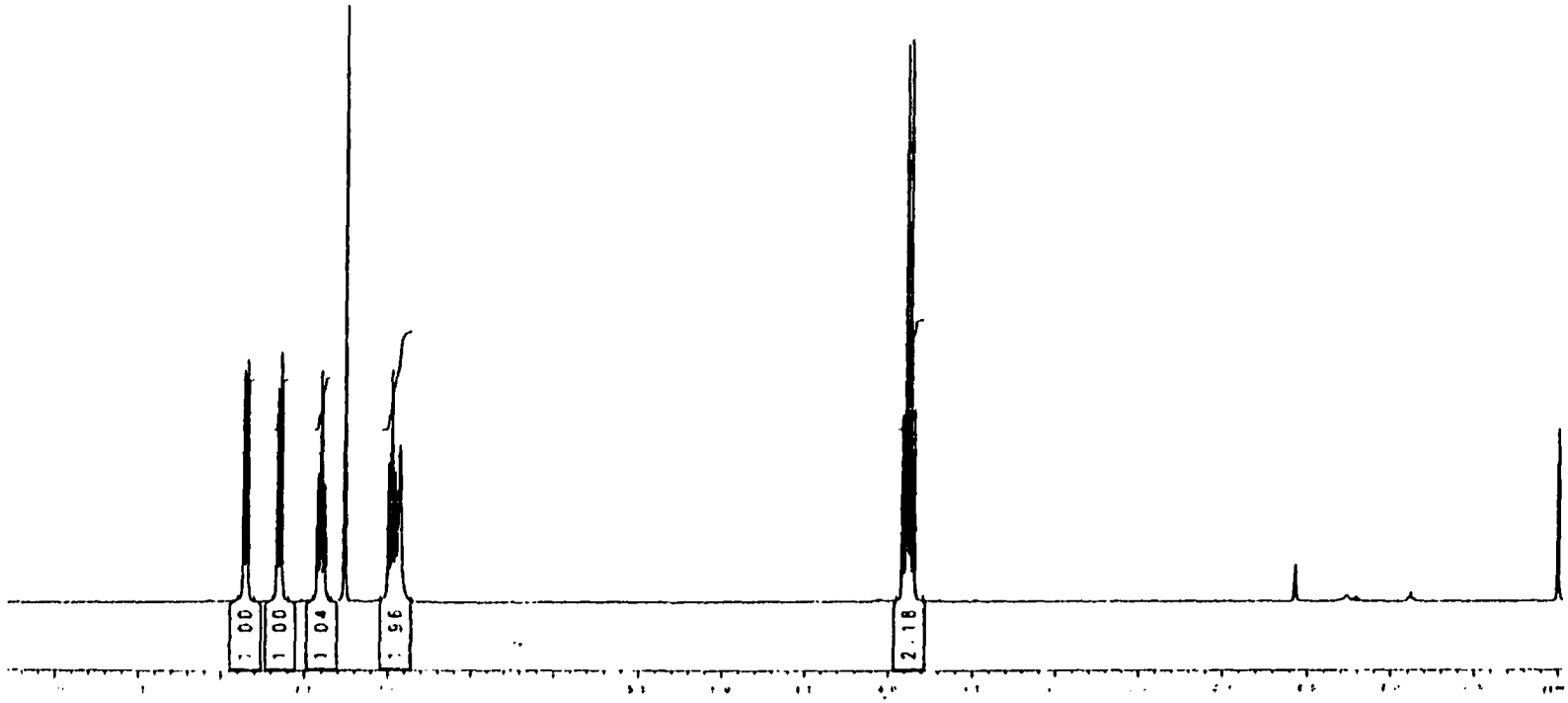
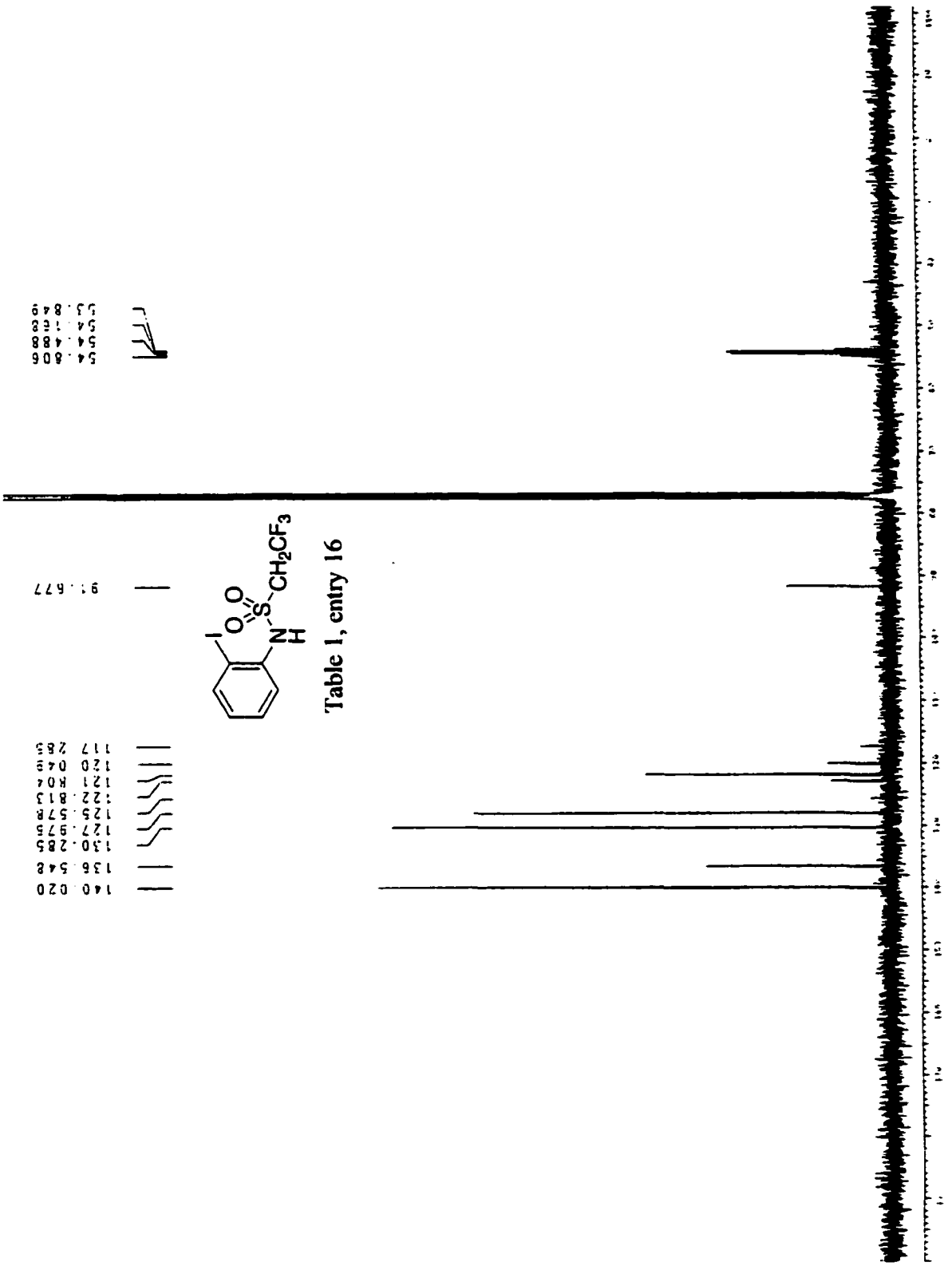
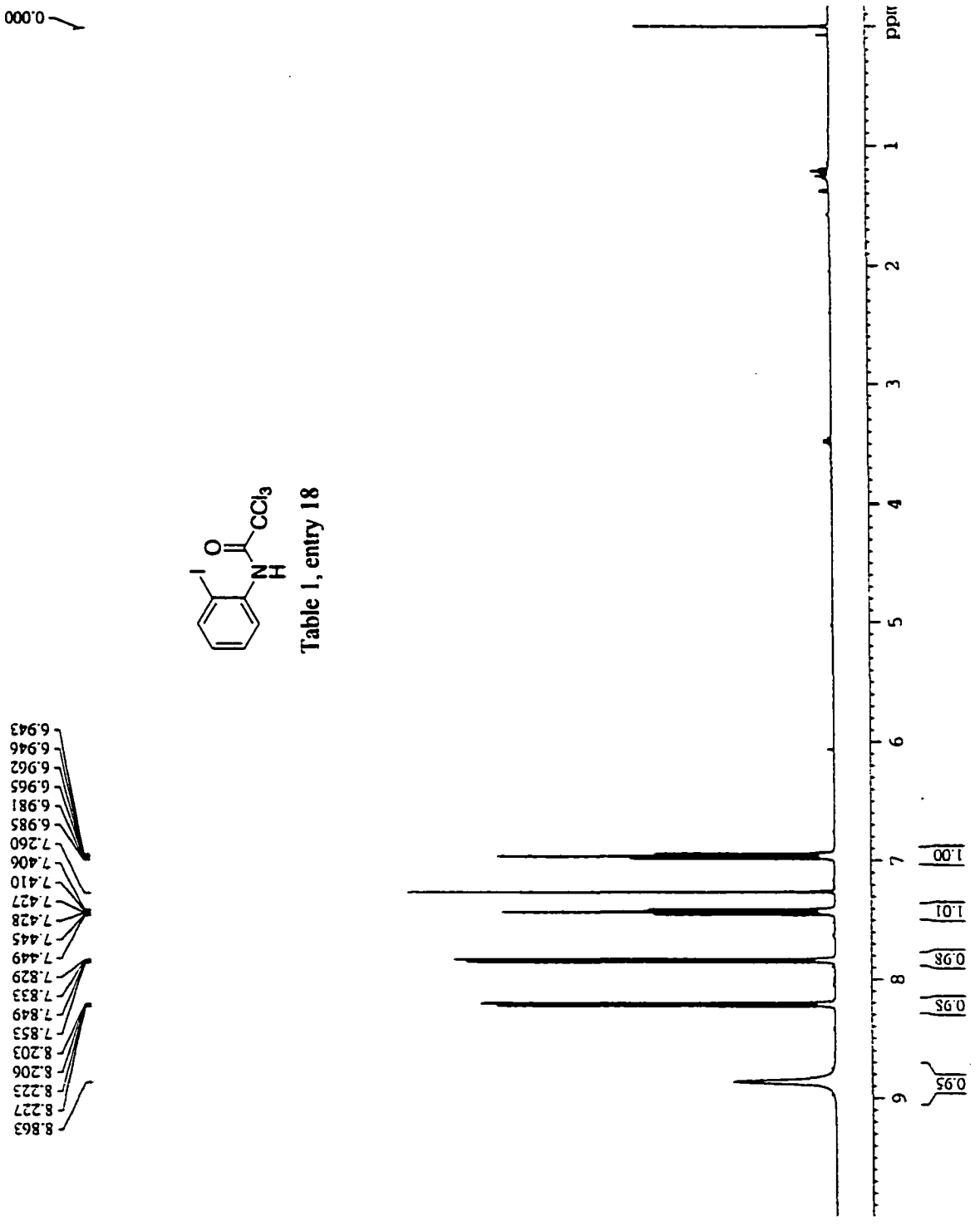


Table 1, entry 16




54.806
54.488
54.168
53.849
91.677
140.020
136.548
130.285
127.975
125.578
122.813
121.804
120.049
117.285
Table 1, entry 16


0.000
8.863
8.227
8.223
8.206
8.203
7.853
7.849
7.833
7.829
7.449
7.445
7.428
7.427
7.410
7.406
7.260
6.985
6.981
6.965
6.962
6.946
6.943
O
CCl3
N
H
I
Table 1, entry 18
ppm
1
2
3
4
5
6
7
8
9
1.00
1.01
0.98
0.95
0.95

159.673
139.352
136.856
129.762
127.663
121.811
92.941
90.535
77.545
77.430
77.228
76.910
Table 1, entry 18
ppm

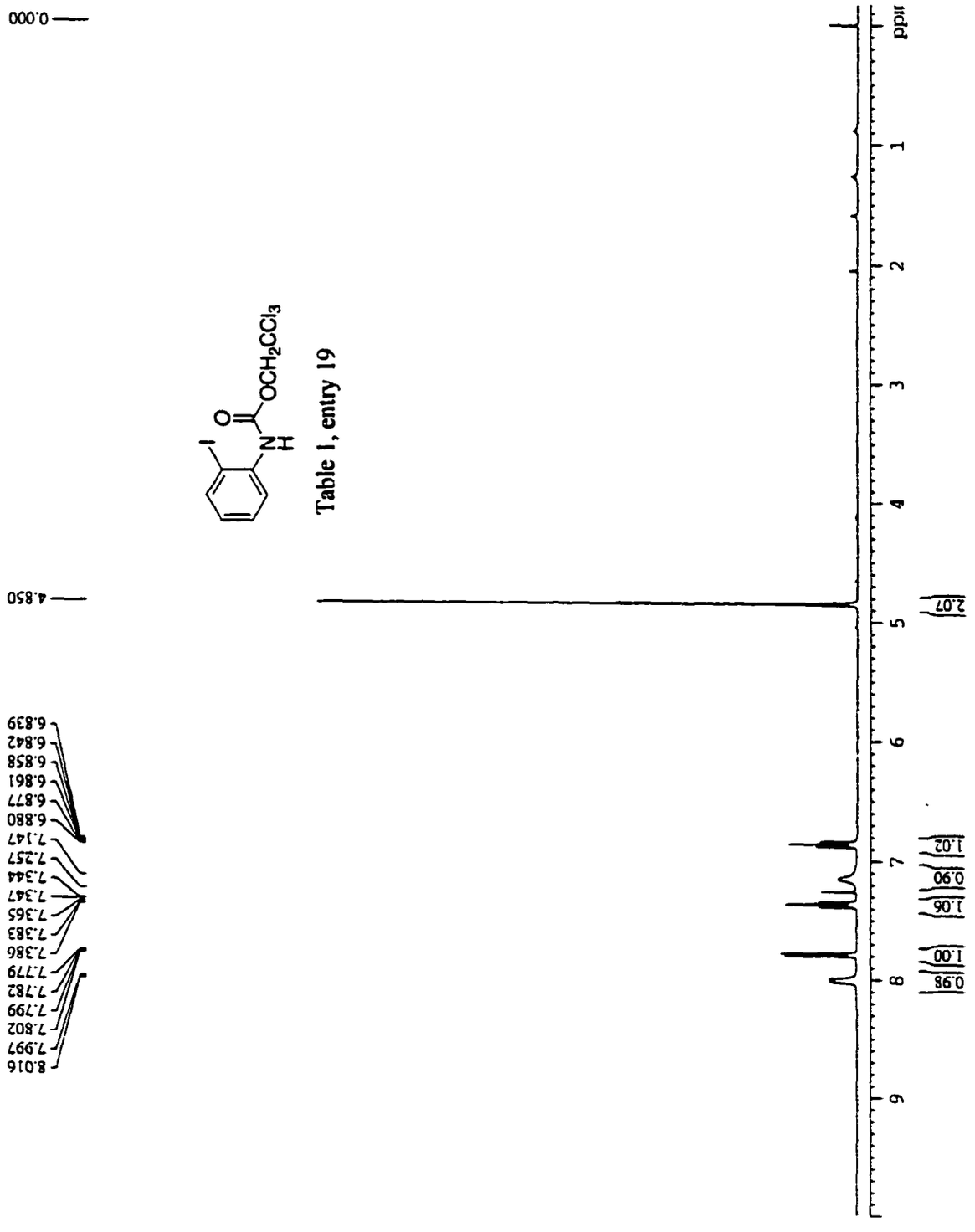


Table 1, entry 19
OCH2CCl3
O
N
H
ppm
0.000
4.850
8.016
7.997
7.802
7.799
7.782
7.779
7.386
7.383
7.365
7.347
7.344
7.257
7.147
6.880
6.877
6.861
6.858
6.842
6.839
2.07
1.02
0.90
1.06
1.00
0.98

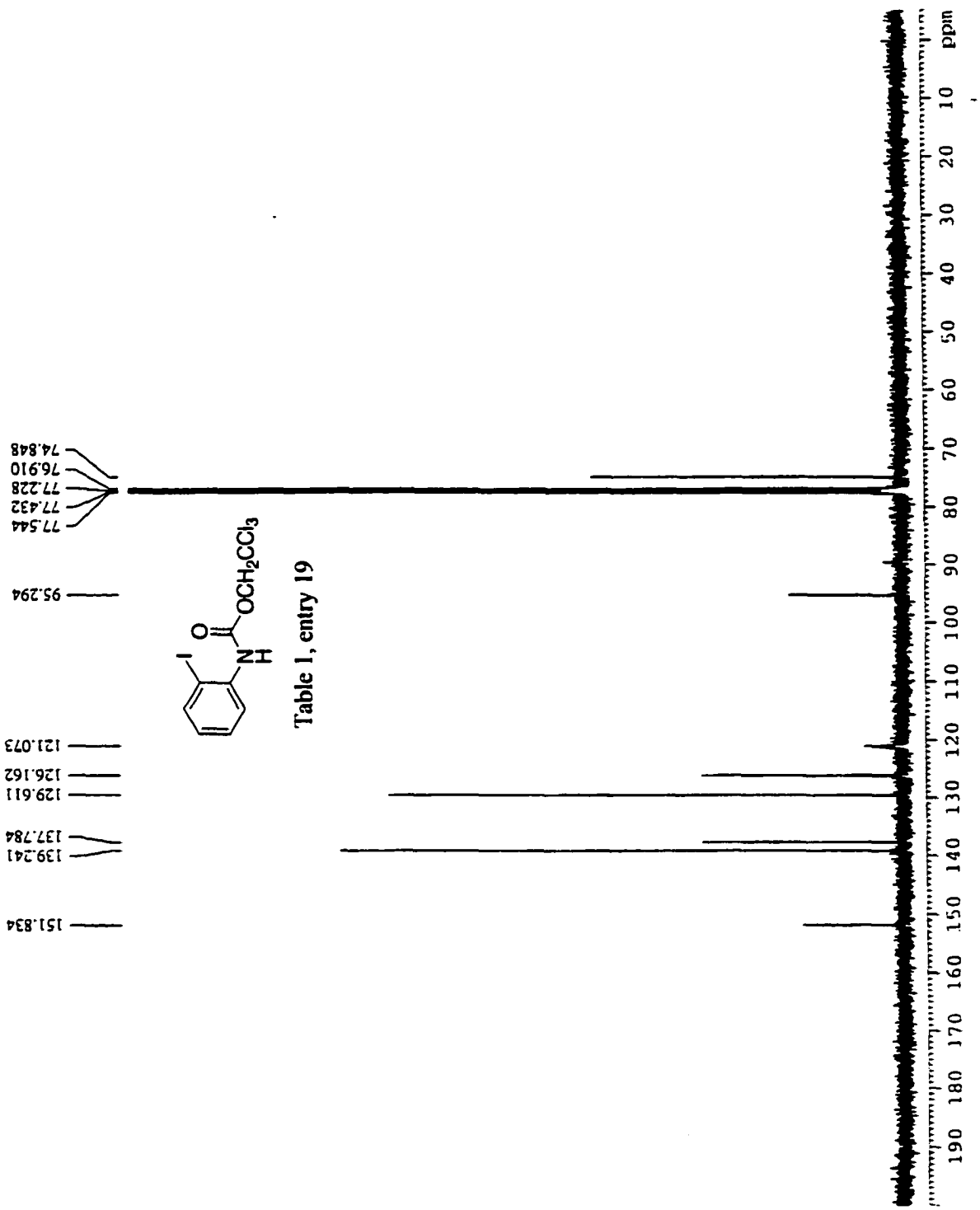
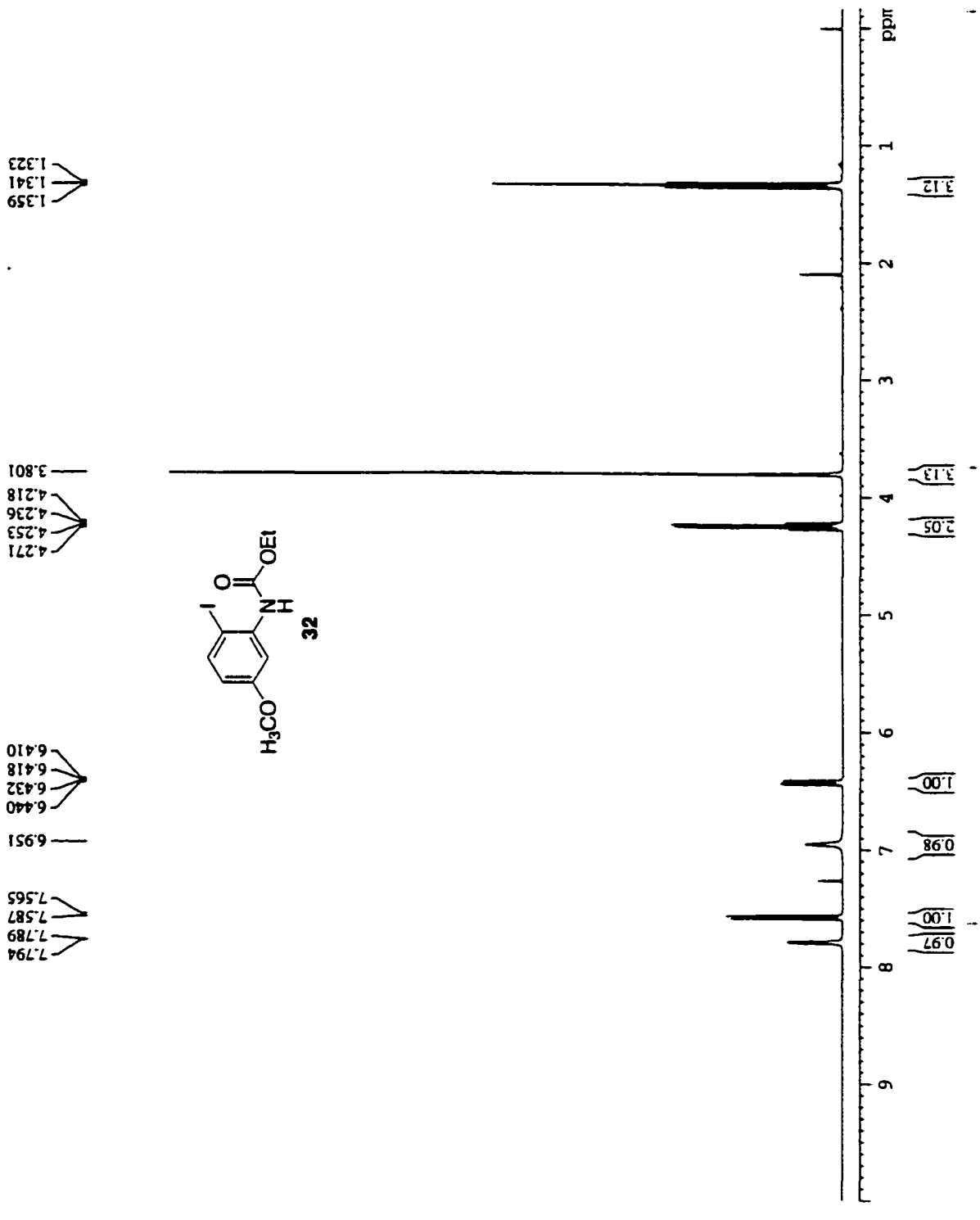
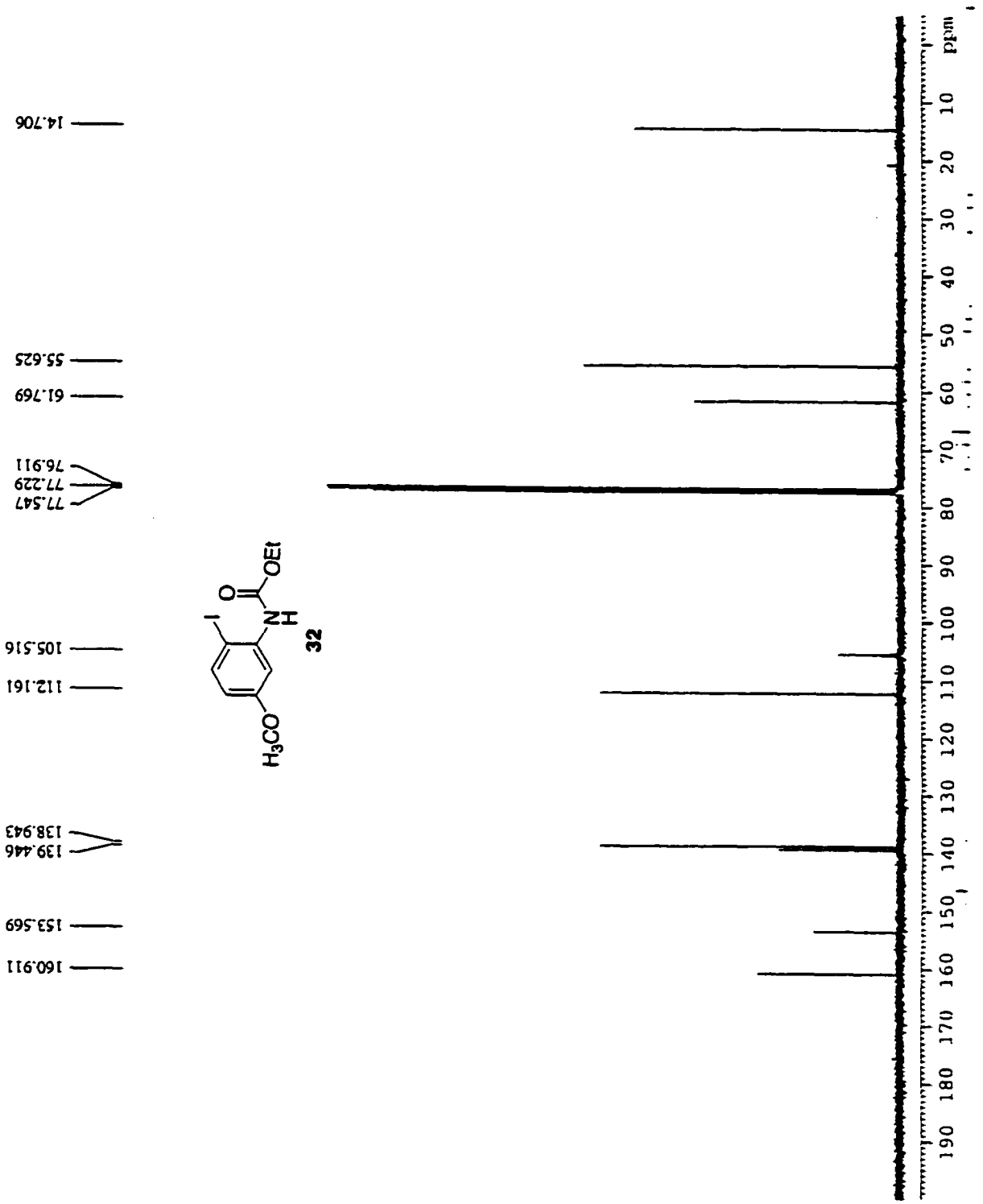
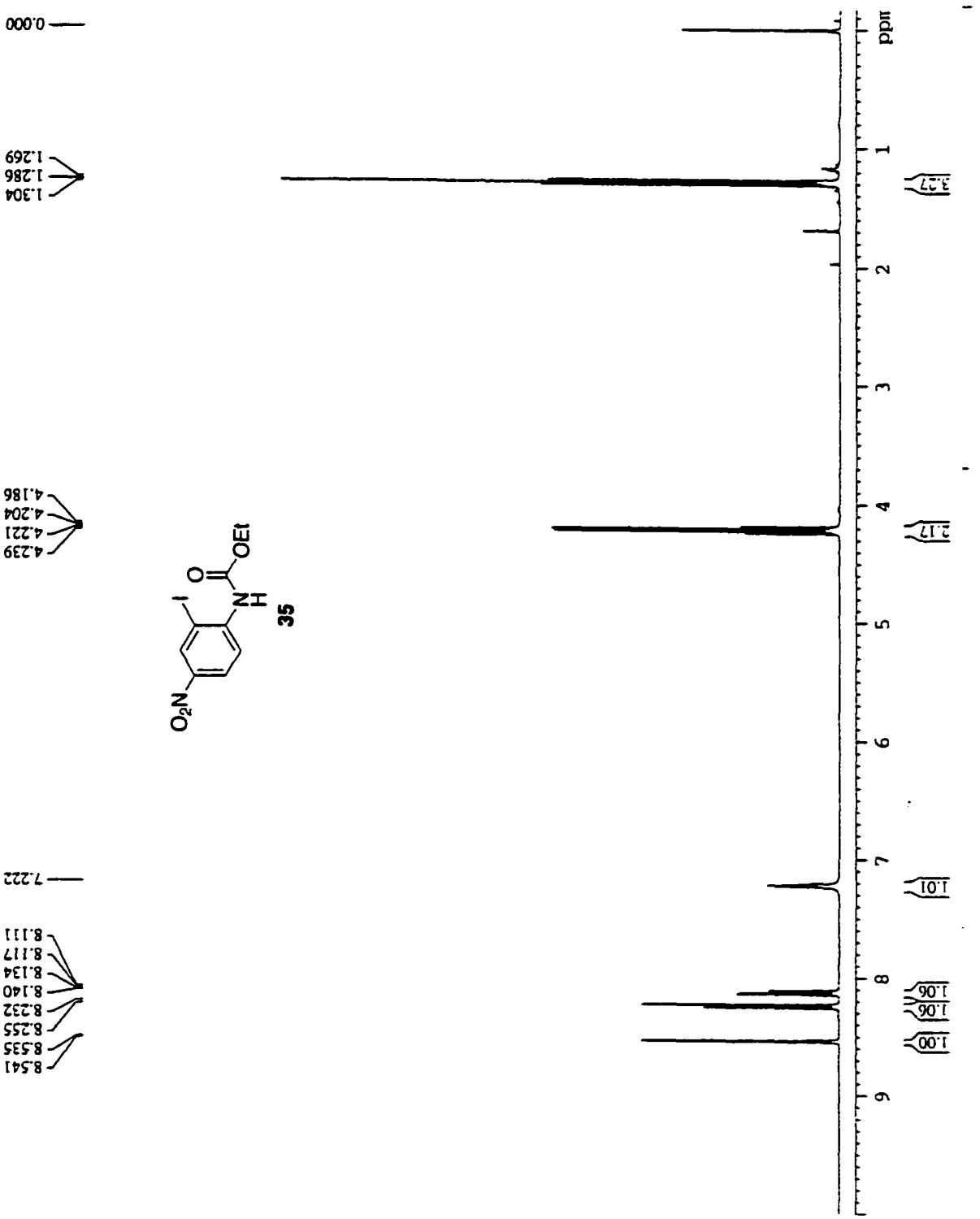
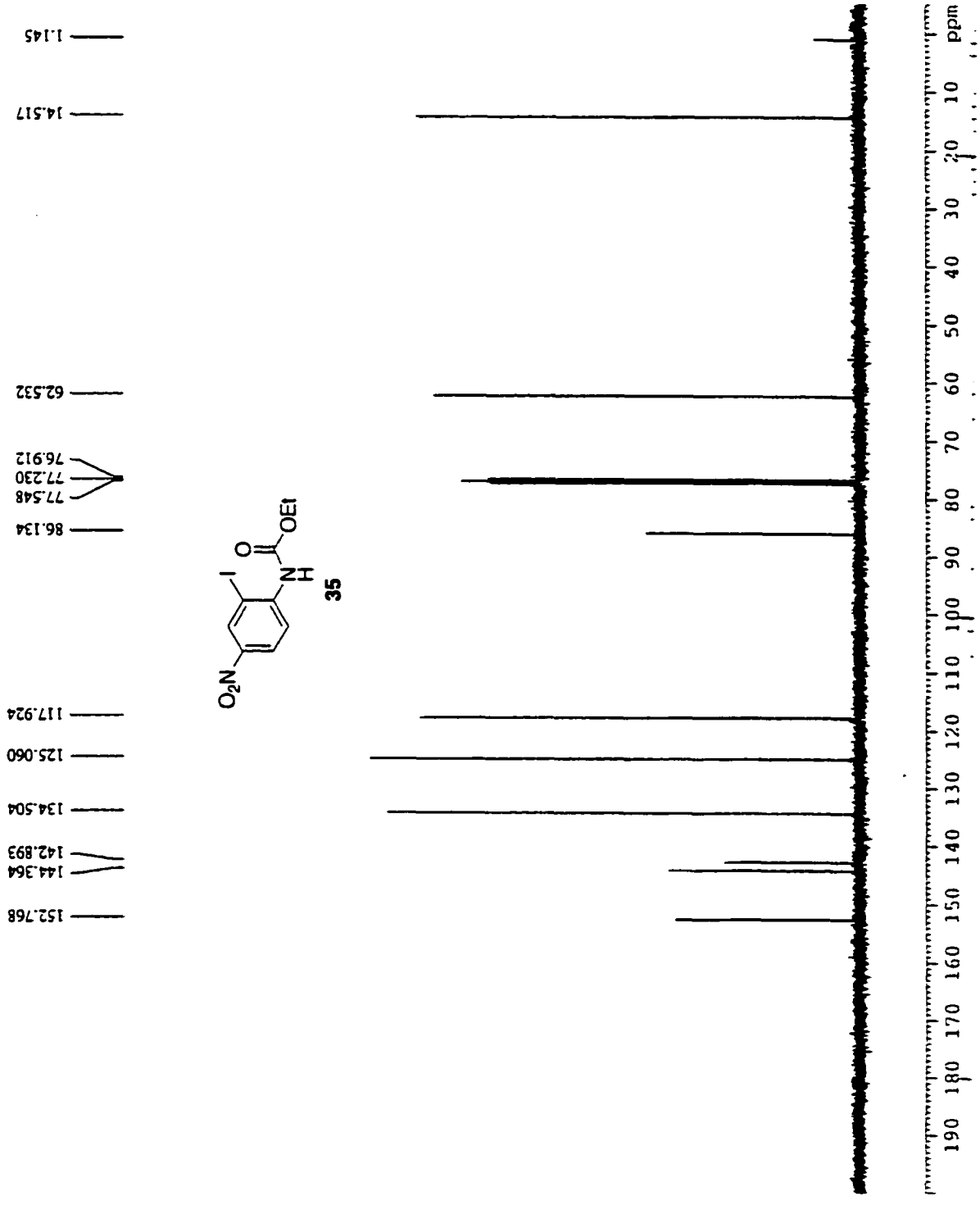


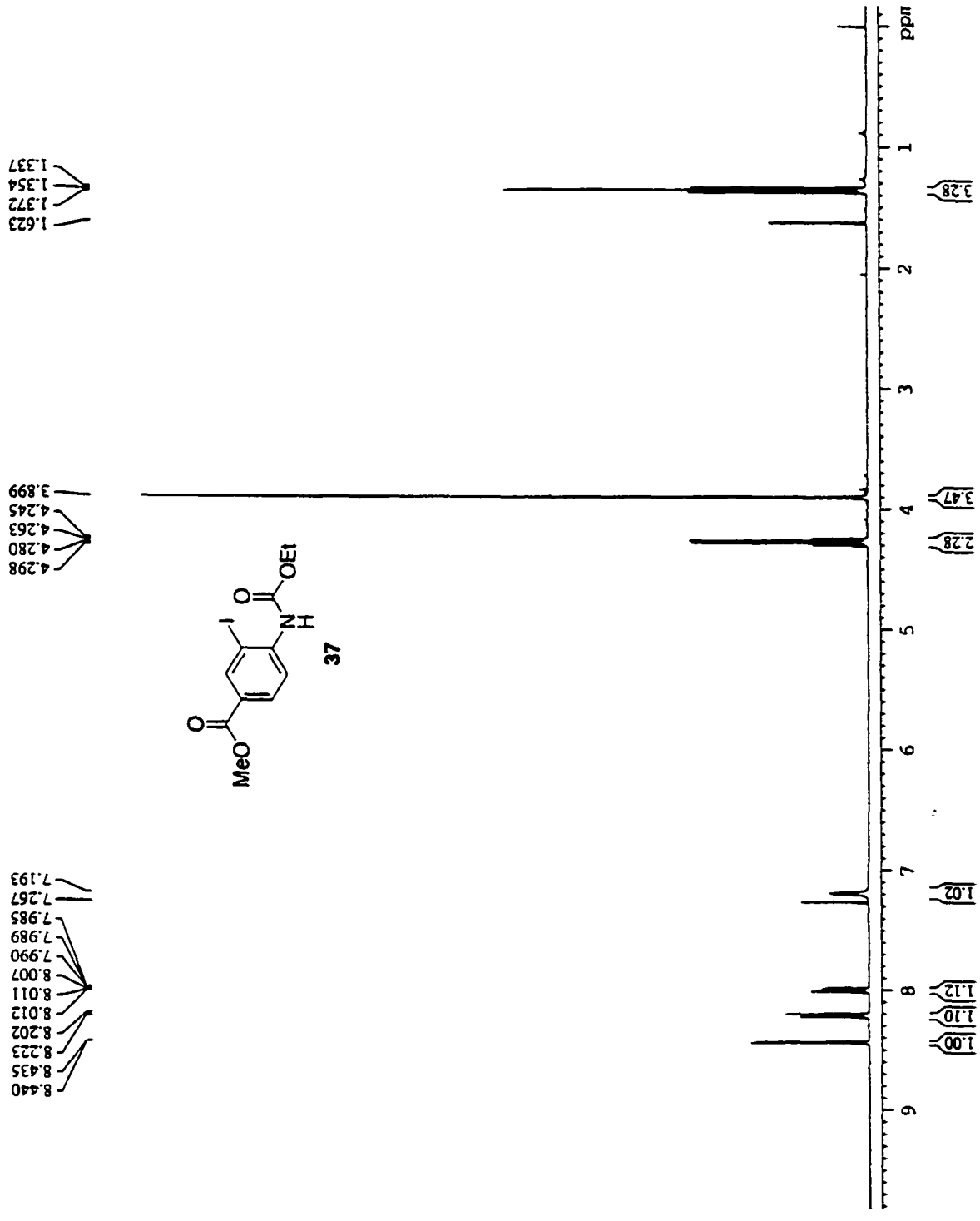
Table 1, entry 19

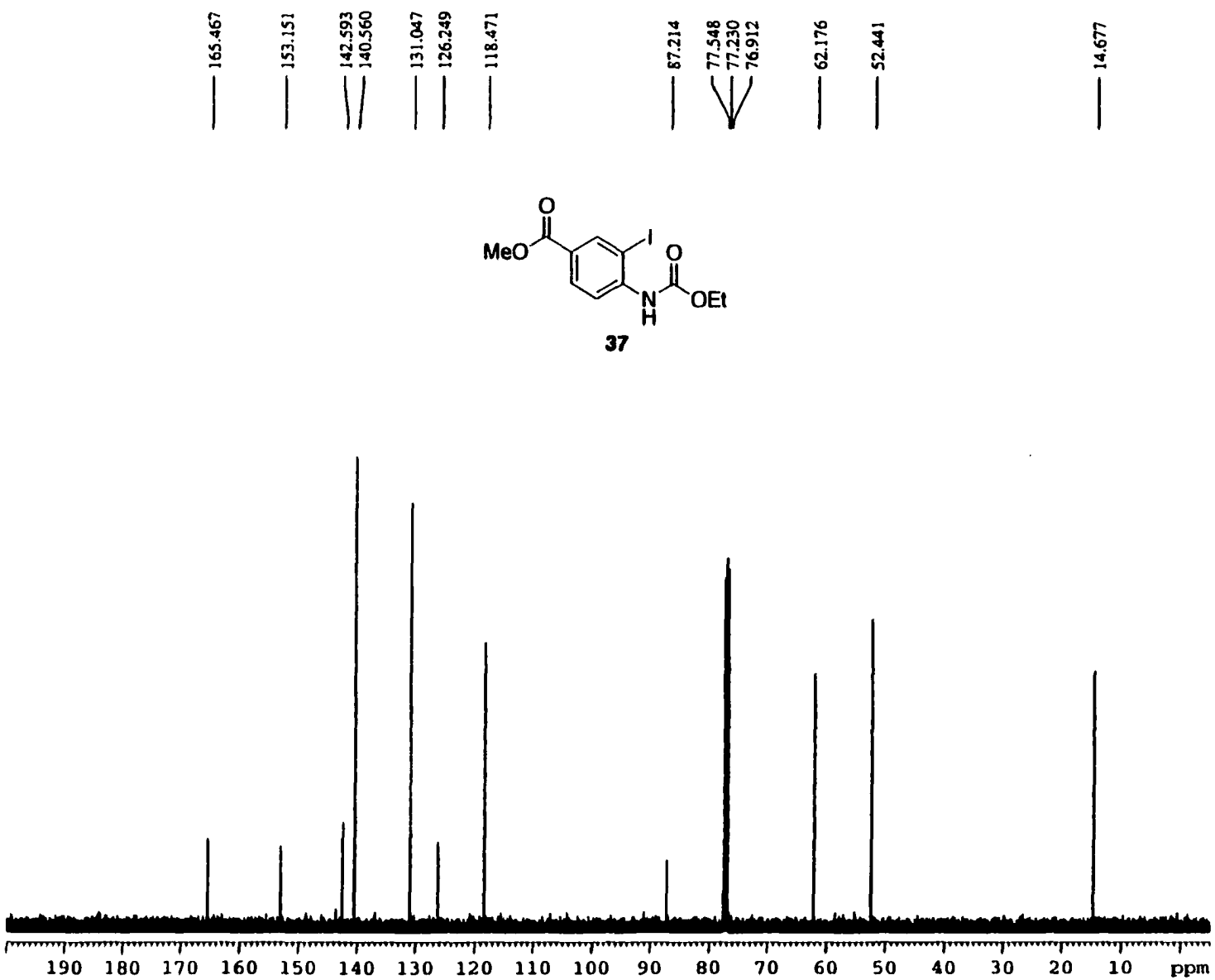

1.323
1.341
1.359
3.801
4.218
4.236
4.253
4.271
6.410
6.418
6.432
6.440
6.951
7.565
7.587
7.789
7.794
OEt
O
N
H
I
H3CO
32
ppm
1
2
3
4
5
6
7
8
9
3.12
3.13
2.05
1.00
0.98
1.00
0.97

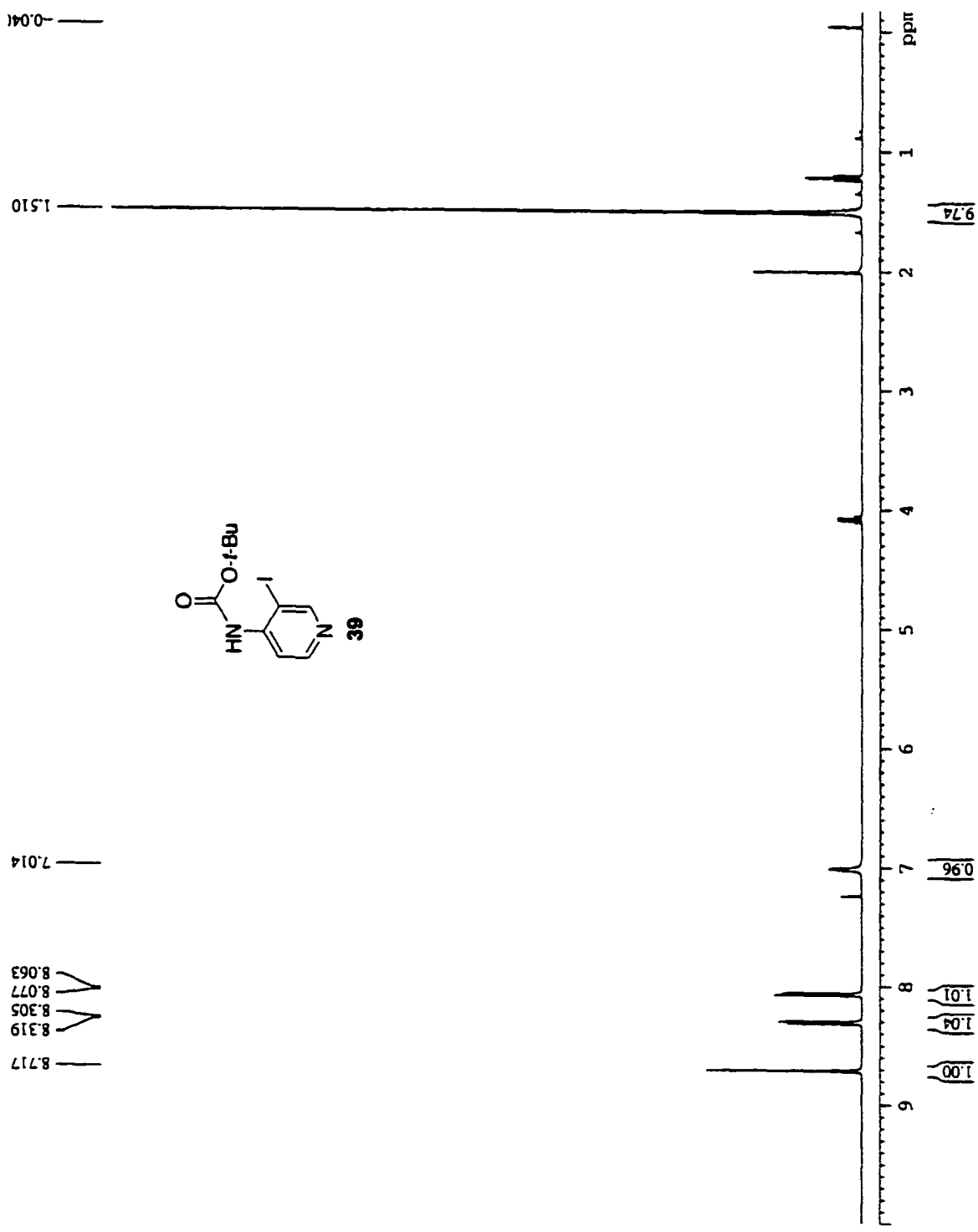

14.706
55.625
61.769
76.911
77.229
77.547
105.516
112.161
138.943
139.446
153.569
160.911
O
OEt
N
H
I
H3CO
32
ppm

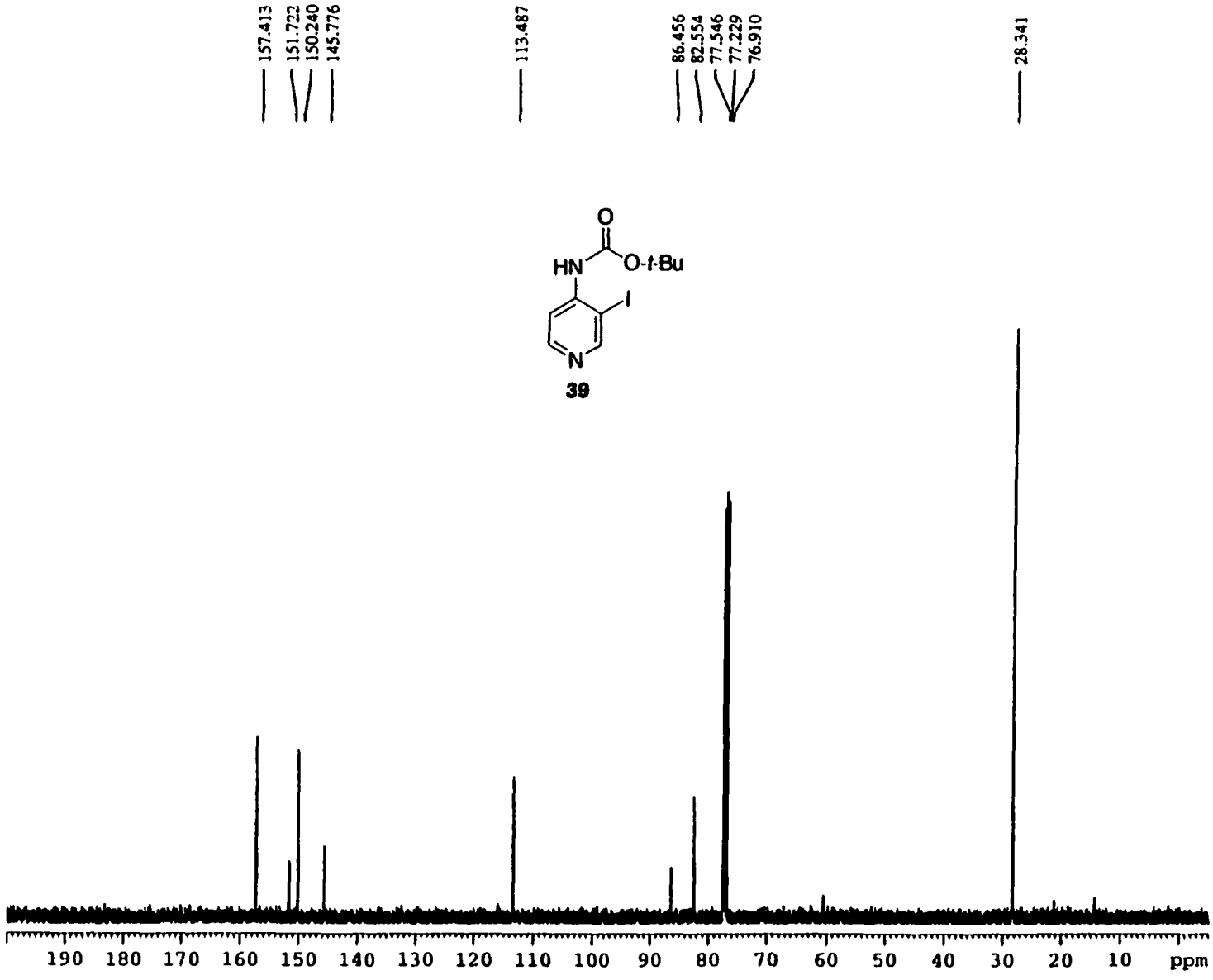

0.000
1.269
1.286
1.304
4.186
4.204
4.221
4.239
7.222
8.111
8.117
8.134
8.140
8.232
8.255
8.535
8.541
OEt
O
N
H
I
O2N
35
ppm
1
2
3
4
5
6
7
8
9
3.27
2.17
1.01
1.06
1.06
1.00


1.145
14.517
62.532
76.912
77.230
77.548
86.134
117.924
125.060
134.504
142.893
144.364
152.768
35
ppm

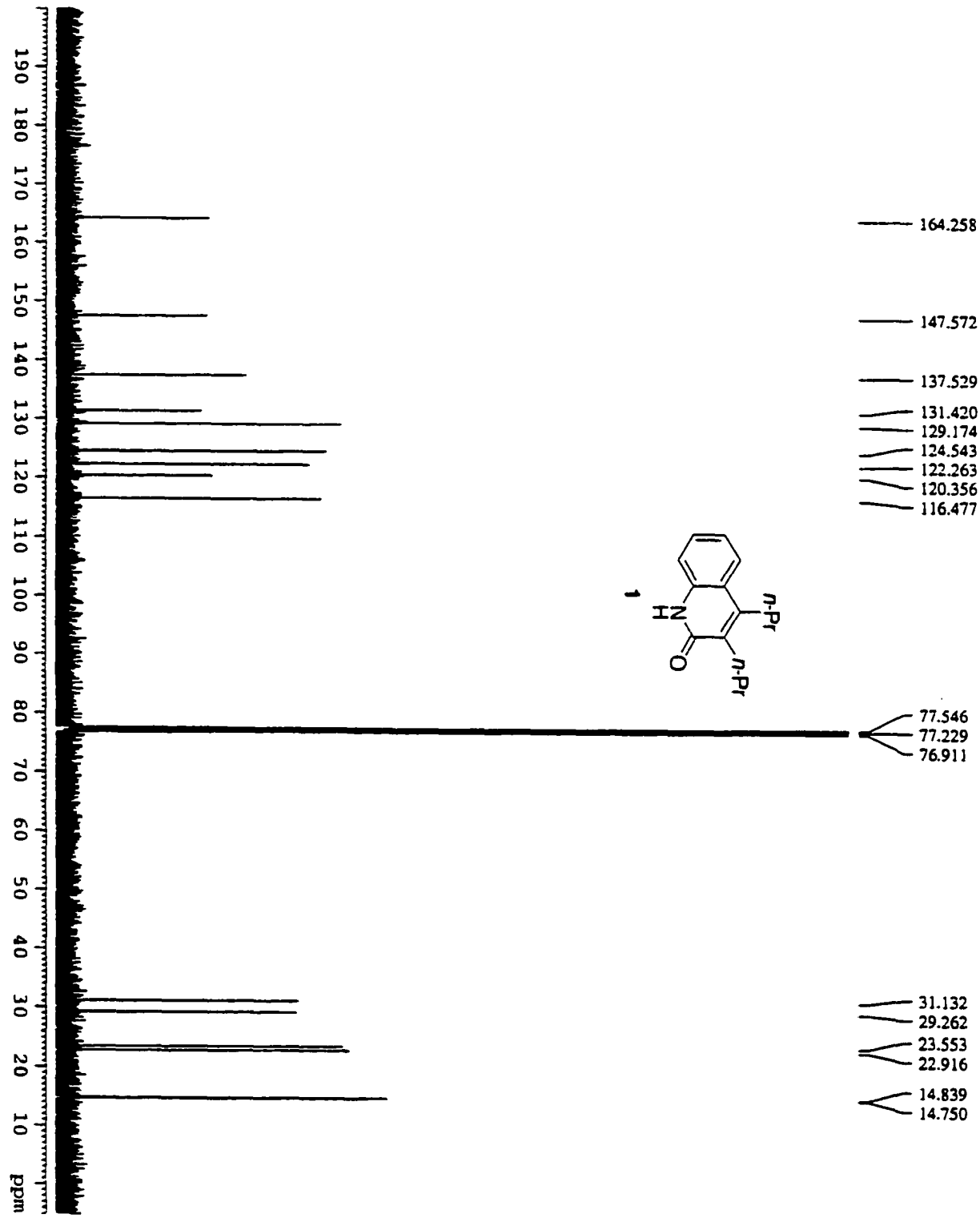

ppm
1
2
3
4
5
6
7
8
9
3.28
3.47
2.28
1.02
1.12
1.10
1.00
1.623
1.372
1.354
1.337
4.298
4.280
4.263
4.245
3.899
8.440
8.435
8.223
8.202
8.012
8.011
8.007
7.990
7.989
7.985
7.267
7.193
MeO
O
O
NH
O
OEt
37

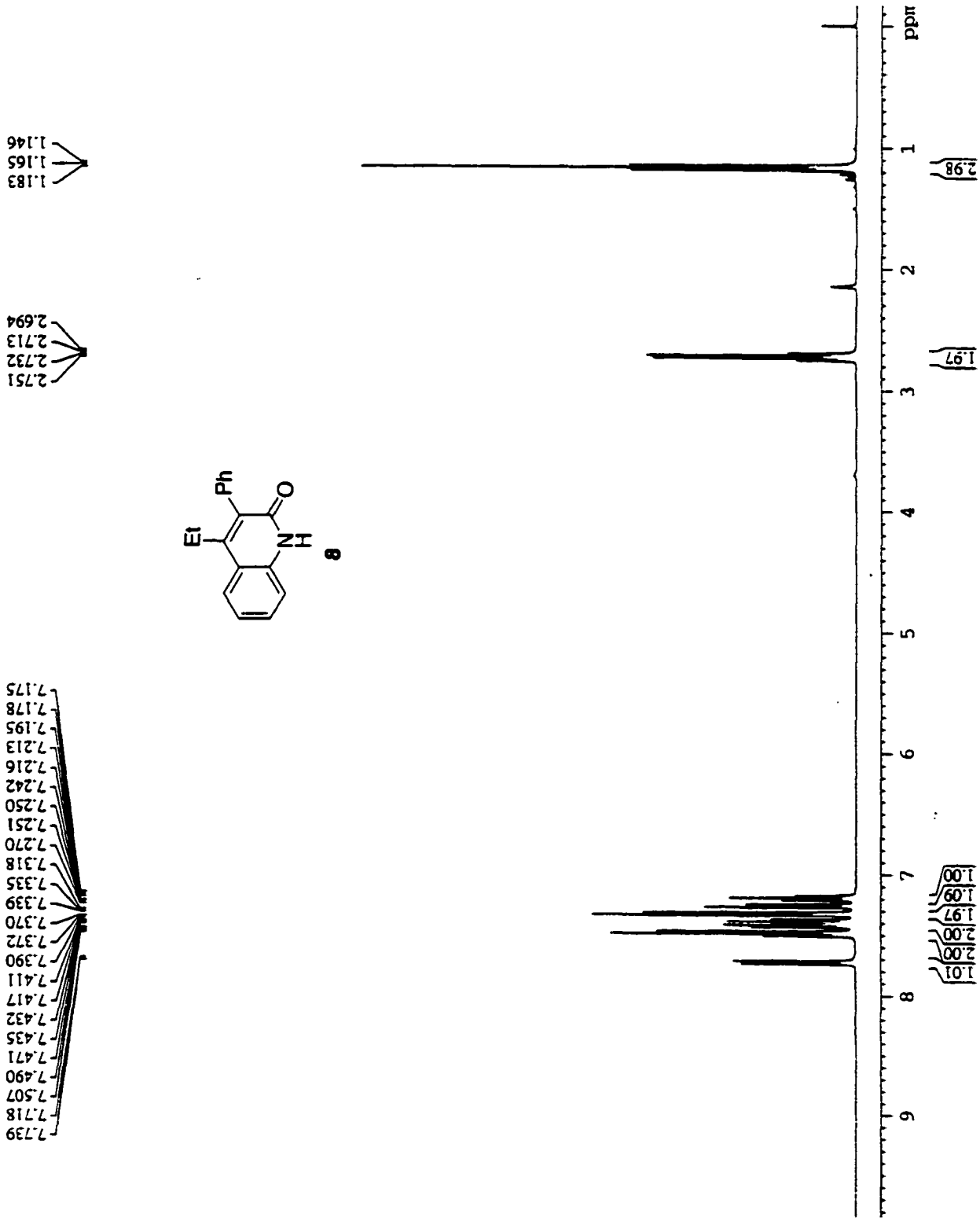

165.467
153.151
142.593
140.560
131.047
126.249
118.471
87.214
77.548
77.230
76.912
62.176
52.441
14.677
MeO
O
I
O
N
H
OEt
37
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

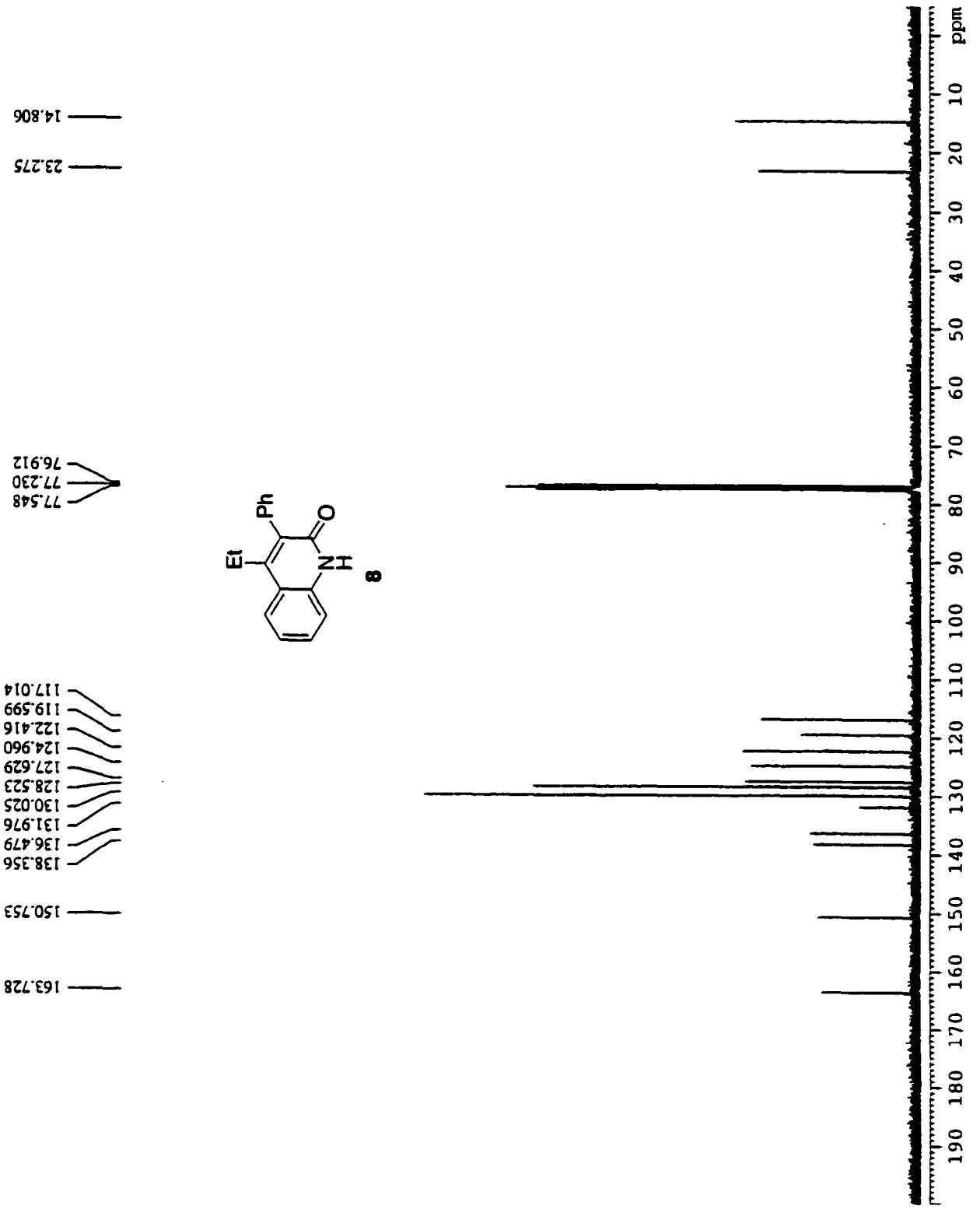

8.717
8.319
8.305
8.077
8.063
7.014
1.510
0.041
9.74
0.96
1.01
1.04
1.00
ppm
O
O-t-Bu
HN
I
N
39


157.413
151.722
150.240
145.776
113.487
86.456
82.554
77.546
77.229
76.910
28.341
O
HN
O-t-Bu
I
N
39
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

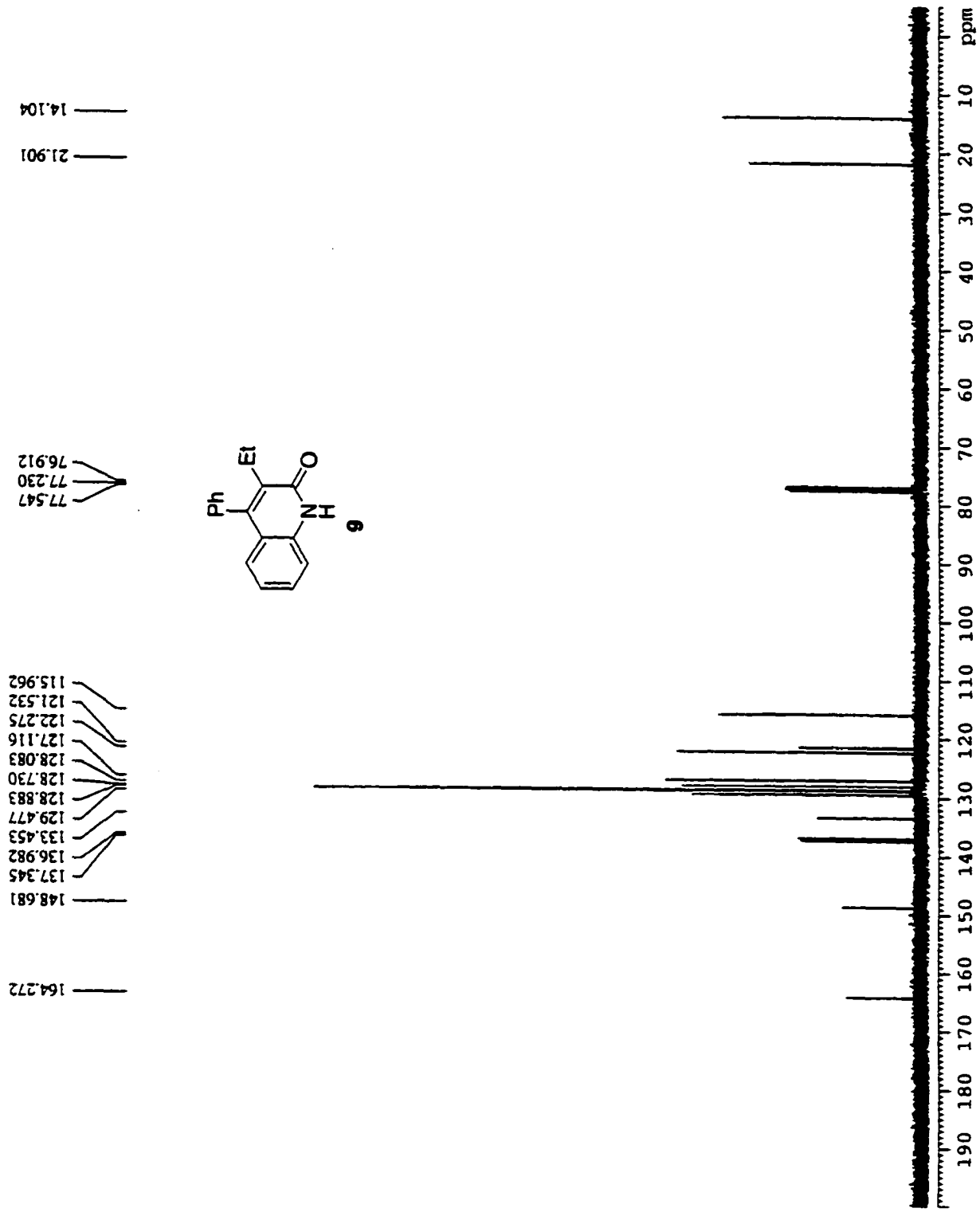
7.686
7.666
7.457
7.454
7.437
7.434
7.419
7.417
7.395
7.392
7.375
7.372
7.259
7.216
7.212
7.195
7.178
7.175
2.901
2.887
2.881
2.874
2.860
2.775
2.761
2.756
2.750
2.736
1.712
1.694
1.673
1.670
1.662
1.651
1.631
1.612
1.593
1.122
1.103
1.091
1.085
1.073
1.054
0.000
0.99
1.00
1.01
1.00
2.00
2.02
4.06
6.07
ppm
n-Pr
n-Pr
1


164.258
147.572
137.529
131.420
129.174
124.543
122.263
120.356
116.477
77.546
77.229
76.911
31.132
29.262
23.553
22.916
14.839
14.750
n-Pr
n-Pr
H
N
O
1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

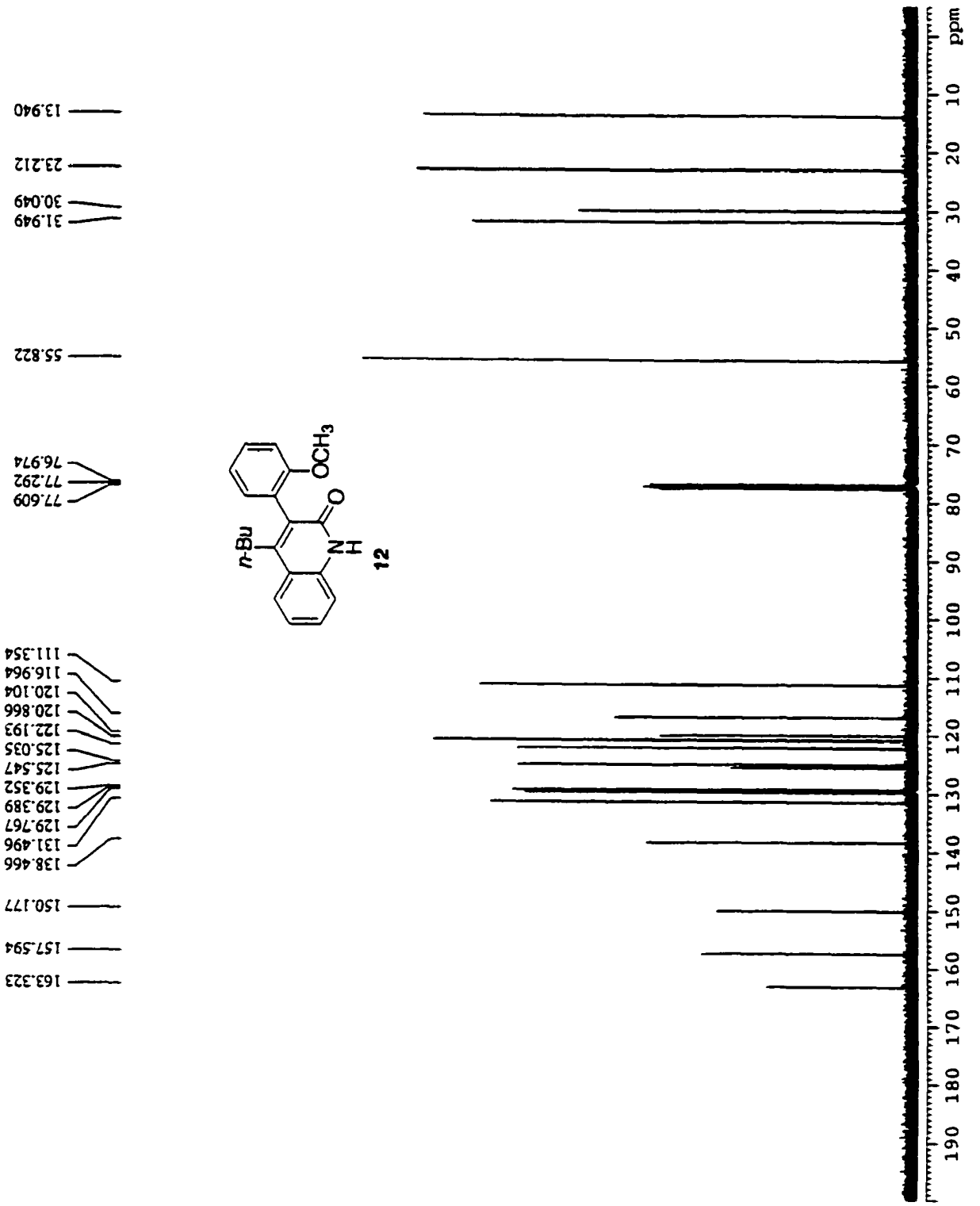

ppm
1
2
3
4
5
6
7
8
9
2.98
1.97
1.01
2.00
2.00
1.00
1.09
1.97
2.00
1.00
Et
Ph
O
NH
8
1.146
1.165
1.183
2.694
2.713
2.732
2.751
7.175
7.178
7.195
7.213
7.216
7.242
7.250
7.251
7.270
7.318
7.335
7.339
7.370
7.372
7.390
7.411
7.417
7.432
7.435
7.471
7.490
7.507
7.718
7.739

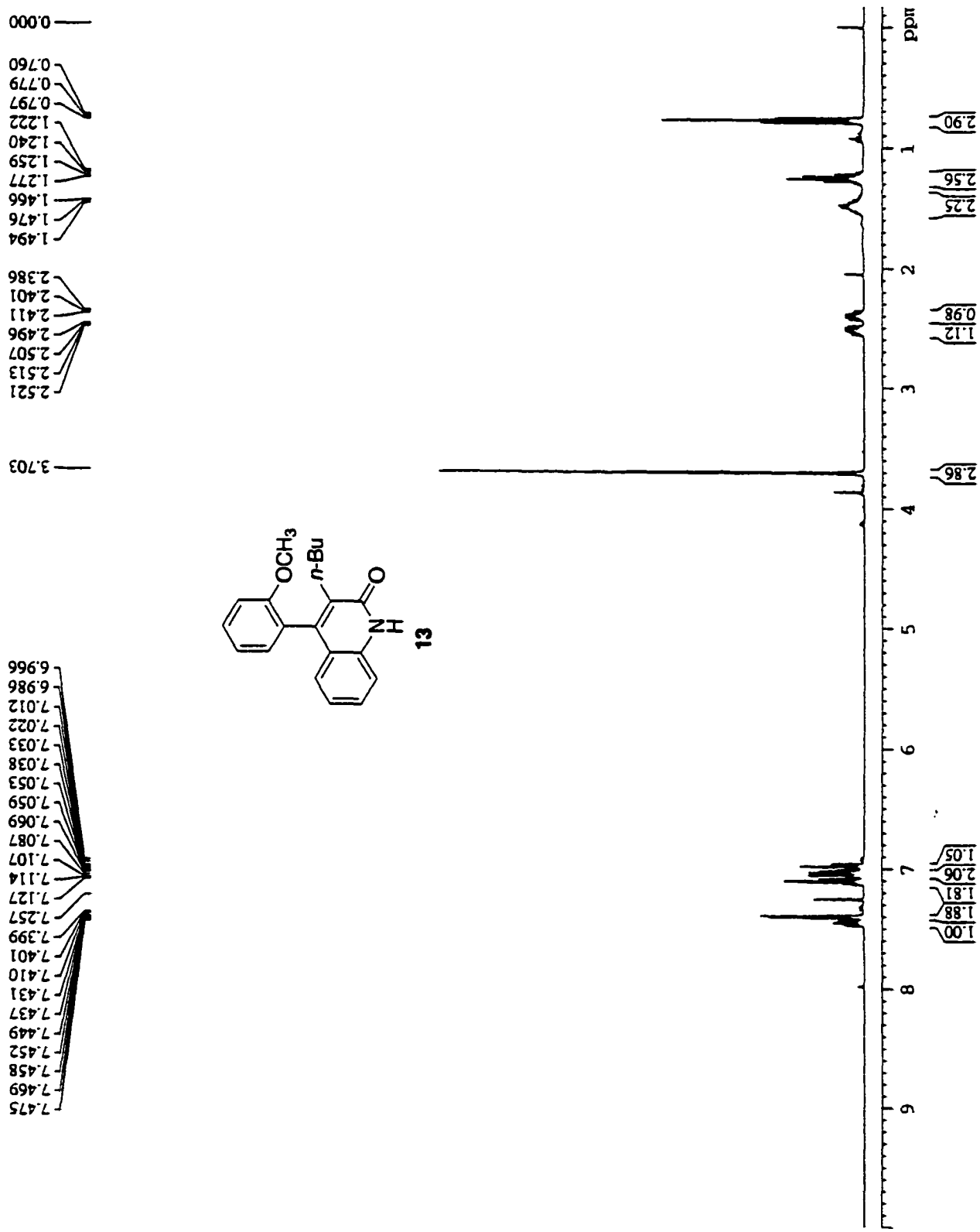

14.806
23.275
76.912
77.230
77.548
117.014
119.599
122.416
124.960
127.629
128.523
130.025
131.976
136.479
138.356
150.753
163.728
Et
Ph
O
NH
8
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

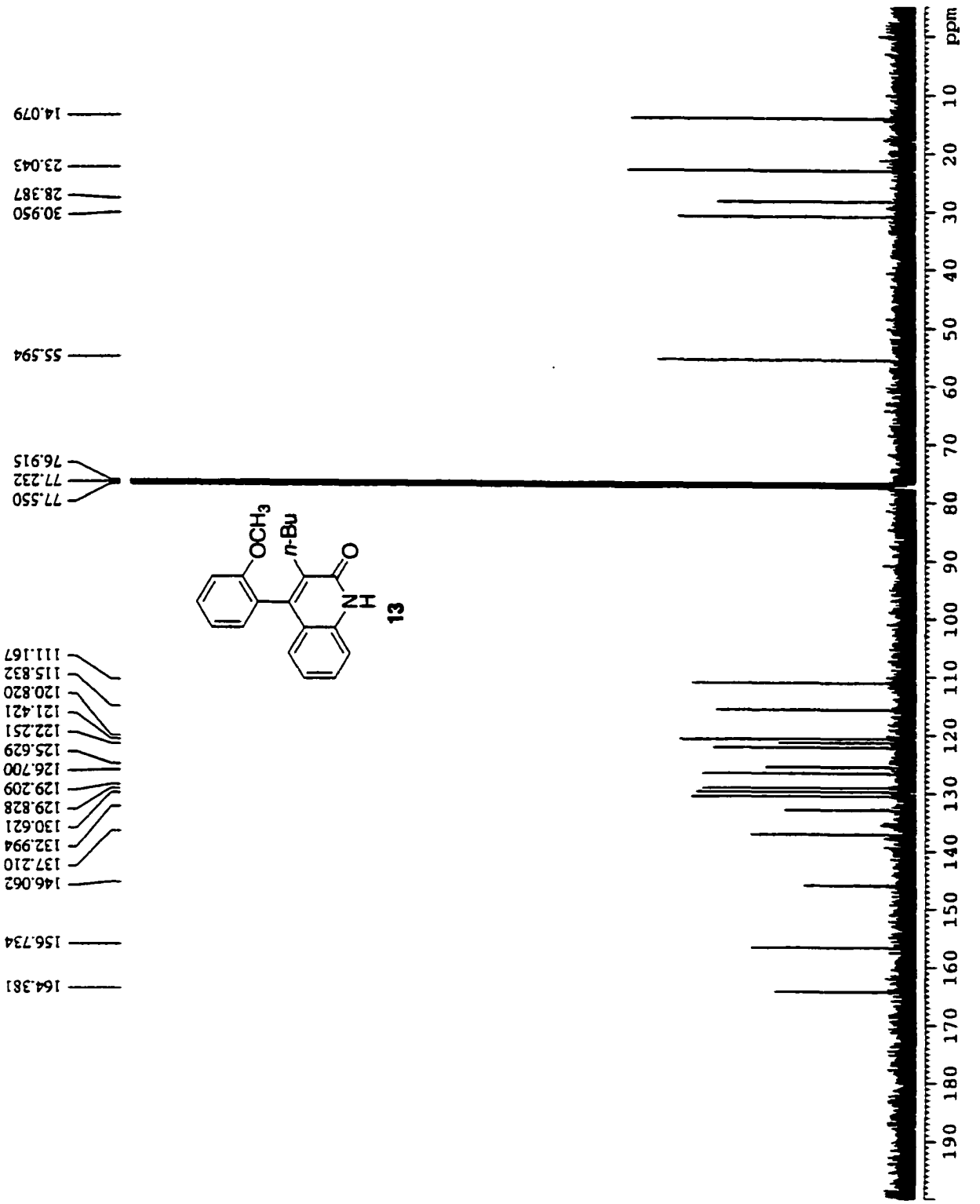
7.547
7.542
7.538
7.526
7.522
7.507
7.495
7.493
7.489
7.475
7.466
7.459
7.456
7.442
7.439
7.422
7.284
7.280
7.263
7.261
7.073
7.070
7.053
7.050
7.036
7.033
7.014
7.013
7.011
6.994
6.990
2.564
2.545
2.527
2.508
1.149
1.131
1.112
6
Ph
Et
O
N
H
5.08
2.15
2.00
1.98
2.90
ppm

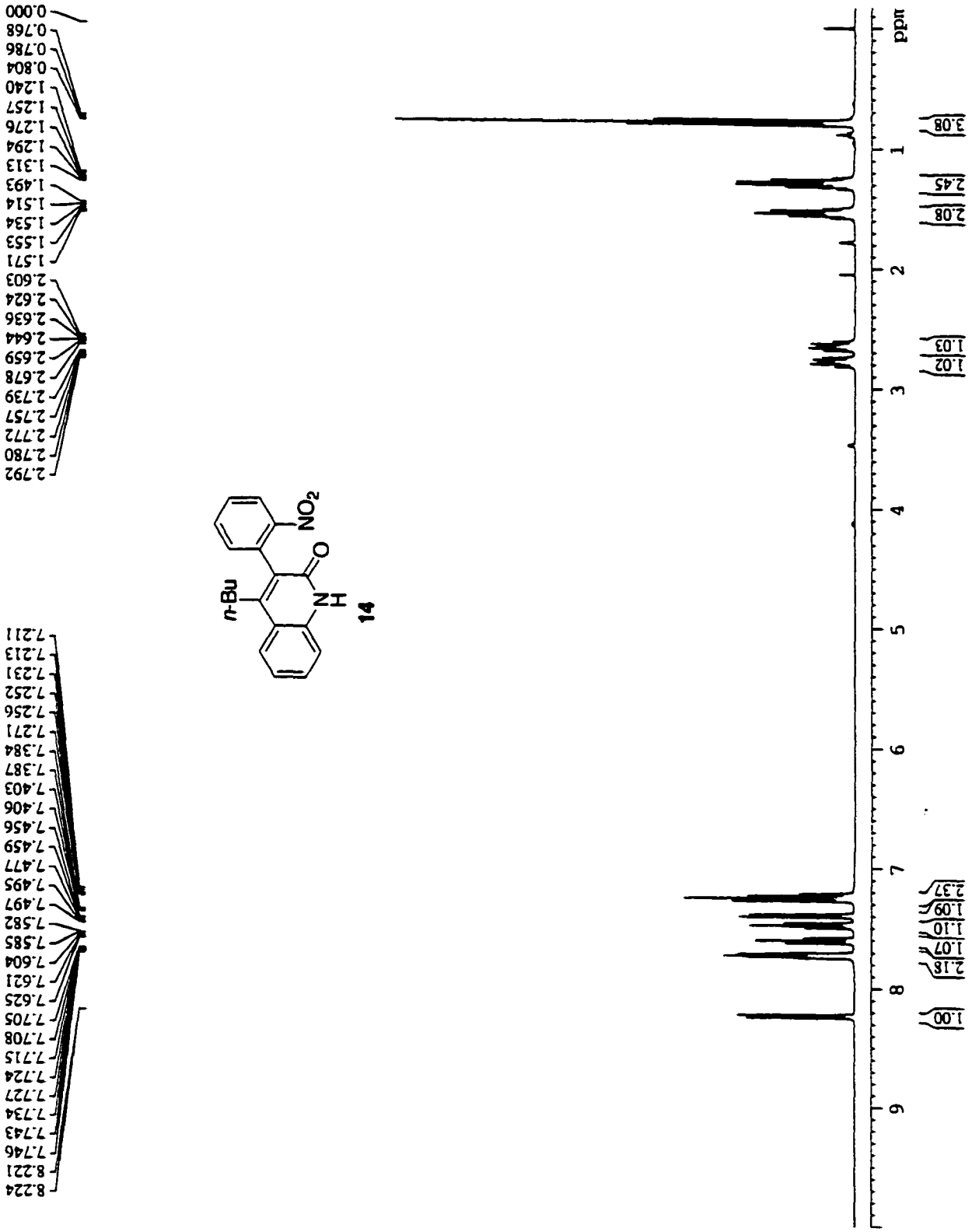

14.104
21.901
76.912
77.230
77.547
115.962
121.532
122.275
127.116
128.083
128.730
128.883
129.477
133.453
136.982
137.345
148.681
164.272
Et
O
Ph
NH
6
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

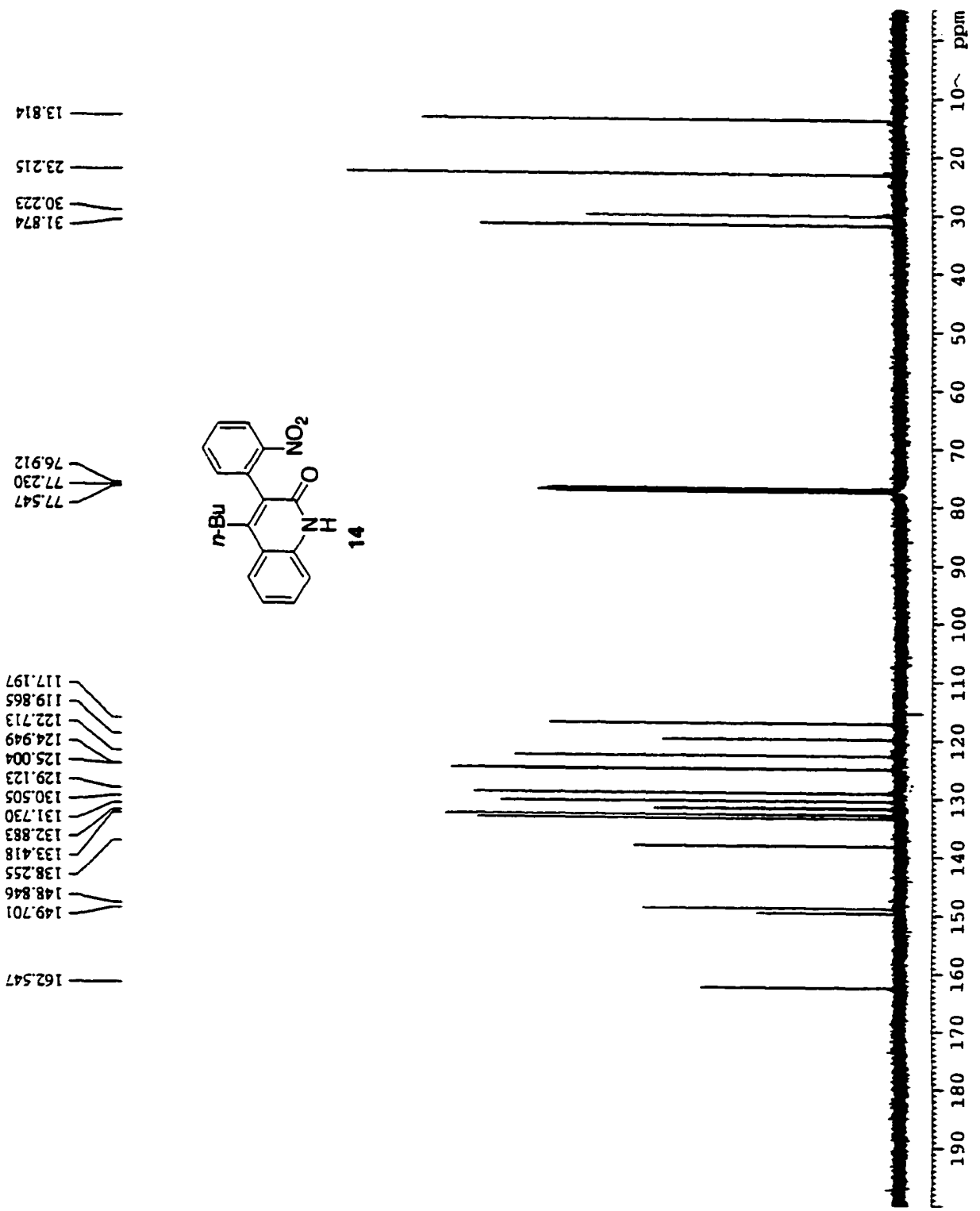
7.718
7.698
7.428
7.424
7.405
7.385
7.367
7.365
7.285
7.265
7.249
7.196
7.192
7.188
7.178
7.174
7.170
7.161
7.159
7.088
7.070
7.051
7.039
7.018
3.746
2.712
2.706
2.698
2.693
2.679
2.666
2.599
2.584
2.572
2.567
2.557
2.551
1.532
1.524
1.517
1.506
1.490
1.479
1.472
1.464
1.279
1.261
1.243
1.224
0.787
1.00
2.07
1.18
2.10
2.06
3.11
0.95
0.94
1.92
2.05
2.93
ppm
12
n-Bu
OCH3


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
13.940
23.212
30.049
31.949
55.822
76.974
77.292
77.609
111.354
116.964
120.104
120.866
122.193
125.035
125.547
129.352
129.389
129.767
131.496
138.466
150.177
157.594
163.323
OCH3
O
N
H
n-Bu
12


0.000
0.760
0.779
0.797
1.222
1.240
1.259
1.277
1.466
1.476
1.494
2.386
2.401
2.411
2.496
2.507
2.513
2.521
3.703
6.966
6.986
7.012
7.022
7.033
7.038
7.053
7.059
7.069
7.087
7.107
7.114
7.127
7.257
7.399
7.401
7.410
7.431
7.437
7.449
7.452
7.458
7.469
7.475
OCH3
n-Bu
O
NH
13
ppm
1
2
3
4
5
6
7
8
9
2.90
2.56
2.25
0.98
1.12
2.86
1.00
1.88
1.81
2.06
1.05


14.079
23.043
28.387
30.950
55.594
76.915
77.232
77.550
111.167
115.832
120.820
121.421
122.251
125.629
126.700
129.209
129.828
130.621
132.994
137.210
146.062
156.734
164.381
OCH3
n-Bu
O
NH
13
ppm


0.000
0.768
0.786
0.804
1.240
1.257
1.276
1.294
1.313
1.493
1.514
1.534
1.553
1.571
2.603
2.624
2.636
2.644
2.659
2.678
2.739
2.757
2.772
2.780
2.792
7.211
7.213
7.231
7.252
7.256
7.271
7.384
7.387
7.403
7.406
7.456
7.459
7.477
7.495
7.497
7.582
7.585
7.604
7.621
7.625
7.705
7.708
7.715
7.724
7.727
7.734
7.743
7.746
8.221
8.224
NO2
O
NH
n-Bu
14
ppm
1
2
3
4
5
6
7
8
9
3.08
2.45
2.08
1.03
1.02
1.00
2.37
1.09
1.10
1.07
2.18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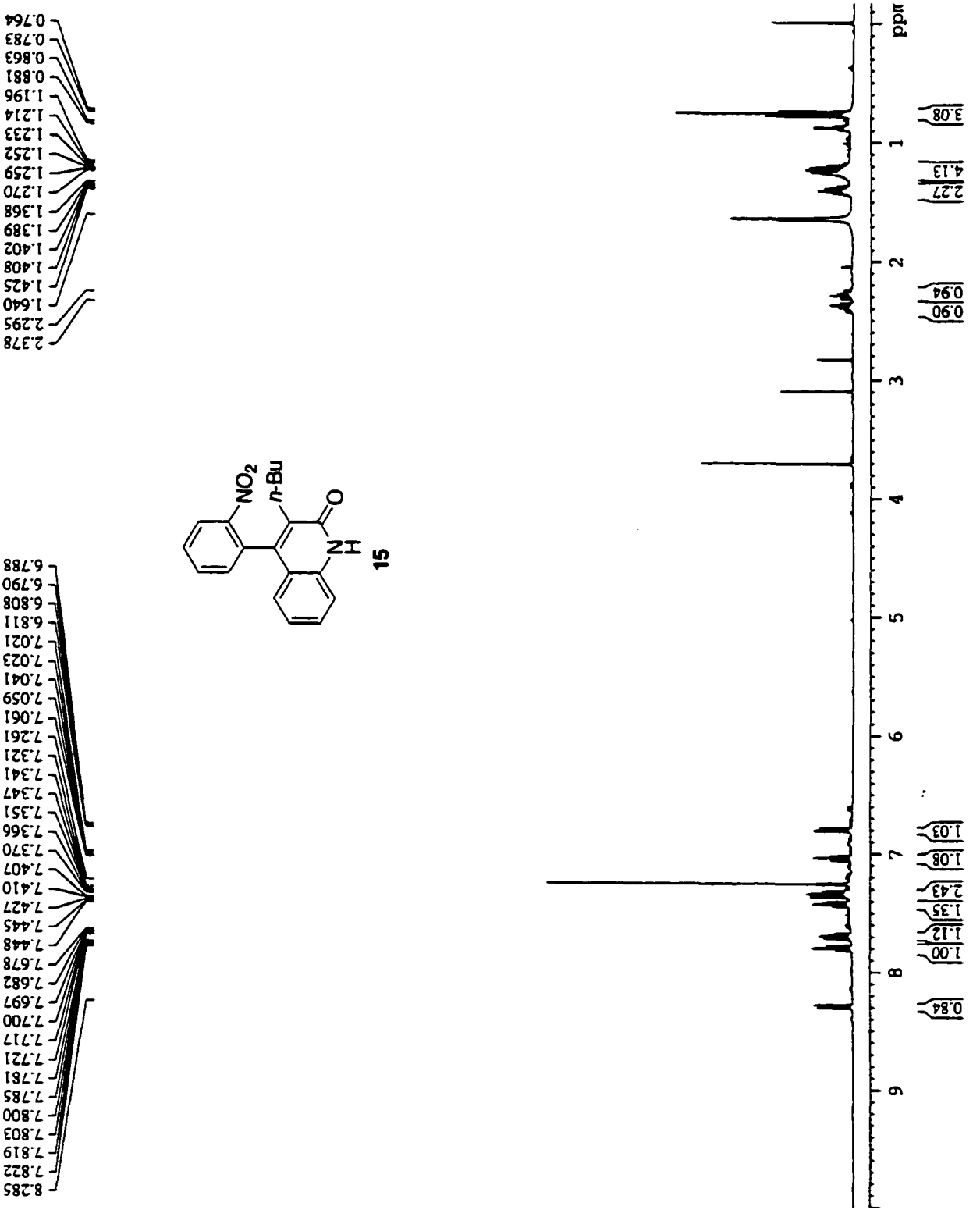
23.215
30.223
31.874
76.912
77.230
77.547
117.197
119.865
122.713
124.949
125.004
129.123
130.505
131.730
132.883
133.418
138.255
148.846
149.701
162.547
n-Bu
NO2
O
N
H
14
ppm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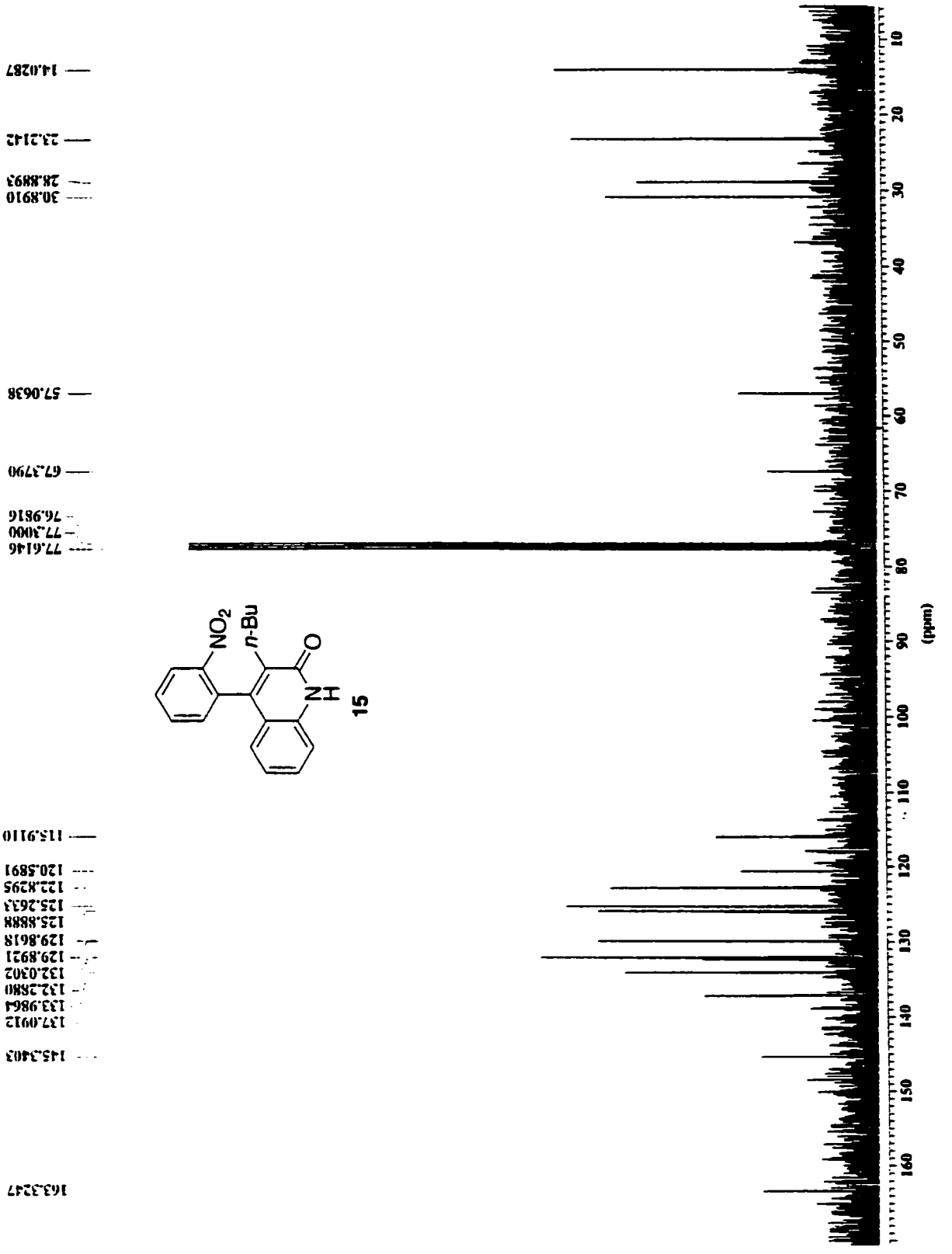
0.783
0.863
0.881
1.196
1.214
1.233
1.252
1.259
1.270
1.368
1.389
1.402
1.408
1.425
1.640
2.295
2.378
6.788
6.790
6.808
6.811
7.021
7.023
7.041
7.059
7.061
7.261
7.321
7.341
7.347
7.351
7.366
7.370
7.407
7.410
7.427
7.445
7.448
7.678
7.682
7.697
7.700
7.717
7.721
7.781
7.785
7.800
7.803
7.819
7.822
8.285
NO2
n-Bu
O
NH
15
0.84
1.00
1.12
1.35
2.43
1.08
1.03
3.08
2.27
4.13
0.90
0.94
ppm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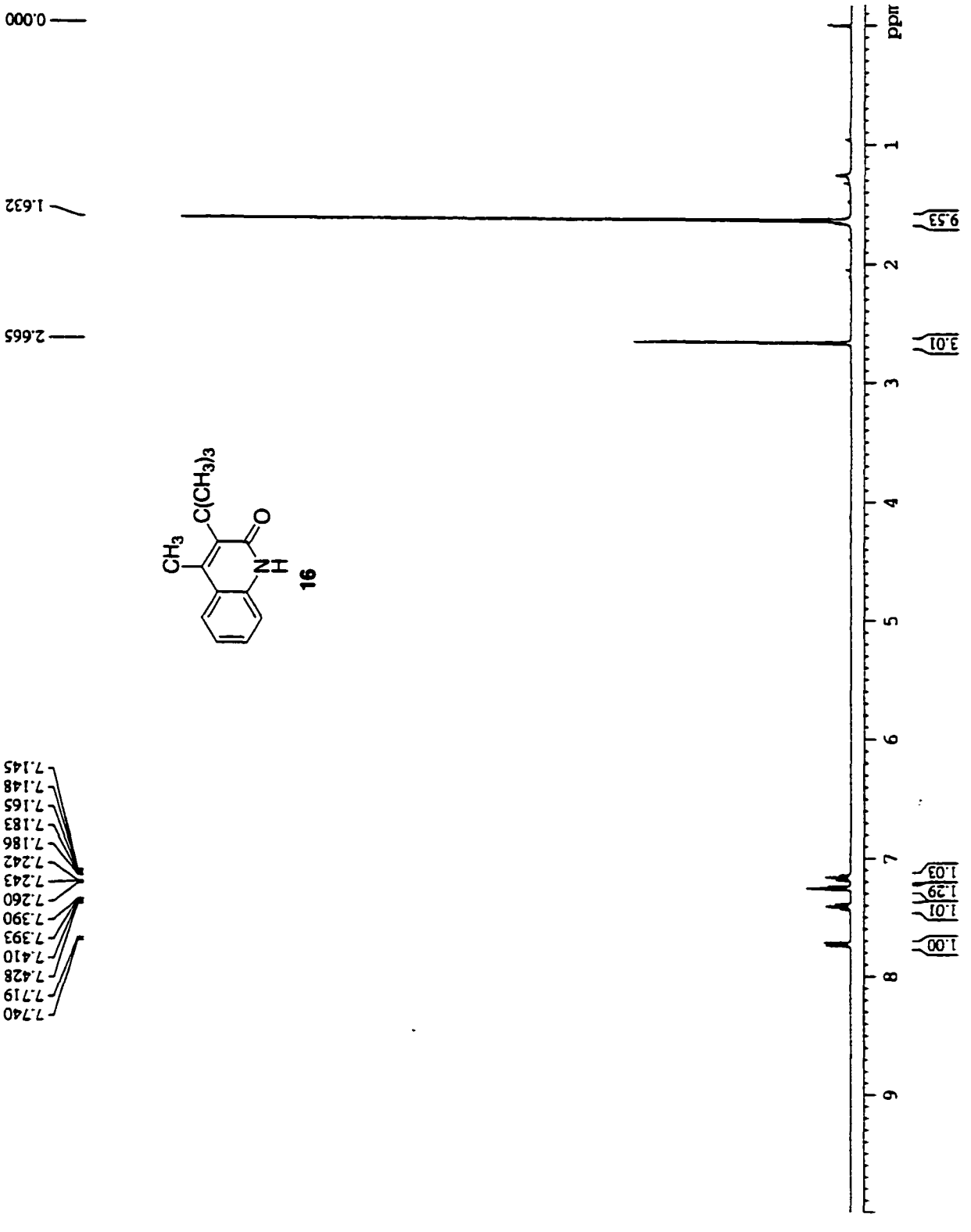
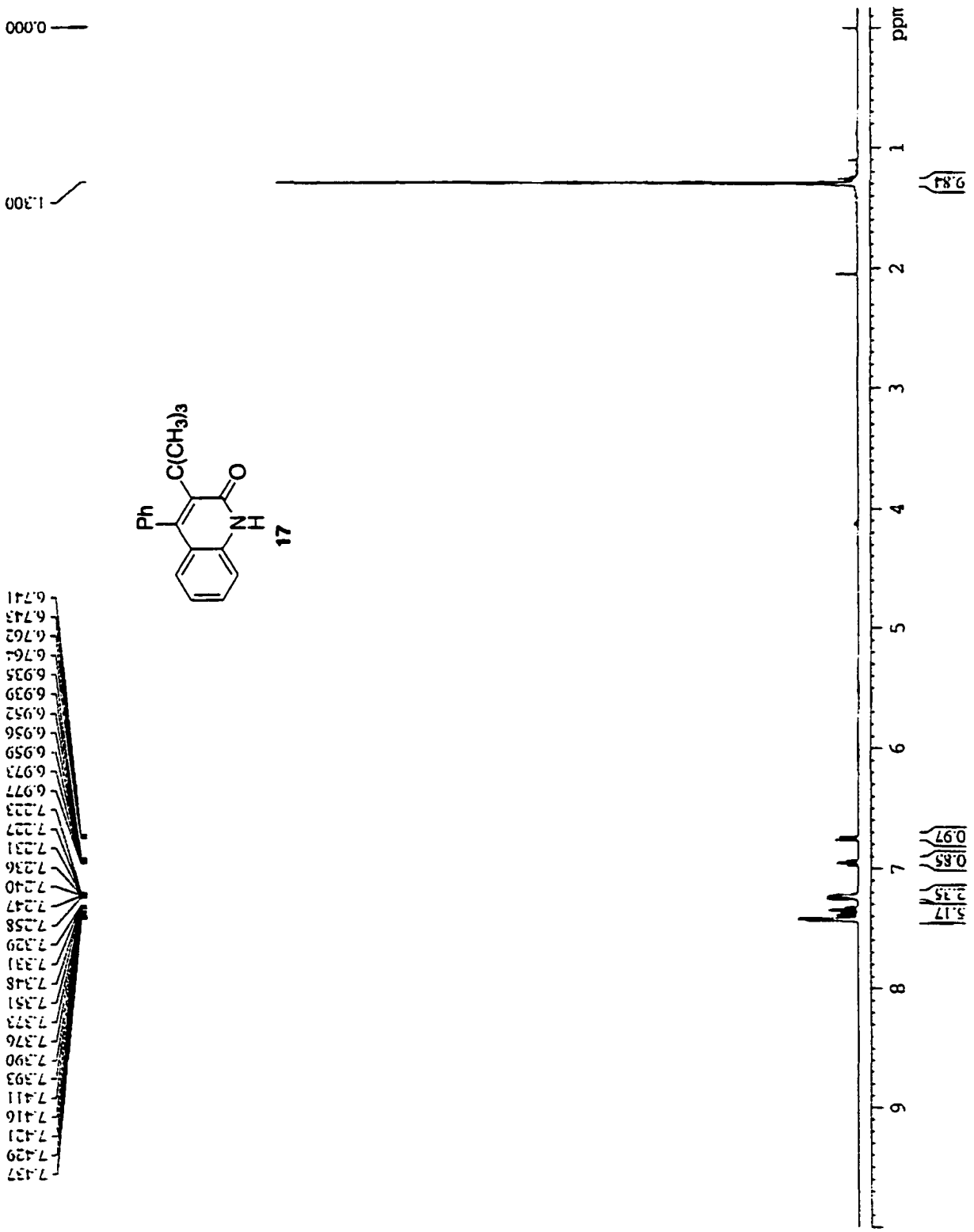
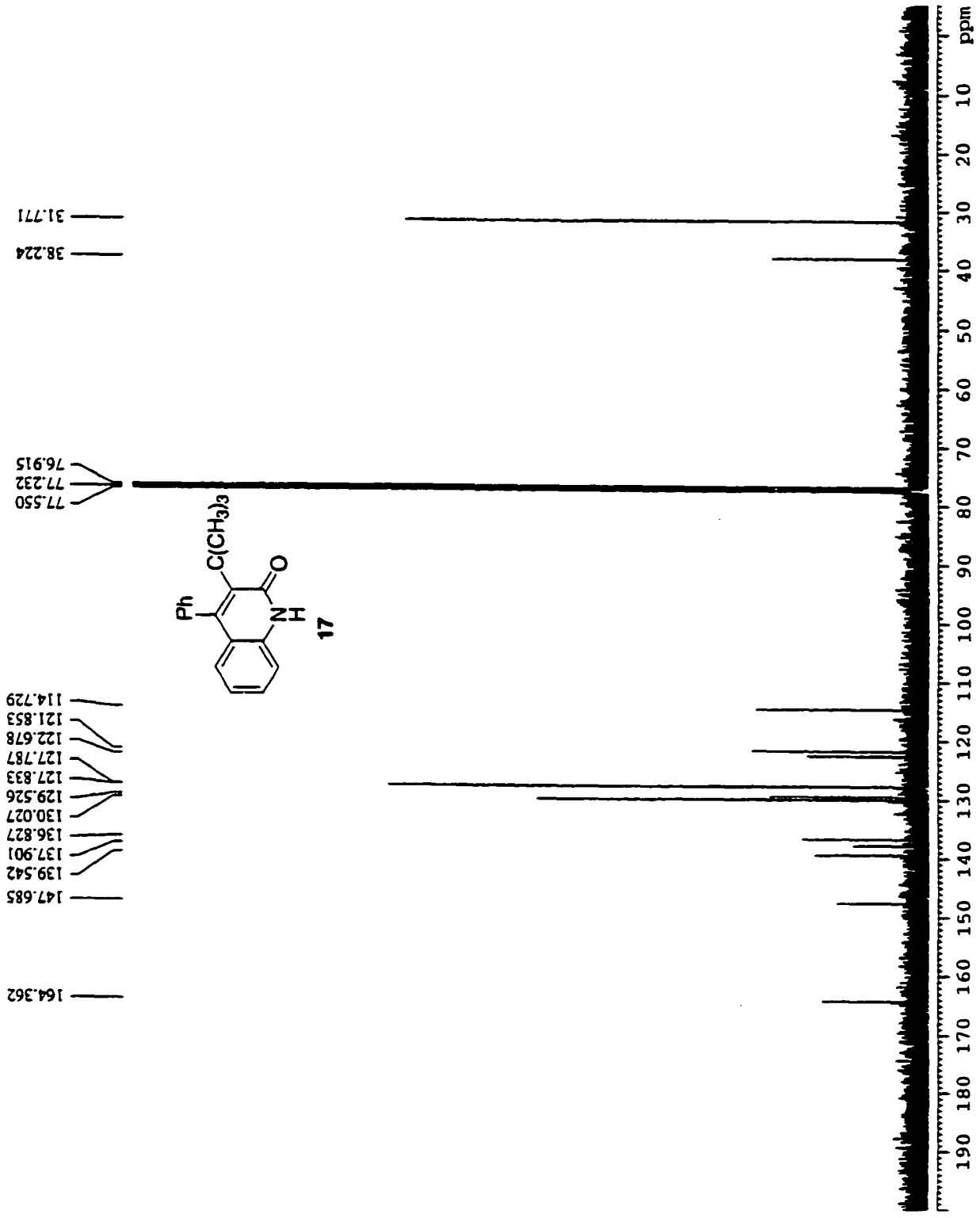
23.2142
28.8893
30.8910
57.0638
67.3790
76.9816
77.3000
77.6146
115.9110
120.5891
122.8295
125.2633
125.8888
129.8618
129.8921
132.0302
132.2880
133.9864
137.0912
145.3403
163.3247
NO2
n-Bu
O
NH
15
(ppm)

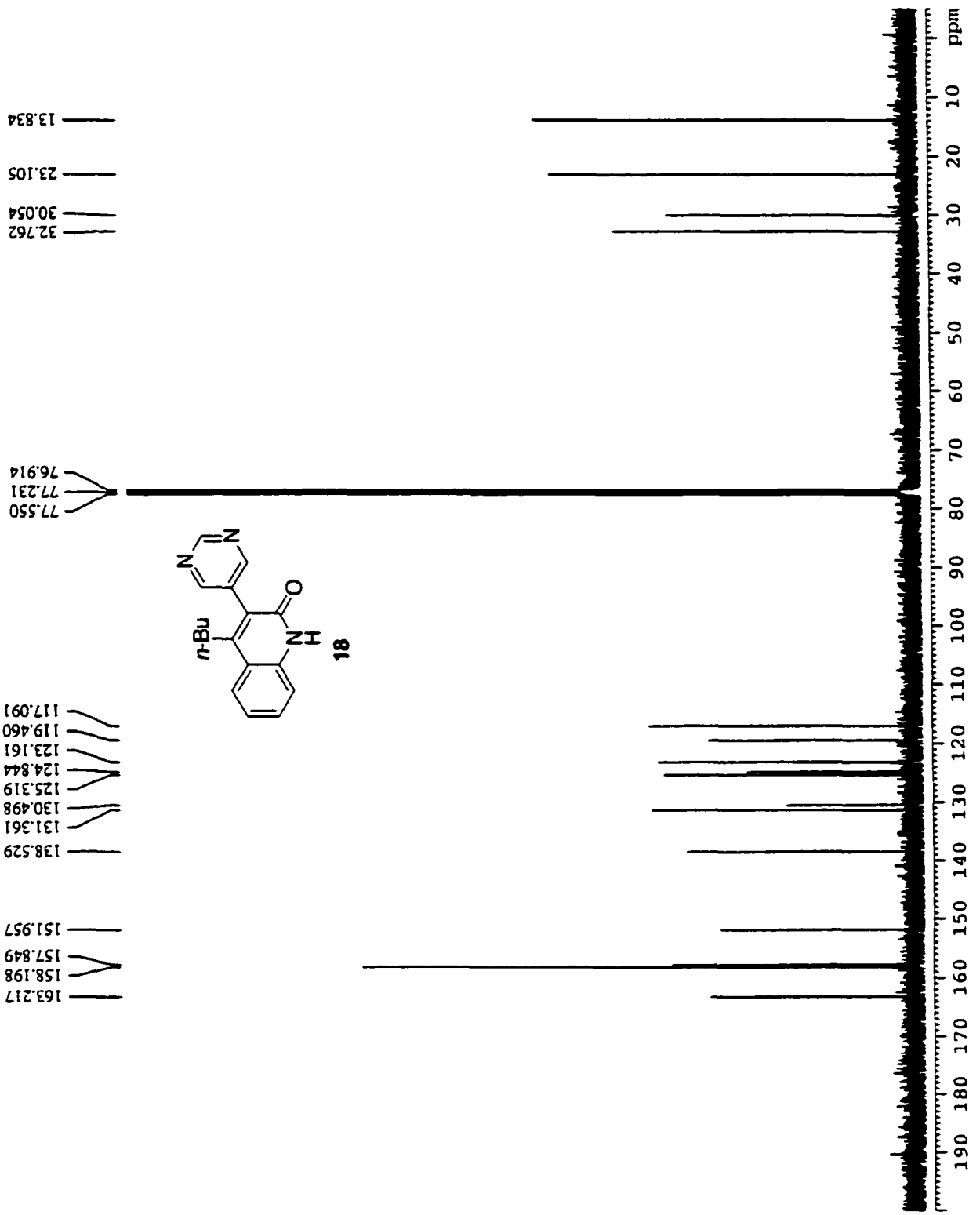

0.000
1.632
2.665
7.740
7.719
7.428
7.410
7.393
7.390
7.260
7.243
7.242
7.186
7.183
7.165
7.148
7.145
C(CH3)3
CH3
O
N
H
16
ppm
1
2
3
4
5
6
7
8
9
9.53
3.01
1.03
1.29
1.01
1.00

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
164.075
143.308
138.339
136.672
129.231
124.561
122.644
121.991
115.144
37.734
31.928
19.001
16
N
H
O
CH3
C(CH3)3

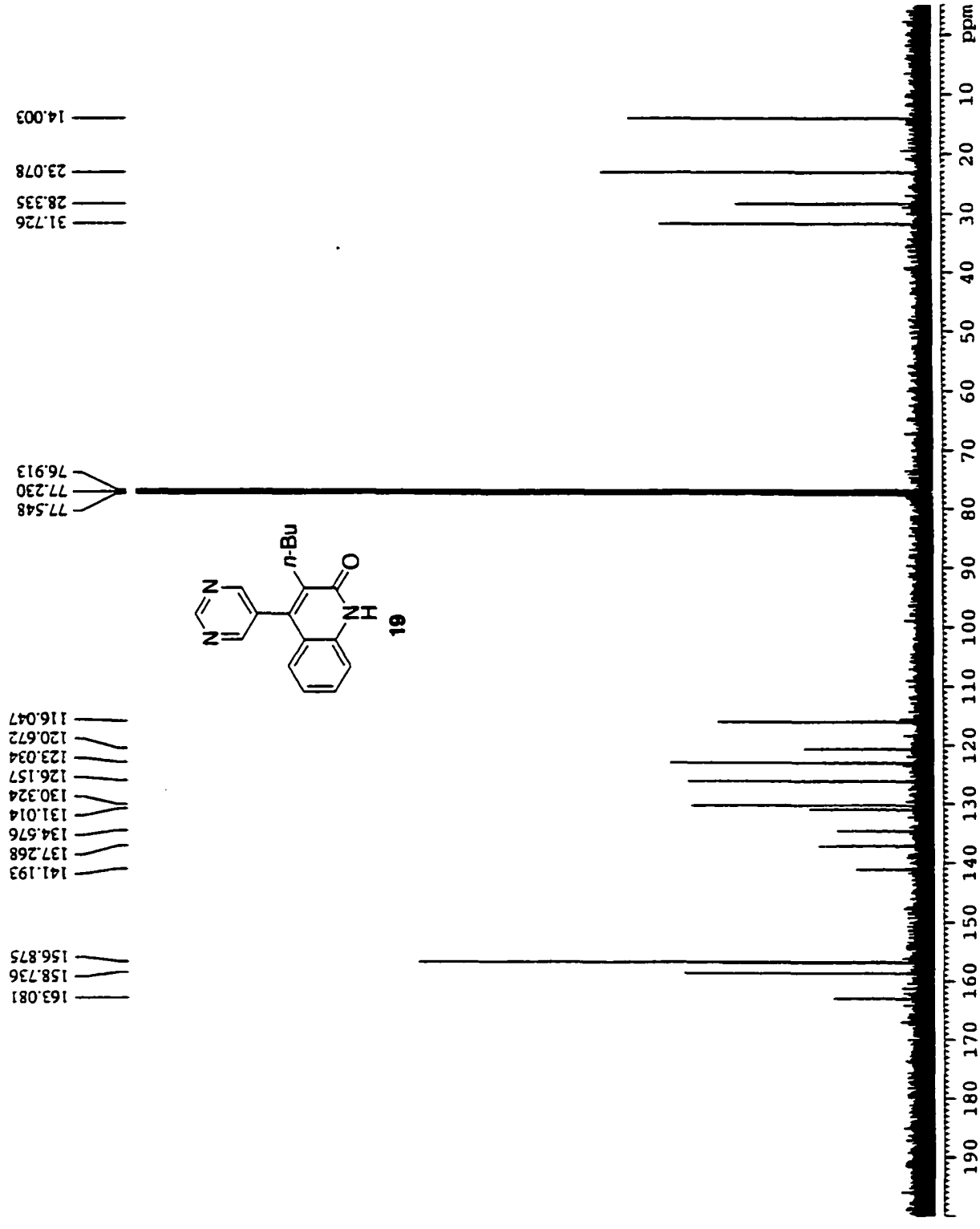

0.000
1.300
ppm
1
2
3
4
5
6
7
8
9
9.84
5.17
2.15
0.85
0.97
Ph
C(CH3)3
O
N
H
17
7.241
7.243
7.262
7.264
6.935
6.939
6.952
6.956
6.959
6.973
6.977
7.223
7.227
7.231
7.236
7.240
7.247
7.258
7.329
7.331
7.348
7.351
7.373
7.376
7.390
7.393
7.411
7.416
7.421
7.429
7.437

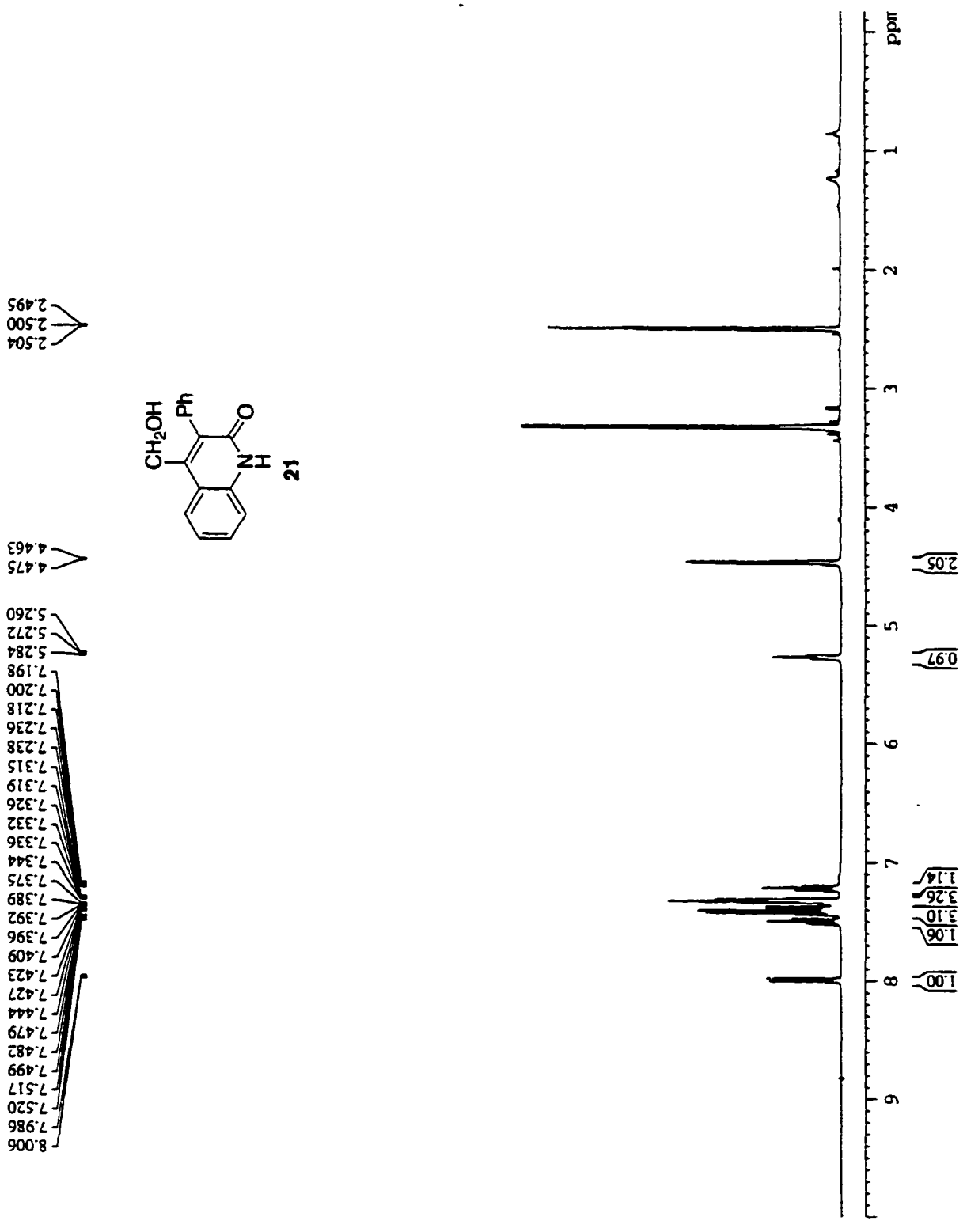

31.771
38.224
76.915
77.232
77.550
C(CH3)3
O
Ph
NH
17
114.729
121.853
122.678
127.787
127.833
129.526
130.027
136.827
137.901
139.542
147.685
164.362
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

0.97
1.94
1.00
1.01
2.18
1.98
2.02
2.02
2.99
ppm
9.300
8.796
7.783
7.764
7.546
7.544
7.526
7.508
7.505
7.338
7.319
7.317
7.303
7.301
7.283
7.272
7.265
7.262
2.788
2.768
2.748
1.605
1.592
1.585
1.576
1.566
1.360
1.342
1.323
1.305
1.245
0.862
0.844
0.825
0.000
18
t-Bu

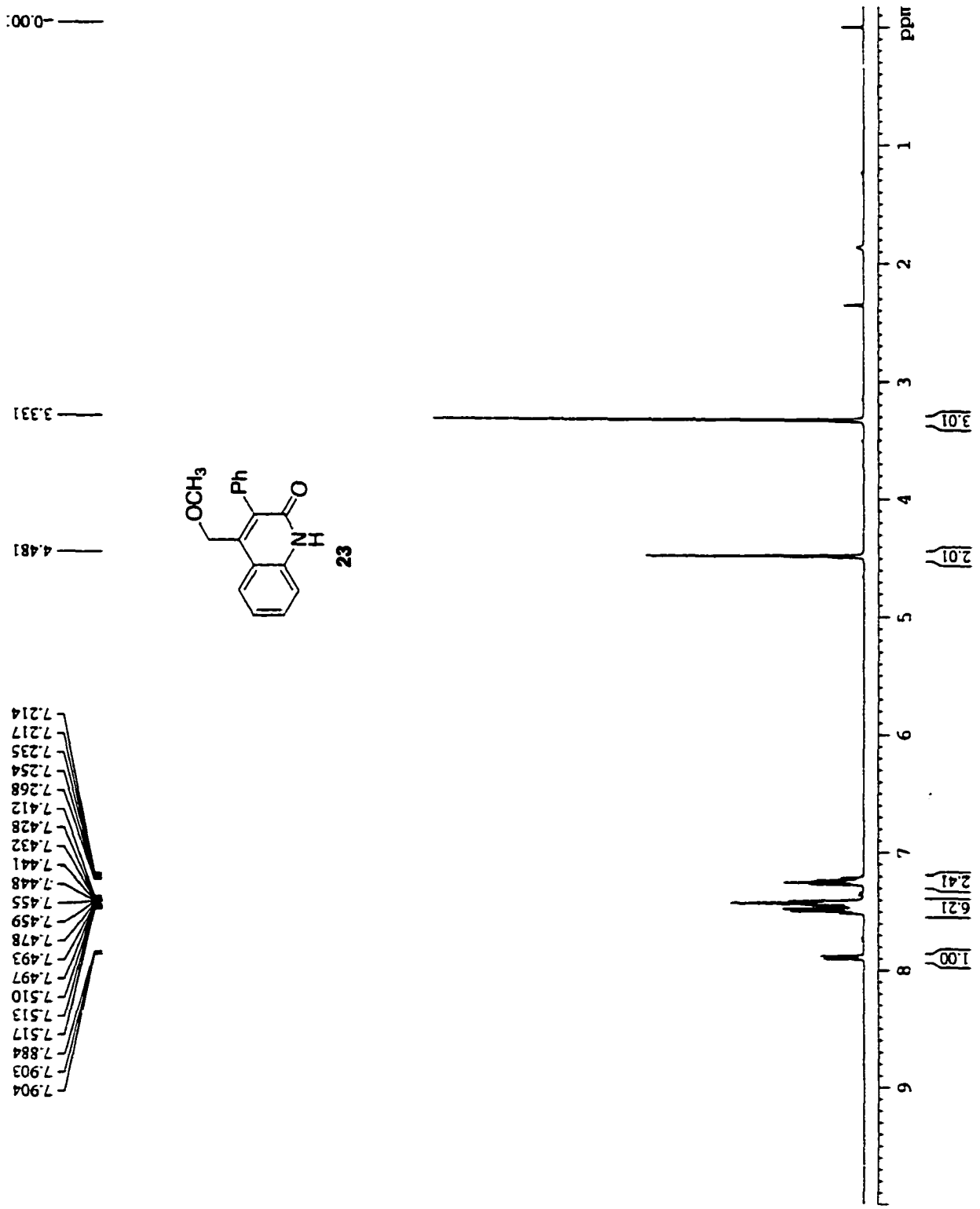

13.834
23.105
30.054
32.762
77.550
77.231
76.914
117.091
119.460
123.161
124.844
125.319
130.498
131.361
138.529
151.957
157.849
158.198
163.217
n-Bu
18
ppm

0.91
1.95
1.01
1.02
1.02
1.00
2.00
1.99
2.12
2.95
ppm
9.389
8.731
7.533
7.530
7.513
7.510
7.495
7.492
7.426
7.425
7.406
7.264
7.156
7.153
7.136
7.133
7.118
7.115
6.925
6.923
6.905
6.902
2.498
2.478
2.459
1.636
1.518
1.498
1.490
1.485
1.479
1.473
1.315
1.296
1.278
1.259
0.844
0.826
0.808
0.000
19
n-Bu


14.003
23.078
28.335
31.726
76.913
77.230
77.548
116.047
120.672
123.034
126.157
130.324
131.014
134.676
137.268
141.193
156.875
158.736
163.081
n-Bu
O
NH
N
N
19
ppm


2.495
2.500
2.504
4.463
4.475
5.260
5.272
5.284
7.198
7.200
7.218
7.236
7.238
7.315
7.319
7.326
7.332
7.336
7.344
7.375
7.389
7.392
7.396
7.409
7.423
7.427
7.444
7.479
7.482
7.499
7.517
7.520
7.986
8.006
Ph
CH2OH
O
N
H
21
ppm
1
2
3
4
5
6
7
8
9
2.05
0.97
1.14
3.26
3.10
1.06
1.00

161.260
144.746
138.228
135.255
132.318
130.320
129.792
127.570
127.335
126.461
121.576
118.914
115.046
58.175
40.136
39.926
39.718
39.509
39.301
39.093
38.883
21
CH2OH
Ph
N
H
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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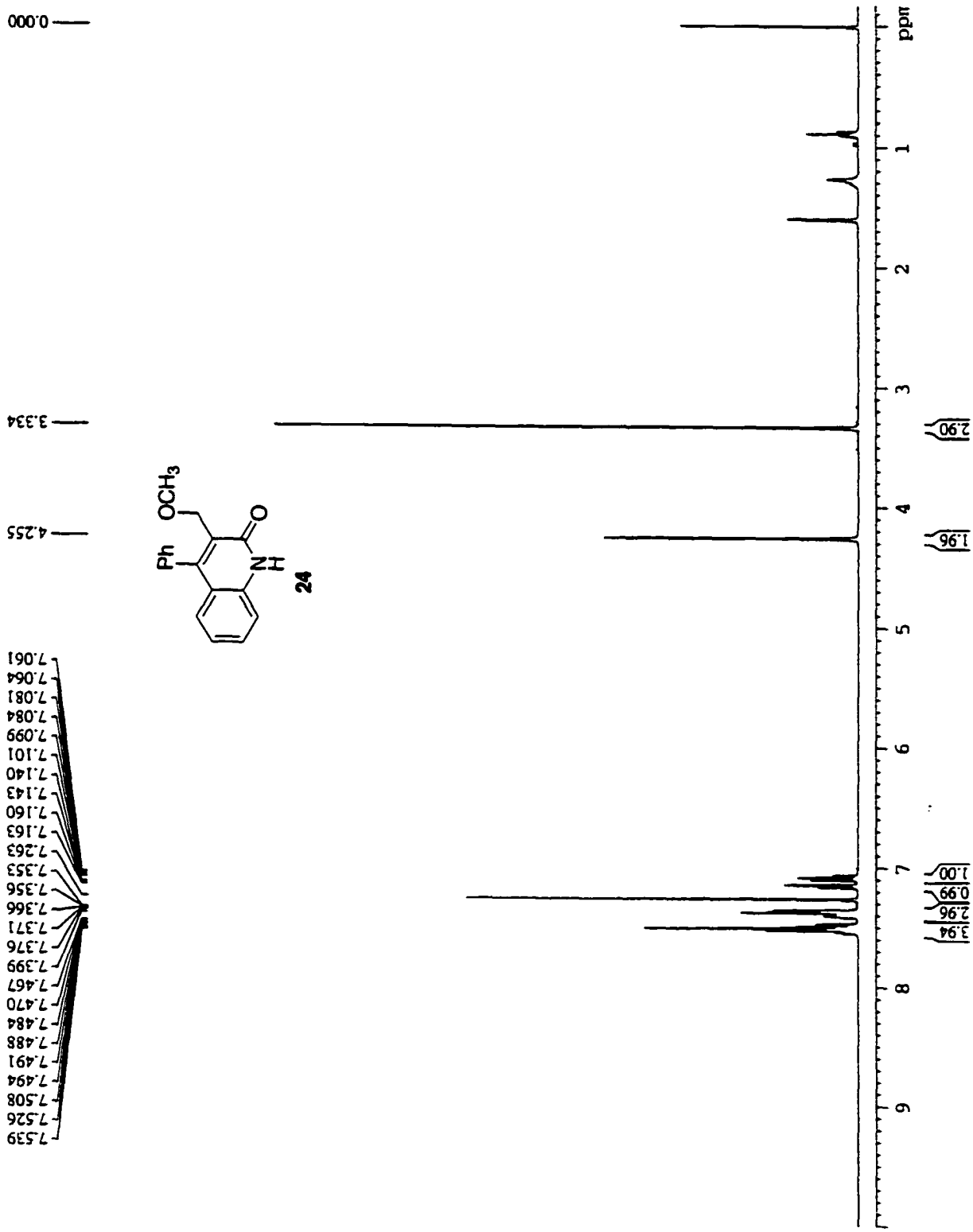
3.331
4.481
7.214
7.217
7.235
7.254
7.268
7.412
7.428
7.432
7.441
7.448
7.455
7.459
7.478
7.493
7.497
7.510
7.513
7.517
7.884
7.903
7.904
OCH3
Ph
O
N
H
23
ppm
1
2
3
4
5
6
7
8
9
3.01
2.01
2.41
6.21
1.00

163.405
143.006
138.069
135.016
134.242
130.593
130.393
128.306
128.197
125.962
122.879
119.906
116.416
69.299
58.645
23
OCH3
Ph
O
N
H
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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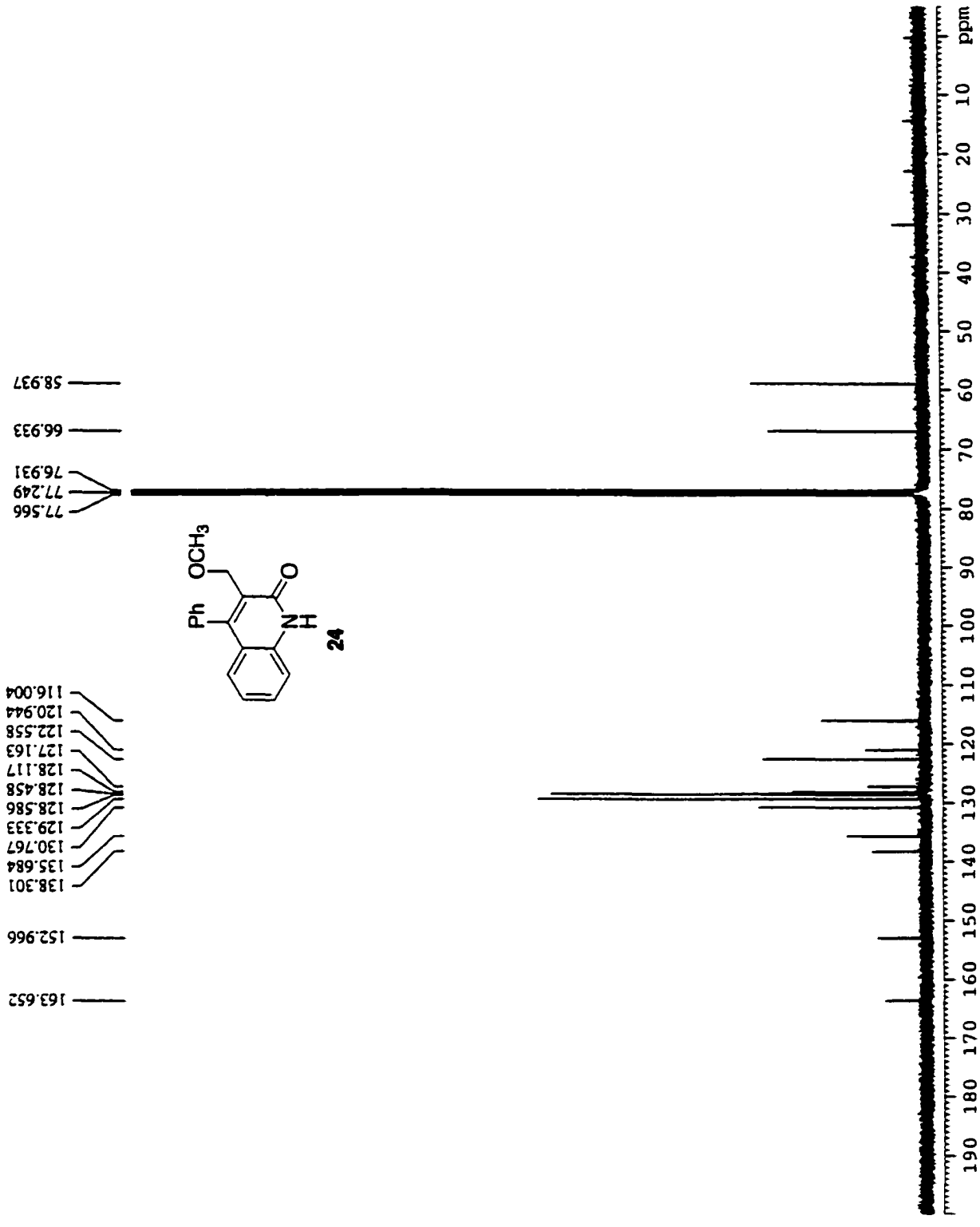
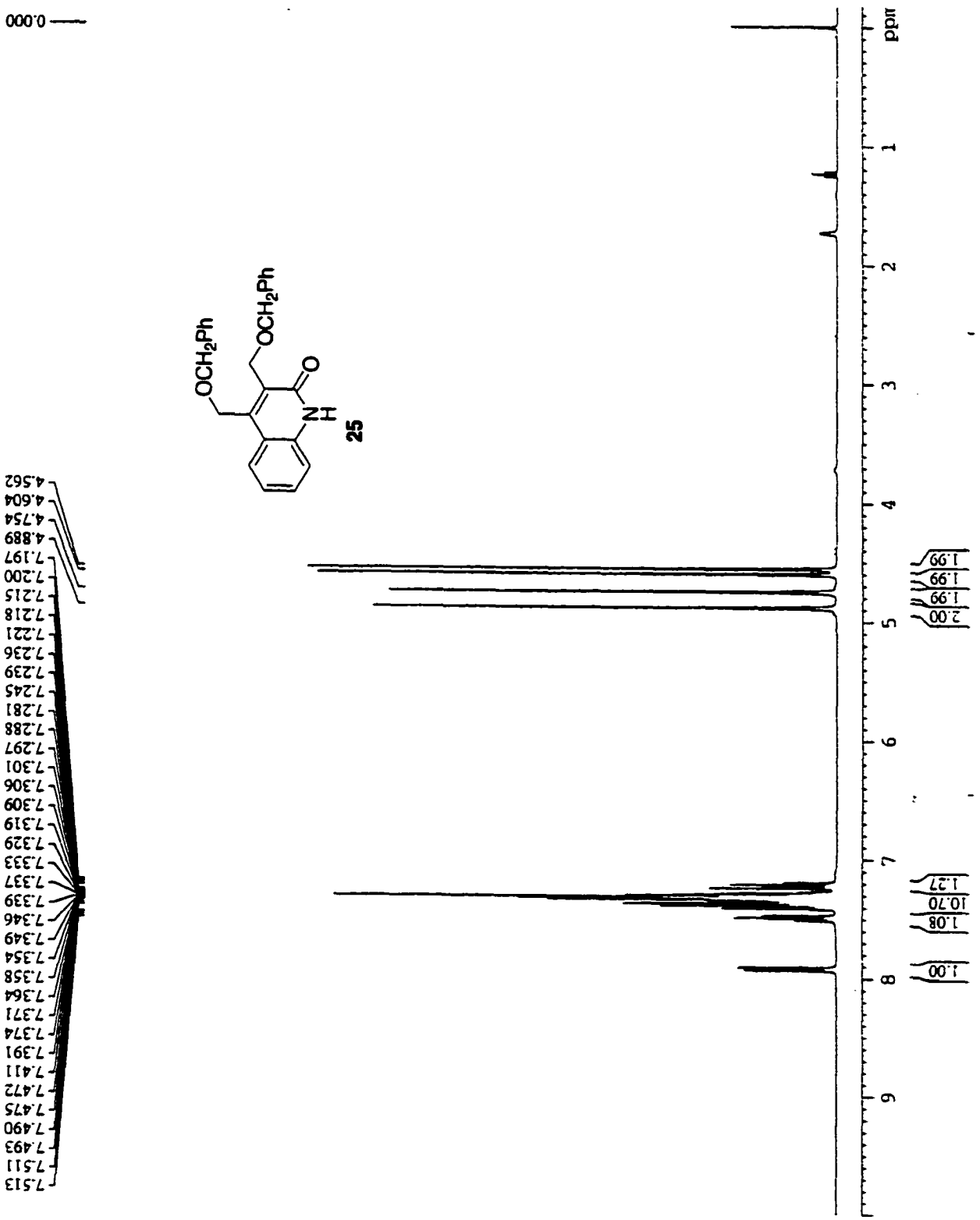
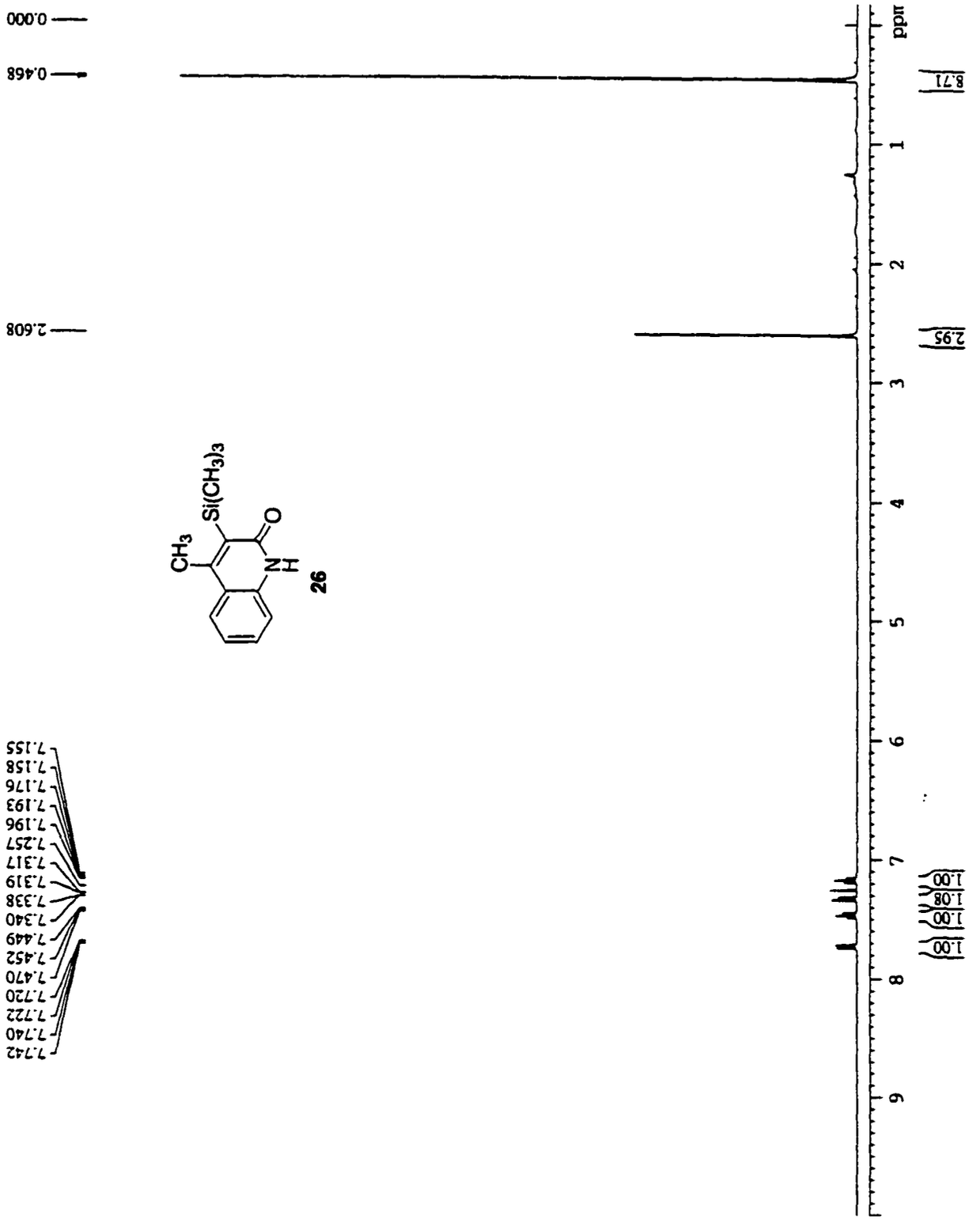
3.334
4.255
7.061
7.064
7.081
7.084
7.099
7.101
7.140
7.143
7.160
7.163
7.263
7.353
7.356
7.366
7.371
7.376
7.399
7.467
7.470
7.484
7.488
7.491
7.494
7.508
7.526
7.539
Ph
OCH3
O
N
H
24
ppm
1
2
3
4
5
6
7
8
9
2.90
1.96
1.00
0.99
2.96
3.94

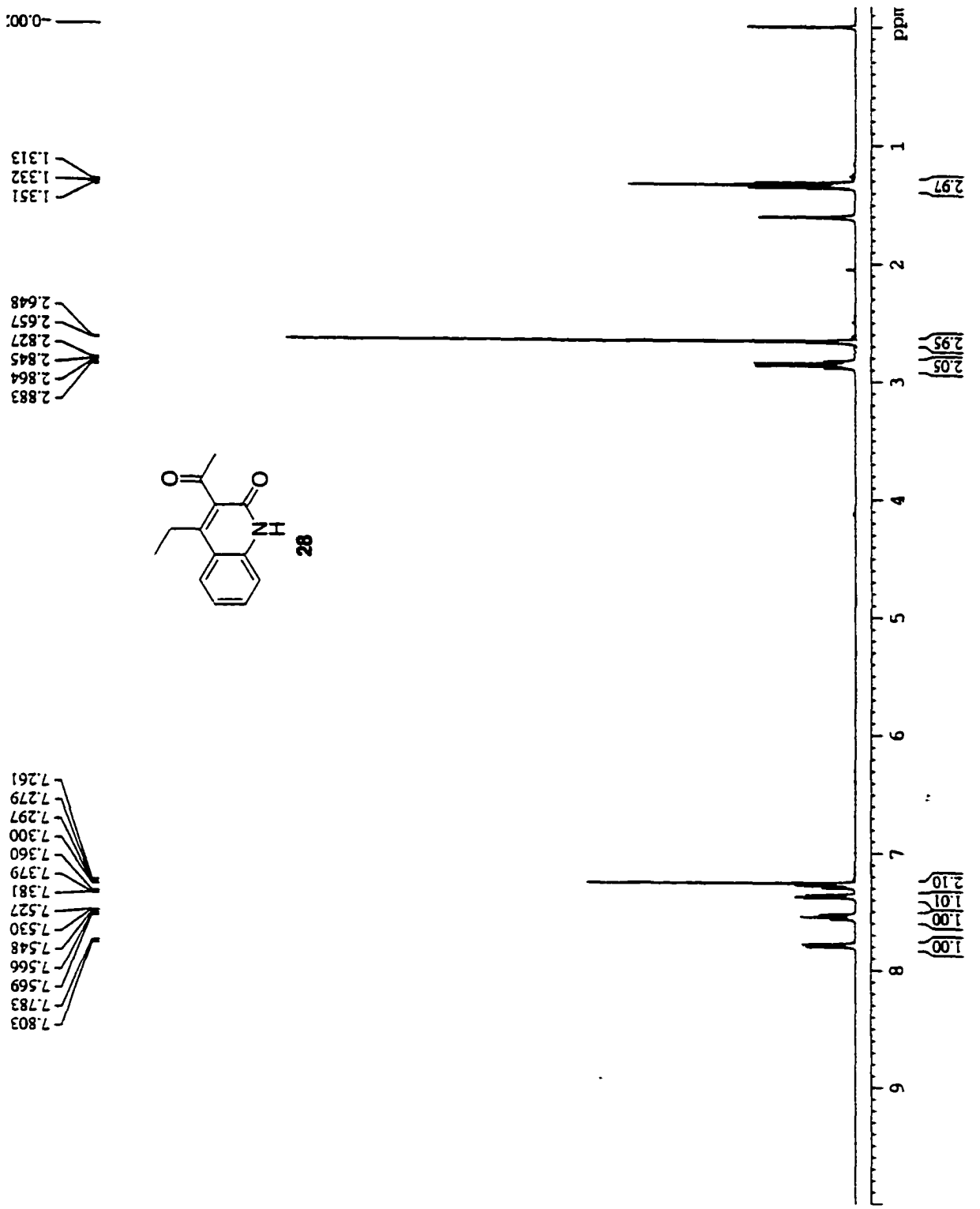

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
58.937
66.933
76.931
77.249
77.566
116.004
120.944
122.558
127.163
128.117
128.458
128.586
129.333
130.767
135.684
138.301
152.966
163.652
OCH3
Ph
O
NH
24

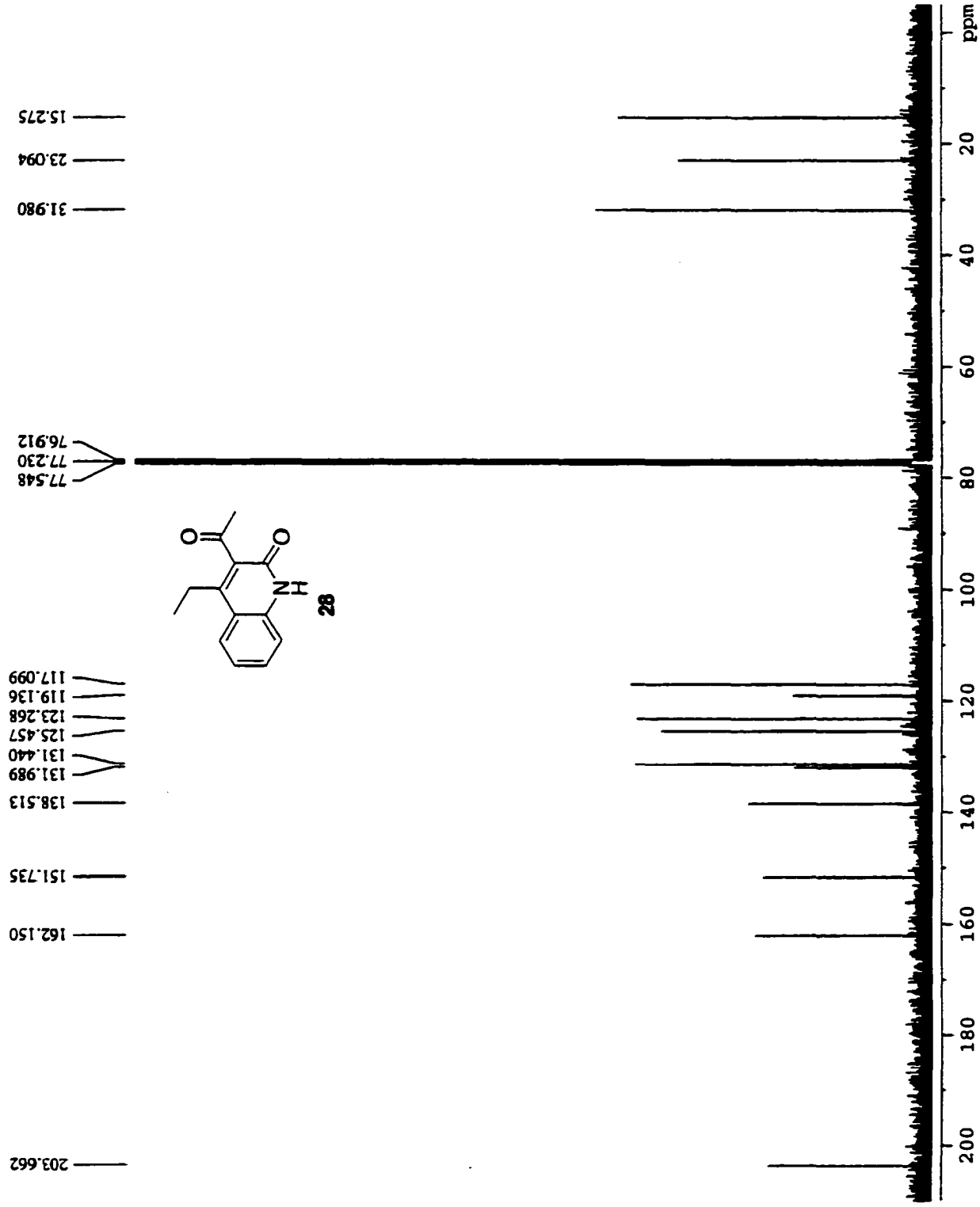

OCH2Ph
OCH2Ph
O
NH
25
ppm
1.00
1.08
10.70
1.27
2.00
1.99
1.99
1.99
1.99
0.000
4.562
4.604
4.754
4.889
7.197
7.200
7.215
7.218
7.221
7.236
7.239
7.245
7.281
7.288
7.297
7.301
7.306
7.309
7.319
7.329
7.333
7.337
7.339
7.346
7.349
7.354
7.358
7.364
7.371
7.374
7.391
7.411
7.472
7.475
7.490
7.493
7.511
7.513

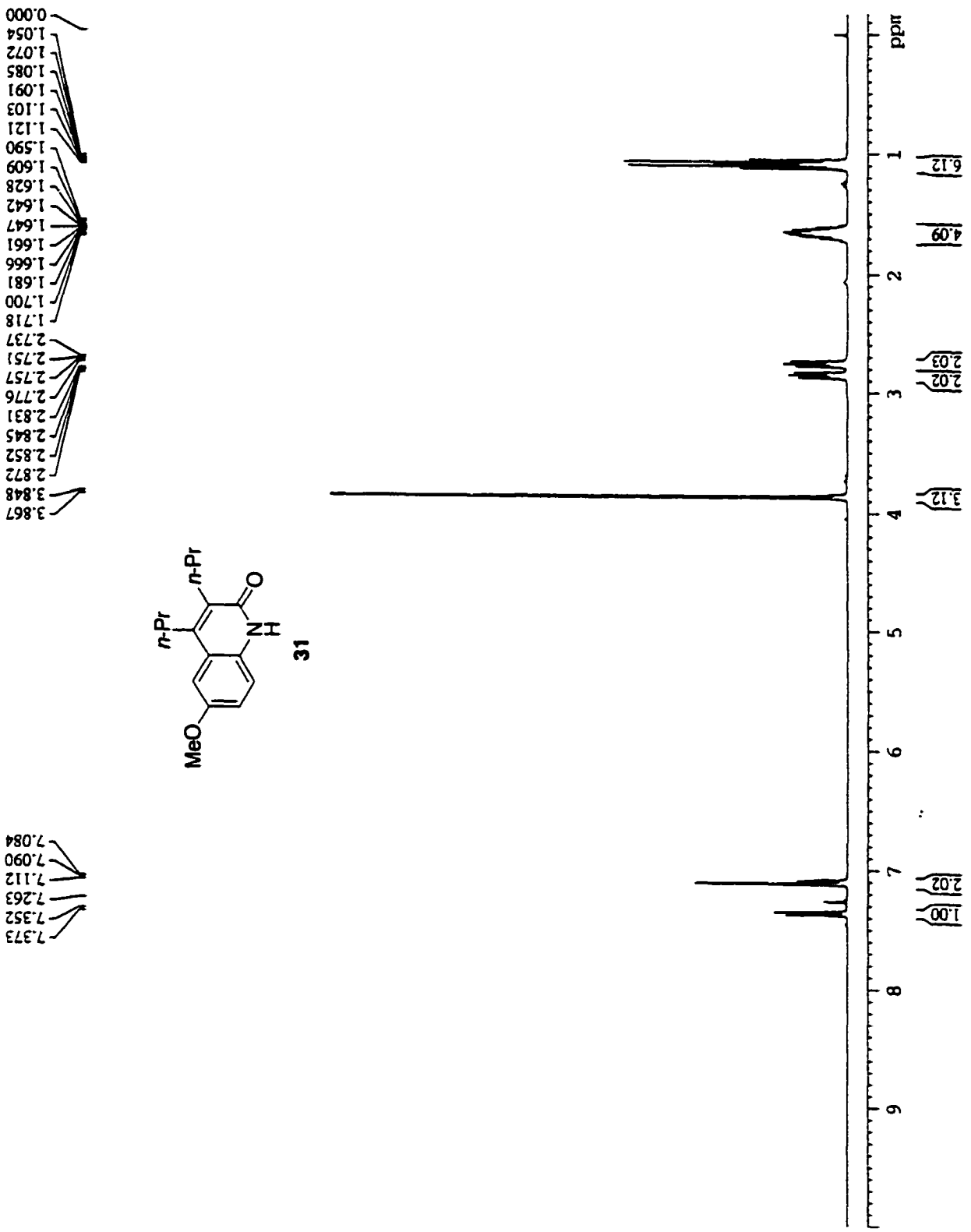
164.061
146.921
138.499
138.440
137.909
130.737
128.806
128.671
128.561
128.269
128.211
128.138
127.868
126.145
122.822
119.945
116.477
77.549
77.231
76.914
73.073
73.022
65.374
62.784
25
OCH2Ph
OCH2Ph
ppm


0.000
0.468
2.608
8.71
2.95
1.00
1.00
1.08
1.00
ppm
1 2 3 4 5 6 7 8 9
7.742
7.740
7.722
7.720
7.470
7.452
7.449
7.340
7.338
7.319
7.317
7.257
7.196
7.193
7.176
7.158
7.155
Si(CH3)3
CH3
O
N
H
26

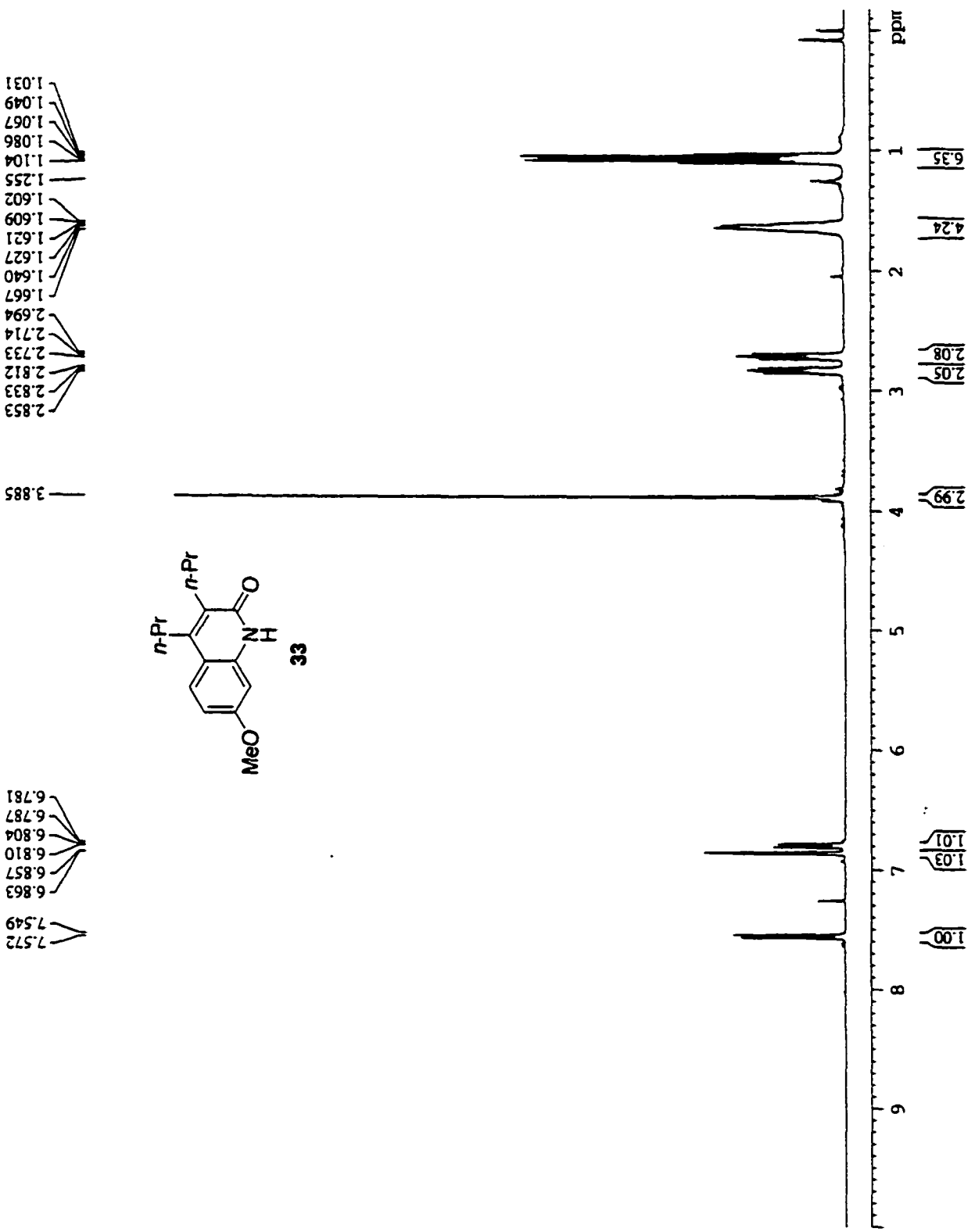
167.324
155.471
138.952
130.738
130.499
124.658
122.054
121.371
116.097
77.546
77.228
76.910
19.202
2.382
26
CH3
Si(CH3)3
O
N
H
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

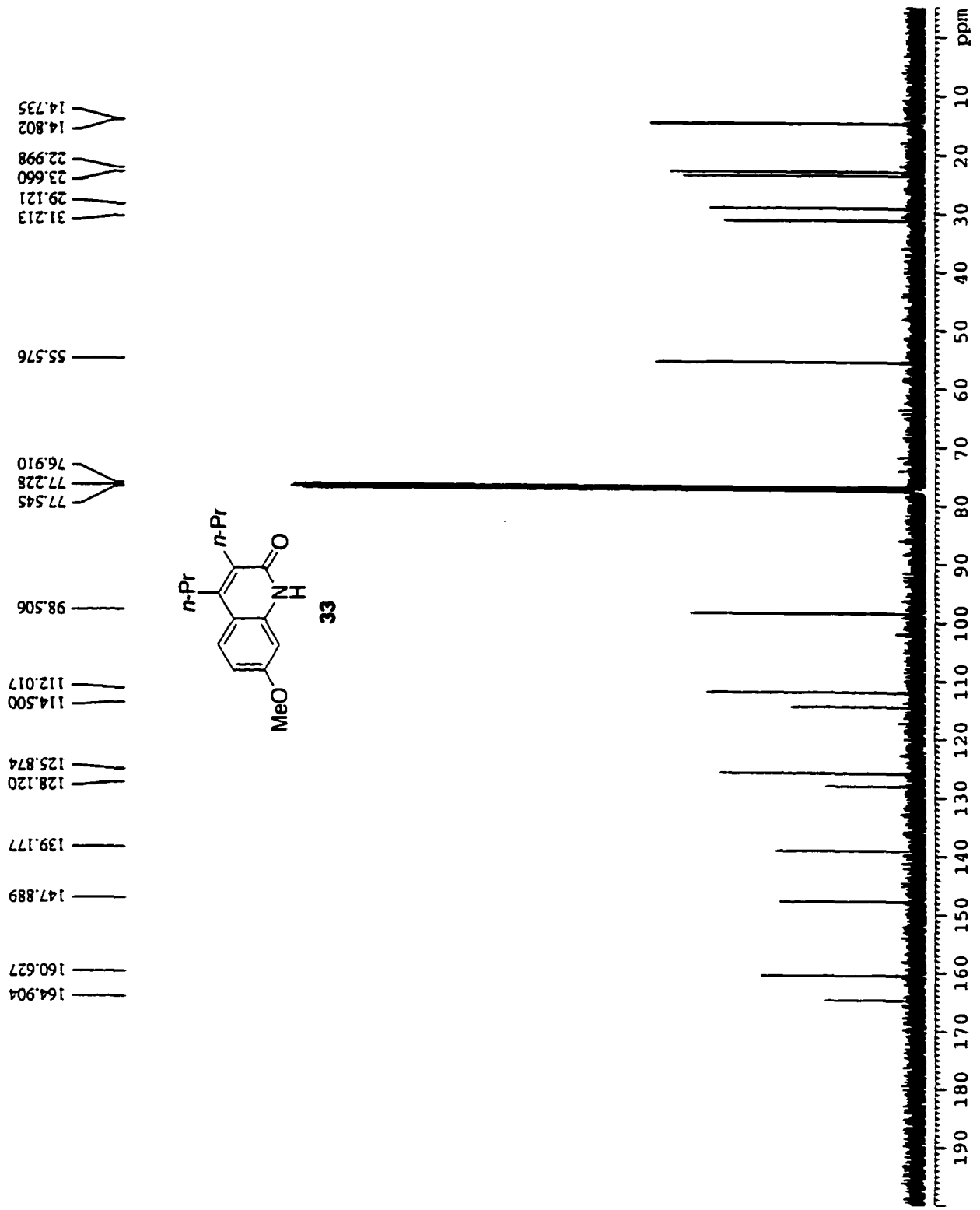

ppm
1
2
3
4
5
6
7
8
9
2.97
2.95
2.05
1.00
1.01
1.00
2.10
7.803
7.783
7.569
7.566
7.548
7.530
7.527
7.381
7.379
7.360
7.300
7.297
7.279
7.261
2.883
2.864
2.845
2.827
2.657
2.648
1.351
1.332
1.313
0.000
O
O
NH
28


ppm
20
40
60
80
100
120
140
160
180
200
15.275
23.094
31.980
76.912
77.230
77.548
117.099
119.136
123.268
125.457
131.440
131.989
138.513
151.735
162.150
203.662
O
O
NH
28


0.000
1.054
1.072
1.085
1.091
1.103
1.121
1.590
1.609
1.628
1.642
1.647
1.661
1.666
1.681
1.700
1.718
2.737
2.751
2.757
2.776
2.831
2.845
2.852
2.872
3.848
3.867
7.373
7.352
7.263
7.112
7.090
7.084
n-Pr
n-Pr
O
NH
MeO
31
ppm
1
2
3
4
5
6
7
8
9
6.12
4.09
2.03
2.02
3.12
2.02
1.00

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
MeO
n-Pr
n-Pr
N
H
O
31
163.876
155.004
146.958
132.183
131.825
121.029
117.677
117.552
107.293
77.548
77.230
76.913
55.919
31.236
29.372
23.287
22.931
14.854
14.759


1.031
1.049
1.067
1.086
1.104
1.255
1.602
1.609
1.621
1.627
1.640
1.667
2.694
2.714
2.733
2.812
2.833
2.853
3.885
6.781
6.787
6.804
6.810
6.857
6.863
7.549
7.572
n-Pr
n-Pr
O
N
H
MeO
33
ppm
1
2
3
4
5
6
7
8
9
6.35
4.24
2.08
2.05
2.99
1.01
1.03
1.00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23.660
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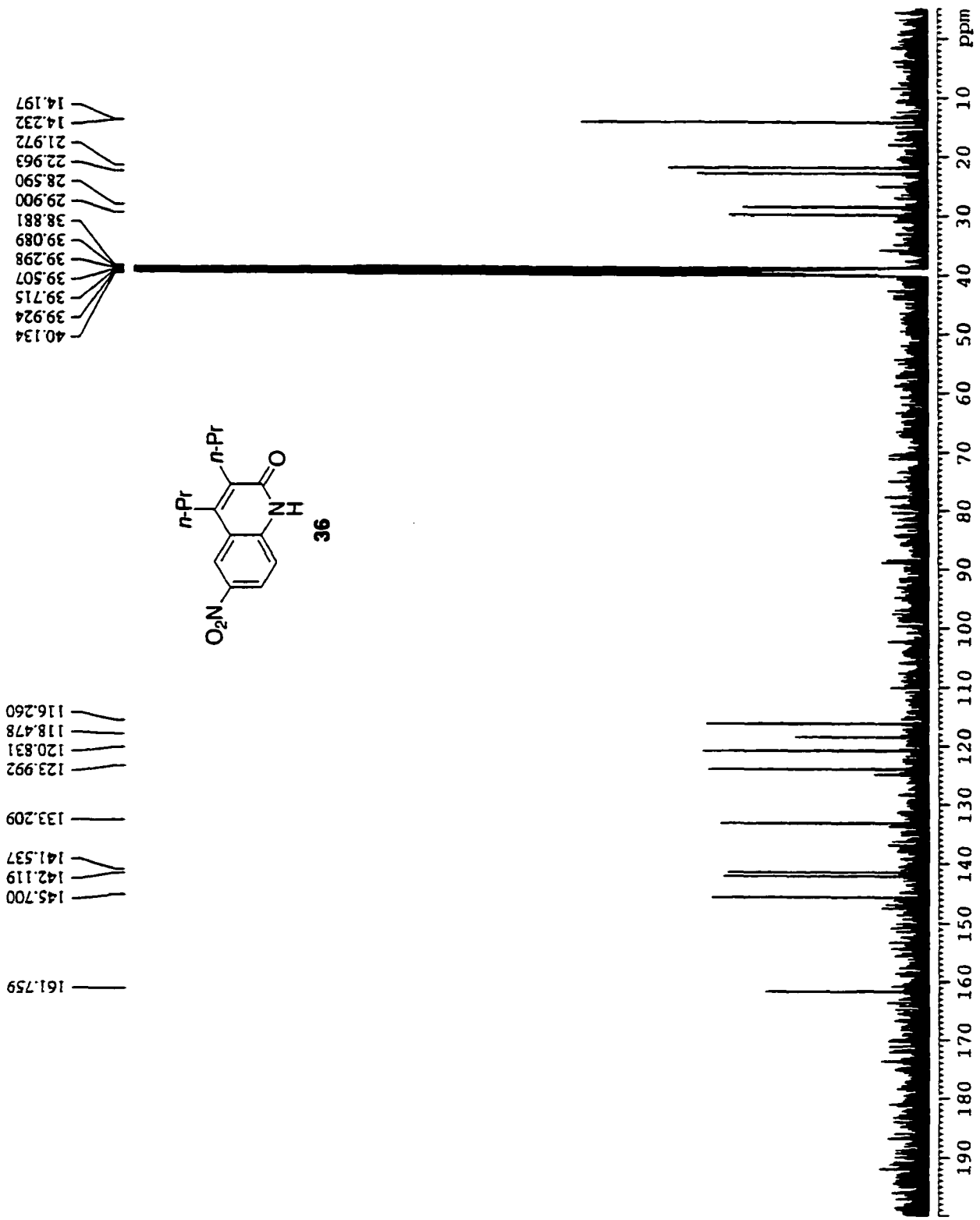
31.213
55.576
76.910
77.228
77.545
98.506
112.017
114.500
125.874
128.120
139.177
147.889
160.627
164.904
n-Pr
n-Pr
O
NH
MeO
33
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

0.99
1.00
1.01
1.99
2.02
4.27
3.17
3.33
ppm
8.502
8.496
8.287
8.281
8.265
8.259
7.425
7.403
3.331
2.906
2.886
2.866
2.598
2.579
2.559
2.500
1.984
1.600
1.581
1.562
1.543
1.525
1.514
1.495
1.476
1.457
1.438
1.420
1.168
1.070
1.052
1.033
0.977

O2N
n-Pr
n-Pr
N
H
O

36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14.232
21.972
22.963
28.590
29.900
38.881
39.089
39.298
39.507
39.715
39.924
40.134
n-Pr
n-Pr
O
NH
O2N
36
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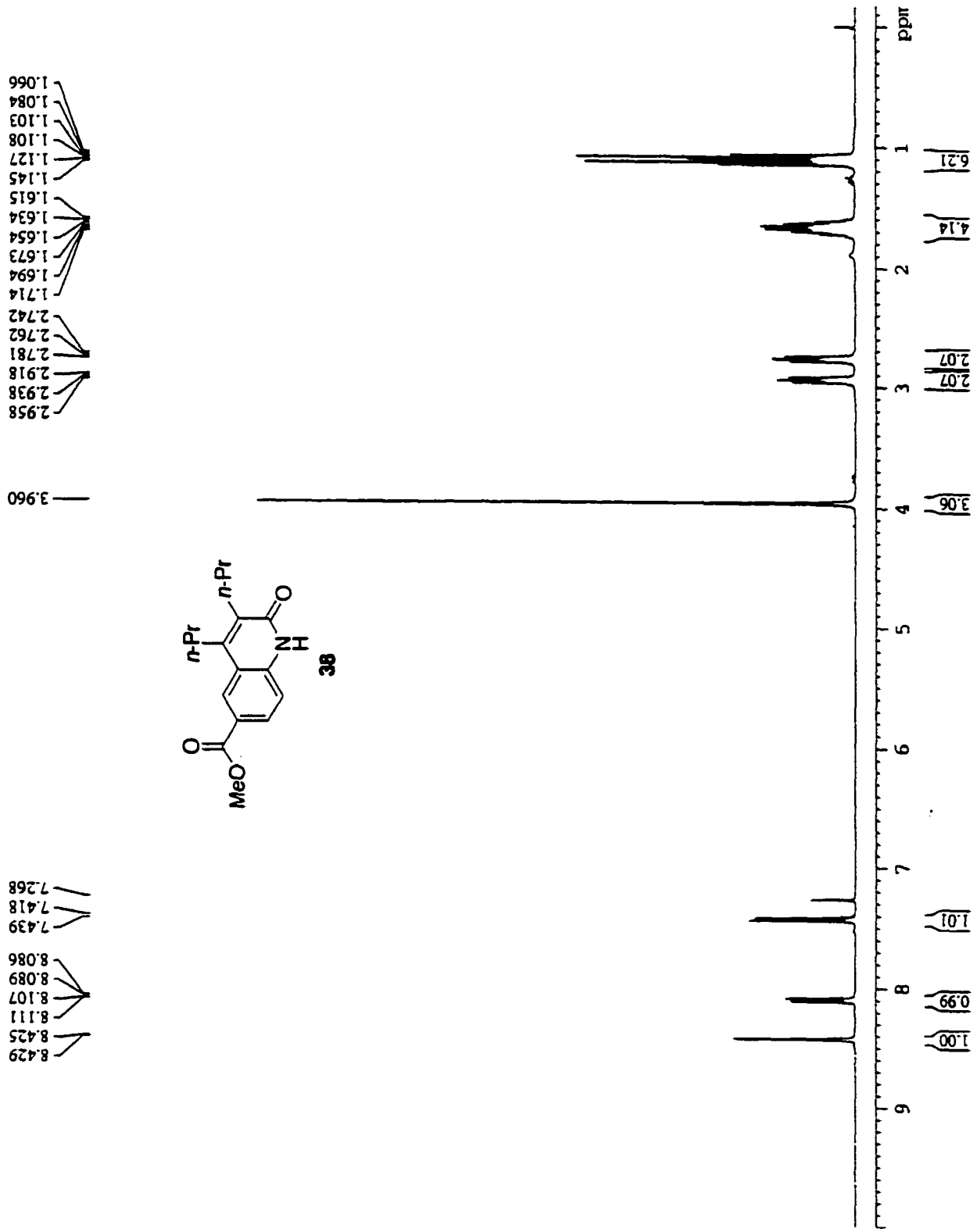
118.478
120.831
123.992
133.209
141.537
142.119
145.700
161.759
ppm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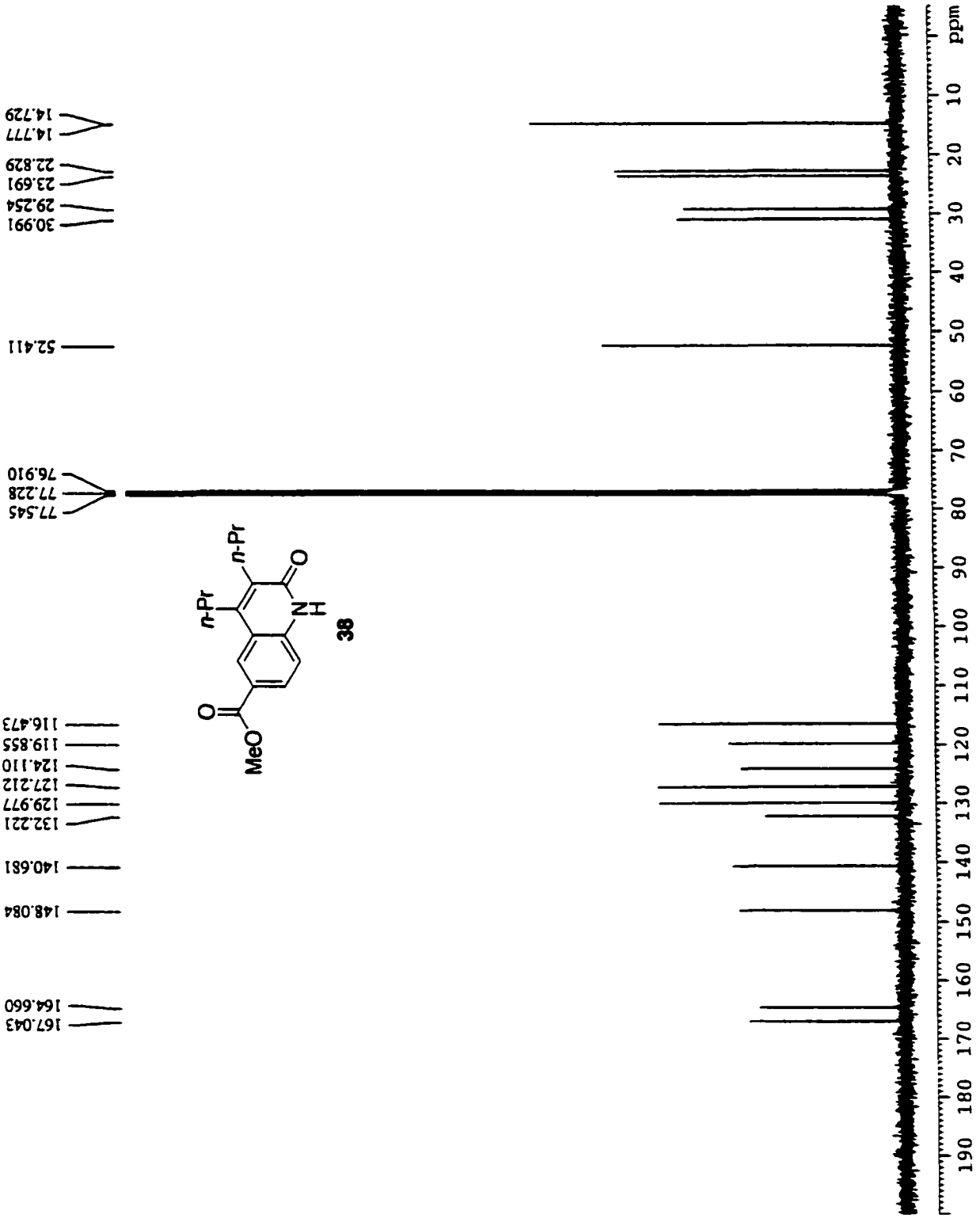
1.084
1.103
1.108
1.127
1.145
1.615
1.634
1.654
1.673
1.694
1.714
2.742
2.762
2.781
2.918
2.938
2.958
3.960
7.268
7.418
7.439
8.086
8.089
8.107
8.111
8.425
8.429
n-Pr
n-Pr
O
NH
O
MeO
38
ppm
1
2
3
4
5
6
7
8
9
6.21
4.14
2.07
2.07
3.06
1.01
0.99
1.00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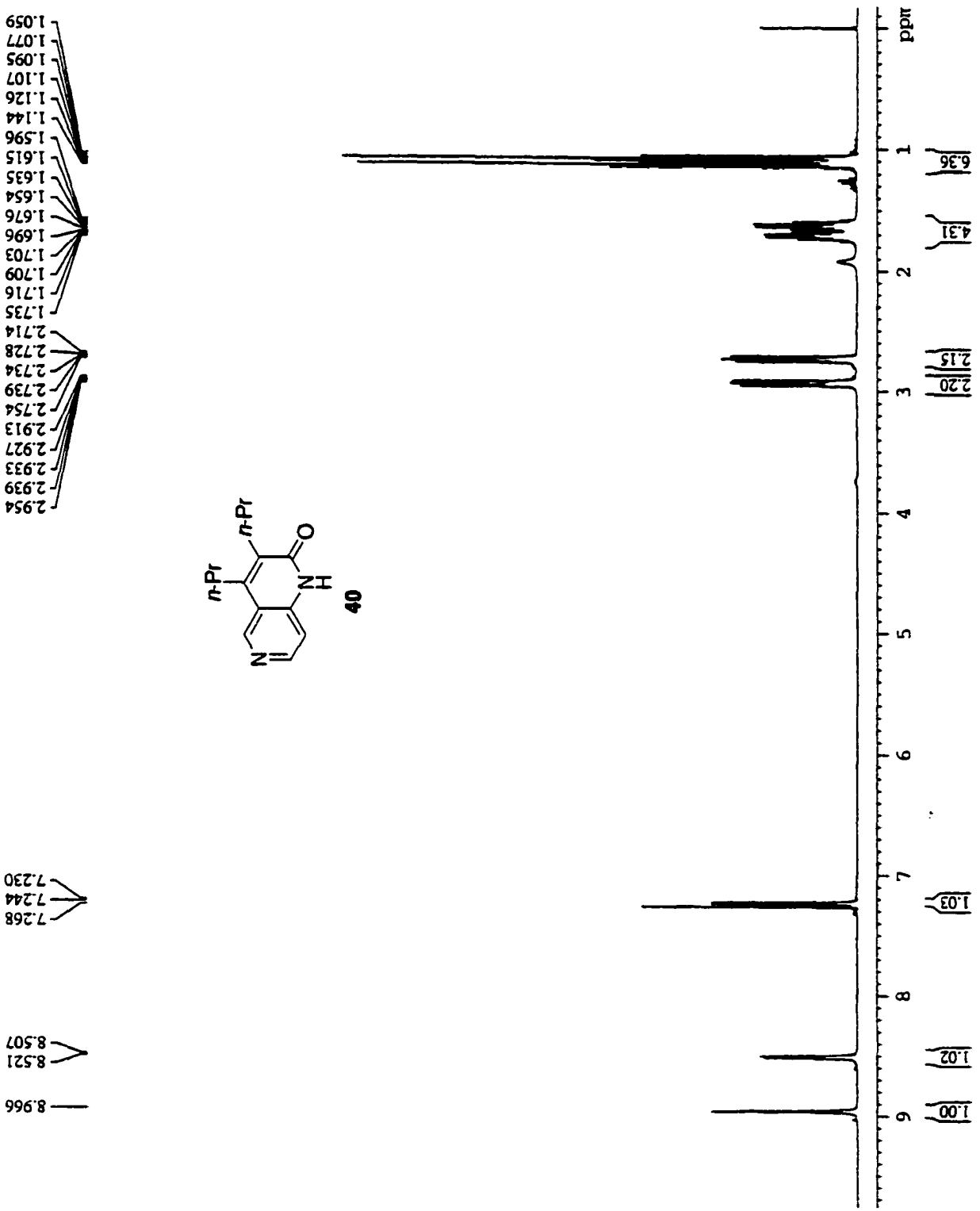
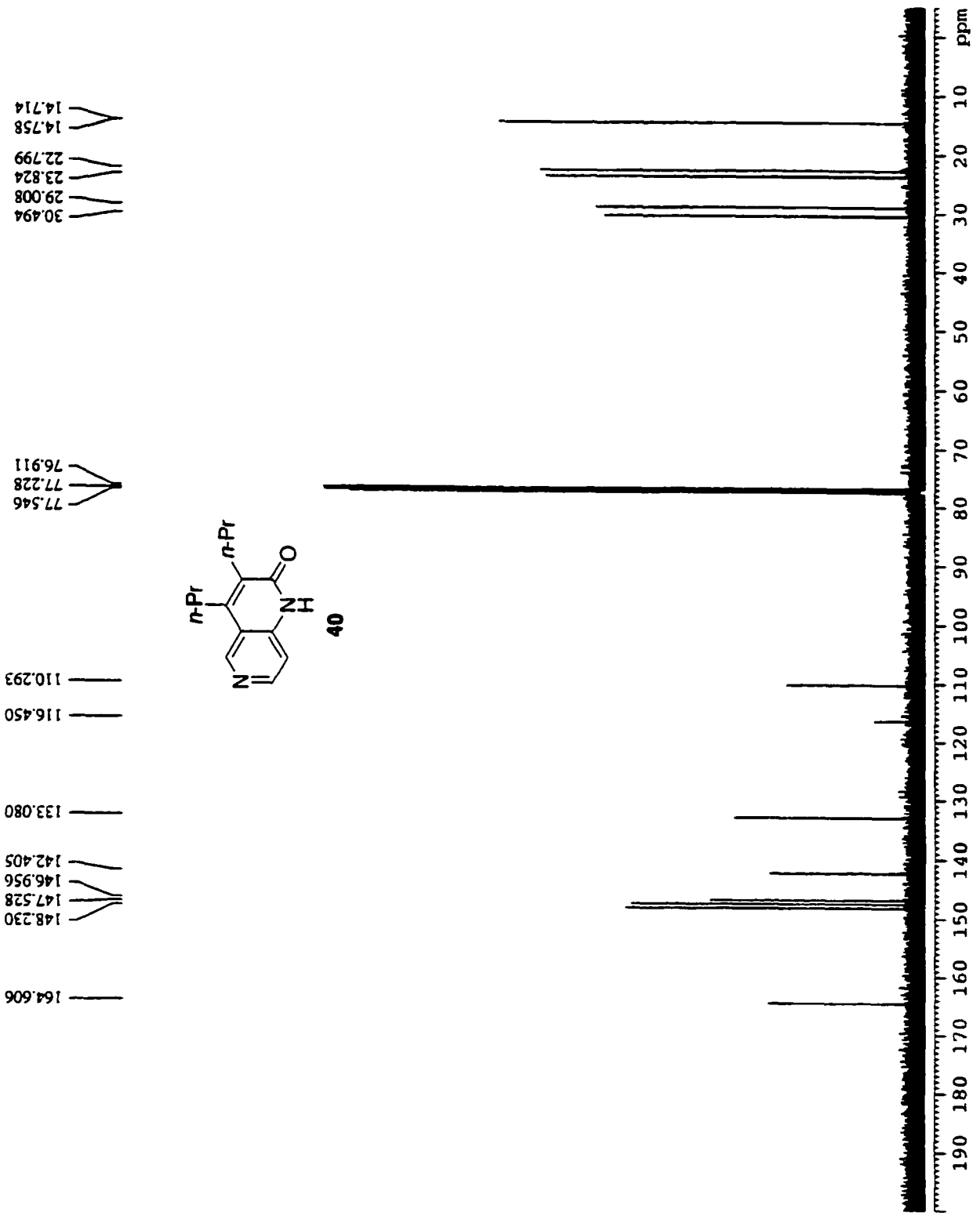
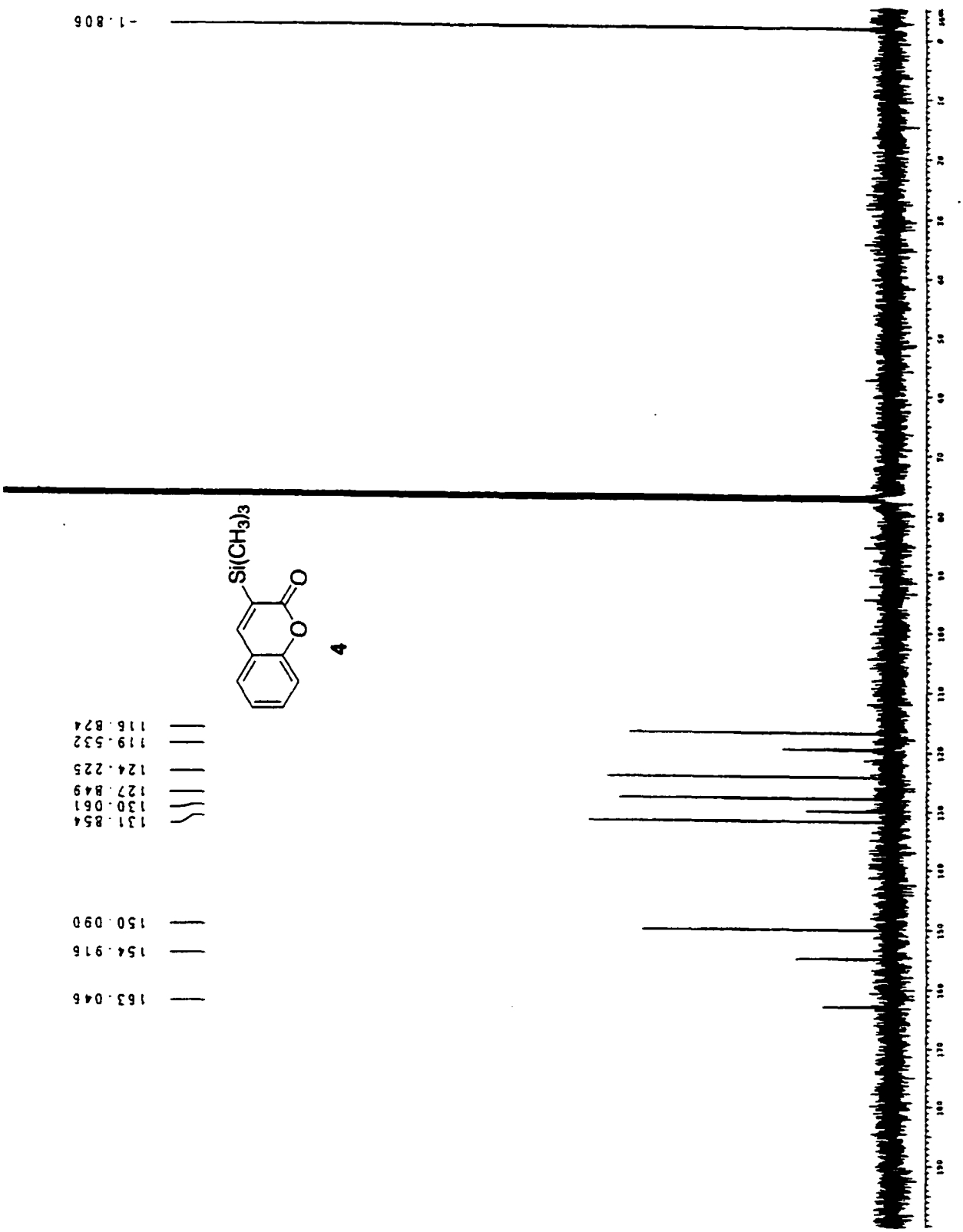
14.777
22.829
23.691
29.254
30.991
52.411
76.910
77.228
77.545
116.473
119.855
124.110
127.212
129.977
132.221
140.681
148.084
164.660
167.043
n-Pr
n-Pr
O
NH
O
MeO
38
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

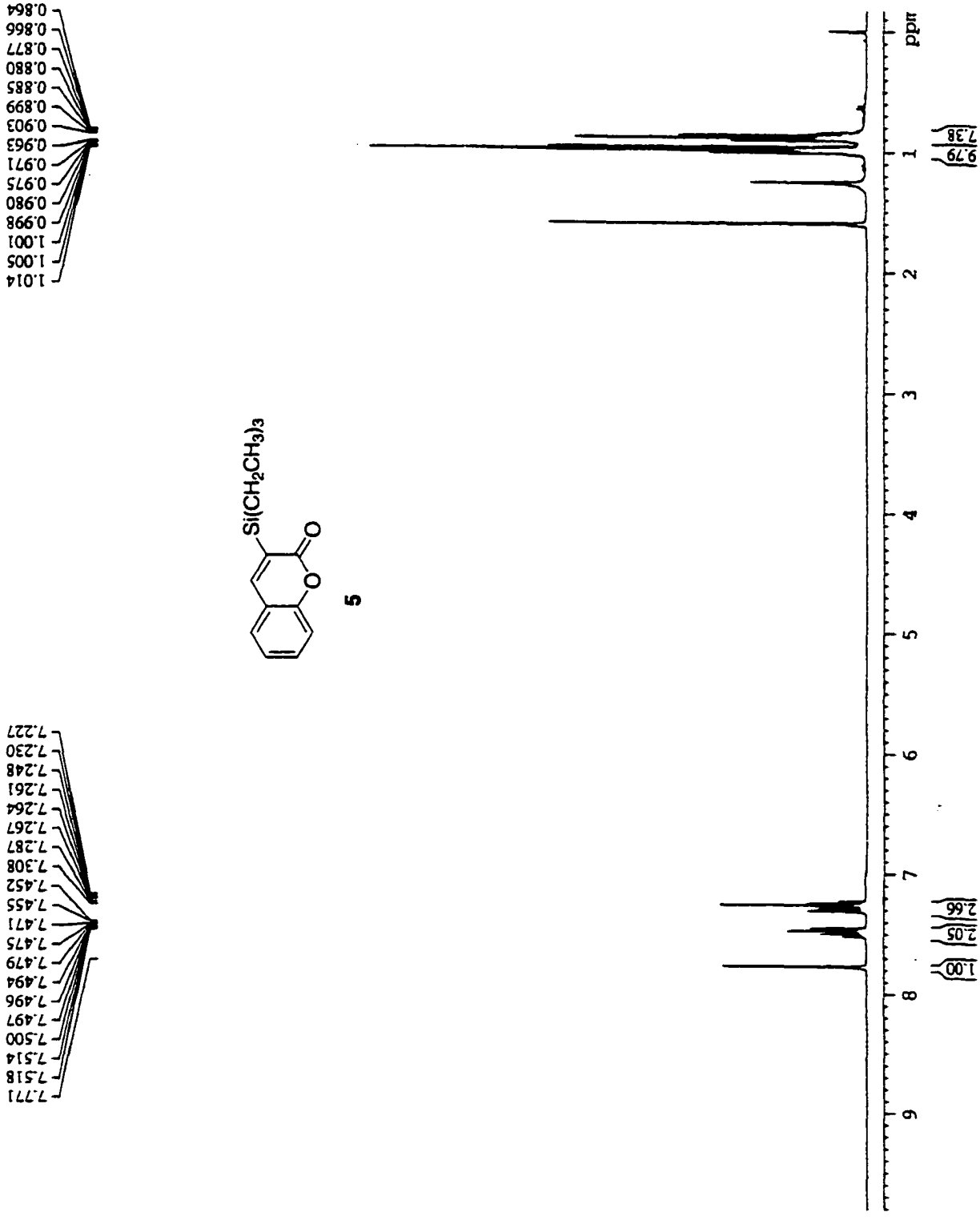

1.059
1.077
1.095
1.107
1.126
1.144
1.596
1.615
1.635
1.654
1.676
1.696
1.703
1.709
1.716
1.735
2.714
2.728
2.734
2.739
2.754
2.913
2.927
2.933
2.939
2.954
7.230
7.244
7.268
8.507
8.521
8.966
n-Pr
n-Pr
O
N
H
N
40
ppm
1
2
3
4
5
6
7
8
9
6.36
4.31
2.15
2.20
1.03
1.02
1.00

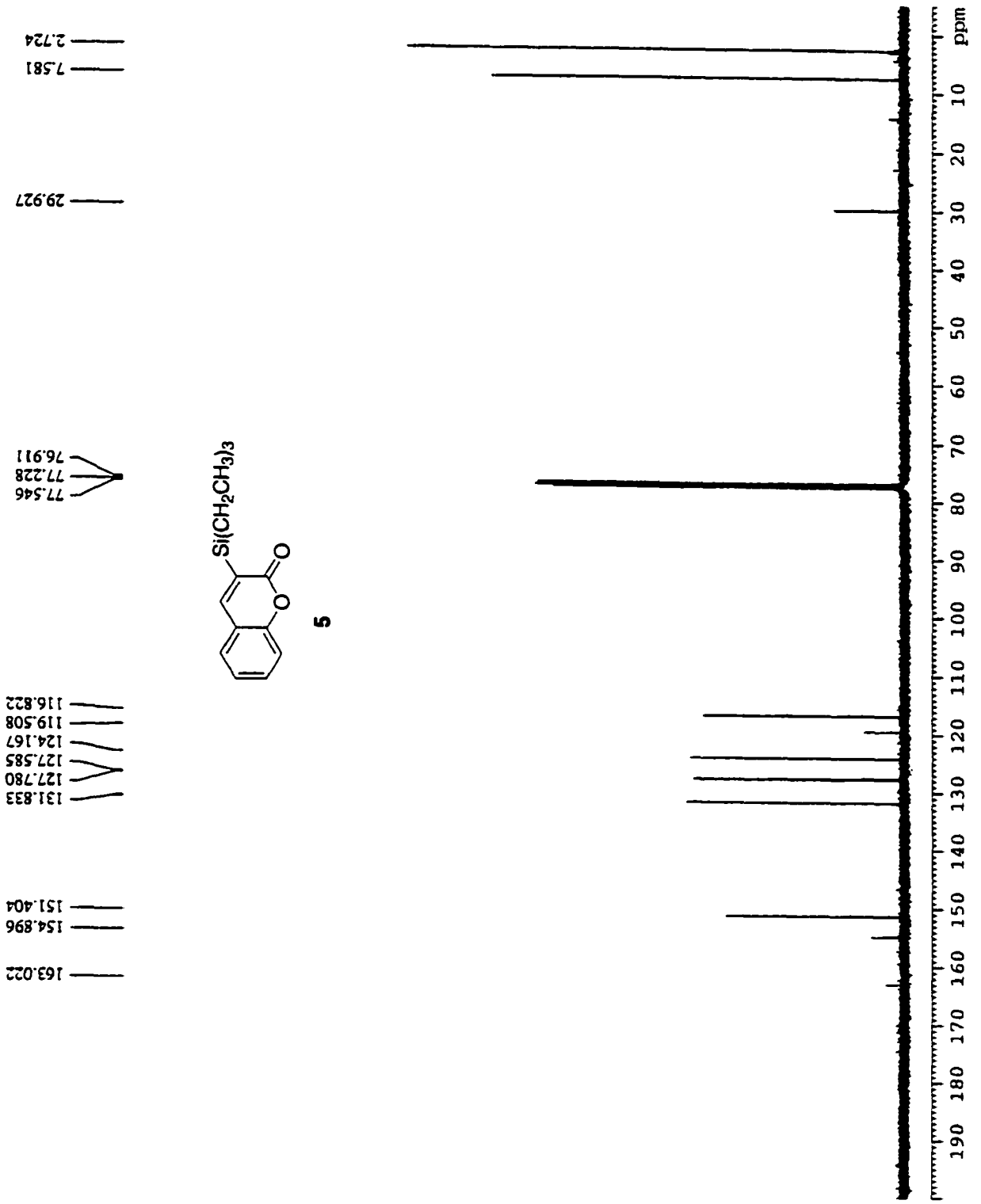

14.714
14.758
22.799
23.824
29.008
30.494
76.911
77.228
77.546
110.293
116.450
133.080
142.405
146.956
147.528
148.230
164.606
n-Pr
n-Pr
O
NH
N
40
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

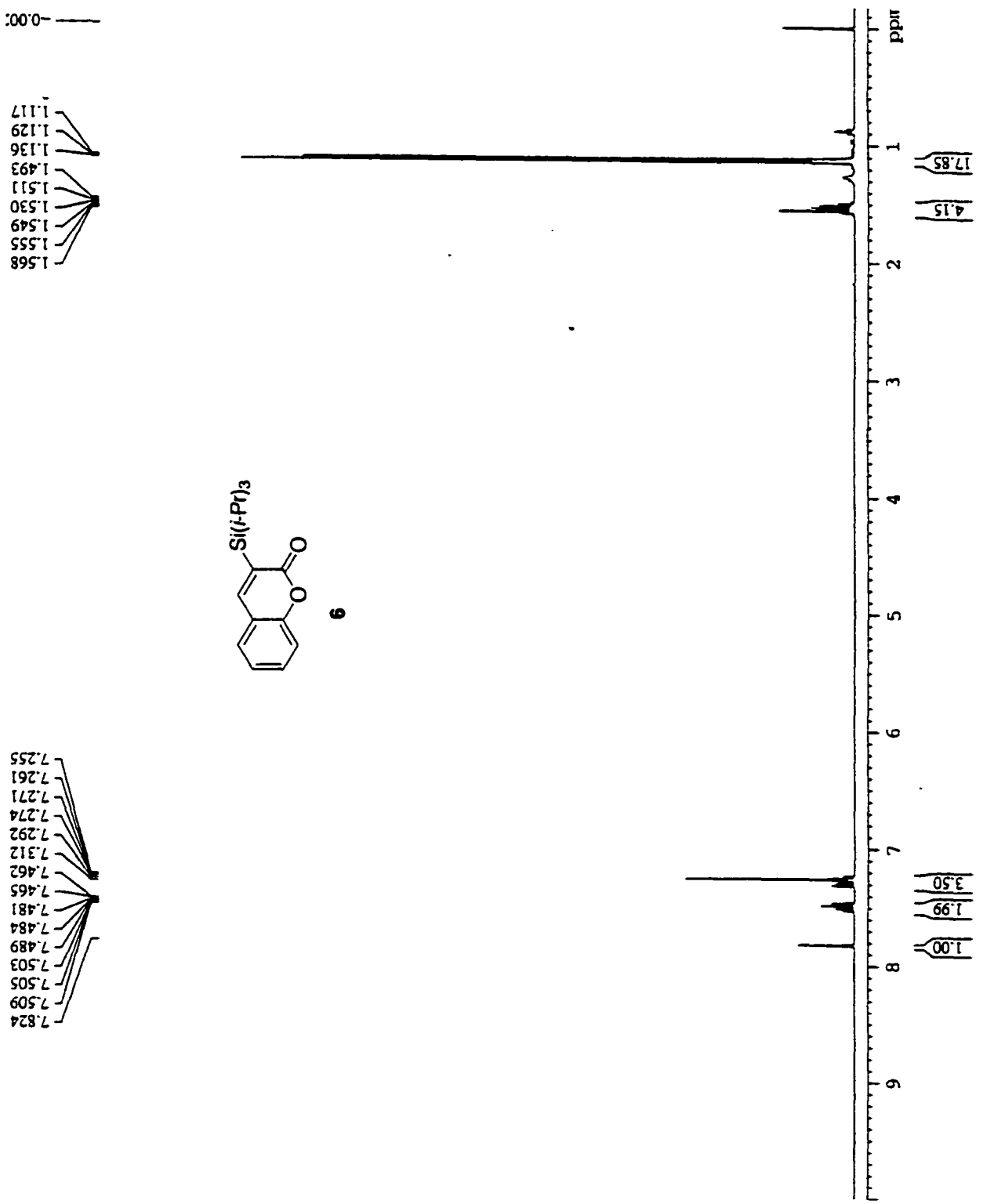
APPENDIX C. CHAPTER III ^{1}H AND ^{13}C NMR SPECTRA

0.330
8.81
2.51
2.01
1.00
7.790
7.519
7.515
7.501
7.497
7.494
7.476
7.458
7.455
7.311
7.310
7.291
7.268
7.249
7.247
7.230
7.228
Si(CH3)3
O
O
4

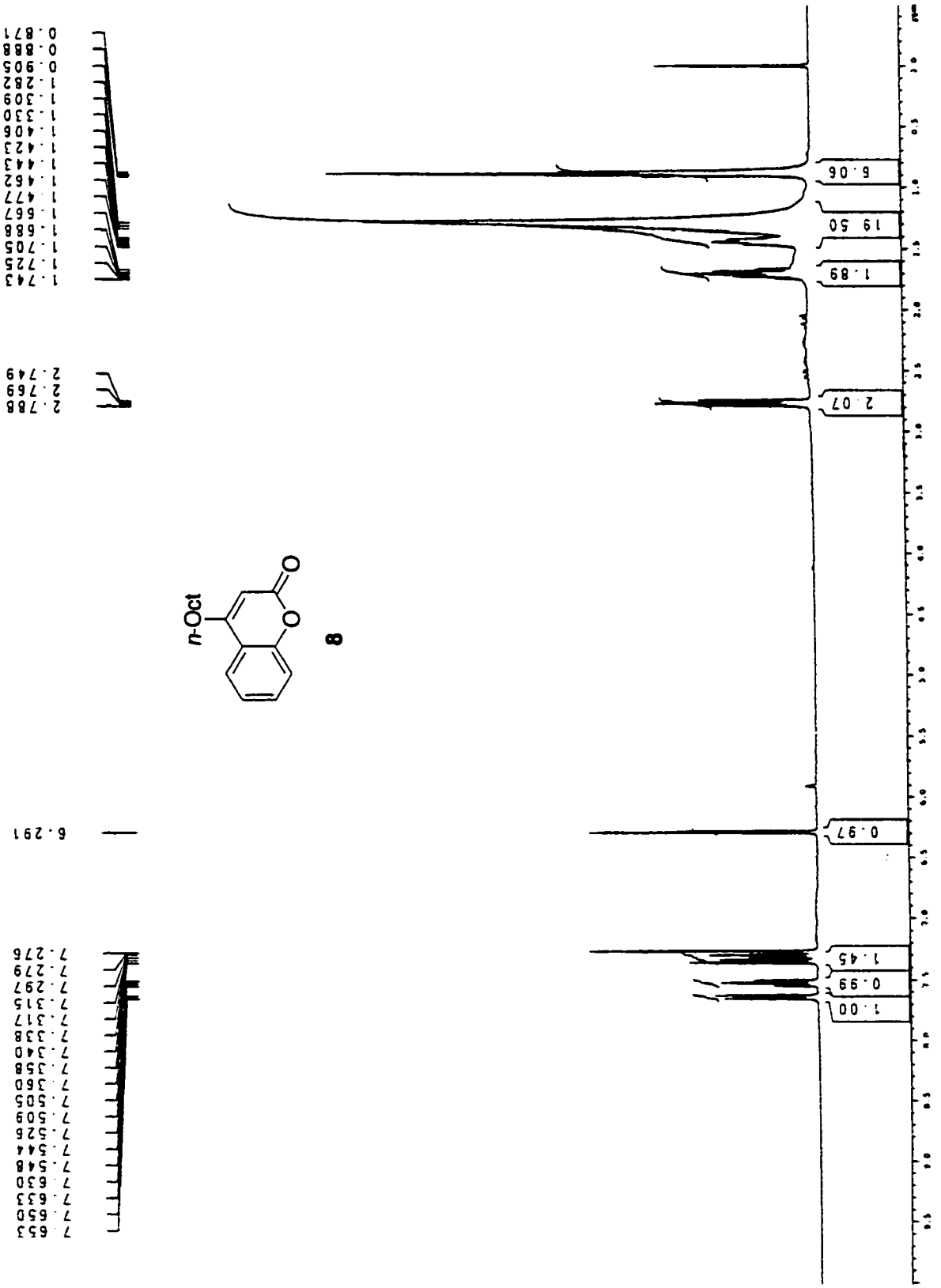

-1.806
Si(CH3)3
O
O
4
116.874
119.532
124.225
127.849
130.061
131.854
150.090
154.916
163.046

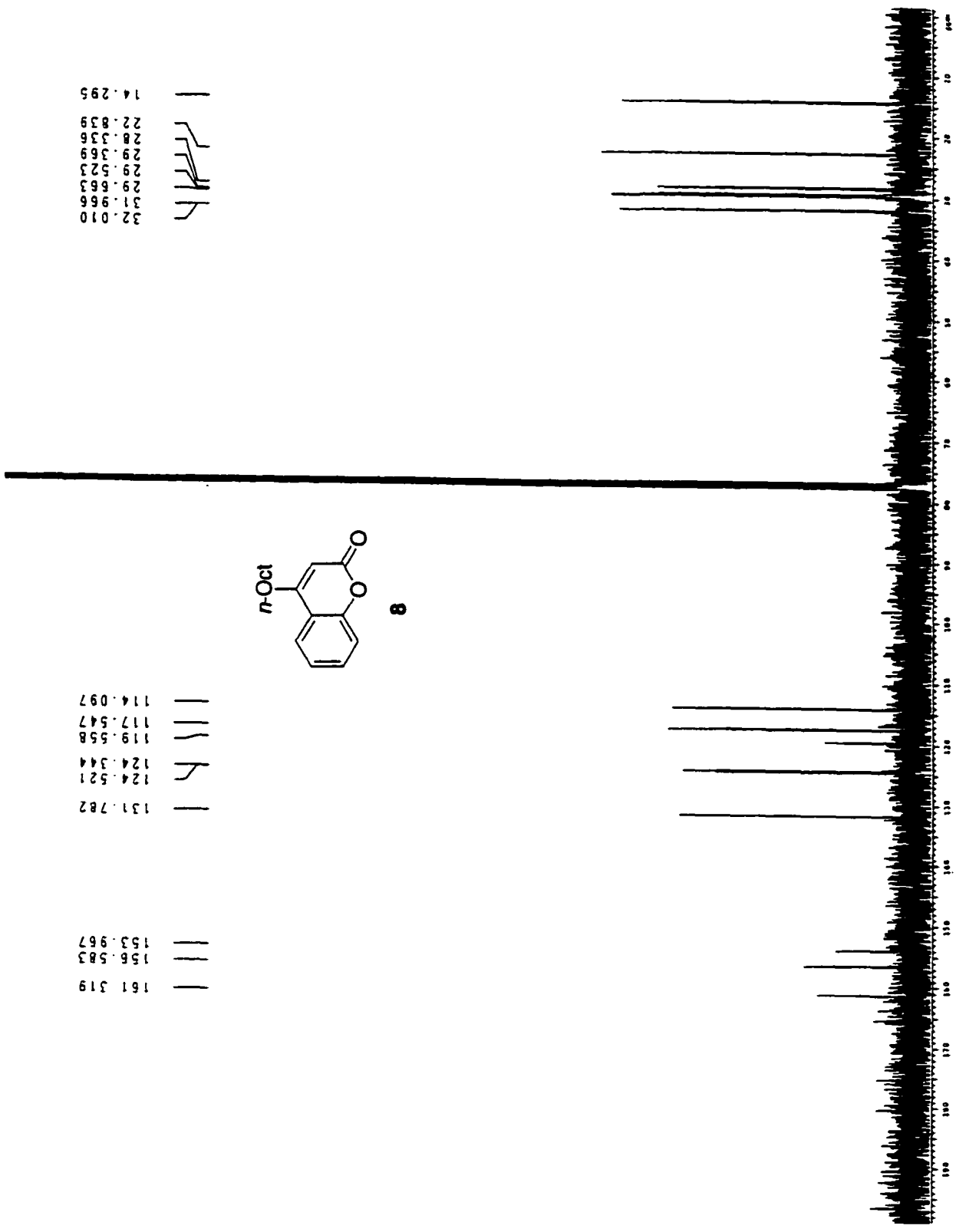

0.864
0.866
0.877
0.880
0.885
0.899
0.903
0.963
0.971
0.975
0.980
0.998
1.001
1.005
1.014
7.227
7.230
7.248
7.261
7.264
7.267
7.287
7.308
7.452
7.455
7.471
7.475
7.479
7.494
7.496
7.497
7.500
7.514
7.518
7.771
Si(CH2CH3)3
O
O
5
ppm
1
2
3
4
5
6
7
8
9
9.79
7.38
1.00
2.05
2.66

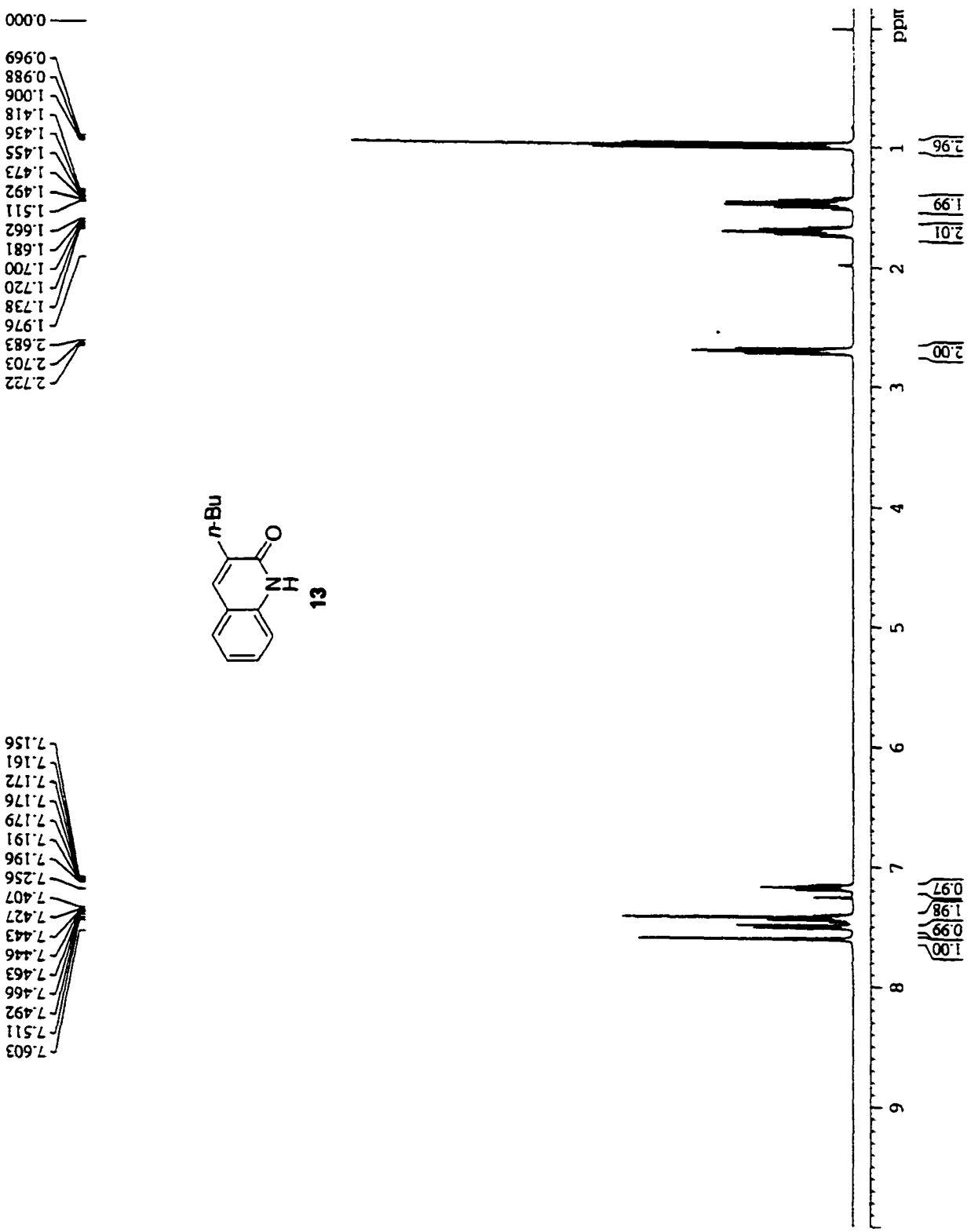

2.724
7.581
29.927
76.911
77.228
77.546
116.822
119.508
124.167
127.585
127.780
131.833
151.404
154.896
163.022
Si(CH2CH3)3
O
O
5
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


Si(i-Pr)3
O
O
6
ppm
17.85
4.15
3.50
1.99
1.00
0.000
1.117
1.129
1.136
1.493
1.511
1.530
1.549
1.555
1.568
7.255
7.261
7.271
7.274
7.292
7.312
7.462
7.465
7.481
7.484
7.489
7.503
7.505
7.509
7.824

ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
163.245
154.860
152.325
131.876
127.831
126.139
124.135
119.410
116.741
77.546
77.229
76.911
18.888
11.294
6
Si(i-Pr)3


n-Oct
O
O
O
8
6.06
19.50
1.89
2.07
0.97
1.45
0.99
1.00
6.291
7.653
7.650
7.633
7.630
7.548
7.544
7.526
7.509
7.505
7.360
7.358
7.340
7.338
7.317
7.315
7.297
7.279
7.276
2.788
2.769
2.749
1.743
1.725
1.705
1.688
1.667
1.477
1.462
1.443
1.423
1.406
1.330
1.309
1.282
0.905
0.888
0.871


n-Oct
O
O
O
8
161.319
156.583
153.967
131.782
124.521
124.344
119.558
117.547
114.097
32.010
31.966
29.663
29.523
29.369
28.336
22.839
14.295

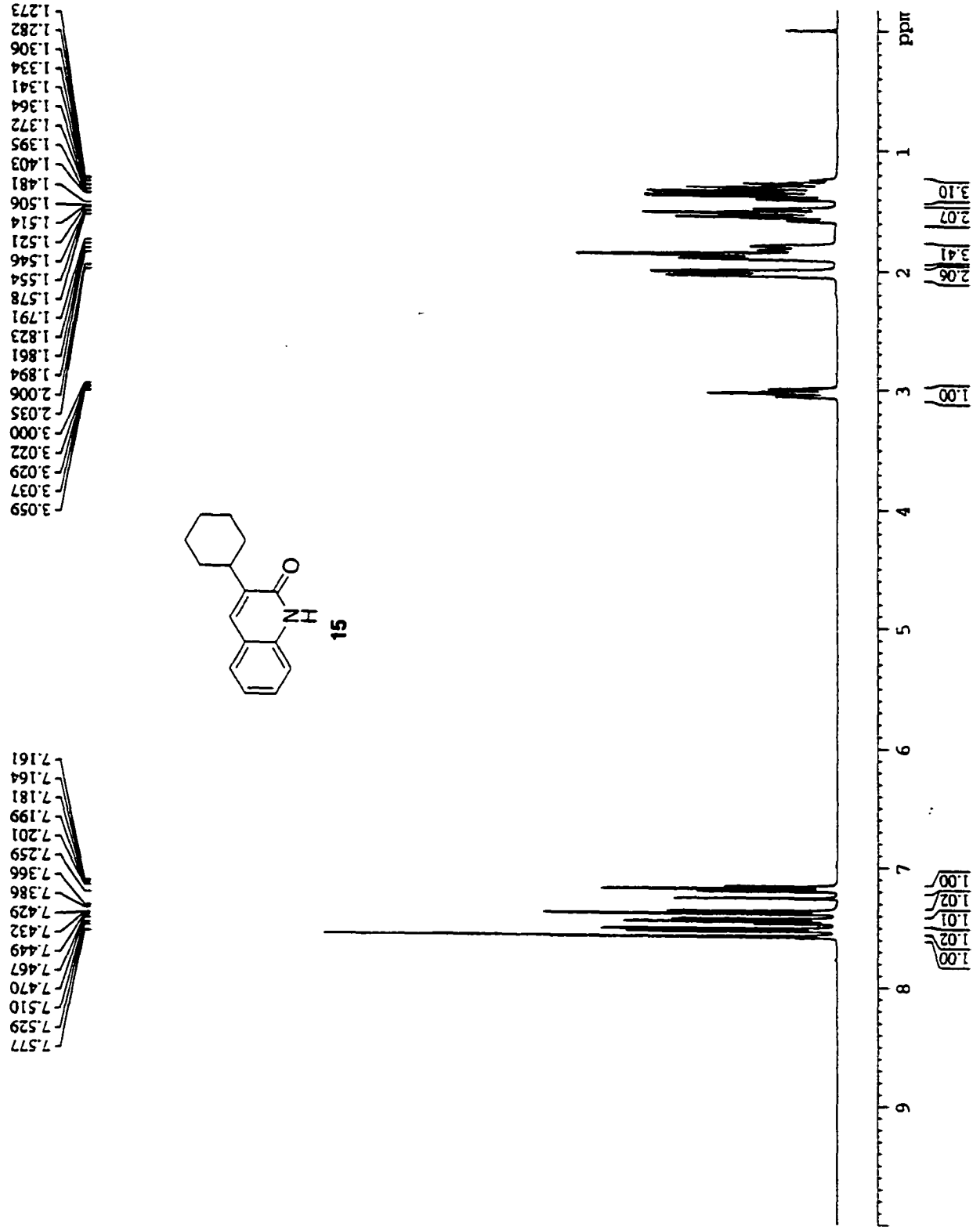

0.000
0.969
0.988
1.006
1.418
1.436
1.455
1.473
1.492
1.511
1.662
1.681
1.700
1.720
1.738
1.976
2.683
2.703
2.722
n-Bu
O
NH
13
7.156
7.161
7.172
7.176
7.179
7.191
7.196
7.256
7.407
7.427
7.443
7.446
7.463
7.466
7.492
7.511
7.603
ppm
1
2
3
4
5
6
7
8
9
2.96
1.99
2.01
2.00
0.97
1.98
0.99
1.00

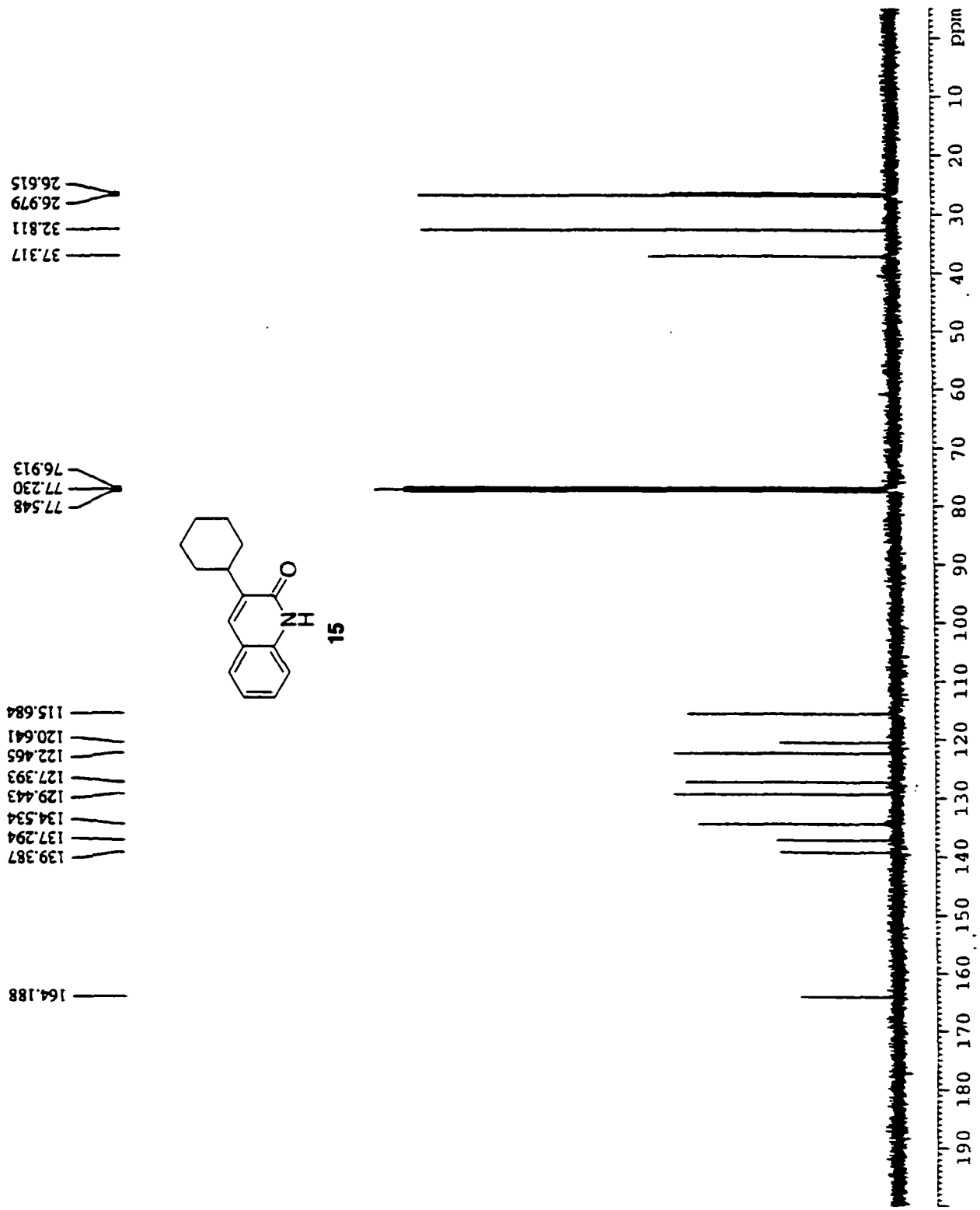
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
164.739
137.710
136.639
134.489
129.411
127.148
122.488
120.537
115.885
77.548
77.230
76.912
30.794
30.143
22.757
14.239
13
n-Bu

1.04
2.04
0.98
1.00
2.06
2.07
2.05
3.05
ppm
7.737
7.717
7.502
7.493
7.482
7.266
7.250
7.242
7.239
7.230
7.219
7.209
6.607
2.887
2.868
2.849
1.760
1.741
1.722
1.715
1.703
1.683
1.523
1.504
1.485
1.466
1.448
1.430
1.000
0.982
0.964
0.000

14
n-Bu
N
H
O

164.843
153.584
138.847
130.499
124.330
122.591
120.081
119.563
117.135
77.549
77.231
76.914
32.162
31.142
22.801
14.094
14
n-Bu
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


15
ppm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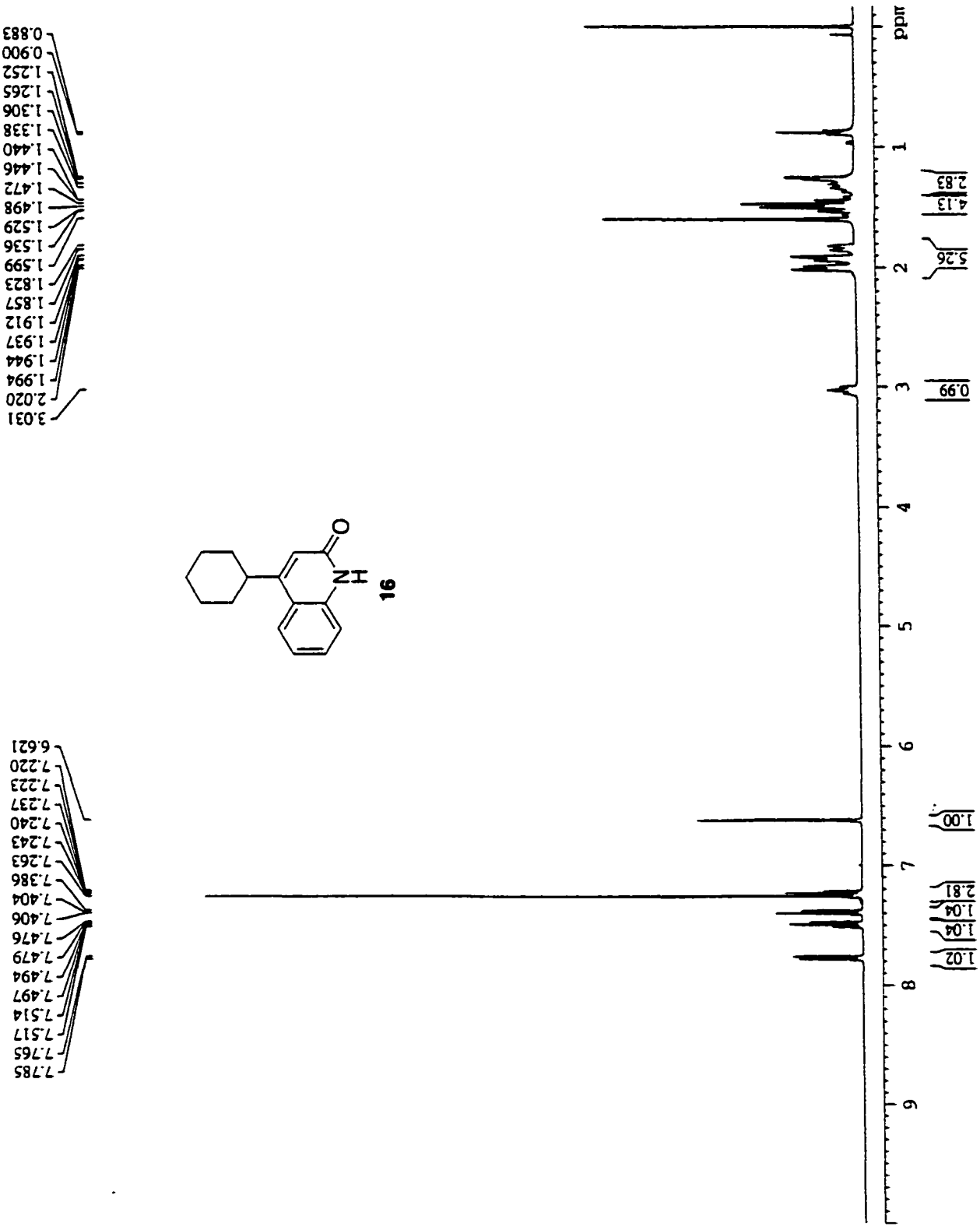
139.387
137.294
134.534
129.443
127.393
122.465
120.641
115.684
77.548
77.230
76.913
37.317
32.811
26.979
26.615
15
ppm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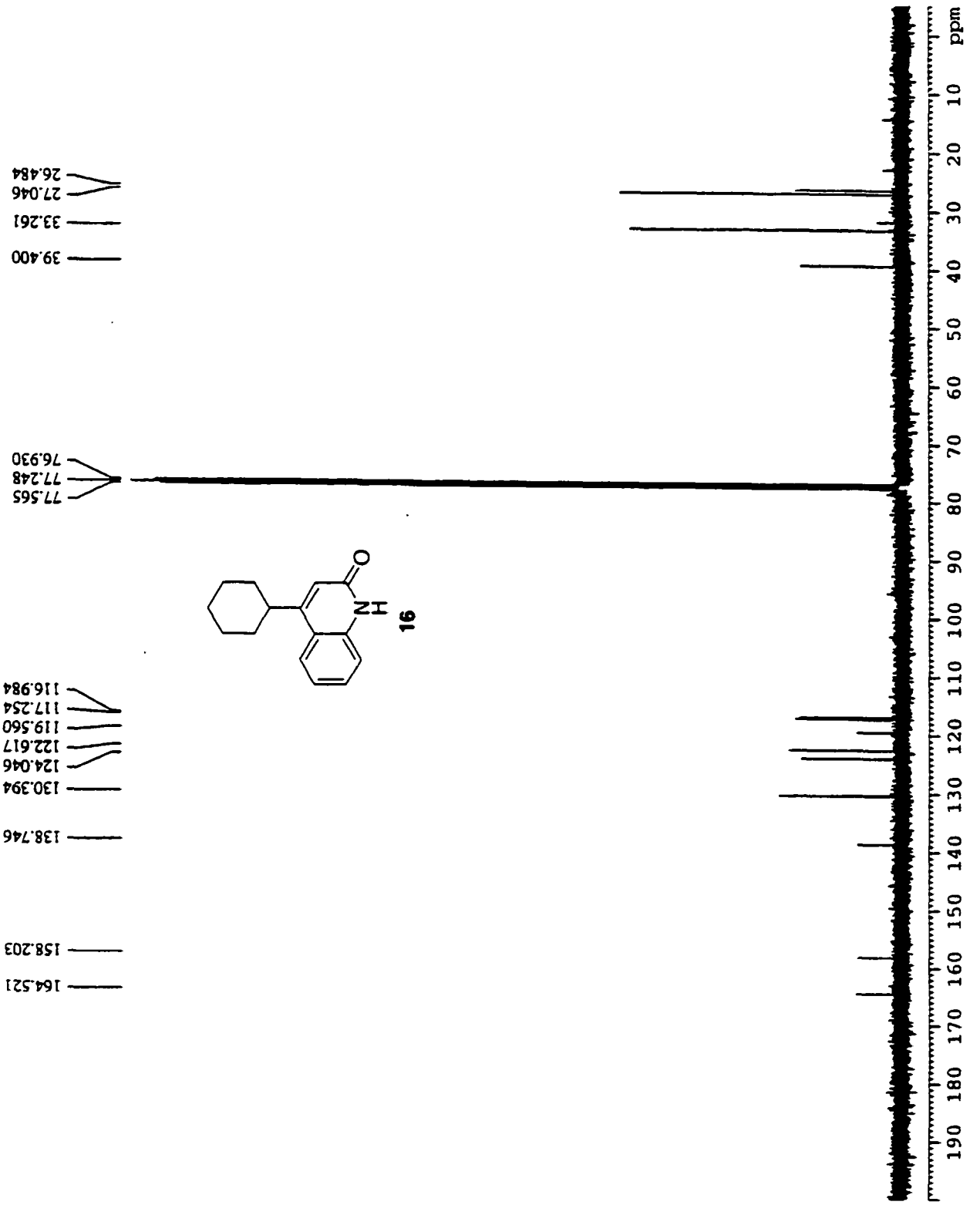
0.900
1.252
1.265
1.306
1.338
1.440
1.446
1.472
1.498
1.529
1.536
1.599
1.823
1.857
1.912
1.937
1.944
1.994
2.020
3.031
7.785
7.765
7.517
7.514
7.497
7.494
7.479
7.476
7.406
7.404
7.386
7.263
7.243
7.240
7.237
7.223
7.220
6.621
O
N
H
16
ppm
1
2
3
4
5
6
7
8
9
1.02
1.04
1.04
2.81
1.00
0.99
5.26
4.13
2.83


164.521
158.203
138.746
130.394
124.046
122.617
119.560
117.254
116.984
77.565
77.248
76.930
39.400
33.261
27.046
26.484
O
NH
16
ppm
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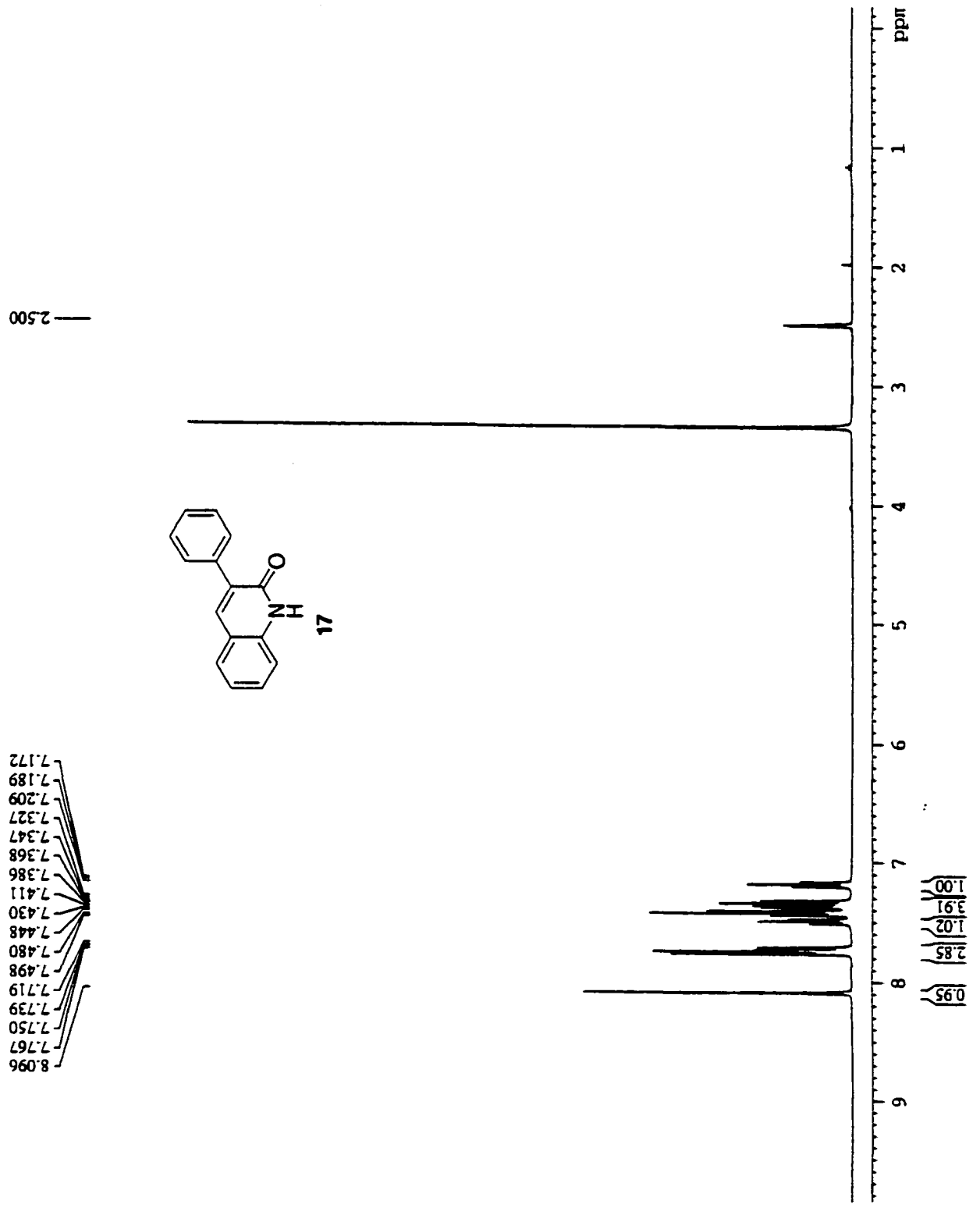
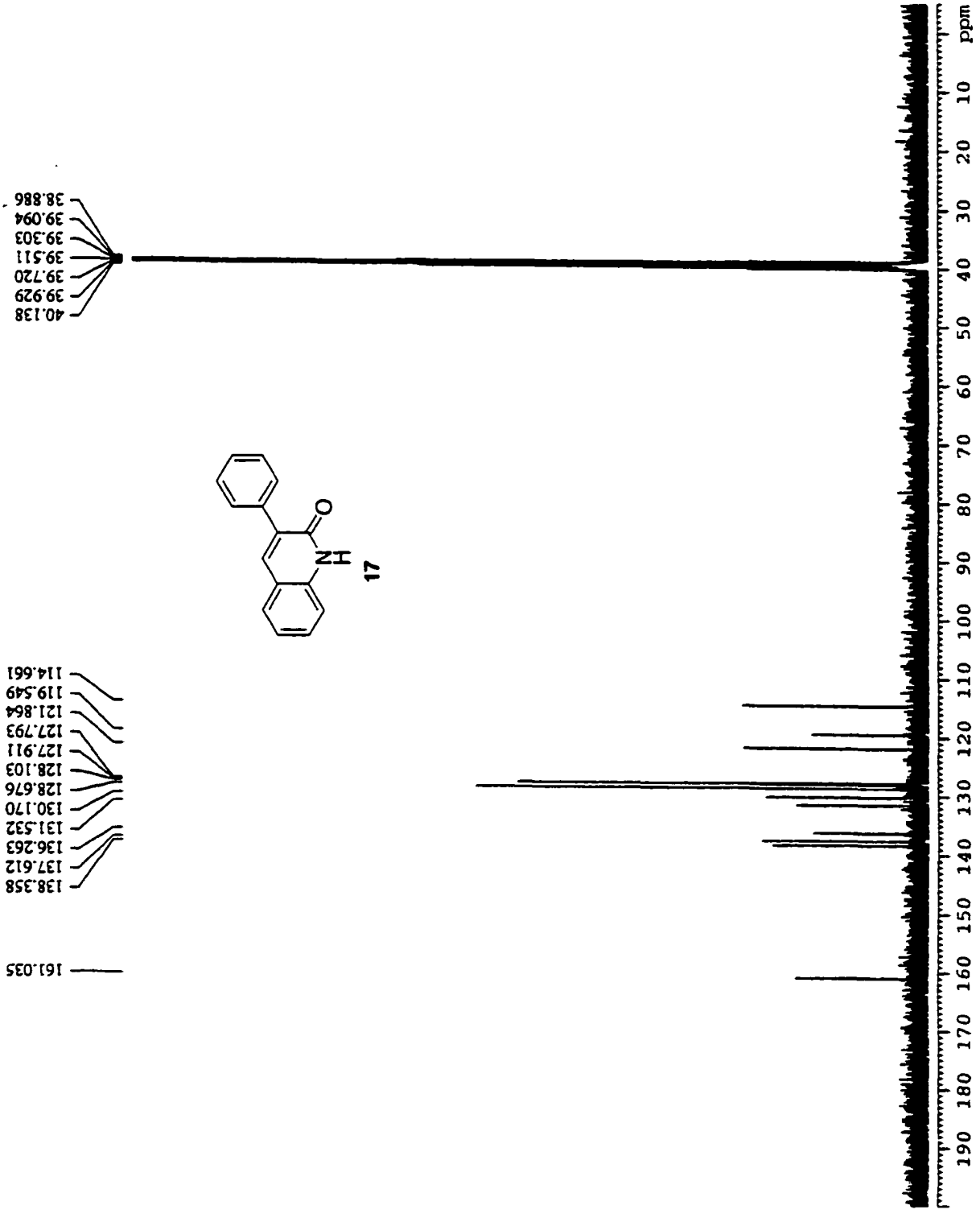
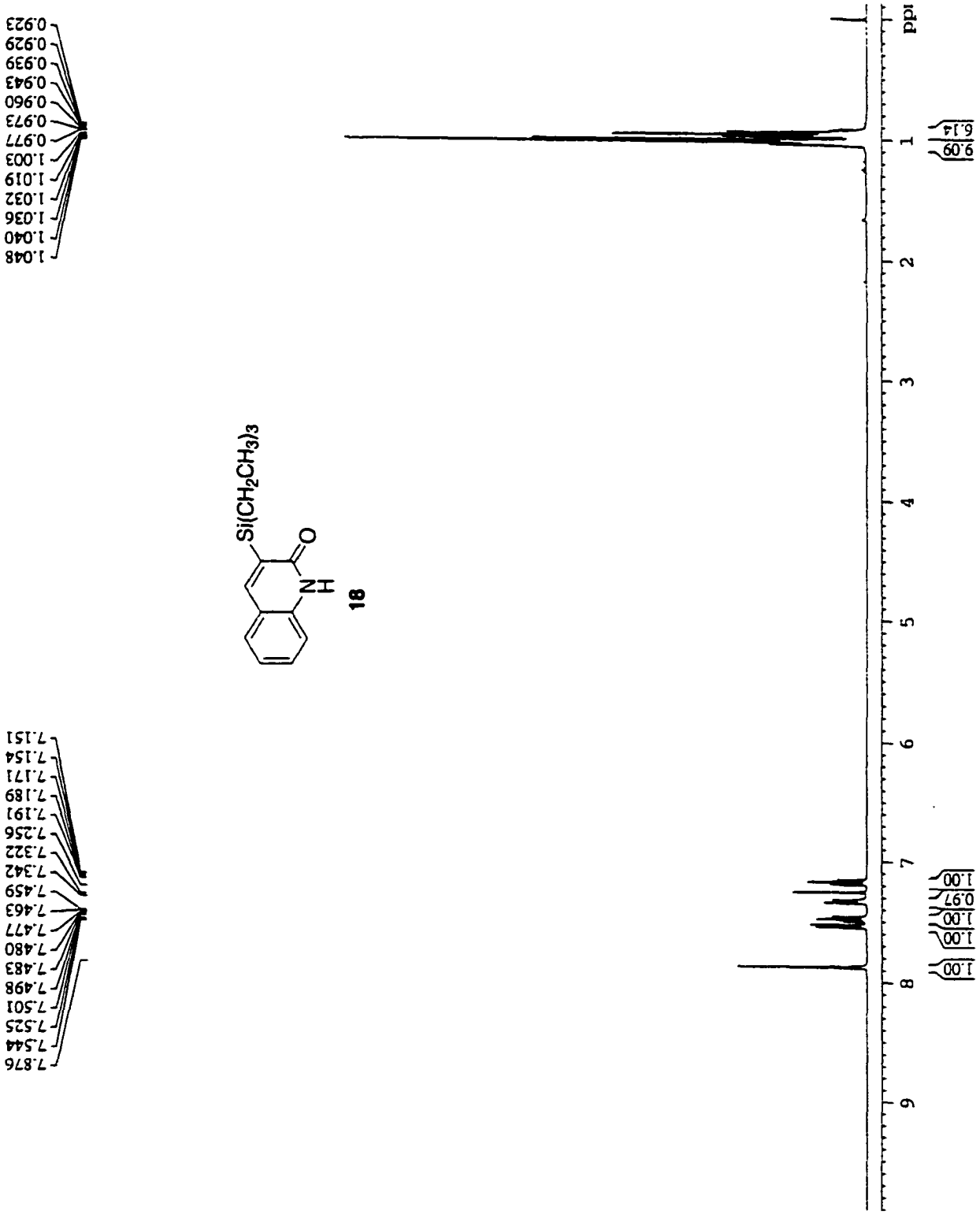
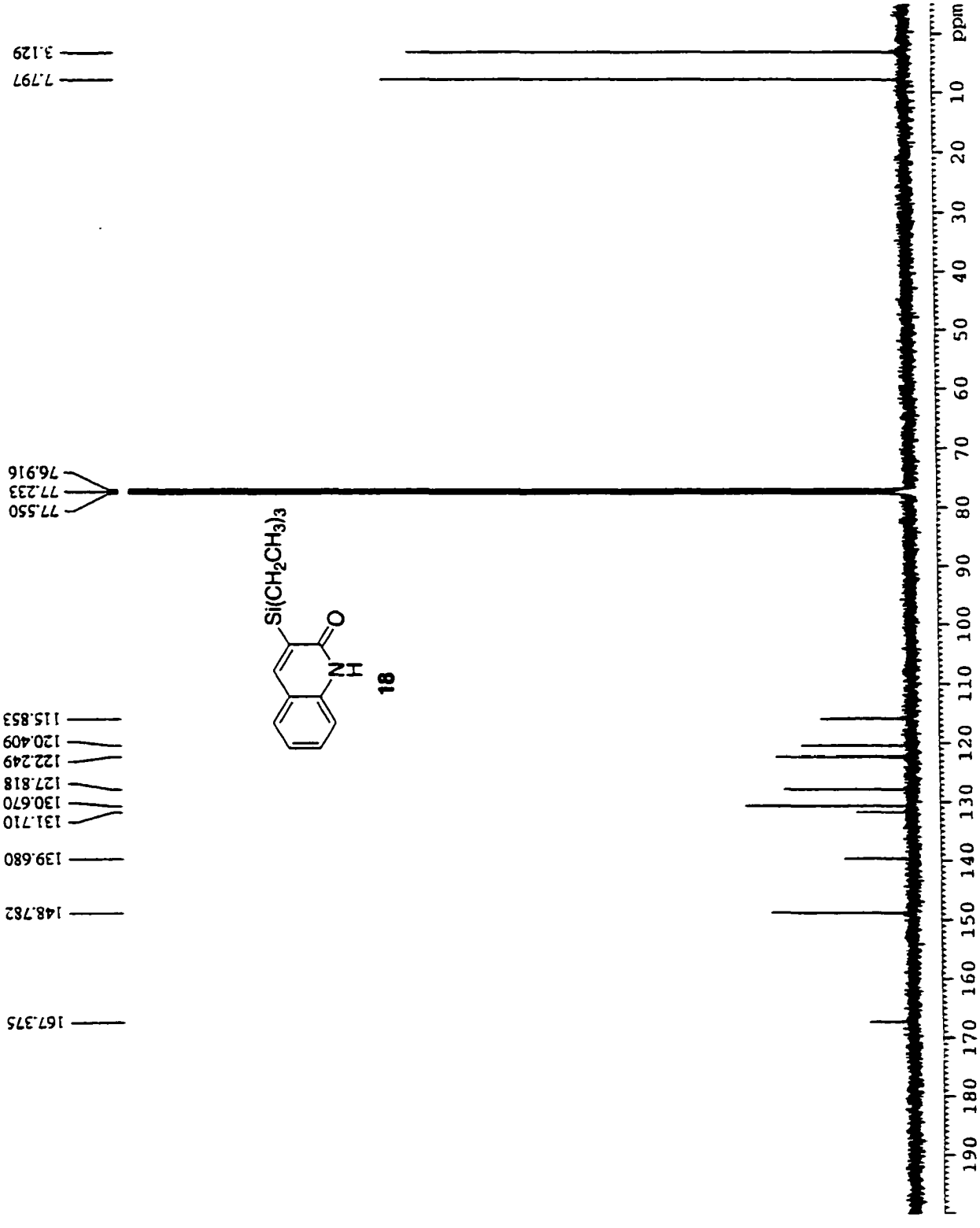
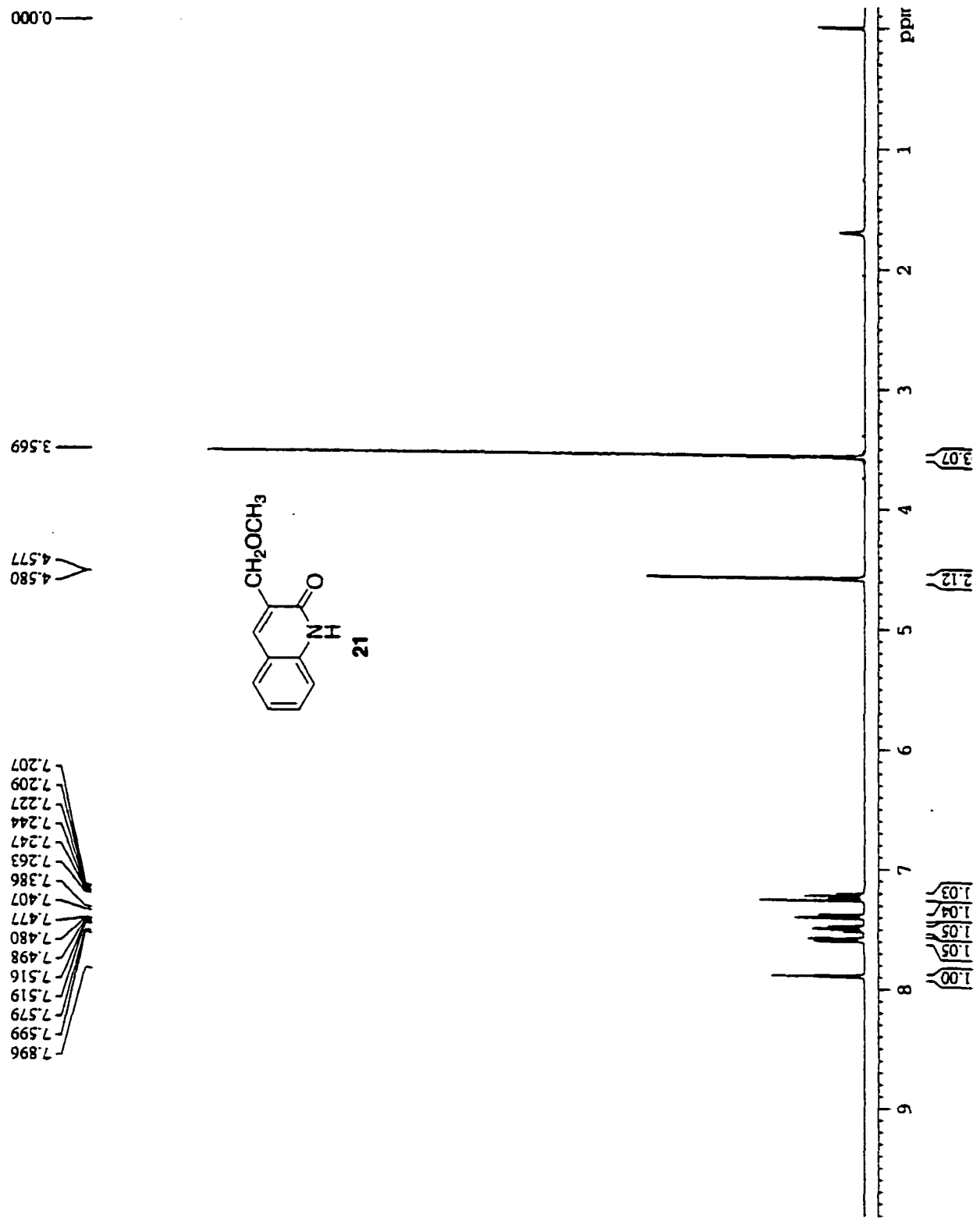
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


ppm
1
2
3
4
5
6
7
8
9
0.95
2.85
1.02
3.91
1.00
2.500
8.096
7.767
7.750
7.739
7.719
7.498
7.480
7.448
7.430
7.411
7.386
7.368
7.347
7.327
7.209
7.189
7.172
O
NH
17

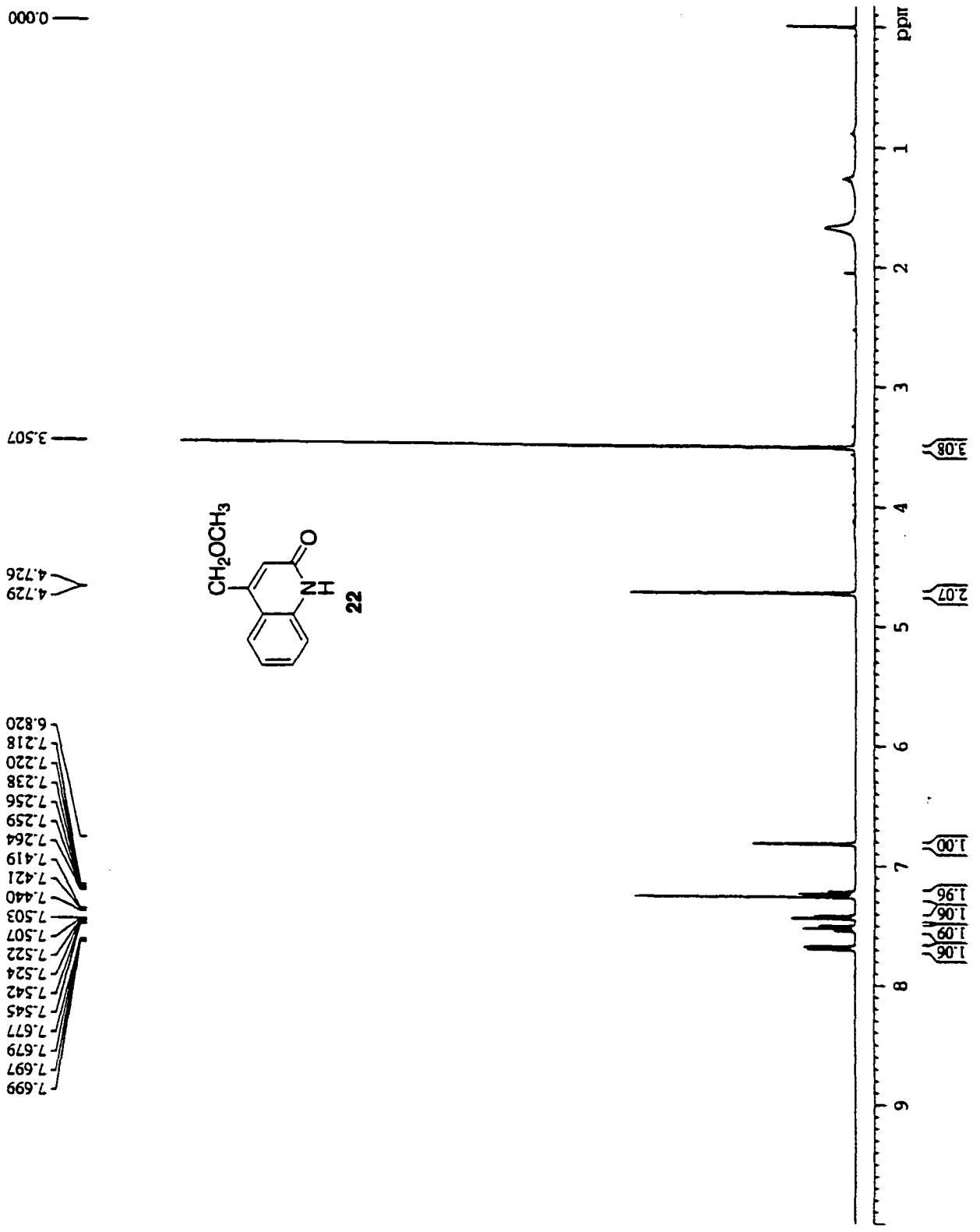

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
38.886
39.094
39.303
39.511
39.720
39.929
40.138
114.661
119.549
121.864
127.793
127.911
128.103
128.676
130.170
131.532
136.263
137.612
138.358
161.035
O
NH
17

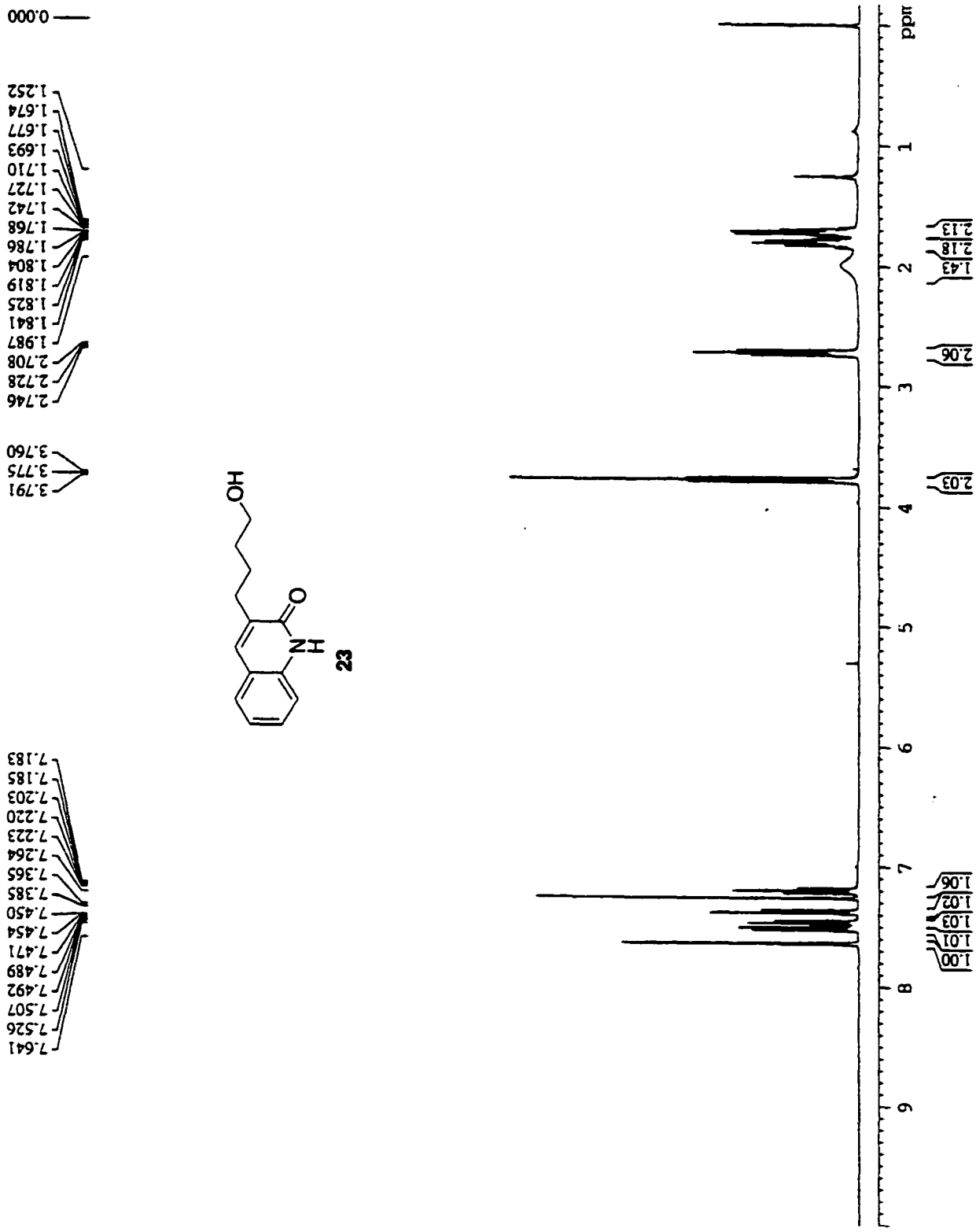

0.923
0.929
0.939
0.943
0.960
0.973
0.977
1.003
1.019
1.032
1.036
1.040
1.048
7.151
7.154
7.171
7.189
7.191
7.256
7.322
7.342
7.459
7.463
7.477
7.480
7.483
7.498
7.501
7.525
7.544
7.876
Si(CH2CH3)3
O
N
H
18
ppm
1
2
3
4
5
6
7
8
9
9.09
6.14
1.00
0.97
1.00
1.00
1.00


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
3.129
7.797
76.916
77.233
77.550
115.853
120.409
122.249
127.818
130.670
131.710
139.680
148.782
167.375
Si(CH2CH3)3
O
N
H
18


0.000
3.569
4.580
4.577
7.207
7.209
7.227
7.244
7.247
7.263
7.386
7.407
7.477
7.480
7.498
7.516
7.519
7.579
7.599
7.896
CH2OCH3
N
H
O
21
ppm
1
2
3
4
5
6
7
8
9
3.07
2.12
1.03
1.04
1.05
1.05
1.00

163.393
137.769
136.509
130.160
130.134
127.888
122.867
120.196
116.035
77.550
77.232
76.915
69.547
59.191
21
CH2OCH3
O
N
H
ppm


0.000
3.507
4.729
4.726
7.699
7.697
7.679
7.677
7.545
7.542
7.524
7.522
7.507
7.503
7.440
7.421
7.419
7.264
7.259
7.256
7.238
7.220
7.218
6.820
3.08
2.07
1.00
1.96
1.06
1.09
1.06
ppm
1
2
3
4
5
6
7
8
9
CH2OCH3
O
N
H
22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1.693
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1.819
1.825
1.841
1.987
2.708
2.728
2.746
3.760
3.775
3.791
7.183
7.185
7.203
7.220
7.223
7.264
7.365
7.385
7.450
7.454
7.471
7.489
7.492
7.507
7.526
7.641
OH
O
NH
23
ppm
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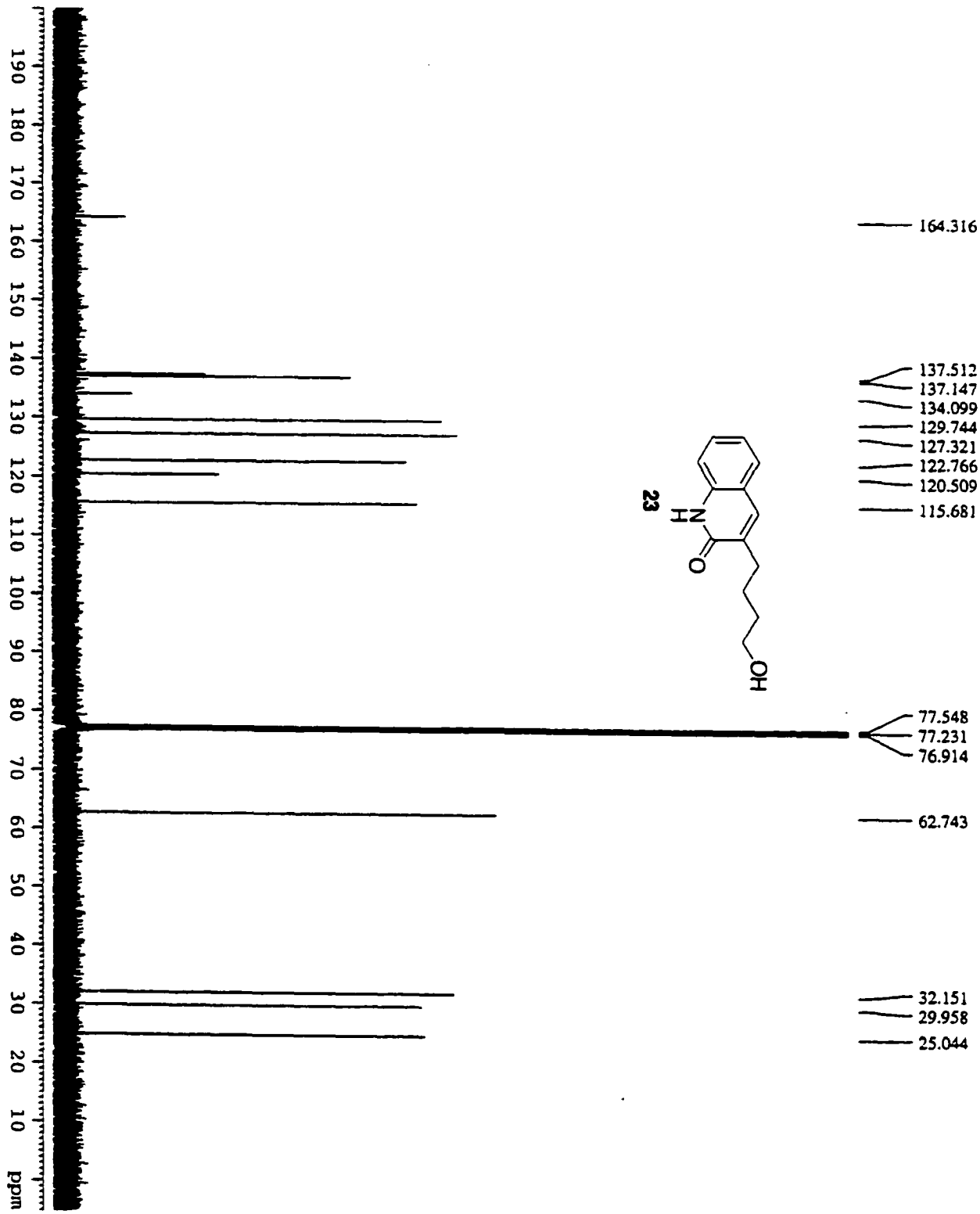
1.01
1.03
1.02
1.06
2.03
2.06
1.43
2.18
2.13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137.147
134.099
129.744
127.321
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120.509
115.681
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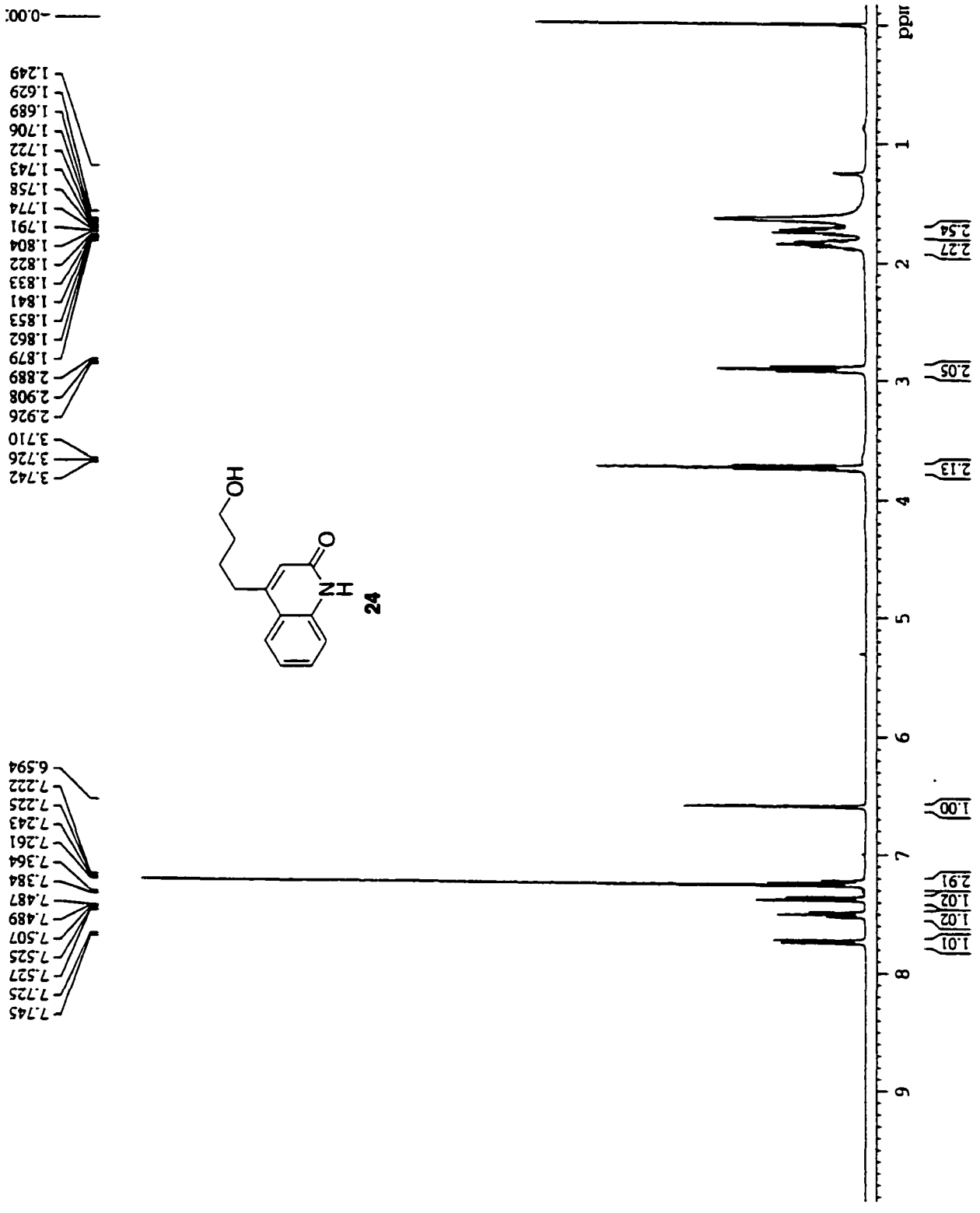
77.231
76.914
62.743
32.151
29.958
25.044
23
HO
ppm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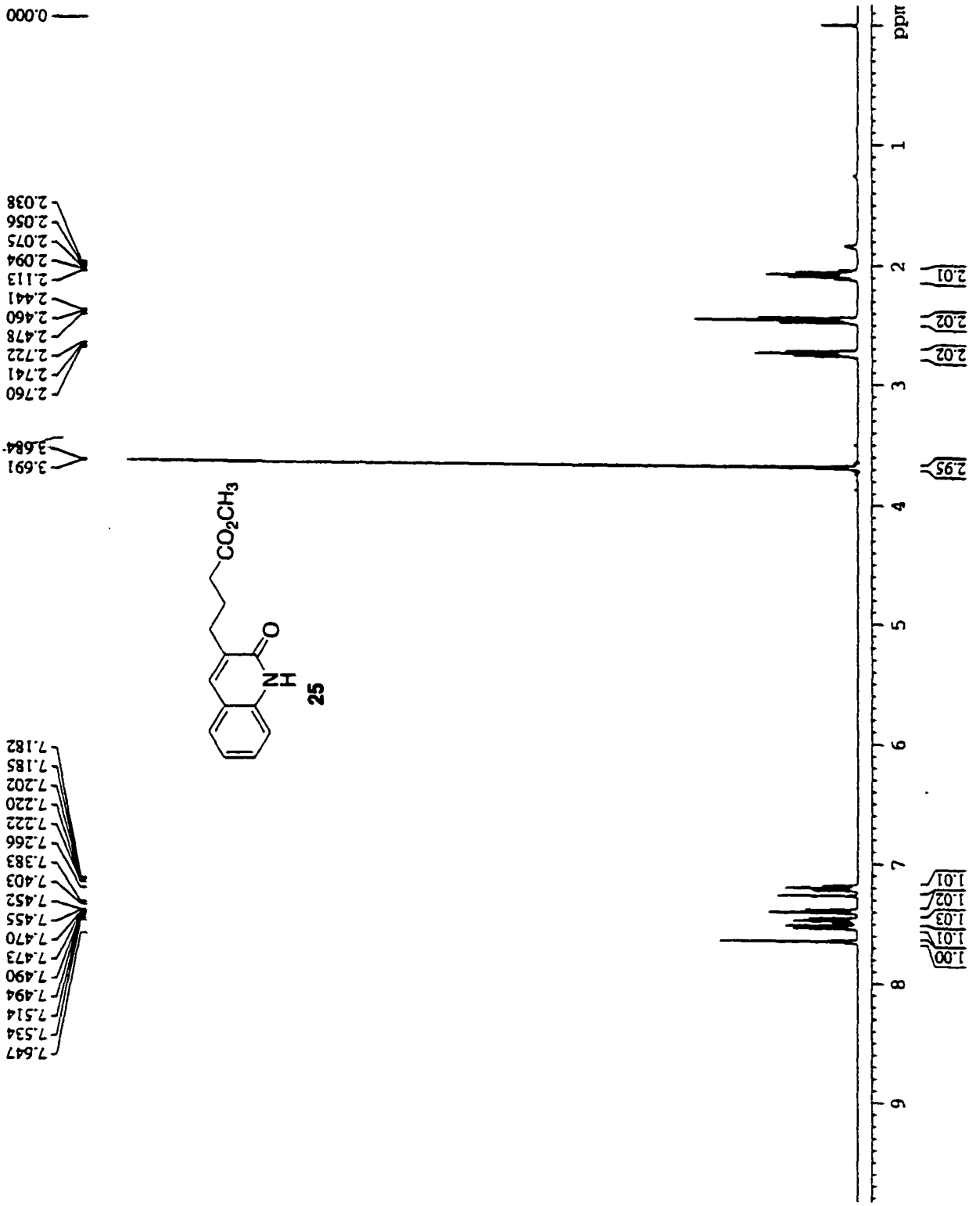
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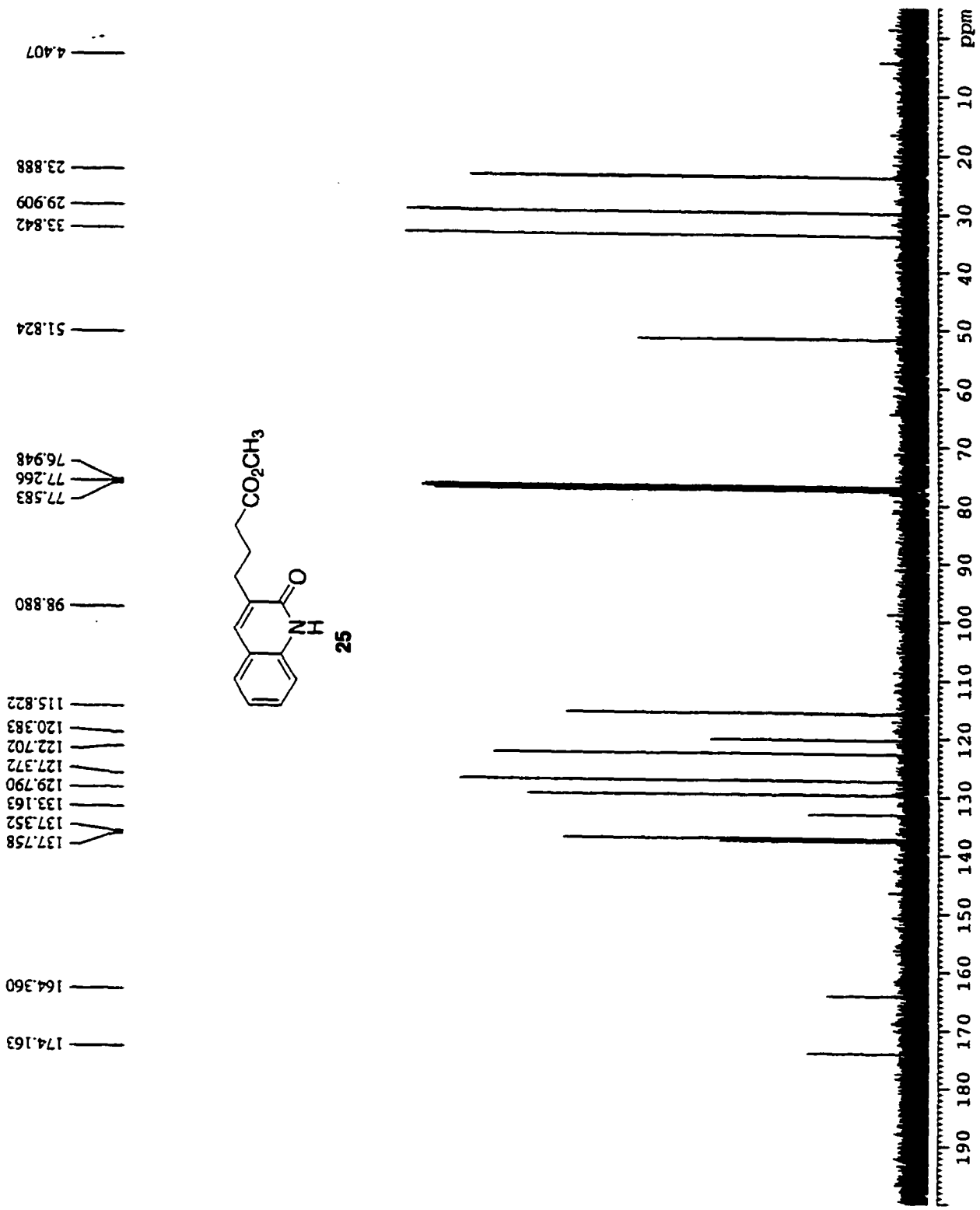
2.075
2.094
2.113
2.441
2.460
2.478
2.722
2.741
2.760
3.684
3.691
7.182
7.185
7.202
7.220
7.222
7.266
7.383
7.403
7.452
7.455
7.470
7.473
7.490
7.494
7.514
7.534
7.647
CO2CH3
O
N
H
25
ppm
1
2
3
4
5
6
7
8
9
2.01
2.02
2.02
2.95
1.00
1.01
1.03
1.02
1.01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23.888
29.909
33.842
51.824
76.948
77.266
77.583
98.880
115.822
120.383
122.702
127.372
129.790
133.163
137.352
137.758
164.360
174.163
CO2CH3
O
NH
25
ppm
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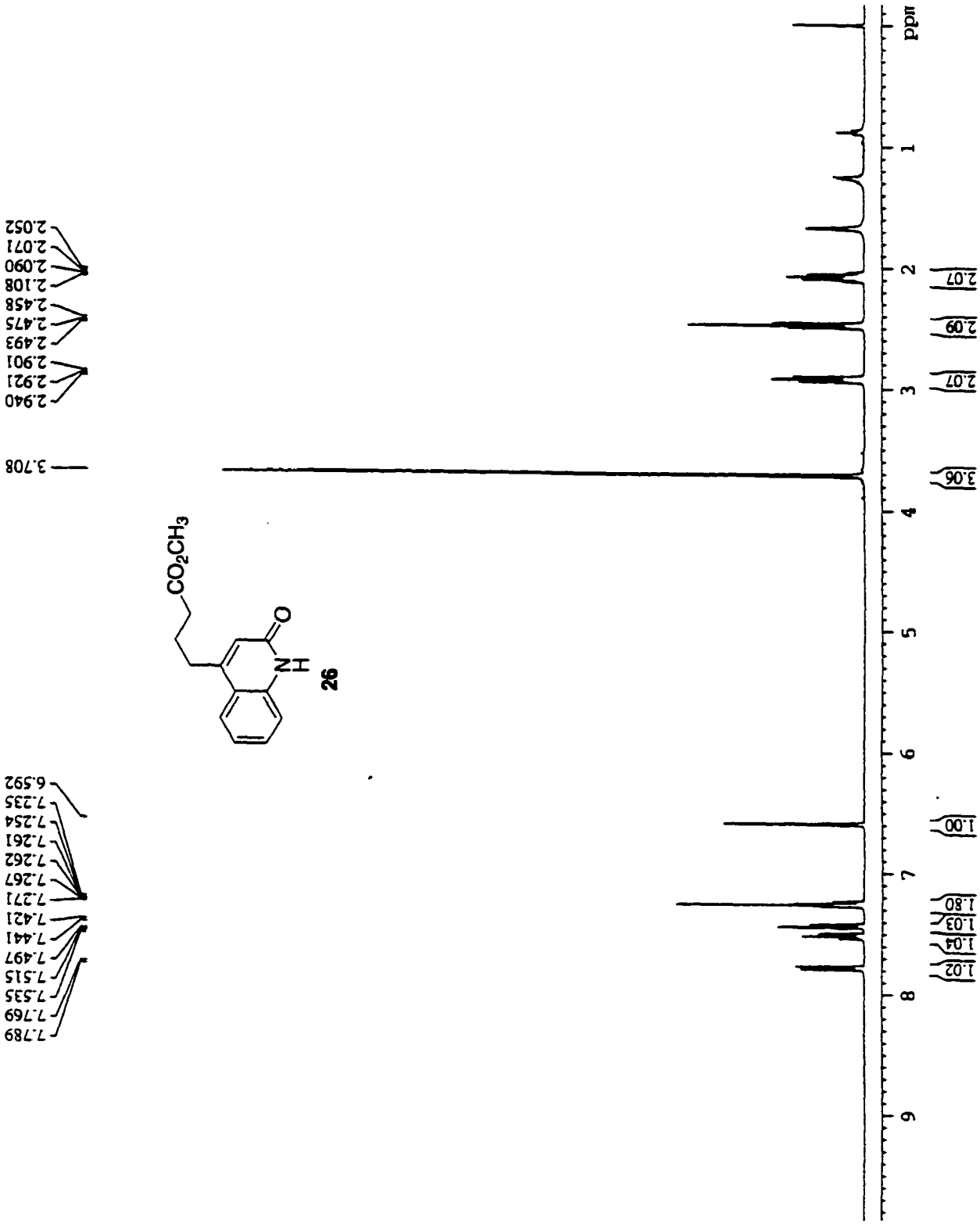
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190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2.071
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2.108
2.458
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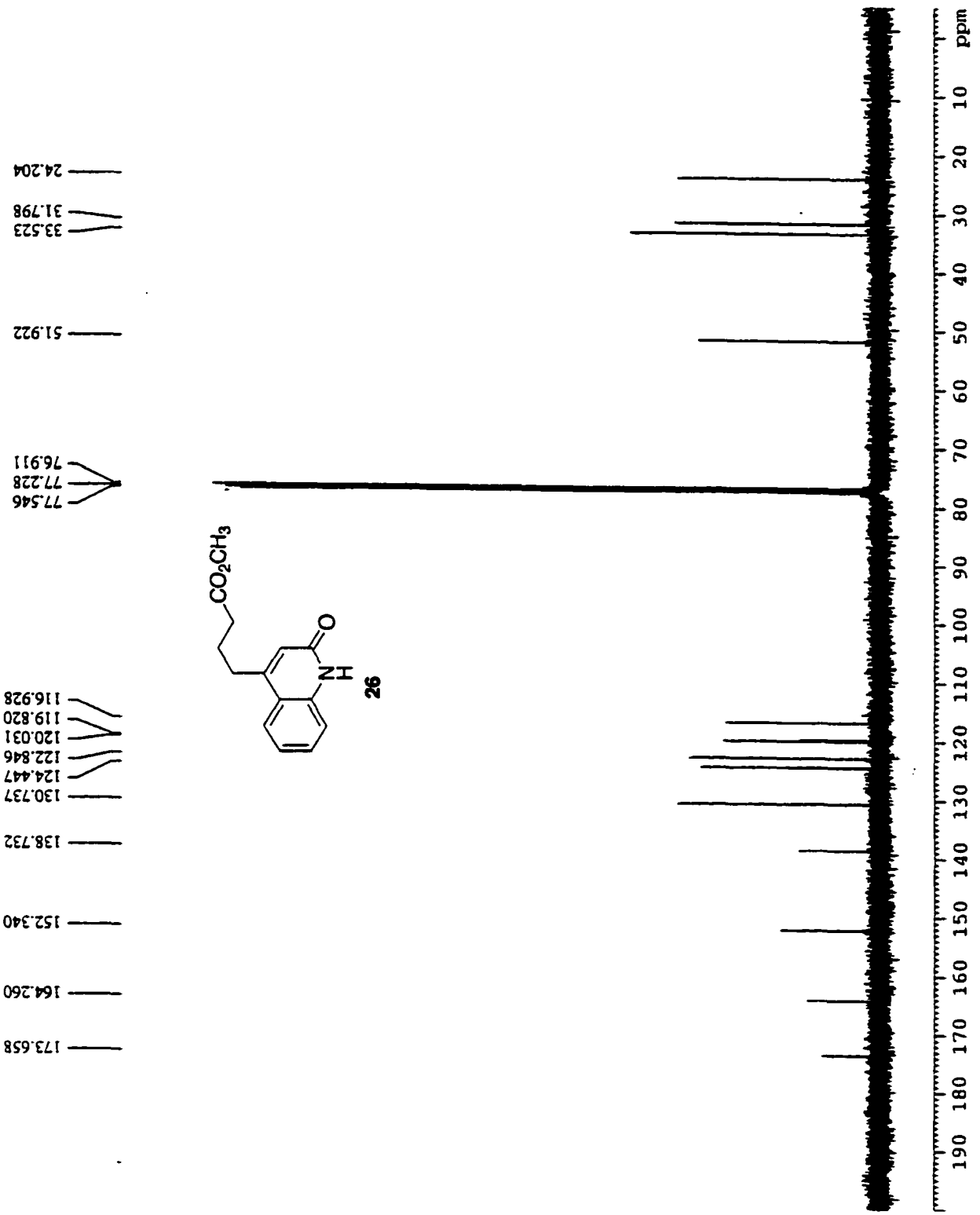
2.493
2.901
2.921
2.940
3.708
6.592
7.235
7.254
7.261
7.262
7.267
7.271
7.421
7.441
7.497
7.515
7.535
7.769
7.789
CO2CH3
O
N
H
26
ppm
1
2
3
4
5
6
7
8
9
2.07
2.09
2.07
3.06
1.00
1.80
1.03
1.04
1.02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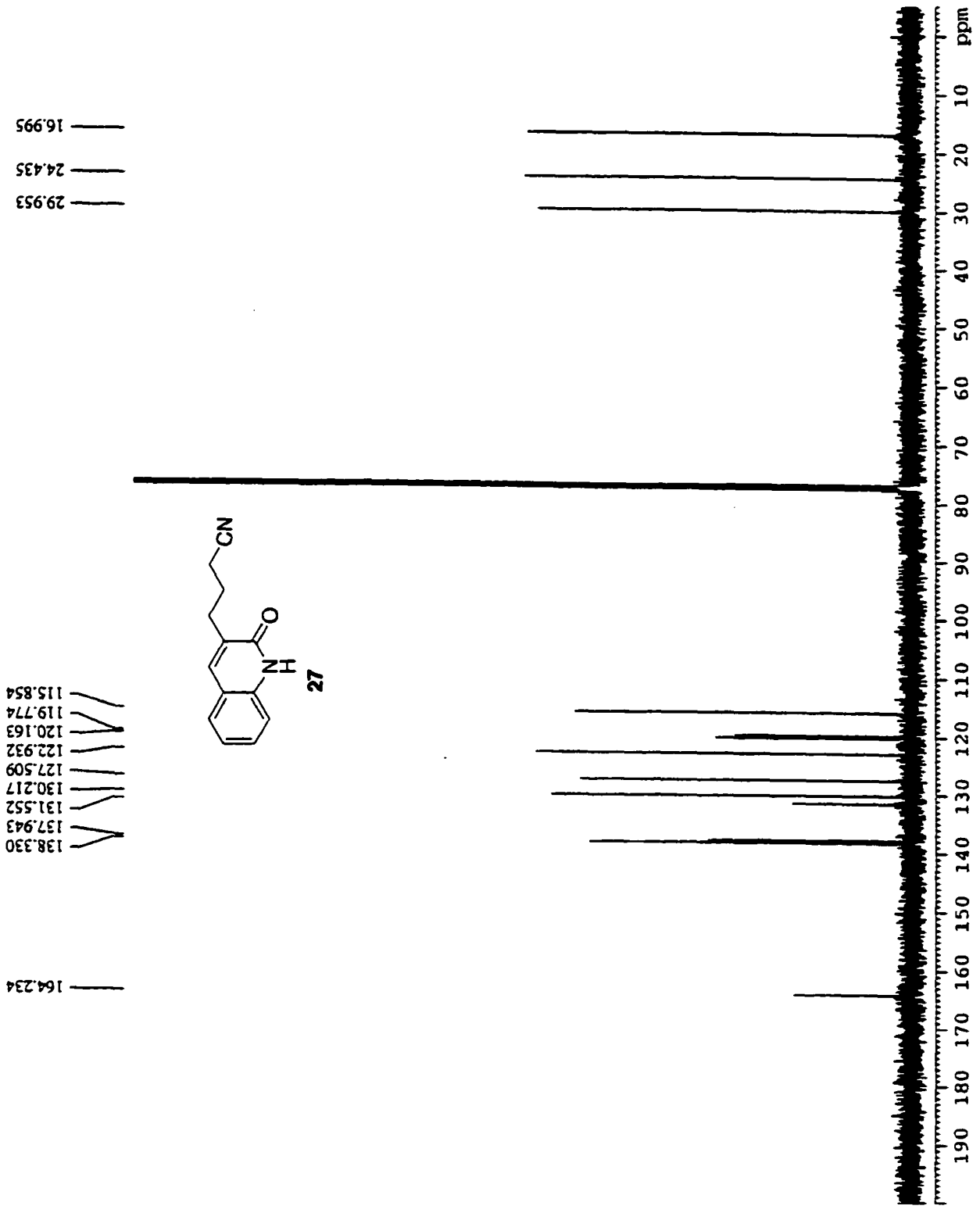
31.798
33.523
51.922
76.911
77.228
77.546
116.928
119.820
120.031
122.846
124.447
130.737
138.732
152.340
164.260
173.658
CO2CH3
O
NH
26
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

7.702
7.557
7.537
7.527
7.523
7.506
7.503
7.488
7.485
7.416
7.395
7.264
7.248
7.246
7.228
7.211
7.208
2.881
2.863
2.845
2.470
2.452
2.434
2.160
2.142
2.123
2.105
2.087
0.000
1.00
2.00
1.00
1.00
2.03
2.14
2.06
ppm
1
2
3
4
5
6
7
8
9
27
N
H
O
CN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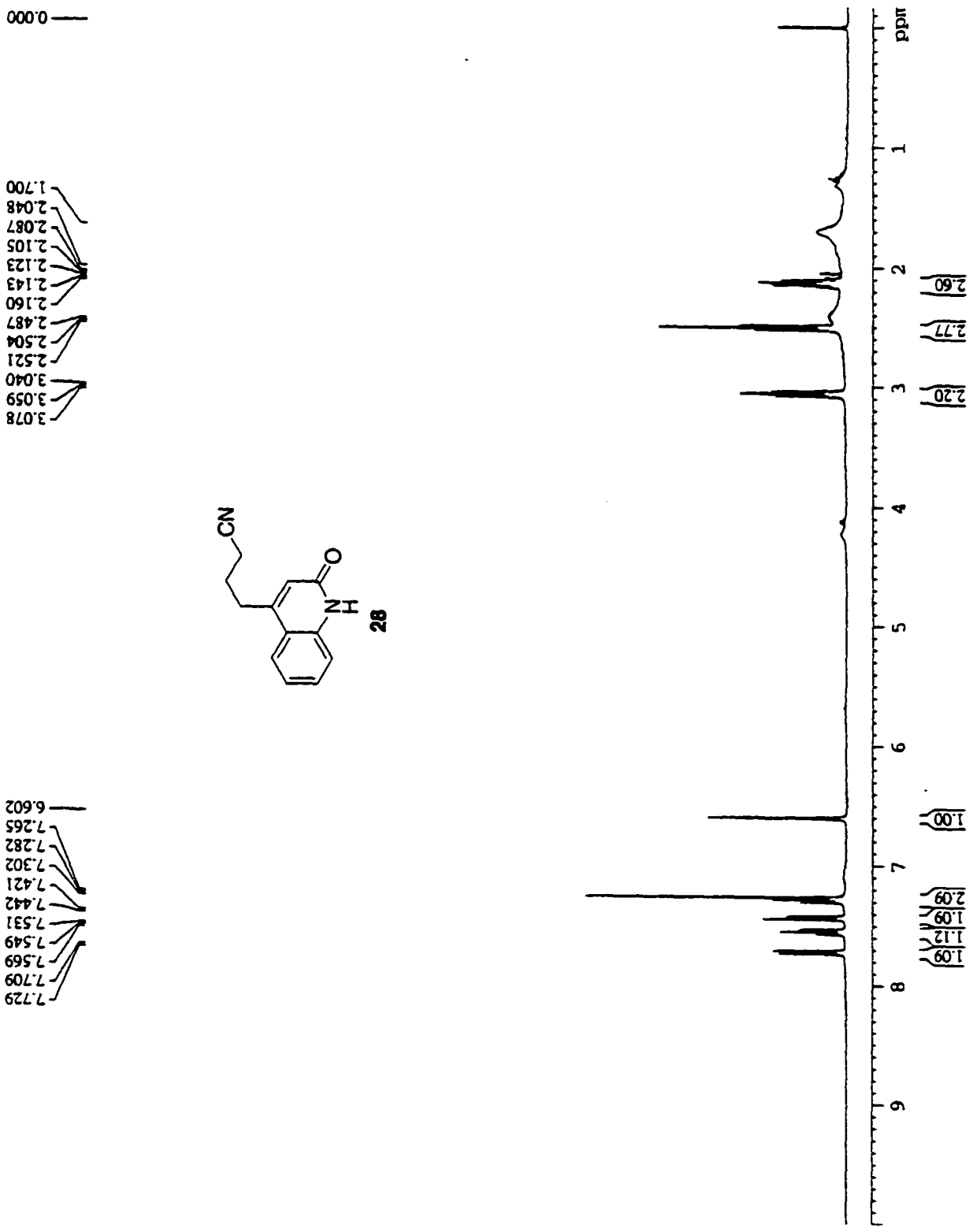
24.435
29.953
115.854
119.774
120.163
122.932
127.509
130.217
131.552
137.943
138.330
164.234
CN
O
N
H
27
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190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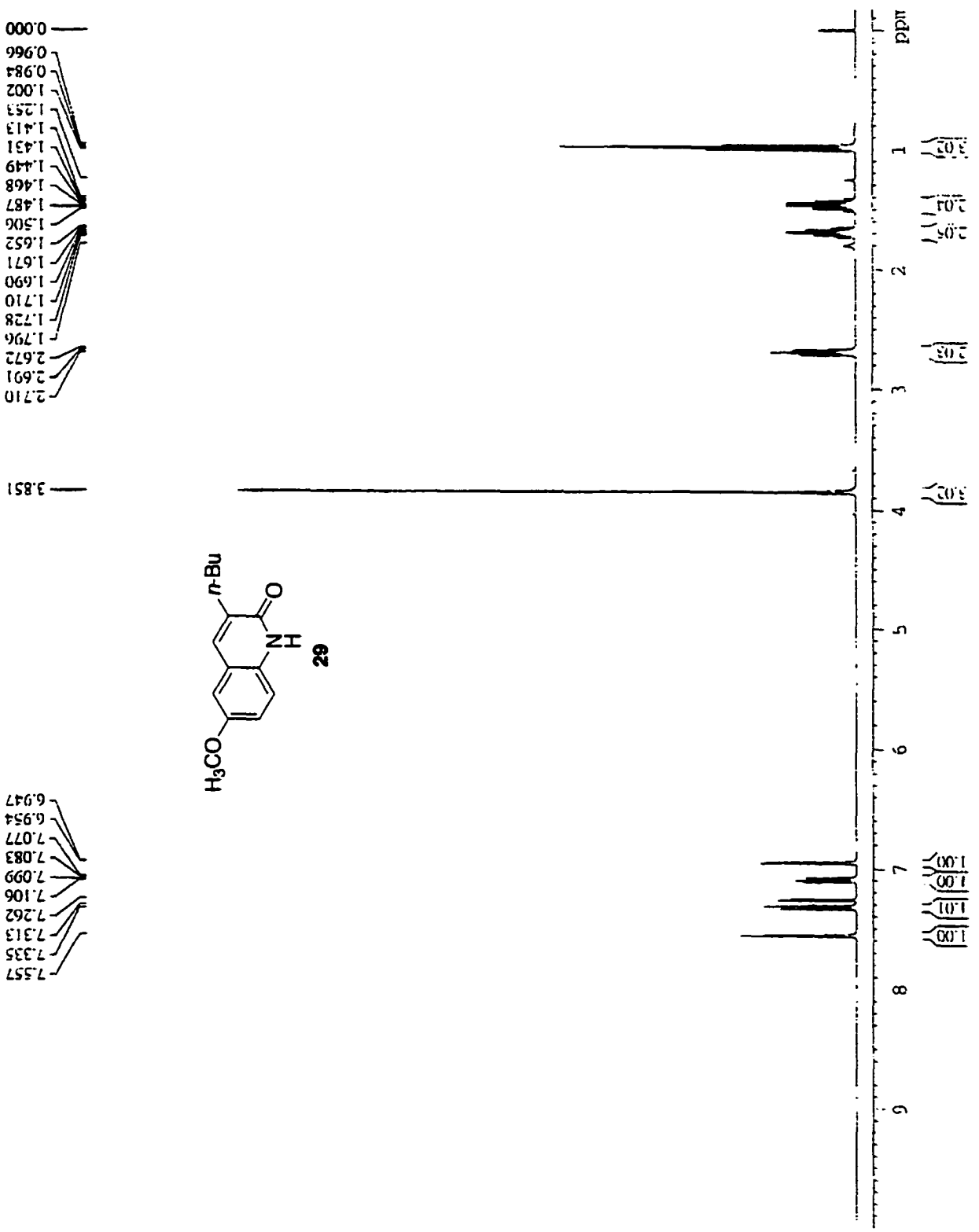
2.048
2.087
2.105
2.123
2.143
2.160
2.487
2.504
2.521
3.040
3.059
3.078
6.602
7.265
7.282
7.302
7.421
7.442
7.531
7.549
7.569
7.709
7.729
CN
O
N
H
28
ppm
1
2
3
4
5
6
7
8
9
1.09
1.12
1.09
2.09
1.00
2.20
2.77
2.60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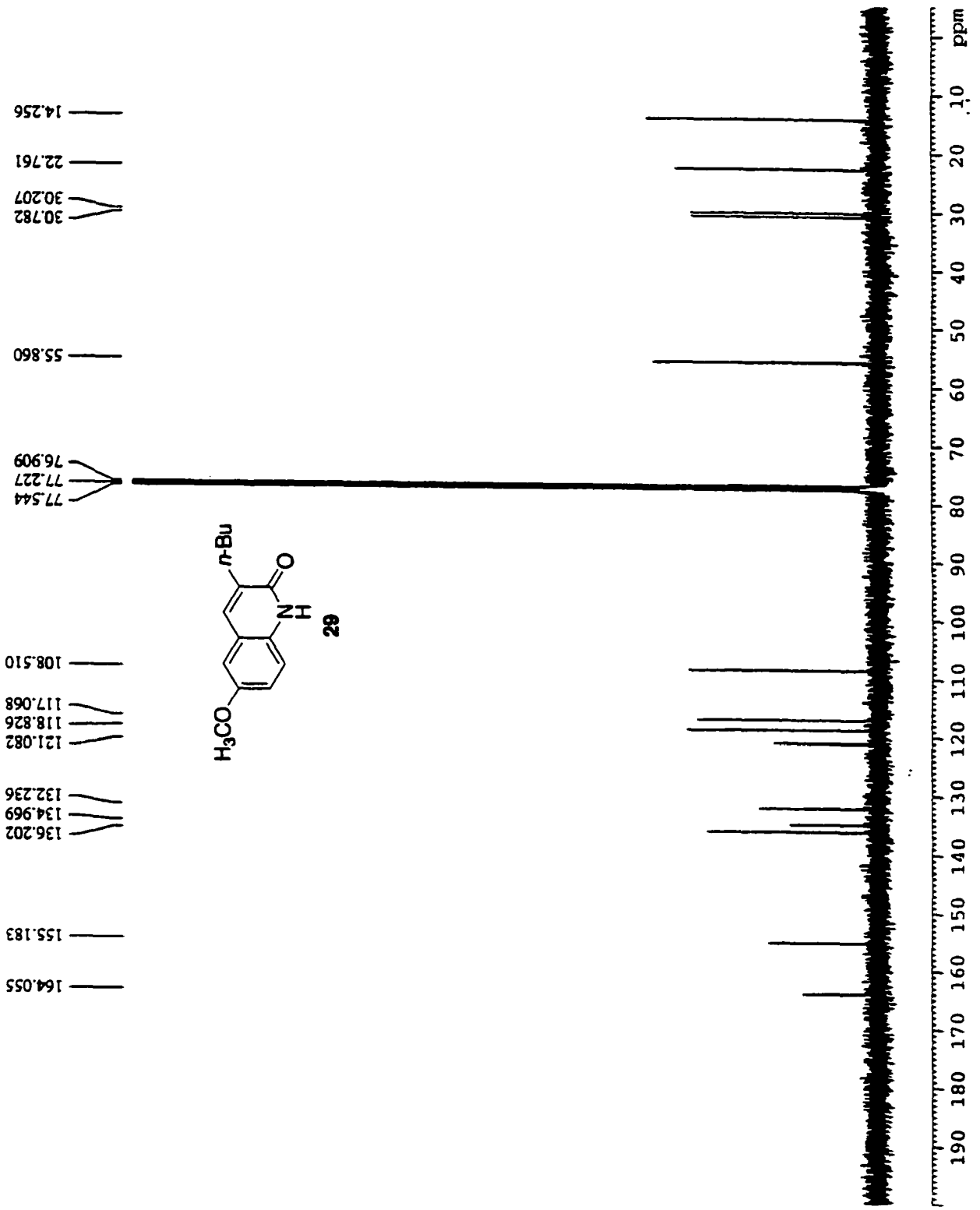
0.984
1.002
1.253
1.413
1.431
1.449
1.468
1.487
1.506
1.652
1.671
1.690
1.710
1.728
1.796
2.672
2.691
2.710
3.851
6.947
6.954
7.077
7.083
7.099
7.106
7.262
7.313
7.335
7.557
n-Bu
O
NH
H3CO
29
ppm
1
2
3
4
5
6
7
8
9
3.02
2.04
2.05
3.05
3.02
1.00
1.00
1.01
1.00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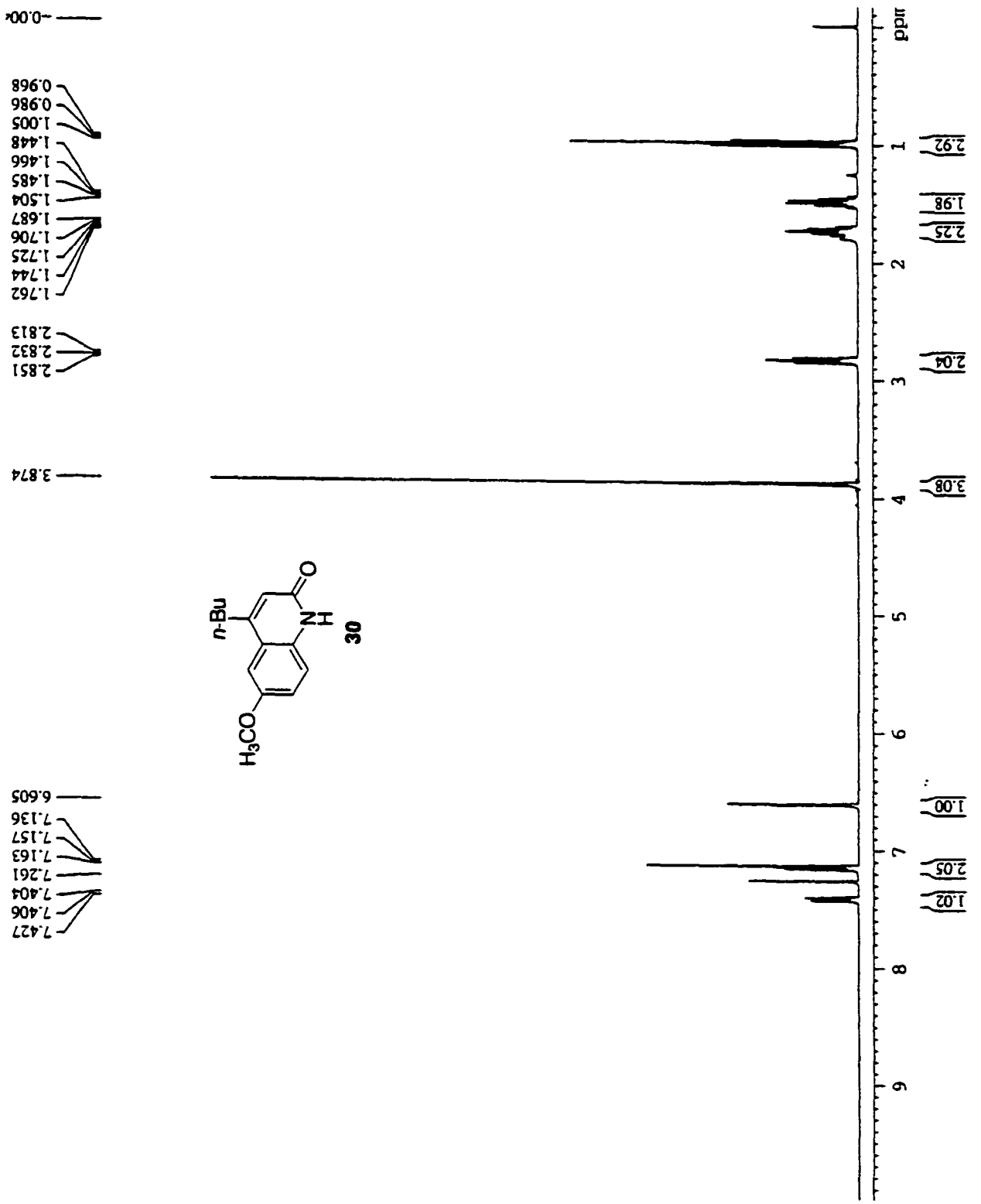
30.207
30.782
55.860
76.909
77.227
77.544
108.510
117.068
118.826
121.082
132.236
134.969
136.202
155.183
164.055
n-Bu
O
N
H
H3CO
29
ppm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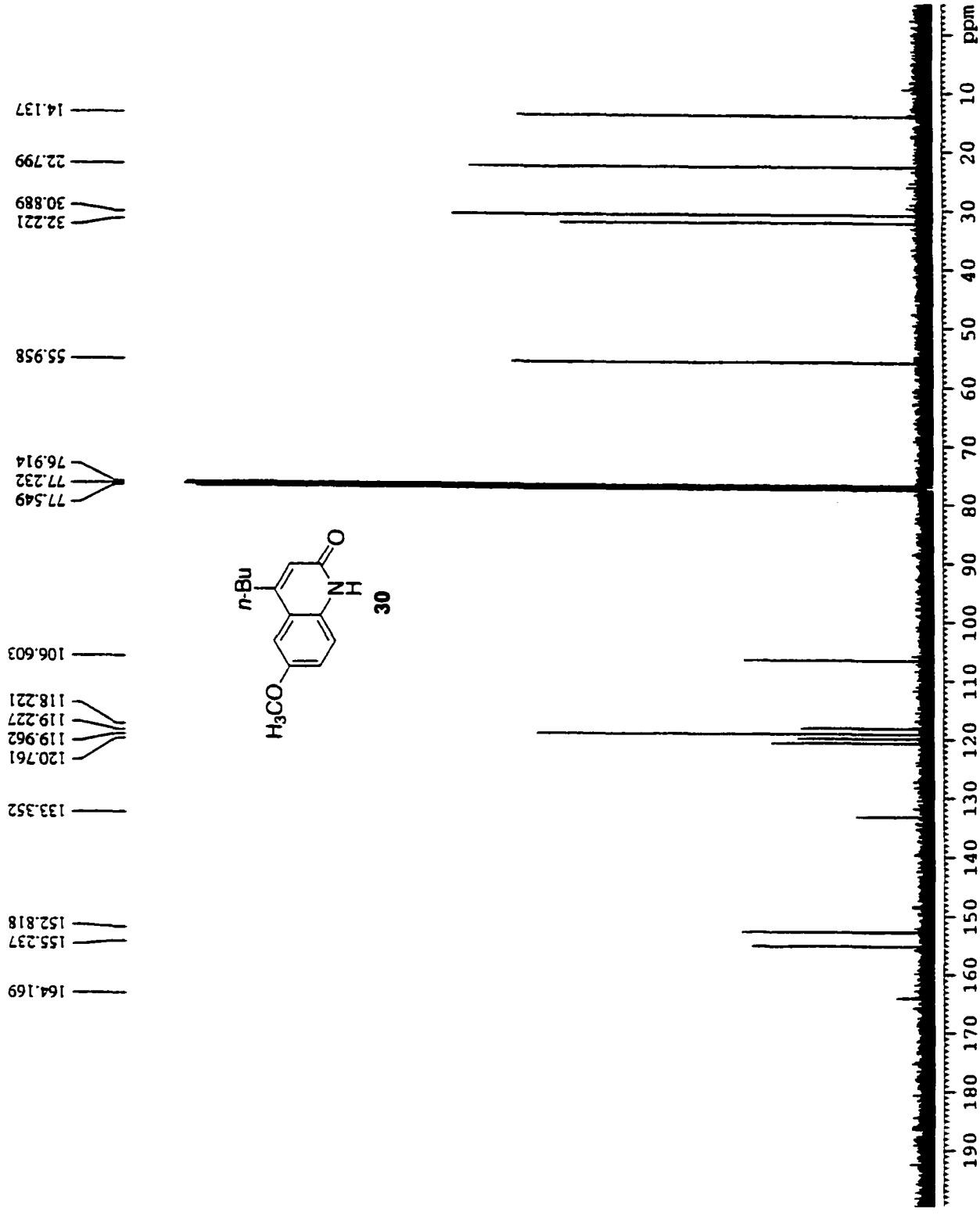
0.968
0.986
1.005
1.448
1.466
1.485
1.504
1.687
1.706
1.725
1.744
1.762
2.813
2.832
2.851
3.874
6.605
7.136
7.157
7.163
7.261
7.404
7.406
7.427
n-Bu
H3CO
30
ppm
2.92
1.98
2.25
2.04
3.08
1.00
2.05
1.02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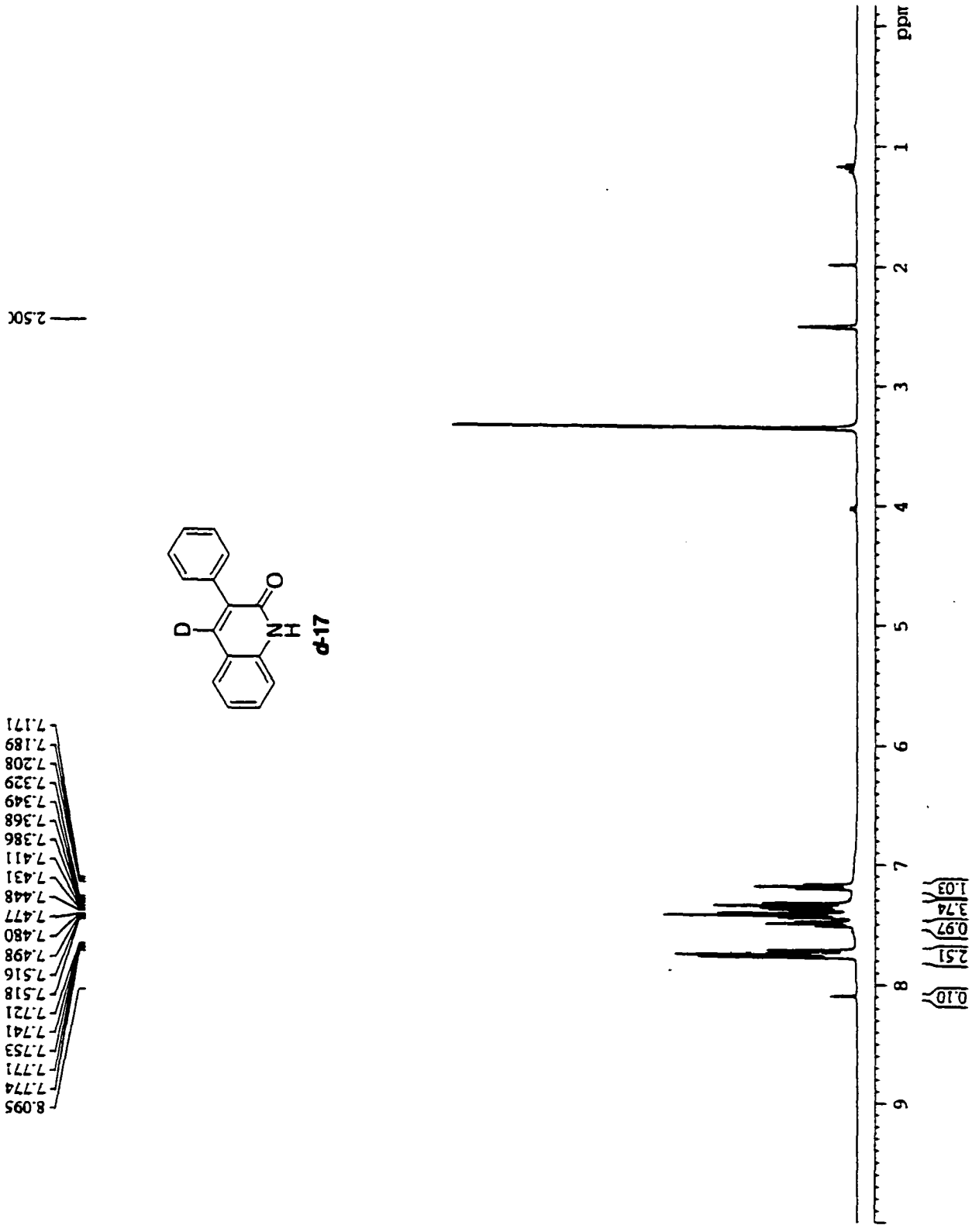
30.889
32.221
55.958
76.914
77.232
77.549
106.603
118.221
119.227
119.962
120.761
133.352
152.818
155.237
164.169
n-Bu
O
N
H
H3CO
30
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190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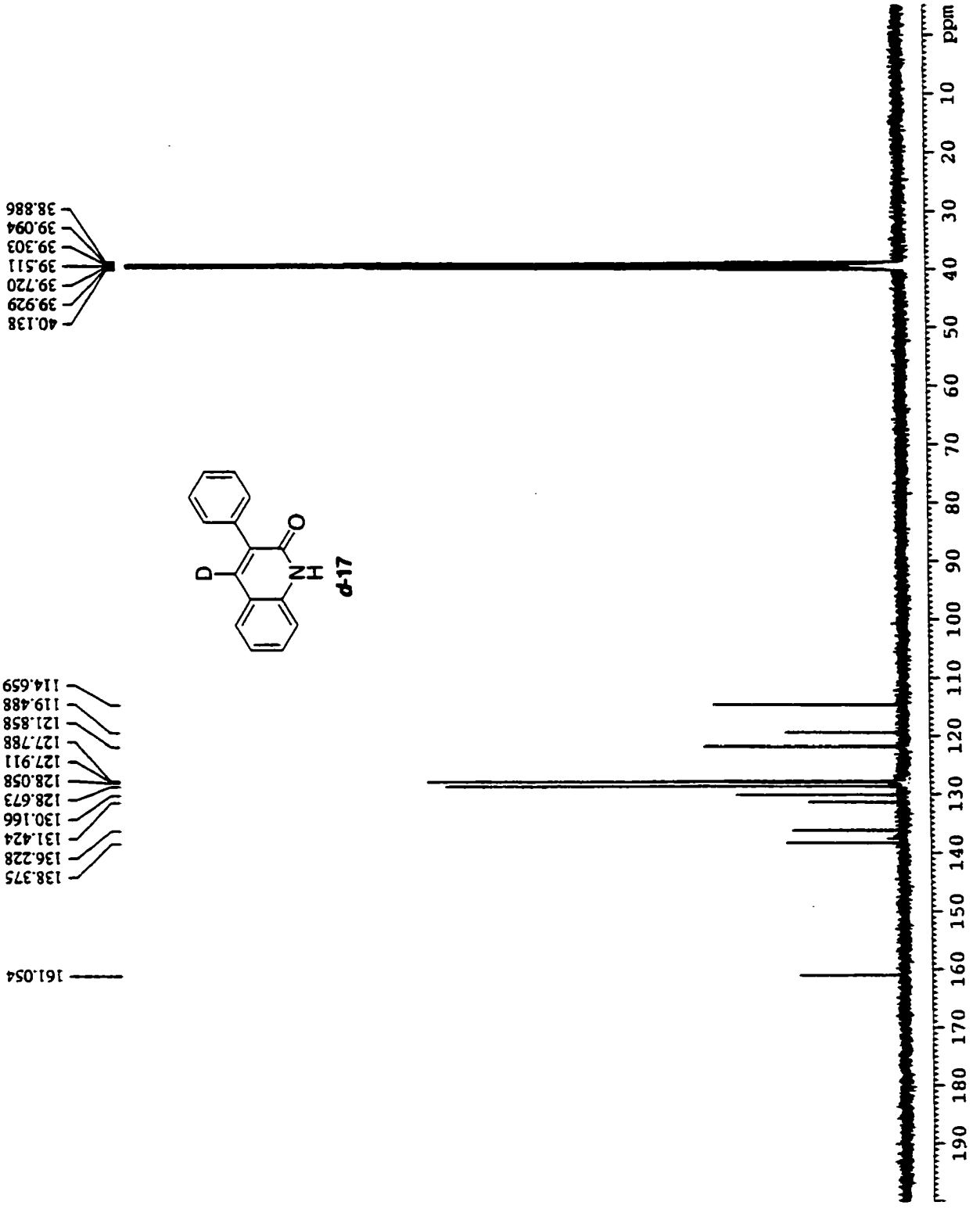
7.774
7.771
7.753
7.741
7.721
7.518
7.516
7.498
7.480
7.477
7.448
7.431
7.411
7.386
7.368
7.349
7.329
7.208
7.189
7.171
2.50
D
O
NH
d-17
0.10
2.51
0.97
3.74
1.03
ppm


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
38.886
39.094
39.303
39.511
39.720
39.929
40.138
114.659
119.488
121.858
127.788
127.911
128.058
128.673
130.166
131.424
136.228
138.375
161.054
O
NH
D
d-17